Clinical Study Report Synopsis	
Drug Substance	Osimertinib (AZD9291)
Study Code	D5169C00001
Edition Number	1.0
Date	04 August 2023
EudraCT Number	2019-000650-61
NCT Number	NCT04035486

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

Study dates: First subject enrolled: 15 May 2020

The analyses presented in this report are based on a data cut-off date of 03 April 2023 and database lock date of 04 May 2023

Phase of development: Therapeutic confirmatory (III)

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This study was performed in compliance with International Council for Harmonisation Good Clinical Practice, including the archiving of essential documents.

This document contains trade secrets and confidential commercial information, disclosure of which is prohibited without providing advance notice to AstraZeneca and opportunity to object.

Study centre(s)

Patients were enrolled in 151 sites in 21 countries across Europe, Asia-Pacific, North America, South America, and Africa.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Objectives and Endpoints

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

Table S1 Objectives and Endpoints

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

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

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

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

Table S1 Objectives and Endpoints

Objectives	Endpoints/Variable

PK = pharmacokinetic(s); PRO = patient-reported outcomes; PS = Performance Status; QoL = quality of life; RECIST = Response Evaluation Criteria in Solid Tumours; TFST = time to first subsequent therapy; TSST = time to second subsequent therapy; WHO = World Health Organization.

Study design

The FLAURA2 study is a global, Phase III, open-label, randomised study of osimertinib with or without pemetrexed and platinum-based chemotherapy conducted in patients with locally-advanced or metastatic EGFR mutation positive (EGFRm; Ex19del and/or L858R) NSCLC who had not received any prior therapy for advanced disease.

The FLAURA2 study has been conducted in 2 parts: the Safety run-in period, and the open-label, Phase III, Randomised period. Following a positive recommendation by the Safety Review Committee based on the evaluation of data from the Safety run-in period, the Randomised period was initiated, and this synopsis describes the design and results of the Randomised period only.

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

In the Randomised period, patients were to be randomised in a 1:1 ratio (using an interactive voice/web response system) to one of the following treatment groups:

- **Osimertinib + chemotherapy arm** (osimertinib in combination with pemetrexed plus either cisplatin or carboplatin for 4 cycles, followed by osimertinib plus pemetrexed maintenance).
- **Osimertinib arm**

Details of study treatment dosage and administration is provided in **Table S2**.

Prior to randomisation, the Investigator decided which chemotherapy regimen (carboplatin/pemetrexed or cisplatin/pemetrexed) a patient would receive if they were randomised to osimertinib + chemotherapy arm. Patients receiving pemetrexed/cisplatin or pemetrexed/carboplatin with osimertinib who discontinued cisplatin alone or carboplatin alone could, at the Investigator's discretion, be switched to the alternative platinum-based agent in combination with pemetrexed and osimertinib for the remainder of the platinum doublet therapy cycles, up to a maximum of 4 cycles. Crossover between treatment arms was not permitted within the study.

Patients were stratified by race (Chinese/Asian vs. non-Chinese/Asian vs. non-Asian), WHO PS (0 vs. 1), and method for tissue testing (central vs. local). It was anticipated that approximately 60% Asian patients and 40% non-Asian patients would be recruited.

Target population and sample size

The target population was adults with locally-advanced or metastatic EGFRm (Ex19del and/or L858R) NSCLC or recurrent NSCLC who had not received any prior therapy for advanced disease.

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

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

Investigational product and comparator(s): dosage, mode of administration and batch numbers

Table S2 Study Treatments

Study treatment name	Osimertinib (AZD9291)	Chemotherapy		
		Carboplatin	Cisplatin	Pemetrexed
Dosage formulation	80 mg oral tablet	5 mg/mL/min (AUC 5)	75 mg/m^2	500 mg/m^2
Route of administration	Oral	IV infusion	IV infusion	IV infusion
Dosing instructions	One tablet, once daily, commencing on Cycle 1 Day 1 until RECIST 1.1-defined disease progression.	Administration in accordance with local practice and labels Q3W for 4 cycles.	Administration in accordance with local practice and labels Q3W for 4 cycles.	Administration in accordance with local practice Q3W for 4 cycles, followed by maintenance therapy Q3W until RECIST 1.1-defined disease progression.

Table S2 Study Treatments

Study treatment name	Osimertinib (AZD9291)	Chemotherapy		
		Carboplatin	Cisplatin	Pemetrexed
Packaging and labelling	Provided in HDPE bottles with child-resistant closures. Each bottle was labelled in accordance with GMP Annex 13 and per local regulatory requirement.	Sourced locally by site [a]	Sourced locally by site [a]	Sourced locally by site [a]
Provider	AstraZeneca	Sourced locally by site [a]	Sourced locally by site [a]	Sourced locally by site [a]
Manufacturing Batch Numbers	16 batches of osimertinib were used in this study. Individual batch numbers and further information is included in the Clinical Study Report	Not applicable	Not applicable	Not applicable

[a] Under certain circumstances when local sourcing is not feasible, AstraZeneca centrally sourced the drug, which was labelled with text translated to local language in accordance with regulatory guidelines.

AUC = area under the concentration-time curve during any dosing interval; GMP = Good Manufacturing Practice; HDPE = high-density polyethylene; IV = intravenous; Q3W = every 3 weeks.

Duration of treatment

Randomised treatment continued until RECIST 1.1-defined progression or until another discontinuation criterion was met.

Patients could continue to receive study treatment with osimertinib beyond RECIST 1.1-defined progression if, in the judgement of the Investigator, they were receiving clinical benefit and did not meet any discontinuation criteria. However, if the patient was deemed to have clinically significant unacceptable or irreversible toxicities, rapid tumour progression, or symptomatic progression requiring urgent medical intervention, study treatment must have been discontinued.

Statistical methods

The primary analysis of PFS based on Investigator assessment (according to RECIST 1.1) occurred when approximately 278 PFS events and at least 16 months of follow-up after last subject in, had occurred in the 556 randomised patients (approximately 50% maturity). Progression-free survival was analysed using a log-rank test stratified by race, WHO PS, and method used for EGFR tissue testing for randomisation.

Subgroup analyses were conducted to compare the primary endpoint of PFS (Investigator assessment per RECIST 1.1) between the osimertinib + chemotherapy arm and osimertinib monotherapy arm in the pre-specified subgroups. Sensitivity analyses were also performed to

test for the presence of bias, including an evaluation of PFS by BICR assessment for all randomised patients.

In order to provide strong control of the type I error rate at a two-sided $\alpha = 0.05$, the primary endpoint PFS and the key secondary efficacy endpoint OS were tested in sequential order. If the previous analysis in the sequence was not statistically significant, the alpha was not to be transferred to subsequent analyses.

Additional secondary efficacy endpoints of ORR, DoR, DCR, depth of response and post-progression endpoints were also evaluated, in addition to the exploratory endpoint of CNS efficacy.

Safety and tolerability were assessed in terms of AEs, deaths, laboratory data, vital signs, electrocardiograms, LVEF, and WHO performance status. These data are summarised descriptively.

All analyses were based on a data cut-off (DCO) date of 03 April 2023.

Study population

The study population (full analysis set [FAS]) comprised a total of 557 patients (osimertinib + chemotherapy arm: 279 patients; osimertinib arm: 278 patients), of whom 276 patients in the osimertinib + chemotherapy arm, and 275 patients in the osimertinib arm received at least one dose of study treatment (Safety Analysis Set).

At the current DCO date, 277 patients (50.3%) were continuing to receive any study treatment: 154 patients (55.8%) in the osimertinib + chemotherapy arm (of which all were continuing to receive osimertinib treatment and 68 patients [24.6%] were continuing to receive pemetrexed) and 123 patients (44.7%) in the osimertinib arm.

In total, 274 patients (49.7%) had discontinued all study treatments at the DCO date: 122 patients (44.2%) in the osimertinib + chemotherapy arm, and 152 patients (55.3%) in the osimertinib arm. In the osimertinib + chemotherapy arm, the most frequently reported reason for osimertinib treatment discontinuation was disease progression (68 patients [24.6%]), with AEs reported as the most frequent reason for carboplatin/cisplatin and pemetrexed treatment discontinuation (47 patients [17.0%] and 119 patients [43.1%], respectively). In the osimertinib arm, the most frequently reported reason for treatment discontinuation was disease progression (118 patients [42.9%]).

Of the 169 patients (30.3%) who had terminated study participation at the current DCO date, the main reason was death in both treatment arms (osimertinib + chemotherapy arm: 70/82 patients; osimertinib arm: 77/87 patients).

Overall, demographics and patient characteristics were representative of the target patient population and were well balanced between treatment arms. The majority of patients randomised in this study were Asian (63.7%), female (61.4%), never smokers (66.2%), with a median age of 61.0 years (range 26 to 85 years). In total, 30.5% of patients were aged ≥ 65 to < 75 years, and 8.4% of patients were aged ≥ 75 years. Baseline disease characteristics were representative of the intended patient population, and were generally balanced between the treatment arms.

Per protocol, all randomised patients had primary lung cancer (557 patients [100%]) of predominantly adenocarcinoma histology (550 patients [98.7%]), with majority of patients having metastatic disease at baseline (536 patients [96.2%]), including CNS metastases (226 patients [40.6%]), liver metastases (109 patients [19.6%]), and bone metastases (274 patients [49.2%]).

Summary of efficacy results

The FLAURA2 study met its primary objective: treatment with osimertinib in combination with pemetrexed and platinum-based chemotherapy resulted in a statistically significant and clinically meaningful 38% reduction in the risk of disease progression or death in absence of documented disease progression compared to osimertinib (by Investigator assessment per RECIST 1.1 criteria) (HR = 0.62 [95% confidence interval {CI}: 0.49, 0.79]; p-value < 0.0001). The analysis of PFS by BICR was consistent with the Investigator-based analysis (HR = 0.62 (95% CI: 0.48, 0.80; nominal p-value = 0.0002), indicating no evidence of ascertainment bias in this open-label study.

Osimertinib + chemotherapy resulted in an 8.8-month improvement in median PFS compared to osimertinib, with a median PFS of 25.5 months in the osimertinib + chemotherapy arm vs. 16.7 months in the osimertinib arm. At 6, 12, 18, and 24 months, a higher proportion of patients in the osimertinib + chemotherapy arm were alive and progression-free compared to the osimertinib arm, and there was early separation of the Kaplan-Meier curves from the second RECIST scan evaluation at 3 months post-randomisation in favour of the osimertinib + chemotherapy arm for the entire duration of the follow-up.

Sensitivity analyses of PFS were consistent with the primary PFS analysis, and confirmed the robustness of the PFS benefit observed in the osimertinib + chemotherapy arm, and the improvement in PFS in favour of the osimertinib + chemotherapy arm was consistently observed across all pre-specified subgroups for which there were sufficient events for analysis. A supplementary pre-planned analysis indicated that that deaths related to COVID-19 did not impact the scientific integrity of the primary PFS analysis (HR = 0.62 [95% CI: 0.49, 0.79; nominal p-value < 0.0001]. The COVID-19 pandemic was therefore not judged to have had a meaningful impact on and interpretation of efficacy results.

Overall survival data at the current DCO were immature (26.8% maturity), with no detriment in OS for patients randomised to receive osimertinib + chemotherapy compared to those randomised to receive osimertinib observed (HR = 0.90 [adjusted 99.84% CI: 0.54, 1.51], p-value = 0.5238).

As expected, high response rates (> 75%) and DCR (> 90%) and were observed in both treatment arms, with a numerically higher ORR based on Investigator assessment (83.2% vs. 75.5%) and a clinically meaningful 8.7 month improvement in median DoR was observed in the osimertinib + chemotherapy arm compared to the osimertinib arm. Depth of response was comparable between treatment arms. Collectively these data are strongly supportive of the PFS benefit observed.

Whilst data are immature at the current DCO, the post-progression endpoints of TFST, PFS2, and TSST indicated that the PFS benefit was largely preserved to the next disease progression after the start of subsequent therapy, with a 30% reduction the risk of second progression or death (HR = 0.70 [95% CI: 0.52, 0.93]) in favour of the osimertinib + chemotherapy treatment arm noted, which is supportive of the long-term benefits of this treatment regimen.

The exploratory evaluation of CNS endpoints by CNS BICR in a large subgroup of patients (39.9% of the study population) demonstrated an enhanced and clinically meaningful benefit for the combination of osimertinib and chemotherapy in patients with CNS lesions at baseline compared to osimertinib:

- In the pre-defined central nervous system FAS, a clinically meaningful 42% reduction in the risk of CNS disease progression or death for patients with CNS metastases at baseline was observed in the osimertinib + chemotherapy arm compared to patients in the osimertinib arm (HR = 0.58 [95% CI: 0.33, 1.01]; nominal p-value = 0.0548). Additionally, deep and durable CNS responses were observed, with a high CNS response rate (> 65%) in both treatment arms and a notably high rate of complete responses in the osimertinib + chemotherapy arm (59.3% of patients) compared to the osimertinib arm (43.3% of patients). Median DoR was not reached in the osimertinib + chemotherapy arm and was 26.2 months in the osimertinib arm.
- In the post-hoc CNS evaluable for response analysis set, CNS responses were reported for > 85% of patients in both treatment arms, with approximately half of all patients (47.5%) in the osimertinib + chemotherapy arm reporting a CNS complete response compared to 15.8% of patients in the osimertinib arm, indicating a further enhanced CNS benefit for patients with measurable CNS lesions at baseline.

Overall, PRO data demonstrated a clinically meaningful improvement for coughing in both treatment arms, and a trend towards improvement in health-related QoL and several symptoms with osimertinib + chemotherapy treatment after completion of platinum chemotherapy, with any negative impact on PROs associated with the addition of chemotherapy to osimertinib

being transient (ie, reverted to baseline or improved) after completion of the 4 platinum-based chemotherapy cycles. Descriptive PRO CTCAE results also indicated that from the patients' perspective, osimertinib + chemotherapy and osimertinib monotherapy were similarly well-tolerated.

Summary of pharmacokinetic results

Overall, PK exposures of osimertinib and its metabolite, AZ5104, were similar between the osimertinib + chemotherapy arm and the osimertinib arm. A relatively flat PK profile with limited fluctuation in concentrations was observed at C2D1 and beyond suggesting steady-state concentrations are maintained across the dosing interval.

Summary of safety results

At the DCO of the primary PFS analysis, the number of patients exposed and the totality of exposure to each study treatment (455.3 treatment-years in the osimertinib + chemotherapy arm and 415.3 treatment-years in the osimertinib arm) were considered adequate to characterise the safety profile of osimertinib + chemotherapy in comparison to osimertinib in the target patient population.

The median total duration of exposure to treatment was 22.31 months in the osimertinib + chemotherapy arm and 19.32 months in the osimertinib arm.

As expected, the overall incidences of patients with CTCAE ≥ Grade 3 AEs, AEs leading to dose modifications, serious adverse events (SAEs), and AEs leading to discontinuation of any study drug were notably higher in the osimertinib + chemotherapy arm compared to the osimertinib arm (63.8% vs. 27.3%, 71.7% vs. 20.4%, 37.7% vs. 19.3%, and 47.8% vs. 6.2% of patients, respectively). These differences were mainly driven by expected chemotherapy related toxicities, and overall, the most commonly reported AEs comprised events that are expected for both osimertinib treatment (eg, diarrhoea, rash, stomatitis) and chemotherapy agents (eg, nausea, decreased appetite, haematological toxicities), consistent with the known safety profiles of the individual study treatments.

While the proportion of patients with AEs leading to dose modifications and discontinuation of any study treatment was higher in the osimertinib + chemotherapy arm as compared with the osimertinib arm, fewer patients reported a dose modification or discontinuation of osimertinib treatment (47.5% and 10.9%, respectively) compared to chemotherapy (56.9% and 45.3%, respectively) in the osimertinib + chemotherapy arm. These data indicate toxicities were primarily managed by chemotherapy dose modifications (per standard clinical practice guidelines) or discontinuation, and when given concurrently with chemotherapy, osimertinib was well tolerated. Of note, in both treatment arms, the actual median exposure to osimertinib was similar to the total median exposure, indicating that any dose modifications had a minimal impact on osimertinib exposure.

The majority of deaths reported were due to the disease under study; AEs with a fatal outcome were reported for a low proportion of patients in both treatment arms (6.5% in the osimertinib + chemotherapy arm, and 2.9% in the osimertinib arm), with no pattern or clustering of specific events identified.

As the majority of the study took place during the pandemic, AEs of COVID-19 were reported during the study (in 20.7% in the osimertinib + chemotherapy arm and 14.2% in the osimertinib arm), including during the period in which pre/post-exposure prophylaxis (including vaccines) was not widely available and therapeutic options were limited. Upon review, no new safety signal in relation to COVID-19 was identified.

A number of adverse events of special interest (AESIs) were predefined prior to the start of the study based nonclinical findings, emerging data from osimertinib clinical studies, pharmacological effects of approved EGFR-tyrosine kinase inhibitors, and the known adverse drug reactions of the individual chemotherapy agents. These AESI comprised Preferred Terms in the grouped terms of interstitial lung disease (ILD)/pneumonitis, cardiac effects (cardiac failure), and haematological toxicities. Upon evaluation:

- The combination of osimertinib and chemotherapy did not result in an increased incidence or severity of events of ILD/pneumonitis when compared with osimertinib monotherapy, with no evidence of additive toxicity.
- At a study population level, no notable changes in cardiac contractility (as measured by LVEF) over time were observed in either treatment arm, and any differences in the incidence of AEs indicative of cardiac failure between treatment arms were not considered to be clinically meaningful. Overall, AEs indicative of cardiac failure were comparable with the type and frequency of AEs reported in the osimertinib monotherapy clinical development programme to date, and no new safety signal for cardiac effects was identified.
- As expected, at a study population level, decreases in key haematological parameters (haemoglobin, leucocytes, platelets, and neutrophils) were noted after the initiation of treatment in both treatment arms, with a greater magnitude of difference noted in the osimertinib + chemotherapy arm. However, these decreases were acute in nature and stabilised with continued study treatment, and were concordant with the established safety profiles of the individual study treatments. Adverse events of haematological toxicities were also observed more frequently in patients in the osimertinib + chemotherapy arm compared to the osimertinib arm, which is aligned with the known safety profiles of the individual study treatments. Few patients overall (6.5%) had SAEs indicative of anaemia, neutropenia, and/or thrombocytopenia (which were reported only in the osimertinib + chemotherapy arm), and none resulted in a fatal outcome. The majority of patients with AEs indicative of anaemia, neutropenia and/or thrombocytopenia in both treatment arms

did not require treatment for the events, and none required discontinuation of osimertinib treatment; for the majority of patients, these events were reported as resolved/resolving.

No clinically significant safety findings were noted in relation to clinical chemistry, vital signs, physical examination, and WHO PS.

Overall, the totality of safety data demonstrated that osimertinib in combination with pemetrexed and platinum-based chemotherapy has a manageable safety and tolerability profile in the target patient population, with the types, frequencies and severity of AEs reported as expected based on the established safety profiles of osimertinib, cisplatin/carboplatin and pemetrexed. No evidence of synergistic toxicity was observed when osimertinib was given in combination with chemotherapy, and no new safety findings were identified that would impact on the benefit-risk profile of osimertinib + chemotherapy.

Conclusion(s)

This ongoing, Phase III, open-label, randomised study of osimertinib with or without platinum-based chemotherapy plus pemetrexed, as first-line treatment in patients with advanced EGFRm NSCLC demonstrated:

- Patients randomised to osimertinib + chemotherapy had a statistically significant and clinically meaningful improved PFS, with deep and durable responses in comparison to patients randomised to osimertinib. This benefit was observed consistently across all assessed demographic and key patient/disease characteristics, per the prespecified subgroup analyses. In addition, osimertinib + chemotherapy vs. osimertinib treatment in the first-line setting offered an enhanced and clinically meaningful CNS benefit in patients with CNS metastases.
- Osimertinib in combination with chemotherapy had an acceptable safety and tolerability profile for treating patients with advanced EGFRm NSCLC, with safety findings consistent with the known safety profiles of the individual treatments.
- Overall, a positive benefit-risk balance was observed for patients treated with osimertinib + chemotherapy in the first-line advanced metastatic setting.