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]

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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]

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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.

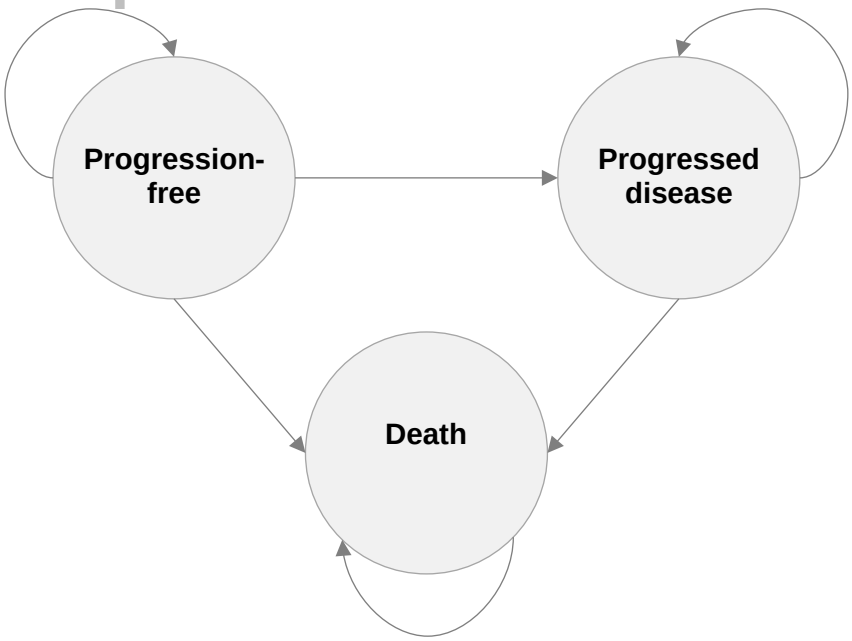

Figure 1 Structure of the company model

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

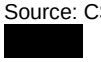

Figure 5 Tornado diagram showing OWSA results for treatment with osimertinib versus erlotinib

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.

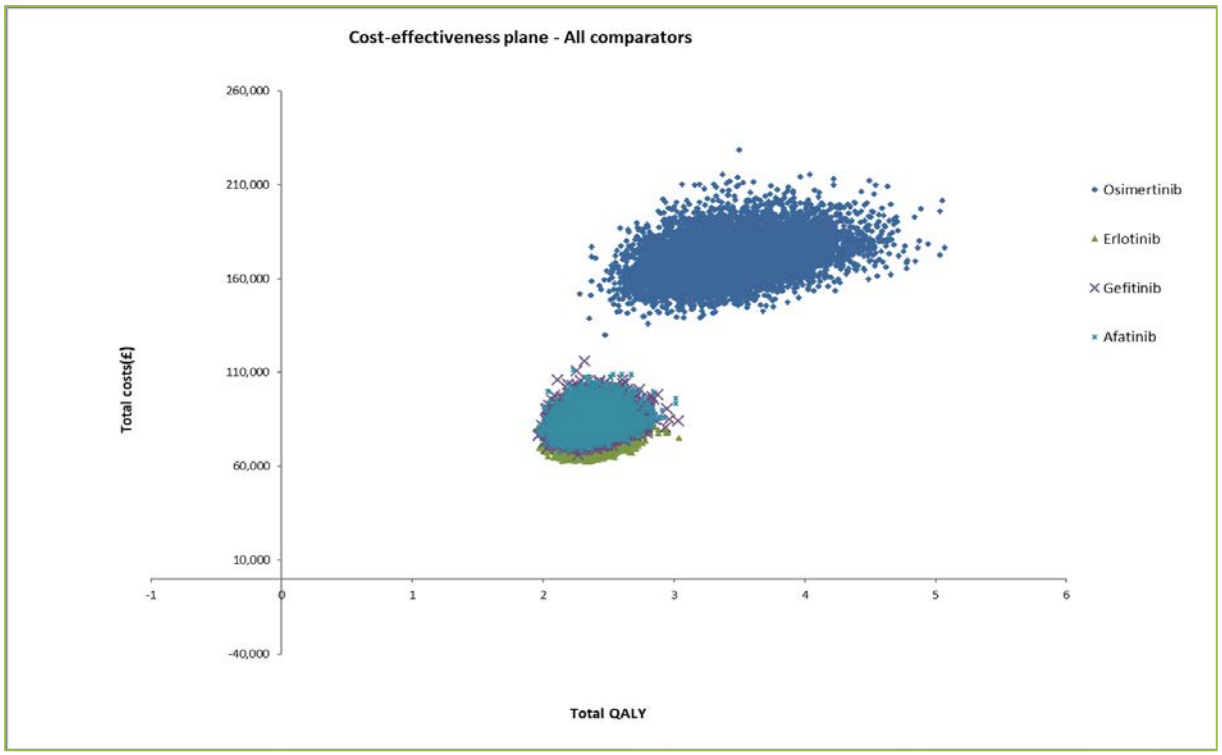

Figure 7 Scatter plot – cost effectiveness of treatment with osimertinib versus afatinib, erlotinib and gefitinib based on 10,000 iterations

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.

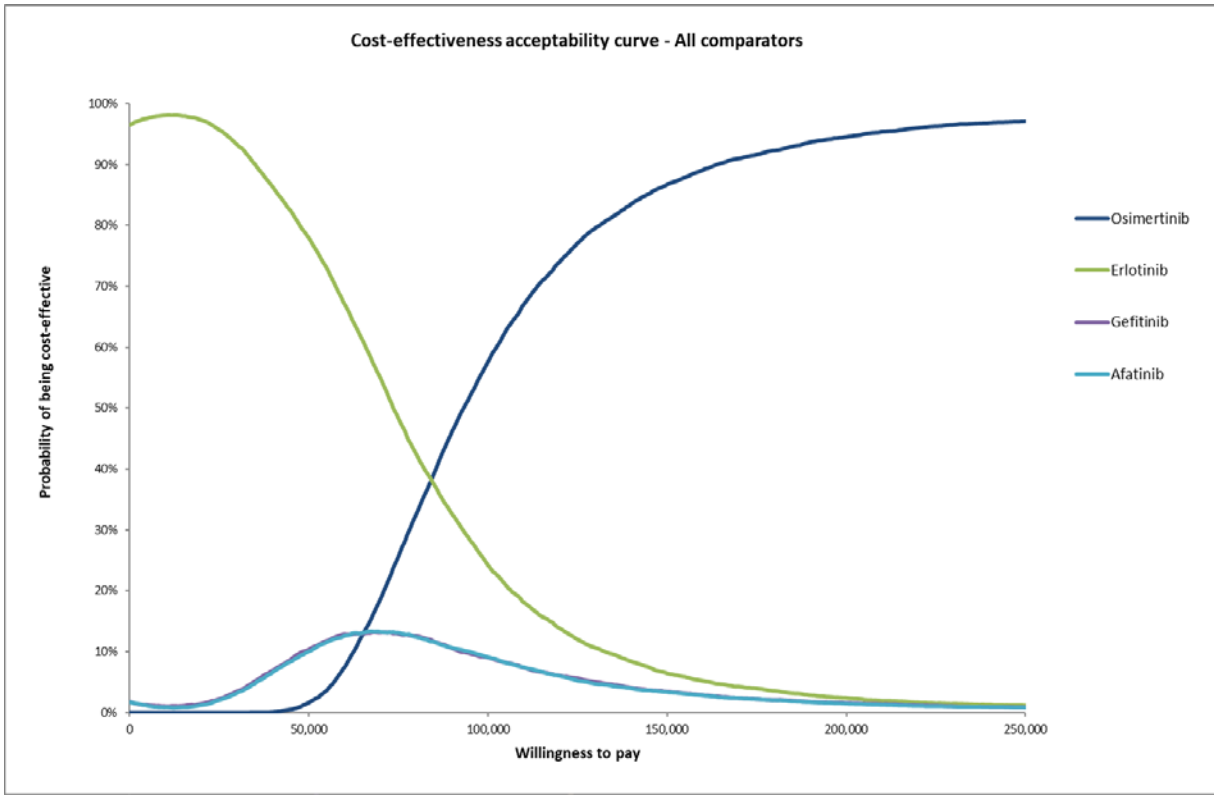

Figure 8 Cost effectiveness acceptability curve of treatment with osimertinib versus afatinib, erlotinib and gefitinib

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.

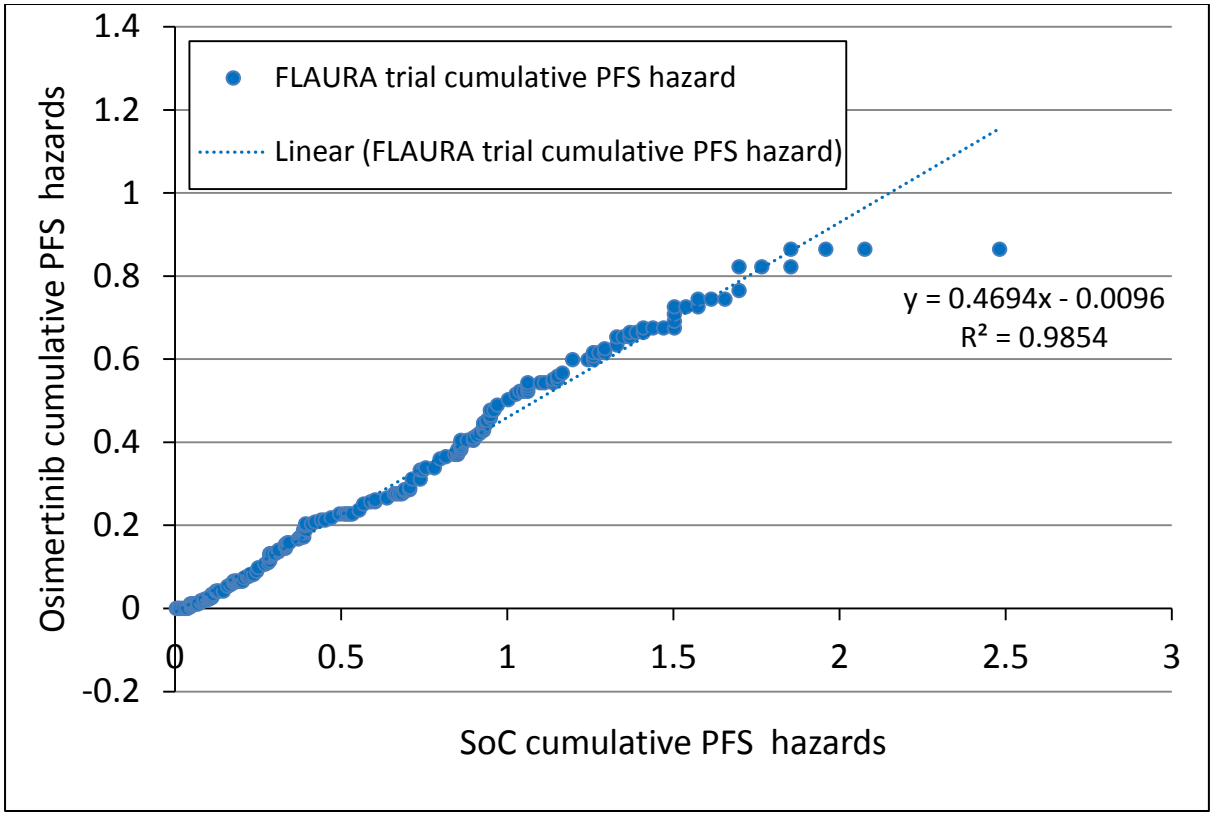

Figure 9 H-H plot for investigator-assessed PFS data from the FLAURA trial

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.

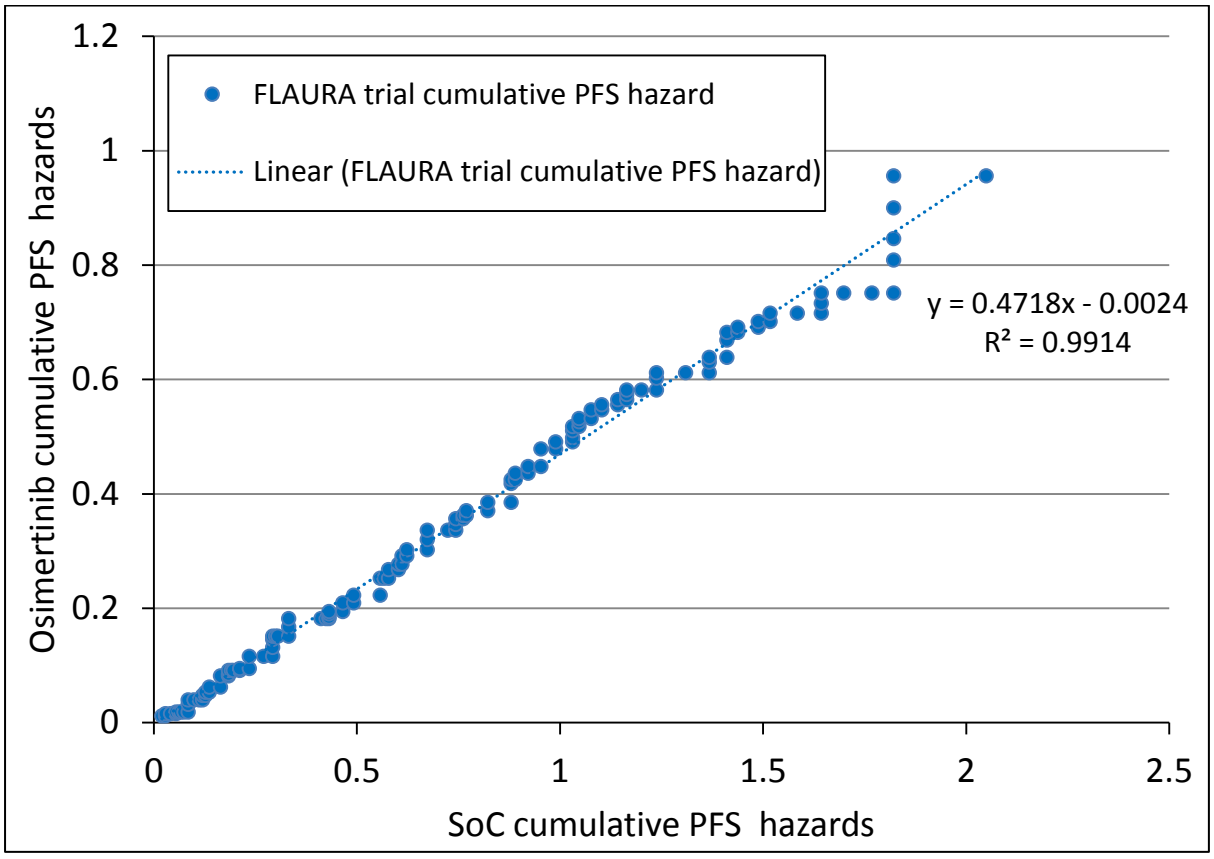

Figure 10 H-H plot for BICR-assessed PFS data from the FLAURA trial

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

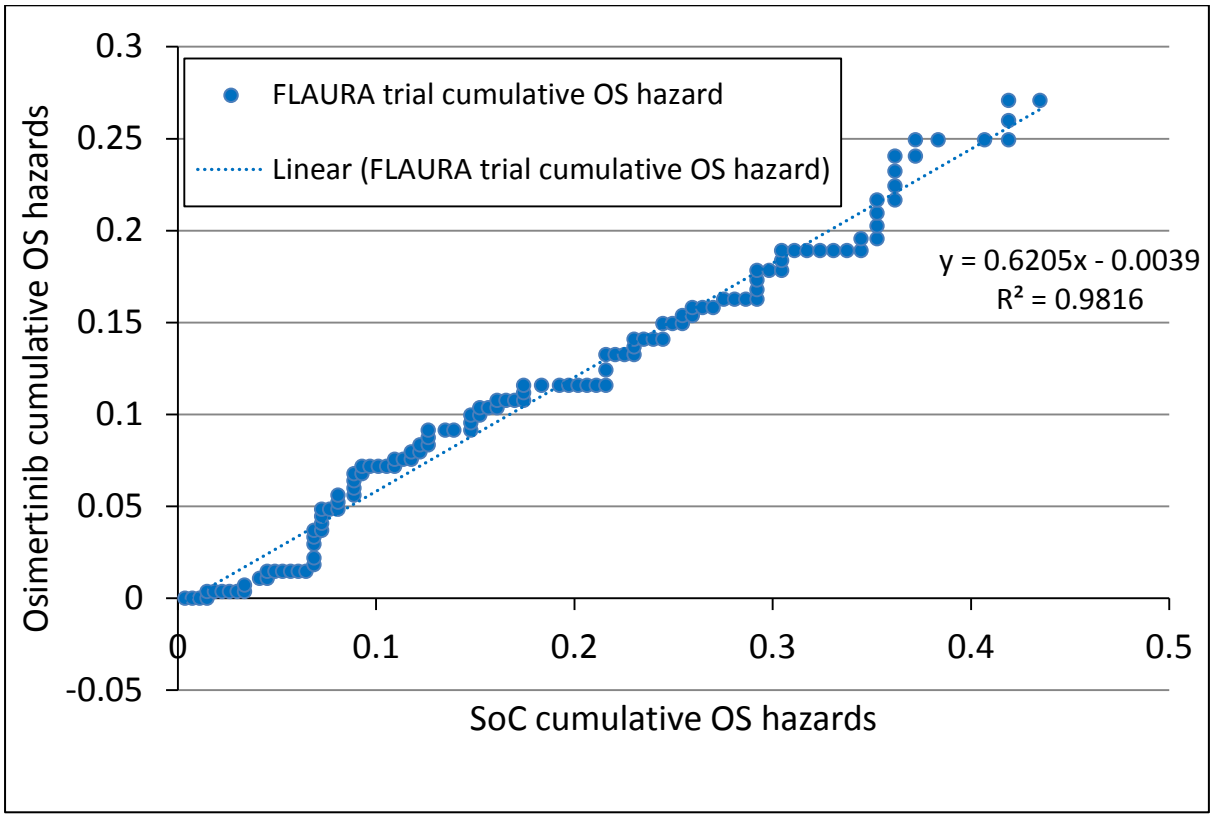

Figure 11 H-H plot for OS data from the FLAURA trial

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.

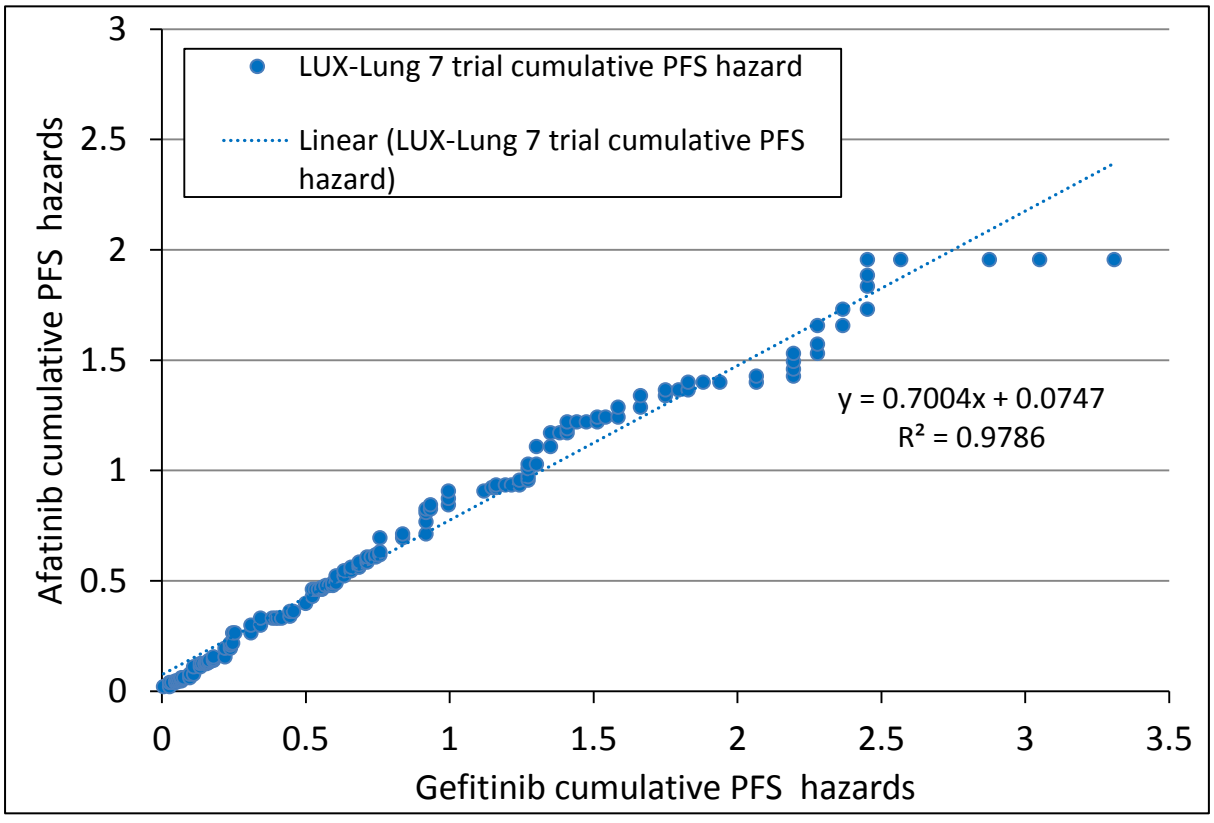

Figure 12 H-H plot for investigator-assessed PFS data from the LUX-Lung 7 trial

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.

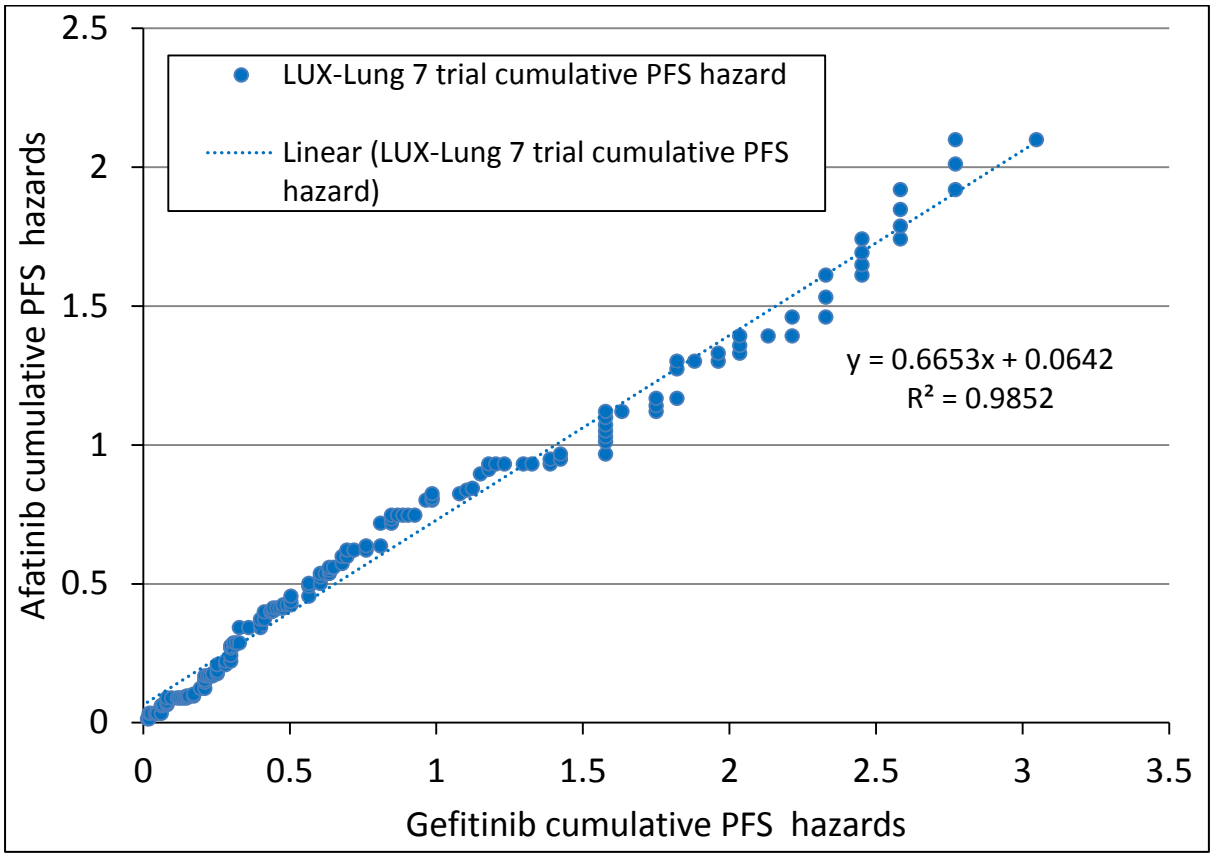

Figure 13 H-H plot for BICR-assessed PFS data from the LUX-Lung 7 trial

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.

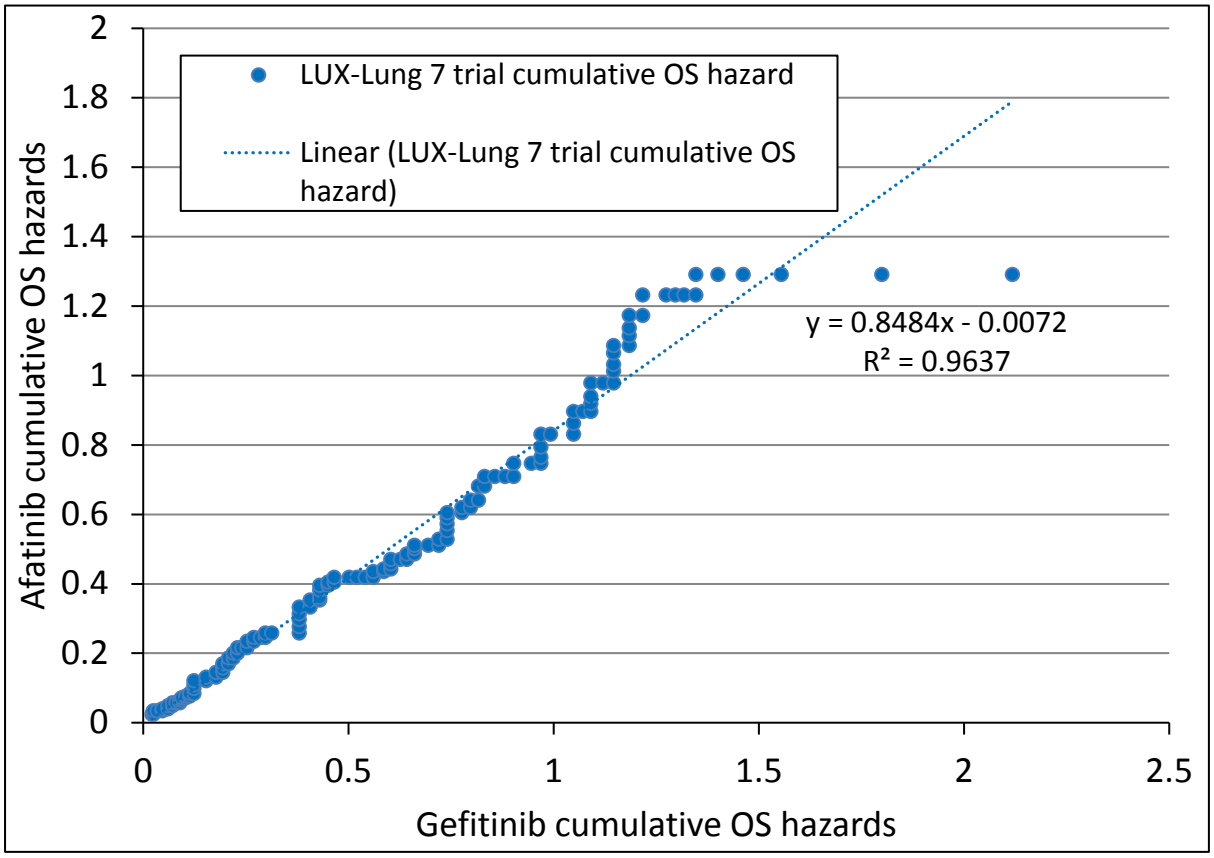

Figure 14 H-H plot for OS data from the LUX-Lung 7 trial

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