30 May 2024
EMA/291598/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

TAGRISSO

International non-proprietary name: Osimertinib

Procedure No. EMEA/H/C/004124/II/0053

Note

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

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List of abbreviations

ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ALP	alkaline phosphatase
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	area under the concentration-time curve during any dosing interval
AUCss	area under the concentration-time curve at steady state
AZD9291	Osimertinib, TAGRISSO
BICR	blinded independent central review
cEFR	central nervous system evaluable for response
cFAS	central nervous system full analysis set
Chemo	chemotherapy
CI	confidence interval
CLIA	Clinical Laboratory Improvement Amendments
CLss/F	apparent total body clearance after oral administration (at steady state)
Cmax,ss	maximum plasma concentration at steady state
cMET	hepatocyte growth factor receptor
Cmin,ss	minimum plasma concentration at steady state
CNS	central nervous system
COVID-19	coronavirus-19
CR	complete response
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumour DNA
CYP	cytochrome P450
DAE	discontinuation of investigational product due to an AE
DCO	data cut-off
DCR	disease control rate

DoR	duration of response
ECG	electrocardiogram
eCRF	electronic case report form
EGFR	epidermal growth factor receptor
EGFRm	epidermal growth factor receptor mutation positive
EORTC	European Organisation for Research and Treatment of Cancer
ERA	Environmental risk assessment
Ex19del	exon 19 deletion, an in-frame deletion occurring within exon 19, which encodes part of the kinase domain
FAS	full analysis set
GCP	Good Clinical Practice
gCV%	geometric coefficient of variation
HDPE	high-density polyethylene
HER2	human epidermal growth factor receptor
HR	hazard ratio
ICF	informed consent form
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
ILD	interstitial lung disease
IP	investigational product(s)
IPD	important protocol deviation
IRB	Institutional Review Board
IV	intravenous
IxRS	interactive voice/web response system
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
LSI	last subject in
LVEF	left ventricular ejection fraction
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
MET	tyrosine-protein kinase Met
MMRM	mixed models repeated measures

MRI	magnetic resonance imaging
MUGA	multigated acquisition
NA	not applicable
NC	not calculable
NSCLC	non-small cell lung cancer
OAE	other significant adverse event (ie, significant AEs, other than SAEs and DAEs, which are of particular clinical importance in this development program)
ORR	objective response rate
OS	overall survival
Osi	osimertinib
PD	progressive disease
PD-1	programmed cell death 1
PD-L1	programmed cell death ligand 1
PFS	progression-free survival
PFS2	time to second progression
PGIS	patient global impression of severity
PK	pharmacokinetic(s)
PR	partial response
PRO	patient-reported outcomes
PS	Performance Status
PT	Preferred Term
Q3W	every 3 weeks
QoL	quality of life
QTc	corrected QT interval
QTcF	corrected QT interval by Fridericia
RECIST	Response Evaluation Criteria in Solid Tumours
RDI	relative dose intensity
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SMQ	Standardised MedDRA Query
SmPC	Summary of product characteristics
SOC	System Organ Class
std	standard deviation

TFST	time to first subsequent therapy
TKI	tyrosine kinase inhibitors
Tmax,ss	time to peak (maximum) plasma concentration at steady state
TSST	time to second subsequent therapy
TTD	time to deterioration
ULN	upper limit of normal
US(A)	United States (of America)
VAS	Visual analogue scale
VEGF	vascular endothelial growth factor
WHO	World Health Organization

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, AstraZeneca AB submitted to the European Medicines Agency on 16 August 2023 an application for a variation.

The following variation was requested:

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

Extension of indication to include TAGRISSO in combination with pemetrexed and platinum-based chemotherapy for the first-line treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating epidermal growth factor receptor (EGFR) mutations, based on final results from study FLAURA2 (D5169C00001); this is a Phase III, open-label, randomized study of osimertinib with or without platinum plus pemetrexed chemotherapy, multicentre study to assess the efficacy and safety of TAGRISSO as first-line treatment in patients with EGFR mutation-positive, locally advanced or metastatic NSCLC. 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 in accordance. Version 16 of the RMP has also been submitted.

The variation 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(s) P/0222/2017 on the granting of a (product-specific) waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the 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 did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Carolina Prieto Fernandez

Timetable	Actual dates
Submission date	16 August 2023
Start of procedure:	16 September 2023
CHMP Rapporteur Assessment Report	23 November 2023
PRAC Rapporteur Assessment Report	16 November 2023
PRAC Outcome	30 November 2023
CHMP members comments	04 December 2023
Updated CHMP Rapporteur(s) (Joint) Assessment Report	8 December 2023
Request for supplementary information (RSI)	14 December 2023
CHMP Rapporteur Assessment Report	27 March 2024
PRAC Rapporteur Assessment Report	27 March 2024
PRAC Outcome	11 April 2024
CHMP members comments	15 April 2024
Updated CHMP Rapporteur Assessment Report	19 April 2024
Request for supplementary information (RSI)	25 April 2024
CHMP Rapporteur Assessment Report	16 May 2024
CHMP members comments	21 May 2024
Updated CHMP Rapporteur Assessment Report	24 May 2024
Opinion	30 May 2024

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 is indicated in combination with pemetrexed and platinum-based chemotherapy for the first-line treatment of adult patients with locally advanced or metastatic NSCLC with activating EGFR mutations.

Epidemiology

Primary lung cancer is the leading cause of cancer related mortality, with an estimated 1.8 million deaths globally in 2020 (Sung et al., 2021). Although death rates for lung cancer have been declining, there are

still more deaths from lung cancer than from breast, prostate, colorectal, and brain cancers combined (Siegel et al., 2022).

Approximately 85% of lung cancer is NSCLC, and 70% to 80% of patients with NSCLC have locally advanced or metastatic disease at diagnosis, with limited treatment options and poor prognosis (Herbst et al., 2008; Howlader et al., 2021). The 5-year survival rate for patients with metastatic disease is below 5% (Gulhane and Singh 2023, NCCN 2023, Snee et al., 2021), however higher 5-year survival rates, ranging from 15% to 50%, have been reported for patients eligible for targeted therapies or immunotherapies (Ettinger et al., 2023, NCCN 2023).

Biologic features

The EGFR gene mutation is one of the most common oncogenic drivers in NSCLC, and the most common EGFR mutations are the Ex19del and Exon 21 L858R substitution, accounting for 85% to 90% of all EGFR mutations in NSCLC (Lynch et al., 2004; Paez et al., 2004; Herbst et al., 2008). EGFR mutations have a higher prevalence in Asian patients compared to Caucasian patients (50% vs. 15%, respectively), and are found more frequently in women, never-smokers, and the adenocarcinoma histological subtype (Leonetti et al., 2019; Marchetti et al., 2005; Novello et al., 2016). Another common feature of EGFRm NSCLC is the development of CNS metastases, which are detected in approximately 25% of patients at the time of diagnosis, and overall can affect approximately 50% of all patients within 3 years from diagnosis (Rangachari et al., 2015).

The presence of EGFR Ex19del or Exon 21 (L858R) mutations are predictive of treatment benefit from EGFR-TKI therapy, and the survival and clinical outcomes of patients with advanced EGFRm NSCLC have improved remarkably with EGFR-TKIs.

Management

The treatment of advanced NSCLC is currently guided by the identification of specific biomarkers, and over the last decade, EGFR-TKIs have replaced chemotherapy as the standard of care for the first-line treatment of patients with advanced EGFRm NSCLC[1][2][3]. Osimertinib, a third generation EGFR-TKI, is currently the preferred first-line therapy for patients with advanced EGFRm NSCLC. Other agents approved in the EU and that may be an option in the first-line setting include TKIs of first or second generation such as gefitinib, erlotinib, afatinib or dacomitinib, all of them administered as monotherapy.

While osimertinib monotherapy has improved the clinical outcomes of patients with advanced EGFRm NSCLC, the majority of patients experience disease progression[4]. Disease progression on first-line treatment can be due to a combination of intrinsic and diverse acquired resistance mechanisms, which pose a challenge to the effective long-term management of this patient population[5][6]. Depending on the pattern of disease progression, the current treatment guidelines recommend either EGFR TKI, or switching to platinum doublet chemotherapy as second line therapy for symptomatic progression with multiple systemic lesions [1][2][3][7].

[1] NCCN 2023
[2] ESMO Treatment Guidelines 2023 [Hendriks et al.]
[3] ASCO Living Guideline 2022 [Owen et al.]
[4] Shimamura et al., 2022
[5] Herbst et al.
[6] Fu et al., 2022
[7] Postmus et al.,2017

2.1.2. About the product

Osimertinib (AZD9291) is a Tyrosine Kinase Inhibitor (TKI). It is an irreversible inhibitor of EGFRs harboring sensitising-mutations (EGFRm) and TKI-resistance mutation T790M. It was first approved in the EU in 2016 as monotherapy for the treatment of adult patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC. In 2018, an extension of indication was approved for the first-line treatment of adult patients with locally advanced or metastatic NSCLC with activating EGFR mutations. Osimertinib has also been approved in 2021 as adjuvant treatment after complete tumour resection in adult patients with stage IB-IIIA NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations.

The initially applied indication was:

Tagrisso is indicated in combination with pemetrexed and platinum-based chemotherapy for the first-line treatment of adult patients with locally advanced or metastatic NSCLC with activating EGFR mutations.

The final agreed indication was:

TAGRISSO is indicated in combination with pemetrexed and platinum-based chemotherapy for the first-line treatment of adult patients with advanced NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations.

The proposed recommended dose is 80 mg osimertinib once a day when taken with pemetrexed and platinum-based chemotherapy.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

The efficacy and safety of osimertinib in patients with locally advanced or metastatic EGFRm NSCLC has been studied in D5160C00001A/B (AURA), D5160C00001C (AURA extension), D5160C00002 (AURA2), D5160C00003 (AURA3) and D5160C00007 (FLAURA). The efficacy and safety of osimertinib in the adjuvant setting has been studied in ADAURA study.

The FLAURA2 study was designed to assess the efficacy and safety of osimertinib in combination with pemetrexed and platinum-based chemotherapy (cisplatin/carboplatin) vs. osimertinib monotherapy for the first-line treatment of patients with advanced EGFRm NSCLC.

Further to the current approved indications, the osimertinib clinical development programme also comprises studies conducted with the goal of advancing the use of osimertinib to replace the standard of care in additional treatment settings (Study D5160C00048 [LAURA] and Study D516AC00001 [NeoADAURA]), and studies which follow a biomarker-driven approach to assign targeted therapies to be given in combination with osimertinib to address specific resistance mechanisms. This includes Study D5160C00006 (TATTON), Study D6186C00001 (ORCHARD), Study D5084C00007 (SAVANNAH), and Study D5087C00001 (SAFFRON).

Scientific advice

The MAH did not request any scientific advice from the EMA.

2.1.4. General comments on compliance with GCP

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 GCP, as documented by the ICH.

2.2. Non-clinical aspects

No new clinical data regarding pharmacology, pharmacokinetics or toxicology have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

The calculations for the refined PEC performed in the previously submitted environmental risk assessment took into account the entire adult patients with locally advanced or metastatic NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations. Therefore, in accordance with the European Medicines Agency guidance, EMA/CHMP/SWP/4447/00 corr 21*CHMP 2006 and EMA/CHMP/SWP/44609/2010 Rev. 1, an environmental risk assessment for osimertinib mesylate is not required and was not provided with this variation, as the environmental exposure resulting from the current extension of indication is covered by the previous ERA.

2.3. Clinical aspects

2.3.1. 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	D5169C00001 FLAURA2	5.3.5.1	SRI period: To evaluate the tolerability of osimertinib plus chemotherapy Randomised period: To assess the efficacy of osimertinib plus chemotherapy treatment compared to osimertinib, as measured by progression-free survival	SRI period: Non-randomised Randomised period: Phase III, open-label, randomised, study	SRI period: Osimertinib 80 mg once daily in combination with either carbo/pem or cis/pem (carbo and cis Q3W for 4 cycles plus pem Q3W until RECIST 1.1-defined progression) Randomised period: Osimertinib 80 mg tablet once daily, with or without chemotherapy (either carbo or cis Q3W for 4 cycles; plus pem Q3W until RECIST 1.1-defined progression)	SRI period: 30 Random-ised period: 551	Adult patients with newly diagnosed locally advanced (Stage IIIB, IIIC) or metastatic NSCLC (Stage IVA or IVB), or recurrent NSCLC (per version 8 of the IASLC Staging Manual in Thoracic Oncology) with a centrally confirmed EGFR mutation (Ex19del and L858R)	Patients received osimertinib with or without chemotherapy until RECIST 1.1-defined progression, or until another discontinuation criterion was met	Ongoing; DCO of 19 Feb 2020: Full CSR (SRI period) DCO of 03 Apr 2023: CSR Addendum (SRI period); and Full CSR (Randomised period)

2.3.2. Pharmacokinetics

This application is being submitted to support the additional indication for use of osimertinib 80 mg, orally, once daily in combination with pemetrexed plus platinum -based chemotherapy, as a first -line treatment for patients with locally advanced or metastatic NSCLC whose tumours have EGFR exon 19

deletions (Ex19del) or exon 21 (L858R) substitution mutations. Support for the use of osimertinib in this indication is provided by efficacy, safety, and PK data from the Phase III study FLAURA2 (D5169C00001), as well as cumulative safety and PK data from the osimertinib clinical development programme. The data cut -off date for the FLAURA2 study was 03 April 2023.

The clinical pharmacology data package provided in this submission provides the PK of osimertinib and its metabolite, AZ5104 (hereafter referred to as AZ5104), following administration of osimertinib, 80 mg, orally, once daily, either as monotherapy or in combination with pemetrexed and platinum -based chemotherapy. As the contribution of metabolite AZ7550 towards efficacy and safety is unlikely, no further characterisation of this metabolite has been performed.

In the previous submissions, population PK (PopPK) and exposure -response (ER) analyses have been performed using data from AURA Phase I, AURA extension, AURA2, AURA3, FLAURA and ADAURA studies. This submission includes a summary of an updated PopPK model of osimertinib using pooled exposure dataset from the above -mentioned studies and FLAURA2. In addition, this submission also includes the exposure -response and exposure -safety analyses from all PK evaluable patients enrolled in the osimertinib + chemotherapy arm of the FLAURA2.

Analytical methods

Bioanalytical methods for the determination of osimertinib (AZD9291) and its metabolite AZ5104 in human EDTA plasma were developed and validated at Labcorp (formerly Covance) UK Ltd, Harrogate, UK. Samples derived in China were analysed in Labcorp's (formerly Covance's) Shanghai facility in China.

Prior to commencement of the bioanalysis of samples from study D5169C00001 (FLAURA2), a review across the osimertinib development programs showed that the metabolite AZ7550 assayed in previous studies did not contribute towards the efficacy and safety after administration of osimertinib. Subsequently, the previous methods HB-12-128/AZ3LHPP and HB-13-050/AZ3HHPP, the validations of which were submitted in previous procedures, were amended to remove AZ7550. Since this was the only change to the methods, partial validations (single accuracy and precision batches) were performed (study reference numbers 8384097 and 8409-602) to demonstrate the quantification of osimertinib and AZ5104 were not detrimentally impacted. The new methods were identified as AZ9LHPP and AZ9HHPP for the low and high ranges assays, respectively. Only method AZ9HHPP was used in study D5169C00001.

Table 1: Bioanalytical method for osimertinib and AZ5104 in human plasma samples

Method	Analyte	Matrix	Validation Report Number	LLOQ ng/mL (nM)	Linear Range ng/mL (nM)
AZ9LHPP	Osimertinib AZ5104	K_2 EDTA Plasma	8384097	0.025 (0.05) 0.025 (0.0515)	25.0 (0.05) to 4000 (50) 0.025 (0.0515) to 25.0 (51.5)
AZ9HHPP	Osimertinib AZ5104	K_2 EDTA Plasma	8384097/8409- 602 [a]	8.00 (16) 0.800 (1.65)	8.00 (16) to 4000 (8010) 0.800 (1.65) to 400 (824)

[a] Partial validation data of assay used in Labcorp's Shanghai, China lab, reported in bioanalysis contribution report. (reference number 8409- 602) for clinical study D5169C00001

The partial validation accuracy and precision summary data are presented in Table 2 below.

Table 2: Validation accuracy and precision summary data for bioanalytical methods for osimertinib and AZ5104 in human plasma

	Analyte	Method AZ9LHPP	Method AZ9HHPP
Within -run accuracy (%)	Osimertinib	104.0-113.0	100.5-107.0
	AZ5104	99.5-105.8	101.9-108.5
	Osimertinib [a]	NA	93.1-103.2
	AZ5104 [a]	NA	90.9-105.1

	Analyte	Method AZ9LHPP	Method AZ9HHPP
Within- run precision (%)	Osimertinib	2.1-8.5	2.2-10.3
	AZ5104	1.3-5.2	3.1-7.6
	Osimertnib [a]	NA	1.2-5.1
	AZ5104 [a]	NA	1.0-6.0

[a] Labcorp Shanghai, China partial validation data

NA = Not applicable

Both analytes have been found to demonstrate acceptable stability in K_2EDTA human plasma up to 1021 days when stored between -60 and -80°C (report reference 8386-634)

Pharmacokinetics in the target population

FLAURA2 (D5169C00001)

FLAURA2 (D5169C00001) is a global Phase III, open -label, randomised study, designed to assess the efficacy and safety of osimertinib, with or without platinum plus pemetrexed chemotherapy, in patients with locally advanced (clinical stage IIIB or IIIC) or metastatic (clinical stage IVA or IVB) EGFRm (Ex19del and/or L858R) NSCLC. The PK narratives of osimertinib and AZ5104 observed in the randomized part of FLAURA2 are summarized in this section.

Secondary Objective:

To assess the PK of osimertinib administered as a monotherapy or in combination with chemotherapy. The endpoints reported are: steady -state plasma concentrations and PK parameters (Cmax,ss, Tmax,ss, Cmin,ss, AUCss, CLss/F) of osimertinib and of AZ5104, as data permits.

In the randomized part of FLAURA2, eligible patients (N=557) enrolled in FLAURA2 were randomized 1:1 to receive osimertinib 80 mg, once daily as monotherapy or in combination with pemetrexed (500 mg/m2) plus either cisplatin (75 mg/m2) or carboplatin (AUC5), with both chemotherapy treatments administered on Day 1 of 21 -day cycles for 4 cycles, followed by osimertinib 80 mg, once daily plus pemetrexed maintenance (500 mg/m2) Q3W, in subsequent cycles.

PK Sampling:

Samples for determination of plasma concentrations of osimertinib and AZ5104 were collected at the following timepoints: pre -dose and 1 hour after dosing on Day 22 (C2D1), pre -dose,1, 2, 4 and 6 hours after dosing on Day 43 (C3D1), and pre -dose and 1 hour after dosing on Day 106 (C6D1). The FLAURA2 steady state PK parameters of osimertinib and AZ5104 have been derived for C3D1 (Day 43) in all PK evaluable subjects, using PK concentration data and actual elapsed sample times, using non – compartmental analysis (Phoenix® WinNonLin® Version 8.1). As data permits, Cmax,ss, Tmax,ss, Cmin,ss, AUCss, CLss/F (osimertinib only), and metabolite to parent ratio based on AUCss and Cmax,ss, have been estimated as specified in the statistical analysis plan.

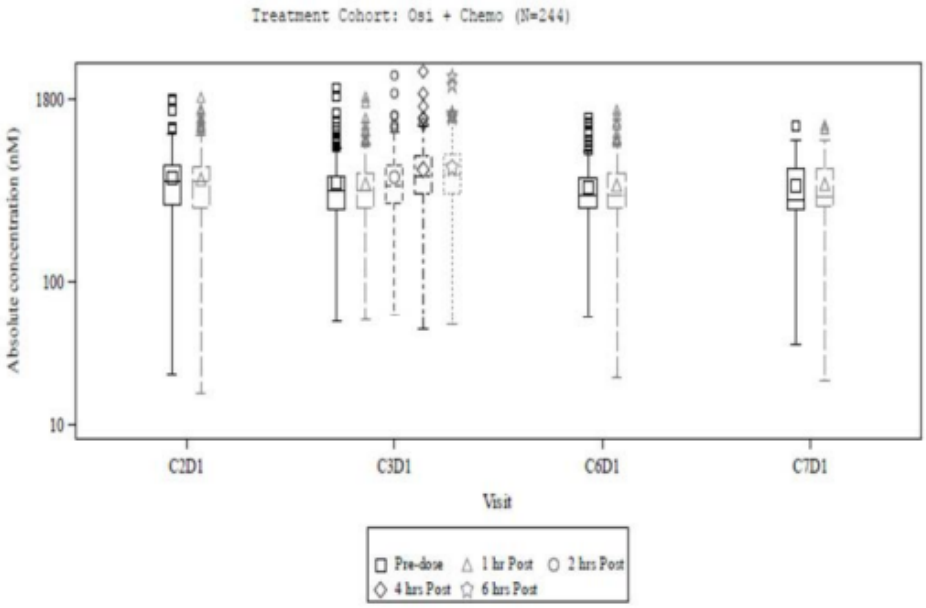
Results:

Of the 557 patients in the FAS, 507 patients had at least one PK measurement and were therefore included in the PK Analysis Set.

Plasma concentrations of osimertinib and its metabolite, AZ5104 were determined for both treatment arms, with at least one PK measurement reported for 244 patients in the osimertinib + chemotherapy arm, and 263 patients in the osimertinib arm.

Box plots of plasma concentration time profiles of osimertinib and AZ5104 in both treatment arms at Day 22 (C2D1), Day 43 (C3D1), and Day 106 (C6D1) are presented in Figure 1, Figure 2, Figure 3 and Figure 4 below.

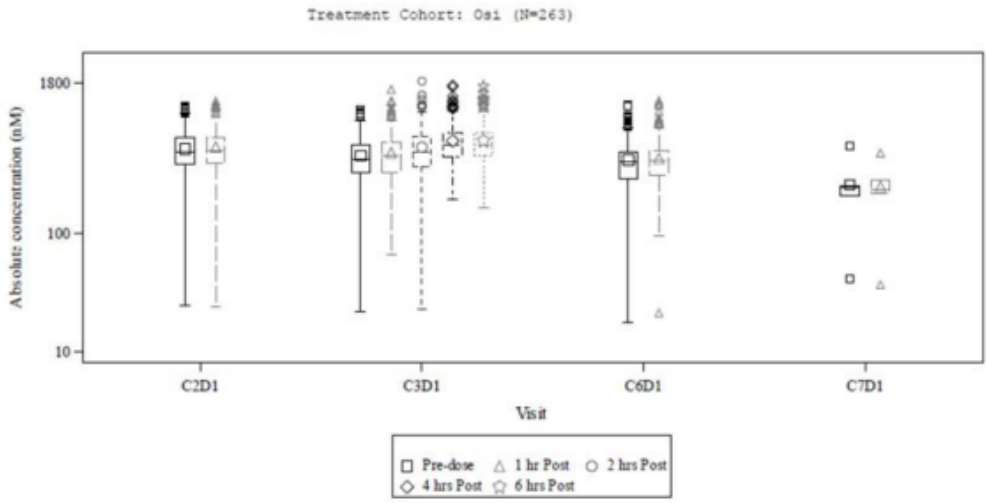
Figure 1: Summary of Plasma Concentrations of Osimertinib in FLAURA2 Osimertinib + Chemotherapy Arm



While the last scheduled PK visit was at C6D1, as specified in the D5169c0001 CSP, missed/unscheduled PK visits were collected at the next scheduled visit (C7D1)

Source: Figure 14.2.17.3b of FLAURA2 CSR

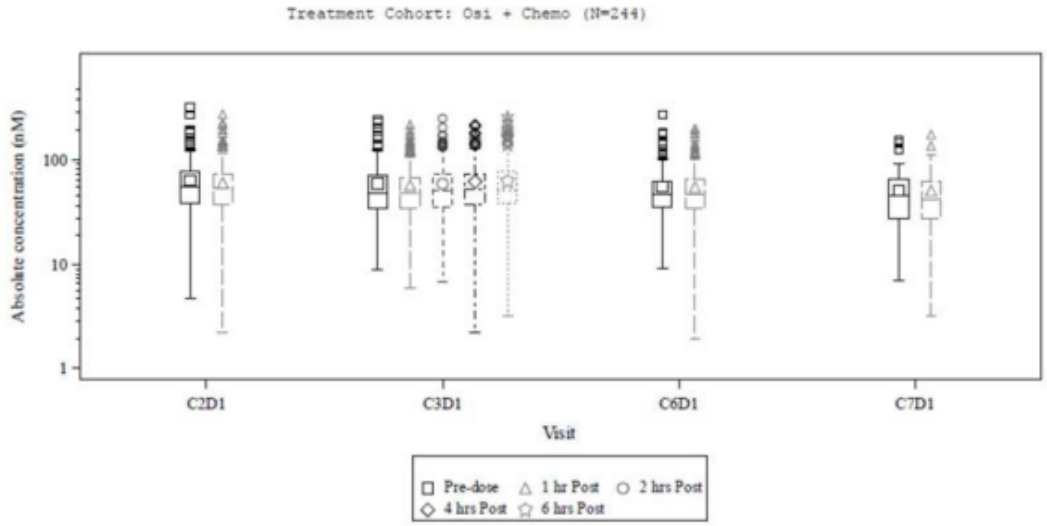
Figure 2: Summary of Plasma Concentrations of Osimertinib in FLAURA2 Osimertinib Monotherapy Arm



While the last scheduled PK visit was at C6D1, as specified in the D5169c0001 CSP, missed/unscheduled PK visits were collected at the next scheduled visit (C7D1)

Source: Figure 14.2.17.3b of FLAURA2 CSR

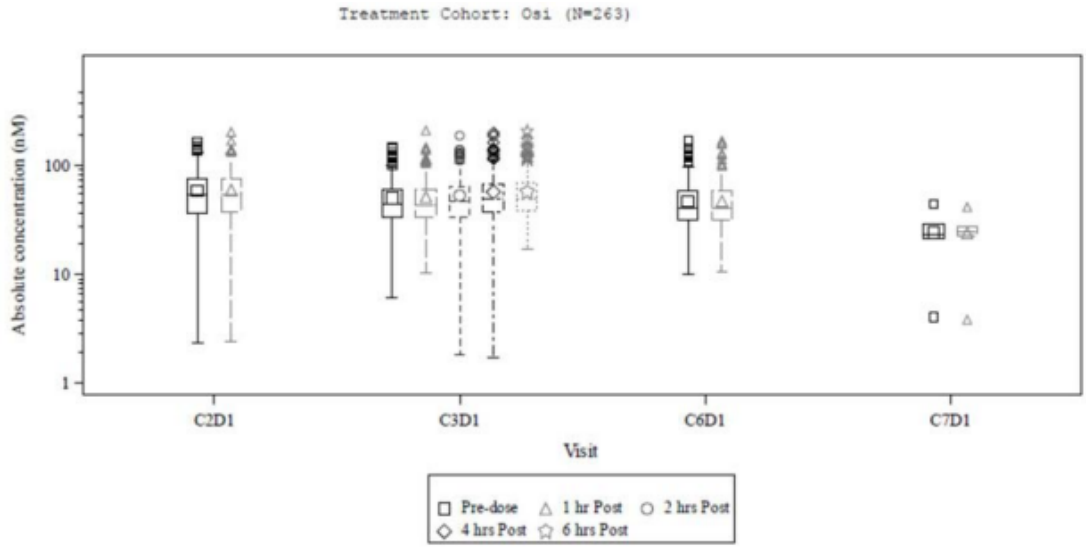
Figure 3: Summary of Plasma Concentrations of AZ5104 Following Oral Administration of Osimertinib in FLAURA2 Osimertinib + Chemotherapy Arm



While the last scheduled PK visit was at C6D1, as specified in the D5169c0001 CSP, missed/unscheduled PK visits were collected at the next scheduled visit (C7D1).

Source: Figure 14.2.17.3b of FLAURA2 CSR

Figure 4: Summary of Plasma Concentrations of AZ5104 following Oral Administration of Osimertinib in FLAURA2 Osimertinib Monotherapy Arm



While the last scheduled PK visit was at C6D1, as specified in the D5169c0001 CSP, missed/unscheduled PK visits were collected at the next scheduled visit (C7D1)

Source: Figure 14.2.17.3b of FLAURA2 CSR

Based on a plasma concentration time profile on D43 (C3D1) in the osimertinib monotherapy arm, systemic absorption maxima was achieved at a median (range) Tmax,ss of 4.03 hours (0 to 7.17) and 4.0 hours (0 to 7.17) for osimertinib and AZ5104, respectively; in the osimertinib + chemotherapy arm median (range) Tmax,ss of osimertinib and AZ5104 was estimated at 4.5 hours (0 to 8.07) and 4.0 hours (0 to 6.37), respectively.

The inter -patient variability based on gCV% in Cmax,ss and AUCss for osimertinib generally ranged from 37 -45% in both treatment arms; the gCV% of AZ5104 ranged from 46 -47% in osimertinib monotherapy arm and 54 -60% in osimertinib + chemotherapy arm. The metabolite to parent ratios were similar in both treatment arms, with the metabolite being approximately 9.3% to 10.8% of the parent, based on the geometric mean AUCss and Cmax,ss.

Based on the observed concentration time -profile on D43 (C3D1), the plasma exposures of osimertinib and AZ5104 were similar between the osimertinib monotherapy and osimertinib + chemotherapy arm (Figure 5 and Figure 6).

Figure 5: Steady State GeoMean (+/ -GeoSD) Plasma Concentration of Osimertinib in FLAURA2

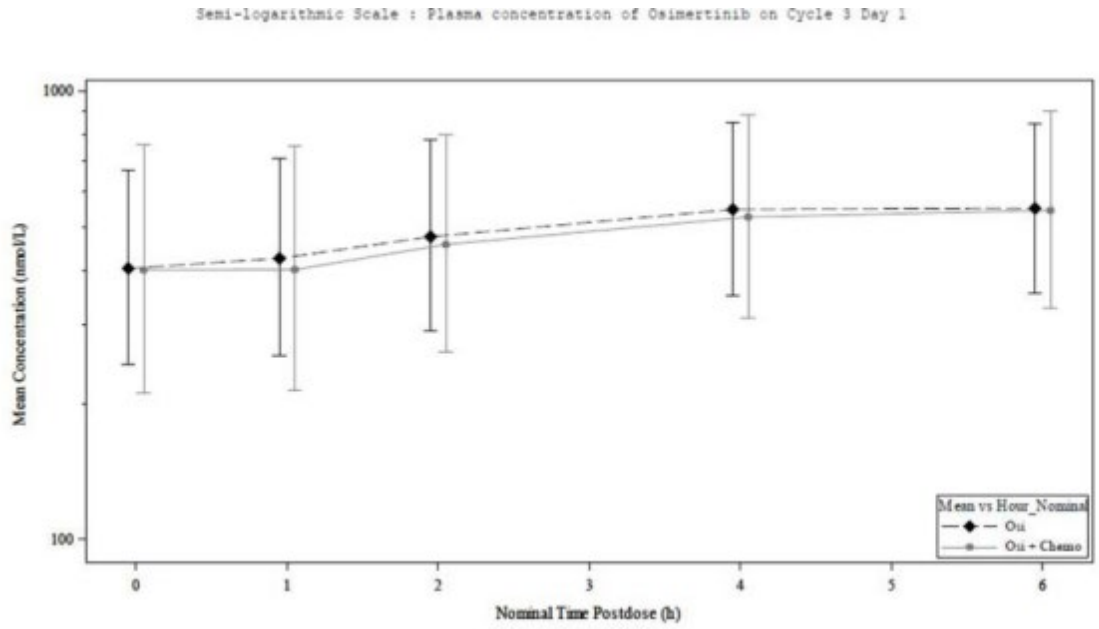
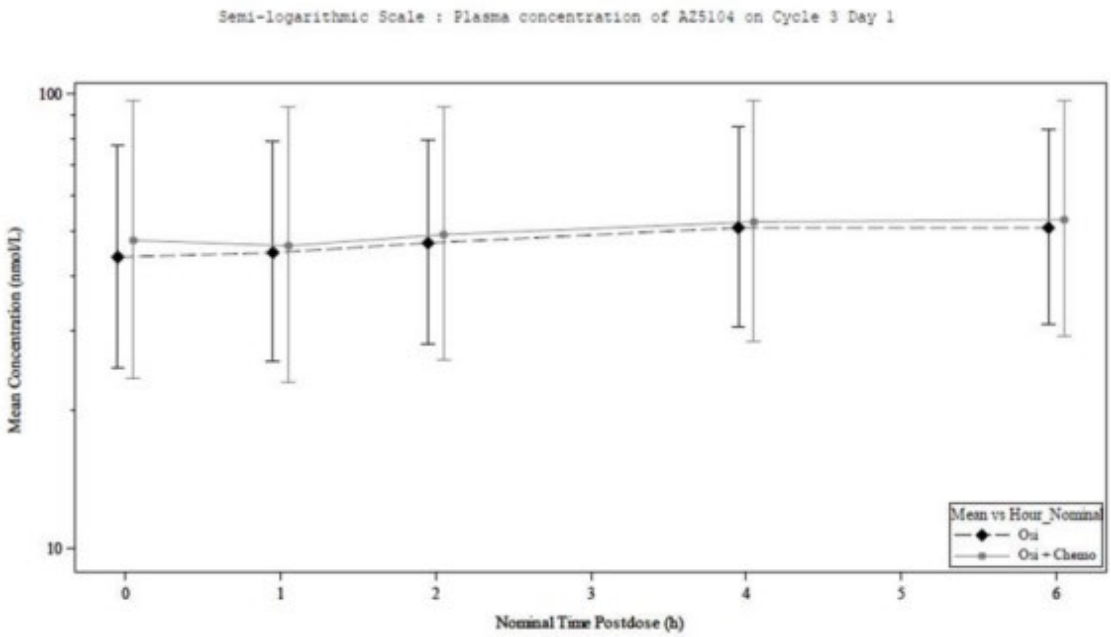


Figure 6: Steady State GeoMean (+/ -GeoSD) Plasma Concentration of AZ5104 Following Administration of Osimertinib in FLAURA2



Population Pharmacokinetic (PopPK) Model

The objectives of this analyses were:

- To characterize the PK of osimertinib, using FLAURA2 data pooled with data from five previous clinical trials (AURA, AURA2, AURA3, FLAURA, and ADAURA)
- To assess the impact of predefined intrinsic and extrinsic covariates on the PK of osimertinib and AZ5104
- To derive individual predicted exposure metrics (including AUCss, Cmin,ss and Cmax,ss) of osimertinib and AZ5104 for patients enrolled in the investigational arm of FLAURA2 study, using individual empirical bayes estimates (EBE) from the updated PopPK model
- To assess osimertinib exposure and efficacy relationship for progression free survival (PFS) in the FLAURA2 osimertinib + chemotherapy arm
- To assess the osimertinib exposure and safety relationship for Grade ≥ 3 haematological toxicities (anaemia, neutropenia or thrombocytopenia), treatment emergent AESIs (ILD/pneumonitis, cardiac effects), Aes leading to treatment discontinuation, dose interruption or dose reduction, in investigational arm (osimertinib + chemotherapy) of FLAURA2.

The dataset for the population PK analysis was created by merging the previous concentration dataset (AURA, AURA2, AURA3, FLAURA, and ADAURA) with concentration dataset from FLAURA2 study.

Table 3 provides a stratification of the data used in the population PK analysis per study.

Table 3: Population PK Analysis – Summary of the Data

Study	Number of Subjects [a]	Total Number of Obs. [b]	Number (%) of Obs. Below the LLOQ (total) [c]
D5160C00001 (AURA)	599	14991	1228 (8.19)
D5160C00002 (AURA2)	210	5980	478 (7.99)
D5160C00003 (AURA3)	277	7858	685 (8.72)
D5160C00007 (FLAURA)	278	9233	748 (8.10)
D5164C00001 (ADAURA)	325	6077	65 (1.07)
D5169C00001 (FLAURA2)	507	8199	46 (0.561)
Total	2196	52338	3250 (6.21)

[a] PK Evaluable
[b] Obs : Observations
[c] LLOQ: Lower Limit Of Quantification
Source:/projects/qcp/QCP_MODELING/ONC/azd9291/eda_20230522_FLAURA2_submission/Scripts/1.0.osimertinib -pk -eda_Flaura2.v1.Rmd, Reference: blq table prepost dose pk EVAL

Table 4 and Table 5 summarize the continuous and categorical characteristics of the population in the PopPK analysis dataset, stratified by FLAURA2 and previous studies.

Table 4: Summary of Continuous Covariates

	AURA + AURA2 + AURA3 + FLAURA + ADAURA (N=1689)	FLAURA2 (N=507)	Overall (N=2196)
Baseline Alkaline Phosphatase (U/L)			
Mean (SD)	143 (159)	145 (130)	144 (153)
Median [Min, Max]	95.0 [18.0, 3930]	107 [33.0, 1180]	97.6 [18.0, 3930]
Missing	10 (0.6%)	2 (0.4%)	12 (0.5%)
Baseline Bilirubin (umol/L)			
Mean (SD)	9.70 (4.82)	9.46 (3.90)	9.64 (4.62)
Median [Min, Max]	8.55 [0.342, 49.0]	8.79 [1.00, 26.7]	8.55 [0.342, 49.0]
Missing	8 (0.5%)	1 (0.2%)	9 (0.4%)

Source:/projects/qcp/QCP_MODELING/ONC/azd9291/eda_20230522_FLAURA2_submission/Scripts/1.0.osimertinib -pk -eda_Flaura2.v1.Rmd, Reference: Cont Cov table by Study

Table 5: Summary of Categorical Covariates

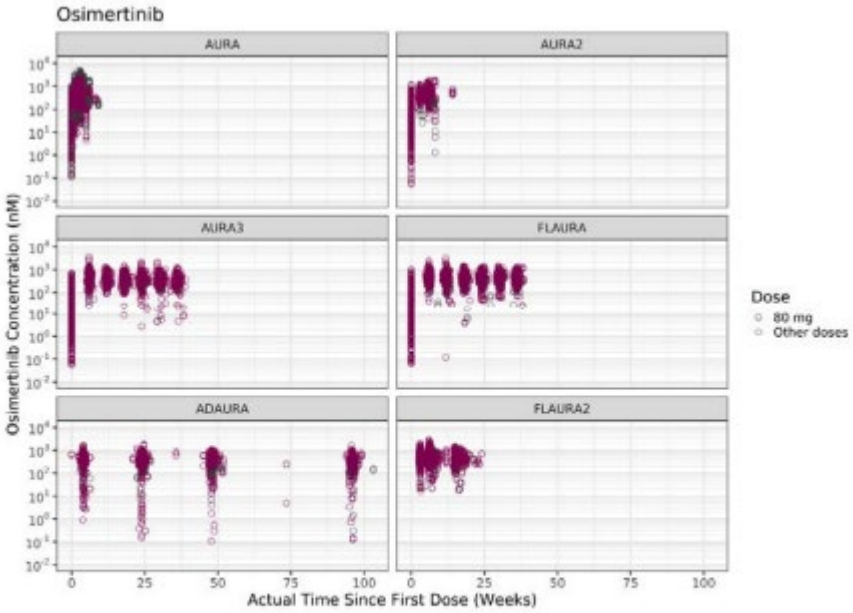
	AURA + AURA2 + AURA3 + FLAURA + ADAURA (N=1689)	FLAURA2 (N=507)	Overall (N=2196)
Age category1			
< 65	979 (58.0%)	319 (62.9%)	1298 (59.1%)
>= 65	710 (42.0%)	188 (37.1%)	898 (40.9%)
Age Category2			
< 65	979 (58.0%)	319 (62.9%)	1298 (59.1%)
>= 65 and < 75	505 (29.9%)	149 (29.4%)	654 (29.8%)
>= 75	205 (12.1%)	39 (7.7%)	244 (11.1%)
Sex			
Male	586 (34.7%)	194 (38.3%)	780 (35.5%)
Female	1103 (65.3%)	313 (61.7%)	1416 (64.5%)
Grouped Ethnicity			
White	477 (28.2%)	107 (21.1%)	584 (26.6%)
Asian (excluding Chinese and Japanese)	399 (23.6%)	103 (20.3%)	502 (22.9%)
Chinese	367 (21.7%)	134 (26.4%)	501 (22.8%)
Japanese	301 (17.8%)	83 (16.4%)	384 (17.5%)
Other	145 (8.6%)	80 (15.8%)	225 (10.2%)

	AURA + AURA2 + AURA3 + FLAURA + ADAURA (N=1689)	FLAURA2 (N=507)	Overall (N=2196)
Nicotine Use			
Never	1132 (67.0%)	336 (66.3%)	1468 (66.8%)
Current Smoker	38 (2.2%)	7 (1.4%)	45 (2.0%)
Former Smoker	519 (30.7%)	164 (32.3%)	683 (31.1%)
Line of Therapy			
First line	338 (20.0%)	507 (100%)	845 (38.5%)
Second line	468 (27.7%)	0 (0%)	468 (21.3%)
Third line onwards	558 (33.0%)	0 (0%)	558 (25.4%)
Adjuvant	325 (19.2%)	0 (0%)	325 (14.8%)
Renal Impairment Status			
Normal	605 (35.8%)	227 (44.8%)	832 (37.9%)
Mild	742 (43.9%)	256 (50.5%)	998 (45.4%)
Moderate	323 (19.1%)	24 (4.7%)	347 (15.8%)
Severe	5 (0.3%)	0 (0%)	5 (0.2%)
Missing	14 (0.8%)	0 (0%)	14 (0.6%)
Grouped Renal Impairment Status			
Normal	605 (35.8%)	227 (44.8%)	832 (37.9%)
Mild	742 (43.9%)	256 (50.5%)	998 (45.4%)
>= Moderate	328 (19.4%)	24 (4.7%)	352 (16.0%)
Missing	14 (0.8%)	0 (0%)	14 (0.6%)
Hepatic Impairment Status			
Normal	1513 (89.6%)	453 (89.3%)	1966 (89.5%)
Mild	158 (9.4%)	52 (10.3%)	210 (9.6%)
Moderate	8 (0.5%)	0 (0%)	8 (0.4%)
Severe	0 (0%)	0 (0%)	0 (0%)
Missing	10 (0.6%)	2 (0.4%)	12 (0.5%)
Grouped Hepatic Impairment Status			
Normal	1513 (89.6%)	453 (89.3%)	1966 (89.5%)
>= Mild	166 (9.8%)	52 (10.3%)	218 (9.9%)
Missing	10 (0.6%)	2 (0.4%)	12 (0.5%)
WHO Performance Status			
0	706 (41.8%)	190 (37.5%)	896 (40.8%)
1	983 (58.2%)	317 (62.5%)	1300 (59.2%)

Source:/projects/qcp/QCP_MODELING/ONC/azd9291/eda_20230522_FLAURA2_submission/Scripts/1.0.osimertinib -pk -eda_Flaura2.v1.Rmd, Reference: Cont Cov table by Study

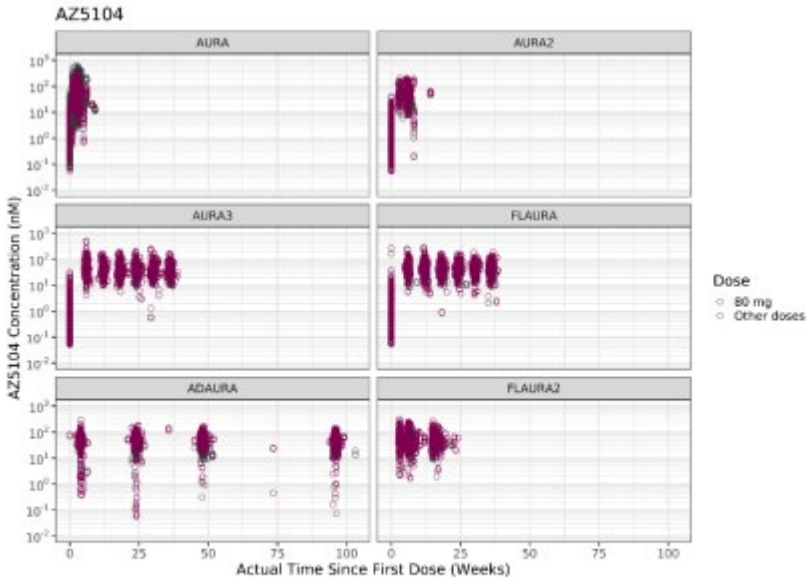
Osimertinib and AZ5104 Plasma Concentrations

Figure 7: Osimertinib Concentration vs Time Since First Dose by Study



Source:/projects/qcp/QCP_MODELING/ONC/azd9291/eda_20230522_FLAURA2_submission/Scripts/1.0.osimertinib -pk -eda_Flaura2.v1, Reference: log scale Osi conc. Vs time per dose by Study

Figure 8: AZ5104 Concentration vs Time Since Last Dose by Study



Source:/projects/qcp/QCP_MODELING/ONC/azd9291/eda_20230522_FLAURA2_submission/Scripts/1.0.osimertinib -pk -eda_Flaura2.v1.Rmd, Reference: log scale AZ5104 conc. Vs time per dose by Study

Initial PopPK Model

Based on the most recent PopPK model (Comisar et al 2015, Johnson 2017), the observed osimertinib and its metabolite (AZ5104) concentrations were described by the following structural model:

- The model was described by first order absorption (KA), one compartment distribution and elimination of osimertinib, and one compartment for its metabolite, AZ5104. The drug is absorbed into the parent (osimertinib) compartment at a rate constant KA (first order absorption).

Osimertinib is either eliminated from the system or transformed into AZ5104 which is subsequently eliminated with a first order elimination rate constant.

- Inter individual variability (IIV) was characterized on the absorption rate (KA), the clearance (CL/F, CLM/F) and volume (V1/F, VM/F) of both osimertinib and AZ5104
- A combined proportional and additive residual error model was applied to both osimertinib and its metabolite (AZ5104)
- Baseline body weight (WT) is a statistically significant covariate on apparent osimertinib clearances (CL/F), apparent AZ5104 clearance (CLM/F), and osimertinib volume of osimertinib (V1/F)
- Baseline albumin (BALB) is a statistically significant covariate on apparent clearance of osimertinib (CL/F), and AZ5104 (CLM/F), and volume of osimertinib (V1/F), and AZ5104 (VM/F)
- Asian (excluding Chinese and Japanese) and Japanese race categories were statistically significant covariates on AZ5104 clearance (CLM/F)

PK parameters and random effects were estimated by fitting the model to the pooled PK dataset.

Covariate Model

In this step, the full covariate model was re -evaluated based on the current data and previous developed model structure. The covariate analysis was then conducted in two steps:

- Covariates included in the full covariate model were removed one by one to assess their impact to obtain a starting model for the following step
- In the next step, other covariates of interest including combination with chemotherapy were evaluated using forward inclusion approach
- Graphical inspected all covariate effects and covariates of interest were tested to assess their impact on the full covariate model

The results of this backward elimination suggested that all covariates are statistically significant except Chinese race and other ethnicity.

In the following step, a few covariates of interest were evaluated on CL/F and V1/F as shown in Table 6. These analyses re -confirmed the covariates listed were not significant for osimertinib and AZ5104, therefore, run114.mod was considered the final model.

Table 6: Assessment of Additional Covariate on Full Covariate Model

MODEL	COMMENT	OFV	ΔOFV	df	Sig
114	-	421435.3082	-	-	
302	Add WT to VM/F	421435.2328	-0.07545	1	10.83
303	Add ETHL to CL/F	421431.4209	-3.88735	4	18.47
304	Add BCRCL on CL/F	421435.0888	-0.21943	1	10.83
305	Add BCRCL on CLM/F	421429.7452	-5.56309	1	10.83
306	Add HISTL on CL/F	421434.4459	-0.86236	1	10.83
307	Add HISTL on CLM/F	421432.7889	-2.51931	1	10.83
308	Add RISTL on CL/F	421427.5291	-7.77912	2	13.82
309	Add RISTL on CLM/F	421432.5926	-2.71569	2	13.82
310	Add Chemotherapy on CL/F	421435.0817	-0.22659	1	10.83
311	Add Chemotherapy on CLM/F	421435.1633	-0.1449	1	10.83

OFV = objective function value; df = degree of freedom; Sig = significant level

Source:/projects/qcp/QCP_MODELING/ONC/azd9291/eda_20230522_FLAURA2_submission/Models/Forward Selection.xlsx

Final model

The parameter estimates for the final updated model are reported in Table 7.

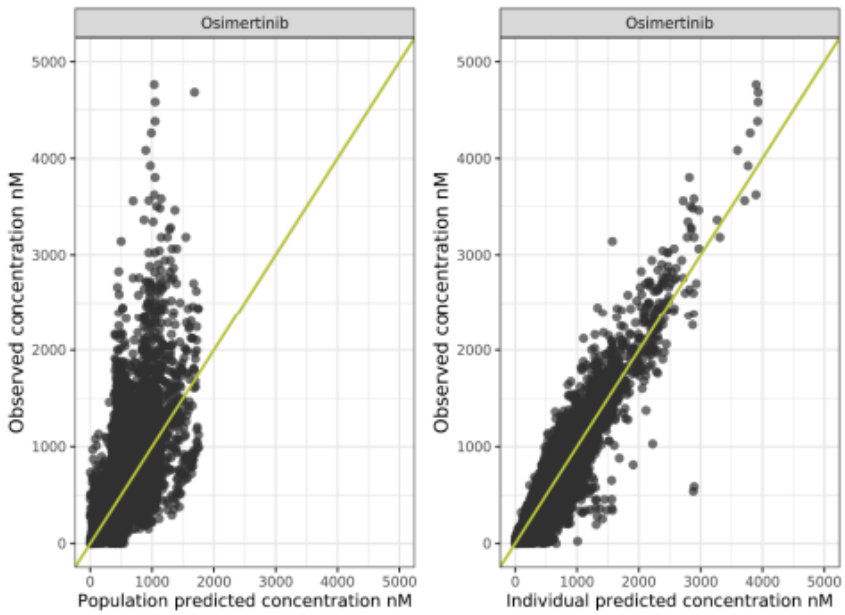
Table 7: Population PK Model Parameter Estimates (Final Model – run114.mod)

Parameter	Estimate	RSE (%)	Bootstrap Median	Bootstrap 95%CI	Shrinkage (%)	Unit
Population Parameter						
CL/F (osimertinib)	14.35	0.98	14.35	[14.26; 14.69]	-	L/hr
CLM/F (metabolite)	32.05	1.22	32.06	[31.78; 32.82]	-	L/hr
KA	0.26	3.41	0.26	[0.24; 0.28]	-	1/hr
V1/F (osimertinib)	1151	2.10	1151.11	[1118.02; 1223.34]	-	L
FM (Fraction metabolized)	0.25	-	0.25	-	-	-
VM/F (metabolite)	151	2.95	151.01	[140.02; 162.81]	-	L
Covariate						
Weight on CL/F	0.36	11.73	0.36	[0.29; 0.44]	-	-
Albumin on CL/F	0.67	11.34	0.68	[0.60; 0.81]	-	-
Weight on V1/F	0.64	14.01	0.64	[0.53; 0.88]	-	-
Albumin on V1/F	1.57	9.84	1.58	[1.53; 2.06]	-	-
Weight on CLM/F	0.74	6.53	0.74	[0.69; 0.84]	-	-
Albumin on CLM/F	0.72	11.74	0.72	[0.62; 0.87]	-	-
Albumin on Vm/F	-0.65	27.43	-0.68	[-1.28; -0.42]	-	-
Asian (Non -Chinese or non -Japanese) on CLM/F	0.16	10.36	0.16	[0.13; 0.19]	-	-
Japanese on CLM/F	0.18	11.47	0.18	[0.15; 0.21]	-	-
Interindividual Variability						
ETA CL/F	0.19	2.45	0.19	[0.18; 0.20]	3.62	-
Correlation CL/F & CLM/F	0.19	2.64	0.19	[0.17; 0.19]	-	-
ETA CLM/F	0.24	2.61	0.24	[0.22; 0.24]	3.99	-
ETA KA	0.70	5.85	0.7099	[0.62; 0.84]	41.09	-
ETA V1/F	0.54	4.06	0.54	[0.51; 0.61]	21.76	-
ETA VM/F	0.51	5.50	0.51	[0.42; 0.59]	46.12	-
Residual Variability						
Proportional component (Osimertinib)	0.22	0.25	0.22	[0.21; 0.23]	-	-
Additive component (Osimertinib)	29.52	0.98	29.52	[26.13; 34.23]	-	nM
Proportional component (Metabolite)	0.23	0.05	0.23	[0.22; 0.24]	-	-
Additive component (Metabolite)	0.36	3.30	0.36	[0.31; 0.42]	-	nM

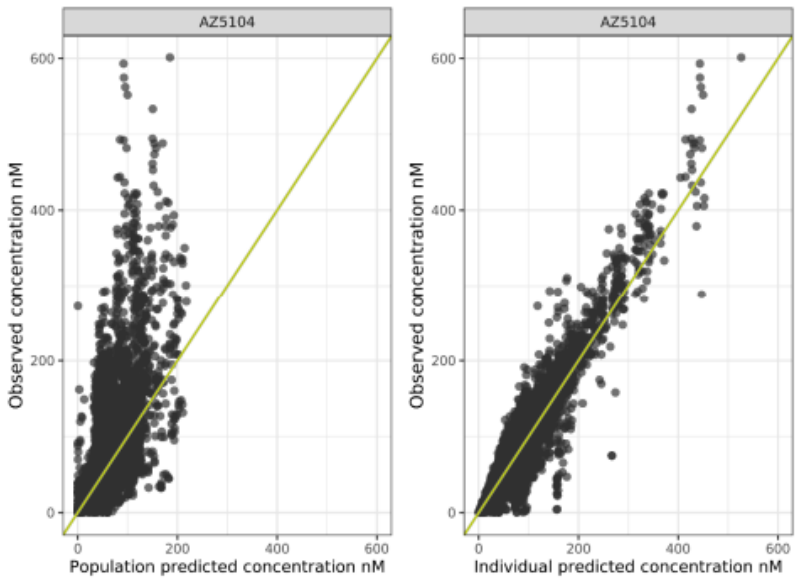
CI = confidence interval; CL/F = apparent osimertinib clearance; CLM/F = apparent metabolite clearance; ETA = random effect; KA = absorption rate;. RSE = relative standard error; V1/F = apparent osimertinib volume of distribution; VM/F = apparent metabolite volume of distribution

Source:/projects/qcp/QCP_MODELING/ONC/azd9291/eda_20230522_FLAURA2_submission/Scripts/2.0.PK - postprocessing -gof.v2.Rmd, Reference: Parameter tabboot

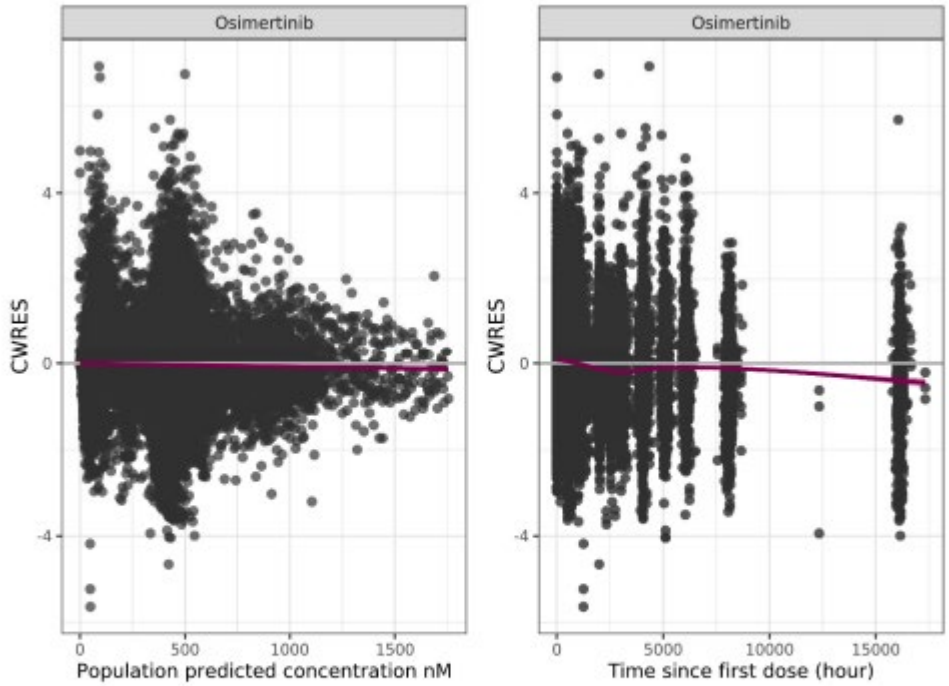
Figure 9: Final Model – Basic Goodness of Fit (GoF) Plots (run114.mod)



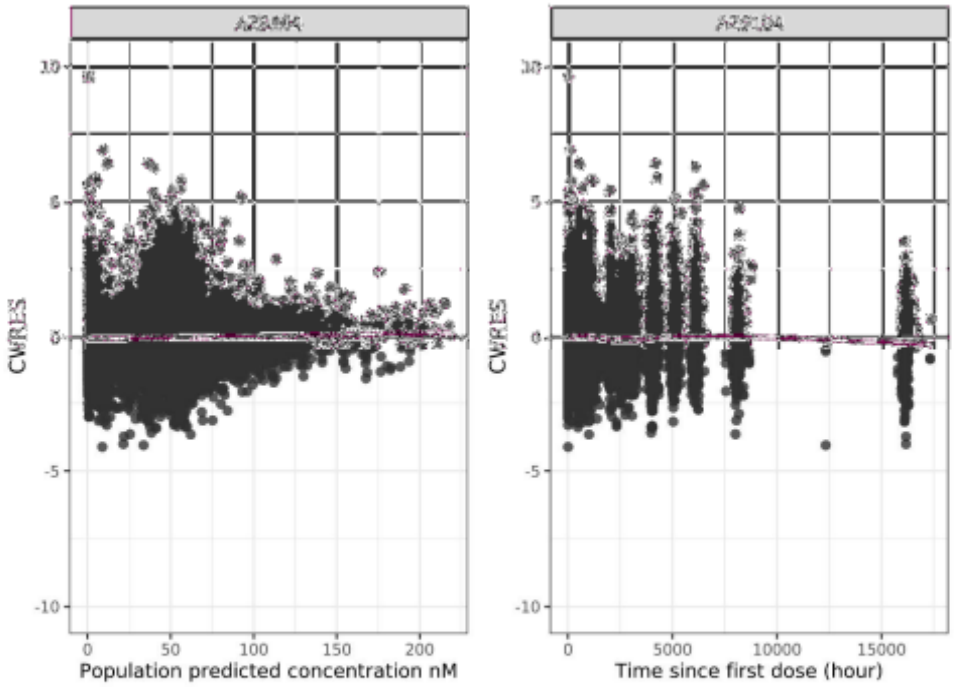
Yellow line = the line of unity (slope of 1)
Source: /projects/qcp/QCP_MODELING/ONC/azd9291/eda_20230522_FLAURA2_submission/Scripts /2.0.PK -postprocessing -gof.v2.Rmd, Reference: osi dv pred ipred no loess cart scale comb



Yellow line = the line of unity (slope of 1)
Source:/projects/qcp/QCP_MODELING/ONC/azd9291/eda_20230522_FLAURA2_submission/Scripts/2.0.PK -postprocessing -gof.v2.Rmd, Reference: AZ5104 dv pred ipred no loess cart scale comb



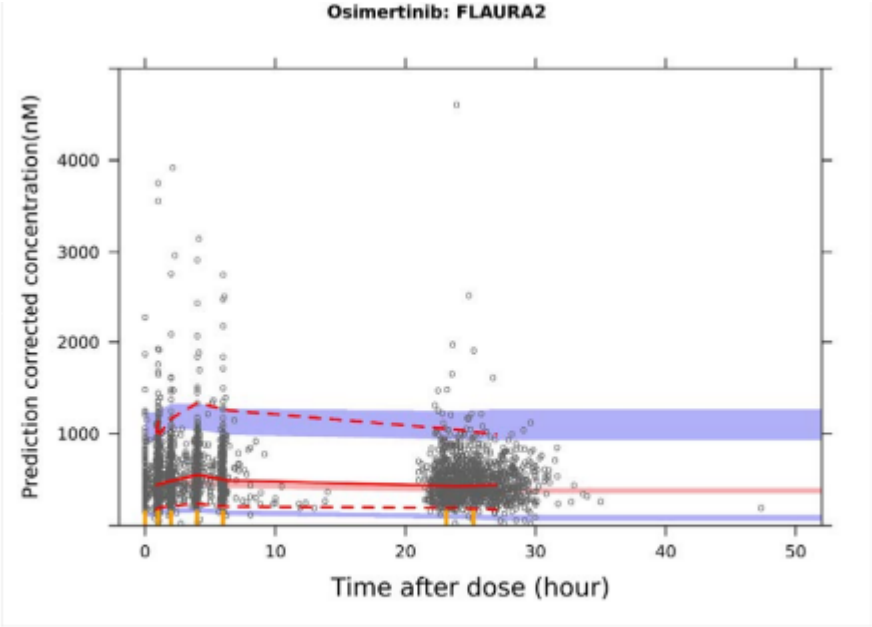
CWRES = conditional weighted residuals
Source:/projects/qcp/QCP_MODELING/ONC/azd9291/eda_20230522_FLAURA2_submission/Scripts/2.0.PK - postprocessing -gof.v2.Rmd, Reference: osi cwres model lm comb TAFD



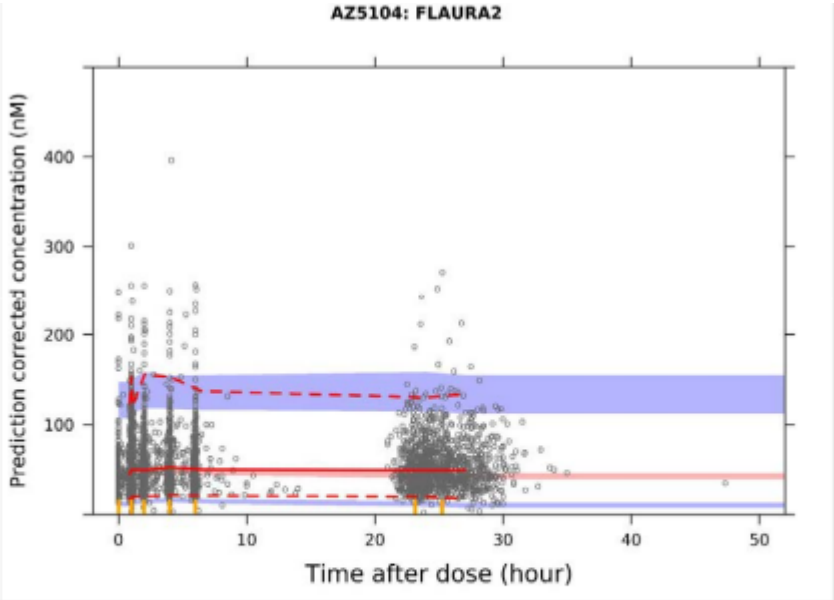
CWRES = conditional weighted residuals
Source:/projects/qcp/QCP_MODELING/ONC/azd9291/eda_20230522_FLAURA2_submission/Scripts/2.0.PK - postprocessing -gof.v2.Rmd, Reference: AZD5104 cwres model lm comb TAFD

The pcVPC for FLAURA2 are presented in Figure 10.

Figure 10: pcVPC of the Final Model vs Time after Dose – FLAURA2 Study



Source:/projects/qcp/QCP_MODELING/ONC/azd9291/eda_20230522_FLAURA2_submission/Scripts/2.1.PK - postprocessing -vpc.model114.rmd, Reference: vpc all with observation by Studies B

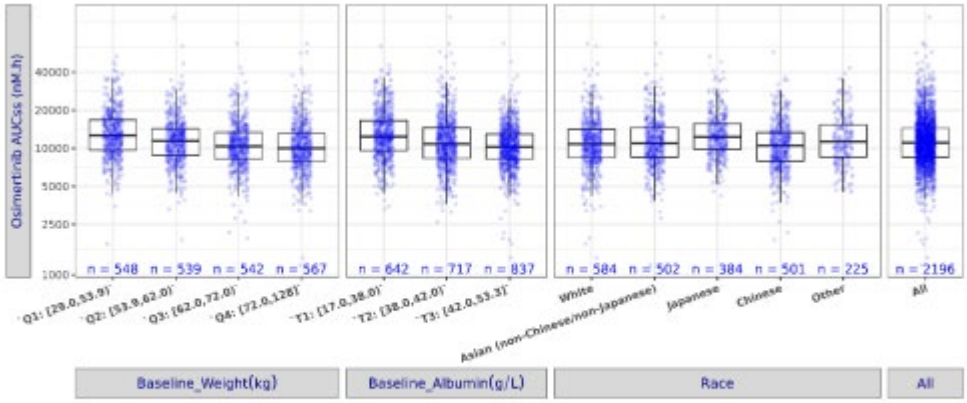


CI = confidence interval; pcVPC = prediction -corrected visual predictive check
Solid and dashed lines = the median, 5th, and 95th percentiles of the observations; Shaded red and blue areas = the 95% confidence interval of the median, 5th, and 95th percentiles predicted by the model
Source:/projects/qcp/QCP_MODELING/ONC/azd9291/eda_20230522_FLAURA2_submission/Scripts/2.1.PK - postprocessing -vpc.model114.rmd, Reference: vpc all with observation by Studies B

Impact of Covariates on Osimertinib and AZ5104 PK

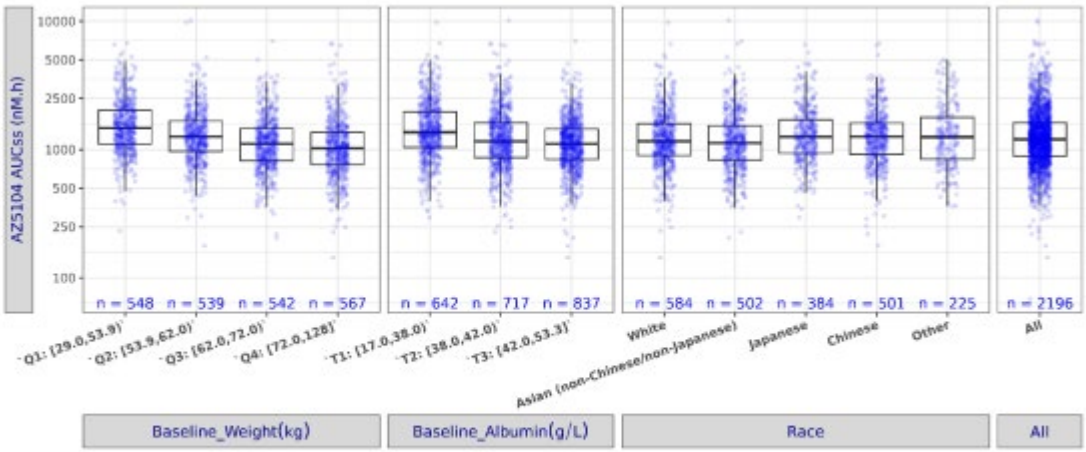
The impact of the significant covariates on osimertinib and AZ5104 AUCss were assessed based on a simulation from the final model considering individual EBEs. Osimertinib AUCss were estimated at a dose of 80 mg, orally, once daily. The results are presented as boxplots in Figure 11 and Figure 12.

Figure 11: Impact of Covariates on Osimertinib AUCss



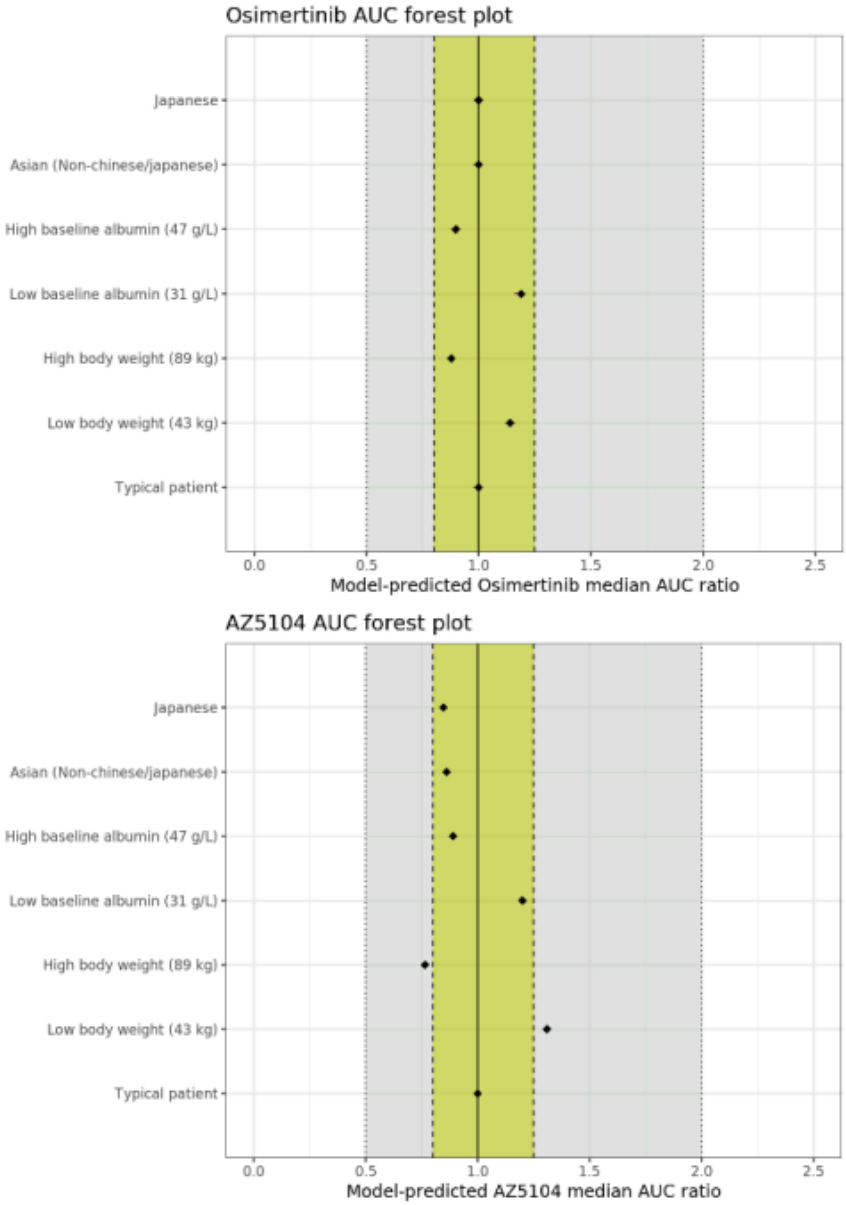
Source:/projects/qcp/QCP_MODELING/ONC/azd9291/eda_20230522_FLAURA2_submission/Scripts/2.2.PK - exposure -simulation_QC_EXPBOX_v4.Rmd, Reference: Impact of Covariates on osimertinib AUCss

Figure 12: Impact of Covariates on AZ5104 AUCss



Source:/projects/qcp/QCP_MODELING/ONC/azd9291/eda_20230522_FLAURA2_submission/Scripts/2.2.PK - exposure -simulation_QC_EXPBOX_v4.Rmd, Reference: Impact of Covariates on AZ5104 AUCss

Figure 13: Forest plot of the covariates impact on osimertinib and AZ5104 Cmax and AUC at steady state



Note: These are the ratio of exposure parameter for the 5th and 95th percentile of the relevant covariate relative to the median exposure estimates for continuous covariates, or relative to most frequent category for categorical covariate. The reference (typical patient) is a simulation based on white ethnicity with a median baseline body eight (62kg) and median baseline albumin(40g/L).

Pharmacokinetics of Osimertinib in NSCLC Patients

The investigation of the PK of osimertinib after single doses in healthy volunteers or multiple doses in metastatic NSCLC patients have been summarized in the previous submissions (AURA3, FLAURA and ADAURA). No clinical pharmacology studies have been conducted other than those already presented with the previous submissions.

The typical values of clearance (CL/F), volume of distribution of osimertinib (V1/F), and terminal half -life were 14.4 L/h, 1151 L, and ~56 hours, respectively. Based on the PopPK model, osimertinib and AZ5104 PK were at steady state by Day 12 of once daily osimertinib administration.

Table 8: Comparison of Steady State PK Parameters of Osimertinib in FLAURA2 and Pooled PopPK Analysis

PK Parameters of Osimertinib (80 mg, once Daily)	FLAURA2 SRI (Osimertinib +Carboplatin +Pemetrexed)	FLAURA2 SRI (Osimertinib +Cisplatin +Pemetrexed)	FLAURA2 (Osimertinib +Chemo)	FLAURA2 (Osimertinib Monotherapy)	Pooled PopPK [b,c]
Cycle/Day	C3/D1	C3/D1	C3/D1	C3/D1	NA
N	13	10	179	233	507
T_{max} (h) median (range) [a]	6.00 (2.00–6.03)	5.91 (0.00–6.05)	4.50 (0 -8.07)	4.03 (0 -7.17)	NC
$C_{ss,max}$ (nM) Geomean (gCV%)	515.4 (39.4)	513.3 (51.2)	587.5 (46.4)	593.4 (37.3)	533.1 (43.1)
C_{ss} (nM) Geomean (gCV%)	326.9 (62.3)	326.9 (48.0)	392.5 (50.5)	397.2 (40.4)	439.3 (47.9)
CLss/F (L/h) Mean (SD)	17.15 (7.2)	17.24 (7.7)	14.80 (6.4)	14.48 (5.2)	14.0 (5.6)
AUC_{ss} (nM*h) Geomean (gCV%)	10190 (47.2)	10100 (45.3)	11840 (45.5)	11790 (37.4)	11918 (44.3)

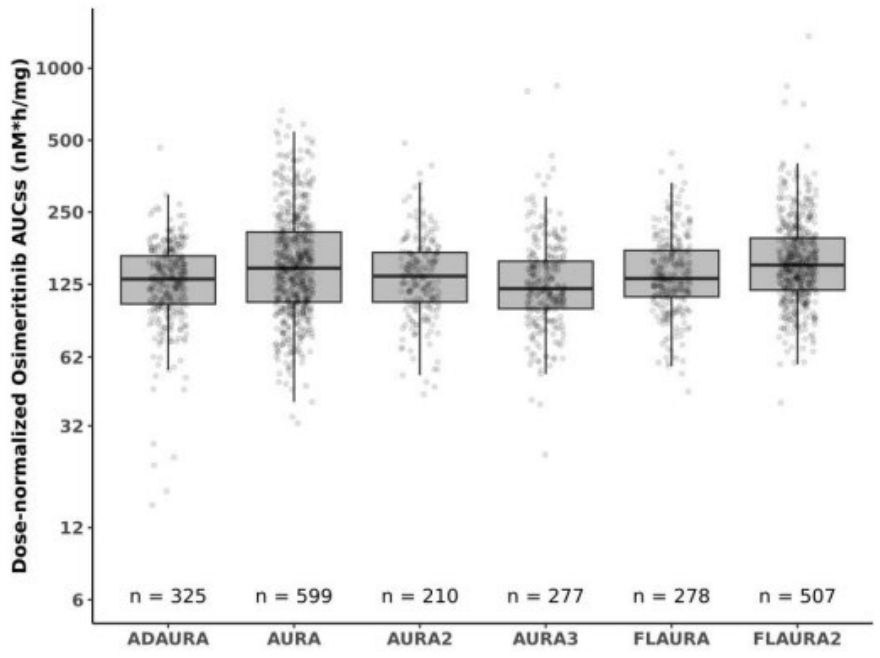
[a] Median (min -max) shown

[b] AUC_{ss}, $C_{ss,max}$ and $C_{ss,min}$ values are based on the population analysis (N=507)

[c] PopPK ERES report (Module 5.3.3.5)

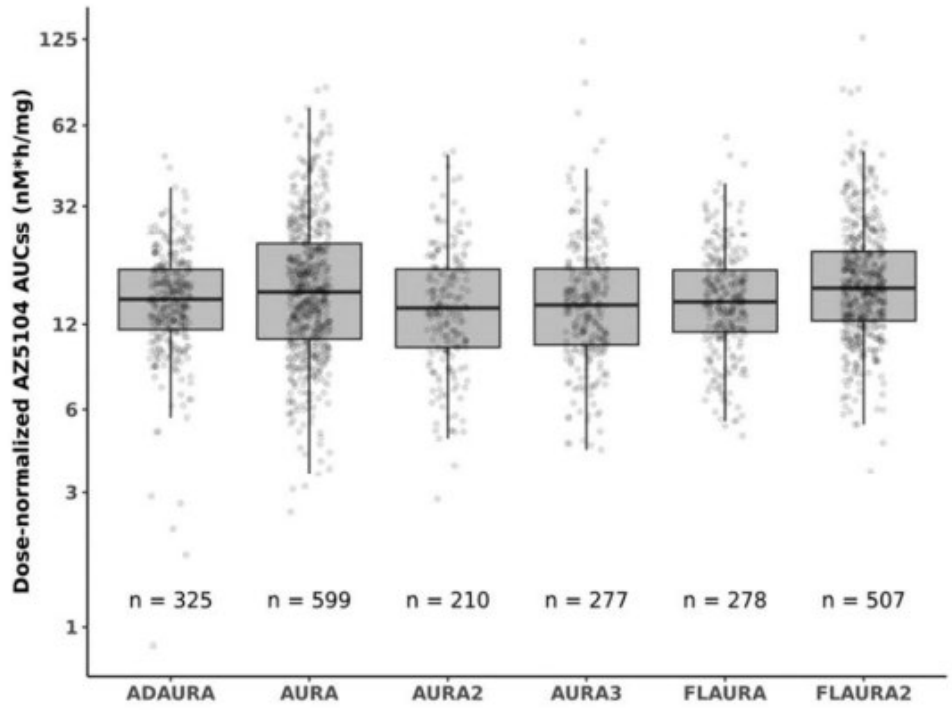
NA = not applicable; NC = not calculated; SRI = safety run -in

Figure 14: Box -and -Whiskers Plot of Dose -Normalized Steady State AUCss of Osimertinib as Monotherapy or in Combination with Chemotherapy in FLAURA2



Source: Figure 5 of PopPK ER ES report

Figure 15: Box -and -Whiskers Plot of Dose -Normalized Steady State AUCss of AZ5104 following Osimertinib Administration as Monotherapy or in Combination with Chemotherapy in FLAURA2



Source: Figure 6 of PopPK ER ES report.

Special populations

Impaired renal function

Mass balance study (D5160C00011) showed renal elimination to be a negligible pathway of clearance. In the population PK analysis, there was no impact of baseline creatinine clearance on the PK of osimertinib [N=2196, median (min -max) baseline creatinine clearance = 82.1 (20.5 -196) mL/min].

Based on the population pharmacokinetic analysis of 998 patients with mild renal impairment (CLcr 60 to less than 90 mL/min), 347 patients with moderate renal impairment (CLcr 30 to less than 60 mL/min), 5 patients with severe renal impairment (CLcr 15 to less than 30 mL/min) and 832 patients with normal renal function (greater than or equal to 90 mL/min), osimertinib apparent clearance (and exposures) were similar across all of these subgroups.

Impaired hepatic function

Based on a population pharmacokinetic analysis of 210 patients with mild hepatic impairment (total bilirubin ≤ULN and AST >ULN or total bilirubin between 1.0 to 1.5x ULN and anyAST), 8 patients with moderate hepatic impairment (total bilirubin between 1.5 times to 3.0 times ULN and any AST) and 1966 patients with normal hepatic function (total bilirubin less than or equal to ULN and AST less than or equal to ULN), osimertinib exposures were similar across all of these subgroups.

Gender

The population PK analysis determined sex (males (N=780) and females (N=1416)) to not be a significant covariate on the clearance of osimertinib (CL/F), and its metabolite AZ5104 (CLM/F), and osimertinib volume of osimertinib (V1/F).

Weight

The population PK analysis determined baseline body weight (WT) to be a significant covariate on osimertinib clearance (CL/F), and its metabolite AZ5104 (CLM/F), and osimertinib volume of osimertinib (V1/F). In this analysis, the median (min -max) body weight based on N=2196 was 62.0 (29.0 -128) kg. However, as shown in Figure 7, baseline body weight (WT), did not significantly impact the AUCss of osimertinib.

Pharmacokinetic interaction studies

In FLAURA2, exposures of osimertinib and AZ5104 following administration of osimertinib, 80 mg, once daily were similar when administered with or without carboplatin (AUC 5 mg/mL/min) or cisplatin (75 mg/m2) plus pemetrexed (500 mg/m2) in advanced or metastatic NSCLC patients with EGFRm. Similarly, the osimertinib and metabolite AZ5104 PK data from FLAURA2 were similar to that observed in prior studies where osimertinib has been dosed as a monotherapy.

2.3.3. PK/PD modelling

Exposure response analyses for safety and efficacy were conducted for patients enrolled in the investigational arm (osimertinib +chemotherapy) of FLAURA2.

Exposure response was conducted using osimertinib exposures (AUCss, Cminss, and Cmaxss) for patients in the osimertinib + chemotherapy group. Osimertinib monotherapy arm was used for PFS comparison purposes only.

Exposure metrics of osimeritinib were estimated using individual post hoc PK parameters following administration of osimertinib, once daily at the most prevalent dose.

Table 9 and Table 10 summarize the continuous and categorical covariates in the analysis dataset, stratified by treatment arm.

Table 9: Continuous Covariates

	Osimertinib	Osimertinib + Chemotherapy
Individuals		
N	263	244
Baseline Age (years)		
Mean (SD)	60.3 (10.6)	60.5 (9.94)
Median (IQR)	61.0 (53.0 -68.0)	61.0 (54.0 -68.0)
Min -max	30.0 -85.0	26.0 -82.0
Baseline Bodyweight (kg)		
Mean (SD)	64.8 (13.7)	65.2 (14.6)
Median (IQR)	62.5 (54.5 -73.0)	62.7 (54.5 -75.0)
Min -max	38.0 -115	38.1 -128
Baseline CrCL (ml/min)		
Mean (SD)	92.8 (26.6)	89.8 (25.0)
Median (IQR)	87.1 (73.9 -107)	85.7 (69.8 -103)
Min -max	41.4 -196	41.6 -183
Baseline Albumin (g/L)		
Mean (SD)	39.9 (4.78)	40.6 (4.21)
Median (IQR)	40.0 (37.0 -44.0)	41.0 (38.0 -43.7)
Min -max	22.0 -53.0	24.0 -51.5
Osimertinib AUC,ss (nM.h)		
Mean (SD)	12497 (4591)	13902 (9971)
Median (IQR)	11612 (9544 -14507)	11658 (8928 -15455)
Min -max	3836 -32008	2335 -108773

	Osimertinib	Osimertinib + Chemotherapy
Osimertinib Cmax,ss (nM)		
Mean (SD)	561 (205)	613 (418)
Median (IQR)	522 (430 -654)	525 (399 -692)
Min -max	179 -1469	113 -4547
Osimertinib Cmin,ss (nM)		
Mean (SD)	462 (181)	527 (415)
Median (IQR)	431 (340 -537)	431 (325 -609)
Min -max	130 -1316	72.7 -4507
Osimertinib Metabolite AUC,ss (nM.h)		
Mean (SD)	1371 (621)	1593 (1140)
Median (IQR)	1247 (977 -1665)	1291 (955 -1754)
Min -max	350 -3893	269 -10138
Osimertinib Metabolite Cmax,ss (nM)		
Mean (SD)	59.6 (26.4)	68.5 (47.4)
Median (IQR)	54.0 (42.7 -70.8)	55.9 (42.4 -77.0)
Min -max	16.0 -177	12.8 -423
Osimertinib Metabolite Cmin,ss (nM)		
Mean (SD)	53.8 (25.5)	63.6 (47.8)
Median (IQR)	47.5 (36.4 -65.6)	51.0 (36.9 -71.1)
Min -max	12.6 -154	8.97 -422

Source:/projects/qcp/QCP_MODELING/ONC/azd9291/eda_20230522_FLAURA2_submission/FLAURA2_az -osi -pfs -er.v7.Rmd, Reference: conttab

Table 10: Categorical Covariates

	Osimertinib	Osimertinib + Chemotherapy
Individuals		
N	263	244
T790M mutation status by central review		
T790M mutation negative	231 (87.8%)	221 (90.6%)
T790M mutation positive	3 (1.14%)	2 (0.820%)
Unknown	29 (11.0%)	21 (8.61%)
Gender		
Male	101 (38.4%)	93 (38.1%)
Female	162 (61.6%)	151 (61.9%)

	Osimertinib	Osimertinib + Chemotherapy
Grouped Ethnicity		
White	63 (24.0%)	44 (18.0%)
Asian (other than Chinese/Japanese)	54 (20.5%)	49 (20.1%)
Chinese	69 (26.2%)	65 (26.6%)
Japanese	44 (16.7%)	39 (16.0%)
Other/Missing	33 (12.5%)	47 (19.3%)
Line of therapy		
First Line	263 (100%)	244 (100%)
Grouped WHO performance status		
Grouped WHO performance status 0	97 (36.9%)	93 (38.1%)
Grouped WHO performance status 1	166 (63.1%)	151 (61.9%)
Age Group		
<65	162 (61.6%)	157 (64.3%)
65 -75	79 (30.0%)	70 (28.7%)
>=75	22 (8.37%)	17 (6.97%)
Grouped Renal Impairment		
Normal	118 (44.9%)	109 (44.7%)
Mild	132 (50.2%)	124 (50.8%)
>= Moderate	13 (4.94%)	11 (4.51%)
Grouped Hepatic Impairment		
Normal	233 (88.6%)	222 (91.0%)
>= Mild	30 (11.4%)	22 (9.02%)

Source:/projects/qcp/QCP_MODELING/ONC/azd9291/eda_20230522_FLAURA2_submission/FLAURA2_az -osi -pfs -er.v7.Rmd, Reference: cattab

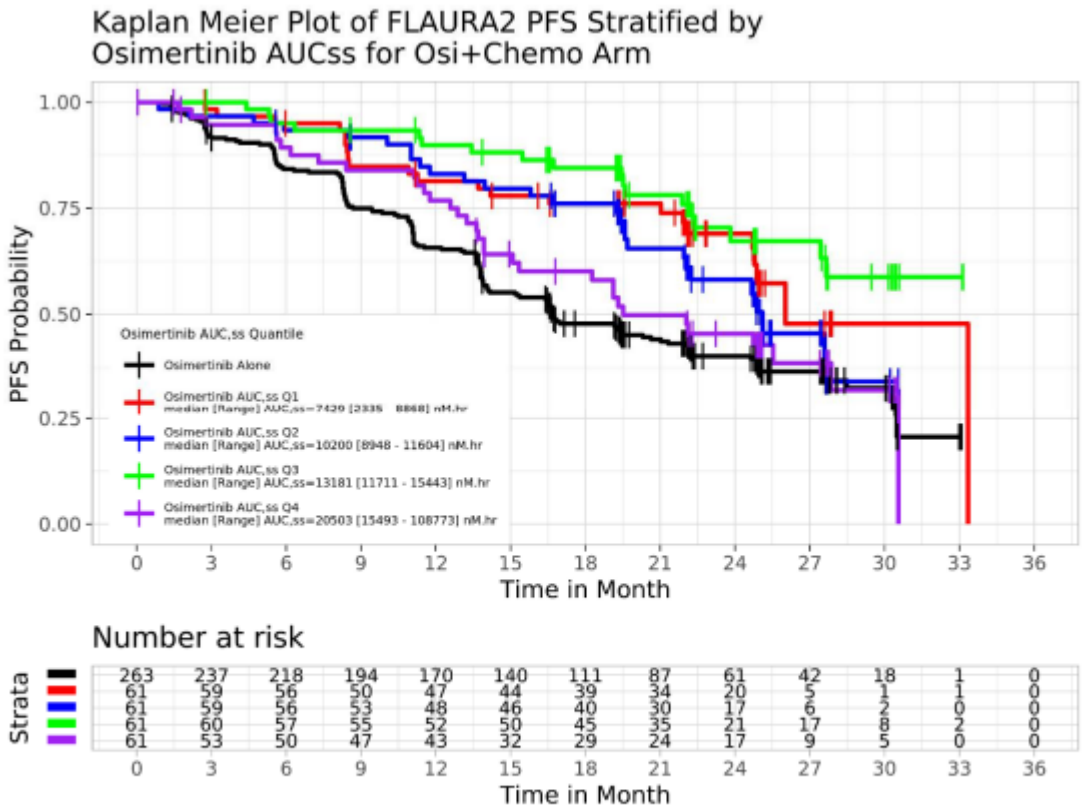
Osimertinib and AZ5104 exposure metrics (AUCss, Cmax,ss, Cmin,ss) were compared to assess the correlation between the steady -state osimertinib and AZ5104 exposure relationship. In FLAURA2, AZ5104 was estimated to be ~10% of osimertinib exposures based on AUCss; this is consistent with observations from prior studies. Therefore, it has been assumed that the overall trends in ER and ES of osimertinib and AZ5104 will be similar; thus, no ER/ ES analyses were conducted for AZ5104.

Exposure Efficacy Analysis

Exposure Response Analysis of PFS in FLAURA2 Investigational Arm

Exposure -response relationship between osimertinib exposures (AUCss, Cmax,ss, and Cmin,ss) and PFS in the investigational arm (osimertinib + chemotherapy) was assessed via Kaplan -Meier (KM) plot with patients stratified by quartiles of osimertinib exposure (AUCss)(Figure 16).

Figure 16: PFS Kaplan Meier Plots for Osimertinib Exposure Metrics by Quartiles at Steady State



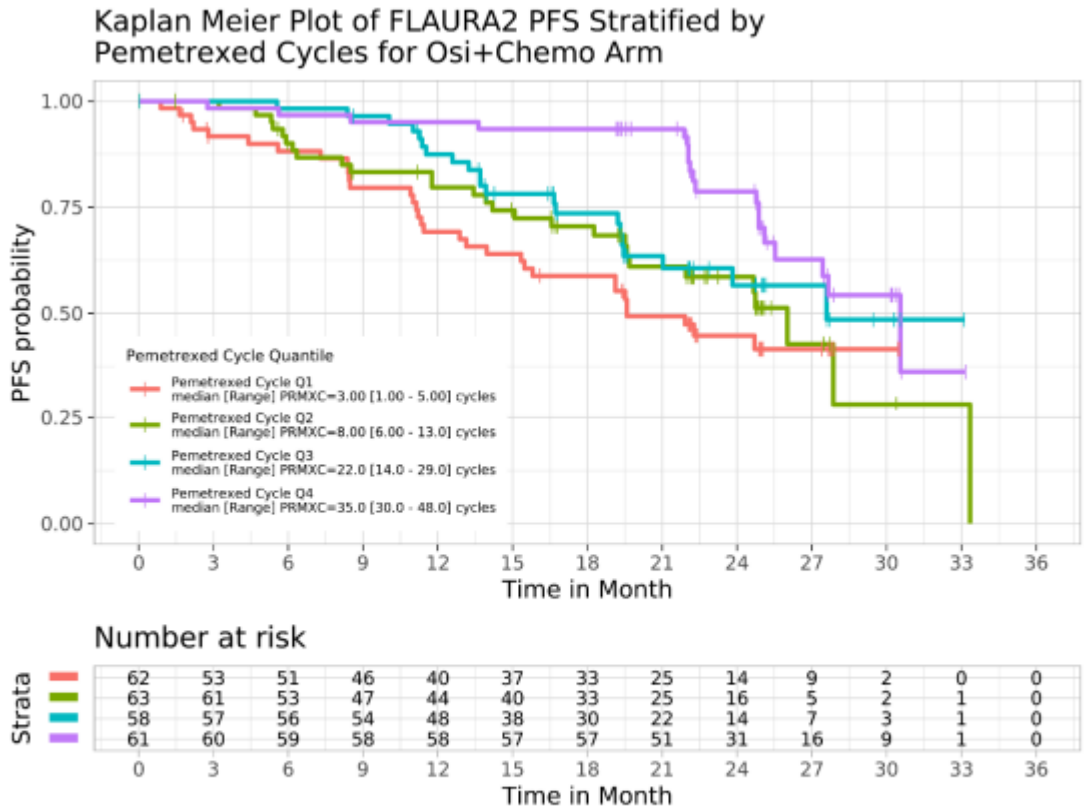
Source:/projects/qcp/QCP_MODELING/ONC/azd9291/eda_20230522_FLAURA2_submission/FLAURA2_az -osi -pfs -er.v7.Rmd, Reference: PCAUCssP km

Cox Proportion Hazard Model for PFS

The Cox proportional hazard model was developed to understand the effect of different factors on PFS of patients in the investigational arm (osimertinib +chemotherapy) of FLAURA2.

Following the likelihood ratio test, the osimertinib exposure metrics (AUCss, Cmax,ss, Cminss) were not statistically significant; similarly, baseline demographics including baseline body weight, age, race, gender, WHO status, baseline creatinine clearance, renal impairment, and hepatic impairment status were not statistically significant covariates of PFS. In the first step of covariate searching (univariate analysis), number of pemetrexed cycles (PRMXC) and baseline albumin (BALB – data not shown) were identified as significant covariates on PFS ($p<0.01$).

Figure 17: PFS Kaplan Meier Plots with Patients Stratified by the Quartiles of Pemetrexed Cycles



Source:/projects/qcp/QCP_MODELING/ONC/azd9291/eda_20230522_FLAURA2_submission/az -FLAURA2 -PFS -post -process.v7.Rmd, Reference: PRMXC quantile plot

In the second step of covariate searching, only the number of pemetrexed cycles remained as a statistically significant covariate on PFS, while none of remaining covariates including baseline albumin, baseline body weight, age, race, gender, WHO, baseline creatinine clearance, renal impairment, and hepatic impairment status was significantly associated with PFS (Table 11).

Table 11: Final Cox PH model for Progression Free Survival

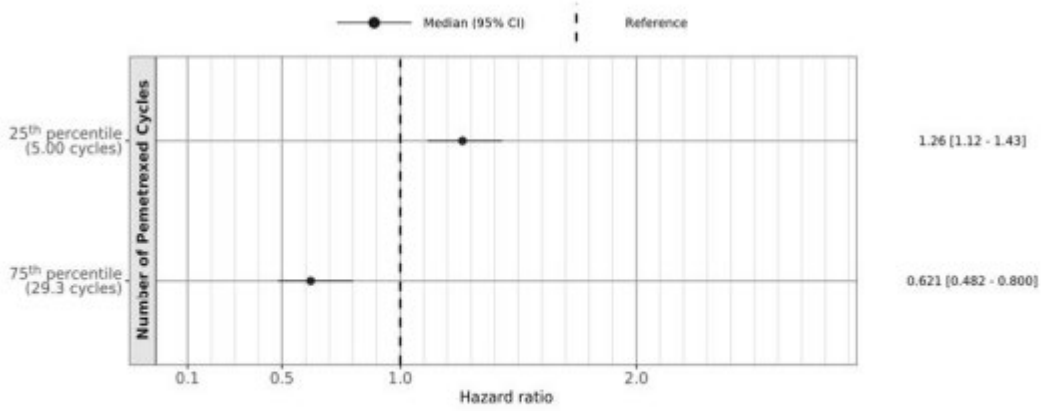
Predictor	β	se	exp(β)	95% CI β	*p* value	AIC
PRMXC	-0.0293	0.0079	0.971	[-0.0449 ; -0.0137]	<0.001	956.07

BALB= Baseline albumin level; CI=Confidence interval; β = coefficient of the Cox PH model; exp(β) = Hazard ratio; PRMXC = Number of pemetrexed cycles

Source:/projects/qcp/QCP_MODELING/ONC/azd9291/eda_20230522_FLAURA2_submission/az -FLAURA2 -PFS -post -process.v7.Rmd, Reference: tata1

Forest plot of final Cox PH model is presented in Figure 18 showing the hazard ratio of 25th and 75th percentiles of pemetrexed cycle on PFS suggesting a significant difference in hazard ratio due to pemetrexed cycles.

Figure 18: Forest Plot for Cox Proportional Hazards Model



Source:/projects/qcp/QCP_MODELING/ONC/azd9291/eda_20230522_FLAURA2_submission/az -FLAURA2 -PFS -post -process.v7.Rmd, Reference: p_forest_p2

Exposure Safety Analysis

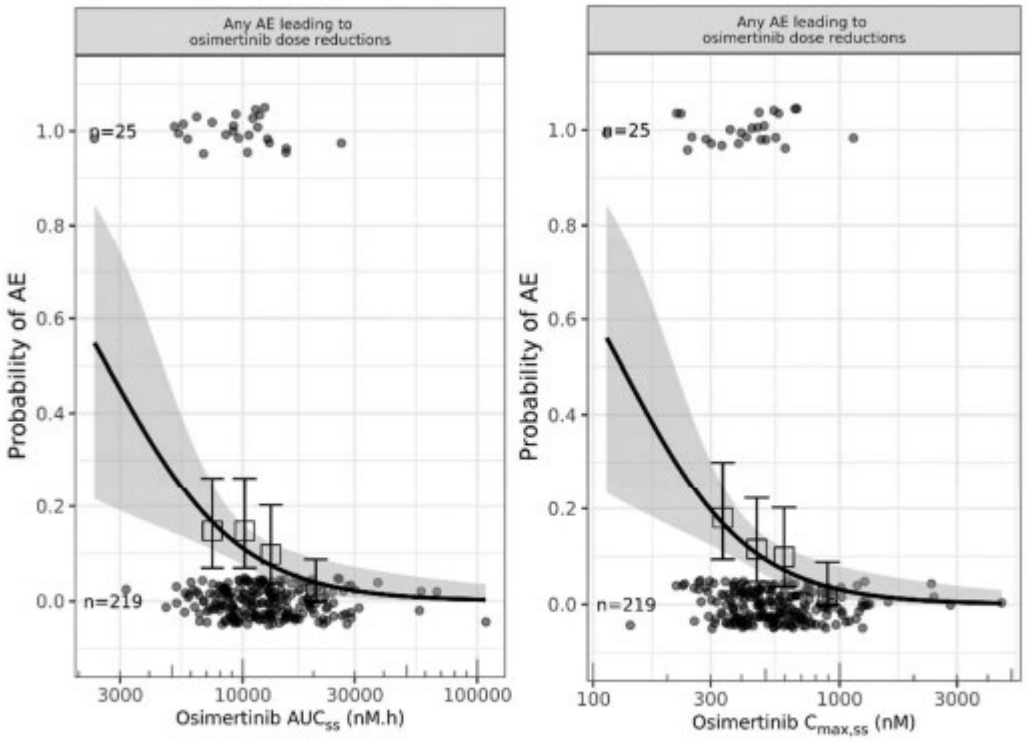
For the exposure safety analysis, both exploratory and logistics regressions were performed on AEs of interest for the investigational arm, osimertinib + chemotherapy. These AEs included Grade ≥ 3 AEs causally related to osimertinib, any AEs leading to osimertinib dose interruption/reduction/discontinuation, Grade ≥ 3 haematological AEs (anaemia, neutropenia, and thrombocytopenia), cardiac effects (including cardiac failure), LVEF decreases (pre -defined as "≥ 10 percentage points decrease from baseline and absolute value <50%"), and Grade ≥ 1 ILD/pneumonitis (ILD grouped terms included "interstitial lung disease", "pneumonitis", and "organising pneumonia") causally related to osimertinib.

Note: AEs with <5% occurrence were not feasible to include in ER -safety analyses due to insufficient data. Additionally, based on PopPK model, as osimertinib steady state exposures correlated well with those of AZ5104, ES analyses based on osimertinib exposure metrics (AUC,ss, Cmax,ss, and Cmin,ss) can be used as surrogates of exposure -safety relationship for AZ5104.

Exploratory analysis of exposure distribution in patients with or without the AE did not show any trends in exposure for any of these adverse effects. Logistic regression analysis to assess the probability of developing AEs and exposure metrics lead to non-statistical p-values for any of the AEs evaluated except for AE Leading to Osimertinib Dose Reduction and Osimertinib AUCss and Cmaxss (Figure 19).

The probability of any AE leading to osimertinib dose reduction calculated in quartiles of the osimertinib AUCss as shown in Figure 19.

Figure 19: Relationship Between Probability of Developing Any AE Leading to Osimertinib Dose Reduction and Osimertinib AUCss and Cmaxss in the Investigational Arm (Osimertinib + Chemotherapy Arm)



Source: FLAURA2_az -osi -es -ae.v11.Rmd, Reference: 9e46e9:f68794 and Reference: c63b02:6eb6c4

Table 12: Summary of the Effect of Different Exposure Metrics on the Probability of Any AE Leading to Osimertinib Dose Reduction in the Investigational Arm (Osimertinib + Chemotherapy Arm)

Exposure metric	Estimate (% Relative standard error)	95% Confidence interval	P -value (based on LRT)	Loglikelihood	AIC	Number of subjects
Osimertinib Steady State AUC (Parent)	-0.000133 (40.3)	(-0.000249, -0.0000387)	0.003	-76.14	156.3	244
Osimertinib Steady State Cmax (Parent)	-0.00331 (38.1)	(-0.00601, -0.00107)	0.002	-75.64	155.3	244
Osimertinib Steady State Cmin (Parent)	-0.00285 (45)	(-0.00563, -0.000624)	0.007	-77.02	158	244

AE = adverse event; AIC = Akaike's information criteria; AUC = area under the serum concentrationtime curve; Cmax = maximum serum concentration; Cmin = minimum serum concentration; LRT = likelihood ratio test

Source: FLAURA2_az -osi -es -ae.v11.Rmd, Reference: e1fbb3:fdc729

2.3.4. Discussion on clinical pharmacology

The MAH characterised the clinical pharmacology properties of the combination of osimertinib with pemetrexed and platinum-based chemotherapy in the treatment of patients with locally advanced or metastatic NSCLC whose tumours have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations. Data from the pivotal phase III study FLAURA2 was pooled with data from five previous clinical trials (AURA, AURA2, AURA3, FLAURA, and ADAURA).

Analytical methods

Overall, the method validation and sample analysis were carried out in accordance with ICH M10 Guideline. Sample analysis was performed at two Labcorp laboratories (located in the UK and China) and a cross validation was carried out between both analytical sites. Initial issues raised, mainly regarding cross-validation, selection of QCs, ISR performance, stability validation and inspection history, were addressed and solved during the procedure.

Of note, for AZD9291 and AZ13575104, the MQC was 560 nM and 57.7 nM, respectively, and thus not within 30-50% of the ULOQ. The MAH justified that MQC was set at the approximate geometric mean of the HQC and LQC and that it was shown that the QC levels employed covered the majority of sample concentrations observed. Considering the aforementioned, the fact that an additional QC within 30-50% of the ULOQ was not included was not further pursued in this procedure. Nevertheless, for future procedures, the MAH should include the low QC, medium QC and high QC that comply with the ICH M10 Guideline, apart from including an additional QC representative of the analysed concentrations.

Population PK analysis

The pharmacokinetic properties of osimertinib and its metabolite AZ5104 have been characterised using a previous population PK model. The modelling strategy is endorsed, since it allows to re-use and apply the previous knowledge of the structural and covariate effects of osimertinib to describe its concentration time-course in patients treated with the intended combination.

The population PK analysis was based on a pooled dataset from 6 studies, which includes data of osimertinib from studies in adult patients with EGFR positive NSCLC. The final dataset for the current population PK model development included 52238 observation records from 2196 subjects of which 8199 observation records and 507 subjects are from the FLAURA2 study.

PK samples of osimertinib below the lower limit of quantification (LLQ) were low (6.21 %) and were excluded from the analysis. M1 method for handling BLQ-data is considered acceptable.

The previous model was fitted using the final dataset where PK parameters and random effects were estimated. The covariate model was re-evaluated and combination therapy was tested as a covariate.

The pharmacokinetics was described with a 1-compartment model of osimertinib and 1-compartment for its metabolite. The model assumes that the drug is absorbed with a first order absorption process and the parent drug eliminated from the system or transformed into its metabolite also with a first order process.

The final PK model contains 9 covariates effects including WT on CL, V1 and CLM, Albumin on CL, V1, CLM and Vm, Asian on CLM and Japanese on CLM. The final parameter estimates of the final model are adequate based on the non-parametric bootstrap analysis and the value of RSE, which is <33%. Shrinkage values were 3.62%, 3.99%, 41.09%, 21.76% and 46.12% for CL, CLM, Ka, V1 and VM respectively. Moderate to high inter-individual variability has been characterized on CL (44.75%), CLM(52.08%), KA (100.68%), V1(84.61%) and VMF (81,56%). Standard GOF suggest no relevant model deviations for the combination therapy, showing the adequacy of the final population PK model to describe the observed data. Model evaluation was conducted through pc-VPC, showing no relevant bias (minor over-estimation of the inter-individual random effects on the 5^{th} percentile) across the different analytes from FLAURA2 study and the pooled dataset.

The impact of covariates has been evaluated on osimertinib and its metabolite steady-state exposure metrics (AUCss, Cmaxss and Cminss). The simulation-based analysis using EBE suggests a relevant trend on AUCss of osimertinib at different quartiles or terciles of baseline body-weight and baseline albumin. However, moderate eta-shrinkage was estimated on V1/F (21.76%) and VM/F (46.12%) that could bias the evaluation of this relationship. In this sense, a more informative analysis (forest-plot) was requested to fully understand the contribution of each covariate on osimertinib exposure (Figure 13). The impact of

covariate effect on Cmaxss and AUCss of osimertinib and AZ5104 based on univariate assessment was covered.

The values of clearance (CL/F), volume of distribution of osimertinib (V1/F), and terminal half -life were similar to those reported in previous submissions.

The pharmacokinetics of osimertinib in patients treated with osimertinib + chemotherapy are similar to that of osimertinib monotherapy in FLAURA2 and across the pooled studies used in the updated model (Table 8) which included patients in adjuvant setting (ADAURA), first -line (AURA and FLAURA), second -line (AURA, AURA2, and AURA3) and ≥ third -line setting (AURA and AURA2); Figure 14 and Figure 15 below demonstrate similarity of exposures of osimertinib and AZ5104, following administration of osimertinib as a monotherapy across different studies and lines of therapy and as a combination with chemotherapy.

The analysis at steady state did not identify changes in exposure out of the reference range (0.80-1.25), except for high body weight (89 kg) and low body weight (43 kg), which would show a 24% lower Cmaxss and AUCss and 31% higher Cmaxss and AUCss for AZ51104, respectively. Despite it is very likely that larger differences in the exposure of metabolite would be achieved in patients with lower body weight than 43 kg and higher body weight than 89 kg, the flat exposure-response relationship and the low impact of the metabolite in the efficacy/safety outcomes leads to support the appropriateness of the proposed dosage regimen.

Special populations

As renal impairment has no significant impact on exposures of osimertinib, no dose adjustment is required based on renal function. Caution should be exercised when treating patients with severe and end stage renal impairment, as patients with CLcr less than 15 mL/min (end stage renal disease or on dialysis) were not included in the clinical trials.

The overall findings from the PopPK analysis are consistent with prior observations demonstrating that no dose adjustment is required for osimertinib when treating patients with mild (Child Pugh A or based on NCI -ODWG) or moderate (Child Pugh B or based on NCI -ODWG) hepatic impairment.

The PK properties of osimertinib in special populations have been updated with the pooled analysis. No relevant differences were seen compared to previous rounds. There is no impact on the SmPC dose recommendations for patients with impaired renal function, impaired hepatic function.

Pharmacokinetics data were not suggestive of a PK drug -drug interaction when osimertinib, 80 mg, once daily is administered in combination with chemotherapy.

Exposure-efficacy relationship

The exposure-efficacy analysis was performed with data from subjects in the combination therapy arm of FLAURA2 study. PFS was used as the efficacy outcome and predicted AUCss, Cminss and Cmaxss as exposure metrics.

Kaplan-Meier plots stratified by quartiles of exposures were constructed. The results from the Kaplan-Meier suggest that PFS seems to be independent of exposure (high degree of overlapping of Q1, Q2 and Q3 while Q4 seems to have lower PFS), which was then confirmed with the Cox regression models for PFS as the exposure metrics were not statistically significant.

The range of exposure evaluated is too limited to be able to identify differences on the efficacy endpoint. In the absence of an informative exposure-efficacy study, with different dose levels that allow for a greater range of exposure, it can only be concluded that the exposure-efficacy relationship in the present analysis is flat at the proposed dosing regimen. However, these results cannot be extrapolated to dosage

regimens or dose levels other than those evaluated, for which it will be necessary to have additional experimental information.

Of all the covariates evaluated only the number of pemetrexed cycles was statistically significant where increasing number of cycles were associated with increasing PFS.

Exposure-safety relationship

The exposure-safety analysis was performed with data from subjects in the combination therapy arm of FLAURA2 study. AEs of interest that included Grade ≥ 3 AEs causally related to osimertinib, any AEs leading to osimertinib dose interruption/reduction/discontinuation, Grade ≥ 3 haematological AEs (anaemia, neutropenia, and thrombocytopenia), cardiac effects (including cardiac failure), LVEF decreases (pre -defined as "≥ 10 percentage points decrease from baseline and absolute value <50%"), and Grade ≥ 1 ILD/pneumonitis (ILD grouped terms included "interstitial lung disease", "pneumonitis", and "organising pneumonia") causally related to osimertinib were used as safety outcome and predicted AUCss, Cminss and Cmaxss as exposure metrics.

Exploratory analysis of exposure distribution in patients with or without the AE did not show any trends in exposure for any of these adverse effects. Logistic regression analysis to assess the probability of developing AEs and exposure metrics lead to non-statistical p-values for any of the AEs evaluated except for AE Leading to Osimertinib Dose Reduction and Osimertinib AUCss and Cmaxss (Figure 19). However, the negative relationship found between osimertinib exposure and the probability of developing any AE leading to osimertinib dose reduction is not clinically relevant.

2.3.5. Conclusions on clinical pharmacology

The clinical pharmacology properties of osimertinib and its main metabolite (AZ5104) have been characterized in the treatment of patients with locally advanced or metastatic NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations in combination with pemetrexed and platinum-based chemotherapy. Overall, the strategy is endorsed and the analysis confirms the conclusions obtained in previous studies of osimertinib. The exposure-response analysis suggests a flat relationship with efficacy and absence of relevant relationships between exposure and safety.

2.4. Clinical efficacy

2.4.1. Dose response study

No new dose response studies have been performed. The proposed dose for osimertinib is the currently authorised 80 mg once daily.

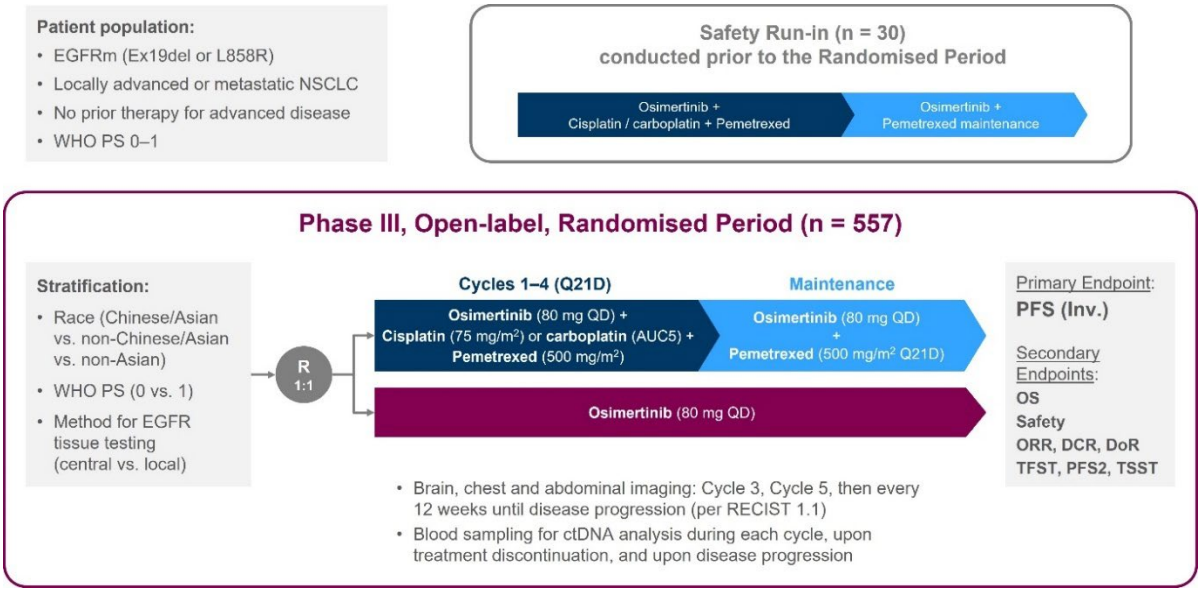
2.4.2. Main study

A Phase III, Open-label, Randomised Study of Osimertinib With or Without Platinum Plus Pemetrexed Chemotherapy, as First line Treatment in Patients with Epidermal Growth Factor Receptor Mutation Positive, Locally Advanced or Metastatic Non-small Cell Lung Cancer (FLAURA2)

Study D5169C00001 (FLAURA2) is an ongoing, global, Phase III, open-label, randomised study of osimertinib with or without pemetrexed and platinum-based chemotherapy in patients with locally advanced (not amenable to curative surgery or chemoradiotherapy) or metastatic EGFRm NSCLC (Ex19del and/or L858R) who had not received prior therapy for advanced disease. Prior adjuvant or

neoadjuvant therapies, or definitive radiation/chemoradiation were permitted if treatment was completed at least 12 months prior to development of recurrent disease (Figure 20).

Figure 20. Flow Chart of FLAURA2 Study Design



The FLAURA2 study has been conducted in 2 parts: the Safety run-in period, and the open-label, Phase III, Randomised period. The primary analysis of the Safety run-in period (which was conducted to evaluate the safety and tolerability of osimertinib when given in combination with platinum-based chemotherapy and pemetrexed, with a DCO date of 19 February 2020) has previously been completed. Following a positive recommendation by the Safety Review Committee based on the evaluation of data from the Safety run-in period, the Randomised period was initiated.

Efficacy and safety data from FLAURA2 presented from 557 patients is based on the primary analysis data from the randomised period (DCO date: 03 April 2023), unless otherwise indicated. The pivotal dataset is supplemented with long-term efficacy data (30 patients) from the final analysis of the safety run-in period of FLAURA2 (DCO date: 03 April 2023).

Methods

Study participants

Inclusion criteria

For inclusion in any treatment period of the study participants had to fulfil all of the following criteria:

1. Capable of giving signed informed consent, which included compliance with the requirements and restrictions listed in the informed consent form (ICF) and in the protocol.

2. Provision of signed and dated, written ICF prior to any mandatory study-specific procedures, sampling, and analyses.

3. For patients who agreed to the optional genetic testing, provision of signed and dated genetic testing section of the written Main ICF prior to collection of a sample for genetic analysis for inclusion in the optional genetic research as allowed by local regulations.

4. Male or female, at least 18 years of age; patients from Japan at least 20 years of age.

5. Pathologically confirmed non-squamous NSCLC; NSCLC of mixed histology is allowed.

6. Newly diagnosed locally advanced (clinical Stage IIIB, IIIC) or metastatic NSCLC (clinical Stage IVA or IVB) or recurrent NSCLC (per version 8 of the International Association for the Study of Lung Cancer Staging Manual in Thoracic Oncology), not amenable to curative surgery or radiotherapy.

7. The tumour harboured one of the 2 common EGFR mutations known to be associated with EGFR-TKI sensitivity (Ex19del or L858R), either alone or in combination with other EGFR mutations, which may have included T790M, assessed by a CLIA-certified (US sites) or an accredited (outside of the US) local laboratory or by central prospective tissue testing.

8. Mandatory provision of a baseline plasma sample and an unstained, archival tumour tissue sample in a quantity sufficient to allow for central confirmation of the EGFR mutation status.

9. Patients had to have untreated advanced NSCLC not amenable to curative surgery or radiotherapy. Prior adjuvant and neo-adjuvant therapies (chemotherapy, radiotherapy, immunotherapy, biologic therapy, investigational agents), or definitive radiation/chemoradiation with or without regimens including immunotherapy, biologic therapy, investigational agents, were permitted as long as treatment was completed at least 12 months prior to the development of recurrent disease.

10. WHO PS of 0 to 1 at screening with no clinically significant deterioration in the previous 2 weeks.

11. Life expectancy > 12 weeks at Day 1.

12. At least one lesion, not previously irradiated that could be accurately measured at baseline as $\geq$ 10 mm in the longest diameter (except lymph nodes, which must have had a short axis of $\geq$ 15 mm) with computed tomography (CT) or magnetic resonance imaging (MRI), and that was suitable for accurate repeated measurements. If only one measurable lesion existed, it was acceptable to be used (as a target lesion) as long as it had not been previously irradiated and as long as it had not been biopsied within 14 days of the baseline tumour assessment scans.

13. Female patients who were not abstinent (in line with the preferred and usual lifestyle choice of the patient) and intended to be sexually active with a male partner must have been using highly effective contraceptive measures, must not have been breast feeding, and must have had a negative pregnancy test prior to first dose of investigational product (IP) or must have had evidence of non-child-bearing potential by fulfilling one of the following criteria at screening:

- Post-menopausal, defined as more than 50 years of age and amenorrhoeic for at least 12 months following cessation of all exogenous hormonal treatments
- Women under 50 years old were considered as postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatments and had luteinizing hormone and follicle-stimulating hormone levels in the post-menopausal range for the institution.
- Documentation of irreversible surgical sterilization by hysterectomy, bilateral oophorectomy, or bilateral salpingectomy but not tubal ligation.

14. Male patients must have been willing to use barrier contraception.

Exclusion criteria

Any of the following were regarded as a criterion for exclusion from the study:

1. Spinal cord compression; symptomatic and unstable brain metastases, except for those patients who had completed definitive therapy, were not on steroids, and had a stable neurological status for at least 2

weeks after completion of the definitive therapy and steroids. Patients with asymptomatic brain metastases could be eligible for inclusion if in the opinion of the investigator immediate definitive treatment is not indicated.

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

3. 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 jeopardize compliance with the protocol, or active infection including hepatitis B, hepatitis C, and human immunodeficiency virus. Screening for chronic conditions was not required.

4. Any of the following cardiac criteria:

- Mean resting corrected QT interval (QTc) > 470 msec, obtained from 3 electrocardiograms (ECG), 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 increased the risk of QTc prolongation or risk of arrhythmic events such as electrolyte abnormalities including serum/plasma potassium*, magnesium* and calcium* below the lower limit of normal (LLN), heart failure, 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 and cause Torsades de Pointes.
- Correction of electrolyte abnormalities to within normal ranges could be performed during screening

5. Inadequate bone marrow reserve or organ function as demonstrated by any of the following laboratory values:

- Absolute neutrophil count below the LLN (< LLN) *
- Platelet count below the LLN *
- Haemoglobin < 90 g/L *

** The use of granulocyte colony stimulating factor support, platelet transfusion and blood transfusions to meet these criteria was not permitted.*

- ALT > 2.5 x upper limit of normal (ULN) if no demonstrable liver metastases or > 5 x ULN in the presence of liver metastases
- AST > 2.5 x ULN if no demonstrable liver metastases or > 5 x ULN in the presence of liver metastases
- Total bilirubin > 1.5 x ULN if no liver metastases or > 3 x ULN in the presence of documented Gilbert's Syndrome (unconjugated hyperbilirubinemia) or liver metastases
- Creatinine clearance < 60 mL/min calculated by Cockcroft and Gault equation or 24-hour urine collection.

6. Any concurrent and/or other active malignancy that required treatment within 2 years of first dose of IP.

7. Any unresolved toxicities from prior systemic therapy (eg, adjuvant chemotherapy) greater than Common Terminology Criteria for Adverse Events (CTCAE) Grade 1 at the time of starting study treatment, with the exception of alopecia and Grade 2 prior platinum-therapy related neuropathy.

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

9. Prior treatment with any systemic anti-cancer therapy for advanced NSCLC not amenable to curative surgery or radiation including chemotherapy, biologic therapy, immunotherapy, or any investigational drug. Prior adjuvant and neo-adjuvant therapies (chemotherapy, radiotherapy, immunotherapy, biologic therapy, investigational agents), or definitive radiation/chemoradiation with or without regimens including immunotherapy, biologic therapies, investigational agents were permitted as long as treatment was completed at least 12 months prior to the development of recurrent disease.

10. Prior treatment with an EGFR-TKI.

11. Major surgery within 4 weeks of the first dose of IP. Procedures such as placement of vascular access, biopsy via mediastinoscopy or biopsy via video assisted thoracoscopic surgery were permitted.

12. Radiotherapy treatment to more than 30% of the bone marrow or with a wide field of radiation within 4 weeks of the first dose of IP.

13. Use of (or unable to stop use prior to receiving the first dose of study treatment) medications or herbal supplements known to be strong inducers of CYP3A4 (at least 3 weeks prior).

14. Participation in another clinical study with an investigational product during the 4 weeks prior to Day 1. Patients in the follow-up period of an interventional study were permitted.

15. Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and staff at the study site).

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

17. Previous treatment allocation (Safety run-in) or randomisation (Randomisation period) in the present study.

18. Pregnant (confirmed with positive pregnancy test) or breast-feeding.

19. History of hypersensitivity to active or inactive excipients of IP or drugs with a similar chemical structure or class to IP.

20. Contraindication for pemetrexed and cisplatin/carboplatin according to local approved label.

21. In addition, the following were considered criteria for exclusion from the exploratory genetic research:

- Prior allogeneic bone marrow transplant
- Non-leukocyte depleted whole blood transfusion within 120 days of genetic sample collection

Treatments

The FLAURA2 study has been conducted in 2 parts: the Safety run-in period, and the open-label, Phase III, Randomised period.

In the Randomised period, patients were randomised to one of the following treatment groups:

- Osimertinib + chemotherapy arm (osimertinib in combination with pemetrexed plus either cisplatin or carboplatin for 4 cycles, followed by osimertinib plus pemetrexed maintenance): osimertinib 80 mg oral tablets once daily with pemetrexed (500 mg/m^2) and either cisplatin (75 mg/m^2) or carboplatin (AUC5), with both treatments administered on Day 1 of 21-day cycles for 4 cycles, followed by osimertinib 80 mg once daily and pemetrexed maintenance (500 mg/m^2) Q3W.
- Osimertinib monotherapy arm: osimertinib 80 mg oral tablets once daily.

Crossover between treatment arms was not permitted within the study.

Prior to randomisation, the investigators could choose either carboplatin or cisplatin as the platinum-based therapy for patients in the osimertinib + chemotherapy arm according to local clinical practice. Patients who discontinued cisplatin alone or carboplatin alone could, at the investigator's discretion, be switched to the other allowed platinum agent (carboplatin or cisplatin) with pemetrexed and osimertinib for the remainder of the platinum doublet cycles, up to a maximum of 4 cycles of platinum. Antiemetic premedication could be administered according to local standards of care.

Patients were to continue on their randomised treatment until disease progression as defined by RECIST 1.1, unacceptable toxicity, or until a treatment discontinuation criterion was met.

Following study treatment discontinuation, subsequent therapies were given at the discretion of the investigator. Patients were followed for second progression on a subsequent treatment, defined according to local practice, and for survival.

Patients could continue to receive study treatment with osimertinib beyond RECIST 1.1, defined progression if, in the judgement of the investigator, they were receiving clinical benefit and did not meet any of the discontinuation criteria. However, if the patient was deemed to have clinically significant unacceptable or irreversible toxicities, rapid tumour progression, or symptomatic progression requiring urgent medical intervention (eg, CNS metastases, respiratory failure, spinal cord compression) study treatment was to be discontinued.

An Independent Data Monitoring Committee (IDMC) oversaw the safety and tolerability of the Randomised period, as per International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines. The conduct and operating procedures of the IDMC were documented in an IDMC Charter, in alignment with ICH guidance.

Objectives

Primary Objective:

To assess the efficacy of osimertinib + chemotherapy treatment compared with osimertinib in terms of Progression-free survival (PFS) based on investigator assessment per RECIST 1.1.

Secondary Objectives:

To further assess the efficacy of osimertinib + chemotherapy compared with osimertinib in terms of overall survival (OS), objective response rate (ORR), duration of response (DoR), depth of response, disease control rate (DCR), time from randomisation to second progression or death (PFS2), time to first subsequent therapy (TFST) and time to second subsequent therapy or death (TSST), ant patient reported outcomes (PRO)

To assess the impact of osimertinib + chemotherapy compared with osimertinib on patient-reported outcomes and to characterise the PK of osimertinib and its metabolite.

The safety objective was to evaluate the safety and tolerability profile of osimertinib+chemotherapy compared with osimertinib.

Objectives and endpoints for the randomized period FLAURA2 are shown in Table 13.

Table 13: Study FLAURA 2 efficacy objectives and endpoints for the randomized period

Objectives	Endpoints/Variable
Primary	
To assess the efficacy of osimertinib plus chemotherapy treatment compared with osimertinib	• PFS using Investigator assessment, as defined by RECIST 1.1 • Sensitivity analysis of PFS using BICR assessment, as defined by RECIST 1.1
Secondary	
To further assess the efficacy of osimertinib plus chemotherapy compared with osimertinib	• OS • Landmark OS at 1, 2, and 3 years • ORR • DoR • Depth of response • DCR by Investigator
To further assess the efficacy of osimertinib plus chemotherapy compared with osimertinib post progression	• PFS2 • TFST • TSST
To assess disease-related symptoms and health-related QoL in patients treated with osimertinib plus chemotherapy compared with osimertinib	• Change from baseline and time to deterioration in EORTC QLQ-C30 • Change from baseline and time to deterioration in EORTC QLQ-LC13
To assess the PK of osimertinib when given with or without chemotherapy	• Steady-state plasma concentrations and appropriate PK parameters (CLss/F, Cmax,ss Cmin,ss and AUCss) of osimertinib and its metabolite, AZ5104 will be summarised. [a]
To compare the local EGFR mutation test result used for patient selection with the retrospective central cobas® EGFR Mutation Test v2 results from baseline tumour samples	• Concordance of EGFR mutation status between the local EGFR mutation test and the central cobas® EGFR Mutation Test v2 results from tumour samples with evaluable results
To determine efficacy of osimertinib monotherapy vs. osimertinib combined with chemotherapy based on the cobas® EGFR Mutation Test v2 plasma screening test result for Ex19del or L858R EGFR mutations	• PFS by Investigator by plasma EGFR mutation status
To evaluate the safety and tolerability of osimertinib plus chemotherapy compared with osimertinib	• AEs graded by CTCAE v5 • Clinical chemistry, haematology, and urinalysis • Vital signs (pulse and blood pressure); physical examination; weight; LVEF; ECG parameters • WHO PS

Objectives	Endpoints/Variable
Exploratory	
To assess the impact of osimertinib plus chemotherapy compared with osimertinib on patient reported treatment related symptoms	• PRO-CTCAE symptoms
To assess patients' overall impression of severity of cancer symptoms	• PGIS
To compare health resource use associated with osimertinib plus chemotherapy treatment vs. osimertinib	• Health Resource Use Module
To assess the impact of osimertinib plus chemotherapy compared with osimertinib on patient reported health state utility	• EQ-5D-5L
To assess the efficacy of osimertinib plus chemotherapy treatment compared with osimertinib on CNS metastases in patients with CNS metastases at baseline	• Neuro-radiologist assessments according to CNS RECIST 1.1 to calculate: – CNS PFS – CNS ORR – CNS DoR – CNS DCR – Best percentage change in CNS tumour size (target lesion)
To assess the efficacy of osimertinib plus chemotherapy treatment compared with osimertinib on the prevention of CNS metastases	• Neuro-radiologist assessments according to CNS RECIST 1.1 to determine the presence/absence of CNS lesions at progression in patients without CNS metastases at baseline
To compare concordance of the cobas® EGFR Mutation Test v2 vs. alternative EGFR tissue testing methods for diagnostic development [b]	• Concordance of EGFR mutation status between the cobas® EGFR Mutation Test v2 and an alternative devices.
To explore how changes in plasma-based biomarkers (eg, ctDNA, proteomic) correlate with response [b]	• Quantitative ctDNA analysis using specific EGFR biomarkers or broader cancer biomarker panel in longitudinal plasma samples, to assess ctDNA clearance and correlate with response (eg, PFS)
To collect and store DNA for genetic research to explore how genetic variations may affect clinical parameters, risk and prognosis of diseases, and the response to medications [b]	• Correlation of polymorphisms with variation in PK, pharmacodynamics, safety or response observed in patients treated with osimertinib plus chemotherapy compared with osimertinib
To explore efficacy biomarkers and biomarker changes in baseline, longitudinal and progression samples (plasma and tumour tissue) for correlation with response [b]	• Assessment of innate and acquired resistance mechanisms and biomarkers of response including but not limited to mutations in, amplifications and expression of EGFR, TP53, HER2, MET and relevant pathway genes • Proteomic and/or gene expression analysis eg, biomarkers of inflammation
To collect and store tumour, serum, and plasma samples for potential exploratory research into factors that may influence susceptibility to development of NSCLC and/or response to osimertinib and/or chemotherapy (where response is defined broadly to include efficacy, tolerability or safety) and to assess the relationship between tissue and/or bloodborne biomarkers and selected efficacy endpoints. Tissue and plasma samples may be used to support diagnostic development [b]	• Key genetic, gene expression and proteomic markers to include, but not limited to, EGFR mutations, HER, and proto-oncogene encoding cMET expression and/or amplification. • Relationship between PK and blood-borne biomarkers. • Diagnostic development.

[a] If feasible, further PK parameters may be derived using population PK analysis and reported separately from the CSR.

[b] Results from this exploratory analysis, if conducted, will be reported separately.

AE = adverse event; AUCss = area under the concentration-time curve at steady state; BICR = blinded independent central review; CLss/F = apparent total body clearance after oral administration (at steady state); Cmax,ss = maximum plasma concentration at steady state; cMET = hepatocyte growth factor receptor; Cmin,ss = minimum plasma concentration at steady state; CNS = central nervous system; CSR = Clinical Study Report; CTCAE = Common Terminology Criterial for Adverse Events; ctDNA = circulating tumour DNA; DCR = disease control rate; DoR = duration of response; ECG = electrocardiogram; EGFR = epidermal growth factor receptor; EORTC = European Organisation for Research and Treatment of Cancer; HER2 = human epidermal growth factor receptor; LVEF = left ventricular ejection fraction; MET = tyrosine-protein kinase Met; NSCLC = non-small cell lung cancer; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PFS2 = time to second progression; PGIS = patient global impression of severity; PK = pharmacokinetic(s); PRO = patient-reported outcomes; PS = Performance Status; QoL = quality of life; RECIST = Response Evaluation Criteria in Solid Tumours; TFST = time to first subsequent therapy; TSST = time to second subsequent therapy; WHO = World Health Organization.

Outcomes/endpoints

The primary efficacy endpoint was Progression Free Survival (PFS) based on Investigator assessment using RECIST v1.1.

The main secondary endpoints were:

- Overall survival (OS) of osimertinib plus chemotherapy compared with osimertinib, Landmark OS at 1, 2, and 3 years.
- Tumour response endpoints (Objective Response Rate (ORR), Duration of Response (DoR), Disease Control Rate (DCR), and depth of response) according to investigator assessment
- Post-progression endpoints (Time to first subsequent therapy (TFST), PFS2, and Time to second subsequent therapy (TSST)).

  Following objective radiological progression, patients had their progression status recorded every 12 weeks per local standard clinical practice to assess time to PFS2 at the DCO of the primary PFS analysis. PFS2 events occurred after discontinuation of study treatment and upon administration of subsequent anticancer therapy after the initial PFS event.
- Patient reported outcomes (PRO), as measured using the EORTC QLQ-C30 and the complementary lung cancer questionnaire EORTC QLQ-LC13, also the PRO-CTCAE symptoms. Patient-reported disease-related symptoms and health-related quality of life were assessed using EORTC QLQ-C30 and EORTC QLQ-LC13. The most important EORTC QLQ-C30 and QLQ-LC13 scales were patient-reported global health status/QoL, physical function and lung cancer symptoms (dyspnoea, cough, chest pain, fatigue, nausea and vomiting, alopecia, and appetite loss). Data from the PRO-CTCAE measurement system were collected as exploratory endpoints.

The main exploratory endpoints were:

- Assessment of the CNS efficacy of osimertinib + chemotherapy compared with osimertinib monotherapy. Endpoints evaluated were CNS PFS, CNS ORR, CNS DoR, CNS DCR, and CNS depth of response
- Tumour and ctDNA were gathered to explore biomarker effects on efficacy of both osimertinib plus chemotherapy and osimertinib, these data will be reported at a later time.

Efficacy assessments of PFS, ORR, DoR, DCR, and depth of response using RECIST 1.1 assessments based on Investigator evaluation. In addition, all images, including unscheduled visit scans, were assessed by BICR according to RECIST 1.1 up to the point of the primary PFS analysis DCO.

Brain scans were to be performed for all patients (preferably with MRI) at screening and progression using the same modality. Patients who had brain metastases or a history of brain metastases at screening were to be followed-up at every imaging visit. If brain metastases were not detected or if the patient did not have a history of brain metastases, the patient was not required to undergo scheduled brain imaging assessments, unless clinically indicated or metastases were suspected by the investigator, or until disease progression by RECIST 1.1 was assessed by the investigator.

All brain scans were assessed by a CNS BICR composed of independent neuro radiologists. The CNS BICR included a review of CT/MRI brain scans using modified RECIST guidelines

Sample size

It was anticipated that approximately 556 patients would be randomised, in a 1:1 ratio (osimertinib + chemotherapy vs. osimertinib monotherapy) in the Randomised period of this study. The primary endpoint of the study is PFS based on Investigator assessment (according to RECIST 1.1), which was initially planned to be analysed when approximately 278 PFS events (approximately 50% maturity) had occurred.

If the true PFS HR for the comparison of osimertinib with chemotherapy vs. osimertinib monotherapy was 0.68, 278 progression events would provide 90% power to demonstrate a statistically significant difference in PFS at a 5% two-sided significance level. This translates to an improvement in median PFS from 19 months to 28 months, assuming exponential distribution and proportional hazards. The minimum critical HR is 0.79, which translates to an approximate median PFS improvement from 19 months to 24 months.

Sample size estimates were calculated using EAST®version 6.4.

Based on clinical study protocol (CSP) version 2.0, an additional criterion for the primary analysis was added, which specified that at least 16 months of follow-up after last subject in (LSI) must have also occurred. This was initially expected to occur approximately 33 months after the first patient is randomised (under an assumed 15-month exponential recruitment); however, the actual DCO for the primary PFS analysis was to be determined such that both criteria are met.

Randomisation

In the Randomised period of the study, eligible patients were centrally randomised in a 1:1 ratio to receive either osimertinib + chemotherapy or osimertinib monotherapy, using an interactive voice/web response system (IxRS system).

All patients were stratified prior to randomisation by race (Chinese/Asian vs. Non-Chinese/Asian vs. Non-Asian), WHO PS (0 vs. 1), and method for tissue testing (central vs. local). Approximately 60% Asian patients and 40% non-Asian patients were to be recruited in the randomised period of the study.

Patients were eligible for randomization in the study based upon either: a pre-existing positive local tumour tissue EGFR result obtained in CLIA-certified (for US sites) or accredited laboratories (for sites outside of the US); or prospective tumour tissue analysis of EGFR mutation status performed using the cobas® EGFR Mutation Test v2 in a central laboratory.

Blinding (masking)

FLAURA2 is an open-label study.

Statistical methods

Analysis sets

Full Analysis Set (FAS): The FAS includes all randomised patients. The FAS is used for all efficacy analyses, and treatment arms are compared on the basis of randomised study treatment, regardless of the treatment actually received.

CNS Full Analysis Set (cFAS): The cFAS includes all patients who undertook a brain scan in the screening/baseline period, had their scan sent for CNS BICR review, and were identified by that review as

having non-measurable and/or measurable brain disease at baseline (ie, at least one non-measurable and/or one measurable brain lesion noted at baseline).

Safety Analysis Set (SAF): The safety analysis set consists of all randomised patients who received at least one dose of study treatment. Safety data are not formally analysed but are summarised descriptively according to treatment actually received (eg, a patient who was randomised to osimertinib plus chemotherapy but who received only osimertinib is summarised under the osimertinib monotherapy arm).

Pharmacokinetic Analysis Set: The PK analysis set consists of all patients in the Safety Analysis Set who have at least one measurable PK concentration without any protocol deviation that affects the PK, supported by the relevant date and time of the sample; and, for each time a PK sample was taken, the dosing data for that day, and for the samples taken after multiple dosing, the dosing data for the day prior to the sample day required.

Progression free survival (PFS)

PFS is defined as the time from randomization or from the first dose of study treatment for the safety run-in until the date of objective disease progression or death (by any cause in the absence of progression), regardless of whether the patient withdraws from study treatment or receives another anti-cancer therapy prior to progression. Patients who have not progressed or died at the time of analysis will be censored at the time of the latest date of assessment from their last evaluable RECIST assessment (with results CR, PR, SD, PD).

However, if the patient progresses or dies immediately after two or more consecutive missed visits, the patient will be censored at the time of the latest evaluable RECIST 1.1 assessment prior to the two missed visits (Note: NE visit is not considered as missed visit).

If the patient has no evaluable visits or does not have evaluable baseline RECIST 1.1 data they will be censored at study day 1 unless they die within two scheduled RECIST assessments of baseline (12 weeks plus 1 week allowing for a late assessment within the visit window from the randomization date or the first dose date for the safety run-in), in which case their date of death will be used as an event.

The PFS time will always be derived based on scan/assessment dates not visit dates.

RECIST assessments/scans contributing towards a particular visit may be performed on different dates. The following rules will be applied:

- For BICR assessments, the date of progression will be determined based on the earliest of the scan dates of the component that triggered the progression for the adjudicated reviewer selecting PD or of the reviewer who read baseline first if there is no adjudication for BICR data.
- For investigational assessments, the date of progression will be determined based on the earliest of the dates of the component that triggered the progression.
- For both BICR and investigational assessments, when censoring a patient for PFS the patient will be censored at the latest of the dates contributing to a particular overall visit assessment.

Table 14: Censoring rules for primary PFS

Situation	Event or Censored	Event Date/ Censored Date
No evaluable post-baseline visits or does not have baseline RECIST 1.1 data, and didn't die within two visits of baseline	C	Randomization Date (Study day 1)
No evaluable post-baseline visits or does not have baseline RECIST 1.1 data, die within two visits of baseline	E	Death Date
Progresses or dies immediately after two or more consecutive missed visits	C	Latest evaluable RECIST 1.1 assessment prior to the two missed visits
Disease progression or death (by any cause in the absence of progression) without two or more consecutive missed visits regardless of whether the patient withdraws from randomized therapy or receives another anti-cancer therapy prior to progression	E	Disease progression date, or death date if no PD
Not progressed or died at the time of analysis	C	Latest date of assessment from their last evaluable RECIST assessment

PFS sensitivity analyses

Randomization bias (Quantitative interactions)

A Cox proportional hazards model will be employed to assess the effect of the pre-specified covariates. A model will be constructed, containing treatment and the stratification factors alone, to ensure that any output from the Cox model is likely to be consistent with the results of the primary analysis using the stratified log-rank test. The results from the initial model and the model containing additional covariates (in the MODEL statement) will be presented.

This analysis evaluates the treatment effect, adjusting for any potential imbalances in baseline prognostic factors that are not balanced by stratification.

The model will include all additional covariates regardless of whether their inclusion significantly improves the fit of the model, providing there is enough data to make them meaningful. Missing covariate data will be imputed using the mean (for continuous variables) or the most common category (for categorical factors).

Ascertainment bias

Ascertainment bias will be assessed by analysing the BICR data. The stratified log rank test will be repeated on PFS using the BICR data based upon RECIST. The HR and CI will be presented.

If there is an important discrepancy between the primary analysis using the Investigator data and this sensitivity analysis using BICR data, then the proportion of patients with Investigator assessment but no central confirmation of progression will be summarized; such patients have the potential to induce bias in the central review due to informative censoring. An approach of imputing an event at the next visit in the central review analysis may help inform the most likely HR value (Fleischer et al 2011), but only if an important discrepancy exists.

Disagreements between Investigator and central reviews of RECIST overall response (CR, PR, SD, PD) will be presented for each visit and each treatment group.

Evaluation-time bias

A sensitivity analysis will be performed to assess possible evaluation-time bias that may be introduced if scans are not performed at the protocol-scheduled time points. The midpoint between the time of progression and the previous evaluable RECIST assessment (using the final date of the assessment) will be analysed using a stratified log-rank test, as described for the primary analysis of PFS. For patients whose death was treated as a PFS event, the date of death will be used to derive the PFS time used in the analysis. To support this analysis, the mean of patient-level average inter-assessment times will be tabulated for each treatment. This approach will use the Investigator RECIST assessments.

Change of censoring rule for PFS evaluation-time bias sensitivity

Situation	Event or Censored	Event Date/ Censored Date
Progresses or dies immediately after two or more consecutive missed visits	C	The midpoint between the time of progression and the previous evaluable RECIST assessment (using the final date of the assessment)

Attrition bias

Attrition bias will be assessed by repeating the PFS analysis except that the actual PFS event times, rather than the censored times, of patients who progressed or died in the absence of progression immediately following 2 or more non-evaluable tumour assessments will be included. In addition, and within the same sensitivity analysis, patients who take subsequent anti-cancer therapy (note that for this analysis radiotherapy is not considered a subsequent anti-cancer therapy) prior to their last evaluable RECIST assessment or progression or death will be censored at their last evaluable assessment prior to taking the subsequent therapy. This analysis will be supported by a Kaplan-Meier plot of the time to censoring using the PFS data from the primary analysis and where the censoring indicator of the PFS analysis is reversed.

Change of censoring rules for PFS attrition bias sensitivity analysis

Situation	Event or Censored	Event Date/ Censored Date
Progresses or dies immediately after two or more consecutive missed visits	E	Disease progression date, or death date if no PD
Take subsequent therapy prior to their last evaluable RECIST assessment or progression or death	C	Last evaluable assessment prior to taking the subsequent therapy

Overall survival (OS)

The analysis of OS will be conducted at 2 time points: at the time of the primary analysis of PFS and at approximately 60% maturity, when approximately 334 death events (across both arms) have occurred. Of note, due to the low maturity of OS at the time of the primary PFS analysis a second interim OS analysis was also performed in advance of the final OS analysis. A small alpha spend of 0.000001 was applied.

The alpha will be split between the two analyses with the overall Type 1 error controlled at 5% (2 sided) for the testing of OS under an O'Brien and Fleming spending rule. Under assumed medians of 40 months and 52 months (HR = 0.77) for osimertinib monotherapy and osimertinib with chemotherapy, respectively, 170 observed events (information fraction of 0.51) are expected at the time of the primary PFS analysis with 2-sided alpha of 0.0034, with the remaining alpha assigned to the final OS analysis (0.0490).

Overall survival data will be analysed using the same methodology and model as for the analysis of PFS, provided there are sufficient events (≥ 20 deaths) available for a meaningful analysis; otherwise, descriptive summaries will be provided. The percentage OS with 95% CI at specific timepoints (e.g. 6, 12, 18, 24 month, etc.) will be summarised for the analysis of OS at the primary PFS analysis, and the percentage OS at additional months (e.g., 36 months, 42 months, etc.) will also be summarised for the analysis of OS at the final survival follow up.

An exploratory analysis will be conducted to report the 5 year overall survival rate. The data cut-off will occur 5 years after the last patient has been randomized or all patients have died, whichever occurs first. No p-value will be presented as this analysis is excluded from the alpha spending rule.

Log-rank vs Cox

Time-to-event data (e.g. PFS, OS) will be analysed using a stratified log-rank test.

The log-rank test will be stratified according to the values recorded in the randomization system, as the analysis is then consistent with the possible permutations of the randomization.

A Cox proportional hazards model containing treatment and the stratification factor(s) alone will be used to estimate the PFS HR to ensure that output from the Cox model is likely to be consistent with the results of the primary analysis using the stratified log-rank test.

Handling of ties

Efron method will be used to handle ties in Cox proportional model.

Hazard ratio and confidence interval estimation

The primary analysis, progression free survival per the Investigator assessment for patients in the FAS, will be analysed using a log rank test stratified by race (Chinese/Asian vs. Non- Chinese/Asian vs. Non-Asian), WHO performance status (0 vs. 1), and method used for tissue testing (central vs. local) for generation of the p-value, using the Efron method for handling ties.

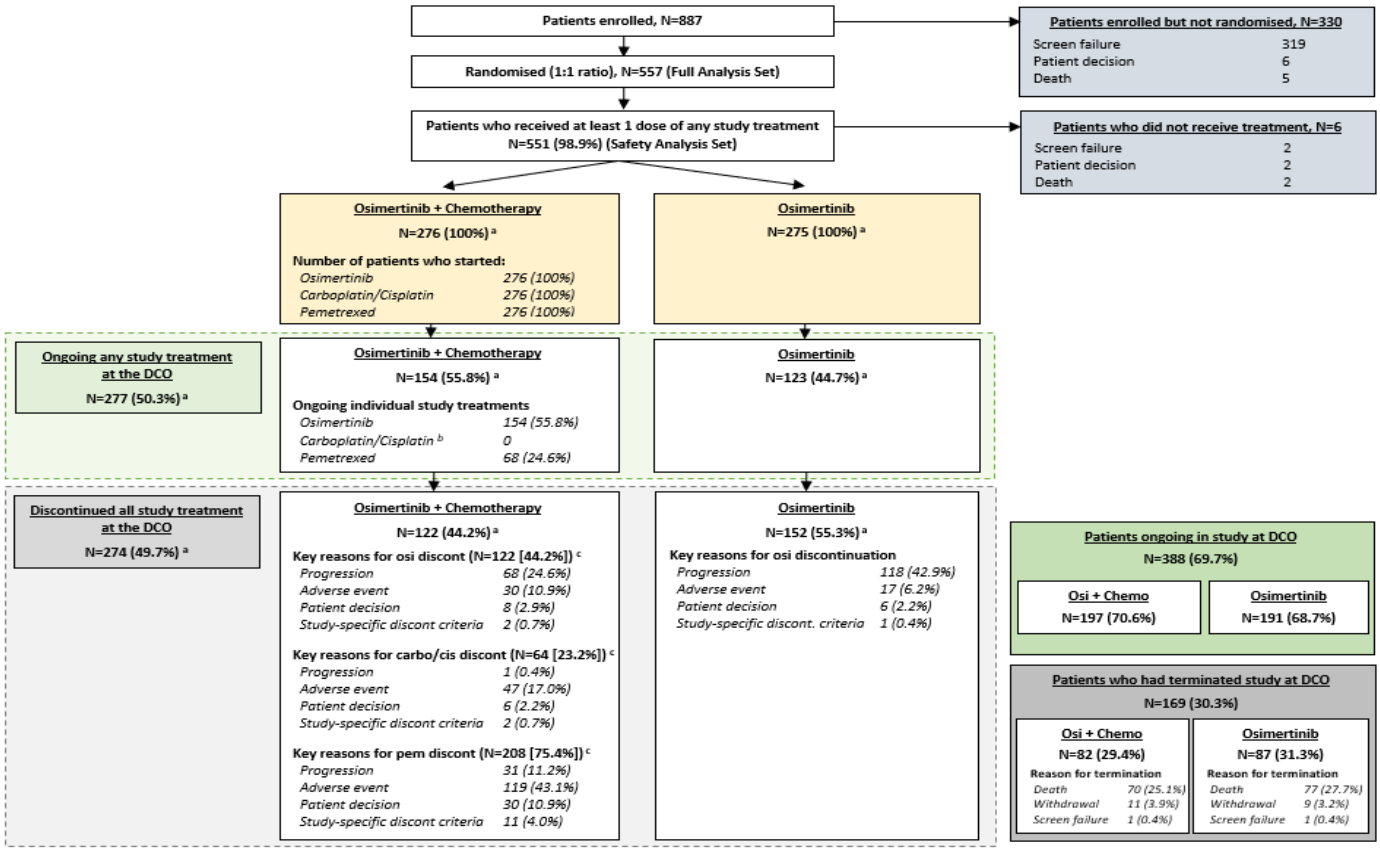
If the resulting strata are too small (i.e., < 20 events) the strata will be collapsed in the following pre-defined order to allow analysis. The China cohort strata will be collapsed first (to Asian vs. Non-Asian), followed by race, and then WHO PS, and finally central/local tissue testing.

Results

Participant flow

The disposition of the participants in this study is summarised in Figure 21.

Figure 21. Patient Disposition (All Patients)



a Percentages are based on safety analysis set. One patient was randomised to the osimertinib + chemotherapy arm, but only received osimertinib and is therefore included in the osimertinib arm for the Safety analysis set.

b Platinum treatment was to be administered for a maximum of 4 cycles.

c This list presents only selected reasons for treatment discontinuation; see Table 14.1.1.1b FLAURA2 Randomised period CSR, Module 5.3.5.1 for details of all reasons.

DCO: 03 April 2023

In total, 887 patients were enrolled in the randomised period study and underwent screening, of which 330 were not randomised. The primary reason for patients not proceeding to randomisation was screen failure (319 patients). In total, 557 patients were randomised to receive study treatment: 279 patients in the osimertinib + chemotherapy arm; and 278 patients in the osimertinib arm.

Of the 557 randomised patients, 551 (98.9%) proceeded to receive at least one dose of any study treatment, comprising 276 patients in the osimertinib + chemotherapy arm, and 275 patients in the osimertinib arm. The reasons for not proceeding to receive study treatment post-randomization are documented in Figure 21; these were all considered an important protocol deviation (IPD).

Recruitment

Following confirmation of eligibility, a total of 557 patients at 136 study centres in 21 countries worldwide were randomised in a 1:1 ratio to either the osimertinib + chemotherapy arm (279 patients) or the osimertinib arm (278 patients). The enrolment of patients occurred over an approximately 18-month period, with the first patient enrolled on 15 May 2020, and the last patient enrolled on 30 November 2021. Of note, the study was conducted during the COVID-19 pandemic.

Conduct of the study

Protocol amendments:

The original protocol was amended once to revise details of the timing of the primary analysis to include the requirement for at least a 16-month follow-up from the time of LSI, in addition to approximately 278 PFS events. Changes in the conduct of the study that were implemented by protocol amendment(s) are provided and briefly described in Table 15.

Table 15: Protocol Amendments Related to Changes in Study Conduct

Amendment Number/Date	Key details of amendment	Main reason(s) for amendment
Amendments made *before* the start of participant recruitment		
None		
Amendments made *after* the start of participant recruitment		
Amendment 1 26 August 2021	Details of the timing of the primary analysis was revised to include the requirement for at least a 16-month follow-up from the time of LSI, in addition to approximately 278 PFS events.	COVID-19 has impacted study enrolment in non-Asia countries, and therefore the primary analysis will not be conducted until the specified follow-up period from the time of LSI has been reached to ensure a sufficient timeframe to observe disease progression events.

Protocol deviations

The overall incidence of SAP-defined non-COVID-19-related important protocol deviations (IPDs) was low (38 patients [6.8%]) and balanced between treatment arms with regard to frequency and type (Table 16).

The table below summarizes important protocol deviations (randomised Period FLAURA2 –FAS).

Table 16: Important Protocol Deviations (Randomised Period – FAS)

Important protocol deviations [a]	Number (%) of patients		
	Osi + Chemo (N = 279)	Osimertinib (N = 278)	Total (N = 557)
Number of patients with at least one IPD	19 (6.8)	19 (6.8)	38 (6.8)
Patient failed inclusion criteria	1 (0.4)	2 (0.7)	3 (0.5)
Patient met exclusion criteria	2 (0.7)	2 (0.7)	4 (0.7)
Incorrect IP administration/study treatment [b]	3 (1.1)	4 (1.4)	7 (1.3)
Patient received prohibited concomitant therapy	2 (0.7)	3 (1.1)	5 (0.9)
Non-compliance with RECIST 1.1 assessment	11 (3.9)	9 (3.2)	20 (3.6)

[a] Important deviations before the start of treatment and during treatment.

[b] Includes 6 patients who were randomised and did not receive treatment, and one patient who was randomised to the osimertinib + chemotherapy arm but only received osimertinib treatment.

The same patient may have had more than one important protocol deviation.
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Study disruptions related to COVID-19

At the DCO date of the current analysis, 38 patients (6.8%) had experienced one or more disruption due to the COVID-19 pandemic: 23 patients (8.2%) in the osimertinib + chemotherapy arm and 15 patients (5.4%) in the osimertinib arm. These were most frequently disruptions that impacted study visits (4.7% vs. 5.0%) or study drug (3.9% vs. 0.7%).

Important protocol deviations due to COVID-19 were reported for 59 patients (10.6%) overall, which was balanced between treatment arms (osimertinib + chemotherapy arm: 33 patients [11.8%]; osimertinib arm: 26 patients [9.4%]). Non-compliance with RECIST 1.1 assessments comprised approximately half of all COVID-19-related IPDs (31 patients [6.5%] overall), with a similar incidence between arms (osimertinib + chemotherapy: 14 patients [5.0%]; osimertinib arm: 17 patients [6.1%]).

Baseline data

Demographic and disease characteristics

Demographic and disease characteristics by treatment group for the ITT set in the FAS are presented in the tables below.

Table 17: Baseline Demographics and Disease Characteristics in FLAURA2 (Randomised Period, FAS)

Characteristic	Osi + Chemo (N = 279)	Osimertinib (N = 278)	Total (N = 557)
Age, years [a]			
Mean (std)	61.0 (10.03)	60.7 (10.57)	60.8 (10.29)
Median	61.0	61.5	61.0
Min, Max	26, 83	30, 85	26, 85
Age group, years, n (%) [a]			
< 50	38 (13.6)	44 (15.8)	82 (14.7)
≥ 50 to < 65	136 (48.7)	122 (43.9)	258 (46.3)
≥ 65 to < 75	82 (29.4)	88 (31.7)	170 (30.5)
≥ 75	23 (8.2)	24 (8.6)	47 (8.4)
Sex, n (%)			
Male	106 (38.0)	109 (39.2)	215 (38.6)
Female	173 (62.0)	169 (60.8)	342 (61.4)
Race, n (%)			
Black or African	2 (0.7)	3 (1.1)	5 (0.9)
Native Hawaiian or other Pacific Islander	0	0	0
American Indian or Alaska Native	11 (3.9)	6 (2.2)	17 (3.1)
Asian	179 (64.2)	176 (63.3)	355 (63.7)
White	74 (26.5)	83 (29.9)	157 (28.2)
Other	13 (4.7)	10 (3.6)	23 (4.1)
Ethnic group, n (%) [b]			
Asian (not specified)	108 (38.7)	107 (38.5)	215 (38.6)
Chinese	71 (25.4)	69 (24.8)	140 (25.1)
Other	99 (35.5)	100 (36.0)	199 (35.7)
Missing	1 (0.4)	2 (0.7)	3 (0.5)

Characteristic	Osi + Chemo (N = 279)	Osimertinib (N = 278)	Total (N = 557)
Smoking status, n (%)			
Never	188 (67.4)	181 (65.1)	369 (66.2)
Smoker	91 (32.6)	97 (34.9)	188 (33.8)
Current	4 (1.4)	4 (1.4)	8 (1.4)
Former	87 (31.2)	93 (33.5)	180 (32.3)
WHO performance status, n (%)			
0	104 (37.3)	102 (36.7)	206 (37.0)
1	174 (62.4)	176 (63.3)	350 (62.8)
2 [c]	1 (0.4)	0	1 (0.2)
EGFR mutation tissue testing method for randomisation, n (%)			
Central test	123 (44.1)	117 (42.1)	240 (43.1)
Local test	156 (55.9)	161 (57.9)	317 (56.9)
EGFR mutation type at randomisation, n (%)			
Exon 19 deletion [d]	172 (61.6)	169 (60.8)	341 (61.2)
Exon 21 L858R	106 (38.0)	107 (38.5)	213 (38.2)
EGFRm unknown	1 (0.4)	2 (0.7)	3 (0.5)
Time from initial diagnosis to the first dose, months			
n	277	274	551
Mean (std)	3.6 (12.03)	3.6 (16.20)	3.6 (14.25)
Median	1.1	1.1	1.1
Min, Max	0, 125	0, 213	0, 213
Overall extent of disease at study entry, n (%)			
Locally advanced [e]	14 (5.0)	7 (2.5)	21 (3.8)
Metastatic [f]	265 (95.0)	271 (97.5)	536 (96.2)
CNS metastases [g]	116 (41.6)	110 (39.6)	226 (40.6)
Liver metastases [h]	43 (15.4)	66 (23.7)	109 (19.6)
Extra-thoracic metastases [h]	147 (52.7)	149 (53.6)	296 (53.1)
Baseline target lesion tumour size, mm [i]			
n	278	277	555
Mean (std)	65.1 (42.36)	64.1 (38.87)	64.6 (40.62)
Median	57.0	57.0	57.0
Min, Max	10, 284	11, 221	10, 284

Characteristic	Osi + Chemo (N = 279)	Osimertinib (N = 278)	Total (N = 557)

[a] Age at study entry.
[b] Based on data recorded in the eCRF.
[c] Patient had a WHO PS of 1 at the time of randomisation but prior to study drug administration on Cycle 1 Day 1 had a record of WHO PS 2 attributed to mobility issues. This was transient with the WHO PS returning to 1 at Cycle 2 Day 1.
[d] Patients with both Exon 19 deletion and L858R are included in the Exon 19 deletion subgroup.
[e] Patients had only locally advanced sites of disease.
[f] Patients had any metastatic site of disease.
[g] CNS lesions as identified by the Investigator and recorded in the eCRF based on CNS lesion site at baseline, medical history, and/or prior surgery, and/or prior radiotherapy to CNS metastases.
[h] This is a programmatically derived composite endpoint with a list of contributing eCRF data sources.
[i] Sum of longest diameters of target lesions at baseline.
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Table 18: Other Disease Characteristics at Baseline (Randomised Period FLAURA2– FAS)

Characteristic	Osi + Chemo (N = 279)	Osimertinib (N = 278)	Total (N = 557)
AJCC stage (8th edition) at initial diagnosis, n (%)			
Stage IIIB	9 (3.2)	4 (1.4)	13 (2.3)
Stage IIIC	4 (1.4)	3 (1.1)	7 (1.3)
Stage IVA	98 (35.1)	104 (37.4)	202 (36.3)
Stage IVB	168 (60.2)	167 (60.1)	335 (60.1)
Histology type, n (%)			
Adenocarcinoma [c]	275 (98.6)	275 (98.9)	550 (98.7)
Adenosquamous carcinoma	2 (0.7)	0	2 (0.4)
Other	2 (0.7)	3 (1.1)	5 (0.9)
Baseline target lesion tumour size, mm [g]			
n	278	277	555
Mean (std)	65.1 (42.36)	64.1 (38.87)	64.6 (40.62)
Median	57.0	57.0	57.0
Min, Max	10, 284	11, 221	10, 284

[c] Represents a combination of the following adenocarcinoma categories: NOS, acinar, papillary, bronchiolo-alveolar, and solid with mucous formation.
[f] This is a programmatically derived composite endpoint with a list of contributing data sources.
[g] Sum of longest diameters of target lesions at baseline.
AJCC = American Joint Committee on Cancer.
DCO: 03 April 2023
Source: Table 14.1.8.1b

Bone metastasis

A number of 274 patients (49.2%) had bone metastases at baseline.

Determination of EGFR mutation status

Overall, 240 patients (43.1%) were randomised based on prospective tumour tissue analysis performed using the cobas® EGFR Mutation Test v2 in a central laboratory, and 317 patients (56.9%) were randomised based on a pre-existing positive local tumour tissue EGFR result obtained in CLIA-certified (for US sites) or accredited laboratories (for sites outside of the US).

Based on both prospective central and pre-existing local EGFRm test results, in total, 60.5% of patients had EGFR Exon 19 deletion (60.6% in the osimertinib + chemotherapy arm and 60.4% in the osimertinib monotherapy arm), 38.2% had EGFR Exon 21 L858R mutation (38.0% and 38.5%, respectively), and

0.7% of patients had tumours which harboured both Ex19del and L858R mutations (1.1% and 0.4%, respectively). Other EGFR mutations were T790M mutations (10 patients), exon 20 insertion (5 patients), S768I mutation (3 patients), and L861Q and G719X mutations (1 patient each).

Of the 317 patients randomised on the basis of a pre-existing local tissue test result, 310 patients had a valid central cobas® test result with either tumour tissue sample or plasma sample when tissue was unavailable or inadequate for central testing. Of these, 295/317 patients (93.1%) were centrally confirmed to have EGFRm tumours, and 15/317 patients (4.7%) had EGFRm not detected based on the central cobas® test result. The remaining 7/317 patients (2.2%) had EGFRm status unknown based on the central cobas® test result (due to inadequate sample or central test failure).

Table 19: EGFRm Testing Method and Mutation Type at Randomisation (Randomised Period FLAURA2 - FAS)

EGFR Testing Method Mutation Type	Number (%) of patients		
	Osi + Chemo (N = 279)	**Osimertinib (N = 278)**	**Total (N = 557)**
Central test	**123 (44.1)**	**117 (42.1)**	**240 (43.1)**
Exon 19 deletion	75 (26.9)	67 (24.1)	142 (25.5)
Exon 21 L858R	47 (16.8)	49 (17.6)	96 (17.2)
EGFRm unknown / not detected [a]	1 (0.4)	1 (0.4)	2 (0.4)
Local test	**156 (55.9)**	**161 (57.9)**	**317 (56.9)**
Exon 19 deletion	94 (33.7)	101 (36.3)	195 (35.0)
Exon 21 L858R	59 (21.1)	58 (20.9)	117 (21.0)
Both Exon 19 deletion and Exon 21 L858R	3 (1.1)	1 (0.4)	4 (0.7)
EGFRm not detected [b]	0	1 (0.4)	1 (0.2)

[a] One patient was randomised based on an invalid central tissue result (and was therefore categorised as EGFRm status of unknown); a retrospective baseline ctDNA result was Ex19del positive. One patient was randomised based on a negative central tissue result (and was therefore categorised as EGFRm status of not detected); a retrospective baseline ctDNA result was L858R positive.

[b] One patient was randomised based on local result of L858R positive, which was subsequently updated to L861Q positive and confirmed by central test result.

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Medical and surgical history

General medical history was reported for 497 patients overall (89.2%), with a similar proportion of patients in each treatment arm having one or more medical history entry at baseline (247 patients [88.5%] in the osimertinib + chemotherapy arm and 250 patients [89.9%] in the osimertinib arm).

The most frequently reported medical history events (ie, with an incidence of ≥ 10% of patients in either treatment arm) were for osimertinib + chemotherapy arm vs. osimertinib arm, respectively: hypertension (33.7% vs. 36.7%), cough (19.0% vs. 24.5%), back pain (11.1% vs. 12.6%), dyspnoea (9.0% vs. 10.1%).

Overall, 227 (40.8%) patients had undergone surgery prior to study entry, which was similar between treatment arms (38.8% in the osimertinib + chemotherapy arm and 43.2% of patients in the osimertinib arm). The thoracic surgery reported in ≥ 10 patients in either treatment arm was lung lobectomy (3.9% and 4.0%, respectively).

Prior anti-cancer therapies

Per protocol, patients could have been previously treated for NSCLC in the adjuvant and neoadjuvant setting. Overall, 76 patients (13.6%) reported any prior anticancer therapy use, out of which 68 patients (12.2%) reported receiving prior radiotherapy, and 10 patients (1.8%) received prior cytotoxic chemotherapy. Of these, previous cytotoxic chemotherapy had been received by 10 patients overall

(1.8%) (osimertinib + chemotherapy arm: 6 patients [2.2%]; osimertinib arm: 4 patients [1.4%]), with platinum compounds as the most frequently received mediations in this therapy class (osimertinib + chemotherapy arm: 5 patients [1.8%]; osimertinib arm: 4 patients [1.4%]). No patient had received prior treatment with an EGFR TKI therapy.

Palliative concomitant radiotherapy

Palliative radiotherapy during the study treatment was permitted in patients with no evidence of overall clinical or radiographic progression per RECIST 1.1, and was reported to 39 (7.0%) patients (18 [6.5%] patients in the osimertinib + chemotherapy arm and 21 [7.6%] in the osimertinib arm).

Use of concomitant medication

The majority of patients (549 patients [98.9%]) received at least one permitted concomitant medication during the study (276 patients [98.9%] in the osimertinib + chemotherapy arm and 273 patients [98.2%] in the osimertinib arm).

Pemetrexed maintenance therapy in the experimental arm:

Table 20 summarises the number of cycles of pemetrexed maintenance treatment patients received up to the time of the DCO. Of the 209 patients who received pemetrexed maintenance, 116 patients received pemetrexed maintenance for ≥13 cycles (ie, approximately ≥9 months), 103 patients received ≥17 cycles (ie, approximately ≥1 year), and 68 patients received pemetrexed maintenance for ≥26 cycles (ie, approximately ≥ 18 months).

Table 20: Pemetrexed Treatment Cycles Received During the Maintenance Period (Randomised Period – Safety Analysis Set

No. of cycles	Osi + Chemo (N = 276)
n	209
Mean (SD)	17.1 (12.44)
Median (min, max)	16.00 (1, 43)
Q1, Q3	5.0, 28.0
Number of pemetrexed treatment cycles, n (%)	**Pemetrexed (m = 276)**
≥1	209 (75.7)
≥2	196 (71.0)
≥3	182 (65.9)
≥4	174 (63.0)
≥5	160 (58.0)
≥10	132 (47.8)
≥13	116 (42.0)
≥17	103 (37.3)
≥20	91 (33.0)
≥26	68 (24.6)
≥30	42 (15.2)
≥40	9 (3.3)

The maintenance period follows the discontinuation of platinum chemotherapy.
m = number of patients who received pemetrexed in the study; n = number of patients who are ongoing pemetrexed treatment after the discontinuation of platinum chemotherapy.
Percentages are based on m, the number of patients who received pemetrexed in the study.
A cycle is counted if one dose of study drug is started, even if the full dose is not delivered.
A cycle equals to a period of 21 days.
Reference: ext_imt0002

Post-study treatment anticancer therapies

Aumolertinib	0	3 (1.1) [2.0]
VEGF Inhibitor – Monoclonal antibody	14 (5.0) [11.4]	38 (13.7) [25.2]
PD-1/PD-L1 inhibitor - Immunotherapy	10 (3.6) [8.1]	22 (7.9) [14.6]
Other	11 (3.9) [8.9]	19 (6.8) [12.6]

[a] The number of patients is shown with percentages (%) calculated as the proportion of patients in the FAS and secondly [%] as the proportion of patients who discontinued randomised study treatment.
A patient may be counted in multiple rows if they receive more than one post treatment anticancer therapy. Includes anticancer therapies with a start date after the last dose date of study treatment.
Note: Treatment beyond progression is not counted as a subsequent anticancer therapy (see Section 11.1.2.6 for further details).
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Source: Table IMT1247PB1

First and second post-treatment anticancer therapies are summarised in Table 21.

Table 21: First and Second Post-treatment Anticancer Therapy (Randomised Period – FAS)

	Number (%) of patients [a]	
	Osi + Chemo (N = 279)	Osimertinib (N = 278)
Discontinued randomised study treatment	123 (44.1)	151 (54.3)
Received first post-treatment anticancer therapy		
Yes	57 (20.4)	91 (32.7)
No	66 (23.7)	60 (21.6)
Types of first post-treatment anticancer therapy received		
Cytotoxic chemotherapy	37 (13.3) [30.1]	75 (27.0) [49.7]
Platinum compounds	17 (6.1) [13.8]	71 (25.5) [47.0]
Folic acid analogues (pemetrexed)	7 (2.5) [5.7]	43 (15.5) [28.5]
Taxanes	22 (7.9) [17.9]	24 (8.6) [15.9]
EGFR-TKI	12 (4.3) [9.8]	13 (4.7) [8.6]
First or second generation EGFR-TKI	9 (3.2) [7.3]	5 (1.8) [3.3]
Third generation EGFR-TKI	3 (1.1) [2.4]	8 (2.9) [5.3]
Osimertinib	3 (1.1) [2.4]	7 (2.5) [4.6]
Aumolertinib	0	1 (0.4) [0.7]
VEGF Inhibitor – Monoclonal antibody	12 (4.3) [9.8]	32 (11.5) [21.2]
PD-1/PD-L1 inhibitor - Immunotherapy	7 (2.5) [5.7]	17 (6.1) [11.3]
Other	8 (2.9) [6.5]	13 (4.7) [8.6]
Received second post-treatment anticancer therapy		
Yes	21 (7.5)	54 (19.4)
No (*received only one post-treatment anticancer therapy*)	36 (12.9)	37 (13.3)
Types of second post-treatment anticancer therapy received		
Cytotoxic chemotherapy	11 (3.9) [8.9]	26 (9.4) [17.2]
Platinum compounds	2 (0.7) [1.6]	11 (4.0) [7.3]
Folic acid analogues (pemetrexed)	0	11 (4.0) [7.3]
Taxanes	5 (1.8) [4.1]	11 (4.0) [7.3]
EGFR-TKI	5 (1.8) [4.1]	18 (6.5) [11.9]
First or second generation EGFR-TKI	2 (0.7) [1.6]	10 (3.6) [6.6]
Third generation EGFR-TKI (osimertinib)	3 (1.1) [2.4]	8 (2.9) [5.3]
VEGF Inhibitor – Monoclonal antibody	1 (0.4) [0.8]	9 (3.2) [6.0]
PD-1/PD-L1 inhibitor - Immunotherapy	3 (1.1) [2.4]	3 (1.1) [2.0]
Other	3 (1.1) [2.4]	6 (2.2) [4.0]

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

A patient may be counted in multiple rows if they receive more than one post treatment anticancer therapy. Includes anticancer therapies with a start date after the last dose date of study treatment.

Note: Treatment beyond progression is not counted as a subsequent anticancer therapy (see Section 11.1.2.6 for further details).

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Source: Table IMT1247PB2 and Table IMT1247PB3

Numbers analysed

The analysis sets and the number (%) of participants in each analysis set are summarised in Table 22.

Of note, one patient randomised to the osimertinib + chemotherapy arm received Osimertinib only, so is included in the osimertinib arm in the Safety Analysis Set.

Table 22: Analysis Sets (Randomised Period – All patients)

	Number of patients		
	Osi + Chemo	Osimertinib	Total
Patients included in the FAS	279	278	557
Patients included in the Safety Analysis Set	276	275	551
Patients included in the PK Analysis Set	244	263	507
Patients included in the cFAS	118	104	222
Patients included in the cEFR Analysis Set	40	38	78

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Source: Table 14.1.5.1b and Table IMT1260SA

Outcomes and estimation

Primary efficacy endpoint: Progression-Free Survival

The DCO date (03 Apr 2023) for the ongoing FLAURA2 study was PFS-event driven, and occurred approximately 33 months after the first patient was dosed (19 Jun 2020) and approximately 16 months after the last patient was first dosed (23 Dec 2021), with at least 16 months of follow-up after last subject in (LSI).

The study met its primary objective: treatment with osimertinib + chemotherapy was associated with a statistically significant improvement in PFS compared to osimertinib, based on Investigator assessment per RECIST 1.1 (HR = 0.62 [95% CI: 0.49, 0.79]; p-value < 0.0001) (Table 23).

Table 23: Progression-Free Survival by Investigator Assessment (Randomised Period – FAS)

	Osi + Chemo (N = 279)	Osimertinib (N = 278)
Progression status, n (%)		
Progression - total	**120 (43.0)**	**166 (59.7)**
RECIST progression [a]	95 (34.1)	158 (56.8)
Target lesions [b]	51 (18.3)	75 (27.0)
Non-target lesions [b]	31 (11.1)	68 (24.5)
New lesions [b]	46 (16.5)	73 (26.3)
Death [c]	25 (9.0)	8 (2.9)
No progression - total	**159 (57.0)**	**112 (40.3)**
Censored RECIST progression due to missing visits [d]	1 (0.4)	0
Censored death due to missing visits [d]	6 (2.2)	2 (0.7)
Progression free at time of analysis [e]	143 (51.3)	106 (38.1)
Lost to follow-up [f]	0	0
Withdrawn consent [f]	8 (2.9)	3 (1.1)
Discontinued study for other reasons [f]	1 (0.4)	1 (0.4)
Comparison between groups		
Hazard ratio (95% CI)	0.62 (0.49, 0.79)	
2-sided p-value	< 0.0001	
Median PFS		
Median PFS (months) (95% CI) [g]	25.5 (24.7, NC)	16.7 (14.1, 21.3)

PFS rate at 6 months (%) (95% CI) [g]	90.7 (86.6, 93.6)	83.5 (78.6, 87.4)
PFS rate at 12 months (%) (95% CI) [g]	79.7 (74.3, 84.1)	65.5 (59.5, 70.8)
PFS rate at 18 months (%) (95% CI) [g]	70.6 (64.7, 75.7)	48.5 (42.4, 54.3)
PFS rate at 24 months (%) (95% CI) [g]	57.2 (50.4, 63.3)	40.8 (34.7, 46.9)
Median (range) follow-up for PFS in all patients (months) [h]	19.5 (0, 33.3)	16.5 (0, 33.1)
Median (range) follow-up for PFS in censored patients (months) [i]	22.2 (0, 33.1)	23.7 (0, 33.1)

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

[b] Target lesions, non-target lesions and new lesions are not necessarily mutually exclusive categories.

[c] Death in the absence of RECIST progression, within 2 visits of baseline. or last RECIST assessment (Not Evaluable is not considered as missing visit)

[d] RECIST progression or death occurred more than 2 consecutive scheduled visits (plus visit window) after last previous evaluable RECIST assessment or baseline if no valid post-baseline assessment. Patients are censored at last previous evaluable RECIST assessment or randomisation date.

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

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

[g] Calculated using the KM method.

[h] Calculated as the median minimum, maximum time from randomisation to date of progression or date of censoring in all patients.

[i] Calculated as the median minimum, maximum time from randomisation to date of censoring (date last known to have not progressed) in censored (not progressed) patients only.

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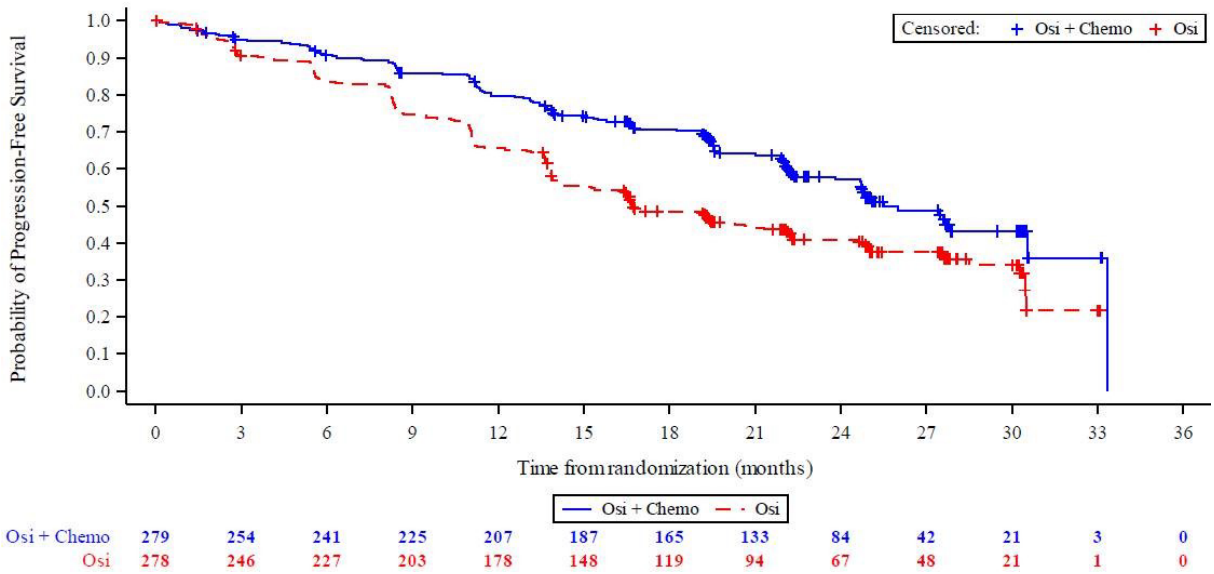
Figure 22: KM Plot of Progression-Free Survival (Months) by Investigator Assessment (Randomised Period – FAS)



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Progression-Free Survival - Sensitivity Analyses

Ascertainment Bias (PFS by BICR)

Ascertainment bias is assessed by analysing PFS by BICR in the FAS (Table 24).

Table 24: Progression-Free Survival by BICR Assessment (Randomised Period – FAS)

	Osi + Chemo (N = 279)	**Osimertinib (N = 278)**
Progression status, n (%)		
Progression - total	**102 (36.6)**	**138 (49.6)**

RECIST progression [a]	75 (26.9)	124 (44.6)
Target lesions [b]	48 (17.2)	79 (28.4)
Non-target lesions [b]	21 (7.5)	34 (12.2)
New lesions [b]	23 (8.2)	47 (16.9)
Death [c]	27 (9.7)	14 (5.0)
No progression - total	**177 (63.4)**	**140 (50.4)**
Censored RECIST progression due to missing visits [d]	1 (0.4)	0
Censored death due to missing visits [d]	11 (3.9)	16 (5.8)
Progression free at time of analysis [e]	154 (55.2)	119 (42.8)
Lost to follow-up [f]	0	0
Withdrawn consent [f]	10 (3.6)	4 (1.4)
Discontinued study for other reasons [f]	1 (0.4)	1 (0.4)
Comparison between groups		
Hazard ratio (95% CI)	0.62 (0.48, 0.80)	
2-sided p-value	0.0002	
Median progression-free survival		
Median PFS (months) (95% CI) [g]	29.4 (25.1, NC)	19.9 (16.6, 25.3)
Progression free at 6 months (%) (95% CI) [g]	89.7 (85.5, 92.8)	83.3 (78.3, 87.3)
Progression free at 12 months (%) (95% CI) [g]	79.8 (74.5, 84.2)	67.3 (61.2, 72.6)
Progression free at 18 months (%) (95% CI) [g]	71.2 (65.2, 76.3)	54.0 (47.6, 60.0)
Progression free at 24 months (%) (95% CI) [g]	61.6 (54.8, 67.7)	46.8 (40.2, 53.2)
Median (range) follow-up for PFS in all patients (months) [h]	19.4 (0, 33.2)	14.6 (0, 33.2)
Median (range) follow-up for PFS in censored patients (months) [i]	22.1 (0, 33.1)	22.0 (0, 33.2)

[a] Only includes progression events that occur within 2 consecutive scheduled visits (plus visit window) of the last evaluable assessment (or randomisation).
[b] Target lesions, non-target lesions, and new lesions are not necessarily mutually exclusive categories.
[c] Death in the absence of progression, within two visits of baseline or last RECIST assessment (not evaluable is not considered as missing visit).
[d] RECIST progression or death occurred more than 2 consecutive scheduled visits (plus visit window) after last previous evaluable RECIST assessment or baseline if no valid post-baseline assessment. Patients are censored at last previous evaluable RECIST assessment or randomisation date.
[e] Includes patients, known to be alive, with no evaluable baseline RECIST assessment (censored at Day 1) or censored at last evaluable RECIST assessment.
[f] Patients censored at last evaluable RECIST assessment or randomisation.
[g] Calculated using the KM method.
[h] Calculated as the median minimum and maximum time from randomisation to date of progression or date of censoring in all patients.
[i] Calculated as the median time minimum and maximum from randomisation to date of censoring (date last known to have not progressed) in censored (not progressed) patients only.

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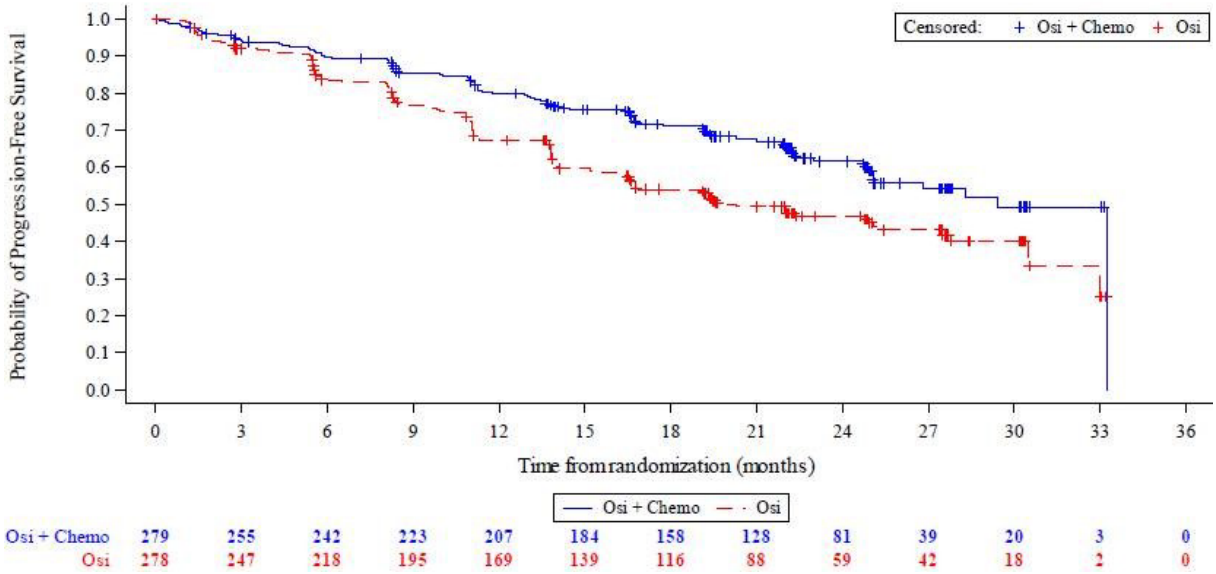
Figure 23: KM Plot of Progression-Free Survival (Months) By BICR Assessment (Randomised Period – FAS)



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Concordance between Investigator and BICR assessments of RECIST progression

Analysis of discrepancy rates between Investigator and BICR assessment of PFS showed 82.1% agreement (100% - [12.5% + 5.4%]) on progressions and non-progressions in the osimertinib + chemotherapy arm, and a 75.6% agreement (100% - [18.3% + 6.1%]) on progressions and non-progressions in the osimertinib arm (Table 25).

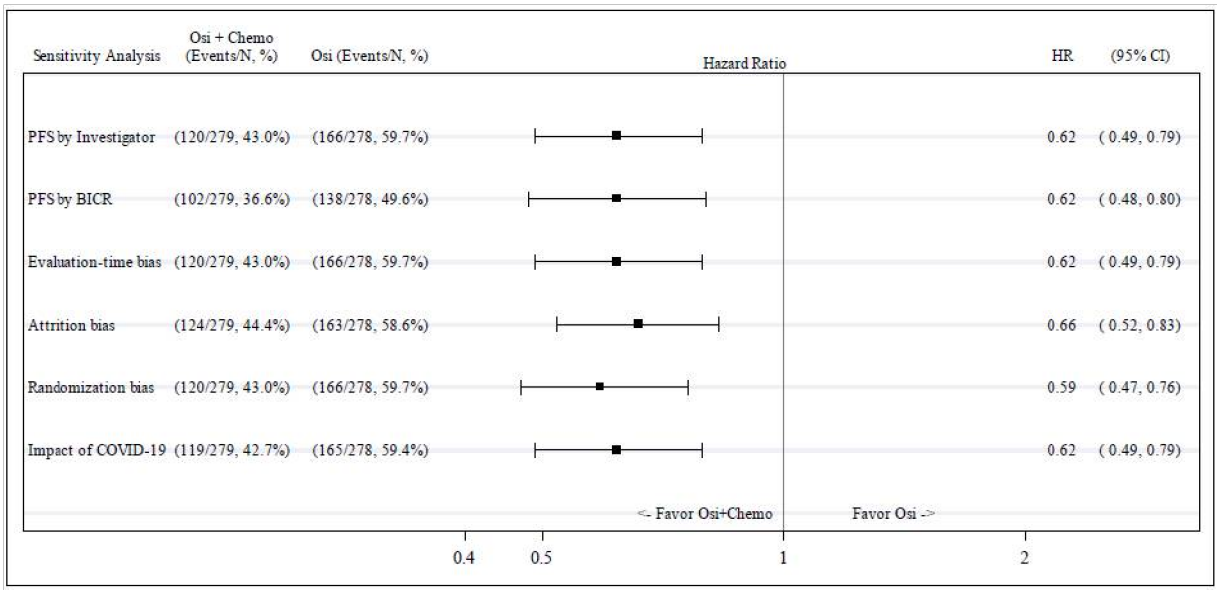
Table 25: Disagreements Between Investigator and BICR Assessment of RECIST Progression (Randomised Period – FAS)

	Osi + Chemo (N = 279)	Osimertinib (N = 278)	Difference (Osi + Chemo) – Osi
Discrepancy rate, %			
Early discrepancy rate [b]	41.3	37.3	3.8
Late discrepancy rate [c]	48.7	48.2	0.5
RECIST progression [a] declared by: (n [%])			
Investigator but not central review	35 (12.5)	51 (18.3)	NA
Central review but not investigator	15 (5.4)	17 (6.1)	NA
Investigator and central review	60 (21.5)	107 (38.5)	NA
Progression data agreement (within 2 weeks)	34 (12.2)	61 (21.9)	NA
Progression date ⩾ 2 weeks earlier by central review than by Investigator	22 (7.9)	38 (13.7)	NA
Progression date ⩾ 2 weeks earlier by Investigator than by central review	4 (1.4)	8 (2.9)	NA

Other Sensitivity Analyses (Evaluation-Time Bias, Attrition Bias, Randomisation Bias, and Impact of COVID-19)

A forest plot presenting the results of the primary PFS analysis and corresponding sensitivity analyses is provided in Figure 24.

Figure 24: Sensitivity Analysis of Progression-Free Survival (Months) (Randomised Period – FAS)



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Secondary endpoints

- **Overall survival (Key Secondary Endpoint)**

Overall survival data were tested per the hierarchical testing procedure at the DCO of the primary PFS analysis (03 April 2023) in the first of 2 pre-planned analyses. The final OS analysis will be conducted when data are approximately 60% mature (approximately 334 death events across both treatment arms). Of note, due to the low maturity of OS at the time of the primary PFS analysis a second interim OS analysis was also performed in advance of the final OS analysis. A small alpha spend of 0.000001 was applied.

At the first interim OS analysis, the number of event was 149 (26.8%). The HR at the time of the interim OS analysis was 0.90 (adjusted 99.84% CI: 0.54, 1.51; p-value = 0.5238) (Table 26), and was not statistically significant per the O'Brien-Fleming spending function (which required a p-value of < 0.00158 to declare statistical significance at the interim analysis). Median OS was not reached in either treatment arm.

Table 26: Overall Survival (Randomised Period – FAS)

	Osi + Chemo (N = 279)	**Osimertinib (N = 278)**
Survival status, n (%)		
Death	71 (25.4)	78 (28.1)
Still in survival follow-up [a]	197 (70.6)	191 (68.7)
Terminated Prior to death [b]	11 (3.9)	9 (3.2)
Completed	0	0
Withdrawal by subject	10 (3.6)	8 (2.9)
Lost to follow-up	0	0
Other	1 (0.4)	1 (0.4)
Comparison between groups		
Hazard ratio (95% CI)	0.90 (0.65, 1.24)	
Adjusted 99.84% CI	0.54, 1.51	
2-sided p-value	0.5238	

	Osi + Chemo	**Osimertinib**

	(N = 279)	(N = 278)
Median overall survival		
Median OS (months) (95% CI) [c]	NC (31.9, NC)	NC (NC, NC)
OS at 6 months (%) (95% CI) [c]	93.5 (89.9, 95.9)	94.9 (91.6, 97.0)
OS at 12 months (%) (95% CI) [c]	88.8 (84.4, 92.0)	92.0 (88.1, 94.7)
OS at 18 months (%)(95% CI) [c]	85.4 (80.7, 89.1)	84.2 (79.3, 88.0)
OS at 24 months (%)(95% CI) [c]	78.9 (73.4, 83.4)	73.0 (66.9, 78.1)
Median (range) follow-up for OS in all patients (months) [d]	23.9 (0.1, 34.1)	23.7 (0.1, 33.9)
Median (range) follow-up for OS in censored patients (months) [e]	25.0 (0.2, 34.1)	25.1 (0.1, 33.9)

[a] Includes patients known to be alive at DCO.

[b] Includes patients with unknown survival status or patients who were lost to follow-up.

[c] Calculated using the KM method.

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

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

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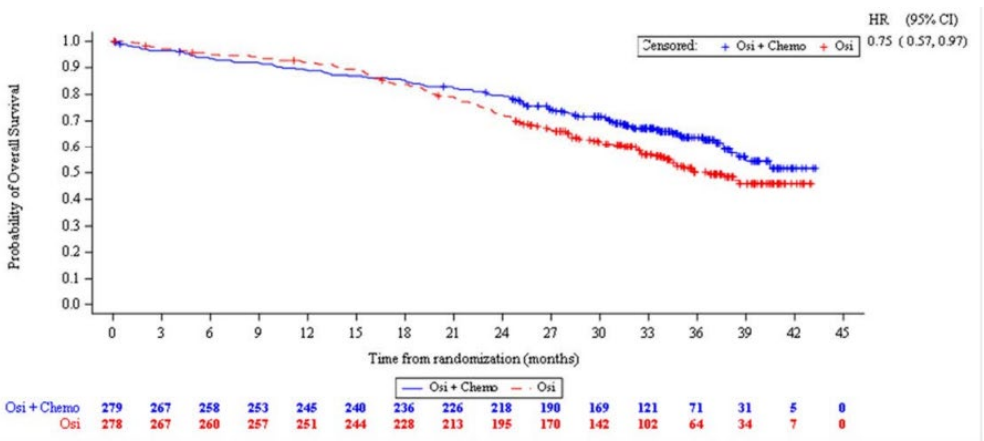
Updated OS data (DCO: 08 January 2024)

At the time of the data cut-off (DCO) for the second interim OS analysis (08 January 2024), 9 months after the primary progression-free survival (PFS) and interim OS analysis (03 April 2023) when all patients had the opportunity for 25 months follow-up, OS maturity increased to 40.6% with a total of 226 death events across both treatment arms (100 patients in the osimertinib + chemotherapy arm and 126 patients in the osimertinib arm). The information fraction at this updated analysis was 67.7%.

The median OS was not calculable (NC; 95% CI: 38.0, NC) in the osimertinib + chemotherapy arm and was 36.7 months (95% CI: 33.2, NC) in the osimertinib arm (HR: 0.75; 95% CI 0.57 to 0.97; p = 0.028, not statistically significant since a p-value < 0.000001 would be required at this time given the agreed 10-6 alpha spend). A 79.7% vs. 72.1% of patients treated with osimertinib + chemotherapy vs. osimertinib were alive at 24 months and 63.7% vs. 50.3%, respectively, were alive at 36 months.

Figure 25: Overall Survival, Kaplan-Meier Plot (FAS) (DCO 08 January 2024)



FAS, full analysis set.

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

Reference: Figure 14.2.2.2b, Appendix B (DCO 08 January 2024).

- **Objective Response Rate (ORR)**

ORR Based on Investigator assessment

The ORR based on investigator and BICT assessments are shown in Table 27.

Table 27: Objective Response by Investigator and BICR Assessment per RECIST 1.1 (Randomised Period – FAS)

	Investigator Assessment		BICR Assessment	
	Osi + Chemo (N = 279)	**Osimertinib (N = 278)**	**Osi + Chemo (N = 279)**	**Osimertinib (N = 278)**
Best objective response, n (%)				
Response [a]	**232 (83.2)**	**210 (75.5)**	**256 (91.8)**	**230 (82.7)**
Complete response	1 (0.4)	2 (0.7)	2 (0.7)	1 (0.4)
Partial response	231 (82.8)	208 (74.8)	254 (91.0)	229 (82.4)
Non-response	**47 (16.8)**	**68 (24.5)**	**23 (8.2)**	**48 (17.3)**
SD ≥ 35 days [b]	34 (12.2)	51 (18.3)	10 (3.6)	29 (10.4)
Progression	7 (2.5)	12 (4.3)	9 (3.2)	15 (5.4)
RECIST progression	1 (0.4)	9 (3.2)	3 (1.1)	12 (4.3)
Death	6 (2.2)	3 (1.1)	6 (2.2)	3 (1.1)
Not evaluable	6 (2.2)	5 (1.8)	4 (1.4)	4 (1.4)
SD ≤ 35 days	0	0	0	0
Death (> 13 weeks) with no evaluable RECIST assessment	0	1 (0.4)	1 (0.4)	0
Other not evaluable	6 (2.2)	4 (1.4)	3 (1.1)	4 (1.4)
Comparison between groups				
Unadjusted response rate (95% CI) [c]	83.15 (78.24, 87.35)	75.54 (70.05, 80.48)	91.76 (87.89, 94.70)	82.73 (77.77, 86.99)
Odds ratio (95% CI) [d]	1.60 (1.05, 2.42)		2.32 (1.37, 3.94)	
2-sided p-value [d, e]	0.0261		0.0013	
Adjusted response rate (95% CI) [f]	84.40 (79.51, 88.30)	77.10 (71.52, 81.85)	92.33 (88.51, 94.96)	83.77 (78.68, 87.84)
Odds ratio (95% CI) [f]	1.61 (1.06, 2.44)		2.33 (1.37, 3.96)	
2-sided p-value [f]	0.0261		0.0017	

[a] Response did not require confirmation.

[j] Stable disease must have been observed at least 6 weeks minus 1 week to allow for an early assessment within the assessment window (study day 35) following randomization.

[b] The CI is calculated using the Clopper-Pearson exact method for binomial proportions.

[k] This analysis was performed using logistic regression with a factor for treatment.

[l] The p-value was calculated based on the likelihood ratio test which compared 2 models (one model with the intercept only and a second model including the treatment factor).

[m] The analysis was performed using a logistic regression stratified by race (Chinese/Asian vs. Non-Chinese/Asian vs. Non-Asian), WHO performance status (0 vs. 1), and method used for tissue testing (central vs. local).

An odds ratio > 1 favours osimertinib + chemotherapy.

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- **Duration of response (DoR) by Investigator and BICR assessment**

Table 28. Duration of Response in Patients in Objective Response by Investigator and BICR Assessment per RECIST 1.1 (Randomised Period – FAS)

	Investigator Assessment		BICR Assessment	
	Osi + Chemo (N = 279)	Osimertinib (N = 278)	Osi + Chemo (N = 279)	Osimertinib (N = 278)
Number (%) of patients with objective response	232 (83.2)	210 (75.5)	256 (91.8)	230 (82.7)
Number (%) of responders who subsequently progressed or died [a]	99 (42.7)	127 (60.5)	87 (34.0)	103 (44.8)
Duration of response				
Median DoR (months) (95% CI) [b]	24.0 (20.9, 27.8)	15.3 (12.7, 19.4)	28.3 (23.7, NC)	21.0 (17.8, NC)
KM estimated percentages remaining in response				
DoR rate at 6 months (95% CI) [c]	91.1 (86.6, 94.2)	83.5 (77.7, 87.9)	93.2 (89.3, 95.7)	90.6 (85.9, 93.7)
DoR rate at 12 months (95% CI) [c]	79.7 (73.7, 84.4)	63.8 (56.8, 70.0)	81.4 (75.9, 85.8)	72.7 (66.2, 78.2)
DoR rate at 18 months (95% CI) [c]	69.1 (62.4, 74.9)	44.2 (37.1, 51.0)	69.6 (63.1, 75.3)	56.1 (48.8, 62.8)
DoR rate at 24 months (95% CI) [c]	48.9 (40.5, 56.7)	34.6 (27.4, 42.0)	56.3 (47.8, 63.9)	44.5 (36.2, 52.4)
Time to onset of response, weeks				
Mean (std)	10.33 (9.940)	11.28 (13.496)	Not done	Not done
Median	6.36	6.29	Not done	Not done
Min, max	4.9, 61.0	4.6, 99.0	Not done	Not done

[a] Percentage is based on the number of patients with response.
[b] Calculated using the KM method.
[c] KM estimated percentages remaining in response.

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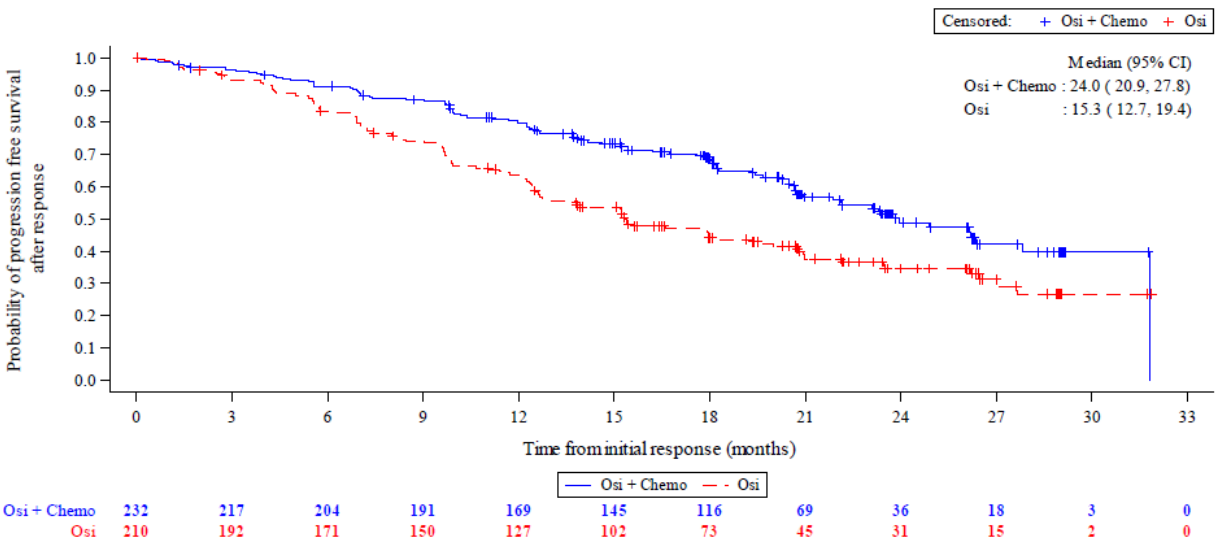
Figure 26: KM Plot of DoR (Months) in Patients with an Objective Response by Investigator Assessment per RECIST 1.1 (Randomised Period – FAS)



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- **Depth of response (Tumour Shrinkage) by Investigator and BICR assessment**

Table 29**:** Depth of Response by Investigator Assessment per RECIST 1.1 (Randomised Period – FAS)

	Osi + Chemo (N = 279)	**Osimertinib (N = 278)**
Number of patients with a baseline and on-treatment tumour measurements	275	276
Best percentage change from baseline for sum of longest diameters		
Mean (std)	-50.12 (22.978)	-46.80 (26.004)
Median	-52.63	-50.00
Min, max	-100, 20.0	-100, 40.4
Number (%) of patients with best % change from baseline		
≥ 30% reduction	233 (83.5)	213 (76.6)
≥ 50% reduction	152 (54.5)	139 (50.0)
≥ 70% reduction	46 (16.5)	42 (15.1)
Comparison between groups in best % change from baseline [a]		
Treatment effect least square mean (95% CI)	-50.77 (-53.75, -47.78)	-47.41 (-50.39, -44.43)
Least square mean differences (95% CI)	-3.36 (-7.44, 0.72)	
2-sided p-value	0.1067	

[a] The analysis was performed using analysis of covariance with baseline tumour size and time from baseline scan to randomisation as covariates and with factors race (Chinese/Asian vs. Non-Chinese/Asian vs. Non-Asian), WHO PS (0 vs. 1), and method used for tissue testing (central vs. local). A difference in least square means < 0 favours osimertinib + chemo.

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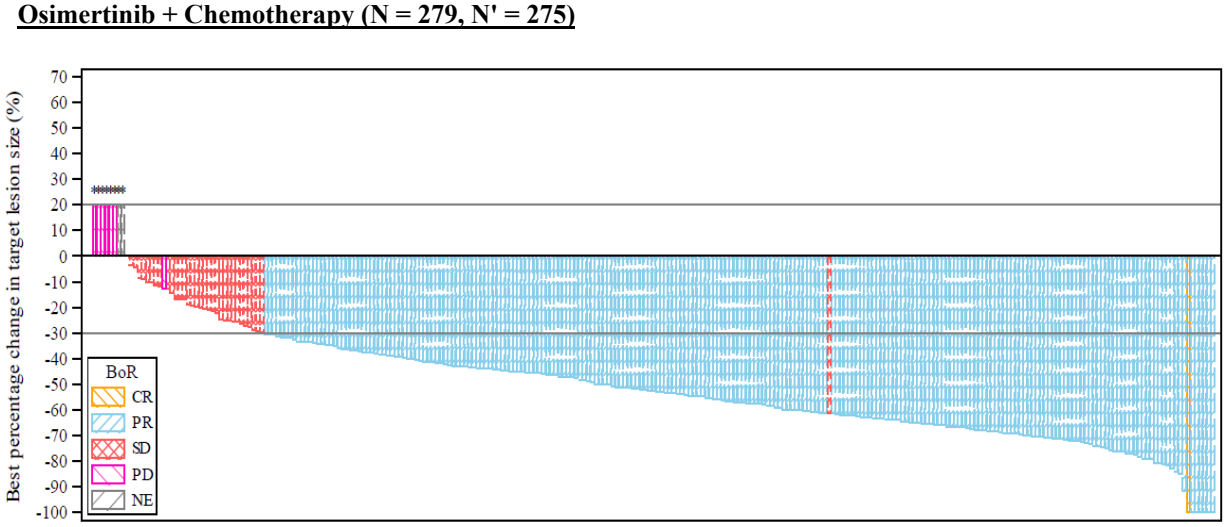
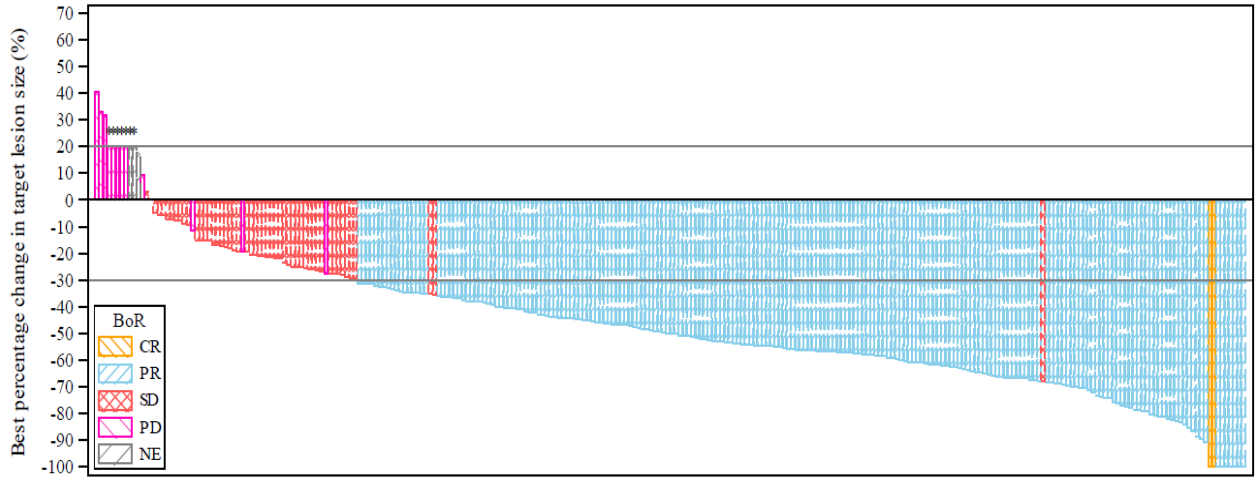
Figure 27: Waterfall Plots of Target Lesion Size, Best Percentage Change from Baseline by Investigator assessment per RECIST 1.1 (Randomised Period – FAS)



Osimertinib (N = 278, N' = 276)



N' = number of patients with non-missing best percentage change in target lesion size, including imputed value.

* represents imputed values: If the best percentage change could not be calculated due to missing data (including if the patient has no target lesions at baseline), a value of + 20% was imputed as the best percentage change from baseline in the following situations (otherwise best percentage change was left as missing): If a patient had no post-baseline assessment and had died; If a patient had new lesions or progression of non-target lesions; If a patient had withdrawn due to PD and had no evaluable target lesion data before or at PD.

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- **Disease Control Rate (DRC) by Investigator assessment**

A DCR above 90% was observed in both treatment arms (95.3% in the osimertinib + chemotherapy arm [95% CI: 92.16, 97.50], and 93.9% in the osimertinib arm [95% CI: 90.39, 96.40]). When accounting for stratification factors using logistic regression, the adjusted DCR was 96.22% (95% CI: 93.14, 97.95) in the osimertinib + chemotherapy arm, and 95.02% (95% CI: 91.52, 97.12) in the osimertinib arm, with an odds ratio of 1.33 (95% CI: 0.63, 2.81; nominal p-value = 0.4483).

Post-progression endpoints

Continuation of randomised treatment beyond investigator-Assessed RECIST Progression

Patients could continue randomised study treatment after Investigator-assessed RECIST progression if they were continuing to derive clinical benefit. This is considered as continuation of first-line therapy.

A summary of treatment beyond progression is provided in Table 30.

Table 30. Summary of Treatment Beyond Progression (Randomised Period – FAS)

	Osi + Chemo (N = 279)	Osimertinib (N = 278)
Osimertinib exposure beyond RECIST progression		
n	81	133
Median (months)	1.84	1.94
Min, max (months)	0.1, 22.9	0.1, 25.6
Cumulative exposure to osimertinib		
≥ 2 months	39 (48.1)	66 (49.6)
≥ 6 months	17 (21.0)	30 (22.6)
≥ 12 months	10 (12.3)	11 (8.3)

	Osi + Chemo (N = 279)	Osimertinib (N = 278)
Pemetrexed exposure beyond RECIST progression		
n	27	NA
Median (months)	3.65	NA
Min, max (months)	0.7, 23.5	NA
Cumulative exposure to pemetrexed		
≥ 2 months	18 (66.7)	NA
≥ 6 months	5 (18.5)	NA
≥ 12 months	3 (11.1)	NA

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- **Time to First Subsequent Therapy (TFST)**

Table 31. Analysis of Time to First Subsequent Therapy or Death (Randomised Period – FAS)

gre	Osi + Chemo (N = 279)	Osimertinib (N = 278)
Number of patients with an event, n (%)	104 (37.3)	129 (46.4)
Patient started first subsequent therapy [a]	59	95
Patient died	45	34
Median TFST (months) (95% CI) [b]	30.7 (27.3, NC)	25.4 (22.8, NC)
Comparison between groups		
Hazard ratio (95% CI)	0.73 (0.56, 0.94)	
2-sided p-value	0.0159	

[a] Of note, an additional 2 patients in the osimertinib + chemotherapy arm and 4 patients in the osimertinib arm are included in this analysis as compared to number of patients receiving a subsequent anticancer therapy; this discrepancy is due to either errors in data entry (conflicting/incomplete information on the post-lines of therapy [3 patients]) or because patients had no post-study treatment systemic anticancer therapy (received radiotherapy or osimertinib treatment through progression [3 patients]).

[b] Calculated using the KM method.

A HR < 1 favours osimertinib + chemotherapy.

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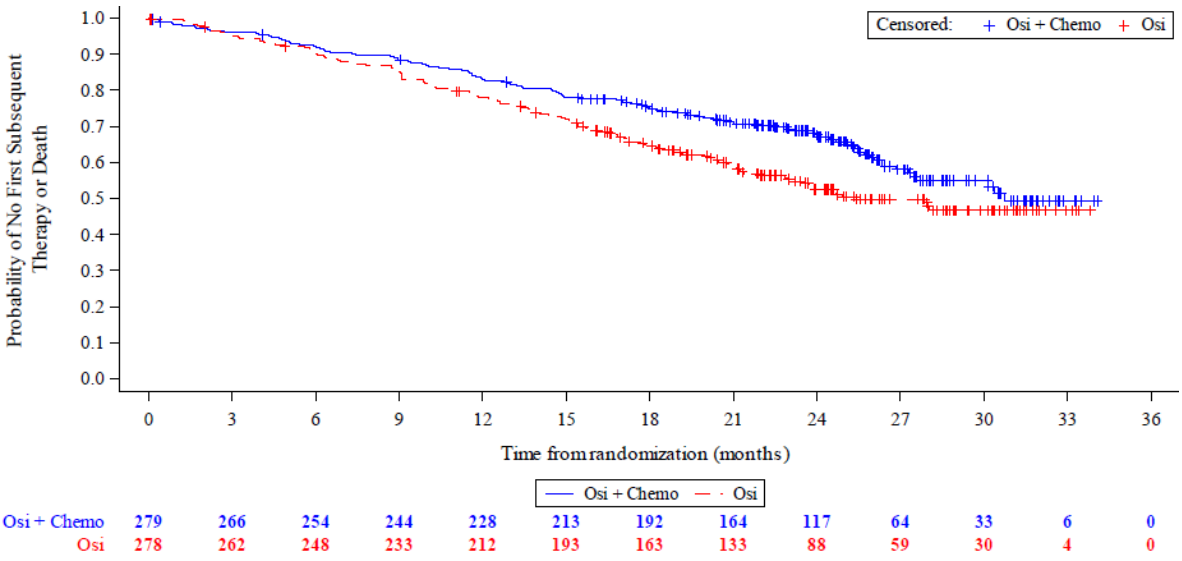
Figure 28: KM Plot of Time to First Subsequent Therapy or Death (Randomised Period – FAS)



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- ***Second Progression-Free Survival (PFS2)***

Table 32. Analysis of PFS2 by Investigator Assessment (Randomised Period – FAS)

	Osi + Chemo (N = 279)	Osimertinib (N = 278)
Progression status, n (%)		
Second progression	**81 (29.0)**	**110 (39.6)**
Objective radiological progression	23 (8.2)	57 (20.5)
Symptomatic progression	3 (1.1)	9 (3.2)
Other progression	0	1 (0.4)
Death [a]	55 (19.7)	43 (15.5)
No second progression	198 (71.0)	168 (60.4)
Progression free at time of analysis	143 (51.3)	106 (38.1)
Subject with first progression	48 (17.2)	58 (20.9)
Lost to follow-up [b]	0	0
Withdrawn consent [b]	6 (2.2)	3 (1.1)
Discontinued study for other reason [b]	1 (0.4)	1 (0.4)
Comparison between groups		
Hazard ratio (95% CI)	0.70 (0.52, 0.93)	
2-sided p-value	0.0132	
Median PFS2		
KM estimated median (95% CI)	30.6 (29.0, NC)	27.8 (26.0, NC)
Days between first and second progression [c]		
n [d]	48	100
Mean (std)	202.9 (142.54)	221.6 (138.00)
Median	170.0	192.5
Min, max	5, 585	8, 672

[a] This category includes deaths in the absence of first or second progression.

[b] Patients censored at last evaluable progression assessment.

[c] The number of days is calculated from the date of first progression to date of second progression (or death).

[d] 'n' is the number of patients with both a first and second progression date.

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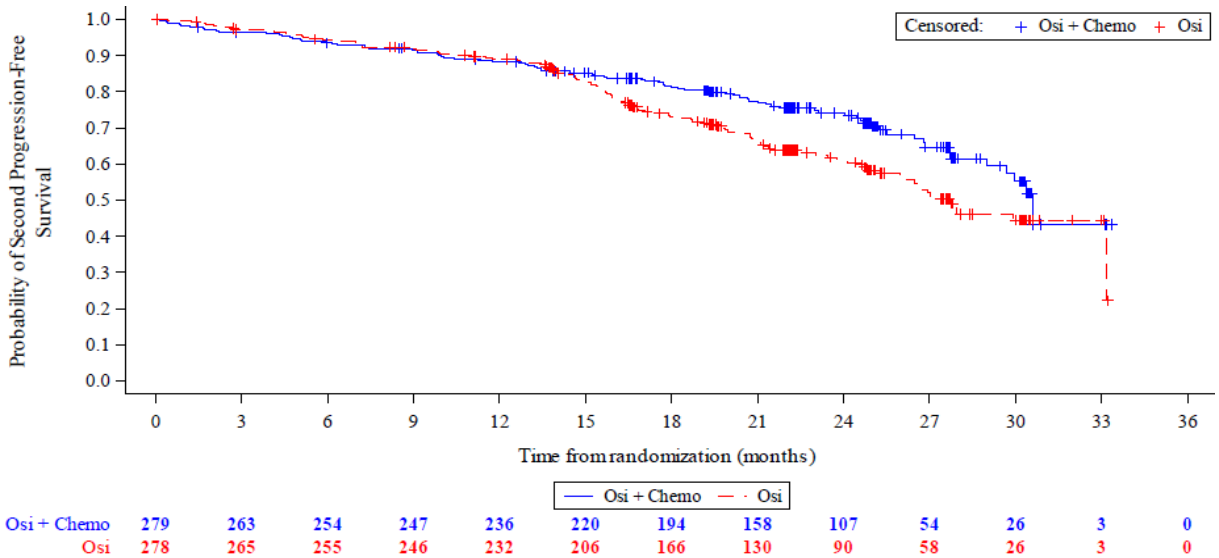
Figure 29: KM Plot of PFS2 (Randomised Period – FAS)



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- **Time to Second Subsequent Therapy (TSST)**

Table 33: Analysis of Time to Second Subsequent Therapy or Death (Randomised Period – FAS)

	Osi + Chemo (N = 279)	Osimertinib (N = 278)
Number of patients with an event, n (%)	74 (26.5)	103 (37.1)
Patient started second subsequent therapy	13	55
Patient died	61	48
Median TFST (months) (95% CI) [a]	NC (NC, NC)	33.2 (28.2, NC)
Comparison between groups		
Hazard ratio (95% CI)	0.69 (0.51, 0.93)	
2-sided p-value	0.0157	

[n] Calculated using the KM method.

A HR < 1 favours osimertinib + chemotherapy.

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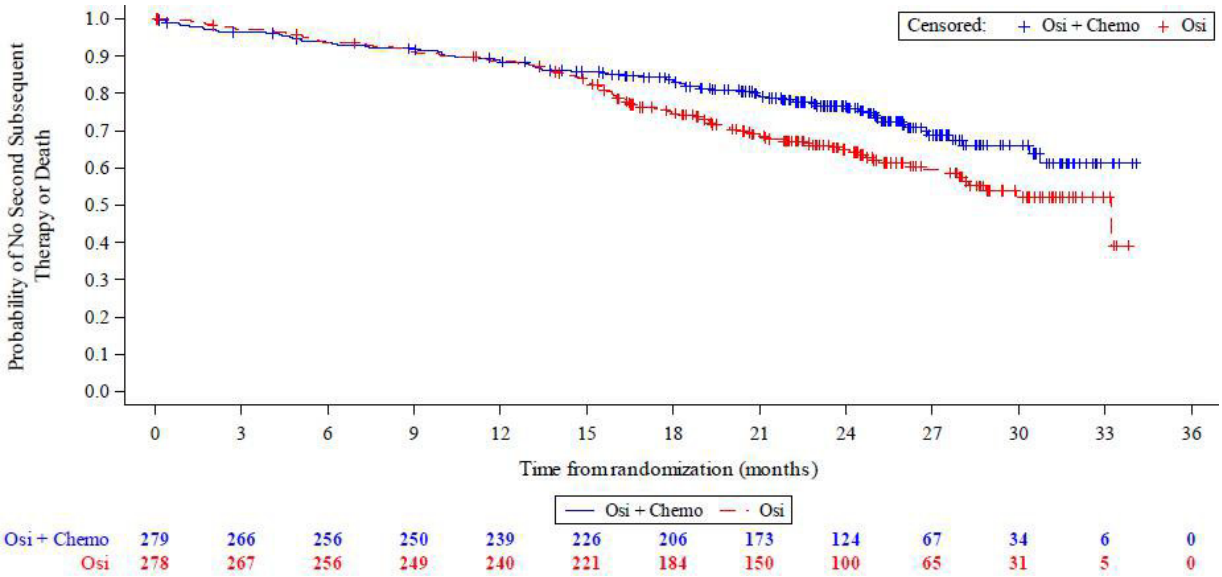
Figure 30: KM Plot of Time to Second Subsequent Therapy or Death (Randomised Period – FAS)



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Other secondary endpoints

Patient-Reported Outcomes (PROs)/health-related quality of life (HRQoL)

EORTC QLQ-C30 and EORTC QLQ-LC13

Patient-reported disease-related symptoms and health-related quality of life were assessed based on the following prespecified items: global health status/QoL (2 items scale in EORTC QLQ-C30), physical function (5 items scale in EORTC QLQ-C30), fatigue (3 items scale in EORTC QLQ-C30), appetite loss (1 item scale in EORTC QLQ-C30), dyspnoea (3 items scale in EORTC QLQ-LC13), cough (1 item in EORTC QLQ-LC13) and chest pain (1 item in EORTC QLQ-LC13). All PRO data were collected from randomisation until PFS2.

The overall compliance rates for the completion of the QLQ-C30 and QLQ-LC13 questionnaires were > 91% in both treatment arms at baseline) and remained ≥ 80% until Week 82 (Month 19).

Baseline QLQ-C30 and QLQ-LC13 scores were ≥ 63 for overall functioning and global health status/QoL based on the QLQ-C30 questionnaire, with scores ≤ 34 for symptomatology, based on data from both questionnaires.

A summary of the average change from baseline in the prespecified primary PRO scales from the QLQ-C30 and QLQ-LC13 questionnaires by mixed models repeated measures (MMRM) modelling is presented in Table 34.

Table 34: Summary of Change From Baseline in Primary PRO Domains and Symptoms, MMRM (Randomised Period – FAS)

Primary PRO scales	Treatment arm	N	Average LS mean [a] (95% CI)	Average difference in change from baseline in LS means [a] (Osi Chemo – Osi) (95% CI)
Scale (EORTC QLQ-C30 questionnaire)				
Global health status / QoL	Osi + Chemo	253	3.32 (1.67, 4.98)	-4.06 (-6.42, -1.69)
	Osimertinib	253	7.38 (5.70, 9.07)	
Physical function	Osi + Chemo	253	2.37 (0.70, 4.04)	-4.37 (-6.75, -1.99)
	Osimertinib	253	6.74 (5.04, 8.43)	
Fatigue	Osi + Chemo	253	-0.03 (-1.91, 1.84)	6.28 (3.60, 8.96)
	Osimertinib	253	-6.31 (-8.22, -4.40)	
Appetite loss	Osi + Chemo	253	2.87 (0.82, 4.92)	7.45 (4.52, 10.38)
	Osimertinib	253	-4.58 (-6.67, -2.48)	
Symptoms (EORTC QLQ-LC13 questionnaire)				
Dyspnoea	Osi + Chemo	253	-3.09 (-4.70, -1.49)	2.57 (0.28, 4.86)
	Osimertinib	251	-5.67 (-7.30, -4.04)	
Coughing	Osi + Chemo	253	-13.23 (-14.85, -11.62)	-2.04 (-4.35, 0.26)
	Osimertinib	251	-11.19 (-12.83, -9.55)	
Pain in chest	Osi + Chemo	253	-6.33 (-7.66, -4.99)	0.29 (-1.62, 2.20)
	Osimertinib	251	-6.61 (-7.98, -5.25)	

[a] Average includes all patients contributing to the MMRM model over all visits (ie, over 19 months or until progression disease). The score values are calculated by averaging across patients overall mean across all visits. The analysis was performed using a MMRM analysis on the change from baseline in PRO symptom score or functional at each visit up to 19 months (579 days), including subject (as a random effect), treatment, visit (as fixed effect and repeated measure) and treatment by visit interaction as explanatory variables, with the baseline PRO score as a covariate along with the baseline PRO score by assessment interaction. Approach to select the covariance structure is specified in the SAP.

LS = least squares.

DCO: 03 April 2023

Source: Table 14.2.10.3.1b and Table 14.2.10.3.2b

A summary of the time to confirmed deterioration in the prespecified primary PRO domains and symptoms of the QLQ-C30 and QLQ-LC13 questionnaires is presented in Table 35.

Table 35: Analysis of Time to Confirmed Deterioration in Primary PRO Domains and Symptoms (Randomised Period – FAS)

Primary PRO scales	Treatment arm	N	Number (%) of patients with events [a]	Median TTD (months) (95% CI) [b]	Hazard ratio (95% CI)
Scale (EORTC QLQ-C30 questionnaire)					
Global health status / QoL	Osi + Chemo	279	115 (41.2)	25.8 (20.1, NC)	1.30 (0.98, 1.71)
	Osimertinib	278	90 (32.4)	NC (24.6, NC)	
Physical function	Osi + Chemo	279	118 (42.3)	25.5 (17.2, NC)	1.51 (1.14, 1.99)
	Osimertinib	278	86 (30.9)	NC (29.6, NC)	
Fatigue	Osi + Chemo	279	159 (57.0)	5.9 (2.6, 11.8)	1.51 (1.19, 1.92)
	Osimertinib	278	122 (43.9)	20.0 (13.8, 28.4)	
Appetite loss	Osi + Chemo	279	139 (49.8)	10.1 (5.1, 23.0)	1.58 (1.22, 2.03)
	Osimertinib	278	103 (37.1)	28.4 (21.0, NC)	
Symptoms (EORTC QLQ-LC13 questionnaire)					
Dyspnoea	Osi + Chemo	279	150 (53.8)	9.0 (5.6, 13.1)	1.25 (0.99, 1.59)
	Osimertinib	278	128 (46.0)	19.4 (13.7, 24.6)	
Coughing	Osi + Chemo	279	80 (28.7)	NC (30.4, NC)	0.77 (0.57, 1.04)
	Osimertinib	278	98 (35.3)	24.7 (21.3, NC)	
Pain in chest	Osi + Chemo	279	96 (34.4)	NC (25.7, NC)	1.09 (0.81, 1.46)
	Osimertinib	278	87 (31.3)	NC (25.2, NC)	

[a] Percentages are based on number of patients included in the analysis n. Events comprise confirmed deterioration, or death in the absence of confirmed deterioration.

[b] Calculated using the KM method

Patients with baseline scores of < 10 for global health status/QoL and functioning, baseline scales of > 90 for symptom scales were censored at day 1. The analysis was performed using a log rank test stratified by race (Chinese/Asian vs. Non-Chinese/Asian vs. Non-Asian), WHO performance status (0 vs. 1), and method used for tissue testing (central vs. local).

A hazard ratio < 1 favours osimertinib + chemotherapy.

DCO: 03 April 2023

Source: Table 14.2.10.4.1b, Table 14.2.10.4.2b, Table 14.2.10.4.5b, and Table 14.2.10.4.6b

PRO-CTCAE - Patient-reported outcomes - Common Terminology Criteria for Adverse Events (Exploratory Endpoint)

Patient-reported treatment tolerability was explored using 9 predefined symptoms in the PRO-CTCAE item library. The overall compliance rates for the planned visits of PRO-CTCAE were above 85% in both treatment arms at baseline and remained above 75% high up to Week 82 in both treatment arms.

Descriptive PRO-CTCAE results indicated that from the patients' perspective, osimertinib + chemotherapy and osimertinib monotherapy were similarly tolerated in terms of frequency for the majority of the patient-reported treatment-related symptoms selected from the PRO-CTCAE item library, with the exception of more patients reporting nausea and vomiting in the osimertinib + chemotherapy arm after each platinum chemotherapy administration. Where reported, the majority of symptoms were mild or moderate in both treatment arms and/or with limited interference to patients' usual or daily activities.

PGIS - Patient global impression of severity (Exploratory Endpoint)

Patients' global impression of the severity of their cancer symptoms was assessed using the PGIS. The overall compliance rate for the completion of the PGIS questionnaire was ≥ 88% in both arms at baseline) and remained ≥ 75%. up to Week 82 in both treatment arms.

Descriptive PGIS results indicated that approximately two-thirds of patients in both treatment arms reported cancer symptoms at baseline, with most patients reporting very mild, mild or moderate symptoms.

Post-baseline, the proportion of patients reporting cancer symptoms remained predominantly stable throughout the treatment period; however, the proportion of patients reporting severe or very severe cancer symptoms decreased from baseline in both treatment arms.

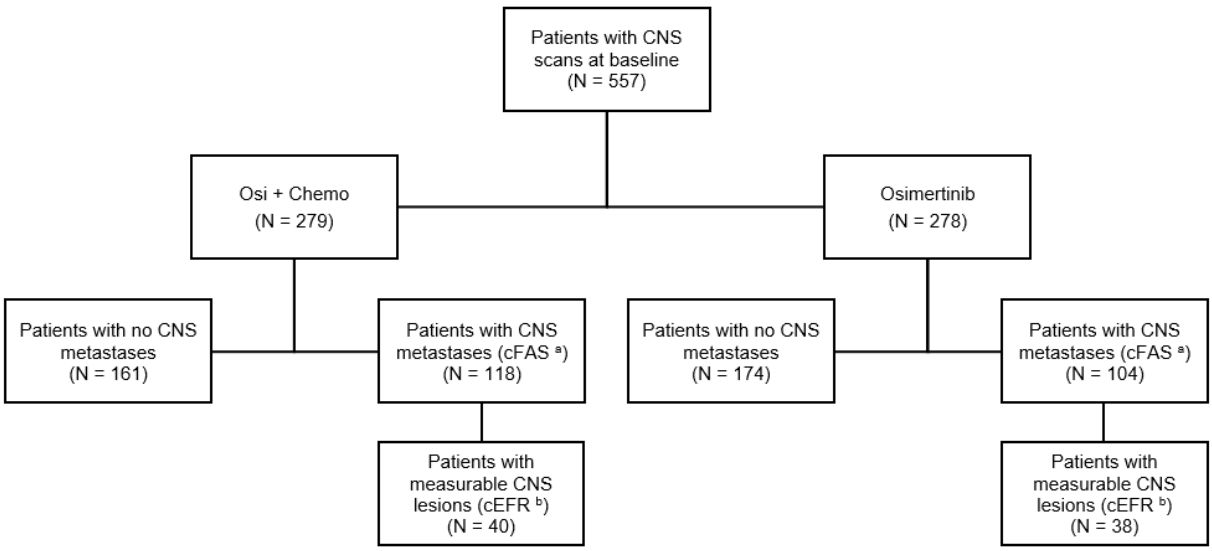
Exploratory endpoints

Central Nervous System by CNS BICR

Brain scans at baseline were mandatory for all patients, and all scans underwent CNS BICR assessment for the evaluation of the exploratory CNS endpoints (which was separate from the whole-body BICR and comprised of independent neuro-radiologists). In total, 222 patients (39.9%) were identified as having a CNS lesion at baseline by CNS BICR.

CNS efficacy endpoints by CNS BICR were primarily evaluated on the prespecified cFAS, which includes patients with at least one non-measurable and/or one measurable brain lesion at baseline, and comprises 118 patients in the osimertinib + chemotherapy arm and 104 patients in the osimertinib arm (Figure 31). A post hoc cEFR analysis set was also created as a subset of the cFAS, which includes only patients with at least one CNS measurable lesion at baseline. In total, 40 patients in the osimertinib + chemotherapy arm and 38 patients in the osimertinib arm are included in the cEFR analysis set.

Figure 31: Central Nervous System BICR Analysis Sets



[a] The cFAS is a subset of the FAS population.

[b] The cEFR analysis set is a subset of cFAS population.

DCO: 03 April 2023

Progression-Free Survival (CNS PFS - CNS BICR)

Table 36: CNS PFS by CNS BICR Assessment (Randomised Period – cFAS and cEFR)

	Number (%) patients			
	cFAS		cEFR	
	Osi + Chemo (N = 118)	Osimertinib (N = 104)	Osi + Chemo (N = 40)	Osimertinib (N = 38)
CNS progression status				
CNS Progression	**28 (23.7)**	**31 (29.8)**	**11 (27.5)**	**18 (47.4)**
CNS RECIST progression [a]	11 (9.3)	20 (19.2)	5 (12.5)	13 (34.2)
CNS Target lesions [b]	2 (1.7)	7 (6.7)	2 (5.0)	7 (18.4)
CNS Non-target lesions [b]	0	4 (3.8)	0	3 (7.9)
CNS New lesions	9 (7.6)	12 (11.5)	3 (7.5)	6 (15.8)
Death [c]	17 (14.4)	11 (10.6)	6 (15.0)	5 (13.2)
No CNS progression	**90 (76.3)**	**73 (70.2)**	**29 (72.5)**	**20 (52.6)**
Censored CNS RECIST progression due to missing visits	1 (0.8)	0	0	0
Censored death due to missing visits [d]	13 (11.0)	16 (15.4)	8 (20.0)	4 (10.5)
CNS Progression free at time of analysis [e]	71 (60.2)	55 (52.9)	20 (50.0)	14 (10.5)
Lost to follow-up [e]	0	0	0	0
Withdrawn consent [e]	4 (3.4)	2 (1.9)	1 (2.5)	2 (5.3)
Discontinued study for other reasons [e]	1 (0.8)	0	0	0
Comparison between groups				
Hazard ratio (95% CI)	0.58 (0.33, 1.01)		0.40 (0.19, 0.84)	
2-sided p-value	0.0548		0.0157	
Median CNS PFS				
Median CNS PFS (months) (95% CI) [f]	30.2 (28.4, NC)	27.6 (22.1, NC)	NC (23.0, NC)	17.3 (13.9, NC)
CNS progression-free at 6 months (%) (95% CI) [f]	93.7 (87.2, 96.9)	89.6 (81.6, 94.3)	92.2 (77.7, 97.4)	85.9 (69.3, 93.9)
CNS progression-free at 12 months (%) (95% CI) [f]	86.7 (78.5, 91.9)	82.6 (73.1, 89.0)	89.2 (73.7, 95.8)	73.2 (54.6, 85.1)
CNS progression-free at 18 months (%) (95% CI) [f]	82.1 (73.1, 88.4)	68.3 (56.3, 77.7)	79.3 (61.2, 89.7)	49.1 (29.5, 66.1)
CNS progression-free at 24 months (%) (95% CI) [f]	73.5 (62.5, 81.7)	54.1 (39.0, 67.0)	64.9 (42.5, 80.3)	37.4 (18.2, 56.7)
Median (range) follow-up for CNS PFS in all patients (months) [g]	20.1 (0, 33.3)	13.9 (0, 33.1)	19.4 (0.4, 33.3)	13.2 (1.1, 30.2)
Median (range) follow-up for CNS PFS in censored patients (months) [h]	22.0 (0, 33.3)	16.4 (0, 33.1)	22.0 (1.6, 33.3)	14.0 (1.4, 30.2)

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

[b] CNS target lesions, CNS non-target lesions, and CNS new lesions are not necessarily mutually exclusive categories.

[c] Death in the absence of CNS progression, within 2 visits of baseline or last evaluable CNS RECIST assessment.

[d] RECIST CNS progression or death occurred more than 2 consecutive scheduled visits (plus visit window) after last previous evaluable CNS RECIST assessment or baseline if no valid post-baseline assessment. Patients are censored at last previous evaluable CNS RECIST assessment or randomisation date.

[e] Patients known to be alive and censored at last evaluable CNS RECIST assessment.

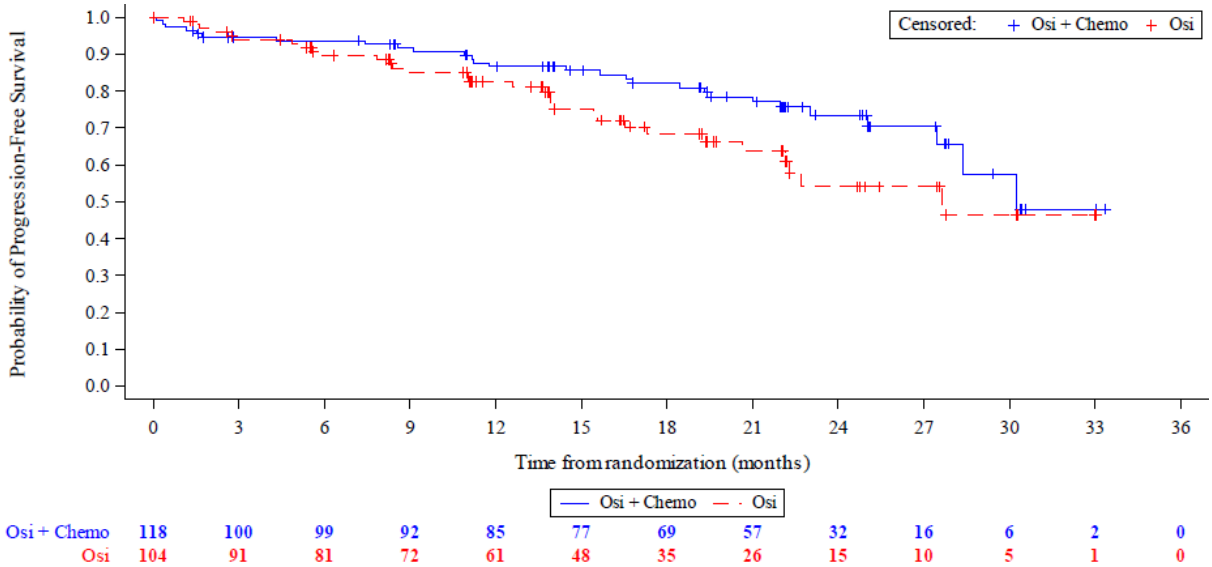
[f] Calculated using the KM method.

[g] Calculated as the minimum, median, and maximum time from randomisation to date of CNS progression or date of censoring in all patients.

[h] Calculated as the minimum, median, and maximum time from randomisation to date of censoring (date last known to have not progressed) in censored (not CNS progressed) patients only.

CNS RECIST
DCO: 03 April 2023

Figure 32: KM Plot of CNS PFS by CNS BICR Assessment (Randomised Period – cFAS)



DCO: 03 April 2023

Objective Response Rate (CNS ORR - CNS BICR)

Table 37: CNS Objective Response by CNS BICR Assessment (Randomised Period – cFAS and cEFR)

	Number (%) patients			
	cFAS		cEFR	
	Osi + Chemo (N = 118)	Osimertinib (N = 104)	Osi + Chemo (N = 40)	Osimertinib (N = 38)
Best objective response, n (%)				
Response [a]	**86 (72.9)**	**72 (69.2)**	**35 (87.5)**	**33 (86.8)**
Complete response	70 (59.3)	45 (43.3)	19 (47.5)	6 (15.8)
Partial response	16 (13.6)	27 (26.0)	16 (40.0)	27 (71.1)
Comparison between groups				
Unadjusted response rate (95% CI) [b]	72.88 (63.92, 80.65)	69.23 (59.42, 77.91)	87.50 (73.20, 95.81)	86.84 (71.91, 95.59)
Odds ratio (95% CI) [c]	1.19 (0.67, 2.14)		1.06 (0.28, 4.00)	
2-sided p-value [c, d]	0.5492		0.9308	
Adjusted response rate (95% CI) [e]	74.61 (65.21, 82.16)	71.75 (61.12, 80.41)	NA	NA
Odds ratio (95% CI) [e]	1.16 (0.64, 2.10)		NA	
2-sided p-value [e]	0.6333		NA	

[a] Response did not require confirmation.

[b] The CI is calculated using the Clopper-Pearson exact method for binomial proportions.

[c] This analysis was performed using logistic regression with a factor for treatment.

[d] The p-value was calculated based on the likelihood ratio test which compared 2 models (one model with the intercept only and a second model including the treatment factor)

[e] The analysis was performed using a logistic regression stratified by race (Chinese/Asian vs. Non-Chinese/Asian vs. Non-Asian), WHO performance status (0 vs. 1), and method used for tissue testing (central vs. local).

DCO: 03 April 2023. CNS RECIST. An odds ratio > 1 favours osimertinib + chemotherapy.

Duration of Response (CNS DoR - CNS BICR)

Table 38: CNS DoR by CNS BICR Assessment (Randomised Period – cFAS and cEFR)

	Number (%) patients			
	cFAS		cEFR	
	Osi + Chemo (N = 118)	Osimertinib (N = 104)	Osi + Chemo (N = 40)	Osimertinib (N = 38)
Number (%) of patients with CNS response	86 (72.9)	72 (69.2)	35 (87.5)	33 (86.8)
Number (%) of responders who subsequently CNS progressed or died [a]	17 (19.8)	19 (26.4)	8 (22.9)	13 (39.4)
Duration of CNS response				
Median CNS DoR (months) (95% CI) [b]	NC (23.8, NC)	26.2 (19.4, NC)	NC (21.6, NC)	20.9 (12.6, NC)
KM estimated percentages remaining in response				
6 months (95% CI) [c]	98.8 (91.7, 99.8)	86.8 (75.2, 93.2)	100 (100, 100)	77.9 (57.1, 89.5)
12 months (95% CI) [c]	93.3 (84.5, 97.1)	81.1 (68.4, 89.1)	93.0 (74.7, 98.2)	74.0 (52.9, 86.7)
18 months (95% CI) [c]	82.1 (69.7, 89.8)	72.9 (57.7, 83.3)	80.1 (58.3, 91.3)	58.4 (35.7, 75.6)
24 months (95% CI) [c]	61.5 (40.3, 77.1)	56.6 (37.7, 71.8)	56.6 (27.3, 77.9)	44.5 (21.6, 65.3)
Time to onset of response, weeks				
Mean (std)	18.85 (20.117)	17.03 (16.455)	Not done	Not done
Median	11.79	8.36	Not done	Not done
Min, max	5.3, 92.0	5.1, 68.4	Not done	Not done

[a] Percentage is based on the number of patients with CNS response.

[b] Calculated using the KM method.

[c] KM estimated percentages remaining in response.

DCO: 03 April 2023. CNS RECIST

Depth of Response (Tumour Shrinkage) - CNS BICR

Table 39: Best Percentage Change From Baseline in CNS Target Lesion Size by CNS BICR Assessment (Randomised Period – cFAS)

	Osi + Chemo (N = 118)	Osimertinib (N = 104)
Number (%) of patients with brain measurable lesion(s) [a]	40 (33.9)	38 (36.5)
Best percentage changes from baseline for sum of longest diameters		
n	38	38
Mean (std)	-77.98 (27.806)	-59.75 (33.443)
Median	-93.86	-61.26
Min, max	-100.0, 6.5	-100.0, 68.1

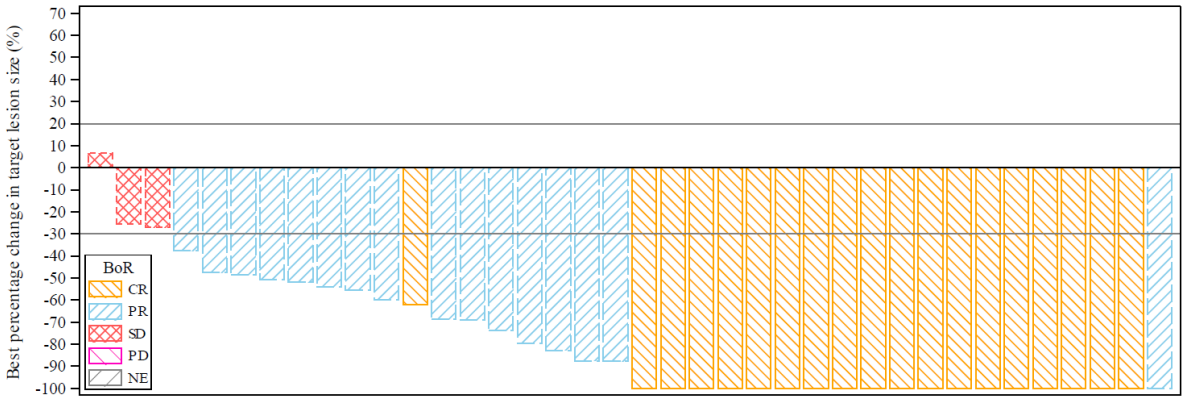
a As this evaluation only includes patients with changes in CNS target lesions, the cFAS and cEFR analysis sets are synonymous.

CNS RECIST.

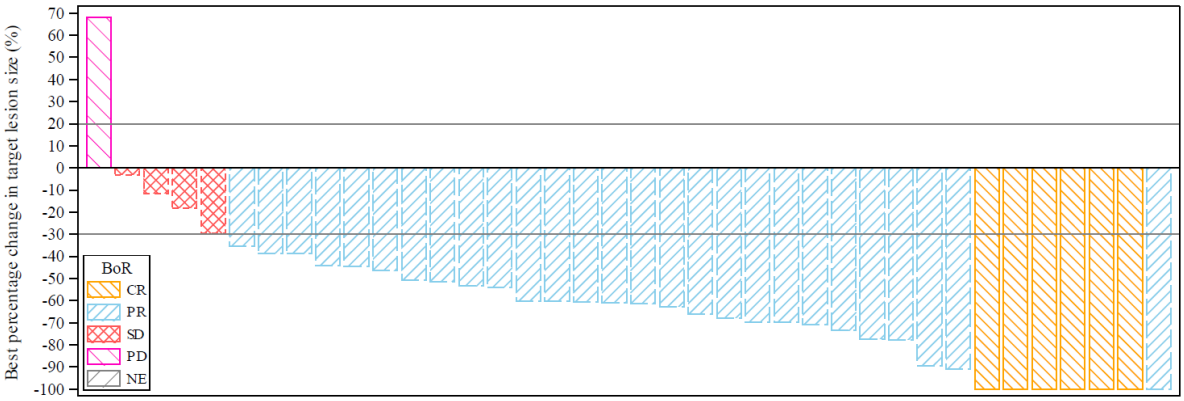
DCO: 03 April 2023

Figure 33: Waterfall Plots of CNS Target Lesion Size, Best Percentage Change From Baseline by CNS BICR Assessment (Randomised Period – cFAS)

Osimertinib + Chemotherapy (N = 118, N' = 38)



Osimertinib (N = 104, N' = 38)



Note: As this evaluation only includes patients with changes in CNS target lesions, the cFAS and cEFR analysis sets are synonymous.
N' = number of patients with non-missing best percentage change in CNS target lesion size, including imputed value.
DCO: 03 April 2023

Disease Control Rate (CNS DCR - CNS BICR)

CNS DCR in the cFAS

Table 40: CNS DCR by CNS BICR Assessment (Randomised Period – cFAS)

	Osi + Chemo (N = 118)	**Osimertinib (N = 104)**
Number (%) of patients with CNS disease control	107 (90.7)	97 (93.3)
Comparison between groups		
Unadjusted response rate (95% CI) [a]	90.68 (83.93, 95.25)	93.27 (86.62, 97.25)
Odds ratio (95% CI) [b]	0.70 (0.26, 1.88)	
2-sided p-value [b, c]	0.4781	
Adjusted response rate (95% CI) [d]	93.72 (86.33, 97.24)	95.91 (89.35, 98.49)
Odds ratio (95% CI) [d]	0.64 (0.23, 1.73)	
2-sided p-value [d]	0.3767	

[a] The CIs are calculated using the Clopper-Pearson exact method for binomial proportions.

[b] This analysis was performed using logistic regression with a factor for treatment.

[c] The p-value was calculated based on the likelihood ratio test which compared 2 models (one model with the intercept only and a second model including the treatment factor).

[d] The analysis was performed using a logistic regression stratified by race (Chinese/Asian vs. Non-Chinese/Asian vs. Non-Asian), WHO performance status (0 vs. 1), and method used for tissue testing (central vs. local).

[o] An odds ratio > 1 favours osimertinib + chemotherapy.

DCO: 03 April 2023

CNS DCR in the cEFR Analysis Set

In an analysis based on the post-hoc cEFR analysis set, the CNS DCR was 95.0% in the osimertinib + chemotherapy arm (95% CI: 83.08, 99.39), and 97.4% in the osimertinib arm (95% CI: 86.19, 99.93), with unadjusted DCR odds ratio of 0.51 [95% CI: 0.04, 5.91]; nominal p value = 0.5827).

Ancillary analyses

Subgroup analyses

Progression-Free Survival

Table 41: Subgroup Analysis of Progression Free Survival By Investigator Assessment (Randomised Period – FAS)

Subgroups [a]	Treatment group	N	Number (%) of patients with events	Comparison between groups	
				Hazard Ratio	95% CI
All patients (stratified by log-rank) [b]	Osi + Chemo	279	120 (43.0)	0.62	(0.49, 0.79)
	Osimertinib	278	166 (59.7)		
All patients (unadjusted Cox PH) [c]	Osi + Chemo	279	120 (43.0)	0.62	(0.49, 0.78)
	Osimertinib	278	166 (59.7)		
Gender					
Male	Osi + Chemo	106	51 (48.1)	0.54	(0.37, 0.77)
	Osimertinib	109	73 (67.0)		
Female	Osi + Chemo	173	69 (39.9)	0.67	(0.49, 0.92)
	Osimertinib	169	93 (55.0)		
Race					
Chinese/Asian	Osi + Chemo	71	26 (36.6)	0.49	(0.30, 0.81)
	Osimertinib	69	43 (62.3)		
Non-Chinese/Asian	Osi + Chemo	107	54 (50.5)	0.76	(0.53, 1.09)
	Osimertinib	107	65 (60.7)		
Non-Asian	Osi + Chemo	101	40 (39.6)	0.55	(0.37, 0.83)
	Osimertinib	102	58 (56.9)		
Method used for tissue testing					
Central	Osi + Chemo	121	52 (43.0)	0.73	(0.51, 1.05)
	Osimertinib	119	67 (56.3)		
Local	Osi + Chemo	158	68 (43.0)	0.55	(0.40, 0.74)
	Osimertinib	159	99 (62.3)		
Age at screening					
<65 years	Osi + Chemo	174	73 (42.0)	0.59	(0.44, 0.80)

Subgroups [a]	Treatment group	N	Number (%) of patients with events	Comparison between groups	
				Hazard Ratio	95% CI
	Osimertinib	166	97 (58.4)		
≥ 65 years	Osi + Chemo	105	47 (44.8)	0.68	(0.47, 0.98)
	Osimertinib	112	69 (61.6)		
Smoking history					
Yes	Osi + Chemo	91	43 (47.3)	0.63	(0.42, 0.94)
	Osimertinib	97	57 (58.8)		
No	Osi + Chemo	188	77 (41.0)	0.61	(0.46, 0.82)
	Osimertinib	181	109 (60.2)		
EGFR mutation type [d]					
Exon 19 deletion	Osi + Chemo	172	65 (37.8)	0.60	(0.44, 0.83)
	Osimertinib	169	94 (55.6)		
L858R	Osi + Chemo	106	55 (51.9)	0.63	(0.44, 0.90)
	Osimertinib	107	70 (65.4)		
EGFR mutation by central ctDNA cobas test					
Positive	Osi + Chemo	214	96 (44.9)	0.62	(0.48, 0.81)
	Osimertinib	206	130 (63.1)		
Negative	Osi + Chemo	41	15 (36.6)	0.82	(0.39, 1.69)
	Osimertinib	40	15 (37.5)		
Missing	Osi + Chemo	24	9 (37.5)	0.42	(0.19, 0.92)
	Osimertinib	32	21 (65.6)		
EGFR mutations by central cobas tissue test					
Positive	Osi + Chemo	249	111 (44.6)	0.65	(0.51, 0.84)
	Osimertinib	240	141 (58.8)		
Missing	Osi + Chemo	26	9 (34.6)	0.47	(0.21, 1.06)
	Osimertinib	34	22 (64.7)		
WHO PS					
0	Osi + Chemo	101	48 (47.5)	0.79	(0.54, 1.16)
	Osimertinib	102	57 (55.9)		
1	Osi + Chemo	178	72 (40.4)	0.53	(0.39, 0.72)
	Osimertinib	176	109 (61.9)		
CNS metastases status at baseline [e]					
Yes	Osi + Chemo	116	52 (44.8)	0.47	(0.33, 0.66)
	Osimertinib	110	79 (71.8)		
No	Osi + Chemo	163	68 (41.7)	0.75	(0.55, 1.03)
	Osimertinib	168	87 (51.8)		
Central confirmation of EGFR mutation					
Centrally confirmed tissue or ctDNA EGFR positive result	Osi + Chemo	266	115 (43.2)	0.64	(0.50, 0.81)
	Osimertinib	269	158 (58.7)		

[a] Subgroup 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.

[b] The analysis was performed using a log rank test stratified by race (Chinese/Asian vs. Non-Chinese/Asian vs. Non-Asian), WHO performance status (0 vs. 1), and method used for tissue testing (central vs. local).

[c] The analysis was performed using a Cox proportional hazards model which contains the treatment group as a covariate.

[d] Patients with both Exon 19 deletion and L858R are included in Exon 19 deletion group.

Subgroups [a]	Treatment group	N	Number (%) of patients with events	Comparison between groups	
				Hazard Ratio	95% CI

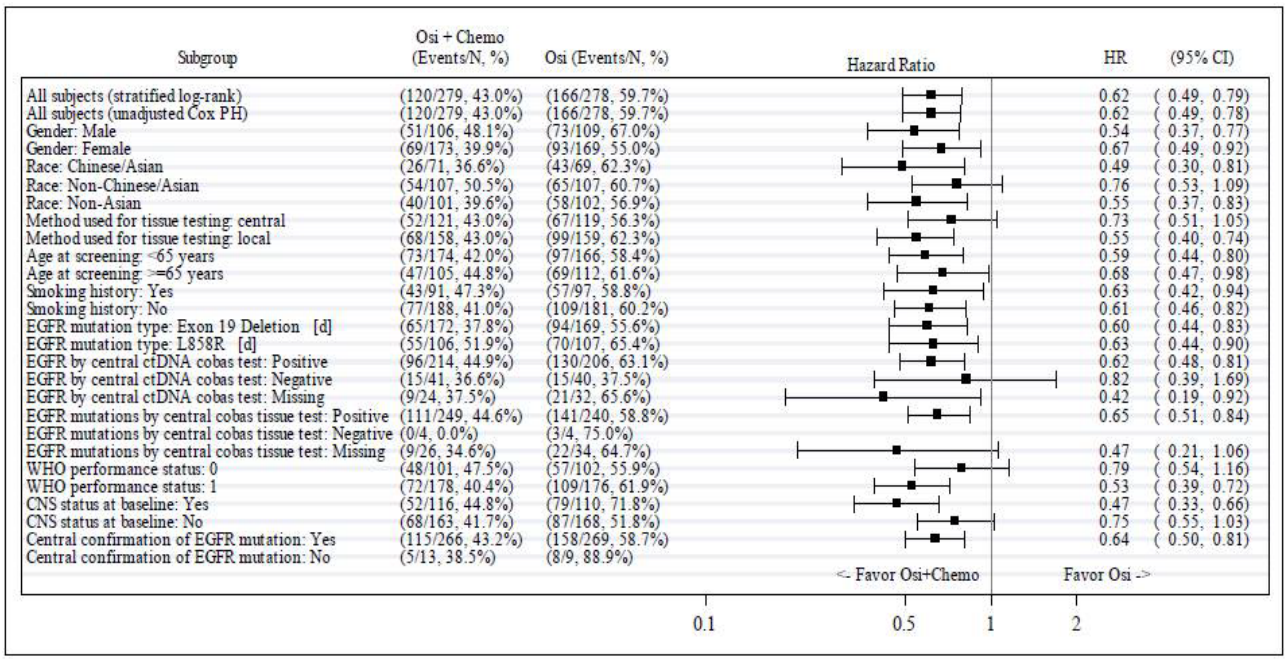
[c] As identified by the Investigator and recorded in the eCRF based on CNS lesion site at baseline, medical history, and/or prior surgery, and/or prior radiotherapy to CNS metastases.

A hazard ratio < 1 favours osimertinib + chemotherapy.

RECIST version 1.1.

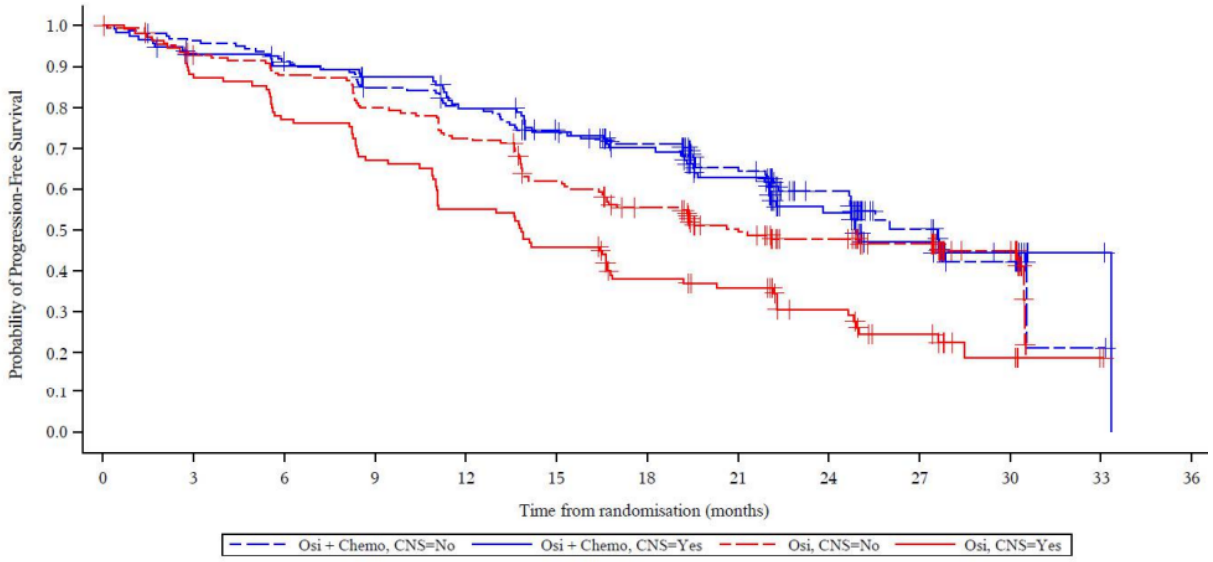
DCO: 03 April 2023

Figure 34: Subgroup Analysis of Progression-Free Survival (Months) By Investigator Assessment, Forest Plot (Randomised Period – FAS)



For EGFR mutation type (flagged with symbol [d]), patients with both Exon 19 deletion and L858R are included in Exon 19 deletion group
DCO: 03 April 2023

Figure 35: KM Plot of Investigator-Assessed PFS by CNS Status at Baseline (Randomised Period – FAS)



Number of patients at risk

Months	0	3	6	9	12	15	18	21	24	27	30	33	36
Osi + Chemo, CNS=No	163	153	143	132	123	110	95	75	50	23	13	1	0
Osi + Chemo, CNS=Yes	116	101	98	93	84	77	70	58	34	19	8	2	0
Osi, CNS=No	168	151	143	130	118	98	82	62	46	35	16	0	0
Osi, CNS=Yes	110	95	84	73	60	50	37	32	21	13	5	1	0

+ Censored patients. RECIST version 1.1.
DCO: 03 April 2023
Source: Figure IMT1262SA1

Summary of main study(ies)

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

Table 42: Table 1. Summary of Efficacy for the FLAURA2 trial

Title: A Phase III, Open-label, Randomised Study of Osimertinib With or Without Platinum Plus Pemetrexed Chemotherapy, as First line Treatment in Patients with Epidermal Growth Factor Receptor Mutation Positive, Locally Advanced or Metastatic Non-small Cell Lung Cancer (FLAURA2)		
Study identifier	Study Code: D5169C00001 EudraCT Number:2019-000650-61 NCT Number: NCT0403548	
Design	Ongoing, phase III, global, open-label, randomised study, with a safety run-in (SRI) period and a randomised period	
	Duration of main randomised phase:	15 May 2020 (FSI) to 03 April 2023 (DCO)
Hypothesis	Superiority over osimertinib	
Treatments groups	Osimertinib + chemotherapy	Osimertinib 80 mg, orally, once daily, in combination with IV pemetrexed (500 mg/m2) (with vitamin supplementation) plus either cisplatin (75 mg/m2) or carboplatin (AUC5), with both treatments administered on Day 1 of 21-day cycles for 4 cycles, followed by osimertinib 80 mg, orally, once daily plus IV pemetrexed maintenance (500 mg/m2) Q3W; n=279
	Osimertinib	Osimertinib 80 mg, orally, once daily; n=278

Endpoints and definitions	Primary endpoint	PFS by Investigator assessment	Time from randomisation until the date of objective disease progression or death (by any cause in the absence of progression), regardless of whether the patient withdrew from study treatment or received another anticancer therapy prior to progression. PFS using Investigator assessment as defined by RECIST 1.1
	Primary endpoint	Sensitivity analysis of PFS using BICR	Sensitivity analysis of PFS using BICR assessment as defined by RECIST 1.1 (as described above).
	Key Secondary endpoint	OS	Time from the date of randomisation until death due to any cause regardless of whether the patient withdraws from study treatment or receives another anticancer therapy (ie, date of death or censoring – date of randomisation + 1).
Database lock	04 May 2023		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	The primary and key secondary efficacy analyses were conducted on the ITT population (defined as the FAS) at the DCO of 03 April 2023. The FAS includes all randomised patients, and treatment arms are compared on the basis of randomised study treatment, regardless of the treatment actually received.		
Descriptive statistics and estimate variability	Treatment group	Osi + Chemo	Osimertinib
	Number of subject	279	278
	PFS by Investigator assessment (median, months)	25.5	16.7
	95% CI	24.7, NC	14.1, 21.3
	Sensitivity analysis of PFS using BICR (median, months)	29.4	19.9
	95% CI	25.1, NC	16.6, 25.3
Effect estimate per comparison	PFS by Investigator assessment	Comparison groups	Osi + Chemo vs. Osimertinib
		Hazard ratio	0.62
		95% CI	0.49, 0.79
		2-sided P-value	< 0.0001
	Sensitivity analysis of PFS using BICR	Comparison groups	Osi + Chemo vs. Osimertinib
		Hazard ratio	0.62
		95% CI	0.48, 0.80
		2-sided P-value	0.0002
Notes	In total, 120 PFS events (43.0%) were reported on the osimertinib + chemotherapy arm and 166 PFS events (59.7%) were reported in the osimertinib arm, with an overall data maturity of 51.3% Ascertainment bias is assessed by analysing PFS by BICR in the FAS, and was consistent with the Investigator-based analysis.		

Analysis description	**Key Secondary analysis**		
Analysis population and time point description	The key secondary efficacy analysis of OS was conducted on the ITT population (defined as the FAS), at the DCO of 08 January 2024 (second interim analysis).		
Descriptive statistics and estimate variability	Treatment group	Osi + Chemo	Osimertinib
	Number of subjects	279	278
	OS (median, months)	NC	36.7
	95% CI	38.0, NC	33.2, NC
Effect estimate per comparison	OS	Comparison groups	Osi + Chemo vs. Osimertinib
		Hazard ratio	0.75
		95% CI	0.57, 0.097
		2-sided P-value	0.0280
Notes	At the second interim OS analysis, 100 patients (35.8%) having died in the osimertinib + chemotherapy arm, and 126 patients (45.3%) having died in the osimertinib arm (40.6% maturity of data). The majority of patients in both treatment arms died of the disease under study. The HR at the time of the interim OS analysis was not statistically significant per the O'Brien Fleming spending function (which required a p-value of < 0.000001 to declare statistical significance at the interim analysis). The final OS analysis will be conducted when data are approximately 60% mature (approximately 334 death events across both treatment arms)		

Analysis description	Exploratory Endpoints CNS metastasis at baseline n=222 (cFAS) DCO: 03 April 2023		
	Treatment group	Osi + Chemo n=118	Osimertinib n=104
Descriptive statistics and estimate variability	PFS Median months (IC 95%)	30.2 (28.4, NC)	27.6 (22.1, NC)
	ORR n (%)	86 (72.9)	72 (69.2)
Effect estimate per comparison	PFS	Comparison groups	Osi + Chemo vs. Osimertinib
		Hazard ratio	0.58
		95% CI	0.33, 1.01
		2-sided P-value	0.548
	ORR	Comparison groups	Osi + Chemo vs. Osimertinib
		Odds ratio	1.19
		95% CI	0.67, 2.14
		2-sided P-value	0.5492

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

Not applicable.

Clinical studies in special populations

Not applicable.

Supportive study

Safety Run-in Period – FLAURA2 study

Prior to the start of the Randomised period of FLAURA2, the Safety run-in was conducted with the primary objective of assessing the safety and tolerability of osimertinib in combination with pemetrexed and either cisplatin or carboplatin. Secondary objectives were to assess the efficacy of osimertinib + chemotherapy, and to assess the PK of osimertinib when given with chemotherapy.

A total of 30 patients with advanced NSCLC with EGFR exon 19 deletions (Ex19del) or exon 21 (L858R) substitution mutations were enrolled in a non-randomised fashion into 2 cohorts: osimertinib + cisplatin + pemetrexed and osimertinib + carboplatin + pemetrexed. Fifteen patients per cohort were to receive osimertinib 80 mg orally once daily plus pemetrexed (500 mg/m^2) and 4 cycles (Q3W) of either cisplatin (75 mg/m^2) or carboplatin (AUC of 5 mg/mL/min), followed by continuous osimertinib 80 mg orally once daily and pemetrexed maintenance (500 mg/m2) Q3W until RECIST 1.1-defined progression, or another discontinuation criterion was met.

Per protocol, the primary analysis of the Safety run in period (DCO date: 19 February 2020) occurred when at least 12 patients in each cohort had either received ≥ 3 cycles of study treatment, or had discontinued study treatment due to unacceptable toxicity. Following the primary analysis, patients who participated in the Safety run in period were not included in the Randomised period, but could continue to receive their allocated treatment (and were followed up) until the DCO date of the primary analysis of the Randomised period (DCO date: 03 April 2023). At this time, the clinical study database was to be closed to new data for these patients.

As no formal statistical testing was conducted within the Safety run in period, no sample size calculation was made. Safety and efficacy data are summarised descriptively. No formal statistical testing was conducted for efficacy within the Safety run in period.

Results (as of DCO date of 03 April 2023):

Study participants

At the DCO date of the final analysis (03 April 2023), 14/30 patients (46.7%) were ongoing on at least one study treatment: 6 patients (40.0%) in the osimertinib + carboplatin + pemetrexed (osi carbo pem) cohort, and 8 patients (53.3%) in the osimertinib + cisplatin + pemetrexed (osi cis pe) cohort. The remaining 16/30 (53.3%) patients had discontinued all study treatment: 9 patients (60.0%) in the osi carbo pem cohort, and 7 patients (46.7%) in the osi cis pem cohort. The majority of osimertinib treatment discontinuations were due to subjective disease progression (10 of 16 patients) and few were due to AEs (2 of 16 patients).

The majority of patients were Asian, and female, with a median age of 61.0 years (range: 45 years to 84 years). In total, 40.0% of patients (12/30) were aged ≥ 65 years. All patients treated in the Safety run-in period had metastatic NSCLC of adenocarcinoma histology, and approximately half of all patients had a WHO PS of 1 at baseline (56.7%).

Efficacy

Efficacy data are presented based on all patients in the safety analysis set (N = 30) and not by chemotherapy cohort.

At the DCO date of the final analysis of the Safety run-in period (03 April 2023) objective tumour responses was seen in 26/30 patients treated with osimertinib in combination with pemetrexed and platinum-based chemotherapy (confirmed ORR: 86.7% [95% CI: 69.28, 96.24]). The remaining patients had a best overall response of SD (4/30 patients, 13.3%).

Responses were durable, with a median DoR of 33.99 months (range: 2 months to 43 months). The median best percentage change from baseline in target lesion size was 59.55% (range: -100% to -6.4%). All 30 patients had a reduction in target lesion size.

2.4.3. Discussion on clinical efficacy

The MAH applied for an extension of the indication for osimertinib in combination with pemetrexed and platinum-based chemotherapy for the first-line treatment of adult patients with advanced NSCLC with activating EGFR mutations.

The efficacy data supporting this application are from the primary analysis of the Randomised period of the clinical study D5169C00001 (FLAURA2), an ongoing, Phase III, open-label, randomised study of osimertinib with or without pemetrexed and platinum-based chemotherapy in patients with locally advanced (not amenable to curative surgery or chemoradiotherapy) or metastatic EGFRm NSCLC (Ex19del and/or L858R) who had not received prior therapy for advanced disease, with a DCO date of 03 April 2023. In addition, updated OS data based on a second interim analysis (DCO 08 January 2024) were provided.

Design and conduct of clinical studies

The FLAURA2 study has been conducted in 2 parts: the Safety run-in period, and the open-label, Phase III, Randomised period. The primary analysis of the Safety run-in period (which was conducted to evaluate the safety and tolerability of osimertinib when given in combination with platinum-based

chemotherapy and pemetrexed, with a DCO date of 19 February 2020) has previously been completed. Following a positive recommendation by the Safety Review Committee based on the evaluation of data from the Safety run-in period, the Randomised period was initiated. The pivotal dataset is supplemented with long-term efficacy data (30 patients) from the final analysis of the safety run-in period of FLAURA2 (DCO date: 03 April 2023).

Patient population

Overall, the inclusion and exclusion criteria are generally acceptable. The exclusion of patients with severe or uncontrolled systemic disease, prolonged QT interval or a history of ILD is appropriate and reflected in the SmPC.

Treatments

Patients were randomised in a 1:1 ratio to receive either osimertinib + chemotherapy (pemetrexed plus either cisplatin or carboplatin) for 4 cycles, followed by osimertinib plus pemetrexed maintenance or osimertinib monotherapy. Randomisation was stratified by race (Chinese/Asian vs. Non-Chinese/Asian vs. Non-Asian), WHO PS (0 vs. 1), and method for tissue testing (central vs. local). The stratification factors can be endorsed. The chemotherapy doses and dosing regimens selected for use in the FLAURA2 study are all in accordance with approved product labelling and current treatment guidelines for advanced NSCLC.

Patients were to continue on their randomised treatment until disease progression as defined by RECIST 1.1, unacceptable toxicity, or until a treatment discontinuation criterion was met. Treatment beyond progression was allowed. Of note, patients who discontinued cisplatin or carboplatin alone could, at the investigator's discretion, be switched to the other allowed platinum agent with pemetrexed and osimertinib for the remainder of the platinum doublet cycles. However, no patients switched platinum-based chemotherapy (ie, cisplatin to carboplatin or vice versa). Crossover between treatment arms was not permitted within the study.

The comparator can be considered adequate since osimertinib is the preferable first-line treatment option for patients with activating EGFR mutations (exon 19 deletion or exon 21 L858R) and in fact, it is part of the combination treatment.

Platinum-based chemotherapy doublets have been one of the treatment options in the first-line setting of advanced NSCLC. In this regard, several platinum-based regimens are available and according to the ESMO guideline, for non-squamous NSCLC, any platinum-based doublet with a third-generation agent including pemetrexed, gemcitabine, vinorelbine or taxanes can be used. In the study FLAURA2 osimertinib has been investigated in combination with a regimen including pemetrexed, consisting on 4 cycles of carboplatin/cisplatin + pemetrexed followed by pemetrexed maintenance. The addition of pemetrexed maintenance to osimertinib after chemotherapy and the duration (or number of cycles) of pemetrexed maintenance may contribute to additional benefit as noted by the increase in PFS with increasing pemetrexed cycles. However, less than half of patients received pemetrexed as maintenance during at least 10 cycles. The study was not designed to assess the contribution of pemetrexed maintenance to the experimental arm, thus, the additional benefits of pemetrexed maintenance in combination with osimertinib in this setting are uncertain. However, this issue will not be further pursued.

Endpoints

The primary endpoint was PFS, based on Investigator assessment according to RECIST 1.1. PFS is considered an acceptable primary endpoint in the first-line setting of advanced NSCLC. In the context of an open-label trial, the assessment based on a BICR would have been preferred but since this analysis has been included as a sensitivity analysis, this is considered acceptable.

OS was included as a key secondary endpoint. Additional secondary efficacy endpoints were those defining tumour response (ORR, DoR, DCR, and depth of response) and post-progression outcomes (TFST, PFS2, and TSST). Patient-reported outcomes assessed using the EORTC QLQ-C30 and EORTC QLQ-LC13 questionnaires was a secondary endpoint, although the open-label design of the study, poses limitations to the interpretation of the results.

A pre-specified, exploratory analysis of CNS BICR efficacy endpoints (CNS PFS, CNS ORR, CNS DoR, CNS DCR, and CNS depth of response) was also performed in the CNS analysis sets (cFAS).

Other exploratory endpoints evaluated were PFS, ORR, DoR, DCR, and depth of response using RECIST 1.1 assessments based on Investigator evaluation, assessments tumour and ctDNA to explore biomarker effects on efficacy of both osimertinib plus chemotherapy and osimertinib. The results of the exploratory endpoint to explore biomarker effects on efficacy of both osimertinib plus chemotherapy and osimertinib monotherapy arms, should be provided when they are available (REC).

Potential mechanisms of resistance to osimertinib have not been investigated in the FLAURA2 trial. Blood samples for ctDNA testing and optional tumour samples were collected from patients in both treatment arms at time of progression to explore the potential mechanisms of resistance. These results are expected to be provided once available (REC).

Statistical methods

Regarding the estimation of the sample size, the MAH has described the assumptions considered to calculate the sample size of 556 patients and the methodology is considered acceptable.

For the primary comparison (PFS per the Investigator assessment), the MAH considered objective disease progression or death (by any cause in the absence of progression) as events, regardless of whether the patient withdraws from study treatment or receives another anti-cancer therapy prior to progression, following the treatment policy approach for these intercurrent events. This approach is acceptable.

OS will be tested hierarchically at the primary analysis of PFS and once approximately 60% of the events for this endpoint are reached. The O'Brien and Fleming approach is adopted to maintain the Type I error at 5% (two-sided). Of note, due to the low maturity of OS at the time of the primary PFS analysis a second interim OS analysis was also performed in advance of the final OS analysis. A small alpha spend of 0.000001 was applied. This proposal is acceptable.

Efficacy data and additional analyses

In total, 887 patients were enrolled in the randomised period study and underwent screening, of which 330 were not randomised. The primary reason for not being randomised was screen failure (319 patients). Finally, 557 patients were randomised to receive study treatment: 279 patients in the osimertinib + chemotherapy arm and 278 patients in the osimertinib arm. Protocol amendments and protocol deviations:

The original protocol (dated 19 Mar 2019) was amended once (26 Aug 2021). The most relevant changes were the addition of one condition to trigger the final analysis of the primary endpoint, which consist of having at least a 16-month follow-up from the time of last subject; and a set of analyses to assess the potential impact of COVID-19 deaths on PFS. Overall, these changes can be acceptable.

Overall, the number of important protocol deviations was low and comparable between treatment arms and do not raise any concerns regarding the overall conduct or quality of the study.

Most of the deviations were related to RECIST 1.1 imaging schedule.

Baseline characteristics

Overall, demographics and baseline disease characteristics were well-balanced between treatment arms, and representative of the target population. The majority of patients were Asian (63.7%), female (61.4%), never-smokers (66.2%) and with a median age of 61.0 years (range: 26, 85). In total, 8.4% of patients were aged ≥ 75 years. Patients had NSCLC of predominantly adenocarcinoma histology (98.7%), most of them with metastatic disease (96%) and a WHO PS of 0 (37%) or 1 (63%). A total of 226 patients (40.6%) had CNS metastases at baseline and around 20% had liver metastasis, with a higher proportion in the control arm (15% vs 24%).

In FLAURA2 the patients were required to have tumours with one of the 2 common EGFR mutations known to be associated with EGFR-TKI sensitivity (Ex19del or L858R), either alone or in combination with other EGFR mutations. Other EGFR mutations were T790M mutations (10 patients), exon 20 insertion (5 patients), S768I mutation (3 patients), and L861Q and G719X mutations (1 patient each).

The exclusion of patients with other less common EGFR mutations has been done in previous clinical trials (i.e. FLAURA). Of note, a broad indication was given to osimertinib in the first line setting regardless of the type of activating EGFR mutations based on the available preclinical and limited clinical data. However, considering the lack of clinical data of osimertinib + chemotherapy in patients with other EGFR mutations different from Ex19del or L858R, particularly exon 20 insertions that have therapeutic/pharmacodynamic relevance, and for which sensitivity to EGFR TKI is decreased, the indication has been restricted to the studied patient population, i.e., patients whose tumour have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations.

Outcomes and estimation

The efficacy data provided are based on a DCO date of 03 April 2023, unless otherwise indicated.

At this DCO date with a total of 286 PFS events per investigator assessment (51.3% maturity), the study met its primary objective, with statistically significant results in favour of the osimertinib + chemotherapy arm (HR 0.62 [95% CI: 0.49, 0.79]; p-value < 0.0001). Median PFS was 25.5 vs. 16.7 moths with osimertinib + chemotherapy vs. osimertinib monotherapy arm, respectively. The PFS results by BICR assessment were consistent with the Investigator assessment (HR 0.62; 95% CI: 0.48, 0.80), with a concordance between Investigator and BICR of 82.1% in the osimertinib + chemotherapy arm and 75.6% in the osimertinib arm.

Results of other sensitivity analyses were consistent with the primary analysis. Moreover, the PFS benefit of osimertinib + chemotherapy compared to osimertinib was observed consistently across all predefined subgroups analysed.

Regarding the censorships in PFS due to missing visits, a slight imbalance between treatment arms is noticeable, depending on who assessed the results: Investigator and BICR (7 vs 12 in osimertinib + chemo arm, 2 vs 16 in osimertinib arm), however these differences are considered to have no impact on the benefit-risk assessment.

OS was tested at the time of the primary PFS analysis, data were with overall 26.8% of event. No statistically significant differences were observed between treatment arms (HR = 0.90; adjusted 99.84% CI: 0.54, 1.51; p-value = 0.5238). Median OS was not reached in either treatment arm. Updated OS data were submitted (DCO: 08 January 2024) with 226 events (40.6% maturity; IF: 67.7%) and when all patients had the opportunity for 25 months follow-up. A trend in favour of the osimertinib+chemotherapy arm is observed (HR 0.75; 95% CI 0.57 to 0.97; p = 0.028) although statistical significance was not reached since the pre-specified boundary (p-value < 0.000001) was not crossed. The median OS was not calculable (95% CI: 38.0, NC) in the osimertinib + chemotherapy arm and was 36.7 months (95% CI: 33.2, NC) in the osimertinib arm. Separation of the Kaplan-Meier curves is not observed until approximately 16 months. Based on the updated results, a detrimental effect in OS appears unlikely. However, the MAH was recommended to provide the final OS analysis (approximately when 334 death

events across both arms, 60% maturity) once available (REC). According to the MAH this analysis is estimated to be available in 2026.

The ORR was higher in the osimertinib + chemotherapy arm vs. the osimertinib arm (83.2% vs. 75.5%, respectively) based on investigator assessment. The majority of patients in both treatment arms had PRs to study treatment, with only 1 CR in the osimertinib + chemotherapy arm and 2 CR in the osimertinib arm. Response did not require confirmation. Results based on BICR were overall consistent (91.8% osimertinib + chemotherapy vs. 82.7% osimertinib). The median DoR was 24.0 months in the osimertinib + chemotherapy arm vs. 15.3 months in the osimertinib arm.

The median best percentage change in target lesion size from baseline per investigator assessment and DCR (95.3% osimertinib + chemotherapy vs. 93.9% osimertinib) were quite similar between treatment arms. Consistent results were observed by BICR.

Post-progression endpoints

Treatment beyond progression was allowed as per protocol. The proportion of patients who received osimertinib treatment beyond disease progression was similar between treatment arms (85% in the osimertinib + chemotherapy arm vs. 84% in the osimertinib arm), with comparable median durations of osimertinib treatment beyond (investigator-assessed) disease progression between treatment arms (1.84 months in the osimertinib + chemotherapy arm and 1.94 months in the osimertinib arm). In the osimertinib + chemotherapy arm, 27 patients continued to receive pemetrexed beyond RECIST progression, with a median duration of 3.65 months.

Post-progression endpoints of TFST, TSST and PFS2 showed results in favour of the experimental arm. With a data maturity of 41.8%, a HR in favour of osimertinib + chemotherapy was observed in relation to TFST (HR = 0.73 [95% CI: 0.56, 0.94]; nominal p-value = 0.0159,Table 31). Similar results were observed for TSST with a data maturity of 31.8% (HR 0.69 [95% CI: 0.51, 0.93]; Table 33). With a data maturity of 34.3%, the median PFS2 by investigator assessment was 30.6 months vs. 27.8 months in osimertinib + chemotherapy vs. osimertinib arm, respectively, with a HR of 0.70 (95% CI: 0.52, 0.93). Of note, a total of 25 patients received EGFR TKI treatment after having been treated with osimertinib in FLAURA2 trial. Updated efficacy data of these secondary post-progression endpoints should be provided with the final OS analysis (REC).

Thus, at baseline, the study population was generally mildly symptomatic, reflecting the good overall WHO PS.

Overall, an improvement in global health status/QoL and physical functioning was observed in both treatment arms but could not be considered clinically meaningful. Moreover, while a trend towards worse score was observed for some PRO functioning and symptoms subscales, including nausea, in the osimertinib+chemotherapy arm, there is not sufficient evidence to suggest that the difference is clinically meaningful.

Central Nervous System by CNS BICR (exploratory endpoints).

Efficacy analyses were conducted in the subgroup of patients with CNS metastasis at baseline. In total, 222 patients (39.9%) were identified as having a CNS lesion at baseline by CNS BICR.

Among patients with CNS metastasis, an improvement in CNS-PFS was observed with osimertinib + chemotherapy versus osimertinib monotherapy both in the cFAS population (HR 0.58 [95% CI: 0.33, 1.01]) and in the eEFR analysis set (HR 0.40 [95% CI: 0.19, 0.84]). CNS response rates were similar between treatment arms. P

Despite being an exploratory analysis, these results indicate an effect in CNS. No further data on PFS or CNS efficacy endpoints has been collected, and therefore no updates on PFS or CNS outcomes are expected.

2.4.4. Conclusions on the clinical efficacy

In the FLAURA2 study a statistically significant improvement in PFS with osimertinib in combination with pemetrexed and platinum-based chemotherapy vs. osimertinib as monotherapy was observed. In addition, the consistency of the effect in PFS was shown across subgroups and different sensitivity analyses. The results of a second OS interim analysis (40.6% maturity of data) showed also a trend in favour of the combination arm, although statistical significance was not reached, and a detrimental effect appears unlikely.

In addition, post-progression measures (PFS2, TFST, TTST) favoured also the combination arm, although data were still immature. The results of the final OS analysis will be presented when available in addition to updated post-progression endpoints (REC).

Considering the lack of clinical data of osimertinib + chemotherapy in patients with other EGFR mutations different from Ex19del or L858R, particularly exon 20 insertions, the therapeutic indication has been restricted to the studied population, i.e., patients whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations.

2.5. Clinical safety

Introduction

Safety data for this evaluation is primarily based on data from the randomised period of the study FLAURA2 (D5169C00001; N=557 patients; DCO date of 03 April 2023), supported by comparisons with a pooled dataset (N=1813) of patients with EGFRm NSCLC who received osimertinib monotherapy, that includes data from the clinical studies in patients treated with 80 mg osimertinib, as first line (N=643) [from first line cohort of AURA study, FLAURA and FLAURA2 monotherapy arm], patients who received osimertinib as ≥second-line therapy (833 patients) [from AURA, AURA2, AURA3 studies], or who received osimertinib as adjuvant setting (N=337) [from ADAURA study] for EGFR mutation-positive NSCLC.

In addition, data on the safety from the run-in period of the study FLAURA2 (N=30), study namely its primary analysis dataset (DCO date of 19 February 2020) and the final analysis (DCO date of 03 April 2023) have been provided also to support the safety and tolerability for the proposed indication (osimertinib in combination with pemetrexed and platinum-based chemotherapy for patients with locally advanced or metastatic EGFRm NSCLC).

The pooled patient population used in the integrated safety analysis included patients from the safety datasets in each study. The pooled population did not include patients who were assigned any starting dose other than 80 mg once daily, as well as patients who received osimertinib in combination with any other agent, or patients who crossed over to osimertinib after disease progression on their initial treatment (ie, those randomised to the platinum based chemotherapy arm in the AURA3 study, and those randomised to the standard-of-care arm in the FLAURA study). Data collected from patients who received open label osimertinib upon recurrence in the ADAURA study are also excluded.

Of note, one patient randomised to the osimertinib + chemotherapy arm in the FLAURA2 study received osimertinib only, so is included in the osimertinib arm in the FLAURA2 Safety Analysis Set, and therefore also included in the osimertinib monotherapy safety pool.

Patient exposure

Table 43: Duration of Exposure to Osimertinib

	FLAURA2 Study		Osimertinib monotherapy safety pool (N=1813)
	Osi + Chemo (N=276)	Osimertinib (N=275)	
Total exposure (months) [a]			
Mean (sd)	19.7 (9.05)	18.1 (8.91)	20.8 (13.45)
Median	22.3	19.3	19.3
Min, Max	0.07, 33.84	0.10, 33.77	0.03, 52.24
Total treatment years [b]	452.30	415.30	3142.75
Actual exposure (months) [c]			
Mean (sd)	19.3 (9.03)	17.9 (8.90)	20.6 (13.37)
Median	21.8	19.0	19.1
Min, Max	0.07, 33.38	0.10, 33.77	0.03, 52.24
Total treatment years [b]	444.46	411.29	3107.17
Cumulative actual exposure over time [c]; number (%) of patients			
≥1 day	276 (100)	275 (100)	1813 (100)
≥6 months	238 (86.2)	235 (85.5)	1489 (82.1)
≥12 months	213 (77.2)	198 (72.0)	1208 (66.6)
≥18 months	176 (63.8)	146 (53.1)	950 (52.4)
≥24 months	99 (35.9)	76 (27.6)	704 (38.8)
≥30 months	25 (9.1)	22 (8.0)	543 (30.0)
≥36 months	0	0	240 (13.2)

[a] Total treatment duration=(last dose date - first dose date +1)/(365.25/12).
[b] Total treatment years was calculated by adding the durations for each patient in the treatment group.
[c] Actual treatment duration=total treatment duration, excluding dose interruptions.

A total of 109 patients (39.5%) in the osimertinib + chemotherapy arm received osimertinib for ≥ 24 months, compared to 77 patients (28.0%) in the osimertinib arm of FLAURA2

Table 44: Extent of exposure in FLAURA2 (Randomised period-Safety analysis set)

	Osi + Chemo (N = 276)				
	Osimertinib (n = 276)	Carboplatin/Cisplatin (n = 276)	Pemetrexed (n = 276)	Overall (n = 276) [a]	Osimertinib (N = 275)
All study treatment: Total exposure (months) [b, c]					
Mean (std)	19.67 (9.053)	2.58 (0.742)	12.06 (9.836)	19.80 (9.016)	18.12 (8.908)
Median	22.26	2.76	8.28	22.31	19.32
Min, max	0.1, 33.8	0.7, 4.1	0.7, 33.8	0.7, 33.8	0.1, 33.8
Total treatment years	452.3	59.3	277.3	455.3	415.3
All study treatment: Cumulative total exposure over time					
≥ 1 day	276 (100.0)	276 (100.0)	276 (100.0)	276 (100.0)	275 (100.0)
≥ 1 month	267 (96.7)	253 (91.7)	254 (92.0)	268 (97.1)	274 (99.6)
≥ 3 months	256 (92.8)	45 (16.3)	216 (78.3)	256 (92.8)	256 (93.1)
≥ 12 months	214 (77.5)	0	118 (42.8)	214 (77.5)	200 (72.7)
≥ 24 months	109 (39.5)	0	53 (19.2)	113 (40.9)	77 (28.0)
Osimertinib: Actual exposure (months) [d]					
Mean (std)	19.32 (9.032)	NA	NA	19.36 (9.004)	17.95 (8.904)
Median	21.83	NA	NA	21.83	19.02
Min, max	0.1, 33.4	NA	NA	0.1, 33.4	0.1, 33.8
Total treatment years	444.5	NA	NA	445.3	411.3
Osimertinib: Cumulative actual exposure over time					
≥ 1 day	276 (100.0)	NA	NA	276 (100.0)	275 (100.0)
≥ 1 month	266 (96.4)	NA	NA	266 (96.4)	274 (99.6)
≥ 3 months	255 (92.4)	NA	NA	256 (92.8)	256 (93.1)
≥ 6 months	238 (86.2)	NA	NA	239 (86.6)	235 (85.5)
≥ 12 months	213 (77.2)	NA	NA	213 (77.2)	198 (72.0)
≥ 24 months	99 (35.9)	NA	NA	99 (35.9)	76 (27.6)

[a] Patient received any of the study drugs (osimertinib, cisplatin, carboplatin, or pemetrexed).

Table 45: Osimertinib Dose Modifications (Randomised Period-Safety Analysis Set)

	Osi + Chemo (N = 276)	Osimertinib (N = 275)
	Osimertinib (n = 276)	
Number of patients with a dose modification	150 (54.3)	84 (30.5)
Dose interruptions, n (%)		
Number of patients with a dose interruption	133 (48.2)	76 (27.6)
1 interruption	80 (29.0)	51 (18.5)
2 interruptions	23 (8.3)	13 (4.7)
> 2 interruptions	30 (10.9)	12 (4.4)
Reason for dose interruption [a]		
AE	119 (43.1)	56 (20.4)
Creatinine clearance change	1 (0.4)	0
Lab abnormality not reported as an AE	10 (3.6)	5 (1.8)
Other	15 (5.4)	16 (5.8)
Radiotherapy	2 (0.7)	4 (1.5)
Subject decision	7 (2.5)	4 (1.5)
Surgery	1 (0.4)	2 (0.7)
Technical issue	1 (0.4)	1 (0.4)
Median duration of interruption (days) [b]	13.0	13.0
Minimum-maximum duration of interruption (days) [b]	1, 208	1, 97
Dose reductions, n (%)		
Number of patients with a dose reduction	29 (10.5)	11 (4.0)
1 reduction	29 (10.5)	11 (4.0)
Reason for dose reduction [a]		
AE	27 (9.8)	9 (3.3)
Lab abnormality not reported as an AE	1 (0.4)	1 (0.4)
Other	1 (0.4)	0
Technical issue	0	1 (0.4)

[a] Reasons for dose interruption and reduction are not mutually exclusive for patients with multiple interruptions/reductions, although will be counted only once per category.
[b] If a patient has more than one dose interruption, each interruption is counted separately
DCO: 03 April 2023
Source: Table 14.3.1.3b and Table 14.3.1.5b

Study FLAURA2 Safety Run-in Period

At the DCO date of the final analysis (03 April 2023), the overall duration of exposure to any study treatment in the Safety run-in period Safety Analysis Set ranged from 1.9 to 44.8 months, with a median total exposure of 38.64 months. This corresponds to approximately 3 years of additional exposure compared to the previous DCO (19 February 2020).

Table 46: Extent of exposure (SRI SAS)

	Osi + Carbo + Pem (N=15)				Osi + Cis + Pem (N=15)				Total (N=30)			
	Osi	Carbo	Pem	Overall [a]	Osi	Cis	Pem	Overall [a]	Osi	Carbo / Cis	Pem	Overall [a]
Total exposure (months) [b]												
Mean (sd)	4.88 (1.361)	2.57 (0.646)	4.76 (1.705)	4.88 (1.361)	3.30 (0.712)	2.49 (0.848)	3.22 (1.205)	3.30 (0.712)	4.09 (1.338)	2.53 (0.742)	3.99 (1.649)	4.09 (1.338)
Median	4.63	2.76	4.83	4.63	3.35	2.79	3.09	3.35	3.81	2.76	4.14	3.81
Min, Max	2.7, 7.1	0.7, 3.2	0.7, 7.6	2.7, 7.1	1.9, 5.1	0.7, 3.3	0.7, 5.5	1.9, 5.1	1.9, 7.1	0.7, 3.3	0.7, 7.6	1.9, 7.1
TTY	6.1	3.2	6.0	6.1	4.1	3.1	4.0	4.1	10.2	6.3	10.0	10.2
Actual exposure (months) [c]												
Mean (sd)	4.87 (1.366)	NA	NA	4.87 (1.366)	3.27 (0.740)	NA	NA	3.27 (0.740)	4.07 (1.351)	NA	NA	4.07 (1.351)
Median	4.63	NA	NA	4.63	3.35	NA	NA	3.35	3.76	NA	NA	3.76
Min, Max	2.7, 7.1	NA	NA	2.7, 7.1	1.9, 5,1	NA	NA	1.9, 5.1	1.9, 7.1	NA	NA	1.9, 7.1
TTY	6.1	NA	NA	6.1	4.1	NA	NA	4.1	10.2	NA	NA	10.2
Treatment cycles received												
≥ 1	15 (100)	15 (100)	15 (100)	15 (100)	15 (100)	15 (100)	15 (100)	15 (100)	30 (100)	30 (100)	30 (100)	30 (100)
≥ 2	15 (100)	15 (100)	15 (100)	15 (100)	15 (100)	13 (86.7)	14 (93.3)	15 (100)	30 (100)	28 (93.3)	29 (96.7)	30 (100)
≥ 3	15 (100)	13 (86.7)	14 (93.3)	15 (100)	14 (93.3)	12 (80.0)	13 (86.7)	14 (93.3)	29 (96.7)	25 (83.3)	27 (90.0)	29 (96.7)
≥ 4	15 (100)	13 (86.7)	14 (93.3)	15 (100)	13 (86.7)	10 (66.7)	11 (73.3)	13 (86.7)	28 (93.3)	23 (76.7)	25 (83.3)	28 (93.3)
≥ 6	13 (86.7)	NA	11 (73.3)	13 (86.7)	3 (20.0)	NA	3 (20.0)	3 (20.0)	16 (53.3)	NA	14 (46.7)	16 (53.3)
≥ 8	6 (40.0)	NA	6 (40.0)	6 (40.0)	1 (6.7)	NA	1 (6.7)	1 (6.7)	7 (23.3)	NA	7 (23.3)	7 (23.3)
Median	7.0	4.0	7.0	7.0	5.0	4.0	4.0	5.0	6.0	4.0	5.0	6.0

[a] Received any of the study drugs.
[b] For osimertinib, Total exposure=[min(last dose date where dose > 0 mg, date of death, date of DCO) – first dose date + 1]/30.4375. For Pemetrexed, Cisplatin and Carboplatin, Total exposure=[min(last dose date where dose > 0 mg, date of death, date of DCO) – first dose date + 21]/30.4375.
[c] Actual exposure=[total exposure – total duration of dose interruptions (ie, number of days with dose=0mg)]/30.4375.
Total treatment years is the sum of treatment durations of all subjects by treatment cohort. One subject switched from cisplatin to carboplatin, only exposure to initial treatment (cisplatin) is summarised.
Abbreviations: TTY, total treatment years.

Demographic and other characteristics of the study population

A summary of key demographic characteristics in the pivotal FLAURA2 study, presented alongside data from the osimertinib monotherapy safety pool, is provided in Table 17.

Adverse events

Study FLAURA2 Randomised Period

Safety data are presented for the on-treatment period, ie, 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 treatment, and on or before starting subsequent cancer therapy, whichever is sooner, or until the DCO date.

Table 47: Adverse Events in Any Category

	Number (%) of patients [a]		
	FLAURA2 Study		Osimertinib monotherapy safety pool (N=1813)
	Osi + Chemo (N=276)	Osimertinib (N=275)	
Any AE	**276 (100)**	**268 (97.5)**	**1783 (98.3)**
Any AE, causally related to osimertinib [b]	241 (87.3)	241 (87.6)	1620 (89.4)
Any AE of CTCAE ≥ Grade 3	**176 (63.8)**	**75 (27.3)**	**674 (37.2)**
Any AE of CTCAE ≥ Grade 3, causally related to osimertinib [b]	81 (29.3)	29 (10.5)	254 (14.0)
Any AE with outcome of death	**18 (6.5)**	**8 (2.9) [c]**	**69 (3.8)**
Any AE with outcome of death, causally related to osimertinib [b]	3 (1.1)	1 (0.4)	10 (0.6)

	Number (%) of patients [a]		
	FLAURA2 Study		Osimertinib monotherapy safety pool (N=1813)
	Osi + Chemo (N=276)	Osimertinib (N=275)	
Any SAE (including those with an outcome of death)	**104 (37.7)**	**53 (19.3)**	**521 (28.7)**
Any SAE (including those with an outcome of death), causally related to osimertinib [b]	36 (13.0)	15 (5.5)	109 (6.0)
Any AE leading to discontinuation of osimertinib	**30 (10.9)**	**17 (6.2)**	**194 (10.7)**
Any AE leading to discontinuation of osimertinib, causally related to osimertinib [b]	15 (5.4)	10 (3.6)	120 (6.6)
Any AE leading to dose modification of osimertinib	**131 (47.5)**	**56 (20.4)**	**502 (27.7)**
Any AE leading to dose modification of osimertinib, causally related to osimertinib [b]	77 (27.9)	35 (12.7)	308 (17.0)
Any AE leading to dose reduction of osimertinib	**27 (9.8)**	**8 (2.9)**	**96 (5.3)**
Any AE leading to dose reduction of osimertinib, causally related to osimertinib [b]	25 (9.1)	8 (2.9)	91 (5.0)
Any AE leading to dose interruption of osimertinib	**120 (43.5)**	**52 (18.9)**	**459 (25.3)**
Any AE leading to dose interruption of osimertinib, causally related to osimertinib [b]	63 (22.8)	31 (11.3)	257 (14.2)

[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 assessment, and programmatically derived from individual causality assessments.

[c] Of note, 9 patients are captured as having an AE with a fatal outcome during the treatment period in the osimertinib arm; however only 8 patients are captured in this table. This discrepancy is related to one patient who had an AE that occurred after the start date of subsequent therapy, so did not meet the criteria for inclusion in this table.

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

Common adverse events

Table 48: Most Common AEs, by PT (Reported in ≥10% Patients in Either Treatment Arm of the FLAURA2 Study)

	Number (%) of patients		
	FLAURA2 Study		Osimertinib monotherapy safety pool (N=1813)
MedDRA Preferred Term	Osi + Chemo (N=276)	Osimertinib (N=275)	
Patients with any AE	276 (100)	268 (97.5)	1783 (98.3)
Anaemia	128 (46.4)	22 (8.0)	241 (13.3)
Diarrhoea	120 (43.5)	112 (40.7)	845 (46.6)
Nausea	119 (43.1)	28 (10.2)	319 (17.6)
Decreased appetite	85 (30.8)	26 (9.5)	347 (19.1)
Constipation	82 (29.7)	28 (10.2)	276 (15.2)
Rash	77 (27.9)	57 (20.7)	269 (14.8)
Fatigue	76 (27.5)	26 (9.5)	265 (14.6)
Vomiting	73 (26.4)	17 (6.2)	234 (12.9)
Neutropenia	68 (24.6)	9 (3.3)	109 (6.0)
Stomatitis	68 (24.6)	50 (18.2)	341 (18.8)
Paronychia	65 (23.6)	73 (26.5)	472 (26.0)
Neutrophil count decreased	62 (22.5)	16 (5.8)	124 (6.8)

MedDRA Preferred Term	Number (%) of patients		
	FLAURA2 Study		Osimertinib monotherapy safety pool (N=1813)
	Osi + Chemo (N=276)	Osimertinib (N=275)	
Alanine aminotransferase increased	57 (20.7)	21 (7.6)	143 (7.9)
COVID-19	57 (20.7)	39 (14.2)	42 (2.3)
Platelet count decreased	51 (18.5)	19 (6.9)	161 (8.9)
Thrombocytopenia	51 (18.5)	12 (4.4)	138 (7.6)
Dry skin	50 (18.1)	66 (24.0)	454 (25.0)
Aspartate aminotransferase increased	49 (17.8)	13 (4.7)	145 (8.0)
Blood creatinine increased	46 (16.7)	12 (4.4)	104 (5.7)
White blood cell count decreased	44 (15.9)	18 (6.5)	162 (8.9)
Oedema peripheral	42 (15.2)	12 (4.4)	120 (6.6)
Dermatitis acneiform	37 (13.4)	36 (13.1)	261 (14.4)
Urinary tract infection	36 (13.0)	28 (10.2)	165 (9.1)
Leukopenia	35 (12.7)	11 (4.0)	98 (5.4)
Insomnia	34 (12.3)	18 (6.5)	169 (9.3)
Dizziness	32 (11.6)	16 (5.8)	138 (7.6)
Weight decreased	32 (11.6)	22 (8.0)	146 (8.1)
Cough	31 (11.2)	29 (10.5)	353 (19.5)
Pyrexia	31 (11.2)	15 (5.5)	158 (8.7)
Arthralgia	28 (10.1)	32 (11.6)	259 (14.3)
Pruritus	22 (8.0)	31 (11.3)	311 (17.2)

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

Adverse events by severity

Table 49: Summary of AEs by Maximum Reported CTCAE Grade (Randomised Period – Safety Analysis Set)

Maximum Reported CTCAE Grade	Number (%) of patients	
	Osi + Chemo (N = 276)	Osimertinib (N = 275)
Total	276 (100.0)	268 (97.5)
1	7 (2.5)	48 (17.5)
2	93 (33.7)	145 (52.7)
3	136 (49.3)	63 (22.9)
4	22 (8.0)	3 (1.1)
5	18 (6.5)	9 (3.3) [a]

[a] One patient died one day after the DCO date of the current analysis; a maximum CTCAE Grade 5 event (AE of organising pneumonia) was reported for this patient, however, at the time of the DCO the outcome was recorded as 'not recovered/not resolved' in the clinical database. This patient is therefore not included in the summary of AEs leading to death.

Includes AE with onset date on or after the date of first dose and up to and including 28 days following discontinuation of treatment but prior to the start of a new anti-cancer therapy.

MedDRA version 25.1

DCO: 03 April 2023

Source: Table 14.3.2.6.1b

Table 50**:** AEs of CTCAE Grade 3 or Higher (Reported in ≥ 2 Patients in Either Treatment Arm of the FLAURA2 Study)

MedDRA Preferred Term	Number (%) of patients		
	FLAURA2 Study		Osimertinib monotherapy safety pool (N=1813)
	Osi + Chemo (N=276)	Osimertinib (N=275)	
Patients with any CTCAE ≥ Grade 3 AE	176 (63.8)	75 (27.3)	674 (37.2)
Anaemia	55 (19.9)	1 (0.4)	31 (1.7)
Neutropenia	37 (13.4)	2 (0.7)	17 (0.9)
Neutrophil count decreased	31 (11.2)	2 (0.7)	23 (1.3)
Platelet count decreased	21 (7.6)	0	11 (0.6)
Thrombocytopenia	19 (6.9)	3 (1.1)	10 (0.6)
Febrile neutropenia	11 (4.0)	0	2 (0.1)
White blood cell count decreased	9 (3.3)	1 (0.4)	10 (0.6)
Decreased appetite	8 (2.9)	2 (0.7)	21 (1.2)
Diarrhoea	8 (2.9)	1 (0.4)	26 (1.4)
Ejection fraction decreased	8 (2.9)	3 (1.1)	15 (0.8)
Fatigue	8 (2.9)	1 (0.4)	11 (0.6)
Leukopenia	8 (2.9)	0	8 (0.4)
Pneumonia	6 (2.2)	5 (1.8)	52 (2.9)
Pulmonary embolism	6 (2.2)	3 (1.1)	40 (2.2)
Alanine aminotransferase increased	4 (1.4)	1 (0.4)	25 (1.4)
Dermatitis acneiform	4 (1.4)	2 (0.7)	2 (0.1)
Electrocardiogram QT prolonged	4 (1.4)	1 (0.4)	18 (1.0)
Nausea	4 (1.4)	0	11 (0.6)
Urinary tract infection	4 (1.4)	1 (0.4)	9 (0.5)
Blood creatine phosphokinase increased	3 (1.1)	0	5 (0.3)
COVID-19	3 (1.1)	0	0
Cardiac failure	3 (1.1)	0	3 (0.2)
Lymphopenia	3 (1.1)	0	4 (0.2)
Sepsis	3 (1.1)	2 (0.7)	9 (0.5)
Vomiting	3 (1.1)	0	9 (0.5)
Acute kidney injury	2 (0.7)	1 (0.4)	8 (0.4)
Chronic kidney disease	2 (0.7)	0	1 (0.1)
Colitis	2 (0.7)	0	0
Drug-induced liver injury	2 (0.7)	0	1 (0.1)
Dyspnoea	2 (0.7)	2 (0.7)	21 (1.2)
Embolism	2 (0.7)	1 (0.4)	5 (0.3)
Erythema multiforme	2 (0.7)	0	0
Hepatic function abnormal	2 (0.7)	0	4 (0.2)
Hyponatraemia	2 (0.7)	1 (0.4)	27 (1.5)
Muscular weakness	2 (0.7)	1 (0.4)	2 (0.1)
Paronychia	2 (0.7)	1 (0.4)	7 (0.4)
Weight decreased	2 (0.7)	3 (1.1)	10 (0.6)
COVID-19 pneumonia	1 (0.4)	5 (1.8)	5 (0.3)
Hypertension	1 (0.4)	4 (1.5)	13 (0.7)
Hypokalaemia	1 (0.4)	3 (1.1)	14 (0.8)
Syncope	1 (0.4)	2 (0.7)	7 (0.4)
Chronic obstructive pulmonary disease	0	2 (0.7)	3 (0.2)

MedDRA Preferred Term	Number (%) of patients		
	FLAURA2 Study		Osimertinib monotherapy safety pool (N=1813)
	Osi + Chemo (N=276)	Osimertinib (N=275)	
Dermatitis	0	2 (0.7)	2 (0.1)
Hypertriglyceridaemia	0	2 (0.7)	2 (0.1)
Interstitial lung disease	0	4 (1.5)	13 (0.7)
Lymphocyte count decreased	0	2 (0.7)	17 (0.9)
Mitral valve disease	0	2 (0.7)	2 (0.1)
Pleural effusion	0	3 (1.1)	11 (0.6)

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

Serious adverse event/deaths/other significant events

Serious adverse events (SAEs)

In the FLAURA2 study, a 37.7%patients had experienced an SAE in the osimertinib + chemotherapy arm compared to 19.3% in the osimertinib arm.

Table 51 SAEs, by PT (Reported in ≥ 2 Patients in Either Treatment Arm of the FLAURA2 Study)

MedDRA Preferred Term	Number (%) of patients		
	FLAURA2 Study		Osimertinib monotherapy safety pool (N=1813)
	Osi + Chemo (N=276)	Osimertinib (N=275)	
Patients with any SAE	104 (37.7)	53 (19.3)	521 (28.7)
Anaemia	9 (3.3)	0	5 (0.3)
COVID-19	7 (2.5)	2 (0.7)	2 (0.1)
Pneumonia	7 (2.5)	6 (2.2)	58 (3.2)
Febrile neutropenia	6 (2.2)	0	1 (0.1)
Platelet count decreased	6 (2.2)	0	2 (0.1)
Pulmonary embolism	6 (2.2)	2 (0.7)	33 (1.8)
Decreased appetite	4 (1.4)	1 (0.4)	6 (0.3)
Diarrhoea	4 (1.4)	1 (0.4)	10 (0.6)
Cardiac failure	3 (1.1)	0	3 (0.2)
Nausea	3 (1.1)	0	5 (0.3)
Sepsis	3 (1.1)	2 (0.7)	9 (0.5)
Urinary tract infection	3 (1.1)	1 (0.4)	8 (0.4)
Vomiting	3 (1.1)	0	7 (0.4)
Coronary artery stenosis	2 (0.7)	0	0
COVID-19 pneumonia	2 (0.7)	5 (1.8)	6 (0.3)
Drug-induced liver injury	2 (0.7)	0	2 (0.1)
Embolism	2 (0.7)	1 (0.4)	4 (0.2)
Interstitial lung disease	2 (0.7)	5 (1.8)	19 (1.0)
Nephrolithiasis	2 (0.7)	0	0
Neutrophil count decreased	2 (0.7)	0	1 (0.1)
Pyrexia	2 (0.7)	1 (0.4)	10 (0.6)
Renal failure	2 (0.7)	0	2 (0.1)

MedDRA Preferred Term	Number (%) of patients		
	FLAURA2 Study		Osimertinib monotherapy safety pool (N=1813)
	Osi + Chemo (N=276)	Osimertinib (N=275)	
Ischaemic stroke	2 (0.7)	0	2 (0.1)
Dyspnoea	1 (0.4)	2 (0.7)	15 (0.8)
Pneumothorax	1 (0.4)	3 (1.1)	11 (0.6)
Vertigo	0	2 (0.7)	4 (0.2)
Pleural effusion	0	2 (0.7)	15 (0.8)

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

Deaths

Table 52 Summary of Deaths (Safety Analysis Set)

	Number (%) of patients		
	FLAURA2 Study		Osimertinib monotherapy safety pool (N=1813)
	Osi + Chemo (N=275)	Osimertinib (N=276)	
Total number of deaths	70 (25.4)	77 (28.0)	785 (43.3)
Death related to disease under investigation only	49 (17.8)	64 (23.3)	684 (37.7)
AE with outcome of death only	8 (2.9)	4 (1.5)	42 (2.3)
AE with outcome of death only (AE start date falling after 28 day follow up period)	0	1 (0.4)	5 (0.3)
Number of patients with death related to disease and an AE with outcome of death	10 (3.6)	5 (1.8)	28 (1.5)
Other deaths [a]	3 (1.1)	3 (1.1)	26 (1.4)

[a] Patients who died more than 28 days after the discontinuation of study treatment and who 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 with an outcome of death

There was no notable clustering of events leading to death in either treatment arm. In the osimertinib + chemotherapy arm, the AEs leading to death reported in more than one patient were pneumonia and pulmonary embolism. In the osimertinib arm, the only AE with an outcome of death reported in more than one patient was COVID-19 pneumonia.

Adverse events in the ILD/pneumonitis and cardiac effects (cardiac failure) grouped terms were considered AESIs in the FLAURA2 study. ILD/pneumonitis AEs with a fatal outcome (2 patients; 1 in each treatment arm), and cardiac effects AEs with a fatal outcome (3 patients in the osimertinib + chemotherapy arm).

Table 53. AEs with an Outcome of Death by PT (Reported in ≥ 2 Patients in Either Treatment Arm of the FLAURA2 Study)

MeDRA Preferred Term	Number (%) of patients	
	Osi + Chemo (N=276)	Osimertinib (N=275)
Patients with AE with outcome of death	18 (6.5)	8 (2.9) [a]
Pulmonary embolism	3 (1.1)	0
Pneumonia	3 (1.1)	0
Cardiac failure	2 (0.7)	0
COVID-19 pneumonia	0[b]	4 (1.5)

[a] Of note, 9 patients are captured as having an AE with a fatal outcome during the treatment period in the osimertinib arm; however only 8 patients are captured in this table. This discrepancy is related to the following patients: The patient had an AE that occurred after start date of subsequent therapy, so does not meet the criteria of a TEAE for inclusion in this table. The patient died one day after DCO of the current analysis, and therefore is not included in the summary of AEs leading to death.

[b] On patient in the Osi + Chemo arm had an AE with a fatal outcome recorded as COVID-19 and not COVID-19 pneumonia, and thus was not captured in this table

Includes AEs with an onset date on or after the date of the first dose of study treatment, up to and including the follow-up period, or until the DCO date.

Adverse Events of Special Interest (AESI)

ILD and Pneumonitis

This AESI topic was evaluated by review of grouped PTs, comprising the following MedDRA PTs: interstitial lung disease, pneumonitis, acute interstitial pneumonitis, alveolitis, diffuse alveolar damage, idiopathic pulmonary fibrosis, lung disorder, organising pneumonia, pulmonary toxicity, and pulmonary fibrosis. Collectively, these are referred to as AEs of ILD/pneumonitis for brevity.

Table 54 Summary of ILD and Pneumonitis AESIs

	Number (%) of patients		
	FLAURA2 Study		Osimertinib monotherapy safety pool (N=1813)
	Osi + Chemo (N=276)	Osimertinib (N=275)	
Patients with any ILD/pneumonitis	9 (3.3)	10 (3.6)	73 (4.0)
Patients with any ILD/pneumonitis by maximum CTCAE Grade			
CTCAE Grade 1	2 (0.7)	1 (0.4)	20 (1.1)
CTCAE Grade 2	5 (1.8)	4 (1.5)	28 (1.5)
CTCAE Grade 3	1 (0.4)	3 (1.1)	17 (0.9)
CTCAE Grade 4	0	1 (0.4)	1 (0.1)
CTCAE Grade 5	1 (0.4)	1 (0.4)	7 (0.4) [a]
Patients with any SAE of ILD/pneumonitis	3 (1.1)	6 (2.2)	37 (2.0)
Patients with any AE of ILD/pneumonitis by outcome [b]			
Recovered/resolved	5/9 (55.6)	2/10 (20.0)	38/73 (52.1)
Recovering/resolving	0	3/10 (30.0)	13/73 (17.8)
Recovered/resolved with sequelae	0	1/10 (10.0)	1/73 (1.4)
Not recovered/not resolved	3/9 (33.3)	4/10 (40.0)	15/73 (20.5)
Fatal [c]	1/9 (11.1)	0	6/73 (8.2) [d]
Patients with any AE of ILD/pneumonitis by ethnicity [b]			
Japanese only	7/47 (14.9)	4/46 (8.7)	36/322 (11.2)

Asian and non-Japanese only	0/113 (0)	3/112 (2.7)	17/742 (2.3)
Non-Asian only	2/116 (1.7)	3/117 (2.6)	20/749 (2.7)

[a] Patients with multiple events within the same preferred term are counted under the worst outcome.

[b] Denominator is the number of patients with the outcome for the event.

[c] Outcome of death as recorded on the AE form.

[d] One patient died (AE of organising pneumonia) one day after the DCO date of the current analysis; a maximum CTCAE Grade 5 was reported for this patient, but at the time of DCO, the reported outcome was 'not recovered/not resolved' rather than fatal.

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

Median time to onset of AEs of ILD/pneumonitis was comparable between treatment arms, comprising 161 days (range: 14 to 730 days) in the osimertinib + chemotherapy arm, and 131 days (range: 1 to 485 days) in the osimertinib arm. The median duration of AEs of ILD/pneumonitis was 92 days (range: 22 to 673 days) in the osimertinib + chemotherapy arm and 79.5 days (range: 12 to 587 days) in the osimertinib arm.

Table 55: Summary of ILD and Pneumonitis AESIs (Grouped Term) (Randomised Period-Safety Analysis Set)

	Osi + Chemo (N = 276)		Osimertinib (N = 275)	
	Number (%) of patients	Rate per 100 patient-years [a]	Number (%) of patients	Rate per 100 patient-years [a]
Any AE of ILD/pneumonitis	9 (3.3)	2.0	10 (3.6)	2.4
Any SAE of ILD/pneumonitis	3 (1.1)	0.7	6 (2.2)	1.4
Any AE of ILD/pneumonitis leading to discontinuation of any study drug	8 (2.9)	1.7	10 (3.6)	2.4
Discontinuation of osimertinib [b]	8 (2.9)	1.7	10 (3.6)	2.4
Discontinuation of carboplatin/cisplatin	1 (0.4)	0.2	NA	NA
Discontinuation of pemetrexed	4 (1.4)	0.9	NA	NA
Any CTCAE ≥ Grade 3 AE of ILD/pneumonitis	2 (0.7)	0.4	5 (1.8)	1.2
Any AE of ILD/pneumonitis related to any study drug	7 (2.5)	1.5	10 (3.6)	2.4
Related to osimertinib	7 (2.5)	1.5	10 (3.6)	2.4
Related to carboplatin/cisplatin	0	0	NA	NA
Related to pemetrexed	4 (1.4)	0.9	NA	NA

[a] Number of patients with AEs divided by the total patient years multiplied by 100.

[b] As per CSP, osimertinib discontinuation was recommended for all patients with ILD/pneumonitis. Of note, one patient with an AE of organising pneumonia in the osimertinib + chemotherapy arm had an action taken of "dose not changed" with osimertinib, carboplatin/cisplatin, and pemetrexed. This event was also reported as not related to any study treatment by the reporting Investigator.

Total patient-years is the sum of the duration on treatment (including safety follow-up period if discontinued the study treatment) across all patients in given treatment group. Safety follow-up = min((last dose date +28), date of first new anti-cancer therapy, date of withdrawal of consent, date of death, DCO) – first dose date +1. Total patient years was 460.1 in the osimertinib + chemotherapy arm and 425.5 in the osimertinib arm.

DCO: 03 April 2023

Cardiac Effects (Cardiac failure)

This AESI topic is evaluated by the review of both Investigator-reported AEs (from the MedDRA SMQs of Cardiac failure and Cardiomyopathy) assessed in conjunction with changes in cardiac contractility (via

LVEF) observed during study treatment (hereafter referred to as AEs indicative of cardiac failure for brevity), to identify any clinically significant risks to patients. Individual patients could be represented in more than one subgroup.

The CSP specifically excluded enrolment of patients with any factors that would increase the risk of QTc prolongation, including heart failure. At study entry, 25 patients (9.0%) in the osimertinib + chemotherapy arm and 26 patients (9.4%) in the osimertinib arm had medical history within the Cardiac Disorders SOC. A medical history of hypertension was also reported for 196 patients (35.2%), which was balanced between treatment arms.

Changes in cardiac contractility - LVEF measurements over time

Assessment of LVEF was performed by echocardiography/MUGA scans at screening, every 12 weeks whilst on study treatment (and whenever clinically indicated), and at treatment discontinuation.

In the osimertinib + chemotherapy arm, median LVEF at baseline was 65.0%, which remained stable over time, with a lowest recorded median LVEF value of 64.0%. In the osimertinib arm, median LVEF was 66.0% at baseline, which remained stable over time, with a lowest recorded median LVEF value of 64.0%.

Table 56: Absolute Change in LVEF Data During Treatment

	Number (%) of patients		
	FLAURA2 Study		Osimertinib monotherapy safety pool (N=1813)
	Osi + Chemo (N=276)	Osimertinib (N=275)	
Subject with both baseline value and at least one on-treatment assessment [a]	262 (94.9)	266 (96.7)	1557 (85.9)
LVEF outlier category			
≥ 10 percentage points decrease from baseline and absolute value < 50% [a,b]	21 (8.0)	8 (3.0)	65 (4.2)
≥ 15 percentage points decrease from baseline and absolute value ≥ 50% [a,b]	31 (11.8)	21 (7.9)	120 (7.7)

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

[b] Occurring at the same echocardiography assessment, at any post-baseline time point. Baseline is defined as the last non-missing measurement prior to dosing with osimertinib Percentages have been calculated using the number of patients with a baseline and post-baseline echocardiography assessment.

Review of cardiac effects (cardiac failure) AEs

In the FLAURA2 study, a numerical difference in the incidence of AEs indicative of cardiac failure was observed between the osimertinib + chemotherapy arm (26 patients [9.4%]) and the osimertinib arm (10 patients [3.6%]), corresponding to an AE incidence rate of 5.7 per 100 patient-years and 2.1 per 100 patient-years, respectively. This difference was primarily driven by the PTs of ejection fraction decreased and cardiac failure; all other PTs were reported infrequently.

Table 57 Cardiac Effects AESIs by PT

MedDRA Preferred Term	Number (%) of patients		
	FLAURA2 Study		Osimertinib monotherapy safety pool (N=1813)
	Osi + Chemo (N=276)	Osimertinib (N=275)	
Patients with any cardiac effects	26 (9.4)	10 (3.6)	68 (3.8)
Ejection fraction decreased	17 (6.2)	9 (3.3)	53 (2.9)

MedDRA Preferred Term	Number (%) of patients		
	FLAURA2 Study		Osimertinib monotherapy safety pool (N=1813)
	Osi + Chemo (N=276)	Osimertinib (N=275)	
Cardiac failure	5 (1.8)	1 (0.4)	9 (0.5)
Brain natriuretic peptide decreased	2 (0.7)	1 (0.4)	2 (0.1)
Pulmonary oedema	2 (0.7)	0	4 (0.2)
Cardiac failure chronic	0	0	1 (0.1)
Cardiac failure congestive	0	0	1 (0.1)
Atrial septal defect acquired	1 (0.4)	0	0
Cardiomyopathy	1 (0.4)	0	2 (0.1)
Congestive cardiomyopathy	1 (0.4)	0	0

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

The majority of patients the osimertinib + chemotherapy arm (22/26 patients) and all patients in the osimertinib arm (10/10 patients) had non-serious AEs indicative of cardiac failure. Upon review, the majority of AEs indicative of cardiac failure were reported as resolved or resolving at the current DCO date, without requiring a dose modification (AEs indicative of cardiac failure that led to a dose modification of any study treatment were reported for 7 patients [2.5%] in the osimertinib + chemotherapy arm and 4 patients [1.5%] in the osimertinib arm.

Serious AEs indicative of cardiac failure were reported only in the osimertinib + chemotherapy arm (4 patients [1.4%]). Of these, one patient had a CTCAE Grade 3 AE of cardiac failure which was considered serious due to requiring or prolonging hospitalisation, and which subsequently resolved after a dose reduction of carboplatin and pemetrexed (osimertinib was continued without any change). The remaining 3 patients had fatal (CTCAE Grade 5) AEs, 2 AEs of cardiac failure and one of pulmonary oedema; all in the osimertinib + chemotherapy arm, and one reported in the osimertinib monotherapy safety pool (cardiac failure congestive).

Table 58: Summary of Cardiac Effects AESIs (Grouped Term) (Randomised Period – Safety Analysis Set)

	Osi + Chemo (N = 276)		Osimertinib (N = 275)	
	Number (%) of patients	Rate per 100 patient-years	Number (%) of patients	Rate per 100 patient-years
Any AE of cardiac effects	26 (9.4)	5.7	10 (3.6)	2.4
Any SAE of cardiac effects	4 (1.4)	0.9	0	0
Any AE of cardiac effects leading to discontinuation of any study drug	5 (1.8)	1.1	0	0
Discontinuation of osimertinib	4 (1.4)	0.9	0	0
Discontinuation of carboplatin/cisplatin	1 (0.4)	0.2	NA	NA
Discontinuation of pemetrexed	2 (0.7)	0.4	NA	NA
Any CTCAE ≥ Grade 3 AE of cardiac effects	12 (4.3)	2.6	3 (1.1)	0.7
Any AE of cardiac effects related to any study drug	17 (6.2)	3.7	6 (2.2)	1.4
Related to osimertinib	16 (5.8)	3.5	6 (2.2)	1.4
Related to carboplatin/cisplatin	3 (1.1)	0.7	NA	NA
Related to pemetrexed	5 (1.8)	1.1	NA	NA

DCO: 03 April 2023
Source: Table 14.3.2.12.1b, Table 14.3.2.12.4b, Table 14.3.2.12.3.1b, Table 14.3.2.12.3.2b, Table 14.3.2.12.3.3b, Table 14.3.2.12.3.4b, Table 14.3.2.12.6b, Table 14.3.2.12.2.1b, Table 14.3.2.12.2.2b, Table 14.3.2.12.2.3b, and Table 14.3.2.12.2.4b

Haematological toxicities

This AESI topic is evaluated by the review of investigator-reported haematological AEs in the MedDRA SMQ of Haematopoetic cytopenias, in order to identify any clinically significant risks to patients.

Deteriorations as compared to baseline in protocol-mandated laboratory values were only to be reported as AEs if they fulfilled any SAE criteria, were the reason for study treatment discontinuation, or were considered to be clinically relevant (eg, may have required treatment or a non-planned study visit, or may have required modification in the dose or schedule of any study drug) as judged by the investigator.

Overall, in the FLAURA2 study, an incidence of AEs in the haematological toxicities grouped term were reported in 197 patients [71.4%] in the osimertinib + chemotherapy arm compared to 66 patients [24.0%] in the osimertinib arm.

Table 59: Summary of Haematological Toxicity AESIs

	Number (%) of patients		
	FLAURA2 Study		Osimertinib monotherapy safety pool (N=1813)
	Osi + Chemo (N=276)	Osimertinib (N=275)	
Patients with any AE of haematological toxicities	197 (71.4)	66 (24.0)	636 (35.1)
Patients with any SAE of haematological toxicities	23 (8.3)	1 (0.4)	13 (0.7)
Patients with any haematological toxicities by maximum CTCAE Grade			
Maximum CTCAE Grade 1	15 (5.4)	29 (10.5)	243 (13.4)
Maximum CTCAE Grade 2	60 (21.7)	27 (9.8)	279 (15.4)
Maximum CTCAE Grade 3	107 (38.8)	10 (3.6)	112 (6.2)
Maximum CTCAE Grade 4	15 (5.4)	0	2 (0.1)
Maximum CTCAE Grade 5	0	0	0

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

Table 60: Summary of Haematological Toxicity AESIs (Grouped Term) (Randomised Period- Safety Analysis Set)

	Osi + Chemo (N = 276)		Osimertinib (N = 275)	
	Number (%) of patients	Rate per 100 patient-years	Number (%) of patients	Rate per 100 patient-years
Any AE of haematological toxicities	197 (71.4)	42.8	66 (24.0)	15.5
Any SAE of haematological toxicities	23 (8.3)	5.0	1 (0.4)	0.2
Any AE of haematological toxicities leading to discontinuation of any study drug	47 (17.0)	10.2	0	0
Discontinuation of osimertinib	0	0	0	0
Discontinuation of carboplatin/cisplatin	18 (6.5)	3.9	NA	NA
Discontinuation of pemetrexed	42 (15.2)	9.1	NA	NA
Any CTCAE ≥ Grade 3 haematological toxicities	122 (44.2)	26.5	10 (3.6)	2.4
Any AE of haematological toxicities related to any study drug	186 (67.4)	40.4	59 (21.5)	13.9
Related to osimertinib	90 (32.6)	19.6	59 (21.5)	13.9
Related to carboplatin/cisplatin	152 (55.1)	33.0	NA	NA
Related to pemetrexed	173 (62.7)	37.6	NA	NA

DCO: 03 April 2023
Source: Table 14.3.2.12.1b, Table 14.3.2.12.4b, Table 14.3.2.12.3.1b, Table 14.3.2.12.3.2b, Table 14.3.2.12.3.3b, Table 14.3.2.12.3.4b, Table 14.3.2.12.6b, Table 14.3.2.12.2.1b, Table 14.3.2.12.2.2b, Table 14.3.2.12.2.3b, and Table 14.3.2.12.2.4b

Table 61: Haematological Toxicity AESIs by PT (Reported in ≥ 1% of Patients in Either Treatment Arm of the FLAURA2 Study)

MedDRA Preferred Term	Number (%) of patients		
	FLAURA2 Study		Osimertinib monotherapy safety pool (N=1813)
	Osi + Chemo (N=276)	Osimertinib (N=275)	
Patients with any haematological toxicities	197 (71.4)	66 (24.0)	636 (35.1)
Anaemia	128 (46.4)	22 (8.0)	241 (13.3)
Neutropenia	68 (24.6)	9 (3.3)	109 (6.0)
Neutrophil count decreased	62 (22.5)	16 (5.8)	124 (6.8)
Platelet count decreased	51 (18.5)	19 (6.9)	161 (8.9)
Thrombocytopenia	51 (18.5)	12 (4.4)	138 (7.6)
White blood cell count decreased	44 (15.9)	18 (6.5)	162 (8.9)
Leukopenia	35 (12.7)	11 (4.0)	98 (5.4)
Lymphocyte count decreased	13 (4.7)	13 (4.7)	48 (2.6)
Febrile neutropenia	11 (4.0)	0	2 (0.1)
Lymphopenia	7 (2.5)	3 (1.1)	30 (1.7)

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.

AEs Indicative of anaemia, neutropenia, and thrombocytopenia

In the FLAURA2 study, in the overall study population (FAS), 82 patients (29.4%) in the osimertinib + chemotherapy arm and 3 patients (1.1%) in the osimertinib arm received concomitant treatment with colony stimulating factors as either prophylaxis, or as treatment for an AE or haematological laboratory abnormality. Furthermore, red blood cell transfusion, platelet transfusion and transfusion (not otherwise specified) were reported for 29 patients (10.4%), 3 patients (1.1%), and 17 patients (6.1%), respectively, in the osimertinib + chemotherapy arm, with one patient (0.4%) in the osimertinib arm receiving a red blood cell transfusion.

Table 62: Summary of AEs by Haematopoietic Cytopenia Group

Group MedDRA Preferred Term	Number (%) of patients		
	FLAURA2 Study		Osimertinib monotherapy safety pool (N=1813)
	Osi + Chemo (N=276)	Osimertinib (N=275)	
Patients with any AE in haematopoietic cytopenia group	193 (69.9)	57 (20.7)	562 (31.0)
AEs indicative of anaemia	**129 (46.7)**	**22 (8.0)**	**249 (13.7)**
Anaemia	128 (46.4)	22 (8.0)	241 (13.3)
Haemoglobin decreased	2 (0.7)	0	12 (0.7)
Maximum CTCAE Grade 3 [a]	55 (19.9)	1 (0.4)	33 (1.8)
Maximum CTCAE Grade 4 [a]	0	0	0
Any SAEs indicative of anaemia	9 (3.3)	0	6 (0.3)
Any AEs indicative of anaemia leading to discontinuation of osimertinib	0	0	1 (0.1)
Concomitant medication received [b]			
Yes	59 (45.7)	5 (22.7)	71 (28.5)
No	70 (54.3)	17 (77.3)	178 (71.5)
AEs indicative of thrombocytopenia	**87 (31.5)**	**28 (10.2)**	**288 (15.9)**

Group MedDRA Preferred Term	Number (%) of patients		
	FLAURA2 Study		Osimertinib monotherapy safety pool (N=1813)
	Osi + Chemo (N=276)	Osimertinib (N=275)	
Thrombocytopenia	51 (18.5)	12 (4.4)	138 (7.6)
Platelet count decreased	51 (18.5)	19 (6.9)	161 (8.9)
Maximum CTCAE Grade 3 [a]	32 (11.6)	3 (1.1)	20 (1.1)
Maximum CTCAE Grade 4 [a]	6 (2.2)	0	1 (0.1)
Any SAEs indicative of thrombocytopenia	7 (2.5)	0	4 (0.2)
Any AEs indicative of thrombocytopenia leading to discontinuation of osimertinib	0	0	0
Concomitant medication received [b]			
Yes	41 (47.1)	7 (25.0)	27 (9.4)
No	46 (52.9)	21 (75.0)	261 (90.6)
AEs indicative of neutropenia	**114 (41.3)**	**25 (9.1)**	**218 (12.0)**
Neutropenia	68 (24.6)	9 (3.3)	109 (6.0)
Neutrophil count decreased	62 (22.5)	16 (5.8)	124 (6.8)
Maximum CTCAE Grade 3 [a]	52 (18.8)	4 (1.5)	37 (2.0)
Maximum CTCAE Grade 4 [a]	12 (4.3)	0	2 (0.1)
Any SAEs indicative of neutropenia	3 (1.1)	0	2 (0.1)
Any AEs indicative of neutropenia leading to discontinuation of osimertinib	0	0	2 (0.1)
Concomitant medication received [b]			
Yes	53 (46.5)	2 (8.0)	28 (12.8)
No	61 (53.5)	23 (92.0)	190 (87.2)

[a] Each patient has only been represented with the maximum reported CTCAE grade for each preferred term.
[b] Patients summarised as having received treatment if treatment has been received for at least one AE. Denominator is the number of patients with any AE in the haematopoietic cytopenia group.

Patients with multiple events in the same term are counted only once in that term. Patients with events in more than one term are counted once in each of those terms.

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.

Adverse Drug Reactions (ADRs)

A summary of data pertaining to the frequency and severity of designated osimertinib ADRs in the osimertinib + chemotherapy arm of FLAURA2 and the osimertinib monotherapy safety pool is provided in the table below. It is noted that dependent on their nature, ADRs are characterised either by AE incidence, clinically relevant QT prolongation parameters, or worsening CTCAE grade shifts for specific laboratory parameters.

In total, at least one ADR was reported by 94.2% of patients in the osimertinib + chemotherapy arm and 86.5% of patients in the osimertinib arm of the FLAURA2 study, and 89.4% of patients in the osimertinib monotherapy safety pool.

The most commonly reported ADRs (occurring in ≥ 20% of patients) in the osimertinib + chemotherapy arm of the FLAURA2 study were rash, diarrhoea, stomatitis, paronychia, and dry skin; these ADRs were reported with a similar frequency in the osimertinib arm of FLAURA2, and in the osimertinib monotherapy safety pool.

Table 63 Summary of ADR Frequency Determinations

ADR	FLAURA2 Study												Osimertinib monotherapy safety pool (N=1813)					
	Osi + chemotherapy arm (N=276)						Osimertinib arm (N=275)											
	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	Any	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Patients with any AE designated as an ADR	260 (94.2)	57 (20.7)	104 (37.7)	82 (29.7)	16 (5.8)	1 (0.4)	238 (86.5)	113 (41.1)	104 (37.8)	19 (6.9)	1 (0.4)	1 (0.4)	1621 (89.4)	746 (41.1)	698 (38.5)	167 (9.2)	3 (0.2)	7 (0.4)
Aplastic anaemia	0	0	0	0	0	0	0	0	0	0	0	0	1 (0.1)	0	0	1 (0.1)	0	0
Leukopenia	35 (12.7)	7 (2.5)	20 (7.6)	8 (2.9)	0	0	11 (4.0)	10 (3.6)	1 (0.4)	0	0	0	98 (5.4)	40 (2.2)	50 (2.8)	8 (0.4)	0	0
Lymphopenia	7 (2.5)	1 (0.4)	3 (1.1)	3 (1.1)	0	0	3 (1.1)	2 (0.7)	1 (0.4)	0	0	0	30 (1.7)	13 (0.7)	13 (0.7)	4 (0.2)	0	0
Thrombocytopenia	51 (18.5)	19 (6.9)	13 (4.7)	16 (5.8)	3 (1.1)	0	12 (4.4)	6 (2.2)	3 (1.1)	3 (1.1)	0	0	138 (7.6)	101 (5.6)	27 (1.5)	10 (0.6)	0	0
Neutropenia	68 (24.6)	4 (1.5)	27 (9.8)	30 (10.9)	7 (2.5)	0	9 (3.3)	3 (1.1	4 (1.5)	2 (0.7)	0	0	109 (6.0)	34 (1.9)	58 (3.2)	17 (0.9)	0	0
Decreased appetite	85 (30.8)	49 (17.8)	28 (10.1)	8 (2.9)	0	0	26 (9.5)	18 (6.6)	6 (2.2)	2 (0.7)	0	0	347 (19.1)	234 (12.9)	92 (5.1)	21 (1.2)	0	0
Cardiac failure	5 (1.8)	1 (0.4)	1 (0.4)	1 (0.4)	0	2 (0.7)	1 (0.4)	0	1 (0.4)	0	0	0	9 (0.5)	1 (0.1)	5 (0.3)	3 (0.2)	0	0
Epistaxis	20 (7.2)	16 (5.8)	3 (1.1)	1 (0.4)	0	0	18 (6.5)	16 (5.8)	2 (0.7)	0	0	0	114 (6.3)	110 (6.1)	4 (0.2)	0	0	0
Interstitial lung disease [a]	9 (3.3)	2 (0.7)	5 (1.8)	1 (0.4)	0	1 (0.4)	10 (3.6)	1 (0.4)	4 (1.5)	3 (1.1)	1 (0.4)	1 (0.4) [k]	73 (4.0)	20 (1.1)	28 (1.5)	17 (0.9)	1 (0.1)	7 (0.4) [k]
Diarrhoea	120 (43.5)	83 (30.1)	29 (10.5)	8 (2.9)	0	0	112 (40.7)	89 (32.4)	22 (8.0)	1 (0.4)	0	0	845 (46.6)	663 (36.6)	156 (8.6)	26 (1.4)	0	0
Stomatitis [b]	86 (31.2)	53 (19.2)	32 (11.6)	1 (0.4)	0	0	59 (21.5)	39 (14.2)	19 (6.9)	1 (0.4)	0	0	432 (23.8)	321 (17.7)	103 (5.7)	8 (0.4)	0	0
Keratitis [c]	2 (0.7)	1 (0.4)	1 (0.4)	0	0	0	0	0	0	0	0	0	10 (0.6)	3 (0.2)	6 (0.3)	1 (0.1)	0	0
Rash [d]	135 (48.9)	89 (32.2)	39 (14.1)	7 (2.5)	0	0	121 (44.0)	87 (31.6)	30 (10.9)	4 (1.5)	0	0	836 (46.1)	665 (36.7)	156 (8.6)	15 (0.8)	0	0
Paronychia [e]	75 (27.2)	35 (12.7)	38 (13.8)	2 (0.7)	0	0	87 (31.6)	50 (18.2)	36 (13.1)	1 (0.4)	0	0	609 (33.6)	380 (21.0)	221 (12.2)	8 (0.4)	0	0

Table 63 Summary of ADR Frequency Determinations

ADR	FLAURA2 Study												Osimertinib monotherapy safety pool (N=1813)					
Dry skin [f]	65 (23.6)	54 (19.6)	11 (4.0)	0	0	0	84 (30.5)	74 (26.9)	10 (3.6)	0	0	0	580 (32.0)	501 (27.6)	77 (4.2)	2 (0.1)	0	0
Pruritus [g]	22 (8.0)	17 (6.2)	5 (1.8)	0	0	0	31 (11.3)	30 (10.9)	1 (0.4)	0	0	0	311 (17.2)	256 (14.1)	54 (3.0)	1 (0.1)	0	0
Alopecia	24 (8.7)	22 (8.0)	2 (0.7)	0	0	0	15 (5.5)	14 (5.1)	1 (0.4)	0	0	0	90 (5.0)	79 (4.4)	11 (0.6)	0	0	0
Urticaria	4 (1.4)	2 (0.7)	1 (0.4)	1 (0.4)	0	0	4 (1.5)	1 (0.4)	3 (1.1)	0	0	0	35 (1.9)	19 (1.0)	14 (0.8)	2 (0.1)	0	0
Palmar-plantar erythrodysaesthesia syndrome	15 (5.4)	10 (3.6)	5 (1.8)	0	0	0	9 (3.3)	7 (2.5)	2 (0.7)	0	0	0	38 (2.1)	31 (1.7)	7 (0.4)	0	0	0
Erythema multiforme	4 (1.4)	2 (0.7)	0	2 (0.7)	0	0	1 (0.4)	1 (0.4)	0	0	0	0	6 (0.3)	4 (0.2)	2 (0.1)	0	0	0
Toxic epidermal necrolysis [h]	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Cutaneous vasculitis [h]	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Stevens-Johnson syndrome [h]	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Blood creatine phosphokinase increased	9 (3.3)	6 (2.2)	0	2 (0.7)	1 (0.4)	0	9 (3.3)	5 (1.8)	4 (1.5)	0	0	0	34 (1.9)	21 (1.2)	8 (0.4)	5 (0.3)	0	0
Myositis	0	0	0	0	0	0	1 (0.4)	1 (0.4)	0	0	0	0	3 (0.2)	3 (0.2)	0	0	0	0

Number (%) of patients who had a QTcF prolongation > 500msec			
QTc interval prolongation [i]	5 (1.8)	5 (1.8)	20 (1.1)
Left ventricular ejection fraction decreased	21 (8.0)	8 (3.0)	65 (4.2)

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**	***n***	**Any**	**1-grade**	**2-grade**	**3-grade**	**4-grade**

Table 63 Summary of ADR Frequency Determinations

ADR	FLAURA2 Study												Osimertinib monotherapy safety pool (N=1813)					
Leucocytes decreased [j]	***275***	241 (87.6)	70 (25.5)	116 (42.2)	48 (17.5)	7 (2.5)	***275***	147 (53.5)	105 (38.2)	33 (12.0)	8 (2.9)	1 (0.4)	***1787***	1157 (64.7)	823 (46.1)	302 (16.9)	29 (1.6)	3 (0.2)
Lymphocytes decreased [j]	***275***	214 (77.8)	65 (23.6)	106 (38.5)	39 (14.2)	4 (1.5)	***275***	151 (54.9)	69 (25.1)	64 (23.3)	15 (5.5)	3 (1.1)	***1786***	1139 (63.8)	517 (28.9)	475 (26.6)	133 (7.4)	14 (0.8)
Platelet count decreased [j]	***275***	235 (85.5)	147 (53.5)	43 (15.6)	34 (12.4)	11 (4.0)	***275***	121 (44.0)	107 (38.9)	9 (3.3)	3 (1.1)	2 (0.7)	***1794***	953 (53.1)	876 (48.8)	54 (3.0)	14 (0.8)	9 (0.5)
Neutrophils decreased [j]	***275***	233 (84.7)	60 (21.8)	74 (26.9)	74 (26.9)	25 (9.1)	***275***	111 (40.4)	60 (21.8)	38 (13.8)	11 (4.0)	2 (0.7)	***1787***	635 (35.5)	290 (16.2)	273 (15.3)	64 (3.6)	8 (0.4)
Blood creatinine increased [j]	***275***	60 (21.8)	42 (15.3)	17 (6.2)	0	1 (0.4)	***275***	23 (8.4)	23 (8.4)	0	0	0	***1793***	153 (8.5)	139 (7.8)	11 (0.6)	3 (0.2)	0

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

[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 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: 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.

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

[g] Includes cases reported within the clustered terms: pruritus, eyelids 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 ECG findings (QTcF value > 500 ms at any time during treatment), not of reported AEs.

[j] Represents the incidence of laboratory findings, not of reported AEs.

[k] One patient died (AE of organising pneumonia) one day after the DCO date of the current analysis; a maximum CTCAE Grade 5 was reported for this patient, but at the time of DCO, the reported outcome was 'not recovered/not resolved' rather than fatal.

Adverse events FLAURA2 Safety Run-in Period

Table 64: Adverse Events in Any Category in the FLAURA2 Safety Run-in Period (Safety Analysis Set)

Adverse event category	Number (%) of patients [a]		
	Osi + Carbo + Pem (N=15)	Osi + Cis + Pem (N=15)	Total (N=30)
Any AE	**15 (100)**	**14 (93.3)**	**29 (96.7)**
Any AE possibly causally related to treatment [b]	15 (100)	14 (93.3)	29 (96.7)
Causally related to osimertinib	14 (93.3)	11 (73.3)	25 (83.3)
Causally related to carboplatin/cisplatin	13 (86.7)	12 (80.0)	25 (83.3)
Causally related to pemetrexed	14 (93.3)	13 (86.7)	27 (90.0)
Any AE of CTCAE Grade 3 or higher	**5 (33.3)**	**10 (66.7)**	**15 (50.0)**
Any AE of CTCAE Grade 3 or higher, causally related to treatment [b]	3 (20.0)	7 (46.7)	10 (33.3)
Causally related to osimertinib	0	2 (13.3)	2 (6.7)
Causally related to carboplatin/cisplatin	3 (20.0)	6 (40.0)	9 (30.0)
Causally related to pemetrexed	3 (20.0)	6 (40.0)	9 (30.0)
Any AE with outcome of death	**2 (13.3)**	**0**	**2 (6.7)**
Any AE with outcome of death, causally related to treatment [b]	0	0	0
Any SAE (including events with outcome of death)	**5 (33.3)**	**6 (40.0)**	**11 (36.7)**
All SAEs (including events with outcome of death), possibly causally related to treatment [b]	1 (6.7)	2 (13.3)	3 (10.0)
Causally related to osimertinib	0	0	0
Causally related to carboplatin/cisplatin	1 (6.7)	2 (13.3)	3 (10.0)
Causally related to pemetrexed	1 (6.7)	1 (6.7)	2 (6.7)
Any AE leading to discontinuation of any study drug	**7 (46.7)**	**4 (26.7)**	**11 (36.7)**
Leading to osimertinib discontinuation	1 (6.7)	0	1 (3.3)
Leading to carboplatin/cisplatin discontinuation	2 (13.3)	2 (13.3)	4 (13.3)
Leading to pemetrexed discontinuation	6 (40.0)	4 (26.7)	10 (33.3)

[p] 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.

[q] As assessed by the investigator. Causally related to any study drug.

Included AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of treatment or the day before first administration of crossover treatment.
MedDRA version 25.1.
DCO: 03 April 2023

Dose modifications (interruption/delay and/or reduction) of any study treatment due to AEs were reported in 17 patients (56.7%): 8 patients (53.3%) in the osi carbo pem cohort, and 9 patients (60.0%) in the osi cis pem cohort. AEs leading to dose reductions were reported for one patient (6.7%) in the osi-carb-pem cohort (pemetrexed reduction) and 1 patient (6.7%) in the osi-cis-pem cohort (osimertinib reduction).

On a population level, decreases from baseline in median values for key haematological parameters (haemoglobin, leucocytes, platelets, and neutrophils) were observed early in treatment. These median values appeared to stabilise after an initial decrease, with the majority of patients experiencing 1 or 2 CTCAE grade shifts.

Although there was an increase in the absolute levels of creatinine, median values remained stable until the end of treatment and were within the normal range, and there were no clinically meaningful changes in creatinine clearance over time.

With an additional approximate 3 years of safety data collected from the DCO date of the primary analysis to the time of the final analysis, there were few newly reported deaths (1 additional patient [6.7%], unrelated to treatment), SAEs (5 additional patients [16.7%]; all unrelated to treatment), AEs of CTCAE Grade ≥ 3 (4 additional patients [13.3%]; all unrelated to treatment), and DAEs (4 additional patients [13.3%]; all related to pemetrexed only).

Laboratory findings

Haematology

Table 65: Haematology, Maximum Worsening CTCAE Grade Shift (Decreases) From Baseline During Treatment

Parameter	Number (%) of patients with CTCAE grade shift [a]																	
	Osi + Chemo (N=276)						Osimertinib (N=275)						Osimertinib monotherapy safety pool (N=1813)					
	N	Any grade shift	1-grade shift	2-grade shift	3-grade shift	4-grade shift	N	Any grade shift	1-grade shift	2-grade shift	3-grade shift	4-grade shift	N	Any grade shift	1-grade shift	2-grade shift	3-grade shift	4-grade shift
Haemoglobin (g/L)	**275**	257 (93.5)	134 (48.7)	89 (32.4)	34 (12.4)	0	**275**	154 (56.0)	144 (52.4)	8 (2.9)	2 (0.7)	0	**1794**	929 (51.8)	823 (45.9)	94 (5.2)	12 (0.7)	0
Leukocytes (10^9/L)	**275**	241 (87.6)	70 (25.5)	116 (42.2)	48 (17.5)	7 (2.5)	**275**	147 (53.5)	105 (38.2)	33 (12.0)	8 (2.9)	1 (0.4)	**1787**	1157 (64.7)	823 (46.1)	302 (16.9)	29 (1.6)	3 (0.2)
Platelets (10^9/L)	**275**	235 (85.5)	147 (53.5)	43 (15.6)	34 (12.4)	11 (4.0)	**275**	121 (44.0)	107 (38.9)	9 (3.3)	3 (1.1)	2 (0.7)	**1794**	953 (53.1)	876 (48.8)	54 (3.0)	14 (0.8)	9 (0.5)
Neutrophils (10^9/L)	**275**	233 (84.7)	60 (21.8)	74 (26.9)	74 (26.9)	25 (9.1)	**275**	111 (40.4)	60 (21.8)	38 (13.8)	11 (4.0)	2 (0.7)	**1787**	635 (35.5)	290 (16.2)	273 (15.3)	64 (3.6)	8 (0.4)
Lymphocytes (10^9/L)	**275**	214 (77.8)	65 (23.6)	106 (38.5)	39 (14.2)	4 (1.5)	**275**	151 (54.9)	69 (25.1)	64 (23.3)	15 (5.5)	3 (1.1)	**1786**	1139 (63.8)	517 (28.9)	475 (26.6)	133 (7.4)	14 (0.8)

[a] Includes all on-treatment assessments (after the first dose administration of study drug and up to and including 28 days following discontinuation of treatment).

Baseline is defined as the last result obtained prior to the start of study treatment.

Percentages have been calculated using the number of patients (n) with a baseline value and at least one on-treatment value.

Only worsening shifts in CTCAE grade are included (where the maximum on-treatment CTCAE grade > baseline CTCAE grade).

Clinical Chemistry

- **General clinical chemistry**

Table 66: Clinical chemistry, Maximum Worsening CTCAE Grade Shift From Baseline During Treatment (Randomised Period – Safety Analysis Set)

Parameter	Number of patients with CTCAE Grade shift [a], n (%)											
	Osi + Chemo (N = 276)						Osimertinib (N = 275)					
	N	Any Grade shift	1-Grade shift	2-Grade shift	3-Grade shift	4-Grade shift	N	Any Grade shift	1-Grade shift	2-Grade shift	3-Grade shift	4-Grade shift
Sodium (mmol/L) (increased)	275	24 (8.7)	22 (8.0)	2 (0.7)	0	0	275	27 (9.8)	27 (9.8)	0	0	0
Sodium (mmol/L) (decreased)	275	137 (49.8)	104 (37.8)	14 (5.1)	17 (6.2)	2 (0.7)	275	78 (28.4)	57 (20.7)	9 (3.3)	12 (4.4)	0
Potassium (mmol/L) (increased)	275	48 (17.5)	38 (13.8)	8 (2.9)	2 (0.7)	0	275	49 (17.8)	44 (16.0)	4 (1.5)	1 (0.4)	0
Potassium (mmol/L) (decreased)	275	84 (30.5)	73 (26.5)	1 (0.4)	10 (3.6)	0	275	39 (14.2)	32 (11.6)	2 (0.7)	5 (1.8)	0
Glucose (mmol/L)	273	36 (13.2)	32 (11.7)	3 (1.1)	0	1 (0.4)	275	31 (11.3)	27 (9.8)	3 (1.1)	0	1 (0.4)
Albumin (g/L)	274	95 (34.7)	77 (28.1)	17 (6.2)	1 (0.4)	0	275	54 (19.6)	44 (16.0)	9 (3.3)	1 (0.4)	0
Magnesium (mmol/L) (increased)	274	8 (2.9)	0	0	8 (2.9)	0	275	5 (1.8)	0	0	5 (1.8)	0
Magnesium (mmol/L) (decreased)	274	149 (54.4)	147 (53.6)	2 (0.7)	0	0	275	74 (26.9)	73 (26.5)	0	0	1 (0.4)

[a] Includes all on-treatment assessments.
Baseline is defined as the last result obtained prior to the start of study treatment. Percentages have been calculated using the number of patients (n) with a baseline value and at least one on-treatment value. Only worsening shifts in CTCAE Grade are included (where the maximum on-treatment CTCAE Grade > baseline CTCAE Grade). All laboratory parameters with CTCAE grades are included.
DCO: 03 April 2023
Source: Table 14.3.7.1.3b

- **Hepatic biochemistry**

At baseline, 9.0% of patients in the osimertinib + chemotherapy arm and 8.3% of patients in the osimertinib arm had a medical history of hepatobiliary disorders. Furthermore, 15.4% of patients in the osimertinib + chemotherapy arm, and 23.7% of patients in the osimertinib arm had liver metastases at baseline (based on the FAS).

In both treatment arms, all patients had hepatic biochemistry parameters assessed as CTCAE Grade 0 (normal) at baseline, which generally remained at Grades 0 or 1 for the majority of patients in both treatment arms while on study treatment.

A higher proportion of patients in the osimertinib + chemotherapy arm had grade shifts for AST (70.2%) and ALT (63.1%) than in the osimertinib arm (41.1% and 26.4%, respectively); most were 1-grade or 2-grade shifts. Alkaline phosphatase and total bilirubin grade shifts were less frequently reported and were similar between the treatment arms.

  - **Hepatic biochemistry AEs**

Adverse events in the Hepatobiliary SOC were reported in 25 patients (9.1%) in the osimertinib + chemotherapy arm, and in 7 patients (2.5%) in the osimertinib arm. The most commonly reported AEs within this SOC were hepatic function abnormal (9 patients [3.3%] in the osimertinib + chemotherapy arm, and 3 patients [1.1%] in the osimertinib arm) and hypertransaminasaemia (6 patients [2.2%] in the osimertinib + chemotherapy arm, and 2 patients [0.7%] in the osimertinib arm).

Hepatic AEs which led to study treatment discontinuation were only reported in the osimertinib + chemotherapy arm and included one event each of bile duct stone, hepatic function abnormal, hepatotoxicity and hypertransaminasaemia

The following AEs in the Investigation SOC relating to hepatic biochemistry parameters were more commonly reported in the osimertinib + chemotherapy arm than in the osimertinib arm:

ALT increased (56 patients [20.3%] vs 21 patients [7.6%], respectively). One event of ALT increased in the osimertinib + chemotherapy arm led to study drug discontinuation.

AST increased (48 patients [17.4%] vs 13 patients [4.7%], respectively). One event of AST increased in the osimertinib + chemotherapy arm led to study drug discontinuation

Transaminases increased (10 patients [3.6%] vs 2 patients [0.7%], respectively).

One AE of ALT increased and one AE of AST increased in the osimertinib + chemotherapy arm led to discontinuation of any study drug.

In total, 28 patients (22 patients in the osimertinib + chemotherapy arm and 6 patients in the osimertinib arm) met the biochemical criteria for potential drug induced liver injury. Of these, the biochemical definition of potential Hy's law was met for 5 patients (3 patients in the osimertinib + chemotherapy arm, and 2 patients in the osimertinib arm). Upon review, clear alternative aetiologies for the elevations in liver biochemistry parameters were identified for all 5 patients, and consequently none of the potential Hy's Law cases were assessed as confirmed Hy's Law.

Table 67: Liver Function Tests, Maximum Worsening CTCAE Grade Shift From Baseline During Treatment

Parameter	Number (%) of patients with CTCAE grade shift [a], n (%)																	
	Osi + Chemo (N=276)						Osimertinib (N=275)						Osimertinib monotherapy safety pool (N=1813)					
	N	Any grade shift	1-grade shift	2-grade shift	3-grade shift	4-grade shift	N	Any grade shift	1-grade shift	2-grade shift	3-grade shift	4-grade shift	N	Any grade shift	1-grade shift	2-grade shift	3-grade shift	4-grade shift
ALT (µkat/L)	**275**	193 (70.2)	125 (45.5)	41 (14.9)	24 (8.7)	3 (1.1)	**275**	113 (41.1)	87 (31.6)	16 (5.8)	9 (3.3)	1 (0.4)	**1792**	702 (39.2)	532 (29.7)	90 (5.0)	72 (4.0)	8 (0.4)
AST (µkat/L)	**274**	173 (63.1)	151 (55.1)	14 (5.1)	7 (2.6)	1 (0.4)	**273**	71 [b] (26.0)	65 [b] (23.8)	4 (1.5)	1 (0.4)	1 (0.4)	**1789**	510 (28.5)	449 (25.1)	34 (1.9)	26 (1.5)	1 (0.1)
Total bilirubin (µmol/L)	**273**	79 (28.9)	44 (16.1)	28 (10.3)	7 (2.6)	0	**275**	75 (27.3)	42 (15.3)	27 (9.8)	3 (1.1)	3 (1.1)	**1791**	271 (15.1)	198 (11.1)	60 (3.4)	8 (0.4)	5 (0.3)

[a] Includes assessments on or after the date of first dose and up to and including 28 days following discontinuation of randomised treatment. Baseline is defined as the last result obtained prior to the start of study treatment. Percentages have been calculated using the number of patients (n) with a baseline value and at least one on-treatment value. Only worsening shifts in CTCAE grade are included (where the maximum on-treatment CTCAE grade > baseline CTCAE grade).

[b] In the FLAURA2 CSR, one additional patient is counted here (see Table 65, FLAURA2 – Randomised period CSR, Module 5.3.5.1) because of a different method for deriving the on-treatment period for CTCAE grade shifts (calculated as actual last dose date [from exposure form] +28 days for the Clinical Summary versus end of treatment date +28 days for the CSR.

- **Renal biochemistry**

Table 68: Creatinine, Maximum Worsening CTCAE Grade Shift From Baseline During Treatment

	N	Number (%) of patients with CTCAE grade shift [a]				
		Any grade shift	1-grade shift	2-grade shift	3-grade shift	4-grade shift
FLAURA2 Study: Osi + Chemo arm (N=276)	275	60 (21.8)	42 (15.3)	17 (6.2)	0	1 (0.4)
FLAURA2 Study: Osimertinib arm (N=275)	275	23 (8.4)	23 (8.4)	0	0	0
Osimertinib monotherapy safety pool (N=1813)	1793	153 (8.5)	139 (7.8)	11 (0.6)	3 (0.2)	0

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

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

- **Renal biochemistry AEs**

Adverse events in the Renal and urinary disorders SOC were reported for 52 patients (18.8%) in the osimertinib + chemotherapy arm and 26 patients (9.5%) in the osimertinib arm. No PTs were reported in >5% of patients and no specific clustering of PTs was noted.

In the Investigations SOC, 13 patients (4.7%) in the osimertinib + chemotherapy arm had PTs of creatinine renal clearance decreased; none were reported in the osimertinib arm. Blood creatinine increased was also reported for more patients in the osimertinib + chemotherapy arm (46 patients [16.7%]) than in the osimertinib arm (12 patients [4.4%]), as were AEs of glomerular filtration rate decreased (4 patients [1.4%] vs 1 patient [0.4%]) and glomerular filtration rate abnormal (1 patient [0.4%] vs no patients).

Electrocardiogram data

At a study population level, no clinically significant change in median QTcF interval was noted in either treatment arm over the course of the FLAURA2 study.

The proportion of patients who experienced a QTcF of > 500 msec with a > 60 msec increase from baseline was similar between the treatment arms (5 patients [1.8%] in the osimertinib + chemotherapy arm and 4 patients [1.5%] in the osimertinib arm).

In the osimertinib monotherapy safety pool, 0.7% of patients experienced a QTcF of > 500 msec with a > 60 msec increase from baseline.

In the FLAURA2 study, 24 patients (8.7%) in the osimertinib + chemotherapy arm and 23 patients (8.4%) in the osimertinib arm had an AE of electrocardiogram QT prolonged, which is a previously identified ADR for osimertinib; this was consistent with the osimertinib monotherapy safety pool (7.1% of patients)

No AEs of arrhythmia as a consequence of drug-induced QTc prolongation were reported in the FLAURA2 study.

Safety in special populations

Intrinsic Factors

Effect of Gender

Table 69: Adverse Events in Any Category and AESIs by Grouped Term - Patient Level by Gender

	Number (%) of patients					
	Male			Female		
	FLAURA2 Study			FLAURA2 Study		
	Osi + Chemo (N=104)	Osi (N=107)	Osi mono safety pool (N=641)	Osi + Chemo (N=172)	Osi (N=168)	Osi mono safety pool (N=1172)
Any AE	104 (100)	105 (98.1)	631 (98.4)	172 (100)	163 (97.0)	1152 (98.3)
Any AE of ≥ CTCAE Grade 3	58 (55.8)	33 (30.8)	242 (37.8)	118 (68.6)	42 (25.0)	432 (36.9)
Any AE with outcome of death	8 (7.7)	3 (2.8)	25 (3.9)	10 (5.8)	5 (3.0)	44 (3.8)
Any SAE (including events with outcome of death)	41 (39.4)	21 (19.6)	194 (30.3)	63 (36.6)	32 (19.0)	327 (27.9)
Any AE leading to discontinuation of osimertinib	13 (12.5)	10 (9.3)	80 (12.5)	17 (9.9)	7 (4.2)	114 (9.7)
Any AE leading to dose modification of osimertinib	47 (45.2)	23 (21.5)	159 (24.8)	84 (48.8)	33 (19.6)	343 (29.3)
Any AE leading to dose reduction of osimertinib	5 (4.8)	4 (3.7)	20 (3.1)	22 (12.8)	4 (2.4)	76 (6.5)
Any AE leading to dose interruption of osimertinib	46 (44.2)	21 (19.6)	148 (23.1)	74 (43.0)	31 (18.5)	311 (26.5)
Any AESI	81 (77.9)	33 (30.8)	233 (36.3)	127 (73.8)	47 (28.0)	499 (42.6)
Cardiac Effects (Cardiac Failure)	14 (13.5)	5 (4.7)	23 (3.6)	12 (7.0)	5 (3.0)	45 (3.8)
Haematological Toxicities	76 (73.1)	26 (24.3)	197 (30.7)	121 (70.3)	40 (23.8)	439 (37.5)
ILD and Pneumonitis	4 (3.8)	6 (5.6)	31 (4.8)	5 (2.9)	4 (2.4)	42 (3.6)

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.

Table 70: Summary of AEs by PT (Reported in ≥ 20% Patients of Either Gender in the FLAURA2 Study) - Patient Level by Gender

	Number (%) of patients					
	Male			Female		
	FLAURA2 Study			FLAURA2 Study		
MedDRA PT	Osi + Chemo (N=104)	Osi (N=107)	Osi mono safety pool (N=641)	Osi + Chemo (N=172)	Osi (N=168)	Osi mono safety pool (N=1172)
Any AE	104 (100)	105 (98.1)	631 (98.4)	172 (100)	163 (97.0)	1152 (98.3)
Anaemia	49 (47.1)	5 (4.7)	54 (8.4)	79 (45.9)	17 (10.1)	187 (16.0)
Diarrhoea	44 (42.3)	42 (39.3)	279 (43.5)	76 (44.2)	70 (41.7)	566 (48.3)
Nausea	41 (39.4)	9 (8.4)	88 (13.7)	78 (45.3)	19 (11.3)	231 (19.7)
Rash	**38 (36.5)**	**19 (17.8)**	**98 (15.3)**	**39 (22.7)**	**38 (22.6)**	**171 (14.6)**
Decreased appetite	34 (32.7)	12 (11.2)	115 (17.9)	51 (29.7)	14 (8.3)	232 (19.8)
Fatigue	28 (26.9)	10 (9.3)	91 (14.2)	48 (27.9)	16 (9.5)	174 (14.8)
Constipation	27 (26.0)	14 (13.1)	102 (15.9)	55 (32.0)	14 (8.3)	174 (14.8)
Platelet count decreased	24 (23.1)	10 (9.3)	71 (11.1)	27 (15.7)	9 (5.4)	90 (7.7)
Neutropenia	23 (22.1)	2 (1.9)	16 (2.5)	45 (26.2)	7 (4.2)	93 (7.9)
Stomatitis	23 (22.1)	18 (16.8)	110 (17.2)	45 (26.2)	32 (19.0)	231 (19.7)
Vomiting	23 (22.1)	5 (4.7)	60 (9.4)	50 (29.1)	12 (7.1)	174 (14.8)
Paronychia	**21 (20.2)**	**21 (19.6)**	**139 (21.7)**	**44 (25.6)**	**52 (31.0)**	**333 (28.4)**
Neutrophil count decreased	20 (19.2)	3 (2.8)	29 (4.5)	42 (24.4)	13 (7.7)	95 (8.1)
COVID-19	16 (15.4)	14 (13.1)	14 (2.2)	41 (23.8)	25 (14.9)	28 (2.4)
ALT increased	17 (16.3)	8 (7.5)	61 (9.5)	40 (23.3)	13 (7.7)	82 (7.0)
Dry skin	**13 (12.5)**	**17 (15.9)**	**139 (21.7)**	**37 (21.5)**	**49 (29.2)**	**315 (26.9)**

Patients with multiple events in the same preferred term are counted only once in that preferred term. Patients with events in more than one preferred term are counted once in each of those preferred terms.
Preferred terms presented in order of frequency in male patients in the osimertinib + chemotherapy arm of the FLAURA2 study.
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.☐Bolding indicates that the PT has a ≥ 10% difference between genders in one or both of the treatment arms of the FLAURA2 study.

Effect of Age

In the FLAURA2 study, the overall AE incidence and incidence of each of the AE categories generally increased with increasing age group in both treatment arms. The safety profile by age at the AE category level in the osimertinib arm of the FLAURA2 study showed alignment with the osimertinib monotherapy safety pool.

The profile of AESIs by age group in the osimertinib arm of the FLAURA2 study showed alignment with the overall safety profile.

Table 71: Adverse Events in Any Category and AESIs by Grouped Term - Patient Level by Age

	Number (%) of patients								
	<65 years			65 to74 years			≥ 75 years		
	FLAURA2 Study			FLAURA2 Study			FLAURA2 Study		
	Osi + Chemo (N=172)	Osi (N=164)	Osi mono safety pool (N=1043)	Osi + Chemo (N=81)	Osi (N=88)	Osi mono safety pool (N=563)	Osi + Chemo (N=23)	Osi (N=23)	Osi mono safety pool (N=207)
Any AE	172 (100)	160 (97.6)	1026 (98.4)	81 (100)	85 (96.6)	551 (97.9)	23 (100)	23 (100)	206 (99.5)
Any AE of ≥ CTCAE Grade 3	105 (61.0)	37 (22.6)	340 (32.6)	57 (70.4)	26 (29.5)	219 (38.9)	14 (60.9)	12 (52.2)	115 (55.6)
Any AE with outcome of death	6 (3.5)	4 (2.4)	31 (3.0)	8 (9.9)	3 (3.4)	19 (3.4)	4 (17.4)	1 (4.3)	19 (9.2)
Any SAE (including events with outcome of death)	64 (37.2)	23 (14.0)	250 (24.0)	28 (34.6)	21 (23.9)	181 (32.1)	12 (52.2)	9 (39.1)	90 (43.5)
Any AE leading to discontinuation of osimertinib	11 (6.4)	7 (4.3)	76 (7.3)	11 (13.6)	9 (10.2)	75 (13.3)	8 (34.8)	1 (4.3)	43 (20.8)
Any AE leading to dose modification of osimertinib	74 (43.0)	29 (17.7)	238 (22.8)	44 (54.3)	19 (21.6)	167 (29.7)	13 (56.5)	8 (34.8)	97 (46.9)
Any AE leading to dose reduction of osimertinib	12 (7.0)	4 (2.4)	47 (4.5)	9 (11.1)	2 (2.3)	31 (5.5)	6 (26.1)	2 (8.7)	18 (8.7)
Any AE leading to dose interruption of osimertinib	68 (39.5)	27 (16.5)	219 (21.0)	41 (50.6)	19 (21.6)	152 (27.0)	11 (47.8)	6 (26.1)	88 (42.5)
Any AESI	127 (73.8)	49 (29.9)	408 (39.1)	63 (77.8)	22 (25.0)	224 (39.8)	18 (78.3)	9 (39.1)	100 (48.3)
Cardiac Effects (Cardiac Failure)	15 (8.7)	4 (2.4)	26 (2.5)	9 (11.1)	4 (4.5)	29 (5.2)	2 (8.7)	2 (8.7)	13 (6.3)
Haematological Toxicities	125 (72.7)	43 (26.2)	365 (35.0)	58 (71.6)	17 (19.3)	189 (33.6)	14 (60.9)	6 (26.1)	82 (39.6)
ILD and Pneumonitis	1 (0.6)	5 (3.0)	36 (3.5)	3 (3.7)	4 (4.5)	27 (4.8)	5 (21.7)	1 (4.3)	10 (4.8)

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.
Source: Table 2.7.4.s2bs and Table 2.7.4.s6bs, FLAURA2 Pooled Analysis, Module 5.3.5.3.

Table 72: Summary of AEs by PT (Reported in ≥ 20% Patients in Any Age Group in the FLAURA2 Study) – Patient Level by Age Group

MedDRA PT	Number (%) of patients								
	<65 years			65 to 74 years			≥ 75 years		
	FLAURA2 Study			FLAURA2 Study			FLAURA2 Study		
	Osi + Chemo (N=172)	Osi (N=164)	Osi mono safety pool (N=1043)	Osi + Chemo (N=81)	Osi (N=88)	Osi mono safety pool (N=563)	Osi + Chemo (N=23)	Osi (N=23)	Osi mono safety pool (N=207)
Any AE	172 (100)	160 (97.6)	1026 (98.4)	81 (100)	85 (96.6)	551 (97.9)	23 (100)	23 (100)	206 (99.5)
Nausea	**78 (45.3)**	**15 (9.1)**	**191 (18.3)**	**29 (35.8)**	**10 (11.4)**	**95 (16.9)**	**12 (52.2)**	**3 (13.0)**	**33 (15.9)**
Anaemia	**77 (44.8)**	**10 (6.1)**	**113 (10.8)**	**43 (53.1)**	**11 (12.5)**	**86 (15.3)**	**8 (34.8)**	**1 (4.3)**	**42 (20.3)**
Diarrhoea	**70 (40.7)**	**69 (42.1)**	**495 (47.5)**	**40 (49.4)**	**38 (43.2)**	**255 (45.3)**	**10 (43.5)**	**5 (21.7)**	**95 (45.9)**
Fatigue	51 (29.7)	19 (11.6)	150 (14.4)	20 (24.7)	6 (6.8)	84 (14.9)	5 (21.7)	1 (4.3)	31 (15.0)
Constipation	50 (29.1)	15 (9.1)	157 (15.1)	26 (32.1)	10 (11.4)	83 (14.7)	6 (26.1)	3 (13.0)	36 (17.4)
ALT increased	**48 (27.9)**	**15 (9.1)**	**84 (8.1)**	**9 (11.1)**	**6 (6.8)**	**45 (8.0)**	**0**	**0**	**14 (6.8)**
Rash	**47 (27.3)**	**37 (22.6)**	**167 (16.0)**	**20 (24.7)**	**16 (18.2)**	**75 (13.3)**	**10 (43.5)**	**4 (17.4)**	**27 (13.0)**
Neutropenia	**46 (26.7)**	**5 (3.0)**	**70 (6.7)**	**14 (17.3)**	**2 (2.3)**	**30 (5.3)**	**8 (34.8)**	**2 (8.7)**	**9 (4.3)**
Neutrophil count decreased	**46 (26.7)**	**11 (6.7)**	**78 (7.5)**	**16 (19.8)**	**4 (4.5)**	**33 (5.9)**	**0**	**1 (4.3)**	**13 (6.3)**
Vomiting	**45 (26.2)**	**7 (4.3)**	**138 (13.2)**	**19 (23.5)**	**6 (6.8)**	**62 (11.0)**	**9 (39.1)**	**4 (17.4)**	**34 (16.4)**
Decreased appetite	**44 (25.6)**	**14 (8.5)**	**160 (15.3)**	**31 (38.3)**	**10 (11.4)**	**123 (21.8)**	**10 (43.5)**	**2 (8.7)**	**64 (30.9)**
COVID-19	**42 (24.4)**	**24 (14.6)**	**26 (2.5)**	**12 (14.8)**	**11 (12.5)**	**12 (2.1)**	**3 (13.0)**	**4 (17.4)**	**4 (1.9)**
AST increased	**40 (23.3)**	**10 (6.1)**	**89 (8.5)**	**9 (11.1)**	**3 (3.4)**	**40 (7.1)**	**0**	**0**	**16 (7.7)**
Paronychia	**40 (23.3)**	**41 (25.0)**	**279 (26.7)**	**22 (27.2)**	**29 (33.0)**	**147 (26.1)**	**3 (13.0)**	**3 (13.0)**	**46 (22.2)**
Stomatitis	40 (23.3)	32 (19.5)	201 (19.3)	23 (28.4)	15 (17.0)	108 (19.2)	5 (21.7)	3 (13.0)	32 (15.5)
Dry skin	32 (18.6)	40 (24.4)	255 (24.4)	15 (18.5)	19 (21.6)	152 (27.0)	3 (13.0)	7 (30.4)	47 (22.7)
Thrombocytopenia	**29 (16.9)**	**7 (4.3)**	**70 (6.7)**	**14 (17.3)**	**3 (3.4)**	**49 (8.7)**	**8 (34.8)**	**2 (8.7)**	**19 (9.2)**
Blood creatinine increased	27 (15.7)	5 (3.0)	44 (4.2)	17 (21.0)	5 (5.7)	42 (7.5)	2 (8.7)	2 (8.7)	18 (8.7)
Oedema peripheral	**25 (14.5)**	**7 (4.3)**	**54 (5.2)**	**11 (13.6)**	**4 (4.5)**	**42 (7.5)**	**6 (26.1)**	**1 (4.3)**	**24 (11.6)**

Patients with multiple events in the same preferred term are counted only once in that preferred term. Patients with events in more than one preferred term are counted once in each of those preferred terms.
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.
Preferred terms presented in order of frequency in the < 65 years age category in the osimertinib + chemotherapy arm of the FLAURA2 study.
Bolding indicates that the PT has a ≥ 10% difference between any age group in one or both of the treatment arms of the FLAURA2 study.
Source: Table 2.7.4.s3bs, FLAURA2 Pooled Analysis, Module 5.3.5.3.

Effect of Race

Table 73: Adverse Events in Any Category and AESIs by Grouped Term - Patient Level by Race

	Number (%) of patients					
	Asian			Non-Asian		
	FLAURA2 Study			FLAURA2 Study		
	Osi + Chemo (N=176)	Osi (N=176)	Osi mono safety pool (N=1170)	Osi + Chemo (N=100)	Osi (N=99)	Osi mono safety pool (N=635)
Any AE	176 (100)	175 (99.4)	1163 (99.4)	100 (100)	93 (93.9)	612 (96.4)
Any AE of ≥ CTCAE Grade 3	117 (66.5)	43 (24.4)	426 (36.4)	59 (59.0)	32 (32.3)	246 (38.7)
Any AE with outcome of death	9 (5.1)	2 (1.1)	36 (3.1)	9 (9.0)	6 (6.1)	33 (5.2)
Any SAE (including events with outcome of death)	74 (42.0)	29 (16.5)	305 (26.1)	30 (30.0)	24 (24.2)	214 (33.7)
Any AE leading to discontinuation of osimertinib	16 (9.1)	11 (6.3)	123 (10.5)	14 (14.0)	6 (6.1)	71 (11.2)
Any AE leading to dose modification of osimertinib	75 (42.6)	28 (15.9)	329 (28.1)	56 (56.0)	28 (28.3)	171 (26.9)
Any AE leading to dose reduction of osimertinib	11 (6.3)	4 (2.3)	67 (5.7)	16 (16.0)	4 (4.0)	29 (4.6)
Any AE leading to dose interruption of osimertinib	71 (40.3)	26 (14.8)	300 (25.6)	49 (49.0)	26 (26.3)	157 (24.7)
Any AESI	137 (77.8)	58 (33.0)	510 (43.6)	71 (71.0)	22 (22.2)	219 (34.5)
Cardiac Effects (Cardiac Failure)	17 (9.7)	5 (2.8)	43 (3.7)	9 (9.0)	5 (5.1)	25 (3.9)
Haematological Toxicities	128 (72.7)	51 (29.0)	446 (38.1)	69 (69.0)	15 (15.2)	187 (29.4)
ILD and Pneumonitis	7 (4.0)	7 (4.0)	54 (4.6)	2 (2.0)	3 (3.0)	19 (3.0)

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.

Of note, there was a higher incidence of AEs of ILD/pneumonitis in Japanese patients.

Table 74: Summary of AEs by PT (Reported in ≥ 20% Patients in Either Race Category in the FLAURA2 Study) - Patient Level by Race

MedDRA PT	Number (%) of patients					
	Asian			Non-Asian		
	FLAURA2 Study			FLAURA2 Study		
	Osi + Chemo (N=176)	Osi (N=176)	Osi mono safety pool (N=1170)	Osi + Chemo (N=100)	Osi (N=99)	Osi mono safety pool (N=635)
Any AE	176 (100)	175 (99.4)	1163 (99.4)	100 (100)	93 (93.9)	612 (96.4)
Anaemia	87 (49.4)	19 (10.8)	165 (14.1)	41 (41.0)	3 (3.0)	76 (12.0)
Diarrhoea	**70 (39.8)**	**73 (41.5)**	**540 (46.2)**	**50 (50.0)**	**39 (39.4)**	**300 (47.2)**
Nausea	**67 (38.1)**	**12 (6.8)**	**169 (14.4)**	**52 (52.0)**	**16 (16.2)**	**148 (23.3)**
Neutrophil count decreased	**58 (33.0)**	**16 (9.1)**	**115 (9.8)**	**4 (4.0)**	**0**	**8 (1.3)**
Constipation	56 (31.8)	17 (9.7)	170 (14.5)	26 (26.0)	11 (11.1)	104 (16.4)
Decreased appetite	56 (31.8)	17 (9.7)	216 (18.5)	29 (29.0)	9 (9.1)	130 (20.5)
Stomatitis	**53 (30.1)**	**42 (23.9)**	**267 (22.8)**	**15 (15.0)**	**8 (8.1)**	**71 (11.2)**
Paronychia	**50 (28.4)**	**56 (31.8)**	**374 (32.0)**	**15 (15.0)**	**17 (17.2)**	**94 (14.8)**
Rash	48 (27.3)	35 (19.9)	184 (15.7)	29 (29.0)	22 (22.2)	85 (13.4)
Platelet count decreased	**47 (26.7)**	**17 (9.7)**	**131 (11.2)**	**4 (4.0)**	**2 (2.0)**	**30 (4.7)**
ALT increased	**45 (25.6)**	**14 (8.0)**	**102 (8.7)**	**12 (12.0)**	**7 (7.1)**	**41 (6.5)**
Vomiting	44 (25.0)	12 (6.8)	143 (12.2)	29 (29.0)	5 (5.1)	91 (14.3)
White blood cell count decreased	**43 (24.4)**	**18 (10.2)**	**156 (13.3)**	**1 (1.0)**	**0**	**6 (0.9)**
AST increased	**41 (23.3)**	**9 (5.1)**	**105 (9.0)**	**8 (8.0)**	**4 (4.0)**	**40 (6.3)**
COVID-19	38 (21.6)	27 (15.3)	27 (2.3)	19 (19.0)	12 (12.1)	15 (2.4)
Dry skin	33 (18.8)	40 (22.7)	309 (26.4)	17 (17.0)	26 (26.3)	143 (22.5)
Fatigue	**33 (18.8)**	**11 (6.3)**	**124 (10.6)**	**43 (43.0)**	**15 (15.2)**	**141 (22.2)**
Neutropenia	**33 (18.8)**	**3 (1.7)**	**60 (5.1)**	**35 (35.0)**	**6 (6.1)**	**47 (7.4)**
Thrombocytopenia	30 (17.0)	8 (4.5)	67 (5.7)	21 (21.0)	4 (4.0)	71 (11.2)
Urinary tract infection	**15 (8.5)**	**15 (8.5)**	**91 (7.8)**	**21 (21.0)**	**13 (13.1)**	**74 (11.7)**

Patients with multiple events in the same preferred term are counted only once in that preferred term. Patients with events in more than one preferred term are counted once in each of those preferred terms.
Preferred terms presented in order of frequency in Asian patients in the osimertinib + chemotherapy arm of the FLAURA2 study.
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.
Bolding indicates that the PT has a ≥ 10% difference between the race categories in one or both of the treatment arms of the FLAURA2 study.

Effect of performance status

In the FLAURA2 study, the overall AE incidence and incidence of each of the AE categories generally increased in patients with restricted activity compared to those with normal activity in both treatment

arms. The difference between WHO PS categories was ≥ 10% for SAEs in both treatment arms, and for AEs of ≥ CTCAE grade 3 and AEs leading to dose interruption of osimertinib in the osimertinib arm.

Table 75: Adverse Events in Any Category and AESIs by Grouped Term - Patient Level by WHO performance status

	Number (%) of patients					
	Normal activity			Restricted activity		
	FLAURA2 Study			FLAURA2 Study		
	Osi + Chemo (N=103)	Osi (N=101)	Osi mono safety pool (N=590)	Osi + Chemo (N=172)	Osi (N=174)	Osi mono safety pool (N=812)
Any AE	103 (100)	98 (97.0)	578 (98.0)	172 (100)	170 (97.7)	797 (98.2)
Any AE of ≥ CTCAE grade 3	61 (59.2)	20 (19.8)	152 (25.8)	115 (66.9)	55 (31.6)	333 (41.0)
Any AE with outcome of death	5 (4.9)	0	4 (0.7)	13 (7.6)	8 (4.6)	41 (5.0)
Any SAE (including events with outcome of death)	32 (31.1)	13 (12.9)	119 (20.2)	72 (41.9)	40 (23.0)	243 (29.9)
Any AE leading to discontinuation of osimertinib	12 (11.7)	2 (2.0)	54 (9.2)	18 (10.5)	15 (8.6)	102 (12.6)
Any AE leading to dose modification of osimertinib	44 (42.7)	24 (23.8)	162 (27.5)	86 (50.0)	32 (18.4)	220 (27.1)
Any AE leading to dose reduction of osimertinib	13 (12.6)	4 (4.0)	39 (6.6)	14 (8.1)	4 (2.3)	39 (4.8)
Any AE leading to dose interruption of osimertinib	37 (35.9)	21 (20.8)	144 (24.4)	82 (47.7)	31 (17.8)	200 (24.6)
Any AESI	76 (73.8)	23 (22.8)	216 (36.6)	131 (76.2)	57 (32.8)	337 (41.5)
Cardiac Effects (Cardiac Failure)	10 (9.7)	4 (4.0)	29 (4.9)	16 (9.3)	6 (3.4)	30 (3.7)
Haematological Toxicities	68 (66.0)	19 (18.8)	176 (29.8)	128 (74.4)	47 (27.0)	295 (36.3)
ILD and Pneumonitis	4 (3.9)	2 (2.0)	28 (4.7)	5 (2.9)	8 (4.6)	30 (3.7)

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.

Table 76: Summary of AEs by PT (Reported in ≥ 20% Patients in Either WHO PS Category in the FLAURA2 Study) - Patient Level by WHO PS

	Number (%) of patients					
	Normal activity			Restricted activity		
	FLAURA2 Study			FLAURA2 Study		
MedDRA PT	Osi + Chemo (N=103)	Osi (N=101)	Osi mono safety pool (N=590)	Osi + Chemo (N=172)	Osi (N=174)	Osi mono safety pool (N=812)
Any AE	103 (100)	98 (97.0)	578 (98.0)	172 (100)	170 (97.7)	797 (98.2)
Diarrhoea	**55 (53.4)**	**42 (41.6)**	**275 (46.6)**	**65 (37.8)**	**70 (40.2)**	**373 (45.9)**
Nausea	42 (40.8)	15 (14.9)	74 (12.5)	76 (44.2)	13 (7.5)	146 (18.0)
Anaemia	**40 (38.8)**	**6 (5.9)**	**54 (9.2)**	**88 (51.2)**	**16 (9.2)**	**118 (14.5)**
Paronychia	**36 (35.0)**	**28 (27.7)**	**171 (29.0)**	**29 (16.9)**	**45 (25.9)**	**200 (24.6)**
Rash	**36 (35.0)**	**23 (22.8)**	**69 (11.7)**	**40 (23.3)**	**34 (19.5)**	**94 (11.6)**
Stomatitis	**35 (34.0)**	**26 (25.7)**	**141 (23.9)**	**33 (19.2)**	**24 (13.8)**	**135 (16.6)**
Decreased appetite	32 (31.1)	8 (7.9)	89 (15.1)	52 (30.2)	18 (10.3)	160 (19.7)
Constipation	30 (29.1)	10 (9.9)	65 (11.0)	51 (29.7)	18 (10.3)	117 (14.4)
Vomiting	26 (25.2)	9 (8.9)	56 (9.5)	47 (27.3)	8 (4.6)	110 (13.5)
COVID-19	23 (22.3)	18 (17.8)	20 (3.4)	34 (19.8)	21 (12.1)	22 (2.7)
Fatigue	23 (22.3)	10 (9.9)	61 (10.3)	53 (30.8)	16 (9.2)	132 (16.3)
Neutropenia	23 (22.3)	4 (4.0)	34 (5.8)	44 (25.6)	5 (2.9)	50 (6.2)
Neutrophil count decreased	22 (21.4)	3 (3.0)	32 (5.4)	40 (23.3)	13 (7.5)	60 (7.4)
Dry skin	21 (20.4)	20 (19.8)	153 (25.9)	28 (16.3)	46 (26.4)	189 (23.3)
Alanine aminotransferase increased	20 (19.4)	7 (6.9)	40 (6.8)	37 (21.5)	14 (8.0)	60 (7.4)
Platelet count decreased	14 (13.6)	5 (5.0)	27 (4.6)	37 (21.5)	14 (8.0)	77 (9.5)
Thrombocytopenia	14 (13.6)	2 (2.0)	46 (7.8)	37 (21.5)	10 (5.7)	58 (7.1)

Patients with multiple events in the same preferred term are counted only once in that preferred term. Patients with events in more than one preferred term are counted once in each of those preferred terms.
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.
Preferred terms presented in order of frequency in patients with WHO PS of normal activity in the osimertinib + chemotherapy arm of the FLAURA2 study.
Bolding indicates that the PT has a ≥ 10% difference between the WHO PS categories in one or both of the treatment arms of the FLAURA2 study.

Effect of body weight

Table 77: Adverse Events in Any Category and AESIs by Grouped Term - Patient Level by Weight

	Number (%) of patients					
	< 50 kg			≥ 50 kg		
	FLAURA2 Study			FLAURA2 Study		
	Osi + Chemo (N=38)	Osi (N=30)	Osi mono safety pool (N=284)	Osi + Chemo (N=238)	Osi (N=245)	Osi mono safety pool (N=1520)
Any AE	38 (100)	30 (100)	282 (99.3)	238 (100)	238 (97.1)	1493 (98.2)
Any AE of ≥ CTCAE grade 3	22 (57.9)	8 (26.7)	137 (48.2)	154 (64.7)	67 (27.3)	536 (35.3)
Any AE with outcome of death	4 (10.5)	1 (3.3)	15 (5.3)	14 (5.9)	7 (2.9)	54 (3.6)
Any SAE (including events with outcome of death)	14 (36.8)	5 (16.7)	88 (31.0)	90 (37.8)	48 (19.6)	432 (28.4)
Any AE leading to discontinuation of osimertinib	5 (13.2)	5 (16.7)	40 (14.1)	25 (10.5)	12 (4.9)	153 (10.1)
Any AE leading to dose modification of osimertinib	13 (34.2)	5 (16.7)	104 (36.6)	118 (49.6)	51 (20.8)	398 (26.2)
Any AE leading to dose reduction of osimertinib	3 (7.9)	1 (3.3)	28 (9.9)	24 (10.1)	7 (2.9)	68 (4.5)
Any AE leading to dose interruption of osimertinib	11 (28.9)	5 (16.7)	94 (33.1)	109 (45.8)	47 (19.2)	365 (24.0)
Any AESI	27 (71.1)	7 (23.3)	149 (52.5)	181 (76.1)	73 (29.8)	579 (38.1)
Cardiac Effects (Cardiac Failure)	4 (10.5)	0	15 (5.3)	22 (9.2)	10 (4.1)	52 (3.4)
Haematological Toxicities	26 (68.4)	6 (20.0)	129 (45.4)	171 (71.8)	60 (24.5)	503 (33.1)
ILD and Pneumonitis	0	2 (6.7)	16 (5.6)	9 (3.8)	8 (3.3)	57 (3.8)

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

Table 78: Summary of AEs by PT (Reported in ≥20% Patients in Either Weight Category in the FLAURA2 Study) - Patient Level by Weight

	Number (%) of patients					
	< 50 kg			≥ 50 kg		
	FLAURA2 Study			FLAURA2 Study		
MedDRA PT	Osi + Chemo (N=38)	Osi (N=30)	Osi mono safety pool (N=284)	Osi + Chemo (N=238)	Osi (N=245)	Osi mono safety pool (N=1520)
Any AE	38 (100)	30 (100)	282 (99.3)	238 (100)	238 (97.1)	1493 (98.2)
Anaemia	16 (42.1)	2 (6.7)	62 (21.8)	112 (47.1)	20 (8.2)	175 (11.5)
Nausea	15 (39.5)	3 (10.0)	49 (17.3)	104 (43.7)	25 (10.2)	268 (17.6)
Diarrhoea	**14 (36.8)**	**16 (53.3)**	**149 (52.5)**	**106 (44.5)**	**96 (39.2)**	**690 (45.4)**
Neutrophil count decreased	**13 (34.2)**	**1 (3.3)**	**36 (12.7)**	**49 (20.6)**	**15 (6.1)**	**88 (5.8)**
Paronychia	**13 (34.2)**	**12 (40.0)**	**102 (35.9)**	**52 (21.8)**	**61 (24.9)**	**369 (24.3)**
Stomatitis	**13 (34.2)**	**8 (26.7)**	**82 (28.9)**	**55 (23.1)**	**42 (17.1)**	**257 (16.9)**
COVID-19	11 (28.9)	4 (13.3)	4 (1.4)	46 (19.3)	35 (14.3)	38 (2.5)
Constipation	10 (26.3)	4 (13.3)	39 (13.7)	72 (30.3)	24 (9.8)	236 (15.5)
Decreased appetite	10 (26.3)	2 (6.7)	67 (23.6)	75 (31.5)	24 (9.8)	280 (18.4)
Dry skin	**10 (26.3)**	**12 (40.0)**	**88 (31.0)**	**40 (16.8)**	**54 (22.0)**	**365 (24.0)**
Dermatitis acneiform	**9 (23.7)**	**6 (20.0)**	**49 (17.3)**	**28 (11.8)**	**30 (12.2)**	**210 (13.8)**
Vomiting	9 (23.7)	3 (10.0)	41 (14.4)	64 (26.9)	14 (5.7)	192 (12.6)
Neutropenia	8 (21.1)	1 (3.3)	20 (7.0)	60 (25.2)	8 (3.3)	88 (5.8)
Platelet count decreased	**3 (7.9)**	**1 (3.3)**	**24 (8.5)**	**48 (20.2)**	**18 (7.3)**	**137 (9.0)**
ALT increased	**3 (7.9)**	**0**	**19 (6.7)**	**54 (22.7)**	**21 (8.6)**	**123 (8.1)**
Fatigue	**7 (18.4)**	**3 (10.0)**	**28 (9.9)**	**69 (29.0)**	**23 (9.4)**	**237 (15.6)**
Rash	**6 (15.8)**	**5 (16.7)**	**39 (13.7)**	**71 (29.8)**	**52 (21.2)**	**229 (15.1)**
Pruritus	**3 (7.9)**	**6 (20.0)**	**43 (15.1)**	**19 (8.0)**	**25 (10.2)**	**265 (17.4)**
Thrombocytopenia	**3 (7.9)**	**1 (3.3)**	**14 (4.9)**	**48 (20.2)**	**11 (4.5)**	**123 (8.1)**

Patients with multiple events in the same preferred term are counted only once in that preferred term. Patients with events in more than one preferred term are counted once in each of those preferred terms.
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.
Preferred terms presented in order of frequency in patients with body weight < 50 kg in the osimertinib + chemotherapy arm of the FLAURA2 study.
Bolding indicates that the PT has a ≥ 10% difference between the weight categories in one or both of the treatment arms of the FLAURA2 study.
Source: Table 2.7.4.s3fs, FLAURA2 Pooled Analysis, Module 5.3.5.3.

Safety related to drug-drug interactions and other interactions

No new data on drug-drug interactions were reported.

Discontinuation due to adverse events

- **Adverse events leading to discontinuation of treatment**

Table 79: AEs Leading to Discontinuation of Osimertinib, by PT (Reported in ≥ 1% of Patients in Either Treatment of the FLAURA2 Study)

MedDRA Preferred Term	Number (%) of patients		
	FLAURA2 Study		Osimertinib monotherapy safety pool (N=1813)
	Osi + Chem (N=276)	Osimertinib (N=275)	
Patients with any AE leading to discontinuation of osimertinib	30 (10.9)	17 (6.2)	194 (10.7)
Interstitial lung disease	5 (1.8)	6 (2.2)	34 (1.9)
Ejection fraction decreased	3 (1.1)	0	2 (0.1)
Pneumonitis	3 (1.1)	3 (1.1)	26 (1.4)
Pneumonia	4 (1.4)	1 (0.4)	9 (0.5)

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

Table 80: Adverse Events Leading to Study Drug Discontinuation by PT (Reported in ≥ 1% of Patients in Either Arm) (Randomised Period –Safety Analysis Set)

MedDRA Preferred Term	Number (%) of patients	
	Osi + Chemo (N = 276)	Osimertinib (N = 275)
Patients with any AE leading to discontinuation of any study drug	132 (47.8)	17 (6.2)
Patients with any AE leading to discontinuation of osimertinib	*30 (10.9)*	*17 (6.2)*
Interstitial lung disease	5 (1.8)	6 (2.2)
Pneumonia	4 (1.4)	1 (0.4)

Pneumonitis	3 (1.1)	3 (1.1)
Ejection fraction decreased	3 (1.1)	0
Patients with any AE leading to discontinuation of carboplatin/cisplatin	*46 (16.7)*	*NA*
Thrombocytopenia	6 (2.2)	NA
Neutrophil count decreased	5 (1.8)	NA
Anaemia	4 (1.4)	NA
Nausea	4 (1.4)	NA
Creatinine renal clearance decreased	3 (1.1)	NA
White blood cell count decreased	3 (1.1)	NA
Neutropenia	3 (1.1)	NA
Vomiting	3 (1.1)	NA
Pneumonia	3 (1.1)	NA
Patients with any AE leading to discontinuation of pemetrexed	*119 (43.1)*	*NA*
Anaemia	14 (5.1)	NA
Neutropenia	13 (4.7)	NA
Blood creatinine increased	12 (4.3)	NA
Creatinine renal clearance decreased	9 (3.3)	NA
Thrombocytopenia	7 (2.5)	NA
Neutrophil count decreased	6 (2.2)	NA
Fatigue	6 (2.2)	NA
Glomerular filtration rate decreased	4 (1.4)	NA
Nausea	4 (1.4)	NA
Pneumonia	3 (1.1)	NA
Renal impairment	3 (1.1)	NA
Interstitial lung disease	3 (1.1)	NA
Decreased appetite	3 (1.1)	NA

Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of treatment but prior to the start of a new anticancer therapy.
MedDRA version 25.1
DCO: 03 April 2023
Source: Table 14.3.5.1.1b, Table 14.3.5.1.2b, Table 14.3.5.1.3b, and Table 14.3.5.1.4b

- **Adverse events leading to dose modifications**

The proportion of patients with AEs leading to dose modifications was higher in the osimertinib + chemotherapy arm (198 patients [71.7%]) as compared with the osimertinib arm (56 patients [20.4%]).

Note: The number of dose modifications due to AEs in the exposure summary (see above) differs from the number of AEs resulting in a dose modification in this section due to the differences in data capture between the exposure and AE eCRFs: in the exposure summary, each action taken for an AE is taken into account; whereas within the AE datasets, only the highest action taken for an AE is recorded and summarised. Hence, there are discrepancies between numbers of patients with dose modifications between the exposure analysis and the AE analysis.

- **Adverse events leading to dose reductions**

Table 81: AEs Leading to Dose Reduction of Osimertinib by PT (Reported in ≥ 2 Patients in Either Treatment Arm of the FLAURA2 Study)

MedDRA Preferred Term	Number (%) of patients		
	FLAURA2 Study		Osimertinib monotherapy safety pool (N=1813)
	Osi + Chemo (N=276)	Osimertinib (N=275)	
Patients with any AE leading to osimertinib dose reduction	27 (9.8)	8 (2.9)	96 (5.3)
Diarrhoea	3 (1.1)	2 (0.7)	9 (0.5)
Rash	3 (1.1)	0	1 (0.1)
ECG QT prolonged	2 (0.7)	0	10 (0.6)
Fatigue	2 (0.7)	0	4 (0.2)
Neutropenia	2 (0.7)	0	5 (0.3)
Platelet count decreased	2 (0.7)	0	2 (0.1)
Thrombocytopenia	2 (0.7)	1 (0.4)	4 (0.2)
Blood creatine phosphokinase increased	2 (0.7)	0	2 (0.1)
Ejection fraction decreased	0	2 (0.7)	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 treatment and on or before starting subsequent cancer therapy.

Table 82: Adverse Events Leading to Study Drug Dose Reduction (≥ 1% Patients in Either Treatment Arm) (Randomised Period – Safety Analysis Set)

MedDRA Preferred Term [a]	Number (%) of patients	
	Osi + Chemo (N = 276)	Osimertinib (N = 275)
AEs leading to a dose reduction of any study drug	91 (33.0)	8 (2.9)
AEs leading to osimertinib dose reduction	*27 (9.8)*	*8 (2.9)*
Diarrhoea	3 (1.1)	2 (0.7)
Rash	3 (1.1)	0
AEs leading to carboplatin/cisplatin dose reduction	*49 (17.8)*	*NA*
Platelet count decreased	8 (2.9)	NA
Neutrophil count decreased	7 (2.5)	NA
Neutropenia	6 (2.2)	NA
Thrombocytopenia	6 (2.2)	NA
Anaemia	5 (1.8)	NA
Decreased appetite	4 (1.4)	NA
Fatigue	4 (1.4)	NA
Nausea	3 (1.1)	NA
AEs leading to pemetrexed dose reduction	*64 (23.2)*	*NA*
Anaemia	13 (4.7)	NA
Neutrophil count decreased	10 (3.6)	NA
Neutropenia	9 (3.3)	NA
Fatigue	8 (2.9)	NA
Platelet count decreased	7 (2.5)	NA
Thrombocytopenia	7 (2.5)	NA
Decreased appetite	4 (1.4)	NA
Febrile neutropenia	3 (1.1)	NA
Leukopenia	3 (1.1)	NA

[b] Patients may have had more than one AE leading to dose reduction.
Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of treatment but prior to the start of a new anti-cancer therapy.
MedDRA version 25.1
DCO: 03 April 2023
Sources: Table 14.3.2.9.1.1b, Table 14.3.2.9.1.2b, Table 14.3.2.9.1.3b, and Table 14.3.2.9.1.4b

- **Adverse events leading to dose interruptions and/or chemotherapy cycle delays**

Table 83: AEs Leading to Dose Interruption of Osimertinib by PT (Reported in ≥ 1% of Patients in Either Treatment Arm of the FLAURA2 Study)

MedDRA Preferred Term	Number (%) of patients		
	FLAURA2 Study		Osimertinib monotherapy safety pool (N=1813)
	Osi + Chemo (N=276)	Osimertinib (N=275)	
Patients with any AE leading to osimertinib dose interruption	120 (43.5)	52 (18.9)	459 (25.3)

MedDRA Preferred Term	Number (%) of patients		
	FLAURA2 Study		Osimertinib monotherapy safety pool (N=1813)
	Osi + Chemo (N=276)	Osimertinib (N=275)	
Anaemia	13 (4.7)	1 (0.4)	10 (0.6)
Neutropenia	12 (4.3)	2 (0.7)	21 (1.2)
Diarrhoea	10 (3.6)	1 (0.4)	35 (1.9)
Neutrophil count decreased	10 (3.6)	0	19 (1.0)
COVID-19	9 (3.3)	5 (1.8)	7 (0.4)
Febrile neutropenia	9 (3.3)	0	1 (0.1)
Thrombocytopenia	8 (2.9)	1 (0.4)	9 (0.5)
Platelet count decreased	7 (2.5)	1 (0.4)	5 (0.3)
Rash	5 (1.8)	0	1 (0.1)
Decreased appetite	4 (1.4)	0	14 (0.8)
Ejection fraction decreased	4 (1.4)	1 (0.4)	10 (0.6)
Nausea	4 (1.4)	1 (0.4)	8 (0.4)
Stomatitis	4 (1.4)	3 (1.1)	14 (0.8)
Alanine aminotransferase increased	3 (1.1)	2 (0.7)	22 (1.2)
Electrocardiogram QT prolonged	3 (1.1)	1 (0.4)	26 (1.4)
Fatigue	3 (1.1)	0	6 (0.3)
Pulmonary embolism	3 (1.1)	2 (0.7)	9 (0.5)
Suspected COVID-19	3 (1.1)	0	0
Vomiting	3 (1.1)	0	13 (0.7)
Leukopenia	3 (1.1)	0	11 (0.6)
Pneumonia	2 (0.7)	3 (1.1)	29 (1.6)
Paronychia	1 (0.4)	5 (1.8)	14 (0.8)

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

Table 84: Adverse Events Leading to Dose Interrruptions and/or Chemotherapy Cycle Delays, by Preferred Term, (Reported in ≥1% of Patients in Either Treatment Arm) (Randomised Period-Safety Analysis Set)

MedDRA Preferred Term [a]	Number (%) of patients	
	Osi + Chemo (N = 276)	Osimertinib (N = 275)
Any AE leading to dose interruption of any study drug	175 (63.4)	52 (18.9)
AEs leading to osimertinib dose interruption	*120 (43.5)*	*52 (18.9)*
Anaemia	13 (4.7)	1 (0.4)
Neutropenia	12 (4.3)	2 (0.7)
Diarrhoea	10 (3.6)	1 (0.4)
Neutrophil count decreased	10 (3.6)	0
COVID-19	9 (3.3)	5 (1.8)
Febrile neutropenia	9 (3.3)	0
Thrombocytopenia	8 (2.9)	1 (0.4)
Platelet count decreased	7 (2.5)	1 (0.4)
Rash	5 (1.8)	0
Stomatitis	4 (1.4)	3 (1.1)
Ejection fraction decreased	4 (1.4)	1 (0.4)
Nausea	4 (1.4)	1 (0.4)
Decreased appetite	4 (1.4)	0
Alanine aminotransferase increased	3 (1.1)	2 (0.7)
Pulmonary embolism	3 (1.1)	2 (0.7)
Electrocardiogram QT prolonged	3 (1.1)	1 (0.4)
Leukopenia	3 (1.1)	0
Suspected COVID-19	3 (1.1)	0
Vomiting	3 (1.1)	0
Fatigue	3 (1.1)	0
Pneumonia	2 (0.7)	3 (1.1)
Paronychia	1 (0.4)	5 (1.8)
AEs leading to carboplatin/cisplatin cycle delay	*50 (18.1)*	*NA*
Neutropenia	13 (4.7)	NA
Anaemia	12 (4.3)	NA
Neutrophil count decreased	7 (2.5)	NA
Thrombocytopenia	5 (1.8)	NA
Leukopenia	4 (1.4)	NA
AEs leading to pemetrexed cycle delay	*117 (42.4)*	*NA*
Anaemia	24 (8.7)	NA
Neutropenia	21 (7.6)	NA
Neutrophil count decreased	20 (7.2)	NA

Post marketing experience

As of 31 March 2023, the total cumulative post-marketing exposure to osimertinib for all doses and all countries is estimated to be approximately 583786 patient-years.

Table 85: Patient-years of Cumulative Osimertinib Exposure to 40 mg and 80 mg Tablets, by Region

Formulation	Europe	North America	Japan	Rest of the World	Total
40 mg tablets	8680	6958	21481	1246	38365
80 mg tablets	67810	54870	52431	370310	545421

As of 31 March 2023, the majority of post-marketing cases received are in keeping with the patient population being treated and the known safety profile of osimertinib.

Since first marketing approval of osimertinib (13 November 2015), the core label for TAGRISSO has been updated with the following information:

Addition of new ADRs of alopecia, aplastic anaemia, blood creatinine increased, blood creatine phosphokinase increased, cutaneous vasculitis, epistaxis, erythema multiforme, keratitis, palmar-plantar erythrodysaesthesia syndrome, QTc prolongation, Stevens-Johnson Syndrome, toxic epidermal necrolysis, and urticaria.

Further characterisation of the listed haematological ADRs.

Addition of the MedDRA PT of onychalgia to further characterise the listed ADR of paronychia.

Addition of the MedDRA PT of mouth ulceration to further characterise the listed ADR of stomatitis.

Addition of the MedDRA PT of pustule to further characterise the listed ADR of rash.

Addition of the MedDRA PT of organising pneumonia to further characterise the listed ADR of ILD.

Further to these updates, ongoing pharmacovigilance activities and processes have not identified any change in the benefit/risk profile of TAGRISSO in the currently indicated patient population.

2.5.1. Discussion on clinical safety

The safety profile of osimertinib in the new claimed indication is based mainly on 557 patients from the randomised period (FAS) of the FLAURA2 study (DCO date of 03 April 2023), of whom 551 received at least one dose of any study treatment, comprising 276 patients that received 80 mg osimertinib in combination with pemetrexed and platinum-based chemotherapy and 275 patients that osimertinib monotherapy (Safety Analysis Set). Of note, one patient randomised to the osimertinib + chemotherapy arm received osimertinib only, so is included in the osimertinib arm in the Safety Analysis Set. This dataset from the randomised period of the study FLAURA2 is supported by comparisons with a pooled safety data from pivotal monotherapy clinical studies in patients with EGFRm NSCLC treated with 80 mg osimertinib (N=1813) including FLAURA2 monotherapy arm.

Additionally, safety data from the run-in period of the study FLAURA2 (N=30) are also provided in support of the safety assessment for the proposed indication of osimertinib as a supplementary safety dataset which is not integrated into the main evaluation of safety.

Patient exposure

In the FLAURA2 study, the median actual exposure to osimertinib [21.8 months in the osimertinib + chemotherapy arm vs. 19.0 in the osimertinib arm] was similar to the median total exposure [22.3 months in the osimertinib + chemotherapy arm vs. 19.3 in the osimertinib arm], suggesting that the frequency and duration of dosing interruptions had a minimal impact on osimertinib exposure, and was slightly higher in the experimental arm. Based on this data, it appears that added toxicity of chemotherapy did not impacted the osimertinib exposure.

With regards to chemotherapy the median exposure to cisplatin/carboplatin was 2.76 months (range: 0.7 to 4.1 months), corresponding to median of 4 treatment cycles (range: 1 to 6 cycles), and the median actual exposure to pemetrexed was 8.28 months (range: 0.7 to 33.8 months), corresponding to median of 12 treatment cycles (range: 1 to 48 cycles). It seems that several patients received more than 4 cycles of cisplatin/carboplatin. In response to RSI, the MAH has clarified that there were two patients who received 5 and 6 carboplatin cycles, respectively. The patient who received one additional carboplatin cycle (on study day 84) did not have any additional event included haematological adverse events, while the patient who received two extra cycles of carboplatin (on days 84 and 105) developed a Grade ≥3 anaemia (on day 63) that was resolved (on day 106) with no change to any study therapies and was considered as unrelated to study treatment by the investigator.

Adverse events (AEs)

The safety profile reported is in line with the adverse reactions that have previously been described for osimertinib treatment. No new safety signals were identified for osimertinib in combination with pemetrexed and platinum-based chemotherapy. However, the overall proportion of patients with CTCAE ≥ Grade 3 AEs, AEs leading to dose modifications, SAEs, DAEs, AEs with an outcome of death and AE reported as causally related to the treatment was higher in the osimertinib + chemotherapy arm compared to the osimertinib arm, which suggests that the addition of chemotherapy does significantly worsen the toxicity profile.
The most frequently reported AEs (≥10% of patients) were anaemia (46.4%), diarrhoea (43.5%), and nausea (43.1%), in the osimertinib + chemotherapy arm; whereas in the osimertinib arm were diarrhoea (40.7%), paronychia (26.5%), and dry skin (24.0%). These AEs all represent previously identified ADRs for one or more of the individual study treatments, and were therefore expected.

Overall, AEs reported with a higher incidence (by > 10% more patients) in the osimertinib + chemotherapy arm compared to the osimertinib arm were: anaemia, nausea, neutropenia, decreased appetite, vomiting, constipation, fatigue, neutrophil count decreased, thrombocytopenia, ALT increased, AST increased, blood creatinine increased, platelet count decreased, and oedema peripheral. Overall, AEs reported with a higher incidence in the osimertinib + chemotherapy arm compared to the osimertinib arm were primarily well characterised chemotherapy-related ADRs. Haematological toxicities were designated AESIs in this study. Other AEs were generally reported with a similar incidence in both treatment arms.

There were significant differences observed between treatment arms in the incidences of AEs regardless of causality, particularly in the SOC of blood and lymphatic system disorders. This is however not unexpected due to the (known) added toxicity of chemotherapy.

Adverse events by severity

A higher proportion of patients reported AEs of CTCAE ≥ Grade 3 in the osimertinib + chemotherapy arm (63.8%) compared to the osimertinib arm (27.3%). The most frequently reported CTCAE ≥ Grade 3 AEs in the osimertinib + chemotherapy arm were anaemia, neutropenia, and neutrophil count decreased reflecting the known haematological toxicity profile of the individual chemotherapy components. Whereas, in the osimertinib arm, the most frequently reported CTCAE ≥ Grade 3 AEs were pneumonia and COVID-19 pneumonia, which are expected given the disease under study and the timing of the study in relation to the COVID-19 pandemic. Of these, 52.9% in the osimertinib + chemotherapy arm and 10.5% in the osimertinib monotherapy arm, were considered as related to study treatment by the investigator.

The incidence of AEs CTCAE Grade 4 (life-threating) was higher also in the osimertinib + chemotherapy arm [22 patients (8.0%)] compared to the osimertinib arm [3 patients (1.1%)].

Serious adverse events (SAEs)

A higher proportion of patients had experienced an SAE in the osimertinib + chemotherapy arm (37.7%) compared to the osimertinib arm (19.3%). The most frequently reported SAEs (≥ 2% of patients) in the osimertinib + chemotherapy arm were anaemia, pneumonia, COVID-19, pulmonary embolism, febrile neutropenia, and platelet count decreased; while in the osimertinib arm was pneumonia.

Of note, the following SAEs were reported in a higher proportion of patients in the osimertinib arm than in osimertinib + chemotherapy arm: COVID-19 pneumonia [5 patients (1.8%) vs. 2 patients (0.7%)], interstitial lung disease [5 patients (1.8%) vs. 2 patients (0.7%)], pneumotorax [3 (1.1%) vs. 1 (0.4%)].

Additionally, 2 patients (0.7%) from the osimertinib + chemotherapy arm reported vertigo and pleural effusion while in the osimertinib arm there were no cases of vertigo and pleural effusion.

Deaths

Overall, the number of patients who died was comparable between treatment arms: 70 patients (25.4%) in the osimertinib + chemotherapy arm vs. 77 patients (28.1%) in the osimertinib arm in the safety analysis set. The majority of deaths in both treatment arms were considered to be related to the disease under investigation, 50 (17.9%) in the osimertinib + chemotherapy arm, and 65 (23.4%) in the osimertinib arm.

There were 26 deaths reported as AEs with outcome of death during the treatment period [18 (6.5%) osimertinib + chemotherapy arm vs. 9 (3.3%) osimertinib arm]. Regarding the causality, 5 (1.8%) of these deaths in the osimertinib + chemotherapy arm and one (0.4%) in the osimertinib arm, were considered related to study treatment by the investigator.

The causes of death of 18 subjects (6.5%) in the osimertinib + chemotherapy arm were: pneumonia (n=3), pulmonary embolism (n=3), cardiac failure (n=2), COVID-19 (n=1), pneumonitis (n=1), respiratory failure (n=1), general physical health deterioration (n=1), sepsis (n=1), completed suicide (n=1), sudden death (n=1), pulmonary oedema (n=1), hypovolaemic shock (n=1), and ischaemic stroke (n=1). In the osimertinib arm, the causes of death of 8 subjects (2.9%) were COVID pneumonia (n=4), brain herniation (n=1), lymphangitis, respiratory tract infection (n=1), death (unknown reason; n=1), haemoptysis (n=1).

Adverse Events of Special Interest (AESI)

ILD and pneumonitis:

ILD grouped term was reported by 9 patients (3.3%) in the osimertinib + chemotherapy arm and 10 patients (3.6%) in the osimertinib arm, being low the proportion of patients with an AE of CTCAE Grade ≥3 (2/9 patients in the osimertinib + chemotherapy arm, and 5/10 patients in the osimertinib arm). It is important to note however that patients with a history of ILD or clinical active ILD were not enrolled in the study.

The majority of patients with AEs of ILD/pneumonitis had either recovered/resolved or were recovering/resolving at the time of DCO (5/9 events in the osimertinib + chemotherapy arm and 5/10 events in the osimertinib arm). However, two patients had a CTCAE Grade 5 (fatal) AE: one patient (0.4%) in the osimertinib + chemotherapy arm (PT of pneumonitis), and one patient (0.4%) in the osimertinib arm (PT of organising pneumonia).

Cardiac effects (cardiac failure):

The proportion of patients with a decrease in LVEF was higher in the osimertinib + chemotherapy arm as compared to the osimertinib arm in both predefined outlier categories, ≥10% (8% vs 3%) and ≥15% (11.8% vs 7.9%) points decrease from baseline and absolute value ≥50%.

The incidence of cardiac failure AEs was also higher in the osimertinib + chemotherapy arm (9.4%) compared with the osimertinib arm (3.6%), corresponding to an AE incidence rate of 5.7 per 100 patient-years and 2.1 per 100 patient-years, respectively. Most of the cardiac effects were LVEF decrease (6.2% in osi + chemo vs. 3.3% in osi arm) and cardiac failure (1.8% in osi + chemo vs.0.4% in osi arm), all other PTs were reported infrequently. Of these, 4 (1.4%) patients in the osimertinib + chemotherapy arm reported AEs that were considered serious and 3 of them were fatal (2 cardiac failure and 1 pulmonary oedema). Both cardiac failure and LVEF decrease are known ADRs of osimertinib.

Even though no new safety signal for cardiac effects were identified and these data could be comparable with the type and frequency of AEs indicative of cardiac failure reported in the osimertinib monotherapy clinical development program to date, the fact that the SAEs of cardiac failure were reported in the osimertinib + chemotherapy arm only should be pointed out.

Haematological toxicities:

Overall, a higher incidence of AEs in the haematological toxicities grouped term were reported in the osimertinib + chemotherapy arm (71.4%) compared to the osimertinib arm (24.0%), which was expected based on the known safety profile of chemotherapy. As expected, the incidences of SAEs in the haematological toxicities were also higher in the osimertinib + chemo arm compared to the osimertinib arm (8.3% vs. 0.4%). Moreover, 17% of patients in the osimertinib + chemo arm had an AE of haematological toxicities which led to discontinuation of any study drug, the majority of discontinuations concerned pemetrexed (15.2 %), while none haematological toxicities led to discontinuation of study drug in the osimertinib arm.

The most frequently reported AEs in the haematological toxicities grouped term were anaemia, (46.4% in the osimertinib + chemotherapy arm and 22 patients (8.0% in the osimertinib arm), neutropenia (24.6% vs 3.3%) and neutrophil count decreased (22.5% vs. 5.8%).

Leucocytes decreased, lymphocytes decreased, platelet count decreased, neutrophils decreased were already identified as ADR for Tagrisso and reported under the SOC Investigation. Corresponding adverse reactions under the SOC Blood and lymphatic system disorders: leukopenia, lymphopenia, thrombocytopenia and neutropenia are added to the ADR table in the SmPC. Anaemia, although reported with high frequency in FLAURA2, was not added to the SmPC considering that it could be mainly associated to the chemotherapy.

Laboratory findings

Haematology

Greater decreases from baseline in median values for haemoglobin, leukocytes, neutrophils, lymphocytes and platelets counts were observed initially among patients treated with osimertinib + chemotherapy compared to patients in the osimertinib arm; however values remained stable throughout the study period for all patients.

Shifts of 3 and 4 grades were more noted for leukocytes, neutrophils lymphocytes and platelets, being the incidence in all cases higher in the osimertinib + chemotherapy arm. Shifts of grade 3 but no 4-grade shifts were observed in either treatment arm for haemoglobin.

General clinical chemistry

Overall, no unexpected changes from baseline or trends in clinical chemistry values (sodium, potassium, magnesium, albumin, and glucose) over time were observed in either treatment arm. In both treatment arms, the majority of patients had clinical chemistry parameters assessed as CTCAE Grade 0 (normal) or 1 at baseline, which generally remained at a maximum of Grade 0 or 1 for the majority of patients in both treatment arms while on study treatment.

Hepatic biochemistry

Hepatobiliary SOC AEs were reported in a higher proportion of patients in the osimertinib + chemotherapy arm than in the SoC osimertinib arm (9.1% vs. 2.5%). The most commonly reported AEs within this SOC were hepatic function abnormal (3.3% in the osimertinib + chemotherapy arm vs 1.1% in the osimertinib arm) and hypertransaminasaemia (2.2% in the osimertinib + chemotherapy arm and 0.7% in the osimertinib arm).

The following AEs in the Investigation SOC relating to hepatic biochemistry parameters were more commonly reported in the osimertinib + chemotherapy arm than in the osimertinib arm: ALT increased (20.3% vs 7.6%); AST increased (17.4% vs 4.7%); and transaminases increased (3.6% vs 0.7%).

Regarding the maximum shifts from baseline during treatment in liver function tests (LFTs), a higher proportion of patients in the osimertinib + chemotherapy arm had grade shifts for AST (70.2%) and ALT (63.1%) than in the osimertinib arm (41.1% and 26.4%, respectively) although most were 1-grade or 2-grade shifts.

Renal biochemistry

In both treatment arms, median creatinine values over time increased gradually, but remained under the ULN for the entire study duration. Note that patients with a creatinine clearance < 60 mL/min (calculated by Cockcroft and Gault equation or 24 hour urine collection) were excluded from participation in the study.

In both treatment arms, all patients had a creatinine level assessed as CTCAE Grade 0 (normal) or 1 at baseline, which primarily remained at Grade 0 for the majority of patients in both treatment arms while on study treatment. However, more patients in the osimertinib + chemotherapy arm had a creatinine value of maximum CTCAE Grade 2 during treatment in the osimertinib + chemotherapy arm as compared to the osimertinib arm. A higher proportion of patients in the osimertinib + chemotherapy arm had any grade shifts (21.8%) compared with the osimertinib arm (8.4%); the majority of shifts were 1 grade or 2-grade but there was a 4-grade shift (0.4%) in the osimertinib + chemotherapy arm.

Electrocardiogram data

The proportion of patients who experienced a QTcF of > 500 msec with a > 60 msec increase from baseline was low and was similar between the treatment arms (5 patients [1.8%] in the osimertinib + chemotherapy arm and 4 patients [1.5%] in the osimertinib arm).

Moreover, a similar proportion of patients had an AE of electrocardiogram QT prolonged in the osimertinib + chemotherapy arm (8.7%) compared to the osimertinib arm (8.4%), which is a known ADR for osimertinib.

Special populations

The safety profile by WHO PS at the AE category level in the osimertinib arm of the FLAURA2 study showed alignment with the osimertinib monotherapy safety pool.

Overall, the safety profile of osimertinib + chemotherapy appears consistent by gender and no major issues have been identified although some slight differences are observed between treatment arms but most of them in line with the observed in the osimertinib arm.

With regards to age, in patients ≥ 75 years age group, the proportion of AESIs was higher in the osimertinib arm (39.1%) compared with patients < 65 years (29.9%) and 65 to 74 years (25.0%). In the osimertinib + chemotherapy arm, there was a higher proportion of patients in the ≥ 75 years age group with AESIs of ILD/pneumonitis (21.7%) compared with patients < 65 years (0.6%) and 65 to 74 years (3.7%).

Of the 276 patients treated with osimertinib in combination with pemetrexed and platinum-based chemotherapy, 104 patients were ≥65 years and 23 patients were ≥75 years of age. Older patients (≥65 years) reported similar Grade 3 or higher adverse reactions compared to <65 years old patients (36% versus 36%) respectively. Dose modification for adverse reactions were reported in a higher proportion of patients ≥65 years as compared to <65 years (34% vs 20%).

Asian patients had a higher incidence of SAEs in the osimertinib+ chemotherapy arm (42.0%) compared to non-Asian patients (30.0%), although there was a lower proportion of SAEs in Asian patients in the osimertinib arm (16.5% compared to 24.2%), which was consistent with the osimertinib monotherapy safety pool. In response to RSI, the MAH has provided the SAEs reported in >2 patients in either subgroups (Asian vs Non-Asian subpopulations) in the osimertinib + chemotherapy arm. The most common SAEs reported in the Asian subgroup were haematological toxicities, anaemia (4.5%), platelet count decreased (3.4%) and febrile neutropenia (2.8%), besides COVID-19 (2.8%) and pneumonia (2.8%). In the non-Asian subgroup, the most common SAEs reported were pulmonary embolism (3.0%), COVID-19 (2.0%), pneumonia (2.0%), urinary tract infection (2.0%), and vomiting (2.0%). With the exception of the SAEs of pulmonary embolism (1.7% vs 3.0%), UTIs and vomiting (0.6% vs 2.0% each), the others SAEs (≥2% of patients) were reported in a higher proportion in the Asian subpopulation, in the osimertinib + chemotherapy arm. The incidence of anaemia which is the most commonly reported SAEs was higher in Asian patients (4.5%) compared to non-Asian (1.0%) together with platelet count decreased (3.4% vs 0) and febrile neutropenia (2.8% vs 1.0%). However, this appears to be related mostly to chemotherapy, since no events of haematological toxicity were observed in the osimertinib monotherapy arm, neither in Asian patients nor in non-Asian. In the osimertinib monotherapy arm, with the exception of SAEs of ILD (2.3% vs 1.0%), pneumothorax (1.1% vs 1.0%), vertigo (1.1% vs 0%), and UTI, diarrhoea and decreased appetite (0.6 % vs 0% each); the other SAEs (≥ 2% of patients) were reported in a higher proportion in the Non-Asian subpopulation. The most common SAEs reported in the Non-Asian subgroup in the osimertinib arm were pneumonia and COVID-19 pneumonia (4.0% each), while haematological toxicities were not reported in the osimertinib arm. Therefore, the higher incidence of SAEs between the two subpopulations differs in the two study arms.

Moreover, AESIs were also more frequent in Asian patients, although this observation was more notable in the osimertinib arm than in the osimertinib + chemotherapy arm, largely driven by a difference in haematological toxicities (29.0% of Asian patients vs 15.2% of Non-Asian patients in the osimertinib arm). Of note, ILD/pneumonitis was more frequent in Japanese patients which has already been shown.

The overall AE incidence of AEs in the FLAURA2 study was similar between patients with body weight < 50 kg and those with body weight ≥ 50 kg. Overall, the categorical AEs in both arms of the FLAURA2 study were balanced between body weight categories.

Patients who received osimertinib in combination with pemetrexed and platinum-based chemotherapy with low body weight (<50 kg) reported 32% frequencies of Grade ≥3 adverse reactions versus 37% when compared to patients with higher body weight (≥50 kg). In contrast, dry skin (34% versus 22%) and stomatitis (40% versus 30%) were reported at higher frequencies in patients with low body weight (<50 kg) versus higher body weight (≥50 kg).

Dose modifications and discontinuations due to adverse events

Discontinuation of study treatment due to AEs was reported in a higher proportion of patients in the osimertinib + chemotherapy arm (47.8%) compared to the osimertinib arm (6.2%), which was mainly due to discontinuation of chemotherapy (45.3%). AEs leading to discontinuation of chemotherapy were primarily due to haematological AEs.

The proportion of patients with AEs leading to dose modifications was higher in the osimertinib + chemotherapy arm (71.7%) as compared with the osimertinib arm (20.4%).

In total, 120 patients (43.5%) in the osimertinib + chemotherapy arm and 52 patients (18.9%) in the osimertinib arm had AEs leading to osimertinib dose interruption. AEs leading to an osimertinib dose interruptions reported in ≥ 5 patients in the osimertinib + chemotherapy arm were anaemia, neutropenia, diarrhoea, neutrophil count decreased, COVID-19, febrile neutropenia, thrombocytopenia, platelet count decreased, and rash; and in the osimertinib arm were paronychia and COVID-19.

Regarding dose interruptions, a higher proportion of patients had AEs leading to dose interruption of any study drug in the osimertinib + chemotherapy arm (63.4%) compared to the osimertinib arm (18.9%), which were predominantly due to pemetrexed cycle delays (42.4%) and/or osimertinib dose interruptions (43.5%). Of note, AEs leading to dose interruptions of osimertinib were also more frequent in the experimental arm. The AEs leading to carboplatin/cisplatin and/or pemetrexed cycle delays were predominantly haematological in nature, which is expected for the individual chemotherapeutic agents.

No new clinically significant safety findings were noted in the Safety run-in period in relation to ILD/pneumonitis, cardiac effects, other clinical chemistry parameters, vital signs and physical examination, cardiac parameters, and WHO PS.

Overall, the safety profile in the osimertinib arm of the FLAURA2 study reflected that of the osimertinib monotherapy safety pool, and the safety of osimertinib given in combination with chemotherapy in the FLAURA2 study was consistent with the osimertinib monotherapy safety pool and the known safety profiles of the individual chemotherapy treatments.

2.5.2. Conclusions on clinical safety

Overall, the safety profile of osimertinib in combination with chemotherapy appears consistent with the already known safety profile of the individual components and no new safety signals have been identified.

However, with the addition of chemotherapy the severity of the toxicity is considerable, with a higher incidence of Grade ≥3 AEs, SAEs, deaths due to AEs, AESIs and treatment discontinuations due to AEs. This should be valued against the observed benefit.

2.5.3. PSUR cycle

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

2.6. Risk management plan

The 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 16.2 is acceptable.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 16.2 with the following content:

Safety concerns

Table 86: Summary of safety concerns - Osimertinib

Important identified risks	• Interstitial lung disease • Cardiac failure
Important potential risks	• None
Missing information	• None

No changes to the safety concerns have been proposed following the application for the new indication in combination with chemotherapy. So far, no new safety concerns have been identified. No new safety data or new information on the known risks have been identified from the submitted data supporting the sought that impact the classification of current safety concerns.

However, as requested in EMEA/H/C/PSUSA/00010472/202111 and EMEA/H/C/004124/II/0052, the risk of cardiac failure has been reclassified to important identified risk

Pharmacovigilance plan

No changes are proposed to the pharmacovigilance plan.

Routine pharmacovigilance is considered sufficient to identify and characterise the risks of the product.

Risk minimisation measures

Table 87: Summary table of risk minimisation measures

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risks		
ILD	<u>*Routine risk minimisation measures:*</u> • EU SmPC Section 4.8 (*Undesirable effects*) • EU SmPC Section 4.2 (*Posology and method of administration*) and Section 4.4 (*Special warnings and special precautions for use*) • PIL Section 2 (*What you need to know before you take TAGRISSO*) • PIL Section 4 *(Possible side effects)*	<u>*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection*</u>: • Targeted follow-up questionnaire

Table 87: Summary table of risk minimisation measures

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Cardiac failure	<u>*Routine risk minimisation measures:*</u> • PTs cardiac failure and LVEF decreased: EU SmPC Section 4.8 *(Undesirable effects)* • EU SmPC Section 4.4 (*Special warnings and special precautions for use)* • PIL Section 2 (*What you need to know before you take TAGRISSO*) • PIL Section 4 *(Possible side effects)*	<u>*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection*</u>: • Targeted follow-up questionnaire

Abbreviations: ADR, Adverse Drug Reaction; EU SmPC, European Union Summary of Product Characteristics; ILD, interstitial lung disease; PIL, Patient Information Leaflet.

The proposed routine risk minimisation measures are considered sufficient to minimise the risks of the product in the proposed indication(s).

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

2.7.1. 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 for the following reasons:

It is considered that the submitted Type II variation to extend the currently approved indications for Tagrisso in combination with pemetrexed and platinum-based chemotherapy for the first-line treatment of adult patients with locally advanced or metastatic NSCLC with activating EGFR mutations, does not involve a relevant impact on the PIL.

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 revised claimed indication for osimertinib is in combination with pemetrexed and platinum-based chemotherapy for the first-line treatment of adult patients with advanced non-small cell lung cancer (NSCLC) whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations.

3.1.1. Disease or condition

Lung cancer is the leading cause of cancer related deaths, with an estimated 1.8 million deaths globally in 2020 (Sung et al 2021). NSCLC represents approximately 85% of all lung cancers and around 70% to 80% of patients with NSCLC have locally advanced or metastatic disease at diagnosis, with limited treatment options and poor prognosis (Herbst et al., 2008; Howlader et al., 2021).

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. The EGFR gene mutation is one of the most common oncogenic drivers in NSCLC, with a higher prevalence in Asian patients compared to Caucasian patients (50% vs. 15%, respectively), and are found more frequently in women, never-smokers, and the adenocarcinoma histological subtype (Leonetti et al., 2019; Marchetti et al., 2005; Novello et al., 2016).

3.1.2. Available therapies and unmet medical need

Tyrosine kinase inhibitors (TKIs) have become the standard first-line treatment for patients with advanced NSCLC with activating EGFR mutations, being osimertinib, a third generation TKI, the preferred treatment option. First or second generation TKIs such as gefitinib, erlotinib, afatinib or dacomitinib are also approved in the EU as monotherapy in the first-line setting (ESMO Treatment Guidelines 2023 [Hendriks et al.]).

While these treatments improved the clinical outcomes of patients with advanced EGFRm NSCLC, the majority of patients experience disease progression (Shimamura et al., 2022). Disease progression on first-line osimertinib treatment can be due to a combination of intrinsic and diverse acquired resistance mechanisms, which challenge the effective long-term management of this patient population (Herbst et al., 2008, Fu et al., 2022). Depending on the pattern of disease progression, the current treatment guidelines recommend either continuing EGFR TKI, switching to platinum doublet chemotherapy as second line therapy or enrolment in a clinical trial.

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

3.1.3. Main clinical studies

The pivotal efficacy data to support this application are from the randomised phase of the FLAURA2 study, a Phase III, open-label, randomised study of osimertinib with or without pemetrexed plus platinum-based chemotherapy, as first-line treatment in patients with locally advanced (not amenable to curative surgery or radiotherapy) or metastatic EGFRm NSCLC (Ex19del or L858R) who have not received prior therapy for advanced disease.

3.2. Favourable effects

Results presented below are from the Investigator´s assessment, unless otherwise specified.

The primary endpoint of PFS was met at the DCO date of the primary PFS analysis (03 April 2023) with a median PFS of 25.5months in the osimertinib + chemotherapy arm versus 16.7 months in the osimertinib monotherapy arm (HR 0.62; 95% CI: 0.49, 0.79; p-value < 0.0001). PFS results by BICR assessment were consistent with the Investigator assessment (HR 0.62; 95% CI: 0.48, 0.80). Further sensitivity

analyses were supportive of the primary analysis. Subgroup analyses also showed consistent results in the subgroups analysed.

OS data, tested per the hierarchical testing procedure at the DCO of 03 April 2023, was not statistically significant (HR = 0.90; adjusted 99.84% CI: 0.54, 1.51; p-value = 0.5238). Median OS was not reached in either treatment arm. Updated results with 46.1% maturity based on a second IA (DCO 08 January 2024), were also not statistically significant (HR = 0.75; 95% CI: 0.57, 0.97; p-value = 0.028) but indicate a lack of detrimental effect on OS.

In the subgroup of 222/557 (40%) patients with CNS measurable and/or non-measurable lesion, CNS response rate was >65% in both treatment arms with a higher complete response rate in the osimertinib with pemetrexed and platinum-based chemotherapy arm (59.3% of patients) compared to the osimertinib monotherapy arm (43.3% of patients).

3.3. Uncertainties and limitations about favourable effects

OS data (46.1% maturity) at the time of the DCO for the second interim analysis were not statistically significant although a trend in favour of the osimertinib+chemotherapy arm is observed, with a separation of the Kaplan-Meier curves at month 16. Based on the available data a detrimental effect appears unlikely. However, the MAH will submit the final OS data to provide further reassurance on this effect (REC).

The preliminary data of post-progression measures (PFS2, TFST, TSST) appear in favour of the osimertinib + chemotherapy treatment arm. However, the immaturity of the data at the time of the data cut-off do not allow to reach firm conclusions, updated results will be submitted together with final OS data (REC).

3.4. Unfavourable effects

The following safety findings were observed in FLAURA2 study unless otherwise indicated.

The most frequently reported AEs (≥10% of patients) by PT were anaemia, diarrhoea, and nausea, in the osimertinib + chemotherapy arm; whereas in the osimertinib arm were diarrhoea, paronychia, and dry skin.

A higher proportion of patients reported ADRs of CTCAE ≥ Grade 3 in the osimertinib + chemotherapy arm (35.9%) compared to the osimertinib arm (7.7%). The most frequently reported CTCAE ≥ Grade 3 AEs in the osimertinib + chemotherapy arm were anaemia, neutropenia, and neutrophil count decreased; whereas in the osimertinib arm were COVID-19 pneumonia. The incidence of AEs CTCAE Grade 4 (life-threating) was also higher in the osimertinib + chemotherapy arm (8.0%) compared to the osimertinib arm (1.1%).

The most frequently reported SAEs (≥ 2% of patients) in the osimertinib + chemotherapy arm were anaemia, pneumonia, COVID-19, pulmonary embolism, febrile neutropenia, and platelet count decreased; while in the osimertinib arm was pneumonia. A higher proportion of patients experienced an SAE in the osimertinib + chemotherapy arm (37.7%) compared to the osimertinib arm (19.3%).

There were 26 deaths reported as AEs with outcome of death during the treatment period [18 (6.5%) in the osimertinib + chemotherapy arm and 9 (3.3%) in the osimertinib arm]. Regarding the causality, 5 (1.8%) of these deaths in the osimertinib + chemotherapy arm and one (0.4%) in the osimertinib arm, were considered related to study treatment by the investigator.

Adverse events of special interest include ILD/pneumonitis, cardiac failure and haematological toxicities.

AESI ILD/pneumonitis was reported in 9 patients (3.3%) in the osimertinib + chemotherapy arm and 10 patients (3.6%) in the osimertinib arm.

AESI cardiac effects (cardiac failure): the incidence of cardiac failure AEs was also higher in the osimertinib + chemotherapy arm (9.4%) compared with the osimertinib arm (3.6%), corresponding to an AE incidence rate of 5.7 per 100 patient-years and 2.1 per 100 patient-years, respectively. Most of the cardiac effects were LVEF decrease (6.2% in osi + chemo vs. 3.3% in osi arm) and cardiac failure (1.8% in osi + chemo vs.0.4% in osi arm)

AESI haematological toxicities: a higher incidence of AEs in the haematological toxicities grouped term was reported in the osimertinib + chemotherapy arm (71.4%) compared to the osimertinib arm (24.0%).

Discontinuation of study treatment due to AEs was reported in a higher proportion of patients in the osimertinib + chemotherapy arm (47.8%) compared to the osimertinib arm (6.2%), mainly due to discontinuation of chemotherapy (45.3%). The most frequently reported AEs leading to osimertinib treatment discontinuation in both treatment arms were primarily ILD and pneumonitis.

Overall, the safety profile and type of AEs reported in the FLAURA2 study for the combination of osimertinib + chemotherapy is in line with the known toxicities of osimertinib and pemetrexed + cisplatin/carboplatin treatments.

3.5. Uncertainties and limitations about unfavourable effects

N/A

3.6. Effects Table

Table 88: Effects Table for osimertinib in combination with pemetrexed and platinum based chemotherapy for the first-line treatment of patients with locally advanced or metastatic NSCLC whose tumours have EGFR Exon 19 Deletions or Exon 21 (L858R) substitution mutations (data cut-off: 03 April 2023)

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
Primary endpoint						
PFS INV	Progression free survival by investigator	Median; Months)	25.5	16.7	HR 0.62 (95% CI: 0.49, 0.79) p< 0.0001	CSR
Key secondary enpoint						
OS[a]	Overall survival	Median; Months	NC	NC	HR 0.75 (95% CI:0.57, 0.97) p = 0.028	CSR
Unfavourable Effects						
AEs related	Adverse events causality related to treatment	%	87.3	87.6		
AEs grade ≥3	Adverse events of CTCAE grade ≥3	%	63.8	27.3		
AEs grade ≥3 related	Adverse events of CTCAE grade ≥3 causality related to treatment	%	29.3	10.5		
SAEs	Serious AEs regardless causality	%	37.7	19.3		
SAEs related	Serious AEs causality related to treatment	%	13.0	5.5		
Deaths	AE with outcome of death	%	6.5	2.9		

Abbreviations: BICR = blinded independent central review; CI = confidential interval; CSR = Clinical Study Report;

HR = Hazard ratio; INV = investigator; NC = not calculable; OS = Overall survival; PFS = Progression free survival.

Notes: [a] Updated OS data based on a DCO 08 January 2024.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Results from the FLAURA2 study have shown a statistically significant benefit in terms of PFS with osimertinib in combination with pemetrexed and platinum-based chemotherapy versus osimertinib as monotherapy, for the first-line treatment of patients with advanced EGFRm NSCLC. ORR was also higher with the combination. In terms of OS, a trend in favour of osimertinib+chemotherapy was observed at the second IA and a detrimental effect appears unlikely. The MAH will submit the final OS analysis once available to further characterise the benefit (REC). A trend in favour of the combination has also been observed in post-progression endpoints, such as PFS2, although results at the time of analysis were not mature enough to draw firm conclusion.

It is notable that there is increased toxicity related to the addition of chemotherapy to osimertinib,, with a higher incidence of Grade ≥3 AEs, SAEs, deaths due to AEs, AESIs and treatment discontinuations due to AEs, which should be weighed against the observed benefit. However the resulted toxicity was manageable and the safety profile of osimertinib in combination with chemotherapy appears consistent with the already known safety profile of the individual components and no new safety signals have been identified.

The wording of the indication has been restricted to the studied patient population (i.e. patients whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations). Furthermore, "locally advanced or metastatic" has been replaced by "advanced" in line with the indication recently approved for other TKIs in biomarker targeted NSCLC indications.

3.7.2. Balance of benefits and risks

Osimertinib in combination with pemetrexed and platinum based chemotherapy has demonstrated a statistically significant improvement in PFS and a favourable OS trend, although not statistically significant over osimertinib alone. Despite an increased toxicity and a poorer tolerability of the combination compared to osimertinib as monotherapy, the added benefit contributes to an overall positive B/R of osimertinib used in combination in the final indication.

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 variation acceptable and therefore recommends by consensus the variation to the terms of the Marketing Authorisation, concerning the following change:

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

Extension of indication to include TAGRISSO in combination with pemetrexed and platinum-based chemotherapy for the first-line treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating epidermal growth factor receptor (EGFR) mutations, based on final results from study FLAURA2 (D5169C00001); this is a Phase III, open-label, randomized study of osimertinib with or without platinum plus pemetrexed chemotherapy, multicentre study to assess the efficacy and safety of TAGRISSO as first-line treatment in patients with EGFR mutation-positive, locally advanced or metastatic NSCLC. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 16.2 of the RMP has also been agreed.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I and IIIB and to the Risk Management Plan are recommended.