Clinical Study Report Addendum Synopsis	
Drug Substance	Osimertinib (AZD9291)
Study Code	D5164C00001
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A Phase III, Double-blind, Randomized, Placebo-Controlled Multi-centre, Study to Assess the Efficacy and Safety of AZD9291 versus Placebo, in Patients with Epidermal Growth Factor Receptor Mutation Positive Stage IB-IIIA Non-small Cell Lung Carcinoma, following Complete Tumour Resection With or Without Adjuvant Chemotherapy (ADAURA)

Study dates:	First subject enrolled: 21 October 2015 Last subject last visit: Not applicable The analyses presented in this report are based on a data cut-off date of 11 April 2022 and database lock date of 17 May 2022.
Phase of development:	Therapeutic confirmatory (III)
International Co-ordinating Investigator:	PPD Smilow Cancer Hospital at Yale, 35 Park Street, New Haven, CT 06511 (USA) PPD National Cancer Center Hospital East, 6 Chome-5-1 Kashiwanoha, Kashiwa, Chiba 277-8577 (Japan) PPD Guangdong General Hospital, 106 Zhongshan 2nd Rd, Yuexiu District, Guangzhou, Guangdong Province (China)
Sponsor's Responsible Medical Officer:	PPD Global Clinical Head, AstraZeneca, Global Medicine Development, City House, Cambridge, CB2 8PA, United Kingdom

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

Study Centre(s)

Patients were enrolled in the study globally at 185 study centres in 24 countries across Europe, Asia-Pacific, North America, and South America.

Publications

Herbst RS, Tsuboi M, John T, Grohé C, Majem M, Goldman JW, et al. LBA5 - Osimertinib as adjuvant therapy in patients (pts) with stage IB–IIIA EGFR mutation positive (EGFRm) NSCLC after complete tumor resection: ADAURA. J Clin Oncol 2020; 38(18_suppl).

Wu YL, Tsuboi M, He J, John T, Grohé C, Majem M, et al. Osimertinib in Resected EGFR-Mutated Non-Small-Cell Lung Cancer. N Engl J Med 2020; 383:1711-1723.

Tsuboi M, Wu Y, He J, John T, Grohé C, Majem M, et al. LBA1 - Osimertinib adjuvant therapy in patients (pts) with resected EGFR mutated (EGFRm) NSCLC (ADAURA): Central nervous system (CNS) disease recurrence. Annals of Oncology 2020; 31(suppl_4): S1142-S1215.

Objectives and Criteria for Evaluation

This Clinical Study Report (CSR) Addendum has been prepared in order to report the data from an exploratory analysis of the primary and key secondary efficacy endpoint of disease-free survival (DFS), in addition to providing updated patient-reported health-related quality-of-life (HRQoL) and safety data.

All primary, secondary, and exploratory objectives of the ADAURA study are listed in full in the ADAURA CSR (see Section 8, ADAURA CSR, dated 31 July 2020).

Study Design

ADAURA is an ongoing, Phase III, double-blind, randomised, placebo-controlled study, designed to assess the efficacy and safety of osimertinib versus placebo in patients with stage IB-IIIA epidermal growth factor receptor mutation positive (EGFRm) non-small cell lung cancer (NSCLC) who have undergone complete tumour resection, with or without postoperative adjuvant chemotherapy.

Approximately 700 patients were planned to be randomised, under the assumption that approximately 60% of patients will be recruited from Asia and 40% from non-Asian countries. The proportion of patients randomised with stage IB cancer and stages II-IIIA cancer was to be capped at 30% and 70%, respectively. Patients were stratified by disease stage (IB versus II versus IIIA), mutation subtype (Ex19del or L858R), and race (Asian or non-Asian).

Patients were randomised 1:1 (using an interactive voice response system [IVRS]) to receive either osimertinib (80 mg, oral, once daily) or matching placebo. Patients must have sufficiently recovered from surgery and completed any standard-of-care adjuvant chemotherapy (if applicable) prior to randomisation; and must have been randomised within 10 weeks of complete surgical resection (if adjuvant chemotherapy was not administered), or within 26 weeks if adjuvant chemotherapy (comprising platinum-based doublet treatment, for a maximum of 4 cycles) was administered.

Target Population and Sample Size

The target population was male or female adult patients with stage IB-IIIA NSCLC with a centrally confirmed common sensitising epidermal growth factor receptor (EGFR) mutation (Ex19del and/or L858R, either alone or in combination with other EGFR mutations), who have undergone complete tumour resection, with or without postoperative adjuvant chemotherapy.

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

The study was event-driven, with approximately 247 disease recurrence events required in approximately 490 stage II-IIIA patients (ie, non-IB) in the Full Analysis Set (FAS) at the planned time of the primary analysis (50% maturity). The original sample size calculation was based on the assumption that if the true DFS hazard ratio (HR) for the comparison of osimertinib versus placebo in this patient population was 0.70, then 247 disease recurrence events at the time of the primary analysis would provide 80% power to demonstrate a statistically significant difference in DFS at a 5% 2-sided significance level, which could translate to an improvement in median DFS from 40 months to 57 months, assuming DFS is exponentially distributed. Under these conditions, the minimum DFS HR that would be statistically significant ($p < 0.05$, 2-sided) was 0.78.

Investigational Product and Comparator(s): Dosage, Mode of Administration and Batch Numbers

	Osimertinib	Placebo
Study treatment name:	AZD9291	AZD9291-matching placebo
Dosage formulation:	80 mg tablets 40 mg tablets	NA

	Osimertinib	Placebo
Batch numbers:	Blinded 80 mg tablets: CCI Blinded 40 mg tablets: CCI	Placebo 80 mg matching tablets: CCI Placebo 40 mg matching tablets: CCI
Provider:	AstraZeneca	AstraZeneca
Route of administration:	Oral	Oral
Dosing instructions:	Patients were instructed to swallow 1 tablet daily. Tablets were to be taken whole with approximately 240 mL water, with or without food. Doses were to be taken approximately 24 hours apart, at the same time point each day. Doses should not have been missed. If a patient missed 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 should not have been 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 should have taken the next scheduled dose. Any changes from the dosing schedule, dose interruption or dose reduction were recorded in the eCRF.	
Packaging and labelling:	Tablets were packed in high-density polyethylene bottles, with child-resistant closures. Bottles were dispensed to patients in the AstraZeneca packing provided. The packaging included bottles, caps, and a label. Bottle tampers should not have been broken prior to dispensing the study drug to a patient. Labels were in accordance with Good Manufacturing Practice and local regulatory guidelines. Label text was translated into local language, as applicable. The label included the Name of the Sponsor, Study Code, 'For Clinical Trial use only', and/or any other market specific requirements.	

Duration of Treatment

All patients receive randomised treatment until recurrence of disease, a treatment discontinuation criterion was met, or the 3-year (156 weeks) treatment period was completed.

Statistical Methods

The primary endpoint of DFS was to be tested in a subset of patients with stage II-IIIA disease at the time of diagnosis, as well as in the overall population.

At the data cut-off (DCO) date of the primary analysis (17 January 2020), the primary study objective was met and a statistically significant improvement in DFS was observed for patients randomised to receive osimertinib treatment compared to patients randomised to receive placebo. All further analyses of DFS are therefore to be considered exploratory in nature, and consequently, p-values are not reported.

All safety and efficacy endpoints presented in this report were evaluated using the same statistical methodology as previously defined for the primary analysis (as reported in the ADAURA CSR, dated 31 July 2020).

All analyses reported herein are based on a DCO date of 11 April 2022.

Study Population

The overall study population (FAS) comprised a total of 682 patients randomised to treatment in a 1:1 ratio (osimertinib arm: 339 patients; placebo arm: 343 patients) at 185 study centres in 24 countries, of whom 337 osimertinib arm patients and 343 placebo arm patients received at least 1 dose of study treatment (Safety Analysis Set). Out of the overall study population, 470 patients had stage II-IIIA disease (osimertinib arm: 233 patients; placebo arm: 237 patients).

At the DCO date of the current analysis (11 April 2022), 361 patients (53.1%) had completed study treatment (as reported by the investigator), with a greater proportion of patients in the osimertinib arm completing the 3-year study treatment period than in the placebo arm: 222 osimertinib-treated patients (65.9%) versus 139 placebo-treated patients (40.5%).

Overall, 318 patients had discontinued their randomised study treatment prior to the planned 3-year treatment duration (osimertinib: 114 patients [33.8% of those who received treatment]; placebo: 204 patients [59.5%]). In the osimertinib arm, the most frequently reported reason for study treatment discontinuation was adverse event (AE; 41 patients [12.2% of those who received treatment]). In the placebo arm, the most frequently reported reason for study treatment discontinuation was disease recurrence (172 patients [50.1% of those who received treatment]).

The majority of patients were ongoing in the study (539 patients overall [79.0% of all randomised patients]: 284 osimertinib-treated patients [83.8%], and 255 placebo-treated patients [74.3%]).

Summary of Efficacy Results

At the DCO of the current analysis (11 April 2022), in patients with stage II-IIIA disease, all patients (100.0%) had the opportunity for at least 3-years of follow-up, 120 patients (25.5%) having had the opportunity for at least 5 years follow-up.

In patients with stage II-IIIA disease, 75 patients (32.2%) in the osimertinib arm and 167 patients (70.5%) in the placebo arm had experienced a DFS event at the DCO date of the current analysis. In this patient population at the DCO date of the primary analysis (17 January 2020), a highly statistically significant and clinically meaningful improvement in DFS for patients randomised to receive osimertinib compared to patients randomised to receive placebo was observed (HR = 0.17; 99.06% confidence interval [CI]: 0.11, 0.26; p-value < 0.0001). At the DCO date of the current analysis, this clinically meaningful improvement in DFS in osimertinib-treated patients was maintained (HR = 0.23; 95% CI: 0.18, 0.30), based on a total of 242 DFS events having been recorded in 470 evaluable patients (51.5% maturity of data). This represents an 18.3% increase in maturity of data in this patient population since the DCO date of the primary analysis (previously 33.2% data maturity).

In the overall study population (FAS; all patients with stage IB-IIIA disease), all patients (100.0%) had had the opportunity for at least 3 years of follow-up, with 189 patients (27.7%) having had the opportunity for at least 5 years of follow-up. Overall, 94 patients (27.7%) in the osimertinib arm and 211 patients (61.5%) in the placebo arm had experienced a DFS event at the DCO date of the current analysis. In this overall study population, at the DCO date of the primary analysis, a highly statistically significant and clinically meaningful improvement in DFS for patients randomised to receive osimertinib compared to patients randomised to receive placebo was observed (HR = 0.20; 99.12% CI: 0.14, 0.30; p-value < 0.0001). At the DCO date of the current analysis, this clinically meaningful improvement in DFS in osimertinib-treated patients was maintained (HR = 0.27; 95% CI: 0.21, 0.34), based on 305 DFS events having been recorded in 682 evaluable patients (44.7% maturity of data). This represents a 16.0% increase in maturity of data in this patient population since the DCO date of the primary analysis (previously 28.7% data maturity).

A further analysis of DFS by specific demographic and patient/disease characteristic subgroups demonstrated that this observed overall benefit with osimertinib was also consistently seen in all pre-specified subgroups.

For both the stage II-IIIA and overall populations, the Kaplan-Meier (KM) curves for DFS separated after the first scan at 12 weeks post-randomisation, with separation clearly maintained to the planned treatment duration of 36 months and throughout the DFS follow-up period.

The KM estimates of median duration of DFS in both the stage II-IIIA and overall populations was 65.8 months in the osimertinib arm (95% CI: 54.4, non-calculable [NC; stage II-IIIA patients] and 61.7, NC [overall population]) compared to 21.9 months (95% CI: 16.6, 27.5) for stage II-IIIA patients and 28.1 months (95% CI: 22.1, 35.0) in the overall population in the placebo arm. In both populations, a greater proportion of patients in

the osimertinib arm were alive and disease-free at all assessed timepoints compared with those in the placebo arm. It is noted that the landmark DFS rate at 60 months and the median DFS for osimertinib are to be interpreted with caution due to limited data available at this timepoint.

Summary of Safety Results

The median total duration of exposure to treatment was 35.8 months for patients in the osimertinib arm and 25.1 months for patients in the placebo arm, with patients in the osimertinib arm having a longer total exposure time to study drug (798.2 treatment years versus 648.9 treatment-years for the placebo arm). The actual median exposure in the osimertinib arm was similar to the total median exposure, indicating that the frequency of dosing interruptions for any reason and their median duration had almost no impact on osimertinib exposure.

Whilst almost all patients treated with osimertinib reported an AE (97.9%), the majority were non-serious, mild or moderate in severity, and did not lead to treatment discontinuation. The majority of patients (90.1%) also experienced at least 1 AE in the placebo arm.

The most commonly reported AEs in the osimertinib arm were consistent with those that have previously been identified as osimertinib ADRs, and no relevant differences in nature of these AEs (in terms of reporting frequency and severity) was noted from the established osimertinib safety profile. The most frequently reported (≥ 15% of patients) individual AEs in the osimertinib arm were diarrhoea, paronychia, dry skin, pruritus, cough, stomatitis, and upper respiratory tract infection. The most frequently reported AEs in the placebo arm were diarrhoea and cough.

Overall, the proportion of patients who had a Common Terminology Criteria for Adverse Events (CTCAE) ≥ Grade 3 AE was low in both treatment arms (osimertinib: 23.4%; placebo: 14.0%), indicating that the majority of AEs reported in the study were mild or moderate in severity. The most common AEs of CTCAE ≥ Grade 3 were diarrhoea, stomatitis, pneumonia, and electrocardiogram QT prolonged in the osimertinib arm; and pneumonia and hypertension in the placebo arm.

Interstitial lung disease (ILD; grouped term) was reported in 11 patients (3.3%) in the osimertinib arm (Preferred Terms of ILD in 8 patients and Pneumonitis in 3 patients), and 0 patients in the placebo arm. In the adjuvant setting, all events of ILD were mild or moderate in severity and in the osimertinib arm. No new information on this important identified risk was obtained since the previous DCO of 17 January 2020.

A very similar percentage of patients in both treatment arms (1.8% of patients in the osimertinib arm versus 1.5% of patients receiving placebo) experienced a left ventricular ejection fraction (LVEF) decrease of ≥ 10 percentage points (pp) to an absolute LVEF

of < 50% during the study. More patients in the osimertinib arm than the placebo arm had a decrease in LVEF of ≥ 15 pp to an absolute LVEF of ≥ 50% at the current DCO; however, when adjusting for exposure, the incidence of patients with an LVEF decrease of ≥ 15 pp to an absolute LVEF of ≥ 50% was broadly similar between treatment arms (2.76 events per 100 patients-years in the osimertinib arm versus 1.70 events per 100 patients-years in the placebo treatment arm).

In the osimertinib arm, 1 patient (0.3%) was reported to have experienced an AE with a fatal outcome (respiratory failure, considered unrelated to study treatment by the reporting Investigator). In the placebo arm, 2 patients (0.6%) were reported to have experienced an AE with a fatal outcome (pulmonary embolism and death, both considered unrelated to study treatment by the reporting Investigator).

Serious adverse events (SAEs) were reported in 20.2% of patients in the osimertinib arm and 13.7% of patients in the placebo arm. The most frequently reported SAE in both treatment arms was pneumonia.

Adverse events leading to permanent discontinuation of randomised treatment (DAEs) were reported in low proportion of patients (12.8% in the osimertinib arm, and 2.6% in the placebo arm). As expected, more patients in the osimertinib arm reported a DAE than in the placebo arm; however a noteworthy proportion of DAEs in the osimertinib arm were due to the protocol-mandated discontinuation criteria of ILD (9/43 patients with a DAE, which includes 1 DAE of pneumonitis) which is consistent with the known osimertinib safety profile.

Whilst worsening CTCAE grade shifts in haematology and clinical chemistry parameters were noted in both treatment arms (primarily 1- and 2-grade shifts), none of the changes in laboratory parameters were deemed to have a significant clinical sequelae on the individual patient by way of reporting of a concurrent AE, or requiring any clinical intervention.

Overall, no new safety concerns were identified at the current DCO, and with a 13-month median increase in total exposure in osimertinib-treated patients since the previous DCO, a review of all safety parameters in the current report has demonstrated consistency with the interpretation of the osimertinib safety profile of osimertinib in the adjuvant setting at the previous DCO.

Overall, osimertinib has been shown in this study to provide an acceptable safety and tolerability profile in patients with stage IB-IIIA EGFRm NSCLC who had undergone complete tumour resection (with or without postoperative adjuvant chemotherapy).

Conclusion(s)

Data from the exploratory analysis of final DFS data in this ongoing, Phase III, double-blind, randomised, placebo-controlled study in patients with stage IB-IIIA EGFRm NSCLC who have undergone complete tumour resection (with or without postoperative adjuvant chemotherapy) demonstrated:

- In patients with stage II-IIIA disease and in the overall study population, efficacy, and safety results at the current DCO date of the final DFS analysis were consistent with previous findings reported at the time of the primary analysis (DCO date of 17 January 2020).
- Patients randomised to osimertinib continued to derive a clinically meaningful improvement in DFS in comparison to patients randomised to placebo.
- Osimertinib continued to demonstrate an acceptable safety and tolerability profile for treating patients with EGFRm NSCLC in the adjuvant setting, consistent with previous clinical studies and post-marketing experience in the advanced/metastatic setting.
- Overall, the positive osimertinib benefit-risk balance observed at the DCO date of the primary analysis was enhanced by the maturity of efficacy and safety data at the current DCO date, and remains supportive of the long-term use of osimertinib in the curative setting.