NICE National Institute for Health and Care Excellence

Single Technology Appraisal

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

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

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

Contents:

The following documents are made available to consultees and commentators:

1. **Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)**

2. **Comments on the Appraisal Consultation Document from AstraZeneca**
   - Response to ACD cover letter
   - Response to ACD and new evidence

3. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   - Roy Castle Lung Cancer Foundation
   - Boehringer Ingelheim
   - Joint response from Royal College of Physicians

There were no comments submitted by the clinical or patient experts.

4. **Comments on the Appraisal Consultation Document received through the NICE website**

5. **Evidence Review Group critique of company comments on the ACD**

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

Osimertinib for untreated EGFR mutation-positive non-small-cell lung cancer

Single Technology Appraisal

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Type of stakeholder:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and Social Care and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal document (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health and Social Care, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
1	Company	AstraZeneca	Inaccurate reporting of FLAURA inclusion/exclusion criteria In paragraph 3.2 (p6), the ACD states that the committee was aware that "…people with many comorbidities were not included in the (FLAURA) trial." This is inaccurate. The full list of inclusion and exclusion criteria for patients recruited to FLAURA is available in the Clinical Study Report provided to NICE and summarised in Table 12 of the Company submission. The only inclusion criterion that could be considered restrictive relates to World Health Organization Performance Status (WHO PS) of 0 to 1 with no clinically significant deterioration over the previous 2 weeks and a minimum life expectancy of 12 weeks. As noted previously, 25% of patients in the real world (SACT data) had a performance status of 2 or more (Supplementary FLAURA analyses submission. p11); the level of co-morbidities for these patients is clearly not captured in FLAURA.	Thank you for your comment. Section 3.2 of the final appraisal document (FAD) has been revised as follows: "The inclusion criteria allowed people with stable brain metastases to enter the trial but limited the trial population to people with an Eastern Cooperative Oncology Group (ECOG) performance score of 0 or 1. For this reason, the committee was aware that the clinical trial population may be in better health than people with stage IIIb or IV NSCLC in the NHS and that people with many comorbidities may not have been included in the trial."
2	Company	AstraZeneca	EGFRm TKI do not all have equal efficacy It is unclear why the Committee have concluded in paragraph 3.4 (p7/8) that "there was evidence of improved PFS with afatinib compared with gefitinib, and erlotinib and gefitinib cannot be assumed to have equal efficacy with afatinib." This conclusion is not supported by • previous appraisals (TA258 and TA310), • the original Company submission (Section B2.9) or • the ERG report (Section 4.9 and 4.10, pages 53-61). Of note, the ERG states that a key difficulty when drawing conclusions about the relative effectiveness of afatinib, erlotinib and gefitinib is that the trials are from heterogeneous populations and that overall: "PFS may be improved with afatinib versus gefitinib and notes that PFS may also be improved for erlotinib versus gefitinib but considers there is insufficient evidence to draw any firm conclusions." It should also be noted that the LUX-Lung 7 study was an open-label Phase 2b study with no formal hypothesis defined. Furthermore, as the ERG report stated: "one of the LUX-Lung 7 trial authors has stated in published correspondence, that while the trial results are	Thank you for your comment. . The committee's conclusion was based on awareness of evidence from previous trials, such as LUX-Lung 7, which showed a statistically significantly improved progression-free survival compared with gefitinib. In addition, the clinical experts stated that people taking afatinib had a better response rate to treatment, a longer duration of response and longer progression-free survival

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			clinically significant, “these data are not sufficient to claim superiority of afatinib over gefitinib (LUX-Lung 7 was an exploratory, not a superiority trial).” When the ERG conducted their own indirect comparison, it was highlighted by them 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 and for OS data from both the FLAURA and LUX-Lung 7 trial.” Given the evidence and conclusions of both the original company submission and the ERG report which are in broad agreement with each other, AZ maintains the position set out in our original submission that there is little evidence to support a clear departure from the conclusions of previous appraisals TA258 and TA310.	compared with erlotinib and gefitinib. They also usually remained on afatinib for longer. See section 3.4 of the FAD.
3	Company	AstraZeneca	Duration of additional OS benefit In Paragraph 3.5, the ACD reports that (The clinical experts) stated that (the effects of osimertinib) could plausibly give about 3 months of additional benefit after stopping treatment with osimertinib compared with erlotinib and gefitinib.” This is inaccurate as the clinical experts have said the effect could persist for between 3 and 12 months after stopping treatment (Correspondence with clinical expert [redacted] We remind the committee that OS is immature at time of submission and that we believe osimertinib is a good candidate for consideration of entering the CDF. For the purposes of modelling, we urge the committee to consider that if a limit on the treatment benefit of osimertinib must be applied, it should be considered appropriate at the upper limit of any range of possible time points. We believe this is supported by the CDF Clinical Lead who expressed confusion about the basis for limiting the duration of treatment effect for osimertinib at all (paragraph 17 of NHS England CDF Clinical Lead statement). “NICE’s position concerning 3 and 5 year treatment waning effects in NSCLC has been following appraisal of fixed durations of immunotherapy with a mode of action which involves the immune system having a plausible more durable impact on the cancer than just during the treatment period. Osimertinib has a completely different mode of action and is not given for a fixed duration of treatment. Patients still on treatment with osimertinib at 3 years or 5 years or any other duration of treatment will still be benefitting from treatment with osimertinib.” This is in agreement with our own position that assumptions agreed by NICE committees for molecules with one mode of action should not necessarily be applied across all other molecules in a particular disease area without due regard to biology.	Thank you for your comment. The committee chair asked the clinical experts about this issue at the committee meeting. They stated that osimertinib could plausibly give about 3 months of additional benefit after stopping treatment compared with erlotinib and gefitinib. Comment noted. Thank you for your comment. The document states that it was not appropriate to compare immunotherapy treatments with osimertinib as they have different mechanisms of action. With regard to applying the upper limit of possible time points, the committee was aware that a 6-year duration of treatment effect would mean that people who stopped taking osimertinib within 1 or 2 years of starting it would still benefit for the full 6 years. For this reason, the committee believd this to be optimistic and without more evidence, it agreed that

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				the ERG's analyses using a 3- or 5-year duration of treatment effect were more appropriate (please see section 3.5 of the FAD).
4	Company	AstraZeneca	Assumption that the ICER compared to afatinib would increase In paragraph 3.8 it is stated that "…given the available evidence from LUX-Lung 7 and clinical expert opinion, it is possible that afatinib has greater efficacy than gefitinib and erlotinib and if so, the ICER for osimertinib compared with afatinib would increase." It should be noted that the superior efficacy of afatinib compared to erlotinib or gefitinib has not been demonstrated and that any increase in the ICER for osimertinib compared with afatinib would be dependent on more than the relative time in PFS or on OS (e.g. time on treatment is an important input into any cost-effectiveness model). Indeed, the median treatment duration from LUX-Lung 7 (time to treatment failure) was 13.7 months which is more than 2 months longer than the median TDT for Standard of Care in FLAURA of 11.5 months. Thus, it is likely that this additional cost in the comparator arm is likely to offset any residual PFS gain that might be modelled from the LUX-Lung 7 afatinib data.	Thank you for your comment. The wording has been amended – please see section 3.8 of the FAD
5	Company	AstraZeneca	**Consideration of End of Life criteria** Supportive evidence for our conclusion that patients in FLAURA who most closely represent the characteristics and experience of patients treated in the NHS has been provided separately. In addition to the new analyses provided, it is important to consider that in standard UK clinical practice, patients under consideration (i.e. newly diagnosed with EGFRm advanced/metastatic NSCLC) are typically expected to receive no more than 2 lines of therapy (as demonstrated by the RWE presented and discussed in this appraisal). If it is accepted that few patients in the NHS receive more than 2 lines of treatment, and that patients in international studies are more likely to receive multiple lines of treatment (i.e. >2), it may be reasonable to consider using an alternative outcome from RCTs to judge life expectancy in current NHS practice. Several post-progression endpoints were presented in the original submission (p78). We believe it is useful to consider the time from randomisation to second PFS (PFS2) in the context of a healthcare setting where few patients receive more than 2 lines of systemic therapy in total. In FLAURA, the median PFS2 for patients randomised to SoC in 1L was 20.0 months (95% CI, 18.2 – NR). Median PFS2 in the osimertinib arm was not reached at this level of maturity. In terms of relative efficacy, the HR between the two arms was 0.58 (95% CI, 0.44-0.78; 2-sided p-value 0.0004). Figure 1. Kaplan Meier survival curves of PFS, PFS2 and OS for patients receiving SoC 1L.	Thank you for the additional supportive evidence. See section 3.11 of the FAD for the committee's considerations of this evidence.

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			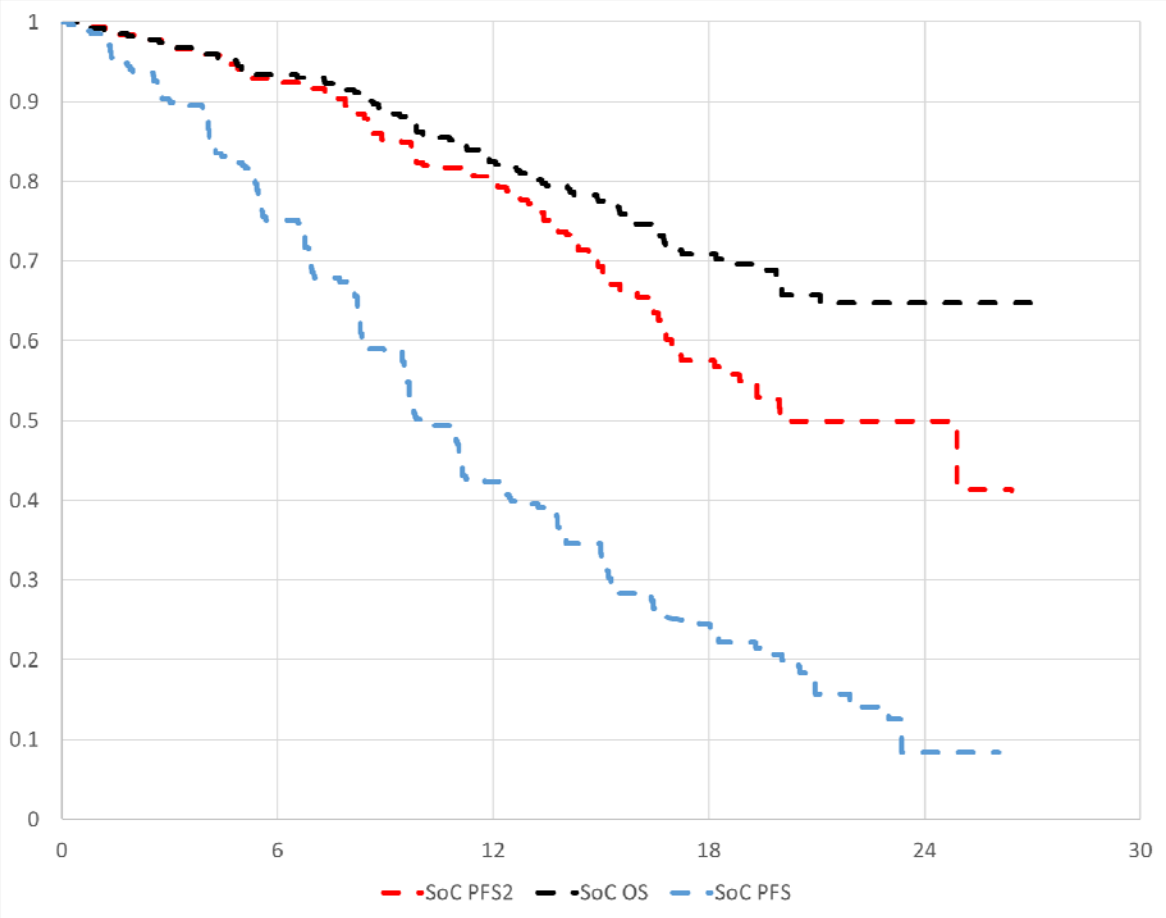 Figure 2. Kaplan Meier survival curves of PFS, PFS2 and OS for patients receiving osimertinib 1L.	

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			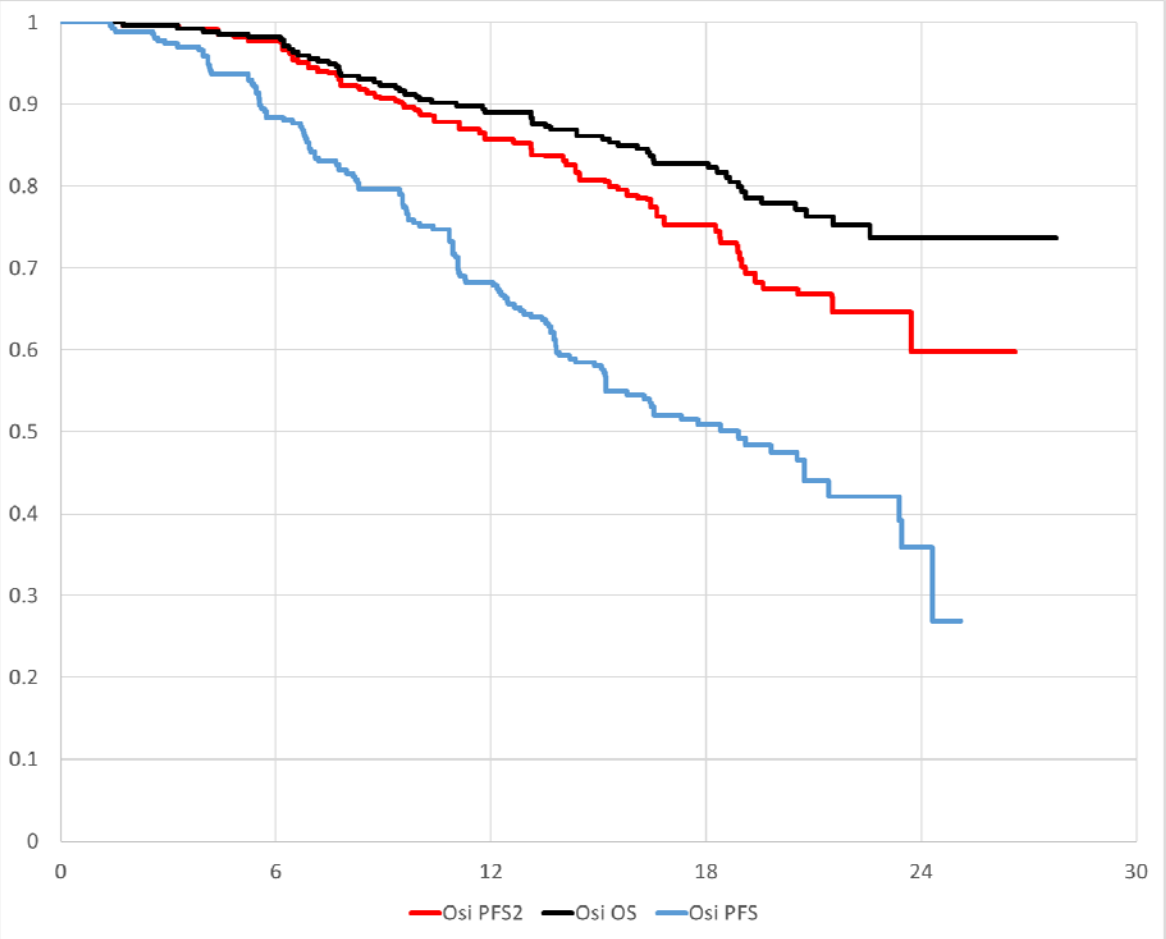 It should be acknowledged that the PFS2 outcomes presented do not take account of the widespread use of non-standard treatment options in 2L which are not standard practice in NHS England (e.g. re-challenge with a second TKI, use of osimertinib in T790M patients, use of immunotherapies or bevacizumab-based treatments). As a result, PFS2 from FLAURA is likely to be an optimistic estimate of the expected time to second progression in practice. **Thus, we believe that if FLAURA is considered in the context of standard NHS practice (i.e. patients receive no more than 2 lines of therapy), it is possible to meet the short life expectancy criterion in the**	

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			ITT population and therefore be considered an End of Life medicine.	
6	Web comment		"Not enough consideration given to the burden of testing for 2nd line mutations (often whilst on ineffective but costly drugs). Burden on patients and also medical resources with increased need for radiology, biopsy and repeat EGFR testing."	Thank you for your comment. The burden on people having T790M mutation testing was discussed at committee. See sections 3.1 and 3.12 of the FAD)
7	Web comment		I was a senior Lung CNS in the private sector when Osimertinib received its second and first -line licence for T790M and EGFR positive nsclc respectively. Based on the evidence, we started to manage our patients accordingly. There is no doubt it has been practice changing. Overall, this treatment has been a positive experience with limited in side effects generally and improved quality of life subsequently. I can think of one patient in particular who came to us after progressing on first line TKI, and was unable to complete further chemotherapy due to poor QOL related to side effects and progression. He had T790M but due to certain restrictions, was unable to have Osimertinib at his local provider. He presented to us as Performance status (PS) 3. We commenced Osimetinib treatment. Within 1 month, he was PS 0 and back out working on his farm. He and his wife felt they were living again, as opposed to dying from the disease. Clinically, this drug provides a another excellent treatment, with apparently fewer side- effects and evidence of CNS penetration, in the growing arena of targeted treatments. This is an important and unfortunately growing, often younger population to that which is traditionally associated with a lung cancer diagnosis. However, prognosis can be just as challenging and quality of life equally as important.	Thank you for your comment. The committee agreed that additional options would be beneficial and concluded that osimertinib would be a useful addition to first-line treatment.
8	Web comment		I think this is a disappointing response, especially for our patients. It is important to recognise that in the relevant trial of first line osimertinib, that patients in the control arm were able to cross over to open label osimertinib if T790M was found, and to treatments which are not standard of care within the NHS if T790M was absent, potentially giving them more treatment lines that applicable here and yielding a potential discrepancy between trial data and 'real world NHS data'.	Thank you for your comment. The committee recognised that there was potential value in real-world evidence from the NHS in England to help inform its decision making. However, it considered there were several reasons why it was not appropriate to use these as the primary data source in isolation for its decision-making on the short life expectancy criterion. Please see section 3.10 of the FAD.
			I note that you correctly identify that afatanib does not feature in FLAURA. However, you can not conclude that afatanib is a better drug (based on LUX-lung 7) as the trial is not powered to look at this - therefore they have to be considered equivalent (in the face of an absence of statistically significant, adequately powered data), to say anything else is simply observational.	Thank you for your comment. The committee understood that LUX-Lung 7 was not powered (that is, it did not have enough people in the trial) to show a difference in overall survival

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				compared with gefitinib. But it was aware that there was evidence of improved progression-free survival with afatinib compared with gefitinib, and on this basis, it concluded that erlotinib and gefitinib cannot be assumed to have equal efficacy with afatinib.
			I was lead author on a poster presented at this year's British Thoracic Oncology Group annual meeting in Dublin (Missing the boat: real world analysis of second line osimertinib use across North West London – abstract from which can be accessed here: https://www.sciencedirect.com/journal/lung-cancer/vol/127/suppl/S1). The data reveals a number of potentially relevant real world data: 1) We demonstrated that the most commonly prescribed EGFR TKI across 5 hospitals in NW London was gefitinib, largely due to a better tolerability profile, with only the fittest patients seemingly being considered for afatinib. Out of 52 patients identified through the chemotherapeutic management system, ARIA, 44 were either prescribed gefitinib or erlotinib first line (39 gefitinib, 5 erlotinib), and 8 were commenced on afatinib. So while there may be some observational data that afatinib may be associated with a longer mPFS, it is not what is used most as first line in this longitudinal real world study. 2) Of these 52 patients, 26 progressed on first line treatment within the study window (01.01.16 through to 30.09.18). Assuming a T790M rate of 60%, as per the NICE and FDA submissions for second-line use, one would expect around 15 patients to be eligible for second line osimertinib use. On review of case notes, we identified that on progression, all patients were ECOG 0-2. We also found that 11 patients (42% of those who progressed) did not undergo any form of T790M testing at all (3 patients were offered invasive biopsy but declined), for reasons that were largely unclear. Just 7 patients (27% of all patients) went on to receive osimertinib. Although it would only be speculation to draw conclusions, you do have to wonder what the overall survival would look like in these patients if a) T790M was a reflex test and b) if patients got up front osimertinib, negating the need for an assessment of T790M on progression, and avoiding not only national variability, but also variability between neighbouring hospitals, in T790M assessment availability.	Thank you for your comment. The committee considered this information at the second committee meeting. However, NHS England have reported that afatinib is the most used treatment in the first line setting while acknowledging there is still substantial use of erlotinib and gefitinib (Please see section 3.4 of the ACD) The company's economic model assumed that 33% of people who had a first-line TKI went on to have osimertinib after disease progression (provided they had the T790M resistance mutation). Please see section 3.6 of the FAD
			I do wonder if, rather than the less than 'real world' nature of a clinical trial (and clinical trial patients), whether our own, NHS wide data could be used. The cancer registration record could be used to identify patients, the SACT database would identify those who progress on first line therapy, what treatment they get next (if any active treatment is given), and crude survival could be calculated from the Spine, or other data sets. I so wonder what real world survival would look like, as I am not convinced (on account of crossover and non-conventional therapies in the control arm) are robust enough.	The committee recognised that there was potential value in real-world evidence from the NHS in England to help inform its decision making. However, it considered there were several reasons why it was not appropriate to use these as the primary data source in isolation for its decision-making on the

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				short life expectancy criterion. Please see section 3.10 of the FAD.
			This is before considering those 'special' subgroups - the 1% of patients who present with T790M mutant cancer up front (de novo) and those with CNS disease, whereby you want a good CNS penetrant option (akin to alectinib for ALK-rearranged lung cancer).	Comment noted. In technology appraisal 416, the company did not present cost effectiveness evidence for people with untreated EGFR T790M NSCLC. The company and the clinical experts stated that osimertinib would only be used for people with EGFR mutation-positive NSCLC whose disease had progressed after first-line EGFR TKIs.
9	Web comment		I would agree with this real-life data. A UK network audit which included patients with performance status ranging from 0-2 reported a median OS of 15.6 months only for patients treated with either a first- or second-generation tyrosine kinase inhibitor. This data was presented at ELCC 2019 meeting. Osimertinib is a more potent drug in common mutations (19/21) and is better tolerated. I would urge that the real-life data in consideration with the data provided by the company in the reassessment of this decision	Thank you for your comment. The committee recognised that there was potential value in real-world evidence from the NHS in England to help inform its decision making. However, it considered there were several reasons why it was not appropriate to use these as the primary data source in isolation for its decision-making on the short life expectancy criterion. Please see section 3.10 of the FAD.
10		Boehringer Ingelheim Limited	Place in therapy, sequencing of other TKIs vs osimertinib: First line (first and second generation) TKIs followed by osimertinib should be a valid comparator to first line osimertinib followed by chemotherapy in this assessment, to maximise options for patients Regardless of choice of first-line EGFR TKI, acquired resistance to therapy is a reality. Therefore, a key consideration when assessing therapeutic choices is the availability of subsequent treatment options following disease progression. It has been demonstrated in phase 3 trials of first generation TKIs (erlotinib and gefitinib) that rates of subsequent therapy were high (60-70%). For afatinib, the second-generation TKI, detailed analysis of the	Thank you for your comments and study references. Thank you for your comment. During the appraisal, the

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			LUX-Lung 3, 6 and 7 trials showed that 71% of patients received a further line of treatment. This is of importance, as it is known that a proportion of patients who receive 1st line Osimertinib will develop an acquired resistance mutation that is not sensitive to current targeted treatments. These patients may have limited treatment options once they progress on first line treatment; and the chance that they go onto only receiving chemotherapy as a second line option may be increased, as was seen in FLAURA with the breakdown of crossover and subsequent anticancer therapy. Few data are available that have assessed the cumulative benefit of sequential EGFR TKIs in patients with EGFR mutation-positive NSCLC. An example of this can be seen in the form of real world data from the GioTag study. This observational, global, retrospective multicenter study was the first to evaluate outcomes of patients who received first-line afatinib followed by osimertinib (4). Sustained clinical benefit was observed in use of this strategy with median time on treatment of 27.6 months reported for a broad patient population that also included patients who have not been well represented in prior studies, such as those with ECOG PS ≥2 (n = 31, 15.3%). Furthermore, of note, this clinical benefit was consistent across all patient subgroups, with particularly encouraging results seen for those with Del19-positive disease (median time on treatment 30.3 months) and Asian patients (median time on treatment 46.7 months). NICE could help maximize options for patients across lines of therapy by keeping Osimertinib as an option for the second line treatment option within its existing license if and when the patient develops the T790M mutation, this being the main molecular resistance mechanism to gefitinib, erlotinib and afatinib (present in approximately 50–70% of tumors at the time of acquired resistance). Given the predominance of T790M-driven resistance and high uptake of postprogression therapy, around 50% of patients could ultimately benefit from sequential EGFR TKIs. Girard N. Optimizing outcomes in EGFR mutation-positive NSCLC: which tyrosine kinase inhibitor and when? Future Oncol. 14(11),1117–1132 (2018). 2 Sequist L, Wu Y, Schuler M et al. Subsequent therapies post-afatinib among patients with EGFR mutation-positive NSCLC in LUX-Lung (LL) 3, 6 and 7. Ann. Oncol. 28(Suppl. 5), v460–v496 (2017). 3 Arcila ME, Oxnard GR, Nafa K et al. Rebiopsy of lung cancer patients with acquired resistance to EGFR inhibitors and enhanced detection of the T790M mutation using a locked nucleic acid-based assay. Clin. Cancer Res. 17(5), 1169–1180 (2011).Crossref, Medline, CAS, Google Scholar 4 Sequist LV, Waltman BA, Dias-Santagata D et al. Genotypic and histological evolution of lung cancers acquiring resistance to EGFR inhibitors. Sci. Transl. Med. 3(75), 75ra26 (2011).Crossref, Medline, Google Scholar	committee understood the subsequent treatments available in both the clinical trial and economic model (please see sections 3.2 and 3.6 of the FAD) Thank you for your comment and publication reference. Thank you for your comment and publication reference.
11		Boehringer Ingelheim Limited	Regarding the statement that the FLAURA trial is broadly generalizable to people with untreated advanced or metastatic EGFR mutation-positive NSCLC: its worth highlighting that the FLAURA study did not include any patients with uncommon EGFR mutations. FLAURA included only patients with common EGFR mutations (exon 19 deletion or p.Leu858Arg (L858R) mutation. Although these mutations make up >85% of all mutation-positive cases and are known to confer sensitivity to EGFR TKI's, there is still a proportion of patients whom treatment is limited. The uncommon	Thank you for your comment. During the appraisal, the clinical experts stated that the exon 19 deletion (del19) or exon 21 (L858R) EGFR mutations account for around 90% of all EGFR mutations.

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			EGFR mutations account for 10–18% of all EGFR mutations and primarily consist of exon 20 insertions, exon 18 point mutations and complex mutations. Improved detection techniques have broadened the spectrum of reported aberrations within the uncommon group but response to TKIs is variable and not fully elucidated. 5 O'Kane, G. M., Bradbury, P. A., Feld, R., Leighl, N. B., Liu, G., Pisters, K. M., ... Shepherd, F. A. (2017). Uncommon EGFR mutations in advanced non-small cell lung cancer. Lung Cancer, 109, 137-144 6 T. De Pas ,F. Toffalorio ,M. Manzotti ,et al. Activity of epidermal growth factor receptor-TKIs in patients with non-small cell lung cancer harboring rare epidermal growth factor receptor mutations. J. Thorac. Oncol.. 2011;6 :1895-1901 7J.C. Yang ,L.V. Sequist ,S.L. Geater ,et al. Clinical activity of afatinib in patients with advanced non-small-cell lung cancer harbouring uncommon EGFR mutations: a combined post-hoc analysis of LUX-Lung 2, LUX-Lung 3, and LUX-Lung 6. Lancet Oncol.. 2015;16 :830-838	Also, most trials only include people with these mutations including trials that were of carried out with other tyrosine kinase inhibitors. The committee were aware that the marketing authorisation indication is not restricted to these 2 mutations (see section 2). It therefore agreed that the EGFR mutation status of patients in FLAURA generally reflected that seen in NHS clinical practice in England.
12		Boehringer Ingelheim Limited	Regarding the statement that the FLAURA trial is broadly generalizable to people with untreated advanced or metastatic EGFR mutation-positive NSCLC: it's worth highlighting further that the FLAURA study design may have missed patients who were asymptomatic or undiagnosed with CNS metastases therefore limiting the conclusions of the efficacy of Osimertinib on this population of patients. FLAURA study included only patients with stable brain metastases. Baseline imaging was mandated only in patients with known or suspected CNS metastases not of the entire patient cohort. This meant that only baseline scans were undertaken in 200 of the 556 randomized patients. In addition, 25% of patients in the study were pre-treated with radiotherapy; this could further confound the evidence. From the results of FLAURA, there was no significant difference in duration of CNS response between patients treated with Osimertinib verus those treated with the tyrosine kinase inhibitor of choice (15.2 vs 18.7 months.) The statement that "Osimertinib helps to control brain metastases" in section 3.5 . implies that Osimertinib limits the progression of CNS metastases. Inferences are made those improvements in PFS (& % of events of CNS progression) in the Osimertinib subgroup of patients compared to the standard TKI are due to cerebral penetration. FLAURA has not demonstrated brain penetration - brain penetration data for osimertinib come from studies in monkeys. Further, the presence of drug within the brain following penetration of the blood-brain- barrier does not necessarily equate to clinical efficacy, which remains to be demonstrated in humans in this case. Girard N. Optimizing outcomes in EGFR mutation-positive NSCLC: which tyrosine kinase inhibitor and when? Future Oncol. 14(11),1117–1132 (2018).	Thank you for your comments and study reference. During the appraisal, the committee understood the inclusion and exclusion criteria of FLAURA, possible confounders and importantly the inclusion of people with CNS metastases, which not all trials do when studying TKIs in EGFR NSCLC. Clinical experts explained that the evidence from FLAURA was broadly generalisable to NHS clinical practice. Please see section 3.2 of the FAD.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
13		Boehringer Ingelheim Limited	Regarding the OS analysis in the FLAURA trial, cross-over of patients is a significant confounder: • A protocol amendment allowed patients who had been assigned to the erlotinib/gefitinib arm to cross over to open-label osimertinib BUT ONLY after confirmation of objective disease progression by blinded independent central review AND post-progression documentation of T790M mutation status by means of plasma or tissue testing • The blinded independent central review confirmation does not help for quick access to the subsequent treatment line potentially delaying treatment initiation • At time of amendment already about 7% of comparator arm patients had progressed, with no chance to cross-over The ERG demonstrated via the ITC, there was no statistically significant difference in overall survival between Osimertinib and Afatinib. In line with our comment #1 above, sequencing of osimertinib after first line TKI will have an impact on the OS across the first and second line therapies.	Thank you for your comment. The committee were aware . Comment noted. The committee was aware of this. See section 3.4 of the FAD.
14		Boehringer Ingelheim Limited	Regarding the point on innovation, the statement that Osimertinib will reduce the need for repeat bronchoscopic biopsies is not a substantial argument. Most patients with NSCLC require this procedure in order for a tissue sample of the tumor to be obtained for pathological purposes and importantly for histology. The practice of obtaining tumor tissue is essential to the staging process and will still occur even in those patients suitable for receiving Osimertinib first line. Comment was made by FLAURA investigators themselves in study publication that tissue-based analyses of resistance mechanisms will be necessary to fully characterize resistance to Osimertinib, so the need for repeat biopsies upon treatment failure will remain. In addition, with the implementation of the NHS Genomic Testing strategy, and the NHS Long Term Plan, the use of molecular diagnostics, through routine genomic testing will become an integral part of patient management across the UK with the ultimate aim of improving services and detection rates.	Thank you for your comment. The committee took this statement into account in its decision making (please see sections 3.1 and 3.12 of the FAD) Thank you for your comment. See section 3.12 of the FAD Comment noted.
15		Roy Castle Lung Cancer Foundation	We are disappointed that the Appraisal Committee's preliminary decision is not to recommend Osimertinib in this indication. We note the clinical benefit of first line Osimertinib, as compared with Gefitinib and Erlotinib. However, as noted in the ACD, Afatinib is now the most widely used therapy in this first line EGFR positive setting. There is no direct data available between Afatinib and Osimertinib. We note that Osimertinib is available through the Cancer Drugs Fund in second line for EGFR T790M positive patients, who have progressed after first line. However, this would necessitate that patients undergo a biopsy – which, for technical reasons, may not be possible or successful. Biopsy can be distressing for patients. Availability of Osimertinib for untreated EGFR mutation positive patients would negate the necessity of biopsy.	Comment noted. Thank you for your agreement in the wording of the FAD. Thank you for your comment. Sections 3.1 and 3.12 of the FAD.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			Most definitely a more patient focused approach. We understand the uncertainty of the data, on which the Appraisal Committee are making this decision. With that in mind, on behalf of the lung cancer patients who would derive benefit from this therapy in this indication, we strongly urge dialogue between the Manufacturer, NICE and NHS England, to ensure cost issues do not prohibit this therapy being available, potentially through the Cancer Drugs Fund, until data has matured.	Thank you for your comment.
16		NCRI-ACP-RCP-RCR	In addition to its statistically and clinically significant benefit in extending PFS, and likely benefit in improving OS compared to existing first-line treatment options (i.e. gefitinib, erlotinib and afatinib), first-line osimertinib is a clinically more attractive treatment option for this patient population due to: a) its improved CNS penetration and reduced risk of CNS progression (publication of planned sub-group analysis of FLAURA data – Reungwetwattana et al. CNS response to osimertinib versus standard epidermal growth factor receptor tyrosine kinase inhibitors in patients with untreated EGFR-mutated advanced non-small-cell lung cancer. Journal of Clinical Oncology. DOI: 10.1200/JCO.2018.78.3118), and b) its improved tolerability, including reduced G1 and G2 skin toxicity, which impacts quality of life of patients on treatment. As per section 3.10 of the draft consultation document, the committee were unable to determine the effects of these factors, likely positive in favour of osimertinib, on the ICER, and thus they were disregarded, however these factors are important considerations that need to be included in the appraisal. Inclusion of osimertinib in the Cancer Drug Fund would provide a potential route for collecting data around these areas to enable a more informed analysis of the ICER for a future final determination.	Thank you for your comment and study reference. Comment noted.

Document processed	Organisation name – Stakeholder or respondent	Disclosure on tobacco funding / links	Number of comments extracted	Comments

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Friday, May 5th, 2019

Dear Professor Gary McVeigh,

AstraZeneca welcomes the opportunity to comment on the Appraisal Consultation Document (ACD) for osimertinib in previously untreated EGFRm-positive NSCLC [ID1302].

We are disappointed that the Committee was unable to reach a positive decision following the first Committee meeting. However, AstraZeneca remain committed to working with NICE to achieve access to osimertinib for UK patients.

One of the key issues identified by the Committee in our submission was that osimertinib did not meet the short life expectancy criterion and therefore does not meet end-of-life criteria. The Committee maintained the opinion that the same data source used to derive estimates of cost-effectiveness should also be used to inform usual life expectancy on current SoC (i.e., the FLAURA trial), rather than using the SACT registry data showing that overall survival is less than 24 months for UK patients.

Accordingly, on the 1st of May, AstraZeneca have presented data [redacted] from the FLAURA clinical trial that most closely reflect the real-world cohort of UK patients, both in terms of baseline characteristics as well as the overall treatment pathway in the NHS, to support the applicability of EoL criteria ([redacted])

Although illustrative and based on immature data from a small number of patients, these analyses nonetheless highlight that life expectancy in these groups are closer to what is observed in UK real-world practice: patients who did not receive a subsequent EGFR-TKI following discontinuation of randomised therapy in the first-line setting are estimated to have a median OS of [redacted] months without adjusting for ethnicity or performance status differences seen in UK healthcare practice.

With mature OS data, a more detailed analysis of survival outcomes in these groups of patients will become available in [redacted]. In the interim, we urge the Committee to exercise discretion and consider the initial findings from these analyses (in addition to UK RWE previously provided) in the context of applicability of EoL criteria.

In view of the remaining uncertainties, we would like to reiterate our interest in being considered for CDF inclusion and would like to offer a NET price of £[redacted]. [redacted].

We would also like to reiterate that osimertinib is an innovative treatment that has the potential to transform care for patients in the first-line setting. Lung cancer survival outcomes in the UK are amongst the worst in Europe, with 1-year OS in Stage III disease of 42.5% in 2017, falling to just 15.5% in Stage IV disease, clearly highlighting the need for additional treatment options. For clinically appropriate patients, osimertinib could offer an unprecedented improvement in progression-free and overall survival outcomes, with improved tolerability compared with currently available TKIs.

In light of the FLAURA subgroup analyses supporting end-of-life criteria, revised NET price, and clinical benefits of osimertinib in this setting, we request that NICE reconsiders its preliminary decision, and recommends osimertinib for use within the NHS.

Yours sincerely,

[redacted]
[redacted] AstraZeneca UK

Copy Peter Clark, Linda Landells, Helen Knight

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

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	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced.
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	AstraZeneca UK
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Comment number	Comments Insert each comment in a new row.

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	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	**Inaccurate reporting of FLAURA inclusion/exclusion criteria** In paragraph 3.2 (p6), the ACD states that the committee was aware that *"…people with many comorbidities were not included in the (FLAURA) trial."* This is inaccurate. The full list of inclusion and exclusion criteria for patients recruited to FLAURA is available in the Clinical Study Report provided to NICE and summarised in Table 12 of the Company submission. The only inclusion criterion that could be considered restrictive relates to World Health Organization Performance Status (WHO PS) of 0 to 1 with no clinically significant deterioration over the previous 2 weeks and a minimum life expectancy of 12 weeks. As noted previously, 25% of patients in the real world (SACT data) had a performance status of 2 or more (Supplementary FLAURA analyses submission. p11); the level of co-morbidities for these patients is clearly not captured in FLAURA.
2	**EGFRm TKI do not all have equal efficacy** It is unclear why the Committee have concluded in paragraph 3.4 (p7/8) that "*there was evidence of improved PFS with afatinib compared with gefitinib, and erlotinib and gefitinib cannot be assumed to have equal efficacy with afatinib."* This conclusion is not supported by • previous appraisals (TA258 and TA310), • the original Company submission (Section B2.9) or • the ERG report (Section 4.9 and 4.10, pages 53-61). Of note, the ERG states that a key difficulty when drawing conclusions about the relative effectiveness of afatinib, erlotinib and gefitinib is that the trials are from heterogeneous populations and that overall: "*PFS may be improved with afatinib versus gefitinib and notes that PFS may also be improved for erlotinib versus gefitinib but considers* ***there is insufficient evidence to draw any firm conclusions****."* It should also be noted that the LUX-Lung 7 study was an open-label Phase 2b study with no formal hypothesis defined. Furthermore, as the ERG report stated: *"one of the LUX-Lung 7 trial authors has stated in published correspondence, 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)."* When the ERG conducted their own indirect comparison, it was highlighted by them 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 and for OS data from both the FLAURA and LUX-Lung 7 trial."* Given the evidence and conclusions of both the original company submission and the ERG report which are in broad agreement with each other, AZ maintains the position set out in our original submission that there is little evidence to support a clear departure from the conclusions of previous appraisals TA258 and TA310.

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3	**Duration of additional OS benefit** In Paragraph 3.5, the ACD reports that *(The clinical experts) stated that (the effects of osimertinib) could plausibly give about 3 months of additional benefit after stopping treatment with osimertinib compared with erlotinib and gefitinib."* This is inaccurate as the clinical experts have said the effect could persist for between 3 and 12 months after stopping treatment (Correspondence with clinical expert [redacted]). We remind the committee that OS is immature at time of submission and that we believe osimertinib is a good candidate for consideration of entering the CDF. For the purposes of modelling, we urge the committee to consider that if a limit on the treatment benefit of osimertinib must be applied, it should be considered appropriate at the upper limit of any range of possible time points. We believe this is supported by the CDF Clinical Lead who expressed confusion about the basis for limiting the duration of treatment effect for osimertinib at all (paragraph 17 of NHS England CDF Clinical Lead statement). *"NICE's position concerning 3 and 5 year treatment waning effects in NSCLC has been **following appraisal of fixed durations of immunotherapy with a mode of action which involves the immune system having a plausible more durable impact** on the cancer than just during the treatment period. **Osimertinib has a completely different mode of action** and is not given for a fixed duration of treatment. Patients still on treatment with osimertinib at 3 years or 5 years or any other duration of treatment will still be benefitting from treatment with osimertinib."* This is in agreement with our own position that assumptions agreed by NICE committees for molecules with one mode of action should not necessarily be applied across all other molecules in a particular disease area without due regard to biology.
4	**Assumption that the ICER compared to afatinib would increase** In paragraph 3.8 it is stated that *"…given the available evidence from LUX-Lung 7 and clinical expert opinion, it is possible that afatinib has greater efficacy than gefitinib and erlotinib and if so, the ICER for osimertinib compared with afatinib would increase."* It should be noted that the superior efficacy of afatinib compared to erlotinib or gefitinib has not been demonstrated and that any increase in the ICER for osimertinib compared with afatinib would be dependent on more than the relative time in PFS or on OS (e.g. time on treatment is an important input into any cost-effectiveness model). Indeed, the median treatment duration from LUX-Lung 7 (time to treatment failure) was 13.7 months which is more than 2 months longer than the median TDT for Standard of Care in FLAURA of 11.5 months. Thus, it is likely that this additional cost in the comparator arm is likely to offset any residual PFS gain that might be modelled from the LUX-Lung 7 afatinib data.

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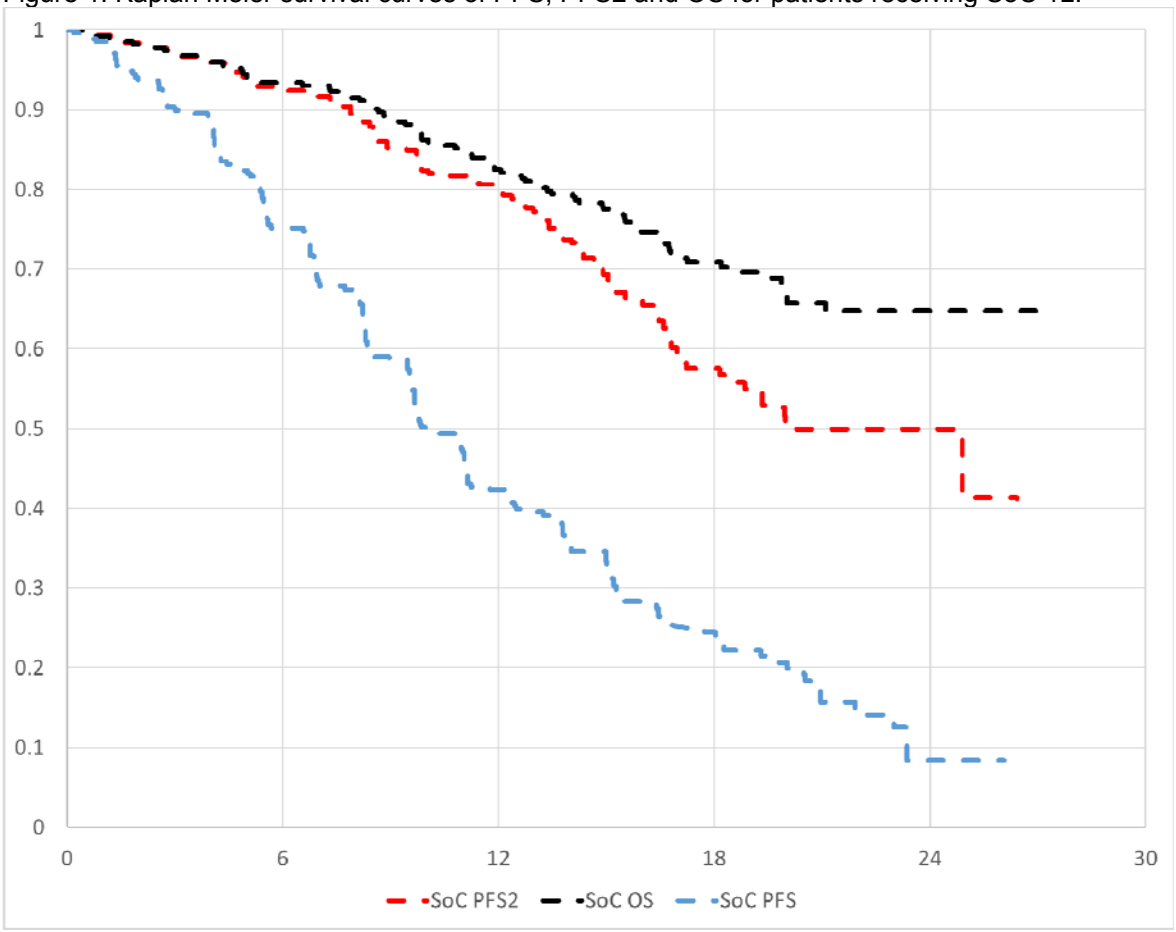
5	**Consideration of End of Life criteria** Supportive evidence for our conclusion that patients in FLAURA who most closely represent the characteristics and experience of patients treated in the NHS has been provided separately. In addition to the new analyses provided, it is important to consider that in standard UK clinical practice, patients under consideration (i.e. newly diagnosed with EGFRm advanced/metastatic NSCLC) are typically expected to receive no more than 2 lines of therapy (as demonstrated by the RWE presented and discussed in this appraisal). If it is accepted that few patients in the NHS receive more than 2 lines of treatment, and that patients in international studies are more likely to receive multiple lines of treatment (i.e. >2), it may be reasonable to consider using an alternative outcome from RCTs to judge life expectancy in current NHS practice. Several post-progression endpoints were presented in the original submission (p78). We believe it is useful to consider the time from randomisation to second PFS (PFS2) in the context of a healthcare setting where few patients receive more than 2 lines of systemic therapy in total. In FLAURA, the median PFS2 for patients randomised to SoC in 1L was 20.0 months (95% CI, 18.2 – NR). Median PFS2 in the osimertinib arm was not reached at this level of maturity. In terms of relative efficacy, the HR between the two arms was 0.58 (95% CI, 0.44-0.78; 2-sided p-value 0.0004). Figure 1. Kaplan Meier survival curves of PFS, PFS2 and OS for patients receiving SoC 1L. 

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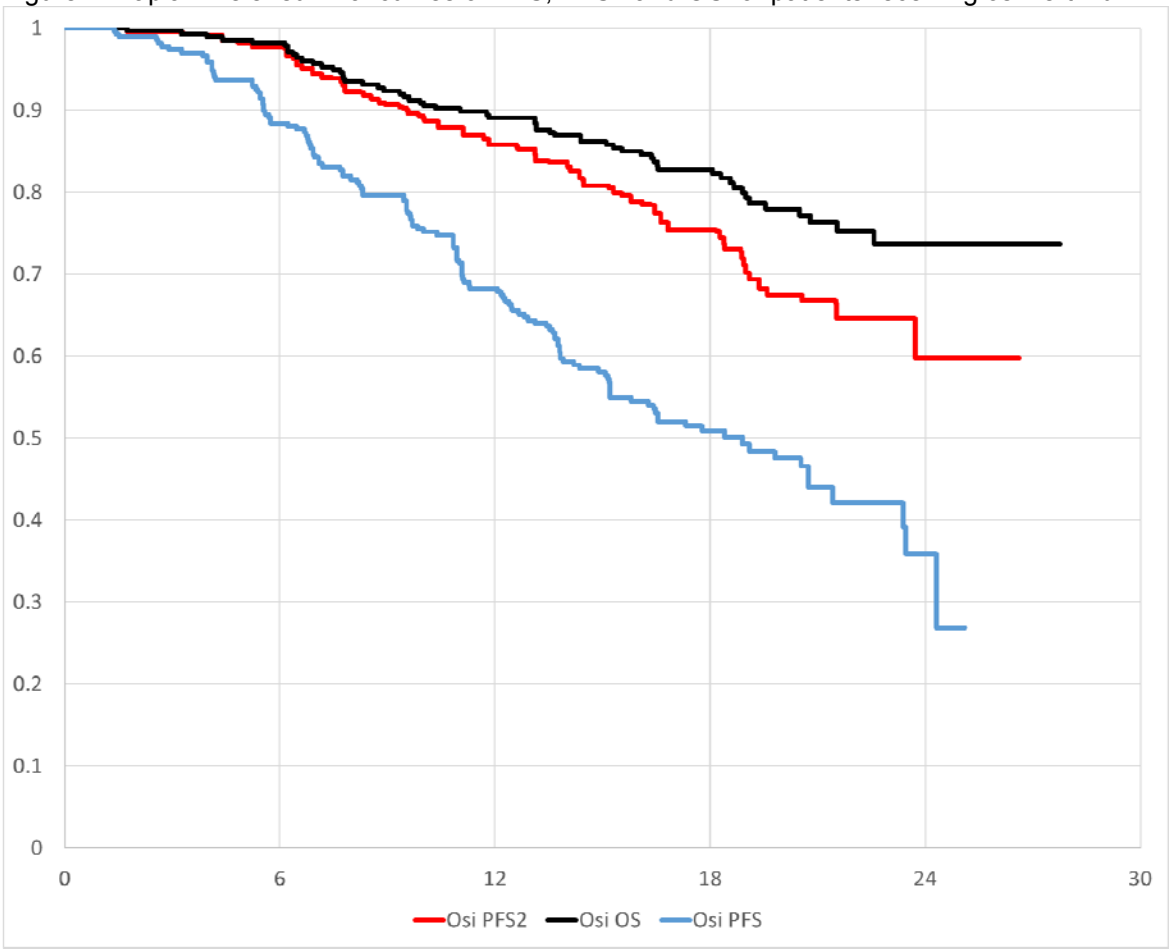
Figure 2. Kaplan Meier survival curves of PFS, PFS2 and OS for patients receiving osimertinib 1L.



It should be acknowledged that the PFS2 outcomes presented do not take account of the widespread use of non-standard treatment options in 2L which are not standard practice in NHS England (e.g. re-challenge with a second TKI, use of osimertinib in T790M patients, use of immunotherapies or bevacizumab-based treatments). As a result, PFS2 from FLAURA is likely to be an optimistic estimate of the expected time to second progression in practice.

Thus, we believe that if FLAURA is considered in the context of standard NHS practice (i.e. patients receive no more than 2 lines of therapy), it is possible to meet the short life expectancy criterion in the ITT population and therefore be considered an End of Life medicine.

Insert extra rows as needed

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accept more than 1 set of comments from each organisation.

- Do not paste other tables into this table – type directly into the table.
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- Do not include medical information about yourself or another person from which you or the person could be identified.
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- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

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CONFIDENTIAL: Additional data analyses from FLAURA to support the applicability of short life expectancy criterion for End-of-Life

Background:

Following the Appraisal Committee Meeting for osimertinib in first-line treatment of EGFRm advanced and metastatic NSCLC (ID1302, March 20th), the Appraisal Consultation Document describing the Committee's decision was produced for consultation. One of the key issues identified by the Committee in our submission was that osimertinib did not meet the short life expectancy criterion and therefore does not meet the end of life criteria.

The Committee acknowledged that differences between the FLAURA patient population and UK cohort of patients in terms of fitness/PS and use of subsequent post-progression therapies, may contribute to the observed differences in OS in FLAURA and RWE datasets; however, they maintained the opinion that, for consistency in decision-making, the same data source that was used to derive estimates of cost-effectiveness should also be used to inform usual life expectancy on current SoC.

Therefore, in this document, we present additional analyses on subgroups of patients from the FLAURA clinical trial that most closely reflect the real-world cohort of UK patients both in terms of baseline characteristics as well as the overall treatment pathway in the NHS, to support the applicability of EoL criteria even when using the Committee-preferred RCT dataset.

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Summary of analyses and findings

To determine life expectancy of those patients in FLAURA who most closely match UK real-world populations, three different subgroups were considered (Table 1). 1-year survival rates in all three groups was lower than what was observed in the ITT population. Although illustrative and based on immature data from a small number of patients, these analyses nonetheless highlight that life expectancy in these groups are closer to what is observed in UK real-world practice. More-mature OS data will undoubtedly provide further insights and allow a more detailed analysis of survival outcomes in these groups of patients. In the interim, we urge the Committee to exercise discretion and consider the initial findings from these analyses (in addition to UK RWE previously provided) in the context of applicability of EoL criteria.

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Table 1: Summary of survival for subgroups presented in this response

Subgroup	Rationale	1-year OS on SoC
ITT	**Base case assumptions in the economic model**	**82.5%**
Patients who did not receive a subsequent EGFR-TKI following discontinuation of randomised therapy in the first-line setting	• Many subsequent treatments used in the trial are not routinely used in the NHS (paragraph 3.2, ACD) o high rates of re-challenge with other EGFR-TKIs in FLAURA (paragraph 15, CDF Clinical Lead statement) o Use of osimertinib in 2L setting is NOT considered standard of care in England (paragraph 8, CDF Clinical Lead statement) • Different subsequent therapies would mean different survival prospects (paragraph 3.6, ACD).	[redacted]
Performance Status 1	To reflect the fact that patients in real-world settings are typically less fit than clinical trial populations (paragraph 3.2, ACD).	[redacted]
Non-Asian populations	Committee conclusion that the effectiveness of afatinib in clinical practice in England is best represented by clinical effectiveness data in the Non-Asian group (TA310).	[redacted]
SACT RWE cohort	**Overall patient population identified in the SACT database (Jan 2014 – Dec 2015): PS 0/1 = 52%, PS>=2 = 18%, missing = 31%**	**57%**
	PS 0/1 subgroup – most similar to ITT FLAURA patient cohort	**63%**

Analysis presentation and discussion

The committee have agreed that despite differences between FLAURA and expected clinical practice, evidence from FLAURA was broadly generalisable to the NHS clinical practice (paragraph 3.2, ACD).

The following patient characteristics were considered in this updated FLAURA analysis to reflect clinical practice in the NHS, in England:

1. Post-progression treatment considerations: patients in the NHS do not routinely have access to subsequent TKI treatments
2. Performance Status considerations: Patients in FLAURA do not include patients with a poorer prognosis as seen in real life
3. Ethnicity considerations: Treatment effect can be expected to be better for Non-Asian patients – which could best represent UK clinical practice (ref TA310)

The modelled overall survival for patients not receiving subsequent TKIs is presented and estimated to be [redacted] months. However, it is reasonable to believe that this should be regarded as an over-estimate when considering the observed one year survival for patients with poorer prognosis (PS 1 in FLAURA and RWE submitted including PS2) and when focusing on non-Asian patients in FLAURA (patients considered to be closer to the UK patient characteristics).

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1. *Post-progression treatment considerations: Patients in the NHS do not routinely benefit from subsequent TKI treatments*

It has been recognised by multiple stakeholders in this appraisal that the expected treatment pathway for patients in the NHS differs significantly from that in many other countries.

The Cancer Drugs Fund Clinical Lead states in paragraph 15 of their statement in their report that there were high rates of re-challenge with other EGFR-TKIs in FLAURA.

In NHS practice, in England, EGFR-TKIs such as erlotinib, afatinib and gefitinib are not used as subsequent lines of treatment as they are only commissioned in the first line setting.

Indeed, the Committee note in the ACD that many subsequent treatments used in the trial are not routinely used in the NHS (paragraph 3.2) and that different subsequent therapies would mean different survival prospects (paragraph 3.6). We accept and agree with the acknowledgement that although an individual patient simulation model could potentially better account for these issues, the trial data is currently too immature for this to be a feasible option.

Given the limitations of the data maturity, we provide an analysis of the baseline characteristics and survival outcomes for patients in FLAURA who did not receive a subsequent EGFR-TKI following discontinuation of randomised therapy in the first-line setting.

In addition, in the CDF report, it was noted that NHS England does not regard the use of osimertinib as 2nd line TKI treatment as standard therapy in England as it is in the CDF (point 8 of CDF Clinical Lead statement). And for the purpose of this analysis we have not included osimertinib 2nd line TKI treatment.

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

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Results:

A total of [redacted] of 277 ([redacted] %) patients randomised to SoC in FLAURA had not received a second EGFR-TKI compared to [redacted] of 279 ([redacted] %) patients in the osimertinib arm and their baseline characteristics are broadly similar to those of the ITT population (Table 2).
Of the [redacted] patients in the SoC arm, [redacted] had died at DCO1 ([redacted] % maturity), compared to [redacted] of the [redacted] patients in the osimertinib arm ([redacted] % maturity) and the overall maturity of the survival for this subgroup was very similar to the complete cohort at [redacted] % ([redacted] events in [redacted] patients), (Table 3).

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Table 2: Baseline characteristics of patients not receiving TKI after progression on randomised treatment

	Full analysis set			No subsequent TKI exposure subgroup	
	Osimertinib (N=279)	**SoC (N=277)**	**Total (N=556)**	**Osimertinib (N=[redacted])**	**SoC (N=[redacted])**
Age, Mean (SD)	62.7 (10.7)	63.3 (10.9)	63 (10.79)	[redacted]	[redacted]
Age, Median (Range)	64 (26 - 85)	64 (35 - 93)	64 (26 - 93)	[redacted]	[redacted]
Female, n (%)	178 (63.8)	172 (62.1)	350 (62.9)	[redacted]	[redacted]
Asian, n (%)	174 (62.4)	173 (62.5)	347 (62.4)	[redacted]	[redacted]
PS 1, n (%)	167 (59.9)	160 (57.8)	327 (58.8)	[redacted]	[redacted]
Stage IV at diagnosis, n (%)	226 (81.0)	230 (83.0)	456 (82.0)	[redacted]	[redacted]
Time from diagnosis/recurrence to randomisation (months), Mean (SD)	1.9 (5.57)	1.8 (3.24)	1.9 (4.56)	[redacted]	[redacted]
Time from diagnosis/recurrence to randomisation (months), Median (Range)	1.2 (0 - 82)	1.2 (0 - 37)	1.2 (0 - 82)	[redacted]	[redacted]
Metastatic disease, n (%)	264 (94.6)	262 (94.6)	526 (94.6)	[redacted]	[redacted]
CNS metastases, n (%)	53 (19.0)	63 (22.7)	116 (20.9)	[redacted]	[redacted]
Baseline tumour size (mm), Mean (SD)	55.3 (34.65)	56.7 (33.55)	56 (34.08)	[redacted]	[redacted]
Baseline tumour size (mm), Median (Range)	47.5 (10 - 207)	50 (10 - 176)	48 (10 - 207)	[redacted]	[redacted]
Adenocarcinoma, n (%)	234 (83.9)	246 (88.8)	480 (86.3)	[redacted]	[redacted]
Non-adenocarcinoma, n (%)	4 (1.4)	5 (1.8)	9 (1.6)	[redacted]	[redacted]
Exon 19 deletion, n (%)	175 (62.7)	174 (62.8)	349 (62.8)	[redacted]	[redacted]

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Table 3:OS for patients in FLAURA who did not receive subsequent EGFRm-TKI after randomised treatment

					Estimated proportion of patients alive, %, at:	
Patient population	**Treatment**	**Patients with events, n (%)**	**Median OS, months (95% CI)**	**HR (95% CI; 2-sided p-value)**	**6 months**	**12 months**
ITT	**Osimertinib (n=279)**	**58 (20.8)**	**NC (NC)**	**0.63 (0.45, 0.88; <0.0068)**	**98.2**	**89.1**
	SoC (n=277)	**83 (30.0)**	**NC (NC)**		**93.4**	**82.5**
No subsequent TKI	Osimertinib (n=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	SoC (n=[redacted])	[redacted]	[redacted]		[redacted]	[redacted]

Overall method of modelling survival for patients not receiving subsequent TKIs

The survival analysis of OS for the subgroup of patients who did not receive a subsequent TKI after discontinuation of their first-line treatment was conducted using the approach outlined in the Technical Support Document for survival analysis published by the NICE Decision Support Unit. The model selection process is presented graphically in Figure A5. In summary:

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

A summary of the non-parametric data for OS from the subgroup of patients in FLAURA who did not receive a subsequent TKI after discontinuation of their first-line treatment is presented in Table 4.

Table 4. OS summary data

	Osimertinib (n=[redacted])	**SoC (n=[redacted])**
Total events (%)	[redacted] ([redacted]%)	[redacted] ([redacted]%)
Median months (95% CI)	NR (NR, NR)	NR (NR, NR)

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

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

- Straight parallel lines were observed in the log cumulative hazard plot where the data are most prevalent (Figure A6)
- The Cox-Snell residuals (Figure A7) had a slope equal to one for the majority of the plot, indicating that a Cox model fitted the data well
- The KM curves show a clear separation up to ~5 months, after which they slightly converge reaching a minimum separation at ~8 months. Beyond this point the two curves diverge steadily over time (Figure A8)

Given that the proportional hazard assumption was not violated, it was considered appropriate to fit dependent parametric models with a treatment coefficient for osimertinib.

The fitted parametric models are presented in Figure 1, the statistical fit of the models is presented in (Table 5) and mean, median and landmark rates are presented in (Table 6 and Table 7) for osimertinib and SoC respectively. The log-logistic and log-normal models are associated with the lowest AIC/BIC followed by the Weibull and the generalised gamma models. The Gompertz distribution predicts all patients in both arms to be dead before 8 years.

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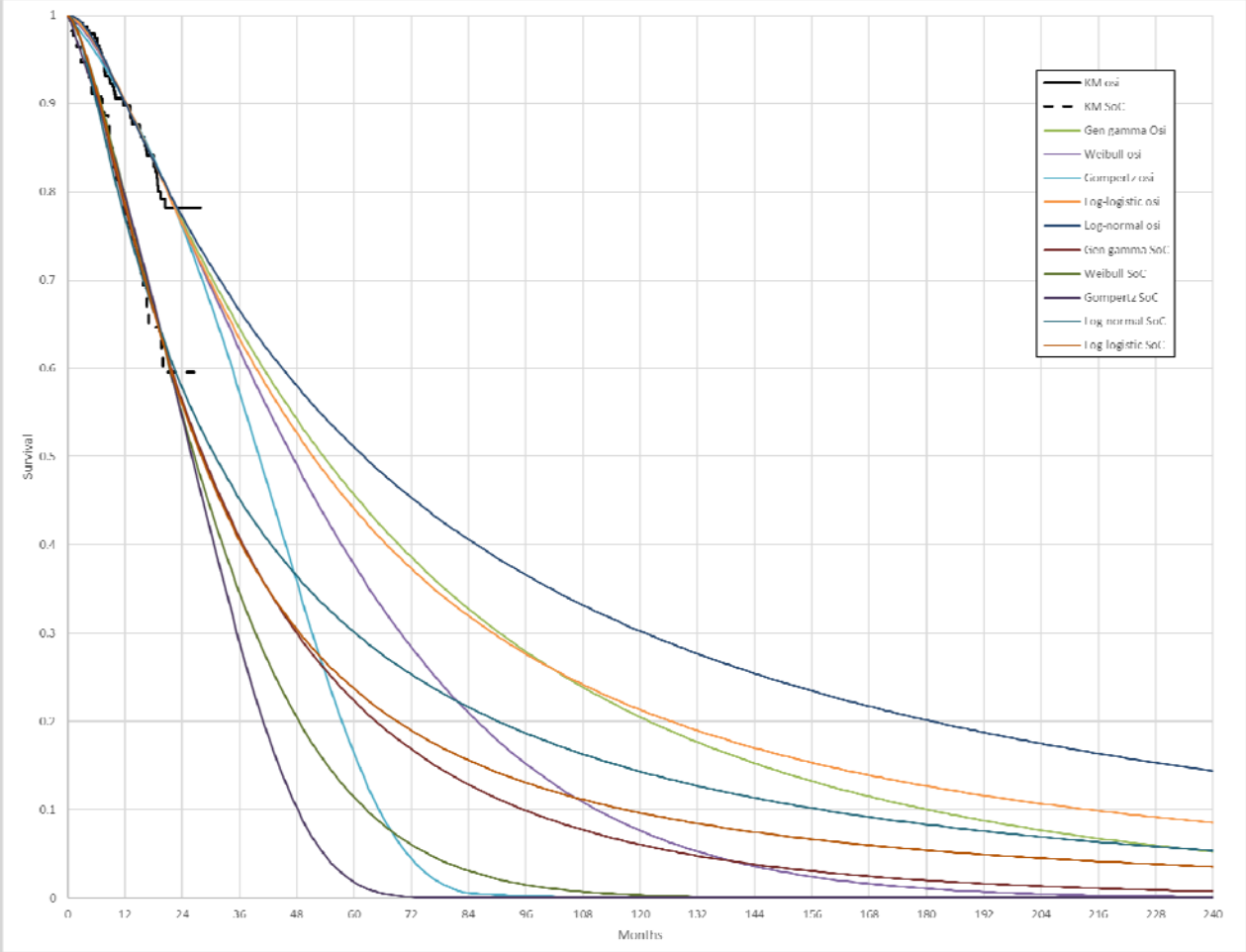
Figure 1. Fitted parametric models



KM: Kaplan Meier; SoC: standard of care

Table 5: Goodness of fit statistics (OS; dependent; FLAURA)

	Weibull	Gompertz	Log-logistic	Log-normal	Generalised gamma
AIC	1061.81	1066.81	1060.54	1061.51	1062.48
Rank	3	5	1	2	4
BIC	1073.88	1078.87	1072.60	1073.57	1078.56
Rank	3	5	1	2	4

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

Table 6. Osimertinib predicted and observed mean, median and landmark rates

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

OS: overall survival

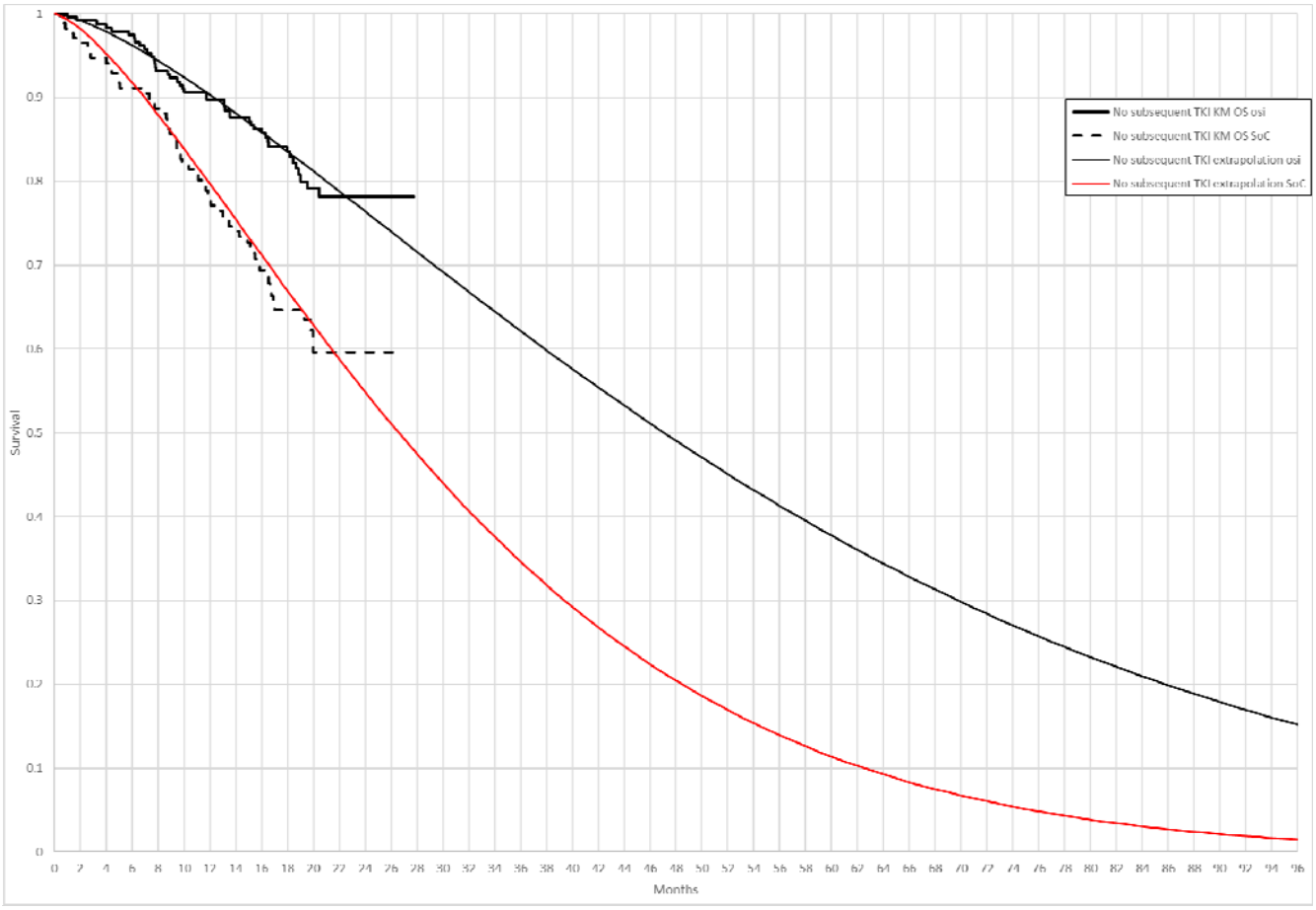
Table 7. SoC predicted and observed mean, median and landmark rates

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

OS: overall survival; SoC: standard of care

Based on the statistical goodness of fit and the long-term plausibility of the extrapolations, the Weibull distribution was considered the most appropriate distribution (Figure 2).

Figure 2. OS Kaplan Meier curves and Weibull dependant parametric distribution



KM: Kaplan Meier; Osi: osimertinib; SoC: standard of care; TKI: tyrosine kinase inhibitor

Therefore, in this exploratory subgroup of patients in FLAURA who did not receive a subsequent EGFR-TKI following their randomised treatment, median OS in SoC is potentially [redacted] months at [redacted] % maturity. The survival expectation of similar patients receiving osimertinib in first line is expected to be approximately [redacted] months (an increase of over [redacted] months) and very similar to the extrapolation in the ITT population informing the cost-effectiveness model in the submission.

When considering the data presented here it is important to recall that although this post-hoc subgroup is more reflective of the expected standard treatment pathway of

patients in the NHS, some important differences in the patients themselves from the trial and real world remain. The analyses described below will help address this.

2. *Performance Status considerations: Patients in real life have a poorer prognosis than seen in FLAURA*

It was concluded by the Committee that patients recruited to randomised clinical trials are generally younger (median age in FLAURA vs SACT was 64 vs 68, respectively) and fitter than those encountered in routine clinical practice. Recruitment of patients to FLAURA was restricted to patients with performance status 0 or 1 (as measured using the World Health Organisation score) and this was a stratification variable for subgroup analysis. In contrast, as demonstrated in the original submission, approximately 25% of patients routinely treated with targeted therapies for EGFRm advanced and metastatic NSCLC and for whom performance data exists, have a PS >1; i.e. restricted to bed at least some of the time.

Table 8: Performance status of patients in SACT RWE and FLAURA

	Overall SACT	PS 0/1 SACT	FLAURA
Number of patients	*N=652*	**N=336**	**N=556**
PS 0	*130 (20%)*	**130 (39%)**	**228 (41%)**
PS 1	*206 (32%)*	**206 (61%)**	**327 (59%)**
PS ≥2	*112 (18%)*	-	-
PS Missing	*204 (31%)*	-	-

At DCO1, the magnitude of PFS benefit was approximately equal in patients with poorer performance status (PS1) vs the entire cohort (HR: [redacted] versus HR: [redacted], respectively), although the median PFS for patients receiving osimertinib was slightly reduced ([redacted] months; 95% CI: [redacted], versus [redacted] months; 95% CI: [redacted], respectively) (Table 9 and Figure 3).

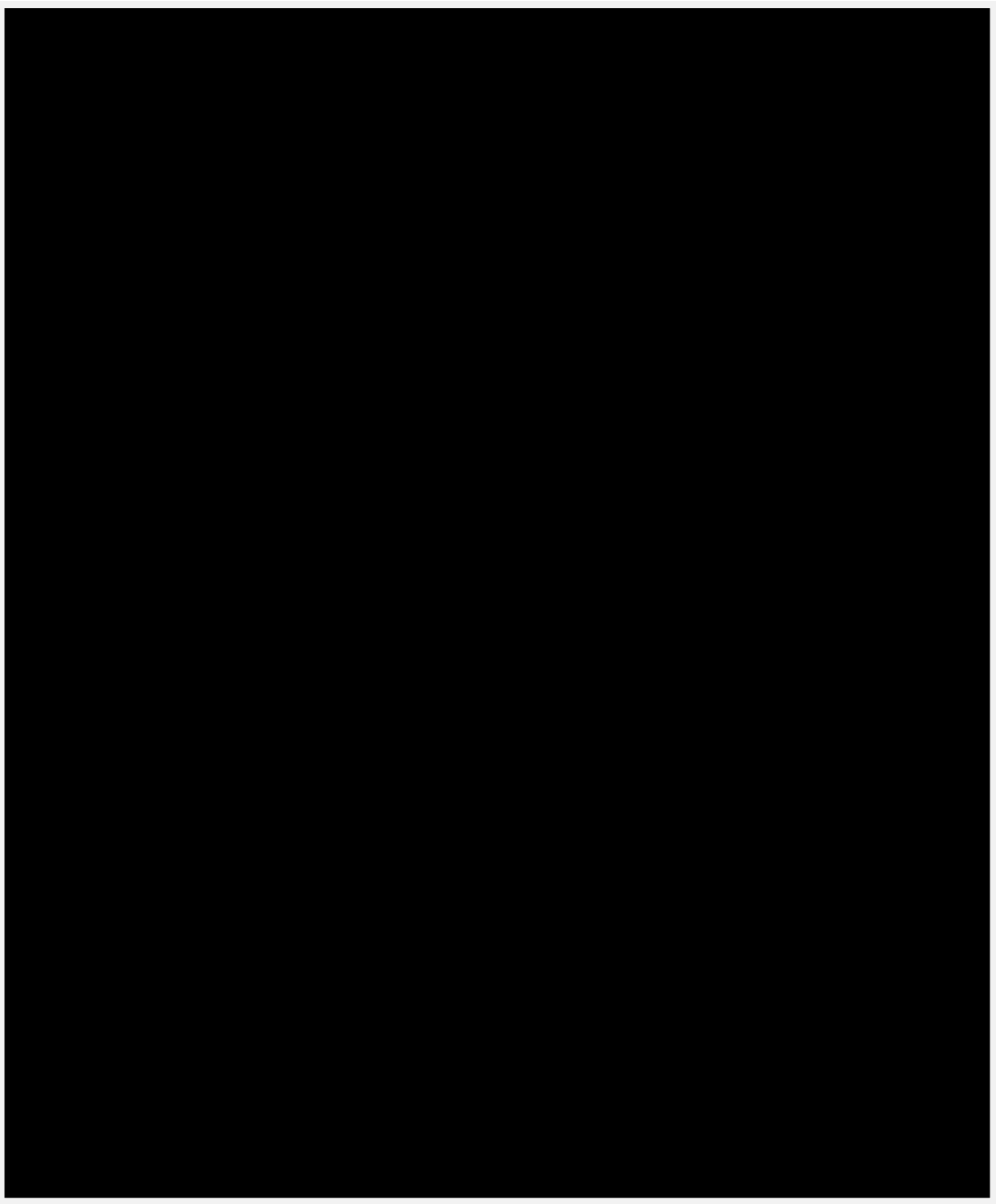
The additional data presented here for overall survival demonstrates that at DCO1, when 25% of all patients had died, the relative efficacy of osimertinib on survival in patients with poorer performance status was no different from the overall population (HR: [redacted], versus HR: 0.63; 95% CI: 0.45, 0.88, respectively),

although approximately 5% more patients had died in both arms relative to the ITT population. **Similar to the ITT population, median OS had not been reached for either arm at DCO1, but the lower confidence interval for median OS in the SoC arm of this subgroup is [redacted] months.**

Table 9: PFS and OS for patients in FLAURA with Performance Status 1

PFS					Estimated proportion of patients alive and progression-free, %, at:	
Patient population	**Treatment**	**Patients with events, n (%)**	**Median PFS, months (95% CI)**	**HR (95% CI; 2-sided p-value)**	**6 months**	**12 months**
ITT	**Osimertinib (n=279)**	**136 (48.7)**	**18.9 (15.2, 21.4)**	**0.46 (0.37, 0.57; <0.0001)**	**88.4**	**68.2**
	SoC (n=277)	**206 (74.4)**	**10.2 (9.6, 11.1)**		**75.2**	**42.3**
PS 1 (Restricted activity)	Osimertinib (n=167)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	SoC (n=160)	[redacted]	[redacted]		[redacted]	[redacted]
OS					Estimated proportion of patients alive, %, at:	
Patient population	**Treatment**	**Patients with events, n (%)**	**Median OS, months (95% CI)**	**HR (95% CI; 2-sided p-value)**	**6 months**	**12 months**
ITT	**Osimertinib (n=279)**	**58 (20.8)**	**NC (NC)**	**0.63 (0.45, 0.88; <0.0068)**	**98.2**	**89.1**
	SoC (n=277)	**83 (30.0)**	**NC (NC)**		**93.4**	**82.5**
PS 1 (Restricted activity)	Osimertinib (n=167)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	SoC (n=160)	[redacted]	[redacted]		[redacted]	[redacted]

Figure 3: PFS and OS Kaplan Meier curves for FLAURA stratified according to performance status (AZD: osimertinib)



Overall, this data supports the hypothesis that the relative efficacy of osimertinib in patients with poorer performance status is no different from the ITT population, although the absolute life expectancy is reduced.

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Within the post-hoc subgroup of patients who did not receive a subsequent EGFR-TKI after randomised treatment, approximately [redacted] % had the poorest performance status ([redacted], Table 2). It is therefore reasonable to expect that for the majority of patients (expected to have a poorer PS than the ITT of FLAURA) in NHS practice, overall survival in would be reduced even further than predicted by the simple subgroup analysis provided in Section 1.

3. Ethnicity Considerations: Patients treated in real life are more similar to the Non-Asian subgroup of FLAURA

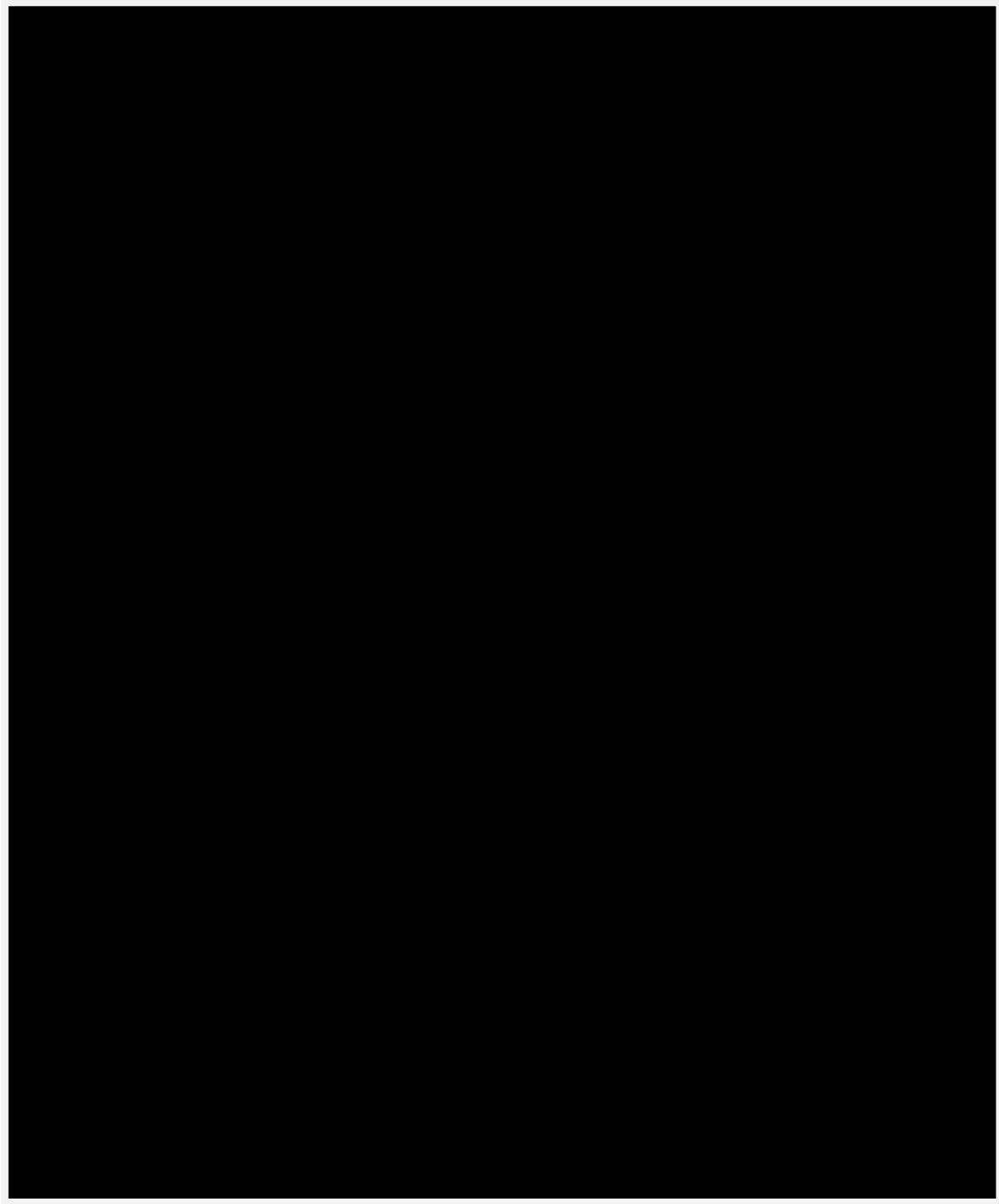
The pre-specified subgroup analysis of ethnicity, or race according to Asian vs Non-Asian populations, was presented in the original submission and is of interest from a UK perspective, as the UK population predominantly comprises people of non-Asian ethnicity, and so results in this subgroup may be more relevant to the UK setting.

At DCO1, fewer patients in the osimertinib non-Asian subgroup had experienced a progression event than in the Asian subgroup. The magnitude of PFS benefit was higher in non-Asian patients than in Asian patients (HR: 0.34; 95% CI: 0.23, 0.48, versus HR: 0.55; 95% CI: 0.42, 0.72, respectively) (Table 10, Figure 4). The additional data presented here for overall survival demonstrates that at DCO1, a higher proportion of Non-Asian patients had died in the SoC arm compared to the ITT population ([redacted]), whilst there was a similar proportion of patients randomised to osimertinib to have died at this timepoint ([redacted]). This is also reflected in the improvement in the HR for OS at this early stage of the study ([redacted]).

Table 10: PFS and OS for Non-Asian patients in FLAURA

PFS					Estimated proportion of patients alive and progression-free, %, at:	
Patient population	**Treatment**	**Patients with events, n (%)**	**Median PFS, months (95% CI)**	**HR (95% CI; 2-sided p-value)**	**6 months**	**12 months**
ITT	**Osimertinib (n=279)**	**136 (48.7)**	**18.9 (15.2, 21.4)**	**0.46 (0.37, 0.57; <0.0001)**	**88.4**	**68.2**
	SoC (n=277)	**206 (74.4)**	**10.2 (9.6, 11.1)**		**75.2**	**42.3**
Non-Asian	Osimertinib (n=105)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	SoC (n=104)	[redacted]	[redacted]		[redacted]	[redacted]
OS					Estimated proportion of patients alive, %, at:	
Patient population	**Treatment**	**Patients with events, n (%)**	**Median OS, months (95% CI)**	**HR (95% CI; 2-sided p-value)**	**6 months**	**12 months**
ITT	**Osimertinib (n=279)**	**58 (20.8)**	**NC (NC)**	**0.63 (0.45, 0.88; <0.0068)**	**98.2**	**89.1**
	SoC (n=277)	**83 (30.0)**	**NC (NC)**		**93.4**	**82.5**
Non-Asian	Osimertinib (n=105)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	SoC (n=104)	[redacted]	[redacted]		[redacted]	[redacted]

Figure 4: PFS and OS Kaplan Meier curves for FLAURA stratified according to ethnicity (AZD: osimertinib)



These data suggest that for patients in FLAURA who have similar ethnic background to patients routinely treated in the NHS, the use of SoC in the first-line setting is expected to result in reduced survival compared to the ITT population. In contrast, survival outcomes for patients receiving osimertinib as first-line treatment are not expected to be significantly different from those in the ITT population.

Within the post-hoc subgroup of patients who did not receive a subsequent EGFR-TKI after randomised treatment, approximately one third were Non-Asian (Table 2). It is therefore reasonable to expect that for the majority of patients in NHS practice, overall survival would be reduced even further than that predicted by the simple subgroup analysis provided in Section 1.

External sources of evidence for shorter survival in Non-Asian patients

The conclusion that Non-Asian patients in international RCTs in this population have poorer survival outcomes compared to Asian patients in the same trials is supported by subgroup analysis of the ARCHER-1050 study (Mok et al., 2018).

Median survival of the approximately 100 Non-Asian patients in that study was, on average, between 5 and 6 months shorter than the ITT cohort with very similar HR (Table 11).

Table 11: Subgroup analyses of OS for Non-Asian patients in recent RCTs EGFRm NSCLC.

Study	Treatment	N	Median OS	HR (95% CI)
ARCHER-1050 ITT	Dacomitinib	103/227 (45.4)	34.1 (29.5 – 37.7)	0.76 (0.582 – 0.993)
	Gefitinib	117/225 (52.0)	26.8 (23.7 – 32.1)	
ARCHER-1050 Non-Asian	Dacomitinib	29/57 (50.9)	29.5 (20.7 – NC)	0.721 (0.433 – 1.201)
	Gefitinib	31/49 (63.3)	20.6 (16.1 – 25.5)	
FLAURA ITT	Osimertinib	58/279 (20.8)	NC (NC)	0.63 (0.45 – 0.88)
	SoC	83/277 (30.0)	NC (NC)	
FLAURA Non-Asian	Osimertinib	[redacted]	[redacted]	[redacted]
	SoC			

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Appendix

Figure A5. Survival model selection process recommended by NICE

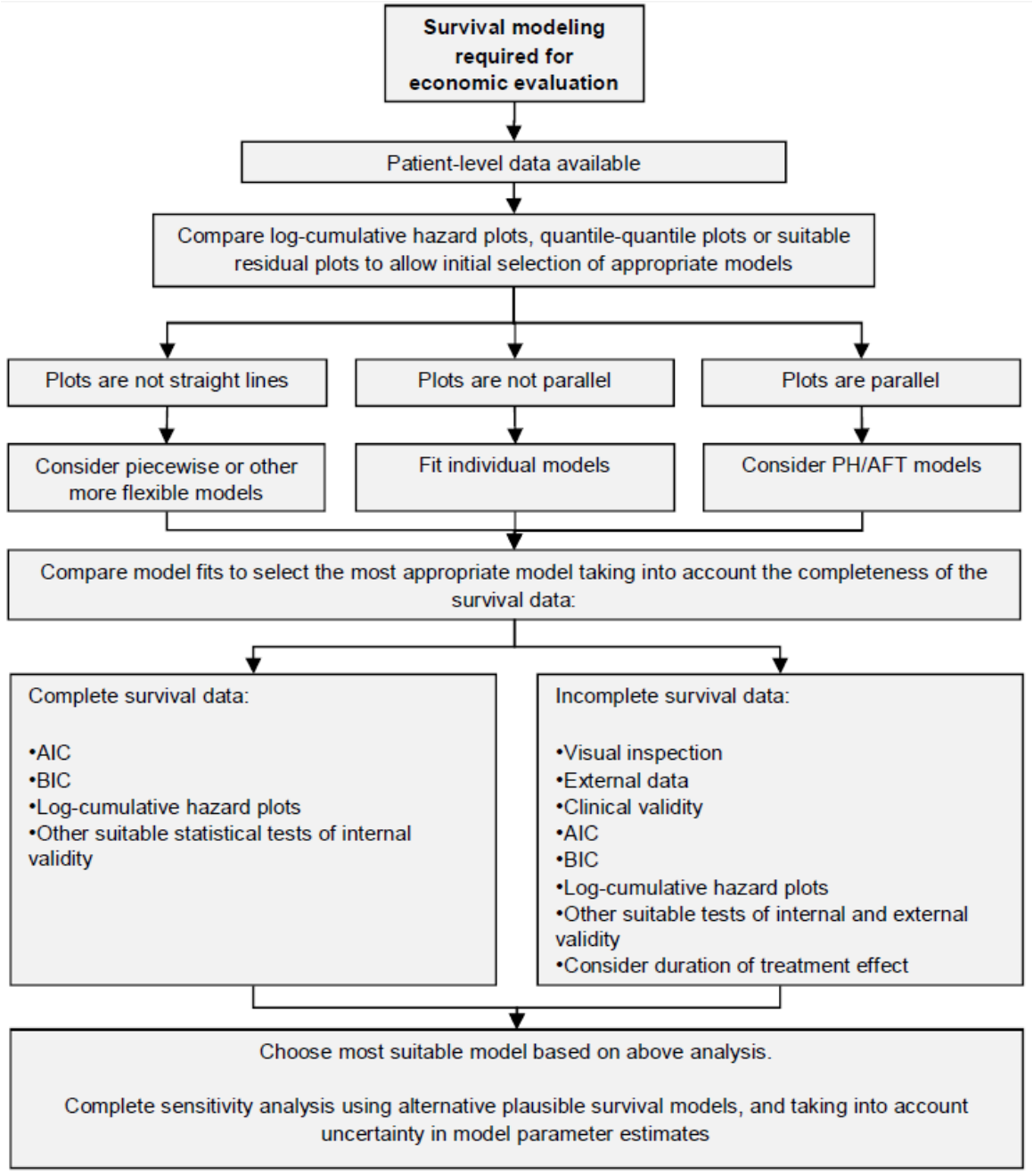
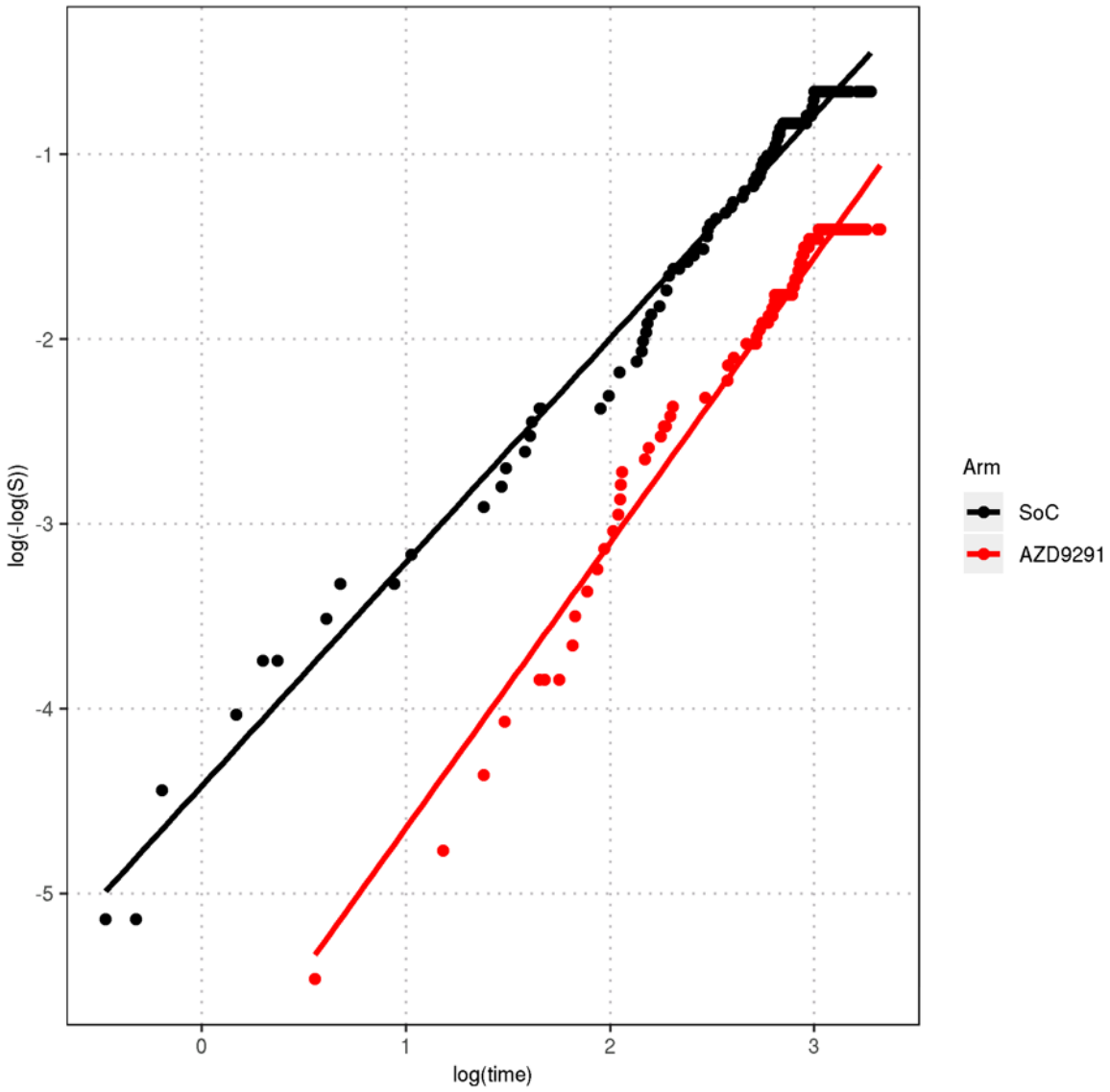


Figure A6. Log cumulative hazard plot



AZD9291: osimertinib; SoC: standard of care

Figure A7. Cox Snell residuals

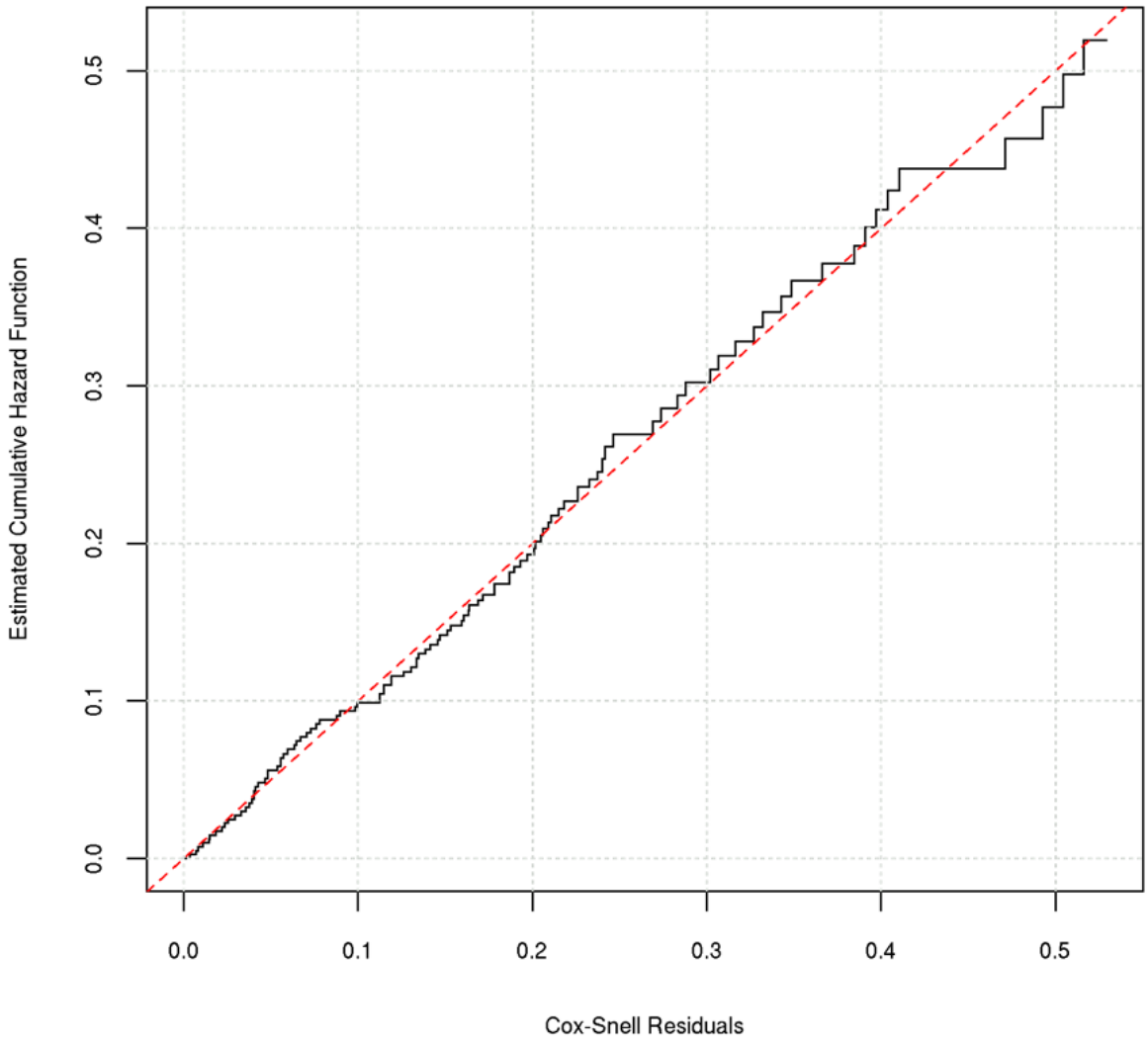


Figure A8. Kaplan Meier plot

Response to the National Institute for Health and Care Excellence's Appraisal Consultation Decision (ACD) on Osimertinib for untreated EGFR mutation positive lung cancer. [ID1302]

This response is submitted by Roy Castle Lung Cancer Foundation.

- We are disappointed that the Appraisal Committee's preliminary decision is not to recommend Osimertinib in this indication.

- We note the clinical benefit of first line Osimertinib, as compared with Gefitinib and Erlotinib. However, as noted in the ACD, Afatinib is now the most widely used therapy in this first line EGFR positive setting. There is no direct data available between Afatinib and Osimertinib.

- We note that Osimertinib is available through the Cancer Drugs Fund in second line for EGFR T790M positive patients, who have progressed after first line. However, this would necessitate that patients undergo a biopsy – which, for technical reasons, may not be possible or successful. Biopsy can be distressing for patients. Availability of Osimertinib for untreated EGFR mutation positive patients would negate the necessity of biopsy. Most definitely a more patient focused approach.

- We understand the uncertainty of the data, on which the Appraisal Committee are making this decision. With that in mind, on behalf of the lung cancer patients who would derive benefit from this therapy in this indication, we strongly urge dialogue between the Manufacturer, NICE and NHS England, to ensure cost issues do not prohibit this therapy being available, potentially through the Cancer Drugs Fund, until data has matured.

Roy Castle Lung Cancer Foundation
May 2019

NICE National Institute for Health and Care Excellence

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	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced.
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Boehringer Ingelheim Limited
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None we are aware of
Name of commentator person completing form:	[redacted]

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NICE National Institute for Health and Care Excellence

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Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Comment #1 (refers to ACD sections 1, 3.1, 3.4, and 3.9)	**Place in therapy, sequencing of other TKIs vs osimertinib: First line (first and second generation) TKIs followed by osimertinib should be a valid comparator to first line osimertinib followed by chemotherapy in this assessment, to maximise options for patients** Regardless of choice of first-line EGFR TKI, acquired resistance to therapy is a reality. Therefore, a key consideration when assessing therapeutic choices is the availability of subsequent treatment options following disease progression. It has been demonstrated in phase 3 trials of first generation TKIs (erlotinib and gefitinib) that rates of subsequent therapy were high (60-70%). For afatinib, the second-generation TKI, detailed analysis of the LUX-Lung 3, 6 and 7 trials showed that 71% of patients received a further line of treatment. This is of importance, as it is known that a proportion of patients who receive 1st line Osimertinib will develop an acquired resistance mutation that is not sensitive to current targeted treatments. **These patients may have limited treatment options once they progress on first line treatment**; and the chance that they go onto only receiving chemotherapy as a second line option may be increased, as was seen in FLAURA with the breakdown of crossover and subsequent anticancer therapy. Few data are available that have assessed the cumulative benefit of sequential EGFR TKIs in patients with *EGFR* mutation-positive NSCLC. An example of this can be seen in the form of real world data from the GioTag study. This observational, global, retrospective multicenter study was the first to evaluate outcomes of patients who received **first-line afatinib followed by osimertinib (4). Sustained clinical benefit was observed in use of this strategy with median time on treatment of 27.6 months** reported for a broad patient population that also included patients who have not been well represented in prior studies, such as those with ECOG PS ≥2 (n = 31, 15.3%). Furthermore, of note, this clinical benefit was consistent across all patient subgroups, with particularly encouraging results seen for those with Del19-positive disease (median time on treatment 30.3 months) and Asian patients (median time on treatment 46.7 months). **NICE could help maximize options for patients across lines of therapy by keeping Osimertinib as an option for the second line treatment option within its existing license** if and when the patient develops the T790M mutation, this being the main molecular resistance mechanism to gefitinib, erlotinib and afatinib (present in approximately 50–70% of tumors at the time of acquired resistance). Given the predominance of T790M-driven resistance and high uptake of postprogression therapy, around 50% of patients could ultimately benefit from sequential EGFR TKIs. [1] Girard N. Optimizing outcomes in EGFR mutation-positive NSCLC: which tyrosine kinase inhibitor and when? Future Oncol. 14(11),1117–1132 (2018). [2] Sequist L, Wu Y, Schuler M et al. Subsequent therapies post-afatinib among patients with EGFR mutation-positive NSCLC in LUX-Lung (LL) 3, 6 and 7. Ann. Oncol. 28(Suppl. 5), v460–v496 (2017). [3] Arcila ME, Oxnard GR, Nafa K et al. Rebiopsy of lung cancer patients with acquired resistance to EGFR inhibitors and enhanced detection of the T790M mutation using a locked nucleic acid-based assay. Clin. Cancer Res. 17(5), 1169–1180 (2011).Crossref, Medline, CAS, Google Scholar [4] Sequist LV, Waltman BA, Dias-Santagata D et al. Genotypic and histological evolution of lung cancers acquiring resistance to EGFR inhibitors. Sci. Transl. Med. 3(75), 75ra26 (2011).Crossref, Medline, Google Scholar
Comment #2 (refers to ACD sections 2 and 3.2)	Regarding the statement that the FLAURA trial is broadly generalizable to people with untreated advanced or metastatic EGFR mutation-positive NSCLC**:** its worth highlighting that **the FLAURA study did not include any patients with uncommon EGFR mutations**. FLAURA included only patients with common EGFR mutations (exon 19 deletion or p.Leu858Arg (L858R) mutation. Although these mutations make up >85% of all mutation-positive cases and are known to confer sensitivity to EGFR TKI's, **there is still a proportion of patients whom treatment is limited. The uncommon EGFR mutations account for 10–18% of all EGFR mutations** and primarily consist of exon 20 insertions, exon 18 point mutations and complex mutations. Improved detection techniques have broadened the spectrum of reported aberrations within the uncommon group but response to TKIs is variable and not fully elucidated. [5] O'Kane, G. M., Bradbury, P. A., Feld, R., Leighl, N. B., Liu, G., Pisters, K. M., ... Shepherd, F. A. (2017). Uncommon EGFR mutations in advanced non-small cell lung cancer. Lung Cancer, 109, 137-144 [6] T. De Pas ,F. Toffalorio ,M. Manzotti ,et al. Activity of epidermal growth factor receptor-TKIs in patients with non-small cell lung cancer harboring rare epidermal growth factor receptor mutations. J. Thorac. Oncol.. 2011;6 :1895-1901 [7]J.C. Yang ,L.V. Sequist ,S.L. Geater ,et al. Clinical activity of afatinib in patients with advanced non-small-cell lung cancer harbouring uncommon EGFR mutations: a combined post-hoc analysis of LUX-Lung 2, LUX-Lung 3, and LUX-Lung 6. Lancet Oncol.. 2015;16 :830-838
Comment #3 (refers to ACD sections 2, 3.2, and 3.5)	Regarding the statement that the FLAURA trial is broadly generalizable to people with untreated advanced or metastatic EGFR mutation-positive NSCLC**:** it's worth highlighting further that the **FLAURA study design may have missed patients who were asymptomatic or undiagnosed with CNS metastases therefore limiting the conclusions of the efficacy of Osimertinib on this population of patients**. FLAURA study included only patients with stable brain metastases. Baseline imaging was mandated only in patients with known or suspected CNS metastases not of the entire patient cohort. This meant that only baseline scans were undertaken in 200 of the 556 randomized patients.

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	In addition, **25% of patients in the study were pre-treated with radiotherapy**; this could further confound the evidence. From the results of FLAURA, there was **no significant difference in duration of CNS response between patients treated with Osimertinib verus those treated with the tyrosine kinase inhibitor of choice (15.2 vs 18.7 months.)** The statement that "Osimertinib helps to control brain metastases" in section 3.5 . implies that Osimertinib limits the progression of CNS metastases. Inferences are made those improvements in PFS (& % of events of CNS progression) in the Osimertinib subgroup of patients compared to the standard TKI are due to cerebral penetration. FLAURA has not demonstrated brain penetration - brain penetration data for osimertinib come from studies in monkeys. Further, **the presence of drug within the brain following penetration of the blood-brain- barrier does not necessarily equate to clinical efficacy**, which **remains to be demonstrated in humans** in this case. Girard N. Optimizing outcomes in EGFR mutation-positive NSCLC: which tyrosine kinase inhibitor and when? Future Oncol. 14(11),1117–1132 (2018).
Comment #4 (refers to ACD section 4)	Regarding the **OS analysis in the FLAURA trial, cross-over of patients is a significant confounder**: • A protocol amendment allowed patients who had been assigned to the erlotinib/gefitinib arm to cross over to open-label osimertinib BUT ONLY after confirmation of objective disease progression by blinded independent central review AND post-progression documentation of T790M mutation status by means of plasma or tissue testing • The blinded independent central review confirmation does not help for quick access to the subsequent treatment line potentially delaying treatment initiation • At time of amendment already about 7% of comparator arm patients had progressed, with no chance to cross-over The ERG demonstrated via the ITC, there was no statistically significant difference in overall survival between Osimertinib and Afatinib. In line with our comment #1 above, sequencing of osimertinib after first line TKI will have an impact on the OS across the first and second line therapies.
Comment #5 (refers to ACD section 3.10)	Regarding the point on **innovation**, the statement that Osimertinib will reduce the need for repeat bronchoscopic biopsies is not a substantial argument. Most patients with NSCLC require this procedure in order for a tissue sample of the tumor to be obtained for pathological purposes and importantly for histology. **The practice of obtaining tumor tissue is essential to the staging process and will still occur even in those patients suitable for receiving Osimertinib first line.** Comment was made by FLAURA investigators themselves in study publication that tissue-based analyses of resistance mechanisms will be necessary to fully characterize resistance to Osimertinib, so the need for repeat biopsies upon treatment failure will remain. In addition, with the implementation of the NHS Genomic Testing strategy, and the NHS Long Term Plan, the use of molecular diagnostics, through routine genomic testing will become an integral part of patient management across the UK with the ultimate aim of improving services and detection rates.

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

NICE National Institute for Health and Care Excellence

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	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced.
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	NCRI-ACP-RCP-RCR
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Comment number	Comments
	Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.

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1	In addition to its statistically and clinically significant benefit in extending PFS, and likely benefit in improving OS compared to existing first-line treatment options (i.e. gefitinib, erlotinib and afatinib), first-line osimertinib is a clinically more attractive treatment option for this patient population due to: a) its improved CNS penetration and reduced risk of CNS progression (publication of planned sub-group analysis of FLAURA data – Reungwetwattana et al. CNS response to osimertinib versus standard epidermal growth factor receptor tyrosine kinase inhibitors in patients with untreated EGFR-mutated advanced non-small-cell lung cancer. Journal of Clinical Oncology. DOI: 10.1200/JCO.2018.78.3118), and b) its improved tolerability, including reduced G1 and G2 skin toxicity, which impacts quality of life of patients on treatment. As per section 3.10 of the draft consultation document, the committee were unable to determine the effects of these factors, likely positive in favour of osimertinib, on the ICER, and thus they were disregarded, however these factors are important considerations that need to be included in the appraisal. Inclusion of osimertinib in the Cancer Drug Fund would provide a potential route for collecting data around these areas to enable a more informed analysis of the ICER for a future final determination.

Insert extra rows as needed

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Comments on the ACD received from the public through the NICE Website

Name	[redacted]
Notes	
Comments on the ACD:	
Has all of the relevant evidence been taken into account*?** Not enough consideration given to the burden of testing for 2nd line mutations (often whilst on ineffective but costly drugs). Burden on patients and also medical resources with increased need for radiology, biopsy and repeat EGFR testing. ***Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? Yes ***Are the recommendations sound and a suitable basis for guidance to the NHS?*** No. As above. More account needs to be taken of issues surrounding repeat testing and biopsy for second line mutations. This is not needed for osimertinib. ***Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?*** No	

Name	[redacted]
Notes	
Comments on the ACD:	
Has all of the relevant evidence been taken into account? yes ***Are the recommendations sound and a suitable basis for guidance to the NHS?*** Yes ***General comment*** I was a senior Lung CNS in the private sector when Osimertinib received its second and first -line licence for T790M and EGFR positive nsclc respectively. Based on the evidence, we started to manage our patients accordingly. There is no doubt it has been practice changing. Overall, this treatment has been a positive experience with limited in side effects generally and improved quality of life subsequently. I can think of one patient in particular who came to us after progressing on first line TKI, and was unable to complete further chemotherapy due to poor QOL related to side effects and progression. He had T790M but due to certain restrictions, was unable to have Osimertinib at his local provider. He presented to us as Performance status (PS) 3. We commenced Osimetinib treatment. Within 1	

month, he was PS 0 and back out working on his farm. He and his wife felt they were living again, as opposed to dying from the disease. Clinically, this drug provides a another excellent treatment, with apparently fewer side- effects and evidence of CNS penetration, in the growing arena of targeted treatments. This is an important and unfortunately growing, often younger population to that which is traditionally associated with a lung cancer diagnosis. However, prognosis can be just as challenging and quality of life equally as important.

Name	[redacted]
Notes	

Comments on the ACD:

General comment

I think this is a disappointing response, especially for our patients.

It is important to recognise that in the relevant trial of first line osimertinib, that patients in the control arm were able to cross over to open label osimertinib if T790M was found, and to treatments which are not standard of care within the NHS if T790M was absent, potentially giving them more treatment lines that applicable here and yielding a potential discrepancy between trial data and 'real world NHS data'.

I note that you correctly identify that afatanib does not feature in FLAURA. However, you can not conclude that afatanib is a better drug (based on LUX-lung 7) as the trial is not powered to look at this - therefore they have to be considered equivalent (in the face of an absence of statistically significant, adequately powered data), to say anything else is simply observational.

I was lead author on a poster presented at this year's British Thoracic Oncology Group annual meeting in Dublin (Missing the boat: real world analysis of second line osimertinib use across North West London – abstract from which can be accessed here: https://www.sciencedirect.com/journal/lung-cancer/vol/127/suppl/S1). The data reveals a number of potentially relevant real world data:

1) We demonstrated that the most commonly prescribed EGFR TKI across 5 hospitals in NW London was gefitinib, largely due to a better tolerability profile, with only the fittest patients seemingly being considered for afatinib. Out of 52 patients identified through the chemotherapeutic management system, ARIA, 44 were either prescribed gefitinib or erlotinib first line (39 gefitinib, 5 erlotinib), and 8 were commenced on afatinib. So while there may be some observational data that afatinib may be associated with a longer mPFS, it is not what is used most as first line in this longitudinal real world study.

2) Of these 52 patients, 26 progressed on first line treatment within the study window (01.01.16 through to 30.09.18). Assuming a T790M rate of 60%, as per the NICE and FDA submissions for second-line use, one would expect around 15 patients to be eligible for second line osimertinib use. On review of case notes, we identified that on progression, all patients were ECOG 0-2. We also found that 11 patients (42% of those who progressed) did not undergo any form of T790M testing at all (3 patients were offered invasive biopsy but declined), for reasons that were largely unclear. Just 7 patients (27% of all patients) went on to receive osimertinib. Although it would only be speculation to draw conclusions, you do have to wonder what the overall survival would look like in these patients if a) T790M was a reflex test and b) if patients got up front osimertinib, negating the

need for an assessment of T790M on progression, and avoiding not only national variability, but also variability between neighbouring hospitals, in T790M assessment availability.

I do wonder if, rather than the less than 'real world' nature of a clinical trial (and clinical trial patients), whether our own, NHS wide data could be used. The cancer registration record could be used to identify patients, the SACT database would identify those who progress on first line therapy, what treatment they get next (if any active treatment is given), and crude survival could be calculated from the Spine, or other data sets. I so wonder what real world survival would look like, as I am not convinced (on account of crossover and non-conventional therapies in the control arm) are robust enough.

This is before considering those 'special' subgroups - the 1% of patients who present with T790M mutant cancer up front (de novo) and those with CNS disease, whereby you want a good CNS penetrant option (akin to alectinib for ALK-rearranged lung cancer).

Name	[redacted]
Notes	
Comments on the ACD:	
Comment on committee discussion	

I would agree with this real-life data. A UK network audit which included patients with performance status ranging from 0-2 reported a median OS of 15.6 months only for patients treated with either a first- or second-generation tyrosine kinase inhibitor. This data was presented at ELCC 2019 meeting.
Osimertinib is a more potent drug in common mutations (19/21) and is better tolerated. I would urge that the real-life data in consideration with the data provided by the company in the reassessment of this decision

ERG response (post ACM1)

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

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

ERG comments on AstraZeneca UK additional information provided following ACM1

Confidential until published

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CONTAINS ACADEMIC IN CONFIDENCE DATA

UNIVERSITY OF LIVERPOOL | LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

1 INTRODUCTION

Following the first Appraisal Committee Meeting (ACM1) for the National Institute for Health and Care Excellence (NICE) Single Technology Appraisal (STA) of the clinical and cost effectiveness of osimertinib for untreated epidermal growth factor receptor-positive (EGFR+) non-small cell lung cancer (NSCLC), AstraZeneca UK (the company) submitted additional information for consideration at the second Appraisal Committee Meeting (ACM2).

The additional information provided by the company comprises results from overall survival (OS) and progression-free survival (PFS) analyses for three subgroups of patients participating in the FLAURA trial, namely patients:

- who did not receive a subsequent tyrosine kinase inhibitor (TKI) following discontinuation of randomised therapy in the first-line setting
- of non-Asian ethnicity
- with Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) 1 at baseline.

NICE asked the Evidence Review Group (ERG) to provide a critique of these additional results.

2 CRITIQUE OF THE ADDITIONAL INFORMATION PROVIDED BY THE COMPANY AFTER ACM1

The original company submission included real world data (from the Systemic Anti-Cancer Therapy [SACT] dataset) that suggested that OS for patients with untreated EGFR-positive NSCLC was less than 24 months. However, the Appraisal Committee (AC) considered that, as (i) the company's cost effectiveness results and (ii) the company's estimate of the extension to life expectancy that would be achieved by patients treated with osimertinib were generated from FLAURA trial data, the assessment of osimertinib against the NICE End of Life criteria should also be made using data from the FLAURA trial. During ACM1, the AC reached the conclusion that, based on OS results from the standard of care (SoC) arm of the FLAURA trial, treatment with osimertinib for this indication did not meet the criteria necessary for osimertinib to be considered as an End of Life treatment.

Following ACM1, the company identified three subgroups of the FLAURA trial intention-to-treat (ITT) population that they considered were most representative of patients treated in the NHS. The company then presented NICE with OS results for each subgroup. The company's stated aim was to demonstrate that, for these patients, OS would be of a magnitude that would allow osimertinib to be considered as an End of Life treatment. The company states that, in contrast to the FLAURA trial ITT population, NHS patients do not routinely have access to second-line TKIs, they are predominantly of non-Asian ethnicity and, on average, have worse baseline performance status. The results from the company's FLAURA trial subgroup analyses can be summarised as follows:

- At the time of latest data cut-off from the FLAURA trial, median OS had not been reached in either the osimertinib or SoC arms, for any of the three subgroups.

- The company extrapolated available FLAURA trial OS Kaplan-Meier data from patients who had not received a second-line TKI. In the SoC arm, depending on the distribution chosen, mean OS varied between [redacted]. and [redacted]., and median OS varied between [redacted]. and [redacted]..

- OS at 12 months for patients of non-Asian ethnicity receiving SoC was [redacted]. compared to [redacted]. for the ITT population. This suggests that survival may be lower for patients of non-Asian ethnicity, but the difference is small; no statistical testing of the difference was undertaken.

- OS at 12 months for patients with ECOG PS1 in the SoC arm was [redacted]. compared with [redacted]. for the ITT population. This suggests that survival may be lower for patients with ECOG PS1; no statistical testing of the difference was undertaken.

The ERG did not have access to the FLAURA trial data and was, therefore, unable to verify results from the company analyses.

Assuming that the company's results are accurate, the ERG considers that they do not support the company position that osimertinib meets the NICE End of Life criterion that expected life expectancy for NHS patients is less than 24 months as the company's OS estimates are all greater than 24 months.

If results from the company's three subgroups are to be used to justify treatment with osimertinib meeting the NICE End of Life criteria, then the company must demonstrate that treatment with osimertinib is cost effective for these subgroups. The company did not present any incremental cost effectiveness ratios (ICERs) per quality adjusted life year (QALY) gained for these subgroups. This means that no assessment of cost effectiveness can be made. Even if the ICERs per QALY gained were presented for these subgroups, it is unclear how these could be used by NICE to make a recommendation for the population described in the final scope issued by NICE; each subgroup is linked to a single characteristic and there are no results for a subgroup that includes patients with all three relevant NHS patient population characteristics.

In summary, the ERG does not consider that the new evidence presented by the company changes the assessment of osimertinib as an End of Life treatment made by the AC during ACM1.