Postoperative Chemotherapy Use and Outcomes From ADAURA: Osimertinib as Adjuvant Therapy for Resected EGFR-Mutated NSCLC

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Introduction: Adjuvant chemotherapy is recommended in patients with resected stages II to IIIA (and select IB) NSCLC; however, recurrence rates are high. In the phase 3 ADAURA study (NCT02511106), osimertinib was found to have a clinically meaningful improvement in disease-free survival (DFS) in patients with resected stages IB to IIIA EGFRm NSCLC. Here, we report prespecified and exploratory analyses of adjuvant chemotherapy use and outcomes from ADAURA.

Methods: Patients with resected stages IB to IIIA EGFRm NSCLC were randomized 1:1 to receive osimertinib or placebo for 3 years. Adjuvant chemotherapy before randomization was not mandatory, per physician and patient choice. DFS in the overall population (IB–IIIA), with and without adjuvant chemotherapy, was a prespecified analysis. Exploratory analyses included the following: adjuvant chemotherapy use by patient age, disease stage, and geographic location; DFS by adjuvant chemotherapy use and disease stage.

Results: Overall, 410 of 682 patients (60%) received adjuvant chemotherapy (osimertinib, n = 203; placebo, n = 207) for a median duration of 4.0 cycles. Adjuvant chemotherapy use was more frequent in patients: aged less than 70 years (338 of 509; 66%) versus more than or equal to 70 years (72 of 173; 42%); with stages II to IIIA (352 of 466; 76%) versus stage IB (57 of 216; 26%); and enrolled in Asia (268 of 414; 65%) versus outside of Asia (142 of 268; 53%). A DFS benefit favoring osimertinib versus placebo was observed in patients with (DFS hazard ratio = 0.16, 95% confidence interval: 0.10–0.26) and without adjuvant chemotherapy (hazard ratio = 0.23, 95% confidence interval: 0.13–0.40), regardless of disease stage.

Conclusions: These findings support adjuvant osimertinib as an effective treatment for patients with stages IB to IIIA EGFRm NSCLC after resection, with or without previous adjuvant chemotherapy.

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Keywords: Adjuvant chemotherapy; EGFR; EGFR-TKI; NSCLC; Osimertinib

Introduction

Approximately 30% of patients with NSCLC present with resectable disease at diagnosis.1–3 For these patients, surgery with curative intent is the primary treatment option.4,5 After surgery, adjuvant cisplatin-based chemotherapy is recommended for patients with resected stages II to IIIA NSCLC and select patients with stage IB disease.5,6 Real-world studies have reported that approximately 48% to 57% of patients with resected stages IB to IIIA NSCLC received adjuvant chemotherapy in clinical practice, with increased use in stages II (55%–67% of patients) and IIIA disease (65%–71% of patients), compared with stage IB.7,8 Nevertheless, rates of disease recurrence after surgery remain high across

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ABSTRACT

Introduction: Adjuvant chemotherapy is recommended in patients with resected stages II to IIIA (and select IB) NSCLC; however, recurrence rates are high. In the phase 3 ADAURA study (NCT02511106), osimertinib was found to have a clinically meaningful improvement in disease-free survival (DFS) in patients with resected stages IB to IIIA EGFRm NSCLC. Here, we report prespecified and exploratory analyses of adjuvant chemotherapy use and outcomes from ADAURA.

Methods: Patients with resected stages IB to IIIA EGFRm NSCLC were randomized 1:1 to receive osimertinib or placebo for 3 years. Adjuvant chemotherapy before randomization was not mandatory, per physician and patient choice. DFS in the overall population (IB–IIIA), with and without adjuvant chemotherapy, was a prespecified analysis. Exploratory analyses included the following: adjuvant chemotherapy use by patient age, disease stage, and geographic location; DFS by adjuvant chemotherapy use and disease stage.

Results: Overall, 410 of 682 patients (60%) received adjuvant chemotherapy (osimertinib, n = 203; placebo, n = 207) for a median duration of 4.0 cycles. Adjuvant chemotherapy use was more frequent in patients: aged less than 70 years (338 of 509; 66%) versus more than or equal to 70 years (72 of 173; 42%); with stages II to IIIA (352 of 466; 76%) versus stage IB (57 of 216; 26%); and enrolled in Asia (268 of 414; 65%) versus outside of Asia (142 of 268; 53%). A DFS benefit favoring osimertinib versus placebo was observed in patients with (DFS hazard ratio = 0.16, 95% confidence interval: 0.10–0.26) and without adjuvant chemotherapy (hazard ratio = 0.23, 95% confidence interval: 0.13–0.40), regardless of disease stage.

Conclusions: These findings support adjuvant osimertinib as an effective treatment for patients with stages IB to IIIA EGFRm NSCLC after resection, with or without previous adjuvant chemotherapy.

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Introduction

Approximately 30% of patients with NSCLC present with resectable disease at diagnosis.1–3 For these patients, surgery with curative intent is the primary treatment option.4,5 After surgery, adjuvant cisplatin-based chemotherapy is recommended for patients with resected stages II to IIIA NSCLC and select patients with stage IB disease.5,6 Real-world studies have reported that approximately 48% to 57% of patients with resected stages IB to IIIA NSCLC received adjuvant chemotherapy in clinical practice, with increased use in stages II (55%–67% of patients) and IIIA disease (65%–71% of patients), compared with stage IB.7,8 Nevertheless, rates of disease recurrence after surgery remain high across
all disease stages (approximately 45% of patients with stage IB disease; 62% of patients with stage II disease; 76% of patients with stage III disease), regardless of adjuvant chemotherapy use.9

EGFR tyrosine kinase inhibitors (TKIs) are recommended for the first-line treatment of patients with EGFR-mutated (EGFRm) advanced NSCLC,10,11 and previous studies have indicated that there may be a role for first-generation EGFR TKIs in the EGFRm resected treatment setting, although these data did not lead to changes in clinical practice.12–15 Osimertinib is a third-generation, irreversible, oral EGFR TKI that potently and selectively inhibits both EGFR TKI sensitizing and EGFR T790M resistance mutations and has been found to have efficacy in patients with NSCLC with central nervous system metastases.16–21 Osimertinib is recommended as the optimal first-line treatment option for patients with EGFRm (exon 19 deletion [Ex19del] or exon 21 L858R [L858R] mutations) advanced NSCLC and is the treatment of choice for patients with acquired T790M after disease progression on other first-line EGFR TKIs.10,11 Furthermore, osimertinib was recently approved by the U.S. Food and Drug Administration, China National Medical Products Administration, and European Commission22–24 for the adjuvant treatment of adult patients with EGFRm (Ex19del or L858R mutations) early-stage NSCLC after tumor resection, on the basis of results from the phase 3 ADAURA trial (NCT02511106), which evaluated osimertinib versus placebo in patients with stages IB to IIIA EGFRm NSCLC after complete tumor resection, with or without adjuvant chemotherapy.25

In ADAURA, adjuvant osimertinib was found to have a statistically significant and clinically meaningful improvement in disease-free survival (DFS) compared with placebo in patients with completely resected stages IB to IIIA EGFRm NSCLC (hazard ratio [HR] = 0.20, 99.12% confidence interval [CI]: 0.14–0.30, p < 0.001).25,26 A DFS benefit favoring osimertinib treatment versus placebo was observed consistently across all predefined subgroups, including disease stages IB, II, and IIIA and the use or nonuse of adjuvant chemotherapy.25

To gain further insights into adjuvant chemotherapy use and its impact on efficacy outcomes in resected NSCLC, we report prespecified and exploratory analyses of adjuvant chemotherapy use and outcomes from the ADAURA trial.

Materials and Methods

Patients

Full details of the trial methodology have been published previously.25,27 Briefly, eligible patients were aged more than or equal to 18 years (≥20 y old in Japan and Taiwan), with histologically confirmed primary nonsquamous NSCLC of postsurgical pathologic stage IB, II, or IIIA (classified according to the seventh edition of the American Joint Committee on Cancer Staging Manual25), a WHO performance score (WHO PS) of 0 to 1, and centrally confirmed EGFR mutation (Ex19del or L858R). Complete surgical resection of the primary NSCLC (with negative margins) was mandatory. Magnetic resonance imaging or a computed tomography scan of the brain was required before surgery or randomization.

Postoperative (adjuvant) chemotherapy, comprising platinum-based doublet treatment for a maximum of four cycles before randomization, was allowed but not mandatory (decided by the physician and patient before enrollment). Complete recovery from surgery (a minimum of 4 weeks) and adjuvant therapy (if applicable) was required before randomization. For patients who received adjuvant chemotherapy, a minimum of 2 weeks was required between the last administered dose of chemotherapy and randomization. The maximum time interval permitted between surgery and randomization was 26 weeks for patients who received adjuvant chemotherapy and 10 weeks for patients who did not. Those patients who received adjuvant chemotherapy must have recovered from all grade greater than or equal to one toxicities associated with previous therapy before starting the study treatment, with the exception of alopecia and grade 2 neuropathy related to previous platinum therapy. Preoperative, postoperative, or planned radiation therapy was not permitted. Preoperative (neoadjuvant) chemotherapy was also not permitted.

Trial Design and Treatment

ADAURA (NCT02511106) is a phase 3, double-blind, placebo-controlled, randomized, global trial conducted in 26 different countries across Europe, the Asia-Pacific, North America, and South America. Patients were stratified according to disease stage (IB, II, or IIIA), EGFR mutation status (Ex19del or L858R), and race (Asian or non-Asian) and were randomly assigned in a 1:1 ratio to receive osimertinib 80 mg orally once daily or placebo. Screening and randomization occurred after the patients had undergone surgery and received adjuvant chemotherapy (if applicable). Patients received osimertinib or placebo for up to 3 years or until disease recurrence or fulfillment of a discontinuation criterion.25

The ADAURA trial was conducted in accordance with the provisions of the Declaration of Helsinki, Good Clinical Practice guidelines (as defined by the International Conference on Harmonisation), applicable regulatory requirements, and the policy on bioethics and human biological samples of the trial sponsor,
AstraZeneca. All patients provided informed written consent before participation.

**Trial End Points**

The primary end point of the study was DFS according to investigator assessment among patients with stages II to IIIA disease. Secondary end points included DFS in the overall population (patients with stages IB–IIIA disease), overall survival, health-related quality of life, and safety. The primary analysis, including key secondary end points, has been reported previously.\(^{25}\) Health-related quality of life data are to be reported separately. Post hoc exploratory analyses of adjuvant chemotherapy use and its impact on clinical outcomes were also performed and are reported here. These include an overview of adjuvant chemotherapy use by patient age (<70 and ≥70 years), disease stage (stages IB, II, and IIIA), and geographic location (enrolled in Asia [People’s Republic of China, Japan, South Korea, Taiwan, Thailand, and Vietnam], and outside of Asia [Europe, Australia, United States, Canada, and Brazil]). A pre-specified subgroup analysis of DFS in the overall patient population (stages IB–IIIA disease), with and without adjuvant chemotherapy, will be reported. Post hoc exploratory analyses of DFS by adjuvant chemotherapy use (yes versus no) and by disease stage (stage IB versus II versus IIIA) will also be reported here.

**Trial Assessments and Statistical Methods**

DFS was 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). Baseline assessments for disease recurrence were performed within 28 days before treatment initiation; subsequent assessments were performed at weeks 12 and 24, then every 24 weeks until 5 years, and yearly thereafter. Disease recurrence was defined by computed tomography or magnetic resonance imaging scan, or pathologic disease on biopsy by investigator assessment. The statistical analysis plan, including sample size estimation, has been published previously.\(^{25}\) Briefly, analysis of DFS in prespecified subgroups in the overall population (full analysis set, including all randomized patients) was conducted to compare DFS between treatment arms in patients with and without adjuvant chemotherapy. Exploratory DFS subgroup analyses were performed in the following subgroups: stage IB disease without adjuvant chemotherapy; stage II disease with and without adjuvant chemotherapy; and stage III disease with and without adjuvant chemotherapy. Subgroup categories with less than 20 events, such as patients with stage IB disease who received adjuvant chemotherapy, were excluded from the analysis. The Kaplan-Meier (KM) method was used to summarize DFS data by treatment group. The total number of events and median DFS (calculated from the KM plot, with two-sided 95% CIs) were summarized. For each subgroup level, HRs and 95% CIs were calculated using a Cox proportional hazards model including a term for treatment, the subgroup covariate of interest, and the treatment-by-subgroup interaction term. No adjustment to the significance level for testing was made for the exploratory analyses because these are only supportive of the primary analysis of DFS. Data cutoff was January 17, 2020.

**Results**

**Patients and Treatment**

From November 2015 to February 2019, a total of 682 patients with completely resected stage IB, II, or IIIA NSCLC were randomized to receive either osimertinib (n = 339) or placebo (n = 343). Of all randomized patients, 680 (99.7%) received at least one dose of study treatment (337 patients in the osimertinib arm and 343 in the placebo arm). As previously reported, baseline characteristics were well balanced between the treatment arms.\(^{25}\) Patients were predominantly Asian (64% in both arms) with WHO PS of 0 (64% in both arms). The median age (range) was 64 (30–86) years in the osimertinib arm and 62 (31–82) years in the placebo arm.\(^{25}\)

**Adjuvant Chemotherapy Use**

Overall, 410 of 682 patients received adjuvant chemotherapy, which was consistent across the osimertinib (n = 203) and placebo (n = 207) arms (60% in both arms) and received for a median duration of 4.0 cycles (Quartile 1: 4.0, Quartile 3: 4.0). Most patients (409 of 410) received platinum-based chemotherapy, predominantly cisplatin based (n = 275) or carboplatin based (n = 139) (Table 1). One patient received single-agent, non-platinum chemotherapy (pemetrexed) as adjuvant treatment, with an adjunct traditional Chinese medicine (protocol deviation). Of the 466 patients with stages II to IIIA disease, 76% of patients (352 of 466) received adjuvant chemotherapy (stage II = 35% [165 of 466]; stage IIIA = 40% [187 of 466]), compared with 26% of patients (57 of 216) with stage IB disease. Adjuvant chemotherapy use was more frequent in patients aged less than 70 years (338 of 509; 66%) compared with those aged greater than or equal to 70 years (72 of 173; 42%) and in patients enrolled in Asia (268 of 414; 65%; People’s Republic of China, Japan, South Korea, Taiwan, Thailand, and Vietnam) compared with those enrolled outside of Asia (142 of 268; 53%; Europe, Australia, United States, Canada, and Brazil). There seemed to be no difference in adjuvant...
chemotherapy use between patients with WHO PS of 0 (261 of 434; 60%) and WHO PS of 1 (149 of 248; 60%).

**DFS in Patients With and Without Adjuvant Chemotherapy in the Overall Population (Stages IB–IIIA Disease)**

Among the 410 patients in the overall population (stages IB–IIIA disease) who received adjuvant chemotherapy, disease recurrence or death occurred in 125 patients (30% maturity); 22 DFS events were observed in the osimertinib arm (11% maturity) and 103 in the placebo arm (50% maturity) (Fig. 1A). As previously reported, the percentage of patients who were alive and disease-free at 24 months was 89% (95% CI: 83–93) in the osimertinib arm and 58% (95% CI: 49–67) in the placebo arm (overall HR = 0.23, 95% CI: 0.13–0.40), as previously reported (Fig. 1B).25 Median DFS was not reached in the osimertinib arm (95% CI: NC–NC) and 33.1 months in the placebo arm (95% CI: 23–NC; Fig. 1B). The median follow-up for DFS was 22.1 months in the osimertinib arm and 18.2 months in the placebo arm.

**DFS in Patients With and Without Adjuvant Chemotherapy, by Disease Stage**

The DFS benefit with osimertinib was observed consistently, regardless of adjuvant chemotherapy use and disease stage, with DFS HRs ranging between 0.10 and 0.38 (Figs. 2 and 3 and Table 2). For each disease stage, with and without adjuvant chemotherapy, DFS KM curves revealed early separation between the osimertinib and placebo arms (Fig. 3). Among those patients treated with osimertinib versus placebo who received previous adjuvant chemotherapy, 81% (95% CI: 52–94) versus 66% (95% CI: 44–81), 91% (95% CI: 81–96) versus 59% (95% CI: 46–69), and 89% (95% CI: 79–94) versus 33% (95% CI: 22–44) remained alive and disease-free at 24 months in stages IB, II, and IIIA, respectively. Among those patients treated with osimertinib versus placebo who did not receive previous adjuvant chemotherapy, 90% (95% CI: 78–95) versus
74% (95% CI: 60–83), 89% (95% CI: 70–96) versus 47% (95% CI: 26–65), and 86% (95% CI: 55–97) versus 27% (95% CI: 12–45) remained alive and disease-free at 24 months in stages IB, II, and IIIA, respectively.

Discussion

As previously reported, a DFS benefit favoring osimertinib versus placebo was observed in the ADAURA trial (DFS HR = 0.20, 99.12% CI: 0.14–0.30, p < 0.001),
### Table 2. DFS in Patients With and Without Previous Adjuvant Chemotherapy, by Disease Stage

<table>
<thead>
<tr>
<th>Disease stage</th>
<th>Patients Who Received Adjuvant Chemotherapy</th>
<th>Patients Who Did Not Receive Adjuvant Chemotherapy</th>
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<tr>
<td></td>
<td>Osimertinib ( (n = 203) )</td>
<td>Placebo ( (n = 207) )</td>
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<tr>
<td><strong>Stage IB</strong></td>
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<tr>
<td>Total number of patients</td>
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<td>30</td>
</tr>
<tr>
<td>Number (%) of patients with recurrence events</td>
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<td>11 (37)</td>
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<tr>
<td>Percentage of patients alive and disease-free at 24 mo (95% CI)</td>
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<td>66 (44-81)</td>
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<td>48.2 (21-48)</td>
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<td>Hazard ratio (95% CI)</td>
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<td>Total number of patients</td>
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<td>Number (%) of patients with recurrence events</td>
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<td>36 (42)</td>
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<tr>
<td>Percentage of patients alive and disease-free at 24 mo (95% CI)</td>
<td>91 (81-96)</td>
<td>59 (46-69)</td>
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<td>Hazard ratio (95% CI)</td>
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<td><strong>Stage IIIA</strong></td>
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<td>Total number of patients</td>
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<td>Number (%) of patients with recurrence events</td>
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<td>Percentage of patients alive and disease-free at 24 mo (95% CI)</td>
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<td>33 (22-44)</td>
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<td>Median DFS, mo (95% CI)</td>
<td>38.8 (34-NC)</td>
<td>12.9 (11-19)</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.13 (0.06-0.23)</td>
<td></td>
</tr>
</tbody>
</table>


CI, confidence interval; DFS, disease-free survival; NC, not calculable; NR, not reached.

Figure 2. Subgroup analysis of DFS in patients with and without adjuvant chemotherapy, by disease stage. ADAURA data cut-off: January 17, 2020. Performed using a Cox PH model including treatment, subgroup, and a treatment-by-subgroup interaction term. *Subgroup categories with less than 20 events, such as patients with stage IB disease with adjuvant chemotherapy (15 events in total; four patients in the osimertinib arm and 11 patients in the placebo arm) were excluded from the analysis. HR of less than 1 favors osimertinib. CI, confidence interval; DFS, disease-free survival; HR, hazard ratio; PH, proportional hazards.
irrespective of whether patients received previous chemotherapy or not. In this exploratory analysis, we investigated adjuvant chemotherapy use and outcomes in ADAURA. Overall, adjuvant chemotherapy use in ADAURA was broadly in line with uptake observed in previous studies and clinical practice, irrespective of subsequent randomization to either osimertinib or placebo. In the phase 3 RADIANT trial, which compared adjuvant erlotinib versus placebo in patients with stages IB to IIIA NSCLC, uptake of chemotherapy in patients with EGFR mutation was 49%; 45% in the erlotinib arm and 56% in the placebo arm. RADIANT had a slightly higher proportion of patients with EGFRm stage IB disease (47%), compared with stages II (29%) and IIIA (22%). RADIANT also had a larger proportion of patients with stage IB disease (47%), compared with stages II (36%) and IIIA (17%). In ADAURA, which conversely had a larger proportion of patients with stages II (34%) and IIIA (34%) disease, compared with stage IB (32%), the proportion of patients who received previous chemotherapy (60% of patients in both the osimertinib and the placebo arms) was slightly higher than those reported in these studies. This is as expected on the basis of previous real-world evidence, wherein higher disease stage has been found to be associated with increased chemotherapy use.

Chemotherapy use can vary across different geographic regions. It has been previously reported that the proportion of patients with stages IB to IIIA NSCLC who receive adjuvant chemotherapy in clinical practice is 48% across Europe (62% in France, 52% in Germany, and 33% in the United Kingdom) and 57% in the United States. One population-based study reported the uptake of platinum-based adjuvant chemotherapy in East Asia (Taiwan) to be 19% of patients, although these data included patients with stages IA to IIIA NSCLC. In ADAURA, previous adjuvant chemotherapy use was more frequent in patients enrolled in Asia (65%; People’s Republic of China, Japan, South Korea, Taiwan, Thailand, and Vietnam), compared with outside of Asia (53%; Europe, Australia, United States, Canada, and Brazil).

A DFS benefit with osimertinib versus placebo was observed across disease stages IB to IIIA in ADAURA, irrespective of whether patients received previous chemotherapy or not. It should be noted that the
ADAURA trial was not designed to define the optimal role of adjuvant chemotherapy in resected EGFRm NSCLC. Patients were not randomized to compare adjuvant chemotherapy versus adjuvant osimertinib, nor were they stratified by adjuvant chemotherapy use. Hence, we cannot compare efficacy in these two groups within treatment arms. In this respect, the ADAURA trial design differs from previous studies of first-generation EGFR TKIs versus chemotherapy in the resected NSCLC setting. For example, in the phase 3 ADJUVANT/CTONG1104 trial, Chinese patients with completely resected stages II to IIIA (N1–N2) EGFRm NSCLC were randomly assigned to receive either gefitinib or standard vinorelbine plus cisplatin chemotherapy. In the phase 3 IMPACT trial, Japanese patients with completely resected stages II to III EGFRm NSCLC were randomly assigned to receive either gefitinib or vinorelbine plus cisplatin chemotherapy. In the phase 2 EVAN trial, Chinese patients with resected stage IIIA EGFRm NSCLC were randomly assigned to either erlotinib or vinorelbine plus cisplatin chemotherapy. Furthermore, in the phase 3 EVIDENCE trial, patients with completely resected stages II to IIIA EGFRm NSCLC were randomly assigned to either icotinib or vinorelbine plus cisplatin chemotherapy. In ADAURA, delivery of adjuvant chemotherapy was allowed (not mandatory), per physician and patient choice, before randomization. Specific reasons to why patients did not receive adjuvant chemotherapy were not documented but may have included patient decision, age, disease stage, geographic variation, timing after the surgical resection, or patients being deemed clinically unfit.

In ADAURA, higher disease recurrence rates were observed among patients in the placebo arm who received adjuvant chemotherapy, compared with those who did not. This may have been driven by the large proportion of patients with stage II and IIIA disease who received adjuvant chemotherapy in ADAURA, as disease stage is a known prognostic factor for clinical outcome. Although the ADAURA study was not designed to evaluate the efficacy of adjuvant chemotherapy, the ADAURA results do not indicate that chemotherapy is harmful and should not displace the use of adjuvant chemotherapy in the resected NSCLC setting. To date, adjuvant chemotherapy is one of the only treatments that, even if modest, was found to have an overall survival benefit in resected NSCLC. As such, physicians should continue to deliver adjuvant chemotherapy in accordance with guidelines and local practice. As the treatment landscape evolves, future studies designed to understand the role of adjuvant chemotherapy in resected EGFRm NSCLC are required.

Nevertheless, the DFS benefit observed in ADAURA with osimertinib versus placebo across disease stages IB to IIIA, with or without previous chemotherapy, coupled with the favorable tolerability profile previously reported, suggests that adjuvant osimertinib could be an effective treatment option for patients, regardless of adjuvant chemotherapy use. Therefore, these data advocate the need for EGFR mutation testing across all NSCLC disease stages, not only advanced disease, to guide treatment decisions.

Nevertheless, it should be noted that at the current data cutoff, these data are limited by low DFS event numbers and the subgroups of patients with and without chemotherapy at each disease stage were small. Data with a longer duration of follow-up and increased maturity will therefore be of further value once available.

In conclusion, a DFS benefit with osimertinib versus placebo was observed across disease stages IB to IIIA in ADAURA, irrespective of whether patients received previous chemotherapy or not, further supporting adjuvant osimertinib as a highly effective treatment for patients with stages IB to IIIA resected EGFRm NSCLC, with or without adjuvant chemotherapy, as indicated.

CRediT Authorship Contribution Statement

**Yi-Long Wu:** Conceptualization, Investigation, Resources, Writing - review & editing, Visualization, Supervision.

**Thomas John:** Conceptualization, Investigation, Resources, Writing - review & editing, Supervision.

**Christian Grohe:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Writing - original draft, Writing - review & editing, Supervision.

**Margarita Majem:** Validation, Writing - review & editing.

**Jonathan W. Goldman:** Formal analysis, Investigation, Resources, Data curation, Writing - review & editing.

**Sang-We Kim, Terufumi Kato:** Investigation, Resources, Data curation, Writing - review & editing.

**Konstantin Laktionov:** Writing - review & editing.

**Huu Vinh Vu:** Conceptualization, Resources, Data curation.

**Zhijie Wang, Charuwan Akewanlop:** Investigation, Resources, Writing - review & editing.

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