ERG REPORT ERRATUM

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Osimertinib for untreated epidermal growth factor receptor (EGFR) mutation-positive non-small-cell lung cancer [ID1302]

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CONTAINS ACADEMIC IN CONFIDENCE AND COMMERCIAL IN CONFIDENCE DATA

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A MEMBER OF THE RUSSELL GROUP

The company identified 20 issues in relation to factual inaccuracies in the original Evidence Review Group (ERG) report. The pages of the original ERG report where the ERG considered minor changes were required are presented here.

1.3 Summary of the clinical evidence submitted by the company

Direct evidence

The company literature search identified only one randomised controlled trial (RCT) of osimertinib for the first-line treatment of advanced EGFR+ NSCLC, the FLAURA trial. The FLAURA trial is an ongoing international, double-blind, randomised, Phase III, multi-centre trial of osimertinib versus EGFR-TKI standard of care (SoC EGFR-TKI) in patients with advanced EGFR+ NSCLC. In the FLAURA trial, the SoC EGFR-TKI arm consisted of erlotinib or gefitinib. After investigator-assessed objective disease progression based on response evaluation criteria in solid tumours (RECIST) v1.1, patients randomised to the SoC EGFR-TKI arm had the option to cross over to treatment with open-label osimertinib provided that specific criteria were met. The criteria included the need for confirmation of the presence of the T790M mutation.

Baseline characteristics of patients enrolled into the FLAURA trial were well-balanced between the osimertinib and SoC EGFR-TKI arms. The majority of patients were female (63%), had never smoked (64%) and had metastatic disease (95%). Around a fifth of patients (21%) were considered to have CNS metastases, while most patients were classified as 'Asian' (62%) as opposed to 'White' (36%) and had Exon 19 deletions (58%) as opposed to L858R point mutations (42%). The majority of patients had World Health Organization (WHO) performance status (PS) 1 (restricted activity) (59%) as opposed to PS 0 (normal activity) (41%) and the median age of all patients was 64 years.

The analysis of the primary outcome of investigator-assessed progression-free survival (PFS) was carried out after a median duration of 15.0 months (range: 0 to 25.1) follow-up in the osimertinib arm and 9.7 months (range 0 to 26.1) follow-up in the SoC EGFR-TKI arm (61.5% maturity for PFS overall). This is the final analysis for PFS but is an interim analysis for OS. A final OS analysis will be conducted at 60% maturity, with data expected to be available in [redacted].

For the primary outcome of investigator-assessed PFS, patients in the osimertinib arm experienced statistically significantly longer PFS in comparison to patients in the SoC EGFR-TKI arm (hazard ratio [HR]=0.46, 95% confidence interval [CI]: 0.37 to 0.57 ; p<0.001). Median PFS was 18.9 months (95% CI: 15.2 months to 21.4 months) and 10.2 months (95% CI: 9.6 months to 11.1 months) in the osimertinib and SoC EGFR-TKI arms, respectively. PFS assessed by blinded independent central review (BICR) was analysed as a sensitivity analysis for the primary outcome. The results from this analysis were consistent with the investigator-assessed PFS results. In addition, numerically fewer patients in the osimertinib arm [redacted] experienced CNS progression than in the SoC EGFR-TKI arm and [redacted].

The company performed subgroup analyses for investigator-assessed PFS for several pre-specified characteristics. Treatment with osimertinib was favoured over treatment with Soc EGFR-TKI for all pre-specified subgroups, including subgroups defined according to the presence or absence of CNS metastases at trial entry, ethnicity (Asian versus non-Asian) and EGFR mutation type (Exon 19 deletions or L858R point mutations). CNS PFS was also nominally statistically significantly improved in patients with CNS metastases.

There was no statistically significant difference between the osimertinib and SoC EGFR-TKI arms in terms of investigator-assessed ORR, osimertinib: 80% (95% CI: 75% to 85%) and SoC EGFR TKI: 76% (95% CI: 70% to 81%), odds ratio (OR)=1.27 (95% CI: 0.85 to 1.90). However, the disease control rate (DCR) and duration of response were improved with osimertinib versus Soc EGFR-TKI. A statistically significant OR was observed for DCR (OR=2.78, 95% CI: 1.25 to 6.78; p=0.01) and the difference in duration of response was described as clinically meaningful.

Overall survival (OS) data were very immature (25% of events) and confounded by treatment crossover (55 [20%] patients in the SoC EGFR-TKI arm crossed over and received osimertinib as second-line therapy). Nonetheless, the reported HR for osimertinib versus SoC EGFR-TKI was 0.63 (95% CI: 0.45 to 0.88; p=0.007). Due to the hierarchical statistical testing strategy employed in the FLAURA trial, a p-value of less than 0.0015 was required to achieve statistical significance in this instance. Therefore, it was not possible to conclude that osimertinib statistically significantly improved OS in comparison to Soc EGFR-TKI. Since median OS (i.e., the 50% percentile of OS) could not be calculated, the company presented the 25th percentile of OS as a "conservative estimate of the survival gain in the mature population". The 25th percentile of OS was observed at approximately 22.5 months in the osimertinib arm, and at approximately 15.9 months in the SoC EGFR-TKI arm, corresponding to a survival gain of 6.6 months.

The company also examined the three post-progression endpoints: time to first subsequent therapy (TFST), time to second progression by investigator assessment or death by any cause in patients who have stopped randomised therapy (PFS2) and time to second subsequent therapy (TSST). For each of these post-progression endpoints, the reported HRs suggested that treatment with osimertinib was statistically significantly more effective than treatment with Soc EGFR-TKI. The company states that the improvements in these post-progression endpoints are clinically meaningful. Furthermore, the company states that these post-progression endpoint results demonstrate that the PFS advantage of osimertinib is largely preserved beyond initial progression and provide reassurance that a clinically meaningful OS benefit will be observed in the fully mature dataset.

Overall, rates of adverse events (AEs) were generally similar between the two FLAURA trial treatment arms, although there were lower rates of Grade ≥3 AEs, less frequent hepatic and rash AEs and a lower treatment discontinuation rate due to AEs in the osimertinib arm when compared with the SoC EGFR-TKI arm.

As part of the FLAURA trial, patient reported symptoms and health-related quality of life (HRQoL) data were collected via the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Lung Cancer 13 items (EORTC QLQ-LC13) and European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30 items (EORTC QLQ-LC30) questionnaires. No statistically significant or clinically meaningful differences were reported between arms. European Quality of Life 5-Dimension (EQ-5D) data were not collected as part of the FLAURA trial.

Indirect evidence

Although direct evidence for osimertinib versus afatinib is lacking, the company decided not to perform an indirect comparison of osimertinib versus afatinib for two reasons. First, the proportional hazards (PH) assumption was possibly violated for OS in the FLAURA trial and the PH assumptions for PFS and OS were possibly violated in the LUX-Lung 7 trial. Second, available evidence from a recent network meta-analysis and the conclusions reached by an Appraisal Committee (AC) during a previous NICE STA (TA310) suggest that assuming equivalence of efficacy of afatinib, erlotinib and gefitinib is reasonable.

1.4 Summary of the ERG's critique of clinical effectiveness evidence submitted

Direct evidence

As is usually the case with clinical trials, patients were fitter in the trial than are routinely seen in NHS clinical practice. Results from a recent analysis of real-world data (652 patients treated with EGFR-TKIs for advanced first-line EGFR+ NSCLC in clinical practice in England), showed that where PS was known (in 448 patients), [redacted] had PS 2 or 3. The FLAURA trial only included patients with PS ≤1.

Generally, the ERG considers that the company's approach to analysing the data from the FLAURA trial was appropriate. The ERG also assessed the validity of the PH assumption for the outcomes of PFS (investigator assessed and BICR-assessed) and OS, since these are the relevant time-to-event outcomes listed in the final scope issued by NICE. The ERG agrees with the company that the PH assumption is reasonable for both investigator-assessed and BICR-assessed PFS. However, the ERG considers that the PH assumption may be violated for OS and, consequently, that the reported OS HR should be interpreted with caution. It is

not possible to know whether the reported HR overestimates or underestimates the effect of osimertinib versus Soc EGFR-TKI. The ERG also notes that whilst HRs for TFST, PFS2, TSST and CNS PFS were presented in the CS, the company did not report it had tested the PH assumption for any of these outcomes and therefore, the reliability of these HRs is uncertain.

FLAURA trial results, including the primary outcome of PFS, suggest that treatment with osimertinib is more efficacious than the Soc EGFR-TKI and has a similar, if not better, safety profile. The FLAURA trial is the first trial to have demonstrated a PFS benefit in patients with CNS metastases although to the ERG's knowledge, the LUX-Lung 7 trial of afatinib versus gefitinib is the only other trial to have conducted a subgroup analysis in a similar group of patients.

The ERG agrees with the company that the FLAURA trial OS results are encouraging and appear to be supported by post-progression endpoints (TFST, PFS2 and TSST), notwithstanding the caveat that the PH assumption may be violated for OS and it has not been reported that it was tested for TFST, PFS2 or TSST. The ERG also highlights that is difficult to predict whether the OS benefit observed at an early interim analysis will be maintained in the longer-term.

The company considers that osimertinib is generally well tolerated and that FLAURA trial safety findings are generally consistent with the known safety profile of osimertinib (including QT prolongation, cardiac effect and interstitial lung disease). However, the ERG observes that compared to previous studies of osimertinib reported in the European Medicines Agency European Public Assessment Report (EPAR), the rates of serious adverse events (SAEs) in the osimertinib arm of the FLAURA trial (21.5%) were lower than previously reported (35.3% to 46.7%). The same is also true for treatment-related SAEs (2.9% in the FLAURA trial, 5.6% to 13.3% in previous trials).

Indirect evidence

The ERG notes that previous ACs have concluded that afatinib is likely to have similar efficacy to erlotinib and gefitinib. However, the ERG is also aware that in the exploratory Phase IIb LUX-Lung 7 trial, afatinib resulted in a statistically significant improvement in PFS compared with gefitinib. In the absence of any estimates of efficacy for osimertinib versus afatinib, the ERG therefore decided to conduct a simple indirect comparison. The results of the ERG's indirect comparison suggest that osimertinib statistically significantly improves PFS (by both investigator assessment [HR=0.59, 95% CI: 0.43 to 0.82] and BICR [HR=0.62, 95% CI: 0.44

2.2 Company's overview of current service provision

The company's overview of current service provision, presented in the CS, is summarised in Sections 2.2.1 to 2.2.5 of this ERG report. The ERG considers that the information in these sections presents an accurate summary of current service provision.

2.2.1 Goals of treatment

As highlighted by the company (CS, p32), treatment intent is not curative in advanced NSCLC, and goals usually focus on prolonging survival, improving quality of life, and alleviating symptoms. Potential benefits of treatment should be balanced with the risk of additional toxicities.[14]

2.2.2 First-line treatment for patients with EGFR+ NSCLC

Prior to first-line treatment for advanced NSCLC, patients in NHS clinical practice with non-squamous cancers have their tumours routinely tested for EGFR status. As noted by the company (CS, p25), tumour tissue biopsy is the preferred method for EGFR testing. The ERG notes that patients' tumours are also typically tested for programmed death-ligand 1 (PD-L1) expression and anaplastic lymphoma kinase (ALK) mutations at the same time that they are tested for EGFR.

If a patient is found to harbour EGFR mutations, they usually receive targeted therapy, namely an EGFR tyrosine kinase inhibitor (EGFR-TKI). First-generation EGFR-TKIs include erlotinib and gefitinib and second-generation EGFR-TKIs include afatinib and dacomitinib. Currently, afatinib, erlotinib and gefitinib are the EGFR-TKI treatments recommended by NICE for advanced EGFR+ NSCLC[15] and are considered standard of care (SoC) in the first-line setting (CS, p13). Dacomitinib is not presently used in NHS clinical practice but is currently being appraised by NICE, in a different Single Technology Appraisal (STA), versus afatinib, erlotinib and gefitinib with final guidance expected to be published in August 2019.[16]

If a patient is found to have a tumour expressing PD-L1 (PD-L1+ NSCLC), they may also receive targeted therapy. Typically, this will either be an EGFR-TKI assuming they tested positive for EGFR (i.e. EGFR+ NSCLC) or pembrolizumab, which is a type of immunotherapy.

Clinical advice to the ERG is that EGFR mutations and ALK mutations are usually mutually exclusive, the theory being there can only be one driver gene mutation. Therefore, no further consideration is given to patients with tumours that test positive for ALK in this ERG report.

2.3 Number of patients potentially eligible for first-line treatment

The company estimates that approximately 1600 patients in England are likely to be diagnosed with advanced EGFR+ NSCLC of whom, 79% may be eligible for first-line treatment with an EGFR-TKI (Table 2).

Table 2 Company's estimate of the number of patients with advanced EGFR+ NSCLC eligible for first-line treatment in England

Number	Assumption	Source
55,619,400	Population of England (2017), adjusted with an annual growth factor of 0.6%	ONS
37,231	Incidence of lung cancer in the UK (0.067% back-calculated)	RCP[2]
32,950	Patients with NSCLC (88.5%)	RCP[2]
20,099	Advanced stage NSCLC (Stage IIIb or Stage IV) (61%)	RCP[2]
16,080	Tested for EGFR (80%)	Assumption
1608	With a confirmed EGFR mutation (10%)	Li et al 2013[45]
1270	Recorded as treated with an anticancer drug (79%)	Assumption

NSCLC=non-small cell lung cancer; RCP=Royal College of Physicians
Source: CS, Table 3

The ERG questions some of the assumptions employed to generate the numbers displayed in Table 2, namely:

- The incidence of lung cancer in the UK cited by the company is 37,231; this figure is stated to be taken from the RCP National Lung Cancer Audit (NLCA) Annual Report 2017;[2] the ERG observes that 37,761 cases are in fact cited in this report.[2]
- The incidence of patients with advanced stage NSCLC (61%) is lower than the previously cited 70% in the CS (p13 – see also Section 2.1 of this ERG report), despite both data sources being reported to be the same (RCP NLCA Annual Report 2017);[2] the proportion in Table 2 is also lower than that reported by Cancer Research UK (72% to 76% of patients with known stage, 67% of all patients in England in 2014).[46]
- The proportion of patients who are tested for EGFR is reported to be 80%, this appears to be a low estimate (see also Section 2.2.2 of this ERG report).
- The proportion of patients classified as EGFR+ is slightly lower than previously cited in the CS (CS, p13; see also Section 2.1 of this ERG report); the company has employed a lower estimate of a range (10% to 20%) for people classified as 'whites' from a 2013 review[45] in Table 2 when it previously cited a different review which found the incidence to be 12% in England.[9]
- The assumed proportion of patients treated with an anticancer drug (79%) matches neither of the estimates cited later in the CS (p48): 62.5% from the RCP NLCA Annual Report 2017[2] (which refers to all lung cancer patients, not NSCLC only) and 85% from the Ipsos MORI study.[17]

The ERG, therefore, considers that the company's estimate may be slightly low. The ERG estimates that the number of patients diagnosed with advanced EGFR+ NSCLC in England may be approximately 2200 patients, of whom 85% may be treated with an EGFR-TKI (Table 3).

Table 3 Alternative estimate of the number of patients with advanced EGFR+ NSCLC eligible for first-line treatment in England

Number	Assumption	Source
36,761	Incidence of lung cancer in England and Wales (2016)	RCP[2]
32,533	Patients with NSCLC (88.5%)[a]	RCP[2]
21,797	Advanced stage NSCLC (Stage IIIb or Stage IV) (74%)[b]	CRUK[46]
18,528	Tested for EGFR (85%)[c]	Assumption
2223	With a confirmed EGFR mutation (12%)	Midha et al 2015[9]
1890	Estimated to be treated with an anticancer drug (85%)	IPSOS Mori[17]

CRUK=Cancer Research UK; EGFR=epidermal growth factor receptor; NSCLC=non-small cell lung cancer; RCP=Royal College of Physicians

[a] RCP Information for public reports incidence of patients with NSCLC to be 85% to 90%;[2] estimate of 88.5% used to be consistent with company

[b] Reported to be 72% to 76% by CRUK[46] and so mid-value used

[c] Estimate from clinical advice to the ERG

randomised treatment beyond disease progression. Dose reductions were permitted for patients treated with osimertinib (to 40mg) and erlotinib (to 100mg). Dose interruptions were also permitted for patients treated with osimertinib, erlotinib or gefitinib. Treatment beyond progression and dose reductions or interruptions occurred at the investigator's discretion; treatment beyond progression if a continuation of clinical benefit was expected, dose reductions or interruptions if a patient experienced a Grade ≥3 AE and/or unacceptable toxicity.

After investigator-assessed objective disease progression based on response evaluation criteria in solid tumours (RECIST) v1.1, patients randomised to the SoC EGFR-TKI arm had the option to crossover to treatment with open-label osimertinib provided specific criteria were met (CS, p70). The criteria included the need for confirmation that a patient had EGFR T790M+ NSCLC from biological material collected after disease progression. Confirmation had to be from tissue biopsy or, in countries that approved ctDNA testing, from plasma.

The outcomes relevant to the final scope[47] issued by NICE and the decision problem addressed by the company were analysed: PFS by investigator assessment (primary outcome) and blinded independent central review (BICR), ORR, OS, AEs and HRQoL In addition, other outcomes included time to first subsequent therapy (TFST), time to second progression by investigator assessment or death by any cause in patients who have stopped randomised therapy (PFS2), time to second subsequent therapy (TSST) and CNS PFS by BICR.

The median duration of follow-up for PFS was 15.0 months (range: 0 to 25.1) in the osimertinib arm and 9.7 months (range: 0 to 26.1) in the SoC EGFR-TKI arm. A final OS analysis will be conducted at 60% maturity, with data expected to be available in [redacted] (CS, p17).

4.3.2 Baseline characteristics of patients in the FLAURA trial

The company reports (CS, p61) that baseline characteristics were well balanced between the osimertinib and SoC EGFR-TKI arms. The ERG concurs with the company's view. As expected from a clinical trial of a population of patients with advanced EGFR+ NSCLC, the majority of patients were female (63%), had never smoked (64%) and had metastatic disease (95%) (CS, Table 15). Around one fifth of patients (21%) were considered to have CNS metastases, while most patients were classified as 'Asian' (62%) as opposed 'White' (36%) and had Exon 19 deletions (63%) as opposed to L858R point mutations (37%). The majority of patients had WHO PS 1 (restricted activity) (59%) as opposed to WHO PS 0 (normal activity) (41%) and the median age of all patients was 64 years. As is generally the case with clinical trials, the ERG observes that trial patients were fitter than patients who are commonly seen in NHS clinical practice. Results from a recent real-world analysis of data from 652 patients

4.6 Statistical approach adopted for the FLAURA trial

Information relevant to the statistical approach taken by the company has been extracted from the clinical study report (CSR),[65] the trial statistical analysis plan (TSAP),[66] the trial protocol,[67] and from the CS.

A summary of checks made by the ERG to assess the statistical approach used to analyse data from the FLAURA trial is provided in Table 8.

Table 8 ERG assessment of statistical approach used to analyse data from the FLAURA trial

Review process	ERG comment
Was an appropriate sample size calculation specified in the trial protocol/TSAP?	Yes, in the protocol (pp99-100).
Were all primary and secondary outcomes presented in the CS pre-specified?	The primary outcome and key secondary outcomes were pre-specified in the protocol (pp101-108). Various other outcomes were also reported for the cFAS and cEFR populations (CS, pp87-90); these analyses were mostly pre-specified in the TSAP (pp62-70). The ERG notes that the outcomes of CNS DCR and time to CNS response were presented for both the cFAS and cEFR populations, but these outcomes were both pre-specified to be analysed for the cEFR population only (TSAP, p66).
Were definitions for all relevant outcomes provided?	Definitions for the primary outcome and key secondary outcomes were provided in the protocol (pp101-108). As part of the ERG clarification letter to the company, the ERG requested that the company provide definitions for various outcomes measured only in the cFAS and/or cEFR populations, as these definitions were not explicitly stated in the TSAP/protocol. The company provided these definitions in their response to questions A15, A19 and A21 of the ERG clarification letter.
Were all relevant outcomes defined and analysed appropriately?	The company used a hierarchical testing strategy; PFS, OS and CNS PFS were tested in this sequential order as pre-specified in the TSAP (p40). This strategy was employed to preserve the overall type 1 error rate (alpha) at 0.05. If any previous analysis in the sequence was not statistically significant, then the following outcome would not be tested for statistical significance. Since two analyses of OS were planned (interim and final), the Lan DeMets approach that approximates the O'Brien and Fleming spending function was pre-specified (TSAP, p40), in order to maintain the overall alpha at 0.05 across the two planned analyses of OS. For the interim analysis of OS presented in the CS, a p-value of less than 0.0015 was required to determine statistical significance. The ERG notes that HRs were calculated for several time-to-event outcomes presented in the CS. The company confirmed in their clarification response (question A6) that the PH assumption was assessed for the outcomes of investigator-assessed PFS, BICR-assessed PFS and OS by visually assessing cumulative hazard plots and concluded that the assumption of PH for these outcomes is reasonable. However, the ERG notes that the company did not state that the PH assumption was assessed for other time-to-event outcomes presented in the CS (see text below table for more information).

Review process	ERG comment
Were all subgroup analyses and sensitivity analyses presented in the CS pre-specified?	The company performed subgroup analyses for the primary outcome, investigator-assessed PFS, for several patient characteristics that were pre-specified in the TSAP (pp46-47). The company also presented efficacy analyses for secondary outcomes for key subgroups of interest (presence versus absence of CNS metastases at baseline by investigator assessment, Exon 19 deletions versus L858R point mutations, and Asian versus non-Asian ethnicity) (CS, pp86-87, pp91-94). The ERG notes that these subgroup analyses were pre-specified in the TSAP for PFS and ORR (TSAP, pp46-50, p68), but not for OS and DCR. Various other outcomes were also reported for the cFAS and cEFR populations (CS, pp87-90); these analyses were mostly pre-specified in the TSAP (pp62-70). The ERG notes that the analyses of CNS DCR and time to CNS response on the cFAS population were not pre-specified (see ERG comment on "Were all primary and secondary outcomes presented in the CS pre-specified?"). The analysis of PFS by BICR-assessment was presented as a sensitivity analysis in the CS (pp73-75); this analysis was pre-specified in the TSAP (p45).
Were all protocol amendments carried out prior to analysis?	Protocol amendments and rationale for these amendments are provided in the CSR (CSR, pp78-89). The ERG is satisfied with the rationale for the amendments and notes that all amendments were made before the data cut-off date for the primary analysis (12 June 2017), so amendments were not driven by the results of the trial. A key change to the protocol was that the hierarchical testing strategy was updated; the company removed the testing of PFS in the subgroup of T790M+ patients and instead tested CNS PFS in the cFAS population. The reason for this change was that, initially, the company had evidence that up to 40% of TKI-naïve, EGFR+, NSCLC patients are T790M+.[68,69] However, during the conduct of the study, it became apparent to the company that this high incidence of de novo T790M+ may have been the result of a tissue preparation artefact.[70,71] Indeed, only 5 patients in the FAS population were T790M+ (based on tissue and/or ctDNA testing), and the company therefore did not perform an analysis of PFS in the T790M+ patient subgroup. Due to recent evidence of clinical activity of osimertinib in CNS,[72] CNS PFS was instead included in the multiple testing strategy.
Was a suitable approach employed for handling missing data?	The company's approach for handling missing data was pre-specified in the TSAP (TSAP, p25, pp27-31, pp33-34). The ERG considers the company's approach to be suitable.

BICR=blinded independent central review; cEFR=CNS evaluable for response set; cFAS=CNS full analysis set; CNS=central nervous system; CSR=clinical study report; ctDNA=circulating tumour DNA; DCR=disease control rate; EGFR=epidermal growth factor receptor; FAS=full analysis set; HR=hazard ratio; NSCLC=non-small cell lung cancer; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; PH=proportional hazards; TKI=tyrosine kinase inhibitor; TSAP=trial statistical analysis plan
Source: CS, CSR, trial protocol, TSAP and ERG comment

Generally, the ERG considers that the company's statistical approach for the analysis of data from the FLAURA trial was appropriate.

The analyses of CNS DCR and time to CNS response on the cFAS population were not pre-specified, and the subgroup analyses for presence versus absence of CNS metastases at baseline by investigator assessment, Exon 19 deletions versus L858R point mutations, and Asian versus non-Asian ethnicity were not pre-specified for the outcomes of OS and DCR. The reporting of analyses that were not pre-planned, without justification for why these additional analyses were performed, raises concerns about whether "data dredging" might have occurred, i.e. performing multiple statistical tests which are not based on pre-specified

study hypotheses, in the hope of finding statistically significant or favourable results. Each additional statistical test performed for a trial increases the likelihood of false positives occurring, and this ought to be considered when interpreting the results of post-hoc analyses.

Furthermore, the testing of the proportional hazards (PH) assumption was not reported for several time-to-event outcomes for which HRs were presented in the CS, and the ERG assessed that the PH assumption may be violated for OS data from the FLAURA trial. HRs are only an appropriate measure of treatment effect if the PH assumption is valid, that is, if the event hazards associated with the intervention and comparator data are proportional over time.[73] A summary of the company's and ERG's assessments of PH for each of the outcomes for which HRs were presented in the CS is provided in Table 9.

Table 9 Summary of the company and ERG assessments of PH for time-to-event outcomes from the FLAURA trial

Outcome(s)	Company assessment of PH	Company conclusion	ERG assessment of PH	ERG conclusion
PFS by investigator assessment	Visual examination of the log-cumulative hazard plot and Cox-Snell residuals plot (CS, Figure 34 and Figure 35)	PH assumption is appropriate	Visual examination of the HH plot (Appendix 2 to this ERG report, Section 9.2, Figure 9)	PH assumption is appropriate
PFS by BICR	Visual examination of the log-cumulative hazard plot (CS, Figure 30)	PH assumption is appropriate	Visual examination of the HH plot (Appendix 2 to this ERG report, Section 9.2, Figure 10)	PH assumption is appropriate
OS	Visual examination of the log-cumulative hazard plot (CS, Figure 37 and Figure 38)	"No clear violation of PH" (CS, p125). In the company's economic base-case analysis, the company has assumed that PH holds for OS beyond 7.9 months	Visual examination of the HH plot (Appendix 2 to this ERG report, Section 9.2, Figure 11)	PH assumption may be violated; reported HR should be interpreted with caution. It is unknown whether the reported HR would overestimate or underestimate treatment effect
• TFST • PFS2 • TSST • CNS PFS (by BICR)	None reported in the CS or company's response to clarification question A6 from the ERG	N/A	None (outcomes not listed in the final scope issued by NICE)	It is unknown whether the PH assumption, and consequently the reported HR, is valid for each of these outcomes

BICR=blinded independent central review; CNS=central nervous system; HR=hazard ratio; HH plot=a plot to show the relationship between the cumulative hazard for each trial event at common time points in the two trial arms; N/A=not applicable; OS=overall survival; PFS=progression-free survival; PFS2=time to second progression or death by any cause in patients who have stopped randomised therapy; PH=proportional hazards; TFST=time to first subsequent therapy; TSST=time to second subsequent therapy

4.7 Efficacy results from the FLAURA trial (all included patients)

The data cut-off date for all results presented in Section 4.6 is 12 June 2017, the date of the primary PFS analysis.

sequential use of EGFR-TKIs, use of bevacizumab and other treatments not recommended by NICE.

4.7.5 Secondary outcomes: post-progression endpoints

The results of the analyses of post-progression endpoints, TFST, PFS2 by investigator assessment and TSST are provided in Table 13.

Table 13 Results of the analyses of post-progression outcomes (FAS)

Outcome		Osimertinib (N=279)	SoC EGFR-TKI (N=277)
TFST	Median, months (95% CI)	[redacted]	[redacted]
	HR (95% CI); p-value	[redacted]	
PFS2 by investigator assessment	Median, months (95% CI)	[redacted]	[redacted]
	HR (95% CI); p-value	[redacted]	
TSST	Median, months (95% CI)	[redacted]	[redacted]
	HR (95% CI); p-value	[redacted]	

CI=confidence interval; EGFR-TKI=epidermal growth factor receptor tyrosine kinase inhibitor; FAS=full analysis set; HR=hazard ratio; NC=not calculable; PFS2=time to second progression or death by any cause in patients who have stopped randomised therapy; SoC=standard of care; TFST=time to first subsequent therapy; TSST=time to second subsequent therapy
Source: information drawn from CS, p77 and CSR, Table 30

For each of these post-progression endpoints, the reported HRs suggest that treatment with osimertinib was statistically significantly more effective than treatment with Soc EGFR-TKI. The company states in the CS (p18) that the results for these post-progression endpoints demonstrate that the PFS advantage of osimertinib is largely preserved beyond initial progression and provide reassurance that a clinically meaningful benefit in OS will be observed in the fully mature dataset. The ERG notes that the company did not report that it had performed any assessment of the PH assumption for these outcomes (clarification question A6). HRs are not an appropriate summary of treatment effect when the PH assumption does not hold, it is therefore unknown whether the presented HRs are valid.

It should also be noted that patients could be treated beyond progression in both arms of the trial if the trial investigator considered patients were still receiving benefit from the treatment. As reported in the published paper for the FLAURA trial, this occurred in approximately two thirds of all patients (67% in the osimertinib arm and 70% in the SoC EGFR-TKI arm). Treatment beyond progression may have impacted upon all three post-progression endpoints by helping to prolong results for each of these outcomes. Nonetheless, if this is the case, it does still suggest that treatment beyond progression with osimertinib is more efficacious than treatment beyond progression with SoC EGFR-TKI.

Table 14 Key efficacy outcomes by presence or absence of CNS metastases at baseline (investigator assessment, FAS)

	CNS metastasis		No CNS metastasis	
	Osimertinib (N=53)	SoC EGFR-TKI (N=63)	Osimertinib (N=226)	SoC EGFR-TKI (N=214)
PFS				
No. of patients with PFS event, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
HR (95% CI); p-value		[redacted]		[redacted]
OS				
No. of patients who died, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
HR (95% CI); p-value		[redacted]		[redacted]
ORR				
No. of patients with objective response, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
OR (95% CI); p-value		[redacted]		[redacted]
DCR				
No. of patients with disease control, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
OR (95% CI); p-value		[redacted]		[redacted]

CI=confidence interval; CNS=central nervous system; DCR=disease control rate; EGFR-TKI=epidermal growth factor receptor tyrosine kinase inhibitor; FAS=full analysis set; HR=hazard ratio; OR=odds ratio; ORR-objective response rate; OS=overall survival; PFS=progression-free survival; SoC=standard of care
Source: CS, Table 23

Median PFS values were presented according to the presence or absence of CNS metastases at baseline in the European Public Assessment Report (EPAR) (EPAR, Table 27).[42] Median PFS in the group of patients with CNS metastases at baseline was 15.2 months (95% CI: 12.1 to 21.4) in the osimertinib arm, and 9.6 months (95% CI: 7.0 to 12.4) in the SoC EGFR-TKI arm. Median PFS in the group of patients without CNS metastases at baseline was 19.1 months (95% CI: 15.2 to 23.5) in the osimertinib arm, and 10.9 months (95% CI: 9.6 to 12.3) in the SoC EGFR-TKI arm.

cFAS and cEFR populations

The company reported various outcomes for the cFAS population, which consisted of patients who had a baseline CNS scan available for assessment by CNS BICR, and who had at least one measurable or non-measurable CNS lesion (N=128). The company also reported various outcomes for the cEFR population, which consisted of patients from the cFAS population who had at least one measurable CNS lesion (N=41). Definitions for the outcomes of CNS PFS, CNS ORR and CNS DCR are provided in Appendix 3 (Section 9.3).

All patients with a history of, or suspected, CNS lesion were required to have a baseline scan. However, if that brain scan came back with no evidence of CNS disease, further scans were not mandated by the protocol. If the patient subsequently became symptomatic, the investigator used clinical judgement on whether to scan the patient.

The company provides results for the outcome of CNS PFS by BICR assessment in the cFAS population, stating (CS, p87) that there was a "nominally statistically significant and clinically meaningful improvement in CNS PFS" for patients in the osimertinib arm in comparison to patients in the SoC EGFR-TKI arm ([redacted]). The company states that the result is "nominally statistically significant", since the analysis of CNS PFS was third in the hierarchical statistical testing strategy (see Section 4.6) and, as OS did not reach formal statistical significance, CNS PFS could not be formally tested for statistical significance.

The ERG notes that the company did not perform any assessment of the PH assumption for the outcome of CNS PFS (clarification question A6); HRs are not an appropriate summary of treatment effect when the PH assumption does not hold. Therefore, it is unknown whether the presented HR is valid, and the ERG highlights that the HR should be interpreted with caution.

Median CNS PFS was not calculable ([redacted]) in the osimertinib arm versus [redacted] in the SoC EGFR-TKI arm. The company provides a K-M plot for CNS PFS in the cFAS population in Figure 26 of the CS.

A breakdown of CNS progression events is provided in Table 24 of the CS, and reproduced here in Table 15.

Table 15 CNS progression events by BICR assessment in the cFAS population

Patients with progression, n (%)	Osimertinib (N=[redacted])	SoC EGFR-TKI (N=[redacted])
Total number of events (CNS progression or death)[a]	[redacted]	[redacted]
CNS progression other than death	[redacted]	[redacted]
Progression due to death	[redacted]	[redacted]
CNS progression[b]		
Progression in target CNS lesions	[redacted]	[redacted]
Progression in non-target CNS lesions	[redacted]	[redacted]
Progression due to new CNS lesions	[redacted]	[redacted]
Unknown reason for CNS progression[c]	[redacted]	[redacted]

[a] Progression events that did not occur within 2 scheduled visits (plus visit window) of the last evaluable assessment (or randomisation) were censored and therefore excluded in the number of events
[b] Target lesions, non-target lesions and new lesions were not necessarily mutually exclusive categories
[c] Patients were identified as having progression but their first lesion progression could not be determined
BICR=blinded independent central review; cFAS=CNS full analysis set; CNS=central nervous system; EGFR-TKI= epidermal growth factor receptor tyrosine kinase inhibitor; SoC=standard of care
Source: Adapted from CS, Table 24

CNS ORR was higher in the osimertinib arm than in the SoC EGFR-TKI arm in both the cFAS and cEFR populations (Table 16).

4.9 Relative efficacy of EGFR-TKIs

In this Section the ERG has compared the results from the SoC EGFR-TKI arm of the FLAURA trial, to results reported for SoC EGFR-TKI treatments (i.e., erlotinib and gefitinib) in previous EGFR-TKI trials. This is in order to explore whether, based on previous trial evidence, the results in the EGFR-SoC arm in the FLAURA trial appear unusual in any way. In addition, since the company did not compare osimertinib with afatinib (either directly in the FLAURA trial, or indirectly, see also Section 4.10), the ERG has also explored whether it can be assumed whether erlotinib and gefitinib can be considered to be as equally efficacious as afatinib.

4.9.1 Comparison of previous EGFR-TKI trials to FLAURA trial

A summary of efficacy results for EGFR-TKIs across trials[22,24-31,33,51] is provided in Table 17. While all trials mostly only included patients with PS 0 to 1 and excluded patients with symptomatic and unstable brain metastases, there were notable differences in the geographic locations of trials (and, therefore, possible differences in SoC before and after treatment with an EGFR-TKI) and median ages of patients (and possibly, therefore, prognosis). Furthermore, not all patients in the CTONG 0901 trial[31] received their EGFR-TKI as a first-line treatment, although approximately two-thirds of patients did. Nonetheless, efficacy results have been broadly consistent in trials conducted to date:

- Eight trials[22,24,25,27-30,33] compared an EGFR-TKI with PDC (including cisplatin or carboplatin plus gemcitabine, docetaxel, paclitaxel or pemetrexed). All of these eight trials found the EGFR-TKIs to improve PFS and ORR,[22,24,25,27-30,33] but did not improve OS,[20,22,23,27-30,34] versus PDC. However, a pooled analysis of LUX-Lung 3 and LUX-Lung 6 trial data[32] has shown an OS benefit for afatinib versus PDC (cisplatin plus pemetrexed in the LUX-Lung 3 trial and cisplatin plus gemcitabine in the LUX-Lung 6 trial) in the subgroup of patients with Exon 19 deletions. It should be noted that these results should be interpreted with caution. This is because subgroup analyses did not form part of the confirmatory analysis strategy, no adjustment for multiplicity was done, and p values are descriptive in nature.
- Median PFS in the SoC EGFR-TKI arm of the FLAURA trial (10.2 months) was within the range of median PFS reported for EGFR-TKI treatments in all previous trials,[22,24-31,33] although only three trials[24,25,27] actually recorded a lower median PFS. Median PFS for erlotinib ranged from 9.7 to 13.1 months (4 trials)[27,30,31,33] and for gefitinib ranged from 9.2 to 10.9 months (5 trials).[22,24-26,31] Median PFS for patients treated with afatinib has consistently been found to be approximately 11 months in three trials,[26,28,29] which is reasonably similar to median PFS in the SoC EGFR-TKI arm of the FLAURA trial.
- ORR for patients in the SoC EGFR-TKI arm of the FLAURA trial (76%) was also within the range of ORRs reported for EGFR-TKI treatments in previous trials, with only one trial reporting a higher ORR:[33] ORRs for erlotinib ranged from 56% to 83% (4 trials)[27,30,31,33] and for gefitinib ranged from 52% to 74% (5 trials).[22,24-26,31] For patients treated with afatinib, ORRs ranged from 56% to 70%,[26,28,29] these rates are lower than those for patients in the SoC EGFR-TKI arm of the FLAURA trial.

5.2 ERG summary of the company's submitted economic evaluation

The company developed a de novo economic model to compare the cost effectiveness of treatment with osimertinib versus afatinib, erlotinib and gefitinib in adults with advanced EGFR mutation type (Exon 19 deletions or L858R point mutations) NSCLC.

5.2.1 Model structure

The company model structure (implemented as a partitioned survival model), as shown in Figure 1, comprises three mutually exclusive health states that are designed to reflect the natural course of the disease. The modelled population enters the model in the progression-free (PF) health state. At the end of every 30-day cycle, patients in the PF health state can experience disease progression and enter the progressed disease (PD) health state or remain in the PF health state. Patients in the PD health state can also remain in that health state at the end of each cycle but cannot return to the PF health state. Transitions to the death health state can occur from either the PF health state or the PD health state. Death is an absorbing health state from which transitions to other health states are not permitted.

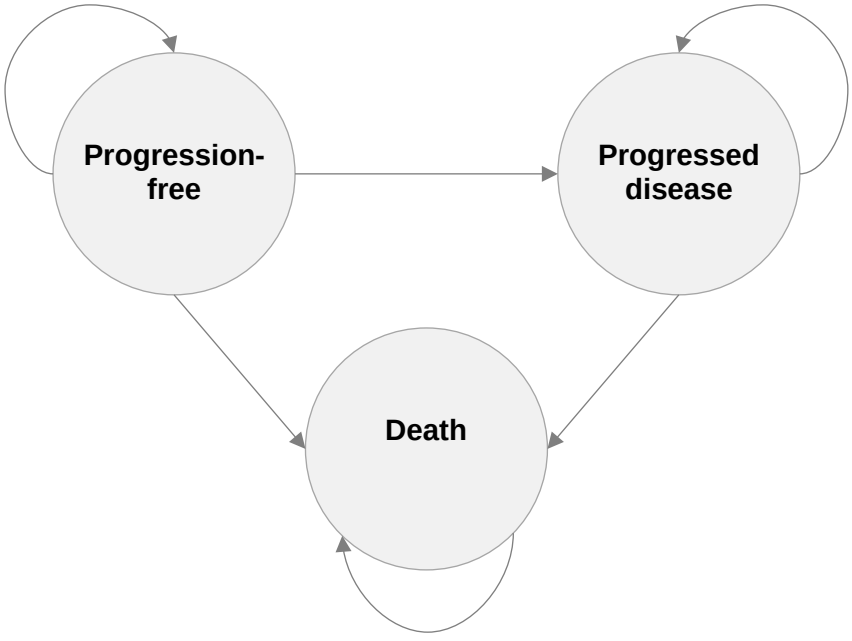

Figure 1 Structure of the company model

Source: Developed by the ERG based on text in the CS, Section B.3.2

5.2.2 Population

The population reflected by the company model is patients with advanced EGFR+ NSCLC. The population is consistent with the FLAURA trial population and that described in the final

scope[47] issued by NICE. The starting age of the cohort (63 years) is the same as the mean age and similar to the median age (64 years), at baseline, of the patients in the FLAURA trial.

5.2.3 Interventions and comparators

Intervention

Treatment with osimertinib is implemented in the model in line with the licensed dosing regimen[42] i.e. one 80mg tablet taken once daily until disease progression or unacceptable toxicity. However, clinical advice to the company is that osimertinib is expected to be used beyond disease progression if clinical benefit is observed and, therefore, administration of osimertinib (80mg) beyond disease progression was implemented in the company model.

Comparators

The comparators are afatinib[57], erlotinib[55] and gefitinib.[56] The dosing and administration frequencies for these drugs are also in line with their marketing authorisations and UK clinical practice, where treatment is continued beyond disease progression. Afatinib (40mg), erlotinib (150mg) and gefitinib (250mg) were implemented as one tablet once a day.

5.2.4 Perspective, time horizon and discounting

The company states that the economic evaluation is undertaken from the perspective of the NHS and Personal Social Services (PSS), which is in line with the NICE reference case.[82] The model has a 30-day cycle length and the time horizon is set at 20 years. As justification for the length of the time horizon, the company cites the advanced nature of the disease and projections from the FLAURA study, which showed that fewer than 2.5% of patients would live beyond 20 years. An annual discount rate of 3.5% was applied to costs and outcomes. Half cycle correction was applied to all costs in the model except to drug acquisition and administration costs for treatment with osimertinib, afatinib, erlotinib and gefitinib.

5.2.5 Treatment effectiveness and extrapolation in the base case

The company economic model reflects patient-level data from the FLAURA trial. In the FLAURA trial, treatment with osimertinib was compared to SoC EGFR-TKI (that is, erlotinib or gefitinib). The follow-up period in the trial was shorter than the model time horizon and, therefore, extrapolations of the PFS, OS and time to discontinuation of treatment (TDT) K-M data from the FLAURA trial were necessary. The extrapolations involved identification of parametric survival models that reflected FLAURA trial PFS, OS and TDT K-M data.

Progression-free survival

The company undertook an assessment to determine whether the PFS data from the two arms of the FLAURA trial were proportional (log-cumulative hazard plot and Cox-Snell residuals)

Table 28 Utility values used in the cost effectiveness model

Health state	Utility value	Source/description
Progression-free	[redacted]	Mapped value from FLAURA trial
Progressed disease (1L treatment)	[redacted]	Mapped value from FLAURA trial
Progressed disease (subsequent treatment or BSC)	0.640	Labbe (2017)[87]
Death	0.000	By definition

1L=first-line treatment; BSC=best supportive care
Source: CS, Table 51

5.2.7 Resources and costs

The resource use and costs associated with treatment acquisition, treatment administration, disease management and AEs were included in the company model.

Drug costs in the first-line setting

Estimates of the quantity of osimertinib, afatinib, erlotinib and gefitinib used per patient per 30-day model cycle were derived from FLAURA trial data, as were relative dose intensity (RDI) multipliers. The afatinib RDI multiplier was assumed to be the same as for treatment with erlotinib and gefitinib. An oral treatment administration cost of £9 per model cycle (based on a dispensing time of 12-minutes [band 6 pharmacist]) was applied to all first-line therapies. Selected details of the drug costs are shown in Table 29 of this ERG report and full details are presented in Tables 58, 59, 60, 61 and 67 of the CS.

Table 29 Treatment dosing and drug acquisition costs for primary treatments

		Osimertinib	Afatinib	Erlotinib	Gefitinib
Label information	Administration method	Oral	Oral	Oral	Oral
	Dose per administration	80mg	40mg	150mg	250mg
	Administration frequency	1 per day	1 per day	1 per day	1 per day
Package information	Formulation	80mg	40mg	150mg	250mg
	Pack size	30 tablets	28 tablets	30 tablets	30 tablets
	List price	£5,770.00	£2,023.28	£1,631.53	£2,167.71
Dosing used in model	Required dose	80mg	40mg	150mg	250mg
	Tablets per administration	1.00	1.00	1.00	1.00
	Relative dose intensity	98.9 1%	98.1%	98.1%	98.1%
	Cost per model cycle	£5,706.53	£2,126.61	£1,600.53	£2,126.52

mg=milligram
Source: information drawn from CS, Tables 58, 60 and 61

Drug costs for subsequent treatments

The costs of subsequent lines of therapies are applied as one-off costs. The company states that the nature of partitioned survival modelling means that it is not possible to accurately estimate the proportion of patients who discontinue first-line therapy and die in the same cycle. Therefore, the difference in the proportion of patients on treatment between two consecutive 30-day cycles (from TDT K-M extrapolation) was used a proxy for the proportion of patients

months). However, there are no published utility values that reflect the HRQoL of patients whose disease has progressed following first-line treatment and go on to receive best supportive care (BSC) or active therapies in the second- and/or third-line settings before BSC. Ideally, the model should have included different health states to reflect the different treatment pathways. Given that the company model structure means that one utility value has to capture the range of HRQoL of patients receiving second-line treatment, third-line treatment and BSC, the ERG considers that a utility value of 0.678 (the utility value from reported in TA416[43] from the he AURA 2 trial[98] [second-line treatment with osimertinib]) is more representative of the HRQoL of patients in the PD health state than the value used by the company (0.64). However, the ERG acknowledges that this value may still not be an accurate reflection of the HRQoL of patients in the PD health state.

Compared with the company base case, applying a utility value of 0.678 to reflect patient HRQoL in the PD health state resulted in incremental QALYs for the comparison of treatment with osimertinib versus erlotinib increasing from 1.046 to 1.074 and the ICER reducing by £2,343 to £87,357 per QALY gained.

Lifetime duration of treatment effect with osimertinib

FLAURA trial OS data were only available for a 2-year time period. The ERG considers that any extrapolation of 2 years of OS data over 20 years will always be uncertain, especially when there are structural breaks (i.e., where, at different points in time, survival starts following different trajectories) in the K-M data over that time period. Within the model, the company OS is represented by direct use of FLAURA trial OS K-M data for the first 8 months of the time horizon and a Weibull distribution (a different one for each arm) thereafter. The ERG is satisfied that the company's choice of a Weibull distribution to reflect long-term OS for patients in both the intervention and comparator arms of the model was supported by the available K-M data from the FLAURA trial. However, the ERG highlights that the use of these functions result in mortality for patients in the osimertinib arm being approximately 36% lower than in the SoC EGFR-TKI arm over the period that survival is extrapolated i.e. up to 20 years.

The ERG considers that it is clinically implausible that patients receiving first-line treatment with osimertinib will continue to experience a survival advantage over those receiving first-line treatment with a first- or second-generation EGFR-TKI for many years after treatment has ceased. Furthermore, such claims have not been accepted by NICE Appraisal Committees (ACs) during previous appraisals of drugs to treat NSCLC. During the appraisal of pembrolizumab for treating PD-L1 positive NSCLC after chemotherapy (Pembrolizumab for treating PD-L1-positive non-small-cell lung cancer after chemotherapy [TA428][60]), the AC considered a treatment effect of 3 years was realistic, whilst during the appraisal of

atezolizumab for treating NSCLC after platinum-based chemotherapy (Atezolizumab for treating locally advanced or metastatic non-small-cell lung cancer after chemotherapy [TA520][41]) a different AC considered that 5 years was realistic.

The company model has a partitioned survival structure and the application of a 'duration of treatment effect' within such a structure is not straightforward as the effect is likely to vary by patient and to depend on time on treatment and level of response. Given the model structure, a crude approach to limiting the duration of treatment effect on OS is to set the morality hazard for the intervention and comparator arms to be equal after a given timepoint.

Given that, in the past, ACs have accepted that treatment durations of 3 and 5 years are realistic, the ERG has run scenarios in which the effect of treatment with osimertinib has been limited to these two durations. In addition, to reflect the period of time for which FLAURA trial data are available, the ERG has run a scenario in which the effect of treatment with osimertinib has been limited to 2 years. The 2-year scenario effectively provides an estimate of the ICER per QALY gained for the comparison of treatment with osimertinib versus SoC EGFR-TKI based on available evidence (i.e., with no modelling).

Compared with the company base case, using a 2-year duration of treatment effect, the ICER for the comparison of osimertinib versus erlotinib increased by £119,753 to £209,453 per QALY gained, a 3-year duration of treatment effect increased the ICER by £72,562 to £162,262 per QALY gained and a 5-year duration of treatment effect increased the ICER by £33,607 to £123,307 per QALY gained.

Place of immunotherapy in the treatment pathway

Data presented in the CS (Figure 14) show that during the first 3 months of 2018, 10% of patients in the UK with advanced EGFR+ NSCLC who were tested for the T790M mutation were treated with pembrolizumab. This was prior to the publication of TA531[99] (Pembrolizumab for untreated PD-L1-positive metastatic non-small-cell lung cancer) and TA520[41] (Atezolizumab for treating locally advanced or metastatic non-small-cell lung cancer after chemotherapy), which could have increased the use of immunotherapy in patients with advanced EGFR+ NSCLC after first-line treatment.

During the process of validating the model, the company was advised by clinicians (CS, p201) that the survival projections used in the model may not reflect the use of immunotherapies in the third-line setting (or the use of osimertinib as a second-line treatment). It is not known what proportion of patients in either of the model arms would be eligible, and fit enough, to receive

6 END OF LIFE CRITERIA

The company puts forward a case that osimertinib, as a first-line treatment for advanced EGFR+ NSCLC, meets the NICE End of Life criteria[82] (see Table 43).

Table 1 End of Life criteria

NICE End of Life criteria	Data presented by the company
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	OS for patients with confirmed EGFR+, Stage IIIb/IV NSCLC in England and Wales is estimated to be [redacted] based on analysis of Public Health England data collected between 2014 and 2016 (n=652) (see CS, p28 for details)[a]
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	• Results from the FLAURA trial show that, compared with SoC EGFR-TKI treatment, osimertinib extended PFS by 8.7 months (18.9 months versus 10.2 months). Treatment with osimertinib also demonstrated a substantial improvement in post-progression endpoints, including a [redacted] in time to first subsequent treatment • Whilst OS data were immature at the time of data cut-off, the HR for death was 0.63 (95% CI: 0.45 to 0.88; p=0.007), reflecting a meaningful survival advantage over SoC EGFR-TKI. In addition, early separation of the K-M curves was observed. At 18 months, 82.8% of patients receiving osimertinib were still alive, compared with 70.9% of those receiving SoC EGFR-TKI • In the absence of median OS (i.e. the 50th percentile of OS), a survival gain at other percentiles of OS may be considered as a conservative estimate of the survival gain in the mature population.[100b] The 25th percentile of OS was observed at approximately 22.5 months in the osimertinib arm, and at approximately 15.9 months in the SoC EGFR-TKI arm. This reflects an improvement of 6.6 months, and while not a substitute for median OS, is clearly higher than the 3-month life extension needed to meet End of Life criteria

CI=confidence interval; EGFR-TKI= epidermal growth factor receptor tyrosine kinase inhibitor; NSCLC=non-small cell lung cancer; OS=overall survival; PFS=progression-free survival; SoC=standard of care

[A] During the clarification process, the company also provided the data by performance status (PS) (See response to A28). Median OS was very similar for 336 patients with PS≤1 [redacted] to that of 240 patients with unknown or missing PS [redacted], both estimates being similar to median OS for all patients reported here; median OS was shorter for 112 patients with PS>=2 [redacted].

[b] Precise figures for quantiles were not available; the survival estimates reflect the 75.2% percentile for osimertinib and 75.1% percentile for SoC EGFR-TKI

Source: CS, Table 29

Short life expectancy

The company presents registry data (CS, Table 5) to demonstrate that patients with advanced EGFR+ NSCLC in England and Wales have a life expectancy of less than 24 months. The company explains that this evidence is more representative of the population treated in NHS clinical practice than trial data as outcomes for NHS patients are 'considerably worse' than those of patients recruited to clinical trials who are often 'younger and fitter' (CS, p14) than NHS patients. The ERG accepts the company's argument that trial evidence may overestimate the life expectancy of the population of interest compared with that of patients treated in the NHS but considers that it is inconsistent to accept trial evidence as a measure of effectiveness but not as a measure of life expectancy. There is no real world evidence available that compares the effectiveness of treatment with osimertinib versus afatinib, erlotinib or gefitinib.

At the time of data cut off, median OS had not been reached in either arm of the FLAURA trial, but after 24 months over half (64.7%) of patients in the SoC EGFR-TKI arm were still alive.

The ERG, therefore, considers that, based on available evidence, the average life expectancy of people with advanced EGFR+ NSCLC who are eligible for treatment with afatanib, erlotinib or gefitinib is likely to exceed 24 months.

Treatment benefit

The company uses FLAURA trial PFS data in support of their claim that OS for patients treated with osimertinib is longer than that of patients treated with Soc EGFR-TKI. The ERG highlights findings from published studies[102,103] that demonstrate that PFS is not a good proxy for OS, which means that this line of argument is not robust. However, the economic modelling undertaken by the ERG (see Section 5.3) supports the company position that, compared with treatment with afatinib, erlotinib or gefitinib, treatment with osimertinib extends patient life expectancy by at least 3 months.

ERG conclusion

The ERG considers that patients with advanced EGFR+ NSCLC who are eligible for first-line treatment with afatinib, erlotinib or gefitinib have a life expectancy that is greater than 24 months. Thus, one of the NICE criteria for applying a less restrictive assessment of cost effectiveness for End of Life treatments has not been met.