EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 February 2017
EMA/CHMP/134310/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

TAGRISSO

International non-proprietary name: osimertinib

Procedure No. EMEA/H/C/004124/II/0009/G

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Assessment Timetable / Steps taken for the assessment

Timetable	Planned dates	Actual dates
Start of procedure	17 October 2016	17 October 2016
CHMP Rapporteur Assessment Report	15 November 2016	28 November 2016
PRAC Rapporteur Assessment Report	18 November 2016	18 November 2016
PRAC members comments	23 November 2016	28 November 2016
Updated PRAC Rapporteur Assessment Report	24 November 2016	N/A
PRAC Outcome	1 December 2016	1 December 2016
CHMP members comments	5 December 2016	7 December 2016
Updated CHMP Rapporteur Assessment Report	8 December 2016	9 December 2016
Request for Supplementary Information (RSI)	15 December 2016	15 December 2016
Submission of responses	24 January 2017	23 January 2017
Restart date	25 January 2017	25 January 2017
CHMP Rapporteur response Assessment Report	8 February 2017	13 February 2017
Comments from CHMP	13 February 2017	14 February 2017
Updated CHMP Rapporteur response Assessment Report	16 February 2017	N/A
Opinion	23 February 2017	23 February 2017

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1. Background information on the procedure

1.1. Requested group of variations

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, AstraZeneca AB submitted to the European Medicines Agency on 30 September 2016 an application for a group of variations.

The following changes were proposed:

Variations requested		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I and IIIB
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Update of SmPC sections 4.2, 4.4, 4.8, 5.1 and 5.2 based on the results from study D5160C00003 (AURA3) and the updated CSRs for studies D5160C00001 (AURAex) and D5160C00002 (AURA2). The Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to make editorial changes in the SmPC and Package Leaflet. The application included an updated RMP version 6.0. The provision of the CSR from study AURA3 addresses the Specific Obligation for Tagrisso and hence the MAH requests the conversion from a Conditional Marketing Authorisation to a Marketing Authorisation not subject to Specific Obligations.

The requested group of variations proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

1.2. Rationale for the proposed changes

The current Marketing Authorisation for TAGRISSO 40 mg and 80 mg tablets is a Conditional Marketing Authorisation (CMA) with the following Specific Obligation (SOB) with a due date of 30 June 2017:

> *"In order to further confirm the efficacy and safety of osimertinib in the treatment of patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC, the applicant should submit the clinical study report of the phase III study AURA3 comparing osimertinib to platinum based doublet chemotherapy"*

This is a grouped application comprising three type II variations; the provision of the final CSR from study AURA3 (SOB) and updated data from the AURAex and AURA2 studies, for which earlier data-cuts were used as the basis for the initial CMA.

With submission and eventual conclusion of this grouped variation including the AURA3 specific obligation study, the MAH requests conversion from CMA to a MA not subject to Specific Obligations, based on the confirmation of osimertinib efficacy and safety in the comparative, randomised Phase III study, AURA3 (*D5160C00003, A Phase III, open label, randomised study of AZD9291 vs. platinum based doublet chemotherapy for patients with locally advanced or metastatic NSCLC whose disease has progressed with previous EGFR TKI therapy and whose tumours harbour an EGFRT790M mutation within the EGFR gene.).* Both progression-free survival (PFS) and overall survival (OS) data from AURA3 are required to fulfil the SOB for the CMA, and allow conversion to a MA not subject to SOBs. As the CSR and data for AURA3 included in

this submission is based on evaluation of PFS data only, it has been agreed that as an exception the OS data will be provided in this procedure in response to a Request for Supplementary Information (RSI).

In addition, updated CSRs (edition number 3, data cut-off of 01 November 2015), for studies:
- D5160C00001 (*A Phase I/II, Open-Label, Multicentre Study to Assess the Safety, Tolerability, Pharmacokinetics and Anti-tumour 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 (AURAex));*
- AndD5160C00002 (*A Phase II, Open Label, Single-arm Study to Assess the Safety and Efficacy of AZD9291 in Patients with Locally Advanced/Metastatic Non Small Cell Lung Cancer whose Disease has Progressed with Previous Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor Therapy and whose Tumours are Epidermal Growth Factor Receptor Mutation and T790M Mutation Positive (AURA2));*
are also provided as part of the application. CSRs, with a data cut-off of 01 May 2015 were provided to EMA during review of the initial MAA. The data from the updated CSRs provides additional data supporting changes to the SmPC.

2. Overall conclusion and impact on the benefit/risk balance

The MAH is hereby requesting an update of SmPC sections 4.2, 4.4, 4.8, 5.1 and 5.2 based on the results from study D5160C00003 (AURA3) and the updated CSRs for studies D5160C00001 (AURAex) and D5160C00002 (AURA2). The MAH is also proposing a switch from a conditional marketing authorisation to a 'standard' marketing authorisation (i.e. a marketing authorisation not subject to specific obligations) for osimertinib (AZD9291, TAGRISSO) for the treatment of adult patients with locally-advanced or metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive non-small cell lung cancer (NSCLC). The company is basing this request on the provision of the phase III AURA3 study.

AURA3 is a Phase III, open-label, randomised study (2:1 ratio [osimertinib:platinum-based chemotherapy]) specifically designed to compare the efficacy of osimertinib vs. platinum- based doublet chemotherapy (pemetrexed plus carboplatin or pemetrexed plus cisplatin, followed by optional pemetrexed maintenance) as second-line treatment in patients with confirmed advanced EGFR T790M mutation-positive NSCLC who had progressed following 1st line treatment with an approved EGFR-TKI.

Results from the AURA3 trial confirmed the previous positive benefit risk balance shown on the basis of the studies AURA extension and AURA2. The outcomes in terms of PFS, ORR, DoR and DCR were considered clinically meaningful and further support the efficacy ascertained at the time of the marketing authorisation based exclusively on response outcomes (ORR), whereas the safety profile of patients treated with osimertinib was consistent to that known from previous studies.

During the procedure, the MAH was requested to provide preliminary OS results. As expected, data are currently not mature enough so as to draw firm conclusions about the potential longer survival of those patients treated with osimertinib, even though the current HR seems reassuring, highlighting a positive trend for osimertinib (HR: 0.72 [99.96% CIs: 0.34, 1.52]). A second analysis of OS will be performed when the OS data are approximately 50% mature (approximately 205 deaths events). A third analysis of OS will be performed when the OS data are approximately 70% mature (approximately 287 deaths events). Nevertheless, it seems doubtful that the expected longer survival can be shown in future analyses, seeing as 94/140 [67.1%] patients in the chemotherapy arm crossed over to receive treatment with osimertinib after RECIST progression. Neither the PFS2 data are capable of shedding light on the long-term effects of osimertinib, since the high number of censures does not allow achieving further conclusions. Despite the inability to collect informative mature OS data, the magnitude of effect seen with PFS, ORR, DoR and DCR,

supported by the reassuring HR in terms of OS in the first interim analysis, allow to conclude that the condition has been fulfilled with the provision of comprehensive data on the benefit-risk balance.

A marketing authorisation not subject to specific obligation can be recommended at present based on the positive results observed in PFS and ORR, but with the commitment of submitting the two pending analyses of OS when available. The MAH has made appropriate commitments in this regard and provided a Letter of Recommendations accordingly. This approach is considered acceptable especially in view of the fact that no new safety concerns have been identified and that results from the phase III trial (including the primary endpoint) are consistent with the already known efficacy data from previous studies.

Thus, as the specific obligations are fulfilled, the CHMP is of the view that a switch from a conditional marketing authorisation to a full marketing authorisation can be recommended. The updated RMP version 6.0 is agreed as well as the changes to the product information stemming from the CSR of study D5160C00003 (AURA3) and the updated CSRs for studies D5160C00001 (AURAex) and D5160C00002 (AURA2).

The benefit-risk balance of TAGRISSO remains positive.

Scientific Summary for the EPAR

Please refer to Scientific Discussion Tagrisso-H-C-4124-II-09-G

3. Recommendations

Based on the review of the submitted data, this application regarding the following changes:

Variations accepted		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I and IIIB
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Update of SmPC sections 4.2, 4.4, 4.8, 5.1 and 5.2 based on the results from study D5160C00003 (AURA3) and the updated CSRs for studies D5160C00001 (AURAex) and D5160C00002 (AURA2). The Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to make editorial changes in the SmPC and Package Leaflet. The provision of the CSR from study AURA3 addressed the remaining Specific Obligation for Tagrisso and hence it is recommended to convert the Marketing Authorisation from a Conditional Marketing Authorisation to a Marketing Authorisation not subject to Specific Obligations. Annex II has been updated in accordance. An updated RMP version 6.0 was agreed during the procedure.

☒is recommended for approval.

The group of variations leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

4. Scientific discussion

4.1. Introduction

AstraZeneca is seeking full marketing approval for the use of osimertinib (AZD9291, TAGRISSO™) for the treatment of adult patients with locally-advanced or metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive non-small cell lung cancer (NSCLC).

On 2 February 2016, the European Commission (EC) granted Conditional Marketing Authorisation (CMA) (EU/1/16/1086) for osimertinib 80 mg once daily (40 mg and 80 mg oral tablets) for use in this indication across the European Union (EU). The Marketing Authorisation Application (MAA) was reviewed via the Accelerated Assessment procedure of the European Medicines Agency (EMA). The CMA was based on the objective response rate (ORR) (according to Response Evaluation Criteria in Solid Tumors version 1.1 [RECIST v1.1]) as determined by blinded independent central review (BICR) of data from 2 open-label, single-arm Phase II studies of osimertinib (AURA extension [D5160C00001 Phase II component] and AURA2 [D5160C00002]); and on the duration of response (DoR) and progression-free survival (PFS) by BICR in 1 Phase I study (AURA [D5160C00001] Phase I component as of the DCO of 1 May 2015. The safety labelling was further informed by data from the 90-day safety update as of the second DCO (DCO2) of 1 May 2015. These 2 Phase II studies included a total of 411 patients with locally-advanced or metastatic NSCLC(advanced NSCLC hereafter) whose tumors carried the EGFR T790M mutation, as centrally confirmed by the cobas® EGFR Mutation Test [Roche Molecular Systems, Inc.]), who had progressed on prior systemic therapy that included at least 1 EGFR-TKI (second-line and ⩾third-line patients; Ranson et al. 2013). Both Phase II studies are ongoing and updated data at the third DCO (DCO3) date of 1 November 2015 are now available (Yang et al 2016).

The application for full approval is based on the confirmation of osimertinib efficacy and safety in an pivotal, comparative, randomised Phase III study, AURA3(D5160C00003), conducted in 419 patients with advanced EGFR T790M mutation-positiveNSCLC in second-line therapy versus (vs.) platinum-based chemotherapy (pemetrexed pluscisplatin or carboplatin), followed by pemetrexed maintenance, with PFS based on investigator assessment as the primary efficacy endpoint; overall survival (OS) and ORR are key secondary endpoints. Longer follow-up data (1 November 2015 DCO) from the 2 pooled single-arm Phase II studies of osimertinib in second-line and later-lines of therapy that were the basis for conditional approval, AURA extension and AURA2, are provided to support the consistency and durability of efficacy findings, to show the absence of unexpected additional toxicity burden with longer follow-up, and, especially, to inform and support prescribing information in the broader T790M population (second and ⩾third-line of therapy), in line with the current indication. Additional support for the characterisation of the safety profile ofosimertinib in patients with advanced EGFR T790M mutation-positive NSCLC is provided through an integrated safety analysis performed on larger pooled datasets taken from AURAPhase I study (N = 402); AURA extension (N = 201); AURA2 (N = 210); and AURA3osimertinib arm (N = 279).

4.2. Clinical Pharmacology aspects

The osimertinib clinical pharmacology programme was designed to characterise osimertinib pharmacokinetics and to investigate the key factors that could potentially contribute to variability in exposure to osimertinib in the target NSCLC population.

Elimination of osimertinib is primarily via hepatic metabolism, hence liver impairment may impact exposure of osimertinib. A clinical study evaluating the impact of hepatic impairment on the exposure of osimertinib is currently ongoing (Study 8; D5160C00008).

A reduced design renal impairment study is ongoing for osimertinib (Study 35); however, as renal elimination of osimertinib and its related components is low (<15% of the dose and mostly as metabolites,

unchanged osimertinib <1% of the dose; Study 11), the impact of renal impairment on the exposure of osimertinib is likely to be minimal.

Bioanalytical methods for the determination of osimertinib and its metabolites AZ7550 and AZ5104 in human EDTA plasma were developed and validated, on behalf of AstraZeneca, at Covance UK Ltd, Harrogate, UK were presented in the original NDA submission. Only the long term frozen stability data was updated (8277090 addendum) which shows that Osimertinib is stable for 400 days and the metabolites are stable for 169 days at -80°C.

4.2.1. Results

Population PK evaluation

A population pharmacokinetic model for osimertinib and its main metabolite AZ5104 had previously been developed, based on data from AURA, AURA2 and D5160C00005 (healthy subject data). Osimertinib was characterized in Non-small cell lung cancer (NSCLC) patients over a wider (20 to 240 mg) dose range including PK samples up to 6 weeks (Cycle 3 Day 1).

According to the previous popPK analysis, osimertinib pharmacokinetics (PK) was dose proportional across the 20 to 240 mg dose range studied and time independent. The typical value of clearance, volume of distribution and half-life of osimertinib were estimated as 14.2 L/h, 986 L, and 48 h, respectively. The between subject variability for clearance and volume of distribution of osimertinib were estimated as 45.6 and 51.8 (expressed as % coefficient of variation), respectively. Body weight on apparent clearances of osimertinib and AZ5104, bodyweight and baseline albumin on apparent volume of distribution of osimertinib and ethnicity on apparent clearance of AZ5104 were identified as significant covariates to explain the variability in the data. However, effect of these parameter-covariate relationships did not show any clinical meaningful changes in PK exposure metrics. The covariates age, gender, smoking status, renal and hepatic function had no impact on PK of osimertinib and its metabolite AZ5104 within the population studied.

An updated population PK model for osimertinib and AZ5104 was developed based on plasma concentrations of osimertinib and AZ5104 from Phase I/II/III studies in NSCLC patients.

The objective of this analysis was to update the previously developed pharmacokinetic model using pharmacokinetic data from the AURA3 (Phase III) study along with AURA (Phase I/II) and AURA2 (Phase II) data, including the following aspects:

- ☐ Characterization of the dose/plasma concentration relationship of osimertinib and its main metabolite of interest (AZ5104) and the associated between-subject variability in NSCLC patients, following oral administration.
- ☐ Re-evaluate the impact of selected intrinsic and extrinsic covariates of interest on the PK variability of osimertinib (ethnicity, body weight, gender, age, hepatic markers (ALT, AST and bilirubin), baseline albumin levels, creatinine clearance, smoking status, renal and hepatic impairment status).
- ☐ Assessment of the impact of longer duration of treatment on pharmacokinetics of osimertinib.

Methods:

Plasma concentration-time data were analyzed using a non-linear mixed effects modelling approach (non-linear mixed effects modelling software [NONMEM], version 7.2). Model development was driven by data and based on various goodness-of-fit indicators, including visual inspection of diagnostic and covariate scatter plots, precision of parameter estimates, and the minimum objective function value.

After identification of the base model, covariates were evaluated using a stepwise covariate model search process by backward elimination (P<0.001) following forward inclusion (P<0.01). The significance of a covariate effect was also evaluated with respect to clinical and/or physiological relevance.

The final population PK model was used to obtain individual exposure estimates of osimertinib and AZ5104 for patients included in the datasets and to simulate an 80-mg steadystate exposure.

In the previous analysis, a common (combined additive and proportional) error model was applied to estimate the residual variability for both osimertinib and its metabolite AZ5104. This residual error model was updated considering individual error models (combined additive and proportional) to estimate the residual variability for osimertinib and its metabolite AZ5104, separately. These initial changes were applied using plasma concentration and covariates information from AURA and AURA2 only. After these initial changes, the population PK model consisted the following characteristics and used as a starting point for the analysis:

- Linear 1-compartment model to characterise PK for each analyte
- First-order absorption of parent into the parent's central compartment
- Fraction of osimertinib metabolized to AZ5104 was fixed to 0.25
- Linear elimination from osimertinib (parent) and AZ5104 (metabolite) from their respective central compartments
- Between subject variability was considered on all the PK parameters
- Correlation of random effects between CL/F and CLM/F was included
- Error models (combined additive and proportional) to estimate the residual variability for osimertinib and its metabolite AZ5104 separately.
- Model parameters were estimated using SAEM algorithm as implemented in NONMEM

Results:

The dataset used for analysis consisted of a total of 31428 plasma concentration samples, obtained from 1088 subjects, treated with osimertinib.

The population in AURA3 was fairly similar to the population that was studied in AURA and AURA2. The main difference in these populations is that in AURA3 100% of the patients obtained treatment with osimertinib in second line, while in AURA and AURA2 only about 24% received osimertinib in second line and the majority (69%) in ≥third line. However, in the previous analysis (Comisar, 2015), lines of therapy was not identified as a covariate having an influence on the PK of osimertinib.

AURA3 study showed a slightly lower pre-dose steady-state concentrations (about 21% lower) compared to AURA and AURA2 studies. Based on these data based observations, it is expected that the apparent clearances are higher in AURA3 than in AURA and AURA2.

The updated population PK parent and metabolite model was comprised of first order oral absorption of osimertinib followed by two compartments in series: one-compartment for osimertinib followed by a compartment for AZ5104. The final model described the osimertinib/AZ5104 concentration data well for subsequent exposure response modelling purposes.

The primary predictors of variability in osimertinib and AZ5104 PK were body weight and serum albumin. Ethnicity had only a negligible effect on osimertinib and AZ5104 exposure. There were no factors identified that would require dose adjustment in patients.

In the final population pharmacokinetic model, the typical (%RSE) value of CL/F and Vz/F are 14.2 (1.67) L/h and 997 (3.96) L, which is very similar to the CL/F and Vz/F estimated in the previous model as 14.2 (1.80) L/h and 986 (2.80) L, respectively.

The expected typical values of osimertinib AUCss, and Css,max for an 80-mg osimertinib dose in NSCLC patients are 11184 nM.h and 509 nM, respectively. The expected typical values of AZ5104 AUCss and Css,max for an 80-mg osimertinib dose in NSCLC patients are 1320 nM*h, and 58 nM, respectively.

Table 7 Population PK parameter estimates for final model

Parameter	Value	RSE (%)	Shrinkage (%)
CL/F (L/h)	14.2	1.67[a]	
CLm/F (L/h)	30.6	2.41[a]	
Fraction Metabolised (FM)	0.25	(FIX)	
V/F (L)	997	3.96[a]	
Vm/F (L)	167	4.93[a]	
ka (1/hour)	0.201	5.54[a]	
Between Subject Variability (as %CV)			
CL/F	47.1	2.19	3.9
CLm/F	52.3	2.15	3.5
FM	0	(FIX)	-
V/F	83.3	2.11	26.8
Vm/F	82	3.87	38.9
Ka	111	2.61	37.6
Correlation (CL/F and CLm/F)	0.896	0.753	
Parameter-Covariate Estimates			
Baseline albumin on CL/F	0.899	(12.8)	
Baseline bodyweight on CL/F	0.451	(15.2)	
Baseline albumin on CLm/F	0.986	(12.7)	
Asian (non-Chinese, non-Japanese) on CLm/F	0.191	(12.3)	
Chinese on CLm/F	0.0911	(25.8)	
Japanese on CLm/F	0.175	(16.1)	
Non-Asian, non-White on CLm/F	0.0947	(27.7)	
Baseline bodyweight on CLm/F	0.858	(8.97)	

Baseline albumin on V/F	1.99	(10.9)
Baseline bodyweight on V/F	0.661	(21.8)
Residual Variability		
Additive error Osimertinib (nM)	28.3	(1.1)
Additive error AZ5104 (nM)	0.561	(2.63)
Proportional error Osimertinib	0.192	(0.484)
Proportional error AZ5104	0.198	(0.402)
Objective function[b]	223751.09	
Condition Number - FULL	391.12	
Condition Number - Fixed effects	52.92	
Condition Number - Random effects and error parameters	12.79	

[a] Relative standard errors for the fixed effect parameters have been obtained by sampling in the log domain and back transformation into the normal domain (due to the use of MU referencing).
[b] The objective function was determined using importance sampling (IMP) with settings EONLY=1 and

VPC showed that the final model is adequately able to describe the steady-state pharmacokinetics of osimertinib for the totality of the AURA, AURA2, and AURA3 data.

Based on the covariate/parameter relationships in the final model and the simulation based analysis, the following changes in exposure (AUCss) are expected compared to the AUC,ss for a white patient with a median bodyweight of 60 kg and a median baseline albumin of 39 g/L:

- ☐ Bodyweight on osimertinib CL/F and V/F: accounts for less than 20% change in osimertinib AUC,ss would be expected across a bodyweight range of 43 to 89 kg.
- ☐ Bodyweight on AZ5104 CLm/F: a -29% to +36% change for AZ5104 AUC,ss would be expected across a bodyweight range of 43 to 89 kg
- ☐ Baseline albumin on osimertinib CL/F and V/F: a -15% to +30% change in osimertinib AUC,ss would be expected across a albumin range of 29 to 46 g/L.
- ☐ Baseline albumin on AZ5104 CLm/F and Vm/F: a -15% to +36% change in AZ5104 AUC,ss would be expected across a albumin range of 29 to 46 g/L.
- ☐ For all ethnic classes (Chinese, Japanese, Asian other and non-Asian-non-white), a decrease in AZ5104 AUC,ss of 7% to 17% vs white patients may be expected, which is unlikely to have clinically relevant impact.

Changes in exposure due to these covariate-parameter relationship are small and not likely to be clinically significant based on the exposure-response relationship of osimertinib and hence, no dose adjustments are necessary.

This updated analysis including PK data from Phase I, Phase II and Phase III studies supports the prior conclusions regarding no need for dose adjustment due to age,gender, bodyweight, ethnicity, smoking status, mild/moderate/severe renal impairment status and mild/moderate hepatic impairment status.

Table 8 Impact of covariates on steady-state exposure metrics for osimertinib (for 80 mg dose)

Varying covariate	Weight[a] (kg)	Albumin[a] (g/L)	Ethnicity[a]	C_{max}[b] (nM)	AUC[b] (nM*hour)
Typical patient	60	39	White	509 (245-1040)	11184 (5112-23448)
Weight at baseline	43	39	White	601 (295-1228)	13104 (6120-27816)
	89	39	White	423 (201-859)	9312 (4248-19512)
Albumin at baseline	60	29	White	687 (334-1437)	14544 (6744-31560)
	60	46	White	430 (209-881)	9504 (4416-20184)
Ethnicity	60	39	Asian (no Chinese, no Japanese)	508 (245-1037)	11112 (5088-23376)
	60	39	Chinese	508 (248-1049)	11160 (5136-23688)
	60	39	Japanese	506 (246-1039)	11064 (5232-23424)
	60	39	Non-White, Non-Asian	510 (247-1053)	11136 (5184-23808)
Worst case[c]	43	29	White	809 (392-1683)	17016 (7848-36984)

[a] Values based on median (typical) and 5th/95th percentile of values in the analyzed population for continuous covariates and reference vs. other categories for categorical covariates.
[b] Exposure metrics for different cases obtained through simulation of the final PK model. Median and 90 percent prediction interval are displayed for N=10000 simulated patients for each covariate combination.
[c] Worst case constructed to obtain maximum impact (highest values) on C_{max} and AUC.

While the typical subject at 60 kg is predicted to have a median osimertinib Cmax,ss of 509 nM (and an AUCss of 11184 nM*hour), a subject with the extreme combination of bodyweight (43 kg) and baseline albumin (29 g/L) covariates, is predicted to have an increase in median steady-state Cmax,ss and AUCss of approximately 58% and 51%, respectively. This shows that even in extreme and unlikely scenarios, a typical subject is expected to have less than 60% change in exposure.

Pharmacokinetic/pharmacodynamic relationships and exposure/response relationships of osimertinib

The previously submitted PK-PD analysis was updated with AURA3 data and the updated results are consistent with the previous analysis. Individual values of AUCss from the final population PK model were used to assess the PK-PD relationships for efficacy and safety.

PK-PD relationships are analyzed either as dose-response or exposure response relationships against either safety or efficacy outcomes.

Individual AUCss values from the final population PK model were used to assess PK-PD relationships for efficacy and safety.

Effect of exposure on efficacy outcomes

Graphical analysis indicated that there was no relationship observed between best percentage change in tumour size from baseline or DoR and osimertinib or AZ5104 exposure. Graphical exploration of best overall

response or PFS indicated patients in the high AUCss quartile (AUCss>15690 nM*hr) had a numerically shorter PFS than the patients in the lower 3 quartiles; importantly, osimertinib treatment effect was significantly greater than the chemotherapy treatment across all quartiles of exposure. Kaplan-Meier plot of PFS stratified by quartiles of Osimertinib AUCss and chemotherapy is shown in Figure 11.

A model-based analysis was conducted to explain the numerically shorter PFS observed with patients in the high exposure quartile. This analysis showed a statistically significantassociation of AUCss (exposure) of osimertinib/AZ5104 with PFS, indicating an increase inexposure may be associated with a decrease in PFS. However, when baseline albumin levels (<39 g/L compared to ≥39 g/L) and the WHO status (WHO≥1 compared to WHO =0) wereincluded as predictors of PFS, the exposure relationship with osimertinib or AZ5104 was no longer statistically significant (Figure 12). This indicated that the reason for numerically shorter PFS observed in the high exposure quartile is likely to be a consequence of an excess of patients with poor prognostic features in the high exposure quartile and is not related to osimertinib or AZ5104 exposure levels. This is consistent from literature (Gupta et al, 2010) which shows that shorter survival time is associated with low levels of pre-treatment serum albumin. Additionally, from the population PK analysis (Johnson 2016) it is known that baseline albumin levels are positively correlated with apparent clearance of both osimertinib and AZ5104.

These findings of no relationship between efficacy and osimertinib exposure are in agreement with the dose-response analysis where there was no clear relationship between dose and efficacy with all doses examined (20 to 240 mg) demonstrated clinical activity as indicated in the initial MAA submission in a Dose Justification Document.

Figure 11 Kaplan-Meier representation of PFS stratified by quartiles of osimertinib AUCss and Chemotherapy

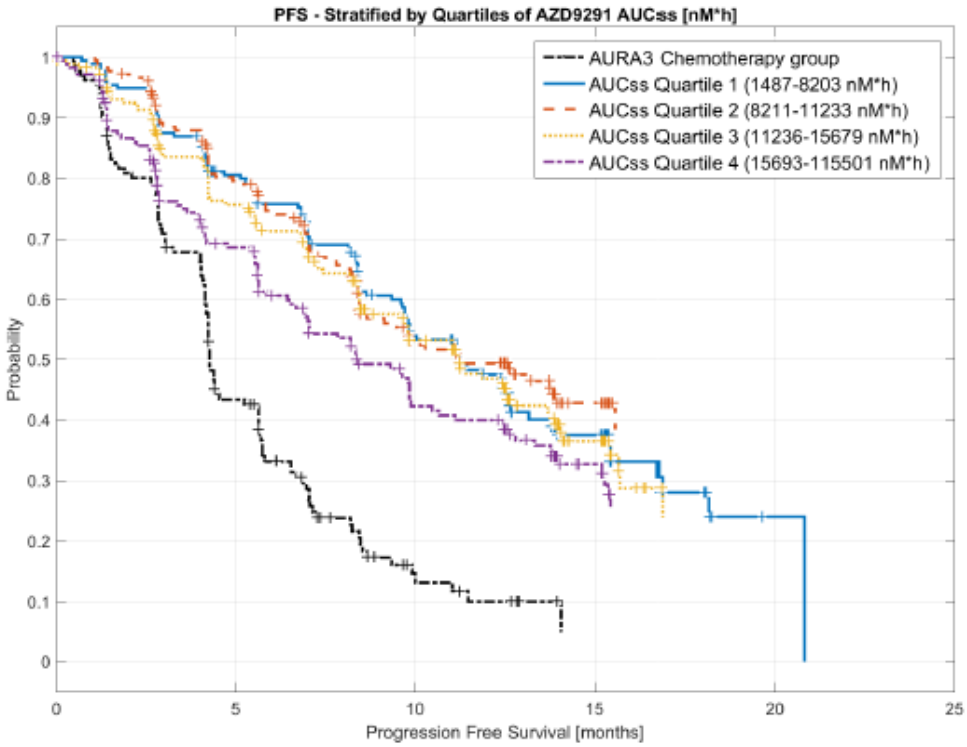
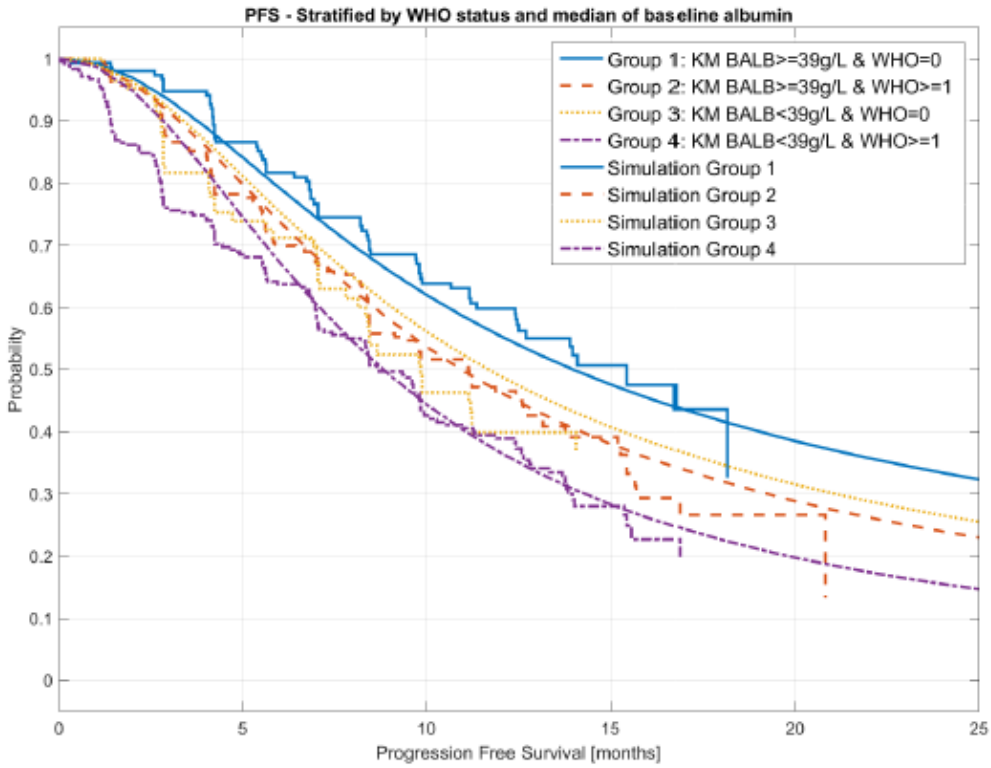


Figure 12 **Kaplan-Meier plot for PFS stratified by WHO status and median of baseline albumin**



Effect of exposure on key safety parameters

An earlier assessment (included in the initial MAA) of the occurrence of classical EGFR TKI toxicities of rash, diarrhoea and both rash and diarrhoea in patients from AURA and AURA2 indicated the probability of a patient experiencing rash or diarrhoea increased with osimertinib AUCss exposure. AURA3 findings have shown that the frequency and severity of the events of rash and diarrhoea were similar to those in the Phase II studies and did not increase with increased duration of exposure to osimertinib. In this PK-PD analysis, only the effect of osimertinib exposure on ILD (interstitial lung disease) or ILD-like events or on the LVEF (left ventricular ejection fraction) changes wereanalyzed.

The proportion of patients showing ILD or ILD-like events at different osimertinib AUCss quartiles is presented in Figure 13 and it shows that the incidence of ILD is related to osimertinib treatment. The data indicates that a probability of patient experiencing ILD events are likely to increase with increasing osimertinib exposure.

Figure 14 indicates that at a similar AUCss of osimertinib, patients of Japanese ethnicity tend to have higher incidence of ILD compared to Non-Asian and Asian (non-Japanese) patients.

However, it was noted that the model predicted incidence rate for non-osimertinib or placebo treatment was much lower (0.005%) than the ILD incidence rate available in literature for placebo or chemotherapy treatment (0.9 to 2%). This indicates that the exposure-ILD model might overestimate the slope of the ILD incidence at higher exposure and hence, the estimated magnitude of osimertinib exposure on the probability of patient experiencing ILD event is expected to be potentially lower than estimated by the current model.

Figure 13 **Proportion of patients showing ILD events at different AUCss quartiles of osimertinib**

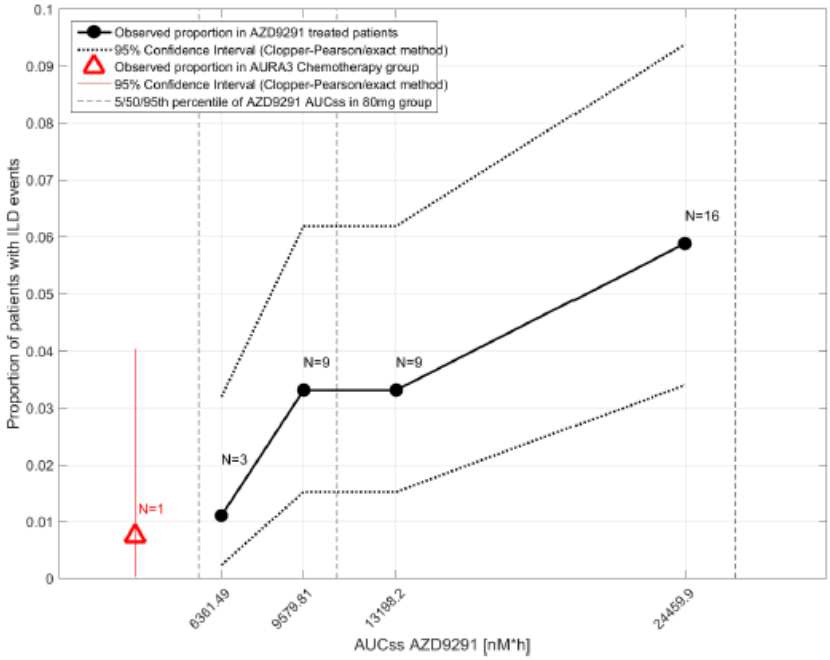
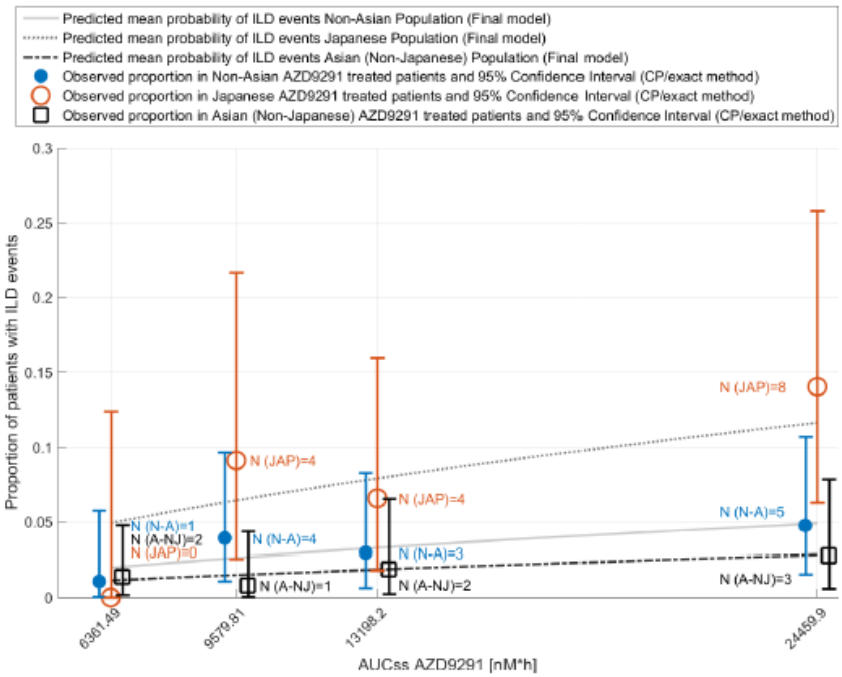
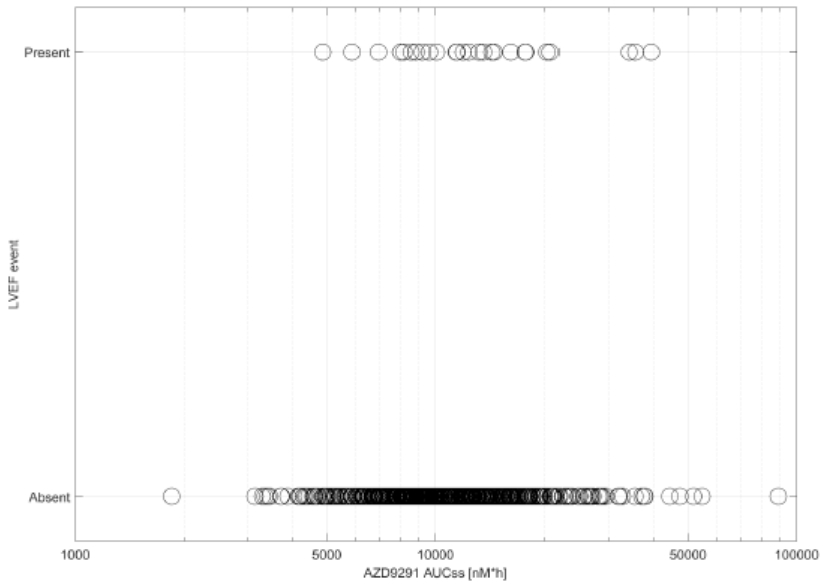


Figure 14 **Predicted mean probability of ILD events in different Osimertinib treated patients**



Initial graphical assessments using minimum or maximum change from baseline LVEF measurement (LVEF changes) during the osimertinib treatment did not indicate any quantifiable relationship with osimertinib and AZ5104 exposure (Figure 15). However, LVEF event (a 10% absolute change from baseline LVEF along with a drop to <50% LVEF) indicated an exposure dependent effect and hence, a model based assessment was evaluated to quantify this effect. Models that take into account the rare nature of these events (penalized logistic regression and zero-inflated Poisson) were implemented and the model based assessments suggested that there was no relationship between exposure and the occurrence of LVEF events at the pre-specified statistical significance threshold ($p<0.001$).

Figure 15 Relationship between occurrence of LVEF events and osimertinib AUCss



4.2.2. Discussion

The updated popPK analysis showed that pharmacokinetics of osimertinib and AZ5104 was similar between patients in AURA3 and AURA/AURA2 studies. Lower pre-dose steady-state concentrations (about 21% lower) were observed in AURA3 compared to AURA and AURA2 studies. Based on these observations, higher apparent clearances are expected in AURA3 than in AURA and AURA2.

The PPK analysis was based on the one previously developed and was performed using well recognized model building techniques. The validity of the final model seems to be overall acceptable. Shrinkage was small (≤5%) in clearance parameters, but higher (26-40%) in volume of distribution and absorption rate constant ETAs. The applicant justifies that the higher shrinkage in volume of distribution and absorption rate constant is expected given the large amount of sparse data taken from the AURA3 trial. Caution is advised when interpreting volume of distribution and absorption data.

The updated population PK parent and metabolite model was comprised of first order oral absorption of osimertinib followed by two compartments in series: one-compartment for osimertinib followed by a compartment for AZ5104. The final model described the osimertinib/AZ5104 concentration data well for subsequent exposure response modelling purposes.

In the final population pharmacokinetic model, the typical (%RSE) value of CL/F and Vz/F are 14.2 (1.67) L/h and 997 (3.96) L. These values are pretty similar to those estimated in the previously submitted popPK analysis. SmPC has been updated accordingly.

The updated popPK analysis confirms previous findings. There is no impact of age, gender, bodyweight, smoking status, mild/moderate/severe renal impairment status and mild/moderate hepatic impairment status on the PK of osimertinib and AZ5104. Data regarding patients with severe renal impairment is still considered limited (n=5) and the lack of information should be maintained in SmPC. No patients with severe hepatic impairment were included in the trials. Ethnicity showed a minor impact on the pharmacokinetics of osimertinib and is not considered clinically relevant.

Regarding body weight, less than 20% change in osimertinib AUCss (compared to the AUCss for the median body weight of 60 kg) would be expected across a body weight range of 43 kg to 89. Similar but greater change (−15% to +30%) in osimertinib AUCss would be expected across the albumin range of 29 g/L to 46

g/L (compared to the median baseline albumin of 39 g/L). A −15% to +36% chance in AZ5104 AUCss would be expected across the similar range. The magnitude of the observed changes does not justify new recommendations on dose adjustment based on body weight or baseline albumin.

PK-PD analysis has been updated with AURA3 data. Individual values of AUCss from the final population PK model were used to assess the PK-PD relationships for efficacy and safety. This includes effect of exposure on PFS, on probability of experiencing interstitial lung disease and on experiencing changes of left ventricular ejection fraction (LVEF).

The exposure-PFS analysis showed that the patients in the highest quartile of osimertinib AUCss showed shorter PFS. This finding is however likely to be confounded by disease related factors such as WHO performance status or baseline albumin levels (a misbalance was noted between quartile groups). Having said that, no exposure-PFS relation can be established. Regarding safety, there appears to be a higher probability of experiencing ILD or ILDlike events increased with increasing osimertinib exposure, however data are limited and should be interpreted with caution.

4.3. Clinical Efficacy aspects

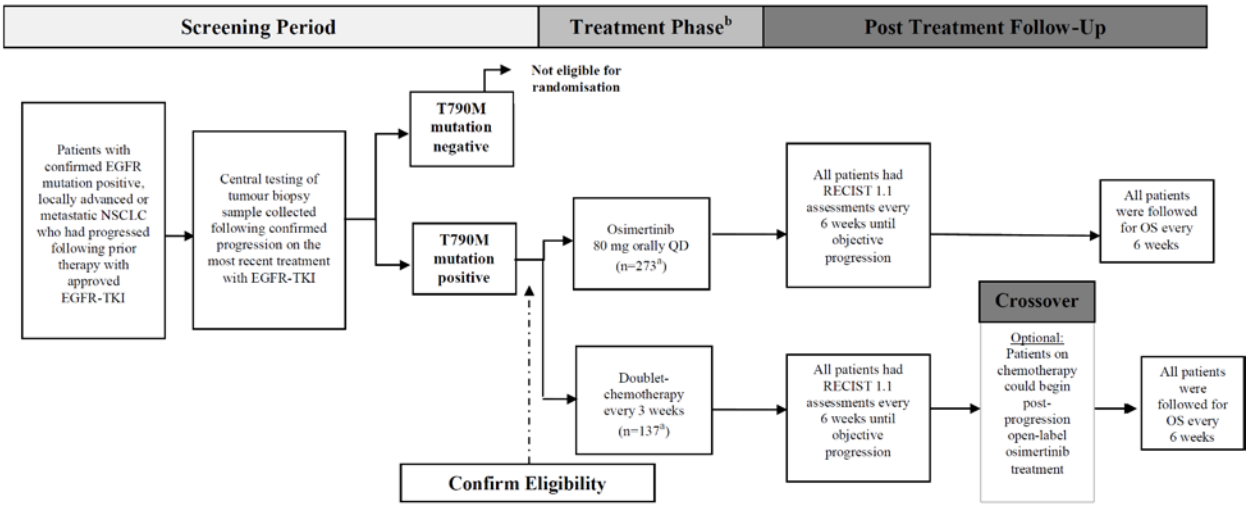
Data cut-off (DCO) dates

Study acronym (number)	Data cut-off date
AURA extension (D5160C00001 Phase II component)	DCO1: 9 January 2015 DCO2: 1 May 2015 DCO3: 1 November 2015
AURA2 (D5160C00002)	DCO1: 9 January 2015 DCO2: 1 May 2015 DCO3: 1 November 2015
AURA3 (D5160C00003)	DCO: 15 April 2016 (for primary analysis of progression-free survival [PFS])

MAIN STUDY: Study D5160C00003 (AURA3)

This was a Phase III, Open label, Randomized Study of AZD9291 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 (EGFR TKI) Therapy and whose Tumours Harbour a T790M mutation within the Epidermal Growth Factor Receptor Gene.

Figure 1 Flow chart of study design



4.3.1. Methods – analysis of data submitted

- **Study participants**

Patients aged ≥18 years (≥20 years for patients from Japan) with locally advanced or metastatic NSCLC (Histologically- or cytologically-documented not amenable to surgery or radiotherapy) who had progressed (radiologically) following prior first-line therapy with an approved EGFR-TKI agent. Patients had to have EGFR mutation-positive tumours, with centrally-confirmed T790M mutation-positive status**.**All patients had to have measurable dissease at baseline.

All patients were to have adequate cardiac, hepatic and renal function, World Health Organization (WHO) performance status of 0 or 1 with no deterioration over the previous 2 weeks and a minimum life expectancy of 12 weeks.Patients with CNS metastases were eligible if they were asymptomatic, stable and not requiring steroids for at least 4 weeks prior to start of study treatment.

Previous treatment with osimertinib or a third generation EGFR-TKI was not premitted (eg. CO-1686).

- **Treatments**

Osimertinib was to be administered orally as a single daily dose of 80 mg.

Pemetrexed was to be administered at 500 mg/m2 on Day 1 of each 21-day cycle is as per the US and EU prescribing Information with either Cisplatin at 75 mg/m2 on Day 1 of each 21-day cycle, or Carboplatin at a dose producing an AUC5 on Day 1 of each 21-day cycle. Pemetrexed as maintenance therapy was to be administered at a dose of 500 mg/m2 on Day 1 of each 21-day cycle.

In the osimertinib arm, patients could continue on treatment as long as they were deriving clinical benefit, as judged by the investigator, or until a treatment discontinuation criterion was met. In the chemotherapy arm, patients could receive up to 6 cycles of pemetrexed plus cisplatin or carboplatin as initial treatment. Those patients whose disease had not progressed after 4 cycles of platinum-based doublet chemotherapy could continue on maintenance monotherapy with pemetrexed according to the approved label use or local practice guidelines. Patients who progressed according to RECIST v1.1 prior to completion of the initial doublet chemotherapy treatment or during pemetrexed maintenance monotherapy, could continue with chemotherapy as long as they showed clinical benefit, as judged by the investigator.

Once patients in the chemotherapy arm were determined to have objective radiological progression according to RECIST v1.1 by the investigator, with confirmation by blinded independent central review (BICR), they were given the opportunity to begin treatment with osimertinib 80 mg once daily. These patients could continue treatment with osimertinib, as long as they showed clinical benefit, as determined by the investigator. Patients who did not have BICR confirmation of objective disease progression were not allowed to cross-over to osimertinib. If it was considered to be in the patient's best interest, and only if further randomised chemotherapy was warranted, the patient could continue to receive randomised doublet chemotherapy (if the initial doublet chemotherapy treatment had not yet been completed) or pemetrexed maintenance monotherapy.

- **Objectives**

Primary Objective:

To assess the efficacy of osimertinib compared with platinum-based doublet chemotherapy by assessment of PFS.

Secondary Objectives:

To further assess the efficacy of osimertinib compared with platinum-based doublet chemotherapy in terms of ORR, DoR, DCR, tumour shrinkage, and OS; to assess the effect of osimertinib compared to platinum-based doublet chemotherapy on subjects' disease-related symptoms and HRQoL; and, to characterise the pharmacokinetics (PK) of osimertinib and metabolites in subjects receiving osimertinib.

- **Outcomes/endpoints**

Primary endpoint

PFS was defined as the time from randomisation until the date of objective disease progression using investigator assessment as defined by RECIST v1.1 or death (by any cause in the absence of progression) regardless of whether the patient withdrew from randomised therapy or received another anti-cancer therapy prior to progression.

Baseline radiological tumour assessments were to be performed within 28 days before randomisation. During the study, scans were to be performed every 6 weeks relative to randomisation until disease progression to evaluate the response. Patients were to be assessed according to the intended scanning schedule relative to randomisation to prevent the bias in analysis that could occur if 1 treatment group was assessed more or less often than the other.

Patients who had not had progressive disease (PD) or died at the time of analysis were censored at the time of the latest date of assessment from their last evaluable RECIST assessment.However, if the patient progressed or died after 2 or more missed visits, that patient was censored at the time of the latest evaluable RECIST assessment. Any patient who had no evaluable visits or did not have baseline data, was censored at 0 day unless that patient diedwithin 2 visits of baseline.

Sensitivity analysis of PFS was planned using BICR assessment of RECIST v1.1.

Secondary endpoints

The secondary outcomes variables were ORR, DoR, DCR, tumour shrinkage, QoL and OS, according to RECIST 1.1 with sensitivity analysis by BICR.

Exploratory endpoints

Effect of osimertinib vs. chemotherapy on post-progression outcomes (time fromrandomisation to second progression [PFS2] and time to subsequent anti-cancer treatments) was explored.

- **Sample size**

The primary efficacy endpoint was PFS. Per amendment 3 to the protocol (dated 21 March 2016, before PFS data cut off), the primary analysis of PFS was to occur when at least 221 progression events had been observed out of the 419 patients randomized, which occurred on 15 April 2106.

With 221 progression events, the study has at least 80% power to show a statisticallysignificant PFS at the 5% two-sided significance level if the assumed treatment effect was a hazard ratio (HR) of 0.67. This would translate into a 3-month improvement on an estimatedmedian PFS of 6 months in the chemotherapy arm, assuming PFS is exponentially distributed.

The smallest treatment difference that would be statistically significant is a PFS HR of 0.76, which translates approximately into a 2-month improvement on the estimated median PFS of 6 months in the control arm assuming PFS is exponentially distributed.

For the rationale for change in planned analyses see protocol amendments below.

- **Randomisation**

Suitable patients were centrally randomised to receive either osimertinib 80 mg orally once daily or platinum-based doublet chemotherapy (pemetrexed 500 mg/m2 + carboplatin AUC5 or pemetrexed 500 mg/m2 + cisplatin 75 mg/m2) on Day 1 of every 21-day cycle in a 2:1 ratio (osimertinib: platinum-based doublet chemotherapy) using the IVRS/IWRS system.

Prior to randomisation, the investigational site declared their choice of chemotherapy for that patient in IVRS/IWRS.

Patients were stratified at randomisation based on ethnicity (Asian/Non-Asian).

- **Blinding (masking)**

The study was open label.

- **Statistical methods**

The FAS was defined as all randomised patients. The FAS was used for all efficacy and exploratory analyses, including the history of CNS disease evaluation. For the CNS BICR analyses, a CNS FAS (cFAS) and a CNS evaluable for response (cEFR) were identified.

The primary analysis of PFS was based on investigator-recorded assessment of disease progression by RECIST v1.1. Progression-free survival was analyzed using a log rank test stratified by ethnicity (Asian, Non-Asian). A sensitivity analysis by BICR was also performed. Secondary endpoints of ORR, DoR, DCR, and tumour shrinkage were analyzed at the time of the primary PFS analysis.

Interim analyses

Three analyses of OS will be conducted. The DCO for the first OS analysis was approximately 4 months after the PFS DCO of 15 April 2016. A second analysis of OS will be performed when the OS data are approximately 50% mature (approximately 205 deaths events). A third analysis of OS will be performed when the OS data are approximately 70% mature (approximately 287 deaths events).

In order to provide strong control of the type I error rate (2-sided 5%), the primary endpoint of PFS and the key secondary endpoints of ORR and OS were tested in this sequential order. If any previous analysis in the sequence was not statistically significant, the alpha spending could not be transferred to subsequent analyses. Since 3 OS analyses were planned, the LanDeMets approach that approximates the O'Brien and

Fleming spending function were used to maintain strong control of the 2-sided 5% type I error across the testing of 3 planned analyses of OS.

Pre-specified CNS metastases analysis:

Patients enrolling in AURA3 were permitted to have asymptomatic, stable brain metastases, defined as not requiring steroids for 4 weeks prior to initiation of study treatment. Central nervous system metastases were assessed by default as non-target lesions (NTLs) for the scope of the study primary and secondary efficacy analyses. CNS exploratory analysis was conducted in AURA3 to explore CNS efficacy in 2 subgroups of patients.

The first analysis explored the CNS efficacy of osimertinib vs. chemotherapy in patients identified as having measurable and/or non-measurable CNS metastases at baseline. The second analysis explored the efficacy of osimertinib vs. chemotherapy in patients with and without a history of CNS metastases as identified by the investigator based on screening/baseline brain scans, and medical history of prior surgery and/or radiotherapy to CNS metastases.

Central nervous system ORR was analysed using logistic regression. Results were presented as an OR with associated 95% profile likelihood CI. As the predefined CNS metastases analyses were considered exploratory, no adjustment was made to the significance level for the statistical testing of the CNS metastases efficacy endpoint

4.3.2. Results

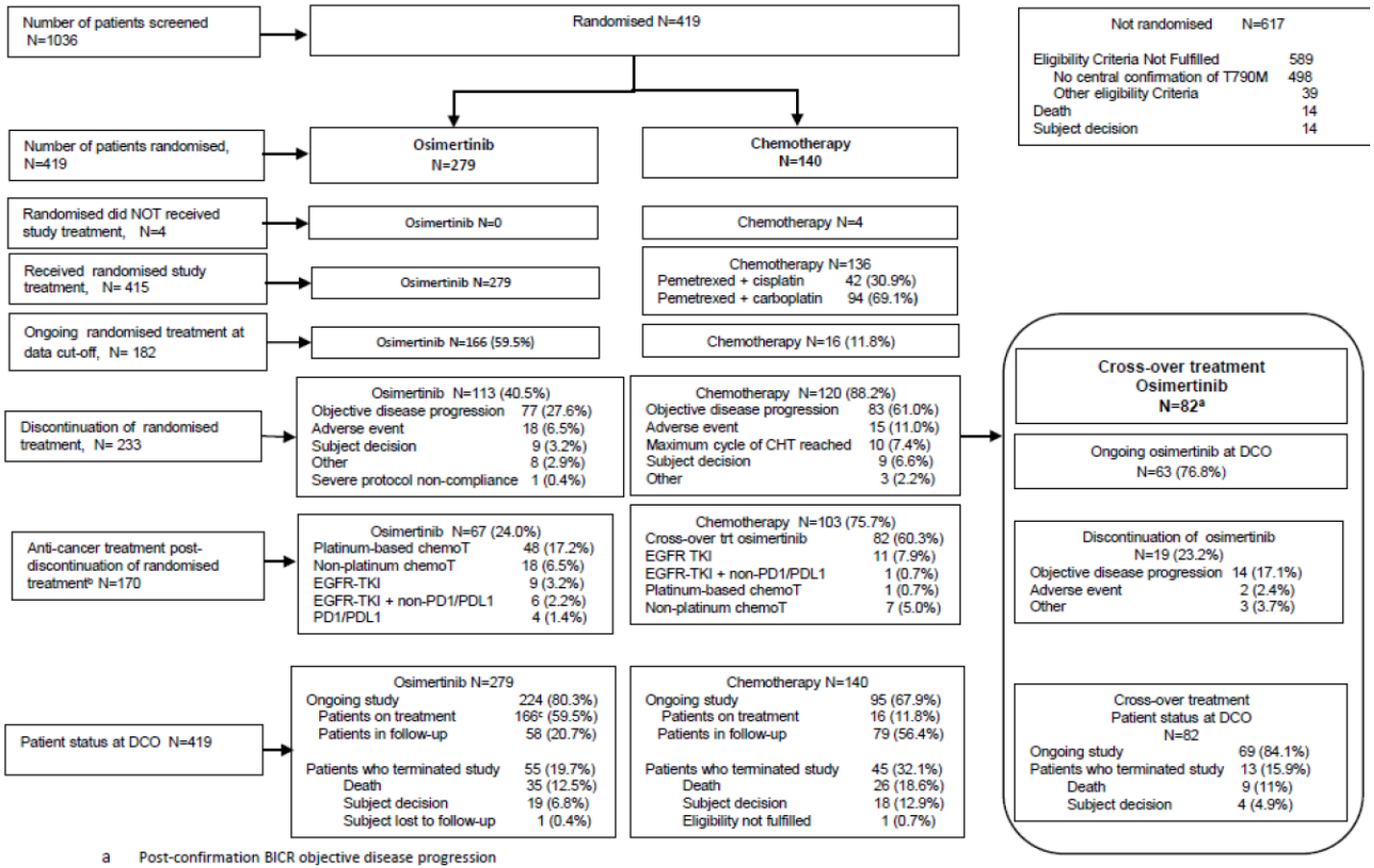
- **Participant flow**

A total of 1036 patients were enrolled in the study (ie, signed informed consent and were screened). A total of 617 patients failed screening as follows:

- Overall, 589/617 (95.5%) patients failed screening because they did not meet eligibility criteria, 14 (2.3%) died during the screening period, and 14 (2.3%) withdrew consent to participate in the study.
- Of the 589 patients who did not meet eligibility criteria, 498 (80.7% of all screen failures) did not have a centrally-confirmed T790M mutation;

A total of 419 patients were randomised to treatment in a 2:1 ratio, 279 (66.6%) to osimertinib 80 mg once daily and 140 (33.4%) to platinum-based doublet chemotherapy. Four (1%) of the randomised patients, all in the chemotherapy group, did not receive treatment: 3 of the 4 patients withdrew consent to participate after randomisation (E2809303 E3205301, and E6002303); and 1 patient (E6001301) had deterioration of liver function tests (LFTs) before treatment started. Thus a total of 415 patients received study treatment (osimertinib, 279; chemotherapy, 136).

Of the 136 patients in the chemotherapy arm, 42 (30.9%) received pemetrexed plus cisplatin and 94 (69.1%) received pemetrexed plus carboplatin based on investigator choice. One hundred (73.5%) patients completed at least 4 cycles of chemotherapy. Of these, 27 patients stopped pemetrexed and carboplatin or cisplatin on the same day or within 1 day; and 73 (53.7%) patients went on to receive pemetrexed maintenance monotherapy. The mean time of pemetrexed maintenance was 3.8 months (sd, 2.73); the median time was 3.1 months (range: 0.7-11.7).



a Post-confirmation BICR objective disease progression

b Patients could have more than 1 line of therapy post discontinuation of randomised treatment

c Patients could continue on osimertinib treatment after objective disease progression

- **Recruitment**

Patients were randomised to treatment at 126 study centres in 18 countries, including Australia (4), Canada (4), China (17), France (5), Germany (6), Hong Kong (5), Hungary (1), Italy (5), Japan (18), South Korea (13), Mexico (2), Netherlands (3), Russia (5), Spain (6), Sweden (3), Taiwan (10), the UK (9), and the USA (10). No individual country randomised more than 20% of patients.

243 (58%) patients were recruited in Asia, 46 (11%) in the Americas, and 130 (31%) in Europe and the rest of the world.

The first patient was randomised and dosed on 20 August 2014; the last 2 patients were randomised on 28 October 2015. The last first dose was administered on 4 November 2015.

- **Conduct of the study**

Protocol amendments:

Two substantial amendments were made to the AURA3 planned analyses. In Amendment 2 to AURA3 clinical study protocol (CSP; dated 6 May 2015), the number of patients to be randomised in the study was reduced from 610 to 410. Although the primary endpoint was PFS, the study had been initially sized to characterise the secondary endpoint of OS and was over-powered for PFS (>95% power to detect a difference in PFS assuming the true HR is 0.67 at a 5% two-sided significance level). Due to the introduction of crossover, the interpretation of OS was compromised and therefore, the study was re-sized to focus on the primary endpoint of PFS, resulting in a sample size reduction. After Amendment 2, the study had 90% power to demonstrate a statistically significant PFS assuming the original hypothesised treatment effect of PFS HR of 0.67 at a 5% two-sided significance level.

In Amendment 3 (dated 21 March 2016, before the DCO for PFS of 15 April 2016), the Sponsor made a reduction in power to detect a statistically significant difference for the primary analysis of PFS from 90% to 80% (assuming an HR of 0.67 and 5% 2-sided significance level). The decision to change the power was based on the compelling results from the Phase II osimertinib monotherapy studies (AURA extension and AURA2 [1 May 2015 DCO]), and from a non-randomised, adjusted comparison of efficacy and safety outcomes from the pooled Phase II trials (AURA extension and AURA2) with the control arm (standard of care [SoC] platinum-based doublet chemotherapy arm [5 May 2014 DCO]) from the IRESSA™ IMPRESS study in the subset of patients with EGFR T790M mutation-positive locally-advanced or metastatic NSCLC. Based on this indirect adjusted comparison using BICR, the ORR was significantly greater in the osimertinib group compared with the SoC group (64.6% vs. 34.8%, respectively, with an OR of 4.76 [95% CI: 2.21, 10.26; p<0.001). The PFS based on BICR was significantly longer in the osimertinib group compared with the SoC group; the HR was 0.28 (95% CI: 0.19, 0.42; p<0.0001), indicating a 72% reduction in risk of disease progression or death in the osimertinib group compared with the SoC group. The median PFS was 9.7 months in the osimertinib group compared with 5.3 months in the SoC group, a 4.4-month improvement in median PFS in the osimertinib group compared with the SoC. For OS, the median OS for osimertinib was NC; the median OS for the SoC group was 21.7 months. The KM plots were overlapping for the 2 groups; the HR was 1.02 (95% CI: 0.39, 2.70; p<0.9654). Data were immature for both osimertinib and SoC, so meaningful conclusions on OS data could not be drawn.

Based on the above, if the assumed treatment effect were still an HR of 0.67 (which translatesto approximately 3 months of improvement on an estimated median PFS of 6 months in the control arm assuming proportional hazards), then 221 progression events would provide 80% power to demonstrate a statistically significant difference in PFS at the 5% two-sided significance level (as compared with the 295 progression events required for assuring the originally planned 90% power to demonstrate a statistically significant PFS for a hypothesised treatment effect of PFS HR of 0.67 at a 5% 2-sided significance level).

Additionally, in order to maximise the maturity of the OS data at the time of the first analysis, the DCO for the first OS analysis was to be performed approximately 4 months after the DCO for the primary PFS analysis (OS DCO: 2 September 2016). At the time of the primary PFS analysis, a summary of the frequency of deaths and primary cause of death were provided for safety purposes, and no additional summaries or analyses were performed in order to protect the integrity of the first OS analysis.

The approach to control the overall Type I error at 5% (two-sided) over 3 OS analyses was modified to the LanDeMets approach that approximates the O'Brien and Fleming spending function.

No interim clinical outcome analyses were conducted prior to the PFS DCO whenAmendments 2 and 3 to the statistical analyses were introduced by the Sponsor. Thus the amendments protected the integrity of the study and are considered to be reasonable and constitute a sound approach to the interpretation of the results.

Protocol deviations:

Important protocol deviations that occurred during the study are summarised in Table 15. One hundred and six (25.3%) patients had at least 1 important protocol deviation, with a similar proportion of patients with at least 1 important protocol deviation in each arm: 67 (24.0%) patients in the osimertinib arm and 39 (27.9%) patients in the chemotherapy arm (Table 15). In general, within each category of protocol deviations, the treatment groups were also balanced.

1 additional patient in the osimertinib arm (E1308307 who is not reported in Table 15) was randomised with screening AST and ALT values above the 2.5 x ULN threshold and was therefore considered to be a protocol violator as there was no evidence the patient fulfilled all entry criteria (Appendix 12.2.8.2). However, subsequent communication from the site confirmed that further clinical chemistry tests performed the day before randomisation showed AST and ALT values below the 2.5 x ULN threshold, which were not reported in the study database; thus the patient was in fact eligible (data on file).

Table 15 Important protocol deviations (Full analysis set)

	Number (%) of patients		
Important protocol deviation[a]	**AZD9291 80 mg (N=279)**	**Chemotherapy (N=140)**	**Total (N=419)**
Number of patients with at least 1 important deviation	67 (24.0)	39 (27.9)	106 (25.3)
Failed Inclusion Criteria	7 (2.5)	4 (2.9)	11 (2.6)
Inclusion Criterion 5: No radiological documentation of disease progression following 1st line EGFR TKI treatment but who have not received further treatment	1 (0.4)	1 (0.7)	2 (0.5)
Inclusion Criterion 7: No documentation that the tumour harbours an EGFR mutation (at any time since the initial diagnosis of NSCLC) known to be associated with EGFR TKI sensitivity (including G719X, exon 19 deletion, L858R, L861Q)	2 (0.7)	0	2 (0.5)
Inclusion Criterion 8: No central confirmation of tumour T790M mutation positive status from a biopsy sample taken after documented disease progression on first line treatment with an approved, EGFR tyrosine kinase inhibitor	4 (1.4)	2 (1.4)	6 (1.4)
Inclusion Criterion 10: No lesions, not previously irradiated and not chosen for biopsy during the study screening period, that can be accurately measured at baseline as = 10 mm in the longest diameter (except lymph nodes which must have short axis = 15 mm) with computerized tomography (CT) or magnetic resonance imaging (MRI) which is suitable for accurate repeated measurements	0	1 (0.7)	1 (0.2)
Inclusion Criterion 11: Females not using adequate contraceptive measures, be breast feeding or have positive pregnancy test prior to dose start if of child-bearing potential	1 (0.4)	0	1 (0.2)
Met Exclusion Criteria	11 (3.9)	8 (5.7)	19 (4.5)

Exclusion Criterion 1: >1 prior treatment, EGFR-TKI 8 days, IP, anticancer drug, AZD9291, 3-generation EGFR-TKI, (neo)adjuvant chemo 6 mo., major surgery, radiotherapy >30% bone marrow, wide-field radiation 4 wk, CYP3A4 inhibitor/inducer, drug 5 x half-life.	10 (3.6)	7 (5.0)	17 (4.1)
Exclusion Criterion 8: Inadequate bone marrow reserve or organ function, assessed against: absolute neutrophil count, platelet count, haemoglobin, AST, ALT, total bilirubin and creatinine.	1 (0.4)	1 (0.7)	2 (0.5)
Other Protocol Deviations excluding eligibility criteria	55 (19.7)	33 (23.6)	88 (21.0)
Baseline tumour assessments (RECIST v1.1) performed more than 28 days before the randomization	2 (0.7)	0	2 (0.5)
Other reason	9 (3.2)	9 (6.4)	18 (4.3)
Patient did not receive any study treatment	0	4 (2.9)	4 (1.0)
Patient experienced pneumonitis in 2015 but was not discontinued from the study treatment	1 (0.4)	0	1 (0.2)
Protocol-required procedure not adhered to	23 (8.2)	13 (9.3)	36 (8.6)
RECIST scans performed outside of the scheduled window on more than 2 occasions	14 (5.0)	8 (5.7)	22 (5.3)
Received incorrect investigational treatment/dose	13 (4.7)	3 (2.1)	16 (3.8)
Received prohibited concomitant medication	1 (0.4)	0	1 (0.2)

Important deviations before the start of treatment and during treatment. Note that the same patient may have had more than 1 important protocol deviation

Important protocol deviations that could potentially affect the primary efficacy analysis of PFS were as follows:

- Two patients in the osimertinib arm (E1301316 and E6004307) were identified as having protocol deviations due to 'no documentation of any EGFR TKI sensitising mutation at any time since the initial diagnosis of NSCLC.' In both situations, an exon 19 deletion mutation was identified from the initial diagnostic biopsy before the date of the histopathological diagnosis of NSCLC being confirmed from the same biopsy. As both mutation result and histopathological diagnosis were obtained from the same sample, this technical protocol deviation does not impact the assessment of efficacy of osimertinib in either patient.
- Six patients (1.4%) did not have centrally confirmed T790M mutation-positive status (Table 15). Of these 6 patients:
  - 2 patients in the osimertinib arm (E4319311 and E6004307) were reported as having missing results but were T790M mutation-positive: E4319311 had a T790M positive result recorded under the patient's previous Ecode; and E6004307 had a positive T790M result recorded on the laboratory report, which was missing from the database by error. No plasma T790M status for these patients was available: E4319311 did not provide a ctDNAplasma sample and E6004307 had insufficient plasma for testing.
  - In addition, Patient E7803301 (chemotherapy arm) is listed as negative as this patient appeared to have had the tumour sample taken after the date of randomisation and was thus not considered as having centrally-confirmed T790M prior to randomisation in the database. However, subsequent communication from the site confirmed the year of sample collection was incorrectly recorded in the study database (2015 instead of 2014), and therefore the patient was T790M positive prior to randomisation (data on file). The ctDNA plasma sample from this patient was negative for T790M.
  - Therefore, 3 patients (2 in the osimertinib arm [E0303304 and E1005310] and 1 in the chemotherapy arm [E5001301]) were tumour T790M negative and were randomised in error. Results from ctDNA plasma samples were positive for E0303304, negative for E1005301, and negative for E5001301.

- Two patients (E0303303 and E6204310), both in the osimertinib arm, had their baseline RECIST scan assessment more than 28 days before randomisation (32 days prior to randomisation for E0303303 and 42 days prior to randomisation for E6204301) (Table 15).
- Sixteen patients had more than 1 prior line of therapy (10 [3.6%] in the osimertinib arm and 6 [4.3%] in the chemotherapy arm): 15 patients had 2 prior lines of therapy and 1 patient had 3 prior lines of therapy. Reasons why patients were classified as having received more than 1 prior line of therapy included: administration of adjuvant or neo-adjuvant chemotherapy less than 6 months prior to the start of the EGFR-TKI therapy; the sequential administration of more than 1 EGFR-TKI agent (changing from first-generation to second-generation EGFRTKI, or the restart of EGFR-TKI after more than 12 months off-treatment); or the addition of anti-cancer agents such as cytotoxic chemotherapy or cMet monoclonal antibody towards the end of the prior monotherapy EGFR-TKI regimen. For the latter 2 examples, although the reason for sequential EGFR-TKI administration or addition of a subsequent agent onto the EGFR-TKI could not be confirmed as due to clinical suspicion of impending disease progression, the most cautious approach was taken and these examples were classified as being a second prior-treatment regimen.
- The proportion of patients with RECIST scans performed outside of the protocol schedule (±1-week window) on more than 2 occasions was low and balanced between arms (5% in the osimertinib arm and 5.7% in the chemotherapy arm).
- Four patients, all in the chemotherapy arm, were randomised but did not receive treatment (Table 15).

Concomitant treatment

Overall, 34 (8.1%) patients received concomitant anti-cancer therapies (including radiotherapy) during the study, with a greater proportion in the chemotherapy arm (16 [11.4%] patients) compared to the osimertinib arm (18 [6.5%] patients).

Radiotherapy while on treatment was administered to 17 (6.1%) patients in the osimertinib arm vs. 14 (10.0%) patients in the chemotherapy arm. On-study radiotherapy was only allowed for palliation of painful bone metastases.

Three patients were reported as receiving concomitant anti-cancer therapy during the study.

- Two patients received concomitant chemotherapy:
  - Patient E1002327 (chemotherapy arm) had a >2-week interruptionbetween chemotherapy cycles and was classified as having discontinuedchemotherapy, but received 1 further cycle of chemotherapy beforecrossing over to osimertinib after disease progression.
  - Patient E1314303 (osimertinib arm) received therapy with cisplatin,pemetrexed, and bevacizumab starting on 9-Nov-2015, but onlypermanently discontinued osimertinib on 16-Nov-2015.
- One additional patient (E6208302 in the chemotherapy arm) who startedchemotherapy on 16-Jul-2015, was randomised while still receiving first-lineEGFR-TKI, received the last dose of EGFR-TKI on 5-Jul-2015, and wasconsequently reported on the “on-study treatment” case report form (CRF) in thestudy database.

One osimertinib patient (E1301316) received a disallowed concomitant medication (carbamazepine), which was discontinued only 8 days prior to randomisation, a shorter withdrawal period than the 3-week mandated by the protocol.

The vast majority of patients (408 [97.4%] overall; osimertinib: 270 [96.8%]; chemotherapy: 138 [98.6%]) received allowed concomitant medications during the study.Concomitant medications were

generally representative of medications commonly administered to patients with advanced NSCLC and were not considered to affect the study results.

- In the osimertinib arm, the most common types of concomitant medications administered during the study (at least 30% of patients), by ATC class, were Anilides (36.2%; mostly paracetamol [34.4%]) and Glucocorticoids (31.5%, including dexamethasone [20.1%]).
- In the chemotherapy arm:
  - In line with prescribing recommendations for pemetrexed toxicity management, 91 (65%) patients received folic acid and derivatives compounds, (including folic acid, 89 [63.6%]), 111 (79.3%) patients received Vitamin B12 (cyanocobolamin and analogues), and 31 (22.1%) received Multivitamins plain (Vitamins NOS) (Table 11.1.14.2). Similarly, 125 (89.3%) patients received Glucocorticoids, which were mostly dexamethasone (112 [80%]) and dexamethasone sodium phosphate (24 [17.1%]).
- The most common ATC types of other concomitant medications administered during the study (at least 30% of patients) were Serotonin (5HT3) antagonists (80.0%, the most frequent of which were ondansetron [25.0%], palonosetron hydrochloride [15.7%], ondansetron hydrochloride [15.0%], and granisetron [15.0%]); Proton pump inhibitors (45.7%, the most frequent of which were lansoprazole [12.1%], esomeprazole magnesium [10.7%], and omeprazole [9.3%]); Propulsives (45.0%, mostly metoclopramide [36.4%]); Other antiemetics (41.4%, including Aprepitant [33.6%]); Anilides (30.7%, mostly paracetamol [29.3%]); and Osmotically acting laxatives (30.7%, including magnesium oxide [15.7%]).

The pattern of concomitant medications was as anticipated for patients with advanced NSCLC receiving these categories of anti-cancer agents (ie, EGFR-TKI and platinum-based doublet chemotherapy).

Treatment compliance

One (0.4%) patient in the osimertinib arm (E1314303) was withdrawn from the study due to severe non-compliance to treatment. The patient received platinum-based chemotherapy and bevacizumab during treatment with osimertinib, which was contraindication per protocol.

- **Baseline data**

At study entry, the median age of the 419 patients randomised to treatment was 62.0 years (range: 20-90); 64 (15.3%) patients were ≥75 years in age. The treatment groups were well balanced with regard to age, with a median of 62.0 years (range: 25-85 years) in the osimertinib arm and 63.0 years (range: 20-90 years) in the chemotherapy arm.

The majority of patients were female (269 [64.2%] patients). There was a slightly greater proportion of female patients in the chemotherapy arm than in the osimertinib arm (osimertinib, 172 [61.6%]; chemotherapy, 97 [69.3%]).

The treatment groups were well balanced with regard to race. Nearly two-thirds of patients (65.4%) were of Asian racial origin; the remainder of patients were mainly White.

The treatment arms were well balanced with regard to smoking status. Most patients (67.5%) had never smoked . The remainder were mainly former smokers (27.2%). Only 5.3% patients were current smokers.

Table 17 Demographic characteristics (Full analysis set)

Demographic characteristic		Osimertinib 80 mg (N=279)	Chemotherapy (N=140)	Total (N=419)
Age (years)	n	279	140	419
	Mean	61.5	62.0	61.7
	sd	11.64	11.91	11.72
	Median	62.0	63.0	62.0
	Min	25	20	20
	Max	85	90	90
Age group (years) n (%)	<50	44 (15.8)	20 (14.3)	64 (15.3)
	≥50 - <65	121 (43.4)	57 (40.7)	178 (42.5)
	≥65	114 (40.9)	63 (45.0)	177 (42.2)
	≥75	42 (15.1)	22 (15.7)	64 (15.3)
Sex n (%)	Male	107 (38.4)	43 (30.7)	150 (35.8)
	Female	172 (61.6)	97 (69.3)	269 (64.2)
Race n (%)	White	89 (31.9)	45 (32.1)	134 (32.0)
	Black or African American	4 (1.4)	1 (0.7)	5 (1.2)
	Asian	182 (65.2)	92 (65.7)	274 (65.4)
	American Indian or Alaska Native	0	1 (0.7)	1 (0.2)
	Other	4 (1.4)	1 (0.7)	5 (1.2)
Ethnic group n (%)	Hispanic or Latino	5 (1.8)	3 (2.1)	8 (1.9)
	Asian (other than Chinese and Japanese)	53 (19.0)	34 (24.3)	87 (20.8)

Table 17 Demographic characteristics (Full analysis set)

Demographic characteristic		Osimertinib 80 mg (N=279)	Chemotherapy (N=140)	Total (N=419)
	Chinese	88 (31.5)	36 (25.7)	124 (29.6)
	Japanese	41 (14.7)	22 (15.7)	63 (15.0)
	Other	92 (33.0)	45 (32.1)	137 (32.7)
Smoking status, n (%)	Never	189 (67.7)	94 (67.1)	283 (67.5)
	Current	14 (5.0)	8 (5.7)	22 (5.3)
	Former	76 (27.2)	38 (27.1)	114 (27.2)

sd = standard deviation.
Data cut-off: 15 April 2016
Source: Table 11.1.5 and Table 11.1.11.

Disease characteristics

All 419 randomised patients had locally advanced or metastatic NSCLC and 413 (98.6%) had central confirmation of the T790M mutation-positive status of their tumours (Table 18).

6 patients (4 on osimertinib and 2 on chemotherapy) did not have central confirmation their tumours were T790M mutation-positive in the study database, although 3 of the 6 patients (2 in the osimertinib arm and 1 in the chemotherapy arm) were subsequently found to be tumour T790M mutation-positive. Thus 416 patients had T790M mutation-positive tumours at randomisation. One of the 3 patients who was tumour T790M negative had a positive plasma ctDNA T790M status.

Per protocol, all patients were to be in second-line therapy. The vast majority of patients (88.8% were in second-line therapy after having progressed on a single regimen of EGFR-TKI prior to enrollment. Fifteen (3.6%) patients overall (osimertinib, 9 [3.2%]; chemotherapy, 6 [4.3%]) had received 2 prior anti-cancer regimen at study entry; and 1 (0.2%) patient in the osimertinib arm had received 3 prior regimens prior to study entry.

Baseline disease characteristics were generally well balanced in the 2 treatment arms (Table 18).

- The majority of patients had metastatic NSCLC (96.4).
- The most common NSCLC histological type was adenocarcinoma (98.6% patients overall). 3 patients (1.1%), all in the osimertinib arm, had squamous cell carcinoma. All 3 patients were ongoing in the study at DCO after 180 days, 199 days, and 297 days, respectively, with a best objective response of SD, PR, and PR, respectively.
- The most common EGFR sensitising mutations based on Roche cobas® EGFR Mutation Test were exon 19 deletion (278 [66.3%] patients overall; osimertinib, 191 [68.5%]; chemotherapy, 87 [62.1%]) and exon 21 L858R (128 [30.5%] overall; osimertinib, 83 [29.7%]; chemotherapy, 45 [32.1%]). The proportion of patients with exon 19 deletion was slightly higher in the osimertinib arm than in the chemotherapy arm (Table 18).
- A total of 144 (34.4%) patients (osimertinib, 93 [33.3%]; chemotherapy, 51 [36.4%]) had CNS metastases at baseline, with the patients identified on the study level FAS by CNS lesion site at baseline, medical history, and/or prior surgery, and/or radiotherapy to CNS metastases (Table 18).
- Over half of the patients had extra-thoracic visceral metastases at baseline (225 [53.7%] patients overall). The proportion of patients with visceral metastases was slightly lower in the osimertinib arm (145 [52.0%]) than in the chemotherapy arm (80 [57.1%]) (Table 18). Similarly, the proportion of patients with liver metastases (including patients with locally advanced and/or metastatic disease, with a site of disease recorded as “Liver” or “Hepatic [including gallbladder]) was lower in the osimertinib arm (56 [20.1%]) than in the chemotherapy arm (41 [29.3%]) (Table IMT0346).
- A smaller proportion of patients had bone/locomotor metastatic disease in the osimertinib arm (105 [37.6%] patients) than in the chemotherapy arm (68 [48.6%]) (Table 11.1.10). Please note: As recorded in the CRF, 3 further patient shad bone/locomotor metastases reported as a locally-advanced site of NSCLC.
- The mean tumour burden (TL size) at baseline was 55.1 mm (standard deviation [sd], 33.92) overall and well balanced between treatment arms (55.2 mm [sd, 34.04] in the osimertinib arm vs. 54.9 mm [sd, 33.79] in the chemotherapy arm) (Table 18).
- Most patients had a WHO performance status of 1 (261 [62.3%] patients overall; osimertinib, 177 [63.4%]; chemotherapy, 84 [60.0%]) (Table 18).

Table 18 Disease characteristics at baseline (Full analysis set)

	Number (%) of patients		
	AZD9291 80 mg (N=279)	Chemotherapy (N=140)	Total (N=419)
WHO performance status			
0 (Normal activity)	102 (36.6)	56 (40.0)	158 (37.7)
1 (Restricted activity)	177 (63.4)	84 (60.0)	261 (62.3)
Overall disease classification			
Metastatic[a]	266 (95.3)	138 (98.6)	404 (96.4)
Locally advanced[b]	13 (4.7)	2 (1.4)	15 (3.6)
CNS metastases[c]	93 (33.3)	51 (36.4)	144 (34.4)
No CNS metastases[c]	186 (66.7)	89 (63.6)	275 (65.6)
Extrathoracic visceral metastases[d]	145 (52.0)	80 (57.1)	225 (53.7)
No extrathoracic visceral metastases[d]	134 (48.0)	60 (42.9)	194 (46.3)
EGFR mutations by cobas® central test[e,f]			
EGFR EXON 20 T790M	275 (98.6)	138 (98.6)	413 (98.6)
EGFR EXON 21 L858R	83 (29.7)	45 (32.1)	128 (30.5)
EGFR EXON 19 Deletion	191 (68.5)	87 (62.1)	278 (66.3)
G719X	4 (1.4)	2 (1.4)	6 (1.4)
S768I	1 (0.4)	1 (0.7)	2 (0.5)
EGFR EXON 20 Insertion	1 (0.4)	2 (1.4)	3 (0.7)
Baseline tumour size (mm)			
n	279	140	419

Table 18 Disease characteristics at baseline (Full analysis set)

	Number (%) of patients		
	AZD9291 80 mg (N=279)	Chemotherapy (N=140)	Total (N=419)
Mean	55.2	54.9	55.1
SD	34.04	33.79	33.92
Median	46.0	47.0	46.0
Min	10	11	10
Max	174	166	174
Baseline tumour size category (mm) n (%)			
<40	114 (40.9)	55 (39.3)	169 (40.3)
40 - 79	105 (37.6)	56 (40.0)	161 (38.4)
80 - 119	42 (15.1)	22 (15.7)	64 (15.3)
>=120	18 (6.5)	7 (5.0)	25 (6.0)

Abbreviations: sd = standard deviation; WHO = World Health Organization; EGFR = epidermal growth factor receptor; NOS = not otherwise specified.

[a] Metastatic disease - Patient had any metastatic site of disease.

[b] Locally advanced - Patient had only locally advanced sites of disease.

[c] CNS metastases were determined programmatically from baseline data of CNS lesion site, medical history, and/or surgery, and/or radiotherapy. One patient was identified as having locally advanced disease in the brain.

[d] Extra-thoracic visceral metastases were determined programmatically from baseline data where the disease site was "Adrenal, "Ascites," Brain/CNS," "Gastrointestinal," "Genitourinary," "Hepatic (including gallbladder)," "Liver," "Other CNS," "Pancreas," "Peritoneum," or "Spleen", and/or those "Other metastatic sites" such as "Eye" and "Thyroid" as identified as extra-thoracic visceral sites by AZ Physicians.

[e] EGFR mutation identified by the Roche cobas® EGFR Mutation Test (by biopsy taken after confirmation of disease progression on the most recent treatment regimen).

[f] Two patients reported in the database as missing samples were T790M mutation positive (E4319311 and E6004307, both in the osimertinib arm)

Data cut-off: 15 April 2016

Source: Table 11.1.9

Prior anti-cancer therapy

Per protocol, all randomised patients were to have received only 1 prior line of treatment with an EGFR-TKI for advanced NSCLC and were to be in second-line therapy. All patients had received prior EGFR-TKI therapy.

Of the 419 randomised patients, 403 (96.2%) had received only 1 prior EGFR-TKI as per protocol, including 269 (96.4%) patients in the osimertinib arm and 134 (95.7%) in the chemotherapy arm (Table 19). As

described in the protocol deviations section (Section 6.2), 16 (3.8%) patients overall (osimertinib, 10 [3.6%]; chemotherapy, 6 [4.3%]) had received more than 1 prior anti-cancer regimen at study entry (Table 19); 15 patients had received 2 prior lines of therapy and 1 (0.2% overall) patient in the osimertinib arm had received 3 prior regimens prior to study entry. Reasons why patients were classified as having received more than 1 prior line of therapy included: administration of adjuvant or neo-adjuvant chemotherapy less than 6 months prior to the start of the EGFR-TKI therapy; the sequential administration of more than 1 EGFR-TKI agent (changing from first-generation to second generation EGFR-TKI, or the restart of EGFR-TKI after more than 12 months off-treatment); or the addition of anti-cancer agents such as cytotoxic chemotherapy or cMet monoclonal antibody towards the end of the prior monotherapy EGFR-TKI regimen. For the latter 2 examples, although the reason for sequential EGFR-TKI administration or addition of a subsequent agent onto the EGFR-TKI could not be confirmed as due to clinical suspicion of impending disease progression, the most cautious approach was taken and these examples were classified as being a second prior-treatment regimen. In addition, 1 patient started first line EGFR-TKI therapy in combination with bevacizumab on the same day and was counted as receiving a single regimen.

The treatment arms were well-balanced with regard to prior anti-cancer therapy (Table 19).

- Approximately two-third of patients overall (253 [60.4%]) had received prior treatment with gefitinib (osimertinib, 166 [59.5%]; chemotherapy, 87 [62.1%]). The second most frequently administered prior EGFR-TKI was erlotinib(145 [34.6%] patients overall; osimertinib, 96 [34.4%], chemotherapy, 49 [35.0%]). Twenty-four (5.7%) patients had received prior afatinib, the majority of which were in the osimertinib arm (20 [7.2%] compared to 4 [2.9%] patients in the chemotherapy arm). One patient in the chemotherapy arm (E6208302) was excluded from the prior EGFR-TKI summary in Table 19 because she was still receiving gefitinib for 3 days after randomisation (but stopped gefitinib 10 days before starting chemotherapy); thus this patient was reported as receiving concomitant anti-cancer therapy rather than prior EGFR-TKI.
- The mean time between the most recent disease progression and randomisation in the study was 71.1 days (sd, 54.78) overall and was well balanced between treatment arms (71.3 days [sd, 55.34] in the osimertinib arm and 70.7 days [sd, 53.85) in the chemotherapy arm (Table 11.1.8). The median time was 58.0 days (osimertinib, 60.0 days; chemotherapy, 55.0 days) and ranged from 3 days to 550 days (osimertinib, 3-550; chemotherapy, 15-344). The extreme outlying patients with the longest duration in both treatment arms were due to the date of first diagnosis being reported in error instead of the most recent disease progression. The extreme outlying patients with the shortest duration were due to further disease progression being reported from the baseline RECIST scan performed during the screening period.
- The duration of the prior EGFR-TKI therapy was ≥6 months in the vast majority of patients (395 [94.3%] overall), including 262 (93.9%) patients in the osimertinib arm 133 (95.0) patients in the chemotherapy arm (Table 19).
- Approximately one-third of patients overall (139 [33.2%]) had received prior radiotherapy before study entry, including 90 (32.3%) in the osimertinib arm and 49 (35.0%) in the chemotherapy arm.
- Thirty-five (8.4%) patients overall had received prior adjuvant/neo-adjuvant therapy completed at least 6 months prior to the start of the EGFR-TKI agent (osimertinib:25 [9.0%]; chemotherapy: 10 [7.1%]) (Table 19).

Table 19 Previous disease-related treatment modalities (Full analysis set)

	Number (%) of patients		
Previous treatment modalities	Osimertinib 80 mg (N=279)	Chemotherapy (N=140)	Total (N=419)
Radiotherapy	90 (32.3)	49 (35.0)	139 (33.2)
Number of previous anti-cancer regimens for advanced disease			
1	269 (96.4)	134 (95.7)	403 (96.2)
2	9 (3.2)	6 (4.3)	15 (3.6)
3	1 (0.4)	0	1 (0.2)
Mean	1.0	1.0	1.0
sd	0.21	0.20	0.21
Median	1.0	1.0	1.0
Min	1	1	1
Max	3	2	3
Any EGFR-TKI	279 (100)	139 (99.3)	418 (99.8)
Gefitinib	166 (59.5)	87 (62.1)	253 (60.4)
Erlotinib	96 (34.4)	49 (35.0)	145 (34.6)
Afatanib	20 (7.2)	4 (2.9)	24 (5.7)
EGFR-TKI therapy			
Duration of prior EGFR TKI			
<6 months	17 (6.1)	7 (5.0)	24 (5.7)
≥6 months	262 (93.9)	133 (95.0)	395 (94.3)
Prior adjuvant/neo-adjuvant treatment	25 (9.0)	10 (7.1)	35 (8.4)

<Abbreviations: EGFR TKI = Epidermal growth factor receptor tyrosine kinase inhibitor; sd = standard deviation.

- Numbers analysed

The analysis sets and the number of patients in each analysis set are summarised in Table 16.

Table 16 Analysis sets

	Number of patients		
	Osimertinib 80 mg	Chemotherapy	Total
Patients randomised	279	140	419
Patients included in full analysis set	279	140	419
Patients included in safety analysis set	279	136	415
Patients excluded from safety analysis set[a]	0	4	4
Did not receive treatment	0	4	4
Patients included in PK analysis set	250	0	250
Patients excluded from PK analysis set[a]	29	140	169
Patient had detectable pre-dose concentration of osimertinib above the LLQ at Cycle 1 Day 1	12	0	12
No relevant data, time and dosing data for any sample	15	0	15
No measurable post-dose PK concentration	2	140	142

[a] Patients could have been excluded for more than 1 reason.

- **Outcomes and estimation**

Primary efficacy analysis: PFS based on investigator assessment

At the DCO for the primary analysis of PFS (15 April 2016), There was a statistically significant (p-value <0.001; Table 12) and clinically meaningful improvement in PFS for patients on osimertinib compared to patients on chemotherapy. The HR was 0.30 (95% CI: 0.23, 0.41), indicating a 70% reduction in the risk of disease progression or death in the absence of RECIST progression in the osimertinib arm compared to the chemotherapy arm.

The median PFS of 10.1 months (95% CI: 8.3, 12.3) in the osimertinib arm compared to 4.4 months (95% CI: 4.2, 5.6) in the chemotherapy arm indicated a clinically meaningful 5.7-month improvement in median PFS in favour of osimertinib.

Table 1 Primary analysis of progression-free survival in AURA3 - investigator and BICR assessments on FAS - log-rank test

Treatment arm	N	Number (%) of patients with events[a]	Comparison between groups		
			Hazard ratio	95% CI	2-sided p-value
Log-rank test for PFS by investigator assessment (primary analysis)					
Osimertinib 80 mg	279	140 (50.2)	0.30	0.23, 0.41	<0.001
Chemotherapy	140	110 (78.6)			
Log-rank test for PFS by BICR (sensitivity analysis)					
Osimertinib 80 mg	279	116 (41.6)	0.28	0.20, 0.38	<0.001
Chemotherapy	140	103 (73.6)			

a Progression events that did not occur within 14 weeks of the last evaluable assessment (or randomisation) were censored and therefore excluded in the number of events..
Data cut-off: 15 April 2016.

At the DCO, 250 patients had progressed based on investigator assessment or died in the absence of progression (59.7% maturity); data had an appropriate maturity for the analysis to be meaningful (Table 12). The statistical design requirements for the study were met as the number of PFS events provided adequate power (at least 80%) to detect the PFS HR (0.67) the study was designed for assuming a 2-sided type-I error of 5% level.

A smaller proportion of patients had a progression event or died without RECIST progression in the osimertinib arm (140 patients; 50.2%) compared to the chemotherapy arm (110 patients; 78.6%).

Most of the progression events were due to progression by RECIST criteria (osimertinib, 129/140 events [92.1%]; chemotherapy 104/110 events [94.5%]). Fewer patients had progression in Non-target lesion (NTLs) and new lesion (NLs) in the osimertinib arm compared to chemotherapy (osimertinib: 27 [9.7%] and 72 [25.8%], respectively; chemotherapy: 47 [33.6%] and 61 [43.6%]). The number of deaths without RECIST progression was similar between treatment arms (osimertinib: 11 [3.9%] patients; chemotherapy: 6 [4.3%] patients).

The median follow-up for censored patients was longer in the osimertinib arm (8.4 months) than in the chemotherapy arm (5.5 months). This is likely to be driven by the greater number of patients in the chemotherapy arm that were censored at Day 1 (10 patients in the chemotherapy arm vs. 1 patient in the osimertinib arm). Further, the median follow-up for censored patients was 8.0 months in the chemotherapy arm compared to 8.4 months in the osimertinib arm when these 11 patients are excluded.

Based on a KM analysis of PFS by BICR, the estimated proportion of patients alive and progression-free at 6 months was 68.8% (95% CI: 62.9, 74.0) in the osimertinib arm vs. 36.9% (95% CI: 28.5, 45.3) in the chemotherapy arm, and at 12 months was 44.0% (95% CI: 36.9, 50.9) in the osimertinib arm vs. 9.8% (95% CI: 4.9, 16.9) in the chemotherapy arm (Table 13 and Figure 4). There was a clear separation of the KM curves in favour of osimertinib for the duration of the study.

Sensitivity analyses of PFS did not indicate any evidence of evaluation time bias (which could occur if scans were not performed at the protocol-scheduled time points). The HR in this analysis (0.29 [95% CI: 0.22, 0.40]) was consistent with the primary analysis. A sensitivity analysis to evaluate attrition bias indicated that the censoring rules applied did not affect the outcome of the primary analysis (HR: 0.30 [95% CI: 0.22, 0.40]).

There was no evidence of a lack of proportional hazards from the plot of log-log (PFS survivor function) vs. log (PFS time) by investigator assessment. The median number of days between RECIST assessments by investigator was similar in both treatment arms (41.8 days [range: 9 to 56] in the osimertinib arm and 42.0 days [range: 13 to 74] in the chemotherapy arm). There was no evidence of a difference in frequency of RECIST assessments between treatment groups.

At the PFS DCO of 15 April 2016, 73 (26.2%) of the 279 patients on osimertinib had NLs based on investigator assessment compared to 63 of 140 (45.0%) those on chemotherapy. The proportional difference in incidence of NLs between treatment arms was mostly driven by NLs in the chemotherapy arm compared to the osimertinib arm in the CNS (14.3% vs. 4.7%, respectively) and in the lung (17.9% vs. 8.6%, respectively).

The BICR assessment of NLs was generally consistent with the investigator, with 78 (28.0%) patients with NLs in the osimertinib arm compared to 53 (37.9%) in the chemotherapy arm.

Progression-free survival by BICR (sensitivity analysis)

The analysis of PFS by BICR on the FAS was performed as a sensitivity analysis, and was consistent with the investigator-based analysis (HR: 0.28, 95% CI: 0.20, 0.38; p<0.001) (Table 12 and Table 13) indicating a 72% reduction in the risk of disease progression or death in absence of RECIST progression in the osimertinib group compared to the chemotherapy group. Median PFS was comparable between analyses (osimertinib: 10.1 months by investigator assessment vs. 11.0 months by BICR; chemotherapy: 4.4 months by investigator vs 4.2 months by BICR), indicating a 6.8 month improvement in median PFS by BICR.

Based on a KM analysis, the estimated proportion of patients alive and progression-free at 6 months was 69.6% (95% CI: 63.6, 74.8) in the osimertinib arm vs. 34.1% (95% CI: 25.8, 42.5) in the chemotherapy arm and at 12 months was 46.9% (95% CI: 39.1, 54.4) in the osimertinib arm vs. 11.3% (95% CI: 5.6, 19.1) in the chemotherapy arm. There was a clear separation of the KM curves in favour of osimertinib for the entire duration of the follow-up (Figure 5).

The overall concordance between the BICR and investigator-assessed disease progression was 82.6%. There was disagreement in the assessment of disease progression status for 73 patients (Table 14).

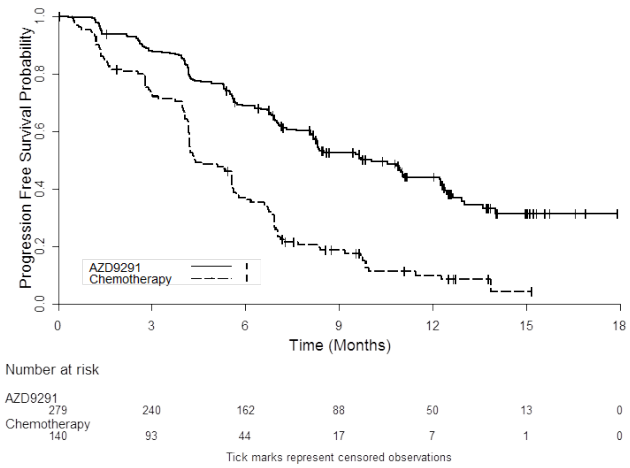
The concordance was 77.8% in the osimertinib arm, with disagreement for 62 patients. The concordance was 92.1% in the chemotherapy arm, with disagreement for 11 patients. The difference in concordance between treatment arms may be due in part to the mandatory BICR confirmatory review of scans at the time of disease progression for chemotherapy patients before cross-over to osimertinib was allowed. Comparison of the BICR and investigator-assessed date of progression demonstrated that most of the discordant PD dates were recorded earlier by BICR than by investigator (osimertinib: 44.3% [based on 43/97 patients]; chemotherapy: 32.7% [based on 33/101 patients]). There was a consistent selection of TLs and NTLs between the BICR radiologists and investigator.

Table 2 Primary analysis of progression-free survival in AURA3 - investigator and BICR assessments

	AURA3 osimertinib arm (N=279)	AURA3 chemotherapy arm (N=140)
Median PFS based on investigator assessment of the FAS		
Total number of events[a]	140	110
Median PFS (months)[b]	10.1	4.4
95% CI for median PFS	8.3, 12.3	4.2, 5.6
Progression-free at 6 months (%)[b]	68.8	36.9
95% CI for PFS at 6 months	62.9, 74.0	28.5, 45.3
Progression-free at 12 months (%)[b]	44.0	9.8
95% CI for PFS at 12 months	36.9, 50.9	4.9, 16.9
Median follow-up for PFS (months)[c]	8.4	5.5
Median PFS based on BICR assessment of the FAS (sensitivity analysis)		
Total number of events[a]	116	103
Median PFS (months)	11.0	4.2
95% CI for median PFS	9.4, NC	4.1, 5.6
Progression-free at 6 months (%)[b]	69.6	34.1
95% CI for PFS at 6 months	63.6, 74.8	25.8, 42.5
Progression-free at 12 months (%)[b]	46.9	11.3
95% CI for PFS at 12 months	39.1, 54.4	5.6, 19.1
Median follow-up for PFS (months)[c]	8.2	5.6

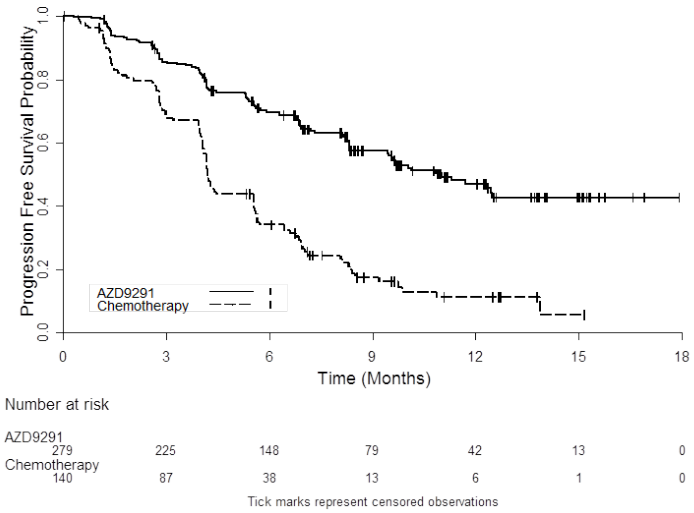
a Progression events that did not occur within 14 weeks of the last evaluable assessment (or randomisation) were censored and therefore excluded in the number of events.
b Calculated using the KM technique.
c Calculated as the median time from randomisation to date of censoring (date last known to be non-progression) in censored (not progressed) patients only.
Progression included deaths in the absence of RECIST progression.
RECIST version 1.1.
BICR=blinded independent central review; CI=confidence interval; CSR=clinical study report; FAS=full analysis set; KM=Kaplan-Meier; NC=not calculable; PFS=progression-free survival; RECIST=Response Evaluation Criteria in Solid Tumors.

Figure 1 Progression-free survival in AURA3 by investigator assessment, Kaplan-Meier plot (FAS)



Progression events that did not occur within 14 weeks of the last evaluable assessment (or randomisation) were censored and therefore excluded in the number of events.
Data cut-off: 15 April 2016.

Figure 2 Progression-free survival in AURA3 by BICR, Kaplan-Meier plot (FAS)



Progression events that did not occur within 14 weeks of the last evaluable assessment (or randomisation) are censored and therefore excluded in the number of events.

Table: Progression status at time of progression-free survival analysis by investigator assessment (full analysis set)

Progression status	Type of event	Number (%) of patients	
		AZD9291 80 mg (N=279)	Chemotherapy (N=140)
Progression[a]	Total	140 (50.2)	110 (78.6)
	RECIST progression	129 (46.2)	104 (74.3)
	Target lesions[c]	65 (23.3)	41 (29.3)
	Non target lesions[c]	27 (9.7)	47 (33.6)
	New lesions[c]	72 (25.8)	61 (43.6)
	Death[b]	11 (3.9)	6 (4.3)
No progression	Total	139 (49.8)	30 (21.4)
	Censored RECIST progression[d]	0	1 (0.7)
	Censored death[e]	0	1 (0.7)
	Progression free at time of analysis[f]	130 (46.6)	19 (13.6)
	Lost to follow-up[g]	0	0
	Withdrawn consent[g]	9 (3.2)	9 (6.4)
	Withdrawn from study for other reasons	0	0

[a] Only included progression events that occurred within 14 weeks of the last evaluable assessment.
[b] Death in the absence of RECIST progression.
[c] Target Lesions, Non Target Lesions, and New Lesions were not necessarily mutually exclusive categories.
[d] RECIST progression event occurred >14 weeks after last evaluable RECIST assessment (or randomisation).
[e] Death occurred >14 weeks after last evaluable RECIST assessment (or randomisation).
[f] Included patients, known to be alive, with no evaluable baseline RECIST assessment (censored at day 0).
[g] Patients at last evaluable RECIST assessment.

Table 3 Concordance in AURA3 between investigator-assessed and BICR-assessed disease progression (FAS)

			Disease progression per BICR	
			Progressive disease	**No progression**
Overall (N=419)	Disease progression per investigator	Progressive disease	198 (47.3%)	52 (12.4%)
		No progression	21 (5.0%)	148 (35.3%)
Osimertinib (N=279)	Disease progression per investigator	Progressive disease	97 (34.8%)	43 (15.4%)
		No progression	19 (6.8%)	120 (43.0%)
Chemotherapy (N=140)	Disease progression per investigator	Progressive disease	101 (72.1%)	9 (6.4%)
		No progression	2 (1.4%)	28 (20.0%)

BICR=blinded independent central review; CSR=clinical study report; FAS=full analysis set.
Source: Table 11.2.1.6 of the AURA3 CSR in Module 5.3.5.1.

Secondary efficacy variables

- Secondary efficacy variable of overall survival

At the PFS DCO of 15 April 2016, no formal analysis of OS had been performed; as per the CSP, the DCO for the first OS analysis occurred on 2 September 2016, approximately 4 months after the PFS DCO of 15 April 2016. Data for the first OS analysis will be provided as part of the RSI responses and are not included herein.

As no formal analysis was performed, only a summary of death events was provided. Overall there were 61 (14.6%) deaths (35 [12.5%] in the osimertinib arm vs. 26 [18.6%] in the chemotherapy arm).

As stated previously, 3 analyses of OS will be conducted. A second analysis of OS will be performed when the OS data are approximately 50% mature (approximately 205 deaths events). A third analysis of OS will be performed when the OS data are approximately 70% mature (approximately 287 deaths events).

- Objective response rate by investigator assessment

There was a clinically meaningful and statistically significant improvement in ORR for patients in the osimertinib arm compared to those on chemotherapy, with patients approximately five times more likely to respond to osimertinib compared to chemotherapy based on investigator assessment: the OR was 5.39 (95% CI: 3.47, 8.48) (p-value: <0.001) (Table 15). The ORR (unadjusted) by investigator assessment was 70.6% (95% CI: 64.9, 75.9) in the osimertinib arm and 31.4% (95% CI: 23.9, 39.8) in the chemotherapy arm.

The BORs based on investigator assessment included 4 (1.4%) patients with CRs and 193 (69.2%) patients with PRs in the osimertinib arm vs. 2 (1.4%) patients with CR and 42 (30.0%) with PR in the chemotherapy arm (Table 16). A smaller proportion of patients in the osimertinib arm had a BOR of SD≥6 weeks (63 [22.6%] patients, compared to 60 [42.9%] patients in the chemotherapy arm). This is due to the higher incidence of patients with CR and PR in the osimertinib arm.

The ORR based on BICR analysis of the FAS was consistent with that based on the investigator assessment (Table 15 and Table 16), with an improvement in ORR for patients on osimertinib compared to those on chemotherapy (OR: 3.63 [95% CI: 2.37, 5.64], p-value: <0.001). The ORR (unadjusted) based on BICR was 64.9% (95% CI: 59.0, 70.5) in the osimertinib arm and 34.3% (95% CI: 25.6, 42.8) in the chemotherapy arm.

Based on assessment by BICR, 3 (1.1%) patients had a CR and 178 (63.8%) had a PR in the osimertinib arm vs. none with CRs and 48 (34.3%) with PR in the chemotherapy arm (Table 11.2.4.1.2 of the AURA3 CSR in Module 5.3.5.1).

The ORR based on BICR was 64.9% (95% CI: 59.0, 70.5) in the osimertinib arm and 34.3% (95% CI: 25.6, 42.8) in the chemotherapy arm.

Table 4 Objective response rate (investigator and BICR assessments) in AURA3 on FAS - logistic regression

Treatment arm	N	Number (%) of patients with response[a]	Adjusted response rate (%)	Comparison between groups		
				Odds ratio	95% CI	2-sided p-value
ORR by investigator assessment						
Osimertinib 80 mg	279	197 (70.6)	72.8	5.39	3.47, 8.48	<0.001
Chemotherapy	140	44 (31.4)	33.1			
ORR by BICR (sensitivity analysis)						
Osimertinib 80 mg	279	181 (64.9)	67.4	3.63	2.37, 5.64	<0.001
Chemotherapy	140	48 (34.3)	36.3			

a Response did not require confirmation.
Objective response rate was defined as the number (%) of randomised patients with at least one visit response of CR or PR.
The analysis was performed using logistic regression adjusted for ethnicity (Asian/non-Asian).
An odds ratio >1 favours osimertinib 80 mg.
RECIST version 1.1.
Data cut-off: 15 April 2016.
CI=confidence interval; CR=complete response; CSR=clinical study report; BICR=blinded independent central review; FAS=full analysis set; ORR=objective response rate; PR=partial response; RECIST=Response Evaluation Criteria in Solid Tumors.
Source: Tables 11.2.4.2.1 and 11.2.4.2.2 of the AURA3 CSR in Module 5.3.5.1.

Table 5 Best objective response in AURA3 by investigator and BICR assessments (FAS)

	AURA3 osimertinib arm (N=279)	AURA3 chemotherapy arm (N=140)
BOR based on investigator assessment of the FAS		
Response, total[a]	197 (70.6)	44 (31.4)
Complete response[a]	4 (1.4)	2 (1.4)
Partial response[a]		42 (30.0)
	193 (69.2)	
Non-response	82 (29.4)	96 (68.6)
Stable disease ≥6 weeks[b]	63 (22.6)	60 (42.9)
Progression	18 (6.5)	26 (18.6)
RECIST progression	15 (5.4)	22 (15.7)
Death	3 (1.1)	4 (2.9)
Not evaluable	1 (0.4)	10 (7.1)
Stable disease <6 weeks	0	0
No evaluable follow-up assessments	1 (0.4)	10 (7.1)
No valid baseline assessment	0	0
BOR based on BICR assessment of the FAS (sensitivity analysis)		
Response, total[a]	181 (64.9)	48 (34.3)
Complete response[a]	3 (1.1)	0
Partial response[a]	178 (63.8)	48 (34.3)
Non-response	98 (35.1)	92 (65.7)
Stable disease ≥6 weeks[b]	75 (26.9)	54 (38.6)
Progression	21 (7.5)	26 (18.6)
RECIST progression	18 (6.5)	22 (15.7)
Death	3 (1.1)	4 (2.9)
Not evaluable	2 (0.7)	12 (8.6)
Stable disease <6 weeks	0	2 (1.4)
No evaluable follow-up assessments	2 (0.7)	10 (7.1)
No valid baseline assessment	0	0

a Response did not require confirmation.
b Stable disease ≥6 weeks includes RECIST visit window (±7 days).
Patients with no evidence of disease could only be assessed for no-evidence of disease or progression.
Note: for 1 patient with CR (E4104302) and 1 patient with SD (E4327302), there were no target lesions at baseline by BICR.
RECIST version 1.1. Data cut-off: 15 April 2016.
BOR=best objective response; BICR=blinded independent central review; CR=complete response; CSR=clinical study report; FAS=full analysis set; RECIST=Response Evaluation Criteria in Solid Tumors; SD=stable disease.

- Duration of response by investigator assessment

At DCO, duration of response was longer in patients on osimertinib compared to those on chemotherapy. The median DoR based on investigator assessment (by KM analysis) was 9.7 months (95% CI: 8.3, 11.6; 44.7% maturity) in the osimertinib arm vs. 4.1 months (95% CI: 3.0, 5.6; 81.8% maturity) in the chemotherapy arm, with a difference of over 5 months (Table 17). There was a statistically significant improvement in EDoR for patients on osimertinib compared to those on chemotherapy (ratio of EDoR: 6.22; 95% CI: 4.04, 9.57; p-value: <0.001; calculated according to the formulae provided in Ellis et al 2008), with a mean DoR of 15.4 months for patients on osimertinib vs. 5.6 months for those on chemotherapy (Table 18).

Table 6 Duration and onset of objective response in patients with objective response in AURA3 by investigator assessment (FAS)

	AURA3 osimertinib arm (N=279)	AURA3 chemotherapy arm (N=140)
Number of responders	197	44
Number of responders who subsequently progressed or died	88	36
DoR from onset of response (months)[a,b]		
Median	9.7	4.1
95% CI for median	8.3, 11.6	3.0, 5.6
Estimated percentage remaining in response[b]		
at 3 months (95% CI)	86.0 (80.2, 90.2)	65.9 (50.0, 77.8)
at 6 months (95% CI)	70.1 (62.8, 76.3)	30.2 (17.2, 44.2)
at 9 months (95% CI)	53.0 (44.5, 60.9)	15.7 (6.2, 29.1)
at 12 months (95% CI)	37.8 (28.1, 47.5)	10.5 (2.5, 24.9)
Number and percentage remaining in response, n (%)		
>3 months	163 (82.7)	29 (65.9)
>6 months	96 (48.7)	12 (27.3)
>9 months	56 (28.4)	4 (9.1)
>12 months	21 (10.7)	1 (2.3)
Time to onset of response from randomisation (weeks)[b]		
25th percentile	5.7	6.0
Median	6.1	6.4
95% CI for median	NC, NC	6.3, 7.0
Time to onset of response from randomisation, n (%)[c]		
≤6 weeks	161 (81.7)	29 (65.9)
≤12 weeks	187 (94.9)	39 (88.6)
≤18 weeks	194 (98.5)	41 (93.2)
≤24 weeks	196 (99.5)	43 (97.7)

a Duration of response is the time from the first documentation of CR/PR until the date of progression, or the last evaluable RECIST assessment for patients that do not progress.
b Calculated using KM technique.
c One week window was allowed around the 6, 12, 18, and 24-week time points.
RECIST version 1.1.
Data cut-off: 15 April 2016.
CI=confidence interval; CR=complete response; CSR=clinical study report; DoR=duration of response; FAS=full analysis set; KM=Kaplan-Meier; PR=partial response; RECIST=Response Evaluation Criteria in Solid Tumors.
Source: Table 11.2.4.4 of the AURA3 CSR in Module 5.3.5.1.

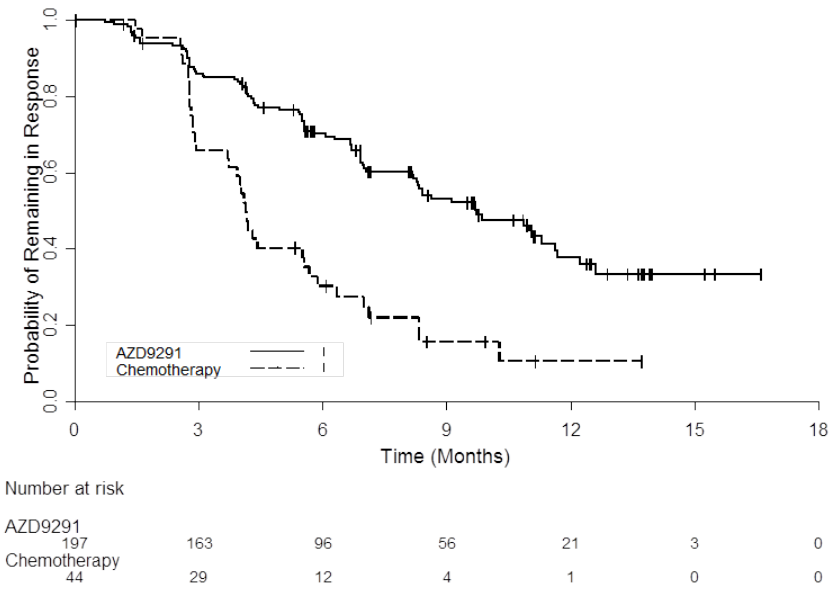
Table 7 **Duration of response in AURA3 by investigator assessment, test of treatment effect (FAS)**

Treatment arm	N	Response rate (%)	Mean DoR[a]	SE Mean DoR[b]	Comparison between groups			
					EDoR[c]	Ratio of EDoR[d]	95% CI	p-value
Osimertinib 80 mg	279	70.6	467.7	0.01	330.2	6.22	4.04, 9.57	<0.001
Chemotherapy	140	31.4	169.0	0.01	53.1			

a DoR=duration of response in responding patients (days).
b SE Mean DoR=standard error of mean duration of response (days) on the basis of the log normal distribution.
c EDoR=expected duration of response (days).
d Ratios >1 favour osimertinib 80 mg.
95% CI and p-value calculated according to the formulae provided in Ellis S et al 2008. Treatments were compared by calculating the ratio of EDoRs using the Log Normal probability distribution for DoR in responding patients. RECIST version 1.1.

Based on a KM analysis, the estimated proportion of patients remaining in response at 6 months was 70.1% (95% CI: 62.8, 76.3) in the osimertinib arm vs. 30.2% (95% CI: 17.2, 44.2) in the chemotherapy arm, and at 9 months was 53.0% (95% CI: 44.5, 60.9) in the osimertinib arm vs. 15.7% (95% CI: 6.2, 29.1) in the chemotherapy arm (Table 17). There was a clear separation of KM curves in favour of osimertinib from 3 months onwards (Figure 6).

Figure 3 **Duration of response in AURA3 by investigator assessment, Kaplan-Meier plot (FAS)**



Patients with missing censoring information were not included. Duration of response is the time from the first documentation of CR/PR until the date of progression or the last evaluable RECIST assessment for patients who do not progress.

At DCO, 88 of the 197 responders (44.7% maturity) had progressed or died in the absence of progression in the osimertinib arm vs. 36 of the 44 responders (81.8% maturity) in the chemotherapy arm.

The median time to onset of objective response from randomisation was 6.1 weeks (95% CI: NC, NC) in the osimertinib arm vs. 6.4 weeks (95%CI: 6.3, 7.0) in the chemotherapy arm (Table 17), reflecting the timing of the first scan at 6 weeks. Most responders (161 [81.7%] patients in the osimertinib arm and 29 [65.9%] in the chemotherapy arm) had a first documented objective response at their first scheduled follow-up RECIST scan (ie, at Week 6±1 week). Almost all responders in both treatment arms (osimertinib, 187

[94.9%]; chemotherapy, 39 [88.6%]) responded by their second scheduled follow-up RECIST scan (Week 12±1 week). The onset of response at the first scan was similar in both treatment arms, with a median time to onset of objective response from randomisation of 6.1 weeks (95% CI: NC, NC) in the osimertinib arm vs. 6.4 weeks (95% CI: 6.3, 7.0) in the chemotherapy arm. However, some of the chemotherapy responses were not maintained and were generally less durable, as evidenced by the median DoR (4.1 months) and estimated percentage of patients remaining in response at 9 and 12 months (15.7% [95% CI: 6.2, 29.1] and 10.5% [95% CI: 2.5, 24.9], respectively, in the chemotherapy arm vs. 53.0% [95% CI: 44.5, 60.9] and 37.8% [95% CI: 28.1, 47.5] in the osimertinib arm).

The DoR per BICR was consistent with the investigator assessment. The median DoR based on BICR was 11.2 months (95% CI: 8.3, NC) in the osimertinib arm vs. 3.1 months (95% CI: 2.9, 4.3) in the chemotherapy arm.

Based on a KM analysis, the estimated proportion of patients remaining in response at 6 months was 71.4% (95% CI: 63.3, 78.0) in the osimertinib arm vs. 25.6% (95% CI: 13.8, 39.1) in the chemotherapy arm; and at 9 months was 53.5% (95% CI: 43.5, 62.5) in the osimertinib arm vs. 14.6% (95% CI: 5.3, 28.4) in the chemotherapy arm (Table 19). There was a clear separation of the KM curves after 3 months.

- Disease control rate by investigator assessment

There was a statistically significant improvement in DCR for patients on osimertinib compared to those on chemotherapy, with an OR of 4.76 (95% CI: 2.64, 8.84) (p-value: <0.001) (Table 20). The DCR (defined as CR+PR+SD≥6 weeks) based on investigator assessment was 93.2% (95% CI: 89.6, 95.9) in the osimertinib arm vs. 74.3% (95% CI: 66.2, 81.3) in the chemotherapy arm.

Table 8 Disease control rate in AURA3 by investigator assessment, logistic regression (FAS)

Treatment arm	N	Number (%) of patients with disease control	Adjusted response rate (%)	Comparison between groups		
				Odds ratio	95% CI	2-sided p-value
Osimertinib 80 mg	279	260 (93.2)	93.7	4.76	2.64, 8.84	<0.001
Chemotherapy	140	104 (74.3)	75.7			

Disease control rate was defined as the number (%) of patients who had a best overall response of CR, PR, or SD at ≥6 weeks, prior to any disease progression event. The analysis was performed using logistic regression adjusted for ethnicity (Asian/non-Asian).

The DCR based on BICR was consistent with DCR findings by investigator assessment. The DCR based on BICR assessment was 91.8% (95% CI: 87.9, 94.7) in the osimertinib arm vs. 72.9% (95% CI: 64.7, 80.0) in the chemotherapy arm.

- Tumour shrinkage

Overall, 278/279 (99.6%) patients in the osimertinib arm and 131/140 (93.6%) patients in the chemotherapy arm had baseline and on-treatment tumour measurements. A greater proportion of patients had tumour shrinkage in the osimertinib arm compared to the chemotherapy arm (257 [92.4%] patients vs. 103 [78.6%] patients, respectively; Figure 8 [osimertinib arm] and Figure 9 [chemotherapy arm]).

There was a statistically significant difference in tumour shrinkage between treatment arms, with a greater mean percentage tumour shrinkage from baseline in patients on osimertinib (Table 21). The unadjusted mean tumour shrinkage was -46.1% (sd, 29.50) in the osimertinib arm vs. -24.4% (sd, 29.27) in the chemotherapy arm (difference in least square [LS] means between the treatment arms: -21.62; 95% CI:

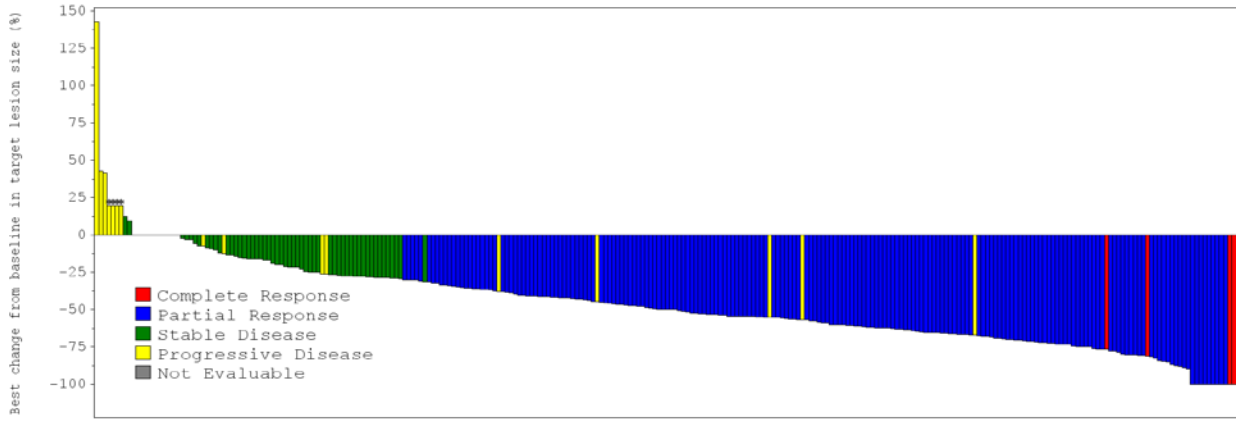
-27.71, -15.52; p-value: <0.001). In both treatment arms, evidence of tumour shrinkage was usually documented at the first scheduled follow-up RECIST scan, at Week 6±1 week.

Table 9 Target lesion size, best percentage change from baseline in AURA3 by investigator assessment, analysis of covariance model (FAS)

Treatment arm	N	Unadjusted mean (sd)	LS mean	Treatment effect		
				Difference in LS means	95% CI	2-sided p-value
Osimertinib 80 mg	278	-46.1 (29.50)	-46.93	-21.62	-27.71, -15.52	<0.001
Chemotherapy	131	-24.4 (29.27)	-25.31			

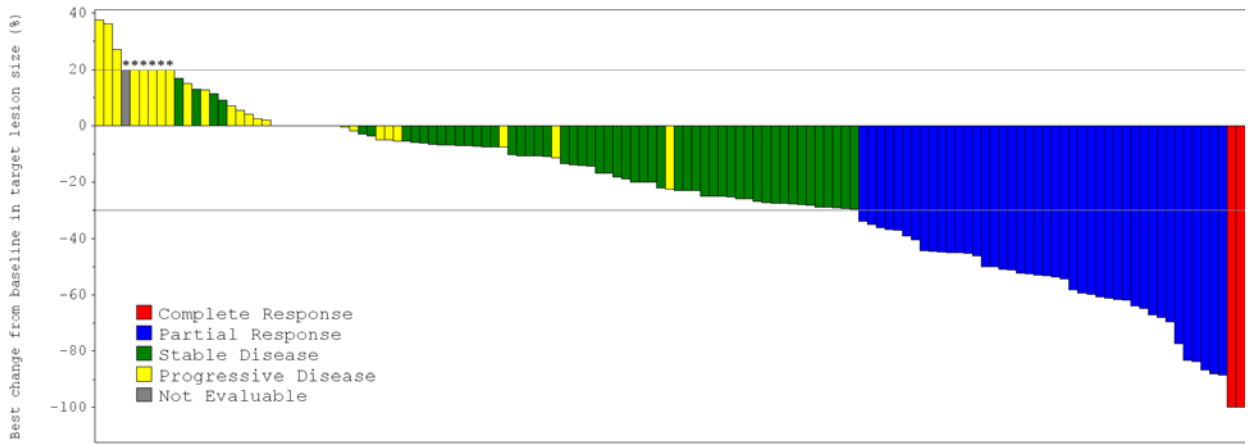
The analysis was performed using analysis of covariance model with covariates for ethnicity (Asian, non-Asian) and the baseline sum of diameters of target lesion. A difference in LS means <0 favours osimertinib 80 mg

Figure 4 Target lesion size, best percentage change from baseline in AURA3 by investigator, waterfall plot (FAS) – osimertinib arm



Best percentage change in target lesion size is the maximum reduction from baseline or the minimum increase.
* represents imputed values: if it was known that the patient had died, had new lesions or progression of assessments, best change was imputed as 20%.
RECIST version 1.1. FAS=full analysis set.

Figure 5 Target lesion size, best percentage change from baseline in AURA3 by investigator, waterfall plot (FAS) – chemotherapy arm



Best percentage change in target lesion size is the maximum reduction from baseline or the minimum increase.
* represents imputed values: if it was known that the patient had died, had new lesions or progression of assessments, best change was imputed as 20%.
RECIST version 1.1. FAS=full analysis set.

- Patient-reported outcomes: lung cancer symptoms and health-related quality of life

The compliance to the EORTC QLQ-C30 and QLQ-LC13 was high up to approximately 54 weeks of treatment.

PRO primary analysis (MMRM)

The primary analyses for patient-reported outcomes was performed using mixed model for repeated measures (MMRM) analyses of change from baseline over the overall time period from randomisation until 6 months in 5 key lung cancer symptoms (dyspnoea, appetite loss, fatigue, cough and pain in chest).

Osimertinib improved patient-reported lung cancer symptoms compared to chemotherapy by demonstrating a statistically significant difference in mean change from baseline vs. chemotherapy for all 5 pre-specified primary PRO symptoms.

- The adjusted mean change from baseline during the overall time period from randomisation until 6 months for cough showed an improvement of −12.22 in the osimertinib arm vs. an improvement of −6.69 in the chemotherapy arm (estimated difference: −5.53 [95% CI: −8.89, −2.17]; p-value=0.001).
- The adjusted mean change from baseline during the overall time period from randomisation until 6 months for dyspnoea showed an improvement of −5.61 in the osimertinib arm vs. a deterioration of 1.48 in the chemotherapy arm (estimated difference: −7.09 [95% CI: −9.86, −4.33]; p-value <0.001).
- The adjusted mean change from baseline during the overall time period from randomisation until 6 months for pain in chest showed an improvement of −5.15 in the osimertinib arm vs. a deterioration of 0.22 in the chemotherapy arm (estimated difference: −5.36 [95% CI: −8.20, −2.53]; p-value <0.001).
- The adjusted mean change from baseline during the overall time period from randomisation until 6 months for fatigue showed an improvement of −5.68 in the osimertinib arm vs. a deterioration of 4.71 in the chemotherapy arm (estimated difference: −10.39 [95% CI: −14.55, −6.23]; p-value <0.001).
- The adjusted mean change from baseline during the overall time period from randomisation until 6 months for appetite loss showed an improvement of −5.51 in the osimertinib arm vs. a deterioration of 2.73 in the chemotherapy arm (estimated difference: −8.24 [95% CI: −12.88, −3.60]; p-value <0.001).

Time to PRO symptom deterioration

Analysis of time to symptom deterioration was performed on symptoms from the EORTC QLQ-LC13 questionnaire only and was calculated based on patients who had individual baseline scores ≤90 to allow for deterioration according to cut-offs. Time to symptom deterioration was defined as the time from randomisation until the date of first clinically meaningful deterioration. Osimertinib prolonged the time to symptom deterioration (see Table 11.2.6.5 of the AURA3 CSR in Module 5.3.5.1). The HR for time to PRO symptom deterioration for the 2 primary EORTC QLQ-LC13 symptoms of dyspnoea and cough were 0.42 (95% CI: 0.31, 0.58; p-value <0.001) and 0.75 (95% CI: 0.53, 1.05; p-value=0.093), respectively (HR<1 favoured osimertinib). The HR for all other EORTC QLQ-LC13 PRO symptoms were also in favour of osimertinib.

Symptom improvement rate

Symptom improvement rate was calculated based on patients who had individual baseline scores ≥10 to leave room for improvements according to cut-offs. Symptom improvement was defined as a clinically

meaningful improvement (a decrease from baseline score ≥10 for LC13 and C30) in that item/scale at 2 consecutive visits.

The ORs for symptom improvement rate for the 5 primary PRO symptoms was 1.96 (95% CI: 1.20, 3.22; p-value=0.008) for fatigue; 2.50 (95% CI: 1.31, 4.84, p-value=0.006) for appetite loss; 2.71 (95% CI: 1.60, 4.68, p-value <0.001) for dyspnoea; 1.51 (95% CI: 0.87, 2.61, p-value=0.144) for cough; and 1.66 (95% CI: 0.83, 3.34, p-value=0.149) for chest pain (an OR>1 favouring osimertinib) (see Table 11.2.6.6 of the AURA3 CSR in Module 5.3.5.1).

Analyses of the pre-defined symptoms of interest, global health status and physical functioning domains of the EORTC-C30 scales, showed OR in favour of osimertinib (OR physical functioning 2.40, p-value=0.005; OR global health status 1.84, p-value=0.025).

The OR for symptom improvement rate for all other PRO symptoms from EORTC QLQ-LC13 and EORTC QLQ-C30 were also in favour of osimertinib, with the exception of diarrhoea and pain medication.

- **Ancillary analyses**

Subgroup analyses

Clinically meaningful and statistically superior improvement in PFS for patients on osimertinib compared to those on chemotherapy was seen consistently across subgroups of interest, which included ethnicity (Asian vs. Non-Asian), age at screening (<65 years vs. ≥65 years), gender (male vs. female), smoking history (yes vs. no), CNS metastases status at entry (yes vs. no), mutation status at baseline (exon 19 deletion vs. L858R mutation), and duration of prior treatment with EGFR-TKI (<6 months vs. ≥6 months).

All calculated HRs for PFS in subgroups were below 0.50, indicating a minimum of a 50% reduction in the risk of progression or death for the assessed subgroups. Improvements in PFS for patients on osimertinib compared to those on chemotherapy were observed both in patients with and without CNS metastases at study entry, with HRs of 0.32 (95% CI: 0.21, 0.49) and 0.40 (95% CI: 0.29, 0.55), respectively.

Numerically greater improvements in PFS with respect to chemotherapy were observed in Asian compared to Non-Asian patients (HR=0.32 vs. 0.48, respectively), in female compared to male patients (HR=0.34 vs. 0.43, respectively) and in patients with tumours that harboured an exon 19 deletion compared to an L858R mutation (HR=0.34 vs. 0.46, respectively).

A global interaction test did not provide evidence of any treatment-by-covariate interaction for the covariates of ethnicity, gender, age, mutation status, duration of prior EGFR-TKI, CNS metastases, smoking history (2-sided p-value=0.231).

A post-hoc analysis of PFS was performed based on the subgroups of type of chemotherapy regimen used. The superiority of osimertinib over chemotherapy was independent of chemotherapy regimen, with a HR for osimertinib vs. pemetrexed/carboplatin of 0.24 (95% CI: 0.17, 0.35; 2-sided p-value <0.001); median PFS was 10.1 months (95% CI: 8.3, 12.3) vs. 4.3 months (95% CI: 4.2, 5.6) and a HR for osimertinib vs. pemetrexed/cisplatin of 0.33 (95% CI: 0.20, 0.54; 2-sided p-value <0.001); median PFS was 10.1 months (95% CI: 8.3, 12.3) vs. 5.0 months (95% CI: 4.1, 7.0) (see Figure 13 and Tables IMT0323A1, IMT0323A2, IMT0323B1 and IMT0323B2 of the AURA3 CSR in Module 5.3.5.1).

Table 10 Progression-free survival in AURA3 by investigator assessment, Cox proportional hazards model, subgroup analysis (FAS)

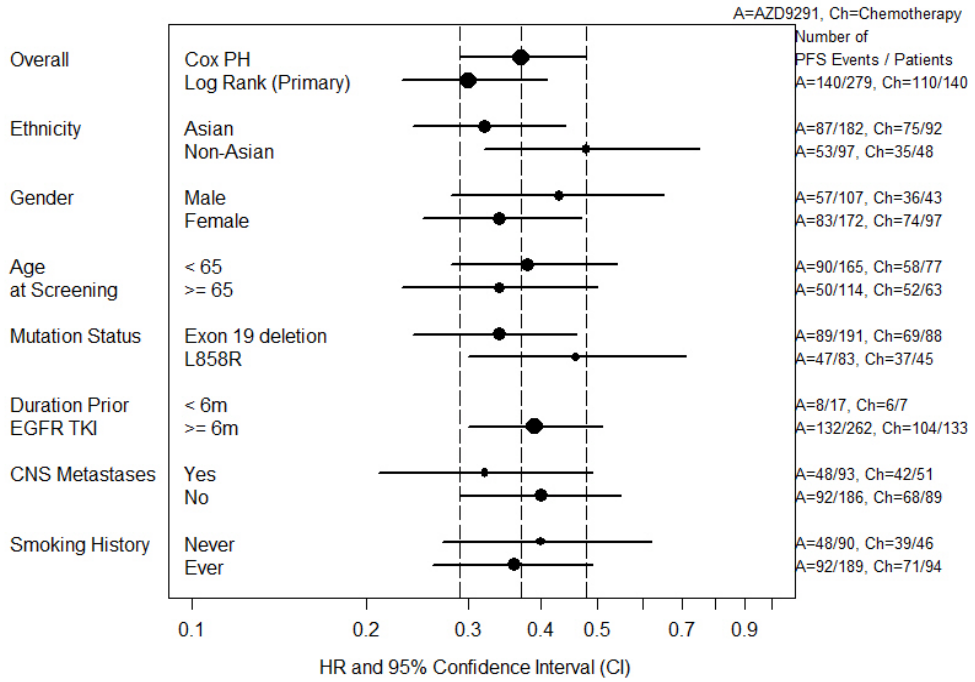
Subgroup	Treatment arm	N	Number (%) of patients with events[a]	Comparison between groups	
				Hazard ratio[b]	95% CI
All patients	Osimertinib	279	140 (50.2)	0.30	0.23, 0.41
	Chemotherapy	140	110 (78.6)		
Ethnicity					
Asian	Osimertinib	182	87 (47.8)	0.32	0.24, 0.44
	Chemotherapy	92	75 (81.5)		
Non-Asian	Osimertinib	97	53 (54.6)	0.48	0.32, 0.75
	Chemotherapy	48	35 (72.9)		
Gender					
Male	Osimertinib	107	57 (53.3)	0.43	0.28, 0.65
	Chemotherapy	43	36 (83.7)		
Female	Osimertinib	172	83 (48.3)	0.34	0.25, 0.47
	Chemotherapy	97	74 (76.3)		
Age at screening					
<65 years	Osimertinib	165	90 (54.5)	0.38	0.28, 0.54
	Chemotherapy	77	58 (75.3)		
≥65 years	Osimertinib	114	50 (43.9)	0.34	0.23, 0.50
	Chemotherapy	63	52 (82.5)		
EGFR mutation prior to start of study					
Exon 19 deletion	Osimertinib	191	89 (46.6)	0.34	0.24, 0.46
	Chemotherapy	88	69 (78.4)		

Table 10 Progression-free survival in AURA3 by investigator assessment, Cox proportional hazards model, subgroup analysis (FAS)

Subgroup	Treatment arm	N	Number (%) of patients with events[a]	Comparison between groups	
				Hazard ratio[b]	95% CI
L858R mutation	Osimertinib	83	47 (56.6)	0.46	0.30, 0.71
	Chemotherapy	45	37 (82.2)		
Duration of prior EGFR-TKI					
<6 months	Osimertinib	17	8 (47.1)	NC	NC
	Chemotherapy	7	6 (85.7)		
≥6 months	Osimertinib	262	132 (50.4)	0.39	0.30, 0.51
	Chemotherapy	133	104 (78.2)		
CNS metastases status at study entry					
Yes	Osimertinib	91	48 (51.6)	0.32	0.21, 0.49
	Chemotherapy	51	42 (82.4)		
No	Osimertinib	188	92 (49.5)	0.40	0.29, 0.55
	Chemotherapy	89	68 (76.4)		
Smoking history					
Yes	Osimertinib	90	48 (53.3)	0.40	0.27, 0.62
	Chemotherapy	46	39 (84.8)		
No	Osimertinib	189	92 (48.7)	0.36	0.26, 0.49
	Chemotherapy	94	71 (75.5)		

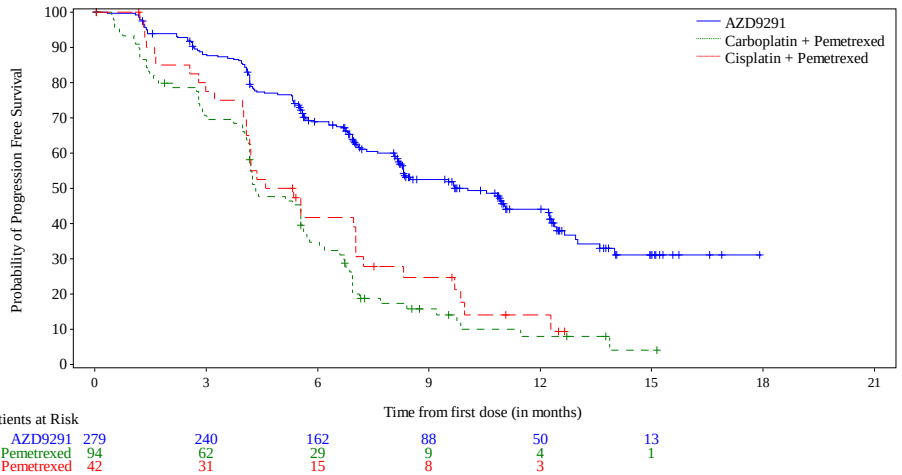
a Progression events that did not occur within 14 weeks of the last evaluable assessment (or randomisation) were censored and therefore excluded in the number of events.
b If there are <20 events in at least 1 treatment of a subgroup then the analysis was not performed.
Each subgroup analysis was performed using a single Cox proportional hazards model containing the treatment, the subgroup of covariate of interest, and the treatment by subgroup interaction, and using the Efron approach for handling ties.
An HR <1 favours osimertinib 80 mg.

Figure 6 **Progression-free survival in AURA3 by investigator assessment, Forest plot, by subgroup (FAS)**



Hazard ratio (osimertinib 80 mg: chemotherapy) and 95% CI.
A hazard ratio <1 implies a lower risk of progression on osimertinib 80 mg.
Cox proportional hazards model included randomised treatment, the subgroup covariate of interest, and the treatment by subgroup interaction.
Size of circle is proportional to the number of events. All patient analysis was performed using a log-rank test stratified by ethnicity.
Grey band represents the 95% CI for the overall (all patients) hazard ratio.
Progression included deaths in the absence of RECIST progression.

Figure 7 **Progression-free survival in AURA3 by investigator assessment by chemotherapy regimen, Kaplan-Meier plot (Safety Analysis Set)**



Analysis performed on the safety analysis set (all randomised patients who received at least 1 dose of randomised treatment and for whom post-dose data were available) since 4 patients, all in the chemotherapy arm, were randomised but did not receive treatment

Progression-free survival by chemotherapy regimen (full analysis set)

	Pemetrexed plus carboplatin		Pemetrexed plus cisplatin	
	Osimertinib (N = 279)	Chemotherapy (N = 94)	Osimertinib (N = 279)	Chemotherapy (N = 42)
Patients with PFS events, n/N (%)	140/279 (50.2%)	77/94 (81.9%)	140/279 (50.2%)	33/42 (78.6%)
Median PFS (months)	10.1	4.3	10.1	5.0
95% CI	8.3, 12.3	4.2, 5.6	8.3, 12.3	4.1, 7.0
PFS HR (95% CI)	0.24 (0.17, 0.35)		0.33 (0.20, 0.54)	

Source: Table IMT0323A1 and Table IMT0323A3 in AURA3 CSR in Module 5.3.5.1

Subgroup based on baseline ctDNA samples

In the subgroup of 371 patients with a baseline plasma (ctDNA) T790M status, the HR for patients with positive plasma T790M status (n = 172) was 0.42 (95% CI: 0.29, 0.61) and the median PFS was 8.2 months (95% CI: 6.8, 9.7) in the osimertinib arm compared to 4.2 months (95% CI: 4.1, 5.1) in the chemotherapy arm. The HR for patients with negative plasma T790M status (n = 168) was 0.34 (95% CI: 0.22, 0.52) and the median PFS was 12.5 months (95% CI: 10.1, NC) in the osimertinib arm compared to 5.6 months. (95% CI: 4.1, 6.8) in the chemotherapy arm.

Please note that plasma samples were not tested in China patients due to sample export limitations, thus 48 China patients were excluded from this analysis.

Efficacy of osimertinib in patients with central nervous system metastases (AURA3)

Overall, 134/279 (48.0%) patients in the osimertinib arm and 71/140 (50.7%) patients in the chemotherapy arm had a baseline brain scan performed as part of the RECIST overall assessment and subsequently sent for CNS BICR assessment.

In the osimertinib arm:

- cFAS population includes patients with measurable and non-measurable CNSlesions (n=75).
- cEFR population includes the patients with measurable CNS lesions only (n=30).

In the chemotherapy arm:

- cFAS population includes patients with measurable and non-measurable CNSlesions (n=41)
- cEFR population includes the patients with measurable CNS lesions only (n=16)

Both the cFAS and cEFR populations were used for the CNS BICR analysis.

Central nervous system BICR analysis in AURA3

Central nervous system BICR analysis in AURA3 A BICR assessment of CNS efficacy based on RECIST v1.1 in the subgroup of 116/419 (27.7%) patients identified to have CNS metastases on a baseline brain scan was performed in order to characterise the CNS efficacy of osimertinib. Evaluation of radiological-assessed CNS metastases showed a clinically meaningful improvement for patients randomised to receive osimertinib vs. chemotherapy. The improvement in CNS efficacy outcomes were consistent across multiple analyses.

- For patients with measurable CNS metastases at baseline (CNS evaluable for response [cEFR]), a clinically meaningful and statistically significant improvement in CNS ORR was reported for patients in the osimertinib arm (70% [21/30 patients; 95% CI: 50.60, 85.27]) compared to those on chemotherapy (31.3% [5/16 patients; 95% CI: 11.02, 58.66]), with patients approximately 5 times

more likely to respond in CNS metastases to osimertinib compared to chemotherapy (OR: 5.13 [95% CI: 1.44, 20.64; p-value=0.015]).

- For patients with measurable and non-measurable CNS metastases at baseline (CNS full analysis set [cFAS]), a clinically meaningful and statistically significant improvement in CNS ORR was reported for patients in the osimertinib arm (30/75 patients; 40.0% [95% CI: 28.85, 51.96]) compared to those on chemotherapy (7/41 patients; 17.1% [95% CI: 7.15, 32.06]), with patients approximately 3 times more likely to respond in CNS metastases to osimertinib compared to chemotherapy (OR: 3.24 [95% CI: 1.33, 8.81]; p-value=0.014).
-

Table 2 CNS efficacy by BICR in patients with CNS metastases on a baseline brain scan in AURA3

Efficacy parameter	Osimertinib 80 mg	Chemotherapy
CNS ORR (cEFR)[a]	N = 30	N = 16
CNS ORR, n (%)	21 (70%)	5 (31.3%)
95% CI for CNS ORR	50.6, 85.3	11.0, 58.7
OR (95% CI); p-value	5.13 (1.44, 20.64); p-value = 0.015	
CNS DoR (cEFR)[b]	N = 30	N = 16
Median CNS DoR (months)	8.9	5.7
95% CI for median CNS DoR	4.3, NC	NC, NC
CNS DCR (cFAS)	N = 75	N = 41
CNS DCR, n (%)	65 (86.7%)	28 (68.3%)
95% CI for CNS DCR	76.8, 93.4	51.9, 81.9
OR (95% CI); p-value	3.02 (1.19, 7.87); p-value = 0.021	
CNS PFS (cFAS)	N = 75	N = 41
No. of CNS events (% maturity)	19 (25.3%)	6 (39.0%)
Median CNS PFS (months)	11.7 (10.0, NC)	5.6 (4.2, 9.7)
HR (95% CI); p-value	0.32 (0.15, 0.69); p-value = 0.004	

a CNS ORR and DoRdeterminedby RECIST v1.1 by CNS BICR in the evaluable for response population(CNS measurabledisease at baselineby BICR);
b Basedonpatientswith CNS response only; DoRdefined as the time fromthe date of firstdocumentedresponse.

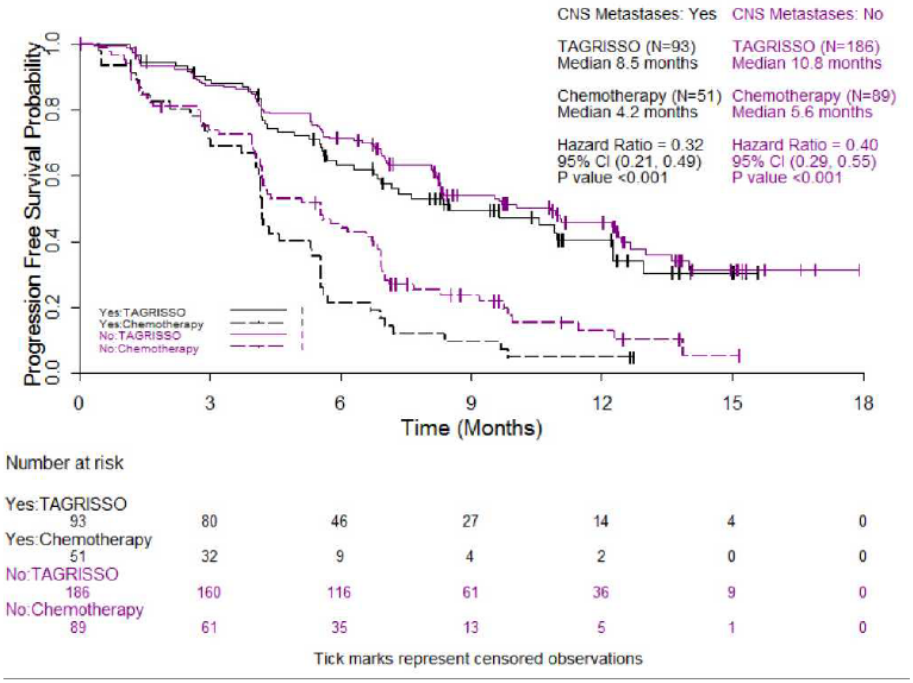
In the cFAS, prior brain radiation was reported for 37.3% of patients in the osimertinib arm, including 18.7% of patients who completed radiation treatment within 6 months before starting treatment. In the chemotherapy arm, prior brain radiation was reported in 46.3% of patients, including 22.0% who completed radiation treatment within 6 months before starting treatment. Central nervous system responses were observed irrespective of prior brain radiotherapy. The CNN ORR for patients who received prior brain radiotherapy within 6 months of randomisation was 64.3% for osimertinib and 22.2% for chemotherapy. The CNS ORR for patients who received no prior brain radiotherapy or brain radiotherapy >6 months prior to the start of study treatment was 34.4% for osimertinib and 15.6% for chemotherapy.

Efficacy analyses by CNS metastases status at baseline in AURA3

An efficacy analysis based on investigator assessment of the FAS (n = 419) using RECIST v1.1 was performed based on CNS metastases status (yes or no) at study entry. The CNS metastases status was identified by CNS lesion site at baseline, medical history, and/or prior surgery, and/or prior radiotherapy to CNS metastases.

Irrespective of CNS metastases status at study entry, a statistically significant and clinically meaningful improvement in PFS based on investigator assessment using RECIST v1.1 was observed in the patients on osimertinib compared to patients on chemotherapy. There was a clear separation of the KM curves in favour of osimertinib for the duration of the study, irrespective of the history of CNS metastases status at study entry.

Figure 3 **PFS by CNS metastases status at baseline in AURA3**



Analysis of appearance of new CNS lesions in AURA3

In AURA3, based on investigator assessment using RECIST v1.1, osimertinib decreased the appearance of new CNS metastases as compared with chemotherapy (4.7% vs. 14.3%, respectively). Based on BICR assessment, new CNS metastases were seen in 2.5% of patients on osimertinib vs. 9.3% of patients on chemotherapy. Osimertinib reduced the proportion of patients developing new CNS lesions compared with the chemotherapy arm, irrespective of CNS metastases status at baseline.

SUPPORTIVE SINGLE-ARM PHASE II STUDIES: AURA extension and AURA2

In order to provide a mature data perspective on efficacy in a broader patient population, including both second-line therapy and ≥third-line therapy, and to show the consistency of efficacy findings in AURA3 with the known efficacy profile of osimertinib, pooled efficacy findings of Phase II AURA extension and AURA2 studies at DCO3 (1 November 2015) are provided in this application.

These more mature DCO3 data (Yang et al 2016) support the durability of efficacy findings in this broad patient population, allow longer-term characterisation of the safety profile and confirm the consistency of the Phase II data with the osimertinib arm of AURA3. The patient population enrolled in these Phase II studies was similar to that in AURA3, consisting of pre-treated patients with locally advanced or metastatic NSCLC whose tumours were EGFR mutation-positive and T790M mutation-positive, as confirmed by central testing, and who had progressed on or after receiving at least 1 prior regimen of EGFR-TKI therapy. The

primary difference to the AURA3 population was the inclusion of patients receiving ≥third-line therapy; approximately one-third (31.4%) of patients were receiving osimertinib as second-line therapy and two-thirds (68.6%) as ≥third-line.

Key study design features, including inclusion and exclusion criteria and follow-up criteria were similar between AURA3 and the Phase II studies. At DCO3, most patients in the Phase II studies had approximately 12 months of follow-up; the total treatment exposure of patients enrolled in AURA extension and AURA2 ranged from 0 months to 17.6 months 13 months).

Table 2 Design characteristics of Phase II and III studies in support of submission

	AURA3	AURA2	AURA extension
No. of patients dosed	415	210	201
Study No.	D5160C00003	D5160C00002	D5160C00001 (Phase II extension)
Phase / Region	Phase III / Global	Phase II / Global	Phase II / Global
Title	A Phase III, open label, randomized study of AZD9291 versus platinum-based doublet chemotherapy for patients with locally advanced or metastatic NSCLC whose disease has progressed with previous EGFR-TKI therapy and whose tumours harbour a T790M mutation within the EGFR gene (AURA3)	A Phase II, open-label, single-arm study to assess the safety and efficacy of AZD9291 (Osimertinib) in patients with locally advanced/metastatic NSCLC whose disease has progressed with previous EGFR-TKI therapy and whose tumours are EGFR mutation and T790M mutation positive (AURA2)	A Phase I/II, open-label, multicentre study to assess the safety, tolerability, pharmacokinetics and anti-tumour activity of ascending doses of AZD9291 (Osimertinib) in patients with advanced NSCLC who have progressed following prior therapy with an EGFR-TKI agent (AURA)
Efficacy and safety objectives	*Primary*: To assess the efficacy of osimertinib compared with platinum-based doublet chemotherapy by assessment of PFS.	*Primary*: To investigate the efficacy of osimertinib by assessment of ORR.	*Primary*: The primary objective of the AURA study was 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.
	Secondary: • To further assess the efficacy of osimertinib compared with platinum-based chemotherapy in terms of: ORR, DoR, DCR, tumour shrinkage, and OS; • To assess the effect of osimertinib compared to platinum-based doublet	*Secondary*: • To further assess the efficacy of osimertinib in terms of DoR, DCR, tumour shrinkage, PFS, and OS; • To assess the safety and tolerability profile of osimertinib;	*Secondary, extension component*: • To characterise the pharmacokinetics of osimertinib and its metabolites (AZ5104 and AZ7550) after multiple oral doses; • To obtain additional assessments of the anti-tumour activity of

Table 2 Design characteristics of Phase II and III studies in support of submission

	AURA3	AURA2	AURA extension
	chemotherapy on subjects' disease-related symptoms and HRQoL; • To characterise the pharmacokinetics (PK) of osimertinib and metabolites in subjects receiving osimertinib. *Safety*: • To assess the safety and tolerability profile of osimertinib compared with platinum-based doublet chemotherapy.	• To investigate the effect of osimertinib on QT interval corrected for heart rate (QTc) after oral dosing to NSCLC patients; • To assess the impact of osimertinib on patients' disease-related symptoms and HRQoL; • To characterise the pharmacokinetics of osimertinib and its metabolites (AZ5104 and AZ7550).	osimertinib by evaluation of DoR, DCR, tumour shrinkage, and PFS, using RECIST v1.1 as assessed by a BICR of radiological information, and OS; • To assess the relationship between pharmacokinetics and selected efficacy, pharmacodynamic and/or safety endpoints. • To provide evidence for biological modulation of pharmacodynamic markers in EGFR mutation-positive T790M mutation-positive tumours at a selected clinical dose.
Study design	Phase III open-label, randomised study	Single arm, open-label, non-randomised Phase II study	Single-arm, open-label, non-randomised, Phase II dose-extension part of AURA study
Dosing and patient cohorts	Osimertinib 80 mg oral tablet once daily (n=279) Intravenous pemetrexed (500 mg/m^2) plus cisplatin (75 mg/m^2) or carboplatin (AUC5) on Day 1 of every 21-day cycle, n=136 patients Followed by optional pemetrexed maintenance (500 mg/m^2 on Day 1 of every 21-day cycle) Cross-over from chemotherapy to osimertinib after confirmed	Osimertinib 80 mg oral tablet once daily (n=210) • *Second-line* patients (pre-treated with 1 EGFR-TKI and no other treatment regimen), n=68 • ≥*Third-line* patients (pre-treated with at least 1 EGFR-TKI and 1 platinum-based doublet chemotherapy regimen), n=142	Osimertinib 80 mg oral tablet once daily (n=201) • *Second-line* patients (pre-treated with 1 EGFR-TKI and no other treatment regimens), n=61 • ≥*Third-line* patients (pre-treated with at least 1 EGFR-TKI and 1 other prior line of therapy), n=140

Table 2 Design characteristics of Phase II and III studies in support of submission

	AURA3	AURA2	AURA extension
	progression, n=82 Second-line patients (pre-treated with 1 EGFR-TKI and no other treatment regimen), n=4		
T790M central testing	Performed prospectively following progression on first-line of therapy; central result (**cobas®** EGFR Mutation Test) mandatory to determine eligibility	Performed prospectively following progression on latest line of therapy; central result (**cobas®** EGFR Mutation Test) mandatory to determine eligibility	Performed prospectively following progression on latest line of therapy; central result (**cobas®** EGFR Mutation Test) mandatory to determine eligibility
Study period as of DCO	*First patient randomised/dosed*: 20 August 2014 *Last patient first dose*: 4 November 2015	*First patient dosed*: 13 June 2014 *Last patient first dose*: 27 October 2014	*First patient dosed*: 14 May 2014 *Last patient first dose*: 21 October 2014
DCO dates	15 April 2016 (DCO for primary analysis of PFS)	**1 November 2015 (DCO3)**	**1 November 2015 (DCO3)**
Treatment exposure at DCO, Median (range)	8.1 months (0.2-18.5 months) in the osimertinib arm and 4.2 months (0.4-14.5 months) in the chemotherapy arm	13.0 months (<0.1-16.7 months)	13.2 months (0.1-17.6 months)

AUC5=area under the curve of 5 mg/mL/minute; BICR=blinded independent central review; CSR=clinical study report; DCO=data cut-off; DCR=disease control rate; DoR=duration of response; EGFR=epidermal growth factor receptor; HRQoL=health related quality of life; NSCLC=non-small cell lung cancer; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; PK=pharmacokinetics; QTc=corrected QT interval; RECIST=Response Evaluation Criteria in Solid Tumors; TKI=tyrosine kinase inhibitor.

Efficacy results from pooled Phase II studies

Efficacy findings in the pooled Phase II studies at DCO3 (1 November 2015) were consistent with those reported in the original MAA. These more mature data confirm the durability of osimertinib effects in a broader population (compared to AURA3) of pre-treated patients (including second-line and ≥third-line) with advanced EGFR T790M mutation-positive NSCLC with longer follow-up.

The consistency of osimertinib effects was further supported by the similarity of findings in the osimertinib arm of the Phase III AURA3 study with those reported in the pooled Phase II studies, AURA extension and AURA2.

Table 11 Summary of overall efficacy in AURA3 and pooled Phase II studies (AURA extension and AURA2)

Efficacy parameters	AURA3 at DCO Osimertinib N=279	AURA3 at DCO Chemotherapy N=140	Pooled Phase II at DCO2 (1 May 15) Osimertinib N=411	Pooled Phase II at DCO3 (1 Nov 15) Osimertinib N=411
DCO	15 April 2016		1 May 2015	1 November 2015
Objective response rate				
BICR assessment[a]				
Number of patients evaluable	279	140	398	397[c]
Number of patients with confirmed CR or PR	181	48	263	262
ORR, % (95% CI)	64.9 (59.0, 70.5)	34.3 (25.6, 42.8)	66.1 (61.2, 70.7)	**66.0 (61.1, 70.7)**
Investigator assessment of FAS[b]				
Number of patients evaluable	279	140	411	411
Numberof patients with confirmed CR or PR	197	44	290	296
ORR, % (95% CI)	70.6 (64.9, 75.9)	31.4 (23.9, 39.8)	70.6 (65.9, 74.9)	72.0 (67.4, 76.3)
Disease control rate				
BICR assessment of EFR analysis set[a]				
Number of patients evaluable	-	-	398	397[c]
Number of patients with confirmed CR, PR or SD≥6 weeks	-	-	362	361
DCR, % (95% CI)	-	-	91.0 (87.7, 93.6)	90.9 (87.7, 93.6)
Investigator assessment of FAS				
Number of patients evaluable	279	140	411	411
Number (%) of patients with confirmed CR, PR or SD≥6 weeks	260	104	385	383
DCR, % (95% CI)	93.2 (89.6, 95.9)	74.3 (26.5, 42.8)	93.7 (90.9, 95.8)	93.2 (90.3, 95.4)

Table 11 Summary of overall efficacy in AURA3 and pooled Phase II studies (AURA extension and AURA2)

Efficacy parameters	AURA3 at DCO Osimertinib N=279	AURA3 at DCO Chemotherapy N=140	Pooled Phase II at DCO2 (1 May 15) Osimertinib N=411	Pooled Phase II at DCO3 (1 Nov 15) Osimertinib N=411
Best percentage change from baseline in target lesion size				
BICR assessment of EFR analysis set				
Number of patients evaluable	-	-	397	396[c]
Mean (sd)	-	-	−45.0 (28.0)	−47.5 (30.0)
Median (min, max)	-	-	−47.6 (−100.0, +90.8)	−50.0 (−100.0, +90.8)
Investigator assessment of FAS				
Number of patients evaluable	278	131	408	409
Mean (sd)	-46.1 (29.50)	-24.4 (29.27)	−49.5 (28.97)	−49.5 (41.82)
Median (min, max)	-	-	−53.1 (−100.0, +50.0)	−54.2 (−100.0, +550.0)
Duration of objective response				
BICR[a]				
Number of responders	181	48	263	262[c]
Number of responders who subsequently progressed or died (%)	62	38	60 (22.8)	116 (44.3)
Median DoR (95% CI)	11.2 (8.3, NC)	3.1 (2.9, 4.3)	NC (8.3, NC)	12.5 (11.1, NC)
Estimated percentage remaining in response[d]				
at 6 months, % (95% CI)	71.4 (63.3, 78.0)	25.6 (13.8, 39.1)	78.4 (72.1, 83.5)	77.5 (71.8, 82.2)
at 9 months, % (95% CI)	53.5 (43.5, 62.5)	14.6 (5.3, 28.4)	55.3 (40.6, 67.8)	65.0 (58.5, 70.6)
at 12 months, % (95% CI)	47.5 (35.5, 58.6)	7.3 (0.8, 24.3)	-	52.9 (45.9, 59.4)

Table 11 Summary of overall efficacy in AURA3 and pooled Phase II studies (AURA extension and AURA2)

Efficacy parameters	AURA3 at DCO Osimertinib N=279	AURA3 at DCO Chemotherapy N=140	Pooled Phase II at DCO2 (1 May 15) Osimertinib N=411	Pooled Phase II at DCO3 (1 Nov 15) Osimertinib N=411
Investigator assessment of FAS				
Number of responders	197	44	290	296
Number of responders who subsequently progressed or died (%)	88 (44.7)	36 (81.8)	80 (27.6)	155 (52.4)
Median DoR (95% CI)	9.7 (8.3, 11.6)	4.1 (3.0, 5.6)	8.5 (8.5, NC)	11.3 (10.1, 12.6)
Estimated percentage remaining in response[b]				
at 6 months, % (95% CI)	70.1 (62.8, 76.3)	30.2 (17.2, 44.2)	71.8 (65.4, 77.2)	74.7 (69.3, 79.3)
at 9 months, % (95% CI)	53.0 (44.5, 60.9)	15.7 (6.2, 29.1)	48.1 (25.3, 67.8)	62.2 (56.4, 67.5)
at 12 months, % (95% CI)	37.8 (28.1, 47.5)	10.5 (2.5, 24.9)	-	48.8 (42.6, 54.7)
Median progression-free survival				
BICR assessment of FAS				
Number of patients evaluable	279	140	411	411
Total number of events (% maturity for PFS)	116 (41.6)	103 (73.6)	159 (38.7)	227 (55.2)
Median PFS (95% CI) (months)	11.0 (9.4, NC)	4.2 (4.1, 5.6)	9.7 (8.3, NC)	11.0 (9.6, 12.4)
Median follow-up for PFS (months)	8.2	5.6	7.2	12.6
Progression-free at 6 months, % (95% CI)	69.6 (63.6, 74.8)	34.1 (25.8, 42.5)	70.9 (66.1, 75.1)	70.4 (65.7, 74.7)
Progression-free at 9 months, % (95% CI)	-	-	51.9 (45.3, 58.1)	56.9 (51.8, 61.6)
Progression-free at 12 months, % (95% CI)	46.9 (39.1. 54.4)	11.3 (5.6, 19.1)	-	47.5 (42.4, 52.5)
Investigator assessment of FAS				
Number of patients evaluable	279	140	411	411

Table 11 Summary of overall efficacy in AURA3 and pooled Phase II studies (AURA extension and AURA2)

Efficacy parameters	AURA3 at DCO Osimertinib N=279	AURA3 at DCO Chemotherapy N=140	Pooled Phase II at DCO2 (1 May 15) Osimertinib N=411	Pooled Phase II at DCO3 (1 Nov 15) Osimertinib N=411
Total number of events (% maturity for PFS)	140 (50.2)	110 (78.6)	158	243 (59.1)
Median PFS (95% CI) (months)[d]	10.1 (8.3, 12.3)	4.4 (4.2, 5.6)	9.7 (8.3, NC)	11.1 (9.7, 12.5)
Median follow-up for PFS (months)	8.4	5.5	6.9	13.7
Estimated progression-free at 6 months, % (95% CI)	68.8 (62.9, 74.0)	36.9 (28.5, 45.3)	73.0 (68.4, 77.1)	72.8 (68.2, 76.9)
Estimated progression-free at 9 months, % (95% CI)	-	-	53.5 (47.2, 59.4)	58.1 (53.2, 62.8)
Estimated progression-free at 12 months, % (95% CI)	44.0 (36.9, 50.9)	9.8 (4.9, 16.9)	-	47.9 (42.9, 52.6)
Median overall survival				
Number of patients evaluable			411	411
Total number of deaths (% maturity for OS)	35 (12.5%)	26 (18.6%)	52 (12.7)	98 (23.8)
Median OS (95% CI) (months)[d]	-	-	NC (NC, NC)	16.4, NC
Median follow-up for OS (months)	-	-	7.4	13.4
Estimated survival at 6 months, % (95% CI)	-	-	92.3 (89.3, 94.5)	91.9 (88.8, 94.2) ññ
Estimated survival at 9 months, % (95% CI)	-	-	85.3 (80.9, 88.7)	84.9 (81.1, 88.1)
Estimated survival at 12 months, % (95% CI)	-	-	-	79.8 (75.6, 83.4)

CI=confidence interval; DoR=duration of response; ORR=objective response rate; PFS=progression-free survival; RECIST=Response Evaluation Criteria in Solid Tumors.
a In line with the RECIST framework in randomised, controlled Phase III studies, responses in AURA3 could be confirmed or unconfirmed.
b Data are total treatment duration.
Source: Tables 11.1.5, 11.1.7.2, 11.2.1.3.1, 11.2.4.2.1 and 11.2.4.4 of the AURA3 CSR in Module 5.3.5.1; Tables 1.4.2, 1.6.2, 3.1.1, 2.6.2.2, 2.1.1.2, 2.3.1.2 of the Pooled Phase II Efficacy in Module 5.3.5.3.

4.3.3. Discussion

AURA3 is a Phase III, open-label, randomised study (2:1 ratio [osimertinib:platinum-based chemotherapy]) specifically designed to compare the efficacy of osimertinib vs. platinum- based doublet chemotherapy (pemetrexed plus carboplatin or pemetrexed plus cisplatin, followed by optional pemetrexed maintenance) as second-line treatment in patients with confirmed advanced EGFR T790M mutation-positive NSCLC who had progressed following 1 line of treatment with an approved EGFR-TKI.

Patient population

Patients with locally advanced or metastatic NSCLC (histologically or cytologically confirmed), with a documented EGFR mutation known to be associated with EGFR-TKI sensitivity, were recruited. All patients were to have centrally confirmed T790M mutant-positive status from a tissue biopsy sample taken after documented disease progression on first-line treatment with an approved EGFR-TKI. Of note, there was no requirement that radiological progression had to occur while receiving continuous treatment with an EGFR-TKI or that randomisation had to occur within 4 weeks of radiological progression.

Patients who had received more than one prior line of therapy for advanced NSCLC were excluded, as were those with any contraindication for pemetrexed and cisplatin/carboplatin (e.g. predominantly squamous cell histology). All patients were to have adequate cardiac, hepatic and renal function, World Health Organization (WHO) performance status of 0 or 1 with no deterioration over the previous 2 weeks and a minimum life expectancy of 12 weeks. Patients with CNS metastases were eligible if they were asymptomatic, stable and not requiring steroids for at least 4 weeks prior to start of study treatment. On comparing these inclusion/exclusion criteria with those from the phase II studies, they seem to be pretty similar, with the main difference in the number of prior treatment lines received. In AURA 3 all patients were to receive study treatments as second line therapy, whereas in AURA and AURA2 only about 24% received osimertinib in second line and the majority (69%) in ≥third line.

Treatments

In the osimertinib arm, patients could continue on treatment as long as they were deriving clinical benefit, as judged by the investigator, or until a treatment discontinuation criterion was met. In the chemotherapy arm, patients could receive up to 6 cycles of pemetrexed plus cisplatin or carboplatin as initial treatment. Those patients whose disease had not progressed after 4 cycles of platinum-based doublet chemotherapy could continue on maintenance monotherapy with pemetrexed according to the approved label use or local practice guidelines. The use of carboplatin or cisplatin based therapy in the clinical practice is based on the expected tolerability and preferences by oncologist. According to the current clinical guidelines cisplatin could have a slightly superior efficacy to carboplatin in meta-analysis, even though it may not be worth the added toxicity in the palliative care setting.

Once patients in the chemotherapy arm were determined to have objective radiological progression by the investigator, with confirmation by blinded independent central review (BICR), they were given the opportunity to begin treatment with osimertinib 80 mg once daily. This crossover even affecting the OS data is considered ethical.

Endpoints

The primary efficacy endpoint of AURA3 was PFS in the FAS, based on investigator assessment according to RECIST v1.1, which is agreed. However, considering the poor prognosis of this setting (survival of 1 to 2 years), the submission of data in terms of OS appears mandatory even if considering the potential confounding effect of the cross-over of patients as well as the effect of next-line therapies. OS data at the time of submission of responses are awaited.

Main secondary endpoints were DoR, DCR, OS and QoL. Apparently data on PFS 2 has been collected as an

exploratory endpoint; this is considered of great value, especially in the subgroup of patients crossing-over from the chemotherapy arm to the osimertinib one. Data on PFS2 should be submitted.

Randomisation and SAP

Suitable patients were centrally randomised to receive either osimertinib 80 mg or platinum-based doublet chemotherapy in a 2:1 ratio. Patients were stratified at randomisation based on ethnicity (Asian/Non-Asian).

According to the statistical analysis plan, three analyses of OS will be conducted. The DCO for the first OS analysis was approximately 4 months after the PFS DCO of 15 April 2016. A second analysis of OS will be performed when the OS data are approximately 50% mature (approximately 205 deaths events). A third analysis of OS will be performed when the OS data are approximately 70% mature (approximately 287 deaths events). It is highly questionable the number of interim analyses planned.

Results

A total of 1036 patients were enrolled in the study (ie, signed informed consent and were screened) but a total of 617 patients failed screening. This was mainly due to the lack of central confirmation of T790M (81%).

Despite patients were randomised to treatment at 126 study centres in 18 countries, no individual country randomised more than 20% of patients.

Amendments to protocol (two substantial amendments were carried out) were mainly related to statistical issues and appear to be driven by the updated knowledge subsequent to results of AURA and AURA2 trial.

The number of protocol deviations is overall high (25.3%), however most of them were finally solved (e.g. from the 6 patients with no centrally confirmed T790M mutation-positive status, only 3 were tumour T790M negative and in one of them ctDNA plasma sample was positive).

The most frequent protocol deviation related to inclusion/exclusion criteria was the number of treatment lines previously received, taking into account that the trials that gave rise to the conditional approval of osimertinib (AURA2 and AURA extension) demonstrated the efficacy of osimertinib in a more pre-treated population (second line and ≥ thrid line therapy) than the population studied in AURA3 and taking into account that percentages of this protocol deviation are low and more or less balanced between trial arms (3.6% in the osimertinib arm and 4.3% in the chemotherapy arm; only 1 patient (in the osimertinib arm) received 3 prior lines of therapy) this deviation is not considered susceptible from impacting study result

- Baseline characteristics

Patient demographic seem to be well-balanced between arms. The median age was 62 years (range 20 to 90 years), with 64 patients (15.3%) aged ≥75 years. There was a greater proportion of female patients (64.2%) and the population was predominantly Asian (65.4%) and white (32%). Two-thirds of patients had never smoked (67.5%) and a low percentage of patients (5.3%) were current smokers.

Regarding disease characteristics, most patients had a WHO performance status of 1. The main histological type was adenocarcinoma (98.6%). The most common EGFR sensitising mutations were exon 19 deletion, being higher in the osimertinib arm (68.5% vs.62.1%) and exon 21 L858R (29.7% osimertinib vs. 32.1% chemotherapy). All patients but 3 were centrally confirmed as T790M mutation-positive.

The vast majority of patients had metastatic disease, however some imbalances are noted in the proportion of patients with liver metastases, (20.1% in the osimertinib arm vs. 29.3% in the chemotherapy arm) and in the proportion of patients with bone/locomotor metastases (37.6% in the osimertinib arm vs. 50.7% in the chemotherapy arm).

334.4% of patients presented brain metastases, however these were required to be asymptomatic, stable and not requiring steroids for at least 4 weeks prior to the start of study treatment.

Overall the main demographic and disease characteristics are comparable to that of populations recruited in AURA2 and AURA extension trials (pooled Phase II trials). Prior therapies is the most important difference between AURA3 and the previous trials. In AURA3 all patients but 16 had previously received only 1 EGFR-TKI agent. 3.6% in the osimertinib and 4.3% in the chemotherapy arm had received 2 prior lines. Only one patient in the osimertinib arm had received ≥3 lines. Two thirds of patients had received gefitinib and one thirderlotinib, the great majority received EGFR-TKI therapy for more than 6 months. The median time from progression on EGFR-TKI to randomisation was 55 days.

In the chemotherapy arm investigators chose to administer a combination of pemetrexed plus carboplatin for 94 (69.1%) patients, with 42 (30.9%) patients receiving a combination of pemetrexed plus cisplatin. No patient switched from cisplatin to carboplatin during randomised treatment on the study. 73 (53.7%) patients went on to receive pemetrexed maintenance monotherapy.

- Outcomes

A statistically significant and clinically meaningful improvement in terms of the primary endpoint, PFS (HR: 0.30 [95% CI: 0.23, 0.41]; p-value: <0.001), was shown by osimertinib compared to the control arm.

Treatment with osimertinib resulted in a 5.7-month improvement in median PFS compared to chemotherapy (10.1 months [95% CI: 8.3, 12.3] vs. 4.4 months [95% CI: 4.2, 5.6]).

The sensitivity analysis of PFS by BICR on the FAS was consistent with the investigator-based analysis, showing 6.8-months of improvement in median PFS in the osimertinib arm (11 months) compared to the chemotherapy arm (4.2 months) (HR: 0.28 [95% CI: 0.20, 0.38]).

The percentage of patients without progression at the time of DCO was approximately 50% and 21% in osimertinib and chemotherapy arms respectively.

Results in terms of PFS seem robust enough. In this sense, all the sensitive analyses carried out did not reveal significant differences regarding the main analysis.

PFS results in the subgroups analyses were consistent with the whole population of the study. Due to the limited number of patients, there are no data in terms of HR in those patients with duration of the prior EGFR-TKI < 6 months, however, the median PFS in the osimertinib arm was 12.4 months (95% CI: 6.8, NC) compared to 4.2 months (95% CI: 1.7, 6.7).

On contextualising PFS results for chemotherapy in the AURA3 study, the median PFS with first-line platinum doublet in EGFR mutation-positive NSCLC ranges from 4.6 months to 6.9 months, and the ORR from 15% to 47%. Bearing in mind that the patients in AURA3 study had been previously treated with EGFR-TKI therapy, the indirect comparison could be biased. However when results in the chemotherapy arm from the IMPRESS trial are considered, ORR and to some extent PFS, show similar results to those obtained in the AURA3 study.

At the DCO for the primary analysis of PFS, no OS analysis was performed, a high cross-over rate has already been reported which will put interpretability of results at risk. Data are awaited at the time of submission of responses. Data on PFS2, an exploratory endpoint, will help in the interpretation of results, especially in the subgroup of patients crossing over to osimertinib arm. The applicant should clarify whether data on PFS2 will be available.

Results in terms of secondary endpoints consistently support primary findings. An ORR by investigator of 70.6% (95% CI: 64.9, 75.9) was observed in the osimertinib arm and of 31.4% (95% CI: 23.9, 39.8) in the chemotherapy arm (investigator assessment) [OR of 5.39 (95% CI: 3.47, 8.48) (p-value: <0.001)]. Results by BICR were consistent, which add robustness to the results seeing as no confirmation of response was required. The median DoR based on investigator assessment at 51.9% maturity was 9.7 months (95% CI: 8.3, 11.6) in the osimertinib arm vs. 4.1 months (95% CI: 3.0, 5.6) in the chemotherapy arm. ORR results are consistent with primary endpoint data from the phase II trials (updated data at data cut-off of 1/Nov/15)

that gave rise to the conditional approval of osimertinib ORR of pooled phase II trials 66.0% (95% CI: 61.1, 70.7). The historical ORR obtained by chemotherapy, or TKI re-challenge, are considerably lower than those seen in all the AURA studies.

The disease control rate based on investigator assessment was 93.2% (95% CI: 89.6, 95.9) in the osimertinib arm vs. 74.3% (95% CI: 66.2, 81.3) in the chemotherapy arm and there was a greater mean percentage tumour shrinkage from baseline in patients on osimertinib compared to patients on chemotherapy.

PRO endpoints showed an overall improvement of symptoms associated to the disease, however due to the open label design, no firm conclusions can be drawn from QoL

It should be noted the antitumor activity of osimertinib in patients with measurable CNS metastases at baseline (asymptomatic, stable and not requiring steroids for at least 4 weeks prior to the start of study treatment) 70% [21/30 patients; 95% CI: 50.60, 85.27]) compared to those on chemotherapy (31.3% [5/16 patients; 95% CI: 11.02, 58.66].

No data in those patients who received osimertinib after progression of chemotherapy (60%) have been offered.

Finally, results from the AURA3 study confirm the previous data obtained from the AURA extension and AURA2.

In conclusion, osimertinib seems to offer a clinically meaningful result for those patients with T790M positive. Nevertheless, OS data and PFS2 results should be submitted before conclusion of this variation.

4.4. Clinical Safety aspects

4.4.1. Methods – analysis of data submitted

The safety evaluation to inform the benefit-risk assessment for this application focuses on the comparative safety profile of osimertinib 80 mg vs. chemotherapy in 415 patients in AURA3 as of the DCO1 for progression-free survival (PFS) of 15 April 2016. More mature (ie, longer duration of exposure) safety data from the 411 patients in the pooled Phase II studies of osimertinib at DCO3 (1 November 2015) are used to support the absence of unexpected additional toxicity burden with longer exposure to osimertinib and its use in second- and ≥third-line therapy.

AURA3 safety data are based on the DCO date for the primary efficacy analysis of PFS: 15 April 2016.

For the pooled Phase II studies, the DCO used is the third DCO: 1 November 2015.

For the AURA Phase I component, as part of the pooled safety analysis for cardiac effects and ILD, the DCO used is the second DCO: 1 May 2015.

Table: Summary of datasets used to characterise osimertinib safety profile

Dataset	Objective	Number of osimertinib patients
AURA3	Primary evaluation of safety data in support of this Type II variation Confirmation of the safety profile of osimertinib, and comparison with the safety data of platinum-based doublet-based chemotherapy	279
Pooled global Phase II studies (AURA extension and AURA2) – 1 Nov 15 DCO	Provide information in second-line and ≥third-line patients Demonstrate consistent safety data across pivotal studies Provide information on any additional toxicity with longer follow-up	411
Any patient who received at least 1 dose of 80 mg osimertinib as second-line in a Phase II or Phase III study; cross-over patients from AURA3 are not included	Provide a larger pooled dataset consisting of patients who received at least 1 dose of 80 mg osimertinib in the pivotal studies with the purpose of updating Section 4.8 (Undesirable Effects) of the SmPC	690
Any patients enrolled in the global Phase I and Phase II studies (AURA Phase I, AURA extension, AURA2 and AURA3) who received at least 1 dose of osimertinib 80 mg in the second-line or later setting.	Provide frequency and estimates of ADRs and events considered to require warnings and precautions in the product label: QTcF prolongation review ILD/pneumonitis review Keratitis review Review of changes in cardiac contractility Closely matched to intended patient population	833
Any patient enrolled in the global Phase I and Phase II studies (AURA Phase I, AURA extension, or AURA2) or AURA3, who received osimertinib, with the exclusion of cross-over patients from AURA3.	Provide sensitivity analysis on broader patient population to corroborate results from analysis in 833 patients in ≥second line therapy: ILD/pneumonitis review Keratitis review Review of cardiac contractility	1092

DCO = data cut-off; ILD = interstitial lung disease; QTcF = QT corrected by Fredericia's method; SmPC = Summary of Product Characteristics

4.4.2. Results

Table: Adverse events in any category in AURA3 (Safety analysis set)

AE Category	Number (%) of patients [a]	
	Osimertinib 80 mg (N=279)	Chemotherapy (N=136)
Any AE	273 (97.8)	135 (99.3)
Any AE causally related to treatment [b]	231 (82.8)	121 (89.0)
Any AE of CTCAE grade 3 or higher	63 (22.6)	64 (47.1)
Any AE of CTCAE grade 3 or higher, causally related to treatment [b]	16 (5.7)	46 (33.8)
Any AE with outcome = death	4 (1.4)	1 (0.7)
Any AE with outcome = death, causally related to treatment [b]	1 (0.4)	1 (0.7)
Any SAE (including events with outcome = death)	50 (17.9)	35 (25.7)
Any SAE (including events with outcome = death), causally related to treatment [b]	8 (2.9)	17 (12.5)
Any AE leading to discontinuation of treatment	19 (6.8)	14 (10.3)
Any AE leading to discontinuation of treatment, causally related to treatment [b]	10 (3.6)	12 (8.8)

[a] Patients with multiple events in the same category are counted only once in that category. Patients with events in more than 1 category are counted once in each of those categories.
[b] As assessed by the Investigator, and programmatically derived from individual causality assessments.
Includes AEs with an onset date on or after the date of first dose and up to and including 28 days following the date of last dose of study medication.
AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events version 4.0; SAE = serious adverse event
Data cut-off date: 15 April 2016

Table: Adverse events in any category in Phase II studies - patient level (Safety analysis set)

Adverse event category	Osimertinib 80 mg (N=411)[a]
Any AE	406 (98.8)
Any AE causally related to osimertinib [b]	364 (88.6)
Any AE of CTCAE grade 3 or higher	149 (36.3)
Any AE of CTCAE grade 3 or higher, causally related to osimertinib [b]	56 (13.6)
Any AE with outcome = death	14 (3.4)
Any AE with outcome = death, causally related to osimertinib [b]	4 (1.0)
Any SAE (including events with outcome = death)	107 (26.0)
Any SAE (including events with outcome = death), causally related to osimertinib [b]	23 (5.6)
Any AE leading to discontinuation of osimertinib	26 (6.3)
Any AE leading to discontinuation of osimertinib, causally related to osimertinib [b]	16 (3.9)
Any AE leading to dose modification of osimertinib	91 (22.1)
Any AE leading to dose interruption of osimertinib	87 (21.2)
Any AE leading to dose reduction of osimertinib	16 (3.9)

[a] Patients with multiple events in the same category are counted only once in that category. Patients with events in more than 1 category are counted once in each of those categories.
[b] As assessed by the Investigator, and programmatically derived from individual causality assessments.
Includes AEs with an onset date on or after the date of first dose and up to and including 28 days following the date of last dose of study medication.
AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events version 4.0; SAE = serious adverse event
Data cut-off date: 1 November 2015

Table: Summary of categorical safety data in osimertinib patients in Phase II and Phase III safety datasets (Safety analysis set)

	Dataset		
	AURA3 (N=279)	Pooled Phase II studies (N=411)	Patients receiving 80 mg osimertinib in Phase II or Phase III studies (N=690)
Duration of exposure (months)			
Mean (SD)	8.8 (4.1)	11.1 (4.7)	10.2 (4.6)
Median	8.2	13.0	11.1
Range	0.2 – 18.5	0.0-17.6	0.03 – 18.5
Any adverse event	273 (97.8)	406 (98.8)	679 (98.4)
Any AE causally related [b]	231 (82.8)	364 (88.6)	595 (86.2)
Any AE with outcome of death	4 (1.4)	14 (3.4)	18 (2.6)
Any AE with outcome of death, causally related [b]	1 (0.4)	4 (1.0)	5 (0.7)
Any AE of CTCAE ≥grade 3	63 (22.6)	149 (36.3)	212 (30.7)
Any AE of CTCAE ≥grade 3, causally related [b]	16 (5.7)	56 (13.6)	72 (10.4)
Any SAE (including AEs with outcome of death)	50 (17.9)	107 (26.0)	157 (22.8)
Any SAE (including AEs with outcome of death), causally related [b]	8 (2.9)	23 (5.6)	31 (4.5)
Any AE leading to discontinuation of study drug	19 (6.8)	26 (6.3)	45 (6.5)
Any AE leading to discontinuation of study drug, causally related [b]	10 (3.6)	16 (3.9)	26 (3.8)

Source: Table 3.1.1 in the Pooled Phase II Safety in Module 5.3.5.3 and Table 11.3.1.3 and 11.3.2.1.3 in Pooled

- **Extent of exposure**

AURA 3

All patients randomised to osimertinib received at least 1 dose of study medication. Of the 140 patients randomised to the chemotherapy arm, 136 were dosed. Median exposure was 8.1 months (range: 0.2-18.5) in the osimertinib arm. Actual exposure was similar to intended exposure in the osimertinib arm (median 7.9 months). A maximum of 6 cycles for the platinum-based doublet chemotherapy was allowed in the chemotherapy arm; the median duration was 4.2 cycles (range: 0.4-14.5). Of the 136 patients in the chemotherapy arm, 42 (30.9%) received pemetrexed plus cisplatin and 94 (69.1%) received pemetrexed plus carboplatin based on Investigator choice

Table: Duration of exposure in AURA3 (Safety analysis set)

		Number (%) of patients	
		Osimertinib 80 mg (N=279)	Chemotherapy (N=136)
Total treatment duration (months)[a]	Mean (SD)	8.6 (4.1)	4.8 (3.3)
	Median	8.1	4.2
	Minimum	0.2	0.4
	Maximum	18.5	14.5
	Total treatment years	200.3	54.5
Actual treatment duration (months)[b]	Mean (SD)	8.5 (4.1)	NA
	Median	7.9	
	Minimum	0.2	
	Maximum	18.5	
	Total treatment years	198.3	
Relative dose intensity (RDI)[c]	Mean (SD)	98.4 (6.2)	
	Median	100.0	
	Minimum	49.2	
	Maximum	100.0	

[a] Treatment durations were calculated by adding the curation for each patient in the treatment group. Total treatment duration for osimertinib = (last dose date - first dose date +1)/(365.25/12). Total treatment duration for chemotherapy = ((start date of last cycle + 20) – start date of first cycle + 1) / 365.25/12).
[b] Actual treatment duration = total treatment duration, excluding dose interruptions. Interruptions to chemotherapy infusions were not captured.
[c] Relative dose intensity is the percentage of the actual dose intensity delivered relative to the intended dose intensity through treatment discontinuation.
If a patient has not discontinued, then the data cut-off date is used in place of last dose date.
Data cut-off date: 15 April 2016

Extent of exposure in the pooled Phase II studies

Since osimertinib is dosed continuously without a maximum duration, longer study follow-up may result in longer duration of exposure. Hence, due to the longer follow-up time, patients in the 2 Phase II studies had longer duration of exposure than those in AURA3 (median of 13.0 months and 8.1 months, respectively) and provide additional safety information for the potential use of osimertinib in the longer term.

At the time of the 1 November 2015 DCO for these studies, 228 (55.5%) patients remained on osimertinib treatment (106/201 patients [52.7%] in AURA extension, and 122/210 patients [58.1%] in AURA2). The median duration of exposure for the 411 patients was 13.0 months (range: 0.0-17.6 months), with the majority of patients (188 [45.7%]) receiving 12-15 months of treatment. Actual exposure was similar to intended exposure (median: 12.9 months; range: 0.0-17.6 months), indicating that the frequency and median duration of interruptions had low impact on exposure. Overall mean and median relative dose intensity (RDI) was 98.5% and 100.0%, respectively.

- **Dose modifications**

AURA 3

A total of 76 (27.2%) patients in the osimertinib arm had interruptions vs the following delays in administration of chemotherapy: 57 (41.9%) pemetrexed, 16 (38.1%) cisplatin, 28 (29.8%) carboplatin. The proportion of patients with dose modifications (overall and those requiring modifications due to AEs), dose interruption/delay (overall and those requiring interruption/delay due to AEs), and dose reductions (overall and those requiring reduction due to AEs) were also less frequent in the osimertinib arm than in the chemotherapy arm.

Table: Treatment interruptions and dose reductions in the osimertinib arm (Safety analysis set)

		Osimertinib 80 mg (N=279)
Received planned starting dose	Yes	279 (100.0)
Patients with an interruption	Any	76 (27.2)
	1 interruption	50 (17.9)
	2 interruptions	14 (5.0)
	> 2 interruptions	12 (4.3)
Reasons for interruption [b]	Adverse event	38 (13.6)
	Patient forgot	27 (9.7)
	Laboratory abnormality	1 (0.4)
	Patient decision	1 (0.4)
	Surgery	1 (0.4)
	Other	20 (7.2)
Patients with a dose reduction	Any	8 (2.9)
Reasons for dose reduction	Adverse event	8 (2.9)

[a] Number of patients with an interruption/delay and/or a dose reduction.
[b] Reasons for interruptions are not mutually exclusive for patients with multiple interruptions although patients are counted only once per category.

Dose modifications in the pooled Phase II studies

At the time of the 1 November 2015 DCO for the Phase II studies, 152/411 (37%) of patients had a dose interruption, the majority (84 [20.4%]) due to AEs; 19 (4.6%) of patients had a dose reduction, all due to AEs

- **Adverse events**

Common adverse events in AURA 3

Adverse events were most frequently reported (≥50% of patients) in the SOCs of Gastrointestinal (189 [67.7%] patients), Skin & Subcutaneous Tissue Disorders (159 [57.0%] and Infections and Infestations (142 [50.9%] in the osimertinib arm and Gastrointestinal Disorders (106 [77.9% patients]) and General Disorders & Administration Site Conditions (88 [64.7%]) in the chemotherapy arm. The incidence of AEs was at least 10 percentage points higher in the osimertinib arm than in the chemotherapy arm for diarrhoea (40.5% osimertinib vs 11.0% chemotherapy), dry skin (18.6% vs 4.4%), paronychia (16.5% vs 1.5%), and dermatitis acneiform (12.9% vs 2.2%). The incidence of AEs was at least 10 percentage points lower in the osimertinib arm than in the chemotherapy arm for nausea (16.1% osimertinib vs 49.3% chemotherapy), decreased appetite (17.9% vs 36.0%), constipation (14.0% vs 34.6%), fatigue (15.8% vs 27.9%), anaemia (6.8% vs 27.9%), and platelet count decreased (4.3% vs 15.4%).

Table Most common adverse events (frequency of ≥10% in either treatment group) in AURA3 (Safety analysis set)

MedDRA preferred term	Number (%) of patients [a]	
	Osimertinib 80 mg (N=279)	Chemotherapy (N=136)
Patients with any adverse event	273 (97.8)	135 (99.3)
AEs with higher incidence in osimertinib arm		
Diarrhoea	113 (40.5)	15 (11.0)
Dry skin	52 (18.6)	6 (4.4)
Paronychia	46 (16.5)	2 (1.5)
Cough	46 (16.5)	19 (14.0)
Dermatitis acneiform	36 (12.9)	3 (2.2)
Pruritus	35 (12.5)	6 (4.4)
Back pain	29 (10.4)	12 (8.8)
Nasopharyngitis	28 (10.0)	7 (5.1)
AEs with higher incidence in chemotherapy arm		
Nausea	45 (16.1)	67 (49.3)
Decreased appetite	50 (17.9)	49 (36.0)
Constipation	39 (14.0)	47 (34.6)
Fatigue	44 (15.8)	38 (27.9)
Anaemia	19 (6.8)	38 (27.9)
Vomiting	31 (11.1)	27 (19.9)
Stomatitis	41 (14.7)	21 (15.4)
Platelet count decreased	12 (4.3)	21 (15.4)
Asthenia	20 (7.2)	20 (14.7)
Dyspnoea	24 (8.6)	18 (13.2)
Neutropenia	10 (3.6)	18 (13.2)
Neutrophil count decreased	13 (4.7)	16 (11.8)
Headache	28 (10.0)	15 (11.0)
Alanine aminotransferase increased	18 (6.5)	15 (11.0)
Aspartate aminotransferase increased	14 (5.0)	15 (11.0)
Pyrexia	18 (6.5)	14 (10.3)
Malaise	11 (3.9)	14 (10.3)

[a] Number (%) of patients with AEs, sorted in descending frequency of PT in the osimertinib arm for AEs more common in the osimertinib arm and sorted in descending frequency of PT in the chemotherapy arm for AEs more common in the chemotherapy arm.
Includes AEs with an onset date on or after the date of first dose and up to and including 28 days following the date of last dose of study medication.
MedDRA version 19.0.
Data cut-off date: 15 April 2016

Common adverse events in Phase II studies

The nature and severity of AEs in the pooled Phase II studies are consistent with those in the osimertinib arm in AURA3, with similar incidences and severity of the overall grouped term. The exceptions to this were a higher incidence of the individual PT of rash reported in the pooled Phase II studies (24.6%) compared to the 2.5% incidence in the osimertinib arm in AURA3, and the higher incidence of dermatitis acneiform in the osimertinib arm of AURA3 (12.9%) compared to the pooled phase II studies (8.3%). These exceptions may reflect differences in reporting patterns from a generic “rash” PT used in Phase II studies to the more specific PT of dermatitis acneiform in AURA3. In all studies, fewer than half of patients were treated for events in the Skin Effects grouped term, and <1% of Skin Effects AEs led to dose reduction or dose discontinuation.

Among the 411 patients in the Phase II studies, 406 (98.8%) reported AEs. The most commonly reported SOCs were GI disorders (303 [73.7%]), Skin and Subcutaneous Tissue Disorders (283 [68.9%]), and Infections and Infestations (243 [59.1%]).

The most commonly reported PTs were diarrhoea (187 [45.5%] patients), dry skin (105 [25.5%]), rash (101 [24.6%]), paronychia (89 [21.7%]), decreased appetite (84 [20.4%]), and nausea (82 [20.0%]).

Adverse events of CTCAE grade 3 or higher in AURA3

In the osimertinib arm, CTCAE ≥grade 3 AEs were reported in a wide range of PTs, covering multiple SOCs. Pulmonary embolism was reported in 4 (1.4%) patients and neutrophil count decreased, asthenia, decreased appetite, diarrhoea, fatigue, ALT increased, AST increased, and dyspnoea were reported in 3 (1.1%) patients each. Adverse events CTCAE ≥grade 3 considered by the Investigator to be possibly related to the study drug were reported at a lower frequency in the osimertinib arm than in the chemotherapy arm (16 [5.7%] vs 46 [33.8%]).

Table: Adverse events of CTCAE grade 3 or higher in at least 2 patients in either treatment arm in AURA3, by preferred term (Safety analysis set)

	Number (%) of patients [a]	
Preferred term	Osimertinib 80 mg (N=279)	Chemotherapy (N=136)
Any CTCAE ≥grade 3 AE	63 (22.6)	64 (47.1)
Pulmonary embolism	4 (1.4)	3 (2.2)
Neutrophil count decreased	3 (1.1)	9 (6.6)
Asthenia	3 (1.1)	6 (4.4)
Decreased appetite	3 (1.1)	4 (2.9)
Diarrhoea	3 (1.1)	2 (1.5)
Fatigue	3 (1.1)	1 (0.7)
Alanine aminotransferase increased	3 (1.1)	1 (0.7)
Aspartate aminotransferase increased	3 (1.1)	1 (0.7)
Dyspnoea	3 (1.1)	0
Nausea	2 (0.7)	5 (3.7)
Pneumonia	2 (0.7)	1 (0.7)
Spinal cord compression	2 (0.7)	1 (0.7)
Respiratory failure	2 (0.7)	0
Erythema	2 (0.7)	0
Anaemia	1 (0.4)	15 (11.0)
Neutropenia	1 (0.4)	8 (5.9)
Thrombocytopenia	1 (0.4)	5 (3.7)
Hyperglycaemia	1 (0.4)	3 (2.2)
Hyponatraemia	1 (0.4)	3 (2.2)
Vomiting	1 (0.4)	3 (2.2)
Haemoglobin decreased	1 (0.4)	2 (1.5)
Platelet count decreased	0	5 (3.7)
Hypokalaemia	0	3 (2.2)
Epilepsy	0	3 (2.2)
White blood cell count decreased	0	3 (2.2)
Febrile neutropenia	0	2 (1.5)
Leukopenia	0	2 (1.5)
Deep vein thrombosis	0	2 (1.5)
Abdominal pain	0	2 (1.5)
Stomatitis	0	2 (1.5)
Lymphocyte count decreased	0	2 (1.5)

[a] Number (%) of patients with AEs of CTCAE grade 3 or higher, sorted by decreasing order of PTs within the osimertinib group.

Patients with multiple AEs of CTCAE grade 3 or higher are counted once for each preferred term

Includes AEs with an onset date on or after the date of first dose and up to and including 28 days following discontinuation of randomised treatment or the day before first administration of cross-over treatment.

CTCAE = Common Terminology Criteria for Adverse Events (version 4.0).

MedDRA version 19.0.

Data cut-off date: 15 April 2016

Adverse events of CTCAE grade 3 or higher in Phase II studies

CTCAE ≥grade 3 AEs were reported in a higher proportion of patients in the pooled Phase II studies (36.3%) than in the osimertinib arm of AURA3 (22.6%).

Among the 411 patients in the Phase II studies, 149 (36.3%) had at least 1 AE of CTCAE≥grade 3. Events were reported in a wide range of PTs, covering multiple SOCs, mostly with 1 or 2 events per PT.

The following AEs of CTCAE ≥grade 3 were reported in ≥1% of patients: pneumonia (11 [2.7%]), anaemia and pulmonary embolism (10 [2.4%] patients each), dyspnoea and neutrophil count decreased (9 [2.2%] patients each), ALT increased (8 [1.9%]), neutropenia (7 [1.7%]), white blood cell (WBC) count decreased (6 [1.5%]), asthenia, QT prolonged, and hyponatraemia (5 [1.2%]) patients each, and diarrhoea, ILD, nausea, pneumonitis, and thrombocytopenia (4 [1.0%] patients each.

- **Analysis of adverse events by organ system or syndrome: adverse events of special interest**

Interstitial lung disease in AURA3

At the DCO, ILD (grouped term) was reported in 10 (3.6%) patients in the osimertinib arm vs 1 (0.7%) patient in the chemotherapy arm.

Among the 10 patients with ILD or ILD-like events in the osimertinib arm, 4 (40%) patients were Caucasian, 3 (30%) were Japanese, and 3 (30%) were Asian non-Japanese. The incidence per ethnicity was 4/89 (4.5%) in Caucasian patients, 3/41 (7.3%) in Japanese patients, and 3/141 (2.1%) in Asian-non-Japanese patients.

ILD was reported as an SAE in 3 (1.1%) patients in the osimertinib arm and 1 (0.7%) patient in the chemotherapy arm.

Among the 10 (3.6%) patients in the osimertinib arm who had ILD or ILD-like events, 9 had ILD events that were a maximum of CTCAE grade 1 (3/10 [30%]) or grade 2 (6/10 [60%]) and there were no CTCAE grade 3 or grade 4 events. One osimertinib patient had a CTCAE grade 5 (fatal) ILD. In the chemotherapy arm, the 1 event of ILD was CTCAE grade 3.

The median time to onset for ILD grouped-term events was 105.5 days (range: 8-253) in the osimertinib arm and 68.0 days in the 1 patient in the chemotherapy arm.

In the osimertinib arm, the ILD outcome was reported as recovered for 4 (1.4%) patients, as recovering for 1 (0.4%) patient, as not recovered for 4 (1.4%) patients, and as fatal for 1 (0.4%) patient. For the 1 patient in the chemotherapy arm, the outcome of ILD was reported as recovered.

Interstitial lung disease with a fatal outcome was reported in 1 (0.4%) patient in the osimertinib arm and no patient in the chemotherapy arm.

Interstitial lung disease in pooled Phase II studies

The incidence of ILD (grouped term) events was similar between the pooled Phase II studies and the osimertinib arm of AURA3 (2.9% and 3.6%, respectively). At the DCO of 1 November 2015, ILD (grouped term) was reported in 12/411 (2.9%) patients. ILD was reported as an SAE in 9/12 (75.0%) patients. Maximum CTCAE grade for AEs of ILD was reported as grade 1 for 4/12 (33.3%) patients, grade 3 for 4/12 (33.3%) patients, and grade 5 for 4/12 (33.3%) patients. The median time to onset for ILD grouped-term events was 84.0 days (range: 17-468). Outcome for AEs of ILD was reported as recovered for 5/12 (41.7%)

patients, as recovering for 1/12 (8.3%), as not recovered for 2/12 (16.7%), and as fatal for 4/12 (33.3%) patients.

Cardiac effects in AURA3

Adverse events in the overall Cardiac Effects (QT) grouped term were reported in 12 (4.3%) patients in the osimertinib arm vs 6 (4.4%) patients in the chemotherapy arm.

Table: Cardiac effects adverse events, by grouped term and MedDRA preferred term in AURA3 (Safety analysis set)

	Number (%) of patients [a]	
Grouped term Subgroup Preferred term	**Osimertinib 80 mg (N=279)**	**Chemotherapy (N=136)**
Cardiac effects (QT)	12 (4.3)	6 (4.4)
Torsade de pointes/QT prolongation (SMQ)	10 (3.6)	1 (0.7)
Electrocardiogram QT prolonged	10 (3.6)	1 (0.7)
Arrhythmias (SMQ)	0	0
ICH E14 terms	3 (1.1)	5 (3.7)
Epilepsy	2 (0.7)	4 (2.9)
Seizure	1 (0.4)	0
Syncope	0	1 (0.7)
Cardiac effects (cardiac failure)	9 (3.2)	0
Cardiac failure (SMQ)	9 (3.2)	0
Ejection fraction decreased	6 (2.2)	0
Cardiac failure	3 (1.1)	0
Pulmonary oedema	1 (0.4)	0
Cardiomyopathy (SMQ)	6 (2.2)	0
Ejection fraction decreased	6 (2.2)	0

[a] Number (%) of patients with AEs of special interest, sorted on AESI grouped term and descending frequency for preferred term.
Included AE with an onset date on or after the date of first dose and up to and including 28 days following discontinuation of randomised treatment or the day before first administration of cross-over treatment.
Specific AEs of interest may either be grouped MedDRA preferred terms or individual MedDRA preferred terms.
MedDRA = Medical Dictionary for Regulatory Activities; SMQ = standardised MedDRA query
MedDRA version 19.0.
Data cut-off date: 15 April 2016

Changes from baseline of >30 msec in mean QTcF were observed in 86 (30.8%) patients in the osimertinib arm and 7 (5.1%) patients in the chemotherapy arms. Five patients (1.8%) in the osimertinib arm had QTcF increases >60 msec during the study vs. none in the chemotherapy arm. No patient in either arm had >90 msec increases in QTcF from baseline during the study. Patients were allowed to be enrolled in the study with a QTcF value ≤470 msec. A mean QTcF value >450 msec at any time was reported in 64 patients (22.9%) in the osimertinib arm and 12 patients (8.8%) in the chemotherapy arm. A QTcF value >480 msec at any time was reported in 5 patients (1.8%) in the osimertinib arm and 1 patient (0.7%) in the chemotherapy arm.

The maximum median change from baseline in LVEF was similar in the 2 treatment arms: -2.0% in the osimertinib arm at Cycle 9 (range: −45% to +16%) and Cycle 13 (range: −24% to +16%) vs. a maximum median change of −1.5% in the chemotherapy arm at Cycle 9 (range: −14% to +11%). Fourteen patients (5.0%) in the osimertinib arm had a LVEF decrease ≥10 percentage points (pp) from baseline to a LVEF value of <50% compared to 0 patients in the chemotherapy arm. Fourteen patients (5.0%) in the osimertinib arm

and 1 patient (0.7%) in the chemotherapy arm had a LVEF decrease ≥15 percentage points to a LVEF value ≥50%. Conversely, 23 patients(9.0%) in the osimertinib arm had a LVEF increase ≥10 ppfrom baseline vs. 4 patients (4.3%) in the chemotherapy arm. Fourteen (5.0%) patients in the osimertinib arm and no patients in the chemotherapy arm had a LVEF decrease ≥10 pp from baseline to a LVEF value of <50%. An LVEF decrease ≥15 pp to a LVEF value ≥50% was reported for 14 (5.0%) patients in the osimertinib arm and 1 (0.7%) patient in the chemotherapy arm. LVEF increase ≥10 pp from baseline was seen in 23 (9.0%) patients in the osimertinib arm vs. 4 patients (4.3%) in the chemotherapy arm.

Table: Changes in left ventricular ejection fraction (LVEF) over time, incorporating absolute LVEF value for decreases =10% (Safety analysis set)

	Osimertinib 80 mg			Chemotherapy		
	Cycle 5	Cycle 9	Cycle 13	Cycle 5	Cycle 9	Cycle 13
Patients with post-baseline echocardiography assessment[a,b]	253	207	120	90	44	18
LVEF increase ≥10% - <20%	9 (3.6%)	5 (2.4%)	6 (5.0%)	3 (3.3%)	1 (2.3%)	0
LVEF change <10%	218 (86.2%)	175 (84.5%)	101 (84.2%)	81 (90.0%)	40 (90.9%)	17 (94.4%)
LVEF decrease ≥10% to <20% and absolute value <50%[c]	4 (1.6%)	3 (1.4%)	2 (1.7%)	0	0	0
LVEF decrease ≥10% to <20% and absolute value ≥50%[c]	17 (6.7%)	17 (8.2%)	8 (6.7%)	6 (6.7%)	3 (6.8%)	1 (5.6%)
LVEF decrease ≥20% to <30% and absolute value <50%[c]	2 (0.8%)	3 (1.4%)	2 (1.7%)	0	0	0

[a] The post-baseline assessment closest to the scheduled visit date (calculated from day of first dose) is summarised.
[b] Included assessments on or after the date of first dose and up to and including 28 days following discontinuation.
[c] Occurring at the same echocardiography assessment, at any post-baseline time point.
Baseline was defined as the last non-missing measurement prior to dosing with osimertinib/chemotherapy.
Note: the 95% CI intervals are derived using the Clopper Pearson exact method for binomial proportions.
NE = not estimable
If a patient's maximum increase = maximum decrease, then only the maximum decrease is reported.
Data cut-off: 15 April 2016

Cardiac effects in Phase II studies

The incidence of AEs in the Cardiac Effects (cardiac function) grouped term in the pooled Phase II studies was 1.7% (7). Five (1.2%) patients in the pooled Phase II studies had a PT of ejection fraction decreased (3 patients with CTCAE grade 2 and 2 patients with CTCAE grade 3), 1 (0.2%) patient had a PT of CTCAE grade 5 cardiac failure congestive, and 1 (0.2%) had a PT of CTCAE grade 2 pulmonary oedema. LVEF was observed in the overall population, with no deterioration of cardiac function observed. In AURA extension, in 174 patients who had a post-baseline LVEF assessment, 3 (1.5%) had an LVEF decrease of ≥10 percentage points from baseline, to an LVEF value<50%, and 18 (10.3%) patients had an LVEF increase of ≥10 percentage points from baseline. In AURA2, in 195 patients who had a post-baseline LVEF assessment, 9 (4.3%) had an LVEF decrease of ≥10 percentage points from baseline, to an LVEF value <50% and 20 (10.3%) had an LVEFincrease of ≥10 percentage points from baseline

In the pooled Phase II studies, AEs with PTs in the TdP/QT prolongation SMQ category were reported in 19 (4.6%) patients. All of these were PTs of electrocardiogram QT prolonged. The maximum CTCAE grade was grade 1 in the majority of patients (11 [2.7%]), with CTCAE grade 2 in 3 (0.7%) patients and CTCAE grade 3 in 5 (1.2%) patients

Diarrhoea in AURA3

Adverse events of diarrhoea were reported in 113 (40.5%) patients in the osimertinib arm and 15 (11%) patients in the chemotherapy arm; in most patients the events were CTCAE grade 1 (96/113 [85.0%] osimertinib; 10/15 [66.7%] chemotherapy) or CTCAE grade 2 (14/113 [12.4%] osimertinib, 3/15 [20.0%] chemotherapy. No SAEs or CTCAE grade 4 or grade 5 events were reported in either treatment arm. No events of diarrhoea led to discontinuation of treatment in either arm.

CTCAE grade 3 events were similar between the 2 treatment groups: 3 (1.1%) patients in the osimertinib arm and 2 (1.5%) patients in the chemotherapy arm.

Analysis was performed to identify patients with AEs of diarrhoea in conjunction with AEs of dehydration, renal failure, or electrolyte abnormality (defined as a patient having any of the following preferred terms: hyperkalaemia, hypokalaemia, hypernatraemia, hyponatraemia, hypermagnesaemia, hypomagnesaemia).

No patient experienced diarrhoea concurrently with AEs of dehydration or renal failure in either treatment arm. Two (0.7%) patients in the osimertinib arm and no patient in the chemotherapy arm had diarrhoea concurrent with an electrolyte abnormality AE

On an episode level, 197 events of diarrhoea were reported among the 113 patients with events in the osimertinib arm and 22 events were reported among the 15 patients with events in the chemotherapy arm.

Events not requiring supportive medication: 141/197 (71.6%) events in the osimertinib arm, 18/22 (81.8%) events in the chemotherapy arm.

The median time to onset of first event of diarrhoea was 22 days (range: 1 to 491) in the osimertinib arm vs. 8 days (range: 2 to 157 days) in the chemotherapy arm. After an initial increase during the first month of treatment with osimertinib, the prevalence of diarrhoea remained relatively constant over the duration of treatment, with approximately 15% of patients experiencing diarrhoea at any one point.

Diarrhoea in the pooled Phase II studies

Diarrhoea is a well-described and very common AE with osimertinib. Findings in the pooled Phase II studies were consistent with those in AURA3 in terms of the frequency of occurrence, nature, severity, clinical course and outcome of the events.

Among the 411 patients in the Phase II studies, diarrhoea was reported in 187 (45.5%) patients during treatment with osimertinib 80 mg. Most events were CTCAE grade 1, in

158/411 (38.4%) patients overall, which was 84.5% of the 187 patients with an AE of diarrhoea. CTCAE grade 2 events were reported in 24 (5.8%) patients, and CTCAE grade 3 in 4 (1.0%) patients. No CTCAE grade 4 or grade 5 AEs of diarrhoea were reported

Skin effects in AURA3

The AESI of Skin Effects was evaluated by review of 4 subgroups: Rashes & Acnes, Pruritus, Dry Skin, and Exfoliative Rash.

Adverse events in the Skin Effects grouped term were reported more frequently in the osimertinib arm (140 [50.2%] patients) than in the chemotherapy arm (20 [14.7%] patients), with the most common subgroup in both treatment groups being Rashes & Acnes. The most commonly reported PTs were dry skin (52 [18.6%] vs 6 [4.4%]), dermatitis acneiform (36 [12.9%) osimertinib vs 3 [2.2%] chemotherapy), and pruritus (35 [12.5%] vs 6 [4.4%]).

The severity of Skin Effects AEs was similar between the 2 treatment groups, with the majority of events being CTCAE grade 1 (mild): 120 (43.0%) patients in the osimertinib arm and 16 (11.8%) patients in the chemotherapy arm. CTCAE grade 2 events were reported in 18 (6.5%) and 4 (2.9%) patients, respectively.

Two (0.7%) patients in the osimertinib arm had CTCAE grade 3 events (both erythema). There were no CTCAE grade 4 or grade 5 events in either treatment group. No SAEs or discontinuations, dose reductions, or dose interruptions/delays due to Skin Effects AEs were reported.

There were no severe bullous, severe blistering, or severe exfoliative rash events, no events suggestive of hypersensitivity reactions, including Stevens Johnson Syndrome or toxic epidermal necrosis (Lyell's syndrome), and no events of phototoxicity.

The median time to onset of Skin Effects was 16.0 days (range: 1-295) in the osimertinib arm and 11.5 days (range: 3-120) in the chemotherapy arm

Table: Skin effects adverse events in AURA3, by grouped term (safety analysis set)

	Number (%) of patients[a]	
Grouped term Subgroup	**Osimertinib 80 mg (N=279)**	**Chemotherapy (N=136)**
Skin effects	140 (50.2)	20 (14.7)
Rashes & acnes	94 (33.7)	8 (5.9)
Dry skin	65 (23.3)	6 (4.4)
Pruritus	36 (12.9)	7 (5.1)
Exfoliative rash	3 (1.1)	0

[a] Number (%) of patients with AEs of special interest, sorted on AESI grouped term and descending frequency for preferred term.
Includes AE with an onset date on or after the date of first dose and up to and including 28 days following the date of last dose of randomised treatment or the day before first administration of cross-over treatment.
MedDRA version 19.0.
Data cut-off date: 15 April 2016

The most commonly reported PTs (for Rashes & Acnes) were dermatitis acneiform (36 [12.9%] patients in the osimertinib arm vs 3 [2.2%] patients in the chemotherapy arm), and rash maculo-papular (16 [5.7%] vs 3 [2.2%]).

No SAEs or discontinuations, dose reductions, or dose interruptions/delays due to AEs in the subgroup of Rashes & Acnes AEs were reported.

On an episode level, AEs in the Rashes and Acnes subgroup were more common in the osimertinib arm than in the chemotherapy arm: 130 events vs 9 events. No medication was administered for 67/130 (51.5%) AEs of rash in the osimertinib arm and 5/9 (55.6%) AEs of rash in the chemotherapy

arm. None of the untreated AEs of rash resulted in dose modification. In the osimertinib arm, 46/67 (35.4%) of the untreated AEs of rash resolved and 21 (16.2%) were ongoing at DCO

The median time to onset of events in the Rashes & Acnes subgroup was 16.0 days (range: 1-266) in the osimertinib arm vs 5.5 days (range: 3-43) in the chemotherapy. After an initial increase during the first month of treatment with osimertinib, the prevalence of rash remained relatively constant over the duration of treatment, with approximately 15-25% patients experiencing rash at any time point.

Skin effects AESIs in the pooled Phase II studies

Skin reactions are well-described AEs with osimertinib, with most events being mild to moderate in nature and easily managed. The incidence of AEs in the Skin Effects (grouped term) was higher in the pooled Phase II studies than in the osimertinib arm of AURA3: 265 (64.5%) vs 140 (50.2%) patients, respectively.

Two subgroups accounted for most of this difference: AEs within the Rashes & Acnes subgroup were reported for 188 (45.7%) patients in the pooled Phase II studies, vs 94 (33.7%) in the osimertinib arm of AURA3; AEs within the Dry Skin subgroup were reported for 136 (33.1%) and 65 (23.3%), respectively. The

other 2 subgroups were more similar between the pooled Phase II studies and the osimertinib arm of AURA3: in the majority of patients, Skin Effects AEs were CTCAE grade 1 (226 [55.0%] patients, which was 85.3% of the 265 patients who had a Skin Effects AE). Among the 265 patients with a Skin Effects AE, 36/365 (9.9%) patients had AEs of CTCAE grade 2, and 3/265 (1.17%) had AEs of CTCAE grade 3. The CTCAE grade 3 events consisted of erythema in 1/265 (0.4%) patient and rash maculo- papular in 2/265 (0.8%) patients. Within the Skin Effects subgroups, only events of Rashes & Acnes led to dose modification (in 3 [0.7%] patients) or discontinuation (in 1 [0.2%] patient).

Upper GI tract inflammatory events in AURA3

Adverse events in the Upper GI Tract Inflammatory Events grouped term were reported at a similar frequency in the 2 treatment arms (70 [25.1%] patients in the osimertinib arm vs 30 [22.1%] patients in the chemotherapy arm). All events in the osimertinib arm were CTCAE grade 1 (58 [20.8%] osimertinib vs 18 patients [13.2%] chemotherapy) or CTCAE grade 2 (12 [4.3%] osimertinib vs. 9 [6.6%] chemotherapy). There were no CTCAE ≥grade 3 events in the osimertinib arm.

Table: Upper GI tract inflammatory events in AURA3, by grouped term (Safety analysis set)

	Number (%) of patients[a]	
Grouped term **Subgroup**	**Osimertinib 80 mg (N=279)**	**Chemotherapy (N=136)**
Upper GI Tract Inflammatory Events	70 (25.1)	30 (22.1)
Oral inflammation	54 (19.4)	21 (15.4)
Non-oral upper GI tract inflammatory events	31 (11.1)	11 (8.1)
GI tract inflammation of unspecified location	1 (0.4)	0

[a] Number (%) of patients with AEs of special interest, in descending order of sub-group term within the osimertinib arm.
Includes AE with an onset date on or after the date of first dose and up to and including 28 days following the date of last dose of randomised treatment or the day before first administration of cross-over treatment
MedDRA version 19.0.

A greater proportion of patients with epistaxis events were reported in the osimertinib arm than the chemotherapy arm (15 [5.4%] vs 2 [1.5%], respectively). However, all events were reported as non-serious and CTCAE grade 1, and only 1 (in the osimertinib arm) received medical management (cutaneous sodium furosemide).

Upper gastrointestinal tract inflammatory events in the pooled Phase II studies

At the DCO of 1 November 2015, AEs in the grouped term of Upper GI inflammatory events were reported in a similar proportion of patients in the pooled Phase II studies as in the osimertinib arm of AURA3 (26.8% vs 25.1%). AEs reported within the 3 subgroups were also similar: Oral inflammation (18.0% vs 19.4%), Non-oral upper GI tract inflammatory events (12.4% vs 11.1%), and GI tract inflammation of unspecified location (0% vs 0.4%).

The only PT reported in >5% of patients was stomatitis (60 [14.6%]), in the subgroup term of Oral inflammation, which did not lead to osimertinib discontinuation, dose interruption or dose modification

Nail effects in AURA3

Nail Effects were evaluated by review of the Nail Effects grouped term, which included PTs reported in AURA3 of paronychia, nail infection, nail discolouration, nail disorder, nail dystrophy, nail ridging, and onychoclasis)

Nail Effects (grouped term) AEs were reported by 61 (21.9%) patients in the osimertinib arm vs. 2 (1.5%) patients in the chemotherapy arm (Table 31). Paronychia was the most commonly reported nail effect PT,

reported in 46 (16.5%) patients in the osimertinib arm vs. 2 (1.5%) patients in the chemotherapy arm. No other nail effects were observed in the chemotherapy arm.

All Nail Effects AEs were CTCAE grade 1 (47 [16.8%] osimertinib, 1 [0.7%] chemotherapy) or CTCAE grade 2 (14 [5.0%] osimertinib, 1 [0.7%] chemotherapy). There were no CTCAE ≥grade 3 Nail Effects AEs or SAEs in either treatment arm.

Nail effects in the pooled Phase II studies

Adverse events in the grouped term of Nail effects were reported in a higher proportion of patients in the pooled Phase II studies than in the osimertinib arm of AURA3: 123 (29.9%) vs 61 (21.9%) patients, respectively.

Infections in AURA3

Evaluation of the safety topic of infection was performed at a SOC level. Additional analysis was provided by Infection (grouped term) which consisted of the PTs of Pneumonia and Sepsis. There were no reports of sepsis during the treatment period or the 28-day follow-up period.

Within the Infections and Infestations SOC, AEs were reported in 142 (50.9%) patients in the osimertinib arm and 49 (36.0%) patients in the chemotherapy arm. The difference between the treatment arms in this SOC is due largely to the higher incidence of paronychia in the osimertinib arm.

Adverse events within this SOC were mostly grade 1 (78 [28.0%] osimertinib, 16 [11.8%) chemotherapy) or CTCAE grade 2 (54 [19.4%] osimertinib, 26 [19.1%] chemotherapy). Nine (3.2%) patients and 7 (5.1%) patients in the respective treatment arm had CTCAE grade 3 AEs. One patient (E2604303) in the osimertinib arm had CTCAE grade 4 SAE bronchiolitis.

There was a low incidence of pneumonia in each of the 2 treatment arms: 8 [2.9%] osimertinib, 4 (2.9%) chemotherapy, with the majority of events in each arm of mild or moderate severity.

Infections in the pooled Phase II studies

Infection was not evaluated as a grouped term in the pooled Phase II studies.

Within the Infections and Infestations MedDRA SOC, AEs were reported in 243 (59.1%) patients. Incidence of specific PTs was consistent between the pooled Phase II studies and AURA3, with the Phase II studies reporting the following PTs in ≥3% of patients: paronychia (89 [21.7%] patients vs 16.5% in AURA3), upper respiratory tract infection (42 [10.2%] vs 9.3%), nasopharyngitis (40 [9.7%] vs 10.0%), urinary tract infection (28 [6.8%] vs 6.1%), pneumonia (19 [4.6%] vs 2.9%), and conjunctivitis (15 [3.6%] vs 3.2%).

The incidence of AEs of pneumonia in the pooled Phase II studies (4.6%) was similar to that in the osimertinib arm of AURA3 (2.9%)

- **Serious adverse events**

Serious adverse events in AURA3

Serious AEs were less common in the osimertinib arm than the chemotherapy arm (50 [17.9%] vs 35 [25.7%] patients), with most events reported in ≤ 2 patients in both treatment arms and no individual PT reported in more than 4 patients

Table: Serious adverse events, by preferred term in ≥2 patients in either treatment arm in AURA3 (Safety analysis set)

	Number (%) of patients [a]	
Preferred term	**Osimertinib 80 mg (N=279)**	**Chemotherapy (N=136)**
Patients with any SAE	50 (17.9)	35 (25.7)
Pulmonary embolism	4 (1.4)	2 (1.5)
Pneumonia	3 (1.1)	0
Dyspnoea	3 (1.1)	0
Vomiting	2 (0.7)	1 (0.7)
Cardiac failure	2 (0.7)	0
Interstitial lung disease	2 (0.7)	0
Respiratory failure	2 (0.7)	0
Back pain	2 (0.7)	0
Pyrexia	2 (0.7)	2 (1.5)
Road traffic accident	2 (0.7)	0
Nausea	1 (0.4)	2 (1.5)
Non-cardiac chest pain	1 (0.4)	2 (1.5)
Deep vein thrombosis	0	4 (2.9)
Anaemia	0	3 (2.2)
Epilepsy	0	3 (2.2)
Decreased appetite	0	2 (1.5)

[a] Number (%) of patients with SAEs, sorted in decreasing frequency of PT in the osimertinib arm. Includes SAEs with an onset date on or after the date of first dose and up to and including 28 days following the date of last dose of study medication.
MedDRA version 19.0.
Data cut-off date: 15 April 2016

The most frequently reported SAEs in the osimertinib arm (≥1% of patients) were pulmonary embolism (4 [1.4%] patients vs. 2 [1.5%] patients in the chemotherapy arm); pneumonia(3 [1.1%] vs. 0 on chemotherapy); and dyspnoea (3 [1.1%] vs. 0 on chemotherapy)

Serious AEs considered to be possibly related to study drug were less common in the osimertinib arm (8 [2.9%] patients) than the chemotherapy arm (17 [12.5%] patients). The only SAE considered to be possibly causally related to osimertinib in more than 1 patient was cardiac failure: 2 (0.7%) patients vs 0 patients in the chemotherapy arm. The following SAEs were considered to be possibly causally related to chemotherapy in more than 1 patient (vs 0 patients in the osimertinib arm): anaemia (3 [2.2%]), decreased appetite (2 [1.5%]), and nausea (2 [1.5%]).

The 2 reported SAEs of road traffic accident (RTA) in the osimertinib arm were not secondary to any specific drug related signs or symptoms

Serious adverse events in pooled Phase II studies

Serious AEs occurred in a higher percentage of patients in the pooled Phase II studies (26.0%) than in the osimertinib arm of AURA3 (17.9%). As in AURA3, pneumonia and pulmonary embolism were the most commonly reported PTs, at 2.9% each, reflecting the incidence of these events in advanced NSCLC.

- **Deaths**

Deaths in AURA3

Overall 35/279 (12.5%) patients in the osimertinib arm and 26/136 (19.1%) patients in the chemotherapy arm died, including those who died during the crossover period (for patients in the chemotherapy arm who crossed over to osimertinib after BICR-confirmed disease progression on chemotherapy) or after the

follow-up period. The majority of deaths were considered to be related to the disease under investigation only: 30 of the 35 (85.7%) in the osimertinib arm vs. 21 of 26 (80.8%) in the chemotherapy arm.

The 35 deaths that occurred in patients in the osimertinib arm are summarised below:

- 12 (4.3%) deaths occurred on treatment or during the 28-day follow-up period:
  - 8 (2.9%) due to disease under investigation only
  - 2 (0.7%) due to disease under investigation and an AE: respiratory failure (considered not causally related to osimertinib by the Investigator) in Patient E4901302; respiratory failure (considered not causally related to osimertinib by the Investigator) in Patient E4901303
  - 2 (0.7%) due to AE only: pneumonitis (possibly causally related) in Patient E6005325; ischaemic stroke (considered not causally related to osimertinib by the Investigator) in Patient E6201301)
- 23 (8.2%) deaths occurred after the 28-day follow-up period
  - 22 due to disease under investigation only
  - 1 due to 'lung failure' (not reported as an AE)

9 (6.6%) deaths occurred after the patient crossed-over to the osimertinib arm after BICR-confirmed disease progression on chemotherapy

Deaths in Phase II studies

The incidence of death was higher in the Phase II studies (98 [23.8%]) than in the osimertinib arm in AURA3 (35 [12.5%]), which was expected considering the longer follow-up and unfavourable prognostic of advanced NSCLC. Among the 411 patients in Phase II,

83 (20.2%) patient deaths were considered by the Investigator to be related to only the disease under investigation, 9 (2.2%) to be related to the disease under investigation and a fatal AE, and 5 (1.2%) to be related to only a fatal AE. Fatal AEs in these 14 patients were as follows (note that some patients had multiple fatal AEs): 3 (3.7%) patients each with pneumonia and ILD, and 1 (1.2%) patient each with urinary tract infection, failure to thrive, cerebral haemorrhage, cerebrovascular accident, congestive cardiac failure, dyspnoea, aspiration pneumonia, pneumonitis, respiratory failure, rectal haemorrhage, and liver disorder. Of the 14 deaths due to AEs alone or AEs plus disease under investigation, 4 were considered by the Investigator to be possibly related to osimertinib.

- **Clinical laboratory results**

Haematology in AURA3

For haemoglobin-related changes reported as AEs (anaemia and haemoglobin decreased), the incidence and severity of AEs were lower in the osimertinib arm than in the chemotherapy arm. No CTCAE grade 4 or grade 5 events were reported in either treatment arm. No serious AE related to haemoglobin reduced were reported in the osimertinib arm. In the osimertinib arm, the majority of haemoglobin-related events did not require medication and no event required dose modification, interruption or discontinuation. Worsening in CTCAE grade shifts in haemoglobin was recorded in a lower proportion of patients in the osimertinib arm than in the chemotherapy arm (42.7% vs 79.4%%).

Adverse events related to a reduction in platelet count (ie, thrombocytopenia and platelet count decreased) were reported in a lower proportion of patients in the osimertinib arm vs the chemotherapy arm. Most of the events in both treatment arms were reported as CTCAE grade 1. CTCAE grade 3 events were reported in only 1 (0.4%) patient and no ≥grade 4 was reported in the osimertinib arm, in contrast to the chemotherapy arm, in which 8 (5.9%) patients had CTCAE grade 3 and 2 (1.5%) patients had CTCAE grade 4 events reported.

No SAEs related to thrombocytopenia or platelet count decreased were reported in either treatment arm.In addition, a lower proportion of patients in the osimertinib arm than in the chemotherapy arm reported non-serious AEs of bleeding, bruising or haemorrhage concomitantly with platelet count below the LLN: 9 (3.2% osimertinib vs 8 (5.9%) chemotherapy.

Adverse events of leukopenia or WBC count decreased were reported in a lower proportion of patients in the osimertinib arm compared to the chemotherapy arm: 22 (7.9%) vs 20 (14.7%). Most patients in both treatment arms had events that were CTCAE grade 1 or grade 2. There were no CTCAE ≥grade 3 AEs or SAEs in the osimertinib arm. In the chemotherapy arm, 4 (1.4%) patients had CTCAE grade 3 AEs and 1 (0.7%) had a CTCAE grade 4 SAE of leukopenia. In the osimertinib arm, 22 (7.9%) patients experienced 35 events with leukopenia changes and in the chemotherapy arm, 20 (14.7%) patients experienced 43 events with leukopenia changes.

Adverse events relating to neutrophil changes (neutropenia and neutrophil count decreased) were reported in a lower proportion of patients in the osimertinib arm compared to the chemotherapy arm: 22 (7.9%) vs 31 (22.8%). Adverse events of neutropenia were reported in a lower proportion of patients in the osimertinib arm than in the chemotherapy arm: 10 (3.6%) vs 18 (13.2%). One (0.4%) patient in the osimertinib arm and 5 (3.7%) in the chemotherapy arm had a CTCAE grade 3 AE of neutropenia. In the osimertinib arm no patients had a CTAE grade 4 event and none had neutropenia reported as an SAE. Adverse events of febrile neutropenia were not reported in patients in the osimertinib arm vs 2 (1.5%) patients in the chemotherapy arm. Worsening in CTCAE grade shifts in neutrophil values were reported in a lower proportion of patients in the osimertinib arm (27.0% vs 48.9%). In the osimertinib arm, at a population level, a decrease from baseline in neutrophil count (median: 4.9 x 10^9/L) was seen from Cycle 1 Day 8 onwards (median: 3.89 x 10^9/L), which stabilised over time.

Haematology in AURA Phase II studies

As in AURA3, in the Phase II studies, decreases from baseline in median values for platelets, neutrophils and leukocytes were observed early during treatment with osimertinib and appeared to stabilise after the initial drop. The majority of patients experienced either no change in CTCAE grade or a 1 - grade shift.

The most commonly reported haematology-related AE, reported under the Blood and lymphatic disorders SOC was anaemia (58/411 (14.1% patients). Among these 58 patients, 25/58 (43.1%) reported events of CTCAE grade 1 and 23/58 (39.7%) reported events of CTCAE grade 2. In 10 (17.2%) of the 58 patients, the anaemia was CTCAE grade 3.

- **Safety in special groups and situations**

Effect of gender in AURA3

Assessment of the safety profile by gender showed alignment with the overall safety profile.

The overall incidence of AEs was similar across male (N=107) and female (N=172) patients (both >97%). Adverse events of CTCAE ≥grade 3 were more frequent among males (28.0%) vs females (19.2%), as were SAEs (21.5% males vs 15.7% females). The 2 groups were similar in terms of the most commonly reported PTs, with diarrhoea, decreased appetite, fatigue, nausea, constipation, stomatitis, dry skin, cough, vomiting, paronychia, and pruritus reported in >10% of each group. There were no PTs with a >10-pp difference, although there was a doubling of incidence between genders for the PT of headache (4.7% males, 13.4% females).

None of the grouped terms of interest (Skin Effects, ILD/pneumonitis, or Cardiac Effects [cardiac failure] had a difference of >10 pp between male and female patients, although there was a numerical difference in Skin Effects (grouped term): 56.1% malesvs 46.5% females.

Effect of gender in pooled Phase II studies

Consistent with AURA3, the overall incidence of AEs was similar across male (N=133) and female (N=278) patients (both >97%).

Effect of age in AURA3

An assessment of the safety profile of osimertinib at the AE category level in patients aged <65 years (N=165), 65-74 years (N=72) and ≥75 years (N=42) showed alignment with the overall safety profile.

Table: Adverse events in any category, by age group at baseline among patients in the osimertinib arm in AURA3 (Safety analysis set)

	Number (%) of patients[a]		
Adverse event category	**<65 years (N = 165)**	**65-74 years (N = 72)**	**≥75 years (N = 42)**
Any AE	159 (96.4)	72 (100)	42 (100)
Any AE causally related to osimertinib[b]	135 (81.8)	66 (91.7)	30 (71.4)
Any AE of CTCAE grade 3 or higher	32 (19.4)	16 (22.2)	15 (35.7)
Any AE of CTCAE grade 3 or higher, causally related to osimertinib[b]	9 (5.5)	4 (5.6)	3 (7.1)
Any AE with outcome = death	4 (2.4)	0	0
Any AE with outcome = death, causally related to osimertinib[b]	1 (0.6)	0	0
Any SAE (including events with outcome = death)	27 (16.4)	14 (19.4)	9 (21.4)
Any SAE (including events with outcome = death), causally related to osimertinib[b]	4 (2.4)	2 (2.8)	2 (4.8)
Any SAE leading to discontinuation of osimertinib	6 (3.6)	2 (2.8)	2 (4.8)
Any AE leading to discontinuation of osimertinib	11 (6.7)	4 (5.6)	4 (9.5)
Any AE leading to discontinuation of osimertinib, causally related to osimertinib[b]	7 (4.2)	2 (2.8)	1 (2.4)

[a] Patients with multiple events in the same category are counted only once in that category. Patients with events in more than 1 category are counted once in each of those categories.
[b] As assessed by the Investigator assessment and programmatically derived from individual causality assessments.
Includes AEs with an onset date on or after the date of first dose and up to and including 28 days following discontinuation of randomised treatment or the day before start of new anticancer treatment (including cross-over treatment for AURA3 patients).
CTCAE = Common Terminology Criteria for Adverse Events version 4.0.
MedDRA version 19.0.
Data cut-off: 16 April 2016

The 2 groups were similar in terms of the most commonly reported PTs, with the following PTs reported in >10% of each group: diarrhoea, nausea, decreased appetite, constipation, fatigue, dry skin, and paronychia. There was at least a 10-pp difference in incidence among patients <65 years, patients 65-74 years, and patients ≥75 years of age in the following PTs: cough (15.8%, 23.6%, 7.1%, respectively), pruritus (<10%, 22.2%, <10%), stomatitis (18.8%, 11.1%, and 4.8%), and anaemia (4.2%, 6.9%, and 16.7%). Among the grouped terms of interest (Skin Effects, ILD/pneumonitis, Cardiac Effects [cardiac failure]) a doubling of incidence between any 2 of the age groups was seen in Cardiac Effects (cardiac failure) (1.8% in <65, 4.2% in 65-74, and 7.1% in ≥75%).

Effect of age in the pooled Phase II studies

Consistent with AURA3, the overall incidence of AEs was similar (>98%) across the 3 age groups: patients <65 years of age (N=224), patients 65-75 years of age (N=133) and patients >75 years of age (N=54). The incidence of AEs of CTCAE ≥grade 3 considered by the Investigator to be possibly causally related to osimertinib was higher in patients >75 (24.1%) than in patients <65 (10.3%) or those 65-75 (15.0%), while the incidence of SAEs considered at least possibly causally related to osimertinib was higher in patients 65-75 (9.8%) than in patients <65 (3.1%) or those >75 (5.6%).

Effect of comorbidity of hypertension in AURA3

Assessment of the safety profile of osimertinib at the AE category level among patients with a co-morbidity of hypertension (N=87) and those with no hypertension (N=192) showed alignment with the overall safety profile.

The overall incidence of AEs was similar between the 2 groups; although AEs of CTCAE grade 3 or higher were more frequent for patients with hypertension than for patients without hypertension (27.6% vs 20.3%). The 2 groups were similar in terms of the most commonly reported PTs, with the following PTs reported in >10% of each group: diarrhoea, nausea, decreased appetite, fatigue, constipation, cough, dry skin, pruritus, dermatitis acneiform, and paronychia. No PT had a >10-pp difference in incidence between patients with a co-morbidity of hypertension and those without. None of the grouped terms of interest (Skin Effects, ILD/pneumonitis, or Cardiac Effects [cardiac failure]) had a difference of at least a 10 pp between the 2 hypertension groups, although AEs in the Skin Effects grouped term were reported for 43.7% of patients with co- morbidity of hypertension vs 53.1% of patients with no co-morbidity.

Effect of comorbidity of hypertension in the pooled Phase II studies

Consistent with AURA3, the overall incidence of AEs was similar (>98%) between patients with a comorbidity of hypertension (N=146) and patients without comorbidity of hypertension (N=265). There were no notable differences between the 2 groups in any of the categorical parameters.

Among the most common AEs (>10% frequency) the only PTs for which there was at least a 10-pp difference or a doubling of incidence between patients with hypertension vs those without hypertension was AST increase (4.8% vs 10.6%, respectively), and vomiting (6.8% vs 15.8%).

Effect of baseline renal function and renal related AEs in AURA3

Study exclusion criteria mandated that patients with creatinine>1.5 times ULN concurrent with creatinine clearance <50 mL/min were to be excluded from being enrolled, as severe renal impairment may influence the elimination of renally-eliminated medicinal products.

A reduced design severe renal impairment study is planned and will be submitted at a later date.

Overall, the safety profile of osimertinib was similar in patients with normal renal function (N=115), mild renal impairment (N=113), or moderate renal impairment (N=48).

Adverse events in the Renal and Urinary Disorders SOC occurred in 21 (7.5%) patients in the osimertinib arm and 8 (5.9%) patients in the chemotherapy arm. Events were CTCAE grade 1 in 15 (5.4%) patients in the osimertinib arm and 5 (3.7%) patients in the chemotherapy arm, and grade 2 in 5 (1.8%) and 3 (2.2%), respectively. CTCAE grade 3 events were reported in 1 (0.4%) patient in the osimertinib arm and 0 in the chemotherapy arm. Dose reductions occurred in 2 (1.5%) patients with CTCAE grade 1 AEs of renal impairment in the chemotherapy arm. The majority of renal-related AEs in the Investigations SOC were AEs of blood creatinine increased (13 [4.7%] osimertinib, 8 [5.9%] chemotherapy), all of which were CTCAE grade 1 or grade 2. Evaluation of renal toxicity did not show any association between osimertinib treatment and renal impairment. In the osimertinib arm, a small number of patients had AEs of creatinine increase (13 [4.7%] patients), which were mostly low grade in severity. None of the osimertinib patients had CTCAE $\geq$ grade 3 creatinine increased.

Patients with grade shifts in creatinine were identified by applying the CTCAE version 4.0 definition of creatinine increases. CTCAE grade shifts in creatinine (hyper) from baseline were seen in the majority of patients during treatment: 269 (96.4%) patients in the osimertinib arm and 113 (86.3%) patients in the chemotherapy arm. A total of 238 (85.3%) patients in the osimertinib arm and 98 (74.8%) in the chemotherapy arm had a 1 grade shift; 31 (11.1%) and 15 (11.5%), respectively, had a 2-grade shift. No patients experienced a 3- or 4-grade shift

Effect of baseline hepatic function and hepatic AEs in AURA3

A hepatic impairment study (D5160C00008) is ongoing and will be submitted at a later date.

Overall, the safety profile of osimertinib was similar in patients with normal hepatic function (N=248) or mild hepatic impairment (N=25). The 2 groups were similar in terms of the most commonly reported PTs, with the following PTs reported in >10% of each group: diarrhoea, nausea, decreased appetite, fatigue, cough, stomatitis, dry skin, paronychia, headache, and nasopharyngitis. There was a >10-pp difference or a doubling in incidence between groups in 2 PTs: diarrhoea (40.3% in patients with normal function vs 52.0% in patients with mild impairment), and constipation (15.3% normal vs 4.0% mild impairment)

Adverse events in the Hepatobiliary Disorders SOC were reported in 7 patients (2.5%) in the osimertinib arm and 8 patients (5.9%) in the chemotherapy arm. In the osimertinib arm, PTs included hepatic function abnormal (3 patients [1.1%]); and cholecystitis chronic, hepatotoxicity, hyperbilirubinaemia, and hypertransaminasaemia (1 patient [0.4%] each). The majority of hepatobiliary AEs were CTCAE grade 1 in severity (osimertinib, 5 patients [1.8%]; chemotherapy, 7 patients [5.1%]). Three hepatobiliary AEs were CTCAE grade 3 in severity: 2 patients (0.7%) in the osimertinib arm had CTCAE grade 3 cholecystitis chronic and hypertransaminasaemia (1 patient [0.4%] each); and 1 patient (0.7%) in the chemotherapy arm had CTCAE grade 3 hepatic function abnormal. One of these CTCAE grade 3 events (hypertransaminasaemia) led to osimertinib dose interruption.

Table: Adverse events related to hepatic function in the investigations system organ class in AURA3 (Safety analysis set)

	Number (%) of patients [a]			
	Osimertinib 80 mg (N=279)		Chemotherapy (N=136)	
Preferred term	All CTCAE grades	CTCAE ≥grade 3	All CTCAE grades	CTCAE ≥grade 3
Alanine aminotransferase increased	18 (6.5)	3 (1.1)	15 (11.0)	1 (0.7)
Aspartate aminotransferase increased	14 (5.0)	3 (1.1)	15 (11.0)	1 (0.7)
Blood alkaline phosphatase increased	3 (1.1)	0	4 (2.9)	1 (0.7)
Blood bilirubin increased	3 (1.1)	0	1 (0.7)	0
Gamma-glutamyltransferase increased	3 (1.1)	1 (0.4)	4 (2.9)	0
Transaminase increased	2 (0.7)	0	0	0
Bilirubin conjugated increased	1 (0.4)	0	0	0
Blood bilirubin unconjugated increased	1 (0.4)	0	0	0
Hepatic enzyme increased	1 (0.4)	0	1 (0.7)	0

[a] Number (%) of patients with AEs, in descending incidence of PTs within the osimertinib arm. A patient could have one or more PTs reported under a given system organ class. Includes AEs with an onset date on

Hepatic parameters were unchanged from baseline in the majority of patients during treatment. The majority of the changes from baseline were shifts of 1 or 2 grades. Only 3 patients in the osimertinib arm had a 3-grade shift in AST and/or ALT. No patient had any 3-grade shift in bilirubin or alkaline phosphatase. No potential cases of Hy's law were identified. No patient on osimertinib had ALT or AST ≥3 × ULN and total bilirubin ≥2 × ULN at any time during the study.

Effect of smoking status in AURA3

Overall, there were no notable differences between Never smokers (N=189) and Former smokers (N=76). Compared with the other 2 groups, Current smokers had a higher incidence of AEs causally related to osimertinib (92.9% vs 83.6% for Never smokers and 78.9% for Former smokers) and a lower incidence of AEs at CTCAE ≥grade 3 (7.1% vs 21.7% for Never smokers and 27.6% for Former smokers). Of note, the "Current smoker" group has included only 14 patients so differences mentioned above may due to variability

driven by the small number of patients in this sub-group. The 3 groups were similar in terms of the most commonly reported PTs, with diarrhoea, constipation, dry skin, and paronychia reported in >10% of each group. There was a >10-pp difference or a doubling in incidence between groups in the following PTs, with no clear pattern of higher incidence in any 1 group: diarrhoea (39.7% in Never Smokers, 39.5% in Former Smokers, and 57.1% in Current Smokers), nausea (18.0%, 13.2%, 7.1%), decreased appetite (19.0%, 17.1%, 7.1%), cough (20.1%, 10.5%, 0%), vomiting (11.1%, 13.2%, 0%), paronychia (16.9%, 11.8%, 35.7%), headache (11.1%, 7.9%, 7.1%).

None of the grouped terms of interest (Skin Effects, ILD/pneumonitis, or Cardiac Effects [cardiac failure]) had a >10 pp difference between the 3 smoking status groups or a clinically relevant doubling of incidence among the groups

Effect of smoking status in the pooled Phase II studies

In the pooled Phase II studies, smoking status was reported as Never (N=294) vs Ever (N=117). Consistent with AURA3, the overall incidence of AEs was similar (>97%) between the 2 groups. There were no notable differences between the 2 groups in any of the categorical parameters. Among the most common AEs (>10% frequency), no PT had a 10-pp difference or a doubling of incidence between Never Smokers and Ever Smokers.

- **Discontinuations, dose reductions and dose interruptions/delays**

Discontinuations due to adverse events in AURA3

Adverse events led to permanent discontinuation of a lower proportion of patients in the osimertinib arm than in the chemotherapy arm: 19 (6.8%) vs 14 (10.3%).

Of the patients who discontinued study treatment due to AEs, the Investigator considered the event to be possibly causally related to study drug in a lower proportion of patients in the osimertinib arm than in the chemotherapy arm: 10 (3.6%) vs 12 (8.8%).

Table: Adverse events leading to discontinuation of study drug in more than 1% of patients in either treatment group in AURA3, by preferred term (Safety analysis set)

	Number (%) of patients [a]	
Preferred term	**Osimertinib 80 mg (N=279)**	**Chemotherapy (N=136)**
Any AE leading to discontinuation	19 (6.8)	14 (10.3)
Pneumonitis	5 (1.8)	0
Interstitial lung disease	4 (1.4)	0
Cardiac failure	3 (1.1)	0
Vomiting	0	3 (2.2)
Nausea	0	2 (1.5)

[a] Number (%) of patients with an AE leading to discontinuation of study drug (action taken permanently stopped), with preferred terms sorted in descending order within the osimertinib arm.
Patients with multiple AEs were counted once for each preferred term.
Includes AEs with an onset date on or after the date of first dose and up to and including 28 days following the date of last dose of study drug.
MedDRA version 19.0
Data cut-off date: 15 April 2016

Discontinuations due to adverse events in Phase II studies

The proportion of patients who discontinued due to AEs was similar between the pooled Phase II studies and the osimertinib arm in AURA3 (26 [6.3%] and 19 [6.8%] patients, respectively). ILD was the most common AE that led to discontinuation (6 [1.5%] patients), followed by pneumonitis (5 [1.2%]), cerebrovascular

accident and pulmonary embolism (2 [0.5%] patients each), and lung infection, pneumonia, decreased appetite, failure to thrive, cerebral infarction, cognitive disorder, embolic cerebral infarction, dyspnoea, hypoxia, diarrhoea, vomiting, drug-induced liver injury, rash maculopapular, back pain, neck pain, asthenia, and neutrophil count decreased (1 [0.2%] patient each).

Dose reductions due to adverse events in AURA3

A smaller proportion of patients in the osimertinib arm than in any component of the chemotherapy arm required dose reductions: 8 (2.9%) osimertinibvs 17/136 (12.5%) pemetrexed, 12/42 (28.6%) cisplatin, and 10/94 (10.6%) carboplatin. There was no evidence of a single type of toxicity causing dose reductions, with only the PT of diarrhoea leading to dose reduction in more than 1 patient in the osimertinib arm (2 [0.7%] patients)

Dose reductions due to adverse events in the pooled Phase II studies

Dose reductions due to AEs in the pooled Phase II studies (3.9%) were consistent with those in AURA3 (2.9%). Events (PTs) leading to dose reduction included electrocardiogram QT prolonged (3 [0.7%]), thrombocytopenia (2 [0.5%] patients), and paronychia, neutropenia, decreased appetite, dehydration, keratitis, nausea, vomiting, rash, myalgia, fatigue, ejection fraction decreased, lymphocyte count decreased, platelet count decreased, and WBC count decreased (1 [0.2%] patient each)

Dose interruptions or delays due to adverse events in AURA3

Given that osimertinib was dosed continuously while chemotherapy was administered once every 21 days, dose interruption of osimertinib and dose delay of chemotherapy cannot be compared side by side. However, both AEs leading to dose interruption and AEs leading to dose delay provide an indication of management of toxicities.

Adverse events with an action taken of dose interruption were reported in 36 (12.9%) patients in the osimertinib arm. Of the 36 patients who required dose interruptions due to AEs, 29 (80.1%) patients did not have subsequent dose reductions for the same AE or discontinue due to that AE, 5 patients had subsequent dose reductions for the same AE without subsequent dose discontinuation,

1 patient had subsequent dose reduction followed by dose discontinuation for the same AE (Patient E7404302, cardiac failure), and 1 patient had subsequent dose discontinuation without dose reduction. There did not appear to be any single AE driving the interruption rate in the osimertinib arm, as only 5 events led to dose interruption in more than 1 patient: ECG QT prolonged (5 [1.8%]), AST increased (3 [1.1%]), and neutropenia, ALT increased, GGT increased, and pneumonia (2 [0.7%] patients each); with the exception of the 2 events of pneumonia, all these events were considered by the Investigator to be possibly causally related to osimertinib.

In contrast, in the chemotherapy arm, delays in dosing due to AEs occurred in 28/136 (20.6%) patients receiving pemetrexed, 5/42 (11.9%) receiving cisplatin, and 15/94 (16.0%) receiving carboplatin.

Dose interruptions due to adverse events in Phase II studies

Adverse events led to dose interruption in a higher percentage of patients in the pooled Phase II studies than in the osimertinib arm of AURA3: 87 (21.2%) vs 36 (12.9%) patients, respectively.

There was no consistent pattern in the type of AE leading to dose interruption, with the following AEs leading to interruption in ≥3 patients: electrocardiogram QT prolonged (8 [1.9%]), ALT increased and neutrophil count increased (6 [1.5%] each), neutropenia (5 [1.2%]), pneumonia, upper respiratory tract infection, diarrhoea, and AST increased (4 [1.0%] each), and leukopenia and thrombocytopenia (3 [0.7%] patients each) interruption.

- **Results of analyses on pooled datasets**

Table: Summary of adverse events of interest across pooled safety datasets (Safety analysis set)

Topic	Pooled Phase II (N=411)		AURA3 (N=279)		Patients receiving 80 mg osimertinib in Phase II or Phase III studies (N=690)		Patients receiving 80 mg osimertinib as ≥second-line therapy (N=833)		All enrolled patients receiving at least 1 dose of osimertinib (N=1092)	
	Any grade (%)	CTCAE grade 3-4 (%)	Any grade (%)	CTCAE grade 3-4 (%)	Any grade (%)	CTCAE grade 3-4 (%)	Any grade (%)	CTCAE grade 3-4 (%)	Any grade (%)	CTCAE grade 3-4 (%)
ILD (grouped term) [a]	2.9	1.0	3.6	0	3.2	0.6	3.5	1.1	3.4	1.1
QTcF prolongation (grouped term) [b]	4.6	1.2	3.6	0.4	4.2	0.9	4.4	0.8	NC	NC
Keratitis (grouped term) [c]	0.7	0	1.1	0	0.9	0	0.7	0	0.6	0.1
Diarrhoea	45.5	1.0	40.5	1.1	43.5	1.0	NC	NC	NC	NC
Stomatitis	14.6	0	14.7	0	14.6	0	NC	NC	NC	NC
Rash (grouped term) [d]	45.7	0.7	33.7	0.7	40.9	0.7	NC	NC	NC	NC
Dry skin (grouped term) [e]	33.1	0	23.3	0	29.1	0	NC	NC	NC	NC
Pruritus (grouped term) [f]	15.8	0	12.9	0	14.6	0	NC	NC	NC	NC
Nail effects (grouped term) [g]	30.1	0	21.9	0	27.1	0	NC	NC	NC	NC
Cardiomyopathy (grouped term) [h]	1.2	0.5	2.2	0.4	1.6	0.4	1.3	0.4	1.0	0.3

Topic	Pooled Phase II (N=411)		AURA3 (N=279)		Patients receiving 80 mg osimertinib in Phase II or Phase III studies (N=690)		Patients receiving 80 mg osimertinib as ≥second-line therapy (N=833)		All enrolled patients receiving at least 1 dose of osimertinib (N=1092)	
	Any grade (%)	CTCAE grade 3-4 (%)	Any grade (%)	CTCAE grade 3-4 (%)	Any grade (%)	CTCAE grade 3-4 (%)	Any grade (%)	CTCAE grade 3-4 (%)	Any grade (%)	CTCAE grade 3-4 (%)
Investigations (findings based on test results presented as CTCAE grade shifts)										
Platelet count decreased	59.9	2.9	45.5	0.7	54.1	2.0	NC	NC	NC	NC
Leukocyte count decreased	69.8	3.2	60.9	1.1	66.3	2.3	NC	NC	NC	NC
Neutrophil count decreased	36.0	5.8	26.5	2.2	32.2	4.3	NC	NC	NC	NC

PTs within each grouped term are as follows (note that not every PT was seen in each individual studies or datasets):

a ILD grouped term: interstitial lung disease, pneumonitis

b AEs included in the TdP/QT prolongation SMQ

c Keratitis grouped term: keratitis, corneal epithelium defect, punctate keratitis, corneal defect, corneal erosion

d Rash grouped term: rash, rash generalised, rash macular, rash maculo-papular, rash vesicular, rash follicular, rash pustular, folliculitis, acne, dermatitis, dermatitis acneiform, drug eruption, rash erythematous, rash papular, rash pruritic, erythema

e Dry skin grouped term: eczema, dry skin, skin fissures, xerosis

f Pruritus grouped term: pruritus, pruritus generalised

g Nail effects grouped term: nail bed disorder, nail bed infection, nail bed inflammation, nail discolouration, nail disorder, nail dystrophy, nail infection, nail pigmentation, nail ridging, nail toxicity, onychoclasis, onycholysis, onychomadesis, onychomalacia, paronychia

h Cardiomyopathy grouped term: ejection fraction decreased

NC Indicates variable not calculated for this dataset

Table: Adverse drug reactions reported in patients in the Phase II and Phase III studies (Safety analysis set)

Grouped term or preferred term	Number (%) of patients [a] (N = 690)						
	Any grade	CTCAE grade					SAE
		Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	
Keratitis (grouped term)	6 (0.9)	2 (0.3)	4 (0.6)	0	0	0	0
ILD (grouped term)	22 (3.2)	7 (1.0)	6 (0.9)	4 (0.6)	0	5 (0.7)	12 (1.7)
Diarrhoea (PT)	300 (43.5)	254 (36.8)	38 (5.5)	7 (1.0)	0	0	1 (0.1)
Dry skin (PT)	157 (22.8)	144 (20.9)	13 (1.9)	0	0	0	0
Nail effects (grouped term)	187 (27.1)	141 (20.4)	46 (6.7)	0	0	0	0
Rash (PT)	108 (15.7)	97 (14.1)	11 (1.6)	0	0	0	0
Stomatitis	101 (14.6)	82 (11.9)	19 (2.8)	0	0	0	0
Pruritus (grouped term)	100 (14.5)	86 (12.5)	14 (2.0)	0	0	0	0

Grouped term or preferred term	Number (%) of patients [a] (N = 690)						
	Any grade	CTCAE grade					SAE
		Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	
Investigations (findings based on test results presented as CTCAE grade shifts – N=689) [b]							
Platelet count decreased	373 (54.1)	344 (49.9)	15 (2.2)	6 (0.9)	8 (1.2)	0	n/a
Neutrophil count decreased	222 (32.2)	95 (13.8)	97 (14.1)	23 (3.3)	7 (1.0)	0	n/a
Leukocyte count decreased	457 (66.3)	330 (47.9)	111 (16.1)	10 (1.5)	6 (0.9)	0	n/a

a Number (%) of patients with AEs, sorted in decreasing frequency of PT
b Number of patients with a baseline value and at least 1 on-treatment value
Includes AEs with an onset date on or after the date of first dose and up to and including 28 days following discontinuation of randomised treatment or the day before start of new anticancer therapy
CTCAE = Common Terminology Criteria for Adverse Events version 4.0.
MedDRA version 19.0
Data cut-off date: 16 April 2016

Table: Adverse drug reactions and events considered to require specific warnings and precautions, by grouped term reported in patients receiving 80 mg osimertinib as ≥second-line therapy (Safety analysis set)

Subgroup Preferred Term	Number (%) of patients [a] (N = 833)						
	Any grade	CTCAE grade					SAE
		Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	
ILD/pneumonitis (grouped term)	29 (3.5)	8 (1.0)	7 (0.8)	9 (1.1)	0	5 (0.6)	17 (2.0)
Pneumonitis	17 (2.0)	5 (0.6)	3 (0.4)	7 (0.8	0	2 (0.2)	9 (1.1)
ILD	12 (1.4)	3 (0.4)	4 (0.5)	2 (0.2)	0	3 (0.4)	8 (1.0)
Cardiac failure (SMQ)	16 (1.9)	0	11 (1.3)	4 (0.5)	0	1 (0.1)	3 (0.4)
Cardiac failure	3 (0.4)	0	2 (0.2)	1 (0.1)	0	0	2 (0.2)
Cardiac failure congestive	1 (0.1)	0	0	0	0	1 (0.1)	1 (0.1)
Ejection fraction decreased	11 (1.3)	0	8 (1.0)	3 (0.4)	0	0	0
Pulmonary oedema	2 (0.2)	0	2 (0.2)	0	0	0	0
Cardiomyopathy (SMQ)	11 (1.3)	0	8 (1.0)	3 (0.4)	0	0	0
Ejection fraction decreased	11 (1.3)	0	8 (1.0)	3 (0.4)	0	0	0
QTcF prolongation (grouped term)[b]	37 (4.4)	19 (2.3)	11 (1.3)	7 (0.8)	0	0	1 (0.1)
ECG QT prolonged	36 (4.3)	19 (2.3)	10 (1.2)	7 (0.8)	0	0	1 (0.1)
ECG QT interval abnormal	1 (0.1)	0	1 (0.1)	0	0	0	--
Keratitis	6 (0.7)	2 (0.2)	4 (0.5)	0	0	0	0
Keratitis	3 (0.4)	1 (0.1)	2 (0.2)	0	0	0	0
Punctate keratitis	3 (0.4)	1 (0.1)	2 (0.2)	0	0	0	0
Corneal epithelium defect	1 (0.1)	1 (0.1)	0	0	0	0	0

[a] Number (%) of patients with AEs, sorted in decreasing frequency of PT; patients may be included in more than one grouped term or PT

[b] AEs included in the TdP/QT prolongation SMQ. No events reported under the Cardiac arrhythmia, non-specific SMQ

Includes AEs with an onset date on or after the date of first dose and up to and including 28 days following discontinuation of randomised treatment or the day before start of new anticancer therapy
CTCAE = Common Terminology Criteria for Adverse Events version 4.0.
MedDRA version 19.0
Data cut-off date: 16 April 2016

Table: Adverse drug reactions and events considered to require specific warnings and precautions, by grouped term reported in patients receiving any dose of osimertinib (Safety analysis set)

Grouped term/ Subgroup Preferred term	Number (%) of patients [a] (N = 1092)						
		CTCAE grade					
	Any grade	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	SAE
ILD/pneumonitis	37 (3.4)	10 (0.9)	10 (0.9)	11 (1.0)	1 (0.1)	5 (0.5)	21 (1.9)
Pneumonitis	24 (2.2)	7 (0.6)	6 (0.5)	9 (0.8)	0	2 (0.2)	12 (1.1)
ILD	13 (1.2)	3 (0.3)	4 (0.4)	2 (0.2)	1 (0.1)	3 (0.3)	9 (0.8)
Cardiac contractility	23 (2.1)	2 (0.2)	14 (1.3)	5 (0.5)	1 (0.1)	1 (0.1)	5 (0.5)
Cardiac failure (SMQ)	22 (2.0)	--	--	--	--	--	4 (0.4)
Cardiac failure	3 (0.3)	0	2 (0.2)	1 (0.1)	0	0	2 (0.2)
Cardiac failure congestive	3 (0.3)	2 (0.2)	0	0	0	1 (0.1)	1 (0.1)
Cardiac failure acute	1 (0.1)	0	0	1 (0.1)	0	0	1 (0.1)
Ejection fraction decreased	11 (1.0)	0	8 (0.7)	3 (0.3)	0	0	0
Pulmonary oedema	5 (0.5)	0	5 (0.5)	0	0	0	0
Cardiomyopathy (SMQ)	12 (1.1)	0	8 (0.7)	3 (0.3)	1 (0.1)	0	1 (0.1)
Ejection fraction decreased	11 (1.0)	0	8 (0.7)	3 (0.3)	0	0	1 (0.1)
Stress cardiomyopathy	1 (0.1)	0	0	0	1 (0.1)	0	1 (0.1)
Keratitis	7 (0.6)	2 (0.2)	4 (0.4)	1 (0.1)	0	0	1 (0.1)
Keratitis	3 (0.3)	1 (0.1)	2 (0.2)	0	0	0	0
Punctate keratitis	3 (0.3)	1 (0.1)	2 (0.2)	0	0	0	0
Corneal erosion [b]	1 (0.1)	1 (0.1)	0	0	0	0	1 (0.1)
Corneal epithelium	1 (0.1)	1 (0.1)	0	0	0	0	0

[a] Number (%) of patients with AEs, sorted in decreasing frequency of PT; patients may be included in more than one grouped term or PT

[b] One AE of CTCAE grade 3 corneal erosion associated with ongoing Sjögren's syndrome was reported in a patient in the 80 mg first-line cohort of the AURA Phase I study.

Includes AEs with an onset date on or after the date of first dose and up to and including 28 days following discontinuation of randomised treatment or the day before start of new anticancer therapy

CTCAE = Common Terminology Criteria for Adverse Events version 4.0.

MedDRA version 19.0

Data cut-off date: 16 April 2016

- **Post-marketing data**

Post-marketing data have been summarized in the first PBRER that included data from 13 November 2015 to 12 May 2016. In this PBRER, the total cumulative post-marketing exposure to osimertinib for all doses and all countries as of 30 April 2016 was 672.8 patient- years

In the PBRER period from first launch 13 November 2015 to 12 May 2016, the majority of post-marketing cases received were in keeping with the patient population being treated and the known safety profile of Tagrisso. A complete breakdown of events by SOC is provided in the PBRER (see Appendix 2 of the PBRER in Module 5.3.6). The most frequently reported events were from the Gastrointestinal Disorders SOC (n=49), the majority of which were non- serious (n=31) and consisted largely of reports of dyspepsia (n=18, of which 13 were non- serious). There were also 48 events from the General Disorders and Administration Site Conditions SOC, of which 26 were non-serious, with the most frequently reported events being death (n=8) and non-serious fatigue (n=7). A total of 37 events were reported from the Respiratory, Thoracic and Mediastinal Disorders SOC, of which the most frequently reported was dyspnoea (n=11, including 8 non-serious reports).

No severe ocular surface effects such as ulcerative keratitis or corneal perforation have been seen to date in osimertinib trials. Post-marketing data have been summarized in the first PBRER that included data from 13

November 2015 to 12 May 2016 (see PBRER in Module 5.3.6). Since first approval of osimertinib monotherapy (13 November 2015),

1 report of corneal ulcer from marketed use (Case number 2016SE11972, a non-serious event, with unknown outcome; the action taken with osimertinib is unknown); and 2 reports (case numbers 2015SF29918 and 2016SE48153) of serious keratitis (considered medically important) from a compassionate use programme of osimertinib (both serious events considered to be related to osimertinib by the reporter; 1 event was recovering at the time of reporting and the other recovered) have been reported in the AstraZeneca global safety database. Based on an evaluation of all available data as of July 2016 according to AstraZeneca internal processes, keratitis (defined by MedDRA grouped terms: keratitis, punctate keratitis, corneal erosion, corneal epithelium defect, and corneal defect) was established as causally associated with osimertinib. Consequently, keratitis has been added to the osimertinib CDS in the Warnings and Precautions section as uncommon ADR, with a frequency of 0.7%.

No further changes to the reference safety information have been made since marketing approval of osimertinib.

4.4.3. Discussion

The safety assessment is mainly based on 415 patients from the AURA3 study (DCO for PFS of 15 April 2016). In addition, safety data from the 411 patients in the pooled Phase II studies at DCO3 (1 November 2015) are also used. Lastly, two others pooled database provide further characterisation of the safety profile of osimertinib (patients randomised to receive 80 mg osimertinib as ≥second-line therapy; n=833 and all patients, all doses, all lines of therapy; n = 1092).

Study AURA3

Overall, the safety profile of osimertinib appears better than that reported for chemotherapy within the AURA3 study. There were less AEs grade 3 or higher (regardless of causality), SAEs and AEs leading to discontinuations.

At the time of the DCO for PFS (15 April 2016), 166/279 (59.5%) patients were still on treatment in the osimertinib arm and 16/136 (11.8%) were still on treatment in the chemotherapy arm of AURA3. Therefore, an update from AURA3 study is warranted.

Median exposure was 8.1 months (range: 0.2-18.5) in the osimertinib arm, whereas in the chemotherapy arms, the median exposure was 4.2 months. In those patients who received pemetrexed as maintenance (53.7%) the median maintenance duration was 3.1 months.

There were no big differences in the percentages of patients with AEs between osimertinib and chemotherapy arms (97.8% vs 135 99.3% respectively). Adverse events were most frequently reported (≥50% of patients) in the SOCs of Gastrointestinal (189 [67.7%] patients), Skin & Subcutaneous Tissue Disorders (159 [57.0%] and Infections and Infestations (142 [50.9%] in the osimertinib arm. The profile of adverse events of oximertinib is mainly characterised (>15% of patients) by diarrhoea (40.5%); dry skin (18.6%); decreased appetite (17.9%); paronychia and cough (16.5% each); nausea (16.1%); and fatigue (15.8%). This toxicity contrasts with that observed for the chemotherapy, where nausea (49.3%); decreased appetite (36.0%); constipation (34.6%); fatigue (27.9%); anaemia (27.9%); vomiting (19.9%); and platelet count decreased and stomatitis (15.4%each) were the most frequent AEs (>15% of patients). Diarrhoea (40.5% on osimertinib vs. 11.0% on chemotherapy), dry skin (18.6% vs. 4.4%, respectively), paronychia (16.5% vs. 1.5%), and dermatitis acneiform (12.9% vs. 2.2%) were the AEs where the treatment with osimertinib was clearly worse than chemotherapy, whereas nausea (16.1% on osimertinib vs. 49.3% on chemotherapy), decreased appetite (17.9% vs. 36.0%, respectively), constipation (14.0% vs.

34.6%), fatigue (15.8% vs. 27.9%), anaemia (6.8% vs. 27.9%), and platelet count decreased (4.3% vs. 15.4%) were worse for the chemotherapy arm.

Regarding the severity of AEs, grade ≥ 3 were more frequently reported in the chemotherapy arm (22.6% vs47.1%). Pulmonary embolism, decreased appetite, dyspnoea, diarrhoea, asthenia, fatigue, ALT increased, AST increased, and neutrophil count decreased, were the most frequently AEs grade 3 or higher associated to the use of osimertinib. However, the frequency was around 1%.

ILD-like events, cardiac events, skin effects, diarrhoea, upper GI tract inflammatory effects, nail effects, ocular effects, thromboembolic events, haemorrhages, and infections, have been identified as AEs of special interest.

ILD-like events had a greater incidence in the osimertinib arm than in the chemotherapy (3.6% vs 0.7%). 3 out of 10 patients (event rate, 4.91 per 100 patient-years) with ILD were considered SAEs (no grade 3 or 4). There was a fatal outcome reported in one patient in the osimertinib arm.

Adverse events in the overall Cardiac Effects (QT) grouped term were reported in 12 (4.3%) patients in the osimertinib arm vs 6 (4.4%) patients in the chemotherapy arm. However, Adverse events in the Torsade de Pointes/QT prolongation SMQ category were reported in 10 (3.6%) patients in the osimertinib arm and 1 (0.7%) patient in the chemotherapy arm, even though neither arrhythmias nor TdP were reported. QT prolongation is considered an important identified risk for osimertinib and it is clearly reflected in the SPC. Regarding the rest of cardiac effects, they were reported as ejection fraction decreased in 6 (2.2%) patients (5 CTCAE grade 2 and 1 CTCAE grade 3); cardiac failure in 3 (1.1%) patients (2 CTCAE grade 2 and 1 CTCAE grade 3); and pulmonary oedema in 1 (0.4%) patient (CTCAE grade 2). Fourteen (5.0%) patients in the osimertinib arm and no patients in the chemotherapy arm had a LVEF decrease ≥10 pp from baseline to a LVEF value of <50%. The longer treatment exposure on the osimertinib arm, and the higher frequency of cardiac co-morbidities in the osimertinib arm, could be argued as confusion factors when it comes to explaining these imbalances cardiac contractility. Even though a clear relationship cannot be firmly established, the absence of that cannot be fully ruled out. In this regard, a special warning into the section 4.4 has been included, recommending cardiac monitoring and assessment of LVEF at baseline and during treatment (in patients with cardiac risk factors and those with conditions that can affect LVEF).

Within the rest of AEs of special interest, it should be noted diarrhoea, reported in 40.5% of patients treated with osimertinib (55.48 per 100 patient-years), but without SAEs or CTCAE grade 4 or grade 5. The prevalence of diarrhoea remained relatively constant over the duration of treatment, with approximately 15% of patients experiencing diarrhoea at any one point. Almost 29% of the events of diarrhoea required supportive medication. No information about the duration of diarrhoea according to the severity has been submitted.

Serious AEs were less common in the osimertinib arm than the chemotherapy arm (50 [17.9%] patients vs. 35 [25.7%] patients, respectively). The most frequently reported SAEs in the osimertinib arm (≥1% of patients) were pulmonary embolism (4 [1.4%] patients vs. 2 [1.5%] patients in the chemotherapy arm); pneumonia(3 [1.1%] vs. 0 on chemotherapy); and dyspnoea (3 [1.1%] vs. 0 on chemotherapy).

Overall 35 (12.5%) patients in the osimertinib arm and 26 (18.6%) patients in the chemotherapy arm died, including those who died during the crossover period. However, in the osimertinib arm, 12/279 (4.3%) deaths occurred on treatment or during the 28-day follow-up period, whereas in the chemotherapy arm 4 /136 (2.9%) deaths occurred on treatment or during the 28-day follow-up period. This apparently greater incidence of deaths in the osimertinib arm were majority due to disease progression and the same percentage of deaths was found (0.7%) in the category of “due to the disease under investigation and an AE”.

Dose modifications (interruptions or reduction to 40 mg) were reported in 76 (27.2%) patients on osimertinib, and 19 (6.8%) patients discontinued osimertinib due to AEs. Dose modifications (delays or dose

reductions) were reported in 65 (47.8%) patients for pemetrexed, 25 (59.5%) patients for cisplatin, and 35 (37.2%) patients for carboplatin in the chemotherapy arm; 14 (10.3%) patients discontinued chemotherapy due to AEs.

Adverse events in the Renal and Urinary Disorders SOC occurred in 21 (7.5%) patients in the osimertinib arm (most of which were mild in severity) and 8 (5.9%) patients in the chemotherapy arm. The overall toxicity of osimertinib seems similar according to the different subgroups of renal impairment. Of note, a severe renal impairment study is planned.

Adverse events in the Hepatobiliary Disorders SOC were reported in 7 (2.5%) patients in the osimertinib arm and 8 (5.9%) patients in the chemotherapy arm. No important safety differences were observed between normal and mild hepatic impairment. A hepatic impairment study (D5160C00008) is ongoing

Low-grade decreases from baseline in median values for platelets, neutrophils, and leukocytes were observed early in treatment with osimertinib. Median values appeared to stabilise after the initial drop, with the majority of patients experiencing no change in CTCAE grade or a single grade change.

Safety profile in males and females was overall similar, but with more AEs grade 3 or higher and SAEs in males. Patients older than 75 years had a greater incidence of AEs grade 3 or higher, SAEs, and SAEs-AEs leading to discontinuation.

Phase II studies

Overall, toxicity and tolerability were comparable to the findings from the AURA3 study. It seems that the additional 6 months of follow-up in the phase II studies did not reveal new worrisome AEs.

Conclusion

The safety profile of osimertinib seems consistent to that previously reported from phase II studies. Overall, the tolerability of osimertinib appears manageable and better tolerated than chemotherapy when AEs grade 3 or higher, SAEs and AEs leading to discontinuation, are bearing in mind.

4.5. Risk management plan

The RMP has been updated throughout to include information from the AURA3 study. The MAH has submitted an updated RMP version 6.0.

Summary of safety concerns

The MAH identifies the following safety concerns, with the newly included safety concern of 'changes to cardiac contractility'. The MAH also proposes to change the safety concern "Ocular toxicity" into "Severe ocular effects"

Table 1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	- Interstitial lung disease - QT prolongation
Important potential risks	- Developmental toxicity - Changes in cardiac contractility - Severe skin reactions - Severe diarrhoea - Severe ocular effects - Hepatotoxicity
Missing information	- Long term exposure

Summary of safety concerns	
	- Use during lactation - Use in patiets with severe renal impairment - Use in patients with moderate or severe hepatic impairment - Use in patients with ECOG performance status ≥2 - Use in patients with symptomatic brain metastases - Potential for drug-drug interactions with non-CYP3A4 mediated PXR substrates - Potential for transporter inhibition - Potential for P-gp inhibition - Use in very elderly patients (≥75 years old)

The MAH proposes to add 'Changes in cardiac contractility' to the list of safety concerns. In the AURA3 study a numerical imbalance in the number of patients with an AE from the Cardiac Failure SMQ or Cardiomyopathy SMQ and in LVEF decreases between the 2 treatment arms was noted. The MAH states that this is most likely due to the 2:1 randomisation in favour of osimertinib.
There is evidence from in vitro pharmacology studies that osimertinib inhibits HER2 in cancer cell lines, and HER2 inhibition has been associated with the risk of a decrease in LVEF in some patients receiving trastuzumab following anthracycline-based therapy. However, further analyses of LVEF in more recent HER2 small molecule inhibitors shows the link between HER2 inhibition and LVEF decrease is not conclusive. Further information is needed, and it is agreed to include 'changes in cardiac contractility' as an important potential risk in the RMP.

The MAH proposes to change the important potential risk 'ocular toxicity' to 'severe ocular effects'. As it is not toxicity in general that is considered an important potential risk, but the possible serious effects to the eye. These serious effects have not yet been observed to date; however mild ocular effects (keratitis) have been observed. The change in the name of this safety concern is accepted.

Having considered the updated data in the safety specification the PRAC Rapporteur agrees that the safety concerns listed by the MAH are appropriate.

Pharmacovigilance Plan

Concerning the safety concern 'changes in cardiac contractility', the MAH proposes to use data from the ongoing FLAURA study in patients not previously exposed to cytotoxic treatments to obtain additional information. This is accepted. The FLAURA study was already part of the Pharmacovigilance Plan as a category 3 study.
Relevant information on cardiac contractibility from other ongoing studies should be included in the further analysis of this safety concern as well.

Table 2: Ongoing and planned studies in the PhV development plan

Activity / Study title	Objectives	Safety concerns addressed	Status Planned, started,	Date for submission of interim or final reports (planned or actual)
D5165C00001 (CAURAL) A phase III, multi-centre, open label, randomized study to assess the efficacy and safety of osimertinib in combination with	Primary Objective: • To assess the efficacy of osimertinib in combination with MEDI4736 versus osimertinib monotherapy in terms of PFS as 2nd	- ILD - QT prolongation - Severe skin reactions	Started	May 2018 (planned)

Activity / Study title	Objectives	Safety concerns addressed	Status Planned, started,	Date for submission of interim or final reports (planned or actual)
MEDI4736 versus Osimertinib monotherapy in patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC who have received prior EGFR TKI therapy Category 3	line or higher treatment for patients who have progressed following an approved EGFR-TKI therapy. Secondary Objectives: • To further assess the efficacy of osimertinib in combination with MEDI4736 versus osimertinib monotherapy in terms of ORR, DoR, DCR, tumour shrinkage, OS and PFS landmark analyses. • To assess the impact of osimertinib in combination with MEDI4736 versus osimertinib monotherapy on disease-related symptoms and HRQoL in NSCLC patients. • To assess the PK of osimertinib as a single agent and in combination with MEDI4736. • To characterise the PK, immunogenicity and pharmacodynamics of MEDI4736 after single dosing and at steady state after multiple dosing when given intravenously to patients with EGFRm NSCLC in combination with osimertinib To assess the safety and tolerability profile of osimertinib as a single agent and in combination with MEDI4736	- Severe diarrhoea - Severe ocular effects - Hepatotoxicity - Long term exposure		
D5160C00017 A Phase II, open label, single-arm study to assess the safety and efficacy of osimertinib in Asia Pacific patients with locally advanced/metastatic NSCLC whose disease has progressed with previous EGFR TKI therapy and whose tumours harbour a EGFR T790M mutation within the EGFR gene Category 3	Primary Objective: • To assess the efficacy of osimertinib by assessment of ORR. Secondary Objectives: • To further assess the efficacy of osimertinib in terms of PFS, DoR, DCR, tumour shrinkage, and OS. • To assess the safety and tolerability profile of osimertinib. • To assess the impact of osimertinib on patients' disease-related symptoms and HRQoL	- ILD - QT prolongation - Severe skin reactions - Severe diarrhoea - Severe ocular effects - Hepatotoxicity - Long term exposure	Primary analysis complete	Final report Nov 2016 (planned)

Activity / Study title	Objectives	Safety concerns addressed	Status Planned, started,	Date for submission of interim or final reports (planned or actual)
D5160C00022 (ASTRIS) Open label, multinational, multicentre, real world treatment study of single agent osimertinib for patients with advanced/ metastatic EGFR T790M mutation positive NSCLC who have received prior therapy with an EGFR TKI. Category 3	The primary objective of this study is to assess the efficacy and safety of single agent osimertinib in a real world setting in adult patients with advanced or metastatic, EGFR T790M mutation positive NSCLC, who have received prior EGFR TKI therapy	- ILD - QT prolongation - Severe skin reactions - Severe diarrhoea - Severe ocular effects - Hepatotoxicity - Long term exposure - Use in patients with ECOG performance status ≥2 - Use in patients with symptomatic brain metastases	started	Q1 2020 (planned)
D5160C00007 (FLAURA) A Phase III, double-blind, randomised study to assess the efficacy and safety of osimertinib vs. a SoC EGFR TKI as first-line treatment in patients with EGFRm locally advanced or metastatic NSCLC. Category 3	Primary Objective: • To assess the efficacy of single agent osimertinib compared with SoC EGFR TKI therapy as measured by PFS. Secondary objectives: • To assess the efficacy of osimertinib compared with SoC EGFR TKI therapy by assessment of PFS in patients with positive (or negative) pre-treatment, EGFR T790M (amino acid substitution at position 790 in EGFR, from a threonine to a methionine) mutation; EGFR Ex19del or L858R mutation; or EGFRm (Ex19del or L858R) detectable in plasma-derived ctDNA. • To further assess the efficacy of osimertinib compared with SoC	- ILD - QT prolongation - Severe skin reactions - Changes in cardiac contractibility - Severe diarrhoea - Severe ocular effects - Hepatotoxicity - Long term exposure	started	January 2018

Activity / Study title	Objectives	Safety concerns addressed	Status Planned, started,	Date for submission of interim or final reports (planned or actual)
	EGFR TKI therapy. • To characterise the PK of osimertinib and its metabolites (AZ5104 and AZ7550). • To assess the impact of osimertinib compared to SoC EGFR TKI therapy on patients' disease-related symptoms and HRQoL. • To assess patient satisfaction with treatment when receiving osimertinib compared with SoC EGFR TKI therapy.			
D6030C00001 (BLOOM) A Phase I, open-label, multicentre study to assess the safety, tolerability, pharmacokinetics and preliminary anti-tumour activity of AZD3759 or osimertinib in patients with EGFRm advanced stage NSCLC Category 3	Primary Objective: • To investigate the safety and tolerability of AZD3759 (both Part A and Part B) when given orally to patients with advanced stage EGFRm NSCLC who have progressed following prior therapy, including Maximum Tolerated Dose determination, if possible (Part A only) Secondary Objectives (osimertinib specific only): • To evaluate anti-tumour efficacy and safety in patients treated with osimertinib (only for patients with brain metastasis [BM] and/or leptomeningeal metastasis [LM])). • To determine the pharmacokinetics of osimertinib and metabolites in blood and CSF following multiple oral dosing (only for patients with LM and/or BM). • To evaluate the changes from baseline in CNS symptoms (analysed from BN20) in patients with LM treated with AZD3759/osimertinib	- Use in patients with ECOG performance status ≥2 - Use in patients with symptomatic brain metastases	started	May 2017 (planned)

Activity / Study title	Objectives	Safety concerns addressed	Status Planned, started,	Date for submission of interim or final reports (planned or actual)
D5160C00008 A Phase I, open-label, nonrandomised study designed to determine the PK profile, safety and tolerability of osimertinib following a single oral dose in patients with advanced solid tumours and normal hepatic function or mild or moderate hepatic impairment. This is a 2-part study: • Part A will investigate the PK of osimertinib in patients with mild or moderate hepatic impairment compared to patients with normal hepatic function; • Part B will allow any patient with mild or moderate hepatic impairment or normal hepatic function, who completes Part A, continued access to osimertinib after the PK phase and will provide additional safety data.	Primary Objective: • To characterise the effect of hepatic impairment on the PK of osimertinib after a single oral dose of 80 mg to patients with advanced solid tumours and mild or moderate hepatic impairment or normal hepatic function. Secondary Objectives: • To characterise the effect of hepatic impairment on the PK of osimertinib metabolites AZ5104 and AZ7550 after a single oral dose of 80 mg to patients with advanced solid tumours and mild or moderate hepatic impairment or normal hepatic function. • To investigate the safety and tolerability of single and multiple oral doses of osimertinib in advanced solid tumour patients with mild or moderate hepatic impairment and in those with normal hepatic function	- Use in patients with moderate or severe hepatic impairment - hepatotoxicity	started	Main CSR: November 2018 Addendum: March 2019 (planned)
D5160C00035 An open-label, nonrandomised, multicentre, Phase I study to assess the Pharmacokinetics, safety and tolerability of osimertinib following a single oral 80 mg dose to patients with advanced solid tumours and normal renal function or severe renal impairment	Clinical pharmacology reduced-dosing study in patients with severe renal impairment	- Use in patients with moderate or severe hepatic impairment	planned	Q4 2018 (planned)
D5160C00036 An open-label, non-randomised, Phase I study to assess the effect of single and multiple oral doses of osimertinib on the pharmacokinetics of a	Drug-drug interaction study with a substrate for another PXR regulated enzyme (different to CYP3A4), incorporating an in vivo assessment of the potential of osimertinib to inhibit P-gp	- Potential for drug-drug interactions between osimertinib and nonCYP3A4 mediated PXR	Planned	Q4 2017 (planned)

Activity / Study title	Objectives	Safety concerns addressed	Status Planned, started,	Date for submission of interim or final reports (planned or actual)
Pglycoprotein probe drug (fexofenadine) in patients with advanced EGFRm NSCLC that have progressed on a prior EGFR-TKI regimen		substrates - Potential for P-gp inhibition		

The PRAC Rapporteur, having considered the updated data submitted, was of the opinion that the proposed post-authorisation PhV development plan is sufficient to identify and characterise the risks of the product.

Risk minimisation measures

Table 3: Summary table of Risk Minimisation Measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risk		
ILD	Section 4.2, 4.4 and 4.8 of the SmPC	None
QT prolongation	Section 4.2, 4.4, 4.8 and 5.1 of the SmPC	None
Important potential risk		
Developmental toxicity	Section 4.6 and 5.2 of the SmPC	None
Changes in cardiac contractility	Section 4.4 of the SmPC	None
Severe skin reactions	Section 4.2 of the SmPC	None
Severe diarrhoea	Section 4.2 of the SmPC	None
Severe ocular effects	Section 4.4 of the SmPC	None
Hepatotoxicity	None	None
Missing Information		
Long term exposure	None	None
Using during lactation	Section 4.6 of the SmPC	None
Use in patients with severe renal impairment	Section 4.2 and 5.2 of the SmPC	None
Use in patients with moderate or severe hepatic impairment	Section 4.2 and 5.2 of the SmPC	None
Use in patients with ECOG performance status ≥2	None	None
Use in patients with symptomatic brain metastases	None	None
Potential for drug-drug interactions between osimertinib	None	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
and nonCYP3A4 mediated PXR substrates		
Potential for transporter inhibition	None	None
Potential for P-gp inhibition	None	None
Use in very elderly patients (≥75 years old)	None	None

The PRAC, having considered the updated data submitted, was of the opinion that the proposed risk minimisation measures remain sufficient to minimise the risks of the product in the proposed indication(s)

The updated RMP version 6.0 is acceptable.

4.6. Changes to the Product Information

As a result of this group of variations, sections 4.2, 4.4, 4.8, 5.1 and 5.2 are being updated based on the results from study D5160C00003 (AURA3) and the updated CSRs for studies D5160C00001 (AURAex) and D5160C00002 (AURA2). The Package Leaflet is being updated accordingly. In addition, the MAH took the opportunity to make editorial changes in the SmPC and Package Leaflet.
The provision of the CSR from study AURA3 addressed the remaining Specific Obligation for Tagrisso and hence the MAH requested the conversion from a Conditional Marketing Authorisation to a Marketing Authorisation not subject to Specific Obligations. Annex II has been updated in accordance.

Please refer to Attachment 1 which includes all agreed changes to the Product Information.

5. Request for supplementary information

5.1. Other concerns

Clinical aspects

1. Results from AURA3 trial confirm the previous positive benefit risk balance shown on the basis of AURA extension and AURA2 however, data on OS should be submitted before a full marketing authorisation can be granted.
2. PFS2 was included as an exploratory endpoint in AURA3 protocol. Data on time from randomisation to second progression will help in interpretation of trial results, being especially important for the subgroup of patients who received osimertinib after progression on chemotherapy arm (60%). The applicant should clarify whether data on PFS2 will be available.
3. 53.7% of patients in the chemotherapy arm went on to receive pemetrexed as maintenance therapy. Comparative data (osimertimib arm vs. chemotherapy arm) in terms of the main efficacy endpoints (i.e. PFS, ORR and OS) should be submitted for this subgroup of patients.
4. At the time of the DCO for PFS (15 April 2016), 166/279 (59.5%) patients were still on treatment in the osimertinib arm and 16/136 (11.8%) were still on treatment in the chemotherapy arm of AURA3. Therefore, a safety update from AURA3 study is warranted. Please provide.
5. Diarrhoea was reported in 40.5% of patients treated with osimertinib (55.48 per 100 patient-years), but without SAEs or CTCAE grade 4 or grade 5. The prevalence of diarrhoea remained relatively

constant over the duration of treatment, with approximately 15% of patients experiencing diarrhoea at any one point. Almost 29% of the events of diarrhoea required supportive medication. However, no information about the duration of diarrhoea according to the severity has been submitted. Please submit.

6. Assessment of responses to Request for Supplementary Information

Question 1

Results from AURA3 trial confirm the previous positive benefit risk balance shown on the basis of AURA extension and AURA2 however, data on OS should be submitted before a full marketing authorisation can be granted.

Response:

Results of the first overall survival (OS) analysis, with a data cut-off of 02 September 2016 (DCO2), are provided to fulfil the Specific Obligation associated with the Conditional Marketing Authorisation.

At the time of the initial OS analysis (2 September 2016), 109/419 patients overall had died, including 69 (24.7%) patients in the osimertinib arm and 40 (28.6%) patients in the chemotherapy arm. Thus the maturity of the OS was low (26.0%). There was a numerical advantage in OS for patients on osimertinib compared to patients on chemotherapy, which did not reach statistical significance (HR: 0.72 [99.96% CIs: 0.34, 1.52]; p-value = 0.121). The median OS was not calculable in either arm due to the low number of deaths. Based on a KM analysis, at 6 months, the estimated proportion of patients alive was 95.3% (95% CI: 92.0, 97.2) in the osimertinib arm vs. 87.8% (95% CI: 80.8, 92.3) in the chemotherapy arm; and at 12 months, was 83.6% (95% CI: 78.6, 87.6) in the osimertinib arm vs. 76.9% (95% CI: 68.4, 83.3) in the chemotherapy arm. The interpretation of the OS results was confounded by the high proportion of patients who received at least 1 subsequent systemic anti-cancer therapy post-discontinuation (osimertinib: 34.4%; chemotherapy: 76.4%), particularly given that 94/140 (67.1%) of patients randomised to chemotherapy subsequently crossed over to receive treatment with osimertinib.

Overall the numerical advantage observed in OS for osimertinib compared to chemotherapy, in AURA3, even in the presence of a high rate of subsequent anti-cancer usage on the chemotherapy arm, provides further support for the positive benefit-risk of osimertinib.

Assessment of the Applicant's response

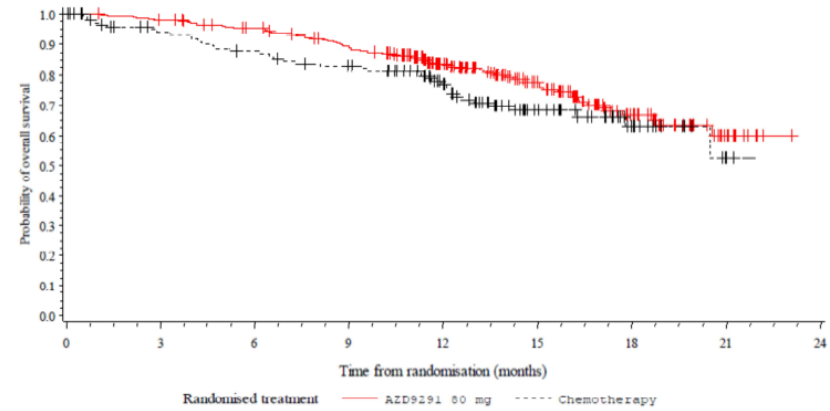
The Applicant has submitted the data for the first OS analysis. As expected, data are not mature enough so as to draw firm conclusions about the potential longer survival of those patients treated with osimertinib. Although this immature HR is reassuring, highlighting a positive trend for osimertinib (HR: 0.72 [99.96% CIs: 0.34, 1.52]) (since 3 OS analyses are planned, the significance level for testing OS was adjusted to 0.0004; 99.96% CIs are presented) the percentage of events at the cutoff date (24.7% and 28.6% for osimertinib and chemotherapy respectively; 2 September 2016) does not allow reaching further conclusions from this analysis. . Despite the inability to collect informative mature OS data, the magnitude of effect seen with PFS, ORR, DoR and DCR, supported by the reassuring HR in terms of OS in the first analysis, provide reassurance.

Table 2 Overall survival, stratified log-rank test (full analysis set)

			Comparison between groups			
Group	N	Number (%) of patients with events	Hazard Ratio	95% CI	99.96% CI[a]	2-sided p-value
Osimertinib 80 mg	279	69 (24.7)	0.72	0.48, 1.09	0.34, 1.52	0.121
Chemotherapy	140	40 (28.6)				

CI = Confidence interval.
[a] Confidence interval in line with the adjusted significance level of 0.0004 used at the first overall survival analysis.
Overall survival was defined as the time from the date of randomisation until death due to any cause. Patients not known to have died at the time of analysis were censored at the last recorded date on which the patient was known to be alive.
The p-value was determined using log-rank test stratified by ethnicity, using the Breslow approach for handling ties.
The hazard ratio and 95% CI were calculated as HR = exp(U/V) and 95% CI for HR = (exp{U/V - 1.96/sqrt(V)}, exp{U/V + 1.96/sqrt(V)}) where U is the log-rank test statistic and sqrt(V) the standard deviation of the log-rank test statistic obtained from the LIFETEST procedure with a STRATA term for the stratification variable.
A hazard ratio <1 favours osimertinib 80 mg.
RECIST version 1.1.
DCO2: 2 September 2016

Figure 1 Overall survival, Kaplan-Meier plot (full analysis set)



Number of patients at risk

Months	0	3	6	9	12	15	18	21	24
Chemotherapy	140	121	112	103	80	42	17	2	0
AZD9291 80mg	279	271	257	236	179	109	52	11	0

Patients not known to have died at the time of analysis were censored (+) at the last recorded date on which the patient was known to be alive.
DCO2: 2 September 2016

The rates of patients alive at 6 and 12 months in the osimertinib arm (95.3% and 83.6% respectively) seem comparable to those previously observed in the pooled data from the phase II studies (91.9% and 79.8%; 6 and 12 months respectively).

Table 3 Median overall survival (full analysis set)

	Osimertinib 80 mg (N=279)	Chemotherapy (N=140)
Total number of deaths	69	40
Median overall survival (months)[a]	NC	NC
95% CI for median overall survival	20.53, NC	20.47, NC
Survival at 6 months (%)[a]	95.3	87.8
95% CI for survival at 6 months	92.01, 97.23	80.80, 92.32
Survival at 12 months (%)[a]	83.6	76.9
95% CI for survival at 12 months	78.55, 87.61	68.37, 83.34
Median follow-up for overall survival (months) in all patients[b]	13.7	12.5

NC = not calculated
[a] Calculated using the Kaplan-Meier technique.
[b] Time from randomisation to date of death or to date of censoring for censored patients.
[c] Time from randomisation to date of censoring (date last known to be alive) for patients who have not died at the time of analysis.
DCO2 = 2 September 2016

As stated previously, 3 analyses of OS will be conducted. A second analysis of OS will be performed when the OS data are approximately 50% mature (approximately 205 deaths events). A third analysis of OS will be performed when the OS data are approximately 70% mature (approximately 287 deaths events). Nevertheless, it seems doubtful that this expected longer survival can be shown in future analyses, seeing

as 94/140 [67.1%] patients in the chemotherapy arm crossed over to receive treatment with osimertinib after RECIST progression.

Point solved as the first OS analysis has been submitted.

Question 2

PFS2 was included as an exploratory endpoint in AURA3 protocol. Data on time from randomisation to second progression will help in interpretation of trial results, being especially important for the subgroup of patients who received osimertinib after progression on chemotherapy arm (60%). The applicant should clarify whether data on PFS2 will be available.

Response:

The time from randomisation to second progression (PFS2) was included as an exploratory endpoint in AURA3, and was defined as time from the date of randomisation to the earliest date of a progression event subsequent to that used for the primary variable PFS, or death in the absence of second disease progression. Second progression was determined by the Investigator based on local clinical practice and the determination could be made by clinical and/or radiographic assessment of the patient. Patients alive and for whom a second disease progression was not observed were censored at the last date they were known to be alive and without second disease progression.

In line with the statistical analysis plan, the post-progression exploratory endpoint of PFS2 as well as time from randomisation to first subsequent therapy (TFST) and time from randomisation to second subsequent therapy (TSST) have been assessed at the time of the OS analysis (DCO2: 2 September 2016) since these endpoints were considered important to the interpretation of OS (Table 1). However, it should be noted that following the primary analysis for PFS at DCO1 (15 April 2016), collection of RECIST data was not continued and this impacted PFS2; for example the censoring of PFS2, which utilises this data for patients who did not have a PFS2 event (ie, in patients without a PFS event and thus who were yet to be assessed for a PFS2 event). This situation occurred more frequently in the osimertinib arm than in the chemotherapy arm. In the osimertinib arm, 139/279 (49.8%) patients did not have a PFS event at DCO1; at DCO2, 121 of the 139 patients were censored for PFS2 at their PFS censoring date. In chemotherapy arm, 30/140 (21.4%) patients did not have a PFS event at DCO1; at DCO2, 25 of the 30 patients were censored for PFS2 at their PFS censoring date.

In addition, per the protocol, patients could remain on their randomised treatment after the first RECIST-defined progression if they continued to derive clinical benefit, as judged by the investigator. Overall, more patients who had progressed continued to receive their randomised treatment beyond first disease progression for at least 7 days in the osimertinib arm compared to the chemotherapy arm (84/279 [30.1%] patients vs. 14/140 [10.0%] patients, respectively). The median time to discontinuation of therapy (TDT) was 13.8 months (95% CI: 12.4, 15.7) in the osimertinib arm and 3.7 months (95% CI: 3.5, 4.4) in the chemotherapy arm.

Assessment of PFS2 was originally intended to describe the time of the first subsequent progression event on the first subsequent anti-cancer received after randomised treatment. However, in the osimertinib arm only, a number of investigators reported PFS2 while patients were still receiving randomised treatment, which was not in line with a general principle of PFS2 reflecting progression on next line of therapy:

- In the osimertinib arm, of the 84 patients who had a second progression event only (other than death), 37 (44.0%) patients were still receiving osimertinib treatment at the time of their PFS2 event;
- In the chemotherapy arm, of the 34 patients who had a second progression event only (other than death), no patients were receiving chemotherapy at the time of their PFS2 event

The evidence that patients randomised to osimertinib continued beyond second disease progression and thus delayed start of next treatment regimen can be further observed by the fact that on the osimertinib arm the median PFS2 time is numerically shorter at 13.2 months than both the median time to discontinuation of randomised treatment and the median time to start of first subsequent therapy of 13.8 months and 16.9 months, respectively.

Table 1 Comparative data for post-progression exploratory endpoints

	Osimertinib 80mg (N=279)	Chemotherapy (N=140)	Comparison between groups HR (95% CI); p-value
Time to first subsequent therapy *, number of events (%)	131 (47.0)	117 (83.6)	
Median 95% CI	16.9 months 95% CI: 13.8, 18.7	5.7 months 95% CI: 5.1, 6.8	HR: 0.15 95% CI: 0.11, 0.21; 2 sided p-value <0.001
Time to second subsequent therapy **, number of events (%)	95 (34.1)	50 (35.7)	
Median 95% CI	NC 95% CI: 17.2, NC	18.9 months 95% CI: 16.6, NC	HR: 0.80 95% CI: 0.56, 1.14; p-value = 0.212
PFS2, number of events (%)	120 (43.0)	62 (44.3)	
Median 95% CI	13.2 months 95% CI: 12.4, 15.6	14.2 months 95% CI: 11.8, 16.6	HR: 1.06 95% CI: 0.78, 1.43; 2-sided p value = 0.730
Time to discontinuation of randomised treatment, number of events (%)	153 (54.8%)	131 (93.6%)	
Median 95% CI	13.8 months 95% CI: 12.4, 15.7	3.7 months 95% CI: 3.5, 4.4	–

*Most common first subsequent therapy after randomised treatment was cytotoxic platinum-based chemotherapy in the osimertinib arm (25.4%) and cross-over therapy with osimertinib in the chemotherapy arm (93/140 [66.4%] patients [1 patient receiving cross-over therapy was captured under time to second subsequent therapy as an event]).

**Most common second subsequent therapy after randomised treatment were cytotoxic platinum-based chemotherapy (4.3%) and EGFR-TKI monotherapy in the osimertinib arm (3.9%); and other non-platinum cytotoxic chemotherapy (4.3%) in the chemotherapy arm

Overall, the results of PFS2 at DCO2 (2 September 2016) indicated there was no statistical difference between treatment arms in second progression-free survival (PFS2); the HR was 1.06 (95% CI: 0.78, 1.43; 2-sided p value = 0.730). However the analysis of PFS2 at DCO2 was confounded by the large proportion of patients in the osimertinib arm who reported an event (PFS2) while still on randomised treatment, and by the difference in timing between the PFS2 (DCO2) and PFS (DCO1) analyses, making interpretation challenging; therefore PFS2 does not truly reflect time to second progression on the next line of therapy.

Other post-progression outcomes of time to first subsequent therapy (TFST), and time to second subsequent therapy (TSST) assessed at the time of the OS analysis are presented in Table 1 above. In particular, it should be noted that the endpoint of TSST could be considered a surrogate of when second progression occurs given movement onto next line of therapy typically follows a progression event.

Assessment of the applicant's response

The analysis of PFS2 does not reveal any difference between osimertinib arm and chemotherapy group (HR 1.06; 95% CI: 0.78, 1.43; 2-sided p value = 0.730). This apparently absence of difference could suggest altered tumour behaviour after the osimertinib influence or alternatively making more attractive the chemo-osimertinib sequence. Nevertheless, a deeper analysis of the data cast important doubts about the interpretation of the PFS2 result.

First of all, PFS2 according to the protocol was defined as time from the date of randomisation to the earliest date of a progression event subsequent to that used for the primary variable PFS, or death in the absence of second disease progression. This definition is not exactly the same that the anticancer guideline states (time from randomisation to objective tumour progression on next-line treatment or death from any cause) where a second treatment is included.

Secondly, the number of patients who were censored was high, mainly due to the lack of PFS event at DCO1 and as a consequence of that the absence of RECIST data from that point, which led to censure those patients without event at first DCO.

And thirdly, there were many patients who continued the osimertinib treatment even after the 1st progression

All together make difficult to drawn conclusions about PFS2 and the apparently similarity in terms of PFS2 between the two arms should be taken very cautiously.

In the end, PFS2 was an exploratory endpoint that could have been useful in this scenario of immature OS data, but unfortunately, due to the reasons above described, it resulted in uncertain variable uneasy to understand

Question solved as submitted

Question 3

53.7% of patients in the chemotherapy arm went on to receive pemetrexed as maintenance therapy. Comparative data (osimertinib arm vs. chemotherapy arm) in terms of the main efficacy endpoints (i.e. PFS, ORR and OS) should be submitted for this subgroup of patients.

Response:

In the AURA3 study, a total of 419 patients were randomised to treatment: 279 (66.6%) to osimertinib and 140 (33.4%) to platinum-based doublet chemotherapy. Per the protocol and clinical practice, patients whose disease had not progressed after 4 to 6 cycles of platinum- based doublet chemotherapy could continue on maintenance monotherapy with pemetrexed according to the approved label use or local practice guidelines. Of the 140 patients randomised to the chemotherapy arm, 136 patients received treatment and of these 100 (73.5%) patients completed at least 4 cycles of chemotherapy and 73 (53.7%) patients went on to receive pemetrexed maintenance monotherapy. Based on the pivotal pemetrexed maintenance studies, this represents the proportion of patients expected to continue on pemetrexed maintenance (Paz-Ares et al 2012).

Review of demography by randomised treatment (osimertinib, chemotherapy) and the chemotherapy arm split by pemetrexed maintenance status (ie patients did/did not continue pemetrexed) indicated that patients who went on to receive pemetrexed maintenance therapy after platinum-based chemotherapy were broadly consistent with patients who did not have maintenance therapy.

Review of disease characteristics at baseline highlighted that patients who went on to receive maintenance therapy on the chemotherapy arm had disease characteristics consistent with a better clinical prognosis: more patients had performance status 0, compared with all patients randomised to osimertinib and in

particular compared with patients who did not receive pemetrexed maintenance therapy (49.3%, 36.6% and 29.9% respectively); the median sum of baseline target lesion measurements were smaller, compared with all patients randomised to osimertinib and in particular compared with patients who did not receive pemetrexed maintenance therapy (42.0mm, 46.0mm and 53.0mm respectively).

There is no prior literature on the efficacy of platinum doublet chemotherapy in patients with T790M positive NSCLC in patients whose disease has progressed on prior EGFR TKI therapy. The median PFS with first-line platinum doublet in EGFR mutation-positive NSCLC ranges from 4.6 months to 6.9 months, and the ORR from 15% to 47%, as summarised in the Clinical Overview. There have been a small number of Phase III trials investigating first line platinum doublet chemotherapy in treatment naïve advanced non-squamous NSCLC (Paz- Ares et al 2012, Okamoto et al 2014). In the PARAMOUNT study (patients were not selected by EGFR mutation status), maintenance pemetrexed following pemetrexed-cisplatin induction resulted in an improvement in a median PFS by investigator assessment by 1.3 months (4.1 months versus 2.8 months for the placebo arm, Paz-Ares et al 2012.

It should be noted that any comparison of the osimertinib arm (all randomised patients) with the subset of the chemotherapy arm who went on to receive pemetrexed maintenance in this study is biased in favour of this pemetrexed maintenance subgroup by the fact that this subgroup is defined by a post-randomisation status which requires patients who initially received chemotherapy to: a) did not progress/die up to cycle 4 of treatment; b) have received at least 4 cycles of platinum treatment (ie no early discontinuation of IP due to toxicities); and c) be fit enough to continue pemetrexed maintenance therapy per approved label/local practice guidelines. This can be noted by review of the time to event variables, for example the PFS and OS Kaplan-Meier curves by treatment status highlight that the pemetrexed maintenance group curve does not decline until after cycle 4, ie, the second RECIST assessment.

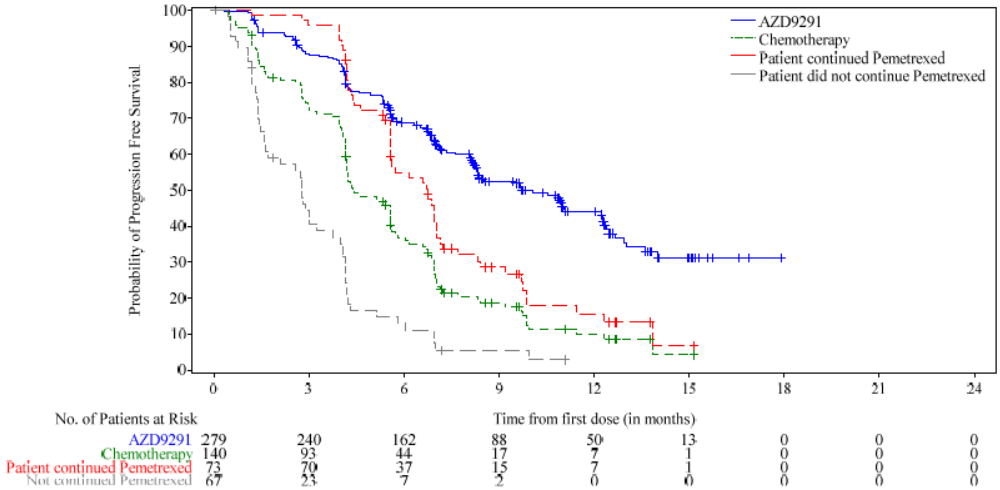
The comparative data for the primary efficacy variables are summarised in Table 2 below. Overall comparative data comparing the osimertinib arm (all randomised patients) with the subset of the chemotherapy arm who went on to receive pemetrexed maintenance is presented in full for the main efficacy endpoints (i.e. PFS, ORR and OS).

Table 2 **Comparative data for primary efficacy variables overall and by pemetrexed maintenance status**

	Osimertinib 80mg (N=279)	Chemotherapy (N=140)	Pemetrexed maintenance therapy subset (N=73)	No pemetrexed maintenance subset (N=67)
Median PFS, months	10.1	4.4	6.7	2.8
(95% CI)	(8.3, 12.3)	(4.2, 5.6)	(5.6, 7.0)	(1.6, 3.7)
ORR, %	70.6	31.4	47.9	13.4
(95% CI)	(64.9, 75.9)	(23.9, 39.8)	(36.1, 60.0)	(6.3, 24.0)
Median OS, months	NC	NC	NC	14.2
(95% CI)	(20.5, NC)	(20.5, NC)	(20.5, NC)	(11.6, NC)

Derived from Tables IMT0409C, IMT0409E, IMT0409G in Appendix C

Figure IMT0409D Progression-free survival by investigator assessment (Full analysis set)



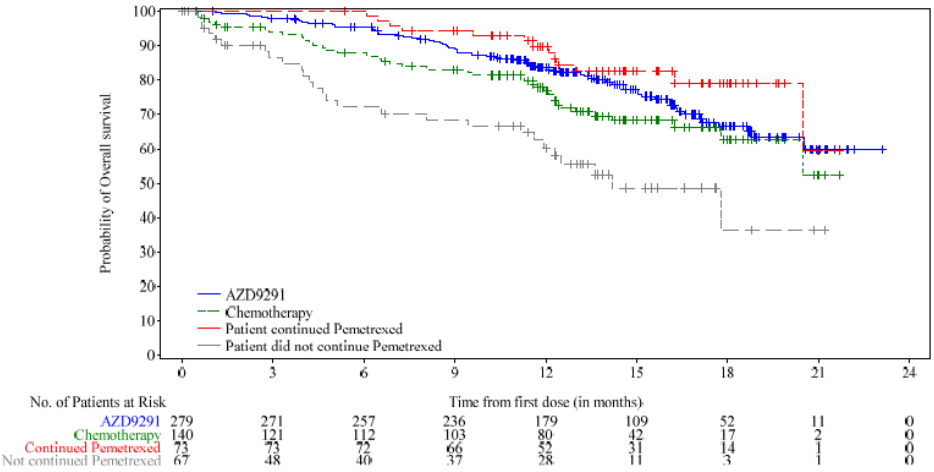
Subjects are censored at the date last known to be non-progressor.
Crosses indicate censored observations.
Note: 4 patients in the chemotherapy arm who were assigned to the 'Patient did not continue Pemetrexed' subgroup did not receive any Chemotherapy on study.

Table IMT0409E Median overall survival by investigator assessment (Full analysis set)

	AZD9291 80 mg (N=279)	Chemotherapy (N=140)	Patient continued Pemetrexed (N=73)	Patient did not continue Pemetrexed (N=67)
Total number of deaths	69	40	13	27
Median overall survival (months)[a]	NC	NC	NC	14.2
95% CI for median overall survival	20.5, NC	20.5, NC	20.5, NC	11.6, NC
Survival at 6 months (%)[a]	95.3	87.8	100.0	72.2
95% CI for survival at 6 months (%)[a]	92.0, 97.2	80.8, 92.3	100.0, 100.0	58.6, 82.0
Survival at 12 months (%)[a]	83.6	76.9	89.8	60.3
95% CI for survival at 12 months (%)[a]	78.6, 87.6	68.4, 83.3	79.8, 95.0	46.0, 71.9
Median follow-up for overall survival (months) in censored patients[b]	14.5	14.0	14.9	12.6

[a] Calculated using the Kaplan-Meier technique.
[b] Time from randomisation to date of censoring (date last known to be alive) for patients who have not died at the time of analysis.
Note: 4 patients in the chemotherapy arm who were assigned to the 'Patient did not continue Pemetrexed' subgroup did not receive any Chemotherapy on study.
NC - Not Calculable

Figure IMT0409F Overall survival (Full analysis set)



No. of Patients at Risk									
AZD9291	279	271	257	236	179	109	52	11	0
Chemotherapy	140	121	112	103	80	42	17	2	0
Continued Pemetrexed	73	73	72	66	52	31	14	1	0
Not continued Pemetrexed	67	48	40	37	28	11	3	1	0

Subjects are censored at the date last known to be alive.
Crosses indicate censored observations.
Note: 4 patients in the chemotherapy arm who were assigned to the 'Patient did not continue Pemetrexed' subgroup did not receive any Chemotherapy on study.

To summarize the data above and presented in tabular form:

- Patients in the chemotherapy arm who received pemetrexed maintenance therapy had a better clinical prognosis than those who did not receive maintenance with regards to a better WHO Performance Status and lower baseline disease burden.
- Approximately half (52.1%) the patients in the chemotherapy arm received pemetrexed maintenance therapy, as expected based on local guidelines.
- Median PFS and ORR were longer/greater for the pemetrexed maintenance therapy subgroup compared to the no pemetrexed maintenance subset. Median OS data were too immature to perform robust comparisons.
- Median PFS and ORR were longer/greater on the osimertinib treatment arm compared to the pemetrexed maintenance subgroup with no overlap of 95% CIs for either PFS or ORR. Median OS data were too immature to perform robust comparisons.

The data presented above supports that there was a numerical and clinically meaningful advantage in efficacy outcomes for patients who were randomised to receive osimertinib even when compared to a better prognostic subgroup of pemetrexed maintenance.

Assessor's comment

Despite the biases associated to this analysis, it results interesting (in a certain way expected) to observe the PFS and OS curves for the pemetrexed maintenance group. There does not seem to be doubt that osimertinib looks superior to pemetrexed maintenance subset in terms of PFS and ORR. A longer PFS is observed for osimertinib especially from month 4th forwards, where a rapid decrease in the PFS curve is seen for the maintenance group. However, it should be noted the beginning of the curve, where the osimertinib curve is below the maintenance curve, pointing out a greater delay in tumour progression than that observed for osimertinib. To what extend the latter can be associated to imbalances in baseline characteristics and/or prognostics factors is unknown. Nonetheless, it is worth looking at the OS curve, where pemetrexed maintenance group seems to offer a better result. Obviously, the number of events is still low and the final picture could change.

Question solved until final data on OS are available

Question 4

At the time of the DCO for PFS (15 April 2016), 166/279 (59.5%) patients were still on treatment in the osimertinib arm and 16/136 (11.8%) were still on treatment in the chemotherapy arm of AURA3. Therefore, a safety update from AURA3 study is warranted. Please provide.

MAH´s Response:

The AURA3 safety data, at DCO2 (02 September 2016), are provided as an Addendum to the AURA3 CSR in Module 5.3.5.1 of the CTD and for the convenience of the reviewer a summary is also appended in Appendix D to this response (see Appendix D).

The majority of patients in the chemotherapy arm had already discontinued chemotherapy at AURA3 DCO1 (15 April 2016), with only a small proportion of patients (12% as compared to 60% on osimertinib) still ongoing on their randomised treatment. The median total exposure to chemotherapy was, therefore, unchanged at DCO2 from DCO1, which is reflected in the little to no change in safety variables seen in the chemotherapy arm at DCO2: at DCO2, the median exposure increased from DCO1 on osimertinib (11.4 months vs. 8.1 months, respectively) while it was unchanged on chemotherapy (4.2 months). The increased differential in duration of exposure between treatment arms at DCO2 should be considered when reviewing the safety and tolerability profile of osimertinib vs. chemotherapy.

Comparison of the 2 treatment arms at DCO2 confirms the finding from DCO1 (15 April 2016) that osimertinib is generally well tolerated and has an acceptable safety profile compared to chemotherapy. Adverse events are generally less frequent and less severe in the osimertinib arm than in the chemotherapy arm. Osimertinib adverse reactions are generally manageable through supportive care and dose interruptions, with fewer requirements for dose reductions or drug discontinuation compared with chemotherapy.

Overall, the osimertinib safety profile in AURA3 as of DCO2 (2 September 2016), with an additional 4 months of follow-up, is consistent with that seen at DCO1 (15 April 2016), with no new signals identified.

Assessment of the applicant response:

Updated safety data as of the data cut-off of 2 September 2016 has been submitted (last update from 15 April 2016). Overall, adverse events of any grade were reported in similar proportions of patients in the 2 treatment arms and as previously observed there was a lower rate AEs grade 3 or higher (regardless of causality), causally-related SAEs and AEs leading to discontinuations in the osimertinib arm compared to chemotherapy arm.

At the time of this new DCO for safety (2 September 2016), 45.2% of patients were on osimertinib treatment and a small proportion of patients were still on chemotherapy treatment in the osimertinib arm and (3.7%) of AURA3.

Median exposure had increased approximately 3 months from DCO1 in the osimertinib arm (11.4 months vs. 8.1 months, respectively), while it was unchanged from DCO1 in the chemotherapy arm (4.2 months). Whereas no change or very little change is observed in the chemotherapy safety data compared to the previous DCO, more matrure data and slightly higher rates of AES are observed on osimertinib treatment.

The percentages of patients with AEs between osimertinib and chemotherapy arms was similar (97.8% vs 99.3% respectively) and this proportions remained unchanged from last DCO.

As previously seen sdverse events were most frequently reported were in the SOCs of Gastrointestinal, Skin & Subcutaneous Tissue Disorders and Infections and Infestations in the osimertinib arm.

The profile of adverse events of osimertinib is mainly characterised (>15% of patients) by diarrhoea (41.2%); dry skin (19.0%); decreased appetite (20.4%); paronychia (18.6%)and cough (17.9%); nausea (20.1%); and fatigue (17.2%) and constipation (15.4%). All the rates in the osimertinib arm slightly increased from last DCO (the greatest increase of 4% is observed for nausea) .

The toxicity in the chemotherapy arm continues constrasting with that of osmertinib: Diarrhoea (41.2% on osimertinib vs. 11.0% on chemotherapy), dry skin (19.0% vs. 4.4%, respectively), paronychia (18.6% vs. 1.5%), and dermatitis acneiform (14% vs. 2.2%) were the AEs where the treatment with osimertinib was clearly worse than chemotherapy, whereas nausea (20.1% on osimertinib vs. 49.3% on chemotherapy), decreased appetite (20.4% vs. 36.0%, respectively), constipation (15.4% vs. 34.6%), fatigue (17.2% vs. 28.7%), anaemia (7.9% vs. 27.9%), and platelet count decreased (5.0% vs. 15.4%) were worse for the chemotherapy arm.

Regarding the severity of AEs, grade ≥ 3 were more frequently reported in the chemotherapy arm (29.4% vs 47.1%). Pulmonary embolism, ALT increased, diarrhoea, fatigue, decreased appetite, AST increased, neutrophil count decreased, asthenia, dyspnoea and pneumonia were the most frequently AEs grade 3 or higher associated to the use of osimertinib. However, the frequency lower than 2% for all of them.

The overall number of deaths increased from the last DCO. Now 69/279 (24.7%) patients in the osimertinib arm died (35/279; 12.5% fromerly) and 40/140 (28.6%) patients in the chemotherapy arm died (18.6% formerly), including those who died during the crossover period. As previoulsy observed, the proportion of deaths that occurred on treatment or during the 28-day follow-up period is greater for osimertinib (6.5% vs 2.9%), whereas the percentaje of deaths due to disease under investigation only was similar (21.5% osimertinib vs. 22.1% placebo) and due to due to the disease under investigation and an AE a greater percentaje is observed in the chemotherapy arm (0.7% vs. 4.3%).

Serious AEs are now observed in a similar proportion in the osimertinib and chemotherapy arms (65 [23.3%] patients vs. 35 [25.7%] respectively). The most frequently reported SAEs in the osimertinib arm (≥1% of patients) were pulmonary embolism (6 [2.2%] patients vs. 2 [1.5%] patients in the chemotherapy arm); pneumonia(4 [1.4%] vs. 0 on chemotherapy); and dyspnoea (4 [1.4%] vs. 0 on chemotherapy).

The common AEs that characterise the osimertinib safety profile (diarrhoea and skin effects) generally did not lead to discontinuation of treatment.

Dose modifications (interruptions or reduction to 40 mg) were reported in 30.8% of patients on osimertinib, and 7.9% patients discontinued osimertinib due to AEs. Dose modifications (delays or dose reductions) were reported in 48.5% of patients for pemetrexed, 59.5% of patients for cisplatin, and 37.2% of patients for carboplatin in the chemotherapy arm; 11.0% of patients discontinued chemotherapy due to AEs.

Regarding AEs of special interest: ILD-like events continue to have a greater incidence in the osimertinib arm than in the chemotherapy (4.3% vs 1.5%). There were no CTCAE grade 3 or grade 4 events nas 2 fatal outcomes were reported in the osimertinib arm.

Adverse events in the overall Cardiac Effects (QT) grouped term were reported in 13 (4.7%) patients in the osimertinib arm vs 6 (4.4%) patients in the chemotherapy arm. Percentajes remain similar to those previously seen.

Adverse events in the Torsade de Pointes/QT prolongation SMQ category were reported in 11 (3.9%) patients in the osimertinib arm and 1 (0.7%) patient in the chemotherapy arm, even though neither arrhythmiasn or TdP were reported. QT prolongation is considered an important identified risk for osimertinib and it is clearly reflected in the SPC.

Regarding the rest of cardiac effects, they were reported as ejection fraction decreased in 8 (2.9%) patients (6 CTCAE grade 2 and 2 CTCAE grade 3); cardiac failure in 3 (1.1%) patients (2 CTCAE grade 2 and 1 CTCAE

grade 3); and pulmonary oedema in 1 (0.4%) patient (CTCAE grade 2). One of the patients with ejection fraction decreased also had an AE of cardiac failure.

Fifteen (5.4%) patients in the osimertinib arm and no patients in the chemotherapy arm had a LVEF decrease ≥10 pp from baseline to a LVEF value of <50%. The longer treatment exposure on the osimertinib arm, and the higher frequency of cardiac co-morbidities in the osimertinib arm, could be argued as confusion factors when it comes to explaining these imbalances cardiac contractility. Even though a clear relationship cannot be firmly established, the absence of that cannot be fully ruled out. In this regard, a special warning into the section 4.4 has been included, recommending cardiac monitoring and assessment of LVEF at baseline and during treatment (in patients with cardiac risk factors and those with conditions that can affect LVEF).

Within the rest of AEs of special interest, it should be noted diarrhoea, reported in 41.2% of patients treated with osimertinib, but without CTCAE grade 4 or grade 5. No events of diarrhoea led to discontinuation of treatment in either arm. One patient in each treatment arm had diarrhoea reported as an SAE. CTCAE grade 3 events of diarrhoea were similar between the 2 treatment groups: 4 (1.4%) patients in the osimertinib arm and 2 (1.5%) patients in the chemotherapy arm. There were no events of gastrointestinal (GI) perforation or haemorrhagic diarrhoea in either treatment arm. Almost one third (28.4%) of the events of diarrhoea required supportive medication. Information about the duration of diarrhoea according to the severity has been submitted (please refer to the following question).

Overall, the updated osimertinib safety profile in AURA3 (DCO 2 September 2016) seems comparable to that observed in the previous submissionn of data (15 April 2016) and no new safety signals have been identified.

At the time of the DCO2 (2 September 2016), 45.2% patients were still on treatment on osimertinib arm of AURA3 (only 3.7% in the chemotherapy arm). The applicant should commit to provide safety data update at the time of next submission of OS data.

The MAH made a commitment accordingly.

Issue resolved

Question 5

Diarrhoea was reported in 40.5% of patients treated with osimertinib (55.48 per 100 patient-years), but without SAEs or CTCAE grade 4 or grade 5. The prevalence of diarrhoea remained relatively constant over the duration of treatment, with approximately 15% of patients experiencing diarrhoea at any one point. Almost 29% of the events of diarrhoea required supportive medication. However, no information about the duration of diarrhoea according to the severity has been submitted. Please submit.

MAH´s Response:

Overall, the profile for diarrhoea events seen in the osimertinib arm of AURA3 was as expected given the improved margin of selectivity that osimertinib has against WT EGFR. Reported events were all non-serious and tended to be mild or moderate severity with a low likelihood of clinical sequelae. As discussed below, no apparent pattern in duration or resolution of diarrhoea events by severity has been noted.

At the time of the primary PFS analysis (DCO1: 15th April 2016), 197 diarrhoea events were reported in 113/279 (40.5%) patients in the osimertinib arm of AURA3. This incidence is consistent with the pooled Phase II studies (45.5%). Some individuals may have experienced more than one event (mean number of diarrhoea AEs in AURA3 for those patients who reported events was 1.7).

Duration data for all grades, and broken down by maximum CTCAE grade: grade 1 and 2 are presented by patient level data and event level data, as well as CTCAE grade 3 diarrhoea events. These tables also include diarrhoea event and duration information from the AURA3 chemotherapy arm for comparative purposes. The median total duration of all events of diarrhoea was 29 days (range 1 to 467 days). It should be noted that calculations also include AEs of intermittent episodes of diarrhoea. The duration of the episodes are captured as continuous events and therefore in such instances durations maybe overestimated due to the inclusion of days/periods without diarrhoea.

- CTCAE grade 1 events were reported in 96/279 (34.4%) of patients in the osimertinib arm. Median total duration was 35 days (range 1 to 467 days) per patient.
- CTCAE grade 2 events were reported in 14/279 (5.0%) patients in the osimertinib arm. Median total duration was 5.5 days (range 1 to 253 days) per patient.
- CTCAE grade 3 events were reported in 3/279 (1.1%) patients. These individual events were of 3, 4 and 19 day's duration
- There were no SAE or CTCAE grade 4 or 5 events of diarrhoea. No event of diarrhoea led to discontinuation of osimertinib.
- The median proportion of time on osimertinib treatment with diarrhoea was very low (7%)
- Less than a third (28.4%) of events had treatment for diarrhoea:
  - For the 56 events that did receive treatment the median duration of the event was 28.5 days (range 1 to 467; SD 135.02). At the time of DCO1, 38/56 (67.9%) were reported as resolved, and 18/56 (32.1%) were reported as ongoing. Antipropulsives were the most commonly administered class of anti-diarrhoea medication, given in 43/56 (21.8%) events.
  - For the 141 events that did not receive treatment, the median duration of the event was 3 days (range 1 to 435; SD 91.6)). At the time of DCO1 124/141 (87.9%) events were reported as resolved, with 17/141 (12.1%) reported as ongoing.

It should be noted there is a high level of variability in the treatment duration data, as shown by the wide range and high SDs. Duration of individual events by maximum CTCAE grade are also based on a very small number of events that are grade >1, making it difficult to draw conclusions by severity. The majority of events did not require treatment and resolved quickly (141 events received no treatment, median duration of these events: 3 days, 124/141 resolved). Further reassurance is provided by the non-serious nature of diarrhoea events and the lack of any real association with clinical sequaelae.

In conclusion, at a population level diarrhoea events associated with osimertinib treatment have limited clinical impact on patients. Duration of events tend to be low, particularly relative to the duration of exposure to osimertinib, and there is no evidence to suggest that that higher grade events persist for longer periods than lower grade events.

Assessment of the applicant response:

Updated overall data on diarrhoea shows similar results to that previously observed 41.5% of the patients on osimertinib treatment experienced this AE (vs. 11% in the control arm). 34,4% (n=96) of the events were grade 1, 5.0% (n=14) grade 2 and 1.1% grade 3 (n=3) with no grade 4 ≥ reported.

The duration of these events was highly variable, the median duration of grade 1 diarrhoea was 35 days whereas it was shorter for for grade 2 events (5.5 days) and for the 3 grade 3 events reported (3 events of 3,4 and 19 days).

In spite of the fact that most of the AEs of diarrhoea were of mild or moderate severity, the hifg frequency observed toguether with the duration of the events makes necessary the inclusion of a warning under section 4.4. of SmPC.

Point resolved provided that information is addedd on SmPC.

The MAH provided an updated version of the product information accordingly.

Issue resolved

Post-Authorisation Measures

Following the assessment of the data provided, the MAH was recommended to undertake the following:

Description	Recommended within Proc. No
1. At the time of DCO2 (2 September 2016) for AURA3, 45.2% patients were still on osimertinib treatment (only 3.7% on chemotherapy arm). The applicant should commit to provide an update of safety at the time of next submission of OS data.	EMEA/H/C/004124/II/0009/G
2. Two analyses of OS are foreseen when the OS data are approximately 50% and 70% respectively mature. These analyses should be submitted, as available, including comparative data of OS overall and by pemetrexed maintenance status.	EMEA/H/C/004124/II/0009/G

The MAH agreed and provided a Letter of Recommendations accordingly dated 16 February 2017.

Conclusion

☒ Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☐ No need to update overall conclusion and impact on benefit-risk balance