NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Osimertinib for treating metastatic EGFR and T790M mutation-positive non-small-cell lung cancer [ID874]

The following documents are made available to the consultees and commentators:

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

2. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   - AstraZeneca
   - Roy Castle Lung Cancer Foundation
   - British Thoracic Society
   - Royal College of Physicians

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

4. **Additional evidence provided by the company, AstraZeneca**
   - Appendix 1 clinical effectiveness analysis
   - Appendix 2 cost effectiveness analysis
   - Appendix 3 indirect comparison of osimertinib versus standard of care

5. **ERG response to the additional evidence provided by AstraZeneca**

6. **ERG exploratory analyses following company additional evidence**

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Osimertinib for treating locally advanced or metastatic EGFR T790M mutation-positive non-small-cell lung cancer

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

Definitions:

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 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 determination (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, 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.

Comments received from consultees

Consultee	Comment [sic]	Response
AstraZeneca	**Executive Summary** AstraZeneca does not agree that the summaries of clinical and cost effectiveness presented within the ACD are reasonable interpretations of the available evidence, in particular we disagree that: • *Osimertinib does not meet the criteria to be considered a life-extending, end-of-life treatment* • *Osimertinib is not a cost-effective use of NHS resources* Many of the issues highlighted by the Appraisal Committee and the ERG, leading to the negative recommendation in the ACD, relate to the immaturity of the evidence presented by AstraZeneca in the original manufacturer submission. Since our original submission more mature evidence from the phase I/II AURAext and phase II AURA2 studies has become available, based on a November 2015 data cut off (DCO), providing 6 months of additional evidence. In addition, a final, pre-planned, overall survival (OS) analysis of the IMPRESS trial, the placebo arm of which is used as the comparator arm in the health-economic model, has now been completed and used in our updated analyses. These updated data and associated analyses clearly demonstrate that patients with EGFRm T790M positive NSCLC meet the criteria for life expectancy (<24 months) and that osimertinib is highly likely to have at least a 3 month overall survival benefit in this population vs current standard of care. Importantly, the cost-effectiveness analysis in the original submission should be considered as being highly conservative given that over two-thirds (68%) of the osimertinib patients (AURA study populations) had failed at least 2	Comments noted. The committee noted the additional evidence submitted by the company. The committee concluded that because the estimates of overall survival were so immature and not sufficiently robust, and the uncertainty in the clinical- and cost-effectiveness data too great, it could not recommend osimertinib for routine use in the NHS for treating EGFR T790M mutation-positive NSCLC. However, The committee concluded that osimertinib met the criteria to be considered for inclusion in the Cancer Drugs Fund, and recommended osimertinib as an option for use within the Cancer Drugs Fund for people with EGFR T790M mutation-positive NSCLC whose disease had progressed after first-line EGFR TKI therapy if the conditions in the managed access agreement for osimertinib are followed. See section 4.19 of the FAD.

Consultee	Comment [sic]	Response
	prior lines of treatment for their advanced disease whereas all patients in the IMPRESS comparator cohort were treated at disease progression after only one line of prior therapy. Consistent with the NICE scoping guidance, and as the expected position of osimertinib in the treatment pathway is second-line, we have simplified the modelling to ensure the base case comparison is between EGFRm T790M positive NSCLC patients receiving either osimertinib or platinum doublet chemotherapy as 2nd line treatment after failing an initial EGFR-TKI. However, this comparison should continue to be considered as conservative as patients were only enrolled into the IMPRESS trial if they had responded to or had durable stable disease on the EGFR-TKI used as their initial treatment, whereas patients in the osimertinib studies were enrolled regardless of initial treatment response. In addition to this additional evidence, AstraZeneca has taken into account the main challenges and issues raised by the Appraisal Committee. In this response to the ACD using the updated modelling and health-economic analysis based on the more mature survival data we demonstrate that: *(i) Osimertinib is associated with a statistically significant survival benefit and therefore meets End-of-Life criteria* *(ii) Osimertinib is a cost-effective treatment option for patients who are likely to be seen in UK clinical practice with an ICER of £41,705 per QALY compared to platinum-doublet chemotherapy* A summary of the supporting evidence for each of the above statements is provided in the following pages. In light of the emerging evidence from the key studies, AstraZeneca does not agree that all of the relevant evidence has been taken into account in producing the ACD and therefore, the current recommendations are not a suitable basis for guidance to the NHS. ***[AstraZeneca submitted a detailed summary with appendices of new***	

Consultee	Comment [sic]	Response
	analyses which can be found in the committee papers]	

Comments received from clinical experts and patient experts

Nominating organisation	Comment [sic]	Response
British Thoracic Society	Has all of the relevant evidence been taken into account? Yes as far as we are aware. Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? Yes Are the provisional recommendations sound and a suitable basis for guidance to the NHS? Yes on the basis of cost, however the manufacturer should be encouraged to renegotiate access arrangements with NHS to make this important treatment affordable.	Comments noted. No action required.
Roy Castle Lung Cancer Foundation	We are very disappointed that the Appraisal Committee's preliminary decision is not to recommend Osimertinib in this indication. We do, however, welcome the ongoing nature of the appraisal process and hope that the Appraisal Committee will re-consider their decision and ensure that this important new technology is made available within the NHS at the earliest opportunity. We would remind the Appraisal Committee that patients with advanced lung cancer generally have a poor outlook. Osimertinib is	Comments noted. The committee considered the comments received at consultation and the additional evidence submitted by the company in response to consultation. The committee concluded that osimertinib met the criteria to be considered for inclusion in the Cancer Drugs Fund, and recommended osimertinib as an option for use within the Cancer Drugs Fund for people with EGFR T790M mutation-positive NSCLC whose disease had progressed after first-line EGFR TKI therapy if the conditions in the managed access agreement for osimertinib are followed. See section 4.19 of the FAD.

Nominating organisation	Comment [sic]	Response
	the first therapy shown to have benefits in EGFR T790M positive nsclc patients. As such, it represents a therapy option, for a very small number of clearly defined patients. It is an oral therapy and has a good side effect profile, as compared with conventional chemotherapy for nsclc. We welcome the willingness of the Appraisal Committee to review this decision, on the availability of the AURA3 study results (paragraph 5.1, indicates this may be available in June 2016) and hope this data will be available and dialogue will take place. We also welcome the opportunity to attend the second appraisal committee meeting for this therapy. On behalf of the lung cancer patients who would derive benefit from this therapy, we strongly urge dialogue between the Manufacturer, NICE and NHS England, to ensure that areas of uncertainty and cost issues are addressed. Advanced lung cancer remains a devastating disease for many. We hope that compromise and agreement can be reached and that the ultimate Final Appraisal Decision will be a positive recommendation. These patients do not have time to wait.	
Royal College of Physicians	1. Has all the relevant evidence been taken into account? – No	Comments noted. The committee considered the comments received at consultation and the additional evidence submitted by the company in response to consultation. The committee

Nominating organisation	Comment [sic]	Response
	The committee accepts the clinical importance and innovative nature of osimertinib in treating patients with T790M NSCLC, and comments on high response rates (66%), long duration of progression free survival (PFS 9.7 months) with longer duration of clinical benefit (as was demonstrated by an additional 1.6 months on treatment following disease progression) with an improved side effect profile compared to chemotherapy. However the grounds for not recommending Osimertinib were the lack of mature survival data (which is at least in part due to patients experiencing less events because of a more effective treatment than one might anticipate in a NSCLC patient population) and the uncertainty around the cost per QALY as a result. Demonstration of overall survival benefit with osimertinib is likely to be very difficult due to crossover and post progression treatment, in the chemotherapy arm, when the AURA 3 trial reports in 2017. There is indirect evidence of the survival benefit from historical data on patients with NSCLC who had a targetable mutation (EGFR, ALK or KRAS) and received an appropriate targeted therapy compared to those who did not. The retrospective study of more than a thousand patients demonstrated. It is unlikely that we will ever be able to demonstrate the true improvement in overall survival generated by osimertinib, and it is	concluded that osimertinib met the criteria to be considered for inclusion in the Cancer Drugs Fund, and recommended osimertinib as an option for use within the Cancer Drugs Fund for people with EGFR T790M mutation-positive NSCLC whose disease had progressed after first-line EGFR TKI therapy if the conditions in the managed access agreement for osimertinib are followed. See section 4.19 of the FAD.

Nominating organisation	Comment [sic]	Response
	disappointing that the committee remain unable to establish other means of appraising such a highly effective, well-tolerated innovative treatment.	
Royal College of Physicians	**2. Are the recommendations sound and a suitable basis for guidance to the NHS?** – No The NHS cannot afford to fund every treatment regardless of cost and a key driver in healthcare is the need to deliver more effective personalised medicine. The recommendations are not sound and do not support the efforts of the lung cancer research community and patients who have participated in clinical trials in order to develop personalised treatments for a well-defined population of lung cancer patients who gain maximum benefit from therapy. Osimertinib leads the way in the field of personalized therapy, as has been acknowledged by the international regulatory authorities when it was granted accelerated approval by the FDA and recommended by the EMA's accelerated assessment, based on tumour response rates and duration of response (not survival).	Comments noted. The committee considered the comments received at consultation and the additional evidence submitted by the company in response to consultation. The committee acknowledged that there were still uncertainties with the utility estimates used in the model and that the largest uncertainty was related to robustly estimating overall survival with very immature data, which could affect the ICER and should be taken into account. The committee concluded that osimertinib met the criteria to be considered for inclusion in the Cancer Drugs Fund, and recommended osimertinib as an option for use within the Cancer Drugs Fund for people with EGFR T790M mutation-positive NSCLC whose disease had progressed after first-line EGFR TKI therapy if the conditions in the managed access agreement for osimertinib are followed. See section 4.19 of the FAD.

Nominating organisation	Comment [sic]	Response
Royal College of Physicians	3. Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity? – Yes There are some older patients who may not suitable for platinum based doublet chemotherapy who would be prevented from accessing an effective therapy by this decision. In summary, osimertinib is a therapy which is innovative and extremely effective, as is demonstrated by a number of measures of clinical outcome. It may well be that the time has arrived to re-examine the way in which we assess targeted therapies within this area of rapid development and to recognize that true improvement in overall survival may not demonstrable. We hope that these comments are helpful in reaching a final decision.	Comments noted. The committee concluded that osimertinib is innovative, but there were no additional benefits associated with this treatment that could not be captured in the economic analysis. See section 4.16 of the FAD.

Comments received from commentators

None

Comments received from members of the public

Role*	Section	Comment [sic]	Response
NHS Professional	1	I agree that the control arm of IMPRESS is a good comparator. This drug looks like a blockbuster in EGFR mutation positive lung cancer. At ELCC meeting this year some very impressive first line data was prefented from AURA. The FLAURA trial (first line) has completed accrual and we await results. THis drug is highly inovative. I have experience of using it in compassionate use and trials. As a 3rd gen EGFR inhibitor, wild type activity is minimised. As a result this is much better tolerated than 1st gen TKI's. In addition IGFR activity was rationally designed out (unlike rocelitinib). There is emerging evidence of activity in leptomeningeal disease (huge unmet need in EGFR mutation positive lung cancer). The pooled data from AURA and AURA 2 look very impressive. mOS not reached, more than 6 month greater PFS than IMPRESS (5 vs 11 m). I am a clinician with lots of trial experience and the shape of the OS KM curve is such that it is inconcievable that the mOS will not exceed 3 months compared to IMPRESS control arm. We currenly have no targeted options for NHS patients who develop acquired resistance T790M. I really do think this drug should be made available even if only through the CDF. I think it should be considered to meet end of life criteria for the reasons outlined	The committee concluded that osimertinib is innovative, but there were no additional benefits associated with this treatment that could not be captured in the economic analysis. See section 4.16 of the FAD. The committee considered the comments received at consultation and the additional evidence submitted by the company in response to consultation. The committee acknowledged that there were still uncertainties with the utility estimates used in the model and that the largest uncertainty was related to robustly estimating overall survival with very immature data, which could affect the ICER and should be taken into account. The committee concluded that osimertinib met the criteria to be considered for inclusion in the Cancer Drugs Fund, and recommended osimertinib as an option for use within the Cancer Drugs Fund for people with EGFR T790M mutation-positive NSCLC whose disease had progressed after first-line EGFR TKI therapy if the conditions in the managed access agreement for osimertinib are followed. See section 4.19 of the FAD.

* When comments are submitted via the Institute's web site, individuals are asked to identify their role by choosing from a list as follows: 'patent', 'carer', 'general public', 'health professional (within NHS)', 'health professional (private sector)', 'healthcare industry (pharmaceutical)', 'healthcare industry'(other)', 'local government professional' or, if none of these categories apply, 'other' with a separate box to enter a description.

Role*	Section	Comment [sic]	Response
NHS Professional	1	We the undersigned wish to express our disagreement with proposed guidance for osimertinib (GID-TA10022) 	

Role*	Section	Comment [sic]	Response
	2	The argument that the 3 month overall survival hurdle has not been reliably met and that the drug should not be considered within the end of life criteria is difficult to justify. The response rates and progression free survival were sufficiently strong to justify the designation of osimertinib as a promising innovative medicine and open an Early Access to Medicine Scheme. The data as to tumour control is relatively robust. All clinical experts agree this would be given as an additional treatment option, with platinum doublet chemotherapy been used afterward for patients who could tolerate it. Data both from EGFR mutants with the 1st and 2nd generation EGFR inhibitors, from other NSCLC patients with molecular abnormalities such as ALK fusions suggests the ability to target the tumour with a specific inhibitor is associated with a prolonged survival when compared to patients who can not access the drug. The suggestion that as the drug has only been used since 2013 and few events have been seen (due to the efficacy of the drug) means that statistically we can not be sure the survival benefit will exceed 3 months does not take account of what we know about this disease and global clinical opinion. As lung oncologists we strongly believe that adding in an effective drug that on average gives 9 months to 12 months of disease control will be associated with at least a 3 month improvement in survival. The experience of using this drug in clinical practice strongly mirrors that in the trials with patients responding well, quickly with an improvement in tumour related symptoms and with minor toxicity.	Comments noted. The committee noted the additional evidence submitted by the company. The committee concluded that because the estimates of overall survival were so immature and not sufficiently robust, and the uncertainty in the clinical- and cost-effectiveness data too great, it could not recommend osimertinib for routine use in the NHS for treating EGFR T790M mutation-positive NSCLC. See section 4.18. However, The committee concluded that osimertinib met the criteria to be considered for inclusion in the Cancer Drugs Fund, and recommended osimertinib as an option for use within the Cancer Drugs Fund for people with EGFR T790M mutation-positive NSCLC whose disease had progressed after first-line EGFR TKI therapy if the conditions in the managed access agreement for osimertinib are followed. See section 4.19 of the FAD.

Role*	Section	Comment [sic]	Response
	3	The opinion fails to take sufficient account of the innovative nature of this drug. This is the 1st time we have been able to track the emergence of resistance to therapy in a cancer and target it effectively in a scientific manner. In addition we have robust data to support the use of circulating tumour DNA to detect the emergence of resistance. Both of these are tools that show us the way that not only lung cancers, but also other cancers may be treated in the future.	Comments noted. The committee concluded that osimertinib is innovative, but there were no additional benefits associated with this treatment that could not be captured in the economic analysis. See section 4.16 of the FAD.
	4	The opinion fails to take sufficient account of the impact of this drug on tumour related symptoms and in particular the impact of central nervous system disease. This is a major problem in this group of patients with up to 40% developing CNS disease at some point. Platinum doublet chemotherapy has limited efficacy in this setting. Osimertinib has been shown to be effective in the treatment of CNS disease with improvement in symptoms. This has been reflected in clinical experience with the drug.	Comments noted. The committee noted comments from the clinical experts that osimertinib represented a step change in managing NSCLC similar to that seen when TK inhibitors were first introduced for first-line treatment of EGFR-positive NSCLC it was aware that the survival benefit associated with osimertinib was very uncertain. See section 4.16 of the FAD. However, the committee concluded that osimertinib met the criteria to be considered for inclusion in the Cancer Drugs Fund, and recommended osimertinib as an option for use within the Cancer Drugs Fund for people with EGFR T790M mutation-positive NSCLC whose disease had progressed after first-line EGFR TKI therapy if the conditions in the managed access agreement for osimertinib are followed. See section 4.19 of the FAD

Role*	Section	Comment [sic]	Response
	5	We believe this guidance to be discriminatory in terms of age. The guidance assumes that all patients suitable for osimertinib will be suitable for combination doublet chemotherapy. Whilst EGFR mutation lung cancer patients tend to be younger than patients whose lung cancer does not harbour the mutation they are found throughout the whole age spectrum. Rates of treatment with platinum doublet chemotherapy drop significantly with age in the UK, and in particular over the age of 70. The reasons for this are multifactorial and are due to patients performance status, co-morbidities, the presence of polypharmacy, patient wishes and expectations, and the lower rates of physicians offering chemotherapy. Whatever the reason the lower rates of chemotherapy use in the older age group are well established. This guidance assumes that platinum doublet chemotherapy is a valid option for all patients considered for osimertinib when data from the National Lung Cancer Audit and the National Cancer Intelligence Network suggest that this is not the case.	Comments noted. The committee concluded that osimertinib met the criteria to be considered for inclusion in the Cancer Drugs Fund, and recommended osimertinib as an option for use within the Cancer Drugs Fund for people with EGFR T790M mutation-positive NSCLC whose disease had progressed after first-line EGFR TKI therapy if the conditions in the managed access agreement for osimertinib are followed. See section 4.19 of the FAD
	6	"Having treated patients with this drug within clinical trials, the Early Access to Medicine Scheme and the compassionate access programme we believe that the UK real world experience is similar to that seen in the clinical trials and this drug represents a valuable addition to these patients care. This response represents our joint views .	Comments noted.

Role*	Section	Comment [sic]	Response
NHS Professional	1	Osimertinib should be approaved by NICE, it is the only option foe T790M mutation positive patients, the number of patients is small and the benefit is high, the ulternative is standard Chemotherapy which is less effective and far toxic. I have a patient who is curently on it through as access program and has completly transformed her quality of life and prognosis, she has been on it for 10 months when she failed to respond to standard chemotherapy. I think we are under moral responcibility to make this drug available for patients.	Comments noted. The committee concluded that osimertinib met the criteria to be considered for inclusion in the Cancer Drugs Fund, and recommended osimertinib as an option for use within the Cancer Drugs Fund for people with EGFR T790M mutation-positive NSCLC whose disease had progressed after first-line EGFR TKI therapy if the conditions in the managed access agreement for osimertinib are followed. See section 4.19 of the FAD
NHS Professional	1	**A patient perspective of targeted EGFR mutation treatment** **My storey prior to Erlotinib treatment** [redacted] I was diagnosed with metastatic adenocarcinoma of the lung. The cancer had invaded my liver and a string of lymph glands from my mediastinum to my neck. I had weeks or at the most months to live. As someone who had NEVER smoked a single cigarette [redacted] I was devastated. I went on to have two rounds of conventional chemotherapy. The primary tumour in my lung reduced in size but did not disappear. The side effects of my treatment included – neutropenic sepsis, cellulitis of my arm, a dental abscess and severe osteoporosis of my spine and hips. I needed surgery to my thoracic spine and I continue to have regular bisphosphonate infusions. **My story since starting Erlotinib** Two years after my diagnosis I developed temporal lobe epilepsy secondary to a brain metastases. At that point I was started on Erlotinib on the basis [redacted] who had never smoked. My EGFR mutation as recently been identified, thanks to a Cancer Research Campaign funded project.	Comments noted. The committee heard from the clinical experts that people with EGFR mutation-positive NSCLC tended to be diagnosed at a younger age, were fitter and not necessarily smokers compared with other types of lung cancer. See 4.3 of the FAD. The committee noted the additional evidence submitted by the company. The committee concluded that because the estimates of overall survival were so immature and not sufficiently robust, and the uncertainty in the clinical- and cost-effectiveness data too great, it could not recommend osimertinib for routine use in the NHS for treating EGFR T790M mutation-positive NSCLC. See section 4.18. However, The committee concluded that osimertinib met the criteria to be considered for inclusion in the Cancer Drugs Fund, and recommended osimertinib as an option for use within the Cancer Drugs Fund for people with EGFR T790M mutation-positive NSCLC whose disease had progressed after first-line EGFR TKI therapy if the conditions in the

Role*	Section	Comment [sic]	Response
		Within weeks of starting Erlotinib the remaining tumour in my lung had disappeared, as had the brain metastases and the associated symptoms. [redacted] If I had been treated with Erlotinb from the time of my diagnosis I would have avoided severe infections and vertebral fractures that required hospital admission. I might also be still working full time [redacted]. **Quality of life** Gene targeting methodologies for specific mutations are not an end of life treatment but a **magic bullet** without the side effects of chemotherapy and radiotherapy. After 72 months of Erlotinib treatment I am still disease free. [redacted] Would my children have achieved so much if I had not been there for them? **"The greatest gift that you can give a child is your time"** I think you need to refine your assessment of quality of life to include mothers with children. **Responsibilities**	managed access agreement for osimertinib are followed. See section 4.19 of the FAD

Role*	Section	Comment [sic]	Response
		I have a responsibility to speak for all [redacted] who have developed this cancer through no fault of their own. Pharmaceutical companies have a responsibility to make these "**magic bullets**" available at cost or minimal profit - without the NHS (patients, doctors, nurses, technical staff, scientists) and publicly funded cancer research charities they would not have a market for their drugs. NICE has a responsibility to find a measure that better reflects "quality of life" for mothers and the spin-offs from these precisely targeted drugs compared with conventional treatment	

Response to the Appraisal Consultation Document (ACD)

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Osimertinib for locally advanced or metastatic, EGFR and T790M mutation positive non-small cell lung cancer [ID874]

Single technology appraisal (STA)

File name	Version	Contains confidential information	Date
ID874_Osimertinib_ACD_Response_MainResponse[AIC]	1.0	Yes	14 July 2016

AstraZeneca UK Ltd
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Executive Summary

This document outlines AstraZeneca's response to the ACD regarding osimertinib for the treatment of locally advanced or metastatic, EGFR and T790M mutation positive non-small cell lung cancer.

AstraZeneca does not agree that the summaries of clinical and cost effectiveness presented within the ACD are reasonable interpretations of the available evidence, in particular we disagree that:

- *Osimertinib does not meet the criteria to be considered a life-extending, end-of-life treatment*

- *Osimertinib is not a cost-effective use of NHS resources*

Many of the issues highlighted by the Appraisal Committee and the ERG, leading to the negative recommendation in the ACD, relate to the immaturity of the evidence presented by AstraZeneca in the original manufacturer submission. Since our original submission more mature evidence from the phase I/II AURAext and phase II AURA2 studies has become available, based on a November 2015 data cut off (DCO), providing 6 months of additional evidence. In addition, a final, pre-planned, overall survival (OS) analysis of the IMPRESS trial, the placebo arm of which is used as the comparator arm in the health-economic model, has now been completed and used in our updated analyses. These updated data and associated analyses clearly demonstrate that patients with EGFRm T790M positive NSCLC meet the criteria for life expectancy (<24 months) and that osimertinib is highly likely to have at least a 3 month overall survival benefit in this population vs current standard of care.

Importantly, the cost-effectiveness analysis in the original submission should be considered as being highly conservative given that over two-thirds (68%) of the osimertinib patients (AURA study populations) had failed at least 2 prior lines of treatment for their advanced disease whereas all patients in the IMPRESS comparator cohort were treated at disease progression after only one line of prior therapy. Consistent with the NICE scoping guidance, and as the expected position of osimertinib in the treatment pathway is second-line, we have simplified the modelling to ensure the base case comparison is between EGFRm T790M positive NSCLC patients receiving either osimertinib or platinum doublet chemotherapy as 2nd line treatment after failing an initial EGFR-TKI. However, this comparison should continue to be considered as conservative as patients were only enrolled into the IMPRESS trial if they had responded to or had durable stable disease on the EGFR-TKI used as their initial treatment, whereas patients in the osimertinib studies were enrolled regardless of initial treatment response.

In addition to this additional evidence, AstraZeneca has taken into account the main challenges and issues raised by the Appraisal Committee.

In this response to the ACD using the updated modelling and health-economic analysis based on the more mature survival data we demonstrate that:

(i) *Osimertinib is associated with a statistically significant survival benefit and therefore meets End-of-Life criteria*

(ii) *Osimertinib is a cost-effective treatment option for patients who are likely to be seen in UK clinical practice with an ICER of £41,705 per QALY compared to platinum-doublet chemotherapy*

A summary of the supporting evidence for each of the above statements is provided in the following pages.

In light of the emerging evidence from the key studies, AstraZeneca does not agree that all of the relevant evidence has been taken into account in producing the ACD and therefore, the current recommendations are not a suitable basis for guidance to the NHS.

1. The expected position of osimertinib in the treatment pathway is 2nd line

Consistent with the final NICE scope and our initial submission, osimertinib will be used predominately as a second-line treatment after failure on previous EGFR-TKI. This position in the treatment pathway was confirmed by the clinical experts present at the first Appraisal Committee meeting, is in line with the clinical advice provided to the ERG, and is supported by the design of the AURA3 confirmatory Phase III clinical trial, which is studying osimertinib as a second-line treatment of patients with NSCLC tumours harbouring EGFRm T790M mutations after failure of an initial course of an EGFR-TKI.

Within the AURA clinical studies 129 (31%) patients received osimertinib as a second-line treatment after initial treatment with an EGFR-TKI, with the remainder of patients (n=282; 69%) receiving osimertinib as either third-line or greater treatment option. By contrast, the IMPRESS trial recruited only patients who had received one prior EGFR-TKI therapy.

The updated clinical evidence for the AURA studies, presented within this response, provides evidence that, despite unprecedented response and progression free survival in all patients regardless of treatment line, as expected, patients receiving osimertinib as a 3rd line or later treatment option appear to have a worse prognosis than patients receiving osimertinib as a 2nd line treatment (Figure 1). Therefore, separate comparative analyses of these populations, in keeping with clinical reporting practice, is warranted.

Figure 1: Overall survival by treatment cohort and total, Kaplan-Meier plot (FAS) – November 2015 DCO

[Figure Removed]

Furthermore, whilst patients in the AURAext and AURA2 studies were not required to have had a prior treatment response to an EGFR-TKI, patients in the IMPRESS trial had to have had a prior objective clinical benefit (as measured by CR or PR) and a minimum duration on first-line gefitinib treatment of 4 months.

Given the second-line population and selection for good response to initial treatment any comparison between the combined AURA (all lines) and IMPRESS populations are likely to significantly favour the IMPRESS control group, particularly when considering long term outcomes such as overall survival.

In light of the above the response to the ACD presents a revised efficacy comparison and updated cost-effectiveness analysis comparing the second-line cohort (N=129) from the AURA studies with the IMPRESS population in order to ensure an appropriate, reliable, conservative clinical comparison within the main population referred to in the decision problem.

2. Osimertinib is associated with a statistically significant survival benefit and therefore meets End-of-Life criteria

As highlighted in the ACD, given the EMA PRIME designation and associated accelerated marketing authorisation of osimertinib, the data available at the time of the original manufacturer submission (based on a May 2015 data cut-off [DCO]), did not allow a meaningful comparison of overall survival vs the IMPRESS control group due to the immaturity of the overall survival data (12.7% in the AURAext/2 studies).

An updated interim analysis (November 2015 DCO) of the AURAext/2 studies, with all patients having at least 12 months of radiological follow-up, provides a further 6 months of additional follow up on all endpoints and increased data maturity compared with our original submission. In addition, the final OS analysis from the IMPRESS trial has also been recently completed with [redacted] patients in the T790M mutation positive control group having died, compared with 32.8% in the original analysis.

- The median OS was [redacted] in the updated IMPRESS survival analysis, thus clearly demonstrating that the target population meets the end of life criterion of a prognosis with current standard of care of less than 24 months.

- Updated indirect comparisons between the IMPRESS T790M mutation positive control group and the AURA second-line cohort demonstrate a statistically significant and clinically meaningful overall survival benefit in favour of osimertinib [adjusted analysis: [redacted] The magnitude of this effect clearly indicates the criterion for clinical benefit for end of life can be considered to have been met.

Further details on the updated clinical evidence and updated adjusted indirect comparison are provided in Appendix 1 to this response and is summarised below.

2.1 Overall Survival

An overview of the unadjusted and adjusted indirect comparisons on overall survival between the AURAext/2 and IMPRESS studies is presented in Table 1.

The unadjusted overall survival KM analysis (Table 1 and Figure 2), results in a HR of [redacted] when comparing osimertinib with platinum-doublet chemotherapy supporting a substantial OS benefit associated with osimertinib. Similar observations are seen for the adjusted overall survival analysis, with a HR of [redacted] (Table 1 and Figure 3). It should be noted that the upper bound of the 95% confidence intervals in both analyses are less than 0.7 demonstrating the clinical relevance and statistical robustness of this result.

Table 1: Summary of unadjusted and adjusted indirect comparison on overall survival

Outcome		**AURA pooled**	**IMPRESS T790M mutation positive**	**Treatment Effect**
Indication		Second-line Cohort	Second-line	
Treatment		Osimertinib 80 mg	Platinum doublet chemotherapy	
Unadjusted Indirect Comparison				
OS	Number of patients	129	61	[redacted]

Unadjusted	Total events (%)	[redacted]	[redacted]	[redacted]
	Median (95% CI)	[redacted]	[redacted]	
Adjusted Indirect Comparison				
OS Adjusted	Number of PTS	[redacted]	[redacted]	[redacted]
	Total events (%)	[redacted]	[redacted]	
	Median	[redacted]	[redacted]	

At the time of this analysis the median OS has not been reached for osimertinib while the median OS for platinum doublet chemotherapy is [redacted], above that often reported for chemotherapy in second-line line NSCLC patients and likely representing, in part, the selection of patients with better prognosis due to the requirement for initial treatment response on their prior EGFR-TKI. At the 14-month landmark time point for osimertinib, the proportion of patients alive was approximately [redacted]. At 12 months, before the osimertinib data becomes heavily censored, [redacted] of patients were alive compared with less than [redacted] on platinum doublet chemotherapy. These data and visual inspection of the OS KM curve, provide compelling evidence of a significant OS benefit associated with osimertinib, and support the conclusion that osimertinib meets the end-of-life criterion of resulting in at least an additional 3 months extension to life, in particular given the conservative nature of the comparison.

Figure 2: Unadjusted overall survival by central review, Kaplan-Meier plot (FAS) – November 2015 DCO

[Figure Removed]

Figure 3: Adjusted overall survival by central review, Kaplan-Meier plot (FAS) – November 2015 DCO

[Figure Removed]

2.2 Overall Response Rates and Progression-Free Survival

In addition to the updated OS analyses, the updated clinical evidence also demonstrates statistically significant results across the other endpoints used to inform the cost-effectiveness analysis such as ORR and PFS (table 2).

In these analyses osimertinib is associated with a clinically meaningful and statistically significant improvement in progression free survival with a hazard ratio for time to PFS in the unadjusted analysis of [redacted] and in the adjusted analysis of [redacted].

Osimertinib is also associated with unprecedented high response rates in patients with relapsed advanced NSCLC. On osimertinib treatment 67.7% of patients in the 2L treatment cohort had a RECIST response compared with 39.3% of patients in the IMPRESS cohort. The adjusted indirect comparison on objective response rates furthermore demonstrates a statistically significant odds ratio of 5.63 in favour of osimertinib. As highlighted in the ACD (section 4.4), these response rates are important for improvements in the quality of life for people with this condition and explain the rapid improvement on key lung cancer symptoms and pain medication seen with osimertinib, translating into the good HRQoL observed inthe AURA studies.

Table 2: Overview of unadjusted and adjusted indirect comparison on ORR and PFS

Outcome		**AURA pooled**	**IMPRESS T790M mutation positive**	**Treatment Effect**
Indication		Second-line Cohort	Second-line	
Treatment		Osimertinib 80 mg	Platinum doublet chemotherapy	
Unadjusted Indirect Comparison				
ORR Unadjusted	Number of patients	124	61	**Not calculated**
	Total responses (%)	84 (67.7%)	24 (39.3%)	
PFS Unadjusted	Number of patients	127	61	[redacted]
	Total events (%)	[redacted]	[redacted]	
	Median (95% CI)	[redacted]	[redacted]	
Adjusted Indirect Comparison				
ORR Adjusted	Number of patients	89	48	**OR 5.63** (95%CI: 2.32-13.67;p<0.001)
	Total events (%)	60 (67.4%)	16 (33.3%)	
PFS Adjusted	Number of patients	[redacted]	[redacted]	[redacted]
	Total events (%)	[redacted]	[redacted]	
	Median	[redacted]	[redacted]	

3. Osimertinib is a cost-effective treatment compared to platinum-doublet chemotherapy

In order to address the key uncertainties identified by the Committee as described in the ACD, AstraZeneca has updated the cost-effectiveness model. The model structure is identical to that previously submitted, however, the clinical efficacy data (specifically PFS and OS) have been updated based on the latest available data from AURAext/2 (November 2015; DCO3) and the IMPRESS T790M mutation positive population (November 2015) as described in Section 2.

This section first describes a summary of the structure of the updated cost-effectiveness analysis followed by a description of the key modifications made to address concerns raised in the ACD. Finally updated base case results and sensitivity analyses are described alongside a number of scenario analyses.

These updated analyses, taking into account the challenges raised in the ACD regarding utility values, treatment and administration costs, demonstrate that osimertinib is a cost-effective treatment option for patients expected to receive treatment with osimertinib as part of UK standard of care at an ICER of £41,705 per QALY gained.

3.1 Summary of the updated cost-effectiveness analysis

Updated base case analysis

The updated base case analysis focuses on a comparison of osimertinib with platinum doublet chemotherapy in the second-line setting based on data taken from the relevant population in the pooled AURAext/2 studies (n=129) and the T790M mutation positive control arm of the IMPRESS study (n=61). Utilising clinical efficacy data from this population in AURAext/2 reflects the most likely position of osimertinib in the UK treatment pathway with both clinical experts at the first committee meeting commenting that osimertinib would only be used for people with EGFR mutation-positive NSCLC whose disease has progressed after first-line EGFR TKIs (ACD Section 4.2). In addition, restricting the AURAext/2 data to second-line only patients provide the most relevant and robust comparison with the IMPRESS T790M population, which consists of patients who received only one line of prior treatment.

Adjustments of the model incorporating many of the recommendations in the ACD/ERG report have been made. A summary is provided below and a more detailed description is provided in the accompanying technical report in Appendix 2.

- In the ACD the committee concluded that the benefits of improving objective response rates should have been included in the model previously submitted to NICE (ACD Section 4.12). We have updated the model accordingly by adjusting the progression-free state utility values according to objective response rates (ORRs) observed in AURAext/2 for osimertinib and IMPRESS for platinum doublet chemotherapy.
- The ACD states that the clinical experts agreed that the costs of osimertinib based on time-to-treatment discontinuation (TTD) were the most appropriate to use and the Committee concluded that TTD should have been used to calculate the acquisition costs of osimertinib (ACD Section 4.13). In the revised base case model, we have now incorporated time to discontinuation for osimertinib treatment costs using the method applied by the ERG in their sensitivity analysis.
- Other minor adjustments recommended in the ACD or by the ERG or resulting from the updated data cut have also been incorporated in the base case model including

administration costs for osimertinib, calculation of PDC costs per dose, updated safety data, adverse event costs and disutilities and updated osimertinib treatment dosing/compliance rates.

3.2 Summary of key changes in updated cost effectiveness model

3.2.1 Parametric model fit

Recognising the conservative nature of the clinical data comparisons as stated previously, the parametric survival functions for the base case model were selected using assessments of visual fit, statistical fit and clinical plausibility of all candidate parametric survival functions to the updated clinical datasets for 2nd line patients. For the base case model the Gompertz function was selected for PFS and the Weibull function was chosen for OS. Scenario analyses were also conducted based on using the exponential and log-logistic distributions for PFS and OS. Further details on the parametric survival model selection for both the adjusted and unadjusted datasets for AURAext/2 DCO3 and IMPRESS T790M mutation positive population can be found in the supplementary technical report in Appendix 2.

Figure 4: Overall and progression-free survival curves used in the base case analysis – adjusted dataset

[Figure Removed]

3.2.2 Utility values in the model

In section 4.11 of the ACD the Committee concluded that *"there was uncertainty in the utility values used by the company because they were based on non-UK validated EQ-5D-5L data from a small number of people, and there were concerns about the face validity compared with the general population"*.

AstraZeneca believe that the health state utility values (HSUVs) obtained from the AURA2 study are the most relevant source of utility values for the population being considered in this appraisal, that is, patients with EGFR T790M mutation-positive locally advanced or metastatic NSCLC. This study produced utility values of 0.815 for the progression-free state and 0.678 for the progressed state based on data from DCO2 in the original submission.

The ERG argue in their report that it seems implausible that a person with advanced NSCLC will have a higher utility value (0.815) than the average person in the UK of a similar age (0.80), citing the UK population norms for the EQ-5D-3L published in 1999 [Kind 1999]. As the ACD correctly states, because a validated EQ-5D-5L dataset for the UK was not available at the time of submission, it is difficult to compare these EQ-5D-5L crosswalk index values with values derived from sources using the EQ-5D-3L questionnaire and valuation set. However, we do not agree that the empirical data regarding utility estimates in these trials are implausible given the good tolerability, the demonstrated symptom improvement, the high tumour response and the oral route of administration of osimertinib. As the committee concluded, the significant and sustained tumour response rates observed in patients treated with osimertinib (67.7%) in AURAext/2 are likely to be important factors in the demonstrated improved quality of life observed in the AURAext/2 clinical trials and a major factor of treatment benefit for people with this condition, as reflected in the ACD section 4.4. Furthermore, the utility values derived from the AURA2 study are comparable to utility estimates obtained from previous studies of targeted therapies for locally advanced or metastatic NSCLC. In the PROFILE 1007 trial of crizotinib versus chemotherapy in previously treated patients with ALK-positive advanced NSCLC a utility value of 0.82 for patients on crizotinib treatment was reported. A similar objective response rate of 65.3% was reported for crizotinib compared to only 19.5% for the chemotherapy group in the PROFILE 1007 trial, demonstrating a strong correlation between tumour response rates and HRQoL.

In the ACD the committee also concluded that the benefits of improving objective response rates should have been included in the model previously submitted to NICE (ACD Section 4.12)., We have updated the model accordingly by adjusting the progression-free state utility values according to objective response rates (ORRs) observed in AURAext/2 for osimertinib and IMPRESS for platinum doublet chemotherapy. A summary of the utility values incorporating response rates from AURA2 DCO3 and IMPRESS and implemented in the updated cost effectiveness model is provided in Table 5. When incorporating treatment-specific response rates, the estimated HSUVs from AURA2 EQ-5D-5L crosswalk and the IMPRESS EQ-5D-3L values are very similar providing confidence regarding the reproducibility of these data. For the updated base case analysis, the HSUVs from IMPRESS adjusted for treatment-specific response rates were applied for the progression free state to capture the clear clinical difference between patients with a significant tumour regression vs those with stable disease. For the progressed disease state, a value of 0.715 was applied as the midpoint between the respective utility values from AURA EQ-5D-5L crosswalk value (0.751) and IMPRESS EQ-5D-3L (0.679). This represents a conservative modelling assumption compared with applying individual study data from AURA2 and IMPRESS to both study arms. A detailed summary of the methods is provided in the accompanying technical support document in Appendix 2.

Table 5: Summary of HSUVs from AURA2 and IMPRESS incorporating objective response rates

Health State	Mean Utility Value	n	Osimertinib		Platinum doublet chemotherapy	
			Adjusted (ORR 67.4%)	Unadjusted (ORR 67.7%)	Adjusted (ORR 33.3%)	Unadjusted (ORR 39.3%)
(i) AURA2 EQ-5D-5L Crosswalk Values						
PF – CR+PR PF – Stable Disease	0.833 0.753	116 42	0.807	0.807	0.779	0.784
PD – All	0.751	70	0.751			
(iii) IMPRESS EQ-5D-3L Index Values						
PF – CR+PR PF – Stable Disease	0.831 0.751	43 75	0.805	0.805	0.778	0.783
PD – All	0.679	88	0.679			

3.2.4 Costs of Osimertinib treatment (ACD Section 4.13)

The ACD states that the clinical experts agreed that the costs of osimertinib based on time-to-treatment discontinuation (TTD) were the most appropriate to use and the Committee concluded that TTD should have been used to calculate the acquisition costs of osimertinib (ACD Section 4.13).

In the ERG's analysis of TTD data from AURAext/2 (DCO2), a simple linear trend from 0-313 days was estimated and then applied from 313 days to estimate TTD beyond the point data were available. To address this question we have incorporated TTD as the base case assumption in the economic model. Based on the latest November 2015 data cut from AURAext/2 (DCO3), using the same approach as the ERG, a simple linear trend was estimated between 0-431 days for the second-line only population from AURAext/2, with the simple linear trend continued beyond 431 days. This resulted in patients in the second-line population stopping treatment at 973 days (median TTD 16.2 months).

An alternative approach of applying a simple median duration of osimertinib treatment post progression of 2.7 months observed in AURAext/2 was applied in a scenario analysis.

3.3 Updated cost effectiveness model – Base Case Results

Total costs, Life years gained (LYG), QALYs and incremental cost per QALY for osimertinib versus platinum doublet chemotherapy for the adjusted dataset are presented in Table 7. In this analysis, osimertinib generates 1.541 incremental QALYs and £64,283 incremental costs over a lifetime horizon gained compared with platinum doublet chemotherapy, resulting in an ICER of £41,705 per QALY gained. The equivalent probabilistic ICER (based on 10,000 iterations) is £40,581 per QALY gained and the probability of osimertinib being considered cost effective versus platinum doublet chemotherapy is 63% at a cost-effectiveness threshold of £50,000 per QALY gained.

For the unadjusted dataset, which does not adjust for all baseline differences between AURAex/2 and IMPRESS, osimertinib generates 1.313 incremental QALYs and £61,508

incremental costs over a lifetime horizon gained compared with platinum doublet chemotherapy, resulting in an ICER of £48,410 per QALY gained.

Table 7: Base case results – adjusted dataset

Treatment	Total costs (£)	Total LYG	Total QALYs	Incr costs (£)	Incr LYG	Incr QALYs	ICER (£) per QALY gained
Osimertinib	87,441	3.857	2.841	64,283	2.032	1.541	41,705
Platinum doublet chemotherapy	23,159	1.825	1.300				

3.4 Updated cost effectiveness model – Scenario Analyses

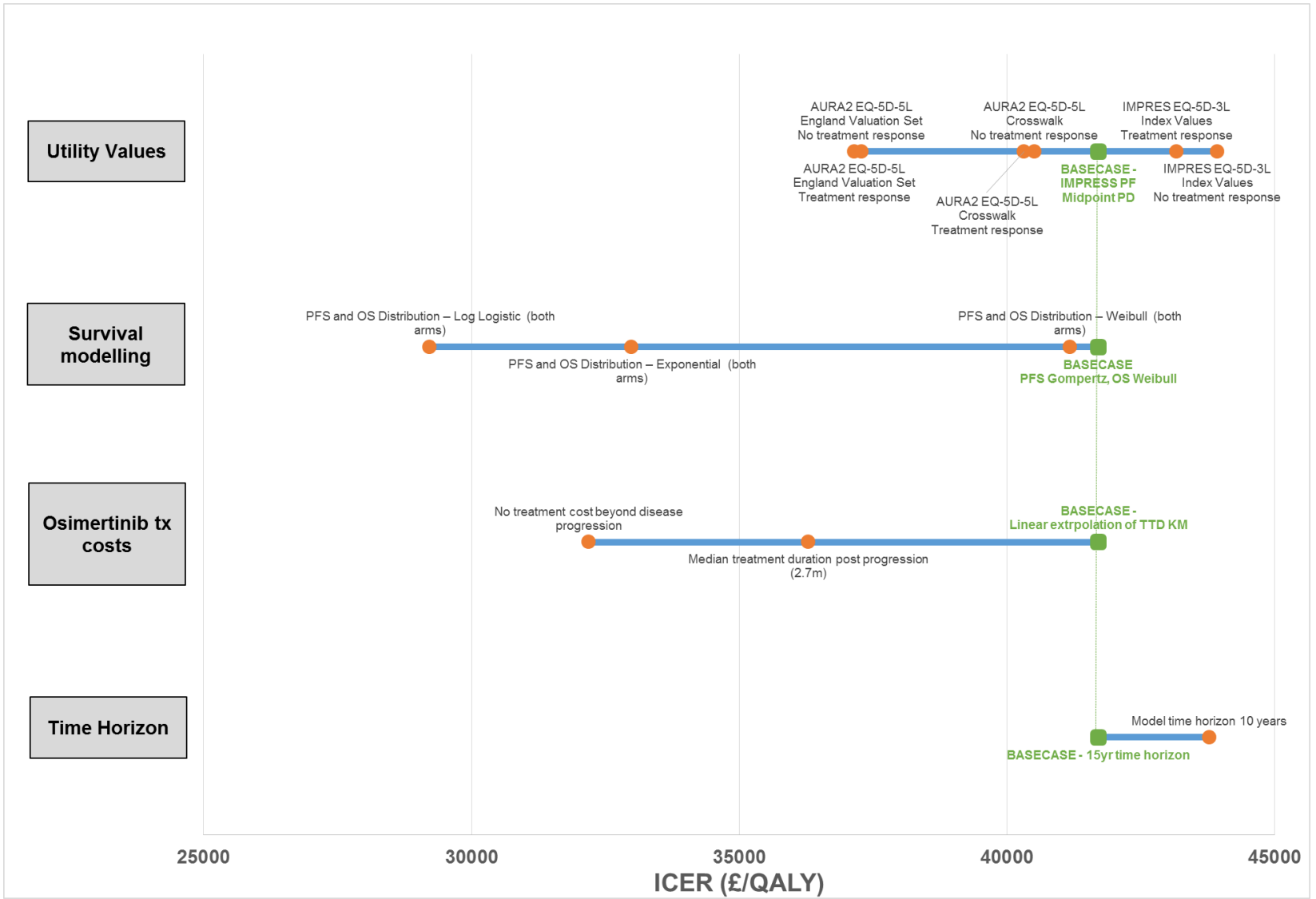
Scenario analyses were conducted to assess the impact of applying other clinically plausible parametric distributions to the non-parametric OS data for the adjusted dataset from AURAext/2 and the IMPRESS T790M mutation positive population. Other scenarios included varying the HSUVs for PF/PD disease including treatment response, assumptions about the costs of osimertinib treatment and applying a 10-year time horizon. Overall, the results as summarized in Table 8 and Figure 6 show that none of the scenarios produced ICERs that exceed £44,000 per QALY gained. Furthermore, Figure 6 illustrates that the revised base case represents a rather conservative estimate of the cost effectiveness compared to other scenarios.

Table 8: Results of model scenario analyses for osimertinib vs platinum doublet chemotherapy - adjusted dataset

Scenario	Total cost (£) Osimertinib	Total cost (£) PDC	Total QALYs Osimertinib	Total QALYs PDC	Incremental costs (£)	Incremental QALYs	ICER per QALY gained (£)
Base case	**87,441**	**23,159**	**2.841**	**1.300**	**64,283**	**1.541**	**41,705**
(a) Survival modelling							
PFS and OS Distribution – Weibull (both arms)	86,975	23,239	2.848	1.300	63,736	1.548	41,173
PFS and OS Distribution – Log Logistic (both arms)	93,784	23,390	3.765	1.356	70,393	2.409	29,224
PFS and OS Distribution – Exponential (both arms)	91,819	23,587	3.510	1.442	68,231	2.068	32,993
(b) Health State Utility Values							
(i) AURA2 EQ-5D-5L Crosswalk Values							
No Treatment Response PF 0.812 – Both arms PD 0.751 – Both arms	87,441	23,159	2.952	1.365	64,283	1.535	40,510
Treatment Response PF 0.808 – Osimertinib PF 0.781 – PDC PD 0.751 – Both arms	87,441	23,159	2.947	1.352	64,283	1.595	40,313
(ii) AURA2 EQ-5D-5L England Valuation Set Values							
No Treatment Response PF 0.874 – Both arms PD 0.821 – Both arms	87,441	23,159	3.214	1.490	64,283	1.724	37,279
Treatment Response PF 0.870 – Osimertinib PF 0.848 – PDC PD 0.821 – Both arms	87,441	23,159	3.210	1.479	64,283	1.731	37,145
(iii) IMPRESS EQ-5D-3L Index Values							
No Treatment Response PF 0.779 – Both arms PD 0.679 – Both arms	87,441	23,159	2.712	1.249	64,283	1.463	43,928

Treatment Response PF 0.806 – Osimertinib PF 0.779 – PDC PD 0.679 – Both arms	87,441	23,159	2.738	1.249	64,283	1.489	43,162
(c) Osimertinib treatment costs							
No treatment cost beyond disease progression	72,775	23,159	2.841	1.300	49,616	1.541	32,190
Median treatment duration post progression (2.7 months)	79,093	23,159	2.841	1.300	55,934	1.541	36,288
(d) Model time horizon 10 years	86,260	23,158	2.741	1.300	63,101	1.441	43,776

Figure 6: Results of model scenario analyses for osimertinib vs platinum doublet chemotherapy - adjusted dataset



3.4 ≥Third-line population: osimertinib versus single-agent chemotherapy (unadjusted dataset)

Currently for patients eligible for continued active anti-neoplastic therapy in the NHS, third line treatment for patients with EGFRm NSCLC who have failed an EGFR-TKI as first line therapy and a subsequent course of chemotherapy, the standard of care is single agent chemotherapy. This was defined as a relevant comparator in the decision problem in this position in the clinical pathway. Consistent with the original NICE submission, we performed a comparative modelling analysis of osimertinib and current standard of care treatment in patients who had received previous treatment with both an EGFR TKI and chemotherapy. It should be noted that while included in the marketing authorisation, the use of osimertinib in this population will likely be small once the existing pool of patients already treated with chemotherapy have been exhausted.

This analysis uses the unadjusted dataset specific to the ≥third-line population from AURAext/2 for osimertinib (n=282) and data from the Schuler 2015 study for single-agent chemotherapy (docetaxel). As patient-level data are unavailable from the Schuler et al study it was not possible to derive an unadjusted comparative dataset with the AURAext/2 ≥third-line population. For simplicity, the parametric distributions selected for these subgroup analyses were equivalent to those used in the base case analysis; the Gompertz distribution was used to extrapolate PFS and the Weibull distribution was used to extrapolate OS. All other model assumptions for this scenario analysis are identical to those used in the analyses for the second-line only comparison described in section 5.1.

The results are presented in Table 9. Compared with the equivalent analysis for the second-line only population, this scenario produced a higher ICER of £56,570 per QALY gained for osimertinib compared with single-agent chemotherapy. Overall, the projected survival for osimertinib in the ≥third-line population from AURAext/2 is significantly lower than that for the second-line only population based on unadjusted AURAext/2 data (2.56 years versus 3.26 years), reflecting the more refractory nature of this patient population.

Table 9: ≥Third-line population: osimertinib versus single-agent chemotherapy – unadjusted dataset

Treatment	Total costs (£)	Total LYG	Total QALYs	Incr costs (£)	Incr LYG	Incr QALYs	ICER (£) per QALY gained
Osimertinib	71,503	2.558	1.913	55,100	1.139	0.974	56,570
Single agent chemotherapy	16,403	1.419	0.939				

Response to the National Institute for Health and Care Excellence's Appraisal Consultation Document (ACD) on Osimertinib for treating locally advanced or metastatic EGFR T790M mutation-positive non small cell lung cancer.

This response is submitted by Roy Castle Lung Cancer Foundation.

- We are very disappointed that the Appraisal Committee's preliminary decision is not to recommend Osimertinib in this indication. We do, however, welcome the ongoing nature of the appraisal process and hope that the Appraisal Committee will re-consider their decision and ensure that this important new technology is made available within the NHS at the earliest opportunity.

- We would remind the Appraisal Committee that patients with advanced lung cancer generally have a poor outlook. Osimertinib is the first therapy shown to have benefits in EGFR T790M positive nsclc patients. As such, it represents a therapy option, for a very small number of clearly defined patients. It is an oral therapy and has a good side effect profile, as compared with conventional chemotherapy for nsclc.

- We welcome the willingness of the Appraisal Committee to review this decision, on the availability of the AURA3 study results (paragraph 5.1, indicates this may be available in June 2016) and hope this data will be available and dialogue will take place. We also welcome the opportunity to attend the second appraisal committee meeting for this therapy.

- **On behalf of the lung cancer patients who would derive benefit from this therapy, we strongly urge dialogue between the Manufacturer, NICE and NHS England, to ensure that areas of uncertainty and cost issues are addressed**. Advanced lung cancer remains a devastating disease for many. We hope that compromise and agreement can be reached and that the ultimate Final Appraisal Decision will be a positive recommendation. These patients do not have time to wait.

[redacted]

Roy Castle Lung Cancer Foundation
July 2016

British Thoracic Society

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Registered as a charity in England and Wales No. 285174
Scottish Charity No. SC041209
Company Registration No. 1645201

To be submitted via NICE docs

July 2016

Dear Sir,

Lung cancer (non-small-cell, EGFR and T790M positive, metastatic) - osimertinib [ID874]

Thank you for inviting comments from the British Thoracic Society on the Appraisal Consultation Document (ACD).

The Society has the following responses to the questions posed:

Has all of the relevant evidence been taken into account?
Yes as far as we are aware.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
Yes

Are the provisional recommendations sound and a suitable basis for guidance to the NHS?
Yes on the basis of cost, however the manufacturer should be encouraged to renegotiate access arrangements with NHS to make this important treatment affordable.

Yours faithfully,

[redacted]
[redacted]
British Thoracic Society

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National Institute for Health and Care Excellence
10 Spring Gardens
London
SW1A 2BU
Kate.Moore@nice.org.uk

19 July 2016

Dear Kate

Re: Osimertinib for treating metastatic EGFR and T790M mutation-positive non-small-cell lung cancer ID874

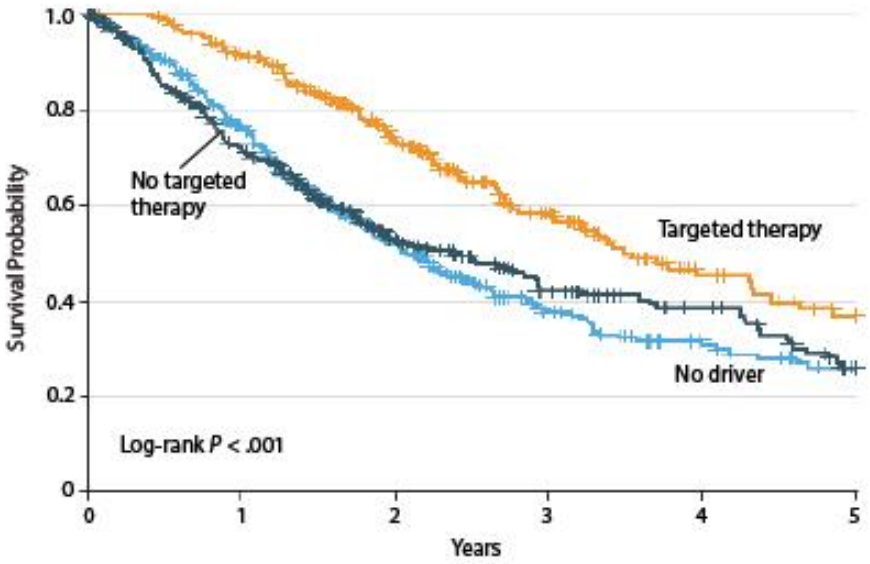
The Royal College of Physicians (RCP) plays a leading role in the delivery of high quality patient care by setting standards of medical practice and promoting clinical excellence. We provide physicians in the United Kingdom and overseas with education, training and support throughout their careers. As an independent body representing over 32,000 Fellows and Members worldwide, we advise and work with government, the public, patients and other professions to improve health and healthcare.

The RCP is grateful for the opportunity to respond to the above consultation. We have liaised with our experts who were disappointed to review the conclusions of the appraisal consultation document and would hope that further consideration will be given to the matter, taking into account the points made below:

1. **Has all the relevant evidence been taken into account?** – No

- The committee accepts the clinical importance and innovative nature of osimertinib in treating patients with T790M NSCLC, and comments on high response rates (66%), long duration of progression free survival (PFS 9.7 months) with longer duration of clinical benefit (as was demonstrated by an additional 1.6 months on treatment following disease progression) with an *improved side effect profile compared to chemotherapy.*
- However the grounds for not recommending Osimertinib were the lack of mature survival data (which is at least in part due to patients experiencing less events because of a more effective treatment than one might anticipate in a NSCLC patient population) and the uncertainty around the cost per QALY as a result. Demonstration of overall survival benefit with osimertinib is likely to be very difficult due to crossover and post progression treatment, in the chemotherapy arm, when the AURA 3 trial reports in 2017. There is indirect evidence of the survival benefit from historical data on patients with NSCLC who had a targetable mutation (EGFR, ALK or KRAS) and received an appropriate targeted therapy compared to those who did not. The retrospective study of more than a thousand patients demonstrated

a clinically meaningful improvement in OS (Kris M, et al. 2014, JAMA):



- It is unlikely that we will ever be able to demonstrate the true improvement in overall survival generated by osimertinib, and it is disappointing that the committee remain unable to establish other means of appraising such a highly effective, well-tolerated innovative treatment.

2. **Are the recommendations sound and a suitable basis for guidance to the NHS?** – No

   - The NHS cannot afford to fund every treatment regardless of cost and a key driver in healthcare is the need to deliver more effective personalised medicine.
   - The recommendations are not sound and do not support the efforts of the lung cancer research community and patients who have participated in clinical trials in order to develop personalised treatments for a well-defined population of lung cancer patients who gain maximum benefit from therapy. Osimertinib leads the way in the field of personalized therapy, as has been acknowledged by the international regulatory authorities when it was granted accelerated approval by the FDA and recommended by the EMA's accelerated assessment, based on tumour response rates and duration of response (not survival).

3. **Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?** – Yes

   - There are some older patients who may not suitable for platinum based doublet chemotherapy who would be prevented from accessing an effective therapy by this decision.

In summary, osimertinib is a therapy which is innovative and extremely effective, as is demonstrated by a number of measures of clinical outcome. It may well be that the time has arrived to re-examine the way in which we assess targeted therapies within this area of rapid development and to recognize that true improvement in overall survival may not demonstrable. We hope that these comments are helpful in reaching a final decision.

Yours sincerely

[redacted]

Comments on the ACD Received from the Public through the NICE Website

Name	[redacted]
Role	NHS Professional
Other role	[redacted]
Organisation	
Location	England
Conflict	I was invited to attend a AZ advisory board to review some of the trial data on osimertinib
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	I agree that the control arm of IMPRESS is a good comparator. This drug looks like a blockbuster in EGFR mutation positive lung cancer. At ELCC meeting this year some very impressive first line data was prefented from AURA. The FLAURA trial (first line) has completed accrual and we await results. THis drug is highly inovative. I have experience of using it in compassionate use and trials. As a 3rd gen EGFR inhibitor, wild type activity is minimised. As a result this is much better tolerated than 1st gen TKI's. In addition IGFR activity was rationally designed out (unlike rocelitinib). There is emerging evidence of activity in leptomeningeal disease (huge unmet need in EGFR mutation positive lung cancer). The pooled data from AURA and AURA 2 look very impressive. mOS not reached, more than 6 month greater PFS than IMPRESS (5 vs 11 m). I am a clinician with lots of trial experience and the shape of the OS KM curve is such that it is inconcievable that the mOS will not exceed 3 months compared to IMPRESS control arm. We currenly have no targeted options for NHS patients who develop acquired resistance T790M. I really do think this drug should be made available even if only through the CDF. I think it should be considered to meet end of life criteria for the reasons outlined
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE	

guidance)	
Section 7 (Proposed date of review of guidance)	

Name	[redacted]
Role	NHS Professional
Other role	[redacted]
Organisation	
Location	England
Conflict	[redacted] has provided advice to AstraZeneca and Clovis on the development of 3rd Generation EGFR Inhibitors. At present he is treating [redacted]
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	We the undersigned wish to express our disagreement with proposed guidance for osimertinib (GID-TA10022) [redacted]
Section 2 (The technology)	"The argument that the 3 month overall survival hurdle has not been reliably met and that the drug should not be considered within the end of life criteria is difficult to justify. The response rates and progression free survival were sufficiently strong to justify the designation of osimertinib as a promising innovative medicine and open an Early Access to Medicine Scheme. The data as to tumour control is relatively robust. All clinical experts agree this would be given as an additional treatment option, with

	platinum doublet chemotherapy been used afterward for patients who could tolerate it. Data both from EGFR mutants with the 1st and 2nd generation EGFR inhibitors, from other NSCLC patients with molecular abnormalities such as ALK fusions suggests the ability to target the tumour with a specific inhibitor is associated with a prolonged survival when compared to patients who can not access the drug. The suggestion that as the drug has only been used since 2013 and few events have been seen (due to the efficacy of the drug) means that statistically we can not be sure the survival benefit will exceed 3 months does not take account of what we know about this disease and global clinical opinion. As lung oncologists we strongly believe that adding in an effective drug that on average gives 9 months to 12 months of disease control will be associated with at least a 3 month improvement in survival. The experience of using this drug in clinical practice strongly mirrors that in the trials with patients responding well, quickly with an improvement in tumour related symptoms and with minor toxicity.
Section 3 (The manufacturer's submission)	The opinion fails to take sufficient account of the innovative nature of this drug. This is the 1st time we have been able to track the emergence of resistance to therapy in a cancer and target it effectively in a scientific manner. In addition we have robust data to support the use of circulating tumour DNA to detect the emergence of resistance. Both of these are tools that show us the way that not only lung cancers, but also other cancers may be treated in the future.
Section 4 (Consideration of the evidence)	The opinion fails to take sufficient account of the impact of this drug on tumour related symptoms and in particular the impact of central nervous system disease. This is a major problem in this group of patients with up to 40% developing CNS disease at some point. Platinum doublet chemotherapy has limited efficacy in this setting. Osimertinib has been shown to be effective in the treatment of CNS disease with improvement in symptoms. This has been reflected in clinical experience with the drug.
Section 5 (Implementation)	We believe this guidance to be discriminatory in terms of age. The guidance assumes that all patients suitable for osimertinib will be suitable for combination doublet chemotherapy. Whilst EGFR mutation lung cancer patients tend to be younger than patients whose lung cancer does not harbour the mutation they are found throughout the whole age spectrum. Rates of treatment with platinum doublet chemotherapy drop significantly with age in the UK, and in particular over the age of 70. The reasons for this are multifactorial and are due to patients performance status, co-morbidities, the presence of polypharmacy, patient wishes and expectations, and the lower rates of physicians offering chemotherapy. Whatever the reason the lower rates of chemotherapy use in the older age group are well established. This guidance assumes that platinum doublet chemotherapy is a valid option for all patients considered for osimertinib when data from the National Lung Cancer Audit and the National Cancer Intelligence Network suggest that this is not the case.
Section 6 (Related NICE guidance)	"Having treated patients with this drug within clinical trials, the Early Access to Medicine Scheme and the compassionate access programme we believe that the UK real world experience is similar to that seen in the clinical trials and this drug represents a valuable

	addition to these patients care. This response represents our joint views .
Section 7 (Proposed date of review of guidance)	

Name	[redacted]
Role	NHS Professional
Other role	[redacted]
Organisation	[redacted]
Location	England
Conflict	
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	Osimertinib should be approaved by NICE, it is the only option foe T790M mutation positive patients, the number of patients is small and the benefit is high, the ulternative is standard Chemotherapy which is less effective and far toxic. I have a patient who is curently on it through as access program and has completly transformed her quality of life and prognosis, she has been on it for 10 months when she failed to respond to standard chemotherapy. I think we are under moral responcibility to make this drug available for patients.
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Name	[redacted]
Role	NHS Professional
Other role	
Organisation	
Location	
Conflict	
Notes	

Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	**A patient perspective of targeted EGFR mutation treatment** **My storey prior to Erlotinib treatment** [redacted] I was diagnosed with metastatic adenocarcinoma of the lung. The cancer had invaded my liver and a string of lymph glands from my mediastinum to my neck. I had weeks or at the most months to live. As someone who had NEVER smoked a single cigarette and [redacted] I was devastated. I went on to have two rounds of conventional chemotherapy. The primary tumour in my lung reduced in size but did not disappear. The side effects of my treatment included – neutropenic sepsis, cellulitis of my arm, a dental abscess and severe osteoporosis of my spine and hips. I needed surgery to my thoracic spine and I continue to have regular bisphosphonate infusions. **My story since starting Erlotinib** Two years after my diagnosis I developed temporal lobe epilepsy secondary to a brain metastases. At that point I was started on Erlotinib on the basis that I [redacted] had never smoked. My EGFR mutation as recently been identified, thanks to a Cancer Research Campaign funded project. Within weeks of starting Erlotinib the remaining tumour in my lung had disappeared, as had the brain metastases and the associated symptoms. [redacted] If I had been treated with Erlotinb from the time of my diagnosis I would have avoided severe infections and vertebral fractures that required hospital admission. I might also be still working full time [redacted]. **Quality of life** Gene targeting methodologies for specific mutations are not an end of life treatment but a **magic bullet** without the side effects of chemotherapy and radiotherapy. After 72 months of Erlotinib treatment I am still disease free. [redacted] Would my children have achieved so much if I had not been there for them?

	"The greatest gift that you can give a child is your time" I think you need to refine your assessment of quality of life to include mothers with children. **Responsibilities** I have a responsibility to speak for all [redacted] who have developed this cancer through no fault of their own. Pharmaceutical companies have a responsibility to make these "**magic bullets**" available at cost or minimal profit - without the NHS (patients, doctors, nurses, technical staff, scientists) and publicly funded cancer research charities they would not have a market for their drugs. NICE has a responsibility to find a measure that better reflects "quality of life" for mothers and the spin-offs from these precisely targeted drugs compared with conventional treatment.
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Response to the Appraisal Consultation Document (ACD)
Appendix 1 – Updated Clinical Evidence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Osimertinib for locally advanced or metastatic, EGFR and T790M mutation positive non-small cell lung cancer [ID874]

Single technology appraisal (STA)

File name	Version	Contains confidential information	Date
ID874_Osimertinib_ACD_Response_Appendix1[AIC]	1.0	Yes	14 July 2016

AstraZeneca UK Ltd
600 Capability Green, Luton LU1 3LU

Executive Summary

This document serves as an appendix to AstraZeneca's response to the ACD regarding osimertinib for the treatment of locally advanced or metastatic, EGFR and T790M mutation positive non-small cell lung cancer.

In April 2016, updated data from the AURA studies, providing the main source of evidence in the manufacturer submission, were presented at the European Lung Cancer Conference (ELCC) in Geneva in, Switzerland, and reinforce the efficacy and safety profile for osimertinib previously seen in the AURA clinical trials programme.

In addition, a final OS analysis from the IMPRESS trial, of which the placebo arm is used as the comparator arm in the health-economic model, was planned and has been conducted in the meantime.

A key summary on the most relevant endpoints is provided within this document.

Updated Clinical Evidence

(i) Progression Free Survival (PFS) in the AURAext/AURA2 studies

In the updated analysis, median PFS in the FAS based on assessments by BICR (55.2% maturity) was 11.0 months (95% CI: 9.6, 12.4) compared to 9.7 months (95% CI: 8.3, NC) based on the previous data cut off (38% maturity). All patients had the opportunity of having at least 12 months of radiological follow-up.

Figure 1: Progression-free survival by central review by treatment cohort and total, Kaplan-Meier plot (FAS) – November 2015 DCO

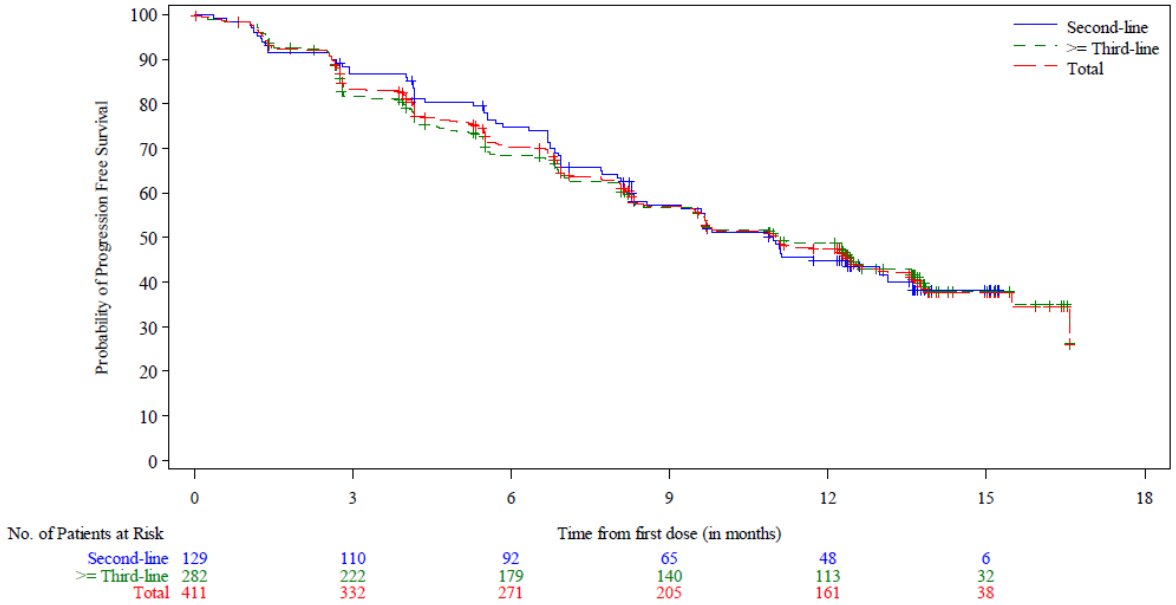


Table 1: Progression-free survival by BICR by treatment cohort (FAS) – November 2015 DCO

	Second-line (N=129)	≥ Third-line (N=282)	Total (N=411)
Total number of events[a]	71	156	227
Median progression free survival (months)[b]	11.0	11.0	11.0
95% CI for median progression free survival	8.3, 13.1	9.5, 12.6	9.6, 12.4
Progression free at 3 months (%)	86.8	81.6	83.3
95% CI for PFS at 3 months	79.6, 91.6	76.5, 85.7	79.3, 86.6
Progression free at 6 months (%)	74.7	68.4	70.4
95% CI for PFS at 6 months	66.2, 81.4	62.5, 73.6	65.7, 74.7
Progression free at 9 months (%)	57.3	56.7	56.9
95% CI for PFS at 9 months	48.0, 65.5	50.5, 62.4	51.8, 61.6
Progression free at 12 months (%)	44.7	48.8	47.5
95% CI for PFS at 12 months	35.6, 53.4	42.6, 54.8	42.4, 52.5
Median follow-up for PFS (Months)	9.2	8.4	8.6
Median follow-up for PFS (Months) (censored patients only)	12.4	13.6	12.6

Based on follow-up at DCO, the Kaplan-Meier estimated probability of being alive and progression-free based on BICR assessment was 83.3% (95% CI: 79.3, 86.6) at 3 months, 70.4% (95% CI: 65.7, 74.7) at 6 months, 56.9% (95% CI: 51.8, 61.6) at 9 months and 47.5% (95% CI: 42.4, 52.5) at 12 months (Table 1). Numbers were similar by treatment cohort.

Based on BICR assessment, of the 411 EGFR T790M mutation-positive patients in the FAS, 227 (55.2%) either progressed (308 patients, 50.4%) or died (20 patients, 4.9%) (Table 2). Of the remaining 184 patients (44.8%), 172 remained alive and progression-free at the time of analysis (41.8%) and 6 (1.5%) had withdrawn consent (Table 2). Numbers were similar by treatment cohort.

Table 2: Progression status at time of data cut-off by central review by study (FAS)

		Number (%) of patients		
Progression status	Type of event	Second-line (N=129)	≥ Third-line (N=282)	Total (N=411)
Progression[a]	Total	71 (55.0)	156 (55.3)	227 (55.2)
	RECIST progression	64 (49.6)	143 (50.7)	207 (50.4)
	Target Lesions[c]	31 (24.0)	56 (19.9)	87 (21.2)
	Non Target Lesions[c]	31 (24.0)	81 (28.7)	112 (27.3)
	New Lesions[c]	41 (31.8)	85 (30.1)	126 (30.7)
	Death[b]	7 (5.4)	13 (4.6)	20 (4.9)
No progression	Total	58 (45.0)	126 (44.7)	184 (44.8)
	Censored RECIST progression or death[d]	2 (1.6)	4 (1.4)	6 (1.5)
	Progression free at time of analysis[e]	55 (42.6)	117 (41.5)	172 (41.8)
	Lost to follow-up[f]	0	0	0
	Withdrawn consent[f]	1 (0.8)	5 (1.8)	6 (1.5)
	Discontinued study[f]	0	0	0

[a] Only includes progression events that occur within 19 weeks of the last evaluable assessment.
[b] Death in the absence of RECIST progression.
[c] Target Lesions, Non Target Lesions and New Lesions are not necessarily mutually exclusive categories.
[d] RECIST progression event occurred 19 weeks after last evaluable RECIST assessment.
[e] Includes patients, known to be alive, with no evaluable baseline RECIST assessment (censored at day 0).
[f] Patients at last evaluable RECIST assessment.
RECIST version 1.1.

(ii) Overall Survival

IMPRESS
The data cut-off for the final OS analysis from IMPRESS was November 16th 2015. Compared to the previous data set, in which 20 (32.8%) out of 61 patients within the T790M mutation positive control group had an event, maturity has greatly increased with [redacted] out of 61 patients now having had an event. Median OS was [redacted]

AURAext/AURA2
As highlighted in the ERG report, the presented OS data in the company submission were very immature (12.7%) and did not illustrate a difference between the 2nd line cohort compared to the ≥ 3rd line cohort.

Consistent with the medical literature, the updated AURA data (November 2015 DCO) now demonstrate emerging evidence of a difference in OS between the second-line cohort compared to the ≥ 3rd line cohort (Figure 2).

Figure 2: Overall survival by treatment cohort and total, Kaplan-Meier plot (FAS) – November 2015 DCO

[Figure Removed]

The updated data whilst still immature (23.8%), provide evidence of a clear separation between the AURA pooled KM data when compared to the IMPRESS OS KM plot as illustrated in Figure 3 resulting in a statistically significant Hazard Ratio of [redacted]. It therefore supports the projected differential OS benefit and results from the previously submitted cost-effectiveness analysis. The KM curve for the AURA studies should be interpreted with caution beyond 13-15 months due to the high degree of censoring leading to a small risk set to inform the curve.

Figure 3: Overall survival by central review, Kaplan-Meier plot (FAS) – November 2015 DCO

[Figure Removed]

The Kaplan-Meier estimate of the proportion of patients alive on osimertinib based on BICR assessment in the second-line cohort was

[redacted] (Table 3). At time of DCO, OS maturity in the second-line cohort was 19% compared to 26% in the 3rd line or greater cohort.

Table 3: Survival status at time of DCO and Median overall survival by treatment cohort – November 2015 DCO

[Table Removed]

Median OS within the IMPRESS population was [redacted]. In the AURA pooled dataset, survival at 14 months is approximately [redacted]. At 12 months, before the AURA data becomes heavily censored, [redacted] of patients were alive compared to less than [redacted] in the IMPRESS dataset, illustrating a high probability of an OS benefit associated with osimertinib. This should be considered in the context of the IMPRESS population being selected for good response on prior EGFR-TKI, making the comparison a conservative one.

(iii) Objective response rates

Osimertinib is associated with high objective response rates. The primary efficacy analysis of ORR (including BOR) was based on BICR of the evaluable-for-response population. Sensitivity analyses of RECIST outcomes were performed based on investigator and BICR assessments in the FAS population.

As of the DCO (1 November 2015), the primary analysis of the pooled confirmed ORR was 66.0% (95% CI: 61.10, 70.65) (Table 4). Of the 397 patients with measurable disease at baseline based on BICR assessment, 262 had confirmed objective responses to osimertinib: 6 patients (1.5%) had a BOR of CR and 256 (64.5%) had a BOR of PR. Results were similar in the FAS based on investigator assessment and on BICR assessment and across lines of therapy.

Table 4: Objective response rate (ORR) by BICR by study (evaluable-for-response set)

Study	N	Number (%) of patients with responses[a]	95% CI
AURA Extension AZD9291 80 mg	198	122 (61.6)	54.46, 68.42
AURA2 AZD9291 80 mg	199	140 (70.4)	63.48, 76.60
Total AZD9291 80 mg	397	262 (66.0)	61.10, 70.65

[a] Responses exclude unconfirmed responses.
Objective response rate is defined as the number (%) of patients with at least one visit response of complete response (CR) or partial response (PR) that is confirmed at least 4 weeks later.
The CIs are calculated using Clopper-Pearson exact method for binomial proportions.
RECIST version 1.1.

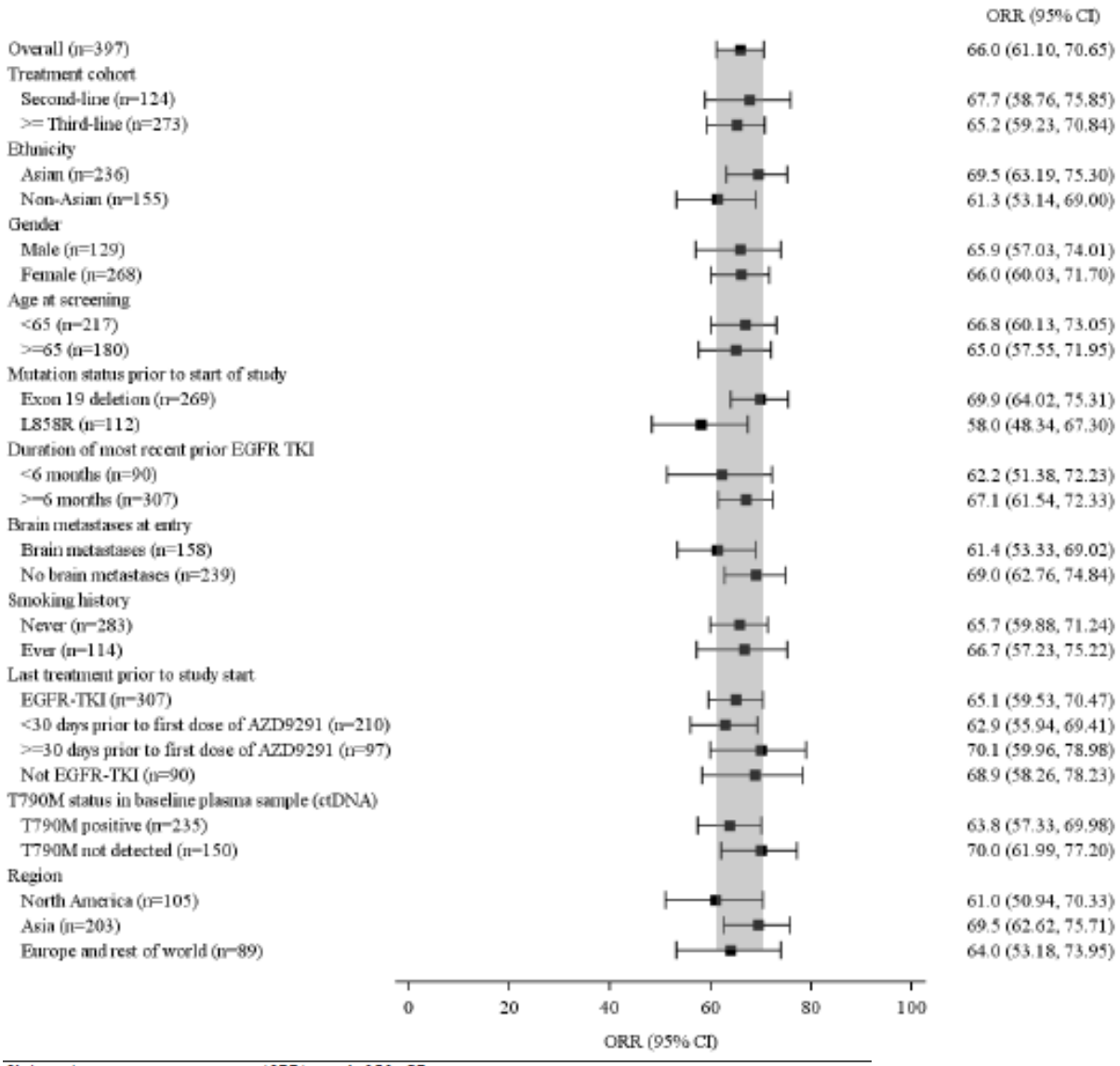
Table 5: Best objective response (BOR) by central review by study (evaluable for response analysis set) from the pooled studies

		Number (%) of patients		
Response status	Best objective response	AURA Extension AZD9291 80 mg (N=198)	AURA2 AZD9291 80 mg (N=199)	Total AZD9291 80 mg (N=397)
Response	Total	122 (61.6)	140 (70.4)	262 (66.0)
	Complete response[a]	0	6 (3.0)	6 (1.5)
	Partial response[a]	122 (61.6)	134 (67.3)	256 (64.5)
Non-response	Total	76 (38.4)	59 (29.6)	135 (34.0)
	Stable disease ≥6 weeks[b]	57 (28.8)	42 (21.1)	99 (24.9)
	Unconfirmed partial response[c]	13 (6.6)	12 (6.0)	25 (6.3)
	Stable disease	44 (22.2)	30 (15.1)	74 (18.6)
	Progression	19 (9.6)	15 (7.5)	34 (8.6)
	Unconfirmed partial response[c]	1 (0.5)	0	1 (0.3)
	RECIST Progression	13 (6.6)	12 (6.0)	25 (6.3)
	Early death	5 (2.5)	3 (1.5)	8 (2.0)
	Not evaluable	0	2 (1.0)	2 (0.5)
	No evaluable follow-up assessments	0	1 (0.5)	1 (0.3)
	Unconfirmed partial response[c]	0	1 (0.5)	1 (0.3)

[a] Responses requires confirmation after 4 weeks.
[b] SD ≥ 6 weeks includes RECIST visit window (±7 days).
[c] PR or CR achieved but either no confirmation assessment performed or a confirmation assessment performed but response not confirmed.
RECIST version 1.1.

ORR by BICR in the evaluable for response population confirmed high ORRs, ranging from 58.0% to 70.1% across all subgroups (Figure 4) including by line of therapy [second-line patients (67.7%; 95% CI: 58.8, 75.9) and ≥third-line patients (65.7%; 95% CI: 59.2, 70.8)].

Figure 4: Objective responses rate (ORR) by central review, Forest plot, by subgroup (evaluable for response analysis set)



Objective response rate (ORR) and 95% CI.
The CIs are calculated using Clopper-Pearson exact method for binomial proportions.
Grey band represents the 95% confidence interval for the overall patients'objective response rate.

(iv) Duration of response

The median DoR based on BICR assessment is 12.5 months (95% CI: 11.1, NC). Of 262 patients with confirmed objective responses by BICR at the time of DCO, 116 had subsequently progressed or died and 146 (55.7%) had ongoing responses at the time of DCO, with DoR ranging from 1.3 months to 15.3 months

Based on a Kaplan-Meier analysis, 94.5% (95% CI: 91.0, 96.7) of responding patients were estimated to have a DoR >3 months, 77.5% (95% CI: 71.8, 82.2) a DoR >6 months, 65.0 (95% CI: 58.5, 70.6) a DoR >9 months, and 52.9% (95% CI: 45.9, 59.4) a DoR >12 months. The median DoR based on investigator assessment was 11.3 months (95% CI: 10.1, 12.6).

(v) Disease control rates

In the pooled population, the DCR (defined as CR + PR + SD ≥6 weeks) was 90.9% (95% CI: 87.7, 93.6), with similar DCR across studies (Table 6). This comprised 6 patients (1.5%) with confirmed CR, 256 patients (64.5%) with confirmed PR, and 99 patients (24.9%) with SD ≥6 weeks. Results were similar in the FAS based on investigator assessment and on BICR assessment and across lines of therapy.

Table 6: Disease control rate (DCR) by BICR and by study (Evaluable for response analysis set)

Study	N	Number (%) of patients with disease control	95% CI
AURA Extension AZD9291 80 mg	198	179 (90.4)	85.42, 94.12
AURA2 AZD9291 80 mg	199	182 (91.5)	86.67, 94.94
Total AZD9291 80 mg	397	361 (90.9)	87.67, 93.57

Disease control = best objective response of confirmed complete response, confirmed partial response or stable disease.
The CIs are calculated using Clopper-Pearson exact method for binomial proportions.
RECIST version 1.1.

(vi) Tumour shrinkage

The median best percentage change from baseline in TL size by BICR in the evaluable-for-response population was −47.65 (minimum: −100%; maximum: +90.8%) (Table 7 and Figure 5). The mean best percentage change from baseline was −47.5% (SD: 30.0). Tumour shrinkage pattern was similar across studies.

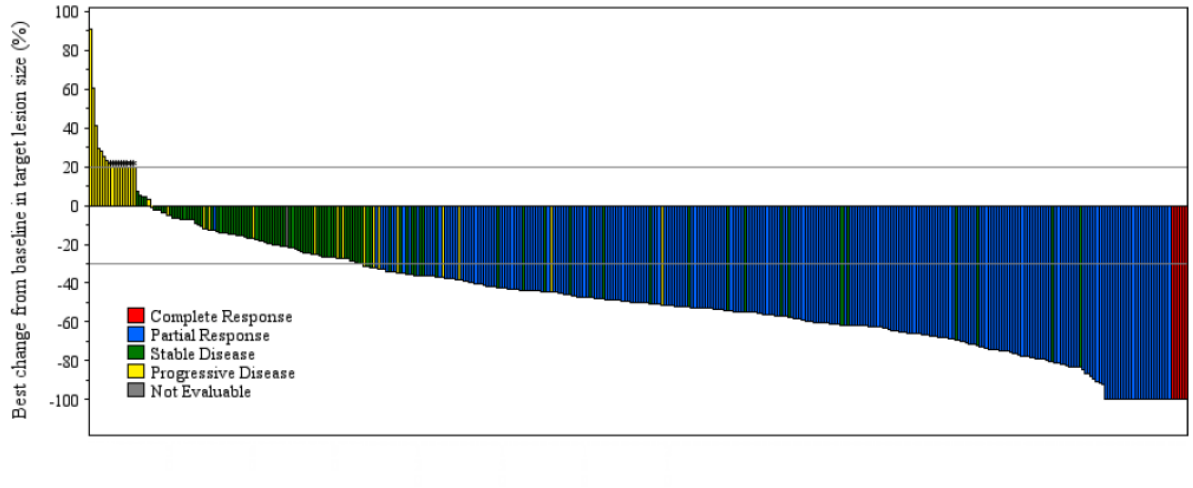
Table 7: Best percentage change from baseline in target lesion size by central review by study (evaluable response analysis set)

Statistic	AURA Extension AZD9291 80 mg (N=198)	AURA2 AZD9291 80 mg (N=199)	Total AZD9291 80 mg (N=397)
n	198	198	396
Mean	-42.66	-52.36	-47.51
SD	25.562	33.279	30.030
Min	-100.0	-100.0	-100.0
Median	-46.35	-54.50	-49.95
Max	25.0	90.8	90.8

Best change in target lesion size is the maximum reduction from baseline or the minimum increase from baseline in the absence of a reduction.
n is the number of patients with at least one post baseline RECIST target lesion assessment scan.
Any changes in target lesion size that are imputed (rules defined in SAP) are included.
A negative change denotes a reduction in target lesion size.
SD=Standard Deviation.
RECIST version 1.1.

In each study, evidence of tumour shrinkage was generally documented at the first scheduled follow-up RECIST scan, at Week 6±1 week).

Figure 5: Target lesion size, best percentage change from baseline by central review – total, waterfall plot (evaluable response analysis set)



Best percentage change in target lesion size is the maximum reduction from baseline or the minimum increase from baseline in the absence of a reduction.

* represents imputed values: if it is known that the patient has died, has new lesions or progression of non-target lesions, has withdrawn due to PD and has no evaluable target lesion (before or at progression) assessments, best change will be imputed as 20%.

RECIST version 1.1.

Adjusted indirect comparison of osimertinib compared with platinum doublet chemotherapy

Section 4.10.3 of the original manufacturer submission presented an adjusted indirect comparison between the AURAext/2 and IMPRESS studies in an attempt to reduce bias in the non-randomized efficacy comparison and balance the non-equivalent cohorts on common observable variables.

As mentioned in the ACD, this approach and methodology was supported by the Committee and ERG. However, due to data immaturity, improvements in overall survival could not be demonstrated in the original analysis.

Since the first AC meeting, AstraZeneca was able to update the original analysis using the updated evidence presented earlier in this ACD response. An executive summary of this analysis is presented below for patients treated with osimertinib or platinum-based doublet chemotherapy as a second-line treatment, in line with the expected position of osimertinib in the treatment pathway.

As the methodology and design of the analysis is no different compared to the original analysis, this section only describes the results for the PFS and OS endpoints as these data inform the health-economic analysis. A full technical report is provided in attachment to this submission which contains details on all other endpoints alongside description of methodology and study design.

(i) Progression Free Survival (PFS)

Analysis of PFS for patients treated with osimertinib or platinum-based doublet chemotherapy as a second-line treatment by a Cox proportional hazards model is presented in Table 8 based on the ICR and the T790M+adj set.

Overall, the PFS results indicate a large treatment effect with the hazard ratio of [redacted] showing a statistically significant improvement for the osimertinib group compared with the platinum doublet chemotherapy group [redacted].

Median PFS was [redacted] months for the osimertinib group compared with [redacted] months in the matched platinum doublet chemotherapy cohort. A KM plot for the primary calculated RECIST-defined PFS is presented in Figure 6. These data, indicate that the treatment effect associated with osimertinib is consistent over time. Results are consistent with the reported data for the 2nd line cohort from AURAext/2 (osimertinib median PFS [redacted] months; [redacted]) and for the platinum doublet chemotherapy arm (n=61) of IMPRESS (median PFS [redacted] months).

Table 8: Summary of Analysis of Progression-Free Survival by Independent Central Review for Second-Line Treatment (T790M+adj Set)

				Treatment effect (osimertinib vs platinum-based doublet chemotherapy)		
Treatment	**N**	**Patients with events, n (%)**	**Median PFS (months) 95% CI**	**HR**	**95% CI**	**Two-sided p-value**
Osimertinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Platinum-based doublet chemotherapy	[redacted]	[redacted]	[redacted]			

The analysis was performed using a Cox proportional hazards model with treatment, subgroup, subgroup-by-treatment as factors and estimated PS as a covariate for each subgroup. HR <1 favours osimertinib.

Progression includes death in the absence of RECIST progression.

Figure 6: Kaplan–Meier Plot of Progression-Free Survival by Independent Central Review for Second-Line Treatment (T790M+adj Set)

[Figure Removed]

A, osimertinib; S, SoC / platinum-based doublet chemotherapy

Analysis of PFS by subgroup in patients treated 2L was performed and presented as a forest plot (Figure 7). This analysis demonstrated [redacted].

Figure 7: Forest Plot of Progression-Free Survival Primary Analysis by Independent Central Review by Subgroup: Second-Line Patients (T790M +adj Set)

[Figure Removed]

(ii) Secondary efficacy variables – objective response rate (ORR)

The ORR was calculated for each treatment for the T790M+adj set evaluation-for-response for patients given second-line treatment. The ORR was calculated for each treatment based on the percentage of patients who had a BOR (according to RECIST) of CR or PR.

The analysis of ORR by logistic regression is summarized in Table 9. Patients treated with osimertinib demonstrated a statistically significant advantage in ORR (67.4% patients) relative to the platinum-based doublet chemotherapy group (33.3% patients) (OR 5.63, 95% CI 2.32 to 13.67, p-value <0.001).

Table 9: Objective response rate, logistic regression (*T790M+adj* set Evaluable for Response)

			Treatment effect (osimertinib vs platinum-based doublet chemotherapy)		
Treatment	**N**	**Patients (%) with response**	**OR**	**95% CI**	**Two-sided p-value**
Osimertinib	89	60 (67.4)	5.63	2.32, 13.67	<0.001
Platinum-based doublet chemotherapy	48	16 (33.3)			

The OR analysis was performed using logistic regression model with treatment as a factor and PS as a covariate. P-values are two-sided. OR >1 favours osimertinib.

(iii) Secondary efficacy variables – disease control rate (DCR)

The DCR analysis was calculated for each treatment for the T790M+adj set evaluation-for-response for patients given second-line treatment. The analysis of DCR by logistic regression is summarized in Table 10.

Patients treated with osimertinib as a second-line treatment demonstrated a statistically significant advantage in DCR (93.3% patients) relative to the platinum-based doublet chemotherapy group (75.0% patients) (OR 5.73, 95% CI 1.84 to 17.88, p-value 0.003).

Table 10: Secondary analysis of DCR (*T790M+adj* set Evaluable for Response)

			Treatment effect (osimertinib vs platinum-based doublet chemotherapy)		
Treatment	**N**	**Patients with response, n (%)**	**OR**	**95% CI**	**Two-sided p-value**
Osimertinib	89	83 (93.3)	5.73	1.84, 17.88	0.003
Platinum-based doublet chemotherapy	48	36 (75.0)			

The OR analysis was performed using logistic regression model with treatment as a factor and PS as a covariate. P-values are two-sided. OR >1 favours osimertinib.

(iv) Overall Survival (OS)

The analysis of OS by Cox proportional hazards model was performed at the time of PFS analysis (for AURA extension, AURA2 and IMPRESS) for the T790M+adj set for patients given second-line treatment; the results are presented in Table 11.

Median OS time for the osimertinib group was not calculable and the median OS time for the platinum-based doublet chemotherapy group was [redacted] months. The HR for OS for osimertinib relative to platinum-based doublet chemotherapy was [redacted]

Table 11: Analysis of Overall Survival for Second Line Treatment (T790M+adj Set)

				Treatment effect (osimertinib vs platinum-based doublet chemotherapy)		
Treatment	**N**	**Patients with events, n (%)**	**Median OS (months) 95% CI**	**HR**	**95% CI**	**Two-sided p-value**
Osimertinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Platinum-based doublet chemotherapy	[redacted]	[redacted]	[redacted]			

The analysis was performed using a Cox proportional hazards model with treatment as a factor and estimated PS as a covariate. HR <1 favours osimertinib. NC* = Not able to calculate.

A Kaplan–Meier plot for Overall Survival for patients given second-line treatment is presented in Figure 8. The Kaplan–Meier curves for the two treatment groups demonstrates the [redacted]

Figure 8: Kaplan–Meier Plot of Overall Survival for Second-Line Treatment (T790M+adj Set)

[Figure Removed]

Analysis of OS by subgroup was performed and presented as a forest plot (Figure 9) for patients treated at 2nd line. Analysis was only conducted if, for each subgroup level, there

were at least 20 events combined for both treatments and at least five events in each individual treatment. Therefore, hazard ratio was not calculable for some subgroups. The analysis demonstrated [redacted].

Figure 9: Forest Plot of Secondary Analysis of Overall Survival by Subgroup (T790M+adj Set) – Second-Line Patients

[Figure Removed]

Further Supportive Evidence

Supportive first line evidence

The phase I data presented at the ELCC show that when osimertinib was used as a first-line treatment among 60 patients (pooled 80mg and 160mg dose cohorts) with epidermal growth factor (EGFR) mutation positive advanced NSCLC:

- 77% of patients responded to treatment as measured by tumour shrinkage (objective response rate or ORR; 95% confidence interval (CI): 64%-87%).
- The median length of time that patients' disease was defined as 'progression-free' was 19.3 months, with 55% of patients remaining progression-free at 18 months (95% CI: 41%-67%).
- The median duration of response was non-calculable (NC) (95% CI: 12.5 months to NC) at the time of data cut off, with 53% of patients continuing to respond at 18 months (95% CI: 36%-67%).
- The most common adverse events were rash (78% overall; 2% ≥Grade 3), diarrhoea (73% overall; 3% ≥Grade 3), dry skin (58% overall; 0 ≥Grade 3) and paronychia (50% overall; 3% ≥Grade 3). All of the Grade 3 or above events in these categories occurred at the 160mg dose.

Leptomeningeal (LM) disease

At the ASCO congress in June 2016, clinical and safety data were presented for osimertinib in patients with leptomeningeal (LM) disease, a complication of epidermal growth factor receptor (EGFR) mutation-positive advanced non-small cell lung cancer (NSCLC), where cancer cells spread to the cerebrospinal fluid (CSF). LM is a devastating disease associated with advanced lung cancer.

The updated BLOOM Phase I trial results showed that irrespective of T790M status of patients, osimertinib led to a change in MRI signal intensity indicative of a reduction in central nervous system (CNS) lesions.[1]

Data from 21 patients treated with osimertinib 160mg once daily showed intracranial radiological improvement in seven patients, neurological function improvement in five patients, and clearance of tumour cells from the CSF at two consecutive visits in two patients.1 None of the 21 patients treated with osimertinib received concomitant radiotherapy or intrathecal chemotherapy. Fifteen patients remained on treatment at data cut-off (10 March 2016), of whom seven had been on treatment for more than nine months. [1]

Further data from the BLOOM study showed that osimertinib crossed the blood-brain barrier, particularly relevant in the context of patients with brain metastases. In six of nine patients, a greater than 50% decrease in EGFR mutation level was observed in the CSF up to cycle 9, day 1 of treatment, with a sustained reduction observed in five. These results support previously reported preclinical data demonstrating that osimertinib crosses the blood-brain barrier.[2]

These latest data in a first line setting and leptomeningeal disease, as well as the updated analysis in the currently licensed population, support the role of osimertinib in meeting a significant unmet medical need and give confidence in the durability of patient responses.

References

1. Yang JCH, *et al*. Osimertinib activity in patients (pts) with leptomeningeal (LM) disease from non-small cell lung cancer (NSCLC): updated results from BLOOM, a Phase I study. Abstract 9002 [Oral Presentation]. Presented at the annual meeting of the American Society of Clinical Oncology, 3-7 June 2016, Chicago, USA.

2. Ballard P, *et al.* Preclinical activity of AZD9291 in EGFR-mutant NSCLC brain metastases. Presented at the World Congress on Lung Cancer, 6-9 September 2015. Denver, Colorado, USA.

Response to the Appraisal Consultation Document (ACD) Appendix 2 – Updated Cost Effectiveness Analysis – Technical Report

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Osimertinib for locally advanced or metastatic, EGFR and T790M mutation positive non-small cell lung cancer [ID874]

Single technology appraisal (STA)

File name	Version	Contains confidential information	Date
ID874_Osimertinib_ACD_Response_Appendix2[CIC_AIC]	1.0	Yes	14 July 2016

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Section 1. Updated disease progression and overall survival model inputs

The updated cost effectiveness model contains PFS and OS data from the November 2015 data cut off (DCO3) for both the pooled data from the AURAext/2 studies and the IMPRESS study.

AURAext/2 pooled data

At the time of the most recent data cut (DCO3), the PFS data were 55% mature and the OS data were 24% mature. PFS was equally mature across lines while OS was more mature in ≥ third line (26%) than in second line patients (19%). The non-parametric analyses for PFS and OS from the AURAext/2 pooled data are summarised in Table 1.

Table 1: Summary of AURAext/2 non-parametric data (DCO3)

Outcome	**Number of patients (N)**	**Second line**	**≥Third line**
		129	282
Progression-free survival	Total number of events (%)	[redacted]	[redacted]
	Median PFS (months) & 95% CI	[redacted]	[redacted]
Overall survival	Total number of events (%)	[redacted]	[redacted]
	Median OS (months) & 95% CI	[redacted]	[redacted]

Platinum doublet chemotherapy – IMPRESS data

The original KM data for platinum doublet chemotherapy collected in the IMPRESS study (PFS and OS) were included for the parametric analyses to be applied in the economic model. There were 132 patients in the IMPRESS platinum doublet chemotherapy arm who received at least one dose of the investigational product (full analysis set). Of these 132 patients, 61 patients were EGFR and T790M mutation positive and were included in the parametric analyses for the base case analysis. At the time of final data cut (November 2015), PFS data were 79% mature and the OS data were 72% mature for this group (see Table 2).

Table 2: Summary of IMPRESS non-parametric data (November 2015 DCO)

Outcome	**Number of patients (N)**	**Platinum doublet chemotherapy, T790M mutation positive patients**
		61
Progression-free survival	Total number of events (%)	48 (79%)
	Median PFS (months) & 95% CI	5.3 (4.0, 5.6)
Overall survival	Total number of events (%)	[redacted]
	Median OS (months) & 95% CI	[redacted]

1.1 Parametric survival models

Consistent with the NICE decision problem and to ensure a relevant clinical comparison, the updated base case analysis focuses on a comparison of patients who received osimertinib after progression on one prior line of treatment for their advanced EGFRm NSCLC with similar patients who had received platinum doublet chemotherapy in the second-line setting. The model is therefore based on data taken from the relevant population in the pooled AURAext/2 studies (n=129) and the T790M mutation positive control arm of the IMPRESS study (n=61). Utilising clinical efficacy data from this population in AURAext/2 reflects the most likely position of osimertinib in the UK treatment pathway, with both clinical experts at the first committee meeting commenting that osimertinib would only be used for people with EGFR mutation-positive NSCLC whose disease has progressed after first-line EGFR TKI treatment (ACD Section 4.2). Restricting the AURAext/2 data to second-line only patients provides the most relevant and robust clinical comparison with the IMPRESS T790M population, which consists of patients who received one line of prior TKI treatment. The results from the adjusted indirect comparison show that osimertinib is associated with a PFS HR of [redacted] and an OS HR of [redacted] compared with platinum doublet chemotherapy.

We provide two approaches to the analysis of the updated PFS and OS data from both studies:

- **Applying adjusted data used for the adjusted indirect comparison between osimertinib and platinum doublet chemotherapy from AURAext/2 DCO3 and IMPRESS (sections 1.2.1 – 1.2.3)**
- **Applying unadjusted data based on a naïve comparison of osimertinib and platinum doublet chemotherapy from AURAext/2 DCO3 and IMPRESS (Appendix 1)**

For both datasets, standard guidance for fitting and selecting survival functions was used and a full step-wise description of the statistical analysis based on published NICE DSU guidance [NICE 2011]. Similar to the original submission, the updated analysis uses independent survival models for osimertinib and platinum doublet chemotherapy. The parametric model fitting is based on the PFS and OS data from AURAext/2 and IMPRESS (T790M subgroup) extrapolated using standard parametric models (exponential, Weibull, Gompertz, log-logistic, log-normal, and generalised Gamma). Visual inspection and statistical goodness-of-fit were used to assess the parametric models for PFS and OS.

1.2.1 Adjusted data from AURAext/2 and IMPRESS DCO3

As summarised previously, the efficacy of osimertinib compared with platinum doublet chemotherapy was assessed using an adjusted indirect comparison of two study data sets: AURA pooled (N=405) and the T790M pemetrexed + cisplatin arm of IMPRESS (N=61).

Prior to the analysis of progression-free survival (PFS) and overall survival (OS), differences between baseline demographic and disease characteristics were accounted for by a three-step process of adjustment, termed cohort balancing. The three steps were:

1. Analysis of statistical differences between baseline variables, selection of variables with p-value <0.2.

2. Generation of a propensity score to represent aggregated differences in variables selected

3. Assessment of overlap in the propensity scores for the two treatment groups and exclusion of patients whose propensity score is outside the overlapped range. This results in a so called trimmed or adjusted dataset.

The survival analysis for the second-line population was then performed applying the inverse probability weighting (IPW) method using the propensity score.

Estimation of propensity scores

The propensity score for an individual is the probability of being treated with osimertinib or platinum doublet chemotherapy conditional on the individual's baseline variables. The propensity score for each patient was estimated using logistic regression modelling. Specifically, the probability of being in the treatment or control cohort conditional on observable variables was estimated. The selection of potential baseline variables was based on those used in the AURA and IMPRESS studies and that were judged to be clinically-relevant for response to treatment. Inclusion of baseline variables in the regression model for estimating the propensity score was based on the difference between the OSI and PDC groups of p-value <0.2 for the specific variable. The following variables remained for inclusion in the regression model:

- Age
- Region
- Ethnicity
- Baseline target lesion size [imputed]
- Smoking pack year history [0=Never, 1=Ever with PYs<30, 2=Ever with PYs>=30]
- Extent of disease: respiratory
- Extent of disease: hepatic (including gall bladder)
- Extent of disease: pericardial effusion
- Prior radiotherapy
- TNM Classification - Distant metastases [1=M0,2=M1,3=MX]
- TNM Classification - Regional lymph nodes [1=N0,2=N1,3=N2,4=N3,5=N4,6=NX]

Table 3 presents the summary statistics used to estimate the propensity scores. Further details of the estimation of propensity scores from AURAext/2 DCO3 and IMPRESS can be found in the full updated technical report [see Appendix 3].

Table 3: Baseline demographic and disease characteristics used for generation of regression model for estimation of the propensity scores

Variable	Osimertinib	Platinum doublet chemotherapy	Std. Diff.	p value
Total number of patients	[redacted]	[redacted]		
Age cont (N) mean, sd median min, max	[redacted]	[redacted]	[redacted]	[redacted]

Region (n, %) Asia Rest of the world	[redacted]	[redacted]	[redacted]	[redacted]
Ethnicity (n, %) Asian Other	[redacted]	[redacted]	[redacted]	[redacted]
Baseline target lesion size imputed (N) mean, sd median min, max	[redacted]	[redacted]	[redacted]	[redacted]
Smoking pack year history [0=Never, 1=Ever with PYs<30, 2=Ever with PYs>=30 (n, %) 0 1 2	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory	[redacted]	[redacted]	[redacted]	[redacted]
Hepatic [including gall bladder]	[redacted]	[redacted]	[redacted]	[redacted]
Pericardial effusion	[redacted]	[redacted]	[redacted]	[redacted]
Prior radiotherapy	[redacted]	[redacted]	[redacted]	[redacted]
TNM Classification - Distant Metastases	[redacted]	[redacted]	[redacted]	[redacted]
TNM Classification - Regional Lymph Nodes N3 or N4	[redacted]	[redacted]	[redacted]	[redacted]

Note: For categorical variables, p-values were based on Chi-Square test or Fishers exact test (50% or more of the cells have expected counts of less than 5). For continuous variables, p-values were based on T-Test or on the Wilcoxon rank-sum test if normality assumption was violated (Shapiro-Wilk test). Platinum doublet chemotherapy=Standard-of-care [=placebo arm of IMPRESS study]

Assessment of overlap in the propensity scores across cohorts and trimming

Overlap is the degree to which cohorts have a shared range of estimated propensity scores. The overlap was defined as all values between the minimum of the propensity score in patients treated with osimertinib and the maximum of the propensity score in patients treated with platinum doublet chemotherapy. Patients outside the overlap were dropped from the analyses, termed trimming, as they are not comparable to patients in the other treatment group. Subjects with propensity scores not included within the overlapping region were not included in subsequent analyses i.e. they were trimmed from the data set. For the second-line population, the adjusted trimmed dataset resulted in n=92 patients in the osimertinib arm and n=53 patients in the platinum doublet chemotherapy arm.

Table 4 summarises the key baseline demographic and disease characteristics of patients retained in the trimmed dataset for the second-line only population. Based on this trimmed dataset, patients in the osimertinib arm were significantly older than patients in the PDC arm (61.8 versus 56.7 years, p-value 0.0082). No statistically significant differences were observed between the two treatment arms for other key baseline patient and demographic characteristics. Consequently, this adjusted dataset provides the best possible approximation to a true randomised comparison between osimertinib and platinum doublet chemotherapy in the second-line setting and was chosen for the updated base case analysis.

Further details of the adjusted indirect comparison can be found in the full updated technical report in Appendix 3 to the ACD Response.

Table 4: Demographic and disease characteristics of patients in adjusted dataset – second-line population

Variable	Osimertinib	Platinum doublet chemotherapy	Std diff.	p-value
Total number (%) of patients	[redacted]	[redacted]	-	-
Age Mean, SD Median Min, max	[redacted]	[redacted]	[redacted]	[redacted]
Sex, n (%) Females Males	[redacted]	[redacted]	[redacted]	[redacted]
Smoking, n (%) Never Ever Current	[redacted]	[redacted]	[redacted]	[redacted]
EGFR mutation, n (%) Exon 19 deletion L858R in exon 21 Unknown	[redacted]	[redacted]	[redacted]	[redacted]
WHO/ECOG PS, n (%) 0 1 2	[redacted]	[redacted]	[redacted]	[redacted]
Metastatic at baseline, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Brain metastatic at baseline, n (%)	[redacted]	[redacted]	[redacted]	[redacted]

Survival analysis with inverse probability weighting

Standard parametric survival models were estimated including a weight for each patient. Patients were assigned a weight based on the inverse of the propensity score. Osimertinib patients were weighted as 1/PS and PDC patients were weighted as 1/(1- PS).

1.2.2 Visual Inspection and Statistical Fit – adjusted dataset

Figures 1 and 2 present the overlaid modelled parametric curves to the non-parametric PFS and OS KM plots for osimertinib and platinum doublet chemotherapy for all candidate survival functions based on the adjusted dataset. The equivalent figures and tables for the unadjusted dataset for AURAext/2 and IMPRESS are provided in Appendix A to this document.

(a) Progression-free Survival

For platinum doublet chemotherapy, the Gompertz, Weibull and Generalised gamma provide adequate PFS estimates and fit to the observed KM data with the log logistic and exponential models overestimating PFS in the tail of the distribution (from approximately 8 months).

For osimertinib, all parametric models provide relatively good provide adequate PFS estimates and fit to the observed KM data. However the log-normal, log-logistic and

potentially the exponential models may tend to overestimate PFS in the tail of the curve with approximately 10% of osimertinib patients still alive and progression free after 5 years. In the absence of longer term clinical data to validate these estimates, the Gompertz and Weibull models distributions provide a more conservative extrapolation (based on the tail of the KM data) and provide a good visual fit to the observed data. The generalized gamma also provides a clinically plausible fit to the observed PFS KM data for osimertinib.

Table 5: PFS rate at various time-points of the parametric survival models applied to the AURAext/2 and IMPRESS T790M mutation positive population

PFS	IMPRESS			AURAext/2		
	4 months	**6 months**	**8 months**	**4 months**	**6 months**	**8 months**
Exponential	45.4%	30.2%	21.1%	77.5%	67.9%	60.5%
Weibull	54.1%	28.5%	13.9%	84.0%	73.3%	63.8%
Gompertz	57.9%	31.4%	12.6%	82.4%	72.8%	64.2%
Log-logistic	50.3%	29.2%	18.8%	84.0%	72.2%	62.3%
Log-normal	47.8%	27.3%	17.1%	81.7%	70.0%	61.8%
Generalised gamma	59.7%	34.7%	12.8%	83.8%	72.7%	63.1%
Non-parametric data (ITC)	**62.6%**	**35.4%**	**14.7%**	**86.4%**	**76.7%**	**63.8%**

Table 6 summarises statistical goodness-of-fit in terms of Akaike's Information Criterion (AIC) and Bayesian Information Criterion (BIC) for the PFS estimates.

Based on the AIC and BIC statistics, the Log-logistic distribution provides the best fit for osimertinib but ranks in fifth place (AIC) for platinum doublet chemotherapy. The Generalized gamma distribution provides the best fit for platinum doublet chemotherapy but ranks third or sixth for osimertinib. The exponential and log-normal generally rank low for both treatments.

Table 6: Goodness-of-fit statistics for PFS for platinum doublet chemotherapy from the control arm of IMPRESS (T790M) and osimertinib from AURAext/2 second-line population

	PDC		Osimertinib	
	AIC (#)	**BIC (#)**	**AIC (#)**	**BIC (#)**
Exponential	934.72 (6)	936.67 (6)	420.6 (6)	423.2 (3)
Weibull	875.7 (3)	879.6 (2)	415.8 (2)	420.9 (2)
Gompertz	871.32 (2)	875.2 (2)	418.6 (5)	423.6 (5)
Log-logistic	903.5 (5)	907.5 (5)	**415.3 (1)**	**420.3 (1)**
Log-normal	889.2 (4)	893.1 (4)	418.5 (4)	423.5 (4)
Gen gamma	**861.8 (1)**	**867.7 (1)**	417.6 (3)	425.2 (6)

In accordance with NICE DSU guidance, the same parametric models were selected for both treatment arms. The Gompertz distribution was selected for PFS in the base case analysis due to having the best statistical fit for PDC and the best visual fit for both treatment groups. A scenario analysis is also presented using the Weibull distribution because it also provides a good visual and statistical fit to the non-parametric data from AURAext/2 and IMPRESS.

Figure 1: Predicted model time in progression-free health state for all parametric distributions compared with observed PFS data (adjusted dataset)

[Figure Removed]

(b) Overall Survival

For platinum doublet chemotherapy, the log-logistic, log-normal and generalised gamma all provide a reasonable fit during the observed data period and also provide an adequate extrapolation beyond the observed data (based on the tail of the KM data). The Gompertz and exponential distributions do not provide adequate visual fit to the observed data ~~up~~. Importantly, the Gompertz and Generalized gamma distributions both produce a clinically implausible situation where the OS curves for osimertinib and platinum doublet chemotherapy intersect, resulting in a longer tail of patients still alive in the PDC arm. Due to the steep curve for the Gompertz distribution, it generates OS estimates that are clinically implausible and lack face validity, due to the curves for osimertinib and PDC crossing over at approximately 40-45 months follow-up depending on the dataset used. This sharp decline is possibly due to the large amount of censoring at the tail of the KM curve. Similarly, the generalised gamma distribution produces a clinically implausible scenario where the OS curves for osimertinib and platinum doublet chemotherapy intersect during patient follow-up.

The visual inspection of the OS curves for osimertinib shows that all curves have very similar fit up to 15 months where approximately 80% of patients are still alive. The Weibull provides the best fit for the observed data and appears to provide clinically plausible extrapolations. However, in our opinion, the log-normal distribution produces an implausibly high OS estimate for osimertinib (median OS=75 months) and the exponential and log-logistic models provide estimates that appear optimistic. The other distributions provide median OS estimates between 29 months and 40 months.

Table 7: Survival rate at various time-points of the parametric survival models applied to the AURAext/2 and IMPRESS T790M mutation positive population

	IMPRESS				**AURAext/2**			
	9 months	**12 months**	**18 months**	**24 months**	**12 months**	**24 months**	**60 months**	**120 months**
Exponential	70.1%	62.3%	49.3%	39.0%	84.3%	71.1%	42.9%	18.4%
Weibull	78.6%	69.8%	52.9%	38.4%	84.5%	68.4%	32.9%	8.1%
Gompertz	72.7%	64.9%	51.1%	39.4%	84.8%	62.2%	15.1%	0.0%
Log-logistic	78.7%	66.9%	46.2%	31.8%	84.5%	69.9%	43.0%	24.3%
Log-normal	79.7%	68.1%	48.4%	34.3%	84.3%	73.5%	55.0%	39.8%
Generalised gamma	77.4%	63.7%	44.8%	33.6%	84.5%	66.8%	20.7%	0.2%
Non-parametric data	**82.2%**	**62.1%**	**43.6%**	**26.4%**	**83.3%**	**N/A**	**N/A**	**N/A**

Table 8 summarises statistical goodness-of-fit in terms of Akaike's Information Criterion (AIC) and Bayesian Information Criterion (BIC) for the OS estimates.

Based on the AIC and BIC statistics, the generalized gamma distribution, followed by the log normal, has the best fit for platinum doublet chemotherapy, whilst only being ranked #6 and #5 for osimertinib, respectively. The exponential model has the best fit for osimertinib but ranks #5 or #6 for platinum doublet chemotherapy.

Table 8: Goodness-of-fit statistics for OS for platinum doublet chemotherapy from the control arm of IMPRESS (T790M) and osimertinib from AURAext/2 second-line only population

	OS			
	PDC		Osimertinib	
	AIC (#)	BIC (#)	AIC (#)	BIC (#)
Exponential	1177.6 (6)	1179.6 (5)	**181.8 (1)**	**184.4 (1)**
Weibull	1156.5 (4)	1160.5 (4)	183.4 (3)	188.4 (3)
Gompertz	1177.2 (5)	1181.1 (6)	183.1 (2)	188.1 (2)
Log-logistic	1124.6 (3)	1128.5 (3)	183.5 (4)	188.6 (4)
Log-normal	1119.4 (2)	1123.3 (2)	185.0 (5)	190.1 (5)
Gen gamma	**1104.0 (1)**	**1109.9 (1)**	185.3 (6)	192.8 (6)

Overall, the Weibull distribution appears to produce the most reasonable fit to the non-parametric OS data, based on the November 2015 DCO from AURAext/2 and IMPRESS (T790M) and was therefore selected to model OS in the base case analysis. Scenario analyses for both datasets are also presented using the exponential and log-logistic distributions for OS.

Figure 2: Predicted model time alive (overall survival) for all parametric distributions compared with observed OS data (adjusted dataset)

[Figure Removed]

1.2.3 Parametric survival models – base case analysis

Figure 3 presents the median PFS based on Gompertz distribution, and OS based on the Weibull distribution for osimertinib and PDC showing an incremental median PFS gain of 6.46 months and an incremental median OS gain of 21 months for osimertinib compared with PDC.

Figure 3. Median duration of the parametric distributions used in the base case analysis – adjusted dataset

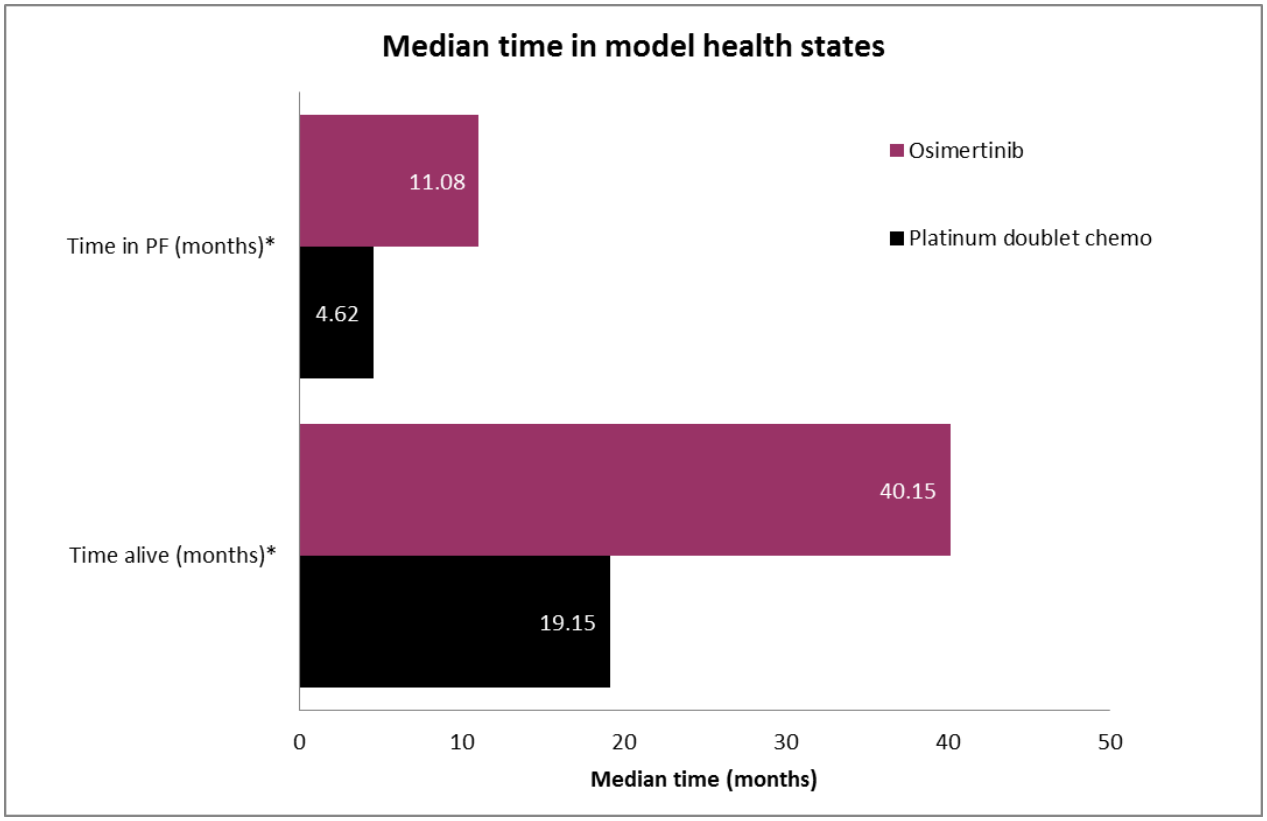


Figure 4 presents the Gompertz PFS and Weibull OS parametric functions used in the base case compared with the observed data from the trials. Approximately 33% of patients treated with osimertinib are alive at 5 years compared with 3% of patients on platinum doublet chemotherapy. After 10 years in the model (120 months in Figure 4), the proportion of patients alive is 8% for osimertinib and 0% for platinum doublet chemotherapy.

Figure 4: Overall and progression-free survival curves used in the base case analysis – adjusted dataset

[Figure Removed]

Section 2. Utility values in the model

In section 4.11 of the ACD the Committee concluded that *"there was uncertainty in the utility values used by the company because they were based on non-UK validated EQ-5D-5L data from a small number of people, and there were concerns about the face validity compared with the general population"*.

AstraZeneca believe that the health state utility values (HSUVs) obtained from the AURA2 study are the most relevant source of utility values for the population being considered in this appraisal, that is, patients with EGFR T790M mutation-positive locally advanced or metastatic NSCLC. This produced utility values of 0.815 for the progression-free state and 0.678 for the progressed state based on data from DCO2 in the original submission. The ERG comment that the utility values were taken from non-UK patients and that the ECOG performance status of 0-1 of patients in AURA2 may not be reflective of a number of patients seen in the UK who would have an ECOG PS of $\geq$2. However, as the Committee heard from the clinical experts, people with EGFR mutation-positive NSCLC are generally younger, fitter and less likely to be smokers than people with other types of lung cancer. The Committee also concluded that the AURAext/2 trials were broadly generalizable to UK clinical practice (ACD section 4.3). Furthermore, the significant and sustained tumour response rates observed in patients treated with osimertinib (66%) in AURAext/2 are likely to be important factors in the improved quality of life for people with this condition, as reflected in the ACD (section 4.4).

The ERG argue in their report that it seems implausible that a person with advanced NSCLC will have a higher utility value (0.815) than the average person in the UK of a similar age (0.80), citing the UK population norms for the EQ-5D-3L published in 1999 [Kind 1999]. As the ACD correctly states, because a validated EQ-5D-5L dataset for the UK was not available at the time of submission, it is difficult to compare these EQ-5D-5L crosswalk values with values derived from sources using the EQ-5D-3L dataset.

We also wish to reiterate that the utility values derived from the AURA2 study are comparable to utility estimates obtained from previous studies of targeted therapies for locally advanced or metastatic NSCLC. For example, the PROFILE 1007 RCT of crizotinib versus chemotherapy in previously treated patients with ALK-positive advanced NSCLC produced a utility value of 0.82 for patients on crizotinib treatment. A similar objective response rate of 65.3% was reported for crizotinib compared to only 19.5% for the chemotherapy group in the PROFILE 1007 trial, demonstrating a strong correlation between tumour response rates and HRQoL.

As commented by the ERG in their report, there are no published alternative utility values that relate explicitly to the population of interest in this appraisal and so they suggest two studies which provide utility values that could be closer to the real utility of the target population: (i) the LUME-Lung 1 trial and (ii) the Nafees et al. study [NICE 2015; Nafees 2008].

We would argue that the ERG's rationale for using utility values from LUME-Lung 1 and Nafees et al. does not hold. The LUME-Lung 1 study collected EQ-5D-3L data across 27 countries and included patients with ECOG PS of 0-1, thus having exactly the same limitations as the AURA2 study suggested by the ERG. Patients in LUME-Lung 1 were not previously treated with an EGFR-TKI and T790M mutation status was unknown at the time of progression on prior therapy. In this study, patients received cytotoxic chemotherapy rather than a tolerable once-a-day tablet formulation such as osimertinib. Furthermore, patients in LUME-Lung 1 were younger (mean age 58.5 years versus 62.9 years) and had

fewer brain metastases at baseline (5.8% versus 28.6%) compared with patients in AURA2. This suggests that the patient cohort in LUME-Lung 1 is and even less generalizable to UK clinical practice than the AURA2 patient cohort and does not represent the population of interest to this appraisal, that is, patients with EGFR and T790M mutation positive advanced NSCLC that has been previously treated with an EGFR-TKI.

We would agree with the committee's statement that the utility values from the Nafees et al. study are not appropriate to use in the model because they are not based on the EQ-5D instrument and hence do not meet the NICE reference case [NICE 2013]. As stated in the ERG report, valuations of health states from Nafees et al. are taken from the general population while the health states themselves were simple hypothetical descriptions based on breast cancer health states. The ERG's suggestion that these values may provide a better reflection of the experience of patients with advanced or metastatic NSCLC is highly questionable.

In light of the above, AstraZeneca proposes three possible sources of HSUVs to be considered in the updated cost-effectiveness analysis:

(i) Updated HSUVs based on DCO3 from AURA2 EQ-5D-5L crosswalk

(ii) Updated HSUVs based on DCO3 from AURA2 EQ-5D-5L England Valuation Set

(iii) HSUVs based on the IMPRESS Study EQ-5D-3L UK Valuation Set

A summary of the HSUVs obtained from these three sources is presented in Table 9.

As described in the original submission, the AURA2 study included EQ-5D-5L collected every 6 weeks, making it possible to derive utility values directly from the trial data. An EQ-5D index score was calculated for each subject and visit and by line of treatment, based on the latest data cut from AURA2 (DCO3). At the time of original submission an EQ-5D-5L UK valuation set had not been formally published or recommended by NICE, therefore the EQ-5D-5L crosswalk index values for the UK were applied. When compared with the HSUVs obtained from AURA2 DCO2, the utility values from DCO3 are similar for the progression-free state (0.812 versus 0.815) but significantly higher for the progressed disease state (0.751 versus 0.678). This could be explained by the high proportion of patients who experienced a complete or partial response to osimertinib as well as the high proportion of patients continuing osimertinib treatment post progression and who continued to benefit from their treatment beyond the point of RECIST-defined progression.

The Office for Health Economics (OHE) recently published a research paper which summarises an EQ-5D-5L value set for England [Devlin 2016]. This study collected data via face-to-face interviews with a representative sample of the adult population in England (n=996) in which participants valued 10 health states using a time trade-off approach and completed seven discrete choice tasks. The data were then used to model values for all 3,125 states described by the EQ-5D-5L instrument. When the EQ-5D-5L value set for England was applied to the data from AURA 2 (DCO3), the resultant utility values for both the PF (0.874) and PD (0.821) states were significantly higher than those obtained from the crosswalk value set. These higher utility values are expected as the authors comment that the EQ-5D-5L value set has a higher value for the worst possible health state (-0.281 versus -0.594) and substantially fewer worse than dead values (4.93% versus 26.7%) compared with the crosswalk value set. To date, no UK or England population norms have been produced for the EQ-5D-5L value set and thus it is not possible to compare these mean utility values with an age and gender-matched cohort in the UK population.

As described in the original submission, the IMPRESS study collected EQ-5D-3L data in a similar manner to the AURA2 study and index scores were calculated using a similar approach. These produced utility values of 0.779 for the PF state and 0.679 for the PD state. We note that the ERG did not comment on the face validity or the appropriateness of these utility values for use in the cost-effectiveness model in their report. Specifically, the utility values from the IMPRESS study address two concerns raised by the committee: (i) the EQ-5D-3L instrument has a validated health state valuation set for the UK and; (ii) the mean PF utility value is lower than the mean utility value of people aged 55-64 in the UK (0.779 versus 0.80). Furthermore, the patient cohort from which the utility values were estimated is relevant to the population being considered in this appraisal as it is based on patients with EGFR mutation-positive NSCLC whose disease has progressed following prior therapy with an EGFR-TKI. Therefore, further consideration should be made by the committee of these values in the cost-effectiveness analysis and the impact on the ICERs for osimertinib compared with platinum doublet chemotherapy.

Table 9: Summary of HSUVs from AURA2 (DCO3) and IMPRESS studies

Health state	n	Mean utility	Standard deviation
(i) AURA2 EQ-5D-5L Crosswalk values			
Progression-free	158	0.812	0.181
Post-progression	70	0.751	0.261
(ii) AURA2 EQ-5D-5L England Value Set			
Progression-free	158	0.874	0.147
Post-progression	70	0.821	0.217
(iii) IMPRESS EQ-5D-3L Index Values (Platinum doublet chemotherapy arm)			
Progression-free	119	0.779	0.210
Post-progression	88	0.679	0.271

Section 2.1 Utility values incorporating response rates

In the ACD the committee concluded that the benefits of improving objective response rates should have been included in the model previously submitted to NICE (ACD Section 4.12). Therefore, we have updated the model accordingly by adjusting the progression-free state utility values according to objective response rates (ORRs) observed in AURAext/2 for osimertinib and IMPRESS for platinum doublet chemotherapy. From both studies it was possible to calculate average EQ-5D utility values split by best objective response (Complete + Partial Response; Stable Disease) for the progression-free state. These utility values were then weighted by the respective ORRs observed in AURAext/2 (second-line population) and IMPRESS for:

(a) adjusted indirect comparison: the analysis of ORR by logistic regression showed that patients treated with osimertinib demonstrated a statistically significant improvement in ORR (n=60/89; 67.4%) compared with platinum doublet chemotherapy (n=16/48; 33.3%) resulting in an odds ratio of 5.63 (95% CI 2.32 to 13.67; p-value <0.001).

(b) unadjusted data from AURAext/2 and IMPRESS: The unadjusted pooled data from AURAext/2 produced an ORR of 67.7% (n=84/124) while the T790M subgroup in the platinum doublet chemotherapy arm of IMPRESS had an ORR of 39.3% (n=24/61).

The model assumed that objective response occurred at treatment initiation and remained constant throughout the duration that the patient remained in the progression-free state. A summary of the utility values incorporating response rates from AURA2 DCO3 and IMPRESS and implemented in the updated cost effectiveness model is provided in Table 10.

Table 10: Summary of HSUVs from AURA2 and IMPRESS incorporating objective response rates

Health State	Mean Utility Value	n	Osimertinib		Platinum doublet chemotherapy	
			Adjusted (ORR 67.4%)	Unadjusted (ORR 67.7%)	Adjusted (ORR 33.3%)	Unadjusted (ORR 39.3%)
(i) AURA2 EQ-5D-5L Crosswalk values						
PF – CR+PR PF – Stable Disease	0.833 0.753	116 42	0.807	0.807	0.779	0.784
PD – All	0.751	70	0.751			
(ii) AURA2 EQ-5D-5L England Value Set						
PF – CR+PR PF – Stable Disease	0.891 0.825	116 42	0.869	0.870	0.847	0.851
PD – All	0.821	70	0.821			
(iii) IMPRESS EQ-5D-3L Index Values						
PF – CR+PR PF – Stable Disease	0.831 0.751	43 75	0.805	0.805	0.778	0.783
PD – All	0.679	88	0.679			

Utility values in updated base case analysis

When incorporating treatment-specific response rates, the estimated HSUVs from AURA2 EQ-5D-5L crosswalk and the IMPRESS EQ-5D-3L values are very similar. However, for the updated base case analysis using both the adjusted and unadjusted AURAext/2 and IMPRESS datasets, the HSUVs from IMPRESS adjusted for treatment-specific response rates were applied for the progression free state. For the progressed disease state, a value of 0.715 was applied as the midpoint between the respective utility values from AURA EQ-5D-5L crosswalk value (0.751) and IMPRESS EQ-5D-3L (0.679). This midpoint value was chosen as it reflects the sustained tumour response experienced by patients in AURAext/2 as well as reflecting the significant proportion (77%) of patients who continued and responded to treatment following RECIST progression.

Section 3. Costs of osimertinib treatment

The ACD states that the clinical experts agreed that the costs of osimertinib based on time-to-treatment discontinuation (TTD) were the most appropriate to use and the Committee concluded that TTD should have been used to calculate the acquisition costs of osimertinib (ACD Section 4.13). However, whilst we acknowledge that a significant proportion of patients in AURAext/2 continued osimertinib treatment post-progression, this can be explained by the fact that a significant proportion of patients in AURAext/2 (68.6%) had received prior treatment with an EGFR-TKI and chemotherapy (≥ third-line population) and thus would have limited treatment options following disease progression. In addition, our recollection from the committee meeting was that the clinical experts agreed that EGFR and T790M mutation positive NSCLC patients seen in UK clinical practice would most likely be second-line only patients and would probably continue to receive osimertinib for no more than a couple of months following disease progression before switching to alternative treatments such as platinum doublet chemotherapy where good performance status is required. The latest data available from AURAext/2 (DCO3) shows that 77.3% of patients in the second-line only population continued on osimertinib treatment after disease progression and that the median duration of treatment after progression was 2.7 months (see Table 11).

Table 11: Duration of osimertinib treatment after progression in AURAext/2 (DCO3) based on investigator assessment

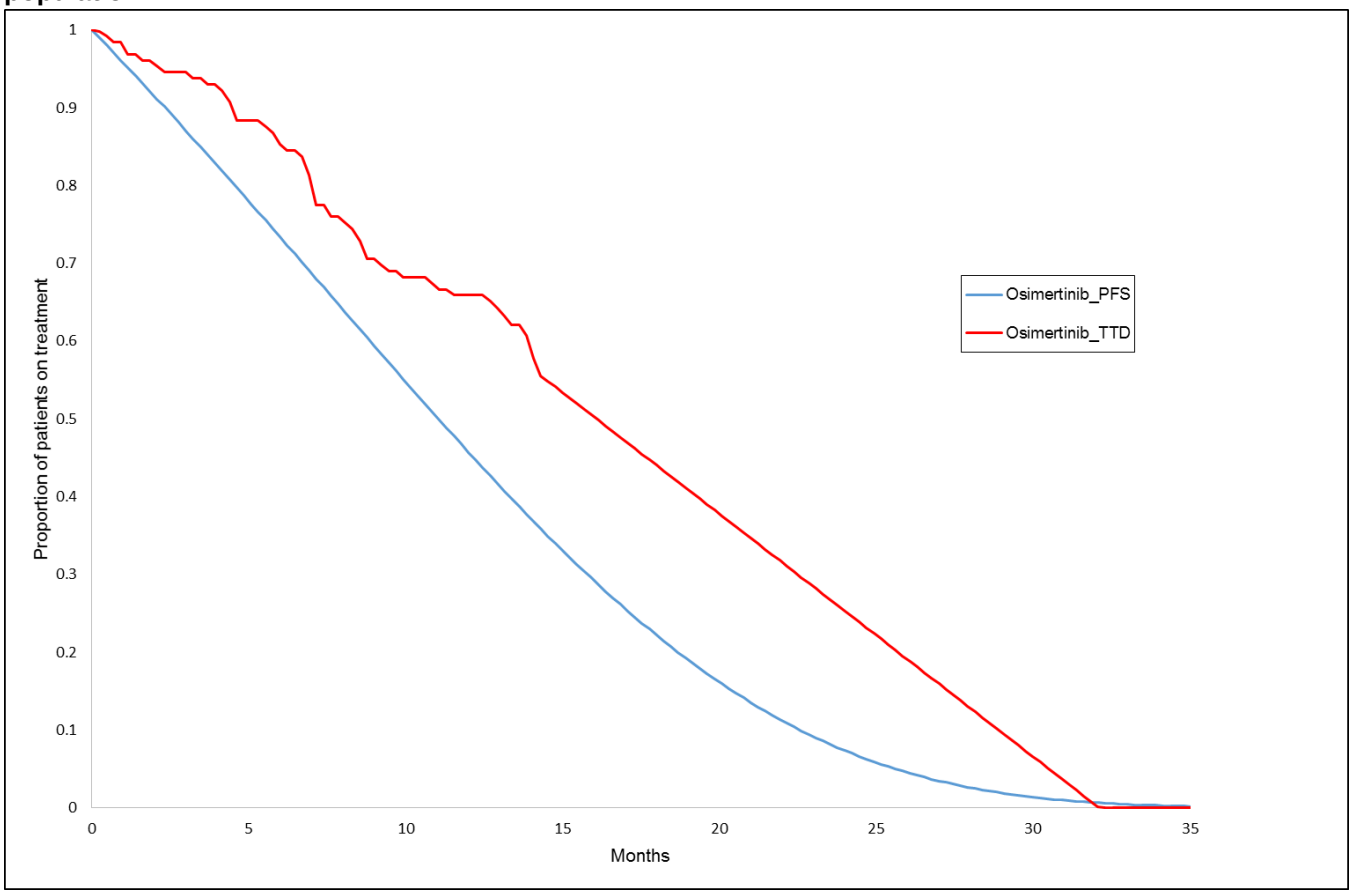
Variable	2nd–line Only (n=129)	≥ Third-Line (n=282)
Number of patients who progressed or died	72	171
Number (%) of patients who progressed	66 (91.7%)	156 (91.2%)
Number (%) of patients who received osimertinib after progression	51 (77.3%)	105 (67.3%)
Median duration of osimertinib treatment after progression (months)	**2.7**	**4.3**

Therefore, we have identified two alternative methods for estimating the costs of osimertinib treatment following disease progression, both of which have been implemented in the updated cost-effectiveness model submitted as part of the ACD response.

3.1 TTD using a simple linear extrapolation

In the ERG's analysis of TTD data from AURAext/2 (DCO2), a simple linear trend from 0-313 days was estimated and then applied from 313 days to estimate TTD beyond the point KM data were available. Based on the latest November 2015 data cut from AURAext/2 (DCO3), TTD data were 40.3% mature (n=52 events) for the second-line only population unadjusted dataset (n=129). Using the same approach as the ERG, a simple linear trend was estimated between 0-431 days for the second-line only population from AURAext/2, with the simple linear trend continued beyond this timepoint. This resulted in patients in the second-line population stopping osimertinib treatment at 973 days (median TTD 16.2 months). A plot of TTD over time from AURAext/2 is presented for the second-line population along with the best-fitting PFS parametric function (Gompertz) in Figure 5.

Figure 5: TTD based on simple linear extrapolation and PFS curve – Osimertinib 2nd-line population



3.2 Median duration of osimertinib treatment post progression

An alternative approach to calculating the costs of osimertinib following disease progression uses the median duration of treatment data from AURAext/2 (DCO3) and is presented in Table 11 for the second-line only and ≥ third-line populations. This approach is implemented in the updated model by using the modelled PFS curve used in the base case analysis (Gompertz distribution) to calculate the treatment cost of osimertinib but with an additional cost of osimertinib applied in each weekly cycle. This additional cost is calculated by taking the number of patients who leave the PF state in each weekly cycle in the model. This is then multiplied by the proportion of patients who enter the PD state from the PF state (91.7% for the second-line only population) and then by the proportion of patients who received osimertinib post progression (77.3% for the second-line only population). This proportion of patients is then multiplied by both the fixed cost of osimertinib for each weekly cycle and the median duration of treatment after progression (2.7 months for the second-line only population).

In the updated base case analysis, the costs of osimertinib treatment were based on a simple linear extrapolation of TTD data from AURAext/2 DCO3. The approach of applying a simple median duration of osimertinib treatment post progression was applied in scenario analyses.

Section 4. Other minor amendments made to the updated cost-effectiveness model

4.1 Cost of osimertinib administration

The ACD states that the clinical experts at the first committee meeting agreed that the administration costs of osimertinib were partially included in the model as part of monthly outpatient visits but highlighted that the model did not include pharmacy dispensing costs (ACD Section 4.14). Therefore, we have updated the cost-effectiveness model with the additional monthly costs involved in dispensing osimertinib. A pharmacy dispensing cost of £14.40 has been applied for each monthly prescription of osimertinib. This is based on the cost of 12 minutes of a hospital pharmacist's time using an hourly rate of a hospital pharmacist of £72 taken from the PSSRU Unit Costs of Health and Social Care [PSSRU 2015]. This approach to applying a monthly cost of dispensing osimertinib is consistent with that taken in the company's cost effectiveness analysis for ceritinib for the second-line treatment of ALK-positive NSCLC [NICE 2016]

4.2 Calculation of Platinum doublet chemotherapy costs per dose

In the original cost-effectiveness model submitted the costs of IV platinum doublet chemotherapy are calculated based on the age, weight and gender distribution of patients in the AURAext/2 studies. In their report (Section 5.6.6; p.108), the ERG considered that the age, weight and distribution used to calculate the costs of IV platinum doublet chemotherapy in the model should be taken from the study by Sacco et al., which identified the characteristics of UK patients receiving palliative chemotherapy [Sacco 2010]. Therefore, the model has been updated accordingly to apply the estimated values for lung cancer patients in terms of body weight (63.4 kg for females and 74.7 kg for males) and mean body surface area (1.66m^2 for females and 1.89m^2 for males).

4.3 Cost of Platinum doublet chemotherapy

In the original cost effectiveness model the maximum number of cycles of platinum doublet chemotherapy (PDC) was set to a maximum of 6 cycles in line with the Summary of Product Characteristics (SPC) for Pemetrexed plus carboplatin/cisplatin. However, as correctly identified by the ERG, NHS protocols in England limit the number of cycles of pemetrexed-cisplatin cycles to four for the treatment of NSCLC. Therefore, the updated cost-effectiveness model limits the maximum number of cycles of platinum doublet chemotherapy to four cycles.

4.4 Updated Safety data

In line with the original submission, grade ≥3 adverse events were included in the model to account for the potential cost and quality of life burden of experiencing events whilst on treatment. The incidence rates were updated in the model based on DCO3 for the unadjusted dataset from AURAext/2 and are summarised along with the incidence rates for platinum doublet chemotherapy and single-agent monotherapy in table 12.

Table 12: Incidence rates of adverse events used in the updated model

	Second-line	≥Third-line	Platinum doublet chemotherapy (IMPRESS)	Docetaxel (Brown 2013)
Sample size (n)	n=129	n=282	n=132	n=100 (assumed)
Diarrhoea	1.6%	0.7%	0.8%	6.4%

Rash	0.0%	0.4%	–	
Nausea	0.8%	1.1%	4.5%	10.2%
Decreased appetite	0.8%	0.7%	2.3%	–
Platelet count decreased	0.8%	0.7%	–	–
Fatigue/asthenia	0.0%	1.4%	3.0%	9.0%
Oedema peripheral	0.0%	0.4%	–	–
Constipation	0.0%	0.4%	–	–
Cough	0.0%	0.4%	–	–
Stomatitis	–	–	0.8%	–
Vomiting	1.6%	0.4%	2.3%	10.2%
Anaemia	1.6%	2.8%	3.8%	–
Dyspnoea	1.6%	2.5%	2.3%	
Headache	0.0%	0.4%	0.8%	–
Febrile neutropenia	–	–	–	2.9%
Neutropenia / Leucopenia / Neutrophil count decreased	0.0%	4.3%	15.2%	62.1%
Back pain	0.0%	1.1%	–	–

4.5 Adverse Events Costs and Disutilities

In their report the ERG commented that the costs applied to Grade 3-4 adverse events in the model may have been too low in a number of instances, for example in the original model zero costs were applied for constipation, cough, stomatitis and headache. Although the ERG do not provide alternative cost estimates in their report, they conclude that the magnitude of AE costs and disutilities only have a minor impact on the ICER for osimertinib compared with platinum doublet chemotherapy. However, unit costs for all adverse events in the model have been updated accordingly based on the relevant estimates for non-elective long stay episodes provided in NHS Reference Costs 2014-15 [NHS 2015].

Similarly, the ERG report suggests that the disutilities associated with Grade 3-4 AEs in the model were implausibly low, although again they do not suggest alternative values in their report. Following an additional review of the relevant literature we were unable to identify any plausible alternative disutilities for nearly all of the Grade 3-4 events experienced in patients enrolled to AURAext/2 and IMPRESS. However, the company submission for nintedanib for previously treated aNSCLC estimated a higher disutility associated with grade 3-4 fatigue of 0.21 [NICE 2015]. Therefore, the updated model applies this disutility instead of the previous value of 0.073 taken from Nafees et al. All other Grade 3-4 disutilities in the model have remained the same.

Table 13: Revised Adverse Event Costs applied in updated cost effectiveness model

Adverse event	Cost	Source/comment
Diarrhoea	£2411.20	NHS Reference Costs 2014–15 FZ36G-FZ36Q Gastrointestinal Infections with Multiple Interventions – Non-elective long stay (Weighted Average)
Rash (grouped term)	£2666.09	NHS Reference Costs 2014–15 JD07A-JD07K Skin Disorders with Interventions – Non-elective long stay (Weighted Average)
Nausea/vomiting	£2245.09	NHS Reference Costs 2014–15 FZ91A-FZ91M Non-Malignant Gastrointestinal Tract Disorders with Multiple Interventions – Non-elective long stay (Weighted Average)
Decreased appetite	£2367.66	NHS Reference Costs 2014–15 FZ49F-FZ49H Nutritional Disorders without Interventions – Non-elective long stay (Weighted Average)
Platelet count decreased	£2425.65	NHS Reference Costs 2014–15 SA12G-SA12K Thrombocytopenia – Non-elective long stay (Weighted Average)
Neutropenia / Leucopenia / Neutrophil count decreased	£2426.86	NHS Reference Costs 2014–15 SA35A-SA35E Agranulocytosis – Non-elective long stay (Weighted Average)
Fatigue/asthenia/ anaemia	£3110.11	NHS Reference Costs 2014–15 SA01G-SA01K Acquired Pure Red Cell Aplasia or Other Aplastic Anaemia – non-elective long stay (Weighted Average)
Oedema peripheral	£1759.98	NHS Reference Costs 2014–15 WH10A-WH10B Unspecified Oedema – Non-elective long stay (Weighted Average)
Constipation	£2367.66	NHS Reference Costs 2014–15 FZ49F-FZ49H Nutritional Disorders without Interventions – Non-elective long stay (Weighted Average)
Cough/Dyspnoea	£1447.73	NHS Reference Costs 2014–15 DZ19J-DZ19N Other Respiratory Disorders – Non-elective long stay (Weighted Average)
Stomatitis	£1483.11	NHS Reference Costs 2014–15 CB02D-CB02F Non-Malignant Ear, Nose, Mouth, Throat or Neck Disorders without Interventions – Non-elective long stay (Weighted Average)
Headache	£1344.07	NHS Reference Costs 2014–15 AA31C-AA31E Headache, Migraine or Cerebrospinal Fluid Leak – Non-elective long stay (Weighted Average)
Back pain	£1679.85	NHS Reference Costs 2014-15 HC32H-HC32K: Low Back Pain Without Interventions – Non-elective long stay (Weighted Average) [NHS 2015]

4.6 Osimertinib treatment dosing and compliance

In the original cost effectiveness model, the dose per administration for osimertinib was calculated as the 80 mg dose multiplied by the overall compliance to osimertinib treatment. In the updated model, the compliance rate from AURAext/2 DCO3 was used by applying the ratio between the mean actual treatment duration and the mean total treatment duration.

The values were calculated for both lines of treatment and are presented in Table 14, a compliance rate of 98.21% (second-line only) was used in the base case resulting in an average treatment dose of 78.6 mg for osimertinib.

Table 14: Osimertinib treatment compliance applied in the model

	Second line **(base case)**	**≥Third line**
Mean total treatment duration (a) - months	11.2	11.1
Mean actual treatment duration (b) - months	11.0	10.9
Compliance % (b/a)	**98.21%**	**98.20%**

The difference between the two estimates of treatment duration (total and actual) is quite small even though almost 37% of the patients had a dose interruption. The reason for this is that the median duration of the dose interruption is only ~1 week which, when compared to the average treatment duration of 11.1 months, is relatively small.

Section 5. Results of updated cost effectiveness analysis

5.1 Base Case Analysis

The revised base case analysis is presented for both the adjusted and unadjusted datasets from AURAext/2 (DCO3) and IMPRESS (November 2015 DCO). A summary of the key updated values applied in the model is presented in table 15. In addition, all minor modifications described in sections 4 are applied in the revised base case analysis.

Table 15: Summary of key variables applied in updated economic model base case analysis

Area	Variable	Value	Ref to section in technical report
Model settings/ patient characteristics	Time horizon	15 years	N/A
	Model cycle length	1 week	
	Starting age	63.3 years	
	Discount rate	3.5%	
	Average body weight (kg)	Males 74.7 kg Females 63.4 kg	4.2
	Body surface area	Males 1.89 m^2 Females 1.66 m^2	
Clinical efficacy data	Overall survival (Adjusted and unadjusted datasets): Osimertinib (second-line) Platinum doublet chemotherapy (second-line, T790M+)	Distribution: Weibull	1
	Progression-free survival (Adjusted and unadjusted datasets): Osimertinib (second-line) Platinum doublet chemotherapy (second-line, T790M+)	Distribution: Gompertz	
Resource use and costs	Cost of osimertinib acquisition (per pack)	[redacted]	N/A
	Cost of osimertinib administration	£14.40	4.1
	Treatment duration - osimertinib	Based on TTD – linear extrapolation	3.1
	Maximum number of Pem+Cis cycles	4	4.3
Utility values	Progression free - Osimertinib	IMPRESS EQ-5D-3L 0.806 (Adjusted dataset) 0.805 (Unadjusted dataset)	2

	Progression free – Platinum doublet chemotherapy	IMPRESS EQ-5D-3L 0.779 (Adjusted dataset) 0.783 (Unadjusted dataset)	
	Progressed disease	0.715	

5.1.1 Base case results – adjusted dataset

Total costs, Life years gained (LYG), QALYs and incremental cost per QALY for osimertinib versus platinum doublet chemotherapy for the adjusted dataset are presented in Table 16. In this analysis, osimertinib generates 1.541 incremental QALYs and £64,283 incremental costs over a lifetime horizon gained compared with platinum doublet chemotherapy, resulting in an ICER of £41,705 per QALY gained.

Table 16: Base case results – adjusted dataset

Treatment	Total costs (£)	Total LYG	Total QALYs	Incr costs (£)	Incr LYG	Incr QALYs	ICER (£) per QALY gained
Osimertinib	87,441	3.857	2.841	64,283	2.032	1.541	41,705
Platinum doublet chemotherapy	23,159	1.825	1.300				

5.1.2 Probabilistic sensitivity analysis – adjusted dataset

The list of model parameters and distributions included in the probabilistic sensitivity analysis (PSA) are identical to those included in the model submitted as part of the original NICE submission (see section 5.8.1, pp.224-225). The PSA was run for 10,000 iterations. Results from the PSA are presented in Table 17. The probabilistic ICER is £40,581 per QALY gained which compares with £41,705 in the deterministic analysis (a less than 3% difference in the ICER).

Table 17: Average results based on the probabilistic sensitivity analysis (10,000 iterations) – adjusted dataset

Treatment	Total costs (£)	Total Life Years	Total QALYs	Incremental Costs (£)	Incremental QALYs	ICER (£) per QALY gained
Osimertinib	87,496	3.920	2.888	64,337	1.585	40,581
PDC	23,159	1.828	1.303			

The cost-effectiveness plane and cost-effectiveness acceptability curve for osimertinib compared with platinum doublet chemotherapy are presented in Figure 6 and Figure 7 respectively. At a cost-effectiveness threshold of £50,000 per QALY gained, the probability of osimertinib being considered cost effective versus platinum doublet chemotherapy was 63%.

Figure 6: Cost-effectiveness plane for osimertinib vs platinum doublet chemotherapy – adjusted dataset

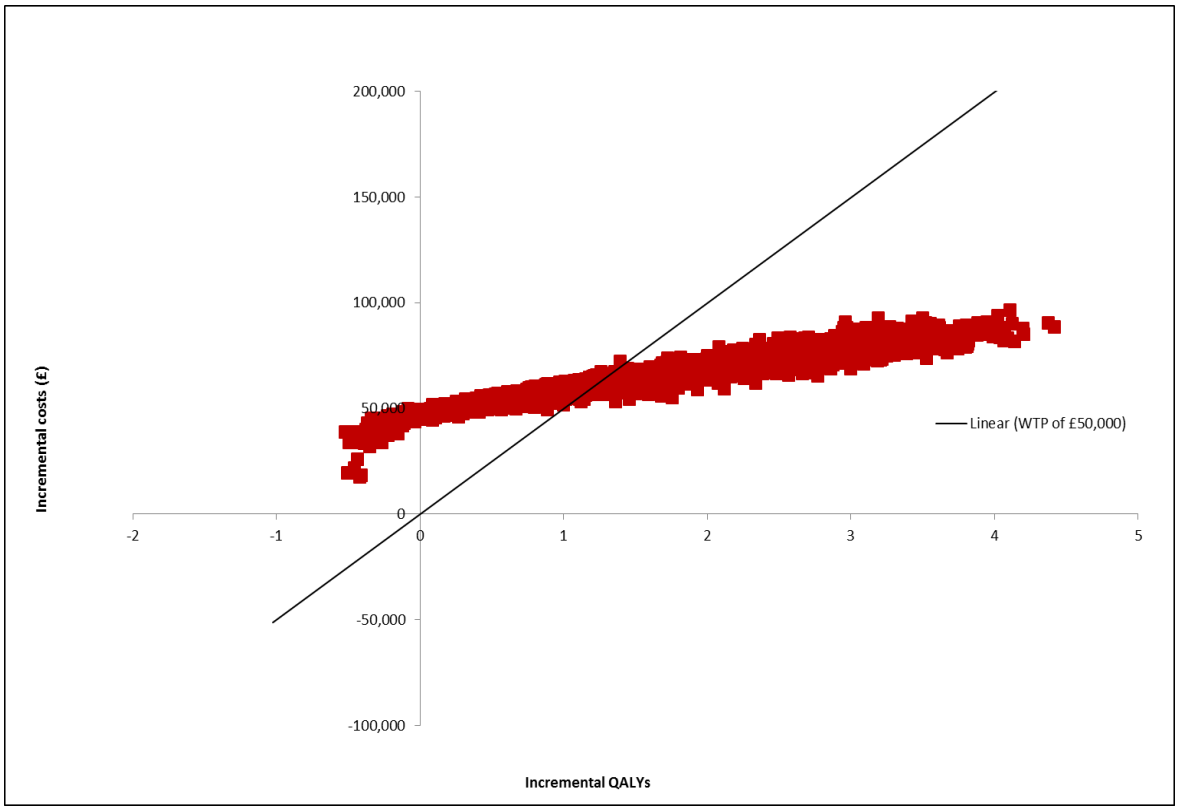
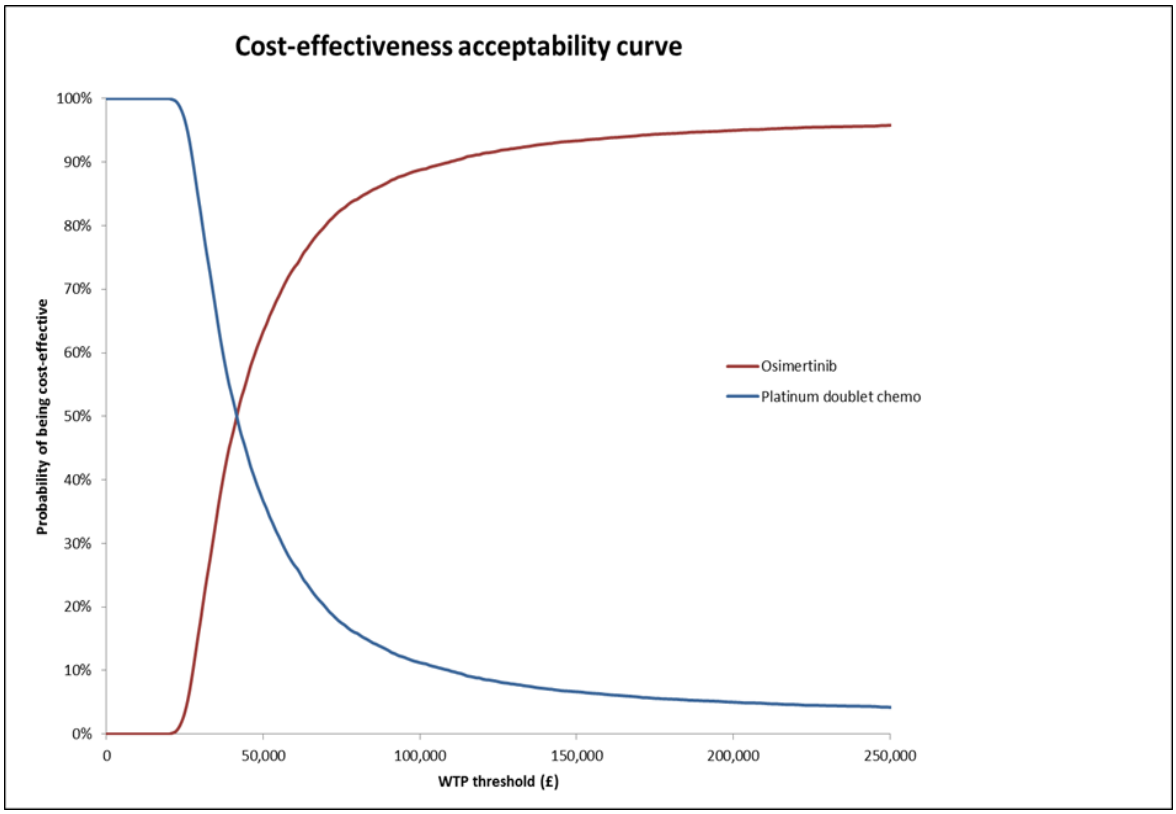


Figure 7: Cost-effectiveness acceptability curve for osimertinib vs platinum doublet chemotherapy – adjusted dataset



5.1.3 Scenario Analyses – Adjusted dataset

(a) Parametric distributions – OS and PFS

Scenario analyses were conducted to assess the impact of applying other clinically plausible parametric distributions to the non-parametric OS data for the adjusted dataset from AURAext/2 and the IMPRESS T790M mutation positive population. In each of these scenarios the same parametric distribution was applied to the non-parametric PFS data.

(i) Weibull
When the Weibull distribution was fitted to both the non-parametric PFS and OS data, this scenario results in an overall survival gain for osimertinib that is identical to the base case analysis but results in slightly lower incremental costs of £63,736 for osimertinib compared with platinum doublet chemotherapy. This scenario results in a slightly lower ICER of £41,173 per QALY gained.

(ii) Log-logistic
When the log-logistic distribution was fitted to the non-parametric OS and PFS data it resulted in 5% of patients in the osimertinib arm still alive and on treatment (in the PF state) at 5 years follow-up and approximately 24% still alive at 10 years follow-up. This scenario consequently results in incremental costs of £70,393 and incremental QALYs of 2.409 for osimertinib versus platinum doublet chemotherapy and a lower ICER of £29,224 per QALY gained.

(iii) Exponential
When the simple exponential distribution was fitted to the non-parametric OS and PFS data it resulted in approximately 2% of patients in the osimertinib arm still alive and on treatment at 5 years and approximately 18% still alive at 10 years follow-up. This results in incremental costs of £68,231 and incremental QALYs of 2.068 for osimertinib compared with platinum doublet chemotherapy and consequently a lower ICER of £32,993 per QALY gained.

(b) Health state utility values

A number of scenario analyses were conducted which involved varying the HSUVs for progression free and progressed disease states according to the source of values and treatment response as described in Table 10, section 2. Overall, the model results were robust to changes in the utility values, with ICERs varying from £37,145 (AURA2 EQ-5D-5L England Valuation set including treatment response) to £43,928 per QALY gained (IMPRESS EQ-5D-3L values with no treatment response included).

(c) Osimertinib treatment costs

When no osimertinib treatment costs were assumed beyond RECIST progression, the total costs of osimertinib treatment fell from £87,441 to £72,775, resulting in a lower overall ICER of £32,190 per QALY gained. When a median duration of treatment post progression of 2.7 months for the second-line only population was applied in the model, the total osimertinib treatment costs fell to £79,093, resulting in an ICER of £36,288 per QALY gained.

(d) Model time horizon

The ERG considered in their report that the base case model horizon of 15 years may be optimistic. Therefore, a scenario was conducted which set the model time horizon to 10 years. In this scenario, the incremental QALY gain for osimertinib decreased by less than 10%, resulting in an ICER of £43,776 per QALY gained.

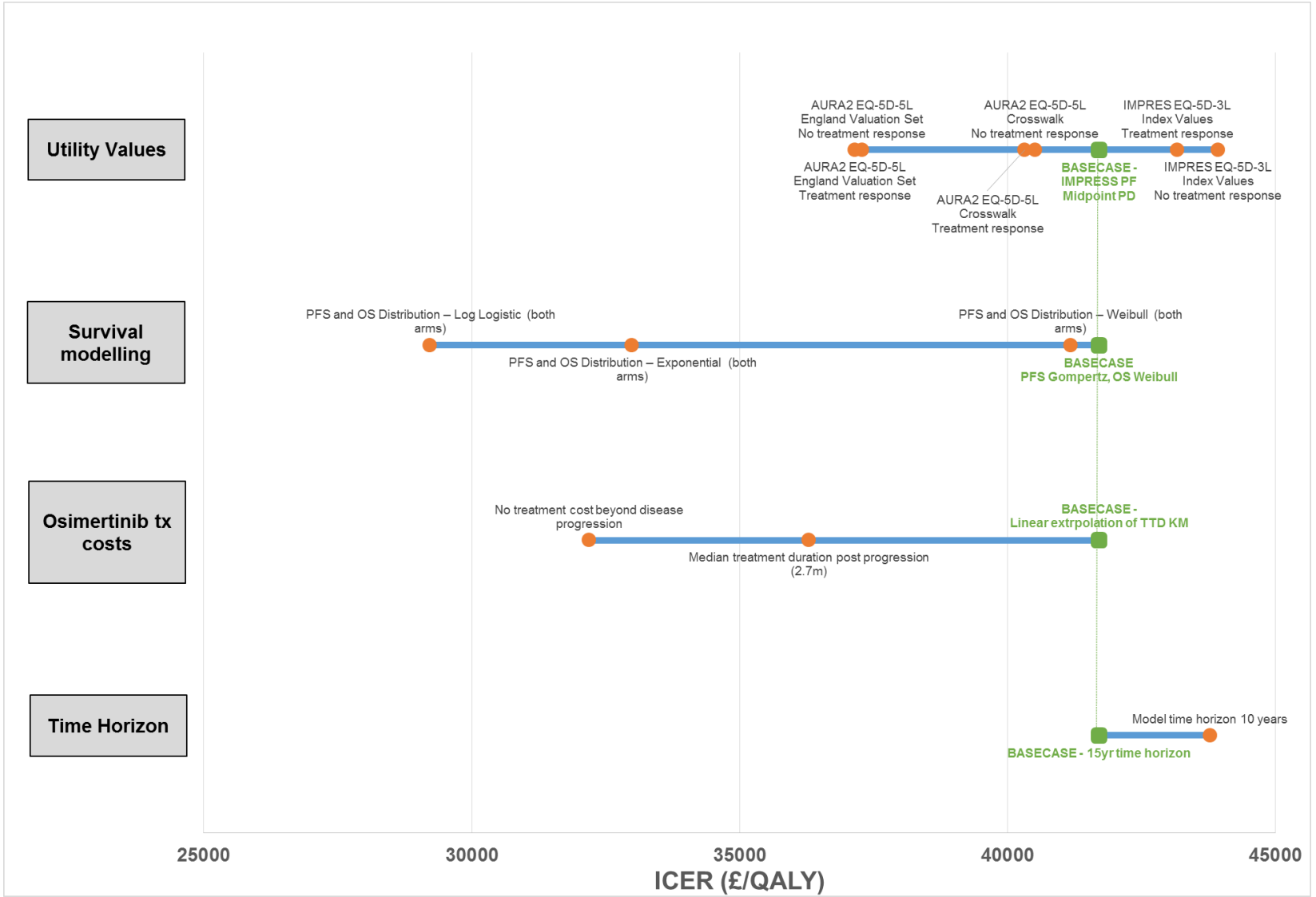
Full results associated with all scenario analyses are presented in Table 18 and Figure 8.

Table 18: Results of model scenario analyses for osimertinib vs platinum doublet chemotherapy - adjusted dataset

Scenario	Total cost (£) Osimertinib	Total cost (£) PDC	Total QALYs Osimertinib	Total QALYs PDC	Incremental costs (£)	Incremental QALYs	ICER per QALY gained (£)
Base case	**87,441**	**23,159**	**2.841**	**1.300**	**64,283**	**1.541**	**41,705**
(a) Survival modelling							
PFS and OS Distribution – Weibull (both arms)	86,975	23,239	2.848	1.300	63,736	1.548	41,173
PFS and OS Distribution – Log Logistic (both arms)	93,784	23,390	3.765	1.356	70,393	2.409	29,224
PFS and OS Distribution – Exponential (both arms)	91,819	23,587	3.510	1.442	68,231	2.068	32,993
(b) Health State Utility Values							
(i) AURA2 EQ-5D-5L Crosswalk Values							
No Treatment Response PF 0.812 – Both arms PD 0.751 – Both arms	87,441	23,159	2.952	1.365	64,283	1.535	40,510
Treatment Response PF 0.812 – Osimertinib PF 0.781 – PDC PD 0.751 – Both arms	87,441	23,159	2.947	1.352	64,283	1.595	40,313
(ii) AURA2 EQ-5D-5L England Valuation Set Values							
No Treatment Response PF 0.874 – Both arms PD 0.821 – Both arms	87,441	23,159	3.214	1.490	64,283	1.724	37,279
Treatment Response PF 0.875 – Osimertinib PF 0.848 – PDC PD 0.821 – Both arms	87,441	23,159	3.210	1.479	64,283	1.731	37,145
(iii) IMPRESS EQ-5D-3L Index Values							
No Treatment Response PF 0.779 – Both arms PD 0.679 – Both arms	87,441	23,159	2.712	1.249	64,283	1.463	43,928

Treatment Response PF 0.810 – Osimertinib PF 0.779 – PDC PD 0.679 – Both arms	87,441	23,159	2.738	1.249	64,283	1.489	43,162
(c) Osimertinib treatment costs							
No treatment cost beyond disease progression	72,775	23,159	2.841	1.300	49,616	1.541	32,190
Median treatment duration post progression (2.7 months)	79,093	23,159	2.841	1.300	55,934	1.541	36,288
(d) Model time horizon 10 years	86,260	23,158	2.741	1.300	63,101	1.441	43,776

Figure 8: Results of model scenario analyses for osimertinib vs platinum doublet chemotherapy - adjusted dataset



5.2.1 Cost effectiveness results – unadjusted dataset

Total costs, Life years gained (LYG), QALYs and incremental cost per QALY for osimertinib versus platinum doublet chemotherapy for the adjusted dataset are presented in Table 19. In this analysis, osimertinib generates 1.313 incremental QALYs and £61,508 incremental costs over a lifetime horizon gained compared with platinum doublet chemotherapy, resulting in an ICER of £48,410 per QALY gained.

Table 19: Results – unadjusted dataset

Treatment	Total costs (£)	Total LYG	Total QALYs	Incr costs (£)	Incr LYG	Incr QALYs	ICER (£) per QALY gained
Osimertinib	82,877	3.256	2.413	61,242	1.647	1.265	48,410
Platinum doublet chemotherapy	21,636	1.609	1.148				

5.2.2 Probabilistic sensitivity analysis – unadjusted dataset

The list of model parameters and distributions included in the probabilistic sensitivity analysis (PSA) are identical to those included in the model submitted as part of the original NICE submission (see section 5.8.1, pp.224-225). The PSA was run for 10,000 iterations. Results from the PSA are presented in Table 20. The probabilistic ICER is £46,851 per QALY gained which compares with £48,410 in the deterministic analysis (a 3.3% difference in the ICER).

Table 20: Average results based on the probabilistic sensitivity analysis (10,000 iterations) – adjusted dataset

Treatment	Total costs (£)	Total Life Years	Total QALYs	Incremental Costs (£)	Incremental QALYs	ICER (£) per QALY gained
Osimertinib	83,204	3.334	2.470	61,508	1.313	46,851
Platinum doublet chemotherapy	21,696	1.622	1.157			

The cost-effectiveness plane and cost-effectiveness acceptability curve for osimertinib compared with platinum doublet chemotherapy are presented in Figure 9 and Figure 10 respectively. At a cost-effectiveness threshold of £50,000 per QALY gained, the probability of osimertinib being considered cost effective versus platinum doublet chemotherapy was 53.4%.

Figure 9: Cost-effectiveness plane for osimertinib vs platinum doublet chemotherapy – unadjusted dataset

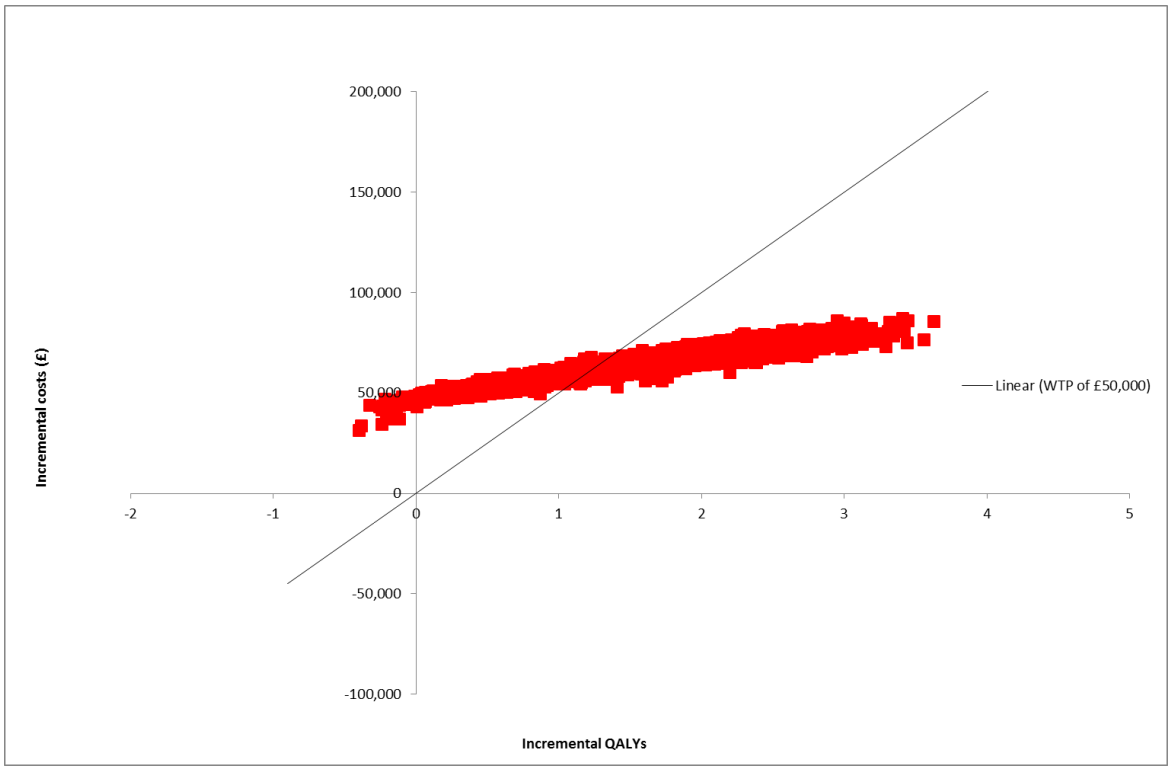
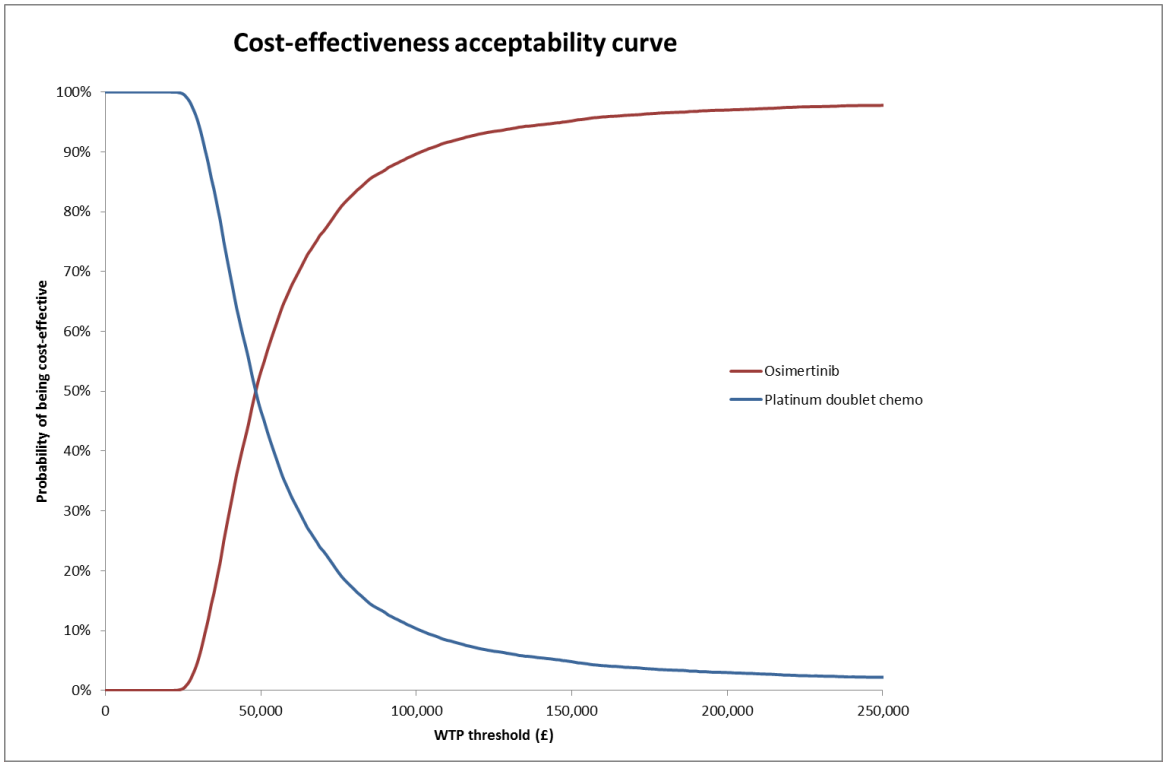


Figure 10: Cost-effectiveness acceptability curve for osimertinib vs platinum doublet chemotherapy – unadjusted dataset



5.2.3 Scenario Analyses – Unadjusted dataset

(a) Parametric distributions – OS and PFS

Scenario analyses were conducted to assess the impact of applying the other parametric distributions to the non-parametric OS data for the unadjusted dataset from AURAext/2 and the IMPRESS T790M mutation positive population. In each of these scenarios the same parametric distribution was applied to the non-parametric PFS data.

(i) Weibull
When the Weibull distribution was fitted to both the non-parametric PFS and OS data, this scenario results in an overall survival gain for osimertinib that is identical to the base case analysis but results in slightly lower incremental costs of £60,588 for osimertinib compared with platinum doublet chemotherapy. This scenario results in a slightly lower ICER of £47,586 per QALY gained.

(ii) Log-logistic
When the log-logistic distribution was fitted to the non-parametric OS and PFS data it resulted in approximately 6% of patients in the osimertinib arm still alive and on treatment (in the PF state) at 5 years follow-up and approximately 19% still alive at 10 years follow-up. This scenario consequently results in incremental costs of £66,794 and incremental QALYs of 2.104 for osimertinib compared with platinum doublet chemotherapy and thus a lower ICER of £31,742 per QALY gained.

(iii) Exponential
When the simple exponential distribution was fitted to the non-parametric OS and PFS data it resulted in approximately 2% of patients in the osimertinib arm still alive and on treatment at 5 years and approximately 15% still alive at 10 years follow-up. This results in incremental costs of £67,118 and incremental QALYs of 1.965 for osimertinib compared with platinum doublet chemotherapy and consequently a lower ICER of £34,157 per QALY gained.

(b) Health state utility values

A number of scenario analyses were conducted which involved varying the HSUVs for progression free and progressed disease according to the source of values and treatment response as described in Table 10, section 2. Overall, the model results were fairly robust to changes in the utility values, with ICERs varying from £43,326 (AURA2 EQ-5D-5L England Valuation set including treatment response) to £50,928 per QALY gained (IMPRESS EQ-5D-3L values with no treatment response included).

(c) Osimertinib treatment costs

When no osimertinib treatment costs were assumed beyond RECIST progression, the total costs of osimertinib treatment fell from £82,887 to £68,641, resulting in a lower overall ICER of £37,156 per QALY gained. When a median duration of treatment post progression of 2.7 months was applied in the model, the total osimertinib treatment costs fell to £74,956, resulting in an ICER of £42,148 per QALY gained.

(d) Model time horizon

The ERG considered in their report that the base case model horizon of 15 years may be optimistic. Therefore, a scenario was conducted which set the model time horizon to 10 years. In this scenario, the incremental QALY gain for osimertinib decreased by less than 3%, resulting in an ICER of £49,387 per QALY gained.

Table 21: Results of scenario analyses for osimertinib vs platinum doublet chemotherapy - unadjusted dataset

Scenario	Total cost (£) Osimertinib	Total cost (£) PDC	Total QALYs Osimertinib	Total QALYs PDC	Incremental costs (£)	Incremental QALYs	ICER per QALY gained (£)
Base case	**82,887**	**21,636**	**2.413**	**1.148**	**61,242**	**1.265**	**48,410**
(a) Survival modelling							
PFS and OS Distribution – Weibull (both arms)	82,295	21,707	2.422	1.148	60,588	1.273	47,586
PFS and OS Distribution – Log Logistic (both arms)	89,201	22,407	3.370	1.265	66,794	2.104	31,742
PFS and OS Distribution – Exponential (both arms)	88,899	21,781	3.233	1.268	67,118	1.965	34,157
(b) Health State Utility Values							
(i) AURA2 EQ-5D-5L Crosswalk Values							
No Treatment Response PF 0.812 – Both arms PD 0.751 – Both arms	82,887	21,636	2.501	1.203	61,242	1.298	47,181
Treatment Response PF 0.807 – Osimertinib PF 0.784 – PDC PD 0.751 – Both arms	82,887	21,636	2.497	1.192	61,242	1.304	46,956
(ii) AURA2 EQ-5D-5L England Valuation Set Values							
No Treatment Response PF 0.874 – Both arms PD 0.821 – Both arms	82,887	21,636	2.721	1.313	61,242	1.409	43,478
Treatment Response PF 0.870 – Osimertinib PF 0.851 – PDC PD 0.821 – Both arms	82,887	21,636	2.717	1.304	61,242	1.414	43,326
(iii) IMPRESS EQ-5D-3L Index Values							
No Treatment Response PF 0.779 – Both arms PD 0.679 – Both arms	82,887	21,636	2.306	1.103	61,242	1.203	50,928

Treatment Response PF 0.805 – Osimertinib PF 0.783 – PDC PD 0.679 – Both arms	82,887	21,636	2.332	1.104	61,242	1.227	49,908
(c) Osimertinib treatment costs							
No treatment cost beyond disease progression	68,641	21,636	2.413	1.148	47,005	1.265	37,156
Median treatment duration post progression (2.7 months)	74,956	21,636	2.413	1.148	53,320	1.265	42,148
(d) Model time horizon 10 years	82,455	21,636	2.380	1.148	60,820	1.231	49,387

Section 6. ≥Third-line population: osimertinib versus single-agent chemotherapy (unadjusted dataset)

Similar to the original NICE submission, this analysis considers a scenario where patients have received previous treatment with both an EGFR TKI and chemotherapy based on DCO3. All relevant graphs and tables for visual and statistical inspection for the ≥third-line population from AURAext/2 can be found in Appendix B of this technical report. This scenario utilises the unadjusted dataset specific to the ≥third-line population from AURAext/2 for osimertinib (n=282) and data from the Schuler 2015 study for single-agent chemotherapy (docetaxel). As patient-level data are unavailable from the Schuler et al study it was not possible to derive an unadjusted comparative dataset with the AURAext/2 ≥third-line population. For simplicity, the parametric distributions selected for these subgroup analyses were equivalent to those used in the base case analysis; the Gompertz distribution was used to extrapolate PFS and the Weibull distribution was used to extrapolate OS. All other model assumptions for this scenario analysis are identical to those used in the analyses for the second-line only comparison described in section 5.1.

The full results of this analysis are presented in Table 22. Compared with the equivalent analysis for the second-line only population, this scenario produced a higher ICER of £56,126 per QALY gained for osimertinib compared with single-agent chemotherapy. Overall, the projected survival for osimertinib in the ≥third-line population from AURAext/2 is significantly lower than that for the second-line only population (2.56 years versus 3.26 years), thus reflecting the more refractory nature of this patient population.

Table 22: ≥Third-line population: osimertinib versus single-agent chemotherapy – unadjusted dataset

Treatment	Total costs (£)	Total LYG	Total QALYs	Incr costs (£)	Incr LYG	Incr QALYs	ICER (£) per QALY gained
Osimertinib	71,503	2.558	1.913	55,100	1.139	0.974	56,570
Single agent chemotherapy	16,403	1.419	0.939				

Appendix A. Visual Inspection and Statistical Fit – unadjusted dataset

This analysis focuses on the unadjusted data taken from the relevant population in the pooled AURAext/2 studies (n=129) and the T790M mutation positive control arm of the IMPRESS study (n=61).

Figures 11 and 12 present the overlaid modelled parametric curves to the non-parametric PFS and OS KM plots for osimertinib and platinum doublet chemotherapy for all candidate survival functions.

(a) Progression-free Survival

Based on IMPRESS (T790M subgroup), all standard parametric distributions tend to slightly underestimate the median PFS, PFS at 4 months and PFS at 6 months, but either underestimate or overestimate PFS at 8 months. Whilst the Gompertz and generalised gamma models, followed by the Weibull model, provide the best median, 4-month and 6-month PFS, they underestimate it at 8 months. Both, the log-logistic, and log-normal models overestimate PFS from approximately 7 months onwards and predict that approximately 10% of patients are still alive and progression free after 5 years and are therefore not suitable. The Gompertz, Weibull and generalised gamma distributions seem to provide generally the most adequate estimates and fit to the observed KM data.

For osimertinib PFS, all parametric models provide relatively accurate median estimates and inspection of the curves shows that all curves are very similar up to 12 months, after which the log-normal, log-logistic and potentially the exponential models tend to overestimate PFS. Among the three distributions that seem to provide a better extrapolation (based on the end of the KM data), the Gompertz and Weibull models appear to provide the best visual fit to the observed data.

Table 23: PFS rate at various time-points of the parametric survival models applied to the AURAext/2 and IMPRESS T790M mutation positive population

	PDC			Osimertinib		
	4 months	**6 months**	**8 months**	**4 months**	**6 months**	**8 months**
Exponential	47.5%	32.4%	23.1%	77.4%	68.2%	60.8%
Weibull	55.6%	29.6%	14.4%	83.1%	72.5%	63.4%
Gompertz	59.2%	32.1%	12.5%	82.3%	72.8%	64.3%
Log-logistic	53.2%	31.6%	20.6%	82.8%	71.3%	62.1%
Log-normal	49.8%	30.1%	19.8%	80.5%	69.2%	60.8%
Generalised gamma	59.4%	32.5%	12.4%	83.0%	72.3%	63.1%
Non-parametric data	**62.5%**	**35.4%**	**15.2%**	**86.8%**	**74.7%**	**64.1%**

Based on the AIC and BIC of the PFS curves, the Weibull distribution provides the best fit for osimertinib and ranks in third place (AIC) for platinum doublet chemotherapy. The Gompertz distribution provides the best fit for platinum doublet chemotherapy but ranks third or fourth for osimertinib. The exponential and log-normal generally rank low for both treatments.

Table 24: Goodness-of-fit statistics for PFS for platinum doublet chemotherapy from the control arm of IMPRESS (T790M) and osimertinib from AURAext/2 second-line population

	PFS				OS			
	PDC		Osimertinib		PDC		Osimertinib	
	AIC (#)	BIC (#)	AIC (#)	BIC (#)	AIC (#)	BIC (#)	AIC (#)	BIC (#)
Exponential	260.4 (6)	262.5 (6)	537.7 (6)	540.6 (3)	363.1 (5)	365.3 (5)	259.1 (2)	**262.0 (1)**
Weibull	244.9 (3)	249.01 (2)	**533.3 (1)**	**539.0 (1)**	357.3 (4)	361.5 (4)	259.9 (3)	265.6 (3)
Gompertz	**243.4 (1)**	**247.6 (1)**	535.1 (3)	540.8 (4)	363.2 (6)	367.4 (6)	**258.7 (1)**	264.5 (2)
Log-logistic	252.9 (5)	257.1 (5)	534.1 (2)	539.8 (2)	351.3 (2)	355.6 (2)	260.3 (4)	266.0 (4)
Log-normal	252.9 (4)	257.1 (4)	536.7 (5)	542.4 (5)	**351.3 (1)**	**355.5 (1)**	262.8 (6)	268.6 (5)
Gen gamma	244.3 (2)	250.6 (3)	535.3 (4)	543.9 (6)	353.1 (3)	359.5 (3)	261.5 (5)	270.1 (6)

Figure 11: Predicted model time in Progression-free health states for all parametric distributions compared with observed PFS data (unadjusted dataset)

[Figure Removed]

(b) Overall Survival

For platinum doublet chemotherapy, all standard parametric distributions included in the analysis overestimate the median OS since the KM data is flat from around 22-23 months follow up. The log-logistic and generalised gamma both have a relatively good fit during the observed data period and seem to provide an adequate extrapolation (based on the end of the KM data). Although caution should be taken when comparing model fits to the observed data based on a single point in time, all candidate parametric models appear to over estimate median OS by 1-3 months.

The visual inspection of the OS curves for osimertinib shows that all curves have very similar fit up to 15 months. The Weibull distribution provides the best fit for the observed data and appears to provide a clinically plausible extrapolation. Similar to the adjusted dataset, the Gompertz and Generalized gamma distributions both produce a clinically implausible situation where the OS curves for osimertinib and platinum doublet chemotherapy intersect, resulting in a longer tail of patients still alive in the PDC arm. The log-logistic and log-normal models have the worst visual fit and appear to overestimate the extrapolation. This can be seen in the median estimate where the log-normal produces a very high OS estimate (59 months), but also the exponential and log-logistic models provide estimates that are relatively high (>40 months). The other distributions provide median OS estimates between 25 months and 34 months.

Table 25: Survival rate at various time-points of the parametric survival models applied to the AURAext/2 and IMPRESS T790M mutation positive population

	PDC				Osimertinib			
	9 months	**12 months**	**18 months**	**24 months**	**12 months**	**24 months**	**60 months**	**120 months**
Exponential	66.4%	58.1%	44.4%	33.9%	82.5%	68.2%	38.6%	14.9%
Weibull	75.4%	65.3%	46.7%	31.6%	82.8%	63.8%	24.4%	3.4%
Gompertz	70.8%	62.2%	46.6%	33.6%	83.3%	52.3%	0.0%	0.0%
Log-logistic	75.0%	62.3%	41.6%	28.1%	82.8%	66.0%	36.9%	18.9%
Log-normal	74.1%	61.9%	42.8%	29.9%	82.7%	70.3%	49.8%	33.9%
Generalised gamma	73.5%	61.1%	42.3%	30.0%	82.8%	60.8%	3.2%	0.0%
Non-parametric data	**77.6%**	**60.0%**	**43.7%**	**25.0%**	**83.4%**	**N/A**	**N/A**	**N/A**

The goodness-of-fit for the OS curves shows that the log-normal model, followed by the log-logistic, have the best fit for platinum doublet chemotherapy, whilst only being ranked #6 and #4 for osimertinib (AIC), respectively. The Gompertz model has the best fit for osimertinib according to AIC and the exponential has the best fit according to BIC. However, the Gompertz and exponential have the worst fits for platinum doublet chemotherapy (#6 and #5 AIC). The generalised gamma provides a generally poor fit for both treatments.

Table 26: Goodness-of-fit statistics for OS for platinum doublet chemotherapy from the control arm of IMPRESS (T790M) and osimertinib from AURAext/2 second-line only population

	PDC		Osimertinib	
	AIC (#)	**BIC (#)**	**AIC (#)**	**BIC (#)**
Exponential	363.1 (5)	365.3 (5)	259.1 (2)	**262.0 (1)**
Weibull	357.3 (4)	361.5 (4)	259.9 (3)	265.6 (3)
Gompertz	363.2 (6)	367.4 (6)	**258.7 (1)**	264.5 (2)
Log-logistic	351.3 (2)	355.6 (2)	260.3 (4)	266.0 (4)
Log-normal	**351.3 (1)**	**355.5 (1)**	262.8 (6)	268.6 (5)
Gen gamma	353.1 (3)	359.5 (3)	261.5 (5)	270.1 (6)

Figure 12: Predicted model alive (OS) for all parametric distributions compared with observed OS data (unadjusted dataset)

[Figure Removed]

Figure 13 presents the median PFS based on Gompertz distribution, and OS based on the Weibull distribution for osimertinib and PDC showing an incremental median PFS gain of 6.23 months and an incremental median OS gain of 16.85 months for osimertinib compared with PDC.

Figure 13: Median duration of the parametric distributions used in the base case analysis – unadjusted dataset

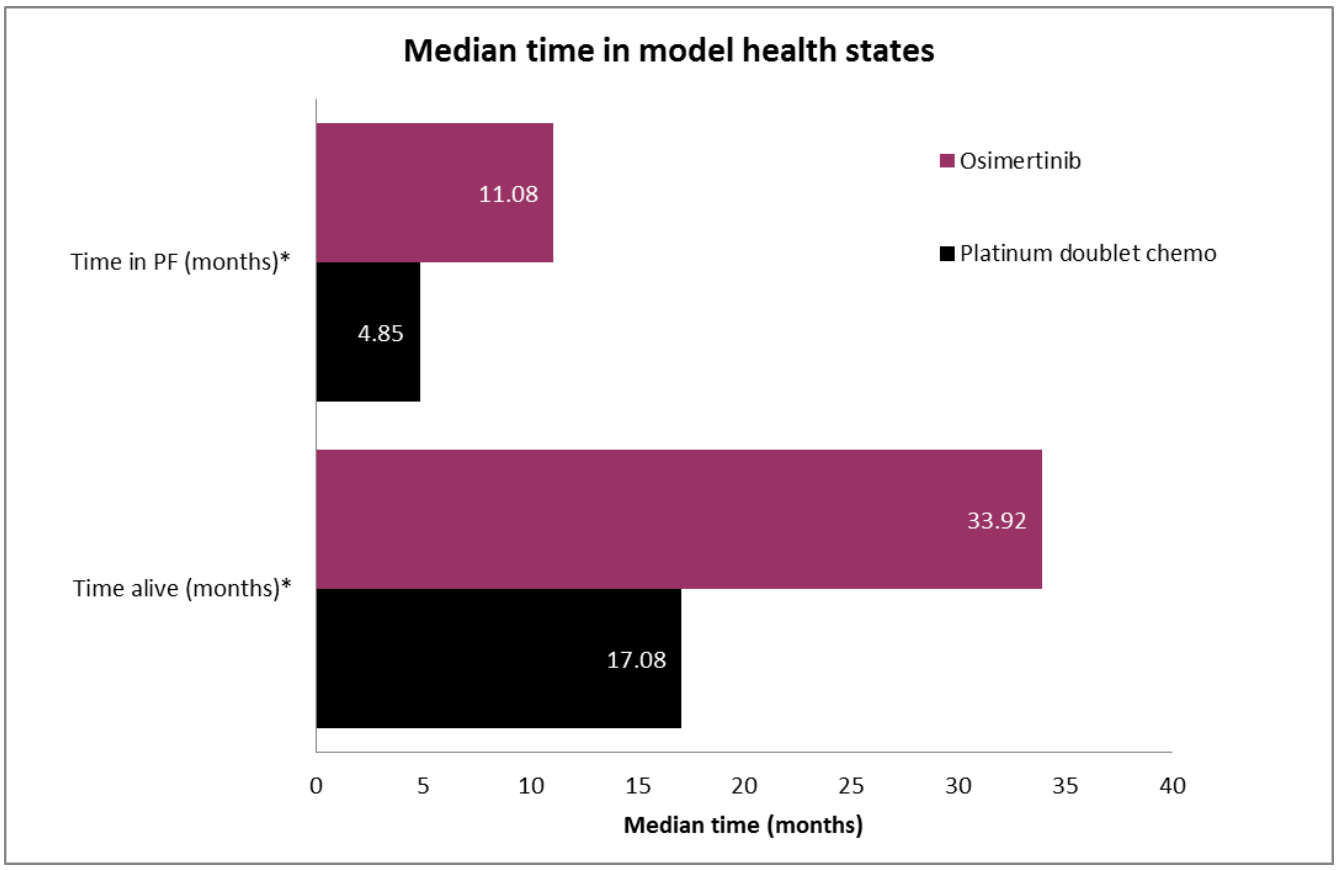


Figure 14 presents the Gompertz PFS and Weibull OS parametric functions used in the base case compared with the unadjusted KM data from AURAext/2 and IMPRESS. Approximately 24% of patients treated with osimertinib are alive at 5 years compared to 1.4% of patients on platinum doublet chemotherapy. After 10 years in the model (120 months in Figure 14), the proportion of patients alive is 3% for osimertinib and 0% for platinum doublet chemotherapy.

Figure 14: Overall and progression-free survival curves used in the base case analysis – unadjusted dataset

[Figure Removed]

Appendix B. Survival model projections for AURAext/2 ≥Third-line population (Unadjusted dataset)

Figure 15: Kaplan-Meier data and extrapolation of parametric models for progression-free survival by central review, ≥third line (AURAext/2, DCO3)

[Figure Removed]

Figure 16: Kaplan-Meier data and extrapolation of parametric models for overall survival by central review, ≥third line (AURA pooled data, DCO3)

[Figure Removed]

Table 27: Statistical goodness-of-fit statistics for osimertinib and single-agent chemotherapy in the ≥third line setting

Parametric function	PFS				OS			
	Osimertinib		Single-agent chemotherapy (Schuler 2015)		Osimertinib		Single-agent chemotherapy (Schuler 2015)	
	AIC (#)	BIC (#)	AIC (#)	BIC (#)	AIC (#)	BIC (#)	AIC (#)	BIC (#)
Exponential	1174.7 (4)	1178.4 (1)	275.6 (5)	277.8 (4)	710.4 (5)	714.0 (1)	345.7 (1)	347.9 (1)
Weibull	1172.4 (2)	1179.7 (3)	274.6 (4)	279.0 (5)	707.4 (2)	714.7 (3)	347.4 (2)	351.8 (2)
Gompertz	1175.0 (5)	1182.3 (4)	276.7 (6)	281.2 (6)	707.1 (1)	714.4 (2)	347.5 (3)	352.0 (3)
Log-logistic	1171.4 (1)	1178.6 (2)	271.6 (3)	276.0 (2)	708.0 (3)	715.3 (4)	348.7 (4)	353.2 (4)
Log-normal	1179.9 (6)	1187.2 (6)	268.4 (1)	272.8 (1)	717.5 (6)	724.8 (6)	350.4 (6)	354.8 (5)
Gen gamma	1173.3 (3)	1184.2 (5)	270.3 (2)	277.0 (3)	709.0 (4)	719.9 (5)	349.3 (5)	356.0 (6)

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Response to the Appraisal Consultation Document (ACD) Appendix 3 – Adjusted Indirect Comparison of osimertinib versus standard of care

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Osimertinib for locally advanced or metastatic, EGFR and T790M mutation positive non-small cell lung cancer [ID874]

Single technology appraisal (STA)

File name	Version	Contains confidential information	Date
ID874_Osimertinib_ACD_Response_Appendix3[AIC]	1.0	Yes	14 July 2016

AstraZeneca UK Ltd
600 Capability Green, Luton LU1 3LU

D5160C0000a Adjusted Indirect Comparison of Osimertinib vs Standard of Care

Drug Substance: Osimertinib (AZD9291)

Date: 28 July 2016

D5160C0000a Adjusted Indirect Comparison of Osimertinib vs platinum doublet chemotherapy

A Comparison of Osimertinib (AZD9291) to a Non-Randomized Control Group Receiving Platinum-Based Doublet Chemotherapy in Patients with Locally Advanced/Metastatic Non-Small Cell Lung Cancer whose Disease has Progressed with Previous Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor Therapy and whose Tumours are Epidermal Growth Factor Receptor Mutation- and T790M-Mutation Positive

Edition 2

Analyses of clinical end-points are based on following DCOs:

AURAext / AURA2	DCO3	1st November 2015
IMPRESS	DCO2	16th November 2015

Analyses of EQ-5D are based on DCO2 and DCO1 for AURA and IMPRESS, respectively.

Treatment: TAGRISSO (osimertinib) is a kinase inhibitor indicated for the treatment of patients with metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive non-small cell lung cancer (NSCLC) who have progressed on or after EGFR tyrosine kinase inhibitor (TKI) therapy.

Dose: Osimertinib 80 mg, oral tablet, once daily.

[Document Redacted]

1 OSIMERTINIB FOR LOCALLY ADVANCED OR METASTATIC, EGFR AND T790M MUTATION POSITIVE NON-SMALL CELL LUNG CANCER [ID874]: ERG COMMENT ON COMPANY RESPONSE TO THE APPRAISAL CONSULTATION DOCUMENT (ACD)

1.1 Overview

As part of the Single Technology Appraisal (STA) process, the company (AstraZeneca) submitted a response to the appraisal consultation document (ACD) issued by the National Institute for Health and Care Excellence (NICE) for the appraisal of osimertinib. The company response comprised four documents: an Executive Summary (17 pages); Appendix 1, Updated Clinical Evidence (17 pages); Appendix 2, Updated Cost Effectiveness Analysis Technical Report (48 pages); Appendix 3, Updated Indirect Treatment Comparison (498 pages). The company also provided an updated model in Excel. NICE asked the ERG to provide comment on the company response.

In summary, within the four documents the company provided:

1. An updated analysis of the key data from the AURA pooled dataset (N=411) based on a later data cut off date of November 2015 (original data May, 2015).

2. The updated ([redacted]) overall survival (OS) data and analyses of the retrospectively identified subgroup of patients ([redacted]) that were T790M mutation positive in the IMPRESS randomised controlled trial (RCT). Osimertinib was not a treatment option in the IMPRESS trial; gefiniitib plus platinum doublet chemotherapy (PDC) was compared with PDC in patients who had progressed after one prior treatment with an EGFR-TKI. The company submission (CS) used this data to inform an indirect treatment comparison (ITC) of PDC with osimertinib.

3. A revised indirect treatment comparison (ITC) based on the updated data.

4. A cost effectiveness model that is based on the updated clinical effectiveness data. The base case in the model is focussed on a comparison of osimertinib with PDC as a second-line treatment only, the original submission was based on treatment at any line. Utility values in the progression-free state have been adjusted according to the objective response rates observed in the AURA pooled dataset and in the IMPRESS trial. Time to treatment discontinuation costs for osimertinib are incorporated alongside changes to cost data.

1.2 ERG comments on the company response

The ERG had only a short time to scrutinise the company documents and has not carried out a detailed assessment. Comments are therefore focussed on three main issues: patient population, OS data and the utility values used in the economic base case. The ERG also comments on the ITC and the company's cost data.

Patient population

The company has restricted the patient cohort in the new economic base case to patients from the AURA pooled dataset, which includes patients from two single arm phase I/II trials, to whom osimertinib was given as a second-line treatment only (n=129, 31% of the overall dataset). The base case described in the original CS included patients treated at any line and the results for patients treated at second-line only were presented as the results of a subgroup analysis. The ERG considers that the population discussed in the company response is different to the base case presented in the original CS and already considered by the Appraisal Committee.

Overall survival

Despite the increased duration of follow-up, the OS data from the AURA pooled dataset remain highly immature at 23.8% in the overall population and [redacted] in the second-line treatment only population. Restricting the base case to patients treated with osimertinib at second-line only reduces the number of patients from 282 to 129.

The final OS data from the IMPRESS trial are more mature at [redacted]; however, the data relate to a small number of patients (n=61).

The small number of patients in each of the comparator arms (92 for osimertinib and 53 for PDC are included in the ITC) means that any change in the number of events has a significant impact on the shape of the OS curves. The majority of the OS gain for osimertinib is continues to be almost entirely reliant on survival modelling and is therefore subject to great uncertainty. A compounding problem is that the OS projection is based on phase I/II data from two single arm trials.

If more time were available, the ERG could make a detailed assessment of the K-M data. However, the key challenge in this appraisal is the immaturity of the OS data and, until more mature data become available, the uncertainty regarding survival gain remains.

Utility values

The company continues to make the case that the most appropriate health state utility values are those derived from the AURA2 study, i.e. utility values of 0.815 for the

progression-free state and 0.678 for the progressed state. The ERG considers that these values are high and questions their validity for the reasons listed below and outlined on p103-4 of the ERG report):

- health states were taken from patients who were not from the UK
- ECOG performance score (PS) of patients was 0 or 1. According to clinical advice to the ERG, this would not be the case for a UK population where a proportion of patients with ECOG PS ≥2 would be treated
- the health related quality of life tool used in AURA2 was the EQ-5D-5L questionnaire and, as acknowledged within the CS (p205), this tool does not yet have a validated health state valuation set for the UK
- the mean utility value of people aged 55-64 in the UK is 0.80. Whilst this mean utility value includes some people who are very ill, it seems implausible that a patient with advanced NSCLC has a higher utility value (0.815) than the average person in the UK who is of a similar age.

The ERG prefers the use of utility values derived from the Nafees study and concedes that the identification of appropriate utility values requires further investigation, including a review of utility values in other cancers. The company's inclusion of a different set of utility values serves to highlight the uncertainty around choice of utility values.

Adjusted indirect treatment comparison of osimertinib with platinum doublet chemotherapy

The company has stated (Appendix 1, page 11) that the methodology and design of the revised adjusted ITC presented in support of the economic base case are the same as in the original adjusted ITC presented in the CS. The ERG's main concerns with the original adjusted ITC were the small patient numbers in the PDC comparator arm and the immaturity of the data.

In the revised adjusted ITC presented in Appendix 1, the ERG notes that the company has also reduced the number of patients in the osimertinib treated comparator arm by restricting the base case to patients who were treated with osimertinib at second-line only. The ERG agrees that the revised adjusted ITC includes mature data for patients treated with PDC; however, the ERG considers that the data from the AURA pooled dataset remain too immature to allow robust decision-making.

The ERG was unable to check the inputs to the adjusted ITC due to time limitations.

Costs and overall response rate

In the limited time available, the ERG was not able to check that the changes to costs made by the company were applied appropriately or verify the objective response rate data (a new feature of the model).

1.3 ERG conclusions

In summary, the ERG considers that the company has provided data for a different population than was presented in the base case of the original STA and in doing so has narrowed the scope of the appraisal. The ERG also considers that the survival data employed in the company model to support the use of osimertinib in patients previously treated with an EGFR-TKI are still too immature to inform a robust cost effectiveness analysis.

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Osimertinib for locally advanced or metastatic EGFR and T790M mutation-positive non-small cell lung cancer [ID874]

Draft response to the NICE request for re-analysis of the company model

This report was commissioned by the NIHR HTA Programme as project number 15/121/09

26th August 2016

DOES NOT CONTAIN CIC/AIC

UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

Following the second Appraisal Committee (AC) meeting to discuss osimertinib for the treatment of locally advanced or metastatic, EGFR and T790M mutation positive non-small cell lung cancer (NSCLC) [ID874], the Evidence Review Group (ERG) was requested by NICE to provide a review and exploratory analysis of the economic model submitted by AstraZeneca during the appraisal consultation process.

In summary, the ERG was requested to:

1. Conduct a routine check of the company's revised model including:
    i. verification of the company's incremental cost effectiveness ratio (ICER) of £41,705 per quality of life year gained (QALY)
    ii. verification that the company's revised assumptions were implemented correctly (e.g. time to treatment discontinuation [TTD] costs)
    iii. checking for errors
2. Explore overall survival (OS) extrapolations using different curves and provide total and incremental costs, QALYs and life years gained (LYG) for the different extrapolations. During the AC, it was agreed that it would be difficult to identify the 'most plausible' extrapolation was still very uncertain and the ERG was asked to investigate extrapolation based on clinical plausibility. One example was to use the Weibull distribution (platinum doublet therapy [PDC]) and generalised gamma (osimertinib)
3. Undertake exploratory analyses using alternative utility values.

This document describes the ERG's responses to NICE's requests.

Routine algorithm and value check of model

The ERG checked the algorithms linked to PDC and osimertinib costs and effectiveness and can confirm that these were accurately implemented within the updated model submitted by the company. The ERG can also confirm that the company has accurately input the TTD data within the model. The ERG agrees that the ICER quoted by the company of £41,705 per QALY gained was accurately generated under the effectiveness, utility and cost assumptions made by the company in their additional company submission (CS).

Alternative OS extrapolations

In the original CS, the company considered a range of distributions to fit the OS data available for both osimertinib and PDC. The ERG has provided the range of possible costs, QALYs, LYG and ICERs, relating to the distributions chosen in Table 1. The ICERs range from £24,651 per QALY gained (log-normal) to £119,616 per QALY gained (Gompertz).

The ERG was also asked to comment on the most plausible ICER or range of ICERs. With such immature data, there is no robust statistical basis from which to select a most plausible distribution for OS for osimertinib. This means that all distributions modelled by the company, or chosen by the ERG, are therefore equally plausible. Conversely, all distributions could also be equally implausible. It is possible that there is a multi-stage distribution with break points unidentified in the present dataset, meaning that no single distribution to accurately model the true underlying OS can be selected at the present time.

In the absence of any statistical basis upon which to determine plausibility, the ERG asked for guidance as to what the AC considered were the most clinically plausible distributions of OS for osimertinib and PDC. The AC considered that a Weibull distribution for PDC and generalised gamma for osimertinib would produce less extreme ICER values than some of the other options; some of the distributions suggested by the company produced exceptionally high and potentially clinically implausible long-term OS. Selecting the Weibull and generalised gamma distributions increases the ICER for osimertinib compared to PDC (£60,663 per QALY gained).

Alternative utility values

In the ERG report for osimertinib, the ERG noted that the utility values incorporated in the company model were implausibly high for patients with metastatic NSCLC who were treated at second line and beyond. In the additional submission, the company presents evidence that purports to demonstrate that the high utility values in the model are credible. The company also introduced a utility differential based upon whether a patient had a complete response to treatment or not.

The ERG considers that the utility values chosen by the company remain implausible. The ERG notes that in a study of 472 patients with a range of cancers[1] (including 44 with lung cancer) and average age of 57 years, Pickard et al report that the average EQ-5D values (UK valuation) by ECOG status were 0.85, 0.73, 0.69 and 0.52 for ECOG status 0, 1, 2 and 3 respectively. This compares to the values of 0.831 for treatment response, 0.751 for stable disease and 0.715 for progressed disease used in the model.

The patients in the key studies of osimertinib (AURAext[2] and AURA2[3]) were all of ECOG status 0 or 1. This suggests that the company utility values for pre-progression survival are not entirely unreasonable; however clinical advice to the ERG is that patients in the UK who would be eligible for treatment with osimertinib

would be likely to have an ECOG status of 1 or 2. In addition, potential patients would be aged between 65 years and 70 years (older than patients in the AURA and the Pickard studies). The ERG considers that a pre- progression utility value of about 0.7 would therefore seem more reasonable than the company's value, accepting that utility could improve with response.

The progressed utility value suggested by the company is just below the value for cancer patients with ECOG status 1 and in the company model the value is maintained from the point of progression until death. The post-progression utility therefore seems especially implausible as it is applied for life and does not decline with age or with worsening symptoms and/or ECOG status.

As stated in the ERG report, the ERG does not believe that there is a utility value in the literature that ideally matches the patient population likely to be treated with osimertinib. However, the ERG considers that values of 0.67 for pre-progression and 0.64 for progressed states (derived from the LUME-Lung 1[4] study) are reasonable. The results of the Pickard study suggest that a value of 0.67 for the progression-free state may be low; however, the ERG notes that the patient population for osimertinib is likely to be older than the patients in the Pickard study. The ERG also notes that the value of 0.64 for the progressed state may be too high to apply to patients over their lifespan from progression to death.

Despite these limitations, the ERG considers that use of the utility values from the LUME-lung 1 study provides an alternative scenario from which to explore how lower (and potentially more plausible) utility values influence the size of the ICER per QALY gained. As the values are not based upon response rates, the ERG alternative utility scenario applied the 0.67 value utility to both the response and stable states and 0.64 to the progressed state.

Using the ERG utilities in the company model resulted in the ICER for osimertinib over PDC increasing to £47,863 per QALY gained. If the OS distributions suggested by the AC for osimertinib and PDC were also employed in the model with the ERG utilities, the ICER would be £70,776 per QALY gained.

References

1. Pickard AS, Ray S, Ganguli A, Cella D. Comparison of FACT- and EQ-5D–Based Utility Scores in Cancer. Value in Health. 2012; 15:305-11.
2. AstraZeneca UK Ltd. Clinical Study Report: AURAext 2016.
3. AstraZeneca UK Ltd. Clinical Study Report: AURA2 2016.
4. Reck M, Kaiser R, Mellemgaard A, Douillard JY, Orlov S, Krzakowski M*, et al.* Docetaxel plus nintedanib versus docetaxel plus placebo in patients with previously treated non-small-cell lung cancer (LUME-Lung 1): A phase 3, double-blind, randomised controlled trial. Lancet Oncol. 2014; 15:143-55.

Table 1 Alternative OS distributions for osimertinib and PDC and impact on cost, QALYs, LYG and the ICER per QALY gained

Distribution for OS	Osimertinib			PDC			Incremental			ICER	
	Cost	QALYs	Life years	Cost	QALYs	Life years	Cost	QALYs	Life years	£/QALY	Change from base case
Osimertinib and PDC with same OS distribution											
Weibull (company's base case)	**£87,441**	**3.857**	**2.647**	**£23,159**	**1.300**	**1.825**	**£64,283**	**1.541**	**2.032**	**£41,705**	
Weibull with ERG preferred utilities	£87,441	2.493	2.647	£23,159	1.150	1.825	£64,283	1.343	2.032	£47,863	£6,158
Exponential	£93,865	3.483	4.754	£24,497	1.440	2.021	£69,368	2.043	2.734	£33,954	-£7,751
Gompertz	£76,486	1.770	2.359	£23,381	1.326	1.861	£53,105	0.444	0.497	£119,616	£77,911
Log-logistic	£95,987	3.723	5.090	£23,649	1.351	1.896	£72,338	2.372	3.194	£30,491	-£11,214
Log-normal	£105,242	4.663	6.405	£23,717	1.356	1.903	£81,525	3.307	4.502	£24,651	-£17,054
Generalised gamma	£81,631	2.264	3.049	£26,534	1.647	2.310	£55,097	0.617	0.739	£89,296	£47,591
Osimertinib and PDC with different distributions											
Generalised gamma (osimertinib), Weibull (PDC)	£81,631	2.264	3.049	£23,159	1.300	1.825	£58,472	0.964	1.225	£60,663	£18,958
Generalised gamma (osimertinib), Weibull (PDC) with ERG preferred utilities	£81,631	1.976	3.049	£23,159	1.150	1.825	£58,472	0.826	1.225	£70,776	£29,071