Friday, 19 July 2019

Mr Tim Irish
Vice chair
National Institute for Health and Care Excellence
10 Spring Gardens
London SW1A 2BU

Dear Mr Irish,

RE: Final Appraisal Determination – osimertinib for untreated EGFR mutation-positive non-small-cell lung cancer

AstraZeneca would like to appeal against the Final Appraisal Determination for the above-mentioned technology appraisal on the following grounds:

GROUND 1: IN MAKING THE ASSESSMENT THAT PRECEDED THE RECOMMENDATION, NICE HAS a) FAILED TO ACT FAIRLY OR b) EXCEEDED ITS POWERS

Ground 1.1: The Appraisal Committee's decision that the FLAURA trial should be the primary data source for determining the short life expectancy criterion disregards the reality for UK patients

Ground 1.2: The trial data relied upon by the Committee in support of FLAURA and its conclusion that life expectancy of patients with stage IIIb or IV non-small cell lung cancer exceeds 24 months is not reflective of the UK population

Ground 1.3: The evidence of the clinical experts in relation to life expectancy is unexplained and should not be preferred to other evidence

Ground 1.4: The Committee's reasons for rejecting the NCRAS data for the purposes of determination of life expectancy are unfair

Ground 1.5: The Committee's reasons for rejecting the sub-group analyses from FLAURA which reflect the characteristics of the real world UK population, when considering the application of the end of life criteria, are unfair.

Ground 1.6: The Appraisal Committee provides no conclusion in relation to the effectiveness of osimertinib compared with afatinib

GROUND 2: THE RECOMMENDATION IS UNREASONABLE IN THE LIGHT OF THE EVIDENCE SUBMITTED TO NICE

Ground 2.1: The Appraisal Committee's conclusions (i) that afatinib produces longer progression-free survival than erlotinib and gefitinib and (ii) erlotinib and gefitinib cannot be assumed to have equal efficacy with afatinib, are not established by the reasons given.

Ground 2.2: The Appraisal Committee's statement that the clinical experts advised that afatinib would usually be the first line TKI offered to patients is unsubstantiated and does not reflect the available evidence

Ground 2.3: The Appraisal Committee's decision to rely on data from the FLAURA trial for the purposes of determining the life expectancy of patients with EGFR-positive NSCLC, despite recognising that the FLAURA population "*may be in better health than people with stage IIIb or IV NSCLC in the NHS*", is unreasonable

INTRODUCTION

Osimertinib is a third generation, irreversible, oral epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI).

Activating mutations in EGFR (EGFRm) are present in an estimated 12% of patients with advanced NSCLC with adenocarcinoma histology. These mutations inhibit apoptosis and promote tumour cell survival. Inhibiting the tyrosine kinase activity of these mutated forms of EGFR can block the associated upregulated survival and proliferation pathways and has therefore become an important treatment strategy. First generation EGFR TKIs (erlotinib and gefitinib) and second generation EFGR TKIs (afatinib) are currently considered standard of care for patients with EGFRm NSCLC in the first line setting.

However, most patients who respond to therapy ultimately develop disease progression after approximately 9-14 months and some 30% of patients with EGFRm NSCLC demonstrate no objective response to first and second generation EGFR TKIs. Patients whose disease progresses on standard of care have limited options and approximately 20-30% do not receive any subsequent therapy; of the remaining patients, around half will test positive for the T790M mutation and be eligible for osimertinib second line and half will receive chemotherapy.

In addition to sub-optimal survival outcomes, first and second generation EGFR TKIs are associated with adverse effects, including skin rashes and diarrhoea, which are caused by the inhibition of wild type EGFR in skin and gut. In addition first and second generation EFGR TKIs penetrate the blood brain barrier poorly and may therefore have limited effect against metastases in the central nervous system (CNS). This is particularly important in view of the fact that patients with EGFRm NSCLC have a higher incidence of brain metastases compared with those patients who have wild type EGFR tumours, with limited treatment options and poor prognoses.

Osimertinib is structurally and pharmacologically different from the first and second generation EGFR TKIs. It was specifically developed to have:

- Improved tolerability through reduced inhibition of wild type EGFR;
- Increased progression free survival through high selectivity for EGFRm and preserved efficacy against T790M EGFRm (a major mechanism for acquired resistance to TKIs); and
- Greater CNS efficacy as a result of improved penetration through the intact blood brain barrier.

Its current authorised indications are as monotherapy for

> "*the first-line treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating epidermal growth factor receptor (EGFR) mutations.*
>
> *the treatment of adult patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC*".

Osimertinib was granted a marketing authorisation by the European Commission on 1 February 2016. The indication under consideration in this technology appraisal (the first of those listed above) was approved by the European Commission on 7 June 2018, following a positive opinion by the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) on 26 April 2018.

PROCEDURAL HISTORY OF THE APPRAISAL

November 2017	Osimertinib referred to NICE for single technology appraisal
March 2018	Final scope issued
7 June 2018	European Commission approves use of osimertinib as first-line treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating epidermal growth factor receptor (EGFR) mutations.
5 September 2018	Submission of evidence by AstraZeneca
14 November 2018	ERG report prepared by Liverpool Reviews and Implementation Group (LRiG)
20 March 2019	The first meeting of the Appraisal Committee
12 April - 9 May 2019	Consultation on Appraisal Consultation Document (ACD)
23 May 2019	Second meeting of the Appraisal Committee
30 June 2019	Final Appraisal Determination (FAD) issued to consultees and commentators.

EGFR MUTATION-POSITIVE NON-SMALL-CELL LUNG CANCER: BACKGROUND INFORMATION

AstraZeneca refers to its original submission dated 5 September 2018 in this appraisal. While a summary is provided below, this is not intended to replace the details originally supplied to NICE.

Lung cancer is one of the commonest cancers and NSCLC is the commonest form of lung cancer, accounting for around 80% of cases. It is typically asymptomatic in the early stages, with the result that presentation and diagnosis is often delayed. An estimated 70% of lung cancer patients are not diagnosed until they have locally advanced or metastatic disease (stage IIIb or stage IV) which is associated with debilitating symptoms and adverse effects on quality of life. CNS metastases are present in some 20-25% of patients at the time of diagnosis and 40% of patients will experience metastatic disease in the CNS during the course of their illness.

Survival rates for patients with lung cancer remain poor as compared with other cancers.

- The Royal College of Physicians National Cancer Audit for 2017 (which addresses patients diagnosed in 2016) stated that the 1 year survival for patients with stage III disease was 42.5% and for patients with stage IV disease was 15.5%.

- While survival rates have increased almost everywhere in Europe:

    - Mortality from lung cancer in the UK is higher than in the four other largest countries in the EU (France, Germany, Italy and Spain)[1]; and

    - The chances of survival in the UK at 5 years after diagnosis are 4% lower than the EU average and exceed survival rates in only one other EU country, Bulgaria[2] .

Clinically relevant tumour mutations are important indicators of survival outcomes and are used to guide targeted treatment decisions. Mutations in EGFR fall into this category and, as explained above EGFRm therefore constitutes an important therapeutic target.

[1] Data from WHO cancer mortality database up to 2013 (the most recent data available) http://www-dep.iarc.fr/WHOdb/WHOdb.htm

[2] EUROCARE, database 5, 2014. Available at http://www.eurocare.it/Database/tabid/77/Default.aspx

Grounds of Appeal

Ground 1a: In making the assessment that preceded the recommendation, NICE has: failed to act fairly or exceeded its powers

1.1. <u>Ground 1.1: The Appraisal Committee's decision that the FLAURA trial should be the primary data source for determining the short life expectancy criterion disregards the reality for UK patients</u>

The threshold values for the determination of cost-effectiveness are modified in cases which satisfy the end of life criteria (as stated in NICE's Guide to the Methods of Technology Appraisal at paragraph 6.2.10) namely:

- *the treatment is indicated for patients with a short life expectancy, normally less than 24 months and*

- *there is sufficient evidence to indicate that the treatment has the prospect of offering an extension to life, normally of a mean value of at least an additional 3 months, compared with current NHS treatment.*

In addition, the Appraisal Committees will need to be satisfied that:

- *the estimates of the extension to life are sufficiently robust and can be shown or reasonably inferred from either progression-free survival or overall survival (taking account of trials in which crossover has occurred and been accounted for in the effectiveness review) and*

- *the assumptions used in the reference case economic modelling are plausible, objective and robust.*

The Appraisal Committee however concluded at paragraphs 3.10 and 3.11 of the FAD that osimertinib does not meet the short life expectancy criterion of the end-of-life criteria. The reason for this was that the Committee concluded that "*it was more appropriate to base the decision about estimating the life expectancy on the FLAURA data which the company had used in the economic model*" (paragraph 3.10 of the FAD). **This conclusion fails to recognise clinical reality in the UK and is therefore unfair:**

a) <u>NICE's procedures do not require the Committee to use the same data for both the assessment of cost-effectiveness and eligibility for the end of life criteria</u>

The determination of cost-effectiveness and eligibility for the end of life criteria involve different assessments and are conducted for different purposes.

- The assessment of cost effectiveness requires detailed consideration of the magnitude of actual benefit measured against cost in the context of sophisticated economic modelling. The amount of assessed benefit will always be relevant in this context.

- In contrast, eligibility for the end of life criteria is a binary "*yes*" or "*no*" decision. In the context of extension to life, as long as the evidence is sufficient to indicate that the treatment has the prospect of offering an extension to life, normally of a mean value of at least an additional 3 months, it is irrelevant whether the estimate (and it can only be an estimate) is 3.1 months or 30 months.

In the context of these differences, **NICE's methods or procedures at no point specify that the same data should be used for both assessments** and a purposive approach to the interpretation of NICE's end of life criteria requires that different data are used in situations where the trial data on, for example, the short life expectancy criterion, do not reflect that of the relevant UK population.

For completeness, AstraZeneca recognises that where it is appropriate to base a conclusion on the short life expectancy criterion on Real World evidence from the UK, rather than data from a randomised controlled trial, then it will also be necessary to consider whether the trial data on efficacy may also require some adjustment in the context of the extension to life assessment - and also potentially in the economic model for the purposes of cost effectiveness. The fact that such adjustments may be needed is not a reason to insist on using the trial data for both cost-effectiveness and end of life assessments if the trial data do not accurately reflect clinical reality in the UK in specific key areas (such as the overall patient experience and access to treatments outside the controlled periods of the study).

In the context of FLAURA, AstraZeneca considered this issue through assessment of sub-groups more closely reflecting the UK population with stage IIIb or IV lung cancer, and **provided evidence that the benefit seen in such patients was likely to be similar to that in the ITT population**.

b) <u>NICE has used different data for the assessment of cost-effectiveness and end of life in other appraisals</u>

In other appraisals, the Appraisal Committee has been willing to adopt a flexible approach and has, in appropriate cases where the clinical trial data do not reflect the life expectancy of UK patients, **been willing to use different evidence for assessments of cost effectiveness and eligibility for the end of life criteria**. By way of example:

- TA509: pertuzumab with trastuzumab and docetaxel for treating HER2-positive breast cancer

  The principal clinical trial used for the purpose of the cost-effectiveness assessment was the CLEOPATRA study. Mean overall survival in the control arm (trastuzumab and docetaxel alone) was 40.8 months. However it was noted that the trial population in CLEOPATRA may have had a better prognosis than UK patients. The manufacturer therefore provided survival estimates of 24-36 months for UK patients receiving trastuzumab and docetaxel. The Appraisal Committee seems to have accepted these estimates in the context of the end of life criteria, noting:

  "*The Committee acknowledged that the wording referring to the end-of-life criteria is **deliberately expressed to provide committees with discretion** required when they consider it reasonable to apply a weight to the QALYs gained in circumstances where one of the criteria does meet the exact level described in the policy*".

- TA487: venetoclax for treating chronic lymphocytic leukaemia

  The clinical trial data which formed the basis for the marketing authorisation comprised one phase I and two phase II single arm studies. For the purposes of economic modelling, the manufacturer conducted an indirect comparison using the control arm of another study investigating other treatments. However, for one subgroup of patients the control arm in the other study produced a mean OS of some 4 years. The Appraisal Committee nevertheless rejected this estimate on the basis that it did not reflect UK treatment pathways. Ultimately it agreed that it could **consider estimates of best supportive care informing the model separately from those informing the short life expectancy end-of-life criterion**.

- TA458: trastuzumab emtansine for treating HER2-positive advanced breast cancer after trastuzumab and a taxane

  The pivotal EMILIA trial provided a mean life expectancy of 25.1 months for the control arm. However, the Appraisal Committee discussed comparators which were not involved in EMILIA and therefore considered other sources of information on life expectancy. A previous clinical trial reported in the literature gave a mean life expectancy of 18.8 months and modelling of data produced a figure of 30.4 months. The Committee stated:

  "*The Committee found it difficult to evaluate this conflicting evidence, but after review of the median survival from several trials of lapatinib plus*

capecitabine, it was prepared to accept that trastuzumab emtansine fulfilled this criterion".

At paragraph 3.11, the FAD states that the Committee discussed whether any flexibilities should be applied in applying the end of life criteria to osimertinib.

> *"The committee concluded there were no exceptional circumstances that demanded additional flexibility in applying the end-of-life criteria (such as to ensure continued access to a highly effective treatment option that was perceived by patients and clinicians to be standard of care, in circumstances where access had been enabled years ahead of NICE publishing any guidance on the technology). The committee also concluded that although the company's economic model suggests that the overall survival gain may potentially be high…the immaturity of the trial data means there is considerable uncertainty about the magnitude of the benefit".*

However, in deciding that no flexibility should be applied in this case, there is no indication that the Committee has taken into account the uncertainties in relation to life expectancy on standard care and the **reality that UK patients with stage IIIb and IV NSCLC have a life expectancy of less than 24 months**, as well as the innovative nature of osimertinib and its beneficial effects on brain metastases as well as the **predicted magnitude of survival benefit** (much greater than 3 months). Overall it is difficult to understand why a flexible approach is accepted in some cases, but not in others and the failure to provide adequate explanations in relation to this issue in this case means that **decision making appears arbitrary and unfair**.

c) <u>Overall survival in the standard of care arm of the FLAURA trial is likely to over-estimate survival in real world UK patients</u>

The Committee concluded that the median overall survival in the standard of care arm of the FLAURA trial was 31.54 months and estimated mean overall survival was 44.39 months. However, as explained in AstraZeneca's response to consultation on the ACD, the ITT population in FLAURA shows **important differences** from the real world patients who would be treated for stage IIIb and stage IV NSCLC in the UK. In particular:

- In FLAURA, a higher proportion of patients received any subsequent treatments compared with what is observed in the SACT dataset

- As recognised at paragraph 3.2 of the FAD, many subsequent treatments used in the trial are not routinely used in the NHS and this will inevitably impact survival.

- The ITT population in FLAURA had high rates of second line treatment with 1st /2nd generation TKIs (afatinib, erlotinib or gefitinib) or with osimertinib, which is not routine NHS practice and seems likely to explain, at least in part, the higher predicted life expectancy as compared with other studies (e.g. LUX-lung 7 and Archer 1050, considered below).

- FLAURA included a large number of patients recruited from Asian centres (62%) who are not typical of the UK population and have a longer life expectancy than non-Asian patients with NSCLC.

- Patients eligible for osimertinib treatment in real world UK clinical practice tend to have worse performance status (i.e. are less well) than those recruited into FLAURA and therefore worse prognosis.

In these circumstances the **overall survival in the standard of care arm in FLAURA is likely to over-estimate survival in real world UK patients** with stage IIIb and IV NSCLC who would receive treatment with osimertinib. The fact that FLAURA is likely to over-estimate survival in the standard of care arm is consistent with the fact that other studies in stage IIIb and IV NSCLC patients (albeit still conducted in patients who are less unwell than those who would receive treatment in the UK) produce estimates of PFS and OS that are materially less than those seen in the FLAURA SoC arm and close to the 24 month threshold.

d) <u>The assessment of life expectancy for the purposes of the end of life criteria should reflect the relevant UK population</u>

The **assessment of the short life expectancy criterion should be based on the relevant UK population**. Given that only 11 of the 556 participants in the FLAURA trial were UK patients (less than 2%), it would be unfair to base decisions on access to medicines in the UK on life expectancy in other countries, and we do not understand NICE's procedures to suggest otherwise.

Phase III clinical trials are conducted internationally and it is unrealistic to expect that trial design should focus on the UK. However, life expectancy may vary in the various trial centres due to factors including ethnic differences and variability in "standard of care", such as subsequent treatments. Furthermore, it is generally accepted that clinical trial participants have better health than patients treated in the "real world".

The lack of fairness which may result from use of international trial data to determine life expectancy in UK patients is increased in cases where, as here, the standard treatment and experience of UK patients in clinical practice is likely to be different to that of patients in other countries, widening the gap between "Real World" experience in the UK and that of participants in international clinical trials. Insistence

on applying international data in these circumstances further disadvantages UK patients by inappropriately excluding new therapies, with the result that life expectancy in the UK falls still further behind that of patients with the same condition in other countries. A conclusion that results in decisions on access to treatment in the UK being based on life expectancy of patients in Japan, the United States and South Korea is conspicuously unfair.

e) <u>The Committee's recognition that the patient population in FLAURA "may be in better health than people with stage IIIb or IV NSCLC in the NHS" has not been taken into account in the context of the end of life criteria</u>

We refer, under Ground 2 below to the fact that the Committee has recognised that patients in the FLAURA trial "*may be in better health than patients with stage IIIb or IV NSCLC in the NHS*", and that in these circumstances it is unreasonable to base conclusions on life expectancy for the purposes of the end of life criteria on the population recruited to FLAURA without proper consideration of these factors.

However, this decision also raises matters of procedural fairness. After recognising that UK patients have worse health than the participants in FLAURA and noting the particular concerns of the clinical experts, the Committee should have taken these matters into account when considering the end of life criteria.

Nevertheless, **despite recognising the issues at paragraph 3.2, there is no indication in the FAD that the Committee took them into account** in the context of the assessment of life expectancy for the purposes of the end of life criteria in the relevant patient population in the UK, and the wording of the FAD suggests that they were not taken into account. Paragraph 3.2 of the FAD states that despite the concerns expressed by the clinical experts, they concluded "*that the evidence from FLAURA was broadly generalisable to NHS clinical practice*" and that "*the Committee agreed with the clinical experts*". However, when the short life expectancy criterion under the end of life are addressed at paragraph 3.10, the Committee's conclusions regarding FLAURA are recorded as being that the trial was *generalisable*, without qualification.

1.2. <u>Ground 1.2 The trial data relied upon by the Committee in support of FLAURA and its conclusion that life expectancy of patients with stage IIIb or IV non-small cell lung cancer exceeds 24 months is not reflective of the UK population</u>

At paragraph 3.10 of the FAD, the Committee relies upon the LUX-Lung 7[3] and Archer 1050[4] trials in support of its use of data from the standard of care arm of

[3] Park K et al. Lancet Oncol 2016; 17: 577
[4] Wu Y-L et al. Lancet Oncol 2017; 18: 1454

FLAURA for the purposes of determining life expectancy in the context of the end of life criteria and its conclusion that median overall survival exceeds 24 months.

Both LUX-Lung 7 and Archer 1050 produced estimates of survival which are materially less than FLAURA and close to the 2 year threshold.

- The LUX-Lung 7 trial compared afatinib with gefitinib and generated estimates of median overall survival of 27.9 and 24.5 months respectively. However, the study was predominantly conducted in Asia (Asian patients typically have a longer life expectancy than non-Asian patients with similar stage disease, as identified in NICE's appraisal of afatinib TA444) and high rates of subsequent treatments (73% in the case of afatinib and 77% in the case of gefitinib) which would not be available in the UK and therefore over-estimate survival in comparable UK patients.

- The Archer 1050 trial compared dacomitinib with gefitinib. The estimate of median overall survival associated with gefitinib in this trial was 26.8 months. However the trial excluded patients with brain metastases, which are associated with poor median overall survival and a high proportion (77%) of participants were Asian. Thus, the life expectancy of patients in this study are typically considered to have a longer life expectancy than patients in the UK.

In determining whether a product is eligible for the end of life criteria, it is clearly essential that the UK patient population in whom the product would be used is considered. It must be inappropriate to consider survival in a non-UK population, who may have access to different treatments or may be less unwell in the context of this assessment and such an approach disadvantages UK patients and is conspicuously unfair.

Therefore, while LUX-lung 7 and Archer 1050 confirm that the survival expectation in the standard of care arm of FLAURA was longer than is usual in stage III and IV NSCLC patients, for the reasons given, the survival expectation is still likely to exceed the typical UK patient eligible for osimertinib treatment and **reliance upon such data for the purposes of the end of life criteria is unfair**.

1.3. Ground 1.3: The evidence of the clinical experts in relation to life expectancy is unsubstantiated and should not be preferred to other evidence

AstraZeneca used a figure of 62% for the proportion of patients receiving standard care who are alive after 2 years for the purposes of the economic model and the assessment of cost effectiveness. This figure and the data for benefits associated with osimertinib treatment were taken from the FLAURA trial.

One of the clinical experts, [redacted] was subsequently contacted by the ERG by telephone in relation to the survival data and asked to confirm his responses by email, provided on 10 December 2018. This note comprises a table listing survival percentages at 1,2, 5 and 10 years and marked with [redacted] observations in red. These observations are limited to replacement figures, indicating disagreement with those proposed or the word "*agree*". In relation to the figure of 62% for survival on standard care at 2 years, [redacted] wrote "*agree*".

It is however unclear what evidence [redacted] answer was based on and whether this is typical of a UK population of patients with stage IIIb or IV NSCLC, or if he was simply confirming the data reported by FLAURA. If [redacted] answer was intended to reflect the UK population, this may reflect his own experience at a highly specialised centre, rather than the position across the wider UK. Furthermore, [redacted] was not asked, so far as AstraZeneca is aware, to comment on the SACT data or how this reflects his own clinical experience.

Overall, reliance on the unexplained one word answer in a table submitted by [redacted] in December 2018, rather than the NCRAS data on life expectancy, is unfair. Such an approach **lacks transparency, may misrepresent his views and is inconsistent with scientific standards of evidence hierarchy**.

1.4. Ground 1.4: The Committee's reasons for rejecting the NCRAS data for the purposes of determination of life expectancy are unfair

The Committee reasons for rejecting the data from the National Cancer Registration and Analysis Service (NCRAS) for the purposes of determination of life expectancy were that: afatinib was not available for most of the time the NCRAS data were collected; and the Committee concluded that the Registry data were difficult to compare directly with the FLAURA data because possible confounders in the Real World population (e.g. co-morbidities) were not taken into account. However **neither of these explanations provides a fair justification for rejecting the NCRAS data**.

a) The Committee's statement that "*afatinib…..was not available for most of the time the NCRAS data were collected*" is not understood. Afatinib has not demonstrated significant improvements in OS over erlotinib/gefitinib, and so the fact the afatinib was not in the registry should not have influenced the results to a great extent. Even if the numerical 3-month benefit for afatinib vs gefitinib in LUX-Lung 7 were incorporated into the life expectancy of patients in the registry (less than 17 months for patients with PS0/1), the overall survival would remain much less than 24 months.

b) The Committee's conclusion that the NCRAS data were difficult to compare directly with the FLAURA data because possible confounders such as co-morbidities, in the real-world population were not taken into account, is not

understood. A key feature of real-world evidence, as compared with clinical trial data, is that the patients who participate in clinical trials are often healthier than real-world patients because participants with co-morbidities are excluded and the presence of co-morbidities is an important factor which improves the applicability of the data to clinical practice.

In this case, however, as shown by the list of inclusion and exclusion criteria for patients recruited in FLAURA, summarised in table 2 of AstraZeneca's original submission in this appraisal, patients with co-morbidities were not in general excluded from participation in FLAURA. However, a key difference between the NCRAS data and FLAURA was the fact that data from UK patients captured by NCRAS showed that these were less well, with worse performance status as compared with participants in FLAURA. This simply reflects the real world condition of patients with stage IIIb and stage IV NSCLC in the UK and supports reliance on the NCRAS data rather than rejection of this evidence.

c) Finally, while the Committee expresses the view at paragraph 3.10 that "*it considered there were several reasons why it was not appropriate to use [the real world evidence from NCRAS] as the primary data source in isolation for its decision-making on the short life expectance criterion*", there is no indication in the FAD that this evidence was taken into account at all whether in determining whether life expectancy in UK patients is less than 24 months or in considering flexibility to the application of the threshold. If the NCRAS evidence was taken into account by the Committee, no explanation of its consideration is provided. On either basis the approach of the Committee is procedurally unfair.

1.5. Ground 1.5: The Committee's reasons for rejecting the sub-group analyses from FLAURA which reflect the characteristics of the real world UK population, when considering the application of the end of life criteria, are unfair.

In response to consultation on the ACD, AstraZeneca provided credible evidence of life expectancy of patients with stage IIIb and IV NSCLC in the UK, obtained through NCRAS which showed a **median overall survival from the date of treatment initiation of 15.8 months (95% CI: 14.1-17.2), substantially below the 24 month limit specified in the end of life criteria**. AstraZeneca then used these data to identify sub-groups in FLAURA which resembled the UK population more closely than the ITT population in the trial. These data confirmed:

- Patients in the standard of care arm of FLAURA who did not receive subsequent treatments (consistent with UK NCRAS data) had reduced life expectancy compared with the ITT population;

- Patients in the standard of care arm of FLAURA who had worse performance status (consistent with UK NCRAS data) had reduced life expectancy compared with the ITT population; and

- Non-Asian patients in the standard of care arm of FLAURA (closer to the UK NCRAS data) had reduced life expectancy compared with the ITT population

The Committee however rejected the sub-group analyses (paragraph 3.11). Its reasons for doing so are unfair:

a) The Committee noted that the Cancer Drugs Fund clinical lead's nominated deputy had said that there were gaps in the NCRAS data which meant that this evidence should be interpreted with caution.

b) The Committee stated that subgroups in the analyses had not been combined to calculate a value for mean or median overall survival which added substantial uncertainty to interpreting the results because it was not possible to determine the degree of overlap between the subgroups.

However, as stated above, median overall survival in the subgroup from FLAURA who did not receive subsequent tyrosine kinase inhibitor treatment (consistent with UK practice) was estimated as [redacted] months, which is close to the 24 month threshold. Once the impact of worse performance status and non-Asian status is also taken into account, the life expectancy shown in the FLAURA data could potentially fall below 24 months, consistent with the NCRAS data provided by AstraZeneca in its original submission in this appraisal. The subgroups should therefore have been considered together with NCRAS and not in isolation.

The data provided to NICE in response to the ACD demonstrate the degree of overlap between the subgroups.

c) The Cancer Drugs Fund clinical lead's nominated deputy commented that "*many people do have more than 2 subsequent therapies after progression on an EGFR tyrosine kinase inhibitor*"

The basis for the Cancer Drugs Fund clinical lead's nominated deputy's comment is not stated and cannot be interrogated. It is unclear whether his comments were intended to be reflective of his own experience in his own centre or to have wider application, potentially in less specialised units.

Furthermore these views do not appear to be consistent with the view of the clinical expert, [redacted] who described current treatment pathways in his original submission to NICE:

"With 1st/ 2nd EGFR inhibitors as 1st line treatment. In patients who progress on these a repeat biopsy is taken. If this shows the cancer has become resistant due to a 2nd mutation in EGFR (T790M) the patient will change therapy to osimertinib.

In the absence of a biopsy or the demonstration of T790M on the biopsy the options are to continue the 1st line therapy beyond progression or switch to platinum doublet chemotherapy. In practice many patients are reluctant to change to chemotherapy in this setting and will continue their initial therapy".

Overall, while useful in the absence of robust data, unsupported expert opinion should not be preferred to observational data, particularly where, as here, expert opinion does not appear to be consistent and such an approach is **inconsistent with the generally accepted hierarchy of evidence**.

d) The Committee agreed that there was no conclusive evidence that ethnicity has an influence on overall survival and that other factors may be more influential

AstraZeneca does not suggest that ethnicity is the most important factor determining survival, but believes it is a factor to be taken into account.

This view is consistent with that of the same Committee when it considered afatinib for treating EGFR mutation positive locally advanced or metastatic NSCLC [TA310] and concluded that

"…although there was uncertainty about the underlying reason, on balance the ERG analysis showed that ethnicity had an impact on the effectiveness of afatinib in clinical practice, and that the effectiveness of afatinib in clinical practice in England would be best represented by clinical effectiveness data in a non-Asian group". (afatinib guidance para 4.5).

If the Committee considers that there is a reason why a different conclusion should be adopted in this appraisal, proper reasons should be provided and in the absence of such reasons, **inconsistency is unfair**.

1.6. Ground 1.6: the Appraisal Committee provides no conclusion in relation to the effectiveness of osimertinib compared with afatinib

At paragraph 1 of the FAD under the heading "*Why the Committee made these recommendations",* the Appraisal Committee criticises the data available for osimertinib on the basis that *"there is no direct evidence comparing osimertinib with afatinib, which may be more effective than erlotinib and gefitinib*".

While AstraZeneca believes that the Committee's conclusion that afatinib results in longer progression-free survival (PFS) than gefitinib and erlotinib is unreasonable (see Appeal point 2.1 below) we also believe the Committee's refusal to consider and/or rely upon an indirect comparison of osimertinib and afatinib conducted by the ERG is unfair.

a) Randomised controlled trials conducted to support regulatory submissions are large and take time. Inevitably treatment patterns will change during the period prior to the conclusion of a trial and it may become necessary to consider the comparative effectiveness of products, not in general use when a trial was commenced. In these circumstances, an indirect comparison is a sensible way to proceed. The Committee do not suggest otherwise.

b) At paragraph 3.4 of the FAD, the Committee refer to an exploratory indirect comparison of osimertinib and afatinib conducted by the ERG which "*suggested that osimertinib statistically significantly improved progression-free survival compared with afatinib, but showed no statically significant difference in overall survival*". However the Committee express no view in relation to the indirect comparison or give any reason for declining to rely upon it

In circumstances where an indirect comparison is likely to be necessary in considering any new medicinal product or indication, a conclusion that a head to head trial is required is unfair. In this case, an indirect comparison was provided to the Committee, who provided no reasons for declining to rely upon it and must therefore be assumed to have disregarded it when forming its conclusions or to have no reasons for refusing to use it.

Ground 2: The recommendation is unreasonable in the light of the evidence submitted to NICE

Ground 2.1: The Appraisal Committee's conclusions (i) that afatinib produces longer progression-free survival than erlotinib and gefitinib and (ii) erlotinib and gefitinib cannot be assumed to have equal efficacy with afatinib, are not established by the reasons given.

The Appraisal Committee's conclusions with respect to the effectiveness of the first and second generation TKIs, erlotinib, gefitinib and afatinib are as follows:

> "*The Committee concluded that there was evidence of improved progression-free survival with afatinib compared with gefitinib, and erlotinib and gefitinib cannot be assumed to have equal efficacy with afatinib*" (paragraph 3.4 of the FAD).

And strengthened still further in the following paragraph:

"*The Committee recalled that afatinib yields longer progression-free survival than erlotinib and gefitinib….*"(paragraph 3.5 of the FAD).

The Committee's reasons are stated at paragraph 3.4:

- The Cancer Drugs Fund (CDF) Clinical Lead stated that "*previous trials such as LUX-Lung 7, showed that afatinib statistically improved progression-free survival compared with gefitinib*";

- The clinical experts agreed that gefitinib and erlotinib are likely to have equal efficacy;

- 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 than erlotinib and gefitinib and they usually stayed on afatinib for longer;

- While LUX-lung 7 did not show a statistically significant increase in overall survival for afatinib compared with gefitinib, the clinical experts explained that LUX-lung 7 was not powered to show a difference in overall survival compared with gefitinib.

However the Committee's conclusions are **inconsistent, incorrect and/or fail to take into account important aspects of the evidence**:

a) Previous technology appraisal guidance relating to gefitinib, erlotinib and afatinib (particularly TA258 and TA310) concluded that:

> *"…. on balance afatinib is likely to have similar clinical efficacy to erlotinib and gefitinib*" (TA 310 para 4.8)

The only formal assessments of the effectiveness of these three products generated since completion of TA310 were those referenced by AstraZeneca in the submission and provided by the ERG in the current appraisal, both of which concluded that no differences between them have been established. No explanation for the Committee's decision to deviate from previous conclusions in these other appraisals has been provided, even though the attention of the Committee was drawn to them (both by the ERG and by AstraZeneca). Accordingly, it seems that the Committee has unreasonably disregarded these earlier analyses.

b) The ERG stated that "*no formal conclusion*" can be drawn from LUX-Lung 7:

> "*The LUX-lung 7 trial was designed as an exploratory phase IIb trial, to broadly explore the differences between afatinib and gefitinib. No formal hypotheses were defined. Median PFS by blinded independent*

assessment was similar in both arms at two different data-cuts (11 months with afatinib versus 10.9 months with gefitinib, in both instances). However the difference between arms was reported to be statistically significantly different (at both data cuts). As the company highlights (CS p36) the statistically significant HR appears to be a result of the late separation of the K-M curves after 12 months".

The important matters raised by the ERG have not however been addressed by the Committee in their interpretation of LUX-lung 7 and it must be assumed that these points and the ERG's views have been disregarded.

c) One of the investigators in the LUX-lung trial has confirmed that the data are not sufficient to claim superiority of afatinib over gefitinib:

"*We acknowledge that these data are not sufficient to claim superiority of afatinib over gefitinib (LUX-Lung 7 was an exploratory, not a superiority trial). Nevertheless, in view of the paucity of head-to-head data, we feel that the totality of the data presented are an important addition to the medical literature and should be considered by physicians when assessing treatment options for their patients*"[5].

In circumstances where one of the LUX-lung 7 investigators has himself concluded that the data are not sufficient to demonstrate superiority of afatinib over gefitinib, it is unreasonable to rely on the data for that purpose.

d) The fact that LUX-lung 7 was not powered to detect differences in overall survival means only that there is no evidence of an OS advantage and **afatinib must be considered equivalent to gefitinib** in this respect.

The ERG also considered the totality of clinical trial data other than LUX-lung 7.

- The ERG considered a network meta-analysis of trials limited to patients with advanced EGFRm NSCLC, performed by Batson et al[6] . The authors reported no difference in PFS (the only outcome considered) between the three TKIs, although they stated that they identified a trend in favour of erlotinib.

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[5] Park K. LUX-Lung 7: is there enough data for a final conclusion? Lancet Oncol 2016; 17(7): https://doi.org/10.1016/S1470-2045(16)30244-3

[6] Batson S et al. Tyrosine kinase inhibitor combination therapy in first-line treatment of non-small-cell lung cancer: systematic review and network. Onco Targets Ther. 2017 May 5;10:2473-2482. doi: 10.2147/OTT.S134382

- The ERG noted that the available trials were conducted in heterogeneous populations and that this also made comparison problematic.

The **totality of clinical trial data do not support a conclusion that afatinib is superior to gefitinib**.

e) The ERG's overall conclusion was that

> "…*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. There is no evidence to suggest that afatinib, erlotinib or gefitinib improves ORR or OS compared to another EGFR-TKI (and evidence is also lacking to show superior OS versus PDC [platinum doublet chemotherapy])*".

The Committee has seemingly disregarded the ERG's overall assessment in relation to the relative effectiveness of afatinib, gefitinib and erlotinib and the fact that it concluded that erlotinib and afatinib may both improve PFS compared with gefitinib.

f) The Committee's conclusion seems to assume, contrary to established scientific methods, that expert opinion (which is unexplained and unreferenced) should be given greater weight than clinical trial data.

The matters identified above have all been drawn to the attention of the Committee, most recently in AstraZeneca's response to the ACD. However the FAD includes no explanations for the Committee's decisions in respect of matters (a) - (f) above and the Consultation Response Document states merely

> "*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 compared with erlotinib and gefitinib. They also usually remained on afatinib for longer*."

The definitive conclusion of the Committee that "*afatinib yields longer progression-free survival than erlotinib and gefitinib…*" is **not therefore based on any reliable evidence and must accordingly be viewed as arbitrary and unreasonable**.

> **<u>Ground 2.2: The Appraisal Committee's statement that the clinical experts advised that afatinib would usually be the first line TKI offered to patients does not reflect the available evidence</u>**

At paragraph 3.1 the FAD states: "*The clinical experts explained that people would usually be offered afatinib based on the clinical evidence (see section 3.4)*".

At paragraph 3.4, the FAD states: "*The Cancer Drugs Fund Clinical Lead noted that afatinib is currently the most prescribed EGFR tyrosine kinase inhibitor in England for this population*".

Paragraph 3.10 of the FAD describes afatinib as "*the currently preferred and most prescribed EGFR tyrosine kinase inhibitor in England for this population*".

However, In his submission to NICE, one of the clinical experts, [redacted] stated "*It is recommended that all patients with lung cancer with a sensitising mutation in EGFR receive a 1st and 2nd generation EGFR inhibitors (gefitinib, erlotinib and afatinib) as 1st line of therapy. There is variation across the country and between clinicians as to which of these are used as preferred therapy*".

The statements in the FAD therefore appear to represent only the views of the Cancer Drugs Fund Clinical Lead and not the clinical experts and the overall conclusion, which disregards the variability in choice of EGFR TKIs across the country, including as a result of variable toxicities is unbalanced.

Ground 2.3: The Appraisal Committee's decision to rely on data from the FLAURA trial for the purposes of determining the life expectancy of patients with EGFR-positive NSCLC, despite recognising that the FLAURA population "may be in better health than people with stage IIIb or IV NSCLC in the NHS", is unreasonable

Under Ground 1 above, we have explained why the Appraisal Committee's approach to assessment of life expectancy for the purposes of the end of life criteria including the individual conclusions reached on specific points, is unfair. However, in addition to the lack of fairness in the approach to assessment of survival in standard of care patients, the overall conclusion by the Committee that it was appropriate to rely on unqualified data from the FLAURA trial for the purpose of determining the life expectancy of patients with Stage IIIb and Stage IV NSCLC, despite accepting that the FLAURA population may be in better health than people with stage IIIb or stage IV NSCLC in the NHS, without any adjustment to reflect the condition of UK patients, is unreasonable.

Conclusion

AstraZeneca requests that this appeal should be determined at an oral hearing and respectfully requests the Appeal Panel recommends the Appraisal Committee reconvenes to consider their initial decision on this technology.

Kind regards

Director of Market Access and Government Affairs

AstraZeneca UK