CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208065Orig1s000

MEDICAL & STATISTICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

DATE: July 24, 2015

FROM: Patricia Keegan, M.D.
Director, Division of Oncology Products 2
Office of Hematology and Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research

SUBJECT: Review Designation memo

Sponsor:	AstraZeneca Pharmaceuticals LP
Product:	osimertinib
Proposed Indication:	For the treatment of patients with (b) (4) metastatic, epidermal growth factor receptor (EGFR) T790M mutation-positive, non-small cell lung cancer (NSCLC), as detected by an FDA-approved test, who have progressed on or after EGFR TKI therapy.

TO: NDA 208065

The review status for the New Drug Application (NDA) submitted under 505(b)(1) is designated to be:

☐ Standard (PDUFA V - 12 Months) ☒ Priority (PDUFA V - 8 Months)

BACKGROUND

Astra Zeneca did not specifically request priority review designation for this NDA, however they referenced FDA's November 6, 2013, letter granting fast track designation for the development program to of AZD9291 (osimertinib) "for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) (b) (4) based on your development program designed to demonstrate a clinically important increase in progression free survival as compared

to available therapy." In addition, Breakthrough Therapy Designation was granted on April 16, 2014 for the treatment of patients with metastatic, EGFR T790M mutation-positive, NSCLC, whose NSCLC has progressed during treatment with an FDA-approved, EGFR tyrosine kinase inhibitor.

The data supporting this NDA were obtained in two single-arm, open-label clinical activity-estimating studies, conducted in198 patients, and 198 patients, respectively, with EGFR T790M mutation-positive lung cancer who have progressed on prior systemic therapy, including an EGFR TKI agent and who received at least one dose of osimertinib. All patients were required to have EGFR T790M mutation-positive, non-small cell lung cancer (NSCLC) identified by the cobas ® EGFR mutation test performed in a central laboratory. All patients received osimertinib 80 mg orally, once daily. The major efficacy outcome measure of these two trials was objective response rate (ORR) according to RECIST v1.1 as evaluated by a Blinded Independent Central Review Committee (BICR). A secondary efficacy outcome measure was durability of response (DoR).

As reported by Astra Zeneca, the ORR were 58% (95% CI: 51%, 65%) and 64% (57%, and 71%) in the AURA Extension and AURA2 studies, with response durations of 1.1+ to 5.6+ months with a minimum follow-up of 12 weeks for all patients. Among 63 patients with EGFR T790M mutation-positive lung cancer, who have progressed on prior systemic therapy, including an EGFR TKI agent and who received at least one dose of osimertinib enrolled in a dose-finding trial, the ORR was 54% (95% CI: 41%, 66%) with a median duration of response of 12.4 months.

ASSESSMENT OF REQUEST

In evaluating the review designation for Astra Zeneca's NDA, I considered their rationale including the summary results of the AURA Extension and AURA2 studies, with supportive information on durability of response from the a subgroup enrolled in the dose-escalation portion of the AURA study, and the following FDA Guidance and MAPP:

- CDER MAPP 6020.3, Priority Review Policy (version 2)
- Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics (May 2014)

As stated in these FDA documents (above), an application for a drug will receive priority review designation if it is for a drug that treats a serious condition and, if approved, would provide a significant improvement in safety or effectiveness. In addition, specific statutory provisions provide for priority review for various types of applications

On a case-by-case basis, FDA determines at the time of NDA, BLA, or efficacy supplement filing whether the proposed drug would be a *significant improvement* in the safety or effectiveness of the treatment, prevention, or diagnosis of a serious condition compared to available therapies.

Significant improvement may be illustrated by the following examples:

- Evidence of increased effectiveness in treatment, prevention, or diagnosis of a condition
- Elimination or substantial reduction of a treatment-limiting adverse reaction
- Documented enhancement of patient compliance that is expected to lead to an improvement in serious outcomes
- Evidence of safety and effectiveness in a new subpopulation

For purposes of determining whether a significant improvement exists over available therapy, FDA generally considers *available therapy* (and the terms *existing treatment* and *existing therapy*) as a therapy that:

- Is approved or licensed in the United States for the same indication being considered for the new drug and
- Is relevant to current U.S. standard of care (SOC) for the indication

FDA's available therapy determination generally focuses on treatment options that reflect the current SOC for the specific indication (including the disease stage) for which a product is being developed. In evaluating the current SOC, FDA considers recommendations by authoritative scientific bodies (e.g., National Comprehensive Cancer Network, American Academy of Neurology) based on clinical evidence and other reliable information that reflects current clinical practice. When a drug development program targets a subset of a broader disease population (e.g., a subset identified by a genetic mutation), the SOC for the broader population, if there is one, generally is considered available therapy for the subset, unless there is evidence that the SOC is less effective in the subset.

A drug would not be considered available therapy if the drug is granted accelerated approval based on a surrogate endpoint or an intermediate clinical endpoint and clinical benefit has not been verified by post-approval studies.

Assessment:
This New Drug Application (NDA) was not submitted under the statutory provisions for which priority review designation is required by statute.

Criterion 1: the drug treats a serious condition

The median survival of patients with EGFR activating, EGFR TKI sensitive (exon 19 deletions, L858R substitutions) averages 19 to 28 months; Douillard et al 2014, Fukuoka et al 2011, Rosell et al 2012, Yang et al 2015, Zhou et al 2012). Most patients with EGFR mutation-positive NSCLC ultimately develop acquired TKI resistance (Douillard et al 2014, Maemondo et al 2010, Mitsudomi et al 2010, Rosell et al 2012, Sequist et al 2013, Wu et al 2014, Zhou et al 2011).

I concur that the indicated population has a serious, life-threatening condition.

Criterion 2: the drug would be a *significant improvement* in the safety or effectiveness of the treatment, prevention, or diagnosis compared to available therapies

There are no drugs which have been approved for the treatment of patients with EGFR T790M mutation-positive NSCLC. There are three drugs (erlotinib, afatinib, and gefitinib) which are approved for treatment of patients with NSCLC containing EGFR exon 19 deletions or exon 21 L858R insertion mutations; all three contain limitations of use that the safety and efficacy have not been evaluated as first-line treatment in patients with metastatic NSCLC whose tumors have EGFR mutations other than exon 19 deletions or exon 21 (L858R) substitution.

The following drugs are FDA-approved for the second-line treatment of NSCLC following a platinum-based regimen [which includes two-thirds of those enrolled in AURA Extension and AURA 2]:

Docetaxel is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of prior platinum-based chemotherapy. Approval was based on two randomized, open-label, active-controlled trials demonstrating an improvement in overall survival as compared to best supportive care [HR 0.56 (95% CI: 0.35, 0.88)], with median survival times of 7.5 months and 4.6 months, respectively; similar survival (5.7 months vs. 5.6 months) was observed for patients receiving docetaxel as compared to either vinorelbine or ifosfamide [HR: 0.82 (0.63, 1.06)]. In both trials, the ORR was relatively low: ORR 5.5% (95% CI: 1.1, 15.1) and ORR 5.7% (95% CI: 2.3, 11.3).

Ramucirumab is indicated, in combination with docetaxel, for the treatment of patients with metastatic NSCLC with disease progression on or after platinum-based chemotherapy. Approval was based on randomized, double-blind, study of ramucirumab plus docetaxel versus placebo plus docetaxel, which demonstrated an improvement in overall survival [HR 0.86 (95% CI: 0.75, 0.98)] and progression-free survival [HR 0.76 (95% CI: 0.68, 0.86)]. The median survival was 10.5 months in patients randomized to ramucirumab plus docetaxel and 9.1 months for patients randomized to placebo plus docetaxel. The ORR was 23% (95% CI: 20, 26) for ramucirumab plus docetaxel.

Pemetrexed is indicated as a single-agent for the treatment of patients with locally advanced or metastatic **non-squamous** NSCLC after prior chemotherapy. Approval was based on a multi-center, randomized, open label, active-control study comparing pemetrexed to docetaxel in patients with NSCLC after prior chemotherapy which demonstrated a marginally significant improvement in overall survival [HR 0.78 (95% CI: 0.61, 1.0)]. The overall response rates were 8.5% (95% CI: 5.2-11.7) for those randomized to pemetrexed and 8.3% (95% CI: 5.1-11.5) for those randomized to docetaxel.

Recommendation: Priority Review

Metastatic NSCLC is a serious and life-threatening disease with a predicted 5-year survival of 4.2%. Even in the subset of NSCLC with an EGFR mutation-positive NSCLC, the median survival ranges from 19-28 months.

There are no FDA-approved drugs for the treatment of patients with (b) (4) metastatic, epidermal growth factor receptor (EGFR) T790M mutation-positive, non-small cell lung cancer (NSCLC), as detected by an FDA-approved test, who have progressed on or after EGFR TKI therapy, thus there is an unmet medical need. In addition, treatment with osimertinib provides a significant improvement in effectiveness over available therapy (docetaxel, alone or with ramucirumab, and pemetrexed) for the second-line treatment of EGFR mutation-positive NSCLC, based on demonstration of substantially higher overall response rates (58% compared to 5-23%).

{See appended electronic signature page}

Patricia Keegan, M.D.
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/s/

PATRICIA KEEGAN
11/13/2015

CLINICAL AND STATISTICAL REVIEW

Application Type	NDA, New Molecular entity
Application Number(s)	208065
Priority or Standard	Priority
Submit Date(s)	06/05/2015
Received Date(s)	06/05/2015
PDUFA Goal Date	02/05/2016
Division/Office	DOP2/OHOP
Reviewer Name(s)	Sean Khozin, MD, MPH (Efficacy), Chana Weinstock, MD (Safety), Joyce Cheng, PhD (Statistics)
Review Completion Date	Friday, October 9, 2015
Established Name	Osimertinib
(Proposed) Trade Name	Tagrisso
Applicant	AstraZeneca
Dosing Regimen	80 mg, 40 mg
Proposed Indication(s)	Patients with (b) (4) metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive-non-small-cell lung cancer (NSCLC), as detected by an FDA-approved test, who have progressed on or after EGFR TKI therapy
Intended Population(s)	Patients with metastatic EGFR T790M mutation-positive NSCLC who have progressed on or after EGFR TKI therapy
Recommendation on Regulatory Action	Accelerated approval
Recommended Indication(s)	Patients with metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive-non-small-cell lung cancer (NSCLC), as detected by an FDA-approved test, who have progressed on or after EGFR TKI therapy.

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Glossary

AC	advisory committee
AE	adverse event
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
CVA	Cerebrovascular accident

DCO	data cut-off
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonization
ILD	interstitial lung disease
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SEALD	Study Endpoints and Labeling Development
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event
TKI	tyrosine kinase inhibitor

1 Executive Summary

1.1. Product Introduction

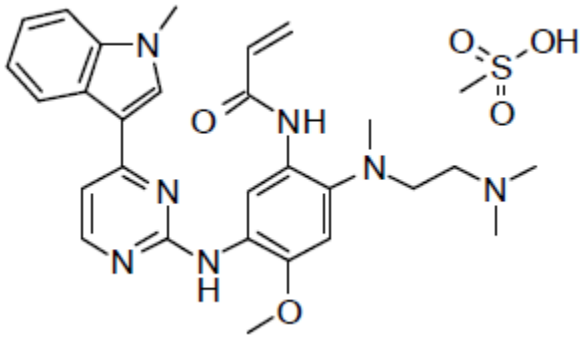
Osimertinib (also known as AZD9291 and TAGRISSO, a new molecular entity [NME]) is an EGFR TKI and an irreversible inhibitor of both EGFRm (TKI-sensitivity conferring mutations) and EGFR T790M mutation positive (TKI-resistance conferring mutation) forms of EGFR. Osimertinib was designed to have limited activity against wild type EGFR.

The proposed indication for osimertinib is for the treatment of patients with (b) (4) metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive non-small-cell lung cancer (NSCLC), as detected by an FDA-approved test, who have progressed on or after EGFR tyrosine kinase inhibitor (TKI) therapy.

Chemical Name

(b) (4)

Structural Formula



1.2. Conclusions on the Substantial Evidence of Effectiveness

[Insert text here.]

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

1. Osimertinib is a tyrosine kinase inhibitor and an irreversible inhibitor of both EGFRm and EGFR T790M mutations. The reviewers recommend granting accelerated approval for osimertinib for the treatment of patients with metastatic EGFR T790M mutation-positive NSCLC, as detected by an FDA-approved test, who have progressed on or after EGFR TKI therapy. This recommendation is based on demonstration of durable ORR of large magnitude and an acceptable safety profile in two single arm trials, leading to a favorable benefit-risk assessment in the target patient population.
2. Lung cancer is the leading cause of cancer deaths worldwide. The majority of the cases are NSCLC, presenting as advanced disease (stage IIIB or stage IV) at the time of diagnosis. EGFR activating mutations are present in about 10% of metastatic NSCLC patients in the US. First-line treatment for these patients is primarily EGFR TKIs with ORR of approximately 60-70% and median PFS of 9 to 14 months. Patients typically develop treatment resistant disease within the first year of treatment. In about 60% of patients, the mechanism of resistance involves development of EGFR T790M mutations.
3. The efficacy of osimertinib was demonstrated in two single arm trials: AURA extension [n=201] and AURA2 [n=210]. These trials with ORR of 57.2% (95% CI: 50.1%, 64.2%) and 61.0% (95% CI: 54.0%, 67.6%), respectively, in patients with metastatic EGFR/T790M positive NSCLC. The majority of patients had ongoing responses at the time of primary analysis of AURA extension and AURA2 and the median DOR had not been reached. Supportive evidence from the phase 1 portion of AURA (AURA phase 1) demonstrated ORR of 50.8% (95% CI: 37.9%, 63.6%) and DOR of 12.4 months (8.3, NC) in 63 patients with metastatic EGFR/T790M positive NSCLC. All patients had received previous treatment with an EGFR TKI.
4. Overall, the safety of osimertinib was assessed by reviewing safety data on 411 patients exposed to osimertinib on AURA extension and AURA2, with supportive safety data reviewed from phase 1 cohorts. The most frequently-observed treatment emergent adverse effects were consistent with expected toxicities based on preclinical data, previous clinical experience with osimertinib, and class effects of other EGFR TKIs. These included diarrhea and rash, which each occurred in 42% of patients. Interstitial lung disease was the most concerning toxicity, causing 4 deaths on study and occurring in 2.7% of patients overall. As these numbers were updated in the 90-day safety update and were additionally consistent with the data on adverse events from the patients on the phase 1 trial with a longer duration of exposure, there is little uncertainty regarding the estimated incidence. However, ongoing experience with the drug in phase 3 trials and in real-world usage will ultimately be needed to confirm the toxicity profile. Warnings and Precautions on the osimertinib label will address ILD, QTc prolongation, and embryo-fetal toxicity. The above conclusions were reached with little uncertainty.
5. Analysis and Recommendation: Recommend accelerated approval under subpart H. Risk management recommendations for osimertinib include several PMRs including a clinical efficacy study which will provide phase 3 confirmatory data on safety and efficacy.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Lung cancer is the leading cause of cancer deaths worldwide. The majority of the cases are NSCLC, presenting as advanced disease (stage IIIB or stage IV) at the time of diagnosis. EGFR activating mutations are present in about 10% of metastatic NSCLC patients in the US. First-line treatment for these patients is primarily EGFR TKIs with ORR of approximately 60-70% and median PFS of 9 to 14 months. Patients typically develop treatment resistant disease within the first year of treatment. In about 60% of patients, the mechanism of resistance involves development of EGFR T790M mutations.	EGFR positive metastatic NSCLC is a serious condition. First-line therapy with EGFR TKIs is the most effective option; however, patients invariably have disease progression within the first year of treatment.
Current Treatment Options	There are no effective treatment options for metastatic EGFR/T790M positive NSCLC. Standard chemotherapy is the usual regimen which is associated with marginal benefit and associated with a wide range of toxicities.	There is a large unmet medical need for patients with metastatic EGFR/T790M positive NSCLC who have disease progression following therapy with currently available EGFR TKIs.
Benefit	The efficacy of osimertinib was demonstrated in two single arm trials (AURA extension [n=201] and AURA2 [n=210]) with ORR of 57.2% (95% CI: 50.1%, 64.2%) and 61.0% (95% CI: 54.0%, 67.6%), respectively, in patients with metastatic EGFR/T790M positive NSCLC. Supportive evidence from the phase 1 portion of AURA (AURA phase 1) demonstrated ORR of 50.8% (95% CI: 37.9%, 63.6%) and DOR of 12.4 months (8.3, NC) in 63 patients with metastatic EGFR/T790M positive NSCLC. All patients had received previous treatment with an EGFR TKI.	Osimertinib meets efficacy standards for accelerated approval under the provisions of subpart H of 21 CFR 314 based on demonstration of durable ORR of large magnitude in two single arm trials. Traditional approval for osimertinib requires confirmation of clinical benefit in adequate and well-control trial(s), which can be randomized if the condition of equipoise exists.
Risk	The safety database was reviewed and was considered adequate in terms of size, exposure to osimertinib, duration of treatment, and disease characteristics with reference to the U.S. target population of patients with metastastic EGFR-mutation positive NSCLC who have progressed on prior EGFR-TKI therapy and have developed a T790M mutation, although there were few African-American	Overall, the safety profile of osimertinib is well-characterized. Its adverse event profile is consistent with known class toxicities. The safety concerns overall are not serious enough to consider either enhanced vigilance via a REMS or a boxed

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	patients included in the trial. Median duration of exposure was 4.4 months in the primary database but increased to >7 months with the 90-day safety update, which was reviewed extensively. This was considered adequate by the reviewer for an accelerated approval with longer follow-up to be submitted with confirmatory studies. The most frequently-observed treatment emergent adverse effects were consistent with expected toxicities based on preclinical data, previous clinical experience with osimertinib, and class effects of other EGFR TKIs. These included diarrhea and rash, which each occurred in 42% of patients. As these numbers were updated in the 90-day safety update and were additionally consistent with the data on adverse events from the patients on the phase 1 trial with a longer duration of exposure, there is little uncertainty regarding the estimated incidence of common toxicity. However, ongoing experience with the drug in phase 3 trials and in real-world usage will ultimately be needed to confirm the toxicity profile. The most important rare but serious identified adverse event that was thought to be the cause of 4 treatment-related deaths on study was interstitial lung disease. This is a known class effect of EGFR TKIs, and occurred at a rate of 2.7% overall in the study population. The Sponsor submitted data from the overall clinical development program, and the numbers were consistent through many studies. There is little uncertainty associated with the estimated incidence. However, ongoing experience with the drug in phase 3 trials and in real-world usage will ultimately be needed to confirm the ILD incidence. Another important identified adverse drug effect was QTc prolongation. This is a known class effect of TKIs. There was also a detailed relevant PK analysis performed for patients on AURA2 and thus there is little uncertainty associated with the	warning in labelling. The safety profile compares favorably to the profile of other approved EGFR TKIs. Other than ILD, there were no deaths due to AEs that were thought to be causally related to osimertinib even in this end-stage, highly pretreated, metastatic lung cancer population. The safety profile of this drug compares favorably to available therapy in this setting, which is chemotherapy (either single agent or platinum-doublet chemotherapy, which are both considerably more toxic than osimertinib). Exposure for this drug was limited to a relatively small patient population in a research setting; potential safety concerns could emerge in the post-market setting when there is wider clinical exposure. Data will be available once phase 3 data is submitted by the sponsor to support traditional approval. There is likely to be little off-label use of osimertinib as there is targeted activity of this drug only in a specific subpopulation of lung cancer patients.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	estimated incidence. Further experience with the drug in phase 3 trials and in real-world usage may uncover more cases of arrhythmic events thought to be drug-related, such as Torsade de pointes. There are few differences in how the drug was studied and administered in the clinical trial versus its expected use in the post-market setting that could in theory lead to increased risk. The prescribing clinicians are expected to be primarily oncologists who are familiar with toxicity management in oncology patients.	
Risk Management	There are four clinical pharmacology PMR studies related to drug interactions, one hepatic impairment study, as well as the clinical PMR to submit the final results of AURA 3 which is a phase 3 trial of osimertinib vs. platinum doublet chemotherapy in advanced lung cancer patients who have progressed on prior TKIs and have evidence of T790M mutation to confirm clinical benefit. For a full list of PMRs, please refer to section 11 of this review. Product labelling will address the incidence of Interstitial Lung Disease and QTc prolongation, as well as potential for embryo-fetal toxicity, through inclusion in section 5, Warnings and Precautions. There is no safety concern that warrants a boxed warning or a REMS.	Risk management recommendations include several PMR studies including a clinical efficacy study which will provide phase 3 confirmatory data on safety and efficacy. Warnings and Precautions on the osimertinib label will address ILD, QTc prolongation, and embryo-fetal toxicity.

2 Therapeutic Context

2.1. Analysis of Condition

Lung cancer is the leading cause of cancer deaths in the United States with an estimated number of new cases of over 220,000 and approximately 160,000 deaths in 2012.[1] About 85% of cases are NSCLC, the majority of which present as advanced disease (stage IIIB or stage IV) at the time of diagnosis.[1] The median survival of patients with advanced NSCLC with supportive care is about 3 to 6 months.[2] Standard systemic treatment for patients with advanced NSCLC consists of platinum-based doublet chemotherapy with response rates of about 30% and a median survival of about 10 months.[3, 4, 5]

EGFR belongs to a family of tyrosine kinase receptors that mediate tumor proliferation, invasion, metastasis, resistance to apoptosis, and angiogenesis.[6] Response rates to EGFR tyrosine kinase inhibitors such as erlotinib are generally higher than platinum-based chemotherapy in NSCLC patients whose tumors harbor somatic EFGR-activating mutations.[7] The most common EGFR-activating mutations are deletions in exon 19 (45%) and a point mutation (L858R) in exon 21 (40-45%).[8] The presence of these mutations is associated with distinct clinicopathologic features such as female sex, never/light smokers, Asian origin and adenocarcinoma histology.[9]

EGFR activating mutations are present in about 10% of metastatic NSCLC patients in the United States. First-line treatment for these patients is primarily EGFR TKIs (gefitinib [IRESSA™], erlotinib [TARCEVA®], afatinib [GILOTRIF™]) with overall response rate (ORR) of approximately 60-70% and median progression-free survival (PFS) of 9 to 14 months. Despite the high magnitude of ORR, patients typically develop treatment resistant disease within the first year of treatment. In about 60% of patients, the mechanism of acquired resistance to EGFR TKIs is thought to involve the emergence of a second-site EGFR point mutation that results in substitution of threonine with methionine at amino acid position 790 (T790M), an amino acid located within the ATP binding site of the EGFR kinase domain. Osimertinib was developed to target the EGFR T790M resistant mutation.

2.2. Analysis of Current Treatment Options

Erlotinib and afatinib are approved for first-line treatment of patients with metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test. Currently there are no specific therapies available for treatment of patients with EGFR T790M resistant mutations. Following progression on initial EGFR TKI therapy, patients are typically treated with standard chemotherapy, in a treatment paradigm that is similar to unselected advanced non-squamous NSCLC. For chemotherapy-naïve patients, this involves a platinum-doublet (e.g., platinum plus pemetrexed). Treatment after platinum doublet involves single agent chemotherapy or combination therapy (e.g., docetaxel with ramucirumab). Chemotherapy for advanced NSCLC is associated with marginal benefit with the best results achieved in the first-line setting with platinum-doublet chemotherapy (ORR of about 30% with approximately 3 month prolongation of OS). In the second-line setting,

combination of docetaxel plus ramucirumab is associated with OS prolongation of about 1.4 month and ORR of about 23%.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Osimertinib is a New Molecular Entity (NME) and currently not marketed in the US.

3.2. Summary of Presubmission/Submission Regulatory Activity

- January 14, 2014. Type C meeting to discuss the overall NSCLC clinical development program for osimertinib to support initial registration as a treatment for (b) (4), T790M positive NSCLC patients. Discussions included nonclinical toxicology studies, dose selection strategy in first-in-human Study D5160C00001 (AURA), and a proposed "phase 3" trial in the first-line setting. FDA generally agreed there is an unmet need for patients with EGFR mutation positive NSCLC whose tumors develop a T790M resistance mutation following appropriate EGFR TKI therapy and that demonstration of a favorable benefit risk profile for osimertinib based ORR of clinically meaningful duration and magnitude in can potentially support approval under the provisions of 21 CFR 314 Subpart H in EGFRm+/T790M+ patients with advanced NSCLC following failure of initial anti-EGFR TKI therapy. FDA also stated general agreement with AstraZeneca's proposal to conduct the confirmatory randomized trial with osimertinib versus standard platinum-based doublet chemotherapy in chemotherapy-naïve patients with acquired resistance to EGFR TKIs and T790M resistance mutations. However, FDA highlighted that for any randomized trial, the condition of equipoise must exist.
- An application for Breakthrough Therapy Designation was submitted on February 27, 2014 and granted on April 16, 2014 for the treatment of patients with metastatic EGFR T790M mutation positive NSCLC whose tumor has progressed on treatment with an FDA-approved, EGFR tyrosine kinase inhibitor.
- October 2, 2014. Type B Breakthrough Therapy-Initial Comprehensive meeting. The primary purpose of the meeting was to discuss and reach agreement on the development program to provide an adequate data package to support an NDA submitted under the provisions of 21 CFR 314 Subpart H (accelerated approval) for osimertinib for the treatment of patients with (b) (4)/metastatic NSCLC whose disease has progressed with previous EGFR TKI therapy and (b) (4) FDA generally agreed that demonstration of blinded independent central review (BICR) confirmed durable responses in a substantial proportion of the second-line patients treated with osimertinib 80 mg once daily in the Phase 1 portion of D5160C00001 AURA (n~50) could potentially enable an adequate assessment of the durability of the confirmed objective responses for the purpose of making a regulatory decision. FDA stated that it could not comment on how this information might inform or be included in labeling. FDA also generally agreed with AstraZeneca's pooling strategy for Studies D5160C00001 (AURA extension) and D5160C00002 (AURA2) in the summaries of safety and efficacy.

- October 7, 2014. Type B CMC meeting.
- December 9, 2014. Type B pre-NDA meeting. FDA agreed with AstraZeneca's approach for rolling submission. The meeting included a synopsis of the confirmatory trial, Study D5160C00007 (FLAURA), a double-blind, randomized study in patients with locally advanced or metastatic EGFR mutation-positive (EGFRm+) NSCLC who are treatment-naïve and eligible for first-line treatment with an EGFR TKI. AstraZeneca stated that the cobas® EGFR Mutation test used to identify patients' EGFR mutation status for the AURA and FLAURA studies is an investigational assay and that the test is identical to the FDA-approved cobas® EGFR Mutation test except it identifies additional EGFR mutations (e.g., T790M) that are not described in the FDA-approved labeling for this test.

3.3. Foreign Regulatory Actions and Marketing History

Osimertinib is not approved in any countries.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

No significant issues that would alter the benefit-risk or osimertinib for the proposed indication. Please refer to discipline-specific reviews for more details.

4.1. Office of Scientific Investigations (OSI)

Two clinical sites were chosen for OSI inspections from Studies D5160C00002 (AURA2) and D5160C0001C (AURA extension). The rationale was based on outlier analysis of the data from all participating sites. The two sites recommended for inspections were among the sites with high enrollment. Preliminary clinical inspection results revealed no issues (Table 1).

Table 1. Preliminary clinical inspection results

Planned inspections:	Scheduled dates for inspection	Status	Preliminary Outcome	Site Number
Sponsor: AstraZeneca	September 28-29, 2015	Completed	NAI (no issues)	N/A
CRO: (b) (4)	September 14-18, 2015	Completed	NAI (no issues)	N/A
CI: Tsai, Chun-Ming (TWN)	August 10-14, 2015	Completed	NAI (no issues)	Site #7401 (Study D5160C00002)
CI: Janne, Pasi (Boston, MA)	August 3-7, 2015	Completed	NAI (no issues)	Site #7800 (Study D5160C0001C)

4.2. Product Quality

No significant issues communicated to clinical team. Please see discipline review.

4.3. Clinical Microbiology

No significant issues communicated to clinical team. Please see discipline review.

4.1. Nonclinical Pharmacology/Toxicology

No significant issues communicated to clinical team. Please see discipline review.

4.2. Clinical Pharmacology

No significant issues communicated to clinical team. Please see discipline review.

4.2.1. Mechanism of Action

Osimertinib is an EGFR TKI, an irreversible inhibitor of both EGFRm (broadly described as TKI-sensitivity conferring mutations) and EGFR T790M mutation positive (TKI-resistance conferring mutation) forms of EGFR. The drug was designed to have limited activity against wild type EGFR. Pre-clinical data has shown EGFR phosphorylation inhibition activity in mutant EGFR cell lines. Tumor regression has been observed in different pre-clinical in vivo disease models, including EGFR T790M mutation positive tumors.

4.2.2. Pharmacodynamics

Exploratory analyses by the applicant did not show a relationship between exposure (AUCss) of osimertinib and ORR, change in tumor size or DOR based on BICR-assessed RECIST criteria for patients treated with the 80 mg dose in AURA extension, AURA2 and AURA Phase I expansion and investigator-assessed outcomes for all other doses in AURA expansion. The probability of a patient experiencing rash and diarrhea may increase with exposure, consistent with the observation of a dose-related increase in the incidence of rash and diarrhea at doses of 160 mg and above supporting selection of an 80 mg dose by the applicant.

4.2.3. Pharmacokinetics

The area under the plasma concentration-time curve (AUC) and maximal plasma concentration (Cmax) of osimertinib increased dose proportionally over 20 to 240 mg dose range (i.e., 0.25 to 3 times the recommended dosage) after oral administration and exhibited linear pharmacokinetics (PK). Oral once daily administration resulted in approximately 3-fold accumulation with steady state exposures achieved after 15 days of dosing. At steady state, the Cmax to Cmin (minimal concentration) ratio was 1.6-fold.

4.3. Consumer Study Reviews

N/A

5 Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

The applicant submitted data from two clinical trials: Studies D5160C00001 (phase 1 portion AURA and AURA extension) and D5160C00002 (AURA2) (
Table 2). Study D5160C00001 was the first-in-human trial with two parts: dose escalation (ARUA phase 1) and dose expansion (AURA extension). Data on 63 patients in the AURA phase 1 part of the trial were submitted to allow for better characterization of duration of response. In addition, the applicant submitted a pooled efficacy analysis based on combined datasets from AURA extension and AURA2. The main differences between AURA extension and AURA2 protocols and conduct of the trials are shown in Table 3. Data from AURA extension and AURA2 were evaluated separately by FDA and the pooled datasets were used for exploratory and subgroup analyses.

Table 2. Clinical trials in support of the proposed indication

	AURA extension	AURA2	AURA Phase 1
No. of patients dosed	201	210	355
Study No.	D5160C00001 ("Phase 2" extension)	D5160C00002	D5160C00001 (Phase 1)
Type	Open-label, single arm trial extension of AURA phase 1 to investigate activity of osimertinib in previously EGFR TKI treated patients with metastatic EGFRm+ T790M+ NSCLC	Open-label, single-arm trial, similar population as in AURA extension	Open-label, single arm, multi-dose cohort trial with ascending doses of osimertinib in patients with advanced NSCLC who have progressed following prior therapy with an EGFR TKI agent
Key objectives	Primary: o To investigate the safety, tolerability and efficacy (ORR) Secondary, extension cohort: o To obtain additional assessments of the anti-tumour activity of osimertinib by evaluation of DOR	Primary: o To assess the efficacy of osimertinib by assessment of ORR. Secondary: o To further assess the efficacy of osimertinib in terms of DOR o To assess the safety and tolerability profile of osimertinib	Primary: o To investigate the safety, tolerability and efficacy (ORR) of osimertinib Secondary, dose-escalation and dose-expansion cohorts: o To obtain a preliminary assessment of the anti-tumour activity of osimertinib by evaluation of DOR
T790M central testing	Performed prospectively; central result (cobas® EGFR mutation test) mandatory to determine eligibility	Performed prospectively; central result (cobas® EGFR mutation test) mandatory to determine eligibility	Performed retrospectively (cobas® EGFR mutation test)
Study period	o First patient dosed: 14 May 2014 o Last patient first dose: 21 October 2014	o First patient dosed: 13 June 2014 o Last patient first dose: 27 October 2014	o First patient dosed: 6 March 2013 (80 mg subset in dose expansion: 2 September 2013) o Last patient first dose: 12 November 2014 (80 mg subset: 12 November 2014)
Data cut-off (DOC)	9 January 2015	9 January 2015	2 December 2014
Treatment exposure at DCO, median and range	Median (range): 4.9 months (0.1 to 7.9 months)	Median (range): 4.0 months (0.0 to 6.9 months)	o Pre-treated T790M mutation-positive in dose expansion (n = 163): Median (range): 8.7 months (0.1 to 17.7 months) o 80 mg pre-treated T790M mutation-positive (n = 63): Median (range): 8.1 months (0.5 to 14.3 months)

Table 3. Key differences between Studies AURA extension and AURA2

Parameters	AURA extension	AURA2	Impact
Study design	Eligible patients were those with advanced NSCLC who progressed following therapy with an EGFR TKI ± additional drug treatment regimens	Two cohorts of pre-treated patients were pre-defined in the inclusion criteria: o Second-line (ie, had received 1 EGFR TKI only and no other treatment) o ≥Third-line (ie, had received 1 EGFR TKI and at least 1 regimen of platinum-based doublet chemotherapy)	The percentages of patients who received prior platinum-based chemotherapy were similar in both studies (60.7% in AURA extension and 64.3% in AURA2)
Inclusion criteria	Patients had to fulfil one of 2 conditions: o Either they had a confirmed EGFR mutation known to be associated with EGFR-TKI sensitivity (G719X, exon 19 deletion, L858R, L861Q) o or they had experienced clinical benefit from EGFR TKI according to Jackman criteria[a] followed by objective progression while on continuous treatment with EGFR TKI.	The 2 cohorts of 2nd-line and ≥3rd-line patients were pre-defined as above. Jackman criteria were not used. All patients had to have central confirmation of EGFR mutation to be enrolled.	The presence of an EGFR mutation known to be associated with TKI sensitivity was confirmed centrally in 98.5% of patients in AURA extension.
Exclusion criteria	Prior treatment with a third-generation EGFR-TKI (eg, CO-1686) not stipulated as exclusionary	Patients excluded if they had prior treatment with a third-generation EGFR-TKI	Only 2 patients in AURA extension had prior treatment with a third-generation EGFR-TKI (CO-1686).

5.2. Review Strategy

The clinical/statistical review was conducted jointly by Drs. Sean Khozin, Chana Weinstock, and Joyce Cheng compiled into a single review document. The two single arm trials, AURA extension and AURA2, formed the basis of both the efficacy and safety review. There was additional data submitted for the AURA phase 1 trial which was used to augment the safety review. The Sponsor's electronic submissions, including the original Clinical Study Report (CSR), were reviewed. The principal review activities for this NDA included:

- Review of the original electronic submission of the NDA, including the Sponsor's CSR;

- Review of electronic submissions from the Sponsor in response to clinical and biostatistical queries;
- Review of Sponsor presentation slides to FDA 01/05/2012;
- Reproduction/auditing of key efficacy and safety analyses with JMP using raw and derived datasets provided by the applicant;
- Performance of sensitivity analyses and exploratory subgroup analyses;
- Review of relevant case report forms and patient narratives;
- Consultation with other disciplines

Review of Relevant Individual Trials Used to Support Efficacy

5.3. Clinical Trials

D5160C00001: AURA Phase I

Objectives

Primary objective:
To investigate the safety, tolerability and efficacy (ORR) of osimertinib when given orally to patients with locally advanced or metastatic NSCLC who had progressed following prior therapy with an EGFR TKI agent.

Key secondary objectives:
To define the maximum tolerated dose; to investigate the safety and tolerability of osimertinib when given orally as first-line therapy to patients who were treatment-naïve for locally advanced or metastatic EGFRm NSCLC; to characterize the PK of osimertinib and its metabolites (AZ5104 and AZ7550) after a single oral dose and at steady-state after multiple oral doses; and to obtain a preliminary assessment of the anti-tumor activity of osimertinib by evaluation of DOR and PFS using RECIST.

Trial Design

This was a first-in-human "Phase 1-2", open-label, multicenter study of osimertinib administered orally as capsule formulation to 355 patients with advanced NSCLC who had progressed following prior therapy with an EGFR TKI agent (± additional chemotherapy regimens). The study design included a dose-escalation (n = 31) and a dose expansion (n = 312, including 252 pre-treated patients and 60 first-line patients). Expansion cohorts were included to investigate specific patient subgroups (according to tumor EGFR T790M mutation status) and to evaluate pharmacodynamic changes (paired biopsy cohorts in patients with EGFR T790M mutation tumors). In addition, 1 cohort of pre-treated EGFR patients (not selected by tumor EGFR T790M mutation status) received 80 mg of osimertinib as Phase 1 tablet formulation (n = 12; United States only). One additional patient assigned to treatment died before receiving the first dose of osimertinib. Efficacy analyses were based on investigator assessment; a BICR assessment was also conducted in the subset of 63 pre-treated patients with T790M mutation-positive NSCLC who received osimertinib 80 mg. The study was ongoing at DCO.

Once the MTD or recommended daily dose was reached, a phase 2 extension component ensued with patients who had EGFR T790M mutation positive status identified by central testing. The results of this extension component were reported by the applicant in a separate CSR. The primary objective of the extension component (AURA extension) was to investigate the safety, tolerability and efficacy (objective response rate [ORR] by BICR) of osimertinib when given orally to patients with locally advanced or metastatic NSCLC who had progressed following prior therapy with an EGFR TKI agent. Secondary objectives included:

- To characterize the pharmacokinetics of osimertinib and its metabolites (AZ5104 and AZ7550) after multiple oral doses.

- To obtain additional assessments of the anti-tumor activity of osimertinib by evaluation of duration of response (DOR), disease control rate (DCR), tumor shrinkage, and progression-free survival (PFS) using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 as assessed by a BICR of radiological information and OS.

Inclusion criteria

For inclusion in the study, patients had to fulfil all of the following criteria:

1. Provision of signed and dated, written informed consent prior to any study-specific procedures, sampling and analyses
    a. If a patient declined to participate in any voluntary exploratory research and/or genetic component of the study, there was no penalty or loss of benefit to the patient and he or she was not to be excluded from other aspects of the study
2. Aged at least 18 years. Patients from Japan aged at least 20 years
3. Histological or cytological confirmation diagnosis of NSCLC
4. Radiological documentation of disease progression while on a previous continuous treatment with an EGFR TKI, eg, gefitinib or erlotinib. In addition, other lines of therapy could have been given. All patients had to have documented radiological progression on the last treatment administered prior to enrolling in the study
5. Patients had to fulfil one of the following:
    a. Confirmation that the tumour harboured an *EGFR* mutation known to be associated with EGFR TKI sensitivity (including G719X, exon 19 deletion, L858R, or L861Q)
    or
    b. Had to have experienced clinical benefit from EGFR TKI, according to the Jackman criteria[1] followed by systemic objective progression (RECIST or World Health Organization [WHO]) while on continuous treatment with EGFR TKI
6. Prior to entry into the extension cohort, a positive result from the central analysis of the patient's EGFR T790M mutation status had to be obtained. Patients had to have

[1] Clinical benefit from treatment with an EGFR TKI as defined by either documented partial or complete response (RECIST or WHO) or significant and durable (≥6 months) clinical benefit (stable disease as defined by RECIST or WHO) after initiation of gefitinib or erlotinib. Patients with only symptomatic improvement while on EGFR TKI but no corresponding evidence of radiographic stability of disease were not to be routinely considered as having sufficient clinical benefit.

confirmation of tumour EGFR T790M mutation status (confirmed positive or negative) from a biopsy sample taken after disease progression on the most recent treatment regimen (irrespective of whether this was EGFR TKI or chemotherapy)

7. A WHO performance status of 0 to 1 with no deterioration over the previous 2 weeks and a minimum life expectancy of 12 weeks
8. At least 1 lesion, not previously irradiated and not chosen for biopsy during the study screening period, that could be accurately measured at baseline as ≥10 mm in the longest diameter (except lymph nodes, which had to have short axis ≥15 mm) with computerised tomography (CT) or magnetic resonance imaging that was suitable for accurate repeated measurements
9. Females were to be using adequate contraceptive measures, were not to be breastfeeding and had to have a negative pregnancy test prior to the start of dosing if of childbearing potential, or had to have evidence of non-childbearing potential by fulfilling one of the following criteria at screening:
    a. Post-menopausal defined as aged more than 50 years and amenorrhoeic for at least 12 months following cessation of all exogenous hormonal treatments
    b. Women under 50 years old were considered post-menopausal if they had been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatments and with luteinising hormone and follicle-stimulating hormone levels in the post-menopausal range for the institution
    c. Documentation of irreversible surgical sterilisation by hysterectomy, bilateral oophorectomy or bilateral salpingectomy but not tubal ligation
10. Male patients were to be willing to use barrier contraception, ie, condoms
11. Patients from Japan were to be willing to remain in hospital from the first dosing day until Day 1 of Cycle 2
12. For inclusion in optional genetic research, the patient had to provide informed consent for genetic research

Exclusion criteria

Patients could not enter the study if any of the following exclusion criteria were fulfilled:

1. Treatment with any of the following:
    a. Treatment with an EGFR TKI (eg, erlotinib or gefitinib) within 8 days or approximately 5 half-lives, whichever was the longer, of the first dose of study treatment. (If sufficient washout time had not occurred due to the schedule or PK properties, an alternative appropriate washout time based on known duration and time to reversibility of drug-related adverse events [AEs] could be agreed upon by AstraZeneca and the investigator)
    b. Any cytotoxic chemotherapy, investigational agents or anti-cancer drugs for the treatment of advanced NSCLC from a previous treatment regimen or clinical study within 14 days of the first dose of study treatment
    c. osimertinib in the present study (ie, dosing with osimertinib previously initiated in this study)
    d. Major surgery (excluding placement of vascular access) within 4 weeks of the first dose of study treatment

   e. Radiotherapy with a limited field of radiation for palliation within 1 week of the first dose of study treatment, with the exception of patients receiving radiation to more than 30% of the bone marrow or with a wide field of radiation that had to be completed within 4 weeks of the first dose of study treatment
   f. Patients currently receiving (or unable to stop use at least 1 week prior to receiving the first dose of osimertinib) medications or herbal supplements known to be potent inhibitors of cytochrome P450 isoenzyme (CYP) 2C8 and potent inhibitors or inducers of CYP3A4 (see Appendix H of the CSP [Appendix 12.1.1])
2. Any unresolved toxicities from prior therapy greater than Common Terminology Criteria for Adverse Events (CTCAE) grade 1 at the time of starting study treatment with the exception of alopecia and grade 2, prior platinum therapy-related neuropathy
3. Spinal cord compression or brain metastases unless asymptomatic, stable and not requiring steroids for at least 4 weeks prior to the start of study treatment
4. Any evidence of severe or uncontrolled systemic diseases, including uncontrolled hypertension and active bleeding diatheses which, in the investigator's opinion, made it undesirable for the patient to participate in the study or which would jeopardise compliance with the protocol, or active infection including hepatitis B, hepatitis C and human immunodeficiency virus. Screening for chronic conditions was not required.
5. Any of the following cardiac criteria:
   a. Mean resting QT (ECG interval measured from the onset of the QRS complex to the end of the T wave) interval corrected for heart rate (QTc) >470 ms obtained from 3 dECGs, using QTc value derived from the study centre dECG machine at screening
   b. Any clinically important abnormalities in rhythm, conduction or morphology of resting dECG, eg, complete left bundle-branch block, third degree heart block, second-degree heart block, PR interval >250 ms
   c. Any factors that increase the risk of QTc prolongation or risk of arrhythmic events such as heart failure, hypokalaemia, congenital long QT syndrome, family history of long QT syndrome or unexplained sudden death under 40 years of age in first-degree relatives or any concomitant medication known to prolong the QT interval
6. Past medical history of interstitial lung disease (ILD), drug-induced ILD, radiation pneumonitis that required steroid treatment, or any evidence of clinically active ILD
7. Inadequate bone marrow reserve or organ function as demonstrated by any of the following laboratory values:
   a. Absolute neutrophil count <1.5 × 109/L
   b. Platelet count <100 × 109/L
   c. Haemoglobin <90 g/L
   d. Alanine aminotransferase (ALT) >2.5 × the upper limit of normal (ULN) if no demonstrable liver metastases or >5 × ULN in the presence of liver metastases
   e. Aspartate aminotransferase (AST) >2.5 × ULN if no demonstrable liver metastases or >5 × ULN in the presence of liver metastases
   f. Total bilirubin >1.5 × ULN if no liver metastases or >3 × ULN in the presence of documented Gilbert's Syndrome (unconjugated hyperbilirubinaemia) or liver metastases

   g. Creatinine >1.5 × ULN concurrent with creatinine clearance <50 mL/min (measured or calculated by Cockcroft and Gault equation); confirmation of creatinine clearance was only required when creatinine was >1.5 × ULN
8. Refractory nausea and vomiting, chronic gastrointestinal diseases, inability to swallow the formulated product or previous significant bowel resection that would preclude adequate absorption of osimertinib
9. History of hypersensitivity to active or inactive excipients of osimertinib or drugs with a similar chemical structure or class to osimertinib
10. Women who were breastfeeding
11. Involvement in the planning and conduct of the study (applied to AstraZeneca staff or staff at the study center)
12. Judgment by the investigator that the patient should not participate in the study if the patient was unlikely to comply with study procedures, restrictions and requirements

In addition, the following was considered a criterion for exclusion from the exploratory genetic research:

13. Previous allogeneic bone marrow transplant
14. Non-leukocyte depleted whole blood transfusion within 120 days of the date of the genetic sample collection

Protocol Amendments with key changes

First final version of the protocol prior to any amendments: 30 Nov 2012

Global Amendment 1: 29 Mar 2013

The option to test an expansion cohort in first line advanced NSCLC patients was added. This was based on emerging pre-clinical in vitro data which suggests that treatment with osimertinib may delay the development of resistance to an EGFR TKI agent via the T790M mechanism. Clarification on DLT criteria was added.

Global Amendment 2: 9 Oct 2013
Preclinical metabolism data and preclinical/class data relating to testicular toxicity and embryo fetal development, added information included drug-drug interactions and recommendations to protect the female partners of male trial subjects from a hypothetical exposure to osimertinib and to protect against a potential embryo fetal risk**.**

US, Amendment 3, Tablet cohort: 25 Nov 2013
Dose escalation cohort increased from 36 to 48. An additional cohort of approximately 12 patients was included to assess the PK profile in patients with advanced NSCLC when osimertinib is administered as an 80mg tablet formulation.

UK, Amendment 2: 3 Jan 2014
Allowed intra-patient dose escalation based on preclinical data that demonstrated that when the clinical efficacy in a dual mutation (L858R/T790M+) mouse xenograft model eventually develops resistance to low dose osimertinib (1mg/kg/day) a dose escalation (to 25mg/kg/day) reverses the tumor re-growth and provides additional durable sustained tumor shrinkage.

Therefore, an increase in dose of osimertinib to 160mg in patients with initial objective responses at a lower dose was allowed.

Global Amendment 3: 27 Feb 2014
Added exploratory objective to characterize the PK of osimertinib and its metabolites (AZ5104 and AZ7550) in cerebrospinal fluid (CSF). Added extension cohort plan for 175 patients who have T790M+ status identified by central testing, to be enrolled to further assess the efficacy and tolerability of osimertinib at MTD/RP2D.

Global Amendment 4: 20 Mar 2014
Revised information included patients taking concomitant medications whose disposition is dependent upon CYP3A4, CYP1A2, CYP2C or p-glycoprotein and which have a narrow therapeutic index.

Japan, Amendment 4: 26 Aug 2014
Addition of a cytology cohort to explore the efficacy of osimertinib in patients enrolled by use of a liquid biopsy sample for detection of the T790M mutation.

D5160C00001: (Phase 2 component, AURA extension)

The primary objective of the extension study (Phase II component) was to investigate the safety, tolerability and efficacy (objective response rate [ORR] by BICR) of osimertinib when given orally to patients with locally advanced or metastatic NSCLC who had progressed following prior therapy with an EGFR TKI agent. The secondary objectives of the trial included:

- To characterize the pharmacokinetics of osimertinib and its metabolites (AZ5104 and AZ7550) after multiple oral doses.

- To obtain additional assessments of the anti-tumor activity of osimertinib by evaluation of duration of response (DoR), disease control rate (DCR), tumor shrinkage, and progression-free survival (PFS) using RECIST version 1.1 as assessed by a BICR of radiological information and OS.

The Phase 2 component of the trial (AURA extension) was planned to include approximately 175 patients who had prospectively confirmed EGFR T790M mutation positive status identified by central testing. Trial eligibility was similar to phase 1 component of the trial. A mandatory biopsy was required for central testing of the EGFR T790M mutation status following confirmed radiological progression on the most recent treatment regimen. The EGFR T790M mutation status of the patient's tumor was prospectively determined by the designated central laboratory using the cobas® EGFR Mutation Test (Roche Molecular Systems). There were 2 cohorts in this portion of the trial: patients whose disease had progressed following either 1 prior therapy with an EGFR TKI (second line; no additional lines of therapy, planned n ~50) or following treatment with at least 2 lines of prior therapy including at least 1 EGFR TKI (≥third line, planned n~125). Patients continued treatment with osimertinib until RECIST defined progression or until a treatment discontinuation criterion was met. There was no maximum duration of treatment as patients could continue to receive osimertinib beyond RECIST defined progression

as long as they continued to show clinical benefit, as judged by the investigator. All patients in this portion of the trial received osimertinib 80 mg once daily, the recommended dose from the dose escalation part of the trial.

The sample size was set at 175 so that the precision of the estimation of ORR would be within ±8% (eg, ORR 40%, 95% CI 33.0%, 47.4%) in the overall study population, within ±13% in the 50 patient cohort who have only received previous TKI treatment, and within ±9% in the 125 patient cohort who have received previous TKI treatment and other anti-cancer therapy. The study also provided an adequate number of patients in which to assess the safety and tolerability of osimertinib; if zero responses were observed in the 175 patients, there would be 95% confidence (2 sided) that the true response rate was less than 2.2%.

D5160C00002: AURA2

Objectives

Primary Objective

- To investigate the efficacy of osimertinib by assessment of objective response rate (ORR)

Secondary Objectives included

- To further assess the efficacy of osimertinib in terms of duration of response (DOR), tumor shrinkage, progression-free survival (PFS) and OS.
- To assess the safety and tolerability profile of osimertinib

It should be noted that time to event endpoints, such as PFS and OS, are not interpretable in single arm studies and are considered exploratory in this setting.

Study Design

Open label, single arm trial assessing the safety and efficacy of osimertinib (80 mg, orally, once daily) in patients with a confirmed diagnosis of EGFRm metastatic NSCLC who had progressed following prior therapy with an approved EGFR TKI agent. A mandatory biopsy was required for central testing of EGFR T790M mutation status following confirmed disease progression on the most recent treatment regimen. The EGFR T790M mutation status of the patient's tumor was prospectively determined by the designated central laboratory using the cobas® EGFR Mutation Test (Roche Molecular Systems).

This trial consisted of 2 cohorts:

1. Second line therapy cohort: patients whose disease had progressed following first line therapy with 1 EGFR TKI agent but who had not received further treatment
2. ≥Third line therapy cohort: patients whose disease had progressed following treatment with both EGFR TKI and a platinum-based doublet chemotherapy (patients may have also received additional lines of treatment)

It was planned to include approximately 50 patients in the second line therapy cohort and approximately 125 patients in the ≥third line therapy cohort.

Patients continued on treatment with osimertinib until RECIST 1.1-defined progression or until a treatment discontinuation criterion was met. There was no maximum duration of treatment as patients could continue to receive osimertinib beyond RECIST 1.1-defined progression as long as they continued to show clinical benefit, as judged by the investigator.

The sample size was set at 175 so that the precision of the estimation of ORR would be within ±8% (eg, ORR 40%, 95% CI 33.0%, 47.4%) in the overall study population, within ±13% in the 50 patient cohort, and within ±9% in the 125 patient cohort. The trial provided an adequate number of patients in which to assess the safety and tolerability of osimertinib; if zero responses were observed in the 175 patients, there would be 95% confidence (2 sided) that the true response rate was less than 2.2%.

Inclusion Criteria

1. Provision of signed and dated, written informed consent prior to any study-specific procedures, sampling and analyses. If a patient declined to participate in any voluntary exploratory research and/or genetic component of the study, there was no penalty or loss of benefit to the patient and he or she was not to be excluded from other aspects of the study.
2. Male or female, aged at least 18 years. Patients from Japan aged at least 20 years
3. Histological or cytological confirmation diagnosis of NSCLC
4. Locally advanced or metastatic NSCLC, not amenable to curative surgery or radiotherapy
5. Radiological documentation of disease progression: following first line EGFR TKI treatment but who had not received further treatment OR following prior therapy with an EGFR TKI and a platinum-based doublet chemotherapy. Patients may have also received additional lines of treatment. All patients had to have documented radiological progression on the last treatment administered prior to enrolling in the study.
6. Confirmation that the tumor harbored an EGFR mutation known to be associated with EGFR TKI sensitivity (including G719X, exon 19 deletion, L858R, L861Q)
7. Patients had to have central confirmation of tumor EGFR T790M mutation positive status from a biopsy sample taken after confirmation of disease progression on the most recent treatment regimen
8. World Health Organization (WHO) performance status 0 to1 with no deterioration over the previous 2 weeks and a minimum life expectancy of 12 weeks
9. At least 1 lesion, not previously irradiated and not chosen for biopsy during the study screening period, that could be accurately measured at baseline as ≥10 mm in the longest diameter (except lymph nodes which had to have short axis ≥15 mm) with computerized tomography (CT) or magnetic resonance imaging that was suitable for accurate repeated measurements
10. Females were to be using adequate contraceptive measures, were not to be breastfeeding and had to have a negative pregnancy test prior to the start of dosing if of childbearing potential, or had to have evidence of non-childbearing potential by fulfilling one of the following criteria at screening:
11. Post-menopausal defined as aged more than 50 years and amenorrheic for at least 12 months following cessation of all exogenous hormonal treatments
12. Women under 50 years old were considered post-menopausal if they had been amenorrheic for 12 months or more following cessation of exogenous hormonal

treatments and with luteinizing hormone and follicle-stimulating hormone levels in the post-menopausal range for the institution
13. Documentation of irreversible surgical sterilization by hysterectomy, bilateral oophorectomy or bilateral salpingectomy but not tubal ligation
14. Male patients were to be willing to use barrier contraception (ie, condoms)
15. For inclusion in the optional genetics research, study patients had to provide informed consent for genetic research

Exclusion criteria

1. Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study center)
2. Treatment with any of the following:
    a. Treatment with an EGFR TKI (eg, erlotinib, gefitinib or afatinib) within 8 days or approximately 5 half-lives, whichever was the longer, of the first dose of study treatment. (If sufficient washout time had not occurred due to the schedule or PK properties, an alternative appropriate washout time based on known duration and time to reversibility of drug-related AEs could be agreed upon by AstraZeneca and the investigator.)
    b. Any cytotoxic chemotherapy, investigational agent or other anti-cancer drugs from a previous treatment regimen or clinical study within 14 days of the first dose of study treatment
    c. Previous treatment with osimertinib or a third generation EGFR TKI (eg, CO-1686)
    d. Major surgery (excluding placement of vascular access) within 4 weeks of the first dose of study treatment
    e. Radiotherapy treatment to more than 30% of the bone marrow or with a wide field of radiation within 4 weeks of the first dose of study treatment
    f. Patients currently receiving (or unable to stop use at least 1 week prior to receiving the first dose of study treatment) medications or herbal supplements known to be potent inhibitors or inducers of cytochrome P450 3A4 (CYP3A4) (see Appendix F of the CSP [Appendix 12.1.1])
3. Any unresolved toxicities from prior therapy greater than CTCAE grade 1 at the time of starting study treatment with the exception of alopecia and grade 2, prior platinum therapy-related neuropathy
4. Spinal cord compression or brain metastases unless asymptomatic, stable and not requiring steroids for at least 4 weeks prior to the start of study treatment
5. Any evidence of severe or uncontrolled systemic diseases, including uncontrolled hypertension and active bleeding diatheses which, in the investigator's opinion, made it undesirable for the patient to participate in the study or which would jeopardize compliance with the protocol, or active infection including hepatitis B, hepatitis C and human immunodeficiency virus. Screening for chronic conditions was not required.
6. Refractory nausea and vomiting, chronic gastrointestinal diseases, inability to swallow the formulated product or previous significant bowel resection that would preclude adequate absorption of osimertinib
7. Any of the following cardiac criteria:
    a. Mean resting QTc >470 ms obtained from 3 ECGs

   b. Any clinically important abnormalities in rhythm, conduction or morphology of resting ECG, eg, complete left bundle-branch block, third-degree heart block, second-degree heart block, partial response (PR) interval >250 ms
   c. Any factors that increase the risk of QTc prolongation or risk of arrhythmic events such as heart failure, hypokalemia, congenital long ECG interval measured from the onset of the QRS complex to the end of the T wave (QT) syndrome, family history of long QT syndrome or unexplained sudden death under 40 years of age in first-degree relatives or any concomitant medication known to prolong the QT interval
8. Past medical history of interstitial lung disease (ILD), drug-induced ILD, radiation pneumonitis that required steroid treatment, or any evidence of clinically active ILD
9. Inadequate bone marrow reserve or organ function as demonstrated by any of the following laboratory values:
   a. Absolute neutrophil count <1.5 × 109/L
   b. Platelet count <100 × 109/L
   c. Hemoglobin <90 g/L
   d. Alanine aminotransferase (ALT) >2.5 × the upper limit of normal (ULN) if no demonstrable liver metastases or >5 times ULN in the presence of liver metastases
   e. Aspartate aminotransferase (AST) >2.5 × ULN if no demonstrable liver metastases or >5 × ULN in the presence of liver metastases
   f. Total bilirubin >1.5 × ULN if no liver metastases or >3 × ULN in the presence of documented Gilbert's Syndrome (unconjugated hyperbilirubinemia) or liver metastases
   g. Creatinine >1.5 × ULN concurrent with creatinine clearance <50 mL/min (measured or calculated by Cockcroft and Gault equation); confirmation of creatinine clearance was only required when creatinine was >1.5 × ULN
10. History of hypersensitivity to active or inactive excipients of osimertinib or drugs with a similar chemical structure or class to osimertinib
11. Women who were breastfeeding
12. Judgment by the investigator that the patient should not participate in the study if the patient was unlikely to comply with study procedures, restrictions and requirements

Protocol Amendments

Amendment 1: 1 April 2014. Added information about hormonal contraceptives that are not prone to drug-drug interactions [IUS Levonorgestrel Intra Uterine System (Mirena), Medroxyprogesterone injections (Depo-Provera)]. Added clarification on concomitant use of medications, herbal supplements and/or ingestion of foods with known potent inhibitors of CYP2C8 and potent inhibitors or inducers of CYP3A4. Added information on tumor assessments and other clinical data obtained as standard of care prior to consent may be used for the study provided the assessments fall within the protocol specified period prior to the first dose of the study treatment. Removed duplication of Collection of cerebrospinal fluid (CSF) section in Section 5.5.2.

Amendment 2: 24 September 2014. Corrected error on PK sampling outcome measures.

Updated data to be analyzed for Primary Analysis and to clarify the calculation of variables to be analyzed. Updated restrictions on CYP2C8 inhibitors based on Drug Metabolism and Pharmacokinetic (DMPK) data with an extended group of CYP isozymes which showed that osimertinib metabolism was mainly via CYP3A4 and the contribution of CYP2C8 to osimertinib clearance was negligible. Provided additional clarification on requirements of study procedures.

Compliance with Good Clinical Practices

The Applicant provided statement that all trials were approved by institutional review boards or independent ethics committees, and followed the International Conference of Harmonization (ICH) good clinical practice (GCP) guidelines, conformed to the declaration of Helsinki, and informed, written consent was obtained from all patients as per GCP requirement.

Financial Disclosure

The majority of the investigators reported no financial interests and financial disclosures were obtained from majority of the investigators. The applicant made reasonable attempts to collect disclosures from investigators whom could not be reached for disclosures. An impact analysis conducted by the applicant revealed that investigators that responded positively (n=3) on financial disclosure forms had few patients enrolled and unlikely to bias study results.

5.3.1. Study Results

Patient Disposition

D5160C00001 (AURA Phase 1):

Fifty patients with locally advanced or metastatic NSCLC who had progressed on or after EGFR TKI therapy were enrolled in the dose escalation part of the study. Of these, 44 pre-treated patients were assigned to study drug (31 patients were dosed with the osimertinib capsule formulation, 12 patients were dosed with the 80 mg tablet formulation of osimertinib and 1 patient died before receiving study drug). Six pre-treated patients were not assigned to study drug (5 patients were screen failures and 1 patient withdrew consent).

451 patients enrolled in the dose expansion part of the study. Of these, 312 patients were assigned to study drug and dosed with the osimertinib capsule formulation (252 patients pre-treated for advanced NSCLC [dose expansion population] and 60 first-line EGFRm patients [treatment-naïve]). A total of 139 patients were not assigned to study drug (130 patients were screen failures, 7 patients withdrew consent, 1 patient died and for 1 patient the reason was missing). The patients in the paired biopsy cohort are included in the 252 patients in the dose expansion population.

Overall, there were 97 patients were treated at 80mg of osimertinib (**Table 4**). Of these, 63 patients were locally advanced or metastatic centrally-tested EGFR T790M mutation positive NSCLC who have progressed on or after EGFR TKI therapy. The information on these patients was submitted and reviewed to better characterize the duration of response.

Table 4. Dose expansion population D5160C00001 (AURA Phase 1): Analysis sets by centrally-tested EGFR T790M mutation status

	Number of patients osimertinib, pre-treated, capsule					
	20 mg	**40 mg**	**80 mg**	**160 mg**	**240 mg**	**Total**
Patients included in safety analysis set	15	52	97	74	14	252
EGFR T790M mutation positive patients	10	32	63	44	14	163
EGFR T790M mutation negative patients	3	17	29	20	0	69
EGFR T790M mutation unknown patients	2	3	5	10	0	20
Patients included in evaluable for response analysis set	15	52	95	71	13	246
EGFR T790M mutation positive patients	10	32	61	41	13	157
EGFR T790M mutation negative patients	3	17	29	20	0	69
EGFR T790M mutation unknown patients	2	3	5	10	0	20

Safety analysis set: All patients who received at least 1 dose of osimertinib.
Evaluable for response analysis set: All dosed patients with a baseline RECIST assessment.
The 20 patients with T790M unknown status were enrolled on the basis of local testing, which was not centrally-confirmed and so remained; however, for interpretation purposes, it was noted that 15 patients were EGFR T790M mutation positive by local testing, 3 patients were EGFR T790M mutation negative by local testing and 2 patients were EGFR T790M mutation unknown by local testing.
Source: CSR Table 11.1.12 (dose expansion) and Table 11.2.1.1 (dose expansion)

D5160C00001 AURA extension (phase 2 component):
Of the 401 patients screened, 201 patients received treatment with the osimertinib 80 mg tablet. Out of the 200 screening failures, the main reason was EGFR T790M mutation status not centrally confirmed positive in 158 patients. All other screening failure reasons were reported in ≤5 patients each.

The first patient started treatment on 14 May 2014 and the last patient started treatment on 21 October 2014. The DCO for the primary analysis was 9 January 2015.

The study was open for enrolment at 46 study centres in Japan (16), the USA (7), South Korea (4), Australia (3), France (3), Germany (3), Spain (3), Italy (3), Taiwan (2) and the UK (2). Patients were both screened and recruited at 40 centres in 10 countries; 50.7% of patients were from Asia, 20.4% from North America, and 28.9% from Europe and rest of world (see Table 11.1.4).

Of the 201 patients who received treatment, there were 61 (30.3%) patients in the second-line therapy cohort and 140 (69.7%) patients in the ≥third line therapy cohort. As of the DCO, 168/201 patients (83.6%) were ongoing on study treatment. Thirty-three patients (16.4%) had discontinued osimertinib treatment.

D5160C00002 AURA2
Of the 472 patients initially screened, 210 patients received treatment with the osimertinib 80 mg

tablet in this Phase II study. Out of the 262 screening failures, the main reason was EGFR T790M mutation status not centrally confirmed positive in 214 patients. Fourteen screen failure patients had WHO performance status >1. All other screening failure reasons were reported in ≤5 patients each.

The first patient started treatment on 13 June 2014 and the last patient started treatment on 27 October 2014. The DCO for AURA2 was 9 January 2015.

The study was open for enrolment at 44 study centers in Canada (3), Hong Kong (2), Italy (5), Japan (14), South Korea (3), Spain (6), Taiwan (2) and the USA (9);51.9% of patients were from Asia, 31.9% were from North America and 16.2% were from Europe and rest of world..

Of the 210 patients who received treatment, there were 68 (32.3%) patients in the second line therapy cohort and 142 (67.6%) patients in the ≥third line therapy cohort.

Protocol Violations/Deviations

D5160C00001 AURA extension (phase 2 component): There were 19 patients had protocol deviations; 5 did not fulfil eligibility criteria, 9 protocol-required procedures were not adhered to, and 5 other reasons.

D5160C00002 AURA2: There were 25 patients identified as having protocol deviation; 12 did not fulfil eligibility criteria, 6 protocol-required procedures were not adhered to, and 5 other reasons. Of these deviations, there were 7 patients in the ≥third line cohort who received 2 or more prior treatment regimens but did not have a platinum-containing doublet regimen as treatment for advanced NSCLC, as required in inclusion criterion 5. Two patients had their tumor assessment performed more than 28 days before first dose.

Table of Demographic Characteristics

Table 5. Demographic characteristics for D5160C00001 (AURA Phase 1)

Demographic characteristic	Dose escalation part (N=31)	Dose expansion part (N=252)
Gender, n (%)		
Male	11 (35.5)	97 (38.5)
Female	20 (64.5)	155 (61.5)
Age (years), median (range)	61.0 (39-81)	60.0 (28-88)
Age, n (%)		
<50 years	3 (9.7)	37 (14.7)
≥50 - <65 years	19 (61.3)	138 (54.8)
≥65 - <75 years	8 (25.8)	52 (20.6)
≥75 years	1 (3.2)	25 (9.9)
Weight (kg), median (range)	60.0 (43-93)	62.0 (38-117)

Demographic characteristic	**Dose escalation part (N=31)**	**Dose expansion part (N=252)**
Race, n (%)		
White	5 (16.1)	84 (33.3)
Black or African American	0	3 (1.2)
Asian	21 (67.7)	152 (60.3)
American Indian or Alaska Native	-	0
Other	1 (3.2)	2 (0.8)
Not reported[a]	4 (12.9)	11 (4.4)
EGFR mutation status[a], n (%)		
Exon 19 deletion	Not required for this part of the study	136 (54.0)
L858R		73 (29.0)
Other		10 (4.0)
None (T790M only)		13 (5.2)
Unknown		20 (7.9)
EGFR T790M mutation status[a1], n (%)		
Positive	Not required for this part of the study	163 (64.7)
Negative		69 (27.4)
Unknown		20 (7.9)
Overall disease classification, n (%)		
Metastatic[b]	28 (90.3)	246 (97.6)
Locally advanced[c]	3 (9.7)	6 (2.4)
WHO performance status, n (%)		
0	10 (32.3)	73 (29.0)
1	21 (67.7)	178 (70.6)
2	0	1 (0.4)
Smoking status, n (%)		
Never	15 (48.4)	159 (63.1)
Current	1 (3.2)	3 (1.2)
Former	15 (48.4)	90 (35.7)

Demographic characteristic	**Dose escalation part (N=31)**	**Dose expansion part (N=252)**
Prior EGFR TKI regimens, median (range)	1.0 (1-4)	2.0 (1-5)
Number of regimens, n (%)		
0	0	0
1	24 (77.4)	125 (49.6)
2	2 (6.5)	82 (32.5)
3	2 (6.5)	28 (11.1)
4	3 (9.7)	10 (4.0)
5	0	7 (2.8)

[a] Study centres in France and the UK did not capture information on race.
[a1] Central T790M and EGFR mutation status.
[b] Metastatic disease - patient has any metastatic site of disease.
[c] Locally advanced - patient has only locally advanced sites of disease.
Source: CSR

Table 6. Patient baseline characteristics for D5160C00001 (AURA extension)

Demographic characteristic		Second-line (N=61)	≥Third-line (N=140)	Total (N=201)
Age (years)	N	61	140	201
	Mean	62.6	60.9	61.4
	sd	10.24	10.73	10.58
	Median	61.0	63.0	62.0
	Min	45	37	37
	Max	89	84	89
Age group (years), n (%)	<50	5 (8.2)	25 (17.9)	30 (14.9)
	≥50 to <65	29 (47.5)	57 (40.7)	86 (42.8)
	≥65 to <75	18 (29.5)	46 (32.9)	64 (31.8)
	≥75	9 (14.8)	12 (8.6)	21 (10.4)
Sex, n (%)	Male	20 (32.8)	48 (34.3)	68 (33.8)
	Female	41 (67.2)	92 (65.7)	133 (66.2)
Race, n (%)[a]	White	24 (40.7)	52 (37.1)	76 (38.2)
	Black or African American	0	1 (0.7)	1 (0.5)
	Asian	32 (54.2)	82 (58.6)	114 (57.3)
	Other	1 (1.7)	3 (2.1)	4 (2.0)
	Not Reported [a]	2 (3.4)	2 (1.4)	4 (2.0)
Ethnic group, n (%)[b]	Hispanic or Latino	3 (4.9)	13 (9.3)	16 (8.0)
	African-American	0	1 (0.7)	1 (0.5)
	Asian (other than Chinese and Japanese)	17 (27.9)	28 (20.0)	45 (22.4)
	Chinese	11 (18.0)	19 (13.6)	30 (14.9)
	Japanese	3 (4.9)	32 (22.9)	35 (17.4)
	Other	27 (44.3)	47 (33.6)	74 (36.8)

[a] Race was not reported for all study canters. The category of "Other" is as collected on the eCRF; the category of "Not Reported" is presented because the UK independent ethics committee approval dictated that any race data collected on the eCRF was not to be reported in summary documents; any race data missing on eCRFs is not reported as a category in summaries of race data.

[b] Caucasian ethnicity is not presented as a category of ethnic group as the collection of ethnicity is prohibited by certain health authorities according to the applicant.

Abbreviations: max, maximum; min, minimum; sd, standard deviation. Source: clinical study report

Table 7. Disease characteristics at baseline for D5160C00001 (AURA extension)

	Number (%) of patients		
	Second-line (N=61)	**≥Third-line (N=140)**	**Total (N=201)**
EGFR sensitising mutations by cobas® central test[a] –			
T790M	59 (96.7)	138 (98.6)	197 (98.0)
Exon 19 deletion	44 (72.1)	98 (70.0)	142 (70.6)
L858R	16 (26.2)	35 (25.0)	51 (25.4)
G719X	1 (1.6)	3 (2.1)	4 (2.0)
S768I	0	3 (2.1)	3 (1.5)
Exon 20 insertion	1 (1.6)	1 (0.7)	2 (1.0)
Overall disease classification			
Metastatic[b]	59 (96.7)	138 (98.6)	197 (98.0)
Locally advanced only[c]	2 (3.3)	2 (1.4)	4 (2.0)
Histology type			
Adenocarcinoma (NOS)	54 (88.5)	117 (83.6)	171 (85.1)
Adenocarcinoma: acinar	3 (4.9)	8 (5.7)	11 (5.5)
Adenocarcinoma: papillary	2 (3.3)	8 (5.7)	10 (5.0)
Adenocarcinoma: bronchiolo-alveolar	1 (1.6)	2 (1.4)	3 (1.5)
Adenosquamous carcinoma	0	1 (0.7)	1 (0.5)
Other	1 (1.6)	4 (2.9)	5 (2.5)
WHO performance status			
0 (Normal activity)	25 (41.0)	43 (30.7)	68 (33.8)
1 (Restricted activity)	36 (59.0)	96 (68.6)	132 (65.7)
2 (In bed less ≤50% of the time)	0	1 (0.7)	1 (0.5)
Baseline target lesion size (mm)			
n	61	138	199
Mean	61.3	61.1	61.2
sd	36.92	37.02	36.90
Median	53.5	52.2	52.5
Minimum	16	12	12

	Number (%) of patients		
	Second-line (N=61)	**≥Third-line (N=140)**	**Total (N=201)**
Maximum	181	229	229
Baseline target lesion size category (mm), n (%)			
<40	20 (32.8)	43 (30.7)	63 (31.3)
40 to 79	26 (42.6)	60 (42.9)	86 (42.8)
80 to 119	9 (14.8)	25 (17.9)	34 (16.9)
≥120	6 (9.8)	10 (7.1)	16 (8.0)
Brain metastases[d]	14 (23.0)	60 (42.9)	74 (36.8)
Visceral metastases[e]	50 (82.0)	123 (87.9)	173 (86.1)

[a] *EGFR* mutation identified by the cobas® EGFR central test (by biopsy taken after confirmation of disease progression on the most recent treatment regimen). Patients may have had more than one EGFR mutation present.
[b] Metastatic disease (Patient had any metastatic site of disease).
[c] Locally advanced (Patient had only locally advanced sites of disease).
[d] Brain metastases (patients with metastatic site of brain and/or those that reported Radiotherapy in anatomical locations unequivocally in the brain and/or those that reported surgical excision of tumour from anatomical locations unequivocally in the brain)
[e] Visceral metastases (Patients in whom the metastatic or locally advanced site was "Brain" or "Hepatic", those where the metastatic site was "Lymph nodes" and/or those that had specified "other sites" such as stomach, spleen, peritoneum, ascites, renal or adrenal).
Abbreviations: EGFR, epidermal growth factor receptor; NOS, not otherwise specified; sd, standard deviation; WHO, World Health Organization.
Source: clinical study report

Table 8. Previous therapies for D5160C00001 (AUR2 extension)

Previous treatment modalities	Number (%) of patients		
	Second-line (N=61)	≥Third-line (N=140)	Total (N=201)
Radiotherapy	26 (42.6)	82 (58.6)	108 (53.7)
Number of previous anti-cancer treatment regimens			
1	61 (100)	0	61 (30.3)
2	0	49 (35.0)	49 (24.4)
3	0	33 (23.6)	33 (16.4)
4	0	22 (15.7)	22 (10.9)
5	0	14 (10.0)	14 (7.0)
>5	0	22 (15.7)	22 (10.9)
Any anti-cancer therapy for advanced disease	61 (100)	140 (100)	201 (100)
EGFR TKI	61 (100)	140 (100)	201 (100)
Platinum-containing chemotherapy regimen	0	122 (87.1)	122 (60.7)
Doublet chemotherapy plus bevacizumab	0	25 (17.9)	25 (12.4)
Other anti-cancer therapies[a]	0	55 (39.3)	55 (27.4)
EGFR TKI			
Gefitinib	32 (52.5)	85 (60.7)	117 (58.2)
Erlotinib	28 (45.9)	88 (62.9)	116 (57.7)
Afatinib	0	36 (25.7)	36 (17.9)
Afatinib + cetuximab	0	4 (2.9)	4 (2.0)
Dacomitinib	1 (1.6)	3 (2.1)	4 (2.0)
Other	0	5 (3.6)	5 (2.5)
EGFR TKI therapy			
Last regimen prior[b]	61 (100)	98 (70.0)	159 (79.1)
<30 days	44 (72.1)	61 (43.6)	105 (52.2)
≥30 days	17 (27.9)	37 (26.4)	54 (26.9)
Not last regimen prior	0	42 (30.0)	42 (20.9)
Duration of most recent prior EGFR TKI			
<6 months	0	43 (30.7)	43 (21.4)
≥6 months	61 (100)	97 (69.3)	158 (78.6)

[a] Does not contain either EGFR TKI or platinum-based doublet chemotherapy
[b] Last regimen prior to start of treatment with study drug. Source: clinical study report

Table 9. Patient demographics (AURA2)

Demographic characteristic		Second-line (N=68)	≥Third-line (N=142)	Total (N=210)
Age (years)	n	68	142	210
	Mean	64.0	62.4	62.9
	sd	11.76	10.48	10.91
	Median	64.5	63.5	64.0
	Min	36	35	35
	Max	88	84	88
Age group (years) n (%)	<50	5 (7.4)	15 (10.6)	20 (9.5)
	≥50 to <65	29 (42.6)	59 (41.5)	88 (41.9)
	≥65 to <75	20 (29.4)	49 (34.5)	69 (32.9)
	≥75	14 (20.6)	19 (13.4)	33 (15.7)
Sex n (%)	Male	24 (35.3)	40 (28.2)	64 (30.5)
	Female	44 (64.7)	102 (71.8)	146 (69.5)
Race n (%)[a]	White	26 (38.2)	46 (32.4)	72 (34.3)
	Black or African American	0	3 (2.1)	3 (1.4)
	Asian	39 (57.4)	93 (65.5)	132 (62.9)
	Native Hawaiian or other Pacific Islander	1 (1.5)	0	1 (0.5)
	Other	2 (2.9)	0	2 (1.0)
Ethnic group, n (%)[b, c]	Hispanic or Latino	2 (3.1)	3 (2.2)	5 (2.5)
	Asian (other than Chinese and Japanese)	17 (26.2)	18 (12.9)	35 (17.2)
	Chinese	12 (18.5)	39 (28.1)	51 (25.0)
	Japanese	10 (15.4)	36 (25.9)	46 (22.5)
	Other	24 (36.9)	43 (30.9)	67 (32.8)

[a] The category of "Other" is as collected on the eCRF; any race data missing on eCRFs was not reported as a category in summaries of RACE data

[b] Caucasian ethnicity is not presented as it was not offered as a category in the eCRF.

[c] Six patients from the United States did not report an "ethnic population" for ethnicity summaries reported in this table (n=204/210); all 6 patients reported themselves as "non-Hispanic or Latino" and all also reported race as "white" in the eCRF.

Abbreviation: eCRF, electronic case report form. Source: CSR.

Table 10. Disease characteristics (AURA2)

	Number (%) of patients		
	Second-line (N=68)	≥Third-line (N=142)	Total (N=210)
EGFR sensitising mutations by cobas® central test[a]			
T790M	68 (100)	140 (98.6)	208 (99.0)
Exon 19 deletion	45 (66.2)	92 (64.8)	137 (65.2)
L858R	20 (29.4)	47 (33.1)	67 (31.9)
G719X	2 (2.9)	2 (1.4)	4 (1.9)
S768I	1 (1.5)	2 (1.4)	3 (1.4)
Exon 20 insertion	0	1 (0.7)	1 (0.5)
T790M only	1 (1.5)	0	1 (1.5)
Overall disease classification			
Metastatic[b]	64 (94.1)	134 (94.4)	198 (94.3)
Locally advanced only[c]	4 (5.9)	8 (5.6)	12 (5.7)
WHO performance status			
0 (normal activity)	29 (42.6)	54 (38.0)	83 (39.5)
1 (restricted activity)	39 (57.4)	88 (62.0)	127 (60.5)
Baseline target lesion size, (mm)			
N	62	136	198
Mean	52.6	63.3	59.9
sd	37.35	41.56	40.50
Median	44.4	55.7	50.5
Minimum	10	12	10
Maximum	208	218	218
Baseline target lesion size category (mm), n (%)			
<40	26 (38.2)	40 (28.2)	66 (31.4)
40 to 79	23 (33.8)	67 (47.2)	90 (42.9)
80 to 119	10 (14.7)	17 (12.0)	27 (12.9)
≥120	3 (4.4)	12 (8.5)	15 (7.1)
Brain metastases[d]	23 (33.8)	65 (45.8)	88 (41.9)
Visceral metastases[e]	53 (77.9)	115 (81.0)	168 (80.0)

[a] EGFR mutation identified by the cobas® EGFR central test (by biopsy taken after confirmation of disease progression on the most recent treatment regimen).
[b] Metastatic disease (patient had any metastatic site of disease).
[c] Locally advanced (patient had only locally advanced sites of disease).

[d] Brain metastases (patients with metastatic site of brain and/or those that reported Radiotherapy in anatomical locations unequivocally in the brain and/or those that reported surgical excision of tumour from anatomical locations unequivocally in the brain).

[e] Visceral metastases (patients in whom the metastatic or locally advanced site was "Brain" or "Hepatic", those where the metastatic site was "Lymph nodes" and/or those that had specified 'other sites' such as stomach, spleen, peritoneum, ascites, renal or adrenal).

Abbreviations: EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; WHO, World Health Organization
Source: CSR.

Table 11. Previous treatments in AURA2

Previous treatment modalities	Number (%) of patients Second-line (N=68)	≥Third-line (N=142)	Total (N=210)
Radiotherapy	27 (39.7)	72 (50.7)	99 (47.1)
Number of previous anti-cancer treatment regimens			
1	68 (100)	1 (0.7)	69 (32.9)
2	0	45 (31.7)	45 (21.4)
3	0	38 (26.8)	38 (18.1)
4	0	22 (15.5)	22 (10.5)
5	0	7 (4.9)	7 (3.3)
>5	0	29 (20.4)	29 (13.8)
Any anti-cancer therapy for advanced disease	68 (100)	142 (100)	210 (100)
EGFR TKI	68 (100)	142 (100)	210 (100)
Platinum-containing chemotherapy regimen	0	135 (95.1)	135 (64.3)
Doublet chemotherapy plus bevacizumab	0	24 (16.9)	24 (11.4)
Other anti-cancer therapies	0	62 (43.7)	62 (29.5)
EGFR TKI			
Gefitinib	32 (47.1)	90 (63.4)	122 (58.1)
Erlotinib	32 (47.1)	86 (60.6)	118 (56.2)
Afatinib	4 (5.9)	34 (23.9)	38 (18.1)
Afatinib + cetuximab	0	3 (2.1)	3 (1.4)
Dacomitinib	0	2 (1.4)	2 (1.0)
Other	0	2 (1.4)	2 (1.0)
EGFR TKI therapy			
Last regimen prior[a]	68 (100)	90 (63.4)	158 (75.2)
<30 days	44 (64.7)	67 (47.2)	111 (52.9)
≥30 days	24 (35.3)	23 (16.2)	47 (22.4)
Not last regimen prior	0	52 (36.6)	52 (24.8)
Duration of most recent prior EGFR TKI			
<6 months	6 (8.8)	44 (31.0)	50 (23.8)
≥6 months	62 (91.2)	98 (69.0)	160 (76.2)

[a] Immediate TKI is a TKI taken as last regimen prior to study entry with no subsequent therapy.
Abbreviations: EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor
Sources: CSR

Efficacy Results

FDA's primary efficacy analyses were based on full analysis set (FAS), defined as all patients enrolled who received at least 1 dose of study treatment. FDA's analysis of ORR and DOR are shown in Table 12. Descriptive statistics were used in these analyses, which are based on blinded independent committee (BICR) assessment. The ORR was defined as the percentage of patients with complete response (CR) or partial response (PR) that was confirmed at least 4 weeks later (ie, a best response of CR or PR) per RECIST v1.1. The primary analysis of ORR was presented together with 95% exact (Clopper-Pearson) confidence intervals (CIs). The DOR was defined as the time from the date of first documented response (that was subsequently confirmed) until the date of documented progression or death in the absence of disease progression. The ORR in both trials are of high magnitude and greater than what would be expected with available therapy (about 10 to 30%). The median DOR in AURA extension and AURA2 were not reached as of the DCO. However, data from AURA phase 1 revealed durable responses in the 63 patients treated at recommended dose of osimertinib.

Table 12. ORR and DOR in AURA phase 1, AURA extension, and AURA2 per BICR assessment

	AURA Phase 1 (n = 63)	**AURA extension (n = 201)**	**AURA2 (n = 210)**	**Combined (AURA extension and AURA2) (n=411)**
ORR (95% CI)	50.8% (37.9%, 63.6%)	57.2% (50.1%, 64.2%)	61.0% (54.0%, 67.6%)	59.1% (54.2%, 63.9%)
CR	0	0	2 (1.0%)	2 (0.5%)
PR	32 (50.8%)	115 (57.2%)	126 (60.0%)	241 (58.6%)
Ongoing*, n	22	113	120	233
Median DOR, months	12.4 (8.3, NC)	Not Reached	Not Reached	Not Reached

*Patients with ongoing responses as of data cut-off date (see Table 2)
DOR, duration of response; ORR, overall (objective) response rate
FDA analysis

Per applicant's analyses according to investigator assessment using FAS, ORR was 68.2% (95% CI: 61.2, 74.5) in AURA extension and 64.3% (95% CI: 57.4% to 70.8%) in AURA2.

Sensitivity Analyses

FDA conducted two sensitivity analyses of ORR: one excluding patient considered having protocol violations; and one considering these patients as non-responders. The results were generally consistent with overall study results (**Table 13** and **Table 14**).

Table 13. Sensitivity analysis of ORR in AURA extension and AURA2 excluding patients flagged as having protocol violation

	AURA extension (n=182)	AURA2 (n=185)	Overall (n=367)
ORR	58.8% (51.3%, 66.0%)	63.2% (55.9%, 70.2%)	61.0% (55.8%, 66.1%)
CR	0	1 (0.54%)	1 (0.27%)
PR	107 (58.8%)	116 (62.7%)	223 (60.8%)

Table 14. Sensitivity analysis of ORR in AURA extension and AURA2 considering patients flagged as having protocol violation as non-responders

	AURA extension (n=201)	AURA2 (n=210)	Overall (n=411)
ORR	53.2% (46.1%, 60.3%)	55.7% (48.7%, 62.5%)	54.5% (49.5%, 59.4%)
CR	0	1 (0.48%)	1 (0.24%)
PR	107 (53.2%)	116 (55.2%)	223 (54.3%)

Exploratory Analyses

FDA's exploratory analyses of clinically relevant subgroups are shown in **Figure 1**. The analysis was conducted using pooled data from AURA extension and AURA2 trials. Of note, Asian patients (n=247) appeared to have higher ORR compared to non-Asian patients (n=164). The reason(s) for this difference in ORR are not clear. The ORR in other subgroups was generally comparable and consistent with overall population results.

FDA conducted the following exploratory responder analysis considering depth of response, defined as the best tumor decrease as measured by best percent change from baseline per BICR. Using pooled depth of response data from AURA extension and AURA2 trials (n=372), patients were divided into two cohorts above (Q2) and below (Q1) the calculated median best percent tumor decrease from baseline (44.6%) and Kaplan-Meier curves of PFS were plotted by cohort (

Figure 2). The results suggest that deeper responses (that is, a greater percent change from baseline) may be associated with longer PFS; however, it is important to note that the results of this analysis are exploratory and preliminary and need to be further explored in future randomized trials and meta-analyses.

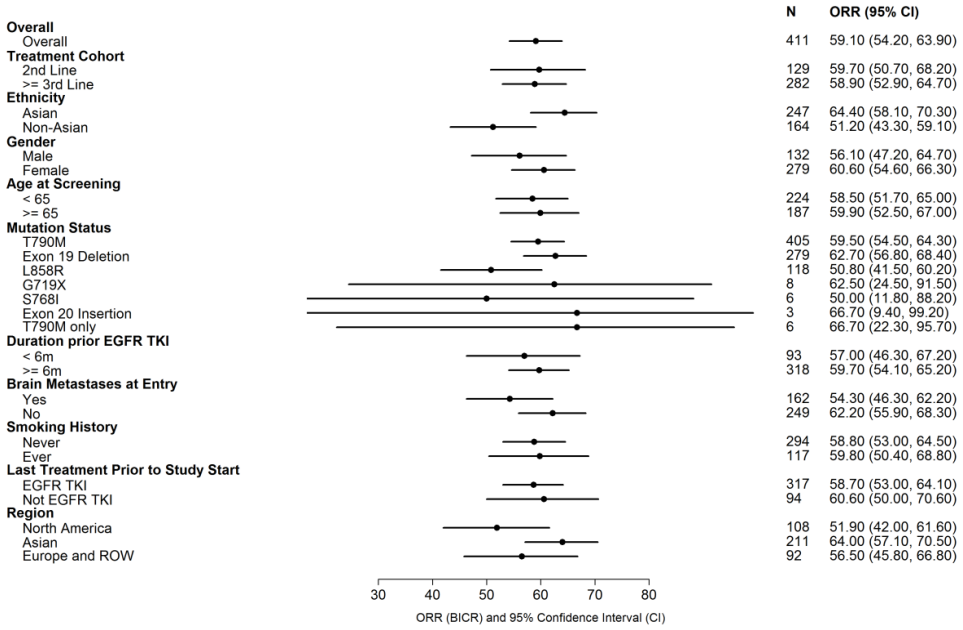
FDA further explored the spectrum of extra-thoracic metastases (bone, liver, brain) and CNS response/relapse pattern in AURA extension and AURA2 (**Table 15**). Per AURA extension and AURA2 protocols, brain metastases were only assessed as non-target lesions (NTL) or new lesions in the study for both Investigator and BICR efficacy assessments. As brain metastases were assessed as NTLs, there was no measurement of metastatic brain lesion diameter, but only overall response of all NTLs combined together across all anatomies including non-brain sites. Therefore; it was not possible to calculate an ORR or DOR for CNS disease. However, as shown in **Table 15**, a small number of patients in AURA extension and AURA2 has CNS primary relapse while on osimertinib, possibly suggestive of some CNS activity. This needs further exploration in future trials specifically designed to measure CNS responses.

FDA also explored treatment beyond RECIST progression (allowed per protocol in AURA extension and AURA2 per investigator assessment of clinical benefit). As shown in **Table 16** and

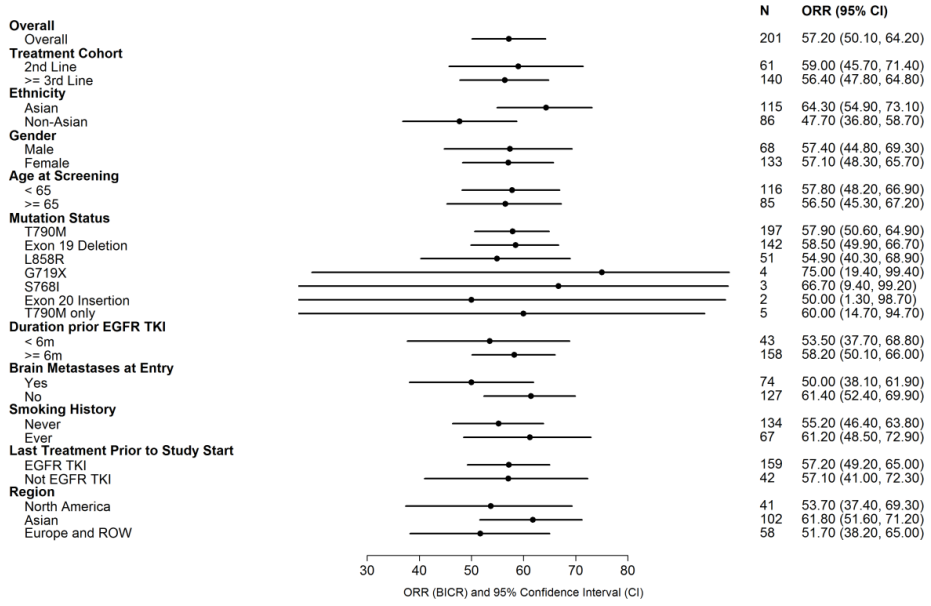
Table 17, the median duration of osimertinib treatment after progression is slightly lower in AURA extension compared with the AURA2 (1.2 month vs 1.8 months), although the maximum is longer by approximately 2 months. The applicant (via an information requested) explained that the reason for this slight difference may be that AURA extension participating sites included a number of oncology Phase I specialist sites that may have a greater opportunity to move onto a new clinical trial in a short timescale. (b) (4)

Figure 1. Subgroup analyses per BICR assessment

Pooled data from AURA extension and AURA2 (n=411)



AURA extension (n=201)



AURA2 (n=210)

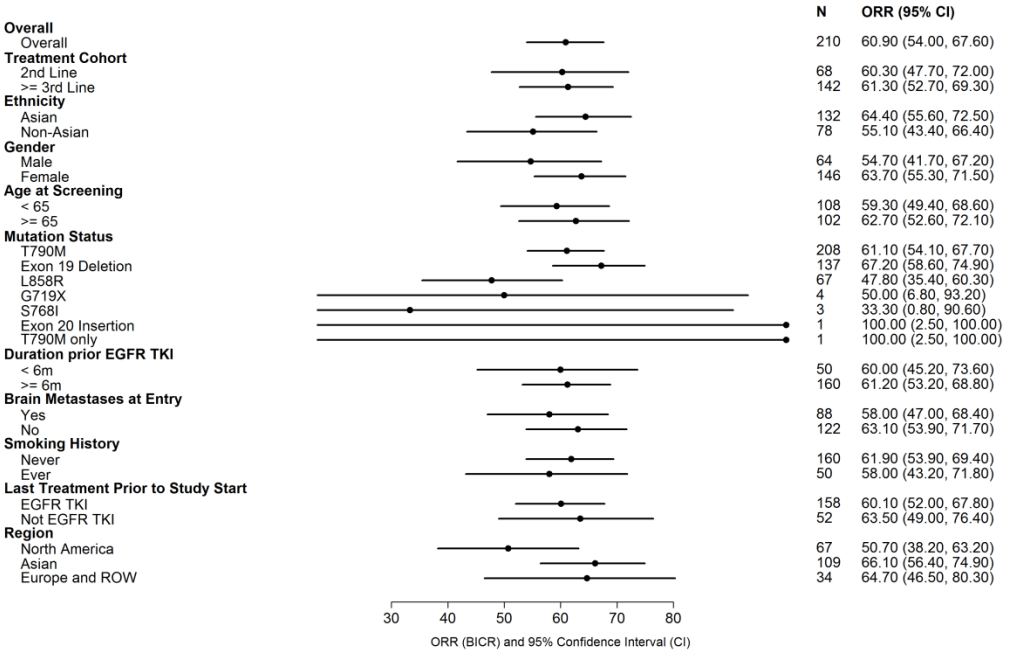

N
ORR (95% CI)
Overall
Overall 210 60.90 (54.00, 67.60)
Treatment Cohort
2nd Line 68 60.30 (47.70, 72.00)
>= 3rd Line 142 61.30 (52.70, 69.30)
Ethnicity
Asian 132 64.40 (55.60, 72.50)
Non-Asian 78 55.10 (43.40, 66.40)
Gender
Male 64 54.70 (41.70, 67.20)
Female 146 63.70 (55.30, 71.50)
Age at Screening
< 65 108 59.30 (49.40, 68.60)
>= 65 102 62.70 (52.60, 72.10)
Mutation Status
T790M 208 61.10 (54.10, 67.70)
Exon 19 Deletion 137 67.20 (58.60, 74.90)
L858R 67 47.80 (35.40, 60.30)
G719X 4 50.00 (6.80, 93.20)
S768I 3 33.30 (0.80, 90.60)
Exon 20 Insertion 1 100.00 (2.50, 100.00)
T790M only 1 100.00 (2.50, 100.00)
Duration prior EGFR TKI
< 6m 50 60.00 (45.20, 73.60)
>= 6m 160 61.20 (53.20, 68.80)
Brain Metastases at Entry
Yes 88 58.00 (47.00, 68.40)
No 122 63.10 (53.90, 71.70)
Smoking History
Never 160 61.90 (53.90, 69.40)
Ever 50 58.00 (43.20, 71.80)
Last Treatment Prior to Study Start
EGFR TKI 158 60.10 (52.00, 67.80)
Not EGFR TKI 52 63.50 (49.00, 76.40)
Region
North America 67 50.70 (38.20, 63.20)
Asian 109 66.10 (56.40, 74.90)
Europe and ROW 34 64.70 (46.50, 80.30)
30
40
50
60
70
80
ORR (BICR) and 95% Confidence Interval (CI)

Figure 2. Exploratory Kaplan-Meier analysis of PFS vs best response (% decrease in tumor response from baseline per BICR) in pooled analysis of AURA extension and AURA2 (n=372)

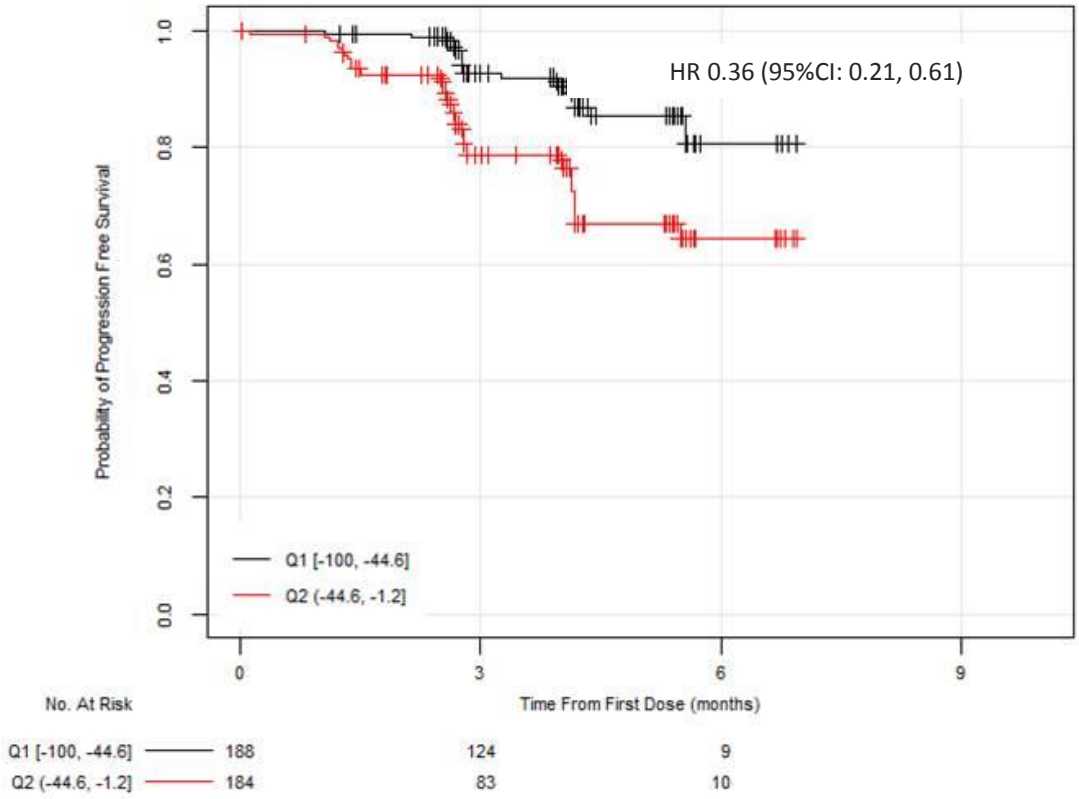


Table 15. Exploratory analyses of extra-thoracic sites of metastasis and CNS relapse/response in AURA extension and AURA2

	AURA extension (n=201) **n, (%) (95% CI)**	**AURA2 (n=210)** **n, (%) (95% CI)**
Patients with following areas of disease at baseline: • Bone • Liver	Bone, n=102 (50.7%) (43.6%, 57.9%) Liver, n=64 (31.8%) (25.5%, 38.8%)	Bone, n=90 (42.9%) (36.1%, 49.8%) Liver, n=55 (26.2%) (20.4%, 32.7%)
Treated brain metastasis at baseline	47 (23.4%) (17.7%, 29.9%) See note 1 below	52 (24.8%) (19.1%, 31.2%) See note 1 below
Untreated brain metastasis at baseline	27 (13.4%) (9.0%, 18.9%)	35 (16.7%) (11.9%, 22.4%)

CNS ORR and DOR in patients with measurable CNS disease (per investigator and BICR assessment)	Data not available	Data not available
Patients with CNS as the primary site of disease recurrence on osimertinib	3/37 RECIST progressions (8.1%) (1.7%, 21.9%)	6/37 RECIST progressions (16.2%) (6.2%, 32.0%)
Patients on corticosteroids for brain metastasis at baseline	1 (0.5%) (0.0%, 2.7%)	0
• Patients who discontinued corticosteroids due to symptom improvement while on osimertinib	1 patient discontinued corticosteroid (on study day 14). This patient was s/p brain radiation at enrollment.	0

1. The AURA extension and AURA2 CSRs have presented only the total number of patients with brain metastases irrespective if these were treated or untreated. In the NDA the total number of patients were derived programmatically and were identified in the RDB dataset ADSL with a flag BMETAFL = "Y". On performing more detailed review of the programming, for one patient in AURA extension it was noted as they were included in error as they had had on-treatment radiotherapy in the brain, not prior radiotherapy in the brain. Therefore the corrected total number of patients with brain metastases at baseline is n=74 in AURA extension and n=87 in AURA2. The number of patients with a history of brain metastases at study entry whose brain metastases were treated prior to the start of osimertinib (at any time prior to first dose of osimertinib) were identified based on medical review of the eCRFs capturing previous anti-cancer therapy (CAPRX) and any other medications (MED) where the reason for therapy given included terms potentially relating to treatment of brain metastases. This was supplemented by programmatically including patients with radiotherapy of the brain in RSCM and surgical history of the brain in RSMH to ensure all sources of treatments for brain metastasis were captured. Selected from datasets RSCM using CMINDC (reasons for therapy) = any of the terms: brain metastasis, control of brain metastasis effects, support care for brain lesions radiotherapy, missing visual field, preven brain edema for radiotherapy, whole brain radiation, intracranial hypertension due to brain radiotherapy, prophylaxis for previous history of brain metastases).
Source: FDA and applicant's analyses

Table 16 Subsequent osimertinib therapy received by patients after progression as declared by investigator assessment in AURA extension (Full analysis set).

AURA Extension	AZD9291, pre-treated, capsule 80 mg		
Subsequent AZD9291 therapy received by patients after progression as declared by investigator assessment (Full analysis set)	2nd line AZD9291 (N=61)	3rd line AZD9291 (N=140)	Total AZD9291 (N=201)
Number of patients who progressed or died	23	57	80
Number of patients who died	3	7	10
Number of patients who received AZD9291 after progression [a]	12	32	44

Duration of AZD9291 treatment after progression (months) [a]			
Median	0.9	1.4	1.2
Min	0.5	0.5	0.5
Max	2.9	8.4	8.4
Number of patients who discontinued AZD9291 study treatment after progression [a]	9	15	24
Adverse Event	1	2	3
Objective Disease Progression	5	11	16
Other*	2	2	4
Subject Decision**	1	0	1

[a] Only patients who continued to receive osimertinib study treatment >7 days after the date of radiological progression are included.

*Additional Information on the 4 patients with "Other" as the reason for discontinuing osimertinib study treatment:

- E4305701 – Clinical progression
- E4310703, E4313707 – Doctors decision to switch cancer therapy after progression
- E7401733 - Subject interrupted study drug over 21 days (on endotracheal tube)

**There is no further information available on the patient for whom the reason is "Subject Decision"

Table 17. Subsequent osimertinib therapy received by patients after progression as declared by investigator assessment in AURA2 (Full analysis set)

AURA2	AZD9291, pre-treated, capsule 80 mg		
Subsequent AZD9291 therapy received by patients after progression as declared by investigator assessment (Full analysis set)	2nd line AZD9291 (N=68)	3rd line AZD9291 (N=142)	Total AZD9291 (N=210)
Number of patients who progressed or died	24	54	78
Number of patients who died	2	7	9
Number of patients who received AZD9291 after progression [a]	16	23	39
Duration of AZD9291 treatment after progression (months) [a]			
Median	1.7	1.9	1.8
Min	0.5	0.4	0.4
Max	5.4	6.4	6.4
Number of patients who discontinued AZD9291 study treatment after progression [a]	6	9	15

Adverse Event	1	1	2
Objective Disease Progression	5	6	11
Other*	0	1	1
Subject Decision**	0	1	1

[a] Only patients who continued to receive AZD9291 study treatment >7 days after the date of radiological progression are included.

*Additional Information on the 5 patients with "Other" as the reason for discontinuing osimertinib study treatment:

- E4305701 – clinical progression
- E4310703, E4313707 – Doctors decision to switch cancer therapy after progression
- E7401733 - Subject interrupted study drug over 21 days (on endotracheal tube)
- E7809201 : Medication held due to headaches becoming more severe, but patient died before restart

**There is no further information available on the two patients for whom the reason is "Subject Decision"

Table 18. Concordance analysis: BICR and investigator assessments in AURA extension and AURA2

AURA extension n=201		Objective response per BICR	
		Response	No Response
Objective response per investigator	Response	95 (47.3%)	42 (20.9%)
	No Response	20 (10.0%)	44 (21.9%)

AURA2 n=210		Objective response per BICR	
		Response	No Response
Objective response per investigator	Response	110 (52.4%)	25 (11.9%)
	No Response	18 (8.6%)	57 (27.1%)

AURA extension + AURA2, n=411)		Objective response per BICR	
		Response	No Response
Objective response per investigator	Response	205 (49.9%)	67 (16.3%)
	No Response	38 (9.2%)	101 (24.6%)

Data Quality and Integrity – Reviewers' Assessment

FDA's analyses using raw datasets did not reveal any significant issues with data quality or integrity. A small random sample of case report forms were audited and did not reveal any major discrepancies with the datasets upon visual inspection by the reviewer(s). No anomalies in study results to indicate deficits in data quality/integrity were noted.

6 Integrated Review of Effectiveness

6.1. Assessment of Efficacy Across Trials

Efficacy evaluated in two single arm trials as described previously, with consistent results in both trials which had similar patient populations.

6.2. Additional Efficacy Considerations

6.2.1. Considerations on Benefit in the Postmarket Setting

The following items can be explored in the post market setting (excludes PMR to verify clinical benefit as described previously):

- Antitumor activity of osimertinib and clinical benefit in:
  - Asian vs non-Asian patients
  - As a function of the sequence of EGFR TKI therapy
  - As a function of baseline EGFR mutations (exon 19 deletions, L858R)

6.2.2. Other Relevant Benefits

N/A

6.3. Integrated Assessment of Effectiveness

Please refer to **Benefit-Risk Summary and Assessment** section of this review.

7 Review of Safety

7.1. Safety Review Approach

In performing the safety analysis for osimertinib, the reviewer primarily included a pooled analysis of data from the two phase 2 trials, AURA extension and AURA2. This population includes patients with NSCLC who tested positive for EGFR mutation and who progressed on prior therapy with both an EGFR TKI and at least one other therapy, and who were biopsy-proven to be T790m positive. The dose of osimertinib was 80 mg PO in both phase 2 study cohorts. In addition, data from additional patients enrolled in the phase 1 portions of AURA1 were used for key analysis including on-study deaths, CVAs, and ILD-related events.

Based on toxicities identified in studies of other EGFR TKIs, there was an expectation that similar toxicities were possible with osimertinib. Known class toxicities include skin rash and nail changes, QT prolongation, diarrhea, ocular events, and interstitial lung disease (ILD).

The datasets used in all analyses performed by the reviewer were those provided by the Sponsor in the form of Adam JMP tables in section 5.3.5 of the NDA submission. Analyses were performed using JMP analysis features as well as using MAED analysis of the data. Data cut-off date (DCO) for the safety database was January 9, 2015 for AURA phase 2 studies, December 2, 2014 for the phase 1 studies, and January 16, 2015 for ILD events. An extended DCO date of April 7, 2015 was used in the initial NDA submission for more inclusive reporting of ILD events.

Where applicable, analysis was redone using updated 90-day safety data submitted by the Sponsor based on a DCO date of May 1, 2015 for all safety events in phase 1 and 2 trials, and an additional DCO date of June 1, 2015 for ILD events.

Using the initial DCO date, the phase 2 studies had an overall rate of 17% (70/411) of patients who required dose interruptions, reductions, or discontinuations of osimertinib due to adverse events. Approximately 4% of patients discontinued osimertinib for adverse reactions. The most frequent adverse reactions that led to discontinuation of osimertinib were pneumonitis/ILD in 2% of patients (n=8) and CVA in 1% of patients (n=4). The most frequent treatment-emergent adverse reactions on osimertinib were rash (38.5%) and diarrhea (37.7%). These numbers increased slightly at the time of the 90-day safety update, to 42% each. The most frequent fatal adverse reactions were pneumonitis/ILD and pneumonia, which led to the deaths of 4 and 2 patients on study, respectively.

7.2. Review of the Safety Database

Safety and tolerability assessment in AURA extension and AURA2 was based on frequency of deaths, adverse events (AEs), serious adverse events (SAEs), AEs leading to discontinuation, AEs leading to dose delay, select AEs, clinical laboratory assessments, and vital sign measurements. Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 17.1. The corresponding verbatim terms included in the datasets were reviewed to check for accuracy of MedDRA coding. Comparison of the applicant's MedDRA PTs to the verbatim terms was undertaken by the reviewer in a sample of 10% of recorded AEs, and this review did not reveal significant discrepancies. Adverse events and laboratory values were graded for severity using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0.

Reviewer's comment: The analysis for safety included all patients in the phase 2 cohorts who received at least one dose of osimertinib. Adverse events included in the safety analysis included only those that were treatment-emergent.

7.2.1. Overall Exposure

Below is a summary of the key clinical studies used in the safety evaluation (Table 19). The two phase 2 trials with 411 total patients were used for the primary safety evaluation; additional data about on-study deaths and adverse events of particular interest were gathered from the AURA phase 1 study cohorts described below.

Table 19: Safety Population

Safety Database for osimertinib N= 766				
Study number	**Description**	**Patient population**	**Patients receiving at least one dose of osimertinib (n= 766)**	**Data cut-off date**
D5160C00001 (AURA extension)	Phase 2 single-arm, open label non-randomized study extension to AURA	Advanced EGFR T790M mutation positive NSCLC patients who progressed following either one prior therapy with an EGFR TKI (second-line chemotherapy-naïve, n=61) or following treatment with both EGFR TKI and at least one other prior line of therapy, such as cytotoxic doublet chemotherapy or immunotherapy (≥third-line, n=140).	**N =201** ≥second-line patients treated with osimertinib 80 mg	**Initial-** January 9, 2015 **90-day safety update-** May 1, 2015
D5160C00002 (AURA2)	Phase 2, single-arm, open label non-randomized study.	Advanced EGFR T790M mutation positive NSCLC patients who progressed following either one prior therapy with an EGFR TKI (second-line chemotherapy-naïve, n=68)	**N=210** ≥second-line patients treated with osimertinib 80 mg	**Initial-** January 9, 2015 **90-day safety update-** May 1, 2015

		or following treatment with at least one EGFR TKI and one prior platinum based doublet chemotherapy (≥third-line, n=142).		
D5160C00001 (AURA Phase 1)	Phase I multi-center, open-label, dose-escalation, & dose-expansion study to determine safety & tolerability, MTD, biologically effective dose, PK, & preliminary anti-tumor activity of osimertinib	Advanced EGFR mutation positive NSCLC patients, who progressed following prior therapy with at least one EGFR TKI agent, but also may have received other prior lines of therapy, such as cytotoxic doublet chemotherapy or immunotherapy or additional EGFR TKI as well as 2 first-line cohorts of advanced EGFR mutation positive NSCLC patients who had not received prior EGFR TKI for advanced stage disease.	**N=355** patients total: . Dose escalation: **n=31** 20, 40, 80, 160, and 240 mg osimertinib capsules once daily . Dose expansion: **n=252** 20, 40, 80, 160, and 240 mg osimertinib capsules once daily . First-line: **n=60** 80 mg and 160 mg osimertinib capsules once daily . Pre-treated tablet: **n=12** osimertinib 80 mg tablet once daily	**Initial-** December 2, 2014 **90-day safety update-** May 1, 2015

Table 20 describes the duration of exposure of all 411 patients treated on the phase 2 studies, including AURA extension and AURA2. Duration of exposure and cumulative dose are presented in Table 21, and dose modifications of osimertinib occurring during the course of treatment that were due to adverse events are presented in Table 22. All data on exposure, cumulative osimertinib dose, and treatment modifications due to AEs were calculated from JMP databases submitted by the sponsor, and numbers were checked for concordance with sponsor's calculated numbers provided in their summary of clinical safety.

Table 20: Duration of exposure to osimertinib, DCO date January 9, 2015

Number of patients exposed to osimertinib, AURA extension and AURA2:			
>=2 months	>=4 months	>=6 months	>= 8 months or longer
N= 401	N= 237	N= 66	N= 0

Table 21: Duration of exposure to osimertinib, DCO date January 9, 2015

	AURA extension N = 210	**AURA2 N = 211**	**Combined N=411**
Total Cumulative Dose (mg) Median	9840	6920	9600
Duration of Treatment (months) Median	4.68	3.89	4.4
Relative Dose Intensity (%) Median	100	100	100

Table 22: Dose modifications due to AEs on osimertinib, DCO date January 9, 2015

	Osimertinib total population N=411 N (%)
Patients with Any Dose Reduction/Interruption due to AEs	57 (13.9%)
1 delay/reduction	40 (9.7%)
>1 delay/reduction	17 (4.1%)
Patients with Dose Reductions due to AEs	55(13.4%)
Patients with Dose Interruptions due to AEs	6 (1.5%)
Patients with AEs Requiring Permanent Dose Discontinuation	16 (3.9%)
Total Number of Patients with Any AE Requiring Dose Reduction/Interruption/Discontinuation	**70 (17%)**

Reviewer's comment: In this phase 2 study population, using the initial DCO date, there was a relatively short overall duration of exposure, with only 66 patients overall (16%) having had exposure to osimertinib for longer than 6 months and no patient exposed to osimertinib for longer than 8 months. However, the majority of the patients in both arms remained on osimertinib at the time of initial DCO date of January 9, 2015 (168 patients, 85.4% in AURA extension and 183 patients, 87.1% in AURA2) so exposure was expected to increase.

Reviewing the 90-day safety update that had a DCO date of May 1, 201 revealed that the median exposure as per the Sponsor had indeed increased to a median of 7.7 months. AE data was reviewed for the update and is included in each relevant section of this review.

Although even at the time of the 90-day safety update, no patient in the phase 2cohorts had been exposed to osimertinib for longer than 12 months, safety data is available from the AURA phase 1 study in which there was a longer overall duration of exposure since its enrollment preceded that of the phase 2 cohorts. As of the phase 1 data cut-off of December 2, 2014, patients in AURA phase 1 have received up to 20 months (609 days) of treatment with osimertinib to date, median 8.1 months (247 days), with 72 patients receiving at least 12 months of therapy.

7.2.2. **Relevant characteristics of the safety population:**

Please also refer to Table 6 and Table 9 for further information on baseline characteristics of the safety population.

Table 23: Baseline Characteristics of Safety Population, Combined AURA Extension and AURA2

Characteristics	N = 411 (%)
Age	
Mean	**62.2**
Min	**35**
Q1	**55**
Median	**63**
Q3	**70**

Max	**89**
Age group	
<50	**50 (12.1)**
>=50-<65	**174 (42.3)**
>=65- <75	**133 (32.3)**
Age 75 and over	**54 (13.1)**
Sex	
Female	**279 (67.9)**
Male	**132 (32.1)**
Race	
Asian	**247 (60.1)**
Black or African American	**4 (1)**
White	**151 (36.7)**
Other	**9 (2.2)**
Ethnicity	
Not Hispanic or Latino	**316 (76.9)**
Hispanic or Latino	**21 (5.1)**
Not reported	**74 (18)**

7.2.3. **Adequacy of the safety database:**

The safety database was reviewed and was considered adequate in terms of size, exposure to osimertinib, duration of treatment, and disease characteristics with reference to the U.S. target population of patients with metastatic EGFR-mutation positive NSCLC who have progressed on prior EGFR-TKI therapy and have developed a T790M mutation. However, the reviewer notes the paucity of African-American patients included in the trial, and notes that this may limit the generalizability of the trial results to the U.S. treatment population in that regard.

7.3. Adequacy of Applicant's Clinical Safety Assessments

7.3.1. **Issues Regarding Data Integrity and Submission Quality**

The applicant's clinical safety assessments were reviewed and were considered adequate. Submission quality overall was adequate. An analysis was undertaken by the reviewer of all sites according to rates of occurrence of adverse events. The results of this analysis showed that overall, there were no sites or countries identified as having lower-than expected rates of adverse events.

7.3.2. **Categorization of Adverse Events**

The definition of AEs and SAEs as provided by the applicant are described below and ***were considered adequate by the reviewer***;

Adverse events:

An adverse event was defined as the development of an undesirable medical condition (symptoms, signs, or abnormal investigation results) or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product, occurring at any time point, including run-in or

washout periods, even if no study treatment was administered. Any deterioration of the disease under study and any event deemed likely due to disease progression were not considered AEs.

Deterioration in results of protocol-mandated laboratory tests, vital signs, ECGs and other safety assessments were reported as AEs if they fulfilled any of the criteria for a SAE, a DLT, or were the reason for discontinuation of treatment with osimertinib. Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment was reported as an AE.

All AEs spontaneously reported by the patient or care provider or reported in response to the open question from the study personnel: 'Have you had any health problems since the previous visit/you were last asked?', or revealed by observation were collected and recorded in the CRF. Additionally, data on ILD, which had been previously identified as an AE of interest, were collected via targeted pulmonary questionnaires sent to Investigators to report each suspected ILD event.

Serious adverse events:

The sponsor considered serious adverse events to be an AE occurring during any study phase (i.e., run-in, treatment, washout, follow-up) that was life-threatening or that resulted in death, required hospitalization or prolonged existing hospitalization, resulted in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions, or any other important medical event that jeopardized the subject or require medical intervention to prevent one of the outcomes listed above.

For each AE, a description of the event including date of onset and resolution, whether it constituted an SAE or not, any action taken (e.g. changes to study treatment, other treatment given, and follow-up tests), and outcome, were provided. In addition, the investigator's assessment of causality was provided.

Management of toxicity was as per protocol, and ***was considered appropriate by the reviewer***:

If a patient experienced a CTCAE grade 3 or higher and/or unacceptable toxicity (any grade) not attributable to the disease or disease-related processes under investigation, where the investigator considered the AE of concern to be specifically associated with osimertinib, dosing was to be interrupted and supportive therapy administered as required in accordance with local practice/guidelines. If the toxicity resolved or reverted to ≤CTCAE grade 2 within 3 weeks of onset, treatment with osimertinib could be restarted at the same dose (80 mg) or at a lower dose (40 mg) with discussion and agreement with the AstraZeneca Study Team Physician as needed. If the toxicity did not resolve to ≤CTCAE grade 2 after 3 weeks, then the patient was to be withdrawn from the study.

If new or worsening pulmonary symptoms or radiological abnormality suggestive of interstitial lung disease was observed, an interruption in study treatment dosing was recommended, and the AstraZeneca study team was to be informed. A questionnaire regarding the results of a full diagnostic workup was to be sent to Investigators. In cases where a confirmatory high-resolution

CT scan existed and other causes of respiratory symptoms had been excluded, a diagnosis of interstitial lung disease was to be considered and study treatment permanently discontinued. Additionally, patients with corneal ulceration were withdrawn from treatment. There were specific recommendations provided to investigators for the management of QTc prolongations, skin reactions, and diarrhea.

AEs were coded using version 17.1 of the Medical Dictionary for Regulatory Activities (MedDRA). The severity of any AE was graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. Certain MedDRA preferred terms were grouped to identify adverse events of special interest (AESI).

The applicant also incorporated data from patient-reported outcomes (PRO) assessments. In AURA extension, patient interviews were conducted on a small number of patients at two time points; at 4-6 weeks; and at 4-6 months. This used two PRO instruments developed by the European Organization for Research and Treatment of Cancer (EORTC); the QLQ-LC13 to directly describe patients' symptoms and the QLQ-C30 to describe their health-related quality of life. In addition, for patients on AURA2, 28 symptoms from the PRO-CTCAE item-bank (81 total items) thought to be applicable to NSCLC patients were selected to capture adverse symptom on a weekly basis for the first 18 weeks of study followed by every 3-weeks' collection.

7.3.3. **Routine Clinical Tests**

For a schedule of study procedures and scheduled assessments for each trial, please refer to the tables in appendix 12.3.

Scheduling of routine laboratory testing for AURA extension and AURA2 involved obtaining blood and urine samples at screening, Days 1, 8 and 15 of cycle 1, Day 1 of cycles 2 to 7, and every 42 days thereafter, and at the study discontinuation visit. The clinical chemistry, hematology and urinalysis were assessed at a local laboratory at or near to the Investigator site. Laboratory values that met the criteria for CTCAE Grade 3 or that had changed significantly from baseline and that were considered to be of clinical concern were repeated/ confirmed within 7 days and followed up as appropriate.

Vital signs were measured at the initial screening visit, weekly during Cycle 1 on Days 1, 8 and 15, every 3 weeks on day 1 of Cycles 2 to 6, and subsequently every 6 weeks until treatment discontinuation, with a final measurement at the discontinuation visit; weight was measured at screening and then Day 1 of each cycle as well as at the discontinuation visit. Digital 12-lead ECGs were performed at screening visit, at Day 1 for Cycles 1 - 6, and then every 6 weeks until treatment discontinuation, as well as at the discontinuation visit. The investigator evaluated the ECG from a clinical perspective. Digital ECG recordings were collected, read by independent external cardiologists and stored by a central ECG vendor. To assess LVEF, an echocardiogram or MUGA scan was performed at screening and every 12 weeks afterwards. A physical examination was performed pre-treatment, and every 3 weeks during treatment for 18 weeks, and then every 6 weeks until treatment discontinuation. Furthermore, ophthalmologic examination was conducted pre-treatment and if clinically indicated post-treatment.

Reviewer's comments: The applicant's assessment schedule for routine laboratory and clinical testing was considered adequate.

7.4. Safety Results

7.4.1. Deaths

Deaths on Study:

As of the OS analysis with a cut-off date of January 9, 2015, there were 24 deaths (5.8% of the enrolled population). Additional data submitted on ILD/pneumonitis events contributed information about 2 additional deaths that occurred by an amended DCO date of April 7, 2015 that specifically identified new ILD/pneumonitis events across the clinical development program. Both additional deaths were in patients who had developed ILD in the interval between the first and second DCO dates. Table 24: Total Deaths, AURA Extension and depicts the overall number and distribution of deaths in each of the phase 2 cohorts.

Table 24: Total Deaths, AURA Extension and AURA2, DCO date January 9, 2015 for all patients and April 7, 2015 for ILD events.

	AURA extension N=201 N (%)	Aura 2 N=210 N (%)	Total N = 411 N (%)
Total	16 (7.5)	10 (4.3)	**26 (6.1)**
Listed Causes of Death			
Disease progression	10 (5)	6 (2.9)	**16 (3.9)**
AEs as primary cause	3 (1.5)	3 (1.5)	**6 (1.5)**
Both AE and disease progression	2 (1)	2 (0.95)	**4 (1.0)**
AEs attributable by investigator to osimertinib as cause of death	2(1)	2 (0.95)	**4 (1.0)**
Deaths within 30 days of last treatment dose	7 (3.4)	6 (2.9)	**13 (3.2)**

Below is the safety reviewer's assessment of each on-treatment death in AURA extension (Table 25) and AURA2 (Table 26), followed by deaths occurring to patients in the AURA 1 study cohorts (Table 27). Patients in the phase 2 studies who died on-study were identified by creating a subset of patients with a "Y" in the DTHFL column in the integrated ISS-IE JMP table. Phase

1 study patients who died were identified by subsetting DTHFL = Y patients in the phase 1 study datasets. These include deaths occurring by the overall DCO date on January 9, 2015. The reviewer then read each relevant CRF and patient narrative to better assess the cause of death and the relatedness of each death to osimertinib. An additional two deaths were identified based on information provided by the sponsor on patients who developed ILD/pneumonitis events while on osimertinib. In cases of ambiguity or missing information, IRs were submitted to the sponsor for clarification of clinical details relevant to patient deaths.

Table 25: Analysis of on-treatment deaths in AURA extension, DCO date January 9, 2016 and April 7, 2015 for ILD events.

#	Patient	Progression Confirmed	Narrative and Comments	Death likely due to drug-related AE?
1	**D5160C0001C/E 0303703** **Age 83** **Prior treatment with erlotinib**	N	83 year old F, hx of longstanding HTN for almost 30 years. Patient died of CVA. Patient had known brain mets. The patient had widely metastatic disease to bone, brain, and pleural effusion. After study enrollment (b) (6)), but prior to starting osimertinib, she developed an MI on August 29, 2014. After this resolved, osimertinib was started on (b) (6) On day 33, CVA leading to death occurred (b) (6) ***Reviewer's comments: patient with known comorbidities and cardiac risk factors. Likely unrelated to osimertinib.***	N
2	**D5160C0001C/E 4311704** **Age 66** **Prior treatment with Gefitinib and Cisplatin/pemetrexed/bevacizumab, as well as erlotinib/bevaciz umab**	N	66 year old F, with metastases to brain and lung as well as bilateral pleural effusion. Osimertinib was started on (b) (6) and on (b) (6)) she was hospitalized due to fatigue, but on day 47 (b) (6)) her condition deteriorated and her saturation decreased to 70% at rest and 78% on room air. There were bilateral infiltrates seen on imaging and this was coded as a CTCAE 5 and drug was stopped on that day. Treatment with high doses of steroids and antimicrobials did not improve the patient's symptoms, and patient died on (b) (6) Listed in CRF as death due to interstitial pneumonitis but autopsy showed primary cause of death lung ca, secondary as hepatic failure. Advisory committee was mixed as to whether this was related to ILD, thought likely not. ***Reviewer's comments: Ultimately, the investigator felt that this was related to ILD and osimertinib.***	Y
3	**D5160C0001C/E 7401701** **Age 60**	Y	60 M with metastases to brain, liver, bone, pleural effusion. Started drug (b) (6), stopped on Aug 20, 2014 due to disease progression. On (b) (6) 45 days after started therapy, admitted with fever to 38 degrees C, CXR showed consolidation/PNA, pt	N

#	Patient	Progression Confirmed	Narrative and Comments	Death likely due to drug-related AE?
	Prior treatment with Gefitinib, gefitinib plus cis/pem, and then erlotinib		intubated, salvage therapy with cis/etoposide given (Sptember 1-3), then broad-spectrum abx started (September 12), patient died (b) (6) primary cause thought to be disease progression, secondary cause PNA.. ***Reviewer's comment: Death appears unrelated to osimertinib.***	
4	**D5160C0001C/E 7806704** **Age 74** **Prior treatment with erlotinib, afatinib, erlotinib, carbo/pem then pem alone.**	N	74 F PmHx of of CHF/diastolic dysfunction and atrial fibrillation. Also chronic UTI. Metastatic disease to lung, liver, lymph nodes. Started osimertinib June 9, 2014. Permanently discontinued on day 106- September 22, 2014 due to declining PS. Began to show worsening LFTs and dehydration on prior visits. Had a CTC grade 2 AE of CHF exacerbation on Aug 26, which resolved (no change in EF on echo). Another CTC grade 2 AE of limb edema started September 15, 2014, osimertinib was stopped on Sept 22, and admitted on (b) (6) due to edema and hypoalbuminemia. Died on (b) (6) ***Reviewer's comment: Death appears unrelated to osimertinib.***	N
5	**D5160C0001C/E 2301702** **Age 66** **Prior therapy with Gefitinib**	Y	66 white F with metastases to bone and malignant pleural effusion. Started therapy on 22-Jul-2014, and drug was discontinued on 02-Sep-2014 (Day 43) due to disease progression. She went on to be treated with carboplatin and pemetrexed beginning on 09-Sep-2014. The patient died on (b) (6). ***Reviewer's comment: Death appears unrelated to osimertinib.***	N
6	**D5160C0001C/E 2301704** **Age 71** **Prior therapy with erlotinib, afatinib plus investigational drug BIBF 1120, then carbo/pemetrexed then pemetrexed.**	Y	71 white M, metastatic disease to brain, lung, liver, and bone. Treatment started on 29-Jul-2014 and was discontinued on 05-Sep-2014 (Day 39) due to disease progression. The patient was then given carboplatin beginning on October 7, 2014. The patient died on (b) (6) due to disease progression. ***Reviewer's comment: Death appears unrelated to osimertinib.***	N
7	**D5160C0001C/E 4311709** **Age 69**	Y	69 Asian F, metastases to brain, lung, LNs, and malignant pleural effusion. Treatment began on (b) (6) but was discontinued on day 4- (b) (6) due to 'disease progression'. The patient had	N

#	Patient	Progression Confirmed	Narrative and Comments	Death likely due to drug-related AE?
	Prior therapy with carboplatin/paclitaxel/bevacizumab followed by bevacizumab, followed by gefitinib		acute cough and hypoxia to 84% with activity. She developed thrombocytopenia to 5.2x104/µL (normal range, 15-35; screening, 26.1), an elevated CRP level of 7.19 mg/dL, and a D-dimer of 100 µg/mL, which subsequently increased to a level above the upper limit of normal. Thrombocytopenia worsened as well to 3.8 x104/µL, and FDP was abnormally elevated as well. On 06-Aug-2014, platelets normalized (12.3 x104/µL) and D-dimer decreased to 170.5 µg/mL. The investigator called the event a CTCAE of DIC grade 2, and the patient was additionally thought to have an 'acute exacerbation of lung cancer', as CT from August 3 showed worsening disease and the patient did not show signs of sepsis such as fever. Patient began treatment with gefitinib on (b) (6) and died on (b) (6) ***Reviewer's comment: DIC event was thought by the investigators to be related to osimertinib, and this reviewer concurs. However, as death occurred more than 60 days after discontinuation of osimertinib, it was unlikely related to investigative agent and more likely a result of lung cancer.***	
8	**D5160C0001C/E 4314702** **Age 64** **Prior therapy with onartuzumab/erlotinib followed by erlotinib**	N	64 Asian F with metastases to brain, lung, bone, and lymph nodes, and metastatic pleural and pericardial effusions. Therapy started (b) (6) but was discontinued on (b) (6) (Day 10) due to clinical progression. Patient died on (b) (6) ***Reviewer's comment. It appears that the patient clinically worsened and had advanced disease at the time of study enrollment. However, it was unclear what the nature of her clinical deterioration was since there was no CT done at the time. Ultimately, an IR was placed to the sponsor and on further review, the patient had symptomatic pleural effusions requiring ongoing medical management with chest draining (b) (6) Oxygen administration (Day 24, day 1 of osimertinib), and Furosemide administration starting on Day 3. Ultimately the diagnosis of clinical worsening of lung cancer causing death seems reasonable, and this seems unrelated to osimertinib.***	N
9	**D5160C0001C/E 6003701** **Age 66** **Prior therapy with cisplatin/gemcita**	Y	66 Asian F with metastases to lung and bone. Treatment started on June 19, 2014 and stopped on August 28, 2014 (day 71) due to disease progression on CT; also thought to have obstructive PNA. osimertinib discontinued; started EBRT to lung. Patient seen in ER on (b) (6) with fever and worsening PNA, she responded to antibiotics and was discharged on (b) (6) She	N

#	Patient	Progression Confirmed	Narrative and Comments	Death likely due to drug-related AE?
	bine, erlotinib, afatinib/nimotuzumab		died on (b) (6), and this was thought to be due to lung cancer. ***Reviewer's comment. Agree with the fact that this death was likely related to progressive disease/ lung cancer.***	
10	**D5160C0001C/E 7002704** **Age 37** **Prior therapy with afatinib and erlotinib**	Y	37 white M with metastases to brain, bone, and LNs. Started therapy on September 9, 2014 and was discontinued on November 11, 2014 (day 64) due to objective disease progression. The patient died on (b) (6) due to progressive disease. ***Reviewer's comment: Agree that death is related to progressive disease/lung cancer.***	N
11	**D5160C0001C/E 7401714** **Age 60** **Prior therapy with gefitinib, pemetrexed/cisplatin and gefitinib or placebo, follwed by docetaxel and erlotinib.**	Y	60 Asian M with metastases to brain, bone, liver. Treatment began on 17-Jul-2014. Dosing was interrupted from 19-Sep-2014 (Day 65) to 29-Sep-2014 due to the AEs of AST increase, ALT increase, and total bilirubin increase. The bilirubin increase was a CTCAE grade 4 event, up to 10.78mg/dL . After ERCP with biliary drainage, bilirubin decreased to 2.98 mg/dL, and dosing resumed. osimertinib was permanently discontinued on 13-Nov-2014 for disease progression per investigator's assessment; but was restarted from November 27, 2014 to (b) (6) along with an investigational drug- MEDI4736 on (b) (6). The patient was admitted on the following day for CTCAE grade 3 renal failure (BUN 48.7 mg/dl and creatinine of 3.4 mg/dl) and a CTCAE grade 3 event of jaundice (total bilirubin of 3.61 mg/dL). The patient died on (b) (6) and the cause of death was listed as peritonitis with a secondary cause of lung cancer, ***Reviewer's comment: Agree that death is related to progressive disease/lung cancer.***	N
12	**D5160C0001C/E 7800706** **Age 40** **Prior treatment with erlotinib, then carbo/pemetrexed**	Y	40 white F with metastases to Brain, adrenal, peritoneum, lung, liver, boine, LNs. Treatment started (b) (6) but was discontinued on (b) (6) (Day 88) due to disease progression. ***Reviewer's comment: Agree that death is related to progressive disease/lung cancer.***	N
13	**D5160C0001C/E 7800718** **Age 41**	N	41 white F with metastases to the brain, lung, liver, bone, lymph nodes, and kidney. Prior history of asthma. Started therapy on (b) (6) but died on (b) (6) (day 8) due to patient's death.	N

#	Patient	Progression Confirmed	Narrative and Comments	Death likely due to drug-related AE?
	Prior treatment with erlotinib/cabozatinib, carboplatin/docetaxel, gemcitabine/irinotecan/erlotinib		***Reviewer's comment. Patient was quite ill at baseline, prior to starting osimertinib. However, acute decompensation with dyspnea and LE edema, while likely related to progressive lung cancer, was initially questioned by reviewer as no imaging or postmortem was done on the day of her death. After submitting IR to the sponsor, further details of the patient's poor clinical condition were noted, including the fact that the day prior to starting osimertinib, the patient was seen and treated for dehydration, sedation, and dyspnea and given IV hydration and PRBC transfusion. This likely represents a death related to clinical deterioration only.***	
14	**D5160C0001C/E7800741** **Age 55** **Prior therapy with Erlotinib**	N	55 white F with metastases to lung, skin/soft tissue, bone, LNs, and malignant pleural effusion. Therapy started on Ocober 1, 2014 and was discontinued on October 9, 2014 (day 9) due to clinical progression. Patient was hypoxic, CTCAE grade 3, and underwent thoracentesis and antbiotic therapy for treatment of possible post-obstructive PNA. Death occurred on (b) (6) ***Reviewer's comment.: Patient's death appears related to hypoxia and respiratory illness, which is likely PNA and progression of her lung cancer. IR submitted to sponsor revealed that the patient had PNA requiring abx prior to starting therapy, on September 25. He developed worsening pleural effusion requiring thoracentesis on Oct 9, and then had progressive hypoxia, delirium, and deterioration until death on*** (b) (6)	N
15	**D5160C0001C/E4310701** **Age 57** **S/p prior therapy with carbo/gem, gefitinib, pemetrexed, pemetrexed/bevacizumab, erlotinib/paclitaxel, erlotinib**	Y	57 Asian F with metastases to lung, LNs, and liver. Patient began therapy on June 11, 2014. On January 26, 2015 (day 229) the patient was diagnosed with PNA after presenting with cough and hypoxia; however, CT chest showed bilateral ground-glass opacities and the diagnosis was changed to ILD. The patient died on (b) (6) the autopsy showed findings consistent with ILD, although small cell lung cancer was also seen in the patient's LLL along with carcinomatous lymphangiosis and obstructive PNA. ***Reviewer's comment: Although the patient had progressive disease confirmed at the time of death, ILD was reported on autopsy and likely contributed to the patient's death.***	Y
16	**D5160C0001C/E7800707** **Age 60**	Y	60 white M with hx of tonsillar SCC and BCC; developed metastases to lung, LNs, pleural effusion. Began therapy June 18, 2014. Developed diffuse ground-glass opacities on imaging on Day 127, Oct	Yes- ILD likely contributed to patient's

#	Patient	Progression Confirmed	Narrative and Comments	Death likely due to drug-related AE?
	s/p 5FU/docetaxel/cisplatin, carboplatin/docetaxel, erlotinib		22, 2014. osimertinib was temporarily held but restarted on November 1, 2014. He had ongoing intermittent aspiration events, and developed a productive cough on Dec 30, 2014. Diffuse ground-glass opacities were seen in L lung, severely worsened, and osimertinib was again stopped with abx added, and osimertinib resuming on Jan 17, 2015. On Jan 25, 2015, osimertinib was permanently discontinued due to CTCAE grade 4 pneumonitis, with diffuse ground-glass opacities seen in L lung. Patient continued therapy with prednisone. The pneumonitis event remained ongoing. CT scan done on Feb 6, 2015 (day 234) showed improved ground-glass on the L but worsening disease and PNA on the R. Erlotinib was started on Febuary 10. However, "much worsened" L-sided ground glass findings were seen on Feb 15, 2015, erlotinib was held, and pt died on (b) (6) due to hypoxemic respiratory failure. No post-mortem was available. ***Reviewer's comment: In this complicated case, many factors could have contributed to the patient's eventual death, but the fact that the SAE of pneumonitis, which was graded as grade 4, was ongoing with clinical evidence of worsening on CT scan, likely contributed to the patient's eventual respiratory failure and death.***	multifactorial death

Table 26: Analysis of on-treatment deaths, AURA2. DCO date January 9, 2015 and April 7, 2015 for ILD events.

#	Patient	Progression Confirmed	Narrative and Comments	Death likely due to drug-related AE?
1	**D5160C00002/ E1002213** **Age 42** **Prior treatment with erlotinib**	N	42 Asian F pmhx Hep B, papillary thyroid ca s/p thyroidectomy, now with NSCLC and metastases to the lung, bone, and lymph nodes, abdominal ascites, and pleural effusion. Received palliative radiation to L chest from Aug 27 2014 – September 3, 2014. Started on osimertinib (b) (6) On Oct 2 (day 14) AE grade 2 aspiration PNA recorded, Cipro started; on (b) (6) patient hospitalized and died from hypoxia, lung infection. Cause of death recorded as disease progression, secondary cause was lung infection. ***Reviewer's comment: Aspiration pneumonia in a young woman seems unlikely, and the quick time course of events raises the possibility that there could be another cause of death, especially since there was no post-mortem examination performed.***	Maybe

#	Patient	Progression Confirmed	Narrative and Comments	Death likely due to drug-related AE?
			Possibilities include PNA (non-aspiration), pulmonary embolus, and radiation pneumonitis. ILD may also be a possibility, especially given her history of papillary thyroid cancer and likely radioactive iodine and recent irradiation to the chest, both have which may have predisposed her to developing lung toxicity.	
2	**D5160C00002/ E4104202** **Age 63** **Prior treatment with cis/gem and cis/vinorelbine in the neoadjuvant/adjuvant setting, along with EBRT and R pneumonectomy. Then Gefitinib, carbo/paclitaxel/ erlotinib, then afatinib**	N	63 white F with hx of trimodality therapy for stage IIIA lung ca;now w stage IV disease, mets to brain, lung, liver, LNs. Started therapy Aug 14, 2014. Oct 11 (day 59) the patient developed CTC AE grade 2 of dyspnea; CT showed ILD. Drug discontinued on Oct 14, 2014. Treated with broad spectrum abx, acyclovir started. Chest CT improved on serial scans Oct 22, then Nov 3. Patient discharged (b) (6) and died (b) (6) Cause of death determined by investigator to be primarily due to ILD, secondarily due to respiratory failure. ***Reviewer's comments: Death likely related to ILD and osimertinib.***	Y
3	**D5160C00002/ E7806201** **Age 50** **Prior therapy with erlotinib**	N	50 white F with mets to lung, liver, LNs. No other medical history. Started treatment (b) (6) Discontinued day 33, (b) (6) admitted with SAE grade 2 SOB. Treated for PNA, hypoxia. Died on (b) (6). Investigator concluded that death was due to disease progression and PNA; considered SAE unrelated to osimertinib. **Reviewer's comments: Death may be related to osimertinib.**	Maybe
4	**D5160C00002/E4 314202** **Age 54** **Prior treatment with carboplatin and Alimta and Tarceva**	N	54 Asian M with mets to lung, brain, and bone. Also with a history of pericardial and pleural effusions. History of HTN, on multiple antihypertensives, and hyperlipidemia. Also history of 'multiple cerebral infarcts'. History of brain/CNS mets but never had radiation. Patient received one dose of osimertinib on (b) (6) and died the same day. Death was listed as due to lung cancer. No post-mortem done. ***Reviewer's comments: Likely unrelated to osimertinib. May have been CVA or hemorrhage due to brain metastasis (no recorded history of EBRT to brain).***	N

#	Patient	Progression Confirmed	Narrative and Comments	Death likely due to drug-related AE?
5	**D5160C00002/E1 001207** **Age 58** **Prior therapy with gefitinib, erlotiniband carboplatin/pem etrexed**	Y	58 white F with mets to lug, brain, liver, bone, LNs. No other relevant medical history. Treatment started on August 21, 2014. This was discontinued on November 10, 2014 (day 82) due to disease progression and patient died on (b) (6) ***Reviewer's comments: Death likely related to disease progression.***	N
6	**D5160C00002/E7 401212** **Age 59** **Prior therapy with Gefitinib, cisplatin/pemetre xed, and erlotinib.**	Y	59 Asian F with mets to brain, lung, and bone. Pmhx of hypertension, bilateral facial palsy. Treatment began on (b) (6) and was interrupted on day 49- (b) (6) due to an AE of QTc prolongation. Dosing with a reduced dose of 40 mg continued on October 16, 2014. However, on day 85- (b) (6) the drug was discontinued due to disease progression. The patient died the following day. ***Reviewer's comments: In this case there was objective confirmation of disease progression, which likely was the major causative factor in the patient's death.***	N
7	**D5160C00002/E7 002208** **Age 60** **Prior therapy with erlotinib, onartuzumab and erlotinib, then carboplatin/pem etrexed.**	Y	60 white M with metastases to lung, malignant pleural effusion, liver. Started therapy on October 8, 2014. Stopped therapy on December 22, 2014 due to disease progression (day 76), and patient died on (b) (6) ***Reviewer's comment: Death likely related to progressive disease.***	N
8	**D5160C00002/E6 001204** **Age 62** **Prior therapy with gefitinib, carboplatin/pacli taxel, and pemetrexed.**	Y	62 M Asian with mets to brain, adrenal, bone, LNs. Hx WBRT. Started treatment July 2, 2014., interrupted from 09-Aug-2014 (Day 39) to 28-Aug-2014 due to an SAE of hearing impairment CTCAE grade 4. A neurosurgeon was consulted and thought the hearing impairment was due to existing seeding metastases around both internal auditory canals, as shown in previous brain MRI, or from whole brain radiotherapy (30 Gy) that the patient received from Apr-2013 to May-2013 osimertinib discontinued on 29-Oct-2014 (Day 120) due to disease progression. Patient then received	N

#	Patient	Progression Confirmed	Narrative and Comments	Death likely due to drug-related AE?
			docetaxel from 31-Oct-2014 to 25-Nov-2014 and methotrexate from 21-Nov-2014 to 28-Nov-2014, He died on (b) (6) the primary cause of death was recorded as respiratory failure ***Reviewer's comment: Death likely related to disease progression.***	
9	**D5160C00002/E7 003211** **Age 73** **Prior therapy with erlotinib.**	Y	73 white F with metastases to liver, soft tissue, and bone. Hx of CRF, dyslipidemia, HTN. Treatment began on began on 07-Jul-2014, with dose interruption from 28-Jul-2014 (Day 22) to 30-Jul-2014 and from 02-Aug-2014 (Day 27) to 13-Aug-2014 due to an SAE of dehydration. The drug was resumed on 13-Aug-2014 but was permanently discontinued on 13-Nov-2014 (Day 130) due to disease progression, and died on (b) (6) ***Reviewer's comment: Death likely related to disease progression.***	N
10	**D5160C0002/E10 02221** **Age 65** **s/p pemetrexed/cisplatin, erlotinib, erlotinib/pemetrexed**	N	65 white M with hx of PE and bilateral DVT. Metastases to bone and omental caking. Began therapy on September 29, 2014. Dosing permanently discontinued on day 44- Nov 11, 2014 due to SAE of acute brain infarction, CTC grade 3, with MRI showing subacute infarct in L TCA and acute infarcts in R cerebellum. On Nov 3, 2014 also had CTC grade 3 splenic infarct. Patient died on (b) (6) ***Reviewer's comment: Agree with investigator that brain infarction could be study-dug related. The fact that his death the following month was listed as related to 'lung cancer progression' may be true but major contribution of the brain infarction in his death can not be ruled out.***	Maybe

Table 27: Deaths on-treatment, AURA phase 1 development program, DCO date December 2, 2014 and April 7, 2015 for ILD events.

#	Dose	Patient	Progression confirmed?		Related to osimertinib?
1	20 mg	D5160C00001/ E6001002 Age 55	Y	55 Asian M. PMhx Primary biliary cirrhosis, HTN. Mets to peritoneum, pleural effusion, brain, lung, liver, skin, bone. Died of PNA and sepsis 29 days after 1st dose, 8 days after last dose. Also AST and ALT increased. Has a new pleural effusion on chest CT beginning on day 14, with malignant cytology. Also new R-sided PNA.	**N- likely multifactorial and related to disease progression**
2	80 mg	D5160C00001/	N	65 F,no relevant medical hx. c/o cough, hypoxia	**N**

#	Dose	Patient	Progression confirmed?		Related to osimertinib?
		E7801002 Age 65 S/p therapy with pemetrexed, erlotinib, afatinib, erlotinib		on day 64. WBC elevated to 21.4. Hospitalized with AKI (creatinine 2.35) and bacteremia (strep canis)on day 64; ATN occurred and she died on day 80, 4 days after last dose.	
3	80 mg	D5160C00001/ E7801003 Age 74 S/p therapy w afatinib, erlotinib/carbo/ pem, afatinib, co-1686, afatinib, carbo/pem.	N	74 white M , metastases to bones, lung, LNs. Hx HTN. Developed TIA on day 1. CTCAE pneumonitis grade 2 developed on Day 19, but also fulfilled RECIST criteria for disease progression. Durg discontinued on Day 19. Docetaxel/afatinib started next day. On day 27, acute CVA. On day 40, the patient was once again hospitalized with SAE CTC grade 3 hypoxia. Died on day 47.	**N**
4	160 mg	D5160C0001B/ E0301507 Age 77 s/p erlotinib, carbo/gem	Y	77 white M with pmhx HTN, metastases to lung, liver, ascites, skin, bone. Started therapy 03-Dec-2013. Scan on 13-Jan-2014 showed progressive disease. Osimertinib discontinued on 22-Jan-2014 (Day 51). The patient died on (b) (6)	**N**
5	40 mg	D5160C0001B/ E2301508 Age 62 s/p cis/pem, erlotinib	Y	62 white M, Hx of DM, CAD, s/p MI. Metastases to brain, liver, bone, lung, LNs. Treatment began 06-Nov-2013. Scan on 13-Dec-2013 showed progressive disease. Drug stopped on 18-Dec-2013 (Day 43).	**N**
6	80 mg	D5160C0001B/ E2301511 Age 58 s/p carbo/ paclitaxel/bev, then pemetrexed, then erlotinib/bev	Y	58 white F. mets to lung, LNs, bone, brain. Hx HTN. New CTCAE pleural effusion day 27 of therapy. Day 64 drug discontinued due to scan showing progressive disease. Died 7 days later due to disease progression.	**N**
7	40 mg	D5160C0001B/ E4301501 Age 74 s/p carbo/paclitaxel /bev, gefitinib, pemetrexedTS-1, amirubicin.	Y	74 Asian F, locally advanced disease to lung, LN, chest wallTreatment began on Aug 14, 2013 and was discontinued on 23-Sep-2013 (Day 41) due to objective disease progression. The patient died on (b) (6)	**N**
8	80 mg	D5160C0001B/ E4301513 Age 64 s/p gefitinib.	Y	64 Asian M, metastases to lung, LN, bone, adrenal. Began therapy on (b) (6) discontinued on (b) (6) (Day 42) due to objective disease progression with enlargement of the primary mass and adrenal metastases, new pleural effusion, obstruction of the right middle and lower bronchus, and infiltrate of the right	**Maybe-death thought to be primarily related to lung cancer but also SAE**

#	Dose	Patient	Progression confirmed?		Related to osimertinib?
				lower lobe. On Nov 6, CT showed bilateral ground glass opacities. The patient was diagnosed with a CTC grade 3 SAE of pneumonitis on day 50. There was no evidence of infection. He died on day 56 due to "disease progression".	**of pneumonitis was thought to be treatment-related.**
9	40 mg	D5160C0001B/ E6001508 Age 45 s/p gefitinib, carbo/gem, pemetrexed.	Y	45 Asian F with metastases to lung, brain, bone, and malignant pleural and pericardial effusion. Began therapy Oct 1, 2013. Discontinued on 12-Nov-2013 (Day 43) for objective disease progression. Died (b) (6)	**N**
10	80 mg	D5160C0001B/ E6002514 Age 76 s/p carboplatin/gemcitabine, gefitinib, pemetrexed, HM-EMSI, irinotecan.	Y	76 Asian F,hx of DM, metastases to lung and LNs. Treatment began on 02-Sep-2013, interrupted from 12-Sep-2012 (Day 11) to 23-Sep-2012 due to CTC grade 3 pulmonary embolism. Discontinued on 08-Oct-2013 (Day 37) for progression. Died on (b) (6) Also had SAEs of hypoglycemia and dehydration unrelated to AZD9192.	**N**
11	80 mg	D5160C0001B/ E6002519 Age 63 s/p cisplatin/gemcitabine, gefitinib, pemetrexed, vinorelbine, docetaxel.	N	63 Asian M with metastases to lung, ascites, pleural and pericardial effusion. Started therapy on September 2, 2013, with two interruptions (day 261 and 351) of esophageal stenosis. These were CTC grade 3. Patinet died on (b) (6) of suicide, s days after being discharged from hospital after treatment of esophageal stenosis.	**N**
12	80 mg	D5160C0001B/ E6003504 Age 52 s/p gefitinib, pemetrexed, gemcitabine/carboplatin, afatinib.	Y	52 Asian F began therapy on (b) (6) . Dosing interrupted on day 22, (b) (6) due to CTCAE grade 3 anemia. Also had dyspnea, neck pain (grade 2) on day 27 due to progressive cervical LAD. Died on (b) (6) (Day 30).	**N**
13	160 mg	D5160C0001B/ E6003507 Age 60 s/p cisplatin/pemetrexed, erlotinib, carboplatin/gemcitabine, afatinib, eribulin, docetaxel.	Y	60 Asian F with metastases to liver, lung, brain, kidney, peritoneum, pleural effusion. Hx of DM, thyroid cancer, breast cancer. Began treatment on (b) (6) CT scan showed progression on (b) (6) (day 84), 2014 but investigator chose to continue until (b) (6) (day 157) when pt died of progressive disease.	**N**
14	80 mg	D5160C0001B/ E6004502 Age 66	Y	66 F with metastases to lung, bone, and liver. Started therapy on Sept 26, 2013. Developed CTCAE grade 3 diarrhea on day 2 requiring	**N**

#	Dose	Patient	Progression confirmed?		Related to osimertinib?
		s/p paclitaxel/carboplatin, erlotinib, pemetrexed, docetaxel, and afatinib.		hospitalization. Restarted therapy on Sept 30; Developed spinal cord compression on day 19; died on (b) (6) due to disease progression/hypercalcemia.	
15	80 mg	D5160C0001B/ E6004504 Age 59 s/p pemetrexed/cisplatin/bevacizumab, gefitinib, pemetrexed, aftinib	N	59 Asian F with metastases to lung, pleural effusion, liver, LN, peritoneum. Patient received 1 dose of drug on Sept 10, 2013 but then did not receive another dose due to development of shock with uncontrollable abdominal pain and hypotension (83/69), hyperkalemia, renal failure. Died on (b) (6)	**Maybe. Investigator determined it was not related to osimertinib but reviewer unable to exclude.**
16	80 mg	D5160C0001B/ E6004507 Age 57 s/p carbo/paclitaxel, gefitinib, pemetrexed	Y	57 Asian F widely metastatic disease started therapy oct 1, 2013. Developed progressive disease on scan on Aug 29, 2014 but stopped drug on oct 27, 2014 (day 392). Spinal compression fracture the following day. Died on (b) (6)	**N**
17	40 mg	D5160C0001B/ E7002504 Age 80 s/p gefitinib	Y	80 white F mets to pericardial effusion, LNs, pleural and pericardial effusion, lung. Treated from Nov 5, 2013 to Nov 26, 2013 (day 25) due to disease progression. Patient died (b) (6)	**N**
18	80 mg	D5160C0001B/ E7002505 Age 45 s/p cisplatin/pemetrexed, erlotinib, gefitinib, erlotinib	Y	45 W male metastases to lung, liver. Began therapy Dec 3, 2013. Developed grade 3 skin toxicity requiring hospitalization on (b) (6) Drug stopped Jan 10, 20114 due to disease progression. Died on (b) (6).	**N**
19	80 mg	D5160C0001B/ E7002506 Age 76 s/p erlotinib, carboplatin/pemetrexed then pemetrexed	Y- clinical	76 white F with metastases to lung, bone, pleural effusion, LNs. Started therapy (b) (6). Discontinued on day 43- (b) (6) due to progression- this was clinical progression only, as scan on April 10 showed no progression but did show a PE (grade 2). Also had been hospitalized with pneumococcal pneumonia CTC grade 3 on Day 8 (b) (6)	**N- had leukocytosis, pneumococcus. Unlikely ILD**
20	20 mg	D5160C0001B/ E7401507 Age 71 s/p treatment with pemetrexed/cisplatin, pemetrexed, erlotinib, docetaxel	Y	71 Asian M with metastases to lung, pleural effusion, bone, liver. Started therapy (b) (6) and discontinued on day 292- (b) (6) because of lung infection. Patient died the following day. In April 2014, patient had re-accumulation of pleural effusions and CTCAE grade 3 lung infection. RECIST scan on May 6, 2014 showed progressive disease.	**N**

#	Dose	Patient	Progression confirmed?		Related to osimertinib?
21	80 mg	D5160C0001B/ E7401516 Age 62 s/p gefitinib, cisplatin/pemetrexed, erlotinib, docetzxel, paclitaxel, gemcitabine, navelbine, and gefitinib	Y	62 Asian M metastases to liver, bone, pleural effusion, pleura, lung. Started therapy on Sept 5, 2013. He had suffered DVT on Sept 3, 2013 and was started on Lovenox. He suffered a stroke on day 9 (sept 13). He continued on therapy until Jan 29, 2014 (day 147) due to disease progression, and died on (b) (6)	**N**
22	80 mg	D5160C0001B/ E7401526 Age 68 s/p gefitinib	N	68 Asian M with metastases to LN, brain, lung, pleural effusion, adrenal. Started therapy on oct 8, 2013. On 20-Nov-2013 (Day 44), osimertinib was permanently discontinued due to mediastinal infection caused by tumor necrosis. Patient died on (b) (6) of PNA and lung cancer.	**N**
23	40 mg	D5160C0001B/ E7401528 Age 52 s/p erlotinib, cisplatin/pemetrexed, gefitinib+INC-280, vinorelbine.	Y	52 Asian F with metastases to R breast, skin, lung, LNs, and pleural effusion. Started therapy Oct 1, 2013. Progressive disease noted on April 29, 2014 but continued the drug. Dose upped to 80 mg on June 19, 2014. Discontinued on Oct 21, 2014 (day 386) due to disease progression; patient died (b) (6)	**N**
24	40 mg	D5160C0001B/ E7401536 Age 48 s/p pemetrexed/cisplatin, and gefitinib	N	48 Asian M metastatic disease to brain, pericardial/pleural effusion, lung, and bone. Dosing began on (b) (6) but was discontinued on (b) (6) (Day 124) due to a fatal SAE of pneumonia. Patient was admitted for PNA and died on that day. As per CRF "X ray showed pneumonia". He also had cough, sputum increase	**N- likely PNA**
25	80 mg	D5160C0001B/ E7401581 Age 77 s/p gefitinib, paclitaxel, erlotinib, pemetrexed	N	77 Asian M with metastases to LN, brain, lung, pleural effusion, liver, bone. Treatment began on (b) (6) On (b) (6) (Day 7), the patient was hospitalised for nutritional support due to a CTC grade 3 SAE of worsening of poor appetite. osimertinib was discontinued on day 15. On (b) (6) (Day 16) hypoxemia was noted. A chest X-ray showed infiltration of the right and left upper lobes. The patient was diagnosed with an SAE of pneumonia The patient died on (b) (6) (Day 24).	**N- likely PNA**
26	40 mg	D5160C0001B/ E7402508 Age 59 s/p afatinib, cisplatin/pemetrexed. Pemetrexed,	N	59 Asian F with metastases to lung, pleural effusion, liver, bone, LNs. Treatment began on (b) (6) and was permanently discontinued on (b) (6) (Day 164) due to the SAE of pneumonia. She had been hospitalized due to fever, diarrhea, and 'PNA' the day prior and died from PNA.	**N- Likely PNA- febrile.**

#	Dose	Patient	Progression confirmed?		Related to osimertinib?
		erlotinib			
27	160 mg	D5160C0001B/ E7800507 Age 51 s/p erlotinib	Y	51 white female with metasatases to lung, pleural effusion, liver, bone, LNs. Treatment began began on (b) (6) On (b) (6) (Day 2) patient suffered narcotic overdose and multifocal ischaemic stroke. (b) (6) (Day 18), patient developed multiple PEs and malignant pleural effusions. Osimertinib was permanently discontinued on 12-Dec-2013 (Day 36) because of disease progression seen on RECIST scan. The following day, the patient's EF decreased to 15-20% and she was found to have CTCAE grade 4 Takutsubo's cardiomyopathy. She died on (b) (6)	**Maybe- the Takutsubo's event that immediately preceded her death may have been related to drug as it is not usually an event associated with malignant disease progression.**
28	80 mg	D5160C0001B/ E7800511 Age 84	N	84 white F with metastases to brain, lung, bone, LN. Started therapy on (b) (6) Stopped therapy on (b) (6) due to SAE of PNA (day 366); died of PNA on day 373, (b) (6)	**No- PNA- Likely unrelated to osimertinib.**
29	80 mg	D5160C0001B/ E7804501 s/p erlotinib, carboplatin/pemetrexed, decetaxel, cetuximab/afatinib	N	50 white F with metastases to lung, adrenal, and liver. Treatment began on (b) (6). On day 19, (b) (6) the patient developed PE and DVT; coded as CTCAE grade 3. On (b) (6) (Day 19), CTC grade 3 AST increased (311 IU/L), grade 2 ALT increased (191 IU/L), grade 2 blood bilirubin increased (1.7 mg/dL), and grade 3 alkaline phosphatase increased (1880 U/L) osimertinib was interrupted on 20-Dec-2013 and was not restarted. The patient died on (b) (6) (Day 37)	**Maybe**
30	240 mg	D5160C0001B/ E7804504 Age 69 s/p carbo/paclitaxel /bevacizumab, erlotinib, afatinib, pemetrexed, erlotinib/gemcitabine	N	69 white M with metastases to lung and skin/soft tissue. Started therapy on (b) (6) Had dose reduced to 200 mg g on (b) (6) (Day 64) then to 160 mg on (b) (6) (Day 85) due to the AE of worsening oral mucositis. Osimertinib was permanently discontinued on (b) (6) (Day 142) due to an SAE of PEA – arrest. Patient died the following day.	**Maybe**

Deaths on AURA extension/ AURA2 **likely** attributable to osimertinib:

In analyzing the deaths that occurred in the phase 2 development program, there were **four** deaths considered by the investigators to be **likely** attributable to osimertinib, three in AURA extension and one in AURA2. All deaths occurred in patients who were over 55 and who

developed interstitial lung disease. These deaths were each reviewed by the FDA and causality of death as likely attributable to osimertinib was confirmed.

When detailed review of on-study deaths was undertaken by the reviewer, there were an additional three deaths identified in AURA2 where death due to the investigative agent could not definitively be ruled out. There were also three deaths in AURA extension which initially seemed related to osimertinib but on further review were not thought to be osimertinib related.

Deaths on AURA extension **possibly** attributable to osimertinib:

There were three cases that on initial review seemed to possibly related to osimertinib since they all occurred **within several days** after starting osimertinib. In one case, the patient was young (age 41) and acutely decompensated with dyspnea and lower extremity edema the day after starting the investigational product. Another patient, age 64, died within 10 days of starting therapy due to what was thought to be clinical worsening of lung cancer, although there was no RECIST restaging of disease to provide confirmation. A third patient, age 55, also died on day 11 after starting therapy due to what was thought to be clinical progression, although there was no CT confirmation of this.

However, in all of the above cases, IRs were submitted to the sponsor and the patients in all three cases appeared to be quite ill prior to starting therapy, and appeared to have rapidly progressing disease, despite having no radiographic confirmation of the above. The reviewer concluded that none of these rapid deaths were likely attributable to toxicity from osimertinib.

Deaths on AURA2 **possibly** attributable to osimertinib:

There were three deaths that were thought by the reviewer to be **possibly** attributable to osimertinib. A 42 year-old female died on day 18 of therapy, with what was called an acute "aspiration pneumonia", although she did have a history of recent chest irradiation and a history of papillary thyroid cancer which most likely was treated with RAI and which could have predisposed her to developing ILD. A 50-year old was admitted with shortness of breath and hypoxia on day 33 of therapy and died on day 38 due to 'disease progression and pneumonia', although no CT confirmation of disease progression was provided. A 65 year-old male had dosing of osimertinib held due to acute brain infarctions on day 44 of therapy and died approximately 6 weeks later. The reviewer felt that an association between the infarctions and osimertinib could not be ruled out, and that the infarctions could have played a role in his eventual death, which occurred in the absence of documented disease progression on imaging.

Deaths on combined AURA phase 1 cohorts:

In the phase 1 development program there were **no deaths** that were thought to be **likely attributable** to osimertinib.

The FDA reviewer could not exclude five deaths as being **possibly attributable** to osimertinib. A 64-year old male on 80 mg of osimertinib discontinued therapy on day 42 due to disease progression but also developed grade 3 pneumonitis on day 50 and died 6 days later. A 59-year-old female received one 80 mg dose of osimertinib and developed shock with multi-organ failure the following day, dying on day 3. A 51 year-old female on 160 mg of osimertinib discontinued therapy on day 36 due to disease progression but then developed a grade 4 acute cardiomyopathy on day 37, dying 12 days later. A 50 year old male on 80 mg of osimertinib developed grade 3 PE and DVT as well as grade 2/3 LFT increases on day 19 of therapy, discontinued therapy on that day, and died on day 37 in the absence of confirmed disease progression. A 69-year old male on 240 mg of osimertinib with subsequent dose decreases to 160 mg due to mucositis died on day 142 of therapy due to PEA arrest in the absence of confirmed disease progression.

Ultimately, the attribution of deaths to osimertinib by FDA reviewer was as follows:

Table 28: Cause of on-study deaths related to osimertinib. DCO date January 9, 2015 as well as 2 ILD deaths occurring up to DCO date of April 7, 2015.

Cause of death on osimertinib	AURA 1 N=5	AURA extension N =3	AURA2 N = 4	Total N = 12
Deaths with likely attribution to drug:				
Pneumonitis/ILD	**0**	**3**	**1**	**4**
Deaths with possible attribution to drug:				
Pneumonitis/ILD	**1**	**0**	**1**	**2**
Respiratory event	**0**	**0**	**1**	**1**
CVA	**0**	**0**	**1**	**1**
Multi-organ failure	**1**	**0**	**0**	**1**
Cardiomyopathy	**1**	**0**	**0**	**1**
PE	**1**	**0**	**0**	**1**
PEA arrest	**1**	**0**	**0**	**1**

Review of the 90-day safety update revealed an additional 26 deaths using the later DCO date, bringing the total number of deaths in the phase 2 studies to 52 (12.7% overall). The majority of these deaths were due to disease progression. There were an additional 3 patients in the updated data with deaths due to adverse events, although in none of these cases did the investigator attribute the deaths to osimertinib. One patient (E4101713) was a 57 year old female who died

of cerebral hemorrhage on day 205 due to bleeding into progressive brain metastases. Another patient (E7004203) was a 79-year old female who died on day 151 of therapy after disease progression and the development of pneumonia. Patient E7800205 was a 53-year old female who died of failure to thrive on day 121 after discontinuing therapy on day 117.

7.4.2. **Serious Adverse Events**

Serious Adverse Events (SAEs) occurred in 52 patients, or 12.7% overall. The majority of these patients had only one SAE recorded while on study; 11 patients had more than one SAE recorded. One patient had 6 SAEs, one had 3 SAEs, and nine patients had 2 recorded SAEs. Nonfatal serious adverse events occurred in 47 patients (11.4%).

Nonfatal SAEs that occurred in ≥1% of patients on either arm and SAEs by system organ class are summarized in the tables below.

Table 29: Nonfatal serious adverse events occurring in >1 patient, combined AURA extension and AURA2. DCO date January 9, 2015

PT	***Events***	***Number of subjects***	***Proportion (%)***
Pneumonia	6	5	1.22
Pulmonary embolism	5	5	1.22
Pneumonitis	3	3	0.73
Abdominal pain	2	2	0.49
Dyspnoea	2	2	0.49
Fatigue	2	2	0.49
Pharyngeal abscess	2	1	0.24
Thrombocytopenia	2	2	0.49

Table 30: Nonfatal Serious adverse events occurring in more than one patient by System Organ Class (SOC), combined AURA extension and AURA2. DCO date January 9, 2015

SOC	*Events*	*Number of subjects*	*Proportion (%)*
Respiratory, thoracic and mediastinal disorders	16	16	3.89
Infections and infestations	14	12	2.92
General disorders and administration site conditions	6	5	1.22
Nervous system disorders	5	4	0.97
Blood and lymphatic system disorders	4	4	0.97
Gastrointestinal disorders	3	3	0.73
Hepatobiliary disorders	2	2	0.49
Metabolism and nutrition disorders	2	2	0.49

Table 31: Osimertinib related nonfatal SAEs, DCO date January 9, 2015

Subject	Event (MedDRA PT)	Grade	Outcome
D5160C00002/E1002221	Cerebral infarction	3	NOT RECOVERED/NOT RESOLVED
D5160C00002/E4303210	Pneumonitis	3	NOT RECOVERED/NOT RESOLVED
D5160C00002/E4304202	Interstitial lung disease	1	RECOVERING/RESOLVING
D5160C00002/E4304204	Pyrexia	1	RECOVERED/RESOLVED
D5160C00002/E4304204	Pleurisy	3	RECOVERED/RESOLVED
D5160C00002/E4304210	Lung infection	3	RECOVERING/RESOLVING
D5160C00002/E7003211	Dehydration	3	RECOVERED/RESOLVED WITH SEQUELAE
D5160C00002/E7809203	Thrombocytopenia	3	RECOVERED/RESOLVED
D5160C0001C/E030173	Thrombocytopenia	3	NOT RECOVERED/NOT RESOLVED
D5160C0001C/E430871	Hepatic function abnormal	3	RECOVERED/RESOLVED
D5160C0001C/E431179	Disseminated intravascular coagulation	2	RECOVERED/RESOLVED
D5160C0001C/E431274	Decreased appetite	3	RECOVERED/RESOLVED
D5160C0001C/E431274	Diarrhoea	3	RECOVERED/RESOLVED
D5160C0001C/E700374	Pneumonitis	3	RECOVERED/RESOLVED
D5160C0001C/E780071	Pneumonitis	3	NOT RECOVERED/NOT RESOLVED

The 90-day safety update data was reviewed, which included events that occurred up to the DCO date of May 1, 2015. At that point 84 patients had experienced SAEs while on treatment, bringing the proportion of patients experiencing nonfatal SAEs up to 18.5% overall. Demographic analysis of differences in SAEs between racial groups did show that Asians were less likely to have nonfatal SAEs on study than Whites, with 13.4% of Asians vs. 27% of Whites

developing nonfatal SAEs. Further analysis of the SAEs occurring in different demographic groups revealed that White patients most commonly suffered from CVAs (N= 8 events), pulmonary emboli (N = 7 events), and pneumonia (N= 5 events). The corresponding numbers of SAEs in Asian patients for these events were CVAs- n = 1, pneumonia N = 6, and pulmonary emboli n = 4.

Reviewer's comments: Nonfatal SAEs were experienced at a relatively low rate overall considering the patient population (11.4%). The most common SOC manifesting SAEs was the "respiratory, thoracic, and mediastinal disorders", and the most common SAEs were pneumonia and pulmonary embolus, each affecting 5 patients. Pneumonitis events occurred in 3 patients, all of whom were over age 65, and all of which were thought to be related to osimertinib. There was an additional ILD event that occurred in a 39-year old patient, also thought to be attributable to osimertinib. Overall, there were 15 nonfatal SAEs in 13 patients that were assessed by the investigator to be causally related to osimertinib, and 6 nonfatal SAEs leading to osimertinib discontinuation.
The 90-day safety update did show that the proportion of nonfatal SAEs had increased overall to 18.5%, with the number of cerebral infarctions and pulmonary emboli increasing, and with the incidence of nonfatal SAEs higher in the White vs. Asian population. After an IR was submitted to the sponsor regarding these incidence rates and after reviewing the literature and data from other clinical trials, it was concluded that the rates of these events were within the rates expected in this study population and that racial differences might be due to chance or to differences in comorbidities of enrolled patients.

7.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

The pre-specified safety withdrawal criteria for AURA extension mandated that a patient experiencing a CTCAE grade 3 and/or unacceptable toxicity not resolving to ≤ CTCAE grade 2 after 14 days be withdrawn from the study and observed until resolution of the toxicity. A protocol amendment later allowed up to 3 weeks for patients to recover from toxicity. Additionally, patients with QTc prolongation fulfilling the DLT criteria (i.e. confirmed QTc prolongation to >500 msec absolute or a > 60 msec increase from baseline) were to have study treatment interrupted and regular ECGs performed until resolution to baseline; if this did not resolve to ≤ grade 1 within 14 days the patient would be permanently withdrawn. Additionally, any patient with corneal ulceration was withdrawn from the study. A protocol amendment added suspected cases of Interstitial Lung Disease as events requiring treatment interruption, and if the diagnosis was confirmed, treatment discontinuation.

AURA2 study withdrawal criteria were similar but allowed up to 3 weeks for recovery from a CTCAE grade 3 or higher and/or unacceptable toxicity leading to dose interruption. QTc prolongation fulfilling the criteria enumerated above resulted in treatment interruption but the patient had up to 3 weeks to return to ≤ grade 1. Additionally, the phase 2 study added Interstitial Lung Disease (ILD) to corneal ulceration as an event which would preclude the patient from further study treatment.

Specific adverse events leading to treatment discontinuation are summarized in Table 32. Overall, 16 patients (3.9%) permanently discontinued treatment due to adverse events. One

patient had 4 separate AEs that led to discontinuation of study drug, three patients had 2 AEs leading to discontinuation, and the rest had one AE leading to study discontinuation. Table 33 shows AE grouped by system organ class that led to permanent treatment discontinuation.

Table 32: Adverse events leading to permanent discontinuation, combined AURA extension and AURA2. DCO date January 9, 2015

Adverse Events Leading to Discontinuation	Number of subjects (%)
Any AE leading to discontinuation	**16 (3.9)**
ILD	**4 (1)**
Pneumonitis	**4 (1)**
Cerebrovascular accident, cerebral infarction, embolic cerebral infarction	**4 (1)**
Asthenia	**1 (0.25)**
Back pain	**1 (0.25)**
Decreased appetite	**1 (0.25)**
Diarrhoea	**1 (0.25)**
Dyspnoea	**1 (0.25)**
Hypoxia	**1 (0.25)**
Neck pain	**1 (0.25)**
Pneumonia	**1 (0.25)**
Rash maculo-papular	**1 (0.25)**
Vomiting	**1 (0.25)**

Table 33: Adverse events leading to permanent discontinuation by System Organ Class (SOC), combined AURA extension and AURA2. DCO date January 9, 2015

Adverse Events Leading to Discontinuation	Number of subjects (%)
Any AE leading to discontinuation	**16 (3.9)**
Respiratory, thoracic and mediastinal disorders	**10 (2.4)**
Nervous system disorders	**4 (1)**
Gastrointestinal disorders	**2 (0.5)**
Musculoskeletal and connective tissue disorders	**2 (0.5)**
General disorders and administration site conditions	**1 (0.25)**
Infections and infestations	**1 (0.25)**
Metabolism and nutrition disorders	**1 (0.25)**
Skin and subcutaneous tissue disorders	**1 (0.25)**

Table 34 shows outcomes of the adverse events leading to treatment discontinuations in the combined phase 2 trials, along with information about grade and investigator attribution for each AE that led to treatment discontinuation.

Table 34: Listing of AEs Leading to Permanent Discontinuation, combined AURA extension and AURA2. DCO date January 9, 2015

Adverse Event Outcome	Adverse Event	Grade	Investigator attribution
FATAL	Interstitial lung disease	5	REASONABLE POSSIBILITY AE RELATED TO IP
	Pneumonia	5	UNLIKELY AE CAUSED BY IP
	Cerebrovascular accident	5	UNLIKELY AE CAUSED BY IP
	Interstitial lung disease	5	REASONABLE POSSIBILITY AE RELATED TO IP
NOT RECOVERED/ NOT RESOLVED	Back pain	2	UNLIKELY AE CAUSED BY IP
	Neck pain	2	UNLIKELY AE CAUSED BY IP
	Cerebral infarction	3	REASONABLE POSSIBILITY AE RELATED TO IP
	Dyspnoea	2	REASONABLE POSSIBILITY AE RELATED TO IP
	Rash maculo-papular	3	REASONABLE POSSIBILITY AE RELATED TO IP
	Pneumonitis	3	REASONABLE POSSIBILITY AE RELATED TO IP
	Hypoxia	2	UNLIKELY AE CAUSED BY IP
	Cerebrovascular accident	3	UNLIKELY AE CAUSED BY IP
	Interstitial lung disease	1	REASONABLE POSSIBILITY AE RELATED TO IP
	Embolic cerebral infarction	3	UNLIKELY AE CAUSED BY IP
	Pneumonitis	3	REASONABLE POSSIBILITY AE RELATED TO IP
RECOVERED/ RESOLVED	Interstitial lung disease	1	REASONABLE POSSIBILITY AE RELATED TO IP
	Pneumonitis	1	REASONABLE POSSIBILITY AE RELATED TO IP
	Asthenia	2	REASONABLE POSSIBILITY AE RELATED TO IP
	Decreased appetite	2	REASONABLE POSSIBILITY AE RELATED TO IP
	Vomiting	1	REASONABLE POSSIBILITY AE RELATED TO IP
	Diarrhoea	1	REASONABLE POSSIBILITY AE RELATED TO IP
	Pneumonitis	3	REASONABLE POSSIBILITY AE RELATED TO IP

Review of the 90-day safety update data submitted by the sponsor showed that an additional 7 patients had discontinued therapy, bringing the total to 5.6% overall, with no new safety signal identified in terms of reasons for treatment discontinuations.

Reviewer's comments: Overall, 5.4% of patients discontinued osimertinib due to an adverse event. Only two patients discontinued therapy due to GI toxicities and one patient discontinued due to skin toxicity, despite the fact that these were the most common sites involved with AEs overall (see section 7.4.4). However, 45% of treatment discontinuations were due to respiratory disorders, with 4 listed AEs leading to drug discontinuation related to ILD or pneumonitis, one due to PNA, and another due to hypoxia. All of the pneumonitis/ILD events were attributable to osimertinib by the investigators. There were also four neurologic events causing treatment discontinuations, although only one event (cerebral infarction grade 3) was thought to be attributable to osimertinib. While this did raise questions as to whether the rates of discontinuation of drug due to CVAs presented a safety concern related to osimertinib, the reviewer eventually concluded that the CVA occurrence rate was within the expected incidence rate for an advanced lung cancer population.

Treatment modifications due to AEs

Overall, there were 87 adverse events leading to dose interruption (n=79) or dose reduction (n=8) in 57 patients (Table 35). The overall rate of treatment modifications due to AEs was 13.9%.

Table 35: Adverse events leading to dose interruption or dose reduction in > 2 patients, AURA extension and AURA2. DCO date January 9, 2015

PT	*Events*	*Number of subjects*	*Proportion(%)*
Electrocardiogram QT prolonged	6	6	1.46
Neutrophil count decreased	6	6	1.46
Alanine aminotransferase increased	4	4	0.97
Leukopenia	3	3	0.73
Anaemia	2	2	0.49
Aspartate aminotransferase increased	2	2	0.49
Blood alkaline phosphatase increased	2	2	0.49
Decreased appetite	3	2	0.49
Dehydration	2	2	0.49
Diarrhoea	3	2	0.49
Fatigue	2	2	0.49
Hyponatraemia	2	2	0.49
Nausea	2	2	0.49
Neutropenia	3	2	0.49
Pneumonia	2	2	0.49
Thrombocytopenia	3	2	0.49

Review of the 90-day safety update revealed that the number of dose modifications or interruptions due to AEs had increased to 20% of patients overall (n=82). The most common causes of treatment modification or interruptions due to AEs were unchanged from those presented above, with the most common causes including QT prolongation (9 patients), and neutropenia/neutrophil count decreased (8 patients).

7.4.4. Significant Adverse Events

There were 77 patients who experienced a total of 111 AEs that met the definition of grade 3 or 4 toxicity according to the CTCAE definitions, including 22 patients who had more than one grade 3-4 adverse event. The overall rate of grade 3-4 AEs as defined by CTCAE was therefore 19%. There were 44 events in 35 patients that were attributed by the investigator as having a reasonable possibility of being related to osimertinib. Table 36 contains information on grade 3-4 AEs that occurred in more than 1 patient in the combined phase 2 cohorts.

Table 36: Grade 3-4 AEs, combined AURA Extension and AURA2, DCO date January 9, 2015

PT	*Events*	*Number of subjects*	*Proportion (%)*
Neutrophil count decreased	**6**	**6**	**1.46**
Dyspnoea	**5**	**5**	**1.22**
Pneumonia	**5**	**5**	**1.22**
Alanine aminotransferase increased	**4**	**4**	**0.97**
Pulmonary embolism	**4**	**4**	**0.97**
Anaemia	**3**	**3**	**0.73**
Diarrhoea	**3**	**3**	**0.73**
Electrocardiogram QT prolonged	**3**	**3**	**0.73**
Hypoxia	**3**	**3**	**0.73**
Leukopenia	**3**	**3**	**0.73**
Pneumonitis	**3**	**3**	**0.73**
Thrombocytopenia	**3**	**3**	**0.73**
Asthenia	**2**	**2**	**0.49**
Fatigue	**2**	**2**	**0.49**
Hyponatraemia	**2**	**2**	**0.49**
Neutropenia	**3**	**2**	**0.49**

An updated list of grade 3-4 AEs affecting patients on study is presented below, based on 90-day safety data. The extended DCO increased the number of patients experiencing grade 3-4 AEs to 28%.

Table 37: Grade 3-4 AEs using 90-day safety update, combined AURA Extension and AURA2, DCO date May 1, 2015

PT	*Events*	*Number of subjects*	*Proportion (%)*
Pneumonia	**9**	**9**	**2.19**
Pulmonary embolism	**10**	**9**	**2.19**
Dyspnoea	**8**	**8**	**1.95**
Neutrophil count decreased	**7**	**7**	**1.7**
Anaemia	**6**	**6**	**1.46**
Alanine aminotransferase increased	**5**	**5**	**1.22**
Electrocardiogram QT prolonged	**6**	**5**	**1.22**
Diarrhoea	**4**	**4**	**0.97**
Hyponatraemia	**5**	**4**	**0.97**
Pneumonitis	**4**	**4**	**0.97**
Thrombocytopenia	**4**	**4**	**0.97**
Asthenia	**4**	**3**	**0.73**
Back pain	**3**	**3**	**0.73**
Decreased appetite	**4**	**3**	**0.73**
Hypoxia	**3**	**3**	**0.73**
Leukopenia	**3**	**3**	**0.73**
White blood cell count decreased	**3**	**3**	**0.73**
Blood creatine phosphokinase increased	**2**	**2**	**0.49**
Cerebral infarction	**2**	**2**	**0.49**
Ejection fraction decreased	**4**	**2**	**0.49**
Fatigue	**2**	**2**	**0.49**
Hypokalaemia	**2**	**2**	**0.49**
Influenza	**2**	**2**	**0.49**
Nausea	**2**	**2**	**0.49**
Neutropenia	**6**	**2**	**0.49**
Platelet count decreased	**2**	**2**	**0.49**
Pleural effusion	**2**	**2**	**0.49**
Presyncope	**2**	**2**	**0.49**
Supraventricular tachycardia	**2**	**2**	**0.49**
Traumatic fracture	**2**	**2**	**0.49**
Vomiting	**2**	**2**	**0.49**

Reviewer's comments: The overall rate of grade 3-4 AEs, while still relatively low, increased to 28% at the 90-day safety update. However, much of this was thought to be related to the underlying characteristics of the study population. For example, pneumonia and pulmonary emboli increased in prominence as causes of grade 3-4 toxicity in the updated database, although this was thought overall to still be within expected range of normal for this study population. The most common toxicities seen on-study, rash and diarrhea, did not account for many grade 3-4 AES (<1% each).

7.4.5. Treatment Emergent Adverse Events

Table 38 is a list of treatment-emergent adverse events occurring in ≥ 5% of patients in the combined AURA extension and AURA2 study populations. AEs occurring in > 10% of the population have been highlighted. When indicated, several related AE terms have been grouped. Additionally, the proportion of patients with grade 3-4 AEs corresponding to the most common AEs are also presented.

Table 38: Treatment-emergent adverse events, combined AURA extension and AURA2, DCO date January 9, 2015.

PT	*All grades*			*Grade 3-4*		
	Events	*# of subjects*	*Proportion (%)*	*Events*	*# of subjects*	*Proportion (%)*
Gastrointestinal/Nutritional						
Diarrhea	210	155	37.71	3	3	0.73
Decreased appetite	53	49	11.92	0	0	0
Nausea	55	46	11.19	1	1	0.24
Stomatitis	46	39	9.49	0	0	0
Constipation	42	37	9	0	0	0
Abdominal pain, including upper	30	28	6.82	1	1	0.24
Vomiting	36	27	6.57	0	0	0
Dermatologic						
Rash (including acne, dermatitis acneiform, dermatitis, erythema, folliculitis, rash maculo-papular, rash generalized, rash macular, rash papular, rash pustular)	205	157	38.2	1	1	0.24
Dry skin (including dry skin, eczema, skin fissures, xerosis)	114	107	26.0	0	0	0
Paronychia and nail disorders (including nail bed disorders, nail bed inflammation, nail bed tenderness, nail discoloration, nail disorder, nail dystrophy, nail infection, nail ridging, nail toxicity, onychalgia, onychoclasis, onycholysis, onychomadesis, paronychia)	106	92	22.4	0	0	0
Pruritus	54	52	12.65	0	0	0
Hematologic						
Platelet count decreased, thrombocytopenia	73	60	14.6	4	4	0.97
White blood cell count decreased (including neutropenia, leukopenia, neutrophil count decreased, lymphopenia)	89	52	12.65	13	11	2.68
Anaemia	35	32	7.79	0	0	0
Pulmonary						
Cough	42	37	9	0	0	0
Dyspnea	26	23	5.6	5	5	1.22
General						
Fatigue	48	46	11.19	2	2	0.49
Edema peripheral	32	29	7.06	0	0	0

PT	*All grades*			*Grade 3-4*		
	Events	*# of subjects*	*Proportion (%)*	*Events*	*# of subjects*	*Proportion (%)*
Asthenia	31	25	6.08	2	2	0.49
Musculoskeletal						
Back pain	36	36	8.76	0	0	0
Arthralgia	30	26	6.33	0	0	0
Musculoskeletal pain	24	23	5.6	1	1	0.24
Central Nervous System						
Headache	35	32	7.79	1	1	0.24
Infections						
Nasopharyngitis	26	24	5.84	0	0	0
Upper respiratory tract infection	25	23	5.6	0	0	0
Pneumonia (including bronchitis, pneumonia aspiration, pneumonia bacterial, bronchopneumonia, lower respiratory tract infection)	29	22	5.35	8	8	1.95
Urinary tract infection	27	21	5.11	0	0	0
Investigations						
Alanine aminotransferase increased	23	22	5.35	4	4	0.97
Aspartate aminotransferase increased	23	21	5.11	0	0	0
Ocular						
Dry eye	22	22	5.35	0	0	0

Table 39: AEs by SOC, AURA extension and AURA2. DCO date January 7, 2015.

SOC	*Events*	*Number of subjects*	*Proportion (%)*
Skin and subcutaneous tissue disorders	459	248	60.34
Gastrointestinal disorders	517	243	59.12
Infections and infestations	253	166	40.39
General disorders and administration site conditions	181	128	31.14
Respiratory, thoracic and mediastinal disorders	210	128	31.14
Musculoskeletal and connective tissue disorders	196	122	29.68
Investigations	215	108	26.28
Nervous system disorders	112	87	21.17
Metabolism and nutrition disorders	113	82	19.95
Blood and lymphatic system disorders	101	65	15.82
Eye disorders	80	64	15.57
Psychiatric disorders	36	34	8.27
Vascular disorders	32	30	7.3
Renal and urinary disorders	24	19	4.62
Cardiac disorders	21	16	3.89
Injury, poisoning and procedural complications	24	14	3.41
Reproductive system and breast disorders	10	10	2.43
Hepatobiliary disorders	7	6	1.46
Ear and labyrinth disorders	6	5	1.22
Neoplasms benign, malignant and unspecified (including cysts and polyps)	2	2	0.49
Immune system disorders	1	1	0.24

Analysis of the updated 90-day safety data showed the continuation of a similar pattern of toxicities as seen above, although most toxicities had increased in frequency compared to earlier data. Below is the updated toxicity data for AEs occurring to more than 10% of patients on osimertinib by the 90-day safety update.

Table 40: Updated AEs, AURA Extension and AURA2, >10% of population, DCO date May1, 2015

PT	*All grades*			*Grade 3-4*		
	Events	*# of subjects*	*Proportion (%)*	*Events*	*# of subjects*	*Proportion (%)*
Diarrhoea	263	174	42.34	4	4	0.97
Rash (grouped terms)	230	172	41.85	2	2	0.49
Dry skin (grouped terms)	127	146	35.5	0	0	0
Nail toxicity (grouped terms)	130	106	25.79	0	0	0
Nausea	81	69	16.79	2	2	0.49
Decreased appetite	74	65	15.82	4	3	0.73
Constipation	70	62	15.09	1	1	0.24
Cough	68	58	14.11	1	1	0.24
Fatigue	62	57	13.87	2	2	0.49
Pruritus	62	57	13.87	0	0	0
Back pain	56	52	12.65	3	3	0.73
Stomatitis	59	49	11.92	0	0	0
Platelet count decreased/ thrombocytopenia	93	68	16.54	6	6	1.46
WBC decreased (grouped terms)	118	63	15.33	21	13	3.16
Headache	49	42	10.22	1	1	0.24

Reviewer's comments: The overall profile of the TEAEs in this population is consistent with other drugs from this class. See below for an in-depth analysis the most common toxicities observed on osimertinib. The updated data did not show any new trends in AE incidences, but did show increasing overall toxicity rates which was thought to be expected given longer exposure times.

7.4.6. **Laboratory Findings**

Shifts in laboratory parameters were assessed via review of the ADLB JMP datasets which were provided for each of the phase 2 studies, AURA extension and AURA2. The sponsor provided pre-calculated shift parameters for each laboratory parameter compared to baseline, and these were analyzed by the reviewer to create the tables below.

Hematologic parameters-
Table 41 represents grade shifts in hematologic parameters occurring to patients while on study.

Table 41: Shifts in hematologic parameters in patients on-study, AURA extension and AURA2. DOC date January 9, 2015

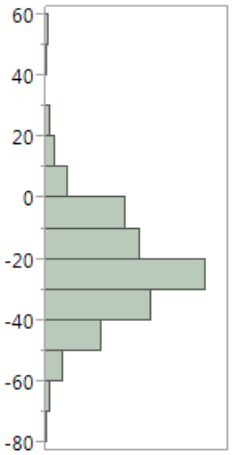
Parameter	Combined N = 411	
	All grade shifts (%)	*Grades 3-4(%)*
Hemoglobin	**38.2**	**0**
Neutrophils	**28.7**	**2.4**
Lymphocytes	**51.8**	**1.2**
Platelets	**48.4**	**0.7**

Platelets- osimertinib caused a grade shift decrease in platelet counts in almost half of the patients; this drop occurred almost immediately after starting osimertinib and was consistently decreased throughout the study; however, this mostly translated to mild decreases that were not of clinical significance.

Almost all patients dropped their platelet counts from baseline by their cycle 1, day 8 visit (Figure 3) with 76% of patients dropping their platelet count by >10% and the mean decrease in platelet value being 23%. Overall, there was a mean decrease in platelet values for all patients over the course of the scheduled study visits by 29% (Figure 4;
Figure **5**).

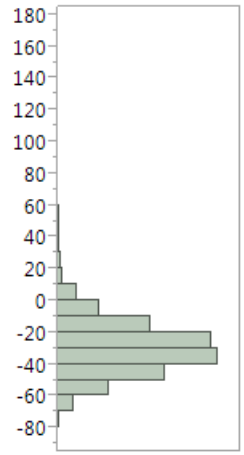
In terms of reported AEs related to a decrease in platelet count, 146 patients (35.5%) experienced grade 1 thrombocytopenia, 23 patients (5.6%) experienced grade 2 thrombocytopenia, 7 patients (1.7%) experienced grade 3 thrombocytopenia, and 1 experienced grade 4 thrombocytopenia. This occurred in a patient who had a CTCAE grade 1 platelet count at baseline; no supportive treatment was administered and no concurrent bleeding events were reported. There were three patients who required dose interruptions due to thrombocytopenia; one of those patients subsequently required dose reduction as well. As per the sponsor, only one patient required a platelet transfusion during the course of the study.

Figure 3: Cycle 1, day 8 platelet values compared to baseline, AURA extension and AURA2, DCO date January 9, 2015



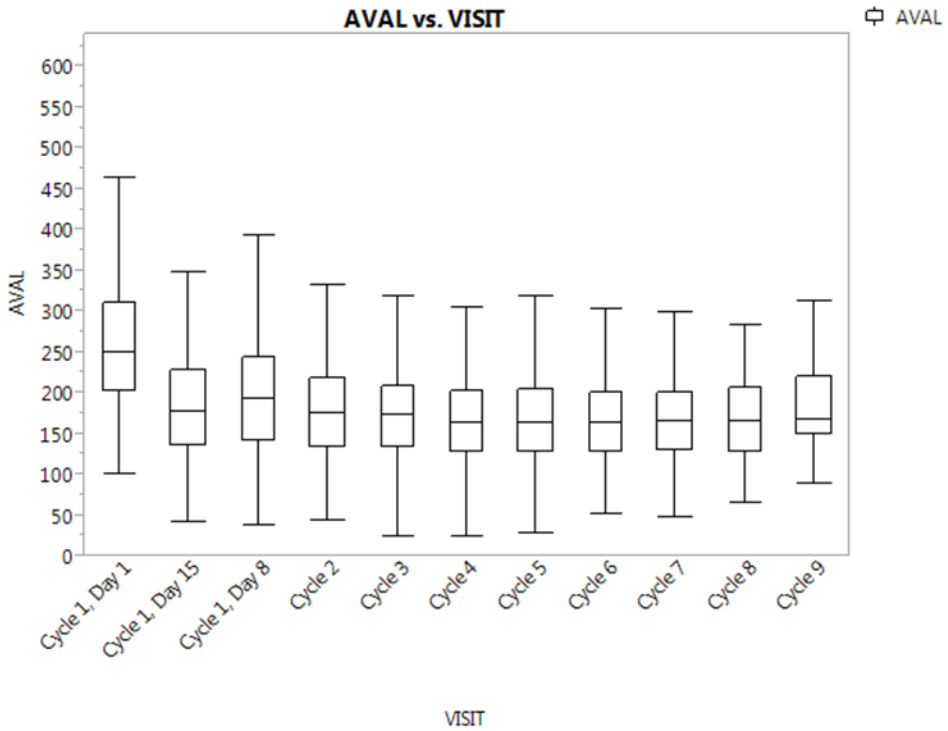
Mean	-23.12793
Std Dev	17.270636
Std Err Mean	0.8560737
Upper 95% Mean	-21.44504
Lower 95% Mean	-24.81082
N	407

Figure 4: Overall platelet values compared to baseline, AURA extension and AURA2, DCO date January 9, 2015



Mean	-29.1619
Std Dev	19.339299
Std Err Mean	0.3515074
Upper 95% Mean	-28.47269
Lower 95% Mean	-29.85112
N	3027

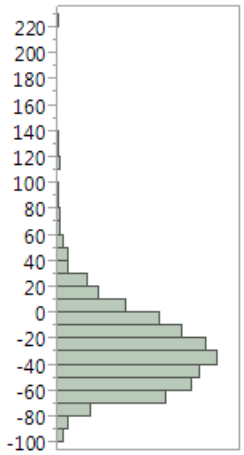
Figure 5: Box plot of platelet values over time, AURA extension and AURA2, DCO date January 9, 2015



Neutrophils- There was a decrease in overall neutrophil count that occurred to patients while on study, with a mean decrease of 28% over the course of the study in all patients (Figure 6, Figure 7). Overall, 120 patients experienced neutropenia of grades 1-3 during treatment. There were 16

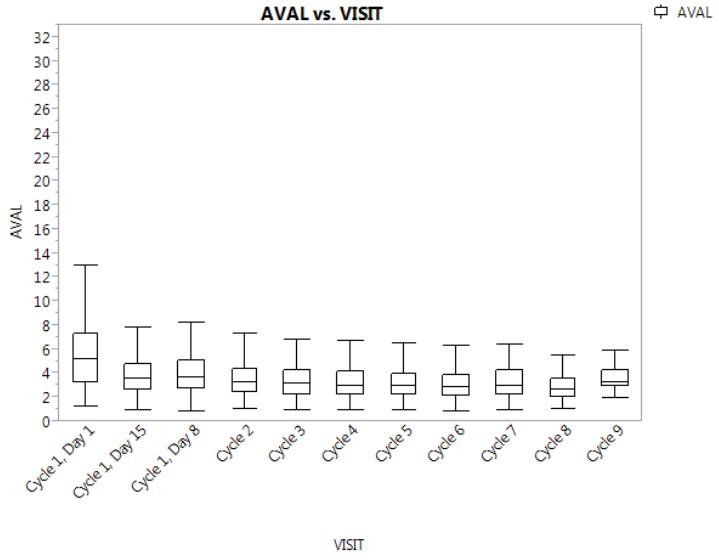
patients who experienced grade 2 neutropenia and two patients for whom an AE of grade 3 neutropenia was reported (0.5%). No patients required a dose reduction of osimertinib for neutropenia, although 8 patients required dose interruptions. Overall, none of these events were considered serious and there were no reported febrile neutropenia events.

Figure 6: Overall neutrophil counts compared to baseline, AURA extension and AURA2, DCO date January 9, 2015



Mean	-28.18335
Std Dev	31.397251
Std Err Mean	0.8373344
Upper 95% Mean	-26.54079
Lower 95% Mean	-29.82591
N	1406

Figure 7: Box plot of neutrophil count over time, AURA extension and AURA2, DCO date January 9, 2015



Other hematologic parameters dropped slightly overall in patients shortly after starting osimertinib, with slight decreases in hemoglobin, lymphocytes, and overall leukocyte counts seen starting at the first monitoring visit (cycle 1, day 15). These decreases generally tapered off soon afterwards and reached a steady state for the remainder of the study. There were three patients with SAEs of anemia while on study, and two patients who required osimertinib dose interruption or modification due to anemia.

Box plots of changes in other hematologic parameters over time on study are presented below (Figure 8; Figure 9).

Figure 8: Box plot of hemoglobin compared to time, AURA extension and AURA2, DCO date January 9, 2015

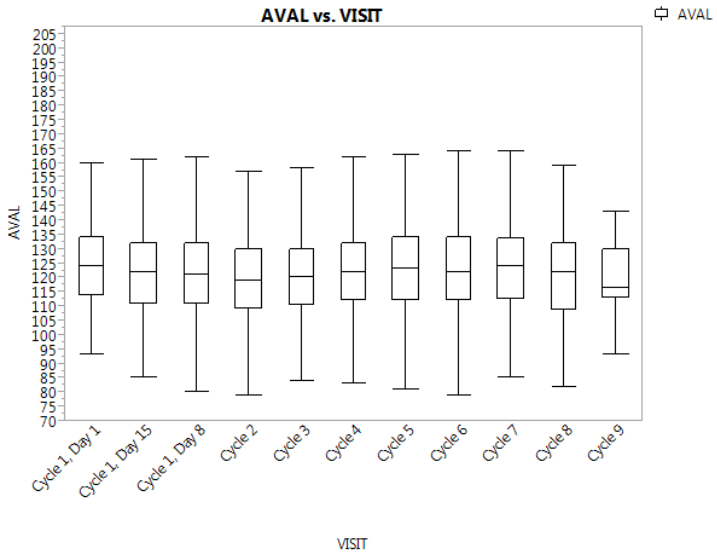
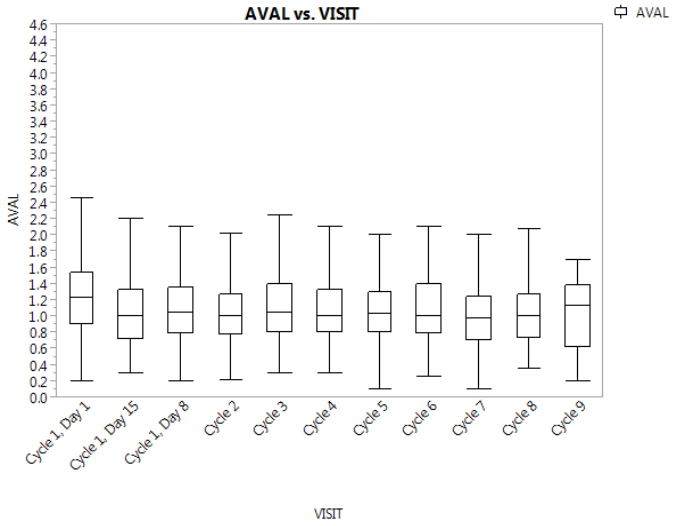


Figure 9: Box plot of lymphocyte values over time, AURA extension and AURA2, DCO date January date 9, 2015



Review of the 90-day safety update showed that patients continued to have decreases in their hematologic parameters on-study, with all grade shifts for platelets- 54%, neutrophils- 33%, hemoglobin- 44% and lymphocytes- 67%. However, none of these parameters were associated with grade shifts of 3-4 in >3% of patients.

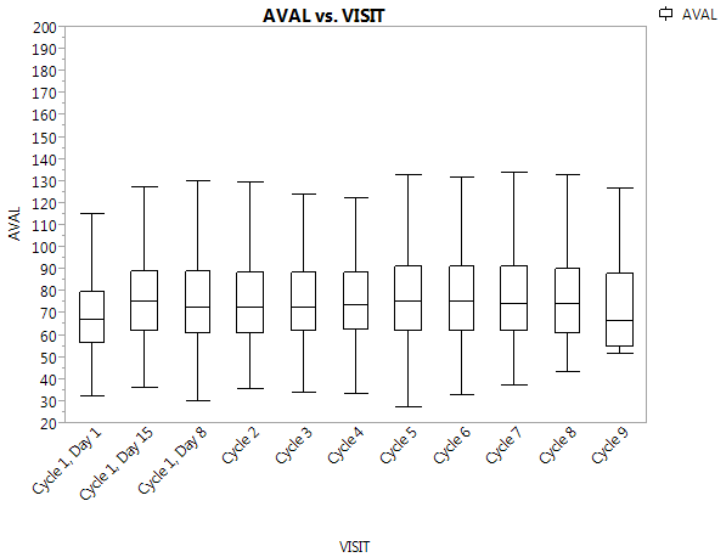
Reviewer's comments: Overall, while the majority of patients had at least one grade shift in a hematologic parameter on study, there were few high grade shifts and few AEs related to decreased hematologic parameters.

Box plots of overall hematologic data showed a levelling of hematologic parameters over time, which suggests no major expected decreases in hematologic parameters with increasing osimertinib exposure, and review of the 90-day safety database confirms that there were no unexpectedly high rates of grade 3-4 grade shifts in hematologic parameters.

Other laboratory values including renal and liver function tests-

Patients experienced minor grade shifts in other laboratory parameters while on study, although this only happened to a small percentage of patients and these events were rarely of clinical significance (Table 42). Creatinine increased slightly in patients immediately after starting osimertinib (**Error! Reference source not found.**). As per the sponsor, 92.8% of patients experienced increases in measured creatinine while on study, but this led to creatinine values that were both increased from baseline AND above the upper limit of normal in only 8% of patients. Calculations done by the reviewer confirmed the above observation.

Figure 10: Box plot of creatinine values, AURA extension and AURA2. DCO date January 9, 2015



Osimertinib did not significantly affect bilirubin and other LFTs, and there were no osimertinib discontinuations or SAEs due to LFT abnormalities, although there were 4 patients who had osimertinib interruptions for AST/ALT elevations.

Table 42: Grade shifts in laboratory values during study, AURA extension and AURA2, DCO date January 9, 2015

Parameter	Combined N = 411	
	All grade shifts (%)	**Grades 3-4(%)**
Creatinine	**8**	**0**
Bilirubin	**6.6**	**0.2**
AST	**12.2**	**0**
ALT	**12.2**	**0.5**

Otherwise, review of the laboratory data provided by the sponsor for the study and review of the adverse events spreadsheets revealed no other concerning trends in laboratory values in patients treated with osimertinib.

Reviewer's comment: Although there were consistent grade shifts in hematologic parameters observed almost immediately after starting osimertinib in almost half of the patients for some parameters (platelets, lymphocytes), and in approximately a third of the patients for others (neutrophils, hemoglobin), this did not translate to an increased occurrence of clinically meaningful AEs. A drop in hematologic parameters is therefore an expected occurrence for patients treated with osimertinib, and practitioners should be aware of this fact, but this does not seem to affect the safety profile of the investigational product negatively. Grade shifts in creatinine and LFTs were seen in a small minority of patients and were not clinically significant.

7.4.7. **Vital Signs**

As per the sponsor, there were no unexpected changes or clinically relevant trends in vital signs or physical examination safety parameters evident and there were no dose dependent changes in vital signs (phase 1) or clinically significant differences between the phase 2 studies. Blood pressure (both systolic and diastolic) did not change over treatment with mean and median values over time remaining consistent and similar. Pulse rate was unaltered throughout study treatment. Weight was unchanged throughout the treatment.

Review of treatment-emergent adverse events revealed 4 events each of hypertension and hypotension, 5 events of tachycardia, and one patient with tachypnea. Only one of these events was attributed by investigator to osimertinib; this was a hypertensive episode of grade 2 that led to dose interruption in a patient but resolved within 7 days. There were no other events related to abnormalities in vital signs such as bradypnea or bradycardia.

7.4.8. **Electrocardiograms (ECGs)**

ECGs were performed at the following times on-study for AURA extension patients (source: AURA phase 1/2 protocol):

- Screening
- First dosing day (Day 1 Cycle 0 for Part A dose escalation, Day 1 Cycle 1 for Parts A and B expansion); pre-dose, 1, 2, 4, 6, 10 and 24 hours post-dose
- First day of multiple dosing, Day 1 Cycle 1 Part A dose escalation only; pre-dose, single ECG
- Presumed steady state, Day 8 Cycle 1; pre-dose, 1, 2, 4, 6, 10 and 24 hours post-dose
- On Day 1 of each subsequent Cycle; one assessment at any time during day
- On occurrence of any cardiac AE
- Discontinuation visit

Paper ECGs were reviewed by the investigator or designated physician and referred to a local

cardiologist if appropriate. All ECG data were collected digitally and were transferred electronically for central analysis. Heart rate, PR, R-R, QRS and QT intervals were determined and reviewed by an external cardiologist.

AURA2 patients had a similar schedule of ECGs (see appendix 12.3 for study assessment schedule table). Additionally, ECGs with PK measurements were done at the following time points;

Digital ECG recording requirements

			Time relative to dose	**Screening (baseline)**
Cycle 1 Day 1	**Cycle 2 Day 1**	**Cycle 3 Day 1**		
Pre-dose (±5 min)	X[1]	X	X	X
1 hour (±5 min)	X	X		X
2 hours (±10 min)	X	X		X
4 hours (±10 min)	X	X		X
6 hours (±10 min)	X	X		X
8 hours (±10 min)	X	X		X
10 hours (±10 min)	X			X
12 hours (±1 hour)	X			X
24 hours (±1 hour)	X			X (D2, pre-dose)

1 Since there is no dosing at Screening, ECG recordings should start at a time that would be consistent with planned dosing times at Cycle 1 Day 1, Cycle 2 Day 1 and Cycle 3 Day 1 (for baseline purposes).

7.4.9. **QT**

The formal IRT recommendation for QT studies for osimertinib is summarized as follows:

A large change in QTc (i.e., >20 ms) was not detected in this trial following single dose or multiple doses of osimertinib. Significant QT prolongation at steady-state was observed with the maximum mean change from baseline (with the upper bound of the two-sided 90% CI) in QTcF of 16.2 (17.6) ms. A pharmacokinetic/ pharmacodynamic analysis suggested a concentration-dependent QTc interval prolongation at 80 mg of 14 ms with an upper bound of 16 ms (90% CI).

In this phase 2, open-label, single-arm study, 210 patients with locally advanced/metastatic non small cell lung cancer received osimertinib 80 mg. Overall summary of findings is presented in Table 43.

Table 43: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for osimertinib 80 mg (FDA QT-IRT Analysis)

Treatment	Day	Time (hour)	ΔQTcF (ms)	90% CI (ms)
osimertinib 80 mg	Cycle 1 Day 1 (Single Dose)	2	2.1	(0.8, 3.3)
osimertinib 80 mg	Cycle 3 Day 1	0	16.2	(14.8, 17.6)

The dose tested in the trial, which represents the anticipated therapeutic dose, is reasonable for the QT evaluation.

The proposed labelling related to QT is as follows;

Section 5: WARNINGS AND PRECAUTIONS:

5.2 QT Interval Prolongation

(b) (4) Of the 411 patients in Study 1 and Study 2, one patient (b) (4) was found to have a QTc greater than 500 msec, and (b) (4) patients (b) (4) had an increase from baseline QTc greater than 60 msec. [see (b) (4) Clinical Pharmacology (12.2)].

In Study 1 and 2, patients with baseline QTc of 470 msec or greater were excluded. (b) (4) congestive heart failure, electrolyte abnormalities, or those who are taking medications known to prolong the QTc interval with monthly ECGs and electrolytes. (b) (4) Permanently discontinue TAGRISSO in patients who develop (b) (4) signs/symptoms of (b) (4) arrhythmia [see Dosage and Administration (2.4)].

Section 12.2 CLINICAL PHARMACOLOGY:

12.2 Pharmacodynamics
Cardiac Electrophysiology

The QT interval prolongation potential of osimertinib was assessed in 210 patients who received TAGRISSO 80 mg daily in Study 2. A central tendency analysis of the QTcF data at steady-state demonstrated that the maximum mean change from baseline was 16.2 (upper bound of two-sided 90% confidence interval (CI) 17.6) msec. A pharmacokinetic/pharmacodynamic analysis in Study 2 suggested a concentration-dependent QTc interval prolongation of 14 msec (upper bound of two-sided 90% CI: 16 msec) at a dose of osimertinib 80 mg.

7.4.10. **Immunogenicity**

There were no relevant immunogenicity issues identified related to osimertinib.

7.5. Analysis of Submission-Specific Safety Issues

A number of adverse events of special interest were prospectively identified by the sponsor based on preclinical data, emerging safety data from clinical trials, and known class effects of EGFR TKIs. The general categories identified were skin effects, diarrhea, upper GI inflammation, interstitial lung disease (ILD)/pneumonitis, nail effects, ocular effects, and cardiac effects (including QT and cardiac contractility). These toxicities were in fact the most clinically relevant toxicities seen during safety review of osimertinib, with ILD being a cause of the only deaths related to osimertinib, and with diarrhea, skin, and nail effects being the most common toxicities, each affecting >20% of patients on-study.

Additionally, the AE of CVA was explored further as a submission-specific safety concern due to the fact that CVAs were responsible for 4 drug discontinuations due to AEs, which was second only to ILD as a cause of drug discontinuation.

7.5.1. **Interstitial lung disease (ILD).**

While a relatively uncommon toxicity seen in patients on osimertinib, ILD was cause of all osimertinib-related deaths. This is not unexpected; fatal cases of ILD have been reported in all other trials of small molecule TKIs in non-small cell lung cancer (NSCLC). Consequently, ILD/pneumonitis appears in the Warnings and Precautions section of labels for all other approved TKIs in NSCLC, of which there are five. Table 44 is a comparison of the rates of occurrence of ILD/pneumonitis using numbers reported on FDA labels for each approved TKI in NSCLC. Please interpret cross TKI comparisons with great caution.

Table 44: ILD/pneumonitis in FDA-approved TKIs in NSCLC

Drug	Receptor target	Rate of ILD	Fatal events	Warning and Precautions?	Comments
Erlotinib	**EGFR**	**1.1% in approximately 32,000 patients from all studies, including combination studies**	**Yes**	**Yes**	**Median onset at 39 days (range 5 days->9 months)**
Afatinib	**EGFR**	**1.5% of 3865 patients overall**	**Yes; 0.4%**	**Yes**	**Appeared to be higher in patients of Asian ethnicity (2.1%) compared to non-Asians (1.2%)**
Gefitinib	**EGFR**	**1%**	**Yes; approx. 1/3 of cases**	**Yes**	
Crizotinib	**ALK**	**1.6% (4 in 255)**	**Yes**	**Yes (as pneumonitis)**	**All cases occurred within 2 months of treatment initiation**
Ceritinib	**ALK**	**4% (out of 255 patients)**	**Yes, in one patient- 0.4%**	**Yes**	

Because of the importance placed on this potential toxicity, the protocols for studies in which osimertinib is used have instructions for investigators to facilitate prompt recognition and

appropriate management of possible ILD cases. The sponsor provided data on all ILD cases that occurred across the osimertinib clinical development program up to a DCO date of April 7, 2015 despite the fact that the major safety databases were compiled with a DCO date of January 9, 2015.

Up to the initial DCO date of January 9, 2015, a total of 21 patients developed ILD on osimertinib; 12 in the aggregate phase 1 cohorts, 5 in AURA extension, and 4 in AURA2.

The later DCO date of April 7, 2015 added an additional 10 cases of ILD to the total, bringing the number of patients who developed ILD to 31 out of 1185 patients dosed with osimertinib across the clinical development program (excluding healthy volunteers). Thus, an overall rate of ILD of **2.6% across the broader clinical development program** has been reported to date, which is approximately twice the rate of ILD/pneumonitis reported with other EGFR TKIs used in lung cancer (Table 44).

The phase 2 experience is as follows; in review of the original AURA extension and AURA2 patient databases (DCO date of January 9, 2015), there were 9 patients (2.2%) with the following reported AEs; 5 ILD and 4 pneumonitis. An additional 2 patients developed events that occurred by the April 7, 2015 DCO, for an **overall rate of 2.7%** (Table 45). The mean age of affected patients was 63 years. All of these events were thought to be related to osimertinib by the investigator and in all but one case osimertinib was withdrawn; one patient had osimertinib interrupted only. Overall, three of these events were fatal, and four more did not resolve. An additional event was categorized by the investigator as an ongoing grade 4 toxicity but was thought by the FDA reviewer to have been a contributing factor in the patient's death. The patient had significant radiographic worsening of ongoing ground-glass opacities that had originally contributed to the ILD diagnosis, with an eventual death due to hypoxia as well as worsening disease. Four patients recovered from the ILD/pneumonitis events after stopping therapy. There was little predictability about the onset of ILD events; they occurred at a median of 105 days from osimertinib initiation, with a large range (17-229 days). The ILD events that led to death occurred at days 47, 59, 204 and 229 of study treatment.

Table 45: ILD/pneumonitis events, AURA extension and AURA2, DCO date April 7, 2015

Patient ID	Age	Sex	Race	Toxicity grade	Study day	Outcome
D5160C0001C/E4311704	**66**	**F**	**ASIAN**	**5**	**47**	**Fatal**
D5160C0001C/E4311707	**66**	**M**	**ASIAN**	**1**	**85**	**Recovered**
D5160C0001C/E6002703	**60**	**F**	**ASIAN**	**1**	**163**	**Recovered**
D5160C0001C/E7003704	**66**	**F**	**WHITE**	**3**	**40**	**Recovered**
D5160C0001C/E7800701	**67**	**M**	**WHITE**	**3**	**148**	**Ongoing**
D5160C00002/E4104202	**63**	**F**	**WHITE**	**5**	**59**	**Fatal**
D5160C00002/E4303210	**84**	**F**	**ASIAN**	**3**	**17**	**Recovered**
D5160C00002/E4304202	**39**	**M**	**ASIAN**	**1**	**79**	**Recovering**
D5160C00002/E6001209	**66**	**F**	**ASIAN**	**1**	**83**	**Recovered**
D5160C0001C/E4310701	**57**	**F**	**ASIAN**	**5**	**229**	**Fatal**
D5160C0001C/E7800707	**60**	**M**	**WHITE**	**4**	**204**	**Ongoing/fatal**

The phase 1 experience is as follows; a total of twelve cases of ILD or pneumonitis were reported prior to the initial DCO date of December 2, 2014. An additional 4 cases were added by the sponsor that had occurred up to the amended DCO of April 7, 2015 for ILD events. These are summarized below in
Table **46**. The mean age of patients who developed ILD during treatment was 64.7 years. These events also occurred in a potentially unpredictable manner, at a mean of day 62 of therapy (range 14-240). None of the events in the AURA 1 cohorts had a fatal outcome, although in there was one case where the FDA reviewer thought that the grade 3 pneumonitis developed by a patient was a possible contributing factor in his death.

Table 46: ILD/pneumonitis events, AURA phase 1 cohorts, DCO date April 7, 2015

Patient ID	Arm	Age	Sex	Race	Toxicity grade	Study day	Outcome
E2301001	**80 mg QD capsule**	**52**	**F**	**OTHER**	**2**	**240**	**RECOVERED/RESOLVED**
E7801003	**80 mg QD tablet**	**74**	**M**	**WHITE**	**2**	**19**	**RECOVERING/RESOLVING**
E2301506	**T790M +ve 160 mg**	**60**	**F**	**WHITE**	**4**	**40**	**RECOVERED/RESOLVED**
E4301506	**1st line 80 mg**	**66**	**M**	**ASIAN**	**2**	**63**	**NOT RECOVERED/NOT RESOLVED**
E4301507	**1st line 80 mg**	**71**	**F**	**ASIAN**	**2**	**14**	**RECOVERED/RESOLVED**
E4301513	**T790M -ve 80 mg**	**64**	**M**	**ASIAN**	**3**	**50**	**NOT RECOVERED/NOT RESOLVED**
E4302513	**Paired biopsy 160 mg**	**67**	**F**	**ASIAN**	**1**	**43**	**NOT RECOVERED/NOT RESOLVED**
E6002520	**T790M +ve 80 mg**	**64**	**F**	**ASIAN**	**3**	**54**	**RECOVERING/RESOLVING**
E7001504	**T790M -ve 160 mg**	**81**	**M**	**WHITE**	**2**	**42**	**RECOVERED/RESOLVED**
E7003503	**T790M +ve 160 mg**	**76**	**F**	**WHITE**	**3**	**27**	**RECOVERED/RESOLVED**
E7402512	**T790M +ve 160 mg**	**57**	**F**	**ASIAN**	**3**	**85**	**RECOVERED/RESOLVED**
E7800519	**1st line 80 mg**	**49**	**F**	**WHITE**	**1**	**43**	**NOT RECOVERED/NOT RESOLVED**
E4302516	**80 mg QD capsule**	**61**	**M**	**ASIAN**	**1**	**84**	**NOT RECOVERED/NOT RESOLVED**
E4313501	**80 mg QD capsule**	**46**	**F**	**ASIAN**	**3**	**130**	**RECOVERING/RESOLVING**
E4313504	**80 mg QD capsule**	**67**	**F**	**ASIAN**	**3**	**42**	**NOT RECOVERED/NOT RESOLVED**
E4313506	**80 mg QD capsule**	**80**	**F**	**ASIAN**	**3**	**21**	**RECOVERING/RESOLVING**

An additional four events of ILD were included by the sponsor that occurred in other studies across the osimertinib clinical development program. These are summarized below (Table 47). None of these events were fatal.

Table 47: Additional ILD cases across clinical trials, DCO date April 7, 2015

Patient ID	Arm	Age	Sex	Race	Toxicity grade	Study day	Outcome
D5160C00006 / E4301001	**Phase I Tatton study 80 mg capsule + MEDI4736**	**77**	**F**	**Asian**	**2**	**23**	**Recovered/resolved**
D5160C00006 / E6002003	**Phase I Tatton study 80 mg capsule + MEDI4736**	**46**	**F**	**Asian**	**3**	**69**	**Ongoing**
D5160C00006 / E6002006	**Phase I Tatton study 80 mg capsule + MEDI4736**	**51**	**F**	**Asian**	**2**	**84**	**Ongoing**
D5160C00012 / E6003203	**osimertinib 80 mg tablet**	**45**	**F**	**Asian**	**2**	**14**	**Recovering**

Analysis of the above cases shows that over the entire clinical development program, mean age of patients who developed ILD/pneumonitis was 62.8 (range 39-82), and that these events occurred starting at a median day 54 (range 14-240). Of these events, 16 (52%) were classified as CTCAE grade 3 or higher; 68% were in Asians and 71% were in female patients.

Additionally, patient narratives were reviewed from SAEs of "pneumonia" that occurred in patients on AURA extension and AURA2 to ensure that they were consistent with diagnoses of infectious pneumonia, by documenting such details as fever and/or radiographic consolidation. There were no cases suspicious for ILD/pneumonitis identified.

Reviewer's comment: ILD and pneumonitis, while rare overall, occurred at rates comparable and even slightly higher than those reported with other EGFR TKIs in NSCLC. There were four deaths in the phase 2 cohorts that occurred in patients who developed ILD/pneumonitis. Review of CRFs for patients on-study showed that often, ILD is difficult to diagnose and occurs in the setting of overlapping lung infection and intraparenchymal progression of disease. The onset of ILD with osimertinib is not predictable in its timing, with events occurring both early and late in the course of therapy. Thus, vigilance about this toxicity is warranted by all practitioners prescribing osimertinib.

7.5.2. Other AEs of Special Interest

There were two other AEs of special interest pre-identified by the sponsor that were found to be the most common AEs to occur overall across AURA extension and AURA2. These were diarrhea and grouped rash events, occurring in 37.7% and 38.2% of patients, respectively, in the initial datasets. While they were common, they very rarely caused patients to develop more than grade 1 toxicity. Other AEs of special interest pre-identified by the Sponsor included nail events, upper GI effects, and ocular toxicity.

Diarrhea. Diarrhea was the most common adverse event occurring on study, with 210 documented AEs affecting 150 (37.7%) of patients. The median day for the development of

diarrhea was day 22. The AE was attributed by the investigator to osimertinib in 88% of cases. The vast majority of events were CTC AE grade 1, with only 7% and 2% of patients with diarrhea (n=11 and 3) developing grade 2 and 3 toxicity, respectively. Of those with diarrhea, 51% required treatment (n=77) and 71% of patients with diarrhea recovered from the AE (n=107). An additional 29% (n = 61) had ongoing diarrhea at the time of the initial DCO date.

There were 2 patients who required osimertinib interruption for diarrhea, and another patient who stopped osimertinib for this reason; the patient also experienced concurrent decreased appetite, asthenia, and vomiting. As per the sponsor, there were no events reported of GI perforation or hemorrhagic diarrhea. The 90-day safety update showed a slight increase in occurrence rate of diarrhea to 42% overall, with no increase in grade 3-4 toxicity.

Rash. The AE of rash was explored by combining the following PTs that were reported for patients on trial; Acne, Dermatitis acneiform, Folliculitis, Rash, Rash generalized, Rash macular, Rash maculo-papular, Rash papular, and Rash pustular. Rash of all grades occurred in 157 patients (38.2%). The median day for development of rash was on day 26 (range 1-175), and the median was on day 42. Almost all of these events were CTC AE grade 1, with only 5.1% and 0.7% of patients with rash (n=21 and 1) developing grade 2 and 3 toxicity, respectively. The AE of rash was attributable by investigator to investigational product in 88% of cases. In 57% of patients with rash (N = 91), the event was ongoing and did not resolve by the DCO date. Out of the 159 patients with rash, 82 (51.6%) required concomitant or additional treatment. There were 2 patients who required interruption of osimertinib rash, and another patient who stopped osimertinib for this reason; the patient had a maculo-papular rash affecting the foot with tenderness, pain, burning, and erythema, but no effect on activities of daily living.

As per the sponsor, there were no severe bullous, severe blistering, or severe exfoliative rash events, no events suggestive hypersensitivity reactions such as Stevens-Johnston Syndrome or Toxic Epidermal Necrolysis, and no events of phototoxicity.

The 90-day safety update showed a slight increase in occurrence rate of rash to 42% overall, with no significant increase in grade 3-4 toxicity.

Nail events. The AE of nail events was explored by including the PTs of; nail bed disorders, nail bed inflammation, nail bed tenderness, nail discoloration, nail disorder, nail dystrophy, nail infection, nail ridging, nail toxicity, onychalgia, onychoclasis, onycholysis, onychomadesis, paronychia. Overall, 106 events were reported in 92 patients across the phase 2 studies, 22.4% overall. None of these events were of grade 3 toxicity or was considered an SAE, and no patients discontinued AZZD9291 or had a dose modification due to nail effects.

Upper GI inflammation. There were 53 patients overall with 62 events that were classified under the higher level terms of oral soft tissue conditions, the most common of which was stomatitis (n = 42 events in 39 patients). There were 28 patients who had non-oral upper GI tract inflammation including dysphagia, epistaxis, gastric ulcer, gastritis, odynophagia, and oropharyngeal pain. In total, 71 patients (17%) had upper GI adverse events occurring on treatment. There were only 11 patients who experienced events of grade 2 toxicity, and no patients experienced events of CTCAE grade 3 or higher toxicity. No patient had their study

drug dosing altered or interrupted due to upper GI events. The median time to onset of first event of upper GI inflammatory AE was 43.0 days (range 2 to 155 days). Approximately half of these events (49%) required treatment.

Ocular effects. Ocular effects were pre-identified as an adverse event of special interest for the study due to preclinical effects seen in animals as well as data on ocular toxicity of other EGFR TKIs. Patients were required to undergo slit-lamp ocular examination upon enrollment and in cases of visual disturbances. When reviewing the safety database, there were 80 cases of eye toxicity reported in 64 patients, with an overall rate of 15.6%. The most common toxicity experienced was dry eye, which occurred in 22 patients (5.4%). None of these events were grade 3 or higher; 13 of these events were classified as CTCAE grade 2. There was no change in dosing of osimertinib due to ocular toxicity. There were three patients who experienced reduced visual acuity or blurry vision that was attributable by investigator to AZD 9291 and did not resolve; all of these were grade 1 events.

Review of the updated 90-day safety data revealed that one patient experienced a grade 3 ocular event of cataract. This was a 74-year old Asian woman, with worsening of existing cataract on day 155. She recovered from the event, which was not thought to be related to osimertinib, and the event did not cause dose interruption or modification. The overall rate of ocular toxicity had increased to 18%.

Cerebrovascular accidents (CVAs). There were eight central nervous system embolic and hemorrhagic events that occurred to patients in the combined phase 2 trials. One event was hemorrhagic in nature and was thought to be due to concomitant use of Lovenox. There was one fatal event that occurred on day 33 of study treatment to an 83-year old White patient. The median day when these events occurred was day 80 (range 17-150), and the median age of the patients was 72.5 (range 58-83). In four cases, patients were removed from study treatment because of the cerebrovascular event, but in only one case was the event thought to be attributable to osimertinib. CTCAE toxicity grading of these events were of grade 3 or higher in six cases.

Since CVA events were responsible for treatment discontinuations in more patients on osimertinib than any other toxicity other than ILD, the AURA 1 combined datasets were also explored for occurrences of CVAs to determine whether this was responsible for treatment discontinuations in the phase 1 cohorts as well. Although there were five events that occurred in patients on AURA 1, they were relatively minor in nature (four were CTCAE grade 1 and one was CTCAE grade 2) and none caused treatment discontinuation or dose interruption/ modification. None of the CVA events occurring on AURA 1 were attributed to osimertinib.

Review of the 90-day safety update revealed four additional CVA events in the combined phase 2 cohorts and one in a phase 1 patient. One of these CVA events, a hemorrhagic stroke in a patient with known progressive brain metastases, was fatal but not attributed by investigator to osimertinib.

Reviewer's comment: Although there seemed to be a possible safety signal with the increased number of treatment discontinuations due to CVAs, on final analysis the reviewer concluded

that these were likely related to underlying risk factors and comorbidities of the study population and were likely not related to an effect of osimertinib.

Cardiac contractility. There was concern based on preclinical data and known class effects of EGFR TKIs that cardiac contractility could potentially be adversely affected by osimertinib, and the patients were therefore monitored with echocardiograms at baseline and with cycles 4 and 9 of therapy. There was no clinically significant change in median LVEF in patients with ≥ 1 post-baseline echocardiograph assessment, based on data provided by the sponsor for the 90% of patients who completed at least one post-baseline echocardiogram. Overall, 11 patients had an LVEF decrease of ≥15 percentage points from baseline to an LVEF value ≥50%. Nine patients had LVEF decreases of ≥10 percentage points from baseline to an LVEF value <50%.

There was one CTCAE grade 5 event of cardiac congestive failure in a patient with pre-existing CHF on medical therapy. Additionally, there were three patients with AEs of ejection fraction decreased; 2 were CTCAE grade 3 events and one was a grade 2 event.

7.6. Specific Safety Studies/Clinical Trials

There were no additional specific safety studies or clinical trials conducted to evaluate specific safety concerns.

7.7. Additional Safety Explorations

7.7.1. Human Carcinogenicity or Tumor Development

There was no safety signal for human carcinogenicity identified for osimertinib.

7.7.2. Human Reproduction and Pregnancy

There were no exposures to osimertinib in pregnant and/or in lactating women.

7.7.3. Pediatrics and Assessment of Effects on Growth

Osimertinib is not intended for use in pediatric patients.

7.7.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

N/A

7.7.5. Demographic variations on safety effects.

Safety events were analyzed to see if there was an identifiable difference in the occurrence of TEAEs based on key demographic variables of age, race, and/or sex. The numbers presented for grade 3-4 events, SAEs, dose modifications, and deaths were obtained from the 90-day safety update, which had higher rates of adverse events in all categories.

The median age at which toxicity was likely to occur to patients on study was age 63. Overall, the occurrence of toxicities was similar by race and by sex. Patients aged 65 and older were

more likely than those under 65 to experience grade 3-4 AEs and were more likely to have dose modifications due to AEs. Interestingly, patients over the age of 65 had a similar rate of SAEs to those over 65, and were not more likely to die of an AE, although numbers of deaths overall were low.

One striking difference observed in analysis of toxicities and AEs in various demographic subgroups was the fact that Whites were twice as likely as Asians to experience SAEs while on therapy (27% vs. 13.4%). Analysis of this discrepancy revealed that there was a marked imbalance between the occurrence of CVAs and VTEs between the two groups, with 30 White patients (20%) experiencing these events overall compared to only 10 (4%) of Asians. This difference was observed on analysis of the updated phase 1 data as well, with an incidence of the combined events of CVA and VTE at 23 out of 127 enrolled White patients (18%) vs. 17 out of 228 enrolled Asian patients (7.5%).

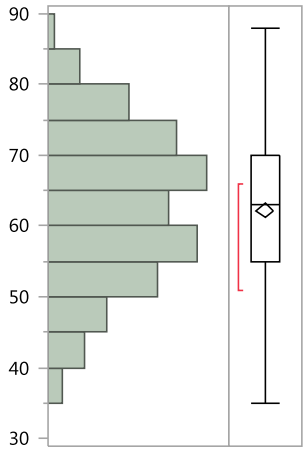
Reviewer's comment: Although there seemed to be a possible safety signal with the increased numbers of CVA and VTE-related events in Whites vs. Asians on AURA extension and AURA2, the reviewer concluded that in the absence of randomized data, this is unlikely due to an osimertinib effect and is likely due to underlying differences in baseline characteristics of patients on study and increased expected incidence of these events in White patients.

White patients were over twice as likely to die from AEs on study than were Asians (5.3% vs. 2%). There was no single cause of death that seemed to drive this effect.

Table 48: Toxicity incidence by demographics, combined AURA extension and AURA2, DCO date May 2, 2015

	All toxicity	Grade 3-4 AEs	SAEs	Dose modification due to AEs	Deaths due to AEs
Race					
Asian	98%	27.5%	13.4%	25.5%	2%
White	97%	29%	27%	22.5%	5.3%
Other (only 13 patients)	100%	23%	15%	15%	0%
Sex					
F	98%	26.5%	16.5%	24.7%	3.6%
M	96%	31%	22.7%	22.7%	2.6%
Age					
< 65	97%	25%	18.3%	21%	4%
≥ 65	98%	31.5%	18.7%	27.8%	2%

Figure 11: AE incidence by age, combined AURA Extension and AURA2, DCO date January 9, 2015.



Quantiles

100.0%	maximum	88
99.5%		87.02
97.5%		81.1
90.0%		76
75.0%	quartile	70
50.0%	median	63
25.0%	quartile	55
10.0%		48
2.5%		40
0.5%		35.98
0.0%	minimum	35

Summary Statistics

Mean	62.194937
Std Dev	10.709357
Std Err Mean	0.5388462
Upper 95% Mean	63.25431
Lower 95% Mean	61.135563
N	395

7.8. Safety in the Postmarket Setting

7.8.1. Safety Concerns Identified Through Postmarket Experience

There is no postmarket experience with osimertinib.

7.8.2. Expectations on Safety in the Postmarket Setting

As part of the agreed-upon PMRs, the Sponsor will provide the FDA with safety data from

AURA 3, a Phase 3, Open Label, Randomized Study of osimertinib versus Platinum- Based Doublet Chemotherapy for Patients with Locally Advanced or Metastatic Non-Small Cell Lung Cancer whose Disease has Progressed with Previous Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor Therapy and (b) (4) This study is expected to provide mature data in June 2018.

7.9. Additional Safety Issues From Other Disciplines

Please refer to section 11 for a list of PMRs related to clinical pharmacology requirements.

7.10. Integrated Assessment of Safety

The safety evaluation primarily focused on the two single-arm phase 2 studies, AURA extension (n = 201 patients) and AURA2 (n = 211 patients), with supportive data from AURA phase 1 cohorts used when applicable. The primary safety analysis safety was performed with the data submitted by the Sponsor with the initial NDA, with a DCO date of January 9, 2015.

The dose of osimertinib given to patients in the phase 2 cohorts was 80 mg daily. The median duration of exposure was 4.4 months. The study population characteristics were: median age 63 years, age <65 (54.4%), female (67.9%), White (35.7%), Asian (60.1%), ECOG PS 0 (37%), PS 1 (63%), brain metastasis (39%). All patients received at least 2 prior therapies for their lung cancer including an EGFR inhibitor as per protocol.

The most common adverse events (>10%, 90-day safety update data) were diarrhea (42%), rash (42%), dry skin (35.5%), nail toxicity (25%), nausea (17%), decreased appetite (16%), and constipation (15%). The majority of the above adverse events were grade 1-2.

The most common laboratory abnormalities (>10%) were decreased lymphocytes (51.8%), decreased platelets (48.4%), decreased hemoglobin (38.2%), and decreased neutrophils (28.7%). Grade 3-4 decreases in hematologic parameters were rare (<3%). Increases in ALT and AST occurred in 12.2% of patients, and fewer than 1% of patients experienced a grade 3-4 shift in either parameter. The most common nonfatal serious adverse events (SAEs) included pneumonia (1.2%), pulmonary embolus (1.2%), and pneumonitis (0.73).

Adverse events of interest likely to be a class effect of EGFR inhibitors include skin effects, diarrhea, upper GI inflammation, interstitial lung disease (ILD)/pneumonitis, nail effects, ocular effects, and cardiac effects (including QT and cardiac contractility). Adverse events of interest unique to osimertinib include CVAs and venous thromboembolic events, which affected 2.7% and 7.3% of patients on study, respectively, and were more likely to occur in White vs. Asian patients.

Dose modifications due to adverse events occurred in 13.9% of patients. The most common adverse events leading to dose reductions or interruptions included prolonged QT and decreased neutrophil count, each occurring in 1.5% of patients. Frequent adverse events that led to discontinuation included ILD/pneumonitis (2%), and cerebrovascular accident (1%).

Fatal adverse events in patients treated with osimertinib occurred in 2.5% of patients. Fatal adverse events with likely attribution to osimertinib included 4 cases of pneumonitis. Other fatal adverse events occurring to patients across the AURA phase 1 and phase 2 cohorts included CVA, multi-organ failure, PE, cardiomyopathy, and PEA arrest.

8 Advisory Committee Meeting and Other External Consultations

There was no advisory committee meeting and/or other external consultations for osimertinib because the safety profile is acceptable for the treatment of patients with EGFR T790M positive metastatic NSCLC who have progressed on EGFR TKI, the application did not raise significant public health questions on the role of osimertinib for this indication, and outside expertise was not necessary since there were no controversial issues that would benefit from an advisory committee discussion.

9 Labeling Recommendations

9.1. Prescribing Information

The following major labelling changes were proposed that differ from the label proposed by Astra-Zeneca;

Section 5 WARNINGS AND PRECAUTIONS

In section 5.1 on interstitial lung disease, the reviewer proposed to use updated numbers on ILD incidence obtained from the data submitted with the 90-day safety update. The final version of the text for the proposed ILD-related content in section 5.1, with updated incidence numbers, reads as follows; (b) (4)

Section 6 ADVERSE REACTIONS

In section 6.1, the proposed labelling was amended to include updated exposure data from the 90-day safety update. The section was also revised to more closely comply with the FDA's Guidance for Industry: Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products- Content and Format.

Adverse reaction incidence rates were updated to include 90-day safety update rates, and the following descriptive text was proposed for this section of the label; "In Studies 1 and 2, the most common adverse reactions (all grades) observed in TAGRISSO-treated patients (>20% all grades) were rash and diarrhea (42%), dry skin (b) (4), nail toxicity (b) (4) Dose reductions occurred in 4.4% of patients treated with TAGRISSO. The most frequent adverse reactions that led to dose reductions or interruptions were: electrocardiogram QT prolonged (2.2%) and neutropenia(1.9%). Serious adverse drug reactions reported in (b) (4) or more of patients were pneumonia, pulmonary embolism, (b) (4) (b) (4) . (b) (4) The most frequent adverse (b) (4) reactions that led to discontinuation were ILD/pneumonitis and cerebrovascular (b) (4)

Table 2, which is an overall table of treatment-emergent adverse events, was updated to include 90-day safety update data and also to include any adverse reactions occurring in >10% of patients for all NCI CTCAE Grades and >2% for Grades 3-4. Table 3, which is a table of laboratory abnormalities occurring to (b) (4) of patients on study, was updated to include 90-day safety update data, (b) (4)

Section 8 USE IN SPECIFIC POPULATIONS

In section 8.5, geriatric use, the higher incidence of Grade 3 and 4 adverse reactions (32% versus 25%) and more frequent dose modification for adverse reactions (b) (4) versus (b) (4)) in patients 65 years or older as compared to those younger than 65 was contrasted with the fact that there was no increase in the incidence of SAEs or in the incidence of deaths due to AEs observed in

patients 65 years or older.

Please refer to the above section 7.2 of this review on QT for labelling recommendations regarding QT effects in sections 5.2 and 12.2 of the osimertinib label.

9.2. Patient Labeling

N/A

9.3. Non-Prescription Labeling

N/A

10 Risk Evaluation and Mitigation Strategies (REMS)

There were no REMS proposed for osimertinib.

10.1. Safety Issue(s) that Warrant Consideration of a REMS

N/A

10.2. Conditions of Use to Address Safety Issue(s)

N/A

10.3. Recommendations on REMSThere is no REMS necessary for osimertinib.

11 Postmarketing Requirements and Commitment

The reports shown below will be provided as postmarketing requirements:

	Study/Data Update	Title	Submission Date
Clinical Pharmacology PMRs under 505(o)			
1	Drug-Drug Interaction - Impact of CYP3A4 Inhibitor (Study D5160C00012) Clinical Study Report	(b) (4) to Assess the Effect of (b) (4) (a CYP3A4 Inhibitor) on the Pharmacokinetics of (b) (4) of osimertinib (b) (4)	Final Report: April 2016

2	Drug-Drug Interaction - Impact on CYP3A4 Inducer (Study D5160C00013) Clinical Study Report	(b) (4) to Assess the Effect of (b) (4) (a CYP3A4 Inducer) on the Pharmacokinetics of osimertinib (b) (4)	Final Report: April 2016
3	Drug-Drug Interaction - Impact on CYP3A4 Substrate (Study D5160C00014) Clinical Study Report	(b) (4) to Assess the Effect of osimertinib on the Pharmacokinetics of (b) (4) CYP3A4 Substrate) (b) (4)	Final Report: April 2016
4	Drug-Drug Interaction - Impact on BCRP Substrate (Study D5160C00019) Clinical Study Report	(b) (4) to Assess the Effect of osimertinib on the Pharmacokinetics of (b) (4) BCRP Substrate) (b) (4)	Final Report: April 2016
5	Hepatic Impairment (Study D5160C00008) Clinical Study Report	(b) (4)	Final Report: November 2018
Accelerated Approval PMR under Subpart H			
1	AURA 3 (Study D5160C00003) Clinical Study Report	Phase 3, Open Label, Randomized Study of osimertinib versus Platinum- Based Doublet Chemotherapy for Patients with Locally Advanced or Metastatic Non-Small Cell Lung Cancer whose Disease has Progressed with Previous Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor Therapy and (b) (4)	Final Report: June 2018

12 Appendices

12.1. References

Please refer to end of this review.

12.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): AURA extention and AURA2

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 390		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): None		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 5		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 3 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 2		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

12.3. Study schedule of assessments

AURA extension (source: Clinical Study Report, AURA Phase 1/2 Trial):

Table 49 Study plan

	Screening	**Multiple Dose/Cycle 1 (21-day cycle)**			**Cycles 2 to 6 (21-day cycle)**	**Cycle 7 and every 6 weeks onwards**	**Discontin -uation**	**28-day follow -up**	**Progression**	**Post-progression survival F/U**	**Detail in CSP section**
Day	**–28 to –1**	**D1**	**D8**	**D15**	**D1**	**D1**				**6 weekly relative to progression**	
Informed consent	X										4
Demography/ baseline characteristics	X										6.3.1
Medical/ surgical history	X										6.3.1
Inclusion/ exclusion criteria	X										4
Physical examination	X	X			X	X	X				6.3.2
WHO performance status	X	X			X	X	X				6.3.2
Ophthalmologic assessment	X										6.3.6
Symptoms/ HRQoL questionnaires	X	X			Every 6 weeks (relative to first dose) until progression		X		X		6.5

Table 49 Study plan

	Screening	**Multiple Dose/Cycle 1 (21-day cycle)**			**Cycles 2 to 6 (21-day cycle)**	**Cycle 7 and every 6 weeks onwards**	**Discontin -uation**	**28-day follow -up**	**Progression**	**Post-progression survival F/U**	**Detail in CSP section**
Day	**–28 to –1**	**D1**	**D8**	**D15**	**D1**	**D1**				**6 weekly relative to progression**	
Pregnancy test (pre-menopausal females only)	X										6.3.5
EGFR T790M mutation status tumour sample (mandatory)	X										6.8.1.1
Archival tumour tissue	X										6.8.1.1
Tumour biopsy (optional)	X			X[a]			X[b]		X[b]		6.8.1.1
Vital signs	X	X	X	X	X	X	X				6.3.3
Height	X										6.3.3
Weight	X	X			X	X	X				6.3.3
Clinical chemistry/ haematology/ urinalysis	X	X	X	X	X	X	X				6.3.5
dECG	X	X	X	X	X	X	X				6.3.4
Echocardiogram /MUGA	X	12 weekly relative to first dose ⟷									6.3.7

Table 49 Study plan

	Screening	**Multiple Dose/Cycle 1 (21-day cycle)**			**Cycles 2 to 6 (21-day cycle)**	**Cycle 7 and every 6 weeks onwards**	**Discontin -uation**	**28-day follow -up**	**Progression**	**Post-progression survival F/U**	**Detail in CSP section**
Day	**–28 to –1**	**D1**	**D8**	**D15**	**D1**	**D1**				**6 weekly relative to progression**	
PK blood sample (including metabolites)		X	X	X	X (Cycle 2 only)						6.6.1
Blood sample for ctDNA	X	X			6 weekly at RECIST visit				X		6.8.1.2
Genetic consent and blood sample (optional)	X										6.8.2
CSF (optional)					X (once only)						6.8.3
RECIST assessments	X	Every 6 weeks (relative to first dose) until progression)									6.10.1
Cognitive patient interview (optional)					4 to 6weeks + 4 to 6 months						6.5.3
Dispense study drug		X			X	X					5
Dose with osimertinib		Daily dosing									5

Table 49 Study plan

	Screening	**Multiple Dose/Cycle 1 (21-day cycle)**			**Cycles 2 to 6 (21-day cycle)**	**Cycle 7 and every 6 weeks onwards**	**Discontin -uation**	**28-day follow -up**	**Progression**	**Post-progression survival F/U**	**Detail in CSP section**
Day	**–28 to –1**	**D1**	**D8**	**D15**	**D1**	**D1**				**6 weekly relative to progression**	
Concomitant medication	◄———	———	———	———	———	———	———	———	———	———►	4.3.1
Adverse events	◄———	———	———	———	———	———	———	———	———►		6.4
Survival										X	6.3.8

AURA phase 2 (source: Clinical Study Report, AURA Phase 2 Trial):

Table 50 Study plan

Visit	**Screening**	**Treatment period (further treatment cycles as per Cycle 7)**								**Follow-up period**			**Detail in CSP section:**
	1	**2**	**3**	**4**	**5**	**6**	**7-9**	**10+**	**Treatment discontinuation**	**28-day follow-up**	**Progression follow-up**	**Survival follow-up**	
Cycle[a]/Day		**C1 D1**	**C1 D8**	**C1 D15**	**C2 D1**	**C3 D1**	**C4-6 D1**	**C7[b]+ D1**	**NA**	**NA**	**NA**	**NA**	
Day	**-28 to -1**	**1**	**8**	**15**	**22**	**43**	**64 to 106**	**127+**	**NA**	**NA**	**NA**	**NA**	

Window (days)	**NA**	**0**	**±2**	**±2**	**±7**	**±7**	**±7**	**±7**	**NA**	**±7**	**±7**	**±7**	
Informed consent[c]	X												3.3 and 4.1
Submit mandatory tumour tissue sample for mutation analysis[d]	X												4.1 and 5.6
Submit tumour tissue for diagnostic development (optional)[e]	X												4.1, 5.6 and 5.6.3.2
Optional tumour biopsy for exploratory research									X				5.6
Archival tumour tissue[f]	X												5.6
Demography and baseline	X												4.1
Medical/surgical history	X												4.1
Inclusion/exclusion criteria	X												3
Physical examination, including weight	X	X[g]			X	X	X	X	X				5.2.3 and 5.2.6.2
Height	X												5.2.6.2
WHO performance status	X	X			X	X	X	X	X				4.1

Table 50 Study plan

Visit	**Screening**	**Treatment period (further treatment cycles as per Cycle 7)**								**Follow-up period**			**Detail in CSP section:**
	1	**2**	**3**	**4**	**5**	**6**	**7-9**	**10+**	**Treatment discontinuation**	**28-day follow-up**	**Progression follow-up**	**Survival follow-up**	
Cycle[a]/Day		**C1 D1**	**C1 D8**	**C1 D15**	**C2 D1**	**C3 D1**	**C4-6 D1**	**C7[b]+ D1**	**NA**	**NA**	**NA**	**NA**	
Day	**-28 to -1**	**1**	**8**	**15**	**22**	**43**	**64 to 106**	**127+**	**NA**	**NA**	**NA**	**NA**	
Window (days)	**NA**	**0**	**±2**	**±2**	**±7**	**±7**	**±7**	**±7**	**NA**	**±7**	**±7**	**±7**	
Pregnancy test (pre-menaopausal females only)	X												5.2.1
Ophthalmolgic assessment	X	← as clinically indicated →											5.2.7.1
Vital signs[g]	X	X	X	X	X	X	X	X	X				5.2.6
Clinical chemistry/ haematology/ urinalysis[g]	X[h]	X	X	X	X	X	X	X	X				5.2.1
Digital ECG	X	X	X[g]	X[g]	X[g]	X	X	X	X				5.2.4
Echocardiogram/ MUGA	X		← every 12 weeks relative to first dose →										5.2.5
PK blood sample (including metabolites)		X			X	X							5.4

Table 50 Study plan

Visit	**Screening**	**Treatment period (further treatment cycles as per Cycle 7)**								**Follow-up period**			**Detail in CSP section:**
	1	**2**	**3**	**4**	**5**	**6**	**7-9**	**10+**	**Treatment discontinuation**	**28-day follow-up**	**Progression follow-up**	**Survival follow-up**	
Cycle[a]/Day		**C1 D1**	**C1 D8**	**C1 D15**	**C2 D1**	**C3 D1**	**C4-6 D1**	**C7[b]+ D1**	**NA**	**NA**	**NA**	**NA**	
Day	**-28 to -1**	**1**	**8**	**15**	**22**	**43**	**64 to 106**	**127+**	**NA**	**NA**	**NA**	**NA**	
Window (days)	**NA**	**0**	**±2**	**±2**	**±7**	**±7**	**±7**	**±7**	**NA**	**±7**	**±7**	**±7**	
Plasma sample for ctDNA[g]	X[i]	X	X	X	X	X	X	every 6 weeks in line with RECIST 1.1 assessments[j]					4.3.3 and 5.6.2
Optional genetic consent and sample	X[k]												5.5
Optional CSF sample					X (once only)[l]								5.4.2
Tumour assessments (RECIST 1.1)[m]	X	every 6 weeks relative to first dose until disease progression											4.2 and 5.1.1
EORTC QLQ-C30 and EQ-5D-5L (by electronic device)		X[g]	every 6 weeks relative to first dose						X		X[n]	X[n]	5.3.2.1 and 5.3.2.2
EORTC QLQ-LC13 (by electronic device)		X[g]	weekly relative to first dose			every 3 weeks relative to first dose			X		X[o]	X[o]	5.3.2.1

Table 50 Study plan

Visit	**Screening**	**Treatment period (further treatment cycles as per Cycle 7)**								**Follow-up period**			**Detail in CSP section:**
	1	**2**	**3**	**4**	**5**	**6**	**7-9**	**10+**	**Treatment discontinuation**	**28-day follow-up**	**Progression follow-up**	**Survival follow-up**	
Cycle[a]/Day		**C1 D1**	**C1 D8**	**C1 D15**	**C2 D1**	**C3 D1**	**C4-6 D1**	**C7[b]+ D1**	**NA**	**NA**	**NA**	**NA**	
Day	**-28 to -1**	**1**	**8**	**15**	**22**	**43**	**64 to 106**	**127+**	**NA**	**NA**	**NA**	**NA**	
Window (days)	**NA**	**0**	**±2**	**±2**	**±7**	**±7**	**±7**	**±7**	**NA**	**±7**	**±7**	**±7**	
PRO-CTCAE (by electronic device)[p]		X[g]	weekly for first 18 weeks of treatment					X[q]	X		X[o]	X[o]	5.3.2.3
Healthcare resource use		←	―	―	―	―	―	―	→				5.3.2.5
Dispense study drug		X			X	X	X	X					3.3 and 7.2
Dose with osimertinib		←	Daily dosing	―	―	―	―	→					7.2
Concomitant medication and procedures		←	―	―	―	―	―	―	→				7.7
Adverse events		←	―	―	―	―	―	―	→		X[r]	X[r]	6.3 and 6.4
Survival status												X[s]	4.3.4

Table 50 Study plan

Visit	**Screening**	**Treatment period (further treatment cycles as per Cycle 7)**								**Follow-up period**			**Detail in CSP section:**
	1	**2**	**3**	**4**	**5**	**6**	**7-9**	**10+**	**Treatment discontinuation**	**28-day follow-up**	**Progression follow-up**	**Survival follow-up**	
Cycle[a]/Day		**C1 D1**	**C1 D8**	**C1 D15**	**C2 D1**	**C3 D1**	**C4-6 D1**	**C7[b]+ D1**	**NA**	**NA**	**NA**	**NA**	
Day	**-28 to -1**	**1**	**8**	**15**	**22**	**43**	**64 to 106**	**127+**	**NA**	**NA**	**NA**	**NA**	
Window (days)	**NA**	**0**	**±2**	**±2**	**±7**	**±7**	**±7**	**±7**	**NA**	**±7**	**±7**	**±7**	
Anti-cancer treatment											X	X^s	4.3.3 and 4.3.4
Subsequent response/progression data												X^t	5.8

CRT Instruction Endnotes

[1] Siegel R, Naishadham D, Jemal A (2012) Cancer Statistics 2012. CA Cancer J Clin; 62(1):10-29
[2] Marino P, Pampallona S, Preatoni A, et al. Chemotherapy vs supportive care in advanced non-small-cell lung cancer. Results of a meta-analysis of the literature. Chest 1994; 106(3): 861-865.
[3] Kelly K, Crowley J, Bunn PA, et al. Randomized Phase III Trial of Paclitaxel Plus Carboplatin Versus Vinorelbine Plus Cisplatin in the Treatment of Patients With Advanced Non–Small-Cell Lung Cancer: A Southwest Oncology Group Trial. JCO. 2001;19(13):3210–3218.
[4] Scagliotti GV. Phase III Randomized Trial Comparing Three Platinum-Based Doublets in Advanced Non-Small-Cell Lung Cancer. JCO. 2002;20(21):4285–4291.
[5] Fossella F, Pereira JR, Pawel J von, et al. Randomized, Multinational, Phase III Study of Docetaxel Plus Platinum Combinations Versus Vinorelbine Plus Cisplatin for Advanced Non–Small-Cell Lung Cancer: The TAX 326 Study Group. JCO. 2003;21(16):3016–3024.
[6] Mollberg N, Surati M, Demchuk C, et al. Mind-mapping for lung cancer: Towards a personalized therapeutics approach. Advances in Therapy. 2011;28(3):173–194.
[7] Pao W, Girard N. New driver mutations in non-small-cell lung cancer. The Lancet Oncology. 2011;12(2):175–180.
[8] Sharma SV, Bell DW, Settleman J, Haber DA. Epidermal growth factor receptor mutations in lung cancer. Nature Reviews Cancer. 2007;7(3):169–181.
[9] Linardou H, Dahabreh IJ, Bafaloukos D, Kosmidis P, Murray S. Somatic EGFR mutations and efficacy of tyrosine kinase inhibitors in NSCLC. Nature Reviews Clinical Oncology. 2009;6(6):352–366.

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/s/

SEAN N KHOZIN
10/14/2015

CHANA WEINSTOCK
10/14/2015

JOYCE H CHENG
10/14/2015

KUN HE
10/15/2015

GIDEON M BLUMENTHAL
10/15/2015

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: NDA 208065 Applicant: AstraZeneca

Drug Name: AZD9291 NDA/BLA Type: NME

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2).	X			505(b)(1)
505(b)(2) Applications					
13.	If appropriate, what is the reference drug?			X	
14.	Did the applicant provide a scientific bridge demonstrating the relationship between the proposed product and the referenced product(s)/published literature?			X	
15.	Describe the scientific bridge (e.g., BA/BE studies)			X	
DOSE					
16.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: D5160C00001 Study Title: A Phase I/II, Open-Label, Multicenter Study to Assess the Safety, Tolerability, Pharmacokinetics and Anti-tumor Activity of Ascending Doses of AZD9291 in Patients with Advanced Non-Small Cell Lung Cancer who have Progressed Following Prior Therapy with an Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor Agent (AURA)	X			

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Sample Size: 252 Arms: 5 cohorts Location in submission: Module 5.3.5.2.				
EFFICACY					
17.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 AURA/AURA Extension (D5160C00001) Indication: (b) (4) EGFRm+/enriched (Jackman criteria)/T790M +non-small cell lung cancer (NSCLC) Pivotal Study #2 AURA2 (D5160C00002) Indication: (b) (4) EGFRm+/T790M+ non-small cell lung cancer (NSCLC)	X			
18.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
19.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
20.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?				
SAFETY					
21.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
22.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?	X			
23.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
24.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?			N/A	
25.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	X			

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
26.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X			
27.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
28.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
29.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
30.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
31.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			Waiver request
ABUSE LIABILITY					
32.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
33.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
34.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
35.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
36.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
37.	Are all datasets to support the critical safety analyses available and complete?	X			
38.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
39.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
40.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE					
41.	Has the applicant submitted the required Financial Disclosure information?	X			

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
GOOD CLINICAL PRACTICE					
42.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ___YES_____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

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/s/

SEAN N KHOZIN
07/14/2015

CHANA WEINSTOCK
07/14/2015

GIDEON M BLUMENTHAL
07/17/2015

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 208065 **Applicant:** AstraZeneca **Stamp Date:** 6/5/15

Drug Name: osimeritnib (AZD9291) **NDA/BLA Type:** New

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	x			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	x			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	x			
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	x			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? __yes___

If the NDA/BLA is not fileable from the statistical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.				
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.				
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.				
Appropriate references for novel statistical methodology (if present) are included.				
Safety data organized to permit analyses across clinical trials in the NDA/BLA.				
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.				

File name: 5_Statistics Filing Checklist for a New NDA_BLA110207

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/s/

JOYCE H CHENG
07/06/2015

KUN HE
07/06/2015