ORIGINAL ARTICLE

Clinical Outcomes of Maintenance Durvalumab After Definitive Concurrent Chemoradiotherapy in Unresectable Locally Advanced Stage III NSCLC According to EGFR and ALK Status: Korean Cancer Study Group LU-22-18

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ABSTRACT

Introduction: The role of maintenance durvalumab after definitive concurrent chemoradiotherapy (CCRT) in unresectable locally advanced NSCLC with *EGFR* mutation or *ALK* translocation remains unclear. We compared the effectiveness of durvalumab maintenance therapy in groups with *EGFR* and *ALK* wild-type versus those with *EGFR* or *ALK* mutations.

Methods: In this retrospective multicenter observational study, patients with locally advanced NSCLC without progression after CCRT followed by maintenance durvalumab and available molecular test results (*EGFR* and *ALK*) were eligible. The primary objective was to compare progression-free survival (PFS) between *EGFR* and *ALK* wild-type and *EGFR* or *ALK* mutant NSCLC. Secondary objectives include overall survival according to *EGFR* or *ALK* mutation and programmed death-ligand 1 (PD-L1) expression.

Results: Among 339 patients, 279 had wild-type *EGFR/ALK*, 41 had *EGFR* mutations and 19 had *ALK* translocations. The median age was 68 years with 276 male individuals (81.4%) and 63 female individuals (18.6%), 165 (49.3%) had adenocarcinoma, 149 (44.5%) had squamous cell carcinoma, and 21 (6.3%) had other histologic types, 120 (35.4%) had stage IIIA, 168 (49.6%) stage IIIB, and 51 (15.0%) had stage IIIC. Most of the patients (n = 288, 85%) achieved partial response to CCRT, two (0.6%) had a complete response, and 49 patients (14.4%) had stable disease. Excluding four patients with unknown PD-L1 tumor proportion score (TPS), 16 (4.8%) had a PD-L1 TPS of 0, 168 (50.1%) had 1 to 49, and 151 (45.1%) had 50 or higher. The median PFS was 21.4 months (95% confidence interval [CI]: 17.3–25.3) for the EGFR/ALK wild-type group and 21.0 months (95% CI: 15.7–not available [NA]) for the *EGFR* or *ALK* mutant group with no difference ($p = 0.74$). Significant differences occurred in PFS on the basis of PD-L1 expression with values of 13.6 (95% CI: 10.5–NA), 18.7 (95% CI: 15.1–26.9), and 24.7 (95% CI: 20.7–NA) months for TPS of 0, 1–49, and 50 or higher, respectively ($p = 0.02$).

Conclusions: Durvalumab maintenance therapy after definitive CCRT in unresectable locally advanced NSCLC patients with *EGFR* or *ALK* mutation demonstrates comparable clinical outcomes to those with wild-type *EGFR/ALK* when PD-L1 expression is present.

Keywords: Unresectable locally advanced non–small cell lung cancer; Durvalumab; Definitive CCRT; EGFR; ALK

Introduction

Patients with unresectable locally advanced stage III NSCLC characterized by a good performance status traditionally undergo platinum-based definitive concurrent chemoradiotherapy (CCRT) as the standard treatment.[1] Nevertheless, the median progression-free survival (PFS) with definitive CCRT alone is limited to approximately eight months, and the five-year survival rate remains at 15%.[2,3] The PACIFIC trial (NCT03519971) was designed in response to the consistent benefits obtained with immune checkpoint inhibitors in NSCLC. This trial incorporates the use of durvalumab, an anti–programmed death-ligand 1 (PD-L1) antibody, as maintenance therapy after definitive CCRT.[4–12] In the trial, the median PFS was 16.8 months (95% confidence interval [CI]: 13.0–18.1) with durvalumab versus 5.6 months (95% CI: 4.6–7.8) with placebo (hazard ratio [HR] = 0.52, 95% CI: 0.42–0.65). Furthermore, maintenance durvalumab significantly improved overall survival (OS) and increased five-year OS rates estimated as 42.9% for durvalumab versus 33.4% for placebo (stratified HR = 0.72, 95% CI: 0.59–0.89),[13–17] leading to the development of the standard of care for unresectable locally advanced stage III NSCLC.[16]

Nevertheless, the benefit of maintenance durvalumab in patients with *EGFR* or *ALK* alterations is not well characterized with limited data available. In a subgroup analysis of the PACIFIC trial, five-year OS for patients with *EGFR* mutations who received maintenance durvalumab did not reveal significant benefits (HR = 0.85, 95% CI: 0.37–1.97).[15–17] Given there were only 29 patients with *EGFR* mutations, the findings with this small sample size should be interpreted with caution and warrant further investigation. Nevertheless, maintenance durvalumab has been approved in all cases regardless of *EGFR* mutation status. Cumulative evidence suggests that the benefit of immune checkpoint inhibitors in NSCLC patients with *EGFR* mutations is very limited.[18–20] This issue is particularly relevant in East Asia, where the prevalence of *EGFR* mutation is higher than in Western populations.[21,22]

In this study, we aimed to investigate the benefit of maintenance durvalumab in unresectable locally advanced stage III patients with NSCLC with *EGFR* or *ALK* mutations.

Materials and Methods

Patient Selection and Data Collection

This study was designed as a multicenter retrospective observational study. We collected data from April 2020 to March 2023, encompassing the period during which reimbursement for maintenance durvalumab was

applicable. Notably, in Korea, only patients with a PD-L1 tumor proportion score (TPS) of 1 or higher are eligible for reimbursement by regulatory authorities for definitive CCRT followed by durvalumab regardless of *EGFR* or *ALK* mutation status. A total of 516 patients from 13 institutions in Korea were enrolled through the Korean Cancer Study Group. All patients had undergone a minimum of two cycles of platinum-based chemotherapy with concurrent radiotherapy and reported no evidence of disease progression after definitive CCRT. The patients were initially categorized on the basis of staging, resulting in 501 individuals. Following the PACIFIC trial protocol, we further segregated patients who underwent four or more cycles of maintenance durvalumab, resulting in 438 patients. As the primary objective of our study was to investigate survival outcomes on the basis of biomarkers, we specifically selected patients who underwent analysis for both *EGFR* and *ALK*. Ultimately, a total of 339 patients were included in the final analysis (Supplementary Fig. 1). Clinical data were obtained from the electronic medical record database.

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki (as revised in 2013) and the Korea Good Clinical Practice guidelines. This study was approved by the institutional review board (IRB) at Samsung Medical Center (IRB number 2022-09-136), and individual consent for this analysis was waived. Patients in the database were identified by patient number only, with personally identifiable information kept confidential according to the IRB protocol.

Definition of Variables and Outcomes

We collected patient demographics such as age, sex, Eastern Cooperative Oncology Group performance score, smoking history, pathology, stage at the time of diagnosis, date of diagnosis, date of death, duration of disease progression, or the date of the last visit. Response Evaluation Criteria in Solid Tumors version 1.1 was used for the response evaluation. In the *EGFR* mutation test, the methods used were as follows: CancerSCAN (Twist Biosciences, CA), Trusight Oncology 500 (Illumina, San Diego, CA), next-generation sequencing tools, real-time polymerase chain reaction (PANAMutyper EGFR kit; Panagene Inc., Daejeon, Republic of Korea), and GenesWell droplet digital polymerase chain reaction–based EGFR mutation test (IUO version 5.2. Gencurix Inc., Seoul, Republic of Korea). For the detection of ALK alterations, we used the Ventana ALK (D5F3) Companion Diagnostics assay (Ventana; recently developed by Roche Diagnostics). The determination of the PD-L1 expression by TPS was done on the basis of results from the Ventana PD-L1 (SP263) assay (Ventana Medical Systems, Tucson, AZ). The PD-L1 TPS was divided into 0, 1 to 49, and 50 to 100 groups. The data we collected included the regimen of definitive CCRT, the duration of CCRT, and the interval between CCRT and maintenance durvalumab. Adverse events were reported on the basis of Common Terminology Criteria for Adverse Event version 5.0 using electronic medical records, and in cases of disease recurrence, the location of recurrent organs was examined.

The primary objective was to compare PFS between *EGFR* and *ALK* wild-type and *EGFR* or *ALK* mutant NSCLC. PFS was defined as the time from the initiation of maintenance durvalumab to the date of disease progression, the date of the last visit, or the date of any cause of death. Secondary objectives include OS according to biomarkers such as *EGFR* or *ALK* mutations and PD-L1 expression. OS was defined as the time from the initiation of maintenance durvalumab to the date of death or the date of the last visit.

Statistical Analysis

To ensure adequate statistical power, we calculated the initial target sample size. With a type 1 error of 0.05 and a Type 2 error of 0.2, assuming a 15% proportion of *EGFR* mutant patients, a 5% proportion of *ALK* mutant patients, and an 80% proportion of *EGFR* wild-type patients,[23] we referenced data from the PACIFIC trial to estimate a relative hazard of 1.6.[14] To achieve an 80% power, a sample size of 222 was determined. The sample size in our analysis was 339, confirming that the analyzed data possessed sufficient statistical power.

To analyze patient characteristics, we divided the cohort into *EGFR* and *ALK* wild-type, *EGFR* mutant, and *ALK* mutant groups. For each characteristic, we compared the composition differences between the two groups using the chi-square test. Data are presented as a number (frequency as percentage), and in cases where characteristics were unknown, they were designated as "unknown" and not included in the frequency calculation. For PFS and OS analysis, we used the Kaplan-Meier method. The Kaplan-Meier method enabled the analysis of median PFS and median OS, along with the determination of their respective 95% CIs. When comparing the two groups, we used the log-rank test. To assess the impact of each variable on PFS, we conducted the analysis using Cox proportional hazard regression. When conducting Cox proportional hazard regression analysis, patients with unknown characteristics were excluded from the analysis. Two-sided tests were performed for all p values, and statistical significance was defined as having a p value of less than 0.05. All statistical analyses were performed using R version 4.2.2.

Table 1. Baseline Characteristics

Clinical Characteristics	EGFR and ALKwt (n = 279)	EGFRm (n = 41)	ALKm (n = 19)
Median age (range)	68 (19-88)	67 (44-81)	57 (34-80)
Age <65 y	90 (32.3)	18 (43.9)	14 (73.7)
Age ≥65 y	189 (67.7)	23 (56.1)	5 (26.3)
Sex			
Male	247 (88.5)	17 (41.5)	12 (63.2)
Female	32 (11.5)	24 (58.5)	7 (36.8)
ECOG performance status			
0-1	269 (96.4)	41 (100)	19 (100)
2-3	9 (3.6)	0 (0)	0 (0)
Not evaluated	1	0	0
Tumor histologic type			
Adenocarcinoma	113 (41.1)	37 (90.2)	15 (78.9)
Squamous cell carcinoma	142 (51.6)	4 (9.8)	3 (15.8)
Others[a]	20 (7.3)	0 (0)	1 (5.3)
Unknown	4	0	0
Smoking status			
Never smoker	30 (11.2)	23 (56.1)	10 (55.6)
Ex/current smoker	238 (88.8)	18 (43.9)	8 (44.4)
Unknown	11	0	1
Disease stage			
Stage IIIa	105 (37.6)	12 (29.2)	3 (15.8)
Stage IIIb	132 (47.3)	25 (61.0)	11 (57.9)
Stage IIIc	42 (15.1)	4 (9.8)	5 (26.3)
Response to CCRT			
Complete remission	1 (0.4)	1 (2.4)	0 (0)
Partial response	238 (85.3)	34 (83.0)	16 (84.2)
Stable disease	40 (14.3)	6 (14.6)	3 (15.8)
Progressive disease	0 (0)	0 (0)	0 (0)
PD-L1 TPS (SP263 assay)			
0	11 (4.0)	2 (5.0)	3 (15.8)
1-49	136 (49.3)	22 (55.0)	10 (52.6)
50-100	129 (46.7)	16 (40.0)	6 (31.6)
Unknown	3	1	0
Interval of CCRT to durvalumab			
1-14 d	33 (11.8)	3 (7.3)	3 (15.8)
>14 d	246 (88.2)	38 (92.7)	16 (84.2)
Chemotherapy regimen during CCRT			
Weekly paclitaxel + carboplatin	157 (56.3)	23 (56.1)	5 (26.3)
Weekly paclitaxel + cisplatin	85 (30.5)	11 (26.8)	6 (31.5)
Pemetrexed + carboplatin	17 (6.0)	4 (9.8)	4 (21.1)
Pemetrexed + cisplatin	14 (5.0)	3 (7.3)	4 (21.1)
Weekly vinorelbine + carboplatin	3 (1.1)	0 (0)	0 (0)
Weekly carboplatin	2 (0.7)	0 (0)	0 (0)
Etoposide + carboplatin	1 (0.4)	0 (0)	0 (0)

Note: All values are n (%) unless otherwise specified.
[a]Others included large cell lung carcinoma, NUT carcinoma, poorly differentiated carcinoma, sarcomatoid carcinoma, lung cancer not otherwise specified.
CCRT, concurrent chemoradiotherapy; ECOG, Eastern Cooperative Oncology Group; m, mutation; NUT, nuclear protein in testis; PD-L1, programmed death-ligand-1; TPS, tumor proportional score; wt, wild-type.

Results

Characteristics of the Study Population

A total of 339 patients were analyzed. Patients were categorized into *EGFR/ALK* wild-type (n = 279), *EGFR* mutant (n = 41), and *ALK* mutant (n = 19) groups (Table 1). The median ages were 68 years in the *EGFR/ALK* wild-type group, 67 years in the *EGFR* mutant group, and 57 years in the *ALK* mutant group. In the *EGFR/ALK* wild-type group, there were 247 male patients (88.5%) and 32 female patients (11.5%). In contrast, the *EGFR* mutant group consisted of 17 male individuals (41.5%) and 24 female individuals (58.5%), and the *ALK* mutant group had 12 male individuals (63.2%) and seven female individuals (36.8%). The histologic distribution in the *EGFR/ALK* wild-type group included adenocarcinoma in

113 patients (41.1%), squamous cell carcinoma in 142 patients (51.6%), and other histologies, including large cell lung carcinoma, nuclear protein in testis carcinoma, poorly differentiated carcinoma, sarcomatoid carcinoma, and lung cancer not otherwise specified, in 20 patients (7.3%). In the *EGFR* mutant group, adenocarcinoma was the most common in 37 patients (90.2%) followed by squamous cell carcinoma in four patients (9.8%), and in the *ALK* mutant group, adenocarcinoma was present in 15 patients (78.9%), squamous cell carcinoma in three patient (15.8%), and other histologies in one patient (5.3%). By stage, in the *EGFR* and *ALK* wild-type group, there were 105 patients (37.6%) with stage IIIA, 132 patients (47.3%) with stage IIIB, and 42 patients (15.1%) with stage IIIC. In the *EGFR* mutant group, 12 patients (29.2%) were in stage IIIA, 25 patients (61.0%) were in stage IIIB, and four patients (9.8%) were in stage IIIC. In the *ALK* mutant group, three patients (15.8%) were in stage IIIA, 11 patients (57.9%) were in stage IIIB, and five patients (26.3%) were in stage IIIC. In the study population, 85% of patients achieved a partial response to CCRT. In the *EGFR/ALK* wild-type group, there were 11 patients (4.0%) with a PD-L1 TPS of 0, 136 patients (49.3%) with a PD-L1 TPS of 1 to 49, and 129 patients (46.7%) with a PD-L1 TPS with 50 or higher. In the *EGFR* mutant group, there were two patients (5.0%) with a PD-L1 TPS of 0, 22 patients (55.0%) with a PD-L1 TPS of 1 to 49, and 16 patients (40.0%) with a PD-L1 TPS of 50 or higher. In the *ALK* mutant group, three patients (15.8%) had a PD-L1 TPS of 0, 10 patients (52.6%) had a PD-L1 TPS of 1 to 49, and six patients (31.6%) had a PD-L1 TPS of 50 or higher.

Among 339 patients in this study, 39 patients (11.5%) had an interval of 14 days or less between CCRT completion and the initiation of durvalumab, whereas 300 patients (88.5%) experienced an interval that exceeded 14 days, 287 patients (84.7%) received paclitaxel plus platinum agent concurrently with radiotherapy, 46 patients (13.6%) received pemetrexed plus platinum agent, and six patients (1.7%) received other chemotherapy. All patients received radiation therapy of 54 gray or more.

Survival Outcomes According to EGFR or ALK Mutation Status

In the total study population of 339 patients with a median follow-up duration of 18.3 months (95% CI: 16.8–20.5), the median PFS was 21.2 months (95% CI: 17.9–25.3), and the median OS was 45.0 months (95% CI: 39.6–not available [NA]) (Figs. 1*A* and *B*).

When patients were stratified into two groups, *EGFR/ALK* wild-type (n = 279) and *EGFR* or *ALK* mutant (n = 60), according to *EGFR* and *ALK* mutation status, the median PFS was 21.4 months (95% CI: 17.3–25.3) and 21.0 months (95% CI: 15.7–NA), respectively. Nevertheless, there was no statistically significant difference (HR = 0.76, 95% CI: 0.40–1.15, $p = 0.74$) (Fig. 2*A*). The median OS in the*EGFR* and *ALK* wild-type group was 45.0 months (95% CI: 39.6–NA), whereas the *EGFR* or *ALK* mutant group did not reach median OS, and this difference was not statistically significant ($p = 0.29$) (Fig. 2*B*).

Our study also compared the survival outcomes between the *EGFR* mutant group and the *EGFR/ALK* wild-type group. The median PFS for the *EGFR* and *ALK* wild-type group was 21.4 months (95% CI: 17.3–25.3), whereas the *EGFR* mutant group had a PFS of 30.1 months (95% CI: 15.7–NA), with no significant difference observed ($p = 0.52$) (Supplementary Fig. 2*A*). The median OS for the *EGFR/ALK* wild-type group was 45.0 months (95% CI: 39.6–NA), and the *EGFR* mutant group did not reach median OS ($p = 0.24$) (Supplementary Fig. 2*B*). In terms of survival outcomes between the *EGFR/ALK* wild-type group and *ALK* mutant group, the median PFS was 21.4 months (95% CI: 17.3–25.3) versus 17.5 months (95% CI: 9.9–NA), respectively, and no significant difference was found ($p = 0.67$) (Supplementary Fig. 3*A*). The median OS was 45.0 months (95% CI: 39.6–NA) versus NA ($p = 0.84$), respectively (Supplementary Fig. 3*B*).

As *EGFR* and *ALK* mutations are predominantly found in adenocarcinoma, we analyzed the survival outcomes of patients with adenocarcinoma in the *EGFR* mutant or *ALK* mutant groups with those in the *EGFR* and *ALK* wild-type groups. Among the patients who had adenocarcinoma, the median PFS for *EGFR/ALK* wild-type patients was 22.1 months (95% CI: 17.9–NA), and in the *EGFR* mutant group, the median PFS was 21.0 months (95% CI: 13.8–NA). There is no statistically significant difference between the two groups ($p = 0.97$) (Supplementary Fig. 4*A*). For adenocarcinoma patients in the *ALK* mutant group, the median PFS was 15.2 months (95% CI: 5.6–NA), and there is no statistically significant difference between the *EGFR/ALK* wild-type and *ALK* mutant ($p = 0.22$) groups (Supplementary Fig. 4*B*).

Subgroup Analysis of Survival Outcomes

PFS analysis was conducted for various clinical characteristics in the context of maintenance durvalumab. PFS associated with durvalumab maintenance therapy did not exhibit significant differences across age, sex, smoking status, histologic diagnosis, presence of *EGFR* mutation or *ALK* mutation, and the interval from CCRT completion to the initiation of durvalumab (Fig. 3).

Nevertheless, a notable significant difference in PFS was observed for stage IIIC (HR = 1.84, 95% CI: 1.11–3.04, $p = 0.02$) (Fig. 3). The median PFS was 24.8 months (95% CI: 20.8–NA) for stage IIIA, 20.1 months (95% CI:

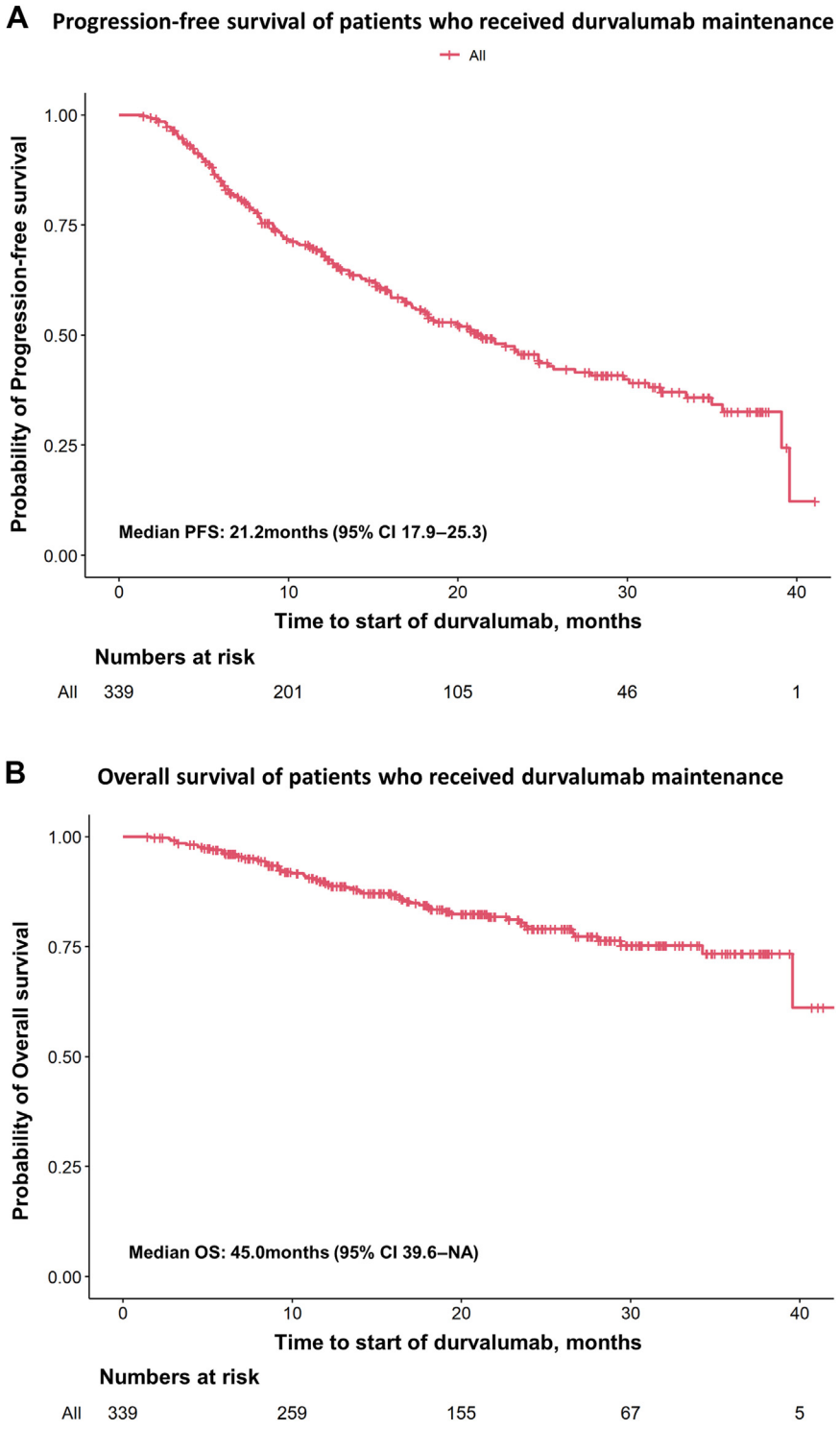

Figure 1. Survival outcomes of patients who received durvalumab maintenance therapy. (*A*) PFS of patients who received CCRT followed by durvalumab maintenance. (*B*) OS of patients who received CCRT followed by durvalumab maintenance. CCRT, concurrent chemoradiotherapy; CI, confidence interval; NA, not available; OS, overall survival; PFS, progression-free survival.

17.3–27.9) for stage IIIB, and 14.6 months (95% CI: 9.8–NA) for stage IIIC, indicating a poorer prognosis with advanced stages (Supplementary Fig. 5*A*).

Furthermore, a significant PFS benefit was observed for patients with a PD-L1 TPS of 50 or higher (HR = 0.40, 95% CI: 0.20–0.80, $p = 0.01$) (Fig. 3). The median PFS

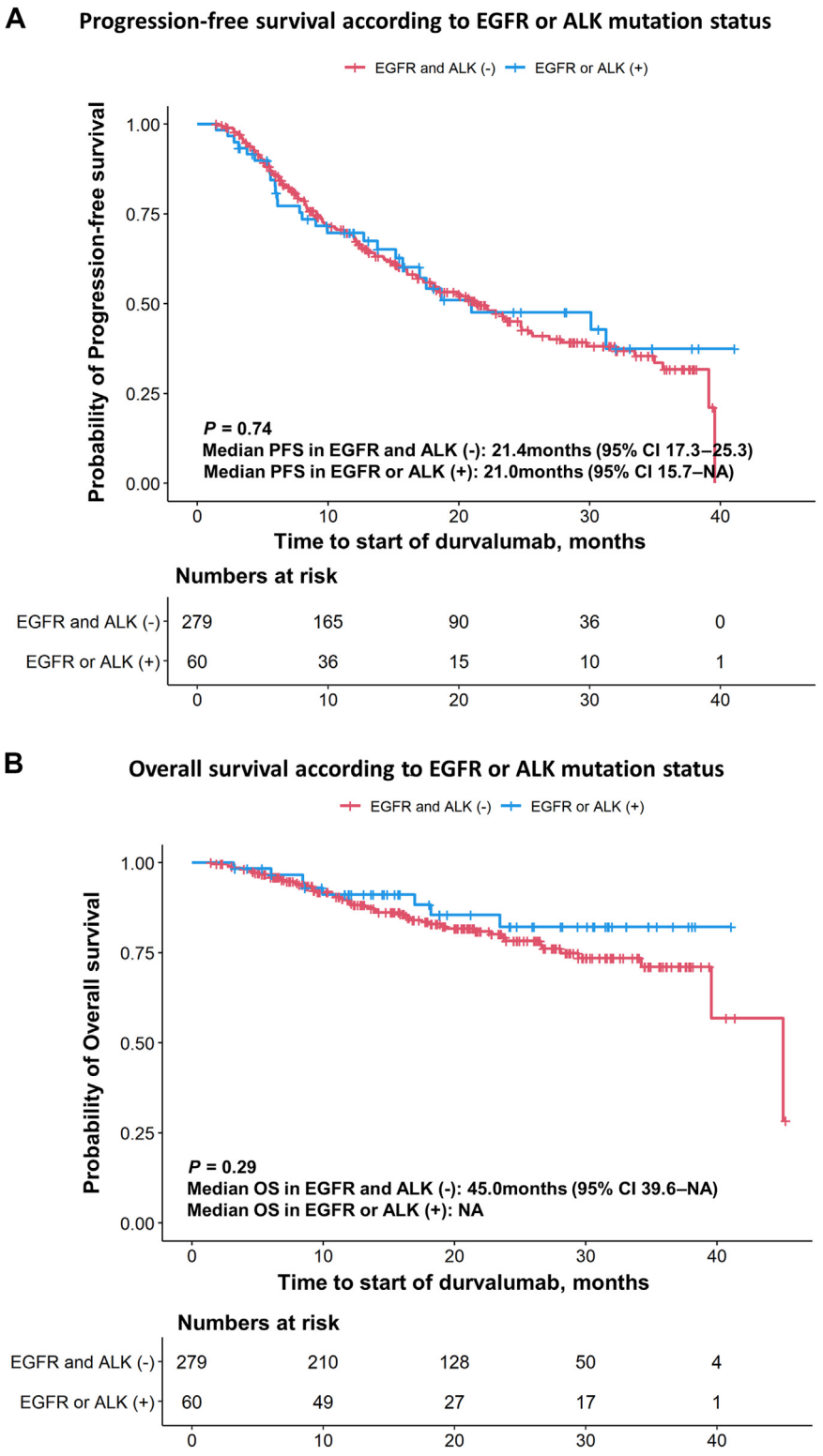

Figure 2. Survival outcomes according to EGFR or ALK mutation status. (*A*) PFS according to *EGFR* or *ALK* mutation status (*EGFR* or *ALK* mutant group versus *EGFR* and *ALK* wild-type group) (red line: *EGFR* and *ALK* wild-type group; blue line: *EGFR* or *ALK* mutant group). (*B*) OS according to *EGFR* or *ALK* mutation status (*EGFR* or *ALK* mutant group versus *EGFR* and *ALK* wild-type group) (red line: *EGFR* and *ALK* wild-type group; blue line: EGFR or ALK mutant group). CI, confidence interval; NA, not available; OS, overall survival; PFS, progression-free survival.

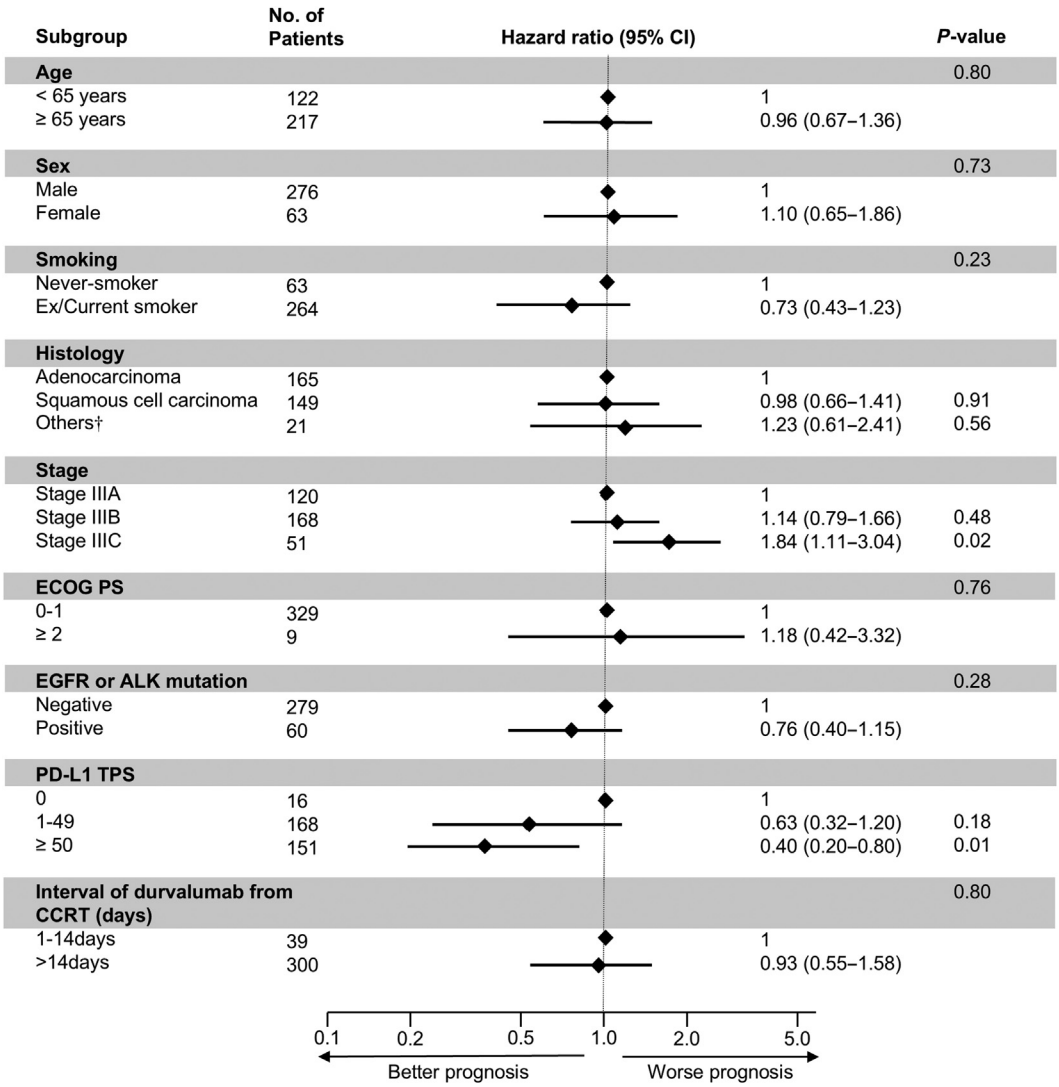

Figure 3. Subgroup analysis for disease progression or death. †Others included large cell lung carcinoma, NUT carcinoma, poorly differentiated carcinoma, sarcomatoid carcinoma, and lung cancer not otherwise specified. CCRT, concurrent chemoradiotherapy; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; NUT, nuclear protein in testis; PD-L1, programmed death-ligand-1; TPS, tumor proportional score.

was 13.6 months (95% CI: 10.5–NA) for a PD-L1 TPS of 0, 18.7 months (95% CI: 15.4 – 26.9) for a PD-L1 TPS of 1 to 49, and 24.7 months (95% CI: 20.7–NA) for a PD-L1 TPS of 50 or higher. This suggests that higher PD-L1 TPS values are associated with a more favorable prognosis (Supplementary Fig. 6*A*).

Further survival analysis showed that overall survival was not statistically significantly different by disease stage ($p = 0.14$) (Supplementary Fig. 5*B*), but there was a trend towards a worse prognosis at advanced stages. Similar to PFS, OS by PD-L1 expression status showed that absent or low PD-L1 expression was associated with a worse prognosis (Supplementary Figs. 6*B* and *C*). Lastly, there was no difference in PFS according to EGFR mutation type ($p = 0.29$) (Supplementary Fig. 7).

Subsequent Treatment in EGFR and ALK Mutant Patients

In a total of 41 patients with *EGFR* mutations, 18 patients experienced disease progression. Among these, five patients (26.3%) received subsequent treatment with gefitinib, two patients (10.5%) with erlotinib, two patients (10.5%) with afatinib, two patients (10.5%) with mobocertinib, and one patient each received either dacomitinib or osimertinib. Two patients did not undergo treatment or were lost to follow-up, whereas two

patients underwent radiotherapy or gamma knife surgery (Supplementary Table 1).

Of 16 patients with *ALK* mutations, nine patients experienced disease progression. Among them, four patients (44.5%) were treated with alectinib, three patients (33.3%) with brigatinib, one patient (11.1%) with crizotinib, and one patient (11.1%) with pemetrexed plus cisplatin (Supplementary Table 2). The patient treated with pemetrexed plus cisplatin was found to have *ALK* fusion after the administration of pemetrexed plus cisplatin.

Safety Profiles

A total of 339 patients were included in the analysis of adverse events in this study. Pneumonitis was observed in 156 patients (46%), with grade 3 or higher pneumonitis occurring in 14 patients (4.1%). Hypothyroidism occurred in 22 patients (6.5%), esophagitis occurred in 15 patients (4.4%), with grade 3 or higher esophagitis occurring in two patients (0.6%). Other grade three or higher adverse events included skin rash in one patient, pruritus in one patient, myositis in one patient, encephalitis in one patient, thrombocytopenia in one patient, and myocarditis in one patient (Table 2).

Discussion

In this study, we found that PFS in patients with *EGFR* or *ALK* mutations was comparable to those with wild-type *EGFR/ALK*. Median PFS was 21.0 months for *EGFR* or *ALK* mutant groups versus 21.4 months for the *EGFR/ALK* wild-type group, with no significant difference. Intriguingly, higher PD-L1 expression was associated with a more favorable prognosis (PD-L1 TPS 0 versus TPS 1 to 49 versus TPS 50 to 100: 13.6 months (95% CI: 10.5–NA) versus 18.7 months (95% CI: 15.1–26.9) versus 24.7 months (95% CI: 20.7–NA).

The median PFS for the entire patient population in our study was 21.2 months (95% CI: 17.9–25.3), demonstrating better outcomes compared with the PACIFIC trial (16.8 mo (95% CI: 13.0–18.1).[17] Nevertheless, in this study, patients with a PD-L1 TPS of 0 accounted for only (4.1%, 14 of 339) owing to the reimbursement policy. In contrast, in the PACIFIC trial, the corresponding figure was approximately four times higher, with 90 of 476 patients (18.9%) having a PD-L1 TPS of 0. The disparity in the proportion of patients with a PD-L1 TPS of 0 can be attributed to differences in PFS between the current study and the PACIFIC trial. Indeed, when focusing on patients with a PD-L1 TPS of 1 or higher in the PACIFIC trial, the PFS was 24.9 months (95% CI: 16.9–38.7), suggesting consistent results in real-world practice.

The *EGFR* and *ALK* wild-type group and the *EGFR* or *ALK* mutant group did not exhibit a statistically significant difference in terms of PFS. In contrast to findings from the PACIFIC trial, where maintenance durvalumab did not reveal a benefit in *EGFR* or *ALK* mutant groups (HR = 0.82, 95% CI: 0.39–1.71), the current study revealed that even in the presence of *EGFR* or *ALK* mutations, there was no significant difference in outcomes compared with the *EGFR* and *ALK* wild-type group, suggesting a benefit from maintenance durvalumab. This

Table 2. Safety Profiles With Durvalumab

	N = 339, n (%)				
Common AE	Total	Grade 1	Grade 2	Grade ≥ 3	Unknown Grade
Pneumonitis[a]	156 (46)	25 (7.4)	92 (27.1)	14 (4.1)	25
Hypothyroidism	22 (6.5)	0 (0)	22 (6.5)	0 (0)	0
Esophagitis	15 (4.4)	7 (2.1)	5 (1.5)	2 (0.6)	1
Skin rash	10 (2.9)	4 (1.2)	5 (1.5)	1 (0.3)	0
Fatigue	7 (2.1)	7 (2.1)	0 (0)	0 (0)	0
Anorexia	5 (1.5)	5 (1.5)	0 (0)	0 (0)	0
Pruritis	3 (0.9)	0 (0)	2 (0.6)	1 (0.3)	0
Hyperglycemia	3 (0.9)	1 (0.3)	2 (0.6)	0 (0)	0
Hepatitis	2 (0.6)	1 (0.3)	1 (0.3)	0 (0)	0
Myositis	1 (0.3)	0 (0)	0 (0)	1 (0.3)	0
Encephalitis	1 (0.3)	0 (0)	0 (0)	1 (0.3)	0
Thrombocytopenia	1 (0.3)	0 (0)	0 (0)	1 (0.3)	0
Myocarditis	1 (0.3)	0 (0)	0 (0)	1 (0.3)	0
Peripheral neuropathy	1 (0.3)	1 (0.3)	0 (0)	0 (0)	0
Adrenal insufficiency	1 (0.3)	1 (0.3)	0 (0)	0 (0)	0

Note: All side effects were reported on the basis of the CTCAE version 5.0.
[a]Pneumonitis included chemotherapy-induced pneumonitis and radiation-induced pneumonitis.
AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events.

unexpected result diverges from our initial hypothesis, as immune checkpoint inhibitors do not generally confer a survival benefit in stage IV patients with *EGFR* mutations,[18] which suggests an unfavorable prognosis for the *EGFR* or *ALK* mutant group. One hypothesis that may explain our findings is that PD-L1 expression status may affect the clinical outcomes of patients with *EGFR* mutations. Considering that more than half of the patients with *EGFR* mutations exhibit negative PD-L1 expression in other studies,[24,25] whereas 39 out of 41 patients with *EGFR* mutations have PD-L1 expression of 1% or higher and only two patients were negative for PD-L1 expression owing to the reimbursement policy in this study. Similarly, except for three patients, 16 patients with *ALK* mutations have PD-L1 expression and no significant difference was observed in PFS. Indeed, other studies have reported 20% to 30% PD-L1 TPS 0% in the presence of oncogenic drivers, and the discrepancy between the results of these studies and ours supports this hypothesis.[26,27] Altogether, the current study suggests that maintenance durvalumab can benefit patients with *EGFR* or *ALK* mutations if PD-L1 expression is present. Osimertinib, a third-generation central nervous system active *EGFR* tyrosine kinase inhibitor, is recommended both in advanced and early-stage *EGFR* mutant NSCLC.[28,29] Currently, osimertinib is under evaluation for efficacy and safety in patients with unresectable stage III *EGFR* mutant NSCLC without progression after definitive CCRT (LAURA trial, NCT03521154).[30] The results of this study might change the treatment landscape of unresectable locally advanced stage III NSCLC with *EGFR* mutations.

We also found that PD-L1 expression status was significantly associated with clinical outcomes. No benefit was observed in patients with PD-L1 expression of less than 1% but PD-L1 expression of 50% or higher was favorable in most patients. These results are consistent with a previous PACIFIC trial, where patients with a PD-L1 TPS of 0 had a median PFS of 10.7 months, for those with a PD-L1 TPS of 1 to 24, the median PFS was 23.9 months, and for individuals with a PD-L1 TPS of 25 or higher, the median PFS was 25.2 months.[17] This indicates that PD-L1 expression is the most important biomarker associated with prolonged PFS in patients receiving durvalumab maintenance therapy.

Another noteworthy consideration is the shift in TNM classification from the seventh edition to the eighth edition in 2017,[31] resulting in the reclassification of T3 N3 and T4 N3 from stage IIIB to stage IIIC. The PACIFIC trial adhered to the TNM classification seventh edition, encompassing only stage IIIA and stage IIIB subgroups. Conversely, our study adopted the TNM classification eighth edition, enabling the analysis of three groups: stage IIIA, stage IIIB, and stage IIIC. Significantly, a notable difference in prognosis emerged between stage IIIA and stage IIIC, with an HR of 1.84 (95% CI: 1.11–3.04, $p = 0.02$). This finding suggests the necessity of exploring alternative treatment strategies beyond durvalumab maintenance therapy, especially for patients with a high tumor burden such as T3 N3 or T4 N3 disease.

In terms of safety, any grade of pneumonitis was observed in 46% of patients; nevertheless, grade 3 or higher pneumonitis only occurred in 4.1%, which is consistent with the PACIFIC trial.[14] This indicates that maintenance durvalumab did not increase the occurrence of high-grade pneumonitis. There was no new safety signal in this study, suggesting maintenance durvalumab can be safely administered in real clinical practice.

This study has several strengths. First, this is one of the largest real-world datasets from the multicenter trial in East Asia, a region characterized by a high incidence of *EGFR* mutation. This also ensures adequate statistical power. Second, the whole study population has molecular test results for *EGFR* or *ALK* mutations, which improves the clarity of the data analysis. Nevertheless, given the retrospective nature of this study, there might be several confounding factors. Secondly, a limited number of patients with negative PD-L1 expression were enrolled in this study, which may not represent the entire population with *EGFR* or *ALK* mutant NSCLC. Despite this limitation, our findings suggest that maintenance durvalumab demonstrates benefits even in patients with *EGFR* or *ALK* mutations and a PD-L1 TPS of 1 or higher. Lastly, the evaluation of pneumonitis was limited by the retrospective nature of the study, which made it difficult to assess whether the pneumonitis was due to actual durvalumab or RT pneumonitis.

In addition, the recent LAURA trial[32] and a retrospective study[27] comparing durvalumab to osimertinib have recently reported that patients with locally advanced EGFR mutant NSCLC are more likely to benefit from osimertinib than from durvalumab. Therefore, the efficacy of maintenance durvalumab reported in this study may not be clinically meaningful, but we believe it provides some evidence that immunotherapy may have some benefit in patients with EGFR mutant NSCLC after tyrosine kinase inhibitor treatment.

In conclusion, maintenance durvalumab after definitive CCRT in unresectable locally advanced NSCLC patients with *EGFR* or *ALK* mutation demonstrates comparable clinical outcomes to those with wild-type *EGFR/ALK* when PD-L1 expression is present.

CRediT Authorship Contribution Statement

Dae-Ho Choi: Conceptualization, Methodology, Formal analysis, Investigation, Data curation, Writing - original draft, Writing - review & editing, Visualization.

Miso Kim: Conceptualization, Methodology, Formal analysis, Investigation, Data curation, Writing - original draft, Writing - review & editing, Visualization.

Myung-Ju Ahn: Conceptualization, Methodology, Formal analysis, Investigation, Resources, Data curation, Writing - original draft, Writing - review & editing, Supervision, Project administration.

Young Saing Kim: Conceptualization, Methodology, Investigation, Writing- review & editing.

Keon Uk Park: Conceptualization, Methodology, Investigation, Writing - review & editing.

Jang Ho Cho: Conceptualization, Methodology, Investigation, Writing - review & editing.

Hongsik Kim: Conceptualization, Methodology, Investigation, Writing - review & editing.

Ki Hyeong Lee: Conceptualization, Methodology, Investigation, Writing - review & editing.

Heejoon Ahn: Conceptualization, Methodology, Investigation, Writing - review & editing.

Il-Hwan Kim: Conceptualization, Methodology, Investigation, Writing - review & editing.

Kyung-Hee Lee: Conceptualization, Methodology, Investigation, Writing - review & editing.

Gyeong-Won Lee: Conceptualization, Methodology, Investigation, Writing - review & editing.

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Disclosure

Dr. M. Kim has disclosed receiving honoraria: Astellas Pharma, Yuhan, Novartis, and Merck. Consulting or Advisory Role: Ipsen, Bristol Myers Squibb, Ono Pharmaceutical, Eisai, Yuhan, Pfizer, Merck Sharp & Dohme, Roche, Janssen, Astellas Pharma, Bayer, Merck, Boryung. Dr. M. Ahn has received consulting fees from Alpha Pharmaceuticals, AstraZeneca, Yuhan Corporation, Takeda, Merck Sharp & Dohme, Amgen, Ono Pharmaceuticals, Roche, Janssen Pharmaceuticals, and Arcus; and received payment or honoraria from AstraZeneca, Yuhan Corporation, Takeda, Merck Sharp & Dohme, Amgen, Ono Pharmaceuticals, Roche, Janssen Pharmaceuticals, and Arcus. Dr. Lee. has received research funding: Merck, consulting or advisory Role: Bristol Myers Squibb, Merck Sharp & Dohme, AstraZeneca, Pfizer, Eli Lilly. Dr. Lee reports receiving research funding for Merck Sharp & Dohme; and is a consultant for Bristol Myers Squibb, Eli Lilly, Pfizer, AstraZeneca, Merck Sharp & Dohme, and Yuhan Corporation. Dr. Jung has received research funding: Yuhan, consulting or advisory role: Yuhan, Guardant Health, AIMEDBIO. Dr. J. Ahn has received honoraria: Pfizer, Roche, BC World Pharmaceutical, Yuhan, Hanmi, Novartis, JW Pharmaceutical, Amgen, Boehringer Ingelheim, Menarini, Kyowa Kirin, AstraZeneca, Bayer, Eli Lilly, Takeda, Boryung, Samyang, and consulting or advisory role: Bayer, Yooyoung Pharmaceutical Co, Ltd., Pharmbio Korea, Guardant Health, Yuhan, ImmuneOncia, Therapex, Daiichi Sankyo Korea, Roche. Dr. S. Lee has disclosed receiving research funding for his institution from Merck, AstraZeneca, and Lunit. In addition, he serves as a consultant or advisor to AstraZeneca, Roche, Merck, Pfizer, Eli Lilly, Bristol-Myers Squibb, Ono, Takeda, Janssen, IMBdx, and Novartis. The remaining authors declare no conflict of interest.

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Ethics Statement

The authors are accountable for all aspects of the work and ensure that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *JTO Clinical and Research Reports* at www.jtocrr.org and at https://doi.org/10.1016/j.jtocrr.2024.100734.

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