Current Trial Report

Adjuvant Osimertinib vs. Placebo in Completely Resected Stage IA2–IA3 EGFR-Mutated NSCLC: ADAURA2

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Abstract

Introduction: Osimertinib is a third-generation, irreversible, oral epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) that potently and selectively inhibits both EGFR-TKI sensitizing and EGFR T790M resistance mutations, with demonstrated efficacy in EGFR mutation-positive (EGFRm) non–small cell lung cancer (NSCLC), including central nervous system (CNS) metastases. Here we present the rationale and study design for ADAURA2 (NCT05120349), which will evaluate adjuvant osimertinib vs. placebo in patients with stage IA2–IA3 EGFRm NSCLC, following complete tumor resection. **Patients and Methods:** ADAURA2 is a phase III, global, randomized, double-blind, placebo-controlled study. Patients will be adults aged ≥18 years with resected primary nonsquamous NSCLC stage IA2 or IA3 and central confirmation of an EGFR exon 19 deletion or L858R mutation. Patients will be stratified by pathologic risk of disease recurrence (high vs. low), EGFR mutation type (exon 19 deletion vs. L858R) and race (Chinese Asian vs. non-Chinese Asian vs. non-Asian), and randomized 1:1 to receive osimertinib 80 mg once daily (QD) or placebo QD until disease recurrence, treatment discontinuation, or a maximum treatment duration of 3 years. The primary endpoint of this study is disease-free survival (DFS) in the high-risk stratum. Secondary endpoints include DFS in the overall population, overall survival, CNS DFS, and safety. Health-related quality of life and pharmacokinetics will also be evaluated. **Results:** Study enrolment began in February 2022 and interim results of the primary endpoint are expected in August 2027.

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Introduction

The current treatment strategy for non–small cell lung cancer (NSCLC) is dependent on the clinical staging of disease.[1,2] Globally, management of patients with stage IA NSCLC is predominantly restricted to observation following complete tumor resection[3]; however, in Japan, adjuvant uracil-tegafur chemotherapy is recommended for patients with stage I NSCLC and a tumor size of >2 cm.[3-5]

Despite the majority of patients with stage IA NSCLC remaining disease-free after surgery, rates of disease recurrence remain considerable.[6,7] Development of distant metastases is a significant predictor of overall survival (OS).[8] A large retrospective multicenter study reported that 37.5% of patients with stage IA (American Joint Committee on Cancer/Union for International Cancer Control [AJCC/UICC] 7th edition) NSCLC experienced disease relapse or death at 5 years.[6] Data from 2 retrospective studies in Korea and Japan reported 5-year disease recurrence or death rates of 12% to 29% in patients with stage IA2 (AJCC/UICC 8th edition) NSCLC following resection, with 1 study reporting 54% of relapses involving a distant site after a lobectomy.[9,10] Approximately 13% of disease recurrences in patients with stage IA (AJCC/UICC 7th edition) epidermal growth factor receptor mutation-positive (EGFRm) NSCLC occur within the central nervous system (CNS).[8] Furthermore, adjuvant chemotherapy has not been shown to signif-

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icantly improve 5-year disease recurrence rates in a retrospective analysis of Japanese patients with high-risk (T1c/T2a lung adenocarcinoma or lymphovascular invasion) stage I (AJCC/UICC 8th edition) EGFRm NSCLC.[11] Therefore, there is a need for improved treatment options that delay or prevent disease recurrence, including in the CNS. Currently there are no widely-approved systemic adjuvant treatments that have demonstrated a disease-free survival (DFS) or OS benefit for patients with stage IA EGFRm NSCLC.

Osimertinib is a third-generation, irreversible, CNS-active, EGFR-tyrosine kinase inhibitor (EGFR-TKI).[12-17] The phase III ADAURA study (NCT02511106) investigated the use of adjuvant osimertinib vs. placebo following complete tumor resection, with or without adjuvant chemotherapy (per physician and patient choice) in patients with stage IB, II, or IIIA (AJCC/UICC 7th edition) EGFRm (exon 19 deletion [Ex19del] or L858R) NSCLC.[18] In the updated analysis, osimertinib showed a clinically meaningful increase in DFS compared with placebo in the overall study population (hazard ratio [HR], 0.27; 95% confidence interval [CI], 0.21, 0.34).[19] Importantly, there was a clinically meaningful 59% reduction in the risk of disease recurrence or death for patients with stage IB (AJCC/UICC 7th edition) NSCLC randomized to osimertinib compared with placebo. A DFS benefit in stage IB was also seen in an exploratory analysis of DFS by the AJCC/UICC 8th edition manual.[19] Based on the ADAURA study, osimertinib is the first targeted adjuvant treatment approved for patients with stage IB–IIIA resected EGFRm NSCLC.[18,20,21] These ADAURA data provide a strong rationale that osimertinib may also provide clinical benefit in patients with stage IA2 and IA3 EGFRm NSCLC.

ADAURA2 (NCT05120349) will evaluate the efficacy and safety of adjuvant osimertinib compared with placebo in patients with stage IA2–IA3 EGFRm (Ex19del or L858R) NSCLC following complete tumor resection.

Patients and Methods

Objectives

The primary objective is investigator-assessed DFS in the high-risk stratum. Secondary objectives include: DFS (overall population), OS, health-related quality of life, CNS DFS (each in the high-risk stratum and overall population), and safety (Table 1).

Key Eligibility Criteria

Key inclusion and exclusion criteria are shown in Table 2. Patients must be ≥18 years (for Japanese patients <20 years, their legally acceptable representative must also provide written informed consent) with histologically documented primary NSCLC (nonsquamous histology), postoperatively classified as pathologic stage IA2 or IA3 (AJCC/UICC, 8th edition).[22] Patients must have an Ex19del or L858R EGFR mutation (cobas® EGFR Mutation Test v2; centrally confirmed), or a pre-existing local EGFR test result using an approved companion diagnostic from an accredited laboratory, and a World Health Organization (WHO) performance status of 0 or 1. Complete surgical resection of the primary NSCLC with negative margins is mandatory.

Study Design

ADAURA2 is a phase III, global, randomized, double-blind, placebo-controlled study (Figure 1). Approximately 380 patients will be randomized across North and South America, Europe, and Asia. The first patient was enrolled in February 2022.

Patients will be randomized 1:1 to either osimertinib 80 mg or placebo, once daily (QD). Study treatment will continue for 3 years or until discontinuation or disease recurrence. Patients who have tumors with at least one of the following high-risk pathologic features will be stratified to the high-risk stratum: largest diameter of invasive component of primary tumor >2 cm, lymphovascular invasion, and/or high-grade histology (≥20% micropapillary, solid, or complex gland adenocarcinoma).[23] Patients will be stratified by risk (high-risk vs. low-risk [patients not defined as high-risk]) according to central pathology assessment, mutation type (Ex19del vs. L858R), and race (Chinese Asian vs. non-Chinese Asian vs. non-Asian). Approximately two-thirds of participants (253 patients) are expected to be stratified to the high-risk stratum. Study assessments are summarized in Table 1.

All patients must provide written consent and the study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with the International Council for Harmonisation/Good Clinical Practice, and applicable regulatory requirements.

Statistical Analysis

The interim analysis of efficacy and safety outcomes is expected August 2027. All patients will be followed up for investigator-assessed disease recurrence and DFS rate will be measured at 2, 3, 4, and 5 years using Kaplan–Meier estimates. The DFS endpoints will be analyzed using a log-rank test, stratified by the randomization stratification factors. Subgroup analyses for DFS will evaluate treatment efficacy in predefined subgroups including risk stratum, EGFR mutation type, race, and stage. Final OS analysis is expected in November 2032.

Discussion

Although the risk of disease recurrence is lower in patients with stage IA disease compared with later stages of disease, 37.5% of patients with stage IA disease experience disease recurrence within 5 years of resection.[6,8] A similar scenario was seen in node-negative, estrogen receptor-positive breast cancer, where a recurrence rate of 24% was observed in the control arm of randomized adjuvant trials.[24] The introduction of adjuvant endocrine therapy reduced the 5-year recurrence rate to 12% in these patients[24] and this is now considered standard of care.[25] The ADAURA2 study will determine whether adjuvant osimertinib can similarly reduce recurrence in stage IA2-IA3 EGFRm NSCLC.

The stage IA NSCLC population is heterogeneous in risk for disease recurrence, due to factors such as race and stage IA subtype.[8,26] Multiple retrospective studies have identified these clinical and pathologic features associated with risk of recurrence. Adenocarcinoma histology, lymphovascular invasion, and tumor size are associated with a higher-risk of recurrence in stage IA NSCLC.[11,26] Furthermore, histological grade of adenocarcinoma is closely correlated with patient outcomes.[23] These risk factors have

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Table 1 ADAURA2 Study Endpoints

Primary endpoints	• DFS according to investigator assessment in the high-risk stratum[a]	DFS is defined as the time from the date of randomization until the date of disease recurrence or death (by any cause, in the absence of recurrence; determined by CT or MRI). Tumor assessments will take place during main screening/baseline and at regular intervals.
Secondary endpoints	• DFS according to investigator assessment in the overall population • OS in the high-risk stratum and overall population • HRQoL determined by SF-36 v2 Acute Physical Functioning domain in both the high-risk stratum and overall population • Pharmacokinetics • CNS DFS according to investigator assessment in both the high-risk stratum and overall population	OS is defined as the time from the date of randomization until death due to any cause and will be analyzed using the same method as the analysis of DFS. Assessment of OS will be performed following disease recurrence or treatment discontinuation and occurs every 24 weeks until the study is closed. Clinically meaningful differences in HRQoL will be evaluated based on mean changes from baseline in the SF-36 v2 Acute Physical Functioning domain, Physical Component Summary, and Mental Component Summary in the high-risk population and the overall population.
Safety/tolerability	• Adverse events • Clinical laboratory studies • Frequency of dose interruptions, reductions, and discontinuations due to AEs	Clinical safety assessments will be performed at baseline and at all on-treatment visits. All AEs will be graded using CTCAE. AEs of special interest to be monitored in this study are ILD[b], including pneumonitis, and cardiac failure.

Abbreviations: AE = adverse event; CNS = central nervous system; CT = computed topography; CTCAE = common terminology criteria for adverse events; DFS = disease-free survival; HRQoL = health-related quality of life; ILD = interstitial lung disease; MRI = magnetic resonance imaging; OS = overall survival; SF-36 = short form-36.
[a] High risk defined as presence of ≥1 of the following factors: largest diameter of invasive component of primary tumor >2 cm, lymphovascular invasion, and/or high-grade histology (≥20% micropapillary, solid, or complex gland adenocarcinoma). Low-risk defined as absence of any high-risk factors.
[b] Patients will be permanently discontinued from study treatment if one of the following occurs: CTCAE grade 3 or greater ILD/pneumonitis, CTCAE grade 2 ILD/pneumonitis where symptoms have not resolved within 4 weeks after dose interruption, or recurrent symptomatic ILD/pneumonitis following prior dose interruption and study treatment rechallenge.

Table 2 Key Inclusion and Exclusion Criteria

Key Inclusion Criteria	Key Exclusion Criteria

• Written informed consent
• Age ≥18 y (patients <20 y and enrolled in Japan must provide written informed consent from the patient and their legally acceptable representative)
• Confirmed postoperatively primary nonsquamous pathologic stage IA2 or IA3 (>1 cm and <3 cm in size) NSCLC[a]
• EGFR mutation (Ex19del or L858R) either alone or in combination with other EGFR mutations
• Complete (R0) surgical resection of the primary tumor with negative margins (by lobectomy, segmentectomy, or sleeve resection)
• Complete recovery from surgery
• Tumor sample submission for central pathology assessment of:
  ○ Invasive tumor size
  ○ Presence of lymphovascular invasion
  ○ Tumor histology
• WHO performance status 0/1
• Minimum life expectancy of >6 mo
	• Mixed small cell and non–small cell histologies
	• Incomplete (R1/R2) resection or underwent pneumonectomy or only wedge resection
	• Prior (neoadjuvant or adjuvant) treatment with any anticancer therapy for NSCLC (including chemotherapy, radiotherapy, immunotherapy, and EGFR-TKIs)
	• Eligible for any other local anticancer treatment
	• Any evidence of severe or uncontrolled systemic disease
	• Active infection including hepatitis B and C and HIV
	• Any clinically important ECG abnormalities or risk factors of cardiac abnormalities
	• History of ILD, drug-induced ILD, or radiation pneumonitis

Abbreviations: AJCC/UICC = American Joint Committee on Cancer/Union for International Cancer Control; ECG = electrocardiogram; EGFR = epidermal growth factor receptor; HIV = human immunodeficiency virus; ILD = interstitial lung disease; NSCLC = non–small cell lung cancer; R0 = negative margins; R1 = microscopic residual tumor; R2 = macroscopic residual tumor; TKI = tyrosine kinase inhibitor; TNM = tumor, nodes, and metastases; WHO = World Health Organization.
[a] Based on the 8th edition AJCC/UICC TNM staging system. Stage IA2 or IA3 included tumors >1 cm and <3 cm in size.

therefore been selected as stratification factors in the ADAURA2 study to determine which patients are at a higher risk of disease recurrence.

In the stage IA NSCLC setting, Asian race has been documented as a prognostic factor for survival and response to chemotherapy.[27,28] Within the ADAURA study, no difference in DFS benefit was observed by race (Asian subgroup, HR, 0.34; 95% CI, 0.25, 0.45 vs. non-Asian subgroup, HR, 0.28; 95% CI, 0.18, 0.43).[19] Similarly, a DFS benefit was observed regardless of EGFR mutation type (Ex19 del or L858R).[19] However, it is still unclear how race or mutation type may impact adjuvant treatment benefit in the stage IA2 and IA3 setting and, therefore, ADAURA2 patients will also be stratified by race (Chinese Asian, non-Chinese Asian, and non-Asian) and mutation type (Ex19del vs. L858R).

The primary endpoint of DFS is being increasingly used in clinical trials in the adjuvant and curative intent treatment settings. An

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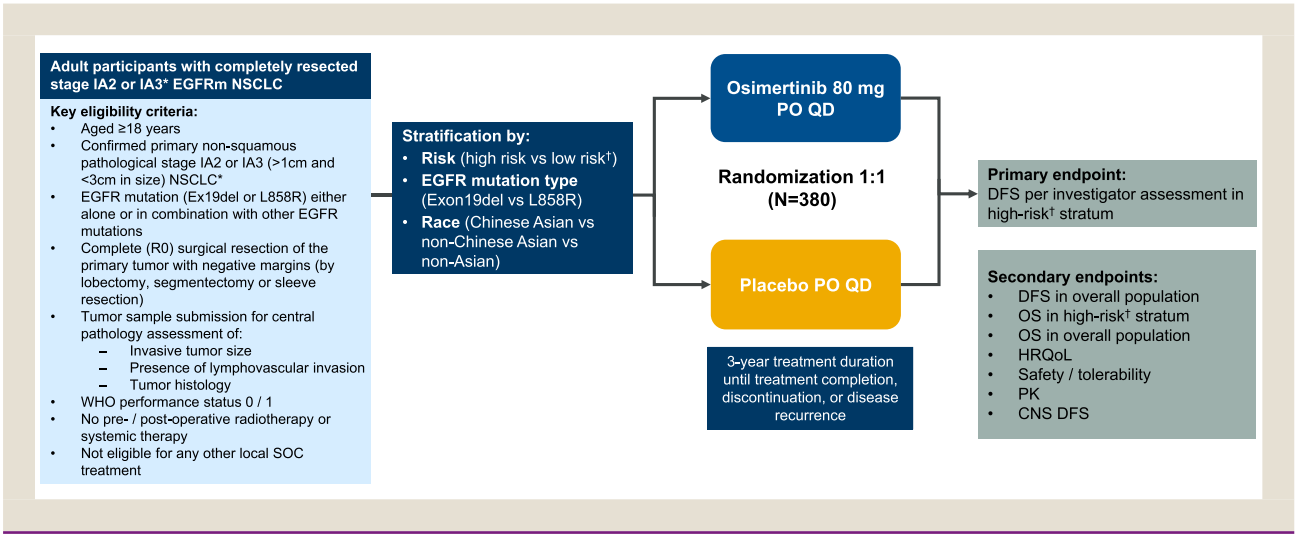
Figure 1 ADAURA2 study design



*Based on the 8th edition AJCC/UICC TNM staging system. Stage IA2 or IA3 included tumors >1 cm and <3 cm in size. †High-risk defined as presence of ≥1 of the following factors based on central pathology review: largest diameter of invasive component of primary tumor >2 cm, lymphovascular invasion, and/or high-grade histology (≥20% micropapillary, solid, or complex gland adenocarcinoma). Low risk defined as absence of any high-risk factors. AJCC/UICC = American Joint Committee on Cancer/Union for International Cancer Control; CNS = central nervous system; DFS = disease-free survival; EGFR = epidermal growth factor receptor; EGFRm = epidermal growth factor receptor mutated; Ex19del, Exon 19 deletion mutation; HRQoL = health-related quality of life; NSCLC = non–small cell lung cancer; OS = overall survival; PK = pharmacokinetics; PO = orally; QD = once-daily; R0 = negative margins; SOC = standard of care; TKI = tyrosine kinase inhibitor; TNM= tumor, nodes and metastases; WHO = World Health Organization.

important treatment goal in this setting is for patients to maintain a disease-free state and DFS has formed the primary basis of regulatory approval for adjuvant targeted lung cancer treatment.[29] Multiple meta-analyses and a retrospective analysis have validated DFS as a surrogate endpoint for OS in NSCLC.[30-36]

Tolerability is an important consideration for an adjuvant treatment, particularly in the stage IA setting due to the lower risk of recurrence compared with later stages of disease.[6] No new safety signals for osimertinib were observed during the ADAURA study where patients received adjuvant osimertinib for up to 3 years.[18] Historical studies reported interstitial lung disease (ILD) in 4% to 5% of patients with advanced/metastatic NSCLC treated with osimertinib.[15,16] Within the ADAURA study ILD was reported in 3% of patients treated with osimertinib and none treated with placebo; these cases were all mild or moderate, and no deaths due to ILD were reported.[18] Discontinuation of osimertinib has been the standard management for all ILD events historically, regardless of severity; however, discontinuations could impact clinical benefit. For the purpose of generating more data on ILD outcomes to inform ILD toxicity management guidelines, the ADAURA2 study will permit patients with grade 1 or 2 ILD to continue or reinitiate treatment after resolution of symptoms, with close monitoring.

Conclusion

The ADAURA2 phase III, global, randomized, double-blind, placebo-controlled study will assess the efficacy and safety of osimertinib compared with placebo as adjuvant therapy in patients with EGFRm stage IA2-IA3 NSCLC following complete tumor resection. The results will help define the clinical benefit of adjuvant osimertinib treatment in EGFRm early-stage NSCLC and help address the unmet need of limited treatment options in this patient population.

Disclosure

Y. Tsutani has undertaken an advisory role for AstraZeneca; received honoraria from AstraZeneca, Bristol-Myers Squibb, Carenet, Chugai Pharmaceutical Co, Ltd, Covidien Japan, Japan Blood Products Organization, Johnson & Johnson, Merck Sharp & Dohme, MiRTeL, Nihon Medi-Physics, Novartis, Ono Pharmaceutical Co, Ltd, Takeda, and Taiho Pharmaceutical Co, Ltd; and has received research support from Boehringer Ingelheim, Chugai Pharmaceutical Co, Ltd, Daiichi Sankyo, and Taiho Pharmaceutical Co, Ltd, J. W. Goldman has received honoraria from AstraZeneca, Bristol-Myers Squibb, Genentech, and Pfizer; has received research support from Advaxis, Array, AstraZeneca, Bristol-Myers Squibb, Eli Lilly and Company, G1 Therapeutics, Genentech, Merck, and Pfizer; and has received travel fees from AstraZeneca. S. Dacic has undertaken advisory roles for AbbVie, AstraZeneca, Eli Lilly and Company, Genentech/Roche, Merck, and Takeda and has undertaken an officer role for Pulmonary Pathology Society. Y. Yatabe has undertaken advisory roles for Amgen Inc, ArcherCDx, AstraZeneca, Chugai Pharmaceutical Co, Ltd, Janssen, Merck Sharp & Dohme, Novartis, Takeda, and Thermo Fisher; has received research grants from ArcherDx, Konica Minolta, and ThermoFisher; and has undertaken speaker's bureau for AbbVie, Amgen, Inc, ArcherDx, AstraZeneca, Bayer, Boehringer Ingelheim, Chugai Pharmaceutical Co, Ltd, Eli Lilly and Company, Merck, Merck Sharpe & Dohme, Novartis, Ono Pharmaceutical Co, Ltd, Takeda, ThermoFisher, and Yansen. M. Majem has undertaken advisory roles for Amgen Inc, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb,

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CRediT authorship contribution statement

Yasuhiro Tsutani: Conceptualization, Methodology, Investigation, Supervision. **Jonathan W. Goldman:** Methodology, Visualization. **Sanja Dacic:** Methodology, Visualization. **Yasushi Yatabe:** Conceptualization, Formal analysis, Supervision, Project administration. **Margarita Majem:** Conceptualization, Validation, Supervision. **Xiangning Huang:** Conceptualization, Methodology. **Allen Chen:** Conceptualization, Methodology, Supervision. **Toon van der Gronde:** Conceptualization, Methodology, Visualization, Supervision. **Jie He:** Methodology, Investigation, Data curation.

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