26 April 2018
EMA/396618/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

TAGRISSO

International non-proprietary name: osimertinib

Procedure No. EMEA/H/C/004124/II/0019

Note

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

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List of abbreviations

AE	Adverse event
AESI	Adverse events of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the curve
AUCss	Area under the concentration-time curve at steady-state
BBB	Blood brain barrier
BICR	Blinded independent central review
cEFR	CNS evaluable-for-response analysis set
cFAS	CNS full analysis set
CI	Confidence interval
Cmax:Cmin	Maximum plasma concentration: minimum plasma concentration
Css,max	Mean maximum plasma concentration at steady state
CNS	Central nervous system
CNS	MTS CNS metastases subgroup of the study FAS
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating tumour deoxyribonucleic acid
DCO	Data cut-off
DCR	Disease control rate
DoR	Duration of response
EGFR	Epidermal growth factor receptor
EGFRm	Epidermal growth factor receptor-tyrosine kinase inhibitor sensitising mutation, including exon 19 deletion and exon 21 L858R substitution
EGFR-TKI	Epidermal growth factor receptor-tyrosine kinase inhibitor
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
Ex19del	Deletion in Exon 19
FAS	Full analysis set
FDA	Food and Drug Administration (US Department of Health and Human Sciences)
GCP	Good Clinical Practice
HR	Hazard ratio
HRQL	Health-related quality of life
ICH	International Conference on Harmonisation
ILD	Interstitial lung disease
ITT	Intention-to-treat
L858R	Sensitising mutation in the EGFR gene with substitution of a leucine with an arginine at position 858 in exon 21
LLN	Lower limit of normal
LVEF	Left ventricular ejection fraction
NCCN	National Comprehensive Cancer Network
NL	New lesion
NSCLC	Non-small cell lung cancer
NTL	Non-target lesion
OR	Odds ratio
ORR	Objective response rate
OS	Overall survival

PD	Progressive disease
PFS	Progression-free survival
PFS2	Time from randomisation to second progression on subsequent anti-cancer therapy
PRO	Patient reported outcomes
PRO-CTCAE	Patient-reported outcomes version of the Common Terminology Criteria for Adverse Events
PS	Performance status
PT	Preferred term
QD	Once daily
QoL	Quality of life
QT	ECG interval measured from the onset of the QRS complex to the end of the T wave
QTc	QT interval corrected for heart rate
RECIST 1.1	Response Evaluation Criteria in Solid Tumours version 1.1
SAE	Serious adverse event
SD	Stable disease
SMQ	Standardised MedDRA query
SoC	Standard of Care
SOC	System organ class
T790M	Second-site EGFR point mutation that results in substitution of threonine with methionine at amino acid position 790 (T790M) in exon 20
TdP	Torsade de pointes
TDT	Time from randomisation to discontinuation of randomised treatment or death
TFST	Time from randomisation to first subsequent therapy or death
TL	Target lesion
TSST	Time from randomisation to second subsequent therapy or death
ULN	Upper limit of normal
WHO	World Health Organisation
WT	Wild-type

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, AstraZeneca AB submitted to the European Medicines Agency on 26 October 2017 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, IIIB and IV

Extension of Indication to include first-line treatment of adult patients with locally advanced or metastatic non-small cell lung cancer whose tumours have epidermal growth factor receptor exon 19 deletions or exon 21 (L858R) substitution mutations, based on data from the FLAURA study (D5160C00007): a phase III, double-blind, randomised study to assess the efficacy and safety of AZD9291 versus a standard of care epidermal growth factor receptor-Tyrosine Kinase Inhibitor as first-line treatment in patients with epidermal growth factor receptor mutation-positive, locally-advanced or metastatic non-small-cell lung cancer; as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 of the SmPC were proposed to be updated and the Package Leaflet was proposed to be updated accordingly. In addition, the MAH took the opportunity to implement editorial changes in the SmPC and Package Leaflet.
As part of this application the MAH is requesting an additional year of market protection for a new indication in accordance with Article 14(11) of Regulation (EC) No 726/2004.
An updated RMP version 8 was submitted as part of the application.

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

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0222/2017 on the granting of a (product-specific) waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

MAH request for additional market protection

The MAH requested consideration of its application in accordance with Article 14(11) of Regulation (EC) 726/2004 - one year of market protection for a new indication.

Scientific advice

The applicant did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Jorge Camarero Jiménez Co-Rapporteur: Bjorg Bolstad

Timetable	Actual dates
Submission date	26 October 2017
Start of procedure	25 November 2017
CHMP Rapporteur Assessment Report	19 January 2018
CHMP Co-Rapporteur Assessment Report	19 January 2018
PRAC Rapporteur Assessment Report	25 January 2018
PRAC members comments	31 January 2018
Updated PRAC Rapporteur Assessment Report	N/A
PRAC Outcome	08 February 2018
CHMP members comments	12 February 2018
Updated CHMP Rapporteur joint Assessment Report	15 February 2018
Request for Supplementary Information (RSI)	22 February 2018
PRAC Rapporteur response Assessment Report	03 April 2018
CHMP Rapporteur joint response Assessment Report	11 April 2018
CHMP Rapporteur Assessment Report on one additional year of Marketing Protection	11 April 2018
PRAC Outcome	12 April 2018
CHMP members comments	19 April 2018
Updated CHMP Rapporteur joint response Assessment Report	20 April 2018
CHMP opinion	26 April 2018
The CHMP adopted a report on the novelty of the indication/significant clinical benefit for Tagrisso in comparison with existing therapies (Appendix 1) for the purpose of granting an additional year of marketing protection in accordance with Article 14(11) of Regulation (EC) No 726/2004	26 April 2018

2. Scientific discussion

2.1. Introduction

Osimertinib (TAGRISSO™2) is an epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI), first approved by the EMA in 2016 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).

This application is being submitted to support the additional indication for use of osimertinib 80 mg (40 mg and 80 mg oral tablets) once daily (QD), as first-line treatment of patients with locally advanced or metastatic NSCLC whose tumours have EGFR exon 19 deletions (Ex19del) or substitution of a leucine with an arginine at position 858 in exon 21 (L858R) mutations.

Disease background

Despite progress in early detection and treatment, in 70% to 80% of patients, NSCLC is diagnosed at a locally advanced or metastatic stage (AJCC Stage IIIB and IV; referred to as advanced hereafter), when it is no longer amenable to curative surgery or chemoradiation (Besse et al 2014). Furthermore, a significant percentage of early-stage NSCLC patients who have undergone surgery subsequently have recurrence with distant metastases and die as a result of their lung cancer, with 30% to 49% of early-stage patients surviving for 5 years (Carnio et al 2011, Hung et al 2012, Uramoto & Tanaka 2014, Varela & Thomas 2014) and a much lower 5- year survival rate was observed for patients who did not undergo surgery (Rosen et al 2016). In summary, advanced NSCLC is an incurable condition.

Recent advances in the knowledge of tumour-specific genomic abnormalities have enabled the identification of specific molecular targets for NSCLC treatment in the current clinical practice (Keedy et al 2011, Leighl et al 2014, NCCN 2017, Novello et al 2016, Travis et al 2011). Several biomarkers have shown to be predictive of therapeutic efficacy of molecularly targeted agents and immune-oncology agents, including the presence of sensitising EGFR mutations, anaplastic lymphoma kinase (ALK) gene rearrangement, ROS proto-oncogene 1 receptor tyrosine kinase (ROS1) gene rearrangement and overexpression of programmed cell death-ligand 1 (PD-L1) and all these biomarkers are now routinely tested to establish the optimal treatment choice.

The EGFR is a member of the ErbB family of receptors tyrosine kinases that are essential to cell proliferation and survival (Shea et al 2016). The sensitising mutations in the kinase domain of EGFR increase the affinity of EGFR towards EGFR-TKIs over ATP and are found in approximately 15% of patients with lung cancer in the US (Keedy et al 2011), 10% of patients with lung cancer in the European Economic Area (Barlesi et al 2013, Esteban et al 2015, Gahr et al 2013, Herbst et al 2008, Rosell et al 2009), and 30% to 50% of patients with lung cancer in Asia (Ahn et al. 2015, Han et al 2015, Shi et al 2014, Tokumo et al 2005, Yoshida et al 2007).

In addition to the higher prevalence of EGFR mutations in Asian patients, overall, EGFR mutations have been found to be more frequent in never-smokers, patients with the adenocarcinoma histological subtype, and in women (Marchetti et al 2005, Novello et al 2016).

The two most frequent sensitising mutations are Ex19del and L858R that account for 85-90% of EGFR-TKI-sensitising mutations found in NSCLC (Lynch et al 2004; Paez et al 2004). Tumours harbouring these mutations are particularly sensitive towards EGFR-TKIs and undergo significant apoptosis in response to exposure to these agents (Mitsudomi and Yatabe 2010). Multiple randomised clinical

studies have shown that the presence of common sensitising EGFR mutations in patients with advanced NSCLC is predictive of response and improved treatment outcome to EGFR-TKIs. Patients with less common sensitising EGFR mutations such as L861Q or G719X, while still benefitting from EGFR-TKIs, have a lesser magnitude of benefit.

Current standard of care in the proposed indication

Molecular testing of tumours in patients with advanced NSCLC is now established practice to determine the preferred choice as first-line therapy.

Epidermal growth factor receptor- TKIs such as such as gefitinib, erlotinib, afatinib are the current standard of care (SoC) as first-line therapy for EGFR mutation-positive NSCLC (NCCN 2017, Novello et al 2016).

Though most tumours initially respond well systemically to the currently approved EGFRTKIs in first-line setting, the vast majority of patients develop TKI resistance with a median PFS of 9 to 13 months. In approximately 50% to 65% of the patients the resistance is due to the development of a second-site EGFR-TKI resistance-conferring 'gatekeeper' point mutation, T790M leading to treatment failure and disease progression (Jackman et al 2009, Maemondo et al 2010, Mitsudomi et al 2010, Mok et al 2009, Oxnard et al 2011, Rosell et al 2012, Sebastian et al 2014).

Patients who develop, or are diagnosed with, central nervous system (CNS) metastases currently have limited treatment options resulting in poorer outcomes (Mak et al 2015). Limited data are available on the efficacy of EGFR-TKIs against CNS metastases in first-line setting, given that CNS metastases have been a typical exclusion criterion in historical studies involving these agents (Bartolotti et al 2012). A selection of trials studying the activity of EGFR-TKIs in patients with NSCLC harbouring EGFR mutations and CNS metastases report response rates of 70-85% (Zimmermann et al 2014).

Despite significant progress achieved since the introduction of EGFR-TKIs into clinical practice more than a decade ago, there is still a considerable unmet medical need for new treatment options for patients in this disease setting. Inevitably, a majority of patients develop resistance to EGFR-TKIs with the most common resistance being associated with secondary T790M mutation. In sites of very common metastatic disease such as the CNS, the suboptimal exposure provided by currently approved EGFR-TKIs allows the disease to spread into the CNS and the formation of CNS metastases.

The applicant requested the approval for the following indication:

TAGRISSO is indicated for the first-line treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) whose tumours have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations.

The indication approved by the CHMP was as follows: TAGRISSO as monotherapy is indicated for the first-line treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating epidermal growth factor receptor (EGFR) mutations.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

The MAH submitted an update of the ERA (Environmental Risk Assessment).

Table 2: Summary of main study results

Substance (INN/Invented Name): Osimertinib (Tagrisso)			
CAS-number: 1421373-66-1			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	pH 4 log Dow = 1.77 pH 7 log Dow = 2.45 pH 9 log Dow = 2.69	Potential PBT (N)
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, refined with prevalence data	0.0023	µg/L	> 0.01 threshold (N)

2.2.2. Discussion on non-clinical aspects

No new non-clinical data have been submitted with this new indication of Tagrisso, which is considered acceptable.

In relation to the ERA, due to the lack of robust epidemiology data available for the prevalence of exon 19 deletions and exon 21 (L858R) substitution mutations, the prevalence rate was not refined for mutation status of EGFR NSCLC and the revised assessment uses a worst-case scenario and is based on the incidence of all EGFR mutations (7-13%).

Thus, the highest reported incidence rates of NSCLC (89%) and EGFR mutation (13%) were applied to the overall prevalence rate of lung cancer for Hungary (European member state with the highest single year prevalence of lung cancer) to calculate the market penetration factor (Fpen = 0.000058).

The data show that the refined PECsurfacewater value for osimertinib mesylate is below the action limit of 0.01 µg/L and it is not a PBT substance, as log Dow does not exceed the trigger value of 4.5. The octanol-water partition values indicate that the risk of bioaccumulation is low.

Thus, osimertinib mesylate is not expected to pose a risk to the environment.

In addition, as required by Directive 2001/83/EC and EMA Quality Review Document, the following statement has been included in the Tagrisso package leaflet: *Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.*

2.2.3. Conclusion on the non-clinical aspects

The updated data submitted in this application do not lead to a significant increase in environmental exposure further to the use of osimertinib.

Considering the above data, osimertinib is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Table 1: Summary of studies included in the current analysis

Study number	Study description	Number of patients with PK information	PK sampling schedule[a]
D5160C00001 (AURA)	Phase I component in EGFR mutation positive advanced NSCLC patients. Doses: 20, 40, 80, 160 and 240 mg (capsule) 80 mg (tablet)	402[b]	Following a single dose: pre-dose, (0.5), 1, 1.5, 2, (3), 4, 6, 8, 10, 12, 24, 48, (72) and (120) hours post dosing Following multiple doses: Cycle 1 Day 8: predose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12 and 24 hours post dosing, or Cycle 2 Day 1: predose, 1, 1.5, 2, 4, 6, 8, 10, 12 and 24 hours post dosing and predose on Cycle 1 day 15.
D5160C00001 (AURA extension)	Phase II in EGFR T790M positive advanced NSCLC patients who have progressed following either 1 prior therapy with an EGFR TKI agent or following treatment with at least 1 EGFR TKI and at least 1 prior platinum-based doublet chemotherapy. Dose: 80 mg (tablet)	201	Cycle 2 Day 1: predose, 1, 1.5, 2, 4, 6, 8, 10, 12 and 24 hours post dosing and predose on Cycle 1 days 1, 8 and 15.
D5160C00002 (AURA2)	Phase II component in EGFR T790M positive advanced NSCLC patients who have progressed following either 1 prior therapy with an EGFR TKI agent or following treatment with both EGFR TKI and at least 1 other prior line of therapy, such as cytotoxic doublet chemotherapy or immunotherapy. Dose: 80 mg (tablet)	210	Following a single dose: predose, 1, 2, 4, 6 and 8 hours post dosing. Following multiple doses on Cycle 2 Day 1 : predose and on Cycle 3 Day 1: predose, 1, 2, 4, 6, 8, 10, 12 and 24 hours post dosing. Dose reductions were allowed.
D5160C00003 (AURA3)	A Phase III, open label, randomized study of AZD9291 vs platinum-based doublet chemotherapy for patients with locally advanced or metastatic non-small cell lung cancer whose disease has progressed with previous epidermal growth factor receptor tyrosine kinase inhibitor therapy and whose tumours harbour a T790M mutation within the epidermal growth factor receptor gene (AURA3). Dose: 80 mg (tablet)	279[b]	Plasma samples were collected at predose, between 0.5 to 1.5 hours and between 2 and 4 hours after dosing on first day of dosing in cycle 1, 3, 5, 7, 9, 11, and 13. Dose reductions were allowed.

D5160C00007 (FLAURA)	A Phase III, double-blind, randomised study to assess the efficacy and safety of AZD9291 vs a standard of care epidermal growth factor receptor tyrosine kinase inhibitor as first-line treatment in patients with epidermal growth factor receptor mutation positive, locally advanced or metastatic non-small cell lung cancer. Dose: 80 mg (tablet)	279	Plasma samples were collected at pre-dose, between 0.5 to 2 hours and between 3 and 5 hours after dosing at Day 1 Cycle 1 and every other cycle thereafter up to and including Cycle 13. Dose reductions were allowed.

[a] In AURA the PK sampling scheme was updated based on emerging PK data and hence single dose samples in brackets were not collected in all patients and multiple dose samples were collected on either Cycle 1 Day 8 or Cycle 2 Day 1; multiple dose PK dosing was repeated once daily oral dosing.
[b] Two patients from each of these studies were not included in the master dataset.
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2.3.2. Pharmacokinetics

The pharmacokinetic (PK) of osimertinib and its main metabolite (AZ5104) in NSCLC patients with the T790M mutation have been characterised in the initial MA and variations submitted post authorisation. This submission provides an updated population PK analysis where the FLAURA data have been added to the data set. As in the previous submissions, data from paediatric subjects were not available.

Plasma samples for osimertinib and AZ5104 were assayed using a liquid chromatographic-tandem mass spectrometric (LC-MS/MS) method. The lower limit of quantification (LLOQ) was 0.05 nM for osimertinib and 0.0515 nM for AZ5104. The bioanalytical methods used in FLAURA were appropriately validated and the results were consistent with the previous analysis.

The objectives of the updated analysis were to

- Characterize the PK of osimertinib and its main metabolite of interest (AZ5104) in NSCLC patients, following oral once daily administration.
- Evaluate the impact of line of therapy on the PK of osimertinib.
- Update the impact of selected intrinsic and extrinsic covariates of interest on the PK variability of osimertinib.

Nonlinear mixed effects modelling was performed using NONMEM v 7.3 (SAEM estimation method). Model development and final model selection was driven by data and based on goodness-of-fit indicators, including visual inspection of diagnostic and covariate scatter plots, parameter estimate precision and minimum objective function value.

Osimeritinib and its main metabolite (AZ5104) have been characterized by a linear 1-compartmental disposition model for both parent and metabolite, with first order oral absorption of osimeritinib into the central compartment and the formation of AZ5104 from osimeritinib (Figure 2).

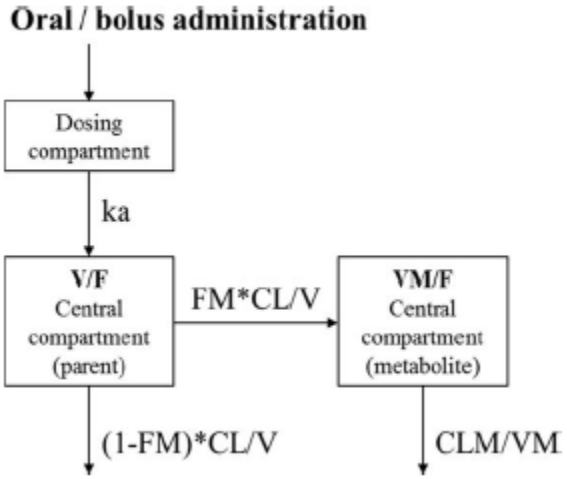

Figure 1: Structure of previous osimertinib population PK model

The characteristics of the final model included:

- Linear 1 compartmental distribution model for each analyte
- Fraction of osimertinib metabolized to AZ5104 (FM) was fixed to 0.25
- First-order absorption of parent into the parent's central compartment
- Linear elimination from parent and metabolite from their central compartments
- Between-subject variability considered on all PK parameters (ka, CL/F, CLM/F,
- V/F, VM/F)
- Correlation of random effects of CL/F and CLM/F
- Additive-proportional residual error models for both analytes
- The covariate/parameter pairs, included in the final model are the following:
- Bodyweight (WT) on CL/F, CLM/F, V/F
- Baseline albumin (BALB) on CL/F, CLM/F, V/F, and VM/F
- Grouped ethnicity (ETHL) on CLM/F

Table 2: Population parameter estimates for final model

Parameter	Typical value	RSE (%)	Shrinkage (%)
CL/F (L/hour)	14.3	1.39[a]	
CLM/F (L/hour)	31.3	2[a]	
FM (fraction)	0.25 (FIX)	-	
V/F (L)	918	3.3[a]	
VM/F (L)	143	4.22[a]	
ka (1/hour)	0.196	5.09[a]	
Between-subject variability (as %CV)			
Omega (CL/F)	44.9	1.86	3.8
Omega (CLM/F)	49.7	1.85	3.5
Omega (FM)	0 (FIX)	-	-
Omega (V/F)	90.9	1.58	28.9
Omega (VM/F)	78.2	3.24	38.1
Omega (ka)	109	2.14	38.6
Correlation of random effects			
Correlation (CL/F and CLM/F)	0.885	0.732	
Parameter-covariate estimates			
Baseline albumin on CL/F	0.825	11.7	
Baseline bodyweight on CL/F	0.421	13.9	
Baseline albumin on CLM/F	0.928	11.4	
Asian (non-Chinese, non-Japanese) on CLM/F	0.182	11.2	
Chinese on CLM/F	0.0763	27.2	
Japanese on CLM/F	0.184	13.1	
Non-Asian, non-White on CLM/F	0.0903	26.4	
Baseline bodyweight on CLM/F	0.822	8.01	
Baseline albumin on V/F	2.27	9.82	
Baseline bodyweight on V/F	0.814	16.9	
Baseline albumin on VM/F	-0.831	28.6	
Residual variability			
Additive error osimertinib (nM)	30.1	1	
Additive error AZ5104 (nM)	0.516	2.48	
Proportional error osimertinib (fraction)	0.205	0.424	
Proportional error AZ5104 (fraction)	0.215	0.357	
Objective function value[b]	299461.2		
Condition number - FULL	274.8		
Condition number - fixed effects	43.83		
Condition number - random effects and error parameters	11.72		

[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 use of MU referencing).

[b] The objective function was determined using importance sampling (IMP) with settings EONLY=1 and MAPITER=0, as suggested in (ICON 2014).

Abbreviations: RSE: Relative standard error; CL/F: Apparent osimertinib clearance; V/F: Apparent osimertinib volume of distribution; CLM/F: Apparent clearance of metabolite AZ5104; VM/F: Apparent volume of distribution of metabolite AZ5104; ka: First-order absorption rate constant; CV%: Percent coefficient of variation; nM: Nano molar.

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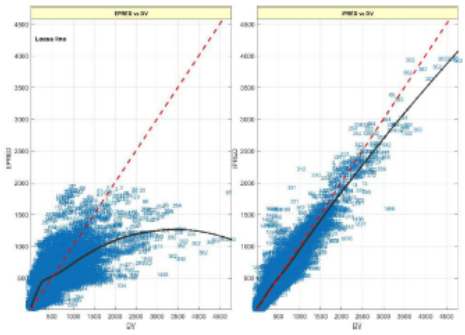
Results from the GOF plots are represented in the following figures.



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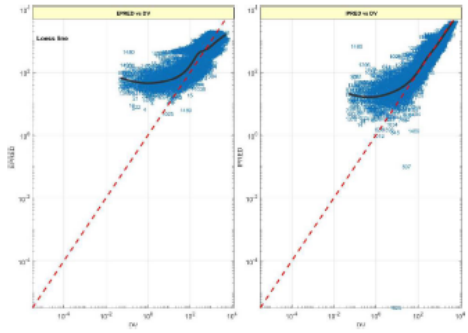

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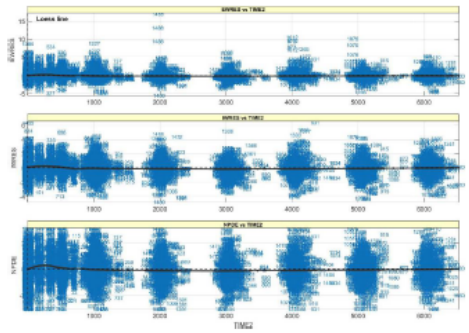

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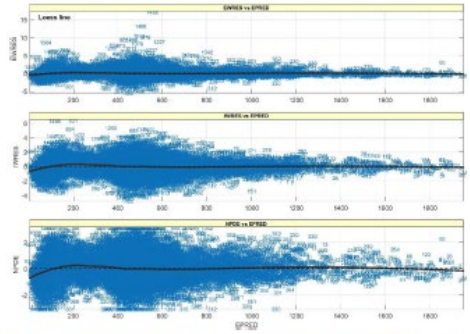

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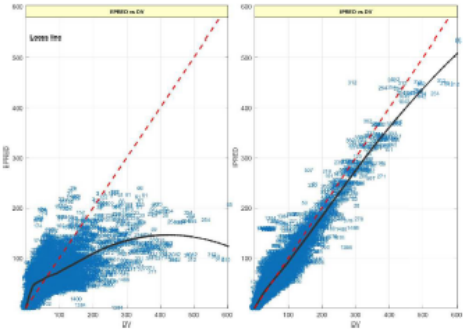
Figure 2: Goodness-of-fit plots osimertinib final model



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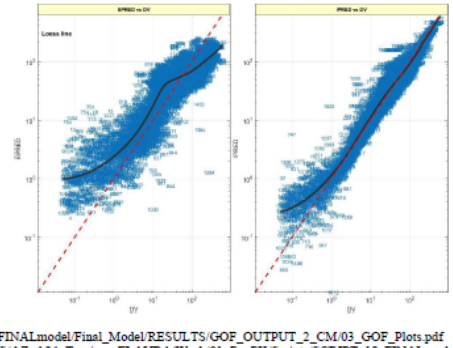

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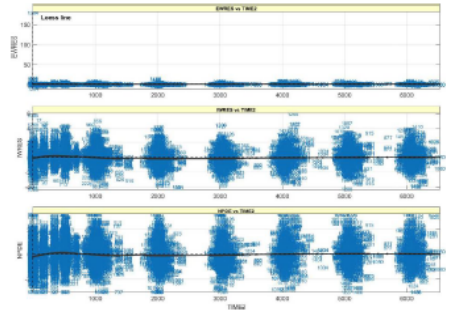

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Page 3

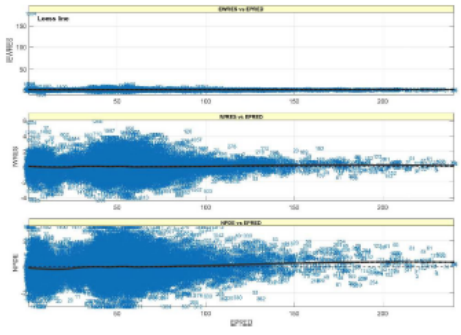

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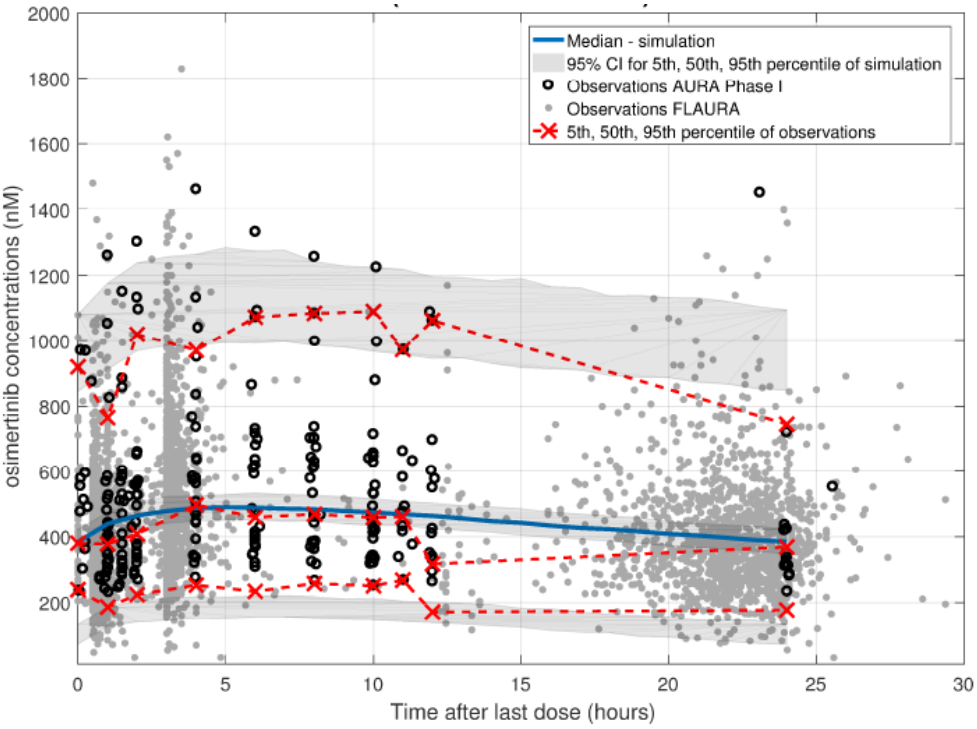
Figure 3: Goodness-of-fit plots AZ5104 final model

Diagnostics of the final model showed that the random effects were adequately normally distributed and the predicted and observed individual concentrations were generally symmetrically distributed around the line of identity. The different residuals and the normalized prediction distribution errors (NPDE) did not show any trends, both over time and over the population prediction. The VPCs suggested that the final model reasonably described the main part of the observed data. The VPCs also showed that observations in second-line patients are slightly overpredicted. This is as expected, as it already had been seen in Figure 5 that pre-dose steady-state concentrations at 80 mg were lower in second-line patients than in third-line patients. Additionally, the covariate analysis showed that line of therapy as a covariate on CL/F and CLM/F was not statistically significant and that the median effect was clearly below 20%. The typical predicted half-life of osimertinib was calculated with a median of 44.4 hours (95% confidence interval: [41.2, 47.7] hours), which is consistent with the results from the previous analysis (Johnson and Schmidt 2016), in which 48 hours was determined.

A non-parametric bootstrap analysis using 1000 bootstrapped datasets was performed. In this bootstrap analysis, all the models converged successfully. The median and confidence intervals of parameter estimates derived from this bootstrap analysis were consistent with the parameter estimates and confidence intervals (CI) derived from the final population PK model.

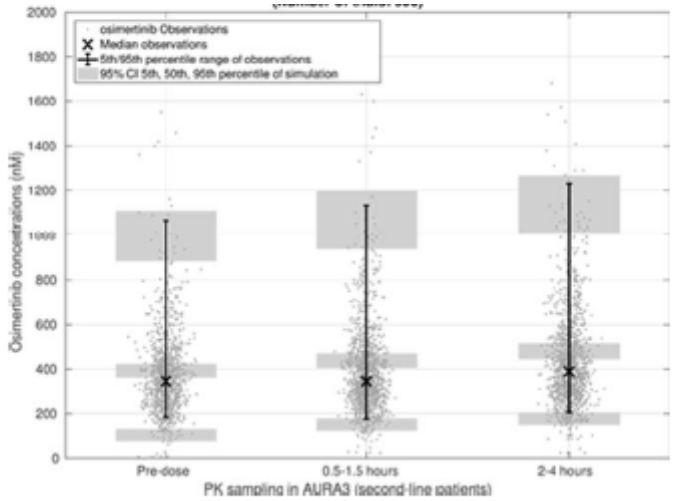
Table 3: Non-parametric bootstrap analysis

Parameter	Final Model estimate	Bootstrap analysis median	Final Model 95% CI	Bootstrap analysis 95% CI
CL/F (L/hour)	14.34	14.34	[13.95, 14.73]	[14, 14.69]
CLM/F (L/hour)	31.31	31.28	[30.08, 32.54]	[30.21, 32.39]
ka (1/hour)	0.1962	0.2047	[0.1767, 0.2158]	[0.1738, 0.2396]
V/F (L)	918.5	934.8	[859.1, 977.8]	[845.3, 1029]
VM/F (L)	143.4	144.5	[131.6, 155.3]	[133.5, 156.7]
Between Subject Variability a				
omega(CL/F)	0.4485	0.4485	[0.4322, 0.4649]	[0.4254, 0.4738]
omega(CLM/F)	0.4972	0.4959	[0.4792, 0.5153]	[0.4734, 0.5222]
omega(ka)	1.088	1.044	[1.043, 1.134]	[0.8507, 1.221]
omega(V/F)	0.9091	0.8981	[0.8809, 0.9374]	[0.8076, 0.993]
omega(VM/F)	0.782	0.7775	[0.7324, 0.8317]	[0.6818, 0.8802]
Correlation of random effects				
Correlation (CL/F and CLM/F)	0.8853	0.8859	[0.8726, 0.8981]	[0.8713, 0.9001]
Parameter-Covariate Estimates				
Baseline bodyweight on CL/F	0.4212	0.4225	[0.3063, 0.5362]	[0.3128, 0.5289]
Baseline albumin on CL/F	0.8255	0.8178	[0.6358, 1.015]	[0.639, 0.9931]
Baseline bodyweight on V/F	0.8144	0.7802	[0.5446, 1.084]	[0.4979, 1.049]
Baseline albumin on V/F	2.266	2.243	[1.83, 2.703]	[1.797, 2.736]
Baseline bodyweight on CLM/F	0.8223	0.8237	[0.6932, 0.9514]	[0.6966, 0.9565]
Baseline albumin on CLM/F	0.9281	0.9197	[0.7207, 1.135]	[0.7166, 1.115]
Baseline albumin on VM/F	-0.8309	-0.7629	[-1.297, -0.3648]	[-1.304, -0.2178]
Asian (non-Chinese, non-Japanese) on CLM/F	0.1822	0.1834	[0.1421, 0.2223]	[0.1453, 0.2203]
Chinese on CLM/F	0.07629	0.07613	[0.03558, 0.117]	[0.03541, 0.1202]
Japanese on CLM/F	0.1835	0.1848	[0.1366, 0.2305]	[0.1424, 0.2282]
Non-Asian, non-White on CLM/F	0.09031	0.09072	[0.04356,	[0.04123, 0.1415]
Residual Variability				
Additive error Osimertinib (nM)	30.08	30.65	[29.49, 30.67]	[26.7, 34.9]
Additive error AZ5104 (nM)	0.2051	0.2035	[0.2034, 0.2068]	[0.1934, 0.2142]
Proportional error Osimertinib (fraction)	0.5161	0.5275	[0.491, 0.5413]	[0.41, 0.7072]
Proportional error AZ5104 (fraction)	0.2152	0.2145	[0.2137, 0.2167]	[0.2073, 0.2225]



../Output/VPCs/FIG_VPC_DAY22_AZD9291_80mg_First-line.pdf
C:/PROJECTS/A52_Tagrisson_Questions/WorkHenning/Scripts/SCRIPT_20_VPCs.m
All data-points, considered in this VPC have been sampled in steady-state conditions, meaning that at least 10 doses of 80 mg had been given in the last 250 hours before sampling of concentrations. Data points sampled before day 22 have been excluded. Data is plotted over actual time after last dose, as nominal profile sampling times were not available in the dataset. The time axis was limited to max. 30hours. Simulations for the VPC have been conducted by simulating a dosing regimen of 80 mg daily for 6 weeks to reach steady-state conditions and plotting only results for the last 24 hour profile. Residual variability was considered in this VPC.

Figure 4: Steady-state VPC, first-line patients for osimertinib following 80 mg dose



All data-points, considered in this VPC have been sampled in steady-state conditions, meaning that at least 10 doses of 80 mg had been given in the last 250 hours before sampling of concentrations. Data points sampled before Day 22 have been excluded. Simulations for the VPC have been conducted by simulating a dosing regimen of 80 mg daily for 6 weeks to reach steady-state conditions and plotting only results for the pre-dose and the 2 post-dose samples from the last 24 hour profile. Residual variability was considered in this VPC.
../Output/16_FINALmodel/Final_Model/../FIG_VPC_DAY22_AZD9291_80mg_Second-line.pdf
/home/iqrun/PROJECTS/AZ_A24_Tagrisso_FLAURA/Work/01_PopPK/Scripts/SCRIPT_19_FINALmodel_VPCs.m
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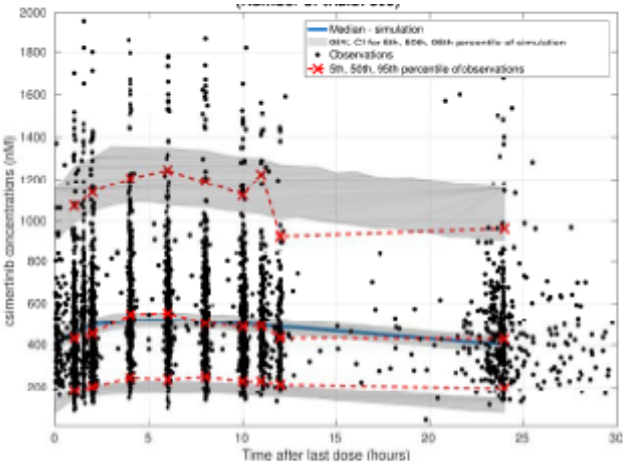
Figure 5: Steady-state VPC, second-line patients, Day 22 for osimertinib following 80 mg dose



All data-points, considered in this VPC have been sampled in steady-state conditions, meaning that at least 10 doses of 80 mg had been given in the last 250 hours before sampling of concentrations. Data points sampled before Day 22 have been excluded. Data are plotted over actual time after last dose, as nominal profile sampling times were not available in the dataset. The time axis was limited to maximum 30 hours. Simulations for the VPC have been conducted by simulating a dosing regimen of 80 mg daily for 6 weeks to reach steady-state conditions and plotting only results for the last 24 hour profile. Residual variability was considered in this VPC.
../Output/16_FINALmodel/Final_Model/../FIG_VPC_DAY22_AZD9291_80mg_Greaterorequalthird-line.pdf
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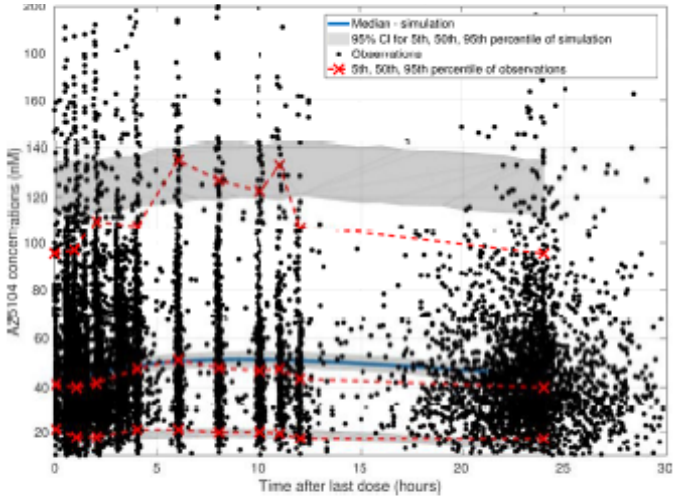
Figure 6: Steady-state VPC, ≥third-line patients, Day 22 for osimertinib following 80 mg dose



All data-points, considered in this VPC have been sampled in steady-state conditions, meaning that at least 10 doses of 80 mg had been given in the last 250 hours before sampling of concentrations. Data points sampled before Day 22 have been excluded. Data are plotted over actual time after last dose, as nominal profile sampling times were not available in the dataset. The time axis was limited to maximum 30 hours. Simulations for the VPC have been conducted by simulating a dosing regimen of 80 mg daily for 6 weeks to reach steady-state conditions and plotting only results for the last 24 hour profile. Residual variability was considered in this VPC.
../Output/16_FINALmodel/Final_Model/../FIG_VPC_DAY22_AZ5104_80mg_Allpatients.pdf
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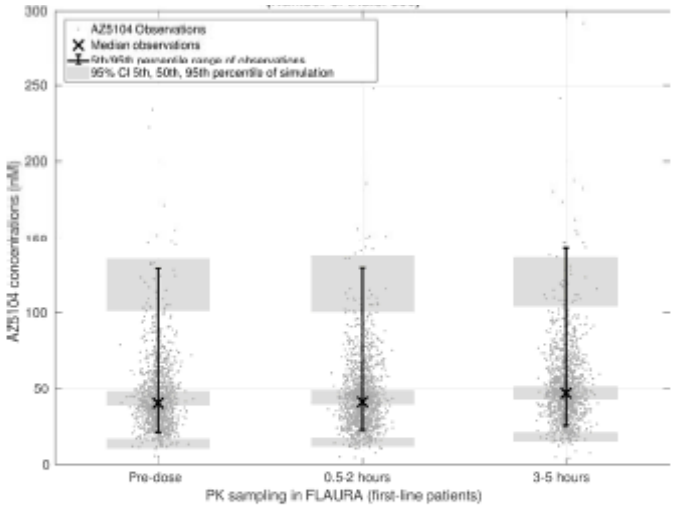
Figure 7: Steady-state VPC, all studies, Day 22 for AZ5104 following 80 mg dose



All data-points, considered in this VPC have been sampled in steady-state conditions, meaning that at least 10 doses of 80 mg had been given in the last 250 hours before sampling of concentrations. Data points sampled before Day 22 have been excluded. Simulations for the VPC have been conducted by simulating a dosing regimen of 80 mg daily for 6 weeks to reach steady-state conditions and plotting only results for the pre-dose and the 2 post-dose samples from the last 24 hour profile. Residual variability was considered in this VPC.
../Output/16_FINALmodel/Final_Model/../FIG_VPC_DAY22_AZ5104_80mg_First-line.pdf
/home/iqrun/PROJECTS/AZ_A24_Tagrisso_FLAURA/Work/01_PopPK/Scripts/SCRIPT_19_FINALmodel_VPCs.m
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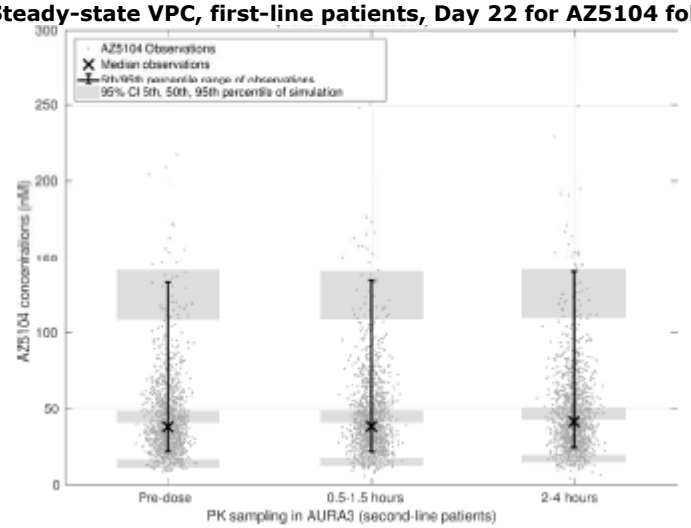
Figure 8: Steady-state VPC, first-line patients, Day 22 for AZ5104 following 80 mg dose



All data-points, considered in this VPC have been sampled in steady-state conditions, meaning that at least 10 doses of 80 mg had been given in the last 250 hours before sampling of concentrations. Data points sampled before Day 22 have been excluded. Simulations for the VPC have been conducted by simulating a dosing regimen of 80 mg daily for 6 weeks to reach steady-state conditions and plotting only results for the pre-dose and the 2 post-dose samples from the last 24 hour profile. Residual variability was considered in this VPC.
../Output/16_FINALmodel/Final_Model/../FIG_VPC_DAY22_AZ5104_80mg_Second-line.pdf
/home/iqrun/PROJECTS/AZ_A24_Tagrisso_FLAURA/Work/01_PopPK/Scripts/SCRIPT_19_FINALmodel_VPCs.m
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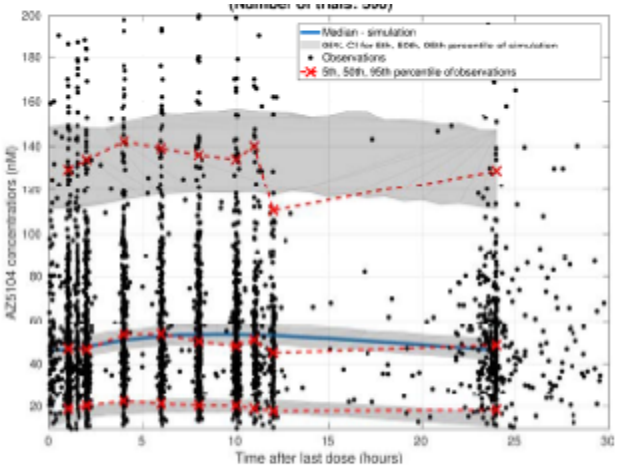
Figure 9: Steady-state VPC, second-line patients, Day 22 for AZ5104 following 80 mg dose



All data-points, considered in this VPC have been sampled in steady-state conditions, meaning that at least 10 doses of 80 mg had been given in the last 250 hours before sampling of concentrations. Data points sampled before Day 22 have been excluded. Data are plotted over actual time after last dose, as nominal profile sampling times were not available in the dataset. The time axis was limited to maximum 30 hours. Simulations for the VPC have been conducted by simulating a dosing regimen of 80 mg daily for 6 weeks to reach steady-state conditions and plotting only results for the last 24 hour profile. Residual variability was considered in this VPC.
../Output/16_FINALmodel/Final_Model/../FIG_VPC_DAY22_AZ5104_80mg_Greaterorequalthird-line.pdf
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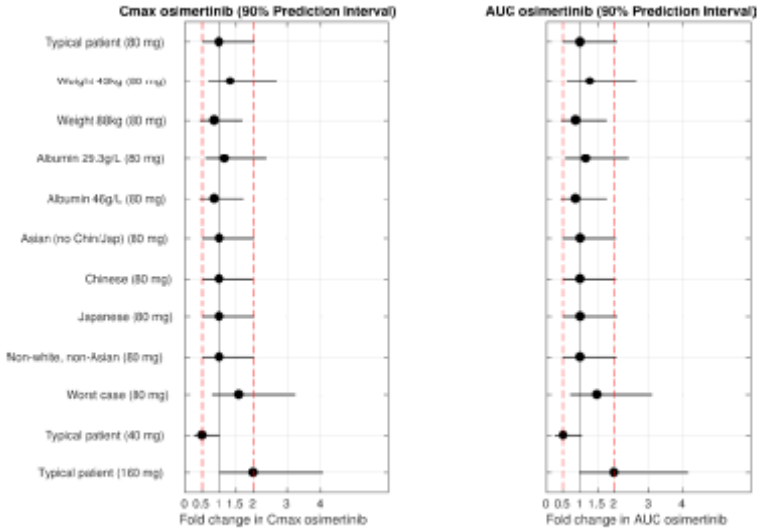
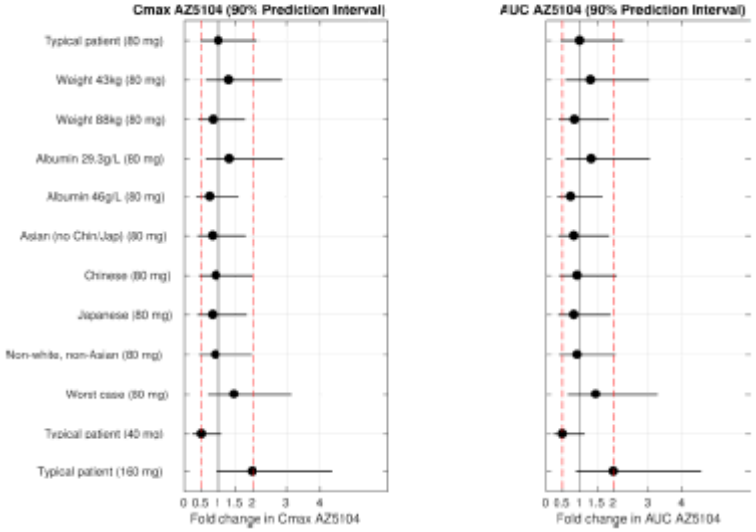
Figure 10: Steady-state VPC, ≥third-line patients, Day 22 for AZ5104 following 80 mg dose

Simulations were conducted to assess the impact of identified important covariate/parameter relationships in the final PK model. These simulations considered only the 80 mg dose level. The simulation based analysis suggested that at typical patient level the changes in exposure metrics related to covariates are not expected to show clinically impactful differences. Considering the therapeutic dose (80 mg once daily), the worst-case combination of covariates (worst-case selected based on safety considerations to obtain the highest values for osimertinib Cmax) consists of patients that have a low bodyweight and low albumin levels and are of Asian (no Chinese, no Japanese) ethnicity. The worst-case combination of covariates considering the 5th percent of covariate distribution of bodyweight (43 kg) and baseline albumin (29.3 g/L) in the dataset, predicted an increase in median steady-state osimertinib Cmaxss and AUCss of approximately 59% and 49%, respectively, in relation to the typical patient.



This figure is a graphical representation of the information in Table 8. A prediction interval of 90% means that the final model predicts that 90% of the population will fall into the indicated range (relative to the typical patient) for a given covariate setting. Typical patient: White, 61 kg bodyweight, 39 g/L baseline serum albumin.

Figure 11: Effect of covariates on osimertinib PK



Typical patient: White, 60 kg bodyweight, 39 g/L baseline serum albumin. Worst case: White, 43 kg bodyweight, 29.3 g/L baseline serum albumin. The last 2 rows contain simulations for the "typical patient" at 40 and 160 mg daily doses for reference.
../Output/16_FINALmodel/Final_Model/../FIG_SIM_02_simulation_Forest_Metabolite.pdf
/home/iqrun/PROJECTS/AZ_A24_Tagrisso_FLAURA/Work/01_PopPK/Scripts/SCRIPT_20_STEP5_Simulations.m
2017-Aug-23 14:09

Figure 12: Effect of covariates on AZ5104 PK

A comparison of osimertinib PK endpoints was performed, when possible, in order to demonstrate the adequacy of the model to characterize the observed exposure of osimertinib for the different studies.

Table 4: Comparison of osimertinib PK parameters between observed and model predicted

PK parameter	Study[a]	n	Observed GeoMean (CV%)	Model predicted (95%PI)[b]
AUC_{ss}	AURA Phase I	60	11410 (55)	11990 (5535, 37187)
[nM*h]	AURA extension	183	11980 (46)	11893 (4949, 36332)
	AURA2	192	10180 (42)	10712 (4570, 22797)
	AURA3	235	NA	9744.5 (4723, 23819)
	FLAURA	183	NA	10915 (4897, 23614)

PK parameter	Study[a]	n	Observed GeoMean (CV%)	Model predicted (95%PI)[b]
C_{ssmax}	AURA Phase I	60	602 (58%)	540 (244, 1532)
[nM]	AURA extension	183	631 (45)	526 (221, 1488)
	AURA2	192	533 (43)	510 (210, 1140)
	AURA3	235	NA	440 (210, 1022)
	FLAURA	183	NA	511 (248, 1100)
C_{ssmin}	AURA Phase I	60	367 (61)	417 (194,1467)
[nM]	AURA extension	183	384 (51)	438 (175, 1406)
	AURA2	192	332 (49)	373 (163, 833)
	AURA3	235	357 (53)[c]	340 (161, 864)
	FLAURA	183	394 (44)[c]	360 (147, 866)

Only patients having received 80 mg as first dose have been considered.

PI: Prediction Interval based on individual model predicted exposures.

predose value from Cycle 3 Day 1 shown

Dose proportionality and time dependencies

Both population pharmacokinetic models supported dose proportionality of the dose-concentration relationship (parent and metabolite) across the 20 to 240 mg dose range that was available in the previous analysis.

Dose-proportionality of the pharmacokinetics of osimertinib and AZ5104 was already assessed in previous reports (Comisar et al 2015, Johnson and Schmidt 2016) and is not repeated in this analysis, as the only change was to add data from FLAURA with a planned single dose level of 80 mg.

Special populations

Based on in vitro data and the human ADME study (Study D5160C00011), osimertinib has been shown to undergo significant metabolic clearance via the liver and hence, a clinical study to evaluate the impact of hepatic impairment (mild and moderate hepatic impairment) on osimertinib exposure has been completed (study D5160C00008). The MAH has submitted the CSR of study D5160C00008 CSR which is currently under evaluation (EMEA/H/C/004124/II/0024).

Renal elimination contributes minimally to total osimertinib clearance; however, at the request of EMA, and based on renal impairment maybe affecting some pathways of hepatic metabolism, a reduced design study to evaluate the impact of severe renal impairment on osimertinib exposure is ongoing (Study D5160C00035) as reflected in the RMP.

Furthermore, at the request of EMA, a study to evaluate the single and multiple dose effect of osimertinib on the exposure of a non-CYP3A4 mediated Pregnane X receptor substrate (P-glycoprotein [P-gp] substrate, fexofenadine) (D5160C00036) has been submitted and is currently under assessment (EMEA/H/C/004124/II/0021).

Pharmacokinetic interaction studies

No additional studies have been submitted.

Pharmacokinetics using human biomaterials

No additional or updated human in vitro studies have been completed to those already presented with the previous submissions.

2.3.3. Pharmacodynamics

Mechanism of action

Osimertinib is an oral, potent, irreversible central nervous system active EGFR-TKI, effective against NSCLC with both EGFR-TKI-sensitizing mutations (EGFRm+) as well as T790M mutation positive (TKI resistance conferring mutation) forms of EGFR, but designed to have limited activity against wild type (WT) EGFR at clinically relevant doses. As a result, osimertinib can effectively block EGFR signaling both in EGFRm+ and EGFRm+/T790M mutation positive cells. In Phase I, II, and III studies, osimertinib has shown to provide clinically meaningful benefit to patients with advanced NSCLC harboring the EGFR T790M resistance mutation after prior treatment with an EGFR-TKI.

Primary and secondary pharmacology

Relation between PK and efficacy

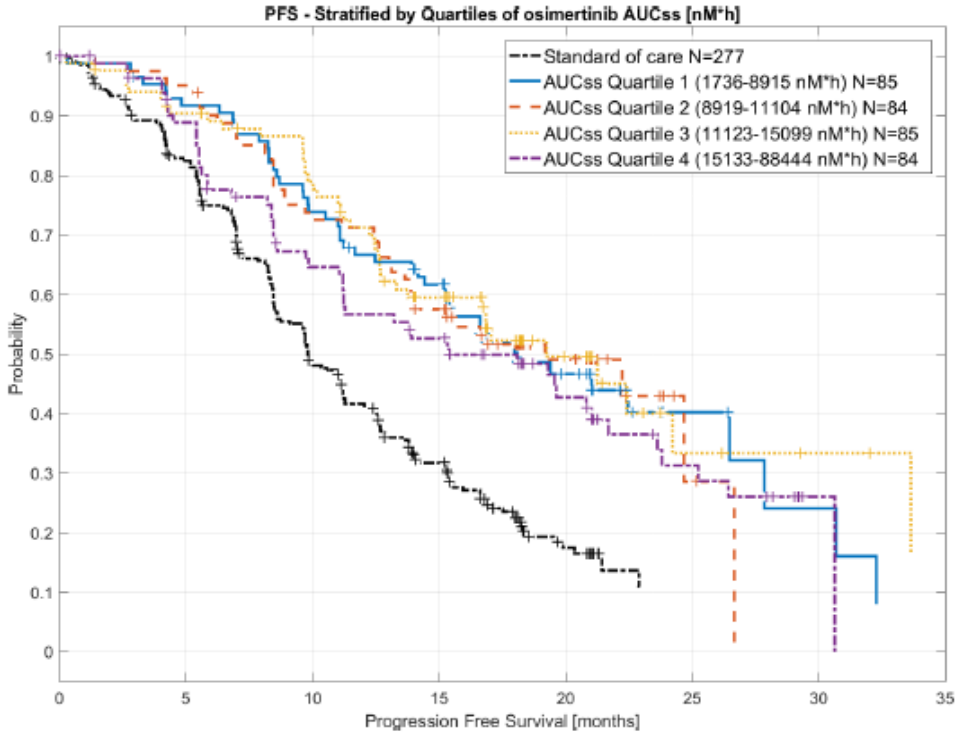


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Figure 13: Kaplan-Meier representation of PFS stratified by quartiles of osimertinib AUCss and SoC – FLAURA studies

Table 5: Median PFS and 95% CI for the FLAURA SoC group and the osimertinib AUCss quartiles

Exposure Metrics	Number patients	Number uncensored events	Median PFS (months)	95% CI (months)
Standard of care	277	204	9.8	8.6, 11.2
Quartile 1 of osimertinib AUC_{ss}	85	48	18.1	15.2, 26.5
Quartile 2 of osimertinib AUC_{ss}	84	42	19.2	13.9, NaN
Quartile 3 of osimertinib AUC_{ss}	85	41	19.2	13.7, 33.6
Quartile 4 of osimertinib AUC_{ss}	84	51	15.4	11.2, 21.7

../Output/21_PFS_SOC_AUC/TAB_01_PFS_survivalTime50_CI_SOC_AZD9291_AUCss_EFFICACY_population.txt
C:/PROJECTS/AZ_A24_Tagrisso_FLAURA/Work/03_Efficacy/Scripts/SCRIPT_21_PFS_SOC_AUC.m
2017-Sep-18 14:12
Abbreviation: NaN not a number, meaning that this value is undefined as information is missing in the data to compute the 50% survival time.

Relation between PK and safety

Left ventricular ejection fraction (LVEF) is considered the most important measurement of ventricular function for distinguishing patients with cardiac systolic dysfunction from patients with preserved systolic function (Swedberg et al 2005).

The below analysis demonstrated that there is no evidence of any quantifiable exposure-related effects on change from baseline LVEF value and incidence of LVEF event.

Table 6: Number of patients within intervals of baseline LVEF values for each dose group

Treatment group	LVEF0 <50	LVEF0 50 to <70	LVEF0 >= 70	$LVEF_{min}$ <50	$LVEF_{min}$ 50 to <70	$LVEF_{min}$ ≥70	$LVEF_{max}$ <50	$LVEF_{max}$ 50 to <70	$LVEF_{max}$ ≥70
AURA3 Chemotherapy	-	67 (71.3%)	27 (28.7%)	1 (1.06%)	75 (79.8%)	18 (19.1%)	-	62 (66%)	32 (34%)
FLAURA SoC	4 (1.56%)	168 (65.6%)	84 (32.8%)	10 (3.91%)	210 (82%)	36 (14.1%)	2 (0.781%)	108 (42.2%)	146 (57%)
Osimertinib 40 mg	-	4 (100%)	-	-	4 (100%)	-	-	3 (75%)	1 (25%)
Osimertinib 80 mg	9 (0.99%)	664 (73%)	236 (26%)	50 (5.5%)	797 (87.7%)	62 (6.82%)	9 (0.99%)	563 (61.9%)	337 (37.1%)
Osimertinib 160 mg	1 (4.76%)	19 (90.5%)	1 (4.76%)	2 (9.52%)	17 (81%)	2 (9.52%)	1 (4.76%)	15 (71.4%)	5 (23.8%)
Osimertinib 240 mg	-	2 (100%)	-	-	2 (100%)	-	-	2 (100%)	-
Osimertinib All Doses	10 (1.07%)	689 (73.6%)	237 (25.3%)	52 (5.56%)	820 (87.6%)	64 (6.84%)	10 (1.07%)	583 (62.3%)	343 (36.6%)
All Groups	14 (1.09%)	924 (71.9%)	348 (27.1%)	63 (4.9%)	1105 (85.9%)	118 (9.18%)	12 (0.933%)	753 (58.6%)	521 (40.5%)

Percentages of patients per group provided in parentheses.
LVEF0 LVEF at baseline, $LVEF_{max}$ Maximum post-baseline LVEF; $LVEF_{min}$ Minimum post-baseline LVEF, N Number of patients.
../Output/11_LVEF_stats_All/TAB_02_NR_patients_LVEF_AZD9291_DOSE_CHEMO_SOC_SAFETY_population.txt
C:/PROJECTS/A24 - Tagrisso FLAURA/Work/05_LVEF/Scripts/SCRIPT_11_stats_All_LVEF.m
2017-Sep-13 15:50

Further analysis indicated no time dependent trend in the change in LVEF over the study days observed.

Rash and diarrhoea are the most common side effects observed with EGFR-TKIs due to wild-type EGFR activity.

Table 7: Summary of the number of first-line patients for each maximum rash CTCAE grade by first dose for osimertinib treated patients and SoC treated patients (safety population)

Dose	Total number of patients (N=615)	Number (%) of Patients			
		No event	Grade 1	Grade 2	Grade 3
80 mg	308	124 (40.26)	151 (49.03)	30 (9.74)	3 (0.97)
160 mg	30	4 (13.33)	13 (43.33)	12 (40.00)	1 (3.33)
SoC	277	60 (21.66)	109 (39.35)	89 (32.13)	19 (6.86)

N Number of patients, percentages of patients per group provided in parentheses. There are no patients with CTCAE Grade ≥4.
../Output/15_Rash_Diarrhoea_Severity_stats_firstline/TAB_01_summary_number_patients_RASH_GRADES_DOSE_SAFETY_population.txt
C:/PROJECTS/A24 - Tagrisso FLAURA/Work/04_Safety/Scripts/SCRIPT_15_Rash_Diarrhoea_Severity_stats_firstline.m
2017-Sep-15 10:52

Table 8: Summary of the number of first-line patients for each maximum diarrhoea CTCAE grade by first dose for osimertinib treated patients and SoC treated patients (safety population)

Dose	Total number of patients (N=615)	Number (%) of Patients					
		No event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
80 mg	308	129 (41.88)	132 (42.86)	41 (13.31)	6 (1.95)	0	0
160 mg	30	4 (13.33)	16 (53.33)	8 (26.67)	2 (6.67)	0	0
SoC	277	118 (42.60)	117 (42.24)	35 (12.64)	6 (2.17)	0	1 (0.36)

N Number of patients, percentages of patients per group provided in parentheses.
../Output/15_Rash_Diarrhoea_Severity_stats_firstline/TAB_02_summary_number_patients_DIAR_GRADES_DOSE_SAFETY_population.txt
C:/PROJECTS/A24 - Tagrisso FLAURA/Work/04_Safety/Scripts/SCRIPT_15_Rash_Diarrhoea_Severity_stats_firstline.m
2017-Sep-15 10:52

2.3.4. PK/PD modelling

Efficacy analysis

Although profound efficacy (BRS, DoR, BPCT and PFS) was observed upon treatment with osimertinib, the magnitude of this efficacy was generally not found to be related to drug exposure (osimertinib AUCss or AZ5104 AUCss) observed in FLAURA and AURA Phase 1 studies. This may possibly be explained by the limited AUCss range in the analysis data. For both osimertinib and AZ5104, the AUCss range is predominantly determined by patients receiving the 80 mg dose.

In order to further investigate the magnitude of efficacy in relation to drug exposure, a Cox-proportional hazard model has been used to assess the relative HRs between SoC treatment, and AUCss quartiles of osimertinib. A similar analysis for AZ5104 has been conducted for AZ5104, showing HRs range from 0.37 to 0.42 for the lower 3 AZ5104 AUCss quartiles and 0.64 for the highest AZ5104 AUCss quartile.

Table 9: Hazard ratios and 95% CI for each osimertinib AUCss quartile vs, SoC arm in FLAURA for the efficacy endpoint PFS

Comparison	HR (95% CI)	p-value
Osimertinib AUCss Q1 vs SoC	0.44 (0.32, 0.61)	p<0.001
Osimertinib AUCss Q2 vs SoC	0.44 (0.32, 0.62)	p<0.001
Osimertinib AUCss Q3 vs SoC	0.4 (0.29, 0.57)	p<0.001
Osimertinib AUCss Q4 vs SoC	0.53 (0.39, 0.73)	p<0.001

../Output/22_PFS_AUC_COX/TAB_02_HRs_95CI_AUCss_quartile_SOC_AZD9291.txt
C:/PROJECTS/AZ_A24_Tagrisso_FLAURA/Work/03_Efficacy/Scripts/SCRIPT_22_PFS_AUC_COX.m
2017-Sep-18 13:21

A Cox regression analysis was performed, considering these covariates one-by-one and the most important ones in combination with AUCss of both osimertinib and AZ5104. With respect to the pre-defined level for detection of statistical significance in the analysis plan of p<0.001, only baseline sum of longest tumour diameter was retained in the covariate model.

The relationship between PFS vs osimertinib Cssmax or Cssmin as a predictor variable was assessed and is shown in the below table.

Table 10: Protocol of Cox regressions for PFS (osimertinib)

Predictor	Coefficients	95% CI of coefficients	OFV (-2xLL)	Change in OFV (to nominal)*
No predictor (nominal)	-	-	1878.5	0
log10(osimertinib AUCss)	0.458	[-0.217 1.13]	1876.7	-1.73
log10(osimertinib Cmaxss)	0.545	[-0.146 1.24]	1876.1	-2.35
log10(osimertinib Cminss)	0.255	[-0.374 0.884]	1877.8	-0.623

* For a single tested covariate, a drop in objective function value of >=10.83 indicates a statistically significant effect with a p-value of p<=0.001.

OFV: Objective function value; LL: log-likelihood CI: confidence interval

Parameter estimates, confidence intervals, and the change in objective function value are shown with 3 significant digits.

Objective function value was shown with 5 significant digits.

../Output/05_PFS_BaseModels_Cmax/TAB_01_COX_protocol_BaseModel.txt

C:/PROJECTS/A52 - Tagrisso Questions/WorkMikael/Scripts/SCRIPT_05_PFS_BaseModels_Cmax.m

2018-Jan-29 12:01

Overall, this analysis indicates that there is no evidence that increasing exposure (AUCss) of osimertinib and AZ5104 is associated with increased efficacy (PFS, BPCT, DoR and BRS).

Safety analysis

A model based analysis was conducted to assess the potential exposure dependency of LVEF events and a potential influence of covariates. This analysis did not support an AUC dependency of LVEF events on the pre-defined significance level (p<0.001). The only identified statistically significant covariate was baseline LVEF. The models using log-transformed osimertinib or AZ5104 AUCss with baseline LVEF as covariate were chosen as final models. These models indicated an exposure dependency of LVEF events even if not meeting the pre-defined level of significance.

Table 11: Final models

Model	Intercept (95% CI)	p-value	Slope on AUC_{ss} (95% CI)	p-value	Baseline LVEF on intercept (95% CI)	p-value
Final model osimertinib	-6.36 (-13.6,1.01)	0.0901	0.921 (0.209,1.61)	0.0116	-0.087 (-0.134,-0.0419)	0.000155
Final model AZ5104	-4.38 (-9.88,1.07)	0.115	0.927 (0.292,1.56)	0.00431	-0.0867 (-0.134,-0.0412)	0.000181

CI Confidence interval.
../Output/22b_finalModelTable/TAB_01_finalModel.txt
SCRIPT_22b_finalModelTable.R
2017-09-13 15:52:38

Since the graphical analysis suggested a relationship between osimertinib exposure and ILD events, model based analysis was conducted. This analysis showed that increasing osimertinib (or AZ5104) exposure increases the probability to develop ILD-like events. However, this relationship was not statistically significant (according to the pre-defined criterion; p<0.001). None of the additional covariates (age, weight, BMI, gender, WHO performance status, history of hypertension, line of therapy, nicotine use and statin use) showed any statistically significant effect on the occurrence of ILD events.

The final models included AUCss (for osimertinib or AZ5104), Japanese, and Asian non-Japanese as predictive variables. Visual predictive checks suggested that both final models (osimertinib and AZ5104) are able to well describe the observed occurrence of ILD across various subpopulations.

The parameter estimates for the final model of the relationship between osimertinib AUCss or Cssmax and ILD are shown in the table below.

Table 12: Comparison of the final model with osimertinib AUCss and Cmaxss as predictor variables for ILD events

Model	Intercept (95% CI)	Slope parameter on exposure (log(AUCss+1) or log(Cmaxss+1)) (95% CI)	Japanese (95% CI)*	Asian, non-Japanese (95% CI)*	Change in OBJ**	Required change in OBJ for p < 0.001***
1 AUCss	-9.350 (-13.800,-4.760)	0.628 (0.149,1.090)	1.140 (0.510,1.800)	-0.567 (-1.380,0.206)	-34.300	16.300
2 Cmaxss	-7.860 (-11.100,-4.600)	0.698 (0.198,1.190)	1.140 (0.512,1.800)	-0.555 (-1.370,0.219)	-35.100	16.300
3 Cminss	-6.930 (-9.810,-4.030)	0.576 (0.113,1.020)	1.130 (0.499,1.790)	-0.571 (-1.390,0.202)	-33.600	16.300

*As covariate on the intercept parameter.

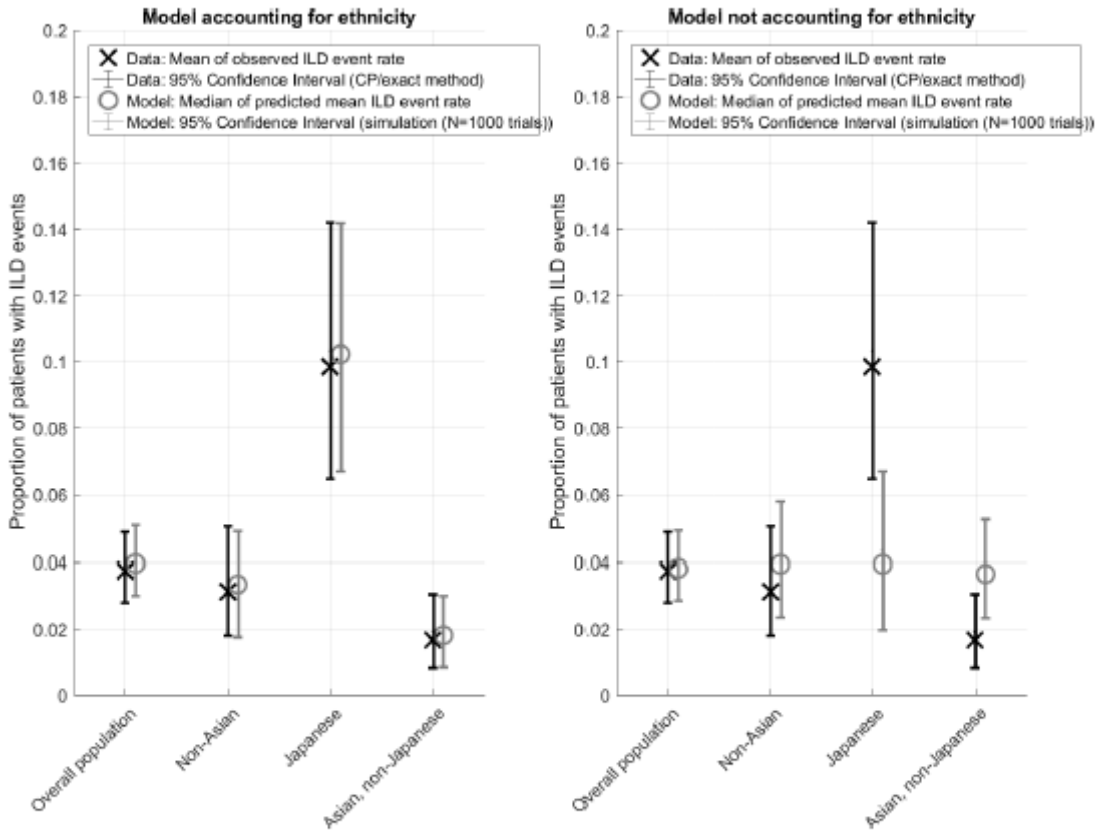
**OBJ=objective function value (-2xLL). LL referred to the penalized fitted log-likelihood function (Firth). Change in OBJ compares the restricted model (model with intercept only) to the full model (model with intercept and variables for exposure and ethnicity covariates).

***Referring to the likelihood ratio test.

../Output/02_ILD_final_model_AZD9291_Cmax/TAB_01_comparison_Osimertinib.txt

SCRIPT_02_final_model_AZD9291_Cmax.R

2018-01-29 11:37:2



Black crosses: The observed proportion of patients with ILD events in data from AURA, AURA2, AURA3, and FLAURA. Black error bars: 95% CI for the observed proportion of ILD events (Clopper-Pearson/exact method). Grey circles: Model estimated probability of ILD events (1000 simulated trial populations). Grey error bars: 95% CI of the model estimated probability of ILD events.
../Output/27_VPCs_Panels_AZD9291/FIG_01_Panel_VPCs_AZD9291.png
C:/PROJECTS/A24 - Tagrisso FLAURA/Work/04_Safety/Scripts/SCRIPT_27_VPCs_Panels_AZD9291.m
2017-Sep-15 10:53

Figure 14: Visual predictive checks for the frequency of ILD events in different populations – for the (osimertinib) final model accounting for ethnicity differences (left), and for the (osimertinib) base model not accounting for ethnicity differences (right)

The incidence and severity of rash appears to increase with increasing dose (and exposure) of osimertinib.

Similar to the observation for rash, the incidence and severity of diarrhoea appear to increase with increasing dose (and exposure) of osimertinib. In the group of first-line 160 mg osimertinib treated patients 86.7% of the patients experienced diarrhoea as compared to 58.1% in the first-line 80 mg osimertinib treated patients.

The relationship between corrected QT interval (QTc) and plasma concentrations upon multiple dosing was assessed via modelling intensive digital electrocardiogram and PK data generated in AURA2 and was included in the previous submissions.

2.3.5. Discussion on clinical pharmacology

The population pharmacokinetic model describes the concentration-time course profiles of osimertinib and its metabolite (AZ5104) orally administered at 80 mg. The same structural pharmacokinetic model as in the previous clinical trials has been proposed in order to characterize the experimental observations from all available clinical trial. Linear absorption, distribution and elimination processes were assumed in a one-compartment model for the parent and metabolite analyte. Inter-individual

variability was incorporated in all PK parameters (ka, V/F, CL/F, CLM/F and VM/F). Several covariates were included in CL/F, CLM/F, V/F, VM/F with the aim of partially explaining the inter-individual variability on osimertinib's PK. Model evaluation was performed through prediction-corrected VPC, showing the population PK model developed is able to reproduce in general the observations after the administration of osimertinib at 80 mg. All parameters in the model were adequately qualified as indicated by the 95% confidence interval from the non-parametric bootstrap. All experimental/predicted ratios obtained from the osimertinib PK parameters (AUCss, Cminss, and Cmaxss) were within the ±20% range.

Then, a dose-exposure response analysis on efficacy and several safety endpoints (LVEF and ILD) have been performed investigating the relationship between osimertinib exposure and PFS or the incidence of safety events for osimertinib treated patients. Once the results from the exposure-response analysis were obtained, AUCss was selected as the most relevant PK variable. A covariate analysis was performed on each exposure-safety model in order to better explain individual differences on safety based on the studied population.

Data management, model development, and model evaluation/qualification procedures seem adequate and acceptable. Condition number of 274.8 indicates no over-parametrization and model stability and the shrinkage values (ETA- and EPS-shrinkage) were low, except for ka and VM/F (38.6 and 38.1%, respectively).

Population PK model

-Line of therapy was not considered as a covariate on absorption rate or bioavailability. During the absorption phase the median observation in 1st line patients is below the 95% confidence interval of the model-predicted median, indicating that the model slightly overpredicts the central tendency. Due to the sparse PK sampling in FLAURA, the absorption profile could not be fully characterized in 1st line patients. The observed prediction bias is acceptable considering the low regulatory impact of the modelling results.

Simulation of the impact of covariate differences on osimertinib exposure

- The impact of the identified covariates <u>in typical patients</u> is too small to be clinically relevant. This supports that the initial fixed dose approach is appropriate. However, due to large, unexplained variability in osimertinib PK, a considerable proportion of patients weighing 43 kg, and even more of the "worst-case" patient group (with baseline albumin equal to 29.3 g/L), will have exposures above the suggested target range (approximately Cmaxss and AUCss of 59% and 49%, respectively), defined by the applicant as exposure between the mean expected exposure at 40 and 160 mg. Patients with low body weight (<50 kg) may be at increased risk of developing adverse events of Grade 3 or higher. Close monitoring is therefore recommended in these patients

Special populations

-Studies investigating severe renal impaired population and P-gp interaction study are ongoing. Therefore, no specific recommendations can be made on these special populations until results are available.

-No specific dose recommendations can be derived on moderate and severe hepatic population based on the low number of individuals included in the dataset (moderate=8 individuals, severe=0 individuals).

No interaction studies have been submitted which is acceptable as osimertinib exposure is consistent between 1st and ≥2nd line of therapy. The results of the previous interaction studies are applicable for all lines of therapy.

Exposure-safety relationship

-The exposure-safety model that accounts for the relationship between AUC-LVEF levels is able to characterize the proportion of patients with LVEF events at 80mg, but no information is provided on 40 and 160 mg. Additionally, the 95% CI of the intercept includes the zero, which indicates lack of significance. Therefore, the model should not be used for simulation or extrapolation purposes.

2.3.6. Conclusions on clinical pharmacology

The population PK model is in general adequate.

Based on results from osimertinib and metabolite (AZ5104) exposure (PK) and efficacy/safety relationship from studies AURA1, AURA2, AURA3, and FLAURA, the recommended dose of 80 mg is acceptable. In terms of efficacy, no exposure-efficacy relationship could be detected, which reduces the impact of model-based predictions in future assessments (dose selections, special populations). An evaluation of other exposure metrics did not increase the prediction of the model in regards to the efficacy endpoints selected.

A model-based assessment was performed to detect any relationship between exposure and incidence of LVEF events, but failed to achieve the significance criterion. The Applicant, however, applied the model in order to simulate different dose regimens and scenarios since the significance of the AUCss as a predictor was borderline non-significant. This approach is fully endorsed as it provides more accurate conclusions and allows for a model-informed drug development process. The incidence of ILD, rash and diarrhoea is low and, in general, comparable to EGFR-TKI SoC treated patients. For ILD events, Japanese and Asian non-Japanese populations were included as significant covariates in the model, and differences between those sub-groups of populations might be explained due to constitutional and environmental factors. Additionally, the more intensive monitoring for ILD and ILD-like incidences in Japanese population could have also contributed to identify more incidences of ILD events.

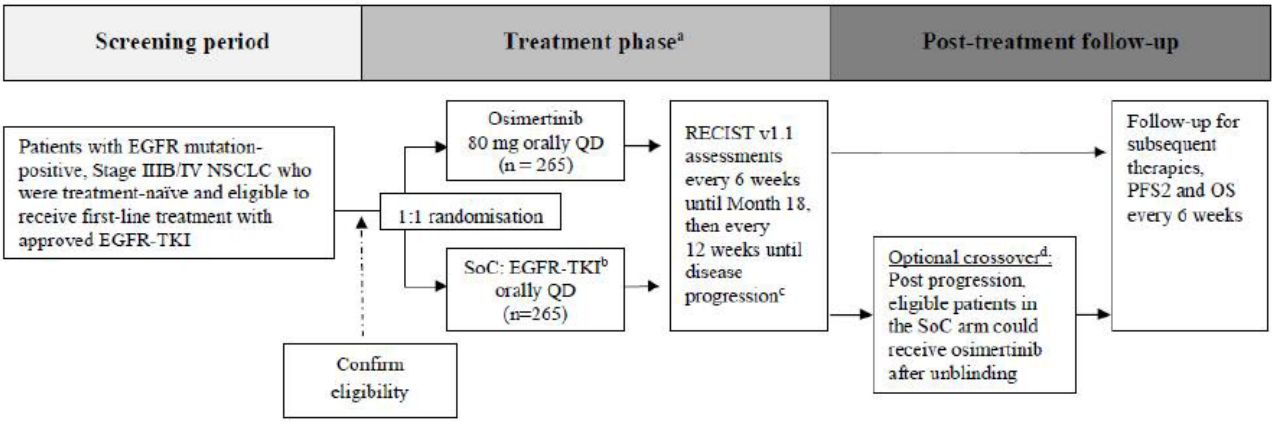
2.4. Clinical efficacy

2.4.1. Dose response study(ies)

No dose response studies specifically in 1st line NSCLC patients were conducted. Using the same dose as the registered dose in ≥2nd line patients is reasonable.

2.4.2. Main study

A Phase III, Double-blind, Randomised Study to Assess the Efficacy and Safety of AZD9291 versus a Standard of Care Epidermal Growth Factor Receptor-Tyrosine Kinase Inhibitor as First-line Treatment in Patients with Epidermal Growth Factor Receptor Mutation-positive, Locally-advanced or Metastatic Non-small-cell Lung Cancer (FLAURA)



EGFR-TKI = epidermal growth factor receptor-tyrosine kinase inhibitor; NSCLC = non-small cell lung cancer; OS = overall survival; PFS2 = second progression-free survival; QD = once daily; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors version 1.1; SoC = standard of care.

[a] Patients received randomised treatment until objective disease progression or as long as they were continuing to show clinical benefit, as judged by the Investigator.

[b] Either gefitinib (250 mg) or erlotinib (150 mg).

[c] Patients who discontinued treatment prior to disease progression continued had RECIST v1.1 assessments until objective progression. Patients who continued treatment after objective progression due to clinical benefit were to be followed as per standard practice post-progression.

[d] Patients in the SoC EGFR-TKI arm who had objective disease progression according to RECIST v1.1 based on Investigator assessment, that was confirmed by independent central imaging review, and who had tumours positive for T790M mutation following progression, after being unblinded were given the opportunity to crossover and begin treatment with osimertinib 80 mg, once daily.

Figure 15: **Flow chart of study design.**

Efficacy and safety data from FLAURA presented in this submission are from the 556 patients randomised globally. As per protocol amendment 1, a China extension cohort of 136 patients was also enrolled in FLAURA to meet China regulatory requirements: this cohort included 19 patients randomised in the global study prior to the end of global recruitment as well as 117 additional patients to be recruited as part of the China extension cohort. Data for the 19 patients randomised in the global study prior to the end of global recruitment are included in the global analysis set. Data for the entire 136- patient China extension cohort will be analysed separately once the PFS data for the China extension cohort has reached similar maturity to that used in the primary analysis of PFS based on Investigator assessment in the globally-recruited patients and will be submitted to the Chinese regulatory authority only.

Methods

Study participants

The key inclusion and exclusion criteria are:

Inclusion criteria

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

1. Informed consent prior to any study-specific procedures, sampling, and analyses;

2. Male or female, aged at least 18 years. Patients from Japan aged at least 20 years;

3. Pathologically-confirmed adenocarcinoma of the lung (eg, this could occur as systemic recurrence after prior surgery for early stage disease or patients could be newly diagnosed with Stage IIIB/IV disease). Patients with mixed histology were eligible if adenocarcinoma was the predominant histology;

4. Locally-advanced or metastatic NSCLC, not amenable to curative surgery or radiotherapy;

5. The tumour harboured 1 of the 2 common EGFR mutations known to be associated with EGFR-TKI sensitivity (Ex19del, L858R), either alone or in combination with other EGFR mutations, as assessed by a CLIA-certified (US sites) or an accredited (outside the US) local laboratory or by central testing;

6. Mandatory provision of an unstained, archived tumour tissue sample in a quantity sufficient to allow for central analysis of EGFR mutation status;

7. Patients had to be treatment-naïve for locally-advanced or metastatic NSCLC and eligible to receive first-line treatment with gefitinib or erlotinib as selected by the participating centre. Prior adjuvant and neo-adjuvant therapy was permitted (chemotherapy, radiotherapy, investigational agents) provided all other entry criteria were satisfied;

8. World Health Organization PS of 0 to 1, with no clinically significant deterioration over the previous 2 weeks and a minimum life expectancy of 12 weeks;

9. At least 1 lesion, not previously irradiated and not chosen for biopsy during the study screening period, that could be accurately measured at baseline as ≥10 mm in the longest diameter (except lymph nodes, which had to have a short axis of ≥15 mm) with computerised tomography (CT) or magnetic resonance imaging (MRI), and which was suitable for accurate repeated measurements. If only 1 measurable lesion existed, it was acceptable to be used as a target lesion (TL) as long as it had not been previously irradiated and baseline tumour assessment scans were done at least 14 days after the screening biopsy was performed;

10. Female patients were to be using adequate contraceptive measures, were not to breast feed, and had to have a negative pregnancy test prior to first dose of study drug; or female patients had to have an evidence of non-child-bearing potential;

11. Male patients were to be willing to use barrier contraception, ie, condoms;

12. For inclusion in the optional genetics research study, patients had to provide informed consent for genetic research.

5.3.2 Exclusion criteria

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

1. Involvement in the planning and/or conduct of the study (applied to both AstraZeneca staff and/or staff at the study site);

2. Treatment with any of the following:

- Prior treatment with any systemic anti-cancer therapy for locally advanced/ metastatic NSCLC including chemotherapy, biologic therapy, immunotherapy or any investigational drug;

- Prior treatment with an EGFR-TKI;

- Major surgery (excluding placement of vascular access) within 4 weeks of the first dose of study drug;

- Radiotherapy treatment to more than 30% of the bone marrow or with a wide field of radiation within 4 weeks of the first dose of study drug;

- Patients who were currently receiving (or unable to stop using at least 1 week prior to receiving the first dose of study drug) medications or herbal supplements known to be potent inducers of cytochrome P450 (CYP) 3A4 (see CSP Amendment 2 Appendix B in Appendix 12.1.1);

- Alternative anti-cancer treatment;

- Treatment with an investigational drug within 5 half-lives of the compound or any of its related material, if known;

3. Any concurrent and/or other active malignancy that had required treatment within 2 years of first dose of study drug;

4. Any unresolved toxicities from prior systemic therapy (eg, adjuvant chemotherapy) greater than CTCAE grade 1 at the time of starting study drug, except for alopecia and grade 2, prior-chemotherapy-induced neuropathy;

5. Spinal cord compression, symptomatic and unstable brain metastases (BM) except for those patients who had completed definitive therapy, were not on steroids, and had a stable neurological status for at least 2 weeks after completion of the definitive therapy and steroids;

6. Any evidence of severe or uncontrolled systemic disease. Screening for chronic conditions was not required;

7. Refractory nausea and vomiting, chronic gastrointestinal (GI) diseases, inability to swallow the formulated product or previous significant bowel resection that would preclude adequate absorption of osimertinib;

8. Any of the following cardiac criteria:

- Mean resting corrected QT interval (QTc) >470 milliseconds (msec);

- Any clinically important abnormalities in rhythm, conduction or morphology of resting ECG;

- Any factors that increased the risk of QTc prolongation or risk of arrhythmic events;

9. Past medical history of interstitial lung disease (ILD), drug-induced ILD, radiation pneumonitis which required steroid treatment or any evidence of clinically-active ILD;

10. Inadequate bone marrow reserve or organ function;

11. Women who were breast feeding;

12. History of hypersensitivity to active or inactive excipients of osimertinib or drugs with a similar chemical structure or class to osimertinib;

13. Judgment by the Investigator that the patient should not participate in the study if the patient was unlikely to comply with study procedures, restrictions, and requirements.

Treatments

After randomization, the investigational products osimertinib 80 mg or the SoC EGFR-TKI (either gefitinib [250 mg] or erlotinib [150 mg]) were administered orally once daily.

Patients were to continue their randomised treatment until disease progression (RECIST v1.1), or until a treatment discontinuation criterion was met. However, patients could continue to receive their randomised treatment beyond RECIST v1.1-defined progression if the Investigator judged the patient was continuing to show clinical benefit on treatment. As per protocol Amendment 1 (13-Apr-2015) after Investigator-assessed objective disease progression, patients randomised to the SoC arm had the

option to crossover to treatment with open-label osimertinib provided they met predefined criteria (confirmation of disease progression by BICR prior to unblinding; no subsequent intervention therapy following discontinuation of randomised treatment; and tissue or plasma confirmation that the tumour was T790M mutation-positive after disease progression).

Objectives

Primary objective:

To assess the efficacy of single-agent osimertinib compared with SoC EGFR-TKI therapy as measured by PFS, by investigator.

Key secondary objectives:

To assess the efficacy of osimertinib compared with SoC EGFR-TKI therapy by assessment of PFS in patients with EGFR Ex19del or L858R mutations, and with EGFRm (Ex19del or L858R) detectable in plasma-derived ctDNA; to further assess the efficacy of osimertinib compared with SoC EGFR-TKI therapy in terms of ORR, DoR, DCR, depth of response, and OS; to characterise the pharmacokinetics (PK) of osimertinib and its metabolites; and to assess the impact of osimertinib compared to SoC on patient-reported outcomes.

To compare the efficacy of osimertinib with SoC EGFR-TKIs based on presence or absence of CNS metastases at study entry (CNS MTS subgroup analysis)

The safety objective was to assess the safety and tolerability profile of osimertinib compared with SoC EGFR-TKI therapy.

Key exploratory objectives:

To further assess the efficacy of osimertinib compared to SoC EGFR-TKI on post-progression outcomes; to assess the agreement between local and central EGFR tumour tissue testing results; and to compare the baseline tumour EGFR mutation status in all screened patients with evaluable results from baseline plasma in all screened patients. Furthermore, CNS efficacy analyses were pre-specified in the SAP finalised prior to database lock for the primary PFS analysis.

Outcomes/endpoints

The primary efficacy endpoint was PFS based on Investigator assessment of radiological data with a sensitivity analysis based on BICR assessment using RECIST v1.1.

The main secondary endpoints were:

- overall survival compared to SoC EGFR-TKI therapy,
- ORR, DoR, DCR, and depth of response compared to SoC EGFR-TKI therapy. All according to RECIST v1.1 using Investigator assessments
- To compare the efficacy of osimertinib with SoC EGFR-TKIs based on presence or absence of CNS metastases at study entry (CNS MTS subgroup analysis). Systemic PFS by Investigator assessment; reason for systemic progression (TL, NTL [CNS NTL or non-CNS NTL], NL [new CNS lesion or no new CNS lesion]); reason for CNS progression, systemic ORR by Investigator assessment; and systemic DoR and onset of response by Investigator assessment.

- Patient reported outcomes, as measured via the EORTC QLQ-C30 and the complementary lung cancer questionnaire EORTC QLQ-LC13.

The main exploratory endpoints were:

- efficacy of osimertinib compared to SoC EGFR-TKI post-progression as measured by PFS2 and time to subsequent treatments, including time from randomisation to discontinuation of any EGFR-TKI or death.
- Tumour and ctDNA were gathered to explore biomarker effects on efficacy of both osimertinib and SoC, these data will be reported at a later time.

Sample size

Per protocol, approximately 530 patients (265 per treatment arm) were to be randomised globally. In order to randomise 530 patients, it is estimated that 980 EGFRm+ patients will need to be screened.

The DCO1 for the primary analysis of PFS was pre-specified to occur after approximately 359 PFS events had occurred in the 530 patients randomised globally, representing approximately 65% maturity.

If the true PFS HR for the comparison of osimertinib and SoC EGFR-TKI is 0.71, 359 PFS events would provide 90% power to demonstrate a statistically significant difference in PFS at a 5% two-sided significance level, translating into an approximate improvement in median PFS from 10 months to 14.1 months assuming exponential data distribution and proportional hazards. The minimum critical HR is 0.81 (e.g. 10 to 12 months).

For the key secondary endpoint of PFS in patients with T790M+ NSCLC confirmed using a highly sensitive assay, there will be approximately 72% power to detect a PFS HR=0.55 (i.e. 10 to 18 months), assuming a prevalence of 20%.

For the OS analysis, there will be approximately 72% power to demonstrate a HR <0.75 (i.e. 25 to 33.3 months) with two-sided 5% significance level. If the 4 month improvement as detailed for PFS is maintained for OS, then there will be approximately 27% power to demonstrate a HR of 0.86 (median OS of 25 months for SOC and 29 months for AZD9291) with two-sided 5% significance level.

Following randomisation of 530 patients in the global portion of the study, additional mainland China patients (until approximately 120 in total) will be randomized to facilitate the China-only analysis dataset.

Randomisation

Eligible patients were centrally randomised in a 1:1 ratio, using the IVRS/IWRS, to receive either osimertinib 80 mg orally once daily or the EGFR-TKI chosen by the site based on site preference and marketing authorisation in the particular country (ie, gefitinib 250 mg orally once daily or erlotinib 150 mg orally once daily). The actual EGFR-TKI had to be selected at a site/country level according to the country's marketing authorisation prior to the site initiation.

Patients were stratified at randomisation based on EGFR mutation status (Ex19del or L858R) and ethnicity (Asian or Non-Asian).

Blinding (masking)

This was a double-dummy study wherein each patient received either the active AZD9291 plus comparator-matching placebo (SoC) or the active comparator (SoC) plus AZD9291-matching placebo. The active and placebo tablets were identical and presented in the same packaging to ensure blinding of the medication. The treatment code could be broken if the appropriate management of the patient required knowledge of the treatment randomisation for medical emergencies or for treatment decisions (eg, cross-over). Study sites were required to select either gefitinib or erlotinib as the sole comparator prior to site initiation, except for the US where all sites used erlotinib (the most commonly used EGFR-TKI for first-line EGFRm NSCLC in the US at the time of study start, in 2014).

The primary efficacy endpoint of the study was PFS based on Investigator assessment according to RECIST v1.1, with a sensitivity analysis based on blinded independent central review (BICR) of the imaging data.

Statistical methods

The primary efficacy endpoint was PFS based on Investigator assessment according to RECIST v1.1. One analysis of the primary endpoint of PFS was planned. The DCO for the primary analysis of PFS was pre-specified to occur after approximately 359 PFS events had occurred in the planned 530 patients to be randomised globally, representing approximately 65% maturity. Progression-free survival was established from programmatically calculated response based on the Investigator assessment for patients in the full analysis set (FAS) using a log-rank test stratified by mutation type (Ex19del or L858R) and ethnicity (Asian vs. Non- Asian) to generate p-value and using the Breslow approach for handling ties. The HR and its confidence interval (CI) were obtained directly from the U and V statistics from a stratified log-rank test.

A sensitivity analysis of PFS based on assessment of response by BICR according to RECIST v1.1 was also conducted. Other PFS sensitivity analyses included the possibility of bias in assessment and measurements by Investigators (ascertainment bias); the possible bias in evaluation-time if scans were not performed at the protocol-scheduled time points (evaluation-time bias); attrition bias; and a post-hoc analysis to assess the potential impact of change in scanning schedule at Month 18 falling close to the median PFS. A posthoc sensitivity analysis was added to assess the impact of change in scanning schedule at Month 18 falling close to the median PFS. Sensitivity analyses were to be performed as per the primary reporting of PFS.

In addition to the primary analysis of PFS, subgroup analyses were conducted by comparing PFS between treatment arms using a Cox-proportional hazards model in the following subgroups: gender (male/female); ethnicity (Asian/Non-Asian); age at screening (<65 years/≥65 years); CNS metastases (CNS MTS) status at study entry (Yes/No); smoking history (Yes/No); baseline WHO performance status (0 or 1); pre-treatment T790M status (positive/negative); EGFR mutation (Ex19del/L858R); EGFR mutation-positive by ctDNA (Yes/No); and centrally-confirmed EGFR mutation-positive (Yes/No).

The analyses of the secondary endpoints of ORR, DoR, DCR, and depth of response also occurred at the time of the primary PFS analysis.

Two OS analyses are planned: an initial interim analysis at the time of the primary PFS analysis and a final analysis when the OS data are approximately 60% mature (approximately 318 deaths). In addition, an analysis of PROs was conducted.

An analysis to establish any efficacy benefit of osimertinib on the CNS (CNS BICR) was also added to the SAP (Amendment to the SAP dated 16 December 2016) and occurred at the time of the primary analysis of PFS. The following variables were evaluated by CNS BICR on the CNS full analysis set

(cFAS) and CNS evaluable-for-response (cEFR) analysis sets: CNS PFS on the cFAS; CNS PFS by number of CNS lesions at baseline on cFAS; CNS ORR on the cFAS and cEFR; CNS DoR and onset of response on the cFAS and cEFR; CNS DCR on the cFAS and cEFR; and CNS ORR by prior brain radiotherapy on cFAS.

A hierarchical procedure was used to adjust for multiplicity in testing the key endpoints of PFS, OS, and CNS PFS. To provide strong control of the Type I error rate (5% two-sided), the primary endpoint of PFS, and the endpoints of OS and CNS PFS were tested in this sequential order. If any previous analysis in the sequence was not statistically significant, the alpha was not to be transferred to subsequent analyses. If the OS analysis was statistically significant at the time of the PFS analysis or the final OS analysis, then the significance testing of CNS PFS was to be performed at the full alpha (5% two-sided) significance level.

If the OS analysis was not statistically significant at the time of the PFS analysis or the final OS analysis, then the significance testing of CNS PFS was not to be performed. Only 1 CNS BICR statistical analysis was to be performed: either at the time of the primary PFS analysis or at the later OS analysis. A 2-sided 5% alpha was used in all testing, except for the OS endpoint. Since 2 analyses of OS are planned, the Lan DeMets approach that approximates the O'Brien and Fleming spending function was used to maintain an overall 2-sided 5% Type I error across the 2 planned OS analyses. Any non-statistically significant OS analysis at the time of the primary PFS analysis did not preclude further testing of OS.

The China extension cohort enrolled 136 patients: 19 patients from China who were randomised in the global study prior to the end of global recruitment and an additional 117 patients recruited in China specifically for the China extension cohort. Data for the 19 patients randomised in the global study prior to the end of global recruitment are included in the global analysis set presented in this report. Data for the entire 136-patient China extension cohort (ie, the 19 China patients in the global study and the additional 117 China extension cohort patients) will be analysed separately and submitted to the Chinese regulatory authority only once the PFS data for the entire China extension cohort has reached similar maturity to that used in the primary analysis of PFS based on Investigator assessment in the globally-recruited patients (ie, approximately 65%). Thus, data from the 19 Chinese patients randomised prior to the end of global enrolment will be part of both the main global analysis and the China extension cohort analysis.

Results

Participant flow

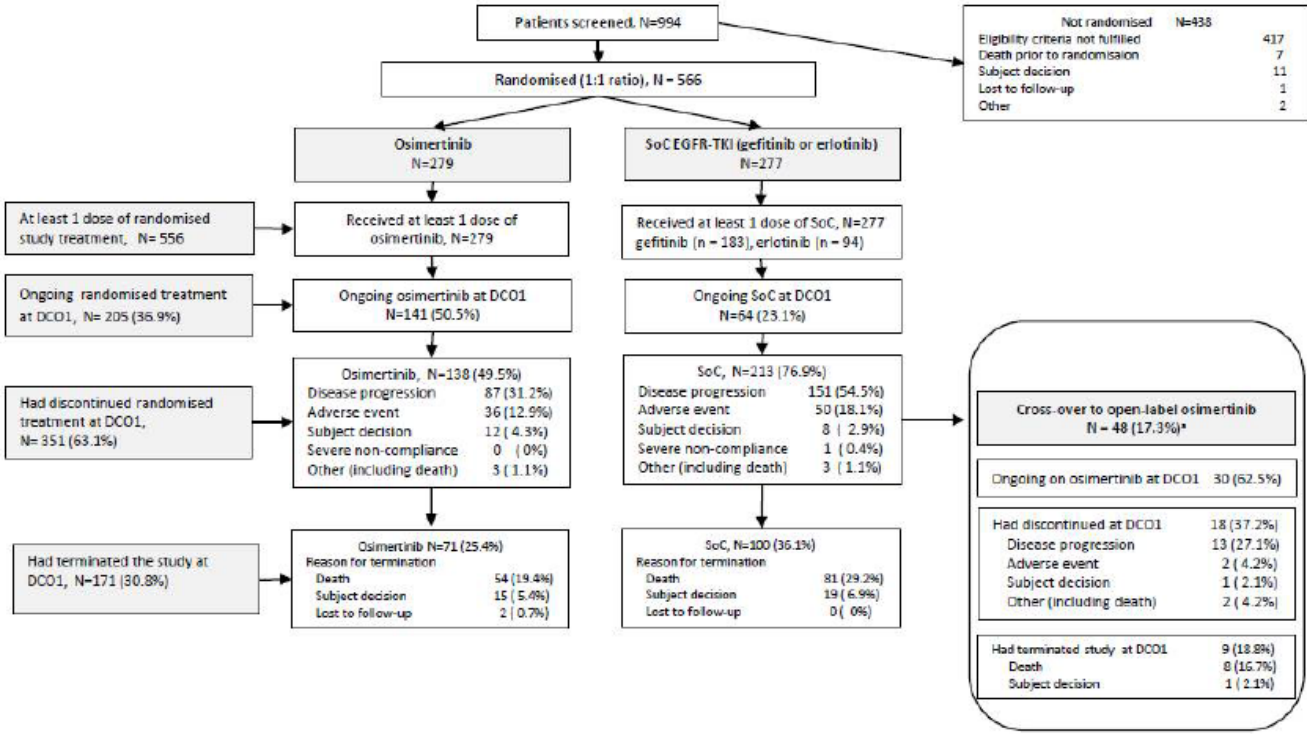


Figure 16: **Disposition of patients**

Recruitment

A total of 556 patients were randomised to treatment at 132 study centres in 29 countries (global recruitment). An additional 17 centres in China enrolled patients into the China extension cohort only.

The first patient was randomised in the global study and dosed on 19 February 2015. The last patient's first dose was administered on 11 March 2016.

Conduct of the study

Protocol amendments:

The study protocol was amended two times. In addition to minor clarifications, the main amendments are described below.

Amendment 1 (13 Apr 2015) was introduced due to advice from the FDA, regulatory requirements from Chinese authorities and emerging data from use of osimertinib after treatment with other EGFR-TKIs. The main changes were:

- Addition of option to continue recruitment in mainland China, following achievement of global recruitment target of 650
- Allow post-progression cross-over for patients receiving SoC to open-label osimertinib provided specific criteria are satisfied.
- Removal of efficacy interim analysis

Amendment 2 (24 Sep 2015) was introduced due to data from the phase I trial. The main changes were:

- Sample size has been reduced from 650 to 530 patients
- The number of patients in each treatment group has been updated based on the change in the sample size
- Disease Control Rate (DCR) has been added to the list of RECIST-based endpoints for completeness.

Protocol deviations

The most frequent of the important protocol deviations in both treatment arms was the nonadherence to a protocol-required procedure, including, in decreasing order of frequency:

- Missing RECIST assessments for efficacy: 67 (12.1%) patients overall (osimertinib: 41 [14.7%]; SoC: 26 [9.4%]). This was the most frequently reported protocol deviation in both treatment arms. None of the missing scans were baseline scans and the majority were single missing assessments.
- RECIST scan performed outside the visit window on more than 2 occasions: 27 (4.9%) patients overall (osimertinib: 18 [6.5%]; SoC: 9 [3.2%])
- Baseline tumour RECIST assessments performed more than 28 days before randomisation: 15 (2.7%) patients overall (osimertinib: 7 [2.5%]; SoC: 8 [2.9%])
- Tumour assessment methods and procedures not compliant with protocol or RECIST v1.1: 14 (2.5%) patients overall (osimertinib: 7 [2.5%]; SoC: 7 [2.5%])
- Administration of prohibited other anti-cancer agents, investigational products or radiotherapy (for reasons other than bone metastases) while the patient was on treatment: 2 (0.4%) patients overall, 1 patient in each arm

The second most frequent important protocol deviation category included patients who did not meet eligibility criteria, including:

- No confirmation that the tumour harboured an EGFR sensitising mutation (Ex19del or L858R): 7 (1.3%) patients (osimertinib: 3 [1.1%]; SoC: 4 [1.4%]).
    - The investigators' interpretation of inclusion criterion 5 (Section 5.3.1) led them to classify these 7 patients as not meeting the criterion. However, based on review of the local and/or central test results, all 7 patients did have tumours harbouring EGFR sensitising mutations. The nature of the deviation was that either the mutation analysis was performed on a biopsy taken from an early disease stage sample (5 patients) or was performed in a local laboratory at a date preceding the laboratory accreditation (2 patients)
- No pathological confirmation that the patient had an adenocarcinoma of the lung: 5 (0.9%) patients (osimertinib: 2 [0.7%]; SoC: 3 [1.1%])
- Patient was not treatment-naïve for locally-advanced or metastatic NSCLC: 3 (0.5%) patients overall (osimertinib: 2 [0.7%]; SoC: 1 [0.4%])
- No lesions not previously irradiated or chosen for biopsy during the screening period that could be accurately measured at baseline as being 10 mm in longest diameter by CT or MRI (except lymph nodes, which had to have a short axis of 15 mm) and were suitable for accurate

repeated measurements: 2 (0.4%) patients, both on osimertinib: 1 patient had no measurable lesion and 1 patient provided measurements, but from a previously irradiated lesion

- During data review, it was discovered that 1 patient in each treatment arm had a mean (from triplicate measurements) QTcF value above 470 msec at study entry. In both patients, a mean QTcF value of 483.3 msec was recorded at screening.

Baseline data

Demographic characteristics

The study enrolled the population intended by protocol. Demographic characteristics were generally well balanced between the treatment arms.

Table 13: **Demographic characteristics (full analysis set).**

Demographic characteristic	Osimertinib (N=279)	SoC (N=277)	Total (N=556)
Age (years)			
Mean	62.7	63.3	63.0
Standard deviation	10.70	10.90	10.79
Median	64.0	64.0	64.0
Min	26	35	26
Max	85	93	93
Age group (years), n (%)			
<50	32 (11.5)	37 (13.4)	69 (12.4)
≥50-<65	121 (43.4)	108 (39.0)	229 (41.2)
≥65-<75	90 (32.3)	89 (32.1)	179 (32.2)
≥75	36 (12.9)	43 (15.5)	79 (14.2)
Sex n (%)			
Male	101 (36.2)	105 (37.9)	206 (37.1)
Female	178 (63.8)	172 (62.1)	350 (62.9)
Race n (%)			
Asian	174 (62.4)	173 (62.5)	347 (62.4)
Black or African American	2 (0.7)	2 (0.7)	4 (0.7)
White	101 (36.2)	100 (36.1)	201 (36.2)
American Indian or Alaska Native	1 (0.4)	1 (0.4)	2 (0.4)
Missing	1 (0.4)	1 (0.4)	2 (0.4)
Ethnic group n (%)			
Asian (other than Chinese and Japanese)	77 (27.6)	94 (33.9)	171 (30.8)
Chinese	32 (11.5)	24 (8.7)	56 (10.1)
Japanese	65 (23.3)	55 (19.9)	120 (21.6)
Other	103 (36.9)	104 (37.5)	207 (37.2)
Missing	2 (0.7)	0	2 (0.4)
Smoking status			
Never	182 (65.2)	175 (63.2)	357 (64.2)
Current	8 (2.9)	9 (3.2)	17 (3.1)
Former	89 (31.9)	93 (33.6)	182 (32.7)

Percentages are based on the FAS.

Baseline disease characteristics

All randomized patients, except for 1 patient in the osimertinib arm with missing data, had locally advanced NSCLC that was not amenable to curative surgery or radiotherapy (29 [5.2%] patients overall) or metastatic NSCLC (526 [94.6%] patients overall).

Per protocol, all patients were to receive study treatment as first-line therapy. However, 3 (0.5%) patients (osimertinib: 2 [0.7%]; SoC: 1 [0.4%]), all enrolled at the same US study site, were not treatment-naïve for locally-advanced or metastatic NSCLC at study entry, an important protocol deviation. Baseline disease characteristics were generally well balanced between the 2 treatment arms.

Table 14: **Disease characteristics at baseline (full analysis set).**

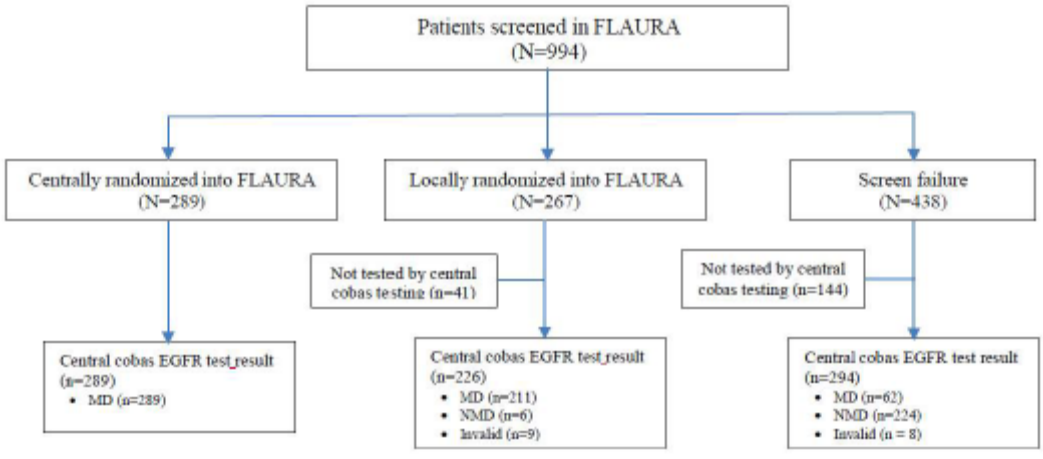
	Number (%) of patients		
	Osimertinib (N=279)	**SoC (N=277)**	**Total (N=556)**
WHO performance status			
0 (normal activity)	112 (40.1)	116 (41.9)	228 (41.0)
1 (restricted activity)	167 (59.9)	160 (57.8)	327 (58.8)
Missing	0	1 (0.4)	1 (0.2)
Overall disease classification			
Metastatic[a]	264 (94.6)	262 (94.6)	526 (94.6)
Locally advanced[b]	14 (5.0)	15 (5.4)	29 (5.2)
Missing	1 (0.4)	0	1 (0.2)
Time from diagnosis/recurrence to randomisation (months)			
n	278	276	554
Mean	1.9	1.8	1.9
Standard deviation	5.57	3.24	4.56
Median	1.2	1.2	1.2
Min	0	0	0
Max	82	37	82
CNS metastases[c]	53 (19.0)	63 (22.7)	116 (20.9)
No CNS metastases[c]	226 (81.0)	214 (77.3)	440 (79.1)
Extra-thoracic visceral metastases	94 (33.7)	103 (37.2)	197 (35.4)
Liver metastases	41 (14.7)	37 (13.4)	78 (14.0)
Bone & locomotor metastases	97 (34.8)	102 (36.8)	199 (35.8)
No extra-thoracic visceral metastases	185 (66.3)	174 (62.8)	359 (64.6)
Baseline tumour size (mm)[d]			
n	278	277	555
Mean	55.3	56.7	56.0
Standard deviation	34.65	33.55	34.08
Median	47.5	50.0	48.0
Min	10	10	10
Max	207	176	207
Baseline tumour size category (mm)[d], n (%)			
<40	111 (39.8)	104 (37.5)	215 (38.7)

40 - <80	102 (36.6)	107 (38.6)	209 (37.6)
80 – <120	52 (18.6)	49 (17.7)	101 (18.2)
≥120	13 (4.7)	17 (6.1)	30 (5.4)
Missing	1 (0.4)	0	1 (0.2)
EGFR mutations by cobas central test[e]			
EGFR exon 19 deletion	158 (56.6)	155 (56.0)	313 (56.3)
EGFR exon 21 L858R	97 (34.8)	90 (32.5)	187 (33.6)
EGFRm not detected	3 (1.1)	3 (1.1)	6 (1.1)
Invalid test	4 (1.4)	5 (1.8)	9 (1.6)
No sample or inadequate sample	17 (6.1)	24 (8.7)	41 (7.4)
EGFR mutations as used for randomisation strata[f]			
EGFR exon 21 L858R	104 (37.3)	103 (37.2)	207 (37.2)
EGFR exon 19 deletion	175 (62.7)	174 (62.8)	349 (62.8)

[a] Metastatic disease - Patient had any metastatic site of disease.
[b] Locally advanced - Patient had only locally advanced sites of disease.
[c] This is a programmatically derived composite endpoint with a list of contributing data sources.
[d] Longest diameter at baseline.
[e] A patient could have more than one mutation.
[f] EGFR mutations based on the test (local or central) used to determine randomisation strata (Ex19del or L858R).

Determination of EGFR mutation status

Of the 994 patients screened in the FLAURA study, 556 were randomised. Of those 556 patients, 267 were randomised based on local testing performed at certified/accredited laboratories. The remaining 289 patients were randomised based on an EGFRm status identified via the cobas® EGFR Mutation Test performed at designated central laboratories (Figure 3).



MD: presence of exon 19 deletion or L858R mutation
NMD: absence of exon 19 deletion and L858R mutation
Not tested by central cobas testing: including tissue sample not available, insufficient tissue, tissue failed pathology review, insufficient DNA yield

Figure 17: **Summary of EGFR local and central testing results.**

Patients who were randomised based on a local EGFRm positive result were also required to provide a tissue specimen for central testing to compare the local testing results with the central cobas® EGFR Mutation Test. Investigators were not required to submit samples for central testing for patients who failed screening based on local EGFR test results.

Of the 267 patients randomised based on a local result, 226 (85%) also had evaluable tumour specimens tested by the central cobas® EGFR Mutation Test. Of these 226 patients, 217 yielded a

valid central cobas test result, of whom 211/217 (97%) patients were retrospectively confirmed to have EGFRm tumours based on central testing (osimertinib: 110 [52%]; SoC: 101 [48%]). The central test did not confirm the presence of an EGFRm mutation in 6 patients (osimertinib: 3; SoC: 3). A further 41 patients were not tested by the central cobas® EGFR Mutation Test; this included patients for whom no sample was supplied and patients for whom the supplied sample did not meet the testing requirements.

The PPA between the cobas® EGFR Mutation Test and the local tests was 97.2% for the 2 EGFR sensitising mutations (Ex19del and L858R) in aggregate, 99.2% for Ex19del, and 94.5% for L858R, excluding invalid test results and no or inadequate samples. The cobas® EGFR Mutation Test showed a high percent agreement with the local tests.

Of the 556 patients randomised into the FLAURA study, 500 (89.9%) were confirmed to have EGFR mutation-positive tumours according to the cobas EGFR Mutation Test (performed centrally). An additional 41 (7.4%) patients had no or inadequate samples, 9 (1.6%) had invalid tests, and 6 (1.1%) had mutations not detected.

Prior anti-cancer therapy

Per protocol, all randomised patients were to be treatment-naïve for their advanced NSCLC. Three patients (2 in the osimertinib arm, 1 in the SoC arm) had received prior treatment for advanced cancer, an important protocol deviation.

Patients could have received prior adjuvant or neo-adjuvant therapy at an earlier stage of the disease: overall, 37/556 (6.7%) patients had received prior adjuvant or neoadjuvant cytotoxic chemotherapy (osimertinib: 21 [7.5%]; SoC: 16 [5.8%]).

Prior radiotherapy had been administered to 104/556 (18.7%) patients overall (osimertinib: 47 [16.8%]; SoC: 57 [20.6%]). Fifteen (2.7%) patients overall had prior brain radiotherapy (osimertinib: 8 [15.1%]; SoC: 7 [11.1%]).

Use of concomitant medication

The vast majority of patients (274 [98.2%] in the osimertinib arm and 272 [98.2%] in the SoC arm) received concomitant medications during the study. Concomitant medications were generally representative of medications commonly administered to patients with advanced NSCLC, in alignment with the concomitant medical conditions, were well balanced between treatment arms, and were not considered to affect the study results.

Radiotherapy while on treatment was administered to 8 (2.9%) patients in the osimertinib arm and 10 (3.6%) patients in the SoC arm.

Two (0.4%) patients (1 in each arm) received a disallowed concomitant medication, an important protocol deviation.

Anti-cancer therapy post-treatment discontinuation (including cross-over treatment).

Table 15: **Post-treatment anti-cancer therapy (including cross-over osimertinib)(FAS set)**

	Number (%) of patients[a]	
Classification/ATC dictionary text	**Osimertinib (N=279)**	**SoC (N=277)**
Discontinued randomised study treatment	138 (49.5)	213 (76.9)
Any post-treatment anti-cancer therapy	82 (29.4)	129 (46.6)
No post-treatment anti-cancer therapy	56 (20.1)	84 (30.3)
Ongoing randomised study treatment	141 (50.5)	64 (23.1)
EGFR-TKI	38 (13.6) [27.5]	99 (35.7) [46.5]
PD1/PDL1	6 (2.2) [4.3]	4 (1.4) [1.9]
Non-platinum chemotherapy	55 (19.7) [39.9]	46 (16.6) [21.6]
Platinum-based chemotherapy	53 (19.0) [38.4]	42 (15.2) [19.7]
Other targeted therapy	3 (1.1) [2.2]	5 (1.8) [2.3]
Anti-VEGF	10 (3.6) [7.2]	14 (5.1) [6.6]

[a] The number of patients is shown with percentages calculated as the proportion of patients in the FAS and secondly (between brackets) as the proportion of patients who discontinued randomised study treatment.

Post-treatment anti-cancer therapies are those with a start date on or after the last dose date of randomised study treatment.

Patients with no post-treatment anti-cancer therapy had discontinued randomised study treatment without starting any other post-treatment anti-cancer therapy.

Patients may be counted in multiple rows if they received more than 1 anti-cancer therapy or a combination therapy that contained drug substances from multiple classifications.

AZ Drug Dictionary version 17.1

DCO1: 12 June 2017

Table 16: First and second post-treatment anti-cancer therapy (including cross-over osimertinib) (FAS)

	Number (%) of patients[a]	
Classification/ATC dictionary text	Osimertinib (N=279)	SoC (N=277)
First post-treatment anti-cancer therapy (including cross-over osimertinib)		
Discontinued randomised study treatment	138 (49.5)	213 (76.9)
First post-treatment anti-cancer therapy	82 (29.4)	129 (46.6)
No post-treatment anti-cancer therapy	56 (20.1)	84 (30.3)
Ongoing randomised study treatment	141 (50.5)	64 (23.1)
First post-treatment anti-cancer therapy		
EGFR-TKI	29 (10.4) [21.0]	97 (35.0) [45.5]
PD1/PDL1	3 (1.1) [2.2]	2 (0.7) [0.9]
Non-platinum chemotherapy	50 (17.9) [36.2]	27 (9.7) [12.7]
Platinum-based chemotherapy	48 (17.2) [34.8]	26 (9.4) [12.2]
Other targeted therapy	2 (0.7) [1.4]	3 (1.1) [1.4]
Anti-VEGF	7 (2.5) [5.1]	4 (1.4) [1.9]
Second post-treatment anti-cancer therapy		
Second post-treatment anti-cancer therapy	24 (8.6)	39 (14.1)
Only 1 post-treatment anti-cancer therapy	58 (20.8)	90 (32.5)
Second post-treatment anti-cancer therapy		
EGFR-TKI	10 (3.6) [7.2]	14 (5.1) [6.6]
PD1/PDL1	2 (0.7) [1.4]	1 (0.4) [0.5]
Non-platinum chemotherapy	11 (3.9) [8.0]	19 (6.9) [8.9]
Platinum-based chemotherapy	4 (1.4) [2.9]	16 (5.8) [7.5]
Other targeted therapy	1 (0.4) [0.7]	2 (0.7) [0.9]
Anti-VEGF	3 (1.1) [2.2]	6 (2.2) [2.8]

[a] The number of patients is shown with percentages calculated as the proportion of patients in the FAS and secondly (between brackets) as the proportion of patients who discontinued randomised study treatment.
The first post-treatment anti-cancer therapy was the first treatment started on or after the last dose date of randomised study treatment. The second post-treatment anti-cancer therapy was the second treatment started on or after the last dose date of randomised study treatment.
Patients with no post-treatment anti-cancer therapy had discontinued randomised study treatment without starting any other post-treatment anti-cancer therapy.

Numbers analysed

The analysis sets and the number (%) of patients in each analysis set are summarised in the table below.

Table 17: **Study-level analysis sets (full analysis set).**

	Number (%) of patients		
	Osimertinib (N=279)	SoC (N=277)	Total (N=556)
Patients included in full analysis set (FAS)	279	277	556
Patients included in safety analysis set	279	277	556
Patients included in pharmacokinetic (PK) analysis set	261	0	261
Patients excluded from pharmacokinetic analysis set[a]	18	277	295
Patients not randomised to osimertinib	0	277	277
Patient had detectable pre-dose osimertinib concentration	18	0	18
Patients included in centrally-confirmed EGFRm analysis set	255	245	500
Patients excluded from centrally-confirmed EGFRm analysis set	24	32	56
No sample or inadequate sample	17	24	41
Invalid sample	4	5	9
EGFRm not detected (negative) by central testing	3	3	6

a Patients could have been excluded for more than 1 reason.
Full analysis set: all randomised patients Safety analysis set: all patients who received at least 1 dose of treatment; Pharmacokinetic analysis set: patients in the FAS randomised to osimertinib who did not have an osimertinib plasma concentration above LLQ at pre-dose Cycle 1 Day 1 and had at least 1 osimertinib plasma concentration above LLQ. Centrally confirmed EGFRm analysis set: all randomised patients who had centrally-confirmed positive EGFR mutation. DCO1: 12 June 2017.

The analysis sets used in the CNS efficacy analyses were as follows (Figure 4):

The cFAS (defined as all randomised patients identified by CNS BICR as having at least 1 CNS lesion at baseline, whether measurable or not) included a total of 128/556 (23.0%) patients (osimertinib: 61/279 [21.9%]; SoC: 67/277 [24.2%]).

- The cEFR (defined as all randomised patients identified by CNS BICR as having at least 1 CNS measurable lesion at baseline) included a total of 41/556 (7.4%) patients (osimertinib: 22/279 [7.9%]; SoC: 19/277 [6.9%]).
- The CNS MTS analysis set included a total of 116/556 (20.9%) patients programmatically classified as having a positive CNS metastases status at baseline (CNS MTS: "Yes") based on baseline characteristics recorded by the investigators on the eCRF pages (osimertinib: 53/279 [19.0%]; SoC: 63/277 [22.7%]); and 440/556 (79.1%) patients determined to have a negative CNS metastases status at baseline (CNS MTS: "No") (osimertinib: 226/279 [81.0%]; SoC: 214/277 [77.3%]).

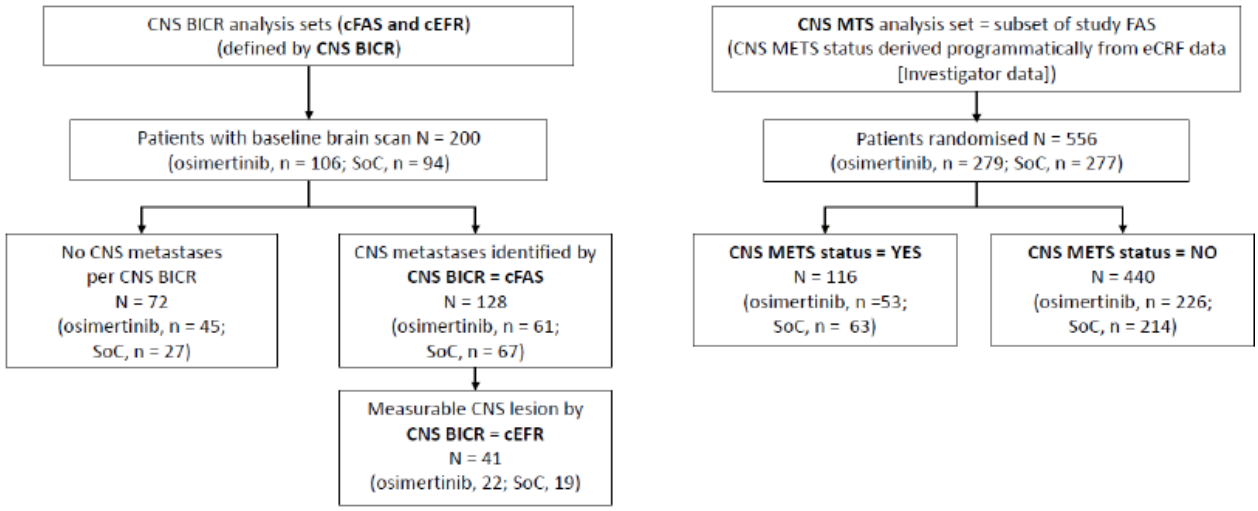


Figure 18: **Central nervous system analysis sets**

The patient characteristics for the patients in the CNS full analysis set are summarised below:

Table 18: **Selected baseline characteristics in the CNS full analysis set**

	Osimertinib (n=61)	Soc (n=67)
Age (median, range)	63.0 (34-83)	63.0 (39-85)
Male sex	23 (37,7 %)	26 (38,8 %)
Asian race	40 (65,6 %)	37 (55,2 %)
WHO performance status		
0 (Normal activity)	16 (26,2 %)	27 (40,3 %)
1 (Restricted activity)	45 (73,8 %)	39 (58,2 %)

Outcomes and estimation

Efficacy results

At the time of DCO the median duration of total treatment exposure was 16.2 months (range, 0.1 to 27.4) for patients receiving osimertinib and 11.5 months (range, 0 to 26.2) for patients receiving SoC.

A summary of the key efficacy data from FLAURA at the time of DCO1 is presented in Table 8.

Table 19: Summary of key efficacy outcome variables (Full Analysis Set).

	Osimertinib 80 mg (N = 279)	Standard of Care (N = 277)
Progression-free survival		
Number of events (%)	136 (48.7)	206 (74.4)
Hazard ratio (95% CI); 2-sided p-value	0.46 (0.37, 0.57); p<0.0001	
Median PFS (95% CI), months	18.9 (15.2, 21.4)	10.2 (9.6, 11.1)
Overall survival (Interim analysis)		
Number of patients with OS events (%)	58 (20.8)	83 (30.0)
Hazard ratio (95% CI); 2-sided p-value	0.63 (0.45, 0.88); 0.0068 (NS)	
Median OS (95% CI) (months)	Not calculable	Not calculable
Survival at 12 months (%) (95% CI)	89.1 (84.7, 92.2)	82.5 (77.4, 86.5)
Survival at 18 months (%) (95% CI)	82.8 (77.7, 86.8)	70.9 (64.8, 76.1)
Objective response rate		
ORR [a]		
Number of patients with response (%)	223 (79.9)	210 (75.8)
95% CI for ORR	74.7, 84.5	70.3, 80.7
Odds ratio (95% CI); 2-sided p-value	1.27 (0.85,1.90); 0.2421	
Confirmed ORR [b]		
Number of patients with response (%)	214 (76.7)	191(69.0)
95% CI for ORR	71.3, 81.5	63.1, 74.4
Odds ratio (95% CI); 2-sided p-value	1.48 (1.02, 2.17); 0.0397	
Duration of response		
Median DoR (95% CI) (months)	17.2 (13.8, 22.0)	8.5 (7.3, 9.8)
Confirmed Median DoR (95% CI) (months)	17.6 (13.8, 22.0)	9.6 (8.3, 11.1)
Disease control rate		
No (%) patients with disease control (CR+PR+SD≥6 weeks)	271 (97.1)	256 (92.4)
95% CI for DCR	94.4, 98.8	88.6, 95.2
Odds ratio (95% CI); 2-sided p-value	2.78 (1.25, 6.78); 0.0110	

DCO1: 12 June 2017

All the results included in this table are based on investigator assessment unless otherwise stated. PFS, ORR and DoR results by investigator assessment were consistent with those reported via Blinded Independent Central Review (BICR); PFS by BICR assessment was 17.7 months [95% CI: 15.1, 21.4] on osimertinib and 9.7 months [95% CI: 8.5, 11.0] on SoC; ORR by BICR assessment was 78.1% on osimertinib and 70.4% on SoC.
HR = Hazard ratio, CI = confidence interval, NC = Not calculable, NS = Not statistically significant
a Responses were unconfirmed as per RECIST guidelines for Phase III trials (Eisenhauer et al 2009).

b Confirmed responses: subset of unconfirmed responses; CI calculated with the Clopper-Pearson method.

Primary efficacy endpoint: PFS based on Investigator assessment

At the DCO1 for the primary analysis of PFS (12 June 2017), 342 (61.5%) RECIST progression events had occurred based on Investigator assessment according to RECIST v1.1.

Table 20: **Analysis of progression-free survival (full analysis set)**

	Number (%) patients	
	Osimertinib (N=279)	**SoC (N=277)**
PFS based on Investigator assessment		
No. (%) patients with PFS events	136 (48.7)	206 (74.4)
Hazard ratio (95% CI)	0.46 (0.37, 0.57)	
2-sided p-value	<0.0001	
Median PFS (95% CI), months	18.9 (15.2, 21.4)	10.2 (9.6, 11.1)
PFS based on BICR assessment		
No. (%) of patients with PFS events	137 (49.1)	198 (71.5)
Hazard ratio (95% CI)	0.45 (0.36, 0.57)	
2-sided p-value	<0.0001	
Median PFS (95% CI), months	17.7 (15.1, 21.4)	9.7 (8.5, 11.0)

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A greater proportion of patients treated with osimertinib were alive and progression-free at 6 months (88.4% [95% CI: 83.9, 91.7]), 12 months (68.2% [95% CI: 62.3, 73.5]), and 18 months (50.9% (95% CI: 44.5, 57.0]) compared to those treated with SoC (6 months: 75.2% [95% CI: 69.5, 79.9]; 12 months: 42.3% [95% CI: 36.3, 48.2]; and 18 months: 24.4% [95% CI: 19.2, 30.0]).

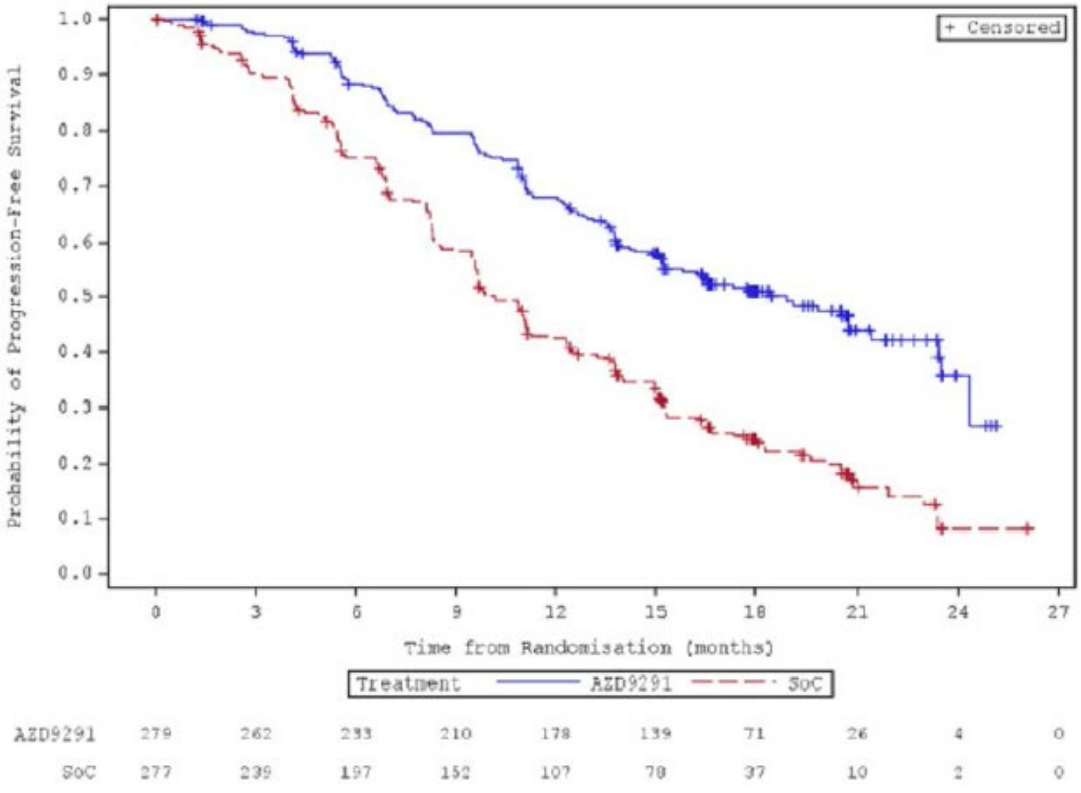

Figure 19: Kaplan-Meier plot of progression-free survival – investigator assessment (full analysis set).
Most of the PFS events were due to progression by RECIST criteria; 11 (3.9%) patients on osimertinib and 14 (5.1%) patients on SoC died in the absence of RECIST progression.

Table 21: Progression-free survival analysis - investigator assessment (full analysis set)

	Number (%) of patients	
Progression status	**Osimertinib (N=279)**	**SoC (N=277)**
Progression status		
Progression		
Total number of patients with PFS events	136 (48.7)	206 (74.4)
RECIST progression[a]	125 (44.8)	192 (69.3)
Target lesions[b]	64 (22.9)	94 (33.9)
Non-target lesions[b]	40 (14.3)	70 (25.3)
New lesions[b]	52 (18.6)	103 (37.2)
Death[c]	11 (3.9)	14 (5.1)
No progression		
Total	143 (51.3)	71 (25.6)
Censored RECIST progression[d]	3 (1.1)	2 (0.7)
Censored death[d]	4 (1.4)	5 (1.8)
Progression-free at time of analysis[e]	129 (46.2)	56 (20.2)
Lost to follow-up[f]	1 (0.4)	0
Withdrawn consent[f]	6 (2.2)	8 (2.9)
Discontinued study for other reasons[f]	0	0
New lesions[g]		
Patients with no new lesions	217 (77.8)	163 (58.8)
Patients with new lesions	62 (22.2)	114 (41.2)
Most common sites of new lesions:		
CNS	15 (5.4)	34 (12.3)
Liver	6 (2.2)	20 (7.2)
Lung	20 (7.2)	41 (14.8)
Bone	11 (3.9)	11 (4.0)
Comparison between arms		
Hazard ratio (95% CI)	0.46 (0.37, 0.57)	
2-sided p-value	<0.0001	

[a] Only included progression events that occurred within 2 scheduled visits (plus visit window) of the last evaluable assessment (or randomisation).

[b] Target lesions, non-target lesions, and new lesions were not necessarily mutually exclusive categories. New lesions presented with the PFS analysis were only counted if they occurred at the time of first progression (PFS analysis).

[c] Death in the absence of progression.

[d] RECIST progression or death occurred more than 2 scheduled visits (plus visit window) after last evaluable RECIST assessment.

[e] Included patients known to be alive, with no evaluable baseline RECIST assessment (censored at Day 1) or censored at last evaluable RECIST assessment.

[f] Patients censored at last evaluable RECIST assessment or randomisation.

[g] Included any new lesions up to DCO, including new lesions that occurred at any time after PD and new lesions in patients who were censored for PFS. The number of new lesions in this analysis is therefore larger than the number of new lesions that contributed to, and were recorded at, PFS.

RECIST version 1.1.
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Sensitivity analysis of PFS based on BICR

Table 22: **Progression-free survival analysis - BICR assessment (full analysis set)**

	Number (%) of patients	
Progression status	**Osimertinib (N=279)**	**SoC (N=277)**
Progression status		
Progression		
Total number of patients with PFS events	137 (49.1)	198 (71.5)
RECIST progression[a]	122 (43.7)	182 (65.7)
Target lesions[b]	66 (23.7)	87 (31.4)
Non-target lesions[b]	39 (14.0)	67 (24.2)
New lesions[b]	21 (7.5)	39 (14.1)
Death[c]	15 (5.4)	16 (5.8)
No progression		
Total	142 (50.9)	79 (28.5)
Censored RECIST progression[d]	0	0
Censored death[d]	4 (1.4)	6 (2.2)
Progression-free at time of analysis[e]	131 (47.0)	64 (23.1)
Lost to follow-up[f]	1 (0.4)	0
Withdrawn consent[f]	6 (2.2)	9 (3.2)
Discontinued study for other reasons[f]	0	0
New lesions[g]		
Patients with no new lesions	236 (84.6)	206 (74.4)
Patients with new lesions	43 (15.4)	71 (25.6)
Comparison between arms		
Hazard ratio (95% CI)	0.45 (0.36, 0.57)	
2-sided p-value	<0.0001	

[a] Only included progression events that occurred within 2 scheduled visits (plus visit window) of the last evaluable assessment (or randomisation).
[b] Target lesions, non-target lesions, and new lesions were not necessarily mutually exclusive categories.
[c] Death in the absence of progression.
[d] RECIST progression or death occurred more than 2 scheduled visits (plus visit window) after last evaluable RECIST assessment.
[e] Included patients known to be alive, with no evaluable baseline RECIST assessment (censored at Day 0).
[f] Patients censored at last evaluable RECIST assessment or randomisation.
[g] Included all new lesions up to DCO, including new lesions that occurred after PD and new lesions in patients who were censored for PFS.

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Other sensitivity analyses of progression-free survival

Further sensitivity analyses to assess bias were found to be consistent with the primary PFS analysis, demonstrating the robustness of the primary outcome.

- There was no evidence of evaluation-time bias affecting PFS, which could occur if scans were not performed at the protocol-scheduled time intervals. The HR of 0.46 (95% CI: 0.37, 0.57; p-value <0.0001) was consistent with the primary analysis.
- The results of the attrition bias sensitivity analysis indicated that the censoring rules applied did not introduce a bias in the outcome of the primary analysis of PFS. The HR was 0.47 (95% CI: 0.37, 0.58; p <0.0001).

- An additional sensitivity analysis was conducted to assess the impact of the change in RECIST scanning schedule at Month 18 from every 6 weeks to every 12 months, which fell close to the median PFS of 18.9 months in the osimertinib arm. The impact of the change in visit schedule was very minor. The median PFS in the osimertinib arm decreased to 18.4 months (95% CI: 15.2, 22.1) from 18.9 months, with no change in the median for the SoC arm. The HR and 95% CI remained unchanged. The median total number of RECIST assessments per patient after Month 18 was 1.0 (range: 1-5).

Secondary efficacy endpoint: Overall survival (interim analysis)

The first of 2 analyses of OS was conducted at the DCO1 for the primary analysis of PFS. A survival status check was conducted on all randomised patients without a death reported 7 days after database DCO date (12 June 2017). A second and final OS analysis will be conducted when data are approximately 60% mature (~334 deaths).

The maturity for OS was 25.4% overall. A majority of patients (osimertinib: 51/58 [87.9%]; SoC 65/83 [78.3%]) died of the disease under study.

Table 23: **Overall survival analysis (full analysis set)**

	Osimertinib (N=279)	SoC (N=277)
Survival status		
Death	58 (20.8)	83 (30.0)
Still in survival follow-up[a]	208 (74.6)	177 (63.9)
Terminated prior to death[b]	13 (4.7)	17 (6.1)
Voluntary discontinuation by patient	11 (3.9)	17 (6.1)
Patient lost to follow-up	2 (0.7)	0
Comparison between arms		
Hazard ratio (95% CI)	0.63 (0.45, 0.88)	
Adjusted CI (99.85%)	0.37, 1.08	
2-sided p-value	0.0068	

The analysis was performed using a log rank test stratified by stratification factors.

Compared to patients treated with SoC, a greater proportion of patients treated with osimertinib were alive at 12 months (osimertinib: 89.1% [95% CI: 84.7, 92.2]; SoC: 82.5% [95% CI: 77.4, 86.5]) and 18 months (osimertinib: 82.8% [95% CI: 77.7, 86.8]; SoC: 70.9% [95% CI: 64.8, 76.1]). At the time of DCO1, every patient had the opportunity for a minimum of 15-month follow-up.

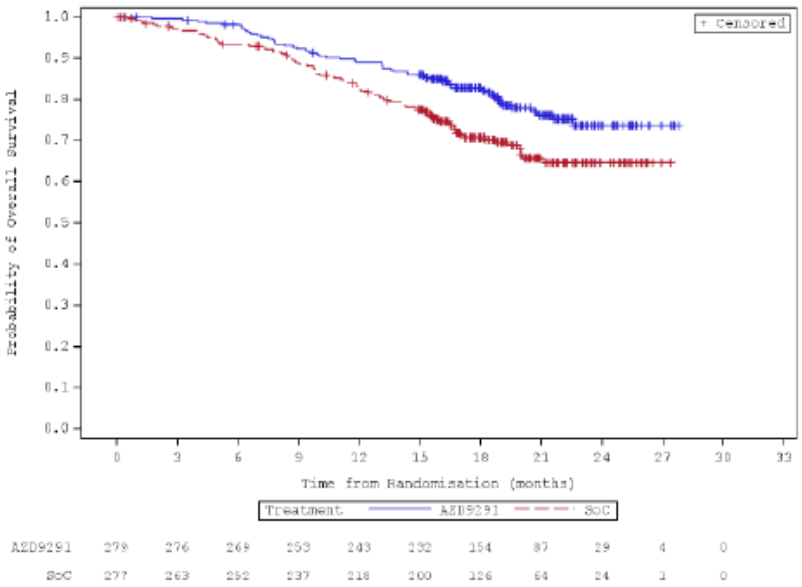


Figure 20: **Kaplan-Meier plot of overall survival (full analysis set)**

Secondary efficacy endpoint: ORR based on Investigator assessment

Table 24: Best objective response analysis – investigator assessment (full analysis set)

	Number (%) of patients	
Best objective response	**Osimertinib (N=279)**	**SoC (N=277)**
Response status[a]		
Response		
Total	223 (79.9)	210 (75.8)
Complete response	7 (2.5)	4 (1.4)
Partial response	216 (77.4)	206 (74.4)
Non-response		
Total	56 (20.1)	67 (24.2)
Stable disease ≥ 6 weeks	47 (16.8)	46 (16.6)
Progression	3 (1.1)	14 (5.1)
RECIST progression	3 (1.1)	9 (3.2)
Death	0	5 (1.8)
Not evaluable	6 (2.2)	7 (2.5)
Incomplete post baseline assessments	6 (2.2)	7 (2.5)
Analysis of ORR[b]		
Objective response rate (%) (95% CI)	76.7 (71.3, 81.5)	69.0 (63.1, 74.4)
Objective response rate adjusted for ethnicity and mutation type (%)	80.7	76.6
Comparison between groups		
Odds ratio (95% CI)	1.27 (0.85, 1.90)	
2-sided p-value for odds ratio	0.2421	
Adjusted odds ratio (95% CI)	1.28 (0.85, 1.93)	
2-sided p-value for adjusted odds ratio	0.2335	
Response status - Confirmed responses[c]		
Response		
Total	214 (76.7)	191 (69.0)
Complete response	6 (2.2)	3 (1.1)
Partial response	208 (74.6)	188 (67.9)
Non-response		
Total	65 (23.3)	86 (31.0)
Stable disease ≥ 6 weeks	55 (19.7)	65 (23.5)
Progression	4 (1.4)	14 (5.1)
RECIST progression	4 (1.4)	9 (3.2)
Death	0	5 (1.8)
Not evaluable	6 (2.2)	7 (2.5)
No evaluable follow-up assessments	6 (2.2)	7 (2.5)
Analysis of ORR[b] - Confirmed responses[c]		
No. (%) of patients with confirmed response	214 (76.7)	191 (69.0)
Objective response rate (%) (95% CI)	76.7 (71.3, 81.5)	69.0 (63.1, 74.4)
Objective response rate adjusted for ethnicity and mutation type (%)	76.0	67.8
Comparison between arms		
Odds ratio (95% CI)	1.48 (1.02, 2.17)	
2-sided p-value for odds ratio	0.0397	
Adjusted odds ratio (95% CI)	1.51 (1.03, 2.22)	
2-sided p-value for adjusted odds ratio	0.036	

[a] Response did not require confirmation.
[b] The analysis was performed using a logistic regression stratified by ethnicity (Asian versus Non-Asian) and mutation type (Ex19del versus L858R). An odds ratio > 1 favours osimertinib.
[c] Confirmed responses were a subset of the responses. CIs were calculated using the Clopper-Pearson method.

ORR based on BICR assessment

The BICR assessment was consistent with the Investigator assessment. The ORR was 78.1% in the osimertinib arm and 70.4% in the SoC arm. Based on assessment by BICR, no patients had CR and 218 (78.1%) had PR in the osimertinib arm vs. 3 (1.1%) patients with CR and 192 (69.3%) patients with PR in the SoC arm. The ORR (adjusted for ethnicity and mutation type) was 78.6% in the osimertinib arm vs. 70.8% in the SoC arm (OR: 1.52 [95% CI: 1.03, 2.24]; p-value = 0.0344).

ORR based on Investigator assessment for patients with centrally-confirmed EGFRm

The ORR results based on Investigator assessment in patients with centrally-confirmed EGFRm were consistent with those in the study FAS. The ORR in patients with centrally-confirmed positive EGFRm was 79.6% in the osimertinib arm and 77.1% in the SoC arm. The ORR (adjusted) was 80.5% in the osimertinib arm vs. 77.9% in the SoC arm (OR [adjusted]: 1.17 [95% CI: 0.76, 1.81]; 2-sided p-value: 0.4728).

Secondary efficacy endpoint: Duration and onset of response based on Investigator assessment

The median DoR based on Investigator assessment (calculated using KM technique) was 17.2 months (95% CI: 13.8, 22.0) in the osimertinib arm vs. 8.5 months (95% CI: 7.3, 9.8) in the SoC arm.

A greater proportion of patients in the osimertinib arm remained in response at 12 months (osimertinib: 64.4% [95% CI: 57.5, 70.5]; SoC: 37.3% [95% CI: 30.6, 44.1]) and 18 months (osimertinib: 48.8% [95% CI: 41.1, 56.0]; SoC: 19.1% [95% CI: 13.3, 25.7]) compared to patients in the SoC arm.

The DoR analysis by BICR was consistent with the Investigator DoR analysis and in line with the improvement in PFS.

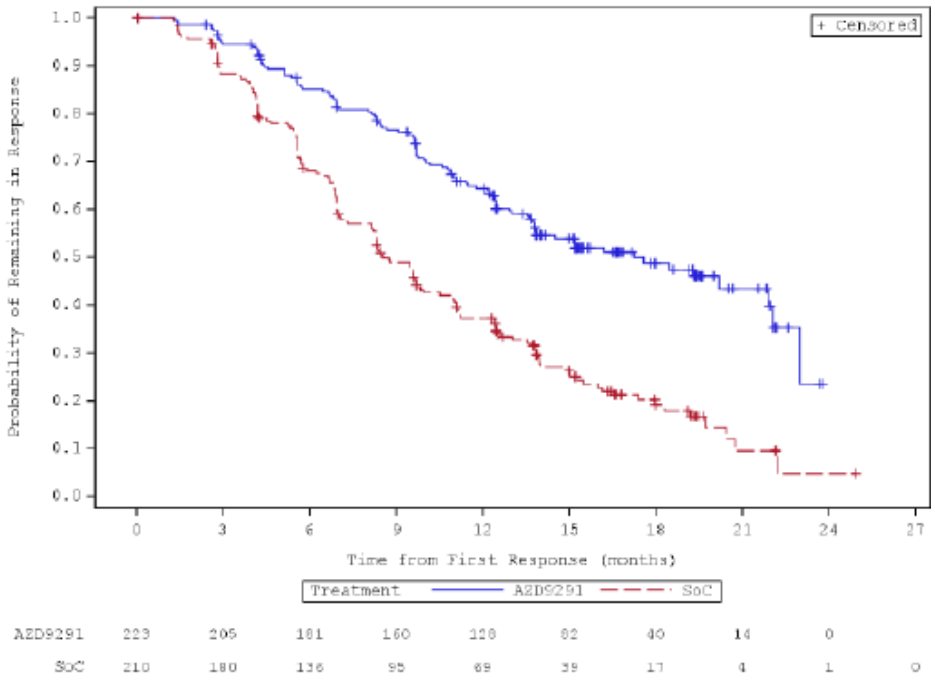


Figure 21: Kaplan-Meier plot of duration of response - investigator assessment (full analysis set)

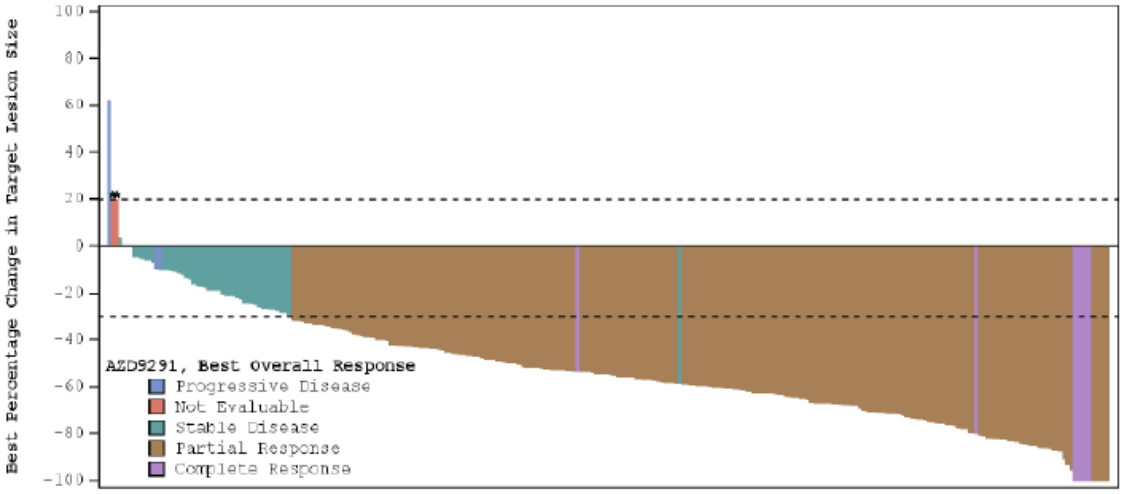
The median time to onset of response from randomisation was similarly rapid in both treatment arms and aligned with the first response assessment at Week 6 (osimertinib, 6.1 weeks [95% CI: 6.0, 6.1]; SoC, 6.1 weeks [95% CI: NC, NC]).

Secondary efficacy endpoint: DCR based on Investigator assessment

The DCR (defined as complete response [CR]+ PR+stable disease [SD] ≥6 weeks) based on Investigator assessment was similar and >90% in both arms.

Secondary efficacy endpoint: Depth of response (tumour shrinkage)

A similar proportion of patients had tumour shrinkage (reduction of the sum of tumour lesion size) in both treatment arms, based on Investigator assessment according to RECIST v1.1, with a similar mean shrinkage of TLs in both arms. The BICR analysis was consistent with the Investigator analysis.



Best percentage change in target lesion size was the maximum reduction from baseline or the minimum increase from baseline in the absence of a reduction.
*represents imputed values: If it was known that the patient had died, had new lesions or progression of non-target lesions, had withdrawn due to PD and had no evaluable target lesion (before or at progression) assessments, best change was imputed as 20%.
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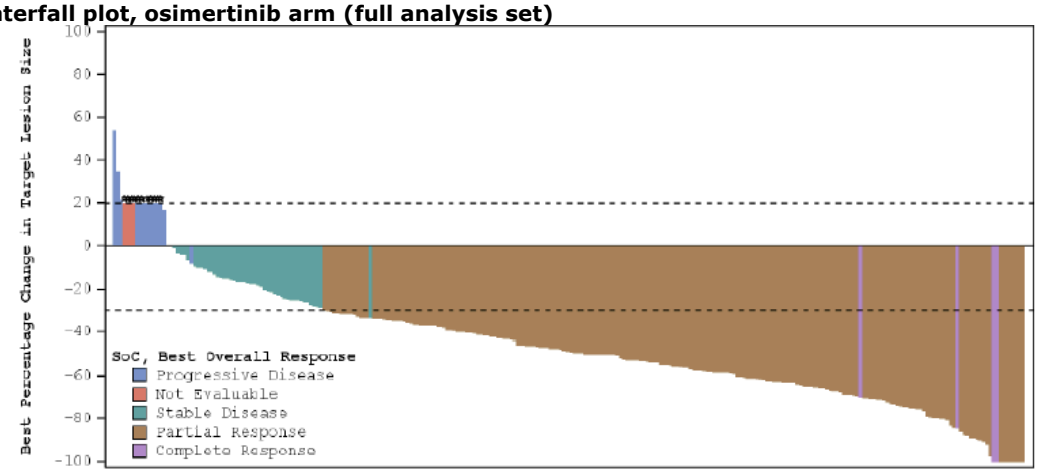
Figure 22: Target lesion size, best percentage change from baseline by investigator assessment – total waterfall plot, osimertinib arm (full analysis set)



Best percentage change in target lesion size was the maximum reduction from baseline or the minimum increase from baseline in the absence of a reduction.
* represents imputed values: If it was known that the patient had died, had new lesions or progression of non-target lesions, had withdrawn due to PD and had no evaluable target lesion (before or at progression) assessments, best change was imputed as 20%.
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Figure 23: Target lesion size, best percentage change from baseline by investigator assessment - total waterfall plot, standard of care arm (full analysis set)

Secondary endpoint of patient-reported outcomes

Overall, compliance rates for EORTC QLQ-C30 were ≥70% up to Week 96 in the osimertinib arm and up to Week 60 in the SoC arm. Compliance rates for EORTC QLQ-LC13 were ≥70% up to Week 93 in the osimertinib arm and up to Week 75 in the SoC arm (with an exception for Week 66 when the compliance rate was 69.2%).

Table 25: Summary of change from baseline in primary PRO symptoms, MMRM (full analysis set)

	Cough		Dyspnoea		Chest pain		Appetite loss		Fatigue	
	Osi	SoC	Osi	SoC	Osi	SoC	Osi	SoC	Osi	SoC
N	248	252	248	252	248	252	252	247	252	247
LS mean	−10.97	−11.65	−4.04	−4.14	−6.62	−6.41	−6.15	−5.64	−5.48	−4.72
95% CI for LS mean	−12.77, −9.17	−13.47, −9.84	−5.63, −2.45	−5.73, −2.54	−8.24, −5.01	−8.04, −4.78	−8.39, −3.90	−7.96, −3.32	−7.45, −3.52	−6.74, −2.69
Difference in LS means (osimertinib minus SoC)	0.68		0.10		−0.21		−0.50		−0.77	
95% CI for difference in LS means	−1.87, 3.24		−2.16, 2.35		−2.51, 2.08		−3.73, 2.73		−3.59, 2.05	

LS = least squares; MMRM = mixed-effects model for repeated measures; Osi = osimertinib.
The analysis was performed using a MMRM analysis on the change from baseline in PRO symptom score at each visit up to 9 month (281 days), including patient (as a random effect), treatment, visit (as fixed effect and repeated measure), and treatment-by-visit interaction as explanatory variables, the baseline PRO score as a covariate along with the baseline PRO score by visit interaction, using an unstructured covariance structure. Using the first covariance structure (in the order: unstructured, toeplitz with heterogeneity, autoregressive with heterogeneity, toepliz, autoregressive) for which convergence could be achieved for all 5 primary PRO symptoms scores.
DCO1: 12 June 2017

Post progression outcomes

Overall, the positive impact of first-line osimertinib therapy continued beyond first RECIST progression, as demonstrated by the analyses of post-progression outcomes.

Table 26: Post-progression outcome endpoints (full analysis set)

	Number (%) patients	
	Osimertinib (N=279)	SoC (N=277)
Time to discontinuation of randomised treatment or death (TDT)		
No. (%) of patients who discontinued treatment or died	138 (49.5)	213 (76.9)
Median (95% CI)	20.8 (17.2, 24.1)	11.5 (10.3, 12.8)
Time from randomisation to first subsequent therapy or death (TFST)		
No. (%) patients who started first subsequent therapy or died	115 (41.2)	175 (63.2)
Median TFST (months) (95% CI)	23.5 (22.0, NC)	13.8 (12.3, 15.7)
Hazard ratio (95% CI)	0.51 (0.40, 0.64)	
2-sided p-value	<0.0001	
Continuation of randomised treatment beyond RECIST progression (Investigator-based)		
No. (%) patients who continued treatment beyond RECIST progression	91 (66.9)	145 (70.4)
Median duration of treatment post-progression (95% CI), weeks	8.1 (6.3, 12.3)	7.0 (5.9, 8.1)
Best objective response rate to first subsequent therapy		
Best objective response rate, % (95% CI)	18.3 (10.6, 28.4)	22.5 (15.6, 30.7)
Time on first subsequent therapy		
No. (%) of patients with first subsequent therapy	82 (29.4)	129 (46.6)
Median duration of first subsequent therapy (95% CI), months	3.45 (0-23.5)	4.99 (0-21.8)
Time from randomisation to second progression after start of subsequent treatment (PFS2)		
No. (%) patients with second progression	73 (26.2)	106 (38.3)
Median PFS2 (months) (95% CI)	NC (23.7, NC)	20.0 (18.2, NC)
Hazard ratio (95% CI)	0.58 (0.44, 0.78)	
2-sided p-value	0.0004	
Time to second subsequent treatment or death (TSST)		
No. (%) patients with second subsequent therapy or death	74 (26.5)	110 (39.7)
Median TSST (months) (95% CI)	NC (NC, NC)	25.9 (20.0, NC)
Hazard ratio (95% CI)	0.60 (0.45, 0.80)	
2-sided p-value	0.0005	
Time to discontinuation of any EGFR-TKI treatment or death[a]		
No. (%) of patients who discontinued any EGFR-TKIs or died	128 (45.9)	167 (60.3)
Median time to discontinuation (months) (95% CI)	23.0 (19.5, NC)	16.0 (14.8, 18.6)

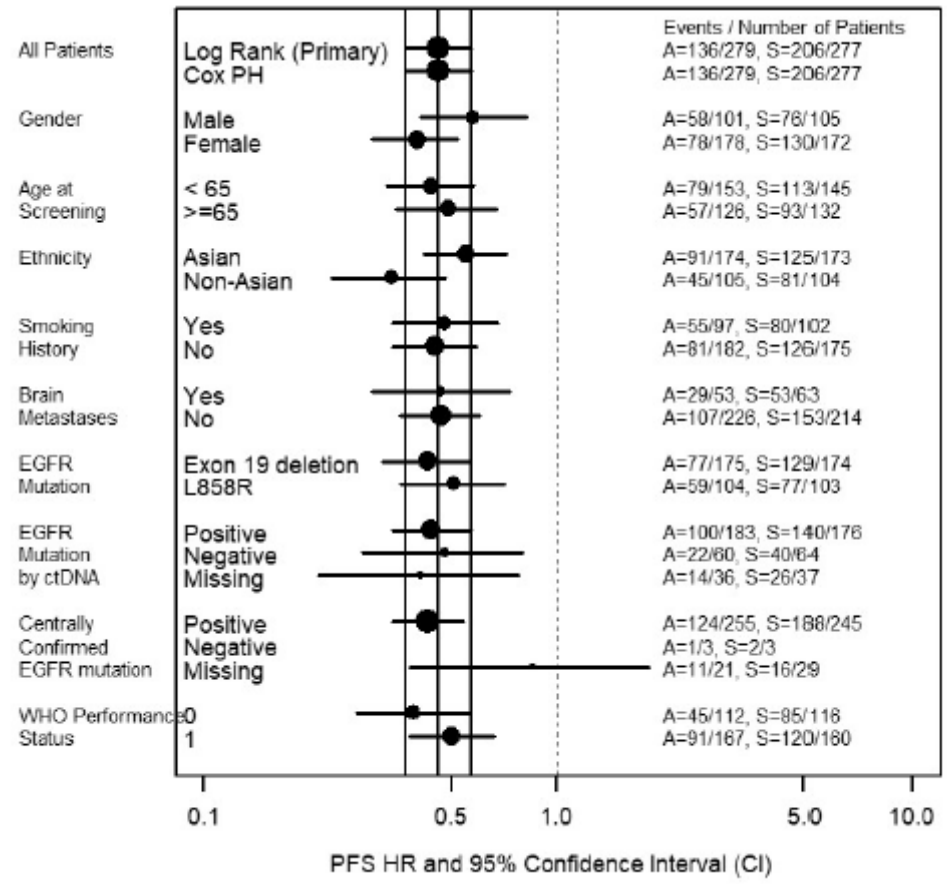
[a] Treatment with EGFR-TKIs was to be sequential, without any intervention therapy in between, except for palliative radiotherapy for painful bone metastases.

DCO1: 12 June 2017

Ancillary analyses

Subgroup analysis of PFS

The superiority of osimertinib over SoC was maintained and consistent across the randomisation stratification factors and all the predefined subgroups with available data for statistical analysis. All PFS HRs were <0.60 in favour of osimertinib for all but the subgroup of patients without a valid EGFRm central test result (HR of 0.85).



EGFR mutation results are by the method used at randomisation.

Figure 24: Progression-free survival, Forest plot, by subgroup (full analysis set)

Table 27: Subgroup analyses of progression-free survival (full analysis set)

Subgroup	Group	N	Number (%) of patients with events	Median PFS (months) (95% CI)	Comparison between arms		
					Hazard ratio	95% CI	2-sided p-value
Gender							
Male	Osimertinib	101	58 (57.4)	16.4 (13.8, 20.5)	0.58	0.41, 0.82	ND
	SoC	105	76 (72.4)	11.0 (9.6, 13.8)			
Female	Osimertinib	178	78 (43.8)	20.7 (15.2, NC)	0.40	0.30, 0.52	ND
	SoC	172	130 (75.6)	9.7 (8.3, 11.1)			
Age at screening							
<65 years	Osimertinib	153	79 (51.6)	17.8 (14.9, 23.4)	0.44	0.33, 0.58	ND
	SoC	145	113 (77.9)	9.7 (9.5, 11.1)			
≥65 years	Osimertinib	126	57 (45.2)	19.8 (13.9, NC)	0.49	0.35, 0.67	ND
	SoC	132	93 (70.5)	11.0 (8.3, 13.8)			
Ethnicity							
Asian	Osimertinib	174	91 (52.3)	16.4 (13.8, 20.7)	0.55	0.42, 0.72	ND
	SoC	173	125 (72.3)	11.0 (9.5, 12.6)			
Non-Asian	Osimertinib	105	45 (42.9)	24.3 (16.3, NC)	0.34	0.23, 0.48	ND
	SoC	104	81 (77.9)	9.7 (8.2, 11.1)			
Smoking history							
Yes	Osimertinib	97	55 (56.7)	16.5 (13.9, 20.5)	0.48	0.34, 0.68	ND
	SoC	102	80 (78.4)	9.7 (8.5, 11.1)			
No	Osimertinib	182	81 (44.5)	20.7 (14.9, NC)	0.45	0.34, 0.59	ND
	SoC	175	126 (72.0)	11.0 (9.0, 12.6)			
CNS metastases at baseline							
Yes	Osimertinib	53	29 (54.7)	15.2 (12.1, 21.4)	0.47	0.30, 0.74	0.0009
	SoC	63	53 (84.1)	9.6 (7.0, 12.4)			
No	Osimertinib	226	107 (47.3)	19.1 (15.2, 23.5)	0.46	0.36, 0.59	<0.0001
	SoC	214	153 (71.5)	10.9 (9.6, 12.3)			
EGFR mutation as used for randomisation							
Exon 19 deletion	Osimertinib	175	77 (44.0)	21.4 (16.5, 24.3)	0.43	0.32, 0.56	<0.0001
	SoC	174	129 (74.1)	11.0 (9.7, 12.6)			
L858R	Osimertinib	104	59 (56.7)	14.4 (11.1, 18.9)	0.51	0.36, 0.71	<0.0001
	SoC	103	77 (74.8)	9.5 (8.1, 11.0)			
EGFR by ctDNA							
EGFRm positive	Osimertinib	183	100 (54.6)	15.2 (13.7, 20.7)	0.44	0.34, 0.57	<0.0001
	SoC	176	140 (79.5)	9.7 (8.4, 11.1)			
EGFRm negative	Osimertinib	60	22 (36.7)	23.5 (17.8, 24.3)	0.48	0.28, 0.80	0.0047
	SoC	64	40 (62.5)	15.0 (9.7, 18.3)			
EGFRm missing	Osimertinib	36	14 (38.9)	17.3 (11.1, 21.4)	0.41	0.21, 0.78	0.0059
	SoC	37	26 (70.3)	8.3 (6.8, 10.2)			
Centrally-confirmed EGFR mutation							
Positive	Osimertinib	255	124 (48.6)	18.9 (15.2, 21.4)	0.43	0.34, 0.54	<0.0001
	SoC	245	188 (76.7)	9.7 (9.5, 11.0)			
Negative	Osimertinib	3	1 (33.3)	NC (2.7, NC)	NC	NC, NC	NC
	SoC	3	2 (66.7)	2.8 (1.4, NC)			
Missing	Osimertinib	21	11 (52.4)	16.5 (11.1, NC)	0.85	0.38, 1.82	0.6813
	SoC	29	16 (55.2)	16.6 (9.7, 23.0)			
WHO performance status							
0 (normal activity)	Osimertinib	112	45 (40.2)	23.5 (18.4, NC)	0.39	0.27, 0.56	ND
	SoC	116	85 (73.3)	11.1 (9.9, 14.0)			
1 (restricted activity)	Osimertinib	167	91 (54.5)	15.2 (12.9, 20.7)	0.50	0.38, 0.66	ND
	SoC	160	120 (75.0)	9.5 (8.2, 10.9)			
Missing	SoC	1	1 (100.0)	NC (NC, NC)			

ctDNA = circulating tumour deoxyribonucleic acid; EGFRm = epidermal growth factor receptor mutation-positive; NC = not calculable; ND = not done
The analysis was performed using a Cox proportional hazards model including covariate for subgroup and a treatment-by-subgroup interaction term. A hazard ratio < 1 favours osimertinib.

Table 28: **Progression-free survival analysis based on investigator assessment by age (≥75 years vs. <75 years) (Full analysis set)**

	Number (%) patients			
	<75 years (N=477)		≥75 years (N=79)	
	Osimertinib (n = 243)	SoC (n = 234)	Osimertinib (n = 36)	SoC (n = 43)
No. (%) patients with PFS events [a]	118 (48.6)	174 (74.4)	18 (50.0)	32 (74.4)
Median PFS, (95%CI), months [b]	19.1 (15.2, 23.4)	10.2 (9.6, 11.1)	12.1 (7.8, NC)	9.9 (7.0, 13.8)
Hazard ratio (95% CI) [c]	0.45 (0.35, 0.57)		0.58 (0.32, 1.02)	

a Progression events that did not occur within 2 scheduled visits (plus visit window) of the last evaluable assessment (or randomisation) are censored and therefore excluded in the number of events.
b Calculated using the Kaplan-Meier method. NC= not calculable
c The analysis was performed using a Cox proportional hazards model including covariate for subgroup and a treatment-by-subgroup interaction term. A hazard ratio < 1 favoured osimertinib
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Subgroup analysis for EGFR mutation status

At baseline, patients were enrolled and stratified by EGFR mutation type, as determined either by local testing or by central testing. Overall, 349 (62.8%) patients had tumours harbouring Ex19del mutation and 207 (37.2%) patients had tumours harbouring L858R mutation.

Progression-free survival, as assessed by the Investigator, was prolonged for patients who received osimertinib compared to patients on SoC irrespective of the EGFR mutation type (Figure 10). Patients with NSCLC harbouring Ex19del in the EGFR gene had numerically longer median PFS in both arms, in line with previous observations (Sebastian et al 2014). However, patients with NSCLC harbouring the less EGFR-TKI responsive L858R treated with osimertinib have better outcomes than patients with NSCLC harbouring the more responsive Ex19del when treated with SoC.

Table 29: Progression-free survival based on investigator assessment by baseline EGFR mutation status used for randomisation (Ex19del or L858R [tissue])

	Number (%) patients			
	Ex19del (N=349)		L858R (N=207)	
	Osimertinib (n = 175)	SoC (n = 174)	Osimertinib (n = 104)	SoC (n = 103)
No. (%) patients with PFS events	77 (44.0)	129 (74.1)	59 (56.7)	77 (74.8)
Median PFS (months), 95% CI	21.4 (16.5, 24.3)	11.0 (9.7, 12.6)	14.4 (11.1, 18.9)	9.5 (8.1, 11.0)
Hazard ratio (95% CI)	0.43 (0.32, 0.56)		0.51 (0.36, 0.71)	
2-sided p-value	<0.0001		<0.0001	

The analysis was performed using a Cox proportional hazards model including covariate for subgroup and a treatment-by-subgroup interaction term. A hazard ratio < 1 favours osimertinib.

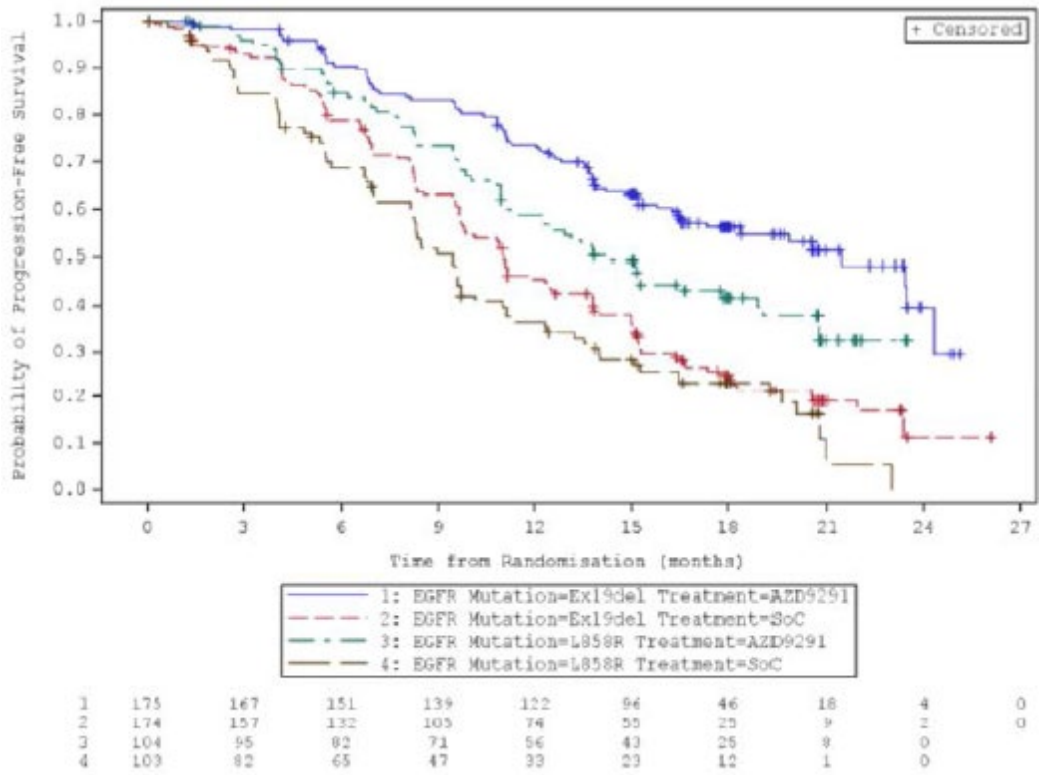

Figure 25: Kaplan-Meier plot of subgroup analyses of PFS by EGFR mutation by Investigator assessment (full analysis set)

Subgroup of patients with locally advanced NSCLC

In 29/556 (5%) patients with locally advanced EGFRm NSCLC (osimertinib: 14 patients; SoC: 15 patients), the ORR, as assessed by the Investigator, was 92.9% (95% CI: 66.1, 99.8) for patients receiving osimertinib and 60.0% (95% CI: 32.3, 83.7) for patients receiving SoC.

The duration of response in this population was not assessed.

Patients with locally advanced disease

Among the 29 patients with locally advanced disease, 20 reported a PFS event by investigator. No formal analysis of PFS in this subgroup has been performed. The Applicant provided a summary table (data not shown) with the relevant PFS data. The results are in line with the overall population.

Central nervous system efficacy analyses

The prespecified CNS analyses conducted on the CNS MTS and CNS BICR (cFAS, cEFR) populations were all prospectively defined.

Subgroup analysis by CNS metastases status at baseline (CNS MTS)

At baseline, 116/556 (20.9%) patients were determined programmatically from eCRF pages to have a CNS MTS status of "Yes" based on Investigator assessment: 53/279 (19.0%) patients in the osimertinib arm and 63/277 (22.7%) patients in the SoC arm. Twenty patients were part only of the subgroup with a CNS MTS status of “Yes” at baseline, but not of the cFAS subgroup, due to either the absence of a CNS CT or MRI scan for CNS BICR assessment or BICR not identifying CNS lesions. Conversely, 32 patients were part only of the cFAS as they were not considered by the Investigator to have baseline CNS metastases and, therefore, were not included in the subgroup of patients with a CNS MTS status of “Yes” at baseline.

Table 30: Efficacy by CNS metastases status at baseline (CNS MTS analysis set, Investigator assessment)

	Number (%) patients			
	CNS MTS of Yes at baseline (N=116)		CNS MTS of No at baseline (N=440)	
	Osimertinib (n = 53)	SoC (n = 63)	Osimertinib (n = 226)	SoC (n = 214)
Progression-free survival based on Investigator assessment				
No. (%) patients with events[a]	29 (54.7)	53 (84.1)	107 (47.3)	153 (71.5)
Median PFS (months), 95% CI[b]	15.2 (12.1, 21.4)	9.6 (7.0, 12.4)	19.1 (15.2, 23.5)	10.9 (9.6, 12.2)
Hazard ratio (95% CI)[c]	0.47 (0.30, 0.74)		0.46 (0.36, 0.59)	
2-sided p-value	<0.001		<0.001	
Patients with progression other than death and reason for progression				
No. (%) patients with progression other than death[d]	25 (47.2)	49 (77.8)	100 (44.2)	143 (66.8)
Progression in TL[e]	12 (22.6)	20 (31.7)	52 (23.0)	74 (34.6)
Progression in NTL[e]	9 (17.0)	19 (30.2)	31 (13.7)	51 (23.8)
Progression in CNS NTL	7 (13.2)	15 (23.8)	0	1 (0.5)[f]
Progression in non-CNS NTL	9 (17.0)	18 (28.6)	31 (13.7)	51 (23.8)
Presence of NL[e]	11 (20.8)	31 (49.2)	41 (18.1)	72 (33.6)
New CNS lesions	4 (7.5)	19 (30.2)	7 (3.1)	15 (7.0)
Non-CNS new lesions	7 (13.2)	13 (20.6)	35 (15.5)	59 (27.6)
Reason for CNS progression				
No. (%) patients with CNS progression[g]	10 (18.9)	27 (42.9)	7 (3.1)	15 (7.0)
Progression in CNS only	3 (5.7)	10 (15.9)	4 (1.8)	12 (5.6)
Progression in CNS NL only	3 (5.7)	9 (14.3)	4 (1.8)	12 (5.6)
Progression in CNS and non-CNS	7 (13.2)	17 (27.0)	3 (1.3)	3 (1.4)
No. (%) patients with non-CNS progression only[g]	0	4 (6.3)	0	0
Objective response rate based on Investigator assessment				
No. (%) patients with response	40 (75.5)	183 (81.0)	54 (85.7)	156 (72.9)
Odds ratio (95% CI)	0.5 (0.2, 1.3)		1.6 (1.0, 2.5)	
2-sided p-value	0.161		0.044	
Duration of response based on Investigator assessment				
Number of responders	40	54	183	156
No. (%) of responders who subsequently progressed or died	22	46	84	112
Median duration of response from onset of response, months, (95% CI)[b]	13.8 (10.8, 20.2)	8.3 (5.5, 9.6)	17.6 (13.8, 23.0)	9.6 (8.1, 11.2)

a Only included progression events that occurred within 2 missing visits (+2 weeks) of the last evaluable assessment. If the patient progressed or died after 2 or more missed visits, the patient was censored at the time of the latest evaluable RECIST assessment. Progression included deaths in the absence of RECIST progression.
b Calculated using the Kaplan-Meier method.

c Hazard ratio was calculated from a Cox proportional hazard model with factors for treatment, CNS MTS, and a treatment by CNS MTS interaction. A HR <1 favours osimertinib.
d Only includes progression events that occurred within 2 missing visits (+2 weeks) of the last evaluable assessment.
e Target lesions, non-target lesions, and new lesions were not necessarily mutually exclusive categories.
f One patient enrolled with liver and respiratory metastatic lesion as only disease extend at baseline, no prior brain surgery and no prior brain radiation and was hence grouped in the CNS MTS='no' subgroup. However, the RECIST baseline by investigator included CNS as NTL and this lesion progressed.
g Progression events that did not occur within 2 scheduled visits (plus visit window) of the last evaluable assessment (or randomisation) were censored and therefore excluded in the number of events. Excluded deaths.NL = new lesion; NTL = non-target lesion; TL = target lesion

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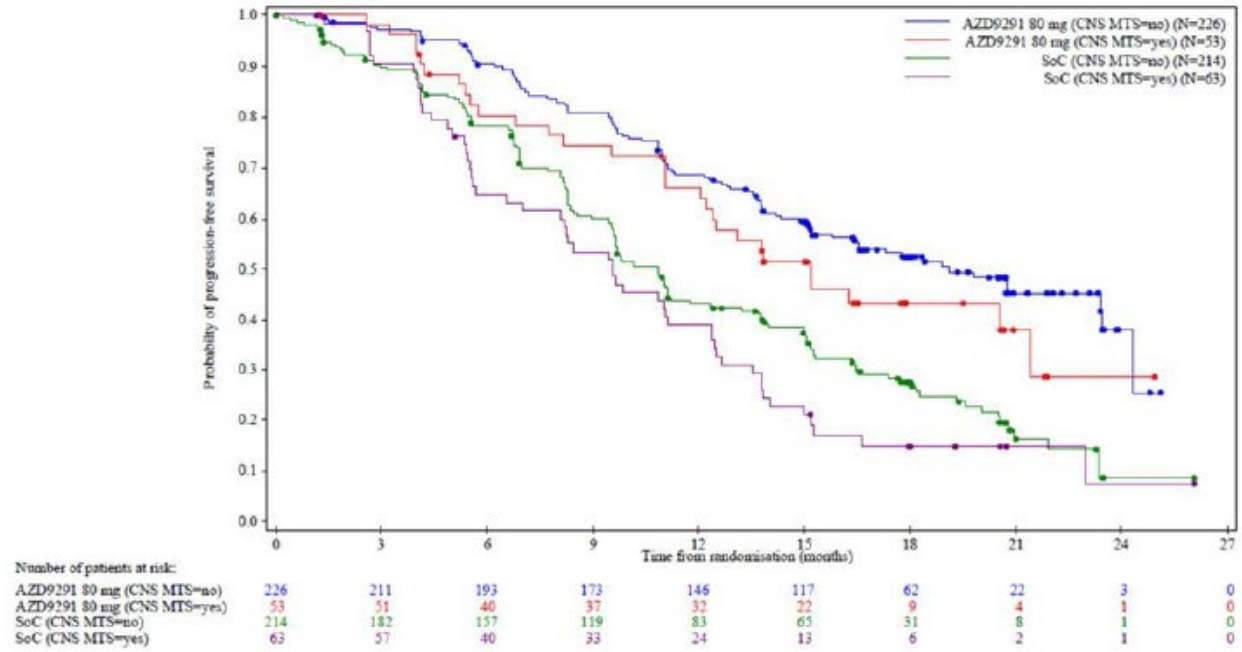

Figure 26: Kaplan-Meier plot of subgroup analysis of PFS: CNS MTS status at baseline (full analysis set)
Irrespective of the CNS MTS status at baseline, based on Investigator assessment, there were fewer patients with new CNS lesions in the osimertinib arm than in the SoC arm.

An analysis of efficacy by CNS MTS status at baseline based on study CNS BICR was consistent with the analysis by the Investigator: the HR for PFS in patients with a CNS MTS status of "Yes" based on BICR was 0.48 (95% CI: 0.30, 0.75; p = 0.001) in favour of osimertinib. The HR for PFS in patients with a CNS MTS status of "No" based on BICR was 0.47 (95% CI: 0.37, 0.61; p<0.0001).

The median DoR and proportion of patients remaining in response at 3 months, 6 months, 9 months, and 12 months favoured osimertinib, irrespective of CNS MTS status at entry. The interpretation of an OR of 0.5 in favour of SoC for patients with a CNS MTS status of "Yes" should therefore take all data into account. Hence, taking all efficacy assessments together, this subgroup analysis demonstrates that irrespective of CNS MTS status at entry, patients receive greater benefit from osimertinib treatment that from treatment with SoC.

Efficacy on CNS metastases based on CNS BICR

The 2 analysis sets evaluated by CNS BICR were the cFAS (patients with measurable and non-measurable CNS metastases at baseline); and the cEFR (patients with measurable CNS metastases at baseline).

Table 31: Efficacy on CNS in cFAS and cEFR analysis sets by CNS BICR

	Number (%) patients			
	cFAS (N=128)		cEFR (N=41)	
	Osimertinib (n = 61)	SoC (n = 67)	Osimertinib (n = 22)	SoC (n = 19)
CNS progression-free survival				
No. (%) patients with CNS PFS events (CNS progression or death)[a]	18 (29.5)	30 (44.8)	-	-
Median CNS PFS (months) (95% CI)[b]	NC (16.5, NC)	13.9 (8.3, NC)	-	-
Hazard ratio (95% CI)[c]	0.48 (0.26, 0.86)		-	
2-sided p-value	0.014[d]		-	
CNS progression-free survival by number of CNS lesions at baseline				
No. of patients with 1-3 CNS lesions at baseline	47	49	-	-
No. (%) patients with CNS PFS events (CNS progression or death)[a]	11 (23.4)	21 (42.9)	-	-
Median CNS PFS (months) (95% CI)[b]	NC (16.6, NC)	13.9 (9.7, NC)	-	-
No. of patients with >3 CNS lesions at baseline	14	18	-	-
No. (%) patients with CNS PFS events (CNS progression or death)[a]	7 (50.0)	9 (50.0)	-	-
Median CNS PFS (months) (95% CI)[b]	16.5 (7.5, NC)	8.3 (4.0, NC)	-	-
CNS objective response rate				
No. (%) patients with CNS response	40 (65.6)	29 (43.3)	20 (90.9)	13 (68.4)
ORR, % (95% CI)[e]	65.6 (52.3, 77.3)	43.3 (31.2, 56.0)	90.9 (70.8, 98.9)	68.4 (43.3, 87.4
CNS confirmed objective response rate				
No. (%) patients with CNS response	35 (57.4)	27 (40.3)	17 (77.3)	12 (63.2)
ORR, % (95% CI)[e]	57.4 (44.1, 70.0)	40.3 (28.5, 53.0)	77.3 (54.6, 92.2)	63.2 (38.4, 83.7)
CNS duration of response[f]				
Median CNS DoR (months) (95% CI)[b]	NC (11.9, NC)	14.4 (7.0, 18.7)	15.2 (4.1, NC)	18.7 (4.2, 18.7)
Patients remaining in response >6 months	30 (75.0)	16 (55.2)	15 (75.0)	6 (46.2)
Patients remaining in response >12 months	16 (40.0)	8 (27.6)	8 (40.0)	4 (30.8)
CNS duration of response for confirmed responses				
Median CNS DoR (months) (95% CI)[b]	NC (11.9, NC)	14.4 (8.3, 18.7)	NC (8.5, NC)	18.7 (4.2, 18.7)
Patients remaining in response >6 months	30 (85.7)	16 (59.3)	15 (88.2)	6 (50.0)
Patients remaining in response >12 months	16 (45.7)	8 (29.6)	8 (47.1)	4 (33.3)
CNS disease control rate				
DCR% (95% CI)	90.2 (79.8, 96.3)	83.6 (72.5, 91.5)	95.5 (77.2, 99.9)	89.5 (66.9, 98.7)

cEFR = central nervous system evaluable-for-response analysis set; cFAS = central nervous system full analysis set.

[a] Progression events that did not occur within 2 scheduled visits (plus visit window) of the last evaluable assessment (or randomisation) were censored and therefore excluded from the number of events.

[b] Calculated using the Kaplan-Meier method.

[c] The HR was calculated from a Cox proportional hazards model with a factor for treatment. The CI was calculated using profile likelihood. An HR <1 favours osimertinib.

[d] nominally statistically significant.

[e] The CIs were calculated using Clopper-Pearson exact method for binomial proportions.

[f] Duration of response is the time from first documentation of CR/PR until the date of progression or death in absence of disease progression. Responses required confirmation at least 4 weeks after the criteria for first response were met.

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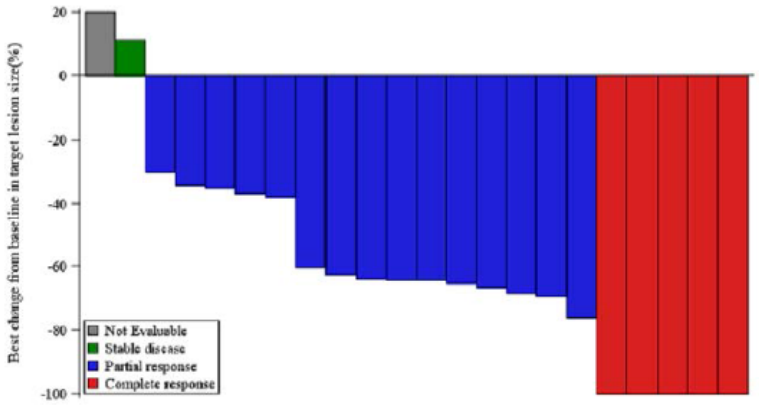
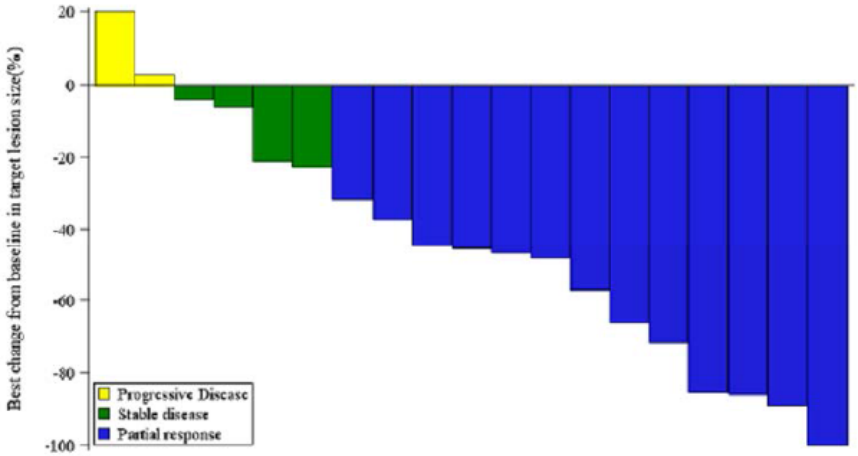
There was a greater decrease in CNS TL size in the osimertinib arm compared to the SoC arm in the cEFR.

Osimertinib arm



SoC arm



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

*represents imputed values: if it was known that a patient had died, had new lesions or progression of non-target lesions, had withdrawn due to PD and had no evaluable target lesions (before or at progression) assessments, best change was imputed as 20%

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Figure 27: CNS target lesion size, best change from baseline, waterfall plot (cEFR analysis set)

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 32: Summary of Efficacy for FLAURA trial

Title: A Phase III, Double-blind, Randomised Study to Assess the Efficacy and Safety of AZD9291 versus a SoC EGFR TKI as First-line Treatment in Patients with EGFR Mutation-positive, Locally-advanced or Metastatic Non-small-cell Lung Cancer (FLAURA)		
Study identifier	2014-002694-11	
Design	Phase 3, multicentre, double-dummy, controlled, randomized study	
	Duration of main phase:	From 19-Feb-2015 (FPR) to 12-Jun-2017 (DCO)
Hypothesis	Superiority over SoC (erlotinib or gefitinib)	

Treatments groups	Osimertinib		Osimertinib 80 mg orally once daily; n= 279
	SoC		Gefitinib 250 mg orally once daily or Erlotinib 150 mg orally once daily; n= 277
Endpoints and definitions	Primary endpoint	PFS	Time from randomisation until date of objective disease progression (RECIST v1.1. assessed by investigator) or death by any cause in the absence of progression.
	Secondary endpoint	OS	Time from date of randomisation until death from any cause
	Secondary endpoint	ORR	Number (%) of randomised patients with at least 1 visit response of CR or PR.
Database lock	12-Jun-2017		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat population (Osimertinib n=279; SoC n=277) DCO of main analysis of PFS (1st IA for OS).		
Descriptive statistics and estimate variability	Treatment group	Osimertinib	SoC
	Number of subject	279	277
	Primary endpoint PFS (INV) Median months	18.9	10.2
	(95% CI)	(15.2, 21.4)	(9.6, 11.1)
	Secondary endpoint OS Median months	NR	NR
	(95% CI)	-	-
	Secondary endpoint ORR n (%)	223 (79.9%)	210 (75.8%)
	(95% CI)	(71.3, 81.5)	(63.1, 74.4)
	Secondary endpoint DoR Median months	17.2	8.5
	(95% CI)	(13.8, 22.0)	(7.3, 9.8)
Effect estimate per comparison	Primary endpoint PFS	Comparison groups	Osimertinib vs. SoC
		HR (stratified)	0.46
		(95% CI)	(0.37, 0.57)
		P-value	<0.0001
	Secondary endpoint OS	Comparison groups	Osimertinib vs. SoC
		HR (stratified)	0.63
		(95% CI)	(0.45, 0.88)
		P-value	0.0068*
	Secondary endpoint ORR	Comparison groups	Osimertinib vs. SoC
		Odds ratio**	1.27
		(95% CI)	(0.85, 1.90)
		P-value	0.2421
Notes	*NES. OS 1st IA: For statistical significance a p-value<0.0015 (O'Brien-Fleming approach) was required. **Data corresponds to unadjusted OR. Adjusted OR (95% CI): 1.28 (0.85, 1.93)		
Analysis description	**Efficacy according to CNS metastases status at baseline** **CNS MTS Yes at baseline n=116 (53 Osimertinib; 63 SoC)** **CNS MTS No at baseline n=440 (226 Osimertinib; 214 SoC)**		
	Treatment group	**CNS MTS Yes**, Osimertinib n=53	**CNS MTS Yes**, SoC n=63
	PFS Median months (IC 95%)	15.2 (12.1, 21.4)	9.6 (7.0, 12.4)
	ORR n (%)	40 (75.5%)	183 (81.0%)
	Treatment group	**CNS MTS No**, Osimertinib n=226	**CNS MTS No**, SoC n=214
	PFS Median months (IC 95%)	19.1 (15.2, 23.5)	10.9 (9.6, 12.2)

	ORR n (%)	54 (85.7%)	156 (72.9%)

Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable

Clinical studies in special populations

Not applicable

Supportive study(ies)

Proof-of-concept of the efficacy of osimertinib in the first-line setting came from a cohort of 30 patients with EGFRm NSCLC treated with osimertinib 80 mg in the Phase I component of Study D5160C00001 (AURA Phase I component). At the time the FLAURA study was designed, results from the first DCO date (2 December 2014) were available. Further confirmation of an efficacy signal was observed with longer follow-up in these patients in first-line, showing, at the third DCO (1 November 2016), a median PFS of 22.1 months (95% CI: 13.7, 30.2); an ORR of 66.7% (95% CI: 47.2, 82.7); a reduction in size of target lesions (TLs) in 97% of patients; and a median DoR at 75% maturity of 19.3 months (95% CI: 12.3, 24.7). As this was a Phase I study without a protocol-mandated scheduled collection of OS throughout the study, full survival follow-up may have been incomplete; thus, OS analysis was not conducted.

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

FLAURA is a Phase III, double-blind, randomised study (1:1 ratio) specifically designed to compare the efficacy of osimertinib vs. SoC (either gefinitib or erlotinib) as first-line treatment in patients with locally-advanced or metastatic EGFRm NSCLC.

Patient population

Patients with locally advanced or metastatic NSCLC (Pathologically-confirmed adenocarcinoma) not amenable to curative surgery or radiotherapy with a documented (centrally or locally) EGFR mutation known to be associated with EGFR-TKI sensitivity (Ex19del, L858R), were recruited. Patients had to be treatment naïve for advanced cancer although adjuvant or neo-adjuvant therapy at an earlier stage of the NSCLC was permitted.

While it is acknowledged that 85 % - 90 % of the patients with activating mutations harbour Ex19del or L858R mutations, no patients with less common mutations were included in FLAURA trial**.** All patients were to have adequate cardiac, hepatic and renal function, WHO-PS of 0 or 1 with no deterioration over the previous 2 weeks and a minimum life expectancy of 12 weeks. Patients were required to have at least 1 measurable lesion at baseline according to the investigator. Patients with CNS metastases were eligible if they were asymptomatic, stable and not requiring steroids for at least 2 weeks prior to start of study treatment, this is relevant as osimertinib is claimed to have superior blood barrier penetration than other licensed TKIs which are considered to have limited efficacy on CNS metastases.

The exclusion of patients with poor general condition (WHO PS 2 or higher), and short life expectancy is a limitation in the study design.

Treatments

Osimertinib was administered at the same dose as that currently authorised one for patients with the T790M mutation, 80 mg once a day.

Erlotinib and gefitinib are considered suitable comparators as both together with afatinib are the standard of care for first-line EGFRm NSCLC. The absence of afatinib is justified based on the fact that it was not widely available at the time of FLAURA trial start. Study centres had to declare their choice of comparator prior to site initiation. In some regions there was only one drug of choice such as in the US (where erlotinib was the only licensed drug at the time of start of the trial) or Japan (where gefitinib was the only investigator´s choice). Both erlotinib and gefitinib, were administered according to SmPC recommended doses and schedules.

Patients progressing in the SoC arm as determined by the investigator, with confirmation by BICR, who had not received any subsequent therapy after discontinuation of study therapy and who had confirmation of T790M mutation, were given the opportunity to be treated with osimertinib 80 mg once daily. This is in line with the currently authorised indication of osimertinib and cross-over is considered ethical, although it will affect OS data.

Endpoints

The primary efficacy endpoint of FLAURA was PFS based on investigator assessment according to RECIST v1.1. For this first-line setting PFS is an acceptable primary endpoint. OS, ORR, DoR, QoL and post progression outcomes (PFS2) were included as secondary endpoints.

OS data as well as PFS2 data are considered of great value in order to assess how osimertinib acts on the development of secondary resistances and whether the early introduction of osimertinib could have some impact on subsequent lines of therapy..

An analysis in a predefined subgroup of patients presenting CNS metastases at baseline was planned. CNS BIRC assessment of PFS and ORR was also performed.

Randomisation and SAP

Suitable patients were centrally randomised to receive either osimertinib 80 mg or SoC in a 1:1 ratio. Patients were stratified at randomisation based on EGFR mutation status (Ex19del or L858R) ethnicity (Asian/Non-Asian).

The DCO for the main PFS analysis (after approximately 359 PFS events) was performed at the DCO of 12-Jun-2017. The first IA on OS was performed at that time. The final analysis for OS has not yet been conducted.

Results

The overall patient population seems reasonably representative for the intended patient population.

As of DCO1 for the primary PFS analysis, 141 (50.5%) patients in the osimertinib arm and 64 (23.1%) patients in the SoC arm patients were ongoing on their randomised treatment.

Two amendments to protocol were carried out, mainly related to the inclusion of the China cohort (as recommended by Chinese regulatory authority), and to allow post progression cross-over to osimertinib for patients in the SoC arm and statistical issues. The MAH is recommended to submit data from the Chinese cohort when available.

The number of protocol deviations is overall high (23.3% osimertinib vs 18.1% SoC) however none is considered to have meaningful impact on study results.

- Baseline characteristics

Patient demographic seem to be well-balanced between arms. The median age was 63 years (range 26 to 93 years), with 79 patients (14.2%) aged ≥75 years. There was a greater proportion of female

patients (62.9%) and the population was predominantly Asian (62.4%) and white (36.2%). The proportion of Asian population is consistent with previous trials with osimertinib (in AURA 3 trial (second line of T790M+ NSCLC) 65.4% of patients were Asian). Pivotal trials with first and second-generation TKIs, on the contrary, were either conducted in Asian population (IPASS trial) or in Caucasic patients (EURTAC trial). Two-thirds of patients had never smoked (64.2%) and a low percentage of patients (3.1%) were current smokers. This is consistent with the known prevalence of sensitising EGFR mutations.

Most patients had a WHO performance status of 1 (58.8%). As per inclusion criteria all patients should have had histological type of adenocarcinoma (or mixed histology with predominance of adenocarcinoma). Based on confirmation by both central and local test, the most common EGFR sensitising mutations were exon 19 deletion (62.7% in osimertinib arm vs. 62.8 in SoC) and exon 21 L858R (37.3% osimertinib vs. 37.2% SoC).

Of the 556 patients randomised in the trial 267 (48%) were randomised based on local testing of EGFR mutations and 289 (52%) based on status identified by central laboratories (cobas® EGFR Mutation Test). All patients centrally analysed were positive for EGFR mutations. From the 267 patients locally analysed, samples from 226 patients were also sent for central confirmation of mutations (84.6%). Mutations were centrally confirmed in 211 patients (211/267; 80%) whereas absence of mutation was centrally confirmed for 6 patients and the sample was invalid for testing in 9 patients. Concordance between central and local test sites was high.

EGFR mutations by cobas central test classified 56.6% of patients in the osimertinib arm vs. 56.0% in the SoC as having exon 19 deletion, 34.8% and 32.5% respectively as exon 21 L858R, 1.1% in each study arm (3 patients each) as EGFRm not detected and 1.4% and 1.8% of patients respectively as invalid test.

Most patients had metastatic disease (94.6%) while only 5.2% (n=29) had locally advanced (stage IIIb) NSCLC not suitable for definitive multimodality therapy. The proportion is in line with what was seen in other recent trials in lung cancer.

Sites of metastases were comparable between study arms.

Central nervous system (CNS) metastases as collected by investigators in the sCRF pages were present in 19% of patients in osimertinib arm (n=53) and 22.7% of patients (n=63) in the SoC arms, however these were required to be asymptomatic, stable and not requiring steroids for at least 2 weeks prior to the start of study treatment.

Overall the main demographic and disease characteristics can be considered representative of targeted population.

8.6% of patients (n=24) from the osimertinib arm and 14.1% from SoC received second post-treatment anticancer therapy.

Efficacy data and additional analyses

A statistically significant and clinically relevant improvement in terms of the primary endpoint, PFS per investigator assessment (HR: 0.46 [95% CI: 37, 0.57]; p-value: <0.0001), was shown by osimertinib compared to the SoC arm. Data can be considered mature enough with 48.7% of events in the osimertinib arm and 74.4% in SoC arm. Treatment with osimertinib resulted in a 8.7-month improvement in median PFS compared to SoC (18.9 months [95% CI: 15.2, 21.4] vs. 10.2 months [95% CI: 9.6, 11.1]). PFS rates consistently favoured osimertinib treatment arm at 6 months (88.4% vs. 75.2%), 12 months (68.2% vs. 42.3%) and 18 months (50.9% vs. 24.4%). K-M curves show a

clear and early separation almost from the beginning of the trial.

PFS results according to BICR on the FAS are consistent with main analysis, HR: 0.45 (95% CI: 0.36, 0.57; p-value <0.0001). Median estimates were close to those estimated by investigator but slightly lower in both arms, 17.7 months (95% CI: 15.1, 21.4) in the osimertinib arm vs. 9.7 months (95% CI: 8.5, 11.0) in the SoC arm. Exploratory analyses carried out in order to estimate the discrepancy degree between BICR and investigator (early discrepancy rate (EDR) and late discrepancy rate (LDR)) did not raise concerns.

Although an analysis in the subgroup of patients presenting at baseline with T790M+ was initially pre-planned, it was finally not performed given the low number of patients (4 patients in the osimertinib arm and 1 patient in the SoC arm). This is compliant with the amended study protocol and SAP.

Different sensitivity analyses were carried out in order to assess robustness of results. They included assessment of ascertainment bias, evaluation-time bias, attrition bias as well as assessment of the impact of the change in RECIST scanning schedule at Month 18 from every 6 weeks to every 12 months, which fell close to the median PFS of 18.9 months in the osimertinib arm. All sensitivity analyses supported the main one with HR between 0.45-0.47 and upper bounds of the 95% CI no greater than 0.58.

A sensitivity analysis comparing the differences in PFS data between osimertinib and gefitinib vs. osimertinib and erlotinib was not planned or performed. The study was not designed or powered to allow a meaningful interpretation of this analysis: randomization into the two study arms was stratified by ethnicity and EGFR mutations, both factors known to impact outcome, however patients randomized into the comparator arms were not stratified to also generate an equal distribution of these factors over the two SoC choices. Taking into account that a separate analysis for gefitinib and erlotinib was likely to be heavily confounded by the unequal distribution of ethnicity and that other previously conducted head-to-head studies of erlotinib versus gefitinib showed no statistically significant difference for efficacy, this issue was not further pursued. Furthermore, no unexpected change in WHO performance status was observed in either arm of the study.

Subgroup analyses for PFS showed consistent results in all subgroups analysed. Previous experience with first and second-generation TKIS suggested better efficacy in patients with Exon19 mutation compared to those with L858R mutations. A similar trend has been observed in the FLAURA trial and the benefit over the SoC is clear for both subgroups. Regarding the analysis of subgroups according to EFGR mutation by ctDNA was also consistent with main findings although CI in some subgroups are widened likely because of the limited sample size (HR of 0.44 (95% CI: 0.34-0.57) for EGFR m+; HR of 0.48 (95% CI: 0.28-0.80) EGFR m-; HR of 0.41 (95% CI: 0.21-0.78) EGFR missing). The HR in the subgroup of patients with centrally confirmed mutation was 0.43 (95% CI: 0.34-0.54).

There were 14% of patients aged ≥75 years. The treatment effect in patients older than 75 years old is not considered critically dissimilar to that of the overall population. Results in terms of PFS for this subgroup are borderline statistically significant (upper limit 95%CI: 1.02) which could be due to the limited sample size.

Osimertinib performed better in the non-Asian population compared to the Asian population with a PFS of 24.3 months (95%CI: 16.4, NC) vs. 16.6 months (95%CI: 13.8, 20.7), respectively. The existing PFS data demonstrated a statistically and clinically relevant benefit over SoC in both Asians and non-Asians.

PFS in patients with locally advanced disease seemed to be in line with the overall population, although the data set is too small to conclude.

PFS results in the comparator arm observed in the FLAURA trial (10.2 months) can be considered in

line with data from previous trials of TKI inhibitors, including those of afatinib, where medians ranging from 8.2 to 13.7 months at best were observed. The most recent phase III trial (ARCHER 1050; Wu et al 2017) compared a new TKI inhibitor with gefitinib and a median PFS of 11.0 months was documented for the latter. PFS results for osimertinib (median 18.9 months) compare favourably to the best outcomes documented in the literature for TKI alternatives (13.7 months).

The first OS interim analysis was submitted showing a HR of 0.63 (CI 95% 0.45, 0.88) that did not reach the pre-specified threshold for statistical significance. Superior rates at different time points consistently favoured osimertinib arm (OS rates at 12 months: 89.1% vs. 82.5%; 18 months: 82.8% vs. 70.9%).

Results from the final analysis would further support the efficacy including subgroup analyses of OS. The MAH is recommended to submit the final OS analysis expected to be available by Q4 2019.

OS data will be submitted together with updates of other relevant endpoints such as TFST and TSST. Although it is acknowledged that the cross-over of patients will unavoidably confound study results.

Regarding secondary endpoints, the superiority in terms of PFS is however not supported by a statistically significant difference in terms of response rates. The ORR (not confirmed) was 79.9% (95% CI: 74.7, 84.5) in the osimertinib arm and 75.8% (95% CI: 70.3, 80.7) in the SoC arm. The confirmed responses were consistent with the unconfirmed ORR data. Acknowledging the limitations of cross-study comparisons, the ORR results observed in this study are in line with the ORRs observed in randomized controlled studies with currently approved EGFR-TKIs (58%-83%, reviewed in Sebastian et al 2014). A longer duration of response has been observed with osimertinib compared to SoC (median 17.2 months vs. 8.5 months). The BICR assessment of ORR was consistent with the Investigator assessment as it was the analysis of ORR according to centrally confirmed EGFRm.

CNS analyses (by BICR and Investigator)

Efficacy analyses were conducted in the subset of patients with CNS metastases at baseline.

Of 556 patients randomized, 200 had available baseline brain scans. CNS efficacy by RECIST v1.1 in FLAURA demonstrated a nominal statistically significant improvement in CNS PFS HR: 0.48 (95% CI: 0.26, 0.86). An ORR of 65.6% (95% CI: 52.3, 77.3) was documented in the osimertinib arm vs. 43.3% (95% CI: 31.2, 56.0) in the SoC arm in the subset of patients with brain metastasis. These findings confirm preclinical investigation suggesting that osimertinib has higher BBB than other TKIs.

Patients reported outcome data

The overall compliance in terms of PRO data over the first 9 months was similar between treatment arms, and ≥60%.

The presented PRO data collected up to nine months showed no significant differences between treatment arms. A clinically relevant improvement from baseline in cough in both treatment arms was shown, and a clinically relevant worsening in diarrhoea in both treatments was also observed and could be expected considering the mechanism of action and safety profile of the studied medicinal products.

Post-progression outcomes (exploratory endpoints)

At DCO1, 73 (26.2%) patients from osimertinib and 106 (38.3%) patients from SoC had second progression events after the start of subsequent therapy or died. The majority of patients in the osimertinib arm received platinum-based therapy after progression on trial treatment and the majority of patients in SoC arm received EGFR-TKI therapy (including 48 patients that were eligible to cross-over to osimertinib). Median PFS2 is longer in the osimertinib arm however data are still immature with low percentage of events.

TFST and TSST favoured osimertinib arm. Median TSST was not reached in both arms (0.60 (0.45, 0.80); P=0.0005) as data are still immature (limited number of patients with second subsequent therapy).

The potential mechanisms of resistance to osimertinib have not been investigated in the FLAURA trial. Blood samples for ctDNA testing and optional tumour samples were collected from patients in both treatment arms at time of progression to explore the potential mechanisms of resistance, results are anticipated to be available by the 3/4Q 2018 and the MAH is recommended to submit them.

Although more mature OS data is still awaited, preliminary data together with post-progression measures (PFS2, TFST) are in favour of osimertinib treatment. This reflects that osimertinib does not negatively impact next-line therapies. Twenty nine (29) patients received an EFGR-TKI as subsequent therapy to osimertinib. Median PFS for this subset of patients was lower than for the overall population. No reliable conclusion can be made on the possible impact of osimertinib treatment on next-line TKI therapies or development of cross-resistances due to the limited sample size.

A broadening of the indication to mutations other than Ex19del or L858R has been considered.

Available evidence, including early preclinical data with mutant cell lines shows activity of osimertinib, against the rare EGFR mutations G719S, L861Q, and the exon 19 insertion mutations (Cross et al 2014). Publications have also reported activity in exon 20 mutations (Lee et al 2017; Kohsaka et al 2017; Ward et al 2016). Clinical data with osimertinib in other mutations are limited, although ongoing clinical trials could provide additional information in the future. It is not expected that osimertinib would have a lower efficacy in other mutations. Alternatives authorised in the treatment of EGFR activating mutations do not have a restricted use based on specific EGFR mutations despite very little or no clinical data in rare mutations.

Based on the above, the CHMP considered that the use of Tagrisso should not be restricted to Ex19del or L858R mutations.

2.4.4. Conclusions on the clinical efficacy

Osimertinib prolong PFS in a clinically relevant manner when compared to SoC (gain 8.7 months), which could likely translate into longer OS for patients (as pointed out by preliminary data). PFS results are well-above findings of first and second-generation TKIs, and although rather similar results in terms of ORR are observed, the duration of responses was significantly longer for osimertinib. This could potentially be due to a delay in TKI resistance development, however no data confirming this hypothesis has been submitted and the potential mechanisms of resistance to osimertinib remain to be investigated.

Although more mature OS data are will be available post authorisation (final OS results expected to be provided by Q4 2019), preliminary data together with post-progression measures (PFS2, TFST) are in favour of osimertinib treatment. On the basis of the available data, it is considered that osimertinib does not negatively impact next-line therapies.

The benefit of osimertinib as first-line for the overall population of EGFR mutated patients therapy overcomes the potential uncertainties about treatment sequencing as it is currently not possible to predict in advance which patients will develop T790M resistance prior to receiving any EGFR-TKI therapy.

2.5. Clinical safety

Introduction

The safety review is based primarily on the results of the Phase III study FLAURA (D5160C00007).

FLAURA safety data are based on the DCO date for the primary efficacy analysis of PFS: 12 June 2017. Moreover, updated data, with an additional follow-up of 90 days have been provided (90 DSU DCO – 25 September 2017).

Safety findings in FLAURA (first-line therapy) were supported by a pooled dataset (N = 1142) that includes data from Phase I-III studies in patients treated with 80 mg osimertinib as first-line (309 patients) or ≥ second-line therapy (833 patients) for EGFR mutation-positive NSCLC: FLAURA (N = 279), AURA3 (N = 279), AURA2 (N = 210), AURA extension (N = 201), and AURA Phase 1 (N =173). The pooled population did not include patients who crossed over to osimertinib after disease progression on their initial treatment.

Table 33: Summary of key clinical studies contributing to the evaluation of the safety of osimertinib

Study	Design	Number of patients	Patient population	Location of report in Module 5
D5160C00007 Phase III (FLAURA) DCO1: 12 June 2017	A Phase III, double-blind, randomised study to assess the efficacy and safety of osimertinib versus a standard-of-care EGFR TKI as first-line treatment Primary objective: To assess the efficacy of single-agent osimertinib compared with SoC EGFR-TKI therapy as measured by progression-free survival (PFS) Key safety objective: To assess the safety and tolerability profile of osimertinib compared with SoC EGFR-TKI therapy	556 first-line patients: 279 treated with osimertinib 80 mg 277 treated with SoC: 94 erlotinib 150 mg 183 gefitinib 250 mg	Patients with EGFR mutation-positive (Exon 19 deletion or L858R), locally advanced or metastatic NSCLC	Module 5.3.5.1
D5160C00003 (AURA3) DCO1: 15 April 2016	Phase III, open-label, randomised study of osimertinib vs. platinum-based doublet chemotherapy Primary objective: To assess the efficacy of osimertinib compared with platinum-based doublet chemotherapy by assessment of PFS. Key safety objective: To assess the safety and tolerability profile of osimertinib compared with platinum-based doublet chemotherapy.	415 second-line patients: 279 treated with osimertinib 80 mg 136 treated with pemetrexed plus cisplatin or pemetrexed plus carboplatin followed by optional pemetrexed maintenance	Patients with advanced EGFR T790M mutation-positive, locally advanced or metastatic, NSCLC whose disease has progressed following treatment with an approved EGFR TKI (second-line).	Edition 2 dated 9 Nov 2016 (AURA3 DCO1 of 15 Apr 2016), in Module 5.3.5.1
D5160C00002 (AURA2) DCO4: 1 November 2016	Phase II, single-arm, open-label, non-randomised study. Primary objective: To assess the efficacy of osimertinib by assessment of ORR. Key secondary safety objective: To assess the safety and tolerability profile of osimertinib.	210 second-line (n=68) and ≥third-line (n=142) patients treated with osimertinib 80 mg	Patients with advanced EGFR T790M mutation positive NSCLC whose disease has progressed following either 1 prior therapy with an EGFR TKI (second-line chemotherapy-naïve, n=68) or following treatment with at least 1 EGFR TKI and 1 prior platinum-based doublet chemotherapy (≥third-line, n=142), in addition further lines of therapy were permitted such as cytotoxic chemotherapy or immunotherapy.	5.3.5.2
D5160C00001 (Phase II component) (AURA extension) DCO4: 1 November 2016	Phase II, single-arm, open-label, non-randomised study extension to AURA Primary objective: To investigate the safety, tolerability and efficacy (objective response rate [ORR]) of osimertinib Key secondary safety objective: To investigate the safety and tolerability of osimertinib given orally as first-line therapy to patients who are treatment-naive.	201 second-line (n=61) and ≥third-line (n=140) patients treated with osimertinib 80 mg	Patients with advanced EGFR T790M mutation positive NSCLC whose disease has progressed following either 1 prior therapy with an EGFR TKI or following treatment with both EGFR TKI and at least 1 other prior line of therapy, such as cytotoxic doublet chemotherapy or immunotherapy.	5.3.5.2
D5160C00001 AURA Phase I (Phase I component) DCO3: 1 November 2016	Phase I component (dose-escalation and dose expansion) of Study D5160C00001. Primary objective: To investigate the safety, tolerability, and efficacy (ORR by BICR) of oral osimertinib Key secondary objectives: To characterise the PK of osimertinib and its metabolites (AZ5104 and AZ7550) after multiple oral doses To obtain additional assessments of the anti-tumour activity of osimertinib by evaluation of DoR, DCR, and PFS	The study evaluated 31 pre-treated patients in the dose-escalation portion and 371 patients (311 pre-treated, 60 first-line*) in the dose-expansion portion	Patients with advanced EGFR-mutation-positive NSCLC who are treatment-naïve (first line, n=60) or whose disease has progressed following prior therapy with an EGFR TKI (≥second line, n=342)*	5.3.5.2

BICR = blinded independent central review; DCO = data cut-off; DCR = disease control rate; DoR = duration of response; EGFR = epidermal growth factor receptor; NSCLC = non-small cell lung cancer; ORR = objective response rate; PFS = progression-free survival; PK = pharmacokinetics; TKI = tyrosine kinase inhibitor

*173 patients are included in the evaluation of safety in this summary: 30 patients who received 80 mg osimertinib as first-line therapy and 143 patients who received 80 mg osimertinib as >=second-line therapy

Patient exposure

Study FLAURA

All patients randomised to osimertinib or SoC received at least 1 dose of study medication. At the time of the 12 June 2017 DCO1, 141/279 (50.5%) patients were still on treatment in the osimertinib arm and 64/277 (23.1%) were still on treatment in the SoC arm. In comparison, at the time of the 90 DSU DCO, 25 September 2017, 127 (45.5%) patients were still on treatment in the osimertinib arm and 50 (18.1%) were still on treatment in the SoC arm.

Exposure to osimertinib and SoC is summarized in the table below.

Table 34: Duration of exposure in FLAURA (Safety analysis set)

		Number (%) of patients			
		Osimertinib 80 mg (N=279)		Standard of Care (N=277)	
		DCO1	90 DSU	DCO1	90 DSU
Total exposure (months)[a]	Mean (SD)	15.05 (6.6)	16.73 (7.9)	11.78 (6.8)	12.47 (7.7)
	Median	16.20	18.79	11.53	11.53
	Minimum	0.1	0.1	0.0	0.0
	Maximum	27.4	30.9	26.2	29.6
	Total treatment years	349.9	389.0	271.9	287.9
Actual exposure (months) [b]	Mean (SD)	14.88 (6.6)	16.55 (7.9)	11.56 (6.8)	12.25 (7.7)
	Median	16.10	18.56	11.50	11.50
	Minimum	0.1	0.1	0.0	0.0
	Maximum	27.4	30.9	26.2	29.6
	Total treatment years	346.0	384.9	266.9	282.7
Cumulative exposure over time	≥9 months	220 (78.9)	220 (78.9)	177 (63.9)	177 (63.9)
	≥12 months	194 (69.5)	194 (69.5)	131 (47.3)	131 (47.3)
	≥15 months	162 (58.1)	167 (59.9)	99 (35.7)	103 (37.2)
	≥18 months	106 (38.0)	150 (53.8)	55 (19.9)	74 (26.7)
	≥21 months	53 (19.0)	99 (35.5)	25 (9.0)	46 (16.6)
	≥24 months	13 (4.7)	54 (19.4)	7 (2.5)	20 (7.2)
	≥27 months	1 (0.4)	16 (5.7)	0	5 (1.8)
	≥30 months		1 (0.4)		0

a Total exposure = [(last dose date where dose >0 mg – first dose date) + 1] / 30.4375.
b Actual exposure = [((last dose date where dose >0 mg – first dose date) + 1) – total duration of dose interruption (ie, number of days with dose = 0 mg)] / 30.4375.
Includes exposure to randomised study treatment during the double-blind treatment phase, not including crossover treatment.
If a patient has not discontinued, then the data cut-off date is used in place of last dose date.
Data cut-off date: DCO1=12 June 2017; 90 DSU DCO=25 September 2017
Source: see Table 5, Module 2.7.4 dated 4 October 2017 and see Table 11.3.1.1, Appendix A

Pooled dataset

In the pooled population, the median duration of osimertinib therapy was 12.9 months (mean, 13.9 months; range, <0.1 – 40.1 months). Actual exposure was similar to intended exposure (median: 12.7; range: 0.0-17.6 months), indicating that the frequency and median duration interruptions had low impact on exposure.

Dose modifications

Table 35: Treatment interruptions and dose reductions in FLAURA (Safety analysis set)

		Number (%) of patients	
		Osimertinib 80 mg (N=279)	Standard of Care (N=277)
Total patients with any dose modification[a]	Any	108 (38.7)	107 (38.6)
Reasons for any modification	Adverse event	71 (25.4)	89 (32.1)
	Patient forgot to take dose	31 (11.1)	23 (8.3)
	Surgery	4 (1.4)	5 (1.8)
	Laboratory abnormality not reported as an AE	3 (1.1)	0
	Other reason	15 (5.4)	10 (3.6)
Patients with a dosing interruption	Any	107 (38.4)	106 (38.3)
	1 interruption	65 (23.3)	67 (24.2)
	2 interruptions	17 (6.1)	17 (6.1)
	> 2 interruptions	25 (9.0)	22 (7.9)
Reasons for interruption	Adverse event	71 (25.4)	88 (31.8)
	Patient forgot to take dose	31 (11.1)	23 (8.3)
	Surgery	4 (1.4)	5 (1.8)
	Laboratory abnormality not reported as an AE	3 (1.1)	0
	Other reason	13 (4.7)	10 (3.6)
Patients with a dose reduction	Any	17 (6.1)	19 (6.9)
Reasons for dose reduction [a]	Adverse event	15 (5.4)	19 (6.9)
	Other	2 (0.7)	0

a Number of patients with a dose interruption and/or a dose reduction. Reasons for dose modifications are not mutually exclusive for patients with multiple modifications although patients are counted only once per category.

Data cut-off date: 12 June 2017

Source: Table 11.3.1.2, FLAURA CSR, Module 5.3.5.1

Adverse events

Study FLAURA

This analysis included AEs with an onset date on or after the date of the first dose, up to and including 28 days following discontinuation of randomised treatment or the day before administration of osimertinib as crossover treatment.

Table 36: Adverse events in any category in FLAURA (Safety analysis set)

	Number (%) of patients [a]			
	Osimertinib 80 mg (N = 279)		Standard of Care (N = 277)	
	DCO1	90 DSU	DCO1	90 DSU
Median duration of exposure (months)	16.2	18.8	11.5	11.5
Any AE	273 (97.8)	273 (97.8)	271 (97.8)	271 (97.8)
Any AE causally related to treatment [b]	253 (90.7)	253 (90.7)	255 (92.1)	254 (91.7)
Any AE of CTCAE grade 3 or higher	95 (34.1)	103 (36.9)	124 (44.8)	125 (45.1)
Any AE of CTCAE grade 3 or higher, causally related to treatment [b]	49 (17.6)	51 (18.3)	78 (28.2)	78 (28.2)
Any AE with outcome = death	6 (2.2)	8 (2.9)	10 (3.6)	9 (3.2) [c]
Any AE with outcome = death, causally related to treatment [b]	0	0	1 (0.4)	1 (0.4)
Any SAE (including events with outcome = death)	60 (21.5)	63 (22.6)	70 (25.3)	72 (26.0)
Any SAE (including events with outcome = death), causally related to treatment[b]	22 (7.9)	22 (7.9)	23 (8.3)	24 (8.7)
Any AE leading to dose interruption	70 (25.1)	72 (25.8)	66 (23.8)	70 (25.3)
Any AE leading to dose reduction	11 (3.9)	11 (3.9)	15 (5.4)	17 (6.1)
Any AE leading to discontinuation of treatment	37 (13.3)	37 (13.3)	49 (17.7)	49 (17.7)
Any AE leading to discontinuation of treatment, causally related to treatment[b]	27 (9.7)	27 (9.7)	38 (13.7)	38 (13.7)

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.
c One fatal AE reported as a SoC patient at DCO1 was determined to be a cross-over patient at the 90 DSU and is reported in Section 6.
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 or the day before first administration of crossover treatment.
AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events version 4.03; SAE = serious adverse event
Data cut-off date: DCO1=12 June 2017; 90 DSU DCO=25 September 2017
Source: see Table 9, Module 2.7.4 dated 4 October 2017 and Table 11.3.1.1, Table 11.3.2.1.1, Table 11.3.2.9.1, Table 11.3.2.9.3 and Table 11.3.5.2.1, Appendix A

Pooled dataset

Table 37: Summary of categorical safety data in patients receiving osimertinib 80 mg in FLAURA and Phase I-III pooled datasets (Safety analysis set)

	AURA Phase I A & B (N = 143)	AURA2 & AURA1C (N = 411)	AURA3 (N = 279)	AURA Phase I first-line (N=30)	FLAURA (N=279)	Total (N=1142)
Duration of exposure (months) [a]						
Mean (standard deviation)	13.9 (10.96)	15.9 (8.99)	8.8 (4.05)	22.3 (11.52)	15.0 (6.64)	13.9 (8.50)
Median	11.1	16.4	8.2	27.1	16.2	12.9
Range	0.1-40.1	0.0-29.7	0.2-18.5	0.5-34.5	0.1-27.4	0.0-40.1
Any adverse event [b]	142 (99.3)	408 (99.3)	273 (97.8)	30 (100)	273 (97.8)	1126 (98.6)
Any AE causally related to osimertinib[c]	131 (91.6)	366 (89.1)	231 (82.8)	29 (96.7)	253 (90.7)	1010 (88.4)
Any AE of CTCAE ≥grade 3	78 (54.5)	180 (43.8)	63 (22.6)	18 (60.0)	95 (34.1)	434 (38.0)
Any AE of CTCAE ≥grade 3, causally related to osimertinib[c]	28 (19.6)	64 (15.6)	16 (5.7)	4 (13.3)	49 (17.6)	161 (14.1)
Any AE with outcome of death	9 (6.3)	22 (5.4)	4 (1.4)	0	6 (2.2)	41 (3.6)
Any AE with outcome of death, causally related to osimertinib[c]	0	4 (1.0)	1 (0.4)	0	0	5 (0.4)
Any SAE (including AEs with outcome of death)	52 (36.4)	145 (35.3)	50 (17.9)	14 (46.7)	60 (21.5)	321 (28.1)
Any SAE (including AEs with outcome of death), causally related to osimertinib[c]	8 (5.6)	28 (6.8)	8 (2.9)	4 (13.3)	22 (7.9)	70 (6.1)
Any AE leading to discontinuation of study drug	17 (11.9)	33 (8.0)	19 (6.8)	3 (10.0)	37 (13.3)	109 (9.5)
Any AE leading to discontinuation of study drug, causally related to osimertinib[b]	7 (4.9)	18 (4.4)	10 (3.6)	2 (6.7)	27 (9.7)	64 (5.6)

a Total treatment duration=(last dose date - first dose date +1)/(365.25/12).
b 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.
c As assessed by the Investigator.
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 4.03; SAE = serious adverse event
Data cut-off dates: 12 June 2017 for FLAURA, 15 April 2016 for AURA3, 1 November 2016 for the Phase I-II studies
Source: Table 2.7.4.1.1 and Table 2.7.4.2.1.1, Pooled Safety, Module 5.3.5.3

Common adverse events

Study FLAURA

Table 38: Most common adverse events (frequency of ≥ 10% in either treatment arm) (Safety analysis set)

	Number (%) of patients [a]			
	Osimertinib 80 mg (N=279)		Standard of Care (N = 277)	
MedDRA preferred term	DCO1	90 DSU	DCO1	90 DSU
Median duration of exposure (months)	16.2	18.8	11.5	11.5
Patients with any adverse event	273 (97.8)	273 (97.8)	271 (97.8)	271 (97.8)
Diarrhoea	161 (57.7)	162 (58.1)	159 (57.4)	161 (58.1)
Dry skin	88 (31.5)	88 (31.5)	90 (32.5)	90 (32.5)
Paronychia	81 (29.0)	82 (29.4)	80 (28.9)	82 (29.6)
Stomatitis	80 (28.7)	80 (28.7)	56 (20.2)	56 (20.2)
Dermatitis acneiform	71 (25.4)	71 (25.4)	134 (48.4)	134 (48.4)
Decreased appetite	56 (20.1)	62 (22.2)	52 (18.8)	54 (19.5)
Pruritus	48 (17.2)	48 (17.2)	43 (15.5)	43 (15.5)
Cough	46 (16.5)	51 (18.3)	42 (15.2)	42 (15.2)
Constipation	42 (15.1)	45 (16.1)	35 (12.6)	36 (13.0)
Nausea	39 (14.0)	45 (16.1)	52 (18.8)	54 (19.5)
Fatigue	38 (13.6)	39 (14.0)	33 (11.9)	33 (11.9)
Rash maculopapular	37 (13.3)	37 (13.3)	45 (16.2)	45 (16.2)
Dyspnoea	35 (12.5)	36 (12.9)	20 (7.2)	21 (7.6)
Anaemia	34 (12.2)	37 (13.3)	25 (9.0)	26 (9.4)
Headache	33 (11.8)	33 (11.8)	19 (6.9)	19 (6.9)
Vomiting	31 (11.1)	36 (12.9)	29 (10.5)	29 (10.5)
Upper respiratory tract infection	28 (10.0)	30 (10.8)	18 (6.5)	18 (6.5)
Electrocardiogram QT prolonged	28 (10.0)	28 (10.0)	11 (4.0)	12 (4.3)
Pyrexia	28 (10.0)	29 (10.4)	11 (4.0)	11 (4.0)
AST increased	26 (9.3)	26 (9.3)	68 (24.5)	68 (24.5)
Back pain	26 (9.3)	31 (11.1)	23 (8.3)	23 (8.3)
Alopecia	20 (7.2)	20 (7.2)	35 (12.6)	35 (12.6)
ALT increased	18 (6.5)	18 (6.5)	75 (27.1)	75 (27.1)

a Number (%) of patients with AEs, sorted in descending frequency of PT in the osimertinib arm at DCO1
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.
ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; MedDRA = Medical Dictionary for Regulatory Activities version 20.0
Data cut-off date: DCO1=12 June 2017; 90 DSU DCO=25 September 2017
Source: see Table 10, Module 2.7.4 dated 4 October 2017 and see Table 11.3.1.1 and Table 11.3.2.6, Appendix A

Pooled dataset

Among 1142 patients in the pooled dataset, 1126 (98.6%) reported AEs. The most commonly reported PTs were diarrhoea (555 [48.6%]), dry skin (295 [25.8%]), paronychia (276 [24.2%]), decreased appetite (253 [22.2%]) and stomatitis (229 [20.1%].

Adverse events of CTCAE grade 3 or higher

Study FLAURA

Table 39: Adverse events of CTCAE grade 3 or higher in at least 1% of patients in either treatment arm in FLAURA, by preferred term (Safety analysis set)

	Number (%) of patients [a]			
	Osimertinib 80 mg (N = 279)		Standard of Care (N = 277)	
	DCO1	90 DSU	DCO1	90 DSU
Median duration of exposure (months)	16.2	18.8	11.5	11.5
Any CTCAE ≥grade 3 AE	95 (34.1)	103 (36.9)	124 (44.8)	125 (45.1)
Decreased appetite	7 (2.5)	7 (2.5)	5 (1.8)	5 (1.8)
Diarrhoea	6 (2.2)	6 (2.2)	7 (2.5)	7 (2.5)
Pneumonia	6 (2.2)	6 (2.2)	6 (2.2)	7 (2.5)
Electrocardiogram QT prolonged	6 (2.2)	6 (2.2)	2 (0.7)	2 (0.7)
Hyponatraemia	4 (1.4)	5 (1.8)	4 (1.4)	4 (1.4)
Pulmonary embolism	4 (1.4)	4 (1.4)	1 (0.4)	1 (0.4)
Neutrophil count decreased	4 (1.4)	5 (1.8)	1 (0.4)	1 (0.4)
Gamma-glutamyltransferase increased	4 (1.4)	4 (1.4)	0	0
Lymphocyte count decreased	4 (1.4)	4 (1.4)	0	0
Anaemia	3 (1.1)	4 (1.4)	3 (1.1)	3 (1.1)
Hypokalaemia	3 (1.1)	3 (1.1)	3 (1.1)	3 (1.1)
Interstitial lung disease	3 (1.1)	3 (1.1)	3 (1.1)	3 (1.1)
Weight decreased	3 (1.1)	3 (1.1)	0	0
Cataract	2 (0.7)	3 (1.1)	1 (0.4)	1 (0.4)
Ejection fraction decreased	2 (0.7)	3 (1.1)	1 (0.4)	1 (0.4)
Aspartate aminotransferase increased	2 (0.7)	2 (0.7)	12 (4.3)	12 (4.3)
Alanine aminotransferase increased	1 (0.4)	1 (0.4)	25 (9.0)	25 (9.0)
Rash maculopapular	1 (0.4)	1 (0.4)	5 (1.8)	5 (1.8)
Dyspnoea	1 (0.4)	1 (0.4)	4 (1.4)	4 (1.4)
Dry skin	1 (0.4)	1 (0.4)	3 (1.1)	3 (1.1)
Dermatitis acneiform	0	0	13 (4.7)	13 (4.7)
Vomiting	0	0	4 (1.4)	4 (1.4)
Drug-induced liver injury	0	0	3 (1.1)	3 (1.1)
Hepatic function abnormal	0	0	3 (1.1)	3 (1.1)
Blood alkaline phosphatase increased	0	0	3 (1.1)	3 (1.1)

a Number (%) of patients with AEs of CTCAE grade 3 or higher, sorted by decreasing order of AEs within the osimertinib arm at DCO1.
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 crossover treatment.
CTCAE = Common Terminology Criteria for Adverse Events (version 4.03); MedDRA = Medical Dictionary for Regulatory Activities version 20.0
Data cut-off date: DCO1=12 June 2017; 90 DSU DCO=25 September 2017
Source: see Table 13, Module 2.7.4 dated 4 October 2017 and see Table 11.3.1.1 and Table 11.3.2.4.1, Appendix A

Pooled dataset

The incidence of CTCAE ≥ grade 3 AEs in the osimertinib arm in FLAURA was similar to the pooled population (34.1% vs. 38%, respectively). The following AEs of CTCAE ≥ grade 3 were reported in ≥ 1% of patients: pneumonia (32 [2.8%]), pulmonary embolism (32 [2.8%]), anaemia (24 [2.1%]), neutrophil count decreased (23 [2.0%]), neutropenia (20 [1.8%]), alanine aminotransferase increased (17 [1.5%]), decreased appetite (16 [1.4%]), dyspnoea (15 [1.3%]), hyponatraemia (15 [1.3%]), diarrhoea (14 [1.2%]), electrocardiogram QT prolonged (13 [1.1%]), asthenia (12 [1.1%]), aspartate aminotranferase increased (11 [1.0%]) and white blood cell count decreased (11 [1.0%]).

Adverse Drug reactions (ADRs)

Table 40: **Adverse reactions reported in FLAURA[a] study**

MedDRA SOC	TAGRISSO (N=279)		EGFR TKI comparator (gefitinib or erlotinib) (N=277)	
NCI Grade[b]	**Any Grade (%)**	**Grade 3 or higher (%)**	**Any Grade (%)**	**Grade 3 or higher (%)**
MedDRA Preferred Term				
Respiratory, thoracic and mediastinal disorders				
Interstitial Lung Disease[c]	3.9	1.1	2.2	1.4
Eye disorders				
Keratitis[d]	0.4	0	1.4	0
Gastrointestinal disorders				
Diarrhoea[e]	58	2.2	57	2.5
Stomatitis	29	0.7	20	0.4
Skin and subcutaneous tissue disorders				
Rash[f]	58	1.1	78	6.9
Dry skin[g]	36	0.4	36	1.1
Paronychia[h]	35	0.4	33	0.7
Pruritus[i]	17	0.4	17	0
Investigations				
QTc interval prolongation[j]	1.1		0.7	
(Findings based on test results presented as CTCAE grade shifts)				
Platelet count decreased[k]	51	0.7	12	0.4
Leukocytes decreased[k]	72	0.4	31	0.4
Lymphocytes decreased[k]	63	5.6	36	4.2
Neutrophils decreased[k]	41	3.0	10	0

In FLAURA, the median duration of study treatment was 16.2 months for patients in the TAGRISSO arm and 11.5 months for patients in the EGFR TKI comparator arm.

[a] Only events for patients receiving at least one dose of TAGRISSO as their randomised treatment are summarised.
[b] National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0
[c] Cases reported within the clustered terms: Interstitial lung disease, pneumonitis.
[d] Cases reported within the clustered terms: Keratitis, punctate keratitis, corneal erosion, corneal epithelium defect.
[e] 1 CTCAE grade 5 event (fatal) was reported in the EGFR TKI comparator arm.
[f] Cases reported within the clustered terms for rash AEs: Rash, rash generalised, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pustular, rash pruritic, rash vesicular, rash follicular, erythema, folliculitis, acne, dermatitis, dermatitis acneiform, drug eruption, skin erosion.
[g] Cases reported within the clustered terms: Dry skin, skin fissures, xerosis, eczema, xeroderma.
[h] Cases reported within the clustered terms: Nail bed disorder, nail bed inflammation, nail bed infection, nail discolouration, nail pigmentation, nail disorder, nail toxicity, nail dystrophy, nail infection, nail ridging, onychoclasis, onycholysis, onychomadesis, onychomalacia, paronychia.
[i] Cases reported within the clustered terms: Pruritus, pruritus generalised, eyelid pruritus.
[j] Represents the incidence of patients who had a QTcF prolongation >500 msec.
[k] Represents the incidence of laboratory findings, not of reported adverse events.

Table 41: Adverse reactions reported in FLAURA and AURA studies[a]

MedDRA SOC	MedDRA term	CIOMS descriptor/ overall frequency (all CTCAE grades)[b]	Frequency of CTCAE grade 3-4
Respiratory, thoracic and mediastinal disorders	Interstitial lung disease[c]	Common (3.9%)[d]	1.5%
Gastrointestinal disorders	Diarrhoea	Very common (49%)	1.2%
	Stomatitis	Very common (20%)	0.2%
Eye disorders	Keratitis[e]	Uncommon (0.7%)	0.1%
Skin and subcutaneous tissue disorders	Rash[f]	Very common (47%)	0.9%
	Dry skin[g]	Very common (31%)	0%
	Paronychia[h]	Very common (25%)	0%
	Pruritus[i]	Very common (14%)	0%
Investigations	QTc interval prolongation[j]	Uncommon (0.9%)	
(Findings based on test results presented as CTCAE grade shifts)	Platelet count decreased[k]	Very common (54%)	1.6%
	Leucocytes decreased[k]	Very common (68%)	1.5%
	Lymphocytes decreased[k]	Very common (67%)	7.2%
	Neutrophils decreased[k]	Very common (35%)	4.1%

a) Data is cumulative from FLAURA and AURA (AURA3, AURAex, AURA 2 and AURA1) studies; only events for patients receiving at least one dose of TAGRISSO as their randomised treatment are summarised.
b) National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.
c) Includes cases reported within the clustered terms: Interstitial lung disease, pneumonitis.
d) 5 CTCAE grade 5 events (fatal) were reported.
e) Includes cases reported within the clustered terms: Keratitis, punctate keratitis, corneal erosion, corneal epithelium defect.
f) Includes cases reported within the clustered terms for rash AEs: Rash, rash generalised, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pustular, rash pruritic, rash vesicular, rash follicular, erythema, folliculitis, acne, dermatitis, dermatitis acneiform, drug eruption, skin erosion.
g) Includes cases reported within the clustered terms: Dry skin, skin fissures, xerosis, eczema, xeroderma.
h) Includes cases reported within the clustered terms: Nail bed disorder, nail bed inflammation, nail bed infection, nail discolouration, nail pigmentation, nail disorder, nail toxicity, nail dystrophy, nail infection, nail ridging, onychoclasis, onycholysis, onychomadesis, onychomalacia, paronychia.
i) Includes cases reported within the clustered terms: pruritus, pruritus generalised, eyelid pruritus.
j) Represents the incidence of patients who had a QTcF prolongation >500msec.
k) Represents the incidence of laboratory findings, not of reported adverse events.

Adverse events of special interest (AESIs)

Adverse events by organ system or syndrome: key safety topics

AESI findings from this study are consistent with known data in terms of the frequency of occurrence, nature, severity, clinical course and outcome of the event.

Table 42: Summary of adverse events of special interest by grouped term and subgrouped term (safety analysis set)

Grouped term Subgrouped term	Number (%) of patients Osimertinib (N=279)	 SoC (N=277)
Cardiac effects (QT)	29 (10.4)	13 (4.7)
Cardiac arrhythmia terms, non-specific (SMQ)	0	1 (0.4)
ICH QT terms	1 (0.4)	2 (0.7)
Torsade de pointes/QT prolongation	28 (10.0)	11 (4.0)
Cardiac effects (cardiac failure)	12 (4.3)	6 (2.2)
Cardiac failure (SMQ)	12 (4.3)	5 (1.8)
Cardiomyopathy (SMQ)	10 (3.6)	6 (2.2)
Diarrhoea	161 (57.7)	159 (57.4)
Diarrhoea	161 (57.7)	159 (57.4)
Hepatic	40 (14.3)	101 (36.5)
Hepatic from Investigations (SOC)	34 (12.2)	86 (31.0)
Hepatobiliary disorders (SOC)	7 (2.5)	16 (5.8)
ILD and pneumonitis	11 (3.9)	6 (2.2)
ILD grouped terms	11 (3.9)	6 (2.2)
Nail effects	97 (34.8)	91 (32.9)
General nail & nail bed conditions	97 (34.8)	91 (32.9)
Ocular effects	48 (17.2)	63 (22.7)
Conjunctival disorders (SMQ)	37 (13.3)	46 (16.6)
Corneal disorders (SMQ)	1 (0.4)	4 (1.4)
Keratitis	1 (0.4)	4 (1.4)
Lacrimal disorders (SMQ)	22 (7.9)	22 (7.9)
Miscellaneous ocular terms	9 (3.2)	14 (5.1)
Periorbital & eyelid disorders (SMQ)	6 (2.2)	14 (5.1)
Renal	36 (12.9)	27 (9.7)
Renal & urinary disorders (SOC)	26 (9.3)	24 (8.7)
Renal from Investigations SOC	12 (14.3)	5 (1.8)
Skin effects	207 (74.2)	236 (85.2)
Dry skin	100 (35.8)	100 (36.1)
Exfoliative rash	8 (2.9)	4 (1.4)
Pruritus	48 (17.2)	46 (16.6)
Rashes & Acnes	161 (57.7)	216 (78.0)
Upper gastrointestinal tract inflammatory events	115 (41.2)	89 (32.1)
Gastrointestinal tract inflammation of unspecified location	1 (0.4)	2 (0.7)
Non-oral upper gastrointestinal tract inflammatory events	35 (12.5)	33 (11.9)
Oral inflammation	94 (33.7)	63 (22.7)

HLT = high level term; SMQ = standard MedDRA query; SOC = system organ class
Included AEs with onset date on or after date of first dose up to and including 28 days following discontinuation of randomised treatment or the day before first administration of crossover treatment.
DCO1: 12 June 2017
Source: Table 11.3.2.12.1.1

Interstitial lung disease

Study FLAURA

ILD (grouped term) was reported in a low but numerically higher proportion of patients in the osimertinib arm than the SoC arm: 12/279 (4.3%) patients vs. 6/277 (2.2%) patients. The overall event rate per 100 patient-years was similar between the 2 treatment arms: 3.14 in the osimertinib arm and 2.21 in the SoC arm.

In all 11 patients with ILD in the osimertinib arm, the outcome was reported as either resolved (7/11 [63.6%]) or resolving (4/11 [36.4%]) at the time of DCO1. ILD grouped terms were reported as SAEs in 6 (2.2%) patients in the osimertinib arm and 4 (1.4%) patients in the SoC arm.

The median time to onset of ILD grouped-term events (first occurrence per patient) was 106.0 days (range: 9-425) in the 11 patients in the osimertinib arm and 83.5 days (range: 11-253) in the 6 patients in the SoC arm.

Table 43: ILD grouped term adverse events in FLAURA, by preferred term and maximum CTCAE grade (Safety analysis set)

	Number (%) of patients							
	Osimertinib 80 mg (N=279)				Standard of Care (N = 277)			
Grouped term	DCO1		90 DSU		DCO1		90 DSU	
MedDRA preferred term	Any grade	≥Grade 3	Any grade	≥Grade 3	Any grade	≥Grade 3	Any grade	≥Grade 3
ILD	11 (3.9)	3 (1.1)	12 (4.3)	3 (1.1)	6 (2.2)	4 (1.4)	6 (2.2)	4 (1.4)
ILD	6 (2.2)	3 (1.1)	6 (2.2)	3 (1.1)	4 (1.4)	3 (1.1)	4 (1.4)	3 (1.1)
Pneumonitis	5 (1.8)	0	5 (1.8)	0	2 (0.7)	1 (0.4)	2 (0.7)	1 (0.4)
Lung disorder	0	0	1 (0.4)	0	0	0	0	0

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 discontinuation of randomised treatment or the day before first administration of crossover treatment. Specific AEs of interest may either be grouped MedDRA preferred terms or individual MedDRA preferred terms.
ILD = interstitial lung disease; MedDRA = Medical Dictionary for Regulatory Activities version 20.0; SMQ = Standardised MedDRA query; CTCAE = Common Terminology Criteria for Adverse Events version 4.03; PT=preferred term
Data cut-off date: DCO1=12 June 2017; 90 DSU DCO=25 September 2017
Source: see Table 19, Module 2.7.4 dated 4 October 2017 and see Table 11.3.2.12.10.1, Appendix A

Pooled dataset

The ILD events reported in FLAURA were generally similar to those in the pooled population in terms of incidence (11 [3.9%] and 45 [3.9%], respectively) and severity, with most events being of CTCAE grade 1 or grade 2 in each arm. There were 4 patients with CTCAE grade 5 AEs in AURA2/AURA1C and 1 patient with grade 5 ILD in AURA3. The incidence of ILD reported in Japanese patients in FLAURA (12.3%) was similar to that seen in previous studies (10.4%), with events remained primarily CTCAE grade 1 or grade 2 with evidence of reversibility.

Cardiac effects

Study FLAURA

Cardiac effects (QT)

Table 44: Cardiac effects adverse events, by grouped term, MedDRA preferred term, and maximum CTCAE grade in FLAURA at Safety analysis set)

Grouped term Subgrouped term MedDRA preferred term	Number (%) of patients							
	Osimertinib 80 mg (N=279)				Standard of Care (N = 277)			
	DCO1		90 DSU		DCO1		90 DSU	
	Any grade	≥Grade 3	Any grade	≥Grade 3	Any grade	≥Grade 3	Any grade	≥Grade 3
Cardiac effects (QT)	29 (10.4)	6 (2.2)	32 (11.5)	6 (2.2)	13 (4.7)	3 (1.1)	15 (5.4)	4 (1.4)
Torsade de pointes/QT prolongation (SMQ)	28 (10.0)	6 (2.2)	28 (10.0)	6 (2.2)	11 (4.0)	2 (0.7)	12 (4.3)	2 (0.7)
ECG QT prolonged	28 (10.0)	6 (2.2)	28 (10.0)	6 (2.2)	11 (4.0)	2 (0.7)	12 (4.3)	2 (0.7)
Arrhythmias (SMQ)	0	0	0	0	1 (0.4)	0	1 (0.4)	0
Heart rate irregular	0	0	0	0	1 (0.4)	0	1 (0.4)	0
ICH E14 terms	1 (0.4)	0	4 (1.4)	0	2 (0.7)	1 (0.4)	3 (1.1)	2 (0.7)
Syncope	1 (0.4)	0	4 (1.4)	0	0	0	0	0
Seizure	0	0	0	0	2 (0.7)	1 (0.4)	2 (0.7)	1 (0.4)
Epilepsy	0	0	0	0	0	0	1 (0.4)	1 (0.4)

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 discontinuation of randomised treatment or the day before first administration of crossover treatment.
Specific AEs of interest may either be grouped MedDRA preferred terms or individual MedDRA preferred terms.
CTCAE = Common Terminology Criteria for Adverse Events version 4.03; MedDRA = Medical Dictionary for Regulatory Activities version 20.0; SMQ = Standardised MedDRA query.
Data cut-off date: DCO1=12 June 2017; 90 DSU DCO=25 September 2017
Source: see Table 21, Module 2.7.4 dated 4 October 2017 and see Table 11.3.2.12.10.1, Appendix A

Dose interruptions for AEs of ECG QT prolonged were reported in 8 (2.9%) patients in the osimertinib arm and 6 (2.2%) patients in the SoC arm. Dose reductions for AEs of ECG QT prolonged were reported in 5 (1.8%) patients in the osimertinib arm and 1 (0.4%) patient in the SoC arm.

Table 45: QTcF intervals above pre-specified thresholds in FLAURA (Safety analysis set)

	Number (%) of patients [a]			
	Osimertinib 80 mg (N=279)		Standard of Care (N=277)	
	DCO1	90 DSU	DCO1	90 DSU
QTcF value above 450/480/500 msec at any time during treatment				
>450 msec	98 (35.1)	99 (35.5)	47 (17.0)	47 (17.0)
>480 msec	17 (6.1)	17 (6.1)	5 (1.8)	5 (1.8)
>500 msec	3 (1.1)	3 (1.1)	2 (0.7)	2 (0.7)
QTcF increase [b] by more than 30/60/90 msec at any time during treatment				
>30 msec	116 (41.6)	116 (41.6)	66 (23.8)	67 (24.2)
>60 msec	14 (5.0)	14 (5.0)	6 (2.2)	6 (2.2)
>90 msec	1 (0.4)	1 (0.4)	0	0
QTcF value above 450/500 msec and QTcF increase [b] by more than 30/60 msec at any time during treatment				
Value >450 (msec) and increase >30 (msec) [b]	62 (22.2)	62 (22.2)	31 (11.2)	31 (11.2)
Value >500 (msec) and increase >60 (msec) [b]	1 (0.4)	1 (0.4)	1 (0.4)	1 (0.4)
QTcF decrease [b] by more than 30/60/90 msec at any time during treatment				
>30 msec	11 (3.9)	13 (4.7)	27 (9.7)	28 (10.1)
>60 msec	0	0	1 (0.4)	1 (0.4)
>90 msec	0	0	0	0

Cardiac effects (cardiac failure)

Table 46: Cardiac effects adverse events, by grouped term, MedDRA preferred term, and maximum CTCAE grade in FLAURA at Safety analysis set)

Grouped term Subgrouped term MedDRA preferred term	Number (%) of patients							
	Osimertinib 80 mg (N=279)				Standard of Care (N = 277)			
	DCO1		90 DSU		DCO1		90 DSU	
	Any grade	≥Grade 3	Any grade	≥Grade 3	Any grade	≥Grade 3	Any grade	≥Grade 3
Cardiac effects (cardiac failure)	12 (4.3)	3 (1.1)	13 (4.7)	4 (1.4)	6 (2.2)	1 (0.4)	6 (2.2)	1 (0.4)
Cardiac failure (SMQ)	12 (4.3)	3 (1.1)	13 (4.7)	4 (1.4)	5 (1.8)	1 (0.4)	5 (1.8)	1 (0.4)
Ejection fraction decreased	10 (3.6)	2 (0.7)	11 (3.9)	3 (1.1)	5 (1.8)	1 (0.4)	5 (1.8)	1 (0.4)
Cardiac failure	1 (0.4)	0	1 (0.1)	0	0	0	0	0
Cardiac failure chronic	1 (0.4)	1 (0.4)	1 (0.4)	1 (0.4)	0	0	0	0
Cardiomyopathy (SMQ)	10 (3.6)	2 (0.7)	11 (3.9)	3 (1.1)	6 (2.2)	1 (0.4)	6 (2.2)	1 (0.4)
Ejection fraction decreased	10 (3.6)	2 (0.7)	11 (3.9)	3 (1.1)	5 (1.8)	1 (0.4)	5 (1.8)	1 (0.4)
Metabolic cardiomyopathy	0	0	0	0	1 (0.4)	0	1 (0.4)	0

Number (%) of patients with AEs of special interest, sorted on AESI grouped term and descending frequency for preferred term in 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 discontinuation of randomised treatment or the day before first administration of crossover treatment.
Specific AEs of interest may either be grouped MedDRA preferred terms or individual MedDRA preferred terms.
MedDRA = Medical Dictionary for Regulatory Activities version 20.0; SMQ = Standardised MedDRA query; CTCAE = Common Terminology Criteria for Adverse Events version 4.03
Data cut-off date: DCO1=12 June 2017; 90 DSU DCO=25 September 2017
Source: see Table 21, Module 2.7.4 dated 4 October 2017 and see Table 11.3.2.12.10.1, Appendix A

A total of 257 (92.1%) patients in the osimertinib arm vs. 253 (91.3%) patients in the SoC arm had both a baseline and a post-baseline assessment. The median maximum change from baseline in LVEF was −3.0% in both treatment arms: in the osimertinib arm at Week 48 and Week 72 (range: −3% to -1%) and in the SoC arm at Week 96 (range: -3% to 0%).

Among all patients who had baseline and post-baseline LVEF assessment (regardless of whether the assessments were within the ±7-day visit window), 8/257 (3.1%) patients in the osimertinib arm and 3/253 (1.2%) patients in the SoC arm had a LVEF decrease from baseline of ≥10 pp, to an LVEF value of <50%. An LVEF decrease of ≥15 pp to an absolute value of ≥50% was seen in 26/257 (10.1%) patients in the osimertinib arm vs. 18/253 (7.1%) patients in the SoC arm.

Patients treated in FLAURA who experienced asymptomatic decreases in LVEF while taking osimertinib recovered from these decreases whilst on full dose of osimertinib, without occurrence of cardiac symptoms.

The median time to onset for AEs in the Cardiac effects (cardiac failure) category was 166.0 days (range: 18-504) in the osimertinib arm and 109.5 days (range: 84-750) in the SoC arm.

Cardiac effects outside the cardiac failure and cardiomyopathy SMQs

Adverse events in the Cardiac Disorders MedDRA SOC were reported for 24 (8.6%) patients in the osimertinib arm and 19 (6.9%) patients in the SoC arm at DCO1. Most of the AEs in the Cardiac Disorders SOC at the 90 DSU DCO were either CTCAE grade 1 (14/26 [53.8%] osimertinib; 15/21 [71.4%] SoC) or CTCAE grade 2 (7/26 [26.9%] osimertinib and 2/21 [9.5%] SoC). CTCAE ≥grade 3 cardiac AEs were reported in 4 (1.4%) patients in the osimertinib arm and 4 (0.4%) patients in the SoC arm. In the osimertinib arm, 2 patients had CTCAE grade 3 AEs (acute myocardial infarction, atrial fibrillation); 1 patient had a CTCAE grade 4 AE (cardiac arrest) and 1 patient had a CTCAE grade 5 AE (myocardial infarction). In the SoC arm, 4 patients had CTCAE grade 3 AEs (angina pectoris, left bundle branch block, pericardial effusion, and ventricular extrasystoles).

Pooled dataset

There was a similar incidence of AEs of ECG QT prolongation in FLAURA than in the pooled population (28/279 [10.0%] vs. 70/142 [6.1%], respectively) and LVEF decreases (10/279 [3.6%] vs. 22/1142 [1.9%]). In both populations, the events were primarily CTCAE grade 1 or grade 2. One (<0.1%) patient had CTCAE grade 5 cardiac failure reported in AURA2/AURA1C. Similar proportions of patients had a QTcF value ≥500 msec (10 (0.9%) pooled population and 3 (1.1%) FLAURA), QTcF increase > 60 msec (41 [3.6%] pooled population and 14 [5%] FLAURA) or an LVEF value with a ≥10 pp change from baseline and an absolute value <50% (35 (3.9%) pooled population vs. 8 (3.1%) FLAURA). Therefore, the differences between the 2 populations are not considered to constitute a change in this safety topic when FLAURA results are included in the pooled population.

Diarrhoea

Study FLAURA

Diarrhoea was the most commonly reported AESI in FLAURA. The incidence of diarrhoea was similar between the 2 treatment arms: 161 (57.7%) patients in the osimertinib arm and 161 (58.1%) patients in the SoC arm.

Table 47: Diarrhoea adverse events by treatment arm and CTCAE grade (safety analysis set)

Event	Any grade	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Osimertinib arm (N = 279)						
Diarrhoea	161 (57.7)	120 (43.0)	35 (12.5)	6 (2.2)	0	0
SoC arm (N = 277)						
Diarrhoea [a]	159 (57.4)	116 (41.9)	35 (12.6)	6 (2.2)	0	1 (0.4)

[a] Includes an AE of unknown severity (CTCAE grade).
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.
MedDRA = Medical Dictionary for Regulatory Activities version 20.0; SMQ = standardised MedDRA query; CTCAE = Common Terminology Criteria for Adverse Events version 4.03
DCO1: 12 June 2017

Diarrhoea led to dose interruption in 7 (2.5%) patients in the osimertinib arm and 4 (1.4%) patients in the SoC arm. No AEs of diarrhoea led to dose reduction or treatment discontinuation in the osimertinib arm. In the SoC arm, 1 (0.4%) patient had a dose reduction due to an AE of diarrhoea, and 5 (1.8%) patients discontinued SoC dosing due to diarrhoea

The median time to onset of first event of diarrhoea was similar between the 2 treatment arms: 17 days (range: 1 to 536) in the osimertinib arm vs. 19 days (range: 1 to 631 days) in the SoC arm.

Events of diarrhoea were of same duration between the 2 treatment arms (median of 44.0 days).

On an episode level, 233 events of diarrhoea were reported among the 161 patients who experienced diarrhoea in the osimertinib arm and 236 events were reported among the 159 patients who experienced diarrhoea in the SoC arm at DCO1. After 3 months, the diarrhoea event rate in both treatment arms remained relatively constant (<5%). The overall event rate per 100 patient years was lower in the osimertinib arm compared to the SoC arm: 46.0 and 58.5, respectively.

The majority of episodes of diarrhoea resolved without treatment.

Pooled dataset

Incidence was higher in FLAURA (161 [57.7%]) than in the pooled population (555 [48.6%]). Nearly all events in the 2 populations were either CTCAE grade 1 or grade 2: 155/161 (96.3%) patients with diarrhoea in FLAURA and 541/555 (97.5%) patients with the event in the pooled population. CTCAE grade 3-4 was reported in 6 patients (2.2%) in the osimertinib arm in FLAURA and 14 patients (1.2%) in the pooled population.

Diarrhoea led to dose reductions in no patients in FLAURA and 0.2% of patients in the pooled population; to dose interruption in 2.5% and 1.4% of patients, respectively; and to discontinuation in no patients and 0.1% of patients, respectively. No events of haemorrhagic diarrhoea or GI perforation were reported in the osimertinib arm.

Skin effects

Study FLAURA

The AESI of Skin effects was evaluated by review of 4 subgroups: Rashes & acnes, Pruritus, Dry skin, and Exfoliative rash.

No severe bullous, severe blistering or severe exfoliative skin events, or severe hypersensitivity reactions, including Stevens-Johnson Syndrome, were reported in either treatment arm. One CTCAE grade 4 SAE of toxic epidermal necrolysis was reported in the SoC arm.

Table 48: Skin effects grouped term adverse events in FLAURA, by subgrouped term and maximum CTCAE grade (safety analysis set)

	Number (%) of patients							
	Osimertinib 80 mg (N=279)				Standard of Care (N = 277)			
	DCO1		90 DSU		DCO1		90 DSU	
Grouped term Subgrouped term	Any grade	≥Grade 3	Any grade	≥Grade 3	Any grade	≥Grade 3	Any grade	≥Grade 3
Skin effects	207 (74.2)	4 (1.4)	207 (74.2)	4 (1.4)	236 (85.2)	21 (7.6)	236 (85.2)	21 (7.6)
Rashes & acnes	161 (57.7)	3 (1.1)	162 (58.1)	3 (1.1)	216 (78.0)	19 (6.9)	217 (78.3)	19 (6.9)
Dry skin	100 (35.8)	1 (0.4)	101 (36.2)	1 (0.4)	100 (36.1)	3 (1.1)	100 (36.1)	3 (1.1)
Pruritus	48 (17.2)	1 (0.4)	48 (17.2)	1 (0.4)	46 (16.6)	0	46 (16.6)	0
Exfoliative rash	8 (2.9)	0	8 (2.9)	0	4 (1.4)	0	4 (1.4)	0

Number (%) of patients with AEs of special interest, sorted on AESI grouped term and descending frequency.
Includes 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 crossover treatment.
Specific AEs of interest may either be grouped MedDRA preferred terms or individual MedDRA preferred terms.
MedDRA = Medical Dictionary for Regulatory Activities version 20.0; CTCAE = Common Terminology Criteria for Adverse Events version 4.03
Data cut-off date: DCO1=12 June 2017; 90 DSU DCO=25 September 2017
Source: see Table 28, Module 2.7.4 dated 4 October 2017 and see Table 11.3.2.12.10.1, Appendix A

Rashes and acnes

The most commonly reported PTs were dermatitis acneiform and rash maculo-papular. The median time to onset of first event in the Rashes and acnes subgroup was 18.0 days (range: 1 to 709 days) in the osimertinib arm vs. 14.5 days (range: 1-379 days) in the SoC arm.
A majority of the episodes of rash required medication (59.6% in the osimertinib arm and 79.5% in the SoC arm). None of the untreated AEs of rash resulted in dose modification. In the osimertinib arm 173 (67.8%) of the AEs of rash resolved and 82 (32.2%) were ongoing at DCO1.

Dry skin

The only PT in this subgroup reported by at least 10% of patients was dry skin (osimertinib: 88 [31.5%] patients; SoC: 90 [32.5%] patients.

The median time to onset of first event in the Dry skin subgroup was 33.5 days (range: 1 to 667 days) in the osimertinib arm vs. 26.0 days (range: 1 to 492 days) in the SoC arm.

Pruritus

The median time to onset of first event of Pruritus (grouped term) AEs was lower in the osimertinib arm than the SoC arm: 16.5 days (range: 1 to 616 days) vs. 48 days (range: 5 to 676 days).
One (0.4%) patient in the osimertinib arm and no patient in the SoC arm had an AE in the Pruritus subgrouped term reported as an SAE. Events led to discontinuation of treatment in 1 (0.4%) patient in the osimertinib arm and no patients in the SoC arm.

Pooled dataset

The incidence of AEs in the Skin Effects (grouped term) was higher in the osimertinib arm of FLAURA (207 [74.2%]) than in the pooled population (746 [65.3%]). The incidence of Rashes & acnes was higher in the osimertinib arm in FLAURA (57.7%) than in the pooled population (46.8%) whereas the incidence of Dry skin was similar between the osimertinib arm in FLAURA (35.8%) and the pooled population (32.6%). The other two subgroups were similar among both arms.

In the majority of patients Skin Effects AEs were CTCAE grade 1: 168 (60.2%) patients in FLAURA and 605 (53.0%) in the pooled population and grade 2: 35 patients (12.5%) in FLAURA and 130 (11.4%) in the pooled population. CTCAE grade 3 were reported in 4 patients (1.4%) in the osimertinib arm in FLAURA and 11 patients (1.0%) in the pooled population. The CTCAE grade 3 events in the pooled population consisted on erythema (3 patients [0.3%]), rash maculo-papular (3 patients [0.3%]), rash erythematous (2 patients [0.2%]), rash macular (2 patients [0.1%]) and dry skin (1 [0.4%]).

Upper gastrointestinal tract inflammatory events

Study FLAURA

The Upper GI Tract Inflammatory Events grouped term included 3 subgroup terms: Oral inflammation, Non-oral upper GI tract inflammatory events, and GI tract inflammation of unspecified location.

The median time to onset of first event of Upper GI Tract Inflammatory Events (grouped term) was similar in the osimertinib arm (26.0 days [range: 2 to 603]) and the SoC arm (20.0 days [range: 1 to540 days]).

The CTCAE grade 4 AE of stomatitis in the osimertinib arm was classified as an SAE; it was considered to be unrelated to osimertinib by the Investigator. None of the other AEs in the Upper Gi tract inflammatory events category were SAEs. In the SoC arm, 2 AEs of mouth ulceration were classified as SAEs.

Table 49: Upper GI tract inflammatory events grouped term adverse events in FLAURA, by subgroup and maximum CTCAE grade (Safety analysis set)

Grouped term Subgrouped term MedDRA PT	Number (%) of patients							
	Osimertinib 80 mg (N=279)				Standard of Care (N = 277)			
	DCO1		90 DSU		DCO1		90 DSU	
	Any grade	≥Grade 3	Any grade	≥Grade 3	Any grade	≥Grade 3	Any grade	≥Grade 3
Upper GI tract inflammatory events	115 (41.2)	3 (1.1)	115 (41.2)	3 (1.1)	89 (32.1)	3 (1.1)	90 (32.5)	3 (1.1)
Oral inflammation	94 (33.7)	2 (0.7)	94 (33.7)	2 (0.7)	63 (22.7)	3 (1.1)	64 (23.1)	3 (1.1)
Stomatitis	80 (28.7)	2 (0.7)	80 (28.7)	2 (0.7)	56 (20.2)	1 (0.4)	56 (20.2)	1 (0.4)
Mouth ulceration	9 (3.2)	0	9 (3.2)	0	5 (1.8)	2 (0.7)	6 (2.2)	2 (0.7)
Aphthous ulcer	4 (1.4)	0	4 (1.4)	0	2 (0.7)	0	2 (0.7)	0
Glossitis	1 (0.4)	0	1 (0.4)	0	0	0	0	0
Oral pain	1 (0.4)	0	1 (0.4)	0	0	0	0	0
Atrophic glossitis	0	0	0	0	1 (0.4)	0	1 (0.4)	0
Non-oral upper GI tract inflammatory events	35 (12.5)	1 (0.4)	38 (13.6)	1 (0.4)	33 (11.9)	0	34 (12.3)	0
Epistaxis	17 (6.1)	0	18 (6.5)	0	14 (5.1)	0	14 (5.1)	0
Oropharyngeal pain	12 (4.3)	0	13 (4.7)	0	9 (3.2)	0	9 (3.2)	0
Dysphagia	4 (1.4)	1 (0.4)	4 (1.4)	1 (0.4)	4 (1.4)	0	4 (1.4)	0
Gastritis	2 (0.7)	0	2 (0.7)	0	3 (1.1)	0	4 (1.4)	0
Gastric ulcer	1 (0.4)	0	2 (0.4)	0	0	0	0	0
Oesophagitis	0	0	0	0	3 (1.1)	0	3 (1.1)	0
Odynophagia	0	0	0	0	2 (0.7)	0	2 (0.7)	0
GI tract inflammation of unspecified location	1 (0.4)	0	1 (0.4)		2 (0.7)	0	2 (0.7)	0
Mucosal dryness	1 (0.4)	0	1 (0.4)	0	1 (0.4)	0	1 (0.4)	0
Mucosal inflammation	0	0	0	0	1 (0.4)	0	1 (0.4)	0

Number (%) of patients with AEs of special interest, sorted on AESI grouped term and descending frequency in 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 discontinuation of randomised treatment or the day before first administration of crossover treatment.
Specific AEs of interest may either be grouped MedDRA preferred terms or individual MedDRA preferred terms.
MedDRA = Medical Dictionary for Regulatory Activities version 20.0; CTCAE = Common Terminology Criteria for Adverse Events version 4.03
Data cut-off date: DCO1=12 June 2017; 90 DSU DCO=25 September 2017
Source: see Table 33, Table 34, and Table 35, Module 2.7.4 dated 4 October 2017 and see Table 11.3.2.12.10.1, Appendix A

The median time to onset of first event of Oral inflammation events (grouped term) was similar between the 2 treatment arms: 22.0 days (range: 2 to 595 days) and 16.0 days (range: 1 to 383 days).

One patient in the osimertinib arm discontinued treatment due to oral pain; no patient in the SoC arm discontinued due to an AE in this grouped term.

The median time to onset of first event of Non-oral upper GI inflammatory events (grouped term) was higher in the osimertinib arm (133 days [range: 6 to 603]) than in the SoC arm (66.0 days [range: 1 to 540 days]).

Pooled dataset

AEs in the grouped term of Upper GI inflammatory events were reported in 115 patients (41.2%) in the osimertinib arm in FLAURA and 381 patients (33.4%) in the pooled population. The incidence of oral inflammation was higher in the osimertinib arm in FLAURA than in the pooled population (94 [33.7%] vs. 277 [24.3%]). In both populations, the incidence of Oral inflammation events was driven primarily by the PT of stomatitis, which was reported in 80 (28.7%) of patients in the osimertinib arm in FLAURA and 229 (20.1%) of patients in the overall pooled population. However, incidence of CTCAE ≥ 3 was similar in both treatment arms (0.2% pooled population vs. 0,7% FLAURA).

AEs reported within the other subgroups were: Non-oral upper GI tract inflammatory events (12.5% FLAURA vs. 14.0% pooled population) and GI Tract Inflammation Of Unspecified Location (0.4% vs. 1.1%).

Nail effects

Study FLAURA

Adverse events in the Nail effects grouped term were reported in 100 (35.8%) patients in the osimertinib arm and 93 (33.6%) patients in the SoC arm, with a lower event rate per 100 patient-years in the osimertinib arm than in the SoC arm: 27.7 and 33.5, respectively.

The vast majority of Nail effects AEs were either CTCAE grade 1 (osimertinib: 52 [18.6%] patients; SoC: 55 [19.9%] patients) or CTCAE grade 2 (osimertinib: 44 [15.8%]; SoC: 34 [12.3%]). CTCAE grade 3 events in the Nail effects grouped term were reported in only 1 (0.4%) patient in the osimertinib arm and 2 (0.7%) patients in the SoC arm. There was no AE greater than CTCAE grade 3 in severity in either treatment arm. No event was reported as an SAE in either treatment arm. One (0.4%) patient in the osimertinib arm discontinued treatment due to an AE of paronychia; no patient in the SoC arm discontinued due to an AE in this grouped term.

The median time to onset of first event of Nail effects (grouped term) was similar in the osimertinib arm (104.0 days [range: 7 to 632]) and the SoC arm (120.0 days [range: 10 to 588 days]).

Pooled dataset

The incidence of Nail effects was similar between the osimertinib arm in FLAURA (34.8%) and the pooled population (31.3%), with the majority of events being CTCAE grade 1 or grade 2 in each arm.

Ocular effects

Study FLAURA

The Ocular effects grouped term was evaluated by review of 4 narrow SMQs (Conjunctival disorders, Corneal disorders, Lacrimal disorders, and Periorbital & eyelid disorders) and the grouped terms of Keratitis and Miscellanous ocular terms.

Adverse events in the Ocular effects grouped term were reported in fewer patients in the osimertinib arm than the SoC arm: 48/279 (17.2%) patients and 64/277 (23.1%) patients, respectively. The event rate per 100 patient-years was lower in the osimertinib arm than in the SoC arm: 13.7 and 23.2 respectively.

There was 1/279 (0.4%) patient in the osimertinib arm that reported grade 1 AE of keratitis grouped term (corneal erosion PT) and 4/277 (1.4%) patients in the SoC arm reported one grade 1 (corneal erosion PT) and three grade 2 AEs of keratitis.

The severity of the events was similar to those of the SoC arm. In most patients, the events were either CTCAE grade 1 (14.7% osimertinib vs. 17.3% SoC) or CTCAE grade 2 (2.5% osimertinib vs. 5.1% SoC). CTCAE grade 3 events in the Ocular effects grouped term were similar between the 2 treatment arms: 0 patients in the osimertinib arm and 1/277 (0.4%) patient in the SoC arm. No CTCAE grade 4 or grade 5 events were reported in either treatment arm.

The median time to onset of first event of Ocular effects AEs (grouped term) was lower in the osimertinib arm (48.0 days [range: 1 to 681]) than in the SoC arm (103.0 days [range: 7 to 585 days]).

No patient in either treatment had an AE in this grouped term that was reported as an SAE or led to discontinuation of treatment.

Within the MedDRA SOC of Eye Disorders, at DCO1 AEs were reported in a similar proportion of patients in the osimertinib arm (45 [16.1%]) than in the SoC arm (55 [19.9%]), with the most common PT being dry eye (21 [7.5%] osimertinib vs. 18 [6.5%] SoC) and conjunctivitis (14 [5.0%] osimertinib vs. 20 [7.2%] SoC). Except for 2 (0.7%) patients in the osimertinib arm with a CTCAE grade 3 cataract and 1 (0.4%) patients each in the SoC arm with CTCAE grade 3 blepharitis and vitreous detachment, no events of CTCAE ≥grade 3, no SAEs, and no treatment discontinuations or dose reductions due to AEs in the Eye Disorders SOC were reported in either treatment arm. Dose interruptions due to Eye disorders AEs were reported in 1 (0.4%) patient with cataract in the osimertinib arm and 2 (0.7%) patients (1 with blepharitis and 1 with vitreous detachment) in the SoC arm.

Pooled dataset

The incidence of Ocular effects grouped term was 48 (17.2%) in the osimertinib arm in FLAURA and 201 (17.6%) in the pooled population. The majority of events were CTCAE grade 1 (14.7% FLAURA vs. 14.0% pooled population) or grade 2 (2.5% FLAURA vs. 3.5% pooled population). One patient (0.1%) in the pooled population had a CTCAE grade 3 adverse event (2 patients in osimertinib arm in FLAURA).

Hepatobiliary

Study FLAURA

Overall, hepatic-related AEs (in the Hepatobiliary disorders SOC or Investigations SOC) were reported in a lower proportion of patients in the osimertinib arm than the SoC arm: 41 (14.7%) vs 101 (36.5%).

Table 16. Hepatic grouped term adverse events in at least 2 patients in either treatment arm in FLAURA, by subgrouped term, preferred term and maximum CTCAE grade (Safety analysis set)

Grouped term Subgrouped term MedDRA PT	Number (%) of patients[a]							
	Osimertinib 80 mg (N=279)				Standard of Care (N = 277)			
	DCO1		90 DSU		DCO1		90 DSU	
	Any grade	≥Grade 3	Any grade	≥Grade 3	Any grade	≥Grade 3	Any grade	≥Grade 3
Hepatic	40 (14.3)	6 (2.2)	41 (14.7)	6 (2.2)	101 (36.5)	32 (11.6)	101 (36.5)	32 (11.6)
Hepatobiliary disorders SOC	7 (2.5)	0	6 (2.2)[a]	0	16 (5.8)	7 (2.5)	16 (5.8)	7 (2.5)
Hepatic function abnormal	2 (0.7)	0	2 (0.7)	0	7 (2.5)	3 (1.1)	7 (2.5)	3 (1.1)
Hyperbilirubinaemia	2 (0.7)	0	1 (0.4)	0	0	0	0	0
Drug-induced liver injury	0	0	0	0	5 (1.8)	3 (1.1)	5 (1.8)	3 (1.1)
Hepatotoxicity	0	0	0	0	2 (0.7)	0	2 (0.7)	0
Hepatic events from Investigations SOC	34 (12.2)	6 (2.2)	35 (12.5)	6 (2.2)	86 (31.0)	26 (9.4)	86 (31.0)	26 (9.4)
AST increased	26 (9.3)	2 (0.7)	26 (9.3)	2 (0.7)	68 (24.5)	12 (4.3)	68 (24.5)	12 (4.3)
ALT increased	18 (6.5)	1 (0.4)	18 (6.5)	1 (0.4)	75 (27.1)	25 (9.0)	75 (27.1)	25 (9.0)
GGT increased	10 (3.6)	4 (1.4)	10 (3.6)	4 (1.4)	2 (0.7)	0	2 (0.7)	0
Blood bilirubin increased	6 (2.2)	0	7 (2.5)	0	12 (4.3)	1 (0.4)	12 (4.3)	1 (0.4)
Transaminases increased	1 (0.4)	1 (0.4)	1 (0.4)	1 (0.4)	3 (1.1)	0	3 (1.1)	0

a An event of hyperbilirubinaemia (E2005002) was removed from the database at the 90 DSU DCO.
Number (%) of patients with AEs of special interest, sorted on AESI grouped term and descending frequency for preferred term in 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 discontinuation of randomised treatment or the day before first administration of crossover treatment.
Specific AEs of interest may either be grouped MedDRA preferred terms or individual MedDRA preferred terms.
ALT = alanine aminotransferase; AST = aspartate aminotransferase; GGT= gamma glutamyltranspeptidase; CTCAE = Common Terminology Criteria for Adverse Events version 4.03; MedDRA = Medical Dictionary for Regulatory Activities version 20.0; PT=preferred term; SOC = system organ class.
Data cut-off date: DCO1=12 June 2017; 90 DSU DCO=25 September 2017
Source: see Table 47, Module 2.7.4 dated 4 October 2017 and see Table 11.3.2.12.10.1, Appendix A

Additional AEs related to hepatic function from the Investigations SOC were also reported in a lower proportion of patients in the osimertinib arm than the SoC arm: 35 (12.5%) vs 86 (31.0%), respectively. The majority of the events were either CTCAE grade 1 or grade 2, with CTCAE grade 4 events reported in no patients in the osimertinib arm and in 4 (1.4%) patients in the SoC arm (all in the PT of ALT increased).

Dose reductions due to hepatic-related AEs in this SOC were reported in 1 (0.4%) patient in the osimertinib arm (GGT increased) and 2 (0.7%) patients in the SoC arm (1 ALT increased and 1 AST increased). Dose interruptions for hepatic AEs in the Investigations SOC were reported as follows: ALT increased (osimertinib: 3 [1.1%] patients; SoC: 18 [6.5%] patients); AST increased (osimertinib: 3 [1.1%]; SoC: 12 [4.3%]); and blood bilirubin increased (osimertinib: 1 [0.4%]; SoC: 0). In the osimertinib arm, no patients discontinued treatment due to hepatic AEs in this SOC. In contrast, in the SoC arm, 8 (2.9%) patients discontinued due to AEs of both ALT increased and AST increased, 4 (1.4%) patients due to an AE of ALT increased, and 1 (0.4%) patient due to an AE of blood bilirubin increased.

In the osimertinib arm, 2 (0.7%) patients had hepatic AEs that were classified as SAEs: 1 (0.4%) patient had SAEs of both ALT increased and AST increased, and 1 (0.4%) patient had an SAE of transaminase increased. In the SoC arm, 5 (1.8%) patients had hepatic events that were classified as SAEs: 1 (0.4%) patient had SAEs of both AST increased and ALT increased, 1 (0.4%) had an SAE of ALT increased, and 3 (1.1%) patients had SAEs of drug induced liver injury.

Pooled dataset

The incidence of hepatic related AEs events in the osimertinib arm in FLAURA (14.3%) was similar to the pooled population (13.9%); with the majority of events being CTCAE grade 1 or grade 2 in each arm. Proportion of CTCAE grade 3 adverse events were similar between both arms (2.2% FLAURA vs. 2.7% pooled population). In the pooled population, 2 patients (0.2%) had a CTCAE grade 4 and 2 patients (0.2%) had CTCAE grade 5. No patient reported CTCAE grade 4 in the osimertinib arm in FLAURA.

Renal effects

Study FLAURA

A total of 21 (7.5%) patients in the osimertinib arm and 33 (11.9%) patients in the SoC arm had a history of Renal and urinary disorders at baseline. No patient in either treatment arm had a history of renal metastases.

Renal-related AEs were reported in 42/279 (15.1%) patients in the osimertinib arm and 27/277 (9.7%) patients in the SoC arm, with a similar event rate per 100 patient years: 10.3 and 9.9, respectively.

In both treatment arms, the vast majority of Renal AEs were either CTCAE grade 1 (osimertinib: 27 [9.7%] patients; SoC: 20 [7.2%] patients) or CTCAE grade 2 (osimertinib: 12 [4.3%] patients; SoC: 6 [2.2%] patients). Two patients (0.7%) in the osimertinib arm (acute kidney injury and proteinuria) and one patient in the SoC arm (proteinuria) had a CTCAE grade 3 Renal AE. One patient in the osimertinib arm experienced a CTCAE grade 5 of renal failure.

Two (0.7%) patients in the osimertinib arm and 1 (0.4%) patient in the SoC arm had Renal AEs classified as SAEs, which included acute kidney injury and renal failure in 1 patient each in the osimertinib arm, and ureterolithiasis in 1 patient in the SoC arm.

Renal AEs did not lead to dose reductions in either arm. The following Renal AEs led to dosing interruptions: acute kidney injury and creatinine renal clearance decreased (1 [0.4%] patient each) in the osimertinib arm; and blood creatinine increased (1 [0.4%] patient) in the SoC arm. One AE of proteinuria in the SoC arm led to treatment discontinuation; no Renal AE led to discontinuation in the osimertinib arm.

Patients with grade shifts in creatinine were identified by applying the CTCAE version 4.03 definition of creatinine increases. At DCO1, grade shifts in creatinine (increased) from baseline were seen in the majority of patients during treatment: 263 (96.7%) patients in the osimertinib arm and 256 (95.2%) patients in the SoC arm. A total of 214 (78.7%) patients in the osimertinib arm and 238 (88.5%) in the SoC arm had a 1-grade shift; 48 (17.6%) and 16 (59%), respectively, had a 2-grade shift; 1 (0.4%) patient and 2 (0.7%), respectively, had a 3-grade shift.

Pooled dataset

Renal effects were reported in 36 patients (12.9%) in the osimertinib arm in FLAURA and 166 patients (14.5%) in the pooled population: with most of the events being CTCAE grade 1 (8.2% FLAURA vs. 9.5% pooled population) or grade 2 (4.3% FLAURA vs. 4.2% pooled population). Incidence of CTCAE grade 3 in the pooled population was 7 (0.6%).

Other AESI

Asthenic conditions

Study FLAURA

AEs in the Asthenic conditions grouped term (DCO1) were reported in a slightly greater proportion of patients in the osimertinib arm (69 [24.7%]) than in the SoC arm (50 [18.1%]). The event rate per 100 patient-years was similar between the 2 treatments: 19.7 and 18.4, respectively.

In the osimertinib arm, AEs were generally mild, with no CTCAE grade 4 or grade 5 events. The frequency and severity of events were similar to those in the SoC arm.

Two (0.7%) patients in the osimertinib arm and 3 (1.1%) in the SoC arm had AEs in the Asthenic conditions grouped term reported as SAEs. Events led to discontinuation of treatment in 2 (0.7%) patients in the osimertinib arm (PT of asthenia) and 1 (0.4%) patient in the SoC arm (PT of fatigue).

Anorexia

Study FLAURA

Adverse events in the Anorexia grouped term (DCO1) were reported in a similar proportion of patients in the 2 treatment arms: 56 (20.1%) patients in the osimertinib arm and 52 (18.8%) patients in the SoC arm. The event rate per 100 patient-years was lower in the osimertinib arm than the SoC arm: 16.0 and 19.1, respectively.

In the osimertinib arm, AEs in the Anorexia grouped term were generally mild, with no CTCAE grade 4 or grade 5 events. The frequency and severity of events were similar to those in the SoC arm.

Two (0.7%) patients in each treatment arm had AEs in the Anorexia grouped term reported as an SAE, neither of which led to treatment discontinuation.

Nausea

Study FLAURA

Nausea was a single-PT AESI in this evaluation and was reported in 39 (14.0%) patients in the osimertinib arm and 52 (18.8%) patients in the SoC arm, with a lower event rate per 100 patient-years in the osimertinib arm than in the SoC arm: 11.2 and 19.1, respectively. In the osimertinib arm, reports of nausea were generally mild (all CTCAE grade 1 or grade 2). The frequency and severity of events were similar to those in the SoC arm. None of the events was classified as an SAE.

Nausea led to dosing interruption in 2 (0.7%) patients on osimertinib vs. 1 (0.4%) patient on SoC. No patient had a dosing reduction due to an AE of nausea in either arm. Nausea led to treatment discontinuation in 1 (0.4%) patient in each treatment arm.

Vomiting

Study FLAURA

Vomiting was a single-PT AESI in this evaluation and was reported in 31 (11.1%) patients in the osimertinib arm and 29 (10.5%) patients in the SoC arm (DCO1), with a similar event rate per 100 patient-years: 8.9 and 10.7, respectively. In the osimertinib arm, reports of vomiting were generally mild (all CTCAE grade 1 or grade 2). The frequency and severity of the events were similar to those in the SoC arm.

One (0.4%) patient in the osimertinib arm and 5 (1.8%) patients in the SoC arm had vomiting AEs reported as an SAE.

Vomiting led to dosing interruption in 1 (0.4%) patient in the osimertinib arm and 3 (1.1%) patients in the SoC arm, and to treatment discontinuation in 1 (0.4%) and 2 (0.7%) patients, respectively.

Pancreatitis

Study FLAURA

No event of Pancreatitis (HLT of Acute and chronic pancreatitis) was reported in either treatment arm.

Dry mouth

Study FLAURA

Dry mouth was a single-PT AESI in this evaluation and was reported in a similar proportion of the 2 treatment arms: 12 (4.3%) patients in the osimertinib arm and 14 (5.1%) patients in the SoC arm, with a similar event rate per 100 patient-years: 3.4 and 5.2, respectively (DCO1).

In the osimertinib arm, reports of dry mouth were mild (all CTCAE grade 1). The frequency and severity of the events were similar to those in the SoC arm.

No patients in either treatment arm had an AE of dry mouth reported as an SAE. and no events led to dose interruption, dose reduction, or discontinuation of treatment in either arm.

Abdominal pain

Study FLAURA

AEs in the GI and abdominal pains HLT were reported in a similar proportion of the 2 treatment arms: 23 (8.2%) patients in the osimertinib arm and 23 (8.3%) patients in the SoC arm (DCO1). The event rate per 100 patient-years was also similar: 6.6 and 8.5, respectively. In the osimertinib arm, reports of this HLT were generally mild, with no CTCAE grade 4 or grade 5 events, and led to dose interruption in 1 patient, no dose reductions, and no discontinuation of treatment. The frequency and severity of events were similar to those in the SoC arm.

One (0.4%) patient in the osimertinib arm had an event of abdominal pain reported as an SAE that led to dose interruption but not discontinuation of treatment. No patient in the SoC arm had an event reported as an SAE.

Pyrexia

Study FLAURA

Pyrexia was a single-PT AESI in this evaluation and was reported in 28 (10.0%) patients in the osimertinib arm and 11 (4.0%) patients in the SoC arm (DCO1).

In the osimertinib arm, reports of pyrexia were generally mild (all CTCAE grade 1 or grade 2), and led to dose interruption in 1 patient, no dose reductions or discontinuation of treatment.

One (0.4%) patient in the osimertinib arm and no patients in the SoC arm had a dose interruption due to pyrexia. Two (0.7%) patients in each treatment arm had an AE of pyrexia reported as an SAE; no events led to discontinuation of treatment in either arm.

Infections and infestations

Study FLAURA

The Infections and Infestations SOC is a large AESI grouping that includes over 100 PTs that cover a wide range of common conditions.

Within this SOC, AEs reported in the osimertinib arm and in the SoC arm were: 185 (66.3%) and 168 (60.6%) patients, respectively (DCO1). The most commonly reported AEs (≥5% of patients) were paronychia (osimertinib: 81 [29%] patients; SoC: 80 [28.9%] patients); upper respiratory tract infection (osimertinib: 28 [10.0%]; SoC: 18 [6.5%]); viral upper respiratory infection (osimertinib: 27 [9.7%]; SoC: 20 [7.2%]); pneumonia (osimertinib: 18 [6.5%]; SoC: 9 [3.2%]); and conjunctivitis (osimertinib: 14 [5.0%]; SoC: 20 [7.2%]).The overall event rate per 100 patient-years of AEs in the Infections and Infestations SOC was lower in the osimertinib arm than in the SoC arm: 52.9 and 61.8, respectively. In both treatment arms, the vast majority of infectious AEs were CTCAE grade 1 or grade 2. CTCAE grade 3 AEs were reported in 16 (5.7%) patients on osimertinib and 17 (6.1%) patients on SoC. There was 1 (0.4%) patient with CTCAE grade 4 AE of pneumonia in the SoC arm. CTCAE grade 5 AEs in the Infections & Infestations SOC were reported in 2 (0.7%) patients on osimertinib (pneumonia [1] and respiratory tract infection [1], both unrelated to osimertinib) and 5 (1.8%) patients on SoC (pneumonia and sepsis [2 each], and endocarditis).

A total of 18 (6.5%) patients in the osimertinib arm and 26 (9.4%) patients in the SoC arm had AEs in this SOC reported as an SAE, with the most common SAE being pneumonia (7 [2.5%] patients in each treatment arm).

Dose interruptions due to AEs in the Infections & Infestations SOC were reported in 21 (7.5%) patients in the osimertinib arm and 14 (5.1%) patients in the SoC arm. Events led to dose reduction in 1 (0.4%) patient in the osimertinib arm (AE of paronychia) and no patients in the SoC arm. Three (1.1%) patients in the osimertinib arm and 5 (1.8%) patients in the SoC arm discontinued treatment due to AEs in the Infections & Infestations SOC.

Pooled population

Adverse events of Infections and infestations (SOC) in the pooled population were reported in 712 (62.3%) patients. The most commonly reported AEs (≥ 3%) were: paronychia (276 [24.2%] vs. 81 [29.0%] in FLAURA), Upper respiratory tract infection (142 [12.4%] vs. 28 [10.0%] in FLAURA), Viral upper respiratory tract infection (132 [11.6%] vs. 27 [9.7%] in FLAURA), Urinary tract infection (89 [7.8%] vs. 12 [4.3%] in FLAURA), pneumonia (67 [5.9%] vs. 18 [6.5%] FLAURA), conjunctivitis (46 [4.0%] vs. 14 [5.0%] in FLAURA) and pharyngitis (35 [3.1%] vs. 10 [3.6%] in FLAURA). Most of the AEs were grade 1 (26.3% vs. 23.7% FLAURA) or grade 2 (28.1% vs. 35.8%). CTAE grade 5 AEs were reported in 13 (1.1%) patients in the pooled population and 2 (0.7%) patients in the osimertinib arm in FLAURA.

Haemorrhages

Study FLAURA

Adverse events in the Haemorrhages SMQ were reported in a similar proportion of patients in the 2 treatment arms: 39 (14.0%) patients in the osimertinib arm and 51 (18.4%) patients in the SoC arm (DCO1). The event rate per 100 patient-years was lower in the osimertinib arm than in the SoC arm: 11.2 and 18.8, respectively. Aside from epistaxis (17 [6.1%] osimertinib vs. 14 [5.1%] SoC), no single PT in this SMQ was reported in >5% of patients in either treatment arm.

In most patients, the events were either CTCAE grade 1 or CTCAE grade 2, with 1 (0.4%) patient in the osimertinib arm having a CTCAE grade 4 subdural haematoma. In the SoC arm, 1 (0.4%) patient had a CTCAE grade 4 pulmonary haemorrhage and 2 (0.7%) patients had grade 5 events (1 each of GI haemorrhage and haemoptysis).

Haemorrhages AEs were classified as SAEs in 3 (1.1%) patients in the osimertinib arm (PTs of haemorrhagic stroke, haemorrhoidal haemorrhage, and subdural haematoma) and 5 (1.8%) patients in the SoC arm (PTs of GI haemorrhage, haemoptysis, melena, pulmonary haemorrhage, and subarachnoidal haemorrhage).

The AE of subarachnoidal haemorrhage in the SoC arm led to dosing interruption; no other Haemorrhages AEs led to dose interruption. There were no dose reductions due to events in this SMQ. Events led to discontinuation of 1 (0.4%) patient in the osimertinib arm (PT of subdural haematoma reported the same day as a head injury) and of 3 (1.1%) patients in the SoC arm (PTs of haemoptysis, GI haemorrhage, and Henoch-Schonlein purpura).

Pooled population

The incidence of Hemorrhages SOC AEs in the osimertinib arm in FLAURA was similar to the pooled population: 39 (14.0%) and 191 (16.7%), respectively. Epistaxis (63 (5.5%) pooled population vs. 17 (6.1%) FLAURA) was the only PT reported in ≥ 5% of patients.

Serious adverse event/deaths/other significant events

SAEs in FLAURA

Table 50: Serious adverse events, by preferred term in ≥ 2 patients in either treatment arm in FLAURA (Safety analysis set)

	Number (%) of patients [a]			
	Osimertinib 80 mg (N = 279)		Standard of Care (N = 277)	
MedDRA Preferred term	DCO1	90 DSU	DCO1	90 DSU
Patients with any SAE	60 (21.5)	63 (22.6)	70 (25.3)	72 (26.0)
Pneumonia	7 (2.5)	7 (2.5)	7 (2.5)	7 (2.5)
Interstitial lung disease	4 (1.4)	4 (1.4)	3 (1.1)	3 (1.1)
Pulmonary embolism	4 (1.4)	4 (1.4)	1 (0.4)	1 (0.4)
Pleural effusion	3 (1.1)	4 (1.4)	3 (1.1)	4 (1.4)
Diarrhoea	2 (0.7)	2 (0.7)	4 (1.4)	4 (1.4)
Decreased appetite	2 (0.7)	2 (0.7)	2 (0.7)	2 (0.7)
Asthenia	2 (0.7)	2 (0.7)	2 (0.7)	2 (0.7)
Pyrexia	2 (0.7)	3 (1.1)	2 (0.7)	2 (0.7)
Gastroenteritis	2 (0.7)	2 (0.7)	1 (0.4)	1 (0.4)
Pneumonitis	2 (0.7)	2 (0.7)	1 (0.4)	1 (0.4)
Deep vein thrombosis	2 (0.7)	2 (0.7)	0	0
Enterocolitis	2 (0.7)	2 (0.7)	0	0
Vomiting	1 (0.4)	1 (0.4)	5 (1.8)	5 (1.8)
Sepsis	1 (0.4)	1 (0.4)	3 (1.1)	3 (1.1)
Dyspnoea	1 (0.4)	1 (0.4)	3 (1.1)	2 (0.7)
Alanine aminotransferase increased	1 (0.4)	1 (0.4)	2 (0.7)	2 (0.7)
Drug-induced liver injury	0	0	3 (1.1)	3 (1.1)
Pneumothorax	0	1 (0.4)	2 (0.7)	2 (0.7)
Respiratory failure	0	0	2 (0.7)	2 (0.7)
Mouth ulceration	0	0	2 (0.7)	2 (0.7)
Dermatitis acneiform	0	0	2 (0.7)	2 (0.7)
Haemoptysis	0	0	1 (0.4)	2 (0.7)

a Number (%) of patients with SAEs, sorted in decreasing frequency of PT in the osimertinib arm at DCO1.

Deaths in FLAURA

Among patients who died due to AE in the osimertinib arm, primary causes of death were: pneumonia, respiratory tract infection, intestinal ischaemia, myocardial infarction, cerebral infarction, pulmonary embolism, multiple organ dysfunction syndrome and sudden death.
Death was reported in 9 of the 48 (18.8%) patients who crossed over to the osimertinib arm.

Table 51: Summary of deaths in FLAURA

	Number (%) of patients			
	Osimertinib 80 mg (N = 279)		Standard of Care (N = 277)	
	DCO1	90 DSU	DCO1	90 DSU
Total number of deaths	58 (20.8)	71 (25.4)	83 (30.0)	97 (35.0)
Cause of death				
Disease under investigation only	51 (18.3)	61 (21.9)	65 (23.5)	78 (28.2)
AE with fatal outcome only	6 (2.2)	8 (2.9)	8 (2.9) [a]	8 (2.9) [a]
AE with fatal outcome only (AE start date falling after 28-day follow-up period)	0	0	1 (0.4)	1 (0.4)
Disease under investigation and AE with fatal outcome	0	0	4 (1.4)	4 (1.4)
Other reason [b]	0	1 (0.4)	3 (1.1)	4 (1.4)
Reason unknown/missing	1 (0.4)	1 (0.4)	2 (0.7)	2 (0.7)

a Includes 3 patients who had AEs leading to death after crossover to osimertinib
b Includes patients who died and are not captured in the earlier categories: osimertinib arm: (acute heart failure, 244 days after last dose); SoC arm: (pneumonia, 83 days after last dose), (disseminated intravascular coagulation, 1 day after last dose), (acute respiratory failure, 55 days after last dose) and (lung cancer progression 73 days after last dose).
Death related to disease under investigation was determined by the Investigator.
Rows are mutually exclusive: patients are reported in only 1 category.
Includes all deaths on or after the date of the first dose of randomised study treatment.
Data cut-off date: DCO1=12 June 2017; 90 DSU DCO=25 September 2017

Laboratory findings

Study FLAURA

Haematology

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.

Haemoglobin

For haemoglobin-related changes reported as AEs (anaemia and haemoglobin decreased), the incidence and severity of AEs were similar in the 2 treatment arms, with no CTCAE grade 4 or grade 5 events and only 1 AE reported as an SAE (CTCAE grade 3 anaemia in the SoC arm). In both treatment arms, there were few dose modifications or discontinuation of treatment.

Worsening in CTCAE grade shifts in haemoglobin was recorded in a higher proportion of patients in the osimertinib arm (60.1%) than in the SoC arm (47.0%), with no 4-grade shifts reported in either arm.

Platelets

Worsening in CTCAE grade shifts in platelets was recorded in a higher proportion of patients in the osimertinib arm (51.6%) than in the SoC arm (11.9%). Almost all shifts in both treatment arms were 1-grade (osimertinib: 134 [49.1%] patients; SoC: 30 [11.2%] patients). CTCAE 2-grade shifts occurred in 4 (1.5%) patients on osimertinib and 1 (0.4%) patient on SoC, and 3-grade shifts in 1

(0.4%) patient in each arm. One (0.4%) osimertinib patient had a 4-grade shift in platelets.

A higher proportion of patients in the osimertinib arm experienced platelet counts below the LLN: 151 (54.1%) osimertinib, 36 (13.0%) SoC. Of the patients who had a shift from baseline in grade of the laboratory parameter of platelets (decreased), 134/141 (95.0%) in the osimertinib arm and 30/32 (93.8%) in the SoC arm were CTCAE grade 1.

Adverse events related to a reduction in platelet count (ie, thrombocytopenia and platelet count decreased) were reported in a higher proportion of patients in the osimertinib arm than the SoC arm: 14.7% vs 1.8%, respectively. Most of the events in both treatment arms were reported as CTCAE grade 1. CTCAE grade 3 events were reported in 2 (0.7%) patients in the osimertinib arm and no patients in the SoC arm. No CTCAE ≥grade 4 events were reported in the osimertinib arm vs. 1 (0.4%) in the SoC arm. One SAE event of platelet count decreased was reported in each treatment arm.

AEs of bleeding, bruising or haemorrhage were reported concomitantly with platelet count below the LLN in 9 (3.2%) patients in the osimertinib arm and in 6 (2.2%) patients in the SoC arm. In the osimertinib arm, the patients with bleeding AEs included 3 patients with epistaxis; and 1 patient each with conjunctival haemorrhage, contusion, gingival bleeding, haematoma, haematuria, haemoptysis, haemorrhoidal haemorrhage, and vaginal haemorrhage. In the SoC arm, bleeding AEs occurring concomitantly with platelet counts below the LLN were haemoptysis (2 patients); and diarrhoea haemorrhagic, disseminated intravascular coagulation, epistaxis, haematochezia, haematuria, and purpura (1 patient each).

Leucocytes

Worsening in CTCAE grade shifts in leukocytes values were reported in a higher proportion of patients in the osimertinib arm (72.6%) than in the SoC arm (32.2%). A majority of grade shifts in leukocytes were 1-grade shifts (osimertinib: 133 [50.0%] patients; SoC: 72 [27.6%] patients), with 2-grade shifts reported in 58 (21.8%) patients on osimertinib and 11 (4.2%) patients on SoC. One patient in the osimertinib arm had a 3-grade shift and one patient in each treatment arm had a 4-grade shift in leukocytes.

Adverse events of leukopenia or WBC count decreased were reported in a higher proportion of patients in the osimertinib arm (45 [16.1%]) than the SoC arm (8 [2.9%]). Most patients in both treatment arms had events that were CTCAE grade 1 or grade 2, with no SAEs and only 1 (0.4%) patient in the osimertinib arm reporting a CTCAE ≥ grade 3 event. The majority of the AEs (71/80 [88.8%] in the osimertinib arm and 8/9 [88.9%] in the SoC arm) did not require medication. Three events required dose interruption and 1 event required dose reduction in the osimertinib arm; no event led to discontinuation. No event required dose interruption, modification or led to discontinuation in the SoC arm.

Adverse events in the Infections & Infestations SOC occurred concomitantly with leukocyte counts below the LLN in 35.1% of patients on osimertinib and 7.9% of patients on SoC.

Neutrophils

Worsening in CTCAE grade shifts in neutrophils was recorded in 110 (41.2%) patients in the osimertinib arm vs. 26 (9.9%) patients in the SoC arm. The vast majority of grade shifts in neutrophils were 1-grade shifts (osimertinib: 52 [19.5%] patients; SoC: 15 [5.7%] patients) and 2-grade shifts (osimertinib: 50 [18.7%]; SoC: 10 [3.8%]). Eight (3.0%) patients on osimertinib (one patient on SoC) had 3-grade shifts in neutrophils. There were no 4-grade shifts in neutrophils in either arm.

Adverse events of neutropenia or neutrophil count decreased were reported in a higher proportion of patients in the osimertinib arm (31 [11.1%]) than in the SoC arm (3 [1.1%]). Six (2.2%) patients in

the osimertinib arm and one (0.4%) patient in the SoC arm had a CTCAE ≥ grade 3 event. No event was reported as an SAE.

Adverse events in the Infections & Infestations SOC occurred concomitantly with neutrophil counts below the LLN in 33 (11.8%) patients on osimertinib and 5 (1.8%) patients on SoC.

Lymphocytes

Adverse events of lymphocyte count decreased were reported in a higher proportion of patients in the osimertinib arm (3.2%) than the SoC arm (0.4%), as were AEs of lymphopenia (2.2% and 1.1%, respectively). No serious AEs of lymphocyte count decreased or lymphopenia were reported.

Worsening CTCAE grade shifts in lymphocyte values were reported in higher percentage of patients in the osimertinib arm than the SoC arm (65.2% vs. 35.7%, respectively). The vast majority of grade shifts in lymphocytes were either 1-grade shifts (osimertinib: 82 [30.7%] patients; SoC: 44 [16.7%]) or 2-grade shifts (osimertinib: 76 [28.5%]; SoC: 39 [14.8%]). 14 (5.2%) patients in the osimertinib arm and 11 (4.2%) patients in the SoC arm had 3-grade shifts in lymphocytes. Two (0.7%) patients in the osimertinib arm had 4-grade shifts in lymphocytes (no patients in the SoC arm).

Pooled population

Results from the pooled dataset show a consistent safety profile for osimertinib as that demonstrated in FLAURA.

The most commonly reported haematology-related AEs PTs were anaemia (13.1% pooled population vs. 12.2% FLAURA), platelet count decreased (8.9% pooled population vs. 5.0% FLAURA), thrombocytopenia (8.1% pooled population vs. 9.3% FLAURA), white blood cell count decreased (7.7% pooled population vs. 8.6% FLAURA) and neutropenia (6.5% pooled population vs. 6.8%).

In the pooled population, neutrophils decreased grade shifts incidence was 34.7%, mostly grade 1 and grade 2 [15%] each; Lymphocytes decreased was 67.1%, mostly grade 1 (33.3%) and grade 2 (26.6%); leukocytes decreased grade shifts incidence was 67.8% mostly grade 1 (47.8%) and platelet count decreased events grade shifts incidence was 54.1%, mostly grade 1 (49.9%).

General clinical chemistry

Analysis of reported clinical chemistry values have been considered in conjunction with any relevant or related clinical biochemistry AEs.

In the osimertinib arm, values remained generally consistent over time and there were no clinically significant changes in median values of albumin, calcium, glucose, magnesium, potassium or sodium observed during treatment in the majority of patients. The majority of CTCAE grade shifts seen were 1-grade shifts, with only a small percentage of patients in the osimertinib arm developing a 3-grade or 4-grade shift.

There was a low frequency of reports of abnormal clinical biochemistry AEs. As would be expected with the small magnitude of these changes, no clinically significant sequelae were observed.

Safety in special populations

Effect of gender

Study FLAURA

The 2 groups were broadly consistent in terms of the most commonly reported PTs, with only vomiting (4.0% males vs. 15.2% females) and ECG QT prolonged (3 [3.0%] males vs. 25 [14.0%] females)

having a difference of ≥10 pp between genders. There was a doubling of incidence between genders for the PTs pneumonia (11.9% male vs. 3.4% female) and anaemia (6.9% male vs. 15.2% female).

The only key safety topic grouped term of interest with a difference of >10 pp between male and female patients was Cardiac effects (QT) (4.0% males vs. 14.0% females). This difference was driven largely by the PT of ECG QT prolonged.

Table 52: Adverse events in any category, by gender among patients in the osimertinib arm in FLAURA (Safety analysis set)

	Number (%) of patients[a]	
Adverse event category	Male (N = 101)	Female (N = 178)
Any AE	100 (99.0)	173 (97.2)
Any AE causally related to osimertinib[b]	92 (91.1)	161 (90.4)
Any AE of CTCAE grade 3 or higher	27 (26.7)	68 (38.2)
Any AE of CTCAE grade 3 or higher, causally related to osimertinib[b]	10 (9.9)	39 (21.9)
Any AE with outcome = death	3 (3.0)	3 (1.7)
Any AE with outcome = death, causally related to osimertinib[b]	0	0
Any SAE (including events with outcome = death)	20 (19.8)	40 (22.5)
Any SAE (including events with outcome = death), causally related to osimertinib[b]	4 (4.0)	18 (10.1)
Any SAE leading to discontinuation of osimertinib	6 (5.9)	14 (7.9)
Any AE leading to discontinuation of osimertinib	12 (11.9)	25 (14.0)
Any AE leading to discontinuation of osimertinib, causally related to osimertinib[b]	8 (7.9)	19 (10.7)

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 crossover treatment for FLAURA patients).
CTCAE = Common Terminology Criteria for Adverse Events version 4.03.
MedDRA version 20.0.

Pooled population

Consistent with FLAURA, the overall incidence of AEs was similar across male (N=400) and female (N=742) patients (98.5% vs. 98.7%, respectively) as well as the incidence of AEs of CTCAE ≥ grade 3 (37.3% vs. 38.4%). AEs of CTCAE ≥ grade 3 that were considered by the investigator to be causally related to treatment were slightly higher among female patients (10.5% vs. 16%).

Effect of race

Study FLAURA

Table 53: Adverse events in any category, by race among patients in the osimertinib arm in FLAURA (Safety analysis set)

Adverse event category	Number (%) of patients[a]	
	White (N = 101)	Asian (N = 174)
Any AE	96 (95.0)	173 (99.4)
Any AE causally related to osimertinib[b]	84 (83.2)	165 (94.8)
Any AE of CTCAE grade 3 or higher	29 (28.7)	66 (37.9)
Any AE of CTCAE grade 3 or higher, causally related to osimertinib[b]	14 (13.9)	35 (20.1)
Any AE with outcome = death	4 (4.0)	2 (1.1)
Any AE with outcome = death, causally related to osimertinib[b]	0	0
Any SAE (including events with outcome = death)	22 (21.8)	38 (21.8)
Any SAE (including events with outcome = death), causally related to osimertinib[b]	8 (7.9)	14 (8.0)
Any SAE leading to discontinuation of osimertinib	8 (7.9)	12 (6.9)
Any AE leading to discontinuation of osimertinib	13 (12.9)	24 (13.8)
Any AE leading to discontinuation of osimertinib, causally related to osimertinib[b]	9 (8.9)	18 (10.3)

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 crossover treatment for FLAURA patients).
CTCAE = Common Terminology Criteria for Adverse Events version 4.03.
MedDRA version 20.0.
Data cut-off: 12 June 2017
Source: Table 2.7.4.s2cs, Pooled safety, Module 5.3.5.3.

Table 54: Most common adverse event, by race among patients in the osimertinib arm in FLAURA (frequency ≥ 10% in either race) (Safety analysis set)

	Number (%) of patients [a]	
MedDRA preferred term	White (N = 101)	Asian (N = 174)
Paronychia	**15 (14.9)**	**65 (37.4)**
Diarrhoea	63 (62.4)	96 (55.2)
Dry skin	29 (28.7)	57 (32.8)
Decreased appetite	24 (23.8)	32 (18.4)
Cough	**24 (23.8)**	**22 (12.6)**
Fatigue	**22 (21.8)**	**15 (8.6)**
Dyspnoea	**22 (21.8)**	**13 (7.5)**
Pruritus	21 (20.8)	27 (15.5)
Nausea	**21 (20.8)**	**17 (9.8)**
Vomiting	**20 (19.8)**	**11 (6.3)**
Stomatitis	**19 (18.8)**	**59 (33.9)**
Thrombocytopenia	**19 (18.8)**	**7 (4.0)**
Dermatitis acneiform	**18 (17.8)**	**51 (29.3)**
Asthenia	**17 (16.8)**	**4 (2.3)**
Headache	15 (14.9)	18 (10.3)
Back pain	15 (14.9)	11 (6.3)
Alopecia	13 (12.9)	7 (4.0)
Pain in extremity	**13 (12.9)**	**4 (2.3)**
Constipation	12 (11.9)	28 (16.1)
Dizziness	11 (10.9)	8 (4.6)
Rash maculopapular	11 (10.9)	26 (14.9)
Anaemia	11 (10.9)	23 (13.2)
Arthralgia	11 (10.9)	6 (3.4)
Muscle spasms	11 (10.9)	5 (2.9)
AST increased	7 (6.9)	19 (10.9)
Upper respiratory tract infection	6 (5.9)	22 (12.6)
Insomnia	6 (5.9)	19 (10.9)
Viral upper respiratory tract infection	4 (4.0)	22 (12.6)
Electrocardiogram QT prolonged	**3 (3.0)**	**25 (14.4)**
White blood cell count decreased	**0**	**24 (13.8)**

a Number (%) of patients with AEs, sorted in descending frequency of PT in White patients
Bolding indicates that the PT has a > 10 pp difference between the races.
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.

Pooled population

Consistent with FLAURA, the overall incidence of AEs was similar between White and Asian patients (97.2% vs. 99.3%, respectively), while the incidence of AEs considered by the investigator to be possibly related to osimertinib was higher for Asian patients (90.8%) than for White patients (83.1%). The incidence of AEs CTCAE grade ≥ 3 causally related to osimertinib was also higher for Asian patients (10.3% vs. 16.3%) whereas SAE were more frequent among White patients (34.6% vs. 24.3%).

Effect of age

Study FLAURA

Table 55: Adverse events in any category, by age group at baseline among patients in the osimertinib arm in FLAURA (Safety analysis set)

	Number (%) of patients[a]		
Adverse event category	<65 years (N = 153)	65-74 years (N = 90)	≥75 years (N = 36)
Any AE	151 (98.7)	87 (96.7)	35 (97.2)
Any AE causally related to osimertinib[b]	141 (92.2)	79 (87.8)	33 (91.7)
Any AE of CTCAE grade 3 or higher	39 (25.5)	34 (37.8)	22 (61.1)
Any AE of CTCAE grade 3 or higher, causally related to osimertinib[b]	18 (11.8)	21 (23.3)	10 (27.8)
Any AE with outcome = death	0	2 (2.2)	4 (11.1)
Any AE with outcome = death, causally related to osimertinib[b]	0	0	0
Any SAE (including events with outcome = death)	24 (15.7)	21 (23.3)	15 (41.7)
Any SAE (including events with outcome = death), causally related to osimertinib[b]	7 (4.6)	9 (10.0)	6 (16.7)
Any SAE leading to discontinuation of osimertinib	3 (2.0)	7 (7.8)	10 (27.8)
Any AE leading to discontinuation of osimertinib	10 (6.5)	14 (15.6)	13 (36.1)
Any AE leading to discontinuation of osimertinib, causally related to osimertinib[b]	9 (5.9)	11 (12.2)	7 (19.4)

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 crossover treatment for FLAURA patients).
CTCAE = Common Terminology Criteria for Adverse Events version 4.03.
MedDRA version 20.0.
Data cut-off: 12 June 2017
Source: Table 2.7.4.s2bs, Pooled safety, Module 5.3.5.3.

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: diarrhoea (58.8%, 50.0%, 72.2%, respectively), dermatitis acneiform (30.7%, 23.3%, 8.3%), headache (17.0%, 4.4%, 8.3%), dyspnoea (15.7%, 10.0%, 5.6%), decreased appetite (13.1%, 28.9%, 27.8%), weight decreased (4.6%, 1.1%, 16.7%) conjunctivitis (3.9%, 3.3%, 13.9%) and pulmonary embolism (1.3%, 2.2, 13.9%).

The key safety topics grouped terms of interest with a difference of >10 pp between patients <65 years of age, patients 64-75 years, and patients ≥75 years, respectively, were: diarrhoea (58.8% vs. 50.0% vs. 72.2% ≥75), nail effects (33.3% vs. 40.0% vs. 27.8%), renal effects (13.7% vs. 7.8% vs. 22.2%, with the PT of acute kidney injury reported in no patients <65 or 65-74 and in 8.3% patients ≥75), skin effects (78.4% vs. 71.1% vs. 63.9%, with the difference driven primarily by the PT of dermatitis acneiform: 30.7% vs. 23.3% vs. 8.3%) upper GI tract inflammatory events (46.4% vs. 34.4% vs. 36.1%).

Pooled population

Consistent with FLAURA, the overall incidence of AEs was similar (> 98%) among the 3 groups: patients < 65 years (N=657), patients 65-74 years (N=338) and patients ≥ 75 years (N=147). As well as in FLAURA study, the incidence of AEs in each category, except AEs causally related to osimertinib, appeared to be age-dependent: AEs of CTCAE grade ≥ 3 (33.3%, 40.5%, 53.1%, respectively), AEs of CTCAE grade ≥ 3 considered by the Investigator to be possibly related to osimertinib (10.7%, 16.3% 24.5%), SAE (25.6%, 29.3%, 36.7%) and SAE considered to be possibly causally related to osimertinib (4.0%, 8.9%, 9.5%).

Effect of baseline performance status

Study FLAURA

Assessment of the safety profile of osimertinib at the AE category level among patients with WHO performance status (PS) at baseline of 0 (N=112) and WHO score of 1 (N=167) in FLAURA showed alignment with the overall safety profile. With the exception of a higher incidence of AEs of CTCAE ≥ grade 3 in patients with the higher baseline WHO score (29.5% score 0 vs. 37.1% score 1).

The only key safety topic grouped terms of interest with a difference of >10 pp between WHO score of 0 and WHO score or 1 patients was Upper GI tract inflammatory events (50.9% for patients with a WHO score of 0 vs. 34.7% for patients with a WHO score of 1). The difference was driven primarily by the PT of stomatitis, which was reported in 39.3% of WHO score of 0 patients and 21.6% of WHO score of 1 patients.

Pooled population

Consistent with FLAURA, the overall incidence of AEs was similar (> 98%) among the 2 groups: patients with WHO PS of 0 (N=420) and PS of 1 (N=721). The incidence of CTCAE grade ≥ 3 AEs (31.2% score 0 vs. 41.9% score 1) and the incidence of CTCAE grade ≥ 3 AEs considered by the Investigator possibly related to osimertinib (10.0% vs. 16.5%) was higher in patients with higher baseline WHO score. The incidence of SAE was also higher in patients with WHO score 1 (23.6% vs. 30.7%). SAE considered to be possibly related to osimertinib were similar between both groups (5.0% WHO score 0 vs. 6.8% WHO score 1).

Effect of comorbidity of hypertension

Study FLAURA

Assessment of the safety profile of osimertinib at the AE category level among patients with a history of hypertension (N=109) and those with no hypertension (N=170) in FLAURA showed alignment with the overall safety profile. The overall incidence of AEs was similar between the 2 groups; AEs causally related to osimertinib were broadly similar for patients with and those without hypertension (89% vs. 91.8%, respectively). A greater proportion of patients with hypertension than patients without hypertension had AEs that were CTCAE ≥ grade 3 (39.8% hypertension vs. 30.6% no hypertension) or were reported as SAEs (29.4% hypertension vs. 16.5% no hypertension).

The 2 groups were broadly consistent in terms of the most commonly reported PTs, with only decreased appetite (26.6% hypertension vs. 15.9% no hypertension) and headache (3.7% hypertension vs. 17.1% no hypertension) having a difference of ≥ 10 pp. The only key safety topic grouped terms of interest with a difference of >10 pp between patients with a co-morbidity of hypertension and those without was Upper GI tract inflammatory events (33.9% co-morbidity of hypertension vs. 45.9% those without). The difference was driven primarily by the PT of stomatitis, which was reported in 27 (24.8%) patients with a co-morbidity of hypertension and 53 (31.2%) patients without.

Pooled population

Consistent with FLAURA the overall incidence of AEs was similar (> 98%) between patients with comorbidity of hypertension (N=393) and patients without comorbidity of hypertension (N=746). The incidence of AEs that were CTCAE ≥ grade 3 was slightly higher in patients with hypertension than patients without hypertension (42.4% vs. 35.7%, respectively). There were no notable differences between the 2 groups in any other of the categorical parameters.

Effect of baseline renal function

Study FLAURA

Table 56: Adverse events in any category, by baseline renal function among patients in the osimertinib arm in FLAURA (Safety analysis set)

	Number (%) of patients[a]		
Adverse event category	Normal renal function (N = 99)	Mild renal impairment (N = 122)	Moderate renal impairment (N = 46)
Any AE	97 (98.0)	120 (98.4)	45 (97.8)
Any AE causally related to osimertinib[b]	91 (91.9)	113 (92.6)	40 (87.0)
Any AE of CTCAE grade 3 or higher	22 (22.2)	48 (39.3)	23 (50.0)
Any AE of CTCAE grade 3 or higher, causally related to osimertinib[b]	12 (12.1)	24 (19.7)	12 (26.1)
Any AE with outcome = death	2 (2.0)	3 (2.5)	1 (2.2)
Any AE with outcome = death, causally related to osimertinib[b]	0	0	0
Any SAE (including events with outcome = death)	17 (17.2)	24 (19.7)	16 (34.8)
Any SAE (including events with outcome = death), causally related to osimertinib[b]	4 (4.0)	10 (8.2)	6 (13.0)
Any SAE leading to discontinuation of osimertinib	4 (4.0)	10 (8.2)	5 (10.9)
Any AE leading to discontinuation of osimertinib	9 (9.1)	20 (16.4)	7 (15.2)
Any AE leading to discontinuation of osimertinib, causally related to osimertinib[b]	8 (8.1)	14 (11.5)	5 (10.9)

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 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 crossover treatment for FLAURA patients).
CTCAE = Common Terminology Criteria for Adverse Events version 4.03.
MedDRA version 20.0.
Data cut-off: 12 June 2017
Source: Table 2.7.4.s2fs, Pooled safety, Module 5.3.5.3.

Pooled population

Consistent with FLAURA the overall incidence of AEs was similar (> 98%) between patients with normal renal function (N=407), mild renal function (N=497) and moderate renal function (N=220). The incidence of AEs of CTCAE ≥ grade 3 considered by the Investigator to be possibly related to osimertinib was higher in patients with moderate impairment (19.5%) than in patients with normal renal function (10.3%) or mild renal function (14.9%). SAE were numerically higher in patients with moderate renal impairment (32.7%) than in patients with normal function (28%) or mild renal function (26.4%).

Effect of baseline hepatic function

Study FLAURA

Table 24. Adverse events in any category, by baseline function among patients in the osimertinib arm in FLAURA (Safety analysis set)

Adverse event category	Number (%) of patients[a]	
	Normal hepatic function (N = 233)	Mild hepatic impairment (N = 40)
Any AE	228 (97.9)	40 (100)
Any AE causally related to osimertinib[b]	211 (90.6)	38 (95.0)
Any AE of CTCAE grade 3 or higher	72 (30.9)	22 (55.0)
Any AE of CTCAE grade 3 or higher, causally related to osimertinib[b]	37 (15.9)	11 (27.5)
Any AE with outcome = death	5 (2.1)	1 (2.5)
Any AE with outcome = death, causally related to osimertinib[b]	0	0
Any SAE (including events with outcome = death)	45 (19.3)	13 (32.5)
Any SAE (including events with outcome = death), causally related to osimertinib[b]	14 (6.0)	6 (15.0)
Any SAE leading to discontinuation of osimertinib	14 (6.0)	6 (15.0)
Any AE leading to discontinuation of osimertinib	27 (11.6)	10 (25.0)
Any AE leading to discontinuation of osimertinib, causally related to osimertinib[b]	19 (8.2)	8 (20.0)

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 crossover treatment for FLAURA patients).
CTCAE = Common Terminology Criteria for Adverse Events version 4.03.
MedDRA version 20.0.
Data cut-off: 12 June 2017
Source: Table 2.7.4.s2gs, Pooled safety, Module 5.3.5.3.

Pooled population

Consistent with FLAURA, the overall incidence of AEs was similar (>98%) in patients with normal hepatic function (N=955) and mild hepatic function (N=169). There were no notable differences between the 2 groups in most of the categorical parameters, apart from the incidence of AEs of CTCAE ≥ grade 3 (37.0% normal function vs. 43.8% mild function).

Effect of smoking status

Study FLAURA

Table 57: Adverse events in any category, by baseline smoking status among patients in the osimertinib arm in FLAURA (Safety analysis set)

Adverse event category	Number (%) of patients[a]	
	Ever smoked (N = 97)	Never smoked (N = 182)
Any AE	96 (99.0)	177 (97.3)
Any AE causally related to osimertinib[b]	90 (92.8)	163 (89.6)
Any AE of CTCAE grade 3 or higher	30 (30.9)	65 (35.7)
Any AE of CTCAE grade 3 or higher, causally related to osimertinib[b]	13 (13.4)	36 (19.8)
Any AE with outcome = death	1 (1.0)	5 (2.7)
Any AE with outcome = death, causally related to osimertinib[b]	0	0
Any SAE (including events with outcome = death)	19 (19.6)	41 (22.5)
Any SAE (including events with outcome = death), causally related to osimertinib[b]	6 (6.2)	16 (8.8)
Any SAE leading to discontinuation of osimertinib	7 (7.2)	13 (7.1)
Any AE leading to discontinuation of osimertinib	16 (16.5)	21 (11.5)
Any AE leading to discontinuation of osimertinib, causally related to osimertinib[b]	12 (12.4)	15 (8.2)

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 crossover treatment for FLAURA patients).
CTCAE = Common Terminology Criteria for Adverse Events version 4.03.
MedDRA version 20.0.
Data cut-off: 12 June 2017
Source: Table 2.7.4.s2hs, Pooled safety, Module 5.3.5.3.

Pooled population

The overall incidence of AEs was similar (> 98%) between Ever smoked patients (N=366) and Never smoked patients (N=776). No differences were observed between the 2 groups in any of the categorical parameters.

Effect of body weight

Study FLAURA

Table 58: Adverse events in any category, by body weight among patients in the osimertinib arm in FLAURA (Safety analysis set)

Adverse event category	Number (%) of patients[ab]	
	Body weight <43 kg (N=15)	Body weight >= 43kg (N=256)
Any AE	15 (100)	251 (98.0)
Any AE causally related to AZD9291[c]	15 (100)	232 (90.6)
Any AE of CTCAE grade 3 or higher	10 (66.7)	84 (32.8)
Any AE of CTCAE grade 3 or higher, causally related to AZD9291[b]	6 (40.0)	43 (16.8)
Any AE with outcome = death	0	6 (2.3)
Any AE with outcome = death, causally related to AZD9291[b]	0	0
Any SAE (including events with outcome = death)	3 (20.0)	56 (21.9)
Any SAE (including events with outcome = death), causally related to AZD9291[b]	2 (13.3)	20 (7.8)

Adverse event category	Number (%) of patients[ab]	
	Body weight <43 kg (N=15)	Body weight >= 43kg (N=256)
Any SAE leading to discontinuation of AZD9291	1 (6.7)	18 (7.0)
Any AE leading to discontinuation of AZD9291	1 (6.7)	35 (13.7)
Any AE leading to discontinuation of AZD9291, causally related to AZD9291[b]	1 (6.7)	26 (10.2)

[a] Patients with multiple events in the same category were counted only once in that category. Patients with events in more than one category were counted once in each of those categories.

There were 8 patients who did not have a baseline weight and were excluded from the table.

As assessed by the investigator assessment, and programmatically derived from individual causality assessments.

Included adverse events 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

CTCAE = Common Terminology Criteria for Adverse Events (version 4.0). MedDRA version 20.0.

Table 59: Most common adverse events, by body weight among patients in the osimertinib arm in FLAURA (frequency of ≥10% in either body weight category) (Safety analysis set)[a]

MedDRA PT	Number (%) of patients	
	Body weight <43kg (N=15)	Body weight ≥43kg (N=256)
Diarrhoea	7 (46.7)	149 (58.2)
Stomatitis	9 (60.0)	69 (27.0)
Dry skin	5 (33.3)	82 (32.0)
Decreased appetite	6 (40.0)	50 (19.5)
Dermatitis acneiform	6 (40.0)	63 (24.6)
Paronychia	8 (53.3)	73 (28.5)
Electrocardiogram QT prolonged	8 (53.3)	20 (7.8)
Nausea	2 (13.3)	35 (13.7)
Alanine aminotransferase increased	2 (13.3)	15 (5.9)
Anaemia	4 (26.7)	28 (10.9)
Aspartate aminotransferase increased	2 (13.3)	23 (9.0)
Rash maculo-papular	3 (20.0)	34 (13.3)
Upper respiratory tract infection	4 (26.7)	24 (9.4)
Viral upper respiratory tract infection	2 (13.3)	25 (9.8)
Constipation	3 (20.0)	39 (15.2)
Fatigue	2 (13.3)	36 (14.1)
Skin fissures	4 (26.7)	12 (4.7)
Vomiting	1 (6.7)	29 (11.3)
White blood cell count decreased	6 (40.0)	18 (7.0)
Alopecia	2 (13.3)	18 (7.0)
Conjunctivitis	2 (13.3)	12 (4.7)
Cough	1 (6.7)	43 (16.8)
Insomnia	2 (13.3)	24 (9.4)
Malaise	3 (20.0)	7 (2.7)
Rash	2 (13.3)	14 (5.5)
Vertigo	2 (13.3)	1 (0.4)
Weight decreased	4 (26.7)	9 (3.5)

MedDRA PT	Number (%) of patients	
	Body weight <43kg (N=15)	Body weight ≥43kg (N=256)
Blood bilirubin increased	2 (13.3)	4 (1.6)
Dizziness	2 (13.3)	16 (6.3)
Dysgeusia	2 (13.3)	16 (6.3)
Dyspnoea	0	33 (12.9)
Headache	1 (6.7)	31 (12.1)
Hypokalaemia	2 (13.3)	10 (3.9)
Hyponatraemia	2 (13.3)	10 (3.9)
Lymphopenia	3 (20.0)	3 (1.2)
Pruritus	0	46 (18.0)
Pyrexia	2 (13.3)	26 (10.2)
Urinary tract infection	2 (13.3)	9 (3.5)
Leukopenia	2 (13.3)	16 (6.3)
Lymphocyte count decreased	2 (13.3)	4 (1.6)
Onychomadesis	2 (13.3)	2 (0.8)
Peripheral sensory neuropathy	2 (13.3)	6 (2.3)

[b] Number (%) of subjects with AEs. Included AEs with onset date on or after the date of first dose up to and including 28 days following discontinuation of randomised treatment or the day before first administration of treatment

MedDRA version 20.0

Safety related to drug-drug interactions and other interactions

No new data on drug-drug interactions were reported.

Discontinuation due to adverse events

At DCO1 A total of 351 (63.1%) patients had discontinued their randomised treatment: 138 (49.5%) in the osimertinib arm and 213 (76.9%) in the SoC arm. In both treatment arms, the most frequent reason for treatment discontinuation was worsening of the condition under investigation (osimertinib: 87 patients [31.2%]; SoC: 151 patients [54.5%]). Other reasons for treatment discontinuation, summarised by primary reason, were: adverse events (osimertinib: 36 [12.9%]; SoC: 50 [18.1%]); subject decision: (osimertinib: 12 [4.3%]; SoC: 8 [2.9%]); severe non-compliance to protocol (osimertinib: 0; SoC: 1 [0.4%]); other reasons: 6 (1.1%) patients (osimertinib: 3 [1.1%]; SoC: 3 [1.1%]).

Adverse events leading to discontinuation

Study FLAURA

The majority of discontinuations were due to single events.

Table 60: Adverse events leading to discontinuation of study drug in more than 1% of patients in either treatment arm in FLAURA, by preferred term (Safety analysis set)

	Number (%) of patients [a]			
	Osimertinib 80 mg (N=279)		Standard of Care (N=277)	
MedDRA preferred term	DCO1	90 DSU	DCO1	90 DSU
Any AE leading to discontinuation	37 (13.3)	37 (13.3)	49 (17.7)	49 (17.7)
Interstitial lung disease	6 (2.2)	6 (2.2)	3 (1.1) [b]	3 (1.1) [b]
Pneumonitis	5 (1.8)	5 (1.8)	1 (0.4) [b]	1 (0.4) [b]
ECG QT prolonged	4 (1.4)	4 (1.4)	1 (0.4)	1 (0.4)
Pneumonia	1 (0.4)	1 (0.4)	3 (1.1)	3 (1.1)
Alanine aminotransferase increased	0	0	12 (4.3)	12 (4.3)
Aspartate aminotransferase increased	0	0	8 (2.9)	8 (2.9)
Diarrhoea	0	0	5 (1.8)	5 (1.8)
Hepatic function abnormal	0	0	4 (1.4)	4 (1.4)
Drug-induced liver injury	0	0	3 (1.1)	3 (1.1)

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.
b Although the protocol mandated discontinuation of study treatment for patients who had ILD, 2 patients in the SoC arm had AEs (ILD and pneumonitis [1 patient each]) but continued on treatment.
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 discontinuation of randomised treatment or the day before first administration of crossover treatment.
MedDRA = Medical Dictionary for Regulatory Activities version 20.0.
Data cut-off date: DCO1=12 June 2017; 90 DSU DCO=25 September 2017

Pooled population

AEs leading to discontinuation of osimertinib in the pooled population was reported by 109 patients (9.5%). AEs events leading of study discontinuation causally related to osimertinib were 64 (5.6%).

Adverse events leading to dose reduction

FLAURA

AEs leading to dose reduction were reported in a low proportion of patients in each treatment arm, although the SoC arm had a numerically higher proportion: 11 (3.9%) osimertinib vs. 17 (6.1%) SoC.

Adverse events leading to dose interruption

FLAURA

Adverse events with an action taken of dose interruption were reported in similar proportion of patients: 72 (25.8%) patients in the osimertinib arm and 70 (25.3%) patients in the SoC arm. There did not appear to be any single AE driving the interruption rate in the osimertinib arm, as 17 events led to dose interruption in more than 1 patient each in the osimertinib arm, none of which was reported in more than 3% of patients. In the SoC arm, increases in transaminases were the primary reason for drug interruptions.

Analysis of safety after crossover in Phase III study FLAURA

48 (17.3%) patients in FLAURA crossed over to osimertinib treatment after BICR-confirmed objective progression on SoC and a T790M positive test result based on tissue or plasma. A new baseline was determined at the start of osimertinib treatment for these patients.

Common adverse events

Adverse events were reported in 37 (77.1%) of the 48 patients randomised to the SoC arm who crossed over to osimertinib following confirmed objective progression on SoC.

The most frequently reported PTs (≥10% of crossover patients) were diarrhoea (9 [18.8%]), and paronychia, cough, dry skin, and nausea (5 [10.4%]). Adverse events of CTCAE ≥grade 3 were reported in 6/48 (12.5%) patients. The CTCAE ≥grade 3 AEs included pneumonia in 2 (4.2%) patients; and bacteraemia, febrile infection, oesophageal candidiasis, oral candidiasis, anxiety, atrial thrombosis, and septic shock in 1 (2.1%) patient each. There were no CTCAE grade 4 AEs in patients after crossover. One case of pneumonia and the case of septic shock were CTCAE grade 5 AEs, both of which were considered to be unrelated to osimertinib.

Adverse events of special interest

In general, no new safety findings were seen in AESIs after crossover. Within the key safety topic AEs, the only PTs reported in >10% of patients after crossover were diarrhoea (9 [18.8%]) and paronychia and dry skin (5 [10.4%] each). No CTCAE ≥grade 3 key safety topic AESIs were reported in any patient after crossover.

Serious adverse events

Serious AEs were reported for 8 (16.7%) of the 48 crossover patients. The only SAE reported in more than 1 patient was pneumonia, in 2 (4.2%) patients. In neither patient was the SAE considered by the Investigator to be possibly related to osimertinib.

Deaths

A total of 9 deaths were reported after patients crossed over to osimertinib following confirmed objective disease progression on the SoC treatment, either during the crossover period or its 28-day follow-up. Seven (77.8%) of the 9 deaths were considered by the Investigator to be related to the disease under investigation only. In 2 (22.2%) of the 9 patients, the death was considered to be due to an AE only.

Clinical laboratory results

Adverse events in the Blood & lymphatic disorders SOC included CTCAE grade 2 anaemia in 1 (2.1%) patient. Adverse events related to haematology tests in the Investigations SOC were neutrophil count decreased in 2 (4.2%) patients (both CTCAE grade 2) and WBC count decreased (CTCAE grade 2) in 1 (2.1%) patient. No SAEs were reported in these SOCs.

Discontinuations and dose modification

Adverse events led to permanent discontinuation of osimertinib in 2 (4.2%) of the 48 patients who crossed over to osimertinib after PD: pneumonia in one patient and septic shock in another patient, each of which led to the patient's death. Neither AE was considered by the Investigator to be possibly related to osimertinib.

In the 48 SoC patients who crossed over to osimertinib therapy after PD, only 1 patient had a dose interruption due to an AE (weight decreased). Adverse events of rash and oral candidiasis each led to dose reduction to 40 mg osimertinib in 1 (2.1%) patient after crossover.

Results of analyses on pooled dataset

Table 61: Summary of key safety topics across pooled safety datasets

Topic[c]	Percentage of patients receiving osimertinib 80 mg in FLAURA[a] (N=279)				Percentage of patients receiving osimertinib 80 mg in Phase I, II or III studies[b] (N=1142)			
	Any CTCAE grade	CTCAE grade 1	CTCAE grade 2	CTCAE grade 3-4	Any CTCAE grade	CTCAE grade 1	CTCAE grade 2	CTCAE grade 3-4
ILD (grouped term)	11 (3.9)	2 (0.7)	6 (2.2)	3 (1.1)	45 (3.9)	11 (1.0)	17 (1.5)	12 (1.1)[d]
Torsade de pointes (TdP)/QT prolongation (SMQ)	28 (10.0)	11 (3.9)	11 (3.9)	6 (2.2)	70 (6.1)	35 (3.1)	22 (1.9)	13 (1.1)
Arrhythmias (SMQ)	0	0	0	0	1 (0.1)	1 (0.1)	0	0
Cardiomyopathy (SMQ)	10 (3.6)	3 (1.1)	5 (1.8)	2 (0.7)	22 (1.9)	3 (0.3)	14 (1.2)	5 (0.4)
Cardiac failure (SMQ)	12 (4.3)	3 (1.1)	6 (2.2)	3 (1.1)	30 (2.6)	3 (0.3)	19 (1.7)	7 (0.6)[d]
Rashes & acnes (grouped term)	161 (57.7)	134 (48.0)	24 (8.6)	3 (1.1)	535 (46.8)	447 (39.1)	78 (6.8)	10 (0.9)
Dry skin (grouped term)	100 (35.8)	87 (31.2)	12 (4.3)	1 (0.4)	372 (32.6)	324 (28.4)	47 (4.1)	1 (0.1)
Pruritus (grouped term)	48 (17.2)	40 (14.3)	7 (2.5)	1 (0.4)	194 (17.0)	162 (14.2)	31 (2.7)	1 (0.1)
Exfoliative rash (grouped term)	8 (2.9)	6 (2.2)	2 (0.7)	0	26 (2.3)	21 (1.8)	5 (0.4)	0
Skin & subcutaneous tissue disorders (grouped term)	20 (7.2)	17 (6.1)	3 (1.1)	0	53 (4.6)	47 (4.1)	6 (0.5)	0
Diarrhoea (PT)	161 (57.7)	120 (43.0)	35 (12.5)	6 (2.2)	555 (48.6)	450 (39.4)	91 (8.0)	14 (1.2)
Oral inflammation events (grouped term)	94 (33.7)	75 (26.9)	17 (6.1)	2 (0.7)	277 (24.3)	214 (18.7)	61 (5.3)	2 (0.2)
Non-oral upper GI tract inflammatory events (grouped term)	35 (12.5)	30 (10.8)	4 (1.4)	1 (0.4)	160 (14.0)	133 (11.6)	23 (2.0)	4 (0.4)
GI tract inflammation of unspecified location (grouped term)	1 (0.4)	1 (0.4)	0	0	12 (1.1)	11 (1.0)	1 (0.1)	0
Nail effects (grouped term)	97 (34.8)	52 (18.6)	44 (15.8)	1 (0.4)	357 (31.3)	242 (21.2)	112 (9.8)	3 (0.3)
Keratitis (grouped term)	1 (0.4)	1 (0.4)	0	0	8 (0.7)	3 (0.3)	4 (0.4)	1 (0.1)

Table 62: Summary of key safety topics across pooled safety datasets

Topic[c]	Percentage of patients receiving osimertinib 80 mg in FLAURA[a] (N=279)				Percentage of patients receiving osimertinib 80 mg in Phase I, II or III studies[b] (N=1142)			
	Any CTCAE grade	CTCAE grade 1	CTCAE grade 2	CTCAE grade 3-4	Any CTCAE grade	CTCAE grade 1	CTCAE grade 2	CTCAE grade 3-4
Conjunctival disorders (SMQ)	37 (13.3)	31 (11.1)	6 (2.2)	0	128 (11.2)	98 (8.6)	30 (2.6)	0
Corneal disorders (SMQ)	1 (0.4)	1 (0.4)	0	0	10 (0.9)	5 (0.4)	4 (0.4)	1 (0.1)
Lacrimal disorders (SMQ)	22 (7.9)	20 (7.2)	2 (0.7)	0	77 (6.7)	69 (6.0)	8 (0.7)	0
Periorbital and eyelid disorders (SMQ)	6 (2.2)	5 (1.8)	1 (0.4)	0	32 (2.8)	25 (2.2)	7 (0.6)	0
Misc ocular terms (grouped term)	9 (3.2)	9 (3.2)	0	0	62 (5.4)	57 (5.0)	5 (0.4)	0
Investigations[c] (findings are based on CTCAE grade shifts from baseline in laboratory test results)								
Platelet count decreased (n=1135 for pooled dataset)	138 (50.5)	132 (48.4)	4 (1.5)	2 (0.7)	614 (54.1)	566 (49.9)	30 (2.6)	18 (1.6)
Leukocyte count decreased (n=1128 for pooled dataset)	191 (71.8)	133 (50.0)	57 (21.4)	1 (0.4)	765 (67.8)	539 (47.8)	209 (18.5)	17 (1.5)
Neutrophil count decreased (n=1128 for pooled dataset)	109 (40.8)	53 (19.9)	48 (18.0)	8 (3.0)	391 (34.7)	171 (15.2)	174 (15.4)	46 (4.1)
Lymphocyte count decreased (n=1127 for pooled dataset)	168 (62.9)	79 (29.6)	74 (27.7)	15 (5.6)	756 (67.1)	375 (33.3)	300 (26.6)	81 (7.2)
Electrocardiogram and echocardiogram results								
QTcF increase >500 msec	3/279 (1.1)				10/1142 (0.9)			
QTcF increase >60 sec	14/279 (5.0)				41/1142 (3.6)			
LVEF values with >10% pp decrease from baseline to an absolute value <50%)	8/257 (3.1)				35/908 (3.9)			

a Each patient has only been represented with the maximum reported CTCAE grade for each preferred term.

b Includes patients from the following studies: FLAURA, AURA3, AURA2, AURAextension, and AURA Phase 1

c Baseline is defined as the last result obtained prior to the start of study treatment. Percentages have been calculated using the number of patients (n) with a baseline value and an on-treatment value. Only worsening shifts in CTC grade are included (where the maximum on treatment CTC grade > baseline CTC grade).

d In addition to the patients shown here, there were 5 patients with a CTCAE grade 5 event of ILD (grouped term) (4 in AURA2/AURA1C and 1 in AURA3) and 1 patient with a CTCAE grade 5 event of cardiac failure in AURA3.

Includes adverse events or assessments 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 crossover treatment for AURA3 and FLAURA patients).

CTCAE = Common Terminology Criteria for Adverse Events (version 4.03); MedDRA = Medical Dictionary for Regulatory Activities, version 20.0.

Data cut-off dates: 12 June 2017 for FLAURA, 15 April 2016 for AURA3, 1 November 2016 for the Phase I-II studies

Source: Table 2.7.4.2.2, Table 2.7.4.2.2.2, Table 2.7.4.6.3, Table 2.7.4.6.6 and Table 2.7.4.7.3, Pooled Safety, Module 5.3.5.3.

Post marketing experience

Post-marketing data have been summarised in the latest PBRER, which included data from 13 November 2016 to 12 May 2017. In this PBRER, the total cumulative post-marketing exposure to osimertinib for all doses and all countries as of 12 May 2017 was 7295.5 patient-years.

In the PBRER period from 13 November 2016 to 12 May 2017, the majority of postmarketing cases received were in keeping with the patient population being treated and the known safety profile of osimertinib. Cumulatively, the most frequent spontaneously reported events were from the Investigations SOC (n=188), the majority of which were non-serious (n=164). The most frequently reported event in this SOC was platelet count decreased (n=38), of which 37 were non-serious. Events in the Gastrointestinal disorders SOC were the next most frequently reported (n=179), the majority of which were non-serious (n=147). The most commonly reported event was dry mouth (n=73; non-serious =61). The third most frequent SOC in terms of reported events was Skin and subcutaneous tissue disorders (n=178; non-serious = 169), with rash being the most commonly reported event (n=59; non-serious = 54).

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

2.5.1. Discussion on clinical safety

The safety profile assessment is based mainly on 556 patients from the FLAURA study (279 received 80 mg osimertinib [DCO 12 June 2017] and 277 patients received SoC). All patients randomised to the SoC arm in the US received erlotinib and all patients randomised in Japan received gefitinib. The results have not been split on gefitinib and erlotinib, but are combined to SoC group.

The accumulated safety population consists of 1142 patients from Phase I-III studies treated with 80 mg osimertinib, including the 279 patients in the FLAURA study.

A total of 48 patients crossed over to osimertinib treatment within the study after confirmed objective disease progression on SoC and a T790M positive test result based on tissue or plasma.

Adverse events (AEs)

No new safety signals have been detected from the FLAURA study. The safety profile reported is in line with the adverse reactions that have previously been described.

Generally, the safety profile of osimertinib appears similar to that of the SoC (erlotinib and gefitinib). However, osimertinib had a more favourable profile regarding severity of AEs with a lower frequency of AEs CTCAE grade 3 or higher causally related to treatment of 18.3% compared to 28.2% for SoC.

The most frequently reported AEs (≥ 50%) in either arm were in the SOCs of Gastrointestinal disorders (78.5% vs. 87.0%, osimertinib and SoC respectively), Skin & subcutaneous tissue disorders (77.4% vs. 87.0%) and Infections and Infestations (66.3% vs. 60.6%). The incidence of AEs was generally similar between the two treatment arms, except for the AEs in the skin & subcutaneous tissue disorders, which were reported in a greater proportion of patients in the SoC arm.

The most commonly reported PTs in the osimertinib arm (≥ 20%) were diarrhoea (58.1% vs. 58.1%, osimertinib and SoC respectively), dry skin (31.5 vs. 32.5%), paronychia (29.4% vs. 29.6%), stomatitis (28.7% vs. 20.2%), dermatitis acneiform (25.4% vs. 48.4%) and decreased appetite (22.2% vs. 19.5%).

Among these most common AEs stomatitis was more frequent in the osimertinib arm whereas dermatitis acneiform was more frequent in the SoC. Other PTs more frequent in the osimertinib arm

were: ECG QT prolonged (10.0% vs. 4.3%), pyrexia (10.4% vs. 4.0%) and dyspnoea (12.9% vs. 7.6%). In the SoC arm the incidence of AST increased (9.3% vs. 24.5%), ALT increased (6.5% vs. 27.1%) and alopecia (7.2% vs. 12.6%) was higher than in the osimertinib arm. In general, the incidence of most common AEs was similar in both treatment arms. Other differences of notice are decrease in platelet count, leucocytes, lymphocytes and neutrophils (some associated with AEs) and cardiac failure (4.7% osimertinib vs 2.2% SoC).

AEs of CTCAE ≥ grade 3 was lower in the osimertinib arm than in the SoC arm (36.9% vs. 45.1%, respectively) as well as those AEs of CTCAE ≥ grade 3 considered by the Investigator to be possibly related to study treatment (18.3% vs. 28.2%). Differences observed between treatment arms seem to be driven to a great extent by hepatic (transaminases increased) and skin related events (dermatitis acneiform mainly), more frequent in the SoC arm. The most frequently reported AEs of CTCAE ≥ grade 3 considered to be possibly related to osimertinib were diarrhoea (2.2%), decreased apetite and ECG QT prolonged (1.8% each), ILD and GGT increased (1.1% each), asthenia, fatigue, AST increased, ejection fraction decreased, neutrophil count decreased and platelet count decreased (0.7% each).

Adverse events of special interest (AESIs)

ILD/pneumonitis: ILD grouped term (ILD and pneumonitis) has a low but numerically higher incidence in the osimertinib arm than in the SoC arm (4.3% vs. 2.2%, respectively).

Cardiac effects (QT): adverse events in the overall cardiac effect grouped term (QT) were reported in a higher proportion of patients in the osimertinib arm than in the SoC arm (11.5% vs. 5.4%, respectively).

Cardiac effects (cardiac failure): cardiac failure AEs were reported in a low but numerically higher proportion in the osimertinib arm (4.7%) than in the SoC arm (2.2%).

None of the comparators gefitinib and erlotinib have included cardiac effects as adverse reaction in the SmPCs (section 4.8) or mentioned it in special warnings and precautions (section 4.4). Cardiac failure is included in the RMP of osimertinib as an important potential risk, QT prolongation is listed as an adverse reaction and left ventricular ejection fraction (LVEF) decrease is mentioned in section 4.4 of the SmPC. QT prolongation is much higher for females compared to males (14.0% females vs. 3.0% males) and Asian compared to white population (14.4% Asian vs. 3.0% white). The analysis of a large number of potential risk factors using the LVEF decrease data together with osimertinib PK exposure did not identify any covariates potentially confounding the exposure-to-LVEF event probability relationship.

Diarrhoea: diarrhoea was the most commonly reported AE in either treatment arm (58.1%, each), with a low incidence of AEs of CTCAE ≥ grade 3 (2.2% osimertinib vs. 2.5% SoC).

Skin effects: incidence of Skin Effects grouped term was lower in the osimertinib arm than in the SoC arm (74.2% vs. 85.2%, respectively); differences observed between treatment arms were driven mainly by PT dermatitis acneiform.

Upper gastrointestinal tract inflammatory events: incidence of AEs in this grouped term was higher in the osimertinib arm than in the SoC arm (41.2% vs. 32.5%, respectively).

Nail effects: AEs in this grouped term were reported in 35.8% patients in the osimertinib arm and 33.6% patients in the SoC arm.

Ocular effects: incidence of AEs ocular effects grouped term was lower in the osimertinib arm than in the SoC arm (17.2% vs. 23.1%), being all of them grade 1 or grade 2 in the osimertinib arm. No SAEs were reported.

Renal effects: renal-related AEs were reported in 15.1% patients in the osimertinib arm and 9.7% patients in the SoC arm.

Hepatobiliary effects: hepatic-related AEs were reported in a lower proportion of patients in the osimertinib arm than in the SoC arm (14.7% vs. 36.5%, respectively), driven most of them by the Investigations SOC (12.5% vs. 31.0%, osimertinib and SoC respectively).

Infections and infestations: infections and infestations were reported in 185 (66.3%) patients in the osimertinib arm and 168 (60.6%) in the SoC arm.

Serious Adverse Events (SAEs)

The incidence of SAEs was similar between the osimertinib and SoC arms (22.6% vs. 26.0%, respectively). The most frequently reported SAEs considered to be possibly related to osimertinib were interstitial lung disease, pneumonitis, diarrhoea, enterocolitis and pyrexia.

Deaths

Overall 71 patients (25.4%) in the osimertinib arm and 97 patients (35.0%) in the SoC arm died. There were 16 deaths reported as AEs (8 osimerinib, 8 SoC) of which one in the SoC arm was considered possibly related to study drug. None of the deaths in the osimertinib arm were considered to be possibly related to study treatment.

Laboratory findings

Early reductions in the median laboratory counts of leukocytes, lymphocytes, neutrophils and platelets have been observed in patients treated with TAGRISSO, which stabilised over time and then remained above the lower limit of normal. Adverse events of leukopenia, lymphopenia, neutropenia and thrombocytopenia have been reported, most of which were mild or moderate in severity and did not lead to dose interruptions.

Special populations

The MAH has conducted additional analyses based on updated data from 1142 patients, of which 197 patients were below 50 kg. Low weight (<50 kg) and high age (>65 years) were identified as significant predictors of developing AEs of CTCAE grade≥ 3. Gender and race were not significant predictors after these effects were accounted for.

According to logistic regression analyses, a patient weighing <50 kg is approximately twice as likely to develop CTCAE grade≥ 3 AE and 2-4 times as likely to develop QT prolongation compared with patients in the higher weight categories. In the QT prolongation analysis, there was also a gender-related difference, with the probability of QT prolongation being 2.3 higher in females compared with males. This gender-related QT prolongation difference is well described in the literature. No effect of race was seen.

At 80 mg dose, patients with low body weight (<50 kg) had higher frequencies of Grade ≥3 adverse events (52% vs. 35%) and QT prolongation (14% vs. 4%) than patients with higher body weight (≥50 kg).

Patients with high age (>65 years) and/or low body weight (<50 kg) are at increased risk of developing adverse events of Grade 3 or higher. Closer monitoring is recommended in these patients.

It is reported that renal events are more than doubled when normal renal function is compared to moderate renal impairment.

Given the low grade of severity of events (mostly grade 1 or 2) and the limited number of cases at this time no further changes to the product information is warranted. The MAH is currently running a phase I study in patients with advanced solid tumours and normal as well as severe renal impairment where PK, safety and tolerability of osimertinib are investigated. The MAH is recommended to submit the results which will provide additional data on patients with renal impairment.

Discontinuation of study treatment due to AEs appears similar among treatment arms: 37 (13.3%) in the osimertinib arm and 49 (17.7%) in the SoC arm. In the osimertinib arm, 27 (9.7%) were considered to be possibly related to study treatment. In relation to dose modifications (interruptions and dose reductions), no differences were reported between osimertinib arm and SoC arm (38.7% vs. 38.6%), however, modifications due to AEs were lower in the osimertinib arm than in SoC arm (25.4% vs. 32.1%).

Overall, safety profile and tolerability of osimertinib in FLAURA study seems similar to that reported from previous studies. No new signals have been identified.

2.5.2. Conclusions on clinical safety

Overall the safety profile of osimertinib in first line locally advanced or metastatic NSCLC with EGFR mutations (exon 19 deletions or exon 21 substitution) is consistent with the known safety profile in patients with the T790M mutation. No new safety signals have been identified in the FLAURA study.

Cardiac effects, QT prolongation, cardiac failure and cardiomyopathy seem to be reported at a higher frequency in FLAURA compared to the pooled population, both regarding total number and numbers with grade 3-4. Cardiac and haematological effects associated with a decrease in counts of platelets, leucocytes, neutrophils and lymphocytes are consistently reported at higher frequencies in the osimertinib arm compared to the gefitinib or erlotinib arm. The majority of these effects were of lower grade and manageable with few SAEs.
AEs that led to discontinuation of treatment and AEs of CTCAE grade 3 or higher causally related to treatment were reported in a lower proportion of patients in the osimertinib arm than in the SoC arm. The proportion of SAEs were similar between treatment arms. The totality of the safety data indicate that osimertinib was at least as well tolerated as the SoC comparator.
The present data confirms that osimertinib is well tolerated considering the disease being treated.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 10 is acceptable.

The CHMP endorsed the Risk Management Plan version 10 with the following content:

Safety concerns

List of safety concerns

Important Identified Risks	• Interstitial lung disease • ~~QT prolongation~~

List of safety concerns	
Important Potential Risks	• ~~Developmental toxicity~~ • *Cardiac failure*~~hanges in cardiac contractility~~ ~~Severe skin reactions~~ ~~Severe diarrhoea~~ ~~Severe ocular effects~~ • ~~Hepatotoxicity~~
Missing Information	• ~~Long term exposure to osimertinib~~ • ~~Use during lactation~~ • Use in patients with moderate or severe hepatic impairment • Use in patients with severe renal impairment • Use in patients with ECOG performance status ≥2 • Use in patients with symptomatic brain metastases • Potential for drug-drug interactions between osimertinib and non-CYP3A4 mediated PXR substrates • Potential for P-gp inhibition • ~~Use in very elderly patients (≥75 years old)~~

No new safety concerns were identified as a result of this extension of indication, but some of the existing safety concerns were deleted based on:

- the results of the FLAURA and the re-evaluation of the overall safety profile of osimertinib (using updated pooled datasets comprising integrated safety data from cross-programme osimertinib Phase I to III studies).
- the revised GVP module V guideline and RMP template (rev.2)

The important identified risk "QT prolongation", while also observed in the Flaura study, was removed from the list because there was no evidence to suggest that the effects of osimertinib on QT interval leads to any undesirable clinical outcomes. Extensive information on risk of QT prolongations will still be provided in the product information.

Pharmacovigilance plan

Ongoing and planned additional pharmacovigilance activities

Study name and description Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates (planned/ actual)
Category 3 - *Required additional pharmacovigilance activities*				
D5165C00001 (CAURAL) A phase III, multi-	*Primary Objective:* • To investigate the safety and tolerability profile of osimertinib in combination with	• ILD	Protocol submission	21 May 2015 (actual)

Ongoing and planned additional pharmacovigilance activities

Study name and description Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates (planned/ actual)
centre, open label, randomized study to assess the efficacy and safety of osimertinib in combination with MEDI4736 versus osimertinib monotherapy in patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC who have received prior EGFR TKI therapy. • **Status**: Ongoing	MEDI4736. *Exploratory Objectives (applicable to osimertinib)*: • To assess the safety and tolerability of osimertinib as a single agent • To obtain a preliminary assessment of the efficacy of osimertinib in combination with MEDI4736 and osimertinib monotherapy • To assess the PK of osimertinib as a single agent and in combination with MEDI4736. • To collect and store deoxyribonucleic acid (DNA) for future exploratory research into genes/genetic variation that may influence PK or response osimertinib as a single agent and in combination with MEDI4736 (i.e. absorption, distribution, metabolism, excretion, safety and efficacy) and/or susceptibility to/development of cancers. • To collect and store tumour samples and blood-based (plasma and serum) samples for potential exploratory research into factors that may influence susceptibility to/development of NSCLC/cancer and/or osimertinib as a single agent and in combination with MEDI4736 (where response is defined broadly to include efficacy, tolerability or safety).		CSR (primary analysis)	May 2018 (planned)
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. • **Status**: Ongoing	*Primary Objective:* • 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	Protocol submission CSR (primary analysis)	08 Jun 2015 (actual) Q1 2020 (planned)
D5160C00008 An open-label, non-randomised, multicentre, comparative, phase	*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	• Use in patients with moderate or	Protocol submission CSR (primary analysis)	22 Jul 2014 (actual) Q1 2018 (planned)

Ongoing and planned additional pharmacovigilance activities

Study name and description Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates (planned/ actual)
I study to determine the pharmacokinetics, safety and tolerability of osimertinib following a single oral dose to patients with advanced solid tumours and normal hepatic function or mild or moderate hepatic impairment • **Status**: Ongoing	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.	severe hepatic impairment		
D5160C00035 An open-label, non-randomised, 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. • **Status**: Ongoing	*Primary Objective:* • To investigate the PK of osimertinib after a single oral dose of 80 mg in patients with advanced solid tumours and normal renal function or severe renal impairment. *Secondary Objectives:* • To investigate the PK of osimertinib and metabolites (AZ5104 and AZ7550) after a single oral dose of 80 mg in patients with advanced solid tumours and normal renal function or severe renal impairment. • To investigate the safety and tolerability of a single oral dose of osimertinib in patients with advanced solid tumours and normal renal function or severe renal impairment.	• Use in patients with severe renal impairment	Protocol submission CSR (primary analysis)	28 Oct 2016 (actual) Dec 2018 (planned)

Ongoing and planned additional pharmacovigilance activities

Study name and description Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates (planned/ actual)
D5160C00036 (BLOOM) A Phase I, open-label, multicentre study to assess the safety, tolerability, pharmacokinetics and preliminary anti-tumour activity of osimertinib in patients with EGFRm advanced stage NSCLC.	*Primary Objective:* • To investigate the safety and tolerability of AZD3759 (both Part A and Part B) when given orally to patients with advanced stage EGFR m+ NSCLC who have progressed following prior therapy, including Maximum Tolerated Dose (MTD) determination, if possible (Part A only) *Secondary Objectives:* • To evaluate anti-tumour efficacy and safety in patients treated with osimertinib • To determine the PK of osimertinib and metabolites in blood and CSF following multiple oral dosing • To evaluate the changes from baseline in CNS symptoms (analysed from BN20) in patients with BM and/or LM	• Use in patients with ECOG performance status ≥2 • Use in patients with symptomatic brain metastases	CSR (primary analysis) CSR (primary analysis)	Q2 2018 (planned) Q1 2018 (planned)

No new safety studies were proposed. Existing routine and additional pharmacovigilance activities remain sufficient to characterise the risks of the product.

Risk minimisation measures

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risks		
ILD	*Routine risk minimisation measures:* • ILD (grouped term) is listed as an ADR in Section 4.8 (*Undesirable effects*) if the current SmPC. • Appropriate wording in Section 4.2 (*Posology and method of administration*) and Section 4.4 (*Special warnings and special precautions for use)*of the current SmPC relating to the importance of detection and subsequent management of this important identified risk. • Advice to patients to report relevant medical history prior to starting treatment, and/or report any relevant symptoms during treatment is provided in the PL. *Additional risk minimisation measures*: • None	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection*: • Targeted follow-up questionnaire *Additional pharmacovigilance activities*: • Study D5165C00001 (CAURAL) • Study D5160C00022 (ASTRIS)

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important potential risks		
Cardiac failure	<u>*Routine risk minimisation measures:*</u> • Appropriate wording Section 4.4 (*Special warnings and special precautions for use)* of the current SmPC advising prescribers to consider monitoring of patients with cardiac risk factors or those who develop relevant cardiac signs/symptoms during treatment. • Advice to patients to report relevant cardiac history prior to starting treatment, and/or report any relevant symptoms during treatment is provided in the PL. <u>*Additional risk minimisation measures*</u>: • None	<u>*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection*</u>: • Targeted follow-up questionnaire <u>*Additional pharmacovigilance activities*</u>: • None
Missing information		
Use in patients with moderate or severe hepatic impairment	<u>*Routine risk minimisation measures:*</u> • Appropriate wording in Section 4.2 (*Posology and method of administration*) and Section 5.2 (*Pharmacokinetic properties*) of the SmPC relating to the administration of osimertinib in this patient population. <u>*Additional risk minimisation measures*</u>: • None	<u>*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection*</u>: • None <u>*Additional pharmacovigilance activities*</u>: • Study D5160C00008
Use in patients severe with renal impairment	<u>*Routine risk minimisation measures:*</u> • Appropriate wording in Section 4.2 (*Posology and method of administration*) and Section 5.2 (*Pharmacokinetic properties*) of the SmPC relating to the administration of osimertinib in this patient population. <u>*Additional risk minimisation measures*</u>: • None	<u>*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection*</u>: • None <u>*Additional pharmacovigilance activities*</u>: • Study D5160C00035
Potential for drug-drug interactions between osimertinib and non-CYP3A4 mediated PXR substrates	<u>*Routine risk minimisation measures:*</u> • Appropriate wording in Section 4.5 (*Interaction with other medicinal products and other forms of interaction*) and Section 5.2 (*Pharmacokinetic properties*) of the current SmPC states that PXR regulated enzyme interactions other than CYP3A4 have not been studied. <u>*Additional risk minimisation measures*</u>: • None	<u>*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection*</u>: • None <u>*Additional pharmacovigilance activities*</u>: • Study D5160C00036
Potential for P-gp inhibition	<u>*Routine risk minimisation measures:*</u> • Appropriate wording in Section 5.2 (*Pharmacokinetic properties*) of the current SmPC states that osimertinib is an inhibitor P gp. <u>*Additional risk minimisation measures*</u>: • None	<u>*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection*</u>: • None <u>*Additional pharmacovigilance activities*</u>: • Study D5160C00036

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Use in patients with ECOG performance status ≥2	*Routine risk minimisation measures:* • None *Additional risk minimisation measures*: • None	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection*: • None *Additional pharmacovigilance activities*: • Study D6030C00001 (BLOOM)
Use in patients with symptomatic brain metastases	*Routine risk minimisation measures:* • None *Additional risk minimisation measures*: • None	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection*: • None *Additional pharmacovigilance activities*: • Study D6030C00001 (BLOOM)

Abbreviations: ECOG, Eastern Co-operative Oncology Group; ILD, interstitial lung disease; SmPC, Summary of Product Characteristics; PL, Package leaflet; P-gp, P-glycoprotein; PXR, Pregnane X receptor

Routine risk minimisation activities remain sufficient to manage the safety concerns of osimertinib also in this indication.
This section was updated in line with the amendments proposed for the safety specification, and was also brought in line with the new RMP template.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated. Particularly, a new warning with regard to increased risk of developing adverse events of Grade 3 or higher in patients > 65 years and <50 kg has been added to the product information. The Package Leaflet has been updated accordingly.

2.7.1. User consultation

No justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH. However, the changes to the package leaflet are minimal and do not require user consultation with target patient groups.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The claimed indication of osimertinib is for first-line treatment of patients with locally advanced or metastatic NSCLC whose tumours have EGFR exon 19 deletions (Ex19del) or substitution of a leucine with an arginine at position 858 in exon 21 (L858R) mutations.

Lung cancer is the fourth most frequently diagnosed cancer in the EU, but remains the leading cause of cancer related deaths. Despite progress in early detection and treatment, in 70% to 80% of patients, NSCLC is diagnosed at a locally advanced or metastatic stage, when it is no longer amenable to curative surgery or chemoradiation (Besse et al 2014).

Recent advances in the knowledge of tumour-specific genomic abnormalities have enabled the identification of specific molecular targets for NSCLC treatment in the current clinical practice (Keedy et al 2011, Leighl et al 2014, NCCN 2017, Novello et al 2016, Travis et al 2011). Several biomarkers have shown to be predictive of therapeutic efficacy of molecularly targeted agents and immune-oncology agents, including the presence of sensitising EGFR mutations.

Sensitising mutations in the EGF-receptor are found in 10% of patients with lung cancer in the European Economic Area and 30% to 50% of patients with lung cancer in Asia. In addition to the higher prevalence of EGFR mutations in Asian patients, overall, EGFR mutations have been found to be more frequent in patients with the adenocarcinoma histological subtype and in women. Smoking is the main cause of lung cancer in general, but is not a risk factor for developing activating mutations in the EGF-receptor, in fact the incidence seems higher in never-smokers than in smokers.

In summary, locally advanced or metastatic NSCLC with EGFR activating mutations is an incurable condition with poor prognosis.

3.1.2. Available therapies and unmet medical need

Epidermal growth factor receptor- TKIs such as such as gefitinib (Iressa), erlotinib (Tarceva), afatinib (Giotrif) are the current standard of care as first-line therapy for EGFR mutation-positive NSCLC. Such treatments result in improved response rate (RR) and progression free survival (PFS), better tolerability and superior quality of life (QoL) compared with platinum-based chemotherapy in the first line setting, as demonstrated in several randomised trials.

Although most tumours initially respond well systemically to the currently approved EGFR TKIs in first-line setting, the vast majority of patients develop TKI resistance with a median PFS of 9 to 13 months. In approximately 50% to 65% of the patients the resistance is due to the development of a second-site EGFR-TKI resistance-conferring 'gatekeeper' point mutation, T790M leading to treatment failure and disease progression.

Limited data are available on the efficacy of EGFR-TKIs against CNS metastases in first-line setting, given that CNS metastases have been a typical exclusion criterion in historical studies involving these agents. A selection of trials studying the activity of EGFR-TKIs in patients with NSCLC harbouring EGFR mutations and CNS metastases report response rates of 70-85%, but these trials were of limited quality.

Despite the progress in treating lung cancer patients with activating mutations in the EGF-receptor, the prognosis of patients with this indication is still poor, demonstrating the need for improved treatment in these patients.

3.1.3. Main clinical studies

To support the application, the MAH submitted efficacy data from one single clinical study. FLAURA is a Phase III, double-blind, randomised study (1:1 ratio) designed to compare the efficacy of osimertinib vs. SoC (either gefinitib or erlotinib) as first-line treatment in patients with locally-advanced or metastatic EGFRm NSCLC.

Stratification factors included EGFR mutation status (Ex19del or L858R) ethnicity (Asian/Non-Asian). The primary efficacy endpoint of FLAURA was PFS based on investigator assessment (RECIST v1.1). OS, ORR, DoR, QoL and post progression outcomes (PFS2) were included as secondary endpoints.

3.2. Favourable effects

At the time of the primary analysis for PFS (per investigator assessment; 48.7% of events in the osimertinib arm and 74.4% in SoC arm) a statistically significant and clinically relevant improvement was shown for osimertinib compared to the SoC arm (HR: 0.46 [95% CI: 37, 0.575]; p-value: <0.0001). Treatment with osimertinib resulted in a 8.7-month improvement in median PFS compared to SoC.

PFS results according to BICR on the FAS are consistent with main analysis. Different sensitivity analyses also support robustness of results. Subgroup analyses for PFS showed consistent results in all subgroups analysed.

Regarding OS, a HR of 0.63 (CI 95% 0.45, 0.88) that did not reach the pre-specified threshold for statistical significance at this interim analysis was observed. Superior rates at different time points consistently favoured osimertinib arm (OS rates at 12 months: 89.1% vs. 82.5%; 18 months: 82.8% vs. 70.9%).

A numerical trend favouring osimertinib was observed for ORR (79.9% (95% CI: 74.7, 84.5) in the osimertinib arm and 75.8% (95% CI: 70.3, 80.7) in the SoC arm). Responses were twice longer in the osimertinib arm than in SoC (median 17.2 months vs. 8.5 months).

CNS efficacy by RECIST v1.1 in FLAURA demonstrated an improvement in CNS PFS HR: 0.48 (95% CI: 0.26, 0.86). An ORR of 65.6% (95% CI: 52.3, 77.3) was documented in the osimertinib arm vs. 43.3% (95% CI: 31.2, 56.0) in the SoC arm in the subset of patients with brain metastasis.

The median PFS2 on subsequent treatment was not reached in the osimertinib arm, with a lower limit of the 95% CI of 23.7 months, and was 20.0 months (95% CI: 18.2, NR) in the SoC arm. A HR of 0.58 (95% CI: 0.44, 0.78; p-value = 0.0004), was observed.

3.3. Uncertainties and limitations about favourable effects

Os data submitted were immature. Final OS data will be submitted together with other relevant endpoints such as TFST and TSST when available.

3.4. Unfavourable effects

Generally, the safety profile of osimertinib appears similar to that of the SoC (erlotinib and gefitinib). Overall incidence of AEs was 97.8% in both treatment arms, with most of the AEs being considered by the Investigator to be possibly related to study treatment.

The most commonly reported PTs in the osimertinib arm (≥ 20%) were diarrhoea (57.7% vs. 57.4%, osimertinib and SoC respectively), dry skin (31.5 vs. 32.5%), paronychia (29.0% vs. 28.9%), stomatitis (28.7% vs. 20.2%), dermatitis acneiform (25.4% vs. 48.4%) and decreased appetite (20.1% vs. 18.8%). Other PTs more frequent in the osimertinib arm were: ECG QT prolonged (10.0% vs. 4.0%), pyrexia (10.0% vs. 4.0%) and dyspnoea (12.5% vs. 7.2%).

The most frequently reported AEs of CTCAE ≥ grade 3 considered to be possibly related to osimertinib were diarrhoea (2.2%), decreased apetite and ECG QT prolonged (1.8% each), ILD and GGT increased (1.1% each), asthenia, fatigue, AST increased, ejection fraction decreased, neutrophil count decreased and platelet count decreased (0.7% each).

ILD grouped term (ILD and pneumonitis) in the osimertinib was 3.9%, AEs grade 3 was 1.1%.

Adverse events in the overall cardiac effect grouped term (QT) were reported in 10.4% of patients.

Incidence of Skin Effects grouped term was 74.2% of patients.

The incidence of AEs in the Upper gastrointestinal tract inflammatory events was 41.2% of patients. Stomatitis was the most frequent PT in the osimertinib arm (28.7%).

The incidence of SAEs was 21.5% with osimertinib. The most frequently reported SAEs (≥ 1%) were pneumonia (7 [2.5%] patients), ILD and pulmonary embolism (4 [1.4%] each), and pleural effusion (3 [1.1%]).

The majority of deaths in the osimertinib arm were considered to be related to the disease under investigation. None of deaths in the osimertinib arm were considered to be possibly related to study treatment.

Safety profile in males and females was overall similar, although AEs ≥ grade 3 was higher in females than in males. A higher incidence of ECG QT prolonged was also reported in female patients (3.0% vs. 14%). Incidence of AEs causally related to osimertinib was higher in Asian patients than in White patients as well as AE of CTCAE ≥ grade 3. Moreover, a higher incidence of ECG QT prolonged (3.0% vs. 14.4%) and dermatitis acneiform (17.8% vs. 29.3%) was also reported in Asian patients than in White patients. In patients ≥ 75 years incidence of AE of CTCAE ≥ grade 3, SAEs and SAEs possibly related to osimertinib was higher.

Discontinuation of study treatment due to AEs was 13.3% in the osimertinib arm, and 9.7% were considered to be possibly related to study treatment. AEs leading to dose interruption were 25.1%, AEs leading to dose reduction were 3.9%. No new signals have been identified.

Patients aged >65 years and/or low body weight (<50 kg) are at increased risk of developing adverse events of Grade 3 or higher.

3.5. Uncertainties and limitations about unfavourable effects

No additional key uncertainties and limitations have been identified.

3.6. Effects Table

Table 63: Effects Table for osimertinib in first-line treatment in patients with locally-advanced or metastatic NSCLC with exon 19 deletions or exon 21 substitution (data cut-off: 12 June 2017)

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
PFS INV	Progression free survival by investigator	Months	18.9	10.2	HR 0.46 (95% CI 0.37, 0.57)	CSR
OS	Overall survival	Months	NR	NR	HR 0.63 (95% CI 0.45, 0.88) NES at the time of this 1st IA	CSR
ORR INV	Overall response rate per invesigator (not confirmed)	%	79.9	75.8		
Unfavourable Effects						
AEs grade ≥3	Adverse events of CTCAE grade ≥3	%	34.1	44.8		
SAEs	Serious AEs regardless causality	%	21.5	25.3		
Deaths	Number of deaths	Absolute value	2.2	3.6		
ILD and pneumonitis	AE of special interest	%	3.9	2.2		
Cadiac effects	AE of special interest	%	4.3	2.2		
QT prolongation	AE of special interest	%	10.0	4.0		

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The use of EGFR TKIs in patients with activating (sensitising) EGFR mutations NSCLC, have improved the clinical outcomes of these patients, with higher antitumor activity, greater delay in the tumour progression and better quality of life as compared to traditional platinum based chemotherapy. TKIs of first or second generation have been considered the SoC in this patient population.

Osimertinib has now proven to prolong PFS in a clinically relevant manner when compared to SoC, erlotinib or gefitinib, which could likely translate into longer OS for patients (as pointed out by preliminary data). The efficacy was observed regardless of CNS metastases, and across other sub-groups. The better clinical outcomes could be a new milestone in the SoC, moving the first choice in the current treatment armamentarium. The uncertainties related to the FLAURA study, lack of mature OS data, do not overcome the benefits associated to this therapy as a clear effect is evident from the preliminary data.

Generally, the safety profile of osimertinib appears similar to that of the SoC (erlotinib and gefitinib). Overall the safety profile of osimertinib in first line locally advanced or metastatic NSCLC with EGFR mutations (exon 19 deletions or exon 21 substitution) is consistent with the known safety profile in the currently authorised indication, in patient harbouring the T790M mutation. No new signals have been identified. Additionally, safety profile and tolerability of osimertinib appear similar to other TKIs (erlotinib and gefitinib), with a lower incidence of severe (CTCAE ≥ grade 3) AEs reported with osimertinib.

Although only patients with Ex19del or L858R mutations were included in the FLAURA study, the available preclinical data and limited clinical data support a broad indication regardless of the type of activating EGFR mutations.

3.7.2. Balance of benefits and risks

Results from FLAURA trial are considered to demonstrate a clinically relevant and significant advantage over the current SoC as first-line treatment of patients with EGFR+ NSCLC whereas the safety profile remains in line with what has been previously described.

3.8. Conclusions

The overall B/R of Tagrisso as first-line therapy in EGFR mutation-positive patients with metastatic or locally advanced NSCLC is considered to be positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of Indication to include (as monotherapy) first-line treatment of adult patients with locally advanced or metastatic non-small cell lung cancer with activating epidermal growth factor receptor (EGFR) mutations, based on data from the FLAURA study (D5160C00007): a phase III, double-blind, randomised study to assess the efficacy and safety of AZD9291 versus a standard of care epidermal growth factor receptor-Tyrosine Kinase Inhibitor as first-line treatment in patients with epidermal growth factor receptor mutation-positive, locally-advanced or metastatic non-small-cell lung cancer; as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 of the SmPC have been updated and the Package Leaflet has been updated accordingly. Further, sections 4.4 and 4.8 of the SmPC have been updated with a new warning with regard to increased risk of developing adverse events of Grade 3 or higher in patients > 65 years and <50 kg. In addition, the MAH took the opportunity to update sections 2 and 4.4 of the SmPC with information regarding the excipient sodium, and to implement editorial changes in the SmPC and Package Leaflet. An updated RMP version 10.0 was agreed during the procedure.

Additional market protection

Furthermore, the CHMP reviewed the data submitted by the MAH, taking into account the provisions of Article 14(11) of Regulation (EC) No 726/2004, and considers that the new therapeutic indication brings significant clinical benefit in comparison with existing therapies.