14 November 2024
EMA/559416/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

TAGRISSO

International non-proprietary name: Osimertinib

Procedure No. EMEA/H/C/004124/II/0056

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

List of abbreviations

Abbreviation	Explanation
ADR	adverse drug reaction
AE	adverse event
AEMPS	Spanish Agency of Medicines and Medical Products
AESI	adverse event of special interest
ASCO	American Society of Clinical Oncology
ATORG	Asian Thoracic Oncology Research Group
BBB	blood brain barrier
BICR	blinded independent central review
BOR	best objective response
CCRT	concurrent chemoradiation therapy
CDx	companion diagnostic
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
$C_{min,ss}$	Minimum plasma concentration at steady state
CNS	central nervous system
CRT	chemoradiation therapy
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumour DNA
DCO	data cut-off
DCR	disease control rate
DFS	disease-free survival
DoR	duration of response
ECG	electrocardiogram
EGFR	epidermal growth factor receptor
EGFRm	epidermal growth factor receptor mutation positive
EGFRwt	epidermal growth factor receptor wild type
EMA	European Medicines Agency
EORTC QLQ LC13	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire - Lung Cancer 13 items
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items
ER	exposure-response
ESMO	European Society for Medical Oncology
EU	European Union
FAS	full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GHS	global health status

Abbreviation	Explanation
HR	hazard ratio
IASLC	International Association for the Study of Lung Cancer
ILD	interstitial lung disease
KM	Kaplan-Meier
LVEF	left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
mPFS	median progression-free survival
mOS	median overall survival
MRI	magnetic resonance imaging
MTP	multiple testing procedure
NC	not calculable
NCCN	National Comprehensive Cancer Network
NR	not reported
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
PD-L1	programmed death-ligand 1
PET	positron emission tomography
PFS	progression-free survival
PFS2	time to second progression
PK	pharmacokinetic(s)
PopPK	population pharmacokinetic(s)
PR	partial response
PRO	patient reported outcomes
PS	Performance Status
PT	Preferred Term
QoL	quality of life
QTc	corrected QT
RECIST v 1.1	Response Evaluation Criteria in Solid Tumours version 1.1
SAE	serious adverse event
SAF	safety analysis set
SAP	Statistical Analysis Plan
SCRT	sequential chemoradiation therapy
SD	stable disease
sNDA	supplemental new drug application
SoC	standard of care
sPMA	supplement premarket approval application
TFST	time to first subsequent therapy
TKI	tyrosine kinase inhibitor
TMG	toxicity management guidelines
TNM	tumour, node, metastasis

Abbreviation	Explanation
TSST	time to second subsequent therapy
TTD	time to treatment discontinuation or death
TTDM	time to death or distant metastases
US	United States (of America)
WHO	World Health Organization
WRO	written responses only

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 9 April 2024 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 treatment of adult patients with locally advanced, unresectable (stage III) NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations and whose disease has not progressed during or following platinum-based chemoradiation therapy for TAGRISSO as monotherapy, based on results from study D5160C00048 (LAURA); this is a Phase III, randomised, double-blind, placebo-controlled, multicenter international study of osimertinib as maintenance therapy in patients with locally advanced unresectable EGFR mutation-positive non-small cell lung cancer (stage III) whose disease has not progressed following definitive platinum-based chemoradiation therapy. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 17.0 of the RMP has also been submitted. In addition, the MAH took the opportunity to introduce minor editorial changes to the Product Information.

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 (EMEA-002125-PIP01-17) 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 : Antonio Gomez-Outes

Timetable	Actual dates
Submission date	9 April 2024
Start of procedure:	27 April 2024
CHMP Rapporteur Assessment Report	4 July 2024
PRAC Rapporteur Assessment Report	1 July 2024
PRAC Outcome	11 July 2024
CHMP members comments	15 July 2024
Updated CHMP Rapporteur(s) (Joint) Assessment Report	19 July 2024
Request for supplementary information (RSI)	25 July 2024
CHMP Rapporteur Assessment Report	23 September 2024
CHMP members comments	7 October 2024
Updated CHMP Rapporteur Assessment Report	10 October 2024
Request for supplementary information (RSI)	17 October 2024
CHMP Rapporteur Assessment Report	30 October 2024
CHMP members comments	04 November 2024
Updated CHMP Rapporteur Assessment Report	07 November 2024
CHMP Opinion	14 November 2024

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

The MAH applied for the following indication:

TAGRISSO in monotherapy is indicated for the treatment of adult patients with locally advanced, unresectable (stage III) NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations and whose disease has not progressed during or following platinum-based chemoradiation therapy.

Epidemiology and risk factors

Primary lung cancer is the second most common form of cancer (11.4% of all new cancers worldwide) after breast cancer and it remains the leading cause of cancer related death overall (18% of all deaths from cancer) (Sung et al 2021). Non-small cell lung cancer (NSCLC) is the most common type of lung cancer, representing approximately 80% to 85% of all lung cancers. Despite advances made in screening, early detection, and staging, the majority of lung cancer patients are diagnosed when the disease has progressed, with 70% to 80% of patients identified with locally advanced, Stage III or Stage IV disease. Of the 20% to 30% of patients presenting with Stage III disease at diagnosis, 60% to 90% have unresectable disease (Agbarya et al 2022, Goldstraw et al 2016, Kato et al 2024).

Stage III NSCLC represents a heterogeneous group of patients. At one end of the spectrum, patients with T3 and N1 disease have tumours that are generally considered resectable. However, patients with T4 disease, i.e., that invades vital central structures (diaphragm, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, oesophagus, vertebral body, and carina) and/or patients with ipsilateral mediastinal nodal involvement (N2), ipsilateral distant nodal disease or contralateral nodal involvement (N3) have disease that is generally considered unresectable, with poor outcome (Goldstraw et al 2016). In those patients with unresectable disease, there is a subset of patients that are not amenable to curative intent with chemoradiation therapy for which the first-line treatment options are considered.

Biologic features

EGFR gene mutation is one of the most common oncogenic drivers in NSCLC, of which exon 19 deletions or exon 21 (L858R) substitution mutations are the most common mutations, accounting for 85% to 90% of EGFR mutations (Lynch et al 2004, Paez et al 2004, Herbst et al 2008). Overall, EGFR mutations are more frequent in Asian patients, women, never-smokers, and patients with the adenocarcinoma histological subtype (Marchetti et al 2005, Novello et al 2016). EGFR mutation rates are influenced by ethnicity and vary greatly by geographic region. Among newly diagnosed cases of NSCLC, EGFR-activating mutations are found in approximately 10% to 15% of patients in the US (Keedy et al 2011, Ryan et al 2019), 10% of patients in Europe (Barlesi et al 2013, Esteban et al 2015, Gahr et al 2013, Herbst et al 2008, Hondelink et al 2023), and 30% to 50% of patients in Asia (Han et al 2015, Shi et al 2014, Tokumo et al 2005, Yoshida et al 2007).

Clinical presentation, diagnosis and stage/prognosis

After the introduction of EGFR-TKIs in the clinical practice, the survival, and clinical outcomes of patients with EGFRm NSCLC improved remarkably, resulting in a 5-year OS of 88% in the adjuvant setting and median OS rates of more than 3 years in metastatic setting (Tsuboi et al 2023, Ramalingam et al 2020).

Although survival outcomes have improved, most patients with locally advanced, unresectable (Stage III), EGFRm NSCLC whose disease has not progressed during or following definitive platinum-based chemoradiation therapy are at risk of recurrence during the surveillance phase.

Management

The primary treatment for patients with locally advanced, unresectable (Stage III) NSCLC, amenable to curative intent therapy is definitive chemoradiation therapy (CRT), which has remained the standard of care for nearly 2 decades. Concurrent CRT (CCRT) is the treatment of choice, but if CCRT is not possible for any reason, sequential chemotherapy followed by definitive RT (SCRT) represents a valid and effective alternative (ESMO 2021).

Durvalumab is approved in the EU for the treatment of patients with locally advanced, unresectable NSCLC whose tumours express PD-L1 on ≥1% and whose disease has not progressed following platinum-based chemoradiation therapy based on results of PACIFIC study (SmPC Imfinzi). However, the study was conducted in an unselected patient population, and patients were randomised regardless of any biomarker status, including PD-L1 or EGFRm. Very few EGFR-mutated patients were included in the PACIFIC study, which impairs drawing any conclusion on the benefits of durvalumab in this subset of patients, which are the object of the current submission.

There are limited data on the outcomes of platinum-based CRT in patients with unresectable, EGFRm NSCLC, which is largely based on single-centre, retrospective analyses, and small prospective studies (Jazieh et al 2022, Nakamura et al 2019, He et al 2022). There have been no Phase III studies of platinum based CCRT in patients with EGFRm NSCLC specifically.

Although definitive platinum-based CRT is given as a treatment of curative intent for patients with unresectable, Stage III disease, the majority of patients subsequently have disease progression.

2.1.2. About the product

Osimertinib is an oral, irreversible Tyrosine Kinase Inhibitor (TKI) of EGFR, effective against both exon 19 deletions or exon 21 (L858R) as well as T790M mutation positive forms of NSCLC.

Tagrisso was authorised in the EU on 01-Feb-2016, and its current indications are as follows:

TAGRISSO as monotherapy is indicated for:

- *the adjuvant treatment after complete tumour resection in adult patients with stage IB-IIIA non-small cell lung cancer (NSCLC) whose tumours have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations (see section 5.1).*
- *the first-line treatment of adult patients with locally advanced or metastatic NSCLC with activating EGFR mutations.*
- *the treatment of adult patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC.*

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.*

Proposed dosage and administration

The recommended dose is 80 mg oral osimertinib once daily, until disease progression or unacceptable toxicity.

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 one Phase I study (D5160C00001A/B [AURA]), 2 Phase II studies (Study D5160C00001C [AURA extension] and Study D5160C00002 [AURA2]), and 2 Phase III studies (AURA3 and FLAURA). Additionally, the efficacy and safety of osimertinib in the adjuvant setting has been studied in the Phase III ADAURA study; collectively, data from these studies have led to marketing approval of osimertinib in markets around the world.

Most recently, a marketing application based on FLAURA2 study was submitted and has been approved based on the efficacy benefit demonstrated for osimertinib + chemotherapy as a first-line treatment for patients with locally advanced or metastatic NSCLC whose tumours have exon 19 deletions or exon 21 (L858R) substitution mutations (Planchard et al 2023).

Scientific advice

The MAH has not requested 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 have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Introduction

Osimertinib (AZD9291), the active pharmaceutical ingredient of Tagrisso, has already been evaluated and approved in the EU in several indications in NSCLC (see section 2.1.2).

With this application, the MAH is seeking approval of Tagrisso for the treatment of patients with locally advanced, unresectable (Stage III) NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations and whose disease has not progressed during or following platinum-based chemoradiation therapy.

2.2.2. Ecotoxicity/environmental risk assessment

The MAH states that it is expected that the approval of this variation will not have any significant effect on the predicted environmental exposure concentration (PECsw) calculated previously (August 2020), as the dose, indication and patient population are adequately covered by the refined PECsw in that environmental risk assessment (ERA). The PECsw value would remain unchanged and below the action limit.

Therefore, according to the guidelines of the European Medicines Agency, EMA/CHMP/SWP/4447/00 corr 21*CHMP 2006 and EMA/CHMP/SWP/44609/2010 Rev. 1, an updated ERA for osimertinib mesylate has not been provided as part of this variation application.

2.2.3. Discussion on non-clinical aspects

No pharmacodynamic, pharmacokinetic, or toxicological studies have been submitted for this application. An ERA has also not been submitted. In accordance with to the current *Guideline on the environmental risk assessment of medicinal products for human use* (EMA/CHMP/SWP/4447/00 corr 2^{1*}), an update of the evaluation of the environmental impact should be made if there is an anticipated increase in the environmental exposure.

Since osimertinib mesylate is already used in existing marketed products and a significant increase in environmental exposure is not anticipated, given that the population of this extension of the indication is included in the previously evaluated ERA, the lack of an updated ERA is considered acceptable.

2.2.4. Conclusion on the non-clinical aspects

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

Regarding the ERA, the extended indication does not affect previous conclusion on environmental exposure further to the use of osimertinib mesylate. Considering the above data, osimertinib mesylate is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

This application has been submitted to support an additional indication for use of Tagrisso 40 mg and 80 mg film-coated tablets once daily as treatment for patients with locally advanced, unresectable (Stage III) NSCLC whose tumours have exon 19 deletions or exon 21 (L858R) substitution mutations, and whose disease has not progressed during or following platinum-based chemoradiation therapy.

Support for the use of osimertinib in this indication is provided by efficacy, safety, and PK data from the results of LAURA (D5160C00048), a Phase III randomised, double-blind, placebo-controlled, multicenter international study of osimertinib as maintenance therapy in patients with locally advanced unresectable EGFR mutation-positive NSCLC (stage III) whose disease has not progressed following definitive platinum-based chemoradiation therapy.

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

Study number (EudraCT number)	EU countries involved	Non-EU countries involved
D5160C00048 (2018-001061-16)	Spain	Argentina, Brazil, China, India, Japan, Malaysia, Mexico, Peru, Russia, South Korea, Taiwan, Thailand, Turkey, United States of America, Vietnam

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	D5160C00048 LAURA	5.3.5.1	To assess the efficacy, safety, tolerability, disease-related symptoms and health-related QoL, and PK of osimertinib versus placebo as maintenance therapy	Phase III randomised, double-blind, placebo-controlled, study	Osimertinib 40 mg and 80 mg tablets, or matching placebo, administered orally once daily	216	Adult patients with locally advanced, unresectable (Stage III) NSCLC with EGFR mutations (Ex19del and L858R) whose disease has not progressed during or following definitive platinum-based CRT	Patients received osimertinib or placebo until RECIST 1.1-defined progression, or until another discontinuation criterion was met	Ongoing; DCO of 05 January 2024: Full CSR

2.3.2. Pharmacokinetics

Analytical methods

In Study D5160C00048, osimertinib (AZD9291) and its metabolite AZ5104 were analysed using two analytical methods: AZ9LHPP and AZ9HHPP for the low and high ranges assays, respectively.

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 were analysed at Labcorp UK Ltd but also at Labcorp's (formerly Covance's) Shanghai facility in China. Therefore, in previous procedures the MAH was asked to submit a cross-validation between analytical sites. A cross-validation study was performed for both the low and high range methods between the two laboratories.

Sample analysis

- Labcorp Pharmaceutical Research and Development, Shanghai

A total of 67 samples from Study D5160C00048 were analysed at Labcorp Pharmaceutical Research and Development (Shanghai) Co., Ltd. Building #9, No.338 Jialilue Road Zhangjiang Hi-Tech Park, Pudong, Shanghai 201203, China, between 25 Mar 2023 and 04 Apr 2023.

Study samples were received between 17 September 2020 and 03 January 2023. All samples were received by Labcorp – Shanghai frozen with dry ice and stored at -60 to -80°C.

The total duration of sample storage was 953 days (from first sample collection on 24 August 2020 to the last sample extracted on 04 April 2023).

As reported in the method validation Labcorp Study Number 8386634, stability of AZD9291 and AZ5104 in human plasma QC samples has been established for up to 1021 days after storage in a freezer set to maintain -50°C to -90°C.

Determination of AZD9291 and AZ5104 in samples from the Study D5160C00048 was carried out in Human Plasma by LC-MS/MS.

For AZD9291, two calibration curves were performed: high range calibration standards were prepared at 9 different concentrations (16.0, 32.0, 64.0, 160, 640, 1280, 3200, 7010 and 8010 nM) and low range calibration standards were prepared at 9 different concentrations (0.05, 0.10, 0.20, 1.00, 4.00, 8.00, 20.0, 44.0, and 50.0 nM). Runs 6 and 7 (high range) included 3 QCs (48.0, 560 and 6400 nM) per duplicate and run 9 (low range) also included 3 QCs (0.15, 2.00 and 40.00 nM) per duplicate.

For AZ5104, two calibration curves were performed: high range calibration standards were prepared at 9

different concentrations (1.65, 3.30, 6.59, 16.5, 65.9, 132, 330, 721 and 824 nM) and low range calibration standards were prepared at 9 different concentrations (0.0515, 0.1030, 0.2060, 1.0300, 4.1200, 8.2400, 20.6000, 45.3000, and 51.5000 nM). Runs 6 and 7 (high range) included 3 QCs (4.94, 57.70 and 659.00 nM) per duplicate and run 9 (low range) also included 3 QCs (0.154, 2.060 and 41.200 nM) per duplicate.

All samples were firstly analysed in run 5. However, the instrument stopped injection on the 58th sample because the system connection was disconnected. This run was rejected and re-injected from beginning in run 6.

For AZD9291 and AZ5104, 5 and 7 samples respectively were re-analysed (due to high internal standard result or BQL result) in run 7 and 9.

No sample dilutions nor reintegrations were reported in the bioanalytical report.

ISR was not performed. Representative chromatograms for Run 6 were provided.

- Labcorp Early Development, UK

A total of 286 samples from Study D5160C00048 were analysed at Labcorp Early Development Laboratories Limited (Harrogate) Otley Road, Harrogate North Yorkshire, HG3 1PY England, between 5 July 2021 and 05 May 2023.

Study samples were received between 13 November 2018 and 25 January 2023. All samples were received by Labcorp – Harrogate frozen with dry ice and stored at -50 to -90°C.

According to the MAH, the total duration of sample storage was 1683 days (from first sample collection on 25 September 2018 to the last sample analysed on 05 May 2023). However, the study samples were analysed in multiple subsets which resulted in the analysis of all samples within 1016 days of collection.

As reported in the method validation Labcorp Study Number 8386634, stability of AZD9291 and AZ5104 in human plasma QC samples has been established for up to 1021 days after storage in a freezer set to maintain -50°C to -90°C.

Determination of AZD9291 and AZ5104 in samples from the Study D5160C00048 was carried out in Human Plasma by LC-MS/MS.

All samples were initially analysed using the high range method (AZ9HHPP). Any samples that generated results below the LLOQ when using the high range method, were subsequently reanalysed using the low range method (AZ9LHPP).

For AZD9291, two calibration curves were performed: high range calibration standards were prepared at 9 different concentrations (16.0, 32.0, 64.0, 160, 640, 1280, 3200, 7010 and 8010 nM) and low range calibration standards were prepared at 9 different concentrations (0.05, 0.10, 0.20, 1.00, 4.00, 8.00, 20.0, 44.0, and 50.0 nM). Runs 1, 2, 4, 5 and 6 (high range) included 3 QCs (48.0, 560 and 6400 nM) per duplicate and runs 3 and 8 (low range) also included 3 QCs (0.15, 2.00 and 40.00 nM) per duplicate.

For AZ5104, two calibration curves were performed: high range calibration standards were prepared at 9 different concentrations (1.65, 3.30, 6.59, 16.5, 65.9, 132, 330, 721 and 824 nM) and low range calibration standards were prepared at 9 different concentrations (0.0515, 0.1030, 0.2060, 1.0300, 4.1200, 8.2400, 20.6000, 45.3000, and 51.5000 nM). Runs 1, 2, 4, 5 and 6 (high range) included 3 QCs (4.94, 57.70 and 659.00 nM) per duplicate and runs 3 and 8 (low range) also included 3 QCs (0.154, 2.060 and 41.200 nM) per duplicate.

For AZD9291 and AZ5104, 12 and 11 samples respectively were re-analysed (as the initial calculated concentrations were below the lower limit of quantification upon initial analysis using the high range method (AZ9HHPP) in run 3 and 8.

No sample dilutions nor reintegrations were reported in the bioanalytical report.

Carry-over was observed for AZD9291 in low range run 3 and high range run 6 whereas for AZ5104 only in low range run 3.

ISR was not performed. Representative chromatograms for Run 4 were provided.

Pharmacokinetics

In LAURA study (Study D5160C00048) only sparse sampling was performed for the assessment of PK and osimertinib and AZ5104 metabolite steady state exposures were evaluated (Ctrough concentrations).

LAURA study (D5160C00048) is a Phase III randomised, double-blind, placebo-controlled, multicenter international study of osimertinib as maintenance therapy in patients with locally advanced unresectable EGFR mutation-positive non-small cell lung cancer (stage III) whose disease has not progressed following definitive platinum-based chemoradiation therapy.

This study consisted of a Screening Phase, an On-treatment Phase and a Post-discontinuation Follow-up Phase.

Osimertinib/matching placebo 80 mg once daily was administered orally until objective radiological disease progression per RECIST v1.1 (as confirmed by BICR), or until another treatment discontinuation criterion was met. The initial dose of osimertinib 80 mg once daily could be reduced to 40 mg to allow for management of study treatment-related toxicities.

- PK Objectives and outcomes/endpoints

PK objectives and endpoints for LAURA study are described in Table 1:

Table 1. Objectives and endpoints

Objectives	Endpoints
Secondary	
To assess the PK of osimertinib	• Trough plasma concentrations of osimertinib, and its metabolite AZ5104 If conducted, PK parameters (CLss/F, Css,min, Css,max, and AUCss) may be derived using population PK analysis and reported separately to the CSR. Data from this study may form part of a pooled analysis with data from other studies [a]

- Sampling times

Samples for PK analysis were collected on treatment phase at pre-dose on day 29, day 85 and day 169 (Table 2). PK analysis was carried out for osimertinib and its metabolite AZ5104.

Table 2. Sample schedule

	Screening		Treatment Period									Follow-up Period		
Visit (V) Name	**Screening visit Part I**	**Screening visit Part II/V1**	**Randomization /V2**	**V3**	**V4**	**V5**	**V6**	**V7-9[a]**	**V10-11[a]**	**V12+[a]**	**Treatment Discontinuation**	**28-day Follow-up[b]**	**Progression Follow-up[c]**	**Survival Follow-up**
Week (W)	NA	NA	1	2	4	8	12	16-24	32-40	48+	NA	NA	NA	NA
Day	NA	-28 to 0	1	15	29	57	85	113-169	225-281	337+	NA	NA	NA	NA
Window (days)	NA	NA	NA	±2	±2	±3	±3	±3	±7	± 7	+ 7	+ 7	± 7	± 7
Pharmacokinetic measurements														
Pre-dose blood sample (including metabolites)[l]					X		X	X Day 169/ Week 24 only						

. Plasma PK sampling (2 mL each) will be performed at pre-dose on day 29 (visit 4/ week 4), day 85 (visit 6/week 12) and day 169 (visit 9/week 24). Pre-dose PK samples should be collected within 1 hr before the dose on the day of collection.

- Pharmacokinetic parameters

Descriptive statistics for osimertinib and AZ5104 metabolite serum concentrations are presented. The following summary statistics were presented for trough concentration: geometric mean, coefficient of variance, standard deviation, arithmetic mean and standard deviation using untransformed data, minimum and maximum.

- Population analysed

Initially, 216 patients were randomised in LAURA study. From those, 143 patients were included in the osimertinib arm and 73 patients in the placebo arm.

Plasma concentrations were determined only for the osimertinib arm. Out of 143, 136 patients had at least one PK concentration measurable and were included in PK analysis set. Of note, 7 patients were excluded from the PK analysis set as they did not have any measurable PK data available, according to the report

Table 3. Analysis set

	Number of patients		
	Osimertinib	**Placebo**	**Total**
Patients included in PK Analysis Set	136	NA	136
Patients excluded from PK Analysis Set	7	NA	7
Patient did not have any measurable PK data available	7	NA	7

- Pharmacokinetic results

Osimertinib and AZ5104 metabolite serum concentrations at the pre-specified timepoints are presented in Table 4 and Table 5. The MAH declared that osimertinib exposures were at steady state, also within the expected exposure range from prior studies and were similar once they reached steady state.

Table 4. Summary of plasma concentrations (nM) of Osimertinib by treatment group

		Time after dose intake (days) [a]		
Treatment group	Summary statistic	Day 29	Day 85	Day 169
Osimertinib (N=136)	n	118	107	95
	n < LLOQ	0	0	0
	Geometric mean	565.9	496.1	414.2
	CV (%)	54.4	54.5	50.5
	Geometric SD	1.664	1.666	1.611
	Geometric mean + geometric SD	941.8	826.3	667.3
	Geometric mean - geometric SD	340.1	297.8	257.1
	Arithmetic mean	638.2	558.8	455.6
	SD	322.2	279.5	196.6
	Median	540.8	513.8	430.9
	Minimum	56.22	54.04	29.99
	Maximum	1700	1623	1421

Table 5. Summary of plasma concentrations (nM) of AZ5104 by treatment group

		Time after dose intake (days) [a]		
Treatment group	Summary statistic	Day 29	Day 85	Day 169
Osimertinib (N=136)	n	118	108	95
	n < LLOQ	0	0	0
	Geometric mean	60.97	53.09	44.31
	CV (%)	66.9	66.3	59.5
	Geometric SD	1.838	1.828	1.734
	Geometric mean + geometric SD	112.0	97.07	76.82
	Geometric mean - geometric SD	33.18	29.04	25.56
	Arithmetic mean	72.65	62.77	50.98
	SD	45.55	38.17	28.21
	Median	58.75	54.83	45.06
	Minimum	6.277	4.623	4.396
	Maximum	300.7	234.7	155.2

Pharmacokinetics in the target population

Following the pre-submission meeting, the Applicant was requested to provide the following analysis:

1. A tabular comparison between patient characteristics from LAURA study vs the patient characteristic from previous clinical studies.
2. Since only trough PK levels were collected in LAURA study, the MAH should conduct a simulation analysis with the already available popPK model to assess whether model predictions could predict the observed experimental PK evidence.
3. Overlay the experimental evidence collected on different efficacy and safety outcomes with the already developed E-R analyses to check whether similar PK/PD relationship exists in the current indication.

1. **A tabular comparison between patient characteristics from LAURA study vs the patient characteristic from previous clinical studies.**

The MAH provided the below for a tabular comparison between patient characteristics from the LAURA study population and the previous clinical studies of osimertinib monotherapy which have been pooled as ISS population.

Table 6. Key Demographic Characteristics

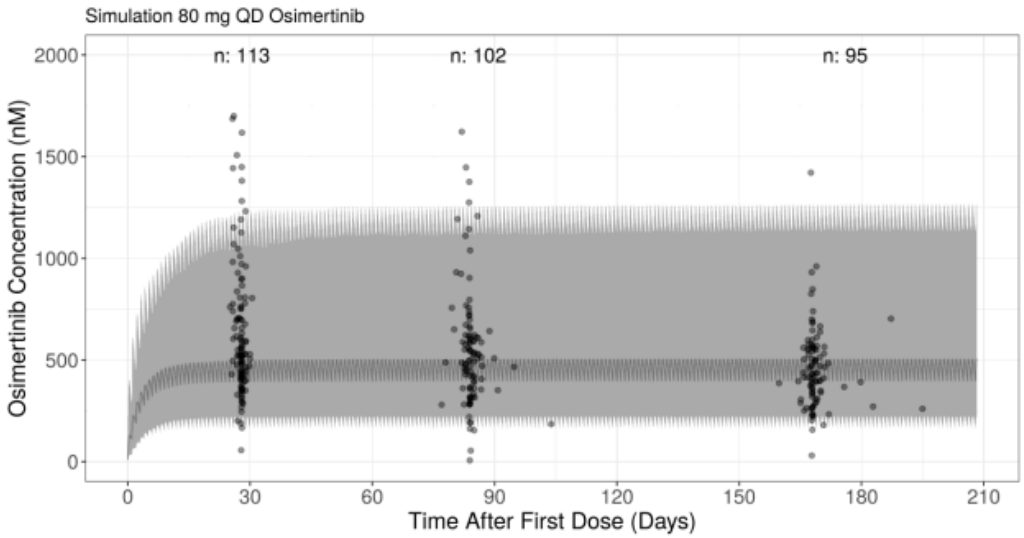
		LAURA Study		Osimertinib monotherapy safety pool (N = 1813)
		Osimertinib (N = 143)	Placebo (N = 73)	
Demographics				
Age (years)	n	143	73	1813
	Mean (sd)	60.9 (10.38)	62.3 (12.01)	61.8 (10.66)
	Median	62.0	64.0	63.0
	Min, Max	36, 84	37, 83	25, 89
Age group (years), n (%)	< 65	81 (56.6)	39 (53.4)	1043 (57.5)
	65 to 74 years	49 (34.3)	20 (27.4)	563 (31.1)
	≥ 65	62 (43.4)	34 (46.6)	770 (42.5)
	≥ 75	13 (9.1)	14 (19.2)	207 (11.4)
Sex, n (%)	Male	53 (37.1)	31 (42.5)	641 (35.4)
	Female	90 (62.9)	42 (57.5)	1172 (64.6)
Race, n (%)	Black or African	0	0	14 (0.8)
	Native Hawaiian or other Pacific Islander	0	0	1 (0.1)
	American Indian or Alaska Native	2 (1.4)	1 (1.4)	6 (0.3)
	Asian	116 (81.1)	62 (84.9)	1170 (64.5)
	White	20 (14.0)	10 (13.7)	593 (32.7)
	Other	5 (3.5)	0	21 (1.2)
	Non-Asian [a]	27 (18.9)	11 (15.1)	635 (35.0)
Patient characteristics				
Weight (kg)	N	142	72	1804
	Mean (sd)	61.5 (12.71)	63.9 (13.94)	63.1 (13.90)
	Median	60.0	61.0	61.7
	Min, Max	35, 106	37, 109	29, 122
Disease characteristics				
WHO PS, n (%)	0 (Normal activity)	80 (55.9)	31 (42.5)	590 (32.5)
	1 (Restricted activity)	63 (44.1)	42 (57.5)	812 (44.8)
Smoking status	Never	102 (71.3)	49 (67.1)	1226 (67.6)
	Ever	41 (28.7)	24 (32.9)	587 (32.4)

[a] Non-Asian includes the race groups White, Black or African American, Native Hawaiian or other Pacific Islander, American Indian or Alaska Native, or Other.

2. **Since only trough PK levels were collected in LAURA study, the MAH should conduct a simulation analysis with the already available popPK model to assess whether model predictions could predict the observed experimental PK evidence.**

To assess the similarity of exposures from LAURA at a population level, the previously established PopPK model (data pooled from AURA, AURA2, AURA3, FLAURA, ADAURA, and FLAURA2) was used as the reference model. Exposures of osimertinib 80 mg, once daily were simulated using EBE of all patients from this previously characterised model.

Figure 1. Comparison of steady-state trough concentrations of osimertinib observed in the LAURA study vs simulated global PopPK exposures of osimertinib 80 mg, once daily



* Grey shaded areas demonstrate the 95% CI concentration-time profile of osimertinib 80 mg. Dark grey line depicts the median steady-state plasma concentration time profile of osimertinib. Grey dots depict steady-state trough-level exposures of osimertinib 80 mg observed in PK-evaluable LAURA patients enrolled globally (N=136).

** The "n" is based on PK observations of 80 mg QD in LAURA with steady-state and PK evaluable flags

3. **Overlay the experimental evidence collected on different efficacy and safety outcomes with the already developed E-R analyses to check whether similar PK/PD relationship exists in the current indication**.

Exposure – efficacy:

In LAURA, the relationships between observed mean osimertinib and AZ5104 Cmin,ss and PFS in patients enrolled in the investigational arm (osimertinib) were assessed via Kaplan Meier plot; patients were stratified by quartiles of mean observed osimertinib and AZ5104 Cmin,ss (Figure 2 and Figure 3). PFS from the placebo arm was overlayed as the control.

In addition, a Cox proportional hazard model was developed to understand the effect of osimertinib Cmin,ss or AZ5104 Cmin,ss on PFS of patients in the investigational arm (osimertinib monotherapy) of LAURA (Table 7).

Table 7. Summary of Likelihood Ratio Test of Mean Observed Osimertinib and AZ5104 Cmin,ss on PFS in the Investigational Arm (Osimertinib Monotherapy)

Run	Model	min2LL *	diff2LL **	Reference	p_value	N
1	Base	472.252	NA	NA	NA	136
2	Mean observed osimertinib Cmin,ss quartiles	471.336	0.916	1	0.822	136
3	Mean observed AZ5104 Cmin,ss quartiles	468.370	3.882	1	0.274	136

*min2LL refers to 2×log likelihood of the model

** diff2LL refers to difference between 2× likelihood of the model and the base model

Figure 2. PFS Kaplan Meier Plots of Patients Stratified by Quartiles of Mean Observed Osimertinib Cmin,ss

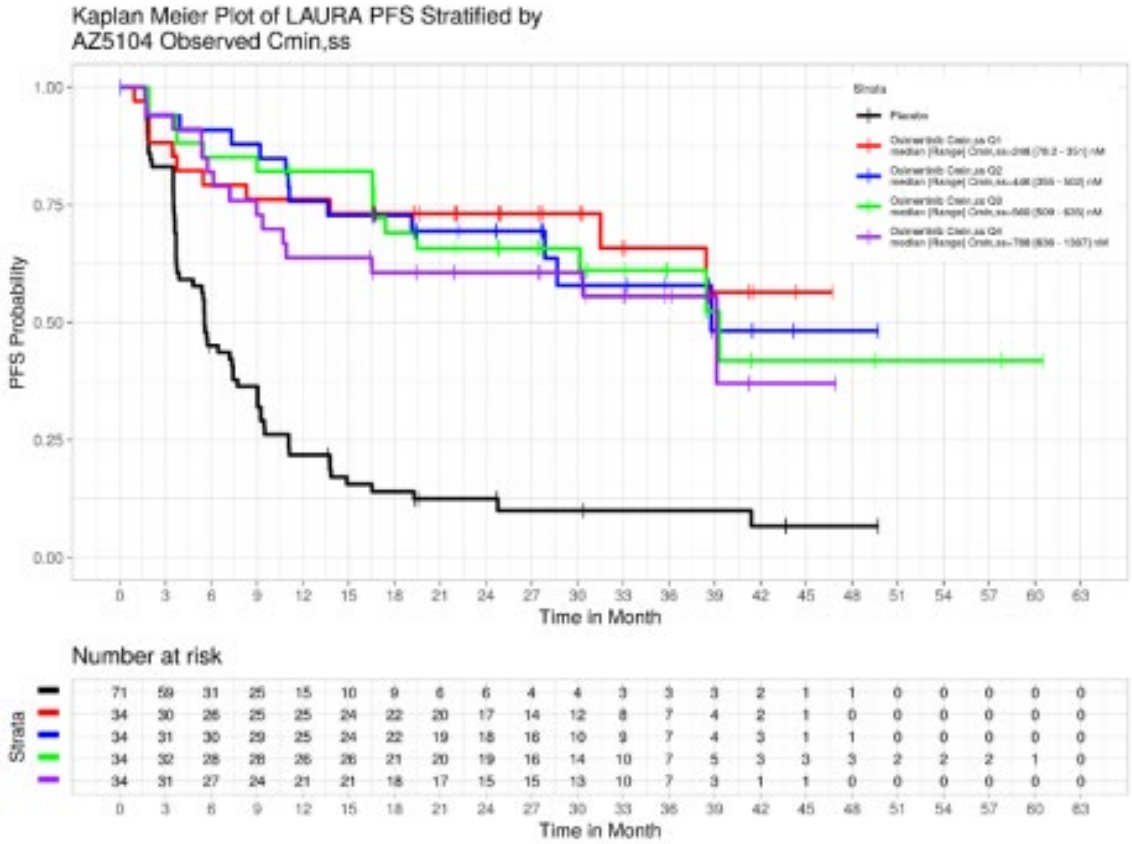
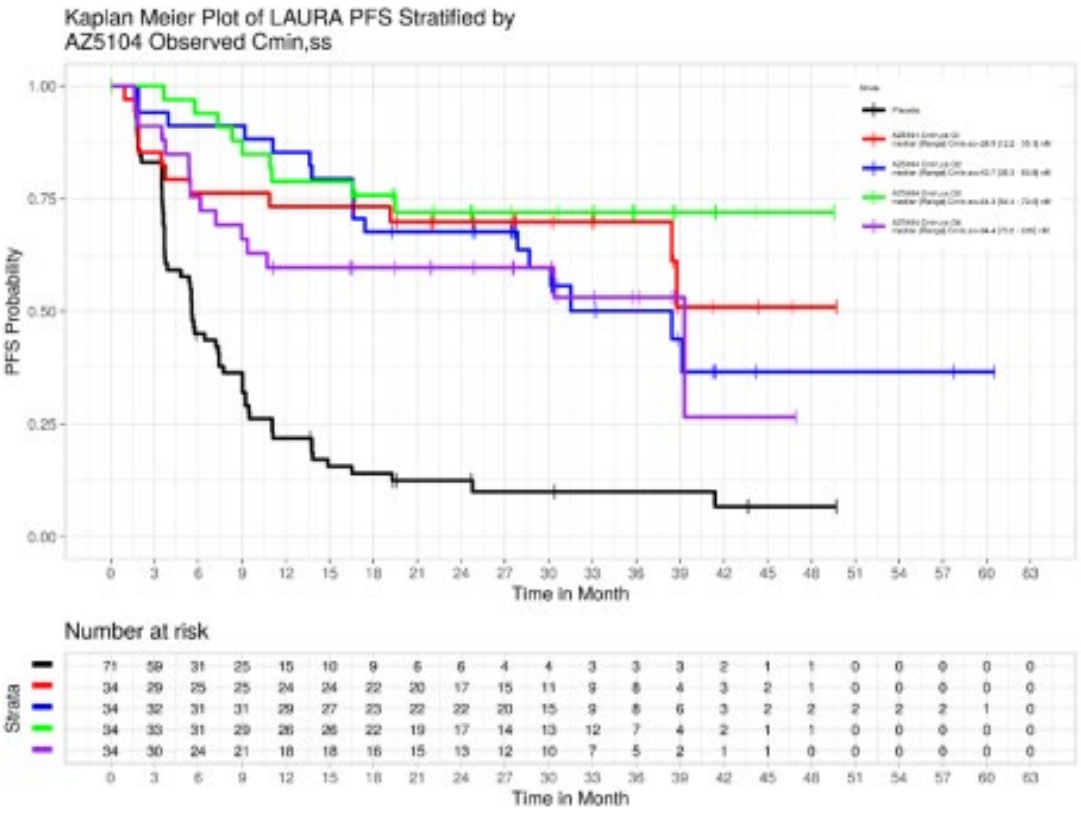


Figure 3. PFS Kaplan Meier Plots with Patients Stratified by Quartiles of Mean Observed AZ5104 Cmin,ss



Exposure-safety:

In the exposure-safety analysis, the following safety endpoints with AE incidence of ≥ 5% in the LAURA investigational arm were evaluated:

- Occurrence of ≥Grade 3 AEs, causally related to osimertinib
- Any AE leading to osimertinib dose interruption
- Any AE leading to osimertinib dose reduction
- Any AE leading to osimertinib dose discontinuation
- Occurrence of Grade ≥1 interstitial lung disease grouped term (inclusive of interstitial lung disease, pneumonitis, and pulmonary fibrosis)
- Occurrence of Grade ≥1 radiation pneumonitis grouped term (inclusive of radiation fibrosis – lung and radiation pneumonitis)

Figure 4. Distribution of Observed Mean Cmin,ss of Osimertinib in Patients Treated with Osimertinib Monotherapy, Categorised by the Presence (Yes) or Absence (No) of Pre-selected Safety Endpoints

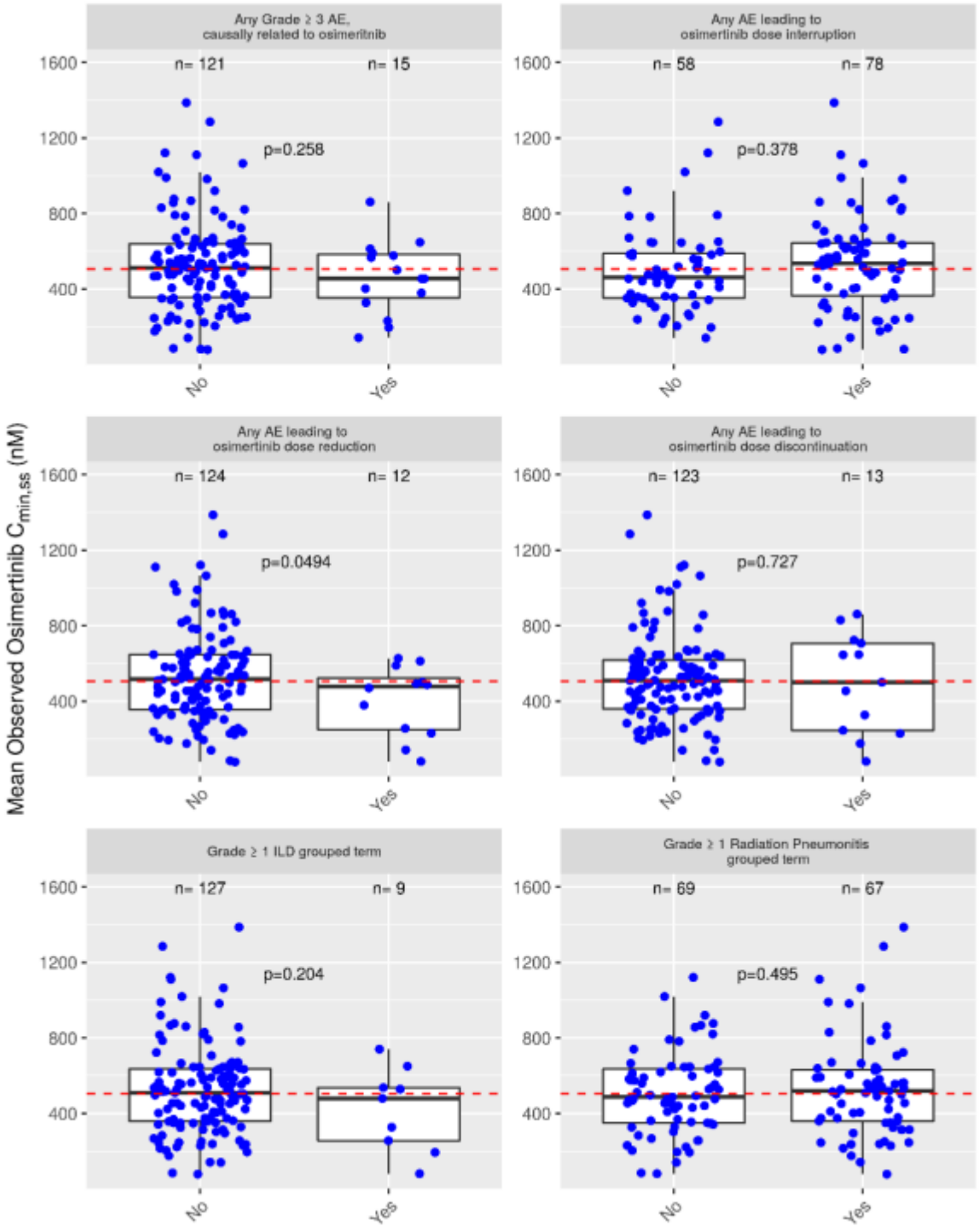
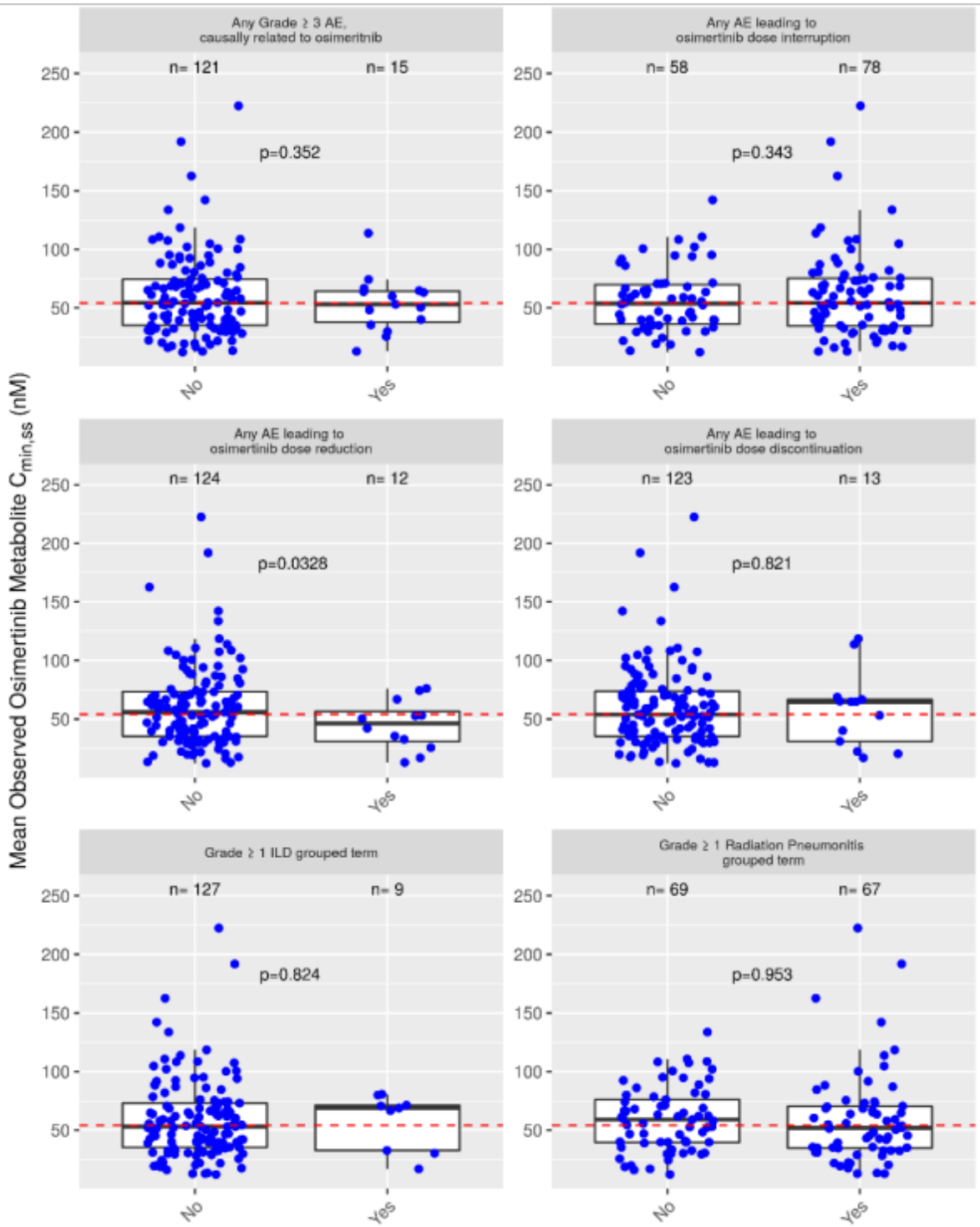


Figure 5. Distribution of Observed Mean Cmin,ss of AZ5104 in Patients Treated with Osimertinib Monotherapy, Categorised by the Presence (Yes) or Absence (No) of Pre-selected Safety Endpoints



2.3.3. Discussion on clinical pharmacology

Osimertinib as monotherapy is currently approved for the adjuvant treatment after complete tumour resection in adult patients with stage IB-IIIA non-small cell lung cancer (NSCLC) whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations, for the first-line treatment of adult patients with locally advanced or metastatic NSCLC with activating EGFR mutations and for the treatment of adult patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC. Most recently, osimertinib has been approved in combination with chemotherapy the first-line treatment of patients with locally advanced or metastatic NSCLC whose tumours have exon 19 deletions or exon 21 (L858R) substitution mutations. The aim of this variation is to seek approval for the treatment of adult patients with locally advanced, unresectable (stage III) NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations and whose disease has not progressed during or following platinum-based chemoradiation therapy.

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. Even so, this cross-validation was not acceptable and the justification provided by the MAH for not performing a new cross validation between both laboratories for low range assay using spiked samples at low concentrations levels (between LLOQ and 15nM) was not acceptable. This issue was not further pursued in this procedure considering that results from LAURA study are not included in popPK model. For future procedures, the MAH should perform a new cross validation between both laboratories for low range assay.

Although the overall analysis was carried out according to the ICH M10 Guideline, carry over was observed for both analytes in two different runs. The MAH has appropriately justified that the contribution of the interference peaks observed was not significant. For future procedures, to avoid the possible influence of carry over, it would be adequate to include two blank samples after every high calibration standard but also after every high QC.

In addition, during the previous variation procedure (EMEA/H/C/004124/II/0053), the MAH was asked to validate stability using one low QC and one high QC for each method, according to the ICH M10 Guideline. Nevertheless, the MAH did not comply with this request. Considering that the result of the study samples analysed with the low range method were disregarded, this issue was not further pursued in this procedure. However, for future procedures, the MAH should validate stability using one low QC and one high QC for each method used during sample analysis.

Of note, for AZD9291 and AZ5104, the MQC used were not within 30-50% of the Upper Limit of Quantification (to be in accordance with ICH M10 Guideline). In previous procedures (EMEA/H/C/004124/II/0053), the MAH provided a justification in this regard. It is acknowledged that the analysis of the samples from Study D5160C00048 was carried out before the assessment of the last procedure. Therefore, the MAH is reminded that for sample analysis that are carried out after April 2023, a low QC, medium QC and high QC that comply with the aforementioned Guideline (apart from additional QCs representative of the analysed concentrations) have to be included.

Pharmacokinetics

During LAURA study, 143 patients were included in the osimertinib arm to receive 80 mg of Tagrisso film-coated tablets. The dose of 80 mg could be reduced to 40 mg due to study treatment-related toxicities. Twelve (12) patients had dose reduction during the study and has also confirmed that those samples obtained after dose reduction, were not included in PK statistical analysis.

Sampling time points (pre-dose at day 29, 85 and 169) are acceptable to evaluate concentrations at steady state since, according to the pharmacokinetic properties of Tagrisso EPAR, "AUC and Cmax increased dose proportionally over 20 to 240 mg dose range. Administration of osimertinib once daily results in approximately 3-fold accumulation with steady-state exposures achieved by 15 days of dosing. At steady-state, circulating plasma concentrations are typically maintained within a 1.6-fold range over the 24-hour dosing interval".

Seven (7) patients were excluded from the PK analysis set as they did not have any measurable PK data available. The MAH has clarified that this was due to different reasons: discontinued study treatment prior to the first PK sample timepoint at Day 29, dose interruptions prior to or on Day 29 that precluded them from having a PK sample taken, Covid-19 pandemic and protocol deviations.

Finally, a summary of plasma concentrations for osimertinib and AZ5104 metabolite was included. As it can be seen, geometric mean of the concentrations through sampling times is similar for both analytes.

Pharmacokinetics in the target population

Taking into consideration that the pharmacokinetics and exposure-response of osimertinib have been previously characterised with data from 2196 EGFRm NSCLC patients in adjuvant, first line, and second line or greater settings and that not meaningful differences were observed in the pharmacokinetics across the different disease settings, it was agreed during the pre-submission meeting that it was not necessary to submit the complete Clinical Pharmacology dossier provided that the following analysis were performed:

1. A tabular comparison between patient characteristics from LAURA study vs. the patient characteristic from previous clinical studies.
2. A simulation analysis with the already available popPK model to assess whether model predictions could predict the observed experimental PK evidence.
3. Overlay the experimental evidence collected on different efficacy and safety outcomes with the already developed E-R analyses to check whether similar PK/PD relationship exists in the current indication.

The comparison between the LAURA study population and the pool population from previous clinical studies of osimertinib in monotherapy (safety pool) showed overall well-balanced characteristics between both populations. However, a higher proportion of Asian patients were randomised in the LAURA study compared to the osimertinib monotherapy safety pool (82.4% vs 64.5%). The reason for that difference is due to the higher prevalence of EGFR mutations in Asian population compared to Caucasian populations (40-50 % vs. 10-15 %). On the other hand, the WHO PS status was only provided from 77.33% of the safety pool population. However, as patients in the safety pool have metastatic of later stage disease compared to LAURA study, it is expected that the safety pool population will have a greater proportion of patients with PS 1. Despite these minor differences, a consistent and similar distribution of demographic characteristics between LAURA study and previous clinical studies has been demonstrated.

The current osimertinib Pop PK model (data pooled from AURA, AURA2, AURA3, FLAURA, ADAURA, and FLAURA2, for further details see procedure EMEA/H/C/004124/II/0053) has been used to simulate exposures of 80 mg of osimertinib administered once daily using empirical bayes estimates (EBE) from all patients from this model. Observed Cmin,ss concentrations from LAURA study were superposed on the simulated plot. The results show a greater experimental variability in the first sample (~30 days) compared to the last sample, which could be explained by differences on achieving steady-state conditions. The 95% CI covers most of the experimental Cmin,ss observations from LAURA study, suggesting that the previously developed population PK model is able to adequately capture the PK

evidence from LAURA study and no relevant differences on the PK processes between previous clinical studies and LAURA study exist.

In order to evaluate whether similar PK/PD relationship exists in the current indication, the experimental evidence exposure and different efficacy and safety outcomes have been overlaid with the previous developed Exposure-Response analysis.

Osimertinib and AZ5104 Cmin,ss have been used as exposure parameters for both efficacy and safety analysis.

In the efficacy analysis, PFS Kaplan Meier plots stratified by quartiles of mean observed osimertinib and AZ5104 Cmin,ss were developed. The results showed that PFS seems to be independent of exposure as high degree of overlapping is observed. Furthermore, a Cox proportional hazard model was constructed and the results indicate no statistically significant differences in PFS among the quartiles of observed osimertinib or AZ5104 Cmin,ss. However, 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.

An exploratory exposure-safety analysis was performed using AEs of interest that included occurrence of ≥Grade 3 AEs, causally related to osimertinib, any AE leading to osimertinib dose interruption, any AE leading to osimertinib dose reduction, any AE leading to osimertinib dose discontinuation, occurrence of Grade ≥ 1 interstitial lung disease grouped term and occurrence of Grade ≥1 radiation pneumonitis grouped term as safety outcomes. No statistically significant relationships were observed between osimertinib or AZ5104 Cmin,ss and the different safety outcomes.

The exposure-response analysis from LAURA study is consistent with previous analysis that included data from AURA3, ADAURA, FLAURA, and FLAURA2.

2.3.4. Conclusions on clinical pharmacology

The pharmacokinetics and exposure-response of osimertinib have been previously characterised with data from EGFRm NSCLC patients in adjuvant, first line, and second line or greater settings. A simulation analysis with the current popPK model could predict the observed experimental evidence from LAURA study, therefore, no relevant differences on the PK processes seem to be present. Furthermore, the exposure-response analysis from LAURA study is consistent with previous analysis that included data from AURA3, ADAURA, FLAURA, and FLAURA2.

2.4. Clinical efficacy

2.4.1. Dose response study(ies)

Not applicable.

2.4.2. Main study(ies)

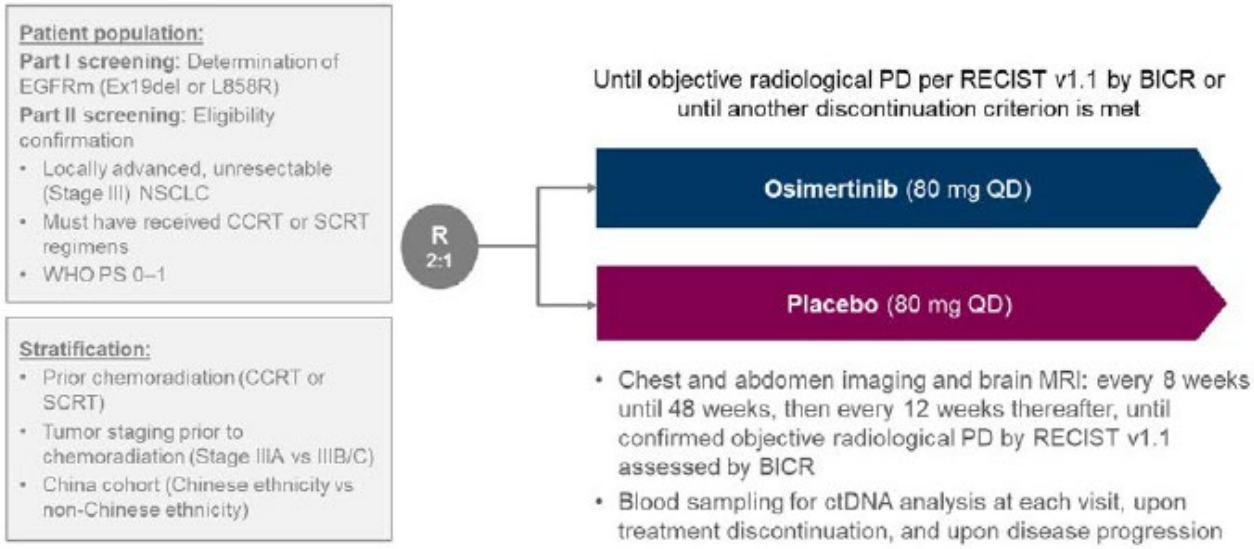
Study LAURA: A Phase III, Randomised, Double-Blind, Placebo-Controlled, Multicentre, International Study of Osimertinib as Maintenance Therapy in Patients with Locally Advanced,

Unresectable EGFR Mutation-Positive Non-Small Cell Lung Cancer (Stage III) Whose Disease Has Not Progressed Following Definitive Platinum-Based Chemoradiation Therapy

Methods

The LAURA study is a Phase III randomised, double-blind, placebo-controlled, multicentre global study comparing the efficacy and safety of osimertinib as a maintenance therapy versus placebo in patients with locally advanced, unresectable (Stage III) NSCLC with centrally-confirmed EGFR mutations (Ex19del and L858R) whose disease has not progressed during or following definitive platinum-based CRT.

Figure 6. Flowchart of Study LAURA design



Study participants

Inclusion criteria

- Part I screening

Part I screening applied only to patients that did not have a pre-existing local EGFR test result, derived from a tissue-based FDA-approved CDx for Tagrisso (i.e., cobas® EGFR Mutation Test v2 or FoundationOne® CDx test), performed in a CLIA-certified (USA sites) or an accredited local laboratory (sites outside of the USA) and conducted according to the manufacturer's instructions for use.

For inclusion in Part I of the study, patients had to fulfil all of the following inclusion criteria (and none of Part II screening exclusion criteria 1, 2, 7, 9-11 and 15-20):

Informed consent

1. Capable of giving signed informed consent which included compliance with the requirements and restrictions listed in the informed consent form (ICF) and Clinical Study Protocol (CSP).
2. Provision of a signed and dated written ICF for Part I screening prior to any mandatory provision of tumour samples for testing of EGFR mutation status.

Age and sex

3. Male or female, aged at least 18 years. Patients from Japan were to be aged at least 20 years.

Type of patient and disease characteristics

4. Patients with histologically documented NSCLC of predominantly non-squamous pathology* who presented with locally advanced, unresectable (Stage III) disease (according to Version 8 of the IASLC Staging Manual in Thoracic Oncology).

** Patients with a Stage III tumour of squamous histology who had a pre-existing local positive test result (Ex19del or L858R), irrespective of EGFR test used or lab accreditation, were eligible for Part I screening*

It was recommended but not required that except for overt cT4 disease, nodal status N2 or N3 should have been proven by biopsy, via endobronchial ultrasound, mediastinoscopy, or thoracoscopy, or in absence of biopsy, should have been confirmed with whole body ^{18}F-fluoro-deoxyglucose PET plus contrast-enhanced CT in addition to or in combination with PET.

Patient could provide an unstained FFPE tumour tissue* sample in a quantity sufficient to allow for prospective central analysis of EGFR mutation status.

** An archived tissue or new biopsy specimen, when no archived tissue was available, was acceptable. Patients should only have had a new biopsy if it was considered a medically acceptable risk by the Investigator.*

- Part II screening

Part II screening applied to: (i) patients that had a pre-existing local EGFR mutation-positive (Ex19del or L858R) test result, derived from a tissue-based FDA-approved CDx for Tagrisso (i.e., cobas® EGFR Mutation Test v2 or FoundationOne® CDx test), performed in a CLIA-certified (USA sites) or an accredited local laboratory (sites outside of the USA) and conducted according to the manufacturer's instructions for use; or (ii) patients who completed Part I screening and had centrally confirmed EGFR mutation (Ex19del or L858R) positive NSCLC.

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

1. Capable of giving signed informed consent which included compliance with the requirements and restrictions listed in the ICF and CSP.
2. Provision of a signed and dated, written ICF for the main study prior to any mandatory study specific procedures, sampling, and analyses.
3. Provision of signed and dated written genetic informed consent prior to collection of sample for genetic analysis for inclusion in the optional genetic research.

Note: If a patient declined to participate in any voluntary exploratory research and/or genetic component of the study for optional test, there was no penalty or loss of benefit to the patient and he/she was not excluded from other aspects of the study.

Age and sex

4. Male or female, aged at least 18 years. Patients from Japan were to be aged at least 20 years.

Type of patient and disease characteristics

5. Patients with histologically documented NSCLC of predominantly non-squamous pathology* who presented with locally advanced, unresectable (Stage III) disease (according to Version 8 of the IASLC Staging Manual in Thoracic Oncology).

** Patients with a Stage III tumour of squamous histology who had a pre-existing local positive test result (Ex19del or L858R), irrespective of EGFR test used or lab accreditation, and confirmed by central testing during Part I screening, were eligible for Part II screening.*

It was recommended but not required that except for overt cT4 disease, nodal status N2 or N3 should have been proven by biopsy, via endobronchial ultrasound, mediastinoscopy, or thoracoscopy, or in absence of biopsy, should have been confirmed with whole body ^{18}F-fluoro-deoxyglucose PET plus contrast-enhanced CT in addition to or in combination with PET.

6. The tumour harboured one of the two common EGFR mutations known to be associated with EGFR-TKI sensitivity (Ex19del, L858R), either alone or in combination with other EGFR mutations, as assessed by a tissue-based FDA-approved CDx for TAGRISSO (i.e., cobas® EGFR Mutation Test v2 or FoundationOne® CDx test), performed in a CLIA-certified (USA sites) or an accredited local laboratory (sites outside of the USA); or by central testing (using the cobas® EGFR Mutation Test v2).
7. Patients must not have had disease progression during or following definitive platinum-based CRT.
8. Patients must have received either CCRT or SCRT regimens as defined below:
    - CCRT: Patients must have received at least 2 cycles of platinum-based chemotherapy (or 5 doses of weekly platinum-based chemotherapy) concurrent with radiation therapy, which must have been completed ≤ 6 weeks prior to randomisation. The final chemotherapy administration must have been completed prior to, or concurrently with, the final dose of radiation. Note: A final cycle of chemotherapy was permitted up to 7 days after the last dose of radiation, if at least 2 cycles had already been given concurrently. Consolidation chemotherapy after radiation was not permitted but administration of chemotherapy prior to CCRT was permitted.
    - SCRT: SCRT is defined as chemotherapy followed by radiation therapy and not radiation therapy followed by chemotherapy. Patients must have received at least 2 cycles of platinum-based chemotherapy prior to radiation treatment, which must have been completed ≤ 6 weeks prior to randomisation. Consolidation chemotherapy after radiation was not permitted.
    - If a patient had received at least 2 cycles of platinum-based chemotherapy and subsequently received one cycle of platinum-based chemotherapy or < 5 doses of weekly platinum-based chemotherapy concurrent with radiation therapy, this was considered SCRT.
    - If a patient had received one cycle of platinum-based chemotherapy and subsequently received one cycle of platinum-based chemotherapy or < 5 doses of weekly platinum-based chemotherapy concurrent with radiation therapy, this was not considered CCRT or SCRT and the patient was not eligible.
9. The platinum-based chemotherapy regimen must have contained one of the following agents: etoposide, vinblastine, vinorelbine, paclitaxel, docetaxel, or pemetrexed, according to the local SoC regimens. Gemcitabine was permitted if used prior to radiation but not with radiation. Where possible, chemotherapy regimens should have been given according to NCCN or ESMO guidelines.
10. Patients must have received a total dose of radiation of 60 Gy ± 10% (54 to 66 Gy) as part of the CRT in order to be randomised. It was recommended but not required that patients eligible for randomisation had a:
    - Mean lung dose < 20 Gy and/or V20 < 35%
    - Mean oesophagus dose < 34 Gy
    - Heart V50 < 25%, V30 < 50%, and V45 < 35%
11. WHO performance status of 0 or 1 at Part II screening and Day 1.

12. Life expectancy > 12 weeks at Day 1.

Reproduction

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 had to use adequate contraceptive measures, must not have been breast-feeding, and had to have a negative pregnancy test prior to first dose of study drug; or female patients had to have evidence of non-child-bearing potential by fulfilling one of the following criteria at screening:
    - Post-menopausal, defined as aged more than 50 years and amenorrhoeic for at least 12 months following cessation of all exogenous hormonal treatments
    - Female patients less than 50 years old were considered post-menopausal if they had been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatments, and with luteinising hormone and follicle-stimulating hormone levels in the post-menopausal range for the institution
    - Documentation of irreversible surgical sterilisation by hysterectomy, bilateral oophorectomy, or bilateral salpingectomy but not tubal ligation.
14. Male patients had to be willing to use barrier contraception; i.e., condoms.

Exclusion criteria

- Part I screening

Patients were eligible to be included in Part I of the study only if none of the following Part II screening exclusion criteria applied: numbers 1, 2, 7, 9-11, and 15-20.

- Part II screening

Patients were eligible to be included in the Part II screening process only if none of the following exclusion criteria applied:

Medical conditions

1. Mixed small cell and NSCLC histology.
2. History of ILD prior to CRT.
3. Symptomatic pneumonitis following CRT.
4. Any unresolved toxicity CTCAE > Grade 2 from the prior CRT. Patients with irreversible toxicity that was not reasonably expected to be exacerbated by study drug could be included (e.g., hearing loss) after consultation with the AstraZeneca medical monitor.
5. Any of the following cardiac criteria:
    - Mean resting QTc > 470 msec, obtained from 3 ECGs
    - Any clinically important abnormalities in rhythm, conduction, or morphology of resting ECG, e.g., complete left bundle branch block, third-degree heart block, second-degree heart block
    - Patient with any factors that increase the risk of QTc prolongation or risk of arrhythmic events such as electrolyte abnormalities (including* serum/plasma potassium < LLN, serum/plasma magnesium < LLN, and serum/plasma calcium < 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 (TdP).

** Correction of electrolyte abnormalities to within normal ranges could be performed during the screening period.*

6. Inadequate bone marrow reserve or organ function, as demonstrated by any of the following laboratory values:
    - Absolute neutrophil count < 1.5 × 109/L
    - Platelet count < 100 × 109/L
    - Haemoglobin < 90 g/L
    - ALT > 2.5 × ULN
    - AST > 2.5 × ULN
    - Total bilirubin > 1.5 × ULN or > 3 × ULN in the presence of documented Gilbert's Syndrome (unconjugated hyperbilirubinemia)
    - Creatinine > 1.5 × ULN concurrent with creatinine clearance < 30 mL/min (measured or calculated by Cockcroft and Gault equation); confirmation of creatinine clearance was only required when creatinine was > 1.5 × ULN.
7. History of other malignancies, except: adequately treated non-melanoma skin cancer or lentigo maligna, curatively treated in-situ cancer, or other solid tumours curatively treated with no evidence of disease for > 5 years following the end of treatment and which, in the opinion of the treating physician, did not have a substantial risk of recurrence of the prior malignancy.
8. Any evidence of severe or uncontrolled systemic diseases, including uncontrolled hypertension and active bleeding diatheses, which in the Investigator's opinion made it undesirable for the patient to participate in the trial or which would jeopardise compliance with the protocol. Active infection, including HBV, hepatitis C and HIV. Active infection included any patients receiving treatment for infection. Patients with a resolved or chronic HBV infection were eligible if they were:
    - Negative for HBsAg and positive for hepatitis B core antibody; or
    - Positive for HBsAg, negative for HBeAg but for > 6 months had had transaminases levels below ULN and HBV DNA levels below 2000 IU/mL (i.e., were in an inactive carrier state).
9. 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.

Prior/concomitant therapy

10. Prior treatment with any chemotherapy, radiation therapy, immunotherapy, or investigational agents for NSCLC outside of that received in the definitive setting for Stage III disease (chemotherapy and radiotherapy in SCRT and CCRT regimens was allowed for treatment of Stage III disease). Prior surgical resection (i.e., Stage I, II or III) was permitted.
11. Prior treatment with EGFR-TKI therapy.
12. Major surgery as defined by the Investigator within 4 weeks of the first dose of study drug.
13. Patients who were receiving (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 to receiving the first dose of study drug). All patients had to try to avoid concomitant use of any medications, herbal supplements and/or ingestion of foods with known inducer effects on CYP3A4.

Prior/concurrent clinical study experience

14. Participation in another clinical study with an investigational product administered in the 4 weeks prior to randomisation (see Section 9.9.1). Patients in the follow-up period of an interventional study were permitted.

Other exclusions

15. Patient with involvement in the planning and/or conduct of the study (applied to both the MAH staff and/or staff at the study site).
16. Judgement by the Investigator that the patient should not participate in the study if the patient was unlikely to comply with study procedures, restrictions and requirements.
17. Patient was previously randomised in the present study.
18. For female patients only – was currently pregnant (confirmed with positive pregnancy test) or breast-feeding.
19. Contraindication to MRI, including but not limited to, claustrophobia, pace-makers, metal implants, intracranial surgical clips and metal foreign bodies.
20. History of hypersensitivity to active or inactive excipients of osimertinib or drugs with a similar chemical structure or class to osimertinib.

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

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

Treatments

Eligible patients were randomised to one of the following arms:

- Osimertinib: 80 mg PO once daily
- Matching Placebo: 80 mg PO once daily.

Table 8. Study treatments

	Osimertinib	Placebo
Study treatment name	Osimertinib (AZD9291)	Placebo
Dosage formulation	80 mg tablets 40 mg tablets	Placebo tablets matched osimertinib tablets in size, colour, weight, and appearance.
Route of administration	Oral	Oral
Provider	AstraZeneca	AstraZeneca

Dosing instructions	Patients were instructed to swallow one tablet daily. Tablets were to be taken whole with approximately 240 mL water, with or without food. The initial dose of osimertinib 80 mg/placebo QD could be reduced to 40 mg QD to allow for management of study treatment-related toxicities (see Section 9.4.5.1). Once the dose of osimertinib/placebo was reduced to 40 mg QD, the patient was to remain on the reduced dose until termination from study treatment. Re-challenge of 80 mg/placebo was not allowed. Doses were to be taken approximately 24 hours apart at the same time each day. Doses were not to be missed. If a patient missed taking a scheduled dose, within a window of 12 hours, it was acceptable to take the dose. If it was more than 12 hours after the scheduled dose time, the missed dose was not to be taken, and patients were instructed to take the next dose at the next scheduled time. If a patient vomited after taking their study drug, they were not to make up for this dose, but were to take the next scheduled dose. On site visit days on which PK samples were scheduled, the dosing was to be delayed until arrival at the site. Patients were not to take their dose until instructed to do so by site personnel.
Packaging and labelling	Tablets were provided in HDPE bottles with child-resistant closures. Each bottle was labelled in accordance with GMP Annex 13 and per country regulatory requirement.

Study treatment was to continue (prior to the primary analysis) until objective radiological disease progression occurred as defined by RECIST v1.1 and as confirmed by BICR or until another discontinuation criterion was met. Patients assigned to osimertinib could continue receiving osimertinib (open-label) after BICR-confirmed progression if, in the opinion of their treating physician, they were continuing to derive clinical benefit, or disease extent has been characterised by CT or MRI scan at the time of progression. Patients assigned to placebo could switch to open-label osimertinib after BICR-confirmed progression, according to local clinical practice and the judgement of their treating physician.

Objectives and endpoints

Table 9. Objectives and endpoints

Objectives	Endpoints
Primary	
To assess the efficacy of osimertinib treatment compared with placebo as measured by PFS	• PFS using BICR assessment according to RECIST v1.1 Sensitivity analysis of PFS using Investigator assessment according to RECIST v1.1
Secondary	
To assess the efficacy of osimertinib treatment compared with placebo by assessment of PFS in patients with: • EGFR Ex19del or L858R mutation • EGFR Ex19del or L858R mutation detectable in plasma-derived ctDNA	• PFS using BICR assessment according to RECIST v1.1 Sensitivity analysis of PFS using Investigator assessment according to RECIST v1.1
To assess the efficacy of osimertinib versus placebo on CNS PFS	• Time to CNS PFS (time to the earliest of CNS progression or death) using BICR assessments according to RECIST v1.1 • Cumulative incidence rate of CNS PFS by BICR at 12 and 24 months
To further assess the efficacy of osimertinib compared with placebo	• OS • ORR • DoR • DCR and tumour shrinkage (depth of response) • TTDM All assessed by BICR according to RECIST v1.1 • TTD
To further assess the efficacy of osimertinib compared to placebo post-progression	• PFS2 • TFST • TSST
To assess disease-related symptoms and health-related QoL in patients treated with osimertinib compared with placebo	• Change from baseline in EORTC QLQ-C30 • Change from baseline in EORTC QLQ-LC13
To assess the safety and tolerability profile of osimertinib compared with placebo	• AEs (graded by CTCAE v5) • Clinical chemistry, haematology, and urinalysis • Vital signs (pulse and blood pressure), physical examination, weight • ECG parameters • LVEF • WHO Performance Status

To assess the PK of osimertinib	• Trough plasma concentrations of osimertinib, and its metabolite AZ5104 If conducted, PK parameters (CLss/F, Css,min, Css,max, and AUCss) may be derived using population PK analysis and reported separately to the CSR. Data from this study may form part of a pooled analysis with data from other studies [a]
Exploratory	
To assess potential treatment-related adverse effects in patients treated with osimertinib compared with placebo using PRO-CTCAE	The PRO-CTCAE questionnaire will be used to identify change in treatment-related symptoms
To assess the patients' overall impression of the severity of their cancer symptoms using PGIS	Proportion of patients assessing current symptom severity
To compare osimertinib treatment with placebo treatment on health state utility	The EQ-5D-5L health state utility index will be used to derive health state utility based on patient-reported data.
To compare health resource use associated with osimertinib treatment versus placebo	Health Resource Use Module
To investigate the relationship between osimertinib (and metabolite) PK and selected endpoints (which may include efficacy, safety and/or PRO), where deemed appropriate	Correlation of PK with other primary, secondary or exploratory endpoints in patients treated with osimertinib.[a]
To compare the baseline tumour EGFR mutation status in screened patients with evaluable results from baseline plasma samples Data may be used to support diagnostic development	Comparison of EGFR mutation status between tumour DNA and plasma-derived ctDNA.[b]
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.	Comparison of EGFR mutation status between the local EGFR mutation test results and central cobas® EGFR Mutation Test v2 results from tumour samples with evaluable results.[b]
To collect and store DNA for future exploratory research into genes/genetic variation that may influence PK or response to osimertinib (ie, absorption, distribution, metabolism, excretion, safety and efficacy) and/or susceptibility to/development of cancers	Correlation of polymorphisms with variation in PK, pharmacodynamics, safety or response observed in patients treated with osimertinib or comparator.[a]
To assess the relationship between PK and blood-borne biomarkers.	Correlation of blood-based biomarkers, including alterations in ctDNA, with variation in PK.[a]

To collect and store tumour samples to evaluate the association between exploratory biomarkers and key efficacy endpoints	Key markers to include, but not limited to mutations, amplifications, or expression changes in EGFR mutations, HER2 and MET.[a]
To collect and store plasma for isolation of ctDNA and to evaluate the association between exploratory biomarkers and key efficacy endpoints	Longitudinal analysis of ctDNA for mutations, amplifications or expression changes in EGFR, HER2, MET and other genes.[a]
To collect and store plasma to assess the relationship between blood-borne biomarkers and key efficacy endpoints	Biomarkers will include but will not be limited to growth factors, or cytokines.[a]
To identify innate resistance mechanisms to study treatment.	Assessment of innate resistance mechanisms including but not limited to identify mutations, amplifications, or expression changes in EGFR, HER2 and MET in baseline ctDNA and/or tissue biopsies.[a]
To identify acquired resistance mechanisms to study treatment	Assessment of resistance mechanisms including but not limited to identify mutations, amplifications, or expression changes in EGFR, HER2 and MET in ctDNA and/or tissue biopsies taken at time of disease progression.[a]
To conduct exploratory research on tissue and plasma samples into factors that may influence susceptibility to/development of NSCLC/cancer and/or response to osimertinib (where response is defined broadly to include efficacy, tolerability, or safety). Tissue and plasma samples may be used to support diagnostic development	Samples may be analysed retrospectively for novel biomarker discovery research and/or diagnostic development.[a]

[a] Results from this analysis, if conducted, will be reported separately.
[b] Due to limited data, these endpoints were not analysed.

Sample size

It was anticipated that approximately 200 patients would be randomised into the study in a 2:1 ratio (osimertinib to placebo). The primary endpoint is PFS by BICR in the FAS population. The primary analysis was to occur when approximately 120 PFS BICR-assessed events (approximately 60% data maturity) have been observed from all randomised patients. With 120 PFS events, the study has 90% power to show a statistically significant difference in PFS at the 2-sided 5% level if the assumed true treatment effect is a HR 0.53; this translates to an approximate 7-month improvement from a median 8-month PFS on placebo. The smallest treatment difference that would be statistically significant is a PFS HR of 0.68 (translating to an approximate 4-month improvement).

Randomisation

Patients were centrally assigned to randomised study treatment in a 2:1 ratio osimertinib:placebo, respectively, using an IxRS. Randomisation was performed within 6 weeks of completion of CRT. Patients were stratified at randomisation based on prior CRT strategy (CCRT versus SCRT), disease stage prior to CRT (IIIA versus IIIB/IIIC) and China cohort (enrolled at a Chinese site and patient declaring themselves of Chinese ethnicity versus enrolled at non-Chinese site or patient declaring themselves of non-Chinese ethnicity).

Blinding (masking)

This study was double-blind.

Statistical methods

Efficacy variables

Table 10. Efficacy variables and analysis methodology

Variable	Analysis description and methodology
Primary endpoint	
	PFS (per RECIST v1.1 as assessed by BICR) is defined as the 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 withdraws from randomised therapy or receives another anti-cancer therapy prior to progression. The full definition of PFS is provided in Section 3.2.1 of SAP Version 3.0, see Appendix 16.1.9. The analysis of PFS uses a stratified log-rank test for generation of the p-value (see Section 9.1 for stratification factors). The stratification factors were based on the values entered into IxRS at randomisation, even if it was subsequently discovered that these values were incorrect. The effect of osimertinib versus placebo is estimated by a HR and 2-sided 95% CI, which was obtained directly from the U and V statistics (Berry et al 1991, Robins et al 1991, Robins 1993, Selke and Siegmund 1983). Data summaries (presented by treatment arm) include a KM plot, the number and percentage of patients experiencing a PFS event and the type of event, and treatment status at progression at the time of analysis. Full details of all PFS analyses are provided in Section 4.2.7.1 of SAP Version 3.0 (see Appendix 16.1.9). **PFS sensitivity analyses** • *Stratification according to the eCRF:* For any mis-stratifications during randomisation, the stratified log rank test is repeated on PFS, where the stratification factors are as recorded according to the eCRF. • *Ascertainment bias:* The possibility of bias in assessment and measurement of PFS by BICR is assessed using the Investigator assessment of disease progression by RECIST v1.1. • *Evaluation-time bias*: This analysis assesses the possibility of bias in evaluation time if scans were not performed at the protocol-specified time points. • *Attrition bias*: Possible attrition bias is assessed by repeating the primary PFS analysis, except that actual PFS event times, rather than censored times, of patients who progressed or died in the absence of progression immediately following 2 or more, non-evaluable tumour assessments are included. • *COVID-19*: In the case that there was a sufficient number of patients with a confirmed or suspected COVID-19 death event (either at least 5 patients and/or at least 2% of the patient population), a sensitivity analysis was to be conducted to assess the potential impact of COVID-19 deaths on PFS. Full details of all PFS sensitivity analyses are provided in Section 4.2.7.2 of SAP Version 3.0 (see Appendix 16.1.9). **Subgroup analysis** Subgroup analyses were conducted to assess the consistency of treatment effect across expected prognostic factors, by comparing PFS between treatments in the following

	planned groups: age group (< 65 versus ≥ 65), sex (male versus female), smoking status (current/former [yes] versus never [no]), prior CRT strategy (CCRT versus SCRT), disease stage prior to CRT (IIIA versus IIIB/IIIC), patients enrolled at a Chinese site and declaring themselves of Chinese ethnicity versus patients enrolled at non-Chinese site or patients declaring themselves of non-Chinese ethnicity, central plasma ctDNA EGFR (Ex19del or L858R) mutation status at screening (positive versus negative versus unknown), tissue EGFR mutation at screening (Ex19del versus L858R), race (Asian versus non-Asian), and response to prior CRT (CR vs PR vs SD vs NE). The subgroup analyses for the stratification factors are based on the values entered into the eCRF. For each subgroup level, the HR and 95% CI are calculated from a Cox proportional hazard model that only contains a term for treatment, the factor and treatment-by-factor interaction term. The HRs and the associated 2-sided 95% CIs are summarised and presented on a forest plot. Quantitative interactions A quantitative interactions analysis was performed to assess whether there is consistent treatment benefit across the pre-defined subgroups. Full details of subgroup analysis for the BICR-assessed PFS are provided in Section 4.2.7.3 of SAP Version 3.0 (see Appendix 16.1.9).
Secondary endpoints	
CNS PFS	CNS PFS (per RECIST v1.1 as assessed by BICR in a separate CNS charter) is defined as the time from randomisation until the date of CNS objective disease progression or death (by any cause in the absence of CNS progression) regardless of whether the patient withdraws from randomised therapy or receives another anti-cancer therapy prior to CNS progression. The full definition of CNS PFS is provided in Section 3.2.2.1 of SAP Version 3.0, see Appendix 16.1.9. CNS PFS data are analysed using the same methodology and model as for the primary analysis of PFS, provided sufficient events were available for a meaningful analysis (≥ 20 CNS PFS events across both treatment arms with at least 5 events per arm); otherwise, descriptive summaries are provided. The analysis is repeated for the Investigator-assessed CNS PFS using RECIST v1.1 assessments as a sensitivity analysis. The cumulative incidence rate of CNS PFS by BICR, at 12 and 24 months were produced using the KM method to assess the competing risk analysis. Full details of all CNS PFS analyses are provided in Section 4.2.8.1 of SAP Version 3.0 (see Appendix 16.1.9).
OS	OS is defined as the time from the date of randomisation until death due to any cause. The full definition of OS is provided in Section 3.2.2.2 of SAP Version 3.0, see Appendix 16.1.9. OS data are analysed using the same methodology and model as for the primary analysis of PFS, provided sufficient events were available for a meaningful analysis (≥ 20 deaths across both treatment arms with at least 5 events per arm); otherwise, descriptive summaries are provided. OS rates with 95% CIs at set time points (eg, 12 months, 24 months) are also provided. Full details of all OS analyses are provided in Section 4.2.8.2 of SAP Version 3.0 (see Appendix 16.1.9). **OS sensitivity analyses** A sensitivity analysis, conducted to assess the potential impact of COVID-19 deaths on OS, was to be performed in the case that there was a sufficient number of patients with a confirmed or suspected COVID-19 death event (≥ 20 deaths across both treatment arms and/or at least 5 events per arm). Full details are provided in Section 4.2.8.3 of SAP Version 3.0 (see Appendix 16.1.9).

ORR	ORR is defined as the percentage of patients with at least one BICR-assessed visit response of CR or PR. The denominator is defined as the subset of all randomised patients. The full definition of ORR is provided in Section 3.2.2.3 of SAP Version 3.0, see Appendix 16.1.9. ORR by BICR is analysed using logistic regression by stratification factors (see Section 9.1). All BICR scans were used regardless of whether they were scheduled or not, and both confirmed and unconfirmed responses were used. The results of the analysis are presented in terms of an odds ratio together with its associated profile likelihood 95% CI and p-value. The ORR analysis is repeated for confirmed responses, and in the Evaluable for Response Analysis Set (see Section 9.8.2). Full details of all ORR analyses are provided in Section 4.2.8.4 of SAP Version 3.0 (see Appendix 16.1.9).
DoR	DoR is defined as the time from the date of first documented response until date of documented progression or death in the absence of disease progression using BICR assessments. The full definition of DoR is provided in Section 3.2.2.4 of SAP Version 3.0, see Appendix 16.1.9. Descriptive data are provided for DoR in patients responding to treatment based on BICR RECIST v1.1 assessments in the FAS, including the associated KM curve and median DoR with associated 95% CI (without any formal comparison or p-value). All BICR scans were to be used regardless of whether they were scheduled or not and both confirmed and unconfirmed responses were to be used. The DoR analysis was to be repeated for confirmed BICR.
DCR and depth of response (tumour shrinkage)	DCR is defined as the percentage of patients who have a BoR of CR or PR or SD at ≥ 8 weeks, prior to any PD event. BoR is calculated based on the overall visit responses from each BICR RECIST assessment. Depth of response (or tumour shrinkage or change in tumour size) is assessed using BICR RECIST v1.1 tumour responses in target lesions. The absolute change and percentage change from baseline in sum of tumour size at each assessment is calculated. The best change in tumour size (ie, depth of response) is the largest decrease from baseline or the smallest increase from baseline in the absence of a reduction and includes all assessments prior to progression or start of subsequent anti-cancer therapy. The definitions of DCR, BoR, and tumour shrinkage are provided in Section 3.2.2.5, Section 3.2.2.6, and Section 3.2.2.7, respectively, of SAP Version 3.0, see Appendix 16.1.9. DCR, by BICR assessment, is analysed using the same method applied to the ORR. Depth of response by BICR is examined by summarising the absolute change in target lesion tumour size from baseline, and percentage change in target lesion tumour size from baseline using descriptive statistics and presented at each time point and by randomised treatment arm. Depth of response is also examined by presenting the proportion of patients who achieve > 30%, > 50% and > 75% reduction in target tumour lesion size. The best percentage change from baseline in target lesion tumour size is also summarised descriptively and presented graphically using waterfall plots. Full details of all tumour shrinkage analyses are provided in Section 4.2.8.7 of SAP Version 3.0 (see Appendix 16.1.9).
TTDM	TTDM is defined as the time from the date of randomisation until the first date of distant metastasis, or date of death in the absence of distant metastasis. The full definition of TTDM is provided in Section 3.2.2.8 of SAP Version 3.0, see Appendix 16.1.9. TTDM data are analysed using the same methodology and model as for the primary analysis of PFS, and a competing risk analysis has also been performed. Full details of all TTDM analyses are provided in Section 4.2.8.8 of SAP Version 3.0 (see Appendix 16.1.9).

TTD	TTD is defined as the time from randomisation to the earlier of the date of study treatment discontinuation (regardless of the reason for study treatment discontinuation) or death. The full definition of TTD is provided in Section 3.2.2.9 of SAP Version 3.0, see Appendix 16.1.9. TTD data are analysed using the same methodology and model as for the primary analysis of PFS.
Post-progression endpoints (PFS2, TFST, TSST)	Post-progression endpoints are defined as: • *PFS2:* The time from the date of randomisation to the earliest of the progression event following first objective disease progression, subsequent to the first subsequent therapy, or death. • *TFST:* The time from the date of randomisation to the earlier of start date of the first subsequent anti-cancer therapy after discontinuation of randomised treatment, or death. • *TSST:* The time from the date of randomisation to the earlier of start date of the second subsequent anti-cancer therapy after discontinuation of randomised treatment, or death. The full definitions of PFS2, TFST and TSST are provided in Section 3.2.2.10, Section 3.2.2.11, and Section 3.2.2.12, respectively, of SAP Version 3.0, see Appendix 16.1.9. Post-progression endpoints are analysed using the same methodology and model as for the primary analysis of PFS.
PROs	The EORTC QLQ-C30 consists of 30 items and measures cancer patients' functioning and symptoms (Aaronson et al 1993). The EORTC QLQ-LC13 is a complementary module measuring lung cancer associated symptoms (Bergman et al 1994). The following analyses are performed: • Time to symptom deterioration is analysed using the same methodology and model as for the primary analysis of PFS, and is presented as a KM plot for each of the symptom scales and functional scales and HRQoL. • The symptom improvement rate for each item from each questionnaire is compared by treatment arm using the same methodology and model as for the ORR analysis. • Changes from baseline in each of the PRO symptom scores are analysed using an MMRM analysis of the post-baseline scores for visits with the use of data from baseline up to 10 months or date of PD (whichever is earlier), excluding visits with excessive missing data (defined as more than 75% missing data). Further details of the analysis methodologies, including the exploratory PRO instruments, PRO-CTCAE, PGIS and EQ-5D-5L, are provided in Sections 3.3 and 4.2.9 of SAP Version 3.0 (see Appendix 16.1.9).

Analysis populations

Table 11. Description of analysis populations

Population	Description	Main analysis / Outcome variable
Full Analysis Set	The FAS includes all randomised patients (ie, the ITT population). Treatment arms are compared by randomised study treatment, regardless of the treatment actually received (ie, patients who were randomised but did not go on to receive study treatment are included in the analysis in the treatment arm to which they were randomised).	• Demography and baseline characteristics • *Efficacy variables*: PFS, OS, CNS PFS, ORR, DoR, DCR, TTDM, TTD, Tumour shrinkage, PFS2, TFST, TSST, HRQoL.
Evaluable for Response Analysis Set *(subset of the FAS)*	The Evaluable for Response Analysis Set includes all patients in the FAS who had measurable disease at baseline according to the BICR of baseline imaging data.	• *Efficacy variables*: PFS and ORR (as sensitivity analyses)
Safety Analysis Set	The Safety Analysis Set includes all randomised patients who received at least one dose of study treatment. Safety data are not formally analysed but summarised using the Safety Analysis Set according to treatment received. Therefore, erroneously treated patients (eg, those randomised to treatment A but actually given treatment B) are summarised according to the treatment actually received in the relevant treatment arm. If a patient receives any active treatment, then they will be summarised in the active treatment arm.	• *Safety variables*: Exposure, AEs, Laboratory measurements, Vital signs, ECG, LVEF, and WHO performance status.
PK Analysis Set	The PK Analysis Set is defined as patients in the Safety Analysis Set who had at least one measurable PK concentration, supported by the relevant date and time of this sample; and for each time a PK sample was taken, the dosing data for that day; and for samples taken after multiple dosing, the dosing data for the 7 continuous days of osimertinib dosing prior to the sample day as well as the sample day. For any individual sample to be included in the PK Analysis Set, the full sample data and dosing data needed to be present for that sample.	• PK variables

Multiple Testing Procedure

In order to strongly control the type I error, a multiple testing procedure was implemented, which defined the significance levels which were to be applied to the interpretation of the raw p-values for the primary and key secondary efficacy endpoints. The family-wise error rate is strongly controlled at 5% (2-sided) for these endpoints.

The testing procedure was sequential and ordered such that after testing the primary endpoint of PFS in the FAS, the key secondary efficacy endpoints of OS (FAS) and CNS PFS (FAS) were then to be tested, in that order. Hypotheses were tested using a multiple testing procedure with an alpha recycling strategy (Burman et al 2009). If the PFS analysis was significant at the primary analysis, then 5% alpha was recycled to the OS endpoint and then to the CNS PFS endpoint. If any previous analysis in the sequence was not statistically significant, the alpha could not be transferred to subsequent analyses. As such, CNS PFS hypothesis was only to be tested if the null hypothesis was rejected for OS, either at the time of the PFS analysis or at the time of the final OS analysis.

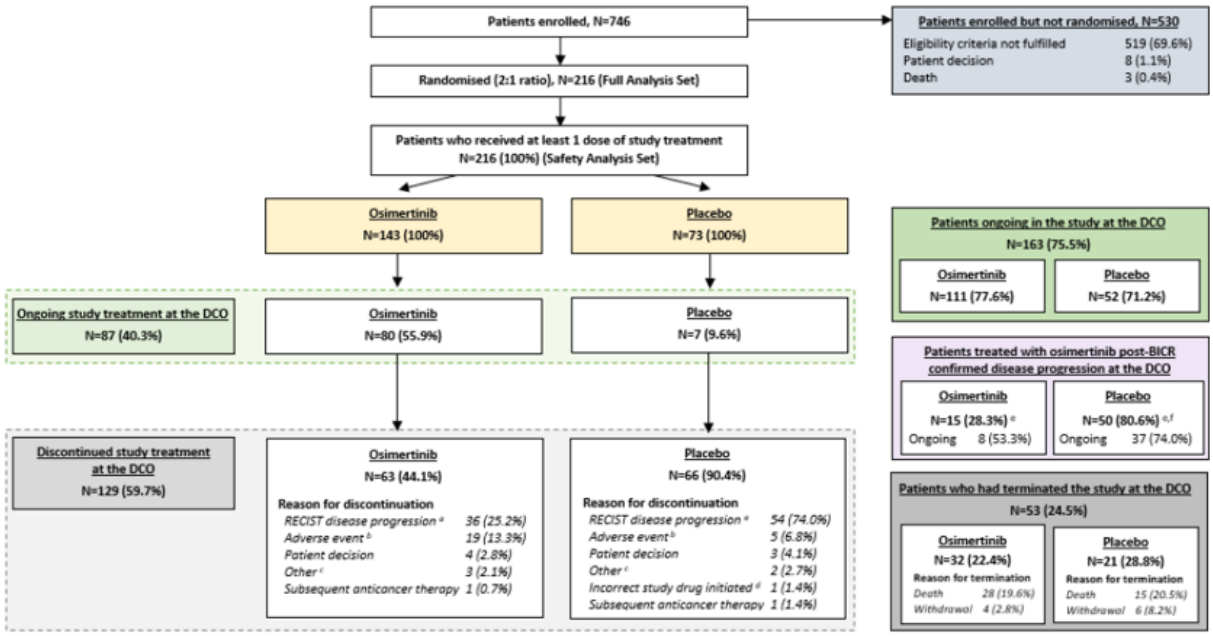
The primary endpoint of BICR-assessed PFS and key secondary efficacy endpoint of CNS PFS were planned to be analysed only once, comprising the primary analysis of this study (as reported herein), when

approximately 120 BICR-assessed PFS events had been observed in 200 patients (approximately 60% data maturity).

Two analyses of the key secondary endpoint of OS are planned: one interim analysis at the time of the primary PFS analysis, and one final analysis. The final analysis of OS is to occur when approximately 120 death events have been reported in approximately 200 patients (approximately 60% data maturity). The alpha (2-sided 5%) level allocated to OS is controlled at the interim and final analyses by using the Lan-DeMets (Lan and DeMets 1983) spending function that approximates an O'Brien Fleming approach, where the alpha level applied at the interim and final analyses depends upon the number of death events observed.

Results

Participant flow



a Prior to primary PFS analysis, assessed by BICR.

b It is noted that the number of patients who discontinued study treatment due to AEs in this disposition summary differs from the number of patients with AEs leading to discontinuation of study treatment in the safety summaries (Table 14.3.5.1.1). This discrepancy is due to AEs in 2 patients (1 patient in each treatment arm) occurring outside of the safety data collection window (see Section 9.8.1.4 of the LAURA CSP, Module 5.3.5.1, for appropriate definition).

c Any reason not specifically captured in earlier categories. Per the eCRF, other reasons for treatment discontinuation were captured as: "Other-Death" (2 patients) and "Other-PD by investigator" (1 patient) in the osimertinib arm; and "Other-Death" (1 patient) and "Other-PD by investigator" (1 patient) in the placebo arm.

d One patient (1.4%) in in the placebo arm [redacted] discontinued study treatment due the reason of "incorrect study treatment initiation". This patient was identified after the start of study treatment as having pre-existing brain metastases and was discontinued at the decision of the Investigator.

e Percentages are calculated out of number of subjects with a BICR-confirmed disease progression.

f Of note, one additional patient [redacted] also received osimertinib post-study treatment discontinuation in the absence of BICR-confirmed disease progression.

DCO: 05 January 2024

Recruitment

First patient enrolled: 19 July 2018.

Last patient randomised: 25 July 2022.

DCO date: 05 January 2024; DBL date: 05 February 2024.

The study was conducted in 121 study sites in 17 countries across Europe, Asia-Pacific, North America and South America.

Conduct of the study

Protocol amendments

Table 12. 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 patient recruitment		
Not applicable	Not applicable	Not applicable
Amendments made *after* the start of patient recruitment		
Amendment 1 28 February 2020	Added that patients may receive open-label osimertinib after BICR-confirmed disease progression, but must not receive any other anti-cancer therapies between discontinuation of study treatment and start of open-label osimertinib.	To aid recruitment and make osimertinib available for patients randomised to placebo, as it was the preferred first-line treatment based on FLAURA OS results. For patients randomised to osimertinib, it could be appropriate to continue on osimertinib (open-label) after BICR-confirmed disease progression if their physician considered they were benefitting from it (NCCN 2022).
	Provided clarifications on the timing of AE, SAE, and AESI collection.	To add clarity
	It was added that patients with a stage III tumour of squamous histology who have a pre-existing local positive test result (Ex19del or L858R) are eligible for Part I screening. Also clarified the tumour tissue specimen required for entry into Part I screening.	To add clarity
	Text was added to clarify that patients are eligible in Part I of the study if none of the Part II screening exclusion criteria 1, 2, 7, 9-11, and 15-20 apply. The exclusion criterion relating to risk of QTc prolongation was also updated, with further definition of electrolyte abnormalities and medical history. In addition, minor changes were made to exclusion criteria 6, 8, 10, and 13.	To add clarity
	Procedures for handling dose interruptions for patients with QTc prolongation were updated to match current recommendations. Guidance for correction of electrolyte levels before first dose was also added.	To match current recommendations for dose interruptions
Amendment 2 03 February 2021	Provided clarifications on the timing of AE, SAE, and AESI collection.	To add clarity
	Clarified that either archival or newly acquired tumour tissue samples can be provided for central EGFR mutation analysis. Also, the instructions relating to the provision of tumour tissue was revised from a minimum of 8 sections to preferably at least 12 (except in China).	To add clarity and aid recruitment

	Text added to include the use of the FoundationOne® CDx test for local EGFR mutation status testing.	To enable the use of the FoundationOne® CDx test for local EGFR mutation status testing.
	Clarification added that the timings given for collection of PROs at treatment discontinuation following BICR-confirmed disease progression are relative to the date of the treatment discontinuation visit; and/or for patients who discontinue prior to BICR progression, the timings of collection of PROs are relative to the disease-progression visit.	To clarify the PRO data collection schedule.
	Added clarifications on the timing of when patients may receive open-label osimertinib, and/or the supply of open-label osimertinib after the final OS analysis.	To add clarity
	Text added/amended to describe when study blind will be broken.	To add clarity
	Part II Screening, Inclusion criterion 5: The following clarification text was added: *Patients with a stage III tumour of squamous histology who have a pre-existing local positive test result (Ex19del or L858R), irrespective of EGFR test used or lab accreditation, and confirmed by central testing during Part I screening, are eligible for Part II screening. Part II Screening, Inclusion criterion 8: Clarified final chemotherapy administration must be completed prior to, or concurrently with, the final dose of radiation. Reference to platinum and pemetrexed doublet therapy removed and changed to a final cycle of chemotherapy is permitted up to 7 days after the last dose of radiation, if at least 2 cycles have already been given concurrently. Part II Screening, Exclusion criterion 5: Text added to specify correction of electrolyte abnormalities to within normal ranges can be performed during the screening period. Part II Screening, Exclusion criterion 8: Updated eligibility for patients with a resolved or chronic HBV infection. Part II Screening, Exclusion criterion 14: Text amended to clarify that patients are excluded if a patient in another clinical study with an IP administered in the previous 4 weeks prior to randomisation.	To provide further clarification on various inclusion and exclusion criteria concerning patient disease characteristics, CCRT, electrolyte correction, eligibility for patients with a resolved or chronic HBV infection, and other study participation criteria.
	Text amended to clarify that dose modifications are only permitted for adverse reactions. In addition, the timing of recovery and permanent study treatment withdrawal for patients with QTc prolongations were clarified as relative to study drug interruption, and additional clarification text regarding restart dose was added.	To add clarity

	Text amended to clarify that dose interruptions are only permitted for adverse reactions (related to osimertinib/matching placebo). In addition, the timing of recovery and permanent study treatment withdrawal, for patients with toxicities, were clarified as relative to study drug interruption. The timing of recovery and permanent study treatment withdrawal, for patients with QTc prolongation toxicities, were clarified as relative to study drug interruption.	To add clarity
Amendment 3 25 February 2022	Added clarification on the nature and timing of AE data collection in relation to the Screening Part I and Screening Part II study periods	To add clarity
	Added clarification on the number of patients planned to be recruited in China	To add clarity
	Removed the requirement for the collection of PROs after the primary analysis	PROs were to be analysed only once, at the time of the primary analysis
Amendment 4 03 November 2023	The multiple testing procedure was updated to change the hierarchy of statistical testing from PFS, CNS PFS, and then OS to PFS, OS, and then CNS PFS, so that OS is tested prior to CNS PFS.	With the changing importance of an OS benefit for EGFRm NSCLC, this increases the chance of formally testing OS.
	Updated text throughout to meet the EU CTR requirements and global company requirements.	To comply with regulatory requirements (EU CTR) and global company requirements.
	Updates made to align with the latest osimertinib Project Specific Safety Requirements, with minor updates to restricted and prohibited concomitant medications, study treatment dose adjustment information for adverse reactions, and management of IP-related toxicities (addition of toxic epidermal necrolysis and anaplastic anaemia)	To align with the most up-to-date osimertinib safety information.

Protocol deviations

Table 13. Important Protocol Deviations per Statistical Analysis Plan (FAS)

Important protocol deviations [a]	Number (%) of patients		
	Osimertinib (N = 143)	Placebo (N = 73)	Total (N = 216)
Number of patients with at least one IPD (excluding COVID-19 related IPDs)	27 (18.9)	17 (23.3)	44 (20.4)
Subject failed inclusion criteria	6 (4.2)	2 (2.7)	8 (3.7)
Subject met exclusion criteria	1 (0.7)	1 (1.4)	2 (0.9)
Incorrect IP administration / study treatment	0	0	0
Subject received prohibited concomitant medication	2 (1.4)	4 (5.5)	6 (2.8)
Non-compliance with RECIST 1.1 scanning schedule	19 (13.3)	10 (13.7)	29 (13.4)

[a] Important deviations before the start of treatment, during treatment and during follow-up period. These data exclude COVID-19 related IPDs.
The same patient may have had more than one IPD.
DCO: 05 January 2024

- Important Protocol Deviations related to COVID-19

The overall incidence of patients with at least one IPD due to COVID-19 was low (8 patients [3.7%]), all of whom had a COVID-19-related IPD which was related to non-compliance with RECIST 1.1 scanning schedule (osimertinib arm: 6 patients [4.2%]); placebo arm: 2 patients [2.7%]).

Baseline data

Demographic and patient characteristics

Table 14. Demographic and Patient Characteristics (FAS)

Characteristic	Osimertinib (N = 143)	Placebo (N = 73)	Total (N = 216)
Age (years)			
Mean (std)	60.9 (10.38)	62.3 (12.01)	61.4 (10.95)
Median	62.0	64.0	62.5
Min, Max	36, 84	37, 83	36, 84
Age group (years), n (%)			
< 50	24 (16.8)	12 (16.4)	36 (16.7)
≥ 50 to < 65	57 (39.9)	27 (37.0)	84 (38.9)
≥ 65 to < 75	49 (34.3)	20 (27.4)	69 (31.9)
≥ 75	13 (9.1)	14 (19.2)	27 (12.5)
Sex, n (%)			
Male	53 (37.1)	31 (42.5)	84 (38.9)
Female	90 (62.9)	42 (57.5)	132 (61.1)
Race, n (%)			
Asian	116 (81.1)	62 (84.9)	178 (82.4)
White	20 (14.0)	10 (13.7)	30 (13.9)
American Indian or Alaska Native	2 (1.4)	1 (1.4)	3 (1.4)

Other	5 (3.5)	0	5 (2.3)
Smoking status, n (%)			
Never	102 (71.3)	49 (67.1)	151 (69.9)
Smoker - Current	4 (2.8)	1 (1.4)	5 (2.3)
Smoker - Former	37 (25.9)	23 (31.5)	60 (27.8)

DCO: 05 January 2024

Baseline disease characteristics

Table 15. Disease Characteristics at Baseline (FAS)

Characteristic	Osimertinib (N = 143)	Placebo (N = 73)	Total (N = 216)
WHO performance status, n (%)			
(0) Normal activity	80 (55.9)	31 (42.5)	111 (51.4)
(1) Restricted activity	63 (44.1)	42 (57.5)	105 (48.6)
Disease stage, n (%) [a]			
Stage IIIA	52 (36.4)	24 (32.9)	76 (35.2)
Stage IIIB	67 (46.9)	38 (52.1)	105 (48.6)
Stage IIIC	24 (16.8)	11 (15.1)	35 (16.2)
Histology type, n (%)			
Adenocarcinoma	139 (97.2)	69 (94.5)	208 (96.3)
Squamous cell carcinoma	3 (2.1)	2 (2.7)	5 (2.3)
Other [b]	1 (0.7)	2 (2.7)	3 (1.4)
Time from unresectable Stage III diagnosis to randomisation (days)			
Mean (std)	117.6 (37.71)	129.2 (47.67)	121.5 (41.60)
Median	111.0	121.0	113.0
Min, Max	55, 265	51, 289	51, 289
Prior CRT strategy, n (%)			
CCRT	131 (91.6)	62 (84.9)	193 (89.4)
SCRT	12 (8.4)	11 (15.1)	23 (10.6)
Response to prior CRT, n (%)			
CR	4 (2.8)	3 (4.1)	7 (3.2)
PR	67 (46.9)	27 (37.0)	94 (43.5)
SD	61 (42.7)	37 (50.7)	98 (45.4)
PD	0	0	0
Non-evaluable	11 (7.7)	6 (8.2)	17 (7.9)
Time from end date of radiotherapy to randomisation date (weeks)			
Mean (std)	4.22 (1.390)	4.05 (1.514)	4.17 (1.432)
Median	4.29	4.29	4.29
Min, Max	0.7, 6.4	0.4, 6.0	0.4, 6.4
Target lesion size by BICR			
Mean (std), mm	33.47 (17.649)	35.93 (17.321)	34.29 (17.535)
Median, mm	29.40	30.50	29.60
No target lesions, n (%)	9 (6.3)	6 (8.2)	15 (6.9)
Overall disease classification at randomisation, n (%)			
Metastatic [c]	0	1 (1.4)	1 (0.5)
Locally advanced [d]	141 (98.6)	72 (98.6)	213 (98.6)
Missing [e]	2 (1.4)	0	2 (0.9)

Characteristic	Osimertinib (N = 143)	Placebo (N = 73)	Total (N = 216)
Central plasma ctDNA EGFRm (Ex19del or L858R) status at screening, n (%) [f]			
Positive	10 (7.0)	4 (5.5)	14 (6.5)
Negative	113 (79.0)	58 (79.5)	171 (79.2)
Unknown [g]	20 (14.0)	11 (15.1)	31 (14.4)
Tissue EGFRm status at screening (Ex19del versus L858R), n (%)			
Ex19del positive	74 (51.7)	43 (58.9)	117 (54.2)
L858R positive	68 (47.6)	30 (41.1)	98 (45.4)
Missing [h]	1 (0.7)	0	1 (0.5)

[a] Disease stage summarised based on values entered into the eCRF and categorised prior to CRT according to AJCC/UICC 8th Edition.
[b] Per the eCRF, these patients had adenosquamous histology and were eligible for inclusion (data on file).
[c] Patient has any metastatic site of disease.
[d] Patient has only locally advanced sites of disease.
[e] These patients had a complete response to prior CRT and therefore their disease was not detectable at randomisation for classification (data on file).
[f] Summarised based on central cobas® EGFR plasma testing results.
[g] Status was unknown due to the unavailability or inadequacy of plasma samples for central testing.
[h] Patients randomised without an approved local positive EGFR test result or central EGFR test result.

DCO: 05 January 2024

Surgical history

Relevant surgical history which may be related to the disease under investigation included:

- Lung lobectomy (osimertinib arm: 8 patients [5.6%]; placebo arm: 1 patient [1.4%])
- Pulmonary resection (reported in 2 patients in the osimertinib arm [1.4%])
- Lung biopsy, cancer surgery, lung operation, mass excision, and pneumonectomy (each reported for 1 patient in the osimertinib arm [0.7%]) and lung neoplasm surgery (reported for 1 patient in the placebo arm [1.4%]).

Other frequently reported surgical history events (i.e., with an incidence of at least 5% in any treatment arm) were hysterectomy (osimertinib arm: 7 patients [4.9%]; placebo arm: 5 patients [6.8%]) and appendicectomy (osimertinib arm: 4 patients [2.8%]; placebo arm: 4 patients [5.5%]).

Prior anticancer therapies

Table 16. Previous disease-related treatment modalities (FAS)

Previous treatment modalities	Number (%) of Subjects		
	Osimertinib (N=143)	Placebo (N=73)	Total (N=73)
Number of subjects with previous disease-related treatment	143 (100)	73 (100)	216 (100)
Chemotherapy	143 (100)	73 (100)	216 (100)
Radiotherapy	143 (100)	73 (100)	216 (100)
3-D CONFORMAL	44 (30.8)	18 (24.7)	62 (28.7)
IMRT	99 (69.2)	55 (75.3)	154 (71.3)
Cytotoxic chemotherapy	143 (100)	73 (100)	216 (100)
DOCETAXEL	3 (2.1)	5 (6.8)	8 (3.7)
ETOPOSIDE	15 (10.5)	8 (11.0)	23 (10.6)
GEMCITABINE	1 (0.7)	1 (1.4)	2 (0.9)
PACLITAXEL	69 (48.3)	34 (46.6)	103 (47.7)
PEMETREXED	39 (27.3)	22 (30.1)	61 (28.2)
VINORELBINE	18 (12.6)	7 (9.6)	25 (11.6)
Platinum chemotherapy	143 (100)	73 (100)	216 (100)
CARBOPLATIN	75 (52.4)	44 (60.3)	119 (55.1)
CISPLATIN	66 (46.2)	29 (39.7)	95 (44.0)
NEDAPLATIN	2 (1.4)	0	2 (0.9)

Subjects may appear under more than one previous treatment type, if they received more than one treatment.
N = Number of subjects in treatment group. WHODrug Global B3-format 2023-09.

Numbers analysed

Table 17. Analysis sets

	Number of patients		
	Osimertinib	Placebo	Total
Patients included in FAS	143	73	216
Patients included in SAF	143	73	216
Patients included in PK Analysis Set	136	NA	136
Patients excluded from PK Analysis Set	7	NA	7
Patient did not have any measurable PK data available	7	NA	7
Patients included in Evaluable for Response Analysis Set	134	67	201
Patients excluded from Evaluable for Response Analysis Set	9	6	15
Patient did not have measurable disease at baseline	9	6	15

DCO: 05 January 2024

Outcomes and estimation

Primary endpoint: PFS by BICR

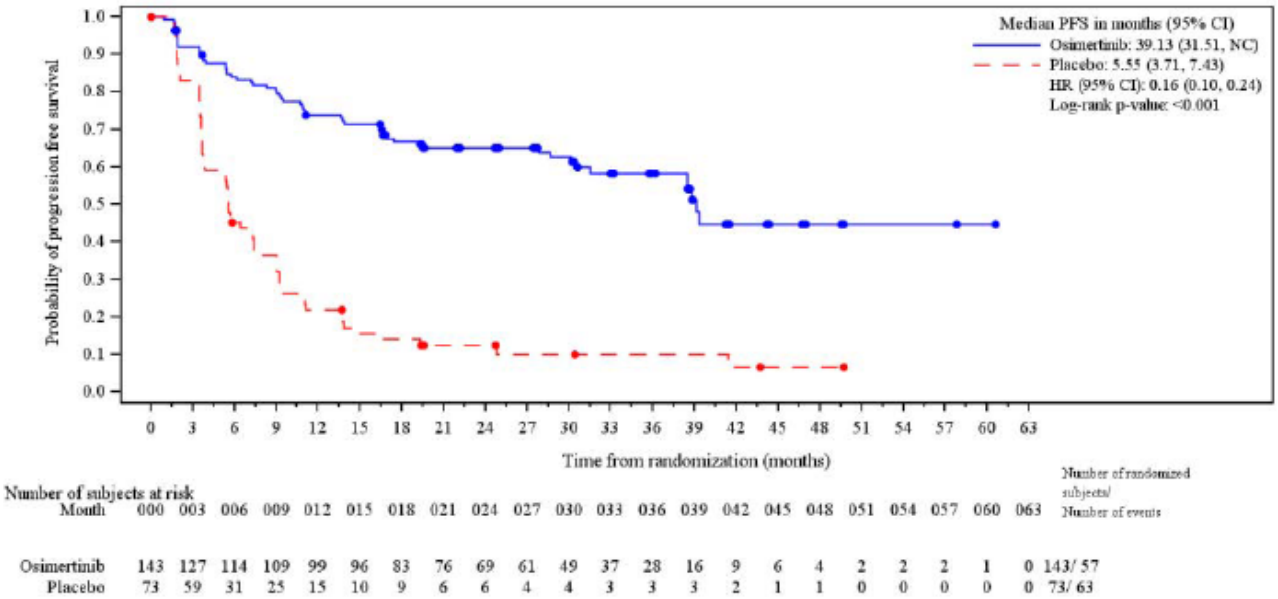
At the DCO date of the primary analysis (05 January 2024) 120 PFS events had occurred across treatment arms (overall data maturity of 55.6%), comprising 57 events (39.9%) in the osimertinib arm and 63 events (86.3%) in the placebo arm.

Table 18. Progression-Free Survival by BICR Assessment, Primary Analysis (FAS)

	Osimertinib (N = 143)	Placebo (N = 73)
Progression status, n (%)		
Total events [a]	**57 (39.9)**	**63 (86.3)**
RECIST progression	53 (37.1)	62 (84.9)
Target lesions [b]	23 (16.1)	16 (21.9)
Non-target lesions [b]	6 (4.2)	5 (6.8)
New lesions [b]	29 (20.3)	45 (61.6)
Death in the absence of progression	4 (2.8)	1 (1.4)
Censored patients, n (%)	**86 (60.1)**	**10 (13.7)**
Censored RECIST progression [c]	1 (0.7)	0
Censored death [c]	0	1 (1.4)
Progression-free at time of analysis	82 (57.3)	6 (8.2)
Withdrawn consent	3 (2.1)	3 (4.1)
Comparison between groups		
HR (95% CI) [d]	0.16 (0.10. 0.24)	
2-sided p-value [d]	< 0.001	
Median PFS		
Median PFS, months (95% CI) [e]	39.13 (31.51, NC)	5.55 (3.71, 7.43)
PFS rate at 6 months, % (95% CI) [e]	84.0 (76.7, 89.2)	45.1 (33.3, 56.1)
PFS rate at 12 months % (95% CI) [e]	73.7 (65.4, 80.3)	21.8 (13.0, 32.1)
PFS rate at 18 months % (95% CI) [e]	66.8 (58.2, 74.0)	14.0 (7.0, 23.4)
PFS rate at 24 months % (95% CI) [e]	65.1 (56.4, 72.6)	12.5 (5.9, 21.6)
PFS rate at 36 months % (95% CI) [e]	58.4 (48.6, 66.9)	10.0 (4.0, 19.2)
Median (range) duration of follow-up in all patients (months)	21.98 (0.03 to 60.55)	5.55 (0.03 to 49.71)
Median (range) duration of follow-up in censored patients (months)	27.71 (0.03 to 60.55)	19.47 (0.03 to 49.71)

[a] PFS events that did not occur within 2 scheduled visits (plus visit window) of the last evaluable assessment (or randomisation) are censored.
[b] Target lesions, non-target lesions and new lesions are not necessarily mutually exclusive categories.
[c] Occurred after 2 or more consecutive missed visits following last non-missing RECIST assessment (or randomisation).
[d] The analysis was performed using a log-rank test stratified by disease stage prior to chemoradiation (IIIA versus IIIB/IIIC) based on values entered into the IxRS, after applying the SAP rule to collapse strata if there were < 10 events per stratum. A HR < 1 favours osimertinib to be associated with a longer PFS than placebo.
[e] Calculated using the KM technique.
Progression determined by BICR RECIST v1.1 assessments.
DCO: 05 January 2024

Figure 7. Kaplan-Meier Plot of Progression-Free Survival by BICR Assessment, Primary Analysis (FAS)



Circles indicate censored observations.
DCO: 05 January 2024

Secondary endpoints

Overall survival

Overall survival data were tested per the hierarchical testing procedure at the DCO of the primary PFS analysis (05 January 2024; data maturity: 19.9%), in the first of 2 pre-planned analyses. The final OS analysis will be conducted when there are approximately 120 death events across both treatment arms (approximate 60% maturity).

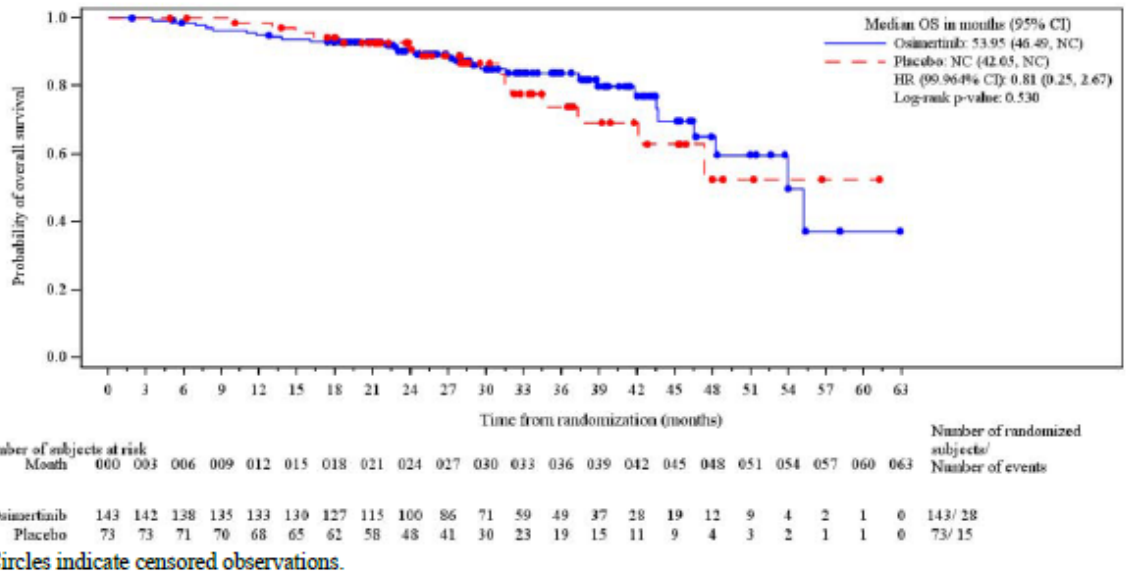
Per protocol, all patients were offered open-label osimertinib following BICR-confirmed disease progression. In the placebo arm 50 patients (80.6%) received osimertinib post-BICR confirmed progression while 15 patients (28.3%) in the osimertinib arm continued to receive osimertinib post-BICR confirmed progression. Therefore, the OS results at the current DCO date should be interpreted taking into account the crossover to osimertinib treatment post-BICR-confirmed progression in the placebo arm. Furthermore, one additional patient in the placebo arm also received osimertinib post-study treatment discontinuation in the absence of BICR-confirmed disease progression per local clinical practice.

Table 19. Overall survival (FAS)

	Osimertinib (N = 143)	Placebo (N = 73)
Survival status, n (%)		
Death	28 (19.6)	15 (20.5)
Censored patients	115 (80.4)	58 (79.5)
Still in survival follow-up [a]	111 (77.6)	52 (71.2)
Terminated prior to death [b]	4 (2.8)	6 (8.2)
Lost to follow-up	0	0
Withdrew consent	4 (2.8)	6 (8.2)
Comparison between groups		
HR (95% CI) [d]	0.81 (0.42, 1.56)	
Adjusted 99.964% CI [e]	0.25, 2.67	
2-sided p-value [d]	0.530	
Median OS		
Median OS, months (95% CI) [c]	53.95 (46.49, NC)	NC (42.05, NC)
Survival rate at 12 months, % (95% CI) [c]	95.0 (89.8, 97.6)	98.6 (90.3, 99.8)
Survival rate at 24 months, % (95% CI) [c]	90.3 (83.8, 94.2)	90.8 (80.5, 95.8)
Survival rate at 36 months, % (95% CI) [c]	83.7 (75.3, 89.4)	73.7 (56.7, 84.9)
Survival rate at 48 months, % (95% CI) [c]	65.1 (47.9, 77.8)	52.4 (26.6, 72.9)
Median (range) duration of follow-up in all patients	29.50 (1.87 to 62.88)	28.09 (4.93 to 61.24)
Median (range) duration of follow-up in censored patients	30.92 (1.87 to 62.88)	28.09 (4.93 to 61.24)

[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 technique.
[d] The analysis was performed using a log-rank test stratified by disease stage prior to chemoradiation (IIIA versus IIIB/IIIC) based on values entered into the IxRS, after applying the SAP rule to collapse strata if there are < 10 events per stratum, provided there are more than 20 deaths across both treatment arms and at least 5 events per arm.
[e] Based on a Lan-DeMets alpha spending function with O'Brien Fleming boundary with the observed number of events, the boundary for declaring statistical significance is 0.00036 for a 5% overall alpha.
A HR < 1 favours osimertinib to be associated with a longer OS than placebo.
DCO: 05 January 2024

Figure 8. Kaplan-Meier plot of overall survival (FAS)



Circles indicate censored observations.
DCO: 05 January 2024

Post-study treatment disease-related anticancer therapies

- All post-study-treatment anticancer therapies

Table 20. Post-study treatment disease-related anticancer therapy

	Number (%) of patients [a]	
	Osimertinib (N = 143)	Placebo (N = 73)
Discontinued randomised study treatment	63 (44.1)	66 (90.4)
Any post-treatment anticancer therapy	42 (29.4)	57 (78.1)
Received 1 line of therapy	*28 (19.6) [44.4]*	*43 (58.9) [65.2]*
Received 2 lines of therapy	*9 (6.3) [14.3]*	*11 (15.1) [16.7]*
Received 3 lines of therapy	*2 (1.4) [3.2]*	*3 (4.1) [4.5]*
Received 4 lines of therapy	*2 (1.4) [3.2]*	*0*
Received ≥ 5 lines of therapy	*1 (0.7) [1.6]*	*0*
No post-treatment anticancer therapy	21 (14.7)	9 (12.3)
Ongoing randomised study treatment	80 (55.9)	7 (9.6)
Types of post-treatment disease-related anticancer therapy received		
EGFR-TKI	28 (19.6) [44.4]	57 (78.1) [86.4]
First or second-generation EGFR-TKI	12 (8.4) [19.0]	7 (9.6) [10.6]
Third generation EGFR-TKI	16 (11.2) [25.4]	52 (71.2) [78.8]
Osimertinib	15 (10.5) [23.8]	51 (69.9) [77.3]
Aumolertinib	1 (0.7) [1.6]	1 (1.4) [1.5]
Furmonertinib	0	1 (1.4) [1.5]
Cytotoxic chemotherapy	21 (14.7) [33.3]	11 (15.1) [16.7]
Platinum compounds	19 (13.3) [30.2]	7 (9.6) [10.6]
Folic acid analogues (pemetrexed)	13 (9.1) [20.6]	6 (8.2) [9.1]
Taxanes	10 (7.0) [15.9]	5 (6.8) [7.6]
Other chemotherapy [b]	5 (3.5) [7.9]	2 (2.7) [3.0]
Radiotherapy	21 (14.7) [33.3]	5 (6.8) [7.6]
VEGF Inhibitor – Monoclonal antibody	8 (5.6) [12.7]	5 (6.8) [7.6]
PD-1/PD-L1 inhibitor - Immunotherapy	5 (3.5) [7.9]	1 (1.4) [1.5]
Other	2 (1.4) [3.2]	2 (2.7) [3.0]

[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.

[b] Includes pyrimidine analogues, vinca alkaloids and analogues, podophyllotoxin derivatives, and topoisomerase 1 inhibitors.

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.
WHO Drug Dictionary version September 2022 format B3. A subsequent medical review has taken place to assign treatment classifications.
DCO: 05 January 2024

- First and second subsequent anticancer therapies

Table 21. First and Second Post-treatment Disease-related Anticancer Therapy (FAS)

	Number (%) of patients [a]	
	Osimertinib (N = 143)	Placebo (N = 73)
Discontinued randomised study treatment	63 (44.1)	66 (90.4)
Received first post-treatment anticancer therapy		
Yes	42 (29.4)	57 (78.1)
No	21 (14.7)	9 (12.3)
Types of first post-treatment disease-related anticancer therapy received		
EGFR-TKI	22 (15.4) [34.9]	56 (76.7) [84.8]
First or second-generation EGFR-TKI	7 (4.9) [11.1]	5 (6.8) [7.6]
Third generation EGFR-TKI	15 (10.5) [23.8]	51 (69.9) [77.3]
Osimertinib	14 (9.8) [22.2]	50 (68.5) [75.8]
Aumolertinib	1 (0.7) [1.6]	1 (1.4) [1.5]
Radiotherapy	17 (11.9) [27.0]	5 (6.8) [7.6]
Cytotoxic chemotherapy	16 (11.2) [25.4]	3 (4.1) [4.5]
Platinum compounds	14 (9.8) [22.2]	2 (2.7) [3.0]
Folic acid analogues (pemetrexed)	9 (6.3) [14.3]	2 (2.7) [3.0]
Taxanes	5 (3.5) [7.9]	2 (2.7) [3.0]
Other [b]	3 (2.1) [4.8]	0
VEGF Inhibitor – Monoclonal antibody	5 (3.5) [7.9]	1 (1.4) [1.5]
PD-1/PD-L1 inhibitor - Immunotherapy	4 (2.8) [6.3]	0
Other	2 (1.4) [3.2]	0
Received second post-treatment disease-related anticancer therapy		
Yes	14 (9.8)	14 (19.2)
No (*received only one post-treatment anticancer therapy*)	28 (19.6)	43 (58.9)
Types of second post-treatment anticancer therapy received		
Cytotoxic chemotherapy	8 (5.6) [12.7]	8 (11.0) [12.1]
Platinum compounds	5 (3.5) [7.9]	5 (6.8) [7.6]
Folic acid analogues (pemetrexed)	4 (2.8) [6.3]	3 (4.1) [4.5]
Taxanes	4 (2.8) [6.3]	3 (4.1) [4.5]
Other [c]	0	2 (2.7) [3.0]
EGFR-TKI	3 (2.1) [4.8]	5 (6.8) [7.6]
First or second-generation EGFR-TKI	2 (1.4) [3.2]	2 (2.7) [3.0]
Third generation EGFR-TKI	1 (0.7) [1.6]	3 (4.1) [4.5]
Osimertinib	1 (0.7) [1.6]	2 (2.7) [3.0]
Furmonertinib	0	1 (1.4) [1.5]
VEGF Inhibitor	3 (2.1) [4.8]	3 (4.1) [4.5]
PD-1/PD-L1 inhibitor - Immunotherapy	2 (1.4) [3.2]	0
Radiotherapy	4 (2.8) [6.3]	0
Other	0	2 (2.7) [3.0]

[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.
[b] Includes pyrimidine analogues and vinca alkaloids and analogues.
[c] Includes podophyllotoxin derivatives and pyrimidine analogues.
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. The second post-treatment anticancer therapy is the second treatment started on or after the last dose date of randomised study treatment.
Note: Per protocol, open-label osimertinib treatment was not to be a second line post-treatment therapy; however, it is included in the count of therapies when determining the second line post-treatment therapy.
WHO Drug Dictionary version September 2022 format B3. A subsequent medical review has taken place to assign treatment classifications.
DCO: 05 January 2024

CNS Progression-free survival

The statistical significance of CNS PFS could not be formally tested at the current DCO date (data maturity: 27.3%) per the multiple testing procedure, as OS did not reach a statistical significance at its interim analysis. Therefore, the calculated p-value is nominal.

Table 22. CNS Progression-Free Survival by Neuroradiologist BICR Assessment (FAS)

	Osimertinib (N = 143)	Placebo (N = 73)
Progression status, n (%)		
Total events [a]	**29 (20.3)**	**30 (41.1)**
CNS RECIST progression	18 (12.6)	26 (35.6)
CNS Target lesions [b, c]	0	0
CNS Non-target lesions [b, c]	1 (0.7)	0
CNS New lesions [b]	17 (11.9)	26 (35.6)
Death in the absence of progression	11 (7.7)	4 (5.5)
Censored patients	**114 (79.7)**	**43 (58.9)**
Censored CNS RECIST progression [d]	1 (0.7)	0
Censored death [d]	12 (8.4)	7 (9.6)
No CNS event observed at time of analysis	98 (68.5)	31 (42.5)
CNS Progression-free at time of analysis	80 (55.9)	6 (8.2)
Non-CNS progression observed	18 (12.6)	25 (34.2)
Withdrawn consent	3 (2.1)	5 (6.8)
Comparison between groups		
HR (95% CI) [e]	0.17 (0.09, 0.32)	
2-sided p-value [e]	< 0.001	
Median CNS PFS		
Median CNS PFS, months (95% CI) [f]	NC (NC, NC)	14.88 (7.36, NC)
CNS PFS rate at 12 months, % (95% CI) [f]	86.7 (79.4, 91.5)	53.0 (38.3, 65.6)
CNS PFS rate at 24 months, % (95% CI) [f]	82.7 (74.7, 88.5)	43.3 (28.0, 57.7)
Median (range) duration of follow-up in all patients (months)	24.64 (0.03 to 60.55)	5.72 (0.03 to 55.06)
Median (range) duration of follow-up in censored patients (months)	27.40 (0.03 to 60.55)	7.39 (0.03 to 55.06)

[a] CNS PFS events that did not occur within 2 scheduled visits (plus visit window) of the last non-missing assessment (or randomisation) are censored.

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

[c] It is noted that whilst patients were free of CNS disease at baseline according to the Investigator, the neuroradiologist BICR reader could independently assign target and non-target lesions during CNS BICR assessment.

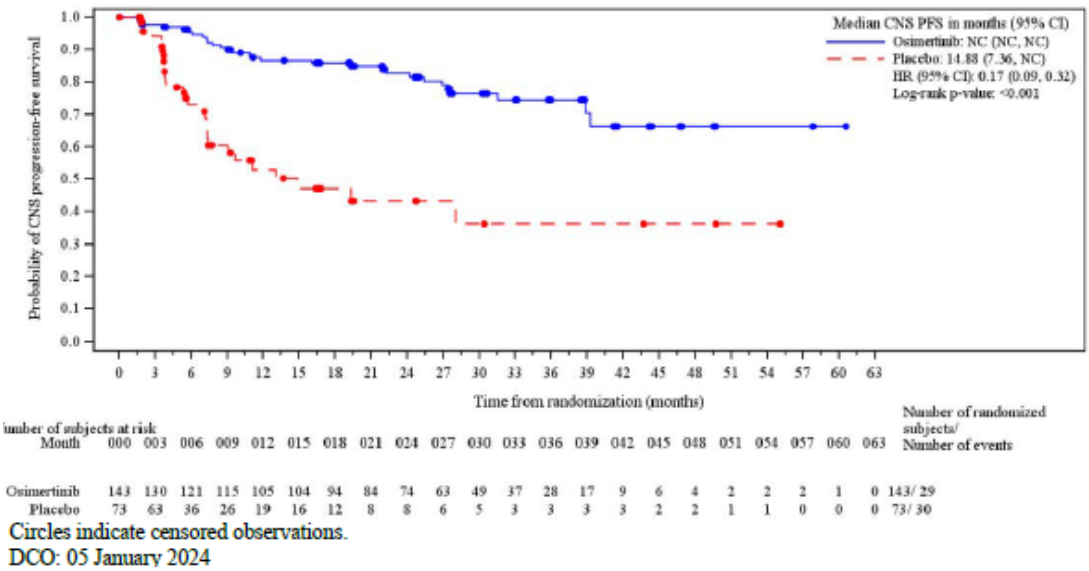
[d] Occurred after 2 or more consecutive missed visits following last non-missing RECIST assessment (or randomisation).

[e] The analysis was performed using a log-rank test stratified by disease stage prior to chemoradiation (IIIA versus IIIB/IIIC) based on values entered into the IxRS, after applying the SAP rule to collapse strata if there are < 10 events per stratum. A HR < 1 favours osimertinib to be associated with a longer CNS PFS than placebo.

[f] Calculated using the KM technique.

DCO: 05 January 2024

Figure 9. KM Plot of CNS PFS by Neuroradiologist BICR Assessment (FAS)

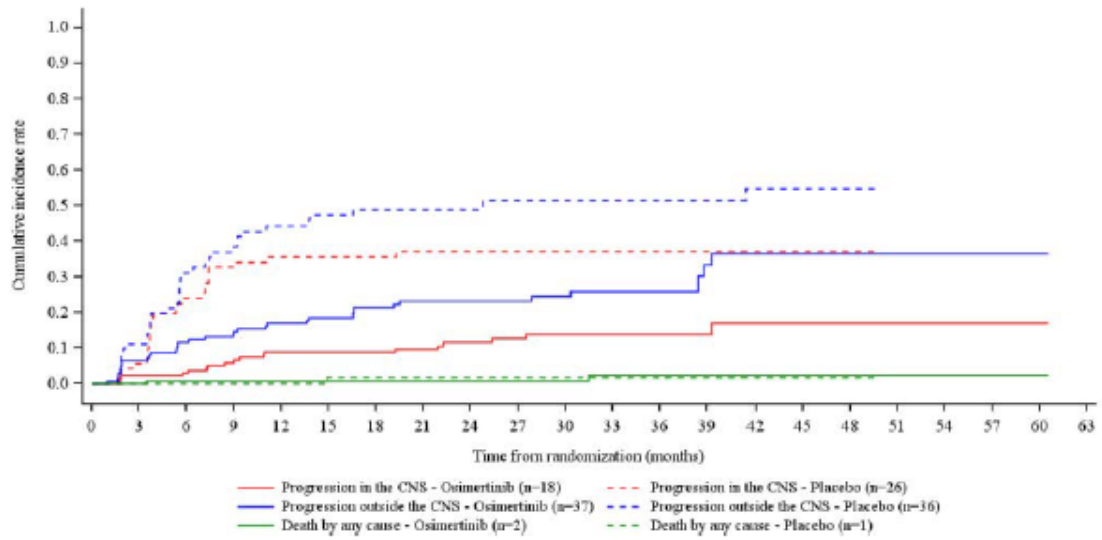


Circles indicate censored observations.
DCO: 05 January 2024

Once a patient progressed, no further scans were required per protocol. Therefore, no brain scans were available for patients with a non-CNS progression (or those who died prior to any potential progression in the CNS) with which to document any later CNS progression. In these cases, a non-CNS progression or death in the absence of CNS progression could hinder the observation of the event of interest (CNS progression). In addition, by observing the non-CNS progression, a patient's treatment strategy may change, thus potentially impacting the CNS outcome.

To account for this, a competing risk analysis was performed, which indicated that the estimated probability of observing a CNS progression event (conditional on the patient not experiencing a competing event of progression outside the CNS or death by that time) was consistently lower in the osimertinib arm than in the placebo arm: 9% (95% CI: 5, 14) in the osimertinib arm versus 36% (95% CI: 24, 47) in the placebo arm at 12 months, and 12% (95% CI: 7, 18) in the osimertinib arm versus 37% (95% CI: 26, 48) in the placebo arm at 24 months.

Figure 10. CNS PFS Competing Risk Analysis – Cumulative Incidence Plot (FAS)



Analysis combines data from CNS BICR and Study BICR. Progression in the CNS includes patients who had documented radiological progression in the CNS at the same overall visit. Event time is the first occurrence of the event. The cumulative incidence function is calculated using the KM method.
DCO: 05 January 2024

Objective Response Rate

Table 23. Objective Response by BICR Assessment (FAS)

	Osimertinib (N = 143)	Placebo (N = 73)
Analysis of ORR [a]		
Best objective response, n (%) [95% CI] [b]		
Response	**82 (57.3) [48.8, 65.6]**	**24 (32.9) [22.3, 44.9]**
Complete response	3 (2.1)	1 (1.4)
Partial response	79 (55.2)	23 (31.5)
Non-response	**61 (42.7)**	**49 (67.1)**
SD (≥ 8 weeks)	45 (31.5)	34 (46.6)
Progression	11 (7.7)	12 (16.4)
Not evaluable	5 (3.5)	3 (4.1)
Comparison between groups		
Odds ratio (95% CI) [c]	2.77 (1.54, 5.08)	
2-sided p-value [d]	< 0.001	
Analysis of ORR – Confirmed responses [e]		
Best objective response, n (%) [95% CI] [b]		
Response	**77 (53.80) [45.3, 62.2]**	**19 (26.0) [16.5, 37.6]**
Complete response	3 (2.1)	0
Partial response	74 (51.7)	19 (26.0)
Non-response	**66 (46.2)**	**54 (74.0)**
SD (≥ 8 weeks)	50 (35.0)	39 (53.4)
Progression	11 (7.7)	12 (16.4)
Not evaluable	5 (3.5)	3 (4.1)
Comparison between groups – Confirmed responses		
Odds ratio (95% CI) [c]	3.33 (1.82, 6.31)	
2-sided p-value [d]	< 0.001	

[a] Response includes both confirmed and unconfirmed BICR responses.
[b] Calculated using the Clopper-Pearson exact method for binomial proportions.
[c] Based on the profile likelihood.
[d] Based on the likelihood ratio test.
[e] Includes confirmed responses only (ie, responses confirmed at least 4 weeks after the initial response).
All BICR scans are used regardless of whether they were scheduled or not. The analysis was performed using logistic regression stratified by disease stage prior to chemoradiation (IIIA versus IIIB/IIIC) based on values entered into the IxRS, after applying the SAP rule to collapse strata to analyse the primary endpoint. An odds ratio > 1 favours osimertinib.
DCO: 05 January 2024

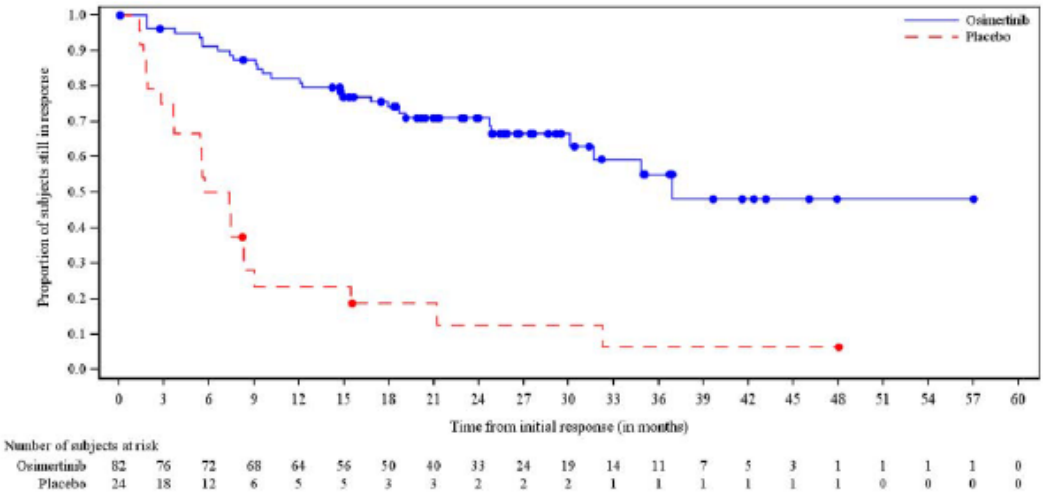
Duration of Response

Table 24. Duration of Response by BICR Assessment (FAS)

	Osimertinib (N = 143)	Placebo (N = 73)
Analysis of DoR [a]		
Number of responders	82	24
Responders who subsequently progressed or died, n (%)	28 (34.1)	21 (87.5)
Median DoR, months (95% CI) [b]	36.9 (30.1, NC)	6.5 (3.6, 8.3)
Time to Onset of Responses, weeks [a]		
Mean (std)	25.90 (28.511)	17.23 (10.203)
Median	16.00	15.79
Min, max	6.9, 180.3	7.6, 40.0
Analysis of DoR – Confirmed responses [c]		
Number of responders	77	19
Responders who subsequently progressed or died, n (%)	25 (32.5)	16 (84.2)
Median DoR, months (95% CI) [b]	36.9 (31.6, NC)	7.4 (5.5, 15.4)

[a] Derived from unconfirmed responses only.
[b] Calculated using KM technique.
[c] Derived from confirmed responses only (ie, responses confirmed at least 4 weeks after the initial response).
DCO: 05 January 2024

Figure 11. Kaplan-Meier Plot of Duration of Response (unconfirmed), by BICR (FAS)



Circles indicates a censored observation.
DCO: 05 January 2024

Disease Control Rate

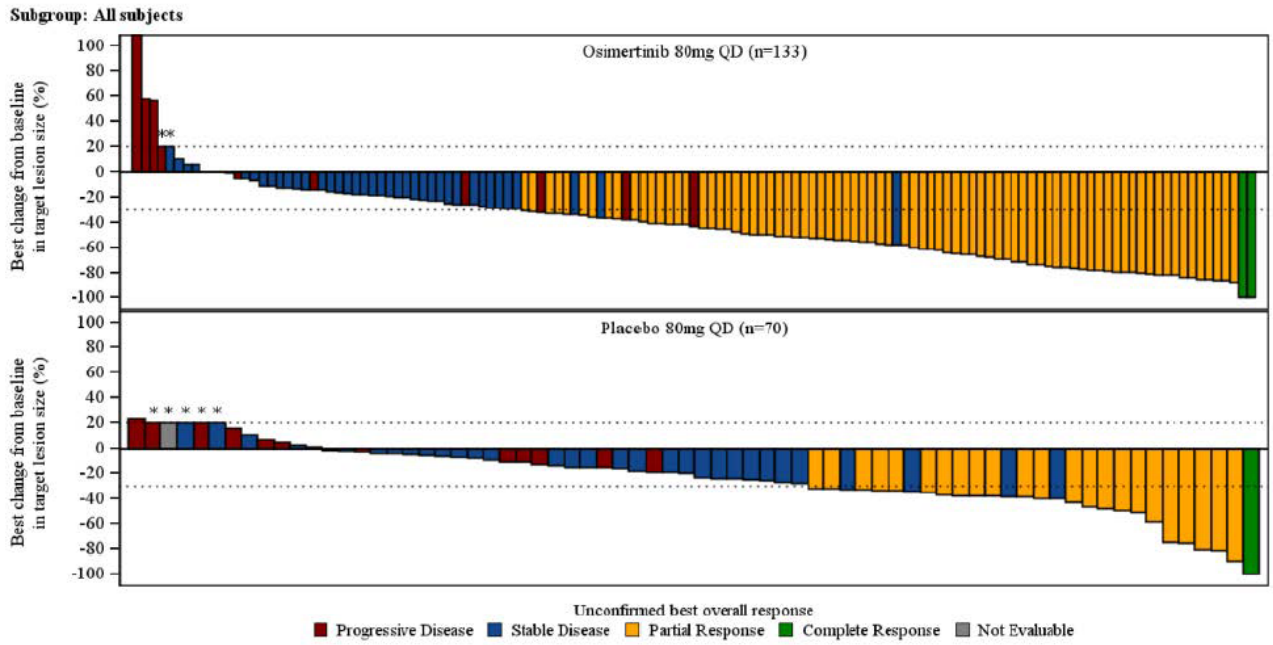
Disease control rate (i.e., best overall response of CR, PR or SD) was 88.8% (95% CI: 82.5, 93.5) in the osimertinib arm and 79.5% (95% CI: 68.4, 88.0) in the placebo arm, with an odds ratio of 2.06 (95% CI: 0.94, 4.47; nominal p-value = 0.069) which favoured the osimertinib arm.

Depth of Response (Tumour Shrinkage)

The best improvement in tumour size observed in the osimertinib arm was a mean reduction of 41.5% and a median reduction of 43.3% (range: −100% to 144%) compared to a mean reduction of 23.5% and a median reduction of 21.9% (range: −100% to 23%) in the placebo arm, with a least square mean difference between arms of −16.6% (95% CI: −25.85, −7.41; nominal p-value < 0.001).

A > 30% reduction in target lesion size from baseline based on BICR assessment was reported for 65% of patients in the osimertinib arm compared to 40% of patients in the placebo arm, with a > 50% reduction in target lesion size reported for 43% of patients in the osimertinib arm and 11% of patients in the placebo arm, and a > 75% reduction in target lesion size reported for 18% of patients in the osimertinib arm and 9% of patients in the placebo arm.

Figure 12. Waterfall Plots for Target Lesion Size, Best Percentage Change from Baseline, by BICR Assessment (FAS – All Patients)



Asterisks indicate values imputed to 20%.
Best change in target lesion size is the maximum reduction from baseline or the minimum increase from baseline in the absence of a reduction. The reference lines at + 20% and -30% correspond to the definitions of progression and 'partial' response, respectively.
DCO: 05 January 2024

Time to Death or Distant Metastases by BICR

Treatment with osimertinib resulted in an improvement in TTDM compared to placebo (HR = 0.21 [95% CI: 0.11, 0.38]; nominal p-value < 0.001), with the median TTDM not reached (95% CI: 39.29, NC) in the osimertinib arm versus 13.04 months (95% CI: 9.03, NC) in the placebo arm.

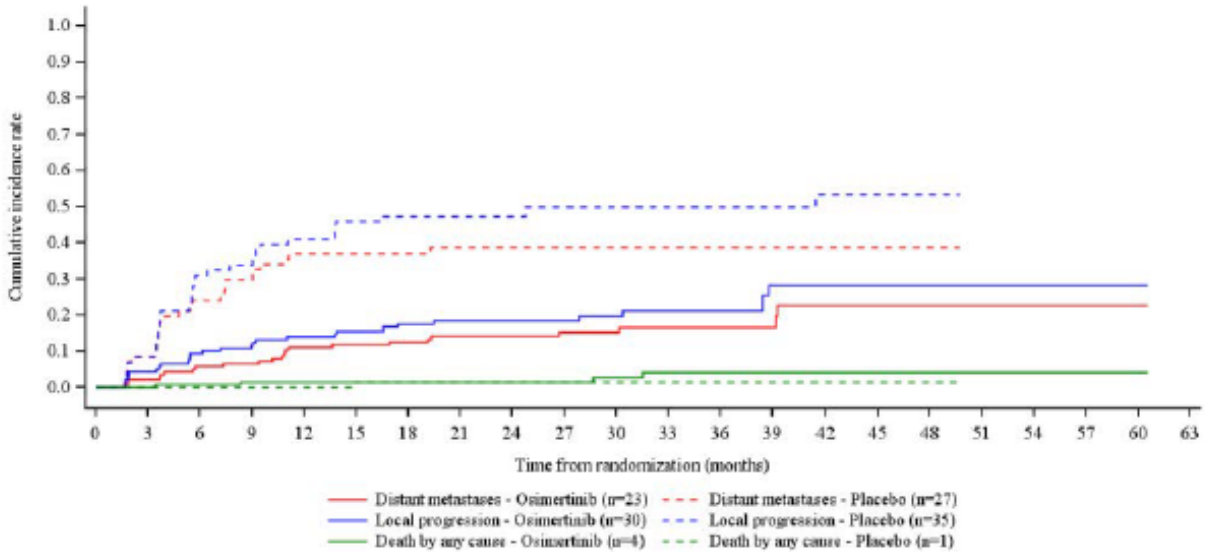
Overall, the proportion of patients with a death or distant metastasis event in the osimertinib arm was approximately 2 times lower than in the placebo arm (33 patients [23.1%] versus 31 patients [42.5%], respectively).

In both treatment arms, local progression was the most common reason for reporting a PFS event (osimertinib arm: 30 patients [21.0%]; placebo arm: 35 patients [47.9%]), with 23 patients (16.1%) in the osimertinib arm and 27 patients (37.0%) in the placebo arm reporting distant metastases (defined as extra thoracic metastases). This suggests that the pattern of disease progression between treatment arms was similar. However, for patients whose disease was assessed as local progression according to BICR and Investigator assessment, no further scans (which may have detected distant metastases at a later time point) were required per protocol.

To account for this, a competing risk analysis was performed, which indicated that the estimated probability of observing a TTDM event (conditional on the patient not experiencing a competing event of local progression or death by that time) was consistently lower in the osimertinib arm than in the placebo arm: 11% (95% CI: 6, 17) in the osimertinib arm versus 37% (95% CI: 26, 48) in the placebo arm at 12

months, and 14% (95% CI: 9, 21) in the osimertinib arm versus 39% (95% CI: 27, 50) in the placebo arm at 24 months.

Figure 13. Time to death or distant metastases by BICR Assessment, Competing Risk Analysis – Cumulative Incidence Plot (FAS)



Distant metastases is defined as any new lesion that is detected on a scan (outside of the radiation field) according to RECIST v1.1 or proven by biopsy. Local progression is radiological documentation of radiological progression, with progression according to RECIST v1.1, but where no new lesions outside of radiation field identified.
The cumulative incidence function is calculated using the KM method.
DCO: 05 January 2024

Time to Treatment Discontinuation or Death

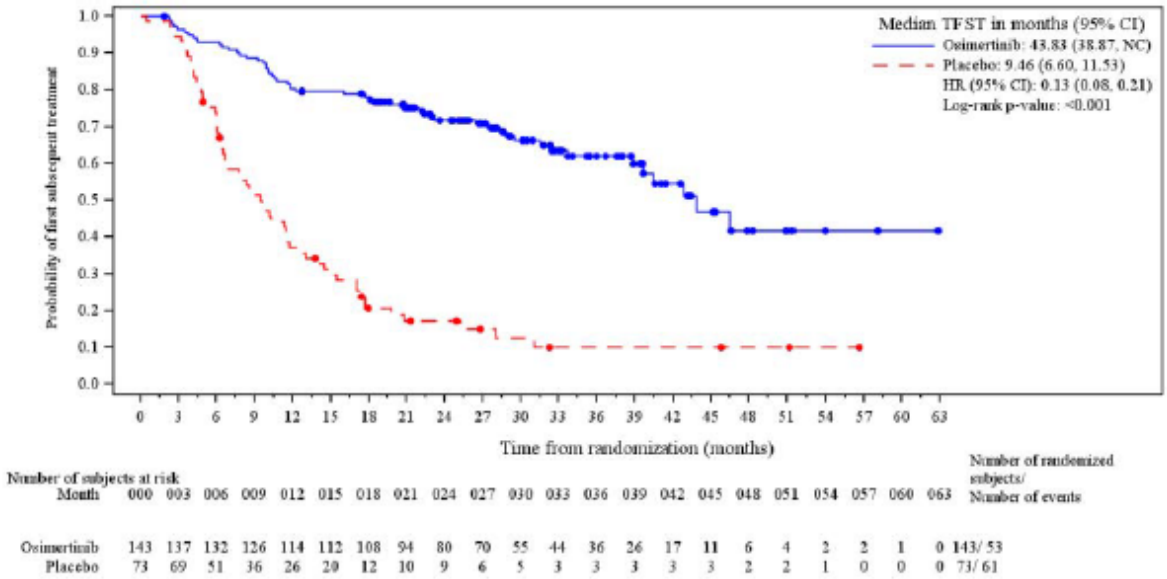
Treatment with osimertinib resulted in an improvement in TTD compared to placebo (HR = 0.21 [95% CI: 0.14, 0.32]; nominal p-value < 0.001), with a median TTD of 40.28 months (95% CI: 32.72, NC) in the osimertinib arm and 8.31 months (95% CI: 6.14, 11.10) in the placebo arm.

- Post-Progression Outcomes

Time to First Subsequent Treatment

Patients in the osimertinib arm had longer median TFST than patients in the placebo arm (43.83 months [95% CI: 38.87, NC] versus 9.46 months [95% CI: 6.60, 11.53]), with a HR of 0.13 (95% CI: 0.08, 0.21; nominal p-value < 0.001) favouring the osimertinib arm. Overall, 53 patients (37.1%) in the osimertinib arm and 61 patients (83.6%) in the placebo arm had a TFST event, with an overall data maturity of 52.8%.

Figure 14. Kaplan-Meier Plot of Time to First Subsequent Treatment (FAS)



Circles indicate censored observations. The median TFST (and 95% CI) were calculated using the KM technique. The HR (and 95% CI) and p-value were calculated using a log-rank test stratified by disease stage prior to chemoradiation (IIIA versus IIIB/IIIC) based on values entered into the IxRS, after applying the SAP rule to collapse strata if there are < 10 events per stratum. 2-sided p-value.
DCO: 05 January 2024

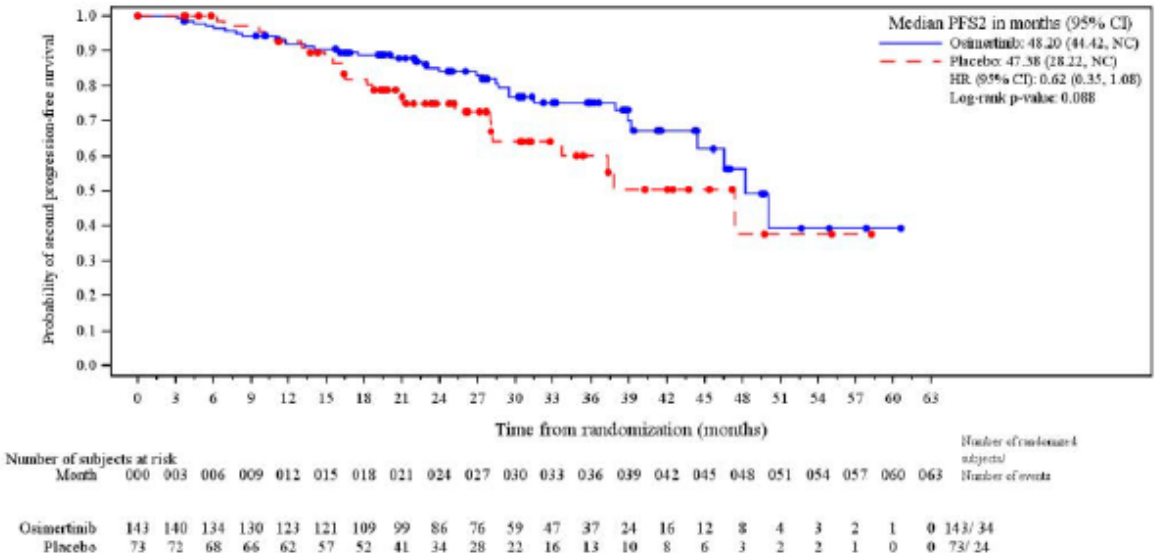
Second Progression-Free Survival (PFS2)

The HR for PFS2 was 0.62 (95% CI: 0.35, 1.08; nominal p-value = 0.088).

Overall, 34 patients (23.8%) in the osimertinib arm and 24 patients (32.9%) in the placebo arm had a PFS2 event, with an overall data maturity of 26.9%. Of note, one patient in the osimertinib arm was misclassified as having a PFS2 event (as second progression occurred prior to starting a subsequent anticancer treatment); however, this single misclassification does not alter the conclusions of the analysis.

Median time to PFS2 was similar between treatment arms (osimertinib arm: 48.20 months [95% CI: 44.42, NC]; placebo arm: 47.38 months [95% CI: 28.22, NC]), despite the low maturity of PFS2 events. However, these medians were estimated based on a single event and should be interpreted with caution considering the limited number of patients who remained at risk at the tail of the KM curve.

Figure 15. Kaplan-Meier Plot of PFS2 on a Subsequent Treatment (FAS)



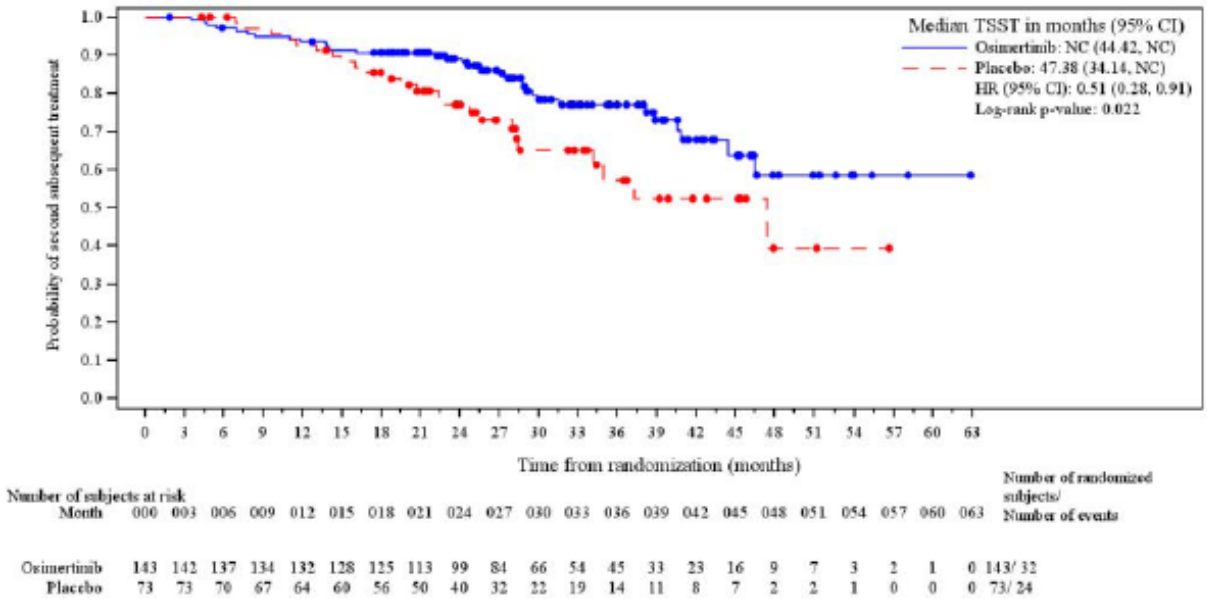
Circles indicate censored observations. The median PFS2 (and 95% CI) were calculated using the KM technique. The HR (and 95% CI) and p-value were calculated using a log-rank test stratified by disease stage prior to chemoradiation (IIIA versus IIIB/IIIC) based on values entered into the IxRS, after applying the SAP rule to collapse strata if there are < 10 events per stratum. 2-sided p-value.
DCO: 05 January 2024

Time to Second Subsequent Treatment

A HR in favour of osimertinib was observed in relation to TSST (HR = 0.51 [95% CI: 0.28, 0.91]; nominal p-value = 0.022), with the benefit of osimertinib post-CRT observed from approximately 15 months post-randomisation which persisted throughout the remainder of the follow-up period, as aligned with PFS2 findings. Overall, 32 patients (22.4%) in the osimertinib arm and 24 patients (32.9%) in the placebo arm had a TSST event, with an overall data maturity of 25.9%.

Median TSST was not reached in the osimertinib arm (95% CI: 44.42, NC) and was 47.38 months (95% CI: 34.14, NC) in the placebo arm.

Figure 16. Kaplan-Meier Plot of Time to Second Subsequent Treatment (FAS)



Circles indicate censored observations. The median TSST (and 95% CI) were calculated using the KM technique. The HR (and 95% CI) and p-value were calculated using a log-rank test stratified by disease stage prior to chemoradiation (IIIA versus IIIB/IIIC) based on values entered into the IxRS, after applying the SAP rule to collapse strata if there are < 10 events per stratum. 2-sided p-value.
DCO: 05 January 2024

Clinical Outcomes Assessment/Quality of Life

Patient-reported outcomes were assessed as secondary endpoints using the EORTC QLQ-C30 and EORTC QLQ-LC13 questionnaires. Based on their clinical relevance to the disease under study, the interpretation of these data is primarily focused on the following key functional/symptom scales/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)
- Coughing (1 item in EORTC QLQ-LC13)
- Pain in Chest (1 item in EORTC QLQ-LC13).

A PGIS scale and selected PRO-CTCAE items were also collected as exploratory PRO endpoints.

All PRO data were collected from randomisation until BICR-confirmed disease progression, and subsequently at 8-, 16- and 32-weeks post-progression.

Of note, a minimum clinically relevant change is defined as a change in the score from baseline of ≥ 10 for scales/items from the EORTC QLQ-C30 and EORTC QLQ-LC13 instruments (Osoba et al 1998).

Secondary Endpoint: EORTC QLQ-C30

Compliance rates for completion of the QLQ-C30 questionnaire in both the osimertinib and placebo arms were > 90% at baseline and remained consistently > 70% until Week 24, with rates broadly comparable between treatment arms.

Baseline QLQ-C30 scores were comparable between treatment arms for all QLQ-C30 functional/symptom scales/items and indicated that patients who participated in this study had intermediate-to-high degrees of overall functioning and global health status/QoL (mean scores of ≥ 71), with low or mild symptomatology (mean scores of ≤ 23). In both treatment arms the most severe symptom of interest at baseline was fatigue (osimertinib arm: 18.83; placebo arm: 22.39).

Overall, patients in both treatment arms were deemed to be well functioning and mildly symptomatic at baseline, with the overall study population exhibiting lower mean baseline scores for all symptom scales when compared to the corresponding NSCLC (all stages) QLQ-C30 reference values (Scott et al 2008).

Time to Deterioration

Overall, 50.4% of patients in the osimertinib arm and 58.8% of patients in the placebo arm did not experience a clinically meaningful deterioration in GHS/QoL or death based on QLQ-C30 data, with no meaningful difference in the risk of deterioration or death observed between treatment arms (HR = 1.14 [95% CI: 0.74, 1.78]). Furthermore, no meaningful differences in the risk of deterioration between treatment arms were observed based on the HRs of all QLQ-C30 functional/symptom scale/items of interest.

In all functional/symptom scales/items of interest, the proportion of patients without deterioration at 6 and 12 months was similar (< 20% difference) between treatment arms.

Table 25. Analysis of Time to Confirmed Deterioration in PRO Symptoms of the QLQ-C30 Questionnaire (FAS)

PRO scale	Treatment arm	N	Number (%) of patients with events	Percentage (95% CI) of patients without deterioration [a]		HR [b] (95% CI)
				at 6 months	at 12 months	
GHS / QoL	Osimertinib	131	65 (49.6)	68.0 (59.1, 75.3)	59.7 (50.5, 67.6)	1.14 (0.74, 1.78)
	Placebo	68	28 (41.2)	68.1 (55.3, 77.9)	58.6 (45.1, 69.8)	
Physical function	Osimertinib	130	56 (43.1)	68.9 (60.0, 76.3)	64.8 (55.7, 72.5)	1.06 (0.65, 1.71)
	Placebo	68	24 (35.3)	74.1 (61.7, 83.1)	70.3 (57.3, 80.0)	
Fatigue	Osimertinib	130	84 (64.6)	46.9 (38.0, 55.3)	42.6 (33.8, 51.1)	1.23 (0.85, 1.80)
	Placebo	68	37 (54.4)	66.7 (53.8, 76.7)	51.3 (37.9, 63.2)	
Appetite loss	Osimertinib	130	58 (44.6)	69.8 (60.9, 77.0)	64.7 (55.6, 72.4)	1.00 (0.63, 1.58)
	Placebo	68	28 (41.2)	84.7 (73.5, 91.5)	61.7 (47.4, 73.1)	

[a] Calculated using the KM technique.

[b] The analysis includes patients with non-missing baseline scores of ≥ 10 (for GHS/QoL and functioning) or ≤ 90 (for symptoms) and was performed using a log-rank test stratified by disease stage prior to chemoradiation (IIIA versus IIIB/IIIC) based on values entered into the IxRS. A HR < 1 favours osimertinib.

DCO: 05 January 2024

Symptom Improvement Rate

The proportion of patients who experienced a clinically meaningful improvement in symptoms was similar between treatment arms.

Change from Baseline (MMRM Evaluation)

In general, only minimal changes from baseline were observed for the functional/symptom scales/items of interest in both treatment arms, and no clinically meaningful changes from baseline (i.e., a deterioration of ≥ 10 points) was observed in any of these scales based on the MMRM analysis.

Table 26. Summary of Change from Baseline in PRO Domains from the QLQ-C30 Questionnaire, MMRM (FAS)

PRO scale	Treatment arm	N	Estimate for treatment arm[a] (95% CI)	Comparison between groups	
				Estimate for difference	95% CI
Global health status / QoL	Osimertinib	128	-3.9 (-5.98, -1.82)	-1.9	-5.89, 2.00
	Placebo	67	-2.0 (-5.30, 1.40)		
Physical function	Osimertinib	128	-4.0 (-6.06, -1.90)	-0.6	-4.42, 3.26
	Placebo	67	-3.4 (-6.63, -0.18)		
Fatigue	Osimertinib	128	5.1 (2.49, 7.68)	1.6	-3.18, 6.46
	Placebo	67	3.4 (-0.62, 7.50)		
Appetite loss	Osimertinib	128	3.3 (0.50, 6.13)	8.1	2.77, 13.37
	Placebo	67	-4.8 (-9.25, -0.26)		

Baseline is defined as the latest evaluable assessment on or prior to the day of first dose. The analysis is performed using a MMRM analysis of change from baseline score for all post-baseline assessments, with patient, treatment, visit and treatment-by-visit interaction as explanatory variables, the baseline score as a covariate along with the baseline score-by-visit interaction. Treatment, visit and treatment-by-visit interaction are fixed effects in the model and patient is included as a random effect. Restricted maximum likelihood estimation is used. An overall adjusted mean estimate to estimate the average treatment effect over visits is derived giving each visit equal weight. The treatment-by-visit interaction is kept in the model regardless of significance. Data are summarised up to the earlier of the date of progression or 10 months follow-up, excluding any visits with missing data that is ≥ 75% of patients at that visit.
DCO: 05 January 2024

Secondary endpoint: EORTC QLQ-LC13

Compliance Rates

Compliance rates for completion of the QLQ-LC13 questionnaire in both the osimertinib and placebo arms were > 90% at baseline and remained > 70% until Week 24, with rates comparable between treatment arms.

Baseline Scores

Baseline QLQ-LC13 scores were comparable between treatment arms for all QLQ-LC13 symptom scale/items and indicated that patients who participated in this study had low or mild symptomatology (mean scores ≤ 25). The most severe symptom/item of interest at baseline was coughing, regardless of treatment arm (osimertinib arm: 20.61 out of 100; placebo arm: 24.51 out of 100).

Overall, patients in both treatment arms were deemed to be mildly symptomatic at baseline, with the overall study population exhibiting lower mean baseline scores for dyspnoea, coughing, and pain in chest when compared to the corresponding NSCLC (all stages) QLQ-LC13 reference values (Scott et al 2008).

Time to Deterioration

Overall, no meaningful differences in the risk of deterioration between treatment arms were observed based on the HRs of the QLQ-LC13 symptom scale/items of interest.

In all functional/symptom scales/items of interest, the proportion of patients without deterioration at 6 and 12 months was similar (< 20% difference) between treatment arms.

Table 27. Analysis of Time to Confirmed Deterioration in PRO Symptoms of the QLQ-LC13 Questionnaire (FAS)

PRO scale	Treatment arm	N	Number (%) of patients with events	Percentage (95% CI) of patients without deterioration [a]		HR [b] (95% CI)
				at 6 months	at 12 months	
Dyspnoea	Osimertinib	131	96 (73.3)	33.2 (25.1, 41.4)	26.9 (19.4, 35.0)	1.30 (0.91, 1.86)
	Placebo	68	40 (58.8)	49.8 (37.4, 61.0)	45.2 (32.6, 57.0)	
Coughing	Osimertinib	130	86 (66.2)	43.4 (34.7, 51.8)	38.2 (29.8, 46.6)	1.17 (0.81, 1.71)
	Placebo	67	37 (55.2)	48.2 (35.7, 59.6)	46.4 (33.9, 57.9)	
Pain in chest	Osimertinib	131	76 (58.0)	54.2 (45.2, 62.3)	48.2 (39.3, 56.6)	1.46 (0.95, 2.23)
	Placebo	68	25 (36.8)	70.0 (57.4, 79.5)	66.1 (53.0, 76.3)	

[a] Calculated using the KM technique.
[b] The analysis includes patients with non-missing baseline scores of ≤ 90 and was performed using a log-rank test stratified by disease stage prior to chemoradiation (IIIA versus IIIB/IIIC) based on values entered into the IxRS. A HR < 1 favours osimertinib.
DCO: 05 January 2024

Symptom Improvement Rate

The proportion of patients who experienced a clinically meaningful improvement in symptoms was similar between treatment arms.

Change from Baseline (MMRM)

In general, only minimal changes from baseline were observed for the symptom scales/items of interest in both treatment arms, and no clinically meaningful changes from baseline (i.e., a deterioration of ≥ 10 points) was observed in any of these scales based on the MMRM analysis.

Table 28. Summary of change from baseline in PRO Domains from the QLQ-LC13 Questionnaire, MMRM (FAS)

PRO scale	Treatment arm	N	Estimate for treatment arm*(95% CI)	Comparison between groups	
				Estimate for difference	95% CI
Dyspnoea	Osimertinib	131	7.6 (5.28, 9.84)	3.1	-0.98, 7.24
	Placebo	68	4.4 (1.04, 7.83)		
Coughing	Osimertinib	131	7.9 (5.00, 10.71)	-0.1	-5.24, 4.97
	Placebo	68	8.0 (3.77, 12.20)		
Pain in chest	Osimertinib	131	4.2 (1.91, 6.42)	0.9	-3.14, 4.87
	Placebo	68	3.3 (-0.00, 6.60)		

Baseline is defined as the latest evaluable assessment on or prior to the day of first dose. The analysis is performed using a MMRM analysis of change from baseline score for all post-baseline assessments, with patient, treatment, visit and treatment-by-visit interaction as explanatory variables, the baseline score as a covariate along with the baseline score-by-visit interaction. Treatment, visit and treatment-by-visit interaction are fixed effects in the model and patient is included as a random effect. Restricted maximum likelihood estimation is used. An overall adjusted mean estimate to estimate the average treatment effect over visits is derived giving each visit equal weight. The treatment-by-visit interaction is kept in the model regardless of significance. Data are summarised up to the earlier of the date of progression or 10 months follow-up, excluding any visits with missing data that is ≥ 75% of patients at that visit.
DCO: 05 January 2024

Exploratory HRQoL/PRO Endpoints

PRO-CTCAE

The PRO-CTCAE scores for the Problems tasting food/drinks, Heartburn, Hiccups, Rash, Acne/Pimples, Itchy Skin, and Skin Burns (from radiation), Difficulty swallowing, Mouth and throat sores, Nausea, Vomiting, Loose or watery stools, and Numbness or tingling symptoms were similar across treatment arms at baseline and during the assessment period, indicating that study treatment in both arms was similarly tolerated over the treatment period.

With regards to severity, the majority of patients reported "None" or "Mild" for each of the assessed PRO-CTCAE items at all timepoints (regardless of the treatment arm), with the exception of Dry Skin, for which more patients in the placebo arm reported "None" for severity, whilst the osimertinib arm patients predominantly reported a "Mild" level of severity. Among the patients who responded differently than "None" on severity, the majority reported a "Not at all" or "A little bit" level of interference, independent of treatment arm.

With regards to frequency, the majority of patients reported "Never" for each of the assessed PRO-CTCAE items in both treatment arms at all assessments, with the exception of Loose or watery stools, for which most patients reported "Never" or "Rarely" on frequency. However, among patients who responded differently than "Never" with regards to frequency, the majority reported a "Mild" level of severity for each of the evaluated PRO-CTCAE items, regardless of the treatment arm.

The majority of patients reported "No" to the occurrence of rash, regardless of the treatment arm.

PGIS

Greater than 60% of patients reported levels of severity of "No symptoms", "Very Mild" or "Mild" for the majority of assessed visits in both treatment arms. For the osimertinib arm, the percentage of patients reporting "No Symptoms" ranged from 21.1% (27/128 patients) at Week 8 to 45.9% (28/61 patients) at Week 120. For the placebo arm, the percentage of patients reporting "No Symptoms" ranged from 24.0% (6/25 patients) at Week 48 to 53.8% (7/13 patients) at Week 72.

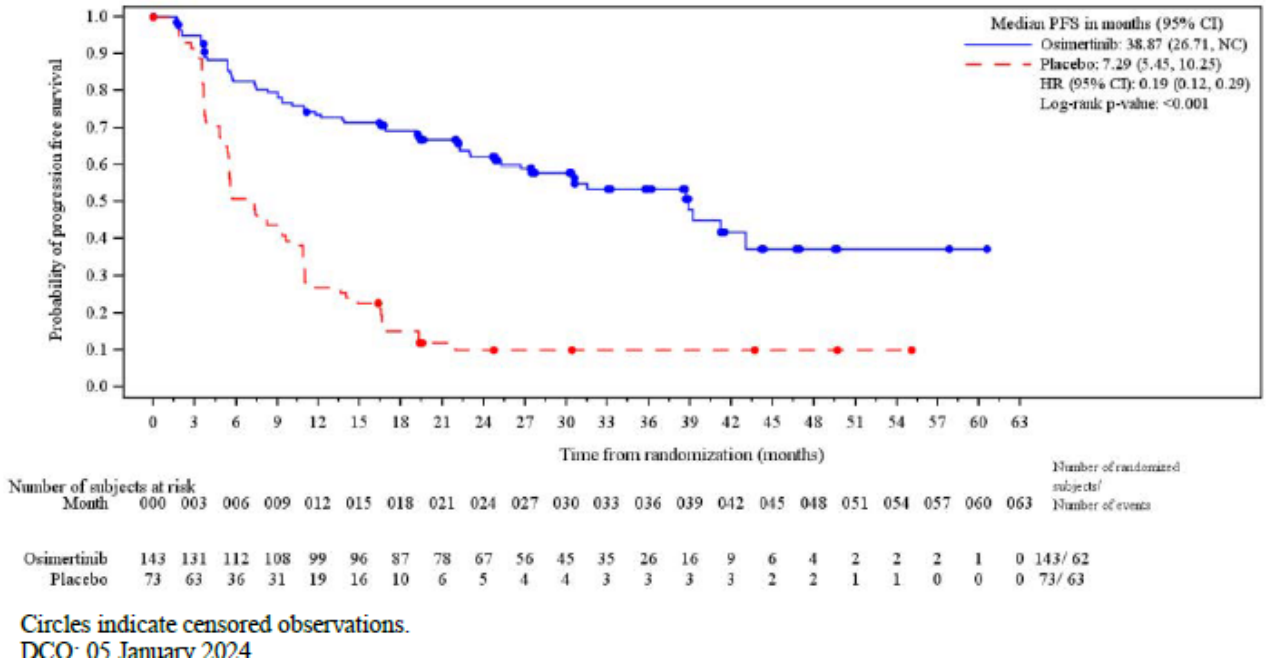
Ancillary analyses

- **Sensitivity analyses**

PFS by investigator assessment

The HR for PFS by Investigator assessment was 0.19 (95% CI: 0.12, 0.29; nominal p-value < 0.001), with an approximate 31.58-month improvement in median PFS observed in the osimertinib arm compared to the placebo arm (mPFS of 38.87 months in the osimertinib arm, and 7.29 months in the placebo arm). Overall, 125 PFS events by Investigator assessment had occurred across treatment arms (overall data maturity of 57.9%), comprising 62 events (43.4%) in the osimertinib arm and 63 events (86.3%) in the placebo arm.

Figure 17. Kaplan-Meier Plot of PFS by investigator assessment



Circles indicate censored observations.
DCO: 05 January 2024

Concordance between BICR and Investigator assessment of PFS was 86.0% in the osimertinib arm and 93.2% in the placebo arm.

Table 29. Disagreements between BICR and investigator assessment of RECIST progression events (FAS)

Progression	Number (%) of Subjects: Osimertinib (N=143)	Number (%) of Subjects: Placebo (N=73)	Difference Osimertinib - Placebo
RECIST progression [a] declared by:			
BICR and Investigator	45 (31.5)	59 (80.8)	NA
Progression date agreement (within 2 weeks)	20 (14.0)	22 (30.1)	NA
Progression date >=2 weeks earlier by Investigator than by BICR	7 (4.9)	7 (9.6)	NA
Progression date >=2 weeks earlier by BICR than by Investigator	18 (12.6)	30 (41.1)	NA
BICR but not Investigator	8 (5.6)	3 (4.1)	NA
Investigator but not BICR	12 (8.4)	2 (2.7)	NA
No progression by both	78 (54.5)	9 (12.3)	NA
Early Discrepancy Rate [b]	0.49	0.53	-0.04
Late Discrepancy Rate [c]	0.42	0.21	0.21

[a] PFS events that do not occur within 2 scheduled visits (plus visit window) of the last assessment (or randomization) are censored.
[b] EDR is the frequency of BICR-declared progressions before Investigator as a proportion of all BICR progressions.
[c] LDR is the frequency of BICR-declared progressions after Investigator as a proportion of all discrepancies.
A negative differential discordance for the EDR and/or positive differential discordance for the LDR are suggestive of a bias in the BICR assessment favoring the osimertinib arm.
BICR = Blinded Independent Central Review. EDR = Early Discrepancy Rate. LDR = Late Discrepancy Rate.
N = Number of subjects in treatment group. NA = Not applicable. PFS = Progression-free survival.
RECIST 1.1 = Response Evaluation Criteria in Solid Tumors (RECIST v1.1).

Other sensitivity analyses

A consistent improvement in PFS was observed in the osimertinib arm versus the placebo arm in sensitivity analyses assessing evaluation-time bias (HR = 0.15 [95% CI: 0.10, 0.24]) and attrition bias (HR = 0.16 [95% CI: 0.10, 0.25]).

A consistent improvement in PFS in the osimertinib arm versus the placebo arm was also observed in sensitivity analyses using stratification data according to the eCRF (HR = 0.16 [95% CI: 0.10, 0.25]), and in the Evaluable for Response Analysis Set - which comprises all patients in the FAS who had measurable disease at baseline according to BICR assessment of baseline imaging data (HR = 0.14 [95% CI: 0.09, 0.22]).

Subgroup analyses of PFS

Table 30. Subgroup Analyses of Progression-Free Survival by BICR Assessment (FAS)

Subgroups	Treatment arm	N	Number (%) of patients with events [a]	Comparison between groups	
				HR	95% CI
All patients (stratified by log-rank)	Osimertinib	143	57 (39.9)	0.16	0.10, 0.24
	Placebo	73	63 (86.3)		
All patients (unadjusted Cox PH)	Osimertinib	143	57 (39.9)	0.23	0.16, 0.33
	Placebo	73	63 (86.3)		
Response to prior CRT					
Complete response	Osimertinib	4	1 (25.0)	NC	NC, NC
	Placebo	3	2 (66.7)		
Partial response	Osimertinib	67	28 (41.8)	0.20	0.11, 0.34
	Placebo	27	25 (92.6)		
Stable disease	Osimertinib	61	24 (39.3)	0.18	0.10, 0.30
	Placebo	37	34 (91.9)		
Non-evaluable	Osimertinib	11	4 (36.4)	NC	NC, NC
	Placebo	6	2 (33.3)		
Age group					
< 65 years	Osimertinib	81	31 (38.3)	0.16	0.10, 0.26
	Placebo	39	36 (92.3)		
≥ 65 years	Osimertinib	62	26 (41.9)	0.33	0.19, 0.57
	Placebo	34	27 (79.4)		
Gender					
Male	Osimertinib	53	23 (43.4)	0.26	0.15, 0.46
	Placebo	31	27 (87.1)		
Female	Osimertinib	90	34 (37.8)	0.21	0.13, 0.34
	Placebo	42	36 (85.7)		
Smoking status					
Current/former (yes)	Osimertinib	41	20 (48.8)	0.26	0.14, 0.48
	Placebo	24	22 (91.7)		
Never (no)	Osimertinib	102	37 (36.3)	0.22	0.14, 0.34
	Placebo	49	41 (83.7)		
Prior CRT strategy [b]					
CCRT	Osimertinib	131	53 (40.5)	0.25	0.17, 0.36
	Placebo	62	54 (87.1)		
SCRT	Osimertinib	12	4 (33.3)	NC	NC, NC
	Placebo	11	9 (81.8)		
Disease stage prior to CRT [b,c]					
IIIA	Osimertinib	52	22 (42.3)	0.28	0.15, 0.52
	Placebo	24	20 (83.3)		
IIIB/IIIC	Osimertinib	91	35 (38.5)	0.21	0.13, 0.33
	Placebo	49	43 (87.8)		
Chinese ethnicity [b]					
Patient enrolled at Chinese site and declaring themselves of Chinese ethnicity	Osimertinib	27	7 (25.9)	NC	NC, NC
	Placebo	13	11 (84.6)		
Patient enrolled at non-Chinese site and declaring themselves of non-Chinese ethnicity	Osimertinib	116	50 (43.1)	0.26	0.17, 0.39
	Placebo	60	52 (86.7)		
Central plasma ctDNA EGFR (Ex19del and L858R) mutation status at screening					
Positive	Osimertinib	10	4 (40.0)	NC	NC, NC
	Placebo	4	4 (100)		
Negative	Osimertinib	113	42 (37.2)	0.22	0.15, 0.34
	Placebo	58	51 (87.9)		
Unknown	Osimertinib	20	11 (55.0)	NC	NC, NC
	Placebo	11	8 (72.7)		
Tissue EGFR mutation status at screening [d]					
Ex19del positive	Osimertinib	74	26 (35.1)	0.17	0.10, 0.29
	Placebo	43	39 (90.7)		
L858R positive	Osimertinib	68	31 (45.6)	0.32	0.19, 0.56
	Placebo	30	24 (80.0)		
Unknown	Osimertinib	1	0	NC	NC, NC
	Placebo	0	0		

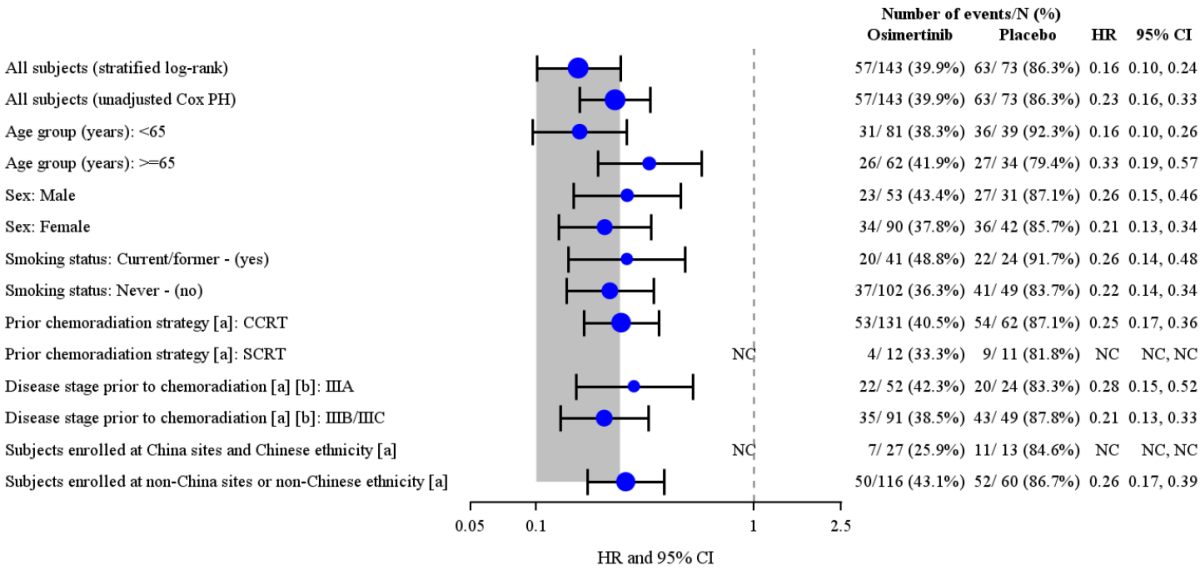
Race					
Asian	Osimertinib	116	43 (37.1)	0.20	0.13, 0.29
	Placebo	62	55 (88.7)		
Non-Asian	Osimertinib	27	14 (51.9)	0.48	0.20, 1.19
	Placebo	11	8 (72.7)		

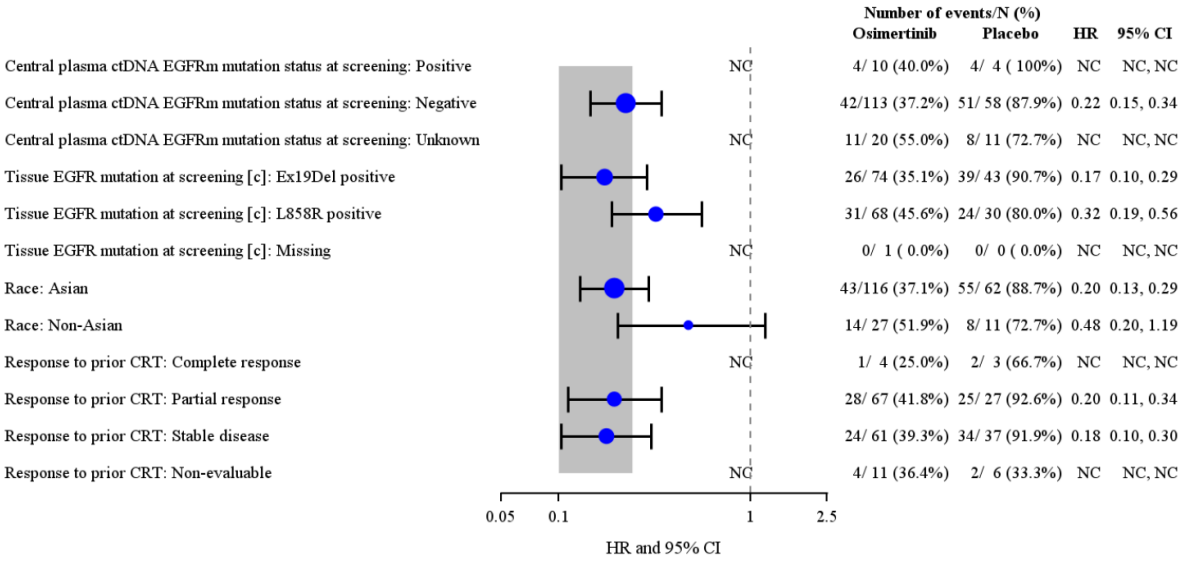
[a] PFS events determined by BICR RECIST v1.1 assessments. Those that did not occur within 2 scheduled visits (plus visit window) of the last evaluable assessment (or randomisation) were censored.
[b] Subgroup analyses for the stratification factors are based on the values entered into the eCRF.
[c] AJCC/UICC 8th Edition.
[d] Summarised based on tissue-based central EGFR testing OR local pre-existing EGFR result.
The HR and 95% CI were calculated from a Cox proportional hazards model that only contains a term for treatment, the factor and treatment-by-factor interaction term. A HR < 1 favours osimertinib to be associated with a longer PFS than placebo.
DCO: 05 January 2024

Table 31 Subgroup analysis of progression-free survival by BICR (Full analysis set)

				Comparison between groups	
Subgroup	Group	N	Number (%) of subjects with events	Hazard ratio	95% CI
WHO PS					
0	Osimertinib	80	27 (33.8)	0.17	0.10, 0.28
	Placebo	31	28 (90.3)		
1	Osimertinib	63	30 (47.6)	0.34	0.20, 0.56
	Placebo	42	35 (83.3)		

Figure 18. Subgroup Analysis of Progression-Free Survival by BICR Assessment, Forest Plot (FAS)





In vitro biomarker test for patient selection for efficacy

In relation to patient selection for inclusion, there was a two-part screening phase. Part I applied only to patients that did not have a pre-existing local EGFR test result derived from a tissue-based FDA-approved CDx for Tagrisso (i.e., cobas® EGFR Mutation Test v2 or FoundationOne® CDx test), performed in an accredited local laboratory (sites outside of the USA) and conducted according to the manufacturer's instructions for use. These patients needed to provide an unstained formalin-fixed paraffin embedded tumour tissue sample in a quantity sufficient to allow for prospective central analysis of EGFR mutation status. Part II screening applied to patients that had a pre-existing local EGFR mutation-positive (Ex19del or L858R) test result, derived from a tissue-based FDA-approved CDx for Tagrisso (i.e., cobas® EGFR Mutation Test v2 or FoundationOne® CDx test) or patients who completed Part I screening and have centrally-confirmed EGFR mutation (Ex19del or L858R) positive NSCLC. If patients had results from a local tumour tissue cobas® EGFR Mutation Test v2 test conducted in a central Covance laboratory following its instructions for use for other AstraZeneca studies, retrospective central analysis of EGFR mutation status was not needed.

According to the study protocol, baseline tumour EGFR mutation status would be compared between tumour DNA and plasma ctDNA using the Kappa coefficient. Analysis would be carried out separately for each sensitizing mutation, Ex19del and L858R. Analysis would be in all Part II screened patients with evaluable results from baseline plasma samples. Baseline tumour EGFR mutation status would also be compared between local and central (cobas® EGFR mutation test v2) tests, using the Kappa coefficient, in subjects with evaluable results from baseline tumour samples. Similarly, analysis would be carried out separately for each sensitizing mutation, Ex19del and L858R, and as well as in aggregate.

In line with EU Regulation 2017/749 ('IVDR') as companion diagnostic (CDx), the MAH submitted the following information:

a) Scientific validity for the choice of the predictive in vitro biomarker test including definition and its validation, which mutation(s) define(s) a patient to be positive for "EGFR exon 19 deletions or exon 21 L858R substitution mutations":

   Two in vitro biomarker tests were utilised for patient selection in the LAURA study; the Roche cobas EGFR Mutation Test v2 (CAP/CLIA, ISO15189 or equivalent accredited) and the FoundationOne CDx.

The scientific validity of using the cobas EGFR Mutation Test v2 as the predictive in vitro biomarker test for TAGRISSO was demonstrated in the phase III FLAURA study. The cobas Mutation Test v2 is an approved CDx for TAGRISSO under IVDD bearing the CE mark.

For the sample tested using the FoundationOne CDx, the scientific validity of this test was established through equivalence testing against the cobas EGFR Mutation test v2. The FoundationOne CDx is also CE marked under IVDD.

The mutations which define a patient to be positive are those which are reported for EGFR exon 19 deletions (Ex19Del) or exon 21 L858R mutation (L858R).

b) Analytical method including assay platform, specimen, pre-analytical processing requirements and read-out method:

The cobas EGFR Mutation Test v2 is a real-time PCR test for the qualitative detection of defined mutations of the EGFR gene in NSCLC. The test is run on FFPE NSCLC specimens which have undergone manual DNA extraction with amplification and detection occurring on the cobas z 480 Analyzer.

FoundationOne® CDx (F1CDx) is a next generation sequencing based in vitro diagnostic device for detection of substitutions, insertion and deletion alterations (indels). Summary performance characteristics are summarised in Section 2 of the F1CDx Technical Information document. FoundationOne CDx (F1CDx) is performed as a laboratory service using DNA extracted from FFPE tumour samples.

c) Analytical performance: For verifying the suitability of an assay, robustness, accuracy, specificity, sensitivity and linearity should be considered depending on the analytical platform:

Analytical performance has been established through analytical verification studies. The analytical verification studies included: Limit of blank, limit of detection, minimal tumour content, cross-reactivity, interfering substances, repeatability and reproducibility.

d) Clinical performance (i.e. indicate why "EGFR exon 19 deletions or exon 21 L858R substitution mutations" being identified by the test is a predictive biomarker, and what data exist to support this predictive performance):

See question a) for the reference to clinical performance.

e) Cut-point selection (i.e. indicate the threshold, rather the cut-point) defining a patient as biomarker positive; provide evidence why this cut-point was selected:

DNA mutation assays, such as for EGFR, generate binary outputs on the presence or absence of mutation. The threshold for the detection of a mutation is governed by the validated analysis software used by the cobas EGFR Mutation Test v2. The cobas test produces a report detailing the identification of the mutations present. The LAURA study used the results as reported by the cobas CE marked software, no modifications to the calling thresholds were made.

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 32. Summary of Efficacy for trial LAURA

Title: A Phase III, Randomised, Double-Blind, Placebo-Controlled, Multicentre, International Study of Osimertinib as Maintenance Therapy in Patients with Locally Advanced, Unresectable EGFR Mutation-Positive Non-Small Cell Lung Cancer (Stage III) Whose Disease has not Progressed Following Definitive Platinum-Based Chemoradiation Therapy (LAURA)			
Study identifier	*Study Code:* D5160C00048 *EudraCT Number:* 2018-001061-16 *NCT Number:* NCT03521154		
Design	Phase III, randomised, double-blind, placebo-controlled, multicentre study		
	Duration of study:		19 July 2018 (FSI) to 05 January 2024 (DCO)
Hypothesis	Superiority		
Treatment groups	Osimertinib		Osimertinib 80 mg, orally, once daily [143 patients randomised]
	Placebo		Placebo tablets matched to osimertinib, orally, once daily [73 patients randomised]
Endpoints and definitions	Primary endpoint	PFS by BICR assessment	PFS using BICR assessment according to RECIST v1.1. Defined as the 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 withdraws from randomised therapy or receives another anticancer therapy prior to progression.
	Primary endpoint – sensitivity analysis	PFS by Investigator assessment	Sensitivity analysis of PFS (as defined above) by Investigator assessment per RECIST v1.1.
	Key Secondary endpoint	OS	Defined as time from the date of randomisation until death due to any cause.
	Key Secondary endpoint	CNS PFS	CNS PFS using neuroradiologist BICR assessment according to RECIST v1.1. Defined as the time from randomisation until the date of CNS objective disease progression or death (by any cause in the absence of CNS progression) regardless of whether the patient withdraws from randomised therapy or receives another anticancer therapy prior to CNS progression.
Database lock	05 February 2024		

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 date of 05 January 2024. 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	Osimertinib	Placebo
	Number of subjects	143	73
	PFS by BICR assessment (median, months) 95% CI	39.13 31.51, NC	5.55 3.71, 7.43
	Sensitivity analysis of PFS by Investigator assessment (median, months) 95% CI	38.87 26.71, NC	7.29 5.45, 10.25
Effect estimate per comparison	PFS by BICR assessment	Comparison groups	Osimertinib vs. Placebo
		Hazard ratio	0.16
		95% CI	0.10, 0.24
		2-sided p-value	< 0.001
	Sensitivity analysis of PFS by Investigator assessment	Comparison groups	Osimertinib vs. Placebo
		Hazard ratio	0.19
		95% CI	0.12, 0.29
		2-sided p-value	< 0.001

Analysis description	**Key secondary analyses**		
Analysis population and time point description	Overall survival data were tested per the hierarchical testing procedure at the DCO date of the primary PFS analysis (05 January 2024), in the first of 2 pre-planned analyses. The interim analysis of OS was conducted on the ITT population (defined as the FAS).		
Descriptive statistics and estimate variability	Treatment group	Osimertinib	Placebo
	Number of subjects	143	73
	OS (median, months) 95% CI	53.95 46.49, NC	NC 42.05, NC
Effect estimate per comparison	OS	Comparison groups	Osimertinib vs. Placebo
		Hazard ratio	0.81
		95% CI	0.42, 1.56
		Adjusted 99.964% CI *	0.25, 2.67
		2-sided p-value	0.530

Analysis population and time point description	The key secondary efficacy analysis of CNS PFS was conducted on the ITT population (defined as the FAS), at the DCO date of 05 January 2024. Of note, the statistical significance of CNS PFS could not be formally tested at the current DCO date per the hierarchical testing procedure, as OS did not reach statistical significance at its interim analysis.		
Descriptive statistics and estimate variability	Treatment group	Osimertinib	Placebo
	Number of subjects	143	73
	CNS PFS (median, months)	NC	14.88
	95% CI	NC, NC	7.36, NC
Effect estimate per comparison	CNS PFS	Comparison groups	Osimertinib vs. Placebo
		Hazard ratio	0.17
		95% CI	0.09, 0.32
		2-sided p-value (nominal)	< 0.001

2.4.3. Discussion on clinical efficacy

The MAH is applying for an extension of the indication of Tagrisso as monotherapy for the treatment of adult patients with locally advanced, unresectable (stage III) NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations and whose disease has not progressed during or following platinum-based chemoradiation therapy.

To support this application, the MAH has submitted the results of the LAURA study, which are the basis of the assessment.

Design and conduct of clinical studies

Design of the study

The LAURA study is a Phase III randomised, double-blind, placebo-controlled, multicentre global study comparing the efficacy and safety of osimertinib as a maintenance therapy versus placebo in patients with locally advanced, unresectable (Stage III) NSCLC with centrally-confirmed EGFR mutations (Ex19del and L858R) whose disease has not progressed during or following definitive platinum-based CRT.

Patients were randomised 2:1 to receive either osimertinib (80 mg as a single oral daily dose) or matching placebo. The 80 mg dose could be reduced to 40 mg to allow for management of treatment related toxicities. The recommended dose and dose modifications are the same as for the other indications approved for Tagrisso and are considered acceptable. Patients were to be treated until objective radiological PD per RECIST v1.1 by BICR or until another discontinuation criterion was met. Treatment beyond progression was allowed for patients that were continuing to derive clinical benefit at the discretion of the treatment physician. Regarding the treatment duration, the MAH states that at the time of the development of the LAURA protocol there were limited published data on EGFR-TKIs to determine the optimal duration of dosing, specifically in patients with EGFRm Stage III NSCLC. The justification provided is based on interim data from the RECEL trial in EGFRm Stage III NSCLC (in which a drop-off in survival at 2 years of FU, when erlotinib was discontinued, was observed), as well as on data available from trials of adjuvant EGFR-TKI therapies in patients with EGFRm NSCLC of varying disease stages. Additionally, it was considered that no safety concerns precluded a dosing to progression duration of treatment. Overall, the duration of treatment can be considered acceptable although it is unknown whether a shorter treatment duration may have been sufficient.

Patients were stratified by prior chemoradiation strategy (CCRT vs. SCRT), tumour stage prior to chemoradiation (IIIA vs. IIIB/IIIC) and China cohort (Chinese ethnicity vs. non-Chinese ethnicity).

According to the MAH, the China cohort was added to allow for a separate reporting in China. Overall, the stratification factors are agreed; although it should be noted that in the SA provided by Spanish national agency (AEMPS) it was recommended to include an additional stratification factor based on "prior response to chemoradiation"; but this stratification factor was not added.

Randomised patients were not to have progressed during or following definitive, platinum-based CRT. Patients were to be randomised within 6 weeks after completion of CRT.

The MAH did not request any CHMP scientific advice for this procedure, although advice was received by the AEMPS in October 2017. Overall, the MAH followed the advice received.

The choice of placebo as comparator is considered acceptable. The only treatment authorised in the EU in this setting is durvalumab, but the number of patients with EGFRm included in the pivotal study was low (43 patients in total, 6% of the overall population), which impairs concluding on the efficacy of durvalumab in this subgroup of patients. Besides, in the EU durvalumab is only approved for patients whose tumours express PD-L1 ≥1%. Due to the limited data available on the efficacy of durvalumab in EGFR-mutated patients and the lack of any other approved therapy in this setting, the use of placebo is considered justified. Additionally, the use of placebo was already agreed on the SA provided by the AEMPS in 2017; although it should be noted that at the moment the advice was given, durvalumab was not yet authorised - the marketing authorisation was granted in 2018.

The primary endpoint was PFS by BICR. OS and CNS PFS were key secondary endpoints and were tested in that order following a hierarchical multiplicity testing procedure. Other secondary endpoints were ORR, DoR, DCR and depth of response, TTDM (time to distant metastases), TTD (time to treatment discontinuation or death) and PROs (EORTC QLQ-C30 and EORT QLQ-LC13). Additionally, post-progression endpoints were also measured: PFS2, TFST (time to first subsequent treatment) and TSST (time to second subsequent treatment).

The choice of PFS as primary endpoint is considered acceptable and was agreed in the national SA given in 2017; although in this SA the need of, at least, discarding a potential detrimental OS effect was also pointed out. It should be noted that cross-over was permitted from the protocol amendment 2 on, which, from a methodological point of view, makes the interpretation of OS data difficult. The secondary endpoints are considered acceptable, including the order for the multiplicity testing procedure (which was the object of protocol amendment 4). Of note, in the national advice a recommendation to consider endpoints such as PFS2 was given, which was followed by the MAH.

The LAURA study included patients with histologically or cytologically documented NSCLC who presented with locally advanced, unresectable (Stage III) disease (according to Version 8 of the IASLC Staging Manual in Thoracic Oncology), and confirmed EGFRm (Ex19del and L858R). CRT, either CCRT or SCRT, must have been completed within 6 weeks prior to randomisation. The study included patients with EGFRm NSCLC who had either a pre-existing local EGFRm (Ex19del or L858R) test result derived from a tissue-based FDA-approved Companion Diagnostic for Tagrisso; or a centrally confirmed EGFR mutation (Ex19del or L858R) positive test. Prior systemic treatment with any chemotherapy, radiation therapy, immunotherapy, or investigational agents for NSCLC outside of that received in the curative setting for Stage III disease, or prior treatment with EGFR-TKI therapy, was not permitted. Prior surgical resection (i.e., Stage I, II, or III) was permitted. Overall, inclusion and exclusion criteria are considered to be representative of the targeted population.

Statistical methods and sample size

The calculation of the sample size was considered adequate: 200 patients would be randomised into the study in a 2:1 ratio.

For the primary comparison, the MAH considered PFS (per RECIST v1.1 as assessed by BICR); defined as the 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 withdraws from study treatment or receives another anti-cancer therapy prior to progression, following the treatment policy approach for these intercurrent events. Possible attrition bias was assessed by means of a sensitivity analysis, which was considered acceptable to ensure the robustness of the primary analysis.

Different scenarios concerning potential mis-stratifications during randomisation, model assumptions or the impact of COVID-19 deaths on PFS have been considered to address different types of biases, which are welcomed and appropriate. However, with regards to the OS analysis, the MAH has not proposed a sensitivity analysis that would enable to control the implications of the crossover allowed per protocol, or the confounding effects of subsequent lines of therapy that may include osimertinib. Overall, crossover leads to contamination of the initial randomised groups due to a mixing of the effects of the control and experimental treatments. The MAH should provide methods to deal with selective treatment switching and adjust the OS analyses (EMA/845963/2018, "*Question and answer on adjustment for cross-over in estimating effects in oncology trials"*) for the final OS analysis (see below).

The multiplicity testing procedure was considered adequate, as well as the techniques used to handle the interim analyses.

Conduct of the study

The original LAURA protocol (dated 23 March 2018) was amended four times. In terms of the design of the study, the most relevant amendment was Amendment 1 (dated 28 February 2020), when it was added that patients may receive open-label osimertinib after BICR-confirmed disease progression. According to the MAH the reason for this amendment was aiding recruitment and making osimertinib available for patients randomised to placebo, after FLAURA OS results became available at the end of 2019, and the ESMO guidelines[1] included in their recommendations the use of osimertinib in these patients ("*Oncogene-addicted metastatic non-small-cell lung cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up*"). Therefore, considering that osimertinib may be a treatment option for patients with locally advanced or metastatic NSCLC with activating EGFR mutations, allowing treatment with osimertinib for those patients in the placebo arm after disease progression seems reasonable from an ethical and logistical point of view, although it hampers interpretation of OS results, as already pointed out. Of note, the percentage of patients randomised based on CSP v1.0 was low (N=61).

The other amendment which had a relevant impact in the design of the study was Amendment 4 (dated 03 November 2023), by which the hierarchy of the multiple testing procedure was changed from "PFS – CNS PFS – OS" to "PFS – OS – CNS PFS". The rationale for this amendment was increasing the chance of formally testing OS, which also seems reasonable.

The number of important protocol deviations was low and balanced between both arms; being "non-compliance with RECIST 1.1 scanning schedule" the most frequently reported protocol deviation.

Patient disposition

Out of 746 enrolled patients, only 216 were randomised (143 to osimertinib and 73 to placebo). At DCO in the osimertinib arm there were 80 patients (55.9%) ongoing the study treatment vs. 7 patients (9.6%) in the placebo arm. It is noted that there is a relevant difference between arms in terms of patients remaining on treatment in the osimertinib arm vs. the placebo arm, which clearly favours osimertinib. At DCO, there

[1] Hendriks LE et al; ESMO Guidelines Committee. Electronic address: clinicalguidelines@esmo.org. Oncogene-addicted metastatic non-small-cell lung cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol. 2023 Apr;34(4):339-357.

were 163 (75.5%) patients still ongoing in the study [111 patients (77.6%) in the osimertinib arm vs. 52 patients (71.2%) in the placebo arm].

Baseline characteristics

In terms of baseline demographic characteristics, both arms were overall well-balanced. Most patients included in the trial were female (61.1%), Asian (82.4%) and never smokers (69.9%), with a median age of 62.5 years old. A slight imbalance in terms of patients older than 75 years old is noted, with 9.1% of patients in the osimertinib arm and 19.2% in the placebo arm.

Special mention should be given to the percentage of non-Asian patients included in this trial. Of note, only 13.9% of patients included in the LAURA study were White, which constitutes a relevantly lower percentage compared with the other clinical trials of osimertinib: in the AURAex and AURA2 studies (which led to the marketing authorisation) there were 36% of White patients vs. 60% of Asian patients; in the AURA3 there were 32% of White patients vs. 65% of Asian patients; in the FLAURA study (procedure EMEA/H/C/004124/II/0019) there 36.2% of White patients vs. 62.4% of Asian patients; and in the ADAURA study (procedure EMEA/H/C/004124/II/0039/G) there were 35.8% of White patients vs. 63.6% of Asian patients. Although the fact that EGFR-activating mutations are more frequently observed in Asian patients than in White patients is acknowledged, the low percentage of White patients included in the trial initially posed concerns regarding the potential extrapolation of results from Asian patients to White patients: only 30 White patients were included in the trial (20 in the osimertinib arm and 10 in the placebo arm). Upon request, the MAH provided further justification on why results in Asian patients could be generalised to White patients, considering that the target EU population will be mainly formed by White patients. This justification is based on the fact that the biology of the tumour remains unaltered among different races, on the pharmacokinetic data which showed no impact of race/ethnicity across global populations on osimertinib exposures, and on the absence of relevant efficacy differences among race subgroups in other studies of the osimertinib in other lines of NSCLC treatment (e.g. FLAURA, ADAURA). This justification is considered acceptable; and, therefore, it is agreed that there are no reasons to expect different responses in White patients than in Asian patients. Additionally, the MAH has also provided reasons why so few White patients were included in the study; mostly due to recruitment issues such as the low percentage of patients who present with locally advanced disease, the unavailability of tissue samples (considering that in the unresectable setting is more difficult to obtain samples than in resectable or metastatic disease) or the fact that at the time of recruitment the ESMO guidelines did not recommend screening for EGFR mutation status in the unresectable stage III setting; which led to increasing the number of Asian centres with the aim of maximising the potential for recruitment in this region in which activating EGFR mutations are known to be more frequent than in other regions.

Regarding disease characteristics, overall no major differences were observed between both arms. Most patients included had a Stage IIIB disease (46.9% in osimertinib vs. 52.1% in placebo) and had an adenocarcinoma (97.2% in osimertinib vs. 96.3% in placebo). A vast majority of patients had received CCRT as prior CRT strategy (91.6% in osimertinib vs. 84.9% in placebo); reflecting that CCRT is the strategy most frequently followed in clinical practice in patients who are fit, as recommended by ESMO guidelines[2]. A higher percentage of patients had received carboplatin (52.4% in osimertinib vs. 60.3% in placebo) compared with cisplatin (46.2% in osimertinib vs. 39.7% in placebo), particularly in the placebo arm; although according to the ESMO guidelines "*In the absence of contraindications, the optimal ChT to be combined with radiation in stage III NSCLC should be based on cisplatin"*. Most patients had had a PR (43.5%: 46.9% in osimertinib vs. 37% in placebo) or SD (45.4%: 42.7% in osimertinib vs. 50.7% in placebo) as response to prior CRT; with almost no patients having achieved a CR in either arm (2.8% in osimertinib vs. 4.1% in placebo). In terms of mutations, 54.2% of patients were Ex19del positive (51.7%

[2] Postmus PE et al; ESMO Guidelines Committee. Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2017 Jul 1;28(suppl_4):iv1-iv21.

in osimertinib vs. 58.9% in placebo); and 45.4% were L858R positive (47.6% in osimertinib vs. 41.1% in placebo). A slight imbalance between both arms was observed in terms of WHO performance status: 55.9% in the osimertinib arm had a WHO status of 0 vs. 42.5% in the placebo arm. A post-hoc subgroup analysis, further discussed under the "subgroup analyses" section, was conducted and submitted by the MAH.

Efficacy data and additional analyses

The LAURA study met its primary endpoint (**PFS by BICR**) at the primary PFS analysis (maturity: 55.6%), with a HR of 0.16 (95% CI: 0.10, 0.24; p-value <0.0001) and a mFU of 21.98 (range: 0.03 to 60.55) months in the osimertinib arm and 5.55 (range: 0.03 to 49.71) months in the placebo arm. mPFS (95%CI) in the osimertinib arm was 39.13 months (31.51, NC), whereas in the placebo arm it was 5.55 months (3.71, 7.43); showing a relevant difference between arms. In the osimertinib arm there were 57 events (39.9%), compared with 63 events (86.3%) in the placebo arm; showing a difference which also highlights the benefit that patients in the osimertinib arm obtained from the treatment with osimertinib over those in the placebo arm. Almost all of the events were progression events (37.1% out of 39.9% in the osimertinib arm, and 84.9% out of 86.3% in the placebo arm). However, in the osimertinib arm there were 4 deaths (2.8%) while in the placebo arm there was only 1 death (1.4%). These deaths were labelled as "death in the absence of progression" and were due to "acute respiratory distress syndrome", "respiratory failure", "NSCLC" (disease progression not BICR-confirmed, reason why it was not formally considered as disease progression) and "road traffic accident" in the osimertinib arm; and "aortic aneurysm rupture" in the placebo arm. Most of the progressions in both arms were new lesions (20.3% in the osimertinib arm vs. 61.6% in the placebo arm), followed by target lesions (16.1% in the osimertinib arm vs. 21.9% in the placebo arm). Regarding the sites of occurrence of new lesions, 28.8% of patients in the placebo arm presented new brain lesions while this percentage was 8.4% in the osimertinib arm. Same trend was observed for other common places of progression, such as liver and lung. Most censored patients in both arms were progression-free at time of analysis (57.3% in the osimertinib arm vs. 8.2% in the placebo arm). In this line, PFS rate at 36 months was 58.4 (95% CI: 48.6, 66.9) in the osimertinib arm, vs. 10 (95% CI: 4.0 19.2) in the placebo arm. KM curves showed a clear separation from month 3, being sustained over time. Overall, PFS results show a clear and rather outstanding benefit of patients treated with osimertinib over those treated with placebo; benefit which seems to be sustained over time.

The MAH presented several sensitivity analyses, which showed robustness of the primary PFS evaluation. Relevantly, PFS by investigator was 0.19 (95% CI: 0.12, 0.29), with similar mPFS results and similar KM curves. With the aim of analysing the discrepancy between PFS assessed by Investigator and by BICR, the MAH has conducted a concordance comparison, resulting in an 86.0% agreement for the osimertinib arm and a 93.2% agreement for the placebo arm which seems acceptable.

Similarly, sensitivity analyses assessing evaluation-time bias and attrition bias, together with sensitivity analyses using data according to the eCRF and in the Evaluable for Response analysis set, showed results akin to the results observed in the primary analysis.

At the DCO of the primary PFS analysis, OS was tested per the hierarchical testing procedure. This interim analysis of **OS** was conducted at 19.9% maturity, with a low number of events (43 in total; 28 [19.6%] in the osimertinib arm and 15 [20.5%] in the placebo arm) and a mFU of around 29 months. This interim analysis was not statistically significant (HR: 0.81 [adjusted 99.964% CI: 0.25, 2.67]; p-value=0.530; p-value needed to declare statistical significance: <0.00036); which is not surprising considering the immaturity of the data at this DCO and that cross-over was allowed. Of note, the KM curves show separation at around month 33.

In the context of the interpretation of the KM curves and the OS data, it is highly important to note that the level of cross-over in the study was very high: 51 out of the 66 patients (77.3%) who discontinued

treatment with placebo received osimertinib as a post-progression therapy; meaning that 69.9% of the total number of patients included in the placebo arm (51/73) received osimertinib as a post-progression therapy. Additionally, it should be noted that out of the 57 patients (78.1%) in the placebo arm who received any post-treatment anticancer therapy, all of them received an EGFR-TKI [7 patients (9.6%) a first of second-generation EGFR-TKI and 52 patients (71.2%) a third generation EGFR-TKI]. Regarding the osimertinib arm, 63 patients (44.1%) discontinued the study treatment, with 42 patients (29.4%) receiving any post-treatment anticancer therapy. Of those patients, 28 patients (19.6%) received an EGFR-TKI as post-treatment disease-related anticancer therapy; 15 (10.5%) of them receiving osimertinib.

Thus, although at DCO a detrimental effect is not observed, no firm conclusions can be drawn from the submitted data since a clear positive OS trend is not observed either. Moreover, interpretation of OS data is hampered by cross-over. Taking into account the clear benefit observed in terms of PFS and the apparent lack of detrimental effect in OS, efficacy can be considered demonstrated. Nevertheless, the final OS analysis, which is planned to be conducted when there are approximately 120 events across both arms (around 60% maturity) should be provided once available. The MAH will submit the final OS analysis when available (**REC**), which is expected to occur in the second half of 2026. Besides, as already stated, additional methods/analyses to adjust for cross-over should also be presented.

CNS PFS by neuroradiologist BICR was included in the hierarchical testing procedure after OS. Since OS was not statistically significant at this interim analysis, CNS PFS could not be formally tested. It is unfortunate that CNS PFS was ordered after OS, since with the high level of cross-over, it is not expected that OS will reach statistical significance in any point of time; and, therefore, CNS PFS will not be formally tested. Nevertheless, the descriptive results seemed to show a relevant clinical effect of osimertinib in CNS PFS, with a HR of 0.17 (95% CI: 0.09, 0.32) based on a data maturity of 27.3%. There were 18 (12.6%) events in the osimertinib arm vs. 26 (35.6%) events in the placebo arm, and the KM curves clearly separate since the beginning of the trial. Additionally, the percentage of new CNS lesions was lower in the osimertinib arm (35.6%; 26 patients) than in the placebo arm (11.9%; 17 patients); and the median CNS PFS in the osimertinib arm was not reached, while in the placebo arm it was 14.88 (95% CI: 7.36, NC) months. A competing risk analysis was performed, which indicated that the estimated probability of observing a CNS progression event (conditional on the patient not experiencing a competing event of progression outside the CNS or death by that time) was lower in the osimertinib arm than in the placebo arm. An imbalance between arms is observed in terms of the censorships in CNS PFS (60.1% vs. 13.7%) mainly due to the fact that most patients were progression-free at time of analysis: 82 out of 86 censored patients in the osimertinib arm were censored because of this reason. Although no statistical testing could be performed, it seems that patients in the osimertinib arm do obtain a clinically relevant benefit in terms of CNS PFS, which is an important outcome considering the high risk of brain metastases that NSCLC patients have, and the high impact that brain metastases have on patients' quality of life.

The results of the other secondary endpoints also favoured the treatment with osimertinib and supported the results of the primary endpoint. **ORR by BICR** was higher in the osimertinib arm [57.3% vs. 32.9%; odds ratio: 2.77 (95% CI: 1.54, 5.08)]; and these results were consistent when repeating the analysis for confirmed responses only [53.8% vs. 26%; odds ratio: 3.33 (95% CI: 1.82, 6.31)]. It should be noted that most responses in both arms were PR (55.2% vs. 31.5%), with very few patients reaching CR in any arm [3 patients (2.1%) vs. 1 patient (1.4%)]. **DoR** was also relevantly longer in the osimertinib arm (mDoR 36.9 months vs. 6.5 months). In terms of **tumour shrinkage**, treatment with osimertinib also resulted in a greater reduction from baseline compared with placebo (median reduction of 43.3% vs. 21.9%). According to the MAH the shrinkage observed in the placebo arm could be due to the delayed effects of CRT; which seems to be a reasonable explanation. **Time to death or distant metastases by BICR** also favoured treatment with osimertinib [23.1% vs. 42.5%; HR: 0.21 (95% CI: 0.11, 0.38); mTDDM not reached vs. 13.04 months]. **Time to treatment discontinuation or death** also resulted in a clinical improvement with osimertinib [HR: 0.21 (95% CI: 0.14, 0.32); mTTD 40.28 months vs. 8.31 months]. The

results of the post-progression outcomes also favoured the osimertinib arm: **time to first subsequent treatment** [HR: 0.13 (95% CI: 0.08, 0.21); mTFST 43.83 months vs. 9.46 months], **PFS2** [HR: 0.62 (95% CI: 0.35, 1.08); mPFS2 48.20 months vs. 47.38 months] and **time to second subsequent treatment** [HR: 0.51 (95% CI: 0.28, 0.91); mTSST not reached vs. 47.38 months].

PRO outcomes were measured as secondary endpoints using the EORTC QLQ-C30 and EORTC QLQ-LC13 questionnaires. Overall, **EORTC QLQ-C30** results did not show relevant changes in terms of QoL between both arms; although a slightly higher percentage of patients in the osimertinib arm experienced a confirmed deterioration in GHS/QoL or death than in the placebo arm [49.6% in osimertinib vs. 41.2% in placebo; HR: 1.14 (95% CI: 0.74, 1.78)], with all the relevant scales contributing to that slight increase (i.e., physical function, fatigue, appetite loss). Nevertheless, based on the MMRM analysis, no clinically meaningful changes from baseline (i.e. a deterioration of ≥ 10 points) were observed in any of these scales. In terms of **EORTC QLQ-C13**, the percentage of patients with confirmed deterioration was also slightly higher in the osimertinib arm compared with the placebo arm in all the relevant scales (i.e., dyspnoea, coughing, pain in chest); although based on the MMRM analysis, no clinically meaningful changes from baseline were observed in any of these scales. Overall, it does not seem that treatment with osimertinib was associated with a relevant change in patients' QoL; although it seems that QoL scales were slightly negatively impacted by the treatment with osimertinib, which could be expectable considering that the control arm was placebo.

Subgroup analyses

The MAH has presented the results of subgroup analyses for PFS.

Apart from the prespecified subgroup analyses, the MAH conducted a post-hoc subgroup analysis due to the observation of a small imbalance between treatment arms in WHO performance status at baseline (WHO performance status 0 vs. WHO performance status 1, see discussion on baseline characteristics). The results of this subgroup analysis, together with the results of the other subgroup analyses, confirmed the consistency of the subgroup results compared with the overall population. All subgroups had HR with CI<1, except for the subgroup of non-Asian patients, in which the HR was 0.48 (95% CI: 0.20-1.19). However, it is noted that the number of events and patients was low (14 events out of 27 patients in the osimertinib arm vs. 8 events out of 11 patients in the placebo arm) and that the CIs were too wide to reach any conclusion.

Based on the overall LAURA study results, administering osimertinib, after definitive chemo-radiotherapy, to patients with stage III unresectable NSCLC has shown a relevant improved benefit compared to placebo. However, it is acknowledged that this can hardly be considered a curative setting, since a high percentage of patients eventually relapse. At relapse, these patients would be candidates to receive osimertinib as 1L treatment in the advanced disease, based on the results from the FLAURA Study. For this reason, the benefit of this earlier new treatment approach should be weighed against the risks associated to a long-term treatment with osimertinib (as opposed to observation).

Wording of the indication

In the wording of the indication initially proposed by the MAH there was a mention to the stage (i.e. stage III). For consistency with prior procedures, this was removed from the wording of the indication. Thus, the finally agreed wording is as follows:

Tagrisso as monotherapy for the treatment of adult patients with locally advanced, unresectable NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations and whose disease has not progressed during or following platinum-based chemoradiation therapy.

2.4.4. Conclusions on the clinical efficacy

The results from the preplanned interim analysis of the LAURA study have shown a statistically significant improvement in PFS by BICR for osimertinib in the treatment of adult patients with locally advanced, unresectable NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations and whose disease has not progressed during or following platinum-based chemoradiation therapy. Although OS data could not be properly interpreted due to the immaturity of data and the high level of cross-over to the osimertinib arm, at DCO a detrimental effect was not observed, which is reassuring.

The differences between arms in terms of PFS, which are quite outstanding, are further supported by the descriptive results of CNS PFS, which could not be formally tested due to the fact that it was placed after OS in the hierarchical testing procedure. Similarly, all secondary endpoints measured further supported the results of the primary endpoint.

2.5. Clinical safety

Introduction

Safety data for this evaluation is primarily based mainly on data from 216 patients from the randomised period (FAS) of the LAURA study (D5160C00048), supported by comparisons with a pooled safety dataset (N=1813) of patients with EGFRm NSCLC who received osimertinib monotherapy. The pooled safety dataset 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.

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 (i.e., 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.

Along this section, safety data from the LAURA study are presented side by side with the data from the 80mg safety pool of osimertinib (N= 1813) for comparison. Safety data cut-off date for LAURA study was the same than for the efficacy data, on 05 January 2024.

Of note, patients who continued to receive open-label treatment are not included in the main evaluation of safety (Safety Analysis Set).

Patient exposure

Table 33. Duration of Exposure

	Number (%) of patients		
	LAURA Study		Osimertinib monotherapy safety pool (N = 1813)
	Osimertinib (N = 143)	Placebo (N = 73)	
Total exposure (months) [a]			
Mean (SD)	23.7 (14.46)	11.8 (10.88)	20.8 (13.45)
Median	24.0	8.3	19.3
Min, Max	0.39, 62.88	0.46, 56.64	0.03, 52.24
Total treatment years	282.54	71.63	3142.75
Actual exposure (months) [b]			
Mean (SD)	23.2 (14.44)	11.5 (10.85)	20.6 (13.37)
Median	23.7	7.9	19.1
Min, Max	0.26, 62.42	0.46, 56.18	0.03, 52.24
Total treatment years	276.27	70.17	3107.17

[a] Total exposure time = Number of days patient received study drug as recorded in the Exposure page / (365.25 / 12).

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

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

A total of 70 patients (49.0%) in the osimertinib arm received treatment for ≥24 months compared to 7 patients (9.6%) in the placebo arm.

Table 34. Summary of Treatment Interruptions and Dose Reductions (Safety Analysis Set)

	Osimertinib (N = 143)	Placebo (N = 73)
Received planned starting dose	143	73
Dose interruptions		
Number (%) of patients with interruptions (any)	79 (55.2)	21 (28.8)
1 interruption	53 (37.1)	15 (20.5)
2 interruptions	19 (13.3)	1 (1.4)
3 interruptions	5 (3.5)	3 (4.1)

	Osimertinib (N = 143)	Placebo (N = 73)
4 interruptions	1 (0.7)	1 (1.4)
5 interruptions	1 (0.7)	1 (1.4)
Reason for interruption, n (%) [a]		
Adverse event	76 (53.1)	19 (26.0)
Surgery	1 (0.7)	1 (1.4)
Laboratory abnormality not reported as an adverse event	1 (0.7)	0
Other [b]	8 (5.6)	2 (2.7)
Total number (%) of interruptions (any) [c]		
Median (days) [d]	14.0	10.5
Minimum-maximum (days) [e]	1-98	1-55
Dose reductions		
Number (%) of patients with dose reduction (any)	12 (8.4)	1 (1.4)
1 reduction	12 (8.4)	1 (1.4)
Reason for dose reduction [f]		
Adverse event	12 (8.4)	1 (1.4)

[a] Reasons for interruption are not mutually exclusive for patients with multiple interruptions although will be counted only once per category. Missed or forgotten doses have not been summarised as dose interruptions.
[b] No specific pattern in the reasons for treatment interruption captured in the 'Other' category was noted from a review of information captured in the eCRF.
[c] Any is defined as the total number of patients with at least one dose interruption.
[d] Median length of interruption. The median number of days of an interruption is calculated across all interruptions and all patients.
[e] Reflects the minimum and maximum duration of individual treatment interruptions.
[f] Reasons for dose reductions are not mutually exclusive for patients with multiple reductions although will be counted only once per category.
DCO: 05 January 2024

Adverse events

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

Table 35. Adverse Events in Any Category (Safety Analysis Set)

	Number (%) of patients [a]		
	LAURA Study		Osimertinib monotherapy safety pool (N = 1813)
	Osimertinib (N = 143)	Placebo (N = 73)	
Any AE	**140 (97.9)**	**64 (87.7)**	**1783 (98.3)**
Any AE causally related to treatment [b]	115 (80.4)	30 (41.1)	1620 (89.4)
Any AE of CTCAE Grade 3 or higher	**50 (35.0)**	**9 (12.3)**	**674 (37.2)**
Any AE of CTCAE Grade 3 or higher, causally related to treatment [b]	19 (13.3)	2 (2.7)	254 (14.0)

Table 35. Adverse Events in Any Category (Safety Analysis Set)

	Number (%) of patients [a]		
	LAURA Study		Osimertinib monotherapy safety pool (N = 1813)
	Osimertinib (N = 143)	Placebo (N = 73)	
Any AE with outcome of death	**3 (2.1)**	**2 (2.7)**	**69 (3.8)**
Any AE with outcome of death, causally related to treatment [b]	1 (0.7)	0	10 (0.6)
Any SAE (including those with an outcome of death)	**55 (38.5)**	**11 (15.1)**	**521 (28.7)**
Any SAE (including those with an outcome of death), causally related to treatment [b]	12 (8.4)	1 (1.4)	109 (6.0)
Any AE leading to discontinuation of treatment	**18 (12.6)**	**4 (5.5)**	**194 (10.7)**
Any AE leading to discontinuation of study treatment, causally related to treatment [b]	9 (6.3)	0	120 (6.6)
Any AE leading to dose modification	**80 (55.9)**	**18 (24.7)**	**502 (27.7)**
Any AE leading to dose modification of study treatment, causally related to treatment [b]	28 (19.6)	4 (5.5)	308 (17.0)
Any AE leading to dose interruption	**80 (55.9)**	**18 (24.7)**	**459 (25.3)**
Any AE leading to dose interruption of study treatment, causally related to treatment [b]	27 (18.9)	4 (5.5)	257 (14.2)
Any AE leading to dose reduction	**12 (8.4)**	**1 (1.4)**	**96 (5.3)**
Any AE leading to dose reduction of study treatment, causally related to treatment [b]	11 (7.7)	1 (1.4)	91 (5.0)

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

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

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

MedDRA version 26.1. CTCAE version 5.0.

Common adverse events

Overall, the most common AEs are reported with a higher incidence (by ≥10% more patients) in the osimertinib arm compared to the placebo arm: radiation pneumonitis (47.6% vs 38.4%), diarrhoea (35.7% vs 13.7%), rash (23.8% vs 13.7%), COVID-19 (20.3% vs 8.2%), and paronychia (16.8% vs 1.4%), cough (16.1% vs 9.6%), decreased appetite (14.7% vs 5.5%), dry skin (12.6% vs 5.5%), pruritus (12.6% vs 6.8%), stomatitis (11.9% vs 2.7%), white blood cell count decreased (11.9% vs 2.7%) and pneumonia (11.2% vs 8.2%).

The AEs were most frequently reported in the MedDRA SOCs (≥50% of patients in the osimertinib arm within each SOC) of Infections and infestations (65.0% vs 32.9%), Gastrointestinal disorders (58.7% vs 32.9%), Skin and subcutaneous tissue disorders (55.2% vs 26.0%), and Injury, poisoning and procedural complications (53.8% vs 46.6%).

Investigator-assessed causally-related AEs were reported in a higher proportion of patients in the osimertinib arm (115 patients [80.4%]) than in the placebo arm (30 patients [41.1%]). The most frequently reported possibly related AEs (≥10% of patients) were diarrhoea (30 patients [21.0%]), rash (29 patients [20.3%]), paronychia (21 patients [14.7%]), dry skin (15 patients [10.5%)], pruritis (15 patients [10.5%]), and white blood cell count decreased (15 patients [10.5%]) in the osimertinib arm. In the placebo arm, the most frequently reported possibly related AEs (≥ 5% of patients) were diarrhoea (6 patients [8.2%]) and rash (4 patients [5.5%]).

Table 36. Most Common AEs, by PT (Reported in ≥ 10% Osimertinib-treated Patients in the LAURA Study) (Safety Analysis Set)

MedDRA Preferred Term	Number (%) of patients		
	LAURA Study		Osimertinib monotherapy safety pool (N = 1813)
	Osimertinib (N = 143)	Placebo (N = 73)	
Patients with any AE	140 (97.9)	64 (87.7)	1783 (98.3)
Radiation pneumonitis	68 (47.6)	28 (38.4)	6 (0.3)
Diarrhoea	51 (35.7)	10 (13.7)	845 (46.6)
Rash	34 (23.8)	10 (13.7)	269 (14.8)
COVID-19	29 (20.3)	6 (8.2)	42 (2.3)
Paronychia	24 (16.8)	1 (1.4)	472 (26.0)
Cough	23 (16.1)	7 (9.6)	353 (19.5)
Decreased appetite	21 (14.7)	4 (5.5)	347 (19.1)
Dry skin	18 (12.6)	4 (5.5)	454 (25.0)
Pruritus	18 (12.6)	5 (6.8)	311 (17.2)
Stomatitis	17 (11.9)	2 (2.7)	341 (18.8)
White blood cell count decreased	17 (11.9)	2 (2.7)	162 (8.9)
Pneumonia	16 (11.2)	6 (8.2)	149 (8.2)

Includes AEs with onset date on or after the date of first dose up to and including 28 days following discontinuation of study treatment and before starting subsequent cancer therapy.
MedDRA version 26.1

Adverse events by severity

In both treatment arms, the majority of patients reported AEs which were maximum CTCAE Grade 1 and 2, indicating that most AEs in the study were mild or moderate in severity.

In the osimertinib arm (N=143), 42 patients (29.4%) reported AEs that were CTCAE Grade 3 (severe) while the majority of patients reported AEs which were maximum CTCAE Grade 1 and 2 (16 patients [11.2%] and 74 [51.7%], respectively). In the placebo arm, the majority of patients reported AEs which were maximum CTCAE Grade 1 and 2 (23 patients [31.5%] and 32 patients [43.8%], respectively).

Table 37. Summary of AEs by Maximum Reported CTCAE Grade (Safety Analysis Set)

Maximum Reported CTCAE Grade	Number (%) of patients	
	Osimertinib (N = 143)	Placebo (N = 73)
1	16 (11.2)	23 (31.5)
2	74 (51.7)	32 (43.8)
3	42 (29.4)	6 (8.2)
4	5 (3.5)	1 (1.4)
5	3 (2.1)	2 (2.7)

CTCAE Version 5.0.
DCO: 05 January 2024
Source: Table 14.3.2.13.1

In the osimertinib arm of LAURA, a higher proportion of patients reported AEs of CTCAE ≥ Grade 3 (50 patients [35.0% (N=143)] compared to the placebo arm (9 patients [12.3% (N=73)].

Table 38. AEs of CTCAE Grade 3 or Higher (Reported in ≥ 2 Osimertinib-treated Patients in the LAURA study) (Safety Analysis Set)

MedDRA Preferred Term	Number (%) of patients		
	LAURA Study		Osimertinib monotherapy safety pool (N = 1813)
	Osimertinib (N = 143)	Placebo (N = 73)	
Patients with any CTCAE ≥ Grade 3 AE	50 (35.0)	9 (12.3)	674 (37.2)
Pneumonia	4 (2.8)	3 (4.1)	52 (2.9)
Diarrhoea	3 (2.1)	0	26 (1.4)
Radiation pneumonitis	3 (2.1)	0	0
Pneumonitis	2 (1.4)	0	11 (0.6)
Gastroenteritis	2 (1.4)	0	7 (0.4)
Blood creatine phosphokinase increased	2 (1.4)	0	5 (0.3)

Includes AEs with onset date on or after the date of first dose up to and including 28 days following discontinuation of study treatment and before starting subsequent cancer therapy.
MedDRA version 26.1

Investigator-assessed causally-related CTCAE ≥Grade 3 AEs were reported in the osimertinib arm in 19 patients (13.3%) and in 2 patients (2.7%) in the placebo arm, which the most frequently reported (≥2 of patients) were pneumonitis (2 patients [1.4%]), diarrhoea (2 patients [1.4%]) and radiation pneumonitis (2 patients [1.4%]) in the osimertinib arm; while in the placebo arm these were neutropenia, pleural effusion and pulmonary embolism.

Serious adverse event/deaths/other significant events

Serious adverse events (SAEs)

In the LAURA study, a higher proportion of patients reported an SAE in the osimertinib arm (55 patients [38.5%]) compared to the placebo arm (11 patients [15.1%]). The most frequently reported SAEs (≥ 2% of patients) in both treatment arms were radiation pneumonitis (15 patients [10.5%] in the osimertinib

arm; 2 patients [2.7%] in the placebo arm) and pneumonia (7 patients [4.9%] in the osimertinib arm; 3 patients [4.1%] in the placebo arm).

Table 39. SAEs, by PT (Reported in ≥ 2 Patients in Either Treatment Arm the LAURA Study) (Safety Analysis Set)

MedDRA Preferred Term	Number (%) of patients		
	LAURA Study		Osimertinib monotherapy safety pool (N = 1813)
	Osimertinib (N = 143)	Placebo (N = 73)	
Patients with any SAE	55 (38.5)	11 (15.1)	521 (28.7)
Radiation pneumonitis	15 (10.5)	2 (2.7)	0
Pneumonia	7 (4.9)	3 (4.1)	58 (3.2)
Pneumonitis	2 (1.4)	0	17 (0.9)
Gastroenteritis	2 (1.4)	0	7 (0.4)

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

MedDRA version 26.1

Overall, 12 patients (8.4%) in the osimertinib arm had an SAE considered by the Investigator to be possibly related to osimertinib treatment, with radiation pneumonitis and pneumonitis the only SAEs reported as possibly related to osimertinib treatment in ≥ 2 patients (3 patients [2.1%] and 2 patients [1.4%], respectively)

One patient (1.4%) in the placebo arm had SAEs considered by the Investigator to be possibly related to placebo treatment; these were pleural effusion and pulmonary embolism.

One patient in the placebo arm had an SAE of drug-induced pneumonitis (maximum CTCAE Grade 3) during treatment with osimertinib post-BICR-confirmed disease progression.

Deaths

In the LAURA study, the number of patients who had died in the Safety Analysis Set was comparable between treatment arms: 28 patients (19.6%) in the osimertinib arm, and 15 patients (20.5%) in the placebo arm. In both treatment arms, the majority of deaths were assessed by the reporting Investigator as related to the disease under study only: 22 patients (15.4%) in the osimertinib arm, and 11 (15.1%) in the placebo arm.

Table 40. Summary of Deaths (All Patients)

	Number (%) of patients		
	LAURA Study		Osimertinib monotherapy safety pool (N = 1813)
	Osimertinib (N = 143)	Placebo (N = 73)	
Total number of deaths	28 (19.6)	15 (20.5)	785 (43.3)
Death related to disease under investigation only	22 (15.4)	11 (15.1)	684 (37.7)
AE with outcome of death only	2 (1.4)	1 (1.4)	42 (2.3)
AE with outcome of death only (AE start date falling after 28 day follow up period)	0	0	5 (0.3)

Table 40. Summary of Deaths (All Patients)

	Number (%) of patients		
	LAURA Study		Osimertinib monotherapy safety pool (N = 1813)
	Osimertinib (N = 143)	Placebo (N = 73)	
Number of patients with death related to disease and any AE with outcome of death	1 (0.7)	1 (1.4)	28 (1.5)
Other deaths [a]	3 (2.1)	2 (2.7)	26 (1.4)

[a] Patients who died and are not captured in the earlier categories.

Death related to disease under investigation are determined by the investigator. Rows are mutually exclusive; patients are only reported in one category.

Adverse events with an outcome of death

In the osimertinib arm, the AEs leading to death reported in 3 patients (2.1%) were pneumonia, pneumonitis and road traffic accident in the osimertinib arm. In the placebo arm the AEs with an outcome of death reported in 2 patients (2.7%) were myocardial infarction and aortic aneurysm rupture.

Adverse events in the ILD/pneumonitis grouped term were considered AESIs in the LAURA study, and consequently the fatal AE of pneumonitis in the osimertinib arm [1 patient (1.4%)] was designated an AESI and was the only fatal AE reported as related to study treatment by the reporting investigator. Pneumonia is a commonly reported comorbidity in patients with the disease under study.

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 (ILD), 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 41. Summary of ILD/Pneumonitis AESIs

	Number (%) of patients		
	LAURA Study		Osimertinib monotherapy safety pool (N = 1813)
	Osimertinib (N = 143)	Placebo (N = 73)	
Patients with any ILD/pneumonitis	11 (7.7)	1 (1.4)	73 (4.0)
Patients with any ILD/pneumonitis by maximum CTCAE Grade			
CTCAE Grade 1	4 (2.8)	1 (1.4)	20 (1.1)
CTCAE Grade 2	4 (2.8)	0	28 (1.5)
CTCAE Grade 3	2 (1.4)	0	17 (0.9)
CTCAE Grade 4	0	0	1 (0.1)
CTCAE Grade 5	1 (0.7)	0	7 (0.4)
Patients with any SAE of ILD/pneumonitis	3 (2.1)	0	37 (2.0)

Table 41. Summary of ILD/Pneumonitis AESIs

	Number (%) of patients		
	LAURA Study		Osimertinib monotherapy safety pool (N = 1813)
	Osimertinib (N = 143)	Placebo (N = 73)	
Events of ILD/pneumonitis by outcome [a]			
Recovered/resolved	3 (25.0)	0	38 (52.1)
Recovering/resolving	1 (8.3)	0	13 (17.8)
Recovered/resolved with sequelae	0	0	1 (1.4)
Not recovered/not resolved	7 (58.3)	1 (100)	15 (20.5)
Fatal [b]	1 (8.3)	0	6 (8.2)
Patients with any AE of ILD/pneumonitis by ethnicity [c]			
Asian only	6 (5.2)	1 (1.6)	54 (4.6)
Japanese only	0	0	36 (11.2)
Asian non-Japanese	6 (6.6)	1 (1.9)	17 (2.3)
Non-Asian only	5 (17.2)	0	20 (2.7)
Patients with any AE of ILD/pneumonitis leading to discontinuation [d]	3 (25.0)	0	61 (83.6)
Median (range) time to onset of first ILD/pneumonitis AE, days	57.0 (26, 755)	167.0 (167, 167)	85.0 (1, 1035)
Median (range) time to onset from last dose of RT, days	91.0 (38, 793)	201.0(201, 201)	NA

[a] Patients with multiple events within the same PT are counted under the worst outcome.
Denominator is the number (percent) of events with the outcome or intervention for the event.
One patient had 1 event of pneumonitis and 1 event of pulmonary fibrosis with different outcomes.

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

[c] Denominator is the number of patients of the respective ethnic grouping.

[d] Patients with multiple events within the same PT are counted under the worst intervention.
Denominator is the number (percent) of patients with the intervention for the event.
Includes AEs with an onset date on or after the date of first dose and up to and including 28 days following discontinuation of randomised treatment and on or before starting subsequent cancer therapy.

AEs of ILD/pneumonitis were reported in a higher proportion of patients in the osimertinib arm (11 patients [7.7%]) compared to the placebo arm (1 patient [1.4%]). Of the 11 patients in the osimertinib arm, 3 patients reported CTCAE Grade ≥3 events, including 1 patient with a fatal event of pneumonitis. The reporting Investigator considered the event to be related to osimertinib and rivaroxaban (concomitant medication), and also considered the patient's death to be related to their underling disease.

Median time to onset of ILD/pneumonitis between treatment arms comprising 57.0 days (range: 26 to 755 days) in the osimertinib arm, and 167.0 days for the single event in the placebo arm. The median duration of AEs of ILD/pneumonitis was 91.0 days (range: 38 to 793 days) in the osimertinib arm and 201.0 days (range: 201 to 201 days) in the placebo arm.

Of the patients experiencing an ILD/pneumonitis AESI, a higher proportion of events in the osimertinib arm (7 events [58.3%] in 6 patients) had not resolved. This is likely impacted by events occurring in the

3 patients in the osimertinib arm who had pulmonary fibrosis (2 of which had pulmonary fibrosis upon entry to the study, as permitted per CSP eligibility criteria), which is generally regarded as a non-reversible condition.

- **Radiation pneumonitis**

This AESI topic was evaluated by review of the MedDRA PTs radiation pneumonitis, radiation fibrosis – lung, pulmonary radiation injury, and radiation alveolitis. Collectively, these are referred to as events of radiation pneumonitis within this section for brevity.

Table 42. Summary of Radiation Pneumonitis AESIs

	Number (%) of patients		
	LAURA Study		Osimertinib monotherapy safety pool (N = 1813)
	Osimertinib (N = 143)	Placebo (N = 73)	
Patients with any Radiation pneumonitis	69 (48.3)	28 (38.4)	6 (0.3)
Patients with any Radiation pneumonitis by maximum CTCAE Grade			
CTCAE Grade 1	22 (15.4)	14 (19.2)	3 (0.2)
CTCAE Grade 2	44 (30.8)	14 (19.2)	3 (0.2)
CTCAE Grade 3	3 (2.1)	0	0
CTCAE Grade 4	0	0	0
CTCAE Grade 5	0	0	0
Patients with any SAE of Radiation pneumonitis	15 (10.5)	2 (2.7)	0
Events of Radiation pneumonitis by outcome [a]			
Recovered/resolved	31 (43.7)	14 (48.3)	2 (33.3)
Recovering/resolving	12 (16.9)	5 (17.2)	0
Recovered/resolved with sequelae	1 (1.4)	2 (6.9)	0
Not recovered/not resolved	27 (38.0)	8 (27.6)	4 (66.7)
Fatal [b]	0	0	0
Patients with any AE of Radiation pneumonitis by ethnicity [c]			
Asian only	66 (56.9)	27 (43.5)	2 (0.2)
Japanese only	19 (82.6)	4 (57.1)	0
Asian non-Japanese	47 (51.6)	23 (42.6)	1 (0.1)
Non-Asian only	3 (10.3)	1 (8.3)	5 (0.7)
Patients with any AE of Radiation pneumonitis leading to discontinuation [d]	7 (9.9)	2 (6.9)	0
Median (range) time to onset of first Radiation pneumonitis AE, days	52.0 (10, 676)	54.0 (15, 113)	755.0 (275, 1262)

Table 42. Summary of Radiation Pneumonitis AESIs

Median (range) time to onset from last dose of RT, days	76.0 (38, 694)	80.5 (47, 136)	NA

[e] Patients with multiple events within the same PT are counted under the worst outcome. Denominator is the number (percent) of events with the outcome or intervention for the event.
[f] Outcome of death as recorded on the AE form.
[g] Denominator is the number of patients of the respective ethnic grouping.
[h] Patients with multiple events within the same PT are counted under the worst intervention. Denominator is the number (percent) of patients with the intervention for the event.
Includes AEs with an onset date on or after the date of first dose and up to and including 28 days following discontinuation of randomised treatment and on or before starting subsequent cancer therapy.

Events of radiation pneumonitis were reported in a numerically higher proportion of patients in the osimertinib arm compared to the placebo arm (69 patients [48.3%] versus 28 patients [38.4%], respectively). The majority of patients had events which were either mild or moderate in severity (CTCAE Grades 1 or 2), non-serious, and did not lead to treatment discontinuation due to the event. Of the 69 patients in the osimertinib arm, 3 patients reported CTCAE Grade 3 events; there were no Grade 4 or 5 events.

Median time to onset of radiation pneumonitis was comparable between treatment arms, comprising 52.0 days (range: 10 to 676) in the osimertinib arm, and 54.0 (range: 15 to 113) in the placebo arm. The median duration of AEs of radiation pneumonitis was similar in both treatment arms, 76.0 days (range: 38 to 694) in the osimertinib arm, and 80.5 days (range:47 to 136) in the placebo arm.

- **Cardiac effects (Cardiac failure)**

This AESI topic is evaluated by the review of both Investigator-reported AEs (from the MedDRA Standard MedDRA Queries of Cardiac failure and Cardiomyopathy) assessed in conjunction with changes in cardiac contractility observed during study treatment, to identify any clinically significant risks to patients. Individual patients could be represented in more than one subgroup.

At study entry, 20 patients (14.0%) in the osimertinib arm and 7 patients (9.6%) in the placebo arm had medical history within the Cardiac Disorders SOC, including 1 patient in each treatment arm with a history of chronic cardiac failure. One patient (0.7%) in osimertinib arm had an AE in the cardiac effects (cardiac failure) which was a CTCAE Grade 2 event of cardiac failure chronic occurred on study day 57 and it was considered unrelated to osimertinib by the reporting Investigator. Osimertinib was interrupted in response to the event and the outcome was not resolved at the DCO date of the current analysis.

Table 43. Summary of Cardiac AESIs

	Number (%) of patients		
	LAURA Study		**Osimertinib monotherapy safety pool (N = 1813)**
	Osimertinib (N = 143)	**Placebo (N = 73)**	
Cardiac effects (cardiac failure)	1 (0.7)	0	68 (3.8)
Ejection fraction decreased	0	0	53 (2.9)
Cardiac failure	0	0	9 (0.5)
Pulmonary oedema	0	0	4 (0.2)
Cardiac failure congestive	0	0	1 (0.1)
Brain natriuretic peptide increased	0	0	2 (0.1)
Cardiac failure chronic	1 (0.7)	0	1 (0.1)

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

- **Changes in cardiac contractility - LVEF measurements over time**

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

Four of 135 patients (3.0%) in the osimertinib arm and no patients in the placebo arm experienced LVEF decreases from baseline ≥10% and an absolute LVEF value of < 50%, which was a numerically lower rate than in the osimertinib monotherapy safety pool (65/1557 patients [4.2%]).

Table 44. Change in LVEF (Safety Analysis Set)

	Number (%) of patients	
	Osimertinib (N = 143)	Placebo (N = 73)
Subject with both baseline value and at least one post-baseline assessment	135 (94.4)	69 (94.5)
LVEF outliers		
≥ 10 percentage points decrease from baseline and absolute value < 50% [a]	4 (3.0)	0
≥ 15 percentage points decrease from baseline and absolute value ≥ 50% [a]	8 (5.9)	3 (4.3)

[a] Occurring at the same echocardiography assessment, at any timepoint following dosing.
Baseline is defined as the last result obtained prior to the start of study treatment. Derived from LVEF data obtained between the start of treatment and up to and including the earlier of 28 days following the date of last dose of study medication and on or before the start of subsequent anticancer therapy.
DCO: 05 January 2024

Adverse Drug Reactions (ADRs)

A summary of data pertaining to the frequency and severity of designated osimertinib ADRs in the osimertinib arm of the LAURA study and the 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 81.12% of patients in the osimertinib arm of the LAURA study, and 89.52% of patients in the osimertinib monotherapy safety pool**.**

The most commonly reported ADRs (occurring in ≥ 20% of patients) in the osimertinib arm of the LAURA study were rash, diarrhoea, and paronychia; these ADRs were reported with a lower frequency (≥10% difference) and with a lower severity in the osimertinib arm of LAURA, compared with the osimertinib monotherapy safety pool.

Table 45. Summary of ADR Frequency Determinations (Safety Analysis Set)

ADR	LAURA Study												Osimertinib monotherapy safety pool (N = 1813)					
	Osimertinib arm (N = 143)						Placebo arm (N = 73)											
	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	116 (81.12)	53 (37.06)	49 (34.27)	13 (9.09)	0	1 (0.70)	31 (42.47)	21 (28.77)	9 (12.33)	1 (1.37)	0	0	1623 (89.52)	748 (41.26)	698 (38.50)	167 (9.21)	3 (0.17)	7 (0.39)
Aplastic anaemia	0	0	0	0	0	0	0	0	0	0	0	0	1 (0.06)	0	0	1 (0.06)	0	0
Keratitis [a]	1 (0.70)	1 (0.70)	0	0	0	0	1 (1.37)	1 (1.37)	0	0	0	0	10 (0.55)	3 (0.17)	6 (0.33)	1 (0.06)	0	0
Epistaxis	1 (0.70)	1 (0.70)	0	0	0	0	0	0	0	0	0	0	114 (6.29)	110 (6.07)	4 (0.22)	0	0	0
Interstitial lung disease [b]	11 (7.69)	4 (2.80)	4 (2.80)	2 (1.40)	0	1 (0.70)	1 (1.37)	1 (1.37)	0	0	0	0	73 (4.03)	20 (1.10)	28 (1.54)	17 (0.94)	1 (0.06)	7 (0.39)
Diarrhoea	51 (35.66)	45 (31.47)	3 (2.10)	3 (2.10)	0	0	10 (13.70)	6 (8.22)	4 (5.48)	0	0	0	845 (46.61)	663 (36.57)	156 (8.60)	26 (1.43)	0	0
Stomatitis [c]	22 (15.38)	13 (9.09)	9 (6.29)	0	0	0	3 (4.11)	2 (2.74)	1 (1.37)	0	0	0	432 (23.83)	321 (17.71)	103 (5.68)	8 (0.44)	0	0
Rash [d]	51 (35.66)	40 (27.97)	10 (6.99)	1 (0.70)	0	0	14 (19.18)	14 (19.18)	0	0	0	0	836 (46.11)	665 (36.68)	156 (8.60)	15 (0.83)	0	0
Paronychia [e]	33 (23.08)	23 (16.08)	10 (6.99)	0	0	0	1 (1.37)	0	1 (1.37)	0	0	0	609 (33.59)	380 (20.96)	221 (12.19)	8 (0.44)	0	0
Dry skin [f]	25 (17.48)	21 (14.69)	3 (2.10)	1 (0.70)	0	0	4 (5.48)	4 (5.48)	0	0	0	0	580 (31.99)	501 (27.63)	77 (4.25)	2 (0.11)	0	0

Table 45. Summary of ADR Frequency Determinations (Safety Analysis Set)

ADR	LAURA Study												Osimertinib monotherapy safety pool (N = 1813)					
	Osimertinib arm (N = 143)						Placebo arm (N = 73)											
Pruritus [g]	18 (12.59)	17 (11.89)	1 (0.70)	0	0	0	5 (6.85)	5 (6.85)	0	0	0	0	311 (17.15)	256 (14.12)	54 (2.98)	1 (0.06)	0	0
Alopecia	2 (1.40)	2 (1.40)	0	0	0	0	0	0	0	0	0	0	90 (4.96)	79 (4.36)	11 (0.61)	0	0	0
PPES	0	0	0	0	0	0	0	0	0	0	0	0	38 (2.10)	31 (1.71)	7 (0.39)	0	0	0
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**
Urticaria	2 (1.40)	1 (0.70)	1 (0.70)	0	0	0	1 (1.37)	1 (1.37)	0	0	0	0	35 (1.93)	19 (1.05)	14 (0.77)	2 (0.11)	0	0
Skin hyperpigmentation	0	0	0	0	0	0	0	0	0	0	0	0	18 (0.99)	16 (0.88)	2 (0.11)	0	0	0
Erythema multiforme	0	0	0	0	0	0	0	0	0	0	0	0	6 (0.33)	4 (0.22)	2 (0.11)	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 CPK increased	5 (3.50)	1 (0.70)	2 (1.40)	2 (1.40)	0	0	0	0	0	0	0	0	34 (1.88)	21 (1.16)	8 (0.44)	5 (0.28)	0	0
Number (%) of patients who had a QTcF prolongation > 500 msec																		
QTc interval prolongation	1 (0.7)						0						20 (1.1)					

Table 45. Summary of ADR Frequency Determinations (Safety Analysis Set)

ADR	LAURA Study												Osimertinib monotherapy safety pool (N = 1813)					
	Osimertinib arm (N = 143)						Placebo arm (N = 73)											
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**
Leucocytes decreased [i]	***142***	94 (66.2)	70 (49.3)	20 (14.1)	4 (2.8)	0	***72***	17 (23.6)	14 (19.4)	3 (4.2)	0	0	***1787***	1157 (64.7)	823 (46.1)	302 (16.9)	29 (1.6)	3 (0.2)
Lymphocytes decreased [i]	***142***	100 (70.4)	47 (33.1)	48 (33.8)	5 (3.5)	0	***72***	29 (40.3)	18 (25.0)	10 (13.9)	1 (1.4)	0	***1786***	1139 (63.8)	517 (28.9)	475 (26.6)	133 (7.4)	14 (0.8)
Platelet count decreased [i]	***142***	73 (51.4)	70 (49.3)	1 (0.7)	2 (1.4)	0	***72***	6 (8.3)	5 (6.9)	0	1 (1.4)	0	***1794***	953 (53.1)	876 (48.8)	54 (3.0)	14 (0.8)	9 (0.5)
Neutrophils decreased [i]	***142***	59 (41.5)	37 (26.1)	19 (13.4)	2 (1.4)	1 (0.7)	***72***	11 (15.3)	10 (13.9)	0	1 (1.4)	0	***1787***	635 (35.5)	290 (16.2)	273 (15.3)	64 (3.6)	8 (0.4)
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**
Blood creatinine increased [i, j]	***142***	27 (19.0)	26 (18.3)	1 (0.7)	0	0	***73***	9 (12.3)	8 (11.0)	1 (1.4)	0	0	***1793***	153 (8.5)	139 (7.8)	11 (0.6)	3 (0.2)	0

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

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

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

[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, eyelid pruritus.

Table 45. Summary of ADR Frequency Determinations (Safety Analysis Set)

ADR	LAURA Study		Osimertinib monotherapy safety pool (N = 1813)
	Osimertinib arm (N = 143)	Placebo arm (N = 73)	

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

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

[j] Note: Creatinine clearance at baseline was < 30 mL/min and < 50 mL/min for LAURA and ISS, respectively.
Note: Both the baseline component and the ULN component was used to define new CTCAE grades as follows:
Grade 1: baseline < Creatinine ≤ 1.5 x baseline AND ULN < Creatinine ≤ 1.5 x ULN;
Grade 2: 1.5 x baseline < Creatinine ≤ 3.0 x baseline AND 1.5 x ULN < Creatinine ≤ 3.0 x ULN;
Grade 3: Creatinine > 3.0 x baseline AND 3.0 x ULN < Creatinine ≤ 6.0 x ULN;
Grade 4: Creatinine > 6.0 x ULN, where ULN is the project reference range.

Table 46 Summary of ADR Frequency Determinations Osimertinib monotherapy safety pool (including LAURA study data)

ADR	Osimertinib monotherapy safety pool (N = 1956)					
Number (%) of patients, by CTCAE Grade						
	Any	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Patients with any AE designated as an ADR	**1781 (91.05)**	**741 (37.88)**	**815 (41.67)**	**214 (10.94)**	**3 (0.15)**	**8 (0.41)**
Alopecia	92 (4.70)	81 (4.14)	11 (0.56)	0	0	0
Aplastic anaemia	1 (0.05)	0	0	1 (0.05)	0	0
Blood CPK increased	39 (1.99)	22 (1.12)	22 (1.12)	7 (0.36)	0	0
Cardiac Failure	9 (0.46)	1 (0.05)	5 (0.26)	3 (0.15)	0	0
Decreased appetite	368 (18.81)	245 (12.53)	101 (5.16)	22 (1.12)		
Diarrhoea	896 (45.81)	708 (36.20)	159 (8.13)	29 (1.48)	0	0
Dry skin [f]	605 (30.93)	522 (26.69)	80 (4.09)	3 (0.15)	0	0
Epistaxis	115 (5.88)	111 (5.67)	4 (0.20)	0	0	0
Erythema multiforme	6 (0.31)	4 (0.20)	2 (0.10)	0	0	0
Interstitial lung disease [b]	84 (4.29)	24 (1.23)	32 (1.64)	19 (0.97)	1 (0.05)	8 (0.41)
Keratitis [a]	11 (0.56)	4 (0.20)	6 (0.31)	1 (0.05)	0	0
Left ventricular ejection fraction decreased	53 (2.71)	11 (0.56)	27 (1.38)	15 (0.77)		
Myositis	3 (0.15)	3 (0.15)	0	0	0	0
Palmar-plantar erythrodysaesthesia syndrome	38 (1.94)	31 (1.58)	7 (0.36)	0	0	0
Paronychia [e]	642 (32.82)	403 (20.60)	231 (11.81)	8 (0.41)	0	0
Pruritus [g]	329 (16.82)	273 (13.96)	55 (2.81)	1 (0.05)	0	0
Rash [d]	887 (45.35)	705 (36.04)	166 (8.49)	16 (0.82)	0	0
Skin hyperpigmentation	18 (0.92)	16 (0.82)	2 (0.10)	0	0	0
Stomatitis [c]	454 (23.21)	334 (17.08)	112 (5.73)	8 (0.41)	0	0
Urticaria	37 (1.89)	20 (1.02)	15 (0.77)	2 (0.10)	0	0
Toxic epidermal necrolysis [h]	0	0	0	0	0	0
Cutaneous vasculitis [h]	0	0	0	0	0	0
Stevens-Johnson syndrome [h]	0	0	0	0	0	0
Number (%) of patients who had a QTcF prolongation > 500 msec						
QTc interval prolongation	21 (1.1)					
Maximum worsening CTCAE grade shift from baseline during treatment						
	n	**Any**	**1-grade**	**2-grade**	**3-grade**	**4-grade**
Leucocytes decreased [i]	***1929***	1 251 (64.9)	893 (46.3)	322 (16.7)	33 (1.7)	3 (0.2)
Lymphocytes decreased [i]	***1928***	1 239 (64.3)	564 (29.3)	523 (27.1)	138 (7.2)	14 (0.7)
Platelet count decreased [i]	***1936***	1 026 (53.0)	946 (48.9)	55 (2.8)	16 (0.8)	9 (0.5)
Neutrophils decreased [i]	***1929***	694 (36.0)	327 (17.0)	292 (15.1)	66 (3.4)	9 (0.5)

ADR	Osimertinib monotherapy safety pool (N = 1956)					
Blood creatinine increased [i, j]	***1935***	180 (9.3)	165 (8.5)	12 (0.6)	3 (0.2)	0

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

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

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

[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, eyelid pruritus.

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

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

[j] Note: Creatinine clearance at baseline was < 30 mL/min and < 50 mL/min for LAURA and ISS, respectively.
Note: Both the baseline component and the ULN component was used to define new CTCAE grades as follows:
Grade 1: baseline < Creatinine ≤ 1.5 x baseline AND ULN < Creatinine ≤ 1.5 x ULN;
Grade 2: 1.5 x baseline < Creatinine ≤ 3.0 x baseline AND 1.5 x ULN < Creatinine ≤ 3.0 x ULN;
Grade 3: Creatinine > 3.0 x baseline AND 3.0 x ULN < Creatinine ≤ 6.0 x ULN;
Grade 4: Creatinine > 6.0 x ULN, where ULN is the project reference range.

Laboratory findings

Haematology

Table 47. Haemoglobin Maximum Worsening CTCAE Grade Shifts from Baseline (Safety Analysis Set)

ADR	LAURA Study												Osimertinib monotherapy safety pool (N = 1813)					
	Osimertinib arm (N = 143)						Placebo arm (N = 73)											
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**
Haemoglobin decreased [a]	***142***	39 (27.5)	36 (25.4)	2 (1.4)	1 (0.7)	0	72	12 (16.7)	10 (13.9)	2 (2.8)	0	0	1794	929 (51.8)	823 (45.9)	94 (5.2)	12 (0.7)	0

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

Worsening in CTCAE grade shifts in haemoglobin was recorded in 39 patients (27.5%) in the osimertinib arm and 12 patients (16.7%) in the placebo arm. In both treatment arms, the majority of CTCAE grade shifts were 1-grade shifts, with 2-grade shifts recorded for 2 patients (1.4%) in the osimertinib arm and 2

patients (2.8%) in the placebo arm. One patient in the osimertinib arm (0.7%) had a 3-grade shift; no grade-4 shifts were recorded in either treatment arm.

Worsening in CTCAE grade shifts in neutrophils, platelets, lymphocytes and leukocytes were reported in the LAURA study which were mostly 1- or 2-grade shifts, and were not associated with any clinically significant events. This is consistent with previous findings in the osimertinib monotherapy safety pool.

Table 48. Summary of AEs Relevant to Decreases in White Blood Cell Count (Safety Analysis Set)

Preferred Term	Osimertinib (N = 143)		Placebo (N = 73)	
	Number (%) of patients	Rate (per 100 pt years) [a]	Number (%) of patients	Rate (per 100 pt years) [a]
Leukopenia	4 (2.8)	1.4	0	0
White blood cell count decreased	17 (11.9)	6.0	2 (2.7)	2.8
Neutropenia	7 (4.9)	2.5	1 (1.4)	1.4
Neutrophil count decreased	6 (4.2)	2.1	0	0
Lymphopenia	2 (1.4)	0.7	1 (1.4)	1.4
Lymphocyte count decreased	0	0	0	0

[a] Number of patients with AEs divided by the total duration of treatment across all patients in given group, multiplied by 100. The total duration of treatment across all patients was: osimertinib = 282.54 years; placebo = 71.63 years.
Patients with multiple events in the same PT are counted only once in that PT. Patients with events in more than one PT are counted once in each of those PT.
Includes AEs with an onset date on or after the date of first dose and up to and including the earlier of 28 days following the date of last dose of study medication and the day before the start of subsequent anticancer therapy.
MedDRA version 26.1
DCO: 05 January 2024

Clinical Chemistry

- **General clinical chemistry**

The majority of CTCAE grade shifts observed were 1-grade shifts, with a low proportion of patients in each treatment arm developing a 2- or 3-grade shift; no patients in the osimertinib arm had a 4-Grade shift.

Table 49. Clinical Chemistry, Maximum Worsening CTCAE Grade Shift from Baseline During Treatment (Safety Analysis Set)

Parameter	n	CTCAE grade shift[a]	Number (%) of patient	
			Osimertinib (N = 143)	Placebo (N = 73)
Calcium, corrected for albumin (mmol/L)	Osimertinib: 142 Placebo: 71	Any Grade shift	85 (59.9)	28 (39.4)
		1-Grade shift	78 (54.9)	25 (35.2)
		2-Grade shift	5 (3.5)	2 (2.8)
		3-Grade shift	2 (1.4)	1 (1.4)
		4-Grade shift	0	0
Sodium (mmol/L)	Osimertinib: 142 Placebo: 72	Any Grade shift	51 (35.9)	17 (23.6)
		1-Grade shift	45 (31.7)	14 (19.4)
		2-Grade shift	1 (0.7)	0
		3-Grade shift	5 (3.5)	1 (1.4)
		4-Grade shift	0	2 (2.8)
Potassium (mmol/L)	Osimertinib: 142 Placebo: 72	Any Grade shift	34 (23.9)	22 (30.6)
		1-Grade shift	30 (21.1)	16 (22.2)
		2-Grade shift	3 (2.1)	3 (4.2)
		3-Grade shift	1 (0.7)	3 (4.2)
		4-Grade shift	0	0

Parameter	n	CTCAE grade shift[a]	Number (%) of patient	
			Osimertinib (N = 143)	Placebo (N = 73)
Magnesium (mmol/L)	Osimertinib: 142 Placebo: 72	Any Grade shift	36 (25.4)	17 (23.6)
		1-Grade shift	32 (22.5)	14 (19.4)
		2-Grade shift	2 (1.4)	3 (4.2)
		3-Grade shift	2 (1.4)	0
		4-Grade shift	0	0
Albumin (g/L)	Osimertinib: 142 Placebo: 72	Any Grade shift	21 (14.8)	8 (11.1)
		1-Grade shift	18 (12.7)	7 (9.7)
		2-Grade shift	3 (2.1)	0
		3-Grade shift	0	1 (1.4)
		4-Grade shift	0	0
Glucose (mmol/L)	Osimertinib: 142 Placebo: 72	Any Grade shift	10 (7.0)	5 (6.9)
		1-Grade shift	8 (5.6)	5 (6.9)
		2-Grade shift	2 (1.4)	0
		3-Grade shift	0	0
		4-Grade shift	0	0

[a] Derived from laboratory assessments between the start of treatment and up to and including the earlier of 28 days following the date of last dose of study medication and the day before the start of subsequent anticancer therapy and is the maximum CTCAE grade.

Baseline is defined as the last result obtained prior to the start of study treatment. If 2 visits were equally eligible to assess patient status at baseline, the average was taken as a baseline value. Percentages have been calculated using the number of patients (n) with a baseline value and a post-baseline value. Only worsening shifts in CTCAE grade are included (where the maximum on-treatment CTCAE grade > baseline CTCAE grade).

DCO: 05 January 2024

Source: Table 14.3.7.4.2

- **Hepatic biochemistry**

At baseline, 15 patients (10.5%) in the osimertinib arm and 5 patients (6.8%) in the placebo arm had a medical history of hepatobiliary disorders (as captured in the Hepatobiliary disorders SOC).

The maximum worsening shifts from baseline during treatment in hepatic laboratory investigations are summarised in the table below. A similar proportion of patients in both treatment arms had any Grade shift in hepatic laboratory investigations from baseline during study treatment, with the majority of grade shifts observed in both treatment arms comprising 1-grade shifts.

Table 50. Hepatic Biochemistry, Maximum Worsening CTCAE Grade Shift from Baseline During Treatment (Safety Analysis Set)

Parameter	n	CTCAE grade shift[a]	Number (%) of patients	
			Osimertinib (N = 143)	Placebo (N = 73)
Alanine aminotransferase (µkat/L)	Osimertinib: 142 Placebo: 72	Any Grade shift	39 (27.5)	18 (25.0)
		1-Grade shift	28 (19.7)	18 (25.0)
		2-Grade shift	7 (4.9)	0
		3-Grade shift	3 (2.1)	0
		4-Grade shift	1 (0.7)	0
Aspartate aminotransferase (µkat/L)	Osimertinib: 142 Placebo: 72	Any Grade shift	35 (24.6)	13 (18.1)
		1-Grade shift	30 (21.1)	13 (18.1)
		2-Grade shift	2 (1.4)	0
		3-Grade shift	3 (2.1)	0
		4-Grade shift	0	0
Alkaline phosphate (µkat/L)	Osimertinib: 142 Placebo: 72	Any Grade shift	17 (12.0)	15 (20.8)
		1-Grade shift	17 (12.0)	14 (19.4)
		2-Grade shift	0	1 (1.4)
		3-Grade shift	0	0
		4-Grade shift	0	0
Bilirubin (µmol/L)	Osimertinib: 142 Placebo: 72	Any Grade shift	13 (9.2)	7 (9.7)
		1-Grade shift	11 (7.7)	5 (6.9)
		2-Grade shift	1 (0.7)	2 (2.8)
		3-Grade shift	1 (0.7)	0
		4-Grade shift	0	0

[a] Derived from laboratory assessments between the start of treatment and up to and including the earlier of 28 days following the date of last dose of study medication and the day before the start of subsequent anticancer therapy and is the maximum CTCAE grade.

Baseline is defined as the last result obtained prior to the start of study treatment.
If 2 visits are equally eligible to assess patient status at baseline, the average is taken as a baseline value.
Percentages have been calculated using the number of patients (n) with a baseline value and a post-baseline value.
Only worsening shifts in CTCAE grade are included (where the maximum on-treatment CTCAE grade > baseline CTCAE grade).
DCO: 05 January 2024

- **Hepatic biochemistry AEs**

Adverse events in the Hepatobiliary disorders SOC were reported in 2 patients (1.4%) in the osimertinib arm (PTs: cholecystitis and hepatic failure), and 0 patients in the placebo arm. The SAE of hepatic failure was CTCAE Grade 3 and led to treatment discontinuation.

A numerical imbalance was observed between treatment arms in the LAURA study for patients who had an AST or ALT elevation of > 3 × ULN (osimertinib arm: 12 patients [8.4%]; placebo arm: 1 patient [1.4%]).

- **Renal biochemistry**

At a study population level, an increase from baseline in median creatinine was observed from the first on-treatment assessment, which subsequently remained generally stable for the remainder of the on-treatment period. The observed changes in creatinine were expected based on the known safety profile of osimertinib. No specific trend in median on treatment creatinine was noted in the placebo arm.

With the calculation of worsening CTCAE Grade shifts in creatinine from baseline based on patients with both a creatinine increase above baseline and within the specified range above the ULN, worsening CTCAE Grade shifts in creatinine from baseline were observed in 27 patients (19.0%) in the osimertinib arm and 9 patients (12.3%) in the placebo arm; in the osimertinib arm, all shifts were 1-grade (26/27 patients) or 2-grade (1/27 patients).

Table 51: Creatinine, Maximum Worsening CTCAE Grade Shift from Baseline During Treatment (Safety Analysis Set)

CTCAE grade shift[a]	Number (%) of patients	
	Osimertinib (N = 143) (n = 142[b])	Placebo (N = 73) (n = 73[b])
Any grade shift	27 (19.0)	9 (12.3)
1-grade shift	26 (18.3)	8 (11.0)
2-grade shift	1 (0.7)	1 (1.4)
3-grade shift	0	0
4-grade shift	0	0

[a] Derived from laboratory assessments between the start of treatment and up to and including the earlier of 28 days following the date of last dose of study medication and the day before the start of subsequent anticancer therapy and is the maximum CTCAE grade.

[b] n = Patients with a baseline value and an on-treatment value.

Baseline is defined as the last result obtained prior to the start of study treatment.
If 2 visits are equally eligible to assess patient status at baseline, the average is taken as a baseline value.
Percentages have been calculated using the number of patients (n) with a baseline value and a post-baseline value.
Only worsening shifts in CTCAE grade are included (where the maximum on-treatment CTCAE grade > baseline CTCAE grade).
DCO: 05 January 2024

- **Renal biochemistry AEs**

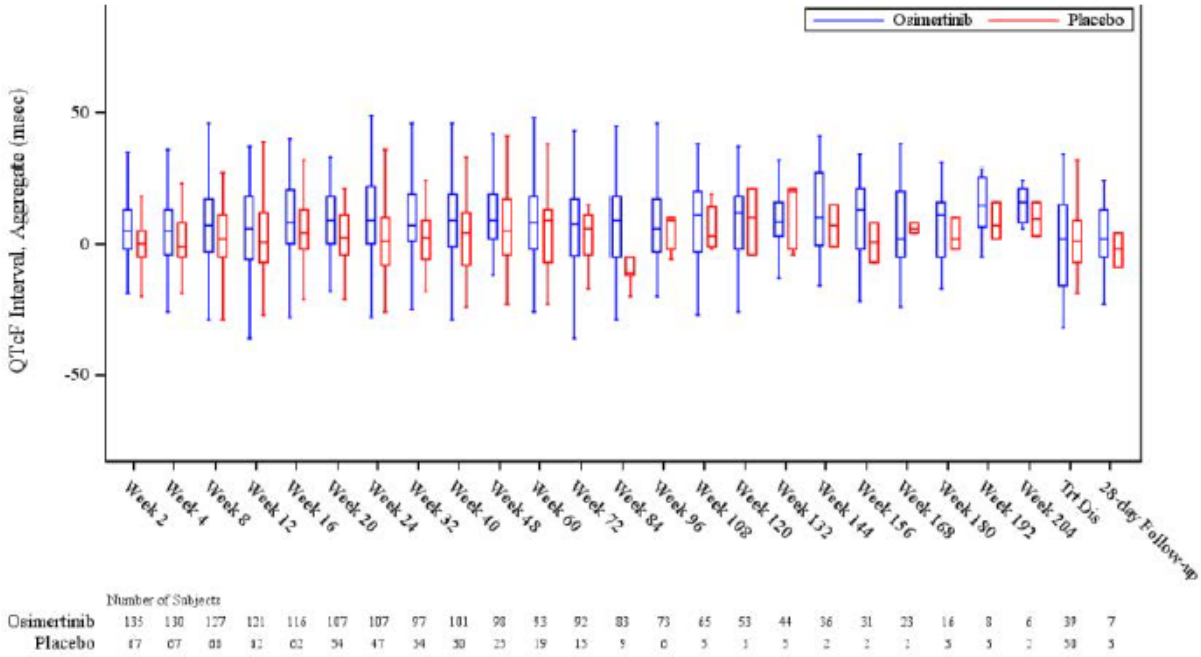
At baseline, 16 patients (11.2%) in the osimertinib arm and 5 patients (6.8%) in the placebo arm had a medical history of renal or urinary disorders (as captured in the Renal and urinary disorders SOC).

Adverse events in the Renal and urinary disorders SOC were reported for 13 patients (9.1%) in the osimertinib arm and 1 patient (1.4%) in the placebo arm. Within this SOC, the only AEs reported in ≥2 patients were dysuria and chronic kidney disease (each reported in 2 patients [1.4%] in the osimertinib arm). Relevant renal AEs reported within the Investigations SOC were blood creatinine increased (osimertinib arm: 5 patients [3.5%]; placebo arm: 1 patient [1.4%]), blood creatine phosphokinase increased (5 patients [3.5%] in the osimertinib arm only), and creatinine renal clearance decreased (1 patient [0.7%] in the osimertinib arm only).

Electrocardiogram data

At a study population level, median QTcF was increased at the first on-treatment assessment in the osimertinib arm, which remained generally stable throughout the remainder of the on-treatment period. No notable findings were observed in the placebo arm.

Figure 19. Box Plot of QTcF Interval, Aggregate Change from Baseline (Safety Analysis Set)



Baseline is defined as the last result obtained prior to the start of study treatment.
Whiskers extend to the most extreme observation within 1.5 × the interquartile range from the nearest quartile. .If 2 visits are equally eligible to assess patient status at baseline, the average is taken as a baseline value. The post-baseline assessment closest to the scheduled visit date (calculated from day of first dosing) is summarised. Derived from ECG data obtained between the start of treatment and up to and including the earlier of 28 days following the date of last dose of study medication and the day before the start of subsequent anticancer therapy. Timepoints are reported by visit for each treatment arm, provided at least one treatment arm has ≥ 5 patients.
Horizontal line: Median. Box: Q1 - Q3. Trt Dis = Treatment Discontinuation
DCO: 05 January 2024

Changes from baseline above pre-specified thresholds in QTcF values were observed in both treatment arms, with 1 patient (0.7%) in the osimertinib arm having a QTcF of > 500 msec and an increase of > 60 msec at any time during treatment; no cardiac AEs were reported in this patient. No patient in the placebo arm had a QTcF of > 500 msec and an increase of > 60 msec at any time during treatment.

In total, 5 patients (3.5%) in the osimertinib arm and 1 patient (1.4%) in the placebo arm reported an AE of electrocardiogram QT prolonged, which is a previously identified ADR for osimertinib. No unexpected safety findings were identified from a review of these events and no AEs of arrhythmia were reported as a consequence of drug-induced QTc prolongation.

Of note, a numerical difference in the proportion of patients with AEs of sinus tachycardia was observed between treatment arms: 8 patients (5.6%) in the osimertinib arm and 1 patient (1.4%) in the placebo arm, of which events in 6 patients in the osimertinib arm [and 0 patients in the placebo arm] were assessed as causally related to study treatment by the reporting Investigator.

Safety in special populations

Intrinsic Factors

Effect of gender

Table 52. Adverse Events in Any Category and AESIs by Grouped Term - Patient Level by Gender

	Number (%) of patients [a]					
	Female			Male		
	LAURA Study		Osi mono safety pool	LAURA Study		Osi mono safety pool
	Osi (N = 90)	Placebo (N = 42)	(N = 1172)	Osi (N = 53)	Placebo (N = 31)	(N = 641)
Any AE	89 (98.9)	34 (81.0)	1152 (98.3)	51 (96.2)	30 (96.8)	631 (98.4)
Any AE of ≥ CTCAE Grade 3	30 (33.3)	4 (9.5)	432 (36.9)	20 (37.7)	5 (16.1)	242 (37.8)
Any AE with outcome of death	1 (1.1)	0	44 (3.8)	2 (3.8)	2 (6.5)	25 (3.9)
Any SAE (including events with outcome of death)	37 (41.1)	5 (11.9)	327 (27.9)	18 (34.0)	6 (19.4)	194 (30.3)
Any AE leading to discontinuation of study treatment	10 (11.1)	2 (4.8)	114 (9.7)	8 (15.1)	2 (6.5)	80 (12.5)
Any AE leading to dose modification of study treatment	53 (58.9)	11 (26.2)	343 (29.3)	23 (43.4)	6 (19.4)	159 (24.8)
Any AE leading to dose reduction of study treatment	1 (1.1)	0	76 (6.5)	0	0	20 (3.1)
Any AE leading to dose interruption of study treatment	53 (58.9)	11 (26.2)	311 (26.5)	23 (43.4)	6 (19.4)	148 (23.1)
Any AESI [b]	51 (56.7)	17 (40.5)	206 (17.6)	32 (60.4)	12 (38.7)	88 (13.7)
Cardiac Effects (Cardiac Failure)	1 (1.1)	0	45 (3.8)	0	0	23 (3.6)
ILD and Pneumonitis	8 (8.9)	0	42 (3.6)	3 (5.7)	1 (3.2)	31 (4.8)
Radiation Pneumonitis	42 (46.7)	16 (38.1)	4 (0.3)	27 (50.9)	12 (38.7)	2 (0.3)

[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] AESIs of Cardiac effects (QT) are included in the overall count of patients with 'Any AESI', although data for this grouped term are not presented in the table.

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

Effect of age

Table 53. Adverse Events in Any Category and AESIs by Grouped Term – Patient Level by Age

	Number (%) of patients [a]											
	< 65 years			65 to 74 years			≥ 65 years			≥ 75 years		
	LAURA Study		Osi mono safety pool	LAURA Study		Osi mono safety pool	LAURA Study		Osi mono safety pool	LAURA Study		Osi mono safety pool
	Osi (N = 81)	Placebo (N = 39)	(N = 1043)	Osi (N = 49)	Placebo (N = 20)	(N = 563)	Osi (N = 62)	Placebo (N = 34)	(N = 770)	Osi (N = 13)	Placebo (N = 14)	(N = 207)
Any AE	79 (97.5)	32 (82.1)	1026 (98.4)	48 (98.0)	18 (90.0)	551 (97.9)	61 (98.4)	32 (94.1)	757 (98.3)	13 (100)	14 (100)	206 (99.5)
Any AE of ≥ CTCAE Grade 3	27 (33.3)	5 (12.8)	340 (32.6)	20 (40.8)	0	219 (38.9)	23 (37.1)	4 (11.8)	334 (43.4)	3 (23.1)	4 (28.6)	115 (55.6)
Any AE with outcome of death	1 (1.2)	0	31 (3.0)	1 (2.0)	0	19 (3.4)	2 (3.2)	2 (5.9)	38 (4.9)	1 (7.7)	2 (14.3)	19 (9.2)
Any SAE (including events with outcome of death)	30 (37.0)	6 (15.4)	250 (24.0)	21 (42.9)	0	181 (32.1)	25 (40.3)	5 (14.7)	271 (35.2)	4 (30.8)	5 (35.7)	90 (43.5)
Any AE leading to discontinuation of study treatment	7 (8.6)	1 (2.6)	76 (7.3)	6 (12.2)	0	75 (13.3)	11 (17.7)	3 (8.8)	118 (15.3)	5 (38.5)	3 (21.4)	43 (20.8)
Any AE leading to dose modification of study treatment	43 (53.1)	10 (25.6)	238 (22.8)	27 (55.1)	4 (20.0)	167 (29.7)	33 (53.2)	7 (20.6)	264 (34.3)	6 (46.2)	3 (21.4)	97 (46.9)
Any AE leading to dose reduction of study treatment	0	0	47 (4.5)	1 (2.0)	0	31 (5.5)	1 (1.6)	0	49 (6.4)	0	0	18 (8.7)
Any AE leading to dose interruption of study treatment	43 (53.1)	10 (25.6)	219 (21.0)	27 (55.1)	4 (20.0)	152 (27.0)	33 (53.2)	7 (20.6)	240 (31.2)	6 (46.2)	3 (21.4)	88 (42.5)
Any AESI [b]	45 (55.6)	17 (43.6)	149 (14.3)	28 (57.1)	8 (40.0)	105 (18.7)	38 (61.3)	12 (35.3)	145 (18.8)	10 (76.9)	4 (28.6)	40 (19.3)

Cardiac Effects (Cardiac Failure)	0	0	26 (2.5)	0	0	29 (5.2)	1 (1.6)	0	42 (5.5)	1 (7.7)	0	13 (6.3)
ILD and Pneumonitis	3 (3.7)	0	36 (3.5)	6 (12.2)	1 (5.0)	27 (4.8)	8 (12.9)	1 (2.9)	37 (4.8)	2 (15.4)	0	10 (4.8)
Radiation Pneumonitis	41 (50.6)	17 (43.6)	2 (0.2)	22 (44.9)	7 (35.0)	4 (0.7)	28 (45.2)	11 (32.4)	4 (0.5)	6 (46.2)	4 (28.6)	0

[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] AESIs of Cardiac effects (QT) are included in the overall count of patients with 'Any AESI', although data for this grouped term are not presented in the table. Includes AEs with an onset date on or after the date of first dose and up to and including 28 days following discontinuation of randomised treatment and on or before starting subsequent cancer therapy.

Effect of race

In the LAURA study, the number of non-Asian patients was small (27 patients in the osimertinib arm and 11 patients in the placebo arm). Differences between race groups should therefore be interpreted with caution. The overall proportion of Asian and non-Asian patients experiencing an AE was similar. AEs of ≥ CTCAE Grade 3 were experienced by 33.6% of Asian patients and 40.7% of non-Asian patients.

AESIs of ILD/pneumonitis were observed in a higher proportion of more non-Asian (18.5%) than Asian (5.2%) patients; the proportion of Asian patients with AESIs of ILD/pneumonitis was similar to that in the osimertinib monotherapy pool. Radiation pneumonitis was observed in a higher proportion of Asian (56.9%) compared to non-Asian (11.1%) patients.

A higher proportion of Asian patients experienced SAEs in the osimertinib arm of the LAURA study (37.9%) compared to the osimertinib monotherapy safety pool (26.1%), though this was largely driven by radiation pneumonitis SAEs (occurring in 12.9% of Asian patients in the osimertinib arm of the LAURA study compared to 0 patients in the osimertinib monotherapy safety pool).

Table 54. Adverse Events in Any Category and AESIs by Grouped Term - Patient Level by Race

	Number (%) of patients [a]					
	Asian			Non-Asian		
	LAURA Study		Osi mono safety pool	LAURA Study		Osi mono safety pool
	Osi (N = 116)	Placebo (N = 62)	(N = 1170)	Osi (N = 27)	Placebo (N = 11)	(N = 635)
Any AE	115 (99.1)	54 (87.1)	1163 (99.4)	25 (92.6)	10 (90.9)	612 (96.4)
Any AE of ≥ CTCAE Grade 3	39 (33.6)	7 (11.3)	426 (36.4)	11 (40.7)	2 (18.2)	246 (38.7)
Any AE with outcome of death	1 (0.9)	2 (3.2)	36 (3.1)	2 (7.4)	0	33 (5.2)
Any SAE (including events with outcome of death)	44 (37.9)	10 (16.1)	305 (26.1)	11 (40.7)	1 (9.1)	214 (33.7)
Any AE leading to discontinuation of study treatment	15 (12.9)	4 (6.5)	123 (10.5)	3 (11.1)	0	71 (11.2)
Any AE leading to dose modification of study treatment	61 (52.6)	12 (19.4)	329 (28.1)	15 (55.6)	5 (45.5)	171 (26.9)
Any AE leading to dose reduction of study treatment	0	0	67 (5.7)	1 (3.7)	0	29 (4.6)
Any AE leading to dose interruption of study treatment	61 (52.6)	12 (19.4)	300 (25.6)	15 (55.6)	5 (45.5)	157 (24.7)
Any AESI [b]	75 (64.7)	27 (43.5)	196 (16.8)	8 (29.6)	2 (18.2)	98 (15.4)
Cardiac Effects (Cardiac Failure)	1 (0.9)	0	43 (3.7)	0	0	25 (3.9)
ILD and Pneumonitis	6 (5.2)	1 (1.6)	54 (4.6)	5 (18.5)	0	19 (3.0)
Radiation Pneumonitis	66 (56.9)	27 (43.5)	2 (0.2)	3 (11.1)	1 (9.1)	4 (0.6)

[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] AESIs of Cardiac effects (QT) are included in the overall count of patients with 'Any AESI', although data for this grouped term are not presented in the table.

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

Effect of performance status

Table 55. Adverse Events in Any Category and AESIs by Grouped Term - Patient Level by WHO PS

	Number (%) of patients [a]						
	Normal activity				Restricted activity		
	LAURA Study		Osi mono safety pool		LAURA Study		Osi mono safety pool
	Osi (N = 80)	Placebo (N = 31)	(N = 590)		Osi (N = 63)	Placebo (N = 42)	(N = 812)
Any AE	79 (98.8)	26 (83.9)	578 (98.0)		61 (96.8)	38 (90.5)	797 (98.2)
Any AE of ≥ CTCAE Grade 3	24 (30.0)	3 (9.7)	152 (25.8)		26 (41.3)	6 (14.3)	333 (41.0)
Any AE with outcome of death	1 (1.3)	1 (3.2)	4 (0.7)		2 (3.2)	1 (2.4)	41 (5.0)
Any SAE (including events with outcome of death)	23 (28.8)	2 (6.5)	119 (20.2)		32 (50.8)	9 (21.4)	243 (29.9)
Any AE leading to discontinuation of study treatment	6 (7.5)	1 (3.2)	54 (9.2)		12 (19.0)	3 (7.1)	102 (12.6)
Any AE leading to dose modification of study treatment	40 (50.0)	5 (16.1)	162 (27.5)		36 (57.1)	12 (28.6)	220 (27.1)
Any AE leading to dose reduction of study treatment	1 (1.3)	0	39 (6.6)		0	0	39 (4.8)
Any AE leading to dose interruption of study treatment	40 (50.0)	5 (16.1)	144 (24.4)		36 (57.1)	12 (28.6)	200 (24.6)
Any AESI [b]	47 (58.8)	11 (35.5)	98 (16.6)		36 (57.1)	18 (42.9)	146 (18.0)
Cardiac Effects (Cardiac Failure)	1 (1.3)	0	29 (4.9)		0	0	30 (3.7)
ILD and Pneumonitis	6 (7.5)	1 (3.2)	28 (4.7)		5 (7.9)	0	30 (3.7)
Radiation Pneumonitis	39 (48.8)	11 (35.5)	2 (0.3)		30 (47.6)	17 (40.5)	1 (0.1)

[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] AESIs of Cardiac effects (QT) are included in the overall count of patients with 'Any AESI', although data for this grouped term are not presented in the table.

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

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**

AEs leading to the discontinuation of study treatment were reported in 18 patients (12.6%) in the osimertinib arm, and in 4 patients (5.5%) in the placebo arm.

Overall, 9 patients (6.3%) in the osimertinib arm and 0 patients in the placebo arm had an AE leading to the discontinuation of study treatment considered by the investigator as possibly related to study treatment.

Table 56. AEs leading to discontinuation of Osimertinib, by PT (Reported in ≥ 2 Osimertinib-treated Patients in the LAURA Study) (Safety Analysis Set)

MedDRA Preferred Term	Number (%) of patients		
	LAURA Study		Osimertinib monotherapy safety pool (N = 1813)
	Osimertinib (N = 143)	Placebo (N = 73)	
Patients with any AE leading to discontinuation	18 (12.6)	4 (5.5)	194 (10.7)
Radiation pneumonitis	7 (4.9)	2 (2.7)	0
Pneumonitis	2 (1.4)	0	26 (1.4)
Pneumonia	2 (1.4)	0	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 study treatment and before starting subsequent cancer therapy. Patients with multiple events in the same category are counted only once in that category. Patients with events in more than 1 category are counted once in each of those categories.

MedDRA version 26.1

- **Adverse events leading to dose modifications**

The proportion of patients with AEs leading to osimertinib dose modifications was higher in the osimertinib arm (80 patients [55.9%]) compared with the placebo arm (18 patients [24.7%]).

- **Adverse events leading to dose reductions**

  The proportion of patients with AEs leading to osimertinib dose reductions in the LAURA study was low in both study arms: 12 patients (8.4%) in the osimertinib arm and 1 patient (1.4%) in the placebo arm.

  Only one AE term (diarrhoea) led to dose reduction in ≥ 2 patients in the osimertinib arm (2 patients [1.4%]), which is a well-characterised osimertinib ADR. No AE leading to a dose reduction was reported by more than one patient in the placebo arm.

- **Adverse events leading to dose interruptions**

  In total, 80 patients (55.9%) in the osimertinib arm, and 18 patients (24.7%) in the placebo arm had an AEs leading to dose interruption. AEs leading to a study treatment interruption were primarily

driven by radiation pneumonitis (46 patients [32.2%] in the osimertinib arm; 10 patients [13.7%] in the placebo arm). Other AEs leading to study treatment interruption in the osimertinib arm reported in ≥ 2 patients were predominately well-characterised osimertinib ADRs (e.g., pneumonitis, neutropenia, ECG QT prolonged), or were common events in patients with the disease under study (pneumonia). It is noted that COVID-19 resulted in an interruption of osimertinib treatment in 6 patients (4.2%) and 0 patients in the placebo arm.

Table 57. AEs Leading to Dose Interruption of Osimertinib by PT (Reported in ≥ 2% of Patients in Either Treatment Arm of the LAURA Study)

MedDRA Preferred Term	Number (%) of patients		
	LAURA Study		Osimertinib monotherapy safety pool (N = 1813)
	Osimertinib (N = 143)	Placebo (N = 73)	
Patients with any AE leading to osimertinib dose interruption	80 (55.9)	18 (24.7)	459 (25.3)
Radiation pneumonitis	46 (32.2)	10 (13.7)	0
COVID-19	6 (4.2)	0	7 (0.4)
Pneumonia	5 (3.5)	1 (1.4)	29 (1.6)
Pneumonitis	4 (2.8)	1 (1.4)	2 (0.1)
Electrocardiogram QT prolonged	3 (2.1)	0	26 (1.4)
Neutropenia	3 (2.1)	1 (1.4)	21 (1.2)

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

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.

MedDRA version 26.1

Post marketing experience

As of 31 October 2023, the total cumulative post-marketing exposure to osimertinib (40 mg and 80 mg) has been estimated to be approximately 700158 patient-years.

Table 58. 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	11213	7615	24932	1581	45341
80 mg tablets	84877	56839	58979	454122	654817

As of 12 November 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, skin hyperpigmentation (including erythema dyschromicum perstans), 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 data from 216 patients from the randomised period (FAS) of the LAURA study (DCO date of 05 January 2024). All 216 randomised patients received at least one dose of study treatment, comprising 143 patients that received 80 mg osimertinib once daily and 73 patients that received placebo (Safety Analysis Set).

This dataset from the randomised period of the study LAURA is supported by comparisons with a pooled safety dataset of patients with EGFRm NSCLC treated with 80 mg osimertinib (N=1813) in other clinical studies.

Patient exposure

In the LAURA study, the median actual exposure in the osimertinib arm (23.7 months) was similar to the median total exposure (24.0 months), suggesting that the frequency and duration of dosing interruptions had a minimal impact on osimertinib exposure. The median total exposure to study treatment was much longer in the osimertinib arm (23.98 months) compared to the placebo arm (8.31 months). Therefore, there was a considerable difference in exposure between study arms. Consequently, safety data have been presented according to exposure-adjusted rates in order to further characterise the difference in safety profile between treatment arms. Of note, 50 patients (80.6%) in the placebo arm received osimertinib after disease progression.

Adverse events (AEs)

Overall, the most common AEs are reported with a higher incidence (by ≥ 10% more patients) in the osimertinib arm compared to the placebo arm: radiation pneumonitis (47.6% vs 38.4%), diarrhoea (35.7% vs 13.7%), rash (23.8% vs 13.7%), COVID-19 (20.3% vs 8.2%), and paronychia (16.8% vs 1.4%), cough (16.1% vs 9.6%), decreased appetite (14.7% vs 5.5%), dry skin (12.6% vs 5.5%), pruritus (12.6% vs 6.8%), stomatitis (11.9% vs 2.7%), white blood cell count decreased (11.9% vs 2.7%) and pneumonia (11.2% vs 8.2%).

The AEs were most frequently reported (≥ 50% of patients in either treatment arm) by SOCs were Infections and infestations (65.0% vs 32.9%), Gastrointestinal disorders (58.7% vs 32.9%), Skin and subcutaneous tissue disorders (55.2% vs 26.0%), and Injury, poisoning and procedural complications (53.8% vs 46.6%). Thus, regarding causality, there were significant differences observed between treatment arms in the incidences of AEs, although the proportions seem also high for the placebo treatment arm.

The proportion of patients with any AE reported as causally related to treatment was higher in the osimertinib arm (80.4%) compared with the placebo arm (41.1%).

Adverse events by severity

A higher proportion of patients reported AEs of CTCAE ≥ Grade 3 in the osimertinib arm (35%) compared to the placebo arm (12.3%). The most frequently reported CTCAE ≥Grade 3 AEs (≥2 patients) in both treatment arms was pneumonia (2.8% osimertinib arm vs 4.1% placebo arm) which was higher in the placebo arm. The remaining CTCAE ≥ Grade 3 AEs (≥2 patients) were only reported in the osimertinib arm and these were diarrhoea, radiation pneumonitis (2.1% each), pneumonitis and blood creatine phosphokinase increased (1.4% each).

Of these CTCAE ≥Grade 3 AEs, 13.3% in the osimertinib arm and 2.7% in the placebo arm were considered as related to study treatment by the investigator, being the most frequently reported (≥2 of patients) pneumonitis, diarrhoea and radiation pneumonitis (2 patients [1.4%] each) in the osimertinib arm; while in the placebo arm these were neutropenia, pleural effusion and pulmonary embolism.

The incidence of AEs CTCAE Grade 4 (life-threating) was higher also in the osimertinib arm (3.5%) compared to the placebo arm (1.4%). However, the AEs CTCAE Grade 5 were a slightly higher in the placebo arm (2.7%) compared to the osimertinib arm (2.1%).

Serious adverse events (SAEs)

A higher proportion of patients experienced an SAE in the osimertinib arm [55 patients (38.5%)] compared to the placebo arm [11 patients (15.1%)]. The most frequently reported SAEs (≥ 2% of patients) in both treatment arms were radiation pneumonitis [15 patients (10.5%) in the osimertinib arm vs 2 patients (2.7%) in the placebo arm) and pneumonia [7 patients (4.9%) in the osimertinib arm vs 3 patients (4.1%) in the placebo arm]. Other SAEs reported in the osimertinib arm were pneumonitis and gastroenteritis, in two patients (1.4% each).

Of these, 12 patients (8.4%) in the osimertinib arm and 1 patient (1.4%) in the placebo arm had a SAE considered as related to study treatment by the investigator. Radiation pneumonitis and pneumonitis were the only SAEs reported as possibly related to osimertinib treatment in ≥ 2 patients (3 patients [2.1%] and 2 patients [1.4%], respectively); in the placebo arm these were pleural effusion and pulmonary embolism.

One patient in the placebo arm had a SAE of drug-induced pneumonitis (maximum CTCAE Grade 3) during treatment with osimertinib post-BICR-confirmed disease progression.

Deaths

Overall, proportion of patients who died was similar between treatment arms [28 patients (19.6%) in the osimertinib arm vs 15 patients (20.5%) in the placebo arm]. Of these, the majority of deaths in the osimertinib arm [22 patients (15.4%)] and all deaths in the placebo arm [15 patients (20.5%)], were considered as related to the disease by the investigator. A total of 3 patients (2.1%) in the osimertinib arm, and 2 patients (2.7%) in the placebo arm had an AE with an outcome of death during the treatment period which were pneumonia, pneumonitis and road traffic accident in the osimertinib arm, while in the placebo arm were myocardial infarction and aneurysm rupture.

Adverse Events of Special Interest (AESI)

ILD and pneumonitis:

ILD grouped term was reported in a higher proportion of patients in the osimertinib arm [11 patients (7.7%)] compared to the placebo arm [1 patient (1.4%)], being low the proportion of patients with an AE of CTCAE Grade ≥3 (3/11 patients in the osimertinib arm, and no patient in the placebo arm). Of the 3 patients (2.1%) with ILD/pneumonitis Grade ≥3, one patient (8.3%) had a fatal event (CTCAE Grade 5 AE) of pneumonitis which was considered as related to osimertinib and rivaroxaban (concomitant medication) by the investigator.

It is important to note however that patients with a history of ILD were not enrolled in the study, and that patients with clinical active ILD were in principle enrolled and continued study treatment unless the

events were CTCAE Grade 3 or 4, or if symptomatic CTCAE Grade ≥ 2 events reoccurred after restarting study treatment.

The majority of patients with AEs of ILD/pneumonitis had not recovered/resolved, (7 events [58.3%] in 6 patients) in the osimertinib arm. Note that 2 patients in the osimertinib arm who had pulmonary fibrosis were enrolled in the study. ILD is a known ADR of osimertinib.

Radiation pneumonitis:

Radiation pneumonitis grouped term was reported in a higher proportion of patients in the osimertinib arm compared to the placebo arm [69 patients (48.3%) versus 28 patients (38.4%), respectively], having the majority of patients events CTCAE Grades 1 (15.4%) or Grade 2 (30.8%) in severity (non-serious) which did not lead to treatment discontinuation. It was the most frequently reported AE in both treatment arms. Of note, the incidence of radiation pneumonitis was higher than the reported in other clinical trials (e.g. study PACIFIC with durvalumab: 34% durvalumab vs 25% placebo [3]). This may be explained by the apparently higher incidence in Asian patients.

However, of the 69 patients in the osimertinib arm with radiation pneumonitis, only 3 patients (2.1%) reported CTCAE Grade 3 events and no Grade 4 or 5 events were reported. While it is acknowledged this AESI seems to be related to prior treatments received, since all patients received CRT prior to randomisation per protocol, the reported higher incidence in the osimertinib arm suggest a potential contribution of osimertinib. A warning has been included in section 4.4 and radiation pneumonitis has been included as an ADR in section 4.8.

Cardiac effects (cardiac failure):

The proportion of patients with a decrease in LVEF (from baseline ≥10% and an absolute LVEF value of < 50%) was low, four of 135 patients (3.0%) in the osimertinib arm and no patients in the placebo arm.

One patient (0.7%) in the osimertinib arm had a cardiac failure (on study day 57) which was CTCAE Grade 2 and it was considered unrelated to osimertinib by the investigator; consequently osimertinib was interrupted and the outcome was not resolved (at the DCO date of the current analysis).

Of note, at study entry 20 patients (14.0%) in the osimertinib arm and 7 patients (9.6%) in the placebo arm had medical history within the Cardiac Disorders SOC, including 1 patient in each treatment arm with a history of chronic cardiac failure.

Laboratory findings

Haematology

Greater decreases from baseline in median values for haemoglobin, leukocytes, neutrophils, lymphocytes and platelets counts were observed among patients treated with osimertinib [39 patients (27.5%)] compared to patients in the placebo arm [12 patients (16.7%)], the majority were 1-grade shifts except for 2 patients (1.4%) in osimertinib arm and 2 patients (2.8%) in placebo arm who had 2-grade shifts, and 1 patient (0.7%) in the osimertinib arm who had a 3-grade shift. 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 (calcium, 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 1 at baseline, with a low proportion of patients in each treatment arm developing a 2- or 3-grade shift; no patients in the osimertinib arm had a 4-grade shift.

[3] European Public Assessment Report Imfinzi - Procedure No. EMEA/H/C/004771/0000.

Hepatic biochemistry

A higher proportion of patients in the osimertinib arm [15 patients (10.5%)] than in the placebo arm [5 patients (6.8%)] had a hepatobiliary medical history at baseline.

Hepatobiliary SOC AEs were reported in 2 patients (1.4%) in the osimertinib arm (PTs: cholecystitis and hepatic failure), and 0 patients in the placebo arm. The SAE of hepatic failure was CTCAE Grade 3 and led to treatment discontinuation.

Regarding the maximum shifts from baseline during treatment in hepatic laboratory, a similar proportion of patients in both treatment arms had any grade shift, with the majority of grade shifts observed in both treatment arms comprising 1-grade shifts, and no clinically meaningful changes in median values were observed. A higher proportion of patients in the osimertinib arm had grade shifts for ALT (27.5%) and for AST (24.6%) in the osimertinib arm than in the placebo arm (25.0% and 18.1%, respectively) although most were 1-grade shift.

Overall, 32 patients (22.4%) in the osimertinib and 11 patients (15.1%) in the placebo arm had at least one elevated hepatic biochemistry test result based on measured laboratory values during the on-treatment period, with a numerical imbalance between treatment arms for patients who had an AST or ALT elevation of > 3 × ULN [12 patients (8.4%) in the osimertinib arm; 1 patient (1.4%) in the placebo arm).

Renal biochemistry

At a study population level, an increase from baseline in median creatinine was observed from the first on-treatment assessment, which subsequently remained generally stable for the remainder of the on-treatment period. No specific trend in median on treatment creatinine was noted in the placebo arm.

Note that patients with creatinine > 1.5 × ULN concurrent with a creatinine clearance < 30 mL/min (measured or calculated by Cockcroft and Gault equation) were excluded from participation in the study (and confirmation of creatinine clearance was only required when creatinine was > 1.5 × ULN).

A higher proportion of patients in the osimertinib arm had any grade shifts (19.0%) compared with the placebo arm (12.3%). However, in both treatment arms, all patients had a CTCAE Grade 1 or Grade 2 with no grade 3 or 4-grade shifts.

Electrocardiogram data

Only 1 patient (0.7%) in the osimertinib arm experienced a QTcF of > 500 msec with a > 60 msec increase from baseline, no patient in the placebo arm.

A higher proportion of patients had an AE of electrocardiogram QT prolonged in the osimertinib arm [5 patients (3.5%)] compared to the placebo arm [1 patient (1.4%)], which is a known ADR for osimertinib.

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

The proportion of patients with AEs of sinus tachycardia was higher in the osimertinib arm [8 patients (5.6%)] compared to the placebo arm [1 patient (1.4%)]. Of these, 6 were considered as related to study treatment by the investigator in the osimertinib arm. After adjusting for exposure, the reported rate was 2.8 events per 100 patient-years in the osimertinib arm and 1.4 events per 100 patient-years in the placebo arm. While differences after adjusting for exposure were lower, the frequency was still double in the osimertinib arm and most of events were considered related to osimertinib by the investigator. The MAH has provided a case-level analysis for sinus tachycardia concluding that a causal relationship between osimertinib and sinus tachycardia is unlikely. Consequently, sinus tachycardia is not considered as an ADR for osimertinib and therefore it is not included in section 4.8.

Special populations

Overall, in the LAURA study the safety profile of osimertinib appears consistent by gender and no major issues have been identified. However, some slight differences are observed between treatment arms, a higher proportion of patients with SAEs and AEs leading to dose modification of study treatment was observed in females (41.1% and 58.9%) compared to males (34.0% and 43.4%), respectively]; while AEs of ≥CTCAE Grade 3, AESIs of ILD and pneumonitis, and radiation pneumonitis were reported higher in males (37.7%, 8.9% and 50.9%, respectively) than in females (33.3%, 3.2% and 46.7%, respectively). AESIs of cardiac effects were reported only in females in one patient (1.1%). The safety profile was also consistent with that of the monotherapy pool.

Regarding the age, the safety profile at the AE category level in patients aged < 65 years (N = 81), 65 to 74 years (N = 49), ≥ 65 years (N = 62), and ≥ 75 years (N = 13) in the osimertinib arm of the LAURA study showed alignment with the osimertinib monotherapy safety pool. The proportion of patients with AEs in each of the AE categories, and the type of AEs most commonly reported was generally similar across age groups. However, the proportion of SAEs was higher (> 10% difference) in the osimertinib arm of the LAURA study compared to the osimertinib monotherapy safety pool, in the age group of patients from 65 to 74 years (42.9% versus 32.1%) and in the < 65 years age group (37.0% versus 24.0%), mainly due to radiation pneumonitis SAEs which occurring in 11.1% of patients in the osimertinib arm vs 12.2% in the placebo arm of the LAURA study, while no patients in the osimertinib monotherapy safety pool.

With respect to the race, non-Asian patients had a higher incidence of AEs of ≥ CTCAE Grade 3 and AESIs of ILD/pneumonitis (40.7%, 18.5%, respectively) compared to the Asian patients (33.3%, 5.2%, respectively) in the osimertinib arm although the number of non-Asian patients was small in the LAURA study (27 patients in the osimertinib arm and 11 patients in the placebo arm). However, Asian patients had a higher proportion of radiation pneumonitis AESIs (56.9%) compared to non-Asian (11.1%) patients. This is reflected in section 4.8 of the SmPC.

A higher proportion of Asian patients experienced SAEs in the osimertinib arm of the LAURA study (37.9%) compared to the osimertinib monotherapy safety pool (26.1%) mainly due to radiation pneumonitis (which occurred in 12.9% of Asian patients in the osimertinib arm and in no one in monotherapy safety pool); while the proportion of Asian patients with AESIs of ILD/pneumonitis was similar to that in the osimertinib monotherapy pool.

The safety profile by WHO PS at the AE category level in the osimertinib arm in the LAURA study showed alignment with the osimertinib monotherapy safety pool except for the SAEs which were reported more frequently in patients with a WHO PS of restricted activity (50.8%) compared to the osimertinib monotherapy safety pool (29.9%), highlighting the proportion of patients with radiation pneumonitis SAEs, 14.3% of patients with restricted activity in the osimertinib arm of the LAURA study compared to 0 patients in the osimertinib monotherapy safety pool.

No differences in the safety profile by weight have been observed between treatment arms.

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 arm (12.6%) compared to the placebo arm (5.5%), with 6.3% in the osimertinib arm and 0% in the placebo arm being considered as related to study treatment by the investigator. The most frequent AE leading to treatment discontinuation were radiation pneumonitis (4.9% in the osimertinib arm and 2.7% in the placebo arm), pneumonitis (1.4% vs 0), and pneumonia (1.4% vs 0).

With respect to the dose modifications, the proportion of patients with AEs leading to dose modifications was higher in the osimertinib arm (55.9%) as compared with the placebo arm (24.7%).

Regarding dose interruptions, AEs leading to dose interruptions of osimertinib were also more frequent in the experimental arm, 80 patients (55.9%) in the osimertinib arm and 18 patients (24.7%) in the placebo arm. AEs leading to a dose interruption of osimertinib reported in ≥ 2 patients in the osimertinib arm were mainly radiation pneumonitis in 46 patients (32.2%) in the osimertinib arm and 10 patients (13.7%) in the placebo arm; in addition to pneumonia (3.5% vs 1.4%), and pneumonitis (2.8% vs 1.4%), neutropenia (2.1% vs 1.4%), ECG QT prolonged (2.1% vs 0%) which are well-characterised osimertinib ADRs.

SmPC

The MAH proposed to include a new column to Table 2 of section 4.8 of the SmPC with the results from Study LAURA. Considering that osimertinib is administered as monotherapy in LAURA study and based on the fact that the safety profile seems comparable to the osimertinib monotherapy pool, this approach was not supported. Safety data from the LAURA study were requested to be included as part of the monotherapy pool, not only the data included in Table 2, but also the information provided in the subsections "Summary of the safety profile" and in the "Description of selected adverse reactions" in section 4.8. Therefore, section 4.8 of the SmPC was updated accordingly. In addition, the updated frequencies have been reviewed (see Table 46).

As a result of the safety data pooling, dose adjustment recommendations in section 4.2 were also updated. Recommendations for ILD/pneumonitis following definitive platinum-based chemoradiation therapy have been merged into "ILD/pneumonitis" (pooled data) and dosing recommendations for "Radiation pneumonitis" have been included separately in Table 1, section 4.2 of the SmPC, since this event is typical from this specific setting.

2.5.2. Conclusions on clinical safety

Overall, the safety profile of osimertinib as monotherapy in patients with locally advanced, unresectable NSCLC tumours which have EGFR exon 19 deletion or exon 21 (L858R) substitution mutation appears quite consistent with the already known safety profile of. However, clarifications are required regarding some AEs such as radiation pneumonitis, since a higher rate was observed in the osimertinib arm

The overall proportion of patients with CTCAE ≥Grade 3 AEs, SAEs, AEs leading to discontinuation, and AEs leading to dose modifications were higher in the osimertinib arm compared to the placebo arm (as could be expected).

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/was requested to submit 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 17.0 is acceptable.

The CHMP endorsed the Risk Management Plan version 17.0 with the following content:

Safety concerns

Table 59. Summary of safety concerns – Osimertinib

Important identified risks	• Interstitial lung disease • Cardiac failure
Important potential risks	• None
Missing information	• None

Pharmacovigilance plan

Not applicable.

Risk minimisation measures

Table 60. Summary table of risk minimisation measures – Osimertinib

Safety concern	Risk minimisation measure	Pharmacovigilance activities
Important identified risks		
ILD	Routine risk minimisation measures: • 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)	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Targeted follow-up questionnaire
Cardiac failure	Routine risk minimisation measures: • 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)	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • 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.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8 and 5.1 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:

- Readability tests were performed for the original dossier and provided during review of TAGRISSO tablets market authorisation (MA) application procedures.
- This type II variation application includes an expansion of the indication for the tablets formulation to indicate for the tablets to be used as a single agent treatment after definitive platinum-based chemoradiation therapy for patients with locally advanced, unresectable (Stage III) EGFRm NSCLC. The administration route of TAGRISSO (oral) and age groups (adults) remains the same. This variation results in a change to the Package Leaflet (PL) for TAGRISSO 40 mg and 80 mg film coated tablets in Section 1 (What TAGRISSO is and what it is used for).
- Overall, the wording in the PL for TAGRISSO is similar to that already tested previously during the MA applications. Therefore, it is justified to consider the Package Leaflet User Testing report for TAGRISSO provided during review of the MA application procedure as relevant for this application, and that no updated document is needed for this submission

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The agreed indication is for the treatment of adult patients with locally advanced, unresectable NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations and whose disease has not progressed during or following platinum-based chemoradiation therapy.

3.1.2. Available therapies and unmet medical need

The primary treatment for patients with locally advanced, unresectable NSCLC, amenable to curative intent therapy is definitive chemoradiation therapy (CRT) (ESMO 2021). However, the majority of patients who receive definitive CRT with curative intent will subsequently have disease progression.

The only treatment authorised in the EU for patients having completed curative intent CRT is durvalumab, authorised for patients whose tumours express PD-L1 ≥ 1% (SmPC Imfinzi). Nevertheless, it is also noted that in the PACIFIC study, which led to the marketing authorisation of durvalumab in this setting, the total number of EGFR-mutated patients was very low (43 patients in total, 6% of the total population). This impairs concluding on the efficacy of durvalumab in this subgroup; which is the target population of the current application for osimertinib. Among patients receiving placebo around 80% had relapsed at 12 months, highlighting the unmet medical need in this setting.

3.1.3. Main clinical studies

The current application is based on the results of the pre-planned interim analysis of the LAURA study. The LAURA study is a Phase III randomised, double-blind, placebo-controlled, multicentre global study comparing the efficacy and safety of osimertinib as a maintenance therapy versus placebo in patients with

locally advanced, unresectable (Stage III) NSCLC with centrally-confirmed EGFR mutations (Ex19del and L858R) whose disease has not progressed during or following definitive platinum-based CRT.

The study randomised 216 patients to receive either 80 mg of osimertinib as a single oral daily dose (N=143) or matching placebo (N=73).

The primary endpoint was PFS by BICR. OS and CNS PFS were key secondary endpoints and were tested in that order following a hierarchical multiplicity testing procedure.

3.2. Favourable effects

At the primary PFS analysis (maturity: 55.6%), osimertinib showed a statistically significant improvement in PFS by BICR [HR: 0.16 (95% CI: 0.10, 0.24; p-value <0.0001)] over placebo. Median PFS (95% CI) in the osimertinib arm was 39.13 months (31.51, NC), whereas in the placebo arm it was 5.55 months (3.71, 7.43). Several sensitivity analyses (including PFS by investigator) were conducted, which further supported the results of the primary analysis. Additionally, subgroup analyses were overall consistent with the results in the overall population.

Since PFS by BICR was statistically significant, OS was tested per the hierarchical testing procedure (maturity: 19.9%). At the interim analysis OS was not statistically significant [HR: 0.81 (adjusted 99.964% CI: 0.25, 2.67); p-value=0.530; p-value needed to declare statistical significance: <0.00036]. Cross-over to osimertinib was permitted, with 69.9% of the total number of patients included in the placebo arm (51/73) receiving osimertinib as a post-progression therapy.

CNS PFS by neuroradiologist BICR could not be formally tested, since it was included in the hierarchical testing procedure after OS. The descriptive HR was 0.17 (95% CI: 0.09, 0.32), based on a data maturity of 27.3%.

All the other secondary endpoints favoured the treatment with osimertinib and supported the results of the primary endpoint.

3.3. Uncertainties and limitations about favourable effects

At the DCO, OS data were still immature (19.9% maturity) and did not reach statistical significance. However, due to the substantial percentage of cross-over from the placebo arm to the osimertinib arm, statistically significant differences would not be expected in the final analysis either. Although at DCO, a detrimental effect is not observed, a positive trend is also not observed. Thus, the final OS data will be submitted once available (REC).

Since OS was not statistically significant, CNS PFS could not be formally tested. Considering that it is not expected that OS statistically significance could be reached in any moment due to the high level of cross-over, it is not expected that CNS PFS will be formally tested and, therefore, no (statistical) conclusions will be drawn on this key secondary endpoint.

The percentage of White patients included in the clinical trial was 13.9%, which constitutes a relevantly low percentage.

3.4. Unfavourable effects

Almost all of the patients in both treatment groups experienced AEs (97.9% vs. 87.7%, for osimertinib and placebo, respectively). Treatment-related AEs were reported more frequent in osimertinib-treated patients (80.4% vs. 41.1% for placebo, respectively).

The most common AEs were: radiation pneumonitis (47.6% and 38.4% for osimertinib and placebo, respectively), diarrhoea (35.7% vs 13.7%), rash (23.8% vs 13.7%), COVID-19 (20.3% vs 8.2%), paronychia (16.8% vs 1.4%), cough (16.1% vs 9.6%), decreased appetite (14.7% vs 5.5%), dry skin (12.6% vs 5.5%), pruritus (12.6% vs 6.8%), stomatitis (11.9% vs 2.7%), white blood cell count decreased (11.9% vs 2.7%) and pneumonia (11.2% vs 8.2%).

Grade ≥3 events were reported in 35.0% and 12.3% of patients, for osimertinib and placebo respectively. The proportion of patients who experienced SAEs was 38.5% and 15.1%, for osimertinib and placebo, respectively. SAEs were more frequently reported in the respiratory, thoracic disorder SOC for both groups: radiation pneumonitis (10.5% and 2.7% for osimertinib and placebo, respectively) and pneumonia (4.9% vs 4.1%).

There were 5 deaths reported as AEs with outcome of death during the treatment period [3 (2.1%) in the osimertinib arm and 2 (2.7%) in the placebo arm]. Regarding the causality, in the osimertinib arm the 3 deaths were due to pneumonia, pneumonitis and road traffic accident, while in the placebo arm the 2 deaths were due to myocardial infarction and aneurysm rupture.

The most frequently reported AESIs were the combined term of radiation pneumonitis (48.3% in the osimertinib arm and 38.4% in the placebo arm), the grouped term of ILD/pneumonitis (7.7% vs 1.4%), and the grouped term of cardiac effects (cardiac failure) (1 patient [0.7%] in osimertinib arm).

A total of 12.6% of patients receiving osimertinib and 5.5% receiving placebo had AEs leading to discontinuation of study medication. The most frequent AEs leading to treatment discontinuation were radiation pneumonitis (4.9% in the osimertinib arm and 2.7% in the placebo arm), pneumonitis (1.4% vs 0), and pneumonia (1.4% vs 0).

3.5. Uncertainties and limitations about unfavourable effects

A higher rate of radiation pneumonitis was reported in patients receiving osimertinib compared to those receiving placebo. While it is acknowledged this AESI seems to be related to prior treatments received, since all patients received CRT prior to randomisation per protocol, the potential contribution of osimertinib cannot be ruled out at this stage. A warning has been included in section 4.4 and radiation pneumonitis has been included as an ADR in section 4.8.

3.6. Effects Table

Table 61. Effects Table for osimertinib for the treatment of adult patients with locally advanced, unresectable (stage III) NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations and whose disease has not progressed during or following platinum based chemoradiation therapy (data cut-off: 05 June 2023)

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
PFS (by BICR)	Progression-free survival	Median, months (95% CI)	39.13 (31.51, NC)	5.55 (3.71, 7.43)	HR: 0.16 (95% CI: 0.10, 0.24); p-value <0.0001	CSR
OS	Overall survival	Median, months (95% CI)	NC (42.05, NC)	53.95 (46.49, NC)	HR: 0.81 (95% CI: 0.42, 1.56); p-value 0.530. * p-value needed to declare statistical	CSR

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
					significance: <0.00036	
Unfavourable Effects						
AEs grade ≥3	Adverse events of CTCAE grade ≥3	%	35.0	12.3		
AEs grade ≥3 related	Adverse events of CTCAE grade ≥3 causality related to treatment	%	13.3	2.7		
SAEs	Serious AEs regardless causality	%	38.5	15.1		
SAEs related	Serious AEs causality related to treatment	%	8.4	1.4		
Deaths	AE with outcome of death	%	2.1	2.7		
Radiation pneumonitis	Adverse event of special interest	%	48.3	38.4		
ILD/pneumonitis	Adverse event of special interest	%	7.7	1.4		

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:

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Osimertinib has demonstrated a statistically significant and clinically relevant improvement in PFS in the treatment of adult patients with locally advanced, unresectable NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations and whose disease has not progressed during or following platinum-based chemoradiation therapy.

The observed PFS benefit with osimertinib is considered quite impressive, taking into account that the differences between arms in terms of mPFS are of around 35 months. Although the uncertainties related to OS remain, and unfortunately, will remain with further OS updates due to the high level of cross over to the osimertinib arm; the observed PFS benefits, together with an apparent lack of OS detrimental effects, outweigh the current uncertainties in terms of OS. PFS in this setting is considered a sufficiently robust endpoint, being sufficiently of clinical relevance for patients, as to conclude on the positive benefit/risk of osimertinib. Nevertheless, the MAH will provide the final OS analysis, with the aim of discarding any potential OS detriment in the long-term.

Importantly, and although no formal statistical analysis could be conducted, the results in CNS PFS are also of great relevance, considering the high impact that CNS progressions have on patients' QoL. Unfortunately, it is unlikely that CNS PFS will be formally tested at any time, as it was placed after OS in the hierarchical testing procedure. Therefore, no firm conclusions can be drawn on the effects of osimertinib on CNS PFS; although the descriptive data available so far are suggesting a clinically relevant effect on this endpoint.

The safety profile of osimertinib in this setting can be considered as expected and consistent with the already known safety profile of osimertinib for other indications. However, some clarifications are required regarding the higher incidence of radiation pneumonitis reported in the osimertinib arm. A higher

incidence of Grade ≥3 AEs, SAEs, AESIs and treatment discontinuations due to AEs was observed with osimertinib compared to placebo.

3.7.2. Balance of benefits and risks

Osimertinib has demonstrated a statistically significant and clinically relevant improvement in PFS in the treatment of adult patients with locally advanced, unresectable NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations and whose disease has not progressed during or following platinum-based chemoradiation therapy. Although OS data are difficult to interpret due to the immaturity and high level of cross-over, a detrimental OS effect does not seem to be observed. Besides, the PFS improvement is considered sufficiently robust as to conclude on the benefits of osimertinib in this setting. It is noted that all secondary endpoints (e.g., CNS PFS and ORR) support the benefits observed for the primary endpoint. The safety profile of osimertinib is similar to that already shown for osimertinib in other indications.

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 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 treatment of adult patients with locally advanced, unresectable NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations and whose disease has not progressed during or following platinum-based chemoradiation therapy for TAGRISSO as monotherapy, based on results from study D5160C00048 (LAURA); this is a Phase III, randomised, double-blind, placebo-controlled, multicenter international study of osimertinib as maintenance therapy in patients with locally advanced unresectable EGFR mutation-positive non-small cell lung cancer (stage III) whose disease has not progressed following definitive platinum-based chemoradiation therapy. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 17.0 of the RMP has also been submitted. In addition, the MAH took the opportunity to introduce minor editorial changes to the Product Information.

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

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.