ORIGINAL ARTICLE

Three-Year Safety, Tolerability, and Health-Related Quality of Life Outcomes of Adjuvant Osimertinib in Patients With Resected Stage IB to IIIA EGFR-Mutated NSCLC: Updated Analysis From the Phase 3 ADAURA Trial

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ABSTRACT

Introduction: In ADAURA, adjuvant osimertinib significantly improved disease-free survival versus placebo in resected stage IB to IIIA EGFR-mutated NSCLC. We report in-depth analyses of three-year safety, tolerability, and health-related quality of life (HRQoL) from ADAURA.

Methods: Patients were randomized 1:1 to osimertinib 80 mg or placebo once daily for up to 3 years. Safety assessments were performed at baseline, week 2, week 4, week 12, and every 12 weeks until treatment completion or discontinuation, and 28 days after treatment was stopped. The SF-36 survey measured HRQoL at baseline, week 12, week 24, and every 24 weeks until recurrence, treatment completion or discontinuation. Data cutoff: April 11, 2022.

Results: Safety and HRQoL analysis sets: osimertinib, n = 337 and n = 339; placebo, n = 343 each. Median (range) total exposure duration was longer with osimertinib versus placebo: 35.8 (0–38) versus 25.1 (0–39) months. Most adverse events (AEs) were first reported within 12 months of starting treatment (osimertinib 97%, placebo 86%). AEs leading to dose reduction, interruption or discontinuation were reported in 12%, 27% and 13% respectively of patients with osimertinib; 1%, 13% and 3% with placebo. Stomatitis and diarrhea were the most common AEs leading to osimertinib dose reduction or interruption; interstitial lung disease was the most common leading to osimertinib discontinuation (per protocol). There were no differences in time to deterioration for SF-36 physical, mental component summaries between osimertinib and placebo.

Conclusions: No new safety signals were reported and HRQoL was maintained with 3 years of adjuvant osimertinib treatment. Combined with significant efficacy benefit, these data further support adjuvant osimertinib in stage IB to IIIA EGFR-mutated NSCLC.

Keywords: Osimertinib; Adjuvant; EGFR; Non–small cell lung cancer; Safety

Introduction

Osimertinib is a third-generation EGFR tyrosine kinase inhibitor (TKI) found to have efficacy in EGFR-mutated

(EGFRm) NSCLC, including central nervous system (CNS) metastases.[1–5] On the basis of results from the phase 3 ADAURA study, osimertinib was the first EGFR TKI approved for use as adjuvant treatment for resected stage IB to IIIA EGFRm (*Exon 19* deletion or L858R) NSCLC, with or without prior adjuvant platinum-based chemotherapy, and is the recommended treatment option after surgery.[6,7] Adjuvant osimertinib was found to have a sustained and clinically meaningful disease-free survival (DFS) benefit versus placebo (DFS hazard ratio [HR] = 0.27, 95% confidence interval [CI]: 0.21–0.34) and reduced risk of local and distant recurrence and improved CNS DFS.[8]

Alongside finding an efficacy benefit, it is important for adjuvant treatments to be well tolerated while maintaining health-related quality of life (HRQoL) in patients who, after surgery with curative intent, are disease free and may receive treatment over several years to reduce the risk of disease recurrence.[9–13] Meta-analyses of adjuvant EGFR TKIs have revealed that patients with early stage EGFRm NSCLC treated with EGFR TKIs have a lower risk of adverse events (AEs) and AEs of grade more than or equal to 3, compared with adjuvant chemotherapy, although risk of diarrhea and rash is greater.[14,15] At the ADAURA primary analysis data cutoff (DCO; January 17, 2020; median osimertinib exposure of 22.5 mo), a low frequency of osimertinib dose reductions (9%) and discontinuations (11%) due to AEs were reported. In the placebo group (median exposure of 18.7 mo), dose reductions and discontinuations were reported in 1% and 3% of patients, respectively. No new safety signals were observed[7] compared with the established safety profile of osimertinib in metastatic NSCLC.[2,3,16,17] Interstitial lung disease (ILD), pneumonitis, and cardiac events such as corrected QT (QTc) interval prolongation and cardiomyopathy, have been identified as AEs of special interest for osimertinib; monitoring of these events is recommended during treatment, and is of particular interest in the adjuvant setting, given the long duration of treatment required.[2,3,7,14,16–19] In the ADAURA primary analysis, ILD events, reported in 3% of patients treated with osimertinib (0% with placebo), were grade 1 or 2; all patients recovered. The incidence of cardiac AEs (ejection fraction decrease, cardiac failure, pulmonary edema, and cardiomyopathy) was similar in the osimertinib (5%) and placebo (3%) groups.[7] Furthermore, HRQoL was maintained with adjuvant osimertinib, with no clinically meaningful differences compared with placebo in the Short-Form—36 (SF-36) physical or mental component summary scores from baseline to week 96.[20]

Here, we report in-depth analyses of tolerability and HRQoL from ADAURA, where all patients had the opportunity to complete 3 years of the study treatment.

Materials and Methods

Trial Design and Patients

The ADAURA study methodology has been published previously[7] (Supplementary Methods and Supplementary Fig. 1). The primary end point was investigator-assessed DFS in patients with stage II to IIIA EGFRm NSCLC; safety and HRQoL were key secondary end points. The DCO for these analyses was April 11, 2022.

The trial was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice guidelines, applicable regulatory requirements, and policy on bioethics and human biological samples of the trial sponsor, AstraZeneca. All patients provided written informed consent.

Safety and HRQoL Assessments

Safety assessments were performed at baseline, week 2, week 4, week 12, and every 12 weeks until treatment completion or discontinuation. A final 28-day follow-up visit was performed after the treatment was stopped. AEs were listed using the Medical Dictionary for Regulatory Activities version 24.1 preferred terms, graded by the Common Terminology Criteria for Adverse Events version 4.03 and assessed by the investigator for causal relation to study treatment.

HRQoL was assessed using the SF-36 health survey version 2, third edition,[21] measuring patients' general health status with a recall period of 4 weeks (Supplementary Fig. 2). A generic survey, rather than a cancer-specific one, was chosen; patients were considered cancer free before receiving osimertinib or placebo, per the trial inclusion criteria.[20] The SF-36 collects scores from 36 items across eight health domains and produces two weighted aggregate scores, the physical component summary (PCS) and mental component summary (MCS) scores. SF-36 data were collected at randomization (pre-dose), week 12, week 24, and then every 24 weeks until recurrence, discontinuation or treatment completion (3 y; Supplementary Fig. 2). HRQoL data were collected at the treatment discontinuation visit if a patient discontinued treatment due to disease recurrence or other discontinuation criteria; no subsequent HRQoL data were collected.

Statistical Methods

Safety. Safety data were summarized descriptively from the safety analysis set, defined as all patients who received more than or equal to one dose of the study treatment. Any AE occurring within 28 days of discontinuation of the study treatment and before the start of subsequent anticancer treatment was included in the summaries. An additional safety summary stratified by sex (male versus female) and age ($<$70 y versus $\geq$70 y) was also conducted.

Post hoc longitudinal analyses of common AEs and selected AEs of clinical interest were exploratory. Exploratory analyses of time to onset and duration for individual AEs were also performed, including temporal dynamics of AE first onset in the three-year treatment period. Common AEs included diarrhea, paronychia, dry skin, pruritus, cough, and stomatitis; selected AEs of clinical interest, identified in the primary ADAURA analysis[7] and in previous osimertinib studies in the metastatic setting,[2,3,16,17] included nausea, skin rash, QTc prolongation, fatigue, cardiac effects (grouped term), and ILD (grouped term). Grouped terms are defined in the Supplementary Methods. All reported AEs are Medical Dictionary for Regulatory Activities preferred terms, unless otherwise specified.

HRQoL. HRQoL analyses were performed for the overall patient population (stages IB–IIIA). SF-36 scores were calculated at each scheduled post-baseline visit using a norm-based scoring method resulting in T-scores, as described previously[20,21] (Supplementary Methods).

Time to deterioration (TTD) was defined as time from randomization to the first clinically important worsening, of any cause and confirmed at subsequent assessment, or death, providing that death occurred within two assessment visits from the last HRQoL assessment, and regardless of whether the patient withdrew from the study treatment or received another anticancer treatment before symptom deterioration.[20]

Additional HRQoL methods are reported in the Supplementary Methods.

Results

Patient Demographics and Treatment

From November 2015 to February 2019, a total of 682 patients were randomized to receive osimertinib (n = 339) or placebo (n = 343). Patient demographics and baseline disease characteristics were well balanced between the treatment groups[7] (Supplementary Table 1).

At DCO (April 11, 2022), of the patients who received more than or equal to one dose of the treatment (osimertinib n = 337; placebo n = 343), 222 (66%) and 139 (41%) completed the planned 3 years of treatment in the osimertinib and placebo groups. In total, 114 (34%) and 204 patients (59%) in the osimertinib and placebo groups discontinued the study treatment before the planned three-year treatment duration.

The median (range) total duration of treatment exposure (including any duration of dose interruptions) was longer with osimertinib (35.8 [0–38] mo) versus placebo (25.1 [0–39] mo).[8] Median actual duration of exposure (excludes the duration of dose interruptions due to any reason) was similar to the median total duration of exposure: 35.4 (0–38) months and 25.1 (0–39) months, with osimertinib and placebo. Dose interruptions due to any reasons were reported in 199 (59%) and 153 (45%) patients in the osimertinib and placebo groups, respectively. Dose reductions due to any reasons were reported in 53 (16%) and 3 (1%) patients. Reasons for dose interruptions and reductions are reported in the Supplementary Results.

Safety

Safety Summary. As previously reported, AEs (of any cause) were reported in 330 (98%) and 309 (90%) patients in the osimertinib and placebo groups, respectively (Supplementary Table 2).[8] The most common AEs (of any grade) with osimertinib were diarrhea (n = 159, 47%), paronychia (n = 92, 27%), and dry skin (n = 84, 25%), which were reported in 20% (n = 70), 1% (n = 5), and 7% (n = 23) of patients in the placebo group (Fig. 1*A* and Supplementary Table 3).[8] Of selected AEs of clinical interest, 10% of patients in the osimertinib group reported nausea (n = 34) and skin rash (n = 33) versus 6% (n = 20) and 3% (n = 12) of patients in the placebo group (Fig. 1*B*).

Grade Greater Than or Equal to 3 AEs. Grade greater than or equal to 3 AEs (of any cause) were reported in 79 (23%) and 48 (14%) patients in the osimertinib and placebo groups, respectively (Supplementary Table 2). The most common were diarrhea (n = 9, 3%), stomatitis (n = 6, 2%), pneumonia (n = 4, 1%), and QTc prolongation (n = 4, 1%) in the osimertinib group, which were also reported in one (<1%), zero, four (1%), and one (<1%) patients in the placebo group, respectively.

Causally Related AEs. The most common AEs considered by the investigator to be causally related to osimertinib were diarrhea, paronychia, and dry skin, which occurred in 135 (40%), 85 (25%), and 73 (22%) patients and were also reported in 49 (14%), four (1%), and 16 (5%) patients in the placebo group, respectively (Table 1).

Serious AEs. Serious AEs (SAEs) occurred in 68 (20%) and 47 (14%) patients in the osimertinib and placebo groups, respectively (Supplementary Table 2), most often pneumonia, reported in five patients (1%) in the osimertinib group and in four patients (1%) in the placebo group (Table 2).

AEs Leading to Discontinuation, Dose Interruption, and Dose Reduction. AEs leading to discontinuation were reported in 43 (13%) and nine (3%) patients

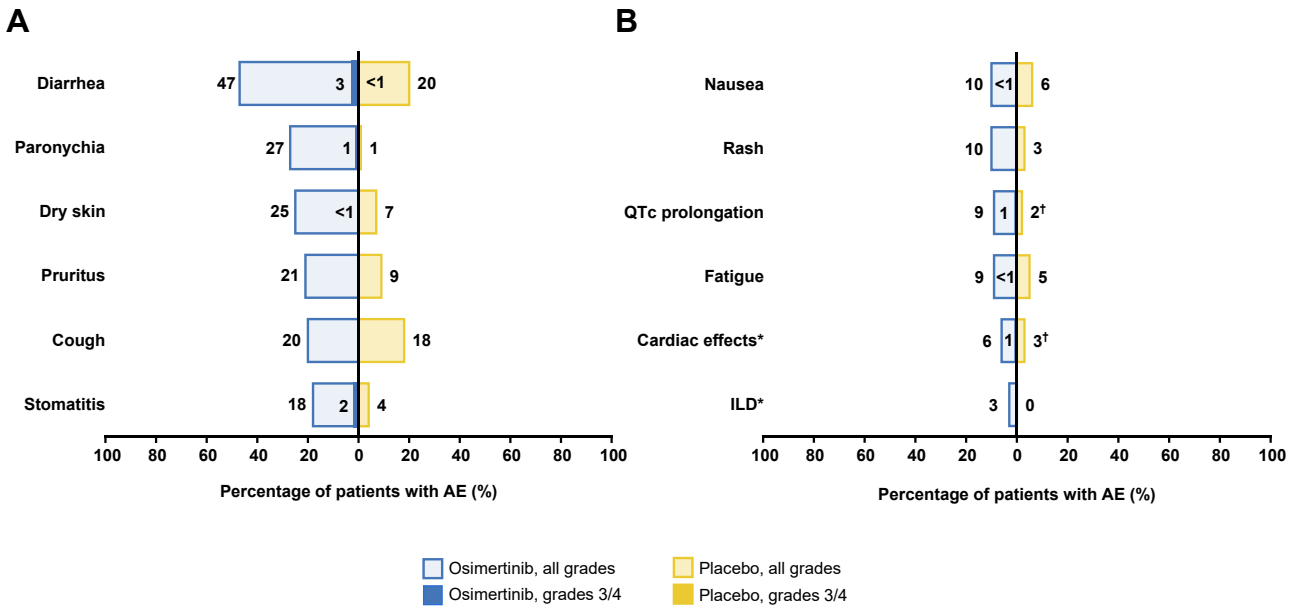

Figure 1. Incidence of (*A*) most common AEs and (*B*) selected AEs of clinical interest. *Grouped terms. ILD (grouped): ILD and pneumonitis; cardiac effects (grouped), including ejection fraction decrease, cardiac failure, pulmonary edema, and cardiomyopathy. †QTc prolongation placebo grades 3 or 4, less than 1%; cardiac effects placebo grades 3 or 4, less than 1%. AEs, adverse events; ILD, interstitial lung disease; QTc, corrected QT interval.

in the osimertinib and placebo groups, respectively (Supplementary Table 2). The most common AE leading to osimertinib discontinuation was ILD (preferred term; n = 8, 2%) (Fig. 2*A*). Per protocol, patients with confirmed ILD or pneumonitis (preferred term) were required to permanently discontinue the study treatment.

Table 1. Most Common Investigator-Assessed Possibly Causally Related AEs Reported in More Than or Equal to 5% of Patients Treated With Osimertinib or Placebo, by Maximum CTCAE Grade

	Osimertinib (n = 337)		Placebo (n = 343)	
AEs	Any Grade n (%)	Grade ≥ 3 n (%)	Any Grade n (%)	Grade ≥ 3 n (%)
Any possibly causally related AE[a]	308 (91)	36 (11)	199 (58)	7 (2)
Diarrhea	135 (40)	7 (2)	49 (14)	1 (<1)
Paronychia	85 (25)	3 (1)	4 (1)	0
Dry skin	73 (22)	1 (<1)	16 (5)	0
Pruritus	62 (18)	0	23 (7)	0
Stomatitis	53 (16)	5 (1)	7 (2)	0
Acneiform dermatitis	36 (11)	0	12 (3)	0
Mouth ulceration	32 (9)	0	7 (2)	0
Decreased appetite	30 (9)	2 (1)	4 (1)	0
QT prolongation	29 (9)	4 (1)	8 (2)	1 (<1)
Rash	28 (8)	0	6 (2)	0
Increased blood creatinine	23 (7)	0	2 (1)	0
Fatigue	23 (7)	1 (<1)	9 (3)	0
Nail disorder	21 (6)	0	2 (1)	0
Decreased neutrophil count	20 (6)	0	1 (<1)	0
Rash maculopapular	20 (6)	0	8 (2)	0
Increased aspartate aminotransferase	18 (5)	0	21 (6)	0
Leukopenia	18 (5)	0	2 (1)	0
Nausea	17 (5)	1 (<1)	4 (1)	0
Increased alanine aminotransferase	16 (5)	0	22 (6)	0

[a]Causally related to any treatment, as assessed by the investigator. Includes AEs with onset date on or after the date of first dose and up to and including 28 days after the discontinuation of study treatment and before starting subsequent cancer treatment.
AE, adverse event; CTCAEs, Common Terminology Criteria for Adverse Events.

Table 2. SAEs Reported in More Than or Equal to Two Patients Treated With Osimertinib or Placebo

SAEs	Osimertinib (n = 337), n (%)	Placebo (n = 343), n (%)
Any[a]	68 (20)	47 (14)
Pneumonia	5 (1)	4 (1)
Hyperuricemia	2 (1)	1 (<1)
Femur fracture	2 (1)	1 (<1)
Diarrhea	2 (1)	0
Influenza	2 (1)	0
Large intestine polyp	2 (1)	0
Cataract	2 (1)	0
Acute kidney injury	2 (1)	0
Ureterolithiasis	2 (1)	0

[a]Includes AEs with onset date on or after the date of first dose and up to and including 28 days after the discontinuation of study treatment and before starting subsequent cancer treatment.
AE, adverse event; SAE, serious adverse event.

The numbers of patients with AEs leading to dose interruption were 91 (27%) and 43 (13%) in the osimertinib and placebo groups, respectively (Supplementary Table 2). The most common AEs leading to interruption with osimertinib were diarrhea (n = 13, 4%) and stomatitis (n = 7, 2%); abdominal pain, gastroenteritis, neutropenia, and vomiting were each reported in four (1%) patients (Fig. 2*B*). With placebo, diarrhea and stomatitis were reported as AEs leading to interruption in four (1%) and zero patients (Fig. 2*B*).

AEs leading to dose reduction were reported in 42 (12%) and three patients (1%) in the osimertinib and placebo groups, respectively (Supplementary Table 2). The most common AEs leading to dose reduction in the osimertinib group were stomatitis (n = 9, 3%), diarrhea (n = 5, 2%), and paronychia (n = 5, 2%), which were reported in zero, one (<1%), and zero patient, respectively, in the placebo group (Fig. 2*C*).

AEs Leading to Death. AEs leading to death occurred in one (<1%; respiratory failure) and two (1%; pulmonary embolism and an unknown fatal event) patients in the osimertinib and placebo groups, respectively (Supplementary Table 2). These events were not considered causally related to the study treatment.

Safety Summary by Sex. In the osimertinib group, there were no differences between male and female patients in the incidence of any-cause AEs (99% [n = 108 of 109] and 97% [n = 222 of 228]) or SAEs (22% [n = 24 of 109] and 19% [n = 44 of 228]); AEs leading to discontinuation (15% [n = 16 of 109] and 12% [n = 27 of 228]) or dose interruption (28% [n = 30 of 109] and 27% [n = 61 of 228]) were also similar. Incidence of AEs of grade greater than or equal to 3 with osimertinib was slightly higher in male versus female patients (27% [n = 29 of 109] versus 22% [n = 50 of 228]). AEs leading to dose reduction with osimertinib were more frequent in female versus male patients (15% [n = 35 of 228] versus 6% [n = 7 of 109]; Supplementary Table 2).

Safety Summary by Age. Rates of AEs, including those causally related to treatment, were generally similar in patients aged below 70 years versus above or equal to 70 years in both treatment groups (Supplementary Table 4). With osimertinib, patients aged above or equal to 70 years had an increased incidence of all-cause SAEs and AEs leading to dose interruptions, reductions, or discontinuations (32% [n = 28 of 87], 39% [n = 34 of 87], 16% [n = 14 of 87], 22% [n = 19 of 87]) compared with patients aged below 70 years (16% [n = 40 of 250], 23% [n = 57 of 250], 11% [n = 28 of 250], 10% [n = 24 of 250]). Patients aged above or equal to 70 years receiving osimertinib had an increased incidence of SAEs, AEs leading to dose interruptions, and AEs leading to discontinuations possibly causally related to treatment (6% [n = 5 of 87], 24% [n = 21 of 87], and 15% [n = 13 of 87]) compared with patients aged below 70 years (2% [n = 5 of 250], 11% [n = 28 of 250], and 9% [n = 22 of 250]; Supplementary Table 4).

Time to Onset and Duration of Most Common AEs and Selected AEs of Clinical Interest. Overall, most AEs were first reported within 12 months of the starting treatment (osimertinib, n = 326 of 330 [99%]; placebo, n = 294 of 309 [95%]) (Fig. 3 and Supplementary Fig. 3*A*). There was no evidence of late emergent AEs in either group (Fig. 3). Across the first 12 months, most AEs were first reported within one month of starting treatment (osimertinib, n = 260 [77%]; placebo, n = 188 [55%]) (Supplementary Fig. 3*B*). Nevertheless, the time period in which most paronychia events were reported in the osimertinib group was 3 to 6 months after the treatment initiation (n = 20, 6%). The median duration of any AEs was longer with osimertinib than placebo treatment (2773 versus 1550 d, cumulative duration for any AEs); median duration of most common AEs and AEs of clinical interest ranged from 40 to 735 days with osimertinib and from zero to 734 days with placebo (Fig. 3). Median time to first onset for any AEs was shorter with osimertinib versus placebo (13 d versus 22 d); median time to onset for most common AEs and AEs of clinical interest ranged from 16 to 421 days with osimertinib and not calculable to 670 days with placebo (Fig. 3).

ILD. ILD (grouped term, including ILD and pneumonitis) was reported in 11 patients (3%) in the osimertinib group (preferred terms: ILD, n = 8; pneumonitis, n = 3) and no patient in the placebo group.[8] For ILD (grouped

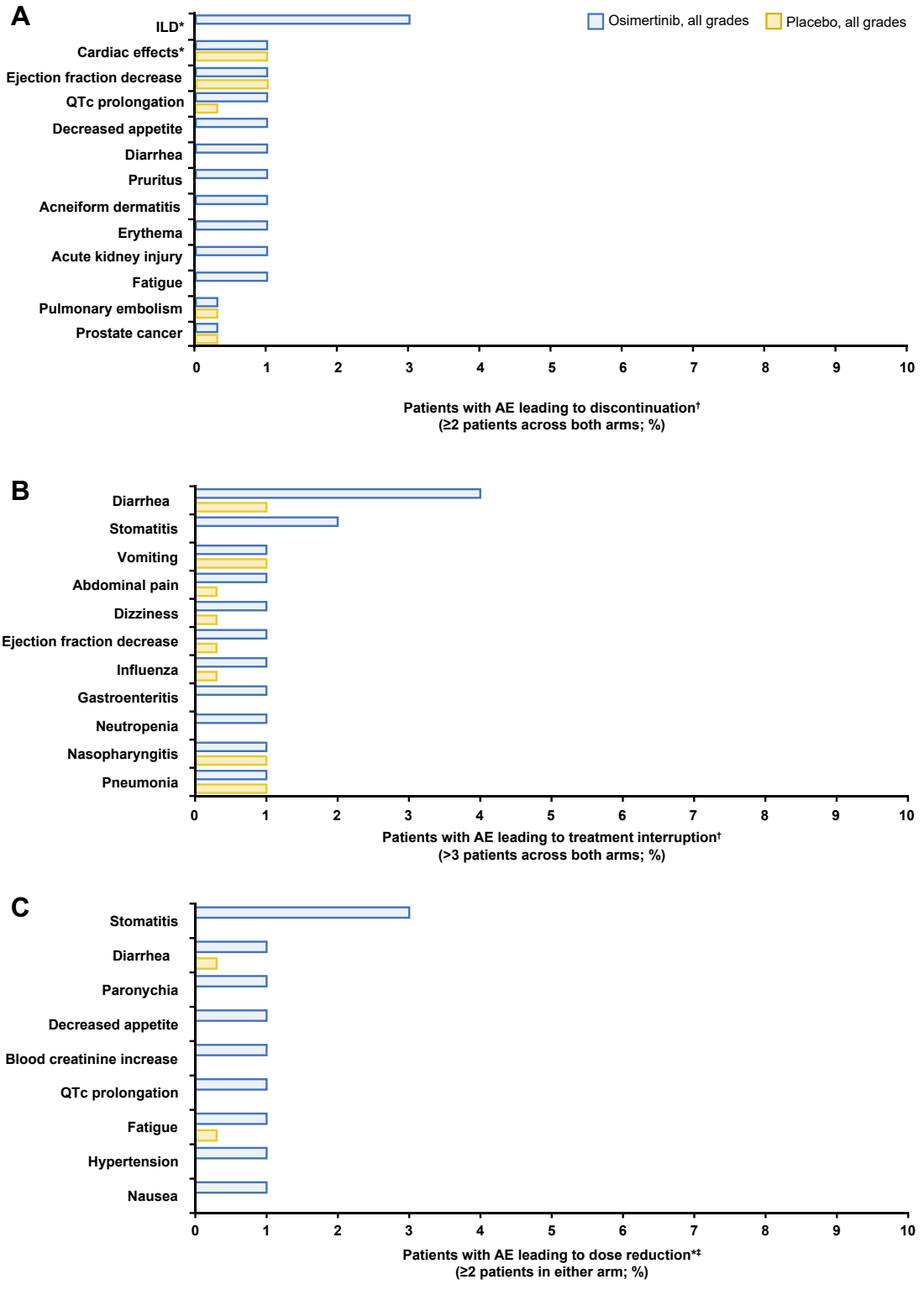

Figure 2. Incidence of AEs leading to (*A*) treatment discontinuation (≥2 patients across both groups); (*B*) treatment interruption (>3 patients across both groups); and (*C*) dose reduction (≥2 patients in either group). *Grouped terms. ILD (grouped): ILD and pneumonitis; cardiac effects (grouped), including ejection fraction decrease, cardiac failure, pulmonary edema, and cardiomyopathy. Per protocol toxicity guidelines, patients with confirmed ILD or pneumonitis were required to permanently discontinue study treatment. †Any causality. Patients with multiple events in the same category counted only once in that category. Patients with events in more than one category counted once in each of those categories. ‡Per protocol, patients were only allowed one dose reduction (from 80 to 40 mg). AEs, adverse events; ILD, interstitial lung disease; QTc, corrected QT interval.

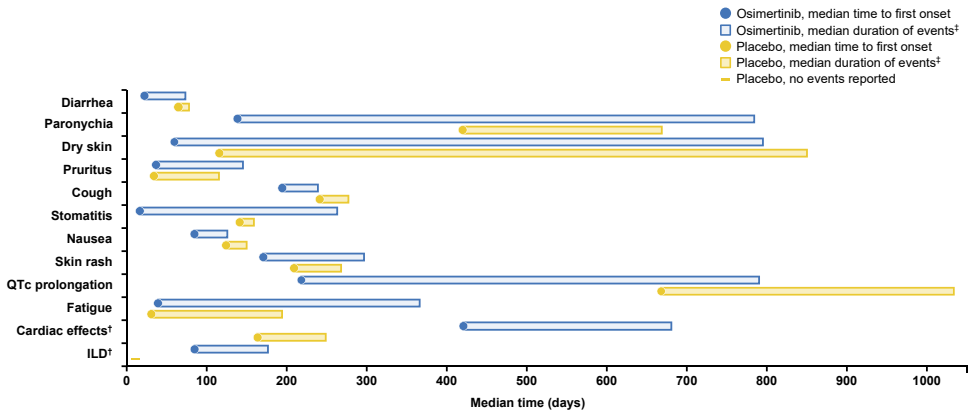

Figure 3. Median time to onset and duration of most common AEs and AEs of special interest. Includes AEs with an onset date on or after the date of first dose and up to and including 28 days after discontinuation of randomized treatment, on or before starting subsequent cancer treatment. †Grouped terms. ILD (grouped): ILD and pneumonitis; cardiac effects (grouped): including ejection fraction decrease, cardiac failure, pulmonary edema, and cardiomyopathy. ‡If an AE occurred more than once, then the total duration was used to calculate the median. AE, adverse event; ILD, interstitial lung disease; QTc, corrected QT interval.

term), median time to onset was 84 (range: 56–1002) days and median duration was 92 (range: 8–295) days. ILD was most frequently reported in patients from Japan (Japan, n = 6; Russia, n = 2; Canada, n = 1; People's Republic of China, n = 1; Taiwan, n = 1). All ILD events (grouped term) were mild to moderate in severity (grade 1, n = 6; grade 2, n = 5). Nine of 11 patients with ILD (grouped term) discontinued osimertinib treatment on the basis of toxicity management guidelines, whereas the two patients with non-causally related events of pneumonitis (preferred term) continued osimertinib. All 11 patients with ILD (grouped term) were reported to have recovered, as determined by investigator assessment.

Cardiac Events. Cardiac effects (grouped term, including ejection fraction decrease, cardiac failure, pulmonary edema, and cardiomyopathy) were reported in 19 (6%) and nine (3%) patients in the osimertinib and placebo groups, respectively. Most patients had grade 1 or 2 events (osimertinib, n = 15; placebo, n = 8); five patients had grade 3 events (osimertinib, n = 4; placebo, n = 1). Ejection fraction decrease was the most frequent cardiac effect reported (osimertinib, n = 15; placebo, n = 9), which led to discontinuation for five patients (osimertinib, n = 2; placebo, n = 3). Most patients with cardiac effects had recovered or were recovering by DCO. See Supplementary Table 5 for exposure-adjusted incidence of ejection fraction decrease.

QTc prolongation was reported in 30 patients (9%) in the osimertinib group and eight patients (2%) in the placebo group and was predominantly grade 1 or 2 in severity (osimertinib, n = 26 [8%]; placebo, n = 7 [2%]); five patients reported grade 3 events (osimertinib, n = 4 [1%]; placebo, n = 1 [<1%]). Five patients discontinued the study treatment due to QTc prolongation (osimertinib, n = 4 [1%], placebo, n = 1 [<1%]); all patients had recovered by DCO. One AE of arrhythmia supraventricular was reported in the osimertinib group, leading to discontinuation; the patient recovered and did not report subsequent cardiac arrhythmias.

HRQoL. All randomized patients were included in HRQoL analyses, and compliance rates were high across time points in both groups (baseline: 93% [n = 314 of 338] and 93% [n = 316 of 341]; week 156: 87% [n = 193 of 221] and 80% [n = 110 of 137]; discontinuation: 73% [n = 82 of 112] and 74% [n = 147 of 198] in the osimertinib and placebo groups, respectively; Supplementary Fig. 4). Baseline SF-36 T-scores were similar between osimertinib and placebo, published previously.[20] SF-36 PCS and MCS mean absolute T-scores followed a similar pattern over time with osimertinib and placebo: for PCS, mean scores ranged from 47 to 50 points with osimertinib and from 46 to 50 points with placebo; for MCS, mean scores ranged from 43 to 50 points with osimertinib and from 44 to 51 points with placebo (Supplementary Fig. 5*A* and *B*). Differences in SF-36 PCS between osimertinib and placebo were minimal at all time points, including at the treatment discontinuation visit (<1.5 points). Differences of less than 3 points were observed across time points for SF-36 MCS. Most patients in both groups remained stable or had improvements in SF-36 PCS and MCS T-scores up to week 156, compared with baseline. On the basis of definitions from the SF-36 third edition scoring manual, there were no clinically meaningful changes from baseline in mean SF-36 PCS or MCS T-scores in either group (Fig. 4*A* and *B*).

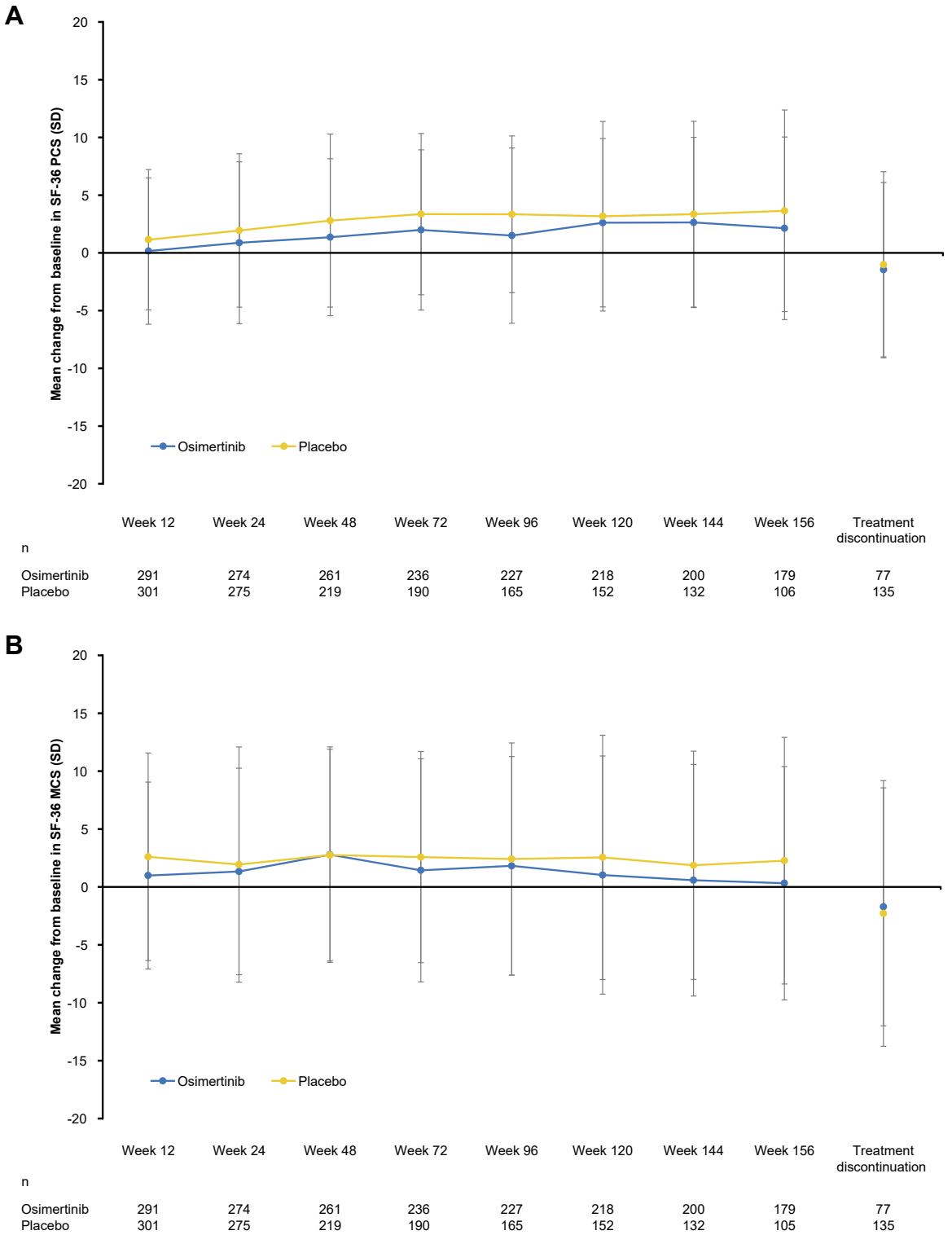

Figure 4. Change in (*A*) SF-36 PCS and (*B*) MCS T-scores from baseline to week 156 and at treatment discontinuation in the overall population. The data illustrated are mean change from baseline in T-scores with error bars representing the SDs. The number of patients with data available at each visit is found below each time point. The treatment discontinuation visit is used only in case of premature discontinuation and happens at different times for each patient. MCS, mental component summary; PCS, physical component summary; SF-36, Short-Form—36 health survey.

In the TTD analyses, 260 (77%) and 271 (79%) patients in the osimertinib and placebo groups did not experience a clinically meaningful deterioration in the PCS or death; 253 (75%) and 259 (76%) patients did not experience a clinically meaningful deterioration in the MCS or death, respectively. In patients who did experience deterioration, there were no differences in TTD of the PCS (HR = 1.00, 95% CI: 0.73–1.39) or MCS (HR = 0.88, 95% CI: 0.64–1.19) between osimertinib and placebo.

Discussion

A key goal of long-term adjuvant treatment is to improve efficacy outcomes with good tolerability and maintained HRQoL.[10–13,22] Here, we report in-depth analyses of long-term tolerability and HRQoL outcomes of an EGFR TKI versus placebo, from the global, phase 3 ADAURA trial.

No new safety concerns were identified after three-year exposure to osimertinib, despite prolonged treatment (median total exposure of 35.8 mo), indicating that this treatment duration had minimal effect on the overall safety and tolerability profile of osimertinib. Most AEs were nonserious, mild, or moderate in severity, and there was no evidence of late-emergent AEs with continued treatment during the three-year period. Overall rates of AEs leading to dose reductions, interruptions, and discontinuations with osimertinib treatment were 12%, 27%, and 13%, respectively, and remained consistent with the primary analysis (9%, 24%, and 11%).[7] The incidences of most common AEs observed with osimertinib were similar to data reported in the primary analysis. Rates of grade more than or equal to 3 AEs and SAEs reported in the osimertinib group (23% and 20%) were also consistent with the primary analysis (20% and 16%).[7] Incidences of most common AEs, grade more than or equal to 3 AEs, and SAEs with osimertinib were similar or lower than data reported in EGFRm advanced NSCLC (FLAURA and AURA3 studies), despite longer median duration of treatment exposure (FLAURA: 20.7 mo; AURA3: 13.8 mo).[3,16]

In ADAURA, median total duration of treatment exposure for osimertinib was similar to median actual duration of exposure (35.8 mo versus 35.4 mo) and was 10 months longer than placebo (25.1 mo for total and actual exposure), indicating little impact of frequency and duration of dose interruptions. Unsurprisingly, median duration of AEs (any AEs, most common AEs and AEs of clinical interest) was longer with osimertinib than placebo, whereas median time to onset of AEs was shorter with osimertinib than with placebo.

The three-year treatment duration in ADAURA is the longest reported in the adjuvant EGFRm NSCLC setting, with other EGFR TKI phase 3 trials reporting efficacy and safety results after 2 years of treatment.[9,23] In ADAURA, the most common AEs reported with osimertinib were diarrhea (47%), paronychia (27%), dry skin (25%), pruritus (21%), cough (20%), and stomatitis (18%). These were also reported among the most common AEs in a subgroup of patients with stage IB to IIIA EGFRm NSCLC (n = 102), receiving 2 years of adjuvant erlotinib in the phase 3 RADIANT study (62%, 13%, 23%, 44%, 27%, and 17% of patients).[23] With adjuvant erlotinib, AEs leading to dose reduction or treatment interruption were reported in 22% of patients, and median treatment duration was 21.2 months in the EGFRm subgroup.[23] In the phase 3 ADJUVANT (CTONG1104) study of two-year adjuvant gefitinib treatment, rates of diarrhea and cough were 26% and 10% in Chinese patients with stages II to IIIA EGFRm NSCLC (n = 106).[9] Median treatment duration of adjuvant gefitinib was 21.9 months.[9] In the phase 3 IMPACT study of two-year adjuvant gefitinib treatment, incidence of diarrhea, rash, and paronychia was 65%, 38%, and 46%, in Japanese patients with stages II to IIIA EGFRm NSCLC (n = 115), respectively.[24]

The incidence of ILD (grouped term) with osimertinib in ADAURA was low (3%) and consistent with that of the primary analysis (3%),[7] and in EGFRm advanced NSCLC studies (FLAURA: 4%; AURA3: 5%).[3,16] In the osimertinib and placebo groups, rates of cardiac effects (grouped term; 6% and 3%), including ejection fraction decrease (4% and 3%) and QTc prolongation (9% and 2%), were consistent with the ADAURA primary analysis (cardiac effects: 5% and 3% with osimertinib and placebo) and the FLAURA study (ejection fraction decrease: 5% and 2% in the osimertinib and comparator groups; QTc prolongation: 10% and 4%).[3,7]

Incidence of grade more than or equal to 3 AEs was slightly higher in male versus female patients (27% versus 22%), and AEs leading to dose reduction were more frequent in female versus male patients (15% versus 6%). Nevertheless, patient numbers in each subgroup were small and data should be interpreted with caution. These differences may have several possible explanations, including that patients in ADAURA were administered the same treatment dose, regardless of sex, age, and weight; alternatively, they could be due to biological differences between sexes or to outliers, due to some patients reporting higher incidence of AEs than the rest of the subgroup. An analysis of treatment-related AEs by sex in phase 2/3 SWOG cancer trials (N = 23,296 patients) revealed a 34% increase in the risk of severe AEs in women versus men receiving immunotherapy, targeted treatment, or chemotherapy, and there was a 25% increased risk in women versus men receiving targeted treatment.[25] The authors concluded

that these differences may be due to pharmacogenomics of drug metabolism and disposition, total dose received, and adherence to treatment.[25]

Previously, there have been few reports of safety data by age in EGFR TKI phase 3 trials. In ADAURA, no unexpected safety signals related to age were observed. Patients aged above or equal to 70 years experienced an increased incidence of SAEs and AEs leading to dose interruptions or discontinuations, compared with patients aged below 70 years. Nevertheless, caution should be observed when interpreting these data due to small patient numbers in some subgroups.

Updated HRQoL outcomes assessed with the SF-36 health survey (up to week 156) were consistent with those observed in the initial ADAURA HRQoL analysis (up to week 96),[20] revealing that HRQoL was maintained with adjuvant osimertinib. In the ADAURA primary analysis, SF-36 PCS and MCS were maintained from baseline up to week 96 in the osimertinib group, with no clinically meaningful differences compared with the placebo group. There were also no differences in TTD of the PCS (HR = 1.17, 95% CI: 0.82–1.67) or MCS (HR = 0.98, 95% CI: 0.70–1.39) between the osimertinib and placebo groups.[20] Updated HRQoL analyses reported here reveal that most patients in both treatment groups remained stable or had improvements in SF-36 PCS and MCS T-scores up to week 156, compared with baseline, and there were no differences in TTD of the PCS or MCS between the treatment groups.

The lack of HRQoL data after disease recurrence or treatment completion could be considered a limitation of this study because the impact of recurrence on HRQoL was not measured. It was also not possible to measure specifically the impact of CNS metastases on HRQoL. Although some of these post hoc safety analyses were exploratory in nature, it is reassuring that the 3-year safety profile of adjuvant osimertinib was consistent with the known profile reported in the ADAURA primary analysis and metastatic setting[3,7,16] and that updated HRQoL results were consistent with those reported in the primary analysis.

In summary, this consistent long-term safety profile, with no evidence of late-emergent AEs and a maintained HRQoL over prolonged exposure, together with a sustained DFS benefit,[8] supports 3 years of adjuvant osimertinib treatment for stages IB to IIIA EGFRm NSCLC.

Credit Authorship Contribution Statement

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Data Sharing Statement

Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data-sharing policy described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure.

Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org and at https://doi.org/10.1016/j.jtho.2023.05.015.

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