22 April 2021
EMA/280219/2021
Committee for Medicinal Products for Human Use (CHMP)

CHMP group of variations including an extension of indication assessment report

Invented name: TAGRISSO

International non-proprietary name: osimertinib

Procedure No. EMEA/H/C/004124/II/0039/G

Marketing authorisation holder (MAH) AstraZeneca AB

Note

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

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List of abbreviations

Abbreviation	Explanation
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
AJCC	American Joint Committee on Cancer
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
AUCss	Area under the concentration-time curve at steady-state
AZD9291	Osimertinib, TAGRISSO
BCRP	Breast cancer resistance protein
CI	Confidence interval
CL/F	Apparent clearance of the parent drug
CLM/F	Apparent clearance of the metabolite
Cmin	Minimum plasma concentration
Cminss	Minimum plasma concentration at steady-state
CNS	Central nervous system
CSP	Clinical study protocol
CSR	Clinical study report
CTCAE [v4.03]	Common Terminology Criteria for Adverse Events version 4.03
CYP	Cytochrome P450
DAE	AEs leading to permanent discontinuation of randomised treatment
DCO	Data cut-off date
DDI	Drug-drug interaction
DFS	Disease-free survival
ECG	Electrocardiogram
EGFR	Epidermal growth factor receptor
EGFRm	Epidermal growth factor receptor-tyrosine kinase inhibitor sensitising mutation, including exon 19 deletions and point mutations in exon 21 (L858R, L861Q) and exon 18 (G719X)
EGFR-TKI	Epidermal growth factor receptor-tyrosine kinase inhibitor
Ex19del	Exon 19 deletion, an in-frame deletion occurring within exon 19, which encodes part of the kinase domain
fu	Fraction of unbound drug in plasma
fu_{inc}	Fraction of unbound drug in incubation
fu_{mic}	Fraction of unbound drug in microsomal incubation
HR	Hazard ratio
HRQoL	Health-related quality of life
HRCT	High-resolution CT

I_2	Maximum intestinal drug concentration
IC_{50}	Half maximal inhibitory concentration
IDMC	Independent Data Monitoring Committee
I_{inmax}	Maximum total liver inlet concentration
I_{infree}	Maximum unbound liver inlet concentration
ILD	Interstitial lung disease
IP	Investigational product
Ki	Inhibition constant
KM	Kaplan-Meier
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
LLOQ	Lower limit of quantification
LVEF	Left ventricular ejection fraction
MATE	Multidrug and toxin extrusion protein
MCID	Minimum clinically important difference
MCS	Mental Component Summary
MedDRA	Medical Dictionary for Regulatory Activities
MUGA	Multi-gated acquisition (scan)
NSCLC	Non-small cell lung cancer
OAT	Organic anion transporter
OATP	Organic anion transporter protein
OCT	Organic cation transporter
OS	Overall survival
PBRER	Periodic benefit-risk evaluation report
PCS	Physical Component Summary
P-gp	P-glycoprotein
PFS	Progression-free survival
PK	Pharmacokinetic(s)
PPES	Palmar-plantar erythrodysaesthesia syndrome
PS	Performance status
PT	Preferred term (MedDRA)
QTc	Corrected QT interval
QTcF	QT interval corrected for heart rate using Fridericia's formula
SAE	Serious adverse event
SAP	Statistical analysis plan
SCS	Summary of Clinical Safety
sd	Standard deviation

SoC	Standard of care
SOC	System organ class (MedDRA)
T790M	EGFR mutation resulting in substitution of threonine with methionine at amino acid position 790 in exon 20 of EGFR
TKI	Tyrosine kinase inhibitor
TTO	Time to onset
UGT	Uridine 5'-diphospho-glucuronosyltransferase
ULN	Upper limit of normal
V/F	Apparent volume of distribution of the parent drug
VM/F	Apparent volume of distribution of the metabolite
VPC	Visual predictive check
WHO	World Health Organization

1. Background information on the procedure

1.1. Type II group of variations

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, AstraZeneca AB submitted to the European Medicines Agency on 26 August 2020 an application for a group of variations.

The following variations were requested in the group:

Variations requested		**Type**	**Annexes affected**
B.I.b.1.e	B.I.b.1.e - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a specification parameter which may have a significant effect on the overall quality of the AS and/or the FP	Type II	None
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 of Tagrisso to include the adjuvant treatment after complete tumour resection in EGFR mutant non-small cell lung cancer (NSCLC) patients, based on the results from the pivotal Phase 3 randomised, placebo-controlled study ADAURA (D5164C00001); as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.3 of the SmPC are updated. The Package Leaflet is updated accordingly. Version 14.1 of the RMP has also been submitted.

The group of variations requested 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 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 MAH 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.

Scientific advice

The MAH received Scientific Advice from the CHMP on 23 April 2015 (EMEA/H/SA/3023/1/2015/III). The Scientific Advice pertained to non-clinical and clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Blanca Garcia-Ochoa Co-Rapporteur: Bjorg Bolstad

Timetable	Actual dates
Submission date	26 August 2020
Start of procedure:	12 September 2020
CHMP Rapporteur Assessment Report	27 November 2020
CHMP Co-Rapporteur Assessment Report	6 November 2020
PRAC Rapporteur Assessment Report	13 November 2020
PRAC members comments	18 November 2020
Updated PRAC Rapporteur Assessment Report	19 November 2020
PRAC Outcome	26 November 2020
CHMP members comments	30 November 2020
Updated CHMP Rapporteur(s) (Joint) Assessment Report	3 December 2020
Request for supplementary information (RSI)	10 December 2020
CHMP Rapporteur Assessment Report	05 March 2021
CHMP members comments	15 March 2021
Updated CHMP Rapporteur Assessment Report	18 March 2021
2nd Request for Supplementary information	25 March 2021
CHMP Rapporteur Assessment Report	08 April 2021
CHMP members comments	12 April 2021
Updated CHMP Rapporteur Assessment Report	16 April 2021
Opinion	22 April 2021

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

This application is being submitted to support the additional indication:

Tagrisso as monotherapy is indicated for the adjuvant treatment after complete tumour resection in adult patients with non-small cell lung cancer (NSCLC) whose tumours have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations.

Epidemiology

Lung cancer is the most common cancer in the world, with approximately 2 million new cases and 1.7 million deaths in 2018 (Globocan 2018). Non-small cell lung cancer (NSCLC) is the most common type of lung cancer, accounting for 80-85% of all lung cancers (Travis et al 2000).

Approximately 20% of patients with NSCLC have tumours with EGFR mutations, with greater incidence in Asia than Europe and North America (Midha et al 2015). The most common EGFR mutations are deletions in exon 19 (Ex19del) and an L858R substitution in exon 21, both of which are in the kinase domain of EGFR and together account for approximately 85% of EGFR mutations (Kobayashi and Mitsudomi 2016).

Biologic features and clinical presentation

Despite progress in early detection and treatment, NSCLC is most often diagnosed at an advanced stage and has a poor prognosis (Herbst et al 2008). Once NSCLC has progressed to a locally advanced or metastatic stage there is no cure and treatment is therefore focused on extending life, delaying disease progression, and improving symptoms and quality of life.

Progress in molecular biology has changed the therapeutic approach to NSCLC, and the treatment of advanced NSCLC can now be guided by the presence of certain mutations, e.g., epidermal growth factor receptor (EGFR), or anaplastic lymphoma kinase (ALK). Since the discovery of the common somatic mutations in the kinase domain of EGFR in 2004 (Lynch et al 2004), NSCLC patients with activating EGFR mutations in exons 18-21 of EGFR (including L858R and exon 19 deletions [Ex19del], collectively described as EGFRm) are considered a subset of NSCLC in terms of pathogenesis, prognosis and treatment.

Overall, EGFR mutations have been found to be more frequent in never smokers, in patients with the adenocarcinoma histologic subtype, and in women. Their prevalence is also higher in East Asian patients than in Caucasian patients (ESMO clinical practice guidelines [Reck et al 2014]).

Management

The primary treatment for patients with stage IB-IIIA NSCLC is complete tumour resection. Meta-analyses of studies have found that post-operative chemotherapy increased 5-year survival in patients with stage I-III NSCLC by 4.0 to 5.4% (NSCLC Meta-analysis Collaborative Group 2010, Pignon et al 2008). As a consequence of these data, adjuvant platinum-based chemotherapy is considered a standard of care for patients with stage II-IIIA disease. The benefit of adjuvant platinum-based chemotherapy in patients with stage IB is less clear and as such its use is only recommended for patients with high risk disease (NCCN Guidelines 2020, Postmus et al 2017).

Although treatment for patients with stage IB-IIIA is given with curative intent, recurrence occurs frequently. After a median follow-up of 5.2 years, the recurrence rate ranges from 45% for patients with stage IB disease to 76% for patients with stage III disease (Pignon et al 2008). Five-year survival rates are suboptimal and range from 36% for patients with pathologic stage IIIA disease to 71% for patients with pathologic stage IB disease (stages are based on the AJCC TNM lung cancer staging 7th edition; Goldstraw et al 2016). The risk of dying from NSCLC increases greatly after disease recurrence in all stages of resected NSCLC and therefore delaying or preventing recurrence is critical to improving long-term patient outcomes (Consonni et al 2015).

Whilst the trials of platinum-based adjuvant chemotherapy that contributed to meta-analyses were conducted prior to the discovery of EGFR mutations in 2004 (Paez et al 2004, Lynch et al 2004), the

guideline recommendations for adjuvant therapy are independent of EGFR mutation status. Following surgery and standard adjuvant chemotherapy no treatments are currently licensed for EGFRm resectable NSCLC.

Over the last decade EGFR-TKIs such as osimertinib, afatinib, gefitinib and erlotinib have replaced chemotherapy as the standard of care for patients with metastatic EGFRm NSCLC. However, in early-stage disease the use of EGFR-TKIs is investigational and there are no targeted treatments currently approved for adjuvant treatment. Several trials (Huang Q, 2016, Zhong WZ, 2017 and Wu JX, 2018) have investigated the use of EGFR-TKIs as adjuvant treatment and have indicated that they may offer improved outcomes compared with chemotherapy.

2.1.2. About the product

Osimertinib (AZD9291, TAGRISSO) is an oral, irreversible inhibitor of EGFRm and T790M mutation-positive forms of EGFR. Osimertinib, as monotherapy, is approved in the EU for the treatment of adult patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC and for the first-line treatment of adult patients with locally advanced or metastatic NSCLC with activating epidermal growth factor receptor (EGFR) mutations.

The CHMP adopted the following indication:

TAGRISSO as monotherapy is indicated for the adjuvant treatment after complete tumour resection in adult patients with stage IB-IIIA non-small cell lung cancer (NSCLC) whose tumours have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations (see section 5.1).

When considering the use of TAGRISSO, EGFR mutation status in tumour specimens should be determined using a validated test method.

Patients should receive treatment until disease recurrence or unacceptable toxicity. Treatment duration for more than 3 years was not studied (see section 4.2 of the SmPC).

The development programme/compliance with CHMP guidance/scientific advice

On 18 December 2014 the MAH AstraZeneca AB requested scientific advice for their product osimertinib EMEA/H/SA/3023/1/2015/III. AstraZeneca requested scientific advice to discuss and reach agreement on a planned nonclinical and clinical development plan to support the use of osimertinib in patients with EGFR Mutation Positive Stage IB-IIIA NSCLC, following complete tumour Resection with or without adjuvant chemotherapy. AstraZeneca's questions covered:

- Acceptability of the timing of availability of chronic toxicity data
- Clinical relevance of magnitude of benefit
- Statistical design parameters
- Duration of treatment
- Key secondary endpoints
- Proposal not to perform PK assessments

A pre-submission meeting was held to discuss with the (Co-)Rapporteurs and EMA the content and format of the ADAURA adjuvant extension of indication application for Tagrisso in the European Union.

2.1.3. General comments on compliance with GLP, GCP

To date there have been no Regulatory Authority site inspections conducted on the pivotal study D5164C00001 (ADAURA).

The pivotal clinical trial was performed in accordance with GCP as claimed by the MAH. The MAH states that procedures, internal quality control measures and audit programmes provide reassurance that the clinical study programme was carried out in accordance with good clinical practice, as documented by the ICH.

2.2. Quality aspects

Sections *S.3.2. Impurities*, *S.4.1. Specification*, *S.4.2. Analytical methods* and *S.4.3. Validation of analytical methods* have been amended.

S.3.2 Impurities

Acceptable intake

An acceptable intake of 10 µg/day of a mutagenic impurity is proposed. This level is calculated based on the principles of ICH M7 and a dosing interval of between 1 and 10 years. This proposed acceptable intake of a potential mutagenic impurity (PMI) in drug substance is in accord with the 'negligible' risk defined in ICH M7.

This 10 µg/day limit would equate to 125 ppm based on an 80 mg/day dose of active substance.

SAR and Ames studies

Structural activity relationship (SAR) evaluation – compounds identified during the route evaluation step were subjected to SAR evaluation using commercial databases, DEREK (6.0.1) and Leadscope (3.5.2) and additionally an in-house database.

Of the 34 compounds that were SAR tested 3 were class 2 and 6 were class 3.

The 3 Class 2 and the 6 Class 3 impurities levels are considered controlled to suitably low limits in line with the ICH M7 control options.

S.4.2 Analytical Procedures for Drug Substance

The analytical procedures used to control the quality of the drug substance are:

- Description by Visual Inspection
- Analytical Procedure for Identification by FT-IR Spectroscopy
- Analytical Procedure for Assay by LC
- Analytical Procedure for Organic Impurities by LC
- Analytical Procedure for Residual Solvents by GC
- Residue on ignition/sulphated ash according to USP/Ph Eur
- Particle Size Distribution by Laser Diffraction
- Water Content by KF according to USP/Ph Eur

Details for all listed procedures, with the exception of Description, Residue on ignition / sulphated ash and Water Content by KF, are provided.

S.4.3 Validation Report for Organic impurities by LC

The experimental work that was performed to validate the analytical procedure for the determination of organic impurities of the drug substance by LC is described. The procedure has been validated in accordance with ICH Q2 (R1).

S.4.5 Justification of Specification

Justification related to one impurity has been removed from the 'Clauses included in the specification' section and a revised justification, concluding that no test is required, presented under the 'Clauses considered but not included in the Specification' heading.

Conclusion on Quality aspects

Regarding mutagenic and potentially mutagenic impurities, an adequate control strategy in line with ICH M7 has been defined.

The process chemistry and process parameters that impact levels of mutagenic impurities are understood. Physico-chemical properties and process factors that influence the fate and purge of impurities are well known. Estimated purge factors for clearance of some impurities by the process are provided and their calculations described.

Analytical data on commercial batches to support the control approach are provided.

In summary, the risk of an impurity residing in the final drug substance above the acceptable limit is determined to be negligible. Therefore, the 3 Class 2 and the 6 Class 3 impurities levels are considered adequately controlled.

The removing of the specification limit for one impurity is considered acceptable.

2.3. Non-clinical aspects

2.3.1. Introduction

Osimertinib was originally developed for advanced cancer, with a limited study program designed/based on the ICH S9 guideline. The proposed indication is, however, covered by ICH M3(R2) guideline and therefore additional nonclinical studies have been conducted to support this application. This AR addresses the additional studies not previously assessed:

- Pharmacology Report 24: An in vitro inhibition of EGFR, downstream signalling and cell proliferation by AZD9291(osimertinib) in two patient derived tumour cell lines carrying activating, uncommon mutations in EGFR
- Pharmacology Report 23: In vitro cellular screening assay for AZ13552748 (AZD9291, osimertinib), AZ13575104 (metabolite of osimertinib) and AZ12656575 (Afatinib)
- Pharmacology Report 25: An in Vivo Tumour Growth of NSCLC PDX harbouring uncommon EGFR mutations at codons G719, S768 and L861
- Plasma protein binding – equilibrium dialysis (studies BS001265-53-AZD9291, BS001265-53-AZ13575104, BS001265-53-AZ13597550)
- SP-PET-0038: An in vivo assessment of brain exposure and regional brain distribution of AZD9291 in cynomolgus monkey using PET microdosing.
- Toxicity studies
    - 20138322: AZD9291: 14-day by Oral (Gavage) Dose Range Finding Toxicity Study in Mice
    - 20138323: AZD9291: 42-day Oral (Gavage) Dose Range Finding Toxicity Study in Mice

    - 528219: AZD9291: Six Month Oral (Gavage) Toxicity Study in the Rat
    - 528224: AZD9291: Nine Month Oral (Gavage) Toxicity Study in the Dog
- 497280: Oral Fertility and Early Embryonic Development Study with Assessment of Recovery in the Female Rat
- 20138324: AZD9291: A 26-week Carcinogenicity Study by Oral Gavage in CByB6F1/Tg rasH2 Hemizygous Mice
- Impurities studies
    - Study 8421524: Genetic Toxicity Evaluation Using the Bacterial Reverse Mutation Test in *Salmonella typhimuriumTA98, TA100, TA1535 and TA1537 and Escherichia coli WP2 uvrA* (pKM101)
    - Study 8443048 : Genetic Toxicity Evaluation Using the Bacterial Reverse Mutation Test in *Salmonella typhimurium TA98, TA100, TA1535 and TA1537 and Escherichia coli WP2 uvrA* (pKM101)

2.3.2. Pharmacology

Previous studies have demonstrated that osimertinib has inhibitory activity against EGFR across a range of clinically relevant EGFR sensitising-mutant and T790M mutant NSCLC cell lines *in vitro*, leading to tumour shrinkage in both EGFRm and T790M NSCLC xenograft and transgenic mouse lung tumour models. Additional studies have been conducted, supporting that osimertinib is also a potent inhibitor of uncommon activating mutations in EGFR (see below).

Primary pharmacodynamic studies

In vitro studies

Inhibition of EGFR phosphorylation in COS7 cells expressing uncommon EGFR mutants

To test the potency of inhibition of EGFR phosphorylation of uncommon EGFR mutations by osimertinib, COS7 cells were transiently transfected to express a variety of uncommon EGFR mutant proteins, treated with osimertinib, and EGFR phosphorylation was measured using a homologous time-resolved fluorescence assay. The potency of the osimertinib metabolite, AZ5104, against the uncommon mutants is greater than osimertinib (apparent geomean IC50 range 1.7 nM – 40.7 nM) representing an average 2.66fold difference in potency compared to osimertinib ($p<0.05$) (see Table 2).

Table 1: Summary of Inhibition of EGFR phosphorylation by osimertinib in COS7 cells expressing uncommon EGFR mutants following a 2-hour pre-incubation (Apparent IC50 geomean, +/- SE, μM)

Cell Line, EGFR mutation	Geomean IC_{50} (μM)	± SE	Number of replicates
Cos 7 EGFR L861Q/G719A	0.0370	0.0083	2
Cos 7 EGFR L861Q/G719S	0.0175	0.0054	2
Cos 7 EGFR S768I/G719A	0.0352	0.0070	3
Cos 7 EGFR S768I/G7198S	0.0407	0.0040	3
Cos 7 EGFR G719C	0.0194	0.0081	2
Cos 7 EGFR G719S	0.0351	0.0144	2
Cos 7 EGFR L816Q	0.0148	0.0047	3
Cos 7 EGFR S768I	0.0240	0.0080	3
Cos 7 EGFR G719A	0.0354	0.0150	2

Cell Line, EGFR mutation	Geomean IC_{50} (μM)	± SE	Number of replicates
Cos 7 EGFR G719C/L861Q	0.0112	0.0050	2
Cos 7 EGFR G719C /S768I	0.0045	0.0021	2
Cos 7 L747S	0.0200	0.0059	3
EGFR Ex19del Control Line	0.0084	0.0017	6
L858R Control Line	0.0119	0.0021	7

Table 2: Inhibition of EGFR phosphorylation by AZ5104 in COS7 cells expressing uncommon EGFR mutants following a 2-hour pre-incubation (Apparent IC50 geomean, +/- SE, μM)

Cell Line, EGFR mutation	Geomean IC_{50} (μM)	± SE	Number of replicates
Cos 7 EGFR L861Q/G719A	0.0200	0.0023	3
Cos 7 EGFR L861Q/G719S	0.0053	0.0007	2
Cos 7 EGFR S768I/G719A	0.0113	0.0022	3
Cos 7 EGFR S768I/G719S	0.0106	0.0003	2
Cos 7 EGFR/G719C	0.0116	0.0018	3
Cos 7 EGFR /G719S	0.0407	0.0155	3
Cos 7 EGFR/L816Q	0.0064	0.0006	3
Cos 7 EGFR/S768I	0.0102	0.0006	3
Cos 7 EGFR/G719A	0.0141	0.0004	2
Cos 7 EGFR G719C/L861Q	0.0023	0.0009	3
Cos 7 EGFR G719C/S768I	0.0017	0.0002	2
Cos 7 L747S	0.0076	0.0005	3
EGFR Ex19del Control Line	0.0072	0.0007	5
L858R Control Line	0.0087	0.0006	6

Inhibition of EGFR Phosphorylation and downstream signalling in patient derived tumour cell lines, in vitro, expressing the EGFR L861Q mutation or the EGFR G719C/S768I mutation

EGFR mutant NSCLC patient-derived cell lines carrying either the EGFR L861Q (YU-1092) or G719C/S768I compound mutation (YU-1099) were used to evaluate inhibition of EGFR and downstream signalling by osimertinib in more disease relevant models, compared to the engineered COS7 model. EGFR phosphorylation (pEGFR) in the YU-1099 was not detected at the lowest concentration of osimertinib (10 nM) but in the YU-1092 cell line the osimertinib concentration required to completely inhibit EGFR phosphorylation was between 30 and 100 nM. In both cell lines osimertinib induced concentration-dependent inhibition of downstream signalling (pAkt, pERK, pS6) and increases in the levels of the pro-apoptotic protein BIM.

Inhibition of proliferation and colony formation, in vitro, in patient derived tumour cell lines expressing the EGFR L861Q mutation or the EGFR G719C/S768I mutation

In a colony formation assay in the YU-1099 cell line carrying the compound EGFR G719C/S768I mutation, osimertinib showed potent inhibition of colony formation with an apparent IC50 of approximately 30 nM. In the YU-1092 carrying an EGFR L861Q mutation the IC50 for inhibition of colony formation was <10 nM.

In vivo studies

In vivo activity of osimertinib against tumour models carrying uncommon EGFR mutations involving codons G719, S768 and L861

Using a dose in mice (25 mg/kg once daily) which provides an exposure to osimertinib that is similar to the human clinical exposure of the 80 mg dose of osimertinib, in vivo efficacy data in PDX models that carry 3 of the commonly reported compound mutations involving G719X and either S768I and L861Q (G719A/S768I, G719C/S768I and G719A/L861Q) is shown in Table 3. The LU1901 model which carries a cMET amplification, is not dependent upon EGFR for tumour growth since tumour regression can be achieved by administration of a selective cMET inhibitor. cMET amplification is an established resistance mechanism for EGFR tyrosine kinase inhibitors.

Table 3: In vivo activity of osimertinib against tumour models carrying EGFR G719 mutations

Model (mutation)	Treatment	% Tumour growth inhibition	Regression %[a]	P-value
LU1901 (G719A; c-MET amplification)	osimertinib 25 mg/kg QD	Not detected	Not detected	NA
LC-F-29 (G719A/S768I)	osimertinib 25 mg/kg QD	>100	81%	<0.001
CTG-2534 (G719C/S768I)	osimertinib 25 mg/kg QD	>100	58%	<0.001
CTG-1082 (G719A/L861Q)	osimertinib 25 mg/kg QD	87	Not detected	<0.001
YLR067 (L861Q)	osimertinib	>100	99%	<0.01 **

NA = not applicable; QD = once daily
Regression was calculated as the percentage reduction in tumour volume from baseline value: % Regression = (1 – RTV) x 100% where RTV = Mean Relative Tumour Volume.

An additional PDX model carrying the L861Q mutation and derived from a patient previously treated with erlotinib has also been tested for response to osimertinib (Figure 1).

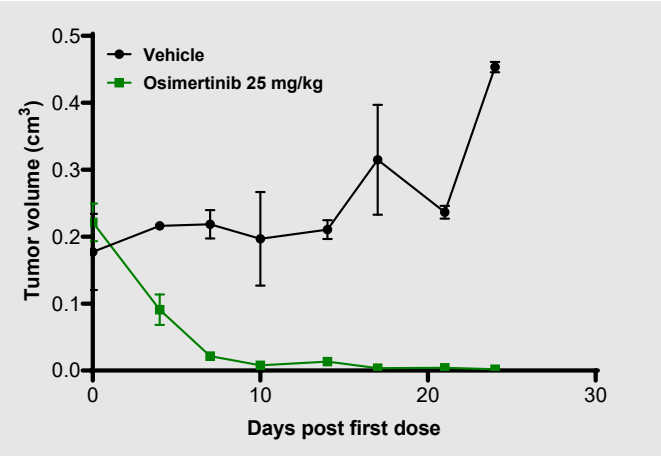
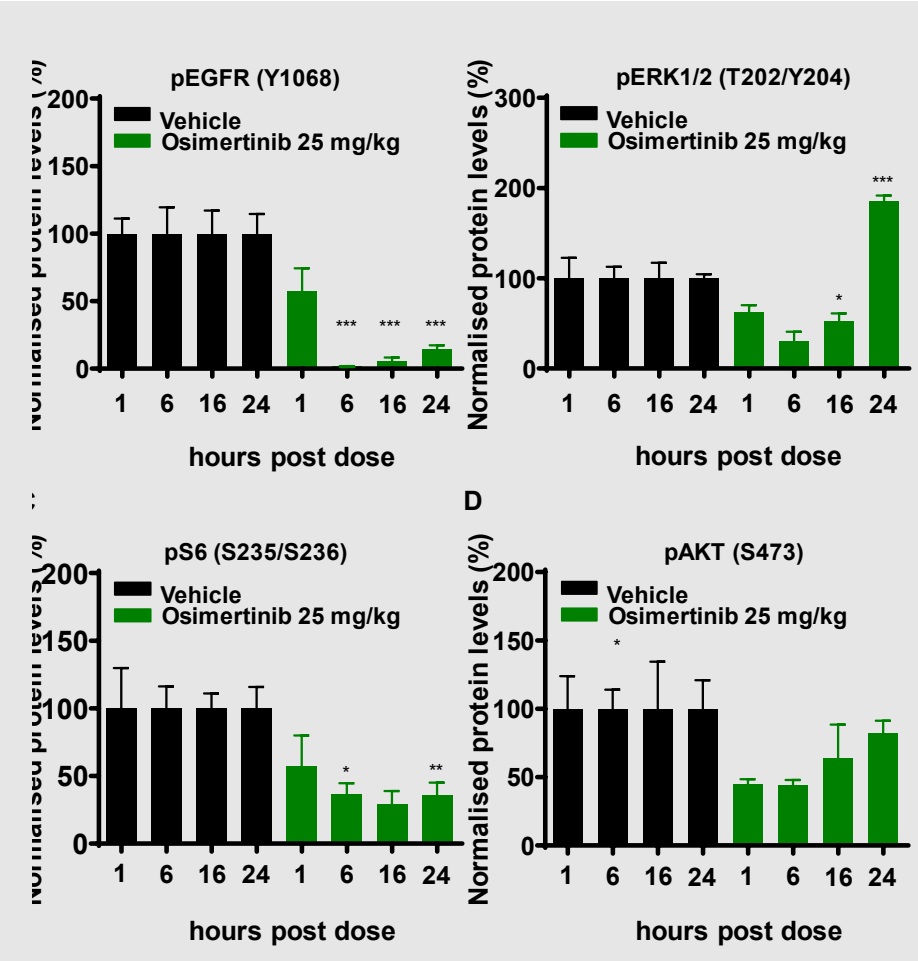


Figure 1: In vivo activity of osimertinib against PDX tumour models carrying an EGFR L861Q mutation

Pharmacodynamic Activity of osimertinib in a PDX tumour model carrying the G719A/S768I uncommon compound mutation in EGFR

A PDX tumour model carrying the G719A/S768I mutation was used to demonstrate time dependent inhibition of EGFR and downstream signalling (pERK, pAkt and pS6) at various time points following a single, oral 25 mg/kg dose of osimertinib. The results are shown in Figure 2.



(A) Quantification of the level of p-EGFR or (B) pERK1/2 or (C) pS6 or (D) pAKT determined by immunoblot on tumours collected 1, 6, 16 and 24 hours following 1 dose of either vehicle or osimertinib. Data are represented as mean ± standard error of the mean (SEM) (n = 4 for vehicle and treated groups).

Figure 2: Osimertinib inhibits EGFR phosphorylation and downstream signalling in vivo in the LC-F-29 PDX model which carries an EGFR G719A/S768I compound mutation

2.3.3. Pharmacokinetics

Plasma protein binding – equilibrium dialysis (studies BS001265-53-AZD9291, BS001265-53-AZ13575104, BS001265-53-AZ13597550)

At the time of the original marketing application a computational approach was used to estimate human plasma protein binding for osimertinib and its metabolites, AZ5104 and AZ7550. These predictions have now been superseded with new experimental data. The in vitro plasma protein binding of osimertinib and its metabolites AZ5104 and AZ7550 was determined in mouse, rat, dog, monkey and human plasma and alpha 1-acid glycoprotein and human serum albumin protein solutions over a concentration range of 0.1-100 µmol/L (0.1-10 µmol/L for AZ7550) by equilibrium dialysis (RED device).

Osimertinib

The in vitro plasma protein binding results for osimertinib are summarised in Table (Study Number BS001265-53-AZD9291).

Table 4. Summary of % plasma unbound of osimertinib in mouse, rat, dog, monkey and human plasma, human alpha 1-acid glycoprotein solution and human serum albumin protein solution

Osimertinib conc. (µmol/L)	**% Plasma Unbound (Mean ± SD)**						
	Mouse	**Rat**	**Dog**	**Monkey**	**Human**	**α1-AGP**	**HSA**
0.1	0.824 ± 0.0173	1.06 ± 0.0595	1.01 ± 0.0389	2.83 ± 0.268	ND	35.3 ± 2.11	14.7 ± 1.58
1	1.25 ± 0.185	1.66 ± 0.216	1.72 ± 0.0601	4.03 ± 0.00367	5.35 ± 0.0822	40.4 ± 1.87	12.2 ± 0.291
10	2.07 ± 0.105	2.30 ± 0.0674	2.09 ± 0.0654	4.48 ± 0.457	5.52 ± 0.412	60.5 ± 3.30	12.9 ± 0.571
100	2.50 ± 0.358	4.19 ± 0.179	3.84 ± 0.216	4.14 ± 0.424	4.95 ± 0.815	63.9 ± 4.69	12.4 ± 0.878
[a] Mean	NC	NC	NC	4.21 ± 0.234	5.27 ± 0.295	NC	13.0 ± 1.11

α1-AGP = Alpha 1-acid glycoprotein solution; HSA = Human serum albumin protein solution; NC = Not calculated; ND = Not determined due to non-quantifiable buffer concentrations

[a] 0.1-100 µmol/L for HSA; 1-100 µmol/L for human and monkey

Metabolite AZ5104

The in vitro plasma protein binding results for AZ5104 are summarised in Table (Study Number BS001265-53-AZ13575104).

Table 5: Summary of % plasma unbound of AZ5104 in mouse, rat, dog, monkey and human plasma, human alpha 1-acid glycoprotein solution and human serum albumin protein solution

AZ5104 conc. (µmol/L)	**% Plasma Unbound (Mean ± SD)**						
	Mouse	**Rat**	**Dog**	**Monkey**	**Human**	**α1-AGP**	**HSA**
0.1	6.22 ± 0.859	6.02 ± 0.782	4.74 ± 0.349	11.9 ± 1.89	7.92 ± 0.377	45.2 ± 5.42	18.8 ± 2.35
1	5.25 ± 0.376	5.64 ± 0.219	5.56 ± 0.290	10.8 ± 0.823	8.47 ± 0.405	49.3 ± 7.71	18.9 ± 1.02
10	5.97 ± 0.757	8.03 ± 0.807	6.18 ± 0.133	11.0 ± 0.664	9.73 ± 0.461	51.4 ± 2.19	19.2 ± 0.487
100	9.15 ± 0.224	14.4 ± 0.772	15.8 ± 0.873	14.2 ± 0.724	12.9 ± 0.310	76.7 ± 1.94	24.7 ± 0.255

α1-AGP = Alpha 1-acid glycoprotein solution; HSA = Human serum albumin protein solution

Metabolite AZ7550

The in vitro plasma protein binding results for AZ7550 are summarised in Table (Study Number BS001265-53-AZ13597550).

Table 6: Summary of % plasma unbound of AZ7550 in mouse, rat, dog, monkey and human plasma, human alpha 1-acid glycoprotein solution and human serum albumin protein solution

AZ7550 conc. (µmol/L)	% Plasma Unbound (Mean ± SD)						
	Mouse	**Rat**	**Dog**	**Monkey**	**Human**	**α1-AGP**	**HSA**
0.1	0.711 ± 0.129	0.916 ± 0.0999	0.598 ± 0.119	1.98 ± 0.417	2.33 ± 0.143	52.8 ± 4.72	5.27 ± 0.537
1	1.49 ± 0.341	2.11 ± 0.0428	1.01 ± 0.0501	3.36 ± 0.213	3.56 ± 0.202	53.5 ± 1.68	7.14 ± 0.244
10	1.97 ± 0.0627	2.77 ± 0.164	1.74 ± 0.0735	3.86 ± 0.152	3.78 ± 0.104	61.2 ± 3.92	7.57 ± 0.394

α1-AGP = Alpha 1-acid glycoprotein solution; HSA = Human serum albumin protein solution

Distribution

Assessment of brain exposure and regional brain distribution of AZD9291 in cynomolgus monkey using PET microdosing

This PET microdosing study demonstrated that [^{11}C]-osimertinib distributed across the blood-brain barrier of the cynomolgus monkey brain and that a microdose of [^{11}C]-osimertinib exhibited a higher level of brain exposure to that of the active metabolite [^{11}C]-AZ5104.

This was in support of three non-clinical studies previously submitted that showed brain penetration of the cynomolgus monkey (i.v. dosing), rat and mouse (oral administration).

2.3.4. Toxicology

Repeat dose toxicity

14-day and 42-day Oral (Gavage) Dose Range Finding Toxicity in Mice (studies 20138322 and 20138323)

Repeat dose toxicology studies were conducted in mice to support dose level selection for the carcinogenicity study.

A dose of 75 mg/kg/day was considered to be the maximum tolerated dose in the 14-day study. Body weight loss at 100 mg/kg/day was the dose limiting toxicity. One female mouse dosed at 45 mg/kg/day for 6 weeks showed ophthalmology findings of corneal opacity and vascularisation. The main target organs identified in the mouse (at ≥10 mg/kg/day) were consistent with EGFR inhibition and included findings in the skin and eyelid (pustules, epidermal hyperplasia and hyperkeratosis, inflammation, follicular dysplasia; ulceration at ≥45 mg/kg/day)), eye (corneal epithelial atrophy; corneal ulceration and neutrophilic inflammation at 45 mg/kg/day). Epithelial atrophy was observed in

the oesophagus (75 mg/kg/day), non-glandular stomach and tongue (75 mg/kg/day) and villous atrophy was noted in the ileum (75 mg/kg/day).

The NOAEL for the 42-day study is considered to be 10 mg/kg/day.

Six Month Oral (Gavage) Toxicity Study in the Rat (study 528219)

Oral administration of osimertinib to rats at 1, 5 or 20 mg/kg/day for up to 6 months was associated with clinical signs at ≥ 5 mg/kg/day and a decrease in bodyweight gain in males at 20 mg/kg/day. Compound-related histopathological changes were present in the skin, cornea, oesophagus, tongue, Harderian gland, lacrimal gland, spleen and lymph nodes at 5 mg/kg/day and above, and also in the non-glandular stomach, kidney, male mammary gland, eyelid tarsal gland, prostate gland, seminal vesicles, uterus, vagina, adrenal gland, bone marrow, lung and thymus at 20 mg/kg/day. There were histopathological findings in the Harderian gland of one female at 1 mg/kg/day, however these were considered to be non-adverse given the minimal severity and lack of any other histopathology or ophthalmology findings in the eye. The low dose of 1 mg/kg/day is therefore considered to be the NOAEL.

Nine Month Oral (Gavage) Toxicity Study in the Dog (study 528224)

Oral administration of osimertinib to dogs at 6 mg/kg/day for 9 months was associated with ocular clinical signs and ophthalmology findings, which resulted in two females being taken off dose for a short period. These signs recovered within 5 days off-dose and 6 mg/kg/day was well tolerated for the remainder of the dosing period with minor clinical signs and a reduction in body weight gain (males only). Doses of 0.5 or 1.5 mg/kg/day were well tolerated for 9 months with ophthalmology findings seen at 1.5 mg/kg/day. Compound-related histopathological changes were present in the testes at all dose levels, in the kidney at ≥1.5 mg/kg/day and in the adrenal gland, liver and eyelid (tarsal gland) at 6 mg/kg/day. As histology findings were present at the low dose a NOAEL was not identified in this study.

Carcinogenicity

A 26-week Carcinogenicity Study by Oral Gavage in CByB6F1/Tg rasH2 Hemizygous Mice (study 20138324)

Oral administration of osimertinib once a day to transgenic mice for a minimum of 26 weeks a doses up to 10 mg/kg/day (AUC 0 t 4.53 µmol x h/L) did not result in any osimertinib related effects on survival, clinical observations, overall body weight, food consumption, gross pathology or neoplastic histopathology findings. However, there was one osimertinib-related, non-neoplastic histopathology finding: minimal epithelial atrophy of the cornea in both sexes at 10 mg/kg/day. This finding was only observed during histopathological evaluation and was not observed during in-life ophthalmology examinations conducted during Week 13 or Week 26 (prior to study termination).

104 Week Oral (Gavage) Carcinogenicity Study in the Rat (study 507363)

The study is ongoing and a preliminary report was provided.

Oral administration of AZD9291 to rats at 1, 3 or 10 mg/kg/day for up to 2 years was associated with clinical signs at ≥ 1 mg/kg/day and a decrease in body weight gain at 10 mg/kg/day. AZD9291 was carcinogenic in the rat with treatment-related proliferative findings noted in the mesenteric lymph node of animals dosed at 10 mg/kg/day (haemangioma in both sexes and angiomatous hyperplasia in females). Lens fibre degeneration was observed at ≥3 mg/kg/day in both sexes and correlated with ophthalmology findings. The no-observed-adverse-effect level (NOAEL) is considered to be 1 mg/kg/day.

Reproduction toxicity

Osimertinib: Oral Fertility and Early Embryonic Development Study with Assessment of Recovery in the Female Rat (study 497280)

Once daily oral administration of osimertinib to female rats at 20 mg/kg/day was associated with transient clinical observations, body weight loss and reductions in food consumption during the pre-pairing dosing period. Administration at 20 mg/kg/day for 14 days prior to pairing, through pairing and until Day 8 of gestation resulted in a decrease in the number of live implants together with an associated increased incidence of early embryonic deaths. After administration at 20 mg/kg/day for 21 days followed by a one-month recovery period prior to pairing for mating, there were no compound-related effects on mating or pregnancy indices. The NOEL for maternal toxicity, reproductive performance, embryonic survival and development was 1 mg/kg/day.

Other toxicity studies

Toxicity assessment of impurities

Osimertinib impurity Bacterial Reverse Mutation Test in Salmonella typhimurium TA98, TA100, TA1535 and TA1537 and Escherichia coli WP2 uvrA (pKM101) (study 8421524)

Osimertinib impurity Bacterial Reverse Mutation Test in Salmonella typhimurium TA98, TA100, TA1535 and TA1537 and Escherichia coli WP2 uvrA (pKM101) (study 8443048).

The osimertinib impurities were found not to be mutagenic in these studies.

Ecotoxicity/environmental risk assessment

An ERA has previously been conducted for osimertinib, refined by on overall prevalence rate of NSCLC with EGFR mutation in Hungary (the EU member state with highest single year prevalence of lung cancer).

A re-evaluation of the ERA has been conducted due to the application for a new indication as a monotherapy for the adjuvant treatment after complete tumour resection in adult patients with NSCLC with activating EGFR mutations, including updated prevalence data.

Predicted Environmental Concentration (PEC) calculation.

In the calculation of the PEC, the highest reported incidence rates of NSCLC (90%) and EGFR mutation (15%) are applied to the overall prevalence rate of lung cancer for Hungary, in order to refine the market penetration factor (Fpen = 0.000080). No consideration ofstage of disease is included in this calculation therefore, the Fpen is considered to provide a worst-case for the calculation of the environmental concentration of osimertinib mesylate.

The unrefined PECsurfacewater for osimertinib mesylate use of 80 mg/day is:

$$PEC_{Surfacewater} = \frac{DOSEai \times Fpen}{WASTEWinhab \times DILUTION}$$

where;

DOSEai = maximum daily dose consumed per inhabitant = 80 mg × inh^{-1} × d^{-1}
Fpen = percentage of market penetration = 0.000080
WASTEWinhab = amount of wastewater per inhabitant per day = 200 L × inh^{-1} × d^{-1}
DILUTION = dilution factor = 10

$$PEC_{Surfacewater} = \frac{80 \times 0.000080}{200 \times 10}$$

= 0.0000032 mg/L

= 0.0032 µg/L

Table 7: ERA table

Substance (INN/Invented Name): Osimertinib (Tagrisso)			
CAS-number (if available):			
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	0.0032	µg/L	> 0.01 threshold (N)

2.3.5. Discussion on non-clinical aspects

Pharmacology

Several studies have been developed to assess the activity of osimertinib to support the additional indication. An *in vitro* study showed that osimertinib and its metabolite AZ5104 inhibit EGFR phosphorylation in COS7 cells expressing uncommon EGFR mutants. A second *in vitro* study was performed with patient-derived tumour cell lines in which osimertinib induced concentration-dependent inhibition of downstream signalling (pAkt, pERK, pS6) and increases in the levels of the pro-apoptotic protein BIM. Furthermore, osimertinib inhibited the cell proliferation in these models.

In addition, an *in vivo* study was performed, and whilst the numbers of mice per treatment group were low (n = 2 per group), a tumour regression in those mice treated once daily with 25 mg/kg osimertinib (similar to human exposure of the 80 mg) was shown.

Consistent with *in vitro* pharmacological and proliferation potency, osimertinib demonstrates high level of tumour inhibitory activity *in vivo* across multiple representative models of clinically relevant uncommon EGFR mutation types.

Pharmacokinetics

Protein binding data have shown that the unbound fraction of osimertinib is substantially higher in human plasma (5.3%) than in mouse plasma (0.8-2.5%). However the differences in plasma protein binding across species have been taken into account when assessing the likelihood of 40 mg vs 80 mg osimertinib providing optimal CNS tumour activity.
The distribution study showed that osimertinib was able to cross the blood-brain barrier in cynomolgus monkeys.

Toxicity

The main findings observed in previous repeat dose toxicity studies up to 3 months in rats and dogs comprised atrophic, inflammatory and/or degenerative changes affecting the epithelia of the cornea (accompanied by corneal translucencies and opacities in dogs at ophthalmology examination), GI tract (including tongue), skin, and male and female reproductive tracts with secondary changes in spleen. These findings were generally reversible but occurred at exposure levels below those seen in patients at the 80 mg therapeutic dose.

Additional findings reported in the 6-month rat, 9 month dog and 6 week mouse studies were considered consistent with findings observed in the previous studies of up to 3 months duration. They were secondary to osimertinib-induced inflammatory changes or were considered to be related to stress/effects on food consumption and body weight. With the exception of corneal opacity showing partial reversibility within 1-month recovery, other findings observed in repeat dose toxicity studies were reversible.

Overall, the results from the new repeat dose toxicity studies do not indicate a cause for concern for this extension of indication.

Oral administration of osimertinib once a day to CByB6F1/Tg rasH2 Hemizygous (transgenic) mice for a minimum of 26 weeks at doses up to 10 mg/kg/day (AUC 0-t 3.49 µmol x h/L) did not result in any osimertinib-related effects on survival, clinical observations, overall body weight, food consumption, gross pathology or neoplastic histopathology findings. However, there was one osimertinib-related, non-adverse, non-neoplastic histopathology finding observed (minimal epithelial atrophy of the cornea in both sexes at 10 mg/kg/day). This finding was only observed during histopathological evaluation and was not observed during in-life ophthalmology examinations conducted during Week 13 or Week 26 (prior to study termination). Given the low severity of the corneal epithelial atrophy, and lack of associated inflammation and ulceration, this finding was considered non-adverse.

Based on these results, there was no carcinogenic effect related to osimertinib administration at any dose in this study.

Based on the preliminary report from a 104 week oral gavage carcinogenicity study, osimertinib was carcinogenic in the rat with a higher incidence of hemangioma and angiomatous hyperplasia in the mesenteric lymph nodes at the high dose level. Due to no existing safety margins in humans at the 80 mg dose, a more thorough discussion of the human relevance of the findings observed is deemed necessary when the final report is presented.

In the eye, a higher incidence and severity of lens fibre degeneration were observed in mid and high dose animals. This finding was consistent with the ophthalmoscopic observation of lens opacities. The human relevance of this finding in rats cannot be ruled out.

Reproductive toxicity

A decrease in the number of live implants together with an associated increased incidence of early embryonic deaths was observed. According to the company the NOEL for maternal toxicity, reproductive performance, embryonic survival and development was 1 mg/kg/day. Data from the

recovery group indicate the effects of osimertinib on female fertility seen in the main study animals would be expected to be reversible.

ERA

Based on the updated data submitted in this application, the extended indication does not lead to a significant increase in environmental exposure related to the use of osimertinib. Osimertinib is not expected to pose a risk to the environment.

2.3.6. Conclusion on the non-clinical aspects

From a non-clinical point of view, the extension of indication is considered approvable. However, a more thorough discussion of the human relevance of the carcinogenic findings observed in the preliminary report of the 104-week oral gavage carcinogenicity study is requested post authorisation (including a potential SmPC update). The MAH is recommended to submit the final report of this study.

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.

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

The MAH 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

Type of study	Study identifier	Location of study report in Module 5	Objective(s) of the study	Study design and type of control	Test products, Dosage regimen, Route of administration	No. of subjects treated	Healthy subjects or diagnosis of patients	Duration of treatment	Study status; type of report
Controlled Clinical Studies									
Efficacy, safety, and PK	D5164C00001 ADAURA	5.3.5.1	To assess the efficacy of AZD9291 compared to placebo as measured by disease free survival (DFS)	Phase III, double-blind, randomised, placebo-controlled study	AZD9291 40 mg and 80 mg tablets, or matching placebo, administered orally once daily	682	Adult patients with stage IB-IIIA NSCLC with a centrally confirmed EGFR mutation (Ex19del and L858R), who had complete tumour resection, with or without postoperative adjuvant chemotherapy	Patients received either AZD9291 or placebo for a planned treatment duration of 3 years, or until disease recurrence or a treatment discontinuation criterion was met	Ongoing; DCO1 (17 January 2020): Full CSR

Efficacy, safety, and PK	D5160C00007 FLAURA	NA	To assess the efficacy and safety of AZD9291 versus a standard-of-care EGFR TKI as first-line treatment in patients with EGFRm, locally advanced or metastatic NSCLC	Phase III, double-blind, randomised study	AZD9291 40 mg and 80 mg tablets, or matching placebo, 80 mg, administered orally once daily in the fasted state; gefitinib 250 mg tablets, or matching placebo; administered orally once daily; erlotinib 100 mg and 150 mg tablets, or matching placebo; administered orally once daily	556	Patients aged ≥18 years (≥20 years in Japan) with EGFRm, locally advanced or metastatic NSCLC. Patients were treatment naïve for advanced NSCLC and eligible for first-line treatment with an EGFR TKI	There was no maximum duration of treatment as patients could receive AZD9291 beyond RECIST defined disease progression if they continue to show clinical benefit, as judged by the investigator	Ongoing; DCO1 (12 Jun 2017): Full CSR DCO2 (25 Jun 2019): CSR Addendum
Efficacy, safety, and PK	D5160C00003 AURA3	NA	To assess the efficacy and safety of AZD9291 vs platinum-based doublet chemotherapy in patients with locally advanced or metastatic NSCLC whose disease has progressed with previous EGFR TKI therapy and whose tumours harbour a T790M mutation within the EGFR gene	Phase III, open-label, randomised study	AZD9291 40 mg and 80 mg tablets, 80 mg once daily, administered orally in the fasted state or platinum-based doublet chemotherapy (pemetrexed 500 mg/m2 + carboplatin AUC 5 or pemetrexed 500 mg/m2 + cisplatin 75 mg/m2) on Day 1 of every 21-day cycle	419	EGFR T790M mutation positive advanced NSCLC patients who have progressed following prior therapy with an EGFR TKI agent (second-line chemotherapy naïve)	There was no maximum duration of treatment as patients could receive AZD9291 beyond RECIST defined disease progression if they continue to show clinical benefit, as judged by the investigator	Ongoing; DCO1 (15 Apr 2016): Full CSR DCO2 (02 Sep 2016): CSR Addendum DCO3 (15 Nov 2017): CSR Addendum DCO4 (25 Jun 2019): CSR Addendum

Type of study	Study identifier	Location of study report in Module 5	Objective(s) of the study	Study design and type of control	Test products, Dosage regimen, Route of administration	No. of subjects treated	Healthy subjects or diagnosis of patients	Duration of treatment	Study status; type of report
Open–label studies									
Efficacy, safety, and PK	D5160C00001 AURA (Phase I component)	NA	The primary objectives of the study were to investigate the safety and tolerability of AZD9291 and to investigate the efficacy of AZD9291 by assessment of objective response rate	Phase I, open-label, multi-centre, dose-escalation (rolling 6 design) and dose expansion study	AZD9291 20 mg and 40 mg capsule; AZD9291 40 mg and 80 mg tablet; 5 cohorts with daily dosing starting at 20 mg once daily for Cohort 1, escalating to 40 mg, 80 mg, 160 mg, and 240 mg once daily for Cohorts 2 through 5, respectively; administered orally in the fasted state	Dose escalation part: 31 Dose expansion: 252	EGFR T790M mutation positive advanced NSCLC patients age ≥18 years (≥20 years in Japan) who progressed following prior therapy with an EGFR TKI agent ±chemotherapy (primarily ≥second-line patients and 2 first-line cohorts)	There was no maximum duration of treatment as patients could receive AZD9291 beyond RECIST defined disease progression if they continue to show clinical benefit, as judged by the investigator	Ongoing; DCO1 (02 Dec 2014): Full CSR DCO2 (01 May 2015): Full CSR DCO3 (01 Nov 2016): CSR Addendum DCO4 (01 Sep 2018): CSR Addendum

Efficacy, safety, and PK	D5160C00001 AURA extension (Phase II component)	NA	The primary objectives of the study were to investigate the safety and tolerability of AZD9291 and to investigate the efficacy of AZD9291 by assessment of objective response rate.	Phase II single-arm, open-label, Nonrandomized extension to D5160C00001 AURA	AZD9291 40 mg and 80 mg tablet; once daily; oral in the fasted state	201	EGFR T790M mutation positive advanced NSCLC patients aged ≥18 years (≥20 years in Japan) 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	There was no maximum duration of treatment as patients could receive AZD9291 beyond RECIST defined disease progression if they continue to show clinical benefit, as judged by the investigator	Ongoing; DCO1 (09 Jan 2015): Full CSR DCO2 (01 May 2015): Full CSR DCO3 (01 Nov 2015): Full CSR DCO4 (01 Nov 2016): CSR Addendum DCO5 (01 May 2018): CSR Addendum

Type of study	Study identifier	Location of study report in Module 5	Objective(s) of the study	Study design and type of control	Test products, Dosage regimen, Route of administration	No. of subjects treated	Healthy subjects or diagnosis of patients	Duration of treatment	Study status; type of report
Efficacy, safety, and PK	D5160C00002 AURA2	NA	The primary objective of the study was to investigate the efficacy of AZD9291 by assessment of objective response rate.	Phase II, single-arm, open-label, non-randomised study to replicate the efficacy and safety data observed in the D5160C00001 (AURA) Extension study	AZD9291 40 mg and 80 mg tablets, 80 mg once daily; administered orally in the fasted state	210	EGFR T790M mutation positive advanced NSCLC patients aged ≥18 years (≥20 years in Japan) 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	There was no maximum duration of treatment as patients could receive AZD9291 beyond RECIST defined disease progression if they continue to show clinical benefit, as judged by the investigator	Ongoing; DCO1 (09 Jan 2015): Full CSR DCO2 (01 May 2015): Full CSR DCO3 (01 Nov 2015): Full CSR DCO4 (01 Nov 2016): CSR Addendum DCO5 (01 May 2018): CSR Addendum

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

2.4.2. Pharmacokinetics

Analytical Methods

The bioanalytical methods used for the determination of osimertinib (AZD9291) and its metabolites AZ7550 and AZ5104 in human K_2EDTA plasma in this study were previously assessed. Since the data were obtained within a study from two different laboratories [Covance UK Ltd, Harrogate, UK and Covance's Shanghai, China (for samples derived in China)], applying the same method, comparison of those data was performed and a cross validation was carried out. The outcome of the cross validation shows that the obtained data were reliable, and they can be compared and used. A partial validation was undertaken, and additional stability data were included.

Based on evaluation of data from previous studies, the AZ7550 metabolite was considered unlikely to contribute to efficacy and safety after osimertinib administration and was, therefore, not analysed in the ADAURA study.

All samples were analysed within the known stability period for AZ9291 and AZ5104, although for AZ5550 some samples were analysed above 400 days stability established. This is considered a minor issue since metabolite AZ7550 was determined to unlikely to contribute to efficacy and safety after osimertinib administration and was removed from the bioanalytical assays for further evaluation.

The interim bioanalytical reports contain data from all active patients received and analysed at Covance Harrogate and Covance's Shangha up to April 24th, 2020.

The samples were analysed in two laboratories and two bioanalytical reports were submitted. Both in-study validations show acceptable calibration standards and QCs. The reasons for the samples re-assayed are considered acceptable. Incurred Sample Reproducibility was performed, and the reanalysis confirms the validity and performance of the Analytical Method Procedure for all analytes.

Absorption

The ADAURA study used the approved commercial formulation of osimertinib which is available as an 80 mg oval, biconvex, beige film-coated tablet and a 40 mg round, biconvex, beige film-coated tablet (hereafter referred to as the film-coated tablet), for oral administration.

No new biopharmaceutical information or changes to the validated bioanalytical methods are included in this supplementary application.

Distribution

In vitro studies conducted to determine human plasma protein binding of osimertinib yielded a percentage unbound value of 5.3% for osimertinib and this measured value replaced the previous estimate (1%) used to support the initial marketing application (see non-clinical section, 2.3.3 Pharmacokinetics).

Pharmacokinetics in the target population

The MAH has characterized the PK and PK/PD properties of osimertinib as adjuvant treatment after complete tumour resection in EGFR mutant non-small cell lung cancer (NSCLC) patients, based on the results from the pivotal Phase 3 randomised, placebo-controlled study ADAURA (D5164C00001).

Population pharmacokinetic analyses have previously been performed [Comisar 2015, Johnson 2016, Johnson 2017], characterizing the PK properties of osimertinib in the dose range from 20 to 240 mg. The impact of the covariates on pharmacokinetic parameters was evaluated in EGFRm NSCLC patients from Phase I (AURA), Phase II (AURA extension, AURA2), and Phase III (AURA3, FLAURA) studies. These popPK models were used to assess the potential relationships between osimertinib exposure (AUCss) and safety/efficacy response variables and included in the interaction with regulatory agencies.

The popPK model described in this report is an external validation of the previous popPK analysis (Johnson 2017), based on data from the confirmatory Phase III, multicentre, double-blind, randomized study, ADAURA. ADAURA compared osimertinib (80 mg once daily) versus placebo as adjuvant therapy in patients with EGFRm NSCLC following complete tumour resection.

The objectives of this analysis were to validate the previously developed pharmacokinetic model [Johnson 2017] with pharmacokinetic data from adjuvant therapy patients from the ADAURA (Phase III)

study and to characterize the PK of osimertinib and its main metabolite of interest (AZ5104) in these patients, following oral once daily administration.

Dataset management

- The percentage of missing covariates was negligible (< 1%)
- Patients with no post-dose observation records were removed from the popPK dataset.
- The observation records with missing DV information were excluded from the analysis. The "IGNORE" column in the NONMEM datasets was set to "Missing DV". These records were flagged in the NONMEM datasets by assigning MDV variable to 1. Additionally, the DV column for these records were set to 0.
- All information related to time of dose and time of sample collection for PK analysis were available and none were missing in the analysis data.
- For two subjects in the ADAURA study, dosing information was incomplete and PK data was completely or partially excluded from popPK analysis.
- Non-zero pre-first-dose records were identified in the master dataset by setting a TAD of 0 and a corresponding entry in the TIME column to 0.01. These records were excluded from the analysis by setting MDV to 1 and setting the content of the IGNORE column to "Non-zero pre-first-dose sample".
- Since only few observation records for plasma concentrations of osimertinib and AZ5104 were below the lower limit of quantification, these data records were excluded from the analysis (NONMEM M1 method). Exclusion was handled by setting the MDV column to 1 and annotate the reason for exclusion in the IGNORE column with "BLLOQ (M1)". For osimertinib 23 out of 3071 post first dose samples (0.75%) and for AZ5104, 42 out of 3071 (1.37%) were below the limit of quantification.
- No data from placebo-treated subjects from the ADAURA study was used in the analysis including exploration of covariates.
- The dataset used in the prior model development from AURA, AURA2, AURA3 and FLAURA studies, consisted of a total of 41461 plasma concentration samples, obtained from 1364 patients, treated with osimertinib. For external validation of the population PK model a total of 325 patients and 3071 post first dose samples from the ADAURA study was available

Modelling strategy

It was expected that the PK profiles for patients in the adjuvant setting would be similar to the already studied EGFRm NSCLC patient populations in Phase I/II and III studies. The previously developed popPK model characterises the pharmacokinetic profile of osimertinib in Phase I/II and III studies in pre-treated (second line and above) and treatment-naïve (first line) EGFRm NSCLC patient populations (Figure 3). Hence, an external model validation approach was applied to evaluate the adequacy of the current model to explain PK variability of patients in ADAURA study. Subjects from ADAURA study with at least one new post-dose PK sample were used for model validation. The existing model was applied to the pooled dataset without reestimation of popPK parameters (MAXEVAL = 0).

In addition, popPK parameters were re-estimated based on the pooled dataset, to identify potential clinically meaningful changes in parameter estimates upon the addition of the new data from the ADAURA study.

Population dataset

The population in ADAURA is similar to the population that was studied in AURA, AURA2, AURA3 and FLAURA. The main difference in these populations is that ADAURA patients received osimertinib as adjuvant therapy, in FLAURA as first line locally advanced and metastatic, in AURA3 as second line metastatic, and in AURA and AURA2 most of the patients received it in ≥ third line.

Table 8: Summary of patients demographic characteristic and baseline characteristics, median (range) (PK population, continuous covariates)

	AURA + AURA2 + AURA3 + FLAURA (n = 1364)	ADAURA (n = 325)	Overall (n = 1689)
Baseline Age (year)			
Mean (SD)	61.6 (10.9)	62.5 (10.3)	61.8 (10.8)
Median [Min, Max]	62.0 [25.0, 91.0]	63.0 [30.0, 86.0]	62.0 [25.0, 91.0]
Baseline Weight (kg)			
Mean (SD)	62.4 (13.9)	65.4 (14.2)	63.0 (14.0)
Median [Min, Max]	61.0 [29.0, 122]	64.0 [35.0, 112]	62.0 [29.0, 122]
Missing	9 (0.7%)	0 (0%)	9 (0.5%)
Baseline Height (m)			
Mean (SD)	1.62 (0.0941)	1.62 (0.0888)	1.62 (0.0931)
Median [Min, Max]	1.62 [1.35, 1.93]	1.60 [1.40, 1.90]	1.61 [1.35, 1.93]
Missing	18 (1.3%)	0 (0%)	18 (1.1%)
Baseline Body Mass Index (kg/m²)			
Mean (SD)	23.6 (4.16)	24.9 (4.31)	23.8 (4.22)
Median [Min, Max]	23.1 [12.9, 42.6]	24.4 [15.1, 41.8]	23.3 [12.9, 42.6]
Missing	20 (1.5%)	0 (0%)	20 (1.2%)
Baseline Body Surface Area (m²)			
Mean (SD)	1.67 (0.219)	1.69 (0.205)	1.67 (0.216)
Median [Min, Max]	1.65 [1.09, 2.45]	1.67 [1.23, 2.29]	1.65 [1.09, 2.45]
Missing	20 (1.5%)	0 (0%)	20 (1.2%)
Baseline Serum Creatinine (umol/L)			
Mean (SD)	68.1 (18.8)	71.6 (17.7)	68.8 (18.6)
Median [Min, Max]	65.4 [26.5, 175]	69.0 [33.6, 129]	66.0 [26.5, 175]
Missing	6 (0.4%)	1 (0.3%)	7 (0.4%)
Baseline Creatinine Clearance (mL/min)			
Mean (SD)	83.7 (27.0)	81.3 (25.6)	83.2 (26.8)
Median [Min, Max]	81.3 [20.5, 196]	76.8 [34.1, 185]	80.2 [20.5, 196]
Missing	13 (1.0%)	1 (0.3%)	14 (0.8%)
Baseline Albumin (g/L)			
Mean (SD)	38.7 (5.02)	42.8 (3.37)	39.5 (5.02)
Median [Min, Max]	39.0 [17.0, 53.3]	43.0 [33.0, 51.8]	40.0 [17.0, 53.3]
Missing	22 (1.6%)	2 (0.6%)	24 (1.4%)
Baseline Alanine Aminotransferase (U/L)			
Mean (SD)	22.3 (19.1)	22.3 (14.8)	22.3 (18.3)
Median [Min, Max]	17.9 [4.00, 277]	18.0 [4.00, 128]	18.0 [4.00, 277]
Missing	7 (0.5%)	1 (0.3%)	8 (0.5%)
Baseline Aspartate Aminotransferase (U/L)			
Mean (SD)	26.0 (15.6)	23.3 (9.25)	25.5 (14.6)
Median [Min, Max]	22.0 [6.00, 258]	21.0 [7.00, 71.0]	22.0 [6.00, 258]
Missing	8 (0.6%)	1 (0.3%)	9 (0.5%)
Baseline Alkaline Phosphatase (U/L)			
Mean (SD)	152 (173)	109 (69.5)	143 (159)
Median [Min, Max]	98.0 [18.0, 3930]	86.0 [18.0, 423]	95.0 [18.0, 3930]
Missing	10 (0.7%)	0 (0%)	10 (0.6%)
Baseline Bilirubin (umol/L)			
Mean (SD)	9.81 (4.87)	9.22 (4.56)	9.70 (4.82)
Median [Min, Max]	8.55 [0.342, 49.0]	8.38 [2.74, 33.2]	8.55 [0.342, 49.0]
Missing	8 (0.6%)	0 (0%)	8 (0.5%)

Note: Numeric columns were formatted as mean (SD) and median [minimum and maximum].
Source: osimertinib-pk-eda.rmd

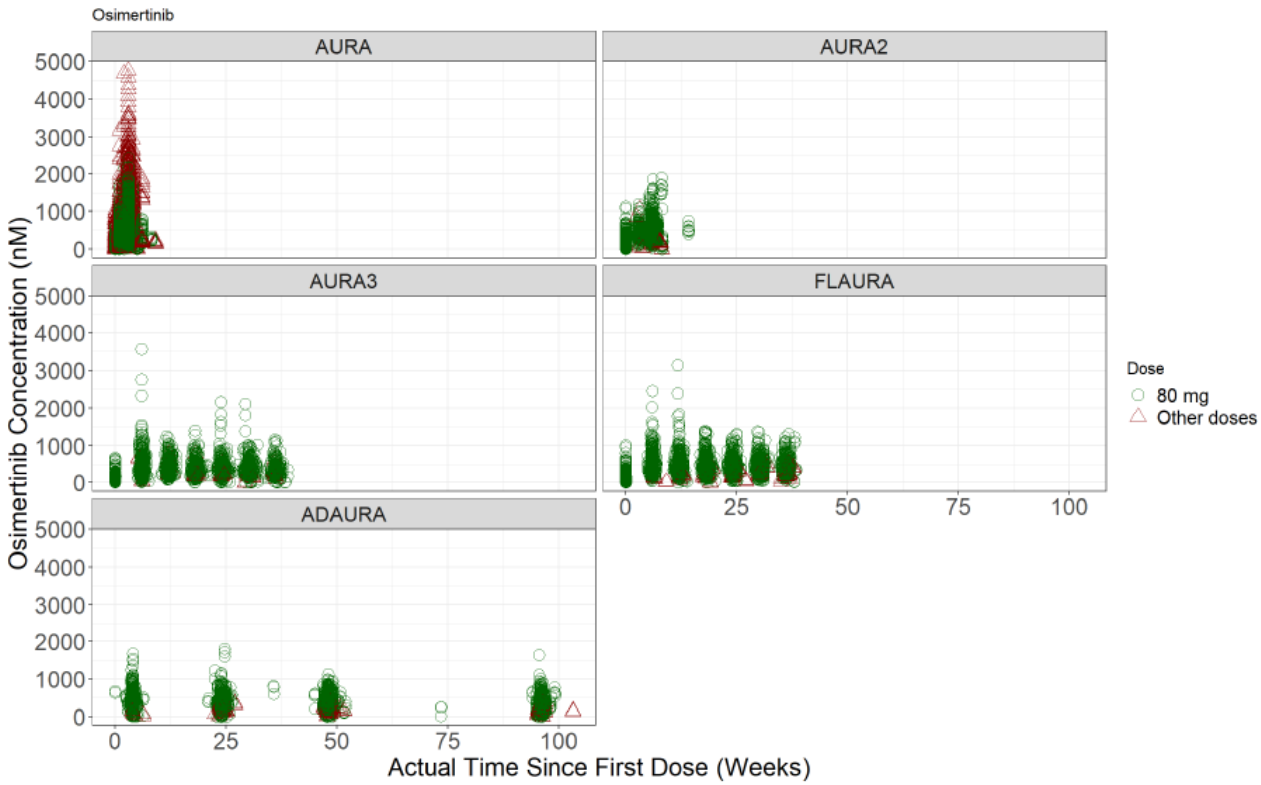
Table 9: Summary of patient demographic characteristics and baseline characteristics, number (%) (PK population, categorical covariates)

	AURA + AURA2 + AURA3 + FLAURA (n = 1364)	ADAURA (n = 325)	Overall (n = 1689)
Sex			
Male	481 (35.3%)	105 (32.3%)	586 (34.7%)
Female	883 (64.7%)	220 (67.7%)	1103 (65.3%)
Race			
White	460 (33.7%)	116 (35.7%)	576 (34.1%)
Black/African American	14 (1.0%)	0 (0%)	14 (0.8%)
Asian	857 (62.8%)	208 (64.0%)	1065 (63.1%)
Native Hawaiian/Pacific Islander	1 (0.1%)	0 (0%)	1 (0.1%)
American Indian/Alaska Native	3 (0.2%)	0 (0%)	3 (0.2%)
Other	29 (2.1%)	1 (0.3%)	30 (1.8%)
Grouped Ethnicity			
White	375 (27.5%)	102 (31.4%)	477 (28.2%)
Asian (excluding Chinese and Japanese)	323 (23.7%)	77 (23.7%)	400 (23.7%)
Chinese	277 (20.3%)	90 (27.7%)	367 (21.7%)
Japanese	254 (18.6%)	46 (14.2%)	300 (17.8%)
Other	135 (9.9%)	10 (3.1%)	145 (8.6%)
Nicotine Use			
Never	911 (66.8%)	221 (68.0%)	1132 (67.0%)
Current Smoker	34 (2.5%)	4 (1.2%)	38 (2.2%)
Former Smoker	419 (30.7%)	100 (30.8%)	519 (30.7%)
Line of Therapy			
First line	338 (24.8%)	0 (0%)	338 (20.0%)
Second line	468 (34.3%)	0 (0%)	468 (27.7%)
Third line onwards	558 (40.9%)	0 (0%)	558 (33.0%)
Adjuvant	0 (0%)	325 (100%)	325 (19.2%)
Grouped Hepatic Impairment Status			
Normal	500 (36.7%)	105 (32.3%)	605 (35.8%)
Mild	592 (43.4%)	150 (46.2%)	742 (43.9%)
Moderate +	259 (19.0%)	69 (21.2%)	328 (19.4%)
Missing	13 (1.0%)	1 (0.3%)	14 (0.8%)
Grouped Renal Impairment Status			
Normal	1214 (89.0%)	299 (92.0%)	1513 (89.6%)
≥ Mild	141 (10.3%)	25 (7.7%)	166 (9.8%)
Missing	9 (0.7%)	1 (0.3%)	10 (0.6%)
WHO Performance Status*			
0	497 (36.4%)	209 (64.3%)	706 (41.8%)
1	867 (63.6%)	116 (35.7%)	983 (58.2%)

Note: Numeric columns were formatted as count (% of total).

* Patients from the Phase 3 ADAURA study typically had a better WHO performance status as compared to the pooled population from previous studies. This was expected, since the previous population includes patients from Phase 1 and 2 as well as Phase 3 studies.

Source: osimertinib-pk-eda.rmd



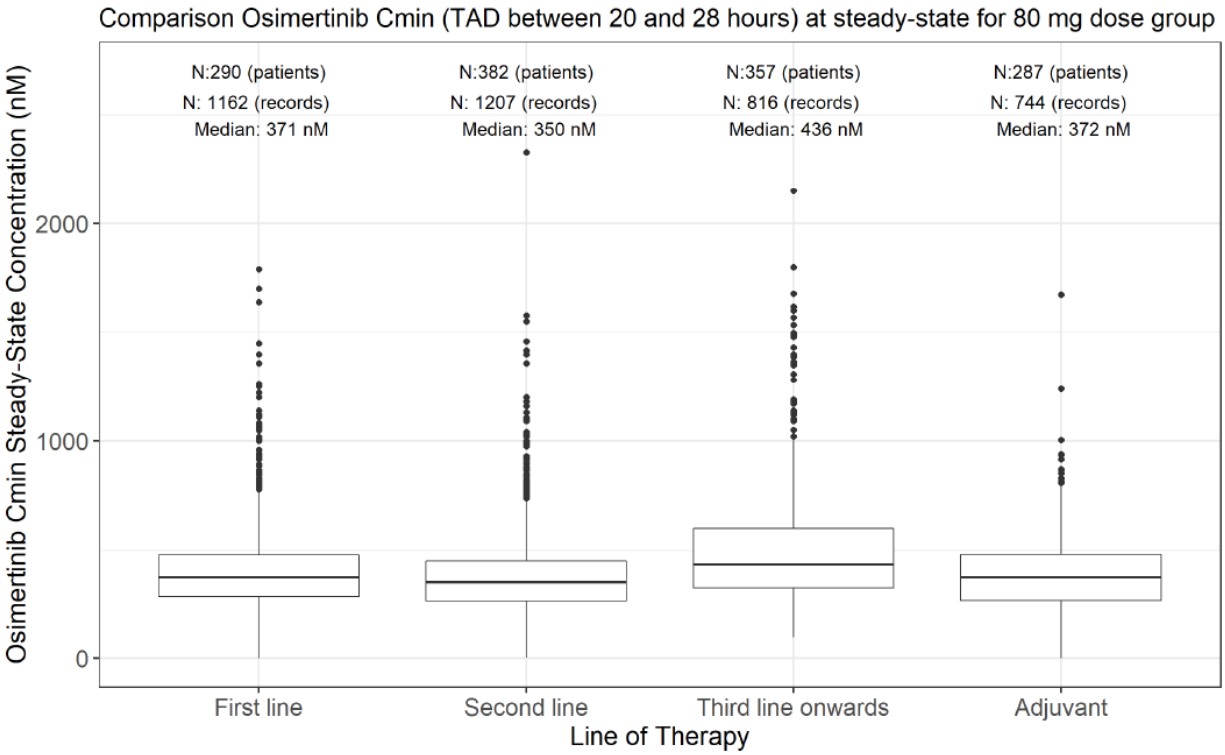
Note: Red symbols in AURA2, AURA3, FLAURA and ADAURA panels indicate dose changes (reductions or increases). 80 mg was the planned dose in these studies, 40 mg and 160 mg were the two other doses given. Red symbols in AURA indicate the other tested dose groups in AURA, ranging from 20 mg to 240 mg.
Source: osimertinib-pk-eda.rmd

Figure 3: Osimertinib observed concentrations vs. time since first dose by study

Table 10: Number (%) of patients with dose reductions and increases

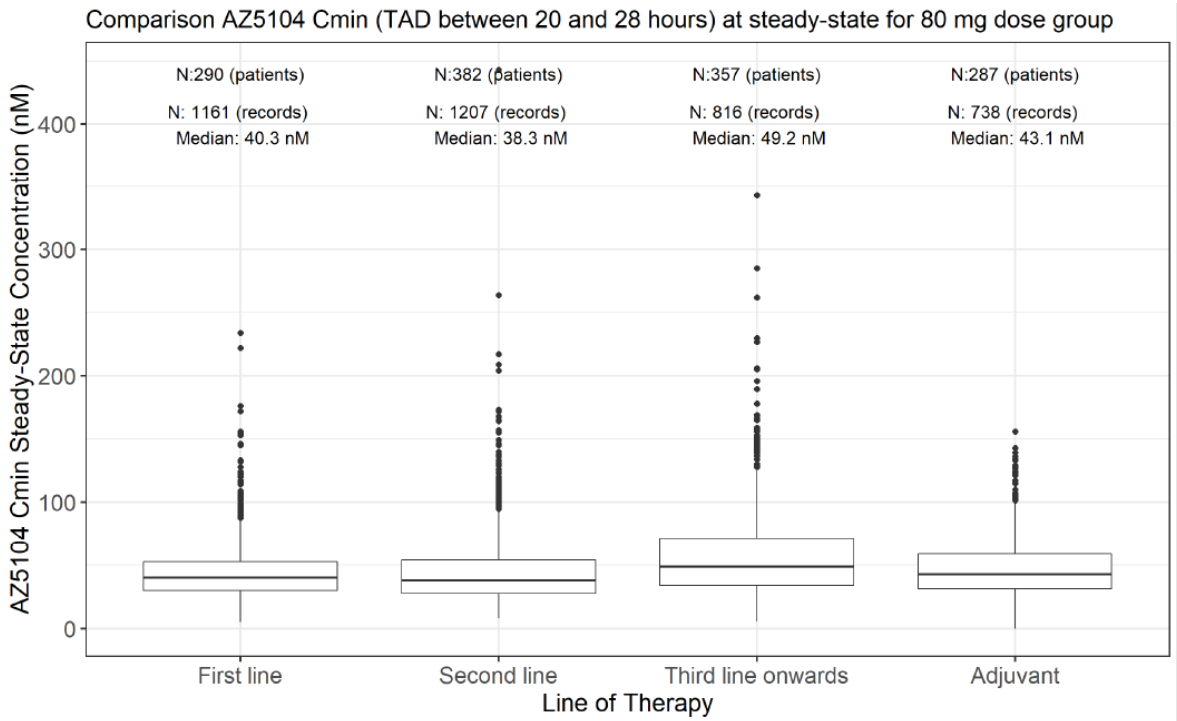
Study	Total N of patients	Patients (%) with dose increases (from any previous dose)[a]	Patients (%) with dose decreases (from any previous dose)[a]
AURA	599	49 (8.18)	99 (16.5)
AURA2	210	8 (3.81)	16 (7.62)
AURA3	277	7 (2.53)	14 (5.05)
FLAURA	278	4 (1.44)	28 (10.1)
ADAURA	325	2 (0.615)	48 (14.8)
Total	1689	70 (4.14)	205 (12.1)

[a] Note that dose reductions and increases are not relative to 80 mg dose. A decrease from 80 to 40 mg in a patient, followed by an increase from 40 to 80 mg was counted as a decrease and an increase.
Source: osimertinib-pk-eda.rmd



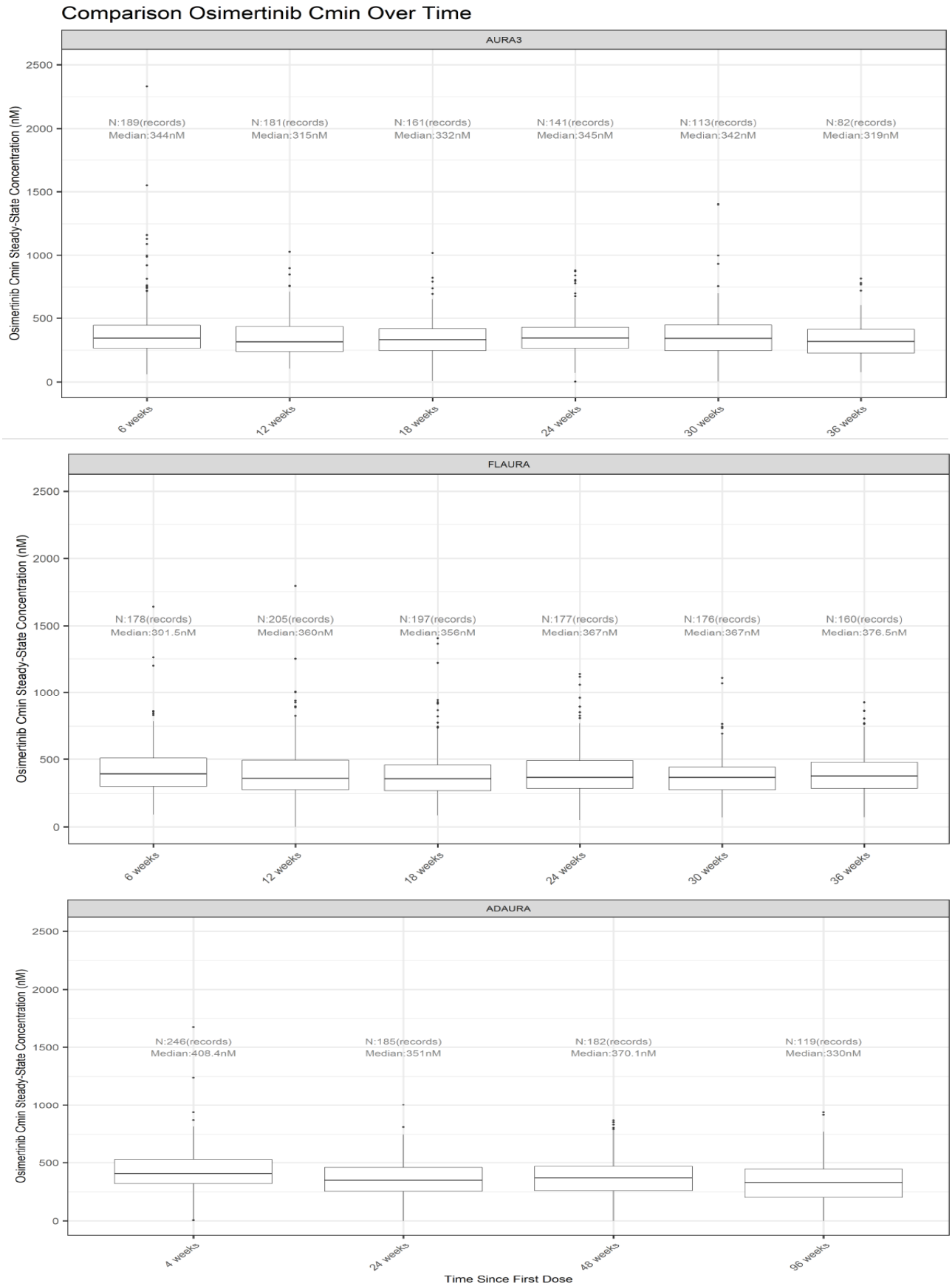
Note: The ends of the box represent the 25th and 75th percentiles of the concentration distribution and the black middle line is showing the median of the distribution. Data above the 95th percentile are shown as black dots.
Source: osimertinib-pk-eda.rmd

Figure 4: Osimertinib observed steady-state Cmin at 80mg stratified by line of therapy



Note: The ends of the box represent the 25th and 75th percentiles of the concentration distribution and the black middle line is showing the median of the distribution. Data above the 95th percentile are shown as black dots.

Figure 5: AZ5104 observed steady-state Cmin at 80mg stratified by line of therapy



Note: The ends of the box represent the 25th and 75th percentiles of the concentration distribution and the black middle line is showing the median of the distribution. Data above the 95th percentile are shown as black dots.

Figure 6: Osimertinib observed steady-state Cmin at 80mg over time

Validation of the previously developed popPK model (external validation wit ADAURA data addition)

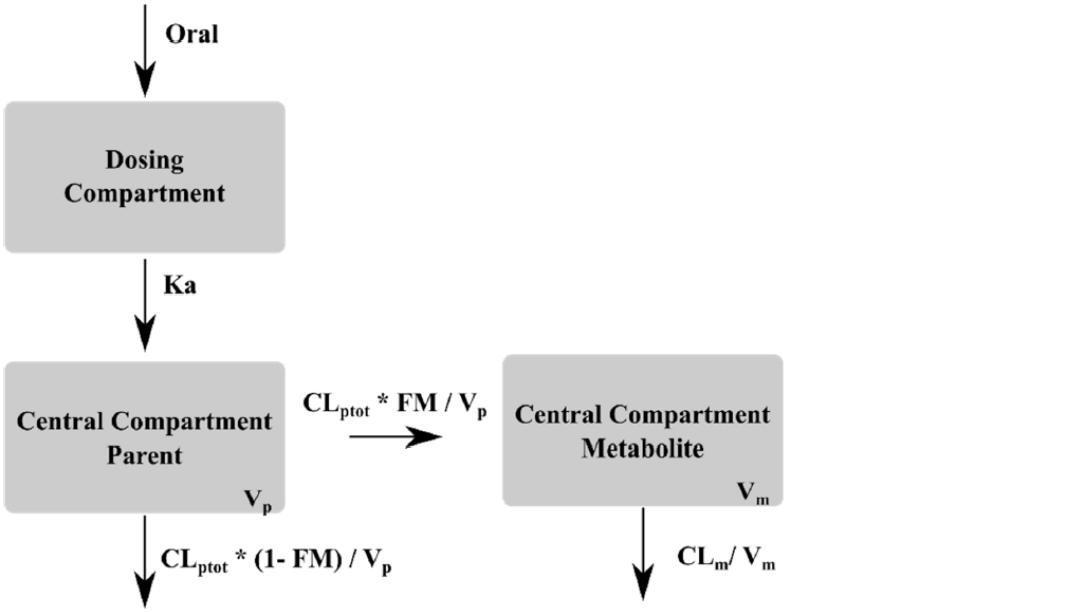
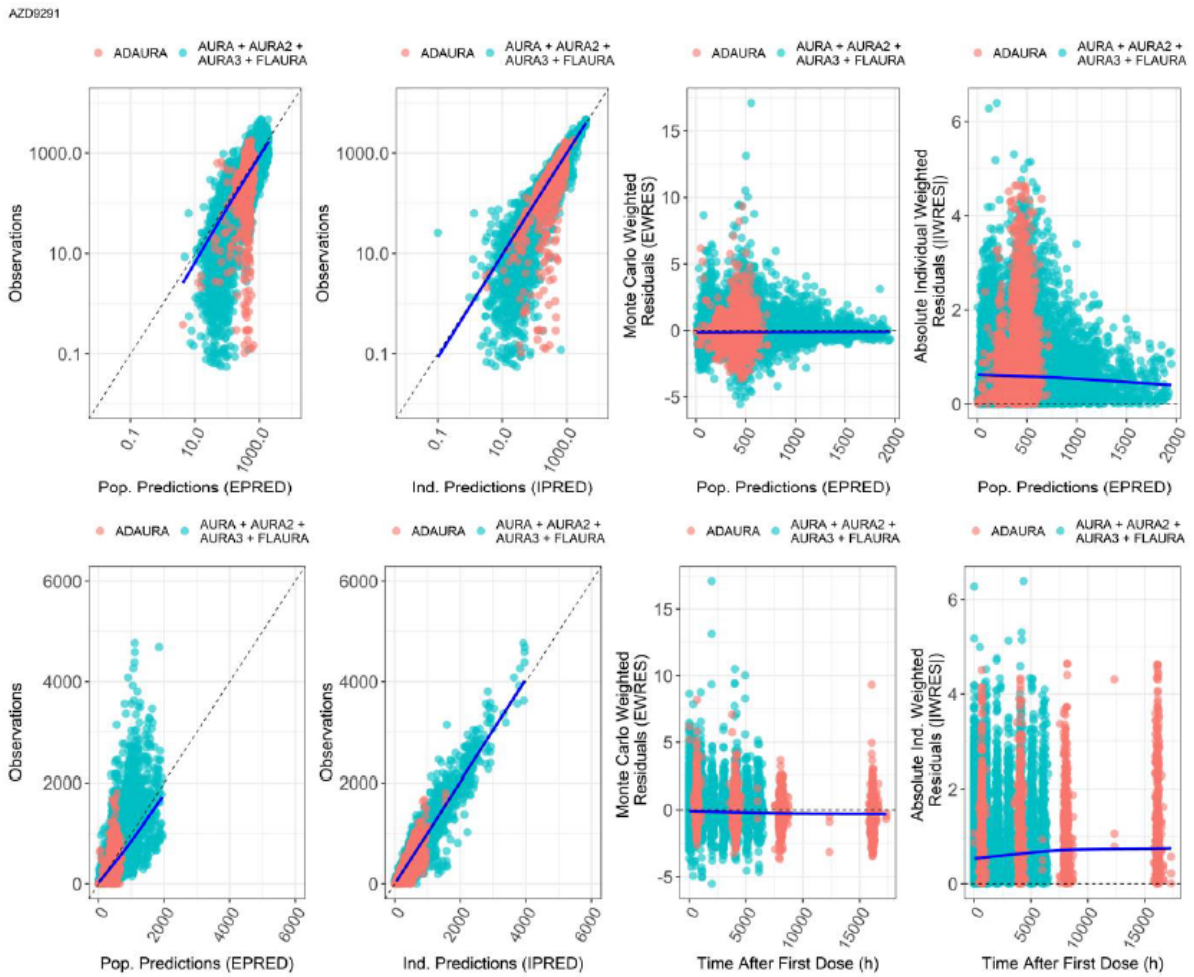


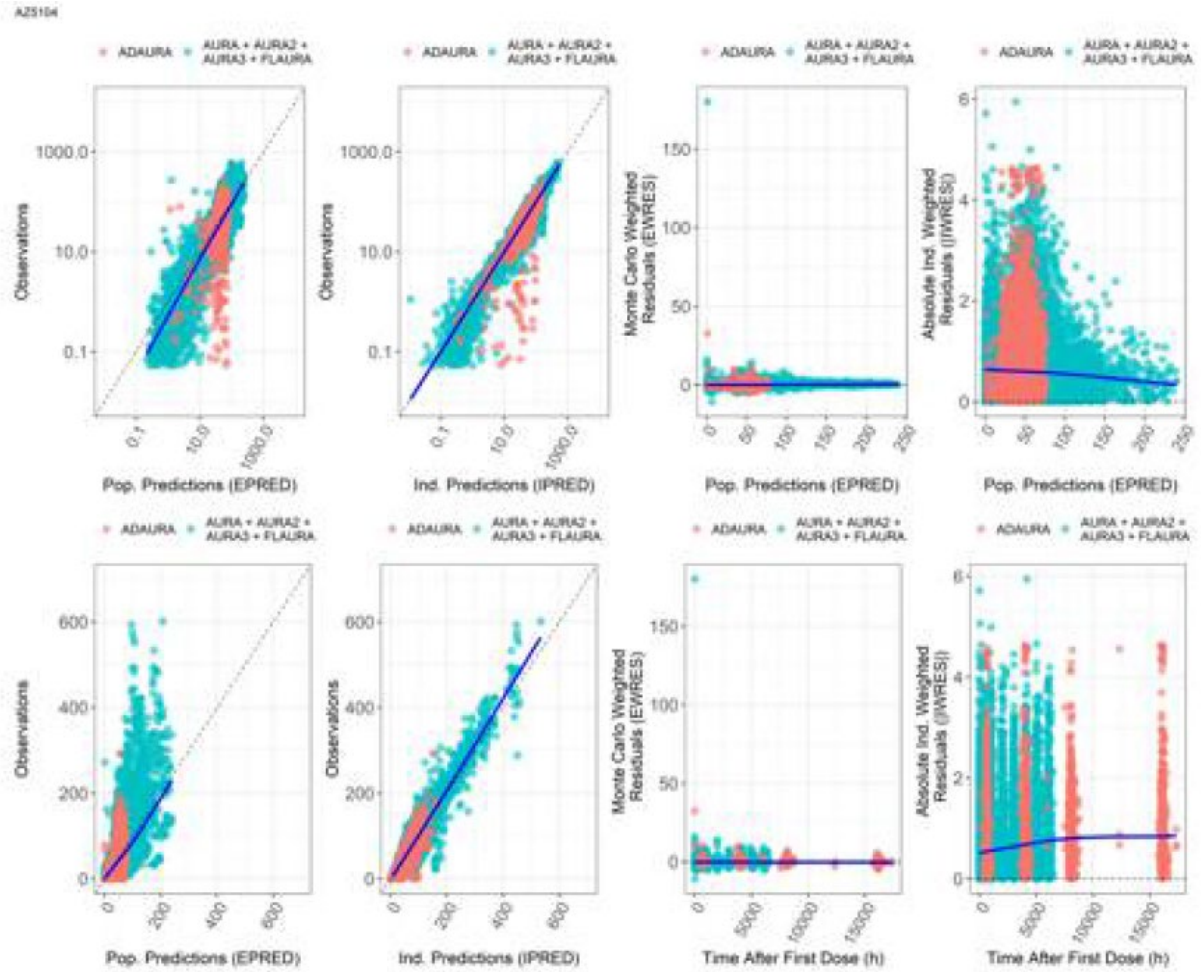
Figure 7: Structure of the Population PK model for osimertinib and AZ5104

The population PK model was applied to the pooled dataset without re-estimation of popPK parameters (MAXEVAL = 0). In order to assess if the model, developed in the previous analysis [Johnson 2017], is adequate for the ADAURA data, the predicted (population and individual) osimertinib concentrations were plotted against the observed concentrations (see Figure 8 for osimertinib and Figure 9 for AZ5104), stratified by AURA/AURA2/AURA3/FLAURA and ADAURA. The figures show that the ADAURA data is enveloped within the AURA/AURA2/AURA3/FLAURA data and the individual predictions are reasonably evenly centred around the line of identity, indicating that the previously developed model describes the ADAURA data as well as it describes AURA, AURA2, AURA3 and FLAURA data.



Notes: The coloured circles represent individual observations; the solid blue lines represent loess line of the presented data, and the solid grey lines represent the identity line for Observations/Population predictions-Individual Prediction plots and the zero line for EWRES and IWRES plots.
Source: osimertinib-pk-run2.rmd

Figure 8: Osimertinib population and individual predictions vs. observed concentrations

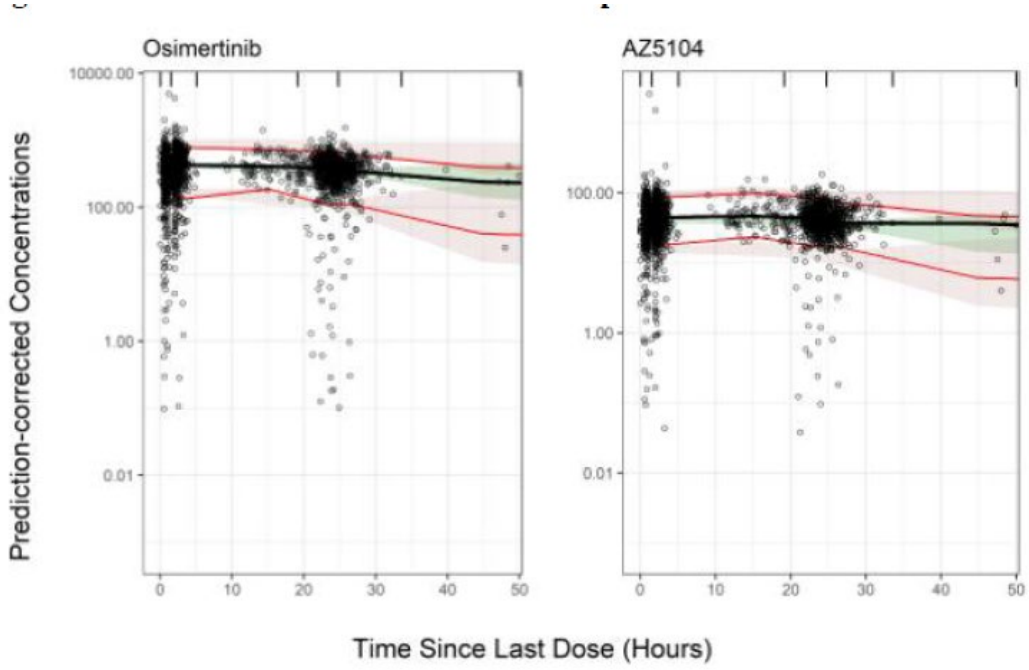


Notes: The coloured circles represent individual observations; the solid blue lines represent loess line of the presented data, and the solid grey lines represent the identity line for Observations/ Population predictions-Individual Prediction plots and the zero line for EWRES and IWRES plots.
Source: osimertinib-pk-run2.rmd

Figure 9: Goodness-of-fit plots AZ5104 – maxeval=0

In addition, plots of weighted residuals versus time after first dose, and weighted residuals versus EPRED are presented in Figure 8 for osimertinib and Figure 9 for AZ5104, showing reasonable centring of both ADAURA and other study residuals around 0 without apparent trends over time after last dose. Figure 9 shows that the correlations of the random effects appear to be minor, the only exception being the correlation between apparent clearances (CL/F and CLM/F), which already was considered in the model.

The prediction-corrected VPC plots in Figure 10 indicate that the steady-state PK of osimertinib and AZ5104 in the adjuvant population is adequately predicted by the final model developed based on data from ≥ first-line NSCLC patients. Only data from patients receiving 80 mg doses were included in the plots.



Note: 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

Figure 10: Prediction corrected visual predictive checks

Based on the totality of model evaluation criteria, it was decided that the previously developed population PK model adequately describes the totality of the data (AURA, AURA2, AURA3, FLAURA and ADAURA).

As an extra assessment, to evaluate the impact of ADAURA subjects on the PK of Osimertinib and its metabolite, the PK parameters were re-estimated with the pooled dataset. Re-estimation of PK parameters were initially performed without considering the adjuvant population as a covariate, and then with inclusion of the adjuvant population as a covariate on CL/F and CLm/F simultaneously. The difference in the primary PK parameter estimates (ie, clearance and volume of distribution of osimertinib and its metabolite) between the previous analysis with data from AURA/AURA2/AURA3/FLAURA and the current pooled analysis including ADAURA data was small and considered not clinically meaningful.

Table 11 : Population parameter estimates: Maxeval=0 and Re-estimation

Parameter	Maxeval = 0	Re-estimation	% R SE	95% CI	Shrinkage (%)
CL/F (L/hour)	14.3	14.4	1.18	[14.1 ; 14.7]	-
CLM/F (L/hour)	31.3	31.5	1.73	[30.4 ; 32.5]	-
Ka (1/hour)	0.196	0.201	4.66	[0.182 ; 0.219]	-
V/F (L)	919	940	3.11	[883 ; 997]	-
FM (fraction)	0.25 (fixed)	0.25 (fixed)	-	-	-
VM/F (L)	143	140	4.26	[129 ; 152]	-
omega (CL/F)	0.201	0.194	2.91	[0.183 ; 0.205]	3
omega (CLM/F)	0.247	0.236	2.88	[0.222 ; 0.249]	2.6
omega (ka)	1.18	1.1	3.81	[1.02 ; 1.18]	35.6
omega (V/F)	0.826	0.813	3.16	[0.763 ; 0.864]	19.7
omega (FM)	-	-	-	-	-
omega (VM/F)	0.612	0.706	4.49	[0.644 ; 0.768]	44.9
Correlation (CL/F and CLM/F)	0.197	0.188	3.02	[0.177 ; 0.199]	-
Baseline bodyweight on CL/F	0.421	0.41	12.2	[0.312 ; 0.507]	-
Baseline albumin on CL/F	0.826	0.805	10.8	[0.634 ; 0.975]	-
Baseline bodyweight on V/F	0.814	0.822	14.8	[0.583 ; 1.06]	-
Baseline albumin on V/F	2.27	2.15	9.99	[1.73 ; 2.57]	-
Baseline bodyweight on CLM/F	0.822	0.79	7.19	[0.678 ; 0.901]	-
Baseline albumin on CLM/F	0.928	0.842	11.2	[0.657 ; 1.03]	-
Baseline albumin on VM/F	-0.831	-0.859	29.9	[-1.36 ; -0.356]	-
Asian (non-Chinese, non-Japanese) on CLM/F	0.182	0.176	10.6	[0.139 ; 0.213]	-
Chinese on CLM/F	0.0763	0.0125	145	[-0.0232 ; 0.0483]	-
Japanese on CLM/F	0.184	0.178	12.6	[0.134 ; 0.221]	-
Non-Asian, non-White on CLM/F	0.0903	0.0799	28.6	[0.0351 ; 0.125]	-
Additive error Osimertinib (nM)	30.1	30.6	0.994	[30 ; 31.2]	6.2
Additive error AZ5104 (nM)	0.516	0.51	2.36	[0.486 ; 0.534]	5.2
Proportional error Osimertinib (fraction)	0.205	0.216	0.383	[0.214 ; 0.218]	-
Proportional error AZ5104 (fraction)	0.215	0.225	0.323	[0.224 ; 0.226]	-

* 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).

Abbreviations: RSE, Relative standard error.

Pharmacokinetic interaction studies

The potential of osimertinib to act as a perpetrator of drug-drug interactions (DDI) has been previously assessed by in vitro studies, basic modelling approaches and in vivo studies. Human plasma protein

binding of osimertinib, as well as unbound fraction of osimertinib in the relevant in vitro assays, have now been determined. Consequently, the potential for DDI in vivo due to inhibition of enzymes and transporters has been re-evaluated.

Inhibition of drug-metabolising enzymes

In vitro, osimertinib has been previously identified as an inhibitor of CYP1A2, CYP2C8 andCYP3A. Inhibition of CYP3A by osimertinib has been investigated in vivo using the CYP3A substrate simvastatin. The updated DDI evaluation using a basic modelling approach in line with EMA guidelines indicated a lower DDI potential than previously concluded, thereby supporting previous conclusions regarding the low risk of clinically relevant inhibition of CYP1A2 and CYP2C8 in vivo. This was further supported by simulations performed with physiologically based pharmacokinetic modelling (PBPK). Existing PBPK model of Osimertinib (AZD9291) was updated with new emerging data on in vitro plasma protein binding (unbound fraction in plasma, fu), fraction unbound in human liver microsomal incubations (fu,mic) and population based PK model estimate of first order absorption rate constant (ka). Updated PBPK (Simcyp PBPK model 3) model was verified by comparing the simulated PK versus observed PK of osimertinib and then applied to assess the perpetrator potential of osimertinib to cause DDI due to inhibition of CYP3A4, CYP1A2 and CYP2C8 respectively.

Model verification

In order to demonstrate the ability of the model to replicate the plasma concentration-time profile of osimertinib seen in patients an example simulation with the same dose regimen as was used in patients dosed at 80 mg in part A of the phase I study D5160C00001 (Ramalingam 2015) was run and compared to the observed data.

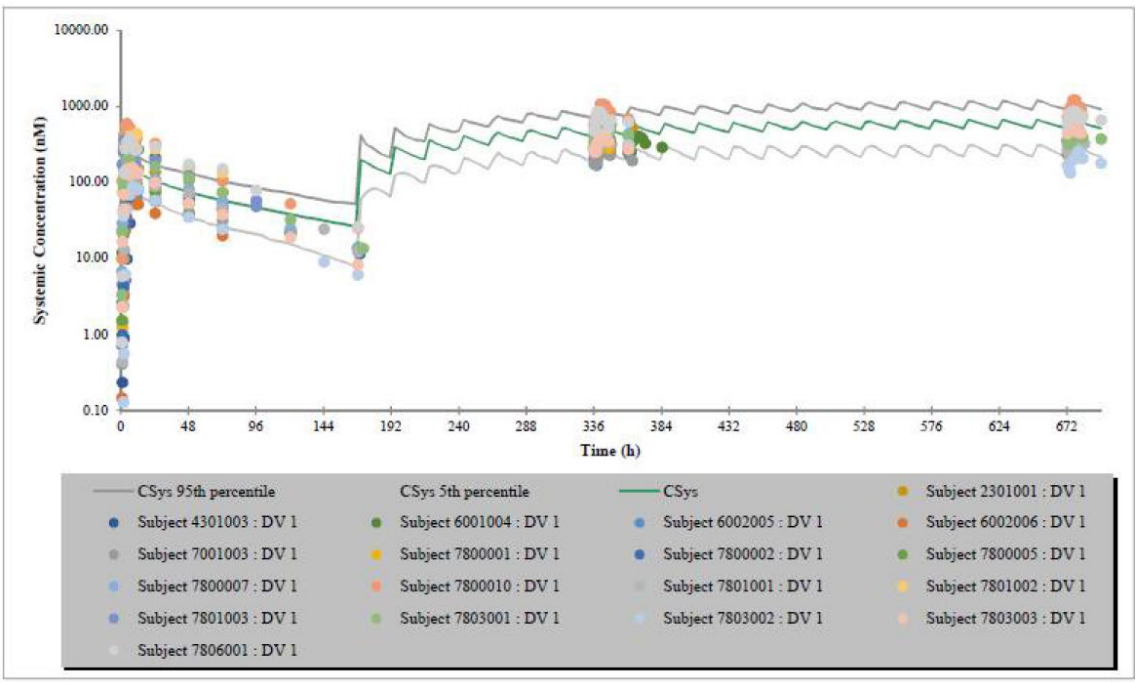


Figure 11: Simulation of osimertinib mean plasma concentrations and observed plasma concentrations following a single 80mg dose of osimertinib at 0h and daily dosing of 80mg of osimertinib from 168 to 672h (Log scale)

Table 12: Comparison of the observed clinical exposure of osimertinib following multiple dosing with the Simcyp model predicted exposure

Osimertinib Dose[a]		Observed *in vivo* clinical data	Simcyp Predicted (n=100)
Multiple doses 80 mg once daily tablet	AUC_{ss} (nMol.h/L) GMean (range), n	10360 (4730 to 22300) n = 11[a]	11008 (4010 to 23885)
	C_{maxss} (nMol/L) GMean (range), n	545 (258 to 1220) n = 11[a]	539 (179 to 1215)

[a] Osimertinib clinical data: Study D5160C00001 (n=11)(Ranson, M and Jänne, PA 2015); AUCss area under curve at steady-state; $C_{ss,max}$:maximum plasma concentration at steady-state.

Model validation (external validation with data from a DDI clinical study)

Table 13: Geometric mean ratio (and 90% confidence interval) of AUC and Cmax from Simcyp simulations investigating the effect of osimertinib on the exposure of simvastatin with Ki=0.55 µM.

	Geomean AUC ratio (90% CI)	Geomean Cmax ratio (90% CI)
Observed DDI	0.9146 (0.772 to 1.084)	0.771 (0.634 to 0.937)
Predicted DDI	0.813 (0.787-0.838)	0.839 (0.817-0.861)

Simvastatin clinical data: Study D5160C00014 (Ramalingam 2015)

Model application

Repaglinide exposure was simulated in the presence and absence of QD dosing of 80 mg of osimertinib.

Table 14: Geometric mean ratio (and 90% confidence interval) of AUC and Cmax from Simcyp simulations investigating the effect of osimertinib on the exposure repaglinide

	Geomean AUC ratio (90% CI)	Geomean Cmax ratio (90% CI)
Predicted DDI	1.050 (1.040-1.060)	1.023 (1.017-1.030)

No DDI was predicted 10-fold range of reported mean in vitro IC50 value (22.8 µM).

Caffeine exposure was simulated in the presence and absence of QD dosing of 80 mg of osimertinib.

Table 15: Geometric mean ratio (and 90% confidence interval) of AUC and Cmax from Simcyp simulations investigating the effect of osimertinib on the exposure of caffeine.

	Geomean AUC ratio (90% CI)	Geomean Cmax ratio (90% CI)
Predicted DDI	1.039 (1.037-1.041)	1.008 (1.008-1.009)

No DDI was predicted within 10-fold range of reported mean in vitro IC50 value (>25.6 µM).

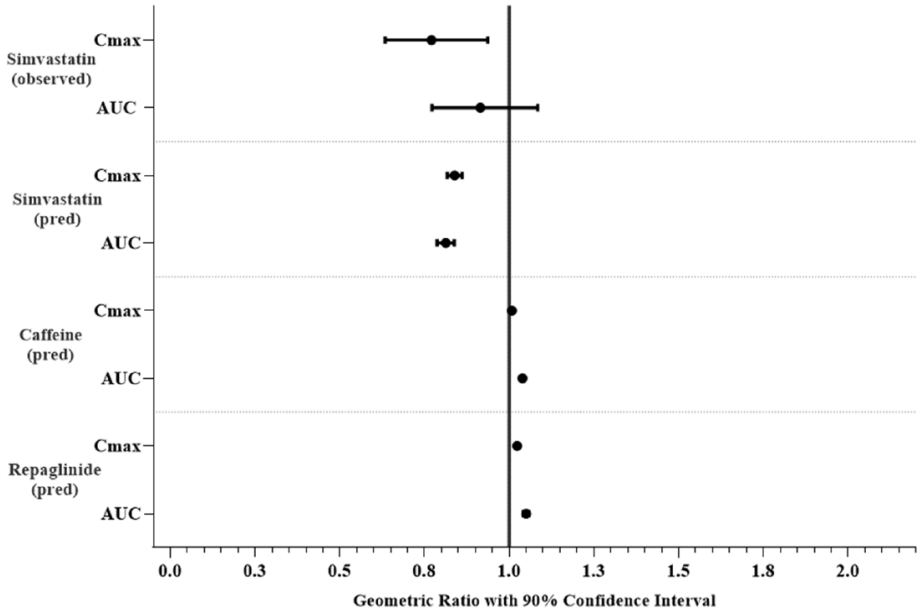


Figure 12: DDI Predictions using Osimertinib (AZD9291) model (Geometric mean AUC and Cmax ratios with 90% CI) vs. observed data

Inhibition of drug transporters

In vitro, osimertinib has been previously identified as an inhibitor of BCRP, OATP1B1, OATP1B3, OCT2, MATE1 and MATE2-K. Inhibition of BCRP by osimertinib has previously been investigated in vivo using the BCRP substrate rosuvastatin. Concomitant administration of osimertinib with simvastatin had no effect on the systemic exposure of simvastatin acid (OATP1B1 substrate). In this application, an updated DDI evaluation was performed using a basic modelling approach in line with EMA guidelines and indicated a lower DDI potential than previously concluded. In vivo inhibition of OATP1B3, OCT2, MATE1 and MATE2-K following a therapeutic dose of osimertinib can therefore be excluded.

2.4.3. Pharmacodynamics

Mechanism of action

No mechanism of action studies have been submitted as part of this application.

Primary and secondary pharmacology

No primary and secondary pharmacology studies have been submitted as part of this application.

2.4.4. PK/PD modelling

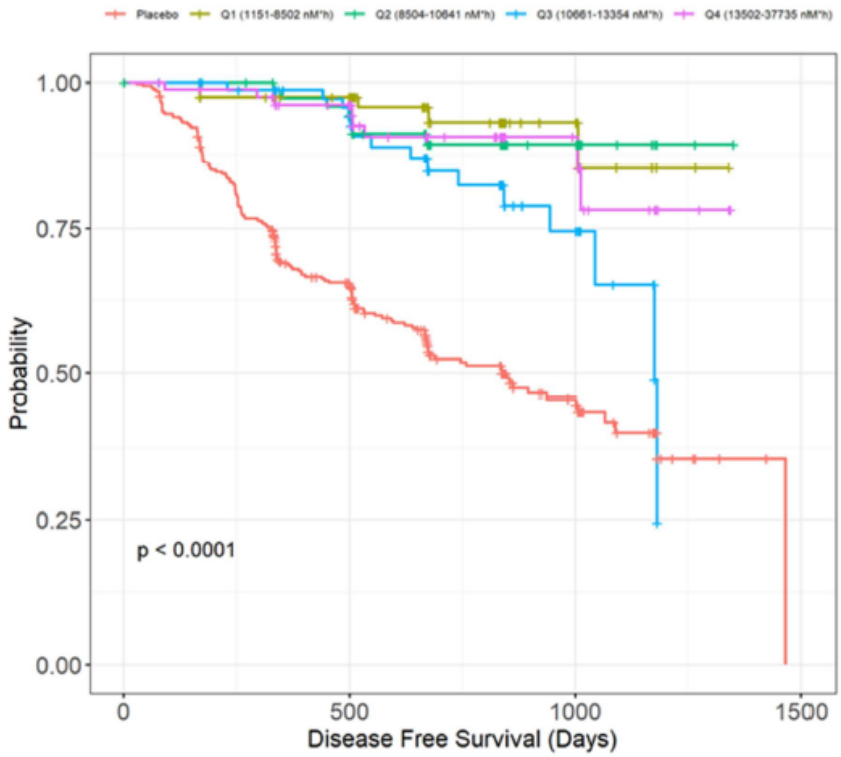
In this analysis, it was investigated whether conclusions from the previous exposure response analysis [Johnson and Schmidt 2017c] are consistent for a larger data set (ie, by inclusion of the ADAURA study).

Systemic exposure in the form of AUCss for osimertinib and AZ5104 was considered in this analysis and used in the model-based analyses. Values of AUCss were derived using individual (post hoc) estimates

of CL/F from the osimertinib and AZ5104 population PK model and the first dose for each patient. For the graphical analysis, the AUCss values were translated into categorical variables by binning into AUCss quartiles.

Efficacy Exposure-Response Analysis

The Kaplan Meier plot of DFS stratified by quartiles of osimertinib AUCss and placebo shows a clear difference between placebo and all the quartiles of osimertinib AUCss suggesting a benefit of osimertinib treatment over the placebo treatment (Figure 13).



Abbreviations: AUC_{ss} = area under the plasma concentration-time curve at steady state; DFS = disease-free survival; p = p-value calculated using log-rank test (with weights = 1); Q1 = AUC_{ss} quartile 1; Q2 = AUC_{ss} quartile 2; Q3 = AUC_{ss} quartile 3; Q4 = AUC_{ss} quartile 4.

Source: osimertinib-efficacy-ad-hoc.rmd

Figure 13: Kaplan-Meier Representation of DFS Stratified by Quartiles of Osimertinib AUCss and Placebo (efficacy population, first dose)

Although profound efficacy was observed upon treatment with osimertinib, the magnitude of this efficacy (as assessed through DFS) was generally not found to be related to drug exposure observed in ADAURA study. Graphical assessment indicated overlapping DFS across AUCss quartiles of osimertinib (Figure 5) and AZ5104 (not shown). The apparently lower DFS in exposure quartile 3 is associated with considerable uncertainty due to a low number of events in each quartile and should be interpreted with caution. This lack of a clear relationship was not unexpected given that all patients received an 80 mg starting dose. The lack of AUCss efficacy relationship in adjuvant patients (within the range of exposures investigated) is consistent with the similar lack of relationship in first and ≥ second line patients observed in the previous analysis [Johnson and Schmidt 2017b]. Overall survival data is not mature and hence, an assessment of AUCss and overall survival was not performed.

Safety Exposure-Response Analysis

Table 16: Summary of the number of patients in the safety population by study and by treatment group (first dose for osimertinib treated patients)

	Number (%) of Patients								
Study	20 mg N = 21 (0.86)	40 mg N = 58 (2.37)	80 mg N = 1461 (59.75)	160 mg N = 128 (5.24)	240 mg N = 21 (0.86)	CHEMO N = 136 (5.56)	SoC[a] N = 277 (11.33)	Placebo N = 343 (14.03)	Total N = 2445 (100)
AURA	21 (0.86)	58 (2.37)	371 (15.17)	128 (5.24)	21 (0.86)	0	0	0	599 (24.5)
AURA2	0	0	210 (8.59)	0	0	0	0	0	210 (8.59)
AURA3	0	0	277 (11.33)	0	0	136 (5.56)	0	0	413 (16.89)
FLAURA	0	0	278 (11.37)	0	0	0	277 (11.33)	0	555 (22.7)
ADAURA	0	0	325 (13.29)	0	0	0	0	343 (14.03)	668 (27.32)

[a] SoC: Standard-of-care EGFR-TKI.
Note: N, Number of patients, percentages of patients per group provided in parentheses. For patients treated with several dose levels only the first dose is considered in this table.

Table 17: Number of patients with dose reductions and increases in AURA2, AURA3, FLAURA and ADAURA (first dose 80mg)

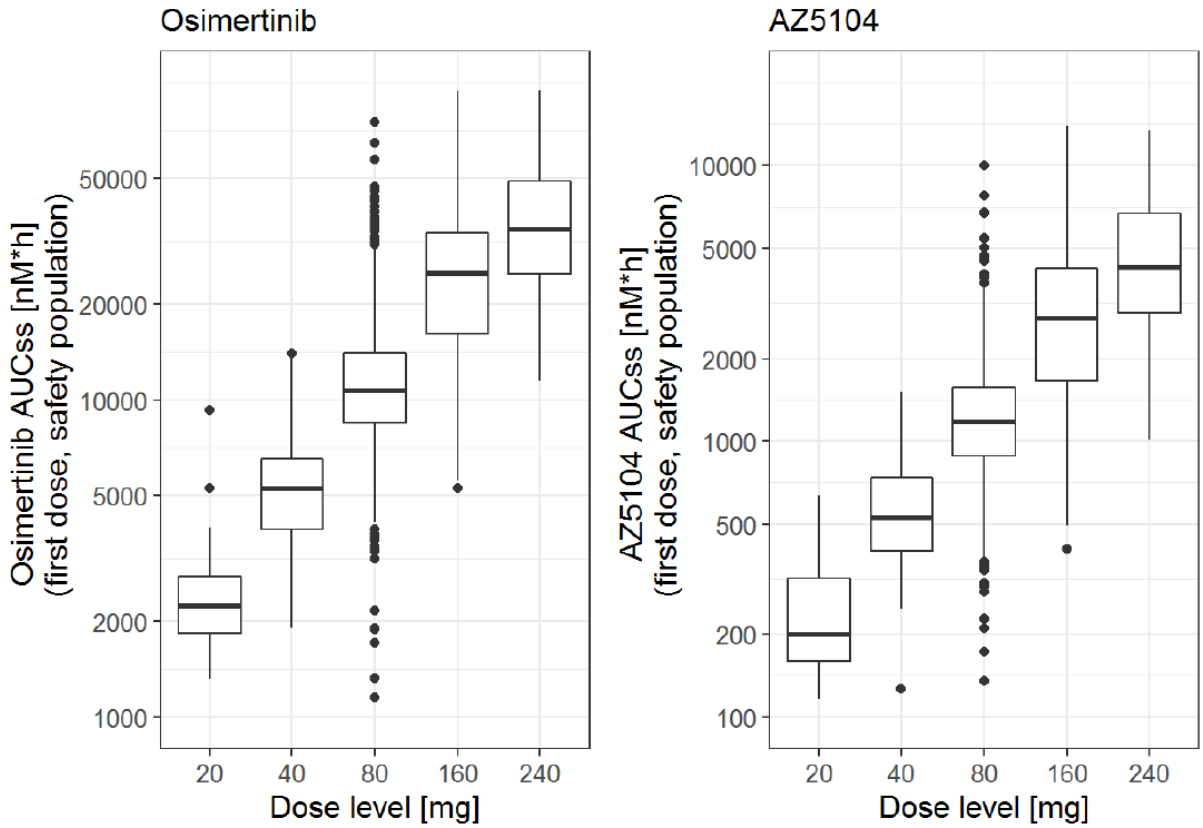
Study	Total number of patients	Patients (%) with dose reductions (from any previous dose)[a]	Patients (%) with dose increases (from any previous dose)[a]
ADAURA	325	48 (14.77%)	2 (0.62%)
AURA extension	199	16 (8.04%)	5 (2.51%)
AURA2	210	16 (7.62%)	8 (3.81%)
AURA3	277	14 (5.05%)	7 (2.53%)
FLAURA	278	28 (10.07%)	4 (1.44%)
Total	1289	122 (9.46%)	26 (2.02%)

[a] Note that dose reductions and increases are not relative to 80 mg dose. A decrease from 80 to 40 mg in a patient, followed by an increase from 40 to 80 mg was counted as a decrease and an increase.

Table 18: Summary of the distribution of osimertinib AUCss (total osimertinib safety population, first dose)

Dose level (mg)	N[a]	Mean	Standard deviation	Minimum	First quartile	Median	Third quartile	Maximum
20	21	2696.6	1805.8	979.91	1729.4	2228.7	2742.8	9321.5
40	58	5972.3	2917	1908.40	3889.5	5267.7	6480.6	14044
80	1461	12068	6123.7	1151.10	8450.8	10755	14039	74859
160	128	28705	17448	5261.40	16216	25408	34312	110980
240	21	39169	21803	11521	25015	34696	48979	94484

[a] Number of patients in this dose group.
Values presented are in the unit of AUC_{ss}: (nM*h).
Values (except for N) truncated to 5 significant digits.



Note: The ends of the box are the lower and upper quartiles of AUC_{ss} with the middle line showing the median. The horizontal lines outside the box indicate the 5th and 95th percentile of the AUC_{ss} range. Data below the 5th and above the 95th percentile are shown as black dots. Only the data with osimertinib $AUC_{ss} < 100000$ are shown in the left plot.

Figure 14: Summary of the distribution of osimertinib and AZ5104 exposure metrics (total osimertinib safety population)

Table 19: Summary of the distribution of osimertinib AUCss by quartile (total osimertinib safety population, first dose)

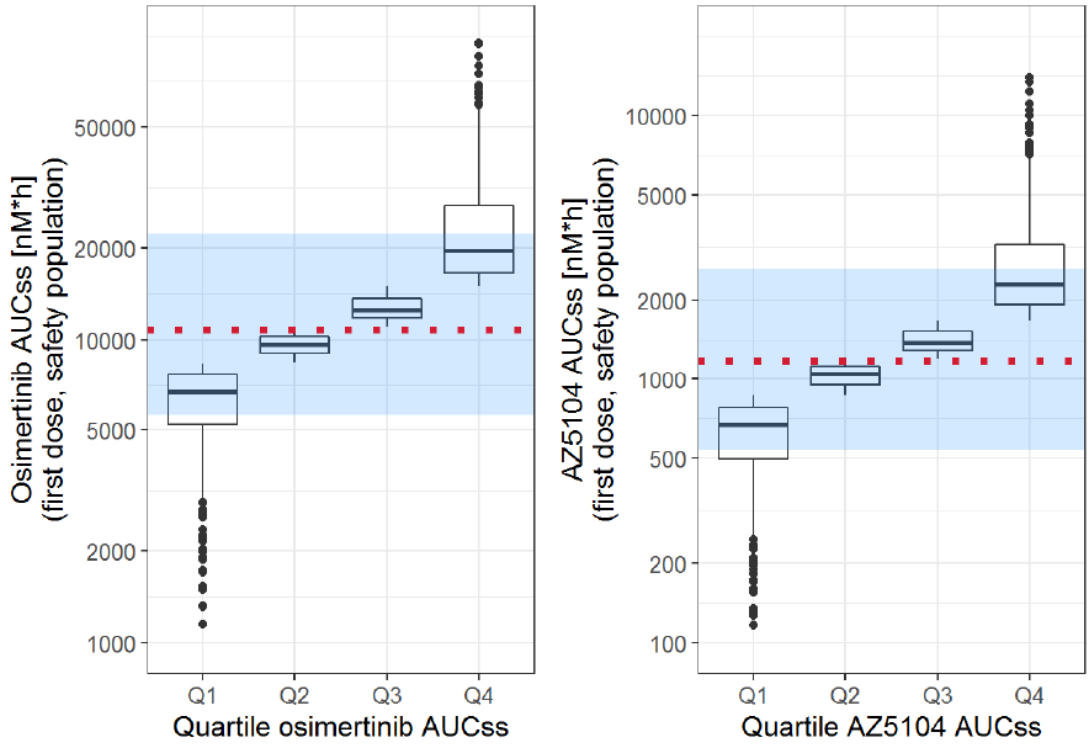
AUC_{ss} quartile	N[a]	Mean	Standard deviation	Minimum	Median	Maximum
1	423	6241.4	1734.70	979.91	5220.7	6640.8
2	422	9660.2	744.84	8366.70	9025.1	9647.3
3	422	12752	1101	11019	11840	12546
4	422	24724	13051	14992	16653	19581

[a] Number of patients in AUC_{ss} quartile.
Values presented are in the unit of AUC_{ss}: (nM*h).
Values (except for N) truncated to 5 significant digits.

Table 20: Summary of the distribution of AZ5104 AUCss by quartile (total osimertinib safety population, first dose)

AUC_{ss} quartile	N[a]	Mean	Standard deviation	Minimum	Median	Maximum
1	423	694.74	271.52	66.29	493.55	694.1
2	422	1049	243.47	491.90	862.71	1032.8
3	422	1415.30	319.66	662.42	1192.10	1354.5
4	422	2850.80	1826.80	789.82	1793.70	2257.9

[a] Number of patients in AUC_{ss} quartile.
Values presented are in the unit of AUC_{ss}: (nM*h).
Values (except for N) truncated to 5 significant digits.



The ends of each box are the lower and upper quartiles of AUC_{ss} with the middle line showing the median. The horizontal lines outside the box indicate the 5th and 95th percentile of the AUC_{ss} range. Data below the 5th and above the 95th percentile are shown as black dots. The thick dashed red line shows the median AUC_{ss} for the patients with first dose 80 mg, and shaded area the corresponding 5th and 95th quantiles. The AUC_{ss} quartiles have been computed for the safety population.

Figure 15: Distribution of osimertinib and AZ5104 exposure metrics in total safety population by quartile, and compared to the distribution for patients treated with 80mg (first dose) osimertinib

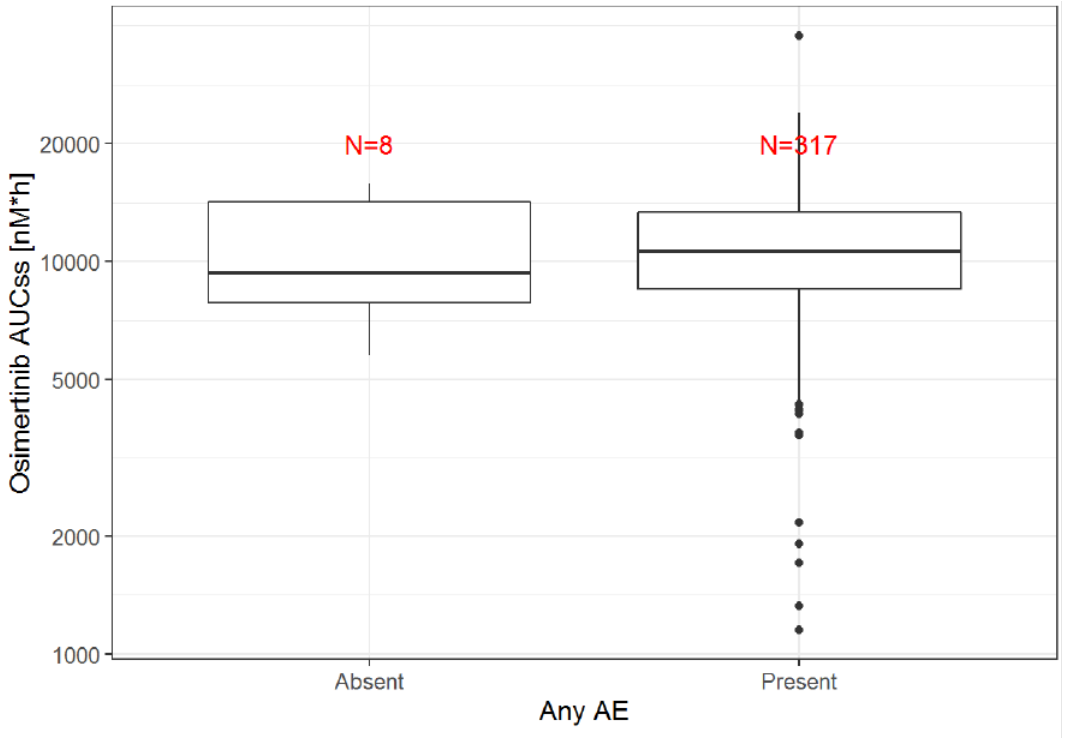


Figure 16: Distribution of osimertinib AUCss stratified by the occurrence of any AE (ADAURA only)

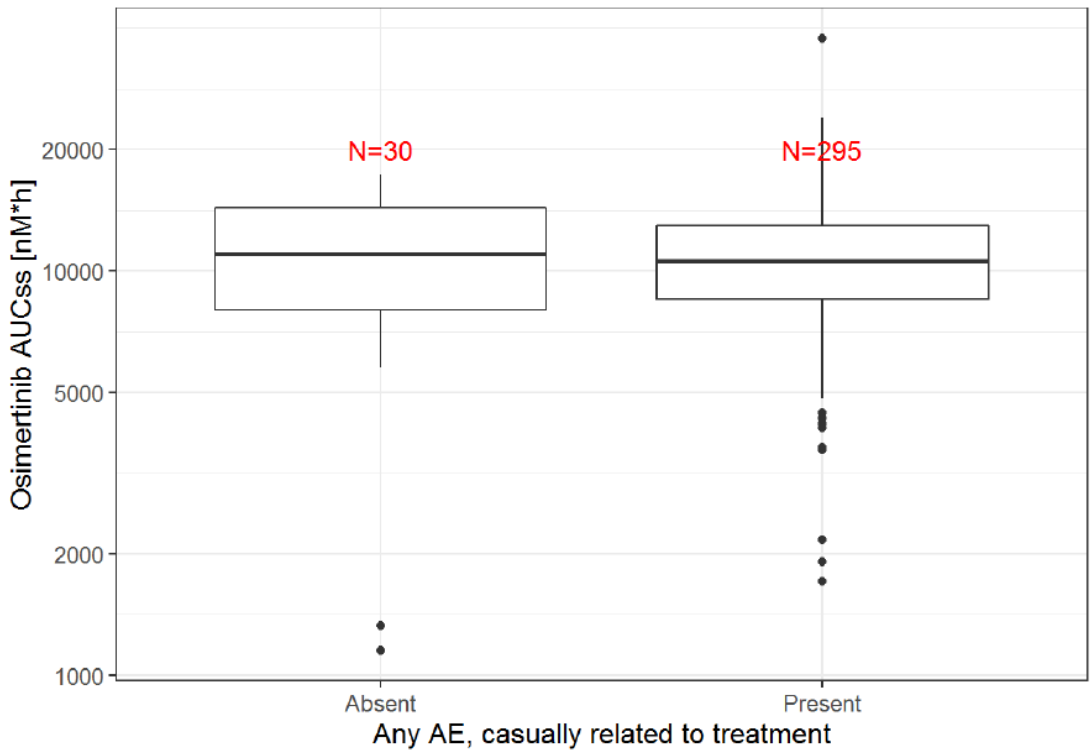


Figure 17: Distribution of osimertinib AUCss stratified by the occurrence of any AE, causally related to treatment (ADAURA only)

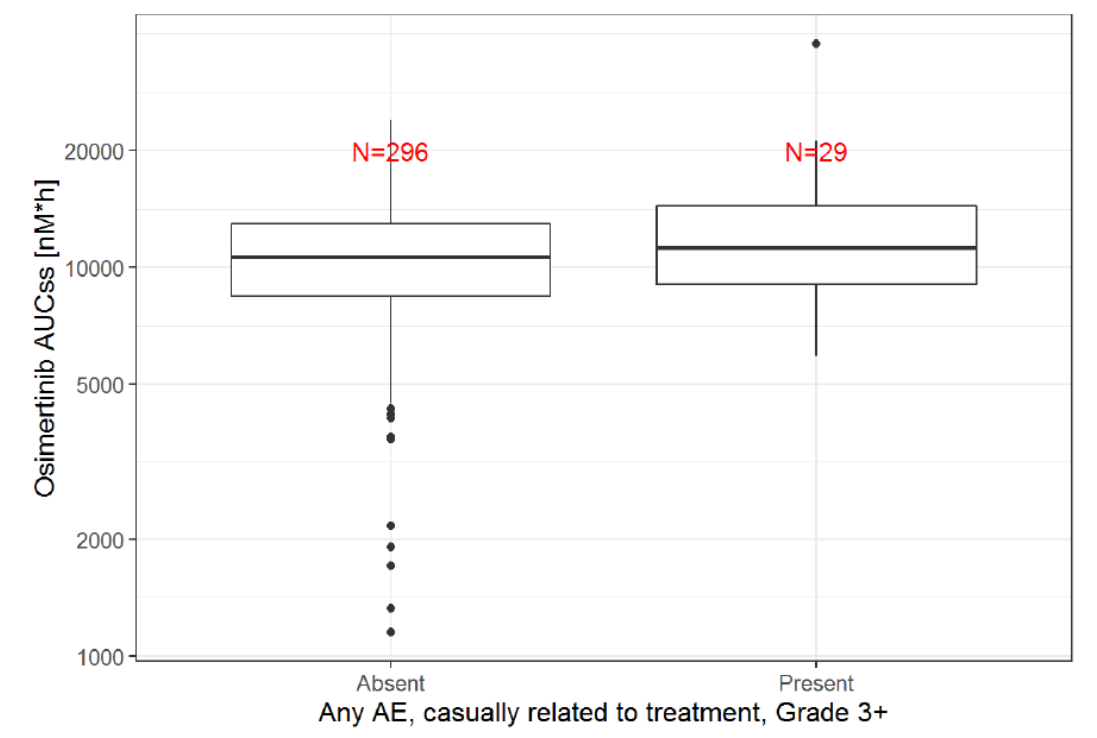


Figure 18: Distribution of osimertinib AUCss stratified by the occurrence of any AE, causally related to treatment, grade 3+ (ADAURA only)

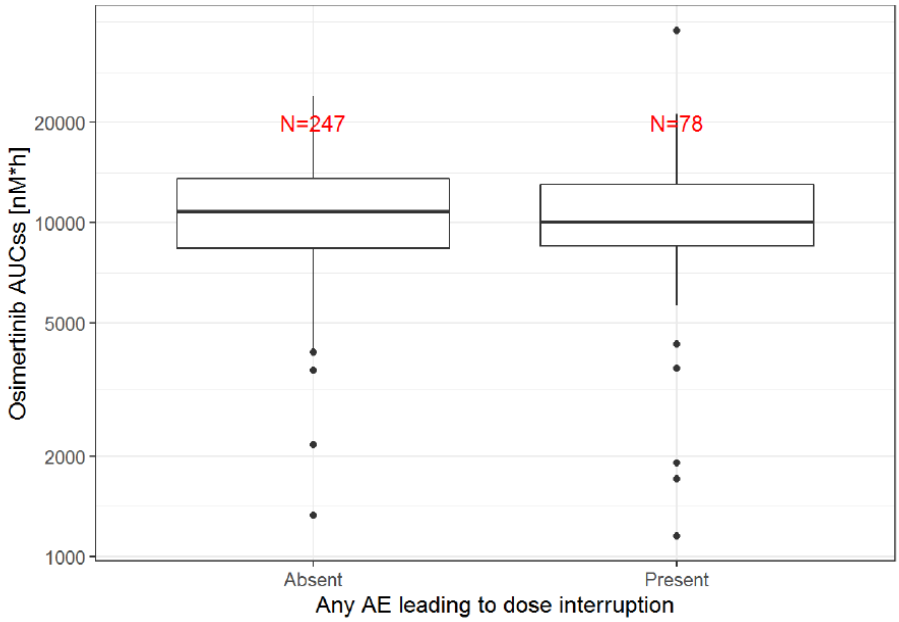
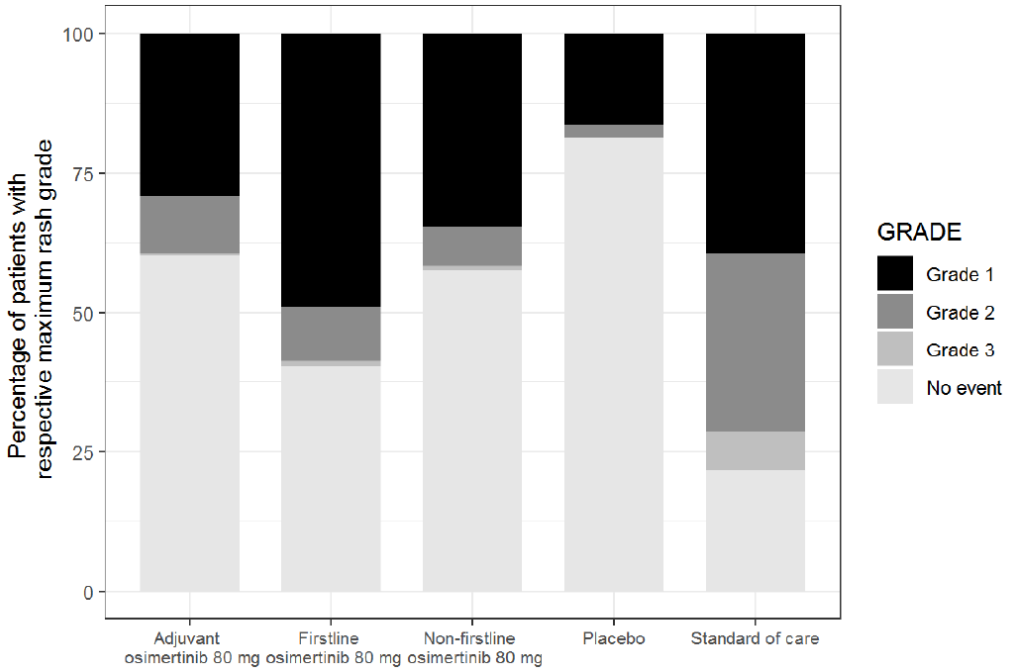


Figure 19: Distribution of osimertinib AUCss stratified by the occurrence of any AE, leading to dose interruption (ADAURA only)

Rash (graphical assessment)

Figure 20 shows the distribution of the maximum (at any study day) rash grade level for adjuvant osimertinib treated patients on 80 mg, first-line osimertinib treated patients on 80 mg, non-first-line osimertinib treated patients on 80 mg and standard-of-care or placebo treated patients. The incidence of rash appears to be lower in adjuvant treated patients compare to first-line osimertinib treated patients.



Abbreviations: Grade, Maximum observed rash CTCAE grade at any study day.

Figure 20: Distribution of maximum rash CTCAE grades

The incidence of rash AEs seems similar in adjuvant patients and non-first line patients. There is a higher frequency of patients with rash in SoC treated patients (78.3%) than in placebo (18.6%).

As new information from study ADAURA is on adjuvant treated patients, the focus of the following analysis is on first line and adjuvant treated patients.

Table 21: Summary of maximum rash (CTCAE grade by first dose for osimertinib treated patients and SoC treated patients (adjuvant /first line population)

Dose	Total number of patients (N = 1283)	Number (%) of Patients			
		No event	Grade 1	Grade 2	Grade 3
80 mg	633	320 (50.55%)	246 (38.86%)	63 (9.95%)	4 (0.63%)
160 mg	30	4 (13.33)	13 (43.33)	12 (40.00)	1 (3.33)
Placebo	343	68 (19.83%)	14 (4.08%)	1 (0.29%)	0 (0%)
SoC	277	60 (21.66)	109 (39.35)	89 (32.13)	19 (6.86)

Table 22: Summary of maximum rash CTCAE grade treated with 80mg osimertinib by study (adjuvant /first-line population)

Study	Total number of patients (N = 633)	Number (%) of Patients			
		No event	Grade 1	Grade 2	Grade 3
ADAURA	325	196 (60.31%)	95 (29.23%)	33 (10.15%)	1 (0.31%)
AURA	30	8 (26.67%)	16 (53.33%)	6 (20%)	0 (0%)
FLAURA Osimertinib	278	116 (41.73%)	135 (48.56%)	24 (8.63%)	3 (1.08%)
TOTAL Osimertinib	633	320 (50.55%)	246 (38.86%)	63 (9.95%)	4 (0.63%)

There are no patients with CTCAE Grade ≥ 4.

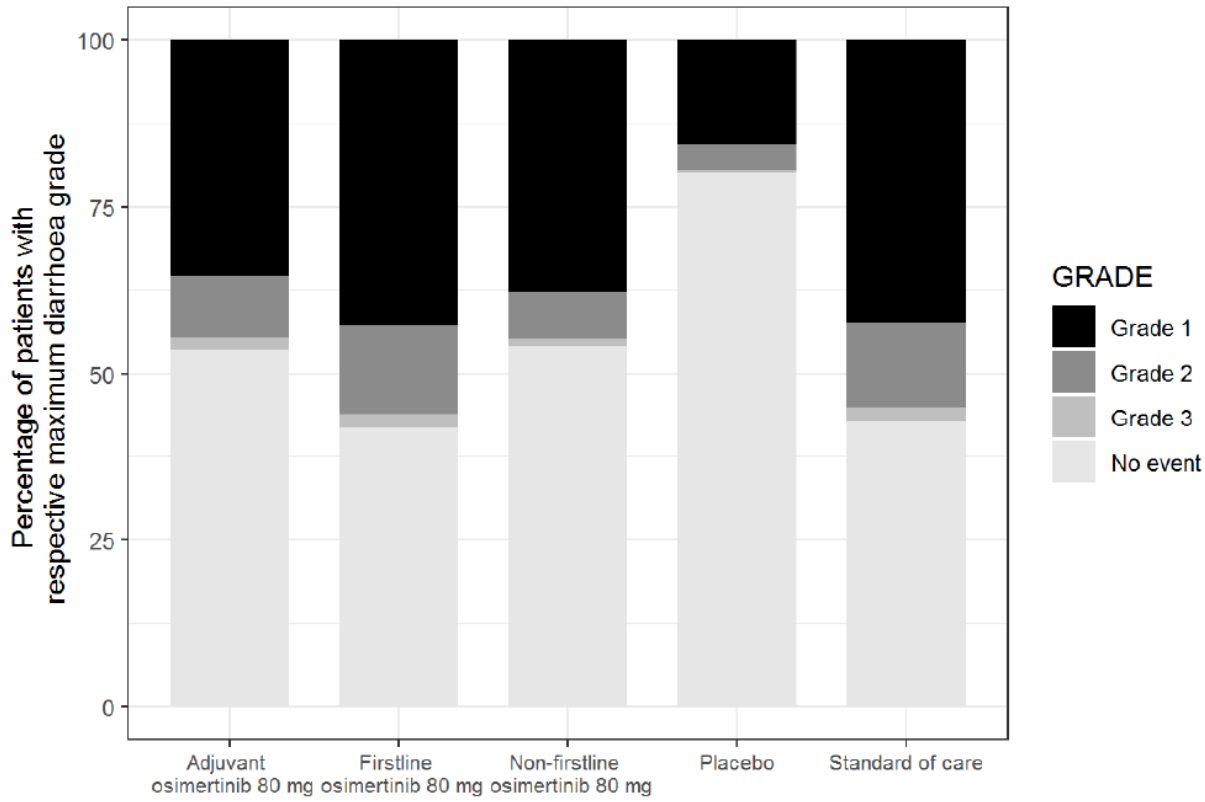
In general, the observed proportion of adjuvant and first-line patients with rash slightly increases with the osimertinib AUCss. However, the proportion of patients with rash in the group of SoC treated patients stays larger than the proportion of patients with rash even in the highest exposure quartile for adjuvant and first-line osimertinib treated patients. The proportion of patients with rash in placebo groups appears substantially lower than in osimertinib exposure quartiles.

Although the number of rash events increase with AUCss, the frequency of moderate to severe events (CTCAE Grades 2 to 3) is similar in the lowest three exposure quartiles and slightly larger in the highest exposure quartile.

Diarrhoea (graphical assessment)

Distribution of maximum CTCAE grades of diarrhoea was initially investigated on total safety population. Comparison of percentage of patients with each maximum diarrhoea grade across type of treatments was performed.

Figure 21 shows the distribution of the maximum (at any study day) diarrhoea grade levels for 80 mg osimertinib treated patients. The incidence and severity of diarrhoea appears to be higher in first-line osimertinib treated patients than in non-first-line treated patients and adjuvant.



Abbreviations: Grade, Maximum observed diarrhoea CTCAE grade at any study day.
Note: One patient (E4201013) treated with SoC experienced a Grade 5 diarrhoea CTCAE event, and has not been included in the plot. No first-line treated patient experienced a diarrhoea Grade 4 CTCAE event.

Figure 21: Distribution of maximum diarrhoea CTCAE grades

As new information from study ADAURA is on adjuvant treated patients, the focus of the analysis is on adjuvant and first-line treated patients.

The incidence of diarrhoea AEs in adjuvant patients appears similar to non-first line patients. It is also confirmed the higher frequency of moderate to severe (CTCAE Grades 2 to 3) diarrhoea events at 160 mg dose than for 80 mg osimertinib treated patients. Placebo patients (ADAURA study) had lower frequency of diarrhoea events, compared with active osimertinib treatment and SoC.

Table 23: Summary of maximum diarrhoea CTCAE grade by first dose (adjuvant/first line population)

Dose	Total number of patients (N = 1283)	Number (%) of Patients					
		No event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
80 mg	633	303 (47.87%)	247 (39.02%)	71 (11.22%)	12 (1.9%)	0 (0%)	0 (0%)
160 mg	30	4 (13.33%)	16 (53.33%)	8 (26.67%)	2 (6.67%)	0 (0%)	0 (0%)
Placebo	343	275 (80.17%)	54 (15.74%)	13 (3.79%)	1 (0.29%)	0 (0%)	0 (0%)
SoC	277	118 (42.60)	117 (42.24)	35 (12.64)	6 (2.17)	0	1 (0.36)

Table 24: Summary of maximum diarrhoea CTCAE grade treated with 80mg osimertinib by study (adjuvant/first line population)

Study	Total number of patients (N = 633)	Number (%) of Patients					
		No event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
ADAURA	325	174 (53.54%)	115 (35.38%)	30 (9.23%)	6 (1.85%)	0 (0%)	0 (0%)
AURA	30	12 (40%)	12 (40%)	6 (20%)	0 (0%)	0 (0%)	0 (0%)
FLAURA Osimertinib	278	117 (42.09%)	120 (43.17%)	35 (12.59%)	6 (2.16%)	0 (0%)	0 (0%)
TOTAL Osimertinib	633	303 (47.87%)	247 (39.02%)	71 (11.22%)	12 (1.9%)	0 (0%)	0 (0%)

There are no patients with CTCAE Grade ≥ 4.

In general, the plot suggests that the proportion of adjuvant and first-line patients with diarrhoea increases with increasing exposure to osimertinib. Based on the new results, it is confirmed that the proportion of SoC treated patients with diarrhoea is similar to that observed for Osimertinib treated patients.

ILD (Graphical assessment and model-based analysis)

The term 'ILD' or 'ILD event' comprised of 'Medical Dictionary for Regulatory Activities' preferred terms including interstitial lung disease, pneumonitis, acute interstitial pneumonitis, alveolitis, diffuse alveolar damage, idiopathic pulmonary fibrosis, lung disorder, pulmonary toxicity, and pulmonary fibrosis. Table 20 shows the number of observed ILD events per treatment group, and Table 21 shows the number of patients for each study in the group of 80 mg osimertinib treated patients.

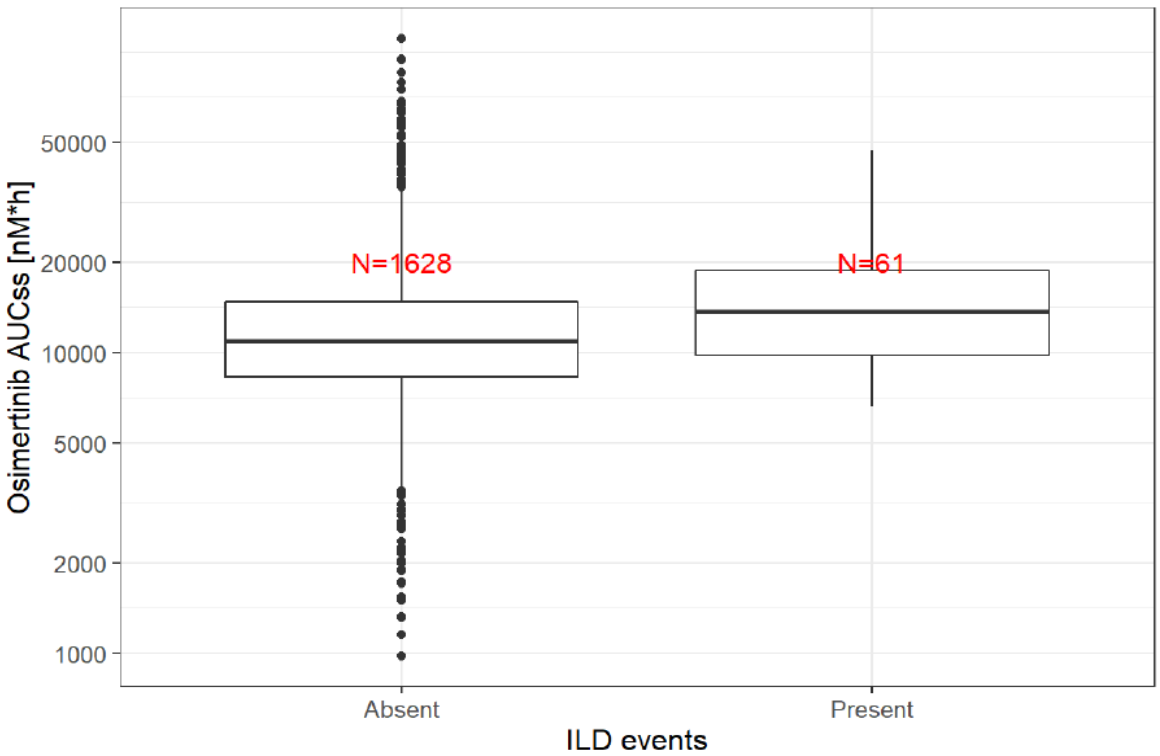
Table 25: Number of patients with ILD events for each treatment group (total safety population)

Treatment group	Number ILD events (%)	Total number of patients
AURA3 Chemotherapy	1 (0.74%)	136
FLAURA SoC	6 (2.17%)	276
ADAURA Placebo	0 (0%)	343
Osimertinib 20mg	0 (0%)	21
Osimertinib 40mg	0 (0%)	58
Osimertinib 80mg	55 (3.76%)	1461
Osimertinib 160mg	6 (4.69%)	128
Osimertinib 240mg	0 (0%)	21
Osimertinib All Doses	61 (3.61%)	1689

Table 26: Number of patients with ILD events treated with osimertinib 80mg by study (total osimertinib safety population)

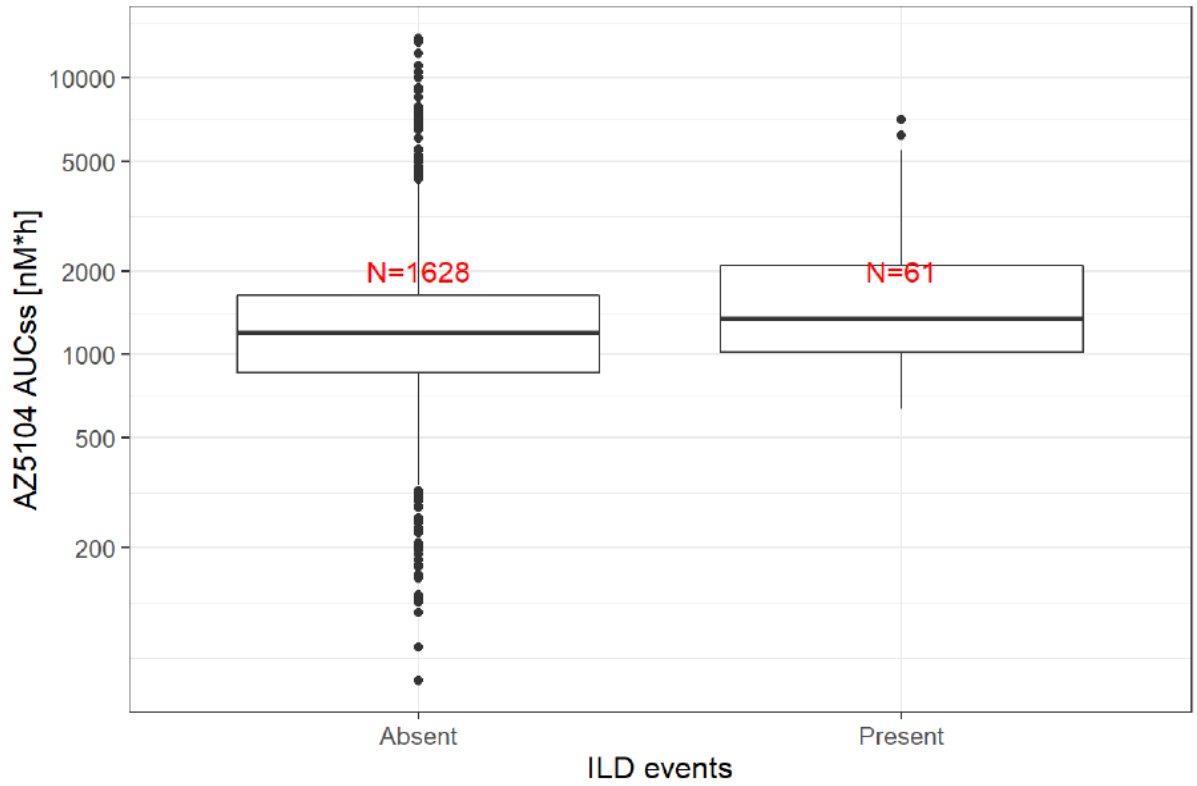
Study	Number ILD events (%)	Total number of patients
AURA	19 (5.12%)	371
AURA2	5 (2.38%)	210
AURA3	10 (3.61%)	277
FLAURA	11 (3.96%)	278
ADAURA	10 (3.08%)	325
TOTAL	55 (3.76%)	1461

The distribution of osimertinib AUCss in all patients (total safety population) stratified by the occurrence of ILD is shown as a box plot in Figure 22.



The ends of the box represent the 25th and 75th percentiles of the AUC_{ss} distribution and the middle line is showing the median of the distribution. Data below the 5th and above the 95th percentile are shown as black dots.

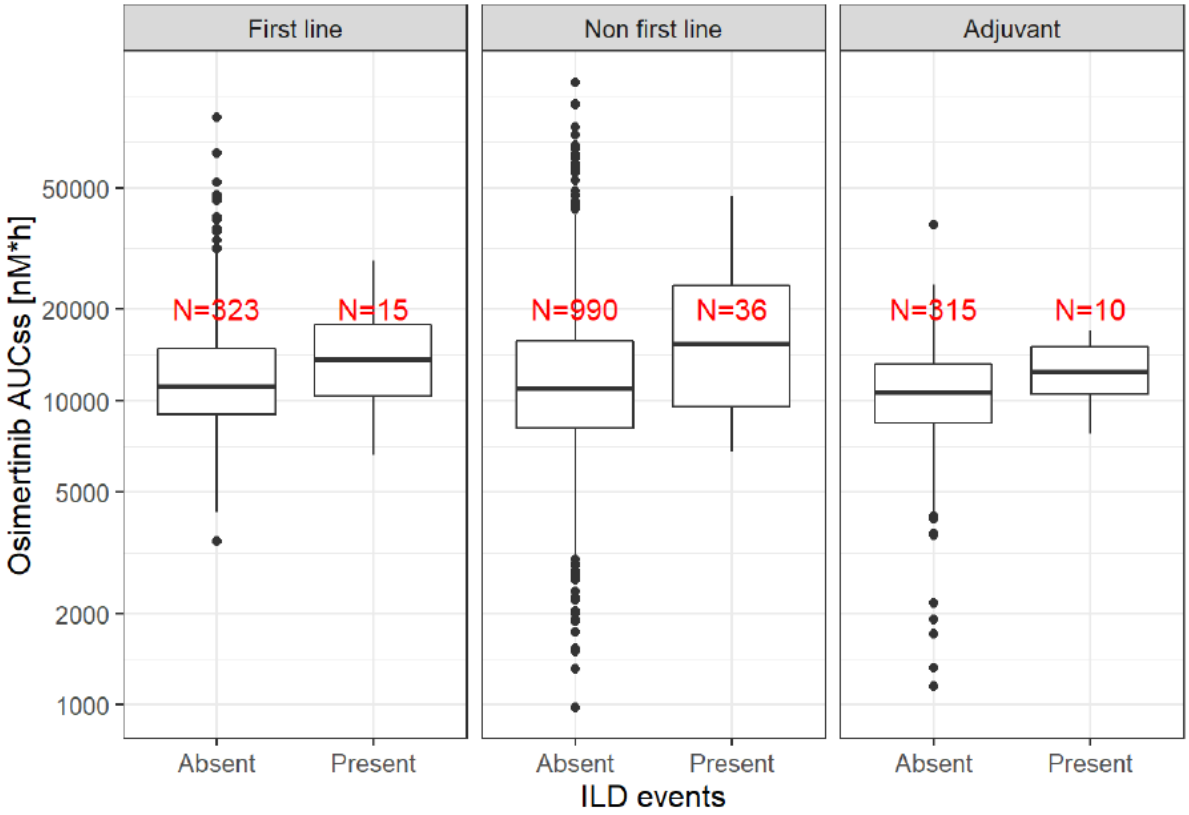
Figure 22: Distribution of osimertinib AUCss stratified by the occurrence of ILD event (total osimertinib safety population)



Note: The ends of the box are the lower and upper quartiles of AUC_{ss} with the black middle line showing the median. Data below the 5th and above the 95th percentile are shown as black dots.

Figure 23: Box plot of the distribution of AUCss for the metabolite (AZ5104) stratified by the occurrence of ILD

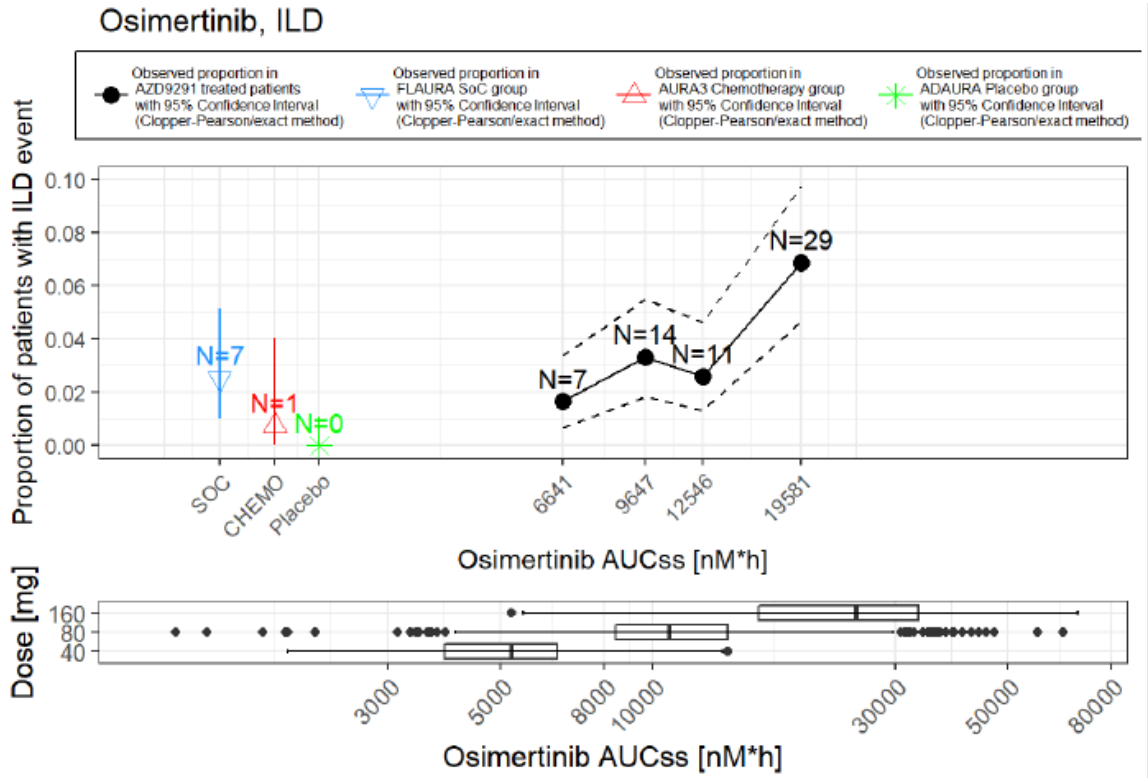
Figure 24 shows analogous information split by type of treatment.



The ends of the box represent the 25th and 75th percentiles of the AUC_{ss} distribution and the black middle line is showing the median of the distribution. Data below the 5th and above the 95th percentile are shown as black dots.

Figure 24: Distribution of osimertinib AUCss stratified by the occurrence of ILD event and by line of treatment (total osimertinib safety population)

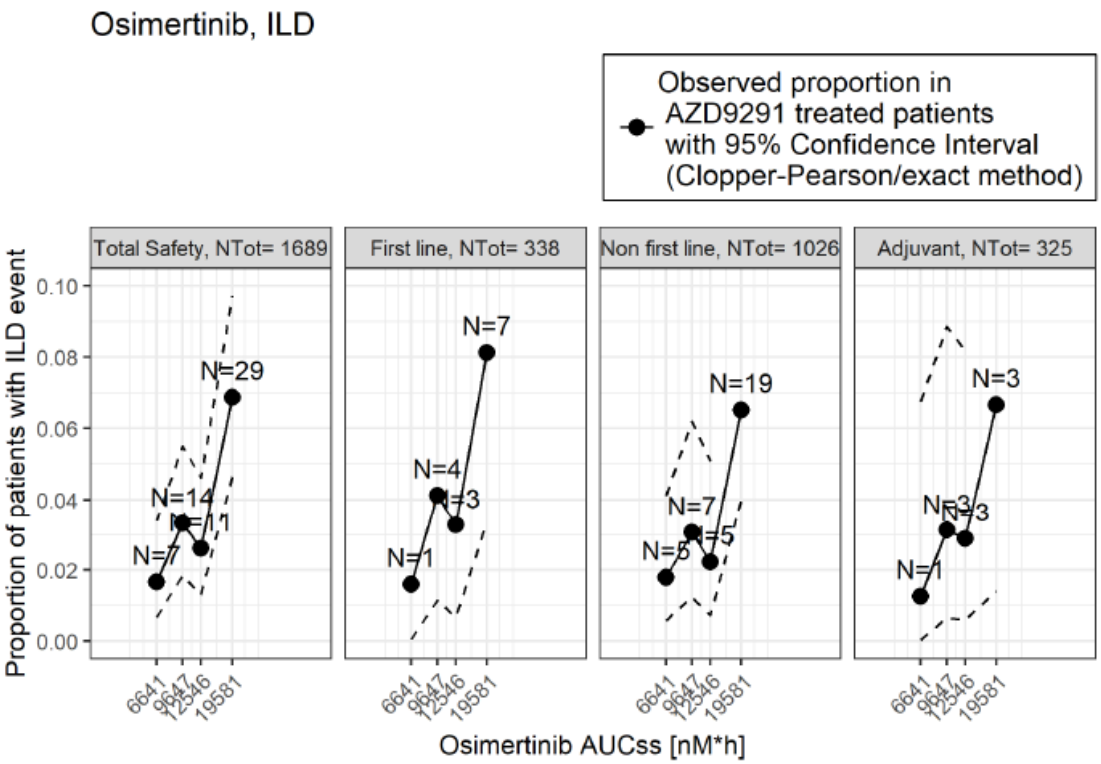
The probability that a patient experiences an ILD event, stratified by the quartiles of osimertinib AUCss, is shown in Figure 25.



Note: Overall observed probability was calculated for each quartile of AUC_{ss}.
Upper figure: The values on the x-axis correspond to the median AUC_{ss} values in each quartile. The blue down-pointing triangle corresponds SoC treated patients (FLAURA), the red upper pointing triangle to chemotherapy treated patients (AURA3), and the green asterisk to placebo patients (ADAURA)
The Clopper-Pearson interval ('exact' method) is based on the cumulative probabilities of the binomial distribution. The true coverage rate of a 95% Clopper-Pearson interval may be wider than it needs to be to achieve 95% confidence.
Lower figure: The AUC_{ss} distribution for the populations of patients on 40, 80, and 160 mg are shown. The ends of the boxes represent the 25th and 75th percentiles and the black middle line shows the median of the distribution. The vertical lines outside the box indicate the 5th and 95th percentiles of the AUC_{ss} distribution. Data below the 5th and above the 95th percentile are shown as black dots.

Figure 25: Proportion of patient with ILD events over osimertinib AUCss quartiles

Figure 26 shows analogous information focusing only on osimertinib treated patients and stratified based on the type of therapy.



Abbreviations: NTot, Number of total patients in each of the treatment populations.
Note: Overall observed probability was calculated for each quartile of AUC_{ss}.
The values on the x-axis correspond to the median AUC_{ss} values in each quartile.
The Clopper-Pearson interval ('exact' method) is based on the cumulative probabilities of the binomial distribution. The true coverage rate of a 95% Clopper-Pearson interval may be wider than it needs to be to achieve 95% confidence.

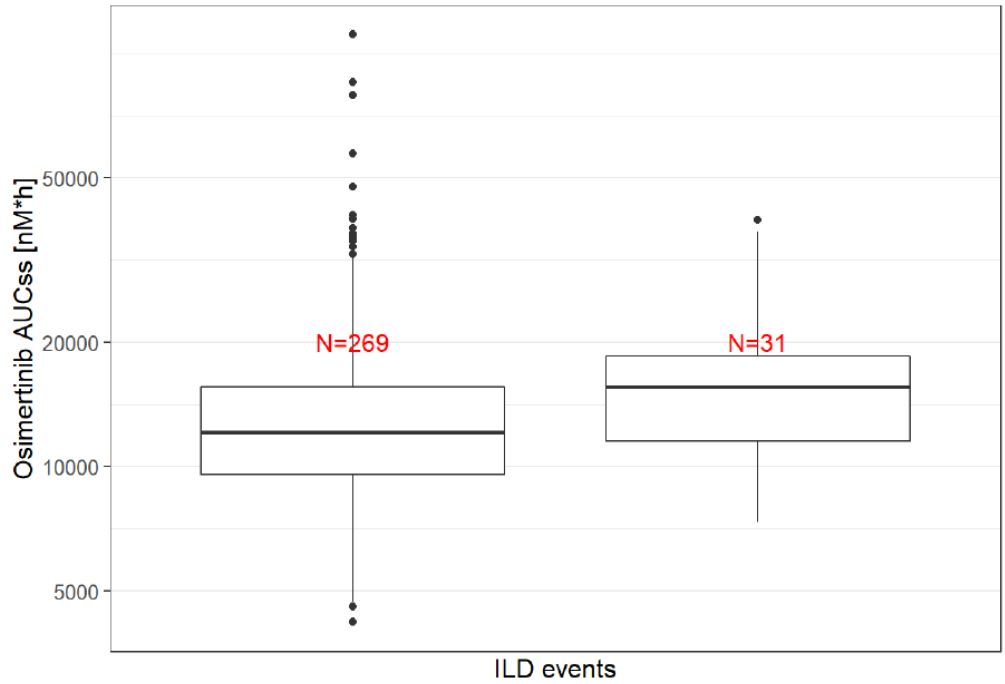
Figure 26: Proportion of patient with ILD events over osimertinib AUCss quartiles by line of treatment

For osimertinib treated patients, as observed in the previous analysis, there is a higher rate of ILD events in Japanese patients than in the overall population (Table below).

Table 27: Number of ILD events in populations of patients treated with osimertinib

Population	Total Patients	Number ILD cases	Percent
All patients	1689	61	3.61%
Non-Asians	622	19	3.05%
Asians	1067	42	3.94%
Asians excluding Japanese	767	11	1.43%
Japanese	300	31	10.33%

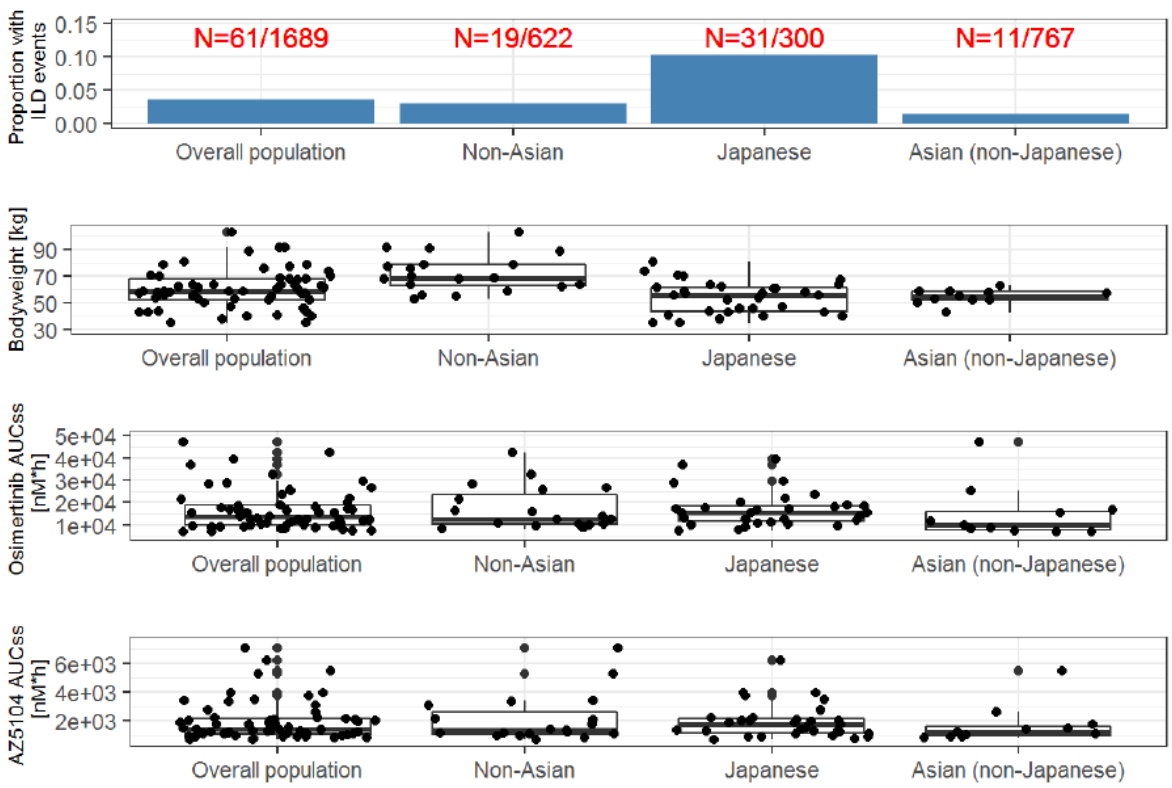
Figure 27 suggests that Japanese patients who had ILD appear to have higher AUCss values than Japanese patients without ILD (as observed in overall population), indicating that increased osimertinib AUCss explains part of higher ILD incidence rate in Japanese patients.



Note: The ends of the box represent the 25th and 75th percentiles of the AUC_{ss} distribution and the black middle line is showing the median of the distribution. Data below the 5th and above the 95th percentile of the AUC_{ss} distribution are shown as black dots.

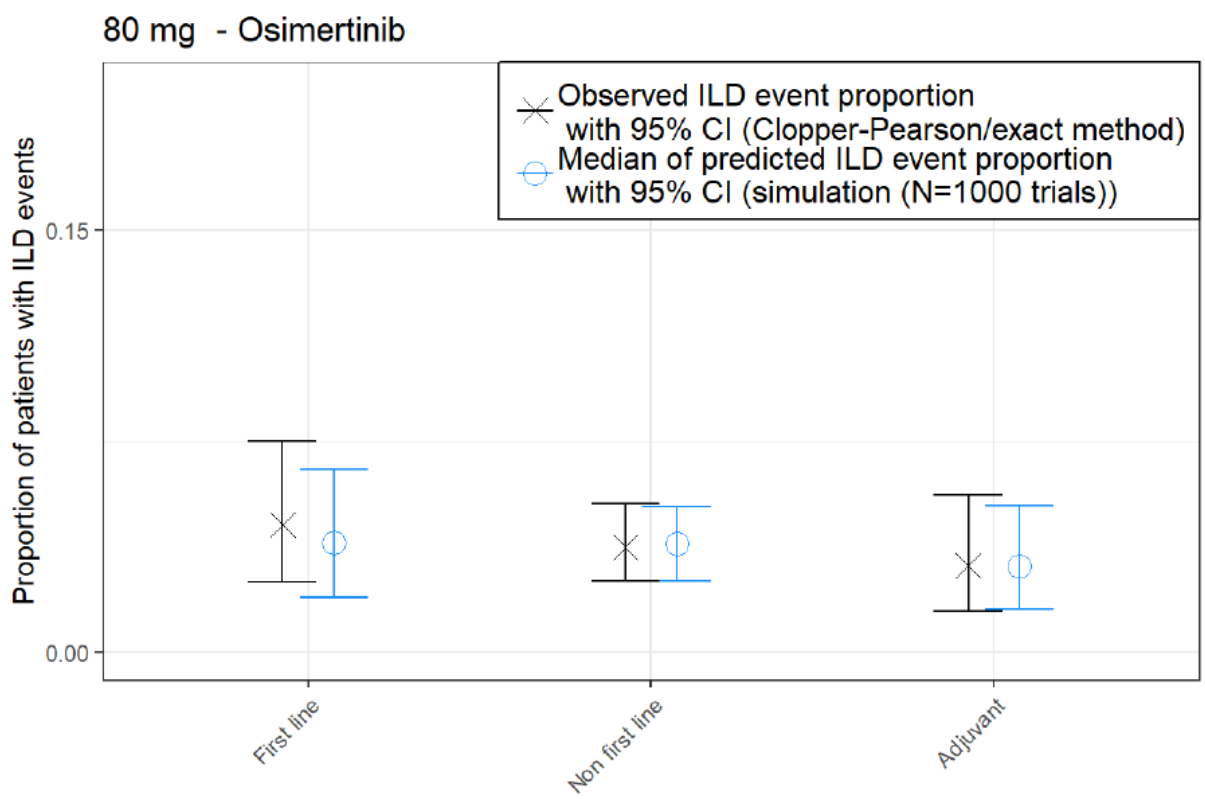
Figure 27: Distribution of osimertinib AUCss stratified by the occurrence of ILD event in Japanese patient (box plot)

Figure 28 shows the distributions of bodyweight and AUCss (osimertinib and AZ5104) for patients who experienced ILD events in the overall population and subpopulations, together with the corresponding individual values (black dots).



Note: Box plots are based on data from patients with ILD events only, and the black dots are the corresponding individual values for patients with ILD events in the different groups. The ends of the box represent the 25th and 75th percentiles of the AUC_{ss} distribution and the black middle line is showing the median of the distribution. The horizontal lines outside the box indicate the 5th and 95th percentiles of the AUC_{ss} distribution.

Figure 28: Proportion of ILD events and distribution of bodyweight and exposure in patients with ILD events in different population

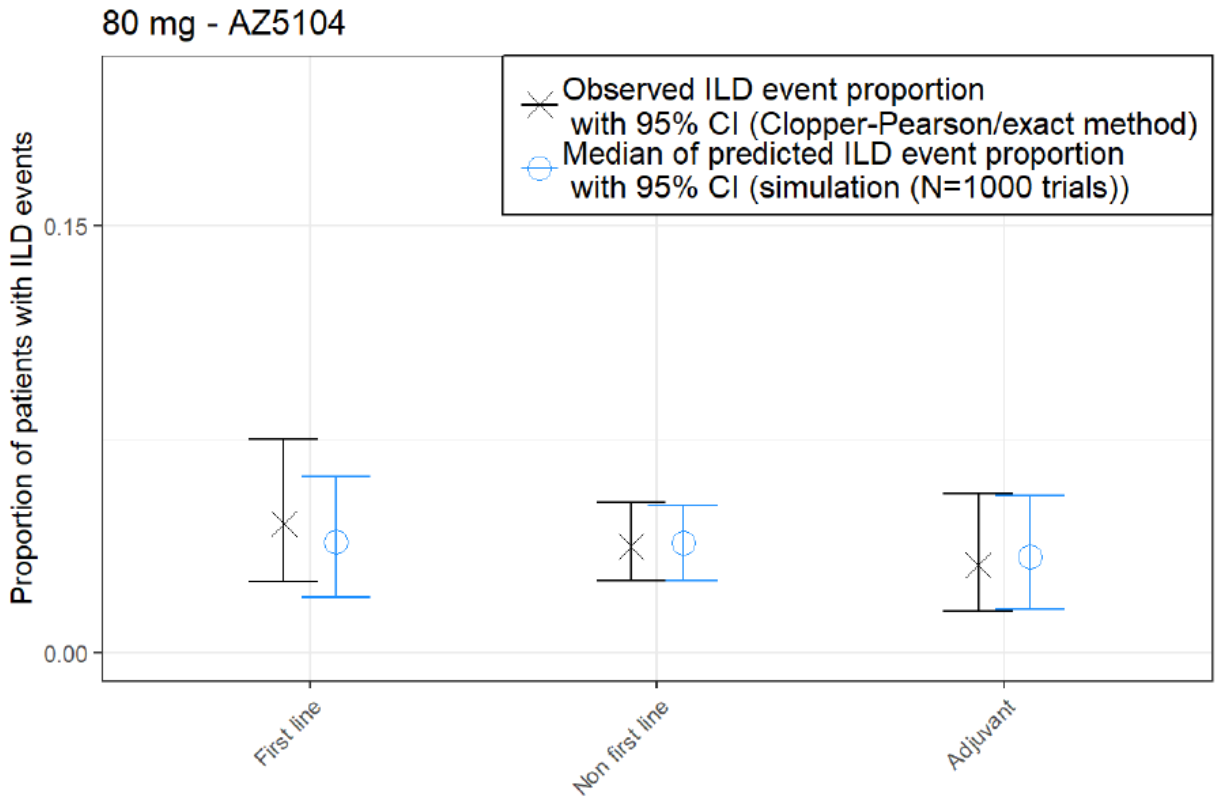


Black crosses: Means of observed probability of ILD events in AURA, AURA2, AURA3, FLAURA and ADAURA. Black error bars: 95% CIs for observed proportion of ILD events (Clopper-Pearson/exact method) Blue circles: Median of model predicted proportion of ILD events. Blue error bars: 95% CIs of ILD events predicted by the final model.

Figure 29: Visual predictive checks for the frequency of ILD events – for the osimertinib ILD model

Table 28: Comparison of observed and model predicted ILD events

Population	Number of observed ILD events	Total number of patients	Observed proportion of patients with ILD event	Predicted proportion of patients with ILD event
First line	14	308	0.045 (0.025 - 0.075)	0.039 (0.019 - 0.065)
Non first line	31	828	0.037 (0.026 - 0.053)	0.039 (0.025 - 0.052)
Adjuvant	10	325	0.031 (0.015 - 0.056)	0.031 (0.015 - 0.052)



Note: Black crosses: Observed probability of ILD events in AURA, AURA2, AURA3, FLAURA and ADAURA. Black error bars: 95% CIs for observed probability of ILD events (Clopper-Pearson/exact method) Blue circles: Median of model predicted probability of ILD events. Blue error bars: 95% CIs of the median of ILD events predicted by the AZ5104 model.

Figure 30: Visual predictive checks for the frequency of ILD events in different populations for the AZ5104 model

Table 29: Summary of bootstrap results (AZ5104 model)

Population	Observed proportion of patients with ILD * (95% CI)	Predicted proportion of patients with ILD ** (95% CI)
First line	0.045 (0.025 - 0.075)	0.039 (0.019 - 0.062)
Non first line	0.037 (0.026 - 0.053)	0.039 (0.025 - 0.052)
Adjuvant	0.031 (0.015 - 0.056)	0.034 (0.015 - 0.055)

* Mean of observed ILD event rate with 95% CI (Clopper-Pearson/exact method).
** Median of predicted mean ILD event rate with 95% CI. Bootstrapping approach (N = 1000)

2.4.5. Discussion on clinical pharmacology

The analytical methods used in this study were previously assessed. Since the data were obtained within a study from two different laboratories, applying the same method, comparison of those data was performed and a cross validation was carried out. The outcome of the cross validation show that the obtained data were reliable, and they can be compared and used.

Both in-study validations show acceptable calibration standards and QCs. The reasons for the samples re-assayed are considered acceptable. Incurred Sample Reproducibility was performed, and the reanalysis confirms the validity and performance of the Analytical Method Procedure for all analytes.

The MAH has characterized the PK and PK/PD properties of osimertinib as adjuvant treatment after complete tumour resection in EGFR mutant NSCLC patients, based on the results from the pivotal Phase 3 randomised, placebo-controlled study ADAURA (D5164C00001).

Pharmacokinetics in the target population

The PK exposure values obtained in the ADAURA clinical study are similar to those obtained in previous studies. No significant time-dependent trends are observed, and the distribution of covariates is similar with respect to previous clinical studies.

The modelling strategy is fully endorsed, since the MAH applied a previously developed population PK model in EGFRm NSCLC patients from Phase I (AURA), Phase II (AURA extension, AURA2), and Phase III (AURA3, FLAURA) studies to predict the individual behaviour of patients from ADAURA study (using maxeval =0) and then, re-estimate the final population PK parameters to evaluate whether significant differences appear when ADAURA dataset is included. The results obtained with the previously developed population PK model suggest good agreement to describe the experimental data from the ADAURA study and no significant changes in the final population PK parameters were detected.

The adjuvant indication had no relevant impact on CL/F for osimertinib with an estimated 0.1% difference between adjuvant and ≥ first-line patients. A small reduction (9%) in CLm/F of was estimated in the adjuvant population compared with ≥ first-line patients, which is not considered to be of clinical relevance. It was reconfirmed that the prior model was valid and that no update of the population PK model was required to describe the totality of the data (AURA, AURA2, AURA3, FLAURA and ADAURA).

Pharmacokinetic interactions and PBPK Model

A new evaluation of DDI potential (osimertinib as perpetrator) was performed due to recent determination of non-specific binding in in vitro assays and human plasma protein binding, indicating a lower potential for inhibition of transporters and enzymes than previously concluded. Previous conclusions regarding a low estimated risk of clinically relevant inhibition of CYP1A2 and CYP2C8 in vivo was further supported by PBPK modelling and simulation.

The development of an updated PBPK model with new in vitro and in vivo data for osimertinib is highly appreciated. The Simcyp PBPK model 3 development is endorsed and well documented, with all the parameters of the model provided and sufficiently detailed and defined.

The updated PBPK model has been verified (accurate predictions of osimertinib exposure) and validated with data from a clinical DDI study (D5160C00014) between osimertinib (perpetrator) and simvastatin (victim), which assess its potential as CYP3A4 inhibitor. The PBPK model is able to predict the absence of a relevant DDI between these drugs. Additionally, the PBPK model 3 has been applied to evaluate its inhibitory ability on CYP2C8 and CYP1A2 enzymes. The PBPK model predicts no DDI between osimertinib and repaglinide (CYP2C8 substrate) nor caffeine (CYP1A2 substrate), although the MAH did not provide the qualification of the PBPK platform's ability to predict in vivo inhibitory effect of CYP1A2 and CYP2C8 enzymes. Therefore, these results suggest that osimertinib would not have a relevant influence on the exposure of substrates of these CYP450 isoenzymes.

Exposure-efficacy relationship

The evaluation of the exposure-efficacy relationship demonstrated the improvement in DFS in patients receiving osimertinib versus placebo, although no exposure-efficacy relationship could be established between AUCss of osimertinib and its metabolite (AZ5104) and DFS. Comparable DFS for patients in

the lowest and highest osimertinib exposure quartile indicates that an 80 mg starting dose leads to similar efficacy across exposure levels in the adjuvant setting.

Exposure-safety relationship

The exploratory assessment between osimertinib AUCss and the incidence of several adverse events (including those casually related to treatment) revealed no clear relationship. A slight increase in the probability and severity of rash and diarrhoea grade≥2 and osimertinib AUCss was established in patients from ADAURA clinical trial, which is in accordance with previous analyses demonstrating the in higher probability of developing rash and diarrhoea in patients receiving osimertinib. These results show that the probability of rash or diarrhoea is manageable at the 80 mg dose of osimertinib.

Furthermore, a positive relationship was characterized between the incidence of ILD and AUCss of osimertinib, which is in accordance with previous studies. Similar relationships were found when AZ5104 was considered as the exposure endpoint. A difference in incidence of ILD between Japanese and non-Japanese Asians and non-Asians was noted. Although the reason for this difference remains unknown, it may relate to constitutional and environment factors specific to Japan, or Japanese patients [Johnson, 2020; Koo et al 2005].

2.4.6. Conclusions on clinical pharmacology

The PK and PK/PD properties of osimertinib as adjuvant treatment after complete tumour resection in EGFR mutant non-small cell lung cancer (NSCLC) patients have been characterized based on the results from the pivotal Phase 3 randomised, placebo-controlled study ADAURA (D5164C00001). The modelling strategy seems adequate to achieve the objectives initially planned. The results obtained with the previously developed population PK model suggest good agreement to describe the experimental data from the ADAURA study and no significant changes in the final population PK parameters were detected. The updated analyses including adjuvant setting patients indicate that PK is similar across lines of treatment and that established dosing recommendations in the ≥1st line setting can be translated to the adjuvant setting.

2.5. Clinical efficacy

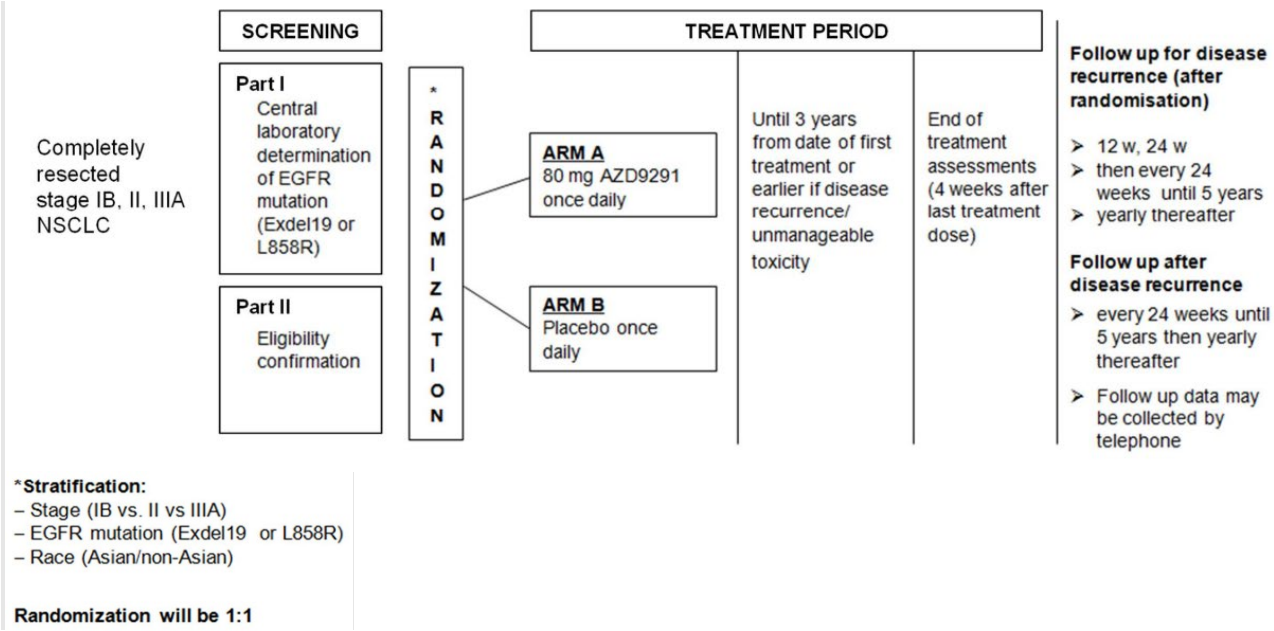
2.5.1. Dose response study(ies)

No further dose response studies have been provided within this submission. The proposed dose for osimertinib is the same which is currently authorised in the advanced setting (i.e. 80 mg once daily).

2.5.2. Main study(ies)

Study ADAURA (D5164C00001): an ongoing Phase 3, double-blind, randomised, placebo-controlled study to assess the efficacy and safety of osimertinib versus placebo in patients with stage IB-IIIA EGFRm NSCLC, who have undergone complete tumour resection, with or without adjuvant chemotherapy

Figure 31. Flow chart of study design



Note: Due to an error in the study design flow chart within the CSP, 'Exdel19' should be interpreted as Ex19del.

The data presented are based on an early unplanned interim analysis performed on the recommendation from IDMC (Independent Data Monitoring Committee) and a data cut-off date (DCO) of 17th January 2020.

Methods

Study participants

Main inclusion criteria

1. Male or female, aged at least 18 years. Patients from Japan/Taiwan aged at least 20 years.
2. Histologically confirmed diagnosis of primary NSCLC, of predominantly non-squamous histology.
3. MRI or CT scan of the brain must have been done prior to surgery (as it is considered standard of care). Patients in whom this was not done prior to surgery may still have been be enrolled if appropriate imaging was performed prior to randomisation, i.e., MRI or CT of brain.
4. Patients must have been classified post-operatively as Stage IB, II or IIIA on the basis of pathologic criteria. Staging was conducted in accordance with the percutaneous transthoracic needle biopsy (pTNM) staging system for lung cancer (7th edition).
5. Confirmation by the central laboratory that the tumour harboured one 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 including T790M.
6. Complete surgical resection of the primary NSCLC was mandatory. All gross disease must have been removed at the end of surgery. All surgical margins of resection must have been negative for tumour. Resection may have been accomplished by open or Video Associated Thoracic Surgery (VATS) techniques.

7. Complete recovery from surgery and standard post-operative therapy (if applicable) at the time of randomisation. Treatment could not commence within 4 weeks following surgery. No more than 10 weeks must have elapsed between surgery and randomisation for patients who did not received adjuvant chemotherapy; and no more than 26 weeks may have elapsed between surgery and randomisation for patients who received adjuvant chemotherapy. Additionally:

    - Complete post-operative wound healing must have occurred following any surgery;

    - For patients who received post-operative adjuvant platinum-based chemotherapy, a minimum of 2 weeks must have elapsed (but no more than 10 weeks) from the last administered dose of chemotherapy to the date of randomisation;

    - Patients must have recovered from all toxicities of prior therapy greater than CTCAE Grade 1 at the time of starting study treatment with the exception of alopecia and Grade 2 prior platinum therapy related neuropathy.

8. World Health Organization Performance Status of 0 to 1.

Main exclusion criteria

1. Previous randomisation and treatment in the present study.

2. Treatment with any of the following:

    - Pre-operative or post-operative or planned radiation therapy for the current lung cancer;

    - Pre-operative (neo-adjuvant) platinum-based or other chemotherapy;

    - Any prior anticancer therapy, including investigational therapy, for treatment of NSCLC other than standard platinum-based doublet post-operative adjuvant chemotherapy;

    - Prior treatment with neoadjuvant or adjuvant EGFR-TKI;

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

    - Patients who were currently receiving (or were unable to stop use prior to receiving the first dose of study treatment) medications or herbal supplements known to be potent inducers of CYP3A4 (at least 3 weeks prior);

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

3. Patients who had only segmentectomies or wedge resections.

4. History of other malignancies, except adequately treated non-melanoma skin cancer, curatively treated in-situ cancer, or other solid tumours curatively treated with no evidence of disease for > 5 years following the end of treatment and which, in the opinion of the treating physician, did not have a substantial risk of recurrence of the prior malignancy.

5. Any unresolved toxicities from prior therapy greater than CTCAE Grade 1 at the time of starting study treatment with the exception of alopecia and Grade 2, prior platinum therapy related neuropathy (CSP Amendment 1 [reflected in Revised CSP Version 2.0]).

6. Any evidence of severe or uncontrolled systemic diseases, including uncontrolled hypertension and active bleeding diatheses, which in the Investigator's opinion made it undesirable for the patient to

participate in the trial or which would jeopardise compliance with the protocol; or active infection including hepatitis B, hepatitis C and human immunodeficiency virus (HIV). Active infection included any patient receiving intravenous treatment for infection; active hepatitis B infection, at a minimum, included all patients who were hepatitis B surface antigen positive (HbsAg positive) based on serology assessment. Screening for chronic conditions was not required.

7. Refractory nausea and vomiting, chronic gastrointestinal diseases, inability to swallow the formulated product, or previous significant bowel resection that would have precluded adequate absorption of osimertinib.

8. Any of the following cardiac criteria:

    - Mean resting corrected QT interval (QTc) > 470 msec, obtained from 3 ECGs, using the screening clinic ECG machine-derived QTcF value;

    - Any clinically important abnormalities in rhythm, conduction, or morphology of resting ECG, eg, complete left bundle branch block, third-degree heart block, second degree heart block;

    - Any factors that increase the risk of QTc prolongation or risk of arrhythmic event such as heart failure, hypokalaemia, congenital long QT syndrome, family history of long QT syndrome, or unexplained sudden death under 40 years of age in first-degree relatives, or any concomitant medication known to prolong the QT interval.

9. Past medical history of 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 as demonstrated by any of the following laboratory values:

    - Absolute neutrophil count < 1.5 x 109/L;

    - Platelet count < 100 x 109/L;

    - Haemoglobin < 90 g/L;

    - Alanine aminotransferase (ALT) > 2.5x the upper limit of normal (ULN);

    - Aspartate aminotransferase (AST) > 2.5 x ULN;

    - Total bilirubin > 1.5 x ULN or > 3 x ULN in the presence of documented Gilbert's Syndrome (unconjugated hyperbilirubinemia);

    - Creatinine > 1.5 x ULN concurrent with creatinine clearance < 50 mL/min (measured or calculated by Cockcroft and Gault equation); confirmation of creatinine clearance is only required when creatinine is > 1.5 x ULN.

11. Women who were breast feeding.

Treatments

Patients were randomised 1:1 to receive either osimertinib 80 mg or matching placebo. Following complete surgical resection and prior to treatment initiation, all patients were required to have a baseline CT scan (chest and abdomen including liver and adrenal glands) within 28 days of treatment initiation to confirm that disease was not present. All patients receive randomised treatment until

recurrence of disease, a treatment discontinuation criterion was met, or until completing the 3-year (156 weeks) treatment period.

Dose modifications (i.e., interruptions or reductions) were allowed during the study. The starting dose of osimertinib was 80 mg QD, with a dose reduction to 40 mg QD permitted due to the occurrence of a clinically significant AE or unacceptable toxicity. Due to the double-blind nature of the study, a matching 40 mg placebo tablet for dose reduction was also available to maintain study integrity. Dose interruptions were also permitted for the same reasons.

Patients undergo regular radiological assessments for disease recurrence at 12 weeks, 24 weeks, every 24 weeks until 5 years (264 weeks), then yearly thereafter. Patients also undergo safety assessments at baseline, 2 weeks, 4 weeks, 12 weeks, and then every 12 weeks until treatment was completed or discontinued; with a 28-day follow-up visit after treatment was stopped.

Patients who discontinued treatment prior to disease recurrence continue to be assessed for DFS. Following disease recurrence, patients undergo radiological imaging for subsequent progression in accordance with local clinical practice and are followed for survival every 6 months until 5 years (264 weeks) post-randomisation, and yearly thereafter (until the closure of the study).

Objectives

Primary Objective	**Endpoint/variable**
To assess the efficacy of osimertinib compared to placebo as measured by disease free survival (DFS)	• DFS by investigator assessment
Secondary Objectives	**Endpoint/variable**
To further assess the efficacy of osimertinib compared with placebo	At time of primary analysis: • DFS rate at 2, 3, 4, and 5 years (*) • Overall Survival (OS) • OS rate at 2, 3, 4 and 5 years (*)
To assess the effect of osimertinib compared with placebo on health-related quality of life (HRQoL)	• Changes in generic HRQoL as measured by the SF-36 (version 2, standard)
To characterise the pharmacokinetics (PK) of osimertinib and its metabolites (AZ5104 and AZ7550)	• PK plasma concentrations of osimertinib, and metabolites AZ5104 and AZ7550; and ratio of metabolite to osimertinib for each PK sample (included in this CSR) PK data from this study will be analysed using a population PK approach and reported separately to this CSR. Data from this study may form part of a pooled analysis with data from other studies.
Safety Objective	**Endpoint/variable**
To assess the safety and tolerability profile of osimertinib compared with placebo	• Adverse events (graded by CTCAE v4) • Clinical chemistry, haematology and urinalysis • Vital signs, Physical Examination, Weight • Digital ECG • LVEF • WHO Performance Status • Ophthalmologic assessment

(*) Considering the analysis of this study is earlier than planned following IDMC recommendation, DFS rate and OS rate is only available up to 3 years.

Outcomes/endpoints

Primary endpoint

- DFS (as determined by the Investigator), defined as the time (in days) from the date of randomisation until the date of disease recurrence or death (by any cause in the absence of recurrence). Disease recurrence is defined as evidence of disease recurrence on CT or MRI scan and/or pathological disease on biopsy by investigational site assessment.

  A sensitivity analysis of DFS and subgroup analyses are also conducted comparing DFS between the treatments in specific subgroups of patient demographics, patient/disease characteristics, and mutation status.

Secondary endpoints

- DFS rate at 2, 3, 4, and 5 years.
- Overall survival (OS), defined as the time from randomisation to the date of death (from any cause), or to the date the patient was last known to be alive.
- OS rate at 2, 3, 4, and 5 years.
- Health-related Quality of Life (HRQoL) is assessed using the SF-36 questionnaire. The SF-36 v2 includes 8 domains: Physical Functioning; Role Limitations Physical, Vitality, General Health Perceptions, Bodily Pain, Social Function, Role Limitations-Emotional, and Mental Health; and is summarised into 2 summary scores: Physical Component Summary (PCS) and Mental Component Summary (MCS).

Exploratory endpoints

- Time to next treatment(s)
- Type of recurrence (local/regional or distant)
- Site(s) of relapse
- Type of next treatment(s) (including procedures, radiotherapy, and anticancer agents)
- PFS, as determined by investigator assessment

Sample size

This study was sized to characterise DFS (based on investigator assessment), assessed primarily in a subset of patients with stage II-IIIA cancer, and additionally in the overall population (additional comprising patients with stage IB disease).

Approximately 700 patients were to be randomised in a 1:1 ratio (osimertinib: placebo) to obtain approximately 247 disease recurrence events in approximately 490 stage II-IIIA patients (i.e. non-IB) in the FAS at the planned time of the primary analysis (50% maturity). The original sample size calculation was based on the assumption that if the true DFS HR for the comparison of osimertinib versus placebo in this patient population was 0.70, then 247 disease recurrence events at the time of the primary analysis would provide 80% power to demonstrate a statistically significant difference in DFS at a 5% 2-sided significance level, which could translate to an improvement in median DFS from

40 months to 57 months, assuming DFS is exponentially distributed. Under these conditions, the minimum DFS HR that would be statistically significant ($p < 0.05$, 2-sided) was 0.78.

In the overall population, 317 disease recurrence events were calculated to provide ~90% power to demonstrate a statistically significant difference in DFS at a 4% 2-sided significance level, which could translate to an improvement in median DFS from 46 months to 66 months, assuming DFS is exponentially distributed). In this population, the minimum DFS HR that would be statistically significant ($p < 0.04$, 2-sided) was 0.79.

Randomisation

Eligible patients were centrally randomised in a 1:1 ratio (to receive either osimertinib or matching placebo) using the IVRS/IWRS system. Patients were stratified at randomisation based on disease stage (IB vs. II vs. IIIA), EGFR mutation status (Ex19del or L858R), and race (Asian or Non-Asian).

Blinding (masking)

The study was double-blind.

Each patient received either the active drug or matching placebo. The active drug and placebo tablets were identical and presented in the same packaging to ensure blinding of the medication. The study drug was labelled using a unique material pack code, which was linked to the randomisation code. The IVRS/IWRS assigned the bottles of study material to be dispensed to each patient.

Statistical methods

Analysis sets

Three analysis populations are defined for the analysis of the ADAURA study.

- *Full Analysis Set (FAS)*

The FAS includes all randomised patients. The FAS (also referred to as the overall population) is used for all demographic summaries and efficacy analyses, and treatment groups will be compared on the basis of randomised study treatment, regardless of the treatment actually received.

It is noted that whilst not formally defined in the SAP, in accordance with the multiple testing procedure (MTP), the **primary analysis population** is **patients who were staged with II-IIIA disease** (as entered into the IVRS at the time of randomisation for stratification purposes). This primary analysis population is a subset of the FAS.

- *Safety Analysis Set*

The safety analysis set comprises all patients who received at least 1 dose of study treatment.

Safety data are not formally analysed, but are summarised using the safety analysis set, according to the treatment received; ie, erroneously treated patients (e.g, those randomised to treatment A but actually given treatment B) are summarised according to the treatment they actually received. If a patient received both treatments, then they are summarised according to the active treatment (i.e. osimertinib).

- *Pharmacokinetic Analysis Set*

The PK analysis set is defined as patients in the safety analysis set who received osimertinib and have at least 1 measurable PK concentration, supported by the relevant date and time of the sample.

For each time a PK sample was taken from a patient, the dosing data for that day and for multiple dosing, the dose date for the two days prior to the sample days must have been available. For any individual sample from a patient to be included in the PK analysis set, the full sample data and dosing data needed to be present for that sample/patient.

Multiple testing strategy

The primary endpoint of DFS and secondary endpoint of OS were to be tested in a subset of patients with stage II-IIIA disease at the time of diagnosis, as well as in the overall population. In order to strongly control the type I error at the 5% 2-sided level, a hierarchical testing procedure was employed across these endpoints.

The hierarchical testing procedure was ordered such that DFS in stage II-IIIA patients was tested first using the full alpha. DFS in the overall population was subsequently only to be tested if statistical significance was shown for DFS in patients with stage II-IIIA disease at the time of diagnosis. OS (in both populations) was only to be tested if statistical significance was shown for DFS in the overall population.

Following the IDMC recommendation to complete a full analysis of efficacy and safety earlier than scheduled, and in consultation with the FDA, the SAP was updated following data unblinding. The alpha allocation required revision to control for the type I error to account for this unplanned interim analysis, which is based on a smaller number of disease recurrence events than originally planned for the primary analysis. No changes were made to the order of the hypothesis being tested.

The revised MTP is presented in the following figure.

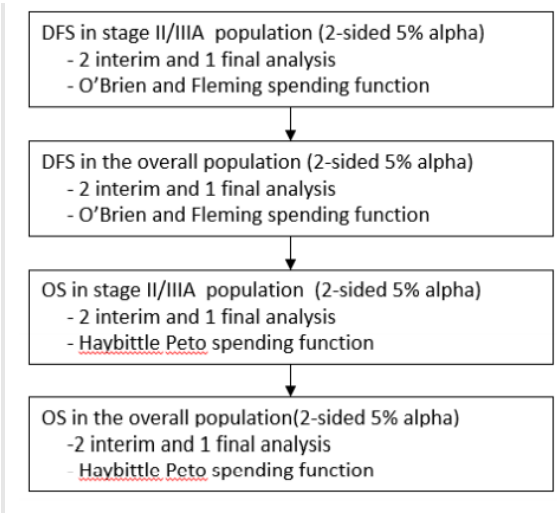


Figure 32: ADAURA: Hierarchical testing procedure

Further details of the revised MTP are provided below:

- DFS in stage II/IIIA patients: The primary analysis was originally planned to be conducted when approximately 247 DFS events were observed in the stage II/IIIA population. This represented an approximate 50% maturity based on the planned sample size of 490 subjects. Two unplanned interim analyses of DFS in the stage II/IIIA population were conducted at the time of observing 86 DFS events and 156 DFS events respectively. The corresponding information fractions were 0.35 and 0.63 where the final number of events would have been 247. The Lan DeMets approach that approximates the O'Brien and Fleming spending function was used to adjust the overall 2-sided 5% type I error for the 2 interim analyses.
- DFS in the overall population: If testing of the DFS in stage II/IIIA population was statistically significant, the full 2-sided 5% alpha could be recycled forward into testing endpoints pre-specified in the hierarchal testing procedure. This constitutes a change from the planned 4% as cited in the original MTP, as the potential second analysis of DFS in the FAS (which originally had 1% alpha allocated) has been removed. The next test in the hierarchal procedure is to test the DFS in the overall population. Two unplanned interim analyses of DFS in the overall population were conducted at the time of observing 109 DFS events and 196 DFS events respectively. This equates to an information fraction of 0.34 and 0.62, where the final number of events would have been 317. 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.
- Overall Survival in Stage II/IIIA population: If the test of DFS in the overall population is statistically significant, OS in stage II/IIIA population will be tested using the Haybittle-Peto boundary with alpha allocation of 0.0002 (2-sided) for each of the interim analyses and overall 2-sided alpha of 5%. Alpha will be fully exhausted at the final OS analysis.
- Overall Survival in overall population: If the test of OS in the stage II/IIIA population is statistically significant, OS in the overall population will be tested using the Haybittle-Peto boundary with alpha allocation of 0.0002 (2-sided) for each of the interim analyses and overall 2-sided alpha of 5%. Alpha will be fully exhausted at the final OS analysis.

Table 30: Amended alpha allocation for DFS under Lan-DeMets with O´Brien-Fleming type spending function

Timepoint	Number of events/ information fraction/maturity	Critical value (HR)	2-sided p-value
Stage II-IIIA patients			
IDMC6 (February 2019) - futility review	86/0.35/18%	0.4590	0.00030
IDMC7 (April 2020) – current analysis	156/0.63/33%	0.6588	0.009384
Primary planned analysis per protocol	247/1.0/53%	0.7763	0.04701
Overall population			
IDMC6 (February 2019) - futility review	109/0.34/16%	0.4938	0.00025
IDMC7 (April 2020) – current analysis	196/0.62/29%	0.6886	0.00885
Primary planned analysis per protocol	317/1.0/47%	0.8002	0.04718

All required changes to the MTP are described in SAP Version 4.0, and a comparison of the planned MTP (SAP Version 2.0) and the updated procedure (SAP Version 4.0) is provided in the table below.

Table 31. Comparison of MTP in SAP Version 2.0 versus MTP in SAP Version 4.0

Endpoint	SAP Version 2.0 - Section 4.2.2 (dated 18 December 2018)	SAP Version 4.0 - Section 7 (dated 23 June 2020)
Primary endpoint: DFS in stage II/IIIA population	• One analysis timepoint • 2-sided 5% alpha • 80% power • Event driven, analysis to be conducted when approximately 247 DFS events have been observed (maturity: 247 DFS events from 490 patients, 50%) • Futility analysis to be conducted when approximately 83 DFS events have been observed, criteria for stopping based on conditional power, no alpha spend	• Overall 2-sided 5% alpha, O'Brien and Fleming spending function • Allows for 3 analyses: – First analysis: IDMC-6 (February 2019) at the time of the futility analysis – Second analysis: IDMC-7 (April 2020) as the IDMC conducted an unplanned efficacy analysis – Third analysis: when approximately 247 DFS events have been observed • Stopping boundaries were calculated with information fractions of 0.35 (86/247) and 0.63 (156/247), based on the final analysis being conducted with 247 DFS events (information fraction of 1) • Given statistical significance has been reached at the second analysis (IDMC7), no further formal testing of DFS will be conducted; exploratory analysis will be conducted once approximately 247 DFS events have occurred.
Secondary endpoint: DFS in the overall population	• Only tested if the primary endpoint is statistically significant (hierarchical testing approach). • Overall 2-sided 5% alpha, Haybittle-Peto spending function. • 90% power. • No pre-specified number of events/maturity required for analysis; timing of analysis is driven by DFS in the stage II/IIIA population. • Allows for 2 analyses: – First analysis to be conducted at the time of the primary endpoint with a 2-sided alpha of 4% – Second analysis can be conducted at a later date if less than approximately 70 DFS events are observed in the IB population at the time of the primary	• Only tested if the primary endpoint is statistically significant (hierarchical testing approach) • Overall 2-sided 5% alpha, O'Brien and Fleming spending function • Allows for 3 analyses: – First analysis: IDMC-6 (February 2019) at the time of the futility analysis – Second analysis: IDMC-7 (April 2020) as the IDMC conducted an unplanned efficacy analysis – Third analysis: when approximately 247* DFS events have been observed in the stage II-IIIA population • Stopping boundaries were calculated with information fractions of 0.34 (109/317) and 0.62 (196/317), based on the final

Endpoint	SAP Version 2.0 - Section 4.2.2 (dated 18 December 2018)	SAP Version 4.0 - Section 7 (dated 23 June 2020)
	analysis with a 2-sided alpha of ~1% (determined at the time of the analysis based on the exact correlation).	analysis being conducted with 317 DFS events (information fraction of 1) • Given statistical significance has been reached at the second analysis (IDMC7), no further formal testing of DFS will be conducted; exploratory analysis will be conducted once 247 DFS events have occurred in the stage II-IIIA population, with a further analysis once approximately 70 DFS events have occurred in the stage IB population (if not the case at the first exploratory analysis) * The information fraction is derived based on 317 DFS events in the overall population; however, the timing of this analysis is driven by the primary endpoint.
Secondary endpoint: OS in stage II/IIIA population	• Only tested if the DFS in the overall population is statistically significant (hierarchical testing approach). • Overall 2-sided 5% alpha, Haybittle-Peto spending function. • Study not powered for OS. • No pre-specified number of events/maturity required for analysis; timing of analysis is driven by DFS in the stage II/IIIA population. • Allows for 2 analyses: – First analysis to be conducted at the time of the primary endpoint with a 2-sided alpha of 4% – Second analysis can be conducted at a later date if less than approximately 70 DFS events are observed in the IB population at the time of the primary analysis with a 2-sided alpha of ~1% (determined at the time of the analysis based on the exact correlation).	• Only tested if the DFS in the overall population is statistically significant (hierarchical testing approach) • Overall 2-sided 5% alpha, Haybittle-Peto spending function • Study not powered for OS • Allows for 3 analyses: – First analysis: IDMC-6 (February 2019) at the time of the futility analysis – Second analysis: IDMC-7 (April 2020) as the IDMC conducted an unplanned efficacy analysis – Third analysis: when approximately 94 deaths have been observed in the stage II-IIIA population (approximately 20% maturity) • Under the Haybittle-Peto spending function, the first and second analysis would each have a 2-sided 0.0002 alpha level, with the full 5% alpha level being exhausted at the third analysis. • No further formal testing after the third OS analysis will be conducted; an additional exploratory analysis reporting the 3-, 4-, and 5-year OS landmarks may be conducted after the final OS analysis.

Endpoint	SAP Version 2.0 - Section 4.2.2 (dated 18 December 2018)	SAP Version 4.0 - Section 7 (dated 23 June 2020)
Secondary endpoint: OS in the overall population (stage IB/II/IIIA)	• Only tested if OS in the stage II/IIIA population is statistically significant (hierarchical testing approach). • Overall 2-sided 5% alpha, Haybittle-Peto spending function. • Study not powered for OS. • No pre-specified number of events/maturity required for analysis; timing of analysis is driven by DFS in the stage II/IIIA population. The protocol notes an example of observing 195 deaths as an estimation of what may have been observed at time of there being 247 DFS events in the stage II/IIIA population under noted recruitment and follow-up time. • Allows for 2 analyses: – First analysis to be conducted at the time of the primary endpoint with a 2-sided alpha of 4% – Second analysis can be conducted at a later date if less than approximately 70 DFS events are observed in the IB population at the time of the primary analysis with a 2-sided alpha of 1%.	• Only tested if OS in the stage II/IIIA population is statistically significant (hierarchical testing approach) • Overall 2-sided 5% alpha, Haybittle-Peto spending function • Study not powered for OS • Allows for 3 analyses: – First analysis: IDMC-6 (February 2019) at the time of the futility analysis – Second analysis: IDMC-7 (April 2020) as the IDMC conducted an unplanned efficacy analysis – Third analysis: when approximately 94 deaths have been observed in the stage II-IIIA population. • Under the Haybittle-Peto spending function, the first and second analysis would each have a 2-sided 0.0002 alpha level, with the full 5% alpha level being exhausted at the third analysis. • No further formal testing after the third analysis will be conducted; an additional exploratory analysis reporting the 3-, 4-, and 5-year OS landmarks may be conducted after the final OS analysis.

Efficacy variable analyses

Disease free survival

Patients who were disease-free and alive at the time of analysis were censored at the date of their last assessment for disease recurrence. However, if the patient had a recurrence event or died immediately after 2 or more consecutive missed visits, the patient was censored at the time of the latest evaluable assessment for disease recurrence prior to the two missed visits.

Sensitivity analyses of DFS were performed to assess the presence of quantitative interactions, possible evaluation-time bias, and possible attrition bias.

DFS in the subset of patients with stage II-IIIA cancer and in the overall population (equivalent to the Full Analysis Set [FAS]) was analysed using a log rank test stratified by stage, mutation type, and race for the generation of the p-value and using the Breslow approach for handling ties. The effect of osimertinib versus placebo was estimated by the hazard ratio (HR) together with its 95% and (1-alpha) confidence intervals (CIs) and p-value. The HR and CIs were obtained directly from the U and V statistics (Berry et al 1991, Selke and Siegmund 1983). Kaplan-Meier plots of DFS in both stage II-IIIA patients and the overall population were presented by treatment group.

Subgroup analyses were conducted by comparing DFS between treatments in the following planned groups: Stage (IB, II, IIIA), EGFR mutation type (Ex19del, L858R), Race (Asian, Non-Asian), Adjuvant chemotherapy (Yes, No), Gender (Male, Female), Age at screening (<65, ≥65), and Smoking history (Never, Ever). No adjustment to the significance level for testing was made since the subgroup analysis is only supportive of the primary analysis of DFS. For each subgroup level, the HR and 95% CI are calculated from a single Cox PH model that contains a term for treatment, the subgroup covariate of interest, and the treatment by subgroup interaction term. The HR is obtained for each level of the subgroup from this model.

Overall survival

OS data were analysed using the same methodology and model as for the analysis of DFS.

Health-related Quality of Life

The scores for each of the 8 domains and for each of the PCS and MCS measures were summarised in terms of mean score and change from baseline values at each post-baseline assessment. The absolute values and change from baseline were calculated for each domain and summary scale at each scheduled post-baseline assessment. The visit response to the SF-36 at each assessment was also categorised as improved, worsened, and stable, based on the changes from baseline using the criteria for a minimum clinically important difference (MCID) as defined in the SAP (see Table below).

Table 32: SF-36 Visit response categories

	Visit response		
Score	**Improved**	**Worsened**	**Stable**
PCS	≥ + 3.1	≤ - 3.1	Otherwise
MCS	≥ + 3.8	≤ - 3.8	Otherwise
PF	≥ + 3.5	≤ - 3.5	Otherwise
RP	≥ + 3.2	≤ - 3.2	Otherwise
BP	≥ + 4.5	≤ - 4.5	Otherwise
GH	≥ + 5.7	≤ - 5.7	Otherwise
VT	≥ + 5.5	≤ - 5.5	Otherwise
SF	≥ + 5.0	≤ - 5.0	Otherwise
RE	≥ + 3.8	≤ - 3.8	Otherwise
MH	≥ + 5.5	≤ - 5.5	Otherwise

The primary HRQoL outcome measures of interest are time to deterioration of 2 aggregated summary scores (MCS and PCS). The probability of making a type I error (5% two-sided) is split equally between these two analyses. Time to deterioration in the subset of patients with stage II-IIIA cancer is analysed using a log-rank test stratified by stage, mutation type, and race using the Breslow approach for handling ties. Time to deterioration of HRQoL is defined as time from date of randomisation to the date of first clinically important worsening confirmed at the subsequent assessment, or death (by any cause) in the absence of a clinically important worsening, provided death occurs within 2 assessment visits of the last assessment where HRQoL could be evaluated, and regardless of whether the patient

withdrew from randomised therapy or received another anticancer therapy prior to symptom deterioration.

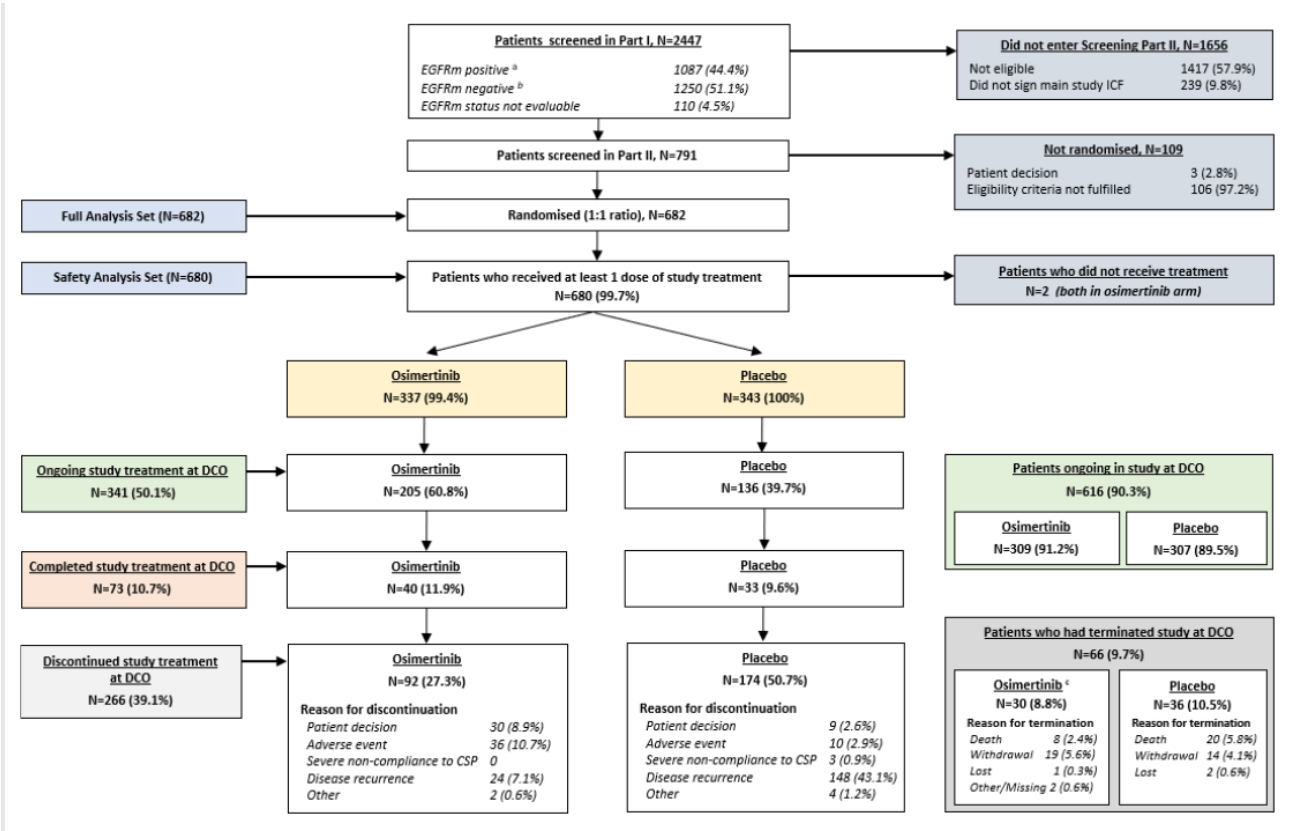
Interim analyses

Table 33: IDMC meetings and recommendations

IDMC date (meeting number)	Data cut-off date	Objective	Number of randomised patients	IDMC recommendation
31 May 2016 (IDMC-1)	18 April 2016	Safety	14	Continue study unmodified
29 November 2016 (IDMC-2)	13 October 2016	Safety	76	Continue study unmodified
30 May 2017 (IDMC-3)	07 April 2017	Safety	186	Continue study unmodified
27 February 2018 (IDMC-4)	15 December 2017	Safety	405	Continue study unmodified
20 August 2018 (IDMC-5)	18 May 2018	Safety	545	Continue study unmodified
26 February 2019 (IDMC-6)	11 December 2018	Safety and futility	655	Continue study unmodified
07 April 2020 (IDMC-7)	17 January 2020	Safety and ad hoc request to review key efficacy parameters	682	Due to the overwhelming efficacy of osimertinib, the IDMC recommended early analysis and reporting

Results

Participant flow



a EGFRm positive: Includes any EGFR mutation detected by the cobas test, not limited to Exon 19 deletions and L858R mutations.
b EGFRm negative: No EGFR mutation detected in targeted EGFR regions by the cobas test.
c One patient in the osimertinib arm (..., did not have an exact date of death recorded and had discontinuation status marked as "not answered". This patients' reason for terminating the study is classed as missing and the death is not included in this figure.
Note: The definitions of EGFRm positive and EGFRm negative above are only applicable to the classification of patients in Screening Part I.

Figure 33: Patient disposition (All patients)

In the osimertinib arm, 2 patients were randomised in error and therefore did not receive any study treatment.

Recruitment

Patients were enrolled in the study globally at 185 study centres in 24 countries across Europe (78 study sites), Asia-Pacific (89 study sites), North America (12 study sites), and South America (6 study sites in Brazil). The number of study sites per geographic region was as follows: 78 in Europe, 89 in Asia-Pacific, 12 in North America and 6 in South America.

The first subject was enrolled on 21 October 2015. The analyses provided are based on a data cut-off date of 17 January 2020 and database lock date of 24 June 2020. The study is still ongoing, at the time of DCO, enrolment was complete and all patients had been followed for at least one year.

Conduct of the study

Protocol amendments

The original study protocol (Version 1.0, dated 04 June 2015) was amended twice prior to the DCO of the current analysis. None of the amendments were implemented for safety concerns and recruitment was not held between amendments.

Table 34: Protocol amendments and other significant changes to study conduct

Number (date of internal approval)	Key details of amendment (Section of this report affected)	Reason for amendment	Person(s)/ group(s) responsible for amendment [a]
Amendments made before the start of patient recruitment			
None			
Amendments made after the start of patient recruitment			
Amendment 1 17 November 2016	CSP Section 1.4 (Study design) – Figure 1 (Study Design) was updated to clarify the screening process (Section 9.1).	Study design figure was updated to clarify Part I and Part II of the screening period.	AstraZeneca Project Team
	CSP Section 3.2 (Exclusion criteria) (Section 9.3.2): • Exclusion criterion 2 was updated to indicate that potent CYP3A4 inhibitors can be used concomitantly with the study treatment (CSP Appendix F was also revised in line with this updated recommendation). • New exclusion criterion 5 was added to reinforce Grade 1 toxicities (with the exception of alopecia and Grade 2 neuropathy related to prior platinum-therapy) should be controlled prior to study entry.	Following new data from drug-drug interaction studies, potent CYP3A4 inhibitors can be used concomitantly with the IP and they no longer need to be mentioned in the exclusion criterion 2 or CSP Appendix F. Clarification about Grade 1 toxicities related to prior therapies were included as a safeguard for potential carry-over toxicities.	AstraZeneca Project Team
	CSP Section 3.8 (Restrictions) revised to update the guidance regarding contraception, medications known to prolong QTc interval, and clarify the management of QTc prolongation, ophthalmologic findings, and overdoses (Section 9.3.3).	Restrictions regarding contraception were updated per defined safety standards for the IP. Restrictions regarding concomitant medications were updated following the availability of new data regarding drug-drug interactions.	AstraZeneca Project Team
	CSP Section 3.9 (Discontinuation of investigational product) (see Section 9.5.1), CSP Section 5.2.3 (ECG) (no corresponding CSR section), CSP Section 6.7.4 (QTc prolongation) (no corresponding CSR section), and CSP Appendix F (Guidance regarding potential interactions with Concomitant medications) (no corresponding CSR section) were updated to clarify QTc prolongation dose modification and study treatment discontinuation criteria.	Rules for IP modification/discontinuation in case of QTc prolongation were updated as per defined safety standards for the IP.	AstraZeneca Project Team
	CSP Section 4 (Study Plan and Timings of Procedures) – Table 1 (Study Plan) were made to clarify the timings of assessments at the randomisation visit (Section 9.1, Table 4).	For the randomisation visit, it was clarified that vital signs, clinical chemistry, haematology, urine analysis, and ECG assessments have to be completed pre-dose on the visit day.	AstraZeneca Project Team
	CSP Section 5.2.6.1 (Ophthalmologic exam) revised to remove requirement for full ophthalmic assessment at study entry (no corresponding CSR section).	Requirements for ophthalmologic exam were updated per defined safety standards for the IP.	AstraZeneca Project Team
	CSP Section 6.7 (General dose adjustments on adverse events) dose modification criteria clarified (no corresponding CSR section).	Rules for dose adjustments on AEs were updated per defined safety standards for the IP.	AstraZeneca Project Team
	CSP Section 6.7.5 (Interstitial lung disease) revised to describe current data collection requirements (no corresponding CSR section).	The description of data collection in case of interstitial lung disease was updated, as information will be captured directly in the eCRF and not a questionnaire. It was also clarified that all image data should be provided to AstraZeneca.	AstraZeneca Project Team
	CSP Section 6.8.1 (Independent Data Monitoring Committee) revised to allow flexibility on IDMC meeting timings (no corresponding CSR section).	It was clarified that the time windows for IDMC meetings were approximately every 6 months for the first 2 years and yearly thereafter. This allowed for time windows to be adjusted based on recruitment rate in order to guarantee proper data samples.	AstraZeneca Project Team
	CSP Section 8.4.1.7 (Health-related Quality of Life and symptoms) and CSP Section 8.5.3 (Analysis of health-related quality of life) revised to update details regarding the analysis of health-related quality of life and symptoms (no corresponding CSR section).	The minimum clinically important difference (MCID) values are not directly relevant to the adjuvant NSCLC population, and were therefore no longer collected.	AstraZeneca Project Team

Number (date of internal approval)	Key details of amendment (Section of this report affected)	Reason for amendment	Person(s)/ group(s) responsible for amendment [a]
CSP Amendment 2 01 August 2019	CSP Section 1.4 (Study design) updated to include information on the follow-up and management of patients for the different planned analyses and end of study (Section 9.1).	To clarify data collection processes.	AstraZeneca Project Team
	CSP Section 2.2 (Secondary objectives), Section 8.4.1.1 (DFS) and Section 8.5.2.1 (DFS rate) were updated to add DFS rate and OS rate for additional timepoints (Section 8 and Section 9.8.1).	To allow further interpretation of the efficacy data.	AstraZeneca Project Team
	Section 2.4 (Exploratory objectives) was revised to add a new objective pertaining to an OS extension approximately 1 year post primary analysis DCO date (Section 8). Due to this, information describing a limited data collection plan during the OS extension period was added to the study design (Section 9.1 and Table 5). CSP Section 8.1 (Statistical considerations), Section 8.5.2.2 (OS), and Section 8.5.2.3 (OS rate) were also updated (Section 9.8.1).	An OS extension period added to allow additional reporting of OS and OS rate approximately 1- year post primary analysis to understand longer-term survival data.	AstraZeneca Project Team
	Section 2.4 (Exploratory objectives) was revised to include genomic analyses beyond EGFRm in plasma samples, and more comprehensive outcome measures including specific analyses around minimal residual disease (MRD) and dynamics of DNA, RNA and/or tumour protein as a proof of principle for early prediction of disease recurrence. Furthermore, the outcome measure 'Correlation of polymorphisms with variation in pharmacodynamics, safety or response observed in patients treated with AZD9291 or comparator' was removed (Section 8).	To update information to ensure consistency of project specific standards from a safety perspective across the development programme.	AstraZeneca Project Team
	Section 3.10 (Criteria for withdrawal from study) was revised to emphasise that survival status for ongoing, withdrawn from the study, and "lost to follow-up" patients should be obtained by site personnel at the time of extended OS analysis (Section 9.5.2).	Survival sweep will be performed for extended OS analysis as well as primary analysis in order to obtain as complete data as possible.	AstraZeneca Project Team
	CSP Section 4.1.2 (Complete resection) and Section 5.1.2 (Evidence of disease recurrence) revised to clarify that although the study will be analysed according to the AJCC 7th edition, all randomised patients will be also staged at baseline and at time of disease recurrence according to the recently released AJCC 8th edition classification (no corresponding CSR section).	Due to changes in internal AstraZeneca CSP authoring standards, the reason for this amendment was not captured at the time of the CSP update.	AstraZeneca Project Team
	CSP Section 6.8.4 (QTc prolongation), Section 6.8.6 (Keratitis) and Section 6.8.7 (Changes in cardiac contractility) updated (Section 9.4.5.3).	Additional instructions added for key safety topics based on emerging osimertinib safety data.	AstraZeneca Project Team
	CSP Section 8.4.1.2 (OS) and Section 8.5.2.3 (OS rate) were updated to specify that OS rate at 2, 3 and 4 years will be also estimated in addition to the OS rate at 5 years specified in the previous CSP version (Section 9.8.1).	OS extension period added to allow additional reporting of OS and OS rate approximately 1-year post primary analysis to understand longer-term survival data. Summary measures of OS rate added at additional timepoints to allow further interpretation of the efficacy data.	AstraZeneca Project Team

[a] All protocol amendments were approved by AstraZeneca before being submitted to a regulatory authority and/or an Institutional Review Board(IRB)/Independent ethics committee (IEC).

Changes to the planned analyses that are reflected in SAP updates are shown in the following table:

Table 35: Changes to planned analyses

Key details of change (Section of this report affected)	Reason for change	Person(s)/ group(s) responsible for change
Changes made before unblinding of study data *(reflected in SAP Version 2.0; see Appendix 16.1.9)*		
The description of the PK Analysis Set was made to indicate that this analysis set is defined using Safety Analysis Set instead of the FAS, as originally specified in the CSP (Section 9.8.2.3).	Patients are only eligible for PK assessment if they have received at least 1 dose of study treatment.	AstraZeneca
List of important protocol deviations for use in the CSR finalised and defined (no corresponding CSR section).	Important protocol deviations are summarised in the CSR, therefore these needed to be clearly established	AstraZeneca
Study day definitions updated to clarify that all FAS summaries are relative to randomisation date, and all Safety Analysis Set summaries are relative to first dose (Section 9.8.1.3).	To clarify the safety analysis and efficacy analysis data sets, as safety analysis is based on patients who received at least 1 dose of study treatment and efficacy analysis is based on randomised patients	AstraZeneca
Summary measures of compliance for patient reported health-related quality of life will be produced (Section 9.8.1.4).	Added to allow the assessment of compliance for patient reported health-related quality of life through SF-36	AstraZeneca
The Healthcare Resource Use Module will be completed by sites for any healthcare resource use between visits. Variables captured for the analysis were added (Section 9.8.1.7).	Added to assess the healthcare resource used in study	AstraZeneca
OS rate will be estimated for 2, 3 and 5 years for stage II-IIIA and overall population (Section 9.8.1.3).	Summary measures of OS rate added at additional timepoints to allow further interpretation of the efficacy data.	AstraZeneca
Changes made after unblinding of study data *(reflected in SAP Version 4.0 [a]; see Appendix 16.1.9)*		
The multiple testing procedure strategy was updated (see Section 9.9.2.1)	To revise alpha allocation due to the early, unplanned primary reporting of this following IDMC recommendation and in consultation with a major health authority.	AstraZeneca
Clarification was added that data collected on the day of randomisation to be used as for baseline assessments (Section 9.8.1.3).	Add data collected on randomisation day to baseline assessments	AstraZeneca
Additional analysis of 'Time to new brain lesion or death' was added as an exploratory efficacy variable (see Section 9.9.2.2).	Added an exploratory CNS DFS analysis to assess the EGFR-TKI treatment benefits on CNS recurrence patients	AstraZeneca

[a] SAP Version 3.0 was created after unblinding; however, following Health Authority interactions regarding the MTP this was superseded by SAP Version 4.0.

Protocol deviations

Table 36: Important protocol deviations per Statistical Analysis Plan (Full analysis set)

Important protocol deviation [a]	Number (%) of patients		
	Osimertinib (N=339)	Placebo (N=343)	Total (N=682)
Number of patients with at least 1 important deviation	97 (28.6)	87 (25.4)	184 (27.0)
Patient did not fulfil the eligibility criteria	5 (1.5)	10 (2.9)	15 (2.2)
Non-compliance with Investigational Product schedule or dose	20 (5.9)	20 (5.8)	40 (5.9)
Patient received prohibited concomitant medication [b]	42 (12.4)	22 (6.4)	64 (9.4)
Lack of compliance with scanning schedule that impacts assessment of disease recurrence	48 (14.2)	45 (13.1)	93 (13.6)

[a] Important deviations before the start of treatment, during treatment, and during follow-up period.

[b] It is noted that the definition of prohibited concomitant medication in this IPD is broader than the definition used to identify disallowed concomitant medications in Table 14.1.12.2, therefore the number of patients who received a disallowed medication (see Section 10.5.1) is not concordant with the number of patients in this table.

Note that the same patient may have had more than 1 important protocol deviation. Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories.

DCO: 17 January 2020

Baseline data

Table 37: Key demographic and patient characteristics (Full Analysis Set)

Characteristic	Osimertinib (N=339)	Placebo (N=343)	Total (N=682)
Age (years)			
Mean (sd)	62.5 (10.27)	61.6 (10.46)	62.1 (10.37)
Median	64.0	62.0	63.0
Min, Max	30, 86	31, 82	30, 86
Sex, n (%)			
Male	109 (32.2%)	95 (27.7%)	204 (29.9%)
Female	230 (67.8%)	248 (72.3%)	478 (70.1%)
Race, n (%)			
White	122 (36.0%)	122 (35.6%)	244 (35.8%)
Asian	216 (63.7%)	218 (63.6%)	434 (63.6%)
Other	1 (0.3%)	2 (0.6%)	3 (0.4%)
Missing [a]	0	1 (0.3%)	1 (0.1%)
Ethnic group, n (%)			
Hispanic or Latino	12 (3.5%)	9 (2.6%)	21 (3.1%)
Asian (other than Chinese and Japanese)	78 (23.0%)	67 (19.5%)	145 (21.3%)
Chinese	95 (28.0%)	100 (29.2%)	195 (28.6%)
Japanese	46 (13.6%)	51 (14.9%)	97 (14.2%)
Other	108 (31.9%)	116 (33.8%)	224 (32.8%)
Body mass index (kg/m^2) [b]			
Mean (sd)	24.8 (4.29)	24.9 (4.36)	24.9 (4.32)
Median	24.4	24.1	24.2
Min, Max	15.1, 41.8	16.6, 42.0	15.1, 42.0

[a] One patient had missing race information due to local law

[b] Body mass index = weight(kg)/[height(m)]^2

DCO: 17 January 2020

Table 38: Key disease characteristics (Full Analysis Set)

Characteristic	Number (%) of patients		
	Osimertinib (N=339)	Placebo (N=343)	Total (N=682)
WHO performance status			
0	216 (63.7)	218 (63.6)	434 (63.6)
1	123 (36.3)	125 (36.4)	248 (36.4)
AJCC stage at diagnosis [a, b]			
IB	107 (31.6)	109 (31.8)	216 (31.7)
IIA	86 (25.4)	90 (26.2)	176 (25.8)
IIB	29 (8.6)	26 (7.6)	55 (8.1)
IIIA	117 (34.5)	118 (34.4)	235 (34.5)
EGFR mutations by central cobas test [c]			
Exon 19 deletions	185 (54.6)	188 (54.8)	373 (54.7)
L858R	153 (45.1) [d]	155 (45.2)	308 (45.2)
Histology type			
Adenocarcinoma: acinar	85 (25.1)	82 (23.9)	167 (24.5)
Adenocarcinoma: papillary, malignant	43 (12.7)	44 (12.8)	87 (12.8)
Adenocarcinoma: malignant	183 (54.0)	188 (54.8)	371 (54.4)
Adenocarcinoma: bronchiolo-alveolar	11 (3.2)	13 (3.8)	24 (3.5)
Adenocarcinoma: solid with mucous formation	4 (1.2)	5 (1.5)	9 (1.3)
Bronchial gland carcinoma (NOS)	1 (0.3)	2 (0.6)	3 (0.4)
Carcinoma, adenosquamous, malignant	4 (1.2)	5 (1.5)	9 (1.3)
Other	8 (2.4)	4 (1.2)	12 (1.8)
Lung cancer resection type			
Lobectomy	328 (96.8)	322 (93.9)	650 (95.3)
Sleeve Resection	1 (0.3)	3 (0.9)	4 (0.6)
Bilobectomy	7 (2.1)	8 (2.3)	15 (2.2)
Pneumonectomy	3 (0.9)	10 (2.9)	13 (1.9)

[a] AJCC TNM lung cancer staging 7th edition.

[b] Note: These data are derived from the eCRF, and differ from the number of patients recorded with each disease stage in the IVRS (see Table 23 for details of numbers within each disease stage captured in the IVRS).

[c] Patients may have more than one EGFR mutation. Note: There were 10 mis-stratified patients in the IVRS. The data presented here show actual numbers confirmed by prospective central testing.

[d] Note: One patient was negative for both mutations and was discontinued from the study before receiving osimertinib.

DCO: 17 January 2020

In addition to the data presented in above table, it is worth noting that 11.4% (78/682) of patients were 75 years or older and 72% were never smokers. ST68I was present in one patient in the placebo arm and there were 9 patients with T790M (4 [1.2%] in the osimertinib arm and 5 [1.5%] in the placebo arm).

Medical and surgical history (excluding lung resection)

The most frequently reported medical history events (ie, with an incidence of at least 10% in any treatment group) were hypertension (osimertinib: 41.9%; placebo: 40.5%), cough (osimertinib: 12.4%; placebo: 11.4%), Type 2 diabetes mellitus (osimertinib: 11.8%; placebo: 10.5%), cataract (osimertinib: 9.1%; placebo: 10.2%), and hyperlipidaemia (osimertinib: 10.0%; placebo: 7.0%).

Prior anti-cancer therapies (including post-operative adjuvant chemotherapy)

A summary of post-operative adjuvant chemotherapy use, by disease stage at diagnosis, is provided in the table below.

The median number of adjuvant chemotherapy cycles received was 4.0 in both the stage IB and stage II-IIIA patient populations in both treatment arms, which is in line with the maximum allowed number of treatment cycles per protocol.

Table 39: Post-operative adjuvant platinum-based chemotherapy use, by stage (Full analysis set)

AJCC Stage [a]	Number (%) of patients		
	Osimertinib (N=339)	Placebo (N=343)	Total (N=682)
Number of patients with adjuvant platinum-based chemotherapy [b]	202 (59.6)	207 (60.3)	409 (60.0)
IB [c]	27 (25.2)	30 (27.5)	57 (26.4)
Non-IB [c]	175 (75.4)	177 (75.6)	352 (75.5)
IIA [c]	60 (69.8)	65 (72.2)	125 (71.0)
IIB [c]	20 (69.0)	20 (76.9)	40 (72.7)
IIIA [c]	95 (81.2)	92 (78.0)	187 (79.6)

[a] AJCC TNM lung cancer staging 7th edition, as recorded in the eCRF.
[b] Excludes 1 patient who received non-platinum based adjuvant chemotherapy
[c] Percentages are calculated from number of patients in FAS with the corresponding AJCC Staging
DCO: 17 January 2020

Per study exclusion criteria, all patients receiving prior anticancer treatment for NSCLC were treated with a standard platinum-based doublet post-operative adjuvant chemotherapy regimen, with the exception of 1 patient. A single patient received only single agent non-platinum chemotherapy (pemetrexed) as adjuvant treatment with an adjunct traditional Chinese medicine (which was recorded as an important protocol deviation).

Table 40: Prior anti-cancer therapies (Full analysis set)

ATC classification / Generic term	Number (%) of patients		
	AZD9291 (N=339)	Placebo (N=343)	Total (N=682)
Number of patients with a prior anti-cancer therapy	203 (59.9)	207 (60.3)	410 (60.1)
FOLIC ACID ANALOGUES	54 (15.9)	61 (17.8)	115 (16.9)
PEMETREXED	40 (11.8)	42 (12.2)	82 (12.0)
PEMETREXED DISODIUM	14 (4.1)	19 (5.5)	33 (4.8)
PLATINUM COMPOUNDS	202 (59.6)	207 (60.3)	409 (60.0)
CARBOPLATIN	75 (22.1)	64 (18.7)	139 (20.4)
CISPLATIN	131 (38.6)	144 (42.0)	275 (40.3)
NEDAPLATIN	3 (0.9)	5 (1.5)	8 (1.2)
PODOPHYLLOTOXIN DERIVATIVES	9 (2.7)	4 (1.2)	13 (1.9)
ETOPOSIDE	9 (2.7)	4 (1.2)	13 (1.9)
PYRIMIDINE ANALOGUES	9 (2.7)	10 (2.9)	19 (2.8)
GEMCITABINE	5 (1.5)	8 (2.3)	13 (1.9)
GEMCITABINE HYDROCHLORIDE	4 (1.2)	2 (0.6)	6 (0.9)
TAXANES	39 (11.5)	31 (9.0)	70 (10.3)
DOCETAXEL	8 (2.4)	12 (3.5)	20 (2.9)
PACLITAXEL	30 (8.8)	20 (5.8)	50 (7.3)
PACLITAXEL LIPOSOME	2 (0.6)	0	2 (0.3)
VINCA ALKALOIDS AND ANALOGUES	92 (27.1)	101 (29.4)	193 (28.3)
VINORELBINE	43 (12.7)	49 (14.3)	92 (13.5)
VINORELBINE TARTRATE	49 (14.5)	52 (15.2)	101 (14.8)

A patient can have one or more generic terms reported under a given ATC text.
Includes post-operative adjuvant anti-cancer therapy that stopped prior to the first dose of study treatment.
WHO Drug Dictionary version WHODrug B3 Sep-19.

Concomitant medication after study entry

The majority of patients (317 patients [93.5%] in the osimertinib arm and 316 patients [92.1%] in the placebo arm) received at least 1 allowed concomitant medications during the study. The most

commonly used concomitant medications (reported for at least 20% of patients in either treatment arm) are summarised in Table 41. The incidence of concomitant medication use, and the types of medications received, were well balanced between treatment arms.

Two (0.6%) patients in the placebo arm received a disallowed concomitant medication (carbamazepine) during study treatment, which were also considered as important protocol deviations.

Table 41: Allowed concomitant medications post randomisation (at least 20% of patients in either treatment arm) (Full Analysis Set)

Generic term	Osimertinib (N=339)	Placebo (N=343)	Total (N=682)
Anilides	96 (28.3)	79 (23.0)	175 (25.7)
Paracetamol	74 (21.8)	57 (16.6)	131 (19.2)
Proton pump inhibitors	86 (25.4)	84 (24.5)	170 (24.9)
Unspecified herbal and traditional medicine	79 (23.3)	75 (21.9)	154 (22.6)

A patient can have one or more generic terms reported under a given ATC text.
Includes medications which are ongoing or with a stop date on or after the first dose date of study treatment (and which started prior to or during study treatment).
WHO Drug Dictionary version WHODrug B3 Sep-19.
DCO: 17 January 2020

Numbers analysed

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

Table 42: Analysis sets

	Number of patients		
	Osimertinib	Placebo	Total
Patients included in Full Analysis Set	339	343	682
Patients included in the FAS with Stage II-IIIA disease [a]	233	237	470
Patients included in Safety Analysis Set	337	343	680
Patients excluded from Safety Analysis Set	2	0	2
Did not receive treatment	0	0	0
Randomised in error	2	0	2
Patients included in Pharmacokinetic Analysis Set	325	0	325
Patients excluded from Pharmacokinetic Analysis Set	14	343	357
Patient did not take osimertinib	0	343	343
Patient has no PK data	12	0	12
Patient not in safety population	2	0	2

[a] It is noted that whilst this patient population was not predefined as an analysis population in the SAP, it is used for the discussion of the primary endpoint throughout this CSR.
Full Analysis Set - All randomised patients.
Safety Analysis Set - All patients who received at least one dose of treatment.
PK Analysis Set - All patients in the safety analysis set who received osimertinib and have at least 1 measurable PK concentration, supported by the relevant date and time of this sample.
DCO: 17 January 2020

Outcomes and estimation

Primary endpoint*: *Disease-free survival (DFS)

- Disease-free survival in the stage II-IIIA population

At the DCO of the current analysis, in patients with stage II-IIIA disease, the majority of patients (98.7%) had had the opportunity for at least 1-year of follow-up, with 61.1% of patients having had the opportunity for at least 2 years of follow-up, and 18.3% of patients having had the opportunity for at least 3-years of follow-up.

Table 43: Disease free survival (Full Analysis Set: Stage II-IIIA patients)

	Osimertinib (N=233)	Placebo (N=237)
Recurrence or death, n (%)		
Number (%) of patients with recurrence events [a]	26 (11.2)	130 (54.9)
Disease recurrence	26 (11.2)	129 (54.4)
Local/regional only	17 (7.3)	48 (20.3)
Distant only	8 (3.4)	67 (28.3)
Local/regional and Distant	1 (0.4)	14 (5.9)
Death [b]	0	1 (0.4)
Comparison between groups [c]		
Hazard ratio (95% CI)	0.17 (0.12, 0.23)	
Adjusted 99.06% CI [d]	0.11, 0.26	
2-sided p-value	< 0.0001	
Median disease-free survival		
Median disease-free survival (months) [e]	NC	19.6
95% CI for median disease-free survival	38.8, NC	16.6, 24.5

	Osimertinib (N=233)	Placebo (N=237)
Disease-free survival rate at 6 months (%) (95% CI)	99.1 (96.5, 99.8)	83.1 (77.6, 87.3)
Disease-free survival rate at 12 months (%) (95% CI)	97.2 (93.9, 98.7)	60.8 (54.1, 66.8)
Disease-free survival rate at 18 months (%) (95% CI)	90.9 (85.7, 94.3)	51.7 (44.8, 58.2)
Disease-free survival rate at 24 months (%) (95% CI)	89.5 (84.0, 93.2)	43.6 (36.5, 50.6)
Disease-free survival rate at 36 months (%) (95% CI) [f]	78.3 (64.5, 87.3)	27.9 (18.9, 37.6)
Median follow-up for disease-free survival in all patients (months) [g]	22.1	14.9
Median follow-up for disease-free survival in censored patients (months) [h]	22.1	21.9
No recurrence or death, n (%)		
Total	207 (88.8)	107 (45.1)
Censored due to alive and disease recurrence free [i]	196 (84.1)	100 (42.2)
Censored due to no evaluable assessments or no baseline data [j]	3 (1.3)	4 (1.7)
Censored due to 2 or more missed visits before recurrence or death [k]	0	1 (0.4)
Censored due to lost to follow-up [i]	0	1 (0.4)
Censored due to withdrawn consent [i]	8 (3.4)	0
Censored due to evidence of disease at study entry [l]	0	1 (0.4)

[a] Disease-free survival events are type of disease recorded as local/regional or distant, or death. Disease-free survival events that do 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] Death in the absence of disease recurrence, or death occurring within 2 visits of baseline where the patient has no evaluable assessments or no baseline data.

[c] Patients who had evidence of disease at study entry have been censored at day 1. The analysis was performed using a log rank test stratified by stage (II versus IIIA), race (Asian versus Non-Asian) and mutation type (Ex19del versus L858R). Stratification factors are as recorded in IVRS. A HR < 1 favours osimertinib. The HR and CI are obtained directly from the U and V statistics (Berry et al 1991; Selke and Siegmund 1983).

[d] The adjusted CI is computed at the 2-sided 99.06% level, considering a 2-sided significance level of 0.0094 for the interim analysis, based on the O Brien and Fleming spending function, assuming 247 DFS events would have been observed for the final analysis.

[e] Calculated using the KM method.

[f] The number of patients at risk at 36 months was 18 patients in the osimertinib arm, and 9 patients in the placebo arm.

[g] Calculated as the median time from randomisation to date of disease recurrence events or to date of censoring in all patients.

[h] Calculated as the median time from randomization to date of censoring (date last known to have not recurred) in censored (not recurred) patients only.

[i] Patients censored at last evaluable assessment for disease recurrence.

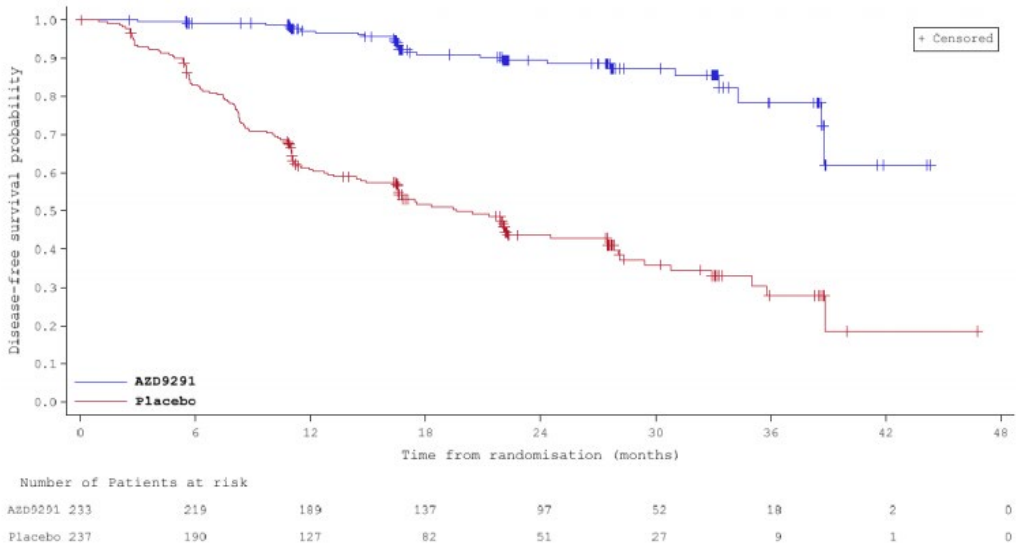
[j] Patients censored at day 1.

[k] Patients censored at last evaluable assessment for disease recurrence prior to the two missed visits.

[l] Patients who had evidence of disease at study entry have been censored at day 1.

Source: Table 14.2.1.4, ADAURA CSR, Module 5.3.5.1; Table 14.2.1.5, ADAURA CSR, Module 5.3.5.1; Table 14.2.1.1, ADAURA CSR, Module 5.3.5.1

Figure 34. Kaplan-Meier plot of disease-free survival (Full Analysis Set: Stage II-IIIA patients)



The values at the base of the figure indicate number of patients at risk.
DCO: 17 January 2020

Table 44: Treatment status at disease recurrence or death (Full Analysis Set: Stage II-IIIA patients)

	Number (%) of patients [a]	
	AZD9291 (N=233)	Placebo (N=237)
Patients who have had disease recurrence or died		
n	26	130
On treatment at time of disease recurrence	15 (57.7)	122 (93.8)
Died on treatment	0	1 (0.8)
Discontinued treatment prior to disease recurrence	11 (42.3)	7 (5.4)
Died following discontinuation of treatment	0	0
Completed treatment prior to disease recurrence	0	0
Died after completing treatment	0	0
Did not receive treatment	0	0
Patients who have not had disease recurrence and did not die (censored)		
n	207	107
On treatment	170 (82.1)	98 (91.6)
Discontinued treatment	23 (11.1)	2 (1.9)
Completed treatment	13 (6.3)	7 (6.5)
Did not receive treatment	1 (0.5)	0

[a] Percentages are calculated from the number of patients who have/have not had disease-free survival event.
A window of 28 days is used to assess if patients were still on treatment at date of disease recurrence, death or date of censoring.
Patients who had evidence of disease at study entry have been censored at day 1.

The majority of the censored patients were censored within 26 weeks prior to the DCO, and the proportion was similar in both arms (osimertinib: 190/207 [91.8%]; placebo: 97/107 [90.7%]).

Differences in the timing of disease recurrence was noted between treatment arms.

- In the osimertinib arm, 24 patients (92.3% of the patients with disease recurrence) had recurrence within the protocol-specified 36 months of study treatment, with the remaining 2 patients (7.7%) having recurrence after the protocol-specified 36 months of study treatment.
- In the placebo arm, 129 patients (99.2% of the patients with disease recurrence) had recurrence within the protocol-specified 36 months of study treatment, with the remaining 1 patient (0.8%) having recurrence after the protocol-specified 36 months of study treatment.

- Disease-free survival in the overall population

At the DCO, almost all patients (99.1%) in the overall study population (FAS) had had the opportunity for at least 1 year of follow-up, with 65.1% of patients having had the opportunity for at least 2 years of follow-up, and 19.5% of patients having had the opportunity for at least 3 years of follow-up.

The majority of the censored patients were censored within 26 weeks prior to the DCO, and the proportion was similar in both arms (osimertinib: 268/302 [88.7%]; placebo: 167/184 [90.8%]).

Table 45: Disease free survival (Full Analysis Set: Overall population)

	Number (%) of patients	
	Osimertinib (N=339)	Placebo (N=343)
Recurrence or death		
Number (%) of patients with events [a]	37 (10.9)	159 (46.4)
Disease recurrence	37 (10.9)	157 (45.8)
Local/regional only	23 (6.8)	61 (17.8)
Distant only	10 (2.9)	78 (22.7)
Local/regional and Distant	4 (1.2)	18 (5.2)
Death [b]	0	2 (0.6)
Comparison between groups [c]		
Hazard ratio (95% CI)	0.20 (0.15, 0.27)	
99.12% CI [d]	0.14, 0.30	
2-sided p-value	< 0.0001	
Median disease-free survival		
Median disease-free survival (months) [e]	NC	27.5
95% CI for median disease-free survival	NC, NC	22.0, 35.0
Disease-free survival rate at 6 months (%) (95% CI)	99.1 (97.2, 99.7)	86.3 (82.1, 89.5)
Disease-free survival rate at 12 months (%) (95% CI)	97.4 (94.9, 98.7)	68.5 (63.2, 73.2)
Disease-free survival rate at 18 months (%) (95% CI)	91.6 (87.6, 94.4)	60.2 (54.6, 65.4)
Disease-free survival rate at 24 months (%) (95% CI)	89.1 (84.5, 92.4)	52.4 (46.4, 58.1)
Disease-free survival rate at 36 months (%) (95% CI) [f]	78.9 (68.7, 86.1)	40.0 (32.1, 47.8)
Median follow-up for disease-free survival in all patients (months) [g]	22.1	16.6
Median follow-up for disease-free survival in censored patients (months) [h]	22.1	22.1
No recurrence or death, n (%)		
Total	302 (89.1)	184 (53.6)
Censored due to alive and disease recurrence free [i]	279 (82.3)	175 (51.0)
Censored due to no evaluable assessments or no baseline data [j]	8 (2.4)	4 (1.2)
Censored due to 2 or more missed visits before recurrence or death [k]	0	1 (0.3)
Censored due to lost to follow-up [i]	0	1 (0.3)
Censored due to withdrawn consent [i,]	14 (4.1) [l]	0
Censored due to evidence of disease at study entry [m]	1 (0.3)	3 (0.9)

[a] Disease-free survival events are type of disease recorded as local/regional or distant, or death. Disease-free survival events that do 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] Death in the absence of disease recurrence, or death occurring within 2 visits of baseline where the patient has no evaluable assessments or no baseline data.

[c] Patients who had evidence of disease at study entry have been censored at day 1. The analysis was performed using a log rank test stratified by stage (II versus IIIA), race (Asian versus Non-Asian) and mutation type (Ex19del versus L858R). Stratification factors are as recorded in IVRS. A hazard ratio < 1 favours osimertinib. The HR and CI are obtained directly from the U and V statistics (Berry et al 1991; Selke and Siegmund 1983).

[d] The adjusted CI is computed at the 2-sided 99.06% level, considering a 2-sided significance level of 0.0094 for the interim analysis, based on the O Brien and Fleming spending function, assuming 247 DFS events would have been observed for the final analysis.

[e] Calculated using the Kaplan-Meier method.

[f] The number of patients at risk at 36 months was 27 patients in the osimertinib arm, and 20 patients in the placebo arm.

[g] Calculated as the median time from randomisation to date of disease recurrence events or to date of censoring in all patients.

[h] Calculated as the median time from randomization to date of censoring (date last known to have not recurred) in censored (not recurred) patients only.

[i] Patients censored at last evaluable assessment for disease recurrence.

[j] Patients censored at day 1.

[k] Patients censored at last evaluable assessment for disease recurrence prior to the two missed visits.

[l] Given the observed imbalance in this reason for censoring, further review of these data were performed. Upon review, no pattern of the reasons for withdrawal of consent were noted for patients in the osimertinib treatment arm.

[m] Patients who had evidence of disease at study entry have been censored at day 1.

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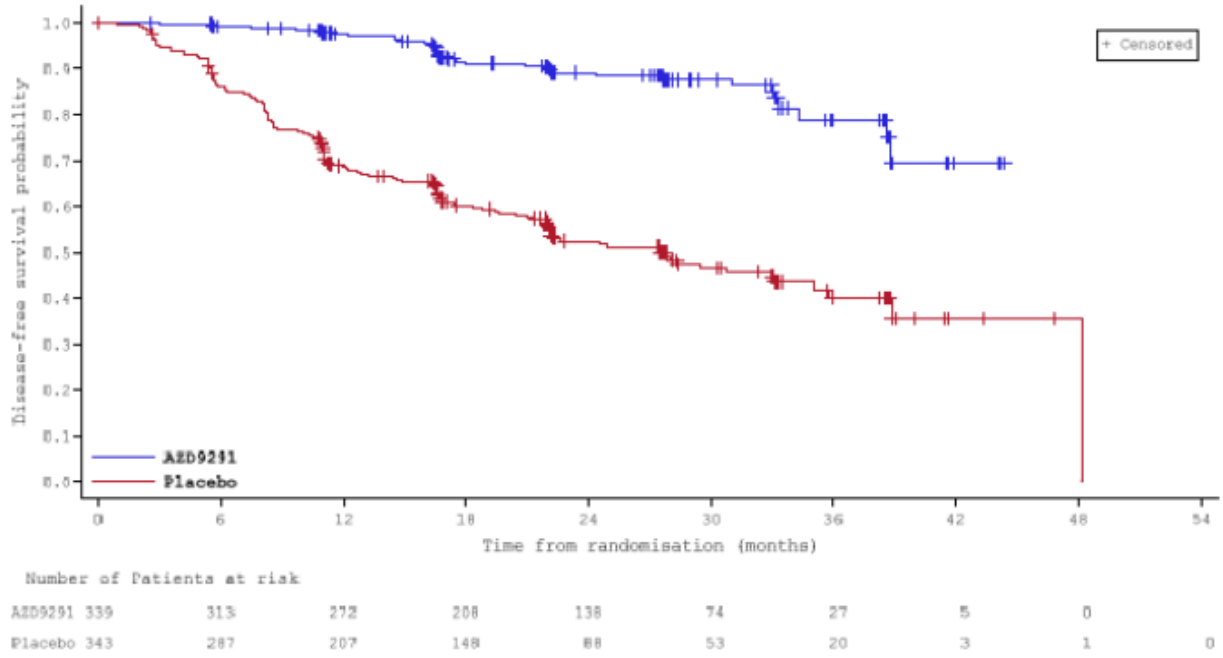


The values at the base of the figure indicate number of patients at risk.
DCO: 17 January 2020

Figure 35: Kaplan-Meier plot of disease-free survival (Full Analysis Set: Overall population)

Table 46: Treatment status at disease recurrence or death (Full analysis set: overall population)

	Number (%) of patients [a]	
	AZD9291 (N=339)	Placebo (N=343)
Patients who have had disease recurrence or died		
n	37	159
On treatment at time of disease recurrence	24 (64.9)	149 (93.7)
Died on treatment	0	1 (0.6)
Discontinued treatment prior to disease recurrence	13 (35.1)	8 (5.0)
Died following discontinuation of treatment	0	1 (0.6)
Completed treatment prior to disease recurrence	0	0
Died after completing treatment	0	0
Did not receive treatment	0	0
Patients who have not had disease recurrence and did not die (censored)		
n	302	184
On treatment	244 (80.8)	162 (88.0)
Discontinued treatment	36 (11.9)	5 (2.7)
Completed treatment	20 (6.6)	17 (9.2)
Did not receive treatment	2 (0.7)	0

[a] Percentages are calculated from the number of patients who have/have not had disease-free survival event.
A window of 28 days is used to assess if patients were still on treatment at date of disease recurrence, death or date of censoring.
Patients who had evidence of disease at study entry have been censored at day 1.

Differences in the timing of disease recurrence was noted between treatment arms.

- In the osimertinib arm, 35 patients (94.6% of the patients with disease recurrence) had recurrence within the protocol-specified 36 months of study treatment, with the remaining 2 patients (5.4%) having recurrence after the protocol-specified 36 months of study treatment.

- In the placebo arm, 157 patients (98.7% of the patients with disease recurrence) had recurrence within the protocol-specified 36 months of study treatment, with the remaining 2 patients (1.3%) having recurrence after the protocol-specified 36 months of study treatment.

Secondary endpoints

- Overall survival (OS)

Per the MTP, OS was formally tested in the stage II-IIIA patients at the current DCO.

Table 47: Overall survival analysis

Stage II-IIIA patients	**Osimertinib (N=233)**	**Placebo (N=237)**
Number (%) of patients with events [a]	8 (3.4)	17 (7.2)
Hazard ratio (95% CI) [b]	0.40 (0.18, 0.89)	
99.98% CI [c]	0.09, 1.83	
2-sided p-value	0.0244	
Median OS (months) (95% CI) [d]	NC (NC, NC)	NC (NC, NC)
OS rate at 2 years(%) (95% CI) [d]	100 (100, 100)	92.6 (87.6, 95.6)
OS rate at 3 years(%) (95% CI) [d]	91.7 (82.4, 96.2)	89.0 (82.1, 93.3)
Median follow-up for OS in all patients (months) [e]	26.1	24.6
Median follow-up for OS in censored patients (months) [f]	26.1	25.2

Number (%) of patients with events [a]	9 (2.7)	20 (5.8)
Hazard ratio (95% CI) [b]	0.48 (0.23, 1.02)	
99.98% CI [c]	0.12, 1.98	
2-sided p-value	0.0553	
Median OS (months) (95% CI) [d]	NC (NC, NC)	48.2 (48.2, NC)
OS rate at 2 years(%) (95% CI) [d]	99.6 (96.9, 99.9)	94.7 (91.4, 96.8)
OS rate at 3 years(%) (95% CI) [d]	93.9 (87.4, 97.1)	91.8 (87.1, 94.9)
Median follow-up for OS in all patients (months) [e]	26.1	25.9
Median follow-up for OS in censored patients (months) [f]	26.1	26.5

[a] Overall survival events that do 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] The analysis was performed using a log rank test stratified by stage (II versus IIIA), race (Asian versus Non-Asian) and mutation type (Ex19del versus L858R). Stratification factors are as recorded in IVRS. A hazard ratio < 1 favours AZD9291. The HR and CI are obtained directly from the U and V statistics (Berry et al 1991; Selke and Siegmund 1983).

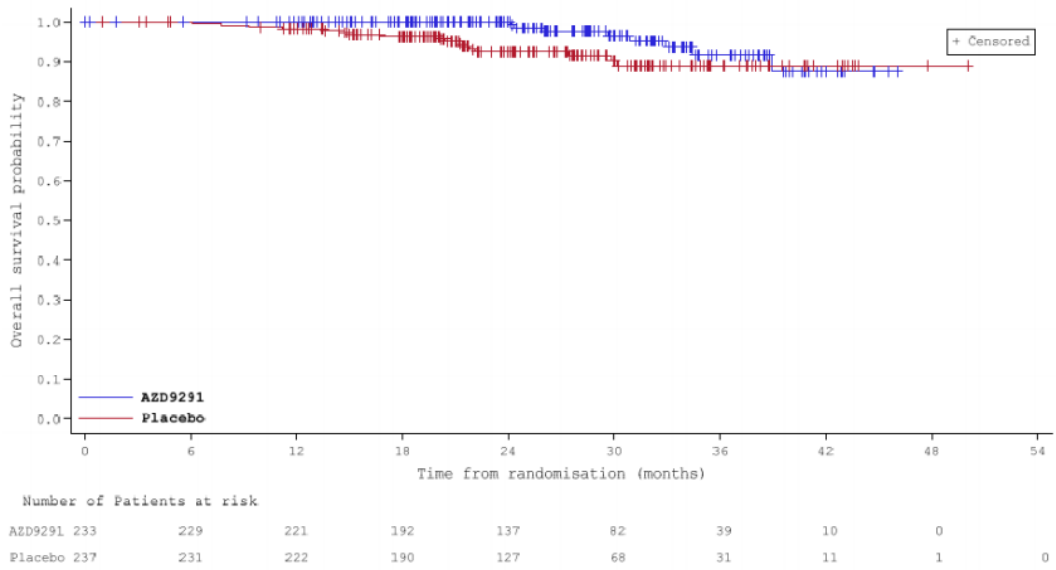
[c] The adjusted CI is computed at the 2-sided 99.98% level, considering a 2-sided significance level of 0.0002 for the interim analysis, based on the Haybittle-Peto spending function.

[d] Calculated using the KM method.

[e] Time from randomisation to date of death or to date of censoring for censored patients.

[f] Time from randomisation to date of censoring (date last known to be alive) for patients who have not died at the time of analysis.

DCO: 17 January 2020

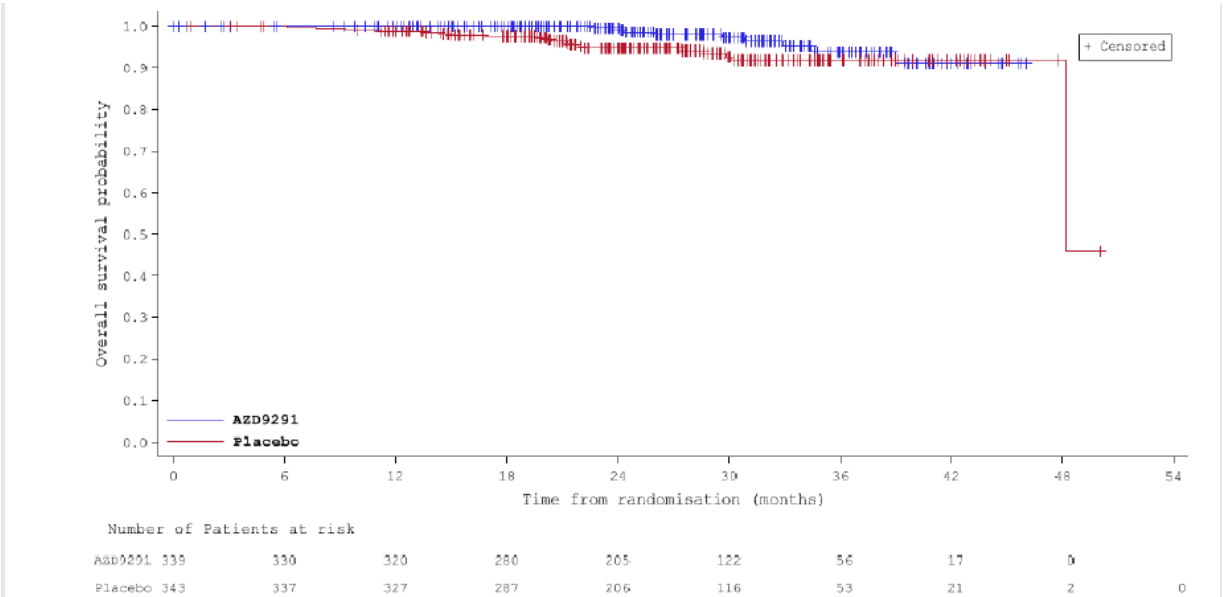


The values at the base of the figure indicate number of patients at risk.
DCO: 17 January 2020

Figure 36: Kaplan-Meier plot of overall survival (Full Analysis Set: Stage II-IIIA patients)

As OS did not reach statistical significance in the primary population, the OS analysis in the overall population is exploratory. In this population, 9 patients (2.7%) in the osimertinib arm and 20 patients (5.8%) in the placebo arm had experienced an OS event. The HR was 0.48 (99.98% CI: 0.12, 1.98; p = 0.0553).

The majority of patients were still in survival follow up (616 patients [90.3%) overall: 309 patients [91.2%] in the osimertinib arm, and 307 patients [89.5%] in the placebo arm).



The values at the base of the figure indicate number of patients at risk.
DCO: 17 January 2020
Source: Figure 14.2.4.4

Figure 37: Kaplan-Meier plot of overall survival (Full Analysis Set: Overall population)

- Patient reported outcomes/Health-related quality of life

Table 48: Compliance with SF-36 by visit (Full analysis set)

Group	Visit	Expected forms [a]	Received forms	Evaluated forms [b]	Compliance rate (%) [c]	Evaluability rate (%) [d]
AZD9291 (N=339)	Baseline	338	314	314	92.9	100.0
	Week 12	316	312	312	98.7	100.0
	Week 24	298	294	294	98.7	100.0
	Week 48	284	280	280	98.6	100.0
	Week 72	236	228	228	96.6	100.0
	Week 96	180	177	177	98.3	100.0
	Week 120	118	114	114	96.6	100.0
	Week 144	61	58	58	95.1	100.0
	Week 156	39	34	34	87.2	100.0
	Treatment Discontinuation	87	71	71	81.6	100.0
Group	Visit	Expected forms [a]	Received forms	Evaluated forms [b]	Compliance rate (%) [c]	Evaluability rate (%) [d]
Placebo (N=343)	Baseline	341	316	316	92.7	100.0
	Week 12	329	324	324	98.5	100.0
	Week 24	301	295	295	98.0	100.0
	Week 48	241	233	233	96.7	100.0
	Week 72	189	183	183	96.8	100.0
	Week 96	136	132	132	97.1	100.0
	Week 120	81	80	80	98.8	100.0
	Week 144	49	46	46	93.9	100.0
	Week 156	33	28	28	84.8	100.0
	Treatment Discontinuation	163	121	121	74.2	100.0

[a] One at baseline, one at withdrawal, and one at each scheduled visit.
[b] The number of forms where items can be determined (i.e. a questionnaire with a completion date and at least one domain that is non-missing).
[c] The number of evaluable forms divided by the number of expected forms x100.
[d] The number of evaluable forms divided by the number of received forms x100.

Baseline SF-36 scores, including both individual health domains and component scores, were comparable between study arms. Mean baseline Physical Component Summary (PCS) scores (47.089 [sd 7.350] in the osimertinib, and 46.605 [sd 7.353] in the placebo arm) and Mental Component Summary (MCS) scores (46.369 [sd 10.352] in the osimertinib, and 46.823 [sd 10.787] in the placebo

arm) indicated that patients enrolled in ADAURA were highly functioning in terms of physical and mental subcomponent of health-related quality of life, with relatively small degree of impairment in comparison to the general population (0.3 - 0.4 standard deviations below the general population normative mean values). Greatest impairment (scores < 46) was observed in the following SF-36 health domains: Role Limitations-Physical, Social Functioning and Role Limitations-Emotional.

Health-related quality of life, as measured by SF-36 health domains and component summary scores, was maintained overall in both treatment arms.

The proportion of patients reporting clinically relevant improvements in PCS over time increased in both osimertinib and placebo arms from Week 12 (29.9% vs. 33.2%) to Week 48 (41% vs. 50.2%), declined transiently at Week 72 (38.7% vs. 50.0%), and again increased at Week 96 (43.0% vs. 53.2%). In both the osimertinib and placebo arms, the proportion of patients reporting clinically meaningful improvement in MCS increased from Week 12 (34.4% vs. 41.5%) to Week 48 (46.4% vs. 49.3%), followed by a trend of decline to Week 96 (37.0% vs. 44.4%).

Time to deterioration in PCS and MCS (stage II-IIIA patients)

At least 70% of stage II-IIIA patients in either arm did not experience a clinically meaningful deterioration in the PCS or death (osimertinib: 70.0%; placebo: 75.9%), or a clinically meaningful deterioration in the MCS or death (osimertinib: 70.2%; placebo: 70.7%) up to month 30 after they were randomised.

Table 49: Summary of SF-36 - Time to deterioration (Full Analysis Set: Stage II-IIIA patients)

	Osimertinib (N=233)	Placebo (N=237)
Physical Component Summary		
Total number of patients with confirmed deterioration or death	58 (24.9)	39 (16.5)
Deterioration	57 (24.5)	37 (15.6)
Death	1 (0.4)	2 (0.8)
Median deterioration free survival (95% CI)	NC (NC, NC)	NC (NC, NC)
Proportion of patients who are deterioration free (95% CI)		
6 months	78.5 (72.4, 83.5)	89.4 (84.4, 92.8)
12 months	76.4 (70.0, 81.6)	82.1 (75.5, 87.1)
18 months	74.4 (67.8, 79.9)	77.4 (69.8, 83.4)
24 months	72.5 (65.5, 78.4)	75.9 (67.7, 82.3)
30 months	70.0 (62.2, 76.4)	75.9 (67.7, 82.3)
Comparison between groups [a]		
Hazard ratio (95% CI)	1.43 (0.96, 2.13)	
Adjusted 97.5% CI [b]	0.90, 2.25	
2-sided p-value	0.0817	
Mental Component Summary		
Total number of patients with confirmed deterioration or death	52 (22.3)	52 (21.9)
Deterioration	51 (21.9)	49 (20.7)
Death	1 (0.4)	3 (1.3)
Median deterioration free survival (95% CI)	39.0 (NC, NC)	NC (NC, NC)
Proportion of patients who are deterioration free (95% CI)		
6 months	83.6 (77.9, 88.0)	81.1 (75.2, 85.8)
12 months	80.9 (74.8, 85.6)	77.1 (70.4, 82.4)
18 months	77.3 (70.6, 82.7)	73.4 (66.1, 79.4)
24 months	74.5 (67.3, 80.4)	70.7 (62.5, 77.4)
30 months	70.2 (60.9, 77.8)	70.7 (62.5, 77.4)
Comparison between groups [a]		
Hazard ratio (95% CI)	0.90 (0.61, 1.33)	
Adjusted 97.5% CI [b]	0.58, 1.40	
2-sided p-value	0.5949	

[a] The analysis was performed using a log rank test stratified by stage (II versus IIIA), race (Asian versus Non-Asian) and mutation type (Ex19del versus L858R). A hazard ratio < 1 favours AZD9291. The HR and CI are obtained directly from the U and V statistics (Berry et al 1991; Selke and Siegmund 1983). Calculated using the Kaplan-Meier method.

[b] Adjusted confidence interval. This analysis is not included in multiple testing procedure.

Time to deterioration of HRQoL is defined as time from date of randomization to the date of first clinically important worsening confirmed at the subsequent assessment, or death (by any cause) in the absence of a clinically important worsening, provided death occurs within two assessment visits of the last assessment where HRQoL could be evaluated and regardless of whether the patients withdraws from randomized therapy or receives another anticancer therapy prior to symptom deterioration. Summary statistics are calculated using the Kaplan-Meier method. Patients with two missed visits prior to confirmed deterioration were censored at last evaluable assessment prior to the two missed visits.

DCO: 17 January 2020

Exploratory endpoints

- Time to first subsequent therapy or death (TFST)

Table 55: Median time to first subsequent anti-cancer therapy or death (Full analysis set: overall population)

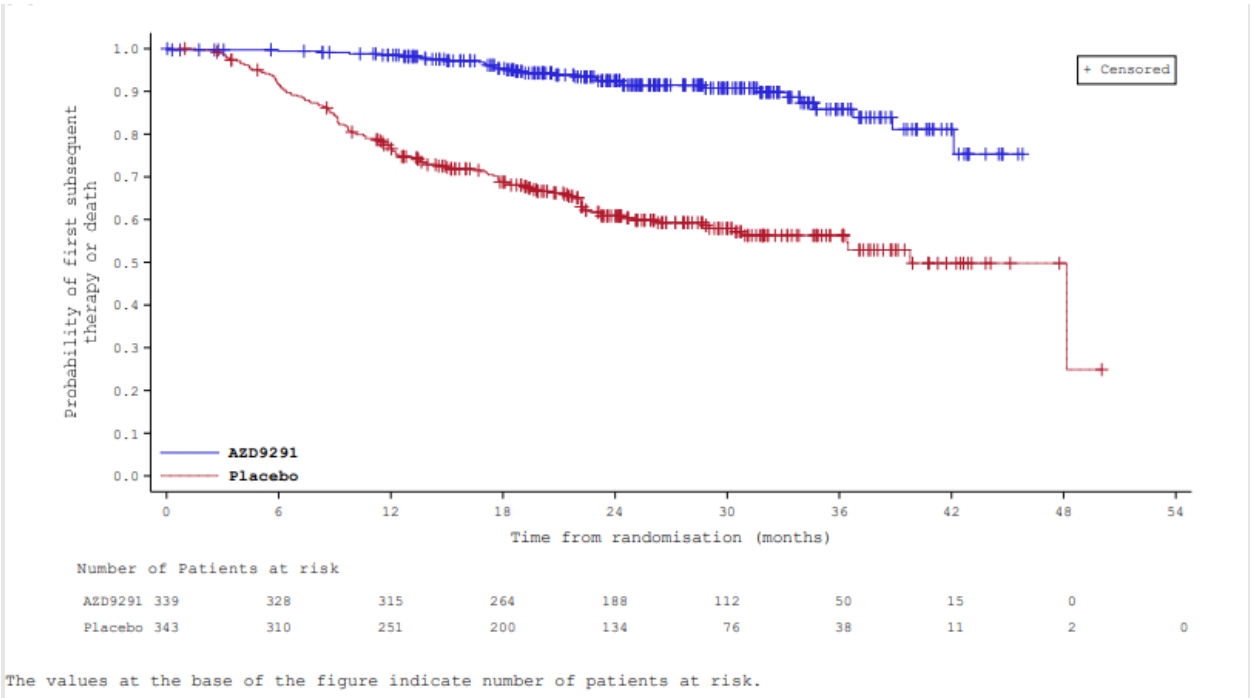
	AZD9291 (N=339)	Placebo (N=343)
Total number of patients with events	31	134
Median TFST (months) [a]	NC	39.8
95% CI for median TFST [a]	NC , NC	30.8, NC
TFST rate at 2 years (%) [a]	92.5	60.8
95% CI for TFST rate at 2 years (%) [a]	88.7, 95.1	55.1, 66.1
TFST rate at 3 years (%) [a]	85.8	56.3
95% CI for TFST rate at 3 years (%) [a]	78.7, 90.7	50.0, 62.1

TFST = Time to first subsequent anti-cancer therapy or death.
[a] Calculated using the Kaplan-Meier method.
NC = not calculable.

Table 56: Analysis of time to first subsequent anti-cancer therapy or death (Full analysis set: overall population)

	AZD9291 (N=339)	Placebo (N=343)
Number (%) of patients with events	31 (9.1)	134 (39.1)
Death	1 (3.2)	9 (6.7)
First subsequent cancer therapy	30 (96.8)	125 (93.3)
Comparison between arms		
Median TFST (months), 95% CI	NC (NC , NC)	39.8 (30.8, NC)
Hazard ratio (95% CI)	0.20 (0.14, 0.27)	
2-sided p-value	<0.0001	

The analysis was performed using a log rank test stratified by stage (IB versus II versus IIIA), race (Asian versus Non-Asian) and mutation type (Ex19del versus L858R). Stratification factors are as recorded in IVRS. A hazard ratio <1 favours AZD9291. The HR and CI are obtained directly from the U and V statistics (Berry, et al., 1991; Selke & Siegnumd, 1983).
NC = not calculable.



The values at the base of the figure indicate number of patients at risk.

Figure 39. Kaplan-Meier Plot of time to first subsequent anti-cancer therapy or death (Full analysis set: overall population)

- Type and site of recurrence

In the osimertinib arm, the majority of disease recurrence events were local/regional only (in 23/37 patients), with 10/37 patients having distant only recurrence, and 4/37 patients having both local/regional and distant recurrence. In the placebo arm, the majority of disease recurrence events (in 78/157 patients) were distant only, with 61/157 patients having a local/regional only recurrence, and 18/157 patients having local/regional and distant recurrence.

Table 50: Disease characteristics at disease recurrence (Full analysis set)

	Number (%) of patients		
Disease characteristic	AZD9291 (N=339)	Placebo (N=343)	Total (N=682)
Tumour recurrence location			
Adrenal	0	2 (0.6)	2 (0.3)
Bone	5 (1.5)	28 (8.2)	33 (4.8)
Central nervous system	5 (1.5)	34 (9.9)	39 (5.7)
Head and neck	2 (0.6)	3 (0.9)	5 (0.7)
Liver	3 (0.9)	8 (2.3)	11 (1.6)
Lung	19 (5.6)	61 (17.8)	80 (11.7)
Peritoneum	0	1 (0.3)	1 (0.1)
Pleura	0	12 (3.5)	12 (1.8)
Renal	1 (0.3)	0	1 (0.1)
Pancreas	0	1 (0.3)	1 (0.1)
Lymph nodes	10 (2.9)	48 (14.0)	58 (8.5)
Pleural effusion	0	6 (1.7)	6 (0.9)
Other	0	1 (0.3)	1 (0.1)
Missing	0	1 (0.3)	1 (0.1)

Table 51: Disease characteristics at disease recurrence of CNS (Full analysis set)

	Number (%) of patients		
Tumour recurrence location [a]	AZD9291 (N=339)	Placebo (N=343)	Total (N=682)
Number of patients with recurrence [b]	38 (11.2)	159 (46.4)	197 (28.9)
CNS [c]	5 (13.2)	34 (21.4)	39 (19.8)
CNS only	4 (10.5)	25 (15.7)	29 (14.7)
CNS + other locations	1 (2.6)	9 (5.7)	10 (5.1)
Not CNS [c]	33 (86.8)	124 (78.0)	157 (79.7)
Missing [c]	0	1 (0.6)	1 (0.5)

[a] Number of patients with disease recurrence regardless of pathology results of the tumor recurrence location.
[b] Number of patients % to be based on big N
[c] % based on 'Number of pts with recurrence'

- Progression free survival (PFS)

Table 52: Progression status at time of progression analysis (Full analysis set: overall population)

		Number (%) of patients	
Progression status	Type of Event	AZD9291 (N=339)	Placebo (N=343)
Progression	Total	13 (3.8)	46 (13.4)
	Radiological progression	6 (1.8)	25 (7.3)
	Symptomatic progression	0	5 (1.5)
	Other progression	1 (0.3)	3 (0.9)
	Death [a]	6 (1.8)	13 (3.8)
No progression	Total	326 (96.2)	297 (86.6)
	Progression free at time of analysis [b]	281 (82.9)	179 (52.2)
	Patient with recurrence [c]	24 (7.1)	113 (32.9)
	Lost to follow-up	1 (0.3)	1 (0.3)
	Withdrawn consent	20 (5.9)	4 (1.2)
	Other	0	0

[a] Death in the absence of progression.

Table 53: Median progression-free survival (Full analysis set: overall population)

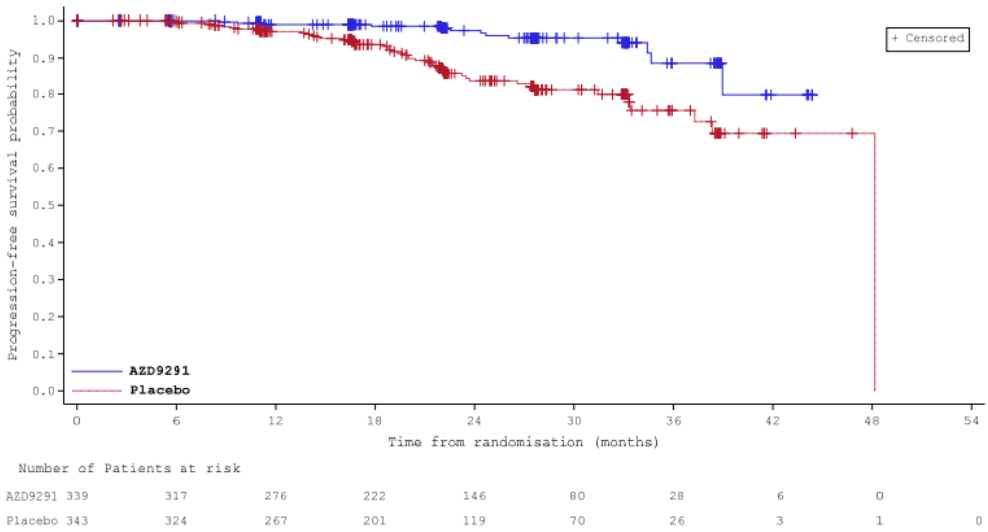
	AZD9291 (N=339)	Placebo (N=343)
Total number of events	13	46
Median progression-free survival (months) [a]	NC	48.2
95% CI for median progression-free survival [a]	NC , NC	NC , NC

[a] Calculated using the Kaplan-Meier method.
NC = not calculable.

Table 54: Analysis of progression-free survival (Full analysis set: overall population)

			Comparison between groups		
Group	N	Number (%) of patients with events [a]	Hazard ratio	95% CI	2-sided p-value
AZD9291	339	13 (3.8)	0.24	0.14, 0.41	<0.0001
Placebo	343	46 (13.4)			

The analysis was performed using a log rank test stratified by stage (IB versus II versus IIIA), race (Asian versus Non-Asian) and mutation type (Ex19del versus L858R). Stratification factors are as recorded in IVRS. A hazard ratio <1 favours AZD9291. The HR and CI are obtained directly from the U and V statistics (Berry, et al., 1991; Selke & Siegnumd, 1983).
[a] PFS events are type of disease progression after disease recurrence or death.
Patients will be censored at the latest progression assessment date or disease recurrence assessment date if the patient has not had a recurrence, progression or death.



The values at the base of the figure indicate number of patients at risk.

Figure 38. Kaplan-Meier plot of progression free survival (Full analysis set: overall population)

Ancillary analyses

Sensitivity analyses

DFS in patients with stage II-IIIA

Sensitivity analyses were conducted to assess the impact of potential biases on DFS, including the possibility of evaluation time bias, and attrition bias.

Evaluation-time bias affecting DFS (which could occur if scans were not performed at the protocol-scheduled time intervals) was assessed by the analysis of the midpoint between the time of recurrence and the previous evaluable assessment, using a log rank test stratified by disease stage, mutation status and race. There was no evidence of evaluation-time bias; the HR of 0.17 (95% CI: 0.12, 0.23; p-value < 0.0001) was consistent with the primary analysis.

Possible attrition bias was assessed by repeating the primary DFS analysis using actual DFS times, rather than the censored times of patients who had recurrence or died in the absence of recurrence immediately following two or more non-evaluable assessments. There was no evidence of attrition bias; the HR was 0.17 (95% CI: 0.12, 0.23; p < 0.0001).

An additional sensitivity analysis was performed to assess the presence of quantitative interactions by means of an overall global interaction test. The results of this sensitivity analysis indicated that there was evidence of a quantitative interaction in EGFR mutation type (Ex19del / L858R) on DFS (p = 0.0132), suggesting that osimertinib showed a treatment benefit in both Ex19del and L858R mutation subgroups, but with a difference in magnitude (significance level of 0.1). No qualitative interaction was identified, suggesting the direction of treatment benefit is consistent across all subgroups.

DFS in the Overall population

Sensitivity analyses were performed to support the evaluation of DFS in the overall population, as described below.

- Evaluation-time bias: There was no evidence of evaluation-time bias; the HR of 0.20 (95% CI: 0.15, 0.27; p-value < 0.0001) was consistent with the primary analysis.
- Attrition bias: There was no evidence of attrition bias; the HR was 0.20 (95% CI: 0.15, 0.27; p < 0.0001).

An additional sensitivity analysis was performed in the overall population to assess the presence of quantitative interactions by means of an overall global interaction test. The results of this sensitivity analysis indicated that there was evidence of a quantitative interaction on DFS for EGFR mutation type (Ex19del / L858R) (p = 0.0115) and disease stage (IB/II/IIIA) (p = 0.0546) (significance level of 0.1), with a greater magnitude of benefit for patients with Ex19del mutations over those with L858R mutations, and in patients with stage II and IIIA disease over patients with stage IB disease. No qualitative interaction was identified, suggesting the direction of treatment benefit is consistent across all subgroups.

Post-hoc analysis

Analysis of CNS recurrence (Post-hoc analysis)

Table 57: Summary of disease recurrence in CNS

Stage II-IIIA patients	Osimertinib (N=233)	Placebo (N=237)
Number (%) of patients with events [a]	4 (1.7)	32 (13.5)
CNS recurrence	3 (1.3)	27 (11.4)
Death [b]	1 (0.4)	5 (2.1)
Hazard ratio (95% CI) [c]	0.14 (0.07, 0.27)	
2-sided p-value	< 0.0001	
Overall population	**Osimertinib (N=339)**	**Placebo (N=343)**
Number (%) of patients with events [a]	6 (1.8)	39 (11.4)
CNS recurrence [d]	4 (1.2)	33 (9.6)
Death [b]	2 (0.6)	6 (1.7)
Hazard ratio (95% CI) [c]	0.18 (0.10, 0.33)	
2-sided p-value	< 0.0001	

[a] Disease-free survival events are defined as disease recurrences in the CNS, or death. Disease-free survival events that do not occur within 2 scheduled visits (plus visit window) of the last evaluable assessment (or randomization) are censored and therefore excluded in the number of events.

[b] Death in the absence of CNS disease recurrence, or death occurring within 2 visits of baseline where the patient has no evaluable assessments or no baseline data.

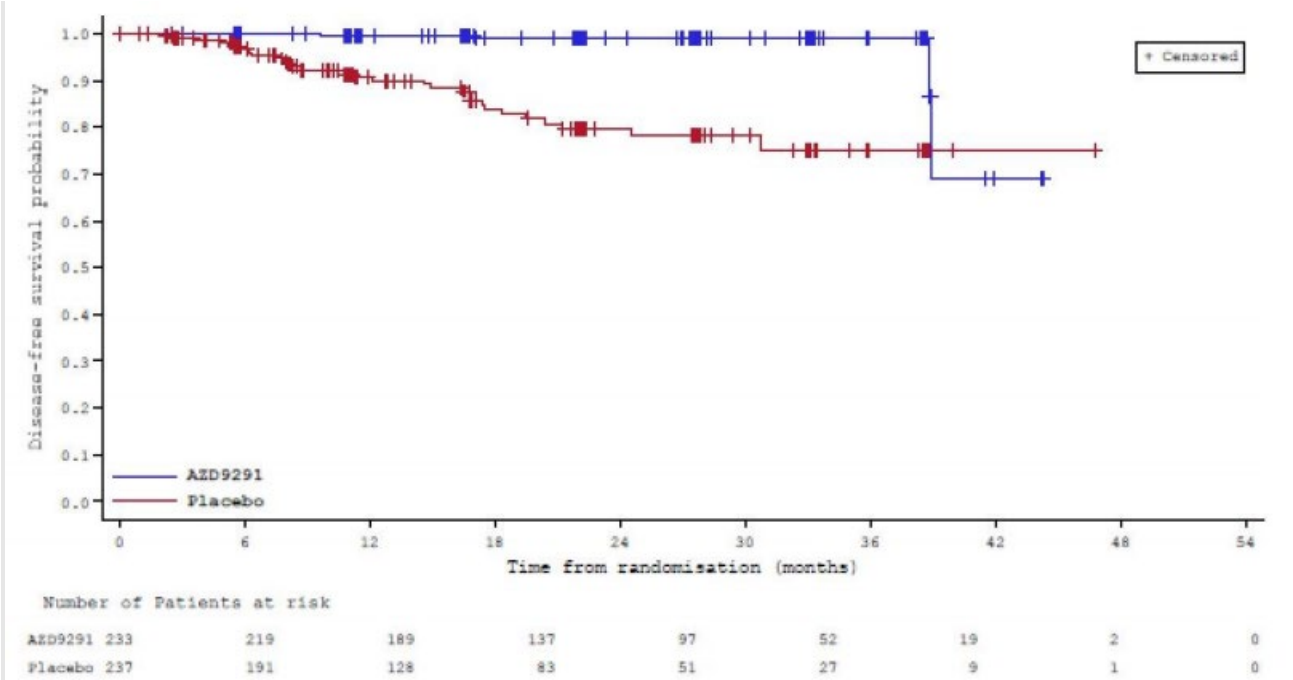
[c] The analysis was performed using an unstratified log rank test due to low event counts in the strata combinations. A hazard ratio < 1 favours osimertinib. The HR and CI are obtained directly from the U and V statistics (Berry et al 1991; Selke and Siegmund 1983).

[d] Patients [redacted] (osimertinib arm) and [redacted] (placebo arm) were included in both Table 14.1.9.1 and Table 14.1.9.2 as having CNS recurrence; however, those patients had CNS metastases at baseline and were therefore censored at Day 1 and are not counted as having CNS recurrence in this table.

DCO: 17 January 2020

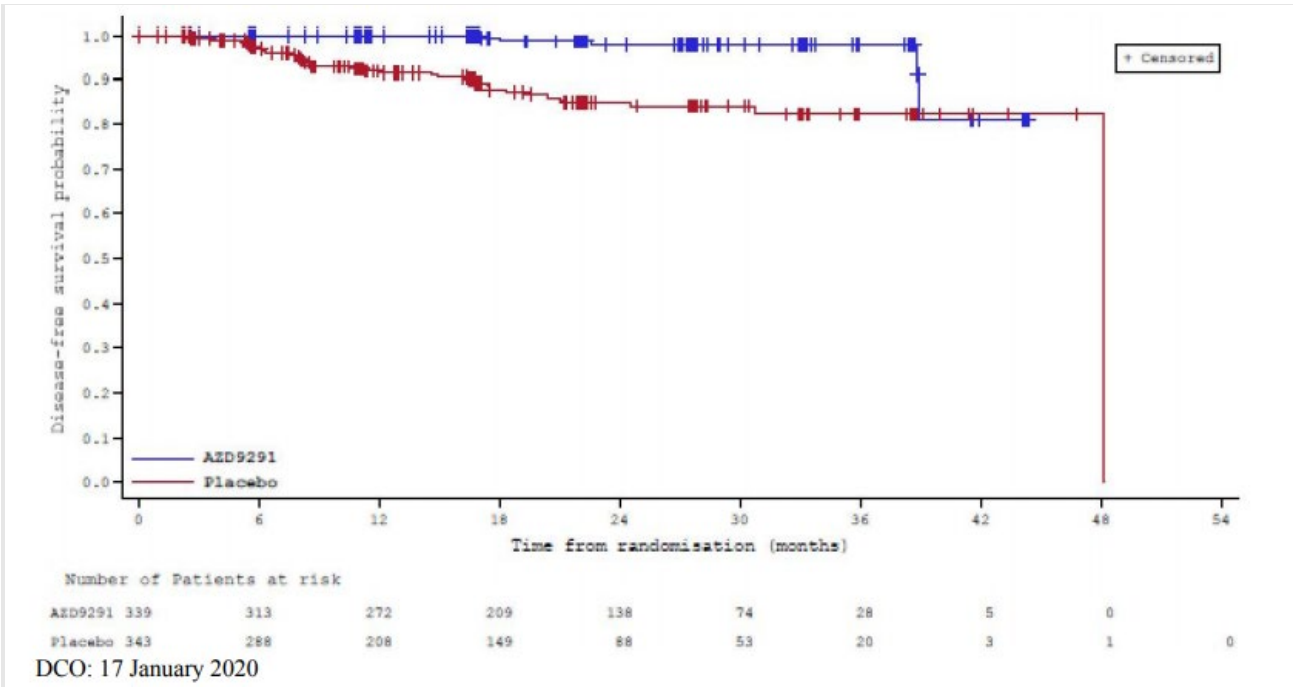
CNS DFS was improved for patients on osimertinib compared to patients on placebo based on investigator assessment was observed with a HR of 0.14 (95% CI: 0.07, 0.27; p < 0.0001) for stage II-IIIA patients, and HR of 0.18 (95% CI: 0.10, 0.33; p < 0.0001) for the overall population.

The median CNS DFS was not reached in the osimertinib arm vs. 48.2 months (95% CI: NC, NC) in the placebo arm. The median on the placebo arm is highly unreliable due to the very low number of patients at risk beyond 42 months (with only 1 patient at risk at 48 months). The landmark CNS DFS rates at 24 months were 98.8% (95% CI: 95.2, 99.7) in the osimertinib arm versus 79.7% (95% CI: 71.7, 85.7) in the placebo arm in the stage II-IIIA population; and 98% (95% CI: 94.6, 99.3) versus 85.0% (95% CI: 79.6, 89.1) in the overall population.



The values at the base of the figure indicate number of patients at risk; however, data for Month 54 are missing and consequently these numbers are mis-aligned with the correct timepoints.
DCO: 17 January 2020

Figure 40: Kaplan-Meier plot of disease-free survival, recurrence in CNS only (Full analysis set: stage IIA-IIIA patients)



DCO: 17 January 2020

Figure 41: Kaplan-Meier plot of disease-free survival, recurrence in CNS only (Full analysis set: overall population)

Subgroup analyses

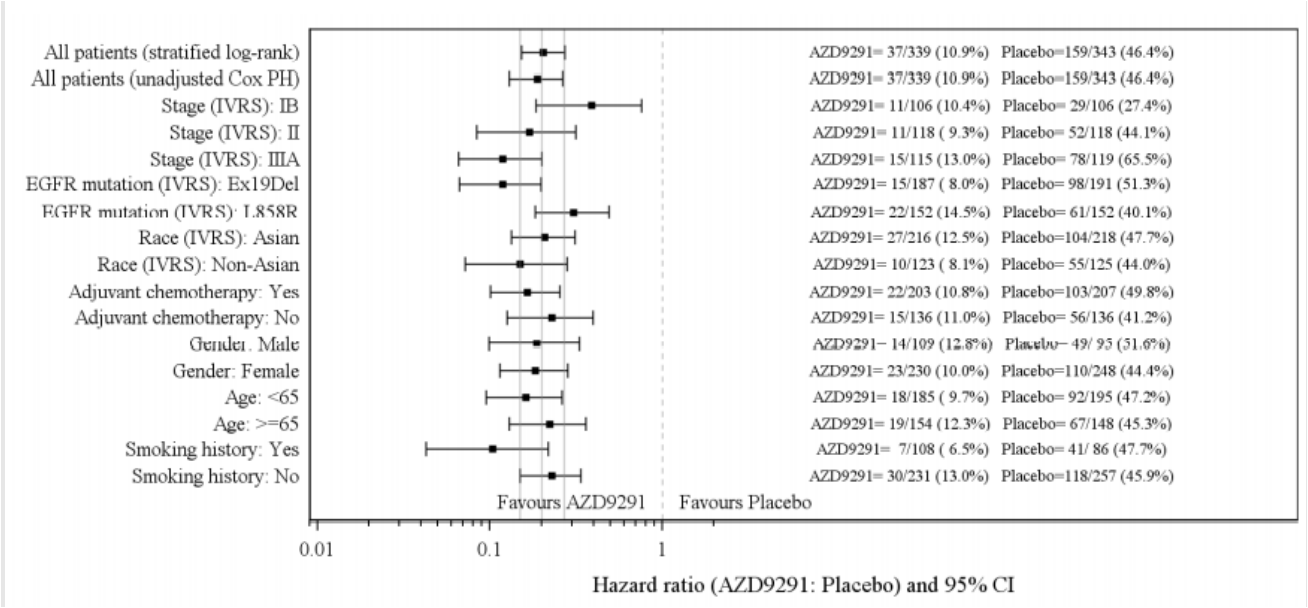
Table 58. Subgroup analyses of disease-free survival (Full Analysis Set: Overall population)

Subgroup	Category	Treatment	N	Number (%) of patients with events	Comparison between groups	
					Hazard ratio	95% CI
All patients (stratified log-rank)		Osimertinib	339	37 (10.9)	0.20	0.15, 0.27
		Placebo	343	159 (46.4)		
All patients (unadjusted Cox PH)		Osimertinib	339	37 (10.9)	0.19	0.13, 0.27
		Placebo	343	159 (46.4)		
Stage (IVRS)[a]	IB	Osimertinib	106	11 (10.4)	0.39	0.18, 0.76
		Placebo	106	29 (27.4)		
	II	Osimertinib	118	11 (9.3)	0.17	0.08, 0.31
		Placebo	118	52 (44.1)		
	IIIA	Osimertinib	115	15 (13.0)	0.12	0.07, 0.20
		Placebo	119	78 (65.5)		
EGFR mutation type (IVRS)[b]	Ex19del	Osimertinib	187	15 (8.0)	0.12	0.07, 0.20
		Placebo	191	98 (51.3)		
	L858R	Osimertinib	152	22 (14.5)	0.31	0.18, 0.49
		Placebo	152	61 (40.1)		
Race (IVRS)	Asian	Osimertinib	216	27 (12.5)	0.21	0.13, 0.31
		Placebo	218	104 (47.7)		
	Non-Asian	Osimertinib	123	10 (8.1)	0.15	0.07, 0.28
		Placebo	125	55 (44.0)		
Adjuvant chemotherapy	Yes	Osimertinib	203	22 (10.8)	0.16	0.10, 0.26
		Placebo	207	103 (49.8)		
	No	Osimertinib	136	15 (11.0)	0.23	0.13, 0.40
		Placebo	136	56 (41.2)		
Gender	Male	Osimertinib	109	14 (12.8)	0.19	0.10, 0.33
		Placebo	95	49 (51.6)		
	Female	Osimertinib	230	23 (10.0)	0.18	0.11, 0.28
		Placebo	248	110 (44.4)		
Age	< 65	Osimertinib	185	18 (9.7)	0.16	0.09, 0.26
		Placebo	195	92 (47.2)		
	≥ 65	Osimertinib	154	19 (12.3)	0.22	0.13, 0.36
		Placebo	148	67 (45.3)		
Smoking history	Yes	Osimertinib	108	7 (6.5)	0.10	0.04, 0.22
		Placebo	86	41 (47.7)		
	No	Osimertinib	231	30 (13.0)	0.23	0.15, 0.34
		Placebo	257	118 (45.9)		

[a] AJCC TNM lung cancer staging 7th edition.

[b] Note: 10 patients were mis-stratified because the EGFR mutation status entered in IVRS differed from the confirmed status resulting from central prospective EGFR testing.

DCO: 17 January 2020



The analysis was performed using a Cox proportional hazards model including treatment, subgroup and a treatment-by-subgroup interaction term. Subgroup categories with less than 20 events were excluded from the analysis. A hazard ratio < 1 favours osimertinib.
DCO: 17 January 2020

Figure 42: Disease-free survival, forest plot, by subgroup (Full Analysis Set: Overall population)

An additional sensitivity analysis was performed in the overall population to assess the presence of quantitative interactions by means of an overall global interaction test. The results of this sensitivity analysis indicated that there was evidence of a quantitative interaction on DFS for EGFR mutation type (Ex19del / L858R) (p = 0.0115) and disease stage (IB/II/IIIA) (p = 0.0546) (significance level of 0.1), with a greater magnitude of benefit for patients with Ex19del mutations over those with L858R mutations, and in patients with stage II and IIIA disease over patients with stage IB disease. No qualitative interaction was identified, suggesting the direction of treatment benefit is consistent across all subgroups.

Summary of main study

The following table 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 59: Summary of Efficacy for trial ADAURA

Title: A Phase III, double-blind, randomized, placebo-controlled multi-centre, study to assess the efficacy and safety of AZD9291 versus placebo, in patients with Epidermal Growth Factor Receptor (EGFR) mutation positive Stage IB-IIIA Non-small Cell Lung Cancer (NSCLC), following complete tumour resection with or without adjuvant chemotherapy (ADAURA)		
Study identifier	D5164C00001 EudraCT Number: 2015-000662-65 NCT Number: NCT02511106	
Design	Ongoing, phase 3, double-blind, randomised, placebo-controlled study	
	Duration of main phase:	21-Oct-2015 (FSI) to 17-Jan-2020 (DCO)
	Duration of Run-in phase:	Not applicable
	Duration of Extension phase:	Not applicable
Hypothesis	Superiority	

Treatment groups	Osimertinib		Osimertinib 80 mg orally once daily; 3 years, n=339
	Placebo		Placebo orally once daily; 3 years, n=343
Endpoints and definitions	Primary endpoint	DFS	Time from the date of randomisation until the date of disease recurrence or death (by any cause in the absence of recurrence).
	Secondary endpoint	OS	Time from randomisation to the date of death (from any cause), or to the date the patient was last known to be alive.
Database lock	24-Jun-2020		

Results and Analysis

Analysis description	**Primary Analysis**
Analysis population and time point description	All efficacy analyses were conducted on the ITT population (defined as the FAS) at the DCO of 17-Jan-2020. The 2 efficacy analysis populations were: • **Stage II-IIIA patients (subset of the FAS):** Osimertinib (n=233); Placebo (n=237) • **Overall population (FAS):**Osimertinib (n=339); Placebo (n=343)

Descriptive statistics and estimate variability

Stage II-IIIA patients		
Treatment group	Osimertinib	Placebo
Number of subjects	233	237
DFS (median, months)	NC	19.6
95% CI	38.8, NC	16.6, 24.5

Overall population		
Treatment group	Osimertinib	Placebo
Number of subjects	339	343
DFS (median, months)	NC	27.5
95% CI	NC, NC	22.0, 35.0

Effect estimate per comparison

DFS

Stage II-IIIA patients	
Comparison groups	Osimertinib vs. Placebo
HR	0.17
Adjusted 99.06% CI *	0.11, 0.26
2-sided p-value	< 0.0001

Overall population	
Comparison groups	Osimertinib vs. Placebo
HR	0.20
Adjusted 99.12% CI **	0.14, 0.30
2-sided p-value	< 0.0001

Notes

* The adjusted CI is computed at the 2-sided 99.06% level, considering a 2-sided significance level of 0.0094 for the interim analysis, based on the O Brien and Fleming spending function, assuming 247 DFS events would have been observed for the final analysis.

** The adjusted CI is computed at the 2-sided 99.12% level, considering a 2-sided significance level of 0.0088 for the interim analysis, based on the O'Brien and Fleming spending function, assuming 317 DFS events for the final analysis.

Analysis description	**Secondary Analysis**
Analysis population and time point description	OS was analysed at the DCO of 17-Jan-2020, in the following populations: • **Stage II-IIIA patients (subset of the FAS):** Osimertinib (n=233); Placebo (n=237) • **Overall population (FAS):** Osimertinib (n=339); Placebo (n=343)

Stage II-IIIA patients		
Treatment group	Osimertinib	Placebo

Descriptive statistics and estimate variability	Number of subjects	233	237
	OS (median, months)	NC	NC
	95% CI	NC, NC	NC, NC
	Overall population		
	Treatment group	Osimertinib	Placebo
	Number of subjects	339	343
	OS (median, months)	NC	48.2
	95% CI	NC, NC	48.2, NC

Effect estimate per comparison	OS	**Stage II-IIIA patients**	
		Comparison groups	Osimertinib vs. Placebo
		HR	0.40
		Adjusted 99.98% CI *	0.09, 1.83
		2-sided p-value	0.0244 **
		Overall population	
		Comparison groups	Osimertinib vs. Placebo
		HR	0.48
		Adjusted 99.98% CI *	0.12, 1.98
		2-sided p-value	0.0553 **
Notes	* The adjusted CI is computed at the 2-sided 99.98% level, considering a 2-sided significance level of 0.0002 for the interim analysis, based on the Haybittle-Peto spending function. ** A 2-sided p-value < 0.0002 was required for statistical significance		

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

Not applicable.

Clinical studies in special populations

Not applicable.

Supportive study(ies)

Not applicable.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Patients in the ADAURA study should have stage IB, II or IIIA NSCLC and had undergone prior complete surgical resection. The proportion of patients with stage IB that could be enrolled was capped at 30% which appears reasonable as already discussed during the scientific advice.

In addition, they were also required to have confirmation by the central laboratory (using the cobas® EGFR Mutation Test on tissue samples), that the tumour harboured one 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 including T790M. As a consequence, when considering the use of Tagrisso as adjuvant treatment in patients with NSCLC, the EGFR mutation positive status (exon 19 deletions (Ex19del) or exon 21 L858R substitution mutations (L858R)) indicates treatment eligibility. A

validated test should be performed in a clinical laboratory using tumour tissue DNA from biopsy or surgical specimen. This is reflected in the SmPC.

Patients with a poor performance status (i.e. WHO >1) were not allowed to enter the study, however, considering the early stage of the disease this may be representative of the intended target population.

The choice of placebo as comparator is considered acceptable, since no treatment options are currently available for this patient population after tumour resection ±adjuvant chemotherapy. As per protocol, treatment was continued until recurrence of disease, a treatment discontinuation criterion was met, up to a maximum of 3 years. According to the MAH, the 3-year treatment period was based on the fact that a significant rate of disease recurrence was observed after 2 years of adjuvant erlotinib in the RADIANT study, suggesting that longer treatment could provide more clinical benefit, and due to the tolerability of osimertinib over first/second generation EGFR TKIs. The optimal duration of treatment in the adjuvant setting is always a matter of debate and was discussed with the MAH during the scientific advice. At that time the possibility to explore different durations of therapy in a comparative way was discussed as the most informative approach. The suggestion has not been followed but the justification provided for the proposed duration was accepted. Although the 3-year treatment duration is considered acceptable, the immaturity of the data has been reflected in the SmPC.

Following recurrence, patients in the placebo arm were allowed to receive osimertinib. This will confound the OS data, but it is considered acceptable.

Overall, the primary and secondary endpoints are endorsed and are in line with EMA guidelines (i.e. Guideline on the evaluation of anticancer medicinal products in man - EMA/CHMP/205/95 Rev.5). DFS is recognised as an acceptable primary endpoint in the adjuvant setting, but OS should also be reported as in the adjuvant setting, the ultimate aim being to increase cure rate.

Regarding HRQoL, for the interpretation of the TTD outcomes pre-defined MCID values were used According to the MAH the MCID values used for calculation of TTD were the commonly used SF-36 MCID values at the individual level, which are recommended in the SF-36 Scoring Manual, 2nd edition (Ware et al 2007). These recommended values were derived using the modified RCI method by Jacobson and Truax 1991, that assumes a baseline-follow-up error correlation of 0.4 and an 80% confidence level. Overall, the approach taken for interpretation of TTD outcomes in the ADAURA study based on the employed MCID criteria for the different scales of the SF-36 questionnaire was appropriate.

Stratification factors are agreed, although prior adjuvant chemotherapy may have been included. In this regard, the fact that the subgroup analysis on DFS did not show important differences according to prior adjuvant chemotherapy is reassuring.

Statistical methods

For the analysis of the DFS and OS a hierarchical testing procedure was employed. The reason of testing DFS and OS for stage II-IIIA patients first (and then for the overall population) was due to the assumption that patients with stage IB disease have a better prognosis and fewer recurrence events than patients with stage II-IIIA disease.

The primary endpoint was initially planned with no interim analysis and to be conducted after 247 DFS events were met. This has not been the analysis conducted by the MAH and it is noted that major changes regarding the MTP have been implemented in the ongoing trial. Those changes were data-driven and based on unblinded data.

Safety data were reviewed by an IDMC and during the unblinded review in meeting (IDMC6), the analysis plan regarding the MTP was changed by the sponsor. According to "Guideline on data monitoring committees (EMEA/CHMP/EWP/5872/03 Corr)" the MAH presented a detailed explanation of the MTP changes chronologically aligned with the IDMC meetings, the status of the trial data (number of events, blinding) and analysis changes (from the first protocol and including also SAP No. 3).

The change in the MTP for a primary outcome in the ongoing trial was extensively discussed as there is a risk that trial results could be biased, treatment effect overestimated, and a reliable inference could not be feasible. According to guidelines "If unplanned interim analysis is conducted, the clinical study report should explain why it was necessary, the degree to which blindness had to be broken, provide an assessment of the potential magnitude of bias introduced, and the impact on the interpretation of the results." [ICH Topic E 9 Statistical Principles for Clinical Trials / Note for Guidance on statistical principles for clinical trials (CPMP/ICH/363/96)].

While it is acknowledged that it cannot be ruled out that analysing data earlier than planned may have introduced bias and the treatment effect may be potentially overestimated, further HR estimations were submitted and even when the HR was increased by a 20 to 50%, the associated confidence intervals , with the upper bound not including 1, remained statistically significant, which demonstrated the robustness of the results.

The study protocol was amended twice up to the data cut-off (17 Jan 2020). Overall, these protocol amendments are not considered to have had a great impact on the results. Regarding protocol deviations, they are not likely to have affected the efficacy estimates.

Overall, demographics and patient characteristics were concordant between treatment arms, with no notable discrepancies evident in any characteristic. Demographic and patient characteristics in patients with stage II-IIIA disease were consistent with this overall population (with the majority of patients' female, and Asian, with a median age of 63.0 years [range 30 to 86 years]), with characteristics well balanced between treatment arms.

The number of patients who received prior adjuvant platinum-based therapy was lower in the subgroup of patients with stage IB (26.4%) compared with patients with stage II-IIIA (75.5%). This is not unexpected, since the benefit of adjuvant chemotherapy is less clear in patients with stage IB. In fact, adjuvant chemotherapy can be considered in patients with resected stage IB disease and other high-risk factors (NCCN 2020; ESMO 2017). However, the decision of adjuvant chemotherapy was made by physicians outside of the ADAURA trial and no information has been provided on whether patients with stage IB included in the study had any risk factor which made them candidates to receive adjuvant chemotherapy. In this context efficacy data available in the subgroup of stage IB patients having received adjuvant chemotherapy vs. those who did not were discussed and the benefit of osimertinib treatment was maintained in the subgroup of patients with stage IB who did not receive adjuvant chemotherapy.

Efficacy data and additional analyses

The primary efficacy endpoint was DFS in the stage II-IIIA population. A statistically significant improvement in DFS was observed with osimertinib compared with placebo in the stage II-IIIA population (HR 0.17; 99.06%CI: 0.11, 0.26, p-value < 0.0001).

Median DFS had not been reached in the osimertinib arm (95%CI: 38.8, NC) and was of 19.6 months (95%CI: 16.6, 24.5) in the placebo arm. Median follow-up for DFS was of 22.1 months in the osimertinib arm and 14.9 months in the placebo arm.

Results in the overall population, which included also patients with stage IB, were consistent with the primary efficacy population (HR 0.20; adjusted 99.12%CI: 0.14, 0.30). Median DFS was not reached in

the osimertinib arm (95%CI: NC, NC) and was of 27.5 months (95%CI: 22.0, 35.0) in the placebo arm. With the inclusion of patients with a less advanced stage of disease, the proportion of events in the placebo arm was reduced (46.4% in the overall population) while remained consistent in the osimertinib arm (10.9%).

The exclusion of patients with other less common EGFR mutations has been done in previous clinical trials (i.e. FLAURA). However, data from in vitro and in vivo studies indicate that osimertinib could be efficacious also in patients with other activating EGFR mutations. In fact, a broad indication was given to osimertinib in the first line setting of advanced/metastatic disease regardless of the type of activating EGFR mutations. Nevertheless, due to the lack of clinical data in the adjuvant setting for patients whose tumours only have uncommon mutations, it is acknowledged that no firm conclusions can currently be drawn on the safety and efficacy of osimertinib in patients with uncommon activating EGFR mutations based on available data from the ADAURA trial. Thus, the proposal to restrict the indication to patients with EGFR exon 19 deletions or exon 21 (L858R) substitution mutations is considered acceptable.

Stage IA patients were excluded from the study. In these lower risk patients adjuvant treatment with chemotherapy is currently not recommended in clinical practice. A positive benefit-risk balance of osimertinib in patients with stage IA cannot be concluded as these patients were not studied in the ADAURA trial and extrapolation from data generated in other stages was not justified. Therefore, the indication was restricted to stage IB-IIIA patients to more accurately reflect the study population.

At the time of the study design, a median DFS of 40 months was assumed in the placebo arm. However, a lower than expected median DFS in the placebo arm has been reported in the ADAURA study. According to the MAH, this assumption was made based on data from global studies in a non-selected patient population and argues that results from the ADAURA study are in line with more recent data from more relevant EGFR patient populations (e.g. RADIANT: Kelly et al 2015, JIPANG: Kenmotsu et al 2020).

In the osimertinib arm most recurrences were local/regional only while in the placebo arm the majority of recurrences were distant. However, data are very immature, and the number of osimertinib-treated patients who experienced recurrence is currently very limited.

The efficacy results were consistent for all the subgroups analysed, including stages IB, II and IIIA, race (Asian and non-Asian), type of EGFR mutation and prior adjuvant chemotherapy. However, since the event rate is around 10% for osimertinib for all of the three disease stages (IB, II and IIIA), the MAH was requested to investigate whether there were any similarities (medical history/baseline characteristics) in this patient group. The review of the available data did not reveal any characteristics that are consistently more frequent in patients with a DFS event compared to those who remained disease free, although data are too limited for a robust interpretation.

Several sensitivity analyses have been provided and results were consistent with the primary analysis for both the stage II-IIIA population and for the overall population.

Even though DFS results can be considered of clinical relevance, the interim analysis was conducted after 156 events (33% maturity), rather than the planned 274 events (50% maturity). Therefore, updated efficacy data are deemed necessary. Moreover, in this adjuvant setting it may be of interest to further elucidate whether or not a favourable effect on cure rate is observed (i.e. in analyses conducted when recurrence rates have reached an apparent plateau). While no further statistical testing of DFS will be conducted after the current analysis (DCO 17 January 2020), the MAH will conduct an exploratory DFS analysis in the stage II-IIIA population and in the overall population once approximately 247 DFS events have occurred (which was the initially planned point for the primary

efficacy analysis). The MAH committed to providing these data as a post authorisation efficacy study (PAES) with the final CSR of the ADAURA study (see Annex II).

OS data at the time of the DCO were rather immature, with a total of 29 deaths in the overall population (9 [2.7%] in the osimertinib arm and 20 [5.8%] in the placebo arm). Median follow-up for OS was 26.1 months in the osimertinib arm and 24.6 months in the placebo arm. In the stage II-IIIA population, statistically significance was not reached (HR 0.40 [99.98%CI: 0.09, 1.83]). As per the MTP, OS in the overall population would only been tested if statistically significance was reached in the stage II-IIIA population. Thus, OS results provided for the overall population are considered exploratory.

The immaturity of the OS data poses concerns on how the delay in the time to recurrence may be translated into an actual benefit in terms of OS. Therefore, the MAH will provide one further analysis with statistical testing of OS. This final analysis of OS will be conducted when approximately 94 deaths have been observed in the stage II-IIIA (approximately 20% maturity). The final analysis of OS will be provided as part of the final CSR of the ADAURA study (see Annex II).

HRQoL was assessed with the SF-36 questionnaire. Overall rate of compliance was high (>90%) through to week 144, where a slight decline is observed. Nevertheless, due to the earlier discontinuation in completing SF-36 in the placebo arm, these data are considered descriptive. Overall, HRQL was maintained in both arms up to 30 months, with at least 70% of patients in the stage II-IIIA population not experiencing a clinically meaningful deterioration in the physical component of the SF-36 or death (70% vs 76% for osimertinib vs placebo), or in the mental component of the SF-36 or death (70% vs 71% for osimertinib vs placebo).

It should also be noted that the observed trend of shorter time to deterioration (or death) did not translate into any particular differences in the discontinuation rates due to adverse events. Although the observed trend of shorter TTD in PCS for osimertinib-treated patients may not be a robust outcome, no firm conclusion can be drawn regarding its clinical relevance based on the available data. Time to deterioration in MCS appears similar between treatment arms (HR 0.90 [97.5% CI: 0.58, 1.40].

Other exploratory post-recurrence endpoints, such as PFS and time to next treatment, appear also in favour of the osimertinib arm, although these results were immature due to the early analysis. In the osimertinib arm 31 (9.1%) patients received first subsequent treatment compared with 125 (36.4%) in the placebo arm.

According to a post-hoc analysis of CNS recurrence, treatment with osimertinib may also reduce the risk of disease recurrence in the CNS compared with placebo although results are based on very few events. The HR was 0.14 (95% CI: 0.07, 0.27; $p < 0.0001$) for stage II-IIIA patients, and 0.18 (95% CI: 0.10, 0.33; $p < 0.0001$) for the overall population. These exploratory endpoints are considered particularly relevant since there is a risk for resistance development against osimertinib that could possibly affect the efficacy of next line therapy. Therefore, The MAH has committed to provide updated data on the following exploratory endpoints: updated CNS recurrence data, updated data on type of next treatment and time to PFS post-recurrence with the final CSR of the ADAURA study (see Annex II).

A final exploratory analysis of biomarkers will be conducted in line with the protocol and will be submitted together with the ADAURA final study report.

The final results of the ADAURA study will be submitted as a PAES according to the following criteria of the EC delegated act: "a) an initial efficacy assessment that is based on surrogate endpoints, which

requires verification of the impact of the intervention on clinical outcome or disease progression or confirmation of previous efficacy assumptions"

2.5.4. Conclusions on the clinical efficacy

In the ADAURA study a statistically significant advantage in terms of DFS for adjuvant treatment with osimertinib after complete tumour resection in patients with stage IB-IIIA NSCLC with exon 19 deletions or exon 21 (L858R) substitution mutations has been reported. The reported DFS results are likely to translate into meaningful clinical benefit. In addition, a consistent effect in DFS is shown across subgroups and between the primary analysis population and the overall population.

Due to the immaturity of the OS data, the extent to which the delay in time to recurrence may be translated into a survival benefit cannot be ascertained. However, no detrimental effect was observed in OS. As these results come from an unplanned interim analysis which led to a change in the multiple testing procedure for the primary outcome, the MAH will submit further analyses on a more mature dataset for DFS, OS and exploratory endpoints. This will be provided with the final CSR of the ADAURA study (Q2 2024).

The following measures are considered necessary to address issues related to efficacy:

PAES (Annex II condition): In order to further evaluate the efficacy of Tagrisso as monotherapy for the adjuvant treatment after complete tumour resection in adult patients with stage IB-IIIA non-small cell lung cancer (NSCLC) whose tumours have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations, the MAH should submit the final results of the ADAURA study.
The clinical study report should be submitted by Q2 2024.

2.6. Clinical safety

Introduction

The primary source of safety data is the pivotal Phase III study ADAURA, supported by analysis of safety data for patients that received at least one dose of osimertinib 80 mg in studies of osimertinib in advanced/metastatic EGFRm NSCLC (AURA, AURA extension, AURA2, AURA3, and FLAURA).

An IDMC was established to regularly review safety data from ADAURA and make a recommendation on whether to amend, stop or continue the study. The IDMC made an ad hoc request to review key efficacy data at their scheduled meeting on 07 April 2020, and following this review made a recommendation that a full analysis of efficacy and safety data from the ADAURA study be performed by the Sponsor as soon as possible for public disclosure, due to the benefit observed for patients treated with osimertinib.

In ADAURA study all safety analyses were conducted based on the Safety Analysis Set, which comprised 680 patients overall, of which 337 patients received at least 1 dose of osimertinib treatment, and 343 patients received at least 1 dose of placebo.

Safety data from ADAURA were pooled with a previously submitted dataset of 1142 patients with advanced/metastatic EGFRm NSCLC that is included in the current label (AURA, AURA extension, AURA2, AURA3, and FLAURA):

- 309 patients received osimertinib as first-line treatment in the FLAURA and AURA1 [first-line cohort] studies,

- and 833 patients received osimertinib as a second-line or greater treatment in the AURA1A/B/C, AURA2, and AURA3 studies)

Table 60: Studies contributing to the osimertinib safety pool

Study	Design, indication	Number of patients included in osimertinib safety pool (N=1479)
D5164C00001 **ADAURA** 17 January 2020 (DCO1)	Phase III double-blind, randomized, placebo-controlled; resected Stage IB-IIIA EGFRm NSCLC	337
D5160C00003 **AURA3** 15 April 2016 (DCO1)	Phase III open-label, randomized, active-controlled; advanced/metastatic EGFR T790M mutation-positive NSCLC	279
D5160C00007 **FLAURA** 12 June 2017 (DCO1)	Phase III double-blind, randomized, active-controlled; advanced/metastatic EGFRm NSCLC	279
D5160C00001A and B **AURA** 01 November 2016 (DCO3)	Phase I uncontrolled; EGFRm NSCLC, 1L (AURA1 first-line cohort) or ≥ 2L (AURA1A/B/C)	173
D5160C00001C **AURA extension** 01 November 2016 (DCO4)	Phase II uncontrolled; EGFR T790M mutation-positive NSCLC, ≥ 2L	201
D5160C00002 **AURA2** 01 November 2016 (DCO4)	Phase II uncontrolled; advanced EGFR T790M mutation-positive NSCLC, ≥ 2L	210

Osimertinib study patients who were assigned any dose other than 80 mg once daily were excluded from the advanced/metastatic NSCLC studies and overall osimertinib safety pool datasets.

Additionally, these datasets do not include patients who crossed over to osimertinib treatment after disease progression on their initial treatment in relevant studies; i.e., those randomised to the platinum-based chemotherapy arm in the AURA3 study, and those randomised to the standard-of-care arm of the FLAURA study. Furthermore, patients enrolled in clinical pharmacology studies are also excluded, as these studies have previously been completed with no new safety concerns identified.

Patient exposure

Table 61: Duration of exposure

	Number (%) of patients				
	ADAURA Study (Adjuvant)		Advanced / metastatic NSCLC Studies		Overall osimertinib safety pool (N=1479)
	Osimertinib (N=337)	Placebo (N=343)	Osimertinib First-line (N=309)	Osimertinib ≥Second-line (N=833)	
Total exposure time (months)[a]					
Mean (sd)	21.7 (10.61)	18.6 (10.71)	15.8 (7.55)	13.1 (8.72)	15.6 (9.60)
Median	22.5	18.7	16.5	11.1	15.0
Min, Max	0, 38 [b]	0, 36	0, 35	0, 40	0, 40
Total treatment years	609.5	532.1	405.8	912.6	1927.90
Actual exposure time (months)[c]					
Mean (sd)	21.5 (10.57)	18.5 (10.68)	15.6 (7.48)	12.9 (8.67)	15.4 (9.56)
Median	22.2	18.3	16.3	11.0	14.6
Min, Max	0, 38	0, 36	0, 35	0, 40	0, 40
Total treatment years	603.2	529.7	400.96	895.59	1899.75
Actual cumulative exposure over time					
≥ 1 day	337 (100)	343 (100)	309 (100)	833 (100)	1479 (100)
≥ 6 months	294 (87.2)	288 (84.0)	265 (85.8)	637 (76.5)	1198 (81.0)
≥ 12 months	274 (81.3)	223 (65.0)	220 (71.2)	389 (46.7)	886 (59.9)
≥ 18 months	221 (65.6)	177 (51.6)	126 (40.8)	232 (27.9)	581 (39.3)
≥ 24 months	148 (43.9)	117 (34.1)	32 (10.4)	156 (18.7)	339 (22.9)
≥ 30 months	88 (26.1)	62 (18.1)	11 (3.6)	16 (1.9)	118 (8.0)
≥ 36 months	8 (2.4)	5 (1.5)	0	6 (0.7)	18 (1.2)

[a] Total treatment duration = (last dose date - first dose date +1) / (365.25/12).

[b] One patient had 38 months of treatment based on the data calculated using exposure. This patient discontinued the study and was no longer on treatment. Last date of exposure was not available as the patient was lost to follow up.

[c] Actual treatment duration = total treatment duration, excluding dose interruptions.

Total treatment years was calculated by adding the durations for each patient in the treatment group.

Two patients randomised to osimertinib received no study treatment and are not in the ADAURA safety analysis set; otherwise, the ADAURA safety analysis set is the same as the full analysis set.

Table 62: Summary of treatment interruptions and dose reductions (Safety Analysis Set)

	Osimertinib (N=337)	Placebo (N=343)
Received planned starting dose	336 (99.7) [a]	343 (100)
Dose interruptions		
Number (%) of patients with interruptions (any)	183 (54.3)	143 (41.7)
1 interruption	79 (23.4)	68 (19.8)
> 2 interruptions	104 (30.9)	75 (21.9)
Reason for interruption [b], n (%)		
Adverse event [c]	106 (31.5)	36 (10.5)
Patient forgot to take the dose	100 (29.7)	108 (31.5)
Patient decision	20 (5.9)	12 (3.5)
Laboratory abnormality not reported as an adverse event	0	1 (0.3)
Other	12 (3.6)	19 (5.5)
Total number (%) of interruptions (any) [d]	124 (36.8)	59 (17.2)
Median (days) [e]	8.0	5.0
Minimum-maximum (days)	1 - 92	1 - 83
Dose reductions		
Number (%) of patients with dose reduction (any) [f]	49 (14.5)	3 (0.9)
Reason for dose reduction [g]		
Adverse event [c]	46 (13.6)	3 (0.9)
Other	3 (0.9)	0

[a] One patient did not receive osimertinib treatment on the day of randomisation, and so was recorded as having missed their planned starting dose. This patient started osimertinib 80 mg 9 days after the date of randomisation.

[b] Reasons for interruption are not mutually exclusive for patients with multiple interruptions although will be counted only once per category.

[c] Note: The number of dose modifications due to AEs in this exposure summary differ from the number of AEs resulting in a dose modification in Section 12.2.4 due to the differences in data capture between the exposure and AE eCRFs. In the exposure summary, each dose modification action is taken into account; whereas within the AE datasets, only the last action taken for an AE is recorded and summarised.

[d] Any is defined as the total number of patients with at least one dose interruption. The total number of interruptions excludes any interruptions where the patient forgot to take their dose.

[e] Median length of interruption.

[f] All patients reported 1 dose reduction.

[g] Reasons for dose reductions are not mutually exclusive for patients with multiple reductions although will be counted only once per category.

DCO: 17 January 2020

Source: Table 14.3.1.2 and Table 14.3.1.3

***Demographic and other characteristics* of the study population**

Table 63: Key demographic characteristics

		ADAURA Study (Adjuvant)		Advanced / metastatic NSCLC Studies		Overall osimertinib safety pool (N=1479)
		Osimertinib (N=337)	Placebo (N=343)	Osimertinib First-line (N=309)	Osimertinib ≥Second-line (N=833)	
Demographics						
Age (years)	Mean (sd)	62.5 (10.28)	61.6 (10.46)	62.6 (10.58)	61.7 (10.89)	62.0 (10.69)
	Median	64.0	62.0	63.0	62.0	63.0
	Min - Max	30, 86	31, 82	26, 85	25, 89	25, 89
Age group (years), n (%)	< 65 years	184 (54.6)	195 (56.9)	170 (55.0)	487 (58.5)	841 (56.9)
	≥ 65 - < 75	117 (34.7)	106 (30.9)	101 (32.7)	237 (28.5)	455 (30.8)
	≥ 75	36 (10.7)	42 (12.2)	38 (12.3)	109 (13.1)	183 (12.4)
Sex, (n (%)	Male	109 (32.2)	95 (27.7)	111 (35.9)	289 (34.7)	509 (34.4)
	Female	228 (67.7)	248 (72.3)	198 (64.1)	544 (65.3)	970 (65.6)
Race, n (%)	White	121 (35.9)	122 (35.6)	108 (35.0)	282 (33.9)	511 (34.6)
	Black or African American	-	-	2 (0.6)	10 (1.2)	12 (0.8)
	Asian	215 (63.8)	218 (63.6)	197 (63.8)	523 (62.8)	935 (63.2)
	Native Hawaiian or other Pacific Islander	-	-	-	1 (0.1)	1 (0.1)
	American Indian or Alaska Native	-	-	1 (0.3)	-	1 (0.1)
	Other	1 (0.3)	2 (0.6)	-	10 (1.2)	11 (0.7)
	Missing	-	1 (0.3)*	-	-	-
Patient characteristics						
Weight (kg)	N	337	340	301	832	1470
	Mean (sd)	65.2 (14.2)	64.3 (13.3)	63.2 (13.7)	61.8 (14.0)	62.9 (14.1)
	Median	63.8	63.0	62.0	60.0	61.0
	Min - Max	35,112	38, 116	29, 117	30, 122	29, 122
Disease characteristics						
WHO PS, n (%)	0 (Normal activity)	214 (63.5)	218 (63.6)	130 (42.1)	290 (34.8)	634 (42.9)
	1 (Restricted activity)	123 (36.5)	125 (36.4)	179 (57.9)	542 (65.1)	844 (57.1)

* One patient had missing race information due to local confidentiality law

All data are derived from the Safety Analysis Set of the included individual studies

Sources: Table 14.1.6, ADAURA CSR, Module 5.3.5.1; Table 14.1.7, ADAURA CSR, Module 5.3.5.1; Table 14.1.8, ADAURA CSR, Module 5.3.5.1; Table 2.7.4.2.5.11

Adverse events

Safety data are presented for AEs with an onset date on or after the date of the first dose of study treatment, up to and including 28 days following discontinuation of study treatment, or the day before administration of any post-IP anti-cancer therapies.

Table 64: Adverse events in any category

AE Category	Number (%) of patients [a]				
	ADAURA Study (Adjuvant)		Advanced / metastatic NSCLC Studies		Overall osimertinib safety pool (N=1479)
	Osimertinib (N=337)	Placebo (N=343)	Osimertinib First-line (N=309)	Osimertinib ≥Second-line (N=833)	
Any AE	329 (97.6)	306 (89.2)	303 (98.1)	823 (98.8)	1455 (98.4)
Any AE causally related to treatment [b]	305 (90.5)	192 (56.0)	282 (91.3)	727 (87.3)	1314 (88.8)
Any AE of CTCAE Grade 3 or higher	68 (20.2)	46 (13.4)	108 (35.0)	313 (37.6)	489 (33.1)
Any AE of CTCAE Grade 3 or higher, causally related to treatment [b]	32 (9.5)	8 (2.3)	53 (17.2)	108 (13.0)	193 (13.0)
Any AE with outcome of death	0	1 (0.3)	6 (1.9)	35 (4.2)	41 (2.8)
Any AE with outcome of death, causally related to treatment [b]	0	0	0	5 (0.6)	5 (0.3)
Any SAE (including those with an outcome of death)	54 (16.0)	42 (12.2)	71 (23.0)	244 (29.3)	369 (24.9)
Any SAE (including those with an outcome of death), causally related to treatment [b]	8 (2.4)	2 (0.6)	26 (8.4)	44 (5.3)	78 (5.3)
Any AE leading to discontinuation of treatment	37 (11.0)	10 (2.9)	40 (12.9)	69 (8.3)	146 (9.9)
Any AE leading to discontinuation of osimertinib, causally related to treatment [b]	31 (9.2)	5 (1.5)	29 (9.4)	35 (4.2)	95 (6.4)

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

[b] As assessed by the investigator, and programmatically derived from individual causality assessments.

Includes AEs with onset date on or after the date of first dose up to and including 28 days following discontinuation of study treatment and before starting subsequent cancer therapy.

MedDRA version 22.1. CTCAE version 4.03.

Sources: Table 14.3.2.1.1, ADAURA CSR (Module 5.3.5.1), and Table 2.7.4.2.1.1

A review of categorical AE data split by disease stage (analysed separately for patients staged with II-IIIA, and IB disease) did not reveal any notable differences in terms of the incidences of patients with any AE, SAEs, CTCAE grade ≥ 3 AEs, DAEs, and AEs leading to dose modifications, to that observed in the overall Safety Analysis Set.

Common Adverse Events

Table 65: Most common AEs, by PT (reported in ≥ 10% osimertinib-treated patients in the ADAURA study)

MedDRA Preferred Term	Number (%) of patients				
	ADAURA Study (Adjuvant)		Advanced / metastatic NSCLC Studies		Overall osimertinib safety pool (N=1479)
	Osimertinib (N=337)	Placebo (N=343)	Osimertinib First-line (N=309)	Osimertinib ≥Second-line (N=833)	
Patients with any AEs	329 (97.6)	306 (89.2)	303 (98.1)	823 (98.8)	1455 (98.4)
Diarrhoea	156 (46.3)	68 (19.8)	178 (57.6)	364 (43.7)	698 (47.2)
Paronychia	85 (25.2)	5 (1.5)	92 (29.8)	184 (22.1)	361 (24.4)
Dry skin	79 (23.4)	22 (6.4)	99 (32.0)	194 (23.3)	372 (25.2)
Pruritus	65 (19.3)	30 (8.7)	55 (17.8)	136 (16.3)	256 (17.3)
Cough	62 (18.4)	57 (16.6)	53 (17.2)	161 (19.3)	276 (18.7)
Stomatitis	59 (17.5)	14 (4.1)	92 (29.8)	130 (15.6)	281 (19.0)
Nasopharyngitis	47 (13.9)	35 (10.2)	28 (9.1)	95 (11.4)	170 (11.5)
Upper respiratory tract infection	45 (13.4)	35 (10.2)	35 (11.3)	107 (12.8)	187 (12.6)
Decreased appetite	44 (13.1)	13 (3.8)	60 (19.4)	175 (21.0)	279 (18.9)
Mouth ulceration	39 (11.6)	8 (2.3)	15 (4.9)	25 (3.0)	79 (5.3)
Dermatitis acneiform	37 (11.0)	16 (4.7)	76 (24.6)	88 (10.6)	201 (13.6)

Includes AEs with onset date on or after the date of first dose up to and including 28 days following discontinuation of study treatment and before starting subsequent cancer therapy.
MedDRA version 22.1
Sources: Table 14.3.2.6, ADAURA CSR, Module 5.3.5.1; Table 2.7.4.2.1.2

1 Grouped term, comprising PTs of: Acne, Acne Pustular, Dermatitis, Dermatitis Acneiform, Drug Eruption, Erythema, Eyelid Folliculitis, Folliculitis, Rash, Rash Erythematous, Rash Follicular, Rash Macular, Rash Maculo-Papular, Rash Maculovesicular, Rash Papular, Rash Pruritic, Rash Pustular, Rash Vesicular, and Skin Erosion.

Adverse events by severity

In ADAURA study a total of 32 patients (9.5%) had AEs of CTCAE ≥ Grade 3 considered by the investigator to be causally related to osimertinib treatment, with PTs of paronychia, stomatitis, diarrhoea, electrocardiogram QT prolonged, and decreased appetite being reported as causally related in ≥ 2 patients.

CTCAE Grade 4 AEs (irrespective of causality) were reported in 3 patients (0.9%) in the osimertinib arm (AEs of appendicitis, blood uric acid increased, and hypokalaemia), and 1 patient (0.3%) in the placebo arm (AE of neutropenia).

Table 66: AEs of CTCAE Grade 3 or higher (reported in ≥ 2 osimertinib-treated patients in the ADAURA study)

MedDRA Preferred Term	Number (%) of patients				
	ADAURA Study (Adjuvant)		Advanced / metastatic NSCLC Studies		Overall osimertinib safety pool (N=1479)
	Osimertinib (N=337)	Placebo (N=343)	Osimertinib First-line (N=309)	Osimertinib ≥Second-line (N=833)	
Patients with any CTCAE ≥ Grade 3 AE	68 (20.2)	46 (13.4)	108 (35.0)	313 (37.6)	489 (33.1)
Diarrhoea	8 (2.4)	1 (0.3)	6 (1.9)	7 (0.8)	21 (1.4)
Stomatitis	6 (1.8)	-	1 (0.3)	-	7 (0.5)
Pneumonia	4 (1.2)	4 (1.2)	7 (2.3)	29 (3.5)	40 (2.7)
Paronychia	3 (0.9)	-	1 (0.3)	2 (0.2)	6 (0.4)
Hypertension	3 (0.9)	4 (1.2)	1 (0.3)	3 (0.4)	7 (0.5)
ECG QT prolonged	3 (0.9)	1 (0.3)	6 (1.9)	7 (0.8)	16 (1.1)
Gastroenteritis	2 (0.6)	-	1 (0.3)	2 (0.2)	5 (0.3)
Upper respiratory tract infection	2 (0.6)	-	-	1 (0.1)	3 (0.2)
Viral upper respiratory tract infection	2 (0.6)	-	-	-	2 (0.1)
Decreased appetite	2 (0.6)	-	7 (2.3)	8 (1.0)	17 (1.1)
Cataract	2 (0.6)	-	2 (0.6)	3 (0.4)	7 (0.5)
Femur fracture	2 (0.6)	1 (0.3)	-	-	2 (0.1)

Includes AEs with onset date on or after the date of first dose up to and including 28 days following discontinuation of study treatment and before starting subsequent cancer therapy.
MedDRA version 22.1

Adverse Drug Reactions (ADRs)

Alopecia, epistaxis, palmar-plantar erythrodysaesthesia syndrome (PPES), decreased appetite and blood creatinine increased have been added as ADRs as a result of the safety review of this application. In addition, the ADR of stomatitis, which previously only included events reported for the preferred term of stomatitis, has been expanded to be a grouped term including stomatitis and mouth ulceration. Following a review of other factors, such as whether a plausible mechanism of action is known and whether each topic is an ADR for other EGFR-TKIs, and in the absence of alternative explanations, these events are now classified as ADRs for osimertinib.

The time to onset of first ADRs was consistent across the adjuvant and advanced/metastatic populations, with a median of 14 days for the osimertinib safety pool. In the adjuvant population (6.8%), there were fewer CTCAE Grade ≥ 3 ADRs than in the advanced/metastatic population (11.0% for first-line patients and 8.2% for second-line or greater patients).

There were also fewer serious ADRs in the adjuvant population (0.9%) than in the advanced/metastatic population (4.2% for first-line patients and 2.9% for second-line or greater patients).

In the overall osimertinib safety pool, Grade 3 and Grade 4 adverse reactions were 10% and 0.1%, respectively.

Alopecia

Although the frequency of reported alopecia in the osimertinib arm of ADAURA was consistent with the osimertinib safety pool, the reported frequency was higher than in the placebo arm (19 patients, 5.6% compared to 7 patients, 2%).

In the overall osimertinib safety pool, AEs of alopecia have been reported in 68 osimertinib treated patients (4.6%), with a median time to onset of 85.5 days (range: 2 to 836 days). All AEs were non-serious, and the majority were mild in severity (CTCAE Grade 1; 58/68 patients).

No patient in the overall osimertinib safety pool required a dose modification due to alopecia; however, 1 patient (in the adjuvant population) permanently discontinued osimertinib treatment due to alopecia. Overall, the majority of patients (44/68 patients; 64.7%) recovered from the event.

Epistaxis

In the ADAURA study, epistaxis was reported in 19 patients (5.6%) in the osimertinib arm and 3 patients (0.9%) in the placebo arm.

In the overall osimertinib safety pool, AEs of epistaxis have been reported in 79 osimertinib treated patients (5.3%), with a median TTO of 97 days (range: 4 to 876 days). All AEs were non-serious, and the majority were mild in severity (CTCAE Grade 1; 78/79 patients). No patient in the overall osimertinib safety pool required a dose modification or permanently discontinued osimertinib treatment due to epistaxis. Overall, the majority of patients (68/79 patients; 86.1%) recovered from the event.

Stomatitis (Grouped Term)

In ADAURA, more patients in the osimertinib arm (39 patients, 11.6%) than the placebo arm (8 patients, 2.3%) had an AE of mouth ulceration.

Palmar-plantar Erythrodysaesthesia Syndrome (PPES)

In ADAURA, no patients in the placebo arm and 6 patients (1.8%) in the osimertinib arm were reported with an AE of PPES.

In the overall osimertinib safety pool, AEs of PPES have been reported in 25 osimertinib-treated patients (1.7%), with a median time to onset of 128 days (range: 12 to 590 days). All AEs were non-serious, and the majority were mild in severity. No patient in the overall osimertinib safety pool required a dose modification or permanently discontinued osimertinib treatment due to PPES. Overall, the majority of patients (17/25 subjects) recovered or were recovering at DCO. With regards to the 8 non-recovered PPES cases seen in the osimertinib arm, it is confirmed that 2 of these 8 patients later recovered from the event of PPES and the remaining 6 patients continued to receive osimertinib without the need for interruption or dose reduction. All events were non-serious, and mild (7 patients) or moderate (1 patient) in severity. In addition, a series of cases of PPES with a temporal relationship with the start of osimertinib treatment have been reported from post-marketing data.

Decreased appetite

Decreased appetite occurred in 44 patients in the osimertinib arm, and 13 patients in the placebo arm. Moreover, there are a number of patients (osimertinib arm: 14 patients [4.2%]; placebo arm: 5 patients [1.5%]) in both arms in whom no alternative explanation for the decreased appetite has been identified.

Blood Creatinine Increased

In ADAURA more patients in the osimertinib arm (32 patients, 9.8%) than the placebo arm (15 patients, 4.5%) had a worsening CTCAE grade shift from baseline for creatinine. The majority of the grade shifts in both treatment arms were 1 CTCAE grade shifts.

Urticaria

Urticaria was identified as an ADR through routine Pharmacovigilance.

In total, 28 patients reported 31 adverse event of urticaria PT. Since 1479 patients have been exposed to Tagrisso in studies in which urticaria could have been detected (Osimertinib Safety pool dataset [N=1479]), the frequency category can, therefore, be considered as 'Common' (1.9%).

Table 67: Summary of ADR frequency determinations

ADR	ADAURA Study (osimertinib arm) (N=337)						Overall osimertinib safety pool (including ADAURA) (N=1479)					
Number (%) of patients, by CTCAE Grade												
	Any	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**	**Any**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Interstitial lung disease [a]	10 (3.0)	6 (1.8)	4 (1.2)	-	-	-	55 (3.7)	17 (1.1)	21 (1.4)	12 (0.8)	-	5 (0.3)
Diarrhoea	156 (46.3)	116 (34.4)	32 (9.5)	8 (2.4)	-	-	698 (47.2)	560 (37.9)	117 (7.9)	21 (1.4)	-	-
Stomatitis [b]	95 (28.2)	64 (19.0)	25 (7.4)	6 (1.8)	-	-	348 (23.5)	262 (17.7)	79 (5.3)	7 (0.5)	-	-
Keratitis [c]	2 (0.6)	-	2 (0.6)	-	-	-	10 (0.7)	3 (0.2)	6 (0.4)	1 (0.1)	-	-
Rash [d]	132 (39.2)	98 (29.1)	33 (9.8)	1 (0.3)	-	-	661 (44.7)	542 (36.6)	108 (7.3)	11 (0.7)	-	-
Dry skin [e]	99 (29.4)	88 (26.1)	10 (3.0)	1 (0.3)	-	-	469 (31.7)	410 (27.7)	57 (3.9)	2 (0.1)	-	-
Paronychia [f]	123 (36.5)	66 (19.6)	54 (16.0)	3 (0.9)	-	-	481 (32.5)	309 (20.9)	166 (11.2)	6 (0.4)	-	-
Pruritus [g]	65 (19.3)	49 (14.5)	16 (4.7)				256 (17.3)	208 (14.1)	47 (3.2)	1 (0.1)	-	-
Erythema multiforme	1 (0.3)	-	1 (0.3)	-	-	-	5 (0.3)	3 (0.2)	2 (0.1)	-	-	-
Stevens-Johnson syndrome [h]	-	-	-	-	-	-	-	-	-	-	-	-
Cutaneous vasculitis [h]	-	-	-	-	-	-	-	-	-	-	-	-
Alopecia	19 (5.6)	15 (4.5)	4 (1.2)	-	-	-	68 (4.6)	58 (3.9)	10 (0.7)	-	-	-
Epistaxis	19 (5.6)	19 (5.6)	-	-	-	-	79 (5.3)	78 (5.3)	1 (0.1)	-	-	-
PPES	6 (1.8)	4 (1.2)	2 (0.6)	-	-	-	25 (1.7)	21 (1.4)	4 (0.3)	-	-	-
Number (%) of patients who had a QTcF prolongation > 500msec												
QTc interval prolongation	2 (0.6)						12 (0.8)					
Maximum worsening CTCAE grade shift from baseline during treatment												
	n	**Any**	**1-grade**	**2-grade**	**3-grade**	**4-grade**	***n***	**Any**	**1-grade**	**2-grade**	**3-grade**	**4-grade**
Platelet count decreased [i]	***324***	153 (47.2)	151 (46.6)	2 (0.6)	-	-	***1459***	767 (52.6)	717 (49.1)	32 (2.2)	9 (0.6)	9 (0.6)
Leucocytes decreased [i]	***324***	175 (54.0)	153 (47.2)	22 (6.8)	-	-	***1452***	940 (64.7)	692 (47.7)	231 (15.9)	16 (1.1)	1 (0.1)
Lymphocytes decreased [i]	***324***	142 (43.8)	77 (23.8)	58 (17.9)	6 (1.9)	1 (0.3)	***1451***	898 (61.9)	452 (31.2)	358 (24.7)	80 (5.5)	8 (0.6)
Neutrophils decreased [i]	***324***	83 (25.6)	44 (13.6)	38 (11.7)	1 (0.3)	-	***1452***	474 (32.6)	215 (14.8)	212 (14.6)	44 (3.0)	3 (0.2)
Blood creatinine increased [i]	***325***	32 (9.8)	31 (9.5)	1 (0.3)	-	-	***1459***	137 (9.4)	126 (8.6)	11 (0.8)	-	-

[a] Includes cases reported within the clustered terms: Interstitial lung disease, pneumonitis.

[b] Includes cases reported within the clustered terms: Stomatitis, mouth ulceration

[c] Includes cases reported within the clustered terms: Keratitis, punctate keratitis, corneal erosion, corneal epithelium defect.

[d] 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, pustule.

[e] Includes cases reported within the clustered terms: Dry skin, skin fissures, xerosis, eczema, xeroderma.

[f] 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, onychalgia, onychoclasis, onycholysis, onychomadesis, onychomalacia, paronychia.

[g] Includes cases reported within the clustered terms: pruritus, pruritus generalised, eyelid pruritus.

[h] This ADR was identified from post-marketing data, and no AEs have been reported in the osimertinib clinical development programme.

[i] Represents the incidence of laboratory findings, not of reported adverse events.

Sources: Table 2.7.4.2.5.2; Table 2.7.4.6.3; Table 2.7.4.7.3; Table 2.7.4.7.6.

Serious adverse event/deaths/other significant events

Serious Adverse Events

Table 68: SAEs, by PT (reported in ≥2 osimertinib-treated patients in the ADAURA study)

MedDRA Preferred Term	Number (%) of patients				
	ADAURA Study (Adjuvant)		Advanced / metastatic NSCLC Studies		Overall osimertinib safety pool (N=1479)
	Osimertinib (N=337)	Placebo (N=343)	Osimertinib First-line (N=309)	Osimertinib ≥Second-line (N=833)	
Patients with any SAE	54 (16.0)	42 (12.2)	71 (23.0)	244 (29.3)	369 (24.9)
Pneumonia	5 (1.5)	4 (1.2)	8 (2.6)	28 (3.4)	41 (2.8)
Cataract	3 (0.9)	-	-	-	3 (0.2)
Diarrhoea	2 (0.6)	-	2 (0.6)	2 (0.2)	6 (0.4)
Acute kidney injury	2 (0.6)	-	1 (0.3)	1 (0.1)	4 (0.3)
Ureterolithiasis	2 (0.6)	-	-	-	2 (0.1)
Femur fracture	2 (0.6)	1 (0.3)	-	-	2 (0.1)

Includes AEs with onset date on or after the date of first dose up to and including 28 days following discontinuation of study treatment and before starting subsequent cancer therapy. Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories.
MedDRA version 22.1

Deaths

Table 69: Summary of Deaths

Category	Number (%) of patients				
	ADAURA Study (Adjuvant)		Advanced / metastatic NSCLC Studies		Overall osimertinib safety pool (N=1479)
	Osimertinib (N=337)	Placebo (N=343)	Osimertinib First-line (N=309)	Osimertinib ≥Second-line (N=833)	
Total number of deaths	9 (2.7)	20 (5.8)	58 (18.8)	252 (30.3)	319 (21.6)
Death related to disease under investigation only	9 (2.7)	18 (5.2)	51 (16.5)	212 (25.5)	272 (18.4)
AE with outcome of death only	-	-	6 (1.9)	18 (2.2)	24 (1.6)
Number of patients with death related to disease and an AE with outcome of death	-	1 (0.3)	-	17 (2.0)	17 (1.1)
Other deaths [a]	-	1 (0.3)	1 (0.3)	5 (0.6)	6 (0.4)

[a] Patients who died and are not captured in the earlier categories.
Death related to disease under investigation are determined by the investigator. Rows are mutually exclusive; patients are only reported in one category.

Adverse Events of Special Interest (AESI)

A number of AEs were prospectively identified as being topics of interest in the ADAURA study before database lock, based on the known osimertinib safety profile to date.

The pre-defined AESI topics for ADAURA are the grouped terms ILD and Cardiac failure.

Cardiac failure is an important potential risk of osimertinib, and ILD is an important identified risk of the risk management plan.

The ILD AESI topic was evaluated by review of grouped preferred terms, comprising: Interstitial lung disease, Pneumonitis, Acute interstitial pneumonitis, Alveolitis, Diffuse alveolar damage, Idiopathic pulmonary fibrosis, Lung disorder, Pulmonary toxicity, and Pulmonary fibrosis. Enrolment of patients with a history of ILD or clinically active ILD was specifically excluded.

The Cardiac failure AESI topic was evaluated by review of Cardiac failure and Cardiomyopathy, and changes in cardiac contractility during treatment as assessed by echocardiogram or multi-gated acquisition scan (performed at screening and every 12 weeks relative to the first dose, or as clinically indicated).

- **Interstitial Lung Disease (ILD)**

In ADAURA, AEs in the ILD grouped term were reported for 10 patients (3%) in the osimertinib arm (all mild or moderate in severity, and 1 SAE [due to hospitalisation]), and no patients in the placebo arm.

Subgroup analyses (Japanese vs Non-Japanese/Asian vs Non-Asian) were performed. The majority of patients reported with ILD were of Japanese ethnicity (6/10 patients with an AE of ILD). There were 45 patients of Japanese ethnicity in ADAURA, 72 in the first-line studies, and 158 in the second-line or greater studies (a total of 275 in the osimertinib safety pool).

The frequency of ILD in ADAURA was consistent with the advanced/metastatic population. However, the events reported in ADAURA were less severe [(60%) reported as mild (6/10 patient with an event of ILD)], and there were fewer SAEs than in the advanced/metastatic population. In total, ILD was reported as serious (due to hospitalisation) in 1 patient (10% of patients with an event of ILD) in the adjuvant population.

In the advanced/metastatic population, whilst the majority of patients had only a mild or moderate event, severe AEs (CTCAE Grade 3) were reported for 26.7% of patients with an event of ILD (12/45 patients). The majority of AEs were reported as serious (in 57.8% of patients with an event of ILD [26/45 patients], and of these, 11.1% of patients (5/45 patients with an event of ILD) experienced an AE of ILD with a fatal outcome.

The median time to onset of ILD (grouped term) was similar in the different settings: 81.5 days in osimertinib treated patients in the adjuvant population, and 91.5 days and 84 days for first-line and second-line or greater patients, respectively, in the advanced/metastatic population.

Per protocol, all 8 patients with a reported event of ILD (PT) were discontinued from study treatment. Of the 2 patients reported with pneumonitis (PT), 1 was discontinued from study treatment, whilst the remaining patient with a non-causally related event of pneumonitis and a concurrent respiratory tract infection continued study treatment. This event subsequently resolved without dose modification.

All patients (100%) who had an AE of ILD in the adjuvant population recovered from the event. In contrast, recovery was recorded for 64.3% of patients in the advanced/metastatic first-line population, and 38.7% of patients in the advanced/metastatic second-line or greater population.

In the overall osimertinib safety pool (1479 patients), ILD (grouped term) was reported at an incidence of 3.7%, with a median time to onset of 84 days (range 8 to 951 days). When split by ethnicity, the incidence of ILD was 10.9% in patients of Japanese ethnicity (30/275 patients), 1.6% in patients of non-Japanese Asian ethnicity (9/572 patients), and 2.5% in non-Asian patients (16/632 patients).

No fatal ILD AEs were reported in the ADAURA study. Upon integrating the data from the ADAURA study with data from studies in the advanced/metastatic treatment setting, the total number of fatal ILDs in the overall osimertinib safety pool remains at 5 patients (0.3%).

- **Cardiac Failure**

Table 70: Change in LVEF data

Category	Number (%) of patients				
	ADAURA Study (Adjuvant)		Advanced / metastatic NSCLC Studies		Overall osimertinib safety pool (N=1479)
	Osimertinib (N=337)	Placebo (N=343)	Osimertinib First-line (N=309)	Osimertinib ≥Second-line (N=833)	
Baseline LVEF assessment	337 (100)	341 (99.4)	272 (88.0)	705 (84.6)	1314 (88.8)
Baseline and post-baseline LVEF assessment [a]	325 (96.4) [b]	331 (96.5)	262 (84.8)	646 (77.6)	1233 (83.4)
LVEF decrease of ≥ 10 percentage points to an absolute value of < 50% [a, c, d]	5 (1.5)	5 (1.5)	8 (3.1)	27 (4.2)	40 (3.2)
LVEF decrease of ≥ 15 percentage points to an absolute value of ≥ 50% [a, c, d]	16 (4.9) [b]	11 (3.2)	25 (9.5)	34 (5.3)	75 (6.1)

[a] Includes assessments on or after the date of first dose and up to and including 28 days following discontinuation of randomised treatment.

[b] Note: These data differ from the Section 12.2.5.2 of the ADAURA CSR (Module 5.3.5.1) where the LVEF measurements up to the study treatment discontinuation were included in Table 14.3.8.11.2. In the ADAURA CSR, 312 patients are reported to have had a baseline and post-baseline LVEF assessment; however there is no meaningful impact resulting from this discrepancy.

[c] Occurring at the same echocardiography assessment, at any post-baseline time point.

[d] Percentages have been calculated using the number of patients with a baseline and post-baseline echocardiography assessment.

Baseline was defined as the last non-missing measurement prior to the first dose of study treatment.
Sources: Table 14.3.8.11.2, ADAURA CSR, Module 5.3.5.1; Table 2.7.4.6.6.

In ADAURA, 16 patients (4.7%) in the osimertinib arm, and 10 patients (2.9%) in the placebo arm reported AEs in the Cardiac failure grouped term, with ejection fraction decreased the most frequently reported AE (osimertinib: 12 patients [3.6%]; placebo: 10 patients [2.9%]). No differences in the severity of AEs indicative of cardiac failure was noted between treatment arms, with the majority of AEs in the Cardiac failure grouped term mild or moderate in severity (CTCAE Grade 1 or 2 events were reported in 13/16 patients in the osimertinib arm and 9/10 patients in the placebo arm).

However, a difference in median time to onset was observed between treatment arms: 418.5 days in the osimertinib arm (range 52 to 1021 days), and 126 days in the placebo arm (range 82 to 832 days). Compared with ADAURA, AEs in the Cardiac failure grouped term were reported at a similar frequency in the first-line patients (4.2%), but less frequently in second-line or greater patients (2%).

In the overall osimertinib safety pool, AEs in the cardiac failure grouped term were reported in 3.1% of patients.

Laboratory findings

Haematology

Haemoglobin: median haemoglobin count in the ADAURA osimertinib arm was within the normal range at baseline and for the duration of the on-treatment period, with no meaningful differences to the placebo arm observed.

No clinically significant changes from baseline or trends in haemoglobin values over time were observed in the adjuvant population, which is consistent with previous findings in the advanced/metastatic population.

Neutrophils, platelets, lymphocytes and leukocytes: Decreases in neutrophil, platelet, lymphocyte and leukocyte counts are considered ADRs for osimertinib, based on previous clinical experience in the advanced/metastatic treatment setting. For these haematological parameters in adjuvant population, median counts in the osimertinib arm were within the normal range at baseline and remained so throughout the on-treatment period.

Clinical chemistry

General clinical chemistry: In the ADAURA study, no clinically significant changes in median values of albumin, calcium, glucose, magnesium, potassium or sodium were observed during osimertinib treatment, with no differences between treatment arms.

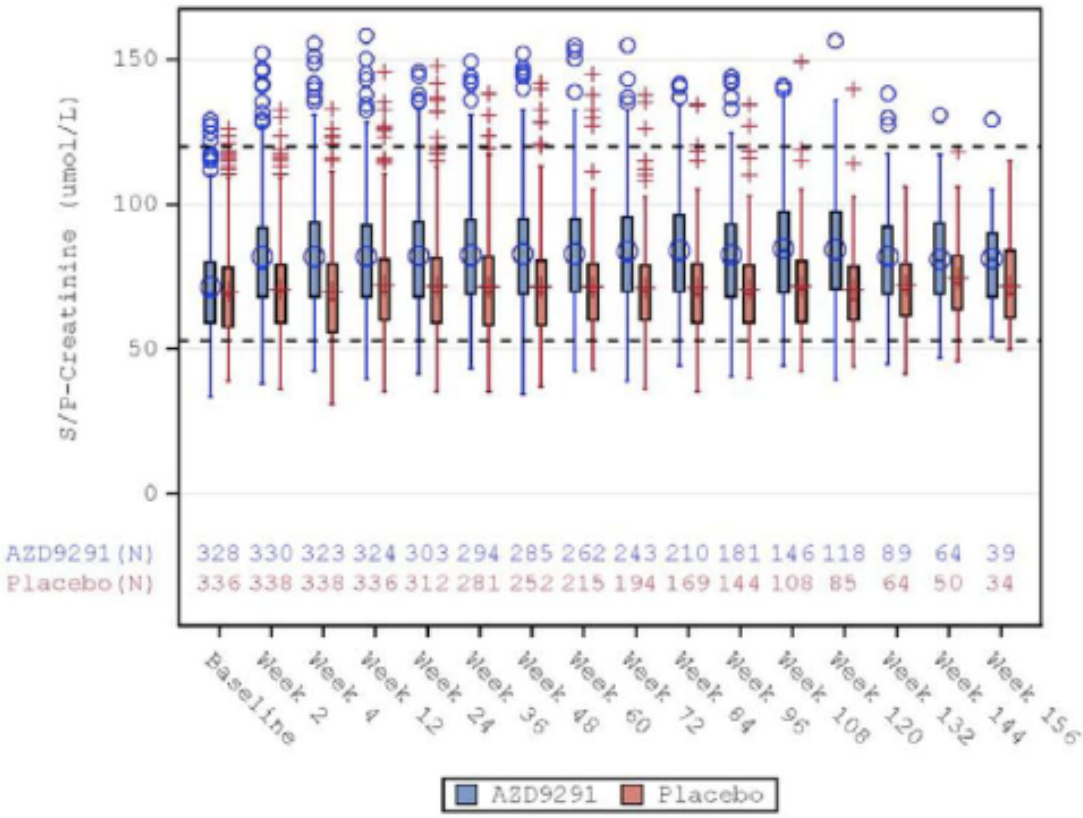
Renal biochemistry: Median creatinine in both treatment arms was within the normal range at baseline (osimertinib: 69 umol/L; placebo: 68.8 umol/L) and for the duration of the on-treatment period.

In the osimertinib arm, a slight increase in median creatinine count from baseline was observed at week 2 (78.3 umol/L; which remained above the LLN), with a corresponding fall in creatinine clearance (from 76.4 mL/min at baseline to 68 mL/min at Week 2), however these counts remained stable for the remaining duration of treatment.

In the ADAURA study, worsening CTCAE grade shifts in creatinine from baseline were seen in 9.8% of patients with data in the osimertinib arm and 4.5% of patients with data in the placebo arm, with the majority of the grade shifts in both treatment arms of CTCAE grade 1 (osimertinib: 31/32 patients; placebo: 13/15 patients).

Worsening CTCAE grade shifts in creatinine from baseline were seen at similar frequencies in the advanced/metastatic population (9.9% of first line patients, and 9% of second-line or greater patients). As observed in osimertinib-treated patients in the adjuvant population, the majority of these were 1-grade shifts (25/30 first-line patients, and 70/75 second-line or greater patients).

Based on the findings, and in consideration of data from all sources, blood creatinine increased as a laboratory finding has been confirmed as an osimertinib ADR; however, following a review of corresponding AE data, no clinically significant sequelae have been observed. In the ADAURA study, AEs in the renal and urinary disorders SOC were reported in 38 patients (11.3%) in the osimertinib arm, and 28 patients (8.2%) in the placebo arm, with no specific clustering of preferred terms noted.



Dotted lines represent AstraZeneca standard reference ranges. Horizontal line: Median, Box: Q1 - Q3. Whiskers extend to the most extreme observation within 1.5 times the interquartile range from the nearest quartile.
Note: There were 15 outliers with values that were beyond the y-axis of this graph (osimertinib: 11 above range, Placebo: 4 above range).
Source: Figure 14.3.7.2, ADAURA CSR, Module 5.3.5.1.

Figure 43: Box plot of absolute values of creatinine (ADAURA study: Safety Analysis Set)

Hepatic biochemistry: In the ADAURA study, no clinically important changes from baseline in AST, ALT or total bilirubin were observed during osimertinib treatment, with no differences between treatment arms noted. At a population level, the median values of all hepatic laboratory investigation were within the normal range at baseline and remained so throughout the entire duration of osimertinib treatment.

This is consistent with previous findings in the advanced/metastatic population.

Vital signs and physical findings: No unexpected or clinically meaningful trends or changes from baseline in vital signs or physical examination safety parameters over time were observed in the ADAURA study.

Electrocardiogram data: In all studies in the osimertinib clinical development programme, patients with aQTcF > 470 msec, any clinically important abnormalities in rhythm or conduction, or with any factors increasing the risk of QT prolongation or arrhythmic events were excluded from participation in the study.

QTc prolongation is considered to be an osimertinib ADR. On a population level, median baseline QTcF in the osimertinib arm was 412.0 msec. Median QTcF had increased at the first on-treatment assessment at Week 4 (median: 422.5 msec; n = 330 patients), which remained generally stable throughout the on-treatment period, with only minor fluctuations in medianQTcF noted at each assessment timepoint (to a maximum median QTcF of 429.7 msec at Week 156; n = 39 patients).

Changes from baseline above pre-specified thresholds in QTcF values have also been observed in individual patients in both the ADAURA study and the studies in the advanced/metastatic treatment setting. A comparable proportion of patients in the adjuvant and the advanced/metastatic first line and second-line or greater populations had a QTcFof > 500 msec and an increase of > 60 msec at any time during osimertinib treatment (0.6%,0.3%, and 0.5% of patients, respectively).

No AEs of arrhythmia were reported in osimertinib-treated patients in the adjuvant population. In total, 22 patients (6.5%) on the osimertinib arm had an AE of electrocardiogram QT prolonged, which is broadly consistent with the incidence of such events observed in the advanced/metastatic population (AEs of electrocardiogram QT prolonged were reported in 9.7% of first-line patients, and 4.7% of second-line or greater patients.

Safety in special populations

The osimertinib safety profile has previously been assessed in relation to the following intrinsic factors:

- Gender (male, female)
- Age group (years) (grouped as < 65, 65 - 75 and ≥ 75)
- Race (grouped as White, Black or African American, Asian, Other)
- WHO PS (0, 1)

Based on cross-programme population PK analysis, no impact of gender, race/ethnicity, or age on the exposure of osimertinib has been observed. The osimertinib safety profile by the intrinsic factors of gender, age group, race and WHO PS is in line with the known overall safety profile of osimertinib, with no safety signals identified.

Extrinsic factors: Smoking status

An assessment of the osimertinib safety profile by smoking status (Ever smoked or Never smoked) in the adjuvant population at the AE category level showed no meaningful differences between treatment arms in relation to smoking status

Furthermore, no notable differences in the most commonly reported AEs were observed in relation to smoking status either between treatment arms in the adjuvant population, or when comparing osimertinib-treatment patients in the adjuvant population with data from the advanced/metastatic population.

Safety related to drug-drug interactions and other interactions

In this application, there is no new information relating to drug interactions; use in pregnancy or lactation; overdose and drug abuse; withdrawal and rebound; or ability to drive or operate machinery.

Discontinuation due to adverse events

A total of 266 patients had discontinued their randomised study treatment prior to the planned 3-year treatment duration: 92 patients (27.3% of those who received treatment) in the osimertinib arm, and 174 patients (50.7%) in the placebo arm. In the osimertinib arm, the most frequently reported reason for study treatment discontinuation was AE (36 patients). In the placebo arm, the most frequently reported reason for study treatment discontinuation was disease recurrence (148 patients). Three patients in the placebo arm (0 patients in the osimertinib arm) discontinued due to severe non-

compliance to the protocol. The number and reasons for discontinuations from treatment do not raise any concerns about the conduct of the study.

At the data cut-off date, the majority of patients were ongoing in the study (616 patients overall [90.3% of all randomised patients]: 309 osimertinib-treated patients [91.2%], and 307 placebo-treated patients [89.5%]). Of the 66 patients overall (9.7%) who terminated the study, the main reason was withdrawal by the patient in the osimertinib arm (19/30 patients), and death in the placebo arm (20/36 patients).

Discontinuation due to Adverse Events

The discontinuation of study treatment was mandatory in the event a patient developed any of the following specific AEs: ILD, and QTc interval prolongation with signs/symptoms of serious arrhythmia. Furthermore, study treatment discontinuation was mandated for all patients in the advanced/metastatic studies with corneal ulceration.

In ADAURA, 37 (11 %) patients in the osimertinib arm and 10 (2.9%) patients in the placebo arm discontinued study treatment due to an AE, with the majority of them reported as non-serious and mild or moderate in severity. For the osimertinib arm, this is similar to the frequency of AEs leading to discontinuation in the advanced/metastatic population (12.9% of first-line patients, and 8.3% of second-line or greater patients).

According to the protocol, any patient that had an AE in the ILD grouped term had to discontinue study treatment, and this was the case for 9 of the 37 patients in the Osimertinib arm who discontinued due to an AE. Other discontinuations were for a range of PTs with no trends or clustering of events, and the majority of AEs leading to discontinuation were nonserious and mild or moderate in severity.

As expected, more patients in the osimertinib arm reported a discontinuation AE than in the placebo arm; however a noteworthy proportion of discontinuation AEs in the osimertinib arm were due to the protocol-mandated discontinuation criteria of ILD (9/37: 8 patients with an AE of ILD, and 1 patient with an AE of pneumonitis), which is consistent with the known osimertinib safety profile. Of the non-protocol mandated discontinuation AEs, the most frequently reported events in the osimertinib arm were diarrhoea and decreased appetite (3 patients each; 0.9%), which correspond with the overall most frequently reported AEs within the osimertinib arm of study.

Upon review of the non-protocol mandated discontinuation AEs, no specific pattern or clustering of events was noted, and no new safety signal was identified.

The overall incidence of discontinuation AEs in osimertinib-treated patients in the adjuvant population (11 %) was consistent with the incidence of discontinuation AEs in the advanced/metastatic population (in which 12.9% of first-line patients, and 8.3% of second-line or greater patients had a DAE), with comparable incidences of individual discontinuation AEs reported across treatment settings.

In the overall osimertinib safety pool, discontinuation AEs were reported for 9.9% of patients overall, with the most frequently reported discontinuation AEs (> 1% of patients) being ILD (1.8%) and pneumonitis (1.5%); both of which were reported at a greater frequency in the advanced/metastatic population than in the adjuvant population. Discontinuation due to adverse reactions was reported in 4.8% of patients overall.

Table 71: DAEs, by PT (reported in ≥2 osimertinib-treated patients in the ADAURA study)

MedDRA Preferred Term	Number (%) of patients				
	ADAURA Study (Adjuvant)		Advanced / metastatic NSCLC Studies		Overall osimertinib safety pool (N=1479)
	Osimertinib (N=337)	Placebo (N=343)	Osimertinib First-line (N=309)	Osimertinib ≥Second-line (N=833)	
Patients with any DAE	37 (11.0)	10 (2.9)	40 (12.9)	69 (8.3)	146 (9.9)
Interstitial lung disease	8 (2.4)	-	6 (1.9)	12 (1.4)	26 (1.8)
Diarrhoea	3 (0.9)	-	-	1 (0.1)	4 (0.3)
Decreased appetite	3 (0.9)	-	-	1 (0.1)	4 (0.3)
Dermatitis acneiform	2 (0.6)	-	-	-	2 (0.1)
Pruritus	2 (0.6)	-	1 (0.3)	-	3 (0.2)
Acute kidney injury	2 (0.6)	-	-	-	2 (0.1)
Fatigue	2 (0.6)	-	-	-	2 (0.1)

Includes AEs with onset date on or after the date of first dose up to and including 28 days following discontinuation of study treatment and before starting subsequent cancer therapy. 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.

MedDRA version 22.1

AEs Leading to Dose Modification:

The incidence of patients with AEs leading to dose modifications (defined as a treatment interruption and/or a dose reduction) was 28.8% in the osimertinib arm and 11.4% in the placebo arm.

It is noted that 12 patients in the osimertinib arm, and 1 patient in the placebo arm had both a dose reduction and a study treatment interruption; these patients are counted within both of the sections below.

AEs Leading to Dose Reduction

In ADAURA, 8.6% of patients in the osimertinib arm and 0.9% of patients in the placebo arm were reported with an AE leading to a dose reduction. Adverse events leading to dose reductions in more than 1 patient in the osimertinib arm were: stomatitis (5 patients; 1.5%), paronychia (4 patients; 1.2%), and hypertension, diarrhoea, nausea, and ECG QT prolonged (2 patients each; 0.6%). These AE (with the exception of hypertension and nausea) are well-characterised osimertinib ADRs, and therefore these findings are not considered unexpected.

No AE leading to a dose reduction was reported by more than 1 patient in the placebo arm.

In the advanced/metastatic population, fewer AEs leading to dose reduction were reported than in ADAURA (4.5% of first line patients, and 4.0% of second line or greater patients). However, these data should be interpreted in the context of longer exposure to osimertinib in ADAURA, and the majority of AEs leading to dose reduction in ADAURA were mild or moderate in severity and did not lead to treatment discontinuation.

In the overall osimertinib safety pool, AEs led to a dose reduction in 5.1% of patients and ADRs led to a dose reduction in 4.8% of patients. No AE leading to a dose reduction was reported in > 1% of

patients; with AEs of ECG QT prolonged (0.7%), paronychia (0.5%), and neutropenia (0.3%), nausea (0.3%), and stomatitis (0.3%) being the only events reported in ≥ 5 patients.

Table 72: AEs leading to dose reduction, by PT (reported in ≥2 osimertinib-treated patients in the ADAURA study)

MedDRA Preferred Term	Number (%) of patients				
	ADAURA Study (Adjuvant)		Advanced / metastatic NSCLC Studies		Overall osimertinib safety pool (N=1479)
	Osimertinib (N=337)	Placebo (N=343)	Osimertinib First-line (N=309)	Osimertinib ≥Second-line (N=833)	
Patients with any AE leading to dose reduction of study treatment	29 (8.6)	3 (0.9)	14 (4.5)	33 (4.0)	76 (5.1)
Stomatitis	5 (1.5)	-	-	-	5 (0.3)
Paronychia	4 (1.2)	-	1 (0.3)	2 (0.2)	7 (0.5)
Diarrhoea	2 (0.6)	1 (0.3)	-	2 (0.2)	4 (0.3)
ECG QT prolonged	2 (0.6)	-	5 (1.6)	3 (0.4)	10 (0.7)
Hypertension	2 (0.6)	-	-	-	2 (0.1)
Nausea	2 (0.6)	-	1 (0.3)	2 (0.2)	5 (0.3)

Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories. Includes 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 and on or before starting subsequent cancer therapy.
MedDRA version 22.1

Adverse events leading to study treatment interruption

Adverse events leading to dose interruption were reported for 23.7% of patients in the osimertinib arm and 10.8% of patients in the placebo arm. For the osimertinib arm, this is similar to the frequency of AEs leading to treatment interruption in the advanced/metastatic population (26.9% of first-line patients, and 22.3% of second-line or greater patients).

In the osimertinib arm of ADAURA, the most common AEs leading to dose interruption were diarrhoea (13 patients, 3.9%) and stomatitis (8 patients, 2.4%), which are both well-characterised osimertinib ADRs.

With the exception of stomatitis (which was reported more frequently in the adjuvant population) and pneumonia (reported more frequently in the advanced/metastatic population), comparable incidences of the most frequently reported AEs leading to treatment interruption were observed across treatment settings.

Table 73: AEs leading to treatment interruption, by PT (reported in ≥2 osimertinib-treated patients in the ADAURA study)

MedDRA Preferred Term	Number (%) of patients				
	ADAURA Study (Adjuvant)		Advanced / metastatic NSCLC Studies		Overall osimertinib safety pool (N=1479)
	Osimertinib (N=337)	Placebo (N=343)	Osimertinib First-line (N=309)	Osimertinib ≥Second-line (N=833)	
Patients with any AE leading to study treatment interruption	80 (23.7)	37 (10.8)	83 (26.9)	186 (22.3)	349 (23.6)
Diarrhoea	13 (3.9)	4 (1.2)	7 (2.3)	9 (1.1)	29 (2.0)
Stomatitis	8 (2.4)	-	2 (0.6)	2 (0.2)	12 (0.8)
Gastroenteritis	4 (1.2)	-	1 (0.3)	3 (0.4)	8 (0.5)
Abdominal pain	4 (1.2)	-	1 (0.3)	-	5 (0.3)
Vomiting	4 (1.2)	3 (0.9)	1 (0.3)	6 (0.7)	11 (0.7)
Influenza	3 (0.9)	-	1 (0.3)	2 (0.2)	6 (0.4)
Paronychia	3 (0.9)	-	-	4 (0.5)	7 (0.5)
Neutropenia	3 (0.9)	-	2 (0.6)	11 (1.3)	16 (1.1)
Decreased appetite	3 (0.9)	-	7 (2.3)	2 (0.2)	12 (0.8)
Dizziness	3 (0.9)	1 (0.3)	1 (0.3)	1 (0.1)	5 (0.3)
Fatigue	3 (0.9)	1 (0.3)	3 (1.0)	1 (0.1)	7 (0.5)
Herpes zoster	2 (0.6)	1 (0.3)	-	1 (0.1)	3 (0.2)
Pyrexia	2 (0.6)	-	1 (0.3)	1 (0.1)	4 (0.3)
Pharyngitis	2 (0.6)	-	-	2 (0.2)	4 (0.3)
Pneumonia	2 (0.6)	2 (0.6)	9 (2.9)	14 (1.7)	25 (1.7)
Anaemia	2 (0.6)	-	2 (0.6)	5 (0.6)	9 (0.6)
Dysgeusia	2 (0.6)	-	-	-	2 (0.1)
Cough	2 (0.6)	-	1 (0.3)	-	3 (0.2)
Ureterolithiasis	2 (0.6)	-	-	-	2 (0.1)
Ejection fraction decreased	2 (0.6)	1 (0.3)	1 (0.3)	2 (0.2)	5 (0.3)
ECG QT prolonged	2 (0.6)	1 (0.3)	8 (2.6)	14 (1.7)	24 (1.6)

Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories. Includes 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 and on or before starting subsequent cancer therapy.

MedDRA version 22.1

Sources: Table IMT1044PA, ADAURA CSR, Module 5.3.5.1; Table 2.7.4.2.1.11.

Safety of Long-term Treatment

As ADAURA was unblinded early, fewer patients had completed the planned treatment duration of 3 years than had been expected at the time of the planned primary analysis.

A total of 40 patients (11.9%) completed 3 years of treatment based on total treatment exposure including treatment interruptions, and 8 patients (2.4%) had 3 years of actual exposure to osimertinib.

The median exposure to osimertinib in ADAURA was 22.5 months, and 43.9% of patients in the osimertinib arm had at least 2 years of exposure. In addition, 60.8% patients in the osimertinib arm were still on treatment at the data cut-off date.

Post marketing experience

As of the latest global periodic benefit-risk evaluation report (DLP 12 November 2019), a total of 10,057 subjects (118 healthy volunteers, 2870 patients in clinical studies, 4,055 patients in Named Patient Supply and Early Access Programme, 3,014 patients in the Real World Evidence Study [D5160C00022]) had been dosed with osimertinib (not including 190 patients who crossed over during study from comparator to osimertinib monotherapy).

In the periodic benefit-risk evaluation report period from 13 November 2018 to 12 November 2019, the majority of post-marketing cases received were in keeping with the patient population being treated and the known safety profile of osimertinib.

The total cumulative post-marketing exposure to osimertinib for all doses and all countries as of 31 October 2019 was 83,723 patient-years.

Table 74. Patient-year of cumulative osimertinib exposure to 40 mg and 80 mg tablets, by region

Formulation	Europe	International	North America	Japan	Total
40 mg tablets	1080	207	1749	4504	7540
80 mg tablets	13398	31665	16443	14677	76183

2.6.1. Discussion on clinical safety

In the ADAURA study, the subjects' median exposure to osimertinib was 22.5 months. The actual median exposure in the osimertinib arm was similar to the total median exposure, indicating that the frequency of dosing interruptions for any reason and their median duration had almost no impact on osimertinib exposure. Treatment interruptions had no significant impact on dose intensity.

Whilst almost all patients treated with osimertinib reported an AE (97.6%), the majority were non-serious, mild or moderate in severity, and did not lead to treatment discontinuation. The most frequently reported (≥20%) were diarrhoea, paronychia and dry skin. The majority of patients (89.2%) also experienced at least 1 AE in the placebo arm.

The proportion of patients with an SAE or CTCAE ≥ Grade 3 AE was lower in the osimertinib arm of ADAURA than in the advanced/metastatic studies, consistent with what may be expected in a patient population with earlier stage disease.

The most common AE are also consistent with the osimertinib known safety profile. The largest difference was seen for "mouth ulceration" which has been added into the grouped term "stomatitis" as an ADR in section 4.8 of the SmPC.

Data from ADAURA study showed that in the adjuvant population, diarrhoea, rashes and acne, and stomatitis occur early in treatment, with no increased risk with long-term osimertinib treatment.

The majority of AEs were mild or moderate in severity (CTCAE Grade 1 or 2), with only a small proportion of patients in both the adjuvant and advanced/metastatic populations reported with an AE that was CTCAE ≥ Grade 3. As expected in a patient population with earlier stage disease, the proportion of patients who had a CTCAE ≥ Grade 3 AE was low in both treatment arms (osimertinib: 20.2%; placebo: 13.4%), despite the longer exposure to study treatment in the osimertinib arm of the ADAURA study. CTCAE ≥ Grade 3 AEs were reported less frequently in osimertinib-treated patients in the adjuvant population than has previously been observed in the advanced/metastatic population

(with the exception of diarrhoea and stomatitis), with overall incidence noted to increase with subsequent lines of treatment.

In the ADAURA study, the only CTCAE ≥ Grade 3 AE with more than a 2-pp difference between treatment arms was diarrhoea.

In the pooled safety dataset, the most frequently reported CTCAE ≥ Grade 3 AEs in osimertinib-treated patients (≥ 2% of patients) remain as pneumonia and pulmonary embolism.

Despite the longer exposure to study treatment in the osimertinib arm of the ADAURA study, SAEs were reported in a similar proportion of patients in both treatment arms.

SAEs were reported less frequently in osimertinib-treated patients in the adjuvant population than have previously been observed in the advanced/metastatic population, with the overall incidence of SAEs increasing with subsequent lines of treatment.

In the ADAURA study, pneumonia was the most frequently reported SAE, which was balanced in terms of incidence between arms (osimertinib: 1.5%; placebo: 1.2%). Upon review of the SAEs reported in ≥ 2 patients, diarrhoea is an expected event for osimertinib, and all other events in the osimertinib arm represent medical conditions that may occur in the general patient population over a prolonged period of evaluation.

Two cases of acute kidney injury were observed in the osimertinib arm, although both cases were assessed as unlikely related to osimertinib therapy.

In the overall osimertinib safety pool, only SAEs of pneumonia and pulmonary embolism have been reported in > 1% of patients (2.8% and 1.8%, respectively), with SAEs of pulmonary embolism reported only in patients treated for advanced/metastatic NSCLC.

Ocular toxicity has been reported in patients treated with osimertinib. In fact, keratitis (including corneal epithelium defect, corneal erosion, keratitis, punctate and keratitis) is currently described in sections 4.4 and 4.8 of the SmPC. In the ADAURA study, a higher incidence of cataracts was observed in patients treated with osimertinib compared with placebo (9 [2.7%] vs. 4 [1.2%. While the incidence appears low, it was more than double in the osimertinib arm. Moreover, a similar pattern was observed in the AURA3 study (4 [1.4%] osimertinib vs. 0 chemotherapy). In the ADAURA study the median time to onset of cataract was 218.5 days (range 39-705). The majority of patients who reported an AE of cataract were Asian and female. This is in line with the statement that cataracts are more prevalent in people of Asian ethnicity compared with Europeans. Most of the events were mild. There was one patient with a serious adverse event of cataract who discontinued treatment with osimertinib and which was considered by the investigator as related to study treatment.

The MAH has identified a total of 37 (2.5%) patients in the osimertinib safety pool (n=1479) who reported an AE from the Narrow lens disorders SMQ (mainly AEs of PT cataract, with 1 each of cataract nuclear, lenticular opacities, and posterior capsule opacification). In most of the patients other confounding factors were present (e.g. advanced age, diabetes mellitus, prior history of cataracts) and therefore it is difficult to establish a causal relationship with osimertinib. However, taking into account lens opacities have been observed in non-clinical trials (see non-clinical section of this AR), cataract is considered a potential risk of osimertinib and will be kept under close surveillance. Cataract will be included to the list of risks to be addressed in the next PSURs. Moreover, the MAH should provide a detailed description, including narratives, of all events of cataract reported in the ADAURA study within the final CSR.

Disease recurrence (as assessed by the Investigator) was the only reported reason for death in the osimertinib arm and was the most common reason for death in the placebo arm. None of the patients

in the osimertinib arm were reported to have died from an AE. To date the deaths reported in ADAURA study do not raise concerns about the safety of osimertinib, although long-term data should be provided to confirm that this trend continues through the study completion date.

The grouped terms ILD and cardiac failure were reported at a similar frequency in ADAURA and the advanced/metastatic setting, and all were mild or moderate in severity. The ILD events reported in ADAURA were less severe and there were fewer SAEs than in the advanced/metastatic population.

Consistent with previous osimertinib clinical studies for the advanced/metastatic patient population, the majority of patients reported with ILD were of Japanese ethnicity. No fatal ILD AEs were reported in the ADAURA study. In the advanced/metastatic population, 5 fatal ILD cases have been observed. The difference in observed fatal ILD cases between adjuvant and advanced/metastatic populations has been reflected in section 4.4. of the SmPC.

Notably, in ADAURA there was no difference between treatment arms in the number of patients who experienced a decrease in LVEF of ≥ 10 pp and a drop to < 50%, despite the longer treatment duration in the osimertinib arm and in contrast to what has been reported from previous studies. This has been reflected in section 4.4 of the SmPC.

Six new ADRs have been identified further to the review of the ADAURA study: alopecia, epistaxis, palmoplantar erythrodysesthesia (PPES), mouth ulceration (a grouped term stomatitis), decreased appetite and increased blood creatinine.

Alopecia has been added as an ADR with the frequency 'common', based on a plausible mechanism of action based on effects of osimertinib on keratinocyte proliferation and keratin production, and based on the fact that alopecia is an ADR for other EGFR-TKIs,

Epistaxis has been added as an ADR with the frequency of 'common' considering the imbalance between treatment arm and placebo arm, a plausible mechanism of action based on possible alteration of nasal mucous epithelium, and the fact that it is an ADR for other EGFR-TKIs,.

In ADAURA, more patients in the osimertinib arm than the placebo arm had an AE of mouth ulceration. The PTs of mouth ulceration and stomatitis will now be reported together under the grouped term ADR Stomatitis, with the frequency of 'very common' (24%).

PPES has been added as an ADR with the frequency of 'common' considering the imbalance in ADAURA, that PPES is an ADR for other EGFR-TKIs, a plausible mechanism of action based on inhibition of EGFR leading to damage to the capillary endothelium which may present as PPES, and reports from osimertinib post-marketing data.

Considering that CTCAE grade shifts from baseline in creatinine have been consistently reported in trials with osimertinib and with a consistent time to onset, blood creatinine increased has been added as a new laboratory finding with a frequency of common.

Based on the large frequency difference of "decreased appetite" between osimertinib and placebo arm, it has been included as an ADR in section 4.8 of the SmPC.

ADR typically occurs shortly after the start of treatment with osimertinib. In ADAURA, the prevalence of the commonly reported ADRs diarrhoea, rashes and acne, and stomatitis peaked within the first 3 months of treatment and either remained relatively constant or decreased over the remaining duration of treatment.

The time to onset of first ADRs was consistent across the adjuvant and advanced/metastatic populations, with a median of 14 days for the osimertinib safety pool. In the adjuvant population

(6.8%), there were fewer CTCAE Grade ≥ 3 ADRs than in the advanced/metastatic population (11.0% for first-line patients and 8.2% for second-line or greater patients).

There were also fewer serious ADRs in the adjuvant population (0.9%) than in the advanced/metastatic population (4.2% for first-line patients and 2.9% for second-line or greater patients). Small changes in the frequency of other ADRs due to the pooling of safety data are also implemented in the SmPC. None of these are considered significant changes.

Through the current variation application, urticaria was also added as a new ADR in section 4.8 of the SmPC with the frequency 'common', based on data from clinical trials, post-marketing use and literature.

There was no impact of intrinsic or extrinsic factors on the safety profile of osimertinib in the adjuvant patient population in ADAURA. These findings were reported as consistent with previous observations.

Most subjects with dose interruptions restarted treatment at their previous osimertinib dose, and the majority of subjects experiencing a dose reduction were able to continue the study The majority of AEs that led to the interruption or reduction of the osimertinib dose appear to be of mild or moderate severity, with an overall lower incidence of severe (i.e. Grade ≥3) AEs.

There is currently limited data from ADAURA beyond 24 months exposure and few patients received osimertinib for the planned 3-year treatment duration. Data on time to onset for ADRs show that ADRs generally occur early in treatment, with no observed significant risk with long-term treatment. Despite this and given that in the adjuvant setting it is key to demonstrate long-term safety, updated safety data should be presented to confirm the absence of long-term AEs/ADRs. These data will be submitted with the final CSR of the ADAURA study.

2.6.2. Conclusions on clinical safety

In the ADAURA study, osimertinib treatment was well-tolerated by most patients. Several new ADRs were identified (alopecia, epistaxis, palmoplantar erythrodysesthesia, mouth ulceration, decreased appetite and increased blood creatinine). Urticaria was also added as a new ADR based on post-marketing events. The frequency of AEs leading to discontinuation was low, and most of these AEs were mild or moderate in severity.

Overall, the safety data from ADAURA are consistent with the known safety profile of osimertinib. Severe or serious ADRs were less frequent in ADAURA than in the advanced / metastatic population

Although, in general terms, the safety of osimertinib does not seem to lead to major concerns, long-term follow-up is considered necessary in the current context of adjuvant treatment. Updated safety data will be provided with the final CSR of the ADAURA study.

2.6.3. 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.

2.7. Risk management plan

The MAH submitted an updated RMP version with this application.

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

The PRAC considered that the risk management plan version 14.3 is acceptable.

The CHMP endorsed the Risk Management Plan version 14.3 with the following content:

No changes to the list of safety concerns, pharmacovigilance plan and risk minimisation measures were made as a result of the new adjuvant indication. Routine pharmacovigilance, as well as routine risk minimisation measures remain sufficient to mitigate Tagrisso's risk in all approved indications.

Safety concerns

Important Identified Risks	• Interstitial lung disease
Important Potential Risks	• Cardiac failure
Missing Information	• None

Pharmacovigilance plan

Not applicable.

Risk minimisation measures

Table 75: Summary table of risk minimisation measures

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risks		
ILD	Routine risk minimisation measures: • SmPC Section 4.8 (Undesirable effects). • SmPC Section 4.2 (Posology and method of administration) and Section 4.4 (Special warnings and special precautions for use).	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Targeted follow-up questionnaire.
Important potential risks		
Cardiac failure	Routine risk minimisation measures: • SmPC Section 4.4 (Special warnings and special precautions for use).	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Targeted follow-up questionnaire

Abbreviations: ILD, interstitial lung disease; SmPC, Summary of Product Characteristics; PL, Package leaflet.

2.8. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 5.3 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

2.8.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package

leaflet has been submitted by the MAH and has been found acceptable.

3. Benefit-Risk Balance

3.1. Therapeutic Context

Osimertinib is an oral, potent, irreversible EGFR-TKI, effective against both EGFRm as well as the T790M mutation positive (TKI resistance conferring mutation) forms of EGFR.

The claimed indication is for the adjuvant treatment after complete tumour resection in adult patients with non-small cell lung cancer (NSCLC) whose tumours have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations.

3.1.1. Disease or condition

Lung cancer is the most common cancer in the world, with approximately 2 million new cases and 1.7 million deaths (Globocan 2018). In Europe, lung cancer is the third most frequently diagnosed cancer and the leading cause of cancer related deaths.

Non-small cell lung cancer (NSCLC) accounts for 80%–90% of lung cancers (Jemal A et al, 2011). It includes two major types: nonsquamous (including adenocarcinoma, large-cell carcinoma and other subtypes) and squamous cell (epidermoid) carcinoma.

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. EGFR tyrosine kinase inhibitors (TKIs) are established effective therapies in patients who have activating and sensitising mutations in exons 18–21 of EGFR (Mok T et al, 2017). Prevalence is around 10%–20% of a Caucasian population with adenocarcinoma but much higher in Asian populations. EGFR mutations have been found to be more frequent in women. Moreover, while smoking is the main cause of lung cancer, is not a risk factor for developing activating mutations in the EGF-receptor, in fact the incidence seems higher in never-smokers subjects.

Around 90% of the most common mutations comprise deletions in exon 19 and the L858R substitution mutation in exon 21. The T790M exon 20 substitution mutation is only rarely found in EGFR TKI-naive disease using standard techniques but is the most frequent cause of resistance to first- and second-generation EGFR TKIs (50%–60% of cases).

3.1.2. Available therapies and unmet medical need

The primary treatment option for patients with stage IB-IIIA NSCLC is complete tumour resection. Adjuvant platinum-based chemotherapy should be offered to patients with resected stage II and III NSCLC and can be considered in patients with resected stage IB disease and other high-risk factors (NCCN 2020; ESMO 2017).

However, although treatment for patients with stage IB-IIIA is given with curative intent, recurrence occurs frequently. After a median follow-up of 5.2 years, the recurrence rate ranges from 45% for patients with stage IB disease to 76% for patients with stage III disease (Pignon et al 2008). Five-year survival rates range from 36% for patients with pathologic stage IIIA disease to 71% for patients with pathologic stage IB disease (Goldstraw et al 2016).

Following surgery and standard adjuvant chemotherapy no treatment options are currently approved in the EU for EGFRm resectable NSCLC. EGFR-TKIs such as osimertinib, afatinib, gefitinib and erlotinib is currently the standard of care for patients with locally advanced or metastatic EGFRm NSCLC. Osimertinib is also indicated for treatment of patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC whose disease has progressed on or after therapy with other EGFR-TKIs. However, in early-stage disease the use of EGFR-TKIs is investigational and there are no targeted treatments currently approved for adjuvant treatment. Patients with resectable EGFRm stage IB-IIIA NSCLC have limited treatment options and poor survival rates despite the curative intent of treatment at this disease stage. Thus, there is a considerable unmet medical need for improved treatment for these patients.

3.1.3. Main clinical studies

In support of this application the MAH has submitted efficacy and safety data from the ADAURA trial: a randomised, double-blind, Phase 3 study comparing osimertinib versus placebo in patients with stage IB, II, IIIA EGFRm (Ex19del or L858R) NSCLC, who have undergone complete tumour resection.

A total of 682 patients were randomised in a 1:1 ratio to receive either osimertinib 80 mg once daily (n=339) or matching placebo (n=343). Treatment was continued until recurrence of disease, a treatment discontinuation criterion was met, up to a maximum of 3 years. Stratification factors included disease stage (IB vs. II vs. IIIA), EGFR mutation status (Ex19del or L858R), and race (Asian or Non-Asian).

The primary endpoint of the study was disease free survival (DFS), as determined by the investigator. Overall survival (OS) and health related quality of life (HRQoL) were included as secondary endpoints.

3.2. Favourable effects

With a total of 26 [11.2%] events in the osimertinib arm and 130 [54.9%] in the placebo arm, a statistically significant improvement in DFS was observed with osimertinib compared with placebo in the primary efficacy population (stage II-IIIA population) (HR 0.17; 99.06%CI: 0.11, 0.26). Median DFS had not been reached in the osimertinib arm (95%CI: 38.8, NC) and was of 19.6 months (95%CI: 16.6, 24.5) in the placebo arm.

In the overall population (stage IB to IIIA), with an event-rate of 10.9% in the osimertinib arm and 46.4% in the placebo arm, DFS results were consistent with the primary efficacy population (HR 0.20; 99.12%CI: 0.14, 0.30). Median DFS was not reached in the osimertinib arm (95%CI: NC, NC) and was of 27.5 months (95%CI: 22.0, 35.0) in the placebo arm.

These results are supported by several sensitivity analyses. In addition, an improvement in DFS in patients receiving osimertinib compared to placebo was consistently observed in all pre-specified subgroups.

In the stage II-IIIA population, statistically significance was not reached for OS, although a weak trend in favour of osimertinib was observed (HR 0.40; 99.98%CI: 0.09, 1.83).

A post-hoc exploratory analysis indicated improvement in disease recurrence in the CNS for patients receiving osimertinib compared to placebo, with HR of 0.14 (95% CI: 0.07, 0.27; $p < 0.0001$) for stage II-IIIA patients, and HR of 0.18 (95% CI: 0.10, 0.33; $p < 0.0001$) for the overall population.

3.3. Uncertainties and limitations about favourable effects

The initial analysis plan for the primary endpoint did not include any interim analysis (IA) and was planned to be conducted after 247 DFS events were met. However, the reported results are based on an IA when 156 events had occurred and it is noted that major changes regarding the MTP have been implemented in the ongoing trial. Therefore, updated DFS analysis on a more mature set of data will be welcomed.

OS data at the time of the data cut-off were rather immature, with a total of 9 (2.7%) deaths in the osimertinib arm and 20 (5.8%) in the placebo arm. To what extent the delay in the time to recurrence may be translated into an actual benefit in terms of OS is unknown.

Although the number of patients who experienced CNS recurrence events was lower in the osimertinib arm (n=4) compared to the placebo arm (n=33) in the overall population, this was subject to post-hoc analysis, and not a pre-defined endpoint analysis. Besides, the number of patients in this analysis was limited.

The post-recurrence endpoints were only exploratory, and currently limited data on type of treatment after recurrence and the outcome, including post-recurrence PFS, are available.

Regarding treatment duration, only 40 (11.9%) patients in the osimertinib arm completed the 3-year study treatment period, thus, more mature data are needed in order to confirm the adequacy of the proposed treatment duration.

These uncertainties are all related to the immature data set which will require confirmation in the context of the PAES to provide the final results of the ADAURA study by Q2 2024 (see Annex II).

3.4. Unfavourable effects

In the ADAURA study, osimertinib treatment was well-tolerated by most patients. Several new ADRs were identified (alopecia, epistaxis, palmoplantar erythrodysesthesia, mouth ulceration, decreased appetite and increased blood creatinine). Urticaria was also added as a new ADR based on post-marketing events. The frequency of AEs leading to dose modification and discontinuation was low, and most of these AEs were mild or moderate in severity.

Overall, the safety data from ADAURA is consistent with the known safety profile of osimertinib. Severe or serious ADRs were less frequent in ADAURA than in the advanced / metastatic population

3.5. Uncertainties and limitations about unfavourable effects

Although the safety of osimertinib did not lead to major concerns, only a total of 40 patients (11.9%) completed 3 years of treatment based on total treatment exposure including treatment interruptions, and 8 patients (2.4%) had 3 years of actual exposure to osimertinib. Longer follow-up for safety is considered necessary in the current context of adjuvant treatment and will be provided with the final results from the ADAURA study (see Annex II)

As the adjuvant treatment is given for a risk rather than a provable disease, some of the included subjects in the ADAURA study are exposed to treatment with possibly no benefit and potential risk of experiencing (unnecessary) AEs. This is of special relevance to patients with stage IB NSCLC, where the rate of recurrence after a median follow-up of 5.2 years is approximately 45% (Pignon et al 2008).

3.6. Effects Table

Table 70: Effects Table for Tagrisso (osimertinib; 80 mg once daily orally) as adjuvant monotherapy after complete tumour resection in patients with NSCLC whose tumours have EGFR exon 19 deletions or exon 21 L858R substitution mutations, based on data from a single pivotal Phase 3 study (D5164C00001; ADAURA). (Data cut-off date: 17 January 2020)

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence
Favourable Effects					
DFS	Disease free survival (by investigator) – Stage II-IIIA population	Median months (95%CI)	NC (38.8, NC)	19.6 (16.6, 24.5)	IA with 11.2% events in the osimertinib arm and 59.9% events in the placebo arm HR 0.17 (95%CI: 0.12, 0.23) (99.06CI[a]: 0.11, 0.26)
	Disease free survival (by investigator)– Overall population (Stage IB-IIIA)	Median Months (95%CI)	NC (NC, NC)	27.5 (22.0, 35.0)	IA with 10.9% events in the osimertinib arm and 46.4% in the placebo arm HR 0.20 (95%CI: 0.15, 0.27) (99.12%CI[b]: 0.14, 0.30)
OS	Overall survival – Stage II-IIIA population	Median Months (95%CI)	NC (NC, NC)	NC (NC, NC)	IA with 3.4% events in the osimertinib arm and 7.2% in the placebo arm HR 0.40 (95%CI: 0.18, 0.89) (99.98%CI[c]: 0.09, 1.83)
Unfavourable Effects					
Patients with any CTCAE Grade ≥3		N (%)	68 (20.2)	46 (13.4)	CTCAE ≥ Grade 3 AEs were reported less frequently in osimertinib-treated patients in the adjuvant population than has previously been observed in the advanced/metastatic population
Grade ≥3 AEs Diarrhoea		N (%)	8 (2.4)	1 (0.3)	
Stomatitis		N (%)	6 (1.8)	-	
Paronychia		N (%)	3 (0.9)	-	
ILD:		N (%)	10 (3.0)	0	Reported at a similar frequency in ADAURA and the advanced/metastatic setting, and all were mild or moderate in severity.
Cardiac failure		N (%)	16 (4.9)	10 (3.2)	

Abbreviations: ILD: Interstitial lung disease

Notes: [a] The adjusted CI is computed at the 2-sided 99.06% level, considering a 2-sided significance level of 0.0094 for the interim analysis, based on the O Brien and Fleming spending function, assuming 247 DFS events would have been observed for the final analysis. [b] The adjusted CI is computed at the 2-sided 99.12% level, considering a 2-sided significance level of 0.0088 for the interim analysis, based on the O'Brien and Fleming spending function, assuming 317 DFS events for the final analysis. [c] The adjusted CI is computed at the 2-sided 99.98% level, considering a 2-sided significance level of 0.0002 for the interim analysis, based on the Haybittle-Peto spending function.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Results from the ADAURA study have shown a statistically significant advantage in terms of DFS of adjuvant treatment after complete tumour resection of osimertinib in patients with stage IB-IIIA NSCLC with exon 19 deletions or exon 21 (L858R) substitution mutations. Considering the poor prognosis of NSCLC patients with activating EGFR mutations (especially stage II-IIIA), the observed magnitude of DFS difference is considered clinically meaningful in the adjuvant treatment of these patients. However, these results come from an unplanned IA that was triggered by the IDMC and which led to a change in the multiple testing procedure for the primary outcome.

The DFS benefit of osimertinib compared to placebo was observed consistently across all subgroups, including disease stages IB, II and IIIA, in the presence or absence of prior adjuvant chemotherapy, as well as in Asian and non-Asian patients. A slightly higher HR for stage IB patients and patients with L858R mutation was observed compared to the stage II-IIIA patients and exon 19 deletions, respectively. Although this seems to indicate slightly less benefit for these two subgroups, the HR was still low in all subgroups.

A weak trend of a better OS was observed for osimertinib compared to placebo, but OS data are very immature and it is therefore not possible to ascertain whether the fact of moving forward treatment with osimertinib could improve the life expectancy of these patients. At least no detrimental effect was observed in OS, which is reassuring. Support from other evidence such as demonstrated lack of impact on responses to subsequent treatment could also be useful but is currently lacking.

A post-hoc exploratory analysis of disease recurrence in the CNS seems to indicate an improvement for patients receiving osimertinib compared to placebo. However, these data are considered preliminary due to the uncertainties caused by the limited number of CNS events as well as the fact that data was obtained from a post-hoc analysis. Of note, non-clinical studies have demonstrated distribution of osimertinib into the CNS, and anti-tumour effects on brain tumours in a xenograft model in mice. As CNS recurrence is associated with poor prognosis, and often unpleasant symptoms, reduction in this type of recurrence events is considered of high clinical importance. A longer follow-up data is needed to confirm the preliminary findings (see Annex II).

The safety profile of osimertinib in the studied population appears consistent with the known safety profile of osimertinib in the advanced disease. No new safety concerns in ADAURA study were identified that could impact on the benefit-risk balance. Overall, osimertinib was relatively well tolerated.

Of note, the incidence of patients with AEs leading to a dose reduction was higher in the ADAURA study compared to studies in the advanced/metastatic population. This might be due to the longer treatment duration, but also the healthier population included in ADAURA, for whom a lower tolerance towards AEs can be expected.

Updated efficacy data and long-term safety will be submitted in Q2 2024 as part of the final CSR of the ADAURA study (Annex II condition – PAES) and will allow to address the uncertainties as highlighted above.

3.7.2. Balance of benefits and risks

While the need for updated efficacy data and long terms safety data is acknowledged and will be submitted as part of the final CSR of the ADAURA study, a statistically significant delay in the time to

recurrence of the disease for osimertinib compared to placebo in patients with stage IB-IIIA NSCLC after complete tumour resection with or without prior adjuvant platinum-based chemotherapy has been reported in the ADAURA study, which should translate into meaningful clinical benefit.

Furthermore, the presented safety data indicates that osimertinib in the adjuvant setting is well tolerated.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable

3.8. Conclusions

The overall B/R of Tagrisso is positive.

4. Recommendations

Outcome

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

Variations accepted		**Type**	**Annexes affected**
B.I.b.1.e	B.I.b.1.e - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a specification parameter which may have a significant effect on the overall quality of the AS and/or the FP	Type II	None
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, II and IIIB

Extension of indication of Tagrisso to include the adjuvant treatment after complete tumour resection in EGFR mutant non-small cell lung cancer (NSCLC) patients, based on the results from the pivotal Phase 3 randomised, placebo-controlled study ADAURA (D5164C00001); as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 5.3 of the SmPC are updated. The Package Leaflet is updated accordingly. Version 14.3 of the RMP has also been agreed.

Obligation to conduct post-authorisation measures

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
Post-authorisation safety studies (PAES): In order to further evaluate the efficacy of Tagrisso as monotherapy for the adjuvant treatment after complete tumour resection in adult patients with stage IB-IIIA non-small cell lung cancer (NSCLC) whose tumours have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations, the MAH should submit the final results of the ADAURA study.	Q2 2024

5. EPAR changes

The EPAR will be updated following Commission Decision for this group of variations. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Tagrisso-H-C-004124-II-0039'

Attachments

1. SmPC, Annex II, Labelling, Package Leaflet (changes highlighted)

Appendix

Not applicable

Reminders to the MAH

1. In accordance with Article 13(3) of Regulation (EC) No 726/2004 the Agency makes available a European Public Assessment Report (EPAR) on the medicinal product assessed by the Committee for Medicinal Products for Human Use. The EPAR is first published after the granting of the initial marketing authorisation (MA) and is continuously updated during the lifecycle of the medicinal product. In particular, following a major change to the MA, the Agency further publishes the assessment report of the CHMP and the reasons for its opinion in favour of granting the change to the authorisation, after deletion of any information of a commercially confidential nature.

   Should you consider that the CHMP assessment report contains commercially confidential information, **please provide the EMA Procedure Assistant your proposal for deletion of commercially confidential information** (CCI) in "track changes" and with detailed justification by 11 May 2021. The principles to be applied for the deletion of CCI are published on the EMA website at https://www.ema.europa.eu/en/documents/other/heads-medicines-agencies/european-medicines-agency-guidance-document-identification-commercially-confidential-information_en.pdf

   In addition, should you consider that the CHMP assessment report contains personal data, please provide the EMA Procedure Assistant your proposal for deletion of these data in "track changes" and with detailed justification by 11 May 2021. We would like to remind you that, according to Article 4(1) of Regulation (EU) 2016/679 (General Data Protection Regulation, "GDPR") 'personal data' means any information, relating to an identified or identifiable natural person (the 'data subject'). An identifiable natural person is one who can be identified, directly or indirectly, in particular by reference to an identifier such as a name, an identification number, location data, an online identifier or to one or more factors specific to the physical, physiological, genetic, mental, economic, cultural or social identity of that natural person.

   It is important to clarify that pseudonymised data are also considered personal data. According to Article 4(5) of GDPR pseudonymisation means that personal data is processed in a manner that the personal data can no longer be attributed to a specific data subject without the use of additional information (e.g. key-coded data).

   Accordingly, the name and the patient identification number are two examples of personal data which may relate to an identified or identifiable natural person. The definitions also encompass for instance: office e-mail address or phone number of a company, data concerning health, e.g. information in medical records, clinical reports or case narratives which relates to an identifiable individual."

2. The MAH is reminded to submit an eCTD closing sequence with the final documents provided by Eudralink during the procedure (including final PI translations, if applicable) within 15 days after the Commission Decision, if there will be one within 2 months from adoption of the CHMP Opinion, or prior to the next regulatory activity, whichever is first. If the Commission Decision will be adopted within 12 months from CHMP Opinion, the closing sequence should be submitted within 30 days after the Opinion. For additional guidance see chapter 4.1 of the Harmonised Technical Guidance for eCTD Submissions in the EU.

3. If the approved RMP is using Rev. 2 of the 'Guidance on the format of the RMP in the EU' and the RMP 'Part VI: Summary of the risk management plan' has been updated in the procedure, the MAH is reminded to provide to the EMA Procedure Assistant by Eudralink a PDF version of the 'Part VI: Summary of the risk management plan' as a standalone document, within 14 calendar days of the receipt of the CHMP Opinion. The PDF should contain only text and tables and be free of metadata, headers and footers.