| **Clinical Study Report Addendum 2 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)

## Final Overall Survival Analysis

**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 27 January 2023 and database lock date of 03 March 2023.

**Phase of development:**
Therapeutic confirmatory (III)

**International Co-ordinating Investigator:**
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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.

Herbst RS, Wu YL, John T, Grohe C, Majem M, Wang J, et al. Adjuvant Osimertinib for Resected EGFR-Mutated Stage IB-IIIA Non-Small-Cell Lung Cancer: Updated Results From the Phase III Randomized ADAURA Trial. J Clin Oncol. 2023;41(10):1830-1840.

**Objectives and criteria for evaluation**

This Clinical Study Report (CSR) Addendum has been prepared in order to report the data from the final planned analysis of the key secondary efficacy endpoint of overall survival (OS), in addition to providing an evaluation of the exploratory post-recurrence endpoints of type of next treatment, time to next treatment, and progression-free survival (PFS).

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 a 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 disease-free survival (DFS) (based on investigator assessment), assessed primarily in the primary analysis population 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<br>40 mg tablets | Not applicable |
| **Batch numbers:** | Blinded 80 mg tablets:<br>CCI<br>Blinded 40 mg tablets:<br>CCI | Placebo 80 mg matching tablets:<br>CCI<br>Placebo 40 mg matching tablets:<br>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.<br>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 electronic case report form. | |
| **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.<br>Labels were in accordance with Good Manufacturing Practice and local regulatory guidelines. Label text was translated into local language, as applicable.<br>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 and key secondary endpoint of overall survival (OS) were to be tested in the primary analysis population of patients with stage II-IIIA disease at the time of diagnosis, as well as in the overall study population (patients with stage IB-IIIA disease at the time of diagnosis). In order to strongly control the type I error at the 5% two-sided level, a hierarchical testing procedure was employed across these endpoints. The hierarchical testing procedure was ordered such that DFS in stage II-IIIA patients was tested first using the full alpha. Disease-free survival in the overall population was subsequently only to be tested if statistical significance was shown for DFS in patients with stage II-IIIA disease at the time of diagnosis. Overall survival (in both populations) was only to be tested if statistical significance was shown for DFS in the overall population.

Overall survival in both populations was to be tested at overall 5% two-sided level using the Haybittle-Peto boundary with alpha allocation of 0.0002 (two-sided) for each of the interim analyses and the remaining alpha (two-sided) for the final OS analysis. The pre-planned final analysis of OS was to be conducted when approximately 94 deaths had been observed in the stage II-IIIA population (approximately 20% maturity). For the final OS analyses, the exact 2-sided alpha was to be calculated based on the exact information fraction at the time of the analysis.

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. Overall survival data were therefore formally tested per the multiple testing procedure at this time, but remained immature. This report describes the results of the planned final analysis of OS, based on a DCO date of 27 January 2023. There was a 2-sided alpha level of 0.0497 remaining for the final OS analysis, per the Haybittle-Peto boundary.

Data pertaining to the exploratory post-recurrence endpoints of time to next treatment, type of next treatment, and PFS are also reported, in addition to applicable safety variables.

**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 previously reported exploratory analysis of final DFS data (11 April 2022; henceforth referred to as the “updated DFS analysis” for brevity), all patients

had the opportunity to complete the 3-year study treatment period. At the DCO date of the current final OS analysis (27 January 2023), all patients had terminated the study, with the majority of patients (72.6%) either disease-free or in survival follow-up at the time of study completion. Overall, a greater proportion of patients completed the study in the osimertinib arm than in the placebo arm (77.0% versus 68.2%, respectively).

**Summary of efficacy results**

At the DCO date of the current final OS analysis:

- A highly statistically significant and clinically meaningful 51% reduction in the risk of death for patients with stage II-IIIA disease randomised to osimertinib compared with patients randomised to placebo (HR = 0.49; 95.03% confidence interval [CI]: 0.33, 0.73; p-value = 0.0004) was observed.
- In the overall population, OS HR was near identical with the population of patients with stage II-IIIA disease (HR = 0.49; 95.03% CI: 0.34, 0.70; p value < 0.0001), and also demonstrated a highly statistically significant and clinically meaningful 51% reduction in the risk of death for all patients in the study randomised to osimertinib compared with patients randomised to placebo.
- For both patients with stage II-IIIA disease and the overall population, separation in the Kaplan-Meier curves between the treatment arms was observed early, the curves subsequently remained clearly separated, indicating a sustained OS benefit beyond 60 months for osimertinib compared with placebo.
- Based on a post-hoc analysis, a clinically meaningful OS benefit of osimertinib was consistently observed in all subgroups.

**Summary of safety results**

At the DCO date of the previously reported updated DFS analysis (11 April 2022), all patients had completed or discontinued study treatment (including the 28-day post treatment discontinuation safety follow-up period). Safety data collection at the DCO date of the current final OS analysis (27 January 2023) was therefore limited to serious adverse events (SAEs) (comprising all SAEs in open-label osimertinib patients, and only study treatment/procedure-related SAEs in all other patients), Adverse events of special interest in open-label osimertinib patients only, and all deaths.

Since the DCO date of the updated DFS analysis, only one new adverse event has been reported. This was a SAE of COVID-19 pneumonia in an open-label osimertinib patient, which was considered to be unrelated to treatment by the reporting investigator; no new safety signal was identified. The overall safety profile of osimertinib in the ADAURA study therefore remains unchanged in the period between the DCO date of the previous updated DFS analysis and the DCO date of the current final OS analysis.

**Conclusions**

Data from the final OS analysis of this 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:

- A highly statistically significant and clinically meaningful improvement in OS for patients randomised to osimertinib treatment in comparison to patients randomised to placebo was observed, which supports the robustness of the overall treatment effect previously demonstrated in the study.
- Overall, the totality of evidence continues to demonstrate that osimertinib has an acceptable safety and tolerability profile for patients treated for stage IB-IIIA EGFRm NSCLC in the adjuvant setting.