NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Osimertinib for untreated EGFR-positive non-small-cell lung cancer [ID1302]

Committee Papers

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SINGLE TECHNOLOGY APPRAISAL

Osimertinib for untreated EGFR-positive non-small-cell lung cancer [ID1302]

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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

Osimertinib for the first-line treatment of locally advanced or metastatic EGFR mutation positive non-small cell lung cancer [ID1302]

Document B

Company evidence submission

August 2018

File name	Version	Contains confidential information	Date
Osimertinib_ID1302_DocB_FINAL	1	Yes (AIC/CIC)	05/09/2018

AstraZeneca

AstraZeneca UK Ltd

600 Capability Green, Luton LU1 3LU

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List of abbreviations

Acronym	Definition
AE	Adverse event
AIC	Akaike information criterion
AKT	Protein kinase B
ALK	Anaplastic lymphoma kinase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AR	Adverse reaction
ASCO	American Society of Clinical Oncology

AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
AWMSG	All Wales Medicines Strategy Group
BBB	Blood brain barrier
BIC	Bayesian Information Criterion
BICR	Blinded independent central review
BSA	Body surface area
BSC	Best-supportive care
CADTH	Canadian Agency for Drugs and Technologies in Health
CDR	Common Drug Review
CDSR	Cochrane Database of Systematic Reviews
CE	Cost-effectiveness
CEA	Cost-effectiveness analysis
CENTRAL	Cochrane Central Register of Controlled Trials
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CLIA	Clinical Laboratory Improvement Amendment
CNS	Central nervous system
CONSORT	Consolidated Standards of Reporting Trials
CR	Complete response
CT	Computerised tomography
CTCAE	Common terminology criteria for adverse events
CTR	Clinical Trial Register
CTSQ	Cancer Therapy Satisfaction Questionnaire
CTSQ	Cancer Therapy Satisfaction Questionnaire
CYP	Cytochrome P450
DARE	Database of Abstracts of Reviews of Effectiveness
DCR	Disease control rate
DNA	Deoxyribonucleic acid
DOR	Duration of response
EBUS-guided TBNA	Endobronchial ultrasound-guided transbronchial needle aspiration
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
ELCC	European Lung Cancer Conference
EMA	European Medicines Agency
EOL	End-of-life
EORTC	European Organisation for Research and Treatment of Cancer

EPAR	European public assessment report
EQ-5D	EuroQol 5-dimensions
ESMO	European Society for Medical Oncology
EU	European Union
EUR	Euro
Exon19del	Deletion in exon 19 of EGFR
FAS	Full analysis set
FDA	Food and Drug Administration
FE	Fixed effects
GBP	Pound Sterling
HIV	Human immunodeficiency virus
HR	Hazard ratio
HRQoL	Health-related quality of life
HS	Health state
HSU	Health state utility
HTA	Health technology assessment
HTAD	Health Technology Assessment Database
HUS	Health utility score
IA	Investigator assessment
IV	Intravenous
ICER	Incremental cost-effectiveness ratio
ICTRP	International Clinical Trials Registry Platform
ILD	Interstitial lung disease
ITC	Indirect treatment comparison
ITT	Intent-to-treat
IV	Intravenous
IVRS	Interactive voice response
IWRS	Interactive Web Response System
KM	Kaplan-Meier
L858R	Amino acid substitution at position 858 in EGFR, from leucine (L) to arginine (R)
LS	Least squares
LVEF	Left ventricular ejection fraction
LYG	Life-year gained
MAE	Mean absolute error
MAP	Mitogen-activated protein
MMRM	Mixed model for repeated measures
MRI	Magnetic resonance imaging
NC	Not calculable

NE	Not evaluable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NR	Not reported
NS	Not significant
NSCLC	Non-small cell lung cancer
OLS	Ordinary least squares
OR	Odds ratio
ORR	Objective response rate
OS	Overall survival
PAS	Patient access scheme
PD-L1	Programmed death-ligand 1
PD	Progressed disease
PF	Progression free
PFS	Progression free survival
PR	Partial response
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PRO	Patient reported outcome
PS	Performance status
PSM	Partitioned-survival model
QALY	Quality-adjusted life-year
QLQ	Quality of life questionnaire
QoL	Quality of life
QTc	QT interval
RAS	Rat sarcoma
RCT	Randomised controlled trial
RDI	Relative dose intensity
RE	Random effects
RECIST	Response evaluation criteria in solid tumours
RTK	Receptor tyrosine kinase
RMSE	Root mean squared error
SACT	Systemic anti-cancer therapy
SD	Stable disease
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SmPC	Summary of product characteristics
SoC	Standard of care

STAT	Signal transducer and activator of transcription
T790M	Amino acid substitution at position 790 in EGFR, from threonine (T) to methionine (M)
TDT	Time to discontinuation of treatment
TK	Tyrosine kinase
TKI	Tyrosine kinase inhibitor
TL	Target lesion
TNM	Tumour nodes metastasis
TSD	Technical support document
TTD	Time to treatment discontinuation
UK	United Kingdom
ULN	Upper limit of normal
US(A)	United States (of America)
VEGF	Vascular endothelial growth factor
WBRT	Whole-brain radiation therapy
WHO	World Health Organization
WT	Wild-type

Executive summary

Disease context

An estimated 44,500 people are diagnosed with lung cancer in the UK each year, of whom over 80% have non-small cell lung cancers (NSCLC).[1] NSCLC is typically asymptomatic in early stages and resulting delays in presentation and diagnosis – along with the aggressive nature of the disease – mean that an estimated 70% of patients will receive a diagnosis at an advanced disease stage (i.e. Stage IIIb and IV).[2] Patients diagnosed with advanced lung cancer can expect to experience multiple, debilitating symptoms,[1, 3] and a profound effect on their quality of life.[4]

Although the prognosis for patients with lung cancer has improved in recent years, survival remains poor compared with other cancers, and outcomes in the UK are amongst the worst in Europe.[5] Reported 1-year overall survival (OS) for Stage III disease was 42.5% in 2017, falling to just 15.5% in Stage IV disease.[2] In addition to disease stage, the presence of clinically relevant mutations at diagnosis are an important predictor of survival outcomes and, along with other characteristics, are used to guide targeted treatment decisions (see A.2, below).

One such molecular marker is the presence of mutations in the epidermal growth factor receptor (EGFR) gene at diagnosis. Activating mutations in EGFR (EGFRm) inhibit apoptosis and promote tumour cell survival, and are present in an estimated 12% of patients with advanced NSCLC of adenocarcinoma histology. In the UK, there are approximately 1600 people diagnosed with advanced or metastatic NSCLC with confirmed EGFRm tumours per year. Inhibiting the tyrosine kinase activity of these mutant forms of EGFR can block upregulated survival and proliferation pathways, and EGFRm has therefore become an important therapeutic target.[6]

Between 2005 and 2013, the EGFR tyrosine kinase inhibitors (TKIs) erlotinib, gefitinib, and afatinib received regulatory approval, and are currently considered standard of care (SoC) in the first-line setting for patients with EGFRm NSCLC.[7] These treatments have demonstrated improved outcomes and tolerability over platinum-based chemotherapy, but most patients who respond to therapy ultimately develop disease progression after about 9 to 12 months.[8-22] Moreover, 30% of all patients with EGFR-TKI sensitising mutations have no objective response to first or second generation TKIs and the disease progresses within 6 months. Such patients represent an NSCLC subgroup that are defined as having inherent or primary resistance to EGFR TKIs; the mechanisms underlying such intrinsic resistance are unclear.

Although well-controlled trials suggest potential survival rates of >50% at 2 years from diagnosis with these EGFRm TKIs, outcomes in UK clinical practice are considerably worse. In a cohort of 652 patients in England from the National Cancer Registration and Analysis Service (NCRAS) with linked data sources (Cancer Registry, Systemic Anti-Cancer Therapy, Office of National Statistics (ONS) mortality; Public Health England) who were diagnosed with stage IIIb/IV NSCLC between 2014 and 2015 and initiated EGFR TKI treatment (afatinib, erlotinib or gefitinib) as first line treatment, median overall survival from the date of EGFR TKI treatment initiation was just 15.8 months (95% CI: 14.1 – 17.2).

Thus, despite recent advances in treatment, UK patients with a diagnosis of EGFRm NSCLC have a significant unmet clinical need and should be considered under NICE's end-of-life criteria.

In addition to suboptimal survival outcomes, early-generation TKIs are associated with side effects that include skin rash and diarrhoea, which are due to the inhibition of wild-type (WT) EGFR in skin and gastrointestinal organs, respectively. The successful use of first and second generation TKIs is also limited by the poor penetration of these molecules across the intact blood-brain barrier (BBB),[23, 24] which may permit brain metastases to develop and grow. [25] This is particularly important, given that patients with EGFRm have a higher prevalence of CNS metastases compared with those with WT EGFR tumours, with limited treatment options and poor prognoses.

The treatment options for patients whose tumour has progressed despite treatment with a SoC TKI are limited. A review of published literature indicates that a substantial group of such patients (20–30%) do not receive any subsequent therapy upon disease progression, through either poor performance status or death before progression. Of those who do receive subsequent treatment, approximately half will test positive for the T790M resistance mutation and be eligible for osimertinib in 2L; those patients not tested or who are negative for T790M will likely receive chemotherapy. As there is no way to identify at initial diagnosis which patients will a) survive to receive targeted 2L therapy and b) develop EGFR T790M resistance, it is important to select the 1L treatment that offers the best clinical outcomes for the highest number of patients.

Place of osimertinib in therapy

Osimertinib (TAGRISSO™) is a 3rd generation irreversible, oral EGFR-TKI that potently and selectively inhibits both EGFR-TKI sensitising (EGFRm) and EGFR T790M resistance mutations while sparing WT EGFR, with class-leading CNS penetration. Structurally and pharmacologically distinct from 1st and 2nd generation EGFR-TKIs, it was specifically developed to have:

- Improved tolerability, through reduced inhibition of the WT EGFR
- Improved progression-free survival, through high selectivity for the mutant forms of EGFR and preserved activity against T790M EGFRm, which represents a major mechanism for acquired resistance against existing TKI's
- Greater CNS efficacy, through improved permeability across the intact blood-brain barrier (BBB).[23, 24]

Osimertinib has the potential to replace 1st and 2nd generation EGFR-TKIs as the standard of care for patients who are newly diagnosed with stage IIIb/IV EGFRm NSCLC, providing a step-change extension of PFS and prolonged survival (Figure 15). Reimbursement of osimertinib in the first-line setting would provide all patients with locally advanced or metastatic NSCLC with activating EGFR mutations access to the best possible clinical outcomes.

Clinical effectiveness

Trial overview

The FLAURA study is an ongoing, Phase 3, double-blind, randomised, controlled trial conducted in 556 patients with EGFR-positive, locally advanced or metastatic lung cancer in 132 study centres in 29 countries worldwide, including 4 centres in the UK.[26] The objective of FLAURA is to assess the efficacy and safety of osimertinib compared with standard-of-care EGFR-TKI therapy, in first-line treatment in patients with locally or centrally confirmed EGFRm locally advanced or metastatic NSCLC.

Eligible patients were treatment-naïve for advanced disease and candidates to receive first-line treatment with the selected comparator EGFR-TKI (gefitinib or erlotinb) in accordance with local prescribing preferences. Notably, in contrast to previous trials of EGFR-TKIs, patients with CNS metastases were eligible to enrol.[26] Patients were randomised 1:1 to receive either osimertinib 80 mg orally, once daily, or standard-of-care EGFR-TKI (either gefitinib [250 mg orally, once daily] or erlotinib [150 mg orally, once daily]) as first-line treatment until disease progression (or discontinuation for another reason).[26] All study sites were required to select either gefitinib or erlotinib as the sole comparator before site initiation except the US, where all sites used erlotinib; the most commonly used TKI at the time of study start in 2014.

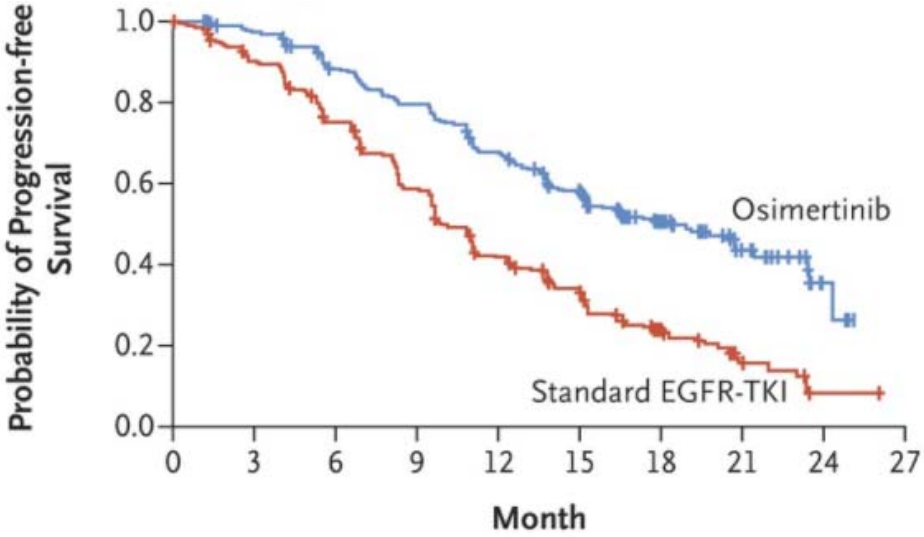
The primary trial endpoint was Investigator-assessed progression-free survival (PFS), defined by RECIST 1.1. Secondary outcomes included overall survival (OS), objective response rate (ORR), duration of response (DoR), disease control rate (DCR), depth of response, symptoms and HRQoL, and safety outcomes.[26]

Results

Baseline characteristics were well-balanced between the osimertinib and SoC TKI arms. The majority of patients were female (63%), Asian (62%), never-smokers (64%), had ECOG PS 1 (59%), Exon19del EGFR mutations (56%), and metastatic disease (95%). 21% of patients had CNS metastases at study entry and the median age was 64 years.

Primary outcome: Osimertinib demonstrated a substantial clinically and statistically meaningful improvement in PFS compared with patients receiving SoC TKI - HR 0.46; 95% CI: 0.37 - 0.57; p<0.001, 61.5% maturity for PFS overall. The median PFS for patients receiving osimertinib was 18.9 months, compared with 10.2 months for SoC TKI; an increase of 8.7 months. In addition, Kaplan-Meier analysis showed early and sustained separation of survival curves between the two groups, as early as the time of first assessment at 6 weeks (Figure 1), demonstrating the rapid benefit all patients receive from osimertinib. It is important to note that 88.4% (95% CI: 83.9 – 91.7) of patients receiving osimertinib had remained progression free at 6 months, compared to 75.2% (95% CI: 69.5 – 79.9) of patients receiving SoC TKIs – a significant reduction in the proportion of patients with intrinsic resistance to first-line targeted therapy.

Figure 1: Kaplan-Meier plot of PFS – Investigator assessment (full analysis set)[26]

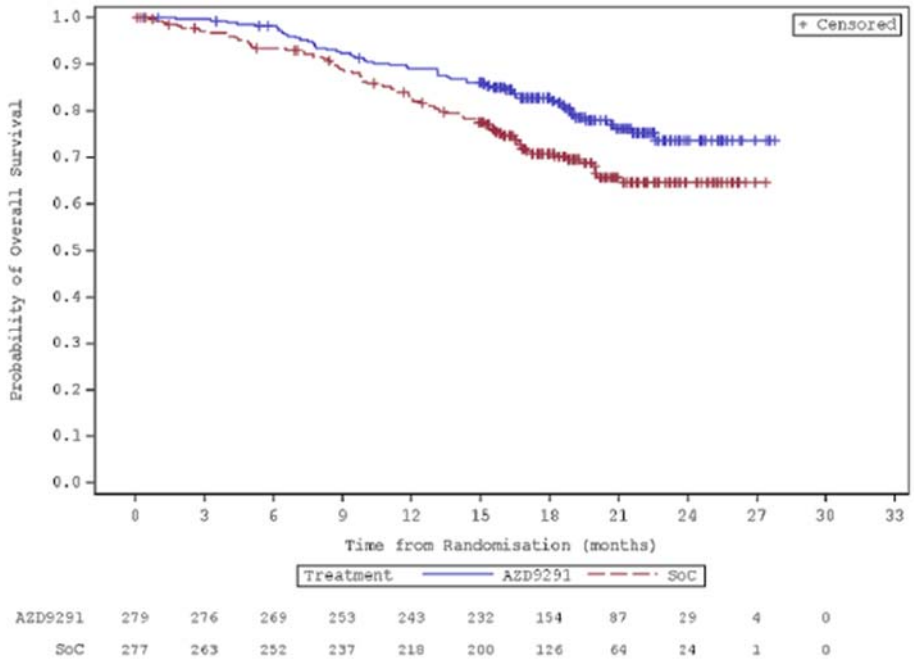


No. at Risk										
Osimertinib	279	262	233	210	178	139	71	26	4	0
Standard EGFR-TKI	277	239	197	152	107	78	37	10	2	0

A consistent PFS benefit for osimertinib over SoC TKIs was observed across all pre-defined subgroups, including those based on EGFR mutation type (Ex19del versus L858R), race (Asian versus non-Asian) and the presence or absence of CNS metastases at trial entry.

Secondary outcomes: Overall survival data, whilst currently immature at 25% of events, indicates a survival advantage for osimertinib compared to SoC TKI; HR 0.63; 95% CI: 0.45 - 0.88; p=0.007. Although this was a clinically meaningful improvement in OS, it did not meet the criteria to be considered statistically significant, set at p<0.0015 for this analysis. Median OS could not be calculated in either treatment group due to the low number of deaths although early and sustained separation of the Kaplan-Meier curves was observed (Figure 2). However, at 12 and 18 months, the estimated proportion of patients who were alive was 89.1% (95% CI: 84.7 – 92.2) and 82.8% (95% CI: 77.7 – 86.8) in the osimertinib group and 82.5% (95% CI: 77.4 -86.5) and 70.9% (95% CI: 64.8 – 76.1) in the SoC TKI group, respectively. A final OS analysis will be conducted at 60% maturity, with data expected in [redacted].

Figure 2: Kaplan-Meier plot of overall survival[26]



AZD9291 = osimertinib

There was also a clinically meaningful delay in several post-progression endpoints for patients randomised to osimertinib compared to SoC TKIs, including, the start of first subsequent anti-cancer therapy or death (TFST, HR: 0.51 [0.40 – 0.64]), time from randomisation to second progression (PFS2, HR: 0.58 [0.44 – 0.78]), and time to second subsequent therapy or death (TSST, HR: 0.60 [0.45 – 0.80]). These observations demonstrate that the PFS advantage of osimertinib is largely preserved beyond initial progression and provide reassurance that a clinically meaningful benefit in OS will be observed in the fully mature dataset.

The CNS analysis showed that, in patients with at least 1 CNS lesion at baseline, there was a clinically meaningful and nominally significant improvement in CNS PFS for patients on osimertinib compared with SoC TKIs. This protective effect of osimertinib was also demonstrated by the lower cumulative incidence of a CNS progression event when considering the competing risks of non-CNS progression and death. For the subgroup of patients with CNS metastases evaluable for response (n=41), osimertinib showed a greater percentage change in lesion size compared to SoC TKIs, as well as a higher CNS ORR (91% vs 68%, respectively).

Safety: Overall, the safety data from FLAURA confirms observations from earlier studies in the 2L, T790M setting that osimertinib is generally well tolerated and has a safety profile that is comparable to that of SoC, with fewer hepatic and skin-related adverse events (AEs), fewer CTCAE >=grade 3 AEs and fewer discontinuations due to AEs than in the SoC arm. The incidence of AEs was similar between the two treatment arms despite the longer exposure in the osimertinib arm (349.9 treatment-years vs. 271.9 treatment-years for the SoC arm). The difference in incidence of CTCAE ≥grade 3 AEs and treatment discontinuations due to AEs was driven largely by the greater incidence of hepatic events in the SoC arm. [26]

End-of-life criteria

Randomised controlled trials (RCTs) are often used as a source of evidence to estimate the overall survival expectation for patients in the real world. However, patients typically recruited to well controlled RCTs tend to be younger and fitter than those treated by clinicians in a real world setting and there is potential for estimates of survival in such controlled settings to be further inflated relative to an uncontrolled environment. Evidence from recent RCTs suggest median OS of approximately 2 years for patients receiving 1st generation TKIs in the 1L setting [REF LL7 (24.5 months) and ARCHER1050 (26.8 months)]. In contrast, overall survival for patients in England and Wales who have the same diagnosis (i.e. confirmed EGFRm, stage IIIb/IV NSCLC) is estimated to be **just 15.8 months (95% CI: 14.1 – 17.2)** based on analysis of Public Health England data between 2014 and 2016 (n = 652, NCRAS). This is similar to the results of an earlier study in the UK (mOS = 15.4 months [95% CI: 12.5 – 19.1], n = 202, Oct 2013) and one in Germany (mOS = 18.4 months [95% CI 16.3 – 21.3], n = 242, data cut-off = Oct 2012). The poor prognosis and survival expectation for patients in UK clinical practice compared with RCTs may be due to disparities in age, performance status and time from diagnosis to treatment. In addition, patients in UK clinical practice are potentially less likely to receive subsequent therapies than in clinical trials, with a correspondingly lower OS.

Thus, there is compelling evidence from a number of sources to suggest that advanced or metastatic NSCLC patients in the UK, eligible for treatment with a TKI in the 1L setting, have a median survival of no more than 2 years and most likely, significantly less.

Cost-effectiveness

In line with previous cost-effectiveness models submitted to NICE within advanced or metastatic NSCLC, a de-novo economic analysis was built as a partitioned-survival model including three health states: progression free (PF), progressed disease (PD), and death. The partitioned survival approach allows for direct modelling of PFS and OS (respectively primary and secondary endpoints in FLAURA) based on trial observed events.

Quality-adjusted life years (QALYs) were estimated using health-related utility values derived from patients in FLAURA for PFS and for patients receiving primary treatment after progression. The value for progressed-disease patients on subsequent active treatment or best supportive care was obtained from the published literature and was in line with those used and accepted by ERGs in previous NSCLC NICE submissions.

In line with the NICE reference case, the model adopted an NHS perspective and included the resource use and costs associated with disease management, treatment acquisition, administration and adverse events. To fully capture the benefits of osimertinib and the comparators included in the analysis, a lifetime horizon (20 years) was used in the base-case setting. This was considered to be appropriate taking into account the starting age of the cohort in the model and the advanced nature of the disease. In line with the NICE scope the tyrosine kinase inhibitors (TKIs) afatinib, erlotinib, and gefitinib were the comparators included in the economic model. An assumption of equal efficacy and safety between gefitinib, erlotinib and afatinib was made within the cost-effectiveness analysis and data from the SoC arm in FLAURA was used to model the three TKIs.

Following the NICE DSU guidance, parametric models were fitted to PFS data from FLAURA (all patients) with a treatment coefficient for osimertinib. Similar to recent NICE submissions, a piecewise approach was used to model OS based on assessment of the proportional hazard assumption: observed data was used up to 7.9 months and dependent parametric models were fitted to the remaining data. Treatment costs were predicted using time to discontinuation of treatment (TDT) data from FLAURA.

The model predicts that treatment with osimertinib is associated with 3.392 QALYs versus 2.346 QALYs for erlotinib, gefitinib, and afatinib. Thus, compared to erlotinib, gefitinib and afatinib, osimertinib is associated with 1.046 QALYs gained. The incremental cost-effectiveness ratios (ICERs) using list prices for all comparators are £89,700 relative to erlotinib, £82,675 relative to gefitinib, and £82,669 relative to afatinib. However, when the proposed PAS discount for osimertinib and the SPA scheme for gefitinib are used, the ICER is [redacted] compared to gefitinib. The results demonstrate that with the proposed PAS osimertinib, as an end of life therapy, meets the NICE criteria to be considered a cost-effective intervention.

Extensive sensitivity analyses showed that the main drivers of the cost-effectiveness analysis are related to the extrapolation of OS and TDT, the utility values, and the costs associated with the use of osimertinib in T790M-positive patients after progression. Results from the probabilistic sensitivity analysis show that, with the proposed PAS, the probability of osimertinib being the most cost-effective treatment (compared to gefitinib) at a threshold of £50,000 per gained QALY is 54%.

Osimertinib is well tolerated, with a lower incidence of side effects compared with 2nd generation EGFR-TKIs whilst also offering potential for greater CNS efficacy. In this regard, osimertinib has the potential to replace 1st and 2nd generation EGFR-TKIs as the standard of care for patients who are newly diagnosed with stage IIIb/IV EGFRm NSCLC, providing a step-change extension of PFS and prolonged survival. Reimbursement of osimertinib in the first-line setting would provide all patients with locally advanced or metastatic NSCLC with activating EGFR mutations access to the best possible clinical outcomes.

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

B.1.1 Decision problem

The submission covers the technology's full marketing authorisation for this indication, i.e. first-line treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating EGFR mutations (Table 1).

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 previously untreated locally advanced or metastatic, EGFR mutation-positive non-small-cell lung cancer	As per scope	N/A
Intervention	Osimertinib (Tagrisso)	As per scope	N/A
Comparator(s)	• Afatinib • Erlotinib • Gefitinib	As per scope	N/A
Outcomes	• overall survival • progression-free survival • response rate • response duration • adverse effects of treatment • health-related quality of life	As per scope	N/A
Subgroups to be considered	N/A	• Presence vs absence of CNS metastases at baseline • Asian vs non-Asian patients • Exon19del vs L858R mutations	• These subgroups represent pre-specified analyses of potentially clinical relevance
Special considerations including issues related to equity or equality	N/A	N/A	N/A

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	Highly selective and irreversible inhibition of activating sensitising EGFR mutation (EGFRm+) and activating resistance mutation T790M, without affecting the activity of wild type EGFR. Inhibition of phosphorylation of EGFR and downstream signalling leads to tumour growth inhibition and also induces cell cycle arrest
Marketing authorisation/CE mark status	For osimertinib in locally advanced or metastatic NSCLC with activating EGFR mutations, EMA approval was granted on 8 June 2018. Osimertinib is also indicated for the treatment of adult patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC (EMA approval 17 December 2015).
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Osimertinib is indicated for: • the first-line treatment of adult patients with locally advanced or metastatic NSCLC with activating EGFR mutations • the treatment of adult patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC.
Method of administration and dosage	Osimertinib is available as 40 mg or 80 mg oral tablets. The recommended dose is 80 mg once a day until disease progression or unacceptable toxicity.
Additional tests or investigations	EGFR mutation status should be determined by a validated test method, using either tumour DNA derived from a tissue sample or circulating tumour DNA (ctDNA) obtained from a plasma sample.
List price and average cost of a course of treatment	The list price for 30 tablets is £5770. At list price, total cost is ~ £120,000 per patient, based on average treatment duration in the pivotal FLAURA study (20.8 months). This does not factor in a proposed confidential discount to England and Wales NHS through a patient access scheme described below.
Patient access scheme (if applicable)	A confidential PAS has been proposed to NHSE

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

Disease burden

Disease overview

Lung cancer is one of the most common malignancies in the UK, with an estimated 44,500 people diagnosed with the disease each year.[1] Over 80% of these people have non-small cell lung cancers (NSCLC), with rapid growth and an aggressive course of disease. NSCLC can be further classified by histology into squamous and non-squamous cell carcinoma.[1]

NSCLC tends to be asymptomatic in early stages, leading to delays in presentation and diagnosis. As a result, an estimated ~70% of lung cancers are diagnosed at an advanced stage (III/IV).[2] Disease stage at diagnosis reflects the extent of cancer in the body and helps to inform treatment decisions and prognosis. Diagnostic lung cancer stages (stage I–IV) and Tumour, Nodes, and Metastasis (TNM) staging are based on the cancer site and tumor size.[27, 28]

- Stage I lung or localised cancer refers to cancer that is only located in the lungs and has not spread to any lymph nodes or other organs[29, 30]
- Stage II lung cancer refers to cancer that has spread from the lungs to the nearby lymph nodes[27]
- In Stage III, which is also described as locally advanced disease, the cancer is found in the lung and the lymph nodes in the middle of the chest[27, 29]
- Stage IV is the most advanced stage of lung cancer and is known as metastatic disease. At this stage, cancer has spread to both lungs, to fluid in the area around the lungs, and/or to another part of the body, such as the liver, brain, or other organs[27, 29]

Clinical presentation

While lung cancer may be asymptomatic in the early stages, most patients will ultimately develop symptoms ranging from mild to highly debilitating. Common NSCLC symptoms at diagnosis include persistent or intense cough, chest pain, pain from coughing, a change in the colour or volume of sputum, breathlessness, vocal changes, harsh sounds with each breath (stridor), recurrent lung problems (i.e. bronchitis or pneumonia), and coughing up phlegm, mucus or blood.[1, 3]

As the disease progresses, often when the tumour has spread to other sites in the body, patients may also experience loss of appetite or unexplained weight loss, cachexia (wasting), fatigue, headaches, bone or joint pain, bone fractures unrelated to accidental injury, neurological symptoms such as unsteady gait or memory loss, neck or facial swelling, general weakness, bleeding, and/or blood clots.[27]

The central nervous system (CNS) is a common metastatic site for NSCLC, with around 20-25% of patients having CNS metastases at diagnosis, and 40% developing CNS metastases over the course of their illness. The most common symptoms of CNS metastasis include headaches, cognitive deficits, ataxia, seizures, and visual and speech problems, which can impact patients' QoL in addition to the symptoms from the primary tumour (see Clinical burden).[31]

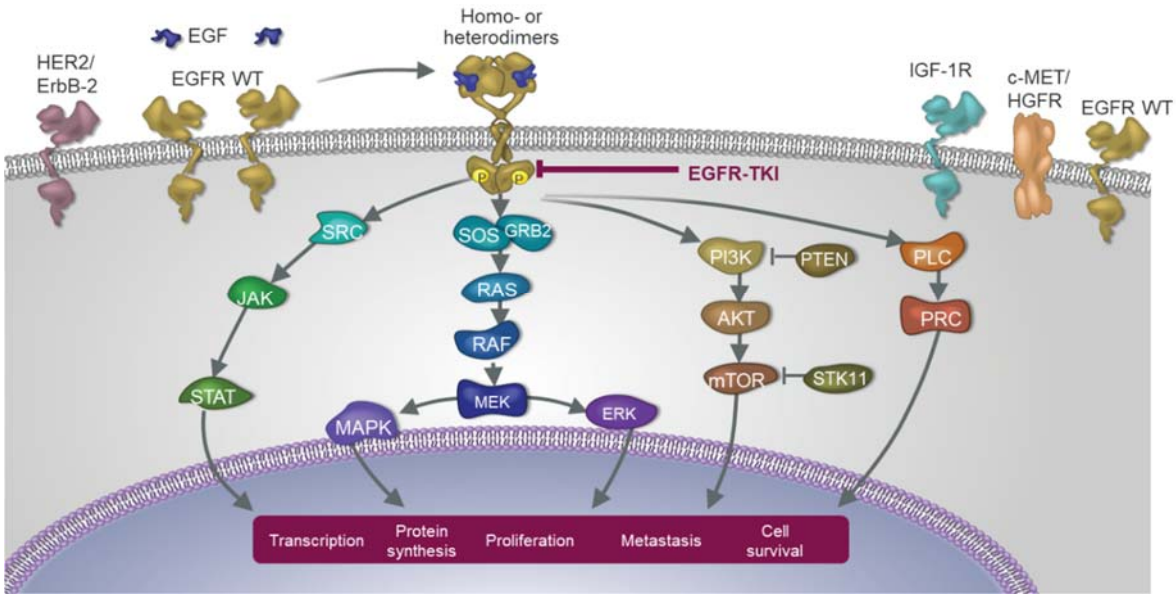
Molecular profiling

Lung cancers are genetically diverse, but the identification of clinically relevant mutations in genes such as epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), serine/threonine-protein kinase B-Raf (BRAF) and translocations in proto-oncogene tyrosine-protein kinase ROS (ROS-1) can help to predict the course of disease and guide targeted treatment decisions. Tumour tissue biopsy is the preferred sample type for genetic mutation testing in advanced NSCLC. Cytology samples may be used if a biopsy is not available, but sample quality and tumour cell content may be lower than with a biopsy sample. Alternatively, circulating tumour DNA (ctDNA) samples can be used if biopsy or cytology samples are not available, but these may have a high false-negative rate.[32, 33]

EGFR mutations

The epidermal growth factor receptor (EGFR) is a receptor tyrosine kinase (RTK) that plays a central role in the pathogenesis and progression of carcinomas (Figure 3). EGFR mutations inhibit apoptosis and promote tumour cell survival through upregulation of pro-survival signal transduction pathways such as RAS, AKT (Protein kinase B), and STAT (signal transducer and activator of transcription).[34] In addition, EGFR mutations reduce the affinity of adenosine triphosphate (ATP) to the EGFR receptor, and thereby sensitise the receptor to inhibition by targeted small molecule EGFR-tyrosine kinase inhibitors (TKIs)[35-37].

Figure 3: Receptor tyrosine kinase signalling



Several known EGFR mutations have been mapped to the tyrosine kinase domain of EGFR. Exon 19 deletions and L858R point mutations account for around 90% of all EGFR mutations, with other mutations only infrequently reported.[38-41] Both Exon19del and L858R mutants are sensitive to EGFR-TKIs, although Exon19del has been reported to be more sensitive to first-generation TKI inhibition than L858R, and may be predictive of clinical response.[42] T790M is the main mechanism of acquired resistance to TKIs (see Resistance to TKIs). EGFR mutations are more common in Asians than in Western populations, in women than in men, and in never-smokers than in ever-smokers [REF]. In the UK, the frequency of EGFR mutations in patients with NSCLC of adenocarcinoma histology is approximately 12%.[43]

Epidemiology

There are no direct sources reporting the prevalence of EGFR-positive advanced NSCLC in the UK, but an estimated 1608 patients would meet these disease criteria under the following assumptions (Table 3).

Table 3: Estimated number of patients with EGFR-positive NSCLC in the UK

Number	Assumption	Source
55,619.400	Population of England (2017), adjusted with an annual growth factor of 0.6%	ONS
37,231	Incidence of lung cancer in the UK (0.067% back-calculated)	NCLA[2]
32,950	Patients with NSCLC (88.5%)	NCLA[2]
20,099	At Stage IIIb/IV (61%)	NCLA[2]
16,080	Tested for EGFR (80.0%)	Assumption
1608	With a confirmed EGFR mutation (10%)	Li 2013[44]

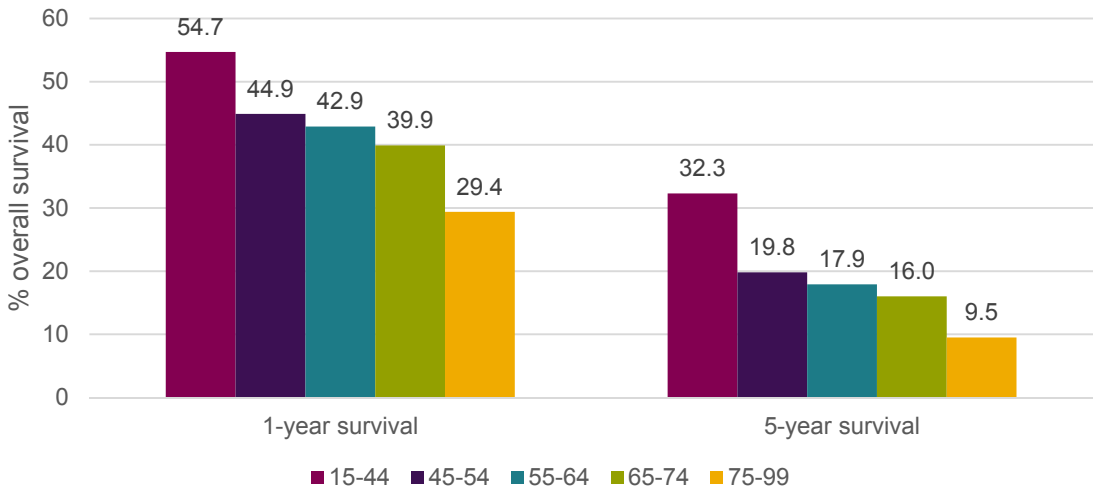
1270	Recorded as treated with an anti-cancer drug (79%)	Assumption

Prognosis

Survival in NSCLC is short and poor compared with many other cancers. Lung cancers represent the leading cause of cancer death in the UK, and accounted for 21% of all cancer deaths in 2016. Survival outcomes in the UK are amongst the worst in Europe; a patient with lung cancer in the UK can expect a 4% lower 5-year survival rate than the European average. Between 2011 and 2015, 39% of people with lung cancer survived for 1 year or longer while only 15% survived for 5 years or longer (based on age-standardised rates).[5]

Outcomes are highly variable depending on prognostic factors such as age, disease stage, and the presence of CNS metastases, as well as predictive factors such as molecular markers. Survival by age group in England is shown in Figure 4.[45] In terms of survival by disease stage, the National Lung Cancer audit reported 1-year survival of 81.7% for people with Stage I disease, decreasing to 64.1% for Stage II, 42.5% for Stage III, and only 15.5% for Stage IV in 2017,[2] highlighting the importance of early diagnosis. For patients with CNS metastases, median OS is 4–9 months with chemotherapy and 7 months for patients receiving whole brain radiation therapy (WBRT).[46, 47] Untreated patients with brain metastases have a median survival of just 2 months.[46, 48]

Figure 4: 1-year and 5-year survival for people diagnosed with lung cancer in England, by age group, between 2011 and 2015[45]



People with EGFR-positive lung cancer may be eligible to receive targeted therapy, in the form of an EGFR-TKI (see sections: Clinical guidelines and General systemic treatment approach). Although first- and second-generation TKIs have been shown to improve PFS and response rates compared with chemotherapy, they have not demonstrated a compelling overall survival benefit to date because of significant crossover and confounding in the 2L setting (see Clinical Efficacy of TKIs). In addition, there is considerable variation in the prescribing of TKIs across the UK, leading to health inequalities nationally (see Treatment patterns).

Survival for patients with EGFRm NSCLC

There are few published sources of estimated survival outcomes for English patients diagnosed with EGFRm NSCLC with locally advanced or metastatic disease, and so we have partnered with the National Cancer Registration and Analysis Service (NCRAS) to produce this analysis. Briefly, analysis was based on patients in England from NCRAS with linked data sources (Cancer Registry, Systemic Anti-Cancer Therapy [SACT], Office of National Statistics [ONS] mortality; Public Health England). Patients were selected if they had a diagnosis (International Classification of Diseases in Oncology codes, ICD-10-0) for NSCLC (C33, C34, C37-C39 and morphology codes in: list) with Stage IIIb/IV between 2014 and 2015 (Cancer registry data) and initiated afatinib, erlotinib or gefitinib less than 60 days prior to their diagnosis date (SACT data). Patients were excluded if they received chemotherapy prior to initiation of EGFR TKI treatment. The latest available data were Cancer Registry/ mortality data from January 2017 and SACT data from August 2017. The latest start date of EGFR TKI treatment included in the analyses was 1 September 2016.

The key baseline characteristics of patients in this real-world cohort are similar to those in FLAURA with respect to gender (63.5% female, compared with 63% in FLAURA) and age (median age at time of treatment was 68 years, compared with 64 years in FLAURA), but had slightly worse PS (Table 4).

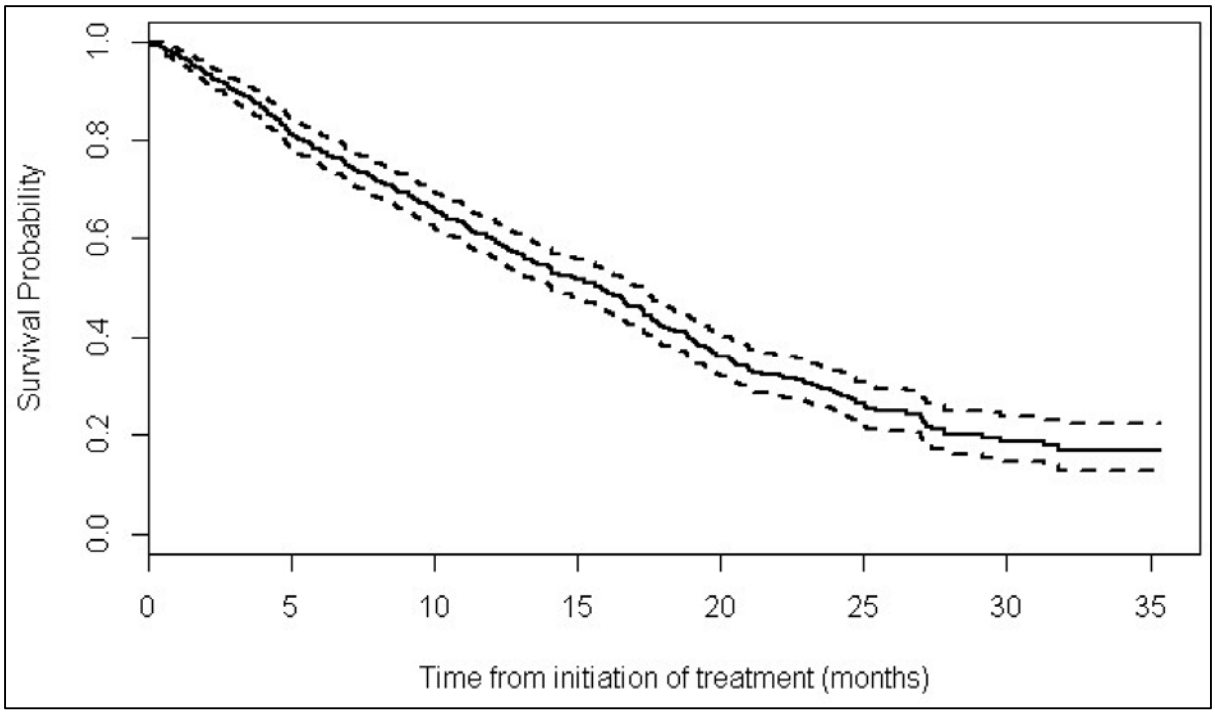
Table 4: Baseline characteristics in the NCRAS analysis, compared with those of FLAURA

N (%)	Real-world NCRAS analysis (N=652)	FLAURA (N=556)
Female, n (%)	414 (63.5%)	350 (63)
Stage of disease, n (%)		
Stage 3b	30 (4.6%)	100% (NR)
Stage 4	622 (95.4%)	
Performance status, n (%)		
PS 0	130 (19.9%)	228 (41%)
PS 1	206 (31.6%)	327 (59%)
PS 2	89 (13.7%)	-

PS≥3	23 (3.5%)	-
Missing	204 (31.3%)	1 (0.2%)
Age, median years	68 (IQR: 61 – 76)	64.0 (range: 26 – 93)
Time to initiation of EGFR TKI treatment from NSCLC diagnosis, median (IQR)	35 days (IQR: 25.7 – 55.0)	1.2 months (range: 0 – 82) [from diagnosis to randomisation]

Median overall survival from the date of EGFR TKI treatment initiation was 15.8 (95% CI: 14.1 – 17.2) months (Figure 5). Seventy-five percent of patients had an OS longer than 6.9 months (95% CI: 6.0 – 8.1), but only 25% had an OS longer than 25.4 months (95% CI: 24.0 – 27.8).

Figure 5: Overall survival for Stage 3b/4 NSCLC patients treated with an EGFR-TKI 1L after diagnosis



Although published studies on UK-specific, real-world survival outcomes for patients with advanced EGFRm NSCLC are scarce, available data are consistent with the findings from the above real-world analysis, indicating an OS for these patients of around 15 months, which is much lower than in the pivotal trials (Table 5).

Table 5: UK-specific survival outcomes for patients receiving an EGFR-TKI

Source	Data cut-off	Fit to FLAURA	OS estimate (median)	Weighting	Similarity to UK practice
SACT 2018, UK	Oct 2016	High	15.8 months (95% CI: 14.1 – 17.2) N=652 (SACT)	High	High
Gefitinib NIS (2014, UK)	Oct 2013	High	15.4 months (12.5-19.1) N=202	Med	High
RUH Bath Audit (2018, UK)	2010-2017	High	15 months (NR) N=38	Low	High
Moller (2018, UK lung cancer variation)	2014	Low	2 year survival: 17-20%	Low	High
Ding et al (2017, Australia)	Jun 2016	Med	23 months (range 0.4–35.8 months)	Low	Med
Literature review	N/A	High	19.3 – 34.8 months (See Table 10)	Low	Low

Clinical burden

A diagnosis of advanced NSCLC has a profound effect on a patient's emotional, physical, and social well-being as well as significant impacts on carers, family and children. In addition to poor prognosis, most patients experience multiple, debilitating symptoms (see Disease overview), with a correlation between disease progression, lower QoL[49, 50],[50, 51] and reduced physical functioning.[3, 50] Depression and anxiety are common and persistent, and are more prevalent in patients with more severe symptoms and functional limitations.[4] Patients with CNS progression may experience further QoL decrements, due to symptoms caused by brain metastases including headaches, cognitive deficits, ataxia, seizures, and visual and speech problems.[31]

In addition, the strong association of lung cancer with smoking can lead to feelings of guilt, self-blame, and distress,[51] even in patients who are not smokers. While an estimated 10-25% of all lung cancers occur in never-smokers, 28-68% of EGFRm lung cancers occur in never-smokers;[52] and there is evidence that the public misconception that 'only smokers get lung cancer' can lead to patients feeling stigmatised by a diagnosis and feeling 'smokers guilt' despite having never smoked.

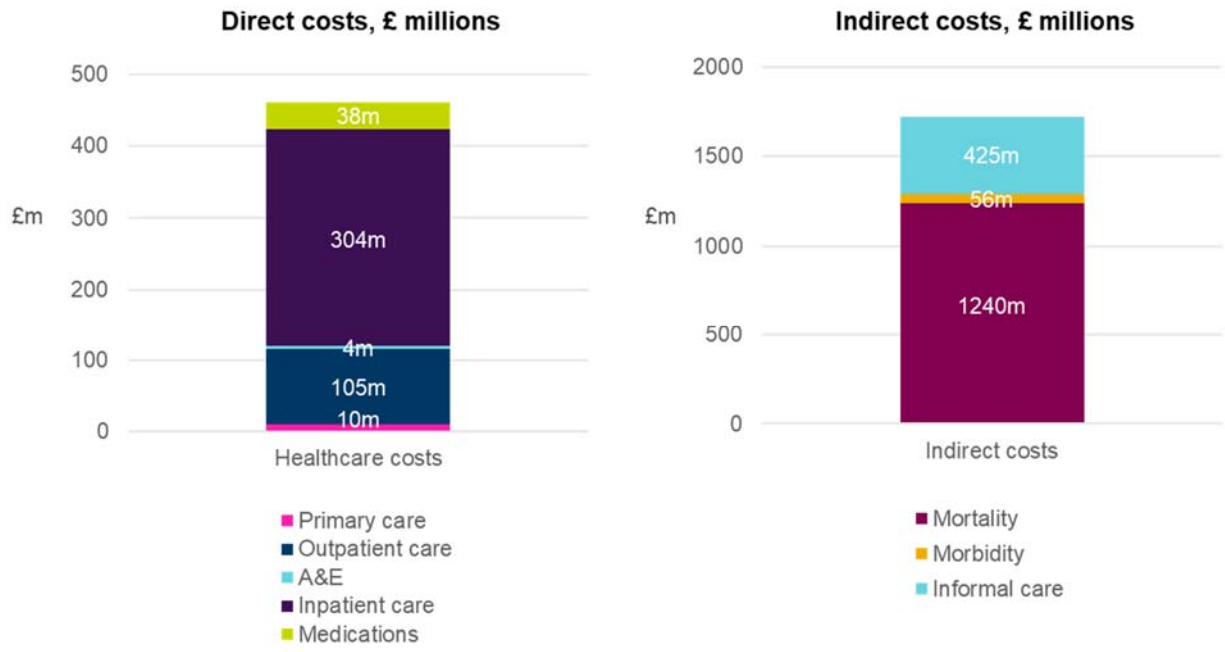
Family, friends, and caregivers are also affected. These groups help to maintain the well-being of people with lung cancer by providing emotional and practical support, but this is often at a significant cost to their own well-being. Carers witness and share much of the illness experience of the patient; themes including distress, grief, stress, and depression are commonly reported, particularly at milestones such as after diagnosis, recurrence, and during the disease's terminal stages.[53]

Societal and economic burden

NSCLC places a significant economic burden on society as a result of disability and premature mortality, as well as direct and indirect health service costs. The main cost drivers are hospitalisation and drug acquisition costs.

A population-based cost analysis published in 2012 reported that the cost of lung cancer to the UK economy is £2.18 billion each year, the highest cost of any cancer. Inpatient care was the biggest contributor to direct costs for lung cancer (£304m of £461m), while indirect costs were driven by premature mortality (£1240m of £1721m) (Figure 6) (note: costs have been inflated from 2009 EUR to 2018 EUR, then converted to GBP). Although the majority of people with advanced lung cancer are over 65 years of age, nearly a quarter die before retirement, and productivity losses for lung cancer were the highest of any cancer.[54]

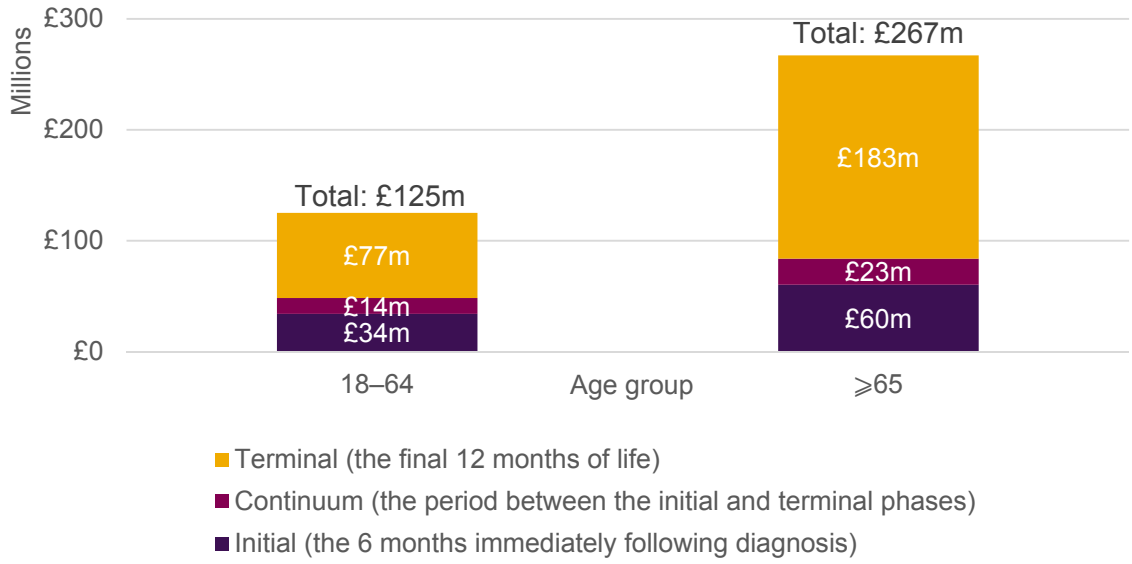
Figure 6: Cost of lung cancer in the UK (millions, EUR 2009 inflated to GBP 2018*)[54]



* Inflation from 2009 to 2018 EUR calculated using https://www.officialdata.org/Euro-inflation (12.5% higher prices in 2018 vs 2009). EUR to GBP conversion done using a rate of 1 EUR to 0.89 GBP, as per Google, June 2018

A retrospective cohort study including all patients age 18 and over with a diagnosis of lung cancer (N=283,940) in England between 2001 and 2010, used population-based, patient-level data to analyse the costs of hospital services accessed by people with lung cancer. The estimated cost of care was £125m for patients aged 16-64, and £267m for those aged 65 and over in 2010. In comparison, comparison group costs (a population without cancer) were £11m and £74m, respectively, representing 11-fold and 3.6-fold differences in the magnitude of costs incurred. The majority of costs for both age groups were accrued in the final 12 months of life (Figure 7), which was attributed to poor survival and a large proportion of patients dying in the year of their diagnosis.[55]

Figure 7: 5-year prevalence costs for lung cancer, by age and disease stage (2010 £)[55]



Current clinical pathway

Goals of treatment

Treatment intent is not curative in advanced NSCLC, and goals usually focus on prolonging survival, improving quality of life, and alleviating symptoms. Potential benefits of treatment should be balanced with the risk of additional toxicities.[56]

General systemic treatment approach

Evolution of targeted therapy options

Gefitinib[57] and erlotinib[58] are reversible small molecule ATP analogues originally designed to inhibit the tyrosine kinase (TK) activity of WT EGFR. During their clinical development, these first-generation TKIs were serendipitously found to be most effective in advanced non-small cell lung cancer (NSCLC) patients whose tumours contained activating mutations in the kinase domain of EGFR.[59, 60] Whilst patients with EGFRm tumours typically show good initial responses to first generation TKIs, most patients who respond to therapy ultimately develop disease progression after about 9-14 months of treatment.[8, 12, 61-63] The mechanism(s) by which tumours develop resistance is (are) unclear, but include acquisition of drug resistant mutations in EGFR (e.g. T790M), and/or through activation of bypass signalling pathways (e.g. c-Met amplification).[64]

Second-generation irreversible EGFR-TKIs were developed to more potently inhibit wild-type and mutant forms of EGFR, including T790M. Anti-T790M activity was demonstrated in the laboratory, but clinical activity was disappointing in patients with disease resistant to gefitinib and erlotinib. In addition, more potent inhibition of wt-EGFR at lower concentrations than those required to inhibit T790M led to increased toxicities, mainly skin and digestive.[5] Afatinib was approved in 2013[65] and, together with gefitinib and erlotinib, is the current standard of care (SoC) for patients with locally advanced or metastatic NSCLC with EGFR activating mutations in the UK.[7] Dacomitinib is a further EGFR-TKI in development, but it has not yet obtained regulatory approval and its place in therapy is yet to be established. Therefore, selective targeting of T790M while sparing activity of wild-type EGFR was a significant unmet need of the time that led to the development of third-generation EGFR TKIs (including osimertinib).

Table 6: Overview of EGFR-TKI characteristics

	First-generation		Second-generation	Third-generation	
Drug	**Gefitinib**[1]	**Erlotinib**[2]	**Afatinib**[3–5]	**Dacomitinib**[6-8]	**Osimertinib**[9-11]
Company	AstraZeneca	Roche	Boehringer Ingelheim	Pfizer	AstraZeneca
Status*	Approved	Approved	Approved	Under regulatory review by the US FDA for 1L EGFRm NSCLC	Approved (1L / 2L‡)
EGFR binding	Reversible	Reversible	Covalent, irreversible	Covalent, irreversible	Covalent, irreversible
Clinical targets	-	-	-	-	-
wt-EGFR	YES	YES	YES	YES	-
EGFRm ex19del	YES	YES	YES	YES	YES
EGFRm L858R	YES	YES	YES	YES	YES
EGFRm T790M	-	-	-	-	YES
wt-HER2	-	-	YES	YES	-
HER2m	-	-		YES	-
HER2 amp	-	-	YES	YES	-
HER4	-	-	YES	YES	-
Recommended dose, mg/day	250	150	40	45	80
Bioavailability	59%	60%	unknown	80%	70%

*Afatinib, dacomitinib and osimertinib have been granted Priority Review by the FDA; **Although the FDA PI refers to preclinical data for afatinib in ex19del, this is not widely available as it comes from a Boehringer Ingelheim data on file; †Preclinical targeting of T790M; ‡Approved for patients with T790M following prior EGFR-TKI treatment.

Early development of osimertinib

Osimertinib is structurally distinct from the other EGFR TKIs, giving it a unique activity profile. Unlike 1st and 2nd generation TKIs which are based on a quinazoline base, osimertinib has a novel pyrimidine scaffold that can more effectively bind in the kinase domain of EGFRm and forms a covalent bond with the C797 residue. Irreversible inhibition leads to a change in the structure of the protein, thus leading to permanent inhibition of downstream activity.

In EGFR recombinant enzyme assays, osimertinib showed an apparent IC50 of 12 nM against L858R and 1 nM against L858R/T790M; these are called apparent since the amount of active enzyme changes over time and thus IC50 is time dependent for irreversible agents. Most importantly, it exhibited nearly 200 times greater potency against L858R/T790M than wild-type EGFR (Table 7), consistent with the design goal of an EGFRm-selective agent in comparison to early generation TKIs.

Table 7: Effect of osimertinib and earlier generation TKIs against enzyme activity of recombinant forms of mutant and wildtype EGFR using Millipore commercial assay. (Data presented as apparent nM IC50)

	EGFR (wt)	EGFR (L858R)	EGFR (L858R/T790M)
Gefitinib	3	<1	155
Afatinib	3	<1	3
Dacomitinib	3	<1	10
Osimertinib	184	12	1

This, and other *in vitro* preclinical data demonstrates the distinct profile of osimertinib compared to earlier generations of TKIs; gefitinib, erlotinib, afatinib, and dacomitinib. Biochemical profiling together with in vitro cellular phosphorylation and phenotype studies have collectively shown that osimertinib is highly potent against EGFR sensitising mutations and T790M resistant EGFR mutants with a wide margin of selectivity against wild type EGFR activity. These characteristics strongly suggested that osimertinib may be used at relatively high therapeutic doses in patients compared with other TKIs, without affecting the normal signalling function of wild-type EGFR in non-tumour cells.

Clinical Efficacy of TKIs

Randomised controlled trials (RCTs) have consistently demonstrated that treatment with an EGFR-TKI is associated with longer PFS, higher response rates, and improved quality of life (QoL) with fewer AEs (e.g. neutropenia) compared with standard platinum-based doublet chemotherapy in patients with sensitising EGFR mutations. However, these trials did not consistently demonstrate an OS benefit of EGFR-TKIs versus chemotherapy, most likely because a high proportion of patients who were originally in the chemotherapy control arm crossed-over to an EGFR-TKI at the end of the initial trial period (between 63 and 88%,Table 10).

Table 8 presents efficacy results from pivotal RCTs for the EGFR-TKIs currently used in 1L EGFRm advanced NSCLC. Generally, erlotinib, gefitinib, and afatinib are considered to have similar efficacy, with comparable PFS results, although afatinib is less well-tolerated. While most TKI trials have been conducted against chemotherapy, LUX-Lung 7 provided directly comparative evidence for afatinib versus gefitinib; median PFS was 11.0 months with afatinib versus 10.9 months with gefitinib (HR, 0.73 [95% CI, 0.57–0.95]; p=0.017).[21, 22] This study was unusual in that the median PFS was nearly identical for patients treated with afatinib and gefitinib, although there was a late separation of the KM curves beyond 12 months which contributed to the statistically significant HR.

It should be noted that most of these trials excluded patients with brain metastases, and as such, could represent an overestimation of overall survival in clinical practice. These trials were also predominantly carried out in Asia, which should be considered when interpreting the results; RWE suggests that outcomes are much worse in the UK (see Prognosis).

Table 8: Summary of efficacy outcomes from key RCTs of EGFR-TKIs used in 1L EGFRm advanced NSCLC

Erlotinib		EURTAC[8]		OPTIMAL[9, 10]		ENSURE [11]	
Trial overview		Randomised, open-label P3 study to assess 1L erlotinib vs chemotherapy in European patients with EGFRm NSCLC		Randomised, open-label P3 study to assess 1L erlotinib vs chemotherapy in Asian patients with EGFRm NSCLC		Randomised, open-label P3 study to assess 1L erlotinib vs chemotherapy in Asian patients with EGFRm NSCLC	
Setting		42 hospitals in France, Italy, and Spain		22 centres in China		30 centres across China, Malaysia, and the Philippines	
N		174		165		217	
Date		2011 (final analysis)		2010 (interim analysis); 2012 (updated survival analysis)		2012 (interim analysis; 73% PFS maturity)	
Treatments		**Erlotinib**	Cisplatin plus docetaxel or gemcitabine	**Erlotinib**	Carboplatin plus gemcitabine	**Erlotinib**	Cisplatin plus gemcitabine
Patients	**% female**	**67%**	78%	**59%**	60%	**62%**	61%
	Median age	**65 years**	65 years	**57 years**	59 years	**58 years**	56 years
	ECOG 0-1	**86%**	86%	**91%**	96%	**94%**	94%
	Brain metastasis	**10%**	13%	**Excluded**	Excluded	**Excluded**	Excluded
	%Exon19del	**66%**	67%	**52%**	54%	**52%**	57%
Duration of treatment		**8.2 months**	2.8 months	**55.5 weeks**	10.4 weeks	**NR**	NR
mPFS		**9.7 months**	5.2 months	**13.1 months**	4.6 months	**11.0 months**	5.5 months
ORR		**64.0%**	18.0%	**83%**	36%	**62.7%**	33.6%
mOS		**19.3 months**	19.5 months	**22.8 months**	27.2 months	**26.3 months**	25.5 months
DCR		**-**	-	**96%**	82%	**89.1%**	76.6%

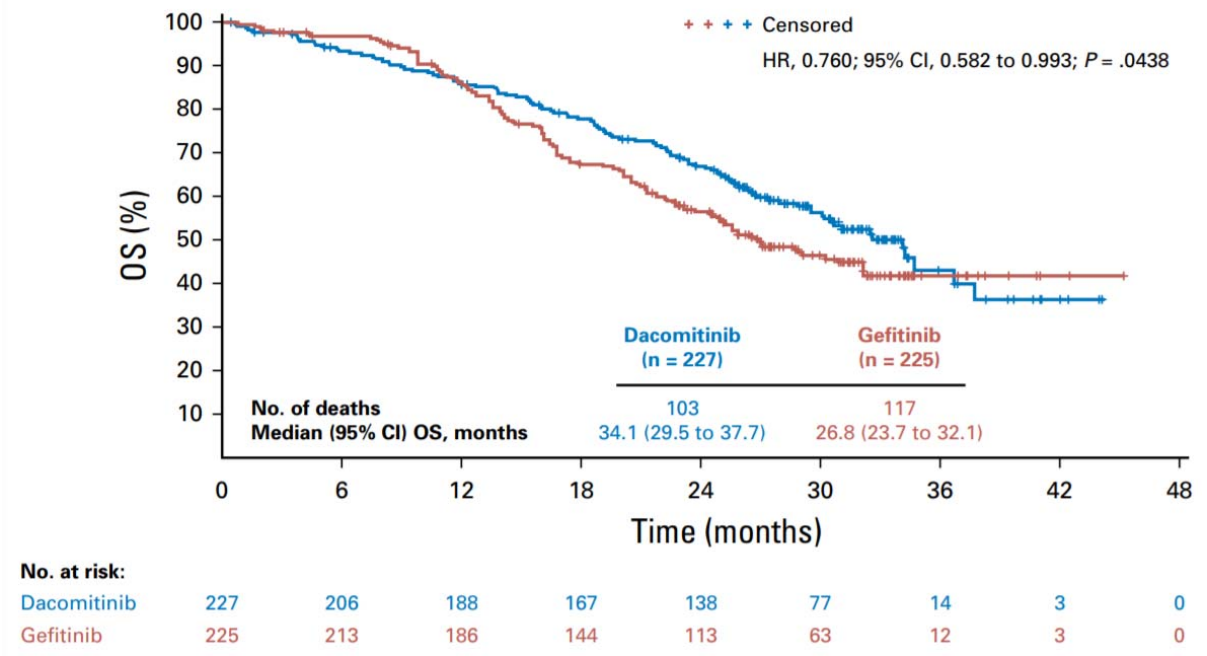
Gefitinib		IPASS[12, 13]		NEJ002[14, 15]		WJTOG3405[16, 17]	
Trial overview		Randomised, open-label P3 study to assess 1L gefitinib vs chemotherapy in East Asian patients with NSCLC of adenocarcinoma histology		Randomised, open-label P3 study to assess 1L gefitinib vs chemotherapy in patients with EGFRm NSCLC		Randomised, open-label P3 study to assess 1L gefitinib vs chemotherapy in patients with EGFRm NSCLC	
Setting		87 centres in Hong Kong, China, Indonesia, Japan, Malaysia, the Philippines, Singapore, Taiwan, Thailand		Multicentre, Japan		36 centres in Japan	
N		1217 (261 EGFRm positive)		230		177	
Date		2008 (interim analysis)		2009 (interim analysis) 2010 (updated survival analysis)		2009 (interim analysis); 2011 (updated survival analysis)	
Treatments		**Gefitinib**	Carboplatin plus paclitaxel	**Gefitinib**	Carboplatin plus paclitaxel	**Gefitinib**	Cisplatin plus docetaxel
Patients	**% female**	**80%**	79%	**63%**	64%	**59**	60
	Median age	**57**	57	**64 (mean)**	63 (mean)	**64**	64
	ECOG 0-1	**90%**	89%	**99%**	98%	**100%**	100%
	Brain metastasis	**NR**	NR	**NR**	NR	**Excluded**	Excluded
	%Exon19del	**30%**	35%	**51%**	52%	**58%**	43%
Duration of treatment		**6.4 months**	3.4 months	**308 days**	Median of 4 3-week cycles	**165 days**	64 days
mPFS		**5.7 months (ITT); 9.5 months (EGFRm)**	5.8 months (ITT); 6.3 months (EGFRm)	**10.8 months**	5.4 months	**9.2 months**	6.3 months
ORR		**43% (ITT); 71% (EGFRm)**	32% (ITT); 47% (EGFRm)	**73.7%**	30.7%	**62.1%**	32.2%
mOS		**18.6 months (ITT); 21.6 months (EGFRm)**	17.3 months (ITT); 21.9 months (EGFRm)	**27.7 months**	26.6 months	**36 months**	39 months
DCR		**72.9% (ITT); 91.7 (EGFRm)**	79.2% (ITT); 87.6% (EGFRm)	**-**	-	**93.1%**	78.0%

Afatinib		LUX-Lung 3[18, 19]		LUX-Lung 6[19, 20]		LUX-Lung 7[21, 22]	
Trial overview		Randomised, open-label P3 study to assess 1L afatinib vs chemotherapy in patients with EGFRm NSCLC		Randomised, open-label P3 study to assess 1L afatinib vs chemotherapy in Asian patients with EGFRm NSCLC		Randomised, open-label P2b study to assess 1L afatinib vs gefitinib in patients with EGFRm NSCLC	
Setting		133 centres in 25 countries spanning Asia, Europe, North America, South America, and Australia		36 centres spanning China, Thailand, and South Korea		64 centres in 13 countries spanning Asia, Europe, Canada, and Australia	
N		345		364		319	
Date		2011 (interim analysis); 2013 (updated survival analysis)		2011 (interim analysis); 2013 (updated survival analysis)		2013 (interim analysis); 2016 (updated survival analysis)	
Treatments		**Afatinib**	Cisplatin plus pemetrexed	**Afatinib**	Cisplatin plus gemcitabine	**Afatinib**	**Gefitinib**
Patients	**% female**	**64%**	67%	**64%**	68%	**57%**	**67%**
	Median age	**61.5**	61.0	**58**	58	**63**	**63**
	ECOG 0-1	**100%**	99%	**100%**	100%	**100%**	**100%**
	Brain metastasis	**NR**	NR	**Excluded**	Excluded	**Excluded**	**Excluded**
	%Exon19del	**49%**	50%	**51%**	51%	**58%**	**58%**
Duration of treatment		**11 months**	6 cycles	**398 days**	89 days	**13.7 months**	**11.5 months**
mPFS		**11.1 months**	6.9 months	**11.0 months**	5.6 months	**11.0 months**	**10.9 months**
ORR		**56%**	23%	**67%**	23%	**70%**	**56%**
mOS		**28.2 months**	28.2 months	**23.1 months**	23.5 months	**27.9 months**	**24.5 months**
DCR		**90%**	81%	**93%**	76%	**91%**	**87%**

DCR: disease control rate; EURTAC: erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer; IPASS: Iressa Pan-Asia Study; mOS: median overall survival; mPFS: median progression-free survival; ORR: objective response rate
Sources: please refer to citations in the table

Dacomitinib, which is still in development, demonstrated equivalent efficacy to erlotinib in patients with previously-treated, advanced EGFRm-positive NSCLC in the ARCHER-1009 trial, with PFS of 2.6 months in both arms.[66] As first-line treatment, dacomitinib significantly improved PFS compared with gefitinib (14.7 months vs 9.2 months) in the open-label ARCHER 1050 trial, albeit at the cost of additional toxicities and in a population which excluded patients with brain metastases. Notably, the PFS curves did not begin to separate until 6 months after treatment initiation, implying limited benefit over gefitinib in patients with primary TKI resistance. ORR was similar between the two treatments (76% vs 70%), so dacomitinib's effect in prolonging PFS in the ITT population was not accompanied by an increase in the proportion of patients achieving an objective response. The final OS analysis described a statistically significant 0.76 HR (34.1 vs 26.8 months mOS), and is the first dataset where a 2nd generation EGFR-TKI has demonstrated superior OS compared to a 1st generation TKI. However, it is important to note that the curves in the Kaplan Meier plot of OS crossed after 12 months, suggesting that gefitinib was superior to dacomitinib in a subgroup of patients (Figure 8). It is unclear why dacomitinib was inferior to gefitinib for the initial part of the study, but one possible explanation concerns the high rates of dose modification in the dacomitinib arm (66% patients had a dose reduction, median time to first dose reduction was 2.8 months, median duration of dose reduction was 11.3 months) resulting in patients potentially receiving sub-therapeutic doses of dacomitinib .[67]

Figure 8: Overall Survival of patients in the ARCHER-1050 open-label randomised controled study comparing dacomitinib and gefitinib.



CNS penetration of TKIs

CNS metastases are common in patients with advanced NSCLC, with around 40–50% of patients developing CNS metastases during the course of their illness. An estimated 30% of patients with advanced NSCLC who are treated with 1st generation EGFR-TKIs (with or without pre-existing CNS metastases) experience disease progression due to the development of CNS metastases.[25] In patients with advanced NSCLC but without pre-existing CNS metastases, the cumulative rates of CNS progression after 6, 12- and 24-month treatment with 1st generation EGFR-TKIs are 1%, 3%, and 15%, respectively. CNS metastases are associated with poor median survival and significant worsening of QoL; median OS is 4–9 months with chemotherapy and 7 months for patients receiving whole brain radiation therapy (WBRT).[46, 47] Untreated patients have a median survival of just 2 months.[46, 48]

To successfully prevent and treat CNS metastases, a treatment must be able to cross the intact blood-brain barrier (BBB). Other cancer treatments, including chemotherapy agents and large monoclonal antibodies, are ineffective to treat CNS metastases, due to their inability to cross the intact BBB.[23] Although erlotinib and afatinib have been reported to exhibit some efficacy in treating and/or preventing the development of brain metastases in patients with EGFRm NSCLC, these treatments have demonstrated only a very limited ability to cross the intact BBB in animal models,[23, 24] and are considered to have poor CNS penetration. However, CNS penetration may be increased in patients with more advanced CNS metastases where BBB disruption has already occurred.[23]

Due to limited CNS penetration, patients with active CNS metastases were largely excluded from the initial pivotal trials of 1st generation EGFR-TKIs, and clinical trial data indicate that approximately one-third of patients develop CNS metastases after an initial response to 1st and 2nd generation EGFR-TKIs.[23, 68] Reports documenting efficacy of EGFR-TKIs in treating, and/or preventing the development of brain metastases in patients with EGFRm advanced NSCLC are generally small and predominately single arm or retrospective with variable evaluation for EGFRm status.[21, 23, 69]

Tolerability of TKIs

Although EGFR-TKIs are better tolerated than cytotoxic chemotherapy, cutaneous and gastrointestinal side effects are commonly experienced, particularly with afatinib. These effects are generally manageable, but may lead to dose reduction or treatment discontinuation, and can affect patients' quality of life.[70] The underlying mechanisms stem from wild-type EGFR inhibition; 1st and 2nd generation TKIs are active against WT EGFR as well as EGFRm, with afatinib demonstrating potent inhibition even at low concentrations (in contrast, osimertinib has comparatively lower selectivity for WT EGFR).[71]

Cutaneous side effects are caused by chemokine expression and apoptotic processes downstream of WT EGFR inhibition, which leads to inflammatory cell recruitment and subsequently cutaneous injury (such as tenderness, papulopustules, and periungual inflammation); in addition, abnormal maturation and differentiation lead to xerosis and pruritis, translating to hair and nail plate disturbance. The causes of EGFR-TKI-related diarrhoea are less well-understood, but hypotheses include excess chloride secretion, changes in gut motility, colonic crypt damage, and altered intestinal microflora.[70]

First generation TKIs were associated with rates of 66% to 80% for rash (2%-13% Grade 3/4), and rates of 25% to 57% for diarrhoea (1%-5% Grade 3/4) in pivotal trials, while afatinib was associated with rates of 81% to 89% for rash (9%-16% Grade 3/4) and 88% to 95% (5%-14% Grade 3/4) for diarrhoea (Table 9).

Table 9: Side effects of 1st and 2nd generation EGFR-TKIs resulting from WT-EGFR inhibition

Treatment	Trial	Rash	Diarrhoea
1st generation			
Gefitinib	IPASS[12, 13]	66% (3% Grade 3/4)	47% (4% Grade 3/4)
	NEJ002[14 15]	71% (5% Grade 3/4)	28% (1% Grade 3/4)
	WJTOG3405[16, 17]	74% (2% Grade 3/4)	47% (1% Grade 3/4)
Erlotinib	EURTAC[8]	80% (13% Grade 3/4)	57% (5% Grade 3/4)
	OPTIMAL[9, 10]	73% (2% Grade 3/4)	25% (1% Grade 3/4)
	ENSURE[11]	71% (6% Grade 3/4)	46% (NR Grade 3/4)
2nd generation			
Afatinib	LUX-Lung 3[18, 19]	89% (16% Grade 3/4)	95% (14% Grade 3/4)
	LUX-Lung 6[19, 20]	81% (15% Grade 3/4)	88% (5% Grade 3/4)
	LUX-Lung 7[21, 22]	88% (9% Grade 3/4)	91% (13% Grade 3/4)
(Dacomitinib)	ARCHER 1050 [72]	13% (4% Grade 3/4)†	86% (8% Grade 3/4)*

* The ARCHER-1050 study also reported one instance of a Grade 5 diarrhoea event (i.e. death)

† The incidence of rash (rashes or acnes/rash grouped term) was not reported in ARCHER-1050, only dermatitis acneiform.

Other common adverse events include skin disorders (e.g. dermatitis acneiform), fatigue, and elevated liver enzymes. Rare cases of interstitial lung disease have also been observed.

Resistance to TKIs

Resistance to TKIs is common, and can be intrinsic or acquired. Primary, or intrinsic resistance, may be defined as having no initial response to treatment or having an initial clinical response followed by disease progression within 6 months. Approximately 30% of patients with EGFR-activating mutations do not exhibit objective responses to EGFR TKI's (i.e., exhibit primary resistance). Relatively little is known about the underlying clinical and molecular drivers; however, some mechanisms have been identified, including:[73-75]

- Germline and *de novo* T790M mutations
- Non-sensitising EGFR mutations
- BIM polymorphisms
- Bypass tracks HGF activating MET signalling
- EGFR downstream gene mutation: PIK3CA, AKT, PTEN, STK11

In contrast, acquired resistance (also called secondary resistance) is defined as tumour progression after an initial ≥6 month response while the patient is still receiving TKI therapy. Most patients with EGFRm advanced NSCLC eventually develop acquired resistance to 1L EGFR-TKIs, which usually occurs within an average of 9–12 months. T790M is the most common mechanism of acquired resistance to 1L EGFR-TKI therapy in advanced NSCLC and accounts for 50–60% of all cases; *de novo* T790M mutations are rarely detected in untreated EGFRm tumours (<5%). The T790M mutation is believed to confer resistance to currently approved EGFR-TKIs by two potential mechanisms. The first is through steric hindrance, in which a change to the spatial structure of the EGFR reduces binding of the EGFR-TKIs, and the second is via increased binding affinity of EGFR for ATP, which reduces the potency of reversible EGFR-TKIs.

Treatment after progression on a TKI

After progression on a TKI, there are three main courses of care based on NICE guidance:

- Osimertinib, for patients who develop T790M resistance on a TKI
- Platinum-based chemotherapy, for patients who are T790M negative and fit enough to receive chemotherapy
- No subsequent therapy/palliative care

Several studies suggest that 20-30% of patients who receive treatment with either 1st or 2nd generation EGFR-TKI's do not receive any further systemic therapy (either another targeted treatment or chemotherapy) after progression (Table 10).

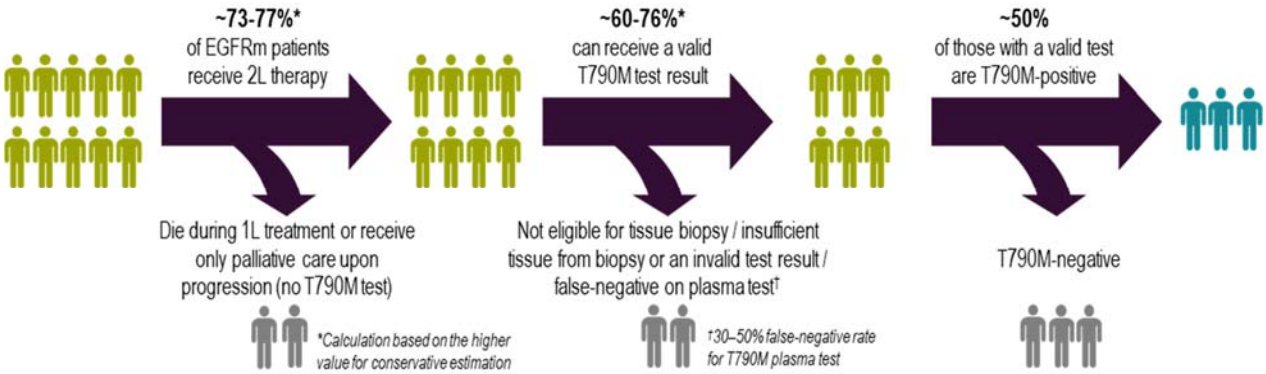
Table 10: Post-progression therapy after 1L EGFR-TKI in RCTs

Study	Most recent publication year	TKI	N	OS, months	Post-TKI treatment	Reference
IPASS	2008	Gefitinib	132	21.6	76%	12, 13
NEJ002	2010	Gefitinib	114	27.7	72%	14, 15
WJTOG3405	2011	Gefitinib	86	34.8	88%	16, 17
EURTAC	2011	Erlotinib	86	19.3	68%	8
OPTIMAL	2012	Erlotinib	82	22.8	63%	9, 10
ENSURE	2012	Erlotinib	128	26.3	66%	
LuxLung3	2013	Afatinib	230	28.2	71%	18, 19
LuxLung6	2013	Afatinib	242	23.1	57%	19, 20
LuxLung7	2016	Afatinib	160	27.9	73%	21, 22
		Gefitinib	169	24.5	77%	
ARCHER 1050	2018	Dacomitinib	227	34.1	63%	67
		Gefitinib	225	26.8	68%	

There are many reasons why EGFRm advanced NSCLC patients may not receive 2L systemic therapy including poor performance status following progression, patient choice and mortality while receiving 1L SoC EGRF-TKIs (erlotinib or gefitinib). Of the 70-80% of patients who will receive a 2L therapy, another 30% will not be tested for T790M because it is not possible to perform a tissue biopsy to obtain tissue for diagnosis or because of tissue biopsy failure (e.g. due to insufficient tissue samples). Plasma testing is an option for patients ineligible for a tissue biopsy or in whom biopsy has failed, but plasma tests have a 30–50% false-negative rate for T790M (non-shedding tumours) due to a low sensitivity of the ctDNA plasma diagnostic (Figure 9).

Patients who are not tested/able to be tested for EGFR T790M at progression after a 1L EGFR-TKI, or are tested but whose tumours are T790M mutation negative, or are T790M mutation positive but do not receive optimum therapies (including treatment with 3rd generation T790M targeted agents) could have a shorter than expected survival. As there is no way to identify upfront which patients will develop T790M resistance and survive until 2L, it is even more important to select an EGFR-TKI 1L therapy that provides an extended and good quality of life.

Figure 9: Around a third of EGFRm patients treated with a 1st and 2nd generation EGFR-TKI are able to receive 2L osimertinib therapy



1L: first-line; 2L: second-line; EGFRm: epidermal growth factor receptor mutation; EGFR-TKI: epidermal growth factor receptor tyrosine kinase inhibitor

Source: [22, 76-84]

In the third-line setting, treatment options are limited, but include atezolizumab, pembrolizumab, chemotherapy, and best supportive care for patients who have progressed after both chemotherapy and targeted treatment. Notably, subgroup analyses of several phase III clinical trials comparing the immunotherapies nivolumab, pembrolizumab, or atezolizumab, versus docetaxel, have failed to demonstrate superior efficacy compared with standard chemotherapy in patients with *EGFR*m-positive tumours.[85, 86]

Clinical guidelines

In the UK, NICE provides recommendations on the diagnosis and management of patients with lung cancer. At the diagnosis stage, patients with known or suspected lung cancer should be offered a contrast-enhanced chest CT scan to further the diagnosis and stage the disease. Other techniques such as ultrasound, surgical assessment, EBUS-guided TBNA, and MRI may be considered in certain patients. Adequate samples of the tumour should be obtained without unacceptable risk to the patient, to permit pathological diagnosis including tumour sub-typing and measurement of predictive markers.[56]

For people with untreated locally advanced or metastatic disease who test positive for the activating EGFR-TK mutation, NICE guidance recommends the TKIs afatinib, erlotinib, and gefitinib as treatment options (NICE technology appraisal guidance 310, 258 and 192 respectively) (Figure 10). Options for people whose tumours do not express an EGFR-TKI sensitising mutation are other targeted treatments such as ceritinib, crizotinib or alectinib for ALK-positive NSCLC (not discussed further), or platinum-based chemotherapy.[7]

Treatment options for previously treated NSCLC may also be informed by the presence or absence of predictive markers. Patients who received an EGFR-TKI in the first-line setting and whose tumours express T790M are eligible for 2L osimertinib, while those who received chemotherapy may be eligible for erlotinib if they received chemotherapy 1L and had delayed confirmation of EGFRm-positive status. Docetaxel monotherapy, nivolumab and nintedanib are also treatment options after progression on 1L chemotherapy. In the third-line setting, pembrolizumab and atezolizumab may be prescribed only after chemotherapy and targeted treatment (Figure 11).[7]

Figure 10: NICE guidance on first-line systemic anticancer treatment for advanced or metastatic NSCLC with EGFRm-positive status (Adapted from the NICE lung cancer pathway[7])

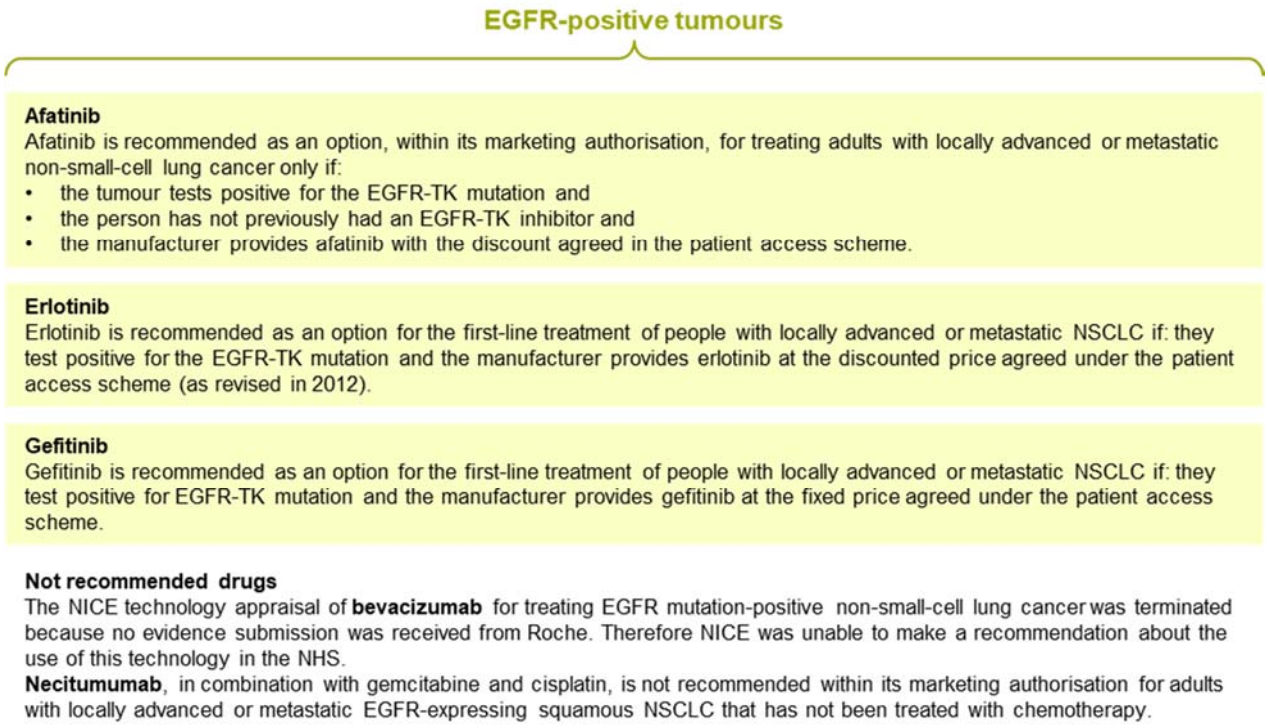
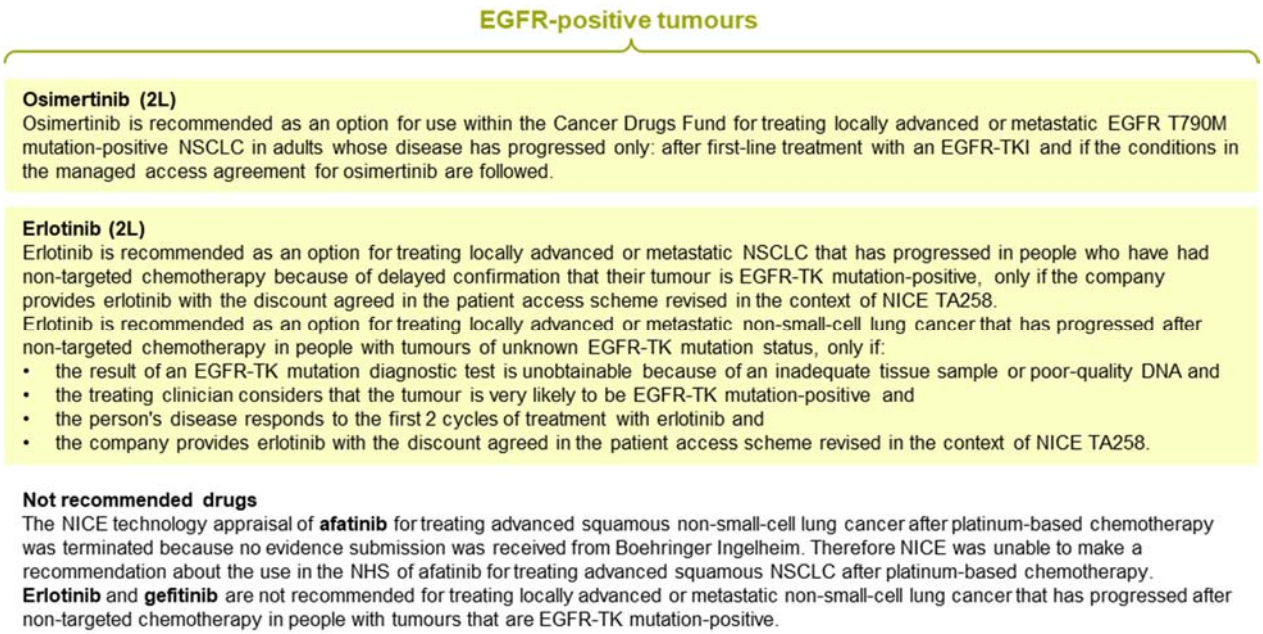
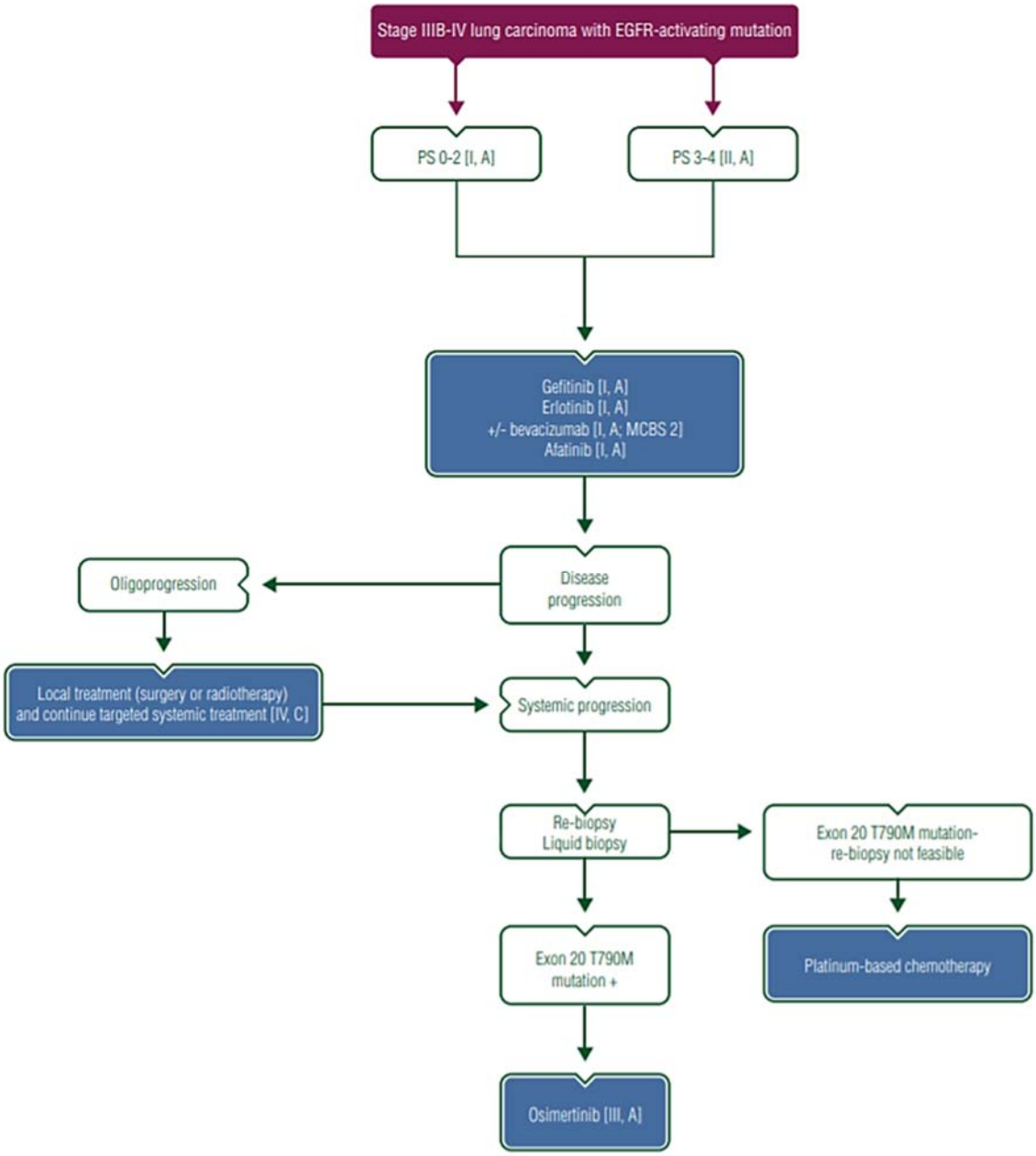


Figure 11: Systemic anticancer treatment for previously treated (2L) advanced or metastatic NSCLC (Adapted from the NICE lung cancer pathway[7])



The European Society for Medical Oncology (ESMO) guidelines also recommend 1L treatment with an EGFR-TKI (erlotinib, gefitinib, or afatinib) for tumours with an activating EGFR mutation. Alternatively, if information on an EGFR-sensitising mutation becomes available during 1L platinum-based chemotherapy, chemotherapy continues for up to four cycles and EGFR-TKI is offered as maintenance treatment in patients achieving disease control, or as 2L treatment at the time of progression (Figure 12).[36]

Figure 12: ESMO treatment algorithm for stage IIIB–IV lung carcinoma with an EGFR-activating mutation[36]

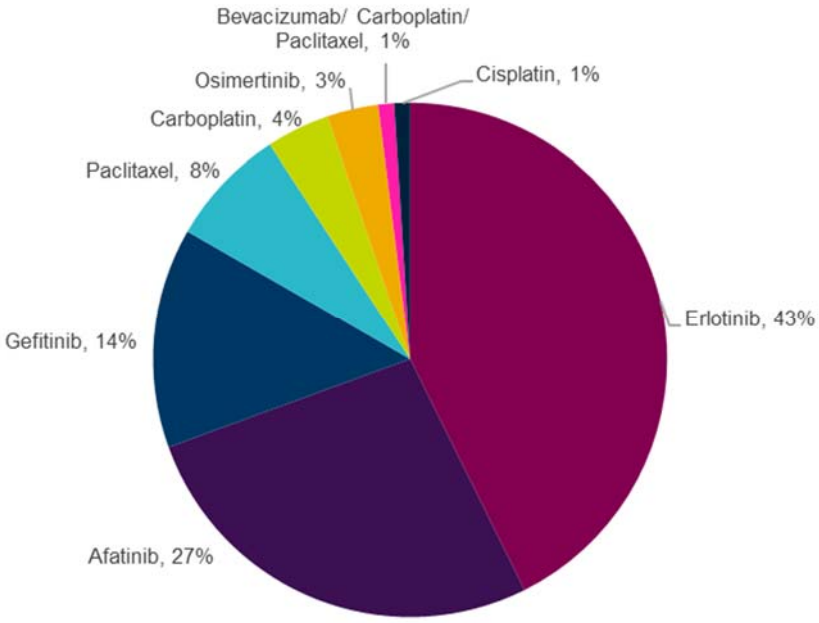


Treatment patterns

Overall, 62% of people with advanced NSCLC and PS 0-1 received systemic anti-cancer treatment in 2017 (England 62.5%, Wales 55.6%; case-mix adjusted range: 25.7% to 100%).[2]

Recently published data on treatment patterns for people with EGFR-positive NSCLC are scarce, but prescribing data available from Ipsos MORI show that around 85% of people whose tumours test positive for EGFRm receive an EGFR-TKI (Figure 13). When considering these figures, it should be noted that around 25% of patients are not tested for EGFR; most of these patients receive chemotherapy.[87]

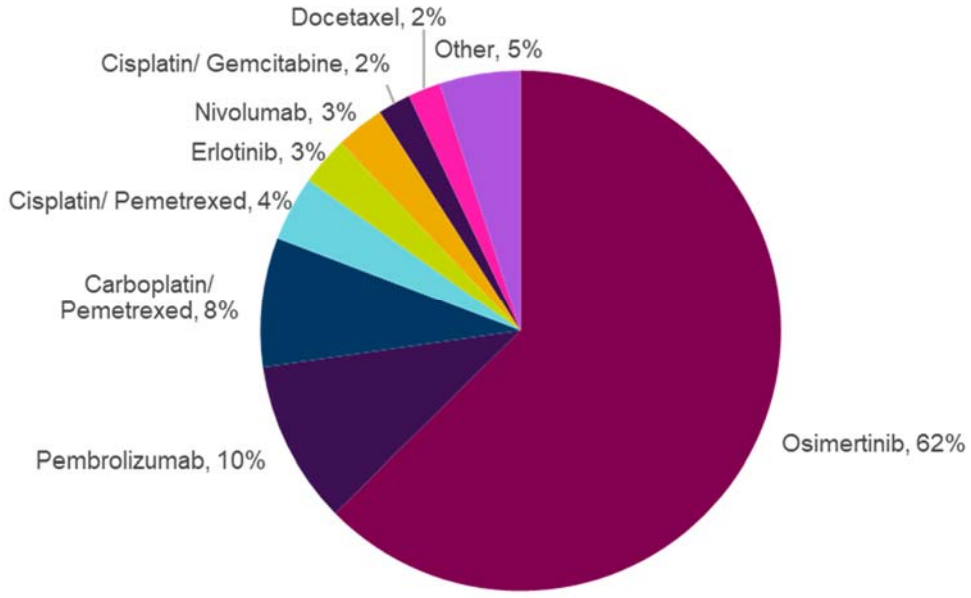
Figure 13: Prescribing patterns for people with EGFR-positive metastatic NSCLC (1L setting, N=148, Jan-18 to Mar-18)



Uptake of TKIs varies substantially nationwide, however. For example, the Innovation Scorecard reports that prescribing of afatinib is 3-times higher in London than in Manchester (measured in mgs per 100,000 population), while there are 8-fold and 105-fold differences between the highest and lowest prescribing regions for gefitinib and erlotinib, respectively.[88] This could lead to health inequalities between regions, and subsequently, differences in survival outcomes.

In the second-line setting, testing rates for T790M increased from around a third of EGFR-positive patients between October 2016 and December 2016 (a NICE recommendation for osimertinib 2L was received in October 2016), to 72% between January 2018 and March 2018. Of those patients who were tested, approximately two-thirds were positive for the T790M mutation (range: 55% to 72% between October 2016 and March 2017), of whom >90% received osimertinib. Other regimens received in the 2L setting for patients tested for T790M included chemotherapy (18%) and immunotherapy (13%) (Figure 14). In patients not tested for T790M, the most commonly received treatment regimens were docetaxel (34%), carboplatin (21%), and paclitaxel (16%).[87]

Figure 14: Prescribing patterns for people with EGFR-positive metastatic NSCLC who are tested for T790M (N=98; Jan-18 to Mar-18)



Other comprises 1% each of gefitinib, carboplatin/gefitinib/paclitaxel, docetaxel/nintedanib, crizotinib, and pemetrexed.

Unmet needs

Low activity against WT-EGFR

As described above, 1st and 2nd generation TKIs are active against wild-type (WT) EGFR as well as EGFRm, leading to toxicities such as rash and diarrhoea.[71] New 1L treatments should aim to spare WT-EGFR, in order to reduce the frequency of these side effects.

Potent activity against T790M

Given that T790M is the primary cause of acquired resistance with first and second generation TKIs,[71] new treatments should demonstrate activity against this mutation, in order to extend time to progression.

CNS penetration and activity

1st and 2nd generation TKIs exhibit poor penetration of the blood-brain barrier,[23, 24] leading to suboptimal activity against brain metastases. For example, around 30% of patients with advanced NSCLC who were treated with 1st generation EGFR-TKIs (with or without pre-existing CNS metastases) experience disease progression due to the development of CNS metastases.[25] Therefore, there exists a clinical need for an EGFR-TKI with improved CNS penetration and increased activity in the brain for patients with advanced NSCLC in the 1L setting, to inhibit the development and/or worsening of CNS metastases.

Place of osimertinib in the current treatment pathway

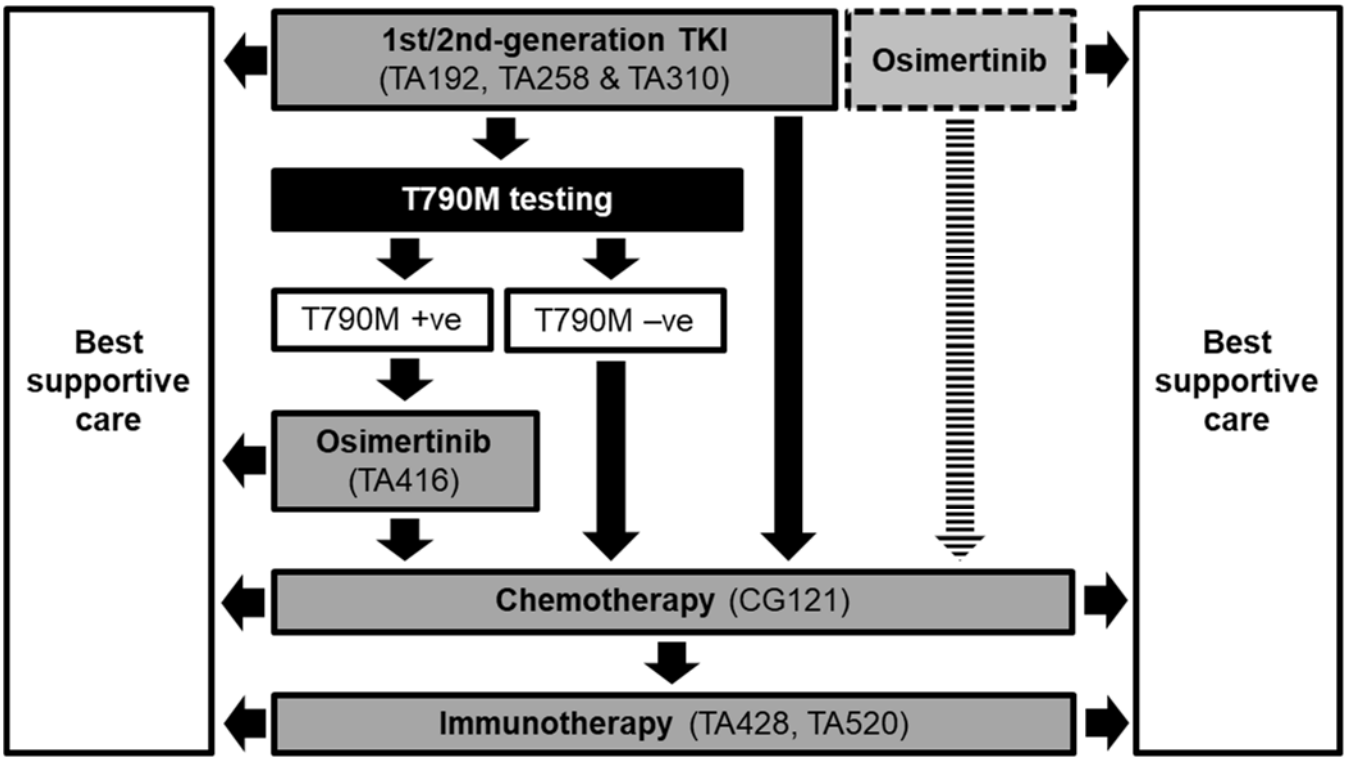
Osimertinib is currently indicated for:

- the first-line treatment of adult patients with locally advanced or metastatic NSCLC with activating EGFR mutations
- the second-line treatment of adult patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC

Reimbursement for the first-line indication would mean that patients with EGFR sensitising-mutation (exon 19 deletions or L858R) positive advanced NSCLC are able to receive osimertinib prior to other EGFR-TKIs, and before they have developed EGFR T790M resistance mutations maximising patient access to improved therapy.

Osimertinib has the potential to replace first-generation TKIs as the standard of care for patients who are newly diagnosed with stage IIIb/IV EGFRm NSCLC (Figure 15), providing a step-change extension of PFS, and efficacy in CNS metastases compared with 1st and 2nd generation EGFR-TKIs. In addition, osimertinib is well tolerated, with a lower incidence of side effects mediated by WT EGFR compared with 2nd generation EGFR-TKIs, such as rash and diarrhoea.[26]

Figure 15: Anticipated positioning of osimertinib in the 1L setting



Note: Treatment pathway has been simplified for clarity. Death can occur at any time. Patients may cycle through multiple chemotherapy rounds before receiving immuno-oncology

B.1.4 Equality considerations

AstraZeneca does not anticipate the use of this technology to result in any particular equality issues.

However, it should be noted that an estimated third of patients with locally advanced or metastatic NSCLC will only receive one treatment, due to rapid progression or ineligibility for further treatment. We believe that it would be inequitable to offer patients a first- or second-generation TKI over osimertinib in the 1L setting, given that there is no prospective way to identify which patients will receive further treatment upon progression. Treatment with osimertinib in the 1L setting offers patients the best chance of prolonged progression-free survival, with fewer side effects mediated by WT-EGFR inhibition, compared with first- or second-generation TKIs.

B.2 Clinical effectiveness

B.2.1 Identification and selection of relevant studies

A systematic literature review was conducted to identify RCTs investigating the efficacy and safety of first-line treatments in the treatment of locally advanced or metastatic EGFR mutation positive (Ex19del or L858R) NSCLC.

See Appendix D.1.1 for full details of the process and methods used to identify and select the clinical evidence relevant to this submission.

B.2.2 List of relevant clinical effectiveness evidence

The evidence supporting the use of osimertinib as first-line treatment for patients with EGFRm-positive, locally advanced or metastatic lung cancer is based on the randomised, controlled FLAURA trial (NCT02296125) (Table 11).

Table 11: Clinical effectiveness evidence

Study	A Phase III, Double-Blind, Randomised Study to Assess the Efficacy and Safety of AZD9291 versus a Standard of Care Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor as First-Line Treatment in Patients with Epidermal Growth Factor Receptor Mutation Positive, Locally Advanced or Metastatic Non-Small Cell Lung Cancer (FLAURA; NCT02296125)		
Study design	Double-blind, randomised, parallel assignment		
Population	Patients aged at least 18 years, with pathologically confirmed adenocarcinoma of the lung; one of the 2 common EGFR mutations known to be associated with EGFR-TKI sensitivity (Ex19del, L858R); locally advanced or metastatic NSCLC; and who are not amenable to curative surgery or radiotherapy		
Intervention(s)	Osimertinib 80 mg, once daily		
Comparator(s)	Erlotinib 150 mg, once daily Gefitinib 250 mg, once daily		
Indicate if trial supports application for marketing authorisation	**Yes**	**Indicate if trial used in the economic model**	Yes
Rationale for use in the model	Pivotal clinical trial reporting patient-relevant outcomes		
Reported outcomes specified in the decision problem	**Overall survival, progression-free survival,** response rate, response duration, **adverse effects of treatment, health-related quality of life**		
All other reported outcomes	Depth of response, disease control rate		

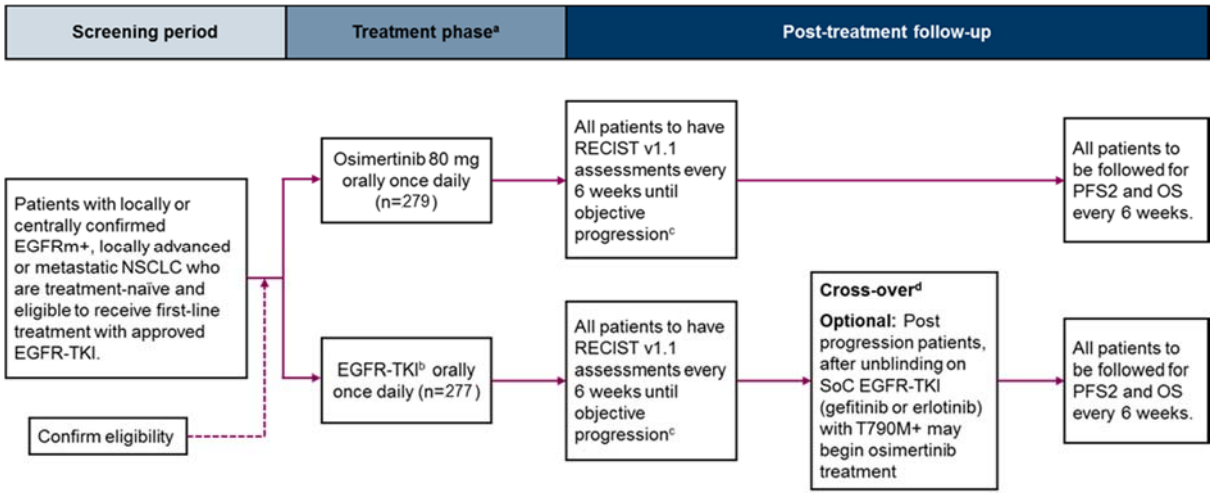
B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

Trial design

FLAURA is an ongoing, Phase 3, double-blind, randomised, controlled trial conducted in 556 patients worldwide. The objective of FLAURA was to assess the efficacy and safety of osimertinib compared with standard-of-care EGFR-TKI therapy, in first-line treatment in patients with locally or centrally confirmed EGFR+ locally advanced or metastatic NSCLC, which is not amenable to curative surgery or radiotherapy.

A summary of the trial design in shown in Figure 16.

Figure 16: FLAURA trial design



a Patients continued to receive study drug until objective disease progression or as long as they continued to show clinical benefit, as judged by the investigator.
b Either gefitinib (250 mg orally, once daily) or erlotinib (150 mg orally, once daily).
c Patients who discontinued treatment prior to disease progression continued to have RECIST v1.1 assessment every six weeks for the first 18 months and then every 12 weeks until objective progression. Patients who continued treatment after objective progression due to clinical benefit were followed up as per standard practice post progression.
d Patients with objective radiological progression according to RECIST 1.1 by the Investigator and confirmed by independent central imaging review who were on SoC EGFR-TKI (gefitinib or erlotinib) after being unblinded and have T790M+ were given the opportunity to cross-over and begin treatment with osimertinib 80mg, once daily. After data cut-off date for the primary PFS analysis, all patients (except those enrolled in China) determined to have objective disease progression according to RECIST 1.1 as per Investigator's assessment were given the opportunity to begin treatment with open-label osimertinib, if eligible; central confirmation of disease progression no longer required.

Eligibility criteria

Eligible participants were male or female patients aged 18 years and over with locally advanced or metastatic pathologically confirmed adenocarcinoma of the lung, not amenable to curative surgery or radiotherapy, with a tumour harbouring one of the most common EGFR mutations known to be associated with EGFR-TKI sensitivity (exon 19 deletion; L858R) either alone or in combination with other EGFR mutations as confirmed by a local or a central test.

Patients were required to be treatment-naïve for advanced disease and eligible to receive first-line treatment with the selected comparator EGFR-TKI in accordance with local prescribing information.

Notably, patients with CNS metastases were eligible to enrol, as long as they had completed definitive therapy, were not on steroids, and had a stable neurologic status for at least 2 weeks after completion of the definitive therapy and steroids. This is in contrast to previous trials of EGFR-TKIs, which excluded patients with CNS metastases.

A list of key inclusion and exclusion criteria is presented in Table 12.

Table 12: FLAURA eligibility criteria

Key inclusion criteria	Key exclusion criteria
1. Provision of informed consent prior to any study specific procedures, sampling, and analyses 2. Male or female, aged at least 18 years. Patients from Japan aged at least 20 years 3. Pathologically confirmed adenocarcinoma of the lung. Patients with mixed histology are eligible if adenocarcinoma is the predominant histology 4. Locally advanced or metastatic NSCLC, not amenable to curative surgery or radiotherapy 5. The tumour harbours one of the 2 common EGFR mutations known to be associated with EGFR-TKI sensitivity (Ex19del, L858R), either alone or in combination with other EGFR mutations, assessed by a CLIA-certified (USA sites) or an accredited (outside of the USA) local laboratory or by central testing. 6. Mandatory provision of an unstained, archived tumour tissue sample in a quantity sufficient to allow for central analysis of EGFR mutation status 7. Treatment- naïve for locally advanced or metastatic NSCLC and eligible to receive first-line treatment with gefitinib or erlotinib as selected by the participating centre. Prior adjuvant and neo-adjuvant therapy is permitted (chemotherapy, radiotherapy, investigational agents) provided all other entry criteria are satisfied 8. World Health Organization Performance Status (WHO PS) of 0 to 1 with no clinically significant deterioration over the previous 2 weeks and a minimum life expectancy of 12 weeks	1. Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site). 2. Treatment with any of the following: • Prior treatment with any systemic anti-cancer therapy for locally advanced/metastatic NSCLC including chemotherapy, biologic therapy, immunotherapy, or any investigational drug • Prior treatment with an EGFR-TKI • Major surgery (excluding placement of vascular access) within 4 weeks of the first dose of study drug • Radiotherapy treatment to more than 30% of the bone marrow or with a wide field of radiation within 4 weeks of the first dose of study drug • Patients currently receiving (or unable to stop use at least 1 week prior to receiving the first dose of study drug) medications or herbal supplements known to be potent inducers of cytochrome P450 (CYP) 3A4 • Alternative anti-cancer treatment • Treatment with an investigational drug within five half-lives of the compound or any of its related material, if known 3. Any concurrent and/or other active malignancy that has required treatment within 2 years of first dose of study drug 4. Any unresolved toxicities from prior systemic therapy (e.g., adjuvant chemotherapy) greater than CTCAE grade 1 at the time of starting study drug with the exception of alopecia and grade 2, prior chemotherapy-induced neuropathy 5. Spinal cord compression, symptomatic and unstable brain metastases, except for those patients who have completed definitive therapy, are not on steroids, have a stable neurologic status for at least 2 weeks after completion of the definitive therapy and steroids 6. Any evidence of severe or uncontrolled systemic diseases, including uncontrolled hypertension and active bleeding diatheses; or active infection including hepatitis B, hepatitis C and HIV

9. At least one lesion, not previously irradiated and not chosen for biopsy during the study Screening period, that can be accurately measured at baseline as ≥10 mm in the longest diameter (except lymph nodes which must have a short axis of ≥15 mm) with CT or MRI, and which is suitable for accurate repeated measurements. If only one measurable lesion exists, it is acceptable to be used (as a target lesion) as long as it has not been previously irradiated and baseline tumour assessment scans are done at least 14 days after the screening biopsy is performed. 10. Female patients should be using adequate contraceptive measures, should not be breast feeding, and must have a negative pregnancy test prior to first dose of study drug; or must have evidence of non-child-bearing potential 11. Male patients should be willing to use barrier contraception, i.e., condoms.	7. Refractory nausea and vomiting, chronic gastrointestinal diseases, inability to swallow the formulated product, or previous significant bowel resection that would preclude adequate absorption of osimertinib 8. Any of the following cardiac criteria: • Mean resting corrected QT interval (QTc) >470 msec, obtained from 3 ECGs, using the screening clinic ECG machine-derived QTcF value • Any clinically important abnormalities in rhythm, conduction, or morphology of resting ECG, e.g., complete left bundle branch block, third-degree heart block, second-degree heart block, PR interval >250 msec • Any factors that increase the risk of QTc prolongation or risk of arrhythmic events such as heart failure, hypokalaemia, congenital long QT syndrome, family history of long QT syndrome, or unexplained sudden death under 40 years of age in first-degree relatives or any concomitant medication known to prolong the QT interval 9. Past medical history of ILD, drug-induced ILD, radiation pneumonitis which required steroid treatment, or any evidence of clinically active ILD 10. Inadequate bone marrow reserve or organ function as demonstrated by any of the following laboratory values • Absolute neutrophil count <1.5 x 109/L • Platelet count <100 x 109/L • Haemoglobin <90 g/L • Alanine aminotransferase (ALT) >2.5x the upper limit of normal (ULN) if no demonstrable liver metastases or >5xULN in the presence of liver metastases • Aspartate aminotransferase (AST) >2.5x ULN if no demonstrable liver metastases or >5x ULN in the presence of liver metastases • Total bilirubin >1.5xULN if no liver metastases or >3xULN in the presence of documented Gilbert's Syndrome (unconjugated hyperbilirubinaemia) or liver metastases • Creatinine >1.5xULN concurrent with creatinine clearance <50 mL/min (measured or calculated by Cockcroft and Gault equation); confirmation of creatinine clearance is only required when creatinine is >1.5xULN 11. Women who are breast feeding 12. History of hypersensitivity to active or inactive excipients of AZD9291 or drugs with a similar chemical structure or class to AZD9291 13. Judgment by the Investigator that the patient should not participate in the study if the patient is unlikely to comply with study procedures, restrictions, and requirement

Settings and locations where the data were collected

A total of 556 patients were randomised to treatment, spanning 132 study centres across 29 countries, including four UK centres (which recruited 11 patients in total).

Trial drugs and concomitant medications

Trial drugs

Patients were randomised 1:1 to receive either osimertinib 80 mg orally, once daily, or standard-of-care EGFR-TKI (either gefitinib [250 mg orally, once daily] or erlotinib [150 mg orally, once daily]) as first-line treatment. Tablets were to be taken whole, with water, approximately 24 hours apart at the same time point each day. If a dose was missed, it was to be taken if within a window of 12 hours; doses missed more than 12 hours after the scheduled time were not to be taken, and patients were instructed to take their next dose at the scheduled time. If the patient vomited after taking their study drug, they were not to make up for this dose, but were advised to take the next scheduled dose.

Patients continued on their randomised treatment until disease progression or until a treatment discontinuation criterion was met. There was no maximum duration of treatment, and patients could continue to receive their randomised treatment beyond disease progression if the Investigator judged a continuation of clinical benefit. Dose reductions (to 40 mg for osimertinib or 100 mg for erlotinib; no option for gefitinib) or interruptions were permitted in the case of Grade 3 or higher and/or unacceptable toxicity, at the discretion of the Investigator.

Following objective disease progression according to RECIST 1.1, patients who were randomised to the control arm were given the option to receive open-label osimertinib if: a) disease progression was confirmed by independent central imaging review prior to unblinding; b) no intervening therapy was given following discontinuation of randomised treatment; and c) the tumour was confirmed as T790M mutation positive following disease progression.

After the data cut-off date for the primary PFS analysis, patients determined to have objective disease progression according to RECIST 1.1 were given the opportunity to begin open-label treatment with osimertinib.

Upon discontinuation of study drug, patients were treated in accordance with the regional SoC.

Concomitant medications

Information was recorded on any treatment given up to 4 weeks prior to initiation of study drug, as well as all concomitant treatments given during or up to 28 days after discontinuation of study drug (or objective disease progression, whichever was later).

Other anti-cancer therapies, investigational agents, and radiotherapy were not permitted to be given during study drug treatment.

Other medication considered necessary for the patient's safety and well-being could be given at the discretion of the Investigator.

Outcomes

Primary outcome

The primary trial endpoint was progression-free survival (PFS), defined by RECIST 1.1 and assessed by the Investigator. Progression-free survival was defined as the time from randomisation until the date of objective disease progression or death (by any cause in the absence of progression), regardless of whether the patient withdrew from randomised therapy or received another anti-cancer therapy prior to progression.

Tumour assessments were carried out every 6 weeks (±1 week) relative to randomisation for the first 18 months and every 12 weeks thereafter, until disease progression.

Secondary outcomes

Key secondary endpoints are described and defined in Table 13.

Table 13: Secondary endpoints in FLAURA

Endpoint	Definition
Overall survival (OS)	The time from the date of randomisation until death due to any cause. Any patient not known to have died at the time of analysis was censored based on the last recorded date on which the patient was known to be alive. Assessments for survival were made every 6 weeks following objective disease progression
Objective response rate (ORR)	The number (%) of randomised patients with a complete response (CR – disappearance of all target and non-target lesions from baseline) or partial response (PR - ≥30% decrease in the sum of the diameters of target lesions) for at least one visit. All tumour responses were assessed at baseline, every 6 weeks thereafter for the first 12 months, and then every 12 weeks until disease progression or death, based on RECIST 1.1 criteria
Duration of response (DOR)	The time from the date of first documented response until the date of documented progression or death in the absence of disease progression
Disease control rate (DCR)	The percentage of patients who have a best overall response of CR, PR, or stable disease (SD) at ≥6 weeks, prior to any PD event
Depth of response	the relative change in the sum of the longest diameters of RECIST target lesions at the nadir, in the absence of new lesions or progression of non-target lesions compared with baseline
Symptoms and HRQoL	patient-reported outcomes (PROs) were assessed using the EORTC QLQ-C30 (measured every 6 weeks until second progression), EORTC QLQ-LC13 (every 3 weeks until second progression), CTSQ-16 (on days 22 and 43), and PRO-CTCAE (weekly for the first 18 weeks and every 3 weeks thereafter until second progression) instruments

Safety variables	safety and tolerability was assessed in terms of AEs, deaths, laboratory data, vital signs (pulse and blood pressure), ECG, LVEF, physical exam, and WHO performance status

All outcomes described above were pre-specified.

At each visit, patients were assigned a visit response of CR, PR, SD, or PD depending on the status of their disease compared with baseline and previous assessments. Unevaluable tumour assessments were assigned a visit response of NE.

Blinded independent central review (BICR) was also carried out for all RECIST-based assessments. Reviews were performed by two independent radiologists for each patient, to give an overall tumour assessment at each time point using RECIST 1.1. Any discrepancies were reconciled by a third independent radiologist and all independent reviewers were blinded to treatment.

Tumour assessments were performed using contrast-enhanced CT or MRI scans of the patient's chest and abdomen, and other regions as clinically indicated. Duplicate images were collected for the BICR.

Table 14: Comparative summary of trial methodology

FLAURA (NCT02296125)	
Location	Global
Trial design	Phase 3, double-blind, randomised, controlled trial
Key eligibility criteria for participants	Aged 18 years and over with locally advanced or metastatic pathologically confirmed adenocarcinoma of the lung, not amenable to curative surgery or radiotherapy, with a tumour harbouring an EGFR mutation (exon 19 deletion; L858R) Treatment-naïve for advanced disease and eligible to receive first-line treatment with the selected comparator EGFR-TKI in accordance with local prescribing information. Patients with stable brain metastases were eligible to enrol, in contrast to previous trials of EGFR-TKIs
Settings and locations where the data were collected	[Approximately 220 sites across Asia, Europe, North America, and South America]
Trial drugs	Trial drugs • Osimertinib (80 mg orally, once daily) + comparator-matching placebo (N=X) • Gefitinib (250 mg orally, once daily) + osimertinib-matching placebo • Erlotinib (150 mg orally, once daily) + osimertinib-matching placebo Study drugs were continued until disease progression or a treatment discontinuation criterion was met, or for as long they were receiving clinical benefit in the opinion of the investigator.

Permitted and disallowed concomitant medication	Other anti-cancer therapies, investigational agents, and radiotherapy were not permitted to be given during study drug treatment. Other medication considered necessary for the patient's safety and well-being could be given at the discretion of the Investigator.
Primary outcomes	PFS according to RECIST 1.1 by Investigator assessment. Tumour assessments were carried out every 6 weeks (±1 week) relative to randomisation for the first 18 months and every 12 weeks thereafter, until disease progression. The primary analysis of PFS was conducted when approximately 359 progression events had occurred.
Other outcomes used in the economic model/specified in the scope	Key secondary endpoints were OS, ORR, DOR, DCR, depth of response, change in EORTC QLQ-C30, symptoms and PRO scores, and safety variables.
Pre-planned subgroups	• Gender (Male / Female) • Race (Asian / Non-Asian) • Age at screening (<65 / ≥65) • History of or current Brain metastases at entry (yes/no) • Smoking history • Baseline WHO Performance Status • Pre-treatment T790M status (positive / negative) • EGFR mutation (Ex19del / L858R) • EGFR+ by ctDNA • Centrally confirmed EGFR+

Patient characteristics

Baseline characteristics were well-balanced between the osimertinib and SoC TKI arms. The majority of patients were female (62.9%) and the median age was 64.0 years. A summary of baseline patient characteristics is shown in Table 15.

Table 15: Baseline patient characteristics in the FLAURA trial

Demographic characteristic	Osimertinib (N=279)	SoC TKI (N=277)	Total (N=556)
Median age, years (range)	64.0 (26-85)	64.0 (35-93)	64.0 (26-93)
Female sex, n (%)	178 (64)	172 (62)	350 (63)
Race n (%)			
Asian	174 (62)	173 (62)	347 (62)
White	101 (36)	100 (36)	201 (36)
Other	4 (1)	4 (1)	8 (1)
Smoking status, n (%)			
Never	182 (65)	175 (63)	357 (64)
Current	8 (3)	9 (3)	17 (3)
Former	89 (32)	93 (34)	182 (33)
WHO performance status, n (%)			

0 (normal activity)	112 (40)	116 (42)	228 (41)
1 (restricted activity)	167 (60)	160 (58)	327 (59)
Missing data	0	1 (0.4)	1 (0.2)
Overall disease classification, n (%)			
Metastatic[a]	264 (95)	262 (95)	526 (95)
Locally advanced[b]	14 (5)	15 (5)	29 (5)
Missing	1 (0.4)	0	1 (0.2)
CNS metastases[c]	53 (19)	63 (23)	116 (21)
Visceral metastases	94 (34)	103 (37)	197 (35)
Liver metastases	41 (15)	37 (13)	78 (14)
EGFR mutations by central test[d]			
EGFR exon 19 deletion	158 (57)	155 (56)	313 (56)
L858R	97 (35)	90 (32)	187 (34)
EGFRm not detected, invalid test, or inadequate sample	24 (9)	32 (12)	56 (10)
EGFR mutations at randomisation[e]			
EGFR exon 21 L858R	104 (37)	103 (37)	207 (37)
EGFR exon 19 deletion	175 (63)	174 (63)	349 (63)

[a] Metastatic disease - Patient had any metastatic site of disease.
[b] Locally advanced - Patient had only locally advanced sites of disease.
[c] This is a programmatically derived composite endpoint with a list of contributing data sources.
[d] A patient could have more than one mutation.
[e] EGFR mutations based on the test (local or central) used to determine randomisation strata (Ex19del or L858R).

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

Hypothesis objective

It was hypothesised that osimertinib has the potential to deliver prolonged clinical benefit versus first-generation TKIs in the first-line setting. T790M+ acquired EGFR-TKI resistance is the most common mechanism of resistance to first-generation TKIs; by preventing this escape mechanism, osimertinib may prolong the duration of tumour response by slowing down the tumour regrowth rate and improving PFS.

Three endpoints were tested over 2 time-points for osimertinib versus SoC TKIs:

- PFS (all globally randomised patients) at the primary PFS analysis
- OS at primary PFS analysis, and at survival follow-up
- PFS in T790M+ subgroup at primary PFS analysis

Sample size

The sample size for this study was selected to be consistent with the research hypothesis. The study was designed so that the primary analysis of PFS was conducted when approximately 359 progression events had been observed in the 530 globally randomised patients. Assuming a true PFS hazard ratio (HR) for the comparison of osimertinib versus SoC EGFR TKI of 0.71, 359 progression events would provide 90% power to demonstrate a statistically significant difference in PFS at a 5% two-sided significance level (translating to an approximate improvement in median PFS from 10 to 14.1 months, assuming exponential data distribution and proportional hazards). The minimum critical HR was 0.81 (i.e. 10 to 12 months).

Two data cut-off points were planned: the primary analysis of PFS (including an interim OS analysis), and the final OS analysis (conducted at approximately 60% maturity, when approximately 318 death events across both arms have occurred). The primary endpoint of PFS, and secondary endpoints of OS and CNS PFS were tested sequentially to control for Type I error.

An estimated 980 patients were needed to be screened in order to randomise approximately 530 EGFR+ patients.

Randomisation and blinding

The Investigators initially obtained a unique enrolment number for each potential participant via the Interactive Web Response System or Interactive Voice Response system (IVRS/IWRS), and determined patient eligibility. At Visit 2, the Principal Investigator or suitably trained delegate obtained a unique randomisation number for each eligible participant via IVRS/IWRS. Patients were subsequently randomised to either osimertinib or the site pre-selected EGFR-TKI in a 1:1 ratio by the IVRS/IWRS system. Study investigators and participants were masked to treatment allocation.

To maintain blinding, study drugs were labelled using a unique material pack code, which was linked to the randomisation code. In addition, patients assigned osimertinib received comparator-matching placebo, while patients assigned gefitinib or erlotinib received osimertinib-matching placebo alongside the study drug. Active and placebo tablets were identical and were presented in the same packaging.

Outcome assessments

All efficacy analyses were carried out on the full analysis set (FAS), comprising all patients who were randomised (i.e., the intent-to-treat [ITT] population). Safety analyses were conducted on the safety analysis set, comprising all patients who received at least one dose of study drug.

Primary efficacy outcome

The primary PFS analysis was conducted using a log rank test stratified by race (Asian versus Non-Asian) and mutation type (Ex19del versus L858R) for generation of the p-value, using the Breslow approach for handling ties. The HR (osimertinib:SoC TKI) was estimated together with its 95% CI and *p*-value. Kaplan-Meier (KM) plots were presented by treatment group. The total number of events, median PFS (calculated from the KM plot, with 95% CIs), and the percentage PFS at 6, 12, 18 and 24 months was summarised.

Subgroup analyses

The consistency of treatment effect for PFS was assessed (using a Cox-Proportional Hazards Model) in the following subgroups:

- Gender (Male / Female)
- Race (Asian / Non-Asian)
- Age at screening (<65 / ≥65)
- History of or current Brain metastases at entry (yes/no)
- Smoking history
- Baseline WHO Performance Status
- Pre-treatment T790M status (positive / negative)
- EGFR mutation (Ex19del / L858R)
- EGFR+ by ctDNA
- Centrally confirmed EGFR+

For each subgroup, the HR and 95% CI was calculated from a single Cox proportional hazards model that contained a term for treatment, the subgroup covariate of interest, and the treatment by subgroup interaction term. HRs and associated two-sided 95% CIs were summarised and presented on a forest plot, along with the results of the overall primary analysis.

Secondary efficacy outcomes

OS was analysed using the same methodology and model as for PFS. The percentage OS at 6, 12, 18, 24, and 36 months was also summarised.

ORR and DCR were analysed using a logistic regression stratified by race (Asian versus Non-Asian) and mutation type (Ex19del versus L858R). The results of the analysis were presented in terms of an odds ratio together with its associated 95% profile likelihood CI and two-sided pvalue.z

Depth of response (i.e. tumour shrinkage / change in tumour size) was examined by presenting the proportion of patients who achieve >30%, >50% and >75% reduction in target lesion tumour size. The best percentage change from baseline in target lesion tumour size was also summarised descriptively and presented graphically using waterfall plots. The effect of osimertinib on best percentage change in tumour size was estimated from an analysis of covariance (ANCOVA) model with covariates for race (Asian versus Non-Asian) and mutation type (Ex19del versus L858R), baseline tumour size and time from baseline scan to randomisation. The number of patients, unadjusted mean, and least squares means for each treatment group was presented, together with the difference in least squares means, 95% CI and corresponding p-value.

Time to discontinuation of treatment or death (TDT) was defined as the time from randomisation treatment discontinuation or death – date of randomisation + 1 (censored at time of DCO1) and analysed using the same method as the analysis of PFS. Time to first subsequent therapy or death was defined as the time from date of randomisation to the earlier of the start date of the first subsequent ant-cancer therapy following discontinuation of randomised treatment, or death (censored at the last follow-up visit). The best response on first subsequent treatment and the time on first subsequent anti-cancer treatment was recorded by the investigator and summarised by treatment arm.

Time from randomisation to second progression (PFS2) was defined as the time from the date of randomisation to the earliest of the progression event subsequent to that used for the primary variable of PFS or date of death after starting subsequent anti-cancer treatment. If a patient died without any progression event, the patient's PFS and PFS2 event dates were equivalent. If a patient died after a primary PFS event but prior to the initiation of a subsequent anti-cancer therapy, the date of death was considered to be the PFS2 event. Patients alive and for whom no second disease progression was observed were censored at the last time they were known to be alive and without second disease progression, ie, at the last progression/disease assessment date (or Day 1 if no post-baseline RECIST data were available) if the patient did not have a second progression or died. Time to second subsequent therapy or death (TSST) was defined as the time from the date of randomisation to the earlier of the start date of the second subsequent anti-cancer therapy following discontinuation of randomised treatment, or death.

PRO outcomes

Change from baseline in the primary PRO symptom scores of dyspnoea (EORTC QLQ-LC13), cough (EORTC QLQ-LC13), pain in chest (EORTC QLQ-LC13), fatigue (EORTC QLQ-C30) and appetite loss EORTC QLQ-LC30) comprised the primary analysis of the PRO questionnaire data, and was analysed using a mixed model for repeated measures (MMRM) analysis of the change from baseline in PRO score for each visit.

The primary analysis also compared the average treatment effect from the point of randomisation for the first 9 months (including visit data obtained at protocolled scheduled time-points of baseline, days 8, 15, 22, 43, 64-106, 127-274 and the discontinuation and follow-up visits if occurring within the first 9 months), unless there was excessive missing data (defined as >75% missing data in either arm).

Descriptive statistics and graphs were reported for the primary PRO symptom scores by time points as well as change in these scores from baseline. These were also reported for the other EORTC QLQ-C30 and EORTC QLQ-LC13 reported symptoms and scales.

For the CTSQ-16 analysis, the three domains of interest (Expectations with Therapy, Feelings about Side-Effects, and Satisfaction with Therapy) were each separately analysed using an ANCOVA general linear model stratified by race (Asian versus Non-Asian) and mutation type (Ex19del versus L858R). The results of the analyses were presented in terms of a least squares mean together with its associated 95% profile likelihood CI. Descriptive statistics and graphs were also reported for the CTSQ-16 three domains of interest by visit as well as change in these domains from baseline.

Safety outcomes

AEs were listed and summarised descriptively by count (n) and percentage (%) for each treatment arm. Summary tables included all AEs that occurred after the start of treatment up until the end of the 28-day follow-up period or before the first administration of cross-over treatment, whichever was sooner. In addition, a truncated AE table of most common AEs, showing all events that occurred in at least 5% of patients overall was summarised by preferred term, by decreasing frequency. AEs were presented by date of onset, date of resolution (if AE was resolved), investigator's assessment of CTCAE grade, and relationship to study drug. AEs of special interest, deaths, and laboratory evaluations were also summarised.

Data management, withdrawals

PFS was recorded at the date of objective disease progression or death regardless of whether the patient withdrew from randomised therapy or received another anti-cancer therapy prior to progression. Patients who had not progressed or died at the time of analysis were censored at the time of the latest date of assessment from their last evaluable RECIST assessment. Reasons for withdrawal from the study included not fulfilling the eligibility criteria, death, withdrawal of consent, or loss to follow-up. If patients withdrew consent, attempts were made to continue to follow them up for survival. Withdrawn patients were not replaced.

Quality control procedures were applied to each stage of data handling to ensure that all data were reliable and processed correctly. Data queries were raised for inconsistent, impossible or missing data. Other than for partial dates, missing data was not imputed and was treated as missing, with exceptions for certain efficacy variables.

Table 16: Summary of statistical analyses

	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
NCT02296125 (FLAURA)	Assess whether osimertinib prolongs PFS over current EGFR TKIs in the first-line setting	All efficacy analyses were performed on the FAS. For PFS, differences between arms were presented using a 95% CI and 2-sided p-value. PFS was analysed using a log rank test stratified by race (Asian versus Non-Asian) and mutation type (Ex19del versus L858R) for generation of the p-value, using the Breslow approach for handling ties	Assuming a true PFS HR for osimertinib versus SoC EGFR TKI of 0.71, 359 progression events would provide 90% power to demonstrate a statistically significant difference in PFS at a 5% two-sided significance level A total of 530 patients were needed to be randomized to achieve the 359 PFS events (68% PFS maturity).	Reasons for withdrawal from the study included not fulfilling the eligibility criteria, death, withdrawal of consent, or loss to follow-up. If patients withdrew consent, attempts were made to continue to follow them up for survival. Withdrawn patients were not replaced.

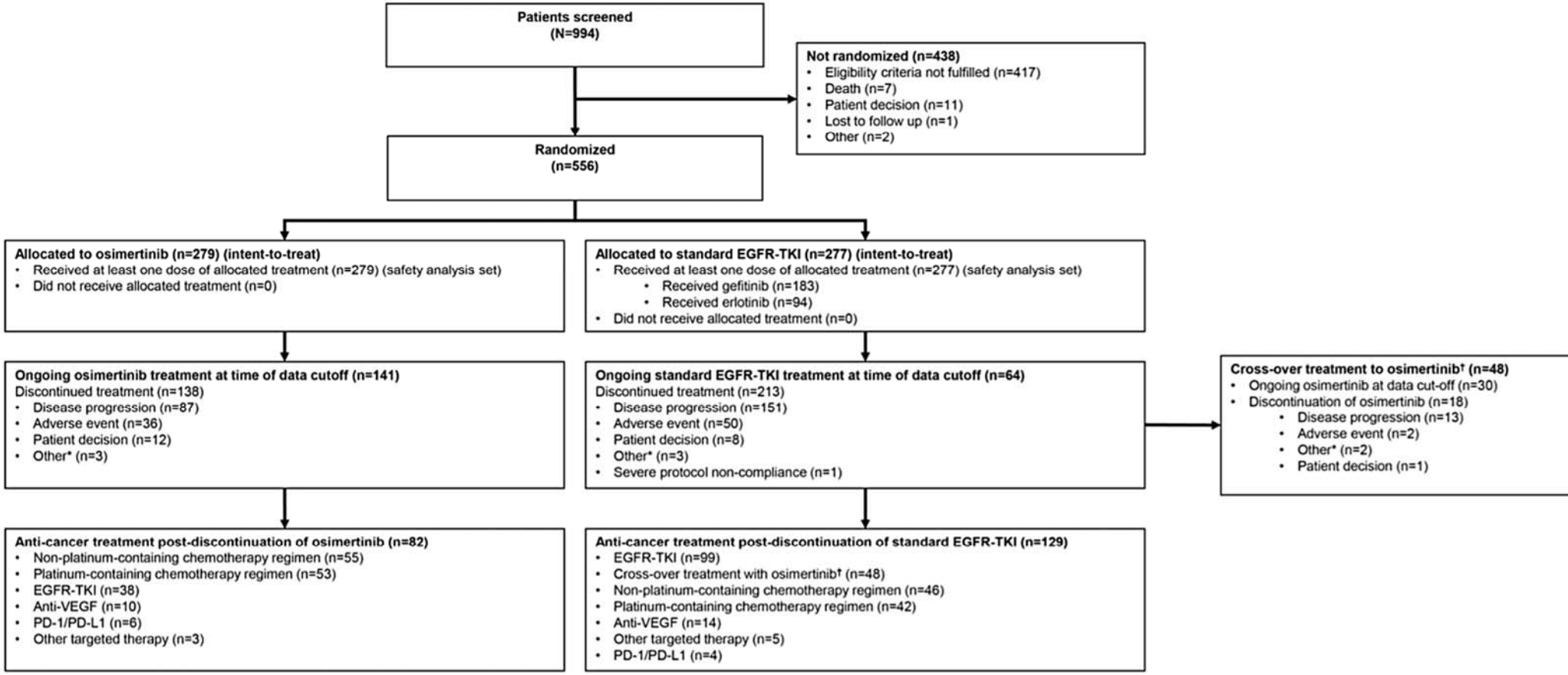
Participant flow

A total of 994 patients were included at the screening stage, 556 of whom met the inclusion criteria and were randomised to treatment in a 1:1 ratio (osimertinib: 279 patients, SoC: 277 patients). All patients received at least one dose of study drug; in the SoC arm, 183/277 (66.1%) received gefitinib and 94/277 (33.9%) received erlotinib.

The flow of patients in FLAURA from screening to data cut-off 1 (DCO1) is shown in Figure 17. As of DCO1 for the primary PFS analysis (12 June 2017), 205 (36.9%) patients were ongoing on their randomised treatment: 141 (50.5%) in the osimertinib arm and 64 (23.1%) in the SoC arm. Of those patients who had discontinued treatment (49.5% for patients receiving osimertinib versus 76.9% for SoC), the most frequent reason for treatment discontinuation was disease progression (31.2% versus 54.5%, respectively), followed by adverse events (12.9% versus 18.1%, respectively).

In the SoC arm, 62 patients received subsequent therapy with osimertinib, including 55 as second-line therapy and 48/277 (17.3%) who fulfilled the criteria for crossover after disease progression (see below). Notably, high rates of re-challenge with an EGFR-TKI were observed in both arms (see below). Overall, 171 (30.8%) patients had terminated the study, due to death (24.3%), withdrawal of consent (6.1%), or loss to follow-up (<1%).

Figure 17: Participant flow in FLAURA



EGFR, epidermal growth factor receptor; PD1, programmed cell death; PD-L1, programmed death-ligand 1; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor
* Any reason not specifically recorded; for example, subject died.
† Crossover patients are patients that crossed over and received at least one dose of open-label osimertinib.

A total of 115/556 (20.7%) patients had at least one important protocol deviation (23.3% in the osimertinib arm and 18.1% in the SoC arm); however, these were considered unlikely to have a meaningful impact on the overall primary study conclusion. The most common protocol deviations were missing RECIST assessments (12.1% of patients), RECIST scan outside the visit window on more than two occasions (4.9%), and baseline tumour RECIST assessments performed more than 28 days before randomisation (2.7%).

Crossover

After Investigator-assessed objective disease progression based on RECIST v1.1, patients randomised to the SoC arm had the option to crossover to treatment with open-label osimertinib provided the following criteria were met and the patient wished to do so.

- Disease progression (while on study treatment or within 28 days of randomised treatment discontinuation) had to be confirmed by BICR of imaging, which had to be established prior to unblinding the patient.
- Patients had not received subsequent intervention therapy following discontinuation of their randomised treatment.
- Confirmation that the tumour was T790M mutation-positive from biological material (tissue or plasma [ctDNA] when country-approved), collected after disease progression.

If a patient in the SoC arm was unblinded and was not eligible for, or chose not to, crossover to osimertinib, that patient could not restart or continue randomised treatment.

Subsequent therapy

A total of 82 patients (29.4%) in the osimertinib arm and 129 patients (46.6%) in the SoC arm received any subsequent therapy. In the SoC arm, the most commonly received subsequent therapies were osimertinib, erlotinib, gefitinib, carboplatin + pemetrexed, and pemetrexed monotherapy; in the osimertinib arm, the most commonly received subsequent treatments were carboplatin + pemetrexed, erlotinib, and gefitinib (Table 17).

Table 17: Summary of subsequent treatments in FLAURA (any subsequent therapy)

Subsequent therapy	Osimertinib (n=279)	%	SoC (n=277)	%
Osimertinib	2	0.7	62	22.4
Erlotinib	14	5	22	7.9
Gefitinib	14	5	15	5.4
Carboplatin + Pemetrexed	16	5.7	13	4.7

Pemetrexed	9	3.2	9	3.2
Afatinib	8	2.9	9	3.2
Cisplatin + Pemetrexed	11	3.9	7	2.5
Carboplatin + Gemcitabine	4	1.4	7	2.5
Carboplatin + Paclitaxel	7	2.5	6	2.2
Bevacizumab + Carboplatin + Pemetrexed	5	1.8	4	1.4
Bevacizumab + Pemetrexed	1	0.4	4	1.4
Docetaxel	4	1.4	3	1.1
Nivolumab	2	0.7	3	1.1
Bevacizumab + Carboplatin + Paclitaxel	3	1.1	2	0.7
Other (<1% in either arm)	13	4.7	26	9.4

Includes cross-over treatment and all anti-cancer therapy (excluding radiotherapy) with a start date on or after the last dose date of study treatment

Details of the treatment that patients received as their first subsequent therapy are presented in Table 18.

Table 18: Summary of first subsequent treatment in FLAURA

First Subsequent Therapy	Osimertinib (N=279)	%	SoC (N=277)	%
Osimertinib	0	0	55	19.9
Erlotinib	8	2.9	17	6.1
Gefitinib	13	4.7	15	5.4
Afatinib	5	1.8	8	2.9
Carboplatin + Pemetrexed	15	5.4	7	2.5
Carboplatin + Gemcitabine	4	1.4	5	1.8
Cisplatin + Pemetrexed	11	3.9	5	1.8
Carboplatin + Paclitaxel	6	2.2	4	1.4
Bevacizumab + Carboplatin + Pemetrexed	4	1.4	1	0.4
Other	16	5.7	12	4.3

Includes first cross-over treatment or anti-cancer therapy (excluding radiotherapy) with a start date on or after the last dose date of study treatment

B.2.5 Quality assessment of the relevant clinical effectiveness evidence

Quality assessment

Table 19 contains a summary of the quality assessment for the FLAURA trial.

Table 19: Summary of the quality assessment for FLAURA

	NCT02296125 (FLAURA)
Was randomisation carried out appropriately?	Yes (page 64) Randomisation was carried out by the IVRS/IWRS in a 1:1 ratio
Was the concealment of treatment allocation adequate?	Yes (page 64) 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 (Table 15) Baseline patient characteristics, including prognostic factors such as ECOG PS, presence of CNS metastases, and age, were well-balanced between arms
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes (page 64) To maintain blinding, study drugs were labelled using a unique material pack code, which was linked to the randomisation code. Each patient received either active osimertinib plus comparator-matching placebo, or the active comparator plus osimertinib-matching placebo. Active and placebo tablets were identical and were presented in the same packaging.
Were there any unexpected imbalances in drop-outs between groups?	No (Figure 17) Discontinuation rates were higher in the SoC arm than in the osimertinib arm, but this was driven by a higher rate of disease progression and discontinuation due to AEs, which was not unexpected
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No (Page 60) 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 (page 65) Analyses were conducted on the FAS (i.e., ITT), comprising all patients randomised to treatment. Data queries were raised for inconsistent, impossible or missing data. Other than for partial dates, missing data was not imputed and was treated as missing, with exceptions for certain efficacy variables.

Please see Appendix D for full details of the quality assessment.

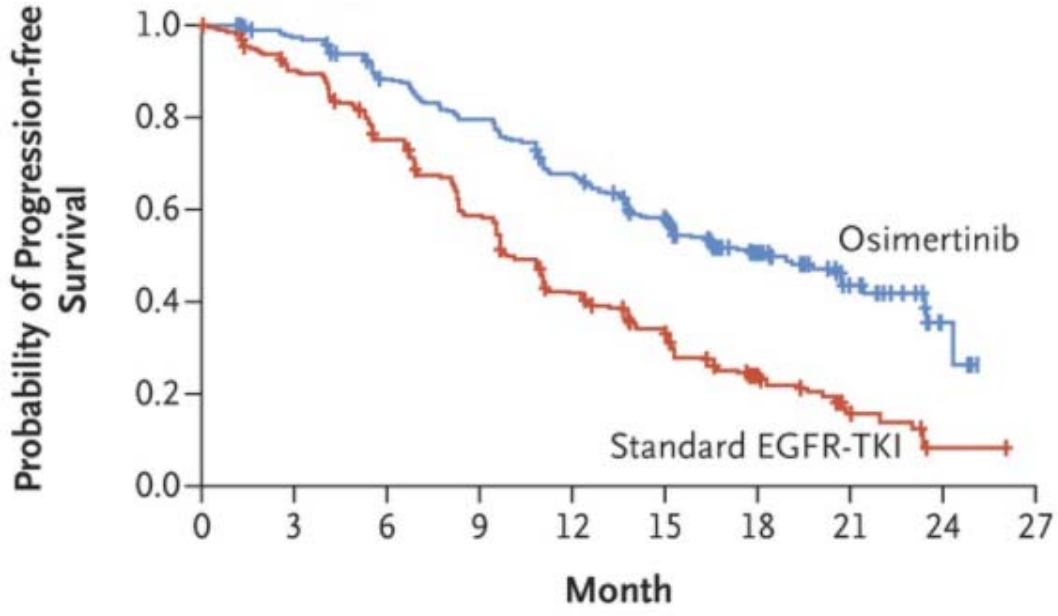
B.2.6 Clinical effectiveness results of the relevant trials

Primary outcome

At the time of data cut-off, an event of RECIST-defined progression or death had occurred in 136 patients (49%) in the osimertinib group and 206 (74%) in the SoC TKI group (61.5% maturity for PFS overall, thus providing sufficient power to detect differences in PFS, as per the study design).

The median progression-free survival (PFS) for patients receiving osimertinib was 18.9 months (95% CI: 15.2 - 21.4), compared with 10.2 months (95% CI: 9.6 - 11.1) for patients receiving SoC EGFR-TKI. The median duration of follow-up for PFS was 15.0 months (range: 0 - 25.1) and 9.7 months (range 0 - 26.1), respectively. The improvement in Investigator-assessed PFS with osimertinib was statistically significant and clinically meaningful (HR for disease progression or death: 0.46; 95% CI: 0.37 - 0.57; p<0.001). In addition, Kaplan-Meier event curves showed early separation between the two groups, from the time of first assessment (at 6 weeks) (Figure 18).

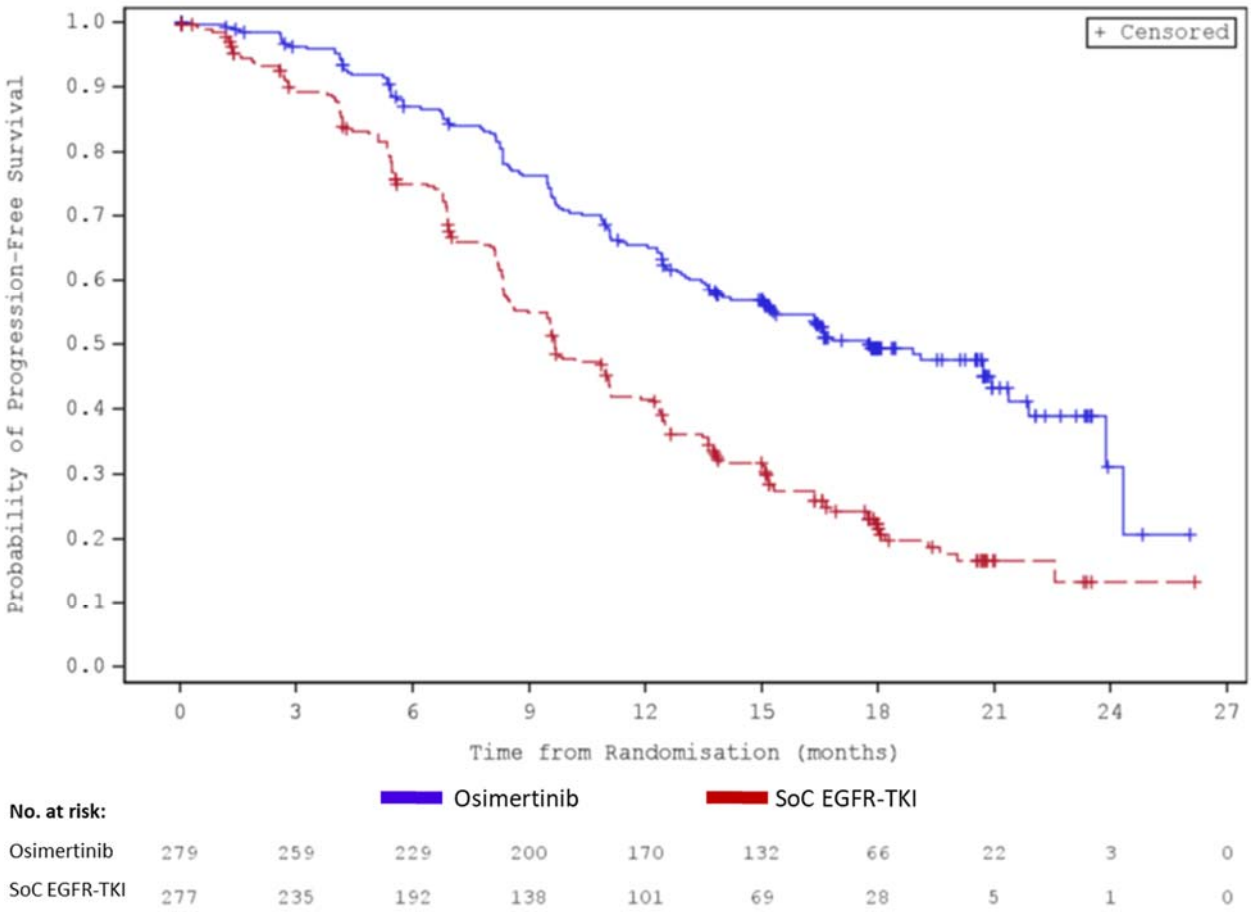
Figure 18: Kaplan-Meier plot of PFS – Investigator assessment (full analysis set)



No. at Risk										
Osimertinib	279	262	233	210	178	139	71	26	4	0
Standard EGFR-TKI	277	239	197	152	107	78	37	10	2	0

FLAURA PFS analysis by blinded Independent Central Review (BICR) was performed as a sensitivity analysis and was consistent with Investigator-assessed outcomes. Osimertinib BICR mPFS was 17.7 months (95% CI, 15.1–21.4) versus 9.7 months (95% CI, 8.5–11.0) for SoC EGFR-TKIs, representing an improvement of 8.0 months duration. The HR for comparison of the BICR mPFS was 0.45 (95% CI, 0.36–0.57; 2-sided p<0.0001) and the Kaplan-Meier analysis of the BICR PFS also demonstrated clear, early separation of the treatment arms, consistent with Investigator assessment (Figure 19).

Figure 19: Kaplan-Meier analysis of FLAURA PFS (BICR-assessed; FAS)



BICR: Blinded Independent Central Review; EGFR-TKI: epidermal growth factor receptor tyrosine kinase inhibitor erlotinib/gefitinib; No: number of patients at risk; FAS: full analysis set; FLAURA: phase III clinical trial; PFS: progression-free survival; SoC: standard of care

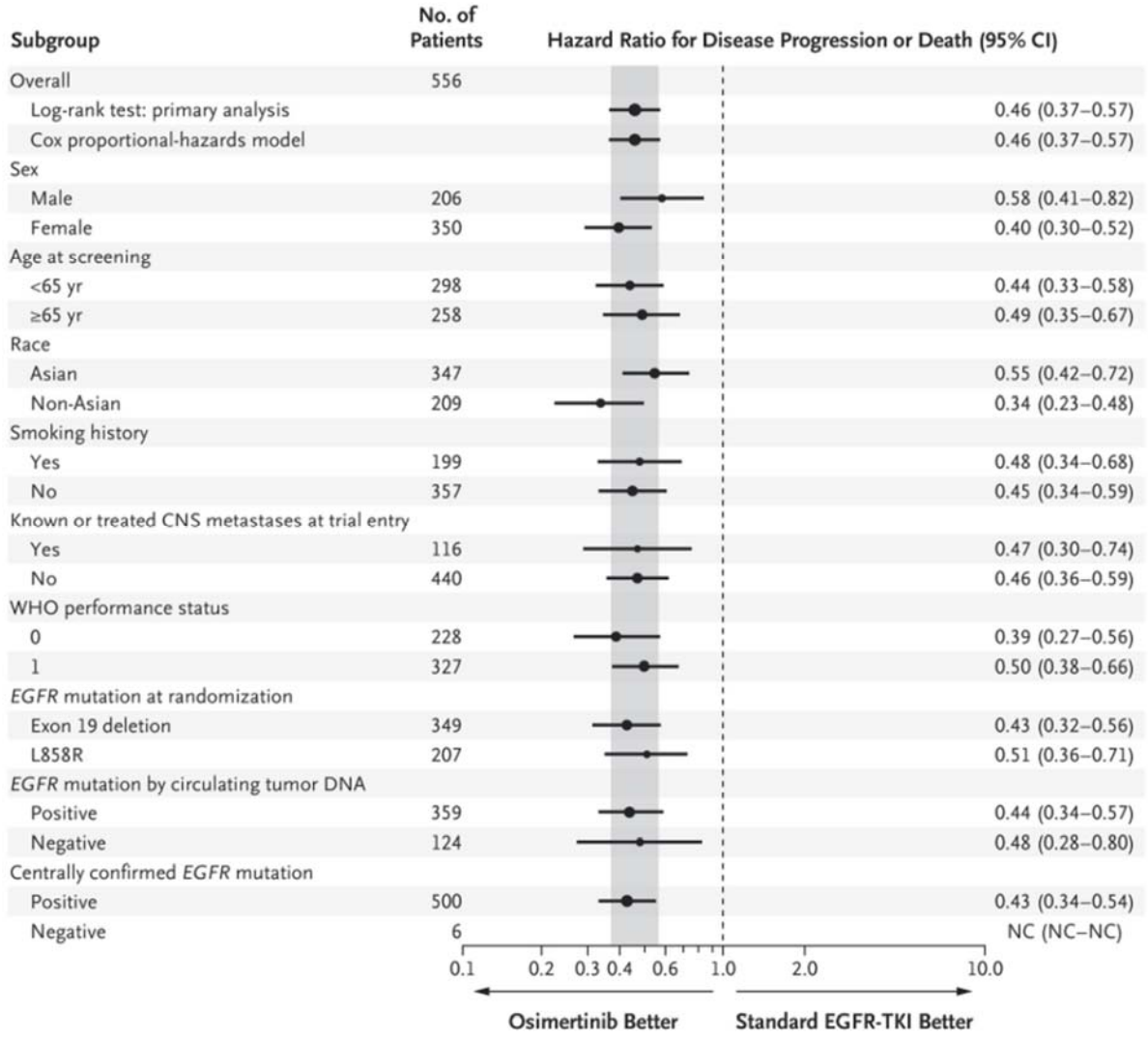
Table 20: Summary of FLAURA PFS analysis (FAS)

Outcome	Investigator assessment		BICR	
	Osimertinib (N=279)	SoC EGFR-TKI (erlotinib/gefitinib) (N=277)	Osimertinib (N=279)	SoC EGFR-TKI (erlotinib/gefitinib) (N=277)
Median PFS, months (95% CI)	18.9 (15.2–21.4)	10.2 (9.6–11.1)	17.7 (15.1–21.4)	9.7 (8.5–11.0)
HR (95% CI; 2-sided p-value)	0.46 (0.37–0.57; p<0.0001)		0.45 (0.36–0.57; p<0.0001)	
Estimated proportion of patients alive and progression free, % (95% CI), at:				
6 months	88.4 (83.9–91.7)	75.2 (69.5–79.9)	87.0 (82.3–90.5)	75.0 (69.4–79.8)
12 months	68.2 (62.3–73.5)	42.3 (36.3–48.2)	65.6 (59.5–71.0)	41.6 (35.4–47.5)
18 months	50.9 (44.5–57.0)	24.4 (19.2–30.0)	49.4 (42.9–55.5)	22.4 (17.1–28.1)
24 months	35.8 (25.6–46.2)	8.4 (3.5–15.9)	31.1 (16.8–46.6)	13.4 (7.0–21.7)
Patients with events, n (%)	136 (48.7)	206 (74.4)	137 (49.1)	198 (71.5)
PFS data maturity overall, %	61.5		60.0	
Median follow-up for PFS in all patients, months	15.0	9.7	13.8	9.0
Median follow-up for PFS in censored patients, months	17.9	16.6	17.8	15.2

BICR: Blinded Independent Central Review; CI: confidence interval; DCO1: data cut-off 12 June 2017; EGFR-TKI: epidermal growth factor receptor tyrosine kinase erlotinib/gefitinib; FAS: full analysis set; FLAURA: phase III clinical trial; HR: hazard ratio; N: number; RECIST 1.1: response evaluation criteria in solid tumours; PFS: progression-free survival; SoC: standard of care

A consistent PFS benefit for osimertinib over SOC EGFR-TKIs was observed across all pre-defined subgroups, including those based on EGFR mutation type (Ex19del versus L858R), the presence or absence of CNS metastases at trial entry, and race (Asian versus non-Asian) (Figure 20). Subgroup analyses are further discussed in Section B.2.7.

Figure 20: Subgroup analyses of progression-free survival



Irrespective of CNS metastases status at trial entry, CNS progression events were observed in 17 patients (6%) in the osimertinib group and 42 (15%) in the standard EGFR-TKI group. However, some cases of asymptomatic progression may not have been detected, because only patients with brain metastases were required to have regular brain scans.

Secondary outcomes

Post-progression endpoints

Compared to SoC EGFR TKIs, osimertinib demonstrated a clinically meaningful, statistically significant delay in post-progression endpoints (Figure 21):

- **Initiation of the first subsequent anti-cancer therapy or death (TFST)**

  The median TFST was 23.5 months (95% CI, 22.0–NC) in the osimertinib arm and 13.8 months (95% CI, 12.3– 15.7) in the SoC arm.

  The time to first subsequent therapy (TFST), from randomisation, was significantly longer in the osimertinib arm compared with the SoC EGFR-TKI arm (HR: 0.51 [95% CI, 0.40–0.64]; 2-sided p-value <0.0001)

- **Time from randomisation to second PFS (PFS2)**

  The median PFS2 on subsequent treatment was not reached in the osimertinib arm, with a lower limit of the 95% CI of 23.7 months, and was 20.0 months (95% CI, 18.2–NC) in the SoC arm. The HR for comparison between the two groups was 0.58 (95% CI, 0.44–0.78; 2-sided p-value 0.0004).

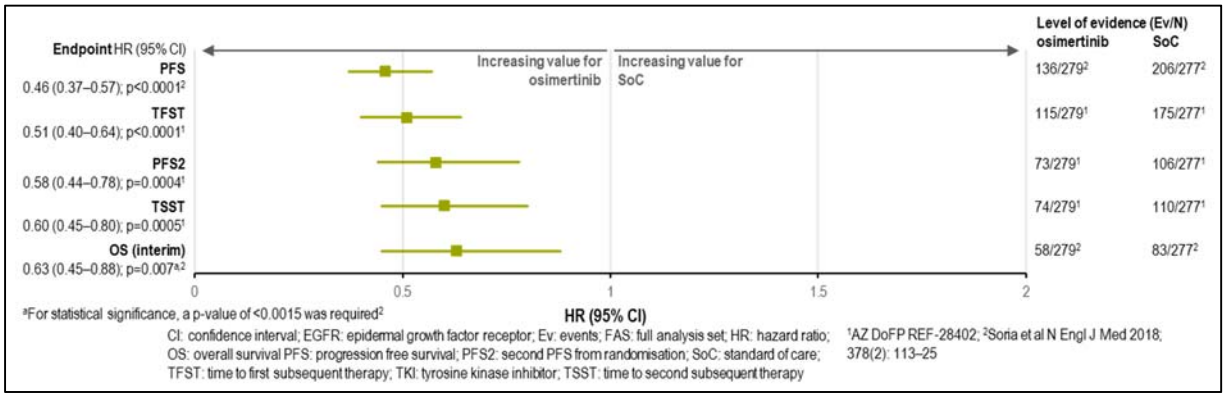
  The mean number of days between first and second progression was 94.5 days (sd: 85.85) in the osimertinib arm vs. 129.9 days (sd: 117.8) in the SoC arm. The longer time between PFS and PFS2 in the SoC arm is most likely driven by crossover to osimertinib therapy

- **Initiation of second subsequent anti-cancer therapy or death (TSST)**

  TSST was statistically significantly longer in the osimertinib arm, compared with SoC EGFR-TKI treatment with erlotinib or gefitinib, with a comparative HR of 0.60 (95% CI, 0.45–0.80; p-value 0.0005). The median TSST was not reached in the osimertinib arm and was 25.9 months (95% CI, 20.0–NC) in the SoC EGFR-TKI (erlotinib/gefitinib) arm.

Median time to discontinuation of any EGFR TKI, or death, was also substantially longer in osimertinib patients (23 months) vs. SoC (16 months).

Figure 21: Hazard ratios were consistent across all post-progression endpoints in FLAURA

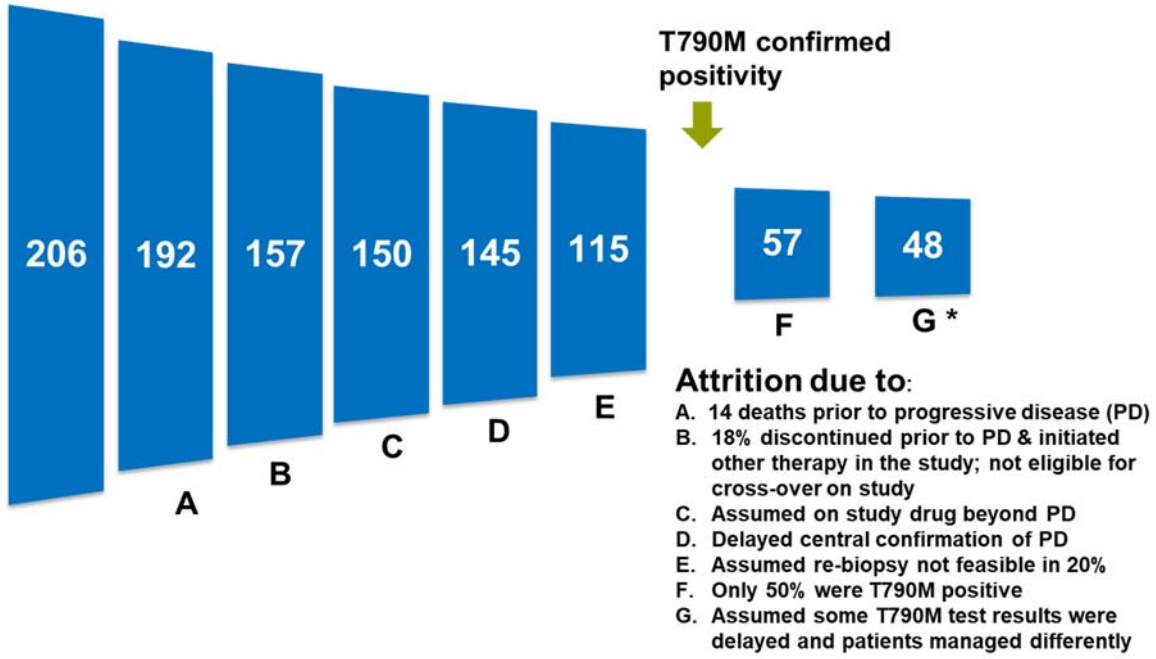


Crossover

At FLAURA DCO1, crossover from the SoC arm to 2L osimertinib was low. A total of 62 patients received osimertinib as a subsequent therapy, including 55 as second-line therapy and 48 as part of the study crossover (patients met the criteria for study crossover if they had confirmed disease progression, had not received subsequent therapy after discontinuation of their randomised treatment, and had a confirmed T790M tumour upon progression).

Investigation of FLAURA data suggests that attrition of patients at several points during the study contributed to this low crossover rate, which could theoretically be as high as 60% given the frequency of acquired T790M resistance after 1L EGFR-TKI treatment. Firstly, 6.8% (14/206) died prior to disease progression and of those remaining 18% (35/192) discontinued randomised treatment prior to disease progression and initiated another therapy in the study (thus were not eligible for crossover on study). Of those remaining 4.5% (7/157) remained on randomised treatment beyond disease progression, and of those remaining 3.3% (5/150) had delayed central confirmation of disease progression (Figure 22). Thus, it is not expected that the use of osimertinib in eligible patients following progression on SoC will significantly compromise the final outcome of OS.

Figure 22: Potential reasons why eligible patients did not crossover to osimertinib treatment during FLAURA (FAS)



*Does not include patients who crossed over outside of the study using commercial supply; additional 7 patients making the total of 55 patients

FLAURA: phase III clinical trial; PD: progressive disease; T90M: acquired epidermal growth factor receptor mutation

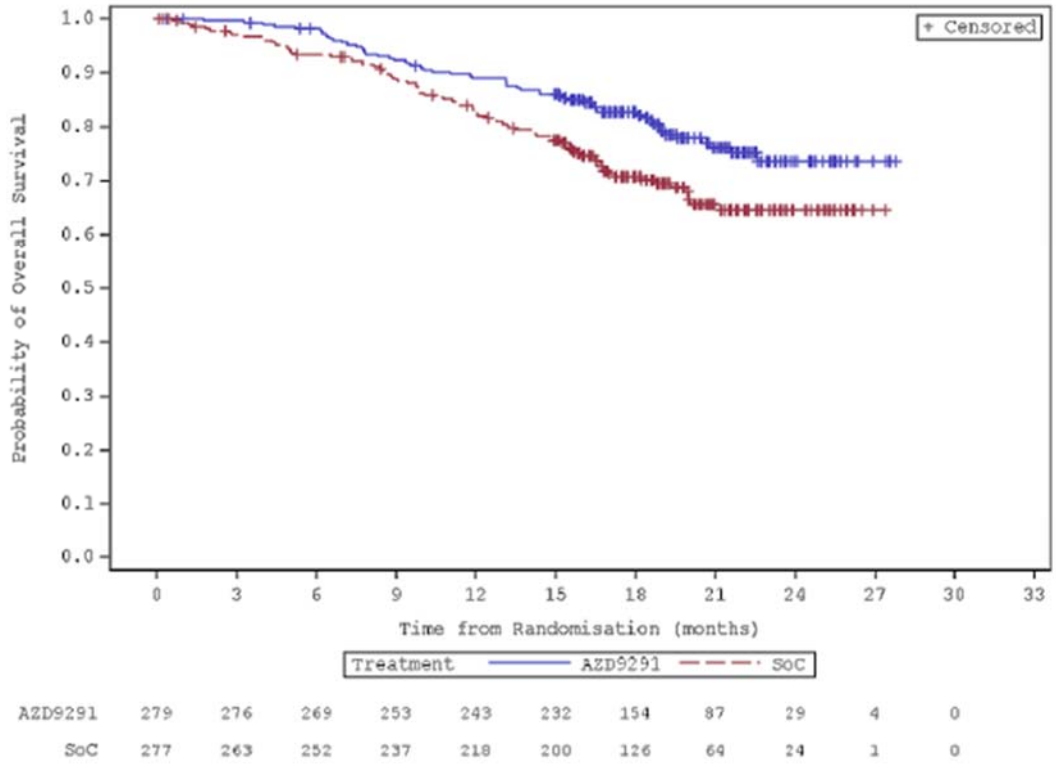
Overall survival

At the time of data cut-off, the median OS could not be calculated in either treatment group due to the low number of deaths (data maturity: 25%). Nevertheless, early separation of the Kaplan-Meier curves could be observed, and a higher percentage of patients who received osimertinib were alive at 12 months and 18 months than patients who received standard EGFR-TKIs (Figure 23). At 18 months, the estimated percentage of patients who were alive was 83% (95% CI: 78 - 87) in the osimertinib group and 71% (95% CI: 65 - 76) in the standard EGFR-TKI group (Table 21).

A total of 141 patients had died overall at DCO1: 58 (21%) in the osimertinib group and 83 (30%) in the standard EGFR-TKI group (HR for death: 0.63; 95% CI: 0.45 - 0.88; p=0.007). For statistical significance at this interim analysis of OS, a P value of less than 0.0015 (determined by the O'Brien-Fleming approach) would have been required.

In the absence of median OS (i.e. the 50th quantile, or 50% percentile of OS), a survival gain at the 25% percentile of OS could be considered as a conservative estimate of the survival gain in the mature population. The 25th percentile of OS was observed at approximately 22.5 months in the osimertinib arm, and at approximately 15.9 months in the SoC arm. This reflects an improvement of 6.6 months, and while not a substitute for median OS, is clearly higher than the 3-month life extension needed to meet EOL criteria.

Figure 23: Kaplan-Meier plot of overall survival



AZD9291 = osimertinib

Tumour response

Investigator-assessed ORR was 80% (95% CI: 75 - 85) for patients receiving osimertinib and 76% (95% CI: 70 - 81) for patients receiving standard EGFR-TKIs (OR: 1.27; 95% CI: 0.85 - 1.90; p=0.24) (Table 21). The disease-control rate was 97% (95% CI: 94 - 99) versus 92% (95% CI: 89 - 95), respectively (OR: 2.78; 95% CI: 1.25 - 6.78; p=0.01). The median best percentage change in target-lesion size (maximum decrease from baseline, or minimum increase from baseline in the absence of a decrease) was −54.7% (range, −100 to 61.9) in the osimertinib group versus −48.5% (range, −100 to 54.1) in the standard EGFR-TKI group (p=0.003).

Among those patients who had a response to trial treatment, an event of disease progression or death had occurred in 106 of 223 patients (48%) in the osimertinib group and 158 of 210 (75%) in the standard EGFR-TKI group at the time of data cut-off. The median duration of response was longer in the osimertinib group (17.2 months [95% CI: 13.8 - 22.0]) than in the standard EGFR-TKI group (8.5 months [95% CI: 7.3 - 9.8]). In the majority of cases, responses were documented at the time of the first scan, with a median time to response of 6.1 weeks (95% CI: 6.0 - 6.1) in the osimertinib group and 6.1 weeks (neither limit of the 95% confidence interval were calculable) in the standard EGFR-TKI group.

Table 21: Key secondary efficacy endpoints

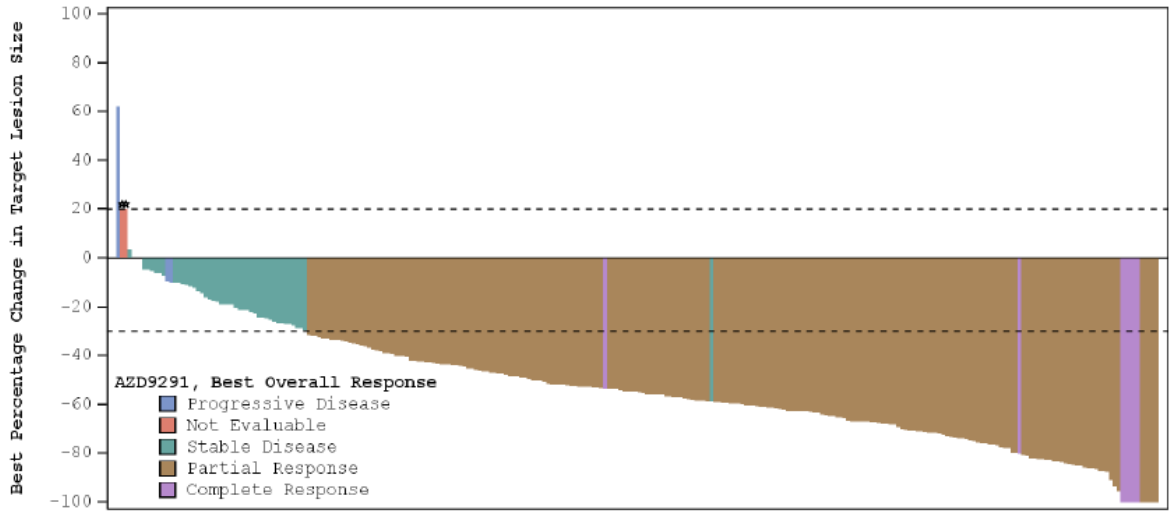
End Point	Osimertinib (N=279)	Standard EGFR-TKI (N=277)
Type of response — no. (%)†		
Complete	7 (3)	4 (1)
Partial	216 (77)	206 (74)
Stable disease for ≥6 wk	47 (17)	46 (17)
Progression	3 (1)	14 (5)
Death	0	5 (2)
Could not be evaluated	6 (2)	7 (3)
Objective response rate — % of patients (95% CI)	80 (75–85)	76 (70–81)
Disease-control rate — % of patients (95% CI)‡	97 (94–99)	92 (89–95)
Time to response§		
No. of weeks — median (95% CI)	6.1 (6.0–6.1)	6.1 (NC–NC)
≤6 wk after first dose — no./total no. (%)	154/223 (69)	148/210 (70)
≤12 wk after first dose — no./total no. (%)	193/223 (87)	180/210 (86)
≤18 wk after first dose — no./total no. (%)	199/223 (89)	196/210 (93)
Duration of response¶		
No. of months — median (95% CI)	17.2 (13.8–22.0)	8.5 (7.3–9.8)
Range	0–23.8	0–24.9
Percent of patients with continued response at 12 mo (95% CI)	64 (58–70)	37 (31–44)
Percent of patients with continued response at 18 mo (95% CI)	49 (41–56)	19 (13–26)
Percent of patients with continued response at 24 mo (95% CI)	NC (NC–NC)	5 (1–16)
Overall survival‖		
No. of months — median (95% CI)	NC (NC–NC)	NC (NC–NC)
Percent of patients alive at 6 mo (95% CI)	98 (96–99)	93 (90–96)
Percent of patients alive at 12 mo (95% CI)	89 (85–92)	82 (77–86)
Percent of patients alive at 18 mo (95% CI)	83 (78–87)	71 (65–76)

* Efficacy analyses included all randomly assigned patients (full analysis set). CI denotes confidence interval, and NC could not be calculated.
† Tumor responses were assessed by the investigators according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1.
‡ The disease-control rate is the proportion of patients who had a complete response, a partial response, or stable disease lasting at least 6 weeks before any disease-progression event.
§ The time to tumor response was calculated with the use of the Kaplan–Meier method from the date of randomization to the date of the first documentation of a partial or complete response. Per the protocol, RECIST assessments occurred every 6 weeks (±1 week) for 18 months, then every 12 weeks (±1 week) until disease progression.
¶ The duration of response was calculated with the use of the Kaplan–Meier method from the date of the first documented response until the date of documented disease progression or death in the absence of disease progression.
‖ Overall survival was calculated from the date of randomization to the date of death due to any cause.

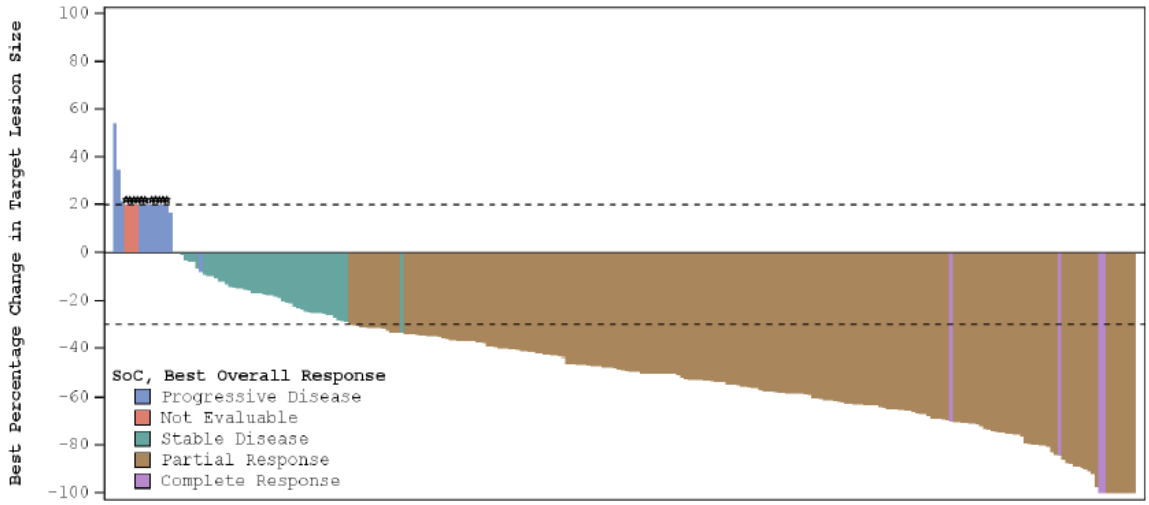
In terms of depth of response, a similar proportion of patients had a reduction of the sum of target lesion size in the osimertinib arm and the SoC arm (97% vs. 93% of patients, respectively). The proportion of patients with >30% reduction in TL size was 82% in the osimertinib arm vs. 77% in the SoC; 59% of patients on osimertinib vs. 45% on SoC had >50% reduction in TL size; and 24% on osimertinib vs. 18% on SoC had >70% reduction in TL size. There was similar mean shrinkage of TLs in the osimertinib arm and the SoC arm, respectively). The difference in LS means for TL tumour shrinkage between the treatment arms was −6.80% (−52.36% vs. −45.66; 2-sided p-value = 0.0025).

Figure 24: Waterfall plot of best percentage change from baseline of target lesion size, based on investigator assessment

Osimertinib arm:



SoC arm:



Best percentage change in target lesion size was the maximum reduction from baseline or the minimum increase from baseline in the absence of a reduction.
*represents imputed values: If it was known that the patient had died, had new lesions or progression of non-target lesions, had withdrawn due to PD and had no evaluable target lesion (before or at progression) assessments, best change was imputed as 20%.

Symptoms and HRQoL

Clinically relevant improvements from baseline were observed in both treatment arms for the symptoms of cough, pain, insomnia, and appetite loss, which were sustained throughout the study period. Small and sustained improvements were also reported for chest pain, fatigue, and dyspnoea in both arms, and for nausea and vomiting in the osimertinib arm. Clinically relevant worsening of diarrhoea was seen from week 6 in both arms, as well as small increases for sore mouth, peripheral neuropathy, and alopecia. There were no meaningful differences between the treatment arms in LS mean change from baseline to month 9 for the five pre-specified PRO symptoms (cough, dyspnoea, chest pain, fatigue, and appetite loss) (**Table 22**).

Table 22: Summary of change from baseline in primary PRO symptoms

	Cough		Dyspnoea		Chest pain		Appetite loss		Fatigue	
	Osimertinib	SoC	Osimertinib	SoC	Osimertinib	SoC	Osimertinib	SoC	Osimertinib	SoC
N	248	252	248	252	248	252	252	247	252	247
LS mean	−10.97	−11.65	−4.04	−4.14	−6.62	−6.41	−6.15	−5.64	−5.48	−4.72
95% CI for LS mean	−12.77, −9.17	−13.47, −9.84	−5.63, −2.45	−5.73, −2.54	−8.24, −5.01	−8.04, −4.78	−8.39, −3.90	−7.96, −3.32	−7.45, −3.52	−6.74, −2.69
Difference in LS means (osimertinib minus SoC)	0.68		0.10		−0.21		−0.50		−0.77	
95% CI for difference in LS means	−1.87, 3.24		−2.16, 2.35		−2.51, 2.08		−3.73, 2.73		−3.59, 2.05	

LS = least squares; MMRM = mixed-effects model for repeated measures;
The analysis was performed using a MMRM analysis on the change from baseline in PRO symptom score at each visit up to 9 month (281 days), including patient (as a random effect), treatment, visit (as fixed effect and repeated measure), and treatment-by-visit interaction as explanatory variables, the baseline PRO score as a covariate along with the baseline PRO score by visit interaction, using an unstructured covariance structure. Using the first covariance structure (in the order: unstructured, toeplitz with heterogeneity, autoregressive with heterogeneity, toepliz, autoregressive) for which convergence could be achieved for all 5 primary PRO symptoms scores.

In terms of quality of life measures, an improvement from baseline was observed for emotional functioning in both arms, occasionally reaching clinical relevance. Improvements were also observed for physical function, role function, social function, and global health status/QoL, although these did not reach the threshold for clinical relevance (≥10pp).

B.2.7 Subgroup analysis

Detailed analyses for key subgroups of interest (presence vs absence of CNS metastases, Exon19del vs L858R EGFR mutation, and Asian vs non-Asian ethnicity) are presented below.

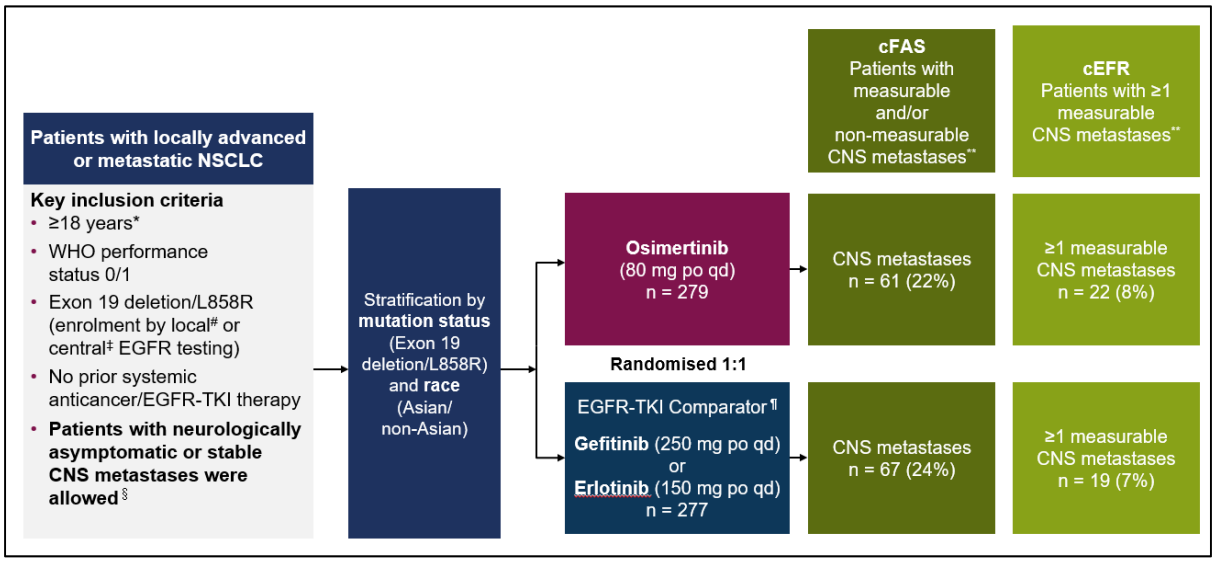
CNS metastases

Patients with CNS metastases represent a subgroup of interest as osimertinib has been hypothesised to have improved penetration of the blood-brain barrier and clinical activity in the brain, compared with first- and second-generation TKIs. Pre-specified subgroup analyses were therefore carried out to assess whether treatment effect is maintained in patients with CNS metastases.

Patient characteristics

A total of 200/556 (36.0%) patients (osimertinib: 106/279 [38.0%]; SoC: 94/277 [33.9%]) had a baseline CNS scan available for assessment by the CNS blinded independent central reviewer. Of these, 128/556 (23.0%) patients (osimertinib: 61/279 [21.9%]; SoC: 67/277 [24.2%]) had at least 1 measurable or non-measurable CNS lesion (the “cFAS" population), and 41/556 (7.4%) patients (osimertinib: 22/279 [7.9%]; SoC: 19/277 [6.9%]) had at least one measurable CNS lesion (the “cEFR" population, Figure 25).

Figure 25: Definition of CNS subgroups in FLAURA



** On baseline brain scan by BICR.

Twenty patients were part only of the subgroup with a CNS metastasis at baseline but were not part of the cFAS subgroup, due to either the absence of a CNS CT or MRI scan for CNS BICR assessment or BICR not identifying CNS lesions. Conversely, 32 patients were only part of the cFAS as they were not considered by the Investigator to have baseline CNS metastases and therefore were not included in the subgroup of patients with a CNS metastasis at baseline.

Most patients (96/128 [75.0%]; osimertinib: 47; SoC: 49) had one to three CNS lesions at baseline, with the remaining 25% (32/128) of patients (osimertinib: 14; SoC: 18) having more than three CNS lesions. The mean number of CNS lesions was 2.9 (sd: 2.15) in the osimertinib arm versus 2.9 (sd: 2.32) in the SoC arm. For those patients with measurable CNS lesions at baseline, the mean size of the TL was smaller in the osimertinib arm (26.7 mm [sd, 19.00]) compared with the SoC arm (37.2 mm [sd, 25.90]). Other disease and demographic characteristics were balanced between arms.

Efficacy

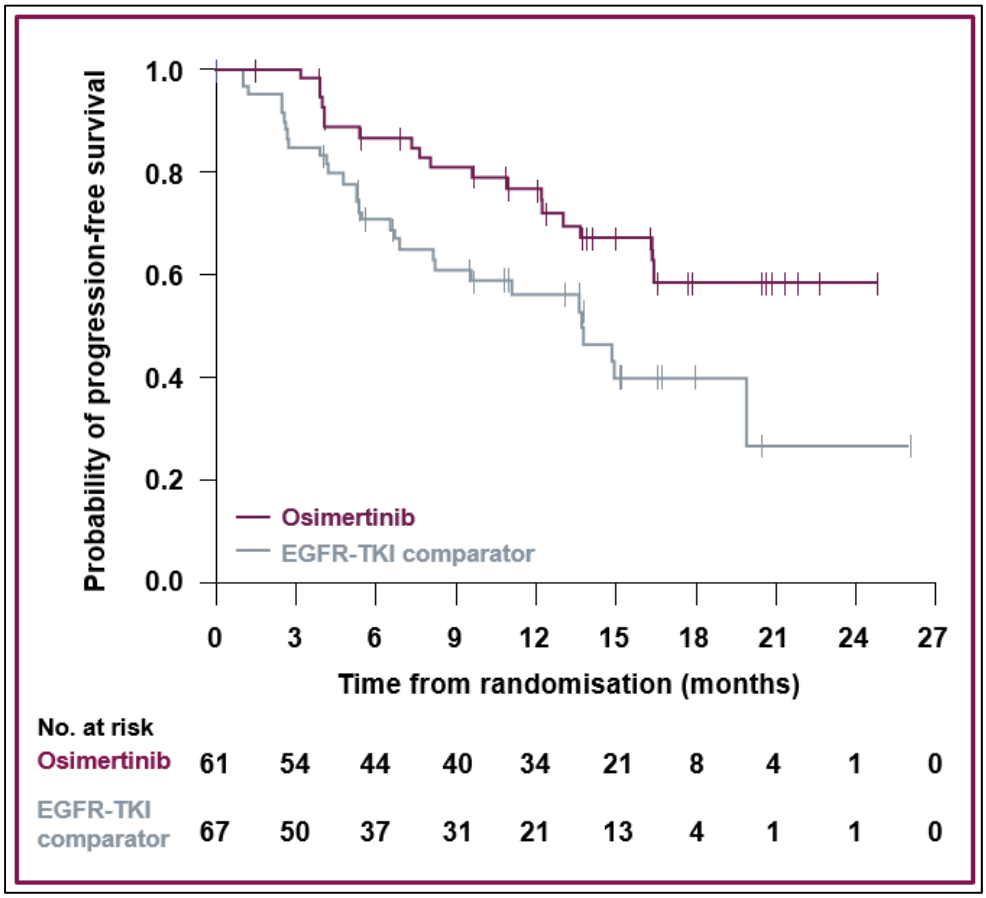
A summary of key efficacy outcomes as measured by investigator assessment is presented in Table 23. While PFS HRs were similar regardless of the presence or absence of CNS metastases at baseline, OS HRs were numerically better in patients without CNS metastases than with. Conversely, the ORR was higher in patients with CNS metastases than without, while the DCR was similar between the two subgroups (Table 23).

Table 23: Key efficacy outcomes by presence or absence of CNS metastasis (Investigator assessment)

Subgroup	Treatment group	Number of patients with event (%)	Hazard ratio	95% CI	P value
PFS		**Progression**			
CNS metastasis	Osimertinib	29/53 (54.7)	0.47	0.30, 0.74	<0.001
	SoC	53/63 (84.1)			
No CNS metastasis	Osimertinib	107/226 (47.3)	0.46	0.36, 0.59	<0.001
	SoC	153/214 (71.5)			
OS		**Death**			
CNS metastasis	Osimertinib	15/53 (28.3)	0.79	0.40, 1.51	0.473
	SoC	22/63 (34.9)			
No CNS metastasis	Osimertinib	43/226 (19.0)	0.59	0.40, 0.87	0.008
	SoC	61/214 (28.5)			
ORR		**Response**	**Odds ratio**	**95% CI**	**P value**
CNS metastasis	Osimertinib	40/53 (75.5)	0.51	0.19, 1.30	0.161
	SoC	54/63 (85.7)			
No CNS metastasis	Osimertinib	183/226 (81.0)	1.58	1.01, 2.49	0.044
	SoC	156/214 (72.9)			
DCR		**Response**			
CNS metastasis	Osimertinib	53/53 (100)	2.57	0.13, 377.96	0.541
	SoC	62/63 (98.4)			
No CNS metastasis	Osimertinib	218/226 (96.5)	2.71	1.23, 6.50	0.013
	SoC	194/214 (90.7)			

At DCO1, there was a nominally statistically significant and clinically meaningful improvement in CNS PFS for patients on osimertinib compared with patients on SoC based on CNS BICR. The HR was 0.48 (95% CI: 0.26, 0.86; p-value = 0.014) in the cFAS population, indicating a 52% reduction in the risk of CNS disease progression or death (in the absence of CNS RECIST progression) in the osimertinib arm compared to the SoC arm. The median CNS PFS was not reached, with a lower limit of the 95% CI of 16.5 months in the osimertinib arm vs. 13.9 months (95% CI: 8.3, NC) in the SoC arm (Figure 26). CNS PFS analysis was third in the hierarchical statistical testing strategy and, as OS did not reach formal statistical significance at this data cut-off, CNS PFS could not be formally tested for statistical significance.

Figure 26: Osimertinib demonstrated a nominally significant improvement in CNS PFS compared to EGFR-TKI comparator (cFAS)



Disease progression was predominately driven by new CNS lesions (as opposed to progression in existing lesions), with 7/61 (11.5%) patients in the osimertinib arm vs. 20/67 (29.9%) patients in the SoC arm experiencing progression due to CNS NLs (new lesions, Table 24). The estimated probability of observing a CNS progression event (conditional on the patient not experiencing a competing risk by that time) at 6 months was 4.9% in the osimertinib arm vs. 18.0% in the SoC arm. Overall, CNS progression events occurred in 17 (6%) versus 42 (15%) patients receiving osimertinib versus EGFR-TKI SoC (all patients).

Table 24: Progression events in cFAS subgroup

Patients with progression, n (%)	**Osimertinib (n = 61)**	**EGFR-TKI comparator (n = 67)**
Total number of events (CNS progression or death)*	18 (30)	30 (45)
CNS progression other than death	**12 (20)**	**26 (39)**
Progression due to death	6 (10)	4 (6)
Any progression[#]		
Progression in target CNS lesions	4 (7)	2 (3)
Progression in non-target CNS lesions	1 (2)	5 (7)
Progression due to new CNS lesions	**7 (12)**	**20 (30)**
Unknown reason for CNS progression[‡]	2 (3)	1 (1)

FLAURA data cut-off: June 12, 2017.

*Progression events that did not occur within 2 scheduled visits (plus visit window) of the last evaluable assessment (or randomisation) were censored and therefore excluded in the number of events. [#]Target lesions, non-target lesions and new lesions were not necessarily mutually exclusive categories. [‡]Patients were identified as having progression but their first lesion progression could not be determined.

CNS ORR was higher with osimertinib in both cFAS and cEFR subsets than in EGFR-TKI comparator group (Table 25).

Table 25: ORR, time to response and DCR for patients in FLAURA with CNS metastases at baseline

Response[1]	cFAS (n = 128)		cEFR (n = 41)	
	Osimertinib (n = 61)	EGFR-TKI comparator (n = 67)	Osimertinib (n = 22)	EGFR-TKI comparator (n = 19)
CNS ORR, (95% CI)	66% (52, 77)	43% (31, 56)	91% (71, 99)	68% (43, 87)
Odds ratio[#] (95% CI); *P*-value[‡]	2.5 (1.2, 5.2); *P* = .011		4.6 (0.9, 34.9); *P* = .066	
Complete response, n (%)	25 (41)	16 (24)	5 (23)	0
Partial response, n (%)	15 (25)	13 (19)	15 (68)	13 (68)
Stable disease ≥6 weeks, n (%)	15 (25)	27 (40)	1 (5)	4 (21)
Median time to response, weeks	6.2	11.9	6.0	6.3
CNS DCR[§] (95% CI)	90% (80, 96)	84% (73, 92)	95% (77, 100)	89% (67, 99)
Odds ratio[#] (95% CI); *P*-value[‡]	1.8 (0.6, 5.5); *P* = .269		2.5 (0.2, 55.8); *P* = .462	

*Responses did not require confirmation, per 1.1 guidance on randomised studies. [#]This analysis was performed using logistic regression with a factor for treatment. [‡]The 2-sided *P*-value was calculated based on the likelihood ratio test, which compared 2 models (one with the intercept only and another including the treatment factor). [§]Complete response + partial response + stable disease ≥6 weeks. [¶]Responses required confirmation after 4 weeks. Confirmed CNS ORR with osimertinib and EGFR-TKI comparator was 57% and 40% in the cFAS, and 77% and 63% in cEFR, respectively.

cEFR, CNS evaluable for response set; cFAS, CNS full analysis set; CI, confidence interval; CNS, central nervous system; DCR, disease control rate; EGFR, epidermal growth factor receptor; ORR, objective response rate; RECIST 1.1, Response Evaluation Criteria In Solid Tumors version 1.1; TKI, tyrosine kinase inhibitor.

Asian vs non-Asian ethnicity

In the pre-specified subgroup analysis, there appeared to be a numerical PFS advantage for non-Asian patients over Asian patients. This is of interest from a UK perspective, as the UK population predominantly comprises people of non-Asian ethnicity, and so results in this subgroup may be more relevant to the UK setting.

At DCO1, fewer patients in the osimertinib non-Asian subgroup had experienced a progression event than in the Asian subgroup. The magnitude of PFS benefit was higher in non-Asian patients than in Asian patients (HR: 0.34; 95% CI: 0.23, 0.48, versus HR: 0.55; 95% CI: 0.42, 0.72, respectively) (Figure 27).

Figure 27: Kaplan-Meier plot of PFS by IA, subgroup analysis by ethnicity (Asian vs non-Asian)

The numerical efficacy advantage for non-Asians over Asians was maintained for the analyses of OS, ORR, and DCR (Table 26).

Table 26: Key efficacy outcomes for the Asian vs non-Asian subgroup (Investigator assessment)

Subgroup	Treatment group	Number of patients with event (%)	Hazard ratio	95% CI	P value
PFS		**Progression**			
Asian	Osimertinib	[redacted]	[redacted]	[redacted]	[redacted]
	SoC	[redacted]			
Non-Asian	Osimertinib	[redacted]	[redacted]	[redacted]	[redacted]

	SoC	[redacted]			
OS		**Death**			
Asian	Osimertinib	[redacted]	[redacted]	[redacted]	[redacted]
	SoC	[redacted]			
Non-Asian	Osimertinib	[redacted]	[redacted]	[redacted]	[redacted]
	SoC	[redacted]			
ORR		**Response**	**Odds ratio**	**95% CI**	**P value**
Asian	Osimertinib	[redacted]	[redacted]	[redacted]	[redacted]
	SoC	[redacted]			
Non-Asian	Osimertinib	[redacted]	[redacted]	[redacted]	[redacted]
	SoC	[redacted]			
DCR		**Response**			
Asian	Osimertinib	[redacted]	[redacted]	[redacted]	[redacted]
	SoC	[redacted]			
Non-Asian	Osimertinib	[redacted]	[redacted]	[redacted]	[redacted]
	SoC	[redacted]			

EGFR mutation status

Previous studies of EGFR-TKIs have indicated that these treatments may be slightly more in efficacious in patients with Exon19del mutations than in patients with L858R mutations, possibly due to the higher binding affinity of TKIs for Exon19del than L858R, as well as differential inhibition of downstream signals.[42, 89] This subgroup is therefore of clinical interest, to determine if osimertinib shows differential efficacy depending on the type of EGFR mutation.

Baseline characteristics between the Exon19del and L858R subgroups were similar, although the proportion of Asian patients was slightly lower in the Exon19del subgroup than in the L858R subgroup (58% vs 69%, respectively).

At DCO1, PFS was numerically higher in patients with Exon19del mutations, with a PFS HR of 0.43 (95% CI: 0.32, 0.56), compared with a HR of 0.51 (95% CI: 0.36, 0.71) in patients with L858R mutations (Figure 28).

Figure 28: Kaplan-Meier plot of PFS by IA, by EGFR mutation (Exon19del vs L858R)

The HR for OS was also numerically better in the Exon19del subgroup compared with the L858R subgroup. ORR and DCR were similar between the two groups (Table 27).

Table 27: Key efficacy outcomes for the Exon19del vs L858R subgroups (Investigator assessment)

Subgroup	Treatment group	Number of patients with event (%)	Hazard ratio	95% CI	P value
PFS		**Progression**			
Exon19del	Osimertinib	[redacted]	[redacted]	[redacted]	[redacted]
	SoC	[redacted]			
L858R	Osimertinib	[redacted]	[redacted]	[redacted]	[redacted]
	SoC	[redacted]			
OS		**Death**			
Exon19del	Osimertinib	[redacted]	[redacted]	[redacted]	[redacted]
	SoC	[redacted]			
L858R	Osimertinib	[redacted]	[redacted]	[redacted]	[redacted]
	SoC	[redacted]			
ORR		**Response**	**Odds ratio**	**95% CI**	**P value**
Exon19del	Osimertinib	[redacted]	[redacted]	[redacted]	[redacted]
	SoC	[redacted]			
L858R	Osimertinib	[redacted]	[redacted]	[redacted]	[redacted]
	SoC	[redacted]			
DCR		**Response**			
Exon19del	Osimertinib	[redacted]	[redacted]	[redacted]	[redacted]
	SoC	[redacted]			
L858R	Osimertinib	[redacted]	[redacted]	[redacted]	[redacted]
	SoC	[redacted]			

B.2.8 Meta-analysis

No meta-analysis was conducted, as only one clinical trial (FLAURA) provides the clinical evidence for osimertinib in this setting.

B.2.9 Indirect and mixed treatment comparisons

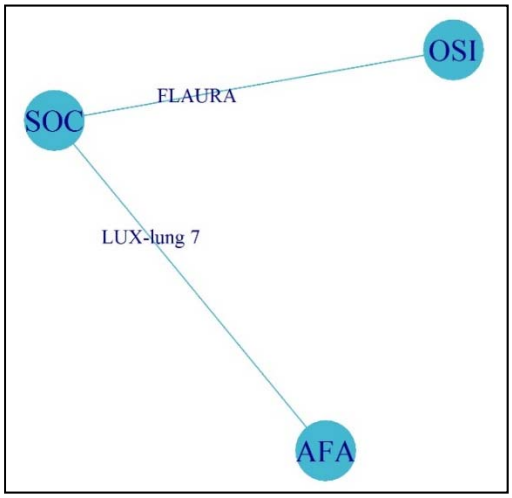
In the standard of care (SOC) arm of the FLAURA study, patients could receive either erlotinib or gefitinib; the treatment patients received was determined by the elected treatment at the site at which the patient attended. An analysis of the relative effect of osimertinib compared separately to erlotinib or gefitinib was not prespecified in the study analysis plan.

ITCs require a common comparator to form the intermediate link between treatments of interest. As the control arm of the FLAURA study includes two treatments, it was necessary to assume that gefitinib and erlotinib are equivalent in efficacy in order to conduct the required ITCs. There is some evidence to suggest that the assumption of equal efficacy between erlotinib and gefitinib may not be unreasonable.

The CTONG 0901 study directly compared erlotinib with gefitinib in NSCLC patients.[18] Subgroup analysis in EGFRm-positive patients showed no significant difference for PFS (hazard ratio [HR]=0.96 [95% confidence interval {CI}: 0.69, 1.35]) or OS (HR=0.98 [95% CI: 0.67, 1.42]) between erlotinib and gefitinib. A previous network meta-analysis (NMA) also indicated there was no significant difference in PFS for the comparison of erlotinib versus gefitinib (HR: 0.87 [95% credible interval {CrI}: 0.72, 1.04]).[19] Furthermore, in a previous NICE technology assessment of erlotinib, the appraisal committee concluded there was insufficient evidence to suggest a difference in clinical effectiveness between erlotinib and gefitinib (TA258).

The clinical SLR identified 34 RCTs, of which three were head-to-head RCTs of EGFR-TKIs in addition to the FLAURA study (ARCHER 1050, LUX-Lung 7 and CTONG 0901).[17, 18, 20] CTONG 0901 was not considered for analysis as this study reduces to a single arm when erlotinib and gefitinib arms are combined. The study was also conducted in a mixture of first- and second-line patients. The ARCHER 1050 study was also not considered for analysis as dacomitinib is not currently licensed for first-line treatment of EGFRm NSCLC and was therefore not considered to be a relevant comparator at the time of analysis. The network of evidence for the primary analysis therefore consisted only of FLAURA and LUX-Lung 7 and is displayed in Figure 29. Both studies presented data for OS and PFS (both PFS-IA and PFS-BICR).

Figure 29:Network of evidence



Key: AFA, afatinib; OSI, osimertinib; SOC, standard of care (gefitinib/erlotinib).

Comparison of patient characteristics

Qualitative heterogeneity evaluations between the two study populations were based on the following patient characteristics:

- Age
- Gender (male/female)
- Race (Asian/non-Asian)
- Central nervous system (CNS) metastasis (yes/no)
- Disease stage (Stage IIIB/IV)
- Smoking status (current versus ex-smokers or never smokers)
- EGFR mutation type (exon 19 deletions, L858R mutation)

The inclusion criteria for both FLAURA and LUX-Lung 7 specified that patients were required to have locally advanced/stage IIIb or metastatic/stage IV disease to enrol in the study. The two studies appeared to be consistent in terms of age, gender, race, proportion of patients with CNS metastases, proportion of patients who never smoked and the distribution of different EGFR mutations (Table 8).

Bucher adjusted indirect comparison

Based on the available evidence base, we concluded the most appropriate analysis to explore would be indirect comparison using the Bucher method:[33]

The Bucher method allows for the comparison of two interventions in the absence of direct head-to-head data via an adjusted indirect comparison. In its simplest form, an adjusted indirect comparison compares results from two separate RCTs through a common comparator, maintaining the randomisation between treatments in each study. The use of HRs within adjusted indirect comparison methods requires the assumption of proportional hazards (PH), that is the HR remains constant over time.

To estimate this indirect effect, the difference in the relative treatment effect in relation to the common comparator in each study was considered. As both endpoints of interest are survival endpoints (OS and PFS), HRs were used to compare treatments. The indirect estimate of the HR between treatments A and B was estimated as follows:

$$\log\left(HR_{AB}^{indirect}\right) = \log\left(HR_{AC}^{direct}\right) - \log(HR_{BC}^{direct})$$

With variance (Var):

$$\mathrm{Var}\{\log(HR_{AB}^{indirect})\} = \mathrm{Var}\{\log(HR_{AC}^{direct})\} + \mathrm{Var}\{\log(HR_{BC}^{direct})\}$$

Results

The PH assumptions for PFS – IA, PFS – BICR and OS were tested using log cumulative hazard plots for both the FLAURA and LUX-Lung 7 studies separately. If the assumption of PH holds for any outcome measure, we expect to see parallel curves for the two treatments in each study.

FLAURA

In the FLAURA study the log cumulative hazard curves for both PFS outcomes were approximately parallel for osimertinib compared to standard of care. The OS from the FLAURA study was based on an interim analysis which resulted in shorter follow up and a high level of censoring in the tails of the KM curve. This led to the log cumulative hazard curves converging over time, although the curves do not meet or cross [FIGURE]. This is likely to be a consequence of the immature interim data, which may be resolved when the final OS data are available.

LUXLung 7

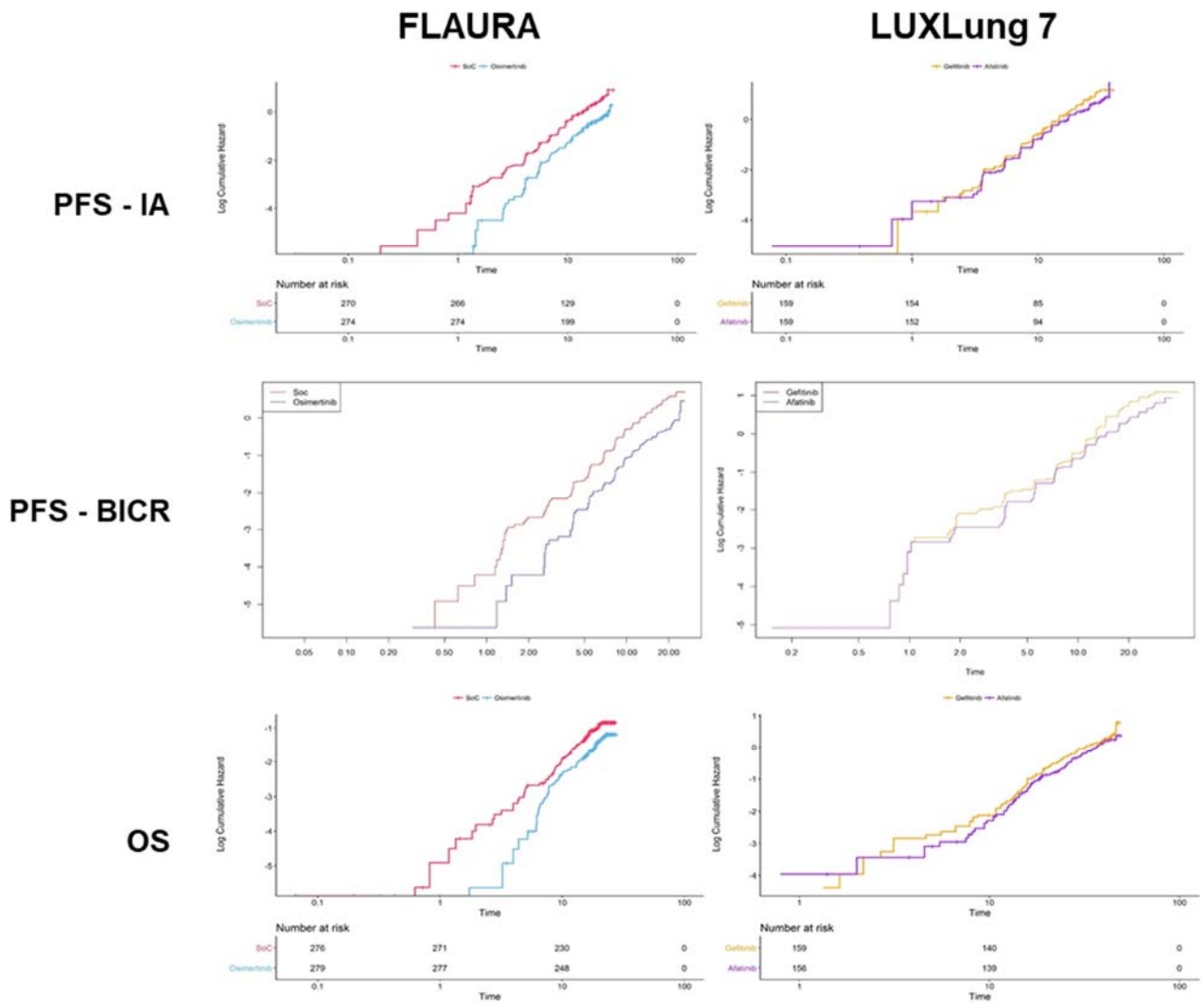
In the LUX-Lung 7 study it is unclear whether the assumption of PH is acceptable for any survival outcome (PFS or OS). The two log cumulative hazards curves for afatinib and gefitinib are very similar and lie one on top of the other [FIGURE]. Although the two curves do cross in all three cumulative hazard plots, it is not clear whether this represents a violation of the PH assumption or simply the fact that the hazard functions for the two treatments are very similar.

Conclusions

Analysis of the log cumulative hazards plots for FLAURA suggest it is likely that the PH assumptions holds for both PFS outcomes and OS when comparing osimertinib to standard of care. However, in the LUXLung 7 study, it is unclear whether the assumption of PH is acceptable for either PFS outcome or OS. In most cases, the curves for afatanib and gefitinib are so close it cannot be determined whether this represents a violation of the PH assumption or a reflection of the fact that the hazard functions for the two treatments are very similar (i.e. there is no meaningful difference between the treatment arms in LUXLung 7).

Given the similarity of the hazard functions for afatanib and gefitinib in LuxLung 7, and evidence from the CTONG 0901 study[18], the previous NMA [19] and the conclusions of the appraisal committee for TA258, we have made the assumption that all three early generation TKIs have equivalent efficacy.

Figure 30: Log cumulative hazard plots for survival outcomes in FLAURA and LUXLung 7



B.2.10 Adverse reactions

The most commonly reported adverse events due to any cause in the FLAURA study (treatment-related or otherwise) were rash or acne (58% in the osimertinib group and 78% in the standard EGFR-TKI group), diarrhoea (58% and 57%, respectively), and dry skin (36% in each group). Median total duration of exposure to treatment in FLAURA was 16.2 months for the osimertinib arm and 11.5 months for the SoC EGFR-TKI (erlotinib/gefitinib) arm, and the median actual duration of exposure (excluding dose interruptions) was 16.1 months for the osimertinib arm and 11.5 months for the SoC EGFR-TKI (erlotinib/gefitinib) arm. One hundred and ninety-four patients (69.5%) had at least 12 months of treatment with 1L osimertinib and 131 patients (47.3%) had at least 12 months of treatment with a SoC EGFR-TKs erlotinib and gefitinib. Actual exposure was similar to total exposure in the osimertinib arm, indicating that dose interruption had a minimal impact on exposure (107/279 [38.4%] patients in the osimertinib arm had at least 1 dose interruption).

Cardiac effects (changes in QT interval) were reported in a higher percentage of patients in the osimertinib group (29 patients [10%]) than in the standard EGFR-TKI group (13 patients [5%]). Across groups, the majority of adverse events in this category were of grade 1 (11 patients [4%] in the osimertinib group and 7 [3%] in the standard EGFR-TKI group) or grade 2 (12 patients [4%] in the osimertinib group and 3 [1%] in the standard EGFR-TKI group). There were no fatal cases of torsades des pointes or prolongation of the QT interval in either treatment group. Analysis of prolongation of the QT interval that was identified on electrocardiography showed a baseline median QT interval corrected for heart rate according to Fridericia's formula (QTcF) of 411.8 msec in the osimertinib group and 408.0 msec in the standard EGFR-TKI group. In both treatment groups, a maximum change from baseline in the median QTcF was reported at week 12 (17.7 msec in the osimertinib group and 10.0 msec in the standard EGFR-TKI group), after which QTcF values remained generally stable across both groups.

Adverse events of interstitial lung disease were reported in 11 patients (4%) in the osimertinib group and 6 (2%) in the standard EGFR-TKI group. No fatal events of interstitial lung disease were reported in either group. In the osimertinib group, the outcome of interstitial lung disease was reported as "recovered" for 7 of 11 patients and "recovering" for the remaining 4 patients. In the standard EGFR-TKI group, the outcome was reported as "recovered" for 4 of 6 patients, "recovering" for 1 patient, and "not recovered" for 1 patient.

Overall, serious adverse events were reported in 60 patients (22%) in the osimertinib group and 70 (25%) in the standard EGFR-TKI group. One patient (in the osimertinib group) had a serious adverse event of prolongation of the QT interval. Serious adverse events of interstitial lung disease occurred in 6 patients in the osimertinib group and 4 in the standard EGFR-TKI group.

Fatal adverse events occurred in 6 patients (2%) in the osimertinib group (pneumonia, respiratory tract infection, cerebral infarction, myocardial infarction, pulmonary embolism, and intestinal ischemia in 1 patient each) and 10 patients (4%) in the standard EGFR-TKI group (sepsis in 2 patients; pneumonia in 1; endocarditis in 1; cognitive disorder and pneumonia in 1; peripheral-artery occlusion in 1; dyspnoea in 1; haemoptysis in 1; diarrhoea, gastrointestinal haemorrhage, respiratory failure, and circulatory collapse in 1; and “death” [the adverse event was not further specified] in 1). None of the fatal adverse events were considered to be possibly related to osimertinib, and one fatal adverse event (of diarrhoea) was considered to be possibly related to standard EGFR-TKIs.

Osimertinib was associated with a numerically lower rate of adverse events leading to permanent discontinuation than were standard EGFR-TKIs (in 37 patients [13%] and 49 patients [18%], respectively). The frequency of dose interruption (25% in the osimertinib group and 24% in the standard EGFR-TKI group) and dose reduction (4% and 5%, respectively) due to adverse events was similar in the two groups (Table 28).

Table 28: Summary of AEs experienced in the FLAURA trial*

Adverse Event	Osimertinib (N=279)					Standard EGFR-TKI (N=277)				
	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4
	number of patients (percent)									
Any adverse event	273 (98)	34 (12)	144 (52)	83 (30)	6 (2)	271 (98)	22 (8)	125 (45)	103 (37)	11 (4)
Rash or acne†	161 (58)	134 (48)	24 (9)	3 (1)	0	216 (78)	110 (40)	87 (31)	19 (7)	0
Diarrhea	161 (58)	120 (43)	35 (13)	6 (2)	0	159 (57)‡	116 (42)	35 (13)	6 (2)	0
Dry skin†	100 (36)	87 (31)	12 (4)	1 (<1)	0	100 (36)	76 (27)	21 (8)	3 (1)	0
Paronychia†	97 (35)	52 (19)	44 (16)	1 (<1)	0	91 (33)	55 (20)	34 (12)	2 (1)	0
Stomatitis	80 (29)	65 (23)	13 (5)	1 (<1)	1 (<1)	56 (20)	47 (17)	8 (3)	1 (<1)	0
Decreased appetite	56 (20)	27 (10)	22 (8)	7 (3)	0	52 (19)	25 (9)	22 (8)	5 (2)	0
Pruritus	48 (17)	40 (14)	7 (3)	1 (<1)	0	43 (16)	30 (11)	13 (5)	0	0
Cough	46 (16)	34 (12)	12 (4)	0	0	42 (15)	25 (9)	16 (6)	1 (<1)	0
Constipation	42 (15)	33 (12)	9 (3)	0	0	35 (13)	28 (10)	7 (3)	0	0
Nausea	39 (14)	28 (10)	11 (4)	0	0	52 (19)‡	32 (12)	19 (7)	0	0
Fatigue	38 (14)	21 (8)	15 (5)	2 (1)	0	33 (12)	23 (8)	8 (3)	2 (1)	0
Dyspnea	35 (13)	24 (9)	10 (4)	1 (<1)	0	20 (7)‡	8 (3)	8 (3)	3 (1)	0
Anemia	34 (12)	19 (7)	12 (4)	3 (1)	0	25 (9)	18 (6)	4 (1)	3 (1)	0
Headache	33 (12)	26 (9)	6 (2)	1 (<1)	0	19 (7)	12 (4)	7 (3)	0	0
Vomiting	31 (11)	25 (9)	6 (2)	0	0	29 (10)	22 (8)	3 (1)	4 (1)	0
Upper respiratory tract infection	28 (10)	16 (6)	12 (4)	0	0	18 (6)	9 (3)	9 (3)	0	0
Pyrexia	28 (10)	27 (10)	1 (<1)	0	0	11 (4)	8 (3)	2 (1)	1 (<1)	0
Prolonged QT interval on ECG	28 (10)	11 (4)	11 (4)	5 (2)	1 (<1)	11 (4)	6 (2)	3 (1)	2 (1)	0
Aspartate aminotransferase elevation	26 (9)	18 (6)	6 (2)	2 (1)	0	68 (25)	38 (14)	18 (6)	12 (4)	0
Alopecia	20 (7)	17 (6)	3 (1)	0	0	35 (13)	31 (11)	4 (1)	0	0
Alanine aminotransferase elevation	18 (6)	11 (4)	6 (2)	1 (<1)	0	75 (27)	31 (11)	19 (7)	21 (8)	4 (1)

* Listed are adverse events that were reported in at least 10% of the patients in any group. Safety analyses included all the patients who received at least one dose of a trial drug (safety analysis set). Some patients had more than one adverse event. ECG denotes electrocardiography.

† This category represents a grouped term for the event. If a patient had multiple preferred-term events within a specific grouped-term adverse event, then the maximum grade (according to the Common Terminology Criteria for Adverse Events) across those events was counted.

‡ In the standard EGFR-TKI group, there were two patients who had missing data on grade, one with diarrhea and one with nausea. In addition, there was one patient with grade 5 diarrhea and one patient with grade 5 dyspnea.

B.2.11 Ongoing studies

The key ongoing AstraZeneca studies investigating osimertinib in EGFRm NSCLC include:

- AURA 1 (NCT01802632; N=603):[95] Phase 1 trial, investigating osimertinib in treatment-naïve (n=60) and previously treated EGFRm-positive tumors
- AURA 2 (NCT02094261; N=210):[96] Phase 2 trial, investigating osimertinib after previous EGFR-TKI therapy in T790M mutation-positive tumors
- AURA 3 (NCT02151981; N=419):[97] Phase 3 trial, investigating osimertinib after previous EGFR-TKI therapy in T790M mutation-positive tumors
- BLOOM (NCT02228369; N=108):[98] Phase 1, open-label study of osimertinib in patients with brain metastases or cytology-confirmed leptomeningeal metastasis, with or without EGFR T790M, who are EGFR-TKI naïve (n=38) or previously treated with an EGFR TKI
- ADAURA (NCT02511106; N=700):[99] a phase 3, randomised study of osimertinib versus placebo as adjuvant therapy, in patients with EGFRm, Stage IB-IIIA NSCLC, following complete tumour resection ± adjuvant chemotherapy
- TATTON (NCT02143466; N=308): a Phase Ib open-label study of osimertinib in combination with novel targeted therapies (durvalumab, savolitinib, or selumetinib), in patients previously treated with an EGFR-TKI

B.2.12 Innovation

Osimertinib is a unique and innovative third-generation TKI that was discovered in the UK, supporting UK leadership in life sciences. Osimertinib is the only TKI to irreversibly and selectively target mutant forms of EGFR (including the TKI-sensitising mutations L858R and exon 19 deletions, as well as the acquired T790M resistance mutation) while sparing wild-type EGFR.

Osimertinib represents a clinically relevant step change in the treatment of EGFRm NSCLC due to the magnitude of clinical improvement over first-generation TKIs. Having demonstrated efficacy in the small subset of patients who develop T790M resistance following treatment with existing TKI's, osimertinib has the potential to become the new SoC in the 1L setting by demonstrating improved survival and reduced treatment-related toxicity for all eligible patients with EGFRm NSCLC, regardless of the site(s) of metastases.

While improved efficacy and tolerability of osimertinib in the 1L setting are captured by the QALY, there are potential uncaptured benefits, like the value of hope for both patients and caregivers, which can be expected from the availability of a much more effective new treatment, as well as the increased chance of prolonged survival for those not eligible for subsequent treatments.[100]

B.2.13 Interpretation of clinical effectiveness and safety evidence

There has been little innovation in EGFRm NSCLC over the past 5 years. The TKIs afatinib, erlotinib, and gefitinib are the current SoC, but are associated with limitations such as activity against WT EGFR (leading to treatment-related toxicities) and low CNS penetration, and prognosis for these patients remains poor.

Osimertinib, an innovative, third-generation TKI, was specifically designed to overcome these limitations and represents a step-change in the management of EGFRm NSCLC.

Efficacy

In the Phase 3, pragmatic, double-blind, randomised FLAURA trial, osimertinib conclusively demonstrated an unprecedented improvement in PFS versus SoC, which was statistically significant and clinically meaningful (HR: 0.46; 95% CI: 0.37 - 0.57; p<0.0001, based on Investigator Assessment). Superiority was maintained and consistent across subgroups including patients with CNS metastases, who have a worse prognosis were largely excluded from previous trials of TKIs. In addition, early separation of the PFS Kaplan-Meier curves may reflect a lower rate of intrinsic resistance to osimertinib than to first-generation TKIs, while the median time to progression of 18.9 months versus 10.2 months, respectively, may suggest that there are no significant early drivers of acquired resistance (unlike with SoC, where ~50% of patients develop acquired resistance to T790M within 9-12 months).

Although OS data are currently immature, the results from the interim OS analysis showed a clinically meaningful improvement in OS in the osimertinib arm (HR: 0.63; 95% CI: 0.45 - 0.88) compared with the SoC arm (p=0.007; maturity: 25.4% overall. For statistical significance at this interim analysis of OS, a P value of less than 0.0015 [determined by the O'Brien-Fleming approach] would have been required). The initial signal for a potential survival benefit is encouraging and strongly supported by the early separation of the OS Kaplan-Meier curves.

PFS and OS data are further strengthened by the post-progression endpoints of TFST, PFS2, and TSST, across which osimertinib also showed a clinically meaningful benefit versus SoC. High response rates (>75%) were seen in both treatment arms and were as expected. Although ORR was similar between arms, there was a clinically meaningful improvement in median DoR for patients on osimertinib compared with patients on SoC, with doubling of the median DoR (osimertinib: 17.2 months [95% CI: 13.8, 22.0]; SoC: 8.5 months [95% CI: 7.3, 9.8]) and a clear separation of confidence intervals, which may be reflective of a delay in TKI resistance development.

Importantly, these clinical benefits were achieved while maintaining HRQOL. Collectively, these data highlight the robust and compelling efficacy of osimertinib in the first-line setting.

Safety

Overall, the safety data from FLAURA indicates that osimertinib is generally well tolerated and has a more favourable safety profile than SoC in the first-line setting. Rates of overall AEs were similar between the two arms, but fewer hepatic and rash AEs, fewer CTCAE ≥grade 3 AEs, and fewer discontinuations due to AEs were observed with osimertinib than with SoC, despite the longer exposure in the osimertinib arm (349.9 treatment-years vs. 271.9 treatment-years for the SoC arm). The difference in incidence of CTCAE ≥grade 3 AEs and treatment discontinuation due to AEs was driven largely by the greater incidence of hepatic events in the SoC arm. The lower rates of rash with osimertinib than with SoC may reflect comparably lower selectivity for WT-EGFR.

Safety findings in the osimertinib arm were broadly consistent with the known safety profile of osimertinib, including QTcF prolongation, cardiac contractility, and ILD, with no new safety signal identified. The pattern of AEs reported in both treatment arms was as expected for an advanced NSCLC patient population receiving an EGFR-TKI in the first-line setting.

Strengths and limitations

Key strengths of the FLAURA trial from an assessment perspective include a double-blind trial design, inclusion of UK patients, the use of commonly used EGFR-TKIs for the standard EGFR-TKI group, independent verification of radiographic outcomes to confirm the results derived from investigator assessment, central confirmation of mutation status in the majority of the patients, the inclusion of patients with CNS metastases, and the option to cross over to osimertinib for patients with T790M-positive tumours after progression during standard EGFR-TKI therapy. In addition, the median progression-free survival in the standard EGFR-TKI group is consistent with that in previous clinical trials of earlier-generation EGFR-TKIs (approximately 9 to 12 months), supporting applicability of the evidence.

The main limitation of the trial is the exclusion of afatinib from the comparator group. At the time of trial initiation, afatinib was not widely used and had not been made available as a global standard-of-care EGFR-TKI. However, clinical outcomes with afatinib are well characterised, and published meta-analyses and the indirect comparison presented in Section B.2.9 found that afatinib produced similar OS results to erlotinib and gefitinib.

The other key limitation relevant for NICE assessment is the immaturity of the survival data. Although median survival had not been reached at the time of DCO1, more patients were alive in the osimertinib arm than the SOC arm, with early separation of the Kaplan-Meier curves supporting a potential survival benefit. A final OS analysis is planned at approximately 60% maturity for OS. A further limitation is that magnetic resonance imaging of the head was not mandated for all patients, limiting the ability to detect asymptomatic brain metastases.

End-of-life criteria

Evidence from randomised controlled trials (RCTs) is useful to understand the effect of a new treatment in a defined patient population and controlled environment, compared with an alternative. However, patients typically recruited to well-controlled RCTs tend to be younger and fitter than those treated by clinicians in a real-world setting, and there is potential for estimates of survival in such artificial and idealised settings to be further inflated relative to an uncontrolled environment. Evidence from recent RCTs suggest median OS of approximately 2 years for patients receiving 1st generation TKIs in the 1L setting.[101, 102] In contrast, overall survival for patients in England and Wales who have the same diagnosis (i.e. confirmed EGFRm, stage IIIb/IV NSCLC) is estimated to be just 15.8 months (95% CI: 14.1 – 17.2) based on analysis of Public Health England data between 2014 and 2016 (n = 652, NCRAS). This is similar to the results of an earlier study in the UK (mOS = 15.4 months [95% CI: 12.5 – 19.1], n = 202, Oct 2013) and one in Germany (mOS = 18.4 months [95% CI 16.3 – 21.3], n = 242, data cut-off = Oct 2012). The poor prognosis and survival expectation for patients in UK clinical practice compared with RCTs may be due to disparities in age, performance status, and time from diagnosis to treatment as well as duration of first-line TKI use. In addition, patients in UK clinical practice are potentially less likely to receive subsequent therapy than in clinical trials, with a corresponding negative impact on OS.

Thus, there is compelling evidence from a number of sources to suggest that advanced or metastatic NSCLC patients in the UK, eligible for treatment with a TKI in the 1L setting, have a median survival of no more than 2 years and most likely, significantly less.

Table 29 End-of-life criteria

Criterion	Data available
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	• OS for patients with confirmed EGFRm, stage IIIb/IV NSCLC in England and Wales is estimated to be **15.8 months (95% CI: 14.1 – 17.2)** based on analysis of Public Health England data between 2014 and 2016 (n = 652, NCRAS)
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	• In the FLAURA trial, osimertinib extended PFS by 8.7 months (18.9 months vs 10.2 months for SoC TKI). Osimertinib also demonstrated a substantial improvement in post-progression endpoints, including a 9.7-month extension in time to first subsequent treatment. • Whilst OS data were immature at the time of data cut-off, the HR for death was 0.63 (95% CI: 0.45 - 0.88; p=0.007), reflecting a meaningful survival advantage over SOC TKI. In addition, early separation of the KM curves was observed. At 18 months, 82.8% of patients receiving osimertinib were still alive, compared with 70.9% of those receiving SoC TKI. • In the absence of median OS (i.e. the 50th percentile of OS), a survival gain at other percentiles of OS may be considered as a conservative estimate of the survival gain in the mature population.[103]* The 25th percentile of OS was observed at approximately 22.5 months in the osimertinib arm, and at approximately 15.9 months in the SoC arm. This reflects an improvement of 6.6 months, and while not a substitute for median OS, is clearly higher than the 3-month life extension needed to meet EOL criteria

*"The median is only one of the quantiles of the distribution of survival times, where the *k*th quantile (or percentile) corresponds to point below which *k*% of the survival times lie above it and (1−*k*)% lie below it. In the case where median survival is not reached by the end of follow-up, it may be informative to compare a different quantile across groups"[103] Note: precise figures for quantiles were not available; the survival estimates reflect the 75.2% percentile for osimertinib and 75.1% percentile for SoC

B.3 Cost effectiveness

B.3.1 Published cost-effectiveness studies

Identification of the studies

A systematic literature review was conducted to identify published evidence to support the development of the cost-effectiveness model for osimertinib for untreated patients with advanced/metastatic EGFRm NSCLC. The review was carried out to identify the cost-effectiveness, cost and resource use, and utility studies and was performed in three parts: a comprehensive and systematic search of the published literature to identify all potentially relevant studies; systematic selection of relevant studies based on explicit inclusion and exclusion criteria to determine eligibility of the studies; and extraction of relevant data from eligible studies.

The search was conducted in key biomedical electronic literature databases recommended by HTA agencies. The details of the search strategy are presented in Appendix G. The following global electronic databases were searched:

- Embase and MEDLINE (using Embase.com)
- MEDLINE In-Process (using Pubmed.com)
- EconLit (using EBSCO.com)
- The Cochrane Library, including the following:
    - Health Technology Assessment database (HTAD)
    - NHS Economic Evaluation Database (NHS EED)

Electronic searching in the literature databases were limited to articles published within the last 10 years. This restriction was applied because of the considerable changes observed over a 10-year period for costs and resource use, inflation rates, and advances in technology (drug therapy, diagnostics, etc.), quality/standard of care and overall living standards. Country limits were not applied at the electronic database searching stage.

In addition, UK HTA websites and databases were also searched for relevant HTA evaluations/models. These included:

- NICE
- Scottish Medicines Consortium (SMC)
- All Wales Medicines Strategy Group (AWMSG)

Furthermore, conference proceedings between 2015–2017 were searched, including:

- International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Annual and European Congress
- European Society for Medical Oncology (ESMO)
- American Society of Clinical Oncology (ASCO)
- European Lung Cancer Conference (ELCC)
- World Conference on Lung Cancer
- Health Technology Assessment International (HTAi)
    - of note, one conference year of HTAi (2015) was not retrievable

Additionally, bibliographies of systematic reviews were checked to identify any potential studies not identified by the searches.

The potentially relevant publications were identified by applying explicit inclusion/exclusion criteria, as summarised in Table 30. Included studies were categorised based on line of therapy at the secondary screening stage.

Table 30: Key criteria for identification of economic evaluations

Category	Economic evaluations
Population	Adult patients with advanced or metastatic EGFRm NSCLC
Line of therapy	Any line of therapy
Interventions	• Osimertinib
Comparators	• Placebo • EGFR-TKIs (including afatinib, erlotinib and gefitinib) • BSC • Platinum doublet chemotherapy • Any treatment from the list above
Outcomes	• Incremental costs, LYs gained and QALYs, and any other measure of effectiveness reported together with costs • Sensitivity analysis
Study type	Economic evaluations (including cost-effectiveness, cost-utility, cost-benefit, and cost-consequence models)
Time limit	Studies published in the last 10 years
Language	English only
Countries	No restrictions

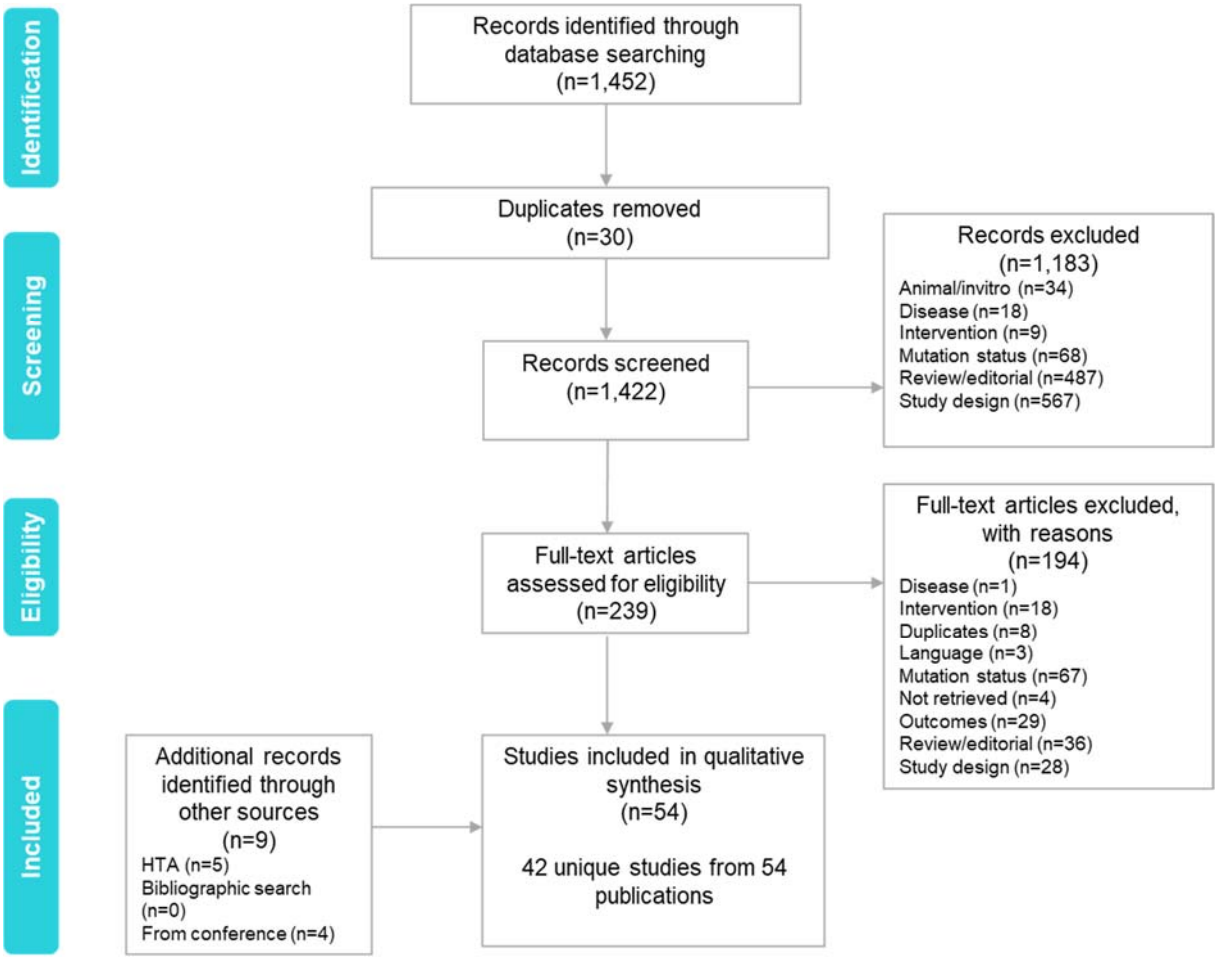
AFA: afatinib; BSC: best supportive care; EGFRm: epidermal growth factor receptor mutation-positive; ERL: erlotinib; GEF: gefitinib; LY: life years; NSCLC: non-small cell lung cancer; OSB: osimertinib; QALY: quality-adjusted life years

Description of identified studies

Systematic database searches (originally performed on 18th May, 2017 and updated on 19th February, 2018 for Embase and MEDLINE databases only) identified 1,452 records. Thirty duplicate records were excluded. After preliminary screening of abstracts, 1,183 records were excluded, and 239 records were included for secondary screening. After secondary screening of full text articles, 193 studies were excluded. In addition, 5 studies were identified from UK HTA websites and four studies from conference proceedings, which resulted in the inclusion of 42 unique studies from 55 publications.

Figure 31 presents the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of studies identified for cost-effectiveness review.

Figure 31: PRISMA diagram for included cost-effectiveness studies



HTA: health technology assessment; PRISMA: preferred reporting items for systematic reviews and meta-analyses

Source: Moher et al., 2009[104]

Among the included studies, four HTAs were submitted to NICE.[105-108] An overview of the four relevant appraisals identified in this review is provided in Table 31. Study characteristics and outcomes of all the studies identified are reported in Appendix G. Quality assessment of the included cost-effectiveness studies was performed using the Drummond and Jefferson checklist and is also presented in Appendix G.[109]

Table 31: Summary of previous NICE submissions for 1L EGFRm NSCLC

Study name	Intervention/ comparator	Line of therapy	Study type	Model type Health states Cycle length	Perspective Time horizon	Outcomes	Costs	ICERs
NICE[TA416] 2016	OSB PEM+CIS	2L	CUA	PSM (cohort based) PFS, PD, and death 1-week	NHS and PSS Lifetime (max. 15 years)	*Adjusted dataset* Total LYG OSB: 3.857 PEM+CIS: 1.825 Incremental: 2.032 Total QALYs OSB: 2.841 PEM+CIS: 1.300 Incremental: 1.541 *Unadjusted dataset* [a] Total LYG OSB: 2.558 PEM+CIS: 1.419 Incremental: 1.139 Total QALYs OSB: 1.913 PEM+CIS: 0.939 Incremental: 0.974	*Adjusted dataset* Total Cost OSB: £87,441 PEM+CIS: £23,159 Incremental: £64,283 *Unadjusted dataset* [a] Total Cost OSB: £71,503 PEM+CIS: £16,403 Incremental: £55,100	*Adjusted dataset* Cost/QALY: £41,705 *Unadjusted dataset* [a] Cost/QALY: £56,570
NICE[TA258] 2012	ERL GEF	1L	CUA	Semi-Markov model PFS, PD, and death	NHS and PSS 10 years	LYG for GEF: 1.796 QALYs for GEF: 1.015	Total cost GEF: £16,046	Base-case analysis with submitted model ICER incremental (QALYs): £48,961

Study name	Intervention/ comparator	Line of therapy	Study type	Model type Health states Cycle length	Perspective Time horizon	Outcomes	Costs	ICERs
				1-month				ICER incremental (LYG): £36,410 Base-case with PAS price ICER incremental (QALYs): £21,874 ICER incremental (LYG): £16,317
NICE[TA310] 2014	AFA GEF ERL	1L	CUA	PSM PFS, PD, and death 1-month	NHS and PSS Lifetime (10 years)	Total LYG GEF: 2.291 ERL: 2.223 AFA: 2.549 Incremental LYG ERL: -0.068 AFA: 0.326 Total QALYs GEF: 1.421 ERL: 1.423 AFA: 1.594 Incremental QALYs ERL: 0.002 AFA: 0.171	Incremental Costs ERL: £1,390 AFA: £1,723	Cost/LYG AFA vs ERL: £5,286 AFA vs GEF: £12,062 Cost/QALY AFA vs ERL: £10,079 AFA vs GEF: £17,933
NICE[TA192] 2010	GEF GEM+CARB GEM+CIS PAX+CARB VNB+CIS	1L	CUA	Markov model Treatment response, SD, PD, and death 3-weeks	NHS and PSS 5 years	Mean QALYs (discounted) GEF: 1.111 GEM+CARB: 0.934	Mean costs (discounted) GEM+CARB: £27,873 GEM+CIS: £27,401	Cost/QALY (discounted) GEM+CARB: £20,744 GEM+CIS: £28,633

Study name	Intervention/ comparator	Line of therapy	Study type	Model type Health states Cycle length	Perspective Time horizon	Outcomes	Costs	ICERs
						GEM+CIS: 0.966 PAX+CARB: 0.923 VNB+CIS: 0.888 Incremental QALYs (discounted) GEM+CARB: 0.177 GEM+CIS: 0.145 PAX+CARB: 0.187 VNB+CIS: 0.223	PAX+CARB: £27,902 VNB+CIS: £23,516 Incremental costs (discounted) GEM+CARB: £3,666 GEM+CIS: £4,138 PAX+CARB: £3,637 VNB+CIS: £8,023	PAX+CARB: £19,402 VNB+CIS: £35,992 Mean cost/QALY GEF vs doublet chemotherapy: £35,700

AFA: afatinib; CARB, carboplatin; CIS: cisplatin; CUA: cost-utility analysis; ERL: erlotinib; GEF: gefitinib; GEM: gemcitabine; ICER: incremental cost-effectiveness ratio; LYG: life years gained; OSB: osimertinib; PAX: paclitaxel; PD: progressive disease; PEM: pemetrexed; PFS: progression-free survival; PSM: partitioned survival model; QALYs: quality-adjusted life years; SD: stable disease; VNB: vinorelbine

[a]Unadjusted dataset specific to the ≥third-line population

B.3.2 Economic analysis

Patient population

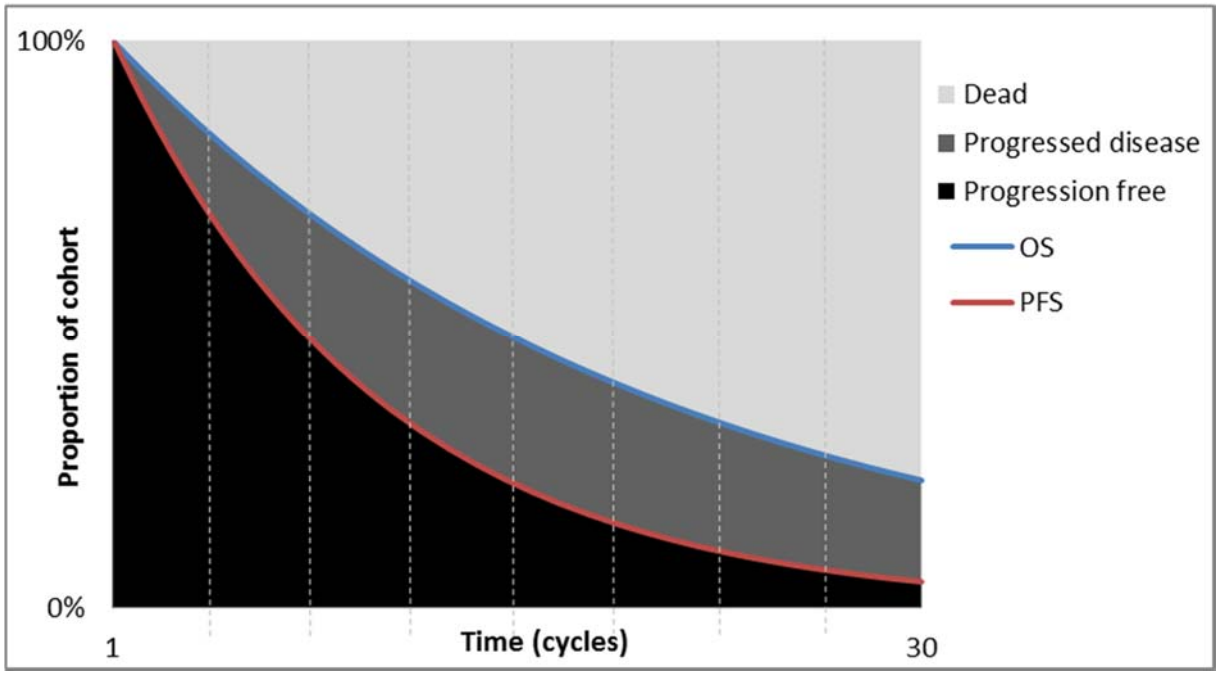
The economic evaluation considers patients with locally advanced or metastatic EGFR mutation-positive (Ex19del or L858R) NSCLC who have not received prior treatment. This is consistent with the population included in the FLAURA trial (page 62) used to support the EU marketing authorisation and with that defined in the NICE scope.

Model structure

In line with previous cost-effectiveness models submitted to NICE within advanced or metastatic NSCLC, a de-novo economic analysis was built as a partitioned-survival model (PSM) including three health states: progression free (PF), progressed disease (PD), and death.

In partitioned-survival modelling, the state occupancy of the simulated cohort is estimated by extrapolating the cumulative survival probability of PFS and OS to a lifetime horizon, and using the curves to estimate, at each time point of the simulation, the proportion of patients who are alive and have not progressed (% on the PFS curve), those who have died (1 - % on the OS curve) and those who are alive but have experienced disease progression (% on OS curve minus % on PFS curve). An illustration of the structure of the traditional three health states PSM is shown in Figure 32. The model does not require explicit transition probabilities, but instead relies on the PFS and OS data at each time point. PFS and OS are required endpoints for regulatory approval, and are therefore commonly reported in clinical trials.

Figure 32: Example of a partitioned survival analysis model



The partitioned survival approach allows for direct modelling of PFS and OS (respectively primary and secondary endpoints in FLAURA) based on trial observed events, generally providing accurate predictions for the within-trial period. However, a limitation of this model structure is that survival functions for OS and PFS are modelled independently and therefore the dependency between the endpoints beyond the trial period is ignored.

The key clinical events that patients may experience during their treatment for NSCLC are progression of disease and death which are associated with changes in HRQoL and resource use. Within the framework of the PSM, the health states of the model (PF, PD, death) appropriately reflect the natural course of the disease: the events are progressive, mutually exclusive, and irreversible (e.g. a patient who experiences disease progression and enters the PD state of the model, cannot recover their progression-free status, and return to the PF state). This approach is consistent with the definitions of PFS and OS from clinical trials, and the approaches used in previous NICE HTA submissions in advanced NSCLC and other advanced cancers.

Patients entered the model in the pre-progression state. Transitions to the death state could occur from either pre-progression or post-progression, while death was an 'absorbing state'. Progressive disease was defined following the RECIST 1.1 criteria, i.e., at least a 20% increase in the sum of diameters of target lesions, and an absolute increase of at least 5 mm, or appearance of one or more new lesions. Patients were assumed to receive up to two lines of subsequent active treatments and/or BSC (as relevant) following progression on first-line therapy; this was included in the PD health state.

In line with the NICE reference case, the model adopted an NHS/PSS perspective and included the resource use and costs associated with disease management, treatment acquisition, administration and adverse events. To fully capture the benefits of osimertinib and the comparators included in the analysis, a lifetime horizon (20 years) was used in the base-case setting.[110] This was considered to be appropriate taking into account the starting age of the cohort in the model (63 years, based on FLAURA) and the advanced nature of the disease (less than 2.5% of patients projected to be alive at 20 years either treatment arm).

A cycle length of 30 days was applied to facilitate comparability with other relevant treatments in the decision problem since the relevant EGFR-TKI treatments included in FLAURA have 30 tablet pack sizes.

Lifetable mid-cycle corrections (calculated as the average of the population in the respective state at the start and the end of the cycle) were applied to all costs and QALYs in the model, with the exception of:

- One-off costs for adverse events, which were applied at the beginning of the model

- Drug acquisition and administration costs, which were applied at the beginning of each model cycle

The reason for applying half-cycle correction is that using the state population at the start or end of a given cycle would result in either over- or under-estimation of the state population for that cycle. Mid-cycle correction was applied to mitigate this inherent bias caused by the use of discrete time in state transition models.[111]

NICE guidance recommends discounting of costs and outcomes to reflect their present value. In line with the NICE reference case, an annual discount rate of 3.5% was applied to costs and outcomes.

Table 32: Features of the economic analysis

Factor	Chosen values	Justification
Time horizon	Lifetime (20 years)	NICE reference case[110]
Health states	Progression-free, progressed, death	Reflects the aim of treatment: prolong survival and improve quality of life
Cycle length	30 days	Aligned with the pack size of all primary treatments
Half-cycle correction	Yes	Mitigates bias due to cycle length
Treatment discontinuation	Treatment allowed beyond progression	Reflects UK clinical practice and in line with FLAURA
Were health effects measured in QALYs; if not, what was used	QALYs (as well as LYs)	NICE reference case
Discount of 3.5% for utilities and costs	Yes	NICE reference case
Perspective (NHS/PSS)	Yes	NICE reference case

LYs, life-years; NHS, national health service; PSS, personal social services; QALYs, quality-adjusted life years

Intervention technology and comparators

For people with locally advanced or metastatic NSCLC who test positive for the activating EGFR-TK mutation and who have not previously received any treatment, NICE guidance recommends the tyrosine kinase inhibitors (TKIs) afatinib, erlotinib, and gefitinib.[105-107] In line with the NICE scope,[110] these were the comparators included in the economic model.

The NICE committee of the Technology Appraisal for erlotinib in the first-line setting in EGFRm patients, having taken into consideration the clinical specialists' view and the similarities between the treatments, concluded that there was insufficient evidence to demonstrate a difference in clinical effectiveness between erlotinib and gefitinib.[106] Further to this, the CTONG 0901 study directly compared erlotinib with gefitinib in NSCLC patients. Subgroup analysis in EGFRm-positive patients showed that there was insufficient evidence to indicate a significant difference for PFS (hazard ratio [HR]=0.96 [95% confidence interval (CI): 0.69, 1.35]) or OS (HR=0.98 [95% CI: 0.67, 1.42]) between erlotinib and gefitinib.[112] A previously published NMA also indicated that there was no significant difference in PFS for the comparison of erlotinib versus gefitinib (HR: 0.87 [95% credible interval: 0.72, 1.04]).[94]

Based on this conclusion, an assumption of equal efficacy and safety between gefitinib and erlotinib was made within the cost-effectiveness analysis and data from the SoC arm in FLAURA was used to model the two first-generation TKIs.

In the LUX-Lung 7 study, the authors concluded that there was no statistically significant difference in OS between afatinib versus gefitinib (HR=0.86 [95% CI: 0.66, 1.12]).[22] Consistent findings were found across key patient subgroups, including age, gender, ethnicity (Asian versus non-Asian), and EGFR mutation type (exon 19 deletion versus L858R). For PFS IA, afatinib was associated with an HR of 0.78 (95% CI 0.61-0.99) versus gefitinib. However, as noted in the publication of LUX-Lung 7, at the time of trial concept and initiation, insufficient data were available to construct a formal testing strategy regarding differences in effect of afatinib and gefitinib in this treatment setting. Therefore, the study was set up as an exploratory open-label phase 2B trial with sufficient patient numbers to broadly explore the differences between the two compounds in terms of progression-free survival, time-to-treatment failure and overall survival. Moreover, a previous mixed treatment comparison used to inform TA310[107] concluded that, although a trend in favour of afatinib over both erlotinib and gefitinib was observed for PFS and OS, the treatment differences were not statistically significant. Furthermore, a recently published meta-analysis concluded that there was little evidence to suggest that afatinib has greater efficacy, especially in terms of overall survival benefit, than either erlotinib or gefitinib in the first-line treatment of EGFRm NSCLC.[112] Therefore, in the cost-effectiveness analysis it was assumed equal efficacy and safety between afatinib and the SoC TKI arm (erlotinib/gefitinib) from FLAURA.

Osimertinib was implemented in the model as per licensed dosing regimen[113] (i.e. 80 mg once daily). The dosing and administration frequencies for the comparators in the evaluation are in line with their marketing authorisations and UK clinical practice.

B.3.3 Clinical parameters and variables

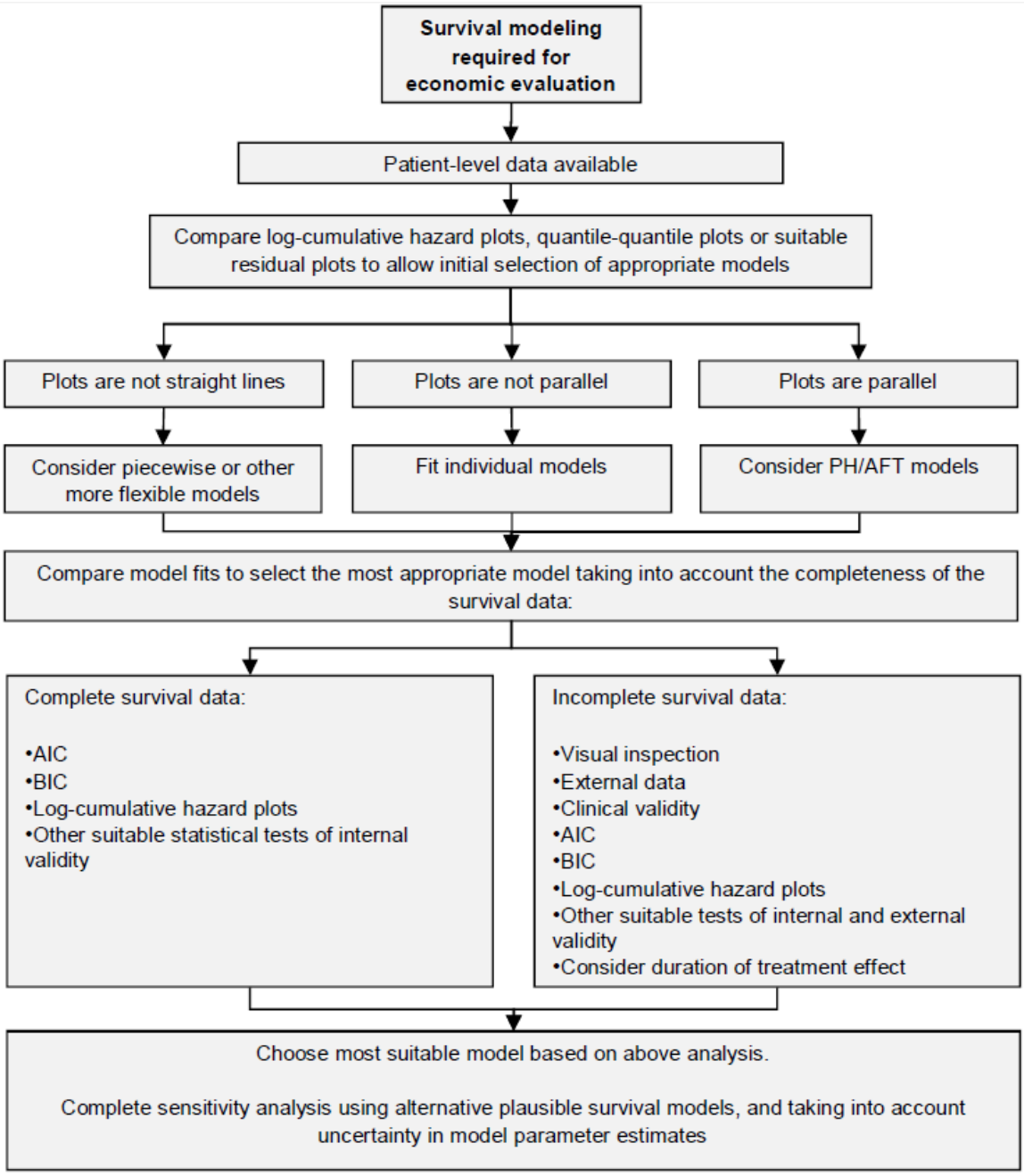
Overall method of modelling survival

The primary data source for the cost-effectiveness model was the data from the FLAURA study (ITT population). The follow-up period in FLAURA was shorter than the model time horizon, and extrapolation was required such that survival data could be usefully incorporated in the model.

The survival analysis of PFS and OS was conducted using the approach outlined in the Technical Support Document for survival analysis published by the NICE Decision Support Unit.[114] The model selection process is presented graphically in Figure 33. In summary:

- The hazards are assessed through plots generated from the patient level data
- Given the conclusions from the hazard plots,
    - a **dependent model** is applied when there is **no clear violation of the proportional hazards** assumption
    - **independent models** are applied when **the proportional hazards assumption is violated**
    - **piecewise/more complex models** may need to be considered when there are **distinct changes in hazards over time**
- Following the selection of model type, in the presence of incomplete survival data, which is the case with FLAURA, the most plausible parametric models are selected based upon statistical and visual fit to the observed data and the clinical plausibility of the extrapolation

Figure 33: Survival model selection process recommended by NICE



Modelling progression-free survival

A summary of the non-parametric data for PFS from FLAURA is presented below in Table 33.

Table 33: PFS summary data

	Osimertinib (n=279)	SoC (n=277)
Total events (%)	136 (48.7%)	206 (74.4%)
Median, months (95% CI)	18.89 (15.21, 21,42)	10.15 (9.56, 11.14)

PFS: progression-free survival; SoC: standard of care

The assessment of the proportional hazard assumption concluded that it was appropriate to assume proportional hazards between PFS osimertinib and SoC. This was observed in the following plots:

- Parallel lines were observed in the log cumulative hazard plot (Figure 34). Based on visual inspection from log time 1 (ignoring prior events likely uninfluenced by treatment) the observations appeared parallel
- In the Cox-Snell residuals (Figure 35) a slope equal to one was generally observed, indicating that a Cox model fitted the data well

Therefore, dependent parametric models with a treatment coefficient for osimertinib were considered in the base-case analysis for PFS.

Figure 34: Log cumulative hazard plot (PFS; FLAURA)

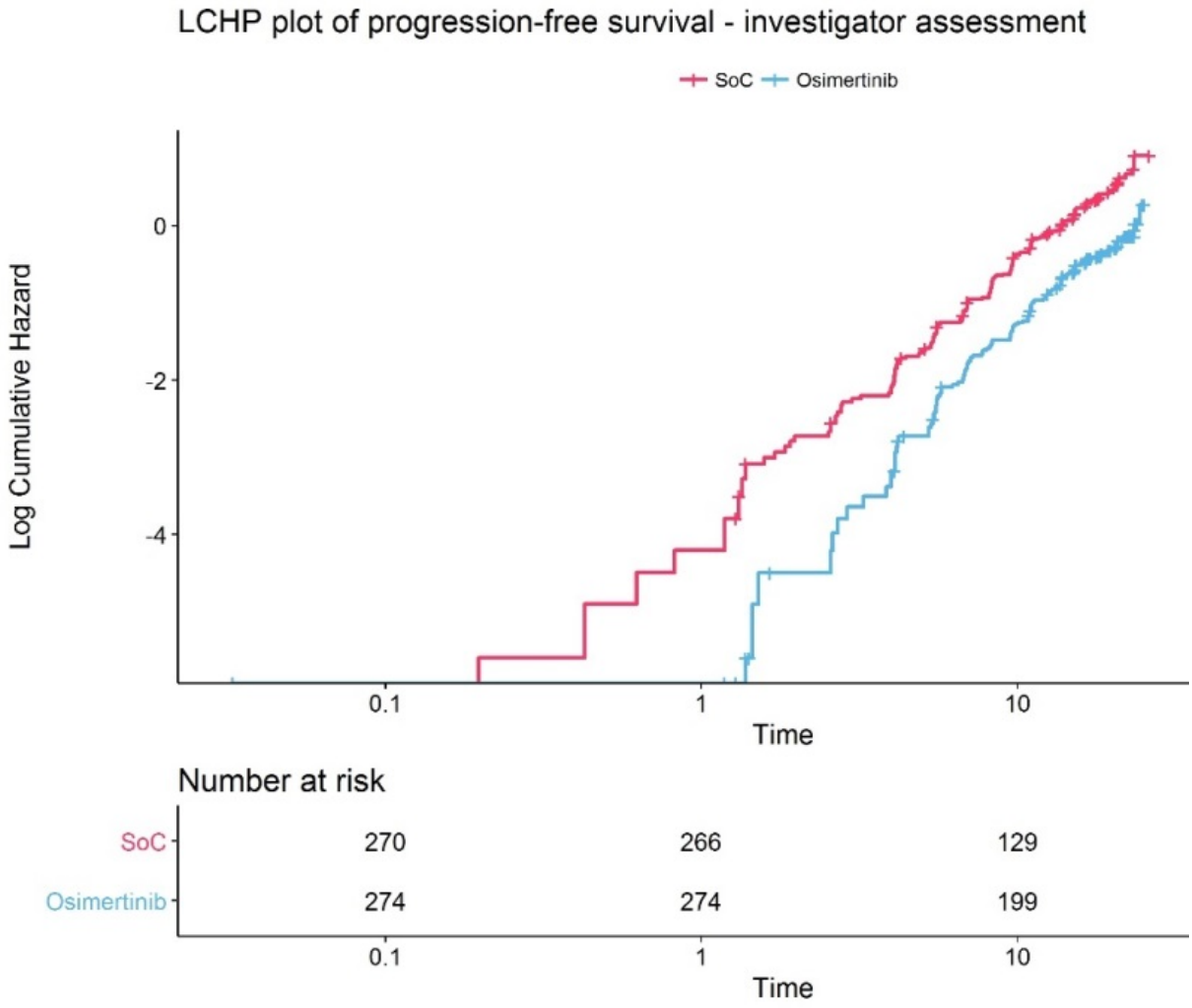
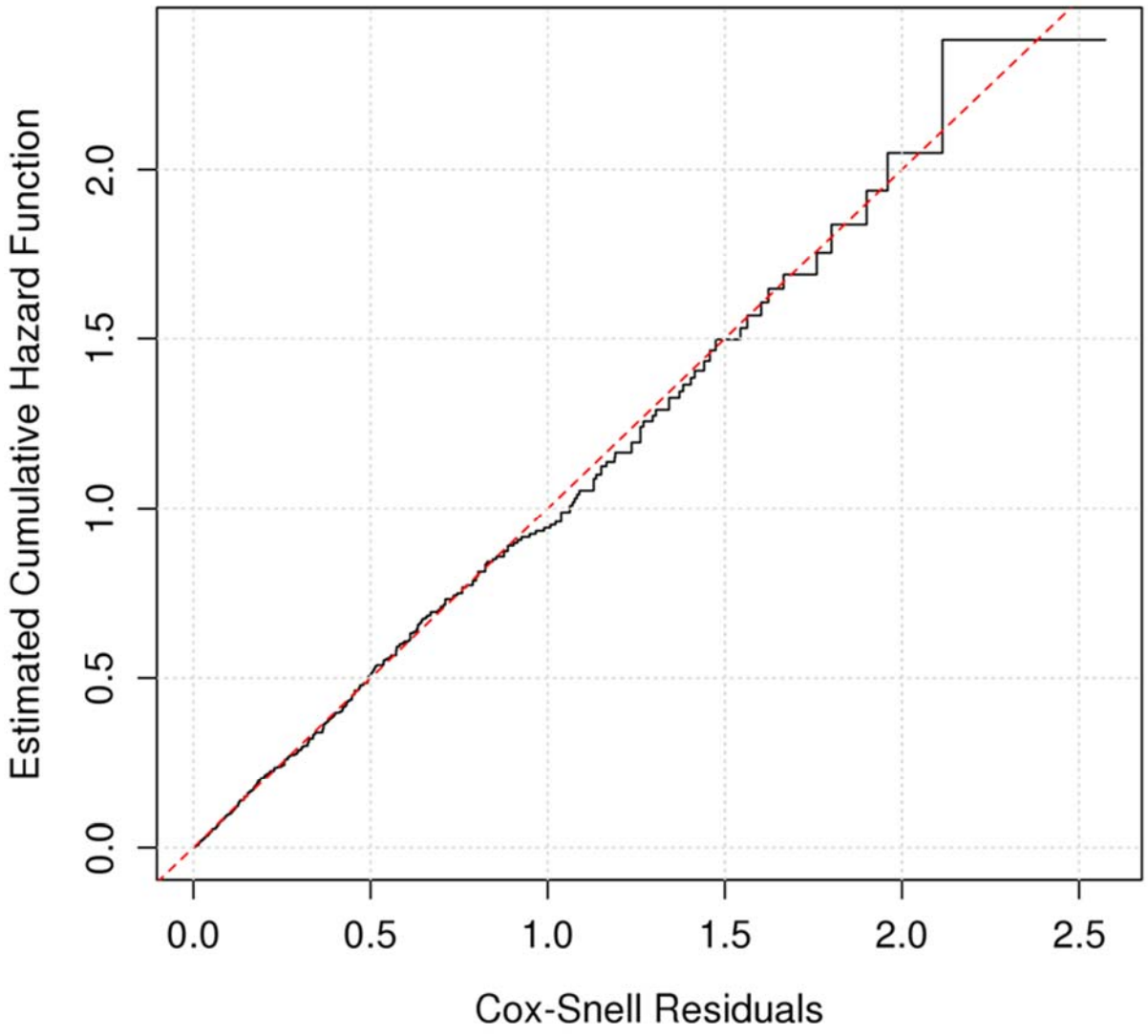
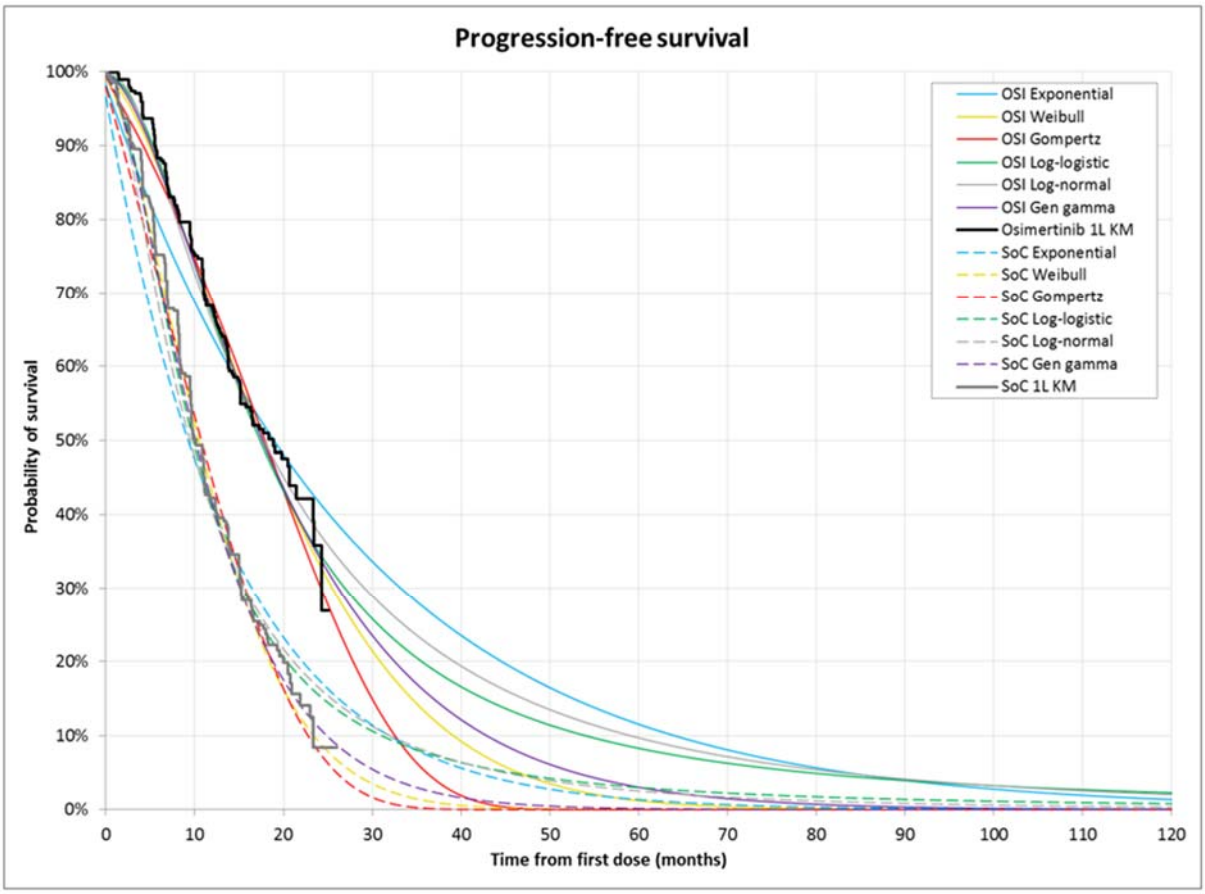


Figure 35: Cox-Snell Residuals (PFS, FLAURA)



The fitted models compared to the observed data are presented in Figure 36. The statistical fit of the models is presented in Table 34; mean, median and landmark rates are presented in Table 35 and Table 36 for osimertinib and SoC, respectively.

Figure 36: Fitted parametric models (PFS; dependent; FLAURA)



Given that 342 progression events occurred (61.5%) across both arms the fit to the observed data was good. The generalised gamma, Weibull and log-logistic models have relatively similar statistical fits (Akaike information criterion [AIC]/Bayesian Information Criterion [BIC]) and visual fits. There is no clear over or underestimation apart from slight underestimation for the first 5 months and months 18 to 23 for osimertinib, however this was the case for all parametric models.

The remaining parametric models have worse statistical and visual fits to the observed data. The exponential model had a significantly worse statistical fit (highest AIC/BIC) and a poor visual fit (underestimation followed by overestimation). The Gompertz model also has a relatively high AIC/BIC compared to other models and underestimates the start of the KM curves especially for osimertinib and then underestimates PFS for both treatments beyond 18 months. The log-normal model has a relatively high AIC/BIC compared to the three best fitting models. It has a good visual fit to osimertinib but underestimates PFS for the SoC TKI arm up to 10 months and then overestimates PFS beyond 18 months.

Table 34: Goodness of fit statistics (PFS; dependent; FLAURA)

	Exponential	Weibull	Gompertz	Log-logistic	Log-normal	Generalised gamma

AIC	2683.56	2612.29	2636.27	2612.84	2626.37	2611.1
Rank	6	2	5	3	4	1
BIC	2692.2	2625.25	2649.23	2625.8	2639.34	2628.39
Rank	6	1	5	2	4	3

AIC: Akaike information criterion; BIC: Bayesian information criterion; PFS: progression-free survival

Table 35: Osimertinib predicted and observed mean, median and landmark rates (PFS; dependent; FLAURA)

	Exponential	Weibull	Gompertz	Log-logistic	Log-normal	Generalised gamma	FLAURA
Mean	28.01	20.75	18.77	27.00	27.72	21.96	--
Median	19.71	17.74	18.73	17.74	18.73	17.74	18.89
% at 1 year	64.4%	68.4%	69.4%	67.5%	66.6%	67.9%	68.2%
% at 2 years	42.2%	34.2%	31.7%	35.5%	38.1%	35.1%	35.8%
% at 3 years	27.7%	13.7%	5.7%	20.1%	23.1%	16.5%	NR
% at 4 years	18.2%	4.6%	0.1%	12.6%	14.8%	7.4%	NR
% at 5 years	11.9%	1.3%	0.0%	8.5%	10.0%	3.2%	NR
% at 10 years	1.4%	0.0%	0.0%	2.3%	2.1%	0.0%	NR

PFS: progression-free survival

Table 36: SoC predicted and observed mean, median and landmark rates (PFS; dependent; FLAURA)

	Exponential	Weibull	Gompertz	Log-logistic	Log-normal	Generalised gamma	FLAURA
Mean	14.07	12.51	12.16	15.98	15.21	12.84	--
Median	9.86	10.84	10.84	9.86	9.86	10.84	10.15
% at 1 year	41.7%	43.6%	45.3%	41.4%	40.9%	42.2%	42.3%
% at 2 years	18.0%	9.6%	8.4%	15.8%	16.8%	11.5%	8.4%
% at 3 years	7.7%	1.3%	0.2%	7.9%	8.2%	2.8%	NR
% at 4 years	3.3%	0.1%	0.0%	4.7%	4.4%	0.7%	NR
% at 5 years	1.4%	0.0%	0.0%	3.1%	2.6%	0.1%	NR
% at 10 years	0.0%	0.0%	0.0%	0.8%	0.3%	0.0%	NR

PFS: progression-free survival; SoC: standard of care

The extrapolations from the three best fitting models were assessed against previous first-line EGFR-TKI trials. LUX-Lung 7[21] and WJTOG 3405[115] were the only studies that reported PFS beyond 3 years however, given that the observed 2-year PFS from FLAURA (8.4%) was most comparable with the gefitinib arm from LUX-Lung 7 (~7.5%), the 3-year PFS rate reported in the gefitinib arm (~4.7%) of LUX-lung 7 was used to assess the plausibility of the parametric models (WJTOG 2-year: ~13.9%; 3-year: ~7.6%).

Therefore, the generalised gamma was applied in the base-case (2.8%), as the Weibull may underestimate (1.3%) and the log-logistic may overestimate (7.9%) the 3-year PFS for SoC. The Weibull and log-logistic models were considered in scenario analyses to test the impact of alternative survival model choices.

Table 37: Observed survival from previous clinical trials

Study	Treatment	% at 1 year	% at 2 years	% at 3 years
Clinical trials				
FLAURA	Erlotinib/Gefitinib	42.3%	8.4%	--
LUX-Lung 7	Gefitinib	41.3%	7.5%	4.7%
WJTOG 3405	Gefitinib	42.5%	13.9%	7.2%
FLAURA most plausible extrapolations				
Generalised gamma (base-case)	Erlotinib/Gefitinib	42.2%	11.5%	2.8%
Weibull	Erlotinib/Gefitinib	43.6%	9.6%	1.3%
Log-logistic	Erlotinib/Gefitinib	41.4%	15.8%	7.9%

Modelling overall survival

A summary of the non-parametric data for OS from FLAURA is presented in Table 38.

Table 38: OS summary data

	Osimertinib (n=279)	SoC (n=277)
Total events (%)	58 (20.8%)	83 (30.0%)
Median months (95% CI)	NR (NR, NR)	NR (NR, NR)

NR: not reached; OS: overall survival; SoC: standard of care

In the SoC arm of FLAURA, a total of 62 patients received osimertinib as subsequent therapy, including 55 patients as second-line therapy (26% of patients that progressed). Since osimertinib is recommended for CDF funding until March 2019, it was not considered necessary to adjust for crossover to second-line osimertinib as it more closely reflects the treatment pathway for patients in England and Wales.[7] It was further confirmed by UK clinical experts that osimertinib is generally the treatment of choice in EGFR and T790M patients progressing after a TKI.

Upon assessment of the proportional hazard assumption the following conclusions were made:

- Straight parallel lines were observed beyond ~8 months in the log cumulative hazard plot where the data are most prevalent (Figure 37)
- The Cox-Snell residuals (Figure 38) had a slope equal to one for the majority of the plot, indicating that a Cox model fitted the data well

- The KM curves show a clear separation up to ~5 months, after which they start converging reaching a minimum separation at ~8 months. Beyond this point the two curves diverge steadily over time (Figure 39)

Therefore, although no clear violation of proportional hazard was identified, it was considered appropriate to use a piecewise model using observed data up to 7.9 months (time point beyond which the log-cumulative hazard plots for osimertinib and SoC become parallel) and fitting dependent parametric models with a treatment coefficient for osimertinib to the remaining data.

Figure 37: Log cumulative hazard plot (OS; FLAURA)

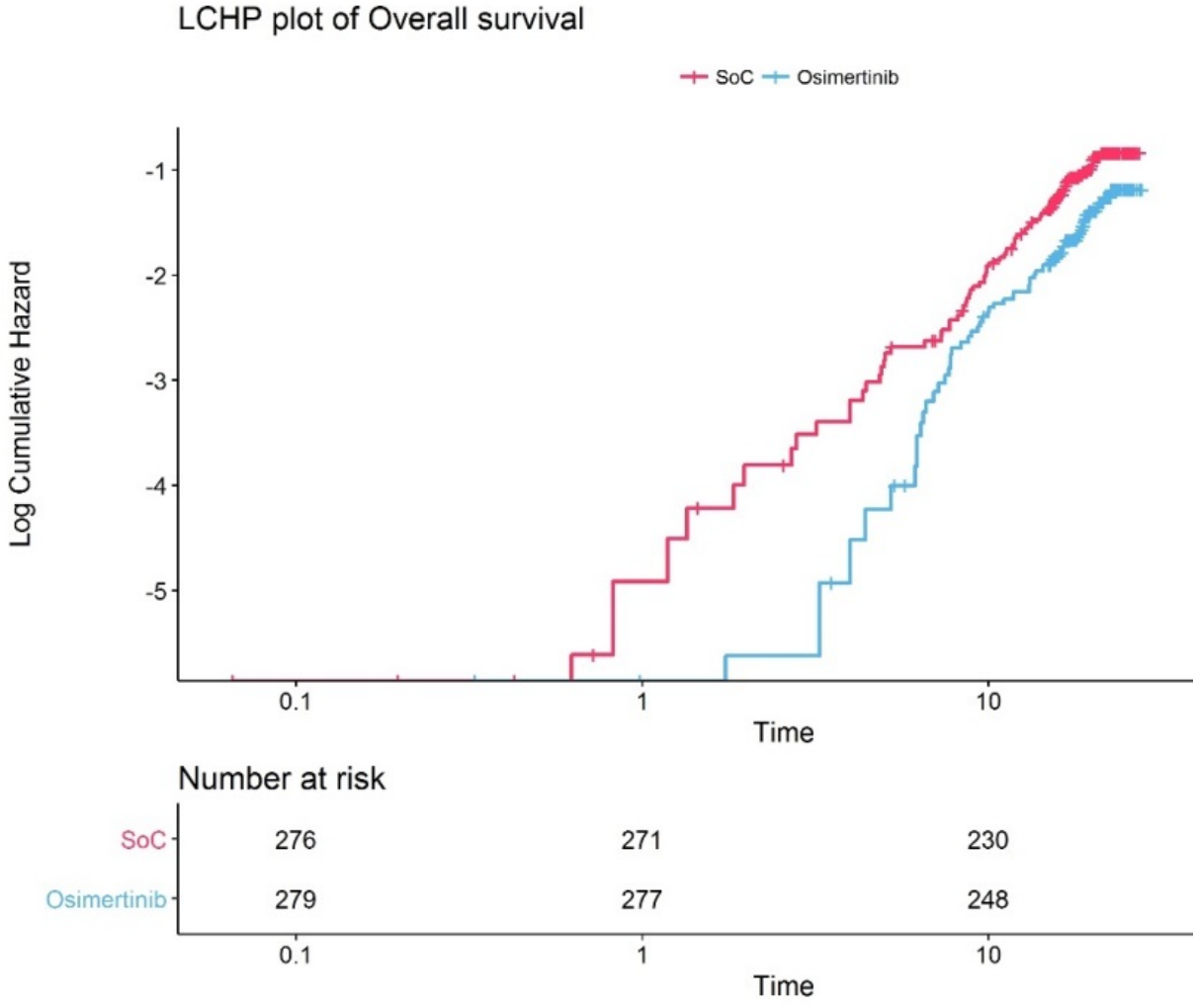
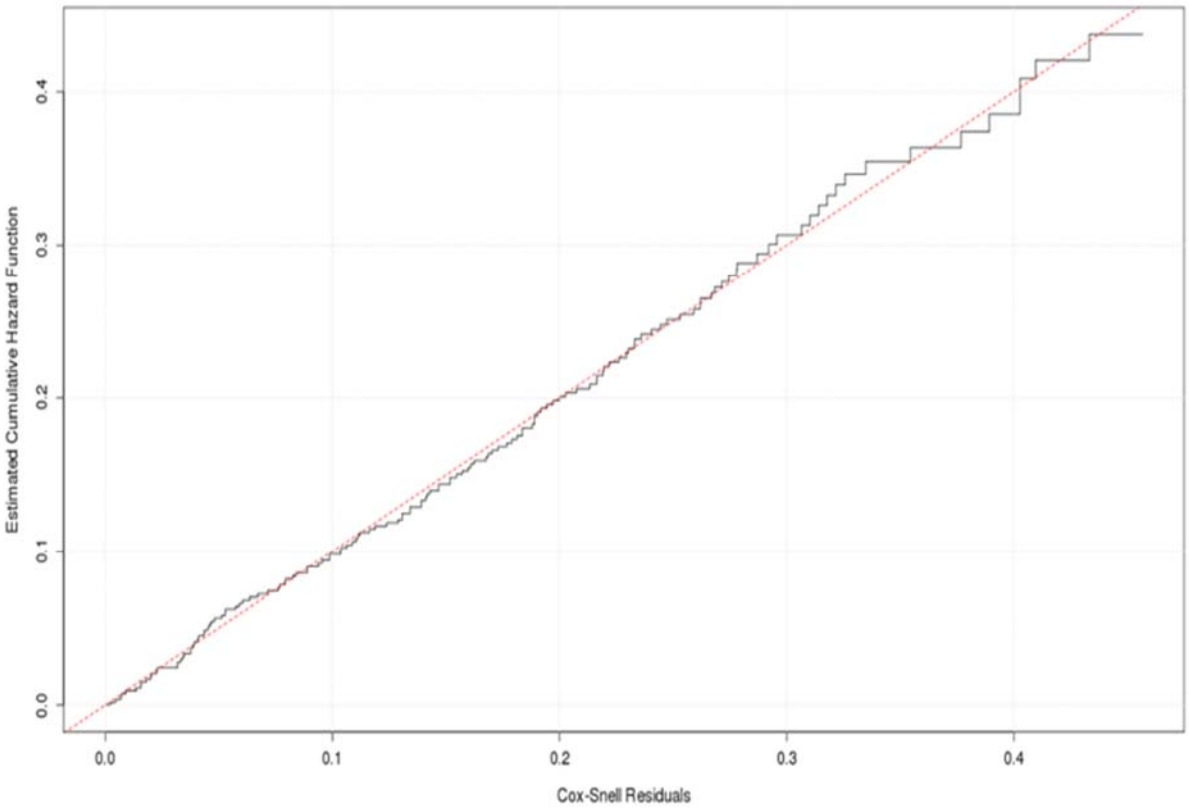


Figure 38: Cox-Snell Residuals (OS, FLAURA)



Piecewise approach

The statistical fit to the observed data is relatively uninformative given the low number of death events observed in FLAURA at the first data cut-off. All models have good visual fits to the observed data with the exponential model associated with the lowest AIC/BIC. The Weibull, Gompertz, log-logistic and log-normal distributions have similar goodness of fit statistics while the generalised gamma distribution has the highest AIC/BIC (Table 39).

Table 39: Goodness of fit statistics (OS; piecewise dependent; FLAURA)

	Exponential	Weibull	Gompertz	Log-logistic	Log-normal	Generalised gamma
AIC	1092.23	1094.15	1094.19	1093.53	1095.13	1095.56
Rank	1	3	4	2	5	6
BIC	1100.70	1106.86	1106.91	1106.24	1107.85	1112.52
Rank	1	3	4	2	5	6

AIC: Akaike information criterion; BIC: Bayesian information criterion; OS: overall survival

Figure 39: Fitted parametric models (OS; piecewise dependent; FLAURA)

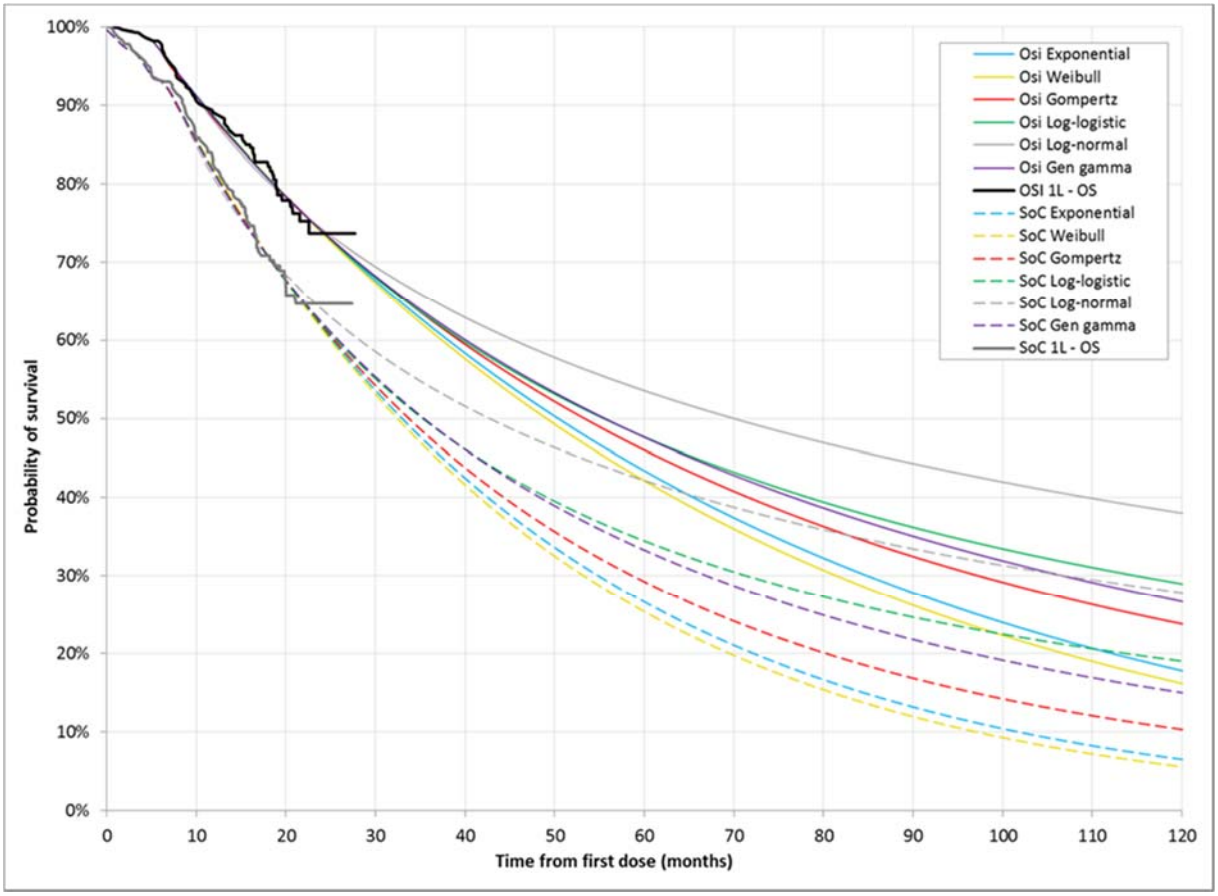


Table 40: Osimertinib predicted and observed mean, median and landmark rates (OS; piecewise dependent; FLAURA)

	Exponential	Weibull	Gompertz	Log-logistic	Log-normal	Generalised gamma	FLAURA
Mean	69.58	66.96	80.76	90.61	107.68	85.28	--
Median	51.25	49.28	54.21	56.18	69.98	56.18	NR
% at 1 year	88.6%	88.7%	88.5%	88.8%	88.2%	88.6%	89.1%
% at 2 years	74.3%	74.2%	74.5%	74.3%	74.6%	74.4%	73.7%
% at 3 years	62.4%	61.8%	63.2%	63.3%	65.7%	63.6%	NR
% at 4 years	52.3%	51.4%	54.0%	54.8%	59.1%	55.0%	NR
% at 5 years	43.9%	42.7%	46.5%	48.1%	53.9%	48.1%	NR
% at 10 years	18.0%	16.4%	23.9%	29.1%	38.1%	26.8%	NR

OS: overall survival

Table 41: SoC predicted and observed mean, median and landmark rates (OS; piecewise dependent; FLAURA)

	Exponential	Weibull	Gompertz	Log-logistic	Log-normal	Generalised gamma	FLAURA
Mean	46.29	44.39	52.45	67.94	84.66	60.23	--
Median	33.51	31.54	34.50	35.48	43.37	35.48	NR

% at 1 year	81.9%	82.2%	81.8%	81.8%	81.0%	81.7%	82.5%
% at 2 years	62.2%	61.9%	62.4%	62.5%	64.3%	62.7%	64.7%
% at 3 years	47.1%	46.4%	48.1%	49.8%	54.4%	49.9%	NR
% at 4 years	35.8%	34.7%	37.6%	41.1%	47.6%	40.7%	NR
% at 5 years	27.1%	25.9%	29.7%	34.8%	42.5%	33.7%	NR
% at 10 years	6.7%	5.7%	10.5%	19.1%	27.9%	15.1%	NR

OS: overall survival; SoC: standard of care

Given the uncertainty in the extrapolated data from FLAURA, external data were explored to identify the most clinically plausible parametric model. Among the studies identified in the clinical systematic literature review, LUX-Lung 7 and ARCHER-1050 were the only trials in which T790M mutation-positive patients received osimertinib or other 3rd generation TKIs after progression on first-line EGFR-TKI therapy. However, the use of 3rd generation TKIs in patients receiving at least one subsequent anti-cancer treatment after progression was significantly lower than that observed in FLAURA. In older trials of first-line EGFR-TKI treatments, osimertinib and other 3rd generation TKIs were not available for patients who acquired the T790M resistance mutation. This was considered a key criterion for the selection of the relevant studies, given the number of patients who received second-line osimertinib in the SoC arm in FLAURA and the impact on survival associated with osimertinib in T790M patients progressing after a 1st or 2nd generation TKI shown in AURAext/2 and AURA3.[97] Observed survival rates from LUX-Lung 7, ARCHER-1050 and FLAURA and the use of osimertinib following progression are reported in Table 42.

Table 42: Observed survival from previous clinical trials

Study	Treatment	Patients treated with a 3rd generation TKI after progression	Patients receiving at least one subsequent therapy	Progressed patients treated with osimertinib*	% at 1 year	% at 2 years	% at 3 years
FLAURA	Erlotinib/ gefitinib	62†	129	48%	83%	65%	--
LUX-Lung 7[116]	Gefitinib	13‡	120	<11%	84%	51%	32%
ARCHER 1050[72]	Gefitinib	25‡	140	<18%	86%	56%	41%

*Proportion of progressed patients treated with osimertinib = # patients treated with osimertinib/# progressed patients who received at least one subsequent therapy

†Includes osimertinib only

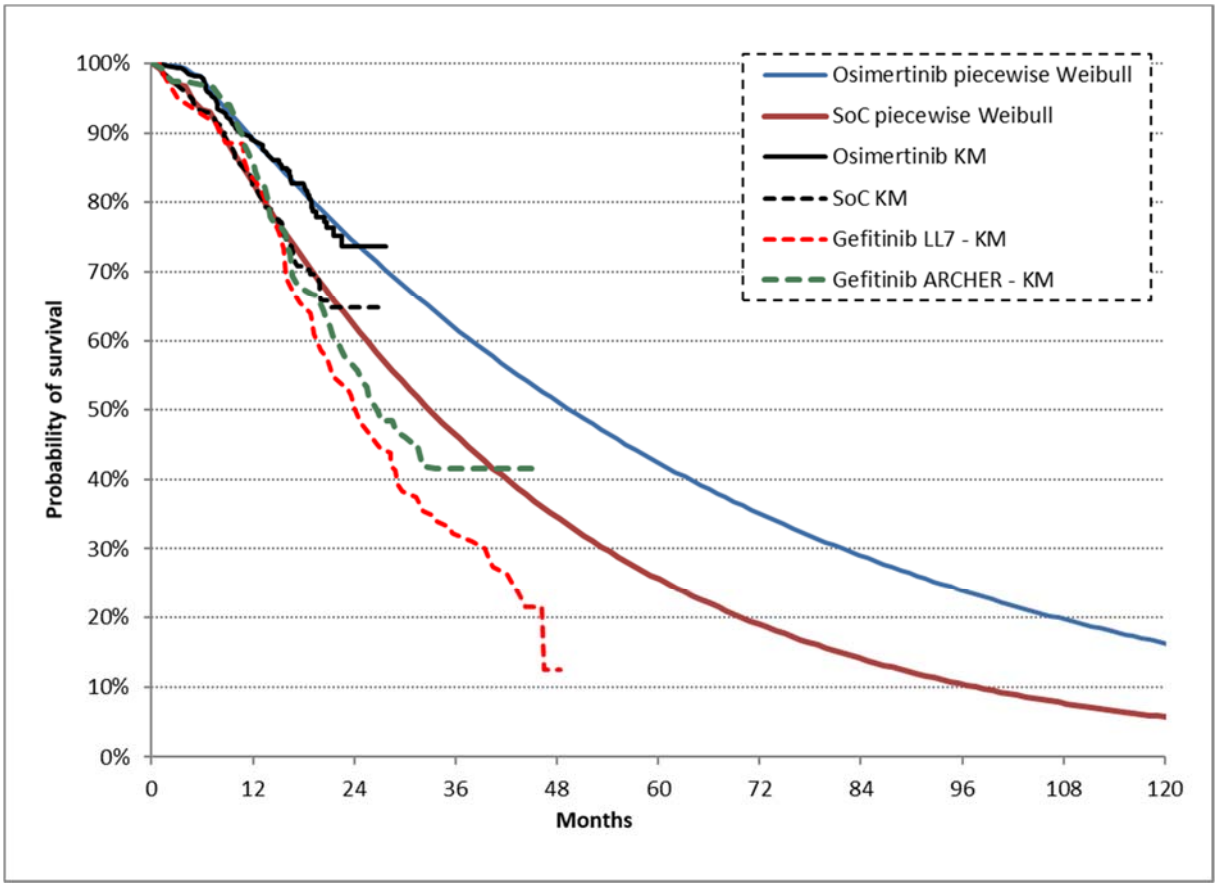
‡Includes osimertinib and other 3rd generation EGFR TKIs

The trials were relatively balanced in terms of baseline characteristics (age, gender, ECOG, stage IV, exon19/21) however, less than 11% of all the patients who received subsequent anti-cancer patients in LUX-Lung 7 and less than 18% in ARCHER-1050 received osimertinib as subsequent therapy compared to 48% in FLAURA. Moreover, the presence of CNS metastases was an exclusion criterion in ARCHER-1050, which may explain the slightly higher reported rates of survival for the gefitinib arm relative to the LUX-Lung 7 study. Both trials reported lower 2-year survival rates for the gefitinib arm compared with FLAURA and this is likely to be due to the lower use of osimertinib as subsequent treatment.

Given the limitations above in the use of LUX-Lung 7 and ARCHER 1050 to validate the long-term extrapolation for the SoC arm in FLAURA and the absence of any other available longer-term data on the use of first-line osimertinib in clinical practice, external validation of the survival estimates for both osimertinib and SoC TKI in terms of clinical plausibility is highly challenging. All piecewise dependent models showed consistent separation over time in the OS curves between osimertinib and SoC. This trend can be considered plausible given the divergence of the KM curves observed after ~8 months in the FLAURA study, the significant PFS benefit associated with osimertinib which was maintained post-progression as captured in the PFS2 and TSST endpoints (Section B.2.6) as well as the protective CNS effect demonstrated by osimertinib compared to the lack of adequate CNS penetration observed with 1st and 2nd generation EGFR-TKIs. However, in light of the immature OS data available at the time of analysis, it was considered appropriate to apply the most conservative piecewise OS extrapolation, the Weibull distribution, for both treatment arms in the base-case analysis.

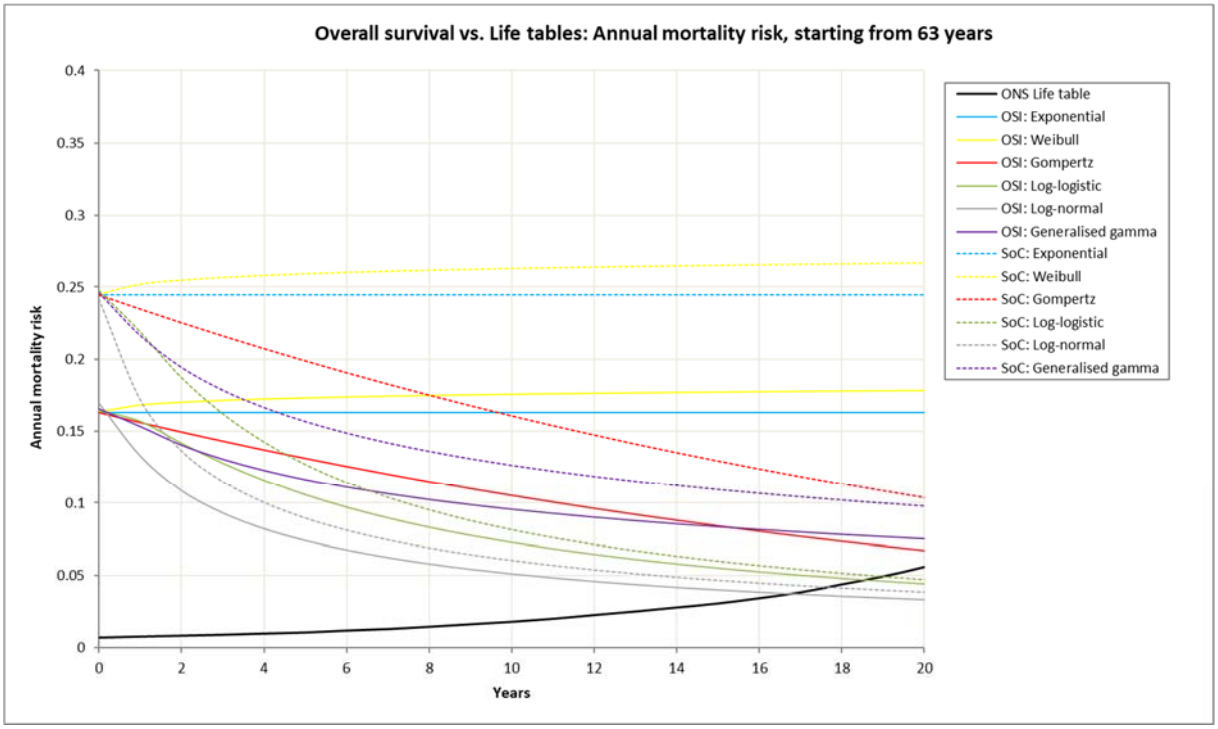
Figure 40 shows the KM curve for the gefitinib arm from LUX-Lung 7 and ARCHER-1050 and the base-case extrapolation (piecewise Weibull) for osimertinib and SoC from FLAURA used in the model.

Figure 40: Observed OS data from FLAURA (both arms), LUX-Lung 7 and ARCHER-1050 (gefitinib arm), and Weibull piecewise model



Further supportive evidence for the selection of the piecewise dependent Weibull model was observed in Figure 41, which compares the annual mortality rate of each piecewise parametric model and the age/gender adjusted annual mortality from UK life tables.[117] The log-logistic and log-normal models predicted long term annual mortality rates lower than those of the general population, which was considered implausible given the expected prognosis for late stage cancer patients, while the Weibull model is associated with a mortality risk that increases over time. In addition, the exponential model, which has the lowest AIC/BIC, predicts similar mortality rates to the Weibull distribution. Therefore, given that the piecewise dependent exponential model had the best statistical fit and produced similar, clinically plausible extrapolations as the Weibull model, this was explored in scenario analysis.

Figure 41: Annual mortality rates predicted by parametric models (piecewise dependent; FLAURA)



Fully parametric approach

As described in the previous section, given that there was no clear violation of proportional hazards upon inspection of the log cumulative hazard plot (Figure 37) and the Cox-Snell residuals (Figure 38), fully parametric dependent models were explored in scenario analyses.

The fitted parametric models are presented in Figure 42, the statistical fit of the models is presented in Table 43 and mean, median and landmark rates are presented in Table 44 and Table 45 for osimertinib and SoC respectively. The log-logistic and log-normal models are associated with the lowest AIC/BIC followed by the Weibull and the generalised gamma models. The exponential model has the worst statistical and visual fit to the observed data while the Gompertz distribution predicts all patients in both arms to be dead before 7 years.

Similar to the piecewise OS model, the dependent Weibull model is associated with an annual mortality risk that increases over time, while all other extrapolations (except the Gompertz function) show a constant or declining mortality risk over time (see Figure 43). Therefore, the fully parametric dependent Weibull distribution was explored in a sensitivity analysis together with the log-logistic model on the basis of being the best fitting (AIC/BIC) model.

Figure 42: Fitted parametric models (OS; dependent; FLAURA)

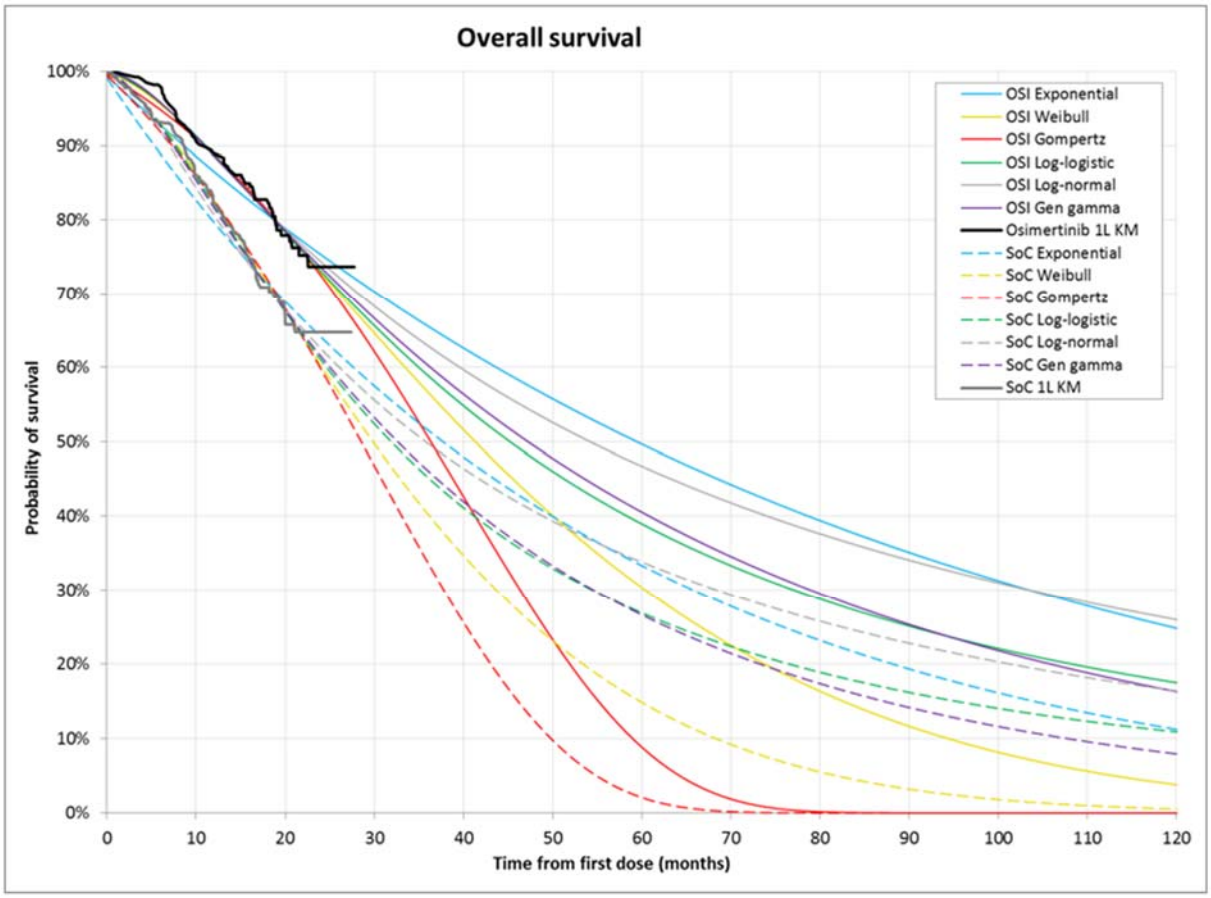


Table 43: Goodness of fit statistics (OS; dependent; FLAURA)

	Exponential	Weibull	Gompertz	Log-logistic	Log-normal	Generalised gamma
AIC	1468.77	1450.23	1458.37	1448.39	1449.53	1450.25
Rank	6	3	5	1	2	4
BIC	1477.41	1463.19	1471.34	1461.35	1462.49	1467.53
Rank	6	3	5	1	2	4

AIC: akaike information criterion; BIC: bayesian information criterion; OS: overall survival

Table 44: Osimertinib predicted and observed mean, median and landmark rates (OS; dependent; FLAURA)

	Exponential	Weibull	Gompertz	Log-logistic	Log-normal	Generalised gamma	FLAURA
Mean	81.17	48.60	36.27	69.59	84.58	67.20	--
Median	60.12	41.40	36.47	45.34	54.21	47.31	NR
% at 1 year	86.7%	89.1%	89.0%	89.1%	88.8%	88.9%	89.1%
% at 2 years	75.6%	73.3%	73.0%	73.5%	74.7%	74.0%	73.7%
% at 3 years	66.0%	57.3%	51.7%	59.5%	63.4%	60.8%	NR
% at 4 years	57.5%	43.0%	28.2%	48.2%	54.4%	49.9%	NR
% at 5 years	50.2%	31.1%	9.8%	39.5%	47.2%	41.1%	NR

% at 10 years	25.0%	3.9%	0.0%	17.6%	26.2%	16.5%	NR

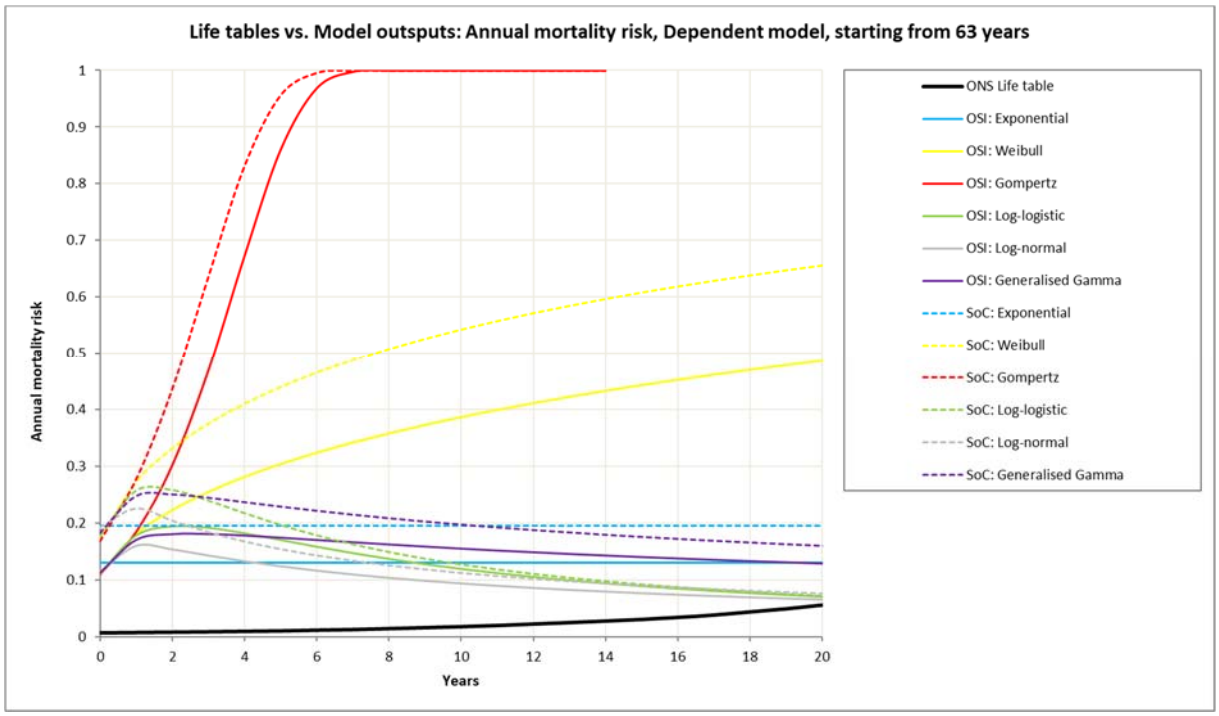
OS: overall survival

Table 45: SoC predicted and observed mean, median and landmark rates (OS; dependent; FLAURA)

	Exponential	Weibull	Gompertz	Log-logistic	Log-normal	Generalised gamma	FLAURA
Mean	54.39	35.26	29.21	52.82	62.84	48.11	--
Median	38.44	30.55	28.58	32.53	36.47	33.51	NR
% at 1 year	80.0%	83.1%	83.0%	82.4%	81.0%	82.0%	82.5%
% at 2 years	64.5%	60.9%	60.5%	61.5%	63.0%	62.0%	64.7%
% at 3 years	52.0%	41.1%	34.8%	45.8%	50.2%	46.7%	NR
% at 4 years	42.0%	25.9%	13.3%	34.9%	41.1%	35.4%	NR
% at 5 years	33.9%	15.5%	2.5%	27.3%	34.2%	27.1%	NR
% at 10 years	11.4%	0.6%	0.0%	11.0%	16.5%	8.0%	NR

OS: overall survival; SoC: standard of care

Figure 43: Annual mortality rates predicted by parametric models (dependent; FLAURA)



Safety

Adverse events (AEs) were included in the evaluation to account for the potential cost and quality of life (QoL) burden of experiencing events whilst on treatment. The incidence rates for erlotinib, gefitinib and afatinib were assumed to be equal to those reported in FLAURA for the SoC arm. Although, afatinib has been shown to be associated with higher rates of grade 3+ AEs including diarrhea, rash/acne and fatigue compared with gefitinib,[118] given the anticipated limited impact of these events in the model, which are usually resolved within the first monthly cycle, it was not considered worthwhile running additional scenario analyses exploring treatment-specific AEs for each EGFR-TKI separately.

The adverse events rates used in the model are reported in Table 46. The inclusion criteria applied was treatment related adverse event of grade ≥3, according to the CTCAE occurring in >1% of patients in any treatment arm. The unit cost and the disutility associated with each AEs were assumed to be the same for all treatments, therefore the difference in terms of AE costs and disutilities were driven by the rates presented in Table 46.

Table 46: Incidence rates of adverse events

	Osimertinib	SoC
Sample size (n)	279	277
Alanine aminotransferase increased	1 (0.4%)	25 (9.0%)
Aspartate aminotransferase increased	2 (0.7%)	12 (4.3%)
Diarrhoea	6 (2.2%)	7 (2.5%)
Fatigue[1]	4 (1.4%)	4 (1.4%)
Rash or acne[2]	6 (2.2%)	27 (9.7%)
Source	FLAURA[26]	

SoCL: standard of care

[1]Grouped term including the following reported preferred terms: asthenia, fatigue, and lethargy

[2]Grouped term including the following reported preferred terms: acne, blister, dermatitis, dermatitis acneiform, dermatitis bullous, dry skin, drug eruption, eczema, erythema, exfoliative rash, folliculitis, Henoch-Schonlein purpura, rash, rash erythematous, rash follicular, rash macular, rash maculopapular, rash popular, rash pruritic, rash pustular, skin erosion, skin exfoliation, skin fissures, skin irritation, skin lesion, skin reaction, skin toxicity, skin ulcer, toxic epidermal necrolysis and urticaria

AEs were applied as one-off events at the start of the simulation. An alternative approach is to convert the events into rates per 30 days and apply AE rates throughout the time on treatment. The benefits of using the one-off event approach are: (1) it already incorporates the time aspect since costs and disutilities are defined as one event, and (2) the rates derived from trial data are based on the full trial population and by applying a one-off event in the first cycle, the adverse events rates are applied to the full model population which should mimic the results in the clinical trials. In contrast, when using rates per 30 days throughout the model, as patients are allowed to progress, adverse events are likely to be underestimated compared to results reported in the clinical trial.

The drawback with the one-off event approach is that, since all costs and disutilities are assumed to occur in the first cycle, they are not discounted properly. However, the model does not apply inter-year discounting (in line with NICE recommendations[110]); therefore, given that the duration of all adverse events is shorter than 1 year, the results will not be affected.

B.3.4 Measurement and valuation of health effects

Health-related quality-of-life data from FLAURA

The EQ-5D questionnaire was not collected in FLAURA and therefore no direct health state utility (HSU) values were derived directly from trial data.

HRQoL was evaluated in FLAURA using EORTC QLQ-C30 (-LC13) (page 85). The questionnaires were collected:

- Every 6 (3) weeks until disease progression
- Upon discontinuation of treatment
- Every 6 (3) weeks following disease progression

In order to use these data in accordance with the NICE methods guide, an algorithm was required to map EORTC QLQ-C30 or QLQ-LC13 to EQ-5D to produce HSU values. A brief overview of the methods to identify the most appropriate mapping algorithm is presented below.

Mapping

Algorithm search strategy

A search was conducted for mapping algorithms of EORTC QLQ-C30 or QLQ-LC13 to the EQ-5D (either EQ-5D-3L or EQ-5D-5L). The inclusion criteria required that lung cancer patients must be included in the study. From each study identified, the authors' preferred algorithm was then extracted, along with the measures used to determine goodness of fit.

The following sources were searched:

- The University of Oxford Health Economics Research Centre (HERC) database of mapping studies (only studies including lung cancer were included)
- PubMed
- A study by Doble et al (2016) reporting on the validation of existing mapping algorithms between the EORTC-QLQ-C30 and the EQ-5D in a large dataset[119]

A summary of the identified algorithms is presented in Table 47.

Table 47: Summary of identified mapping algorithms

Study	PRO-mapped	N	Country of EQ-5D value set	Type of cancer	Type of model	Fit statistics used
Jang et al. (2010)[120]	QLQ-C30 to EQ-5D	172	US	Lung	Linear	Adjusted R^2 MSE
Kim et al. (2012)[121]	QLQ-C30 to EQ-5D	893	Korea	All	OLS	R^2 MAE RMSE
Crott et al. (2013)[122]	QLQ-C30 to EQ-5D	172	UK	Breast	OLS	Adjusted R^2 MAE RMSE
Young et al. (2015)[123]	QLQ-C30 to EQ-5D	771	NA	All	Response mapping	MAE
Khan et al. (2016)[124]	QLQ-C30 to EQ-5D-3L and EQ-5D-5L	98	UK	Lung	Beta-binomial	R^2 MAE RMSE
Khan and Morris (2014)[125]	QLQ-C30 to EQ-5D-3L	670	UK	Lung	Beta-binomial	R^2 MAE RMSE

MAE: mean absolute error; MSE: mean square error; N: number of patients; NA: not applicable; OLS: ordinary least squares; PRO: patient-reported outcome; QLQ-C30: European organisation for research and treatment of cancer quality of life questionnaire core 30; RMSE: root mean square error

Studies in which the UK EQ-5D value set were not used or whose mapping could not be applied to the UK (Jang et al., Kim et al.) were excluded from final consideration. Crott et al. was excluded from final consideration due to the mapping algorithm being developed in breast cancer patients (although the paper attempted to validate it in lung cancer patients). Therefore, the mapping algorithms that were considered appropriate and further validated were those reported by Young et al., Khan and Morris, and Khan et al. Since none of the mapping algorithms utilised the QLQ-LC13 questionnaire, this was not considered in the validation of the algorithms.

Algorithm validation/selection

Data from two studies were combined for validation of the existing algorithms:

- AURA2: a phase 2, open-label, single-arm study assessing the efficacy and safety of osimertinib in patients with EGFR T790M-positive mutations, locally advanced or metastatic (stage IIIB/IV) NSCLC who progressed on previous EGFR tyrosine-kinase inhibitor therapy[46]
- AURA3: a randomized, international, open-label, phase 3 trial comparing the efficacy and safety of osimertinib and pemetrexed plus either carboplatin or cisplatin in patients with EGFR T790M-positive mutations, locally advanced or metastatic (stage IIIB/IV) NSCLC who progressed on previous EGFR tyrosine-kinase inhibitor therapy[47]

Both studies collected data using the EORTC-QLQ-C30 and the EQ-5D-5L questionnaires to estimate health-related quality of life (HRQoL). Observed EQ-5D-3L utility values were derived using the cross-walk[126] algorithm from the EQ-5D-5L observed responses in the AURA trials. The three selected mapping algorithms were applied to the QLQ-C30 data separately to obtain predicted EQ-5D-3L utility values (UK tariff).

The methods utilised to validate the algorithms were as follows:

- Comparison of the populations to identify the level of overlap in demographic and base line disease characteristics between AURA2/3 and the populations from the mapping algorithms
- Graphical summaries and statistical analyses to assess the ability of the algorithms to predict the observed EQ-5D through the use of:
    - scatterplots of predicted versus observed values
    - calculation of mean absolute error (MAE) and root mean squared error (RMSE)
    - scatterplots of the errors
- Subgroup analyses to ensure the algorithms fitted equally across all groups

Considering all the methods used to conduct this validation, the mapping by Young et al. fitted the observed data well and was utilised to map FLAURA EORTC values to EQ-5D. The algorithms by Khan and Morris and Khan et al. did not provide a good fit to the observed data overall and were not considered further for application to the FLAURA dataset. A description of the Young et al. mapping study can be found in Appendix H.

Generated HSU values

Averages for each patient in each health state across all observations were calculated using the mapped EQ-5D utility scores. The HSU values were then calculated as the average across all patients (Table 48). This minimised selection bias, as a simple average across all observations would have provided a greater weighting to those that remained in the PF state and were potentially healthier patients. Table 48 also reports the treatment-specific utility values for the PF health state. However, there was found to be no significant differences between SoC and osimertinib (which favours the osimertinib arm) with the respective 95% confidence intervals overlapping and therefore treatment-specific utilities were not used in the model. Summary tables of mapped EQ-5D utility scores over time are presented in Appendix H.

Table 48: HSU values from mapped FLAURA values (post-baseline)

Health state	n	Mean utility	Standard error	95% CI
Progression-free (all patients)	486	0.794	0.0069	(0.780, 0.807)
Progression-free osimertinib	248	0.803	0.0087	(0.786, 0.820)
Progression-free SoC	238	0.784	0.0107	(0.763, 0.805)
Progressed disease (all-patients)	241	0.704	0.0152	(0.674, 0.734)
Progressed disease osimertinib	92	0.712	0.0235	(0.666, 0.759)
Progressed disease SoC	149	0.699	0.0199	(0.660, 0.738)

The utility value (all patients) derived from FLAURA for the PF health state is in line with that derived from LUX-Lung 3 and used by the manufacturer for the NICE submission of afatinib. The value differs from the PF utility used in the erlotinib NICE submission which was derived from the study by Nafees et al.[127] However, this study reports utility values from the general public for health states related to hypothetical descriptions based on breast cancer health states revised to metastatic NSCLC patients on second-line treatment and may therefore not be reflective the HRQoL of EGFRm NSCLC patients in a first-line setting. In addition, the utility values derived from Nafees et al. are not based on the EQ-5D instrument and hence do not meet the NICE reference case. The utility value (all patients) from FLAURA for the PD health state is similar to that used by the manufacturer in the afatinib submission for the second-line PF state (derived from Chouaid et al.[128]). This is likely to be due to the post-progression EQ-5D data in FLAURA not being able to capture quality of life following second progression due to the limited follow-up at DCO1. The health state utility values used in previous NICE submissions or in relevant economic evaluations identified through the systematic literature review are reported in Table 50.

Health-related quality-of-life studies

Identification and description of studies

A systematic literature review was conducted to identify utility studies relevant to the decision problem. Explicit inclusion/exclusion criteria were applied, as summarised in Table 49.

Table 49: Key criteria for identification of utility studies

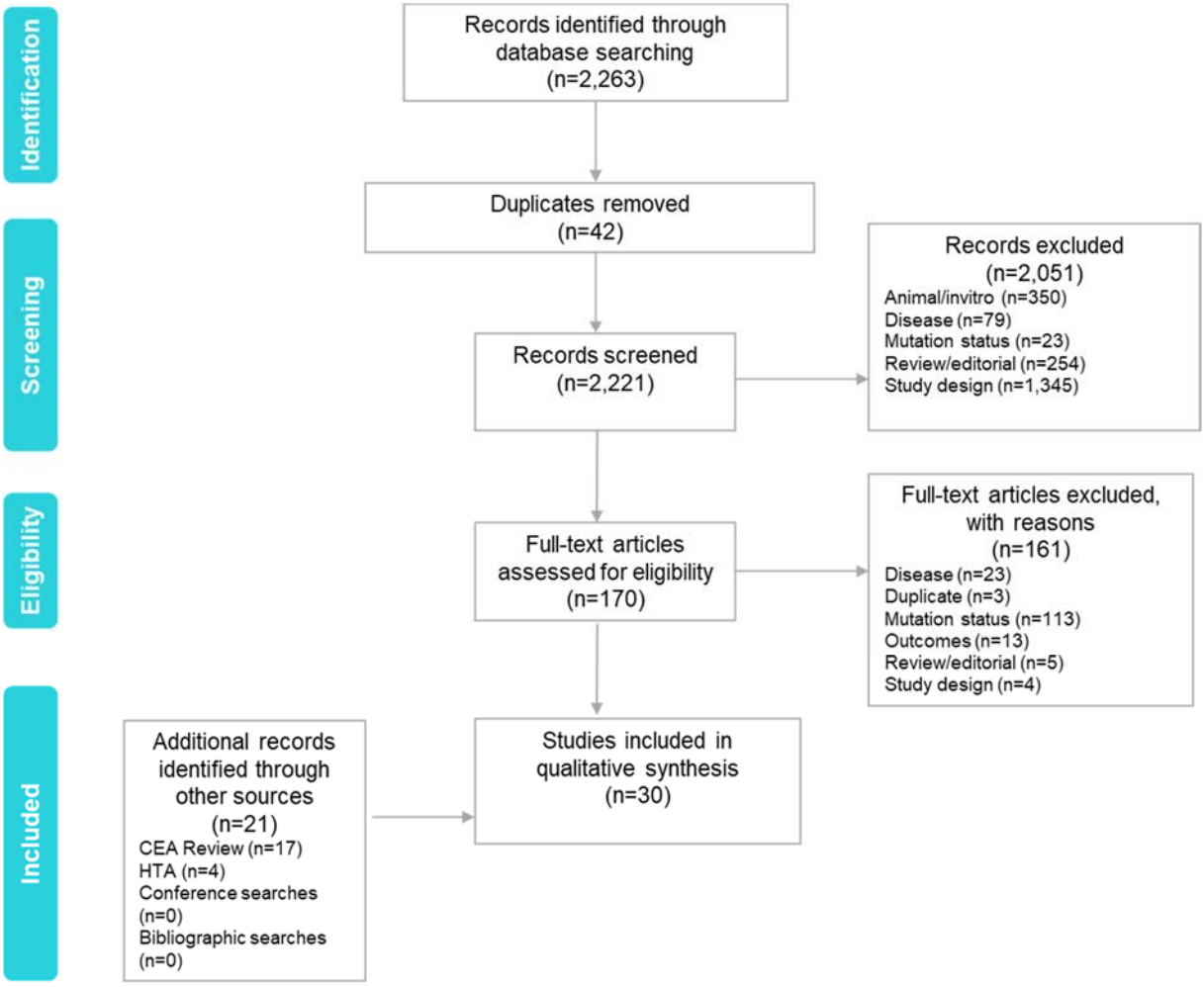
Category	Health-related quality-of-life
Population	Adult patients with advanced or metastatic EGFRm NSCLC
Line of therapy	Any line of therapy
Interventions	No restriction
Comparators	No restriction
Outcomes	• All types of utilities data including EQ-5D, SF-6D, etc. • Health state utility data, disutilities, etc.
Study type	• Economic evaluations • RCTs • Observational studies
Time limit	No restriction
Language	English only
Countries	No restriction

AFA: afatinib; BSC: best supportive care; EGFRm: epidermal growth factor receptor mutation-positive; EQ-5D: Euro-QoL-5D; ERL: erlotinib; GEF: gefitinib; LY: life years; NSCLC: non-small cell lung cancer; OSB: osimertinib; QALY: quality-adjusted life years; RCT: randomised controlled trials

Systematic database searches (originally performed on 18 May 2017 and updated on 19 February 2018 for Embase/Medline databases only) identified 2,263 records. The details of the search strategy are presented in Appendix H. Forty-two duplicate records were excluded. After preliminary screening of abstracts, 2,051 records were excluded, and 170 records were included for secondary screening. After secondary screening of full text articles, 161 studies were excluded. An additional 17 studies were identified from the cost-effectiveness review, and four studies were identified from HTA websites, which resulted in 30 relevant publications. Figure 44 presents the PRISMA flow diagram of studies identified in the utility review.

An overview of study characteristics and results of all the studies identified is presented in Appendix H. Table 50 reports a summary of study characteristics and results of the studies conducted in the UK or of those that reported utility values based on UK conversions.

Figure 44: PRISMA diagram for included utility studies



HTA: health technology assessment; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

Source: Moher et al., 2009[104]

Table 50: Study characteristics and utility values

Study name Year Country Interventions/ comparators	Study type	Cohort size	Method of elicitation Mapping (Yes/No) Source	Health state utilities	AE utilities/ disutilities
Bodnar et al.[129] 2016 UK OSB	nRCT	210	EQ-5D-5L No NR	Mean EQ-5D-5L utility PF:0.812 PD: 0.751 Pre-progression, patients with Complete or partial response (defined by objective response): 0.883 SD: 0.754	NR
Brown et al.[130] 2013 UK GEF DOC+CIS+CARB PAX+CIS+CARB	HTA	NR	EQ-5D Not required Nafees et al., 2008[131]	NR	NR
Griebsch et al.[132] 2014 UK AFA PEM+CIS	OBS	345 [a]	EQ-5D No LUX-LUNG 3 Trial	Estimates of the effects of disease progression on EQ-5D UK Utility from mixed-effects longitudinal models for LUX-Lung 3: Progression effect By Independent review: -0.061 By Investigator assessment: -0.076 Effects of disease progression from mixed-effects longitudinal models for LUX-Lung 3 by randomised treatment By Independent review AFA: -0.068 CIS+PEM: -0.046	NR

				By Investigator assessment AFA: -0.083 PEM+CIS: -0.062	
Labbé et al.[133] 2017 Canada Chemotherapy Targeted therapy Immunotherapy Other therapy No treatment	OBS	183	EQ-5D-3L No NR	<u>Mean utility score for UK</u> SD on most appropriate treatment (TKIs): 0.77 Progressing: 0.64 Clinically SD not on treatment: 0.76 SD on other systemic treatments: 0.72	NR
NICE[TA258][106] 2012 UK ERL GEF	HTA	EURTAC study: 326 OPTIMAL study: 154	EQ-5D Not required Nafees et al[131] values used in NICE TA227, TA192, TA190 and TA181	<u>Utility score</u> PF (SD): 0.6532 PF (Response dummy variable): 0.0193	<u>Disutility score</u> Rash: -0.0325 Diarrhoea: -0.0468 PD (progression dummy variable disutility relative to PFS SD baseline): -0.1798
NICE[TA310][107] 2014 UK AFA GEF ERL	HTA	LUX-Lung 3: 345 LUX-Lung 6: 364	EQ-5D Not required LUX-Lung 3 and 1, Chouaid et al. 2012,[128] Nafees et al. 2008[131]	<u>Mean utility values used in the model in the PF state</u> Derived from LUX-lung trial: 0.784 Derived from Chouaid et al. 2012: 0.710 Derived from Nafees et al. 2008: PF: 0.672 PF (SD): 0.653 PF (weighted): 0.663 <u>Mean utility values used in the model in the PD</u> Derived from Chouaid et al. 2012	<u>Mean disutilities</u> *Derived from LUX-Lung 3 trial* Diarrhoea (Grade 3/4): -0.147 Rash/acne (Grade 3/4): -0.202 *Derived from LUX-Lung 1 trial* Fatigue (Grade 3/4): -0.179

				Second-line PF: 0.73 Third-line BSC PD: 0.46 Third-line PF: 0.62	*Derived from Nafees et al. (2008)* Anaemia: -0.073 Neutropenia: -0.090
NICE[TA416][108] 2016 UK OSB PEM+CIS	HTA	AURA 2 study: 210 IMPRESS study 265	EQ-5D-5L, in AURA 2 study and EQ-5D-3L in IMPRESS study Not required Previous NSCLC HTA submissions to NICE	*Utility values derived from AURA2 study* Mean utility in base-case analysis (≥second-line population) PFS: 0.815 Post-progression: 0.678 Mean utility in second-line only population PFS: 0.853 Post-progression: 0.726 Mean utility in ≥third-line population PFS: 0.798 Post-progression: 0.659 *Utility values derived from IMPRESS study (placebo arm)* Mean EQ-5D-3L index value PFS: 0.779 Post-progression: 0.679	Disutilities (based on assumptions) Platelet count decreased (Assumption based on the nintedanib NICE Appraisal): -0.05 Constipation: -0.05 Oedema peripheral: -0.05 Cough: -0.05 Stomatitis: -0.05 Anaemia (Assumed to be same as fatigue/ asthenia event): -0.073 Headache: -0.05 Back pain: -0.05
NICE[TA192][105] 2010 UK GEF GEM+CARB GEM+CIS	HTA	NR	VAS Not required Nafees et al. 2008,[131] Eli Lilly[134] and ERG report[135]	NR	CTC Grade 3/4 AE utility (range) *Data taken from Eli Lilly (2009)* Anaemia: -0.0735

PAX+CARB VNB+CIS					

AE: adverse event; AFA: afatinib; BSC: best supportive care; CARB: carboplatin; CI: confidence interval; CIS: cisplatin; CTC: common technical criteria; DOC: docetaxel; ERG: evidence review group; ERL: erlotinib; EQ-5D: EuroQol-five dimensions questionnaire; GEF: gefitinib; GEM: gemcitabine; HRQL: health-related quality of life; HTA: health technology assessment; IV: intravenous; NR: not reported; OBS: observational; OSB: osimertinib; PAX: paclitaxel; PD: progressive disease; PEM: pemetrexed; PFS: progression-free survival; nRCT: non-randomised controlled trial; ROC: rociletinib; sd: standard deviation; SD: stable disease; SG: standard gamble; TKI: tyrosine kinase inhibitors; TTO: time trade off; VAS: visual analogue scale; VNB: vinorelbine

[a] Data were back calculated, reported as 97% completed baseline HRQoL

Key differences between the values derived from the literature and those reported in FLAURA

Following review of the studies reporting HSUVs derived from a UK population or using the UK conversion (Table 50), Labbé et al. was the only study considered applicable to the current decision problem.[133] This longitudinal cohort study reports real-world health utility scores (HUSs) in specific subgroups of lung cancer patients in Canada. Using the EQ-5D-3L, health state utility scores were compared by mutational status, therapy, response to treatment and severity of symptoms. Patient and disease characteristics for the EGFRm subgroup were considered broadly similar to those reported in FLAURA, with the only exception being the number of previous lines of treatment, suggesting that the values reported by Labbé et al. are likely to be more conservative than those obtained from FLAURA. The utility value reported for stable disease on a TKI treatment (any line) is slightly lower but close to that derived from PF patients in FLAURA using the mapping algorithm described above. The PD utility value generated by Labbé et. al was obtained by assessment on multiple occasions over time, therefore capturing patients' long-term deterioration of HRQoL. Although the study was not conducted in a UK setting, the authors presented the results based on UK conversions.

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

The utility value derived from patients (overall) in FLAURA who had not experienced disease progression was used to describe QoL associated with the PF health state. The derived value was in line with that used in previous appraisals in a similar setting[107, 108] and recent publications.[129, 133] The mapped utility from FLAURA for patients with PD was used in the model for patients receiving first-line treatment after disease progression. Utilities for PD (patients on subsequent treatments) and utility decrements for AEs were sourced from the published literature. Table 51 presents an overview of all utility values applied in the base-case model (details are provided in the sections below).

Table 51: Summary of utility values for cost-effectiveness analysis

Health state	Utility value	Source/description
Health state utility values		
Progression-free	0.794	Mapped from FLAURA EORTC
Progressed disease (1L treatment)	0.704	Mapped from FLAURA EORTC
Progressed disease (subsequent treatment or BSC)	0.640	Labbé et al.[133]
Death	0.000	By definition
Adverse event disutility per event		
Alanine aminotransferase increased	-0.0020	Table 54
Aspartate aminotransferase increased	-0.0020	

Diarrhoea	-0.0007	
Fatigue	-0.0048	
Rash or acne	-0.0013	

BSC: best supportive care

Progression-free

As shown in Table 51, the utility value estimates for patients in the PF health sate were assumed to be identical for all treatment arms given that in the FLAURA study similar objective response rates (ORR) were observed for osimertinib and SoC (Table 52). Therefore, no further adjustments for different response rates were made as the values used were assumed to represent the weighted average of utilities across responders (complete response, partial response) and non-responders.

Table 52: Best objective response analysis – investigator assessment

Best objective response	Number (%) of patients	
	Osimertinib	SoC
Sample size	279	277
Complete response	7 (2.5)	4 (1.4)
Partial response	216 (77.4)	206 (74.4)
Non-response	56 (20.1)	67 (24.2)
Objective response rate (%) (95% CI)	76.7 (71.2, 81.5)	69.0 (63.1, 74.4)
Odds ratio (95% CI)	1.27 (0.85, 1.90)	
2-sided p-value for odds ratio	0.242	

CI: confidence interval; SoC: standard of care

Progressed disease (1L treatment)

In FLAURA, patients could continue to receive their randomised treatment after progression if they were deriving clinical benefit. The rationale to do so is that the clinician perceives a continued benefit compared to the available second-line treatments (which would normally consist of platinum-based chemotherapy unless the patient is confirmed as EGFR and T790M-mutation positive) from both a safety and efficacy perspective. In order to capture this benefit, a different utility value was used for the proportion of patients receiving first-line treatment after progression (calculated as the difference between the proportion of patients on first-line treatment and the proportion of patients in PF health state). Because no utility value describing HRQoL for patients remaining on a TKI beyond progression was identified from the literature review, the mapped utility from FLAURA for patients with PD was utilised within the model. This is a conservative assumption as PD patients in FLAURA also included subjects on subsequent treatment or BSC, who would be expected to experience a lower HRQoL than those continuing their first-line oral TKI treatment. Nevertheless, given the limited post-progression follow-up available from FLAURA, the estimate was considered reflective of patients remaining on study treatment post-progression (see Table 53).

Table 53: Continuation of study treatment after progression

	Osimertinib	SoC
% of patients who remained on study treatment post-progression	66.9%	70.4%
Duration of treatment post-progression Median (95% CI), weeks	8.1 (6.3, 12.3)	7.0 (5.9, 8.1)

Progressed disease (subsequent treatment or BSC)

Due to the high number of patients still on randomised treatment in FLAURA, the proportion of patients who had a chance to receive more than 1 line of post-progression anti-cancer therapy was low. For this reason and due to the limited post-progression follow-up available in the trial (see page 80), the mapped utility for PD patients was considered unrepresentative of the health state, failing to capture the long-term deterioration in a patient's QoL. The value reported by Labbé et al.[133] for PD in the EGFRm population was considered to be more appropriate as most patients had multiple assessments over time, at various time points of their disease and treatment course. Moreover, as described in the previous section this was also considered to be a conservative assumption.

The PD utility value of 0.64 is also very similar to those used and accepted by ERGs in two previous NSCLC NICE submissions; TA309 and TA347, both of which used a PD utility value of 0.64 obtained from the PARAMOUNT and LUME-Lung 1 clinical trials, respectively.

Therefore, the value from Labbé et al. was used in the base-case to represent HRQoL in the PD health state following discontinuation of 1L TKI treatment. In FLAURA 62 patients from the SoC arm received osimertinib as subsequent therapy. However, an exploratory analysis of PD utility values by treatment arm did not show significant differences between SoC and osimertinib with the respective 95% confidence intervals overlapping. Therefore, an adjustment for different post-progression therapies was not considered appropriate in the base case, or feasible given the low number of EORTC-QLQ responses available on or after disease progression. However, the impact of applying a different PD utility value in the comparators' arms was explored in a scenario analysis: the value was calculated by using the utility value reported by Labbé et al. for stable disease on most appropriate treatment (0.77) for the proportion of patients receiving osimertinib as subsequent treatment in the base case (33%). For the remaining patients in the comparators' arms and for all patients in the osimertinib arm the utility used was 0.64 from Labbé. The resulting weighted average PD utility for the comparators' arm was 0.683.

Adverse reactions

It was not considered appropriate to apply treatment-specific mapped utility values from FLAURA for the PF state. Therefore, in addition to the HSU values, utility decrements for grade 3 and grade 4 adverse events associated with first-line treatments were applied. Similarly to previous technology appraisals in the same setting (see Table 50), utility decrements were obtained from the study conducted by Nafees et al.[131] in which societal based utility values for different stages of NSCLC and associated grade 3 and grade 4 toxicities were elicited from the UK general population using the standard gamble approach. Assumptions were made where information was not available from the literature. Details of the utility decrement and duration associated with each adverse event are presented in Table 54 and an overview of the reference sources is provided in Table 55.

Table 54: Disutility values for adverse events in the base-case

Adverse event	Disutility	Source/description	Duration	Source/description
Alanine aminotransferase increased	-0.0509	Assumption: average of other disutilities	14.66	Assumption: average of other disutilities
Aspartate aminotransferase increased	-0.0509	Assumption: average of other disutilities	14.66	Assumption: average of other disutilities
Diarrhoea	-0.0468	Nafees (2008)[131]	5.53	Study CA046 (TA476)[136]
Fatigue	-0.0735	Nafees (2008)	23.78	PIX301 trial (TA306);[137] Study CA046 (TA476)

Rash or acne	-0.0325	Nafees (2008)	14.66	Assumption: average of other disutilities

Table 55: Adverse event disutility and duration source overview

Source	Disease area	Population (sample size)	Method of valuation	Country
Disutility				
Nafees (2008)[131]	Non-small cell lung cancer	General public (n=100)	SG	UK
Durations				
PIX301 trial (TA306)[137]	Aggressive non-Hodgkin's lymphoma	Trial population (n=144)	--	Europe, India, Russia, South America, the UK and the USA
Study CA046 (TA476)[136]	Metastatic pancreatic adenocarcinoma	Trial population (n=861)	--	North America, Eastern Europe, Australia, Western Europe

SG, standard gamble

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

Cost and healthcare resource use studies

Identification and description of the studies

A systematic review was conducted to identify studies reporting cost and healthcare resource use. Explicit inclusion/exclusion criteria were applied, as summarised in Table 56.

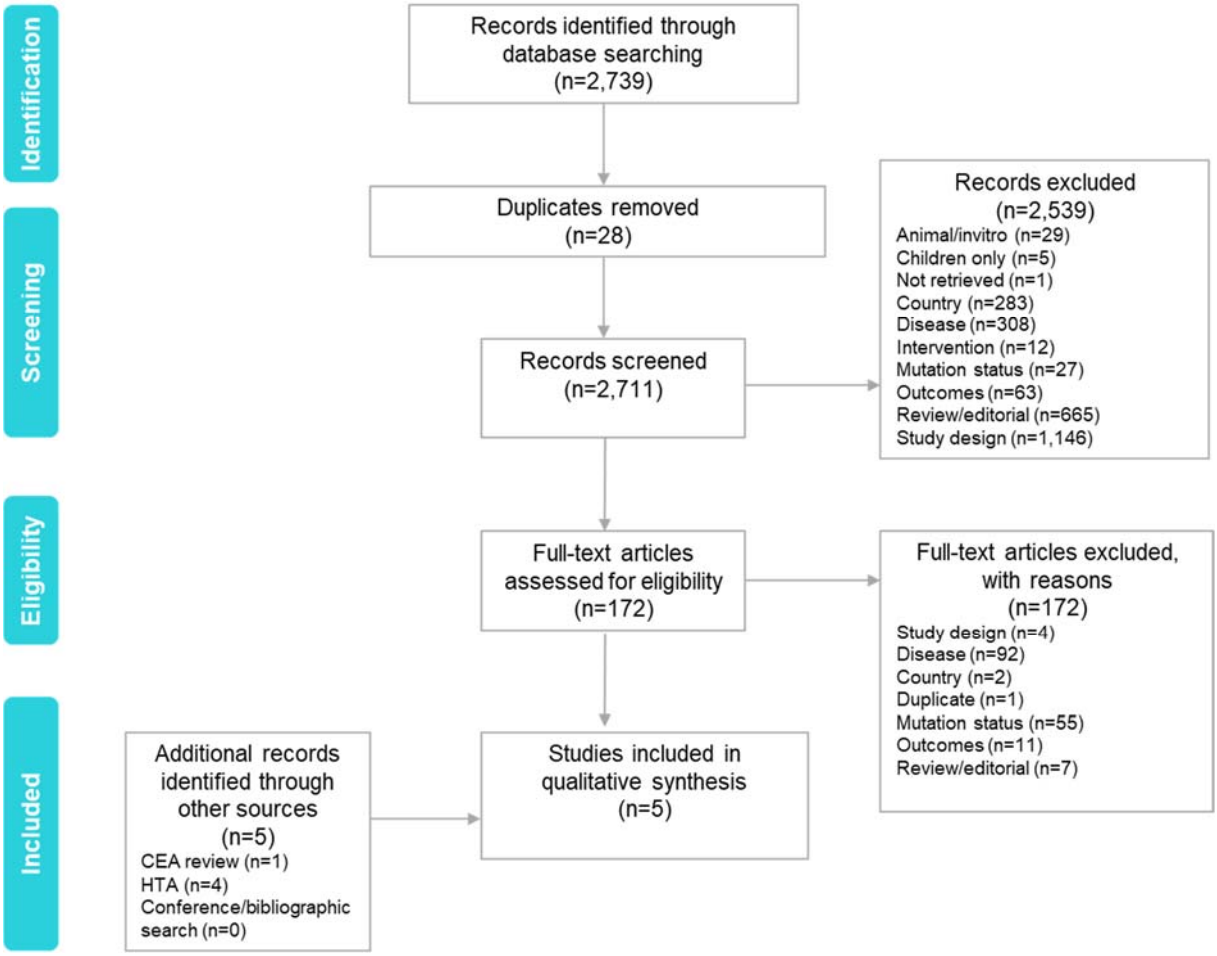
Table 56: Key criteria for identification of cost and resource use studies

Category	Cost and resource use
Population	Adult patients with advanced or metastatic EGFRm NSCLC
Line of therapy	Any line of therapy
Interventions	No restriction
Comparators	No restriction
Outcomes	• Cost outcomes (direct, total, indirect, cost subcomponents) • Resource use studies (hospitalisation, length of stay, number of visits, etc.)
Study type	• Observational/clinical studies reporting cost and resource use data • Economic evaluations reporting cost and resource use data
Time limit	Studies published in the last 10 years
Language	English only

Countries	UK only

Systematic database searches (originally performed on 18 May 2017 and updated on 19th February 2018 for Embase and Medline databases only) identified 2,739 records for cost and resource use related to treatments for advanced/metastatic EGFRm NSCLC. The details of the search strategy are presented in Appendix I. Twenty-eight duplicate records were excluded. After preliminary screening of abstracts, 2,539 records were excluded, and 172 records were included for secondary screening. After secondary screening of full text articles, all the studies were excluded, and an additional four studies were identified from HTA websites and one study from the cost-effectiveness review, which resulted in the inclusion of five studies. Figure 45 presents the PRISMA flow diagram of studies identified for cost and resource review.

Figure 45: PRISMA diagram for included cost and resource use studies



HTA: health technology assessment; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

Source: Moher et al., 2009[104]

Five HTAs were identified through the review and no full publications or conference abstracts were included. All the five HTAs were submitted to NICE (Brown et al.;[130] NICE[TA192];[105] NICE[TA258];[106] NICE[TA310];[107] NICE[TA416][108]).

A summary of characteristics and results of the included studies is presented in Appendix I.

Intervention and comparators' costs and resource use

Drug acquisition costs were calculated based on available formulations; pack sizes, unit costs and price per mg for each (combination of) treatment included in the model. The dosing information was sourced from the EMA label for each treatment and the drug acquisition costs were sourced from the eMit[138] and from the BNF[139] when they were not available on eMit.

The vial sizes used for subsequent intravenous (IV) treatments in the model were those resulting in the lowest monthly acquisition cost, assuming no wastage (i.e. vial sharing is assumed). The impact of assuming vial wastage was explored in a scenario analysis.

Population characteristics

The dosage of subsequent treatments including chemotherapy regimens were determined by the body surface area (BSA), assuming the FLAURA trial to be comparable to the UK population and the mean height and weight were applied in the formula by Gehan[140] to estimate BSA.

Table 57: Patient characteristics used in the model

Parameter	Input	Source / Comment
Body surface area (m2)	1.67	Calculated based on average height and weight using the Gehan and George[140] formula (0.01545*(height^0.54468)*(weight^0.46336))

Treatment regimens

Table 58 and Table 59 present the drug acquisition cost inputs for primary (list prices) and subsequent treatments respectively. Note that for osimertinib as a second-line treatment, the model applies the existing PAS discount.

Table 58: Treatment dosing and drug acquisition costs for primary treatments

		Osimertinib	Erlotinib	Gefitinib	Afatinib
Label information	Admin method	Oral	Oral	Oral	Oral
	Dose per admin	80mg	150mg	250mg	40mg
	Admin frequency	1 per day	1 per day	1 per day	1 per day
Package information	Formulation	80 mg	150mg	250mg	40mg
	Pack size	30	30	30	28

	List price	£5,770.00	£1,631.53	£2,167.71	£2,023.28
Dosing used in model	Required dose	80mg	150mg	250mg	40mg
	Vials / caps per admin (without waste)	1.00	1.00	1.00	1.00

Table 59: Treatment dosing, administration and drug acquisition costs for subsequent treatments

		Osimertinib	PDC		Docetaxel
			Pemetrexed	Cisplatin	
Label information	Admin method	Oral	IV	IV	IV
	Dose per admin	80mg	500 mg/m2	75 mg/m2	75 mg/m2
	Admin frequency	1 per day	1 per 3 weeks	1 per 3 weeks	1 per 3 weeks
Package information	Formulation	80 mg	100mg	50mg	80mg
	Pack size	30	1	1	1
	Price	[redacted]	£160.00	£4.48	£14.74
Dosing used in model	Required dose	80mg	832.82mg	124.92mg	124.9mg
	Vials / caps per admin (without waste)	1.00	8.32	2.49	1.56
	Vials / caps per admin (with waste)	1.00	9.00	3.00	2.00

IV: intravenous; PDC: platinum doublet chemotherapy

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.

Mean RDI estimates and drug acquisition costs per administration and per 30-day cycle for each treatment are presented in Table 60 and Table 61 respectively.

Table 60: Relative dose intensity

Treatment	Mean RDI	Source
Osimertinib	98.9%	FLAURA[26]
Erlotinib	98.1%	FLAURA
Gefitinib	98.1%	FLAURA
Afatinib	98.1%	Assumption: equivalent to SoC in FLAURA
Pemetrexed	100%	Assumption

Cisplatin	100%	Assumption
Docetaxel	100%	Assumption

RDI: relative dose intensity

Table 61: Drug acquisition costs per administration and per 30 days

Treatment	Cost per patient	
	Per admin	Per 30 days
Osimertinib	£5,706.53	£5,706.53
Erlotinib	£1,600.53	£1,600.53
Gefitinib	£2,126.52	£2,126.52
Afatinib	£1,984.84	£2,126.61
PDC (2L)	£1,343.70	£1,919.58
Osimertinib (2L)	[redacted]	[redacted]
Docetaxel (3L)	£23.02	£32.88

PDC: platinum doublet chemotherapy; SoC: standard of care

Treatment duration

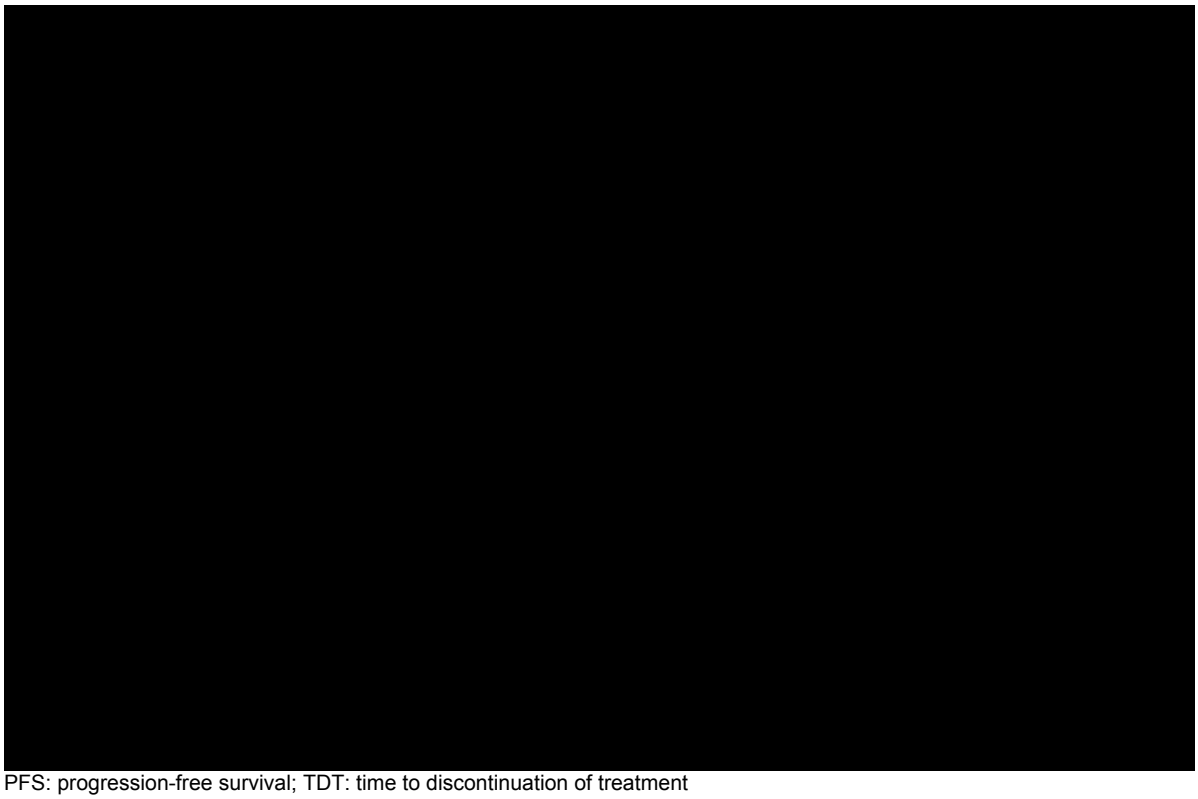
Patient level data on treatment duration was available from FLAURA for osimertinib and SoC. A summary of the non-parametric data for time to discontinuation of treatment (TDT) and the observed treatment discontinuation (or death) compared to PFS are presented in Table 62 and Figure 46 respectively.

In the first 6 months, TDT is slightly shorter than PFS for both treatments; beyond month 6 both treatments are continued for approximately 1 to 2 months post progression.

Table 62: TDT summary data

	Osimertinib (n=279)	SoC (n=277)
Total events (%)	[redacted]	[redacted]
Median (95% CI)	[redacted]	[redacted]

Figure 46: FLAURA PFS vs. TDT KM data



PFS: progression-free survival; TDT: time to discontinuation of treatment

UK clinical experts confirmed that, similar to current practice for 1st and 2nd generation TKIs, osimertinib is expected to be used beyond progression if clinical benefit is observed. In order to reflect expected UK clinical practice and the FLAURA protocol, TDT data was used to model treatment costs.

Dependent models were used in order to align the predicted TDT with PFS and on the basis that the TDT cumulative hazard plots appeared to follow the proportional hazards over time in a similar manner to PFS (Figure 47). The statistical fit of the models is presented in Table 63; mean, median and landmark rates are presented in Table 64 and Table 65 for osimertinib and SoC, respectively. The fitted models compared to the observed data are presented in Figure 48.

Figure 47: Log cumulative hazard plot (TDT; FLAURA)

Table 63: Goodness of fit statistics (TDT; dependent; FLAURA)

	Exponential	Weibull	Gompertz	Log-logistic	Log-normal	Generalised gamma
AIC	2811.42	2796.31	2790.32	2823.51	2865.69	2792.04
Rank	4	3	1	5	6	2
BIC	2820.06	2809.27	2803.28	2836.47	2878.66	2809.32
Rank	4	2	1	5	6	3

AIC: akaike information criterion; BIC: bayesian information criterion; TDT: time to discontinuation of treatment

Figure 48: Parametric models for time to discontinuation of treatment (FLAURA; dependent models)

The generalised gamma distribution was selected for the base-case as it provides a good fit to the KM data (second best fitting model based on AIC/BIC) and to ensure consistency with the base-case PFS parametric function (PFS and TDT assumed to have a similar shape of the hazard function). Also, in line with the observed data, it predicts fewer patients on treatment than progression-free up to the first 6 months and more patients on treatment beyond 6 months for both osimertinib (Table 35) and SoC (Table 36). The impact of using the Gompertz and the Weibull distributions (respectively best and third best fitting models) was explored in sensitivity analyses.

Table 64: Osimertinib time to discontinuation of treatment (FLAURA; dependent models)

	Exponential	Weibull	Gompertz	Log-logistic	Log-normal	Generalised gamma	Generalised gamma (PFS)
Mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
% at 6 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
% at 1 year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
% at 2 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
% at 3 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
% at 4 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

PFS: progression-free survival

Table 65: SoC time to discontinuation of treatment (FLAURA; dependent models)

	Exponential	Weibull	Gompertz	Log-logistic	Log-normal	Generalised gamma	Generalised gamma (PFS)
Mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
% at 6 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
% at 1 year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
% at 2 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
% at 3 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
% at 4 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

PFS: progression-free survival

Drug administration costs

For all oral treatments administration costs were assumed to be equivalent to 12 minutes pharmacist dispensing time aligned with the ERG recommendation in TA416.[108] The drug administration costs for IV treatments include the cost of chemotherapy infusion and premedication with dexamethasone. The administration usage was based on the EMA label information for each treatment and the unit costs of infusion were based on NHS reference cost definitions. The costs and resource use used in the model are summarised in Table 66.

Table 66: Unit costs, resource use and total administration costs used in the model (per administration)

Treatment	Cost item	Numbers per admin	Unit cost (£)	Cost per treatment cycle (£)	Comment
Osimertinib	Pharmacist dispensing (12 minutes) [Band 6 pharmacist[141]]	1	£45 (per hour)	£9.00	--
Erlotinib	[Pharmacist dispensing (12 minutes) [Band 6 pharmacist[141]]	1	£45 (per hour)	£9.00	--
Gefitinib	Pharmacist dispensing (12 minutes) [Band 6 pharmacist[141]]	1	£45 (per hour)	£9.00	--
PDC	Deliver complex chemotherapy, including prolonged infusional treatment – outpatient (SB14Z) – First attendance[142]	1	£355.54	£359.01	130 minutes administration[143]
	Dexamethasone (premedication)[138]	12	£14.46 for 2mg x 50		8 mg per day for 3 days[143]
Docetaxel	Deliver complex chemotherapy, including prolonged infusional treatment – outpatient (SB14Z) – First attendance[142]	1	£355.54	£362.48	60 minutes administration
	Dexamethasone (premedication)[138]	24	£14.46 for 2mg x 50		16mg per day for 3 days[144]

NHS: National Health Service; PDC: platinum doublet chemotherapy

Drug monitoring costs

Costs related to drug monitoring were based on the EMA label information for each treatment (no monitoring specified for oral treatments) and the costs of lab tests were sourced from the latest National Schedule of Reference Costs.[142] Since no frequency data was given in the EMA label information for PDC, it was assumed all test were conducted once every treatment cycle. Table 67 presents a summary of the monitoring costs per treatment cycle used in the model. Monitoring costs are converted into costs per 30 days and applied to all patients whilst on treatment.

Table 67: Unit costs, resource use and total weekly monitoring costs used in the model

Treatment	Cost item	Numbers per treatment cycle	Unit cost (£)	Description	Cost per treatment cycle (£)
PDC	Liver function test	1	£1.13	DAPS04 – Clinical biochemistry[142]	£5.32
	Renal function test	1	£1.13	DAPS04 – Clinical biochemistry[142]	
	Complete blood count	1	£3.06	DAPS05 – Haematology[142]	
Docetaxel	Complete blood count	1	£3.06	DAPS05 – Haematology[142]	£3.06

PDC: platinum doublet chemotherapy

Subsequent treatment costs

In the base-case the analysis accounts for the cost of second-line and third-line treatments, following progression from first-line treatment, in order to reflect the expected clinical pathway. The cost of subsequent treatments was applied as a one-off cost to patients discontinuing their primary treatment. Due to the nature of partitioned survival modelling, it is not possible to accurately account for patients who discontinue their first-line treatment and die in the same cycle. As a proxy the difference in patients on treatment between two consecutive 30-day cycles was used. This can result in a slight overestimation of subsequent treatment costs as it does not account for patients who die prior to discontinuation. However, only 11 patients (4%) in the osimertinib arm and 14 patients (5%) in the SoC arm in FLAURA died before progression.

The cost of subsequent treatments was estimated based on the following parameters:

- *Distribution of patients across second-line and third-line treatments*. The distribution of patients across subsequent treatments is presented in Table 70 and Table 71.
    - Second-line treatments: UK clinical experts' opinion was used to inform the distribution of subsequent treatments for osimertinib and the comparators

included in the analysis as this more closely resembles current UK clinical practice. Clinical experts confirmed that based on their experience, one third of patients progressing on a 1st or 2nd generation TKI are currently identified as T790M positive and therefore treated with osimertinib, one third are not fit enough to receive any further treatments (or refuse to do so) and the remaining patients receive PDC. Similarly, following progression on osimertinib in first-line, one third of patients will be expected to not receive any subsequent treatments and the remaining patients will receive PDC as second-line treatment. This was further confirmed by review of second-line treatments data in FLAURA where a similar proportion of patients in the two arms did not receive any subsequent treatments after progression. The impact of applying the proportion of second-line treatments observed in FLAURA was explored in a scenario analysis: this was done by applying the proportion of progressed patients who received BSC only (39.7% and 37.4% for osimertinib and SoC respectively) and osimertinib (26.7% in the SoC arm only) in each treatment arm, and assuming that the remaining patients received PDC (see Section B.2.4).

    - Third-line treatments: assumptions in regard to 3L treatment in the model reflected the previous NICE submission for Osimertinib in 2L EGFR T790M NSCLC[108] which was informed by and validated by UK clinical expert opinion rather than AURAext/2 (pooled) or AURA3 data which may not have reflected UK clinical practice. This assumed that 80% of EGFR T790M patients treated with second-line osimertinib received third-line PDC and that 50% of patients receiving second-line PDC received third-line docetaxel monotherapy (the remaining patients were assumed to receive best supportive care).

- *Treatment costs (per 30 days).* Acquisition, administration and monitoring costs associated with PDC, osimertinib and docetaxel were included. For patients receiving erlotinib, gefitinib or afatinib in first-line (eligible to receive osimertinib after progression), T790M testing costs were also included. The total treatment costs per 30 days for each second- and third-line treatment are presented in Table 72.
- *Mean duration of treatment (30-day cycles).*
    - In order to accurately capture time on second-line treatments, the latest available TDT data from AURA3[47] (DCO3; 85.2% maturity) was used to model costs associated with osimertinib and PDC after progression on a first-line TKI. This randomized, international, open-label, phase 3 trial, was chosen to inform duration of treatment for osimertinib and PDC in a second-line setting as it provides the most robust available evidence. Within the model, treatment with

PDC was limited to four 21-days cycles to reflect NHS protocols for pemetrexed-cisplatin therapy (number of cycles for PDC was not capped in AURA3). Therefore, the KM curve (truncated at the relevant time point) was used directly to calculate mean time on treatment for PDC as complete data was available. Independent parametric models were fitted to TDT data (osimertinib arm only) and the extrapolated means (rather than the observed medians) were used to inform time on treatment, as recommended by the NICE DSU Technical Support Document 14.[114] The AURA3 KM curves for TDT and the fitted parametric distributions for osimertinib are shown in Figure 49. As described in Section B.3.2, half-cycle correction was not applied to the calculation of drug acquisition and administration costs.

Figure 49: KM and Osimertinib fitted parametric models (TDT; independent; AURA3)

The statistical fit of the models is presented in Table 68, and mean, median and landmark rates are presented in Table 69.

Table 68: Osimertinib goodness of fit statistics (TDT; independent; AURA3)

	Exponential	Weibull	Gompertz	Log-logistic	Log-normal	Generalised gamma
AIC	1770.68	1761.46	1769.32	1756.36	1764.09	1758.45
Rank	6	3	5	1	4	2
BIC	1774.31	1768.72	1776.59	1763.62	1771.35	1769.34
Rank	5	2	6	1	4	3

AIC: akaike information criterion; BIC: bayesian information criterion; TDT: time to discontinuation of treatment

Table 69: Osimertinib predicted and observed mean, median and landmark rates (TDT; independent; AURA3)

	Exponential	Weibull	Gompertz	Log-logistic	Log-normal	Generalised gamma	AURA3
Mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
% at 1 year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
% at 2 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
% at 3 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
% at 5 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
% at 10 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
% at 15 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

TDT: time to discontinuation of treatment

The log-logistic model showed the best fit to the observed data followed by the generalised gamma and the Weibull models. However, the log-logistic model generates a long tail with [redacted]% of patients on treatment at 10 years. Given the considerations above and in order to align TDT for osimertinib in first- and second-line, the generalised gamma model was chosen for the base-case. The impact of using the log-logistic and the Weibull distributions was explored in scenario analyses.

- A study by Schuler et al.,[145] which included singlet chemotherapy in a third-line setting with complete KM data, was identified and used to source duration of treatment for docetaxel in third-line. The study only reported median exposure to chemotherapy (51 days) and due to the limited impact that third-line therapy has on the model results, this was considered a reasonable proxy for time on third-line treatment with docetaxel.
- Duration of treatment for PDC in third-line was assumed to be similar to that in second-line based on the assumption that patients progressing on a TKI (i.e. osimertinib in second-line) are healthier than those progressing on chemotherapy (i.e. PDC in second-line) and will be able to tolerate third-line treatment for a longer period.

Table 70: Distribution of second-line treatments (columns) by primary treatment (rows)

From ↓ To →	PDC (2L T790M ±)	PDC (2L T790M -)	Osimertinib (2L T790M+)	No treatment (2L)
Osimertinib	66.7%	0.0%	0.0%	33.3%

Erlotinib	0.0%	33.3%	33.3%	33.3%
Gefitinib	0.0%	33.3%	33.3%	33.3%
Afatinib	0.0%	33.3%	33.3%	33.3%

PDC: platinum doublet chemotherapy

Table 71: Distribution of third-line treatments (columns) by primary treatment (rows)

From ↓ To →	PDC (3L)	Docetaxel (3L)	No treatment (3L)
Osimertinib	0.0%	33.3%	66.7%
Erlotinib	26.7%	16.7%	56.6%
Gefitinib	26.7%	16.7%	56.6%
Afatinib	26.7%	16.7%	56.6%

PDC: platinum doublet chemotherapy

Table 72: Subsequent treatments costs

	PDC (2L T790M ±)	PDC (2L T790M -)	Osimertinib (2L T790M+)	PDC (3L)	Docetaxel (3L)
T790M Testing[1] (per 30 days)	£0.00	£543.66	£63.25	£0.00	£0.00
Drug acquisition (per 30 days)	£1,919.58	£1,9191.58	[redacted]	£1,919.58	£32.88
Drug administration (per 30 days)	£512.87	£512.87	£9.00	£512.87	£517.83
Drug monitoring (per 30 days)	£7.60	£7.60	£0.00	£7.60	£4.37
Total treatment cost (per 30 days)[2]	£2,440.05	£2,974.25	[redacted]	£2,440.05	£555.08
Duration on subsequent treatment (30-day cycles)	2.40	2.40	20.28	2.40	1.70

PDC: platinum doublet chemotherapy

[1]T790M testing cost (one-off) is divided by treatment duration to avoid double counting

[2]Total costs include: T790 testing (where relevant), drug acquisition, drug administration and drug monitoring costs

T790M testing costs for patients treated with osimertinib in second line

Given that second-line osimertinib is indicated for use in patients with T790M+ NSCLC, the cost of T790M testing was included within the costs for subsequent treatments for patients receiving a 1st or 2nd generation TKI in first-line. Two possible diagnostic strategies were included: 1) tissue biopsy, 2) circulating tumour DNA (ctDNA) plasma followed by tissue biopsy (for those whose result is negative after the ctDNA plasma). In the base-case analysis, it was assumed that of those being tested, 20% undergo tissue biopsy alone and 80% receive a ctDNA plasma test followed by tissue biopsy.[108]

To identify the number of tests required per T790M patient identified, an underlying T790M incidence ($T790i$) was used, where each test has an associated T790M test performance, expressed as sensitivity (SE) and specificity (SP). To estimate the true positives (TP), false positives (FP), true negatives (TN), and false negatives (FN), the following four calculations ($t1$) were used:

$$t1_{TP} = T790_i * t1_{SE} \qquad t1_{FP} = (1 - T790_i) * (1 - t1_{SP})$$

$$t1_{TN} = (1 - T790_i) * t1_{SP} \qquad t1_{FN} = T790_i * (1 - t1_{SE})$$

The T790M incidence and T790M test performance used in the calculations are presented in Table 73.

Table 73: T790M test performance

Model inputs	Incidence		Source
Underlying T790M incidence	60%		Kobayashi,[146] Pao,[60] Sequist,[18] Yu[147]
	Sensitivity	*Specificity*	
Tissue biopsy	88.3%	97.3%	FDA[148]
ctDNA followed by tissue biopsy	80.0%	94.9%	Assumption[108]

ctDNA: circulating tumour deoxyribonucleic acid

The resulting true and false rates and patients needed to test are presented in Table 74. Patients with a T790M positive result, and eligible for osimertinib, comprise true positives and false positives. The number needed to test (1/(FP+TP)) represents the number of patients that needs to be tested with each strategy in order to identify one patient with the T790M mutation and thus eligible for treatment with osimertinib.

Table 74: T790M diagnostic strategy outputs

Test strategy	True T790M-		True T790+		# patients needed to test (per T790M+ patient identified)
	TN	*FN*	*TP*	*FP*	
Tissue biopsy	38.9%	7.0%	53.0%	1.1%	1.85

ctDNA (plasma) followed by tissue biopsy	35.9%	0.4%	61.3%	2.5%	1.57

ctDNA: circulating tumour deoxyribonucleic acid; FN: false negative; FP: false positive; TN: true negative; TP: true positive

The outputs based on the performance of each diagnostic test and on the distribution of testing strategies used in the base-case are presented in Table 75.

Table 75: Combined results from all testing strategies

	Tissue biopsy	ctDNA
Number of tests performed per patient tested	0.52	0.80
Number of tests needed (per T790M+ patient identified)	0.84	1.29
# patients needed to test (per T790M+ patient identified)	1.62	

The cost of the test includes the acquisition cost of the test itself plus other costs incurred during the visit for the test. Table 76 presents the unit costs used in the calculations which are partially based on assumptions.

Table 76: T790M test costs

Resource	Tissue biopsy (cobas®)	Source/comments	ctDNA	Source / Comment
Acquisition cost	£147.31	Based on cost of cobas EGFR test[149] (updated for inflation using HCHS index)[150]	£147.31	Assumed the same as tissue biopsy[108]
Sample procedure	£643.23	DZ70Z Endobronchial Ultrasound Examination of Mediastinum[142]	£330.80	Assumption[108] (updated for inflation using HCHS index)[150]
Total cost	£790.54	-	£478.11	-

ctDNA: Circulating tumour deoxyribonucleic acid

Based on the distribution of patients across diagnostic strategies, the number of tests required to identify one T790M+ patient and the unit cost per test, the total T790M testing cost was estimated as follows

$$(0.84 * £790.54) + (1.29 * £478.11) = £1{,}282.46$$

Health-state unit costs and resource use

The disease management costs are split into PF and PD health state costs per 30 days, as well as costs of end-of-life/terminal care. The disease management costs are thus health state-specific, and not treatment-specific.

Progression-free and progressed disease costs

The resource use data is sourced from the HTA study by Brown et al.[130] and subsequently used by the Assessment Group for the NICE multiple technology appraisal of erlotinib and gefitinib,[151] the company submission for osimertinib in T790M EGFRm NSCLC,[108] and other recent single technology appraisals in NSCLC[152, 153]. The costs were sourced from the latest National Schedule of Reference Costs[142] and Personal Social Services Research Unit (PSSRU) 2017[150] and are summarised in Table 77 and Table 78, which present the costs for PF and PD, respectively.

Table 77: Progression-free health state costs (per 30 days)

Cost item	Resource usage per annum	Units per 30 days	Unit cost (£)	Source / comment
Outpatient visit	9.61	0.79	£136.43	Clinical oncology (consultant led - Service code 800)[142]
Chest radiography	6.79	0.56	£29.78	DAPF - Direct access plain film[142]
CT scan (chest)	0.62	0.05	£112.07	RD24Z - Computerised Tomography Scan of two areas, with contrast[142]
CT scan (other)	0.36	0.03	£122.33	RD26Z - Computerised Tomography Scan of three areas, with contrast[142]
ECG	1.04	0.09	£133.43	EY51Z - Electrocardiogram Monitoring or Stress Testing[142]
Community nurse visit	8.7 home visits (20 minutes)	0.71	£24.55	Cost per 20 mins spent on home visit (incl. qualification) PSSRU 2013[141] updated using HCHS index[150]
Clinical nurse specialist	12 hours contact time	0.99	£110.00	Cost per contact hour band 6 hospital based (nurse specialist)[141]
GP surgery	12 consultations	0.99	£38.00	Per surgery consultation lasting 9.22 minutes (incl. qualification and direct staff costs)[141]
Total cost per 30 days (£)			£308.43	

HCHS: Hospital and Community Health Services; NHS: National Health Service; PSSRU: Personal Social Services Research Unit

Table 78: Progressed disease health state costs (per 30 days)

Cost item	Resource usage per annum	Units per 30 days	Unit cost (£)	Source / comment
Outpatient visit	7.91	0.65	£136.43	Clinical oncology (consultant led - Service code 800)[142]

Chest radiography	6.50	0.53	£29.78	DAPF - Direct access plain film[142]
CT scan (chest)	0.24	0.02	£112.07	RD24Z - Computerised Tomography Scan of two areas, with contrast[142]
CT scan (other)	0.42	0.03	£122.33	RD26Z - Computerised Tomography Scan of three areas, with contrast[142]
ECG	0.88	0.07	£133.43	EY51Z - Electrocardiogram Monitoring or Stress Testing[142]
Community nurse visit	8.7 visits (20 minutes)	0.71	£24.55	Cost per 20 mins spent on home visit (incl. qualification) PSSRU 2013[141] updated using HCHS index[150]
Clinical nurse specialist	12 hours contact time	0.99	£110.00	Cost per contact hour band 6 hospital based (nurse specialist)[141]
GP home visit	26.09	2.14	£117.71	Per out of surgery visit lasting 23.4 minutes with qualification and direct staff costs including travel PSSRU 2012[154] updated for inflation HCHS index[150]
Therapist visit	26.09	2.14	£45.00	Community occupational therapist (local authority) per hour incl. qualification[141]
Total cost per 30 days (£)			£595.25	

HCHS: Hospital and Community Health Services; NHS: National Health Service; PSSRU: Personal Social Services Research Unit

End of life/terminal care costs

The base-case includes costs associated with end-of-life/terminal care. Resource use for end-of-life/terminal care was also based on information from a study by Brown et al.[130] which provides resource use for the time spent either in hospital, hospice, or at home. Costs were sourced from the latest National Schedule of Reference Costs[142] and PSSRU 2017.[150] The terminal costs used in the base-case setting are summarised in Table 79.

Table 79: End-of-life/terminal care costs (one-off)

Resource	Resource use	Unit costs (£)	Source / Comment
Hospital	55.8%	£3,296.11	DZ17L-V Non-elective long stay - Respiratory Neoplasms with no/single/multiple Interventions, with CC Score 0-10+ (weighted average) 0.92 Non-elective inpatients excess bed days[142]

Hospice	16.9%	£4,120.14	25% increase on hospital inpatients care
Home	27.3%	£5740.95	28 hours community nurse visit (incl. travel time) - Cost per hour spent on home visit (incl. qualification) PSSRU 2012 updated using HCHS index[150, 154] 7 GP home visits (incl. travel time) - Cost per out of surgery visit lasting 23.4 minutes (incl. qualification and direct staff costs) PSSRU 2012 updated for inflation using HCHS index[150, 154] Drugs and equipment - Marie Curie report figure of £240 (2003/04) updated for inflation using HCHS index[150, 154, 155]
Total cost		£4,102.81	

HCHS: Hospital and Community Health Services; PSSRU: Personal Social Services Research Unit

Adverse reaction unit costs and resource use

Adverse events were applied in the model as one-off events. This means that the incidence data used is for the whole treatment period and the unit costs are per event. The unit costs for each adverse event were based on Healthcare Resource Group (HRG) code used in previous NICE appraisals[108, 136] and costed using the latest National Schedule of Reference Costs,[142] as summarised in Table 80.

Table 80: Cost per adverse events used in the model

Adverse event	Cost per event	HRG code	Justification
Alanine aminotransferase increased	£2,414.94	GC17A–K. Non-Malignant, Hepatobiliary or Pancreatic Disorders with/without (single/multiple) Interventions with CC Score 0-9+; Non-elective long stay (Weighted Average)	Increased ALT levels are linked to potential liver damage; hepatobiliary includes the liver plus gallbladder or bile ducts
Aspartate aminotransferase increased	£2,414.94	GC17A–K. Non-Malignant, Hepatobiliary or Pancreatic Disorders with/without (single/multiple) Interventions with CC Score 0-9+; Non-elective long stay (Weighted Average)	Assumed same as ALT increased
Diarrhoea	£2,280.06	FD10A-M Non-Malignant Gastrointestinal Tract Disorders with/without (single/multiple) Interventions, with CC Score 0-9+; Non-elective long stay (Weighted Average)	Applied in TA476[136]
Fatigue[1]	£3,048.16	SA01G-SA01K Acquired Pure Red Cell Aplasia or Other Aplastic Anaemia, with CC Score 0-8+; non-elective long stay (Weighted Average)	Applied in TA416[108]
Rash or acne[2]	£2,622.06	JD07A-K Skin Disorders with/without Interventions, with CC Score 0-18;	Applied in TA416[108]

		Non-elective long stay (Weighted Average)	

ALT: alanine aminotransferase; HRG: Healthcare Resource Groups

[1]Grouped term including the following reported preferred terms: asthenia, fatigue, and lethargy

[2]Grouped term including the following reported preferred terms: acne, blister, dermatitis, dermatitis acneiform, dermatitis bullous, dry skin, drug eruption, eczema, erythema, exfoliative rash, folliculitis, Henoch-Schonlein purpura, rash, rash erythematous, rash follicular, rash macular, rash maculopapular, rash popular, rash pruritic, rash pustular, skin erosion, skin exfoliation, skin fissures, skin irritation, skin lesion, skin reaction, skin toxicity, skin ulcer, toxic epidermal necrolysis and urticaria

Table 81 presents a summary of the total adverse event costs, based on the incidence rates in Table 46 and the unit costs in Table 80.

Table 81: Total costs of adverse event by treatment

Treatment	Total costs of adverse events
Osimertinib	£175.09
Erlotinib	£679.79
Gefitinib	£679.79
Afatinib	£718.67

Miscellaneous unit costs and resource use

CNS metastases treatment costs

In the FLAURA study, osimertinib was associated with a lower number of events of CNS progression, irrespective of status with respect to known or treated CNS metastases at trial entry[26] (Table 82).

Table 82: CNS progression in FLAURA

Reason for progression	Osimertinib	SoC
Total number of progression events	136	206
Number of patients with progression due to death	11	14
Number of patients with CNS progression	17	42
% of CNS progression events (excluding deaths)	13.6%	21.9%

CNS: central nervous system; SoC: standard of care

Source: Soria et al.[26]

As previously described in the published literature,[48, 156, 157] treatment of CNS metastases is associated with increased healthcare resource use and additional economic burden. In order to capture the additional costs associated with brain metastases, a one-off cost was applied on progression to the proportion of patients expected to progress due to CNS metastases. In the absence of any reported CNS progression event data for afatinib from the LUX-Lung 7 trial, an assumption was made that the proportion is equivalent to that observed for SoC in FLAURA, based on the comparable CNS penetration for 1st and 2nd generation TKIs.[158] Additional healthcare resource use was obtained from an ongoing NICE technology appraisal[159] of alectinib for untreated ALK-positive NSCLC and is presented in Table 83.

Table 83: Additional resource use for CNS metastases

Resource	% of patients treated	Lifetime exposure	Unit cost	Total treatment cost	Source
SRS	25%	6 doses	£3,098.87	£18,593.22	Clinical experts' opinion in NICE ID925[159] AA71A - Stereotactic intracranial radiosurgery for neoplasms or other neurological conditions, with CC score 4+[142]
WBRT	25%	NR	NR	£4,200.00	ERG report for NICE ID925[159]
One-off cost used in the model				£5,698.31	

CNS: central nervous system; SRS: stereotactic radiosurgery; WBRT: whole brain radiotherapy; NR: not reported

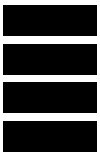
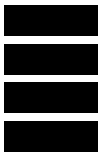
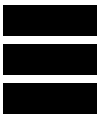
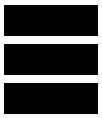
B.3.6 Summary of base-case analysis inputs and assumptions

Summary of base-case analysis inputs

A summary of the key variables used in the base-case setting is presented in Table 84.

Table 84: Summary of variables applied in the economic model

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution	Reference to section in submission
General model parameters			
Time horizon	20 years	Fixed	B.3.2
Model cycle length	30 days	Fixed	B.3.2
Discount rate - efficacy	3.5%	Fixed	B.3.2
Discount rate - costs	3.5%	Fixed	B.3.2
Population parameters			
Starting age	63	Fixed	B.3.2
Body surface area	1.67	s.e. = 0.01 (lognormal)	B.3.5
Parametric curves			

PFS – osimertinib	Generalised gamma (dependent model) μ = 2.53 σ = 0.73 Q = 0.68 Tx = 0.54	95% C.I. (multivariate normal) 2.39 – 2.68 0.63 – 0.85 0.35 – 1.01 0.38 – 0.69	B.3.3
PFS – 1st/2nd generation TKIs	Generalised gamma (dependent model) μ = 2.53 σ = 0.73 Q = 0.68	95% C.I. (multivariate normal) 2.39 – 2.68 0.63 – 0.85 0.35 – 1.01	B.3.3
OS – osimertinib	Weibull (piecewise model) Shape = 1.03 Scale = 41.49 Tx = 0.44	95% C.I. (multivariate normal) 0.86 – 1.22 30.09 – 57.21 0.07 – 0.82	B.3.3
OS – 1st/2nd generation TKIs	Weibull (piecewise model) Shape = 1.03 Scale = 41.49	95% C.I. (multivariate normal) 0.86 – 1.22 30.09 – 57.21	B.3.3
TDT – osimertinib	Generalised gamma (dependent model) 	95% C.I. (multivariate normal) 	B.3.5
TDT – 1st/2nd generation TKIs	Generalised gamma (dependent model) 	95% C.I. (multivariate normal) 	B.3.5
Treatment duration – PDC 2L	2.40	N/A* (log-normal)	B.3.5
TDT – Osimertinib 2L	Generalised gamma 	95% C.I. (multivariate normal) 	B.3.5
Treatment duration – PDC 3L	2.40	N/A* (log-normal)	B.3.5

Treatment duration – Docetaxel 3L	1.70	N/A* (log-normal)	B.3.5
Adverse event rates			
Osimertinib			
Alanine aminotransferase increased	0.004	N/A* (beta)	B.3.3
Aspartate aminotransferase increased	0.007	N/A* (beta)	B.3.3
Diarrhoea	0.022	N/A* (beta)	B.3.3
Fatigue	0.014	N/A* (beta)	B.3.3
Rash or acne	0.022	N/A* (beta)	B.3.3
1st/2nd generation TKIs			
Alanine aminotransferase increased	0.090	N/A* (beta)	B.3.3
Aspartate aminotransferase increased	0.043	N/A* (beta)	B.3.3
Diarrhoea	0.025	N/A* (beta)	B.3.3
Fatigue	0.014	N/A* (beta)	B.3.3
Rash or acne	0.097	N/A* (beta)	B.3.3
Health-state utilities			
Progression-free	[redacted]	[redacted]	B.3.4
Progressed disease (1L treatment)	[redacted]	[redacted]	B.3.4
Progressed disease (2L treatment)	0.64	s.e. = 0.03 (beta)	B.3.4
Adverse event disutilities			
Alanine aminotransferase increased	-0.05	0.00 (log-normal)	B.3.4
Aspartate aminotransferase increased	-0.05	0.00 (log-normal)	B.3.4
Diarrhoea	-0.05	0.00 (log-normal)	B.3.4
Fatigue	-0.07	0.00 (log-normal)	B.3.4
Rash or acne	-0.03	0.00 (log-normal)	B.3.4
Technology acquisition costs			
Osimertinib (per pack)	£5,770.00	Fixed	B.3.5
Erlotinib (per pack)	£1,631.53	Fixed	B.3.5
Gefitinib (per pack)	£2,167.71	Fixed	B.3.5
Afatinib (per pack)	£2,023.28	Fixed	B.3.5
Pemetrexed (per vial)	£160.00	Fixed	B.3.5
Cisplatin (per vial)	£4.48	Fixed	B.3.5
Docetaxel (per vial)	£14.74	Fixed	B.3.5
Administration costs (per 30 days)			
Oral treatments	£8.40	N/A* (gamma)	B.3.5
PDC	£557.25	N/A* (gamma)	B.3.5
Docetaxel	£567.17	N/A* (gamma)	B.3.5

Monitoring costs (per 30 days)			
PDC	£7.80	N/A* (gamma)	B.3.5
Docetaxel	£4.43	N/A* (gamma)	B.3.5
Disease management costs			
Progression-free (per 30 days)	£308.43	N/A* (gamma)	B.3.5
Progressed disease (per 30 days)	£595.25	N/A* (gamma)	B.3.5
Terminal care costs (per event)	£4,102.81	N/A* (gamma)	B.3.5
CNS progression (per event)	£5,698.31	N/A* (gamma)	B.3.5
Adverse event management costs (per event)			
Alanine aminotransferase increased	£2,414.94	N/A* (gamma)	B.3.5
Aspartate aminotransferase increased	£2,414.94	N/A* (gamma)	B.3.5
Diarrhoea	£2,280.06	N/A* (gamma)	B.3.5
Fatigue	£3,048.16	N/A* (gamma)	B.3.5
Rash or acne	£2,622.06	N/A* (gamma)	B.3.5
Cost of T790 test			
Cost of identifying a person with T790M	£1,282.46	N/A* (gamma)	B.3.5

s.e.: standard error; C.I.: confidence interval; PFS: progression-free survival; OS: overall survival; N/A: not available; PDC: platinum doublet chemotherapy; CNS: central nervous system

*Standard error set to 10% to facilitate the analysis

Assumptions

The key assumptions applied in the base-case analysis are described in Table 85.

Table 85: Key assumptions used in the economic model (base-case)

Assumptions
General
Patient characteristics (age and body surface area) were derived from FLAURA and were assumed to be representative of the EGFR+ NSCLC patients in the UK
The cycle length used is 30 days. Thus, a year was assumed to consist of 12.175 cycles of 30 days. Half-cycle correction was applied
A time horizon of 20 years was used
Discounting of costs and outcomes was applied annually (3.5%)
Model structure
Subsequent treatments were incorporated on discontinuation of first-line treatment
The effect of subsequent treatments was assumed to be implicitly incorporated in the OS curve, as patients in the FLAURA study were allowed to receive other anti-cancer treatments on progression from the randomised treatment
The cost of subsequent treatments was computed as a one-off cost, and includes drug acquisition, administration and monitoring, and T790M testing costs (where relevant)
Efficacy

The effect of osimertinib on PFS and OS relative to comparator treatments (erlotinib and gefitinib) was informed by the FLAURA study
Erlotinib and gefitinib were assumed to have equal efficacy
The proportional hazards assumption between osimertinib and SoC was assumed to hold for PFS for the entire time horizon, and for OS beyond 7.9 months
Afatinib was assumed to have equal efficacy of SoC in FLAURA
Safety
Treatment related grade 3+ AEs that had an incidence >1% in any treatment were included in the analysis
AEs were applied upon initiation of first-line treatment
Costs and disutilities of adverse events were applied as one-off events
Utilities
HSU values were applied directly to health states (PF, PD on 1L, PD on subsequent treatments).
HSU values were assumed to be constant over time
HSU values were assumed not to be treatment specific
One-off disutilities (accounting for the incidence rate, utility decrement and duration of each adverse events included in the analysis) were applied upon initiation of first-line treatment to model the impact of adverse events on QoL
The model does not account for the potential impact on HRQoL of subsequent treatments
Costs
The model applies list prices for all the primary treatments
Treatment costs for the primary comparators were modelled based on TDT (parametric) from FLAURA
Only second- and third-line treatments were included. The duration of second-line treatments was based on extrapolated mean time to treatment discontinuation from AURA3. The duration of third-line treatments was assumed to be similar to that in second-line for PDC, and sourced from the literature for docetaxel
Proportion of patients receiving each subsequent treatment and BSC only were based on clinical experts' opinion
Disease management costs during progression-free and progressed disease were included in the analysis
A one-off terminal care cost was applied upon death to account for the cost associated with the additional intensive disease management in the months prior to death
The cost of vial wastage was excluded for IV treatments (no wastage is assumed for oral treatments)
Acquisition and administration costs were applied at the start of cycle population (mid-cycle discontinuation of treatment has no effect on treatment costs [oral treatments are distributed on day 1 of each treatment cycle, IV treatments are administered on day 1 of each treatment cycle])
CNS progression was assumed to be associated with a one-off cost (at progression) to account for additional resource use (compared to non-CNS progression)

EGFRm+: epidermal growth factor receptor mutation positive; NSCLC: non-small cell lung cancer; OS: overall survival; PFS: progression-free survival; SoC: standard of care; AEs: adverse events; HSU: health-state utility; PF: progression-free; PD: progressed disease; QoL: quality of life; HRQoL: health-related quality of life; TDT: time to discontinuation of treatment; PDC: platinum doublet chemotherapy; BSC: best supportive care; IV: intra venous; CNS: central nervous system

B.3.7 Base-case results

Base-case incremental cost-effectiveness analysis results

The key results from the base-case analysis (list prices) are summarised in Table 86. Over a lifetime horizon (20 years), the costs per patient associated with osimertinib treatment are £168,925 compared to £75,094 for erlotinib, £82,443 for gefitinib and £82,448 for afatinib. This represents an incremental cost of £93,832 versus erlotinib, £86,482 versus gefitinib and £86,477 versus afatinib. Treatment with osimertinib is associated with 3.392 QALYs versus 2.346 QALYs for erlotinib, gefitinib, and afatinib. Thus, compared to erlotinib, gefitinib and afatinib, osimertinib is associated with 1.046 QALYs gained. The incremental costs per QALY gained are £89,700 relative to erlotinib, £82,675 relative to gefitinib, and £82,669 relative to afatinib.

The incremental cost-effectiveness results using the proposed PAS for osimertinib and the publicly available PAS for gefitinib (one-off cost of £12,200 to all patients on treatment at the third treatment cycle) are presented in Appendix J. Erlotinib and afatinib are subject to a confidential PAS, therefore the comparison against them could not be conducted. However, the impact of varying the one-off payment for gefitinib was explored in scenario analyses in order to address the uncertainty around the comparators' cost.

Clinical outcomes from the model

Treatment with osimertinib is associated with 4.861 years of life expectancy compared to 3.404 years with comparator treatments. The proportion of patients alive at 1, 2, 5 and 10 years is 89%, 74%, 43% and 16% for those treated with osimertinib compared with 82%, 62%, 26% and 6% for those treated with erlotinib, gefitinib or afatinib.

The predicted mean and median time to disease progression, time in progressed disease and time alive for each arm of the simulation are summarised in Table 87. The predicted mean and median time to disease progression are 21.96 and 16.76 months with osimertinib, compared to 12.84 and 9.86 months with comparator treatments (erlotinib, gefitinib and afatinib). These estimates are in line with the median values from the observed data in FLAURA, although there is a slight underestimation (18.9 and 10.2 for osimertinib and SoC respectively). The predicted mean and median time to death are 66.95 and 48.30 months with osimertinib, compared to 44.75 and 31.54 months with erlotinib, gefitinib and afatinib. Comparison against the observed median OS in the FLAURA study is not possible due to immaturity of the OS data.

Table 86: Base-case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£) vs osimertinib	Incremental LYG vs osimertinib	Incremental QALYs vs osimertinib	ICER – fully incremental (£/QALY)	ICER – pairwise (£/QALY)
Erlotinib	£75,094	3.404	2.346	£93,832	1.457	1.046	Referent	£89,700
Gefitinib	£82,443	3.404	2.246	£86,482	1.457	1.046	Dominated	£82,675
Afatinib	£82,448	3.404	2.346	£86,477	1.457	1.046	Dominated	£82,669
Osimertinib	£168,925	4.861	3.392	--	--	--	£89,700	--

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

Table 87: Survival outcomes: time (mean and median) spent in health states, undiscounted

	Time in PFS (months)		Time in PD (months)		Time alive (months)	
Treatment	*Mean*	*Median*	*Mean*	*Median*	*Mean*	*Median*
Gefitinib	12.84	9.86	31.91	21.68	44.75	31.54
Afatinib	12.84	9.86	31.91	21.68	44.75	31.54
Erlotinib	12.84	9.86	31.91	21.68	44.75	31.54
Osimertinib	21.96	16.76	44.99	31.54	66.95	48.30

PD: progressed disease; PFS: progression-free survival

Disaggregated results of the base-case incremental cost-effectiveness analysis

Table 88 summarises the breakdown of QALYs for each health state over the model time horizon in the base-case analysis. Treatment with osimertinib is associated with more QALYs in the PF and PD health states, with most of the incremental gain coming from the PF health state (55%): a gain of 0.57 QALYs is due to delay in progression and a gain of 0.47 QALYs is due to additional survival. Disutilities associated with adverse events are minimal for all treatments and in line with AE costs they are estimated to be lower for osimertinib than comparators.

Table 88: Breakdown of QALYs

Source of QALYs		Osimertinib	Erlotinib	Gefitinib	Afatinib
Health state	PF	1.410	0.839	0.839	0.839
	PD	1.982	1.507	1.507	1.507
	Death	0.000	0.000	0.000	0.000
Disutilities	AEs	-0.0001	-0.0005	-0.0005	-0.0005
Total QALYs		3.392	2.346	2.346	2.346

AE: adverse events; PF: progression free; PD: progressed disease; QALY: quality adjusted life years

Table 89 presents the breakdown of total costs in the base-case analysis. The largest contributor to the total costs for treatment with osimertinib is the acquisition cost, accounting for 78% of the total costs. Similarly, acquisition cost is the largest contributor of total costs associated with treatment with afatinib (36%). For erlotinib and gefitinib the largest contributor of the total costs is instead the costs of subsequent treatment (35% and 41% for erlotinib, and gefitinib respectively), whereas for osimertinib subsequent treatment costs only account for 2% of total costs.

Treatment with osimertinib is associated with higher absolute disease management costs versus erlotinib, gefitinib and afatinib, and this is due to patients staying progression-free and alive longer. The absolute cost of AEs is higher for comparators given their inferior safety profile.

Table 89: Breakdown of costs

Cost type		Osimertinib	Erlotinib	Gefitinib	Afatinib
Disease management costs	PF	£6,666	£3,969	£3,969	£3,969
	PD	£22,361	£17,011	£17,011	£17,011
	CNS progression	£731	£1,197	£1,197	£1,197
	Terminal care	£3,441	£3,689	£3,689	£3,689
Treatment-related costs	Acquisition	£131,361	£22,362	£29,711	£29,713
	Administration	£207	£126	£126	£130

AE costs	£175	£680	£680	£680
Subsequent treatment costs	£3,982	£26,061	£26,061	£26,061
Total costs	£168,925	£75,094	£82,443	£82,448

AE: adverse events; CNS: central nervous system; PD: progressed disease; PF: progression free

B.3.8 Sensitivity analyses

Probabilistic sensitivity analysis

A PSA using 10,000 iterations was run using the base-case settings and the probability distributions described in Table 84.

The average results of all PSA iterations showed similar results (~2% difference in ICER) as the base-case deterministic results (section B.3.7). This means that, although there is much uncertainty in the results (see next section), the stochastic parametric uncertainty and its applied distributions converge well at 10,000 iterations. The total results were similar compared to the deterministic base-case setting, and the results showed a slightly lower ICER for osimertinib versus erlotinib, gefitinib and afatinib compared to the deterministic base-case.

Table 90: Average results from the probabilistic sensitivity analysis

Treatment	Costs	QALYs	ICER (£/QALY)
Osimertinib	£170,785	3.435	--
Erlotinib	£75,836	2.358	£88,137
Gefitinib	£83,281	2.358	£81,218
Afatinib	£83,294	2.357	£81,152

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

Cost-effectiveness plane

The cost-effectiveness planes (CEP) versus each comparator are presented in Figure 50, Figure 51 and Figure 52, showing the incremental results of all the simulations of the PSA. Osimertinib is associated with higher costs but also higher QALYs in all simulations. The joint distribution of costs and QALYs for each comparator is presented in the cost-effectiveness plane in Figure 53. The graph shows that the uncertainty for all comparators is driven by both costs and QALYs and tends to be larger for osimertinib.

Figure 50: Cost-effectiveness plane - incremental costs and QALYs for osimertinib vs erlotinib (list price)

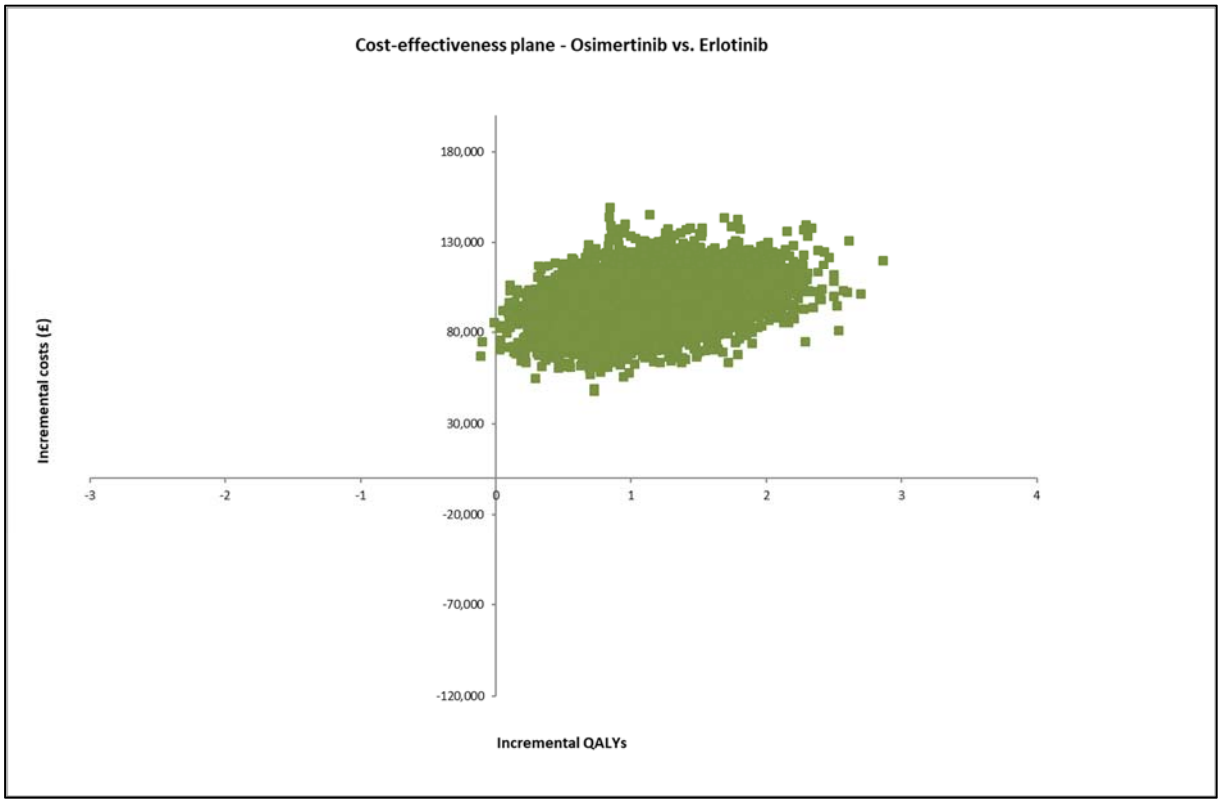


Figure 51: Cost-effectiveness plane - incremental costs and QALYs for osimertinib vs gefitinib (list price)

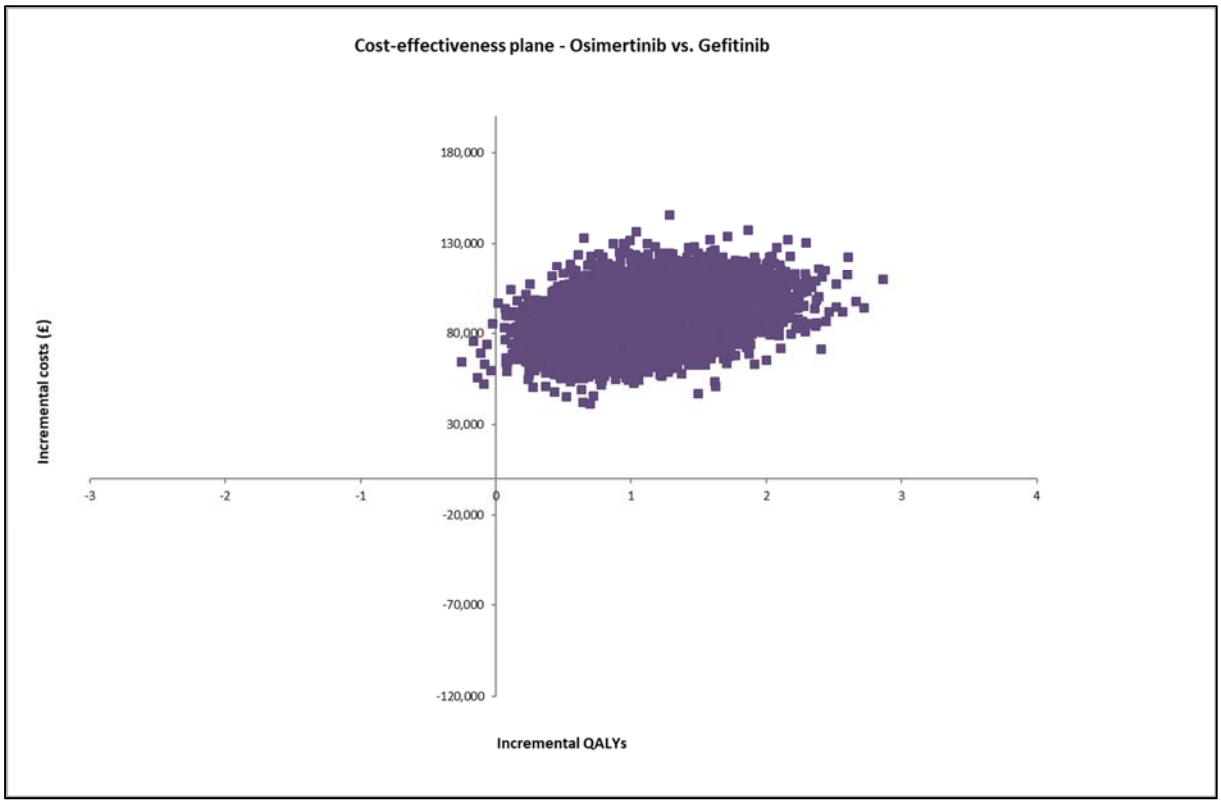


Figure 52: Cost-effectiveness plane - incremental costs and QALYs for osimertinib vs afatinib (list price)

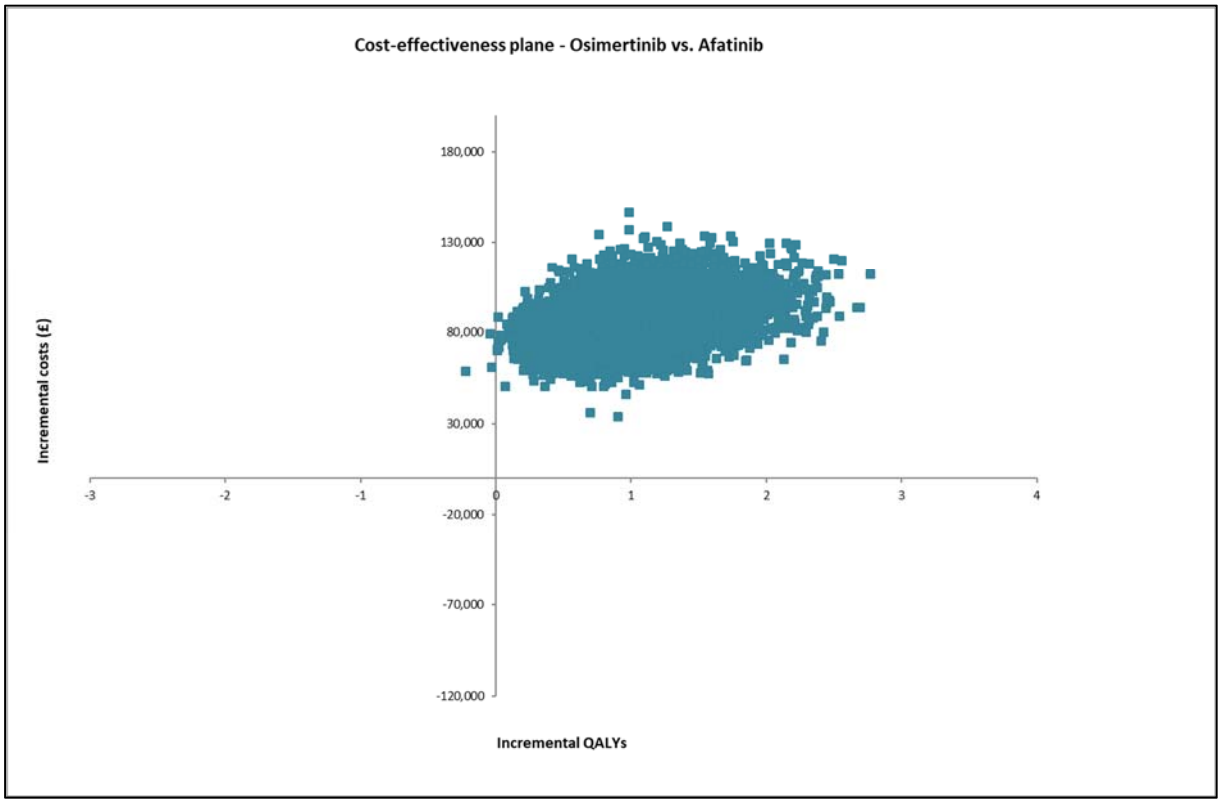
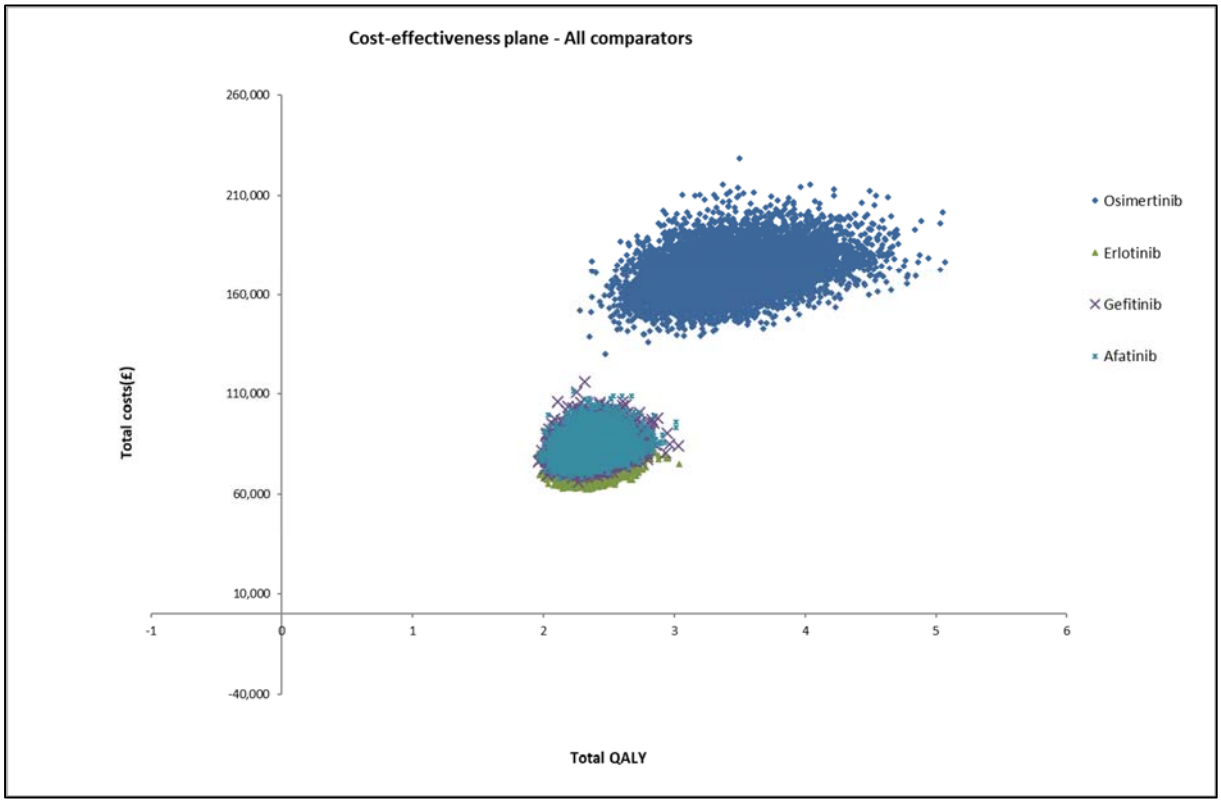


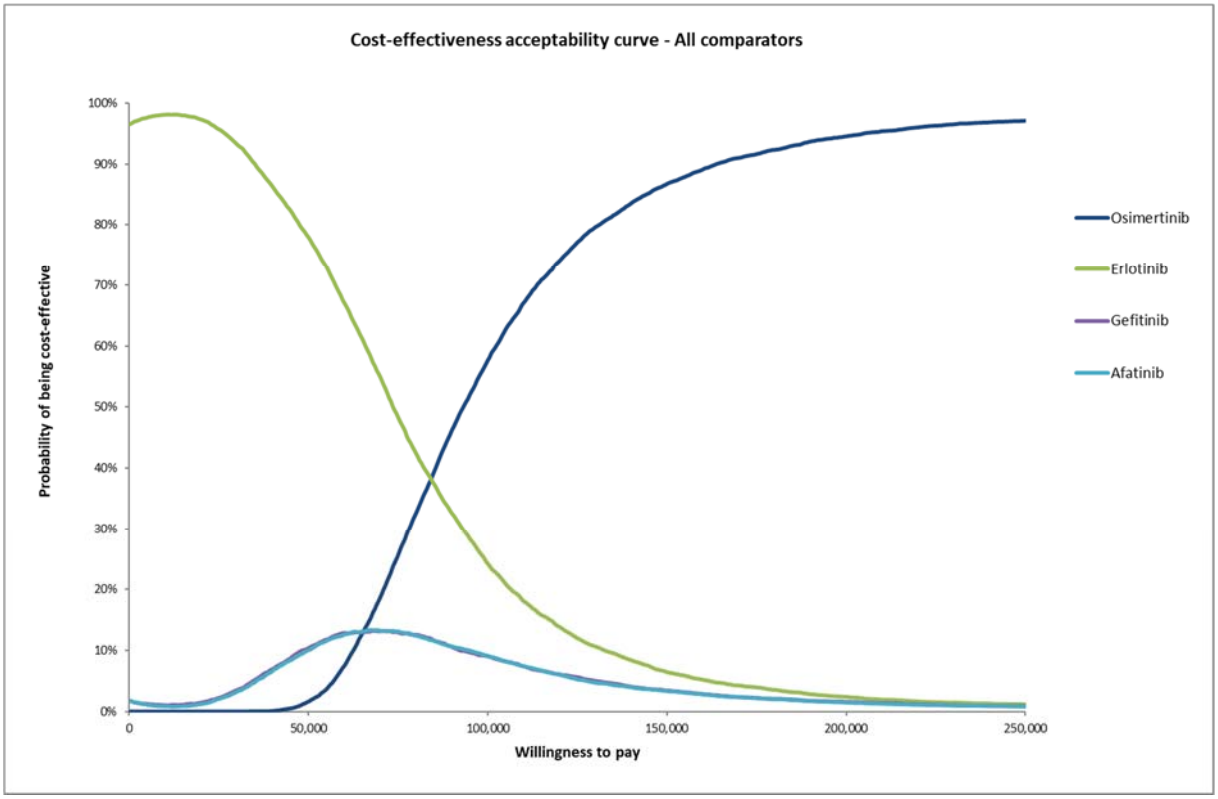
Figure 53: Cost-effectiveness plane - total results for osimertinib and all comparators



Cost-effectiveness acceptability curves

The results from the cost-effectiveness acceptability curves (CEAC) are presented in Figure 54. The CEACs plot the probability that each comparator is cost-effective at a range of decision thresholds. In Figure 54, erlotinib has the highest probability of being cost-effective at a threshold of £50,000 (78%) and up to ~£84,000. At a threshold of £84,500 osimertinib has the highest probability (38%) and increases thereafter.

Figure 54: Cost-effectiveness acceptability curves



Deterministic sensitivity analysis

DSA, or one-way sensitivity analysis, assesses parameters' uncertainty one at a time and allows identifying the main model drivers. A standard ±20% variation was used. The uncertainty parameters and the variations are presented in Table 91.

Table 91: Parameters included in the DSA

Parameter		Parameter values		
		Lower value	*Base-case*	*Upper value*
Body surface area (m²)		1.33	1.67	2.00
Discount rate	Costs	2.8%	3.5%	4.2%
	Outcomes	2.8%	3.5%	4.2%
Survival function – treatment coefficient	PFS	0.43	0.54	0.64
	OS	0.36	0.44	0.53

	TDT	[redacted]	[redacted]	[redacted]
Disease management costs	PF (monthly)	£247	£308	£370
	PD (monthly)	£476	£595	£714
	CNS progression	£4,559	£5,698	£6,838
	Terminal	£3,282	£4,103	£4,923
Health state utility	PF	0.635	0.794	0.953
	PD on 1L treatment	0.563	0.704	0.845
	PD on subsequent treatments	0.512	0.640	0.768
Administration costs (cost per 30 days)	Osimertinib	£7	£9	£11
	Erlotinib	£7	£9	£11
	Gefitinib	£7	£9	£11
	Afatinib	£8	£10	£12
Subsequent treatments: duration (in 30 days)	PDC (2L T790M±)	1.92	2.40	2.88
	Osimertinib (2L T790M+)	[redacted]	[redacted]	[redacted]
	PDC (2L T790M-)	1.92	2.40	2.88
	Docetaxel	1.36	1.70	2.04
Subsequent treatments: total cost (per 30 days)	PDC (2L T790M±)	£1,952	£2,440	2,928
	Osimertinib (2L T790M+)	[redacted]	[redacted]	[redacted]
	PDC (2L T790M-)	£2,379	£2,974	£3,569
	Docetaxel	£444	£555	£666
First subsequent treatments: distributions	Osimertinib to PDC	53%	67%	80%
	Erlotinib to osimertinib	27%	33%	40%
	Erlotinib to PDC	27%	33%	40%
	Gefitinib to osimertinib	27%	33%	40%
	Gefitinib to PDC	27%	33%	40%
	Afatinib to osimertinib	27%	33%	40%
	Afatinib to PDC	27%	33%	40%
Proportion of patients progressing due to CNS metastases	Osimertinib	11%	14%	16%
	Erlotinib	18%	22%	26%
	Gefitinib	18%	22%	26%
	Afatinib	18%	22%	26%

CNS: central nervous system; OS: overall survival; PD: progressed disease; PDC: platinum doublet chemotherapy; PF: progression free; PFS: progression-free survival

The results of the one-way sensitivity analyses are reported in Table 92, Table 93, and Table 94 for the comparison against erlotinib, gefitinib and afatinib respectively. The tornado diagrams in Figure 55 - Figure 57 show the 20 parameters with the largest impact on the ICER. The key drivers of the model results are: the relative treatment effect on OS and TDT, the HSU value for the PF and PD (on subsequent treatments) states, and the proportion of patients receiving osimertinib in second-line, its duration of treatment and costs.

Table 92: Results of deterministic sensitivity analysis (osimertinib versus erlotinib)

Parameter		Absolute change in ICER (£)			% change in ICER (%)	
		Lower value	*Base-case*	*Upper value*	*Lower value*	*Upper value*
Body surface area (m²)		£89,652	£89,700	£89,749	-0.1%	0.1%
Discount rate	Costs	£90,815	£89,700	£88,634	1.2%	-1.2%
	Outcomes	£86,053	£89,700	£93,392	-4.1%	4.1%
Survival function – treatment coefficient	PFS	£91,798	£89,700	£87,209	2.3%	-2.8%
	OS	£107,328	£89,700	£77,083	19.7%	-14.1%
	TDT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Disease management costs	PF (monthly)	£89,184	£89,700	£90,216	-0.6%	0.6%
	PD (monthly)	£88,677	£89,700	£90,723	-1.1%	1.1%
	CNS progression	£89,789	£89,700	£89,611	0.1%	-0.1%
	Terminal	£89,748	£89,700	£89,653	0.1%	-0.1%
Health state utility	PF	£100,680	£89,700	£80,880	12.2%	-9.8%
	PD on 1L treatment	£89,749	£89,700	£89,652	0.1%	-0.1%
	PD on subsequent treatments	£98,608	£89,700	£82,268	9.9%	-8.3%
Administration costs (cost per 30 days)	Osimertinib	£89,661	£89,700	£89,740	0.0%	0.0%
	Erlotinib	£89,724	£89,700	£89,676	0.0%	0.0%
Subsequent treatments: duration (in 30 days)	PDC (2L T790M±)	£89,282	£89,700	£90,118	-0.5%	0.5%
	Osimertinib (2L T790M+)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	PDC (2L T790M-)	£90,059	£89,700	£89,342	0.4%	-0.4%
	Docetaxel	£89,672	£89,700	£89,728	0.0%	0.0%
Subsequent treatments: total cost (per 30 days)	PDC (2L T790M±)	£89,282	£89,700	£90,118	-0.5%	0.5%
	Osimertinib (2L T790M+)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	PDC (2L T790M-)	£90,137	£89,700	£89,263	0.5%	-0.5%

	Docetaxel	£89,672	£89,700	£89,728	0.0%	0.0%
First subsequent treatments: distributions	Osimertinib to PDC	£88,996	£89,700	£90,405	-0.8%	0.8%
	Erlotinib to osimertinib	£93,930	£89,700	£85,470	4.7%	-4.7%
	Erlotinib to PDC	£90,137	£89,700	£89,263	0.5%	-0.5%
Proportion of patients progressing due to CNS metastases	Osimertinib	£89,560	£89,700	£89,840	-0.2%	0.2%
	Erlotinib	£89,929	£89,700	£89,471	0.3%	-0.3%

CNS: central nervous system; OS: overall survival; PD: progressed disease; PDC: platinum doublet chemotherapy; PF: progression free; PFS: progression-free survival

Figure 55: Tornado diagram (osimertinib versus erlotinib)

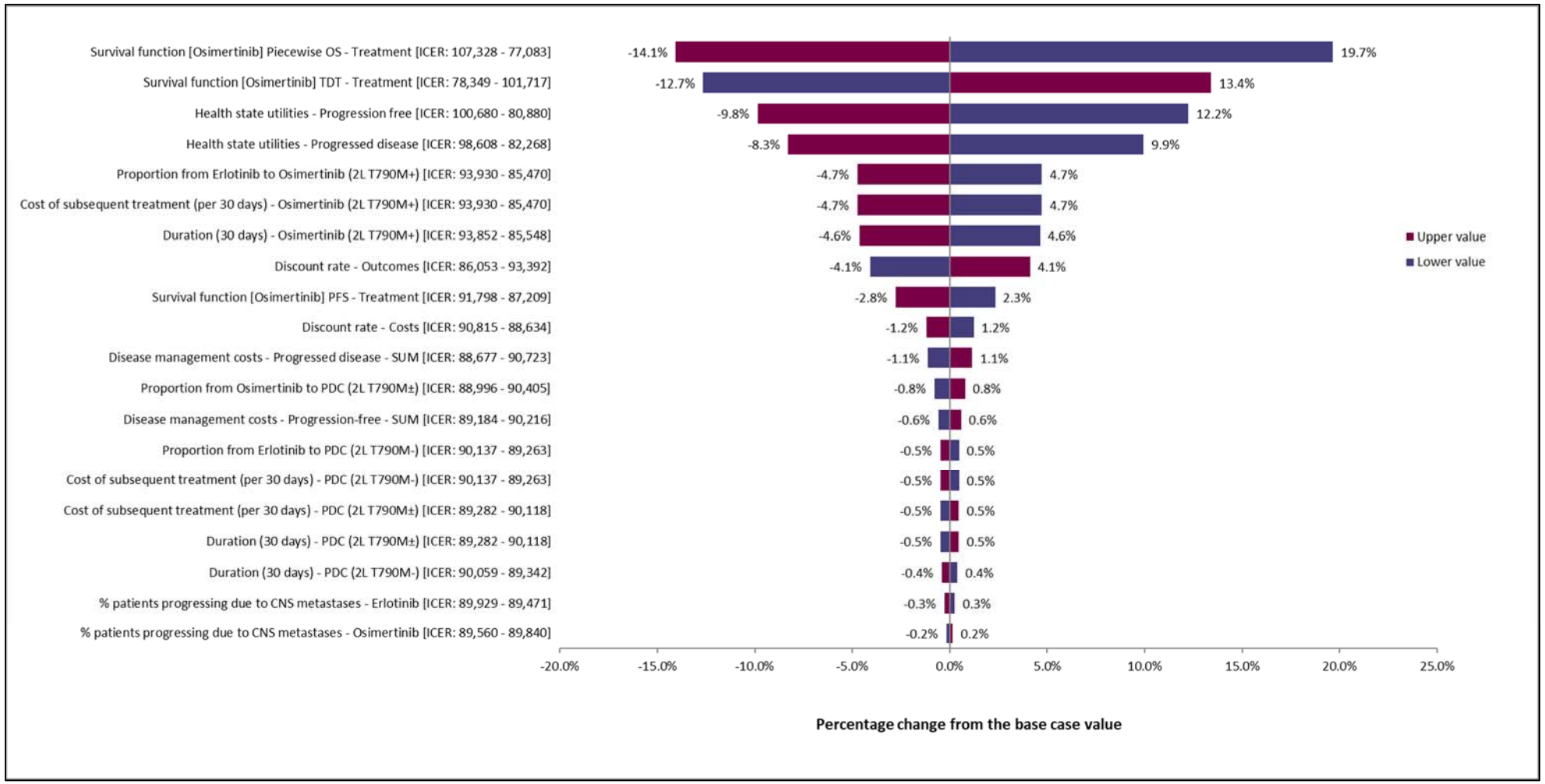


Table 93: Results of deterministic sensitivity analysis (osimertinib versus gefitinib)

Parameter		Absolute change in ICER (£)			% change in ICER (%)	
		Lower value	*Base-case*	*Upper value*	*Lower value*	*Upper value*
Body surface area (m²)		£82,626	£82,675	£82,723	-0.1%	0.1%
Discount rate	Costs	£83,772	£82,675	£81,626	1.3%	-1.3%
	Outcomes	£79,314	£82,675	£86,078	-4.1%	4.1%
Survival function – treatment coefficient	PFS	£84,654	£82,675	£80,330	2.4%	-2.8%
	OS	£98,728	£82,675	£71,184	19.4%	-13.9%
	TDT	[redacted]	£82,675	[redacted]	[redacted]	[redacted]
Disease management costs	PF (monthly)	£82,159	£82,675	£83,190	-0.6%	0.6%
	PD (monthly)	£81,652	£82,675	£83,698	-1.2%	1.2%
	CNS progression	£82,764	£82,675	£82,586	0.1%	-0.1%
	Terminal	£82,722	£82,675	£82,627	0.1%	-0.1%
Health state utility	PF	£92,794	£82,675	£74,545	12.2%	-9.8%
	PD on 1L treatment	£82,719	£82,675	£82,630	0.1%	-0.1%
	PD on subsequent treatments	£90,885	£82,675	£75,825	9.9%	-8.3%
Administration costs (cost per 30 days)	Osimertinib	£82,635	£82,675	£82,714	0.0%	0.0%
	Gefitinib	£82,699	£82,675	£82,651	0.0%	0.0%
Subsequent treatments: duration (in 30 days)	PDC (2L T790M±)	£82,257	£82,675	£83,093	-0.5%	0.5%
	Osimertinib (2L T790M+)	[redacted]	£82,675	[redacted]	[redacted]	[redacted]
	PDC (2L T790M-)	£83,033	£82,675	£82,316	0.4%	-0.4%
	Docetaxel	£82,647	£82,675	£82,703	0.0%	0.0%
Subsequent treatments: total cost (per 30 days	PDC (2L T790M±)	£82,257	£82,675	£83,093	-0.5%	0.5%
	Osimertinib (2L T790M+)	[redacted]	£82,675	[redacted]	[redacted]	[redacted]
	PDC (2L T790M-)	£83,112	£82,675	£82,238	0.5%	-0.5%

	Docetaxel	£82,647	£82,675	£82,703	0.0%	0.0%
First subsequent treatments: distributions	Osimertinib to PDC	£81,970	£82,675	£83,379	-0.9%	0.9%
	Gefitinib to osimertinib	£86,905	£82,675	£78,444	5.1%	-5.1%
	Gefitinib to PDC	£83,112	£82,675	£82,238	0.5%	-0.5%
Proportion of patients progressing due to CNS metastases	Osimertinib	£82,535	£82,675	£82,815	-0.2%	0.2%
	Gefitinib	£82,904	£82,675	£82,446	0.3%	-0.3%

CNS: central nervous system; OS: overall survival; PD: progressed disease; PDC: platinum doublet chemotherapy; PF: progression free; PFS: progression-free survival

Figure 56: Tornado diagram (osimertinib versus gefitinib)

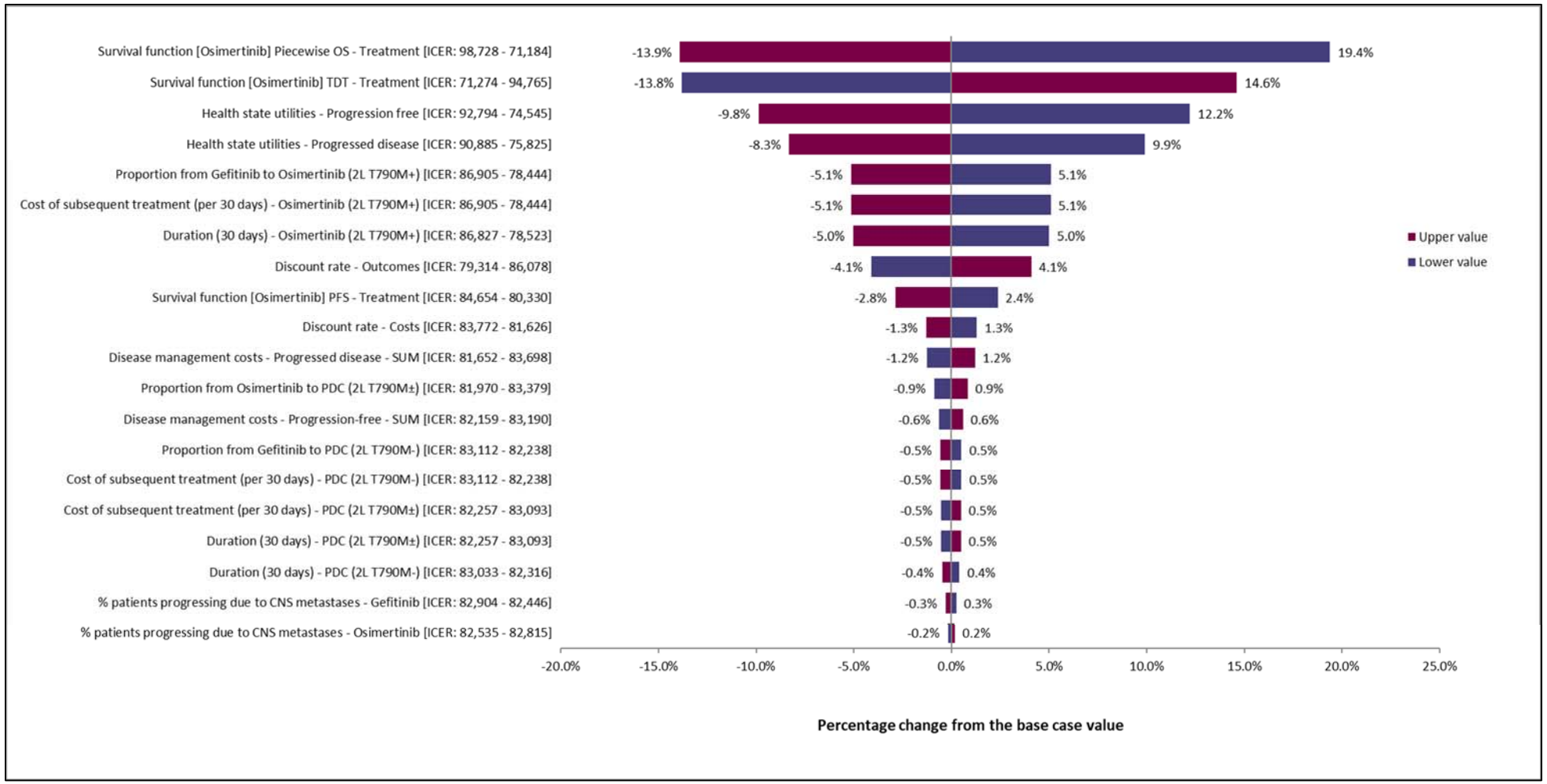


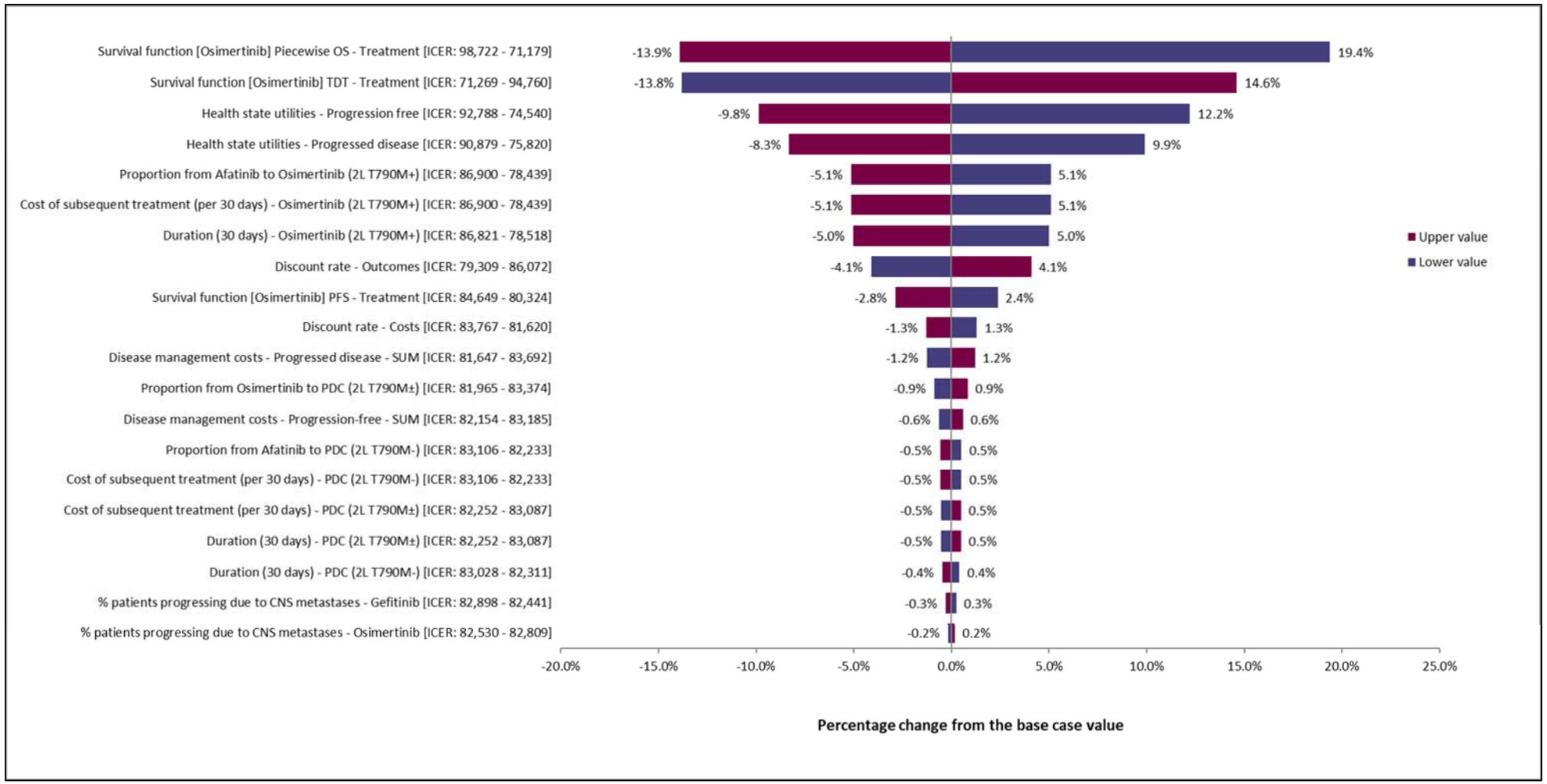
Table 94: Results of deterministic sensitivity analysis (osimertinib versus afatinib)

Parameter		Absolute change in ICER (£)			% change in ICER (%)	
		Lower value	*Base-case*	*Upper value*	*Lower value*	*Upper value*
Body surface area (m²)		£82,621	£82,669	82,718	-0.1%	0.1%
Discount rate	Costs	£83,767	£82,669	81,620	1.3%	-1.3%
	Outcomes	£79,309	£82,669	86,072	-4.1%	4.1%
Survival function – treatment coefficient	PFS	£84,649	£82,669	£80,324	2.4%	-2.8%
	OS	£98,722	£82,669	£71,179	19.4%	-13.9%
	TDT	[redacted]	£82,669	[redacted]	[redacted]	[redacted]
Disease management costs	PF (monthly)	£82,154	£82,669	£83,185	-0.6%	0.6%
	PD (monthly)	£81,647	£82,669	£83,692	-1.2%	1.2%
	CNS progression	£82,758	£82,669	£82,580	0.1%	-0.1%
	Terminal	£82,717	£82,669	£82,622	0.1%	-0.1%
Health state utility	PF	£92,788	£82,669	£74,540	12.2%	-9.8%
	PD on 1L treatment	£82,714	£82,669	£82,625	0.1%	-0.1%
	PD on subsequent treatments	£90,879	£82,669	£75,820	9.9%	-8.3%
Administration costs (cost per 30 days)	Osimertinib	£82,630	£82,669	£82,709	0.0%	0.0%
	Afatinib	£82,694	£82,669	£82,645	0.0%	0.0%
Subsequent treatments: duration (in 30 days)	PDC (2L T790M±)	£82,252	£82,669	£83,087	-0.5%	0.5%
	Osimertinib (2L T790M+)	[redacted]	£82,669	[redacted]	[redacted]	[redacted]
	PDC (2L T790M-)	£83,028	£82,669	£82,311	0.4%	-0.4%
	Docetaxel	£82,642	£82,669	£82,697	0.0%	0.0%
Subsequent treatments: total cost (per 30 days	PDC (2L T790M±)	£82,252	£82,669	£83,087	-0.5%	0.5%
	Osimertinib (2L T790M+)	[redacted]	£82,669	[redacted]	[redacted]	[redacted]
	PDC (2L T790M-)	£83,106	£82,669	£82,233	0.5%	-0.5%

	Docetaxel	£82,642	£82,669	£82,697	0.0%	0.0%
First subsequent treatments: distributions	Osimertinib to PDC	£81,965	£82,669	£83,374	-0.9%	0.9%
	Afatinib to osimertinib	£86,900	£82,669	£78,439	5.1%	-5.1%
	Afatinib to PDC	£83,106	£82,669	£82,233	0.5%	-0.5%
Proportion of patients progressing due to CNS metastases	Osimertinib	£82,530	£82,669	£82,809	-0.2%	0.2%
	Afatinib	£82,898	£82,669	£82,441	0.3%	-0.3%

CNS: central nervous system; OS: overall survival; PD: progressed disease; PDC: platinum doublet chemotherapy; PF: progression free; PFS: progression-free

Figure 57: Tornado diagram (osimertinib versus afatinib)



Scenario analysis

A number of scenario analyses were conducted to assess the impact of using alternative parameter estimates (Table 95). The results are presented in Table 96 - Table 98. Results are consistent across the three comparators. Key parameters that lead to a change in the ICER of +5% are time horizon (10 years), discount rate for costs and outcomes (6%), the choice of the approach to model OS (Weibull dependent; Log-logistic, dependent), the TDT parametric function (Weibull, dependent), the HSUV used for the progressed disease state (adjusted for subsequent treatments) and the exclusion of subsequent treatments costs. Key parameters that lead to a change in the ICER of -5% are discount rate for costs and outcomes (0%; 3.5%, 0%), the assumption around treatment duration (treatment until progression), the TDT parametric function (Gompertz, dependent) and the choice of the parametric function to model osimertinib TDT data from AURA3 (log-logistic, independent). The analysis is not particularly sensitive to the choice of the PFS parametric function, dose estimates accounting for compliance, vial wastage, and exclusion of terminal care costs and additional costs associated with CNS progression.

Table 95: Scenario analyses

Scenario analysis	Base case value	Sensitivity analysis value	Justification
Time horizon	Lifetime	10 years	Explore the impact of using a shorter time horizon
Discount rates (costs and outcomes)	3.5%, 3.5%	• 0%, 0% • 6%, 6% • 3.5%, 0%	• Specified in methods guidance • Specified in methods guidance • Discount applied to costs only (discounting clinical outcomes devalues future life)
PFS parametric function	Generalised gamma, dependent	• Weibull, dependent • Log-logistic, dependent	Structural assumption
OS modelling function	Weibull piecewise	Exponential piecewise	Structural assumption
OS modelling approach	Weibull piecewise	• Weibull dependent • Log-logistic dependent	Explore the impact of assuming the proportional hazards assumption to hold for the entire time horizon
TDT parametric function	Generalised gamma, dependent	• Weibull, dependent • Gompertz dependent	Structural assumption
Acquisition costs	Based on TDT	Based on PFS	Explore the impact of assuming treatment discontinuation at progression
HSU PD on subsequent treatment	Labbé (0.64)	• FLAURA (0.704) • Weighted average for SoC arm only (0.683)	• Explore the impact of using the utility from FLAURA • Adjust for potential higher QoL for patients receiving osimertinib post progression
Drug wastage	Included	Excluded	Explore the impact of costing only for amount of drug administered
RDI	Included	Excluded	Explore the impact of assuming all patients receive planned dose
Terminal cost	Include	Excluded	Evaluate the impact of excluding cost associated with terminal care
TDT for osimertinib in 2L	Generalised gamma, dependent	• Log-logistic, independent • Weibull, independent	Structural assumption
Second-line treatments from FLAURA	Based on clinical experts' opinion	Derived from FLAURA	Explore the impact of costing second-line treatment based on the observed use from FLAURA

Subsequent treatments cost	Included	Excluded	Evaluate the impact of excluding costs associated with subsequent treatments
Cost of CNS progression	Included	Excluded	Evaluate the impact of excluding costs associated with CNS progression

CNS: central nervous system; HSU: health state utility; OS: overall survival; PD: progressive disease; PFS: progression-free survival; RDI: relative dose intensity; TDT: time to discontinuation of treatment

Table 96: Results of scenario analyses (osimertinib versus erlotinib)

Scenario	Osimertinib		Erlotinib		ICER (£/QALY)	ICER (£/QALY)
	Discounted cost	Discounted QALYs	Discounted cost	Discounted QALYs		Relative change
Base-case	£168,925	3.392	£75,094	2.346	£89,700	--
Time horizon (10 years)	£165,215	3.097	£74,019	2.272	£110,552	+23%
Discount rate costs and outcomes (0%)	£178,914	3.859	£78,658	2.556	£76,905	-14%
Discount rate costs and outcomes (3.5%, 0%)	£168,925	3.859	£75,094	2.556	£71,977	-20%
Discount rate costs and outcomes (6%)	£163,005	3.133	£72,948	2.223	£98,928	+10%
PFS (Weibull, dependent)	£169,237	3.382	£75,181	2.343	£90,483	+1%
PFS (Log-logistic, dependent)	£167,784	3.440	£74,330	2.378	£88,039	-2%
OS (Exponential, piecewise)	£170,005	3.490	£75,781	2.408	£87,045	-3%
OS (Weibull, dependent)	£160,955	2.670	£70,665	1.946	£124,833	+39%
OS (Log-logistic, dependent)	£169,486	3.450	£78,182	2.631	£111,395	+24%
TDT (Weibull, dependent)	£182,382	3.403	£76,245	2.349	£100,716	+12%
TDT Gompertz, dependent)	£161,146	3.389	£74,970	2.346	£82,643	-8%
Acquisition costs based on PFS	£163,694	3.384	£74,581	2.341	£85,419	-5%
HSU PD on subsequent treatment (0.704, FLAURA)	£168,925	3.582	£75,094	2.491	£86,046	-4%

HSU PD adjusted for subsequent treatments (0.683 for the comparators only)	£168,925	3.392	£75,094	2.443	£98,999	+10%
Wastage (included)	£170,628	3.392	£75,987	2.346	£90,474	+1%
RDI (excluded)	£170,386	3.392	£75,768	2.346	£90,453	+1%
Terminal cost (excluded)	£165,484	3.392	£71,405	2.346	£89,937	0%
TDT for osimertinib in 2L (Log-logistic, independent)	£168,925	3.392	£79,723	2.346	£85,275	-5%
TDT for osimertinib in 2L (Weibull, independent)	£168,925	3.392	£73,807	2.346	£90,930	+1%
Second-line treatments from FLAURA	£168,545	3.392	£70,580	2.346	£93,652	+4%
Subsequent treatments cost (excluded)	£164,943	3.392	£49,033	2.346	£110,807	+24%
Cost of CNS progression (excluded)	£168,194	3.392	£73,897	2.346	£90,145	0%

CNS: central nervous system; HSU: health state utility; ICER: incremental cost-effectiveness ratio; OS: overall survival; PD: progressive disease; PFS: progression-free survival; QALY: quality adjusted life years; RDI: relative dose intensity; TDT: time to discontinuation of treatment

Table 97: Results of scenario analyses (osimertinib versus gefitinib)

Scenario	Osimertinib		Gefitinib		ICER (£/QALY)	ICER (£/QALY)
	Discounted cost	Discounted QALYs	Discounted cost	Discounted QALYs		Relative change
Base-case	£168,925	3.392	£82,443	2.346	£82,675	--
Time horizon (10 years)	£165,215	3.097	£81,368	2.272	£101,643	+23%
Discount rate costs and outcomes (0%)	£178,914	3.859	£86,103	2.556	£71,194	-14%
Discount rate costs and outcomes (3.5%, 0%)	£168,925	3.859	£82,443	2.556	£66,340	-20%
Discount rate costs and outcomes (6%)	£163,005	3.133	£80,234	2.223	£90,925	+10%
PFS (Weibull, dependent)	£169,237	3.382	£82,530	2.343	£83,413	+1%
PFS (Log-logistic, dependent)	£167,784	3.440	£81,679	2.378	£81,116	-2%
OS (Exponential, piecewise)	£170,005	3.490	£83,130	2.408	£80,256	-3%
OS (Weibull, dependent)	£160,955	2.670	£78,014	1.946	£114,672	+39%
OS (Log-logistic, dependent)	£169,486	3.450	£85,531	2.631	£102,429	+24%

TDT (Weibull, dependent)	£182,382	3.403	£83,961	2.349	£93,394	+13%
TDT (Gompertz, dependent)	£161,146	3.389	£82,297	2.346	£75,615	-9%
Acquisition costs based on PFS	£163,694	3.384	£81,608	2.341	£78,684	-5%
HSU PD on subsequent treatment (0.704, FLAURA)	£168,925	3.582	£82,443	2.491	£79,306	-4%
HSU PD adjusted for subsequent treatments (0.683 for the comparators only)	£168,925	3.392	£82,443	2.443	£91,130	+10%
Wastage (included)	£170,628	3.392	£83,479	2.346	£83,312	+1%
RDI (excluded)	£170,386	3.392	£83,018	2.346	£83,521	+1%
Terminal cost (excluded)	£165,484	3.392	£78,754	2.346	£82,911	0%
TDT for osimertinib in 2L (Log-logistic, independent)	£168,925	3.392	£87,072	2.346	£78,249	-5%
TDT for osimertinib in 2L (Weibull, independent)	£168,925	3.392	£81,156	2.346	£83,905	+1%
Second-line treatments from FLAURA	£168,545	3.392	£77,929	2.346	£86,626	+5%
Subsequent treatments cost (excluded)	£164,943	3.392	£56,382	2.346	£103,782	+26%
Cost of CNS progression (excluded)	£168,194	3.392	£81,246	2.346	£83,120	+1%

CNS: central nervous system; HSU: health state utility; ICER: incremental cost-effectiveness ratio; OS: overall survival; PD: progressive disease; PFS: progression-free survival; QALY: quality adjusted life years; RDI: relative dose intensity; TDT: time to discontinuation of treatment

Table 98: Results of scenario analyses (osimertinib versus afatinib)

Scenario	Osimertinib		Afatinib		ICER (£/QALY)	ICER (£/QALY)
	Discounted cost	Discounted QALYs	Discounted cost	Discounted QALYs		Relative change
Base-case	£168,925	3.392	£82,448	2.346	£82,669	--
Time horizon (10 years)	£165,215	3.097	£81,373	2.272	£101,637	+23%
Discount rate costs and outcomes (0%)	£178,914	3.859	£86,108	2.556	£71,190	-14%
Discount rate costs and outcomes (3.5%, 0%)	£168,925	3.859	£82,448	2.556	£66,336	-20%
Discount rate costs and outcomes (6%)	£163,005	3.133	£80,239	2.223	£90,919	+10%
PFS (Weibull, dependent)	£169,237	3.382	£82,536	2.343	£83,408	+1%

PFS (Log-logistic, dependent)	£167,784	3.440	£81,685	2.378	£81,111	-2%
OS (Exponential, piecewise)	£170,005	3.490	£83,135	2.408	£80,251	-3%
OS (Weibull, dependent)	£160,955	2.670	£78,019	1.946	£114,664	+39%
OS (Log-logistic, dependent)	£169,486	3.450	£85,537	2.631	£102,422	+24%
TDT (Weibull, dependent)	£182,382	3.403	£83,967	2.349	£93,388	+13%
TDT (Gompertz, dependent)	£161,146	3.389	£82,303	2.346	£75,610	-9%
Acquisition costs based on PFS	£163,694	3.384	£81,618	2.341	£78,675	-5%
HSU PD on subsequent treatment (0.704, FLAURA)	£168,925	3.582	£82,448	2.491	£79,301	-4%
HSU PD adjusted for subsequent treatments (0.683 for the comparators only)	£168,925	3.392	£82,448	2.443	£91,239	+10%
Wastage (included)	£170,628	3.392	£83,484	2.346	£83,307	+1%
RDI (excluded)	£170,386	3.392	£83,265	2.346	£83,286	+1%
Terminal cost (excluded)	£165,484	3.392	£78,760	2.346	£82,906	0%
TDT for osimertinib in 2L (Log-logistic, independent)	£168,925	3.392	£87,078	2.346	£78,244	-5%
TDT for osimertinib in 2L (Weibull, independent)	£168,925	3.392	£81,162	2.346	£83,899	+1%
Second-line treatments from FLAURA	£168,545	3.392	£77,935	2.346	£86,621	+5%
Subsequent treatments cost (excluded)	£164,943	3.392	£56,387	2.346	£103,776	+26%
Cost of CNS progression (excluded)	£168,194	3.392	£81,252	2.346	£83,114	+1%

CNS: central nervous system; HSU: health state utility; ICER: incremental cost-effectiveness ratio; OS: overall survival; PD: progressive disease; PFS: progression-free survival; QALY: quality adjusted life years; RDI: relative dose intensity; TDT: time to discontinuation of treatment

B.3.9 Subgroup analysis

Clinical data from the FLAURA trial indicated that the benefits of osimertinib over SoC were consistent across all the pre-specified subgroups (see section B.2.6). Thus, no subgroup analyses were performed.

B.3.10 Validation

Validation of cost-effectiveness analysis

During the development of the cost-effectiveness model, an advisory board with five UK oncologists was held to advise on the treatment pathway for EGFRm-positive NSCLC patients in the UK and other key model parameters from a clinical perspective, given current available data. Details on the clinicians who attended the advisory board are provided in Appendix K.

Clinical experts agreed that since osimertinib has become a second-line option following progression on a 1st or 2nd generation TKI, the proportion of patients receiving BSC only (i.e. not eligible to receive subsequent active treatments or who do not want to receive platinum-based chemotherapy) has dropped from 50% to approximately 30%. They also confirmed that awareness of T790M testing is variable across the UK, however assuming that after progression on a 1st or 2nd generation TKI one third of patients are identified as T790M+, is a plausible estimate, given that not all patients who progress on first-line TKI treatment may be eligible for additional re-biopsy or second-line treatment.

Clinical experts also reviewed the choice of the OS extrapolations and confirmed the plausibility of the estimates generated for the SoC arm. There was consensus that the 5-year survival estimate is likely to be between 10% and 15% for UK patients although this may not reflect the use of subsequent second-line osimertinib in patients who are T790M mutation-positive in the SoC TKI arm or the anticipated future availability of third-line immunotherapy.

Quality control

Internal quality control procedures were undertaken by a health economist that was not involved in the model development and construction to ensure accuracy of the programming and to identify errors or omissions. A number of ‘pressure tests’ were conducted on the model using extreme values.

B.3.11 Interpretation and conclusions of economic evidence

Results summary

Based on the head-to-head comparison, the costs per patient associated with osimertinib treatment are £168,925 compared to £75,094 for erlotinib, £82,443 for gefitinib and £82,448 for afatinib over a lifetime horizon (20 years). This represents an incremental cost of £93,832 versus erlotinib, £86,482 versus gefitinib and £86,477 versus afatinib. Treatment with osimertinib is associated with 3.392 QALYs versus 2.346 QALYs for erlotinib, gefitinib, and afatinib. Thus, compared to erlotinib, gefitinib and afatinib, osimertinib is associated with 1.046 QALYs gained. The incremental costs per QALY gained are £89,700 relative to erlotinib, £82,675 relative to gefitinib, and £82,669 relative to afatinib.

Scenario analyses showed that key parameters that lead to an increase of the ICER are the choice OS parametric functions (Weibull dependent; Log-logistic, dependent), the parametric function to model TDT for the primary treatments (Weibull, dependent), the HSUV used for the progressed disease state (adjusted for subsequent treatments) and the exclusion of subsequent treatments costs. Key parameters that lead to a reduction of the ICER are the assumption around treatment duration (treatment until progression), the parametric function for TDT from FLAURA (Gompertz, dependent), not discounting clinical benefits, and the choice of the distribution to model osimertinib TDT data from AURA3 (log-logistic, independent). The analysis is not particularly sensitive to the choice of the parametric function for PFS, dose estimates accounting for compliance, vial wastage, and exclusion of terminal care costs and costs for CNS progression.

The one-way sensitivity analysis showed that the main drivers of cost-effectiveness are the relative treatment effects of osimertinib on OS and TDT, the HSU values and the costs associated with the use of osimertinib after progression on SoC.

The probabilistic sensitivity analysis was run for 10,000 iterations. Uncertainty tends to be larger for osimertinib than for comparator treatments, which may be a result of the more immature survival data for osimertinib. However, the conclusion does not change. Erlotinib is likely to be the most cost-effective comparator at a willingness-to-pay threshold of £50,000 (78%) and up to ~£84,000. At a threshold of £84,500 osimertinib has the highest probability (38%) which increases thereafter.

Strengths and limitations

This cost-effectiveness analysis presents a number of strengths:

- The analysis is based on a simple, transparent and well accepted model structure, extensively used in oncology modelling
- The estimates of PFS are relatively mature and not subject to significant uncertainty
- In the absence of EQ-5D data directly collected in the FLAURA study, the HSU value for PF were derived based on a published mapping algorithm. The mapping algorithm was tested

and confirmed to perform well resulting in HSU values similar to those seen in previous NSCLC trials for osimertinib
- The resource use and cost data applied in the analysis have been extensively used in previous UK NICE submissions and do not represent a source of uncertainty
- In the base-case, treatment costs were modelled based on TDT, which reflects expected UK clinical practice

There are a number of limitations in this cost-effectiveness analysis which should be noted. Although this analysis provides our best estimate of the health benefit and cost-effectiveness of osimertinib, these are subject to some degree of uncertainty:

- As is common with cost-effectiveness analyses conducted early in the product life cycle, due to immaturity of the OS data in the FLAURA data, the long-term extrapolations are subject to uncertainty and a key driver of the model results. Sensitivity analysis was undertaken to show how different survival models would impact on the results. However, a robust and comprehensive approach was undertaken alongside a number of scenario and sensitivity analyses. It is anticipated that the extrapolations applied in the base case analysis will be confirmed when the final OS results from FLAURA become available
- The impact on costs and outcomes of subsequent treatments are subject to uncertainty given the immaturity of the data available from FLAURA DCO1. The impact on outcomes is implicitly captured in OS and therefore subject to uncertainty. The impact on costs was modelled based on UK clinical experts' opinion and the duration of these treatments was derived from external data which is also subject to immaturity (AURA3 trial).

Conclusions

Osimertinib is well tolerated, with a lower incidence of side effects compared with second-generation EGFR-TKIs whilst also offering potential for greater CNS efficacy. In this regard, osimertinib has the potential to replace 1st and 2nd generation EGFR-TKIs as the standard of care for patients who are newly diagnosed with stage IIIb/IV EGFRm NSCLC, providing a step-change extension of PFS and prolonged survival. The results of the cost-effectiveness analysis showed that when the PAS discount for osimertinib is used, the ICER is [redacted] compared to gefitinib. The results demonstrate that with the proposed PAS osimertinib, as an end of life therapy, meets the NICE criteria to be considered a cost-effective intervention. Extensive sensitivity analyses showed that the main drivers of the cost-effectiveness analysis are related to the extrapolation of OS and TDT, the utility values, the costs associated with the use of osimertinib in T790M-positive patients after progression. Results from the probabilistic sensitivity analysis show that, with the proposed PAS, the probability of osimertinib being the most cost-effective treatment (compared to gefitinib) at a threshold of £50,000 per gained QALY is 54%.

Reimbursement of osimertinib in the first-line setting would provide all patients with locally advanced or metastatic NSCLC with activating EGFR mutations access to the best possible clinical outcomes.

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Appendices

Appendix C: Summary of product characteristics (SmPC) and European public assessment report (EPAR)

C1.1 SmPC

Osimertinib SmPC

C1.2 EPAR

Osimertinib EPAR

Appendix D: Identification, selection and synthesis of clinical evidence

D.1 Results from randomised studies

D1.1 Identification and selection of relevant studies

Search strategy

A systematic literature review (SLR) was conducted to identify relevant studies, in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension statement for SLR incorporating network meta-analyses of health care interventions.[104, 160]

The original SLR was conducted on 18 April 2017, and updated searches were run on 19 February 2018.

The following electronic databases were searched:

- MEDLINE In-Process (www.Pubmed.com)
- Embase and MEDLINE (www.Embase.com)
- The Cochrane Library, including the following:
    - The Cochrane Database of Systematic Reviews (CDSR)
    - Database of Abstracts of Reviews of Effectiveness (DARE)
    - Cochrane Central Register of Controlled Trials (CENTRAL)
    - Health Technology Assessment Database (HTAD)

No lower date limit was applied to the electronic searches.

Hand searching of the following four conferences was also conducted to identify additional studies of interest. These searches were restricted to the last 2 years (2016–2017 in the original SLR and 2017-2018 in the updated SLR). If the 2017 conference was not held by the time the searches were run, the 2015 conference was searched in the original SLR:

- American Society of Clinical Oncology (ASCO) (2016-2017)
- European Lung Cancer Conference (ELCC) (2016-2017)
- European Society for Medical Oncology (ESMO) (2015-2017)
- World Conference on Lung Cancer (2015-2017)

In addition, the following websites were searched:

- NICE

- Canadian Agency for Drugs and Technologies in Health (CADTH) Common Drug Review (CDR)
- Scottish Medicines Consortium (SMC)
- All Wales Medicines Strategy Group (AWMSG)
- US FDA
- ClinicalTrials.gov
- EU Clinical Trial Register (EU CTR)
- WHO International Clinical Trials Registry Platform (WHO ICTRP)

Bibliographies of key systematic reviews and meta-analyses were also screened to capture any other relevant clinical studies.

Study selection

Eligibility criteria

Eligibility criteria applied to the SLR search strategy are described in Table 99. Patients with NSCLC were included only if lung was the primary site of disease. Studies assessing a mixed population (e.g. treatment-naïve and pre-treated NSCLC, EGFR sensitive and EGFR resistant/other receptor mutations) were included only if relevant outcome data were reported for treatment-naïve NSCLC patients with EGFR-TKI sensitive mutations.

Table 99: Eligibility criteria used in the search strategy

Clinical effectiveness	Inclusion criteria	Exclusion criteria
Population	• Adults (≥18 years) with advanced and/or metastatic NSCLC • Previously untreated/treatment naïve (prior adjuvant/neo-adjuvant therapy is permitted) • Patients with EGFR-TKI sensitive mutation	• Healthy volunteers • Paediatric population • Disease other than advanced and/or metastatic NSCLC • Previously treated patients • Patients treated with EGFR-TKI where EGFR mutation status is negative/wild type
Intervention	• Osimertinib • Tyrosine kinase inhibitors – Imatinib – Gefitinib – Erlotinib – Dacomitinib – Afatinib – Dasatinib – Sunitinib – ASP8273	• Non-drug treatments (e.g. surgery, radiotherapy) • Studies assessing interventions – not in the list • Adjuvant and neo-adjuvant setting • Chemo-radiotherapy (chemotherapy + radiotherapy) • Combination therapies (e.g. TKI + chemotherapy)

	• The current scope of review was limited to the above TKI monotherapies. TKIs approved in the first-line treatment setting were included in the review.	
Comparators	• Placebo • Best supportive care • Any treatment from the above list • Any other pharmacological treatment • Studies evaluating combination with chemotherapy were included only if they had one TKI monotherapy group of interest.	• Non-pharmacological treatments
Outcomes	• Efficacy • Safety • Quality of life	• Pharmacokinetics
Study design	• RCTs • Non-RCTs including observational studies (comparative) • Systematic reviews and meta-analysis[a]	• Case reports, case series • Pharmacokinetic and economic studies • Preclinical studies • Reviews, letters, and comment articles • Single arm studies • Studies assessing fewer than 10 patients
Language restrictions	• English language	• Non-English language
Publication timeframe	• Original SLR: No limit (run on 18 April 2017) • Updated SLR: 01 March 2017 onwards (MEDLINE and Embase) and 2017 onwards (Cochrane library) (run on 19 February 2018)	

EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; RCT, randomised controlled trial; TKI, tyrosine kinase inhibitor.
[a] Bibliographies of relevant systematic reviews were screened to check if literature searches missed any potentially relevant studies.

Study selection

Primary (Level 1) screening was performed by two independent reviewers who reviewed each reference (title and abstract) identified by the literature search, applied basic study selection criteria (population, intervention, study design) and decided whether to include or exclude the reference at that stage. Any uncertainty regarding the inclusion of studies was assessed by a third independent reviewer.

Full-text articles were then obtained for potentially relevant studies identified at the first-pass screening stage. These were independently reviewed by two reviewers against each eligibility criterion. Again, any uncertainty regarding the inclusion of studies was assessed by a third independent reviewer.

Data extraction

Data from studies meeting the eligibility criteria were extracted using a pre-specified extraction template. Data extraction was performed by one reviewer and independently checked for errors against the original study report by a second reviewer.

Quality assessment

The NICE checklist for RCTs was used to assess the quality of RCTs;[161] the Downs and Black checklist was used to assess the quality of non-randomised studies.[162]

PRISMA flow

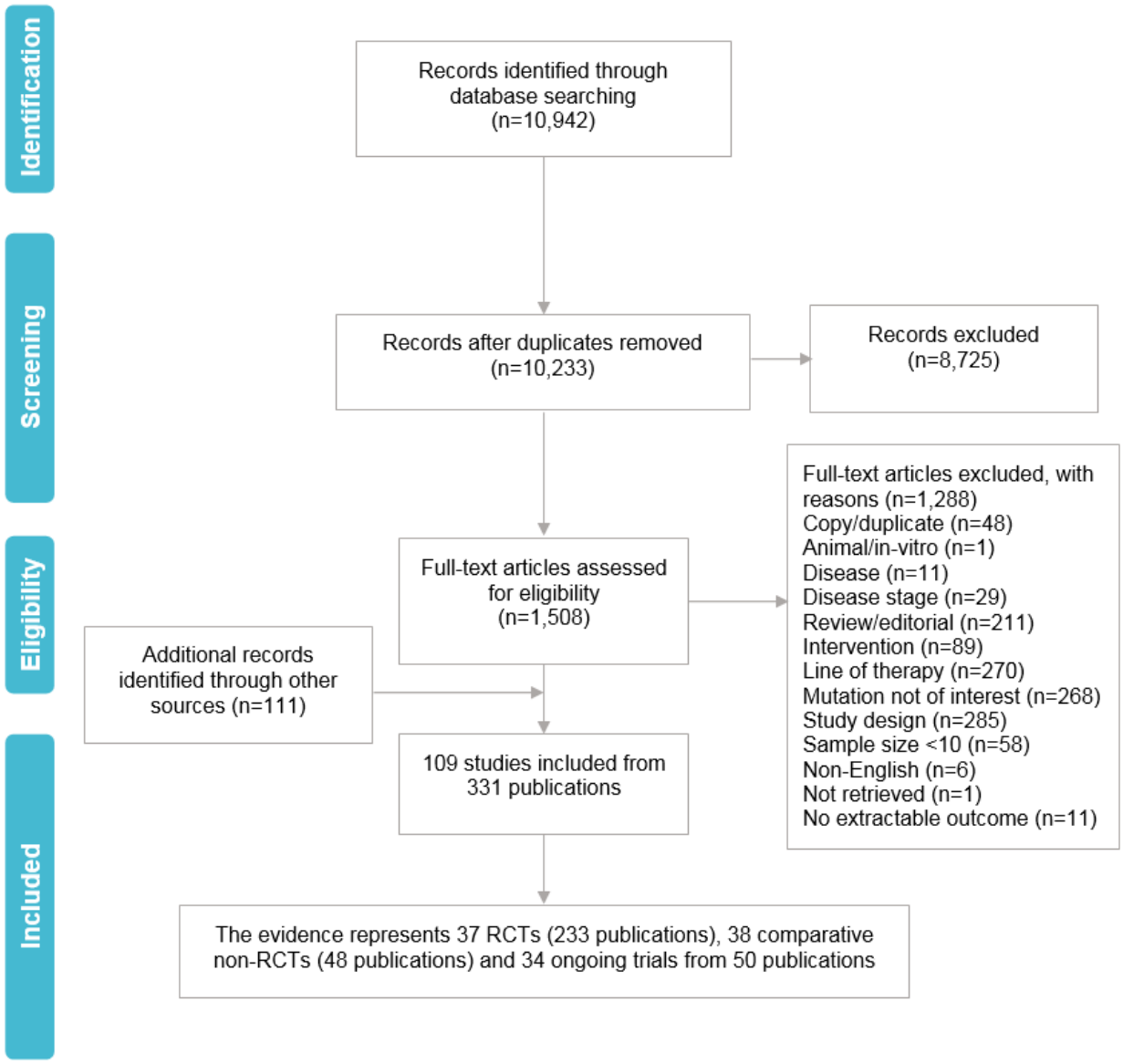
A total of 10,942 potentially relevant papers or abstracts from the electronic databases were identified, including 8,643 for the original review and 2,299 for the updated SLR. Following the removal of duplicate references (553 in the original SLR and 156 in the updated SLR), 10,233 studies (8,090 in the original SLR and 2,143 in the updated SLR) were screened based on the information reported in their titles and/or abstracts. Of these, 8,725 studies (6,867 in the original SLR and 1,858 in the updated SLR) were excluded at the primary screening stage as they were not of relevance to the research question.

A total of 1,508 studies (1,223 articles in the original SLR and 285 articles in the updated SLR) were assessed in full for further evaluation. Of these, 1,288 studies (1,052 in the original SLR and 236 in the updated SLR) were excluded. Papers were excluded due to the following reasons: reviews/editorials, patients with mutations other than EGFR, not investigating first-line treatment, incorrect study designs, investigating other diseases and having no extractable data.

In addition, 111 records (81 records in the original SLR and 30 records in the updated SLR) were included from bibliographic/conference/registry searches. Therefore, 109 studies from 331 publications (252 in the original SLR and 79 in the updated SLR) were included. As some studies were associated with multiple publications, secondary publications were combined. The evidence represented 37 RCTs from 233 publications and 38 non-randomised studies from 48 publications. In addition, 34 ongoing studies from 50 publications were identified but not included in the qualitative analysis.

A PRISMA flow diagram describing the selection process is shown in Figure 58.[104]

Figure 58: PRISMA flow diagram



EGFR, epidermal growth factor receptor; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT, randomised controlled trial.

List of identified studies

Thirty-seven RCTs were included in this review, an overview of which is presented in Table 100. These included three head-to-head trials of EGFR TKIs.[102, 118, 163] Gefitinib was the common comparator across all three trials, and the active interventions were afatinib (LUX LUNG 7 [LL7])[118], erlotinib (CTONG 0901)[163] and dacomitinib (ARCHER 1050).[102] Another trial, FLAURA, compared osimertinib with standard EGFR-TKI treatment that consisted of gefitinib or erlotinib.[164] Seven other trials assessed a TKI in comparison with TKI-chemotherapy combination.[165-171] The TKIs assessed across these seven trials were erlotinib (four studies)[165, 169-171] and gefitinib (three studies).[166-168] Four studies compared a TKI monotherapy with a TKI plus monoclonal antibody (MAb) combination.[172-175] In 14 other studies, a TKI monotherapy was compared with a platinum doublet chemotherapy regimen. The TKIs assessed across these 14 studies were afatinib (two studies: LUX LUNG 3 [LL3][176], LUX LUNG 6 [LL6][177]), erlotinib (six studies: TORCH[178], EURTAC[179], ENSURE[180], OPTIMAL[181], Lilenbaum et al.[182], Zhao 2017[183]) and gefitinib (six studies: IPASS[184], First-SIGNAL[185], NEJ002[15], WJTOG3405[62], Singh et al.[186], Patil et al.[187]). Two studies compared a TKI with chemotherapy; erlotinib vs vinorelbine[188] and gefitinib vs vinorelbine.[189] Additionally, two trials, SATURN[190] and TOPICAL[191], compared erlotinib with placebo while the INFORM trial compared gefitinib with placebo[192]; and the INSTEP study assessed gefitinib-best supportive care (BSC) combination with BSC.[193] INSTEP will be considered as placebo controlled and will be referred to as a gefitinib-versus-placebo trial for the rest of the report.

One study by Yang et al. assessed gefitinib versus combination of gefitinib plus Fuzheng Kang'ai Formula[194], whereas the study by Han et al. was a three-arm trial that assessed gefitinib versus gefitinib plus platinum doublet chemotherapy versus platinum doublet chemotherapy alone.[195]

Fifteen studies were Phase II, and 18 studies were Phase III. One study was Phase II/III[175], whereas phase was not reported in three studies.[167, 186, 194]

In this review, study inclusion was not restricted by blinding. A majority of the studies were open-label (25 studies), followed by eight studies that were double blind[164, 165, 167, 190-194]; blinding status was not reported in four studies.[15, 170, 171, 186]

Cross-over at progression took place in seven studies.[15, 176, 178, 180, 183, 185, 188] Six of these studies compared TKI with platinum doublet chemotherapy, and Chen et al. compared TKI with vinorelbine. In this review, studies that did not allow true cross-over, i.e. patients did not switch between both the treatment arms, were not considered to be cross-over studies, even if reported as such by the authors. However, in eight other studies, progressing patients switched from only one arm to another.[164, 174, 177, 179, 181, 182, 187, 190]

A majority of the studies were active controlled (33 studies), followed by four studies that were placebo controlled.[190-193] A majority of studies assessed progression-free survival (PFS) as the primary outcome (29 studies), followed by overall survival (OS) in four studies.[178, 183, 185, 191]

Of the 37 RCTs, 17 studies reported data for subgroup of patients with specific type of mutations (Exon19del, 17 studies; L858R, 17 studies; T790M, three studies). Seven of these studies referred to L858R mutations as exon 21 L858R mutations[166, 173, 179-181, 184, 195] and eight studies included L858R mutations only[15, 102, 118, 164, 168, 170, 176, 177]; two studies reported data for exon 21 mutation only.[165, 187] One study each described T790M mutations as occurring within exon 20 mutation and T790M only[181], whereas LL6 reported data separately for both these mutations.[177] In the OPTIMAL trial, authors termed the mutation as T790 only.[181]

In this report, exon 21 mutations were considered to refer to L858R mutations, and exon 20 insertion mutations were considered to refer to the T790M mutations.

Table 100: Comparative summary of trial methodology of RCTs

Study name (Trial name/ NCT)	• Line of therapy (%)* • EGFR mutation (%)*	• Study phase • Blinding	• Study setting • Study country	• Intervention • Comparator	• Number enrolled • Number randomised	Analysis type • Efficacy • Safety	Median length of follow-up (weeks)	Subgroup details	Linked references
Soria 2018[164] (FLAURA/ NCT02296125)	• 100 • 100	• Phase III • Double-blind	• Multi-centre international • Australia, Belgium, Brazil, Bulgaria, Canada, China, Czech Republic, France, Germany, Hungary, Israel, Italy, Japan, Republic of Korea, Malaysia, Philippines, Poland, Portugal, Romania, Russian federation, Spain, Sweden, Switzerland, Taiwan, Thailand, Turkey, Ukraine, UK, US, Vietnam	• Osimertinib • Standard EGFR-TKI (Erlotinib/Gefitinib)	• 994 • 556	• ITT • ITT	PFS: Osimertinib: 65 (0–108.77) weeks Standard EGFR-TKI: 42.03 (0–113.1) weeks	• Sex (male vs. female) • Race (Asian vs. non-Asian) • Age at screening (<65 years vs. ≥65 years) • CNS metastases status at entry (yes vs. no) • Smoking history (yes vs. no) • Baseline WHO Performance Status (0 vs 1) • EGFR mutation (exon 19 deletion vs. L858R) • EGFR mutation-positive by ctDNA (positive vs. negative) • Centrally confirmed EGFR mutation (positive vs. negative)	Original: Ramalingam 2015[196], NCT02296125[197], Ramalingam 2015[198] Update: Cho 2017[199], Gray 2017[200], Ohe 2017[201], Ramalingam 2017[202], Vansteenkiste 2017[203]
Goldberg 2017[175] (SWOG S1403/ NCT02438722)	• 100 • 100	• Phase II/III • Open label	• Multi-centre • United States	• Afatinib • Afatinib + cetuximab	• 53 • 53	• Unclear • Unclear	NR	• NR	NCT02438722[204]

Study name (Trial name/ NCT)	• Line of therapy (%)* • EGFR mutation (%)*	• Study phase • Blinding	• Study setting • Study country	• Intervention • Comparator	• Number enrolled • Number randomised	Analysis type • Efficacy • Safety	Median length of follow-up (weeks)	Subgroup details	Linked references
Han 2017[195] (NCT02148380)	• 100 • 100	• Phase II • Open label	• Single-centre • China	• Gefitinib • Gefitinib + carboplatin + pemetrexed • Carboplatin + pemetrexed	• 121 • 121	• ITT • ITT	NR	• Age (<65 vs. ≥65) • Gender (Male vs. female) • Smoking status (Smoker vs. never smoker) • ECOG PS (0 vs. 1) • Stage (IIIB vs. IV) • EGFR mutation type (19del vs. 21L858R)	NL
Leighl 2017[165]	• 100 • 100	• Phase II • Double blind	• Multi-centre international • US, South Korea, Canada, Thailand, Singapore, and Hong Kong	• Erlotinib + linsitinib • Erlotinib + PBO	• 88 • 88	• ITT • mITT	Cut-off date: • Efficacy analyses: February 2013 • Safety analyses: October 2013	• EGFR mutation status (Exon 19 vs. Exon 21) • ECOG PS (0 vs. 1) • Age groups (≤65 vs. >65) • Gender (male vs. female) • Race (Asian vs. Other) • Smoking (Current or former smoker vs. Never smoked) • Histology (Adenocarcinoma vs. Other)	Leighl 2016[205]
Patil 2017[187] (CTRI/2015/08/ 006113)	• 100 • 100	• Phase III • Open label	• Single-centre • India	• Gefitinib	• 497 • 290	• ITT • ITT	61.53 weeks	• Age (>65 vs.<65)	Original SLR: Prabhash 2017[206]

Study name (Trial name/ NCT)	• Line of therapy (%)* • EGFR mutation (%)*	• Study phase • Blinding	• Study setting • Study country	• Intervention • Comparator	• Number enrolled • Number randomised	Analysis type • Efficacy • Safety	Median length of follow-up (weeks)	Subgroup details	Linked references
				• Platinum doublet + pemetrexed				• Gender (male vs. female) • Smoking (Smoker vs. non-smoker) • oral tobacco use (Yes vs. no) • Presence of liver metastasis (Yes vs. no) • Presence of brain metastasis (Yes vs. No) • ECOG PS (0-1, 2) • EGFR mutation (Exon 19 vs. Exon 21)	Update: Prabhash 2017[207], Ramaswamy 2017[208], Joshi 2018[209], Talreja 2017[210], Goel 2017[211]
Scagliotti 2017[172] (Balise/ NCT01897480)	• 100 • 100	• Phase II • Open label	• Multi-centre international • Denmark, France, Germany, Italy, Korea, Republic of, Netherlands, Spain, Taiwan, UK	• Erlotinib • Erlotinib + emibetuzumab	• 181 • 141	• ITT • NR	NR	OS data reported for MET- high expressing patients (treatment-wise).	NCT01897480[212]
Wu 2017[102] (ARCHER 1050/ NCT01774721)	• 100 • 100	• Phase III • Open label	• Multi-centre international • China, Hong Kong, Italy, Japan, Republic of Korea, Poland, Spain	• Dacomitinib • Gefitinib	• 720 • 452	• ITT • mITT	Cut-off date: 29 July 2016 PFS: 95.69 (95% CI: 87.97–103.57) weeks Dacomitinib: 95.76 (95% CI: 87.97–	• Age (<65 years vs. ≥ 65 years) • Sex (Male vs. female) • ECOG PS (0 vs. 1) • Smoking history (Never vs.	Original: Mok 2013a[213],Mok 2013b[214], Mok 2013c[215], Nakagawa 2015[216], EudraCT2012-004977-23 2013[217], NCT01774721[218], Mok 2017[72] Update:

Study name (Trial name/ NCT)	• Line of therapy (%)* • EGFR mutation (%)*	• Study phase • Blinding	• Study setting • Study country	• Intervention • Comparator	• Number enrolled • Number randomised	Analysis type • Efficacy • Safety	Median length of follow-up (weeks)	Subgroup details	Linked references
							103.57) weeks Gefitinib: 99.67 (95% CI: 87.97–111.8) weeks	former or current) • EGFR mutation status (Exon 19 vs. Exon 21) • Race (Japanese vs. mainland Chinese vs. another East Asian vs. non-East Asian)	Nakagawa 2017[219], Wu 2017b[220], Migliorino 2017[221]
Yang 2017[194] (ChiCTR-IOR-14005679)	• 100 • 100	• NR • Double blind	• Single-centre • China	• Gefitinib • Gefitinib+ Fuzheng Kang'ai Formula	• 71 • 70	• ITT • ITT	104 weeks	NR	Yang 2015[222]
Yang 2017[163] (CTONG 0901/ NCT01024413)	• 64.5 • 100	• Phase III • Open label	• Single-centre • China	• Erlotinib • Gefitinib	• 256 • 256	• ITT • ITT	• Last follow-up date: 30 June 2015 • median follow-up time: 95.77 weeks	OS, and RR data • EGFR mutation (Exon 19 and L858R)	Yang 2015[223], Zhou 2015[112], Zhou 2016[224]
Zhao 2017[183] (NCT01131429)	• 100 • 100	• Phase II • Open label	• Single-centre • China	• Erlotinib • Docetaxel + cisplatin	• 92 • 81	• ITT • Unclear	50.31 weeks	NR	NL
An 2016[167]	• 100 • 100	• NR • Double blind	• NR • NR	• Gefitinib + PBO • Gefitinib + pemetrexed	• 90 • 90	• ITT • ITT	NR	NR	NL
Cheng 2016[166] (NCT01469000)	• 100 • 100	• Phase II • Open Label	• Multi-centre international	• Gefitinib • Gefitinib + pemetrexed	• 232	• mITT • mITT	PFS: 78 weeks	• ECOG PS (0 and 1) • Gender	Puri 2013[225], Yang 2016[226], NCT01469000, Cheng 2015[227] Update:

Study name (Trial name/ NCT)	• Line of therapy (%)* • EGFR mutation (%)*	• Study phase • Blinding	• Study setting • Study country	• Intervention • Comparator	• Number enrolled • Number randomised	Analysis type • Efficacy • Safety	Median length of follow-up (weeks)	Subgroup details	Linked references
			• China, Japan, Koran, Taiwan		• 195 G+P: 129 G: 66			• Smoking history (Yes vs. No) • Prior adjuvant/neoadjuvant (Yes vs. No) • Age (< 65 years/≥ 65 years) • Country (Japan, Koran, Taiwan, China) • EGFR (Exon 19 del vs. Exon 21 L858R)	WHO ICTRP [Gefitinib][228]
Mok 2016[174] (P06162/ NCT01039948)	• 100 • 37.7	• Phase II • Open label	• Multi-centre international • Hong Kong, Malaysia, the Philippines, Singapore, the Republic of Korea, the Republic of China, and Thailand.	• Gefitinib • Gefitinib + ficlatuzumab	• 188 • 188	• ITT • mITT	NR	• EGFR sensitive mutation (EGFR SM+) • VS-P • VS-G	NL
Park 2016[118] (LUX-LUNG 7/ NCT01466660)	• 100 • 100	• Phase IIb • Open label	• Multi-centre international • UK, Taiwan, Sweden, Singapore, Norway, Korea, Ireland, Australia, China, France, Germany, Canada,	• Afatinib • Gefitinib	• 571 • 319	• ITT • ITT	PFS: 118.3 weeks Median follow-up: 27·3 months (IQR 15·3–33·9) OS (At cut-off Dec 12, 2016): 49.2 months	• EGFR mutation type (exon 19 del vs. Leu858Arg) • Baseline brain metastases (presence vs. absence) • ECOG PS (0 vs. 1) • Gender	Original: Hirsh 2016[229], Park 2016[230], Paz-Ares 2016[231], Schuler 2016a[232], Paz-Ares 2017[233], Hirsh 2016[234], Yang 2017b [235], Schuler 2017[236], Corral 2017[237], Park 2017[101], Park 2016[238] Update:

Study name (Trial name/ NCT)	• Line of therapy (%)* • EGFR mutation (%)*	• Study phase • Blinding	• Study setting • Study country	• Intervention • Comparator	• Number enrolled • Number randomised	Analysis type • Efficacy • Safety	Median length of follow-up (weeks)	Subgroup details	Linked references
			Spain (64 sites in 13 countries)					• Age (<60, ≥60, <65, ≥65, <70, ≥70, <75, ≥75 years) • Ethnic origin (Asian vs. non-Asian) • Smoking history • Patients who received (<40mg or ≥40mg)	Schuler 2017[239], Schuler 2017[145], Schuler 2017[240], O'Byrne 2016[241], Park 2017[242], Park 2016[243], Park 2017[244]
Singh 2015[186]	• 100 • 100	NR	• NR • NR	• Gefitinib • Carboplatin + paclitaxel	• NR • 60	• Unclear • Unclear	NR	NR	NL
Wu 2015[180] (ENSURE/ NCT01342965)	• 100 • 100	• Phase III • Open label	• Multi-centre international • China, Malaysia, and Philippines	• Erlotinib • Cisplatin + gemcitabine	• 217 • 217	• ITT • mITT	Reverse survival time (25 April 2014.) Erlotinib: 125.23 weeks Cisplatin + gemcitabine: 117.43 weeks	• Country (China vs. Non-China) • ECOG PS (0–1 vs 2) • Mutation (Exon 19 del vs Exon 21) • Gender • Smoking status (Current/previous vs. never)	Original: Wu 2015[245], Wu 2014[246], NCT01342965[247] Update: Wu 2017[248], NCT01342965[249]
Seto 2014[173] (JO25567/ JapicCTI-111390)	• 100 • 98.7	• Phase II • Open label	• Multi-centre • Japan	• Erlotinib • Erlotinib + bevacizumab	• 154 • 154	• mITT • mITT	88.4 weeks (IQR: 75.39–104.43)	• Gender • Age (<75, ≥75) years • Smoking status (Never smoker or former light smoker, Other) • ECOG PS (0, 1) • Histopathological classification	Original: Seto 2014[250], Kato 2014[251], Atagi 2016[252], Atagi 2015[253] Update: Kato 2018[254]

Study name (Trial name/ NCT)	• Line of therapy (%)* • EGFR mutation (%)*	• Study phase • Blinding	• Study setting • Study country	• Intervention • Comparator	• Number enrolled • Number randomised	Analysis type • Efficacy • Safety	Median length of follow-up (weeks)	Subgroup details	Linked references
								(Adenocarcinoma, Large cell or other) • Stage (IIIB or IV, Recurrence) • EGFR Mutation (Exon 19 del and Exon 21 Leu858Arg)	
Wu 2014[177] (LUX-Lung 6/ NCT01121393)	• 100 • 100	• Phase III • Open label	• Multi-centre international • China, Thailand, and South Korea	• Afatinib • Cisplatin + gemcitabine	• 910 • 364	• ITT • mITT	PFS: 71.93 weeks (IQR: 20.36–84.06)	• Gender • Age (<65 years vs ≥65 years) • EGFR mutation (Del19 or Leu858Arg vs. Del19 Leu858Arg) • ECOG PS (0 vs. 1) • Smoking history (Never smoked <15 pack-years and stopped >1 year ago, Other current or ex-smoker)	Geater 2013[255], Geater 2015[256], Wu 2013[257], Wu 2014[258], Yang 2015[259], NICE 2014[260], Schuler 2016[261], Schuler 2017[236], SMC 2013[262], CADTH 2014[263], LL6 2014[264], Chih-Hsin 2013[265], Schuler 2015[266], Sebastian 2014[267], Sequist 2014[168], Wu 2017[268], Yang 2015[269], Yang 2014[270], Schuler 2016[271] Update: Schuler 2017[239], Schuler 2017[145], Schuler 2017[240], Wu 2018[272], Yang 2016[273], Hirsch 2017[274], US FDA[Afatinib] 2013[275]
Yang 2014[168] (NCT01017874)	• 100 • 21.2	• Phase III • Open label	• Multi-centre international • 12 sites of Hong Kong, Republic of Korea, Singapore,	• Gefitinib • Pemetrexed-cisplatin followed by gefitinib	• 253 • 236	• ITT • mITT	NR	• Mutation (Exon 19 del, L858R) • ECOG PS (0 or 1) • Gender • Smoking history (Never-smoker	Boye 2016[276], Kang 2016[277], Yang 2013[278], Yang 2015[279], Yang 2017[280]

Study name (Trial name/ NCT)	• Line of therapy (%)* • EGFR mutation (%)*	• Study phase • Blinding	• Study setting • Study country	• Intervention • Comparator	• Number enrolled • Number randomised	Analysis type • Efficacy • Safety	Median length of follow-up (weeks)	Subgroup details	Linked references
			Taiwan, and Thailand					or light ex-smoker) • Histology (adenocarcinoma or non-adenocarcinoma) • Age (<65 years, ≥65years) • Disease stage (Stage IIIB, IV) • Prior Therapy (Yes/No) • Country (Korea, Taiwan, Thailand) • Lesion Location (Brain, Bone, Liver, or others)	
Sequist 2013[176] (LUX-Lung 3/ NCT00949650)	• 100 • 100	• Phase III • Open label	• Multi-centre international • 133 centres in 25 countries in Asia (Hong Kong, Japan, Korea, Malaysia, Philippines, Taiwan, Thailand), Europe (Austria, Belgium, France, Germany, Hungary, Ireland, Italy, Romania, Russia,	• Afatinib • Cisplatin + pemetrexed	• 1269 • 345	• ITT • mITT	PFS: 71.06 weeks Median follow-up time: 16.4 months OS: 177.6 weeks; IQR: (35–44)	• ECOG PS (0 vs. 1) • Gender (male vs. female) • Age at baseline (<65 vs. ≥65 years; <75 vs ≥75 years) • EGFR mutation (L858R vs Del 19 vs Other) • Race (Asian vs. Non-Asian) • Smoking history (Never smoked vs. <15 pack years and stopped >1 year prior to	LL3 2012[281], LL3 2014[282], Chih-Hsin 2013[265], Griebsch 2014[132], Kato 2015[283], O'Byrne 2012[284], Schuler 2016b[261], Schuler 2015[266], Sebastian 2014[267], Sequist 2014[168], Wu 2014a[258], Wu 2017b[268], Yamamoto 2012[285], Yang 2013b[286], Yang 2015a[259], Yang 2015c[269], Yang 2014[270], O'Byrne 2013[287], Yang 2012[288], NICE 2014[260], Schuler 2016c[271], Schuler 2017[236], SMC 2013[262], CADTH

Study name (Trial name/ NCT)	• Line of therapy (%)* • EGFR mutation (%)*	• Study phase • Blinding	• Study setting • Study country	• Intervention • Comparator	• Number enrolled • Number randomised	Analysis type • Efficacy • Safety	Median length of follow-up (weeks)	Subgroup details	Linked references
			Ukraine, UK), North America (USA, Canada), South America (Argentina, Brazil, Chile, Peru) and Australia					diagnosis vs. Other current or ex-smokers) • Presence of brain metastases at baseline (Yes vs. No)	2014[263], NCT00949650[289] Update: Schuler 2017[239], Schuler 2017[145], Schuler 2017[240], Wu 2018[272], Yang 2016[273], USFDA [Gefitinib][275],Hirsch 2017[274],
Chen 2012[188] (NCT01196078)	• 100 • 21.2	• Phase II (In NCT Phase IV reported) • Open Label	• NR • Taiwan	• Erlotinib • Vinorelbine	• 116 • 113	• ITT • ITT	NR	• Gender • Histology • Smoking status • ECOG PS • EGFR mutation status	NCT01196078[290]
Gridelli 2012[178] (TORCH/ NCT00349219)	• 100 • 5.1	• Phase III • Open Label	• Multi-centre international • Italy, Canada	• Erlotinib • Cisplatin + gemcitabine	• 760 • 760	• ITT • mITT	105.3 weeks	• Gender • Histology • Smoking status • EGFR mutation status	Maio 2012[291], Gridelli 2010[292], EudraCT 2006[293]
Han 2012[185] (First-SIGNAL/ NCT00455936)	• 100 • 13.4	• Phase III • Open label	• Multi-centre • Korea	• Gefitinib • Cisplatin + gemcitabine	• 316 • 313	• mITT • mITT	151.6 weeks (range: 83.63–214.06)	• EGFR mutation-positive patients	Han 2011[294], Lee 2013[295], Lee 2012[296], Lee 2011[297], Lee 2011[298]
Janne 2012[170] (CALGB 30406/ NCT00126581)	• 100 • 36.5	• Phase II • NR	• Multi-centre • United States (Boston, MA)	• Erlotinib • Erlotinib + carboplatin + paclitaxel	• 188 • 181	• ITT • mITT	164.6	• EGFR (Mutant and Wild-type)	Janne 2011[299], Janne 2010[300], NCT00126581[301]
Lee 2012[191] (TOPICAL/ NCT00275132)	• 100 • 4.2	• Phase III • Double blind	• Multi-centre • UK (78 centres)	• Erlotinib • PBO	• 670 • 670	• ITT • mITT	Unclear (follow-up date: March 31, 2011)	• Gender • Histological examination	Lee 2010[302], Lee 2012[303], Lee 2015[304]

Study name (Trial name/ NCT)	• Line of therapy (%)* • EGFR mutation (%)*	• Study phase • Blinding	• Study setting • Study country	• Intervention • Comparator	• Number enrolled • Number randomised	Analysis type • Efficacy • Safety	Median length of follow-up (weeks)	Subgroup details	Linked references
								• Activating EGFR or KRAS mutation • Disease stage • Smoking status • ECOG score • Development of first-cycle rash	
NCT00294762 2012[169]	• 100 • 100	• Phase II • Open Label	• Multi-centre international • UK and US	• Erlotinib • Erlotinib + chemotherapy	• 143 • 143	• ITT • ITT	NR	NR	NL
Rosell 2012[179] (EURTAC/ NCT00446225)	• 100 • 100	• Phase III • Open label	• Multi-centre international • France, Italy, and Spain from 42 institutions	• Erlotinib • Chemotherapy (cisplatin + docetaxel or gemcitabine	• 1227 • 173	• PP • mITT	Cut-off date: December 9, 2013 OS: 214.07 weeks	• Age in years (<65 vs ≥65) • Gender • Smoking status (current smoker vs. past smoker vs. never smoked) • ECOG status (0 vs. 1 vs. 2) • Mutation (Exon 19 deletion vs. L858R mutation) • EGFR mutation in serum (detected vs. not detected) • Histology (adenocarcinoma vs. other) • Previous surgery (Yes vs. No)	Original: Costa 2015[305], Karachaliou 2013[306], Karachaliou 2016[307], Khozin 2014[308], Marinis 2015[309], Rosell 2013[310], Marinis 2011[311], NICE 2011[312], SMC 2011[313] Update: Wu 2017[248], USFDA [Erlotinib][314]

Study name (Trial name/ NCT)	• Line of therapy (%)* • EGFR mutation (%)*	• Study phase • Blinding	• Study setting • Study country	• Intervention • Comparator	• Number enrolled • Number randomised	Analysis type • Efficacy • Safety	Median length of follow-up (weeks)	Subgroup details	Linked references
								• Previous radiotherapy (Yes vs. No) • Previous chemotherapy (Yes vs. No) • T790M status (present vs. absent) • Patients with BIM expression data	
Zhang 2012[192] (INFORM; C-TONG 0804/ NCT00770588)	• 100 • 10.13	• Phase III • Double-blind	• Multi-centre • China	• Gefitinib • PBO	• 298 • 296	• ITT • Unclear	Cut-off date Jan 24, 2011: 68.9 weeks (IQR 35.97–87.97) • OS: 77.26 (95% CI: 66.86–87.66) weeks	EGFR mutation positive	Original: Yang 2015[315], Zhang 2011[316], Zhang 2011[317], Zhang 2011[318], Zhao 2015[319] Update: NCT00770588[320]
Fukuoka 2011[184] (Iressa Pan-Asia Study (IPASS)/ NCT00322452)	• 100 • 21.4	• Phase III • Open Label	• Multi-centre international • 87 centres in Hong Kong elsewhere in China, Hong Kong, Indonesia, Japan, Malaysia, Philippines, Singapore, Taiwan, and Thailand	• Gefitinib • Carboplatin + paclitaxel	• 1329 • 1217	• ITT • mITT	Unclear • PFS: 24.27 weeks • OS: 73.61 weeks	PFS data acc. to • WHO PS (0 or 1, or 2) • Smoking status (non-smoker or former light smoker) • Age (<65 years or ≥65 years) • Disease stage (IIIB or IV) • Presence or absence of biomarkers • Gender	Wu 2012a[321], Wu 2013[322], Wu 2009[323], Wu 2017a[324], IPASS[325], Fan 2011[326], Goto 2012[327], Thongprasert 2011[328], Mok 2009[329], NCT00322452[330], Fukuoka 2009[331], Thongprasert 2010[332], Ohe 2009[333], Wu 2011[334], Yukito 2009[335], Yang 2010[336], NICE 2010[337], SMC 2010[338], SMC 2015[339], SMC 2010[340] Update:

Study name (Trial name/ NCT)	• Line of therapy (%)* • EGFR mutation (%)*	• Study phase • Blinding	• Study setting • Study country	• Intervention • Comparator	• Number enrolled • Number randomised	Analysis type • Efficacy • Safety	Median length of follow-up (weeks)	Subgroup details	Linked references
									USFDA [Gefitinib][341], Mok 2008[342], Yang 2014[343], Yang 2011[344]
Hirsch 2011[171]	• 100 • 15.4	• Phase II • NR	• Multi-centre international • UK, and US (Thirty-seven centres in the US and five in the UK	• Erlotinib • Intercalated erlotinib + chemotherapy (carboplatin/ paclitaxel)	• 240 • 143	• mITT • mITT	NR (follow-up was conducted every 3 months)	Analyses of PFS and OS • Biomarker subsets • Response by biomarker status	Hirsch 2011[345], Hirsch 2009[346], ICTRP 2012 [347]
Zhou 2011[181] (OPTIMAL, CTONG-0802/ NCT00874419)	• 100 • 100	• Phase III • Open label	• Multi-centre • China	• Erlotinib • Carboplatin + gemcitabine	• 549 • 165	• mITT • mITT	Cut-off date: Jan 7, 2011 PFS: 85.8 weeks • OS (till Dec 21, 2012): 112.2 weeks	• Disease stage (IIIB vs IV) • Gender • Age (>65 vs <65) • ECOG PS (0–1 vs 2) • Smoking status (Never-smoker vs Present or former smoker) • Histology (Adenocarcinoma vs Non-adenocarcinoma) • EGFR mutation (Exon 19 vs Exon 21) • Patients who received sequential combination of EGFR-TKI and chemotherapy	Chen 2013[348], Liu 2010[349], Zhou 2010[350], Zhou 2011[351], Zhou 2015[352], Zhou 2011[353], Zhou 2012[354], Wu 2010[355], Zhou 2010[356], NICE 2011[312] Update: Wu 2017[248]

Study name (Trial name/ NCT)	• Line of therapy (%)* • EGFR mutation (%)*	• Study phase • Blinding	• Study setting • Study country	• Intervention • Comparator	• Number enrolled • Number randomised	Analysis type • Efficacy • Safety	Median length of follow-up (weeks)	Subgroup details	Linked references
Cappuzzo 2010[190] (SATURN; BO18192/ NCT00556712)	• 100 • IHC+: 69.8 M+: 5.5	• Phase III • Double blind	• Multi-centre international • Australia, Austria, Belgium, Canada, Chile, China, Czech Republic, Denmark, France, Germany, Greece, Hungary, Italy, Korea Republic of, Lithuania, Malaysia, Netherlands, New Zealand, Poland, Romania, Russian Federation, Slovakia, Slovenia, South Africa, Spain, Ukraine, UK, Venezuela	• Erlotinib • PBO	• 1949 • 889	• ITT • mITT	Cut-off date: May 17, 2008) • Erlotinib 49.4 weeks • PBO: 49.83 weeks	OS and PFS • Disease stage (IIB/IV) • ECOG PS (0,1) • Smoking status • Age • Ethnic origin • Gender • Tumour histology	Capuzzo 2009[357], Casciano 2010[358], Mazieres 2012[359], Mazieres 2013[360], Neal 2010[361], Perez-Soler 2011[362], Wojtowicz-Praga 2012[363], Wu 2012[364], SMC 2010[365] Update: USFDA [Erlotinib][314]
Maemondo 2010[15] (NEJ002/ UMIN-CTR number, C000000376)	• 100 • 100	• Phase III • NR	• Multi-centre • Japan	• Gefitinib • Carboplatin + paclitaxel	• 230 • 230	• mITT • mITT	OS: 102.3 weeks (range 4.27–236.35)	• Age (<70, ≥70) • Gender (Male, Female) • PS (0,1) • Smoking status (Never, Ever) • Histology (Adenocarcinoma, Non-	Fujita 2011[366], Inoue 2009[367], Kinoshita 2009[368], Kobayashi 2009[369], Li 2015[370], Inoue 2013[371], Maemondo 2011[372], Minegishi 2012[373], Oizumi 2012[374], Osamu 2010[375], Fukuharaa 2015[376], SMC 2015[339], Miyauchi 2015[377]

Study name (Trial name/ NCT)	• Line of therapy (%)* • EGFR mutation (%)*	• Study phase • Blinding	• Study setting • Study country	• Intervention • Comparator	• Number enrolled • Number randomised	Analysis type • Efficacy • Safety	Median length of follow-up (weeks)	Subgroup details	Linked references
								adenocarcinoma) • EGFR mutation (Del19, L858R, other)	Update: Yoshizawa 2010[378]
Mitsudomi 2010[62] (WJTOG3405/ UMIN number 000000539)	• 100 • 100	• Phase III • Open label	• Multi-centre • Japan	• Gefitinib • Cisplatin + docetaxel	• 337 • 177	• mITT • mITT	256.1 weeks	• EGFR mutation (Exon 19 del and L858R) • Baseline brain metastases (absence and presence) • ECOG PS (0 and 1; and >1) • Gender • Age (<65 yrs and ≥65 yrs) • Smoking (never and current) • Post-operative occurrence • Disease Stage IIB/ IIIB/IV • Central laboratory, commercial laboratory	Satouchi 2010[379], Yoshioka 2014[115], Mitsudomi 2012[380], SMC 2015[339], NICE 2011[312], Tsurutani [381]
Goss 2009[193] (INSTEP/ NCT00259064)	• 100 • 15.9	• Phase II • Double blind	• Multi-centre international • Australia, Canada, Czech Republic, the Netherlands, UK	• Gefitinib+ BSC • BSC + PBO	• 220 • 201	• ITT • ITT	PFS: Gefitinib: 6.06 weeks PBO: 5.63 OS: Gefitinib: 13.43 weeks PBO: 11.7 weeks	• EGFR FISH positive and negative	NL

Study name (Trial name/ NCT)	• Line of therapy (%)* • EGFR mutation (%)*	• Study phase • Blinding	• Study setting • Study country	• Intervention • Comparator	• Number enrolled • Number randomised	Analysis type • Efficacy • Safety	Median length of follow-up (weeks)	Subgroup details	Linked references
Crino 2008[189] (INVITE/ NCT00256711)	• 100 • 27.5	• Phase II • Open label	• Multi-centre international • Australia, Brazil, Czech Republic, France, Germany, Italy, Republic of Korea, South Africa, Taiwan, UK	• Gefitinib • Vinorelbine	• 205 • 196	• ITT • mITT	PFS: Gefitinib: 12.13 Vinorelbine: 10.83 OS: Gefitinib: 27.8 Vinorelbine: 26.9	NR	Crino 2007[382]
Lilenbaum 2008[182] (NCT00085839)	• 100 • IHC^{+}: 23.3 FISH^{+}: 13.6 M^{+}: 4.8	• Phase II • Open label	• Multi-centre • US	• Erlotinib • Carboplatin + paclitaxel	• 103 • 103	• ITT • ITT	NR	• Histology (adenocarcinoma, squamous cell carcinoma) • Patients who developed rash • Smoking status (never smokers, smokers within 1 year of enrolment)	Lilenbaum 2006[383], NCT00085839[384]

Key: BSC, best supportive care; ECOG PS, eastern cooperative oncology group performance status; IQR, interquartile range; ITT, intent to treat; mITT, modified intent to treat; NL, not linked; NR, not reported; OS, overall survival; PBO, placebo; PFS, progression-free survival; RR, response rate.

Note: *The proportion of patients who received 1L therapy and possessed EGFR+ mutation is calculated from the overall study population and not mutant population.

D.1.2 Population characteristics

The demographic characteristics of the population assessed across the RCTs are presented in Table 101 and Table 102. This section includes only the studies which reported baseline data for the population of interest.

Age and ethnicity

Across the 37 studies, the age of the study population was reported in 17 studies. Mean age was reported in six studies[15, 166, 177, 179, 187, 194], and ranged from 53.1 years in the study by Patil et al.[187] to 64.2 years in EURTAC[179], both for the platinum doublet chemotherapy group. Median age was reported in 14 studies, and varied between 56.0 years for the platinum doublet chemotherapy group in ENSURE[180] and 67 years for both erlotinib and erlotinib plus bevacizumab groups in the study by Seto et al.[173] Three studies reported both mean and median age of the study population.[166, 177, 179] One study each reported data in terms of patient proportion who were <65 years[184] and for the overall population (median age, 58 years).[170] One study each further reported data for patient population who were <65 and ≥65 years.[195]

Data for ethnicity of patients were reported in 19 studies. In EURTAC, the majority of patients were white (>98%).[179] Eleven studies assessed Asian participants only.[62, 163, 166, 168, 177, 180, 181, 183, 187, 188, 192] In LL3 and ARCHER 1050, the majority of patients were Asian (72% and 78.2%, respectively) while the remaining patients were white.[72, 176]

Disease metastasis and prior therapy

Three studies reported data for patients whose disease had metastasised to bone prior to study entry.[118, 167, 179] The proportion of patients varied between 24.4% of the gefitinib plus pemetrexed group in the study by An et al.[167] to 50% of the afatinib group in LL7.[118] The proportion of patients with brain metastases at study entry was reported in nine studies.[118, 164, 167, 168, 173, 176, 177, 179, 187] The proportion of patients varied between none in the erlotinib group in the study by Seto et al.[173] and the study by Yang et al.[168] to 53.3% of the gefitinib plus pemetrexed group in the study by An et al.[167] Three studies reported that 10.0–27.6% of patients had liver metastases at baseline.[118, 167, 187] Two studies also reported data for patients whose disease had metastasised to lung and adrenal glands[118, 167] and one study reported data for patients with visceral metastasis.[164]

Two studies reported that 5.0–13.7% of patients had received prior adjuvant/neoadjuvant therapy.[165, 166] Data for the proportion of patients who had received surgery and radiotherapy prior to study entry were reported in the study by Leighl et al. only.[165]

ECOG/WHO PS

Nineteen studies reported the proportion of patients with Eastern Cooperative Oncology Group (ECOG) performance status (PS) at study entry. Of these, three studies reported data for patients with ECOG PS 0–1, which varied between 80.0–96%.[181, 184, 194] One study reported data for patients who had ECOG PS 0 but for the overall study population and not according to treatment arm (58% of the overall population with a EGFR mutation).[170] Across the other 15 studies, the proportion of patients with ECOG PS 0 varied between 0% in the study by Zhao et al. (erlotinib and docetaxel plus cisplatin)[183] and 60% of the gefitinib group in INFORM.[192]

The proportion of patients with ECOG PS 1 were reported in 16 studies. One study reported data for the overall study population and not by treatment arm (42% of the overall population with a EGFR mutation).[170] Across the other 15 studies, the proportion of patients varied from 33.3% of the gefitinib group in the INFORM study[192] to 93.8% of the group who received carboplatin plus pemetrexed followed by pemetrexed in the study by Patil et al.[187]

The proportion of patients with ECOG PS 2 were reported in ten studies.[15, 176, 179-183, 187, 192, 194] In nine of these studies the proportion of patients with ECOG PS 2 varied from none of the afatinib group in LL3[176] and placebo group in the INFORM study[192] to 100.0% in both the treatment arms (erlotinib and carboplatin plus paclitaxel) in the study by Lilenbaum et al.[182] In the study by Yang et al., it was reported that 14.3% of the gefitinib group and 20.0% of the group receiving gefitinib plus Fuzheng Kang'ai Formula data had ECOG PS 2–3.[194]

None of the studies reported data for patients with ECOG PS 3 or 4.

Smoking status

The proportion of patients who were smokers at study entry was reported in 17 studies. Five studies reported data for patients who were current smokers or former smokers, varying between 21.0% each in both the afatinib and gefitinib groups in LL7[118] and 57.8% of the gefitinib group in the study by An et al.[167] In the 12 other studies, the proportion of current smokers varied between 1.7% of the cisplatin plus pemetrexed group in LL3[176] and 36% of the gefitinib plus pemetrexed group in the study by Cheng et al.[166]

Data for patients who were never smokers were reported in 20 studies. One study reported data for the overall population and not by treatment arm (77% patients were never smokers).[170] Across the 19 other studies, the proportion of never smokers varied from 42.2% of the gefitinib group in the study by An et al.[167] to 94.6% of the carboplatin plus paclitaxel group in IPASS.[184]

Data for patients who were ex-smokers were reported in 11 studies.[102, 118, 164, 170, 173, 176, 177, 179, 180, 187, 192] One of these studies reported data for the overall population and not by treatment arm (23% were ex-smokers).[170] Across the 10 other studies, the proportion of ex-smokers varied from 1.9% of the cisplatin plus gemcitabine group in ENSURE[180] to 42.8% of the placebo group in the INFORM study.[192]

Histology/cancer stage

The proportion of patients with Stage IIIB disease was reported in 18 studies. Patients with Stage IIIB disease varied between none of the erlotinib group in two studies (Leighl et al.[165] and Seto et al.[173]) and 22.5% of the carboplatin plus paclitaxel group in IPASS.[184]

The proportion of patients with Stage IV disease was reported in 19 studies. Across these studies, the proportion of patients with Stage IV disease varied between 73.7% of the carboplatin plus paclitaxel group in NEJ002[15] and 100% in the study by Scagliotti et al. (erlotinib and erlotinib plus emibetuzumab combination)[172] and the erlotinib group in the study by Leighl et al.[165]

Data for patients who had adenocarcinoma were reported in 16 studies. In 15 of these studies, the proportion of patients varied from 78.6% of the placebo group in INFORM[192] to 100% in five studies for both treatment arms.[167, 176, 177, 187, 195] Additionally, the study by Janne et al. reported data for the total study population (86% of the total EGFR mutant population).[170]

Data for patients who had squamous NSCLC were reported in eight studies. Across seven of these studies, the proportion of patients with squamous histology varied between 0% of the erlotinib group in the study by Leighl et al.[165] and the platinum doublet chemotherapy group in EURTAC[179] to 14.3% of the placebo group in INFORM.[192] Additionally, OPTIMAL reported data for the overall population and not by treatment arm (eight patients overall).[181]

Similarly, the proportion of patients with large cell adenocarcinoma varied between none in three studies [erlotinib plus bevacizumab group in Seto et al.[173], carboplatin plus paclitaxel group in NEJ002[15] and both treatment arms (Gefitinib plus Fuzheng Kang'ai formula and gefitinib) in the study by Yang et al.[194]] to 3% of the erlotinib group in EURTAC[179], across five studies.[15, 164, 173, 179, 194] Also, data for patients with other types of histologies were reported in 14 studies. The other forms included, non-adenocarcinoma, non-squamous cell carcinoma and adenosquamous cell carcinoma.

EGFR mutation status

Data for patients with exon 19 del were reported in 24 studies. Two studies reported data for the overall EGFR mutant population (not treatment arm wise) with exon 19 del mutations.[185, 188] Across the other 22 studies, the proportion of the overall study population with exon 19 del mutations varied between 5.6% of the erlotinib plus chemotherapy group in the study by Hirsch et al.[171] and 69.7% of the erlotinib group in the study by Janne et al.[170]

Data for patients with L858R mutations were reported in 25 studies. Two studies reported data for the overall EGFR mutant population (not treatment arm wise) with L858R mutations.[185, 188] Across the 23 other studies the proportion of the overall study population with L858R mutations varied between 1.4% of the erlotinib group in the study by Hirsch et al.[171] and 64.4% of the gefitinib plus pemetrexed group in the study by An et al.[167]

The proportion of patients with T790M mutations were reported in four studies.[15, 177, 184, 192] The proportion of patients with T790M mutations varied between none of the patient in the gefitinib group in INFORM[192] and both the treatment arms (gefitinib and carboplatin plus paclitaxel) in NEJ002[15] and 1% across two studies (placebo group in INFORM[192] and carboplatin plus paclitaxel group in IPASS).[184] In the FLAURA trial, four patients in the osimertinib group and one patient in the standard EGFR-TKI group had T790M mutation based on tissue and cytogenic DNA testing. The data for exon19del and L858R mutation were based on EGFR mutation type at randomisation.[164]

Data for other types of mutations were reported in 11 studies.[15, 166, 168, 171, 176, 177, 182, 184, 187, 192, 271]

Studies not reporting data separately for the EGFR+ subgroup population receiving 1L therapy

Patient demographic data were not reported separately for the EGFR+ subgroup population in 11 studies.[168, 171, 178, 182, 185, 188-191, 193, 271] Patients characteristics at study entry were not reported in two studies as only conference abstracts were available for them thus limiting the information presented.[175, 186] In the WJTOG3405 study, patient characteristics at baseline were not reported separately for patients with disease Stage IIIB/IV.[62] Further in the CTONG 0901 study, demographic data were not reported separately for patients who received 1L therapy.[163] The demographic characteristics across these studies has been presented in Table 101 and Table 102.

The ranges provided in the population characteristics section above do not include these studies.

Table 101: Patient demographics at baseline in RCTs

Study name (Trial name/ NCT)	• Line of therapy (%) • EGFR mutation (%)	Treatment	Number of patients	Age (years) Median (min-max)	Male: n (%)	Metastatic site: n (%) • Bone • Brain • Liver • Other	Prior therapy: n (%) • Adjuvant/neoadjuvant therapy • Surgery • Radiotherapy	Cancer Stage: n (%) • Stage IIIB • Stage IV
Soria 2018 (FLAURA/ NCT02296125)	• 100 • 100	Osimertinib	279	64 (26–85)	101 (36)	• NR • 53 (19) • NR • 94 (34)	NR	• 14 (5) • 264 (95)
		Standard EGFR-TKI	277	64 (35–93)	105 (38)	• NR • 63 (23) • NR • 103 (37)	NR	• 15 (5) • 262 (95)
Han 2017 (NCT02148380)	• 100 • 100	Gefitinib	41	<65 years, n (%): 27 (43.9) ≥ 65 years, n (%): 14 (56.1)	18 (43.9)	NR	NR	• 5 (12.2) • 36 (87.8)
		Gefitinib + carboplatin + pemetrexed	40	<65 years, n (%):27 (57.5) ≥ 65 years, n (%):13 (42.5)	15 (37.5)	NR	NR	• 8 (20) • 32 (80)
		Carboplatin + pemetrexed	40	<65 years, n (%):31 (72.5) ≥ 65 years, n (%):9 (27.5)	17 (42.5)	NR	NR	• 7 (17.5) • 33 (82.5)
Leighl 2017	• 100 • 100	Erlotinib + linsitinib	44	61.5 (44–82)	14 (31.8)	NR	• 6 (13.7) • 13 (29.5) • 8 (18.2)	• 1 (2.3) • 43 (97.7)
		Erlotinib + PBO	44	57.5 (36–85)	12 (27.3)	NR	• 5 (11.3) • 10 (22.7) • 13 (29.5)	• 0 (0) • 44 (100)
Patil 2017 (CTRI/2015/08/006113)	• 100 • 100	Gefitinib	145	54.44[a]	67 (46.2)	• NR • 22 (15.7) • 35 (24.1) • NR	NR	• 2 (1.4) • 143 (98.6)
		Platinum + pemetrexed	145	53.12[a]	97 (66.9)	• NR • 23 (15.9) • 40 (27.6) • NR	NR	• 3 (2.1) • 142 (97.9)
	• 100 • 100	Erlotinib	70	NR	NR	NR	NR	• NR • 70 (100)

Study name (Trial name/ NCT)	• Line of therapy (%) • EGFR mutation (%)	Treatment	Number of patients	Age (years) Median (min-max)	Male: n (%)	Metastatic site: n (%) • Bone • Brain • Liver • Other	Prior therapy: n (%) • Adjuvant/neoadjuvant therapy • Surgery • Radiotherapy	Cancer Stage: n (%) • Stage IIIB • Stage IV
Scagliotti 2017 (Balise/ NCT01897480)		Erlotinib + emibetuzumab	71	NR	NR	NR	NR	• NR • 71 (100)
Wu 2017 (ARCHER 1050/ NCT01774721)	• 100 • 100	Dacomitinib	227	62 (28–87) <65 year: 133	81 (36)	NR	NR	• 18 (8) • 184 (81)
		Gefitinib	225	61 (33–86) <65 year: 140	100 (44)	NR	NR	• 16 (7) • 183 (81)
Yang 2017 (ChiCTR-IOR-14005679)	• 100 • 100	Gefitinib	35	NR (33–85); 58.44 (12.02)[a]	13 (37.1)	NR	NR	• 1 (2.9) • 34 (97.1)
		Gefitinib+ Fuzheng Kang'ai formula	35	NR (39–79); 59.77 (10.31)[a]	13 (37.1)	NR	NR	• 4 (11.4) • 31 (88.6)
Yang 2017 (CTONG 0901/ NCT01024413)*	• 64.5 • 100	Erlotinib	128	≤60 years n (%): 71 (55.5) >60 years n (%): 57 (44.5)	60 (46.9)	• NR • 25 (19.5) • NR • NR	• NR • 36 (28.1) • 13 (10.2)	• 4 (3.1) • 124 (96.9)
		Gefitinib	128	≤60 years n (%): 72 (56.3) >60 years n (%): 56 (43.8)	59 (46.1)	• NR • 22 (17.2) • NR • NR	• NR • 31 (24.2) • 10 (7.8)	• 3 (2.3) • 125 (97.7)
Zhao 2017 (NCT01131429)	• 100 • 100	Erlotinib	43	59 (35–78)	9 (20.9)	NR	NR	• 1 (2.3) • 42 (97.7)
		Docetaxel + cisplatin	38	57 (34–75)	14 (36.8)	NR	NR	• 2 (5.3) • 36 (94.7)
An 2016	• 100 • 100	Gefitinib + PBO	45	66.89 (NR)	25 (55.5)	• 12 (26.6) • 23 (51.1) • 5 (11.1) • 17 (37.7)	NR	• 6 (13.3) • 39 (86.7)
		Gefitinib + pemetrexed	45	65.72 (NR)	25 (55.5)	• 11 (24.4) • 24 (53.3) • 5 (11.1) • 16 (35.5)	NR	• 4 (8.9) • 41 (91.1)
Cheng 2016 (NCT01469000)	• 100 • 100	Gefitinib	65	62 (41–80); 61 (9.5)[a] < 65 years n (%): 43 (66) ≥ 65 years n (%): 22 (34)	24 (37)	NR	• 3 (5) • NR • NR	• NR • 57 (88)
		Gefitinib + pemetrexed	126	62 (33–84); 62 (9.4)[a]	44 (35)	NR	• 10 (8)	• NR

Study name (Trial name/ NCT)	• Line of therapy (%) • EGFR mutation (%)	Treatment	Number of patients	Age (years) Median (min-max)	Male: n (%)	Metastatic site: n (%) • Bone • Brain • Liver • Other	Prior therapy: n (%) • Adjuvant/neoadjuvant therapy • Surgery • Radiotherapy	Cancer Stage: n (%) • Stage IIIB • Stage IV
				< 65 years n (%): 79 (63) ≥ 65 years n (%): 47 (37)			• NR • NR	• 105 (83)
Goldberg 2016 (SWOG S1403/ NCT02438722)*	• 100 • 100	Afatinib	24 (Assessed for safety)	NR	NR	NR	NR	NR
		Afatinib + cetuximab	23 (Assessed for safety)	NR	NR	NR	NR	NR
Mok 2016 (P06162/ NCT01039948)*	• 100 • 37.7	Gefitinib	94	NR	19 (20)	NR	NR	• 8 (8.5) • 86 (91)
		Gefitinib + ficlatuzumab	94	NR	19 (20)	NR	NR	• 2 (2.1) • 92 (98)
Park 2016 (LUX-LUNG 7/ NCT01466660)	• 100 • 100	Afatinib	160	63 (30–86)	69 (43)	• 80 (50) • 26 (16) • 16 (10) • 100 (63)	NR	• 8 (5) • 152 (95)
		Gefitinib	159	63 (32–89)	53 (33)	• 73 (46) • 24 (15) • 24 (15) • 104 (65)	NR	• 3 (2) • 156 (98)
Singh 2015*	• 100 • 100	Gefitinib	60	NR	NR	NR	NR	NR
		Carboplatin + paclitaxel		NR	NR	NR	NR	NR
Wu 2015 (ENSURE/ NCT01342965)	• 100 • 100	Erlotinib	110	57.5 (33–79) <65 years, %: 79.1 ≥65 years, %: 20.9	42 (38.2)	NR	NR	• 10 (9.1) • 100 (90.9)
		Cisplatin + gemcitabine	107	56 (30–78) <65 years, %: 79.4 ≥65 years, %: 20.6	42 (39.3)	NR	NR	• 7 (6.5) • 100 (93.5)
Seto 2014 (JO25567/ JapicCTI-111390)	• 100 • 98.7	Erlotinib	77	67 (60–73) <75 years n (%): 62 (81) ≥75 years n (%): 15 (19)	26 (34)	• NR • 0 (0) • NR • NR	NR	• 0 (0) • 62 (81)
		Erlotinib + bevacizumab	75	67 (59–73) <75 years n (%): 63 (84) ≥75 years n (%): 12 (16)	30 (30)	• NR	NR	• 1 (1) • 60 (80)

Study name (Trial name/ NCT)	• Line of therapy (%) • EGFR mutation (%)	Treatment	Number of patients	Age (years) Median (min-max)	Male: n (%)	Metastatic site: n (%) • Bone • Brain • Liver • Other	Prior therapy: n (%) • Adjuvant/neoadjuvant therapy • Surgery • Radiotherapy	Cancer Stage: n (%) • Stage IIIB • Stage IV
Wu 2014 (LUX-Lung 6/ NCT01121393)	• 100 • 100	Afatinib	242	58 (49–65); 56.7 (11.2)[a]	87 (36)	• NR • 30 (12.4) • NR • NR	NR	• 16 (6.6) • 226 (93.4)
		Cisplatin + gemcitabine	122	58 (49–62); 55.6 (10.1)[a]	39 (32)	• NR • 19 (15.6) • NR • NR	NR	• 6 (4.9) • 116 (95.1)
Yang 2014 (NCT01017874)*	• 100 • 21.2	Gefitinib	118	Mean (range): 59 (31–79) <65 years n (%): 81 (69) ≥65 years n (%): 37 (31)	29 (25)	NR	NR	• 8 (7) • 110 (93)
		Pemetrexed-cisplatin followed by gefitinib	118	Mean (range): 59 (24–81) <65 years: 80 (68) ≥65 years: 38 (32)	30 (25)	NR	NR	• 6 (5) • 112 (95)
Sequist 2013 (LUX-Lung 3/ NCT00949650)	• 100 • 100	Afatinib	230	61.5 (28–86)	83 (36.1)	• NR • 27 (11.74)[b] • NR • NR	NR	• 20 (8.7) • 210 (91.3)
		Cisplatin + pemetrexed	115	61 (31–3)	38 (33)	• NR • 15 (13.04) • NR • NR	NR	• 17 (14.8) • 98 (85.2)
Chen 2012 (NCT01196078)*	• 100 • 21.2	Erlotinib	57	77 (70–90); 78.1[a]	47 (82.5)	NR	NR	• 14 (24.6) • 43 (75.4)
		Vinorelbine	56	77 (70–90); 77.8[a]	45 (80.4)	NR	NR	• 10 (17.9) • 46 (82.1)
Gridelli 2012 (TORCH/ NCT00349219) *	• 100 • 5.1	Erlotinib	380	63 (27–79); <70 years n (%): 361 (95) ≥ 70 years n (%): 19 (5)	252 (66.3)	NR	• NR • 90 (23.7) • NR	• 46 (12.1) • 334 (87.9)
		Cisplatin + gemcitabine	380	62 (34–81); <70 years n (%): 361 (95) ≥ 70 years n (%): 19 (5)	252 (66.3)	NR	• NR • 92 (24.2) • NR	• 37 (9.7) • 343 (90.3)
	• 100 • 13.5	Gefitinib	159	57 (32–74)	19 (12)	NR	NR	• 17 (10.7) • 142 (89.3)

Study name (Trial name/ NCT)	• Line of therapy (%) • EGFR mutation (%)	Treatment	Number of patients	Age (years) Median (min-max)	Male: n (%)	Metastatic site: n (%) • Bone • Brain • Liver • Other	Prior therapy: n (%) • Adjuvant/neoadjuvant therapy • Surgery • Radiotherapy	Cancer Stage: n (%) • Stage IIIB • Stage IV
Han 2012 (First-SIGNAL/ NCT00455936)*		Cisplatin + gemcitabine	150	56.5 (19–74)	16 (10.7)	NR	NR	• 14 (9.3) • 136 (90.7)
Janne 2012 (CALGB 30406/ NCT00126581)	• 100 • 36.5	Erlotinib	66	58 (38–79)	25 (38)	NR	NR	NR
		Erlotinib + carboplatin + paclitaxel				NR	NR	NR
Lee 2012 (TOPICAL/ NCT00275132)*	• 100 • 4.2	Erlotinib	350	77 (72–82); ≥75 years n (%): 200 (63)	215 (61)	NR	NR	• 127 (36) • 223 (64)
		PBO	320	77 (72–81); ≥75 years n (%): 203 (63)	194 (61)	NR	NR	• 107 (33) • 213 (67)
NCT00294762 2012	• 100 • 100	Erlotinib	72	63 (31–81)	28 (38.9)	NR	NR	NR
		Erlotinib + chemotherapy	71	63 (27–90)	40 (56.3)	NR	NR	NR
Rosell 2012 (EURTAC/ NCT00446225)	• 100 • 100	Erlotinib	86	65 (24–82); IQR, 56–72; 63.4 (10.9)[a]	28 (33)	• 28 (33) • 9 (10) • NR • NR	NR	• 6 (7) • 78 (91)
		Chemotherapy (cisplatin + docetaxel/ gemcitabine)	87	65 (29–82); IQR, 60–71; 64.2 (9.2)[a]	19 (22)	• 28 (33) • 11 (13) • NR • NR	NR	• 5 (6) • 82 (94)
Zhang 2012 (INFORM; C-TONG 0804/ NCT00770588	• 100 • 10.13	Gefitinib	15	NR	5 (33.3)	NR	NR	• 2 (13.3) • 13 (86.7)
		PBO	14	NR	9 (64.3)	NR	NR	• 1 (7.1) • 13 (92.9)
Fukuoka 2011 (Iressa Pan-Asia Study (IPASS)/ NCT00322452)	• 100 • 21.4	Gefitinib	132	<65 years n (%): 95 (72.0)	24 (18.2)	NR	NR	• 19 (14.4) • NR
		Carboplatin + paclitaxel	129	<65 years n (%): 90 (69.8)	26 (20.2)	NR	NR	• 29 (22.5) • NR
Hirsch 2011*	• 100 • 7.7	Erlotinib	72	<70 years (%): 72	28 (39)	NR	NR	NR
		Intercalated erlotinib + chemotherapy (carboplatin/ paclitaxel)	71	<70 years (%): 61	40 (56)	NR	NR	NR
	• 100	Erlotinib	82	57 (31–74)	34 (41)	NR	NR	• 11 (13)

Study name (Trial name/ NCT)	• Line of therapy (%) • EGFR mutation (%)	Treatment	Number of patients	Age (years) Median (min-max)	Male: n (%)	Metastatic site: n (%) • Bone • Brain • Liver • Other	Prior therapy: n (%) • Adjuvant/neoadjuvant therapy • Surgery • Radiotherapy	Cancer Stage: n (%) • Stage IIIB • Stage IV
Zhou 2011 (OPTIMAL, CTONG-0802/ NCT00874419)	• 100			<65 years n (%): 63 (77) ≥65 years n (%): 19 (23)				• 71 (87)
		Carboplatin + gemcitabine	72	59 (36–78) <65 years n (%): 51 (71) ≥65 years, n (%): 21 (29)	29 (40)	NR	NR	• 5 (7) • 67 (93)
Cappuzzo 2010 (SATURN; BO18192/ NCT00556712)*	• 100 • IHC+: 69.8 M+: 5.5	Erlotinib	438	60 (33–83)	321 (73)	NR	NR	• 116 (26) • 322 (74)
		PBO	451	60 (30–81)	338 (75)	NR	NR	• 109 (24) • 342 (76)
Maemondo 2010 (NEJ002/ UMIN-CTR number, C000000376)	• 100 • 100	Gefitinib	114	NR (43–75); 63.9 (7.7)[a]	42 (36.8)	NR	NR	• 15 (13.2) • 88 (77.2)
		Carboplatin + paclitaxel	114	NR (35–75); 62.6 (8.9)[a]	41 (36)	NR	NR	• 21 (18.4) • 84 (73.7)
Mitsudomi 2010 (WJTOG3405/ UMIN number 000000539)*	• 100 • 100	Gefitinib	86	64 (34–74)	27	NR	NR	• 10 (NR) • 41 (NR)
		Cisplatin + docetaxel	86	64 (41–75)	26	NR	NR	• 9 (NR) • 41 (NR)
Goss 2009 (INSTEP/ NCT00259064)*	• 100 • 15.9	Gefitinib+ BSC	100	74 (43–89); <45 years n (%): 1 (1) 45–64 n (%): 18 (18) 65–74 n (%): 35 (35) ≥75 n (%): 46 (46)	61 (61)	NR	NR	• 16 (16) • 84 (84)
		BSC + PBO	101	76 (42–90) <45 years n (%): 1 (1) 45–64 n (%): 16 (15.8) 65–74 n (%): 32 (31.7) ≥75 n (%): 52 (51.5)	61 (60.4)	• NR	• NR	• 17 (16.8) • 84 (83.2)
Crino 2008 (INVITE/ NCT00256711)*	• 100 • 27.5	Gefitinib	97	74 (70–89); < 75 years n (%): 51 (52.6) 75–79 years n (%): 28 (28.9) ≥80 years n (%): 18 (18.6)	75 (77.3)	NR	NR	• 19 (19.6) • 78 (80.4)
		Vinorelbine	99	74 (70–86); < 75 years n (%): 52 (52.5)	73 (73.7)	NR	NR	• 26 (26.3) • 73 (73.7)

Study name (Trial name/ NCT)	• Line of therapy (%) • EGFR mutation (%)	Treatment	Number of patients	Age (years) Median (min-max)	Male: n (%)	Metastatic site: n (%) • Bone • Brain • Liver • Other	Prior therapy: n (%) • Adjuvant/neoadjuvant therapy • Surgery • Radiotherapy	Cancer Stage: n (%) • Stage IIIB • Stage IV
				75–79 years n (%): 32 (32.3) ≥80 years n (%): 15 (15.2)				
Lilenbaum 2008 (NCT00085839)*	• 100 • IHC+: 23.3 FISH+: 13.6 M+: 4.8	Erlotinib	52	<70 years n (%): 28 (54) ≥ 70 years n (%): 24 (46)	23 (44)	NR	NR	• 7 (13) • 45 (87)
		Carboplatin + paclitaxel	51	<70 years n (%): 27 (53) ≥ 70 years n (%): 24 (47)	28 (55)	NR	NR	• 7 (14) • 44 (86)

Key: BSC, best supportive care; IQR, interquartile range; NR, not reported; PBO, placebo; SD, standard deviation; TKI, tyrosine kinase inhibitor.
Notes: [a] Data reported as mean (SD); [b] Data discrepancy: associated table reported n=20 for afatinib.
* Study did not report data specifically for EGFR+ advanced/metastatic NSCLC patients receiving 1L therapy thereby, data extracted for overall population

Table 102: Patient demographics at baseline in RCTs (contd.)

Study name (Trial name/ NCT)	• Line of therapy (%) • EGFR mutation (%)	Treatment	Number of patients	Smoking status • Current smokers: n (%) • Never smokers: n (%) • Ex-smokers: n (%)	Race • White • Black/ African American • Asian • Caucasian • Other	EGFR mutation: n (%) • Exon 19 del • L858R • T790m • Other	ECOG PS: n (%) • 0 • 1 • 2	Disease subtype: n (%) • Adenocarcinoma • Squamous • Large cell • Other
Soria 2018 (FLAURA/ NCT02296125)	• 100 • 100	Osimertinib	279	• 8 (3) • 182 (65) • 89 (32)	• 101 (36) • NR • 174 (62) • NR • 4 (1)	• 175 (63) • 104 (37) • 4 (1.4) • NR	• 112 (40) • 167 (60) • NR	• 275 (99) • 1 (0.4) • 2 (0.7) • 1 (0.4)
		Standard EGFR-TKI	277	• 9 (3) • 175 (63) • 93 (34)	• 100 (36) • NR • 173 (62) • NR • 4 (1)	• 174 (63) • 103 (37) • 1 (0.4) • NR	• 116 (42) • 160 (58) • NR	• 272 (98) • 2 (0.7) • 3 (1.1) • 0 (0)
Han 2017 (NCT02148380)	• 100 • 100	Gefitinib	41	• 14 (34.1) • 27 (65.9) • NR	NR	• 21 (51.2) • 20 (47.8) • NR • NR	• 9 (22) • 32 (78) • NR	• 41 (100) • NR • NR • NR

Study name (Trial name/ NCT)	• Line of therapy (%) • EGFR mutation (%)	Treatment	Number of patients	Smoking status • Current smokers: n (%) • Never smokers: n (%) • Ex-smokers: n (%)	Race • White • Black/ African American • Asian • Caucasian • Other	EGFR mutation: n (%) • Exon 19 del • L858R • T790m • Other	ECOG PS: n (%) • 0 • 1 • 2	Disease subtype: n (%) • Adenocarcinoma • Squamous • Large cell • Other
		Gefitinib + carboplatin + pemetrexed	40	• 13 (32.5) • 27 (67.5) • NR	NR	• 21 (52.5) • 19 (47.5) • NR • NR	• 8 (20) • 32 (80) • NR	• 40 (100) • NR • NR • NR
		Carboplatin + pemetrexed	40	• 11 (27.5) • 29 (72.5) • NR	• NR	• 20 (50) • 20 (50) • NR • NR	• 10 (25) • 30 (75) • NR	• 40 (100) • NR • NR • NR
Leighl 2017	• 100 • 100	Erlotinib + linsitinib	44	• 11 (25) • 33 (75) • NR	• 20 (45.5) • 4 (9.1) • 20 (45.5) • NR • NR	• 26 (59.1) • 18 (40.9) • NR • NR	• 21 (47.7) • 23 (52.3) • NR	• 41 (93.2) • 1 (2.3) • NR • Mixed: 2 (4.5)
		Erlotinib + PBO	44	• 12 (27.3) • 32 (72.7) • NR	• 26 (59.1) • 0 (0) • 16 (36.4) • NR • NR	• 25 (56.8) • 19 (43.2) • NR • NR	• 21 (47.7) • 23 (52.3) • NR	• 42 (95.5) • 0 (0) • NR • Mixed: 1 (2.3)
Patil 2017 (CTRI/2015/08/006113)	• 100 • 100	Gefitinib	145	• NR • 113 (77.9) • 32 (22.1)	• NR • NR • 145 (100) • NR • NR	• 76 (52.4) • 65 (44.8) • NR • Exon 18: 4 (2.8)	• 3 (2.1) • 132 (91) • 10 (6.9)	• 145 (100) • 0 (0) • 0 (0) • 0 (0)
		Platinum + pemetrexed	145	• NR • 117 (80.7) • 28 (19.3)	• NR • NR • 145 (100) • NR • NR	• 92 (63.4) • 51 (35.2) • NR • Exon 18: 2 (1.4)	• 2 (1.4) • 136 (93.8) • 7 (4.8)	• 145 (100) • 0 (0) • 0 (0) • 0 (0)
Scagliotti 2017 (Balise/ NCT01897480)	• 100 • 100	Erlotinib	70	NR	NR	NR	NR	NR
		Erlotinib + emibetuzumab	71	NR	NR	NR	NR	NR
Wu 2017 (ARCHER 1050/ NCT01774721)	• 100 • 100	Dacomitinib	227	• 15 (6.6) • 147 (64.8) • 65 (28.6)	• 56 (25) • 1 (0.4) • 170 (74.9) • NR • NR	• 134 (59) • 93 (41) • NR • NR	• 75 (33) • 152 (67) • NR	NR

Study name (Trial name/ NCT)	• Line of therapy (%) • EGFR mutation (%)	Treatment	Number of patients	Smoking status • Current smokers: n (%) • Never smokers: n (%) • Ex-smokers: n (%)	Race • White • Black/ African American • Asian • Caucasian • Other	EGFR mutation: n (%) • Exon 19 del • L858R • T790m • Other	ECOG PS: n (%) • 0 • 1 • 2	Disease subtype: n (%) • Adenocarcinoma • Squamous • Large cell • Other
		Gefitinib	225	• 19 (8.4) • 144 (64) • 62 (27.6)	• 49 (22) • 0 (0) • 176 (78.2) • NR • NR	• 133 (59.1) • 92 (40.9) • NR • NR	• 62 (27.6) • 163 (72.4) • NR	NR
Yang 2017 (ChiCTR-IOR-14005679)	• 100 • 100	Gefitinib	35	• 9 (25.7) • 26 (74.3) • NR	NR	• 20 (57.1) • 15 (42.9) • NR • NR	• 0–1: 30 (85.7) • 2–3: 5 (14.3)	• 32 (91.4) • 2 (5.7) • 0 (0) • Adenosqamous: 1 (2.9)
		Gefitinib+ Fuzheng Kang'ai Formula	35	• 12 (34.3) • 23 (65.7) • NR	NR	• 22 (62.9) • 13 (37.1) • NR • NR	• 0–1: 28 (80.0) • 2–3: 7 (20)	• 33 (94.2) • 1 (2.9) • 0 (0) • Adenosqamous: 1 (2.9)
Yang 2017 (CTONG 0901/ NCT01024413)*	• 64.5 • 100	Erlotinib	128	• 23 (18) (Patients with smoking status: Yes) • 105 (82) (Patients with smoking status: No) • NR	All patients were Chinese	• 74 (57.8) • Exon 21: 54 (42.2) • NR • NR	• NR • NR • 2 (1.6) ECOG 0-1: 126 (98.4)	• 123 (96.1) • NR • NR • NR
		Gefitinib	128	• 35 (27.3) (Patients with smoking status: Yes) • 93 (72.7) (Patients with smoking status: No) • NR	All patients were Chinese	• 74 (57.8) • Exon 21: 54 (42.2) • NR • NR	• NR • NR • 4 (3.1) ECOG 0-1: 124 (96.9)	• 123 (96.1) • NR • NR • NR
Zhao 2017 (NCT01131429)	• 100 • 100	Erlotinib	43	• 5 (11.6) • 38 (88.4) • NR	All patients were Chinese	• 24 (55.8) • 19 (44.2) • NR • NR	• 0 (0) • 35 (81.4) • 8 (18.6)	NR
		Docetaxel + cisplatin	38	• 8 (21.1) • 30 (78.9) • NR	All patients were Chinese	• 23 (60.5) • 15 (39.5) • NR • NR	• 0 (0) • 33 (86.8) • 5 (13.2)	NR

Study name (Trial name/ NCT)	• Line of therapy (%) • EGFR mutation (%)	Treatment	Number of patients	Smoking status • Current smokers: n (%) • Never smokers: n (%) • Ex-smokers: n (%)	Race • White • Black/ African American • Asian • Caucasian • Other	EGFR mutation: n (%) • Exon 19 del • L858R • T790m • Other	ECOG PS: n (%) • 0 • 1 • 2	Disease subtype: n (%) • Adenocarcinoma • Squamous • Large cell • Other
An 2016	• 100 • 100	Gefitinib + PBO	45	• 26 (57.7) • 19 (42.2) • NR	NR	• 17 (37.7) • 28 (62.2) • NR • NR	NR	• 45 (100) • NR • NR • Non-squamous: 100%
		Gefitinib + pemetrexed	45	• 25 (55.5) • 20 (44.4) • NR	NR	• 16 (35.5) • 29 (64.4) • NR • NR	NR	• 45 (100) • NR • NR • Non-squamous: 100%
Cheng 2016 (NCT01469000)	• 100 • 100	Gefitinib	65	• 18 (28) • 47 (72) • NR	All patients were East Asian	• 40 (62) • 23 (35) • NR • 2 (3)	• 21 (32) • 44 (68) • NR	All patients had non-squamous NSCLC
		Gefitinib + pemetrexed	126	• 45 (36) • 81 (64) • NR	All patients were East Asian	• 65 (52) • 52 (41) • NR • 9 (7)	• 39 (31) • 87 (69) • NR	All patients had non-squamous NSCLC
Goldberg 2016 (SWOG S1403/ NCT02438722)*	• 100 • 100	Afatinib	24(Assessed for safety)	NR	NR	NR	NR	NR
		Afatinib + cetuximab	23(Assessed for safety)	NR	NR	NR	NR	NR
Mok 2016 (P06162/ NCT01039948)*	• 100 • 37.7	Gefitinib	94	NR	NR	• 20 (53) • 17 (45) • NR • Exon19 del/L858R: 1 (3)	NR	NR
		Gefitinib + ficlatuzumab	94	NR	NR	• 16 (48) • 15 (45) • NR • Exon 19 del/L858R: 2 (6)	NR	NR
Park 2016 (LUX-LUNG 7/ NCT01466660)	• 100 • 100	Afatinib	160	• 33 (21)[a] • 106 (66) • 21 (13)	• 48 (30) • 1 (1) • 94 (59)	• 93 (58)[b] • 67 (42) • NR	• 51 (32) • 109 (68) • NR	• 159 (99) • NR • NR

Study name (Trial name/ NCT)	• Line of therapy (%) • EGFR mutation (%)	Treatment	Number of patients	Smoking status • Current smokers: n (%) • Never smokers: n (%) • Ex-smokers: n (%)	Race • White • Black/ African American • Asian • Caucasian • Other	EGFR mutation: n (%) • Exon 19 del • L858R • T790m • Other	ECOG PS: n (%) • 0 • 1 • 2	Disease subtype: n (%) • Adenocarcinoma • Squamous • Large cell • Other
					• NR • 17 (11)	• NR		• Mixed: 1 (1)
		Gefitinib	159	• 34 (21)[a] • 106 (67) • 19 (12)	• 54 (34) • 0 (0) • 88 (55) • NR • 17 (11)	• 93 (58)[b] • 66 (42) • NR • NR	• 47 (30) • 112 (70) • NR	• 158 (99) • NR • NR • Mixed: 1 (1)
Singh 2015*	• 100 • 100	Gefitinib	60	• NR	• NR	• NR	• NR	• NR
		Carboplatin + paclitaxel		• NR	• NR	• NR	• NR	• NR
Wu 2015 (ENSURE/ NCT01342965)	• 100 • 100	Erlotinib	110	• 27 (24.5) • 79 (71.8) • 4 (3.6)	All patients were from China, Malaysia and the Philippines	• 57 (52.3) • 52 (47.7) • NR • NR	• 16 (14.7) • 86 (78.9) • 7 (6.4)	• 103 (94.5) • 2 (1.8) • NR • 4 (3.6)
		Cisplatin + gemcitabine	107	• 31 (29) • 74 (69.2) • 2 (1.9)	All patients were from China, Malaysia and the Philippines	• 61 (57) • 46 (43) • NR • NR	• 15 (14.4) • 83 (79.8) • 6 (5.8)	• 101 (94.4) • 2 (1.9) • NR • 4 (3.6)
Seto 2014 (JO25567/ JapicCTI-111390)	• 100 • 98.7	Erlotinib	77	• 26 (33) • 45 (58) Other: 26 (34) • 6 (8)	NR	• 40 (52) • 37 (48) • NR • NR	• 41 (53) • 36 (47) • NR	• 76 (99) • NR • 1 (1) • Adenosquamous: 0 (0)
		Erlotinib + bevacizumab	75	• 24 (32) • 42 (56) Other: 24 (32) • 9 (12)	NR	• 40 (53) • 35 (47) • NR • NR	• 43 (57) • 32 (43) • NR	• 74 (99) • NR • 0 (0) • 1 (1)
Wu 2014 (LUX-Lung 6/ NCT01121393)	• 100 • 100	Afatinib	242	• 17 (7) • 181 (74.8) • 44 (18)	All patients were Asians	• 124 (51.2) • 92 (38) • 2 (0.82) • 26 (10.7)[c]	• 48 (19.8) • 194 (80.2) • NR	• 242 (100) • NR • NR • NR
		Cisplatin + gemcitabine	122	• 10 (8) • 99 (81.1) • 13 (11)	All patients were Asians	• 62 (50.8) • 46 (37.7) • 1 (0.82) • 14 (11.5)[c]	• 41 (33.6) • 81 (66.4) • NR	• 122 (100) • NR • NR • NR

Study name (Trial name/ NCT)	• Line of therapy (%) • EGFR mutation (%)	Treatment	Number of patients	Smoking status • Current smokers: n (%) • Never smokers: n (%) • Ex-smokers: n (%)	Race • White • Black/ African American • Asian • Caucasian • Other	EGFR mutation: n (%) • Exon 19 del • L858R • T790m • Other	ECOG PS: n (%) • 0 • 1 • 2	Disease subtype: n (%) • Adenocarcinoma • Squamous • Large cell • Other
Yang 2014 (NCT01017874)*	• 100 • 21.2	Gefitinib	118	NR	All patients were East Asians	• 11 (9.3) • 14 (11.9) • NR • S7681: 0 (0)	NR	• NR • NR • NR • Non-squamous: 100%
		Pemetrexed-cisplatin followed by gefitinib	118	NR	All patients were East Asians	• 15 (12.7) • 10 (8.5) • NR • S7681: 1 (0.85)	NR	• NR • NR • NR • Non-squamous: 100%
Sequist 2013 (LUX-Lung 3/ NCT00949650)	• 100 • 100	Afatinib	230	• 5 (2.2) • 155 (67.4) • 70 (30.4)	• 61 (26.5) • NR • 165 (71.7) • NR • 4 (1.7)	• 113 (49.1) • 91 (39.6) • NR • 26 (11.3)	• 92 (40) • 138 (60) • 0 (0)	• 230 (100) • NR • NR • NR
		Cisplatin + pemetrexed	115	• 2 (1.7) • 81 (70.4) • 32 (27.8)	• 30 (26.1) • NR • 83 (72.2) • NR • 2 (1.7)	• 57 (49.6) • 47 (40.9) • NR • 11 (9.6)	• 41 (35.7) • 73 (63.5) • 1 (0.9)	• 230 (100) • NR • NR • NR
Chen 2012 (NCT01196078)*	• 100 • 21.2	Erlotinib	57	• 45 (79) • 12 (21) • NR	All patients were from Taiwan	Data for population with activation EGFR mutation (n=24): Exon 19: 21 (87.5) L858R: 3 (12.5)	• 2 (3.5) • 44 (77.2) • 9 (15.8)	• 36 (63.2) • 19 (33.3) • NR • 2 (3.5)
		Vinorelbine	56	• 44 (78.6) • 12 (21.4) • NR	All patients were from Taiwan		• 2 (3.6) • 39 (69.6) • 12 (21.4)	• 37 (66.1) • 13 (23.2) • NR • 6 (10.7)
Gridelli 2012 (TORCH/ NCT00349219)*	• 100 • 5.1	Erlotinib	380	• 302 (79.5) • 78 (20.5) • NR	• NR • NR • 12 (3.2) • NR • 368 (96.8)	• NR • NR • NR • NR	• 197 (15.8) • 183 (48.2) • NR	• 210 (55.3) (Data reported for Adenocarcinoma, bronchioloalveolar) • NR • NR

Study name (Trial name/ NCT)	• Line of therapy (%) • EGFR mutation (%)	Treatment	Number of patients	Smoking status • Current smokers: n (%) • Never smokers: n (%) • Ex-smokers: n (%)	Race • White • Black/ African American • Asian • Caucasian • Other	EGFR mutation: n (%) • Exon 19 del • L858R • T790m • Other	ECOG PS: n (%) • 0 • 1 • 2	Disease subtype: n (%) • Adenocarcinoma • Squamous • Large cell • Other
		Cisplatin + gemcitabine	380	• 301 (79.2) • 79 (20.8) • NR	• NR • NR • 12 (3.2) • NR • 368 (96.8)	• NR • NR • NR • NR	• 185 (48.7) • 195 (51.3) • NR	• 212 (55.8) (Data reported for Adenocarcinoma, bronchioloalveolar) • NR • NR
Han 2012 (First-SIGNAL/ NCT00455936)*	• 100 • 13.5	Gefitinib	159	NR	NR	Exon19del: 27 (64%) L858R: 15 (36%) Mutation: 42	• 41 (25.8) • 104 (65.4) • 14 (8.8)	NR
		Cisplatin + gemcitabine	150	NR	NR		• 31 (90.7) • 105 (70) • 14 (9.3)	NR
Janne 2012 (CALGB 30406/ NCT00126581)	• 100 • 36.5	Erlotinib	33	• NR • 51 (77) • light former smoker: 15 (23)	• 54 (82) • 5 (7) • 6 (9) • NR • 1 (2)	• 23 (69.7) • 10 (30.3) • *6 patients had EGFR exon 20 insertion mutations associated with erlotinib resistance • NR	• 38 (58) • 28 (42) • NR	• 57 (86) • NR • NR • 9 (14)
		Erlotinib + carboplatin + paclitaxel	33			• 16 (48.48) • 17 (51.5) • NR • NR		

Study name (Trial name/ NCT)	• Line of therapy (%) • EGFR mutation (%)	Treatment	Number of patients	Smoking status • Current smokers: n (%) • Never smokers: n (%) • Ex-smokers: n (%)	Race • White • Black/ African American • Asian • Caucasian • Other	EGFR mutation: n (%) • Exon 19 del • L858R • T790m • Other	ECOG PS: n (%) • 0 • 1 • 2	Disease subtype: n (%) • Adenocarcinoma • Squamous • Large cell • Other
Lee 2012 (TOPICAL/ NCT00275132)*	• 100 • 4.2	Erlotinib	350	• 124 (35) • 19 (5) • 207 (59)	• 336 (96) • NR • 7 (2) • NR • 7 (2)	Mutation+: 28 (7) Exon 19: 11 (2.82) Exon 21: 10 (2.56) other: 7 (1.8)	• NR • NR • 194 (55)	• 133 (38) • 136 (39) • 15 (4) • 66 (19)
		PBO	320	• 119 (37) • 18 (6) • 183 (57)	• 314 (98) • NR • 3 (1) • NR • 3 (1)		• NR • NR • 178 (56)	• 123 (38) • 127 (40) • 15 (5) • 55 (17)
NCT00294762 2012	• 100 • 100	Erlotinib	72	NR	• 61 (84.7) • 2 (2.7) • 9 (12.5) • NR • 0 (0)	NR	NR	NR
		Erlotinib + chemotherapy	71	NR	• 52 (73.2) • 7 (9.9) • 4 (5.6) • NR • 8 (11.3)	NR	NR	NR
Rosell 2012 (EURTAC/ NCT00446225)	• 100 • 100	Erlotinib	86	• 7 (8) • 57 (66) • 22 (26)	• 86 (100) • NR • NR • NR • 0 (0)	• 57 (66) • 29 (34) • NR • NR	• 27 (31) • 47 (55) • 12 (14)	• 82 (95) • 1 (1) • 3 (3) • 0 (0)
		Chemotherapy (cisplatin + docetaxel or gemcitabine	87	• 12 (14) • 63 (72) • 12 (14)	• 85 (98) • NR • NR • NR • 2 (2)	• 58 (67) • 29 (33) • NR • NR	• 30 (34) • 45 (52) • 12 (14)	• 78 (90) • 0 (0) • 1 (1) • 8 (9.19)
Zhang 2012 (INFORM; C-TONG 0804/ NCT00770588)	• 100 • 10.13	Gefitinib	15	• 1 (6.7) • 11 (73.3) • 3 (20)	All patients were Chinese	• NR • 4 (3) • 0 (0) • NR	• 9 (60) • 5 (33.3) • 1 (6.7)	• 13 (86.7) • 1 (6.7) • NR • 1 (6.7)
		PBO	14	• 1 (7.1) • 7 (50)	All patients were Chinese	• NR • 6 (4)	• 6 (42.9) • 8 (57.1)	• 11 (78.6) • 2 (14.3)

Study name (Trial name/ NCT)	• Line of therapy (%) • EGFR mutation (%)	Treatment	Number of patients	Smoking status • Current smokers: n (%) • Never smokers: n (%) • Ex-smokers: n (%)	Race • White • Black/ African American • Asian • Caucasian • Other	EGFR mutation: n (%) • Exon 19 del • L858R • T790m • Other	ECOG PS: n (%) • 0 • 1 • 2	Disease subtype: n (%) • Adenocarcinoma • Squamous • Large cell • Other
				• 6 (42.9)		• 1 (1) • NR	• 0 (0)	• NR • 1 (7.1)
Fukuoka 2011 (Iressa Pan-Asia Study (IPASS)/ NCT00322452)	• 100 • 21.4	Gefitinib	132	• NR • 124 (93.9) • NR	NR	• 66 (10.8) • 64 (10.5) • 5 (0.8) • 3 (0.5)	• 0–1: 119 (90.2) • NR • NR	NR
		Carboplatin + paclitaxel	129	• NR • 122 (94.6) • NR	NR	• 74 (34.6) • 47 (7.7) • 6 (1) • 7 (1.2)	• 122 (94.6) • NR • NR	NR
Hirsch 2011*	• 100 • 7.7	Erlotinib	72	NR	NR	• 11 (15.3) • 1 (1.4) • NR • 6 (8.3)	NR	NR
		Intercalated Erlotinib + chemotherapy (carboplatin/ paclitaxel)	71	NR	NR	• 4 (5.6) • 6 (8.5) • NR • 7 (9.9)	NR	NR
Zhou 2011 (OPTIMAL, CTONG-0802/ NCT00874419)	• 100 • 100	Erlotinib	82	• 23 (28) • 59 (72) • NR	• 0 (0) • 0 (0) • 82 (100) • 0 (0) • 0 (0)	• 43 (52) • 39 (48) • NR • NR	• 0–1: 75 (91) • NR • 7 (9)	• 72 (88) • NR • NR • NR
		Carboplatin + gemcitabine	72	• 22 (31) • 50 (69) • NR	• 0 (0) • 0 (0) • 72 (100) • 0 (0) • 0 (0)	• 39 (54) • 33 (46) • NR • NR	• 69 (96) • NR • 3 (4)	• 62 (86) • NR • Overall: (n=8) • NR • Overall: bronchoalveolar carcinoma (n=2), and other histology (n=10)

Study name (Trial name/ NCT)	• Line of therapy (%) • EGFR mutation (%)	Treatment	Number of patients	Smoking status • Current smokers: n (%) • Never smokers: n (%) • Ex-smokers: n (%)	Race • White • Black/ African American • Asian • Caucasian • Other	EGFR mutation: n (%) • Exon 19 del • L858R • T790m • Other	ECOG PS: n (%) • 0 • 1 • 2	Disease subtype: n (%) • Adenocarcinoma • Squamous • Large cell • Other
Cappuzzo 2010 (SATURN; BO18192/ NCT00556712)*	• 100 • IHC+: 69.8 M+: 5.5	Erlotinib	438	• 239 (55) • 77 (18) • 122 (28)	• NR • NR • 62 (14) • 370 (84) • 6 (1)	NR	• 135 (31) • 303 (69) • NR	• 205 (47) • 166 (38) • NR • 67 (15)
		PBO	451	• 254 (56) • 75 (17) • 122 (27)	• NR • NR • 69 (15) • 376 (83) • 6 (1)	NR	• 145 (32) • 306 (68) • NR	• 198 (44) • 194 (43) • NR • 59 (13)
Maemondo 2010 (NEJ002/ UMIN-CTR number, C000000376)	• 100 • 100	Gefitinib	114	• 39 (34.2) • 75 (65.8) • NR	NR	• 58 (50.9) • 49 (43) • 0 (0) • 7 (6.1)	• 54 (47.4) • 59 (51.8) • 1 (0.9)	• 103 (90.4) • 3 (2.6) • 1 (0.9) • 7 (6.2)
		Carboplatin + paclitaxel	114	• 48 (42.1) • 66 (57.9) • NR	NR	• 59 (51.8) • 48 (42.1) • 0 (0) • 7 (6.1)	• 57 (50) • 55 (48.2) • 2 (1.8)	• 110 (96.5) • 2 (1.8) • 0 (0) • 2 (1.8)
Mitsudomi 2010 (WJTOG3405/ UMIN number 000000539)*	• 100 • 100	Gefitinib	86	• 25[a] • 61 • NR	All patients were Japanese	• 50 • 36 • NR • NR	• 56 • 30 • NR	• 83 • 1 • NR • 2 (Non-small-cell lung cancer; not otherwise specified)
		Cisplatin + docetaxel	86	• 29[a] • 57 • NR	All patients were Japanese	• 37 • 49 • NR • NR	• 52 • 34 • NR	• 84 • 0 • NR • 1 (Non-small-cell lung cancer; not otherwise specified)
Goss 2009 (INSTEP/ NCT00259064)*	• 100 • 15.9	Gefitinib + BSC	100	• 90 (90)[a] • 10 (10) • NR	• 96 (96) • NR • 4 (4) • NR	NR	NR	• 45 (45) • 29 (29) • 10 (10) • NR

Study name (Trial name/ NCT)	• Line of therapy (%) • EGFR mutation (%)	Treatment	Number of patients	Smoking status • Current smokers: n (%) • Never smokers: n (%) • Ex-smokers: n (%)	Race • White • Black/ African American • Asian • Caucasian • Other	EGFR mutation: n (%) • Exon 19 del • L858R • T790m • Other	ECOG PS: n (%) • 0 • 1 • 2	Disease subtype: n (%) • Adenocarcinoma • Squamous • Large cell • Other
					• 0 (0)			
		BSC + PBO	101	• 92 (91.1)[a] • 9 (8.9) • NR	• 97 (96) • NR • 3 (3) • NR • 1 (1)	NR	NR	• 46 (45.5) • 25 (24.8) • 11 (10.9) • NR
Crino 2008 (INVITE/ NCT00256711)*	• 100 • 27.5	Gefitinib	97	• 80 (82.5)[a] • 17 (17.5) • NR	• 79 (81.4) • NR • 17 (17.5) • NR • 1 (1)	NR	NR	• 34 (35.1) • 47 (48.5) • NR • 2 (2.1)
		Vinorelbine	99	• 88 (88.9)[a] • 11 (11.1) • NR	• 83 (83.8) • NR • 14 (14.1) • NR • 2 (2)	NR	NR	• 45 (45.5) • 44 (44.4) • NR • 3 (3)
Lilenbaum 2008 (NCT00085839)*	• 100 • IHC$^+$: 23.3 FISH$^+$: 13.6 M$^+$: 4.8	Erlotinib	NR	NR	NR	IHC+: 13 (74) FISH+: 7 (37) Mutation+: 0 (0)	• 0 (0) • 0 (0) • 52 (100)	NR
		Carboplatin + paclitaxel	NR	NR	NR	IHC+: 11 (79) FISH+: 7 (54) Mutation+: 5 (50)	• 0 (0) • 0 (0) • 51 (100)	NR

Key: BSC, best supportive care; ECOG PS, eastern cooperative oncology group performance status IQR, interquartile range; NR, not reported; PBO, placebo; SD, standard deviation; TKI, tyrosine kinase inhibitor.
Notes: [a] Data reported for other current or ex-smokers; [b] One patient in the Afatinib arm with wild-type EGFR was erroneously included in the trial and was reported as exon 19 deletion at the time of randomisation by the investigator; [c] Data reported for uncommon mutation includes patients with T790M.
* Study did not report data specifically for EGFR+ advanced/metastatic NSCLC patients receiving 1L therapy thereby, data extracted for overall population. The ranges discussed in the text do not include these studies.

D.1.3 Efficacy outcomes

Data for the overall response rate (ORR) and the disease control rate (DCR) are presented in Table 103.

Overall response rate

Data for patients who achieved an overall response were reported in 25 studies. In 16 of these studies, ORR was defined as the number of patients who achieved a complete response (CR) or partial response (PR). Across 24 of these studies, the ORR at study endpoint varied between 14.9 % with platinum doublet chemotherapy in EURTAC[179] and 84.6% with gefitinib in FIRST-SIGNAL study.[185] Additionally in the FLAURA trial, the proportion of patients with continued response at 12 months was also reported which was 64% and 37% in the osimertinib and standard EGFR TKI (gefitinib or erlotinib) groups, respectively.[164] In NEJ002, the ORR at 2 year was significantly greater with gefitinib than carboplatin plus paclitaxel; 73.7% versus 30.7%; p<0.001.[35]

Eight studies reported data for subgroup analysis based on the presence of exon 19 del and L858R mutations.[15, 102, 118, 166, 170, 177, 184, 187] Across seven of these studies, the ORR in the exon 19 del subgroup varied from 25.8% with cisplatin plus gemcitabine in LL6[177] to 86% with gefitinib plus pemetrexed in the study by Cheng et al.[166] Similarly, ORR in the L858R subgroup varied from 19.6% with cisplatin plus gemcitabine in LL6[177] to 75% with gefitinib plus pemetrexed in the study by Cheng et al.[166] Additionally, only the odds ratio was reported in IPASS for both the subgroups.[184]

Data for patients with T790M mutations at baseline were reported in two studies.[177, 184] Of the two studies that reported data for patients with T790M mutations, IPASS[184] reported the odds ratio only, whereas in LL6, 50% and 100% patients achieved an overall response in the afatinib and cisplatin plus gemcitabine groups, respectively.[177]

Three studies reported the response rate in patients who had brain metastasis at baseline.[164, 176, 177] In LL3, a significantly greater proportion of patients who had brain metastases achieved response with afatinib compared with cisplatin plus pemetrexed (70% vs 20%; p=0.0058).[176] Similar results were observed in LL6, 75% of the afatinib group achieved response compared with 27.85% in the cisplatin plus gemcitabine group.[177] However, in FLAURA, ORR was numerically greater with standard EGFR-TKI (gefitinib or erlotinib) than osimertinib; 86% versus 75%.[164]

Disease control rate

Data for DCR were reported in 16 studies. All studies reported data at study endpoint. DCR was defined as patients who achieved a complete response (CR), partial response (PR) or stable disease in 11 studies. DCR varied between 47.4% with platinum doublet chemotherapy in EURTAC[179] and 100% with erlotinib in the study by Hirsch et al.[171]

Subgroup data based on the presence of exon 19 del and L858R mutations were reported in two studies each.[166, 177] Across the two studies reporting data for the exon 19 del subgroup, DCR was significantly different between treatment arms in LL6 (94.4% and 75.8% with afatinib and cisplatin plus gemcitabine, respectively; p=0.0006)[177] but not in Cheng et al. (98% and 91% with gefitinib and gefitinib plus pemetrexed, respectively; p=0.279).[166] However, across the subgroup with L858R mutations, DCR was not significantly different across the treatment arms in both the studies: in LL6, DCR was reported as 89.1% for afatinib and 78.4% for cisplatin plus gemcitabine (p=0.0929)[177]; and in Cheng et al., DCR was reported as 87% for gefitinib and 96% for gefitinib plus pemetrexed (p=0.117).[166]

In LL6, 50% and 100% patients with T790M mutations in the afatinib and cisplatin plus gemcitabine groups, respectively, achieved disease control.[177]

DCR in patients with brain metastasis at baseline were reported in two studies.[176, 177] In LL3, the DCR in patients with brain metastases was not significantly greater with afatinib compared with cisplatin plus pemetrexed (95% versus 80%, respectively; p=0.1986).[176] In LL6, the DCR in patients with brain metastases was 89.3% with afatinib compared with 72.2% with cisplatin plus gemcitabine.[177]

Table 103: Overall response rate and disease control rate across RCTs

Study name (Trial name/ NCT)	Intervention Comparator	Assessor	ITT N	Number of patients	ORR		DCR	
					n (%) p-value	Definition	n (%) p-value	Definition
Soria 2018 (FLAURA/ NCT02296125)	Osimertinib	Investigator assessed (12-month)	279	223	143 (64)	ORR, defined as the proportion of randomised patients with at least one visit response of CR or PR. Data for patients who had continued response at 12 months RECIST v1.1. ORR, 95% CI: • Osimertinib: 58–70 • Standard EGFR-TKI: 31–44	NR	DCR is the proportion of patients who had a CR, a PR, or SD lasting at least 6 weeks before any PD event. RECIST v1.1. DCR, 95% CI: • Osimertinib: 94–99 odds ratio, 2.78; 95% CI, 1.25–6.78; p=0.01 • Standard EGFR-TKI: 89–95
	Standard EGFR-TKI		277	210	78 (37)		NR	
	Osimertinib	Investigator assessed (Endpoint)	279	279	223 (80)	ORR, 95% CI: • Osimertinib: 75–85 odds Ratio: 1.27; 95% CI 0.85–1.90; p=0.24 • Standard EGFR-TKI: 70–81	271 (97)	
	Standard EGFR-TKI		277	277	210 (76)		255 (92)	
Han 2017 (NCT02148380)	Gefitinib	Investigator assessed	41	41	27 (65.9)	NR RECIST	NR	NR
	Gefitinib + carboplatin + pemetrexed		40	40	33 (82.5)		NR	
	Carboplatin + pemetrexed		40	40	13 (32.5)		NR	
Leighl 2017	Erlotinib + linsitinib	NR	44	44	21 (47.7); p=0.02	ORR, defined as proportion of patients with CR or PR acc. to RECIST v1.1. ORR, 95% CI: • Erlotinib + linsitinib: 32.5–63.3 • Erlotinib + PBO: 59.7–86.8	34 (77.3); p=0.03	DCR, defined as CR, PR, or SD for ≥ 6 weeks. DCR, 95% CI: • Erlotinib + linsitinib: 62.2–88.5 • Erlotinib + PBO: 84.5–99.4
	Erlotinib + PBO		44	44	33 (75)		42 (95.5)	

Study name (Trial name/ NCT)	Intervention Comparator	Assessor	ITT N	Number of patients	ORR		DCR	
					n (%) p-value	Definition	n (%) p-value	Definition
Patil 2017 (CTRI/2015/08/006113)	Gefitinib	Investigator assessed	145	137	87 (63.5)	RECIST v1.1	NR	NR
	Carboplatin + pemetrexed followed by pemetrexed		145	130	59 (45.3)		NR	
Wu 2017 (ARCHER 1050/ NCT01774721)	Dacomitinib	IRC assessed	227	227	170 (75); p=0.3883	Best OR of either CR or PR, where best OR is the best response recorded from the start of treatment until PD RECIST v1.1 95% CI: • Dacomitinib: 69–80 • Gefitinib: 65–77	NR	NR
	Gefitinib		225	225	161 (72)		NR	
	Dacomitinib	Investigator assessed	227	227	171 (75); p=0.2224	95% CI: • Dacomitinib: 69–81 • Gefitinib: 64–76	NR	
	Gefitinib		225	225	158 (70)		NR	
Yang 2017 (ChiCTR-IOR-14005679)	Gefitinib	NR	35	35	20 (57.1)	NR	28 (80)	NR
	Gefitinib + Fuzheng Kang'ai formula		35	35	23 (65.7); p>0.05		33 (94.3); p>0.05	
Yang 2017 (CTONG 0901/ NCT01024413)	Erlotinib	Investigator assessed	128	81	47 (58); p=0.466	RECIST v1.1 Data captured for patients receiving erlotinib in first-line setting.	NR	NR
	Gefitinib		128	84	44 (52.4)		NR	NR
Zhao 2017 (NCT01131429)	Erlotinib	NR	43	43	NR	RECIST ORR was evaluated every two cycles.	NR	NR
	Docetaxel + cisplatin		38	38	NR		NR	
An 2016	Gefitinib + PBO	NR	45	45	33 (73.33)	CR + PR. RECIST v1.1	44 (97.8)	CR + PR + SD
	Gefitinib + pemetrexed		45	45	36 (80)		39 (86.7); p<0.05	
Cheng 2016 (NCT01469000)	Gefitinib	Investigator assessed	65	65	48 (74)	CR + PR. RECIST v1.1	61 (94)	CR+PR+SD. RECIST v1.1
	Gefitinib + pemetrexed		126	126	101 (80)		117 (93)	
Park 2016	Afatinib	IRC assessed	160	160	116 (72.5);	CR + PR.	146 (91)	CR+PR+SD.

Study name (Trial name/ NCT)	Intervention Comparator	Assessor	ITT N	Number of patients	ORR		DCR	
					n (%) p-value	Definition	n (%) p-value	Definition
(LUX-LUNG 7/ NCT01466660)					p=0.0018	RECIST v1.1 Odds ratio: 2·121 [95% CI 1·32–3.40]; p=0·0018		RECIST v1.1 Odds ratio 1·55 [95% CI 0·75–3·22]; p=0·24 Median duration of disease control: • Afatinib: 12·7 months (IQR 7·3–20·2) • Gefitinib: 11·1 months (7·4–14·7)
	Gefitinib		159	159	89 (56)		139 (87)	
Singh 2015	Gefitinib	NR	NR	NR	NR (70)	NR	NR	NR
	Carboplatin + paclitaxel		NR	NR	NR (30)	NR	NR	NR
Wu 2015 (ENSURE/ NCT01342965)	Erlotinib	Investigator-assessed	110	110	69 (62.7)	CR + PR every 6 weeks. RECIST v1.1	98 (89.1)	NR
	Cisplatin + Gemcitabine		107	107	36 (33.6)		82 (76.6)	
Seto 2014 (JO25567/ JapicCTI-111390)	Erlotinib	IRC assessed	77	77	49 (64)	RECIST v1.1 95%CI: • Erlotinib: 52–74 • Erlotinib + bevacizumab: 58–80	68 (88)	RECIST v1.1
	Erlotinib + bevacizumab		77	75	52 (69); p=0.4951		74 (99); p=0.0177	
Wu 2014 (LUX-Lung 6/ NCT01121393)	Afatinib	IRC assessed	242	242	162 (67.8); p<0.0001	CR + PR. For patients with common mutations (Exon 19 del/L858R) • Afatinib (N:216): 145/216 (67.1%); p<0.0001 • Cisplatin + gemcitabine (N:108): 25/108 (23.1%) As assessed by independent review.	224 (92.6); p<0.0001	RECIST v1.1 Odds Ratio 3·84, 95% CI 2·04−7·24; p<0·0001. Median duration of disease control: • Afatinib: 11·1 months (95% CI 9·7–13·8) • Cisplatin + gemcitabine: 5·7 months (5·5–6·9). Data for patients with common mutations (Exon 19 del/L858R)
	Cisplatin + gemcitabine		122	122	28 (23)		93 (76.2)	

Study name (Trial name/ NCT)	Intervention Comparator	Assessor	ITT N	Number of patients	ORR		DCR	
					n (%) p-value	Definition	n (%) p-value	Definition
								• Afatinib (N:216): 199/216 (92.1%); p=0.0002. • Cisplatin + gemcitabine (N:108): 83/108 (76.9%)
	Afatinib	Investigator assessed	242	242	180 (74.4); p<0.0001	Odds Ratio: 6·53, 95% CI 4·02−10·60; p<0·0001	225 (93)	Median duration of disease control: • Afatinib: 13.8 months (12·5–14.9) • Cisplatin + gemcitabine: 6.4 months (5.5–6.9)
	Cisplatin + gemcitabine		122	122	38 (31.1)		92 (75.4)	
Yang 2014 (NCT01017874)	Gefitinib	NR	118	24	17 (70.8)	CR + PR. RECIST v1.0 95% CI: • Gefitinib: 48.9–87.4 • Pemetrexed-cisplatin followed by gefitinib: 44.3–82.8	21 (87.5)	CR + PR + SD RECIST v1.0 95% CI: • Gefitinib: 67.6–97.3 • Pemetrexed-cisplatin followed by gefitinib: 65.1–95.6
	Pemetrexed-cisplatin followed by gefitinib		118	26	17 (65.4); p=0.767		22 (84.6); p=1.0	
Sequist 2013 (LUX-Lung 3/ NCT00949650)	Afatinib	IRC assessed	230	230	129 (56); p=0.001	CR + PR. Data for common mutation • Afatinib (N:204): 60.8%; p<0.0001; 95% CI: 49.4–62.6 • Odds ratio (95% CI): 2.774–7.828; p<0.0001. • Cisplatin + pemetrexed (N:104): 22.1% • 95% CI: 15.3–31.3	207 (90)	CR/PR + SD. Median duration of disease control • Afatinib: 13.6 months (95% CI:85.4–93.6); Odds ratio 95% CI: 1.134–4.037; p=0.0189 • Cisplatin + pemetrexed: 8.1 months (95% CI: 72.5–87.6).
	Cisplatin + pemetrexed		115	115	26 (23)		93 (81)	

Study name (Trial name/ NCT)	Intervention Comparator	Assessor	ITT N	Number of patients	ORR		DCR	
					n (%) p-value	Definition	n (%) p-value	Definition
						• Odds ratio (95% CI): 2.774–7.828; p<0.0001.		
	Afatinib	Investigator assessed	230	230	159 (69); p=0.001	CR + PR. Data for common mutation • Afatinib (N:204): 75%; p<0.0001 • Cisplatin + pemetrexed (N:104): 43.3%	NR	NR
	Cisplatin + pemetrexed		115	115	51 (44)		NR	NR
Gridelli 2012 (TORCH/ NCT00349219)	Erlotinib	NR	380	19	8 (42.1)	ORR, defined as the number of patients with CR or PR at any time divided by the total number of patients enrolled onto each arm.	NR	NR
	Cisplatin + gemcitabine		380	20	5 (25)		NR	NR
Han 2012 (First-SIGNAL/ NCT00455936)	Gefitinib	Investigator assessed	159	26	22 (84.6); p=0.002	NR	NR	NR
	Cisplatin + gemcitabine		154	16	6 (37.5)		NR	NR
Janne 2012 (CALGB 30406/ NCT00126581)	Erlotinib	NR	81	33	23 (70)	95% CI: • Erlotinib: 51–84 • Erlotinib + carboplatin + paclitaxel: 18–44	NR	NR
	Erlotinib + carboplatin + paclitaxel		100	33	24 (73)		NR	NR
Rosell 2012 (EURTAC/ NCT00446225)	Erlotinib	Investigator assessed	86	86	50 (58.1) p<0.0001	A patient was considered to be a responder if their best OR was either CR or PR. RECIST v1.0	67 (77.9); p=0.0951	DCR, defined either as response (CR, PR) or maintained disease stabilisation (SD for at least 6 weeks).
	Chemotherapy (cisplatin + docetaxel or gemcitabine)		87	87	13 (14.9)		57 (65.8)	
	Erlotinib	IRC assessed	86	NR	NR		61 (71.4); p=0.0024	
	Chemotherapy (cisplatin + docetaxel or gemcitabine)		87	NR	NR		41 (47.4)	
Fukuoka 2011	Gefitinib	NR	609	132	94 (71.2)	CR+PR.	121 (91.7)	CR+PR+SD.

Study name (Trial name/ NCT)	Intervention Comparator	Assessor	ITT N	Number of patients	ORR		DCR	
					n (%) p-value	Definition	n (%) p-value	Definition
(Iressa Pan-Asia Study (IPASS)/ NCT00322452)	Carboplatin + paclitaxel		608	129	61 (47.3)	Odds Ratio: 2.75 (95CI%: 1.65–4.60) p<0.0001. Tumour response was assessed every 6 weeks until PD. ORR was significantly higher with gefitinib (84.8%) vs carboplatin/ paclitaxel (43.2%; Odds ratio, 7.23; 95% CI, 3.19–16.37) in the exon 19 deletions subgroup and numerically higher in the L858R subgroup (60.9% vs 53.2%; Odds ratio, 1.41; 95% CI, 0.65–3.05).	113 (87.6)	
Hirsch 2011	Erlotinib	NR	72	12	8 (67)	CR + PR. RECIST v1.0	12 (100)	CR + PR + SD. RECIST v1.0
	Intercalated Erlotinib + chemotherapy (carboplatin/paclitaxel)		71	10	3 (33)		7 (67)	
Zhou 2011 (OPTIMAL, CTONG-0802/ NCT00874419)	Erlotinib	Investigator assessed	83	82	68 (83)	CR + PR. RECIST v1.0	79 (96); p=0.0022	CR + PR + SD. RECIST v1.0
	Cisplatin + gemcitabine		82	72	26 (36)		59 (82)	
Maemondo 2010 (NEJ002/ UMIN-CTR number, C000000376)	Gefitinib	External review	114	114	84 (73.7); p<0.001	RECIST v1.0 %age of patients in whom there was either a CR or PR was considered to be ORR.	NR	NR
	Carboplatin + paclitaxel		114	114	35 (30.7)		NR	NR

Key: BSC, best supportive care; CI, confidence interval; CR, complete response; DCR, disease control rate; IQR, interquartile range; IRC, independent review committee; ITT, intent to treat; NR, not reported; OR, overall response; ORR, overall response rate; PBO, placebo; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; TKI, tyrosine kinase inhibitor.

Note: The assessments were made at study endpoint

D.1.4 Survival outcomes

Data for survival outcomes are presented in Table 104.

Across these studies, the outcomes were assessed by IRC (nine studies)[15, 102, 118, 164, 173, 176, 177, 179, 180], investigator (twelve studies)[72, 102, 118, 163, 164, 176, 177, 179-181, 185, 190, 195] and was not reported in the other studies.

Only INFORM reported data for time to first subsequent treatment (TFST), progression-free survival on next line of therapy (PFS2) and depth of response.[164]

Overall survival

Data for OS were reported in 33 studies. The median OS across 25 of these studies ranged from 3.7 months with placebo in the TOPICAL study[191] to 46.8 months with gefitinib in INFORM.[192] In three other studies, the OS data were still immature.[102, 172, 173] In the SATURN study, median OS was reported for EGFR IHC positive patients and was 12.8 months with erlotinib compared to 11 months with placebo. However, OS data were not mature for EGFR mutation positive patients.[190] The INSTEP, FLAURA and INVITE studies reported the hazard ratio (HR) only for gefitinib vs placebo[193], osimertinib versus standard EGFR TKI[164] and gefitinib vs vinorelbine, respectively.[189] Also, the study by Mok et al. reported HR ratio only for gefitinib plus ficlatuzumab versus gefitinib.[174]

Nine studies reported OS data for subgroups of patients based on the presence of exon 19 del and L858R.[15, 118, 168, 170, 176, 177, 180, 181, 187] The median OS ranged from 18.4 months with cisplatin plus gemcitabine in LL6[177] to 45.7 with gefitinib in the study by Yang et al.[168] in the subgroup with exon 19 del. The median OS across the L858R subgroups varied from 16.5 months with gefitinib in the study by Patil et al.[187] to 41.3 months with gefitinib in the study by Yang et al.[168] Another study by Mok et al. reported data for patients who were likely to have good (VeriStratG) or poor (VeriStratP) survival outcomes upon treatment with TKIs, based on the VeriStrat® blood test, which was designed to assist clinicians in making treatment decisions for patients with advanced NSCLC who lack an EGFR mutation.[271] In the VeriStratG subgroup, the median OS was not reached. However, in the VeriStratP subgroup, patients who received gefitinib plus ficlatuzumab had a longer median OS compared with those who received gefitinib monotherapy (17 months vs 10.4 months).

Three studies reported OS data for subgroup of patients who had brain metastasis at baseline.[385] Across these studies, the median OS ranged from 18.3 months with gefitinib in the study by Patil et al.[187] to 33.2 months with cisplatin plus pemetrexed in LL3.[176]

Data for patients who were alive were reported in 23 studies. Survival rates were reported in six studies.[15, 164, 167, 169, 171, 190] The SATURN study reported the survival rate for EGFR IHC positive patients at study endpoint, which was 52% in the erlotinib group and 47% in the placebo group.[190] Four studies reported data for 1-year survival rates, which ranged between 41.7% with erlotinib plus chemotherapy and 100% with erlotinib, both in the study by Hirsch et al.[171] One study each reported data for 2-year (NEJ002)[15] and 3-year survival rates (An et al.).[167] In NEJ002, the 2-year survival rate was 57.9% with gefitinib and 53.75% with carboplatin plus paclitaxel.[15] In the study by An et al., the 3-year survival rate was 35.6% with gefitinib and 44.4% with gefitinib plus pemetrexed.[167] The OS rate at 6-month was reported in FLAURA as 98% with osimertinib and 93% with standard EGFR TKI (gefitinib or erlotinib).[164]

Thirteen studies reported only the number of events (death).[102, 118, 165, 166, 173, 176, 177, 179, 181, 184, 192, 195, 271] Across these studies, the proportion of events varied between 11.4% with erlotinib plus linsitinib in the study by Leighl et al.[165] and 86.0% with placebo in INFORM.[192] Additionally, three studies reported data for the overall study population and not by treatment arm.[187, 189, 193] In the study by Yang et al., it was reported that because of a high censoring rate of 60.2%, OS data were immature.[168]

Only the OPTIMAL trial reported the number of events in both subgroup of patients, which were exon 19 del and L858R mutations.[181] In the OPTIMAL study, the number of events in the exon 19 del subgroup was 36 with erlotinib and 26 with carboplatin plus gemcitabine, while in the L858R subgroup, the number of events was 32 with erlotinib and 26 with carboplatin plus gemcitabine.[181] Another study by Mok et al. reported data for patients who were likely to have good or poor survival outcomes upon treatment with TKIs based on the VeriStrat test.[271] In the VeriStratG subgroup, the same number of events was reported observed in both treatment groups, gefitinib and gefitinib plus ficlatuzumab (11 each). However, in the VeriStratP subgroup, patients receiving gefitinib experienced more events than those receiving gefitinib plus ficlatuzumab (5 versus 3 events, respectively). None of the studies reported data for patients with brain metastases or T790M mutation.

Progression-free survival

Data for PFS were reported in 35 studies. Across 33 of these studies the median PFS ranged from 2.14 months with erlotinib in a group of patients who were immunohistochemistry (IHC) positive in the study by Lilenbaum et al.[182] to 18.9 months with osimertinib in FLAURA.[164] The INSTEP and INVITE studies reported HR values only.[189, 193]

Data for subgroups of patients based on presence of exon 19 del and L858R were reported in 15 studies.[102, 118, 164-166, 170, 173, 176, 177, 179-181, 184, 187, 195] In 11 of these studies, the median PFS ranged between 4.2 months with cisplatin plus gemcitabine in ENSURE[180] and 27.5 months with erlotinib plus chemotherapy in the study by Janne et al.[170] In 11 of the studies reporting data for L858R subgroup, the median PFS ranged from 6 months with chemotherapy in EURTAC[179] to 14.4 months with osimertinib in FLAURA.[164] In four other studies, only the HR values were reported for both subgroups.[176, 177, 181, 195]

Data for patients with T790M mutations were reported in three studies.[177, 181, 184] In LL6 and OPTIMAL, median PFS varied from 0.6 months with erlotinib in OPTIMAL[181] to 7.6 months with afatinib in LL6.[177] In the IPASS study, only HR values were reported.[184]

Another study by Mok et al. reported data for patients who were likely to have good or poor survival outcomes upon treatment with TKIs based on VeriStrat test.[271] In the VeriStratP subgroup, a statistically significant improvement in median PFS was observed upon the addition of ficlatuzumab to gefitinib compared with gefitinib alone (10.1 months versus 2.3 months, respectively; p=0.004). However, this was not observed in the VeriStratG subgroup, the median PFS with gefitinib and gefitinib plus ficlatuzumab was reported to be 9.3 and 9.1 months, respectively.

Five studies reported data for patients who had brain metastases.[118, 164, 176, 177, 187] Across these studies, the median PFS ranged from 4.7 months with cisplatin plus gemcitabine in LL6[177] to 15.2 months with osimertinib in FLAURA.[164]

Data for patients who were progression-free and alive were reported in 20 studies. PFS rate was reported in nine studies.[15, 118, 167, 169, 171, 176, 177, 179] Three studies[169, 171, 177] reported data for PFS rate at 6 months, which varied between 26.4% with erlotinib plus chemotherapy in NCT00294762[169] and 88.9% with erlotinib in the study by Hirsch et al.[171] Five studies reported 1-year PFS rates[15, 118, 176, 177, 179] which varied from 2.1 months with cisplatin plus gemcitabine as determined by central independent review to 56.4 months with afatinib based on investigator assessment, both in LL6.[177] The study by An et al. reported data for 2-year PFS rate, which was significantly greater in the gefitinib plus pemetrexed group compared with the gefitinib group (20% versus 8.9%, respectively; p<0.05).[167] LL3 also presented data for PFS rate at study endpoint where the PFS rate was 20% in afatinib group and 3% in cisplatin plus pemetrexed group.[176]

LL3 reported PFS rate data at both 1 year and study endpoint. Similarly, LL6 reported data at both time points: 6 months and 1 year.

Thirteen studies reported only the proportion of events (progression or death). Across eight of these studies, the proportion of events varied between 52.3% with erlotinib in the study by Leighl et al.[165] to 100.0% with placebo in the INFORM study.[192] Also, the SATURN trial reported that 79.5% and 89.4% of EGFR-IHC positive patients in the erlotinib and placebo arms either had progressive disease or had died.[190] Three studies reported data for the proportion of events for the overall population and not according to treatment arm.[187, 189, 193] In FLAURA, it was reported that at data cut off an event of progression or death had occurred in 49% in osimertinib arm and 74% in standard EGFR TKI arm, as assessed by investigator.[164] Additionally, the IRC assessment reported that at data cut off an event of progression or death had occurred in 49% in osimertinib arm and 71% in standard EGFR TKI arm.

Four studies each reported subgroup data for proportion of events based on the presence of exon 19 del and L858R mutations.[102, 118, 165, 187] The proportion of events in the exon 19 del subgroup across three of these studies varied from 44.0% with erlotinib in the study by Leighl et al.[165] to 78.5% with afatinib in LL7.[118] Similarly, the proportion of events in the L858R subgroup across the three studies varied from 44.4% in erlotinib plus linsitinib plus erlotinib in the study by Leighl et al.[165] to 82.6% in the ARCHER 1050 study.[102]

Another study by Mok et al. reported data for patients who were likely to have good or poor survival outcomes upon treatment with TKIs based on the VeriStrat test.[271] In the VeriStratG subgroup, the gefitinib group experienced a greater proportion of events compared with the gefitinib plus ficlatuzumab group (VeriStratG: 87.5% versus 79.3%). However, in the VeriStratP subgroup, proportion of events were similar across the two groups (100%).

The FLAURA trial reported data for the proportion of progression events in patients with brain metastasis to be 55% and 84% in the osimertinib and standard EGFR TKI groups, respectively.[164]

Table 104: Survival outcomes (continuous)

Study name (Trial name/ NCT)	Intervention Comparator	Assessment	Number of patients	OS		PFS	
				Median (95% CI)	HR (95% CI); p value	Median (95% CI)	HR (95% CI); p value
Soria 2018 (FLAURA/ NCT02296125)	Osimertinib	Investigator assessed	279	Not calculated	0.63 (0.45–0.88); p=0.007*	18.9 (15.2–21.4)	0.46 (0.37–0.57); p<0.001
	Standard EGFR-TKI		277	Not calculated		10.2 (9.6–11.1)	
	Osimertinib	BICR	279	NR	NR	17.7 (15.1–21.4)	0.45 (0.36–0.57); p<0.001
	Standard EGFR-TKI		277	NR		9.7 (8.5–11)	
Han 2017 (NCT02148380)	Gefitinib	Investigator assessed	41	28.5 (21.3–30.2)	1.03 (0.58–1.81); p=0.926 (vs carboplatin + pemetrexed)	5.7 (5.2–6.3)	0.35 (0.21–0.60); p<0.001 (vs carboplatin + pemetrexed)
	Gefitinib + carboplatin + pemetrexed		40	32.6 (25.5–39.8)	0.36 (0.2–0.67); p=0.001 (vs carboplatin + pemetrexed)	17.5 (15.3–19.7)	0.16 (0.09–0.29); p<0.001 (vs carboplatin + pemetrexed)
	Carboplatin + pemetrexed		40	24.3 (17.7–30.1)		11.9 (9.1–14.6)	
Leighl 2017	Erlotinib + linsitinib	NR	44	Not reached	0.77 (0.24–2.42); p=0.65	8.4 (7.1–13.8)	1.37 (0.76–2.45); p=0.29
	Erlotinib + PBO		44	19.5 (17.3–not reached)		12.4 (9.7–16.8)	
Patil 2017	Gefitinib	NR	145	18 (15.2–20.8)	0.78 (0.56–1.09); p=0.133	8.4 (6.3–10.5)	0.66 (0.513–0.851); p=0.001

Study name (Trial name/ NCT)	Intervention Comparator	Assessment	Number of patients	OS		PFS	
				Median (95% CI)	HR (95% CI); p value	Median (95% CI)	HR (95% CI); p value
(CTRI/2015/08/006113)	Carboplatin + pemetrexed followed by pemetrexed		145	22.6 (18.6–26.6)		5.6 (4.2–7)	
Scagliotti 2017 (Balise/ NCT01897480)	Erlotinib	NR	70	NR	NR	9.5	0.89; p=0.534 (HR for erlotinib + emibetuzumab vs erlotinib)
	Erlotinib + emibetuzumab		71	NR		9.3	
Wu 2017 (ARCHER 1050/ NCT01774721)	Dacomitinib	IRC assessed	227	NR	NR	14.7 (11.1–16.6)	0.59 (0.47–0.74); p<0.0001
	Gefitinib		225	NR		9.2 (9.1–11)	
	Dacomitinib	Investigator assessed	227	NR	NR	16.6 (12.9–18.4)	0.62 (0.5–0.78); p<0.0001
	Gefitinib		225	NR		11 (9.4–12.1)	
Yang 2017 (ChiCTR-IOR-14005679)	Gefitinib	NR	35	18.3 (17.97–18.63)	NR	8.4 (6.3–10.5)	NR; p=0.5
	Gefitinib + Fuzheng Kang'ai formula		35	21.5 (17.28–25.73)	NR; p<0.01	12.5 (3.3–21.69)	NR; p<0.01
Yang 2017 (CTONG 0901/ NCT01024413)	Erlotinib	Investigator assessed	81	22.4	0.98 (0.67–1.42); p=0.902	13.2	0.96 (0.67–1.42); p=0.827
	Gefitinib		84	20.7		11.1	
An 2016	Gefitinib + PBO	NR	45	32 (26.7–37.2)	p>0.05	14 (11.8–16.2)	p<0.05
	Gefitinib + pemetrexed		45	34 (28.7–39.2)		18 (15.7–16.2)	
Cheng 2016 (NCT01469000)	Gefitinib	NR	65	NR	NR	10.9 (9.7–13.8)	0.69 (0.49–0.96); p=0.28 (HR for gefitinib + pemetrexed vs gefitinib)
	Gefitinib + pemetrexed		126	NR		15.8 (12.6–18.3)	
Park 2016 (LUX-LUNG 7/ NCT01466660)	Afatinib	IRC assessed	160	27.9 (25.1–32.2)	0.86 (0.66–1.12); p=0.258	11 (10.6–12.9)	0.73 (0.57–0.95); p=0.017

Study name (Trial name/ NCT)	Intervention Comparator	Assessment	Number of patients	OS		PFS	
				Median (95% CI)	HR (95% CI); p value	Median (95% CI)	HR (95% CI); p value
	Gefitinib		159	25 (20.6–29.3)		10.9 (9.1–11.5); HR: 1.0	
	Afatinib	Investigator assessed	160	NR	NR	12.8 (10.9–14.7)	0.78 (0.61–0.99); p=0.042
	Gefitinib		159	NR		11.2 (9.4–12.8)	
Singh 2015	Gefitinib	NR	NR	30	NR	10	NR
	Carboplatin + paclitaxel		NR	24	NR	5	NR
Wu 2015 (ENSURE/ NCT01342965)	Erlotinib	IRC	110	NR	NR	11	0.42 (0.27–0.66)
	Cisplatin + gemcitabine		107	NR	NR	5.6	
	Erlotinib	Investigator assessed	110	26.3	0.91 (0.63–1.31)	11	0.34 (0.22–0.51)
	Cisplatin + gemcitabine		107	25.5		5.5	
Seto 2014 (JO25567/ JapicCTI-111390)	Erlotinib	IRC assessed	77	NR	NR	9.7 (5.7–11.1)	0.54 (0.36–0.79); p=0.0015 (HR for erlotinib + bevacizumab vs erlotinib)
	Erlotinib + bevacizumab		75	NR		16 (13.9–18.1)	
Wu 2014 (LUX-Lung 6/ NCT01121393)	Afatinib	IRC assessed	242	23.1 (20.4–27.33)	0.934 (0.715–1.219); p=0.6137	11 (9.7–13.7)	0.28 (0.2–0.39); p<0.0001
	Cisplatin + gemcitabine		122	23.5 (18–25.56)		5.6 (5.1–6.7)	
	Afatinib	Investigator assessed	242	NR	NR	13.7 (11.5–13.9)	0.26 (0.19–0.36); p<0.0001
	Cisplatin + gemcitabine		122	NR		5.6 (5.1–6.8)	
Yang 2014 (NCT01017874)	Gefitinib	NR	25	45.7 (25.8–NE)	1.57 (0.72–3.39) (HR for pemetrexed-cisplatin vs gefitinib)	16.6	0.83 (0.42–1.62) (HR for pemetrexed-cisplatin vs gefitinib)
	Pemetrexed-cisplatin followed by gefitinib		27	32.4 (19.3–NE)		12.9	

Study name (Trial name/ NCT)	Intervention Comparator	Assessment	Number of patients	OS		PFS	
				Median (95% CI)	HR (95% CI); p value	Median (95% CI)	HR (95% CI); p value
Sequist 2013 (LUX-Lung 3/ NCT00949650)	Afatinib	IRC assessed	230	28.2 (24.6–33.6)	0.88 (0.66–1.17); p=0.39	11.1 (9.63–13.63)	0.58 (0.43–0.78); p=0.0004
	Cisplatin + pemetrexed		115	28.2 (20.7–33.2)		6.9 (5.39–8.25)	
	Afatinib	Investigator assessed	230	NR	NR	11.1 (9.66–13.6)	0.49 (0.37–0.65)
	Cisplatin + pemetrexed		115	NR		6.7 (5.42–8.1)	
	Afatinib 30 mg	After 6 months of dose reduction	122	NR	NR	11.3	1.25 (0.91–1.72); p=0.175 Afatinib 30mg versus 40mg)
	Cisplatin + pemetrexed		NR	NR		NR	
	Afatinib 40 mg		107	NR		11	
	Cisplatin + pemetrexed		NR	NR		NR	
Chen 2012 (NCT01196078)	Erlotinib	NR	9	22.8	NR	8.4	p=0.2255
	Vinorelbine		15	29.9		3.9	
Gridelli 2012 (TORCH/ NCT00349219)	Erlotinib	NR	19	NR	NR	9.7 (5.7–18.2)	NR
	Cisplatin + gemcitabine		20	NR		6.9 (6.6–9.6)	
Han 2012 (First-SIGNAL/ NCT00455936)	Gefitinib	Investigator assessed	26	27.2	1.043 (0.498–2.182)	8	0.544 (0.269–1.1)
	Cisplatin + gemcitabine		16	25.6		6.3	
Janne 2012 (CALGB 30406/ NCT00126581)	Erlotinib	NR	33	31.3 (23.8–NA)	NR	14.1 (7–19.6)	NR
	Erlotinib+ carboplatin + paclitaxel		33	38.1 (19.6–NA)		17.2 (8.2–28.7)	
Lee 2012 (TOPICAL/ NCT00275132)	Erlotinib	NR	17	10.4 (5.5–15.1)	NR	4.8 (1.6–8.8)	NR
	PBO		11	3.7 (0.3–49.3)		2.9 (0.3–10.1)	
NCT00294762 2012	Erlotinib	NR	69	16.7 (0.26–29.01)[a]	NR	2.7 (0.03–28.85)[a]	NR

Study name (Trial name/ NCT)	Intervention Comparator	Assessment	Number of patients	OS		PFS	
				Median (95% CI)	HR (95% CI); p value	Median (95% CI)	HR (95% CI); p value
	Erlotinib + chemotherapy		68	11.43 (0.49–29.04)[a]		4.6 (0.03–24.51)[a]	
Rosell 2012 (EURTAC/ NCT00446225)	Erlotinib	Investigator (ITT analysis)	86	22.9 (17–29.5)	p=0.97	10.4 (8.4–12.9)	0.34 (0.23–0.49); p<0.001
	Chemotherapy (cisplatin + docetaxel or gemcitabine)		87	22.1 (16.5–28.4)		5.1 (4.5–5.6)	
	Erlotinib	(PP analysis)	77	21.6	1 (0.76–1.33); p=0.99	NR	NR
	Chemotherapy (cisplatin + docetaxel or gemcitabine)		73	21.9		NR	
Zhang 2012 (INFORM; C-TONG 0804/ NCT00770588)	Gefitinib	NR	15	46.87	0.39 (0.15–0.97); p=0.036	16.6 (9.4–22.7)	0.17 (0.07–0.42); p=0.0063
	PBO		15	20.97		2.8 (1.3–4.1)	
Fukuoka 2011 (Iressa Pan-Asia Study (IPASS)/ NCT00322452)	Gefitinib	NR	132	21.6	1 (0.76–1.33); p=0.99	9.5	0.48 (0.36–0.64); p<0.001
	Carboplatin + paclitaxel		129	21.9		6.3	
Hirsch 2011	Erlotinib	NR	9	NR	NR	18.2	NR
	Intercalated erlotinib + chemotherapy (carboplatin/paclitaxel)		6	11.4		4.9	
Zhou 2011 (OPTIMAL, CTONG-0802/ NCT00874419)	Erlotinib	Investigator assessed	82	22.8	1.19 (0.83–1.71); p=0.2663	13.7 (10.58–15.28)	0.164 (0.105–0.256); p<0.0001
	Cisplatin + gemcitabine		72	27.2		4.6 (4.21–5.42)	
Cappuzzo 2010 (SATURN; BO18192/ NCT00556712)	Erlotinib (EGFR IHC positive)	Investigator assessed	308	12.8 (11.1–14.7)	0.78 (0.66–0.93); p=0.005	2.8 (2.77–4.08)	0.69 (0.58–0.82); p<0.0001
	PBO (EGFR IHC positive)		313	11 (9.7–12.8)		2.6 (1.64–2.7)	

Study name (Trial name/ NCT)	Intervention Comparator	Assessment	Number of patients	OS		PFS	
				Median (95% CI)	HR (95% CI); p value	Median (95% CI)	HR (95% CI); p value
	Erlotinib (EGFR mutation positive)	Investigator assessed	308	NR	NR	10.15	0.1 (0.04–0.25); p<0.0001
	PBO (EGFR mutation positive)		313	NR		3.23	
Maemondo 2010 (NEJ002/ UMIN-CTR number, C000000376)	Gefitinib	External review	114	27.7	0.887 (0.634–1.241); p=0.483	10.8	0.32 (0.236–0.438); p<0.001
	Carboplatin + paclitaxel		114	26.6		5.4	
Mitsudomi 2010 (WJTOG3405/ UMIN number 000000539)	Gefitinib	NR	51	27.5	1.264 (0.816–1.958); p=0.293	8.6	0.478 (0.319–0.717); p<0.001
	Cisplatin + docetaxel		50	32.7		5.8	
Goss 2009 (INSTEP/ NCT00259064)	Gefitinib + BSC	NR	12	NR	0.44 (0.17–1.12)	NR	0.29 (0.1–0.73)
	BSC + PBO		20	NR		NR	
Crino 2008 (INVITE/ NCT00256711)	Gefitinib	NR	30	NR	2.88 (1.21–6.83)	NR	3.13 (1.45–6.76)
	Vinorelbine		24	NR		NR	
Lilenbaum 2008 (NCT00085839)	Erlotinib (IHC positive)	NR	13	10.4	NR	2.1	NR
	Carboplatin+ paclitaxel (IHC positive)		11	15.5		3.5	

Key: BSC, best supportive care; CI, confidence interval; HR, hazard ratio; IHC, immunohistochemistry; IRC, independent review committee; NA, not available; NR, not reported; OS, overall survival; PBO, placebo; PFS, progression-free survival; TKI, tyrosine kinase inhibitor.

Notes: [a] Data reported as median (min–max).

* "For statistical significance at the interim analysis of OS, a p-value of less than 0.0015 (determined by the O'Brien-Fleming approach) was required
The HR ratio reported was between the treatment in the upper row versus lower row unless specified otherwise.

D.1.5 Safety outcomes

Adverse events due to any cause

Fifteen studies reported data for the proportion of patients who experienced adverse events (AEs) due to any cause. Across 11 of these studies[15, 102, 118, 164, 169, 176, 177, 179-181, 187], the incidence varied from 88.3% with gefitinib in the study by Patil et al.[187] to 100% with afatinib in two trials (LL3[176] and LL6[177]) and gefitinib in LL7.[118] Additionally, qualitative data were presented in four studies.[167, 172, 173, 193]

The proportion of patients who experienced at least a Grade 3/4 AE were reported in 12 studies.[15, 102, 118, 164, 167, 173, 176, 177, 179-181, 194] Across 11 of these studies, the incidence varied from 2.8% of the group receiving gefitinib plus Fuzheng Kang'ai Formula in the study by Yang et al.[194] to 91% of the erlotinib plus bevacizumab group in the study by Seto et al.[173] Only qualitative data were reported in the study by An et al.[167]

Eleven studies reported data for the proportion of patients who experienced a serious adverse event (SAE).[102, 164, 166, 169, 173, 176, 177, 179-181, 194] Across these studies the incidence varied from none with both the treatment arms (gefitinib and gefitinib plus Fuzheng Kang'ai Formula) in the study by Yang et al.[194] to 39.7% of the erlotinib plus chemotherapy group in NCT00294762.[169] Only the ENSURE study reported data for Grade 3/4 severe AEs, where 40% of the erlotinib and 56.7% of the cisplatin plus gemcitabine group experienced severe AEs.[180]

The incidence of diarrhoea of any grade was reported in 11 studies.[15, 102, 164, 169, 173, 175, 177, 179, 180, 194, 195] The incidence varied between 6.2% with carboplatin plus paclitaxel in NEJ002[15] and 89.5% with afatinib in LL6.[177] The incidence of Grade 3/4 diarrhoea was reported in 11 studies.[15, 102, 164, 167, 173, 175, 177, 179, 180, 194, 195 175] In the study by Han et al., none of the patients in three treatment arms (gefitinib, gefitinib plus carboplatin and pemetrexed, carboplatin plus pemetrexed) experienced Grade 3/4 diarrhoea.[195] Across the other ten studies, none of the patients experienced Grade 3/4 diarrhoea in the platinum doublet chemotherapy group in four studies.[15, 177, 179, 180] Also, none of the patients receiving gefitinib plus Fuzheng Kang'ai formula in the study by Yang et al. and those receiving afatinib plus cetuximab in the study by Goldberg et al. experienced Grade 3/4 event of diarrhoea.[175, 194] The maximum incidence was reported as 17% in the afatinib group in the study by Goldberg et al.[175]

The incidence of fatigue of any grade was reported in 10 studies.[15, 102, 164, 169, 173, 175, 177, 179, 180, 195] The data varied between 4% with erlotinib in the study by Seto et al.[173] and 71.9% with chemotherapy in EURTAC.[179] The incidence of Grade 3/4 fatigue was reported in nine studies.[15, 102, 164, 167, 173, 175, 177, 179, 195] Across these studies, the incidence varied from none in the erlotinib group in the study by Seto et al.[173] and gefitinib group in the study by Han et al.[195] and 20% of the chemotherapy group in EURTAC.[179] This also included the study by Goldberg et al. in which none of the patients in both the treatment groups experienced a Grade 3/4 event of fatigue.[175]

Fourteen studies reported data for incidence of rash of any grade.[15, 102, 164, 169, 173, 175, 177, 179, 180, 184, 186, 191, 194, 195] Across 13 of these studies, the incidence varied between 5% with chemotherapy in EURTAC[179] and 100% with erlotinib in two studies.[173, 191] Additionally, in the study by Singh et al. only qualitative data was reported for the incidence of rash.[186] The incidence of Grade 3/4 rash was reported in 11 studies.[15, 102, 164, 167, 173, 175, 177, 179, 180, 187, 195] Across these studies, the incidence varied from none with chemotherapy, cisplatin plus gemcitabine and afatinib in EURTAC[179], LL6[177] and Goldberg et al.[175], respectively, to 69.7% with carboplatin plus pemetrexed followed by pemetrexed in the study by Patil et al.[187] Also, none of the patients in the gefitinib and carboplatin plus pemetrexed group experienced a Grade 3/4 rash in ARCHER 1050[102] and Han et al.[195], respectively.

The incidence of anaemia of any grade was reported in eight studies[15, 102, 164, 169, 177, 179, 180, 195], across which the data varied between 1.5% with erlotinib in NCT00294762[169] and 64.6% with carboplatin plus paclitaxel in NEJ002.[15] The incidence of Grade 3/4 anaemia varied between none in the gefitinib arm in NEJ002[15] and 78.7% with gefitinib in the study by Patil et al.[187] across nine studies.[15, 102, 164, 167, 177, 179, 180, 187, 195] In the study by Han et al., none of the patients in the three treatment arms (gefitinib, gefitinib plus carboplatin plus pemetrexed and carboplatin plus pemetrexed) experienced a Grade 3/4 anaemia.[195]

The incidence of neutropenia of any grade was reported in eight studies, across which the data varied from none in the erlotinib group in EURTAC[179] and erlotinib plus bevacizumab in the study by Seto et al.[173] and 77% with carboplatin plus paclitaxel in NEJ002.[15] The incidence of Grade 3/4 neutropenia was reported in 10 studies.[15, 102, 164, 167, 173, 177, 179, 180, 187, 195] The incidence varied between none with erlotinib in EURTAC[179], gefitinib in Han et al.[195], standard EGFR TKI therapy in FLAURA[164], dacomitinib in ARCHER 1050[102] and erlotinib plus bevacizumab in Seto et al.[173], and 65.5% with carboplatin plus paclitaxel in NEJ002.[15]

The incidence of thrombocytopenia of any grade was reported in six studies.[15, 169, 177, 179, 180, 195] Across these studies, the incidence varied from none with erlotinib plus chemotherapy in NCT00294762[169] to 28.3% with carboplatin plus paclitaxel in NEJ002.[15] The incidence of Grade 3/4 thrombocytopenia was reported in seven studies.[15, 167, 177, 179, 180, 187, 195] The incidence varied from none with gefitinib in NEJ002[15] and with erlotinib in EURTAC[179] and ENSURE[180], to 40.4% with gefitinib in the study by Patil et al.[187] None of the patients in the study by An et al. and Han et al. experienced Grade 3/4 thrombocytopenia in either of the treatment arms.[167, 195]

Drug-related adverse events

The data for safety variables are presented in Table 105.

Eight studies reported data for the proportion of patients who experienced a drug-related AE of any grade.[118, 165, 166, 176, 177, 179-181] The incidence varied from 87% with erlotinib in OPTIMAL[181] to 100% in both the treatment arms (erlotinib and erlotinib plus linsitinib) in the study by Leighl et al.[165] The proportion of patients experiencing an event of Grade 3/4 AE was reported in five studies.[118, 165, 166, 176, 177] The incidence varied from 19% with gefitinib in the study by Cheng et al.[166] to 60% with cisplatin plus gemcitabine in LL6.[177]

Eight studies reported data for the proportion of patients who experienced drug-related SAEs.[102, 118, 166, 176, 177, 179-181] The incidence ranged from 2% with erlotinib in OPTIMAL[181] and gefitinib in the study by Cheng et al.[166] to 20% with platinum doublet chemotherapy in EURTAC.[179] None of the studies reported data for the proportion of patients who experienced drug-related SAEs of Grade 3/4.

The proportion of patients who experienced diarrhoea of any grade was reported in seven studies.[118, 164-166, 176, 177, 181] The incidence varied from 6% with cisplatin plus gemcitabine in OPTIMAL[181] to 95.2% with afatinib in LL3.[176] The incidence of Grade 3/4 diarrhoea was reported in seven studies.[118, 164-166, 176, 177, 181] The incidence varied from none with cisplatin plus pemetrexed in LL3[176] and with cisplatin plus gemcitabine in two studies, LL6[177] and OPTIMAL[181], to 14.4% with afatinib in LL3.[176]

The incidence of fatigue of any grade was reported in seven studies.[118, 165, 166, 172, 176, 177, 181] Across six of these studies, the incidence varied from 5% with erlotinib in OPTIMAL[181] to 46.8% with cisplatin plus pemetrexed in LL3.[176] In the study by Scagliotti et al., it was reported that fatigue was one of the more frequent drug-related AEs.[172] Six studies reported data for the proportion of patients who experienced Grade 3/4 fatigue.[118, 165, 166, 176, 177, 181] The incidence varied between none with erlotinib in OPTIMAL and with gefitinib in the study by Cheng et al. and LL7, and 12.6% with cisplatin plus pemetrexed in LL3.

The incidence of rash of any grade was reported in seven studies.[118, 164, 165, 176, 177, 181, 191] The incidence varied from 6.3% with cisplatin plus pemetrexed in LL3[176] to 100% with erlotinib in TOPICAL.[191] The incidence of Grade 3/4 rash was reported in six studies[118, 164, 165, 176, 177, 181], which varied from none with cisplatin plus pemetrexed in LL3[176] and cisplatin plus gemcitabine in two studies (LL6[177] and OPTIMAL[181]), to 16.2% with afatinib in LL3.[176]

The incidence of anaemia was reported in four studies[166, 176, 177, 181], which varied from none with gefitinib in the study by Cheng et al.[166] to 72% with cisplatin plus gemcitabine in OPTIMAL.[181] The incidence of Grade 3/4 anaemia was reported in four studies[166, 176, 177, 181], which varied from none with erlotinib and gefitinib in OPTIMAL[181] and Cheng et al.[166], respectively, to 13% with cisplatin plus gemcitabine in OPTIMAL.[181]

The incidence of neutropenia of any grade was reported in five studies.[118, 166, 176, 177, 181] The incidence varied from 0.9% with afatinib in LL3[176] to 69% with cisplatin plus gemcitabine in OPTIMAL.[181] The incidence of Grade 3/4 neutropenia was reported in five studies.[118, 166, 176, 177, 181] The incidence varied from none with erlotinib in OPTIMAL[181] and with gefitinib in LL7[118] to 42% with cisplatin plus gemcitabine in OPTIMAL.[181]

The incidence of thrombocytopenia of any grade was reported in two studies.[177, 181] In LL6, the incidence was 0.8% with afatinib and 18.6% with cisplatin plus gemcitabine.[177] In OPTIMAL, the incidence was significantly higher with cisplatin plus gemcitabine than erlotinib; 64% versus 4%, $p<0.0001$.[181] The incidence of Grade 3/4 thrombocytopenia was reported in two studies.[177, 181] In LL6, the incidence was 0.4% with afatinib and 9.7% with cisplatin plus gemcitabine.[177] In OPTIMAL, the incidence was none with erlotinib compared with 40% with cisplatin plus gemcitabine.[181]

Table 105: Drug-related adverse events in RCTs

Study name (Trial name/ NCT)	Intervention/ Comparator	Number of patients	Any AE n (%) p-value		Any SAE n (%) p-value		Diarrhoea n (%) p-value		Fatigue n (%) p-value		Rash n (%) p-value	
			Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4
Soria 2018 (FLAURA/ NCT02296125)	Osimertinib	279	NR	NR	NR	NR	138 (49)	6 (2)	NR	NR	152 (54)	3 (1)
	Standard EGFR-TKI	277	NR	NR	NR	NR	142 (51)	5 (2)	NR	NR	205 (74)	19 (7)
Leighl 2017	Erlotinib + linsitinib	43	43 (100)	22 (51.2)	NR	NR	29 (67.4)	1 (2.3)	16 (37.2)	4 (9.3)	36 (83.7)	3 (6.9)
	Erlotinib + PBO	44	44 (100)	10 (22.7)	NR	NR	33 (75)	4 (9.1)	16 (36.4)	1 (2.3)	43 (97.7)	3 (6.8)
Wu 2017 (ARCHER 1050/ NCT01774721)	Dacomitinib	227	NR	NR	21 (9.3)	NR	NR	NR	NR	NR	NR	NR
	Gefitinib	225	NR	NR	10 (4.5)	NR	NR	NR	NR	NR	NR	NR
Cheng 2016 (NCT01469000)	Gefitinib	65	60 (92)	12 (19)	1 (2)	NR	31 (48)	1 (2)	6 (9)	0 (0)	NR	NR
	Gefitinib + pemetrexed	126	118 (94)	53 (42); p=0.001	11 (9)	NR	56 (44)	1 (1)	35 (28)	7 (6)	NR	NR
Park 2016 (LUX-LUNG 7/ NCT01466660)	Afatinib	160	156 (97.5)	50 (31.3)	17 (11)	NR	144 (90)	21 (13.1)	33 (21)	9 (6)	142 (88.7)	15 (9)
	Gefitinib	159	153 (96.2)	31 (19.5)	7 (4)	NR	97 (61)	2 (1)	23 (14)	0 (0)	129 (81)	5 (3)
Wu 2015 (ENSURE/ NCT01342965)	Erlotinib	110	96 (87.3)	NR	3 (2.7)	NR	NR	NR	NR	NR	NR	NR
	Cisplatin + gemcitabine	104	97 (93.3)	NR	11 (10.6)	NR	NR	NR	NR	NR	NR	NR
Wu 2014 (LUX-Lung 6/ NCT01121393)	Afatinib	239	236 (98.7)	86 (36)	15 (6.3)	NR	211 (88.3)	13 (5.4)	24 (10)	1 (0.4)	193 (80.8)	35 (14.6)
	Cisplatin + gemcitabine	113	112 (99.1)	68 (60)	9 (8)	NR	12 (10.6)	0 (0)	41 (36.3)	1 (0.9)	10 (8.8)	0 (0)
Sequist 2013	Afatinib	229	228 (99.6)	112 (48.9)	33 (14.4)	NR	218 (95.2)	33 (14.4)	40 (17.5)	3 (1.3)	204 (89.1)	37 (16.2)

Study name (Trial name/ NCT)	Intervention/ Comparator	Number of patients	Any AE n (%) p-value		Any SAE n (%) p-value		Diarrhoea n (%) p-value		Fatigue n (%) p-value		Rash n (%) p-value	
			Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4
(LUX-Lung 3/ NCT00949650)	Cisplatin + pemetrexed	111	106 (95.5)	53 (47.7)	16 (14.4)	NR	17 (15.3)	0 (0)	52 (46.8)	14 (12.6)	7 (6.3)	0 (0)
Lee 2012 (TOPICAL/ NCT00275132)	Erlotinib	17	NR	NR	NR	NR	NR	NR	NR	NR	17 (100)	NR
	PBO	11	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Rosell 2012 (EURTAC/ NCT00446225)	Erlotinib	84	78 (93)	NR	5 (6)	NR	NR	NR	NR	NR	NR	NR
	Chemotherapy (cisplatin + docetaxel or gemcitabine	82	78 (95)	NR	16 (20)	NR	NR	NR	NR	NR	NR	NR
Zhou 2011 (OPTIMAL, CTONG-0802/ NCT00874419)	Erlotinib	83	72 (87)	NR	2 (2)	NR	21 (25)	1 (1)	4 (5); p=0·00085	0 (0)	61 (73); p<0.0001	2 (2)
	Carboplatin + gemcitabine	72	68 (94)	NR	10 (14)	NR	4 (6)	0 (0)	17 (24)	1 (1)	14 (19)	0 (0)

Key: AE, adverse event; BSC, best supportive care; NR, not reported; PBO, placebo; SAE, serious adverse event; TKI, tyrosine kinase inhibitor.

Table 106: Drug-related adverse events in RCTs (contd.)

Study name (Trial name/ NCT)	Intervention/ Comparator	Number of patients	Anaemia n (%) p-value		Neutropenia n (%) p-value		Thrombocytopenia n (%) p-value	
			Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4
Cheng 2016 (NCT01469000)	Gefitinib	65	0 (0)	0 (0)	1 (2)	1 (2)	NR	NR
	Gefitinib + pemetrexed	126	23 (18)	4 (3)	22 (18)	6 (5)	NR	NR
Park 2016 (LUX-LUNG 7/ NCT01466660)	Afatinib	160	NR	NR	3 (2)	1 (1)	NR	NR
	Gefitinib	159	NR	NR	1 (1)	0 (0)	NR	NR
Wu 2014 (LUX-Lung 6/ NCT01121393)	Afatinib	239	13 (5.4)	1 (0.4)	5 (2.1)	1 (0.4)	2 (0.8)	1 (0.4)
	Cisplatin + gemcitabine	113	31 (27.4)	10 (8.8)	61 (54)	30 (26.5)	21 (18.6)	11 (9.7)

Study name (Trial name/ NCT)	Intervention/ Comparator	Number of patients	Anaemia n (%) p-value		Neutropenia n (%) p-value		Thrombocytopenia n (%) p-value	
			Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4
Sequist 2013 (LUX-Lung 3/ NCT00949650)	Afatinib	229	7 (3.1)	1 (0.4)	2 (0.9)	1 (0.4)	NR	NR
	Cisplatin + pemetrexed	111	31 (27.9)	7 (6.3)	35 (31.5)	20 (18)	NR	NR
Zhou 2011 (OPTIMAL, CTONG-0802/ NCT00874419)	Erlotinib	83	4 (5)	0 (0)	5 (6)	0 (0)	3 (4)	0 (0)
	Carboplatin + gemcitabine	72	52 (72)	9 (13)	50 (69); p<0.0001	30 (42)	46 (64); p<0.0001	29 (40)

Key: NR, not reported.

D.1.6 Tolerability outcomes

Data for study withdrawals/treatment discontinuation due to any reason were reported in 15 studies.[15, 102, 118, 164-166, 173, 176, 177, 179-181, 187, 192, 195] Twelve of these studies reported data for the proportion of patients who discontinued treatment.[15, 102, 118, 164-166, 173, 176, 177, 179, 180, 187] Across eleven of these studies, treatment discontinuations ranged from none in both the treatment arms (gefitinib and carboplatin plus paclitaxel) of NEJ002[15] to all (100%) of the platinum doublet chemotherapy group in two studies, LL3 (cisplatin plus pemetrexed)[176] and LL6 (cisplatin plus gemcitabine).[177] In the study by Seto et al., it was reported that among the 75 patients who received erlotinib plus bevacizumab, 55 patients discontinued erlotinib and 63 patients discontinued bevacizumab and 85.7% discontinued from the erlotinib alone group.[173] LL3 and ENSURE also reported data for patients who withdrew from the study.[176, 180] In LL3, 65.6% and 73.9% withdrew from study in the afatinib and platinum doublet chemotherapy group, respectively.[176] In ENSURE, 99% and 100% patients withdrew from the study in the erlotinib and platinum doublet chemotherapy group, respectively.[180]

Three other studies reported data for study discontinuations only: OPTIMAL[181], Han et al.[195] and INFORM.[192] In OPTIMAL, 73.5% of the erlotinib group discontinued from the study compared with 100% of the cisplatin plus gemcitabine group.[181] In INFORM, 27.0% of the gefitinib group discontinued from the study compared with 7.0% of the placebo group.[192] The data in INFORM were reported for patients who were lost to follow-up. In the study by Han et al., the proportion of patients who withdrew from study due to disease progression and protocol violation was 97.5%, 95% and 85% from the gefitinib, carboplatin plus pemetrexed and gefitinib plus carboplatin and pemetrexed groups, respectively.[195]

Four studies reported data for treatment discontinuations in the subgroup of patients with exon 19 del and L858R mutations.[118, 176, 177, 187] In three of these studies, treatment discontinuations ranged between 88.7% in the afatinib group in LL6[177] and 100% in the cisplatin plus pemetrexed group in LL3[176] and the cisplatin plus gemcitabine group in LL6, in the subgroup of patients with exon 19 del mutations.[177] Similarly, across subgroup of patients with L858R mutations, the treatment discontinuations ranged between 91.3% in the afatinib group in LL6[177] and 100% in the cisplatin plus pemetrexed group in LL3[176] and the cisplatin plus gemcitabine group in LL6.[177] In the study by Patil et al., temporary stoppage of gefitinib was required in 20.5% with exon 19 del and 18.6% of patients who discontinued treatment with L858R mutations.[187]

Eleven studies reported data for patients who discontinued treatment due to AEs.[102, 118, 164, 166, 173, 175-177, 179, 180, 187] Across 10 of these studies, the proportion of patients who discontinued treatment varied from 3.6% of the erlotinib group in ENSURE[180] to 39.8% of the cisplatin plus gemcitabine group in LL6.[177] In the study by Seto et al., it was reported that among the patients who received erlotinib plus bevacizumab, 12 patients discontinued erlotinib and 31 patients discontinued bevacizumab due to AEs and 18.2% of patients discontinued from the erlotinib alone group.[173] In the EURTAC study, treatment discontinuations from the safety population were also reported.[179]

Withdrawals due to drug-related AEs were reported in nine studies.[102, 118, 164-166, 176, 177, 179, 180] Across these studies the data varied from none of the erlotinib group in the study by Leighl et al.[165] to 39.8% of the cisplatin plus gemcitabine group in LL6.[177]

Withdrawal due to deaths were reported in nine studies.[166, 167, 173, 176, 177, 179, 180, 187, 195] Across these studies the proportion of patients who withdrew varied from none in three studies with gefitinib and gefitinib plus pemetrexed[167], gefitinib[166] and erlotinib[180], to 97.5% with gefitinib in the study by Han et al.[195] The study by Han et al. reported data for withdrawals due to PD or death.[195]

A summary of dose modifications across the RCTs is presented in Table 107.

Table 107: Summary of dose modifications across RCTs

Study name	Treatment	Dosing details	Rules for stopping the study treatment
Soria 2018	Osimertinib	Where dose modifications were required to manage toxicity, patients were required to undergo dose interruption prior to considering a dose reduction. If restarting at the same dose level, patients were closely monitored for 3 days following the restart of treatment. If, within 3 days, there was a recurrence of the same toxicity, a dose reduction was considered at the investigator's discretion. If the toxicity did not resolve to CTCAE Grade ≤1 after 2 weeks, then the patient was withdrawn from the trial treatment and observed until resolution of the toxicity. There was no individual modification to the treatment schedule in response to toxicity, only potential dose reduction or dose interruption. If an AE subsequently required a dose interruption, the trial drug was restarted at the same dose, on resolution/improvement of the AE at the discretion of the investigator. Reduced dose: 40 mg	Treatment continued until disease progression, the development of unacceptable side effects, or withdrawal of consent. Treatment beyond the point of disease progression (as assessed by the investigator according to RECIST, version 1.1) was allowed as long as there was continued clinical benefit, as judged by the investigator. Dosing was interrupted, and supportive therapy administered as required in accordance with local practice/guidelines, in patients experiencing a CTCAE Grade 3 or higher AE and/or unacceptable toxicity (any grade), not attributable to the disease under investigation, and considered by the investigator to be specifically associated with the trial drug. If the toxicity resolved or reverted to CTCAE Grade ≤1 within 2 weeks of onset, the trial drug was restarted at the same dose, or reduced dose. 25% patients had dose interruption due to AEs. The most frequently experienced AEs leading to dose interruption in the osimertinib group were QT prolongation (8 patients), decreased appetite (7 patients), diarrhoea (7 patients), and pneumonia (5 patients), The median time to discontinuation of randomised treatment or death was longer in the osimertinib group (20.8 months) versus the standard EGFR-TKI group (11.5 months).
	Standard EGFR-TKI	Where dose modifications were required to manage toxicity, patients were required to undergo dose interruption prior to considering a dose reduction. No dose reduction for gefitinib was possible; thus, the reduced dose for gefitinib was the same as the starting dose because the 250 mg tablets are the lowest dose available. If restarting at the same dose level, patients were closely monitored for 3 days following the restart of treatment. If, within 3 days, there was a recurrence of the same toxicity, a dose reduction was considered at the investigator's discretion. If the toxicity did not resolve to CTCAE Grade ≤1 after 2 weeks, then the patient was withdrawn from the trial treatment and observed until resolution of the toxicity. There was no individual modification to the treatment schedule in response to toxicity, only potential dose reduction or dose interruption. If an AE subsequently required a dose interruption, the trial drug was restarted at the same dose, on resolution/improvement of the AE at the discretion of the	Treatment continued until disease progression, the development of unacceptable side effects, or withdrawal of consent. Treatment beyond the point of disease progression (as assessed by the investigator according to RECIST, version 1.1) was allowed as long as there was continued clinical benefit, as judged by the investigator. 24% patients had dose interruption due to AEs. The most frequently experienced AEs leading to dose interruption in the standard EGFR-TKI group dose interruption was driven by alanine aminotransferase increase (18 patients),

Study name	Treatment	Dosing details	Rules for stopping the study treatment
		investigator. No dose reduction for gefitinib was possible; thus, the reduced dose for gefitinib was the same as the starting dose because the 250 mg tablets are the lowest dose available. Erlotinib Reduced dose: 100 mg	aspartate aminotransferase increase (12 patients), QT prolongation (6 patients) and dermatitis acneiform (5 patients). The median time to discontinuation of randomised treatment or death was longer in the osimertinib group (20.8 months) versus the standard EGFR-TKI group (11.5 months).
Goldberg 2017	Afatinib	Dose reductions were performed for Grade 3–4 or intolerable or medically concerning Grade 2 AEs per CTCAE v4.0	NR
	Afatinib + cetuximab		
Han 2017	Gefitinib	NR	All therapies were continued until progression, unacceptable toxicity or death.
	Gefitinib + carboplatin + pemetrexed		
	Carboplatin + pemetrexed		
Leighl 2017	Erlotinib + Linsitinib	Linsitinib + Erlotinib (N = 43) Dose reductions due to drug-related AEs, n(%): 14 (32.6) Dose interruption drug-related AEs, n(%): 19 (44.2) Dose modification: Linsitinib Interruptions: 26 (60.5) Reductions: 30 (69.8) Erlotinib; Interruptions: 26 (60.5) Reductions: 15 (34.9) •Reasons for reduction Linsitinib Treatment-related AE: 11 (25.6) Nontreatment-related AE: 0 (0) Patient noncompliance: 13 (30.2) Toxicity improved: 11 (25.6) Other: 17 (39.5) Erlotinib Treatment-related AE: 9 (20.9) Nontreatment-related AE: 0 (0) Patient noncompliance: 0 (0) Toxicity improved: 8 (18.6) Other: 4 (9.3)	NR
	Erlotinib	Dose modifications at the investigator's discretion were permitted for toxicity of either drug, or both where the contribution of either drug was uncertain.	NR

Study name	Treatment	Dosing details	Rules for stopping the study treatment
		Reescalation was permitted for erlotinib only. Erlotinib + Placebo (N = 44) Dose reductions due to drug-related AEs: 20.5% (n = 9) Dose interruption drug-related AEs: 20.5% (n = 9) •Dose modification: Erlotinib Interruptions: 21 (47.7) Reductions: 10 (22.7) Placebo Interruptions: 20 (45.5) Reductions: 26 (59.1) •Reasons for reduction Erlotinib Treatment-related AE: 8 (18.2) Nontreatment-related AE: 0 (0) Patient noncompliance: 0 (0) Toxicity improved: 5 (11.4) Other: 4 (9.1) Placebo Treatment-related AE: 4 (9.1) Nontreatment-related AE: 4 (9.1) Patient noncompliance: 12 (27.3) Toxicity improved: 4 (9.1) Other: 14 (31.8)	
Wu 2017	Dacomitinib	First dose reduction was 30 mg QD and second dose reduction was 15 mg QD	Treatment was continued until disease progression, a new anticancer therapy is instituted, intolerable toxicity, withdrawal of consent, death, or investigator decision dictated by protocol compliance, whichever occur first
	Gefitinib	Dose reduction was 250 mg every two days	
Yang 2017	Gefitinib	NR	Treatment continued until progression of the disease, or development of unacceptable toxicities, or withdrawal of treatment.
	Gefitinib+ Fuzheng Kang'ai formula		
Yang 2017	Erlotinib	Erlotinib and gefitinib dose delays of ≤14 days were permitted for Grade ≥3 non-haematological toxicities until resolution to Grade 1 or baseline, and treatment was reintroduced at a reduced dosage depending on the toxicity.	Treatment continued until unacceptable toxicity, disease progression, or another discontinuation criterion was met.
	Gefitinib		
An 2016	Gefitinib + Placebo	NR	NR
	Gefitinib + pemetrexed	Dose reductions of gefitinib were not allowed.	Pemetrexed was only administered if the patient had a leukocyte count of ≥3,000/μl and a platelet count of ≥100,000/μl. If the leukocyte or platelet count had not returned to these levels

Study name	Treatment	Dosing details	Rules for stopping the study treatment
			on Day 1 of the next cycle of chemotherapy, both drugs were withheld until complete recovery of the counts.
Cheng 2016	Gefitinib	For gefitinib-treated patients with poorly tolerated diarrhoea, skin adverse drug reactions, or any other gefitinib-related AE, dosing could be delayed up to 14 days. Patients with acute onset or worsening of pulmonary symptoms (dyspnoea, cough, or fever) could undergo gefitinib dose delay, and appropriate treatment was initiated. If interstitial lung disease was confirmed, gefitinib was discontinued. • The proportion of patients experiencing gefitinib treatment interruption as a result of an AE was 15% (10 of 65 patients).	NR
	Gefitinib + pemetrexed	Patients requiring pemetrexed dose reduction continued on the reduced dose for the remainder of the study. Patients who experienced toxicity requiring a third dose reduction had to permanently discontinue pemetrexed but could continue to receive gefitinib. Dosing could be delayed for up to 42 days for drug-related toxicities. Patients in the P+G arm who discontinued gefitinib could continue receiving pemetrexed. • The proportion of patients experiencing gefitinib treatment interruption as a result of an AE was 33% (42 of 126 patients). • The proportion of patients requiring pemetrexed dose delay in gefitinib plus pemetrexed arm was 43% (54 of 126)	Patients who experienced toxicity requiring a third dose reduction had to permanently discontinue pemetrexed but could continue to receive gefitinib.
Park 2016	Afatinib	Dose escalation to 50 mg was allowed after 4 weeks of treatment for patients who did not experience rash, diarrhoea, mucositis, or any other drug-related AE (National Cancer Institute CTCAE, version 3.0) of more than Grade 1. If patients had any Grade 3 or higher drug-related AE, or Grade 2 diarrhoea lasting 2 days or more, or nausea or vomiting for 7 days consecutively or more despite best supportive care, then the study drug was paused for no more than 14 days until recovery to at least Grade 1. After treatment interruption and recovery to Grade 1 or less (or grade present at baseline), the afatinib dose was reduced by 10mg decrements to a minimum dose of 20mg. Nine (6%) of 160 patients had afatinib dose escalations to 50 mg per day, 63 (39%) patients had dose reductions to 30 mg, of whom 21 (13%) patients had further reductions to 20 mg. The authors reported that dose reductions due to AEs were undertaken mostly with afatinib (67 [42%] of 160 patients) rather than gefitinib (three [2%] of 159 patients), but it should be noted that gefitinib only has one dose strength (250 mg) and no dose reduction scheme was specified in the summary of product characteristics or prescribing information.	Treatment was permanently discontinued in patients who did not recover to Grade 1 or less, or baseline grade, within 14 days. In both treatment groups, treatment was continued until disease progression, intolerable AEs as judged by the investigator, or other reasons necessitating withdrawal; treatment beyond radiological progression was allowed in the case of continued clinical benefit as judged by the investigator.
	Gefitinib	Modifications in administration of gefitinib were allowed according to the summary of product characteristics or prescribing information or institutional guidelines. Treatment interruptions of up to 14 days were allowed but no dose reduction	

Study name	Treatment	Dosing details	Rules for stopping the study treatment
		schemes were specified according to the summary of product characteristics or prescribing information because gefitinib is only available in one dose formulation.	
Seto 2014	Erlotinib alone group	Dose reduction of erlotinib was allowed for up to two doses (100 mg/day and 50 mg/day) in a stepwise decrease. After two steps of dose reduction, erlotinib was discontinued. Patients who required suspension of erlotinib for more than 3 weeks consecutively, or of bevacizumab for more than 6 weeks from the date of previous administration, were discontinued from study treatment.	After two steps of dose reduction, erlotinib was discontinued. Patients who required suspension of erlotinib for more than 3 weeks consecutively, or of bevacizumab for more than 6 weeks from the date of previous administration, were discontinued from study treatment. In the erlotinib plus bevacizumab group, if either drug was discontinued, the other could be continued.
	Erlotinib + Bevacizumab group	The dose of bevacizumab was not to be reduced except when dose adjustment was needed because of change in body weight. Dose reduction of erlotinib was allowed for up to two doses (100 mg/day and 50 mg/day) in a stepwise decrease. After two steps of dose reduction, erlotinib was discontinued. Patients who required suspension of erlotinib for more than 3 weeks consecutively, or of bevacizumab for more than 6 weeks from the date of previous administration, were discontinued from study treatment. In the erlotinib plus bevacizumab group, if either drug was discontinued, the other could be continued.	
Wu 2014	Afatinib	Patients treated with afatinib 40 mg per day could have their dose increased to 50 mg per day from the second cycle to account for interpatient variability in afatinib exposure and to tailor dosing to individual tolerability. Dose escalation to 50 mg per day was allowed in the absence of predefined levels of toxic effects – i.e. rash, diarrhoea, mucositis, or any other treatment-related AE greater than Grade 1 in the first 21 days of treatment. After the first cycle of treatment, 38 of 239 (15·9%) patients in the afatinib group had their dose escalated to 50 mg per day. 67 of 239 (28·0%) patients in the afatinib group had their dose reduced to 30 mg, and 10 (4·2%) had further reductions to 20 mg. 16% patients had an afatinib dose escalation to 50mg; 27% of patients had 1 afatinib dose reduction and 65 had 2 dose reductions.	As per protocol, if the patient had any Grade 3 or higher treatment-related AE, prolonged Grade 2 diarrhoea (≥48 h), Grade 2 nausea or vomiting for 7 days or more consecutively despite appropriate supportive care, or Grade 2 or more worsening renal function, afatinib was withheld for up to 14 days until the severity fell to Grade 1 or less or to baseline levels. Afatinib could then be resumed at a lower dose (10 mg reductions to a minimum dose of 20 mg).
	Cisplatin + gemcitabine	For patients who had AEs related to gemcitabine and cisplatin, treatment was delayed or the dose was reduced (by 50% for nonhaematological toxic effects or 75% for haematological toxic effects as judged by the treating physicians) on the basis of the patient's tolerability and abnormal laboratory measurements, in accordance with the guidance in the current summary of product characteristics and institutional guidelines. Overall, 62 of 101 (61·4%) patients receiving more than one cycle of gemcitabine and cisplatin required dose delay.	Patients received six treatment courses unless they had disease progression or unacceptable AEs, or if the patient or investigator requested permanent discontinuation of study drug.
Yang 2014	Gefitinib	Patients with diarrhoea or skin reactions could be managed by providing a brief (614 days) therapy interruption followed by reinstatement of the 250-mg daily dose.	Gefitinib was administered until progression, discontinuation or death.
	Pemetrexed-cisplatin followed by gefitinib	After a maximum of six cycles of PC, nonprogressing patients received oral gefitinib (250mg/day) as maintenance therapy. For pemetrexed- and cisplatin-related toxicities, dose adjustments at the start of a	Patients who did not recover within 42 days were discontinued unless approved by the sponsor. Patients requiring a toxicity-related

Study name	Treatment	Dosing details	Rules for stopping the study treatment
		new cycle were based on the lowest haematological counts or maximum non-haematological toxicity from the preceding cycle. Treatment could be delayed for ≥42 days from Day 1 of cycles to allow time for recovery.	third dose reduction were discontinued from study therapy. Patients who had not progressed received gefitinib until progression, discontinuation, or death
Sequist 2013	Afatinib	Recommendations for management of AEs and dose reductions were provided to all investigators, including reduction of afatinib by 10-mg decrements down to 20 mg per day for treatment-related Grade 3 or selected prolonged Grade 2 AEs according to the National Cancer Institute CTCAE. Patients randomly assigned to afatinib were permitted to dose escalate to 50 mg daily after the first 21-day cycle if they did not experience rash, diarrhoea, mucositis, or any other drug-related AE > Grade 1 in severity. Dose reduction to less than 40mg per day was required for 120 patients (52%), with 43 (19%) having more than one dose reduction. Five patients erroneously began afatinib at 50mg/day, and 16 (7%)exercised the option to increase from 40 to 50mg/day after the first cycle.	Treatment continued until investigator-assessed progression.
	Cisplatin + pemetrexed	Eighteen patients (16%) had a chemotherapy dose reduction for AEs, and treatment administration was delayed by 6 days in 41 patients (40%).	
Chen 2012	Erlotinib	NR	NR
	Vinorelbine	The vinorelbine dose could increase to 80 mg/m^2 beginning from cycle 2 provided the patient did not suffer from any more than or equal to Grade 2 toxicity	
Gridelli 2012	Erlotinib	Erlotinib dose could be reduced up to two levels (100 mg at first reduction, 50 mg at second reduction) or could be interrupted for up to 2 weeks. Dose re-escalation was not permitted except in the case of erlotinib-related rash. Dose re-escalation was not permitted except in the case of erlotinib related rash	Stopped on failure. Failure was defined as progression, death, or any event that led to stopping erlotinib within 9 weeks from random assignment.
	Cisplatin + Gemcitabine	Dose reductions for chemotherapy were planned on Day 8 for Grade 2 neutropenia or thrombocytopenia, and chemotherapy was withheld for hematologic toxicity Grade ≥ 3. Dose reductions for Day 1 were not planned, but chemotherapy could be postponed for up to 14 days for persistent hematologic and nonhematologic toxicities grade≥ 2. Dose re-escalation was not permitted except in the case of erlotinib related rash	NR
Han 2012	Gefitinib	For patients receiving 250 gefitinib, no dose reduction was allowed, but dose interruption was used in case of toxicity (taken from supplementary)	All patients received treatment until disease progression, intolerable toxicity, or discontinuation for any other reasons including reaching the maximum number of chemotherapy cycles. Further therapy after progression of disease was at the physician's discretion.
	Cisplatin + Gemcitabine	Any patient who requires dose reduction on Day 1 of gemcitabine or cisplatin will continue to receive the dose for the remainder of the study. Any patient who has had two-Day 1 dose reductions and who experiences a toxicity that would cause a third dose reduction must be discontinued from study therapy. No dose escalation was allowed.	

Study name	Treatment	Dosing details	Rules for stopping the study treatment
Janne 2012	Erlotinib	Dose reductions for erlotinib were to 100 mg and 50 mg daily; one dose-level reduction was performed for Grade 3 rash or diarrhoea and Grade ≥2 conjunctivitis.	Erlotinib was discontinued for interstitial pneumonitis, Grade 4 diarrhoea or rash, and Grade ≥ 2 keratitis.
	Erlotinib+ carboplatin+ paclitaxel	Standard dose reductions were used for paclitaxel and carboplatin. Patients developing toxicity with paclitaxel and/or carboplatin had the option to continue one of the chemotherapy agents alone along with erlotinib or with erlotinib alone.	Erlotinib was discontinued for interstitial pneumonitis, Grade 4 diarrhoea or rash, and Grade ≥2 keratitis. Patients in arm B were required to have an absolute neutrophil count ≥1,500/mL and platelets ≥ 100,000/mL on Day 1 of each cycle; treatment could be delayed up to 2 weeks
Lee 2012	Erlotinib	The dose could be reduced to 100 mg, then 50 mg in cases of substantial toxic effects.	Treatment continued until disease progression, adverse side-effects judged by the treating clinician to warrant discontinuation, or patient withdrawal. The main reasons for stopping trial treatment were toxic effects or disease progression.
	Placebo	NR	NR
Rosell 2012	Erlotinib	NR	Erlotinib was continued until disease progression, development of intolerable toxic effects, or withdrawal of consent.
	Chemotherapy (cisplatin + docetaxel or gemcitabine)	NR	Chemotherapy was scheduled for four cycles unless development of intolerable toxic effects or disease progression occurred.
Zhang 2012	Gefitinib	Upon disease progression, patients were offered subsequent anticancer treatment at their physician's discretion.	Treatment continued until objective disease progression, intolerable toxic effects, dose delay or interruption for more than 14 days, withdrawal of consent, or serious non-compliance with study protocol.
	Placebo		
Fukuoka 2011	Gefitinib	NR	Treatment continued until progression of the disease, development of unacceptable toxic effects, a request by the patient or physician to discontinue treatment, serious noncompliance with the protocol, or completion of six chemotherapy cycles. Among patients assigned to gefitinib therapy, those whose tumour progressed were offered the opportunity to switch to treatment with carboplatin–paclitaxel; however, if the patient declined or was not a good candidate for that treatment, he or she could receive another approved therapy of the
	Carboplatin + Paclitaxel		

Study name	Treatment	Dosing details	Rules for stopping the study treatment
			physician's choice. Among patients who were receiving carboplatin–paclitaxel, further therapy after progression of the disease was at the physician's discretion.
Zhou 2011	Erlotinib	Dose reductions were in 50 mg increments, first to 100 mg, then to 50 mg, if needed, according to the protocol. Treatment interruption was allowed for a maximum of 3 weeks; after this period, the patient was discontinued from the study. Erlotinib dose adjustment or interruption was allowed after Grade 3 or 4 AEs. If interstitial lung disease (ILD) was suspected, study guidelines stated that treatment should be stopped immediately. If no ILD was confirmed, treatment with the study drug could be resumed. The minimum allowed dose of erlotinib was 50 mg/day; any patient receiving an erlotinib dose lower than 50 mg/day was withdrawn from the study. Dose reduction was necessary in five (6%) erlotinib-treated patients; treatment discontinuation was needed in one (1%) patient on erlotinib. Dose reduction due to an AE: 5 (6%) Dose reduction due to a drug-related AE: 5 (6%)	NR
	Carboplatin + gemcitabine	Dose reduction was necessary in 40 (56%) chemotherapy-treated patients; treatment discontinuation was needed in seven (10%) on chemotherapy. Dose reductions or treatment discontinuations were attributable to AEs, except for five patients in the chemotherapy group who discontinued for personal reasons (n=3), intolerable toxic effects (n=1), or at the judgment of the investigator (n=1). Dose reduction due to an AE: 38 (53%) Dose reduction due to a drug-related AE: 38 (53%)	NR
Cappuzzo 2010	Erlotinib	In case of AEs, dose reductions (in decrements of 50mg) and interruptions (for ≤2 weeks) were permitted, at the investigator's discretion. On disease progression, the choice of further therapy was at the investigator's discretion, and unblinding was permitted only if the investigator judged that an EGFR TKI was the only possible second-line treatment option. The sponsor remained blinded to this information. Most patients did not require dose reductions or interruptions. 70 patients (16%) receiving erlotinib required a dose reduction or interruption due to an AE, compared with 15 patients (3%) receiving placebo.	NR
	Placebo	Most patients did not require dose reductions or interruptions. 70 patients (16%) receiving erlotinib required a dose reduction or interruption due to an AE, compared with 15 patients (3%) receiving placebo.	
Mitsudomi 2010	Gefitinib	Treatment continued until progression of the disease, development of unacceptable toxic effects, a request by the patient to discontinue treatment, serious non-compliance with the protocol, or completion of three to six chemotherapy cycles. Further therapy after progression of the disease was at the physician's discretion.	NR

Study name	Treatment	Dosing details	Rules for stopping the study treatment
	Cisplatin + docetaxel	NR	NR
Goss 2009	Gefitinib + Best Supportive Care	Dose interruptions of up to 14 days were allowed to manage toxicity. All patients were observed for at least 2 months. Any patient who discontinued for reasons other than objective disease progression was to continue, where possible, to have objective tumour assessments every 6 weeks (including patients who subsequently started alternative anticancer therapies). Patients who had not progressed or died by the date of data cut-off were censored at their latest assessable objective tumour assessment, including patients lost to follow-up or who withdrew consent. Patients were to receive gefitinib or placebo until clinical (in the opinion of the investigator non-measurable lesion(s) or deterioration in health such that the patient could not complete objective assessment) or objective (radiological) progression (by RECIST), unacceptable toxicity, or patient withdrawal.	NR
	Best Supportive Care + placebo		NR
Lilenbaum 2008	Erlotinib	Dose modifications for erlotinib included one reduction to 100 mg for Grade 3 or greater diarrhoea and/or Grade 2 or greater skin rash. Further reductions were not allowed.	The need for palliative radiation was considered as indicative of progression, and such patients were discontinued from the study.
	Carboplatin+ paclitaxel	For chemotherapy, the first dose reduction was to carboplatin AUC 5 and paclitaxel 175 mg/m^2; the second to AUC 4 and 150 mg/m^2, respectively. Further reductions were not allowed.	

Key: AE, adverse event; AUC, area under the curve; CTCAE, Common Terminology Criteria for Adverse Events; NR, not reported; RECIST, Response Evaluation Criteria in Solid Tumors; TKI, tyrosine kinase inhibitor.

D.1.7 Quality of life

Data for QoL outcomes for European Organization for Research and Treatment of Cancer (EORTC) questionnaires are provided in Table 108.

None of the studies used the 36-Item Short Form Survey (SF-36) for the measurement of QoL.

EORTC QLQ C-30

The EORTC 30-item core Quality of Life Questionnaire (QLQ-C30) is a multidimensional, cancer-specific, self-administered questionnaire. The QLQ-C30 comprises 30 questions across five functional scales (physical, role, cognitive, emotional and social), three symptom scales (fatigue, pain, and nausea/vomiting), a global health status (GHS)/QoL scale and various single items (e.g. dyspnoea, diarrhoea). QoL scores using EORTC-QLQ-C30 were reported in four studies.[102, 176, 177, 185]

In the First-SIGNAL study, significant differences in the pain subscale (p=0.049) were observed that favoured gefitinib. However, no significant differences between the treatment arms were observed for the GHS/QoL and dyspnoea subscales.[185] In LL3, afatinib showed significantly better mean scores over time in GHS/QoL (p=0.015) compared with cisplatin plus pemetrexed. Patients with progression consistently experienced poorer QoL than patients without disease progression. There was no significant difference between the treatment groups with respect to the estimates of the effects of progression in each treatment group separately, obtained from mixed-effects longitudinal models (GHS: -4.65 and -4.34 for afatinib and cisplatin plus pemetrexed, respectively; p=0.85).[176] In LL6, GHS/QoL was significantly improved in the afatinib group compared with the cisplatin plus gemcitabine group, p<0.0001.[177] In ARCHER 1050, the overall improvement in GHS/QoL from baseline was significantly greater with gefitinib compared with dacomitinib; 4.94 versus 0.20, p<0.0002 in patients wuth L858R mutations.

EORTC-QLQ-LC13

The EORTC Quality of Life Questionnaire Lung Cancer 13 (QLQ-LC13) is the lung cancer-specific module of EORTC QLQ C30. The QLQ-LC13 comprises 13 questions across one multi-item scale to assess dyspnoea and various other single items (e.g. chest pain, cough, sore mouth). None of the studies assessed QoL using QLQ-LC14 questionnaire.

QoL data for EORTC-QLQ-LC13 were reported in five studies.[102, 176-178, 185] In LL3, mean scores over time significantly favoured afatinib compared with chemotherapy for cough (p <0.0001) and dyspnoea (p <0.0001), as well as for the individual item of dyspnoea, but not for pain.[176] Similarly, in LL6, afatinib significantly improved mean scores over time compared with gemcitabine and cisplatin for cough, dyspnoea and pain (p<0.05).[177]

In both TORCH and First-SIGNAL, there were no significant differences between symptoms such as dyspnoea, coughing, pain in chest, arm or shoulder, in other parts and pain medication.[178, 185]

In ARCHER 1050, mean overall improvement from baseline in the lung cancer symptom of pain in chest was significantly greater with dacomitinib than with gefitinib; -10.24 versus -7.44, p=0.02. In other scales such as dyspnoea, cough, pain in arms or shoulder, the overall improvement was numerically greater with dacomitinib than with gefitinib.[102]

EQ-5D

In EuroQol (EQ-5D®), utility scores range from 0 (worst health) to 1 (full health) and visual analogue scale (VAS) scores range from 0 (worst imaginable) to 100 (best imaginable) health states.

In LL7, QoL was assessed using EQ-5D utility and VAS scores. There was no significant clinically meaningful difference in mean EQ-5D baseline to post-baseline between afatinib and gefitinib (afatinib: 0.72 to 0.77 and gefitinib: 0.73 to 0.80; p=0.142). Similarly, there was also no significant clinically meaningful difference in mean VAS scores between the two treatment arms (afatinib: 69.7 to 74.5 and gefitinib: 71.2 to 76.0; p=0.2).[118]

In LL3, estimates of the effects of progression in each treatment group obtained from a mixed-effects longitudinal model showed no significant differences between afatinib and cisplatin plus pemetrexed as measured by both EQ-5D utility (-0.068 vs -0.046; p=0.34) and EQ VAS (-4.0 vs -2.74; p=0.33).[176]

FACT-L questionnaire

The Functional Assessment of Cancer Therapy-Lung (FACT-L) questionnaire incorporates a number of general questions across the domains of physical well-being (including pain, nausea and fatigue), social/family well-being, emotional well-being (including depression and anxiety) and functional well-being (including sleep).

The FACT-L questionnaire was used in four studies to measure QoL.[173, 180, 181, 184] In IPASS, rates of improvement significantly favoured gefitinib over carboplatin plus paclitaxel (70.2% versus 44.5%; p<0.001).[184] In the study by Seto et al., FACT-L scores were not significantly different between erlotinib and erlotinib plus bevacizumab, and addition of bevacizumab did not significantly impact QoL.[173] However, in the ENSURE study, it was observed that erlotinib was associated with improved FACT-L scores compared with cisplatin plus gemcitabine.[180] In the OPTIMAL study, erlotinib provided clinically relevant improvements in QoL (improvement of ≥6 points) compared with carboplatin plus gemcitabine, with the difference reaching statistical significance at cycle 2 for physical well-being (p=0.0032), emotional wellbeing (p=0.0357) and lung cancer subscale (p=0.0041).[181]

Table 108: Quality of life outcomes in RCTs

Study name (Trial name/ NCT)	Intervention Comparator	Time point (Assessor)	Number of patients	EORTC-QLQ-C30	EORTC-QLQ-LC13/ LC14
Wu 2017 (ARCHER 1050/ NCT01774721)	Dacomitinib	Endpoint (NR)	227	Composite endpoint of pain, dyspnoea, fatigue or cough and its individual symptoms items: HR (95% CI)*; p value compared to gefitinib: Composite (pain, dyspnoea, fatigue, cough): 0.99 (0.81–1.20); 0.8901 Pain (chest; arm or shoulder): 0.89 (0.70–1.14); 0.8901 Dyspnoea: 0.85 (0.66–1.09); 0.7189 Fatigue: 0.96 (0.76–1.21); 0.8901 Cough: 0.75 (0.55–1.03); 0.3769	NR
	Gefitinib		225		NR
Wu 2014 (LUX-Lung 6/ NCT01121393)	Afatinib	Baseline (NR)	242	Mean (SD): Short of breath (N:229): 26 (23) Pain (N:232): 24 (22)	Mean (SD): Cough: 37 (24) Dyspnoea: 25 (19) Pain in chest: 22 (22)
	Cisplatin + gemcitabine		122	Mean (SD): Short of breath (N:109): 23 (23) Pain (N:109): 23 (23)	Mean (SD): Cough: 29 (26) Dyspnoea: 24 (21) Pain in chest: 21 (23)
	Afatinib	Endpoint (cut-off date Oct 29, 2012) (NR)	242	Differences in mean scores over time for GHS/QoL and functioning scores favours afatinib GHS/QoL: Adjusted mean difference (N:364) GHS/QoL: - 8.8 Functional scales Physical: -9.4 Role: -8.1 Emotional: -5.6 Cognitive: -5.9 Social: -10.5 GHS/ QoL was significantly improved in afatinib treated patients compared with chemotherapy across all prespecified analyses. More patients treated with afatinib vs cisplatin/gemcitabine showed improvements in GHS/QoL (p<0.0001) and physical (p<0.0001), role (p=0.013), and social (p<0.001) functioning	HR; 95% CI: Cough: 0.5 (0.30–0.69); p=0.0001 Dyspnoea: 0.5 (0.40–0.73); p<0.0001 Pain in chest: 0.7 (0.51–0.96); p=0.03
	Cisplatin + gemcitabine		122		NR

Study name (Trial name/ NCT)	Intervention Comparator	Time point (Assessor)	Number of patients	EORTC-QLQ-C30	EORTC-QLQ-LC13/ LC14
				scales, and the symptom of fatigue (77.2% vs 52.5%; p<0.0001).	
Sequist 2013 (LUX-Lung 3/ NCT00949650)	Afatinib	Baseline (NR)	Unclear	NR	Mean (SD): Cough: 35 (26) Dyspnoea: 23 (19) Pain in chest: 26 (24)
	Cisplatin + pemetrexed		Unclear	NR	Mean (SD): Cough: 33 (25) Dyspnoea: 25 (24) Pain in chest: 24 (26)
	Afatinib	Endpoint (IRC)	Unclear	-4.65; p=0.85 Compared with afatinib, a greater percentage of chemotherapy treated patients had worsening of fatigue (25% vs 39%, respectively) and nausea (42% vs 61%, respectively), whereas more patients on afatinib had worsening of diarrhoea (83% vs 24%, respectively), sore mouth (81% vs 61%, respectively), and dysphagia (57% vs 38%, respectively. Longitudinal analysis results were also consistent (worse scores for fatigue, nausea, appetite, and constipation with chemotherapy and worse scores for diarrhoea, dysphagia, and sore mouth with afatinib; all p<0.001). In addition, significant improvements were observed for afatinib in the longitudinal analysis of individual items related to exercise and activity, such as strenuous activity (-5.69, p<0.001), long walk (-7.22, p<0.001), short walk (-4.17, p=0.008), and leisure activities (-6.52, p<0.001). In the corresponding longitudinal analysis, patients on afatinib had significantly better mean EORTC scores over time for GHS/QoL, physical role, and cognitive functioning.	HR; 95% CI: Cough: 0.6 (0.41–0.87); p=0.007 Dyspnoea rested: 0.8 (0.55–1.21); p=0.304 Dyspnoea walked: 0.6 (0.44–0.89); p=0.008 Dyspnoea stairs: 0.6 (0.46–0.91); p=0.011 Pain in chest: 0.6 (0.45–0.94); p=0.023
	Cisplatin + pemetrexed		Unclear	-4.3	NR
	Afatinib	Endpoint (Investigator)	Unclear	-5.8; p=0.72	HR; 95% CI: Cough: 0.60 (0.41–0.87); p=0.007 Dyspnoea: 0.68 (0.50–0.93); p=0.01 Mean scores over time significantly favoured afatinib compared with chemotherapy for

Study name (Trial name/ NCT)	Intervention Comparator	Time point (Assessor)	Number of patients	EORTC-QLQ-C30	EORTC-QLQ-LC13/ LC14
					cough (p <0.0001) and dyspnoea (p <0.0001) as well as for the individual item of dyspnoea, but not for pain
	Cisplatin + pemetrexed		Unclear	-5.2	NR
Han 2012 (First-SIGNAL/ NCT00455936)	Gefitinib	Endpoint (NR)	26	Pain: p=0.049 Insomnia: p=0.017 Significant differences in the evolution of pain (p=0.049) Insomnia (p=0.017) functions were reported in favour of gefitinib for EGFR mutant patients. No significant difference between GHS/QoL, physical, role, emotional, cognitive, social functions, fatigue, nausea and vomiting, dyspnoea, appetite loss, constipation, diarrhoea, and financial difficulties symptoms.	NR
	Cisplatin + gemcitabine		16	NR	NR

Key: BSC, best supportive care; CI, confidence interval; GHS, global health status; HR, hazard ratio; NR, not reported; PBO, placebo; QoL, quality of life; SD, standard deviation.

D.1.8 Quality assessment using NICE checklist

The results of RCT quality assessment using the NICE checklist are provided in Table 109.

Table 109: Results of NICE checklist for RCTs

Study name (Trial name/ NCT)	1	2	3	4	5	6	7
Soria 2018 (FLAURA/ NCT02296125)	Yes	No	Yes	Yes	No	No	Yes
Goldberg 2016 (SWOG S1403/ NCT02438722)*	Unclear	Unclear	Unclear	No	Unclear	Unclear	Unclear
Han 2017 (NCT02148380)	Yes	No*	Yes	No	No	No	Yes
Leighl 2017	No*	No*	Yes	Yes	No	No	Yes
Patil 2017 (CTRI/2015/08/006113)	Yes	No	No	No	No	Yes	Yes
Scagliotti 2017 (Balise/ NCT01897480)	Unclear	Unclear	Unclear	No	Unclear	Unclear	Yes
Wu 2017 (ARCHER 1050/ NCT01774721)	Yes	Yes	Yes	No	No	No	Yes
Yang 2017 (ChiCTR-IOR-14005679)	Yes	Yes	Yes	Yes	No	No	Yes
Yang 2017 (CTONG 0901/ NCT01024413)	No*	No*	Yes	No	No	No	Yes
Zhao 2017 (NCT01131429)	No*	No*	Yes	No	No	No	Yes
An 2016	No*	No*	Yes	Yes	No	No	Yes
Cheng 2016 (NCT01469000)	Yes	Yes	Yes	No	No	No	No
Mok 2016 (P06162/ NCT01039948)	No*	No*	Yes	No	No	No	Yes
Park 2016 (LUX-LUNG 7/ NCT01466660)	Yes	Yes	Yes	No	No	No	Yes
Singh 2015	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Wu 2015 (ENSURE/ NCT01342965)	Yes	No*	Yes	No	No	No	Yes
Seto 2014 (JO25567/ JapicCTI-111390)	Yes	Yes	Yes	No	No	No	No
Wu 2014 (LUX-Lung 6/ NCT01121393)	Yes	Yes	Yes	No	No	No	Yes
Yang 2014 (NCT01017874)	Yes	Yes	Yes	No	No	No	Yes
Sequist 2013 (LUX-Lung 3/ NCT00949650)	Yes	Yes	Yes	No	No	No	Yes
Chen 2012 (NCT01196078)	Yes	No*	Yes	No	No	No	Yes
Gridelli 2012 (TORCH/ NCT00349219)	Yes	Yes	Yes	No	No	No	Yes
Han 2012 (First-SIGNAL/ NCT00455936)	Yes	No*	Yes	No	No	No	No
Janne 2012 (CALGB 30406/ NCT00126581)	No*	No*	Yes	No*	No	Yes	Yes
Lee 2012 (TOPICAL/ NCT00275132)	Yes	Yes	Yes	Yes	No	Yes	Yes
NCT00294762 2012	Unclear	Unclear	Unclear	No	Unclear	Unclear	Unclear
Rosell 2012 (EURTAC/ NCT00446225)	Yes	Yes	Yes	No	No	No	Yes
Zhang 2012 (INFORM; C-TONG 0804/ NCT00770588	Yes	Yes	Yes	Yes	No	No	Yes
Fukuoka 2011 (Iressa Pan-Asia Study (IPASS)/ NCT00322452)	Yes	Yes	Yes	No	No	No	Yes
Hirsch 2011	Yes	Yes	Yes	No*	No	No	No
Zhou 2011 (OPTIMAL; CTONG-0802/ NCT00874419)	Yes	Yes	Yes	No	No	Yes	No
Cappuzzo 2010 (SATURN; BO18192/ NCT00556712)	Yes	Yes	Yes	Yes	No	No	Yes
Maemondo 2010 (NEJ002/ UMIN-CTR number, C000000376)	No*	No*	Yes	No*	No	No	No

Study name (Trial name/ NCT)	1	2	3	4	5	6	7
Mitsudomi 2010 (WJTOG3405/ UMIN number 000000539)	Yes	Yes	Yes	No*	No	No	No
Goss 2009 (INSTEP/ NCT00259064)	Yes	Yes	Yes	Yes	No	Yes	Yes
Crino 2008 (INVITE/ NCT00256711)	No*	No*	Yes	No	No	No	Yes
Lilenbaum 2008 (NCT00085839)	No*	No*	Yes	No	No	No	Yes

Notes: 1. Was randomisation carried out appropriately?

2. Was the concealment of treatment allocation adequate?

3. Were the groups similar at the outset of the study in terms of prognostic factors?

4. Were the care providers, participants and outcome assessors blind to treatment allocation?

5. Were there any unexpected imbalances in drop-outs between groups?

6. Is there any evidence to suggest that the authors measured more outcomes than they reported?

7. Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?

* Full text publications were available for these studies however, this information was not reported and thus has been marked as No

Selection bias

The method of randomisation was not reported in nine studies.[15, 163, 165, 167, 170, 182, 183, 189, 271] In four studies, the method of randomisation was unclear as the available publication was a conference abstract for three of these[172, 175, 186] and one study was extracted from clinical trial.gov only.[169] In the remaining 24 studies, randomisation was carried out appropriately. The most commonly used methods of randomisation were interactive voice response system, central randomisation and stratified randomisation.

Adequate methods for the concealment of treatment allocation were used in 19 studies. However, the method of allocation concealment was not reported in 14 studies.[15, 163-165, 167, 170, 180, 182, 183, 185, 188, 189, 195, 271] The method used for allocation concealment was unclear in four studies as only conference abstracts were available for three of them[172, 175, 186] and one study was extracted from clinical trial.gov.[169]

For 33 studies, the treatment groups were similar in terms of demographic characteristics at study outset. However, in two studies, the authors reported an imbalance in ECOG PS[170, 177], and in two studies an imbalance in mutation types was reported[62, 177] between the treatment groups. In the study by Patil et al., gender distribution was not balanced between the two treatment arms.[187] In the three other studies, the information on patient demographics was unclear as the available publication was a conference abstract; thus, limited information was available.[172, 175, 186] In the study extracted from clinicaltrials.gov, the available information was suggestive that the treatment groups were similar in terms of demographic characteristics at study outset; however, it was unclear as the full text publication was not available.[169]

Performance and detection bias

Eight studies were double blind, i.e. the study personnel were blinded to the treatment.[164, 165, 167, 190-194] In the study by Leighl et al., it was reported that the trial was unblinded after randomisation due to the inferiority in the linsitinib arm.[165] Also, 25 studies were open-label, and blinding status was not reported in three studies[15, 170, 171] and was unclear in the study by Singh et al. as only a conference abstract was available.[186] Across six of the 25 open-label studies, it was reported that the outcome assessors/reviewers were blinded.[102, 118, 173, 176, 177, 185] In the NEJ002 study, it was reported that treatment response and PFS were determined by external review of the CT films by experts who were not aware of the treatment assignments.[15] In IPASS, although the study was open-label, the EGFR mutation status was not known by either the patients or the clinicians during the conduct of the study, and thus would not have affected the efficacy outcomes.[184]

Like IPASS, the study by Janne et al. also reported that the mutation analyses were blinded to the participants' clinical outcome, although information on blinding was not reported.[170] The study by Hirsch et al. did not provide any information regarding blinding, although it was a full-text publication.[171]

Attrition bias

No unexpected imbalances in drop-outs between arms were reported in 33 studies. Information regarding drop-outs was unclear in four studies, as only conference abstracts were available for three of these[172, 175, 186] and one study was extracted from clinicaltrials.gov only.[169]

Reporting bias

In 28 studies, there was no evidence to suggest that the authors measured more outcomes than reported. In four studies, it was unclear whether the authors reported all outcomes they measured, as only conference abstracts were available for three of these studies.[172, 175, 186] and as the other study was extracted from clinicaltrials.gov only.[169] In five other studies, more outcomes may have been measured than reported.[170, 181, 187, 191, 193]

In 27 studies, the analysis included an intent-to-treat (ITT) analysis. Also, across these 27 studies, safety analysis included modified intent-to-treat (mITT) analysis in 14 studies.[102, 165, 168, 170, 176-180, 184, 189-191, 271] In seven other studies, both efficacy and safety analyses included mITT analyses.[15, 62, 166, 171, 173, 181, 185] The population analysed was unclear in three studies, as only conference abstracts were available for two of these[175, 186] and one study was extracted from clinicaltrials.gov only.[169]

D.2 Results from non-randomised studies

D.2.1 Overview of studies

Thirty-eight studies were included in this review, which are presented in Table 110. These included 35 retrospective observational studies, two non-randomised clinical trials[386, 387] and one prospective observational study.[388]

Across these studies, 14 studies were head-to-head trials comparing erlotinib with gefitinib.[386, 389-401] Eight studies assessed three TKIs: erlotinib, gefitinib and afatinib.[388, 402-408]

In two studies, gefitinib/erlotinib/afatinib were compared with chemotherapy[409, 410], while in one other study, these were compared with dacomitinib.[411] One study each evaluated a TKI (erlotinib/gefitinib) versus ginsenoside[412],versus chemotherapy[413] and versus afatinib[414].

In two studies, gefitinib was compared to gefitinib plus platinum-based chemotherapy[415] and platinum doublet chemotherapy with/without bevacizumab.[416]

One study assessed erlotinib versus chemotherapy[417]; three studies assessed gefitinib versus a platinum doublet chemotherapy regimen[418-420]; one study assessed gefitinib and afatinib[421]; and two studies assessed gefitinib, erlotinib and icotinib.[422, 423] In the AURA trial, two doses of osimertinib (80mg and 160mg) were compared[387], in which first-line treatment was administered to the expansion cohort only.

Of the two non-randomised studies, only AURA was open-label.[387] No information regarding blinding was provided in the other study by Udupa et al.[386] The other 36 studies were retrospective/prospective observational studies. However, in one study it was reported that the matching procedure was conducted blindly, without any information about patient outcomes.[417]Cross-over occured post-progression in two studies.[395, 399]

All studies were active controlled, with a majority of studies reporting data for PFS and OS (23 studies each) followed by response rate (18 studies).

One study by Kashima et al. assessed all patients with brain metastases at study entry.[395]

In this section, only the studies reporting efficacy/safety outcomes are presented in tables. For the non-randomised trials – except AURA and the study by Udupa et al.[386, 387], which were nRCTs – all were observational studies, and so the type of assessment was not reported.

Table 110: Comparative summary of trial methodology of non-randomised studies

Study name	• Line of therapy (%)* • EGFR mutation (%)*	Blinding	Study setting Study country	Number enrolled/ screened	Treatment	Median length of follow-up (weeks)	List of outcomes reported in the study	Subgroup details	Secondary publications
Arriola 2018[413]	• 92.8 • 79.8	NR	• Multi-centre • Spain	168	• Gefitinib • Erlotinib • CT • CT followed by TKI	• 57.63 (range 1.73–164.66) weeks	• Management patterns of EGFR positive patients • ORR • DCR • PFS • 1-year PFS rate • OS • 1-year OS rate	• NR	Arriola 2014[424]
Corre 2018[405]	• 83.2 • 100	NR	• Multi-centre • France	114	• Gefitinib • Erlotinib • Afatinib	• NR	• OS* • PFS	• NR	Corre 2017[425]
Hung 2018[406]	• 100 • 100	NR	• Single-centre • Taiwan	131	• Gefitinib • Erlotinib • Afatinib	• NR	• Response rate	• NR	NL
Yang 2018[388]	• 80.5 • 100	NR	• Single-centre • Taiwan	344	• Afatinib • Erlotinib • Gefitinib	• NR	• PFS	• Patients with newly diagnosed lung cancer • Patients with common EGFR mutations	NL
Barnet 2017[411]	• 100 • 100	NA	• Single-centre • Australia	477	• Dacomitinib • Erlotinib • Gefitinib • Afatinib	• NR	• CR	• NR	NL
Frega 2017[410]	• 100 • 95.6	NR	• Single-centre • Italy	23	• Gefitinib • Erlotinib • Afatinib • CT	• 38 weeks	• Best response • Safety	• Response and survival for rare mutations in exon 18; exon 19; exon 20; complex mutation • Multivariate and univariate analysis data	Pasello 2016[426]
He 2017[415]	• 100 • 100	NR	• NR • NR	65	• Gefitinib	• NR	• PFS* • ORR	• NR	NL

Study name	• Line of therapy (%)* • EGFR mutation (%)*	Blinding	Study setting Study country	Number enrolled/ screened	Treatment	Median length of follow-up (weeks)	List of outcomes reported in the study	Subgroup details	Secondary publications
					• Gefitinib + pemetrexed/ gemcitabine and platinum		• OS • Toxicity		
Hsia 2017[420]	• 100 • 100	NA	• NR • Taiwan	240	• Gefitinib • Platinum-based CT	• NR	• OS	• NR	NL
Koyama 2017[401]	• 100 • 100	NA	• NR • Japan	104	• Erlotinib • Gefitinib	• NR	• Time to failure • Median survival time (MST) • Median CNS-PFS	• NR	Saida 2017[427]
Kuan 2017[403]	• 100 • 44.5	NR	• Single-centre • Taiwan	1006	• Gefitinib • Erlotinib • Afatinib	Median duration of follow-up for PFS • Gefitinib: 52.43 weeks (IQR: 23.65–70.95) • Erlotinib: 48.53 weeks (IQR: 21.07–71.81) • Afatinib: 44.63 weeks (IQR: 30.1–61.06)	• PFS	• EGFR mutation (exon 19 del and L858R) • Baseline brain metastases (absence and presence) • ECOG PS (0 and 1; and >1) • Gender • Age (<65 yrs and ≥65 yrs) • Smoking (never and current or ever)	NL
Li 2017[409]	• 100 • 100	NR	• Multi-center • US	886	• Gefitinib • Erlotinib • Afatinib • CT	• NR	• Time to next treatment	• NR	NL
Li 2017[399]	• 100 • 100	NR	• Multi-centre • China	358	• Erlotinib • Gefitinib	Cut-off date: December 31, 2014)	• OS • PFS	• Patients without cerebral metastasis	NL

Study name	• Line of therapy (%)* • EGFR mutation (%)*	Blinding	Study setting Study country	Number enrolled/ screened	Treatment	Median length of follow-up (weeks)	List of outcomes reported in the study	Subgroup details	Secondary publications
						• 171 surviving patients (erlotinib: 73; gefitinib: 98); median follow-up: 95.33 weeks (range, 13–424.67 weeks)	• Time to neurological progression • Incidence rates of cumulative CNS progression with EGFR mutations in response to first-line treatment with EGFR-TKI • Related death risk of CNS progression after EGFR-TKI	prior to EGFR-TKIs first-line treatment • Patients with cerebral metastasis prior to EGFR-TKIs first-line treatment	
Ramalingam 2017[387]	• 100 • 100	Open label	• Multi-centre international • US, Australia, France, Germany, Italy, Japan, Republic of Korea, Spain, Taiwan, UK	60	• Osimertinib: 80mg • Osimertinib: 160mg	Cut-off date: 1 November 2016 • median length of follow-up: 82.77 weeks • Osimertinib 80mg: 73.66 weeks • Osimertinib 160 mg: 83.63 weeks	• ORR • DCR • DOR • PFS • Safety • Tolerability	• EGFR mutation (Exon 19 vs L858R vs other)	Yang 2015[428], Ramalingam 2016[429], Ramalingam 2015[430]
Shen 2017[403]	• 89.2 • 100	NR	• Single-centre • China	56	• Afatinib • Gefitinib/Erlotinib	• NR	• Response rate	• Exon 20 insertion	NL
Skrickova 2017[408]	• 100 • 100	NR	• NR • Czech Republic	287	• Gefitinib • Afatinib • Erlotinib	• NR	• Response rate • DCR	• NR	NL

Study name	• Line of therapy (%)* • EGFR mutation (%)*	Blinding	Study setting Study country	Number enrolled/ screened	Treatment	Median length of follow-up (weeks)	List of outcomes reported in the study	Subgroup details	Secondary publications
Tu 2017[407]	• 100 • 100	NR	• Single-centre • Taiwan	467	• Gefitinib • Erlotinib • Afatinib	• NR	• TTF	• TTF based on mutation types (Exon 19 del, L858R and uncommon) • Dose (30 mg vs 40 mg)	NL
Udupa 2017[386]	• 100 • 100	NR	• Single-centre • India	85	• Erlotinib • Gefitinib	• NR Note: Patients were followed up for every month till disease progression	• Safety	• NR	NL
Wang 2017[400]	• NR (only mentioned first line) • 85.7	NA	• NR • China	602	• Erlotinib • Gefitinib	• NR	• Survival	• NR	NL
Wang 2017[404]	• 100 • 100	NR	• NR • Taiwan	104	• Afatinib • Erlotinib • Gefitinib	• NR	• Response rate • OS • PFS	• Age <65; ≥ 65 • Gender: Male; female • Smoking: Ever smoker; Never smoker • Mutation type: L858R; Deletion 19 • Stage: IIIb; IV • Drug: Gefitinib; Erlotinib; Afatinib • Liver metastasis Bone metastasis Brain metastasis Lung to lung metastasis • Malignant PE Presence of PE	NL

Study name	• Line of therapy (%)* • EGFR mutation (%)*	Blinding	Study setting Study country	Number enrolled/ screened	Treatment	Median length of follow-up (weeks)	List of outcomes reported in the study	Subgroup details	Secondary publications
Batra 2016[392]	• 100 • 100	NR	• Single-centre • India	43	• Erlotinib • Gefitinib	• NR	• PFS	• Gender • Mutations (exon 19 del vs exon 21 mutation) • Presence of BM (with vs without)	NL
Guerreiro 2016[393]	• 100 • 100	NR	• Single-centre • Portugal	86	• Erlotinib • Gefitinib	Cut-off date: May 2016 • 47.67 weeks	• OS • PFS • ORR	NR	NL
Inoue 2016[416]	• 100 • 100	NR	• Multi-center • Japan	1660	• Gefitinib • Platinum-doublet CT ± BV	• NR	• OS • Prognostic factors, real-world treatment patterns • Efficacy of gefitinib	• NR	Yoshida 2016[431], Yoshioka 2016[432], Yoshida 2017[433]
Ito 2016[115]	• 100 • 100	NR	• Multi-centre • Japan	Screened: 310 Enrolled: 145	• Afatinib • Gefitinib • Erlotinib	• NR	• TTF • OS • Response rate	• Presence of BM (with vs without)	NL
Jiang 2016[394]	• 100 • 100	NR	• Single-centre • China	623	• Erlotinib • Gefitinib	Cut-off date: March 31, 2016 • NR	• PFS • ORR	• Gender • Age (≤61 yrs. vs >61 yrs.) • Smoking (never vs current vs former) • Disease stage (IIIb vs IV) • PS (0–1 vs 2–3) • Mutation (exon 19 del vs L858R) • p16 HD (negative vs positive)	NL
Kashima 2016[395]	• 100 • 100	NR	• Single-centre • Japan	269	• Erlotinib • Gefitinib	• NR	• OS	NR	NL

Study name	• Line of therapy (%)* • EGFR mutation (%)*	Blinding	Study setting Study country	Number enrolled/ screened	Treatment	Median length of follow-up (weeks)	List of outcomes reported in the study	Subgroup details	Secondary publications
Li 2016[412]	• 100 • 100	NR	• Multi-centre • China	720	• Erlotinib • Erlotinib + ginsenoside • Gefitinib or icotinib • Gefitinib or icotinib + ginsenoside	• 99.157	• PFS • OS • ORR • Side effects	• Gender • Age (≤ 58 yrs. or >58 yrs.) • Smoking (ever or current, never) • ECOG PS (0–1 or 2) • Disease stage (IIIb or IV) • Subtype (adenocarcinoma or non- adenocarcinoma) • Mutation (exon 19 del or L858R or unrecorded EGFR mutation sites)	NL
Liu 2016[417]	• 51.2 • 100	Single blind	• Single-centre • China	2,270	• Erlotinib • CT	• 93.16	• Time to BM • Incidences of BM within 2 yrs. • OS • 2-year survival rates	• Line of treatment (first or second) • Disease stage (IIIB or IV) • Mutation (exon 19 del or L858R)	NL
Lv 2016[422]	• 48.4 • 48.4	NR	• Single-centre • University of Malaya Medical Centre	Enrolled: 192	• Gefitinib • Erlotinib • Icotinib	• NR	• PFS • Response rate	• Gender • Age (≤61.8yrs or >61.8yrs) • Smoking (yes or no) • ECOG PS (0–1 or 2) • Disease stage (IIIB or IV) • HDL-C (≤0.945 or >0.945mmol/L) • Mutation (Exon 19, Exon 21, Exon 19+21)	NL
Shee 2016[396]	• 100 • 100	NR	• Single-centre • China	98	• Gefitinib • Erlotinib	• NR	• PFS • OS • ORR	NR	NL

Study name	• Line of therapy (%)* • EGFR mutation (%)*	Blinding	Study setting Study country	Number enrolled/ screened	Treatment	Median length of follow-up (weeks)	List of outcomes reported in the study	Subgroup details	Secondary publications
							• DCR		
Suh 2016[397]	• 100 • 100	NR	• Single-centre • Korea	151	• Erlotinib • Gefitinib	• NR	• PFS • OS	• Age (<65 or ≥65yrs) • Gender • ECOG PS (0 or 1/2 or 3) • Smoking (never smoker/ever-smoker) • Neuron-specific enolase (normal/ elevated) • CNS metastasis at diagnosis (Yes or no) • Mutation (Exon 19 del or L858R) • Subsequent chemotherapy regimen among the patients with elevated neuron-specific enolase	NL
Wu 2016[421]	• 100 • 100	NR	• Single-centre • Taiwan	189	• Gefitinib • Afatinib	• NR	• OS • Maximal tumour shrinkage	NR	NL
Yoshida 2016[398]	• 100 • 100	NR	• Single-centre • NR	175	• Gefitinib • Erlotinib	• NR	• PFS • OS	• CNS progression (with or without)	NL
Yu 2016[423]	• 52.6 • 100	NR	• Single-centre • China	1127	• Erlotinib • Gefitinib • Icotinib	Cut-off date: September 2014 • median PFS (entire cohort): 54.16 weeks (95% CI, 48.16–58.91 weeks).	• OS • PFS • ORR • DCR • Best response • Association of the EGFR mutations with the multiple genes	• Mutation (exon 19 del or L858R)	NL

Study name	• Line of therapy (%)* • EGFR mutation (%)*	Blinding	Study setting Study country	Number enrolled/ screened	Treatment	Median length of follow-up (weeks)	List of outcomes reported in the study	Subgroup details	Secondary publications
Zhang 2015[391]	• 44.1 • 44.1	NR	• Single-centre • China	136	• Erlotinib • Gefitinib	Cut-off date: January 2015 • Unclear	• PFS • OS • Response rate • DCR	• Patients with adenocarcinoma • According to EGFR mutation status	NL
Lin 2014[390]	• 100 • 100	NR	• Single-centre • China	99	• Erlotinib • Gefitinib	• Cut-off date: January 31, 2014 (approx. 104 weeks)	• PFS • OS	• Age (<65 or ≥65 yrs) • Gender • ECOG PS (<2 or ≥2) • Mutation (L858R or Exon 19 del) • Subtype (non-squamous cell carcinoma or squamous cell carcinoma) • Neutrophil-lymphocyte ratio (<3.5 or ≥3.5)	NL
Lee 2013[389]	• 100 • 100	NR	• NR • China	452	• Erlotinib • Gefitinib	• Cut-off date: May 31, 2012 • median follow-up: 200.2 weeks (range, 3.12–312.43 weeks)	• PFS • OS • ORR	• EGFR mutations	NL
Verduyn 2012[419]	• 100 • 100	NR	• Single-centre • Netherlands	NR	• Gefitinib • Carboplatin + paclitaxel • Cisplatin + gemcitabine • Cisplatin + pemetrexed	• NR	• PFS	NR	NL
Yoshida 2010[418]	• 100 (of the EGFR+ population	NR	• Single-centre • Japan	100	• Gefitinib • Cytotoxic CT	• Median follow-up time for the	• ORR • DCR • PFS	• EGFR mutation (yes or no)	NL

Study name	• Line of therapy (%)* • EGFR mutation (%)*	Blinding	Study setting Study country	Number enrolled/ screened	Treatment	Median length of follow-up (weeks)	List of outcomes reported in the study	Subgroup details	Secondary publications
	• 48					survivors: 87.53 weeks (range 41.17–323.27 weeks)	• OS	• Disease stage (IIIB or IV) • Age (>60 or ≤60 yrs) • Gender • Smoking (yes or no) • PS (0–1 or 2–4)	

Key: CNS, central nervous system; CR, complete response; CT, chemotherapy; DCR, disease control rate; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; EFS, event-free survival; HDL, high density lipoprotein; IQR, interquartile range; NR, not reported; NSCLC, non-small cell lung cancer; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; PS, performance status; SD, stable disease; TKI, tyrosine kinase inhibitor; TTF, time to treatment failure.
Notes: [a] The only non-randomised controlled study; the rest are retrospective observational studies, [b] The publication reported that 92.8% patients received 1L therapy, however, data were reported for 82.8% patients.
*The proportion of patients who received 1L therapy and possessed EGFR+ mutation is calculated from the overall study population and not mutant population.

D.2.2 Population characteristics

The baseline characteristics of the population assessed across the studies are presented in Table 111 and Table 112.

Age and ethnicity

Across the 38 studies, the age of the population assessed was reported in 20 studies. Mean age was reported in four studies[388, 389, 403, 410], median age was reported in seven studies[386, 387, 389, 395, 398, 414, 416], and both mean and median age were reported in one study.[389] Mean age ranged from 58 years in the chemotherapy group to 70.8 years in the gefitinib group, both in the study by Frega et al.[410] Across the seven studies, the median age ranged from 53 years in the erlotinib group in the study by Udupa et al.[386] to 70.7 years in the gefitinib/erlotinib group in the study by Shen et al.[414] Six studies reported data for the overall population and not by treatment arm.[399, 405-407, 411, 413] Three studies reported the proportion of patients who had a median age of <65 and ≥65 years.[399, 404, 420] One study by Skrickova et al. reported qualitative data, which mentioned that there was no statistically significant difference in age between the treatment groups (p=0.031).[408]

The proportion of male patients at study entry was reported in 18 studies. Six studies provided data for the overall population and not by treatment arm .[404-406, 409, 411, 413] One study by Skrickova et al. reported qualitative data showing that there was no statistically significant difference in gender between the treatment groups (p=0.972).[408] Across the 11 other studies, the proportion of male patients varied between 9.1% of the erlotinib group in the study by Kashima et al.[395] to 66.6% of the afatinib group in the study by Frega et al.[410]

Data for the proportion of Asian patients were reported in 12 studies.[386, 387, 389, 391, 394, 395, 399, 403, 412, 413, 416, 418] In 10 of these studies, all of the patients were Asian.[386, 389, 391, 394, 395, 399, 403, 412, 416, 418] However, in AURA, the majority of patients (77% in osimertinib 80mg group and 67% in osimertinib 160mg group) were Asian and the remainder were Caucasian/others.[387] In the study by Arriola et al., 98.3% of the total population were Caucasian, and data were not reported by treatment arm.[424]

Disease metastasis and prior therapy

The proportion of patients with brain metastases at baseline was reported in nine studies[387-389, 398, 399, 403, 404, 406, 413] Across six of these studies the proportion of patients with brain metastases varied between 12.9% in the gefitinib group of the study by Li et al.[399] to 48.9% in the erlotinib group of the study by Yang et al.[388]

Three other studies reported data for patients with brain metastasis, metastasis to bone and liver, for the overall population and not by treatment arm.[404, 406, 413]

Data for the proportion of patients who had received radiotherapy prior to study entry were reported in the study by Li et al.[399] Data were reported for patients who had received whole brain radiation therapy in combination with either TKI, surgery or stereotactic radiosurgery in this study.

ECOG/WHO PS

The proportion of patients with ECOG PS 0 was reported in five studies.[387, 389, 408, 413, 416] One of these studies reported data for the overall population[413], while one study reported qualitative data only.[408] Across the three other studies, the proportion of patients with ECOG PS 0 varied from none of the erlotinib group in the study by Lee et al.[389] to 60% of the osimertinib (80mg) group in the AURA study.[387]

The proportion of patients with ECOG PS 0–1 was reported in nine studies.[388, 395, 399, 403, 405, 406, 411, 414, 420] Four of these studies reported data for the overall population and not according to treatment arm.[405, 406, 411, 420] Across five other studies, the proportion of patients with ECOG PS 0–1 ranged from 68.8% of the gefitinib/erlotinib group in the study by Shen et al. to 98.1% of the erlotinib group in the study by Li et al.[399]

Four studies reported the proportion of patients with ECOG PS 1 at baseline.[387, 389, 413, 416] The study by Arriola et al. reported data for the overall population.[413] Across the three other studies, the proportion of patients with ECOG PS 1 varied between 39.7% in the gefitinib group in the study by Inoue et al.[416] to 89.9% of gefitinib group in the study by Lee et al.[389]

Seven studies reported the proportion of patients with ECOG PS 2.[389, 395, 399, 411, 413, 416, 420] Across five of these studies, the proportion varied between 1.9% in the study by Li et al.[399] to 22.6% in the study by Lee et al.[389], both in the erlotinib groups. Two other studies reported data for the overall population and according to treatment arm.[411, 413]

Furthermore, two studies reported the proportion of patients with ECOG PS 2–4[388, 414], while one study reported the proportion of patients with ECOG PS ≥2 for the overall population.[406] In the study by Kuan et al., data were reported for patients with ECOG PS >1, who represented 13.6%, 11.1% and 24% of patients in the afatinib, erlotinib and gefitinib groups, respectively.[403] In the OCTUMUT study data were reported for overall population who had PS 2–3.[405]

The proportion of patients with ECOG PS 3 at baseline were reported in three studies.[389, 413, 416] Across two of these studies, the proportion varied from none of the patients in the erlotinib group to 7.5% of the gefitinib group in the study by Inoue et al.[416] The other study by Arriola et al. reported data for the overall population.[413]

The study by Kashima et al. reported data for patients with ECOG PS 3–4, which was 17.3% and 18.2% in the gefitinib and erlotinib groups, respectively.[395]

Only the study by Inoue et al. reported the proportion of patients with ECOG PS 4 at baseline, which was 1.2% in the gefitinib group, while it was not reported for the platinum-doublet chemotherapy with/without bevacizumab group.[416]

Smoking status

Patients who were smokers at baseline were reported in 11 studies.[386, 389, 395, 399, 403, 404, 406, 408, 410, 413, 416] Four studies reported the proportion of patients who were current smokers for the overall population.[404, 406, 413, 416] Only qualitative data were reported in one study.[408] Across the other six studies, the proportion of patients varied from 4.3% of the gefitinib group in the study by Lee et al.[389] to 42.3% of the gefitinib group in the study by Kashima et al.[395]

Data for patients who were never smokers were reported in 12 studies. Six of these studies reported data for the overall population and not by treatment arm.[404-406, 409, 413, 416] Across the six other studies[389, 395, 399, 403, 410, 414], the proportion of never smokers varied from 33.3% each in two treatment arms (afatinib and chemotherapy) of Frega et al.[410] to 87.5% of the afatinib in the study by Shen et al.[414]

Six studies reported the proportion of patients who were ex-smokers.[386, 389, 410, 413, 414, 420] One of these studies reported data for overall population[413] Across the other five studies, the proportion of ex-smokers ranged from none in the erlotinib group in the study by Frega et al.[410] to 78.2% of the gefitinib group in the study by Udupa et al.[386]

Histology/cancer stage

The proportion of patients with Stage IIIB and IV disease at baseline was reported in nine and 10 studies, respectively. Five of these studies reported data for the overall population of stage IIIb and IV.[404-406, 413, 416] Across the other four studies[389, 399, 403, 414], the proportion varied from 4.2% of the afatinib group in the study by Shen et al.[414] to 16.1% of the erlotinib group in the study by Lee et al.[389] Across the other five studies that reported data for patients with Stage IV, the proportion varied from 64.3% in study by Li et al.[399] to 100% of both treatment arms (geftinib and platinum based chemotherapy) in Hsia et al.[420]

Data for patients with adenocarcinoma were reported in seven studies. Across three of these studies[389, 399, 416], the proportion varied from 83.8% of the erlotinib group in the study by Lee et al. to 96.7% of the gefitinib group in the study by Inoue et al.[416] Four studies reported data for the overall population.[405, 407, 411, 413]

Data for patients with squamous histology were reported in three studies. One study reported data for the overall population.[413], whereas across the two other studies the proportion of patients with squamous histology varied between none of the gefitinib group to 6.5% of patients in the erlotinib group both in the study by Lee et al. [389]

Two studies reported data for patients with large cell carcinoma, with Arriola et al. reporting data for the overall population.[413] and the study by Inoue et al. reported that 0.2% patients in the gefitinib group had large cell carcinoma while data was NR for platinum doublet chemotherapy group.[416]

Data for patients with other histology types were reported in eight studies[389, 399, 403, 409-411, 416, 424]; these included non-adenocarcinoma, non-squamous carcinoma and adenosquamous carcinoma. Kuan et al. also reported data by grade 1–3; however, it was difficult to determine whether the data were for disease stage or histological subtype.[403]

EGFR mutation status

Data for patients with exon 19 del and L858R mutations at baseline were reported in 12 studies.[387-389, 395, 398, 399, 403-406, 413, 416] Four of these, reported data for the overall patient population and not by treatment arm.[404-406, 413] Across the eight other studies, the proportion of patients with exon 19 del mutations varied between 27.3% in the study by Kashima et al.[395] to 63% in the study by Yoshida et al.[398], both in the erlotinib groups. The proportion of patients with L858R mutations varied between 31.6% of the afatinib group in the study by Yang et al.[388] and 72.7% of the erlotinib group in the study by Kashima et al.[395]

Five studies reported the proportion of patients with T790M mutations.[389, 399, 405, 413, 414] Two studies reported data for the overall population.[405, 413] Across the other three studies, the proportion of patients with T790M mutations varied between none in the study by Li et al. and 12.5% in the afatinib group in the study by Shen et al.[414]

Data for other types of mutations were reported in nine studies.[387-389, 395, 399, 405, 407, 413, 416]

Table 111: Patients demographic at baseline for non-randomised studies

Study name	Intervention Comparator	Number of patients	Age Median (min–max)	Male: n (%)	Metastatic site: n (%) • Bone • Brain • Liver • other	Prior therapy; Radiotherapy: n (%)	Cancer stage: n (%) • Stage IIIB • Stage IV
Arriola 2018[a]	Gefitinib	100	71.4 (62.2–79)	69 (38.1)	• 75 (42.9) • 25 (14.3) • 25(14.3) • NR	NR	• 7 (3.9) • 159 (87.8)
	Erlotinib	22					
	CT	18					
	CT followed by TKI	8					
Corre 2018[a]	Gefitinib	62	NR	12 (22.8)	• NR • NR • NR • NR Pleural cavity: 43/91 (47.3) Lung: 29/91(31.9) Lymph nodes: 18/91(19.8)	NR	• 15 (13.2) • 91 (79.8)
	Erlotinib	45					
	Afatinib	7					
Hung 2018[a]	Gefitinib	99	70 (NR)	59 (45.2)	• 51 (38.9) • 35 (26.7) • 15(11.4) • Adrenal: 9 (6.9) Lung: 42 (32.1)	NR	• 10 (7.6) • 121 (92.4)
	Erlotinib	27					
	Afatinib	5					
Yang 2018	Afatinib	57	60.8 (10.2)[b]	23 (40.4)	• NR • 17 (29.8) • NR • NR	NR	• NR
	Erlotinib	45	61.9 (12.8)[b]	20 (44.4)	• NR • 22 (48.9) • NR • NR	NR	• NR
	Gefitinib	242	63.7 (11.2)[b]	89 (36.8)	• NR	NR	• NR

Study name	Intervention Comparator	Number of patients	Age Median (min–max)	Male: n (%)	Metastatic site: n (%) • Bone • Brain • Liver • other	Prior therapy; Radiotherapy: n (%)	Cancer stage: n (%) • Stage IIIB • Stage IV
					• 54 (22.3); p=0.001 • NR • NR		
Barnet 2017[a]	Dacomitinib	NR	70 (40–88)	21 (38.9)	• NR	NR	• NR
	Erlotinib						
	Gefitinib						
	Afatinib						
Frega 2017	Gefitinib	11	70.81[b] (51–86)	5 (45.45)	NR	NR	• 2 (18.2) • NR
	Erlotinib	3	59.33[b] (56–66)	1 (33.3)	NR	NR	• 0 (0) • NR
	Afatinib	3	66.33[b] (64–71)	2 (66.67)	NR	NR	• 1 (33.3) • NR
	Chemotherapy	6	58[b] (47–68)	3 (50)	NR	NR	• 2 (33.3) • NR
He 2017	Gefitinib	NR	NR	NR	NR	NR	• NR
	Gefitinib + pemetrexed/ gemcitabine and platinum	NR	NR	NR	NR	NR	• NR
Hsia 2017	Gefitinib	120	<65 years: n (%): 76 (63.33) ≥65 years: n (%): 44 (36.67)	60 (50	NR	NR	• NR • 120 (100)
	Platinum-based CT	120	<65, n (%): 75 (62.5) ≥65, n (%): 45 (37.5)	60 (50)	NR	NR	• NR • 120 (100)
Kuan 2017	Gefitinib	304	NR (33–93); 65[b]; <65 years: n (%): 154 (50.7) ≥ 65 years: n (%): 150 (49.3)	114 (37.5)	• NR • 60 (19.7) • NR • NR	NR	• 16 (5.3) • 288 (94.7)
	Erlotinib	63	NR (47–90); 67[b];	24 (38.1)	• NR	NR	• 5 (7.9)

Study name	Intervention Comparator	Number of patients	Age Median (min–max)	Male: n (%)	Metastatic site: n (%) • Bone • Brain • Liver • other	Prior therapy; Radiotherapy: n (%)	Cancer stage: n (%) • Stage IIIB • Stage IV
			<65 years: n (%): 34 (54.0) ≥ 65 years: n (%): 29 (46.0)		• 11 (17.5) • NR • NR		• 58 (92.1)
	Afatinib	81	NR (37–83); 64[b]; <65 years: n (%): 52 (64.2) ≥ 65 years: n (%): 29 (35.8)	39 (48.1)	• NR • 17 (21) • NR • NR	NR	• 7 (8.6) • 74 (91.4)
Li 2017[a]	Gefitinib	NR	69 (NR)	NR (32.3)	NR	NR	• NR
	Erlotinib	NR					
	Afatinib	NR					
	Other CT	NR					
Li 2017	Erlotinib	108	58 (32–84); p=0.343; <65 years: n (%): 63 (58.3) ≥ 65 years: n (%): 45 (41.7)	53 (49.1); p=0.343	• NR • 24 (22.2); p=0.047 • NR • NR	Previous treatment of cerebral metastasis, No. • WBRT + TKI: 14 • Surgery + WBRT: 2 • WBRT + SRS: 4 • None: 4	• 7 (6.5); p=0.088 • 83 (76.9); p=0.088
	Gefitinib	171	58 (32–84); <65 years: n (%): 96 (56.1) ≥ 65 years: n (%): 75 (43.9)	74 (43.3)	• NR • 22 (12.9) • NR • NR	Previous treatment of cerebral metastasis, No. • WBRT + TKI: 11 • Surgery + WBRT: 3 (1) • WBRT + SRS: 5 • None: 3	• 17 (9.9) • 110 (64.3)
	Osimertinib: 80mg	30	62.5 (40–77)	10 (33)	• NR	NR	• NR

Study name	Intervention Comparator	Number of patients	Age Median (min–max)	Male: n (%)	Metastatic site: n (%) • Bone • Brain • Liver • other	Prior therapy; Radiotherapy: n (%)	Cancer stage: n (%) • Stage IIIB • Stage IV
Ramalingam 2017					• 7 (23) • NR • NR		
	Osimertinib: 160mg	30	65 (38–91)	5 (17)	• NR • 8 (27) • NR • NR	NR	• NR
Shen 2017	Afatinib	24	59 (IQR: 33–86)	9 (37.5)	NR	NR	• 1 (4.2) • 25 (95.8)
	Gefitinib/Erlotinib	32	70.7 (IQR: 46–87)	15 (46.9) (0.589)	NR	NR	• 3 (9.4) • 29 (90.6)
Skrickova 2017	Gefitinib	138	NR; p=0.031	NR; p=0.972	NR	NR	• NR
	Afatinib	102					
	Erlotinib	40					
Tu 2017[a]	Gefitinib	210	64 (NR)	NR	NR	NR	• NR
	Erlotinib	147					
	Afatinib	110					
Udupa 2017	Erlotinib	11	53 (NR)	7 (63.6)	NR	NR	• NR
	Gefitinib	23	56 (NR)	14 (60.87)	NR	NR	• NR
Wang 2017[a]	Afatinib	NR	67.5 (42–90) <65 years: n (%): 46 (44.2) ≥ 65 years: n (%): 58 (55.8)	53 (51)	• 41 (39.4) • 19 (18.3) • 16 (15.4) • 43 (41.3)	NR	• 15 (14.4) • 89 (85.6)
	Erlotinib	NR					
	Gefitinib	NR					
Inoue 2016	Gefitinib	929	69 (27–97)	270 (29.1)	NR	NR	• 44 (4.7) • 600 (64.6)
	Platinum-doublet CT ± BV	509	69 (27–97)[a]	584 (35.2)[a]	NR	NR	• 125(7.5)[a] • 1105 (66.7)[a]
Kashima 2016	Erlotinib	11	67; p=0.84	1 (9.1)	NR	NR	NR
	Gefitinib	52	65.5	14 (26.9)	NR	NR	NR

Study name	Intervention Comparator	Number of patients	Age Median (min–max)	Male: n (%)	Metastatic site: n (%) • Bone • Brain • Liver • other	Prior therapy; Radiotherapy: n (%)	Cancer stage: n (%) • Stage IIIB • Stage IV
Yoshida 2016	Gefitinib	148	64.5 (32–81)	NR	• NR • 43 (29) • NR • NR	NR	NR
	Erlotinib	27	62 (27–68)	NR	• NR • 6 (22.2) • NR • NR	NR	NR
Lee 2013	Erlotinib	31	60; 61.7[b]	20 (64.5)	• NR • 9 (29); p=0.372 • NR • NR	NR	• 5 (16.1) • 26 (83.9)
	Gefitinib	139	66; p=0.220; 64.8[b]; p=0.214	36 (25.9)	• NR • 30 (21.6) • NR • NR	NR	• 20 (14.4); p=0.805 • 119 (85.6)

Key: CT, chemotherapy; IQR, interquartile range; NR, not reported; SRS, stereotactic radiosurgery; TKI, tyrosine kinase inhibitor; WBRT, whole brain radiation therapy.
Notes: [a] Data reported for overall population; [b], data reported as mean (SD).

Table 112: Patients demographic at baseline for non-randomised studies (contd.)

Study name	Treatment	Number of patients	Smoking status • Current smokers: n (%) • Never smokers: n (%) • Ex-smokers: n (%)	Race • White • Black/ African American • Asian • Caucasian • Other	EGFR mutation: n (%) • Exon 19 del • L858R • T790m • Other	ECOG PS: n (%) • 0 • 1 • 2 • 3	Disease subtype: n (%) • Adenocarcinoma • Squamous • Other
	Gefitinib	100					

Study name	Treatment	Number of patients	Smoking status • Current smokers: n (%) • Never smokers: n (%) • Ex-smokers: n (%)	Race • White • Black/ African American • Asian • Caucasian • Other	EGFR mutation: n (%) • Exon 19 del • L858R • T790m • Other	ECOG PS: n (%) • 0 • 1 • 2 • 3	Disease subtype: n (%) • Adenocarcinoma • Squamous • Other
Arriola 2018[a]	Erlotinib	22	• 26 (14.9) • 96 (54.9) • 53 (30.3)	• NR • NR • 3 (1.7) • 178 (98.3) • NR	• 96 (57.1) • 38 (22.6) • 7 (4.2) • Rare: 23 (13.7) Exon 21 L861Q mutation = 7 (4.2%) Exon 18 G719X: 10 (5.6) Exon 18 G719A: 3(1.8) Exon 18 G719S: 3 (1.8) Mutations of unknown significance: 4 (2.4) Exon 21 L858Q: 1 (0.6) Exon 21 E829Q: 1 (0.6) Exon 21 R836C: 1 (0.6) Exon 21 T854S: 1 (0.6)	• 46 (27.7) • 87 (52.4) • 26 (15.7) • 7 (8.1)	• 161 (89.0) • 9 (5.0) Large cell: 5(2.8) Adenosquamous: 2(1.1) Carcinoma NOS: 4 (2.2)
	Chemotherapy	18					
	Chemotherapy followed by TKI	8					
Corre 2018[a]	Gefitinib	62	• NR • 87 (76.3) • NR	• NR • NR • NR • 112 (98.3) • NR	• 53 (46.5) • 46 (40.4) • 6 (5.2) • Exon 18: 9 (7.9)	• 73 (71.6) • NR • 2–3: 29 (28.4)	• 109 (95.6)
	Erlotinib	45					
	Afatinib	7					
Hung 2018[a]	Gefitinib	99	• 16 (12.2) • 115 (87.8) • NR	• NR	• 59 (45.0) • 72 (55.0) • NR • NR	• ≤1: 119 (90.8) • ≥2: 12 (9.2)	• NR
	Erlotinib	27					
	Afatinib	5					
Yang 2018	Afatinib	57	• NR	• NR	• NR • 18 (31.6) • NR • 9 (15.8)	• 0–1: 52 (91.2) • 2–4: 5 (8.8)	• NR

Study name	Treatment	Number of patients	Smoking status • Current smokers: n (%) • Never smokers: n (%) • Ex-smokers: n (%)	Race • White • Black/ African American • Asian • Caucasian • Other	EGFR mutation: n (%) • Exon 19 del • L858R • T790m • Other	ECOG PS: n (%) • 0 • 1 • 2 • 3	Disease subtype: n (%) • Adenocarcinoma • Squamous • Other
	Erlotinib	45	• NR	• NR	• NR • 26 (57.8) • NR • 1 (2.2)	• 0–1: 39 (86.7) • 2–4: 6 (13.3)	• NR
	Gefitinib	242	• NR	• NR	• NR • 127 (52.5) • NR • 17 (7)	• 0–1: 220 (90.9) • 2–4: 21 (8.7)	• NR
Barnet 2017[a]	Dacomitinib	NR	• NR	• NR	• NR	• 0–1: 43 (79.6) • 11 (20.4) • NR	• 45 (83.3) • NR • 9 (16.7)
	Erlotinib	NR					
	Gefitinib	NR					
	Afatinib	NR					
Frega 2017	Gefitinib	11	• 2 (18.2) • 6 (54.5) • 2 (18.2)	• NR	• NR	• NR	• NR • NR • 11 (100)
	Erlotinib	3	• 1 (33.3) • 2 (66.67) • 0 (0)	• NR	• NR	• NR	• NR • NR • 3 (100)
	Afatinib	3	• 1 (33.3) • 1 (33.3) • 1 (33.3)	• NR	• NR	• NR	• NR • NR • 3 (100)
	Chemotherapy	6	• 1 (16.67) • 2 (33.3) • 2 (33.3)	• NR	• NR	• NR	• NR • NR • NR
	Gefitinib	120	• NR	• NR	• NR	• 0–1: 113 (94.17)	• NR

Study name	Treatment	Number of patients	Smoking status • Current smokers: n (%) • Never smokers: n (%) • Ex-smokers: n (%)	Race • White • Black/ African American • Asian • Caucasian • Other	EGFR mutation: n (%) • Exon 19 del • L858R • T790m • Other	ECOG PS: n (%) • 0 • 1 • 2 • 3	Disease subtype: n (%) • Adenocarcinoma • Squamous • Other
Hsia 2017			• NR • 41 (34.17)			• 7 (5.83) • NR	
	Platinum-based CT	120	• NR • NR • 41 (34.17)	• NR	• NR	• 0–1: 113 (94.17) • 7 (5.83) • NR	• NR
Kuan 2017	Gefitinib	304	• 78 (25.7)[b] • 226 (74.3) • NR	• NR • NR • 304 (100) • NR • NR	• 148 (48.7) • 156 (51.3) • NR • NR	• 0–1: 231 (76) • NR • >1: 73 (24) • NR	• NR • NR • Grade 1: 59 (19.4) Grade 2: 64 (21.1) Grade 3: 49 (16.1) Grade missing: 132 (43.4)
	Erlotinib	63	• 15 (23.8)[b] • 48 (76.2) • NR	• NR • NR • 63 (100) • NR • NR	• 27 (42.9) • 36 (57.1) • NR • NR	• 0–1: 56 (88.9) • NR • >1: 7 (11.1) • NR	• NR • NR • Grade 1: 12 (19.4)) Grade 2: 19 (30.2) Grade 3: 9 (14.3) Grade missing: 23 (36.5)
	Afatinib	81	• 18 (22.2)[b] • 63 (77.8) • NR	• NR • NR • 81 (100) • NR • NR	• 48 (59.3) • 33 (40.7) • NR • NR	• 0–1: 70 (86.4) • NR • >1: 11 (13.6) • NR	• NR • NR • Grade 1: 25 (30.9) Grade 2: 21 (25.9) Grade 3: 9 (11.1) Grade missing: 26 (32.1)
Li 2017[a]	Gefitinib	NR					

Study name	Treatment	Number of patients	Smoking status • Current smokers: n (%) • Never smokers: n (%) • Ex-smokers: n (%)	Race • White • Black/ African American • Asian • Caucasian • Other	EGFR mutation: n (%) • Exon 19 del • L858R • T790m • Other	ECOG PS: n (%) • 0 • 1 • 2 • 3	Disease subtype: n (%) • Adenocarcinoma • Squamous • Other
	Erlotinib	NR	• NR (54.3) • NR • NR	• NR • NR • NR • NR (55.5) • NR	• NR	• NR	• NR • NR • non-squamous 97.5%
	Afatinib	NR					
	Other CT	NR					
Li 2017	Erlotinib	108	• 38 (35.2); p=0.359 • 70 (64.8); p=0.359 • NR	• All patients were Chinese	• 43 (39.8) • 47 (43.5) • S768I:0 (0) • Exons 18: G719Ab (One patient had G719A and 19 del; one patient had G719A and L858R): 1 (0.9%) G719S: 0 (0) • G719C: 1(0.9%)	• 0–1: 106 (98.1); p=0.491 • NR • 2 (1.9) • NR	• 98 (90.7); p=1.0 • NR • 10 (9.3); p=1.0
	Gefitinib	171	• 51 (29.8) • 120 (70.2) • NR		• 84 (49.1) • 59 (34.5) • S768I:0 (0) • Exons 18: G719Ab (One patient had G719A and 19 del; one patient had G719A and L858R): 2 (1.2%) G719S: 1 (0.6%) • G719C: 1 (0.6%)	• 0–1: 165 (96.5) • NR • 6 (3.5) • NR	• 156 (91.2) • NR • 15 (8.8)
Ramalingam 2017	Osimertinib: 80mg	30	• NR	• 7 (23) • NR • 23 (77) • 6 (20)	• 11 (36) • 15 (50) • NR • 4 (13)	• 18 (60) • 12 (40) • NR • NR	• NR

Study name	Treatment	Number of patients	Smoking status • Current smokers: n (%) • Never smokers: n (%) • Ex-smokers: n (%)	Race • White • Black/ African American • Asian • Caucasian • Other	EGFR mutation: n (%) • Exon 19 del • L858R • T790m • Other	ECOG PS: n (%) • 0 • 1 • 2 • 3	Disease subtype: n (%) • Adenocarcinoma • Squamous • Other
				• 0 (0)			
	Osimertinib: 160mg	30	• NR	• 8 (27) • NR • 20 (67) • 8 (27) • 2 (6)	• 15 (50) • 14 (47) • NR • 1 (3)	• 16 (53) • 14 (47) • NR • NR	• NR
Shen 2017	Afatinib	24	• NR • 21 (87.5) • 3 (12.5)	• NR	• NR • NR • 3 (12.5) • NR	• 0–1: 19 (79.2) • 2–4: 5 (20.8) • NR	• NR
	Gefitinib/Erlotinib	32	• NR • 19 (59.4) • 13 (40.6)	• NR	• NR • NR • 2 (6.3) • NR	• 0–1: 22 (68.8) • 2–4: 10 (31.3)	• NR
Skrickova 2017	Gefitinib	138	• NR; p=0.877	• NR	• NR	• p<0.001, patients treated with afatinib have better PS in common.	• NR
	Afatinib						
	Erlotinib						
Tu 2017[a]	Gefitinib	210	• NR	• NR	• NR	• NR	• NR (75) • NR • NR
	Erlotinib	147					
	Afatinib	110					
Udupa 2017	Erlotinib	11	• 3 () • 8 () • NR	• NR • NR • 11 (100) • NR	• L858R/ exon 19 del: Positive: 10 Negative: 1 • NR	• NR	• NR

Study name	Treatment	Number of patients	Smoking status • Current smokers: n (%) • Never smokers: n (%) • Ex-smokers: n (%)	Race • White • Black/ African American • Asian • Caucasian • Other	EGFR mutation: n (%) • Exon 19 del • L858R • T790m • Other	ECOG PS: n (%) • 0 • 1 • 2 • 3	Disease subtype: n (%) • Adenocarcinoma • Squamous • Other
				• NR	• NR		
	Gefitinib	23	• 5 () • 18 () • NR	• NR • NR • 23 (100) • NR • NR	• L858R/ exon 19 del: Positive: 21 Negative: 2 • NR • NR	• NR	• NR
Wang 2017[a]	Afatinib	NR	• 36 (34.6) • 68 (65.4) • NR	• NR	• 47 (45.2) • 52 (50) • NR • NR	• NR	• NR
	Erlotinib	NR					
	Gefitinib	NR					
Inoue 2016	Gefitinib	929	• 306 (32.9) • 604 (65) • Status unknown: 19	• NR • NR • 929 (100) • NR • NR	• 467 (50.3) • 383 (41.2) • NR • 60 (6.5)	• 334 (36) • 369 (39.7) • 85 (9.1) • 70 (7.5) • ECOG PS 4: 11 (1.2)	• 898 (96.7) • 19 (2) • 10 (1.07) large cell: 2 (0.2)
	Platinum-doublet CT ± BV[a]	509	• 306 (32.9) • 981 (59.2) • Status unknown: 30 (1.8)	• NR • NR • 509 (100) • NR • NR	• 814(49.1) • 667 (40.3) • NR • 146 (8.8)	• 654 (39.5) • 681 (41.1) • 117 (7.1) • 81 (4.9) • ECOG 4: 12 (0.7)	• 1577 (95.2) • 48 (2.9) • 18 (1.1) Adenosquamous: 9 (0.5) Large cell: 5 (0.3)
Jiang 2016	Erlotinib	85	NR	All patients were Chinese	NR	NR	NR
	Gefitinib	42	NR		NR	NR	NR
Kashima 2016	Erlotinib	11	• 3 (27.3) • 8 (72.7) • NR	All patients were Japanese	• 3 (27.3) • 8 (72.7) • NR	• 0–1: 8 (72.7) • NR • 1 (9)	NR

Study name	Treatment	Number of patients	Smoking status • Current smokers: n (%) • Never smokers: n (%) • Ex-smokers: n (%)	Race • White • Black/ African American • Asian • Caucasian • Other	EGFR mutation: n (%) • Exon 19 del • L858R • T790m • Other	ECOG PS: n (%) • 0 • 1 • 2 • 3	Disease subtype: n (%) • Adenocarcinoma • Squamous • Other
					• NR	• 3–4: 2 (18)	
	Gefitinib	52	• 22 (42.3) • 30 (57.7) • NR		• 31 (59.6) • 18 (34.6) • NR • NR	• 0–1: 39 (75) • NR • 4 (7.7) • 3–4: 9 (17.3)	NR
Li 2016	Erlotinib	14	NR	All patients were Chinese	NR	NR	NR
	Erlotinib + ginsenoside	47	NR		NR	NR	NR
	Gefitinib or Icotinib	38	NR		NR	NR	NR
	Gefitinib or Icotinib + ginsenoside	25	NR		NR	NR	NR
Yoshida 2016	Gefitinib	148	NR	NR	• 84 (56.7) • 64 (43.3) • NR • NR	NR	NR
	Erlotinib	27	NR	NR	• 17 (63) • 10 (37) • NR • NR	NR	NR
Zhang 2015	Erlotinib	14	NR	All patients were Chinese	NR	NR	NR
	Gefitinib	46	NR		NR	NR	NR
Lee 2013	Erlotinib	31	• 5 (16.1)[c] • 20 (64.5) • 6 (19.4)	All patients were Chinese	• 12 (38.7) • 12 (38.7) • 1 (3.2)	• 0 (0) • 24 (77.4) • 7 (22.6)	• 26 (83.8) • 2 (6.5) • 3 (9.7)

Study name	Treatment	Number of patients	Smoking status • Current smokers: n (%) • Never smokers: n (%) • Ex-smokers: n (%)	Race • White • Black/ African American • Asian • Caucasian • Other	EGFR mutation: n (%) • Exon 19 del • L858R • T790m • Other	ECOG PS: n (%) • 0 • 1 • 2 • 3	Disease subtype: n (%) • Adenocarcinoma • Squamous • Other
					• 5 (16.1)	• 0 (0)	
	Gefitinib	139	• 6 (4.3)[c] • 116 (83.5) • 17 (12.2)		• 52 (37.4); p=0.893 • 68 (48.9); p=0.303 • 6 (4.3); p=0.782 • 9 (6.47)	• 1 (0.7); p=0.036 • 125 (89.9) • 9 (6.5) • 4 (2.9)	• 128 (92.1); p=0.045 • 0 (0) • 11 (7.9)
Yoshida 2010	Gefitinib	23	NR	All patients were Japanese	NR	NR	NR
	Cytotoxic chemotherapy	25	NR		NR	NR	NR

Key: BSC, best supportive care; CT, chemotherapy; ECOG PS, eastern cooperative oncology group performance status; EGFR, epidermal growth factor receptor; NR, not reported; PBO, placebo; TKI, tyrosine kinase inhibitor.

Notes: [a], data reported for overall population; [b] Current or ever smokers; [c] Chronic smokers.

D.2.3 Efficacy outcomes

Data for ORR and DCR are presented in Table 113.

Overall response rate

Data for patients who achieved an overall response were reported in 11 studies.[387, 391, 393, 396, 402, 404, 408, 413-415, 418] ORR was defined as the percentage of patients achieving a CR or PR in four studies[387, 391, 413, 418] and was not reported in the other studies. Qualitative information was provided in two studies[402, 408], which suggested that there was no significant difference in response rate between afatinib, erlotinib and gefitinib. Across the nine other studies, ORRs ranged from 22.2% of patients in the chemotherapy group in the study by Arriola et al.[413] to 87% with gefitinib and osimertinib (160mg) in the study by Yoshida et al.[418] and AURA[387], respectively.

ORR in subgroups of patients with exon 19 del and L858R mutations was reported in AURA only. ORR in the exon 19 del subgroup was 73% with osimertinib (80mg) compared with 87% with osimertinib (160mg). Similarly, ORR in the L858R subgroup was 67% with osimertinib (80mg) compared with 86% with osimertinib (160mg).[387]

Only the study by Shen et al. reported ORR for the subgroup of patients with T790M mutations.[414] The response rate was 33.3% with afatinib compared with none for gefitinib/erlotinib arm.

Disease control rate

Data for DCR were reported in six studies.[387, 391, 396, 408, 413, 418] In three studies, DCR was defined as the percentage of patients achieving CR or PR or stable disease.[391, 408, 418] However, the definition for DCR was not reported in the other three studies. Across five of the studies, at study endpoint, the DCR ranged from 76.2% in the erlotinib group in the study by Zhang et al.[391], to 100% in the osimertinib (160mg) and TKI plus chemotherapy groups in AURA[387] and the study by Arriola et al.[413], respectively. In the other study by Skrickova et al., only qualitative data were presented, which suggested that no statistically significant difference was observed between the three treatment groups in terms of disease control.[408]

Table 113: ORR and DCR across other non-randomised studies

Study name	Intervention Comparator	Time-point (Assessor)	ITT N	Number of patients	ORR		DCR	
					n (n%) p-value	Definition	n (n%) p-value	Definition
Arriola 2018	Gefitinib	Endpoint (Investigator)	100	100	50 (50); 95% CI: 39.8–60.2	ORR was calculated as the sum of patients achieving CR and PR as the best response achieved. RECIST v1.1	86 (86); 95% CI: 77.6–92.1	NR
	Erlotinib		22	22	8 (36.4); 95% CI: 17.2–59.3		21 (95.5); 95% CI: 77.2–99.9	
	Chemotherapy		18	18	4 (22.2); 95% CI: 6.4–47.6		14 (77.8); 95% CI: 52.4–93.6	
	Chemotherapy followed by TKI		8	8	2 (25); 95% CI: 3.2–65.1		8 (100); 95% CI: 63.1–100.0	
He 2017	Gefitinib	Endpoint (NR)	35	35	14 (38.9); p=0.046	NR	NR	NR
	Gefitinib + Pemetrexed/gemcitabine and platinum		29	29	19 (65.5); p=1.0		NR	
Ramalingam 2017	Osimertinib: 80mg	Endpoint (Investigator assessed)	30	30	20 (67); 95% CI 47–83	ORR is the percentage of patients with at least one visit response of CR or PR that was confirmed at least 4 weeks later, prior to progression or further anti-cancer therapy. Data cut-off: 1 November 2016	28 (93); 95% CI 78–99	NR
	Osimertinib: 160mg		30	30	26 (87); 95% CI 69–96		30 (100); 95% CI 88–100	
	Osimertinib: 80mg	6-month (Investigator assessed)	30	19	18 (95); 95%CI: 68–99		NR	
	Osimertinib: 160mg		30	25	23 (91); 95%CI: 69–98		NR	
	Osimertinib: 80mg	1-year (Investigator assessed))	30	20	16 (79); 95%CI: 52–91		NR	
	Osimertinib: 160mg		30	26	18 (71); 95%CI: 48–85		NR	
Shen 2017	Afatinib	Endpoint (Independent radiological reviews)	24	24	15 (62.5); p=0.35	NR RECIST v1.1	NR	NR
	Gefitinib/ Erlotinib		32	32	16 (50)		NR	
	Afatinib		3	3	1 (33.3); p=1.0		NR	
	Gefitinib/Erlotinib		2	2	0 (0)		NR	

Study name	Intervention Comparator	Time-point (Assessor)	ITT N	Number of patients	ORR		DCR	
					n (n%) p-value	Definition	n (n%) p-value	Definition
Wang 2017	Afatinib	Endpoint (NR)	6	6	5 (83.3); p=0.593	CR + PR+SD/PD RECIST v1.1	NR	NR
	Erlotinib		27	27	23 (85.2)		NR	
	Gefitinib		71	71	54 (76.1)		NR	
Guerreiro 2016	Erlotinib	Endpoint (NR)	51	51	21 (41.2); p=0.652	NR	NR	• NR • No significant difference between groups at data cut-off in May 2016
	Gefitinib		35	35	12 (34.3)		NR	
Ito 2016	Afatinib	Endpoint (NR)	28	28	NR	The efficacy assessment demonstrated that there was no significant difference in response rate among the three EGFR-TKIs.	NR	NR
	Erlotinib		35	35	NR		NR	
	Gefitinib		82	82	NR		NR	
Shee 2016	Gefitinib	Endpoint (NR)	80	80	36 (45)	• NR • Odds ratio: 1.94; 95% CI, 0.63–6.00; p=0.251	61 (76.3)	• NR • Odds ratio: 0.23; 95% CI, 0.03–1.93; p=0.175
	Erlotinib		18	18	6 (33.3)		17 (94.4)	
Wu 2016	Gefitinib	Endpoint (NR)	42	42	Data reported for tumour response (reduction in tumour size): Median maximal tumour shrinkage during first-line EGFR TKI treatment was 53% (interquartile range 30.5%). Maximal tumour shrinkage did not correlate with OS in all patients (R^2=0.0225, p=0.169), or with either	Tumour shrinkage was defined as ≥50% tumour shrinkage.	NR	NR
	Afatinib		49	49			NR	NR

Study name	Intervention Comparator	Time-point (Assessor)	ITT N	Number of patients	ORR		DCR	
					n (n%) p-value	Definition	n (n%) p-value	Definition
					gefitinib (R^2=0.0036, p=0.689) or afatinib (R^2=0.0625, p=0.085).			
Zhang 2015	Erlotinib	Endpoint (NR)	14	14	5 (33.4); p=0.413	• CR + PR • RECIST	11 (76.2); p=0.894	• CR + PR + SD • RECIST
	Gefitinib		46	46	20 (44.4)		36 (77.8)	
Yoshida 2010	Gefitinib	Endpoint (NR)	23	23	20 (87)	CR + PR	20 (87)	CR + PR + SD
	Cytotoxic chemotherapy		25	25	8 (32)		22 (88)	

Key: CR, complete response; DCR, disease control rate; ITT, intent to treat; NR, not reported; ORR, overall response rate; PR, partial response; RECIST, Response Evaluation Criteria In Solid Tumors; SD, stable disease; TKI, tyrosine kinase inhibitor.

D.2.4 Survival outcomes

Data for survival outcomes are presented in Table 114.

Overall survival

Data for OS were reported in 18 studies. Across 11 of these studies[389, 395, 396, 399-402, 404, 413, 416, 417], the median OS ranged from 8.7 months in the study by Shee et al.[396] to 41.0 months in the study by Li et al.[399], both for the erlotinib groups. In the five other studies, only HR values were reported.[390, 397, 412, 421, 423] In the study by Frega et al., it was reported that median OS with overall TKI (gefitinib, erlotinib and afatinib) was 19.4 months compared with 13.8 months with chemotherapy.[410] In the study by Hsia et al., the mean OS was 1.48 life years for gefitinib compared with 1.47 life years for platinum-based chemotherapy.[420]

Data for patients who were alive were reported in five studies.[389, 408, 410, 413, 417] In the study by Liu et al., 2-year survival rates were 38.2% and 44.6% in the erlotinib and chemotherapy groups, respectively.[417] In the study by Lee et al., the authors reported that 89 patients of the total study population were alive at data cut-off; however, the survival rates were not provided by treatment arm.[389] In two other studies, it was reported that OS rate was not significantly different between the treatment groups.[408, 410] In the study by Arriola et al., the 1-year OS rate was reported to be 37.5%, 50%, 59.8% and 66.6% with TKI plus chemotherapy, chemotherapy, gefitinib and erlotinib, respectively.[413]

No subgroup data based on either EGFR mutation or presence of brain metastases were reported.

Progression-free survival

Data for PFS were reported in 23 studies. One study reported mean PFS, which was reported to be 10.5, 6.7, 7.0 and 7.2 months with gefitinib, carboplatin plus paclitaxel, cisplatin plus gemcitabine and cisplatin plus pemetrexed, respectively.[419] Median PFS was reported in 17 other studies. Across 15 of these studies, the median PFS ranged between 4.6 months with gefitinib plus platinum doublet chemotherapy in the study by He et al.[415] and 23 months with erlotinib in the study by Li et al.[399] In the study by Yoshida et al., median PFS were also reported for the overall population who presented with central nervous system progression.[398] In the study by Frega et al., it was reported that median PFS with TKIs (gefitinib, erlotinib and afatinib) was 12.2 months compared to 5.3 months with chemotherapy.[410]

In the five other studies, only HR values were reported.[390, 397, 412, 422, 423]

HR values for subgroups based on the presence of exon 19 del and L858R mutations and of brain metastases were reported in Kuan et al. only.[403]

Data for patients who were progression-free and alive at 1-year were reported in two studies.[387, 413] In the AURA study, PFS rate was 75% and 69% with osimertinib (80mg) and osimertinib (160mg), respectively.[387] In the study by Arriola et al., PFS rate was 0%, 12.5%, 34.1% and 36.6% with chemotherapy, chemotherapy plus TKI, erlotinib and gefitinib, respectively.[413] The PFS rate at 6 months was reported in the AURA study only, which was 83% with osimertinib (80mg) and 90% with osimertinib (160mg).[387]

The study by Lee et al. reported that 58 patients of the total study population were progression-free at data cut-off. PFS rates were not provided by treatment arm.[389] In two other studies, it was reported that the PFS rate was not significantly different between the treatment groups.[408, 410] Only the study by Kuan et al. reported the number of progression events, which were 199, 22 and 25 in the gefitinib, erlotinib and afatinib groups, respectively.[403]

The study by Kuan et al. also reported data based on the presence of EGFR mutations (exon 19 del and L858R) and the presence of brain metastasis.[403] Across the exon 19 del mutation subgroup, the number of events was 102, 8 and 17 in the gefitinib, erlotinib and afatinib groups, respectively. In the subgroup with L858R mutation, the number of events was 97, 14 and 8 in the gefitinib, erlotinib and afatinib groups, respectively. The number of events in patients with brain metastases was 42, 4 and 5 in the gefitinib, erlotinib and afatinib groups, respectively.

Table 114: Survival outcomes in non-randomised studies (continuous)

Study name	Treatment	Number of patients	OS (months)		PFS (months)	
			Median (95% CI)	HR (95% CI); p value	Median (95% CI)	HR (95% CI); p value
Arriola 2018	Gefitinib	100	16.7 (12.4–20.1)	NR	9.9 (8.3–11.7)	NR
	Erlotinib	24	23.7 (15.2–31.5)		9.9 (4.8–15)	
	CT	18	12.7 (9.3–2.1)		5.2 (3.8–7.1)	
	CT followed by TKI	8	16.6 (10.6–26.7)		7.6 (6.1–17.4)	
Yang 2018	Afatinib	57	NR	NR	12.3; IQR: (7.8–37.1)	NR
	Erlotinib	45	NR		12.8; IQR: (6.1–24.7)	
	Gefitinib	242	NR		11.4; IQR: (7.4–21.7); p=0.541	
Frega 2017	Gefitinib	11	NR	NR	NR	NR
	Erlotinib	3	NR		NR	
	Afatinib	3	NR		NR	
	CT	6	13.58 (13.58–13.58)		5.3 (2.53–8.07)	
He 2017	Gefitinib	35	NR	NR	7.2 (5.35–9.05); p=0.008	NR
	Gefitinib + pemetrexed/ gemcitabine and platinum	29	NR		4.6 (4.01–5.19); p=1.0	
Hsia 2017	Gefitinib	120	1.48 life year (mean)	NR	NR	NR
	Platinum-based CT	120	1.47 life year (mean)		NR	
Koyama 2017	Erlotinib	NR	20.2	NR	13.2[a]	NR
	Gefitinib	NR	26		13.8[a]	
Kuan 2017	Gefitinib	304	NR	NR	11.4	HR for erlotinib vs gefitinib: 0.57 (0.37–0.89); p=0.005
	Erlotinib	63			Not reached	

Study name	Treatment	Number of patients	OS (months)		PFS (months)	
			Median (95% CI)	HR (95% CI); p value	Median (95% CI)	HR (95% CI); p value
	Afatinib	81			Not reached	HR for afatinib vs gefitinib: 0.51 (0.34–0.78); p<0.001
Li 2017	Erlotinib	108	41	p=0.112	23	NR; p=0.152
	Gefitinib	171	37		18.4	
Ramalingam 2017	Osimertinib: 80mg	30	NR	NR	22.1 (13.7–30.2)	NR
	Osimertinib: 160mg	30	NR		19.3 (13.7–26)	
Wang 2017	Erlotinib	NR	38; p=0.03	NR	NR	NR
	Gefitinib	NR	34		NR	
Wang 2017	Afatinib	6	NA	NR	NA	NR
	Erlotinib	27	20.7 (18.3–20.7)[b]; p=0.3418		12.2 (10.4–12.2); p=0.3306	
	Gefitinib	71	23.2 (16–28.2)[b]		12 (8.9–15.2)	
Batra 2016	Erlotinib	NR	NR	NR	12.3 (6.2–18.3)	NR
	Gefitinib	NR			11.4 (NR-NR)	
Guerreiro 2016	Erlotinib	51	NR	NR	11	NR
	Gefitinib	35			7	
Inoue 2016	Gefitinib	929	29.07 (26.87–31.6)	NR	11.43 (10.4–12.3)	NR
	Platinum-doublet CT ± BV	509	35.13 (30.7–38.3)		NR	
Ito 2016	Afatinib	NR	NR	NR	NR	NR
	Erlotinib	NR	22.7			
	Gefitinib	NR	24.8			
Jiang 2016	Erlotinib	85	NR	NR	9.3 (8.068–10.532)	0.999 (0.689–1.449); p=0.997 HR for gefitinib vs erlotinib
	Gefitinib	42			9.5 (7.413–11.587)	

Study name	Treatment	Number of patients	OS (months)		PFS (months)	
			Median (95% CI)	HR (95% CI); p value	Median (95% CI)	HR (95% CI); p value
Kashima 2016	Erlotinib	11	25	p=0.45	NR	NR
	Gefitinib	52	18.1			
Li 2016	Erlotinib	14	NR	HR for erlotinib + ginsenoside vs erlotinib: 0.59 (0.24, 1.47); p=0.722 HR for gefitinib or icotinib + ginsenoside vs gefitinib or icotinib: 0.62 (0.33, 1.16); p=0.722	NR	HR for erlotinib + ginsenoside vs erlotinib: 0.7 (0.37–1.31); p=0.877 HR for gefitinib or icotinib + ginsenoside vs gefitinib or icotinib: 0.49 (0.28–0.85); p=0.877
	Erlotinib + ginsenoside	47				
	Gefitinib or icotinib	38				
	Gefitinib or icotinib + ginsenoside	25				
Liu 2016	Erlotinib	66	22.6 (17.35–27.79)	p=0.796	NR	NR
	CT	66	21.2 (15.1–27.24)			
Lv 2016	Gefitinib	56	NR	NR	NR	HR for erlotinib vs gefitinib: 1.124 (0.596–2.118); p=0.718 HR for icotinib vs gefitinib: 1.777 (0.798–3.959); p=1.159
	Erlotinib	12				
	Icotinib	7				
Shee 2016	Gefitinib	80	10.9	0.57 (0.27–1.22); 0.148	7.13	0.73 (0.39–1.38); p=0.335
	Erlotinib	18	8.7		6.03	
Suh 2016	Erlotinib	5	NR	1.799 (0.654–4.949); 0.255	NR	1.55 (0.566–4.247); p=0.394
	Gefitinib	146				
Wu 2016	Gefitinib	42	NR	0.51 (0.29–0.91); 0.022 HR for afatinib vs gefitinib	NR	NR
	Afatinib	49				
Yu 2016	Erlotinib	Unclear	NR	HR for erlotinib vs gefitinib: 1.862 (0.581–5.962); p=0.295 HR for icotinib vs gefitinib: 1.917 (0.551–6.664); p=0.306	NR	HR for erlotinib vs gefitinib: 0.828 (0.531–1.291); p=0.405 HR for icotinib vs gefitinib: 0.652 (0.359–1.184); p=0.160
	Gefitinib	Unclear				

Study name	Treatment	Number of patients	OS (months)		PFS (months)	
			Median (95% CI)	HR (95% CI); p value	Median (95% CI)	HR (95% CI); p value
	Icotinib	Unclear				
Lin 2014	Erlotinib	57	NR	1.99 (1.08–3.68); p= 0.03	NR	1.70 (0.97–2.99); p=0.06
	Gefitinib	24				
Lee 2013	Erlotinib	31	Not reached	1.026 (0.54–1.949); 0.937 HR for gefitinib vs erlotinib	11.2	1.131 (0.674–1.897); p=0.641 HR for gefitinib vs erlotinib
	Gefitinib	139	23.2		11.4	
Verduyn 2012	Gefitinib	NR	NR	NR	10.5[c] (8.9–12.4)	HR for gefitinib vs carboplatin + paclitaxel: 0.43 (0.34–0.53)
	Carboplatin + paclitaxel	NR			6.7[c] (5.9–7.4)	
	Cisplatin + gemcitabine	NR			7[c] (6.1–7.9)	
	Cisplatin + pemetrexed	NR			7.2[c] (6.2–8.2)	
Yoshida 2010	Gefitinib	23	NR	NR	7.8	0.512 (0.275–0.956); p=0.0323
	Cytotoxic chemotherapy	25			5.1	

Key: CI, confidence interval; CNS, central nervous system; CT, chemotherapy; HR, hazard ratio; IQR, interquartile range; NR, not reported; OS, overall survival; PFS, progression-free survival; TKI, tyrosine kinase inhibitor.

Notes: [a], data reported for CNS-PFS; [b] data reported as median (IQR); [c], data reported as mean.

The HR ratio reported was between the treatment in the upper row versus lower row unless specified otherwise.

D.2.5 Safety outcomes

The data for drug-related safety variables are presented in Table 115. The safety data for the AURA study have been reported at a data cut-off of 01 November 2016, unless otherwise mentioned.

Adverse events due to any cause

Data for patients who experienced any grade AE due to any cause were reported in five studies.[386, 387, 405, 408, 410] Two of these studies reported the proportion of patient who experienced any grade AE.[387, 405] All patients in the AURA trial experienced any grade AEs.[387] In the OCTOMUT study, 85.7%, 88.6% and 92.5% of patients in the afatinib, gefitinib and erlotinib groups experienced any grade AE.[405] The study by Frega et al. reported that no statistically significant difference was observed between the three TKI arms (gefitinib, erlotinib and afatinib).[410] Overall, in the three treatment arms, only patients in gefitinib group experienced AEs of Grade 1 [5 (33%)], Grade 2 [6 (35%)] and Grade 3 [1 (6%)]. The study by Skrickova et al. reported qualitative data only.[408] The study mentioned that no statistically significant difference was observed between the treatment arms (gefitinib, erlotinib and afatinib). The study by Udupa et al. reported data for specific AEs such as interstitial fibrosis, increased SGOPT/SGPT, hand foot syndrome and conjunctivitis.[386]

Two studies reported data for the incidence of any Grade 3/4 AEs.[387, 415] In the AURA trial, Grade 3/4 AEs were experienced by 60% of the osimertinib (80mg) group and 63% of the osimertinib (160mg) group.[387] In the study by He et al., only qualitative data were reported, indicating that gefitinib plus platinum doublet chemotherapy was associated with more haematological Grade 3/4 AEs compared to gefitinib.[415]

Only the AURA study reported data for SAE incidence which was 47% and 30% in the 80mg and 160mg groups, respectively.[387] None of the studies reported data for the incidence of Grade 3/4 SAEs.

Data for the incidence of diarrhoea were reported in two studies.[386, 405] In the study by Udupa et al. the incidence was 8.7% with gefitinib and 18.2% with erlotinib..[386] In the OCTOMUT study, the incidence was 43.7%, 66.7% and 100% with gefitinib, erlotinib and afatinib, respectively.[405] The incidence of Grade 3/4 diarrhoea was reported in two studies, OCTUMUT[405] and AURA.[387];In the OCTUMUT study, the incidence was 10%, 14.2% and 33.3% with erlotinib, gefitinib and afatinib, respectively.[405] In the AURA study, at data cut off 04 January 2016, Grade 3/4 diarrhoea was experienced by none in the 80mg group and 7% of the 160mg group.[387]

Only the AURA study reported the incidence of any grade and Grade 3/4 fatigue.[387] Fatigue of any grade was experienced by 23% and 27% in the 80mg and 160mg groups, respectively, and none of the patients in either groups experienced Grade 3/4 fatigue at the data cut-off on 04 January 2016.

None of the studies reported data for incidence of any grade and Grade 3/4 anaemia.

Incidence of any grade neutropenia was reported only in the study by He et al.[415] The incidence was reported to be 0% with gefitinib compared to 27.6% with gefitinib plus platinum-based chemotherapy. None of the studies reported data for incidence of Grade 3/4 neutropenia.

AURA and the study by Udupa et al. reported data for the incidence of rash of any grade.[386, 387] In the study by Udupa et al., the incidence of any grade rash was 30.4% with gefitinib compared to 81.8% with erlotinib. In the AURA study, the incidence of any grade rash was 70% and 87% with osimertinib 80mg and 160mg, respectively at data cut off 04 January 2016.[387] The incidence of Grade 3/4 rash was reported in two studies.[386, 387] In the study by Udupa et al, 4.3% with gefitinib compared to 45.5% with erlotinib.[386] In the AURA study, none of the patients in the osimertinib 80mg group experienced a Grade 3/4 event of rash compared with 3% in the osimertinib 160mg group at data cut off 04 January 2016.[387]

Only the study by He et al. reported data for the incidence of any grade thrombocytopenia.[415] The incidence was 0% with gefitinib and 13.8% with gefitinib plus platinum-based chemotherapy.

Drug-related adverse events

Two studies reported data for the proportion of patients who experienced drug-related AEs due to any cause.[387, 410] In the AURA study, the majority of patients experienced drug-related AEs (97% of 80mg and 100% of 160mg).[387] In the other study by Frega et al., the incidence of AEs was 67%, 73% and 100% with erlotinib, gefitinib and afatinib, respectively.[410] Only the AURA study reported data for Grade 3/4 AEs in which were 13% and 23% of the osimertinib 80mg and 160mg groups, respectively.[387]

Only the AURA study reported data for SAEs which were reported in 13.0% and 3.0% of the 80mg and 160mg groups, respectively.[387]

The incidence of any grade anaemia was reported only in the AURA study which was 23% and 30% with osimertinib 80mg and 160mg, respectively.[387]

Two studies reported data for the incidence of any grade diarrhoea.[387, 410] The incidence was 60% with osimertinib 80mg and 87% with osimertinib 160mg in the AURA study.[387] In the other study by Frega et al., the incidence of any grade diarrhoea was 0%, 45% and 100% with erlotinib, gefitinib and afatinib, respectively.[410] None of the studies reported data for incidence of Grade 3/4 diarrhoea.

Two studies reported data for incidence of any grade fatigue.[387, 410] The incidence was 33% of 80mg and 33% of 160mg in the AURA study.[387] In the other study by Frega et al., the incidence of any grade fatigue was 0%, 36% and 0% with erlotinib, gefitinib and afatinib, respectively.[410] None of the studies reported data for incidence of Grade 3/4 fatigue.

Two studies reported data for the incidence of any grade rash.[387, 410] The incidence was 73% with osimertinib 80mg and 87% with osimertinib 160mg in the AURA study.[387] In the other study by Frega et al., the incidence of any grade rash was 67%, 36% and 33% with erlotinib, gefitinib and afatinib, respectively.[410] None of the studies reported data for incidence of Grade 3/4 rash.

None of the patients experienced an event of drug-related haematological disorder (neutropenia or thrombocytopenia).

Table 115: Drug-related adverse events

Study name	Treatment	Number of patients	Any AE n (n%) p-value		Any SAE n (n%) p-value	
			Any grade	Grade 3/4	Any grade	Grade 3/4
Frega 2017	Gefitinib	11	8 (73)	NR	NR	NR
	Erlotinib	3	2 (67); p=1.0	NR	NR	NR
	Afatinib	3	3 (100)	NR	NR	NR
	Chemotherapy	NR	NR	NR	NR	NR
Ramalingam 2017 (AURA)	Osimertinib: 80mg	30	29 (97)	4 (13)	4 (13)	NR
	Osimertinib: 160mg	30	30 (100)	7 (23)	1 (3)	NR
Key: AE, adverse event; NR, not reported; SAE, serious adverse event.						

D.2.6 Tolerability outcomes

Data for study/treatment withdrawals were reported in five studies.[387, 393, 410, 413, 416] Two studies reported data for patients lost to follow-up, but only for the overall population and not according to treatment arm.[413, 416] In the study by Arriola et al.[413], 5.5% were lost to follow-up, whereas in the study by Inoue et al.[416], 21.7% were lost to follow-up. In the study by Frega et al., no cases of permanent discontinuation were observed.[410] In the AURA study, overall, 35% of patients discontinued treatment; data were not reported according to treatment arm.[387] Also, in the study by Guerreiro et al., it was reported that one patient in the gefitinib arm suspended treatment because of arthritis.[393]

In the AURA study, 10% of patients in each arm discontinued treatment due to AEs.[387] In the study by Frega et al., it was reported that treatment was temporary interrupted in two patients receiving afatinib due to AEs.[410] Similarly, in the AURA study, patients who discontinued treatment due to drug-related AEs were 7% and 3% in the 80mg and 160mg groups, respectively.[387]

The dose modifications across the studies are presented in Table 116..

Table 116: Summary of dose modifications in non-randomised studies

Study name	Treatment	Dosing details
Kuan 2017	Gefitinib	A reduction in the dose being permitted on an individual basis
	Erlotinib	The dose could be reduced to 100 mg if there were intolerable side effects.
	Afatinib	A reduction to 30 mg being permitted if necessary
Ramalingam 2017	Osimertinib: 80mg	Three patients experienced AEs leading to dose reduction to 40 mg
	Osimertinib: 160mg	Eight patients (60%) had their dose reduced to 80 mg, of whom 16 (89%) had dose reductions as a result of an AE. In patients with dose reduction due to AE: 13 of 14 patients in the 160-mg group had a single dose reduction to 80 mg, and one patient had two dose reductions, first to 80 mg then to 40 mg.
Udupa 2017	Erlotinib	Of the nine patients who developed skin rash with erlotinib, 4 required dose reductions from 150 mg to 100 mg. In the other 4 patients, erlotinib was changed to gefitinib, as reducing the dose did not result in decrease in skin toxicities. All four patients tolerated gefitinib well, and three of them had Grade 1 rash. In only one patient, erlotinib was continued at 150 mg after treating skin rash with antihistamines and clindamycin topical ointment.
Guerreiro 2016	Erlotinib	Ten patients in the erlotinib group required dose reductions because of drug related toxic effects, 9 because of rash Grade 3 and 1 because of hepatotoxicity.
	Gefitinib	One patient in the gefitinib group suspended treatment because of arthritis.
Lee 2013	Erlotinib	Permanent dose reduction to 100 mg daily for erlotinib, was used when TKI was suspended for more than 14 days.
	Gefitinib	Permanent dose reduction to 5 days a week for gefitinib, was used when TKI was suspended for more than 14 days. It was also reported that no patient has permanently stopped TKI therapy.

Study name	Treatment	Dosing details
Key: AE, adverse event; NR, not reported; TKI, tyrosine kinase inhibitor.		

D.2.7 Quality of life

Only the study by Yang et al. reported qualitative QoL data that stated that scores using EQ-5D and WHOQoL-Brief questionnaires, did not differ significantly between erlotinib and gefitinib. Also, the scores were lower after 10 months of treatment with afatinib compared with gefitinib.[388]

D.2.8 Quality assessment using Downs and Black checklist

The quality of the non-RCTs was evaluated using the Downs and Black checklist.[162] Each item in this checklist is checked as 'yes', 'no', or 'unable to determine', and these were scored as 1, 0, and 0, respectively. Each item is stated positively; that is, it represents a desired design or reporting feature. A higher score indicates the higher quality of the study.

The results of quality assessment for 38 non-RCTs/observational studies are presented in Table 117 and Table 118. Across these 38 studies, the total score was between 15 and 20 in 18 studies[387, 388, 390, 391, 394, 397, 403, 404, 406, 410-414, 416-418, 422], between 10 and 14 in nine studies[386, 389, 393, 395, 399, 405, 407, 421, 423] and between 5 and 9 in 11 studies.[392, 396, 398, 400-402, 408, 409, 415, 419, 420]

Table 117: Results of Downs and Black checklist

Question No.	Arriola 2018	Corre 2018	Hung 2018	Yang 2018	Barnet 2017	Frega 2017	He 2017	Hsia 2017	Koyama 2017	Kuan 2017	Li 2017	Li 2017	Ramalingam 2017	Shen 2017	Skrickova 2017	Tu 2017	Udupa 2017	Wang 2017	Wang 2017
1.	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unc	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2.	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unc	Unc	Yes	Yes	Yes
3.	Yes	Yes	Yes	Yes	Yes	Yes	Unc	Yes	Unc	Yes	yes	Yes	Yes	Yes	Unc	Unc	Yes	Unc	Yes
4.	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unc	Yes	Yes	Yes	Yes	Unc	Yes	Yes	Yes
5.	No	No	Yes	Yes	No	No	Unc	Unc	Unc	Yes	Unc	Yes	Yes	Yes	Unc	Unc	Yes	Unc	Yes
6.	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
7.	Yes	Yes	Yes	Yes	Yes	Yes	yes	Unc	Unc	Yes	yes	Yes	Yes	Yes	Yes	Yes	No	Unc	No
8.	No	No	No	No	No	yes	Unc	Unc	Unc	No	Unc	No	Yes	No	Unc	Unc	Yes	Unc	No
9.	No	No	No	No	No	No	Unc	Unc	Unc	NA	Unc	NA	No	No	Unc	Unc	No	Unc	Yes
10.	No	No	Yes	Yes	No	Yes	Unc	Unc	Unc	Yes	Yes	Yes	No	Yes	yes	Unc	No	Unc	Yes
11.	Yes	Yes	Yes	Yes	Yes	Yes	Unc	Unc	Unc	Yes	Unc	Yes	Yes	Yes	Unc	Yes	Yes	Unc	Yes
12.	Yes	Yes	Yes	Yes	Yes	Yes	Unc	Unc	Unc	Yes	Unc	No	Yes	Yes	Unc	Yes	Yes	Unc	Yes
13.	Yes	Yes	Yes	Yes	Yes	Yes	Unc	Unc	Unc	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Unc	Yes

Question No.	Arriola 2018	Corre 2018	Hung 2018	Yang 2018	Barnet 2017	Frega 2017	He 2017	Hsia 2017	Koyama 2017	Kuan 2017	Li 2017	Li 2017	Ramalingam 2017	Shen 2017	Skrickova 2017	Tu 2017	Udupa 2017	Wang 2017	Wang 2017
14.	No	No	No	No	NA	No	No	NA	NA	NA	No	NA	No	No	No	No	No	NA	NA
15.	No	No	No	No	NA	No	No	NA	NA	NA	No	NA	No	No	No	No	No	NA	NA
16.	No	No	No	No	Yes	No	Unc	Unc	Unc	No	Unc	No	No	No	Unc	Unc	No	Unc	Yes
17.	Yes	No	No	Yes	No	No	Unc	Unc	Unc	Yes	Unc	No	Yes	No	Unc	Unc	Yes	Unc	Yes
18.	Yes	Yes	Yes	Yes	Yes	Yes	Unc	Unc	Unc	Yes	Unc	Yes	Yes	Yes	Unc	Yes	No	Unc	Yes
19.	No	No	No	No	Yes	No	Unc	Unc	Unc	Yes	Unc	NA	No	No	Unc	Unc	No	Unc	Yes
20.	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unc	Yes	Yes	Yes	Unc	Yes	Yes	Yes	Yes
21.	Yes	Yes	Yes	Yes	Yes	Yes	Unc	Unc	Unc	Yes	Unc	No	No	Yes	Unc	Yes	Yes	Unc	Yes
22.	Yes	Yes	Yes	Yes	Yes	Yes	Unc	Unc	Unc	Yes	Yes	Yes	Yes	Yes	Unc	Yes	Yes	Unc	Yes
23.	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
24.	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
25.	No	No	No	Yes	Yes	No	Unc	Unc	Unc	Yes	Unc	No	No	No	Unc	Unc	No	Unc	Yes
26.	Yes	No	No	No	No	No	Unc	Unc	Unc	No	Unc	NA	No	No	Unc	Unc	No	Unc	Yes

Key: Unc, unclear.

Notes: 1. Is the hypothesis/aim/objective of the study clearly described?

2. Are the main outcomes to be measured clearly described in the introduction or methods section?

3. Are the characteristics of the patients included in the study clearly described?

4. Are the interventions of interest clearly described?

5. Are the distributions of principal confounders in each group of patients to be compared clearly described?

6. Are the main findings of the study clearly described?

7. Does the study provide estimates of the random variability in the data for the main outcomes?

8. Have all important adverse events that may be a consequence of the intervention been reported?

9. Have the characteristics of patients lost to follow-up been described?

10. Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?

11. Were the subjects asked to participate in the study representative of the entire population from which they were recruited?

12. Were those subjects who were prepared to participate representative of the entire population from which they were recruited?

13. Were the staff, places, and facilities where the patients were treated representative of the treatment the majority of patients receive?

14. Was an attempt made to blind study subjects to the intervention they have received?

15. Was an attempt made to blind those measuring the main outcomes of the intervention?

16. If any of the results of the study were based on 'data dredging', was this made clear?

17. In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls?

18. Were the statistical tests used to assess the main outcomes appropriate?

19. Was compliance with the intervention(s) reliable?

20. Were the main outcome measures used accurate (valid and reliable)?

21. Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?

22. Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time?

Question No.	Arriola 2018	Corre 2018	Hung 2018	Yang 2018	Barnet 2017	Frega 2017	He 2017	Hsia 2017	Koyama 2017	Kuan 2017	Li 2017	Li 2017	Ramalingam 2017	Shen 2017	Skrickova 2017	Tu 2017	Udupa 2017	Wang 2017	Wang 2017
23. Were study subjects randomised to intervention groups?																			
24. Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?																			
25. Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?																			
26. Were losses of patients to follow-up taken into account?																			

Table 118: Results of Downs and Black checklist contd.

Question No.	Batra 2016	Guerreiro 2016	Inoue 2016	Ito 2016	Jiang 2016	Kashima 2016	Li 2016	Liu 2016	Lv 2016	Shee 2016	Suh 2016	Wu 2016	Yoshida 2016	Yu 2016	Zhang 2015	Lin 2014	Lee 2013	Verduyn 2012	Yoshida 2010
1.	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2.	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3.	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Unc	Yes	Yes	Yes	Yes	Yes	Yes	Yes
4.	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
5.	Unc	Unc	Yes	Unc	Yes	No	No	Yes	Yes	Unc	Yes	Unc	Unc	No	Yes	Yes	Yes	No	Yes
6.	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
7.	No	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Unc	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
8.	No	Yes	No	No	No	No	Yes	Yes	No	No	No	Unc	Unc	No	No	No	No	No	No
9.	NA	NA	No	NA	NA	Yes	NA	No	No	Unc	No	Unc	No	NA	NA	No	NA	NA	NA
10.	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	yes	Yes	Yes	yes	Yes	Yes	Yes	Yes	Yes
11.	Unc	Unc	No	Unc	Yes	Yes	Yes	Yes	Yes	Unc	Yes	Yes	No	Yes	Yes	Yes	No	No	Yes
12.	Unc	Unc	Yes	Unc	Yes	Yes	Yes	Yes	Yes	Unc	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes
13.	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unc	Yes	Yes	No	Yes	Yes	Yes	No	No	Yes
14.	NA	NA	No	NA	NA	NA	NA	No	No	No	No	Unc	No	NA	NA	No	NA	NA	NA
15.	NA	NA	No	NA	NA	NA	NA	No	No	No	No	Unc	No	NA	NA	No	NA	NA	NA
16.	Unc	Unc	No	Unc	No	No	No	Yes	Yes	Unc	No	Unc	Unc	No	No	No	No	No	No
17.	Unc	Unc	Yes	Unc	No	Yes	Yes	Yes	Yes	No	No	Unc	No	No	No	No	No	No	No
18.	Unc	Unc	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
19.	Unc	Unc	No	Unc	NA	No	Yes	No*	No	Unc	Yes	Unc	Unc	Yes	NA	Yes	NA	No	NA
20.	Unc	Unc	Yes	Unc	Yes	No	Yes	Yes	Yes	Yes	Yes	Unc	Yes	Yes	Yes	Yes	Yes	No	Yes
21.	Unc	Unc	yes	Unc	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes
22.	Yes	Yes	yes	Yes	Yes	Yes	No*	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	No	Yes
23.	NA	NA	NA	NA	NA	NA	NA	No	No	No	No	No	No	NA	NA	No	NA	NA	NA
24.	NA	NA	NA	NA	NA	NA	NA	No	No	No	No	No	No	NA	NA	No	NA	NA	NA

Question N	Batra 2016	Guerreiro 2016	Inoue 2016	Ito 2016	Jiang 2016	Kashima 2016	Li 2016	Liu 2016	Lv 2016	Shee 2016	Suh 2016	Wu 2016	Yoshida 2016	Yu 2016	Zhang 2015	Lin 2014	Lee 2013	Verduyn 2012	Yoshida 2010
25.	Unc	Unc	No	Unc	No	No	No	Yes	Yes	Unc	Yes	Unc	Unc	No	No	Yes	Yes	No	No
26.	NA	NA	Yes	NA	NA	Yes	No	No*	No	Unc	No	Unc	No	No	NA	No	NA	NA	NA

Key: Unc, unclear.

Notes: 1. Is the hypothesis/aim/objective of the study clearly described?

2. Are the main outcomes to be measured clearly described in the introduction or methods section?

3. Are the characteristics of the patients included in the study clearly described?

4. Are the interventions of interest clearly described?

5. Are the distributions of principal confounders in each group of patients to be compared clearly described?

6. Are the main findings of the study clearly described?

7. Does the study provide estimates of the random variability in the data for the main outcomes?

8. Have all important adverse events that may be a consequence of the intervention been reported?

9. Have the characteristics of patients lost to follow-up been described?

10. Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?

11. Were the subjects asked to participate in the study representative of the entire population from which they were recruited?

12. Were those subjects who were prepared to participate representative of the entire population from which they were recruited?

13. Were the staff, places, and facilities where the patients were treated representative of the treatment the majority of patients receive?

14. Was an attempt made to blind study subjects to the intervention they have received?

15. Was an attempt made to blind those measuring the main outcomes of the intervention?

16. If any of the results of the study were based on 'data dredging', was this made clear?

17. In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls?

18. Were the statistical tests used to assess the main outcomes appropriate?

19. Was compliance with the intervention(s) reliable?

20. Were the main outcome measures used accurate (valid and reliable)?

21. Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?

22. Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time?

23. Were study subjects randomised to intervention groups?

24. Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?

25. Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?

26. Were losses of patients to follow-up taken into account?

D.3 Indirect comparison

D.3.1 Methods of the indirect treatment comparison

As described in the main submission, an analysis of the log cumulative hazard plots for survival outcomes in LUXLung 7 suggests that it is appropriate to consider afatanib to have equivalent efficacy to gefitinib.

Appendix E: Subgroup analysis

Relevant subgroup analyses are presented in B.2.7.

Appendix F: Adverse reactions

No studies reporting additional adverse reactions to those described in the main dossier or Appendix D have been identified.

Appendix G: Published cost-effectiveness studies

G1.1 Search strategies

Table 119: Embase and MEDLINE using Embase.com (19 February 2018)

S. No.	Search Terms	Results
1.	'non small cell lung cancer' OR 'non small cell lung cancer'/syn OR 'non small cell lung cancer'/exp OR nsclc OR ('lung'/exp AND ('neoplasm'/exp OR 'cancer'/exp OR 'carcinoma'/exp OR 'malignancy'/exp OR 'tumour'/exp)) OR 'non-small-cell' OR 'non-small cell' OR 'non small cell' OR 'nonsmall cell' OR (lung NEAR/3 (cancer* OR carcin* OR neoplasm* OR tumour* OR tumor* OR squamous OR adenocarcinoma*)):ab,ti	312,627
2.	'tyrosine kinase inhibitor'/exp OR 'protein tyrosine kinase inhibitor'/exp OR 'protein kinase inhibitor'/exp OR 'epidermal growth factor receptor kinase inhibitor'/exp OR 'protein serine threonine kinase inhibitor'/exp OR 'tyrosine kinase inhibitor'/syn OR 'tyrosine kinase inhibitor' OR tki:ab,ti OR tkis:ab,ti OR 'afatinib'/syn OR 'afatinib'/exp OR afatinib OR gilotrif OR 'bibw 2992 ma2' OR 'erlotinib'/syn OR 'erlotinib'/exp OR erlotinib OR tarceva OR 'cp-358774'OR 'osi-774' OR 'gefitinib'/syn OR 'gefitinib'/exp OR gefitinib OR iressa OR 'zd 1839' OR 'imatinib'/syn OR 'imatinib'/exp OR 'imatinib' OR gleevec OR 'sti-571' OR 'sti 571' OR 'dacomitinib'/syn OR 'dacomitinib'/exp OR 'dacomitinib' OR 'pf-00299804' OR 'pf 00299804' OR 'dasatinib'/syn OR 'dasatinib'/exp OR 'dasatinib' OR sprycel OR 'bms-354825' OR 'bms 354825' OR 'sunitinib'/syn OR 'sunitinib'/exp OR 'sunitinib' OR sutent OR 'su11248' OR 'su-11248' OR 'naquotinib'/syn OR 'naquotinib'/exp OR 'naquotinib' OR 'asp8273' OR 'asp-8273' OR 'osimertinib'/syn OR 'osimertinib'/exp OR osimertinib OR mereletinib OR tagrisso OR 'azd9291'	374,993
3.	'economics'/exp OR 'costs and cost analysis'/exp OR 'cost allocation'/exp OR 'cost-effectiveness'/exp OR 'cost-utility'/exp OR 'economic evaluation'/exp OR 'cost effectiveness analysis'/exp OR 'cost utility analysis'/exp OR 'cost minimization analysis'/exp OR 'cost benefit analysis'/exp OR 'cost control'/exp OR 'cost savings'/exp OR 'cost of illness'/exp OR 'cost sharing'/exp OR 'deductibles and coinsurance'/exp OR 'medical savings accounts'/exp OR 'health care costs'/exp OR 'direct service costs'/exp OR 'drug costs'/exp OR 'employer health costs'/exp OR 'hospital costs'/exp OR 'health expenditures'/exp OR 'capital expenditures'/exp OR 'value of life'/exp OR 'economics, medical'/exp OR 'economics, hospital'/exp OR 'economics, nursing'/exp OR 'economics, pharmaceutical'/exp OR 'budget'/exp OR 'fees and charges'/exp OR (low NEXT/1 costs):ab,ti OR (high NEXT/1 costs):ab,ti OR (healthcare NEXT/1 cost*):ab,ti OR	1,552,411

	fiscal:ab,ti OR funding:ab,ti OR financial:ab,ti OR finance:ab,ti OR (cost NEXT/1 estimate*):ab,ti OR (cost NEXT/1 variable*):ab,ti OR (unit NEXT/1 cost*):ab,ti OR economic*:ab,ti OR 'cost-effectiveness':ab,ti OR 'cost-utility':ab,ti OR pharmacoeconomic*:ab,ti OR price*:ab,ti OR pricing:ab,ti OR 'cost effectiveness':ab,ti OR 'cost utility':ab,ti OR 'cost minimization':ab,ti OR 'cost minimisation':ab,ti OR 'economic evaluation':ab,ti OR cea:ab,ti OR cua:ab,ti OR markov:ab,ti OR (decision NEXT/2 tree*):ab,ti OR (decision NEXT/2 analysis*):ab,ti OR (monte NEXT/1 carlo):ab,ti	
4.	#1 AND #2 AND #3	2,577
5.	letter:it OR editorial:it OR (review:it OR 'review literature as topic'/exp OR 'literature review':ti NOT ('meta-analysis':it OR 'meta-analysis as topic'/mj OR 'systematic review':ti OR 'systematic literature review':ti OR 'meta-analysis':ab,ti OR 'meta analysis':ab,ti)) OR ('animal'/exp NOT ('animal'/exp AND 'human'/exp)) OR 'case report*':ab,ti OR 'case series':ab,ti	9,167,961
6.	#4 NOT #5	1,591
7.	#4 NOT #5 AND [english]/lim AND [2007-2018]/py	1,368

Table 120: Medline In-Process using Pubmed.com (19 February 2018)

S. No.	Search Terms	Results
1.	Non small cell lung cancer[MH] OR nsclc[tiab]	53,192
2.	Neoplasm[MH] OR Squamous cell carcinoma[MH] OR Adenocarcinoma[MH]	3,068,342
3.	Lung[MH]	257,708
4.	#2 AND #3	29,792
5.	(lung[tiab] OR pulmon*[tiab] OR brochial[tiab]) AND (cancer*[tiab] OR carcin*[tiab] OR neoplasm*[tiab] OR tumour*[tiab] OR tumor*[tiab] OR squamous[tiab] OR adenocarcinoma*[tiab])	272,334
6.	#4 OR #5	286,910
7.	"non small cell"[tiab] OR "non-small-cell"[tiab] OR "nonsmall cell"[tiab]	53,035
8.	#6 AND #7	52,649
9.	#1 OR #8	62,486
10.	Osimertinib OR Tagrisso	290
11.	Imatinib OR Gleevec	13,860
12.	Gefitinib OR Iressa	6,300
13.	Erlotinib OR Tarceva	5,879
14.	Dacomitinib OR "pf-00299804" OR "pf 00299804"	143
15.	Afatinib OR gilotrif	881
16.	Dasatinib OR sprycel	2,871
17.	Sunitinib OR Sutent	5,172
18.	Naquotinib OR ASP8273	12
19.	#10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18	29,656
20.	#9 AND #19	5,667
21.	#20 AND (publisher[sb] NOT pubstatusnihms NOT pubstatuspmcsd NOT pmcbook) OR (pubstatusaheadofprint)	27

Table 121: HTA and NHSEED using Wiley Interscience (18 May 2017)

S. No.	Search Terms	Results
1	[mh "non small cell lung cancer"] or nsclc:ab,ti,kw	5,775
2	[mh neoplasm] or [mh "squamous cell carcinoma"] or [mh adenocarcinoma]	61,198
3	[mh lung]	3,742

4	#2 and #3	245
5	((lung or pulmon* or bronchial) near/3 (cancer* or carcin* or neoplasm* or tumour* or tumor* or squamous or adenocarcinoma*)):ab,ti,kw	13,005
6	#4 or #5	13,053
7	("non small cell" or "non-small-cell" or "nonsmall cell"):ab,ti,kw	6,880
8	#6 and #7	6,776
9	#1 or #8	7,160
10	(Osimertinib or Tagrisso):ab,ti,kw	23
11	(Imatinib or Gleevec):ab,ti,kw	910
12	(Gefitinib or Iressa):ab,ti,kw	500
13	(Erlotinib or Tarceva):ab,ti,kw	845
14	Dacomitinib:ab,ti,kw or "PF-00299804" or "PF 00299804"	40
15	(Afatinib or Gilotrif):ab,ti,kw	177
16	Dasatinib:ab,ti,kw or "BMS-354825" or "BMS 354825" or SPRYCEL:ab,ti,kw	262
17	(Sunitinib* or Sutent):ab,ti,kw	586
18	(Naquotinib or ASP8273):ab,ti,kw	3
19	#10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18	2,780
20	#9 and #19	869
21	#20 [Publication Year from 2007 to 2017]	803
22	#21 in Technology Assessments	30
23	#21 in Economic Evaluations	20

Table 122: EconLit using EBSCO.com (18 May 2017)

S. No.	Search Terms	Search Options	Results
1	SU non small cell lung cancer OR TI nsclc OR AB nsclc	**Expanders** - Also search within the full text of the articles; Apply equivalent subjects **Search modes** - Find all my search terms	176,256
2	SU neoplasms OR SU squamous cell carcinoma OR SU adenocarcinoma	**Expanders** - Also search within the full text of the articles; Apply equivalent subjects **Search modes** - Find all my search terms	3,788,474
3	SU lung	**Expanders** - Also search within the full text of the articles; Apply equivalent subjects **Search modes** - Find all my search terms	1,107,334
4	S2 AND S3	**Expanders** - Also search within the full text of the articles; Apply equivalent subjects **Search modes** - Find all my search terms	276,114
5	TI ((lung OR pulmon* OR brochial) AND (cancer* OR carcin* OR neoplasm* OR tumour* OR tumor* OR squamous OR adenocarcinoma*)) OR AB ((lung OR pulmon* OR brochial) AND (cancer* OR carcin* OR neoplasm* OR tumour* OR tumor* OR squamous OR adenocarcinoma*))	**Expanders** - Also search within the full text of the articles; Apply equivalent subjects **Search modes** - Find all my search terms	1,223,048

6	S4 OR S5	**Expanders** - Also search within the full text of the articles; Apply equivalent subjects **Search modes** - Find all my search terms	1,301,846
7	TI ("non small cell" OR "non-small-cell" OR "nonsmall cell") OR AB ("non small cell" OR "non-small-cell" OR "nonsmall cell")	**Expanders** - Also search within the full text of the articles; Apply equivalent subjects **Search modes** - Find all my search terms	234,687
8	S6 AND S7	**Expanders** - Also search within the full text of the articles; Apply equivalent subjects **Search modes** - Find all my search terms	233,117
9	S1 OR S8	**Expanders** - Also search within the full text of the articles; Apply equivalent subjects **Search modes** - Find all my search terms	277,937
10	Osimertinib OR Tagrisso	**Expanders** - Also search within the full text of the articles; Apply equivalent subjects **Search modes** - Find all my search terms	2,932
11	Imatinib OR Gleevec	**Expanders** - Also search within the full text of the articles; Apply equivalent subjects **Search modes** - Find all my search terms	171,518
12	Gefitinib OR Iressa	**Expanders** - Also search within the full text of the articles; Apply equivalent subjects **Search modes** - Find all my search terms	97,055
13	Erlotinib OR Tarceva	**Expanders** - Also search within the full text of the articles; Apply equivalent subjects **Search modes** - Find all my search terms	107,467
14	Dacomitinib OR "pf-00299804" OR "pf 00299804"	**Expanders** - Also search within the full text of the articles; Apply equivalent subjects **Search modes** - Find all my search terms	2,285
15	Afatinib OR gilotrif	**Expanders** - Also search within the full text of the articles; Apply equivalent subjects **Search modes** - Find all my search terms	9,669
16	Dasatinib OR sprycel	**Expanders** - Also search within the full text of the articles; Apply equivalent subjects **Search modes** - Find all my search terms	41,258
17	Sunitinib OR Sutent	**Expanders** - Also search within the full text of the articles; Apply equivalent subjects **Search modes** - Find all my search terms	79,557
18	Naquotinib OR ASP8273	**Expanders** - Also search within the full text of the articles; Apply equivalent subjects **Search modes** - Find all my search terms	233
19	S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18	**Expanders** - Also search within the full text of the articles; Apply equivalent subjects **Search modes** - Find all my search terms	376,376
20	S9 AND S19	**Expanders** - Also search within the full text of the articles; Apply equivalent subjects **Search modes** - Find all my search terms	38,078
21	S9 AND S19	**Limiters** - Date Published: 20070101-20170531 **Expanders** - Also search within the full text of the articles; Apply equivalent subjects **Search modes** - Find all my search terms	32,191
22	S9 AND S19	**Limiters** - Date Published: 20070101-20170531	7

	Source: Econlit	**Expanders** - Also search within the full text of the articles; Apply equivalent subjects **Search modes** - Find all my search terms	

G1.2 Critical appraisal of studies identified in economic systematic review

Table 123: Quality appraisal checklist for cost-effectiveness studies

Study name	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36
Cost-effectiveness studies																																				
Belousov et al., 2015	Y	Y	Y	Y	Y	Y	U	Y	Y	NA	Y	U	Y	U	U	U	U	Y	U	Y	U	Y	U	U	U	U	U	U	U	Y	Y	Y	Y	Y	U	U
Bradbury et al., 2010	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	Y	N	N	N	N	N	N	Y	Y	Y	N	Y	N	NA	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
Carlson et al., 2015	Y	Y	Y	Y	Y	Y	Y	U	U	NA	Y	U	U	U	U	U	U	Y	U	Y	U	N	Y	U	NA	N	Y	Y	Y	U	U	U	Y	Y	U	U
Chouaid et al., 2017	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	Y	Y	U	U	N	N	Y	Y	U	Y	U	Y	Y	Y	NA	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	N
Chung et al., 2013	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	Y	U	Y	U	U	U	U	Y	U	N	NA	Y	N	N	N	U	U	U	U	Y	Y	Y	Y	Y	U	U
Fragoulakis et al., 2011	Y	Y	Y	Y	Y	Y	Y	Y	NA	U	Y	U	U	U	U	U	U	Y	U	Y	U	U	Y	U	NA	U	Y	U	U	Y	Y	Y	Y	Y	U	U
Garrido et al., 2012	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	Y	U	U	U	U	U	U	Y	U	Y	U	Y	Y	U	NA	U	Y	U	U	Y	Y	Y	Y	Y	U	U
Graham et al., 2015	Y	Y	Y	Y	Y	Y	Y	Y	U	U	Y	U	U	U	U	U	U	Y	U	Y	Y	Y	Y	Y	NA	N	U	U	U	Y	Y	Y	Y	Y	N	U
Handorf et al., 2012	Y	Y	Y	Y	Y	Y	Y	Y	N	NA	Y	Y	Y	N	NA	Y	N	Y	N	Y	Y	N	N	NA	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N
Huicochea-Bartelt et al., 2015	Y	Y	Y	Y	Y	Y	Y	Y	NA	U	Y	U	U	U	U	U	U	Y	U	Y	U	Y	U	U	U	U	Y	U	U	Y	Y	Y	Y	Y	U	U
Hoang and Nguyen, 2016	Y	Y	Y	Y	Y	Y	Y	Y	U	NA	Y	U	U	U	U	U	U	Y	U	Y	U	Y	U	U	U	N	Y	Y	U	Y	Y	Y	Y	Y	U	U
Holleman et al., 2016	Y	Y	Y	Y	Y	Y	Y	Y	U	NA	Y	U	U	U	U	U	U	Y	U	Y	U	U	U	U	U	N	Y	U	U	Y	Y	Y	Y	Y	U	U
Horgan et al., 2011	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	Y	N	Y	N	N	N	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N	Y	Y	Y	N
Hsia et al., 2017	Y	Y	U	Y	Y	Y	U	Y	N	NA	Y	NA	NA	NA	N	N	U	Y	U	N	N	Y	N	NA	NA	U	N	NA	NA	U	U	N	Y	Y	N	N
Jacob et al., 2010	Y	Y	Y	U	U	Y	Y	Y	Y	NA	Y	U	Y	U	U	U	U	Y	U	Y	Y	Y	U	U	U	N	N	NA	NA	Y	Y	Y	Y	Y	U	U
Lechuga et al., 2012	Y	Y	Y	Y	Y	Y	Y	U	U	NA	Y	U	U	U	U	U	U	Y	U	Y	U	Y	U	U	U	N	U	U	U	Y	Y	Y	Y	Y	U	U
Lee et al.,2013	Y	Y	Y	Y	Y	Y	Y	Y	NA	Y	Y	N	Y	N	N	N	N	Y	Y	Y	Y	Y	Y	Y	NA	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Lester-Coll et al., 2016	Y	Y	Y	Y	Y	Y	Y	Y	N	N	Y	N	N	N	N	Y	N	Y	N	Y	N	Y	N	N	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
Lopes et al., 2012	Y	Y	Y	Y	Y	Y	Y	Y	NA	N	Y	N	N	N	N	N	N	Y	Y	Y	Y	N	N	NA	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
Lu et al., 2017	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N	N	N	Y	Y	Y	Y	Y	Y	Y	U	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
Narita et al., 2015	Y	Y	Y	Y	Y	Y	Y	Y	N	NA	Y	Y	N	N	NA	N	N	Y	Y	Y	Y	Y	Y	Y	NA	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N

Study name	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36
Piha et al., 2015	Y	Y	Y	Y	Y	Y	Y	Y	NA	U	Y	U	U	U	U	U	U	Y	U	Y	U	Y	U	U	U	N	U	U	U	Y	N	N	Y	Y	N	U
Polanco et al.2014	Y	Y	Y	U	Y	Y	U	Y	U	U	Y	N	U	U	U	U	U	Y	Y	Y	U	U	U	U	U	U	Y	U	U	U	Y	Y	Y	Y	U	U
Santoni et al.2017b	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	Y	U	Y	U	U	U	U	Y	Y	Y	Y	Y	Y	Y	NA	Y	U	U	U	Y	Y	Y	Y	Y	N	U
Santoni et al.2017a	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	Y	U	Y	U	U	U	U	Y	Y	Y	Y	Y	Y	Y	NA	Y	U	U	U	Y	Y	Y	Y	Y	N	U
Santoni et al.2017c	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	Y	U	Y	U	U	U	U	Y	Y	Y	Y	Y	Y	Y	NA	Y	U	U	U	Y	Y	Y	Y	Y	N	U
Ting et al.2015	Y	Y	Y	Y	Y	Y	Y	Y	NA	N	Y	N	N	N	N	N	N	Y	N	Y	Y	Y	Y	N	NA	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Tran and Nguyen2016	Y	Y	Y	Y	Y	Y	Y	Y	U	U	Y	U	U	U	U	U	U	Y	U	Y	U	Y	Y	U	NA	Y	U	U	U	Y	Y	Y	Y	Y	U	U
Veenstra et al.2013	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	Y	U	U	U	U	U	U	Y	U	Y	U	U	U	U	U	U	Y	U	U	Y	Y	Y	Y	Y	U	U
Vergnenegre et al.2016	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	Y	N	Y	N	N	N	Y	Y	Y	Y	Y	Y	Y	Y	NA	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
Wang et al.2013	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	Y	N	N	N	N	N	N	Y	N	Y	U	Y	Y	N	NA	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
Wen et al.2016	Y	Y	Y	Y	Y	Y	Y	Y	NA	N	Y	U	Y	U	U	U	U	Y	U	Y	U	U	U	U	U	U	U	U	U	Y	Y	Y	Y	Y	U	U
Yang and Tan2014	Y	Y	Y	Y	Y	Y	U	Y	NA	U	Y	U	U	U	U	U	U	Y	U	U	U	Y	U	U	U	N	U	U	U	Y	Y	Y	Y	Y	N	U
Zaim et al., 2014	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	Y	U	U	U	U	U	U	Y	U	Y	Y	Y	U	U	U	Y	Y	U	U	Y	Y	U	Y	Y	N	N
Zhan et al., 2017	Y	Y	Y	Y	Y	Y	Y	Y	U	U	Y	U	U	U	U	U	U	Y	U	Y	U	U	U	U	U	N	U	U	U	Y	Y	Y	Y	Y	N	U
Zhu et al., 2013	Y	Y	Y	Y	Y	Y	Y	Y	NA	Y	Y	N	Y	N	NA	N	Y	Y	N	Y	Y	Y	Y	Y	NA	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
Zhu et al., 2017	Y	Y	Y	Y	Y	Y	U	U	NA	N	Y	U	U	N	N	N	U	Y	U	Y	U	Y	Y	N	NA	N	U	U	N	Y	N	N	Y	U	N	N
HTA studies																																				
NICE[TA258], 2012	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	NA	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N
NICE[TA310], 2014	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	Y	Y	Y	N	NA	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N
NICE[TA416], 2016	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	NA	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y
NICE[TA192], 2010	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	NA	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y
Brown et al., 2013	Y	Y	Y	Y	Y	Y	Y	N	NA	Y	Y	Y	Y	N	NA	Y	Y	Y	N	Y	Y	Y	Y	Y	NA	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y

Note: Green represents "Y-yes", yellow represents "U-unclear", red represents "N-no", and no colour represents "NA-not applicable" as the answer to the question.

Questions 1-36: 1. Was the research question stated?
2. Was the economic importance of the research question stated?
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?
5. Were the alternatives being compared clearly described?
6. Was the form of economic evaluation stated?
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?

Study name	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36
8. Was/were the source(s) of effectiveness estimates used stated?																																				
9. Were details of the design and results of the effectiveness study given (if based on a single study)?																																				
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?																																				
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?																																				
12. Were the methods used to value health states and other benefits stated?																																				
13. Were the details of the subjects from whom valuations were obtained given?																																				
14. Were productivity changes (if included) reported separately?																																				
15. Was the relevance of productivity changes to the study question discussed?																																				
16. Were quantities of resources reported separately from their unit cost?																																				
17. Were the methods for the estimation of quantities and unit costs described?																																				
18. Were currency and price data recorded?																																				
19. Were details of price adjustments for inflation or currency conversion given?																																				
20. Were details of any model used given?																																				
21. Was there a justification for the choice of model used and the key parameters on which it was based?																																				
22. Was the time horizon of cost and benefits stated?																																				
23. Was the discount rate stated?																																				
24. Was the choice of rate justified?																																				
25. Was an explanation given if cost or benefits were not discounted?																																				
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?																																				
27. Was the approach to sensitivity analysis described?																																				
28. Was the choice of variables for sensitivity analysis justified?																																				
29. Were the ranges over which the parameters were varied stated?																																				
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?																																				
31. Was an incremental analysis reported?																																				
32. Were major outcomes presented in a disaggregated as well as aggregated form?																																				
33. Was the answer to the study question given?																																				
34. Did conclusions follow from the data reported?																																				
35. Were conclusions accompanied by the appropriate caveats?																																				
36. Were the generalisability issues addressed?																																				

G1.3 Description of identified studies

Table 124: Characteristics and results of included cost effectiveness studies

Study name	Intervention/ comparator	Line of therapy	Study type	• Model type • Health states • Cycle length	• Perspective • Time horizon	Outcomes	Costs	ICERs
Cost-effectiveness study								
Belousov et al., (2015)	• AFA • ERL • GEF • PEM+CIS	1L	CUA	• Markov model • NR • NR	• NR • 10 years	Incremental QALYs compared with AFA • ERL: 0.354 • GEF: 0.665 • PEM+CIS: 0.670	Total costs • AFA: 1,917,425 rubles • ERL: 1,544,852 rubles • GEF: 1,205,353 rubles • PEM+CIS: 1,203,865 rubles	Cost/QALY compared with AFA • ERL: 1,052,934 rubles • GEF: 1,067,116 rubles • PEM+CIS: 1,064,708 rubles
Bradbury et al., (2010)	• ERL • Placebo* *Patients previously treated with platinum-based therapy	2L	CUA	NR	• Canadian public health-care system • Less than 1 year	NR	NR	Cost/LYG (95% CI) • EGFRm population: $63,805 ($30,102 to $297,301) • EGFR gene mutation (Exon 19 deletion and/or exon 21 L858R mutation: $138 168 (-$1

								125 890 to $1 377 049)
Carlson et al., (2015)	• ERL • AFA	1L	CUA	• Markov model • Pre-progression, progression, and death • NR	• Payer • NR	Author reported comparable QALYs for both arms	Author reported treatment with ERL rather than AFA resulted in modest decreased costs (-$895)	NR
Chouaid et al., (2017)	• AFA • GEF	1L	CUA	• Partitioned Survival Model (PSM) • Progression-free; Progressed Disease and Death • 1 month	• Payer • 10 years	<u>Mean QALYs</u> • AFA: 1.857 • GEF: 1.687	<u>Total costs</u> • AFA: €62,166 • GEF: €54,469	ICER/QALY: €45,211
Chung et al., (2013)	• ERL • GEM+CIS	1L	CUA	NR	• Canadian Health perspective • Lifetime	<u>Mean QALYs</u> • ERL: 1.40 • CIS+GEM: 1.04	NR	Cost/QALY: $30,301
Fragoulakis et al., (2011)	• GEF • GEM+CARB • PAX+CARB • VNB+CIS • GEM+CIS • PEM+CIS	1L	CUA	• Markov model • Treatment response, SD, PD, and death • 1-month	• Provider and payer NR	<u>Mean QALYs (95% UI)</u> • GEF: 1.10 (0.89-1.28) • PEM+CIS: 1.04 (0.87-1.19) • GEM+CIS: 0.95 (0.80-1.05)	<u>From a provider perspective, total treatment cost per patient (95%UI)</u> • GEF: €61,865 (€52,848-€71,444) • PEM+CIS: €72,817	• GEF dominates all other options apart from VNB+CIS, which is the least costly option • Cost/QALY for GEF vs VNB+CIS

						• GEM+CARB: 0.91 (0.76-1.10) • PAX+CARB: 0.90 (0.77-1.00) • VNB+CIS: 0.87 (0.73-0.99)	(€65,213-€80,014) • GEM+CIS: €59,270 (€52,830-€65,530) • GEM+CARB: €60,842 (€50,113-€71,343) • PAX+CARB: €58,081 (€53,237-€62,628) • VNB+CIS: €54,468 (€46,874-€62,245)	• Provider's perspective: €9,662 • Payer's perspective: €27,369
Garrido et al., (2012)	• ERL • Platinum-based chemotherapy	1L	CEA	• Markov model • PFS, PD, and death • NR	• Spanish National Health System • 7 years	<u>Mean LYG for a cohort of 1,000 patients with a 7-year follow-up</u> • ERL: 2.61 • Platinum-based chemotherapy: 1.555	<u>Total mean treatment cost</u> • ERL: €22,458 • Platinum-based chemotherapy: €5,335	Cost/LYG: €28,261
Graham et al., (2015)	• AFA • ERL	1L	CUA	• PSM • PFS, PD, and death • NR	• US healthcare • 20 years	<u>LYs</u> • AFA: 3.09 • ERL: 2.46 <u>QALYs</u>	Incremental cost per patient for AFA: $ 32,961	• Cost/LYG: $52,401 • Cost/QALY: $74,345

						• AFA: 2.17 • ERL: 1.72		
Handorf et al., (2012)	• ERL • PAX+CARB • PEM+CARB • PEM+CARB+ BEV	1L	CUA	• Decision tree model • SD and PD • NR	• Payer • NR	NR	NR	ERL was cost-effective compared with other regimens
Hoang and Nguyen, (2016)	• ERL • GEM+CARB	1L	CUA	• Markov model • NR • NR	• Vietnamese healthcare payer • Lifetime	QALYs • ERL: 1.51 • GEM+CARB: 0.76 • Incremental: 0.75	Costs • ERL: 884 million VND • GEM+CARB: 283 million VND	• Cost/QALY: 801.3 million VND
Holleman et al., (2016)	• ERL • GEF • AFA	1L	CUA	• Markov model • NR • NR	• Societal • NR	LYG • ERL: 2.25 • GEF: 2.79 • AFA: 2.95 QALYs • ERL: 1.31 • GEF: 1.52 • AFA: 1.61	Costs • ERL: €59,322 • GEF: €67,505 • AFA: €69,037	ICER (Cost/LYG) • GEF vs ERL: €15,205 • AFA vs GEF: • €9,698 • ERL vs AFA: €13,956 ICUR (Cost/QALY) • GEF vs ERL: • €38,098 • AFA vs GEF: €17,924 • ERL vs AFA: • €32,357

Horgan et al., (2011)	• GEF • DOC	Beyond 2L	CCA	• Markov model • SD, response, and PD • 3-weeks	• Canadian public health care system • 1 year	Median PFS • GEF: 7.0 months • DOC: 4.1 months	• Total mean cost estimated per patient until progression: o GEF: $12,753 o DOC: $6,922 • Mean quality-adjusted cost until progression o GEF: $43,825 o DOC: $30,764	NR
Hsia et al., 2017	• GEF • Platinum-based chemotherapy (PBC)	1L	CEA	• NR • NR • NR	• Payer • 2 years	Life years • GEF: 1.48 • PBC: 1.47	Costs • GEF: $78,770 • PBC: $82,684	GEF dominated PBC (was more effective and cost-saving)
Huicochea-Bartelt et al., (2015)	• AFA • GEF • ERL • PEM+CIS	1L	CEA	• Discrete event simulation model • PFS, PD, and death • 1-month	• Public Mexican perspective • 5 years	LYs in PFS • AFA: 1.17 Years • GEF: 1.11 Years • ERL: 1.02 Years • PEM+CIS: 0.63 Years LYs in OS • AFA: 2.21 years • GEF: 2.07 Years	Total treatment costs until death • AFA: US$100,152 • GEF: US$141,040 • ERL: US$141,176 • PEM+CIS: US$175,889	AFA, GEF, and ERL resulted in dominant therapies compared with PEM+CIS

						• ERL: 2.12 Years • PEM+CIS: 2.07 Years		
Jacob et al., (2010)	• GEF • PAX+CARB	1L	CUA	• Markov model • NR • NR	• NR • Lifetime	QALY gained for test and treat strategy for GEF: 0.0116	Incremental cost of GEF: €300	Cost/QALY: €25,900
Lechuga et al., (2012)	• ERL • GEF • GEM+CARB	1L	CUA	• Markov model • Response to treatment, SD, PD, and death • 1-month	• Public health system of Mexico • 5 years	<u>QALYs</u> • ERL: 1.49 • GEF: 1.32 • GEM+CARB: 1.07	<u>Costs per patient</u> • ERL: $51,249 • GEF: $53,817 • GEM+CARB: $53,258	Average Cost/QALY for ERL: $34,456 (dominant)
Lee et al., (2013)	• ERL • GEF	1L	CUA	• Markov model • PFS, PD, and death • 1-month	• Healthcare payer • Lifetime	<u>LYs</u> • ERL: 2.16 • GEF: 1.82 • Incremental: 0.34 <u>QALYs</u> • ERL: 1.23 • GEF: 1.00 • Incremental: 0.23	<u>Total costs</u> • ERL: US$ 31, 434 • GEF: US$ 17, 373 • Incremental: US$ 14, 061 (HK$ 109,395) * *Data reported in HKD (Hong Kong dollars) was extracted from Lee et al. (2012)	• Cost/LYG: US$41 494 • Cost/QALYs: US$62 419 (HK$ 485,619) * **Data reported in HKD (Hong Kong dollars) was extracted from Lee et al. (2012)
Lester-Coll et al., (2016)	• VATS wedge resection • SBRT • ERL*	1L	CUA	• Markov model (state transition) • NR	• Payer • 5 years	<u>QALYs</u> • VATS wedge resection: 1.92 • SBRT: 1.94	<u>Total costs</u> • VATS wedge resection: $162,445	<u>Cost/QALY compared with ERL</u> • VATS wedge resection: $801,097

	*Systemic therapy with ERL (150mg as first line and PEM 500mg/m2 as second line)			• 1-month		• ERL: 1.90	• SBRT: $152,459 • ERL: $147,091	• SBRT: $126,303
Lopes et al., (2012)	• GEF • Standard care* *First-line treatment with chemotherapy (platinum based) followed GEF as second-line treatment	1L	CUA	• Decision tree model • NR • NR	NR	<u>QALYs</u> • GEF o For 9.78 months: 0.67 o For 6 months: 0.41 • Standard care o For 9.78 months: 0.47 o For 6 months: 0.61	EGFR testing followed by first-line GEF for EGFRm and second-line chemotherapy: $44,700	GEF was dominant compared to first-line chemotherapy
Lu et al., (2017)	• PEM+CIS • PEM+CIS (followed by PEM maintenance) • GEF (initial targeted treatment) • ICO (initial targeted treatment)	1L	CUA	• Markov cohort and decision tree model • PFS, PD, and death • 3-weeks	• Chinese health care system • 10 years	<u>LYs</u> • PEM+CIS: 1.058 • PEM+CIS (followed by PEM maintenance): 1.208 • GEF (initial targeted treatment): 1.165 • ICO (initial targeted	<u>LYs</u> • PEM+CIS: $22,127 • PEM+CIS (followed by PEM maintenance): $31,646 • GEF (initial targeted treatment): $24,137 • ICO (initial targeted	<u>Cost/QALY compared with PEM+CIS</u> • PEM+CIS (followed by PEM maintenance): $104,657 • GEF (initial targeted treatment): $28,485 • ICO (initial targeted

						treatment): 1.202 • GEF strategy with PAP: 1.165 • ICO strategy with PAP: 1.202 <u>QALYs</u> • PEM+CIS: 0.513 • PEM+CIS (followed by PEM maintenance): 0.604 • GEF (initial targeted treatment): 0.584 • ICO (initial targeted treatment): 0.607 • GEF strategy with PAP: 0.584 • ICO strategy with PAP: 0.607	treatment): $23,989 • GEF strategy with PAP: $23,721 • ICO strategy with PAP: $23,580	treatment): $19,809 • GEF strategy with PAP: $22,577 • ICO strategy with PAP: $15,451
Narita et al., (2015)	• GEF • PAX+CARB	1L	CUA	• Markov model • PFS, PD, and death • 3-weeks	• Healthcare payer • 5 years	<u>QALYs gained</u> • GEF: 1.180 • PAX followed by CARB: 1.067	<u>Cost per patient</u> • GEF: JP¥ 5.47 million ($52.6)	GEF was cost-effective

							• PAX followed by CARB: JP¥ 5.13 million ($49.4)	
Piha et al., (2015)	• GEF • ERL	1L	CUA	• Markov model • NR • 1-month	• Brazilian private healthcare system • 1 year	Incremental QALYs of GEF: -0.01	Total cost (where genome testing was not performed) • GEF: R$ 21,580.56 (US$ 6,916.67) • ERL: R$ 39,393.24 (US$ 12,626.04) • Incremental: -R$ 17,812.98 (-US$ 5,709.29) Total cost [where genome testing was performed, added R$ 1,000.00 (US$ 320.51) to both arms] • GEF: R$ 22,580.56 (US$ 7,237.36) • ERL: R$ 40,393.24 (US$ 12,946.55)	NR
Polanco et al., (2014)	• GEF • PAX+CARB	1L	CEA	• Markov model • NR • NR	NR	Incremental PFS: 0.37 years	Incremental cost per patient: $2,361	ICER: $7,023

Santoni et al., (2017)	• AFA • GEF	1L	CUA	• Markov model • PFS, PPS, and Death • NR	• Brazilian private healthcare system • 7 years	LYs • AFA: 2.77 • GEF: 2.40 • Incremental: 0.37 QALYs • AFA: 1.72 • GEF: 1.38 • Incremental: 0.33	Total costs • AFA: BRL 219,221 • GEF: BRL 194,330 • Incremental: BRL 24,890	• Cost/LYG: BRL 67,548 • Cost/QALY: BRL 73,757
Santoni et al., (2017)	• AFA • ERL	1L	CUA	• Markov model • PFS, PPS, and Death • NR	• Brazilian private healthcare system • 7 years	LYs • AFA: 2.77 • ERL: 2.64 • Incremental: 0.13 QALYs • AFA: 1.72 • ERL: 1.52 • Incremental: 0.20	Total costs • AFA: BRL 219,221 • ERL: BRL 240,547 • Incremental: -BRL 21,327	AFA dominated ERL
Santoni et al., (2017)	• AFA • PEM+CIS	1L	CUA	• Markov model • PFS, PPS, and Death • NR	• Brazilian private healthcare system • 7 years	LYs • AFA: 2.77 • PEM+CIS: 2.61 • Incremental: 0.16 QALYs • AFA: 1.72	Total costs • AFA: BRL 219,221 • PEM+CIS: BRL 210,671 • Incremental: BRL 8,549	• Cost/LYG: BRL 53,280 • Cost/QALY: BRL 39,162

						• PEM+CIS: 1.50 • Incremental: 0.21		
Ting et al., (2015)	• AFA • ERL • PEM+CIS	1L	CUA	• Markov model • PFS, PD, and death • 1-month	• Societal • Lifetime	<u>QALYs (95% CI)</u> • Comparing all treatments o AFA: 0.33 (0.32–0.35) o PEM+CIS: 0.28 (0.19–0.32) o ERL: 0.44 (0.42–0.46) • ERL vs PEM+CIS o PEM+CIS: 0.28 (0.19–0.32) o ERL: 0.44 (0.42–0.46) <u>Incremental QALYs (95% CI)</u> • Comparing all treatments o AFA: -- o PEM+CIS: Dominated o ERL: 0.11 (0.09–0.13)	<u>Costs (95% CI)</u> • Comparing all treatments o AFA: $ 40,250 ($34,215–$47,077) o PEM+CIS: $ 40,555 ($31,584–$45,781) o ERL: $ 46,972($38,477–$56,563) • ERL vs PEM+CIS o PEM+CIS: $ 40,555 ($31,584–$45,781) o ERL: $ 46,972 ($38,477–$56,563) <u>Incremental Costs (95% CI)</u> • Comparing all treatments o AFA: --	<u>Cost/QALY</u> • Comparing all treatments o AFA: -- o PEM+CIS: Dominated o ERL: $61,809 • ERL vs PEM+CIS o PEM: -- o ERL: $40,106

						• ERL vs PEM+CIS o PEM+CIS: -- o ERL: 0.17 (0.12–0.25)	o PEM+CIS: Dominated o ERL: $ 6,777 (–$3,732 to $17,635) • ERL vs PEM+CIS o PEM+CIS: -- o ERL: $ 6,417 (–$3,678 to $18,733)	
Tran and Nguyen, (2016)	• ERL • Standard therapy* *Includes CIS+DOC, DOC, CIS+GEM, GEM	1L	CUA	• Markov model • SD, PD, and death • 1-month	• Health care insurance organization • Lifetime	<u>QALYs</u> • ERL: 1.38 • Standard therapy: 1.27	<u>Costs</u> • ERL: 534,161,424.0 VND • Standard therapy: 95,141,580 VND	• ICUR (Cost/QALY): 4.1 billion VND • ERL: 388,397,001 VND • Standard therapy: 75,020,318 VND
Veenstra et al., (2013)	• ERL • Platinum-based therapy* *4 cycles of chemotherapy: GEM+CIS, DOC+CIS, GEM+CARB, DOC+CARB	1L	CUA	• Markov model • PFS, PD, and death • NR	• US payer • NR	• Incremental LYs: 0.60 • Incremental QALYs: 0.44	<u>Mean total costs</u> • ERL: $59,300 • Chemotherapy: $17,800	• Cost/QALY: $98,338
Vergnenegre et al., (2016)	• ERL	1L	CUA	• Markov model • PFS, PD, and death	• Healthcare perspective of	<u>Mean LYs*</u> • ERL: 1.873	<u>Mean total costs</u> *France* • ERL: €68,568	ERL is Cost-saving in all three countries

	• Platinum-based doublet chemotherapy			• 1-month	France, Italy, and Spain • 4 years	• Platinum-based doublet chemotherapy: 1.878 <u>Mean QALYs*</u> • ERL: 1.088 • Platinum-based doublet chemotherapy: 0.971 *Values are same for all three countries	• Platinum-based doublet chemotherapy: €87,931 *Italy* • ERL: €75,711 • Platinum-based doublet chemotherapy: €93,383 *Spain* • ERL: €61,845 • Platinum-based doublet chemotherapy: €79,176	
Wang et al., (2013)	• ERL • GEM+CARB	1L	CUA	• Markov model (based on decision tree structure) • PFS, PD, and death • 3-weeks	• Chinese health care system • 10 years	<u>Total QALYs</u> • ERL: 1.4 • GEM+CARB: 1.96 <u>PFS QALYs</u> • ERL: 0.82 • GEM+CARB: 0.24 <u>PD QALYs</u> • ERL: 0.58 • GEM+CARB: 1.72	<u>Total costs</u> • ERL: $40107.95 • GEM+CARB: $88227.3 <u>Mean costs of managing AE</u> • ERL: -- • GEM+CARB: $1620.951 <u>Mean costs in PFS</u> • ERL: $14772.04 • GEM+CARB: $13060.35 <u>Mean costs in PD</u>	• Cost/LYG: $30455.28 • Cost/QALY: $85927.41

							• ERL: $25335.91 • GEM+CARB: $75166.95	
Wen et al., (2016)	• ERL • Platinum-based doublet therapy* *GEM+CIS or GEM+CARB	1L	CUA	• Markov model • PFS, PD, and death • NR	NR	<u>QALYs</u> • ERL: 1.17 • GEM+ doublet chemotherapy: 1.04 • Incremental: 0.13	<u>Total costs</u> • ERL: $55,230.34 • GEM+ doublet chemotherapy: $77668.54	• ICER (Cost/QALY): $174,808.0 • ERL: $53,244.35 • GEM+ doublet chemotherapy: • $66,630.61
Yang and Tan, (2014)	• AFA • GEF • ERL	1L	CUA	NR[b]	• Single-payer BNHI • NR	<u>Incremental QALYS</u> • AFA vs GEF: 0.05 • AFA vs ERL: 0.02	• Incremental cost for AFA vs GEF: NT$21,350.59 • Decremental cost for AFA vs ERL: NT$-56,216	Cost/QALY: NT$457,768.67
Zaim et al., (2014)	• AFA • PEM+CIS	1L	CUA	• PSM • NR • NR	• Health care and societal • Lifetime	NR	Higher incremental cost was reported	• ICUR, cost/QALY: less than • €20,000 For the subgroup of patients harbouring DEL19 mutations (49%), treatment with AFA resulted in cost-savings
Zhan et al., (2017)	• GEF • PAX+CARB	1L	CUA	• Markov model (based decision tree structure)	• Societal • NR	QALY gain for GEF: 0.26	Incremental cost of GEF: $4757.02	Cost/QALY: $18296.23

				• PFS, PD, and death • NR				
Zhu et al., (2013)	• GEF* • Control** *Routine follow up plus GEF maintenance ** Routine follow up only	1L maintenance	CUA	• Markov cohort and decision tree model • PFS, PD with SC, PD with second-line chemotherapy, and death • 3-weeks	• Chinese health care system • 10 years	<u>Progression-free LYs at 10 years</u> • Control: 0.36 • GEF without GPAP: 1.11 • GEF with GPAP: 1.11 <u>Overall LYs at 10 years</u> • Control: 0.57 • GEF without GPAP: 1.31 • GEF with GPAP: 1.31 <u>Overall QALYs at 10 years</u> • Control: 0.33 • GEF without GPAP: 0.79 • GEF with GPAP: 0.79	<u>Costs at 10 years</u> • Control: $4,917.0 • GEF without GPAP: $31,066.9 • GEF with GPAP: $12,095.2	<u>Cost/LYs at 10 years</u> • GEF without GPAP vs control: $35,260.10 • GEF with GPAP vs control: $9,678.90 <u>Cost/QALY at 10 years</u> • GEF without GPAP vs control: $57,066.4 • GEF with GPAP vs control: $15,664.8
Zhu et al., (2017)	• AFA • GEF • ERL • PEM+CIS	1L	CUA	• Decision analytic model • NR • 1 month	• Payer • 10 years	<u>Incremental QALYs</u> • AFA vs PEM+CIS: 0.38	<u>Incremental Costs (including afatinib patient assistance program)</u>	<u>Cost/QALY</u> • AFA vs PEM+CIS: ¥53,834

						• AFA vs GEF: 0.22 • AFA vs ERL: 0.17	• AFA vs PEM+CIS: ¥20,545 • AFA vs GEF: ¥31,760 • AFA vs ERL: -¥10,917	• AFA vs GEF: ¥147,059 • AFA vs ERL: -¥62,812 (AFA dominates Erlotinib)
HTA studies								
NICE[TA416], (2016)[#] UK	• OSB • PEM+CIS	2L and beyond	CUA	• PSM (cohort based) • PFS, PD, and death • 1-week	• NHS and PSS • Lifetime (max. 15 years)	*Adjusted dataset* <u>Total LYG</u> • OSB: 3.857 • PEM+CIS: 1.825 • Incremental: 2.032 <u>Total QALYs</u> • OSB: 2.841 • PEM+CIS: 1.300 • Incremental: 1.541 *Unadjusted dataset* [a] <u>Total LYG</u> • OSB: 2.558 • PEM+CIS: 1.419	*Adjusted dataset* <u>Total Cost</u> • OSB: £87,441 • PEM+CIS: £23,159 • Incremental: £64,283 *Unadjusted dataset* [a] <u>Total Cost</u> • OSB: £71,503 • PEM+CIS: £16,403 • Incremental: £55,100	*Adjusted dataset* • Cost/QALY: £41,705 *Unadjusted dataset* [a] • Cost/QALY: £56,570

						• Incremental: 1.139 Total QALYs • OSB: 1.913 • PEM+CIS: 0.939 • Incremental: 0.974		
NICE[TA258], (2012) UK	• ERL • GEF	1L	CUA	• Semi-Markov model • PFS, PD, and death • 1-month	• NHS and PSS • 10 years	• LYG for GEF: 1.796 • QALYs for GEF: 1.015	Total cost for GEF: £16,046	Base case analysis with submitted model • ICER vs baseline (QALYs) of GEF: £48,961 • ICER incremental (QALYs): £48,961 • ICER/LYG: £36,410 Base case with PAS price • ICER vs baseline (QALYs) of GEF: £21,874 • ICER incremental (QALYs): £21,874 • ICER/LYG: £16,317
NICE[TA310], (2014) UK	• AFA • GEF • ERL	1L	CUA	• PSM • PFS, PD, and death	• NHS and PSS • Lifetime (10 years)	Total LYG • GEF: 2.291 • ERL: 2.223	Incremental Costs • ERL: £1, 390 • AFA: £1, 723	Cost/LYG • AFA vs ERL: £5,286

				• 1-month		• AFA: 2.549 Incremental LYG • ERL: -0.068 • AFA: 0.326 Total QALYs • GEF: 1.421 • ERL: 1.423 • AFA: 1.594 Incremental QALYs • ERL: 0.002 • AFA: 0.171		• AFA vs GEF: £12,062 Cost/QALY • AFA vs ERL: £10,079 • AFA vs GEF: £17,933
NICE[TA192], (2010) UK	• GEF • GEM+CARB • GEM+CIS • PAX+CARB • VNB+CIS	1L	CUA	• Markov model • Treatment response, SD, PD, and death • 3-weeks	• NHS and PSS • 5 years	Mean QALYs (discounted) • GEF: 1.111 • GEM+CARB: 0.934 • GEM+CIS: 0.966 • PAX+CARB: 0.923 • VNB+CIS: 0.888 Incremental QALYs (discounted) • GEM+CARB: 0.177	Mean costs (discounted) • GEM+CARB: £27,873 • GEM+CIS: £27,401 • PAX+CARB: £27,902 • VNB+CIS: £23,516 Incremental costs (discounted) • GEM+CARB: £3,666 • GEM+CIS: £4,138	Cost/QALY (discounted) • GEM+CARB: £20,744 • GEM+CIS: £28,633 • PAX+CARB: £19,402 • VNB+CIS: £35,992 Mean cost/QALY for GEF vs doublet chemotherapy: £35,700

						• GEM+CIS: 0.145 • PAX+CARB: 0.187 • VNB+CIS: 0.223	• PAX+CARB: £3,637 • VNB+CIS: £8,024	
Brown et al., (2013) UK	• GEF • DOC+CIS+CARB • PAX+CIS+CARB	1L	CUA	• Decision tree model • PFS, PD, and death • 3-weeks	• NHS and PSS • 10 years	<u>QALYs in PFS</u> • GEF: 0.6226 • DOC+CIS+CARB: 0.3338 • PAX+CIS+CARB: 0.3338 <u>QALYs in PD</u> • GEF: 0.8731 • DOC+CIS+CARB: 1.0833 • PAX+CIS+CARB: 1.0833 <u>Total QALYs</u> • GEF: 1.4957 • DOC+CIS+CARB: 1.4171 • PAX+CIS+CARB: 1.4171	<u>Deterministic estimated total cost per patient (BNF prices)</u> • GEF: £30,355 • DOC+CIS: £30,998 • DOC+CARB: £29,812 • PAX+CIS: £34,325 • PAX+CARB: £31,866 <u>Deterministic estimated total cost per patient (eMIT prices)</u> • GEF: £33,366 • DOC+CIS: £29,164 • DOC+CARB: £29,203 • PAX+CIS: £26,908	*Deterministic analysis (BNF prices)* • The estimated deterministic ICER for GEF compared with PAX+CIS is £57,440/QALY *Deterministic analysis (eMIT prices)* • The estimated ICER for GEF compared with PAX+CARB £85,848/QALY

							• PAX+CARB: £26,621	

AE, adverse event; AFA, afatinib; BEV, bevacizumab; BNF, British National Formulary; BNHI, Bureau of National Health Insurance; CARB, carboplatin; CCA, cost-consequence analysis; CI, confidence interval; CIS, cisplatin; CUA, cost-utility analysis; DOC, docetaxel; EGFR, epithelial growth factor receptor; eMIT, electronic medicine information tool; ERL, erlotinib; GEF, gefitinib; GEM, gemcitabine; GPAP, gefitinib patient assistance program; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; ICUR, incremental cost-utility ratio; ICO, icotinib; LYs, life years; LYG, life years gained; NR, not reported; OS, overall survival; OSB, osimertinib; PAP, patient assistance program; PAS, patient access scheme; PAX, paclitaxel; PD, progressive disease; PEM, pemetrexed, PFS, progression-free survival; PPS, post-progression survival; PS, progressed survival; QALYs, quality-adjusted life years; SBRT, stereotactic body radiation therapy; SC, supportive care; SD, stable disease; UI, uncertainty interval; VATS, video-assisted thoracic surgery; VNB, vinorelbine

[a] Unadjusted dataset specific to the ≥third-line population; § Assessing second line of therapy; [#] Assessing second-line therapy or beyond.

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

H1.1 Young et al. (2015)

This study utilised 771 patients with all types of cancer (12.8% lung cancer) from Canada. The authors tested a number of different models, including ordinary least squares regression (OLS), Tobit, two-part models, splining, and response mapping. The authors generated a system to rank the models for fit, where all criteria (including predicted mean and standard error, the range of predictions, mean absolute error [MAE], shrinkage, and the reproducibility of the model among different severity states) were equally weighted.

Response mapping was found to be the authors' preferred mapping algorithm based on the ranking system used in this paper. Rather than predicting utility values, response mapping predicts the five EQ-5D dimension levels where multinomial logistic regression models are estimated for each dimension. The estimates from these regressions are used to categorise respondents into levels 1, 2, or 3 of each of the EQ-5D-3L dimensions and thus predict the EQ-5D-3L health state for each respondent. The standard set of UK general population values (or, indeed, any other value set) can then be applied to each predicted health state to obtain EQ-5D-3L values.

The coefficients from the response mapping can be found in Table 125, which determine the probability of each patient belonging to a given level for a particular dimension.[437] For the standard UK tariff, the following equation can be used to calculate predicted utility:[438]

$$Predicted\ utility = 1 - (prob\_Mobility2*0.069) - (prob\_Mobility3*0.314) - (prob\_Self\_care2*0.104) - (prob\_Self\_care3*0.214) - (prob\_Usual\_activities2*0.036) - (prob\_Usual\_activities2*0.094) - (prob\_Pain2*0.123) - (prob\_Pain3*0.386) - (prob\_Anxiety\_depression2*0.071) - (prob\_Anxiety\_depression3*0.236) - ((1-Prob\_Perfect)*0.081) - (Prob\_N3*0.269)$$

Where prob_Mobility2 is the probability of being in mobility level 2 on EQ-5D, prob_Mobility3 is the probability of being in mobility level 3 on EQ-5D, prob_Self_care2 is the probability of being in self-care level 2 on EQ-5D, prob_Self_care3 is the probability of being in self-care level 3 on EQ-5D, prob_Usual_activities2 is the probability of being in usual activities level 2 on EQ-5D, prob_Usual_activities3 is the probability of being in usual activities level 3 on EQ-5D, prob_Pain2 is the probability of being in pain or discomfort level 2 on EQ-5D, prob_Pain3 is the probability of being in pain or discomfort level 3 on EQ-5D, prob_Anxiety_depression2 is the probability of being in anxiety or depression level 2 on EQ-5D and prob_Anxiety_depression3 is the probability of being in anxiety or depression level 3 on EQ-5D. Prob_Perfect is the probability of being in 'perfect health' (i.e. all dimensions are level 1). Prob_N3 is the probability of any of EQ-5D dimensions being at level 3.

Table 125: Coefficients from response mapping algorithm – Young et al. (2015)

	Mobility	Mobility	Self-Care	Self-Care	Usual Activities	Usual Activities	Pain	Pain	Anxiety/Depression	Anxiety/Depression
Level	2	3	2	3	2	3	2	3	2	3
Physical functioning	−0.0715241	−0.1666518	−0.0492088	−0.0989941	−0.0358454	−0.0851464	−0.0008494	−0.0128045	−0.0143092	−0.0441950
Role functioning	−0.0109798	−0.0066196	−0.0165511	−0.0295817	−0.0321869	−0.0550817	0.0012198	−0.0013792	0.0049731	0.0187775
Emotional functioning	0.0104307	0.0237461	0.0078666	0.0082215	0.0205527	0.0279876	0.0086091	0.0112924	−0.0781099	−0.1475690
Cognitive functioning	−0.0108672	−0.0059660	−0.0098743	−0.0088678	0.0035504	−0.0007108	0.0027021	0.0150750	−0.0065868	0.0056511
Social functioning	0.0030962	0.0109563	−0.0093543	−0.0054659	−0.0213392	−0.0343679	0.0052084	−0.0006402	0.0055038	0.0084157
Fatigue	0.0059733	0.0022788	−0.0220344	−0.0250514	0.0278376	0.0330008	0.0071305	0.0063537	−0.0063396	0.0072863
Nausea and vomiting	0.0005879	0.0157504	0.0068145	0.0186905	0.0218262	0.0215693	0.0054720	−0.0035358	−0.0074123	−0.0088818
Pain	0.0228164	0.0430386	0.0158179	0.0244974	0.0200722	0.0229097	0.1004407	0.1643611	0.0020242	−0.0118933
Dyspnea	0.0016023	0.0044787	−0.0046077	−0.0153410	−0.0053466	−0.0154350	0.0101103	0.0077207	0.0001655	−0.0177905
Sleep disturbance	0.0020489	0.0104134	0.0015579	−0.0001904	−0.0010660	−0.0021797	0.0125753	0.0212104	−0.0029185	0.0116847
Appetite loss	−0.0092890	0.0041667	−0.0001746	0.0095717	−0.0101199	−0.0109212	−0.0127206	−0.0081893	0.0061518	0.0160904
Constipation	−0.0042172	−0.0115196	−0.0041213	−0.0089580	−0.0004575	0.0041718	0.0058912	0.0098999	0.0042562	0.0006725
Diarrhea	−0.0049971	0.0097861	0.0030265	0.0051304	−0.0088893	−0.0111202	−0.0036955	−0.0076847	0.0018030	0.0019909
Financial impact	−0.0012006	−0.0032977	0.0049986	0.0146949	0.0077058	0.0064971	0.0099762	0.0116569	0.0123720	0.0146184
Age	0.0284672	−0.0206177	0.0480864	0.1312050					0.0259679	0.0081053
Female	−0.3486546	−1.3967005								
Constant	3.1686465	3.5415101	0.4980388	−6.6185420	3.4935399	5.6750937	−3.2549790	−9.8187423	4.5615723	6.0238621

EORTC QLQ-C30, European Organization for Research and Treatment Quality of Life Questionnaire Core 30.

H1.2 Health-related quality-of-life data from FLAURA

Table 126: Summary of EQ-5D mapped utility scores over time (full analysis set; n=556), all observations

Time point	n	Mean	SD	95% CI	Min	Q1	Median	Q3	Max
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 36	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 42	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 48	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 54	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 60	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 66	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 72	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 78	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 84	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 90	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 96	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 102	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 108	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 114	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Randomised Treatment Discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
28-Day Follow-Up	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Progression Follow-up	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 127: Summary of EQ-5D mapped utility scores over time (full analysis set; n=556), progression-free

Time point	n	Mean	SD	95% CI	Min	Q1	Median	Q3	Max
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 36	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 42	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 48	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 54	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 60	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 66	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 72	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 78	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 84	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 90	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 96	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 102	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 108	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Randomised Treatment Discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
28-Day Follow-Up	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Progression Follow-up	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 128: Summary of EQ-5D mapped utility scores over time (full analysis set; n=556), progressed disease

Time point	n	Mean	SD	95% CI	Min	Q1	Median	Q3	Max
Week 6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Week 24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 36	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 42	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 48	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 54	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 60	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 66	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 72	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 78	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 84	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 90	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 96	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 102	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 108	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 114	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Randomised Treatment Discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
28-Day Follow-Up	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Progression Follow-up	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Survival Follow-up	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

H1.3 Health-related quality-of-life studies

H1.3.1 Search Strategies

Table 129: Embase and MEDLINE using Embase.com (19 February 2018)

S. No.	Search Terms	Results
1.	'non small cell lung cancer'/exp OR nsclc:ab,ti OR ('neoplasm'/exp OR 'squamous cell carcinoma'/exp OR 'adenocarcinoma'/exp AND 'lung'/exp OR ((lung OR pulmon* OR bronchial) NEAR/3 (cancer* OR carcin* OR neoplasm* OR tumour* OR tumor* OR squamous OR adenocarcinoma*)):ab,ti AND ('non small cell':ab,ti OR 'non-small-cell':ab,ti OR 'nonsmall cell':ab,ti))	129,812
2.	'utility':ab,ti OR 'utilities':ab,ti OR 'disutility':ab,ti OR 'disutilities':ab,ti OR 'sf 6':ab,ti OR sf6:ab,ti OR 'short form 6':ab,ti OR 'shortform 6':ab,ti OR 'sf six':ab,ti OR sfsix:ab,ti OR 'shortform six':ab,ti OR 'short form six':ab,ti OR euroqol:ab,ti OR 'euro qol':ab,ti OR 'euroqol 5d':ab,ti OR 'euroqol-5d':ab,ti OR 'euroqol 5-d':ab,ti OR eq5d:ab,ti OR 'eq 5d':ab,ti OR 'health utilities index':ab,ti OR hui:ab,ti OR hui1:ab,ti OR hui2:ab,ti OR 'hui-2':ab,ti OR hui3:ab,ti OR 'hui-3':ab,ti OR 'standard gamble*':ab,ti OR (standard NEXT/1 gamble*):ab,ti OR 'time trade off':ab,ti OR 'time tradeoff':ab,ti OR tto:ab,ti	238,903
3.	#1 AND #2	2,660
4.	letter:it OR editorial:it OR (review:it OR 'review literature as topic'/exp OR 'literature review':ti NOT ('meta-analysis':it OR 'meta-analysis as topic'/mj OR 'systematic review':ti OR 'systematic literature review':ti OR 'meta-analysis':ab,ti OR 'meta analysis':ab,ti)) OR ('animal'/exp NOT ('animal'/exp AND 'human'/exp)) OR 'case report*':ab,ti OR 'case series':ab,ti	9,167,593
5.	#3 NOT #4	2,283
6.	#3 NOT #4 AND [english]/lim	2,242

Table 130: Medline In-Process using Pubmed.com (19 February 2018)

S. No.	Search Terms	Results
1.	Non small cell lung cancer[MH] OR nsclc[tiab]	53,192
2.	Neoplasm[MH] OR Squamous cell carcinoma[MH] OR Adenocarcinoma[MH]	3,068,342
3.	Lung[MH]	257,708
4.	#2 AND #3	29,792
5.	(lung[tiab] OR pulmon*[tiab] OR brochial[tiab]) AND (cancer*[tiab] OR carcin*[tiab] OR neoplasm*[tiab] OR tumour*[tiab] OR tumor*[tiab] OR squamous[tiab] OR adenocarcinoma*[tiab])	264,655
6.	#4 OR #5	279,221
7.	"non small cell"[tiab] OR "non-small-cell"[tiab] OR "nonsmall cell"[tiab]	53,035
8.	#6 AND #7	52,649
9.	#1 OR #8	62,486
10.	utility[tiab] OR utilities[tiab] OR disutility[tiab] OR disutilities[tiab] OR "SF 6"[tiab] OR SF6[tiab] OR "short form 6"[tiab] OR "shortform 6"[tiab] OR "SF six"[tiab] OR "sfsix"[tiab] OR "shortform six"[tiab] OR "short form six"[tiab] OR euroqol[tiab] OR "euro qol"[tiab] OR "euroqol 5d"[tiab] OR "euroqol-5d"[tiab] OR "euroqol 5-d"[tiab] OR eq5d[tiab] OR "eq 5d"[tiab] OR "health utilities index"[tiab] OR hui[tiab] OR hui1[tiab] OR hui2[tiab] OR "hui-2"[tiab] OR hui3[tiab] OR "hui-3"[tiab] OR "standard gamble*"[tiab] OR (standard[tiab] AND gamble[tiab]) OR "time trade off"[tiab] OR "time tradeoff"[tiab] OR tto[tiab]	179,364

11.	#9 AND #10	1,011
12.	#11 AND (publisher[sb] NOT pubstatusnihms NOT pubstatuspmcsd NOT pmcbook) OR (pubstatusaheadofprint)	7

Table 131: HTA and NHSEED using Wiley Interscience (18 May 2017)

S. No.	Search Terms	Results
	[mh "non small cell lung cancer"] or nsclc:ab,ti,kw	5,775
	[mh neoplasm] or [mh "squamous cell carcinoma"] or [mh adenocarcinoma]	61,198
	[mh lung]	3,742
	#2 and #3	245
	((lung or pulmon* or bronchial) near/3 (cancer* or carcin* or neoplasm* or tumour* or tumor* or squamous or adenocarcinoma*)):ab,ti,kw	13,005
	#4 or #5	13,053
	("non small cell" or "non-small-cell" or "nonsmall cell"):ab,ti,kw	6,880
	#6 and #7	6,776
	#1 or #8	7,160
	"utility":ab,ti,kw or "utilities":ab,ti,kw or "disutility":ab,ti,kw or "disutilities":ab,ti,kw or "sf 6":ab,ti,kw or sf6:ab,ti,kw or "short form 6":ab,ti,kw or "shortform 6":ab,ti,kw or "sf six":ab,ti,kw or sfsix:ab,ti,kw or "shortform six":ab,ti,kw or "short form six":ab,ti,kw or euroqol:ab,ti,kw or "euro qol":ab,ti,kw or "euroqol 5d":ab,ti,kw or "euroqol-5d":ab,ti,kw or "euroqol 5-d":ab,ti,kw or eq5d:ab,ti,kw or "eq 5d":ab,ti,kw or "health utilities index":ab,ti,kw or hui:ab,ti,kw or hui1:ab,ti,kw or hui2:ab,ti,kw or "hui-2":ab,ti,kw or hui3:ab,ti,kw or "hui-3":ab,ti,kw or "standard gamble*":ab,ti,kw or (standard next/1 gamble*):ab,ti,kw or "time trade off":ab,ti,kw or "time tradeoff":ab,ti,kw or tto:ab,ti,kw	11,776
	#9 and #10	132
	#11 in Technology Assessments	0
	#11 in Economic Evaluations	11

Table 132: EconLit using EBSCO.com (18 May 2017)

S. No.	Search Terms	Search Options	Results
S1	SU non small cell lung cancer OR TI nsclc OR AB nsclc	**Expanders** - Also search within the full text of the articles; Apply equivalent subjects **Search modes** - Find all my search terms	176,256
S2	SU neoplasms OR SU squamous cell carcinoma OR SU adenocarcinoma	**Expanders** - Also search within the full text of the articles; Apply equivalent subjects **Search modes** - Find all my search terms	3,788,474
S3	SU lung	**Expanders** - Also search within the full text of the articles; Apply equivalent subjects **Search modes** - Find all my search terms	1,107,334
S4	S2 AND S3	**Expanders** - Also search within the full text of the articles; Apply equivalent subjects **Search modes** - Find all my search terms	276,114
S5	TI ((lung OR pulmon* OR brochial) AND (cancer* OR carcin* OR neoplasm* OR tumour* OR tumor* OR squamous OR adenocarcinoma*)) OR AB ((lung OR pulmon* OR brochial) AND (cancer* OR carcin* OR neoplasm*	**Expanders** - Also search within the full text of the articles; Apply equivalent subjects **Search modes** - Find all my search terms	1,223,048

	OR tumour* OR tumor* OR squamous OR adenocarcinoma*))		
S6	S4 OR S5	**Expanders** - Also search within the full text of the articles; Apply equivalent subjects **Search modes** - Find all my search terms	1,301,846
S7	TI ("non small cell" OR "non-small-cell" OR "nonsmall cell") OR AB ("non small cell" OR "non-small-cell" OR "nonsmall cell")	**Expanders** - Also search within the full text of the articles; Apply equivalent subjects **Search modes** - Find all my search terms	234,687
S8	S6 AND S7	**Expanders** - Also search within the full text of the articles; Apply equivalent subjects **Search modes** - Find all my search terms	233,117
S9	S1 OR S8	**Expanders** - Also search within the full text of the articles; Apply equivalent subjects **Search modes** - Find all my search terms	277,937
S10	TI (utility OR utilities OR disutility OR disutilities OR "sf 6" OR sf6 OR "short form 6" OR "shortform 6" OR "sf six" OR sfsix OR "shortform six" OR "short form six" OR euroqol OR "euro qol" OR "euroqol 5d" OR "euroqol-5d" OR "euroqol 5-d" OR eq5d OR "eq 5d" OR "health utilities index" OR hui OR hui1 OR hui2 OR "hui-2" OR hui3 OR "hui-3" OR "standard gamble*" OR (standard W1 gamble*) OR "time trade off" OR "time tradeoff" OR tto) OR AB (utility OR utilities OR disutility OR disutilities OR "sf 6" OR sf6 OR "short form 6" OR "shortform 6" OR "sf six" OR sfsix OR "shortform six" OR "short form six" OR euroqol OR "euro qol" OR "euroqol 5d" OR "euroqol-5d" OR "euroqol 5-d" OR eq5d OR "eq 5d" OR "health utilities index" OR hui OR hui1 OR hui2 OR "hui-2" OR hui3 OR "hui-3" OR "standard gamble*" OR (standard W1 gamble*) OR "time trade off" OR "time tradeoff" OR tto)	**Expanders** - Also search within the full text of the articles; Apply equivalent subjects **Search modes** - Find all my search terms	4,769,412
	S9 AND S10	**Expanders** - Also search within the full text of the articles; Apply equivalent subjects **Search modes** - Find all my search terms	2,789
S11	S9 AND S10 Source: Econlit	**Expanders** - Also search within the full text of the articles; Apply equivalent subjects **Search modes** - Find all my search terms	3

H1.3.2 Description of identified studies

Table 133: Study characteristics and utility values reported in identified utility studies

Study name Year Country • Interventions/ comparators	Study type • Time point of measurement	Cohort size (Patients completing questionnaire)	• Method of elicitation • Valuation • Mapping (Yes/No) • Source	Treatment utilities	Health state utilities	AE utilities/ disutilities
Bodnar et al. 2016 UK • OSB	nRCT • At baseline • At every 6 weeks including during follow-up post-progression; also taken at 60 weeks	210 (175)	• EQ-5D-5L • NR • No • NR	<u>Mean EQ-5D-5L utility for OSB</u> • At baseline: 0.745 • At 6 weeks post treatment initiation: 0.819 • At 60 weeks of treatment: 0.798	<u>Mean EQ-5D-5L utility</u> • PF:0.812 • PD: 0.751 • Pre-progression, patients with Complete or partial response (defined by objective response): 0.883 • SD: 0.754	NR
Brown et al. 2013 UK • GEF • DOC+CIS+CARB • PAX+CIS+CARB	HTA • NR	NR	• EQ-5D • NR • Not required • Nafees et al., 2008	<u>Estimated health-related utility values using the Nafees et al. model</u> • PFS 1 on treatment – GEF: 0.6625 – PAX: 0.5934 • PFS 1 post treatment	NR	NR

				– GEF: 0.6686 – PAX: 0.6623 • PPS 1 following first progression – GEF: 0.4896 – PAX: 0.4896		
Griebsch et al. 2014 UK • AFA • PEM+CIS	OBS • NR	345 (335) [a]	• EQ-5D • NR • No • LUX-LUNG 3 Trial	NR	<u>Estimates of the effects of disease progression on EQ-5D UK Utility from mixed-effects longitudinal models for LUX-Lung 3:</u> • Progression effect (95% CI) – By Independent review: -0.061 (-0.082 to -0.041); p<0.0001 – By Investigator assessment: -0.076 (-0.099 to -0.054); p<0.0001 <u>Effects of disease progression from mixed-effects longitudinal models for LUX-Lung 3 by randomised treatment</u> • By Independent review	NR

					– AFA: -0.068 – CIS+PEM: -0.046; p=0.34 • By Investigator assessment – AFA: -0.083 – PEM+CIS: -0.062; p=0.39	
Handorf et al. 2012 US • ERL • CARB+PAX • CARB+PEM • CARB+PEM+BEV	EM • NR	NR	• NR • NR • NR • Carlson et al., 2009, Nafees et al., 2008, Expert opinion	NR	NR	SD (range) utilities <u>Data reported in Carlson et al. and Nafees et al.</u> • Rash: -0.640 (-0.320 to-0.670) • Febrile neutropenia: -0.563 (-0.282 to-0.670) <u>Data taken from Expert opinion</u> • Neutropenia: -0.670 (-0.335 to -0.670) • Pneumothorax: -0.630 (-0.315 to -0.670) • Haemorrhage: -0.630 (-0.315 to -0.670) • Thrombocytopenia: -0.650 (-0.325 to -0.670)

						• Thrombosis: -0.563 (-0.281 to -0.670) <u>Data reported in Nafees et al.</u> • Nausea/vomiting: -0.605 (-0.303 to -0.670) <u>Data reported in Carlson et al.</u> • Neuropathy: -0.620 (-0.310 to -0.670)
Hirsh et al. 2016 NR • AFA • GEF	RCT • Baseline to post-baseline	160* (NR) Data reported only for AFA arm	• EQ-5D • NR • No • NR	<u>Mean EQ-5D score (baseline to post-baseline)</u> • AFA: 0.72 to 0.77 • GEF: 0.73 to 0.80 • p=0.142 • After Dose reduction of AFA – <40 mg: 0.69 to 0.74 – ≥40 mg: 0.73 to 0.77	NR	NR
Horgan et al. 2011 Canada • GEF • DOC	EM • NR	44 (NR)	• FACT-L • NR • No • INTEREST trial and methodology of Kind and Macran used to	<u>Mean (median) utility</u> • DOC:0.225 (0.203) • GEF (utility until progression): 0.291 (0.312)	NR	NR

			derive utility values from FACT-L scores			
Labbé et al. 2017 Canada • Chemotherapy • Targeted therapy • Immunotherapy • Other therapy • No treatment	OBS • NR	183 (183)	• EQ-5D-3L • NR • No • NR	<u>Mean (sd) utility score</u> • SD on most appropriate treatment (TKIs) (n =112) – GEF (n=71): 0.80 (0.02) – ERL (n=7): 0.81 (0.04) – AFA (n=4): 0.78 (0.08) – OSB (n=14): 0.84 (0.04) – ROC (n=8): 0.78 (0.04) – EGF816 (n=8): 0.84 (0.05) • At diagnosis prior to systemic therapy initiation (n = 24): 0.80 (0.13) – For UK: 0.79 (0.04)	<u>Mean (sd) utility score</u> • SD on most appropriate treatment (TKIs) (n =112): 0.81 (0.02) – For UK: 0.77 (0.02) – For US: 0.82 (0.01) • Progressing (n =81): 0.70 (0.02); p=0.004 (adjusted) and p=0.0001 (unadjusted) – For UK: 0.64 (0.03) – For US: 0.73 (0.02) • Clinically SD not on treatment (n= 8): 0.80 (0.05) – For UK: 0.76 (0.05) – For US: 0.81 (0.04)	NR

				– For US: 0.83 (0.03)	• SD on other systemic treatments (n =17): 0.76 (0.02) – For UK: 0.72 (0.04) – For US: 0.78 (0.03)	
Lester-Coll et al. 2016 US • VATS wedge resection • SBRT • ERL* *Systemic therapy with ERL (150mg as first line and PEM 500mg/m2 as second line)	EM • NR	NR	• NR • NR • NR • Doyle et al 2008, Carlson et al 2009	<u>Base case utility (threshold)</u> *Data reported in Doyle et al. (2008)* • After SBRT: 0.83 (0.87) *Data reported in Carlson et al. (2009)* • ERL: 0.68 (0.64)	NR	NR
Lopes et al. 2012 Singapore • GEF • Standard care* *First-line treatment with chemotherapy followed GEF as second-line treatment	EM • NR	NR	• NR • NR • NR • Nafees et al., 2008 and ERG report 2006	<u>Utility values adapted from Nafees et al., 2008 and ERG report 2006</u> • GEF – First-line: 0.67 – Second-line: 0.47 • Second-line chemotherapy: 0.41	NR	NR

Lu et al. 2017 China • PEM+CIS • PEM+CIS (followed by PEM maintenance) • GEF (initial targeted treatment) • ICO (initial targeted treatment)	EM • NR	NR	• NR • NR • NR • Grutters et al 2010, Chouaid et al 2013	NR	Data reported in Grutters et al. (2010) and Chouaid et al. (2013) Base-Case Utilities: Expected Values (Ranges) • PFS: 0.82 (0.78-0.86) • OS: 0.58 (0.5-0.66)	Data reported in Grutters et al. (2010) Base-Case Utilities: Expected Values (Ranges) Disutility of serious AEs: -0.35 (-0.31 to -0.39)
Narita et al. 2015 Japan • GEF • PAX followed by CARB	EM • NR	NR	• NR • NR • NR • Nafees et al 2008, Fallowfield et al 2005	Data reported in Nafees et al. (2008) • Baseline utility: 0.653 • Response (utility increment): 0.019 Data reported in Fallowfield et al. (2005) • Utility decrement – IV therapy: -0.042	NR	Data reported in Nafees et al. (20080 for utility decrement (Grade 3/4 AE) • Disease progression: -0.1798 • Neutropenia: -0.0897 • Febrile neutropenia: -0.0900 • Fatigue -0.0743

				– Oral therapy: -0.013		• Nausea & vomiting: -0.0480 • Diarrhoea: -0.0466 • Hair loss (partial or complete): -0.0450 • Rash: -0.0325 <u>Data reported in Fallowfield et al. (2005)</u> • Anaemia: -0.0743
NICE[TA258] 2012 UK • ERL • GEF	HTA • NR	• EURTAC study: 326 (NR) • OPTIMAL study: 154 (NR)	• EQ-5D • TTO and SG • Not required • Nafees et al values used in NICE TA227, TA192, TA190 and TA181	<u>Resultant PFS utility score</u> • ERL: 0.661 • GEF: 0.656	<u>Utility score, CI</u> • PF (SD): 0.6532 (0.6096-0.6968) • PF (Response dummy variable): 0.0193 (0.0065-0.0321)	<u>Disutility score, CI</u> • Rash: -0.0325, -0.0554, -0.0095 • Diarrhoea: -0.0468, -0.0772, -0.0164 • PD (progression dummy variable disutility relative to PFS SD baseline): -0.1798 (-0.2223, -0.1373)
NICE[TA310] 2014 UK • AFA • GEF • ERL	HTA • NR	• LUX-Lung 3: 345 (NR) • LUX-Lung 6: 364 (NR)	• EQ-5D • SG • Not required • LUX-Lung 3 and 1, Chouaid et al. 2012, Nafees et al. 2008	<u>Weighted utility in second-line treatment period option (Constant (base case); Proportionally adjusted)</u> • PEM+CIS: 0.487; 0.487 • AFA: 0.517; 0.509	<u>Mean (SE) utility values used in the model in the PF state</u> • Derived from LUX-lung trial: 0.784 (0.009) • Derived from Chouaid et	<u>Mean (SE) disutilities</u> *Derived from LUX-Lung 3 trial* • Diarrhoea (Grade 3/4): -0.147 (-0.045), p=0.0010 • Rash/acne (Grade 3/4): -0.202 (-0.028), p<0.0001

				• ERL: 0.529; 0.509 • GEF: 0.521; 0.509	al.:2012: 0.710 (0.014) • Derived from Nafees et al. 2008: – PF: 0.672 (0.029) – PF (SD): 0.653 (0.022) – PF (weighted): 0.663 (0.026) <u>Mean (SE) utility values used in the model in the PD</u> • Derived from Chouaid et al. 2012 – Second-line PF: 0.73 (0.015) – Third-line BSC PD: 0.46 (0.021) – Third-line PF: 0.62 (0.46)	*Derived from LUX-Lung 1 trial* • Fatigue (Grade 3/4): -0.179 (-0.053) *Derived from Nafees et al. (2008)* • Anaemia: -0.073 (-0.019) • Neutropenia: -0.090 (-0.015)
NICE[TA416] 2016 UK • OSB • PEM+CIS	HTA • AURA2 study collected every 6 weeks	• AURA 2 study: 210 (197) • IMPRESS study 265 (205)	• EQ-5D-5L, in AURA 2 study and EQ-5D-3L in IMPRESS study • NR • Not required • Previous NSCLC HTA submissions to NICE or based	NR	*Utility values derived from AURA2 study* <u>Mean (sd) utility in base case analysis (≥second-line population)</u> • PFS, n=158: 0.815 (0.183) • Post-progression, n=39: 0.678 (0.314)	<u>Disutilities (based on assumptions)</u> • Platelet count decreased (Assumption based on the nintedanib NICE Appraisal): -0.05 • Constipation: -0.05

			on assumptions, [127]		Mean (sd) utility in second-line only population • PFS, n=50: 0.853 (0.139) • Post-progression, n=11: 0.726 (0.319) Mean (sd) utility in ≥third-line population • PFS, n=108: 0.798 (0.198) • Post-progression, n=28: 0.659 (0.316) *Utility values derived from IMPRESS study (placebo arm)* Mean (sd) EQ-5D-3L index value • PFS, n=117: 0.779 (0.210) • Post-progression, n=88: 0.679 (0.271)	• Oedema peripheral: -0.05 • Cough: -0.05 • Stomatitis: -0.05 • Anaemia (Assumed to be same as fatigue/ asthenia event): -0.073 • Headache: -0.05 • Back pain: -0.05
NICE[TA192] 2010 UK • GEF • GEM+CARB • GEM+CIS • PAX+CARB	HTA • NR	NR	• VAS • SG • Not required • Nafees 2008, Eli Lilly (2009) and ERG report 2006	Utility decrements in PF *Data taken from ERG report (2006)* • IV therapy: -0.0425 (0.0032-0.0818)	NR	CTC Grade 3/4 AE utility (range) *Data taken from Eli Lilly (2009)* • Anaemia: -0.0735 (-0.0372 to -0.1097)

• VNB+CIS				• Oral therapy: -0.0139 (0.0000-0.0367)		
Permsuwan et al. 2014 Thailand *Strategy 1 (No testing)* • CARB +PAX followed by GEF and then BSC till death *Strategy 2 (testing)* • GEF followed by CARB+PAX and then BSC till death	EM • At 1 week of treatment, and then at 3, 6, 9, 12, 15,18, 24, 30, 36 and 42 weeks, up until progression of disease	NR	• NR • NR • NR • de Lima Lopes et al, 2012	First-line GEF: 0.67 Second-line GEF: 0.47	NR	NR
Reck et al. 2016 Canada • GEM+CIS+NECI • GEM+CIS	RCT • NR	1093 (96)	NR	<u>EQ-5D index score</u> • GEM+CIS+NECI • (N=42) – Evaluable (n=9) – Patients with events, n(%): 20 (51.3) – Median time to deterioration, months	NR	NR

				(95%CI): 6.4 (1.6-32.9) • GEM+CIS (N=54) – Evaluable (n=42) – Patients with events, n (%): 15 (35.7) – Median time to deterioration, months (95%CI): NE (2.1-NE) • HR (95%CI): 1.16 (0.57-2.35)		
Ting et al. 2015 US • AFA • ERL • CIS+PEM	EM • NR	NR	• NR • NR • NR • Carlson et al 2009	*Data reported in Carlson et al. (2009)* <u>SD, base case (range)</u> • Oral therapy: 0.67 (0.48-0.84) • IV therapy: 0.65 (0.49-0.81) • PD: 0.47 (0.35-0.59)	NR	*Data reported in Carlson et al. (2009)* <u>SD, base case (range)</u> • Neutropenia: -0.56 (-0.42 to -0.7) • Diarrhoea: -0.61 (-0.46 to -0.76) • Stomatitis/mucositis: -0.61 (-0.46 to -0.76) • Rash: -0.62 (-0.47 to -0.78)

Verduyn et al. 2012 The Netherlands • GEM • Doublet therapies (GEM+CIS, PEM+CIS or PAX+CARB)	OBS • NR	261 (251)	• NR • NR • Yes • IPASS study	Utility values • Utility decrement for IV therapy: 0.043 • Utility decrement for oral therapy: 0.014 Output utility values, mean (sd) [b] • At baseline: 0.736 (0.1059) *Weighted CFB utilities* • GEF: 0.0528 (0.0095) • PAX+CARB: 0.0011 (0.018)	NR	NR
Wang et al. 2013 China • ERL • GEM+CARB	EM • NR	NR	• NR • NR • NR • Lewis et al 2010, Nafees et al 2008, Carlson et al 2009	NR	Data reported in Carlson et al., 2009, Base case (range) health utility • PF (with no toxicity): 0.653 • PF - GEM+CARB: 0.56 (0.224- 0.75) *After inclusion of AEs* • PFS (adjusted) GEM+CARB group: 0.56 • ERL: 0.65	NR

					Data reported in Nafees et al. (2008) • The utility scores for the PD state ranged from 0.673-0.473 (with no toxicity) Data reported in Lewis et al. (2010), Nafees et al. (2008), Carlson et al. (2009) • PD for both groups: 0.47	

AE, adverse event; AFA, afatinib; BEV, bevacizumab; BSC, best supportive care; CARB, carboplatin; CFB, change from baseline; CI, confidence interval; CIS, cisplatin; CTC, common technical criteria; DOC, docetaxel; EM, economic modelling; ERG, evidence review group; ERL, erlotinib; EQ-5D, EuroQol-five dimensions questionnaire; FACT-L, functional assessment of cancer therapy-lung; GEF, gefitinib; GEM, gemcitabine; HR, hazard ratio; HRQL, health-related quality of life; HTA, health technology assessment; ICO, icotinib; IV, intravenous; NE, not estimated; NECI, necitumumab; NR, not reported; OBS, observational; OS, overall survival; OSB, osimertinib; PAX, paclitaxel; PD, progressive disease; PEM, pemetrexed; PFS, progression-free survival; nRCT, non-randomised controlled trial; RCT, randomised controlled trial; ROC, rociletinib; SBRT, stereotactic body radiation therapy; sd, standard deviation; SD, stable disease; SG, standard gamble; TKI, tyrosine kinase inhibitors; TTO, time trade off; VAS, visual analogue scale; VATS, video-assisted thoracic surgery; VNB, vinorelbine

[a] Data were back calculated, reported as 97% completed baseline HRQL. [b] In GEF arm, utility increased after start of treatment; after 3 weeks, a steady state level was reached. In the PAX+CARB arm showed a decline in utility in the first week; thereafter, the utility increased again and stabilised for the remainder of the progression-free period. At all-time points in the progression-free state, there was a significant difference between the utilities of the GEF and the doublet chemotherapy arms (unpaired t-test p<0.00001

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

I1.1 Search strategies

Table 134: Embase and MEDLINE using Embase.com (19 February 2018)

S. No.	Search Terms	Results
1.	'non small cell lung cancer' OR 'non small cell lung cancer'/syn OR 'non small cell lung cancer'/exp OR nsclc OR ('lung'/exp AND ('neoplasm'/exp OR 'cancer'/exp OR 'carcinoma'/exp OR 'malignancy'/exp OR 'tumour'/exp)) OR 'non-small-cell' OR 'non-small cell' OR 'non small cell' OR 'nonsmall cell' OR (lung NEAR/3 (cancer* OR carcin* OR neoplasm* OR tumour* OR tumor* OR squamous OR adenocarcinoma*)):ab,ti	312,580
2.	'economics'/exp OR 'costs and cost analysis'/exp OR 'cost allocation'/exp OR 'cost benefit analysis'/exp OR 'cost control'/exp OR 'cost savings'/exp OR 'cost of illness'/exp OR 'cost sharing'/exp OR 'deductibles and coinsurance'/exp OR 'medical savings accounts'/exp OR 'health care costs'/exp OR 'direct service costs'/exp OR 'drug costs'/exp OR 'employer health costs'/exp OR 'hospital costs'/exp OR 'health expenditures'/exp OR 'capital expenditures'/exp OR 'value of life'/exp OR 'economics, medical'/exp OR 'economics, hospital'/exp OR 'economics, nursing'/exp OR 'economics, pharmaceutical'/exp OR 'budget'/exp OR 'fees and charges'/exp OR (low NEXT/1 costs):ab,ti OR (high NEXT/1 costs):ab,ti OR (healthcare NEXT/1 cost*):ab,ti OR fiscal:ab,ti OR funding:ab,ti OR financial:ab,ti OR finance:ab,ti OR (cost NEXT/1 estimate*):ab,ti OR (cost NEXT/1 variable*):ab,ti OR (unit NEXT/1 cost*):ab,ti OR economic*:ab,ti OR pharmacoeconomic*:ab,ti OR price*:ab,ti OR pricing:ab,ti OR fee:ab,ti OR fees:ab,ti OR (value NEXT/2 (money OR monetary)):ab,ti OR 'quality adjusted life year'/exp OR 'quality adjusted life year':ab,ti OR 'quality adjusted life years':ab,ti OR qualy*:ab,ti OR 'hospitalization'/exp OR 'consumer satisfaction'/exp OR 'patient acceptance of health care'/de OR 'disease management'/de OR 'physician practice patterns' OR 'clinical practice'/exp OR 'health care rationing'/de OR ((clinical OR critical OR patient) NEXT/1 path*):ab,ti OR (managed NEXT/2 (care OR clinical OR network)):ab,ti OR (resource* NEXT/2 allocat*):ab,ti	2,109,315
3.	'united kingdom' OR uk:ab,ti OR 'united kingdom'/exp OR 'united kingdom'/syn OR pound*:ab,ti	7,194,214
4.	#1 AND #2 AND #3	4,542
5.	letter:it OR editorial:it OR (review:it OR 'review literature as topic'/exp OR 'literature review':ti NOT ('meta-analysis':it OR 'meta-analysis as topic'/mj OR 'systematic review':ti OR 'systematic literature review':ti OR 'meta-analysis':ab,ti OR 'meta analysis':ab,ti)) OR ('animal'/exp NOT ('animal'/exp AND 'human'/exp)) OR 'case report*':ab,ti OR 'case series':ab,ti	9,167,593
6.	#4 NOT #5	3,291
7.	#4 NOT #5 AND [english]/lim AND [2007-2018]/py	2,690

Table 135: Medline In-Process using Pubmed.com (19 February 2018)

S. No.	Search Terms	Results

1.	Non small cell lung cancer[MH] OR nsclc[tiab]	53,192
2.	Neoplasm[MH] OR Squamous cell carcinoma[MH] OR Adenocarcinoma[MH]	3,068,342
3.	Lung[MH]	257,708
4.	#2 AND #3	29,792
5.	(lung[tiab] OR pulmon*[tiab] OR brochial[tiab]) AND (cancer*[tiab] OR carcin*[tiab] OR neoplasm*[tiab] OR tumour*[tiab] OR tumor*[tiab] OR squamous[tiab] OR adenocarcinoma*[tiab])	264,655
6.	#4 OR #5	279,221
7.	"non small cell"[tiab] OR "non-small-cell"[tiab] OR "nonsmall cell"[tiab]	53,035
8.	#6 AND #7	52,649
9.	#1 OR #8	62,486
10.	United Kingdom[MH] OR "United Kingdom" OR UK[tiab] OR pound*[tiab]	798,356
11.	#9 AND #10	1,110
12.	#11 AND (publisher[sb] NOT pubstatusnihms NOT pubstatuspmcsd NOT pmcbook) OR (pubstatusaheadofprint)	6

Table 136: HTA and NHSEED using Wiley Interscience (18 May 2017)

S. No.	Search Terms	Results
1.	[mh "non small cell lung cancer"] or nsclc:ab,ti,kw	5,775
2.	[mh neoplasm] or [mh "squamous cell carcinoma"] or [mh adenocarcinoma]	61,198
3.	[mh lung]	3,742
4.	#2 and #3	245
5.	((lung or pulmon* or bronchial) near/3 (cancer* or carcin* or neoplasm* or tumour* or tumor* or squamous or adenocarcinoma*)):ab,ti,kw	13,005
6.	#4 or #5	13,053
7.	("non small cell" or "non-small-cell" or "nonsmall cell"):ab,ti,kw	6,880
8.	#6 and #7	6,776
9.	#1 or #8	7,160
10.	[mh "Great Britain"] or "united kingdom" or UK:ab,ti,kw or pound*:ab,ti,kw	82,195
11.	#9 and #10	514
12.	#11 [Publication Year from 2007 to 2017]	458
13.	#12 in Technology Assessments	31
14.	#12 in Economic Evaluations	4

Table 137: EconLit using EBSCO.com (18 May 2017)

S. No.	Search Terms	Search Options	Results
S1	SU non small cell lung cancer OR TI nsclc OR AB nsclc	**Expanders -** Also search within the full text of the articles; Apply equivalent subjects **Search modes -** Find all my search terms	176,256
S2	SU neoplasms OR SU squamous cell carcinoma OR SU adenocarcinoma	**Expanders -** Also search within the full text of the articles; Apply equivalent subjects **Search modes -** Find all my search terms	3,788,474
S3	SU lung	**Expanders -** Also search within the full text of the articles; Apply equivalent subjects **Search modes -** Find all my search terms	1,107,334
S4	S2 AND S3	**Expanders -** Also search within the full text of the articles; Apply equivalent subjects **Search modes -** Find all my search terms	276,114
S5	TI ((lung OR pulmon* OR brochial) AND (cancer* OR carcin* OR neoplasm*	**Expanders -** Also search within the full text of the articles; Apply equivalent subjects **Search modes -** Find all my search terms	1,223,048

	OR tumour* OR tumor* OR squamous OR adenocarcinoma*)) OR AB ((lung OR pulmon* OR brochial) AND (cancer* OR carcin* OR neoplasm* OR tumour* OR tumor* OR squamous OR adenocarcinoma*))		
S6	S4 OR S5	**Expanders -** Also search within the full text of the articles; Apply equivalent subjects **Search modes -** Find all my search terms	1,301,846
S7	TI ("non small cell" OR "non-small-cell" OR "nonsmall cell") OR AB ("non small cell" OR "non-small-cell" OR "nonsmall cell")	**Expanders -** Also search within the full text of the articles; Apply equivalent subjects **Search modes -** Find all my search terms	234,687
S8	S6 AND S7	**Expanders -** Also search within the full text of the articles; Apply equivalent subjects **Search modes -** Find all my search terms	233,117
S9	S1 OR S8	**Expanders -** Also search within the full text of the articles; Apply equivalent subjects **Search modes -** Find all my search terms	277,937
S10	SU United kingdom OR ("united kingdom" OR UK OR pound*)	**Expanders -** Also search within the full text of the articles; Apply equivalent subjects **Search modes -** Find all my search terms	113,654,211
S11	S9 AND S10	**Expanders -** Also search within the full text of the articles; Apply equivalent subjects **Search modes -** Find all my search terms	19,807
S12	S9 AND S10	**Limiters** – Date Published: 20070101-20170531 **Expanders –** Also search within the full text of the articles; Apply equivalent subjects **Search modes –** Find all my search terms	15,369
S13	S9 AND S10 Source: Econlit	**Limiters – Date Published: 20070101-20170531** **Expanders – Also search within the full text of the articles; Apply equivalent subjects** **Search modes – Find all my search terms**	**8**

I1.2Description of identified studies

Table 138: Characteristics of included cost and resource use studies

Study name Line of therapy	Intervention/ comparator	Study type	• Perspective • Cost year • Currency	Key drivers	Sources
NICE[TA416] 2016 ≥Second line	• OSB • PEM+CIS	CUA	• NHS and PSS • 2014-2015 • UK pound (£)	• Utility values • Discount rate for outcomes • Drug and testing costs	• SLRs • NICE TA374, TA347, TA296 • NHS reference costs
NICE[TA258], 2012 First line	• ERL • GEF	CUA and BIA	• NHS and PSS • NR • UK pound (£)	• Indirect comparison of ERL and GEF • Fixed PAS payment treatment of GEF for the proportion of patients	NICE TA227, TA192, TA190, TA181
NICE[TA310], 2014 First line	• AFA • GEF • ERL	CUA	• NHS and PSS • 2011 • UK pound (£)	PFS and PPS	• LUX-Lung 3 and 6 • NICE TA192, TA258, TA295 • BNF 2011
NICE[TA192], 2010 First line	• GEF • GEM+CARB • GEM+CIS • PAX+CARB • VNB+CIS	CUA and BIA	• NHS and PSS • 2007-2008 • UK pound (£)	• Cost of GEM+CARB per cycle administration • Testing cost • Cost of BSC per cycle • Cost Grade 3/4 AEs • Cost g-CSF (per patient)	• BNF 57, NHS Dictionary of Medicines and Devices • NHS reference cost (2007/08) • ERG report • BNF March 2009

Brown et al., 2013 (UK) First line	• GEF • DOC+CIS+CARB • PAX+CIS+CARB	CUA	• NHS and PSS • NR • Pound (£)	Cost of GEF, DOC, PAX, and CARB	NHS Reference Costs

AE, adverse event; AFA, afatinib; BIA, budget impact analysis; BNF, British National Formulary; BSC, best supportive care; CARB, carboplatin; CIS, cisplatin; CMA, cost-minimisation analysis; CUA, cost-utility analysis; DOC, docetaxel; g-CSF, granulocyte colony stimulating factor; EGFR, epithelial growth factor receptor; ERG, evidence review group; ERL, erlotinib; GEF, gefitinib; GEM, gemcitabine; NHS, national health service; NICE, national institute for health and care excellence; NR, not reported; OSB, osimertinib; PAS, patient access scheme; PAX, paclitaxel; PEM, pemetrexed; PFS, progression-free survival; PPS, post-progression survival; PSS, personal social service; SLR, systematic literature review; VNB, vinorelbine

Table 139: Results of included cost and resource use studies

Study name	Resource use	Treatment costs	Health state costs	AEs costs
NICE[TA416] 2016 ≥Second line	<u>Progression-free health state annual resource use</u> • Outpatient visit: 9.61 • Chest X-ray: 6.79 • CT scan (chest): 0.62 • CT scan (other): 0.35 • ECG: 1.04 • Community nurse visit: 8.70 • GP home visit: 12.0 • Clinical nurse specialist: 12.0 <u>Progressed health state annual resource use</u> • Outpatient visit: 7.91 • Chest X-ray: 6.50 • CT scan (chest): 0.24 • CT scan (other): 0.42 • ECG: 0.88	<u>Drug administration costs (IV infusion)</u> • Platinum doublet chemotherapy – First attendance + DEX (8mg/day for 3 days): £245.16 – Subsequent attendances + DEX (8mg/day for 3 days): £332.50 • DOC monotherapy – First attendance + DEX (16mg/day for 3 days): £251.19 – Subsequent attendances + DEX (16mg/day for 3 days): £338.53 <u>Drug monitoring costs</u> • OSB: £0.00	<u>Total weekly cost (sum)</u> • PFS: £77.42 • PD: £139.52 • End-of-life/terminal: £3,905.26	• Diarrhoea: £431.54 • Rash (grouped term): £435.92 • Nausea/vomiting: £449.94 • Decreased appetite: £83.00 • Platelet count decreased: £502.63 • Neutropenia / Leukopenia / Neutrophil count decreased: £478.31 • Fatigue/asthenia/anaemia: £610.63 • Oedema peripheral: £365.66 • Constipation: £0.00 • Cough: £0.00 • Stomatitis: £0.00 • Headache: £0.00 • Febrile neutropenia: £2,426.86

	• Community nurse visit: 8.70 • GP home visit: 26.09 • Clinical nurse specialist: 12.00 • Therapist visit: 26.09 <u>End-of-life/terminal care Resources</u> (% of patients in each care setting/ number required) • Hospital: 55.8%/ 1 + 0.84 excess bed days • Hospice: 16.9%/ 1 • Home: 27.3% – GP home visits: 7 – Community nurse visits: 28 – Macmillan nurse: 50	• Platinum doublet chemotherapy (involves complete blood count, liver and renal function test): £4.61 • DOC (complete blood count): £2.00 <u>Total cost per patient on subsequent treatment (≥second-line)</u> • OSB: £7,304 • Platinum doublet chemotherapy: £609 • DOC: £183 <u>Drug acquisition costs</u> • OSB: £4722 • PEM: £160.00 • CIS: £3.24 • DOC: £20.95 <u>Total testing costs</u> • tissue biopsy: £725 • ctDNA: £472 <u>Total Costs for adjusted dataset</u> • OSB: £87,441 • Platinum doublet chemotherapy: £23,159 <u>Total Costs for unadjusted dataset</u> • OSB: £71,503 • Platinum doublet chemotherapy: £16,403		• Back pain: £421.67

NICE[TA258], 2012 First line	NR	GEF costs • PAS fixed cost payment: £12,200 • Per patient PAS administration cost – one off cost: £70 – per month on-going costs: £35	BSC costs (CI) • PFS Monitoring: £181.46 (£92.54-£270.38) • Monthly PD: £160.06 (£81.63-£238.49) • Terminal Phase: £2,588.25 (£1,320.01-£3,856.49) GEF costs • PFS: £11,860.26 • PD: £4,185.75 • Total: £16,046.01	• Rash: £116 • Diarrhoea: £867
NICE[TA310], 2014 First line	Disease management resource use PFS health state • Outpatients visits *Resource use per three weeks for TKI-naive* – GP: 0.0326 – Specialist: 0.1003 – Nurse: 0.0870 – Occupational therapist: 0.000 – Physiotherapist: 0.0016 *Resource use per month for third line* – GP: 0.0414 – Specialist: 0.1380 – Nurse: 0.0039 – Occupational therapist: 0.0000 – Physiotherapist: 0.0000	Drug acquisition cost per month • ERL: £1,654.19 • PAS cost of GEF: £12,200 on receipt of third pack • AFA: £2,197.82 • DOC: £1,549.25 Drug acquisition BNF cost per pack per month • ERL: £1,631.40 • GEF: £2,167.71 • DOC (total treatment cost): £1,069.50 Drug administration costs • Introductory cost of ERL: £163 • Monthly administration cost (SB14Z) of DOC: £302.41 • GEF PAS set up cost: £70	• First-line PFS: £220 • Second-line PFS: £362 • Third line/ PD £418 • AFA PFS cost: £30,616 • AFA PPS cost: £14,864 • GEF PFS cost: £25,605 • GEF PPS cost: £14,521 • ERL PFS cost: £22,245 • ERL PPS cost: £13,660	NR

	• Outpatients interventions *Resource use per three weeks for TKI-naive* – CT scan: 0.0226 – MRI scan: 0.0071 – Surgical procedure: 0.0054 – Ultrasound: 0.0056 – X-ray: 0.0280 – Radiography: 0.0021 *Resource use per month for third line* – Blood transfusion: 0.0019 – CT scan: 0.0044 – Infusion: 0.0034 – MRI scan: 0.0013 – Physical therapy: 0.0014 – Respiratory therapy: 0.0000 – Surgical procedure: 0.0072 – Ultrasound: 0.0020 – X-ray: 0.0086 – Radiography: 0.5057 • Unscheduled hospitalisations *Resource use per three weeks for TKI-naive* – Hospital stay: 0.0495	• GEF PAS administration cost: £34		

	– ICU visit: 0.0238 – Emergency room visit: 0.0383 *Resource use per month for third line* – Hospital stay: 0.169 – ICU visit: 0.009 – Emergency room visit: 0.0921			
NICE[TA192], 2010 First line	<u>NHS resources included in the evaluation are as follows:</u> • Medication • Delivery of chemotherapy • EGFR testing • Patient monitoring • NHS transport service • Grade 3/4 AE management • BSC • Post-progression active treatment	<u>Doublet chemotherapy costs per 21-day cycle</u> • GEM+CARB: £999 • PAX+CARB: £1,489 • VNB+CIS: £403 • GEM+CIS: £795 • Total costs of patients receiving BSC: £3,342 • Inflated (2007/08) total BSC cost £4,552 • Estimated cost per 21-day cycle for BSC: £600 <u>Disaggregated mean cost: Pre-progression</u> *Drugs costs* • GEM+CARB: £5,047 • PAX+CARB: £7,748 • VNB+CIS: £2,101 • GEM+CIS: £4,158 *Administration and monitoring* • GEF: £874	NR	<u>Costs per AE</u> • Neutropenia: £93 • Febrile neutropenia: £2,286 • Fatigue: £38.90 • Nausea and vomiting £700.79 • diarrhoea: £867.12 • Anaemia: £615.04 • Rash: £117 <u>Disaggregated mean cost: Pre-progression</u> <u>AE management</u> • GEF: £58 • GEM+CARB: £458 • PAX+CARB: £218 • VNB+CIS: £483 • GEM+CIS: £350

		• GEM+CARB: £1,738 • PAX+CARB: £1,034 • VNB+CIS: £2,987 • GEM+CIS: £2,987 *g-CSF prophylaxis* • GEM+CARB: £278 • PAX+CARB: £278 • VNB+CIS: £278 • GEM+CIS: £278 <u>Disaggregated mean cost: Post-Progression:</u> *Post-progression active treatment* • GEF: £12,641 • GEM+CARB: £14,595 • PAX+CARB: £13,439 • VNB+CIS: £12,634 • GEM+CIS: £14,019 *BSC* • GEF: £4,742 • GEM+CARB: £5,475 • PAX+CARB: £5,040 • VNB+CIS: £4,740 • GEM+CIS: £5,259 <u>NHS funded transport</u> • GEM+CARB: £283 • PAX+CARB: £146 • VNB+CIS: £292 • GEM+CIS: £295		

		• NHS patient transport service (per journey): £28 Total costs • GEM+CARB: £27,873 • PAX+CARB: £27,902 • VNB+CIS: £23,516 • GEM+CIS: £27,401		
Brown et al., 2013 (UK) First line	NR	Estimated acquisition cost per cycle of chemotherapy *Estimated cost according to BNF 62 prices and eMIT prices* • GEF oral per patient: £12,200.00 Deterministic estimated cost per patient for base-case analysis (BNF prices): *Drug acquisition* • DOC+CIS: £7,459 • DOC+CARB: £8,327 • PAX+CIS: £5,566 • PAX+CARB: £6,434 • GEF: £13,261 *Drug administration* • DOC+CIS: £1,102 • DOC+CARB: £1,102 • PAX+CIS: £1,722 • PAX+CARB: £1,397 • GEF: £733 *Supportive care* • DOC+CIS: £18,064	NR	Estimated cost per patient of chemotherapy • Diarrhoea: £27 • Fatigue: £22 • Febrile neutropenia: £8 • Hair loss: £0 • Nausea/vomiting: £5 • Neutropenia: £6 • Skin rash: £11 • Total AE cost: £80 Deterministic estimated cost per patient for base-case analysis (BNF prices): *Total cost* • DOC+CIS: £843 • DOC+CARB: £843 • PAX+CIS: £929 • PAX+CARB: £929 • GEF: £507

		• DOC+CARB: £18,064 • PAX+CIS: £18,064 • PAX+CARB: £18,064 • GEF: £16,272 *Terminal care* • DOC+CIS: £3,531 • DOC+CARB: £3,531 • PAX+CIS: £3,552 • PAX+CARB: £3,531 • GEF: £3,531 <u>Deterministic estimated cost per patient for base-case analysis using eMIT prices</u> *Total cost* • DOC+CIS: £5,624 • DOC+CARB: £5,663 • PAX+CIS: £2,661 • PAX+CARB: £2,700 • GEF: £12,302		

AE, adverse events; AFA, afatinib; BIA, budget impact analysis; BNF, British National Formulary; BSC, best supportive care; CARB, carboplatin; CI, confidence interval; CIS, cisplatin; CT, computerised tomography; CTC, common technical criteria; ctDNA, circulating tumour DNA; DEX, dexamethasone; DOC, docetaxel; ECG, electrocardiogram; EGFR, epithelial growth factor receptor; eMIT, electronic Market Information Tool; ERL, erlotinib; g-CSF, granulocyte colony stimulating factor; GEF, gefitinib; GEM, gemcitabine; GP, general practitioner; NHS, National Health Service; NR, not reported; OSB, osimertinib; PAS, patient access scheme; PAX, paclitaxel; PEM, pemetrexed; PFS, progression-free survival; PPS, post-progression survival; VNB, vinorelbine

Appendix J: Clinical outcomes and disaggregated results from the model

J1.1 Deterministic results (with PAS)

REDACTED AS COMMERCIAL IN CONFIDENCE

Appendix K: Adboard attendees

External advisors

- [redacted] Clatterbridge Cancer Centre NHS Foundation Trust
- [redacted] Newcastle General Hospital NHS Foundation Trust
- [redacted] Velindre Cancer Centre
- [redacted] Beatson West of Scotland Cancer Centre
- [redacted] Christie NHS Foundation Trust

AstraZeneca (AZ)

- Chair: [redacted] Market Access Manager
- [redacted] Global Health Economics Director
- [redacted] Health Economics Specialist

ISO.health*

- [redacted] Medical Writer
- [redacted] Account Director

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

Single technology appraisal

Osimertinib for untreated EGFR-positive non-small-cell lung cancer

Dear Kevin Lock,

The Evidence Review Group, Liverpool Reviews and Implementation Group (LRIG), and the technical team at NICE have looked at the submission received on 14 September 2018 from AstraZeneca. In general they felt that it is mostly well presented and clear. However, the ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data and references (see questions listed at end of letter).

The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide your written response to the clarification questions by **5pm** on **16th October 2018**. Your response and any supporting documents should be uploaded to NICE Docs.

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

Please underline all confidential information, and separately highlight information that is submitted as commercial in confidence in turquoise, and all information submitted as academic in confidence in yellow.

If you present data that are not already referenced in the main body of your submission and that are academic/commercial in confidence, please complete the attached checklist for confidential information.

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact Christian Griffiths, Technical Adviser (christian.griffiths@nice.org.uk). Any procedural questions should be addressed to Kate Moore, Project Manager (Kate.Moore@nice.org.uk).

Yours sincerely

Jasdeep Hayre
Associate Director – Appraisals
Centre for Health Technology Evaluation

Encl. checklist for confidential information

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

Section A: Clarification on effectiveness data

A1. **Priority request.** Please provide the most recent versions of the protocol, statistical analysis plan and clinical study report.

FLAURA trial design and conduct

A2. It is stated that one of the endpoints of the FLAURA trial was progression-free survival (PFS) in the T790M+ patient subgroup at the time of the primary PFS analysis (page 62, company submission [CS]). However, no results for this endpoint are presented. Please clarify:

a. Was any testing of this endpoint performed?

b. If no testing was performed, why not?

A3. Please clarify the sample size calculation (page 63, CS):

a. What is the definition of the minimal critical hazard ratio (HR) and how was this HR calculated?

b. Why was the primary PFS analysis performed at a time when only 342 events had occurred (page 72, CS), when it was specified that the primary analysis would be performed when at least 359 progression events had occurred?

A4. Please clarify whether the outcome of PFS2 (page 77, CS) was analysed according to investigator assessment or independent review.

A5. For each of the following outcomes presented in the 'Tumour response' section (pages 80-83, CS):

i. Objective response rate (ORR)
ii. Disease control rate (DCR)
iii. Time to response
iv. Duration of response
v. Median best % change in target lesion size
vi. Percentage who had a reduction of the sum of target lesion size
vii. Proportion of patients with >30%, >50%, and >70% reduction in target lesion size
viii. Difference in lesion size means for target lesion tumour shrinkage

Please clarify:

a. If the full analysis set (FAS) was used.

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Manchester
M1 4BT
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b. If the FAS was used, how were patients who did not respond, or whose response could not be evaluated, included in the analysis.

c. If the outcome was analysed according to investigator assessment or independent review.

A6. Regarding Cox proportional hazards in the FLAURA trial:

a. Please list all analyses presented in the CS that were performed using a Cox proportional hazards model.

b. Please list all analyses presented in the CS for which the proportional hazards assumption was assessed.

c. Please provide the results of any assessments of the proportional hazards assumption.

A7. Regarding the participant flow in the FLAURA trial, please clarify where the patients who received osimertinib second-line, but not as protocol defined crossover, fit into Figure 17 (page 69, CS).

Central nervous system subgroup in FLAURA trial

A8. **Priority request.** Please clarify what is meant by a target lesion, non-target lesion and new lesion and why these are not mutually exclusive.

A9. **Priority request.** Clinical advice to the ERG is that scans for central nervous system (CNS) metastases are only conducted in clinical practice when a patient is suspected of having CNS metastases. Please clarify how and why only [redacted] patients received scans for CNS metastases in the FLAURA trial. If only patients suspected by trial investigators as having CNS metastases received scans for CNS metastases, please clarify how it is possible that "[redacted] patients were only part of the CNS full analysis set (cFAS) as they were not considered by the Investigator to have baseline CNS metastases" (page 85, CS), i.e. please clarify why these [redacted] patients were scanned for CNS metastases.

A10. **Priority request.** Please clarify why [redacted] patients who were scanned for CNS metastases did not have a measurable CNS lesion.

A11. **Priority request.** In relation to patients classified as having CNS in Table 15 (pages 61-62, CS), please clarify exactly how patients were classified as having CNS if not from CNS scans. It is stated in the footnote to the table that: "This is a

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programmatically derived composite endpoint with a list of contributing data sources." Please clarify what this means.

A12. Based on the classification with and without CNS metastases using the "programmatically derived composite endpoint", please clarify whether patients with CNS metastases in the osimertinib arm had similar baseline characteristics to patients with CNS metastases in the standard of care (SOC) arm. Please also clarify whether patients without CNS metastases in the osimertinib arm had similar baseline characteristics to patients without CNS metastases in the SOC arm.

A13. Please clarify whether baseline characteristics of patients with CNS metastases in the cFAS population were similar to those of patients with CNS metastases in the CNS evaluable for response set (cEFR) population. Please also clarify whether the characteristics in either or both of these populations of patients with CNS metastases were similar to those considered to have CNS metastases using the "programmatically derived composite endpoint".

A14. Please clarify whether in all 3 populations of patients with CNS metastases (i.e. defined using the "programmatically derived composite endpoint", cFAS and cEFR), baseline characteristics were similar between the osimertinib and SOC arms?

A15. Please provide definitions for the following outcomes:

a. CNS PFS.

b. CNS ORR.

c. CNS DCR.

A16. For question A15, please clarify if each of these outcomes was analysed according to investigator assessment or independent review.

A17. PFS, overall survival (OS), ORR and DCR were analysed in the subgroup of patients with CNS metastases at baseline by investigator assessment (CNS defined using the "programmatically derived composite endpoint"), CNS PFS was analysed in the cFAS subgroup, and CNS ORR, CNS DCR and median time to response was analysed in the cFAS and cEFR subgroups:

a. Please justify the choice of analysis sets for each outcome, and clarify whether all these analyses were pre-specified.

b. Please also clarify why OS was not chosen as an endpoint for either the cFAS or cEFR subgroups.

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A18. It is stated that for CNS PFS: "the HR was [redacted] in the cFAS population, indicating a [redacted] reduction in the risk of CNS disease progression or death (in the absence of CNS RECIST progression)" (page 87, CS). Please clarify what is meant by "in the absence of CNS RECIST progression."

A19. In Table 25 (page 90, CS), median time to response is presented. Please clarify the following:

a. Does 'median time to response' refer to response of CNS lesions only, or to response of CNS and non-CNS lesions?

b. Was this outcome analysed according to investigator assessment or independent review?

c. How were patients who didn't have a measurable lesion included in the analysis of this outcome in the cFAS population?

A20. In the footnotes to Table 25 (page 90, CS), the percentages of patients with confirmed CNS ORR are presented. What is the definition of confirmed CNS ORR?

A21. Results are presented for 'percentage change in lesion size' in the subgroup of patients with CNS metastases evaluable for response (page 18, CS):

a. Please define the outcome used for this analysis, specifically stating whether only CNS lesions were included in the analysis, or if both non-CNS and CNS lesions were included in the analysis.

b. Please clarify if this analysis was pre-specified.

Other subgroups in the FLAURA trial

A22. For the Asian vs non-Asian ethnicity subgroup, please clarify whether baseline characteristics of Asians were similar to non-Asians. Please also clarify whether baseline characteristics were similar in the osimertinib and SOC arms in both populations.

A23. It is stated that "the numerical efficacy advantage for non-Asians over Asians was maintained for the analyses of OS, ORR, and DCR" (Table 26, page 91, CS). However, from the odds ratios presented in Table 26, Asian patients experience greater clinical benefit from osimertinib (relative to SoC) in terms of both ORR and DCR in comparison to non-Asian patients. Please clarify, is the interpretation of the results presented in Table 26 incorrect?

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City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

A24. For the subgroup analyses by EGFR mutation status, please clarify whether baseline characteristics were similar in the osimertinib and SOC arms in the Exon19del population, and whether baseline characteristics were similar in the osimertinib and SOC arms in the L858R population.

Indirect comparison

A25. It is not explicitly stated why the indirect comparison was not performed. Please provide the rationale for this decision.

A26. It is stated that "The two studies appeared to be consistent in terms of age, gender, race, proportion of patients with CNS metastases, proportion of patients who never smoked and the distribution of different EGFR mutations" (Table 8, page 96, CS). However, Table 8 showing baseline characteristics for the trials does not appear to be presented. Please provide this table.

A27. It is stated that 34 studies were identified; should this instead be 37?

Additional analyses

A28. OS data in the FLAURA trial is from patients with World Health Organization (WHO) performance status (PS) 0-1. As noted by the company, real world OS data differs to that reported in trials. In part, this is because real world OS data includes patients with WHO PS ≥2. If available, from the analysis conducted in partnership with the National Cancer Registration and Analysis Service, please provide OS Kaplan-Meier data for Stage 3b/4 NSCLC patients treated with an EGFR-TKI 1L after diagnosis by performance status (i.e. similar to Figure 5 [page 29, CS]). If possible, please present the data by PS 0-1 and PS ≥2.

A29. Please provide the results of any assessments of the proportional hazards assumption for the LUX-Lung 7 trial.

Section B: Clarification on cost-effectiveness data

B1. **Priority request: Kaplan-Meier data.** Please provide the Kaplan-Meier analyses listed in a to f below to the following specifications:

Trial data set:	*FLAURA trial*
Censoring:	*Censor lost to follow-up and withdrawn patients at the date recorded. Patients alive and still at risk of the target event at the date of data cut-off should be censored at the date of data cut-off, i.e. not when last known to be alive*

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City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

Format: *Please present analysis outputs using the format of the sample table shown below this question*

Population: *ITT population including all patients lost to follow-up or withdrawing from the trial*

a. Time to death from any cause (OS) Kaplan-Meier analysis for patients in the osimertinib arm of the trial

b. Time to death from any cause (OS) Kaplan-Meier analysis for patients in the SoC EGFR-TKI arm of the trial

c. Time to investigator assessed progression or death (PFS) Kaplan-Meier analysis for patients in the osimertinib arm of the trial

d. Time to investigator assessed progression or death (PFS) Kaplan-Meier analysis for patients in the SoC EGFR-TKI arm of the trial

e. Time to study treatment discontinuation Kaplan-Meier analysis for patients in the osimertinib arm of the trial

f. Time to study treatment discontinuation Kaplan-Meier analysis for patients in the SoC EGFR-TKI arm of the trial.

Sample table: Example of output (SAS) required from specified Kaplan-Meier analyses - The LIFETEST Procedure

Product-Limit Survival Estimates						
DAYS		**Survival**	**Failure**	**Survival Standard Error**	**Number Failed**	**Number Left**
0.000		1.0000	0	0	0	62
1.000		.	.	.	1	61
1.000		0.9677	0.0323	0.0224	2	60
3.000		0.9516	0.0484	0.0273	3	59
7.000		0.9355	0.0645	0.0312	4	58
8.000		.	.	.	5	57
8.000		.	.	.	6	56
8.000		0.8871	0.1129	0.0402	7	55

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10.000		0.8710	0.1290	0.0426	8	54
SKIP…		……	……	……	…	…
389.000		0.1010	0.8990	0.0417	52	5
411.000		0.0808	0.9192	0.0379	53	4
467.000		0.0606	0.9394	0.0334	54	3
587.000		0.0404	0.9596	0.0277	55	2
991.000		0.0202	0.9798	0.0199	56	1
999.000		0	1.0000	0	57	0

Section C: Textual clarifications and additional points

C1. Please clarify whether all the data reported for the CNS metastases subgroups should be marked as academic in confidence when much of the data are available in the European Medicines Agency European Public Assessment Report.

C2. Please check all references cited in the company submission are correct. In a number of places, this does not appear to be the case. For example, on page 26, no reference has been inserted to support the claim that "EGFR mutations are more common in Asians than in Western populations, in women than in men, and in never-smokers than in ever-smokers". On page 95, the CTONG-0901 study is cited as reference 18 (and later on in the next paragraph as reference 20, but it's actually reference 112) and a network meta-analysis is cited as reference 19 (it's actually reference 94). In the next paragraph, the ARCHER 1050 study is cited as reference 17 which is incorrect, LUX-Lung 7 as reference 18 (it's reference 22) and the CTONG-0109 study as reference 20. In the reference list, reference 18 is the same as reference 176, and reference 10 is the same as references 63, 72 and 90. Please can the references be updated and corrected where necessary?

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Single technology appraisal

Osimertinib for untreated EGFR-positive non-small-cell lung cancer

Dear Kevin Lock,

The Evidence Review Group, Liverpool Reviews and Implementation Group (LRIG), and the technical team at NICE have looked at the submission received on 14 September 2018 from AstraZeneca. In general they felt that it is mostly well presented and clear. However, the ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data and references (see questions listed at end of letter).

The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide your written response to the clarification questions by **5pm** on **16th October 2018**. Your response and any supporting documents should be uploaded to NICE Docs.

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

Please underline all confidential information, and separately highlight information that is submitted as commercial in confidence in turquoise, and all information submitted as academic in confidence in yellow.

If you present data that are not already referenced in the main body of your submission and that are academic/commercial in confidence, please complete the attached checklist for confidential information.

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact Christian Griffiths, Technical Adviser (christian.griffiths@nice.org.uk). Any procedural questions should be addressed to Kate Moore, Project Manager (Kate.Moore@nice.org.uk).

Yours sincerely

Jasdeep Hayre
Associate Director – Appraisals
Centre for Health Technology Evaluation

Encl. checklist for confidential information

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City Tower
Manchester
M1 4BT
United Kingdom

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Section A: Clarification on effectiveness data

A1. **Priority request.** Please provide the most recent versions of the protocol, statistical analysis plan and clinical study report.

These documents are supplied separately.

FLAURA trial design and conduct

A2. It is stated that one of the endpoints of the FLAURA trial was progression-free survival (PFS) in the T790M+ patient subgroup at the time of the primary PFS analysis (page 62, company submission [CS]). However, no results for this endpoint are presented. Please clarify:

a. Was any testing of this endpoint performed?

The assessment of PFS in patients with positive pre-treatment T790M mutation was not performed.

b. If no testing was performed, why not?

The multiple testing strategy was updated to remove PFS subgroup in T790M mutation-positive patients and instead replace with CNS BICR PFS analysis; this change was implemented prior to database lock in the last version of the SAP (28 February 2017). The reason for the change was that at the time of study initiation, there was evidence that, when using highly sensitive mutation detection assays, T790M occurred in up to 40% of TKI-naive NSCLCs with EGFRm (Maheswaran et al 2008, Rosell et al 2011). Consequently, a subgroup analysis of patients with de novo T790M was included into the FLAURA study in order to be able to analyse patients that had entered the study with a potential osimertinib-resistant NSCLC separately. During the conduct of the study, however, it became apparent that this high incidence of de novo T790M may have been the result of a tissue preparation artefact (Denis et al 2015, Ye et al 2013). Instead, based on recent evidence of clinical activity of osimertinib in CNS (Goss et al 2016), CNS BICR PFS was included in the multiple testing strategy.

Due to the low number of patients with tumours harbouring T790M in this first-line population (N = 5 patients in the FAS based on tissue and/or ctDNA testing), the subgroup analysis based on T790M status was not conducted.

A3. Please clarify the sample size calculation (page 63, CS):

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a. What is the definition of the minimal critical hazard ratio (HR) and how was this HR calculated?

The critical hazard ratio is defined as the HR with 50% power when E events have occurred and therefore is the largest HR which can demonstrate a statistically significant study.
The minimal critical hazard ratio was noted as (SAP, section 1.3):
The primary analysis of PFS will occur when approximately 359 progression events have been observed in the 530 globally randomised patients. If the true PFS hazard ratio (HR) for the comparison of AZD9291 versus SoC EGFR TKI is 0.71, 359 progression events will provide 90% power to demonstrate a statistically significant difference in PFS at a 5% two-sided significance level (translating to an approximate improvement in median PFS from 10 to 14.1 months assuming exponential data distribution and proportional hazards). The minimum critical HR is 0.81 (i.e. 10 to 12 months).
This was obtained using the following assumptions and formula:

$$\exp\left(\frac{-(r+1)(z_{1-\alpha}+z_{0.5})}{\sqrt{rE}}\right)$$

By rearranging this formula and using Excel:

Critical value = exp (ln(a) – (NORMINV(1-0.05/2)*SQRT((POWER((1+b),2)/b)/c)))

where
a is the HR under the null hypothesis (HR=1)
b is the randomisation ratio (1)
c is the number of expected events (359)

b. Why was the primary PFS analysis performed at a time when only 342 events had occurred (page 72, CS), when it was specified that the primary analysis would be performed when at least 359 progression events had occurred?

This will be provided separately.

A4. Please clarify whether the outcome of PFS2 (page 77, CS) was analysed according to investigator assessment or independent review.

PFS2 was assessed by investigator in accordance with disease assessments conducted per routine clinical practice.

A5. For each of the following outcomes presented in the ‘Tumour response’ section (pages 80-83, CS):

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i. Objective response rate (ORR)
ii. Disease control rate (DCR)
iii. Time to response
iv. Duration of response
v. Median best % change in target lesion size
vi. Percentage who had a reduction of the sum of target lesion size
vii. Proportion of patients with >30%, >50%, and >70% reduction in target lesion size
viii. Difference in lesion size means for target lesion tumour shrinkage

Please clarify:

a. If the full analysis set (FAS) was used.
b. If the FAS was used, how were patients who did not respond, or whose response could not be evaluated, included in the analysis.

c. If the outcome was analysed according to investigator assessment or independent review.

Please see summary table overleaf.

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	Was FAS used?	Non-FAS adjustments	Relevant source in CSR	
			Investigator Assessed	Blinded Independent central review
Objective response rate (ORR)	Yes	N/A	Table 11.2.3.1	Table 11.2.3.2
Disease control rate (DCR)		N/A	Table 11.2.5	N/A
Time to response	No	Responders only (N=433)	Table 11.2.3.4	N/A
Duration of response				Table 11.2.4.2
Median best % change in target lesion size		Denominator is number of subjects with a baseline and at least one post-baseline RECIST target lesion assessment scan (n=548).	Table 11.2.6.1.1	Table 11.2.6.1.2
Percentage who had a reduction of the sum of target lesion size				
Proportion of patients with >30%, >50%, and >70% reduction in target lesion size				
Difference in lesion size means for target lesion tumour shrinkage			Table 11.2.6.3.1	Table 11.2.6.3.2

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A6. Regarding Cox proportional hazards in the FLAURA trial:

a. Please list all analyses presented in the CS that were performed using a Cox proportional hazards model.

Figure 20: Subgroup analyses of progression-free survival.

b. Please list all analyses presented in the CS for which the proportional hazards assumption was assessed.

PFS – IA,
PFS – BICR,
OS

c. Please provide the results of any assessments of the proportional hazards assumption.

A visual inspection of the cumulative hazards plots for PFS – IA, PFS – BICR and OS by treatment do not demonstrate sufficient evidence against the proportional hazards assumption for these endpoints. Therefore, the proportional hazards assumption is considered reasonable in these cases.

A7. Regarding the participant flow in the FLAURA trial, please clarify where the patients who received osimertinib second-line, but not as protocol defined crossover, fit into Figure 17 (page 69, CS).

There were 7 patients who received osimertinib second-line, but not as protocol-defined crossover. These are accounted for in Figure 17 of the CS within the 213 patients who discontinued treatment.

Central nervous system subgroup in FLAURA trial

A8. **Priority request.** Please clarify what is meant by a target lesion, non-target lesion and new lesion and why these are not mutually exclusive.

According to the Clinical Study Protocol, target lesion (TL), non-target lesion (NTL) and new lesion (NL) are defined as:

Target lesions (TL)
When more than one measurable lesion is present at baseline, all lesions up to a maximum of 5 in total and 2 lesions per organ, representative of all involved organs are identified as target lesions and recorded and measured at baseline as well as subsequent assessment visits.

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Non-target lesions
All other lesions (or sites of disease) not recorded as TL should be identified as NTL at baseline. Measurements are not required for these lesions, but their status should be followed at subsequent visits.

New lesions
Details of any new lesions will also be recorded with the date of assessment. The presence of one or more new lesions is assessed as progression.

All CNS lesions present at baseline were considered as NTLs. Only non-CNS lesions could be classified as target lesions.

According to RECIST protocol, patients may be judged to have progressed if there is unequivocal evidence of tumour growth or progression in TL or NTL in the presence or absence of NL (see Table 7).

Table 7 Overall visit response

Target lesions	Non-Target lesions	New Lesions	Overall response
CR	CR	No	CR
CR	NA	No	CR
CR	Non CR/Non PD	No	PR
CR	NE	No	PR
PR	Non PD or NE	No	PR
SD	Non PD or NE	No	SD
NE	Non PD or NE	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

A lesion is either classified as target or non-target at baseline and these are mutually exclusive. In the analysis table reporting the reason for progression (for example), patients may be counted more than once if they have progressed in a target and non-target lesion at the same visit documenting progression.

A9. **Priority request.** Clinical advice to the ERG is that scans for central nervous system (CNS) metastases are only conducted in clinical practice when a patient is suspected of having CNS metastases. Please clarify how and why only 200 patients received scans for CNS metastases in the FLAURA trial. If only patients suspected by trial investigators as having CNS metastases received scans for CNS metastases, please clarify how it is possible that “32 patients were only part of the CNS full analysis set

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(cFAS) as they were not considered by the Investigator to have baseline CNS metastases" (page 85, CS), i.e. please clarify why these 32 patients were scanned for CNS metastases.

Per the protocol, patients with asymptomatic brain metastases were not excluded (exclusion criteria 5). If a patient was in screening for the study the site could conduct a brain CT/MRI if it was part of their routine practice or if they suspected the patient to have brain metastases (section 5.1.1 of the protocol). A brain scan was not mandated per the protocol. Therefore, it was only conducted in 200 randomised patients. Only patients in whom the investigator identified a non-target lesion at baseline were required to continue receiving brain scans alongside the required disease assessment.

In the FLAURA study, 200/556 patients received a brain scan at baseline. The investigator assessed these scans and decided if they considered the patient to have brain involvement.

All brain scans received by patients were collected and reviewed by an independent neuro-radiologist. This was a separate assessment to the investigator and there were 32 cases where the investigator did not note a non-target lesion but brain involvement was noted by this independent reviewer. Therefore 32 patients were only part of the CNS FAS but were not considered by the investigator to have brain involvement at baseline.

Figure S1. from the Supplementary material for the recent paper by Reungwetwattana et al. clarifies the status of the 32 patients who had a brain scan but were not considered to be have baseline CNS metastases.

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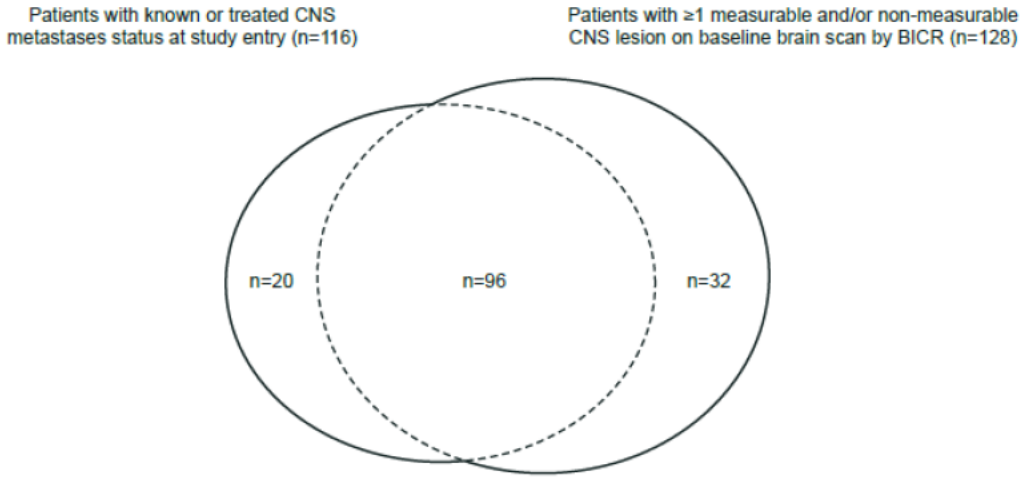
Figure S1. Overlap between the CNS full analysis set and the known or treated CNS metastases at study entry group in the overall FLAURA population



Most patients were included in both the cFAS and the known or treated CNS metastases at study entry group. Twenty patients were included in the known or treated CNS metastases at study entry group but not included in the cFAS, either because baseline scans were not submitted for CNS BICR assessment or because CNS metastases were not confirmed by CNS BICR. Thirty-two patients were included in the cFAS but not in the known or treated CNS metastases at study entry group as they were not considered by the investigator to have baseline CNS metastases.

A10. **Priority request.** Please clarify why 87 patients who were scanned for CNS metastases did not have a measurable CNS lesion.

As discussed, 200 patients with baseline brain scans (either MRI or CT) were evaluated by independent neuroradiologist BICR. Of these, 72 were judged to have **no** CNS lesions. The remaining 128 patients had measurable and/or non-measurable CNS lesions and are described as the cFAS (CNS full analysis set) group. 87 patients in this cFAS group only had non-measurable CNS lesions (e.g. leptomeningeal metastases and other diffuse lesions) and therefore were excluded from the cEFR (CNS evaluable for response) set.
Figure 1

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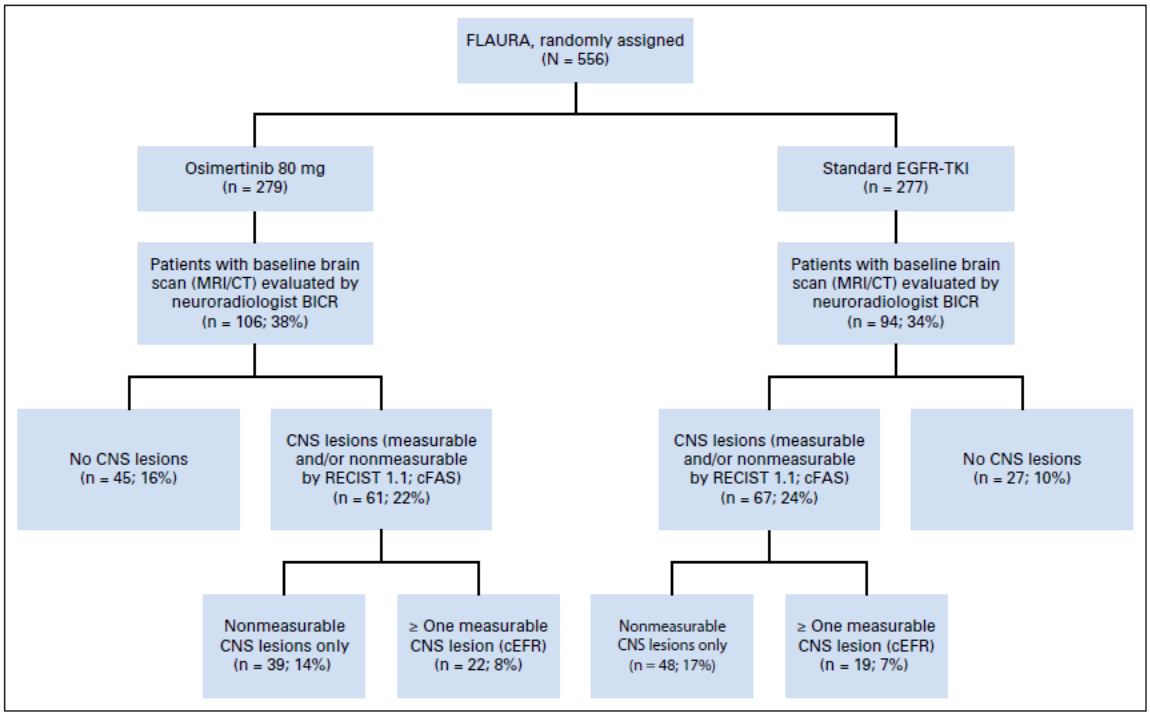

Fig 1. CONSORT diagram. Patient disposition. BICR, blinded independent central review; cEFR, CNS evaluable-for-response set; cFAS, CNS full-analysis set; CT, computed tomography; EGFR, epidermal growth factor receptor; MRI, magnetic resonance imaging; TKI, tyrosine kinase inhibitor.

A11. **Priority request.** In relation to patients classified as having CNS in Table 15 (pages 61-62, CS), please clarify exactly how patients were classified as having CNS if not from CNS scans. It is stated in the footnote to the table that: "This is a programmatically derived composite endpoint with a list of contributing data sources." Please clarify what this means

AstraZeneca conducted a review of the baseline characteristics and prior radiotherapy collected in the eCRF to identify patients as having a positive CNS metastases status at baseline. This reviewed was conducted prior to unblinding and documented in section 4.3.9.1 of the SAP.

A12. Based on the classification with and without CNS metastases using the "programmatically derived composite endpoint", please clarify whether patients with CNS metastases in the osimertinib arm had similar baseline characteristics to patients with CNS metastases in the standard of care (SOC) arm. Please also clarify whether patients without CNS metastases in the osimertinib arm had similar baseline characteristics to patients without CNS metastases in the SOC arm.

The baseline characteristics for these subgroups and the comparison between arms will be presented separately.

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A13. Please clarify whether baseline characteristics of patients with CNS metastases in the cFAS population were similar to those of patients with CNS metastases in the CNS evaluable for response set (cEFR) population. Please also clarify whether the characteristics in either or both of these populations of patients with CNS metastases were similar to those considered to have CNS metastases using the "programmatically derived composite endpoint".

The baseline characteristics for these subgroups and the comparison between populations will be presented separately.

A14. Please clarify whether in all 3 populations of patients with CNS metastases (i.e. defined using the "programmatically derived composite endpoint", cFAS and cEFR), baseline characteristics were similar between the osimertinib and SOC arms?

The baseline characteristics for these subgroups/populations and the comparison between arms will be presented separately.

A15. Please provide definitions for the following outcomes:

a. CNS PFS.

CNS PFS is defined as the time from randomisation until the date of objective CNS disease progression or death (by any cause in the absence of CNS progression) regardless of whether the patient withdraws from randomised therapy or receives another anti-cancer therapy prior to progression. Patients who have not progressed (in the CNS) or died at the time of analysis will be censored at the time of the latest date of CNS assessment from their last evaluable RECIST assessment. However, if the patient progresses or dies after two or more missed visits, the patient will be censored at the time of the latest evaluable RECIST assessment.

b. CNS ORR.

CNS Objective Response rate is defined as the number (%) of randomised patients with at least one visit response of CR or PR in the CNS. Data obtained up until progression or last evaluable assessment in the absence of progression will be included in the assessment of ORR. Patients will only non-measurable disease can only report a response of CR. Responses of CR and PR do not require confirmation in line with RECIST v1.1 criteria for randomised trials.

c. CNS DCR.

CNS Disease control rate is defined as the percentage of patients who have a best overall CNS response of CR or PR or SD at ≥6 weeks, prior to any PD event. The 6-week time point

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will allow for a visit window and be defined as on or after study day 35 (allowing for the visit window).

A16. For question A15, please clarify if each of these outcomes was analysed according to investigator assessment or independent review.

CNS PFS, CNS ORR and CNS DCR were performed on the independent neuro-radiological review.

A17. PFS, overall survival (OS), ORR and DCR were analysed in the subgroup of patients with CNS metastases at baseline by investigator assessment (CNS defined using the "programmatically derived composite endpoint"), CNS PFS was analysed in the cFAS subgroup, and CNS ORR, CNS DCR and median time to response was analysed in the cFAS and cEFR subgroups:

a. Please justify the choice of analysis sets for each outcome, and clarify whether all these analyses were pre-specified.

In the 'programmatically derived composite endpoint' PFS, ORR and DCR were pre-specified. OS was not pre-specified. This is a subgroup of the FAS and therefore this was considered the most appropriate population.

CNS PFS, CNS ORR, CNS DCR and CNS duration of response in the cFAS and cEFR were pre-specified. Given these endpoints were interested in CNS progression/response, they were conducted in patients with CNS involvement at baseline.

b. Please also clarify why OS was not chosen as an endpoint for either the cFAS or cEFR subgroups.

No OS subgroup analysis was pre-specified to be conducted on the interim OS data and therefore an OS analysis was not conducted on these subgroups of patients. This analysis is also not pre-specified for the time of the final OS analysis.

A18. It is stated that for CNS PFS: "the HR was 0.48 (95% CI: 0.26, 0.86; p-value = 0.014) in the cFAS population, indicating a 52% reduction in the risk of CNS disease progression or death (in the absence of CNS RECIST progression)" (page 87, CS). Please clarify what is meant by "in the absence of CNS RECIST progression."

The events of interest in this analysis are either CNS progression (worsening of a lesion present at baseline or a new lesion per RECIST v1.1) or death by any cause. The text 'in the absence of CNS RECIST progression' means that a death is included as an event if the

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patient has **not** had a CNS progression per RECIST v1.1. For a death to be included as an event, the '2 or more missed' visit rule is also applied.

A19. In Table 25 (page 90, CS), median time to response is presented. Please clarify the following:

a. Does 'median time to response' refer to response of CNS lesions only, or to response of CNS and non-CNS lesions?

CNS lesions only.

b. Was this outcome analysed according to investigator assessment or independent review?

This was per the independent neuro-radiologist assessment.

c. How were patients who didn't have a measurable lesion included in the analysis of this outcome in the cFAS population?

A patient with only non-measurable disease was considered a responder if they had a complete response per RECIST v1.1.

Study Code: D5160C00007 Phase III - CNS
Data Cut-Off: 12JUN2017
Table 11.2.18.2.4.1 Best unconfirmed objective CNS response (CNS Full Analysis Set)

Response status	Best objective CNS response	AZD9291 80 mg (N=61)	SoC (N=67)
Response	Total	40 (65.6)	29 (43.3)
	Complete response [a]	25 (41.0)	16 (23.9)
	Complete response	5 (8.2)	0
	Complete response without measurable disease [b]	20 (32.8)	16 (23.9)
	Partial response [a]	15 (24.6)	13 (19.4)
Non-response	Total	21 (34.4)	38 (56.7)
	Stable disease >= 6 weeks [c]	15 (24.6)	27 (40.3)
	Stable disease	1 (1.6)	4 (6.0)
	Stable disease (Non CR/Non PD) [b]	14 (23.0)	23 (34.3)
	Progression	0	5 (7.5)
	RECIST progression	0	4 (6.0)
	Death	0	1 (1.5)
	Not evaluable	6 (9.8)	6 (9.0)
	Stable disease < 6 weeks	0	0
	No evaluable follow-up assessments	6 (9.8)	6 (9.0)

SoC = Standard of Care.
[a] Response does not require confirmation.
[b] Applicable for patients with only non-measurable disease.
[c] SD >= 6 weeks includes RECIST visit window (+/-7 days).
RECIST version 1.1.

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A20. In the footnotes to Table 25 (page 90, CS), the percentages of patients with confirmed CNS ORR are presented. What is the definition of confirmed CNS ORR?

The CNS ORR analysis was repeated for confirmed CNS BICR ORR. A response (CR and PR) was considered confirmed if it was maintained on the scan, performed at least 4 weeks after the criteria for response were first met

A21. Results are presented for 'percentage change in lesion size' in the subgroup of patients with CNS metastases evaluable for response (page 18, CS):

a. Please define the outcome used for this analysis, specifically stating whether only CNS lesions were included in the analysis, or if both non-CNS and CNS lesions were included in the analysis.

CNS lesions only as assessed by independent neuro-radiologist.

b. Please clarify if this analysis was pre-specified.

This analysis was pre-specified and is noted on page 66 of the SAP.

Other subgroups in the FLAURA trial

A22. For the Asian vs non-Asian ethnicity subgroup, please clarify whether baseline characteristics of Asians were similar to non-Asians. Please also clarify whether baseline characteristics were similar in the osimertinib and SOC arms in both populations.

The baseline characteristics for these subgroups and the comparison between arms will be presented separately.

A23. It is stated that "the numerical efficacy advantage for non-Asians over Asians was maintained for the analyses of OS, ORR, and DCR" (Table 26, page 91, CS). However, from the odds ratios presented in Table 26, Asian patients experience greater clinical benefit from osimertinib (relative to SoC) in terms of both ORR and DCR in comparison to non-Asian patients. Please clarify, is the interpretation of the results presented in Table 26 incorrect?

Yes, the interpretation is correct. An odds ratio of 1.35 shows that a patient is 1.35 times more likely to experience a response on osimertinib than SoC in the Asian subgroup. Whereas a patient is only 1.14 times more likely to experience a response on osimertinib than SoC in the non-Asian subgroup. The 95% confidence intervals are wide and large overlap.

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A24. For the subgroup analyses by EGFR mutation status, please clarify whether baseline characteristics were similar in the osimertinib and SOC arms in the Exon19del population, and whether baseline characteristics were similar in the osimertinib and SOC arms in the L858R population.

The baseline characteristics for these subgroups and the comparison between arms will be presented separately.

Indirect comparison

A25. It is not explicitly stated why the indirect comparison was not performed. Please provide the rationale for this decision.

As stated in the CS (p98):

"Given the similarity of the hazard functions of afatinib and gefitinib in LuxLung 7, and evidence from the CTONG 0901 study, the previous NMA and the conclusions of the appraisal committee for TA258, we have made the assumption that all three early generation TKIs have equivalent efficacy."

This paragraph should conclude with the following:

"..and we will not conduct a formal indirect treatment comparison."

A26. It is stated that "The two studies appeared to be consistent in terms of age, gender, race, proportion of patients with CNS metastases, proportion of patients who never smoked and the distribution of different EGFR mutations" (Table 8, page 96, CS). However, Table 8 showing baseline characteristics for the trials does not appear to be presented. Please provide this table.

Table 8 is presented on pages 38 – 40 of the CS.

A27. It is stated that 34 studies were identified; should this instead be 37?

The correct number is 37. The figure of "34" in the text on p96 refers to ongoing studies and is incorrectly used in the context presented.

Additional analyses

A28. OS data in the FLAURA trial is from patients with World Health Organization (WHO) performance status (PS) 0-1. As noted by the company, real world OS data differs to that reported in trials. In part, this is because real world OS data includes patients with WHO PS ≥2. If available, from the analysis conducted in partnership with the National Cancer Registration and Analysis Service, please provide OS Kaplan-Meier data for Stage 3b/4 NSCLC patients treated with an EGFR-TKI 1L after diagnosis by

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performance status (i.e. similar to Figure 5 [page 29, CS]). If possible, please present the data by PS 0-1 and PS ≥2.

The results of the stratified analyses (PS 0-1 and PS ≥2) requested are presented in the amended Table 4 from the CS below. Since a large number of patient records (n=204) had missing or unknown PS and could introduce heterogeneity (and uncertainty) to the results, we present these patients separately.

All analyses are descriptive. No formal statistical analyses have been conducted to assess differences in baseline characteristics across groups or adjust for potential differences when assessing OS.

Table 4 shows broadly similar median ages (68, 69.5 and 67 years, respectively), proportions of Stage IV disease (96.1%, 95.5% and 94.1%) and time from diagnosis to initiation of TKI (35, 37 and 36.5 days). The proportion of females with PS2+ (58%) is slightly less than that with PS0/1 (64.9%) or missing/unknown (64.2%).

Table 4 also provides a comparison of the median OS of patients according to performance status and demonstrates a significant unadjusted difference between patients with PS0/1 (16.7 months [95% CI: 15.3 – 19.1]) and those with PS2+ 11.1 months [95% CI: 8.6 – 13.4]).

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Table 4: Baseline characteristics in the NCRAS analysis, compared with those of FLAURA

			Real-world NCRAS analysis		
N (%)	**Real-world NCRAS analysis (N=652)**	**FLAURA (N=556)**	**PS 0/1 (N=336)**	**PS 2+ (N=112)**	**PS missing/unknown (N=204)**
Female, n (%)	414 (63.5%)	350 (63)	218 (64.9%)	65 (58%)	131 (64.2%)
Stage of disease, n (%)					
Stage 3b	30 (4.6%)	100% (NR)	13 (3.9%)	5 (4.5%)	12 (5.9%)
Stage 4	622 (95.4%)		323 (96.1%)	107 (95.5%)	192 (94.1%)
Performance status, n (%)					
PS 0	130 (19.9%)	228 (41%)	130 (38.7%)		
PS 1	206 (31.6%)	327 (59%)	206 (61.3%)		
PS 2	89 (13.7%)	-		89 (79.5%)	
PS≥3	23 (3.5%)	-		23 (20.5%)	
Missing	204 (31.3%)	1 (0.2%)			204 (100%)
Age, median years	68 (IQR: 61 – 76)	64.0 (range: 26 – 93)	68 (IQR: 61 - 75)	69.5 (IQR: 63.75 - 77)	67 (IQR: 61 - 76)
Time to initiation of EGFR TKI treatment from NSCLC diagnosis, median (IQR)	35 days (IQR: 25.7 – 55.0)	1.2 months (range: 0 – 82) [from diagnosis to randomisation]	35 days (IQR: 26.0 – 49.0)	37 days (IQR: 26.75 - 55.25)	36.5 days (IQR: 24.0 - 60.25)
Median OS (95% CI)	15.8 (95% CI: 14.1 – 17.2)	NR	16.7 (95% CI: 15.3 – 19.1)	11.1 (95% CI: 8.6 – 13.4)	16.6 (95% CI: 13.1 – 18.9)

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A29. Please provide the results of any assessments of the proportional hazards assumption for the LUX-Lung 7 trial.

As the LUX-Lung 7 trial was conducted externally, AZ did not have access to the individual patient data (IPD) and as such were limited to any analyses, including assessment of proportional hazards, based on digitised data in terms of PFS-IA, PFS-BICR and OS. As such we were limited to visual assessment of the log cumulative hazard plots which are shown in Figure 30 of the NICE submission (and reproduced here – see attached). Figures A1 and A2 do not clearly display that the PH holds for PFS-IA or PFS-BICR: the KM displays a distinctive step pattern (progression events appear to be grouped) which may be a result of irregular progression assessments that cause the log cumulative hazard plot to be non-parallel; the curves repeatedly converge and separate but do not cross. Figure A3 indicates that, following 2 months of treatment, the curves appear approximately parallel and PH may be reasonable for OS.

Figure A1: LUX-Lung 7 log-cumulative hazard plot (PFS-IA)

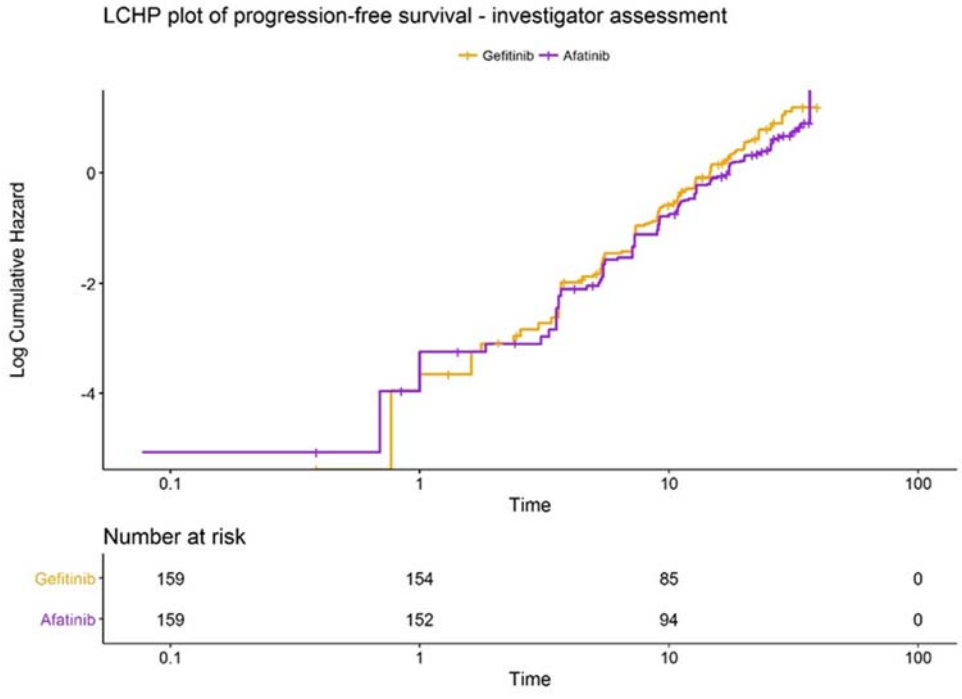

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Figure A2: LUX-Lung 7 log-cumulative hazard plot (PFS-BICR)

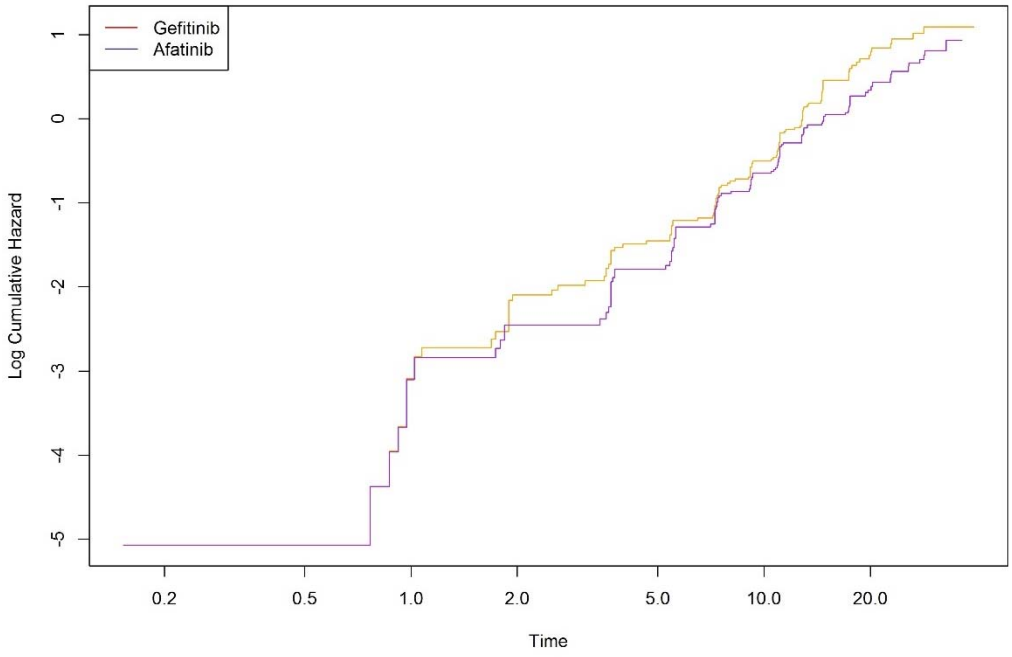
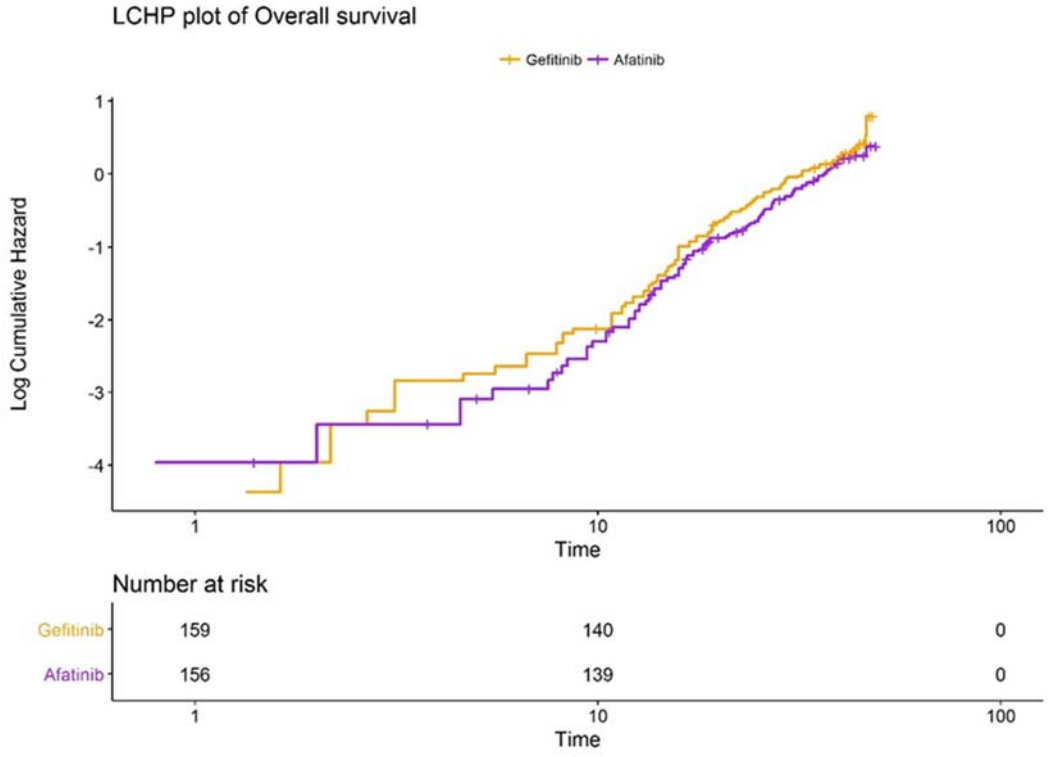


Figure A3: LUX-Lung 7 log-cumulative hazard plot (OS)



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Section B: Clarification on cost-effectiveness data

B1. **Priority request: Kaplan-Meier data.** Please provide the Kaplan-Meier analyses listed in a to f below to the following specifications:

Trial data set:	*FLAURA trial*
Censoring:	*Censor lost to follow-up and withdrawn patients at the date recorded. Patients alive and still at risk of the target event at the date of data cut-off should be censored at the date of data cut-off, i.e. not when last known to be alive*
Format:	*Please present analysis outputs using the format of the sample table shown below this question*
Population:	*ITT population including all patients lost to follow-up or withdrawing from the trial*

a. Time to death from any cause (OS) Kaplan-Meier analysis for patients in the osimertinib arm of the trial

b. Time to death from any cause (OS) Kaplan-Meier analysis for patients in the SoC EGFR-TKI arm of the trial

c. Time to investigator assessed progression or death (PFS) Kaplan-Meier analysis for patients in the osimertinib arm of the trial

d. Time to investigator assessed progression or death (PFS) Kaplan-Meier analysis for patients in the SoC EGFR-TKI arm of the trial

e. Time to study treatment discontinuation Kaplan-Meier analysis for patients in the osimertinib arm of the trial

f. Time to study treatment discontinuation Kaplan-Meier analysis for patients in the SoC EGFR-TKI arm of the trial.

The FLAURA K-M analyses have been performed using the censoring methodology as pre-defined in the SAP and in line with analyses submitted to health authorities and global reimbursement agencies (please see attached file). We have censored at the point last known to be alive (OS), or at the date when the tumour was last assessed (PFS) rather than the date of data cut-off as this approach fairly assumes knowledge to the point until we no longer have it. If there is a time gap between the last known date to be alive and the data cut-off date then censoring at the data cut-off date would assume that we have knowledge of the patient up to this time point and may contribute to influencing the KM estimates. Furthermore, given the pattern of censoring in FLAURA at DCO1, it is likely that the conventional censoring approach could be considered conservative, resulting in K-M analyses in favour of the SoC TKI arm. The use of a later time point (such as DCO) in the

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alternative censoring approach will elevate the osimertinib risk set compared with censoring at the last point known to be alive. The impact on the estimate of the probability of the event at that timepoint will in effect be lower due to the larger number of patients at risk.

Section C: Textual clarifications and additional points

C1. Please clarify whether all the data reported for the CNS metastases subgroups should be marked as academic in confidence when much of the data are available in the European Medicines Agency European Public Assessment Report.

Not all data reported for the CNS metastases subgroups should be marked as confidential. Since the preparation of the CS, some data has been published (DOI: 10.1200/JCO.2018.78.3118 Journal of Clinical Oncology - published online before print August 28, 2018.).

A revised Confidentiality checklist will be provided separately.

C2. Please check all references cited in the company submission are correct. In a number of places, this does not appear to be the case. For example, on page 26, no reference has been inserted to support the claim that "EGFR mutations are more common in Asians than in Western populations, in women than in men, and in never-smokers than in ever-smokers". On page 95, the CTONG-0901 study is cited as reference 18 (and later on in the next paragraph as reference 20, but it's actually reference 112) and a network meta-analysis is cited as reference 19 (it's actually reference 94). In the next paragraph, the ARCHER 1050 study is cited as reference 17 which is incorrect, LUX-Lung 7 as reference 18 (it's reference 22) and the CTONG-0109 study as reference 20. In the reference list, reference 18 is the same as reference 176, and reference 10 is the same as references 63, 72 and 90. Please can the references be updated and corrected where necessary?

The references will be updated and corrected in the CS.

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Single technology appraisal

Osimertinib for untreated EGFR-positive non-small-cell lung cancer

Dear Kevin Lock,

The Evidence Review Group, Liverpool Reviews and Implementation Group (LRIG), and the technical team at NICE have looked at the submission received on 14 September 2018 from AstraZeneca. In general they felt that it is mostly well presented and clear. However, the ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data and references (see questions listed at end of letter).

The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide your written response to the clarification questions by **5pm** on **16th October 2018**. Your response and any supporting documents should be uploaded to NICE Docs.

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

Please underline all confidential information, and separately highlight information that is submitted as commercial in confidence in turquoise, and all information submitted as academic in confidence in yellow.

If you present data that are not already referenced in the main body of your submission and that are academic/commercial in confidence, please complete the attached checklist for confidential information.

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact Christian Griffiths, Technical Adviser (christian.griffiths@nice.org.uk). Any procedural questions should be addressed to Kate Moore, Project Manager (Kate.Moore@nice.org.uk).

Yours sincerely

Jasdeep Hayre
Associate Director – Appraisals
Centre for Health Technology Evaluation

Encl. checklist for confidential information

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Section A: Clarification on effectiveness data

A1. **Priority request.** Please provide the most recent versions of the protocol, statistical analysis plan and clinical study report.

FLAURA trial design and conduct

A2. It is stated that one of the endpoints of the FLAURA trial was progression-free survival (PFS) in the T790M+ patient subgroup at the time of the primary PFS analysis (page 62, company submission [CS]). However, no results for this endpoint are presented. Please clarify:

a. Was any testing of this endpoint performed?

b. If no testing was performed, why not?

A3. Please clarify the sample size calculation (page 63, CS):

a. What is the definition of the minimal critical hazard ratio (HR) and how was this HR calculated?

b. Why was the primary PFS analysis performed at a time when only 342 events had occurred (page 72, CS), when it was specified that the primary analysis would be performed when at least 359 progression events had occurred?

Before analysis can take place a data cut-off (DCO) needs to be declared and a database lock carried out. Multiple processes need to occur before the data is fully clean and ready for analysis. Therefore, the sponsor uses event prediction (on blinded data) to decide when the data cut-off will be declared and this is decided around 6 weeks in advance of the DCO. When event prediction was carried out, it was predicted that approximately 359 progression events would have occurred by 12 June 2017 which was declared as the DCO date. Shortly after the DCO date there had been 342 progression events by investigator assessment per the statistical analysis definition entered into the database. This is within a 5% tolerance limit for the number of events required, which was stated as approximately (and not 'at least') 359 in the protocol.

A4. Please clarify whether the outcome of PFS2 (page 77, CS) was analysed according to investigator assessment or independent review.

A5. For each of the following outcomes presented in the 'Tumour response' section (pages 80-83, CS):

i. Objective response rate (ORR)
ii. Disease control rate (DCR)

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iii. Time to response
iv. Duration of response
v. Median best % change in target lesion size
vi. Percentage who had a reduction of the sum of target lesion size
vii. Proportion of patients with >30%, >50%, and >70% reduction in target lesion size
viii. Difference in lesion size means for target lesion tumour shrinkage

Please clarify:

a. If the full analysis set (FAS) was used.
b. If the FAS was used, how were patients who did not respond, or whose response could not be evaluated, included in the analysis.

c. If the outcome was analysed according to investigator assessment or independent review.

A6. Regarding Cox proportional hazards in the FLAURA trial:

a. Please list all analyses presented in the CS that were performed using a Cox proportional hazards model.

b. Please list all analyses presented in the CS for which the proportional hazards assumption was assessed.

c. Please provide the results of any assessments of the proportional hazards assumption.

A7. Regarding the participant flow in the FLAURA trial, please clarify where the patients who received osimertinib second-line, but not as protocol defined crossover, fit into Figure 17 (page 69, CS).

Central nervous system subgroup in FLAURA trial

A8. **Priority request.** Please clarify what is meant by a target lesion, non-target lesion and new lesion and why these are not mutually exclusive.

A9. **Priority request.** Clinical advice to the ERG is that scans for central nervous system (CNS) metastases are only conducted in clinical practice when a patient is suspected of having CNS metastases. Please clarify how and why only 200 patients received scans for CNS metastases in the FLAURA trial. If only patients suspected by trial investigators as having CNS metastases received scans for CNS metastases, please clarify how it is possible that “32 patients were only part of the CNS full analysis set (cFAS) as they were not considered by the Investigator to have baseline CNS

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metastases" (page 85, CS), i.e. please clarify why these 32 patients were scanned for CNS metastases.

A10. **Priority request.** Please clarify why 87 patients who were scanned for CNS metastases did not have a measurable CNS lesion.

A11. **Priority request.** In relation to patients classified as having CNS in Table 15 (pages 61-62, CS), please clarify exactly how patients were classified as having CNS if not from CNS scans. It is stated in the footnote to the table that: "This is a programmatically derived composite endpoint with a list of contributing data sources." Please clarify what this means.

A12. Based on the classification with and without CNS metastases using the "programmatically derived composite endpoint", please clarify whether patients with CNS metastases in the osimertinib arm had similar baseline characteristics to patients with CNS metastases in the standard of care (SOC) arm. Please also clarify whether patients without CNS metastases in the osimertinib arm had similar baseline characteristics to patients without CNS metastases in the SOC arm.

Please see baseline characteristics of patients with CNS metastases provided (PAY0205 CNS/NoCNS Disease/Demo/Subject). The key baseline characteristics for these subgroups according to CNS metastases are presented in Table 1 below, along with characteristics for the overall FLAURA population (and cFAS and cEFR).

These key baseline characteristics are broadly balanced between the two arms in patients with CNS metastases. Though the relatively small sample size in this subgroup should be noted. This leads to a slight imbalance in percentage of WHO performance status (PS) between arms, with 74% in the osimertinib arm vs. 58% in the SoC arm with PS=1. Also, in disesease stage IV which is 97% vs. 89%. These minor differences are not large enough to suggest a breakdown in the randomisation process or to indicate any issues with the results.

Within patients with no CNS metastases as baseline, again the key baseline characteristics are broadly balanced between the two treatment arms. Here the sample size is larger and there are no differences of potential note.

A13. Please clarify whether baseline characteristics of patients with CNS metastases in the cFAS population were similar to those of patients with CNS metastases in the CNS evaluable for response set (cEFR) population. Please also clarify whether the characteristics in either or both of these populations of patients with CNS metastases were similar to those considered to have CNS metastases using the "programmatically derived composite endpoint".

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Please see baseline characteristics of patients with CNS metastases provided (PAY0205 CNS/NoCNS Disease/Demo/Subject). cFAS and cEFR characteristics are from Table 11.2.18.1.2.1 to 11.2.18.1.2.8 in the CSR.

The key baseline characteristics for the cFAS and cEFR subgroups, along with characteristics for the overall FLAURA population (and the CNS metastases at baseline subgroup) are presented in Table 1 below.

Baseline characteristics are broadly balanced between the 3 populations. The percentage of males is numerically higher in the cEFR population at 41.5% compared to both cFAS (38.5%) and the “programmatically derived composite endpoint” (34.5%) populations. cEFR had a numerically higher percentage of Asians (51.2%) compared to cFAS (60.2%) and “programmatically derived composite endpoint” (61.2%) populations therefore, conversely less whites. WHO status 0 was numerically higher in cFAS (74.1%) compared to cEFR (58.5%) and “programmatically derived composite endpoint” (63.8%) populations. Please note that the sample size is especially small in the cEFR at n=41, with cFAS being n=128 and “programmatically derived composite endpoint” being n=116. These minor differences are not large enough to suggest a breakdown in the randomisation process or to indicate any issues with the results.

A14. Please clarify whether in all 3 populations of patients with CNS metastases (i.e. defined using the “programmatically derived composite endpoint”, cFAS and cEFR), baseline characteristics were similar between the osimertinib and SOC arms?

Please see baseline characteristics of patients with CNS metastases provided (PAY0205 CNS/NoCNS Disease/Demo/Subject). cFAS and cEFR characteristics are from Table 11.2.18.1.2.1 to 11.2.18.1.2.8 in the CSR. In each of the 3 populations of patients with CNS metastases the key baseline characteristics are broadly balanced between the treatment arms. Noting that the numbers are relatively small in these 3 populations particularly in cEFR, gives some slight discrepancies in the percentages between treatment arms. For both cFAS and the “programmatically derived composite endpoint” the percentage of WHO PS 1 patients is numerically higher of in the osimertinib arm and vice versa for WHO PS 0. There are also slight differences in race between the arms in all three populations. These minor differences are not large enough to suggest a breakdown in the randomisation process or to indicate any issues with the results.

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Table 1: Baseline characteristics of patients in CNS metastases subgroups of the FLAURA study

	Overall FLAURA (n=556)		cFAS (n=128)		cEFR (N=41)		Brain Mets at baseline (N=116)		No Brain mets at baseline (N=440)	
	Osimertinib	**SoC**	Osimertinib	SoC	Osimertinib	SoC	Osimertinib	SoC	Osimertinib	SoC
	n=279	**n=277**	n=61	n=67	n=22	n=19	n=53	n=63	n=226	n=214
Sex										
Female	**178 (64%)**	**172 (63%)**	38 (63%)	41 (62%)	14 (64%)	10 (53%)	35 (67%)	41 (66%)	143 (64%)	131 (62%)
Age										
Median (Range)	**64 (26-85)**	**64 (35-93)**	63 (34-83)	63 (39-85)	63.5 (47-80)	62 (39-78)	63 (39-83)	62 (39-85)	64 (26-85)	65 (35-93)
Race										
White	**101 (37%)**	**100 (37%)**	21 (35%)	28 (42%)	12 (55%)	8 (43%)	19 (36%)	25 (40%)	82 (37%)	75 (36%)
Asian	**174 (63%)**	**173 (63%)**	40 (66%)	37 (56%)	10 (46%)	11 (58%)	34 (65%)	37 (59%)	140 (62%)	136 (64%)
Other	**4 (2%)**	**4 (2%)**	0 (0%)	2 (3%)	(0%)	(0%)	0 (0%)	1 (2%)	4 (2%)	3 (2%)
WHO PS										
PS 0	**112 (41%)**	**116 (42%)**	16 (27%)	27 (41%)	5 (23%)	5 (27%)	14 (27%)	27 (43%)	98 (44%)	89 (42%)
PS 1	**167 (60%)**	**160 (58%)**	45 (74%)	39 (59%)	17 (78%)	14 (74%)	39 (74%)	36 (58%)	128 (57%)	124 (58%)
EGFR mutation										
Ex19del	**175 (63%)**	**174 (63%)**	40 (66%)	45 (68%)	12 (55%)	12 (64%)	35 (67%)	39 (62%)	140 (62%)	135 (64%)
L858R	**104 (38%)**	**103 (38%)**	21 (35%)	22 (33%)	10 (46%)	7 (37%)	18 (34%)	24 (39%)	86 (39%)	79 (37%)
Histology										
Adenocarcinoma	**275 (99%)**	**272 (99%)**	61 (100%)	67 (100%)	22 (100%)	19 (100%)	52 (99%)	63 (100%)	223 (99%)	209 (98%)
Baseline CNS										
Yes	**53 (19%)**	**63 (23%)**	NR	NR	NR	NR	53 (100%)	63 (100%)	0 (0%)	0 (0%)
Disease stage										
IV	**226 (82%)**	**230 (84%)**	NR	NR	NR	NR	51 (97%)	56 (89%)	175 (78%)	174 (82%)

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A15. Please provide definitions for the following outcomes:

a. CNS PFS.

b. CNS ORR.

c. CNS DCR.

A16. For question A15, please clarify if each of these outcomes was analysed according to investigator assessment or independent review.

A17. PFS, overall survival (OS), ORR and DCR were analysed in the subgroup of patients with CNS metastases at baseline by investigator assessment (CNS defined using the "programmatically derived composite endpoint"), CNS PFS was analysed in the cFAS subgroup, and CNS ORR, CNS DCR and median time to response was analysed in the cFAS and cEFR subgroups:

a. Please justify the choice of analysis sets for each outcome, and clarify whether all these analyses were pre-specified.

b. Please also clarify why OS was not chosen as an endpoint for either the cFAS or cEFR subgroups.

A18. It is stated that for CNS PFS: "the HR was 0.48 (95% CI: 0.26, 0.86; p-value = 0.014) in the cFAS population, indicating a 52% reduction in the risk of CNS disease progression or death (in the absence of CNS RECIST progression)" (page 87, CS). Please clarify what is meant by "in the absence of CNS RECIST progression."

A19. In Table 25 (page 90, CS), median time to response is presented. Please clarify the following:

a. Does 'median time to response' refer to response of CNS lesions only, or to response of CNS and non-CNS lesions?

b. Was this outcome analysed according to investigator assessment or independent review?

c. How were patients who didn't have a measurable lesion included in the analysis of this outcome in the cFAS population?

A20. In the footnotes to Table 25 (page 90, CS), the percentages of patients with confirmed CNS ORR are presented. What is the definition of confirmed CNS ORR?

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A21. Results are presented for 'percentage change in lesion size' in the subgroup of patients with CNS metastases evaluable for response (page 18, CS):

a. Please define the outcome used for this analysis, specifically stating whether only CNS lesions were included in the analysis, or if both non-CNS and CNS lesions were included in the analysis.

b. Please clarify if this analysis was pre-specified.

Other subgroups in the FLAURA trial

A22. For the Asian vs non-Asian ethnicity subgroup, please clarify whether baseline characteristics of Asians were similar to non-Asians. Please also clarify whether baseline characteristics were similar in the osimertinib and SOC arms in both populations.

Please see the attached tables PAY0283 Asian/NonAsian Disease/Demo/Subject

The key baseline characteristics for these subgroups according to Ethnicity (Asian and Non-Asian) are presented in Table 2, along with characteristics for the overall FLAURA population, and are broadly balanced across treatment arms (except for a small imbalance in the proportion of Non-Asians with PS0 or 1). Between subgroups, it is noticeable that Asian patients were more likely to have a L858R mutation in EGFR.

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Table 2: Baseline characteristics for patients in the Asian/Non-Asian subgroup of FLAURA

		Overall FLAURA (n=556)		Asian (N=347)		Non-Asian (N=209)	
		Osimertinib	**SoC**	Osimertinib	SoC	Osimertinib	SoC
		n=279	**n=277**	n=174	n=173	n=105	n=104
Sex							
	Female	**178 (64%)**	**172 (63%)**	108 (63%)	101 (59%)	70 (67%)	71 (69%)
Age							
	Median (Range)	**64 (26-85)**	**64 (35-93)**	63 (35-93)	64 (35-87)	65 (40-83)	64 (37-93)
Race							
	White	**101 (37%)**	**100 (37%)**	0 (0%)	0 (0%)	101 (97%)	100 (97%)
	Asian	**174 (63%)**	**173 (63%)**	173 (100%)	173 (100%)	1 (1%)	0 (0%)
	Other	**4 (2%)**	**4 (2%)**	1 (1%)	0 (0%)	3 (3%)	4 (4%)
WHO PS							
	PS 0	**112 (41%)**	**116 (42%)**	68 (40%)	67 (39%)	44 (42%)	49 (48%)
	PS 1	**167 (60%)**	**160 (58%)**	106 (61%)	106 (62%)	61 (59%)	54 (52%)
EGFR mutation							
	Ex19del	**175 (63%)**	**174 (63%)**	102 (59%)	102 (59%)	73 (70%)	72 (70%)
	L858R	**104 (38%)**	**103 (38%)**	72 (42%)	71 (42%)	32 (31%)	32 (31%)
Histology							
	Adenocarcinoma	**275 (99%)**	**272 (99%)**	170 (98%)	170 (99%)	105 (100%)	102 (99%)
Baseline CNS							
	Yes	**53 (19%)**	**63 (23%)**	34 (20%)	37 (22%)	19 (19%)	26 (25%)
Disease stage							
	IV	**226 (82%)**	**230 (84%)**	146 (84%)	148 (86%)	80 (77%)	82 (79%)

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A23. It is stated that "the numerical efficacy advantage for non-Asians over Asians was maintained for the analyses of OS, ORR, and DCR" (Table 26, page 91, CS). However, from the odds ratios presented in Table 26, Asian patients experience greater clinical benefit from osimertinib (relative to SoC) in terms of both ORR and DCR in comparison to non-Asian patients. Please clarify, is the interpretation of the results presented in Table 26 incorrect?

A24. For the subgroup analyses by EGFR mutation status, please clarify whether baseline characteristics were similar in the osimertinib and SOC arms in the Exon19del population, and whether baseline characteristics were similar in the osimertinib and SOC arms in the L858R population.

Please see the attached tables PAY0283 L858R/Exon19del Disease/Demo/Subject.

The key baseline characteristics for these subgroups according to EGFR mutation status (L858R and Exon 19 deletion) are presented in Table 3, along with characteristics for the overall FLAURA population, and are broadly balanced across treatment arms. Between subgroups, it is noticeable that patients in the L858R subgroup were more likely to be Asian, and have PS0, than those with Exon 19 deletion, although all differences are small.

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Table 3: Baseline characteristics of patients in the FLAURA study according to EGFR mutation status

		Overall FLAURA (n=556)		L858R subgroup (N=207)		Exon 19 deletion subgroup (N=349)	
		Osimertinib	**SoC**	Osimertinib	SoC EGFR TKIs	Osimertinib	SoC EGFR TKIs
		n=279	**n=277**	n=104	n=103	n=175	n=174
Sex							
	Female	**178 (64%)**	**172 (63%)**	70 (68%)	69 (67%)	108 (62%)	103 (60%)
Age							
	Median (Range)	**64 (26-85)**	**64 (35-93)**	66 (39-85)	66 (35-85)	63 (26-83)	63 (36-93)
Race							
	White	**101 (37%)**	**100 (37%)**	32 (31%)	30 (30%)	69 (40%)	70 (41%)
	Asian	**174 (63%)**	**173 (63%)**	72 (70%)	71 (69%)	102 (59%)	102 (59%)
	Other	**4 (2%)**	**4 (2%)**	0 (0%)	2 (2%)	4 (3%)	2 (2%)
WHO PS							
	PS 0	**112 (41%)**	**116 (42%)**	46 (45%)	46 (45%)	66 (38%)	70 (41%)
	PS 1	**167 (60%)**	**160 (58%)**	58 (56%)	57 (56%)	109 (63%)	103 (60%)
EGFR mutation							
	Ex19del	**175 (63%)**	**174 (63%)**	0 (0%)	0 (0%)	175 (100%)	174 (100%)
	L858R	**104 (38%)**	**103 (38%)**	104 (100%)	103 (100%)	0 (0%)	0 (0%)
Histology							
	Adenocarcinoma	**275 (99%)**	**272 (99%)**	103 (100%)	103 (100%)	172 (99%)	169 (98%)
Baseline CNS							
	Yes	**53 (19%)**	**63 (23%)**	18 (18%)	24 (24%)	35 (20%)	39 (23%)
Disease stage							
	IV	**226 (82%)**	**230 (84%)**	80 (77%)	85 (83%)	146 (84%)	145 (84%)

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City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

Indirect comparison

A25. It is not explicitly stated why the indirect comparison was not performed. Please provide the rationale for this decision.

A26. It is stated that "The two studies appeared to be consistent in terms of age, gender, race, proportion of patients with CNS metastases, proportion of patients who never smoked and the distribution of different EGFR mutations" (Table 8, page 96, CS). However, Table 8 showing baseline characteristics for the trials does not appear to be presented. Please provide this table.

A27. It is stated that 34 studies were identified; should this instead be 37?

Additional analyses

A28. OS data in the FLAURA trial is from patients with World Health Organization (WHO) performance status (PS) 0-1. As noted by the company, real world OS data differs to that reported in trials. In part, this is because real world OS data includes patients with WHO PS ≥2. If available, from the analysis conducted in partnership with the National Cancer Registration and Analysis Service, please provide OS Kaplan-Meier data for Stage 3b/4 NSCLC patients treated with an EGFR-TKI 1L after diagnosis by performance status (i.e. similar to Figure 5 [page 29, CS]). If possible, please present the data by PS 0-1 and PS ≥2.

A29. Please provide the results of any assessments of the proportional hazards assumption for the LUX-Lung 7 trial.

Section B: Clarification on cost-effectiveness data

B1. **Priority request: Kaplan-Meier data.** Please provide the Kaplan-Meier analyses listed in a to f below to the following specifications:

Trial data set:	*FLAURA trial*
Censoring:	*Censor lost to follow-up and withdrawn patients at the date recorded. Patients alive and still at risk of the target event at the date of data cut-off should be censored at the date of data cut-off, i.e. not when last known to be alive*
Format:	*Please present analysis outputs using the format of the sample table shown below this question*

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Population: *ITT population including all patients lost to follow-up or withdrawing from the trial*

a. Time to death from any cause (OS) Kaplan-Meier analysis for patients in the osimertinib arm of the trial

b. Time to death from any cause (OS) Kaplan-Meier analysis for patients in the SoC EGFR-TKI arm of the trial

c. Time to investigator assessed progression or death (PFS) Kaplan-Meier analysis for patients in the osimertinib arm of the trial

d. Time to investigator assessed progression or death (PFS) Kaplan-Meier analysis for patients in the SoC EGFR-TKI arm of the trial

e. Time to study treatment discontinuation Kaplan-Meier analysis for patients in the osimertinib arm of the trial

f. Time to study treatment discontinuation Kaplan-Meier analysis for patients in the SoC EGFR-TKI arm of the trial.

Section C: Textual clarifications and additional points

C1. Please clarify whether all the data reported for the CNS metastases subgroups should be marked as academic in confidence when much of the data are available in the European Medicines Agency European Public Assessment Report.

C2. Please check all references cited in the company submission are correct. In a number of places, this does not appear to be the case. For example, on page 26, no reference has been inserted to support the claim that "EGFR mutations are more common in Asians than in Western populations, in women than in men, and in never-smokers than in ever-smokers". On page 95, the CTONG-0901 study is cited as reference 18 (and later on in the next paragraph as reference 20, but it's actually reference 112) and a network meta-analysis is cited as reference 19 (it's actually reference 94). In the next paragraph, the ARCHER 1050 study is cited as reference 17 which is incorrect, LUX-Lung 7 as reference 18 (it's reference 22) and the CTONG-0109 study as reference 20. In the reference list, reference 18 is the same as reference 176, and reference 10 is the same as references 63, 72 and 90. Please can the references be updated and corrected where necessary?

Submission from Roy Castle Lung Cancer Foundation, for consideration by NICE, in their review of Osimertinib for untreated EGFR-positive non-small cell lung cancer [ID1302]

Submitting Organisation

Roy Castle Lung Cancer Foundation is a UK wide lung cancer charity. We fund lung cancer research, tobacco control initiatives and work in lung cancer patient care (information, support and advocacy activity).

The Foundation has contact with patients/carers through its UK wide network of over 50 monthly Lung Cancer Patient Support Groups, online Forums and its Lung Cancer Information Helpline.

Clearly, our patient group members and contacts are a self-selected group, who have taken the step to seek out information or have accessed specialist support services. As most lung cancer sufferers tend to be older, from lower social class groups and with the five year survival being around 10%, less physically well, we acknowledge that our patients are perhaps not representative of the vast majority of lung cancer patients, who are not so well informed. It is, however, important that the opinions expressed to us, be passed on to NICE, as it considers the place of this product in the management of non small cell lung cancer (nsclc).

General Points

1. For patients with advanced or metastatic nsclc, cure is not a treatment option. In this scenario, improving quality of life, symptom management and even small extensions in duration of life are of considerable significance to the individual and their family.

2. The relatively recent addition of targeted therapies and immunotherapy, in the treatment of nsclc, has ensured active therapy options for many with nsclc. However, overall outcomes for many of this patient population remains poor. The availability of new targets and therapy choices being of key future importance.

3. The importance of 'end of life' therapies. When considering the cost of treatment, it is not appropriate, for example, to give the same weighting to the final six months of life, as to all other six months of life. It is important for this to be part of any numeric equation, which is looking at cost and quality of life. This point is of crucial importance to patients and relatives in this situation

4. Improvement in symptoms. Patients with advanced or metastatic non small cell lung cancer are often debilitated with multiple and distressing symptoms. Symptoms such as breathlessness are very difficult to manage clinically. Therapies with anti-tumour activity often provide the best option for symptom relief.

This Product

1. Very targeted population.
   In US and European lung cancer populations, 10% to 15% have EGFR mutated nsclc. These patients are sensitive to currently available EGFR-TKIs (Gefitinib, Erlotinib and Afatinib). Tumours, however, develop resistance to EGFR-TKIs, leading to disease progression. T790M is a point mutation in the EGFR gene, we understand that it is associated with resistance in around half of such patients.
   Osimertinib is an inhibitor of both EGFR-sensitising and EGFR T790M resisitance mutations. This therapy therefore represents a targeted treatment option, providing benefit to a clearly defined small segment of patients with nsclc.

2. Well tolerated
   Osimertinib is an oral therapy – ease of administration.

   Side effect profile
   Osimertinib has been available through the Cancer Drugs Fund for patients with EGFR T790M mutations. As such, experience in use and side effect management is now commonplace. Common side effects include diarrhea, rash, dry skin and nail toxicity. More rarely, serious adverse events noted - interstitial lung disease (2.7%) and cardiac toxicity. In the anecdotal experience reported to us, it appears to be well tolerated.

3. Outcome of Treatment
   We do not have any information or trial data for this therapy, beyond that which is published and publicly available.

   However, we note the outcomes of the Phase III FLAURA trial, in which Osimertinib improved PFS compared to Erlotinib or Gefitinib in previously untreated patients with locally advanced or metastatic EGFR mutated nsclc. Median PFS was 18.9 months for Osimertinib, compared with 10.2 months for the EGFR-TKI comparator arm. In particular, we note that the PFS benefit for patients with and without brain metastasis was almost identical, suggesting the Osimertinib is active in the brain as well as systemic sites. Brain metastasis are often seen in EGFR mutated patients – we understand around 25% of such patients, increasing to around 40% at 2 years.

Our observations come from a combination of one-to-one discussion with lung cancer patients, published research, on line patient contact and our patient information helpline.

In summary

Patients with advanced and metastatic lung cancer are in a particularly devastating situation. Despite recent advances in defining and treating EGFR mutated lung cancer, there is a need for new therapy options and optimising the use of existing ones. Osimertinib availability in untreated patients provides a new such option.

[redacted] **RCLCF.**

March 2018.

NICE National Institute for Health and Care Excellence

Professional organisation submission

Osimertinib for untreated EGFR-positive non-small-cell lung cancer [ID1302]

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.

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- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**British Thoracic Oncology Group (BTOG)**

3. Job title or position	[redacted]
4. Are you (please tick all that apply):	✓ 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 British Thoracic Oncology Group (BTOG) is the multi-disciplinary group for healthcare professionals involved with thoracic malignancies throughout the UK and Ireland. The vision of BTOG is to ensure equitable access to optimal care for patients with all thoracic malignancies in the UK and Ireland. The mission of BTOG is to support and educate healthcare professionals, creating a professional community to exchange ideas, information and innovation and to foster the development of research, The overall aim is to represent the needs of patients and improve their outcomes. BTOG does not receive any funding from the NHS but is supported through sponsorship and education grants from industry and registration fees.
5b. 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	Palliative treatment: improve symptoms, improve quality of life, prolong survival.

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.)	1. 20%+ reduction in the size of a measurable lesion. 2. Statistically significant improvement in validated symptom score or quality of life index, compared to baseline (pre-treatment).
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes. 1. Therapy with a longer duration of action than the currently available treatments (median progression free survival of which are 9-14 months, depending on the agent). 2. Therapy with less cutaneous toxicity, especially nail changes and paronychia. 3. Therapy with greater efficacy against brain metastases.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	Current licensed, NICE approved agents for first line treatment of stage IIIB/IV EGFR-mutated lung cancer are 1st generation (gefitinib, erlotinib) and 2nd generation (afatinib) EGFR tyrosine kinase inhibitors (EGFR TKIs).

• Are any clinical guidelines used in the treatment of the condition, and if so, which?	**1. NICE guidelines:** Lung cancer: diagnosis and management [CG121] **2. NICE Technology Appraisals:** Afatinib for treating epidermal growth factor receptor mutation-positive locally advanced or metastatic non-small-cell lung cancer [TA310] Erlotinib for the first-line treatment of locally advanced or metastatic EGFR-TK mutation-positive non-small-cell lung cancer [TA258] Gefitinib for the first-line treatment of locally advanced or metastatic non-small-cell lung cancer [TA192] Osimertinib for treating locally advanced or metastatic EGFR T790M mutation-positive non-small-cell lung cancer [TA416] **3. ESMO guidelines:** Metastatic non-small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up: Annals of Oncology 27 (Supplement 5): v1–v27, 2016
• 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.)	It is universally accepted that first line EGFR TKIs are superior to chemotherapy for EGFR-mutated NSCLC. Standard of care, for patients in whom the EGFR result is available in an acceptable time period, is therefore first line EGFR TKI. The choice of EGFR TKI varies from clinician to clinician and hospital to hospital. It is generally felt that geftinib, erlotinib and afatinib increase (in that order) in efficacy as well as toxicity. Consequently Afatinib may be reserved for the patients with a better performance status, and avoided in older patients and those with a poorer performance status.

• What impact would the technology have on the current pathway of care?	If approved by NICE, I would expect the great majority of patients with common EGFR mutations (exon 19 deletions, L858R mutations) to be treated with Osimertinib instead of 1st or 2nd generation EGFR TKIs.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes. No practical changes in nature or frequency of clinic visits or scans. Osimertinib is already recommended by NICE for the second-line treatment of T790M +ve EGFFR mutated lung cancer [TA416]
• How does healthcare resource use differ between the technology and current care?	No difference in resource use between current treatment and new technology in terms of frequency of clinic visits or scans. For Osimertinib: no need for repeat biopsies after disease progression (see question 13). Less input needed for management of cutaneous side effects, including medications (topical therapies and oral antibiotics), and fewer referrals for specialist dermatology review for cases of severe rash.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care oncology units only.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	None.

11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes. Osimertinib has greater efficacy and fewer side effects than the first generation EGFR TKIs. Osimertinib was designed to have activity against the common resistance mutation (T790M) that develops in the majority of patients treated with 1st and 2nd generation EGFR TKI, thereby having greater clinical activity. Meanwhile it has minimal against non-mutated EGFR receptors, responsible for many of the side effects of EGFR inhibitors, which leads to its superior toxicity profile. The FLAURA study (Soria et al., New Eng J Med 2018; 378:113-125) is a large, multi-centre, randomised, phase 3 double-blind study compared Osimertinib with Gefitinib or Elrotinib in treatment naïve, advanced stage, EGFR mutated NSCLC. FLAURA provides robust clinical data to support the superiority of Osimertinib over standard EGFR TKIs.
• Do you expect the technology to increase length of life more than current care?	Yes. The FLAURA study shows a marked increase in median Progression Free Survival (PFS), 18.9 vs. 10.2 months (Hazard Ration, HR = 0.46, p<0.001) and an increased duration of response (17.2 vs. 8.5 months). Survival data was immature at the time of publication of the FLAURA trial in January 2018, and the median overall survival could not be calculated. However, treatment with Osimertinib resulted in higher survival at 12 months (89% vs. 82%) and 18 months (83% vs. 71%) compared to standard EGFR TKI. This, despite the fact that 40% of patients who received standard EGFR TKI 'crossed over' to Osimertinib at disease progression..
• Do you expect the technology to increase health-related quality of life more than current care?	Patient reported outcomes from FLAURA (Leighl et al., J Thor Onc 2018, 13(4), S81-2) show improvement in key symptoms in both study arms with no significant differences between osimertinib and standard EGFR TKI. QLQ-C30 functional and global health/quality of life scores improved from baseline in both arms, again with no clinically relevant differences. Osimertinib is associated with fewer severe (grade 3+) adverse events (34% vs. 45%) than standard EGFR TKIs in FLAURA. Furthermore, Osimertinib has superior PFS in patients with CNS metastases and has a neuroprotective effect (fewer patients on Osimertinib developed CNS progression during therapy). Treatment side effects and the consequence of brain metastases are, in my clinical experience, amongst the greatest causes of reduced quality of life. As such I would expect patient in real-world practice to have a better quality of life on Osimertinib compared to those on standard EGFR TKIs.

12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	In the first line setting, Osimertinib is only appropriate for patients with treatment naïve, locally advanced or metastatic non-small cell lung cancer with proven EGFR mutations (exon 19 deletion or L858R mutations). Patients with rare EGFR mutations (non-exon 19 deletion and non-L858R) were not included in FLAURA, and so it is not possible to assess the effect of Osimertinib on this patient group. The CNS activity of Osimertinib would make it especially beneficial for patients with known CNS metastases, but in my opinion it should not be reserved for this patient group because the benefits of Osimertinib are present across all sub-groups.
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.)	No additional investigations required before initiating therapy, and no change to frequency of clinic visits or re-staging investigations. EGFR testing at diagnosis is already standard of care. No changes in concomitant therapies. Osimertinib is an easier drug to use than 1st and 2nd generation EGFR TKIs due to its improved side effect profile, in particular cutaneous toxicities. There are fewer requirements for medications to treat cutaneous side effects, and for specialist dermatology input. Currently all patients whose disease progresses on 1st or 2nd generation EGFR TKIs require analysis for the EGFR T790M resistance mutation in order to assess whether second-line Osimertinib is an appropriate therapy [see TA416]. This is done by peripheral blood ctDNA and/or biopsy of an area of disease progression, which are associated with costs of the procedures and a recognised complication rate (when invasive biopsy is required). In contrast, patients receiving first-line Osimertinib do not routinely require any of these procedures. In FLAURA, only 43% of patients who received standard EGFR TKI went on to have 2nd line Osimertinib (cross-over). T790M mutations occur in approximately 60% of patients who progress on 1st and 2nd generation EGFR TKIs. The fact that one-third of these did not get Osimertinib on the trial is testament to the challenges in obtaining repeat biopsy samples on patients with relapsed EGFR-mutated lung cancer, even in the highly selected clinical trial population.

14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Treatment with Osimertinib will continue until there is clinical and/or radiological evidence of disease progression. This is no different to the situation with 1st and 2nd generation EGFR TKIs. No additional testing with Osimertinib is required, in contrast to that with 1st and 2nd generation EGFR TKIs (see question 13).
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	No.
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it	Yes. Osimertinib is designed to overcome resistance to 1st and 2nd generation EGFR TKIs, and to minimise the adverse events. In addition, the pre-clinical and clinical evidence of greater CNS penetration, superior clinical activity against brain metastases, and neuroprotective effect against development of new CNS metastases, combine the make this an innovative treatment. The markedly greater clinical activity compared to current EGFR TKIs, is likely to result in a greater chance of disease control, greater duration of disease control, improved overall survival, and fewer adverse events.

improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	In the absence of a definition of what a 'step-change' means, it is difficult to say. However Osimertinib shows marked clinical superiority over 1st line EGFR TKIs, with fewer side effects. This is a rare combination.
• Does the use of the technology address any particular unmet need of the patient population?	1. Prevention of CNS progression of disease. 2. Effective treatment of existing CNS metastases.
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?	Osimertinib is associated with fewer severe (grade 3+) adverse events (34% vs. 45%) than standard EGFR TKIs in FLAURA, and less rash (the commonest side effect of EGFR TKIs). Cardiac side effects were reported in a higher percentage in the Osimertinib arm, although the majority were low grade (1-2) and there were no arrhythmia-associated fatalities. See Question 11 for comments on Quality of Life.
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes, but: 1. FLAURA only included those with Performance Status (PS) 0-1. In reality patients with PS 0-2, and usually those PS=3, would be treated with an EGFR TKI given their impressive efficacy. 2. Afatinib is standard of care 1st line EGFR TKI for a number of centres in the UK. Afatinib was not included in FLAURA.

• If not, how could the results be extrapolated to the UK setting?	I would expect the benefits in PS=2 patients to largely be the same as those seen in FLAURA. Those with PS=3 are likely to have a poorer prognosis in general, but the superiority of Osimertinib is likely to be maintained. Afatinib appears, in a randomised phase 2b study, to have greater efficacy than gefitinib (LUX-Lung7). The benefit of Osimertinib over the 1st generation EGFR TKIs seen in FLAURA is greater than the benefit of Afatinib over gefitinib seen in LUX-Lung7. It is likely that Osimertinib would have shown greater efficacy than afatinib, had this been included in FLAURA.
• What, in your view, are the most important outcomes, and were they measured in the trials?	Overall survival: yes, although overall survival data immature at present. Progression free survival: yes. Quality of life: yes.
• 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?	No.
19. Are you aware of any relevant evidence that might	No.

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 TA310, TA258, TA192 and TA416?	Afatinib [TA310] and Gefitinib [TA192]: Afatinib versus gefitinib as first-line treatment of patients with *EGFR* mutation-positive non-small-cell lung cancer (LUX-Lung 7): a phase 2B, open-label, randomised controlled trial. Part et al., Lancet Oncology 2016, 17(5), 577-589
21. How do data on real-world experience compare with the trial data?	The efficacy of Osimertinib fits with my real-world experience, as does the superior side effect profile. My patients receiving Osimertinib report a better quality of life compared to those on 1st and 2nd generation EGFR TKIs, largely due to fewer mucocutaneous side effects.
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No

22b. Consider whether these issues are different from issues with current care and why.	N/A

Key messages

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

- Osimertinib has greater efficacy than standard EGFR TKIs: survival data is immature, but there is improved 12 and 18 month survival
- Osimertinib has fewer grade 3-4 side effects, and less rash, than 1st generation EGFR TKIs
- Osimertinib has greater activity against CNS metastases than 1st generation EGFR TKIs, including a neuroprotective effect
- First-line Osimertinib removes the need for biopsy and molecular analysis after disease progression
- A significant proportion of patients who progress on 1st generation EGFR TKIs are too unwell to undergo biopsy and/or receive second-line Osimertinib

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

NICE National Institute for Health and Care Excellence

Professional organisation submission

Osimertinib for untreated EGFR-positive non-small-cell lung cancer [ID1302]

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.

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- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**British Thoracic Society**

3. Job title or position	[redacted]
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 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 British Thoracic Society (BTS) is the professional society for respiratory medicine and related health care professions. The Society exists to improve standards of care for people who have respiratory diseases and to support and develop those who provide that care. It is a registered charity and a company limited by guarantee.
5b. 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?	The British Thoracic Society supports this appraisal. There is an urgent need more treatment options for patients with advanced lung cancer given the very poor prognosis.
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.)	
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 TA310, TA258, TA192 and TA416?	
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.	
Key messages	

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

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NICE National Institute for Health and Care Excellence

Patient organisation submission

Osimertinib for untreated EGFR-positive non-small-cell lung cancer [ID1302]

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- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	NLCFN
3. Job title or position	Macmillan Lung Cancer Nurse Specialist
4a. Brief description of the organisation (including who funds it). How many members does it have?	It is a proactive national forum made up of Specialist Lung Cancer and Mesothelioma Nurses. We have approximately 250 members. It is funded via income from educational events and sponsorship from pharmaceutical and law firms.
4b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	NO
5. How did you gather information about the experiences of patients and carers to include in your submission?	Patients and carers frequently feedback (formal and informal routes) experiences of treatments to lung cancer specialist staff. We as a forum share such information. I regularly attend oncology clinics; so speak to patients about their experience of treatments and assess side effects and effectiveness of oncological treatments.

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?	Lung Cancer is a distressing condition to live with. Patients frequently have numerous complex symptoms. Many have other co-morbidities which impact on performance status and quality of life. Any treatment which can improve side effects and quality of life is a bonus. Carers often feel helpless.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	They are always looking for new treatments which will improve symptoms, improve survival without having a negative impact on their quality of life. There is an acknowledgement of hope; as new treatments for lung cancer are evolving.
8. Is there an unmet need for patients with this condition?	Definitely.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	Patients and carers always welcome the development of treatments There is an acknowledgement of hope; as new treatments for lung cancer are evolving.

Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	
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.	Adenocarcinoma with EGFR mutation – at present used 2nd line only when T790M mutation proven More people would be eligible if available 1st line.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	**Not to my knowlegde**

Other issues	
13. Are there any other issues that you would like the committee to consider?	Treatments for lung cancer remain very limited; it is refreshing to see these new technologies being considered. Osimertinib does improve quality of life and survival for certain sub groups of EGFR positive non-small cell lung cancer patients

Key messages

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

- This drug group appears is well tolerated and appears to improve symptoms for this sub group of patients
- Minimal side effects that for most patients; does not have negative impact on quality of life.
- Drug does appear to have survival benefit
- When symptoms improve often associated with improved quality of life; don't underestimate what this means to patients and their carers
- Always consider new treatments that have potential to improve survival for lung cancer patients

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

NICE National Institute for Health and Care Excellence

Professional organisation submission

Osimertinib for untreated EGFR-positive non-small-cell lung cancer [ID1302]

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.

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- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**Submitting on behalf of NCRI-ACP-RCP-RCR**

3. Job title or position	**RCP registrar**
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 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).	
5b. 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,	Palliative. To improve symptoms, to delay disease progression and to extend life.

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.)	Treatment outcomes at least non-inferior to other first-line oral targeted agents (gefitinib, erlotinib or afatinib) currently offered to this patient population. The treatment outcomes achieved with sequential therapy (other currently approved first-line oral targeted agents followed by second-line osimertinib in patients that develop the EGFR T790M resistance mutation) should also be considered.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes, disease progression on first-line therapy is inevitable and there is an unmet need for improved treatments for patients.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	Patients diagnosed with untreated locally advanced or metastatic EGFR mutation positive NSCLC are currently offered an oral targeted therapy (gefitinib, erlotinib or afatinib (TA192, TA258 and TA310 respectively)). On evidence of disease progression, patients are tested for the presence of the EGFR T790M mutation (re-biopsy or circulating tumour DNA). If positive (approximately 50% of patients), patients are then offered osimertinib (TA416) or otherwise treated with platinum-based chemotherapy.

• Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE Lung Cancer clinical guidelines CG121 (https://pathways.nice.org.uk/pathways/lung-cancer) Relevant NICE Technology Assessments on first-line therapy for this patient population: TA192, TA258 and TA310 Relevant NICE Technology Assessments on second-line therapy: TA416
• 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.)	The pathway of care is well defined.
• What impact would the technology have on the current pathway of care?	The technology would increase the number of oral targeted agents available to eligible patients (EGFR mutation advanced NSCLC) at first-line. The use of first-line osimertinib would remove the current need for re-biopsy at disease progression (currently used to access second-line osimertinib).
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	The technology would be used in the same way as other currently approved oral targeted agents.

• How does healthcare resource use differ between the technology and current care?	The use of first-line osimertinib would remove the need for re-biopsy on disease progression to investigate for the presence of the EGFR T790M mutation, which is a gateway to accessing second-line osimertinib.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care within lung cancer clinics.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	None.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes.
• Do you expect the technology to increase length of life more than current care?	The FLAURA study reported significantly improved progression free survival and suggested improved overall survival, although survival data is currently immature.

• Do you expect the technology to increase health-related quality of life more than current care?	The FLAURA study reported a similar safety profile compared to gefitinib or erlotinib. Osimertinib was associated with a lower rate of adverse events ≥ grade 3. However, quality of life measures were not reported.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	As with other EGFR targeted agents, the use of osimertinib would be restricted to patients with EGFR mutation positive advanced NSCLC. The presence of CNS metastases is associated with a poor prognosis. The FLAURA study reported improved progression free survival in patients with known or treated CNS metastases at trial entry treated with osimertinib compared to gefitinib or erlotinib (15.2mths vs 9.6mths), and osimertinib may therefore be particularly attractive as a first-line treatment option in these patients.
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	Similar to current care.

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?	Tumour EGFR mutation testing as already current standard practice for initiating first-line treatment with other TKIs in this patient population. The use of first-line osimertinib would reduce the need for re-biopsy on evidence of disease progression.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	No.
16. Do you consider the technology to be innovative in its potential to make a	Yes - the published results of the FLAURA trial compared first-line osimertinib to first-line gefitinib or erlotinib in EGFR mutated advanced NSCLC. The study reported similar response rates (80% vs 76%), improved progression free survival (18.9mths vs 10.2mths), and suggested improved overall survival

significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	(survival rate at 18mths 83% vs 71%), although survival data remains immature. Osimertinib had a similar safety profile to gefitinib and erlotinib, with fewer adverse events ≥ grade 3 (34% vs 45%). However, quality of life measures were not reported.
• Is the technology a 'step-change' in the management of the condition?	As a third generation EGFR TKI, first-line osimertinib represents an evolution of existing management rather than a 'step-change'.
• Does the use of the technology address any particular unmet need of the patient population?	Yes – the FLAURA study reported significantly improved progression free survival and suggested improved overall survival. Furthermore, compared to gefitinib or erlotinib, sub-group analysis reported that osimertinib improved progression free survival in patients with known or treated CNS metastases at trial entry (15.2mths vs 9.6mths), and lower rates of CNS progression in patients treated with osimertinib (6% vs 15%).
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?	The FLAURA study reported osimertinib had a similar safety profile to gefitinib and erlotinib, with fewer adverse events ≥ grade 3 in patients treated with first-line osimertinib (34% vs 45%), fewer serious adverse events (22% vs 25%), and lower rate of adverse events leading to permanent discontinuation of treatment (13% vs 18%). Fatal adverse events were reported in 2% and 4% of patients.

	Quality of life measures were not reported.
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes. (FLAURA study: NEJM 2018; 378:113-25)
• 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?	FLAURA study: RR, PFS, OS, safety profile – Yes; of note, the OS data is currently immature. PFS in patients treated with first-line gefitinib or erlotinib that crossed over to receive second-line osimertinib was not reported. Quality of life measures were not reported.
• 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?	No.
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No.
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA310, TA258, TA192 and TA416?	No.
21. How do data on real-world experience compare with the trial data?	No published real-world experience of first-line osimertinib for direct comparison, but the trial data is expected to translate reasonably well to clinical practice.
Equality	

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No.
22b. Consider whether these issues are different from issues with current care and why.	

Key messages

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

- The FLAURA study survival data is currently immature and quality of life measures were not reported.
- No change to the care pathway is required to include osimertinib as a first-line treatment option for these patients.
- The use of first-line osimertinib would reduce the need for re-biopsy on disease progression.
- Osimertinib should be available to patients with EGFR mutation positive advanced NSCLC alongside gefitinib, erlotinib and afatinib.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

NICE National Institute for Health and Care Excellence

Clinical expert statement

[ID1302] - Osimertinib for untreated EGFR-positive non-small-cell lung cancer

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

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- Your response should not be longer than 13 pages.

About you	
1. Your name	**Alastair Greystoke**
2. Name of organisation	**Newcastle University**

3. Job title or position	**Senior Lecturer**
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 this condition? ☒ a specialist in the clinical evidence base for this condition 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 nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes

The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Palliate symptoms, shrink tumours and prevent progression as long as possible.
8. 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.)	An improvement in Progression free survival of more than 3 months, an improvement in radiological response rates by 10 % or a reduction in the development of central nervous metastases by 5%.
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes. The 1st and 2nd generation EGFR inhibitors (gefitinib, erlotinib and afatinib) can control the cancer but progression occurs on average within 12 months and then patients and clinicians need effective, well tolerated therapies. Whilst osimertinib is available in the 2nd line setting for some patients this is only in those where it can be demonstrated that they have become resistant to the 1st therapy through acquisition of a second mutation in EGFR (called T790M). Theoretically this is 50% of patients, but in practice it can be difficult to assess due to problems re-biopsying the resistant area of

	tumour. This causes practical problems for both patients and healthcare professional and can lead to morbidity from the procedure, with patients potentially missing out on the benefit from osimertinib. In addition central nervous system metastases are a frequent problem in EGFR mutated lung cancer, both at 1st presentation and later in the disease. Osimertinib is known to have good brain penetration and activity in both brain and leptomeningeal metastases. In addition FLAURA demonstrated a reduction in the development of de novo CNS disease with osimertinib over the 1st generation EGFR inhibitors.
What is the expected place of the technology in current practice?	
10. How is the condition currently treated in the NHS?	With 1st/ 2nd EGFR inhibitors as 1st line treatment. In patients who progress on these a repeat biopsy is taken. If this shows the cancer has become resistant due to a 2nd mutation in EGFR (T790M) the patient will change therapy to osimertinib. In the absence of a biopsy or the demonstration of T790M on the biopsy the options are to continue the 1st line therapy beyond progression or switch to platinum doublet chemotherapy. In practice many patients are reluctant to change to chemotherapy in this setting and will continue their initial therapy.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Yes. ESMO clinical guidelines as to management of metastatic lung cancer Planchard et al. ESMO NSCLC Guidelines 2018 Ann Oncol (2018) 29 (suppl 4): iv192–iv237. NICE technology appraisals TA192, TA258, TA310,TA416 NICE guideline CG121 (being updated)
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Yes. It is recommended that all patients with lung cancer with a sensitising mutation in EGFR receive a 1st and 2nd generation EGFR inhibitors (gefitinib, erlotinib and afatinib) as 1st line of therapy. There is variation across the country and between clinicians as to which of these are used as preferred therapy.

• What impact would the technology have on the current pathway of care?	Osimertinib would replace treatment with the 1st and 2nd generation EGFR inhibitors as the 1st line treatment option for patients with lung cancer with a sensitising mutation in EGFR.
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes. Osimertinib would be given as an oral therapy in oncology clinics to patients at 1st presentation with local advanced or metastatic lung cancer with a sensitising EGFR mutation
• How does healthcare resource use differ between the technology and current care?	Similar, except if osimertinib came int the 1st line setting it would reduce or remove the requirement to rebiopsy on progression.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist oncology clinics.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	None. Osimertinib already used in 2nd line setting and health care professionals well versed in its usage.
12. Do you expect the technology to provide clinically	Yes osimertinib was associated with significantly longer disease control than with the 1st/2nd generation EGFR inhibitors (median increase in PFS from 10.2 to 18.9 months), with improved CNS response in

meaningful benefits compared with current care?	patients with brain metastases, and in delay in the development of brain metastases in those patients without brain metastases at baseline.
• Do you expect the technology to increase length of life more than current care?	Yes. The survival curves appear to be separating despite the cross-over within the study to osimertinib in the standard of care arm. More maturity is needed to determine the exact survival benefit.
• Do you expect the technology to increase health-related quality of life more than current care?	Yes. Osimertinib is associated with longer disease control. In lung cancer the main driver of health related quality of life is cancer symptoms. These will be reduced with osimertinib treatment. In addition osimertinib is better tolerated than some of the agents used in standard care with less skin toxicity and diarrhoea. Whilst these toxicities are often relatively low grade, the chronic nature can often have a major impact on health related quality of life.
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare	It is likely that this will be easier to use than current care. 1) Osimertinib rarely requires dose adjustment; this compares in particular to afaftinib where approximately 50% of patients may require a dose adjustment. 2) There is no food effect and so can be taken with or without food; this compares to erlotinib and afatinib

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.)	that need to be taken in a fasted state. This can have a major impact on the patient particularly if they have other health problems such as diabetes. 3) As discussed above present care requires a repeat biopsy on progression on 1st line therapy; this causes practical issues for both patient and healthcare professionals particularly as access to interventions can be limited in the NHS.
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	No additional testing will be required; EGFR testing at 1st diagnosis is already well embedded in the NHS. Patients will be monitored as previously with oncologist/ specialist nurse review to ensure clinical benefit and tolerability with regular CT scans to document formal response to treatment as with present care.
16. 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	Delay in central nervous system metastases results in significant improvement in health and may not be accurately captured by quality of life data within the study.

quality-adjusted life year (QALY) calculation?	
17. 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?	Yes. This is the 1st time we have seen disease control with an EGFR inhibitor of more than 1 year. This a more effective and well tolerated regimen.
• Does the use of the technology address any particular unmet need of the patient population?	No

18. 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 of osimertinib is that it is well tolerated with minimum need for dose-reductions or discontinuations. It does not require any major change in management. In particular skin toxicity and diarrhoea are les frequent and easier to manage than some of the agents presently used.
Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	Yes. In the standard of care arm patients were treated with either gefitinib or erlotinib and on disease progression if confirmed to have become resistant due to the development of T790M could cross-over to osimertinib. This reflects our current pathways. The only difference would be that in the UK we also use afatinib as one of the 1st lien treatment options. This was not allowed in FLAURA. Afatinib is associated with improved progression free survival compared to gefitinib but not overall survival.
• If not, how could the results be extrapolated to the UK setting?	No major differences.
• What, in your view, are the most important outcomes, and were they measured in the trials?	Overall survival Progression Free Survival Health Related quality of life

	Toxicity Response in known brain metastases and time to develop brain metastases if not present at baseline All were assessed within the FLAURA study.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Not clear how accurately progression free survival predicts overall survival in this setting but overall survival was collected within study.
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No

21. How do data on real-world experience compare with the trial data?	We do have real world data onto the 1st line use of osimertinib. In general real world data as to 2nd line use has matched the experience in clinical trials such as AURA 3. Real world experience with the 1st and 2nd generation EGFR inhibitors (gefitinib, erlotinib and afatinib) matches that reported in clinical trials such as LUX-Lung 7 and Optimal.
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	None
22b. Consider whether these issues are different from issues with current care and why.	N/A
Key messages	

23. In up to 5 bullet points, please summarise the key messages of your statement.

- 1st line Osimertinib has improved outcomes compared to present therapy with 1st/2nd generation EGFR inhibitors
- Introduction into the 1st line setting would reduce/ remove the need to repeat a biopsy on progression of 1st line therapy with impact on quality of life and resource use
- Osimertinib is well tolerated with minimal dose reductions/ discontinuations due to toxicity.
- Osimertinib is active in the brain and can delay the development of CNS disease
-

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.

NICE National Institute for Health and Care Excellence

Clinical expert statement

[ID1302] - Osimertinib for untreated EGFR-positive non-small-cell lung cancer

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About you

NICE National Institute for Health and Care Excellence

1. Your name	**Yvonne Summers**
2. Name of organisation	**The Christie NHS Foundation Trust**
3. Job title or position	**Consultant Medical Oncologist and Honorary Senior Lecturer**
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 this condition a specialist in the clinical evidence base for this condition or technology
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	Nominated by the sponsor, rather than RCP/NIHR/RCR/BTOG

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.)	N/A
The aim of treatment for this condition	
7. 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 aims of osimertinib are: - To prevent/delay progression of the cancer - To cause the tumour to shrink (respond) - To help symptoms and improve quality of life - To improve survival

8. 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.)	A significant response is one which improves progression free survival (PFS) by a clinically meaningful period of time (3 months or more). This response needs to be put into the context of how tolerable the treatment is, eg 3 months extra life may be less valuable if the treatment is very toxic and impairs quality of life. Radiological response is assessed by RECIST criteria in oncology trials which means that absolute measurements are not taken into account. Response is a shrinkage of >30% of target lesions measured, progression is growth by 20% or more of target lesions measured and stable disease is everything between the two. In clinical practice treatment benefit is a balance between radiological features, disease symptoms and side effects of treatment.

9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes. Although the treatment of patients with EGFR mutated NSCLC has improved substantially in recent years with the advent of tyrosine kinase inhibitors (TKI's), which are more effective and less toxic than chemotherapy, the cancer inevitably becomes resistant to treatment and worsens (progresses), usually after about 9-10 months. There is a need for a treatment which controls the cancer for longer than this. The current 1st and 2nd generation TKI's, although substantially better than chemotherapy, have side effects, and despite generally being mild, still have an effect when taken long-term (median 9-12 months in clinical practice). The side effects which most commonly affect patients quality of life are: - Rash - Diarrhoea - Paronychia There is a need for treatments with a more tolerable side effect profile. A second important clinical feature of disease for patients with EGFR mutated NSCLC is that brain metastases are common. Approximately 25% of patients may have brain metastases at diagnosis, and the majority of patients will develop brain metastases during the course of their illness, with potentially devastating effects of quality of life, both in terms of symptoms and independence (patients with brain metastases are barred from driving). There is a need for treatments which have improved control of cancer affecting the brain and delay or prevent spread of cancer to the brain.
What is the expected place of the technology in current practice?	

10. How is the condition currently treated in the NHS?	The condition is currently treated with a first or second generation TKI: - gefitinib - Erlotinib - Afatinib Patients may undergo palliative radiotherapy at any point in their pathway. At the point of disease progression patients, if still well enough, may have second-line treatment with: - Chemotherapy (platinum and pemetrexed) - Osimertinib (if T790M resistance mutation is present, which occurs in about 50% of patients)
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	ESMO and NCCN guidelines recommend the use of Osimertinib in the first line setting for EGFR mutated NSCLC. ASCO guidelines have not been updated since August 2017, at which point osimertinib was recommended in patients who had T790M resistance to initial TKI therapy. This guideline is due to be updated. NICE lung cancer guidelines are currently being updated.

• 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.)	The initial pathway is well defined and varies little in the UK. At the point of disease progression following initial TKI therapy there is some variation in clinical practice. There is a blood test available to detect T790M resistance, but it has a false negative rate of around 20%. In some centres, if the blood test is negative, a repeat tissue biopsy will be planned, (which has a much lower false negative rate) but there are a number of barriers to repeat biopsies: - in about 20% of patients repeat biopsy is not feasible due to technical issues (patient has clinical features making biopsy too high risk, disease is not amenable to biopsy, patient is too unwell) - In about 20-25% of patients where repeat biopsy is carried out, insufficient material is obtained for molecular testing - In some centres repeat biopsy is not a priority for the MDT - initial diagnostic biopsies are the main priority and there are targets to ensure that diagnostic biopsies are carried out in a timely fashion - The expertise needed to obtain repeat biopsies is variable - disease has often responded to initial therapy and may be be more difficult to biopsy than at the time of initial presentation Consequently, a significant proportion of patients who may benefit from second line osimertinib do not have access to therapy. Most countries in European countries have already adopted Osimertinib as first line treatment, as has the USA.
• What impact would the technology have on the current pathway of care?	There would be no impact on initial diagnostic pathway but there would be no need for currently practiced blood or tissue T790M testing at progression.

11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes, it is an oral therapy which would be used in the oncology out-patient setting.
• How does healthcare resource use differ between the technology and current care?	No significant difference
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist Oncology clinics
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	None - oncology teams already experienced with use of the drug in 2nd line treatment.

12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes
• Do you expect the technology to increase length of life more than current care?	Yes, FLAURA study demonstrated median PFS improved by 8.7 months (18.9 vs 10.2; HR 0.46 CI 0.37-0.57). Overall survival data is not yet mature, however, at 18 months 83% of patients on osimertinib were still alive compared 71% on standard therapy (HR 0.46; CI 0.45-0.88).
• Do you expect the technology to increase health-related quality of life more than current care?	Yes. Osimertinib has improved PFS and duration of response rates compared to the current standard of care. In addition it has less EGFR wild type activity than current treatments which translates into less side effects (rash, deranged LFT's).
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Osimertinib is more effective in patients with brain metastases than current treatments. FLAURA demonstrated superiority in the 116 patients with brain metastases with PFS 15.2 vs 9.6 months (HR 0.47; CI 0.30-0.74) for osimertinib and standard care respectively, and CNS progression occurred in 6% versus 15%.

The use of the technology	
14. 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.)	Additional ECG's required to monitor QT at baseline and periodically (approximately 3 monthly). No other technology specific requirements.

15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	There is no change from standard practice - disease progression on scans, patient tolerability of treatment and symptoms are used to guide discontinuation. There is no additional testing (in reality there would be less testing as assessment for T790M at progression is not necessary)
16. 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?	Standard QoL tools are not good at detecting subtle differences associated with low grade toxicity or brain metastases.

17. 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
• Is the technology a 'step-change' in the management of the condition?	Yes, primarily because of the improved control of brain disease. Patients will have less symptoms related to brain metastases and require less radiotherapy (mainly stereotactic radiotherapy, but also whole brain radiotherapy [WBRT] to a lesser degree). In addition less systemic steroids will be needed, resulting in less steroid induced morbidity for patients.
• Does the use of the technology address any particular unmet need of the patient population?	Osimertinib fulfils the need for a treatment which is more effective in controlling the disease for a longer period of time (delays development of resistance), is more effective in patients where cancer has spread to the brain and is better tolerated (less side effects).

18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Treatment is very well tolerated and patients QoL is generally very good. Grade 3 or greater adverse events are less common in patients on osimertinib compared to standard therapy (34% vs 45%). Anecdotally, my patients who have experienced Osimertinib as a second line treatment almost universally describe an improved side effect profile compared to first line treatment. The adverse event reporting in FLAURA does not fully capture the improved safety profile of osimertinib compared to gefitinib and erlotinib, perhaps due to the low grade nature of most adverse events.
Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	Yes and patients were recruited from UK centres.
• If not, how could the results be extrapolated to the UK setting?	NA

• What, in your view, are the most important outcomes, and were they measured in the trials?	The most important outcomes were improved disease control of longer duration (PFS, DOR) and improved intracranial activity and control. Intracranial activity could have been more robustly assessed by carrying out routine brain scans, not just at baseline, but at all time points in all patients (rather than just in those with brain metastases at baseline).
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	PFS is the primary end point. Overall survival (OS) data is not yet mature and in previous studies of targeted therapy in EGFR mutated NSCLC, OS benefit has been difficult to demonstrate, mainly due to post-progression crossover of treatment. The initial OS observations are encouraging with a 12% improvement in 18 month survival (hazard ratio 0.63; CI 0.45- 0.88) but data is still immature.
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
20. Are you aware of any relevant evidence that might	No

not be found by a systematic review of the trial evidence?	
21. How do data on real-world experience compare with the trial data?	Experience using Osimertinib in the second line setting in standard NHS practice and in clinical trials is consistent with the FLAURA data.
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
22b. Consider whether these issues are different from issues with current care and why.	NA
Key messages	

23. In up to 5 bullet points, please summarise the key messages of your statement.

- Osimertinib is a vey effective well tolerated oral therapy for EGFR mutated NSCLC
- There is improved progression free survival (18.9 vs 10.2months; HR 0.46; CI 0.37-0.57) and duration of response (17.2 vs 8.5 months) compared to standard therapy.
- In EGFR mutated NSCLC where brain metastases are a very common cause of morbidity and mortality, there is improved activity in the brain compared with standard therapy
- There is an improved side effect profile compared to standard therapy (adverse events G3 or higher 34% vs 45%)
- Using Osimertinib in the first line, means that patients who currently might not have access to osimertinib in the second line, due to false negative T790M blood test or lack of tissue biopsy but could potentially benefit from treatment, have appropriate therapy

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.

NICE National Institute for Health and Care Excellence

National Institute for Health and Care Excellence

Cancer Drugs Fund Clinical Lead statement

Osimertinib for the 1st line treatment of locally advanced or metastatic non small cell lung cancer with activating epidermal growth factor (EGFR) mutations [ID1302]

Background

1. The treatment pathway for non small cell lung cancer (NSCLC) with activating EGFR mutations has the potential to change in the near future in this appraisal as well as in other appraisals as immunotherapy both moves to earlier lines of treatment in the treatment pathway and is combined with targeted therapies.

2. The testing of NSCLC (at least of the non squamous variety) at diagnosis for activating EGFR mutations is routine practice in NHS England. The testing for the T790M mutation in patients failing EGFR-tyrosine kinase inhibitors (TKIs) is funded by NHS England as a consequence of osimertinib in this indication being in the CDF.

3. The development of brain metastases is an important patient and treatment issue in this population of NSCLC patients with activating EGFR mutations as 40-50% of patients develop brain secondaries during the course of their illness. Brain metastases are especially important in the EGFR mutated NSCLC patients as they bring very significant adverse impacts on patient survival and quality of life.

Treatment pathway and comparators

4. There are currently three 1st line TKI agents used in the treatment of patients with EGFR activating mutations in NSCLC. Erlotinib and gefitinib have been recommended by NICE for a long time and are generally thought to be equally active. It is important to note that since the NICE approval of these 2 agents, the 1st line chemotherapy comparator for EGFR-TKIs in standard practice and trials changed and became more efficacious. Afatinib is the third EGFR-TKI and was recommended by NICE in 2014. It has the best pedigree of these 3 TKIs as it was compared with the optimal 1st line chemotherapy combination of cisplatin plus pemetrexed. Afatinib is superior to gefitinib at least in terms of prolonging progression free survival (PFS) but this benefit did not result in an extension of overall survival (OS). This superior efficacy of afatinib came at the cost of increased toxicity.

5. Of the three 1st line EGFR-TKIs available, afatinib is used the most in NHS England although there is still substantial use of erlotinib and gefitinib. In view of its greater toxicities, afatinib may be used more in those patients who are fitter. All three TKIs result in rapid responses, the speed of these responses being sufficient to result in rapid improvements in quality of life and performance status. As a consequence, use of these 3 TKIs in clinical practice has extended from fitter patients (ECOG performance status 0 or 1 as enrolled in clinical trials of these agents) to less fit patients such as those having an ECOG performance status of 2.

6. The main side-effects of afatinib, erlotinib and gefitinib are cutaneous (especially rash, any grade 70-80% for all three drugs) and diarrhoea (any grade 40-60% for erlotinib and gefitinib and 80-90% for afatinib). The chronic nature of these toxicities is important for patients and for the clinical services required to manage them.

7. Osimertinib is in the CDF as 2nd line therapy for the 50-60% of patients failing 1st line EGFR-TKIs who are tested and have developed the T790M mutation. For detection of the T790M mutation, patients need a blood test for circulating tumour DNA but this has a 30-40% false negative rate and thus many patients still need a bronchoscopy or a mediastinal biopsy to gain tissue for T790M testing.

8. NHS England does not regard the use of osimertinib as 2nd line TKI treatment as standard therapy in England as it is in the CDF. As a consequence, NHS England does not consider that it should be included in the appraisal as part of the comparator treatment pathway. NHS England accepts that the NICE technology appraisal position as to the exclusion of CDF drugs from treatment pathways was only made public in January 2019 and that the company submission to NICE was in late 2018. NHS England also recognises that the FLAURA trial design incorporated the use of 2nd line osimertinib for T790M mutation patients on failure of erlotinib/gefitinib.

9. The next line of treatment following failure of 1st and/or 2nd line targeted therapy is currently cytotoxic chemotherapy in the form of a platinum-based combination with pemetrexed and maintenance pemetrexed as appropriate. The next routinely recommended line of treatment after cytotoxic chemotherapy is currently with immunotherapy monotherapy: atezolizumab for a PD-L1 TPS of 0-100% or pembrolizumab for a TPS of 1-100%. Nivolumab for a TPS of 1-100% is available via the CDF and thus NHS England does not regard this as standard therapy in this setting.

Specific issues for this technology appraisal

10. Whilst there is 62% maturity in the current FLAURA dataset for PFS, there is only 25% maturity for (OS). The OS data is therefore

immature with only a few patients at risk in the OS analysis after 24 months. This immaturity needs to be set in context of the [redacted] life years gained for osimertinib in the company economic model. NHS England notes that the final trial analysis is likely to be due in [redacted] has been achieved. NHS England notes that the cross over to osimertinib allowed in the comparator arm in FLAURA (once the PFS endpoint was attained) will blur the OS data according to the original trial design.

11. NHS England notes that unfortunately there has not been a direct comparison of osimertinib with afatinib, the comparator most often used in England in the activating EGFR mutation NSCLC population.

12. NHS England notes that there was less toxicity from osimertinib than with erlotinib/gefitinib in the FLAURA trial. There were fewer grade 3 and 4 adverse events with osimertinib (32% vs 41%) and less all grade rash/acne (58% vs 78%). Rates of diarrhoea and dry skin were similar. All grade toxicities are important with EGFR-TKIs as patients are on these drugs for considerable times. Feedback to NHS England has been clear that those patients who have a 1st line EGFR-TKI and then osimertinib report a preference for the side-effect profile of osimertinib.

13. Second line treatment rates in the FLAURA trial may be as high as 70-80% but in clinical practice in England, this figure is likely to be about 50-60%.

14. Osimertinib penetrates the blood brain barrier better than other EGFR-TKIs. The FLAURA trial (unlike most other trials of 1st line EGFR-TKIs) allowed patients with treated brain secondaries and not on steroids to enter the trial and 21% of patients fulfilled these criteria. With relatively short follow-up, the rate of progression in the central nervous system was lower with osimertinib (6% vs

15%). In addition, there was no difference in the osimertinib PFS in those with known brain metastases vs those without. In those patients with brain secondaries (with the limitation of small numbers), the PFS rate at 12 months was 77% with osimertinib vs 56% for erlotinib/gefitinib. The effect of reducing the morbidity of brain metastases is an important benefit for patients with EGFR mutated NSCLC.

15. In both FLAURA arms there were high rates of re-challenge with other EGFR-TKIs. This would not occur in England as the current three 1st line EFDR-TKIs are only commissioned as 1st line alternatives and not as sequenced lines of treatment. Some patients in FLAURA were treated with 2nd/3rd line regimens which included bevacizumab and such treatment is not commissioned in NHS England. However, commissioned immunotherapies in England (see paragraph 9 above) were not included in the economic model.

16. The company's economic model assumes lower 3rd line treatment rates of 34% for the osimertinib arm vs 44% for the erlotinib/gerfitinib arm. This is counterintuitive as better initial treatment (and particularly better control of brain metastases) is more likely to result in a greater treatment rate for subsequent therapies and especially so with the availability of immunotherapies in the treatment pathway.

17. NHS England does not understand the Evidence Review Group's position in relation to limiting the duration of treatment effect for osimertinib. NICE's position concerning 3 and 5 year treatment waning effects in NSCLC has been following appraisal of fixed durations of immunotherapy with a mode of action which involves the immune system having a plausible more durable impact on the cancer than just during the treatment period. Osimertinib has a completely different mode of action and is not given for a fixed

duration of treatment. Patients still on treatment with osimertinib at 3 years or 5 years or any other duration of treatment will still be benefitting from treatment with osimertinib.

18. NHS England notes that the treatment cost of delivering oral systemic anti-cancer therapy such as osimertinib/erlotinib/gefitinib is defined by the oral chemo tariff SB11Z which is £120 per 4-weekly cycle as opposed to the £9 figure used in the company's model. Use of the correct figure is likely to have a small effect in the ICER.

19. NHS England notes that there are issues and benefits in the 1st line use of osimertinib that may not have been captured in the economic model. 1) The morbidity of brain metastases over the lifetime of patients with EGFR mutated NSCLC has a very significant impact on reducing quality of life and OS. The follow-up duration in FLAURA is short and thus the beneficial impact of osimertinib in the brain is unlikely to have been fully realised. 2) First line osimertinib will remove the morbidity of the need for repeat bronchoscopic biopsies in patients treated with current 1st line EGFR-TKIs. 3) As osimertinib is better tolerated than current 1st line EGFR-TKIs, there will be a need for fewer dermatology referrals for patient suffering cutaneous toxicities. 4) Economic models will generally only include grade 3 and 4 side-effects and will miss the impact of a higher incidence of chronic grade 1 and 2 cutaneous toxicities associated with current 1st line EGFR-TKIs. 5) Because of the current and future impact of cross over to osimertinib once the primary PFS endpoint of FLAURA was reached and the imperfect ways of adjusting for that crossover, NHS England is concerned that the definition of the benefits of osimertinib may not be captured as regards both the systemic benefits and those associated with control of brain metastases.

20. NHS England notes that the company seeks allocation by the Appraisal Committee of the higher end of life (EOL) threshold of cost effectiveness. It does this by requesting the committee to use the osimertinib data from FLAURA to assess the benefit of osimertinib but at the same time use real world NHS evidence of the benefit of the comparator. This is a wholly inconsistent approach. NHS England's position is that either clinical trial evidence must be used for both the comparator and the osimertinib populations or the company must adjust the outcomes seen with osimertinib in FLAURA to those that might be expected in the real world NHS. The latter approach would introduce great uncertainty: if the real world NHS median survival is about 16 months with 1st line erlotinib and gefitinib (but not afatinib) as opposed to clinical trial figures of about 24 months, then the benefits of osimertinib should be reduced by a third too. NHS England recognises that clinical trial populations generally do better than real world ones, but also states that like must be compared with like and comparisons must be done without introducing very uncertain ways of trying to match clinical trial outcomes to those in the real world.

Commissioning perspective

21. If NICE recommends osimertinib as 1st line treatment in NSCLC patients with activating EGFR mutations, NHS England expects that osimertinib will rapidly gain almost complete market share as 1st line therapy. The use of the other 3 current 1st line EGFR-TKIs will be used for those patients who cannot tolerate osimertinib.

22. The FLAURA trial only enrolled patients with adenocarcinoma of the lung who had activating EGFR mutations. There are a few patients with activating EGFR mutations with non-adenocarcinoma of the lung and if identified, NHS England would wish to

commission the use of osimertinib in any patient with an activating EGFR mutation in NSCLC.

23. If the Appraisal Committee did not recommend osimertinib for routine commissioning but considered that it was plausibly cost effective and further data maturation would resolve its uncertainties, NHS England would welcome a NICE recommendation of osimertinib to the CDF as it regards osimertinib as a promising drug with fewer side-effects than current 1st line TKI therapy.

Generalisability to NHS practice

24. Although the FLAURA trial enrolled patients of only good performance status (ECOG 0 or 1), NHS England would commission use of osimertinib in patients of ECOG performance status 2 in the light of what has been stated in paragraph 5.

Implementing a positive NICE recommendation

NICE recognises that in the event of a positive recommendation, more prescriptive clinical commissioning criteria for treatments commissioned via Specialised Services will be implemented by NHS England to ensure appropriate use within the NHS.

NHS England is responsible for ensuring that the final clinical commissioning criteria are aligned with final guidance (section 1 – recommendation and section 3 – committee discussion).

Draft commissioning criteria

25. If osimertinib is recommended by NICE for treating advanced/metastatic NSCLC with activating EGFR mutations as 1st line therapy and within its marketing authorisation, NHS England proposes to use the following commissioning criteria:

- The patient must have histologically- or cytologically-confirmed NSCLC which is locally advanced (stage IIIB) or distantly metastatic (stage IV) disease.
- The patient's NSCLC must be positive for activating EGFR mutations
- The patient must be treatment naïve to systemic therapy for locally advanced/metastatic disease
- The patient must not have received cytotoxic chemotherapy for his/her stage IIIB or stage IV disease. Patients who have received adjuvant chemotherapy, neoadjuvant chemotherapy or chemotherapy concurrent with radiotherapy for earlier stage disease are eligible for osimertinib
- The patient must have an ECOG performance score of 0 or 1 or 2
- The patient should not have received any previous EGFR-directed TKI therapy
- The patient must not have any symptomatically active brain metastases or leptomeningeal disease
- Treatment with osimertinib will continue until loss of clinical benefit or excessive toxicity or until the patient chooses to stop treatment, whichever is the sooner

If this technology is recommended for routine commissioning in a subpopulation or with certain specifications (for example, a treatment continuation rule), the final commissioning criteria will reflect these conditions.

26. If osimertinib for treating advanced/metastatic NSCLC with activating EGFR mutations is recommended for use in the Cancer Drugs Fund, the final commissioning criteria will reflect the patient eligibility criteria in the managed access agreement

Issues for discussion

27. All relevant issues for discussion have been raised above.

Issues for decision

28. All relevant issues for decision-making have been raised above.

Equality

29. All relevant issues have been raised above.

Author

Professor Peter Clark, NHS England Chair of Chemotherapy Clinical Reference Group and National Clinical Lead for the Cancer Drugs Fund

March 2019

ERG STA REPORT

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Osimertinib for untreated epidermal growth factor receptor (EGFR) mutation-positive non-small-cell lung cancer [ID1302]

Confidential until published

This report was commissioned by the NIHR HTA Programme as project number 17/141/08

Completed 14 November 2018

CONTAINS ACADEMIC IN CONFIDENCE AND COMMERCIAL IN CONFIDENCE DATA

UNIVERSITY OF LIVERPOOL | LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

Title: Osimertinib for untreated epidermal growth factor receptor (EGFR) mutation-positive non-small-cell lung cancer [ID1302]

Produced by: Liverpool Reviews & Implementation Group (LR*i*G)

Authors: Nigel Fleeman, Senior Research Fellow (Clinical Effectiveness), LR*i*G, University of Liverpool

James Mahon, Director, Coldingham Analytical Services, Berwickshire

Marty Richardson, Research Associate (Medical Statistician), LR*i*G, University of Liverpool

Angela Boland, Associate Director, LR*i*G, University of Liverpool

Sophie Beale, Research Associate, LR*i*G, University of Liverpool

Rui Duarte, Health Technology Assessment Lead, LR*i*G, University of Liverpool

Yenal Dundar, Research Fellow (Clinical Effectiveness), LR*i*G, University of Liverpool

Rachel Houten, Health Economic Modeller, LR*i*G, University of Liverpool

Tosin Lambe, Health Economic Modeller, LR*i*G, University of Liverpool

Eleanor Kotas, Information Specialist, LR*i*G, University of Liverpool

Joanne McEntee, Senior Medicines Information Pharmacist, North West Medicines Information Centre, Liverpool

John Green, Consultant in Clinical Oncology, Clatterbridge Centre NHS Foundation Trust

Correspondence to: Nigel Fleeman, Research Fellow, Liverpool Reviews and Implementation Group, University of Liverpool, Whelan Building, The Quadrangle, Brownlow Hill, Liverpool L69 3GB

Date completed: 14 November 2018

Source of funding: This report was commissioned by the NIHR HTA Programme as project number 17/141/08

Acknowledgements: The authors would like to thank Dr Nick Brown, Consultant Medical Oncologist, Calderdale and Huddersfield NHS Foundation Trust, who provided feedback on the final version of the report. Dr Brown has received reimbursement for attending a symposium from AstraZeneca, Roche and MSD and fees for organising education for Pfizer.

Rider on responsibility for report: The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

Declared competing interests of the authors: None.

This report should be referenced as follows: Fleeman N, Mahon J, Richardson M, Boland A, Beale S, Dundar Y, Lambe T, Houten R, Kotas E, Duarte R, McEntee J, Green J. Osimertinib for untreated epidermal growth factor receptor (EGFR) mutation-positive non-small-cell lung cancer [ID1302]: A Single Technology Appraisal. LR*i*G, University of Liverpool, 2018

Contributions of authors:

Nigel Fleeman	Project lead, critical appraisal of the clinical evidence and supervised the final report
James Mahon	Critical appraisal of the economic evidence and critique of the economic model
Marty Richardson	Critical appraisal of the statistical evidence
Angela Boland	Critical appraisal of the clinical and economic evidence, editorial input
Sophie Beale	Critical appraisal of the clinical and economic evidence, editorial input
Yenal Dundar	Critical appraisal of the adverse event data
Tosin Lambe	Critical appraisal of the economic evidence
Rachel Houten	Critical appraisal of the economic evidence
Eleanor Kotas	Cross checking of the submission search strategies
Rui Duarte	Critical appraisal of the clinical and economic evidence, editorial input
Joanne McEntee	Critical appraisal of the company submission
John Green	Clinical advice and critical appraisal of the clinical sections of the company submission

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LIST OF ABBREVIATIONS

AE	Adverse event
ALK	Anaplastic lymphoma kinase
BICR	Blinded independent central review
BSC	Best supportive care
CDF	Cancer Drugs Fund
cEFR	CNS evaluable-for-response
cFAS	CNS full analysis set
CI	Confidence interval
CNS	Central nervous system
CS	Company submission
CSR	Clinical study report
DCR	Disease control rate
EGFR	Epidermal growth factor receptor
EGFR+ NSCLC	Epidermal growth factor receptor-positive non-small cell lung cancer
EGFR-TKI	Epidermal growth factor receptor tyrosine kinase inhibitor
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EQ-5D-3L	European Quality of Life 5-Dimension 3 Level Version
ERG	Evidence review Group
ESMO	European Society for Medical Oncology
FAS	Full analysis set
HRQoL	health-related quality of life
ICER	Incremental cost-effectiveness ratio
NICE	National Institute for Health and Care Excellence
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
PDC	Platinum doublet chemotherapy
PD-L1	Programmed death-ligand 1
PD-L1+ NSCLC	Programmed death-ligand 1 non-small cell lung cancer
PFS	Progression-free survival
PS	Performance status
PSA	Probability sensitivity analysis
PSS	Personal Social Services
QALY(s)	Quality adjusted life year(s)
RCP	Royal College of Physicians
SoC	Standard of care
SPA	Single payment access scheme
T790M+ NSCLC	T790M mutation-positive non-small cell lung cancer
WHO	World Health Organization

1 SUMMARY

1.1 Scope of the submission

The remit of the Evidence Review Group (ERG) is to comment on the clinical and cost effectiveness evidence submitted to the National Institute for Health and Care Excellence (NICE) as part of the Single Technology Appraisal (STA) process. Clinical and economic evidence has been submitted to NICE by AstraZeneca in support of the use of osimertinib (TAGRISSO™) for untreated locally advanced or metastatic (hereafter referred to as advanced) epidermal growth factor receptor-positive (EGFR+) non-small cell lung cancer (NSCLC). Osimertinib was licensed for the treatment of adult patients with advanced EGFR T790M mutation-positive NSCLC in December 2015 and recommended by NICE as an option for use within the Cancer Drugs Fund after first-line treatment with an EGFR tyrosine kinase inhibitor (EGFR-TKI) in October 2016. Relevant to the current STA, the European Commission granted an extension of the marketing authorisation valid throughout the European Union for osimertinib for the first-line treatment of adult patients with advanced NSCLC with activating EGFR mutations in June 2018.

1.2 Critique of the decision problem in the company submission

The company's decision problem matches the final scope issued by NICE. In addition, the company has included evidence for the following subgroup analyses "of potentially clinical relevance": patients with and without central nervous system (CNS) metastases, patients of Asian and non-Asian ethnicity, and patients with and without Exon 19 deletions or L858R point mutations (i.e., two common types of EGFR mutations). The company highlights that osimertinib has been designed to increase CNS penetration and activity through improved permeability across the intact blood-brain barrier.

Comparators specified in the final scope issued by NICE and the company's decision problem are afatinib, erlotinib and gefitinib. These are all EGFR-tyrosine kinase inhibitors (EGFR-TKIs) recommended by NICE for the first-line treatment of advanced EGFR+ NSCLC. As per osimertinib, all treatments are administered orally, once daily. Osimertinib is currently a second-line treatment option for patients with advanced EGFR+ NSCLC previously treated with an EGFR-TKI who test positive for the T790M mutation following disease progression. The T790M mutation is described by the company as the main mechanism of acquired resistance to EGFR-TKIs, accounting for approximately 60% of all cases.

1.3 Summary of the clinical evidence submitted by the company

Direct evidence

The company literature search identified only one randomised controlled trial (RCT) of osimertinib for the first-line treatment of advanced EGFR+ NSCLC, the FLAURA trial. The FLAURA trial is an ongoing international, double-blind, randomised, Phase III, multi-centre trial of osimertinib versus EGFR-TKI standard of care (SoC EGFR-TKI) in patients with advanced EGFR+ NSCLC. In the FLAURA trial, the SoC EGFR-TKI arm consisted of erlotinib or gefitinib. After investigator-assessed objective disease progression based on response evaluation criteria in solid tumours (RECIST) v1.1, patients randomised to the SoC EGFR-TKI arm had the option to cross over to treatment with open-label osimertinib provided that specific criteria were met. The criteria included the need for confirmation of the presence of the T790M mutation.

Baseline characteristics of patients enrolled into the FLAURA trial were well-balanced between the osimertinib and SoC EGFR-TKI arms. The majority of patients were female (63%), had never smoked (64%) and had metastatic disease (95%). Around a fifth of patients (21%) were considered to have CNS metastases, while most patients were classified as 'Asian' (62%) as opposed to 'White' (36%) and had Exon 19 deletions (58%) as opposed to L858R point mutations (42%). The majority of patients had World Health Organization (WHO) performance status (PS) 1 (restricted activity) (59%) as opposed to PS 0 (normal activity) (41%) and the median age of all patients was 64 years.

To date, FLAURA trial results are from an interim analysis for the primary outcome of investigator-assessed progression-free survival (PFS) (61.5% maturity for PFS overall). This analysis was carried out after a median duration of 15.0 months (range: 0 to 25.1) follow-up in the osimertinib arm and 9.7 months (range 0 to 26.1) follow-up in the SoC EGFR-TKI arm. A final OS analysis will be conducted at 60% maturity, with data expected to be available in [redacted].

For the primary outcome of investigator-assessed PFS, patients in the osimertinib arm experienced statistically significantly longer PFS in comparison to patients in the SoC EGFR-TKI arm (hazard ratio [HR]=0.46, 95% confidence interval [CI]: 0.37 months to 0.57 months; p<0.001). Median PFS was 18.9 months (95% CI: 15.2 months to 21.4 months) and 10.2 months (95% CI: 9.6 months to 11.1 months) in the osimertinib and SoC EGFR-TKI arms, respectively. PFS assessed by blinded independent central review (BICR) was analysed as a sensitivity analysis for the primary outcome. The results from this analysis were consistent with the investigator-assessed PFS results. In addition, numerically fewer patients in the

osimertinib arm [redacted] experienced CNS progression than in the SoC EGFR-TKI arm and [redacted].

The company performed subgroup analyses for investigator-assessed PFS for several pre-specified characteristics. Treatment with osimertinib was favoured over treatment with Soc EGFR-TKI for all pre-specified subgroups, including subgroups defined according to the presence or absence of CNS metastases at trial entry, ethnicity (Asian versus non-Asian) and EGFR mutation type (Exon 19 deletions or L858R point mutations). CNS PFS was also nominally statistically significantly improved in patients with CNS metastases.

There was no statistically significant difference between the osimertinib and SoC EGFR-TKI arms in terms of investigator-assessed ORR, osimertinib: 80% (95% CI: 75% to 85%) and SoC EGFR TKI: 76% (95% CI: 70% to 81%), odds ratio (OR)=1.27 (95% CI: 0.85 to 1.90). However, the disease control rate (DCR) and duration of response were improved with osimertinib versus Soc EGFR-TKI. A statistically significant OR was observed for DCR (OR=2.78, 95% CI: 1.25 to 6.78; p=0.01) and the difference in duration of response was described as clinically meaningful.

Overall survival (OS) data were very immature (25% of events) and confounded by treatment crossover (55 [20%] patients in the SoC EGFR-TKI arm crossed over and received osimertinib as second-line therapy). Nonetheless, the reported HR for osimertinib versus SoC EGFR-TKI was 0.63 (95% CI: 0.45 to 0.88; p=0.007). Due to the hierarchical statistical testing strategy employed in the FLAURA trial, a p-value of less than 0.0015 was required to achieve statistical significance in this instance. Therefore, it was not possible to conclude that osimertinib statistically significantly improved OS in comparison to Soc EGFR-TKI. Since median OS (i.e., the 50% percentile of OS) could not be calculated, the company presented the 25th percentile of OS as a "conservative estimate of the survival gain in the mature population". The 25th percentile of OS was observed at approximately 22.5 months in the osimertinib arm, and at approximately 15.9 months in the SoC EGFR-TKI arm, corresponding to a survival gain of 6.6 months.

The company also examined the three post-progression endpoints: time to first subsequent therapy (TFST), time to second progression by investigator assessment (PFS2) and time to second subsequent therapy (TSST). For each of these post-progression endpoints, the reported HRs suggested that treatment with osimertinib was statistically significantly more effective than treatment with Soc EGFR-TKI. The company states that the improvements in these post-progression endpoints are clinically meaningful. Furthermore, the company states that these post-progression endpoint results demonstrate that the PFS advantage of

osimertinib is largely preserved beyond initial progression and provide reassurance that a clinically meaningful OS benefit will be observed in the fully mature dataset.

Overall, rates of adverse events (AEs) were generally similar between the two FLAURA trial treatment arms, although there were lower rates of Grade ≥3 AEs, less frequent hepatic and rash AEs and a lower treatment discontinuation rate due to AEs in the osimertinib arm when compared with the SoC EGFR-TKI arm.

As part of the FLAURA trial, patient reported symptoms and health-related quality of life (HRQoL) data were collected via the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Lung Cancer 13 items (EORTC QLQ-LC13) and European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30 items (EORTC QLQ-LC30) questionnaires. No statistically significant or clinically meaningful differences were reported between arms. European Quality of Life 5-Dimension (EQ-5D) data were not collected as part of the FLAURA trial.

Indirect evidence

Although direct evidence for osimertinib versus afatinib is lacking, the company decided not to perform an indirect comparison of osimertinib versus afatinib for two reasons. First, the proportional hazards (PH) assumption was possibly violated for OS in the FLAURA trial and the PH assumptions for PFS and OS were possibly violated in the LUX-Lung 7 trial. Second, available evidence from a recent network meta-analysis and the conclusions reached by an Appraisal Committee (AC) during a previous NICE STA (TA310) suggest that assuming equivalence of efficacy of afatinib, erlotinib and gefitinib is reasonable.

1.4 Summary of the ERG's critique of clinical effectiveness evidence submitted

Direct evidence

As is usually the case with clinical trials, patients were fitter in the trial than are routinely seen in NHS clinical practice. Results from a recent analysis of real-world data (652 patients treated with EGFR-TKIs for advanced first-line EGFR+ NSCLC in clinical practice in England), showed that where PS was known (in 448 patients), [redacted] had PS 2 or 3. The FLAURA trial only included patients with PS ≤1.

Generally, the ERG considers that the company's approach to analysing the data from the FLAURA trial was appropriate. The ERG also assessed the validity of the PH assumption for the outcomes of PFS (investigator assessed and BICR-assessed) and OS, since these are the relevant time-to-event outcomes listed in the final scope issued by NICE. The ERG agrees

with the company that the PH assumption is reasonable for both investigator-assessed and BICR-assessed PFS. However, the ERG considers that the PH assumption may be violated for OS and, consequently, that the reported OS HR should be interpreted with caution. It is not possible to know whether the reported HR overestimates or underestimates the effect of osimertinib versus Soc EGFR-TKI. The ERG also notes that whilst HRs for TFST, PFS2, TSST and CNS PFS were presented in the CS, the company did not test the PH assumption for any of these outcomes and therefore, the reliability of these HRs is uncertain.

FLAURA trial results for the majority of outcomes, including the primary outcome of PFS, suggest that treatment with osimertinib is more efficacious than the Soc EGFR-TKI and has a similar, if not better, safety profile. The FLAURA trial is the first trial to have demonstrated a PFS benefit in patients with CNS metastases although to the ERG's knowledge, the LUX-Lung 7 trial of afatinib versus gefitinib is the only other trial to have conducted a subgroup analysis in a similar group of patients

The ERG agrees with the company that the FLAURA trial OS results are encouraging and appear to be supported by post-progression endpoints (TFST, PFS2 and TSST), notwithstanding the caveat that the PH assumption may be violated for OS and has not been tested for TFST, PFS2 or TSST. The ERG also highlights that is difficult to predict whether the OS benefit observed at an early interim analysis will be maintained in the longer-term.

The company considers that osimertinib is generally well tolerated and that FLAURA trial safety findings are generally consistent with the known safety profile of osimertinib (including QT prolongation, cardiac effect and interstitial lung disease). However, the ERG observes that compared to previous studies of osimertinib reported in the European Medicines Agency European Public Assessment Report (EPAR), the rates of serious adverse events (SAEs) in the osimertinib arm of the FLAURA trial (21.5%) were lower than previously reported (35.3% to 46.7%). The same is also true for treatment-related SAEs (2.9% in the FLAURA trial, 5.6% to 13.3% in previous trials).

Indirect evidence

The ERG notes that previous ACs have concluded that afatinib is likely to have similar efficacy to erlotinib and gefitinib. However, the ERG is also aware that in the exploratory Phase IIb LUX-Lung 7 trial, afatinib resulted in a statistically significant improvement in PFS compared with gefitinib. In the absence of any estimates of efficacy for osimertinib versus afatinib, the ERG therefore decided to conduct a simple indirect comparison. The results of the ERG's indirect comparison suggest that osimertinib statistically significantly improves PFS (by both investigator assessment [HR=0.59, 95% CI: 0.43 to 0.82] and BICR [HR=0.62, 95% CI: 0.44

to 0.87]) in comparison to afatinib, but that there is no statistically significant difference between osimertinib and afatinib in terms of OS. The ERG concurs with the company that the PH assumptions may be violated for all relevant outcomes in the LUX-Lung 7 trial, as well as for OS in the FLAURA trial. Therefore, the results from the ERG's indirect comparison should be interpreted with caution.

Given that, in TA310, it was concluded that afatinib was associated with some different AEs to erlotinib and gefitinib but had similar toxicity overall, the ERG considers that it is likely that osimertinib is therefore at least as tolerable as afatinib.

1.5 The summary of cost effectiveness evidence submitted by the company

The company developed a de novo partitioned survival model in Microsoft Excel to compare the cost effectiveness of treatment with osimertinib versus afatinib, erlotinib and gefitinib for previously untreated advanced EGFR+ NSCLC. The model comprises three mutually exclusive health states: progression-free (PF), progressed disease (PD) and death. All patients start in the PF health state. The model time horizon is set at 20 years with a 30-day cycle length. The model perspective is that of the UK NHS. Outcomes are measured in quality adjusted life years (QALYs), and both costs and QALYs are discounted at an annual rate of 3.5%, as recommended by NICE.

In the company model, OS, PFS and time to discontinuation of treatment (TDT) were modelled using Kaplan-Meier (K-M) data from the FLAURA trial (osimertinib versus erlotinib or gefitinib). No direct trial evidence was available for the comparison of osimertinib versus afatinib. The company, therefore, assumed, based on published NMA results, that treatment with afatinib, erlotinib and gefitinib were equal in terms of OS, PFS, time to discontinuation of treatment (TDT) and AEs.

The OS K-M data from the FLAURA trial were used up to month 8 followed by Weibull distributions (fitted using standard methods) thereafter. Fitted parametric curves were also used to model PFS and TDT. AEs of Grade ≥3 occurring in >1% of patients in the FLAURA trial were included in the company model.

HRQoL data were collected as part of the FLAURA trial using the EORTC QLQ-LC30 and the EORTC QLQ-LC13 questionnaires. Responses from these questionnaires (stratified by PF and PD) were converted to EQ-5D-3L utility values using a published algorithm and then used to represent the HRQoL of patients in the PF health state and those in the PD health states who were still receiving first-line treatment. The utility value used to represent HRQoL of patients in the PD health state who were not still receiving a first-line treatment was obtained

from the literature. Resource use and cost information were estimated based on information from the FLAURA trial, published sources and clinical experts.

All treatments included in the model are available to the NHS at discounted prices. The company offers a confidential patient access scheme (PAS) for osimertinib and a publicly available single payment access scheme (SPA) is in place for gefitinib. PAS schemes are also available for afatinib and erlotinib. Using the list price for all treatments, results from the company's base case deterministic analysis showed that treatment with osimertinib was more expensive and more effective than all of the comparators in this submission. The pairwise incremental cost effectiveness ratios (ICERs) for the comparisons of treatment with osimertinib versus treatment with afatinib, erlotinib and gefitinib were £82,669, £89,700 and £82,675 per QALY gained respectively. Using the available discounted prices for osimertinib and gefitinib, the ICER for the comparison of treatment with osimertinib versus gefitinib was [redacted] per QALY gained.

The results from the company's probabilistic sensitivity analysis are consistent with the company's base case (deterministic) analysis. Using the list price for all treatments and a willingness-to-pay threshold of £50,000 per QALY gained, the probability of treatment with osimertinib being cost effective was 1.62% (afatinib=10.05%, erlotinib=77.95% and gefitinib=10.38%). Using the discounted prices for osimertinib and gefitinib, the probability of treatment with osimertinib being cost effective was 54% compared with treatment with gefitinib.

The company carried out a wide range of deterministic sensitivity analyses using the list prices of all treatments. The most influential parameter was the choice of parametric function that was used for modelling OS.. All of the scenarios explored by the company using the list prices for all treatments resulted in ICERs that were higher than £65,000 per QALY gained.

1.6 Summary of the ERG's critique of cost effectiveness evidence submitted

The company model comprises two different representations of effectiveness, one to model the experience of patients receiving first-line treatment with osimertinib (intervention arm) and, as afatinib, erlotinib and gefitinib are assumed to be equally effective, one that models the experience of patients receiving any one of these three drugs (the comparator arm) as a first-line treatment.

The ERG considers that the resource use and utility values used in the company's base case analysis to represent patient experience in the PD health state are overly pessimistic, i.e., levels of resource use are too high and utility values are too low. In the model, patients who

had received first-line treatment with osimertinib spent longer in the PD health state than patients who had received first-line treatment with afatinib, erlotinib or gefitinib. Using more realistic (lower) levels of resource use and higher utility values reduces the ICER per QALY gained for the comparison of osimertinib versus comparator drugs.

As OS data were not available for the whole model time horizon, the company used OS data from the FLAURA trial for the first 8 months and then applied Weibull distributions from 8 months to 20 years (essentially lifetime) to both the intervention and comparator arms. This approach demonstrates that the company has implicitly assumed that first-line treatment with osimertinib has a lifetime treatment effect. This means that even 20 years after the start of treatment, the mortality rate of patients who are still alive is lower for those who received first-line treatment with osimertinib than it is for those who received first-line treatment with a comparator drug. The ERG considers that this is implausible and highlights that this assumption was not accepted by NICE ACs during two previous STAs of treatments for advanced or metastatic NSCLC. In one case, the AC considered a limit of 5 years was realistic and, in the other, 3 years was considered to be realistic. The ERG, therefore, carried out three scenarios, adjusting the way in which OS was represented in the company model so that the mortality rates of patients receiving first-line treatment with osimertinib and the comparator drugs became equal after 2 years (reflecting the time period that trial data were available), 3 years and 5 years.

The ERG notes that the effect of treatment with immunotherapies, which are available to some patients who progress on treatment with EGFR-TKIs, was not included in the company model. Given the absence of data on the proportion of patients who would receive an immunotherapy as a second-line treatment, the impact of such treatment on OS and the costs for these patients, the ERG was unable to modify the company model to include immunotherapies as a subsequent treatment option. However, the ERG highlights that the use of immunotherapies will increase the costs and OS associated with treatment with all EGFR-TKIs.

1.7 Summary of company's case for End of Life criteria being met

To meet the NICE End of Life criteria the company must demonstrate that:

- the treatment is indicated for patients with a short life expectancy, normally less than 24 months;
- there is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment.

The company has put forward a case that osimertinib meets NICE's End of Life criteria based on the following points:

- Life expectancy (based on registry data):

- OS for patients with confirmed EGFR+, Stage IIIb/IV NSCLC in England and Wales is estimated to be [redacted] based on analysis of Public Health England data collected between 2014 and 2016 (n=652).
- Life extension (based on results from the FLAURA trial):
- Compared with SoC EGFR-TKI, osimertinib extended PFS by 8.7 months (18.9 months versus 10.2 months). Treatment with osimertinib also demonstrated a substantial improvement in post-progression endpoints, including a [redacted] in time to first subsequent treatment.
- Whilst OS data were immature, the HR for death was 0.63 (95% CI: 0.45 to 0.88). In addition, K-M data showed that, at 18 months, 82.8% of patients receiving osimertinib were still alive compared with 70.9% of those receiving SoC EGFR-TKI.
- The 25th percentile of OS was observed at approximately 22.5 months in the osimertinib arm, and at approximately 15.9 months in the SoC EGFR-TKI arm. This reflects an improvement of 6.6 months.

1.8 ERG commentary on End of Life criteria

The company presents registry data to demonstrate that patients with advanced EGFR+ NSCLC in England and Wales have a life expectancy of less than 24 months but uses trial evidence to demonstrate the relative effectiveness of osimertinib versus afatinib, erlotinib and gefitinib. The ERG accepts the company's argument that trial evidence (generated by patients who are likely to be younger and fitter than most patients treated in the NHS) may overestimate the life expectancy of NHS patients but considers that it is inconsistent to accept trial evidence as a measure of effectiveness but not as a measure of life expectancy.

Life expectancy

At the time of data cut off, median OS had not been reached in the FLAURA trial but, after 24 months, over half (64.7%) of patients in the SoC EGFR-TKI arm were still alive. The ERG, therefore, considers that, based on available trial evidence, the average life expectancy of patients with advanced EGFR+ NSCLC who are eligible for treatment with afatinib, erlotinib or gefitinib is likely to exceed 24 months.

Life extension

The economic modelling undertaken by the ERG supports the company position that compared with afatinib, erlotinib or gefitinib, treatment with osimertinib is likely to extend OS by at least 3 months.

1.9 ERG commentary on the robustness of evidence submitted by the company

1.9.1 Strengths

Clinical evidence

- The company provided a detailed submission that reflected the final scope issued by NICE for the clinical effectiveness analysis. The ERG's requests for additional information were addressed to a good standard.
- Overall, the ERG considers the methods used by the company to conduct a systematic review of clinical effectiveness evidence were satisfactory.
- The company's main source of clinical evidence is the FLAURA trial. The ERG considers that the FLAURA trial is a well-designed and good quality international, double blind, randomised, Phase III, multi-centre, ongoing trial.
- The FLAURA trial compares the efficacy of treatment with osimertinib versus erlotinib or gefitinib (SoC EGFR-TKI arm). Alongside afatinib, erlotinib and gefitinib can be considered as standard of care for many patients with advanced EGFR+ NSCLC in the NHS.
- FLAURA trial results show that, compared with Soc EGFR-TKI, treatment with osimertinib results in a statistically significant and clinically meaningful improvement in in median PFS of 8.7 months
- OS data from the FLAURA trial are immature but results suggest that there is an improved OS benefit for patients treated with osimertinib versus SoC EGFR-TKI and these results appear to be supported by post-progression endpoints.
- In the FLAURA trial, subgroup analyses for patients with CNS metastases show an improvement in PFS for patients treated with osimertinib versus Soc EGFR-TKI.

Cost effectiveness evidence

- The company provided a detailed submission that met the requirements of NICE's scope for the base case analysis. The ERG's requests for additional information were addressed to a good standard.
- The company model was well described within the CS and the ERG's requests for additional information were addressed to a good standard.
- The company carried out a comprehensive range of deterministic sensitivity and scenario analyses.

1.9.2 Weaknesses and areas of uncertainty

Clinical evidence

- In the FLAURA trial, numerically fewer patients in the osimertinib arm experienced CNS progression than in the SoC EGFR-TKI arm; some cases of asymptomatic progression may not have been detected in patients not required to have regular brain scans (i.e. those without confirmed CNS metastases at baseline).
- OS data from the FLAURA trial are very immature and it is unclear whether the apparent OS benefit demonstrated at the time of the interim analysis will be maintained.

- A comparison of OS data from both arms of the FLAURA trial suggests that hazards may not be proportional. This means that it is unclear whether the reported HRs overestimate or underestimate the effect of osimertinib versus Soc EGFR-TKI.
- Direct evidence for osimertinib versus afatinib is lacking. If it is assumed that afatinib is as efficacious as erlotinib and gefitinib, then the relative effects in terms of efficacy observed between osimertinib and SoC EGFR-TKI in the FLAURA trial are likely to be similar between osimertinib and afatinib. However, exploratory evidence from the LUX-Lung 7 trial suggests that afatinib may be result in improved PFS when compared with gefitinib. Results from an indirect comparison (PFS) conducted by the ERG suggest that osimertinib statistically significantly improves investigator assessed PFS and PFS assessed by BICR when compared with afatinib. However, the ERG highlights that results from this analysis should be interpreted with caution due to the possible violation of PH assumptions for investigator assessed PFS and PFS assessed by BICR in the LUX-Lung 7 trial.
- The indirect comparison conducted by the ERG did not yield statistically significant results for OS for osimertinib versus afatinib. However, it is unclear if the PH assumption is violated for OS in the FLAURA trial and if the PH assumption is violated for OS in the LUX-Lung 7 trial.
- While the incidence of SAEs was lower in the osimertinib arm than in the EGFR-TKI SoC arm of the FLAURA trial, it is noticeable that previous studies of osimertinib have reported higher incidences of SAEs than were reported in the FLAURA trial. Reasons for the lower number of SAEs in the FLAURA trial are unknown.

Cost effectiveness evidence

- The ERG considers that the company could have used more realistic values to model resource use and patient HRQoL in the PD health state.
- The company has assumed that the effect of treatment with osimertinib lasts for a lifetime.
- Second- or third-line treatment with an immunotherapy are possible subsequent treatment options for some patients receiving first-line treatment with an EGFR-TKI; however, these options are not included as part of the company model.

1.10 Summary of exploratory and sensitivity analyses undertaken by the ERG

As afatinib, erlotinib and gefitinib are assumed to be equally effective, the only difference, when calculating cost effectiveness, is in terms of the costs of the three comparator drugs. The ERG highlights that erlotinib is the least expensive of the three drugs and, therefore, treatment with erlotinib dominates treatment with afatinib or gefitinib. Thus, all of the ERG's recalculated ICERs per QALY gained relate to the comparison of the cost effectiveness of treatment with osimertinib versus erlotinib.

The ERG changes to resource use and utility of patients in the PD health state reduce the company's base case ICER for the comparison of treatment with osimertinib versus erlotinib to £88,057 and £87,357 per QALY gained respectively.

Limiting the duration of the effect of treatment with osimertinib has a substantial impact on the cost effectiveness of osimertinib versus erlotinib. After changing resource use and the utility of patients in the PD health state, limiting the duration of the effect of treatment with osimertinib to 2, 3 and 5 years, increases the ICER for the comparison of treatment with osimertinib versus erlotinib to £215,753, £162,981 and £120,953 per QALY gained respectively.

2 BACKGROUND

2.1 Critique of company's description of underlying health problem

The company's summary of the underlying health problem presented in the company submission (CS) is summarised in Sections 2.1.1 to 2.1.4 of this ERG report. The ERG considers that this presents an accurate summary of the underlying health problem.

2.1.1 Advanced non-small cell lung cancer: introduction

Briefly, the company states (CS, p13) that:

- An estimated 44,500 people are diagnosed with lung cancer in the UK each year, of whom over 80% have non-small cell lung cancers (NSCLC).[1]
- NSCLC is typically asymptomatic in early stages, resulting in delays in presentation and diagnosis. This, along with the aggressive nature of the disease, means that an estimated 70% of patients receive a diagnosis at an advanced disease stage (i.e., locally advanced [Stage IIIb] or metastatic [Stage IV] NSCLC).[2]

  Note: throughout this ERG report, locally advanced or metastatic NSCLC is referred to as advanced NSCLC.
- Patients diagnosed with advanced NSCLC can expect to experience multiple, debilitating symptoms,[1,3] and this can have a profound effect on their quality of life[4] (and as highlighted later on p30 of the CS, significant impacts on carers, family and children).
- Reported 1-year overall survival (OS) for patients with Stage III disease was 42.5% in 2017, falling to just 15.5% in those with Stage IV disease.[2]

In addition to disease stage, the company highlights that outcomes (OS and health-related quality of life [HRQoL]) are highly variable depending on prognostic factors such as age, molecular markers and the presence of central nervous system (CNS) metastases (CS, p27; see Sections 2.1.2 to 2.1.4 of this ERG report).

2.1.2 Lung cancer and age

In terms of age, as can be seen from data presented in Table 1, OS for patients with lung cancer (in general) decreases with age:

Table 1 Survival rates by age group for people diagnosed with lung cancer in England between 2011 and 2015

Age	1-year survival rate	5-year survival rate
15 to 45 years	55%	32%
45 to 54 years	45%	20%
55 to 64 years	43%	18%
65 to 74 years	40%	16%
≥75 years	29%	10%

Source: CS, Figure 4
Note: data rounded up to nearest whole number

2.1.3 Epidermal growth factor receptor and advanced non-small cell lung cancer

Epidermal growth factor receptor (EGFR) is an important molecular marker, being a receptor tyrosine kinase (RTK) that plays a central role in the pathogenesis and progression of carcinomas (CS, p25). **NSCLC in which EGFR mutations are present is known as EGFR-positive (EGFR+) NSCLC.**

Several known EGFR mutations have been mapped to the tyrosine kinase domain of EGFR with Exon 19 deletions and L858R point mutations accounting for approximately 90% of all EGFR mutations.[5-8] The company highlight (CS, p26) that EGFR mutations are more common in Asian than non-Asian populations, in women than in men and in never-smokers than in ever-smokers (CS, p26). In the UK, the frequency of EGFR mutations in patients with NSCLC of adenocarcinoma histology has been reported to be approximately 12%.[9] Data, collected from UK audits and reported in the CS, suggest that median OS for patients with advanced EGFR+ NSCLC is between 15 months and [redacted] (CS, Table 5).

2.1.4 The central nervous system and advanced non-small cell lung cancer

The CNS is a common metastatic site for NSCLC; approximately 20% to 25% of patients have CNS metastases at diagnosis (CS, p25) and approximately 40% to 50% develop CNS metastases over the course of their illness (CS, p41). The company reports (CS, p27) that for patients with CNS metastases, median OS is between 4 months and 9 months for patients treated with chemotherapy and 7 months for patients receiving whole brain radiation therapy.[10,11]However, clinical advice to the ERG is that selection may distort these outcomes and increasing numbers of patients receive multimodality therapy. Untreated patients with brain metastases have a median survival of 2 months.[10,12] Patients with CNS progression may also experience further deterioration in their quality of life due to CNS-related symptoms, including headaches, cognitive deficits, ataxia, seizures and visual and speech problems.[13]

2.2 Company's overview of current service provision

The company's overview of current service provision, presented in the CS, is summarised in Sections 2.2.1 to 2.2.6 of this ERG report. The ERG considers that the information in these sections presents an accurate summary of current service provision.

2.2.1 Goals of treatment

As highlighted by the company (CS, p32), treatment intent is not curative in advanced NSCLC, and goals usually focus on prolonging survival, improving quality of life, and alleviating symptoms. Potential benefits of treatment should be balanced with the risk of additional toxicities.[14]

2.2.2 First-line treatment for patients with EGFR+ NSCLC

Prior to first-line treatment for advanced NSCLC, patients in NHS clinical practice with non-squamous cancers have their tumours routinely tested for EGFR status. As noted by the company (CS, p25), tumour tissue biopsy is the preferred method for EGFR testing. The ERG notes that patients' tumours are also typically tested for programmed death-ligand 1 (PD-L1) expression and anaplastic lymphoma kinase (ALK) mutations at the same time that they are tested for EGFR.

If a patient is found to harbour EGFR mutations, they usually receive targeted therapy, namely an EGFR tyrosine kinase inhibitor (EGFR-TKI). First-generation EGFR-TKIs include erlotinib and gefitinib and second-generation EGFR-TKIs include afatinib and dacomitinib. Currently, afatinib, erlotinib and gefitinib are the EGFR-TKI treatments recommended by NICE for advanced EGFR+ NSCLC[15] and are considered standard of care (SoC) in the first-line setting (CS, p13). Dacomitinib is not presently used in NHS clinical practice but is currently being appraised by NICE, in a different Single Technology Appraisal (STA), versus afatinib, erlotinib and gefitinib with final guidance expected to be published in August 2019.[16]

If a patient is found to have a tumour expressing PD-L1 (PD-L1+ NSCLC), they may also receive targeted therapy. Typically, this will either be an EGFR-TKI assuming they tested positive for EGFR (i.e. EGFR+ NSCLC) or pembrolizumab, which is a type of immunotherapy. Clinical advice to the ERG is that if a patient's tumour harbours EGFR+ and also expresses PD-L1, EGFR-TKIs tend to be preferred because they have a more favourable safety profile than immunotherapies.

Clinical advice to the ERG is that EGFR mutations and ALK mutations are usually mutually exclusive, the theory being there can only be one driver gene mutation. Therefore, no further consideration is given to patients with tumours that test positive for ALK in this ERG report.

Clinical advice to the ERG is that it typically takes 7 to 10 days to obtain EGFR test results. If a patient needs treatment before the results are available or if they test negative for EGFR, they are typically treated with platinum doublet chemotherapy (PDC).

The ERG notes that in estimating the number of patients potentially eligible for treatment, the company has assumed that 20% of patients are not tested for EGFR (CS, Table 3). However, later in the CS, the company states that UK prescribing data available from Ipsos MORI[17] show 25% of patients are not tested for EGFR. Clinical advice to the ERG is that from clinical experience, the figure is thought to be lower than either estimate, perhaps approximately 15%.

As highlighted in professional and expert clinical submissions to NICE,[18,19] there is variation between clinicians in NHS clinical practice as to which EGFR-TKI is the preferred first-line therapy. The company also reports (CS, Figure 13) that recently published data on treatment patterns for patients with EGFR+ NSCLC are scarce. Ipsos MORI data[17] show that, in the first-line setting, 84% of 148 patients with EGFR+ NSCLC received an EGFR-TKI in the first 3 months of 2018: erlotinib was the most commonly prescribed EGFR-TKI (43%) followed by afatinib (27%) and then by gefitinib (14%).

2.2.3 Resistance to treatment with EGFR-TKIs

The company state that the majority of patients with EGFR+ NSCLC treated with an EGFR-TKI achieve an objective tumour response (CS, p13 and p43). The company, however, notes that approximately 30% of all patients with EGFR+ NSCLC will have no objective response to first- or second-generation EGFR-TKIs and their disease will progress within 6 months of treatment being initiated (primary resistance) (CS, p13 and p43). The mechanisms underlying primary resistance are unclear (CS, p13 and p43).

In the first-line setting, the majority of patients who respond to treatment with an EGFR-TKI experience disease progression after about 9 to 12 months (acquired/secondary resistance) (CS, p13 and p43).[20-34] The company states that the T790M mutation is the main mechanism of acquired resistance to first-line EGFR-TKIs, accounting for approximately 60% of all cases[28,35-37] (CS, p26, p43 and Table 73).

2.2.4 Second-line treatment for patients with EGFR+ NSCLC

Findings from RCTs of EGFR-TKIs[20-34,38] summarised by the company (CS, Table 10) indicate that a substantial group of patients (20% to 30%) do not receive second-line therapy upon disease progression. This is often due to poor performance status (PS) or as a result of death before progression (CS, p14 and pp43-44).

The only EGFR-TKIs that are recommended by NICE as second-line treatment options are erlotinib and the third-generation EGFR-TKI, osimertinib.[39] Erlotinib is, however, only a treatment option if the patient has not previously received an EGFR-TKI. Osimertinib is recommended as second-line treatment option only for patients with tumours that test positive for the T790M mutation (T790M+ NSCLC) and who have previously received treatment with an EGFR-TKI.

In order to receive osimertinib, therefore, patients are required to be tested for T790M. The most reliable method of T790M testing is by a tissue biopsy. Plasma testing is an alternative option, particularly for patients who are not able to have a biopsy. However, plasma tests have a relatively high false-negative rate due to the low sensitivity of the circulating tumour deoxyribonucleic acid (ctDNA) plasma diagnostic. The company states the false-negative rate may be between 30% and 50%. Clinical advice to the ERG is that the company's estimate of false-negative results may be high. The ERG notes that in a clinical expert submission received by NICE, the false-negative rate is reported to be approximately 20%.[40] Therefore, taking into account the number of patients ineligible for testing, those who obtain false-negative results and those who test negative for T790M, up to 30% of all patients treated with a first-line EGFR-TKI go on to receive osimertinib. The majority of other patients who receive second-line treatment receive PDC or, as noted in an expert clinical submission, may continue on their initial EGFR-TKI despite disease progression.[19]

2.2.5 Third-line (and later) treatment for patients with EGFR+ NSCLC

The ERG notes that only a small proportion of patients receive third-line treatment, either due to poor PS or as a result of death before progression. Treatment options in the third-line and later settings for patients with EGFR+ NSCLC include chemotherapy, immunotherapy (atezolizumab or pembrolizumab) and best supportive care (BSC). Atezolizumab is only an option for patients with advanced NSCLC who have received both an EGFR-TKI and chemotherapy.[41] Pembrolizumab is only an option for patients with advanced PD-L1+ NSCLC who have received both an EGFR-TKI and chemotherapy.[39] BSC is an option for patients who have progressed after both chemotherapy and targeted treatment (CS, p45).

2.2.6 Proposed positioning of osimertinib in the treatment pathway

Osimertinib was granted marketing authorisation valid throughout the European Union for the treatment of advanced EGFR T790M+ NSCLC in December 2015.[42] Osimertinib was recommended as an option for use within the Cancer Drugs Fund (CDF) by NICE in October 2016 for patients with EGFR T790M+ NSCLC whose disease has progressed after first-line treatment with an EGFR-TKI.[43] Hence, as noted in Section 2.2.4, osimertinib is currently used as second-line treatment for patients who have previously received treatment with an EGFR-

TKI and who have advanced EGFR T970M+ NSCLC, based either on a biopsy or ctDNA plasma diagnostic test.

Osimertinib received an extension of the marketing authorisation to include the first-line treatment of adult patients with advanced EGFR+ NSCLC in June 2018.[42] Hence, in the current STA, osimertinib is now being proposed as a first-line treatment option for all patients with advanced EGFR+ NSCLC.

The company argues (CS, p14 and p44) that, since there is no way to identify which patients will survive to receive a second-line treatment and/or develop EGFR T790M+ resistance, it is important to select the first-line treatment that offers the best clinical outcomes for the highest number of patients. The company suggests that osimertinib may be most optimally used as a first-line treatment (CS, p52). As highlighted in professional and expert clinical expert submissions to NICE,[19,40] the use of osimertinib as a first-line treatment would also remove the current need for re-biopsy at disease progression to test for T790M.[44]

2.3 Number of patients potentially eligible for first-line treatment

The company estimates that approximately 1600 patients in England are likely to be diagnosed with advanced EGFR+ NSCLC of whom, 79% may be eligible for first-line treatment with an EGFR-TKI (Table 2).

Table 2 Company's estimate of the number of patients with advanced EGFR+ NSCLC eligible for first-line treatment in England

Number	Assumption	Source
55,619,400	Population of England (2017), adjusted with an annual growth factor of 0.6%	ONS
37,231	Incidence of lung cancer in the UK (0.067% back-calculated)	RCP[2]
32,950	Patients with NSCLC (88.5%)	RCP[2]
20,099	Advanced stage NSCLC (Stage IIIb or Stage IV) (61%)	RCP[2]
16,080	Tested for EGFR (80%)	Assumption
1608	With a confirmed EGFR mutation (10%)	Li et al 2013[45]
1270	Recorded as treated with an anticancer drug (79%)	Assumption

NSCLC=non-small cell lung cancer; RCP=Royal College of Physicians
Source: CS, Table 3

The ERG questions some of the assumptions employed to generate the numbers displayed in Table 2, namely:

- The incidence of lung cancer in the UK cited by the company is 37,231; this figure is stated to be taken from the RCP National Lung Cancer Audit (NLCA) Annual Report 2017;[2] the ERG observes that 37,761 cases are in fact cited in this report.[2]
- The incidence of patients with advanced stage NSCLC (61%) is lower than the previously cited 70% in the CS (p13 – see also Section 2.1 of this ERG report), despite both data sources being reported to be the same (RCP NLCA Annual Report 2017);[2] the proportion in Table 2 is also lower than that reported by Cancer Research UK (72% to 76%).[46]
- The proportion of patients who are tested for EGFR is reported to be 80%, this appears to be a low estimate (see also Section 2.2.2 of this ERG report).
- The proportion of patients classified as EGFR+ is slightly lower than previously cited in the CS (CS, p13; see also Section 2.1 of this ERG report); the company has employed a lower estimate of a range (10% to 20%) for people classified as 'whites' from a 2013 review[45] in Table 2 when it previously cited a different review which found the incidence to be 12% in England.[9]
- The assumed proportion of patients treated with an anticancer drug (79%) matches neither of the estimates cited later in the CS (p48): 62.5% from the RCP NLCA Annual Report 2017[2] and 85% from the Ipsos MORI study.[17]

The ERG, therefore, considers that the company's estimate may be low and a more realistic estimate of the number of patients diagnosed with advanced EGFR+ NSCLC in England may be nearer 2500 patients, of whom between 62.5% and 85% may be treated with an EGFR-TKI (Table 3).

Table 3 Alternative estimate of the number of patients with advanced EGFR+ NSCLC eligible for first-line treatment in England

Number	Assumption	Source
37,761	Incidence of lung cancer in England and Wales (2016)	RCP[2]
33,418	Patients with NSCLC (88.5%)[a]	RCP[2]
24,730	Advanced stage NSCLC (Stage IIIb or Stage IV) (74%)[b]	CRUK[46]
21,020	Tested for EGFR (85%)[c]	Assumption
2,522	With a confirmed EGFR mutation (12%)	Midha et al 2015[9]
Recorded as treated with an anticancer drug		
1577	Low estimate (62.5%)	RCP[2]
2144	High estimate (85,0%)	IPSOS Mori[17]

CRUK=Cancer Research UK; EGFR=epidermal growth factor receptor; NSCLC=non-small cell lung cancer; RCP=Royal College of Physicians

[a] RCP Information for public reports incidence of patients with NSCLC to be 85% to 90%;[2] estimate of 88.5% used to be consistent with company

[b] Reported to be 72% to 76% by CRUK[46] and so mid-value used

[c] Estimate from clinical advice to the ERG

3 CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

A summary of the ERG's comparison of the decision problem outlined in the final scope[47] issued by NICE and that addressed within the CS is presented in Table 2 (a more complete table can also be found in Appendix 1, Section 9.1, of this ERG report). Key parameters are discussed in more detail below (Section 3.2 to Section 3.7).

Table 4 Comparison between NICE scope/reference case and company's decision problem

Parameter	Final scope issued by NICE/reference case	Decision problem addressed in CS	Company rationale	ERG comment
Intervention	Osimertinib (Tagrisso)	As per decision problem	N/A	-
Population	People with previously untreated advanced EGFR mutation-positive non-small-cell lung cancer	As per decision problem	N/A	-
Comparator(s)	Afatinib, erlotinib, and gefitinib	As per decision problem	N/A	-
Outcomes	OS, PFS, response rate, response duration, AEs, HRQOL	As per decision problem	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 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 patient access schemes for the intervention or comparator technologies will be taken into account. The use of osimertinib is conditional on the presence of EGFR mutation status. The economic modelling should include the costs associated with diagnostic testing for EGFR mutation in people with 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.	Cost-effectiveness is expressed in terms of incremental cost per quality-adjusted life year gained. The time horizon of the model is 20 years, which is sufficient for this patient population to reflect any differences in costs or outcomes between the technologies being compared. Costs have been considered from an NHS and Personal Social Services perspective	EGFR+ testing is currently performed routinely in this group of patients due to the availability of afatinib, erlotinib and gefitinib as a first-line treatment for EGFR+ NSCLC.	The company notes that EGFR testing is currently performed routinely in this group of patients due to the availability of afatinib, erlotinib and gefitinib as a first-line treatment for EGFR NSCLC and so there is no need for a sensitivity analysis without the cost of the diagnostic test

Parameter	Final scope issued by NICE/reference case	Decision problem addressed in CS	Company rationale	ERG comment
Subgroups to be considered	N/A	Presence vs absence of CNS metastases at baseline Asian vs non-Asian patients Exon 19 deletions vs L858R point mutations	These subgroups represent pre-specified analyses of clinical relevance in the pivotal FLAURA trial	Other subgroups were also pre-specified in the FLAURA trial. However, these are 3 subgroups with characteristics that may have an impact on prognosis. Furthermore, osimertinib has been designed to increase CNS penetration and activity through improved permeability across the intact blood-brain barrier

AEs=adverse events; CNS=central nervous system; EGFR+= epidermal growth factor receptor-positive; HRQoL=health-related quality of life; N/A=not applicable; NSCLC=non-small cell lung cancer; OS=overall survival; PFS=progression-free survival
Source: CS, Information drawn from final scope[47] issued by NICE, CS (Table 1) and ERG comment

3.1 Intervention

The intervention is osimertinib (TAGRISSO™, AstraZeneca) as per the final scope[47] issued by NICE. As explained in the CS (p15), osimertinib is a third generation EGFR-TKI that potently and selectively inhibits both EGFR-TKI sensitising and EGFR T790M resistance mutations while sparing wild-type (WT) EGFR, with class-leading CNS penetration. It is, therefore, structurally and pharmacologically distinct from first- and second-generation EGFR-TKIs and was specifically developed to have:

- Improved tolerability, through reduced inhibition of the WT EGFR. The company states (CS, p14 and p50) that early-generation EGFR-TKIs are associated with side effects that include skin rash and diarrhoea as a result of inhibition of WT EGFR in skin and gastrointestinal organs, respectively.
- Potent activity against T790M (CS, p15 and p50) given that T790M is the primary cause of acquired resistance with first- and second-generation TKIs[48] (see also Section 2.2.3 of this ERG report)
- CNS penetration and activity through improved permeability across the intact blood-brain barrier (BBB). [49,50]

Relevant to the current STA, osimertinib is now licensed for the first-line treatment of adult patients with advanced NSCLC with activating EGFR mutations (June 2018)[42] having been previously licensed for the treatment of adult patients with advanced EGFR T790M mutation-

positive NSCLC in December 2015.[42] Osimertinib was recommended as an option for use within the CDF by NICE, in October 2016, for patients with EGFR T790M mutation-positive NSCLC whose disease has progressed after first-line treatment with an EGFR-TKI.[43]

As described in Table 2 of the CS, osimertinib is available as 40mg or 80mg oral tablets and the recommended dose is 80mg once a day until disease progression or unacceptable toxicity. The list price for 30 tablets (40mg or 80mg tablets) is £5,770. Therefore, the company states that at list price, the total cost is approximately £120,000 per patient, based on the average treatment duration in the pivotal FLAURA trial[51] (20.8 months). However, a confidential discount has been proposed through a Patient Access Scheme (PAS).

3.2 Population

The patient population described in the final scope[47] issued by NICE and discussed in the CS is people with previously untreated advanced EGFR+ NSCLC. This matches the patient population in the marketing authorisation[42] for osimertinib that was issued by the European Medicines Agency (EMA) in June 2018. This is also the same population included in the FLAURA trial, from where the majority of the evidence for the effectiveness of osimertinib as a first-line treatment is derived.

3.3 Comparators

The comparators discussed in the CS are afatinib, erlotinib and gefitinib. These are the comparators specified in the final scope[47] issued by NICE. Afatinib, erlotinib and gefitinib are all EGFR-TKIs approved for first-line treatment of advanced EGFR+ NSCLC in the European Union and have all been recommended by NICE.[52-54] All three EGFR-TKIs are administered orally, once daily.[55-57]

In the FLAURA trial, osimertinib was compared directly with SoC, which comprised erlotinib and gefitinib (and referred to as SoC EGFR-TKI). Afatinib, which, as noted in Section 2.2.2is also commonly used in NHS clinical practice, was not included as part of SoC EGFR-TKI in this trial. The company decided an indirect comparison of osimertinib with afatinib was inappropriate (see Section 4.11 for further information). The company states (CS, p36) that, “Generally, erlotinib, gefitinib, and afatinib are considered to have similar efficacy … although afatinib is less well-tolerated”. However, the ERG notes that, in the professional submission to NICE from the British Thoracic Oncology Group (BTOG), it is stated (p4) that, “It is generally felt that gefitinib, erlotinib and afatinib increase (in that order) in efficacy as well as toxicity. Consequently afatinib may be reserved for the patients with a better performance status, and avoided in older patients and those with a poorer performance status.”[18] Clinical advice to the ERG is that afatinib is commonly used in this way but there is uncertainty as to whether it is

or is not more efficacious and toxic as this has not been conclusively demonstrated by published trial evidence.

Although not a comparator in the final scope[47] issued by NICE, or listed as a comparator in the company's decision problem, the company also refers to another second-generation EGFR-TKI, dacomitinib, (CS, p40). Dacomitinib was compared to gefitinib in the open-label ARCHER 1050 trial,[58,59] and results showed that dacomitinib demonstrated superior progression-free survival (PFS)[59] and OS.[58] However, dacomitinib is not currently used in NHS clinical practice although it is currently being considered by NICE in another STA (the comparators being afatinib, erlotinib and gefitinib) with final NICE guidance expected in August 2019.[16]

3.4 Outcomes

Clinical evidence is reported in the CS for all of the outcomes specified in the final scope[47] issued by NICE: OS, PFS, response rate (reported as type of response, objective response rate [ORR], disease control rate [DCR], time to response and duration of response [DoR]), adverse events (AEs) of treatment and HRQoL. The ERG notes that the OS data that are currently available from the FLAURA trial are still very immature (only 25% of events have occurred).

3.5 Economic analysis

As specified in the final scope[47] issued by NICE, the cost effectiveness of treatments was expressed in terms of the incremental cost per quality adjusted life year (QALY) gained. Outcomes were assessed over a 20-year time period (equivalent to a lifetime horizon) and costs were considered from an NHS perspective.

3.6 Subgroups

No subgroups were specified in the final scope[47] issued by NICE. However, the company has identified three subgroups "of potentially clinical relevance" (CS, Table 1) in its decision problem: patients with and without CNS metastases at baseline, patients of Asian and non-Asian ethnicity, and type of EGFR+ mutation (patients with and without Exon 19 deletions or L858R point mutations). These were all predefined subgroups in the FLAURA trial. As highlighted in Sections 2.1.3 and 2.1.4, these are subgroups with characteristics that may have an impact on prognosis. As further noted in Section 3.1, osimertinib has been designed to increase CNS penetration and activity through improved permeability across the intact BBB.[49,50]

3.7 Other considerations

[redacted]

Afatinib, erlotinib and gefitinib are available to NHS patients only if the treatments are made available in accordance with the agreed arrangements of their respective PASs (afatinib and erlotinib) or single payment access scheme (SPA) (gefitinib). The SPA for gefitinib is publicly available (one-off cost of £12,200 to all patients on treatment at the third treatment cycle) but details of the PAS arrangements for afatinib and erlotinib are confidential. Therefore, the company has only been able to compare the cost effectiveness of osimertinib with gefitinib using discounted prices; all other cost effectiveness comparisons have been performed using list prices only.

As noted in Section 2.2.5, atezolizumab and pembrolizumab are also third-line treatment options.[41,60] The extent to which these targeted therapies lead to improved OS for patients who also have advanced EGFR+ NSCLC and who have been previously treated with an EGFR-TKI is unclear. The company state that no OS benefit has been shown from subgroup analyses in phase III RCTs.[61,62] While the ERG concurs with the company, it should be noted that in each trial, only 85 patients had EGFR+ NSCLC.

It should be noted that pembrolizumab is only a treatment option for patients who have advanced EGFR+ NSCLC and advanced PD-L1+ NSCLC. The proportion of patients with advanced EGFR+ NSCLC that also express PD-L1 is unclear.

4 CLINICAL EFFECTIVENESS

4.1 Systematic review methods

Details of the company's process and methods used to identify and select the clinical evidence relevant to the technology being appraised are presented in Appendix D of the CS. The ERG considered whether the review was conducted in accordance with the key features as summarised in Table 5.

Table 5 ERG appraisal of systematic review methods

Review process	ERG response	Comment
Was the review question clearly defined in terms of population, interventions, comparators, outcomes and study designs?	Yes	
Were appropriate sources searched?	Yes	
Was the timespan of the searches appropriate?	Yes	
Were appropriate search terms used?	Partially	Search terms were not provided by the company but were requested by the ERG, and provided, following the clarification process. Search terms used for Embase and MEDLINE included RCT search filters. However, the company's eligibility criteria did not limit the inclusion of studies to RCTs
Were the eligibility criteria appropriate to the decision problem?	Yes	
Was study selection applied by two or more reviewers independently?	Yes	
Was data extracted by two or more reviewers independently?	Yes	
Were appropriate criteria used to assess the risk of bias and/or quality of the primary studies?	Yes	
Was the quality assessment conducted by two or more reviewers independently?	Not stated	
Were appropriate methods used for data synthesis?	Yes	The company decided an indirect comparison of osimertinib with afatinib was inappropriate (see Section 4.10 for further information) and so it was only possible to present the data from one RCT (the FLAURA trial) narratively

EGFR+ NSCLC=epidermal growth factor receptor-positive non-small cell lung cancer; ERG=Evidence Review Group; RCT=randomised controlled trial

In summary:

- A systematic literature review (SLR) was conducted to identify RCTs investigating the efficacy and safety of first-line treatments for advanced EGFR+ (Exon 19 deletions or L858R point mutations) NSCLC. The original SLR was conducted on 18 April 2017, and updated searches were run on 19 February 2018. Appropriate electronic databases, conferences, registries and webpages were searched. The electronic databases searched included Embase, MEDLINE, MEDLINE In-Process and the Cochrane Library, with no lower date limits applied to the electronic searches.

- Given the company's SLR eligibility criteria did not limit search terms to only RCTs, the inclusion of RCT search filters for Embase and MEDLINE means that not all relevant studies would have been identified (See Table 6 for eligibility criteria employed by the company).
- Hand searching of the American Society of Clinical Oncology (ASCO), European Lung Cancer Conference (ELCC), European Society for Medical Oncology (ESMO) and World Conference on Lung Cancer (WCLC) conference websites was also conducted and searches were limited to between 2015 and 2017. The ERG notes this is a common strategy for searching conference websites as older presentations are likely to have since been published.
- Ongoing trials were identified by searching trial registries, namely: ClinicalTrials.gov, the European Union Clinical Trial Register (EU CTR) and the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP).
- In addition, the following websites were searched: NICE, Canadian Agency for Drugs and Technologies in Health (CADTH), Common Drug Review (CDR), Scottish Medicines Consortium (SMC), All Wales Medicines Strategy Group (AWMSG) and US Food and Drug administration (FDA).
- The eligibility criteria detailed in Appendix D to the CS (Table 99) were appropriate for the decision problem.
- The company examined the feasibility of conducting an indirect comparison but concluded that an indirect comparison of osimertinib with afatinib was inappropriate (see Section 4.10 for further information). Hence the company only presented the data from one RCT (the FLAURA trial) narratively.

Overall, the ERG considers the methods used to conduct the company's systematic review of clinical effectiveness evidence to be satisfactory for identifying relevant RCT evidence.

In addition, the ERG has run its own searches and is confident that the company did not miss any relevant publications of RCTs. However, the ERG also limited its searches of clinical effectiveness evidence to RCTs by also employing an RCT search filter. Therefore, it is unknown if any observational studies of EGFR-TKIs have been missed. However, in relation to osimertinib, the company would be aware of any relevant studies of osimertinib that should have been included.

As described in Section 4.11, the ERG, the ERG considered a simple indirect comparison of osimertinib with afatinib could be conducted, although the ERG highlighted the results should be treated with caution.

Table 6 Eligibility criteria used for the company's systematic literature review

Clinical effectiveness	Inclusion criteria	Exclusion criteria
Population	• Adults (≥18 years) with advanced and/or metastatic NSCLC • Previously untreated/treatment naïve (prior adjuvant/neo-adjuvant therapy is permitted) • Patients with EGFR-TKI sensitive mutation	• Healthy volunteers • Paediatric population • Disease other than advanced and/or metastatic NSCLC • Previously treated patients • Patients treated with EGFR-TKI where EGFR mutation status is negative/wild type
Intervention	• Osimertinib • EGFR-TKIs (Imatinib, gefitinib, erlotinib, dacomitinib, afatinib, dasatinib, sunitinib, ASP8273) • The current scope of review was limited to the above EGFR-TKI monotherapies. EGFR-TKIs EGFR-TKIs approved in the first-line treatment setting were included in the review.	• Non-drug treatments (e.g. surgery, radiotherapy) • Studies assessing interventions – not in the list • Adjuvant and neo-adjuvant setting • Chemo-radiotherapy (chemotherapy + radiotherapy) • Combination therapies (e.g. EGFR-TKI + chemotherapy)
Comparators	• Placebo • Best supportive care • Any treatment from the above list • Any other pharmacological treatment • Studies evaluating combination with chemotherapy were included only if they had one EGFR-TKI monotherapy group of interest.	• Non-pharmacological treatments
Outcomes	• Efficacy • Safety • Quality of life	• Pharmacokinetics
Study design	• RCTs • Non-RCTs including observational studies (comparative) • Systematic reviews and meta-analysis[a]	• Case reports, case series • Pharmacokinetic and economic studies • Preclinical studies • Reviews, letters, and comment articles • Single arm studies • Studies assessing fewer than 10 patients
Language restrictions	• English language	• Non-English language
Publication timeframe	• Original SLR: No limit (run on 18 April 2017) • Updated SLR: 01 March 2017 onwards (MEDLINE and Embase) and 2017 onwards (Cochrane library) (run on 19 February 2018)	

EGFR=epidermal growth factor receptor; EGFR-TKI= epidermal growth factor receptor tyrosine kinase inhibitor; NSCLC=non-small cell lung cancer; RCT=randomised controlled trial

[a] Bibliographies of relevant systematic reviews were screened to check if literature searches missed any potentially relevant studies.

Source: CS, Appendix D.1.1 (Table 99)

4.2 Identified trials

It is stated in Appendix D to the CS that 37 RCTs were included in the company's SLR. However, only one RCT included osimertinib as an intervention or comparator, the FLAURA trial. No comparative observational studies were included in the SLR.

4.3 Characteristics of the FLAURA trial

4.3.1 Trial characteristics

The FLAURA trial is an ongoing international, double-blind, randomised, Phase III, multi-centre trial of osimertinib versus SoC EGFR-TKI (eribulin or gefitinib) in patients with advanced EGFR+ NSCLC. To be included, adult, treatment-naïve, patients had to have a histology of adenocarcinoma (solely or as the predominant histology). Patients also had to have one of the most common EGFR mutations known to be associated with EGFR-TKI sensitivity (Exon 19 deletions or L858R point mutations) either alone or in combination with other EGFR mutations as confirmed by a local or a central test. Patients had to have World Health Organization (WHO) Performance Status (PS) of 0 to 1 and a minimum life expectancy of 12 weeks.

The company highlights (CS, p55) that, "Notably, patients with CNS metastases were eligible to enrol." Exclusion criteria included spinal cord compression, symptomatic and unstable brain metastases, except for patients who had completed definitive therapy, were not on steroids or who had a stable neurologic status for at least 2 weeks after completion of the definitive therapy and steroids (CS, Table 12). The ERG notes these exclusion criteria appear to be similar to exclusion criteria employed in other trials of EGFR-TKIs.[22,24-29,31,33]

A total of 556 patients were enrolled in the FLAURA trial between December 2014 and March 2016 and randomly assigned (1:1) to receive osimertinib (n=279) or SoC EGFR-TKI (n=277). All study sites were required to select either erlotinib or gefitinib as the sole comparator before site initiation, except in the US, where all sites used erlotinib. Randomisation was stratified according to EGFR status (Exon 19 deletions or L858R point mutations) and ethnicity (Asian or non-Asian). In total, patients were recruited from 132 study centres across 29 countries, including four UK centres (which recruited 11 patients in total).

As described in the CS (p58), osimertinib was administered orally at a dose of 80mg once daily. In the SoC EGFR-TKI arm, erlotinib or gefitinib were administered orally once daily at doses of 150mg or 250mg respectively. In both arms, patients continued on their randomised treatment until disease progression or until a treatment discontinuation criterion was met. There was no maximum duration of treatment, and patients could continue to receive their

randomised treatment beyond disease progression. Dose reductions were permitted for patients treated with osimertinib (to 40mg) and erlotinib (to 100mg). Dose interruptions were also permitted for patients treated with osimertinib, erlotinib or gefitinib. Treatment beyond progression and dose reductions or interruptions occurred at the investigator's discretion; treatment beyond progression if a continuation of clinical benefit was expected, dose reductions or interruptions if a patient experienced a Grade ≥3 AE and/or unacceptable toxicity.

After investigator-assessed objective disease progression based on response evaluation criteria in solid tumours (RECIST) v1.1, patients randomised to the SoC EGFR-TKI arm had the option to crossover to treatment with open-label osimertinib provided specific criteria were met (CS, p70). The criteria included the need for confirmation that a patient had EGFR T790M+ NSCLC from biological material collected after disease progression. Confirmation had to be from tissue biopsy or, in countries that approved ctDNA testing, from plasma.

The outcomes relevant to the final scope[47] issued by NICE and the decision problem addressed by the company were analysed: PFS by investigator assessment (primary outcome) and blinded independent central review (BICR), ORR, OS, AEs and HRQoL. In addition, other outcomes included time to first subsequent therapy (TFST), time to second progression by investigator assessment (PFS2), time to second subsequent therapy (TSST) and CNS PFS by BICR.

The median duration of follow-up for PFS was 15.0 months (range: 0 to 25.1) in the osimertinib arm and 9.7 months (range: 0 to 26.1) in the SoC EGFR-TKI arm. A final OS analysis will be conducted at 60% maturity, with data expected to be available in [redacted] (CS, p17).

4.3.2 Baseline characteristics of patients in the FLAURA trial

The company reports (CS, p61) that baseline characteristics were well balanced between the osimertinib and SoC EGFR-TKI arms. The ERG concurs with the company's view. As expected from a clinical trial of a population of patients with advanced EGFR+ NSCLC, the majority of patients were female (63%), had never smoked (64%) and had metastatic disease (95%) (CS, Table 15). Around one fifth of patients (21%) were considered to have CNS metastases, while most patients were classified as 'Asian' (62%) as opposed 'White' (36%) and had Exon 19 deletions (63%) as opposed to L858R point mutations (37%). The majority of patients had WHO PS 1 (restricted activity) (59%) as opposed to WHO PS 0 (normal activity) (41%) and the median age of all patients was 64 years. As is generally the case with clinical trials, the ERG observes that trial patients were fitter than patients who are commonly seen in NHS clinical practice. Results from a recent real-world analysis of data from 652 patients

treated with EGFR-TKIs in clinical practice in England showed that where PS was known, [redacted] had PS ≥2 (CS, p28).

4.4 Baseline characteristics of patients in subgroups relevant to the decision problem

4.4.1 Patients with CNS metastases

There were effectively three different subsets of patients with CNS metastases in the FLAURA trial:

- Patients with CNS metastases at baseline by investigator assessment ('programmatically derived'), a population of patients who had not necessarily received a brain scan
- The CNS full-analysis set (cFAS) population, a population of patients who had received a brain scan and had CNS metastases confirmed by an independent neuro-radiologist (i.e. CNS BICR)
- The CNS evaluable-for-response (cEFR) population, a subset of the cFAS population.

As explained by the company in their clarification response to the ERG (question A9), as per the FLAURA trial protocol, patients with asymptomatic brain metastases were not excluded from the trial. Therefore, during screening for trial entry, a brain scan could be conducted if it was part of a site's routine practice or if the patient was suspected to have brain metastases (see Section 5.1.1 of the FLAURA trial protocol). A brain scan was not mandated in the trial protocol and hence was only conducted at baseline in 200 randomised patients. Therefore, in the table of baseline characteristics, an assessment of whether a patient had CNS metastases was made by trial investigators based on 'programmatically derived' data. During a clarification telephone conference with the company and NICE, it was explained to the ERG that 'programmatically derived' data constituted data either from a scan (if a patient had had one) or from the trial case report form (e.g. an assessment of patient history).

As explained by the company in its clarification response to the ERG (question A9), all brain scans received by patients at baseline were collected and reviewed by CNS BICR. Twenty patients who were considered to have CNS metastases at baseline from 'programmatically derived' data were not considered by the CNS BICR to have CNS metastases. However, there were an additional 32 cases where brain involvement was noted by CNS BICR but not at baseline from 'programmatically derived' data. Therefore 128/556 (23.0%) patients (osimertinib: 61/279 [21.9%]; SoC EGFR-TKI: 67/277 [24.2%]) belonged to the cFAS population, and 41/556 (7.4%) patients (osimertinib: 22/279 [7.9%]; SoC EGFR-TKI: 19/277 [6.9%]) belonged to the cEFR population. A total of 72 patients who received a scan were judged to have no CNS lesions (by both the trial investigator and CNS BICR) (company response to clarification questions A10).

A summary of baseline characteristics for patients with CNS metastases according to investigator assessment from 'programmatically derived' data, the cFAS population and cEFR population was provided by the company during the clarification process (company response to clarification questions A12 to A14). Key baseline characteristics were broadly balanced between the two trial arms and in all three subsets, as well as in the 440 patients who were not classified as having CNS metastases (from 'programmatically derived' data). There were, however, some imbalances between treatment arms in terms of WHO PS in patients with CNS metastases from 'programmatically derived' data and in the cFAS population. In both populations, there were proportionately more patients with WHO PS1 in the osimertinib arm.

4.4.2 Asian versus non-Asian ethnicity

As stated in its clarification response to the ERG (question A22), the key baseline characteristics for the subgroups according to ethnicity (Asian and non-Asian) were broadly balanced across treatment arms. Between subgroups, it is noticeable that Asian patients were more likely to have a L858R point mutation (42%) than non-Asian patients (31%).

4.4.3 Type of EGFR+ mutation

As stated in its clarification response to the ERG (question A24), the key baseline characteristics for the subgroups according to type of EGFR mutation (Exon 19 deletions or L858R point mutations) were broadly balanced across treatment arms. Compared to patients with L858R point mutations, it is noticeable that in the Exon 19 deletions subgroup, there were more patients of Asian ethnicity (70% versus 58%) and with PS 0 (45% versus 39%).

4.5 Quality assessment of the FLAURA trial

The company assessed the risk of bias in the FLAURA trial using the minimum criteria set out in the 'NICE STA: User guide for company evidence submission' template,[63] adapted from the Centre for Reviews and Dissemination's guidance for undertaking reviews in health care.[64] The ERG considers that the FLAURA trial was generally well designed and well conducted and that the trial has a low risk of bias for all domains.

Table 7 Company's quality assessment of the FLAURA trial

Study question	Company assessment	ERG comment
Was randomisation carried out appropriately?	Yes	Agree
Was the concealment of treatment allocation adequate?	No	Allocation concealment appears to be adequate. It is stated in the CS (p63) that eligible patients were centrally randomised using the IVRS/IWRS system
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Agree
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	Agree
Were there any unexpected imbalances in drop-outs between groups?	No	Agree
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	Agree
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	Agree

IVRS=Interactive Voice Response System; IWRS=Interactive Web Response System
Source: company assessment taken from CS, Appendix D.1.8 (Table 109)

4.6 Statistical approach adopted for the FLAURA trial

Information relevant to the statistical approach taken by the company has been extracted from the clinical study report (CSR),[65] the trial statistical analysis plan (TSAP),[66] the trial protocol,[67] and from the CS.

A summary of checks made by the ERG to assess the statistical approach used to analyse data from the FLAURA trial is provided in Table 8.

Table 8 ERG assessment of statistical approach used to analyse data from the FLAURA trial

Review process	ERG comment
Was an appropriate sample size calculation specified in the trial protocol/TSAP?	Yes, in the protocol (pp99-100).
Were all primary and secondary outcomes presented in the CS pre-specified?	The primary outcome and key secondary outcomes were pre-specified in the protocol (pp101-108). Various other outcomes were also reported for the cFAS and cEFR populations (CS, pp87-90); these analyses were mostly pre-specified in the TSAP (pp62-70). The ERG notes that the outcomes of CNS DCR and time to CNS response were presented for both the cFAS and cEFR populations, but these outcomes were both pre-specified to be analysed for the cEFR population only (TSAP, p66).
Were definitions for all relevant outcomes provided?	Definitions for the primary outcome and key secondary outcomes were provided in the protocol (pp101-108). As part of the ERG clarification letter to the company, the ERG requested that the company provide definitions for various outcomes measured only in the cFAS and/or cEFR populations, as these definitions were not explicitly stated in the TSAP/protocol. The company provided these definitions in their response to questions A15, A19 and A21 of the ERG clarification letter.
Were all relevant outcomes defined and analysed appropriately?	The company used a hierarchical testing strategy; PFS, OS and CNS PFS were tested in this sequential order as pre-specified in the TSAP (p40). This strategy was employed to preserve the overall type 1 error rate (alpha) at 0.05. If any previous analysis in the sequence was not statistically significant, then the following outcome would not be tested for statistical significance. Since two analyses of OS were planned (interim and final), the Lan DeMets approach that approximates the O'Brien and Fleming spending function was pre-specified (TSAP, p40), in order to maintain the overall alpha at 0.05 across the two planned analyses of OS. For the interim analysis of OS presented in the CS, a p-value of less than 0.0015 was required to determine statistical significance. The ERG notes that HRs were calculated for several time-to-event outcomes presented in the CS. The company confirmed in their clarification response (question A6) that the PH assumption was assessed for the outcomes of investigator-assessed PFS, BICR-assessed PFS and OS by visually assessing cumulative hazard plots and concluded that the assumption of PH for these outcomes is reasonable. However, the ERG notes that the PH assumption was not assessed for other time-to-event outcomes presented in the CS (see text below table for more information).

Review process	ERG comment
Were all subgroup analyses and sensitivity analyses presented in the CS pre-specified?	The company performed subgroup analyses for the primary outcome, investigator-assessed PFS, for several patient characteristics that were pre-specified in the TSAP (pp46-47). The company also presented efficacy analyses for secondary outcomes for key subgroups of interest (presence versus absence of CNS metastases at baseline by investigator assessment, Exon 19 deletions versus L858R point mutations, and Asian versus non-Asian ethnicity) (CS, pp86-87, pp91-94). The ERG notes that these subgroup analyses were pre-specified in the TSAP for PFS and ORR (TSAP, pp46-50, p68), but not for OS and DCR. Various other outcomes were also reported for the cFAS and cEFR populations (CS, pp87-90); these analyses were mostly pre-specified in the TSAP (pp62-70). The ERG notes that the analyses of CNS DCR and time to CNS response on the cFAS population were not pre-specified (see ERG comment on "Were all primary and secondary outcomes presented in the CS pre-specified?"). The analysis of PFS by BICR-assessment was presented as a sensitivity analysis in the CS (pp73-75); this analysis was pre-specified in the TSAP (p45).
Were all protocol amendments carried out prior to analysis?	Protocol amendments and rationale for these amendments are provided in the CSR (CSR, pp78-89). The ERG is satisfied with the rationale for the amendments and notes that all amendments were made before the data cut-off date for the primary analysis (12 June 2017), so amendments were not driven by the results of the trial. A key change to the protocol was that the hierarchical testing strategy was updated; the company removed the testing of PFS in the subgroup of T790M+ patients and instead tested CNS PFS in the cFAS population. The reason for this change was that, initially, the company had evidence that up to 40% of TKI-naïve, EGFR+, NSCLC patients are T790M+.[68,69] However, during the conduct of the study, it became apparent to the company that this high incidence of de novo T790M+ may have been the result of a tissue preparation artefact.[70,71] Indeed, only 5 patients in the FAS population were T790M+ (based on tissue and/or ctDNA testing), and the company therefore did not perform an analysis of PFS in the T790M+ patient subgroup. Due to recent evidence of clinical activity of osimertinib in CNS,[72] CNS PFS was instead included in the multiple testing strategy.
Was a suitable approach employed for handling missing data?	The company's approach for handling missing data was pre-specified in the TSAP (TSAP, p25, pp27-31, pp33-34). The ERG considers the company's approach to be suitable.

BICR=blinded independent central review; cEFR=CNS evaluable for response set; cFAS=CNS full analysis set; CNS=central nervous system; CSR=clinical study report; ctDNA=circulating tumour DNA; DCR=disease control rate; EGFR=epidermal growth factor receptor; FAS=full analysis set; HR=hazard ratio; NSCLC=non-small cell lung cancer; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; PH=proportional hazards; TKI=tyrosine kinase inhibitor; TSAP=trial statistical analysis plan
Source: CS, CSR, trial protocol, TSAP and ERG comment

Generally, the ERG considers that the company's statistical approach for the analysis of data from the FLAURA trial was appropriate.

The analyses of CNS DCR and time to CNS response on the cFAS population were not pre-specified, and the subgroup analyses for presence versus absence of CNS metastases at baseline by investigator assessment, Exon 19 deletions versus L858R point mutations, and Asian versus non-Asian ethnicity were not pre-specified for the outcomes of OS and DCR. The reporting of analyses that were not pre-planned, without justification for why these additional analyses were performed, raises concerns about whether "data dredging" might have occurred, i.e. performing multiple statistical tests which are not based on pre-specified

study hypotheses, in the hope of finding statistically significant or favourable results. Each additional statistical test performed for a trial increases the likelihood of false positives occurring, and this ought to be considered when interpreting the results of post-hoc analyses.

Furthermore, the proportional hazards (PH) assumption was not assessed for several time-to-event outcomes for which HRs were presented in the CS, and the ERG assessed that the PH assumption may be violated for OS data from the FLAURA trial. HRs are only an appropriate measure of treatment effect if the PH assumption is valid, that is, if the event hazards associated with the intervention and comparator data are proportional over time.[73] A summary of the company's and ERG's assessments of PH for each of the outcomes for which HRs were presented in the CS is provided in Table 9.

Table 9 Summary of the company and ERG assessments of PH for time-to-event outcomes from the FLAURA trial

Outcome(s)	Company assessment of PH	Company conclusion	ERG assessment of PH	ERG conclusion
PFS by investigator assessment	Visual examination of the log-cumulative hazard plot and Cox-Snell residuals plot (CS, Figure 34 and Figure 35)	PH assumption is appropriate	Visual examination of the HH plot (Appendix 2 to this ERG report, Section 9.2, Figure 9)	PH assumption is appropriate
PFS by BICR	Visual examination of the log-cumulative hazard plot (CS, Figure 30)	PH assumption is appropriate	Visual examination of the HH plot (Appendix 2 to this ERG report, Section 9.2, Figure 10)	PH assumption is appropriate
OS	Visual examination of the log-cumulative hazard plot (CS, Figure 37 and Figure 38)	"No clear violation of PH" (CS, p125). In the company's economic base-case analysis, the company has assumed that PH holds for OS beyond 7.9 months	Visual examination of the HH plot (Appendix 2 to this ERG report, Section 9.2, Figure 11)	PH assumption may be violated; reported HR should be interpreted with caution. It is unknown whether the reported HR would overestimate or underestimate treatment effect
• TFST • PFS2 • TSST • CNS PFS (by BICR)	None	N/A	None (outcomes not listed in the final scope issued by NICE)	It is unknown whether the PH assumption, and consequently the reported HR, is valid for each of these outcomes

BICR=blinded independent central review; CNS=central nervous system; HR=hazard ratio; HH plot=a plot to show the relationship between the cumulative hazard for each trial event at common time points in the two trial arms; N/A=not applicable; OS=overall survival; PFS=progression-free survival; PFS2=time to second progression; PH=proportional hazards; TFST=time to first subsequent therapy; TSST=time to second subsequent therapy

4.7 Efficacy results from the FLAURA trial (all included patients)

The data cut-off date for all results presented in Section 4.6 is 12 June 2017, the date of the primary PFS analysis.

4.7.1 Primary outcome: progression-free survival

The primary outcome of the FLAURA trial was investigator-assessed PFS. At the time of data cut-off (61.5% maturity for PFS overall), 136 patients (49%) in the osimertinib arm and 206 (74%) patients in the SoC EGFR-TKI arm had experienced a PFS event. Patients in the osimertinib arm were shown to have experienced statistically significantly longer PFS in comparison to patients in the SoC EGFR-TKI arm (HR=0.46, 95% confidence interval [CI]: 0.37 to 0.57; p<0.001). Median PFS was 18.9 months (95% CI: 15.2 to 21.4) and 10.2 months (95% CI: 9.6 to 11.1) in the osimertinib and SoC EGFR-TKI arms, respectively.

PFS assessed by BICR was analysed as a sensitivity analysis for the primary outcome. The results from this analysis are consistent with the results for investigator-assessed PFS and are shown in Table 10.

Table 10 Summary of PFS data from the FLAURA trial (FAS)

	Investigator-assessed PFS		BICR-assessed PFS	
	Osimertinib (N=279)	SoC EGFR-TKI (N=277)	Osimertinib (N=279)	SoC EGFR-TKI (N=277)
Median PFS, months (95% CI)	18.9 (15.2 to 21.4)	10.2 (9.6 to 11.1)	17.7 (15.1 to 21.4)	9.7 (8.5 to 11.0)
HR (95% CI); 2-sided p-value	0.46 (0.37 to 0.57); p<0.0001		0.45 (0.36 to 0.57); p<0.0001	
Median follow-up for PFS in all patients, months	15.0	9.7	13.8	9.0
Median follow-up for PFS in censored patients, months	17.9	16.6	17.8	15.2

BICR=blinded independent central review; CI=confidence interval; EGFR-TKI=epidermal growth factor receptor tyrosine kinase inhibitor; FAS=full analysis set; HR=hazard ratio; PFS=progression-free survival; SoC=standard of care
Source: CS, Table 20

The company presents Kaplan-Meier (K-M) data for investigator-assessed PFS and BICR-assessed PFS in Figure 18 and Figure 19 of the CS, respectively.

Subgroup analyses for PFS

The company performed subgroup analyses for investigator-assessed PFS for several pre-specified characteristics. The company provides the results of these subgroup analyses in Figure 20 of the CS. Treatment with osimertinib was favoured over treatment with Soc EGFR-TKI for all pre-specified subgroups, including subgroups defined according to EGFR mutation type (Exon 19 deletions versus L858R point mutations), the presence or absence of CNS metastases at trial entry, and ethnicity (Asian versus non-Asian). As highlighted in Section 3.6 of this ERG report, these three subgroups were included as subgroups “of potentially clinical relevance” in the decision problem addressed by the company. The results from these three subgroup analyses alongside ERG consideration of these results are presented in Sections 4.8.1 to 4.8.3 of this ERG report.

4.7.2 CNS progression in the whole trial population

The company presents the numbers of patients experiencing CNS progression events (by investigator assessment) in the full analysis set (FAS), i.e. all patients in the FLAURA trial, irrespective of CNS metastases status at trial entry; [redacted] patients in the osimertinib arm and [redacted] patients in the SoC EGFR-TKI arm experienced CNS progression. However, the company also highlights that some cases of asymptomatic progression may not have been detected, because only patients with brain metastases at baseline were required to have regular brain scans (CS, p76) (see also Section 4.4.1).

4.7.3 Secondary outcomes: tumour response

For all results presented in Section 4.7.3, tumour response was assessed by the investigator. Investigator-assessed ORR in the FAS population was 80% (95% CI: 75% to 85%) in the osimertinib arm and 76% (95% CI: 70% to 81%) in the SoC EGFR-TKI arm. The corresponding odds ratio (OR=1.27; 95% CI: 0.85 to 1.90) suggests that there was no statistically significant difference between the osimertinib and SoC EGFR-TKI arms in terms of investigator-assessed ORR. However, the DCR in the FAS population was improved with osimertinib (97%; 95% CI: 94% to 99%) versus SoC EGFR-TKI (92%; 95% CI: 89 to 95); a statistically significant odds ratio (OR) was observed for this outcome (OR=2.78, 95% CI: 1.25 to 6.78; p=0.01).

In the population of patients who had a response to trial treatment, median duration of response was improved with osimertinib (17.2 months; 95% CI: 13.8 months to 22.0 months) in comparison to SoC EGFR-TKI (8.5 months; 95% CI: 7.3 months to 9.8 months). This difference is described by the company as being clinically meaningful. Indeed, the ERG notes that there is no overlap of the CIs for median duration of response in the osimertinib and SoC EGFR-TKI arm. In this same population, results for time to response were similar between treatment arms, with the median time to response being 6.1 weeks in both arms (approximately the time of the first scan).

4.7.4 Secondary outcomes: overall survival

At the time of data cut-off, 58 patients (21%) had died in the osimertinib arm and 83 patients (30%) had died in the SoC EGFR-TKI arm. Therefore, OS data were immature (25% overall), and median OS could not be calculated for either treatment arm. The ERG notes this analysis of OS was pre-specified to be an interim analysis, and that the final analysis will be conducted at 60% data maturity, with data expected in [redacted].

A summary of the percentages of patients alive at various time-points is provided in Table 11. The results show that each point in time the proportion of patients alive is numerically greater in the osimertinib arm than the SoC EGFR-TKI arm.

Table 11 Percentages of patients alive at various time-points in the FLAURA trial (FAS)

		Osimertinib (N=279)	SoC EGFR-TKI (N=277)
Percentage of patients alive, % (95% CI), at:	6 months	98 (96 to 99)	93 (90 to 96)
	12 months	89 (85 to 92)	82 (77 to 86)
	18 months	83 (78 to 87)	71 (65 to 76)

CI=confidence interval; EGFR-TKI=epidermal growth factor receptor tyrosine kinase inhibitor; FAS=full analysis set; SoC=standard of care
Source: information drawn from CS, Table 21

The reported HR for osimertinib versus SoC EGFR-TKI was 0.63 (95% CI: 0.45 to 0.88; p=0.007). Due to the hierarchical statistical testing strategy employed in the FLAURA trial (see Section 4.6 of this ERG report), a p-value of less than 0.0015 was required to achieve statistical significance at the time of this interim analysis. Therefore, it was not possible to conclude that osimertinib statistically significantly improves OS in comparison to Soc EGFR-TKI as the p-value was greater than 0.0015. Furthermore, the ERG considers that the PH assumption may be violated for OS, and therefore, the reported HR ought to be interpreted with caution.

Since median OS (i.e. the 50% percentile of OS) could not be calculated, the company presents (CS, p80) the 25th percentile of OS as a "conservative estimate of the survival gain in the mature population". The 25th percentile of OS was observed at approximately 22.5 months in the osimertinib arm, and at approximately 15.9 months in the SoC EGFR-TKI arm, corresponding to a survival gain of 6.6 months. The ERG considers that it is difficult to predict whether the OS benefit observed at the time of an early interim analysis will be maintained in the longer-term, therefore, it is unknown whether this estimate is truly conservative.

The ERG highlights that if OS is shown to be improved with osimertinib versus SoC EGFR-TKI, this will be a particularly important finding. To date, no trial comparing EGFR-TKIs with one another in the first-line setting has demonstrated an OS benefit,[26,38] nor has an EGFR-TKI been shown to result in superior OS versus PDC.[20-25,27-30,33,34] A pooled analysis of LUX-Lung 3 and LUX-Lung 6 trial data[32] has however shown an OS benefit in the subgroup of patients with Exon 19 deletions for afatinib versus PDC (cisplatin plus pemetrexed in the LUX-Lung 3 trial and cisplatin plus gemcitabine in the LUX-Lung 6 trial).

Crossover

At the time of the data cut-off, 62 patients had received osimertinib as a subsequent therapy, including 55 patients in the SoC EGFR-TKI arm who received osimertinib as second-line therapy and 48 patients who received osimertinib after crossover. Patients met the criteria for study crossover if they had confirmed disease progression, had not received subsequent therapy after discontinuation of their randomised treatment, and had a confirmed T790M+

tumour upon progression. The ERG considers that the proportion of patients who crossed over from the SoC EGFR-TKI arm was relatively low (48 [17.3%]).

The company concludes that the use of osimertinib in eligible patients crossing over from the SoC EGFR-TKI arm is not expected to significantly compromise the OS data (CS, p78). Since osimertinib has already been recommended by NICE as an option for patients with advanced EGFR T790M+ NSCLC after first-line treatment with an EGFR-TKI, the ERG considers that patient crossover in the FLAURA trial is not an issue of concern, since EGFR T790M+ patients would be likely to receive osimertinib as a second-line treatment in clinical practice.

First subsequent therapy

The ERG notes that the first subsequent therapies/second-line treatments differed between the treatment arms (Table 12). This finding is not unexpected as patients were permitted to crossover from the SoC EGFR-TKI arm to receive osimertinib. Generally, it is evident that patients in the osimertinib arm were most likely to receive PDC whereas patients in the SoC EGFR-TKI arm were more likely to receive a subsequent EGFR-TKI, usually osimertinib. Noticeably, a third of patients in each arm also received subsequent afatinib, erlotinib or gefitinib. As noted in Section 2.2.4 of this ERG report, sequential use of EGFR-TKIs (other than osimertinib following afatinib, erlotinib or gefitinib) is not permitted in NHS clinical practice.

Table 12 Second-line treatment received in the FLAURA trial, as a proportion of patients who received a first subsequent therapy

Type of first subsequent therapy	Osimertinib (N=82)	SoC EGFR-TKI (N=129)
Osimertinib	0	55 (43%)
Afatinib, erlotinib or gefitinib	26 (32%)	40 (31%)
PDC	36 (44%)	21 (16%)
Bevacizumab + carboplatin + pemetrexed	4 (5%)	1 (1%)
Other	16 (20%)	12 (9%)

EGFR-TKI=epidermal growth factor receptor tyrosine kinase inhibitor; PDC=platinum doublet chemotherapy; SoC=standard of care
Source: information drawn from CS, Table 18

All subsequent therapy

While there were imbalances between treatment arms regarding the first subsequent therapy received, the type of all subsequent therapy received appears to be reasonably well balanced, with the expected exception of subsequent osimertinib (CS, Table 17). In total, two (0.7%) patients in the osimertinib arm received subsequent osimertinib and 62 (22%) in the SoC EGFR-TKI arm received subsequent osimertinib. There were, however, still notable deviations from expected NHS clinical practice in terms of the types of treatment received, notably

sequential use of EGFR-TKIs, use of bevacizumab and other treatments not recommended by NICE.

4.7.5 Secondary outcomes: post-progression endpoints

The results of the analyses of post-progression endpoints, TFST, PFS2 by investigator assessment and TSST are provided in Table 13.

Table 13 Results of the analyses of post-progression outcomes (FAS)

Outcome		Osimertinib (N=279)	SoC EGFR-TKI (N=277)
TFST	Median, months (95% CI)	[redacted]	[redacted]
	HR (95% CI); p-value	[redacted]	
PFS2 by investigator assessment	Median, months (95% CI)	[redacted]	[redacted]
	HR (95% CI); p-value	[redacted]	
TSST	Median, months (95% CI)	[redacted]	[redacted]
	HR (95% CI); p-value	[redacted]	

CI=confidence interval; EGFR-TKI=epidermal growth factor receptor tyrosine kinase inhibitor; FAS=full analysis set; HR=hazard ratio; NC=not calculable; PFS2=time to second progression; SoC=standard of care; TFST=time to first subsequent therapy; TSST=time to second subsequent therapy
Source: information drawn from CS, p77 and CSR, Table 30

For each of these post-progression endpoints, the reported HRs suggest that treatment with osimertinib was statistically significantly more effective than treatment with Soc EGFR-TKI. The company states in the CS (p18) that the results for these post-progression endpoints demonstrate that the PFS advantage of osimertinib is largely preserved beyond initial progression and provide reassurance that a clinically meaningful benefit in OS will be observed in the fully mature dataset. The ERG notes that the company did not perform any assessment of the PH assumption for these outcomes (clarification question A6). HRs are not an appropriate summary of treatment effect when the PH assumption does not hold, it is therefore unknown whether the presented HRs are valid.

It should also be noted that patients could be treated beyond progression in both arms of the trial if the trial investigator considered patients were still receiving benefit from the treatment. As reported in the published paper for the FLAURA trial, this occurred in approximately two thirds of all patients (67% in the osimertinib arm and 70% in the SoC EGFR-TKI arm). Treatment beyond progression may have impacted upon all three post-progression endpoints by helping to prolong results for each of these outcomes. Nonetheless, if this is the case, it does still suggest that treatment beyond progression with osimertinib is more efficacious than treatment beyond progression with SoC EGFR-TKI.

4.8 Efficacy results from the FLAURA trial (subgroups relevant to the decision problem addressed by the company)

In interpreting the results from the subgroup analyses, the comparability of the patient characteristics at baseline should be considered (see Section 4.4 of this ERG report). In summary:

- For patients with CNS metastases, generally baseline characteristics appeared well balanced across the subgroups (CNS metastases at baseline by investigator assessment ['programmatically derived'], cFAS and cEFR populations).
- Asian patients were more likely to have a L858R point mutation than non-Asian patients.
- Patients with an L858R point mutation were more likely to be Asian and have PS0 than be non-Asian or have PS1.

4.8.1 Subgroup analyses: CNS metastases

As highlighted in Section 3.1 of this ERG report, osimertinib has been developed to in order to result in CNS penetration and activity through improved permeability across the intact BBB. Subgroups of CNS are therefore of particular clinical relevance. The ERG is only aware of one previous trial that included a subgroup analysis of brain metastases, the LUX-Lung 7 trial.[26] In that trial, no statistically significant differences were reported between patients treated with afatinib or gefitinib for PFS[26] or OS.[38]

CNS metastases at baseline by investigator assessment ('programmatically derived')

The company presents a summary of key efficacy outcomes according to the presence or absence of CNS metastases at baseline according to investigator assessment (CS, Table 23, replicated in this ERG report in Table 14).

Table 14 Key efficacy outcomes by presence or absence of CNS metastases at baseline (investigator assessment, FAS)

	CNS metastasis		No CNS metastasis	
	Osimertinib (N=53)	SoC EGFR-TKI (N=63)	Osimertinib (N=226)	SoC EGFR-TKI (N=214)
PFS				
No. of patients with PFS event, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
HR (95% CI); p-value		[redacted]		[redacted]
OS				
No. of patients who died, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
HR (95% CI); p-value		[redacted]		[redacted]
ORR				
No. of patients with objective response, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
OR (95% CI); p-value		[redacted]		[redacted]
DCR				
No. of patients with disease control, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
OR (95% CI); p-value		[redacted]		[redacted]

CI=confidence interval; CNS=central nervous system; DCR=disease control rate; EGFR-TKI=epidermal growth factor receptor tyrosine kinase inhibitor; FAS=full analysis set; HR=hazard ratio; OR=odds ratio; ORR-objective response rate; OS=overall survival; PFS=progression-free survival; SoC=standard of care
Source: CS, Table 23

Median PFS values were presented according to the presence or absence of CNS metastases at baseline in the European Public Assessment Report (EPAR) (EPAR, Table 27).[42] Median PFS in the group of patients with CNS metastases at baseline was 15.2 months (95% CI: 12.1 to 21.4) in the osimertinib arm, and 9.6 months (95% CI: 7.0 to 12.4) in the SoC EGFR-TKI arm. Median PFS in the group of patients without CNS metastases at baseline was 19.1 months (95% CI: 15.2 to 23.5) in the osimertinib arm, and 10.9 months (95% CI: 9.6 to 12.3) in the SoC EGFR-TKI arm.

cFAS and cEFR populations

The company reported various outcomes for the cFAS population, which consisted of patients who had a baseline CNS scan available for assessment by CNS BICR, and who had at least one measurable or non-measurable CNS lesion (N=128). The company also reported various outcomes for the cEFR population, which consisted of patients from the cFAS population who had at least one measurable CNS lesion (N=41). Definitions for the outcomes of CNS PFS, CNS ORR and CNS DCR are provided in Appendix 3 (Section 9.3).

The company states in its clarification response to the ERG (question A9) that, “Only patients in whom the investigator identified a non-target lesion [i.e. CNS lesion] at baseline were required to continue receiving brain scans alongside the required disease assessment.” The ERG is confused by this statement as it implies that the 32 patients included in the cFAS population that were not considered by trial investigators to have CNS metastases were not

required to have subsequent brain scans. The ERG assumes that all patients in the cFAS population were required to have follow-up brain scans.

The company provides results for the outcome of CNS PFS by BICR assessment in the cFAS population, stating (CS, p87) that there was a "nominally statistically significant and clinically meaningful improvement in CNS PFS" for patients in the osimertinib arm in comparison to patients in the SoC EGFR-TKI arm ([redacted]). The company states that the result is "nominally statistically significant", since the analysis of CNS PFS was third in the hierarchical statistical testing strategy (see Section 4.6) and, as OS did not reach formal statistical significance, CNS PFS could not be formally tested for statistical significance.

The ERG notes that the company did not perform any assessment of the PH assumption for the outcome of CNS PFS (clarification question A6); HRs are not an appropriate summary of treatment effect when the PH assumption does not hold. Therefore, it is unknown whether the presented HR is valid, and the ERG highlights that the HR should be interpreted with caution.

Median CNS PFS was not calculable ([redacted]) in the osimertinib arm versus ([redacted]) in the SoC EGFR-TKI arm. The company provides a K-M plot for CNS PFS in the cFAS population in Figure 26 of the CS.

A breakdown of CNS progression events is provided in Table 24 of the CS, and reproduced here in Table 15.

Table 15 CNS progression events by BICR assessment in the cFAS population

Patients with progression, n (%)	Osimertinib (N=[redacted])	SoC EGFR-TKI (N=[redacted])
Total number of events (CNS progression or death)[a]	[redacted]	[redacted]
CNS progression other than death	[redacted]	[redacted]
Progression due to death	[redacted]	[redacted]
CNS progression[b]		
Progression in target CNS lesions	[redacted]	[redacted]
Progression in non-target CNS lesions	[redacted]	[redacted]
Progression due to new CNS lesions	[redacted]	[redacted]
Unknown reason for CNS progression[c]	[redacted]	[redacted]

[a] Progression events that did not occur within 2 scheduled visits (plus visit window) of the last evaluable assessment (or randomisation) were censored and therefore excluded in the number of events
[b] Target lesions, non-target lesions and new lesions were not necessarily mutually exclusive categories
[c] Patients were identified as having progression but their first lesion progression could not be determined
BICR=blinded independent central review; cFAS=CNS full analysis set; CNS=central nervous system; EGFR-TKI= epidermal growth factor receptor tyrosine kinase inhibitor; SoC=standard of care
Source: Adapted from CS, Table 24

CNS ORR was higher in the osimertinib arm than in the SoC EGFR-TKI arm in both the cFAS and cEFR populations (Table 16).

Table 16 CNS ORR, time to response in CNS lesions and CNS DCR for patients in the FLAURA trial in the cFAS and cEFR populations (responses assessed by BICR)

Response	cFAS (N=[redacted])		cEFR (N=[redacted])	
	Osimertinib (n=[redacted])	SoC EGFR-TKI (n=[redacted])	Osimertinib (n=[redacted])	SoC EGFR-TKI (n=[redacted])
CNS ORR, % (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
OR (95% CI); p-value	[redacted]		[redacted]	
Complete response, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Partial response, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Stable disease ≥6 weeks, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Median time to response in CNS lesions, weeks	[redacted]	[redacted]	[redacted]	[redacted]
CNS DCR, % (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
OR (95% CI); p-value	[redacted]		[redacted]	

BICR=blinded independent central review; cEFR=CNS evaluable for response set; cFAS=CNS full analysis set; CI=confidence interval; CNS=central nervous system; DCR=disease control rate; EGFR-TKI=epidermal growth factor receptor tyrosine kinase inhibitor; OR=odds ratio; ORR=objective response rate; SoC=standard of care
Source: Adapted from CS, Table 25

4.8.2 Subgroup analyses: Asian versus non-Asian ethnicity

The company explains that, in the pre-specified subgroup analysis of PFS, there appeared to be a numerical advantage for non-Asian patients over Asian patients (CS, p91). Since the UK population predominantly comprises people of non-Asian ethnicity, the company therefore performed subgroup analyses for other efficacy outcomes to further investigate the efficacy of osimertinib in non-Asian and Asian patient subgroups.

The company provides a K-M plot of PFS by investigator assessment in Asian and non-Asian subgroups in Figure 27 of the CS, and a summary of key efficacy outcomes (PFS, OS, ORR and DCR, all by investigator assessment) in Asian and non-Asian subgroups in Table 26 of the CS. The magnitude of PFS benefit for osimertinib versus Soc EGFR-TKI was greater in non-Asian patients than in Asian patients ([redacted], respectively). Similarly, OS benefit was greater in non-Asian patients than in Asian patients ([redacted], respectively). Interestingly, the converse result was observed for the outcomes of ORR and DCR; higher ORs were observed (indicating greater treatment benefit) in Asian patients ([redacted]) than in non-Asian patients ([redacted]).

Median PFS values were presented for Asian and non-Asian patient subgroups separately in the EPAR (EPAR, Table 27).[42] Median PFS in the Asian patient subgroup was 16.4 months (95% CI: 13.8 to 20.7) in the osimertinib arm, and 11.0 months (95% CI: 9.5 to 12.6) in the SoC EGFR-TKI arm. Median PFS in the non-Asian patient subgroup was 24.3 months (95% CI: 16.3 to NC) in the osimertinib arm, and 9.7 months (8.2 to 11.1) in the SoC EGFR-TKI arm.

4.8.3 Subgroup analyses: type of EGFR mutation

Previous studies[74,75] have indicated that EGFR-TKIs may be slightly more in efficacious in patients with Exon 19 deletions than in patients with L858R point mutations, possibly due to the higher binding affinity of TKIs for Exon 19 deletions than L858R point mutations, as well as differential inhibition of downstream signals. The company therefore performed subgroup analyses to investigate whether the efficacy of osimertinib varies according to the type of EGFR mutation.

The company provides a K-M plot of PFS by investigator assessment in Exon 19 deletions and L858R point mutations subgroups in Figure 28 of the CS, and a summary of key efficacy outcomes (PFS, OS, ORR and DCR, all by investigator assessment) in Exon 19 deletions and L858R point mutations subgroups in Table 27 of the CS. The magnitude of PFS benefit for osimertinib versus Soc EGFR-TKI was greater in patients with Exon 19 deletions than in patients with L858R point mutations ([redacted], respectively). Similarly, treatment benefit was greater in Exon 19 deletions mutation patients than in L858R point mutations patients for the outcomes of OS (Exon 19 deletions: [redacted]) and DCR ([redacted]). The converse result was observed for ORR; a higher OR was observed (indicating greater treatment benefit) in L858R point mutations patients than in Exon 19 deletions mutation patients ([redacted] respectively).

Median PFS values were presented according to EGFR mutation status in the EPAR (EPAR, Table 27).[42] Median PFS in the Exon 19 deletions mutation patient subgroup was 21.4 months (95% CI: 16.5 to 24.3) in the osimertinib arm, and 11.0 months (95% CI: 9.7 to 12.6) in the SoC EGFR-TKI arm. Median PFS in the L858R point mutations patient subgroup was 14.4 months (95% CI: 11.1 to 18.9) in the osimertinib arm, and 9.5 months (8.1 to 11.0) in the SoC EGFR-TKI arm.

4.9 Relative efficacy of EGFR-TKIs

In this Section the ERG has compared the results from the SoC EGFR-TKI arm of the FLAURA trial, to results reported for SoC EGFR-TKI treatments (i.e., erlotinib and gefitinib) in previous EGFR-TKI trials. This is in order to explore whether, based on previous trial evidence, the results in the EGFR-SoC arm in the FLAURA trial appear unusual in any way. In addition, since the company did not compare osimertinib with afatinib (either directly in the FLAURA trial, or indirectly, see also Section 4.10), the ERG has also explored whether it can be assumed whether erlotinib and gefitinib can be considered to be as equally efficacious as afatinib.

4.9.1 Comparison of previous EGFR-TKI trials to FLAURA trial

A summary of efficacy results for EGFR-TKIs across trials[22,24-31,33,51] is provided in Table 17. While all trials mostly only included patients with PS 0 to 1 and excluded patients with symptomatic and unstable brain metastases, there were notable differences in the geographic locations of trials (and, therefore, possible differences in SoC before and after treatment with an EGFR-TKI) and median ages of patients (and possibly, therefore, prognosis). Furthermore, not all patients in the CTONG 0901 trial[31] received their EGFR-TKI as a first-line treatment, although approximately two-thirds of patients did. Nonetheless, efficacy results have been broadly consistent in trials conducted to date:

- Eight trials[22,24,25,27-30,33] compared an EGFR-TKI with PDC (including cisplatin or carboplatin plus gemcitabine, docetaxel, paclitaxel or pemetrexed). All of these eight trials found the EGFR-TKIs to improve PFS and ORR,[22,24,25,27-30,33] but did not improve OS,[20,22,23,27-30,34] versus PDC. However, a pooled analysis of LUX-Lung 3 and LUX-Lung 6 trial data[32] has shown an OS benefit for afatinib versus PDC (cisplatin plus pemetrexed in the LUX-Lung 3 trial and cisplatin plus gemcitabine in the LUX-Lung 6 trial) in the subgroup of patients with Exon 19 deletions.
- Median PFS in the SoC EGFR-TKI arm of the FLAURA trial (10.2 months) was within the range of median PFS reported for EGFR-TKI treatments in all previous trials,[22,24-31,33] although only three trials[24,25,27] actually recorded a lower median PFS. Median PFS for erlotinib ranged from 9.7 to 13.1 months (4 trials)[27,30,31,33] and for gefitinib ranged from 9.2 to 10.9 months (5 trials).[22,24-26,31] Median PFS for patients treated with afatinib has consistently been found to be approximately 11 months in three trials,[26,28,29] which is reasonably similar to median PFS in the SoC EGFR-TKI arm of the FLAURA trial.
- ORR for patients in the SoC EGFR-TKI arm of the FLAURA trial (76%) was also within the range of ORRs reported for EGFR-TKI treatments in previous trials, with only one trial reporting a higher ORR:[33] ORRs for erlotinib ranged from 56% to 83% (4 trials)[27,30,31,33] and for gefitinib ranged from 52% to 74% (5 trials).[22,24-26,31] For patients treated with afatinib, ORRs ranged from 56% to 70%,[26,28,29] these rates are lower than those for patients in the SoC EGFR-TKI arm of the FLAURA trial.

Table 17 Comparison of key characteristics and efficacy results across trials of EGFR-TKIs

Trial	Trial characteristics				Patient characteristics					Trial findings		
	Location	N	Data-cuts	EGFR-TKI	Female	Age, years, median	PS ≤1	Brain mets[a]	Exon 19 deletions	PFS, median, months	ORR	OS, median, months
IPASS[20,25]	Asia	1217 EGFR+ 261	2008	Gefitinib	80%	57	90%	NR	30%	5.7 EGFR+ 9.5	43% EGFR+ 71%	18.6 EGFR+ 21.6
NEJ002[21,22]	Japan	230	2009 / 2010	Gefitinib	63%	64 (mean)	99%	NR	51%	10.8	74%	27.7
WJTOG3405[23,24]	Japan	177	2009 / 2011	Gefitinib	59%	64	100%	NR	58%	9.2	62%	36.0
OPTIMAL[33,34]	China	165	2010 / 2012	Erlotinib	59%	57	91%	Excluded	52%	13.1	83%	22.8
EURTAC[27]	Europe	174	2011	Erlotinib	67%	65	86%	10%	66%	9.7	64%	19.3
LUX-Lung 3[28,32]	Multi[b]	345	2011 / 2013	Afatinib	64%	61.5	100%	NR	49%	11.1	56%	28.2
LUX-Lung 6[29,32]	Asia	364	2011 / 2013	Afatinib	64%	58	100%	NR	51%	11.0	67%	23.1
ENSURE[30]	Asia	217	2012	Erlotinib	62%	58	94%	NR	52%	11.0	63%	26.3
LUX-Lung 7[26,38]	Multi[c]	319	2013 / 2016	Afatinib	57%	63	100%	16%	58%	11.0	70%	27.9
				Gefitinib	67%	63	100%	15%	58%	10.9	56%	24.5
CTONG 0901[31d]	Asia	128	2015	Erlotinib	53%	58.5	98%	20%	58%	13.0	56%	22.9
		128		Gefitinib	54%		97%	17%	58%	10.4	52%	20.1
FLAURA[51]	Multi[e]	279	2017	Osimertinib	64%	64	100%	19%	57%	18.9	80%	NC
		277		EGFR SoC	62%	64	100%	23%	56%	10.2	76%	NC

CNS=central nervous system; EGFR=epidermal growth factor receptor; EGFR+=EGFR mutation-positive; EGFR-TKI=EGFR-tyrosine kinase inhibitor; mets=metastases; NC=not calculable (median not reached); NR=not reported; ORR=objective response rate; OS-overall survival; PFS=progression-free survival; PS=performance status; SoC=standard of care

[a] Data reported in this column by the ERG differs to that reported by the company in Table 8 following the ERG's examination of the source papers (there were four cases where the company has stated patients with brain metastases were excluded but which in fact only patients with active/symptomatic/uncontrolled brain metastases were excluded,[24,26,29,33], i.e. similar to the exclusion criteria in the FLAURA trial); furthermore, the authors of the LUX-Lung 7 trial[26,38] conduct subgroup analyses by brain metastases

[b] Asia, Europe, North America, South America, and Australia

[c] Asia, Europe, Canada, and Australia

[d] 35.5% of patients in this trial received erlotinib or gefitinib as second-line treatment

[e] Asia, Europe, North America, and South America in the FLAURA trial

Note: Although some trials were only conducted in one country, all trials were multi-centre

Source: CS, information drawn from Table 8 with additional data extracted from source paper

Overall, the ERG is satisfied that patients included in the SoC EGFR-TKI arm of the FLAURA trial are not considerably different to patients that have been previously included in other trials of EGFR-TKIs.

4.9.2 Equivalence of efficacy from treatment with EGFR-TKIs

Only two trials compared an EGFR-TKI with another EGFR-TKI, the CTONG 0901 trial[31] and the LUX-Lung 7 trial.[26] The ERG considers that no firm conclusions can be drawn from these trials because:

- In the CTONG 0901 trial,[31] 35.5% of patients in this trial received erlotinib or gefitinib as second-line treatment. Median PFS was greater in the erlotinib arm compared with the gefitinib arm (13.0 months versus 10.4 months), but the difference was not reported to be statistically significantly different (HR=0.81, 95% CI 0.62 to 1.05, p=0.108). No statistically significant differences in ORR or OS were reported.
- The LUX-Lung 7 trial[26] was designed as an exploratory Phase IIb trial to broadly explore the differences between afatinib and gefitinib. No formal hypotheses were defined. Median PFS by blinded independent assessment was similar in both arms at two different data-cuts (11.0 months with afatinib versus 10.9 months with gefitinib, in both instances).[26,38] However, the difference between arms was reported to be statistically significantly different (at both data-cuts).[26,38] As the company highlights (CS, p36), the statistically significant HR appears to be a result of a late separation of the K-M curves after 12 months. Furthermore, results from a sensitivity analysis of PFS data, conducted at the first data-cut using a restricted mean survival time approach that did not assume PH, showed that afatinib significantly improved PFS versus gefitinib.[26] However, one of the LUX-Lung 7 trial authors has stated in published correspondence[76] that while the trial results are clinically significant, “these data are not sufficient to claim superiority of afatinib over gefitinib (LUX-Lung 7 was an exploratory, not a superiority, trial).” (page e269) No statistically significant differences in ORR or OS were reported.

Furthermore, gefitinib was recommended by NICE as a first-line treatment option for patients with advanced EGFR+ NSCLC in 2010 (TA192).[52] During the subsequent STAs of erlotinib and afatinib, the NICE Appraisal Committees (ACs) reached the following conclusions:

- In 2012, when appraising erlotinib (TA258),[77] the AC considered that there was insufficient evidence to suggest a difference in clinical effectiveness between erlotinib and gefitinib.[77]
- In 2014, when appraising afatinib (TA310),[53] the AC concluded that, on balance, afatinib was likely to have similar clinical efficacy to erlotinib and gefitinib.[53]

Eight of the trials included in Table 17 have previously been included in a network meta-analysis (NMA) performed by Batson et al 2017.[78] The IPASS trial[25] therefore was excluded as it was not limited to patients with advanced EGFR+ NSCLC. The NMA also included a trial of erlotinib in combination with bevacizumab, which is outside the scope of the current STA. Although the NMA incorporated data from trials where the PH assumption for PFS may have

been violated, the NMA incorporated acceleration factors (AFs) rather than HRs and so the possible violation of the PH assumption is not of concern. The results from the NMA showed that all EGFR-TKIs were superior to chemotherapy in terms of PFS (the only outcome studied). However, there were no statistically significant differences in PFS between the EGFR-TKIs. The authors, however, report (p2479) a "trend in favour of erlotinib".

A further difficulty when drawing conclusions about the relative effectiveness of afatinib, erlotinib and gefitinib is that the trials are from heterogeneous populations. For example:

- The IPASS trial[25] of gefitinib included patients who had not tested positive for EGFR+ NSCLC (although results have been reported for the subgroup of patients with EGFR+ NSCLC[20]) and was conducted solely in Asia.
- Five other trials[22,24,29,30,33] included in the NMA, and also the CTONG 0901 trial[31] which was not included in the NMA (as it was published after the search date), were also conducted solely in Asia. The EURTAC trial[27] of erlotinib was conducted solely in Europe. Only two of the afatinib trials (LUX-Lung 3[28,29] and LUX-Lung 7[26]) were conducted, as per the FLAURA trial, across different continents.
- Patients with CNS metastases were reported by the company to be excluded from five trials.[24,26,29,30,33] However, the ERG considers that in four of these trials,[24,26,29,33] including the LUX-Lung 7 trial,[26] only patients with active, uncontrolled or symptomatic brain metastases were excluded, a similar exclusion criterion was used in the FLAURA trial. Notably, as per the FLAURA trial, both the LUX-Lung 7 trial[26] and the CTONG 0901 trial[31] included patients with CNS metastases (16% and 18%, respectively).
- In nine trials of patients with EGFR+ NSCLC,[22,24-26,28-31,33] 50% to 58% of patients had Exon 19 deletions. The proportion with Exon 19 deletions was higher in the EURTAC trial (66%)[27] than in the other nine trials.[22,24-26,28-31,33]

Overall, the ERG considers that PFS may be improved with afatinib versus gefitinib and notes PFS may also be improved for erlotinib versus gefitinib but considers there is insufficient evidence to draw any firm conclusions. There is no evidence to suggest that afatinib, erlotinib or gefitinib improves ORR or OS compared to another EGFR-TKI (and evidence is also lacking to show superior OS versus PDC).

4.10 Indirect comparison of osimertinib with afatinib

Company's indirect comparison feasibility assessment

The company's clinical SLR identified 34 RCTs, of which, in addition to the FLAURA trial, there were three head-to-head RCTs of EGFR-TKIs: the aforementioned CTONG 0901 trial,[31] the LUX-Lung 7 trial[26,38] and the ARCHER 1050 trial[59] which compared dacomitinib with gefitinib. The ARCHER 1050 trial[59] was not considered for analysis as dacomitinib is not considered to be a relevant comparator. Since analyses of FLAURA trial data were not performed separately for erlotinib and gefitinib the company highlight that it would be necessary to assume that erlotinib and gefitinib are of equivalent efficacy (CS, p95). The company considers that based

on non-statistically significant differences in the CTONG 0901 trial,[31] NMA[78] and previous AC conclusions,[53] that this assumption might not be unreasonable (CS, p95). Therefore, the CTONG 0901 trial[31] did not contribute useful data to a network of evidence since the trial reduced to a single arm when the erlotinib and gefitinib arms were assumed to be equivalent. Thus, the network of evidence considered by the company comprised the FLAURA trial and the LUX-Lung 7 trial,[26] linked under the company's assumption of equivalence for erlotinib and gefitinib. Both studies presented data for OS, investigator-assessed PFS and -assessed PFS.

The company considered the FLAURA and LUX-Lung 7 trial[26] to be comparable in terms of key patient characteristics. The ERG agrees with the company's assessment (see Table 18).

Table 18 Comparison of baseline characteristics for the FLAURA and LUX-Lung 7 trials

Demographic characteristic	FLAURA		LUX-Lung 7	
	Osimertinib (N=279)	SoC EGFR-TKI (N=277)	Afatinib (N=160)	Gefitinib (N=159)
Median age, years (range)	64.0 (26-85)	64.0 (35-93)	63 (30–86)	63 (32–89)
Female sex, n (%)	178 (64)	172 (62)	91 (57)	106 (67)
Ethnicity n (%)				
Asian	174 (62)	173 (62)	94 (59)	88 (55)
White	101 (36)	100 (36)	48 (30)	54 (34)
Other[a]	4 (1)	4 (1)	1 (1)	0
Missing[b]	0	0	17 (11)	17 (11)
Never smoker, n (%)	182 (65)	175 (63)	106 (66)	106 (67)
Performance status[c], n (%)				
0	112 (40)	116 (42)	51 (32)	47 (30)
1	167 (60)	160 (58)	109 (68)	112 (70)
Overall disease classification, n (%)[d]				
Metastatic	264 (95)	262 (95)	152 (95)	156 (98)
Locally advanced	14 (5)	15 (5)	8 (5)	3 (2)
CNS metastases[e] n (%)	53 (19)	63 (23)	26 (16)	24 (25)
Liver metastases, n (%)	41 (15)	37 (13)	16 (10)	24 (15)
EGFR mutation category[f], n (%)				
EGFR exon 21 L858R	104 (37)	103 (37)	67 (42)	66 (42)
EGFR exon 19 deletion[g]	175 (63)	174 (63)	93 (58)	93 (58)

CNS=central nervous system; ECOG=Eastern Cooperative Oncology Group; EGFR=epidermal growth factor receptor; SoC=standard of care; TKI=tyrosine kinase inhibitor; WHO=World Health Organization

[a] For the FLAURA trial, the "Other" category includes black, American Indian and Alaska Native. For the LUX-Lung 7 trial,[26] all patients in the "Other" category were black

[b] In the LUX-Lung 7 trial,[26] patients recruited in French sites did not have their ethnic origin recorded

[c] WHO performance status for the FLAURA trial (data missing for 1 patient in SoC EGFR-TKI arm) and ECOG performance status for the LUX-Lung 7 trial[26]

[d] Data missing 1 patient in osimertinib arm of FLAURA trial

[e] For the FLAURA trial, this is a programmatically derived composite endpoint with a list of contributing data sources. For the LUX-Lung 7 trial,[26] this is the number of patients reported to have brain metastases

[f] For the FLAURA trial, EGFR mutations are based on the test (local or central) used to determine randomisation strata (Exon 19 deletion or L858R)

[g] For the LUX-Lung 7 trial,[26] one patient in the afatinib group with wild-type EGFR was erroneously included in the trial and was reported as exon 19 deletion at the time of randomisation by the investigator

Source: FLAURA trial and LUX-Lung 7 trial[26]

However, the company decided not to perform an indirect comparison for two reasons:

- The validity of the results of an indirect comparison based on HRs relies on the assumption that hazards are proportional in each of the trials for each outcome. The company assessed the PH assumption for OS, investigator-assessed PFS and BICR-assessed PFS from each trial. The company concluded that it is likely that the PH assumption holds for all relevant outcomes from the FLAURA trial. However, it is unclear if the PH assumption holds for any of the relevant outcomes from the LUX-Lung 7 trial[26] since the two log cumulative hazard curves for afatinib and gefitinib are very similar and lie one on top of the other (CS, Figure 30).
- The available evidence from the CTONG 0901 trial[31] and NMA[78] in addition to previous AC conclusions,[53] suggests that assuming equivalence of efficacy of afatinib, erlotinib and gefitinib is reasonable.

In relation to the company's reasons for not performing an indirect comparison, the ERG considers:

- As previously discussed in Section 4.6, for the FLAURA trial, while the PH assumption is reasonable for both investigator-assessed and BICR-assessed PFS, the PH assumption may be violated for OS. The ERG also assessed the PH assumption for investigator-assessed PFS, BICR-assessed PFS and OS data from the LUX-Lung 7 trial[26] and concluded that the PH assumption may be violated for each of these outcomes (see Appendix 2, Section 9.2).
- As previously discussed in Section 4.9.2, there is insufficient evidence to draw any firm conclusions regarding the equivalence of PFS of afatinib, erlotinib and gefitinib.

4.11 Simple indirect comparison conducted by the ERG

Given the uncertainty regarding the validity of the PH assumption, given the absence of any estimates of efficacy for osimertinib versus afatinib, and given the uncertainty amongst clinicians as to whether afatinib is superior to erlotinib or gefitinib (see Section 3.3), the ERG decided to conduct a simple indirect comparison. Incorporating HRs from the FLAURA and LUX-Lung 7 trial,[26] the ERG used the Bucher method[79] to perform the indirect comparison, which allows the comparison of two interventions from two separate RCTs through a common comparator. The data inputs for, and the results of the indirect comparison are provided in Table 19.

The ERG is aware that alternative measures of treatment effect measures that do not rely on the PH assumption are available (for example, the AF and restricted mean survival time). Given the uncertainty regarding the validity of PH, alternative methods to the Bucher method[79] may therefore have been preferred. However, methods for performing a simple indirect comparison (i.e., an indirect comparison where two treatments are linked by a single common comparator) using these alternative effect measures are not well-established.

Table 19 ERG indirect comparison: data inputs and results

Outcome	Data inputs		Results
	Osimertinib vs SoC EGFR-TKI	Afatinib vs gefitinib	Osimertinib vs afatinib
PFS by investigator assessment, HR (95% CI)	0.46 (0.37 to 0.57)	0.78 (0.61 to 0.99)	0.59 (0.43 to 0.82)
PFS by BICR, HR (95% CI)	0.45 (0.36 to 0.57)	0.73 (0.57 to 0.95)	0.62 (0.44 to 0.87)
OS, HR (95% CI)	0.63 (0.45 to 0.88)	0.86 (0.66 to 1.12)	0.73 (0.48 to 1.12)

BICR=blinded independent central review; CI=confidence interval; EGFR-TKI=epidermal growth factor receptor tyrosine kinase inhibitor; HR=hazard ratio; OS=overall survival; PFS=progression-free survival; SoC=standard of care

The results of the ERG's indirect comparison suggest that osimertinib statistically significantly improves PFS (by both investigator assessment and BICR) in comparison to afatinib, but that there is no statistically significant difference between osimertinib and afatinib in terms of OS. The ERG highlights that the results of this indirect comparison ought to be interpreted with caution, due to the possible violation of the PH assumption for data for both PFS outcomes from the LUX-Lung 7 trial,[26] and for OS data from both the FLAURA trial and the LUX-Lung 7 trial.[26]

4.12 Safety

4.12.1 Exposure to study drug in the FLAURA trial

Median total duration of exposure to treatment in the FLAURA trial was 16.2 months for the osimertinib arm and 11.5 months for the SoC EGFR-TKI arm, and the median actual duration of exposure (excluding dose interruptions) was 16.1 months for the osimertinib arm and 11.5 months for the SoC EGFR-TKI arm (CS, p99).

4.12.2 Safety profile in the FLAURA trial

The company presents a summary of all AEs occurring in ≥10% of the patients in either treatment arm in the FLAURA trial in Table 28 of the CS. The vast majority of patients in both arms of the trial reported at least one any-grade AE due to any cause (98% in each treatment arm). The frequencies of all AEs were generally similar between arms. The most common any Grade AEs associated experienced by patients in the osimertinib and the SoC EGFR-TKI arms of the FLAURA trial were rash or acne (58% versus 78%), diarrhoea (58% versus 57%), dry skin (36% in each treatment arm), paronychia (nail bed infection) (35% versus 33%), stomatitis (29% versus 20%), decreased appetite (20% versus 19%), pruritus (17% versus 16%), cough (16% versus 15%), constipation (15% versus 13%), nausea (14% versus 19%), fatigue (14% versus 12%) and dyspnea (13% versus 7%).

Disease progression was reported to be the most common reason for treatment discontinuation (31.2% versus 54.5%), followed by AEs (12.9% versus 18.1%). Osimertinib was associated with a lower rate of AEs leading to permanent treatment discontinuation compared to the SoC EGFR-TKI arm (13% versus 18%). AEs leading to dose reductions and dose interruptions were generally similar in the two treatment arms. The most frequently reported AEs leading to dose interruption in the osimertinib arm were QT prolongation, decreased appetite, diarrhoea, and pneumonia, whereas in the SoC EGFR-TKI arm, dose interruptions were guided by increased alanine aminotransferase, increased aspartate aminotransferase, QT prolongation and dermatitis acneiform (CS Appendix D.1.6, Table 107).

4.12.3 Common types of severe (Grade ≥3) adverse events in the FLAURA trial

The ERG notes that despite a longer treatment duration with osimertinib (16.2 versus 11.5 months), overall Grade ≥3 AEs were less common in the osimertinib arm compared to the SoC EGFR-TKI (34% versus 45% as reported in the published paper[51]). As reported in the EPAR for osimertinib[42] (Table 39), the frequencies of all AEs of Grade ≥3 in ≥1% of patients in the FLAURA trial were generally similar in both arms, except for increased alanine

aminotransferase (0.4% versus 9%) and dermatitis acneiform (0% versus 4.7%), both of which were more common in the SoC EGFR-TKI arm.

4.12.4 Adverse events of special interest in the FLAURA trial

Cardiac effects, diarrhoea, skin effects, upper gastrointestinal tract inflammatory events, nail effects, ocular effects, hepato-biliary, renal effects are described as AEs of special interest (AESI) in the EPAR for osimertinib.[42] Of these, diarrhoea was the most frequently reported AESI in the FLAURA trial and the incidence (of any grade) was similar in both treatment arms (58% versus 57%). Other AESI included asthenic conditions, anorexia, nausea, vomiting, pancreatitis, dry mouth, abdominal pain, pyrexia, haemorrhages and infections and infestations (Table 42).

Cardiac effects (changes in QT interval) occurred more frequently in the osimertinib arm than in the SoC EGFR-TKI arm (10% versus 5%). However, the ERG notes that the majority of these events were of Grade 1 or grade 2 and that there were no cases of torsades de pointes reported in either treatment arm.

4.12.5 Serious adverse events and deaths in the FLAURA trial

Overall, rates of SAEs (reported ≥2% of patients in either treatment arm) were slightly lower in the osimertinib arm than in the SoC EGFR-TKI arm (22% versus 25%). It is reported in the EPAR for osimertinib[42] (p119) that the most frequently reported SAEs considered to be possibly related to treatment with osimertinib were interstitial lung disease, pneumonitis, enterocolitis and pyrexia. There were no fatal events due to interstitial lung disease reported in either arm of the trial.

Death due to an AE was reported in 2% of the patients in the osimertinib arm compared with 4% of patients in the SoC EGFR-TKI arm. Primary causes of death in the osimertinib arm were pneumonia, respiratory tract infection, cerebral infarction, myocardial infarction, pulmonary embolism, and intestinal ischemia (1 patient each). Among patients in the SoC EGFR-TKI arm who died due to AEs, the primary causes of death were sepsis (2 patients); pneumonia, endocarditis, cognitive disorder and pneumonia, peripheral-artery occlusion, dyspnoea, haemoptysis, diarrhoea, gastrointestinal haemorrhage, respiratory failure, circulatory collapse and unspecified death (1 patient each).

None of the deaths in the FLAURA trial were considered to be possibly related to osimertinib, whereas one death due to an AE (diarrhoea) in the SoC EGFR-TKI arm was considered to be possibly related to treatment.

4.12.6 Adverse events from the LUX-Lung 7 trial

Results from the LUX-Lung 7 trial, the only trial that compares one of the EGFR-TKIs in the FLAURA trial SoC EGFR-TKI arm (gefitinib) with afatinib, suggest that AEs were manageable and treatment-related discontinuations were low in both the afatinib and gefitinib arms (6% in both arms). AEs reported by more than half of all patients in either arm were diarrhoea (78% versus 60%), rash or acne (79% versus 78%) and stomatitis (60% versus 24%). Most of these AEs were Grade 1 or Grade 2 in severity. The most common treatment-related Grade ≥3 AEs were diarrhoea (13% of patients given afatinib versus 1% of 159 given gefitinib) and rash or acne (9% patients given afatinib versus 3% of those given gefitinib) and liver enzyme elevations (no patients given afatinib versus 9% of those given gefitinib). SAEs occurred in 11% patients in the afatinib arm and 4% in the gefitinib arm. The ERG also notes that, in 2014, when appraising afatinib, the AC for TA310[53] concluded that although afatinib was associated with some different AEs to erlotinib and gefitinib, overall the toxicity of the three EGFR-TKIs was similar. This reflected the EMA's conclusion, in the EPAR for afatinib, that the toxicity profile of afatinib appears similar to that reported for other available EGFR-TKIs.[57]

4.12.7 Summary comment on adverse events

The company considers that osimertinib is generally well tolerated and that safety findings are generally consistent with the known safety profile of osimertinib (including QT prolongation, cardiac effect and interstitial lung disease). However, the ERG observes that compared to previous studies of osimertinib (as reported in the EPAR for osimertinib,[42] Table 37), the rate of SAEs in the osimertinib arm of the FLAURA trial (21.5%) was lower than previously reported (35.3% to 46.7%). The same is also true for treatment-related SAEs (2.9% in the FLAURA trial versus 5.6% to 13.3% in previous trials.

Overall, rates of AEs were generally similar between the two treatment arms in the FLAURA trial, although there were lower rates of Grade ≥ 3AEs, less frequent hepatic and rash AEs and a lower discontinuation rate due to AEs (largely due to the greater incidence of hepatic events in the SoC EGFR-TKI arm) observed with osimertinib than with SoC EGFR-TKI.

Therefore, the safety profile of osimertinib appears similar, if not better, than that of the SoC EGFR-TKI and there are no new safety concerns identified from the FLAURA trial. It is also reported in the EPAR for osimertinib[42] that, despite some cardiac effects, totality of the safety data indicates that osimertinib was at least as well tolerated as the SoC EGFR-TKI comparator. Given that in TA310[53] it was concluded that afatinib was associated with some different AEs to erlotinib and gefitinib but similar toxicity overall, the ERG considers that it is likely that osimertinib is therefore at least as tolerable as afatinib.

In addition to the CS, the ERG notes that additional data were provided in the EPAR for osimertinib[42] with an additional follow-up of 90 days for the FLAURA trial. As would be expected with an additional 90 days exposure, in some instances, the number of AEs increased. Where this was the case, this only occurred in ≥4 patients in any given arm in terms of Grade ≥3 AEs for osimertinib (+8 from 95 to 103 [34.1% to 36.9%]) and dose interruptions in the SoC EGFR-TKI arm (+4 from 66 to 70 [23.8% to 25.3%]).

4.13 Patient reported symptoms and health-related quality of life

The company presents the results from its analysis of patient reported symptoms and HRQoL from data collected via the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Lung Cancer 13 items (EORTC QLQ-LC13) and European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30 items (EORTC QLQ-LC30) questionnaires. It is reported in the CS (p66) that data were collected for the first 9 months at baseline and follow-up visits on days 8, 15, 22, 43, 64-106, 127-274 and the discontinuation and follow-up visits if occurring within the first 9 months. It is reported in the CSR (p143) that data were to be collected [redacted].When interpreting differences between arms, or over time, or with other datasets, the threshold for clinical relevance is reported to be ≥10% (i.e. 10pp) (CS, p84).

Baseline EORTC QLQ-LC13 and EORTC QLQ-LC30 scores are reported in the CSR (p143) and appear [redacted]. However, baseline QLQ-C30 data [redacted].

Clinically relevant improvements were sustained over time in both treatment arms for the symptoms of cough (EORTC QLQ-LC13), pain (EORTC QLQ-LC13), insomnia (EORTC QLQ-LC30) and appetite loss (EORTC QLQ-LC30). An improvement from baseline was also observed in both arms for emotional functioning (EORTC QLQ-LC30), “occasionally reaching clinical relevance” (CS, p84). Improvements in both arms for physical function (EORTC QLQ-LC13), role function (EORTC QLQ-LC13), social function (EORTC QLQ-LC13) and global health status/QoL (EORTC QLQ-LC13) did not reach the threshold for clinical relevance. The only clinically relevant worsening symptom sustained over time in both treatment arms was diarrhoea, from week 6 onwards. It is reported in the EPAR for osimertinib[42] (p73) that this could be expected considering the mechanism of action and safety profile of osimertinib and EGFR-TKIs. It is also reported that a small increase was seen in both arms for the following

symptoms: sore mouth (EORTC QLQ-LC13), peripheral neuropathy (EORTC QLQ-LC13) and alopecia (EORTC QLQ-LC13) (all [redacted]).

The company also states that they also analysed data conducted via the Cancer Therapy Satisfaction Questionnaire-16 items (CTSQ-16) (CS, p66) but no results are presented in the CS. It is reported in the CSR (p146) [redacted]. Furthermore, [redacted] (CS, p146).

No European Quality of Life 5-Dimension 3 Level Version (EQ-5D-3L) data were collected in the FLAURA trial.

The company does not report compliance to the questionnaires over time in the CS but this is reported in the EPAR for osimertinib[42] (p58). Compliance rates for EORTC QLQ-LC13 were ≥70% of eligible patients up to Week 93 in the osimertinib arm and up to Week 75 in the SoC EGFR-TKI arm (with an exception for Week 66 when the compliance rate was 69%). Compliance rates for EORTC QLQ-C30 were reported to be ≥70% of eligible patients up to Week 96 in the osimertinib arm and up to Week 60 in the SoC EGFR-TKI arm.

When interpreting all of the HRQoL results, it is important to consider the number of patients who completed the questionnaires. Whilst compliance was reported to be relatively high over time, the number of eligible patients at each point in time the data were collected decreased, reflecting the higher number of patients who had disease progression over time. This decrease was more pronounced in the SoC EGFR-TKI arm than in the osimertinib arm. Thus, for example, from the CSR (Table 11.2.14.1) as a proportion of patients randomised to each treatment arm, the response rates to the EORTC QLQ-C13 were:

- Week 39 (i.e. 9 months): [redacted] in the osimertinib arm and [redacted] in the SoC EGFR-TKI arm
- Week 75: [redacted] in the osimertinib arm and [redacted] in the SoC EGFR-TKI arm
- Week 93: [redacted] in the osimertinib arm and [redacted] in the SoC EGFR-TKI arm.

Similarly, from the CSR (Table 11.2.13.1) as a proportion of patients randomised to each treatment arm, the response rates to the EORTC QLQ-C30 were:

- Week 42 (the questionnaire was not completed at Week 39): [redacted] in the osimertinib arm and [redacted] in the SoC EGFR-TKI arm
- Week 60: [redacted] in the osimertinib arm and [redacted] in the SoC EGFR-TKI arm
- Week 96: [redacted] in the osimertinib arm and [redacted] in the SoC EGFR-TKI arm.

4.14 Conclusions of the clinical effectiveness section

The majority of the evidence presented in the CS is derived from the ongoing FLAURA trial, an international, double-blind, randomised, Phase III, multi-centre trial of treatment with osimertinib versus SoC EGFR-TKI (erlotinib or gefitinib) in patients with advanced EGFR+ NSCLC (N=556). The FLAURA trial is a well-designed, good quality trial with an appropriate and pre-defined statistical approach to the analysis of efficacy, safety and patient reported outcomes. However, the PH assumption is subject to uncertainty for OS. Therefore, it is not possible to know whether the reported HR overestimates or underestimates the effect of treatment with osimertinib versus SoC EGFR-TKI.

The comparators (erlotinib or gefitinib) in the SoC EGFR-TKI arm of the FLAURA trial are two of the three EGFR-TKIs currently used for treating first-line advanced EGFR+ NSCLC in NHS clinical practice. The results from the FLAURA trial show that, compared with SoC EGFR-TKI, osimertinib results in improved PFS. In addition, while ORRs are similar between treatment arms, the duration of response is improved with osimertinib versus EGFR-TKI.

In the FLAURA trial, OS data are very immature (25% maturity) and are confounded by treatment crossover. Results to date are however suggestive that osimertinib does result in improved OS based on the proportion of patients alive at 6, 12 and 18 months and the 25th percentile of OS. However, median OS has not yet been reached in either arm and the HR may not be valid. Evidence from post-progression endpoints, TFST, PFS2 and TSST show that the PFS advantage of osimertinib is largely preserved beyond initial progression. Mature OS data from the FLAURA trial are awaited. If an OS benefit is demonstrated, this will be an important finding as, to date, studies comparing EGFR-TKIs [31,38] have not reported statistically significant differences between arms. Furthermore, there has also been no evidence that EGFR-TKIs improve OS when compared with PDC.[20,21,23,25,27-30,34,38]

Importantly, the PFS benefit for osimertinib versus SoC EGFR-TKI that is observed for all patients in the FLAURA trial is also observed across pre-defined subgroups, including those specified in the decision problem addressed by the company: patients with and without CNS metastases, patients of Asian and non-Asian ethnicity and type of EGFR+ mutation (patients with and without Exon 19 deletions or L858R point mutations). The FLAURA trial is the first trial to have demonstrated a PFS benefit in patients with CNS metastases although to the ERG's knowledge, the LUX-Lung 7 trial[26] of afatinib versus gefitinib is the only other trial to have conducted such a subgroup analysis in a similar group of patients. Furthermore, in all patients included in the FLAURA trial, numerically fewer patients in the osimertinib arm experienced CNS progression than in the SoC EGFR-TKI arm. However, some cases of

asymptomatic progression may not have been detected in patients not required to have regular brain scans (i.e. those without confirmed CNS metastases at baseline).

Safety data from the FLAURA trial show osimertinib to be at least as equally well tolerated than for patients treated with erlotinib or gefitinib in the SoC EGFR-TKI arm. While the incidence of SAEs was lower in the osimertinib arm than in the EGFR-TKI SoC arm, it is noticeable that previous studies of osimertinib have reported higher incidences of SAEs than were reported in the FLAURA trial. Reasons for the lower number of SAEs in the FLAURA trial are unknown.

Clinically relevant improvements were sustained over time in both treatment arms for the symptoms of cough (EORTC QLQ-LC13), pain (EORTC QLQ-LC13), insomnia (EORTC QLQ-LC30) and appetite loss (EORTC QLQ-LC30). HRQoL data collected in the FLAURA trial did not include EQ-5D-3L data.

The ERG considers that the patient characteristics for patients with advanced EGFR+ NSCLC in the FLAURA trial are reasonably similar to the characteristics of patients who would be seen in NHS clinical practice in England, notwithstanding the usual caveat that trials often include fitter patients. Furthermore, the ERG notes that the results for the SoC EGFR-TKI arm are in line with results previously found for first-line treatment with erlotinib and gefitinib in RCTs. Thus, the results from the FLAURA trial are likely to be generalisable to patients in NHS clinical practice.

In addition to erlotinib and gefitinib, the third EGFR-TKI used for treating first-line advanced EGFR+ NSCLC in NHS clinical practice is afatinib. The company assume equal equivalence in terms of efficacy of afatinib to erlotinib and gefitinib. They support their assumption based on results from an NMA [78] and the conclusions of a previous AC.[53]. If it is assumed that afatinib is as equally efficacious as erlotinib and gefitinib, then the relative benefit of osimertinib versus afatinib will be similar to the relative benefits of osimertinib versus SoC TKI reported in the FLAURA trial. However, the ERG note that some clinicians consider that afatinib may be more efficacious but also more toxic than erlotinib or gefitinib.[18] Exploratory analysis from the LUX-Lung 7 trial [26] suggests that afatinib is more efficacious than gefitinib, in terms of PFS if not OS. Therefore the ERG conducted an indirect comparison of osimertinib versus afatinib using data from the FLAURA trial and LUX-Lung 7 trial.[26] The ERG found osimertinib to result in improved PFS, but not OS, versus afatinib. However, the results of this indirect comparison ought to be interpreted with caution, due to the possible violation of the PH assumption for data for both PFS outcomes from the LUX-Lung 7 trial[26] and for OS data from both the FLAURA trial and the LUX-Lung 7 trial.[26] Given that in TA310[53] it was concluded that afatinib

was associated with some different AEs to erlotinib and gefitinib but similar toxicity overall, the ERG considers that it is likely that osimertinib is therefore at least as tolerable as afatinib.

Finally, while there is evidence from the exploratory analysis in the LUX-Lung 7 trial[26,38] of an improvement in PFS from treatment with afatinib versus gefitinib, the gain in median PFS from this trial was only 0.1 months. In contrast, the difference in median PFS between osimertinib and SoC EGFR-TKI in the FLAURA trial is nearly 9 months. This may be a more clinically meaningful result than was demonstrated in the LUX-Lung 7 trial.[26,38]

5 COST EFFECTIVENESS

This section provides a structured critique of the economic evidence submitted by the company in support of the use of osimertinib versus afatinib, erlotinib and gefitinib for treating people with advanced EGFR T790M+ NSCLC. The two key components of the economic evidence presented in the CS are (i) a systematic review of relevant literature and (ii) a report of the company's de novo economic evaluation. The company has provided an electronic copy of their economic model, which was developed in Microsoft Excel.

5.1 Systematic review of cost effectiveness evidence

5.1.1 Objective of the company's systematic review

The company performed a systematic search of the literature to identify published studies to support the development of their cost effectiveness model. The search was carried out to identify cost effectiveness, cost and resource use, and utility studies.

5.1.2 Company searches

The company searched for articles that had been published since 1 January 2007. The databases listed in Table 20 were initially searched on 18 May 2017 and updated searches (for Embase and MEDLINE databases only) were carried out on 19 February 2018.

Table 20 Databases searched for economic evidence

Database	Interface
Excerpta Medical Database (Embase)	Embase
Medical Literature Analysis and Retrieval System Online (MEDLINE)	Embase
Medical Literature Analysis and Retrieval System Online (MEDLINE) in process	PubMed
Health Technology Assessment database (HTAD)	Wiley Interscience
National Health Service Economic Evaluation Database (NHS EED)	Wiley Interscience
EconLit	Ebsco

Source: CS, adapted from Appendix G

The company also carried out searches to identify relevant proceedings from the following conferences held between 2015 and 2017:

- American Society of Clinical Oncology (ASCO)
- International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Annual European and International Congress
- European Lung Cancer Conference (ELCC)
- European Society for Medical Oncology (ESMO)
- Health Technology Assessment International (HTAi)
- World Conference on Lung Cancer.

Additionally, the websites of NICE, Scottish Medicine Consortium (SMC) and All Wales Medicine Strategy Group (AWMSG) were searched for potentially relevant technology appraisals. Details of the search strategies used by the company are provided in Appendix G of the CS.

5.1.3 Eligibility criteria used in study selection

The main inclusion criteria used by the company to select studies are shown in Table 21. Only relevant studies published in English were included in the review.

Table 21 Key criteria for identification of economic evaluations

Characteristic	Inclusion criteria
Population	• Adult patients with advanced EGFR+ NSCLC on any line of therapy
Interventions	• Osimertinib
Comparator	• Placebo • EGFR-TKIs (including afatinib, erlotinib and gefitinib) • Best supportive care • Platinum doublet chemotherapy • Any treatment from the list above
Outcomes	• Incremental costs, LYs gained and QALYs, and any other measure of effectiveness reported together with costs • Sensitivity analysis
Study design	• Economic evaluations (including cost effectiveness, cost utility, cost benefit, and cost consequence models)
Country	• No restrictions

EGFR+=epidermal growth factor receptor mutation-positive; LY=life years; NSCLC=non-small cell lung cancer; QALY=quality adjusted life year; TKIs=tyrosine kinase inhibitors
Source: CS, Table 30

5.1.4 Included and excluded studies

The company search identified 42 unique studies from 54 full-text publications. Of these, five studies were identified from UK HTA websites and are shown in Table 22. Four of the HTA publications[52,53,77,81] included either afatinib, erlotinib or gefitinib as a comparator in the first-line setting. Only one study[43] included osimertinib as a comparator, but used in the second-line setting. None of the studies compared osimertinib with either afatinib, erlotinib or gefitinib, either in the first- or second-line settings. Details of the screening process and the reasons for the exclusion of the identified studies are presented in the CS (Section B.3.1 and Appendix G).

Table 22 Cost effectiveness studies identified in the company search

Study identifier Line of therapy	Intervention/ comparator (s)	Perspective Cost year Currency
NICE [TA416][43] 2016 ≥Second-line	• Osimertinib • Pemetrexed+cisplatin	NHS and PSS 2014-2015 UK pounds (£)
NICE [TA258][77] 2012 First-line	• Erlotinib • Gefitinib	NHS and PSS Cost year=NR UK pounds (£)
NICE [TA310][53] 2014 First-line	• Afatinib • Gefitinib • Erlotinib	NHS and PSS 2011 UK pounds (£)
NICE [TA192][52] 2010 First-line	• Gefitinib • Gefitinib+carboplatin • Gemcitabine+cisplatin • Paclitaxel+carboplatin • Vinorelbine+cisplatin	NHS and PSS 2007-2008 UK pounds (£)
Brown et al[81] 2013 (UK) First-line	• Gefitinib • Docetaxel+cisplatin+carboplatin • Paclitaxel+cisplatin+carboplatin	NHS and PSS Cost year=NR UK pounds (£)

NHS=National Health Service; NR=not reported; PSS=Personal Social Services
Source: information drawn from CS, Table 31 and from Appendix G, Table 138

5.1.5 Findings from cost effectiveness review

None of the studies identified by the company's literature search compared treatment with osimertinib with any of the comparators specified in the final scope[47] issued by NICE.

5.1.6 ERG critique of the company's review of cost effectiveness evidence

The search terms were relevant and included MeSH and free text as well as a cost effectiveness filter. The search strategies are limited by start date (2007) and English language, except for MEDLINE in process (via PubMed) where the only limit included was for the retrieval of electronically published articles ahead of print (epub ahead of print). The epub ahead of print studies would have been retrieved in the original MEDLINE (via Embase) search strategy, which then means that the limit applied to MEDLINE in process strategy is redundant. Overall, the ERG has re-run the searches and is satisfied that the company's search includes all relevant studies. A summary of the ERG's appraisal of the company's search and selection process is provided in Table 23.

Table 23 ERG appraisal of systematic review methods (cost effectiveness)

Review process	ERG response
Was the review question clearly defined in terms of population, interventions, comparators, outcomes and study designs?	Yes
Were appropriate sources searched?	Yes
Was the timespan of the searches appropriate?	Yes
Were appropriate search terms used?	Yes
Were the eligibility criteria appropriate to the decision problem?	Yes
Was study selection applied, independently, by two or more reviewers?	Not reported
Were data extracted, independently, by two or more reviewers?	Not reported
Were appropriate criteria used to assess the quality of the primary studies?	Yes
Was the quality assessment conducted, independently, by two or more reviewers?	Not reported
Were any relevant studies identified?	No

5.2 ERG summary of the company's submitted economic evaluation

The company developed a de novo economic model to compare the cost effectiveness of treatment with osimertinib versus afatinib, erlotinib and gefitinib in adults with advanced EGFR mutation type (Exon 19 deletions or L858R point mutations) NSCLC.

5.2.1 Model structure

The company model structure (implemented as a partitioned survival model), as shown in Figure 1, comprises three mutually exclusive health states that are designed to reflect the natural course of the disease. The modelled population enters the model in the progression-free (PF) health state. At the end of every 30-day cycle, patients in the PF health state can experience disease progression and enter the progressed disease (PD) health state or remain in the PF health state. Patients in the PD health state can also remain in that health state at the end of each cycle but cannot return to the PF health state. Transitions to the death health state can occur from either the PF health state or the PD health state. Death is an absorbing health state from which transitions to other health states are not permitted.

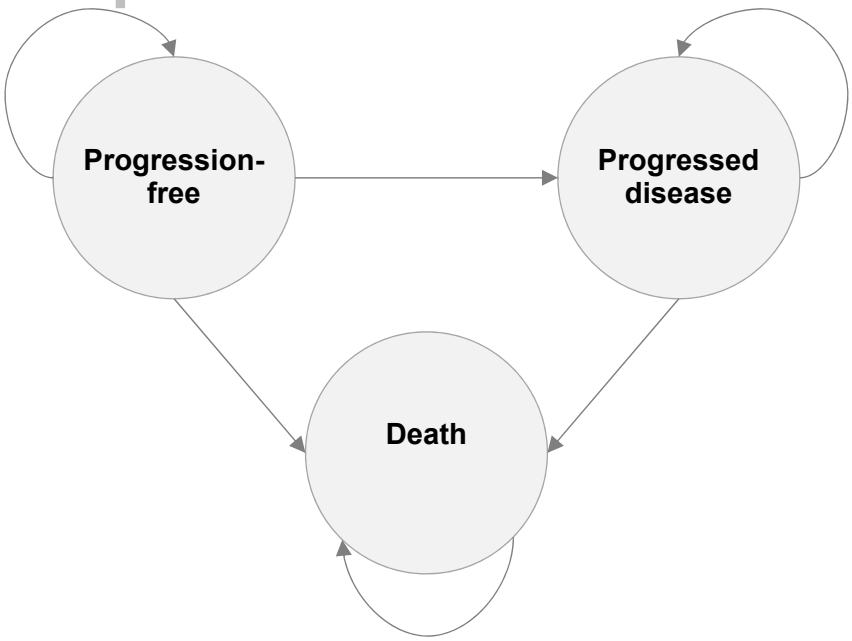

Figure 1 Structure of the company model

Source: Developed by the ERG based on text in the CS, Section B.3.2

5.2.2 Population

The population reflected by the company model is patients with advanced EGFR+ NSCLC. The population is consistent with the FLAURA trial population and that described in the final

scope[47] issued by NICE. The starting age of the cohort (63 years) is similar to the median age, at baseline, of the patients in the FLAURA trial (64 years).

5.2.3 Interventions and comparators

Intervention

Treatment with osimertinib is implemented in the model in line with the licensed dosing regimen[42] i.e. one 80mg tablet taken once daily until disease progression or unacceptable toxicity. However, clinical advice to the company is that osimertinib is expected to be used beyond disease progression if clinical benefit is observed and, therefore, administration of osimertinib (80mg) beyond disease progression was implemented in the company model.

Comparators

The comparators are afatinib[57], erlotinib[55] and gefitinib.[56] The dosing and administration frequencies for these drugs are also in line with their marketing authorisations and UK clinical practice, where treatment is continued beyond disease progression. Afatinib (40mg), erlotinib (150mg) and gefitinib (250mg) were implemented as one tablet once a day.

5.2.4 Perspective, time horizon and discounting

The company states that the economic evaluation is undertaken from the perspective of the NHS and Personal Social Services (PSS), which is in line with the NICE reference case.[82] The model has a 30-day cycle length and the time horizon is set at 20 years. As justification for the length of the time horizon, the company cites the advanced nature of the disease and projections from the FLAURA study, which showed that fewer than 2.5% of patients would live beyond 20 years. An annual discount rate of 3.5% was applied to costs and outcomes. Half cycle correction was applied to all costs in the model except to drug acquisition and administration costs for treatment with osimertinib, afatinib, erlotinib and gefitinib.

5.2.5 Treatment effectiveness and extrapolation in the base case

The company economic model reflects patient-level data from the FLAURA trial. In the FLAURA trial, treatment with osimertinib was compared to SoC EGFR-TKI (that is, erlotinib or gefitinib). The follow-up period in the trial was shorter than the model time horizon and, therefore, extrapolations of the PFS, OS and time to discontinuation of treatment (TDT) K-M data from the FLAURA trial were necessary. The extrapolations involved identification of parametric survival models that reflected FLAURA trial PFS, OS and TDT K-M data.

Progression-free survival

The company undertook an assessment to determine whether the PFS data from the two arms of the FLAURA trial were proportional (log-cumulative hazard plot and Cox-Snell residuals)

and concluded that it was appropriate to assume proportionality. Therefore, in line with guidance on the survival model selection process developed by the Decision Support Unit, the company fitted dependent parametric models to the trial data, with a treatment coefficient for osimertinib.

The company fitted six parametric models to the FLAURA trial data: exponential, generalised gamma, Gompertz, log-logistic, log-normal and Weibull. The Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC) and visual assessment were initially used to identify the parametric model with the best fit. The company determined that the generalised gamma, log-logistic and Weibull models were the three best fitting models.

The extrapolations from the three best fitting models were validated against data from trials that had investigated the effectiveness of an EGFR-TKI in patients with advanced EGFR+ NSCLC. Only the LUX-Lung 7 trial[26] and WJTOG 3405 trial[83] reported PFS beyond 3 years. The company determined that the observed 2-year PFS rate from the FLAURA trial was most comparable with the PFS rate from the gefitinib arm in the LUX-Lung 7 trial[26] (Table 24). The company, therefore, used the 3-year PFS rate from the gefitinib arm of the LUX-Lung 7 trial[26] to assess the plausibility of the three best fitting parametric models. The generalised gamma was consequently chosen as the preferred model.

Table 24 Trial and model-generated progression-free survival

Data source	Treatment	Proportion of population progression-free		
		At 1 year	At 2 years	At 3 years
Clinical trials				
FLAURA	Osimertinib versus erlotinib/gefitinib	42.3%	8.4%	-
LUX-Lung 7[26]	Afatinib versus gefitinib	41.3%	7.5%	4.7%
WJTOG 3405[83]	Gefitinib versus cisplatin+docetaxel	42.5%	13.9%	7.2%
Extrapolation from best models				
Generalised gamma (preferred model)	Erlotinib/gefitinib	42.2%	11.5%	2.8%
Weibull	Erlotinib/gefitinib	43.6%	9.6%	1.3%
Log-logistic	Erlotinib/gefitinib	41.4%	15.8%	7.9%

Source: adapted from CS, Table 37

Overall survival

Company testing (log-cumulative hazard plot and the Cox-Snell residuals plot) of OS data from the two arms of the FLAURA trial showed that the proportional hazard assumption was not violated. It was noted by the company that the log-cumulative hazard plots of data from the osimertinib arm and SoC EGFR-TKI arm remained parallel after 7.9 months. The

company, therefore, modelled OS using observed data up to 7.9 months and dependent parametric curves (with a treatment coefficient for the osimertinib arm) thereafter.

To identify the best parametric curve to append to the OS K-M data from the FLAURA trial, six parametric curves were fitted to the trial data. All the models had a good visual fit to the OS K-M data. The company notes the assessment of statistical fit to the FLAURA trial OS K-M data was relatively uninformative given the low number of observed events/deaths in the trial. Given the uncertainty (Figure 2), other relevant trial OS data were examined to help identify the most clinically plausible parametric model. Among the trials identified by the search for clinical literature, the LUX-Lung 7 trial[38] (afatinib versus gefitinib) and the ARCHER-1050 trial[84] (dacomitinib versus gefitinib) were the only studies in which patients with EGFR T790M+ disease received osimertinib or another third-generation EGFR-TKI after progression on first-line EGFR-TKI therapy. The company determined that the LUX-Lung 7 trial[38] and the ARCHER-1050 trial[84] could be used to validate extrapolated OS rates from the parametric models.

[redacted]

Figure 2 Overall survival Kaplan-Meier curve for the osimertinib arm and standard of care arm of the FLAURA study plus the six parametric models fitted to each study arm

1L=first-line; Gen=generalised; OS=overall survival
Source: CS, Figure 39

On closer examination of the LUX-Lung 7 trial[38] and ARCHER-1050 trial,[84] the company concluded that these trials were not suitable for validating the predicted OS rates from the parametric model. The main reason stated by the company (CS, p128) is that the use of third-generation EGFR-TKIs in patients receiving at least one subsequent anticancer treatment after progression (which has been shown to have a positive impact on OS[85]) was lower in the LUX-Lung 7 trial[38] and in the ARCHER-1050 trial[84] than in the FLAURA trial.The company suggested that the higher 2-year OS rate in the SoC EGFR-TKI arm of the FLAURA trial, compared to similar rates in the gefitinib arms of the LUX-Lung 7 trial[38] and ARCHER-1050 trial[84] (see Table 25), may due to the higher use of osimertinib as a subsequent treatment.

Table 25 Proportion of patients treated with a third-generation tyrosine kinase inhibitor after progression and reported overall survival rates in selected trials and the FLAURA trial

Study	Treatment	Patients treated after progression			Overall survival rate at		
		At least one subsequent therapy	Third-generation EGFR-TKI	osimertinib [a]	1 year	2 years	3 years
FLAURA	Erlotinib/ gefitinib	129/206 (63%)	62/206 (30%)[b]	62/129 (48%)	83%	65%	--
LUX-Lung 7[38]	Gefitinib	120/151 (80%)	23/151 (15%)[c]	17/120 (14%)	84%	51%	32%
ARCHER 1050[84]	Gefitinib	140/207 (68%)	25/207 (12%)[c]	25/140 (18%)[c]	86%	56%	41%

[a] number of patients treated with osimertinib/number of patients whose disease has progressed and who received at least one subsequent therapy
[b] Includes osimertinib only
[c] includes osimertinib and other third-generation EGFR-TKIs
Source: CS, information drawn from Table 42 and published trial results from the LUX-Lung 7 trial[38] and ARCHER 1050 trial[84]

Overall, the LUX-Lung 7 trial[38] and ARCHER 1050 trial[84] were unsuitable for validating the long-term extrapolation for the SoC EGFR-TKI arm in FLAURA trial and there was no longer-term data on the use of first-line osimertinib in clinical practice. The company therefore stated that the most appropriate approach was to append the most conservative OS extrapolation (Weibull model) to the OS K-M data for the osimertinib and SoC EGFR-TKI arms of the FLAURA trial. Figure 3 shows the OS K-M curves for the gefitinib arms of the LUX-Lung 7 trial[38] and ARCHER-1050 trial,[84] and the company's preferred extrapolation model (Weibull) for the osimertinib and SoC EGFR-TKI arms of the FLAURA trial.

[redacted]

Figure 3 Observed overall survival data from the FLAURA trial (both arms), LUX-Lung 7 study and ARCHER-1050 trial (gefitinib arm), and projection from the Weibull piecewise model

ARCHER=ARCHER 1050 study; K-M=Kaplan-Meier; LL7=LUX-Lung 7 study; SoC=standard of care
Source: CS, Figure 40

Time to discontinuation of treatment

Company testing (log-cumulative hazard plot) of TDT data from the two arms of the FLAURA trial showed that the proportional hazard assumption was not violated. The company, therefore, considered the use of dependent parametric models to be appropriate. Six parametric models were fitted to the FLAURA trial data, stratified by treatment arm (that is, dependent models). Goodness of fit was assessed visually and by using AIC and BIC statistics. The generalised gamma model was considered by the company to be the preferred model even though the Gompertz model had the best statistical fit. Only TDT values from the generalised gamma model were used in the cost effectiveness model.

5.2.6 Health-related quality of life

Health-related quality of life (HRQoL) data were collected as part of the FLAURA trial using the (i) European Organisation for Research and Treatment of Cancer (EORTC) quality of life questionnaire Core-30 (QLQ-C30) and (ii) EORTC Lung cancer 13 (LC 13). The questionnaires were administered to patients every 6 weeks until disease progression, at treatment discontinuation, and every 6 weeks following disease progression. These

questionnaires are not preference-based and, therefore, utility estimates could not be directly estimated. However, using a published mapping algorithm,[86] the company estimated EQ-5D-3L utility values for the FLAURA trial population based on their responses to the EORTC QLQ-30 questionnaire. Table 26 shows the mean predicted utility values obtained using the published mapping algorithm.

Table 26 Mean predicted utility values derived from published mapping algorithm

Health state	Number of patients	Mean utility	Standard error	95% confidence interval
Progression-free				
- All patients	[redacted]	[redacted]	[redacted]	[redacted]
- Osimertinib arm	[redacted]	[redacted]	[redacted]	[redacted]
- Standard of care arm	[redacted]	[redacted]	[redacted]	[redacted]
Progressed disease				
- All patients	[redacted]	[redacted]	[redacted]	[redacted]
- Osimertinib arm	[redacted]	[redacted]	[redacted]	[redacted]
- Standard of care arm	[redacted]	[redacted]	[redacted]	[redacted]

Source: adapted from CS, Table 48

The company also conducted a systematic search of the literature to identify published studies from which utility values for people with advanced EGFR+ NSCLC could be obtained. The search identified only one (longitudinal cohort) study by Labbe and colleagues (2017).[87] Labbe (2017) reported real-world utility values (based on responses to EQ-5D-3L questionnaires) in specific subgroups of patients in Canada with lung cancer. Although Labbe (2017)[87] was not conducted in a UK setting, results generated using the UK value set are presented. The company concluded that mean utility estimates from the paper by Labbe (2017),[87] as shown in Table 27, were similar to the mean utility estimates generated, via the mapping algorithm, from FLAURA trial data.

Table 27 Mean utility estimates from Labbe and colleagues

Health state	Utility value
Stable disease	
- On treatment with EGFR-TKIs	0.77
- Off treatment	0.76
- On other systemic treatment	0.72
Progressed disease	0.64

Source: adapted from CS, Table 50

The utility values used in the company are displayed in Table 28.

Table 28 Utility values used in the cost effectiveness model

Health state	Utility value	Source/description
Health state		
Progression-free	[redacted]	Mapped value from FLAURA trial
Progressed disease (1L treatment)	[redacted]	Mapped value from FLAURA trial
Progressed disease (subsequent treatment or BSC)	0.640	Labbe (2017)[87]
Death	0.000	By definition

1L=first-line treatment; BSC=best supportive care
Source: CS, Table 51

5.2.7 Resources and costs

The resource use and costs associated with treatment acquisition, treatment administration, disease management and AEs were included in the company model.

Drug costs in the first-line setting

Estimates of the quantity of osimertinib, afatinib, erlotinib and gefitinib used per patient per 30-day model cycle were derived from FLAURA trial data, as were relative dose intensity (RDI) multipliers. The afatinib RDI multiplier was assumed to be the same as for treatment with erlotinib and gefitinib. An oral treatment administration cost of £9 per model cycle (based on a dispensing time of 12-minutes [band 6 pharmacist]) was applied to all first-line therapies. Selected details of the drug costs are shown in Table 29 of this ERG report and full details are presented in Tables 58, 59, 60, 61 and 67 of the CS.

Table 29 Treatment dosing and drug acquisition costs for primary treatments

		Osimertinib	Afatinib	Erlotinib	Gefitinib
Label information	Administration method	Oral	Oral	Oral	Oral
	Dose per administration	80mg	40mg	150mg	250mg
	Administration frequency	1 per day	1 per day	1 per day	1 per day
Package information	Formulation	80mg	40mg	150mg	250mg
	Pack size	28 tablets	28 tablets	30 tablets	30 tablets
	List price	£5,770.00	£2,023.28	£1,631.53	£2,167.71
Dosing used in model	Required dose	80mg	40mg	150mg	250mg
	Tablets per administration	1.00	1.00	1.00	1.00
	Relative dose intensity	98.1%	98.1%	98.1%	98.1%
	Cost per model cycle	£5,706.53	£2,126.61	£1,600.53	£2,126.52

mg=milligram
Source: information drawn from CS, Tables 58, 60 and 61

Drug costs for subsequent treatments

The costs of subsequent lines of therapies are applied as one-off costs. The company states that the nature of partitioned survival modelling means that it is not possible to accurately estimate the proportion of patients who discontinue first-line therapy and die in the same cycle. Therefore, the difference in the proportion of patients on treatment between two consecutive 30-day cycles (from TDT K-M extrapolation) was used a proxy for the proportion of patients

who discontinued first-line treatment. It was acknowledged by the company that this modelling approach may overestimate the cost of subsequent therapy as it does not account for the proportion of patients who die before stopping first-line therapy. The company concluded that the overestimation was likely to be small since only small proportions of patients in the osimertinib (4%) and SoC EGFR-TKI arms (5%) of the FLAURA trials died before disease progression.

Clinical advice to the company is that (i) a third of patients whose disease progresses whilst they are receiving a first or second generation EGFR-TKI are identified as having EGFR T790M+ NSCLC and would be treated with osimertinib in the second-line setting, (ii) another third of the population would not be fit to receive a subsequent therapy and (iii) the last one-third would receive PDC. The company states that a similar proportion of patients (26.7%) in the SoC EGFR-TKI arm of the FLAURA trial received second-line osimertinib and 37.4% did not receive a subsequent therapy. The company assumed that, in the model, one-third of the patients in the osimertinib arm would not receive a subsequent therapy while the other two-thirds would receive PDC (see Table 30).

Table 30 Distribution of second-line treatments by first-line treatment

From ↓ To →	PDC (2L EGFR T790M ±)	PDC (2L EGFR T790M -)	Osimertinib (2L EGFR T790M+)	No treatment (2L)
Osimertinib	66.7%	0.0%	0.0%	33.3%
Afatinib	0.0%	33.3%	33.3%	33.3%
Erlotinib	0.0%	33.3%	33.3%	33.3%
Gefitinib	0.0%	33.3%	33.3%	33.3%

2L=second-line; PDC=platinum doublet chemotherapy
Source: CS, Table 70

The company states that its modelling of third-line treatment is based on the clinical advice that informed a previous technology appraisal (treatment with osimertinib in the second-line setting for patients with EGFR T790M+ NSCLC[43]). Clinical advice to the company had been that 80% of patients treated with osimertinib in the second-line setting would receive PDC third-line, while others would not receive a third-line treatment. The advice was also that half of the patients receiving PDC second-line would receive third-line treatment with docetaxel monotherapy and the other half would not receive further treatment (Table 31).

Table 31 Distribution of third-line treatments by first-line treatment

From ↓ To →	PDC (3L)	Docetaxel (3L)	No treatment (3L)
Osimertinib	0.0%	33.3%	66.7%
Afatinib	26.7%	16.7%	56.6%
Erlotinib	26.7%	16.7%	56.6%
Gefitinib	26.7%	16.7%	56.6%

3L=third-line; PDC=platinum doublet chemotherapy
Source: CS, Table 71

The time on second-line treatment was obtained from the latest TDT data from the AURA3 trial.[12] The AURA3 trial[12] is a Phase III, open-label RCT designed to investigate the effectiveness of treatment with osimertinib versus pemetrexed-cisplatin in the second-line setting for patients with EGFR T790M+ NSCLC. The company fitted parametric models to TDT data for the osimertinib arm. The company notes that the log-logistic model had the best statistical fit to the observed data followed by the generalised gamma model. However, the log-logistic model generated a long tail with [redacted] of patients remaining on treatment at 10 years. The company, therefore, used the generalised gamma model to represent time on second-line treatment. Although the number of cycles of PDC was not capped in the AURA3 trial, [12] the time on second-line (PDC) treatment in the model was limited to four 21-day cycles to reflect NHS protocols for pemetrexed-cisplatin therapy. Therefore, the TDT K-M data for treatment with pemetrexed-cisplatin in the AURA3 trial[12] was sufficient without the need for any extrapolation. The unit costs for the subsequent therapies are shown in Table 32.

Given that second-line treatment with osimertinib is indicated for use in patients with EGFR T790M+ NSCLC, the company included the cost of EGFR T790M mutation testing within the costs for subsequent treatments (£1,282) for patients receiving first-line treatment with afatinib, erlotinib or gefitinib. This cost was divided by the estimated mean duration on subsequent therapy. For instance, the mean duration of subsequent treatment with PDC was 2.40 cycles (Table 32), so the cost of EGFR T790M mutation testing per cycle was £543.66.

Table 32 Unit cost for subsequent therapies and EGFR T790M mutation testing

	PDC (2L EGFR T790M ±)	PDC (2L EGFR T790M -)	Osimertinib (2L EGFR T790M+)	PDC (3L)	Docetaxel (3L)
EGFR T790M Testing (per 30 days)[a]	£0.00	£543.66	[redacted]	£0.00	£0.00
Drug acquisition (per 30 days)	£1,919.58	£1,919.58	[redacted]	£1,919.58	£32.88
Drug administration (per 30 days)	£512.87	£512.87	[redacted]	£512.87	£517.83
Drug monitoring (per 30 days)	£7.60	£7.60	[redacted]	£7.60	£4.37
Total treatment cost (per 30 days)[b]	£2,440.05	£2,974.25	[redacted]	£2,440.05	£555.08
Duration on subsequent treatment (30-day cycles)	2.40	2.40	[redacted]	2.40	1.70

±=positive or negative; -=negative; +=positive; 2L=second-line; 3L=third-line; PDC=platinum doublet chemotherapy
[a] EGFR T790M testing cost (one-off) is divided by treatment duration to avoid double counting;
[b] cost includes EGFR T790 mutation testing (where relevant), drug acquisition, drug administration and drug monitoring costs;
Source: CS, Table 72

Resource use by health state

Base case resource use and unit cost estimates incurred during the PF and the PD health states are shown in Table 33. Resource use assumptions from a multiple technology appraisal of erlotinib and gefitinib for treating patients with lung cancer in the second-line setting (TA374)[54] and those from a single technology appraisal of osimertinib for treating patients with EGFR T790M+ NSCLC (TA416)[43] were used in the company model. The company notes that the assumptions in these previous technology appraisals[43,54] were also used in recent technology appraisals assessing the use of nivolumab for treating NSCLC (TA483[88] and TA484[89]). Unit costs were obtained from the 2017 edition of NHS Reference Costs[90] and Unit Cost of Health and Social Care.[91] The price base year of the unit costs in the company model is 2016/2017. Unit costs from earlier price years were inflated to the base year, using the Hospital and Community Health Services (HCHS) index.[91]

Table 33 Resource use, unit costs and costs associated with model health states

Cost item	Unit cost	Progression-free health state		Progressed disease health state	
		Usage per annum	Usage per cycle	Usage per annum	usage per cycle
Outpatient visit	£136.43[90]	9.61	0.79	7.91	0.65
Chest radiography	£29.78[90]	6.79	0.56	6.5	0.53
CT scan (chest)	£112.07[90]	0.62	0.05	0.24	0.02
CT scan (other)	£122.33[90]	0.36	0.03	0.42	0.03
ECG	£133.43[90]	1.04	0.09	0.88	0.07
Community nurse home visit	£24.55[91,92]	8.7	0.71	8.7	0.71
Clinical nurse specialist contact	£110.00[92]	12	0.99	12	0.99
GP surgery consultation	£38.00[92]	12	0.99	0	0
GP home visit	£117.71[91,93]	0	0	26.09	2.14
Therapist visit	£45.00[92]	0	0	26.09	2.14
Total cost per 30 days (£)			£308.43		£595.25

ECG=electrocardiogram; CT=computerised tomography
Source: information drawn from CS, Table 77 and 78

CNS metastases

Data from the FLAURA trial showed that 13.6% and 21.9% of patients in the osimertinib and SoC EGFR-TKI arms experienced CNS progression (excluding death) (CS, Table 82). In the company model, a one-off cost of £5,698 was applied, on progression, to these proportions of patients in the osimertinib and SoC EGFR-TKI arms of the model respectively.

End of life/terminal care costs

An end-of-life/terminal care cost of £4,103 was included in the company's base case analysis for transitions from the PF health state and PD health state to the death health state. Resource use estimates for end-of-life/terminal care were obtained from Brown et al[81] and had been used to inform previous technology appraisals (TA374[54], TA416[43], TA483[88] and TA484[89]). Details of the end-of-life/terminal care costs used in the model are presented in Table 79 of the CS.

5.2.8 Adverse events

The AE incidence rates for patients treated with afatinib, erlotinib and gefitinib were assumed to be equal to those reported for the SoC EGFR-TKI arm of the FLAURA study (see Table 34). The company model considered all treatment related AEs of Grade ≥3 occurring in >1% of patients in any treatment arm. The unit costs and the disutilities associated with each AE were assumed to be the same irrespective of the treatment that caused the AE and, therefore, the differences in costs and disutilities were driven by the incidence rates. The sum of the

costs (weight by AE rates) and disutilities (also weighted by AE rates) were applied at the start of the simulation.

Table 34 Proportion of patients with selected adverse events in the osimertinib and SoC EGFR-TKI arm of FLAURA trial, along with associated unit cost and disutility model

Adverse events of Grade ≥3 occurring in >1% of patients in the FLAURA trial	Unit cost	Disutility	Osimertinib[51] (n=279)	SoC EGFR-EGFR-TKI[51] (n=277)
Alanine aminotransferase increased	£2414.94⌂	-0.05*	1 (0.4%)	25 (9.0%)
Aspartate aminotransferase increased	£2414.94⌂	-0.05*	2 (0.7%)	12 (4.3%)
Diarrhoea	£2280.06[94]	-0.05[95]	6 (2.2%)	7 (2.5%)
Fatigue	£3048.16[43]	-0.07[95]	4 (1.4%)	4 (1.4%)
Rash or acne	£2622.06[43]	-0.03[95]	6 (2.2%)	27 (9.7%)

*=value assumed to be equivalent to the average of other disutilities; ⌂=weighted average of non-elective long stay for Non-Malignant, Hepatobiliary or Pancreatic Disorders
Source: information drawn from CS, Table 46, Table 54, Table 80 and company model

5.2.9 Cost effectiveness results

Data in Table 35 show the pairwise base case incremental cost effectiveness ratios (ICERs) per QALY gained for the comparison of treatment with osimertinib versus afatinib, erlotinib and gefitinib. Data in Table 36 show the fully incremental cost effectiveness results for the comparison of treatment with osimertinib, afatinib, erlotinib and gefitinib. Data in Table 37 show that when the proposed PAS discount for osimertinib and the SPA scheme for gefitinib are used, the ICER for the comparison of the cost effectiveness of these two treatments is [redacted] per QALY gained.

Table 35 Base case pairwise incremental cost effectiveness results – list price for all treatments

Treatment	Total cost	Total LYG	Total QALYs	Incremental			Incremental cost per QALY gained (osimertinib versus comparators)
				Cost	LYG	QALYs	
Osimertinib	[redacted]	4.861	[redacted]				
Afatinib	[redacted]	3.404	[redacted]	[redacted]	1.457	[redacted]	£82,669
Erlotinib	[redacted]	3.404	[redacted]	[redacted]	1.457	[redacted]	£89,700
Gefitinib	[redacted]	3.404	[redacted]	[redacted]	1.457	[redacted]	£82,675

LYG=life year gained; QALY=quality adjusted life year
Source: adapted from CS, Table 86

Table 36 Base case fully incremental cost effectiveness results – list price for all treatments

Treatment	Total cost	Total LYG	Total QALYs	Incremental			Inc cost per QALY gained	Fully Inc cost per QALY gained
				Cost	LYG	QALYs		
Erlotinib	[redacted]	3.404	[redacted]	-	-		-	
Gefitinib	[redacted]	3.404	[redacted]	[redacted]	0.000	[redacted]	-	Dominated
Afatinib	[redacted]	3.404	[redacted]	[redacted]	0.000	[redacted]	-	Dominated
Osimertinib	[redacted]	4.861	[redacted]	[redacted]	1.457	[redacted]	£82,669	£89,700

Inc=incremental; LYG=life year gained; QALY=quality adjusted life year; Inc=incremental
Source: information drawn from CS, Table 86 and company model

Table 37 Base case incremental cost effectiveness results – PAS price for osimertinib and SPA discount for gefitinib

Treatment	Total cost	Total LYG	Total QALYs	Incremental			Incremental cost per QALY gained (osimertinib versus gefitinib)
				Cost	LYG	QALYs	
Gefitinib	[redacted]	[redacted]	[redacted]				
Osimertinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

LYG=life year gained; QALY=quality adjusted life year; SPA=single patient access
Source: information drawn from CS, Table 86 and Appendix J, Table 140

5.2.10 Sensitivity analyses

Deterministic sensitivity analyses

The results of the company's one-way sensitivity analyses (OWSA) for treatment with osimertinib versus afatinib, erlotinib and gefitinib show that the (i) OS curve parameters for osimertinib, (ii) TDT curve parameter for osimertinib, (iii) utility value for the PF health state and (iv) the proportion of people who receive osimertinib as a subsequent therapy have the greatest impact on the size of the ICER per QALY gained as shown in Figure 4, Figure 5 and Figure 6.

Figure 4 Tornado diagram showing OWSA results for treatment with osimertinib versus afatinib

2L=second line; CNS=central nervous system; ICER=incremental cost effectiveness ratio; OS=overall survival; PDC=platinum doublet chemotherapy; PFS=progression-free survival; TDT=time to discontinuation of treatment; T790M=Amino acid substitution at position 790 in EGFR, from threonine (T) to methionine (M)
Source: CS, Figure 57

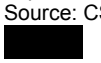

Figure 5 Tornado diagram showing OWSA results for treatment with osimertinib versus erlotinib

2L=second line; CNS=central nervous system; ICER=incremental cost effectiveness ratio; OS=overall survival; PDC=platinum doublet chemotherapy; PFS=progression-free survival; TDT=time to discontinuation of treatment; T790M=Amino acid substitution at position 790 in EGFR, from threonine (T) to methionine (M)
Source: CS, Figure 55

[redacted]

Figure 6 Tornado diagram showing OWSA results for treatment with osimertinib versus gefitinib

2L=second line; CNS=central nervous system; ICER=incremental cost effectiveness ratio; OS=overall survival; PDC=platinum doublet chemotherapy; PFS=progression-free survival; TDT=time to discontinuation of treatment; T790M=Amino acid substitution at position 790 in EGFR, from threonine (T) to methionine (M)
Source: CS, Figure 56

Probabilistic sensitivity analysis

The company varied a large number of input parameters in its probabilistic sensitivity analysis using the list price for all treatment in the model. Figure 7 shows the uncertainty around the estimated mean cost per QALY difference between treatment with osimertinib versus treatment with afatinib, erlotinib and gefitinib. The pairwise probabilistic ICERs were consistently slightly lower than the pairwise deterministic ICERs per QALY gained (see Table 38).

Table 38 Probabilistic pairwise incremental cost effectiveness results – list price for all treatments

Treatment	Total cost	Total QALYs	Incremental cost per QALY gained (osimertinib versus comparators)	
			Probabilistic	Deterministic
Osimertinib	[redacted]	[redacted]		
Afatinib	[redacted]	[redacted]	£81,152	£82,669
Erlotinib	[redacted]	[redacted]	£88,137	£89,700
Gefitinib	[redacted]	[redacted]	£81,218	£82,675

QALY=quality adjusted life year
Source: information drawn from CS, Table 86 and Table 90

For treatment with osimertinib versus each of the three comparators, the difference between the deterministic ICERs and the probabilistic ICERs was less than 2% of the deterministic ICER per QALY gained. For example, the difference between the deterministic and probabilistic ICER for treatment with osimertinib versus afatinib is £1,517 per QALY gained which is 1.8% of £82,669 per QALY gained. The company states that, although there is considerable uncertainty around the results (Figure 7), the stochastic parametric uncertainty and its applied distributions converge well at 10,000 iterations.

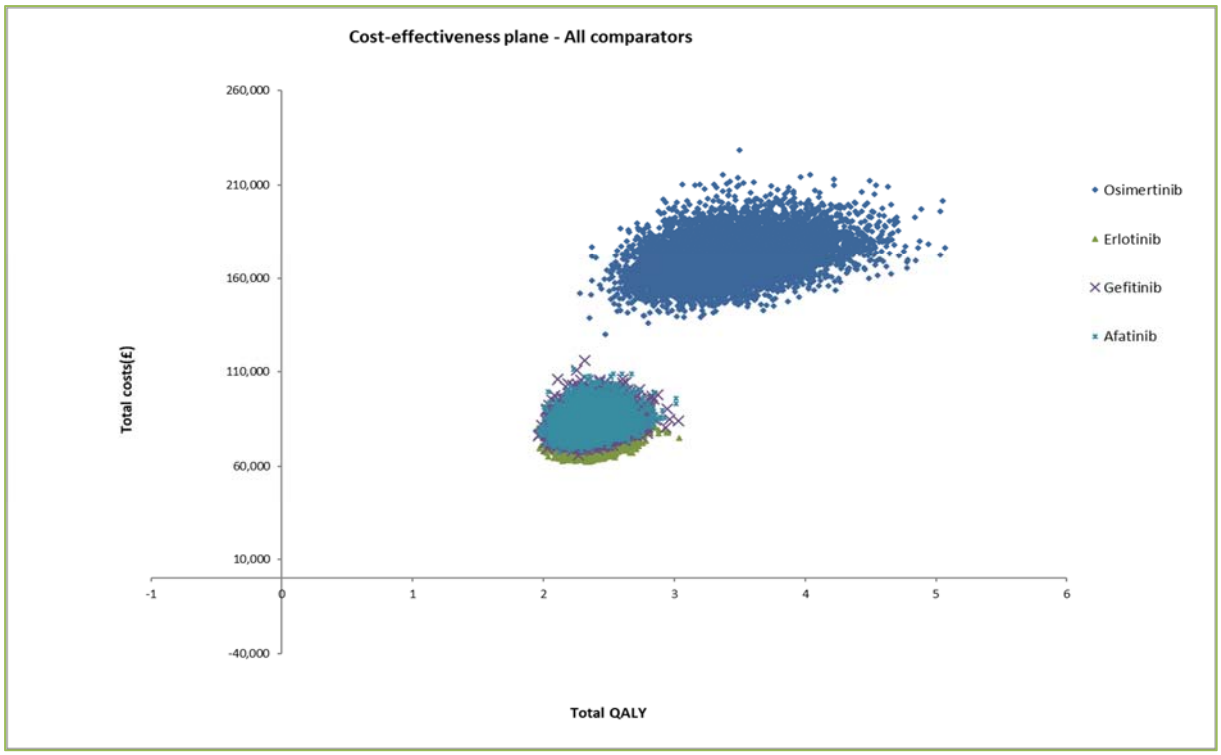

Figure 7 Scatter plot – cost effectiveness of treatment with osimertinib versus afatinib, erlotinib and gefitinib based on 10,000 iterations

Source: CS, Figure 53

The cost effectiveness acceptability curves (CEACs) in Figure 8 show the probability that each comparator is cost effective at a range of willingness-to-pay (WTP) thresholds. Treatment with erlotinib (77.95%) has the highest probability of being cost effective at a threshold of £50,000, followed by treatment with gefitinib (10.38%), afatinib (10.05%) and osimertinib (1.62%). At a threshold of £84,500 osimertinib has the highest probability of being cost effective (38%) and its probability of being cost effective increases as the threshold increases.

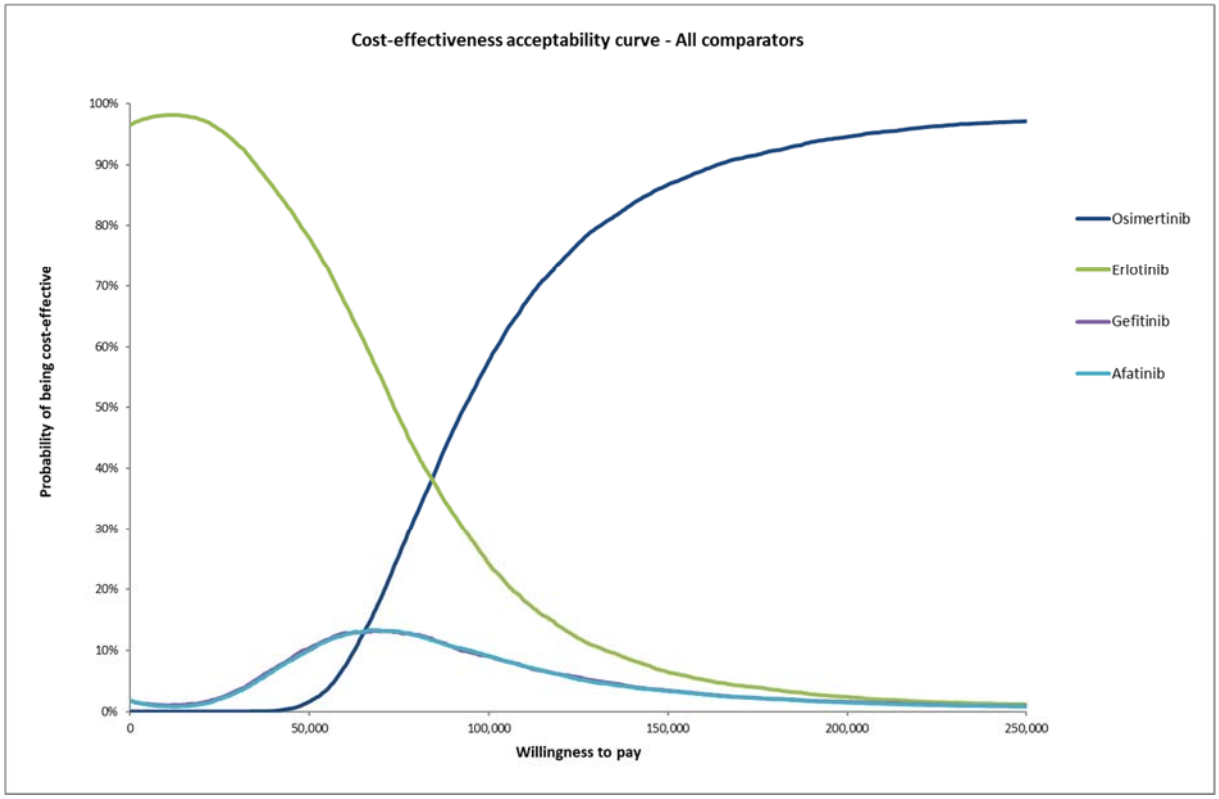

Figure 8 Cost effectiveness acceptability curve of treatment with osimertinib versus afatinib, erlotinib and gefitinib

Source: CS, Figure 54

Using the available discounts, treatment with osimertinib remained more expensive ([redacted]) and more effective (+1.07 QALYs) than treatment with gefitinib. The probabilistic pairwise ICER for treatment osimertinib versus gefitinib was [redacted] per QALY gained. At a WTP threshold of £50,000 per QALY gained, the probability of treatment with osimertinib, compared to gefitinib, being cost effective is 54%.

5.2.11 Scenario analyses

The company notes that the model is not particularly sensitive to the choice of the parametric function used to model PFS, dose estimates accounting for compliance, vial wastage, exclusion of terminal care costs and additional costs associated with CNS progression. The parameters that lead to a marked change in the base case ICERs per QALY gained are (i) discount rate applied to costs and outcomes (ii) time horizon of the model (iii) choice of parametric function used to model OS (iv) choice of parametric function used to model TDT (v) adjustment for the impact of subsequent therapy on utility value for the PD health state, and (vi) exclusion of subsequent therapy costs. Table 39 shows selected company scenario analyses results. Full details of the analyses are presented in the CS, Tables 96, 97 and 98.

Table 39 Selected company scenario analyses results

Scenario	Afatinib		Erlotinib		Gefitinib	
	ICER	% Change	ICER	% Change	ICER	% Change
Base case	£82,669	--	£89,700	--	£82,675	--
Time horizon (10 years)	£101,637	23%	£110,552	23%	£101,643	23%
Discount rate costs and outcomes (0%)	£71,190	-14%	£76,905	-14%	£71,194	-14%
Discount rate costs and outcomes (3.5%, 0%)	£66,336	-20%	£71,977	-20%	£66,340	-20%
Discount rate costs and outcomes (6%)	£90,919	10%	£98,928	10%	£90,925	10%
PFS (Weibull, dependent)	£83,408	1%	£90,483	1%	£83,413	1%
PFS (Log-logistic, dependent)	£81,111	-2%	£88,039	-2%	£81,116	-2%
OS (Exponential, piecewise)	£80,251	-3%	£87,045	-3%	£80,256	-3%
OS (Weibull, dependent)	£114,664	39%	£124,833	39%	£114,672	39%
OS (Log-logistic, dependent)	£102,422	24%	£111,395	24%	£102,429	24%
TDT (Weibull, dependent)	£93,388	13%	£100,716	12%	£93,394	13%
TDT (Gompertz, dependent)	£75,610	-9%	£82,643	-8%	£75,615	-9%
Acquisition costs based on PFS	£78,675	-5%	£85,419	-5%	£78,684	-5%
HSU PD on subsequent treatment (0.704, FLAURA)	£79,301	-4%	£86,046	-4%	£79,306	-4%
HSU PD adjusted for subsequent treatments (0.683 for the comparators only)	£91,239	10%	£98,999	10%	£91,130	10%
Wastage (included)	£83,307	1%	£90,474	1%	£83,312	1%
RDI (excluded)	£83,286	1%	£90,453	1%	£83,521	1%
Terminal cost (excluded)	£82,906	0%	£89,937	0%	£82,911	0%
TDT for osimertinib in 2L (Log-logistic, independent)	£78,244	-5%	£85,275	-5%	£78,249	-5%
TDT for osimertinib in 2L (Weibull, independent)	£83,899	1%	£90,930	1%	£83,905	1%
Second-line treatments from FLAURA	£86,621	5%	£93,652	4%	£86,626	5%
Subsequent treatments cost (excluded)	£103,776	26%	£110,807	24%	£103,782	26%
Cost of CNS progression (excluded)	£83,114	1%	£90,145	0%	£83,120	1%

CNS=central nervous system; HSU=health state utility; ICER=incremental cost effectiveness ratio; OS=overall survival; PD=progressive disease; PFS=progression-free survival; QALY=quality adjusted life years; RDI=relative dose intensity; TDT=time to discontinuation of treatment
Source: information drawn from CS, Tables 96, 97 and 98

5.2.12 Subgroup analyses

The company states that subgroup analyses were not performed as clinical data from the FLAURA trial were consistent across all the pre-specified subgroups.

5.2.13 Model validation and face validity check

The company states that input from clinical experts was sought during the model development. Also, a health economist who had not been involved in model development assessed model programming errors.

5.3 ERG detailed critique of company economic model

5.3.1 NICE reference case checklist

Table 40 NICE Reference case checklist completed by ERG

Element of health technology assessment	Reference case	Does the de novo economic evaluation match the reference case?
Defining the decision problem	The scope developed by NICE	Yes
Comparator(s)	As listed in the scope developed by NICE	Yes
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Yes
Perspective on costs	NHS and PSS	Partly. Social care costs were not considered
Type of economic evaluation	Cost utility analysis with fully incremental analysis	Yes
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes
Synthesis of evidence on health effects	Based on systematic review	N/A
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL	Partly. Utility values were derived from a mapping of EORTC QoL scores from the FLAURA trial onto EQ-5D utility values
Source of data for measurement of HRQoL	Reported directly by patients and/or carers	Yes
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	Yes
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Yes
Discounting rate	The same annual rate for both costs and health effects (3.5%)	Yes

EQ-5D=EuroQol 5-dimensions tool; HRQoL=health-related quality of life; N/A=not applicable; NHS=National Health Service; PSS=Personal Social Services; QALY=quality adjusted life year

5.3.2 Drummond checklist

Table 41 Critical appraisal checklist for the economic analysis completed by the ERG

Question	Critical appraisal	ERG comment
Was a well-defined question posed in answerable form?	Yes	
Was a comprehensive description of the competing alternatives given?	Yes	
Was the effectiveness of the programme or services established?	Partly	Only established over the 24-month period of the FLAURA trial. Lifetime treatment effect - notably on OS - was not established
Were all the important and relevant costs and consequences for each alternative identified?	Yes	
Were costs and consequences measured accurately in appropriate physical units?	Yes	
Were the cost and consequences valued credibly?	No	Costs in the PD health state were based on palliative care values from the literature; patients in the PD health state could have received active treatment
Were costs and consequences adjusted for differential timing?	Yes	
Was an incremental analysis of costs and consequences of alternatives performed?	Yes	
Was allowance made for uncertainty in the estimates of costs and consequences?	Yes	
Did the presentation and discussion of study results include all issues of concern to users?	Yes	

OS=overall survival; PD=progressed disease

5.3.3 Overview

The ERG has identified three areas of concern that cast doubt on the company's cost effectiveness results:

- The ERG considers that the company could have used more realistic values to model resource use and patient HRQoL in the PD health state.
- The company has assumed that the effect of treatment with osimertinib lasts for a lifetime.
- Second- and/or third-line treatment with an immunotherapy are possible subsequent treatment options for some patients receiving first-line treatment with an EGFR-TKI; however, these options are not included as part of the company model.

The company model comprises two different representations of effectiveness, one to model the experience of patients receiving first-line treatment with osimertinib (intervention arm) and, as afatinib, erlotinib and gefitinib are assumed to be equally effective, one that models the experience of patients receiving any one of these three drugs (the comparator arm) as a first-line treatment.

As afatinib, erlotinib and gefitinib are assumed to be equally effective, the only difference, when calculating cost effectiveness, is in terms of the costs of the three comparator drugs. The ERG highlights that erlotinib is the least expensive of the three drugs and, therefore, treatment with erlotinib dominates treatment with afatinib or gefitinib. Thus, all of the ERG's recalculated ICERs per QALY gained relate to the comparison of the cost effectiveness of treatment with osimertinib versus erlotinib.

Resource use (and, therefore, costs) in the progressed disease health state

The ERG considers that resource use during the progressed disease (PD) health state (and, therefore, costs) is overestimated. The PD resource use applied every cycle (i.e., every 30 days) in the company model includes:

- 2.14 GP home visits
- 0.65 outpatient visits
- 0.99 clinical nurse specialist visits
- 2.14 therapist visits

These values were taken from NICE guidelines[96] (Advanced breast cancer: diagnosis and treatment [clinical guidelines CG81]) and the Big Lung Trial[97]. The resource use outlined in CG81[96] relates to a package of care for people with breast cancer who are receiving palliative and supportive care only. The resource use in the Big Lung Trial[97] relates to a population with advanced NSCLC (75% Stage IIIb or IV) receiving supportive care only with a median OS of 5.7 months.

In the company model, patients in the intervention and comparator arms live for an average of 44.99 months and 31.91 months respectively in the PD health state (CS, Table 87). Furthermore, during at least part of the time in the PD health state, the company estimates that 66.7% of patients are on active therapy. The ERG, therefore, considers that the resource use outlined in CG81[96] (palliative and supportive care) and described in the Big Lung Trial[97] report (median OS less than 6 months) do not reflect the likely resource use of the appraisal population whilst in the PD health state.

The ERG was unable to find directly relevant resource use estimates for patients in the PD health state but considers that assumptions can be made that provide a better approximation of likely resource use and, therefore, of the costs in the PD health state. In the company model, when patients progress after first-line treatment, one third of patients receive no further treatment and two thirds of patients are prescribed an active therapy. The ERG has, therefore, assumed that resource use in the PD health state comprises a combination of company PFS and PD health state resource use weighted by the proportion of patients receiving second- and third-line treatments. The ERG estimate comprises one third of the company's PD health state resource use (which can be interpreted as palliative care) and two thirds of the company's PFS health state resource use (to reflect the resource use of patients receiving second- and third-line active therapies).

Compared with the company base case, implementing the ERG's preferred PD health state resource use estimate in the company model reduced the costs per cycle (30 days) in the PD health state from £595.25 to £404.04. The lifetime effect was to reduce the incremental cost of treatment with osimertinib versus erlotinib from £94,832 to £92,113 and the ICER by £1,643 to £88,057 per QALY gained.

Utility values in the progressed disease (PD) health

The utility value used by the company to reflect the HRQoL of patient HRQoL in the PD health state who are not still receiving first-line treatment is 0.64. The company considers, based on findings from their review of studies reporting health state utility values of patients with NSCLC (CS, p147), that this estimate is likely to be pessimistic given that the most relevant utility values identified via the company's literature review ranged from 0.64 to 0.853.

The ERG agrees with the company that a value of 0.64 is likely to be pessimistic as this value represents the HRQoL life of patients with 'progressing' disease and, in the model PD health state, many patients receive active therapies that could stabilise their disease or reduce tumour burden. This treatment benefit is reflected in the mean length of time that model patients spend in the PD health state (intervention arm: 44.99 months, comparator arm: 31.91

months). However, there are no published utility values that reflect the HRQoL of patients whose disease has progressed following first-line treatment and go on to receive best supportive care (BSC) or active therapies in the second- and/or third-line settings before BSC. Ideally, the model should have included different health states to reflect the different treatment pathways. Given that the company model structure means that one utility value has to capture the range of HRQoL of patients receiving second-line treatment, third-line treatment and BSC, the ERG considers that a utility value of 0.678 (the utility value from reported in TA416[43] from the he AURA 2 trial[98] [second-line treatment with osimertinib]) is more representative of the HRQoL of patients in the PD health state than the value used by the company (0.64). However, the ERG acknowledges that this value may still not be an accurate reflection of the HRQoL of patients in the PD health state.

Compared with the company base case, applying a utility value of 0.678 to reflect patient HRQoL in the PD health state resulted in incremental QALYs for the comparison of treatment with osimertinib versus erlotinib increasing from 1.046 to 1.074 and the ICER reducing by £2,343 to £87,357 per QALY gained.

Lifetime duration of treatment effect with osimertinib

FLAURA trial OS data were only available for a 2-year time period. The ERG considers that any extrapolation of 2 years of OS data over 20 years will always be uncertain, especially when there are structural breaks (i.e., where, at different points in time, survival starts following different trajectories) in the K-M data over that time period. Within the model, the company OS is represented by direct use of FLAURA trial OS K-M data for the first 8 months of the time horizon and a Weibull distribution (a different one for each arm) thereafter. The ERG is satisfied that the company's choice of a Weibull distribution to reflect long-term OS for patients in both the intervention and comparator arms of the model was supported by the available K-M data from the FLAURA trial. However, the ERG highlights that the use of these functions result in mortality for patients in the osimertinib arm being lower (approximately 60% lower), over the whole 20-year model time horizon, than that of patients in the comparator arm.

The ERG considers that it is clinically implausible that patients receiving first-line treatment with osimertinib will continue to experience a survival advantage over those receiving first-line treatment with a first- or second-generation EGFR-TKI for many years after treatment has ceased. Furthermore, such claims have not been accepted by NICE Appraisal Committees (ACs) during previous appraisals of drugs to treat NSCLC. During the appraisal of pembrolizumab for treating PD-L1 positive NSCLC after chemotherapy (Pembrolizumab for treating PD-L1-positive non-small-cell lung cancer after chemotherapy [TA428][60]), the AC considered a treatment effect of 3 years was realistic, whilst during the appraisal of

atezolizumab for treating NSCLC after platinum-based chemotherapy (Atezolizumab for treating locally advanced or metastatic non-small-cell lung cancer after chemotherapy [TA520][41]) a different AC considered that 5 years was realistic.

The company model has a partitioned survival structure and the application of a 'duration of treatment effect' within such a structure is not straightforward as the effect is likely to vary by patient and to depend on time on treatment and level of response. Given the model structure, a crude approach to limiting the duration of treatment effect on OS, one that has been accepted by previous ACs (CS, p202), is to set the morality hazard for the intervention and comparator arms to be equal after a given timepoint.

Given that, in the past, ACs have accepted that treatment durations of 3 and 5 years are realistic, the ERG has run scenarios in which the effect of treatment with osimertinib has been limited to these two durations. In addition, to reflect the period of time for which FLAURA trial data are available, the ERG has run a scenario in which the effect of treatment with osimertinib has been limited to 2 years. The 2-year scenario effectively provides an estimate of the ICER per QALY gained for the comparison of treatment with osimertinib versus SoC EGFR-TKI based on available evidence (i.e., with no modelling).

Compared with the company base case, using a 2-year duration of treatment effect, the ICER for the comparison of osimertinib versus erlotinib increased by £119,753 to £209,453 per QALY gained, a 3-year duration of treatment effect increased the ICER by £72,562 to £162,262 per QALY gained and a 5-year duration of treatment effect increased the ICER by £33,607 to £123,307 per QALY gained.

Place of immunotherapy in the treatment pathway

Data presented in the CS (Figure 14) show that during the first 3 months of 2018, 10% of patients in the UK with advanced EGFR+ NSCLC who were tested for the T790M mutation were treated with pembrolizumab. This was prior to the publication of TA531[99] (Pembrolizumab for untreated PD-L1-positive metastatic non-small-cell lung cancer) and TA520[41] (Atezolizumab for treating locally advanced or metastatic non-small-cell lung cancer after chemotherapy), which could have increased the use of immunotherapy in patients with advanced EGFR+ NSCLC after first-line treatment.

During the process of validating the model, the company was advised by clinicians (CS, p201) that the survival projections used in the model may not reflect the use of immunotherapies in the third-line setting (or the use of osimertinib as a second-line treatment). It is not known what proportion of patients in either of the model arms would be eligible, and fit enough, to receive

an immunotherapy, nor how effective immunotherapies are as second- or third-line treatments for patients who have progressed after receiving osimertinib, afatinib, erlotinib or gefitinib. Therefore, the ERG has not been able to incorporate the effect of treatment with an immunotherapy into the company model. However, the ERG highlights that the introduction of immunotherapy as a subsequent therapy in the company model would increase the QALYs and costs for both the intervention and comparator arms.

5.4 Impact on the ICER of additional clinical and economic analyses undertaken by the erg

Cost effectiveness results generated by the ERG's amendments to the company model are provided in Table 42.

Changes to the resource use and utility of patients in the PD health state reduce the company base case ICER for the comparison of treatment with osimertinib versus erlotinib to £88,057 and £87,357 per QALY gained respectively.

Limiting the duration of the effect of treatment with osimertinib has a substantial impact on the cost effectiveness of osimertinib versus erlotinib. After changing resource use and the utility of patients in the PD health state, limiting the duration of effect of osimertinib to 2, 3 and 5 years increases the ICER for comparison of treatment with osimertinib versus erlotinib to £215,753, £162,981 and £120,953 per QALY gained respectively.

Details of all the ERG's Microsoft Excel revisions to the company model are presented in Appendix 4, Section 9.4.

Table 42 ERG adjustments to company base case: osimertinib versus erlotinib (list prices)

Scenario/ERG amendment	Osimertinib			Erlotinib			Incremental			*ICER*	
	Cost	QALYs	Life Years	Cost	QALYs	Life years	Cost	QALYs	Life years	£/QALY	Change from base case
A. Company base case	[redacted]	[redacted]	***4.861***	[redacted]	[redacted]	***3.404***	[redacted]	[redacted]	***1.457***	***£89,700***	
R1) Adjusting resource use in the PD health state	[redacted]	[redacted]	4.861	[redacted]	[redacted]	3.404	[redacted]	[redacted]	1.457	£88,057	-£1,643
R2) Adjusting utility in the PD health state	[redacted]	[redacted]	4.861	[redacted]	[redacted]	3.404	[redacted]	[redacted]	1.457	£87,357	-£2,343
R3) 2-year duration of treatment effect	[redacted]	[redacted]	3.874	[redacted]	[redacted]	3.404	[redacted]	[redacted]	0.470	£209,453	+£119,753
R4) 3-year duration of treatment effect	[redacted]	[redacted]	4.077	[redacted]	[redacted]	3.404	[redacted]	[redacted]	0.672	£162,262	+£72,562
R5) 5-year duration of treatment effect	[redacted]	[redacted]	4.372	[redacted]	[redacted]	3.404	[redacted]	[redacted]	0.968	£123,307	+£33,607
B. ERG preferred scenario with 2-year durations of treatment effect (R1-R3)	[redacted]	[redacted]	**3.874**	[redacted]	[redacted]	**3.404**	[redacted]	[redacted]	**0.470**	**£215,753**	+£125,873
C. ERG preferred scenario with 3-year durations of treatment effect (R1, R2, R4)	[redacted]	[redacted]	**4.077**	[redacted]	[redacted]	**3.404**	[redacted]	[redacted]	**0.672**	**£162,981**	+£73,281
D. ERG preferred scenario with 5-year durations of treatment effect (R1, R2, R5)	[redacted]	[redacted]	**4.372**	[redacted]	[redacted]	**3.404**	[redacted]	[redacted]	**0.968**	**£120,953**	+£31,253

ERG=Evidence Review Group; ICER=incremental cost effectiveness ratio; PD=progressed disease; QALY=quality adjusted life year

5.5 Conclusions of the cost effectiveness section

Whilst the ERG is broadly satisfied with the approach to economic modelling undertaken by the company, the ERG considers that the company has overestimated resource use (and, therefore, costs) and underestimated utility for patients whose disease has progressed after first-line treatment and this has resulted in the company estimate of the cost effectiveness of treatment with osimertinib versus erlotinib being an over-estimate. However, more significantly, the company has assumed that compared with treatment with afatinib, erlotinib or gefitinib, treatment with osimertinib delivers a substantial lifetime effect on mortality for patients with previously untreated Stage IIIb/IV EGFR+ NSCLC. The ERG considers that this is an assumption that cannot be supported by the available trial data: FLAURA trial data are available for a period of 2 years whilst the company model has a time horizon of 20 years. Furthermore, this assumption has not been accepted by ACs during previous appraisals of treatments for patients with advanced or metastatic NSCLC.

When the ERG's preferred PD health state resource use and utility values were used in the model and the duration of the effect of treatment with osimertinib was reduced to 2-, 3- and 5-years, the ICER for the comparison of treatment with osimertinib versus erlotinib increased from the company base case of £89,700 per QALY gained to £215,753, £162,981 and £120,953 per QALY gained respectively.

The ERG highlights that the company model did not include a representation of the effect of treatment with an immunotherapy in the second- and third-line settings. This was not an omission that the ERG was able to rectify. However, the ERG highlights that the use of immunotherapies will increase the costs and OS associated with treatment with all EGFR-TKIs

6 END OF LIFE CRITERIA

The company puts forward a case that osimertinib, as a first-line treatment for advanced EGFR+ NSCLC, meets the NICE End of Life criteria[82] (see Table 43).

Table 43 End of Life criteria

NICE End of Life criteria	Data presented by the company
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	OS for patients with confirmed EGFR+, Stage IIIb/IV NSCLC in England and Wales is estimated to be [redacted] based on analysis of Public Health England data collected between 2014 and 2016 (n=652) (see CS, p28 for details)
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	• Results from the FLAURA trial show that, compared with SoC EGFR-TKI treatment, osimertinib extended PFS by 8.7 months (18.9 months versus 10.2 months). Treatment with osimertinib also demonstrated a substantial improvement in post-progression endpoints, including a [redacted] in time to first subsequent treatment • Whilst OS data were immature at the time of data cut-off, the HR for death was 0.63 (95% CI: 0.45 to 0.88; p=0.007), reflecting a meaningful survival advantage over SoC EGFR-TKI. In addition, early separation of the K-M curves was observed. At 18 months, 82.8% of patients receiving osimertinib were still alive, compared with 70.9% of those receiving SoC EGFR-TKI • In the absence of median OS (i.e. the 50th percentile of OS), a survival gain at other percentiles of OS may be considered as a conservative estimate of the survival gain in the mature population.[100] The 25th percentile of OS was observed at approximately 22.5 months in the osimertinib arm, and at approximately 15.9 months in the SoC EGFR-TKI arm. This reflects an improvement of 6.6 months, and while not a substitute for median OS, is clearly higher than the 3-month life extension needed to meet EOL criteria

* Precise figures for quantiles were not available; the survival estimates reflect the 75.2% percentile for osimertinib and 75.1% percentile for SoC EGFR-TKI
Source: CS, Table 29

Short life expectancy

The company presents registry data (CS, Table 5) to demonstrate that patients with advanced EGFR+ NSCLC in England and Wales have a life expectancy of less than 24 months. The company explains that this evidence is more representative of the population treated in NHS clinical practice than trial data as outcomes for NHS patients are 'considerably worse' than those of patients recruited to clinical trials who are often 'younger and fitter' (CS, p14) than NHS patients. The ERG accepts the company's argument that trial evidence may overestimate the life expectancy of the population of interest compared with that of patients treated in the NHS but considers that it is inconsistent to accept trial evidence as a measure of effectiveness but not as a measure of life expectancy. There is no real world evidence available that compares the effectiveness of treatment with osimertinib versus afatinib, erlotinib or gefitinib.

At the time of data cut off, median OS had not been reached in either arm of the FLAURA trial, but after 24 months over half (64.7%) of patients in the SoC EGFR-TKI arm were still alive.

The ERG, therefore, considers that, based on available evidence, the average life expectancy of people with advanced EGFR+ NSCLC who are eligible for treatment with afatanib, erlotinib or gefitinib is likely to exceed 24 months.

Treatment benefit

The company uses FLAURA trial PFS data in support of their claim that OS for patients treated with osimertinib is longer than that of patients treated with Soc EGFR-TKI. The ERG highlights findings from published studies[102,103] that demonstrate that PFS is not a good proxy for OS, which means that this line of argument is not robust. However, the economic modelling undertaken by the ERG (see Section 5.3) supports the company position that, compared with treatment with afatinib, erlotinib or gefitinib, treatment with osimertinib extends patient life expectancy by at least 3 months.

ERG conclusion

The ERG considers that patients with advanced EGFR+ NSCLC who are eligible for first-line treatment with afatinib, erlotinib or gefitinib have a life expectancy that is greater than 24 months. Thus, one of the NICE criteria for applying a less restrictive assessment of cost effectiveness for End of Life treatments has not been met.

7 OVERALL CONCLUSIONS

7.1 Clinical effectiveness

The data from the FLAURA trial have shown that compared with osimertinib improves PFS when compared with SoC EGFR-TKI (erlotinib or gefitinib). Benefits in PFS and CNS PFS were also reported for patients with CNS metastases, a clinically important subgroup. OS data are very immature but there appears to be evidence that OS is also improved. Safety data from the FLAURA trial show osimertinib to be at least as equally well tolerated than for patients treated with erlotinib or gefitinib in the SoC EGFR-TKI arm. Clinically relevant improvements were sustained over time in both treatment arms for the symptoms of cough (EORTC QLQ-LC13), pain (EORTC QLQ-LC13), insomnia (EORTC QLQ-LC30) and appetite loss (EORTC QLQ-LC30).

Erlotinib and gefitinib are two of the three most commonly used therapies used to treat advanced EGFR+ NSCLC in the first-line setting. The other commonly used EGFR-TKI is afatinib. The company assume equal equivalence in terms of efficacy of afatinib to erlotinib and gefitinib. If it is assumed that afatinib is as equally efficacious as erlotinib and gefitinib, then the relative benefit of osimertinib versus afatinib will be similar to the relative benefits of osimertinib versus SoC TKI reported in the FLAURA trial. From a simple indirect comparison, the ERG found osimertinib to result in improved PFS, but not OS, versus afatinib. However, the results of this indirect comparison ought to be interpreted with caution, due to the possible violation of the PH assumption for data for both PFS outcomes from the LUX-Lung 7 trial[26] and for OS data from both the FLAURA trial and the LUX-Lung 7 trial.[26] Given that in TA310[53] it was concluded that afatinib was associated with some different AEs to erlotinib and gefitinib but similar toxicity overall, the ERG considers that it is likely that osimertinib is therefore at least as tolerable as afatinib

7.2 Cost effectiveness

The cost effectiveness evidence presented by the company suggested that treatment with osimertinib generated an ICER per QALY gained of £89,700 compared to erlotinib (with erlotinib dominating afatinib and gefitinib). The ERG considered the company's progressed disease state costs were too high and utilities were too low. More importantly, for the ICER per QALY gained, the company assumed that treatment with osimertinib had a lifetime effect on mortality compared to afatinib, erlotinib and gefitinib. The ERG considered this assumption was implausible.

The ERG applied more realistic costs and utilities in the progressed disease state and limited the effect of treatment with osimertinib on mortality to 2, 3 and 5 years. Making these changes increased the ICER to £215,753, £162,981 and £120,953 per QALY gained when the effect of treatment with osimertinib on mortality ends after 2, 3 and 5 years respectively.

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9 APPENDICES

9.1 Appendix 1: Summary of comparison of the decision problem outlined in the final scope issued by NICE and that addressed within the CS

Table 44 Comparison between NICE scope/reference case and company's decision problem

Parameter	Final scope issued by NICE/reference case	Decision problem addressed in CS	Company rationale	ERG comment
Intervention	Osimertinib (Tagrisso)	As per decision problem	N/A	-
Population	People with previously untreated advanced EGFR mutation-positive non-small-cell lung cancer	As per decision problem	N/A	-
Comparator(s)	Afatinib, erlotinib, and gefitinib	As per decision problem	N/A	-
Outcomes	OS, PFS, response rate, response duration, AEs, HRQOL	As per decision problem	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 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 patient access schemes for the intervention or comparator technologies will be taken into account. The use of osimertinib is conditional on the presence of EGFR mutation status. The economic modelling should include the costs associated with diagnostic testing for EGFR mutation in people with 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.	Cost-effectiveness is expressed in terms of incremental cost per quality-adjusted life year gained. The time horizon of the model is 20 years, which is sufficient for this patient population to reflect any differences in costs or outcomes between the technologies being compared. Costs have been considered from an NHS and Personal Social Services perspective.	EGFR+ testing is currently performed routinely in this group of patients due to the availability of afatinib, erlotinib and gefitinib as a first-line treatment for EGFR+ NSCLC.	The company notes that EGFR testing is currently performed routinely in this group of patients due to the availability of afatinib, erlotinib and gefitinib as a first-line treatment for EGFR NSCLC and so there is no need for a sensitivity analysis without the cost of the diagnostic test

Parameter	Final scope issued by NICE/reference case	Decision problem addressed in CS	Company rationale	ERG comment
Subgroups to be considered	N/A	Presence vs absence of CNS metastases at baseline Asian vs non-Asian patients Exon 19 deletions vs L858R point mutations	These subgroups represent pre-specified analyses of clinical relevance in the pivotal FLAURA study	Other subgroups were also pre-specified in the FLAURA trial. However, these are 3 subgroups of particular interest
Perspective for outcomes	All direct health effects, whether for patients or, when relevant, carers	All direct health effects from patients' perspective	N/A	-
Perspective for costs	NHS and PSS	As per decision problem	N/A	-
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	20 years	N/A	-
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults	As per decision problem	N/A	-
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	EQ-5D not collected in FLAURA study so mapping algorithm applied to EORTC QLQ-C30 to convert into EQ-5D health state utility values (HSUVs)	EQ-5D data not available from FLAURA	-
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	N/A Based on mapping from EORTC QLQ-C30 collected in FLAURA which is not a preference based measure of quality of life	No preference based quality of life data collected in FLAURA	-
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	No additional equity considerations	N/A	-
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	As per decision problem	N/A	-
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	As per decision problem	N/A	-

Source: CS, Table 1 and ERG comment

9.2 Appendix 2: ERG assessment of the proportional hazards assumption

The validity of the PH assumption within a trial is best assessed by considering the H-H plot which shows the relationship between the cumulative hazard for each trial event at common time points in the two trial arms. For the PH assumption to be valid, two criteria must be met:

- the data should follow a straight line trend, with individual data points randomly distributed close to and on either side of the trend line
- the linear trend line should pass through the graph origin (zero value on both axes).

9.2.1 ERG assessment of the proportional hazards assumption for data from the FLAURA trial

As part of the ERG's clarification letter to the company, the ERG requested K-M data for the outcomes of investigator-assessed PFS and OS to inform the ERG's critique of the company's economic model. The ERG also used this K-M data to assess the validity of the PH assumption for these outcomes. For PFS by BICR assessment, the ERG digitised the K-M graph presented in the CS (CS, Figure 19) to obtain an approximate K-M dataset for which the ERG could assess the PH assumption.

Progression-free survival by investigator assessment

The H-H plot for the PFS data by investigator assessment from the FLAURA trial is provided in Figure 9. The data are distributed fairly evenly about the linear trend line, and the estimated constant (-0.01) of the linear model is very close to zero (95% CI: -0.02 to 0.00). The ERG therefore assumes that the PH assumption may hold for PFS data by BICR assessment from the FLAURA trial.

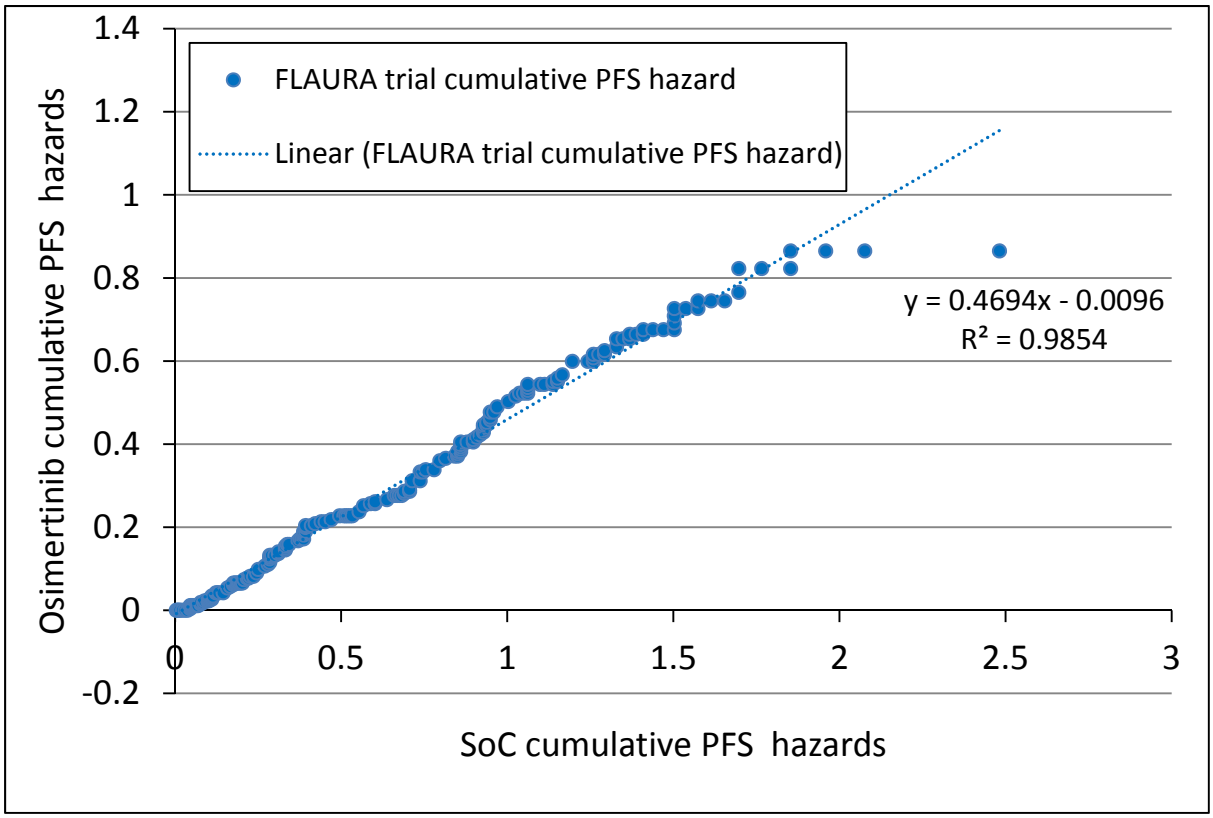


Figure 9 H-H plot for investigator-assessed PFS data from the FLAURA trial

Progression-free survival by blinded independent central review

The H-H plot for the PFS data by BICR assessment from the FLAURA trial is provided in Figure 10. The data are distributed fairly evenly about the linear trend line, and the estimated constant (0.00) of the linear model is not statistically significantly different to zero (95% CI: -0.01 to 0.01), suggesting that the linear trend line may pass through the graph origin. The ERG therefore assumes that the PH assumption may hold for PFS data by BICR assessment from the FLAURA trial.

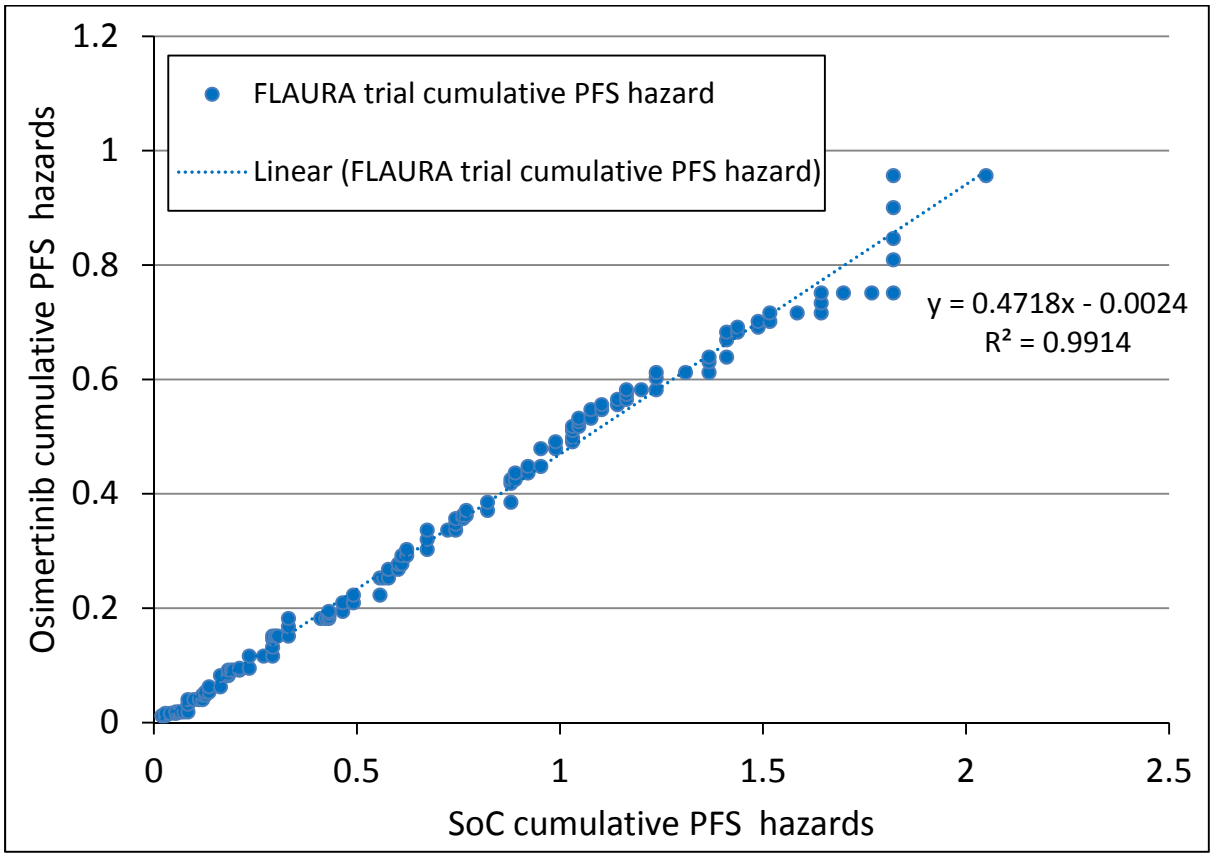


Figure 10 H-H plot for BICR-assessed PFS data from the FLAURA trial

Overall survival

Visual inspection of the H-H plot for OS data from the FLAURA trial (Figure 11) indicates that the PH assumption may not be valid. The data deviate considerably from the linear trend line, particularly in the early stages of the trial

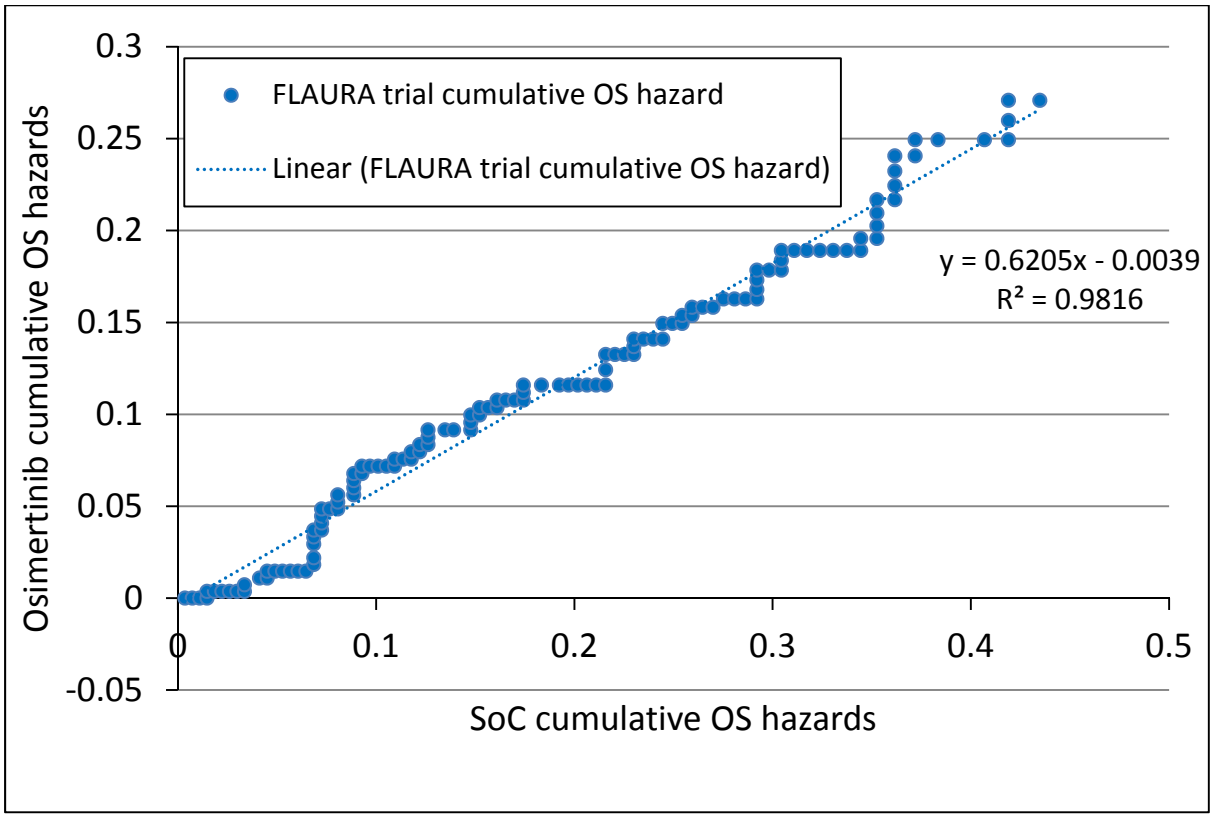


Figure 11 H-H plot for OS data from the FLAURA trial

9.2.2 ERG assessment of the proportional hazards assumption for data from the LUX-Lung 7 trial

The ERG digitised K-M graphs from the published paper for the LUX-Lung 7 trial to obtain approximate K-M datasets for investigator-assessed PFS, BICR-assessed PFS and OS, for which the ERG could assess the PH assumption.

Progression-free survival by investigator assessment

The H-H plot for the PFS by investigator assessment data from the LUX-Lung 7 trial is provided in Figure 12. The data deviate considerably from the linear trend line, and the estimated constant of the linear model (0.07) is statistically significantly different from zero (95% CI: 0.05 to 0.10). The ERG therefore considers that the PH assumption may be violated for PFS by investigator assessment data from the LUX-Lung 7 trial.

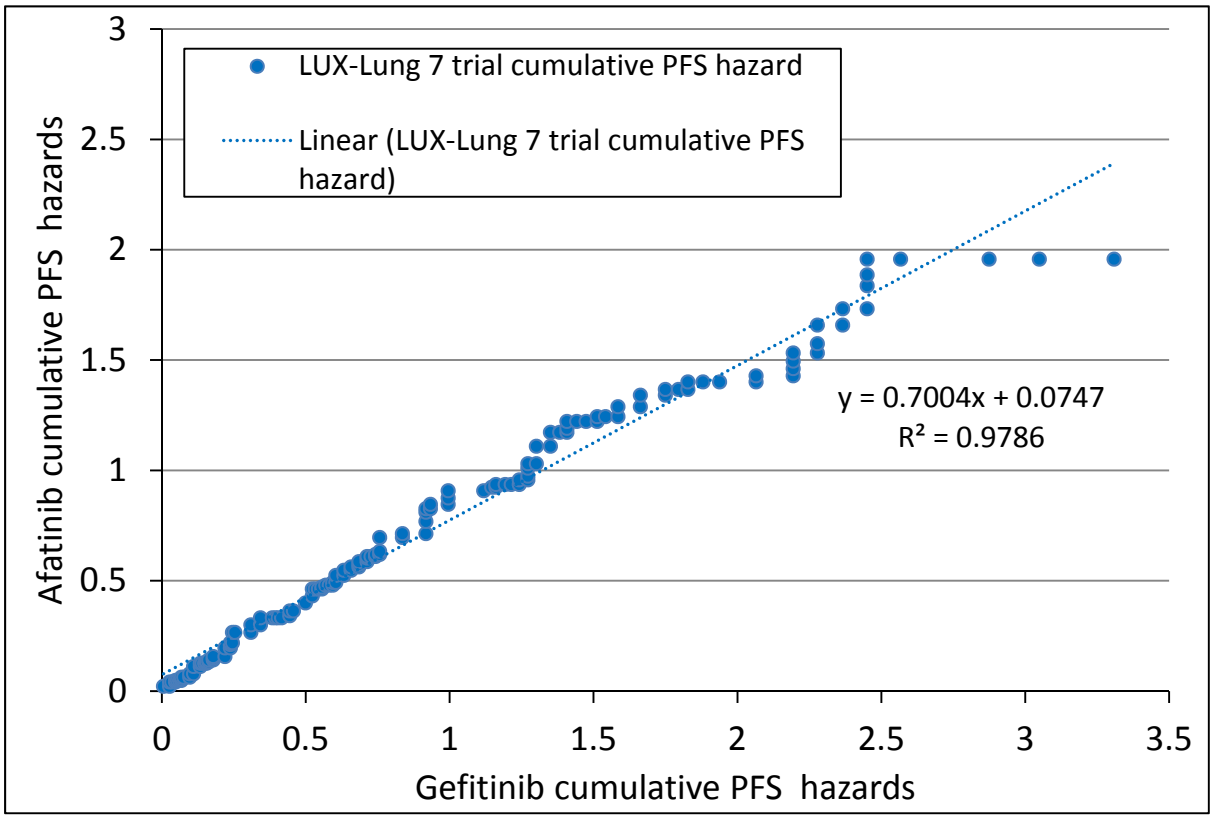


Figure 12 H-H plot for investigator-assessed PFS data from the LUX-Lung 7 trial

Progression-free survival by blinded independent central review

The H-H plot for the PFS by BICR assessment data from the LUX-Lung 7 trial is provided in Figure 13. The data deviate considerably from the linear trend line, and the estimated constant of the linear model (0.06) is statistically significantly different from zero (95% CI: 0.05 to 0.08). The ERG therefore considers that the PH assumption may be violated for PFS by BICR assessment data from the LUX-Lung 7 trial.

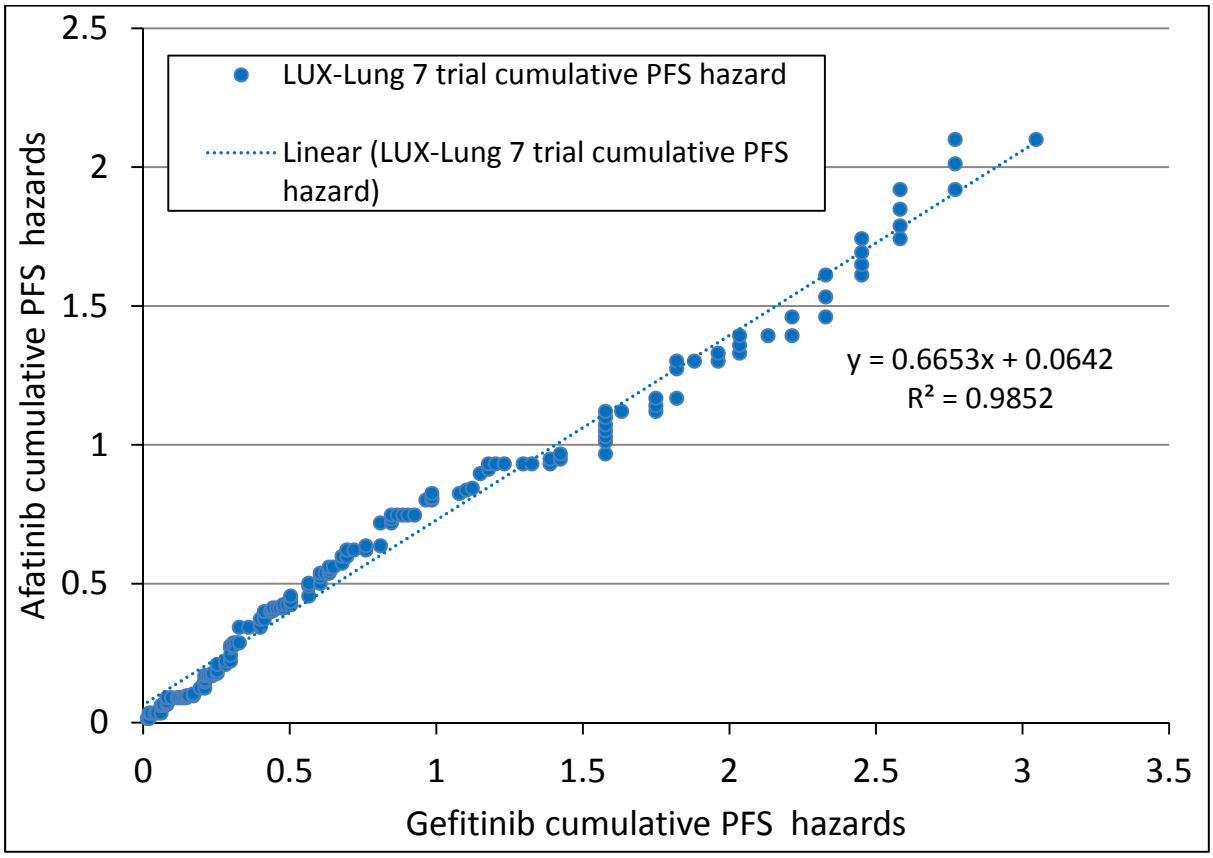


Figure 13 H-H plot for BICR-assessed PFS data from the LUX-Lung 7 trial

Overall survival

The H-H plot for the OS data from the LUX-Lung 7 trial is provided in Figure 14. The data deviate considerably from the linear trend line, particularly in the later stages of the trial, where the linear model underestimates mortality in the afatinib arm. The ERG therefore considers that the PH assumption may be violated for OS data from the LUX-Lung 7 trial.

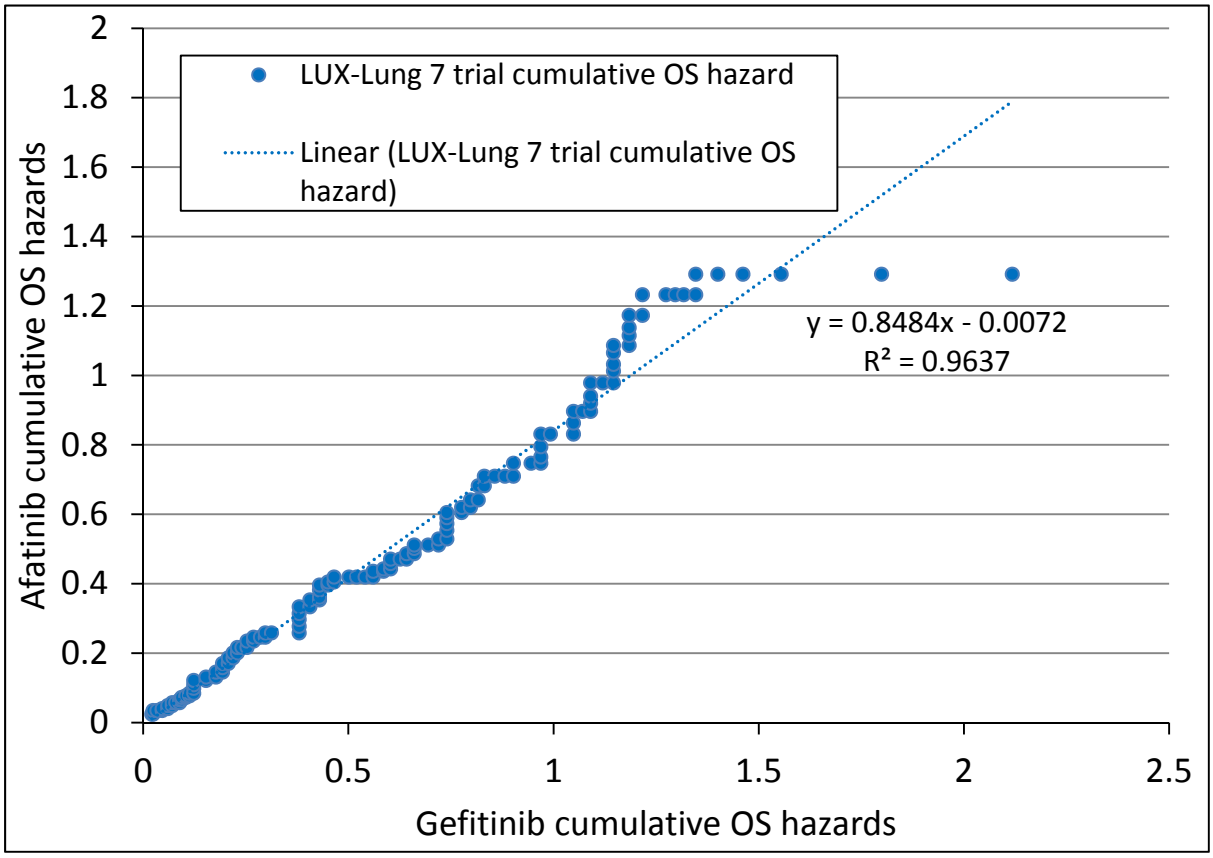


Figure 14 H-H plot for OS data from the LUX-Lung 7 trial

9.3 Appendix 3: Definitions of CNS outcomes

Definitions for the outcomes of CNS PFS, CNS ORR, and CNS DCR are provided in Table 45.

Table 45 Definitions of CNS outcomes

Outcome	Definition
CNS PFS	CNS PFS is defined as the time from randomisation until the date of objective CNS disease progression or death (by any cause in the absence of CNS progression) regardless of whether the patient withdraws from randomised therapy or receives another anticancer therapy prior to progression. Patients who have not progressed (in the CNS) or died at the time of analysis will be censored at the time of the latest date of CNS assessment from their last evaluable RECIST assessment. However, if the patient progresses or dies after two or more missed visits, the patient will be censored at the time of the latest evaluable RECIST assessment
CNS ORR	CNS ORR is defined as the number (%) of randomised patients with at least one visit response of CR or PR in the CNS. Data obtained up until progression or last evaluable assessment in the absence of progression will be included in the assessment of ORR. Patients will only non-measurable disease can only report a response of CR. Responses of CR and PR do not require confirmation in line with RECIST v1.1 criteria for randomised trials
CNS DCR	CNS DCR is defined as the percentage of patients who have a best overall CNS response of CR or PR or stable disease at ≥6 weeks, prior to any PD event. The 6-week time point will allow for a visit window and be defined as on or after study day 35 (allowing for the visit window)

CNS=central nervous system; CR=complete response; DCR=disease control rate; ORR=objective response rate; PD=progressive disease; PFS=progression-free survival; PR=partial response; RECIST=Response Evaluation Criteria In Solid Tumors
Source: Company response to the ERG clarification letter, question A15

9.4 Appendix 4: ERG revisions to the company model

This appendix contains details of the changes that the ERG made to the company model.

ERG revisions	Implementation instructions
R1) Adjusting costs in the PD health state	In Sheets 'Parameters' Set value in cell E671 =£404.04
R2) Adjusting utility in the PD health state	In Sheets 'Parameters' Set value in cell E642 =0.678
R3-R5) Altering duration of treatment effect of osimertinib	In Sheets 'Surv_calcs' Select and copy column N Paste values in column N For 2 year duration of effect (R3) Enter formula in cell N51 =N50*(P51/P50) Copy cell N51 to range N52:N271 For 3 year duration of effect (R4) Enter formula in cell N63 =N62*(P63/P62) Copy cell N63 to range N64:N271 For 5 year duration of effect (R5) Enter formula in cell N87 =N86*(P87/P86) Copy cell N87 to range N88:N271

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Osimertinib for untreated EGFR-positive non-small-cell lung cancer [ID1302]

You are asked to check the ERG report from Liverpool Reviews and Implementation Group (LRIG) to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm on Tuesday 11 December 2018** using the below proforma 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 proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Discussion point in Technical Review

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Testing of PH assumption for post-progression endpoints in FLAURA	Correction of ERG statement.	As part of the parametric modelling process the PH assumption was investigated and the various plots showed no evidence of a deviation from the PH assumption for the various post-progression end points.	The ERG requested information about PH testing during the clarification process (question A6). The company did not provide any information on post-progression endpoints in its response to question A6. In view of the new information, the ERG has amended the text slightly in its report (erratum). However, the ERG is unable to draw any firm conclusions about the reliability of the PH assumption from the new information provided (e.g. more information about the testing would be required before the ERG could conclude that there was no evidence of a deviation from the PH assumption).

Issue 2 Discussion point in Technical Review

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Implausibility of long-term effects of osimertinib on mortality rates and application of assumptions from other appraisals (on pages 15 and 97).	It is important to note the following when considering the suggested assumptions: 1. The appraisals referred to (TA428 and 520) are concerned with immunotherapies in EGFR wt NSCLC patients after chemotherapy, **not** the use of targeted therapies in EGFRm+ NSCLC patients in first-line setting. 2. The maximum duration of therapy for immunotherapies in the NHS is 2 years, whilst TKI's are given until progression or other discontinuation (in our extrapolation of time to treatment discontinuation, we estimate over 40% of patients receiving osimertinib and approximately 15% of those receiving SoC TKIs are still on treatment at 2 years). 3. The mode of action of targeted therapies is completely different from immunotherapies. 4. The disease pathology of tumours with EGFRm is different from tumours with EGFR wt.	We propose the validity of this statement and associated assumptions is discussed during the Technical Review process.	This is not a matter of factual accuracy. No changes made to the ERG report.

Issue 3 Discussion point in Technical Review

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Description of data presented in support of End of Life criteria.	It is important for the ERG to acknowledge the subgroup analysis we provided in response to the specific request in the Clarification questions. This analysis focussed on those patients with PS 0/1 (n=336), which are much more closely aligned to patients entering the FLAURA study, and yet have median OS of less than 17 months.	We propose this is discussed during the Technical Review.	The ERG have added a footnote to Table 43 of its report (erratum) to include the subgroup data presented by the company during clarification. No changes to the body of text of the ERG report (erratum) are required.

Issue 4 Discussion point in Technical Review

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
We note that the ERG have presented the results of an indirect treatment comparison against afatinib and use these estimates in a sensitivity analysis in the cost-effectiveness model. Although caution is advised in interpreting this data it is important to show the consequences of using these estimates on the modelled PFS and OS curves.	The ERG report ought to include figures demonstrating the preferred parametric curves for osimertinib, afatinib and gefitinib/erlotinib used in the cost-effectiveness model over-laid with digitised KM plots from both FLAURA and LuxLung7.	We propose this is discussed during the Technical Review.	This is incorrect. The ERG did not use the indirect comparison against afatinib in a sensitivity analysis in the CE model.

Issue 5 Correction of factual error

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG incorrectly states (page 9) that the FLAURA trial results reported so far are from an interim analysis of the primary outcome.	It should be clarified that DCO1 is the final analysis of the primary outcome in FLAURA.	The current statement may imply that the statistical significance of the reported data is reduced.	Text modified to correct this error in the ERG report (erratum).

Issue 6 Correction of factual error

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The 95% CI for PFS HR have been given units (reported as: hazard ratio [HR]=0.46, 95% confidence interval [CI]: 0.37 **months** to 0.57 **months**; p<0.001).	Delete "months" from this sentence.	Factual error.	Text modified to correct this error in the ERG report (erratum).

Issue 7 Correction of factual error

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The definition of PFS2 on page 10 is incomplete.	PFS2 is defined as "time to second progression by investigator assessment **or death by any cause in patients who have stopped randomised therapy**"	Factual error.	Text modified to correct this error in the ERG report (erratum) on page 10 and also page 37 and footnotes to Table 9 (page 43) and Table 13 (page 48).

Issue 8 Correction of factual error

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG state on page 12 that FLAURA trial results **for the majority of outcomes** …suggest that treatment with osimertinib is more efficacious than the SoC.	Please remove the qualifier **"for the majority of outcomes"** from this sentence.	All of the outcomes reported for the FLAURA study are better in the patients treated with osimertinib than those treated with SoC.	Text deleted in the ERG report (erratum) to correct this error.

Issue 9 Correction of factual error

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
It is inaccurate to state that clinicians prefer to use EGFR-TKIs on patients with EGFR+ and PD-L1+ tumours "because they have a more favourable safety profile than immunotherapies." (page 22)	It should be made clear that treatment choice in EGFR+/PD-L1+ patients is based on efficacy, rather than safety profiles.	It is important to clarify that immunotherapies have not demonstrated any benefit in patients with EGFR+ tumours. Thus, treatment choice in EGFR+/PD-L1+ patients is based on efficacy, rather than safety profiles.	Clinical advice to the ERG was that AEs of EGFR-TKIs are much more favorable than those of pembrolizumab or any immunotherapy. However, the ERG has deleted this sentence from the report (erratum) as the ERG agree it is not the primary reason EGFR-TKIs are preferred for patients with EGFR+/PD-L1+ NSCLC.

Issue 10 Correction of factual error and discussion point in Technical Review

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 2.3 Number of patients potentially eligible for first-line treatment We have identified a number of inaccuracies in the calculation used by the ERG to estimate the number of eligible patients.	Briefly, 1. Lung cancer incidence from NLCA is reported as 3**7**,761 by the ERG, but is 3**6**,761. 2. Proportion of NSCLC diagnosed as advanced is claimed by ERG to be 72-76%. a. Cancer Research UK website estimates Stage III + IV =67% b. NLCA estimates 61% 3. ERG refer to NLCA estimate of 62.5% patients receiving anti-cancer treatment, but this is based on entire population diagnosed with lung cancer.	We propose this is discussed during the Technical Review.	The ERG has checked the highlighted inaccuracies again: 1. The ERG has corrected this error in the ERG report (erratum) 2. It is stated on the Cancer Research UK site that "Lung cancer patients with a **known stage** are most commonly diagnosed at stage IV (49-53%). More people with a known stage are diagnosed at a late stage (72-76% are diagnosed at stage III or IV), than an early stage (24-28% are diagnosed at stage I or II).[1-3]" (emphasis added) However,

			data that can be downloaded from this website does show that in 2014, 67% of patients had Stage III or Stage IV lung cancer in England in 2014 but this does not exclude patients with unknown stage. Since patients with unknown stage should be considered in the calculations, the ERG has used the estimate of 67% in the ERG report (erratum) 3. The ERG has opted to use the IPSOS Mori estimate (85%) since as highlighted by the company, the NLCA estimate is for all lung

			cancer patients, not only NSCLC. Making the corrections above suggests that 2223 patients have EGFR+ NSCLC and 1890 patients are potentially eligible for treatment with an EGFR+ TKI - see ERG report (erratum), Table 3 (page 27). The ERG has corrected the text and table accordingly. Note: Using the company assumptions that 61% have advanced stage NSCLC and 79% are treated with an anticancer drug alongside the other ERG assumptions, 1881 patients are estimated to have EGFR+ NSCLC and 1599 patients are potentially eligible for treatment with an EGFR+ TKI. In the CS, the company has estimated

			that the numbers are 1608 and 1270, respectively.

Issue 11 Correction of factual error

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG incorrectly state on page 42 that "The analyses of CNS DCR and time to CNS response on the cFAS population were not pre-specified…"	This sentence should be amended as required.	Both CNS DCR and onset of CNS response are pre-specified in the study Statistical Analysis Protocol (SAP, page 66) which was provided to the ERG.	The analyses of CNS DCR and time to CNS response on the **cEFR population** were pre-specified in the SAP (p66), however the analyses of CNS DCR and time to CNS response on the **cFAS population** are not pre-specified in the SAP. Therefore, the ERG's statement is factually correct and no amendments are necessary.

Issue 12 Correction of factual error

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG has misinterpreted our response to question A9 of their clarification questions (page 50 of the ERG report). This has led to confusion about the requirement for brain scans in the FLAURA study.	This paragraph should be amended as required.	All patients with a history of, or suspected, CNS lesion were required to have a baseline scan. However, if that brain scan came back with no evidence of CNS disease, further scans were not mandated by the protocol. If the patient subsequently became symptomatic, the investigator used clinical judgement on whether to scan the patient.	Thank you for clarifying this further. In the ERG report (erratum), the ERG has amended this paragraph with the text provided by the company here.

Issue 13 Clarification of factual inaccuracy

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 54 the ERG state that: "…However, a pooled analysis of LUX-Lung 3 and LUX-Lung 6 trial data has shown an OS benefit for afatinib versus PDC (cisplatin plus pemetrexed in the LUX-Lung 3 trial and cisplatin plus gemcitabine in	It should be noted that these subgroup analyses did not form part of the confirmatory analysis strategy, no adjustment for multiplicity was done, and p values are descriptive in nature.	The results of these subgroup analyses should be interpreted with caution.	Additional text added to the ERG report (erratum), as suggested by the company.

the LUX-Lung 6 trial) in the subgroup of patients with Exon 19 deletions.			

Issue 14 Correction of factual error

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
In a number of places within the report, the ERG incorrectly states that: "…the effect of treatment with immunotherapies, which are available to some patients who progress on treatment with EGFR-TKIs , was not included in the company model." Or that a proportion of patients would receive an immunotherapy as a **second-line** treatment	All statements asserting that EGFRm+ patients would receive immunotherapies as a second-line treatment should be amended to make it clear that such patients should also have progressed on a chemotherapy regimen before an immunotherapy is offered, i.e. immunotherapy can only be used in a third-line setting (after progression on a targeted therapy and chemotherapy).	The proposed amendments are aligned with NICE recommendations for the use of immunotherapies in NSCLC.	Figure 14 in the CS showed that 13% of EGFR+ patients tested for T790M received immunotherapy second-line. As it is unlikely that patients who were tested for T790M had not received an EGFR-TKI first-line, this is evidence that some patients in the NHS who receive an EGFR-TKI first-line also receive immunotherapy second-line. No changes made to the ERG report.

Issue 15 Clarification of omitted information

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 75, the ERG states that: "The starting age of the cohort (63 years) is similar to the median age, at baseline, of the patients in the FLAURA trial (64 years)." Without further clarification this implies the inputs for the model and the results of the FLAURA study are not aligned.	We propose the following amendment: The starting age of the cohort (63 years) is **the same as the mean age and** similar to the median age (64 years), at baseline, of the patients in the FLAURA trial.	Without further clarification this statement implies the inputs for the model and the results of the FLAURA study are not aligned.	Text amended for clarity in the ERG report (erratum), as suggested by the company.

Issue 16 Correction of factual error

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 80, the ERG incorrectly states that the results of the Labbe (2017) study were generated using the UK value set.	It should be made clear that the results of the Labbe study were generated using a UK **conversion**.	The existing sentence may imply that UK patients were surveyed when, in fact a conversion algorithm was used on the results of the US-based study.	No change made to the ERG report. The UK value set is required for the conversion stated in Labbe (2017).

Issue 17 Correction of factual error

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
In Table 29, the ERG have incorrectly reported the pack size (**28 tablets**) and relative dose intensity (**98.1%**) of osimertinib.	The correct pack size for osimertinib is **30 tablets**. The correct relative dose intensity for osimirtinib is **98.9%.**	It is important to accurately report the number of tablets in a pack and relative dose intensity to calculate the cost per model cycle.	Text amended in the ERG report (erratum), as suggested by the company.

Issue 18 Clarification of ERG statement

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 97 the ERG highlights that: "the use of these functions result in **mortality** for patients in the osimertinib arm being **lower** (approximately 60% **lower**), over the whole 20-year model time horizon, than that of patients in the comparator arm."	We propose the ERG reconsiders this sentence and either provides clarification of their meaning or removes it entirely.	We note that this sentence may be interpreted in a number of different ways (with appropriate corrections). Does the ERG mean, for example: 1. that mortality **rates** for patients in osimertinib arm are lower (approx. **35%** lower)? Or that: 2. these functions result in **overall survival for patients in the SoC arm** being lower (approximately 58% lower **on average**), than that of patients in the **osimertinib** arm.	Sentence changed in the ERG report (erratum) to 'the use of these functions result in mortality for patients in the osimertinib arm being approximately 36% lower than in the SoC EGFR-TKI arm over the period that survival is extrapolated i.e. up to 20 years)''

Issue 19 Correction of factual error

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 98, the ERG quotes the CS, p202 to support the chosen method to limit the duration of treatment effect on OS.	Please clarify statement and/or correct reference.	The CS contains no acknowledgment of methods to limit treatment effect on OS.	The text 'one that has been accepted by previous ACs (CS p202)' has been deleted from the ERG report (erratum). Whilst factually true that committees used these approaches, 'acceptance' implies satisfaction with the technique which may not be the case.

Issue 20 Correction of mispelling

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 98, the ERG has stated: "…is to set the **morality** hazard for the intervention and comparator arms…"	Please replace highlighted word with "**mortality"**	This is a typographical error.	Text modified in the ERG report (erratum) to correct this error.

ERG REPORT ERRATUM

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Osimertinib for untreated epidermal growth factor receptor (EGFR) mutation-positive non-small-cell lung cancer [ID1302]

Confidential until published

This report was commissioned by the NIHR HTA Programme as project number 17/141/08

Erratum completed 9 January 2019

CONTAINS ACADEMIC IN CONFIDENCE AND COMMERCIAL IN CONFIDENCE DATA

UNIVERSITY OF LIVERPOOL | LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

The company identified 20 issues in relation to factual inaccuracies in the original Evidence Review Group (ERG) report. The pages of the original ERG report where the ERG considered minor changes were required are presented here.

1.3 Summary of the clinical evidence submitted by the company

Direct evidence

The company literature search identified only one randomised controlled trial (RCT) of osimertinib for the first-line treatment of advanced EGFR+ NSCLC, the FLAURA trial. The FLAURA trial is an ongoing international, double-blind, randomised, Phase III, multi-centre trial of osimertinib versus EGFR-TKI standard of care (SoC EGFR-TKI) in patients with advanced EGFR+ NSCLC. In the FLAURA trial, the SoC EGFR-TKI arm consisted of erlotinib or gefitinib. After investigator-assessed objective disease progression based on response evaluation criteria in solid tumours (RECIST) v1.1, patients randomised to the SoC EGFR-TKI arm had the option to cross over to treatment with open-label osimertinib provided that specific criteria were met. The criteria included the need for confirmation of the presence of the T790M mutation.

Baseline characteristics of patients enrolled into the FLAURA trial were well-balanced between the osimertinib and SoC EGFR-TKI arms. The majority of patients were female (63%), had never smoked (64%) and had metastatic disease (95%). Around a fifth of patients (21%) were considered to have CNS metastases, while most patients were classified as 'Asian' (62%) as opposed to 'White' (36%) and had Exon 19 deletions (58%) as opposed to L858R point mutations (42%). The majority of patients had World Health Organization (WHO) performance status (PS) 1 (restricted activity) (59%) as opposed to PS 0 (normal activity) (41%) and the median age of all patients was 64 years.

The analysis of the primary outcome of investigator-assessed progression-free survival (PFS) was carried out after a median duration of 15.0 months (range: 0 to 25.1) follow-up in the osimertinib arm and 9.7 months (range 0 to 26.1) follow-up in the SoC EGFR-TKI arm (61.5% maturity for PFS overall). This is the final analysis for PFS but is an interim analysis for OS. A final OS analysis will be conducted at 60% maturity, with data expected to be available in [redacted].

For the primary outcome of investigator-assessed PFS, patients in the osimertinib arm experienced statistically significantly longer PFS in comparison to patients in the SoC EGFR-TKI arm (hazard ratio [HR]=0.46, 95% confidence interval [CI]: 0.37 to 0.57 ; p<0.001). Median PFS was 18.9 months (95% CI: 15.2 months to 21.4 months) and 10.2 months (95% CI: 9.6 months to 11.1 months) in the osimertinib and SoC EGFR-TKI arms, respectively. PFS assessed by blinded independent central review (BICR) was analysed as a sensitivity analysis for the primary outcome. The results from this analysis were consistent with the investigator-assessed PFS results. In addition, numerically fewer patients in the osimertinib arm [redacted] experienced CNS progression than in the SoC EGFR-TKI arm and [redacted].

The company performed subgroup analyses for investigator-assessed PFS for several pre-specified characteristics. Treatment with osimertinib was favoured over treatment with Soc EGFR-TKI for all pre-specified subgroups, including subgroups defined according to the presence or absence of CNS metastases at trial entry, ethnicity (Asian versus non-Asian) and EGFR mutation type (Exon 19 deletions or L858R point mutations). CNS PFS was also nominally statistically significantly improved in patients with CNS metastases.

There was no statistically significant difference between the osimertinib and SoC EGFR-TKI arms in terms of investigator-assessed ORR, osimertinib: 80% (95% CI: 75% to 85%) and SoC EGFR TKI: 76% (95% CI: 70% to 81%), odds ratio (OR)=1.27 (95% CI: 0.85 to 1.90). However, the disease control rate (DCR) and duration of response were improved with osimertinib versus Soc EGFR-TKI. A statistically significant OR was observed for DCR (OR=2.78, 95% CI: 1.25 to 6.78; p=0.01) and the difference in duration of response was described as clinically meaningful.

Overall survival (OS) data were very immature (25% of events) and confounded by treatment crossover (55 [20%] patients in the SoC EGFR-TKI arm crossed over and received osimertinib as second-line therapy). Nonetheless, the reported HR for osimertinib versus SoC EGFR-TKI was 0.63 (95% CI: 0.45 to 0.88; p=0.007). Due to the hierarchical statistical testing strategy employed in the FLAURA trial, a p-value of less than 0.0015 was required to achieve statistical significance in this instance. Therefore, it was not possible to conclude that osimertinib statistically significantly improved OS in comparison to Soc EGFR-TKI. Since median OS (i.e., the 50% percentile of OS) could not be calculated, the company presented the 25th percentile of OS as a "conservative estimate of the survival gain in the mature population". The 25th percentile of OS was observed at approximately 22.5 months in the osimertinib arm, and at approximately 15.9 months in the SoC EGFR-TKI arm, corresponding to a survival gain of 6.6 months.

The company also examined the three post-progression endpoints: time to first subsequent therapy (TFST), time to second progression by investigator assessment or death by any cause in patients who have stopped randomised therapy (PFS2) and time to second subsequent therapy (TSST). For each of these post-progression endpoints, the reported HRs suggested that treatment with osimertinib was statistically significantly more effective than treatment with Soc EGFR-TKI. The company states that the improvements in these post-progression endpoints are clinically meaningful. Furthermore, the company states that these post-progression endpoint results demonstrate that the PFS advantage of osimertinib is largely preserved beyond initial progression and provide reassurance that a clinically meaningful OS benefit will be observed in the fully mature dataset.

Overall, rates of adverse events (AEs) were generally similar between the two FLAURA trial treatment arms, although there were lower rates of Grade ≥3 AEs, less frequent hepatic and rash AEs and a lower treatment discontinuation rate due to AEs in the osimertinib arm when compared with the SoC EGFR-TKI arm.

As part of the FLAURA trial, patient reported symptoms and health-related quality of life (HRQoL) data were collected via the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Lung Cancer 13 items (EORTC QLQ-LC13) and European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30 items (EORTC QLQ-LC30) questionnaires. No statistically significant or clinically meaningful differences were reported between arms. European Quality of Life 5-Dimension (EQ-5D) data were not collected as part of the FLAURA trial.

Indirect evidence

Although direct evidence for osimertinib versus afatinib is lacking, the company decided not to perform an indirect comparison of osimertinib versus afatinib for two reasons. First, the proportional hazards (PH) assumption was possibly violated for OS in the FLAURA trial and the PH assumptions for PFS and OS were possibly violated in the LUX-Lung 7 trial. Second, available evidence from a recent network meta-analysis and the conclusions reached by an Appraisal Committee (AC) during a previous NICE STA (TA310) suggest that assuming equivalence of efficacy of afatinib, erlotinib and gefitinib is reasonable.

1.4 Summary of the ERG's critique of clinical effectiveness evidence submitted

Direct evidence

As is usually the case with clinical trials, patients were fitter in the trial than are routinely seen in NHS clinical practice. Results from a recent analysis of real-world data (652 patients treated with EGFR-TKIs for advanced first-line EGFR+ NSCLC in clinical practice in England), showed that where PS was known (in 448 patients), [redacted] had PS 2 or 3. The FLAURA trial only included patients with PS ≤1.

Generally, the ERG considers that the company's approach to analysing the data from the FLAURA trial was appropriate. The ERG also assessed the validity of the PH assumption for the outcomes of PFS (investigator assessed and BICR-assessed) and OS, since these are the relevant time-to-event outcomes listed in the final scope issued by NICE. The ERG agrees with the company that the PH assumption is reasonable for both investigator-assessed and BICR-assessed PFS. However, the ERG considers that the PH assumption may be violated for OS and, consequently, that the reported OS HR should be interpreted with caution. It is

not possible to know whether the reported HR overestimates or underestimates the effect of osimertinib versus Soc EGFR-TKI. The ERG also notes that whilst HRs for TFST, PFS2, TSST and CNS PFS were presented in the CS, the company did not report it had tested the PH assumption for any of these outcomes and therefore, the reliability of these HRs is uncertain.

FLAURA trial results, including the primary outcome of PFS, suggest that treatment with osimertinib is more efficacious than the Soc EGFR-TKI and has a similar, if not better, safety profile. The FLAURA trial is the first trial to have demonstrated a PFS benefit in patients with CNS metastases although to the ERG's knowledge, the LUX-Lung 7 trial of afatinib versus gefitinib is the only other trial to have conducted a subgroup analysis in a similar group of patients.

The ERG agrees with the company that the FLAURA trial OS results are encouraging and appear to be supported by post-progression endpoints (TFST, PFS2 and TSST), notwithstanding the caveat that the PH assumption may be violated for OS and it has not been reported that it was tested for TFST, PFS2 or TSST. The ERG also highlights that is difficult to predict whether the OS benefit observed at an early interim analysis will be maintained in the longer-term.

The company considers that osimertinib is generally well tolerated and that FLAURA trial safety findings are generally consistent with the known safety profile of osimertinib (including QT prolongation, cardiac effect and interstitial lung disease). However, the ERG observes that compared to previous studies of osimertinib reported in the European Medicines Agency European Public Assessment Report (EPAR), the rates of serious adverse events (SAEs) in the osimertinib arm of the FLAURA trial (21.5%) were lower than previously reported (35.3% to 46.7%). The same is also true for treatment-related SAEs (2.9% in the FLAURA trial, 5.6% to 13.3% in previous trials).

Indirect evidence

The ERG notes that previous ACs have concluded that afatinib is likely to have similar efficacy to erlotinib and gefitinib. However, the ERG is also aware that in the exploratory Phase IIb LUX-Lung 7 trial, afatinib resulted in a statistically significant improvement in PFS compared with gefitinib. In the absence of any estimates of efficacy for osimertinib versus afatinib, the ERG therefore decided to conduct a simple indirect comparison. The results of the ERG's indirect comparison suggest that osimertinib statistically significantly improves PFS (by both investigator assessment [HR=0.59, 95% CI: 0.43 to 0.82] and BICR [HR=0.62, 95% CI: 0.44

2.2 Company's overview of current service provision

The company's overview of current service provision, presented in the CS, is summarised in Sections 2.2.1 to 2.2.5 of this ERG report. The ERG considers that the information in these sections presents an accurate summary of current service provision.

2.2.1 Goals of treatment

As highlighted by the company (CS, p32), treatment intent is not curative in advanced NSCLC, and goals usually focus on prolonging survival, improving quality of life, and alleviating symptoms. Potential benefits of treatment should be balanced with the risk of additional toxicities.[14]

2.2.2 First-line treatment for patients with EGFR+ NSCLC

Prior to first-line treatment for advanced NSCLC, patients in NHS clinical practice with non-squamous cancers have their tumours routinely tested for EGFR status. As noted by the company (CS, p25), tumour tissue biopsy is the preferred method for EGFR testing. The ERG notes that patients' tumours are also typically tested for programmed death-ligand 1 (PD-L1) expression and anaplastic lymphoma kinase (ALK) mutations at the same time that they are tested for EGFR.

If a patient is found to harbour EGFR mutations, they usually receive targeted therapy, namely an EGFR tyrosine kinase inhibitor (EGFR-TKI). First-generation EGFR-TKIs include erlotinib and gefitinib and second-generation EGFR-TKIs include afatinib and dacomitinib. Currently, afatinib, erlotinib and gefitinib are the EGFR-TKI treatments recommended by NICE for advanced EGFR+ NSCLC[15] and are considered standard of care (SoC) in the first-line setting (CS, p13). Dacomitinib is not presently used in NHS clinical practice but is currently being appraised by NICE, in a different Single Technology Appraisal (STA), versus afatinib, erlotinib and gefitinib with final guidance expected to be published in August 2019.[16]

If a patient is found to have a tumour expressing PD-L1 (PD-L1+ NSCLC), they may also receive targeted therapy. Typically, this will either be an EGFR-TKI assuming they tested positive for EGFR (i.e. EGFR+ NSCLC) or pembrolizumab, which is a type of immunotherapy.

Clinical advice to the ERG is that EGFR mutations and ALK mutations are usually mutually exclusive, the theory being there can only be one driver gene mutation. Therefore, no further consideration is given to patients with tumours that test positive for ALK in this ERG report.

2.3 Number of patients potentially eligible for first-line treatment

The company estimates that approximately 1600 patients in England are likely to be diagnosed with advanced EGFR+ NSCLC of whom, 79% may be eligible for first-line treatment with an EGFR-TKI (Table 2).

Table 2 Company's estimate of the number of patients with advanced EGFR+ NSCLC eligible for first-line treatment in England

Number	Assumption	Source
55,619,400	Population of England (2017), adjusted with an annual growth factor of 0.6%	ONS
37,231	Incidence of lung cancer in the UK (0.067% back-calculated)	RCP[2]
32,950	Patients with NSCLC (88.5%)	RCP[2]
20,099	Advanced stage NSCLC (Stage IIIb or Stage IV) (61%)	RCP[2]
16,080	Tested for EGFR (80%)	Assumption
1608	With a confirmed EGFR mutation (10%)	Li et al 2013[45]
1270	Recorded as treated with an anticancer drug (79%)	Assumption

NSCLC=non-small cell lung cancer; RCP=Royal College of Physicians
Source: CS, Table 3

The ERG questions some of the assumptions employed to generate the numbers displayed in Table 2, namely:

- The incidence of lung cancer in the UK cited by the company is 37,231; this figure is stated to be taken from the RCP National Lung Cancer Audit (NLCA) Annual Report 2017;[2] the ERG observes that 37,761 cases are in fact cited in this report.[2]
- The incidence of patients with advanced stage NSCLC (61%) is lower than the previously cited 70% in the CS (p13 – see also Section 2.1 of this ERG report), despite both data sources being reported to be the same (RCP NLCA Annual Report 2017);[2] the proportion in Table 2 is also lower than that reported by Cancer Research UK (72% to 76% of patients with known stage, 67% of all patients in England in 2014).[46]
- The proportion of patients who are tested for EGFR is reported to be 80%, this appears to be a low estimate (see also Section 2.2.2 of this ERG report).
- The proportion of patients classified as EGFR+ is slightly lower than previously cited in the CS (CS, p13; see also Section 2.1 of this ERG report); the company has employed a lower estimate of a range (10% to 20%) for people classified as 'whites' from a 2013 review[45] in Table 2 when it previously cited a different review which found the incidence to be 12% in England.[9]
- The assumed proportion of patients treated with an anticancer drug (79%) matches neither of the estimates cited later in the CS (p48): 62.5% from the RCP NLCA Annual Report 2017[2] (which refers to all lung cancer patients, not NSCLC only) and 85% from the Ipsos MORI study.[17]

The ERG, therefore, considers that the company's estimate may be slightly low. The ERG estimates that the number of patients diagnosed with advanced EGFR+ NSCLC in England may be approximately 2200 patients, of whom 85% may be treated with an EGFR-TKI (Table 3).

Table 3 Alternative estimate of the number of patients with advanced EGFR+ NSCLC eligible for first-line treatment in England

Number	Assumption	Source
36,761	Incidence of lung cancer in England and Wales (2016)	RCP[2]
32,533	Patients with NSCLC (88.5%)[a]	RCP[2]
21,797	Advanced stage NSCLC (Stage IIIb or Stage IV) (74%)[b]	CRUK[46]
18,528	Tested for EGFR (85%)[c]	Assumption
2223	With a confirmed EGFR mutation (12%)	Midha et al 2015[9]
1890	Estimated to be treated with an anticancer drug (85%)	IPSOS Mori[17]

CRUK=Cancer Research UK; EGFR=epidermal growth factor receptor; NSCLC=non-small cell lung cancer; RCP=Royal College of Physicians

[a] RCP Information for public reports incidence of patients with NSCLC to be 85% to 90%;[2] estimate of 88.5% used to be consistent with company

[b] Reported to be 72% to 76% by CRUK[46] and so mid-value used

[c] Estimate from clinical advice to the ERG

randomised treatment beyond disease progression. Dose reductions were permitted for patients treated with osimertinib (to 40mg) and erlotinib (to 100mg). Dose interruptions were also permitted for patients treated with osimertinib, erlotinib or gefitinib. Treatment beyond progression and dose reductions or interruptions occurred at the investigator's discretion; treatment beyond progression if a continuation of clinical benefit was expected, dose reductions or interruptions if a patient experienced a Grade ≥3 AE and/or unacceptable toxicity.

After investigator-assessed objective disease progression based on response evaluation criteria in solid tumours (RECIST) v1.1, patients randomised to the SoC EGFR-TKI arm had the option to crossover to treatment with open-label osimertinib provided specific criteria were met (CS, p70). The criteria included the need for confirmation that a patient had EGFR T790M+ NSCLC from biological material collected after disease progression. Confirmation had to be from tissue biopsy or, in countries that approved ctDNA testing, from plasma.

The outcomes relevant to the final scope[47] issued by NICE and the decision problem addressed by the company were analysed: PFS by investigator assessment (primary outcome) and blinded independent central review (BICR), ORR, OS, AEs and HRQoL In addition, other outcomes included time to first subsequent therapy (TFST), time to second progression by investigator assessment or death by any cause in patients who have stopped randomised therapy (PFS2), time to second subsequent therapy (TSST) and CNS PFS by BICR.

The median duration of follow-up for PFS was 15.0 months (range: 0 to 25.1) in the osimertinib arm and 9.7 months (range: 0 to 26.1) in the SoC EGFR-TKI arm. A final OS analysis will be conducted at 60% maturity, with data expected to be available in [redacted] (CS, p17).

4.3.2 Baseline characteristics of patients in the FLAURA trial

The company reports (CS, p61) that baseline characteristics were well balanced between the osimertinib and SoC EGFR-TKI arms. The ERG concurs with the company's view. As expected from a clinical trial of a population of patients with advanced EGFR+ NSCLC, the majority of patients were female (63%), had never smoked (64%) and had metastatic disease (95%) (CS, Table 15). Around one fifth of patients (21%) were considered to have CNS metastases, while most patients were classified as 'Asian' (62%) as opposed 'White' (36%) and had Exon 19 deletions (63%) as opposed to L858R point mutations (37%). The majority of patients had WHO PS 1 (restricted activity) (59%) as opposed to WHO PS 0 (normal activity) (41%) and the median age of all patients was 64 years. As is generally the case with clinical trials, the ERG observes that trial patients were fitter than patients who are commonly seen in NHS clinical practice. Results from a recent real-world analysis of data from 652 patients

4.6 Statistical approach adopted for the FLAURA trial

Information relevant to the statistical approach taken by the company has been extracted from the clinical study report (CSR),[65] the trial statistical analysis plan (TSAP),[66] the trial protocol,[67] and from the CS.

A summary of checks made by the ERG to assess the statistical approach used to analyse data from the FLAURA trial is provided in Table 8.

Table 8 ERG assessment of statistical approach used to analyse data from the FLAURA trial

Review process	ERG comment
Was an appropriate sample size calculation specified in the trial protocol/TSAP?	Yes, in the protocol (pp99-100).
Were all primary and secondary outcomes presented in the CS pre-specified?	The primary outcome and key secondary outcomes were pre-specified in the protocol (pp101-108). Various other outcomes were also reported for the cFAS and cEFR populations (CS, pp87-90); these analyses were mostly pre-specified in the TSAP (pp62-70). The ERG notes that the outcomes of CNS DCR and time to CNS response were presented for both the cFAS and cEFR populations, but these outcomes were both pre-specified to be analysed for the cEFR population only (TSAP, p66).
Were definitions for all relevant outcomes provided?	Definitions for the primary outcome and key secondary outcomes were provided in the protocol (pp101-108). As part of the ERG clarification letter to the company, the ERG requested that the company provide definitions for various outcomes measured only in the cFAS and/or cEFR populations, as these definitions were not explicitly stated in the TSAP/protocol. The company provided these definitions in their response to questions A15, A19 and A21 of the ERG clarification letter.
Were all relevant outcomes defined and analysed appropriately?	The company used a hierarchical testing strategy; PFS, OS and CNS PFS were tested in this sequential order as pre-specified in the TSAP (p40). This strategy was employed to preserve the overall type 1 error rate (alpha) at 0.05. If any previous analysis in the sequence was not statistically significant, then the following outcome would not be tested for statistical significance. Since two analyses of OS were planned (interim and final), the Lan DeMets approach that approximates the O'Brien and Fleming spending function was pre-specified (TSAP, p40), in order to maintain the overall alpha at 0.05 across the two planned analyses of OS. For the interim analysis of OS presented in the CS, a p-value of less than 0.0015 was required to determine statistical significance. The ERG notes that HRs were calculated for several time-to-event outcomes presented in the CS. The company confirmed in their clarification response (question A6) that the PH assumption was assessed for the outcomes of investigator-assessed PFS, BICR-assessed PFS and OS by visually assessing cumulative hazard plots and concluded that the assumption of PH for these outcomes is reasonable. However, the ERG notes that the company did not state that the PH assumption was assessed for other time-to-event outcomes presented in the CS (see text below table for more information).

Review process	ERG comment
Were all subgroup analyses and sensitivity analyses presented in the CS pre-specified?	The company performed subgroup analyses for the primary outcome, investigator-assessed PFS, for several patient characteristics that were pre-specified in the TSAP (pp46-47). The company also presented efficacy analyses for secondary outcomes for key subgroups of interest (presence versus absence of CNS metastases at baseline by investigator assessment, Exon 19 deletions versus L858R point mutations, and Asian versus non-Asian ethnicity) (CS, pp86-87, pp91-94). The ERG notes that these subgroup analyses were pre-specified in the TSAP for PFS and ORR (TSAP, pp46-50, p68), but not for OS and DCR. Various other outcomes were also reported for the cFAS and cEFR populations (CS, pp87-90); these analyses were mostly pre-specified in the TSAP (pp62-70). The ERG notes that the analyses of CNS DCR and time to CNS response on the cFAS population were not pre-specified (see ERG comment on "Were all primary and secondary outcomes presented in the CS pre-specified?"). The analysis of PFS by BICR-assessment was presented as a sensitivity analysis in the CS (pp73-75); this analysis was pre-specified in the TSAP (p45).
Were all protocol amendments carried out prior to analysis?	Protocol amendments and rationale for these amendments are provided in the CSR (CSR, pp78-89). The ERG is satisfied with the rationale for the amendments and notes that all amendments were made before the data cut-off date for the primary analysis (12 June 2017), so amendments were not driven by the results of the trial. A key change to the protocol was that the hierarchical testing strategy was updated; the company removed the testing of PFS in the subgroup of T790M+ patients and instead tested CNS PFS in the cFAS population. The reason for this change was that, initially, the company had evidence that up to 40% of TKI-naïve, EGFR+, NSCLC patients are T790M+.[68,69] However, during the conduct of the study, it became apparent to the company that this high incidence of de novo T790M+ may have been the result of a tissue preparation artefact.[70,71] Indeed, only 5 patients in the FAS population were T790M+ (based on tissue and/or ctDNA testing), and the company therefore did not perform an analysis of PFS in the T790M+ patient subgroup. Due to recent evidence of clinical activity of osimertinib in CNS,[72] CNS PFS was instead included in the multiple testing strategy.
Was a suitable approach employed for handling missing data?	The company's approach for handling missing data was pre-specified in the TSAP (TSAP, p25, pp27-31, pp33-34). The ERG considers the company's approach to be suitable.

BICR=blinded independent central review; cEFR=CNS evaluable for response set; cFAS=CNS full analysis set; CNS=central nervous system; CSR=clinical study report; ctDNA=circulating tumour DNA; DCR=disease control rate; EGFR=epidermal growth factor receptor; FAS=full analysis set; HR=hazard ratio; NSCLC=non-small cell lung cancer; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; PH=proportional hazards; TKI=tyrosine kinase inhibitor; TSAP=trial statistical analysis plan
Source: CS, CSR, trial protocol, TSAP and ERG comment

Generally, the ERG considers that the company's statistical approach for the analysis of data from the FLAURA trial was appropriate.

The analyses of CNS DCR and time to CNS response on the cFAS population were not pre-specified, and the subgroup analyses for presence versus absence of CNS metastases at baseline by investigator assessment, Exon 19 deletions versus L858R point mutations, and Asian versus non-Asian ethnicity were not pre-specified for the outcomes of OS and DCR. The reporting of analyses that were not pre-planned, without justification for why these additional analyses were performed, raises concerns about whether "data dredging" might have occurred, i.e. performing multiple statistical tests which are not based on pre-specified

study hypotheses, in the hope of finding statistically significant or favourable results. Each additional statistical test performed for a trial increases the likelihood of false positives occurring, and this ought to be considered when interpreting the results of post-hoc analyses.

Furthermore, the testing of the proportional hazards (PH) assumption was not reported for several time-to-event outcomes for which HRs were presented in the CS, and the ERG assessed that the PH assumption may be violated for OS data from the FLAURA trial. HRs are only an appropriate measure of treatment effect if the PH assumption is valid, that is, if the event hazards associated with the intervention and comparator data are proportional over time.[73] A summary of the company's and ERG's assessments of PH for each of the outcomes for which HRs were presented in the CS is provided in Table 9.

Table 9 Summary of the company and ERG assessments of PH for time-to-event outcomes from the FLAURA trial

Outcome(s)	Company assessment of PH	Company conclusion	ERG assessment of PH	ERG conclusion
PFS by investigator assessment	Visual examination of the log-cumulative hazard plot and Cox-Snell residuals plot (CS, Figure 34 and Figure 35)	PH assumption is appropriate	Visual examination of the HH plot (Appendix 2 to this ERG report, Section 9.2, Figure 9)	PH assumption is appropriate
PFS by BICR	Visual examination of the log-cumulative hazard plot (CS, Figure 30)	PH assumption is appropriate	Visual examination of the HH plot (Appendix 2 to this ERG report, Section 9.2, Figure 10)	PH assumption is appropriate
OS	Visual examination of the log-cumulative hazard plot (CS, Figure 37 and Figure 38)	"No clear violation of PH" (CS, p125). In the company's economic base-case analysis, the company has assumed that PH holds for OS beyond 7.9 months	Visual examination of the HH plot (Appendix 2 to this ERG report, Section 9.2, Figure 11)	PH assumption may be violated; reported HR should be interpreted with caution. It is unknown whether the reported HR would overestimate or underestimate treatment effect
• TFST • PFS2 • TSST • CNS PFS (by BICR)	None reported in the CS or company's response to clarification question A6 from the ERG	N/A	None (outcomes not listed in the final scope issued by NICE)	It is unknown whether the PH assumption, and consequently the reported HR, is valid for each of these outcomes

BICR=blinded independent central review; CNS=central nervous system; HR=hazard ratio; HH plot=a plot to show the relationship between the cumulative hazard for each trial event at common time points in the two trial arms; N/A=not applicable; OS=overall survival; PFS=progression-free survival; PFS2=time to second progression or death by any cause in patients who have stopped randomised therapy; PH=proportional hazards; TFST=time to first subsequent therapy; TSST=time to second subsequent therapy

4.7 Efficacy results from the FLAURA trial (all included patients)

The data cut-off date for all results presented in Section 4.6 is 12 June 2017, the date of the primary PFS analysis.

sequential use of EGFR-TKIs, use of bevacizumab and other treatments not recommended by NICE.

4.7.5 Secondary outcomes: post-progression endpoints

The results of the analyses of post-progression endpoints, TFST, PFS2 by investigator assessment and TSST are provided in Table 13.

Table 13 Results of the analyses of post-progression outcomes (FAS)

Outcome		Osimertinib (N=279)	SoC EGFR-TKI (N=277)
TFST	Median, months (95% CI)	[redacted]	[redacted]
	HR (95% CI); p-value	[redacted]	
PFS2 by investigator assessment	Median, months (95% CI)	[redacted]	[redacted]
	HR (95% CI); p-value	[redacted]	
TSST	Median, months (95% CI)	[redacted]	[redacted]
	HR (95% CI); p-value	[redacted]	

CI=confidence interval; EGFR-TKI=epidermal growth factor receptor tyrosine kinase inhibitor; FAS=full analysis set; HR=hazard ratio; NC=not calculable; PFS2=time to second progression or death by any cause in patients who have stopped randomised therapy; SoC=standard of care; TFST=time to first subsequent therapy; TSST=time to second subsequent therapy
Source: information drawn from CS, p77 and CSR, Table 30

For each of these post-progression endpoints, the reported HRs suggest that treatment with osimertinib was statistically significantly more effective than treatment with Soc EGFR-TKI. The company states in the CS (p18) that the results for these post-progression endpoints demonstrate that the PFS advantage of osimertinib is largely preserved beyond initial progression and provide reassurance that a clinically meaningful benefit in OS will be observed in the fully mature dataset. The ERG notes that the company did not report that it had performed any assessment of the PH assumption for these outcomes (clarification question A6). HRs are not an appropriate summary of treatment effect when the PH assumption does not hold, it is therefore unknown whether the presented HRs are valid.

It should also be noted that patients could be treated beyond progression in both arms of the trial if the trial investigator considered patients were still receiving benefit from the treatment. As reported in the published paper for the FLAURA trial, this occurred in approximately two thirds of all patients (67% in the osimertinib arm and 70% in the SoC EGFR-TKI arm). Treatment beyond progression may have impacted upon all three post-progression endpoints by helping to prolong results for each of these outcomes. Nonetheless, if this is the case, it does still suggest that treatment beyond progression with osimertinib is more efficacious than treatment beyond progression with SoC EGFR-TKI.

Table 14 Key efficacy outcomes by presence or absence of CNS metastases at baseline (investigator assessment, FAS)

	CNS metastasis		No CNS metastasis	
	Osimertinib (N=53)	SoC EGFR-TKI (N=63)	Osimertinib (N=226)	SoC EGFR-TKI (N=214)
PFS				
No. of patients with PFS event, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
HR (95% CI); p-value		[redacted]		[redacted]
OS				
No. of patients who died, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
HR (95% CI); p-value		[redacted]		[redacted]
ORR				
No. of patients with objective response, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
OR (95% CI); p-value		[redacted]		[redacted]
DCR				
No. of patients with disease control, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
OR (95% CI); p-value		[redacted]		[redacted]

CI=confidence interval; CNS=central nervous system; DCR=disease control rate; EGFR-TKI=epidermal growth factor receptor tyrosine kinase inhibitor; FAS=full analysis set; HR=hazard ratio; OR=odds ratio; ORR-objective response rate; OS=overall survival; PFS=progression-free survival; SoC=standard of care
Source: CS, Table 23

Median PFS values were presented according to the presence or absence of CNS metastases at baseline in the European Public Assessment Report (EPAR) (EPAR, Table 27).[42] Median PFS in the group of patients with CNS metastases at baseline was 15.2 months (95% CI: 12.1 to 21.4) in the osimertinib arm, and 9.6 months (95% CI: 7.0 to 12.4) in the SoC EGFR-TKI arm. Median PFS in the group of patients without CNS metastases at baseline was 19.1 months (95% CI: 15.2 to 23.5) in the osimertinib arm, and 10.9 months (95% CI: 9.6 to 12.3) in the SoC EGFR-TKI arm.

cFAS and cEFR populations

The company reported various outcomes for the cFAS population, which consisted of patients who had a baseline CNS scan available for assessment by CNS BICR, and who had at least one measurable or non-measurable CNS lesion (N=128). The company also reported various outcomes for the cEFR population, which consisted of patients from the cFAS population who had at least one measurable CNS lesion (N=41). Definitions for the outcomes of CNS PFS, CNS ORR and CNS DCR are provided in Appendix 3 (Section 9.3).

All patients with a history of, or suspected, CNS lesion were required to have a baseline scan. However, if that brain scan came back with no evidence of CNS disease, further scans were not mandated by the protocol. If the patient subsequently became symptomatic, the investigator used clinical judgement on whether to scan the patient.

The company provides results for the outcome of CNS PFS by BICR assessment in the cFAS population, stating (CS, p87) that there was a "nominally statistically significant and clinically meaningful improvement in CNS PFS" for patients in the osimertinib arm in comparison to patients in the SoC EGFR-TKI arm ([redacted]). The company states that the result is "nominally statistically significant", since the analysis of CNS PFS was third in the hierarchical statistical testing strategy (see Section 4.6) and, as OS did not reach formal statistical significance, CNS PFS could not be formally tested for statistical significance.

The ERG notes that the company did not perform any assessment of the PH assumption for the outcome of CNS PFS (clarification question A6); HRs are not an appropriate summary of treatment effect when the PH assumption does not hold. Therefore, it is unknown whether the presented HR is valid, and the ERG highlights that the HR should be interpreted with caution.

Median CNS PFS was not calculable ([redacted]) in the osimertinib arm versus [redacted] in the SoC EGFR-TKI arm. The company provides a K-M plot for CNS PFS in the cFAS population in Figure 26 of the CS.

A breakdown of CNS progression events is provided in Table 24 of the CS, and reproduced here in Table 15.

Table 15 CNS progression events by BICR assessment in the cFAS population

Patients with progression, n (%)	Osimertinib (N=[redacted])	SoC EGFR-TKI (N=[redacted])
Total number of events (CNS progression or death)[a]	[redacted]	[redacted]
CNS progression other than death	[redacted]	[redacted]
Progression due to death	[redacted]	[redacted]
CNS progression[b]		
Progression in target CNS lesions	[redacted]	[redacted]
Progression in non-target CNS lesions	[redacted]	[redacted]
Progression due to new CNS lesions	[redacted]	[redacted]
Unknown reason for CNS progression[c]	[redacted]	[redacted]

[a] Progression events that did not occur within 2 scheduled visits (plus visit window) of the last evaluable assessment (or randomisation) were censored and therefore excluded in the number of events
[b] Target lesions, non-target lesions and new lesions were not necessarily mutually exclusive categories
[c] Patients were identified as having progression but their first lesion progression could not be determined
BICR=blinded independent central review; cFAS=CNS full analysis set; CNS=central nervous system; EGFR-TKI= epidermal growth factor receptor tyrosine kinase inhibitor; SoC=standard of care
Source: Adapted from CS, Table 24

CNS ORR was higher in the osimertinib arm than in the SoC EGFR-TKI arm in both the cFAS and cEFR populations (Table 16).

4.9 Relative efficacy of EGFR-TKIs

In this Section the ERG has compared the results from the SoC EGFR-TKI arm of the FLAURA trial, to results reported for SoC EGFR-TKI treatments (i.e., erlotinib and gefitinib) in previous EGFR-TKI trials. This is in order to explore whether, based on previous trial evidence, the results in the EGFR-SoC arm in the FLAURA trial appear unusual in any way. In addition, since the company did not compare osimertinib with afatinib (either directly in the FLAURA trial, or indirectly, see also Section 4.10), the ERG has also explored whether it can be assumed whether erlotinib and gefitinib can be considered to be as equally efficacious as afatinib.

4.9.1 Comparison of previous EGFR-TKI trials to FLAURA trial

A summary of efficacy results for EGFR-TKIs across trials[22,24-31,33,51] is provided in Table 17. While all trials mostly only included patients with PS 0 to 1 and excluded patients with symptomatic and unstable brain metastases, there were notable differences in the geographic locations of trials (and, therefore, possible differences in SoC before and after treatment with an EGFR-TKI) and median ages of patients (and possibly, therefore, prognosis). Furthermore, not all patients in the CTONG 0901 trial[31] received their EGFR-TKI as a first-line treatment, although approximately two-thirds of patients did. Nonetheless, efficacy results have been broadly consistent in trials conducted to date:

- Eight trials[22,24,25,27-30,33] compared an EGFR-TKI with PDC (including cisplatin or carboplatin plus gemcitabine, docetaxel, paclitaxel or pemetrexed). All of these eight trials found the EGFR-TKIs to improve PFS and ORR,[22,24,25,27-30,33] but did not improve OS,[20,22,23,27-30,34] versus PDC. However, a pooled analysis of LUX-Lung 3 and LUX-Lung 6 trial data[32] has shown an OS benefit for afatinib versus PDC (cisplatin plus pemetrexed in the LUX-Lung 3 trial and cisplatin plus gemcitabine in the LUX-Lung 6 trial) in the subgroup of patients with Exon 19 deletions. It should be noted that these results should be interpreted with caution. This is because subgroup analyses did not form part of the confirmatory analysis strategy, no adjustment for multiplicity was done, and p values are descriptive in nature.
- Median PFS in the SoC EGFR-TKI arm of the FLAURA trial (10.2 months) was within the range of median PFS reported for EGFR-TKI treatments in all previous trials,[22,24-31,33] although only three trials[24,25,27] actually recorded a lower median PFS. Median PFS for erlotinib ranged from 9.7 to 13.1 months (4 trials)[27,30,31,33] and for gefitinib ranged from 9.2 to 10.9 months (5 trials).[22,24-26,31] Median PFS for patients treated with afatinib has consistently been found to be approximately 11 months in three trials,[26,28,29] which is reasonably similar to median PFS in the SoC EGFR-TKI arm of the FLAURA trial.
- ORR for patients in the SoC EGFR-TKI arm of the FLAURA trial (76%) was also within the range of ORRs reported for EGFR-TKI treatments in previous trials, with only one trial reporting a higher ORR:[33] ORRs for erlotinib ranged from 56% to 83% (4 trials)[27,30,31,33] and for gefitinib ranged from 52% to 74% (5 trials).[22,24-26,31] For patients treated with afatinib, ORRs ranged from 56% to 70%,[26,28,29] these rates are lower than those for patients in the SoC EGFR-TKI arm of the FLAURA trial.

5.2 ERG summary of the company's submitted economic evaluation

The company developed a de novo economic model to compare the cost effectiveness of treatment with osimertinib versus afatinib, erlotinib and gefitinib in adults with advanced EGFR mutation type (Exon 19 deletions or L858R point mutations) NSCLC.

5.2.1 Model structure

The company model structure (implemented as a partitioned survival model), as shown in Figure 1, comprises three mutually exclusive health states that are designed to reflect the natural course of the disease. The modelled population enters the model in the progression-free (PF) health state. At the end of every 30-day cycle, patients in the PF health state can experience disease progression and enter the progressed disease (PD) health state or remain in the PF health state. Patients in the PD health state can also remain in that health state at the end of each cycle but cannot return to the PF health state. Transitions to the death health state can occur from either the PF health state or the PD health state. Death is an absorbing health state from which transitions to other health states are not permitted.

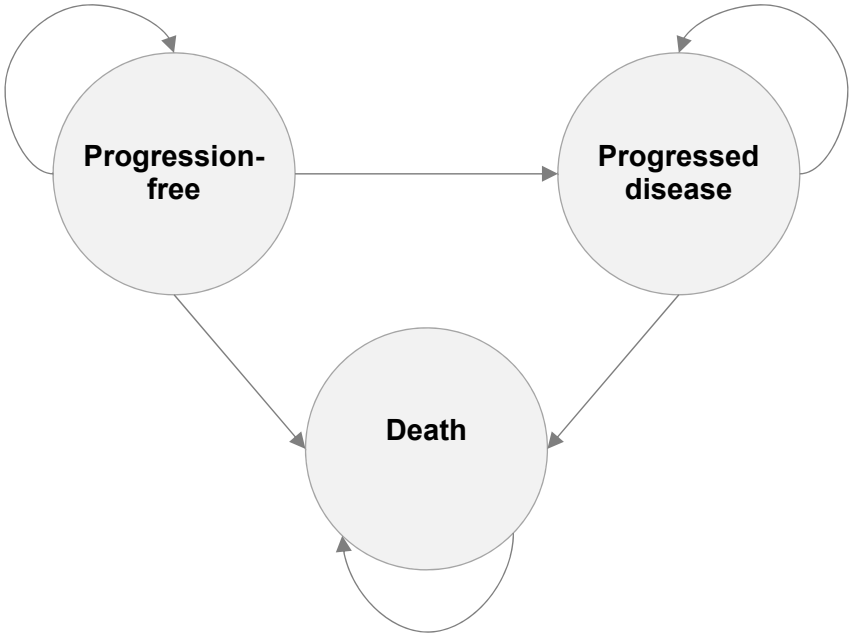


Figure 1 Structure of the company model

Source: Developed by the ERG based on text in the CS, Section B.3.2

5.2.2 Population

The population reflected by the company model is patients with advanced EGFR+ NSCLC. The population is consistent with the FLAURA trial population and that described in the final

scope[47] issued by NICE. The starting age of the cohort (63 years) is the same as the mean age and similar to the median age (64 years), at baseline, of the patients in the FLAURA trial.

5.2.3 Interventions and comparators

Intervention

Treatment with osimertinib is implemented in the model in line with the licensed dosing regimen[42] i.e. one 80mg tablet taken once daily until disease progression or unacceptable toxicity. However, clinical advice to the company is that osimertinib is expected to be used beyond disease progression if clinical benefit is observed and, therefore, administration of osimertinib (80mg) beyond disease progression was implemented in the company model.

Comparators

The comparators are afatinib[57], erlotinib[55] and gefitinib.[56] The dosing and administration frequencies for these drugs are also in line with their marketing authorisations and UK clinical practice, where treatment is continued beyond disease progression. Afatinib (40mg), erlotinib (150mg) and gefitinib (250mg) were implemented as one tablet once a day.

5.2.4 Perspective, time horizon and discounting

The company states that the economic evaluation is undertaken from the perspective of the NHS and Personal Social Services (PSS), which is in line with the NICE reference case.[82] The model has a 30-day cycle length and the time horizon is set at 20 years. As justification for the length of the time horizon, the company cites the advanced nature of the disease and projections from the FLAURA study, which showed that fewer than 2.5% of patients would live beyond 20 years. An annual discount rate of 3.5% was applied to costs and outcomes. Half cycle correction was applied to all costs in the model except to drug acquisition and administration costs for treatment with osimertinib, afatinib, erlotinib and gefitinib.

5.2.5 Treatment effectiveness and extrapolation in the base case

The company economic model reflects patient-level data from the FLAURA trial. In the FLAURA trial, treatment with osimertinib was compared to SoC EGFR-TKI (that is, erlotinib or gefitinib). The follow-up period in the trial was shorter than the model time horizon and, therefore, extrapolations of the PFS, OS and time to discontinuation of treatment (TDT) K-M data from the FLAURA trial were necessary. The extrapolations involved identification of parametric survival models that reflected FLAURA trial PFS, OS and TDT K-M data.

Progression-free survival

The company undertook an assessment to determine whether the PFS data from the two arms of the FLAURA trial were proportional (log-cumulative hazard plot and Cox-Snell residuals)

Table 28 Utility values used in the cost effectiveness model

Health state	Utility value	Source/description
Progression-free	[redacted]	Mapped value from FLAURA trial
Progressed disease (1L treatment)	[redacted]	Mapped value from FLAURA trial
Progressed disease (subsequent treatment or BSC)	0.640	Labbe (2017)[87]
Death	0.000	By definition

1L=first-line treatment; BSC=best supportive care
Source: CS, Table 51

5.2.7 Resources and costs

The resource use and costs associated with treatment acquisition, treatment administration, disease management and AEs were included in the company model.

Drug costs in the first-line setting

Estimates of the quantity of osimertinib, afatinib, erlotinib and gefitinib used per patient per 30-day model cycle were derived from FLAURA trial data, as were relative dose intensity (RDI) multipliers. The afatinib RDI multiplier was assumed to be the same as for treatment with erlotinib and gefitinib. An oral treatment administration cost of £9 per model cycle (based on a dispensing time of 12-minutes [band 6 pharmacist]) was applied to all first-line therapies. Selected details of the drug costs are shown in Table 29 of this ERG report and full details are presented in Tables 58, 59, 60, 61 and 67 of the CS.

Table 29 Treatment dosing and drug acquisition costs for primary treatments

		Osimertinib	Afatinib	Erlotinib	Gefitinib
Label information	Administration method	Oral	Oral	Oral	Oral
	Dose per administration	80mg	40mg	150mg	250mg
	Administration frequency	1 per day	1 per day	1 per day	1 per day
Package information	Formulation	80mg	40mg	150mg	250mg
	Pack size	30 tablets	28 tablets	30 tablets	30 tablets
	List price	£5,770.00	£2,023.28	£1,631.53	£2,167.71
Dosing used in model	Required dose	80mg	40mg	150mg	250mg
	Tablets per administration	1.00	1.00	1.00	1.00
	Relative dose intensity	98.9 1%	98.1%	98.1%	98.1%
	Cost per model cycle	£5,706.53	£2,126.61	£1,600.53	£2,126.52

mg=milligram
Source: information drawn from CS, Tables 58, 60 and 61

Drug costs for subsequent treatments

The costs of subsequent lines of therapies are applied as one-off costs. The company states that the nature of partitioned survival modelling means that it is not possible to accurately estimate the proportion of patients who discontinue first-line therapy and die in the same cycle. Therefore, the difference in the proportion of patients on treatment between two consecutive 30-day cycles (from TDT K-M extrapolation) was used a proxy for the proportion of patients

months). However, there are no published utility values that reflect the HRQoL of patients whose disease has progressed following first-line treatment and go on to receive best supportive care (BSC) or active therapies in the second- and/or third-line settings before BSC. Ideally, the model should have included different health states to reflect the different treatment pathways. Given that the company model structure means that one utility value has to capture the range of HRQoL of patients receiving second-line treatment, third-line treatment and BSC, the ERG considers that a utility value of 0.678 (the utility value from reported in TA416[43] from the he AURA 2 trial[98] [second-line treatment with osimertinib]) is more representative of the HRQoL of patients in the PD health state than the value used by the company (0.64). However, the ERG acknowledges that this value may still not be an accurate reflection of the HRQoL of patients in the PD health state.

Compared with the company base case, applying a utility value of 0.678 to reflect patient HRQoL in the PD health state resulted in incremental QALYs for the comparison of treatment with osimertinib versus erlotinib increasing from 1.046 to 1.074 and the ICER reducing by £2,343 to £87,357 per QALY gained.

Lifetime duration of treatment effect with osimertinib

FLAURA trial OS data were only available for a 2-year time period. The ERG considers that any extrapolation of 2 years of OS data over 20 years will always be uncertain, especially when there are structural breaks (i.e., where, at different points in time, survival starts following different trajectories) in the K-M data over that time period. Within the model, the company OS is represented by direct use of FLAURA trial OS K-M data for the first 8 months of the time horizon and a Weibull distribution (a different one for each arm) thereafter. The ERG is satisfied that the company's choice of a Weibull distribution to reflect long-term OS for patients in both the intervention and comparator arms of the model was supported by the available K-M data from the FLAURA trial. However, the ERG highlights that the use of these functions result in mortality for patients in the osimertinib arm being approximately 36% lower than in the SoC EGFR-TKI arm over the period that survival is extrapolated i.e. up to 20 years.

The ERG considers that it is clinically implausible that patients receiving first-line treatment with osimertinib will continue to experience a survival advantage over those receiving first-line treatment with a first- or second-generation EGFR-TKI for many years after treatment has ceased. Furthermore, such claims have not been accepted by NICE Appraisal Committees (ACs) during previous appraisals of drugs to treat NSCLC. During the appraisal of pembrolizumab for treating PD-L1 positive NSCLC after chemotherapy (Pembrolizumab for treating PD-L1-positive non-small-cell lung cancer after chemotherapy [TA428][60]), the AC considered a treatment effect of 3 years was realistic, whilst during the appraisal of

atezolizumab for treating NSCLC after platinum-based chemotherapy (Atezolizumab for treating locally advanced or metastatic non-small-cell lung cancer after chemotherapy [TA520][41]) a different AC considered that 5 years was realistic.

The company model has a partitioned survival structure and the application of a 'duration of treatment effect' within such a structure is not straightforward as the effect is likely to vary by patient and to depend on time on treatment and level of response. Given the model structure, a crude approach to limiting the duration of treatment effect on OS is to set the morality hazard for the intervention and comparator arms to be equal after a given timepoint.

Given that, in the past, ACs have accepted that treatment durations of 3 and 5 years are realistic, the ERG has run scenarios in which the effect of treatment with osimertinib has been limited to these two durations. In addition, to reflect the period of time for which FLAURA trial data are available, the ERG has run a scenario in which the effect of treatment with osimertinib has been limited to 2 years. The 2-year scenario effectively provides an estimate of the ICER per QALY gained for the comparison of treatment with osimertinib versus SoC EGFR-TKI based on available evidence (i.e., with no modelling).

Compared with the company base case, using a 2-year duration of treatment effect, the ICER for the comparison of osimertinib versus erlotinib increased by £119,753 to £209,453 per QALY gained, a 3-year duration of treatment effect increased the ICER by £72,562 to £162,262 per QALY gained and a 5-year duration of treatment effect increased the ICER by £33,607 to £123,307 per QALY gained.

Place of immunotherapy in the treatment pathway

Data presented in the CS (Figure 14) show that during the first 3 months of 2018, 10% of patients in the UK with advanced EGFR+ NSCLC who were tested for the T790M mutation were treated with pembrolizumab. This was prior to the publication of TA531[99] (Pembrolizumab for untreated PD-L1-positive metastatic non-small-cell lung cancer) and TA520[41] (Atezolizumab for treating locally advanced or metastatic non-small-cell lung cancer after chemotherapy), which could have increased the use of immunotherapy in patients with advanced EGFR+ NSCLC after first-line treatment.

During the process of validating the model, the company was advised by clinicians (CS, p201) that the survival projections used in the model may not reflect the use of immunotherapies in the third-line setting (or the use of osimertinib as a second-line treatment). It is not known what proportion of patients in either of the model arms would be eligible, and fit enough, to receive

6 END OF LIFE CRITERIA

The company puts forward a case that osimertinib, as a first-line treatment for advanced EGFR+ NSCLC, meets the NICE End of Life criteria[82] (see Table 43).

Table 1 End of Life criteria

NICE End of Life criteria	Data presented by the company
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	OS for patients with confirmed EGFR+, Stage IIIb/IV NSCLC in England and Wales is estimated to be [redacted] based on analysis of Public Health England data collected between 2014 and 2016 (n=652) (see CS, p28 for details)[a]
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	• Results from the FLAURA trial show that, compared with SoC EGFR-TKI treatment, osimertinib extended PFS by 8.7 months (18.9 months versus 10.2 months). Treatment with osimertinib also demonstrated a substantial improvement in post-progression endpoints, including a [redacted] in time to first subsequent treatment • Whilst OS data were immature at the time of data cut-off, the HR for death was 0.63 (95% CI: 0.45 to 0.88; p=0.007), reflecting a meaningful survival advantage over SoC EGFR-TKI. In addition, early separation of the K-M curves was observed. At 18 months, 82.8% of patients receiving osimertinib were still alive, compared with 70.9% of those receiving SoC EGFR-TKI • In the absence of median OS (i.e. the 50th percentile of OS), a survival gain at other percentiles of OS may be considered as a conservative estimate of the survival gain in the mature population.[100b] The 25th percentile of OS was observed at approximately 22.5 months in the osimertinib arm, and at approximately 15.9 months in the SoC EGFR-TKI arm. This reflects an improvement of 6.6 months, and while not a substitute for median OS, is clearly higher than the 3-month life extension needed to meet End of Life criteria

CI=confidence interval; EGFR-TKI= epidermal growth factor receptor tyrosine kinase inhibitor; NSCLC=non-small cell lung cancer; OS=overall survival; PFS=progression-free survival; SoC=standard of care

[A] During the clarification process, the company also provided the data by performance status (PS) (See response to A28). Median OS was very similar for 336 patients with PS≤1 [redacted] to that of 240 patients with unknown or missing PS [redacted], both estimates being similar to median OS for all patients reported here; median OS was shorter for 112 patients with PS>=2 [redacted].

[b] Precise figures for quantiles were not available; the survival estimates reflect the 75.2% percentile for osimertinib and 75.1% percentile for SoC EGFR-TKI

Source: CS, Table 29

Short life expectancy

The company presents registry data (CS, Table 5) to demonstrate that patients with advanced EGFR+ NSCLC in England and Wales have a life expectancy of less than 24 months. The company explains that this evidence is more representative of the population treated in NHS clinical practice than trial data as outcomes for NHS patients are 'considerably worse' than those of patients recruited to clinical trials who are often 'younger and fitter' (CS, p14) than NHS patients. The ERG accepts the company's argument that trial evidence may overestimate the life expectancy of the population of interest compared with that of patients treated in the NHS but considers that it is inconsistent to accept trial evidence as a measure of effectiveness but not as a measure of life expectancy. There is no real world evidence available that compares the effectiveness of treatment with osimertinib versus afatinib, erlotinib or gefitinib.

At the time of data cut off, median OS had not been reached in either arm of the FLAURA trial, but after 24 months over half (64.7%) of patients in the SoC EGFR-TKI arm were still alive.

The ERG, therefore, considers that, based on available evidence, the average life expectancy of people with advanced EGFR+ NSCLC who are eligible for treatment with afatanib, erlotinib or gefitinib is likely to exceed 24 months.

Treatment benefit

The company uses FLAURA trial PFS data in support of their claim that OS for patients treated with osimertinib is longer than that of patients treated with Soc EGFR-TKI. The ERG highlights findings from published studies[102,103] that demonstrate that PFS is not a good proxy for OS, which means that this line of argument is not robust. However, the economic modelling undertaken by the ERG (see Section 5.3) supports the company position that, compared with treatment with afatinib, erlotinib or gefitinib, treatment with osimertinib extends patient life expectancy by at least 3 months.

ERG conclusion

The ERG considers that patients with advanced EGFR+ NSCLC who are eligible for first-line treatment with afatinib, erlotinib or gefitinib have a life expectancy that is greater than 24 months. Thus, one of the NICE criteria for applying a less restrictive assessment of cost effectiveness for End of Life treatments has not been met.

Correspondence with clinical expert (Alastair Greystoke – TC and follow up email to confirm responses 10/12/18)

Trial population

Questions to expert	• The osimertinib FLAURA trial recruited people who had a WHO performance status (PS) ≤1. However, published evidence of patients treated with EGFR-TKIs for advanced first-line EGFR positive NSCLC in clinical practice in England showed that where performance status was known, 25% had PS 2 or 3. o Would people with a PS of 2 or 3 be likely to have treatment with an EGFR TKI for 1st line EGFR-positive NSCLC? o In NHS clinical practice, what proportion of people with performance status ≤1 are treated with EGFR-TKIs for advanced first-line EGFR positive NSCLC? Do clinical outcomes (such as overall survival) differ based on performance status? If so, how? o Overall do you think the results of the FLAURA trial are generalisable to UK clinical practice?
Summary of clinical expert input	• Yes, people with a PS of 2 or 3 would have treatment with an EGFR TKI as 1st line • In all forms of lung cancer ~ 50% are PS2 or more (possibly lower in EGFR-positive, eligible for TKIs (~ 25%) – younger and fitter thus approx. 75% performance status ≤1 • Yes, PS is a prognostic factor in survival (on balance: higher PS = shorter survival) • Yes, the trial population is generalisable - in practice 10-15% of people present with active symptomatic brain disease

CNS metastases

Questions to expert	• In the FLAURA trial, around a fifth (21%) of patients were considered to have CNS metastases. Fewer patients in the osimertinib arm experienced CNS progression than in the SoC EGFR-TKI arm. However, some cases of asymptomatic progression may not have been detected, because only patients with brain metastases at the beginning of the trial were required to have regular brain scans. o In NHS clinical practice, is assessment of progression guided by symptoms or radiographic evidence? o Would people with asymptomatic CNS disease progression continue on current treatment until symptoms developed? o Do you think the CNS progression results of the trial are generalisable to UK clinical practice?
Summary of clinical expert input	• In the majority, progression currently guided by symptoms but practice is changing with some centres now undertaking brain scans at presentation and throughout treatment. • Yes, people would continue on treatment unless eligible for stereotactic radiosurgery • Yes, the CNS progression results are generalizable to UK clinical practice

Overall survival estimates

Questions to expert

• The company's model has estimated the following numbers (% still alive) after starting treatment.

Years after starting treatment	Osimertinib	SoC (erlotinib, gefitinib or afatinib)
1	89% Agree	82% Agree
2	74% Agree	62% Agree

	<table><tr><td>5</td><td>43% ~35%</td><td>26% ~20%</td></tr><tr><td>10</td><td>16% ~12%</td><td>6% Agree</td></tr></table> o In your opinion what is a realistic proportion of patients remaining alive with osimertinib and standard care at 1, 2, 5 and 10 years?
Summary of clinical expert input	• **See table above**

Treatment duration effect

Questions to expert	• In its base case, the company model assumes a survival advantage with osirmertinib compared with a 1st or 2nd generation EGFR TKI for many years (20 years) after treatment has stopped. The ERG think that this is not plausible. The company provided a scenario reducing this benefit to 10 years. The ERG explored a 2-year duration of treatment effect because this reflected the time for which FLAURA data are available. In addition they also explored 3- and 5-year duration of treatment effects. Other appraisals of immunotherapy treatments also explored reducing treatment effect to 3 or 5 years. o What would you expect the duration of treatment effect with osimertinib to be? o Does the mechanism of action for osimertinib support the rationale that a longer term treatment benefit can be obtained to a similar extent to the immunotherapy treatments in other types of NSCLC?
Summary of clinical expert input	• Agree that 20 years seems implausible, 2 years is equally too harsh. Between 3 to 5 year duration of treatment effect seems the most realistic. • No, mechanism of action does not support rationale as osimertinib is concerned with a reduction in tumour burden rather than development of longer term immune response.

Equivalent efficacy of comparators

Questions to expert	• The company has assumed that afatinib, erlotinib and gefitinib are equally efficacious within the context of this appraisal. o In your opinion do you consider this assumption to be correct? If not could you explain why?
Summary of clinical expert input	• Yes equally efficacious, although slight variation in treatment effect between the 3 comparators in a variety of outcomes - on balance equally efficacious in this setting.

Utility Values

Questions to expert	The company used a utility value of 0.64 for patients in the progressed disease (PD) health state. The ERG suggested, given that the company model structure means that one utility value has to capture the range of HRQoL of patients receiving second-line treatment, third-line treatment and standard care, that a utility value of 0.678 (the utility value reported in TA416 from the AURA 2 trial [second-line treatment with osimertinib]) is more representative of the HRQoL of patients in the PD health state. o In your opinion, what would you regard as the appropriate utility value for the progressed disease state in this setting?
Summary of clinical expert input	• Utility values very similar and difference between them does not indicate a clinical meaningful difference. Either value could be applied.

Correspondence with clinical expert (Yvonne Summers)

Trial population

Questions to expert	• The osimertinib FLAURA trial recruited people who had a WHO performance status (PS) ≤1. However, published evidence of patients treated with EGFR-TKIs for advanced first-line EGFR positive NSCLC in clinical practice in England showed that where performance status was known, 25% had PS 2 or 3. o Would people with a PS of 2 or 3 be likely to have treatment with an EGFR TKI for 1st line EGFR-positive NSCLC? o In NHS clinical practice, what proportion of people with performance status ≤1 are treated with EGFR-TKIs for advanced first-line EGFR positive NSCLC? o Do clinical outcomes (such as overall survival) differ based on performance status? If so, how? o Overall do you think the results of the FLAURA trial are generalisable to UK clinical practice?
Summary of clinical expert input	• Yes, people with a PS of 2 or 3 would have an EGFR TKI for 1st line treatment • Approximately 75% of people would have a PS of ≤1 • Yes, poorer PS patients have worse outcomes – this holds across disease sites and treatments. There is no good RCT data to be specific about EGFR TKI's • Yes the results are generalisable, given the caveats above (which apply to all TKIs)

CNS metastases

Questions to expert	• In the FLAURA trial, around a fifth (21%) of patients were considered to have CNS metastases. Fewer patients in the osimertinib arm experienced CNS progression

	than in the SoC EGFR-TKI arm. However, some cases of asymptomatic progression may not have been detected, because only patients with brain metastases at the beginning of the trial were required to have regular brain scans. o In NHS clinical practice, is assessment of progression guided by symptoms or radiographic evidence? o Would people with asymptomatic CNS disease progression continue on current treatment until symptoms developed? o Do you think the CNS progression results of the trial are generalisable to UK clinical practice?
Summary of clinical expert input	• Practice is variable and changing. Routine scanning at baseline for brain metastases is becoming more standard (though not in all centres) as there are more effective CNS treatment than previously. Patients with brain metastases at baseline will continue to be scanned, those without will only have further scans on concerning symptoms/signs (the same as in the trial). • If the patient has a good systemic option which is CNS active they may have systemic treatment, if not then radiotherapy (SRS) may be considered. If asymptomatic PD in brain occurs whilst on systemic treatment then SRS may be considered. • Yes, the CNS progression results are generalisable to UK clinical practice

Overall survival estimates

Questions to expert	• The company's model has estimated the following numbers (% still alive) after starting treatment.

Years after starting treatment	Osimertinib	SoC (erlotinib, gefitinib or afatinib)

	<table><tr><td>1</td><td>89%</td><td>82%</td></tr><tr><td>2</td><td>74%</td><td>62%</td></tr><tr><td>5</td><td>43%</td><td>26%</td></tr><tr><td>10</td><td>16%</td><td>6%</td></tr></table> o In your opinion what is a realistic proportion of patients remaining alive with osimertinib and standard care at 1, 2, 5 and 10 years?
Summary of clinical expert input	• The estimates in the table look reasonable

Treatment duration effect

Questions to expert	• In its base case, the company model assumes a survival advantage with osirmertinib compared with a 1st or 2nd generation EGFR TKI for many years (20 years) after treatment has stopped. The ERG think that this is not plausible. The company provided a scenario reducing this benefit to 10 years. The ERG explored a 2-year duration of treatment effect because this reflected the time for which FLAURA data are available. In addition they also explored 3- and 5-year duration of treatment effects. Other appraisals of immunotherapy treatments also explored reducing treatment effect to 3 or 5 years. o What would you expect the duration of treatment effect with osimertinib to be? o Does the mechanism of action for osimertinib support the rationale that a longer term treatment benefit can be obtained to a similar extent to the immunotherapy treatments in other types of NSCLC?
Summary of clinical expert input	• 3-12 months after stopping treatment with the drug

	• Not to the same extent as immunotherapy. There is probably some longer term treatment benefit due to improved duration of response and CNS activity, but there is certainly not the same rationale as for immunotherapy.

Equivalent efficacy of comparators

Questions to expert	• The company has assumed that afatinib, erlotinib and gefitinib are equally efficacious within the context of this appraisal. o In your opinion do you consider this assumption to be correct? If not could you explain why?
Summary of clinical expert input	• There are no substantial differences except afatinib has more side effects and requires dose reduction more frequently

Utility Values

Questions to expert	The company used a utility value of 0.64 for patients in the progressed disease (PD) health state. The ERG suggested, given that the company model structure means that one utility value has to capture the range of HRQoL of patients receiving second-line treatment, third-line treatment and standard care, that a utility value of 0.678 (the utility value reported in TA416 from the AURA 2 trial [second-line treatment with osimertinib]) is more representative of the HRQoL of patients in the PD health state. o In your opinion, what would you regard as the appropriate utility value for the progressed disease state in this setting?

Summary of clinical expert input	• Patients who progress after osimertinib will either be having chemo or supportive care. Their utility value is therefore likely to be less than that measured AURA 2 (assuming this is the value when on treatment with osimertinib in AURA 2)

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Technical report

Osimertinib for untreated epidermal growth factor receptor (EGFR) mutation-positive non-small-cell lung cancer

1. Summary of technical report

1.1 This document is the technical report for this appraisal. It has been prepared by the technical team with input from the lead team and chair of the appraisal committee.

The technical report and stakeholder's responses to it 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 appraisal committee meeting.

The technical report includes:

- a commentary on the evidence received and written statements
- technical judgements on the evidence by the technical team
- reflections on NICE's structured decision-making framework.

This report is based on:

- the evidence and views submitted by the company, consultees and their nominated clinical experts and patient experts and
- the evidence review group (ERG) report.

The technical report should be read with the full supporting documents for this appraisal.

1.2 After technical engagement the technical team has collated the comments received and, if relevant, updated the scientific judgement by the technical team and rationale. Scientific judgments that have been updated after engagement are highlighted in **bold** below.

1.3 In summary, the technical team considered the following:

- The FLAURA trial is broadly generalisable to clinical practice in England (see issue 1).
- **Following input from the clinical experts and the ERG, it is more appropriate to model a treatment benefit duration, from starting treatment, of 3- to 5-years rather than a lifetime treatment effect (see issue 2).**
- A Weibull extrapolation of overall survival is acceptable (see issue 3).
- A combined approach to determine the appropriate resource costs for patients in the progressed disease state is acceptable (see issue 4).
- Osimertinib does not meet the end of life criteria specified in NICE's guide to the methods of technology appraisal (see issue 5).
- Osimertinib **is unlikely to be a candidate** for the Cancer Drugs Fund because it does not have plausible potential to be cost-effective (see issue 6). **However, if there was a plausible potential for it to be cost-effective, data collection (more mature data from the FLAURA trial) would help to resolve uncertainty (see Issue 6).**
- **There is uncertainty about the assumption that afatanib has equal efficacy to the other comparators, gefitinib and erlotinib (see Issue 7).**

1.4 The technical team recognised that the following uncertainties would remain in the analyses and could not be resolved:

- The overall survival (OS) evidence is immature and median OS has not yet been reached for either osimertinib or standard care arms within the FLAURA trial.

1.5 The company updated base-case assumes a 6-year duration of treatment effect and gives a deterministic incremental cost-effectiveness ratio (ICER) of £110,254 per QALY gained for osimertinib compared with erlotinib (based on list prices). The technical team's preferred assumptions result in ICERs ranging from £162,981 (3-year duration of treatment effect) to £120,953 5-year duration of treatment effect) per QALY gained (see tables 1a and 1b). When confidential discounts are applied to both osimertinib and the comparators, all the ICERs for osimertinib remain above the £20,000 to £30,000 per QALY gained range (see issue 2). The committee will be presented with cost effectiveness results that include all the relevant commercial arrangements.

1.6 Osimertinib does not meet the end of life criteria specified in NICE's guide to the methods of technology appraisal. With regard to the life extension criterion, there is uncertainty about the precise size of survival benefit because of the immaturity of the data in the FLAURA trial (25% maturity). The assumption of equal efficacy of afatinib with the other comparators could also be optimistic as there is some evidence of additional clinical benefit associated with afatinib (see issue 7). In addition, FLAURA trial data does not indicate that life expectancy in this population is less than 24 months (see issue 5).

1.7 Osimertinib is unlikely to meet the criteria for inclusion in the Cancer Drugs Fund because there is no plausible potential for it to be cost-effective at its current price. However, if there was a plausible potential for it to be cost-effective, data collection (more mature data from the FLAURA trial) would help to resolve uncertainty (see Issue 6).

1.8 All relevant benefits associated with osimertinib are adequately captured in the model (see table 3).

1.9 No equality issues were identified by the company, consultees and their nominated clinical experts and patient experts (see table 3).

2. Key issues for consideration

Issue 1 – Generalisability of the FLAURA trial population

This issue was resolved at technical engagement and is addressed in Table 3.

Issue 2 – Duration of treatment effect

Questions for engagement	3. Is a 3- to 5-year duration of treatment effect for osimertinib appropriate? 4. Is there any additional evidence which could be used to inform the duration of treatment effect?
Background/description of issue	**The Company** The company, in its base case, assumed a duration of treatment effect of 20 years, that is, for the duration of the time horizon in the model. The company noted that the mode of action of targeted therapies, such as osimertinib, is different from that of immunotherapies and so it is difficult to compare the duration of treatment effect directly. Tyrosine kinase inhibitors (TKI's) are given as treatment to people until disease progression occurs or other discontinuation (in the company's extrapolation of time to treatment discontinuation, they estimated that over 40% of people taking osimertinib and approximately 15% of those having standard of care (SoC) TKIs, are still on treatment at 2 years). **The ERG** The ERG considered that the osimertinib duration of treatment effect was uncertain because the OS data from the FLAURA trial data was immature (median overall survival was not reached in either arm). They also considered it clinically implausible that people having first-line treatment with osimertinib will continue to experience a survival advantage over those having a different first-line EGFR-TKI for many years after treatment has ceased. The ERG considered that a 3 or 5-year duration was more realistic and noted that a lifetime

	assumption was not accepted in previous appraisals of treatments for non-small cell lung cancer (NSCLC) (pembrolizumab for PD-L1-positive NSCLC after chemotherapy (TA428) considered 3 years realistic while atezolizumab for NSCLC after chemotherapy (TA520) considered 5 years). **Clinical expert advice** The clinical experts noted that osimertinib has a different mechanism of action compared with immunotherapies and that although there may be some benefit because of improved duration of response and central nervous system (CNS) activity, it does not support a rationale that longer term treatment benefit would be obtained, to a similar extent, as immunotherapy treatments. One expert stated that the effects would last approximately 3 to 12 months after stopping treatment. Therefore, an assumed treatment effect duration of between 3- and 5-years was realistic for osimertinib.
Why this issue is important	Usually decreasing the assumed treatment effect duration increases the ICER.
Technical team judgement before engagement	Lack of mature overall survival data means there is uncertainty about osimertinib's treatment effect duration (that is, the time after starting treatment). The technical team would like to see more evidence to support the longer duration of treatment effect. Lacking this, it is preferable to model a more conservative duration of between 3 and 5 years.
Summary of comments	Comments received from company Treatment effect duration of 3 years is overly pessimistic because it is not clinically plausible to assume equal mortality between the 2 arms at 3 years because over 20% of patients remain on osimertinib at this time point based on extrapolations of time to discontinuation of treatment (TDT) from FLAURA. The company state that a 6-year effect is more plausible given osimertinib's mechanism of action and because: • At 5 years the model predicts that all people in the SoC arm have discontinued their initial treatment, while 2% are still having osimertinib. Treatment benefit cap should

	apply when all patients in the osimertinib arm have stopped first line treatment (In the company revised base case this is at **6.08 years**). • The nature of cohort partitioned survival models implies that a treatment waning effect cannot be modelled accurately. • Assuming that the hazard ratio returns to one immediately at 3 or 5 years is not realistic when considering the clinically meaningful and significant relative effect size on overall survival. • Reduction in CNS progression with osimertinib, compared with 1st and 2nd generation TKIs, could translate into an improved survival profile beyond treatment discontinuation. • Using past appraisals for NSCLC (TA428 and TA520) to inform a treatment effect duration of between 3 and 5 years needs to be considered with caution. Both conditional on a maximum treatment duration of 2 years while there are no restrictions on treatment duration for TKIs. • UK patients on osimertinib more likely to receive subsequent treatment compared with SoC in FLAURA because of better safety profile and overall treatment experience (only 20% in SACT dataset received subsequent therapy). This will contribute to continued treatment effect for people treated with first-line osimertinib. • 6-year duration of treatment effect more plausible as post-progression outcomes favour osimertinib. In addition, no aggressive mutations or T970M observed post osimertinib.

	Comment received from British Thoracic Oncology Group (BTOG): • 20-year duration of treatment effect is too long. On the basis of the PFS results in the FLAURA study and taking into account treatment benefit beyond this point, a 3- to 5-year duration would seem appropriate. Comment received from NCRI-ACP-RCP-RCR: • A 3- to 5-year duration of treatment effect for osimertinib is appropriate. ERG considerations on updated company position received during technical engagement: • The company has not presented strong evidence that the duration of treatment effect continues after 5 years. In addition, without more evidence, the ERG does not consider that applying a 12-month waning is necessarily more plausible than just applying a hazard ratio of 1 instantaneously at year 5, for example.
Technical team judgement after engagement	The company submitted an amended base-case with a 6-year duration of treatment effect. This resulted in an ICER of £110,254 per QALY gained for osimertinib compared with erlotinib (estimate based on drug list prices). When confidential discounts are applied to both osimertinib and the comparators, the ICER for osimertinib remains above the £20,000 to £30,000 per QALY gained range. There is uncertainty regarding the type of model used to capture the health benefits fully. The model has a partitioned survival structure and the application of a 'duration of treatment effect' is not straightforward as the effect is likely to vary by patient and to depend on both the time spent on treatment and the level of clinical response. In addition, the company model structure means that one utility value has to capture the range of HRQoL of patients receiving second-line treatment, third-line treatment and best supportive care. The company and ERG preferred extrapolation of overall survival for a variety of duration of treatment effects generates the following survival estimates for osimertinib which are summarised in the table below.

	Estimated % of people alive in the economic model when applying different durations of treatment benefit **Years after starting treatment** / Hazard ratio of 1 applied at: 2-years / 3-years / 5-years / 6-years **1**: 89% / 89% / 89% / 89% **2**: 74% / 74% / 74% / 74% **3**: 55% / 62% / 62% / 62% **5**: 31% / 34% / 42% / 42% **10**: 7% / 8% / 10% / 10% For the standard of care arm the survival estimates remain the same (1 year = 82%, 2 years = 62%, 3 years = 46%, 5 years = 26% and 10 years = 3%) In addition, clinical expert feedback provided a range of survival estimates for 2, 5 and 10 years after starting treatment (see issue 3). Following input from the clinical experts and ERG, the technical team consider that an assumption of 3- to 5-year duration of treatment effect is preferable to an assumed lifetime benefit.

Issue 3 – Extrapolation of overall survival (OS)

Questions for engagement	5. What proportion of patients in the osimertinib arm would you expect to be alive at 2, 3 and 5 years? 6. What proportion of patients in the standard of care (SoC) arm would you expect to be alive at 2, 3 and 5 years? 7. Is the Weibull distribution appropriate for modelling overall survival?

Background/description of issue	**The Company** Although no clear violation of proportional hazard was identified, the company considered it appropriate to use a piecewise model using observed Kaplan-Meier (K-M) data up to 7.9 months followed by a parametric distribution to model overall survival beyond the observed data period. In light of the immature overall survival data available, the company applied the most conservative piecewise overall survival extrapolation, the Weibull distribution, for both treatment arms in the base-case analysis. The extrapolation could be made using two different approaches, a fully fitted approach which means that a distribution curve is fitted for the whole of the model time horizon, and a piecewise approach which means that the observed data from the trial is used and then a distribution curve fitted for the rest of the model time horizon. The company explored the following extrapolations in its scenario analyses: • Weibull dependent (fully fitted) • Log-logistic dependent (fully fitted) • Exponential piecewise **The ERG** The ERG was satisfied that the company's choice of a Weibull piecewise distribution to reflect long-term OS for patients in both arms of the model was supported by the available K-M data from the FLAURA trial. The use of these functions result in mortality for people in the osimertinib arm being approximately 36% lower than in the SoC EGFR-TKI arm over the period that survival is extrapolated (up to 20 years). The ERG noted that the difference in mortality rates between the arms are assumed to be constant over the lifetime of the model. **Clinical expert advice** The clinical experts generally agreed with the company's survival estimates for both osimertinib and standard care but one felt that some of the values were over optimistic for 5 and 10 years.

<table>
<tr><td></td><td>
<table>
<tr><th></th><th colspan="2">Osimertinib</th><th colspan="2">Standard care</th></tr>
<tr><th>Years after starting treatment</th><td>Company modelled people still alive (%)</td><td>Clinical expert</td><td>Company modelled people still alive (%)</td><td>Clinical expert</td></tr>
<tr><td>1</td><td>89</td><td>89</td><td>82</td><td>82</td></tr>
<tr><td>2</td><td>74</td><td>74</td><td>62</td><td>62</td></tr>
<tr><td>5</td><td>43</td><td>~35</td><td>26</td><td>~20</td></tr>
<tr><td>10</td><td>16</td><td>~12</td><td>6</td><td>6</td></tr>
</table>
</td></tr>
<tr><td>Why this issue is important</td><td>Choice of OS extrapolation is likely to drive costs and QALYs in the model in addition to the assumed 20-year treatment benefit (see issue 2).</td></tr>
<tr><td>Technical team judgement before engagement</td><td>The scenario analysis is sensitive to the choice of the parametric function for the calculation of the ICER (Exponential piecewise = £87,045; Weibull dependent = £124,833 and Log-logistic dependent = £111,395). Although Weibull is the most conservative extrapolation there is uncertainty with the survival estimates generated between osimertinib and standard of care (such as afatinib, gefitinib and erlotinib).</td></tr>
<tr><td>Summary of comments</td><td><u>Comments received from company</u>
Agree that the Weibull extrapolation fits better than any other function and produces conservative results.
Comments received from British Thoracic Oncology Group (BTOG):
Osimertinib = Agree with company estimates but nearer 30% of patients would be alive at 5 years.
Standard of Care = Agree with company estimates but nearer 15% of patients would be alive at 5 years.</td></tr>
</table>

<table>
<tr><td></td><td>Comment received from NCRI-ACP-RCP-RCR:
Percentage of patients expected to be alive at 2, 5 and 10 years
<table>
<tr><th></th><th>Osimertinib</th><th>Standard care</th></tr>
<tr><td>Years after starting treatment</td><td></td><td></td></tr>
<tr><td>2</td><td>70%</td><td>60%</td></tr>
<tr><td>5</td><td>40%</td><td>30%</td></tr>
<tr><td>10</td><td>Less than 5%</td><td>Less than 5%</td></tr>
</table></td></tr>
<tr><td>Technical team judgement after engagement</td><td>The company’s choice of a Weibull extrapolation fitted the data well and gave more conservative estimates of long-term survival compared with other distributions. The technical team agree that Weibull is likely to be the most appropriate choice of parametric function but do not think it is plausible for there to be a 36% lower mortality versus standard of care (afatinib, gefitinib and erlotinib) over the 20-year model time horizon Therefore, the technical team agree with applying an adjustment (reduction) to the long-term treatment benefit for osimertinib (see issue 2). In addition, there is uncertainty that afatinib can be assumed to have equivalent efficacy EGFR TKIs. There is no head-to-head trial evidence for osimertinib compared with afatinib or afatinib compared with erlotinib (see issue 7).</td></tr>
</table>

Issue 4 – Resource use in the progressed disease health state

This issue was resolved at technical engagement and is addressed in Table 3.

Issue 5 – End of life criteria

Questions for engagement	9. What is the life expectancy of the patient group receiving SoC? 10. What is the extension to life of the patient group receiving osimertinib?
Background/description of issue	**The Company** The company used Public Health England (PHE) registry data to demonstrate that people with advanced EGFR positive NSCLC in England and Wales have a life expectancy of less than 24 months. Median overall survival for people in England and Wales who have the same diagnosis (i.e. confirmed EGFR activating mutation, stage IIIb/IV NSCLC) is estimated to be [redacted] based on analysis of Public Health England data between 2014 and 2016 (n = 652, NCRAS). The company cited other similar results such as those seen in a study in the UK [redacted] and one in Germany (median OS = 18.4 months [95% CI 16.3 to 21.3], n = 242, data cut-off = Oct 2012). They considered this evidence as more representative of the population treated in NHS clinical practice than those in trials. The company's preferred base case model (Weibull piecewise extrapolation), based on the evidence from the FLAURA trial, predicts a mean of 3.69 life years (44.39 months) for people in the SoC arm with a median of 2.63 life years (31.54 months). In the FLAURA trial, osimertinib extended progression-free survival (PFS) by 8.7 months (18.9 months vs 10.2 months for SoC TKI). While OS data was immature at the time of data cut-off, the hazard ratio (HR) for death was 0.63 (95% CI: 0.45 - 0.88; p=0.007), reflecting a meaningful survival advantage over SoC TKI. At 18 months, 82.8% of patients receiving osimertinib were still alive, compared with 70.9% of those receiving SoC TKI. In the absence of median overall survival, the company stated that a survival gain at other percentiles of overall survival may be considered as a conservative estimate of the survival

	gain in the mature population. The 25th percentile of overall survival was observed at approximately 22.5 months in the osimertinib arm, and at approximately 15.9 months in the SoC arm. This reflects an improvement of 6.6 months. **The ERG** The ERG agreed that trial evidence (which included people who are likely to be younger and fitter than most patients with lung cancer treated in the NHS) may overestimate the life expectancy of NHS patients but considered that it is inconsistent to accept trial evidence as a measure of effectiveness but not as a measure of life expectancy. Based on the available FLAURA evidence (after 24 months over half (64.7%) of patients in the SoC arm were still alive), the average life expectancy of people with advanced EGFR positive NSCLC who are eligible for treatment with afatanib, erlotinib or gefitinib is likely to exceed 24 months. The ERG noted that the company used PFS data from the FLAURA trial to support that OS for people treated with osimertinib is longer than that of people treated with SoC EGFR-TKI. The ERG highlighted findings from published studies that suggest PFS is not a good substitute for overall survival. However, the economic modelling done by the ERG supports the company position that, compared with treatment with afatinib, erlotinib or gefitinib, treatment with osimertinib extends life expectancy by at least 3 months.
Why this issue is important	The appraisal committee's judgements about the acceptability of the technology as an effective use of NHS resources will take into account whether the technology meets the criteria for special consideration as a 'life-extending treatment at the end of life'. Technology which meets NICE's end of life criteria has an increased cost-effectiveness threshold.
Technical team judgement before engagement	The technical team highlight that real-world evidence was used to suggest a median life expectancy for people with confirmed EGFR activating mutation, stage IIIb/IV NSCLC as being below 24 months. The FLAURA trial, which almost exclusively contained people with a performance status of ≤1 (generally fitter that those who would be seen in NHS clinical practice), predicted a life expectancy greater than 24 months in the SoC arm. The technical team agreed that osimertinib could provide an overall-survival gain of over 3 months, based

	on the trial evidence presented, and the economic modelled data. However, the technical team does not consider that osimertinib meets the short life expectancy criteria and so does not meet the end of life criteria specified in NICE's guide to the methods of technology appraisal.
Summary of comments	Comments received from company: • The company fundamentally disagrees with the ERG and technical team that patients with EGFR advanced NSCLC do not have a short life expectancy (<24 months). • Patients included in SACT dataset are representative of patients in FLAURA, that is, people who did not receive an effective targeted therapy after progression on standard of care. • Extrapolated median OS for the control arm in FLAURA is 31.5 months which included people who had osimertinib for T790M patient's post-progression at a level that is higher than in UK practice [redacted] in SACT dataset). Company highlighted that only these patients likely to have a survival of more than 24 months. • End of life criteria should apply to all patients starting first line TKI because it is not possible to identify patients who will develop T790M mutation and receive subsequent osimertinib, or people will refuse or be ineligible for further treatment. • Precedent (TA509) in applying a level of flexibility to end-of-life criteria when meaningful survival benefit demonstrated (see company response to technical engagement). o TA509 median survival gain was 15.7 months. o Modelled (extrapolated) OS using FLAURA with a Weibull distribution predicts median survival gain of 16.8 months. Comments received from British Thoracic Oncology Group (BTOG): • Estimate median OS to be approximately 24 months for patients receiving SoC.

	• On the basis of the FLAURA study, estimate a 4 to 5-month extension to life with osimertinib. Comments received from NCRI-ACP-RCP-RCR: • The life expectancy of the patient group receiving SoC is likely to be 2 to 3 years. • Extension to life of the patient group receiving osimertinib is likely to be greater than 3 months, and potentially greater than 6 months. ERG considerations on updated company position received during technical engagement: • Uncertainty in evidence as standard of care in FLAURA trial is not representative of those in the NHS in England. • Cannot identify, in advance, which patients in the trial would be eligible to be used to determine cost-effectiveness. TA509 appraisal used evidence from the trial in considering the end of life criteria.
Technical team judgement after engagement	The technical team considered the **extension to life** of the patient group receiving osimertinib. Evidence and data from the FLAURA trial, used to populate the economic model, indicate an extension to life of over 3 months but the technical team acknowledge there is uncertainty in the precise size of the extension because of the immaturity of the Kaplan-Meier data in the FLAURA trial (7.9 months, 25% maturity). In addition, there is uncertainty about the extension to life between osimertinib and afatinib as there is no direct head-to-head trial evidence (see issue 7). Therefore, the technical team consider that although an extension of life of over 3 months is possible, there is uncertainty, and that this criterion has not yet been proven. The technical team considered the **life expectancy** of the patient group receiving standard of care. The company provided information about overall survival from a real-world data source, there is uncertainty when comparing the population data from a multinational, multicentre trial to that of registry data in England. While some baseline characteristics show

	similarities, many possible confounders (such as co-morbidities and deprivation level) within each population are not provided, making a direct comparison and translation to outcomes such as overall survival more difficult. The FLAURA data do not indicate that life expectancy in this population is less than 24 months: • The mean and median overall survival predicted by the company and ERG preferred models is greater than 24 months. • The clinical experts highlighted that median life expectancy for people receiving current standard care in England is likely to be 24 months or greater. • Data from the ARCHER 1050 and Lux-Lung 7 trials median overall survival in similar populations is more than 24 months Based on this evidence, osimertinib does not meet the short life expectancy criteria specified in NICE's guide to the methods of technology appraisal and therefore does not meet the end of life criteria. The technical team considered whether there was an exceptional case to apply the end of life criteria as applied in the appraisal of pertuzumab with trastuzumab and docetaxel for treating HER2-positive breast cancer (TA509). In TA509, the committee was asked to exercise 'flexibility' around the interpretation of the extension-to-life criteria (which specifies that life expectancy of patients would be normally less than 24 months) because of the substantial extension in overall survival. The median survival gain with pertuzumab of 15.7 months was based on observed evidence collected up to 70 months in the trial. In this appraisal, the estimated median survival gain for osimertinib is based on modelled, extrapolated values from observed K-M data up to 7.9 months and so is uncertain (see issues 2, 3 and 7). While uncertainty remains in the survival estimates generated by the extrapolation of overall survival, the technical team would like to see more observed evidence from the FLAURA trial and cannot directly compare the estimated survival gain with osimertinib with that of pertuzumab. There is additional uncertainty as the mechanism of action of pertuzumab, an immunotherapy to treat metastatic HER2–positive breast

	cancer, is different to that of osimertinib. There is insufficient evidence to suggest that there is an exceptional proportional gain in survival with osimeritnib compared with standard of care for people with EGFR positive NSCLC. The company provided a confidential approach to apply a QALY gain dependent on subsequent treatment for the T790M mutation.

Issue 6 – Cancer Drugs Fund

Questions for engagement	11. Would additional data collection in the Cancer Drugs Fund reduce the uncertainty? 12. Is the technology a good candidate for use in the Cancer Drugs Fund?
Background/description of issue	The technical team is aware of the arrangements for the Cancer Drugs Fund (CDF) agreed by NICE and NHS England in 2016, noting NICE's Cancer Drugs Fund methods guide (addendum). The technical team consider that there is clinical uncertainty that could be reduced through data collection via ongoing studies. For example, uncertainty about the clinical effectiveness of the technology because the overall survival (OS) data is too immature (25% of events at June 2017 data cut). However, taking into account its considerations about the end of life criteria, the technical team does not consider that osimertinib has plausible potential to be cost-effective at the offered price. **The Company** The company proposed, verbally to NICE, that osimertinib could be placed into the Cancer Drugs Fund. The only available direct evidence comes from an ongoing trial (FLAURA) which is due to report final analyses when a predefined number of people in the trial have died.
Why this issue is important	The CDF is a potential option if there is plausible potential for the drug to satisfy the criteria for routine commissioning, but there is significant remaining clinical uncertainty which needs

	more investigation, through data collection in the NHS or clinical studies. This means the CDF will fund the drug, to avoid long delays, but would require information on its effectiveness before it can be considered for routine commissioning (when the guidance is reviewed).
Technical team judgement before engagement	The technical team considers that osimertinib does not show plausible potential for cost effectiveness at the proposed price and does not meet the criteria for inclusion in the Cancer Drugs Fund.
Summary of comments	Comment received from company: • The final data cut for OS is expected in [redacted] to address uncertainties about survival expectations in the short to medium term. Comment received from British Thoracic Oncology Group (BTOG): • Real world data on overall survival would reduce uncertainty. Comments received from NCRI-ACP-RCP-RCR: • FLAURA survival data is currently immature. • Current data indicates osimertinib as an attractive treatment option for clinicians and patients and appears to be a good candidate for use within the CDF whilst further survival data is collected.
Technical team judgement after engagement	At the current value proposition, osimertinib does not appear to have plausible potential for cost-effectiveness with ICERs all above the £20,000 and £30,000 per QALY gained range when commercial arrangements are taken into account. It is therefore unlikely to meet the criteria for inclusion in the Cancer Drugs Fund. The current FLAURA trial data is immature (25% data maturity with a follow-up time of 18 months) with a final data cut (60% maturity) to take place at a later date (approximate date is commercial-in-confidence).

	However, if there was a plausible potential for it to be cost-effective, data collection (more mature data from the FLAURA trial) would help to resolve uncertainty (that is, in relation to the duration of treatment effect [issue 2] and extrapolation of overall survival [issue 3]).

Issue 7 – Relative efficacy of EGFR TKIs (new)

Background/description of issue	There is no head-to-head trial evidence for afatinib compared with osimertinib or afatinib compared with erlotinib and uncertainty remains if afatinib has equal efficacy to erlotinib and gefitinib. Analysis of the exploratory LUX-Lung 7 trial indicated that treatment with afatinib resulted in a statistically significant improvement in progression-free survival (PFS) compared with gefitinib. A simple indirect treatment comparison (ITC) done by the ERG suggests that osimertinib statistically significantly improves progression-free survival (by both investigator assessment [HR=0.59, 95% CI: 0.43 to 0.82] and blinded independent central review [HR=0.62, 95% CI: 0.44 to 0.87]) in comparison to afatinib, but that there is no statistically significant difference between osimertinib and afatinib for overall survival. However, the ERG state that the results of the ITC should be interpreted with caution.
Why this issue is important	A lack of direct evidence adds uncertainty to the true comparative efficacy of the EGFR TKIs
Technical team judgement after engagement	Following discussion and review of the ERG report, the technical team consider there is uncertainty about assuming equal efficacy of between afatinib and the other EGFR TKIs. If afatinib has any benefit over the other EGFR TKIs, this could reduce the incremental QALY benefit between osimertinib and afatinib and increase the ICER estimate.

3. Issues for information

Tables 1 to 3 are provided to stakeholders for information only and not included in the Technical Report comments table provided.

Table 1: Technical team preferred assumptions and impact on the cost-effectiveness estimate (based on list prices)

- 3- to 5-year duration of treatment effect for osimertinib
- Combined approach for resource use in the progressed disease state
- utility value of 0.678 for people in the progressed health state

These estimates do not include the commercial arrangements for the comparator erlotinib because these are confidential and cannot be reported here. Estimates that include these commercial arrangements would be higher than those reported in Tables 1a and b.

Table 1a: Cost effectiveness results comparing osimertinib and erlotinib incorporating the technical team's preferred assumptions' (3-year duration of treatment effect)

Alteration	Technical team rationale	ICER vs erlotinib	Change from base case
Company base case (assumes lifetime treatment benefit for osimertinib)		**£89,700***	
1. Adjusting resource use in the progressed disease (PD) health state	Issue 4	£88,057	−£1,643
2. Adjusting utility in the PD health state	See table 3	£87,357	-£2,343
3. 3-year duration of treatment effect	Issue 2	£162,262	+£72,562

Most plausible ICER based on technical team's preferred assumptions on the cost-effectiveness estimate		**£162,981**	**+73,281**

*deterministic ICER. the company's probabilistic ICER was £88,137 per QALY gained vs erlotinib.

Table 1b: Cost effectiveness results comparing osimertinib and erlotinib incorporating the technical team's preferred assumptions' (5-year duration of treatment effect

Alteration	Technical team rationale	ICER vs erlotinib	Change from base case
Company base case (assume lifetime treatment benefit for osimertinib)		**£89,700**	
1. Adjusting resource use in the progressed disease (PD) health state	Issue 4	£88,057	−£1,643
2. Adjusting utility in the PD health state	See table 3	£87,357	-£2,343
3. 5-year duration of treatment effect	Issue 2	£123,307	+£33,607
Most plausible ICER based on technical team's preferred assumptions on the cost-effectiveness estimate		**£120,953**	**+31,253**

Table 2: Outstanding uncertainties in the evidence base

Area of uncertainty	Why this issue is important	Likely impact on the cost-effectiveness estimate
CNS metastases	In the FLAURA trial, around a fifth (21%) of patients were considered to have CNS	Unknown

	metastases. Fewer patients in the osimertinib arm, [redacted] experienced CNS progression than in the SoC EGFR-TKI arm, [redacted]. All patients with a history of, or suspected, CNS lesion were required to have a baseline scan. However, if that brain scan came back with no evidence of CNS disease, further scans were not required by the protocol. If the patient subsequently became symptomatic, the investigator used clinical judgement on whether to scan the patient. Clinical experts agreed that the CNS progression results of the trial are generalisable to NHS clinical practice. In addition, although assessment of progression is, in the majority of patients guided by symptoms, practice is changing with some centres now undertaking routine brain scans at baseline and throughout treatment.	
Immature evidence base for overall survival	Median overall survival has not yet been reached for either osimertinib or standard care arms within the FLAURA trial. Analyses based on extrapolated values. The reported HR for osimertinib compared with SoC EGFR-TKI was 0.63 (95% CI: 0.45 to 0.88; p=0.007) [Not statistically significant at data cut: 25% maturity].	Unknown. Cost-effectiveness estimates are likely to be optimistic.

Table 3: Other issues for information

Issue	Comments
Generalisability of the FLAURA trial population (Issue 1)	The company submission highlighted that there was a difference between real world evidence from the National Cancer Registration and Analysis Service and the FLAURA trial in terms of patient performance status (PS). People with a PS of 2 or more were not included in FLAURA. **Following technical engagement, the technical team was satisfied that the FLAURA trial population was broadly generalisable to clinical practice in England despite this difference and was appropriate for decision making. Clinical experts and consultation feedback from the British Thoracic Oncology Group and NCRI-ACP-RCP-RCR agreed that people with a performance status of 2 or more would receive EGFR-TKIs for advanced first-line EGFR positive NSCLC.**
Resource use in the progressed disease health state (Issue 4)	In its original submission the company used values from NICE guideline CG81 (advanced breast cancer) the Big Lung Trial to estimate resource use of people in the progressed disease state. The technical team preferred estimate was a combined approach of progressed disease and PFS health state resource use. **Following technical engagement, the company updated its base-case to apply the technical team preferred estimate of resource use. This change had a minimal impact on the company's base-case ICER.**

Health-related quality of life was not measured using EQ-5D-3L	In its original submission the company applied a utility value of 0.64 for people in the progressed disease state (mapped across from EORTC QLQ-LC13 and EORTC QLQ-LC30). The technical team agreed with the ERG that a utility value of 0.678 (the utility value reported in TA416 from the AURA 2 trial, second-line treatment with osimertinib) as more representative. **Following technical engagement, the company updated its base-case to apply the technical team preferred utility value. This change had a minimal impact on the company's base-case ICER.**
Innovation	The company considers osimertinib to be innovative. However, the technical team considers that all relevant benefits associated with osimertinib are adequately captured in the model.
Equality considerations	No potential equality issues have been identified by the company, consultees and their nominated clinical experts and patient experts.

Authors

Gary McVeigh

Appraisal Committee Chair

Stephen Robinson

Technical Lead

Christian Griffiths

Technical Adviser

Jasdeep Hayre & Linda Landells

Associate Directors

With input from the lead team:

Gillian Ells

Lead team member

Rachel Elliott

Lead team member

Malcolm Oswald

Lead team member

NICE National Institute for Health and Care Excellence

Technical engagement response form

Osimertinib for untreated EGFR-positive non-small-cell lung cancer [ID1302]

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical 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 questions below. You do not have to answer every question. 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 summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments **15 February 2019.**

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 technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- 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 any information that is submitted under 'commercial arrangements' 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	**Kevin Lock**
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**AstraZeneca UK**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Questions for engagement

Issue 1: Generalisability of the FLAURA trial population	
Is the FLAURA trial population generalisable to clinical practice in England?	We agree with the technical team's preliminary judgement and rationale that the FLAURA trial population is generalisable to clinical practice in England.
Would people with a performance status (PS) of ≥2 be likely to have treatment with an EGFR TKI for 1st line EGFR-positive NSCLC?	We agree with the technical team's preliminary judgement and rationale that people with a PS ≥2 would be likely to have treatment with an EGFR TKI for 1st line EGFR-positive NSCLC. Restricting treatment to people with a worse PS would likely lead to health inequalities. There exists a strong association between a patient's fitness or performance status and socio-economic deprivation, with patients in the most deprived decile being more likely to have more co-morbidities and less likely to be offered or accept treatment. (Powell HA. Thorax Epub ahead of print: doi:10.1136/thoraxjnl-2018-212362). Further, according to Public Health England data in the NHS Long Term Plan, Lung Cancer is a significant contributor to the health and life expectancy inequalities observed between the most and least deprived deciles in society (0.93 years of 9.4 years life expectancy gap). (https://www.longtermplan.nhs.uk/ Last accessed Feb 2019) Thus, in order to support the NHS's ambition to narrow health inequalities, any recommendation for interventions *proven* to deliver survival benefits must apply to all patients rather than be restricted to the fittest patients.
Issue 2: Duration of treatment effect	

Is a 3- to 5-year duration of treatment effect for osimertinib appropriate?	It is acknowledged that there is remaining uncertainty based on the current FLAURA data set regarding the long-term duration of the treatment effect for osimertinib versus SoC and the difficulty for the committee to identify a single plausible set of assumptions to address this. Assuming a 3 year treatment effect is unduly pessimistic, **with 6 years being more plausible given the unique MOA of osimertinib:** - Firstly, it is implausible to assume that the mortality risk of the two arms is equal at 3 years, when over 20% of patients remain on treatment with osimertinib at this time point, based on the extrapolations of TDT from FLAURA (compared with 2% in the SoC arm). For this reason, the ERG agreed during the Technical Engagement meeting that a treatment effect duration of 3 years is not clinically plausible. - The CEM predicts that **at 5 years**, all patients in the SoC arm have discontinued their initial treatment, whilst a **small proportion of patients (2%) are still receiving osimertinib** in first line, which would still contribute to a treatment effect over SoC beyond 5 years. Therefore, we believe that if a treatment benefit cap is considered more plausible than a lifetime treatment effect, this should be applied when **all** patients in the osimertinib arm have discontinued their first line treatment. Specifically, the CEM predicts 0% patients on treatment at 6.08 years in the osimertinib arm. **Therefore, the company's preferred scenario is a treatment effect duration of 6 years.** - The nature of cohort partitioned survival models implies that a treatment waning effect cannot be modelled accurately. It is generally agreed that assuming that the hazard ratio returns to one immediately is the most simple and straightforward approach (as applied by the ERG). However, in an attempt to address this structural limitation, we have explored an additional scenario where the HR starts increasing gradually at 6 years and reaches the value of 1 at 7 years. - Assuming that the hazard ratio returns to one immediately at 3 or 5 years is not realistic when considering the **clinically meaningful and significant relative effect size** on overall survival. Early separation of the Kaplan-Meier curves was observed, and at 18 months, the estimated

percentage of patients who were alive was 83% (95% CI: 78 - 87) in the osimertinib group and 71% (95% CI: 65 - 76) in the standard EGFR-TKI group.

- Furthermore, the **meaningful reduction in CNS progression with osimertini**b, compared with 1st and 2nd generation TKIs, could translate into an improved survival profile beyond treatment discontinuation. The FLAURA trial demonstrated a 52% reduction in the risk of CNS disease progression or death, and a reduction in median time to onset of CNS response for osimertinib compared with SoC. CNS metastases cause significant morbidity and mortality and their appearance is associated with disabling clinical symptoms, a considerable decrease in QoL, and poor survival. Therefore, a reduction in CNS progression will translate into an improved survival profile beyond treatment discontinuation.
- **Using IO past appraisals** for NSCLC (pembrolizumab for PD-L1 positive NSCLC after chemotherapy (TA428) and atezolizumab for NSCLC after chemotherapy (TA520)) to inform a treatment effect duration of between 3 and 5 years **needs to be considered with caution**, since in both appraisals reimbursement was conditional on a maximum treatment duration of 2 years, while there are no restrictions on treatment duration for TKIs (time on treatment in the cost-effectiveness model is based on the modelled time-to-discontinuation of treatment (TDT) curves from FLAURA). Also, there are considerable differences between the appraisals, not least of which includes the different mode of action for immunotherapies compared with EGFRm TKIs, which mean that this past precedent should not apply here (see Table below).

	Pembrolizumab (TA428)	Atezolizumab (TA520)	Osimertinib (ID1306)
Mode of action	Immunotherapy		TKI
Median TDT	5.0 months	7.8 months	20.8 months
Maximum treatment duration	2 years or until RECIST progression, whichever occurs sooner		Until disease progression
Line of therapy	2L (after chemotherapy)		1L
Responders	62/344 (18.0%)	58/425 (13.6%)	223/279 (80%)

	<table><tr><td>**Duration of response**</td><td>Not reached (20 – 610 days)</td><td>16.3 months (10.0 – NE)</td><td>17.2 months (13.8 – 22.0)</td></tr><tr><td>**CNS activity?**</td><td>Unclear</td><td>Yes</td><td>Yes</td></tr><tr><td>**Agreed Duration of treatment effect**</td><td>3 years</td><td>5 years</td><td>TBC</td></tr></table> - Finally, feedback received by NICE from clinical experts and patient groups for this appraisal suggests that **UK patients on osimertinib in first line are expected to be more likely to receive an active subsequent treatment** compared with patients in the SoC arm, due to an improved safety profile and overall treatment experience (in the SACT dataset only 20% patients received subsequent anti-cancer treatments)**.** This will likely further contribute to a maintained treatment effect beyond discontinuation of their first line treatment. In summary, whilst AZ continues to believe in the continued benefit of osimertinib in this setting, we recognise the uncertainty remaining for the Committee. If a limit on the long-term efficacy of osimertinib on overall survival must be assumed, it is important that the application of that limit is evidence-based. It is our belief that the most conservative assumption in this scenario is to apply a treatment effect when all patients receiving osimertinib have stopped 1L treatment – i.e. 6 years. It must also be recognised that in reality, the hazard ratio is unlikely to change to 1 immediately and it is much more plausible to assume a gradual decline in the true HR over time. However, the nature and duration of such a waning effect is difficult to incorporate into a partitioned survival model which forms the basis of the cost-effectiveness submission.
Is there any additional evidence which could be used to inform the duration of treatment effect?	Further to the above rationale, there are a number of additional compelling reasons to believe that the use of osimertinib 1L will have a sustained effect on OS, with a 6-year duration of treatment effect being more plausible than the estimates provided by the ERG: • Post-progression outcomes including PFS2, TFST, TSST all favour osimertinib and show a benefit well beyond first progression. • No aggressive mutations have been observed so far post osimertinib 1L.

<table>
<tr><td></td><td>

No T790M Mutation has been observed post osimertinib 1L use.

In light of the above, AZ have explored a number of plausible scenarios implementing the waning effect from:

5 years (ERG preferred scenario)
6 years (company’s preferred scenario)
Waning effect starting at 6 years with HR steadily increasing to 1 over 12 months

The table below shows the ICERs for osimertinib vs each comparator assuming the three scenarios above (list price).
<table>
<tr><th>Scenario</th><th>ICER vs Erlotinib</th><th>ICER vs Gefitinib</th><th>ICER vs Afatinib</th></tr>
<tr><td>5 years</td><td>£120,953</td><td>£111,056</td><td>£111,048</td></tr>
<tr><td>6 years</td><td>£110,254</td><td>£101,287</td><td>£101,280</td></tr>
<tr><td>6 years with HR increasing over 12 months</td><td>£107,587</td><td>£98,851</td><td>£98,845</td></tr>
</table>
Further exploratory analyses are presented separately.
</td></tr>
<tr><td colspan="2">Issue 3: Extrapolation of overall survival (OS)</td></tr>
<tr><td>What proportion of patients in the osimertinib arm would you expect to be alive at 2, 3 and 5 years?</td><td>Regardless of the uncertainty surrounding the survival of patients in the osimertinib arm of the FLAURA study, the Weibull extrapolation fits better than any other function and produces conservative results. AZ stands by the estimates provided in the original submission.

Although one of the two clinical experts whose input was sought by NICE considered the estimates of the number of patients still alive at 5 and 10 years to be optimistic (by 8 and 4 % points, respectively), the other expert considered them reasonable. It is not clear that this difference of opinion has been fairly considered by the technical team.</td></tr>
</table>

What proportion of patients in the SoC arm would you expect to be alive at 2, 3 and 5 years?	Regardless of the uncertainty surrounding the survival of patients in the SoC arm of the FLAURA study, the Weibull extrapolation fits better than any other function and produces conservative results. **AZ stands by the estimates provided in the original submission.** Although one of the two clinical experts whose input was sought by NICE considered the estimates of the number of patients still alive at 5 years to be optimistic (by 6 % points), the other expert considered them reasonable. It is not clear that this difference of opinion has been fairly considered by the technical team.
Is the Weibull distribution appropriate for modelling overall survival?	We agree with the technical team's preliminary judgement and rationale that the Weibull extrapolation fits better than any other function and produces conservative results.
Issue 4: Resource use in the progressed disease health state	
What is the most appropriate source of resource use for people with progressed disease?	We agree with the technical team's preliminary judgement and rationale that the ERG's preferred estimate using one third of the costs concerning palliative care and two thirds of costs reflecting second and third line active therapy is appropriate.
Issue 5: End of life criteria	
What is the life expectancy of the patient group receiving SoC?	We **fundamentally disagree** with the ERG and technical team in their assertion that patients with EGFRm advanced NSCLC do not have a short life expectancy (<24 months) and therefore osimertinib does not meet the End of Life criteria for this indication. Real-world evidence from SACT clearly demonstrates that people with lung cancer in the UK have a worse prognosis than those in clinical trials, which is substantially less than 24 months. Osimertinib also fulfils the ≥3 month life extension criterion, based on the predicted unprecedented survival benefit seen in this trial. Evidence supporting these statements is presented below. 1. **The "fitter" patients in SACT are similar to patients in recent RCTs (including FLAURA), but have a much lower life expectancy (16.7 months median OS in SACT)**

The evidence presented in the original submission and in response to subsequent clarification questions, as well as in the Technical Engagement meeting, clearly shows that even using data from the fittest patients treated in England (i.e. PS 0/1 as recruited to FLAURA and other recent RCTs), the baseline characteristics, and average exposure to 1L TKI is comparable to patients in key RCTs (see Table below).

This is supported by the statements from other consultees in relation to this appraisal. One expert stated that:

> *"Real world experience with the 1st and 2nd generation EGFR inhibitors matches that reported in clinical trials such as Lux-Lung 7 and Optimal."*

It is instructive therefore to note the baseline characteristics of patients in these studies, the time spent on treatment in 1L, the exposure to subsequent therapies (after progression on 1L TKI) and OS.

	SACT Overall	SACT PS 0/1	OPTIMAL	LuxLung 7	FLAURA
Number of patients	*N=652*	N=336	N=82 (erlotinib)	N=319	N=556
Recruitment	*Jan 14 – Dec 15*	*Jan 14 – Dec 15*	Aug 08 – Jul 09	Dec 11 – Aug 13	Feb 15 – Mar 16
Female, n (%)	*414 (64%)*	218 (65%)	48 (59%)	197 (62%)	350 (63%)
Age, median years (inter-quartile range; IQR)	*68 (61-76)*	68 (61-75)	57 (range: 31 – 74)	63 (range: 30-89)	64 (range: 26 – 93)
Stage IIIb	*30 (5%)*	13 (4%)	11 (13%)	11 (3%)	556 (100%)
Stage IV	*622 (95%)*	323 (96%)	71 (87%)	308 (97%)	
PS 0	*130 (20%)*	130 (39%)	75 (91%	98 (31%)	228 (41%)
PS 1	*206 (32%)*	206 (61%)		221 (69%)	327 (59%)
PS ≥2	*112 (18%)*	-	7 (9%)	-	-
PS Missing	*204 (31%)*	-	-	-	-
TDT, median months (95% CI)	*9.0 (7.9-10.4)*	10.3 (9.0 – 11.3)	12.8 (95% CI NR)	11·5 (10·1–13·1)	11.5 (10.3 - 12.8)

From the data in the table above, there are some notable similarities between the different data sources:

- **Patients are broadly comparable in terms of baseline characteristics** (% female, age, disease staging and performance status). This is as true for the RCTs as it is for the PS0/1 subgroup of the SACT dataset.

- **The time spent on treatment in 1L setting hasn't changed over time** (e.g. approximately 1 year for patients diagnosed 2008/9 in OPTIMAL to 2015/16 in FLAURA). It is noteworthy that TDT for both the PS0/1 subgroup as well as the overall cohort of patients in SACT is on the lower margin of what is observed in RCTs.

However, there are some very important differences:

- The proportion of patients receiving subsequent therapy in RCTs has increased slightly over time (67% in OPTIMAL vs 77% in LUXLung 7). In contrast, **the proportion of patients in the SACT dataset receiving any subsequent therapy is significantly less, at 20-22%.**

- The OS of patients has remained relatively stable in the period between OPTIMAL and LUXLung 7 (approximately 24 months), but is expected to be markedly increased when OS reaches maturity in FLAURA (predicted to be 31 months for SoC). **The median OS for patients receiving SoC in the PS0/1 subgroup of SACT is 16.7 months.**

	SACT Overall	SACT PS 0/1	OPTIMAL	LuxLung 7	FLAURA
Number of patients	*N=652*	N=336	N=82 (erlotinib)	N=319	N=556
Recruitment	*Jan 14 – Dec 15*	*Jan 14 – Dec 15*	Aug 08 – Jul 09	Dec 11 – Aug 13	Feb 15 – Mar 16
TDT, median months (95% CI)	*9.0 (7.9-10.4)*	10.3 (9.0 – 11.3)	12.8 (95% CI NR)	11·5 (10·1–13·1)	11.5 (10.3 - 12.8)
Receiving anti-cancer treatment after TKI, N (%)	*122 (20%)*	68 (22%)	55 (67%)	77% (116/151)	47% (129/277)

				95% stopped randomised treatment	77% stopped randomised treatment
OS, median months (95% CI)	*15.8 (14.1-17.2)*	16.7 (15.3-19.1)	22.8 (95% CI NR)	24.5 (95% CI NR) 71% mature OS	31 months predicted. 25% mature OS

Thus, the available **evidence from multiple sources clearly demonstrates that OS in patients with advanced EGFRm NSCLC is correlated to both use of TKI in the 1L setting and access to subsequent therapies after progression.** OPTIMAL (although a small study conducted in China) demonstrated that in patients receiving erlotinib in the 1L setting, median OS was significantly longer in patients who subsequently received chemotherapy (28.0 months) compared with those who did not receive any post-progression treatment (18.6 months), HR = 0.53 (0.32 – 0.88). These results are consistent with the evidence from the SACT dataset.

The statement from one of the clinical experts concerning patient preferences for subsequent treatment with chemotherapy following 1L treatment with TKI's is consistent with the low proportion of patients in SACT who received any further anti-cancer treatment following progression or stopping a TKI.

2. **Evidence in the 2L setting shows a positive correlation between osimertinib use and overall survival**

In recent years, the availability of osimertinib in 2L (for patients with T790M resistance mutation) has provided a welcome alternative for eligible patients and it is clear that median OS estimates in recent studies are positively correlated with the proportion of patients treated with osimertinib after progression on a 1st/2nd Generation TKI in 1L (i.e. in LUXLung 7, 20% of therapies in 2L setting after SoC were osimertinib, compared to 43% in FLAURA). It is important to note that no patients in the SACT cohort received osimertinib in the 2L setting and this is likely reflected in the survival outcomes.

3. Precedent dictates a level of flexibility in applying end-of-life criteria, especially where a meaningful survival benefit is demonstrated

In TA509 the committee acknowledged that *"the wording referring to the end-of-life criteria is deliberately expressed to provide committees with discretion required when they consider it reasonable to apply a weight to the QALYs gained in circumstances where one of the criteria does meet the exact level described in the policy*".

It was also stated that "*The committee noted that the survival benefit with pertuzumab met, and far exceeded the 3 month extension to life criteria, and it had heard from the clinical experts that a 15.7 months median survival gain was unprecedented in the treatment of metastatic HER2-positive breast cancer and represented a step-change in the treatment of this condition. The committee noted that the life expectancy of patients on chemotherapy alone based on the unadjusted median overall survival in the control arm of CLEOPATRA was 40.8 months, which exceeds the 24 months stated in the end-of-life criteria. However, people in the CLEOPATRA trial may have a better prognosis than people in UK clinical practice*".

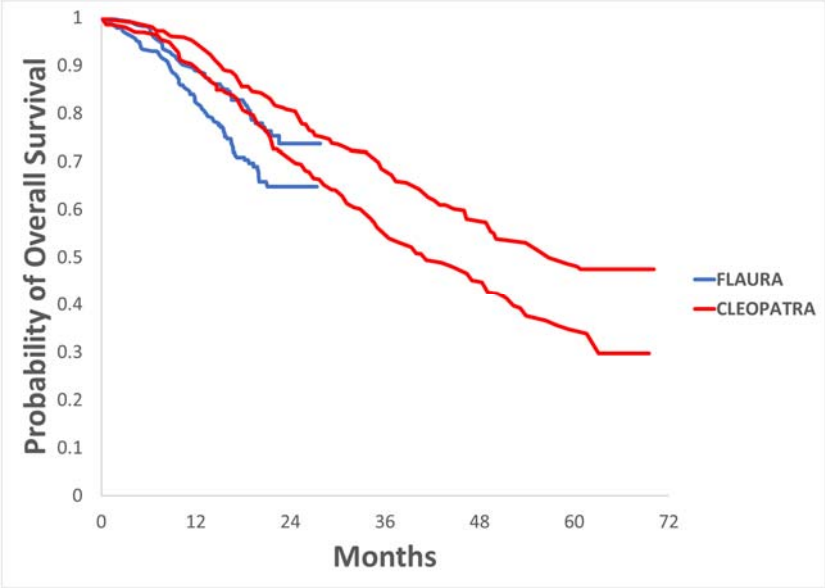
In this regard, AZ would like to highlight that, although FLAURA OS maturity is ~25% at the available follow-up, both the ERG and the clinical experts agreed that the observed PFS benefit and the early separation of the OS curves is unprecedented in this setting (EGFR+ NSCLC patients receiving a TKI). Also, according to the OS extrapolations from FLAURA, even when a treatment waning effect is applied at 5 years or beyond, the predicted median OS gain is of 16.8 months, which exceeds the gain of 15.7 months observed in CLEOPATRA. Moreover, the OS HR reported in CLEOPATRA at ~33% maturity (median follow-up = 30 months) was 0.66 (0.52; 0,84) while in FLAURA the HR was 0.63 (0.45; 0.88) at ~25% (median follow-up = 18 months).

	CLEOPATRA (shorter follow-up)[1]	FLAURA[2]	CLEOPATRA (Longer follow-up)[3]	CEM extrapolations
Maturity (OS)	~33%	~25%	~48%	N/A

Follow-up	30 months	18 months	50 months	N/A
PFS HR	0.68 (0.58; 0.80)	0.46 (0.37; 0.57)	NR	N/A
mPFS benefit	6.3 months	8.7 months	NR	N/A
OS HR	0.66 (0.52; 0,84)	0.63 (0.45; 0.88)	0.68 (0.56; 0.84)	N/A
mOS benefit	N/R	N/R	15.7 months	~16.8 months (predicted)

1: Lancet Oncol 2013; 14: 461–71, 2: N Engl J Med 2018; 378:113-125 , 3: N Engl J Med 2015;372:724-34.

Furthermore, the extrapolated median OS for the control arm in FLAURA is 31.5 months with use after progression of osimertinib for T790M patients, which far exceeds that observed in the UK. It is important to reiterate that based on the SACT dataset, only patients receiving osimertinib after progression (T790M patients) will be likely to exceed the median life expectancy of 24 months and that this small subgroup cannot be identified at initiation of first line TKI treatment.



	We therefore strongly believe that on the basis of the unprecedented clinical results observed in FLAURA, the extrapolated median OS gain, and in order not to penalize the entire EGFR+ NSCLC population due to a small group of patients extending survival, we advocate flexibility on the potential weight applied to the QALYs gained when considering the applicability of end of life. **Summary** The patients included in the SACT dataset are representative of patients in FLAURA who did not receive an effective targeted therapy after progression on SoC TKI, and should be eligible for consideration as an End of Life population. There is a significant subgroup of patients who progressed on SoC TKI in FLAURA with the T790M mutation and received osimertinib 2L. These patients are highly likely to have a survival of more than 24 months and are not considered End of Life patients. There is no way of identifying patients at the start of 1L treatment who will go on to develop the T790M mutation, have it detected and receive osimertinib, who will refuse or be ineligible for further treatment, or who will receive chemotherapy. Therefore, it is our belief that the End of Life criteria should apply to all patients starting 1L TKI treatment and the Committee should demonstrate flexibility in their decision-making.
What is the extension to life of the patient group receiving osimertinib?	We are pleased to note that both the ERG (see below) and the technical team agree that osimertinib is likely to extend overall survival by at least 3 months. Indeed, the ERG has highlighted the importance of the expected unprecedented OS benefit in FLAURA, in the context of clinical studies of EGFRm-TKI treatments in this setting.

	The ERG highlights that if OS is shown to be improved with osimertinib versus SoC EGFR-TKI, this will be a particularly important finding. To date, no trial comparing EGFR-TKIs with one another in the first-line setting has demonstrated an OS benefit,[26,38] nor has an EGFR-TKI been shown to result in superior OS versus PDC.[20-25,27-30,33,34] A pooled analysis of LUX-Lung 3 and LUX-Lung 6 trial data[32] has however shown an OS benefit in the subgroup of patients with Exon 19 deletions for afatinib versus PDC (cisplatin plus pemetrexed in the LUX-Lung 3 trial and cisplatin plus gemcitabine in the LUX-Lung 6 trial).
Issue 6: Cancer Drugs Fund	
Would additional data collection in the Cancer Drugs Fund reduce the uncertainty?	AZ reminds the Technical team that the final data cut for OS is expected later this year and is expected to address uncertainties about survival expectations in the short to medium term.
Is the technology a good candidate for use in the Cancer Drugs Fund?	AZ believes that osimertinib is a good candidate for the CDF given the arguments outlined above and our commitment to exploring all opportunities to ensure this important advance in treatment for patients with a high unmet need is available.

CONFIDENTIAL APPENDIX

Technical engagement response form

Osimertinib for untreated EGFR-positive non-small-cell lung cancer [ID1302]

CONFIDENTIAL

With regards to flexibility in the application of the End of Life criteria, we propose the Committee consider the proportion of patients receiving osimertinib 2L when deciding the proportion of patients starting 1L TKI who would have a life expectancy of more than 24 months. It is important to notice that eligibility for subsequent use of osimertinib after progression on a 1st or 2nd generation TKI is based on the development of T790 mutation at the point of progression (i.e. those patients cannot be identified at initiation of 1L treatment).

According to the NICE Guide to the methods of technology appraisal (PMG9), the most relevant paragraphs covering this proposal are 6.2.9 – 6.2.11. These are reproduced below for reference (our emphasis).

> *6.2.9 In the reference case, the Committee will regard all QALYs as being of equal weight. However, when considering the overall health benefits,* ***the Appraisal Committee can accept analysis that explores a QALY weighting that is different from that of the reference case*** *when a technology appraisal concerns a 'life extending treatment at the end of life', or in other circumstances when instructed by the NICE board.*
>
> *6.2.10 In the case of a 'life-extending treatment at the end of life', the Appraisal Committee will satisfy itself that all of the following criteria have been met:*
>
> - *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 has the prospect of offering an extension to life,* ***normally of a mean value of at least an additional 3 months, compared with current NHS treatment.***
>
> *In addition, the Appraisal Committees will need to be satisfied that:*

- *the estimates of the extension to life are sufficiently robust and can be shown or reasonably inferred from either progression-free survival or overall survival (taking account of trials in which crossover has occurred and been accounted for in the effectiveness review) and*
- *the assumptions used in the reference case economic modelling are plausible, objective and robust.*

6.2.11 When the conditions described in section 6.2.10 are met, the Appraisal Committee will consider: the impact of giving greater weight to QALYs achieved in the later stages of terminal diseases, using the assumption that the extended survival period is experienced at the full quality of life anticipated for a healthy individual of the same age and ***the magnitude of the additional weight that would need to be assigned to the QALY benefits in this patient group for the cost effectiveness of the technology to fall within the normal range of maximum acceptable ICERs, with a maximum weight of 1.7****.*

Our interpretation of this guidance is that the QALY benefits associated with patients treated with osimertinib (i.e. the incremental QALY gain) may be inflated to a maximum of 1.7 times the reference case; i.e. if the QALY benefits associated with the use of osimertinib as a 1L treatment are calculated by the cost-effectiveness model to be 0.743, applying the maximum weight of 1.7 would result in a total QALY gain of 1.263 (0.743 x 1.7) compared to standard treatment.

Since the patient population under consideration in the current appraisal is a mixture of patients who meet and do not meet End of Life, the appropriate QALY weighting is given by the equation:

$$QALY\ weight = (Not\ EoL\ \% * 1) + (EoL\ \% * 1.7)$$

From IMS/IQVIA data, the number of patients receiving a TKI in England has been stable at [redacted] (IMS Data disclosure EGFR TKIs NHS England, Feb 2019). We know from CDF data that approximately [redacted] patients have access to osimertinib (NHS England Data Monitoring Report for osimertinib 28 December 2018). Thus, the proportion of patients who do not meet End of Life in England is approximately [redacted] Given the evidence provided in the SACT dataset, it is reasonable to assume that the remaining xxx receive no further treatment or chemotherapy (and have a life expectancy much less than 24 months). We therefore suggest a reasonable weight for QALYs gained for the entire eligible cohort of patients receiving a TKI in 1L is [redacted] (given by [redacted] x 1.0 QALY weight + [redacted] x 1.7 QALY weight).

[redacted]

Table 1 Revised incremental costs, QALYs and ICERs for 3 scenarios exploring the duration of treatment effect (net price [redacted])

Scenario	Incremental Costs	Incremental QALYs		ICER vs Gefitinib	
		reference case	QALY weight = [redacted]	reference case	QALY weight = [redacted]
5 years	[redacted]	0.743	[redacted]	[redacted]	[redacted]
6 years	[redacted]	0.820	[redacted]	[redacted]	[redacted]
6 years with HR increasing over 12 months	[redacted]	0.841	[redacted]	[redacted]	[redacted]

NICE National Institute for Health and Care Excellence

Technical engagement response form

Osimertinib for untreated EGFR-positive non-small-cell lung cancer [ID1302]

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Deadline for comments **15 February 2019.**

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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)	**British Thoracic Oncology Group (BTOG)**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Questions for engagement

Issue 1: Generalisability of the FLAURA trial population	
Is the FLAURA trial population generalisable to clinical practice in England?	**Yes, except for the following two areas:** **1. FLAURA only includes patients of performance status (PS) 0-1. A significant proportion of patients in real-world practice would be PS=2, and some would even be PS=3 although the latter is a smaller group. The NCRAS data supplied by the company in the Draft Technical Report largely fits with expected clinical practice.** **2. FLAURA only include patients with common EGFR sensitising mutations (exon 19 deletion and exon 21 L858R mutations) alone or in combination with other EGFR mutations. In routine clinical practice patients with only uncommon EGFR sensitising mutations (such as exon 18 mutations) would also receive 1st line EGFR TKI therapy. This group might reflect approximately 5% of all EGFR mutation patients.** **It is important to recognise that although clinical trial populations are often younger and fitter than real-world populations, patients with EGFR mutations are themselves usually younger and fitter than the general lung cancer population. Therefore, the FLAURA trial population is more generalisable to clinical practice than, for example, first-line chemotherapy clinical trials.**
Would people with a performance status (PS) of ≥2 be likely to have treatment with an EGFR TKI for 1st line EGFR-positive NSCLC?	**Yes.** **It is regarded as standard practice to offer patients with performance status 2 an EGFR TKI in this setting. This reflects the high clinical activity of these agents, their favourable side effect profile, ease of administration and the great chance that the patient will improve clinically as a consequence of treatment.**

Issue 2: Duration of treatment effect	
Is a 3- to 5-year duration of treatment effect for osimertinib appropriate?	**In the absence of mature overall survival (OS) data, the duration of treatment effect remains uncertain. The duration of treatment effect will continue beyond the point at which Osimertinib is stopped, reflecting control of disease (and presumably maintained better performance status) and potential greater control of central nervous system (CNS) disease whilst on therapy.** **A 20-year duration of treatment effect is too long. On the basis of the 18.9 months progression free survival (PFS) in the Osimertinib arm of FLAURA, and taking into account treatment benefit beyond this point, a 3- to 5-year duration would seem appropriate.**
Is there any additional evidence which could be used to inform the duration of treatment effect?	**No.**
Issue 3: Extrapolation of overall survival (OS)	
What proportion of patients in the osimertinib arm would you expect to be alive at 2, 3 and 5 years?	**The estimates provided by the company for 2- and 3-year survival (89% and 74% respectively) fit with my approximate expectation.** **I do not think that 43% of patients would be alive at 5 years, and suspect this figure should be nearer 30%.**
What proportion of patients in the SoC arm would you expect to be alive at 2, 3 and 5 years?	**The estimates provided by the company for 2- and 3-year survival (82% and 62% respectively) fit with my approximate expectation.** **I do not think that 26% of patients would be alive at 5 years, and suspect this figure should be 15%.**
Is the Weibull distribution appropriate for modelling overall survival?	**No comment.**
Issue 4: Resource use in the progressed disease health state	

What is the most appropriate source of resource use for people with progressed disease?	**No comment.**
Issue 5: End of life criteria	
What is the life expectancy of the patient group receiving SoC?	**I would estimate median OS to be approximately 24 months for patients receiving SoC.**
What is the extension to life of the patient group receiving osimertinib?	**Osimertinib extended PFS by 8.7 months compared to SoC. The company's submission, using 25th percentile OS data, suggests a 6.6 month increase with Osimertinib.** **On this basis I would estimate 4-5 months extension to life with Osimertinib.**
Issue 6: Cancer Drugs Fund	
Would additional data collection in the Cancer Drugs Fund reduce the uncertainty?	**Real word data on Overall Survival**
Is the technology a good candidate for use in the Cancer Drugs Fund?	**No comment.**

NICE National Institute for Health and Care Excellence

Technical engagement response form

Osimertinib for untreated EGFR-positive non-small-cell lung cancer [ID1302]

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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)	**On behalf of NCRI-ACP-RCP-RCR**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Questions for engagement

Issue 1: Generalisability of the FLAURA trial population	
Is the FLAURA trial population generalisable to clinical practice in England?	**Yes – agree that the FLAURA trial population is broadly generalizable to clinical practice in England, although a proportion of patients seen (approx. 25%) are likely to be PS≥2.**
Would people with a performance status (PS) of ≥2 be likely to have treatment with an EGFR TKI for 1st line EGFR-positive NSCLC?	**Yes**
Issue 2: Duration of treatment effect	
Is a 3- to 5-year duration of treatment effect for osimertinib appropriate?	**Yes**
Is there any additional evidence which could be used to inform the duration of treatment effect?	**-**
Issue 3: Extrapolation of overall survival (OS)	
What proportion of patients in the osimertinib arm would you expect to be alive at 2, 3 and 5 years?	**70%, 40%, <5%**
What proportion of patients in the SoC arm would you expect to be alive at 2, 3 and 5 years?	**60%, 30%, <5%**
Is the Weibull distribution appropriate for modelling overall survival?	**-**
Issue 4: Resource use in the progressed disease health state	

What is the most appropriate source of resource use for people with progressed disease?	**Agree with the use of the ERG's preferred approach.**
Issue 5: End of life criteria	
What is the life expectancy of the patient group receiving SoC?	**The life expectancy of the patient group receiving SoC is likely to be 2 – 3yrs.**
What is the extension to life of the patient group receiving osimertinib?	**From current data, the extension to life of the patient group receiving osimertinib is likely to >3mths, and potentially >6mths.**
Issue 6: Cancer Drugs Fund	
Would additional data collection in the Cancer Drugs Fund reduce the uncertainty?	**Yes – FLAURA survival data is currently immature.**
Is the technology a good candidate for use in the Cancer Drugs Fund?	**Yes – current data indicates significantly improved disease control, improved CNS penetration and a favourable AE profile; Osimertinib therefore represents an attractive treatment option for clinicians and patients, and appears to be a good candidate for use within the CDF whilst further survival data is collected.**

NICE National Institute for Health and Care Excellence

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Osimertinib for untreated EGFR-positive non-small-cell lung cancer [ID1302]

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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)	**NLCFN**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

Questions for engagement

Issue 1: Generalisability of the FLAURA trial population	
Is the FLAURA trial population generalisable to clinical practice in England?	
Would people with a performance status (PS) of ≥2 be likely to have treatment with an EGFR TKI for 1st line EGFR-positive NSCLC?	**YES**
Issue 2: Duration of treatment effect	
Is a 3- to 5-year duration of treatment effect for osimertinib appropriate?	
Is there any additional evidence which could be used to inform the duration of treatment effect?	
Issue 3: Extrapolation of overall survival (OS)	
What proportion of patients in the osimertinib arm would you expect to be alive at 2, 3 and 5 years?	
What proportion of patients in the SoC arm would you expect to be alive at 2, 3 and 5 years?	
Is the Weibull distribution appropriate for modelling overall survival?	
Issue 4: Resource use in the progressed disease health state	

What is the most appropriate source of resource use for people with progressed disease?	
Issue 5: End of life criteria	
What is the life expectancy of the patient group receiving SoC?	
What is the extension to life of the patient group receiving osimertinib?	
Issue 6: Cancer Drugs Fund	
Would additional data collection in the Cancer Drugs Fund reduce the uncertainty?	
Is the technology a good candidate for use in the Cancer Drugs Fund?	

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

ERG technical engagement response 1

Osimertinib for untreated EGFR-positive non-small cell lung cancer [ID1302]

ERG comments on AstraZeneca UK technical engagement response form

This report was commissioned by the NIHR HTA Programme as project number 17/141/08

Completed 4th March 2019

CONTAINS COMMERCIAL IN CONFIDENCE DATA

1 INTRODUCTION

As part of the National Institute for Health and Care Excellence (NICE) Single Technology Appraisal (STA) process to consider the clinical and cost effectiveness of osimertinib for untreated epidermal growth factor receptor-positive (EGFR+) non-small cell lung cancer (NSCLC), AstraZeneca UK (the company) submitted a response to the technical engagement report produced by NICE following the company submission and the Evidence Review Group (ERG) critique of the company submission.

NICE has requested that the ERG provides a general critique of the company response to the technical engagement report with a focus on the following issues:

1. The proposed 6 year duration of treatment effect and tapering of hazard ratio (HR) over 12 months (issue 2 of technical engagement report).

2. The company justifications around meeting End of Life criteria and the proposed approach of applying a weighted quality adjusted life year (QALY) gain (issue 5 of technical engagement report).

3. Validation of the company's scenario incremental cost-effectiveness ratios (ICERs) at list price (p.7 of the comments response document) and associated confidential patient access scheme (cPAS) ICERs.

2 GENERAL CRITIQUE OF THE COMPANY RESPONSE

The ERG critique is focussed on those areas of the company response where the ERG either disagrees with the company conclusions or where the ERG considers that an ERG perspective on the company response would be informative for the NICE Appraisal Committee.

2.1 Duration of treatment effect (issue 2 of technical engagement report)

The ERG considers that the true duration of treatment effect is unknown due to the time horizon of the available clinical effectiveness data and that any application of a duration of treatment effect within the company model will always be speculative.

The ERG does not consider that any of the additional information provided by the company supports the company argument that the duration of treatment effect should be longer than 5 years. The majority of the company response is a description of why or how the treatment effect on overall survival (OS) gained from osimertinib is realised or how it may continue post-treatment discontinuation, but there is no comprehensive discussion of actual duration of treatment effect.

The company argues that a 6 year duration of treatment effect can be assumed given that 2% of patients are still on treatment at 5 years in the company model**.** However, the actual percentage of patients still on treatment and *having survival benefit from treatment* at 5 years is unknown. The company model predicts that 42% of patients receiving first-line osimertinib will be alive at 5 years. Even if 2% of patients had gained a survival benefit from being on treatment at 5 years, it seems implausible to use this as a justification for applying the same survival benefit to the 40% of patients who stopped taking the treatment for a period of less than 5 years. The ERG therefore considers that, whilst there is limited evidence to support a 5 year duration of treatment effect for osimertinib beyond the fact that 98% of patients are no longer receiving osimertinib at 5 years, the company has not presented strong evidence that the duration of treatment effect continues after 5 years.

In the company response, the company states that a waning of treatment effect occurs. This means that the HRs for osimertinib and standard of care (SoC) reach 1 over a period of 12 months; this approach is argued by the company to be more clinically plausible than the assumption that the HRs instantaneously reach 1 at year 5. The ERG considers that, whilst this approach may produce smoother survival curves that appear more visually realistic, without information on how the waning actually occurs, there is no way of knowing whether application of a 1 year waning effect produces more realistic survival results (and therefore

ICERs) than an instantaneous equalisation of mortality HRs. Without more evidence on OS for osimertinib and SoC (such as from the FLAURA trial) or evidence describing how the treatment effect of osimertinib changes over time, the ERG would not consider an ICER per QALY gained with waning of effect to be any more plausible than one without waning of effect.

The ERG re-calculated ICERs per QALY gained with a duration of treatment effect for osimertinib lasting for 6 years and waning between years 5, and 6 and the ERG results agree with the values presented on page 7 of the company response.

2.2 End of life criteria (issue 5 of technical engagement report and confidential appendix)

The company has provided extensive information in their response that the NICE End of Life criteria are met by osimertinib. However, the ERG did not assert that patients with EGFR-positive non-small cell lung cancer had a life expectancy over 24 months. Rather, the ERG considers that if trial data are used to estimate treatment effectiveness, then trial data should also be used for the assessment of OS for patients not receiving the treatment and as part of the End of Life assessment. It is then for the NICE Appraisal Committee to decide whether the treatment meets the NICE End of Life criteria.

In a confidential appendix, the company presented an argument that a QALY weighting of [redacted] should be applied to the QALYs generated by osimertinib first line as the company calculates that [redacted] of patients should be classified as end of life. The ERG notes the following regarding the argument and calculations presented by the company:

- As stated above the ERG remains unconvinced that the NICE End of Life criteria are met for osimertinib.
- The justification for [redacted] of patients meeting the NICE End of Life criteria is based upon the percentage of patients that the company estimates receive osimertinib as a second-line treatment. The company does not present any evidence describing life expectancy in this population, this means it is not possible to confirm whether this is a subgroup that would meet the NICE End of Life criteria.
- In the opinion of the ERG, unless there are clear subgroups that are pre-specified in the NICE scope or have been requested by the Appraisal Committee to explore, NICE End of Life criteria should be assessed against the whole patient population.

- A weighting of up to 1.7 applied to QALYs at the end of life can be applied. However, the results should be considered in line with the usual cost per QALY threshold (i.e., £20,000 to £30,000 per QALY).

2.3 Validation of the company's scenario incremental cost-effectiveness ratios

The ERG has validated the company's scenario incremental cost-effectiveness ratios (ICERs) at list price (p.7 of the comments response document) – see Section 2.1 above.