

Long-Term Safety and Effectiveness of Durvalumab in Unresectable Stage III NSCLC in Japan: A Multicenter Prospective Study (AYAME)



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Received 24 February 2025; revised 10 July 2025; accepted 8 August 2025

Available online - 18 August 2025

ABSTRACT

Introduction: Based on the PACIFIC trial results, durvalumab after chemoradiotherapy (CRT) is the standard of care for unresectable stage III NSCLC. However, few large-scale studies have prospectively evaluated its long-term effectiveness and safety, including subsequent treatment.

Methods: This multicenter, noninterventional study (AYAME) enrolled patients who were prescribed durvalumab for unresectable stage III NSCLC after CRT (July 2019–December 2020; 52 sites; Japan). Patients received durvalumab for a maximum of 12 months and were prospectively followed up for 3 years, including the post-durvalumab treatment period. Primary end points were real-world progression-free survival (rwPFS), the incidence of interstitial lung disease (ILD), and adverse events of special interest (AESIs).

Results: Of the 529 enrolled patients, 512 received durvalumab and 511 comprised the safety analysis population. The median time to onset of the first presentation or occurrence of ILD was 45.0 days. ILD of any grade occurred in 387 patients (75.7%) over the 3-year study period: grade 3, 57 (11.2%); grade 4, none (0.0%); and grade 5, 9 (1.8%). The most common AESIs of any grade during durvalumab treatment were thyroid dysfunction (12.5%), hepatic dysfunction (7.2%), and colitis (2.0%). No durvalumab treatment-related ILD or AESIs

occurred during the post-treatment period. The median [95% confidence interval] rwPFS was 23.2 [18.2, 27.2] months in the effectiveness analysis population (n = 495). rwPFS rates were 62.5%, 54.6%, 49.4%, and 40.4% at 12, 18, 24, and 36 months, respectively.

Conclusions: This first and largest prospective, observational study demonstrated the long-term safety and effectiveness of durvalumab for unresectable stage III NSCLC after CRT in a real-world clinical setting.

Clinical Trial Registration: UMIN000037090 and NCT03995875

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Cite this article as: Kenmotsu H, Saito Y, Ninomiya K, et al. Long-term safety and effectiveness of durvalumab in unresectable stage III NSCLC in Japan: a multicenter prospective study (AYAME). *J Thorac Oncol*. 2026;21:160-173.

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ISSN: 1556-0864

<https://doi.org/10.1016/j.jtho.2025.08.010>

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Keywords: Durvalumab; Chemoradiotherapy; Interstitial lung disease; Real-world evidence; Unresectable stage III NSCLC

Introduction

Lung cancer is the most frequently diagnosed cancer and the leading cause of cancer deaths worldwide.¹ NSCLC accounts for 80% to 90% of lung cancers,² and approximately 20% to 35% of NSCLC cases are diagnosed in stage III.³

Chemoradiotherapy (CRT) has long been established as the standard treatment for locally advanced unresectable NSCLC, with previous reports indicating limited median overall survival (OS) in clinical settings.⁴ In the PACIFIC trial, patients receiving durvalumab, a high-affinity programmed death-ligand 1 (PD-L1) inhibitor, for unresectable stage III NSCLC after CRT demonstrated significantly prolonged progression-free survival (PFS) and OS compared with those receiving placebo.^{5–7} Consolidation durvalumab after concurrent CRT (cCRT; the PACIFIC regimen) has thus become the standard of care for this setting.^{5–8}

In the current treatment landscape, it is known that immune-related adverse events (irAEs) can occur after the discontinuation or completion of treatment with immune checkpoint inhibitors (ICIs)⁹; however, there are few reports on long-term safety and subsequent treatments during the observation period after durvalumab discontinuation.¹⁰ There are also limited data evaluating interstitial lung disease (ILD) in Asian patients receiving the PACIFIC regimen, although the findings of the PACIFIC trial suggested a higher frequency of symptomatic ILD of grade more than or equal to 2 in Asian patients who were originally reported to have a higher incidence of radiation pneumonitis.^{11–13}

In addition, the long-term effectiveness of the PACIFIC regimen in the real-world setting has been reported in the PACIFIC-R study, with a median follow-up of 23.5 months^{14,15}; however, this retrospective study only enrolled patients who participated in the early access program (EAP). Consequently, not all eligible patients were included in the PACIFIC-R study.^{14,15}

To address these knowledge gaps, we conducted the AYAME study, which prospectively assessed the safety events and effectiveness of the PACIFIC regimen for 3 years in Japan, including the subsequent treatment period. Here, we report the results of the final analysis of the AYAME study.

Material and Methods

Study Design

This multicenter, noninterventive cohort study (UMIN000037090; NCT03995875) enrolled patients scheduled to be treated with durvalumab for unresectable stage III NSCLC after cCRT from July 2019 to December 2020 from 52 sites in Japan. The patients were treated with durvalumab after cCRT for a maximum of 12 months and were prospectively followed up for up to 3 years from the start of durvalumab treatment to the date of discontinuation, death, or final survival, as applicable. Patient follow-up was completed in December 2023. Standard patient demographic and clinical data were collected using an electronic case report form ([Supplementary Table 1](#)).

The study was performed in accordance with the ethical principles of the Declaration of Helsinki and the Japanese ethical guidelines for medical and biological research involving human subjects. The final study protocol, informed consent forms, protocol amendments, and advertisements for recruitment were approved by the Ethics Committee at each site.

Patients

Patients with unresectable stage III NSCLC who were going to be newly initiated on durvalumab after CRT, and who provided written informed consent, were enrolled. Patients with recurrence after surgical resection of the primary lesion were eligible, provided that they qualified as having N2 or N3 unresectable stage III NSCLC. This study excluded patients aged below 20 years and those who had participated in any interventional clinical study using unapproved drugs or off-label use of drugs from the first diagnosis to the end of durvalumab treatment.

Safety End Points

The primary end points were the incidence of ILD and adverse events of special interest (AESIs) that occurred within 3 years of the start of durvalumab treatment. ILD of any grade was evaluated throughout the study period. In addition, the presence or absence of multiple adverse events (AEs; AESIs + ILD) during the durvalumab treatment period is reported. AESIs of any grade were recorded during the durvalumab treatment period, and only AESIs of grade more than or equal to 3 were reported throughout the study period. AESIs in this study were selected as events that were identified in the clinical study of durvalumab or were potentially attributable to subsequent treatments as severe irAEs. The AESIs defined in this study are as follows: hepatic dysfunction, thyroid dysfunction, adrenal dysfunction, renal disorder, infusion reaction, colitis or severe diarrhea, type 1

diabetes mellitus, and others. The severity of AEs and ILD was recorded based on investigators' discretion and graded using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. The documented diagnosis of ILD, including pneumonitis through radiological confirmation or imaging, was based on investigators' discretion.

ILDs, including radiation pneumonitis, and AEs were summarized for five evaluation periods: (1) the durvalumab treatment period for a maximum of 12 months, with a 90-day follow-up after the last dose of durvalumab; (2) from the start of durvalumab treatment to the initiation of subsequent treatment; (3) the entire study period (up to 3 y from the start of durvalumab treatment); (4) from the end of durvalumab treatment to the start of subsequent treatment; and (5) from the end of durvalumab treatment to the end of the study.

Effectiveness End Points

The primary end point was real-world PFS (rwPFS) from the start of durvalumab treatment. rwPFS was defined as the time from the start of durvalumab treatment to the occurrence of progressive disease (PD) or death, whichever occurred first. In the absence of PD or death, rwPFS was censored at the last follow-up date or the first date of the first subsequent treatment, whichever occurred first. rwPFS rates at 12, 18, and 24 months after the start of durvalumab treatment were estimated. Per protocol, a computed tomography (CT) scan was recommended at 12, 18, and 24 months from the start of durvalumab treatment for the evaluation of PD.

The secondary end points were OS from the start of durvalumab treatment (median OS and OS rates at 24 and 36 mo were assessed) and rwPFS in the following subset of patients: (1) PD-L1 expression in tumor cells (<1%, ≥1% to <50%, ≥50%); (2) disease stage (IIIA, IIIB, IIIC, postoperative recurrence equivalent to unresectable stage III NSCLC); (3) time to start of durvalumab after CRT (<14 d and ≥14 d); (4) V20 categorization (<25%, ≥25% to <30%, ≥30% to <35%, and ≥35%); and (5) *EGFR* mutation (*EGFRm*) positive (*EGFRm*+) and *EGFRm* negative (*EGFRm*−). OS was defined as the time from the start of durvalumab treatment to death from any cause. If a patient survived the entire study period, OS was censored at the last known alive date, with a maximum of 3 years of follow-up.

Other End Points

Other end points included the reasons for discontinuation of durvalumab treatment (AEs and PD) and details of subsequent treatment. The drugs used for subsequent treatment were categorized into EGFR tyrosine kinase inhibitors (EGFR TKIs) and other TKIs in

combination with chemotherapy ± other, immunoncology (IO) drugs, and IO drugs plus chemotherapy ± other. The chemotherapy ± other category included any drugs other than those listed as EGFR TKIs, other TKIs, and IO drugs. The IO plus chemotherapy ± other category included a combination of drugs listed as IO drugs and chemotherapy ± other drugs (Supplementary Table 2).

Statistical Analysis

Of the enrolled patients, the safety analysis population comprised all patients who received at least one dose of durvalumab, and the effectiveness analysis population was defined as all patients who met the eligibility criteria and received durvalumab.

The date of PD was based on the investigator's judgment, and documentation of progression according to the Response Evaluation Criteria in Solid Tumors (RECIST) was not required. When available, PD was confirmed using a CT scan.

Planned interim analyses were performed annually between 2021 and 2023, and the interim analysis results have been previously presented at conferences without changing the study design; the final analysis data are reported herein. Based on the results of the PACIFIC trial,⁵ the median rwPFS in this real-world study was assumed to be longer, at 18 months. Under this assumption, 500 patients would be required to estimate the median rwPFS with an expected precision (95% confidence interval [CI]) of 15.9 to 20.4 months (Supplementary Table 3). The results were presented using descriptive statistics, such as numbers, proportion, mean (SD), median, range, and duration in days, and all estimates were presented with an appropriate 95% CI. The Kaplan-Meier method was used to analyze the time-to-event data, rwPFS (rwPFS and rwPFS rates at 12, 18, and 24 mo), and OS (OS and OS rates at 24 and 36 mo). Median (95% CI) rwPFS and rwPFS rates were also evaluated for patient subset populations categorized by PD-L1 expression before CRT, disease stage before CRT, days to start of durvalumab after CRT, and V20 (%), as described previously under the section "Effectiveness End Points." AEs and ILD were presented as incidence, mean and median days to onset, and maximum grade of severity. Subsequent treatments were summarized by type, line of therapy, and reasons for discontinuation.

An additional 12-week landmark analysis was performed to evaluate rwPFS for the 3-year study period in patients who did or did not experience AEs within 12 weeks of initiating durvalumab. All analyses were performed using the SAS System Release 9.4 or more updated versions.

Results

Patient Disposition and Baseline Characteristics

A total of 529 patients were enrolled, of whom 512 were initiated on durvalumab: two patients withdrew consent, seven did not meet the eligibility criteria, and eight were excluded for other reasons. The safety analysis population comprised 511 of the 512 patients; one patient was excluded because the informed consent was not appropriate ([Supplementary Fig. 1](#)).

Patients in the safety analysis population had a median (range) age of 69 (31–88) years (119 [23.3%] were aged ≥ 75 y): 76.9% ($n = 393$) were male; 13.9% ($n = 71$) were current smokers; 74.4% ($n = 380$) were former smokers; and 51.3% ($n = 262$) had an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 (1, $n = 239$ [46.8%] and 2, $n = 7$ [1.4%]) before the start of durvalumab treatment. Regarding concurrent diseases at baseline, 11.0% ($n = 56$) of patients had ILD (including radiation pneumonitis; grade 1, 10.6% [$n = 54$]; grade ≥ 2 , 0.4% [$n = 2$]), 17.8% ($n = 91$) had chronic obstructive pulmonary disease, and 66.3% ($n = 339$) had other diseases ([Table 1](#)). Of the 495 patients in the effectiveness analysis population, 156 deaths were reported and 339 patients survived the study period. A total of 210 patients (41.1%) completed the durvalumab treatment period in the safety analysis population.

Safety

ILD. The median time to onset of the first presentation or occurrence of ILD after the start of durvalumab was 45 days over the 3 years of the study period. ILD of any grade occurred in 387 patients (75.7%) over the 3 years of the study period, including the post-durvalumab treatment period: grade 1 in 180 patients (35.2%), grade 2 in 141 (27.6%), grade 3 in 57 (11.2%), grade 4 in none (0.0%), and grade 5 in nine (1.8%). When categorized into two weekly periods over the 3-year period, most cases of ILD occurred between more than or equal to 4 and less than 6 weeks after the start of durvalumab treatment ($n = 75$ [14.7%]), followed by more than or equal to 2 to less than 4 weeks ($n = 64$ [12.5%]) and more than or equal to 6 to less than 8 weeks ($n = 61$ [11.9%]) of follow-up ([Fig. 1](#)).

The median time to the first presentation or occurrence of ILD was 44.0 days during the durvalumab treatment period. ILD of any grade occurred in 380 patients (74.4%) during the durvalumab treatment period: grade 1 in 182 patients (35.6%), grade 2 in 143 (28.0%), grade 3 in 51 (10.0%), grade 4 in none (0.0%), and grade 5 in four (0.8%).

For patients who experienced ILD after durvalumab treatment, the median time to the first presentation or occurrence of ILD was 204 days after the final dose of

durvalumab, including the subsequent treatment period. ILD of any grade occurred in 43 patients (9.0%), of which grade 5 ILD occurred in five patients (1.0%). When categorized into two weekly periods after the end of durvalumab treatment to the end of study, including the subsequent treatment period, most cases of ILD occurred between more than or equal to 10 and less than 12 weeks ($n = 5$ [1.0%]) after the last dose of durvalumab ([Supplementary Fig. 2](#)). ILD of any grade occurred in 13 patients (2.7%) during the period between the last dose of durvalumab treatment and the start of subsequent treatment: grade 1 in five patients (1%), grade 2 in seven (1.5%), grade 3 in one (0.2%), and grade more than or equal to 4 in none. No durvalumab treatment-related ILD was observed during the post-treatment period (data not revealed).

AESIs. The most common AESIs of any grade during the durvalumab treatment period were thyroid dysfunction ($n = 64$ [12.5%]), hepatic dysfunction ($n = 37$ [7.2%]), and colitis ($n = 10$ [2.0%]; [Table 2](#)).

Thyroid dysfunction during the durvalumab treatment period was observed in 64 patients (12.5%), and most of them were grade 2 or lower. Events tended to occur for up to 26 weeks from the start of durvalumab, although events during the later period of administration were also observed ([Supplementary Fig. 3A](#)). The median (range) time to onset of the first presentation or occurrence of thyroid dysfunction in 64 patients was 86.5 (16–416) days during the durvalumab treatment period. Although the incidence of hepatic dysfunction tended to be higher during the early phase of treatment (up to 12 wk), the time to onset was widespread during the evaluation period ([Supplementary Fig. 3B](#)). The median (range) time to the onset of the first presentation or occurrence of hepatic dysfunction in 37 patients was 43.0 (7–348) days during the durvalumab treatment period.

The most common grade more than or equal to 3 AESIs over the 3-year study period were hepatic dysfunction ($n = 20$ [3.9%]) and colitis ($n = 10$ [2.0%]). The most common grade more than or equal to 3 AESIs between the last dose of durvalumab treatment and the last follow-up day, including the subsequent treatment period, were hepatic dysfunction ($n = 8$ [1.7%]) and colitis ($n = 3$ [0.6%]); grade 5 AESIs were not observed. No durvalumab treatment-related AESIs were observed by the treating physician during the post-treatment period.

Among the 22 patients with comorbid autoimmune diseases, seven were being treated with steroids or immunosuppressants before initiating durvalumab, and grade 3 or higher AESIs were observed in two of 22

Table 1. Baseline Characteristics (Safety Analysis Population)

Characteristics	(n = 511)
Age, median (range), y	69.0 (31.0-88.0)
≥20 to <75	392 (76.7)
≥75	119 (23.3)
Sex	
Male	393 (76.9)
Female	118 (23.1)
Smoking status	
Current smoker	71 (13.9)
Former smoker	380 (74.4)
Never	60 (11.7)
ECOG PS before the start of durvalumab treatment	
0	262 (51.3)
1	239 (46.8)
2	7 (1.4)
3	1 (0.2)
4	0 (0.0)
Missing	2 (0.4)
Disease stage	
IIIA	205 (40.1)
IIIB	195 (38.2)
IIIC	62 (12.1)
Postoperative recurrence [equivalent to III]	45 (8.8)
Missing	4 (0.8)
Histology	
Adenocarcinoma	254 (49.7)
Squamous cell cancer	208 (40.7)
Neuroendocrine tumor [non-small cell cancer]	12 (2.3)
Others	37 (7.2)
Presence or absence of concurrent diseases	
Present	377 (73.8)
Absent	134 (26.2)
Details of concurrent diseases ^a	
ILD [including radiation pneumonitis, G1]	54 (10.6)
ILD [including radiation pneumonitis, ≥G2]	2 (0.4)
COPD	91 (17.8)
Others	339 (66.3)
Presence or absence of autoimmune diseases ^a	
Present	22 (4.3)
Absent	489 (95.7)
Presence or absence of use of steroids or immunosuppressants	
Present	7 (1.4)
Absent	504 (98.6)
Missing	0 (0)
Chemotherapy regimen ^b	
CBDCA + PTX	225 (44.0)
CDDP + VNR	108 (21.1)
CDDP + DTX	35 (6.8)
CBDCA	51 (10.0)
CDDP + S-1	62 (12.1)
Others	30 (5.9)

(continued)

Table 1. Continued

Characteristics	(n = 511)
Type of irradiation ^c	
Number of patients for whom the type of radiation therapy was "X-ray"	507
Conventional (2D)	3 (0.6)
3D-CRT	358 (70.6)
IMRT	160 (31.6)
SRT	2 (0.4)
Total radiation dose (actually irradiated dose), median (range), Gy ^d	60.0 (40.0-102.0)
<54	3 (0.6)
≥54 to ≤66	502 (98.2)
>66	6 (1.2)
MLD, median (range) (n = 479), Gy ^e	11.9 (0.9-60.0)
<13	280 (54.8)
≥13	199 (38.9)
V20 (%), median (range) ^e (n = 479)	20.9 (2.3-39.0)
<25	323 (63.2)
≥25 to <30	101 (19.8)
≥30 to <35	46 (9.0)
≥35	9 (1.8)
V5 (%), median (range) ^e (n = 478)	37.9 (3.5-89.4)
<27	117 (22.9)
≥27 to <37	112 (21.9)
≥37 to <47	126 (24.7)
≥47	123 (24.1)
PD-L1 expression rate (tumor proportion score) (%) ^{f,g}	
<1	122 (23.9)
≥1 to <50	114 (22.3)
≥50	119 (23.3)
Unknown	156 (30.5)
PD-L1 assay performed	365
Dako 22C3	340 (93.2)
Dako 28-8	5 (1.4)
Ventana SP142	0 (0.0)
Ventana SP263	15 (4.1)
Others	3 (0.8)
Missing	2 (0.5)
Result of EGFR gene mutation test ^g	
+	55 (10.8)
-	310 (60.7)
Unknown	146 (28.6)
Result of ALK gene translocation test ^g	
+	13 (2.5)
-	311 (60.9)
Unknown	187 (36.6)
Result of ROS1 gene translocation test ^g	
+	5 (1.0)
-	265 (51.9)
Unknown	241 (47.2)
Best response to the previous treatment before the start of durvalumab treatment	
Number of patients whose best response was available ^h	454
CR	6 (1.3)
PR	304 (67.0)

(continued)

Table 1. Continued

Characteristics	(n = 511)
SD	141 (31.1)
PD	0 (0.0)
NE	3 (0.7)

Note: Values are n (%) unless noted otherwise.

^aPatients who had more than one concurrent disease or autoimmune disease were counted for each concurrent disease or autoimmune disease (duplicate count). Autoimmune diseases include hypothyroidism, rheumatoid arthritis, autoimmune thyroiditis, alopecia areata, hyperthyroidism, scleritis, scleroderma, chronic thyroiditis, Cronkhite-Canada syndrome, microscopic polyangiitis, type 1 diabetes mellitus, and immunoglobulin G4-related disease.

^bThe first regimen was counted if multiple regimens are present.

^cPatients who received more than one type of radiation therapy were counted for each radiation therapy (duplicate counting).

^dFor patients who received more than one kind of radiation therapy, values were summed so that one datum per patient was used for the calculation.

^eFor patients who received more than 1 type of radiation therapy with more than 1 value (other than 0) available per patient, data from such patients were handled as “missing” because MLD, V20, and V5 could not be summed.

^fPatients with antibody other than “Dako 22C3, Dako 28-8, and Ventana SP263” detected by PD-L1 status test were categorized into “Unknown.”

^g“Unknown” includes patients in whom the test was not performed.

^hProportion was calculated using the number of patients whose best response was available during each period as assessed by the investigator. 2D, two-dimensional; 3D-CRT, three-dimensional conformal radiation therapy; CBDCA, carboplatin; CBDCA + PTX, carboplatin + paclitaxel; CDDP + DTX, cisplatin + docetaxel; CDDP+S-1, cisplatin + S-1; CDDP+VNR, cisplatin + vinorelbine; COPD, chronic obstructive pulmonary disease; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group Performance Status; ILD, interstitial lung disease; IMRT, intensity-modulated radiation therapy; MLD, mean lung dose; NE, not evaluable; PD, progressive disease; PD-L1, programmed death-ligand 1; PR, partial response; SD, stable disease; SRT, stereotactic radiation therapy.

patients. These included grade 3 hepatic function disorder (4.5%) and grade 3 colitis or severe diarrhea (4.5%). In contrast, among the 489 patients without comorbid autoimmune diseases, excluding others, the top two grade 3 or higher AEs were hepatic function disorder in 14 patients (2.9%) and colitis or severe diarrhea in six patients (1.2%). Notably, grade 5 events were observed in one patient each (0.2%). During the durvalumab treatment period, multiple AEs (≥ 2 AESIs + ILD) occurred in 82 patients (16.0%), a single AE in 333 patients (65.2%), and none in 96 patients (18.8%).

Effectiveness

rwPFS. The median follow-up for the effectiveness analysis population was 1069 days. The median [95% CI] rwPFS was 23.2 [18.2, 27.2] months in the effectiveness analysis population (n = 495). The rwPFS rate [95% CI] was 62.5% [58.0, 66.6], 54.6% [50.0, 58.9], 49.4% [44.8, 53.8], and 40.4% [35.9, 44.9] at 12, 18, 24, and 36 months, respectively (Fig. 2A). A total of 253 patients (51.1%) had disease progression during the 3-year study period, with local recurrence observed in 129 patients (51.0%) and distant metastasis in 129 patients (51.0%) (data not revealed).

OS. The median [95% CI] OS could not be estimated during the 3-year study period in the effectiveness analysis population. The OS rates [95% CI] were 75.5% [71.3, 79.1] and 65.6% [61.0, 69.8] at 24 and 36 months, respectively (Fig. 2B).

rwPFS in Subgroups. The median [95% CI] rwPFS categorized by the PD-L1 tumor proportion score (TPS) before CRT was the longest (median not reached) among the patients with PD-L1 TPS more than or equal to 50%, followed by those with PD-L1 TPS less than 1% (21.4 [12.0, 27.8] mo) and those with PD-L1 TPS more than or equal to 1% to less than 50% (13.5 [9.0, 18.2] mo; Fig. 3A).

The median [95% CI] rwPFS for the 3-year study period was similar among patients categorized by disease stage before CRT: stage IIIA (22.8 [15.3, 30.8] mo), IIIB (22.8 [13.4, 27.2] mo), and IIIC (19.1 [8.7, not evaluable {NE}] mo) disease. Except that the median rwPFS was not reached among patients with post-operative recurrence, and their rwPFS rates at 12, 18, and 24 months were higher than those in patients with stage IIIA, IIIB, or IIIC disease before CRT (Fig. 3B).

When categorized by the duration from completion of CRT to the start of durvalumab treatment, the median [95% CI] rwPFS in patients who started durvalumab less than 14 days after CRT (26.0 [17.6, 35.1] mo) was numerically comparable to that in patients who started durvalumab more than or equal to 14 days after CRT (22.6 [15.3, 25.5] mo; Fig. 3C). The median [95% CI] rwPFS categorized by V20 for the 3-year study period tended to be longer among patients who received V20 less than 25% (25.6 [22.6, 35.3] mo) than among those who received V20 more than or equal to 25% ($\geq 25\%$ to $<30\%$ [14.5 {9.7, 27.1}] mo; $\geq 30\%$ to $<35\%$ [15.6 {7.7, NE}]; and $\geq 35\%$ [11.8 {1.0, NE}]; Fig. 3D). The median [95% CI] rwPFS among *EGFR*⁺, *EGFR*[−], and unknown *EGFR* status patients was 21.4 [11.4, 33.1] months, 22.8 [16.1, 27.1] months, and 26.0 [15.3, NE] months, respectively (Fig. 3E). The median [95% CI] rwPFS for the 3-year study period was numerically longer in patients who experienced (32.7 [21.9, NE] mo) versus did not experience (25.1 [22.0, 32.4] mo) AESIs within 12 weeks of initiating durvalumab (Supplementary Fig. 4).

Other End Points

Reasons for Discontinuation of Durvalumab Treatment. Among patients who discontinued durvalumab (n = 301 [58.9%]), the reasons for discontinuation included PD (n = 112 [37.2%]), AEs (n = 157 [52.2%]), consent withdrawal or voluntary discontinuation (n = 21 [7.0%]), and other reasons (n = 11 [3.7%]).

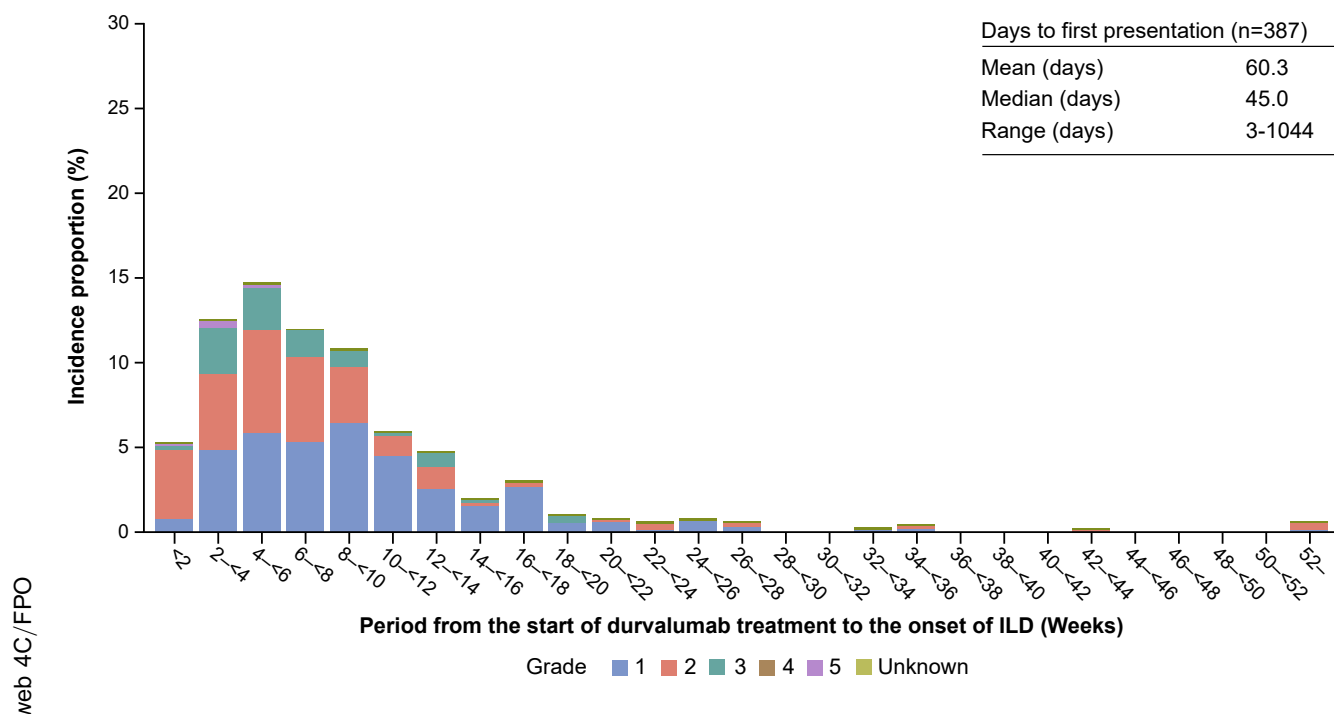


Figure 1. ILD incidence for each grade by timing of the onset during the 3-year study period (safety analysis population). ILD, interstitial lung disease.

Subsequent Treatment. A total of 205 (40.1%), 111 (21.7%), and 57 (11.2%) patients received subsequent treatment as first-, second-, and third-line subsequent therapy, respectively. Among the 174 patients who discontinued first-line subsequent therapy, the most common reasons for discontinuation were PD ($n = 90$ [51.7%]) and AEs ($n = 48$ [27.6%]). Most patients ($n = 121$ [59.0%]) received chemotherapy $\pm$ other as the first-line subsequent therapy, followed by IO plus chemotherapy $\pm$ other ($n = 32$ [15.6%]), EGFR TKIs ($n = 23$ [11.2%]), IO drugs ($n = 20$ [9.8%]), and other TKIs ($n = 9$ [4.4%]). The median (range) duration of the first subsequent treatment was 100 (1–1072) days ([Supplementary Table 2](#)). Further details of the first subsequent treatments are found in [Supplementary Table 4](#).

Discussion

To the best of our knowledge, the AYAME study is the largest cohort study to prospectively evaluate the long-term safety and effectiveness of the PACIFIC regimen. The survival data with long-term follow-up from the AYAME study revealed that the PACIFIC regimen was clinically beneficial in 495 patients, including a wide range of patients who were not eligible for clinical trials. Furthermore, the PACIFIC regimen demonstrated a feasible safety profile for Japanese

patients who are inherently at high risk of ILD, including after the cessation of durvalumab treatment.

The incidence of grade more than or equal to 3 ILD during the durvalumab treatment period in the current study was slightly higher than that reported in two retrospective studies conducted among Japanese patients treated with durvalumab: in one study (grade ≥ 3 , 4.0%)¹⁶ and in another study (grade ≥ 3 , 6.7%).¹⁷ Of note, this study was a prospective, observational study conducted on a larger patient population, and these differences may have caused the slight increase in the incidence rate of grade more than or equal to 3 ILD in this study. The incidence of ILD (2.7%) was low for the period between the last dose of durvalumab treatment and the start of subsequent treatment, suggesting that the delayed onset of ILD was not frequently observed. However, the slightly increased incidence of ILD for the period including subsequent treatment (9.0%) suggested that close monitoring is needed during subsequent treatment. Overall, no new safety signals regarding ILD were found in Japanese patients in real-world clinical practice.

With the standard PACIFIC regimen, we observed that the incidence of thyroid dysfunction and liver dysfunction was more frequent; however, the timing of their appearance was variable and noteworthy. It is necessary to carefully monitor these AEs in clinical practice, as thyroid and liver dysfunction can occur not

Table 2. AEs During the Durvalumab Treatment Period (Safety Analysis Population, n = 511)

Parameters	Hepatic Dysfunction	Thyroid Dysfunction	Adrenal Dysfunction	Renal Disorder	Infusion Reaction	Colitis or Severe Diarrhea	Type 1 Diabetes Mellitus	Others ^a
Presence or absence								
Present	37 (7.2)	64 (12.5)	4 (0.8)	6 (1.2)	4 (0.8)	10 (2.0)	0 (0.0)	6 (1.2)
Absent	474 (92.8)	447 (87.5)	507 (99.2)	505 (98.8)	507 (99.2)	501 (98.0)	511 (100.0)	505 (98.8)
Number of events	46	70	4	6	4	10	0	6
Maximum grade								
1	18 (3.5)	18 (3.5)	0 (0.0)	4 (0.8)	2 (0.4)	1 (0.2)	0 (0.0)	0 (0.0)
2	7 (1.4)	44 (8.6)	4 (0.8)	1 (0.2)	1 (0.2)	2 (0.4)	0 (0.0)	1 (0.2)
3	11 (2.2)	2 (0.4)	0 (0.0)	1 (0.2)	1 (0.2)	6 (1.2)	0 (0.0)	5 (1.0)
4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
5	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Unknown	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	10 (2.0)	0 (0.0)	0 (0.0)
Days to the first onset ^b								
N	37	64	4	6	4	10	0	6
Median (range)	43.0 (7-348)	86.5 (16-416)	46.5 (30-176)	239.0 (86-345)	1.0 (1-1)	95.5 (21-260)	-	241.5 (29-416)

Note: Values are number of patients (%) unless noted otherwise.

^aMyositis, rhabdomyolysis, defective pituitary function, meningitis, immune thrombocytopenic purpura, leukoencephalopathy, Stevens-Johnson syndrome, toxic epidermal necrolysis, Guillain-Barré syndrome, and acute pancreatitis.

^bStart point: The start date of durvalumab treatment.

AEs, adverse event of special interest.

only in the early period of durvalumab administration but also later in the treatment schedule. We also observed grade more than or equal to 3 AEs after the end of the durvalumab treatment period, which was outside the observation period in the PACIFIC study; however, their frequency was relatively lower. Previous reports have revealed that ICI treatment-related AEs occur even after the discontinuation of ICI treatment.^{18,19} The results of this study revealed that the incidence of grade more than or equal to 3 AEs after durvalumab administration was low, which is similar to previous reports.^{18,19} Based on the results of this study, AEs occurring after the end of the durvalumab treatment period would not be considered a major concern. Compared with the PACIFIC study,⁷ the AYAME study reported more treatment discontinuations due to AEs, which could be attributed to the higher percentage of the elderly population in the AYAME study, thereby reflecting actual clinical practice. The study findings of AYAME about multiple AEs in 82 of 511 patients (16.0%) align with those of previous research.²⁰ A single-center retrospective study in Japan reported similar results, with 25 of 112 patients (22.3%) with NSCLC experiencing multiple irAEs.²⁰ Although the AEs collected in the AYAME study are not limited to irAEs, this consistency suggests that the occurrence of multiple AEs is not uncommon in patients with NSCLC undergoing immunotherapy.

The rwPFS and OS rates from AYAME were comparable to previously reported real-world data on the PACIFIC regimen.^{14,15,21} The median rwPFS and 3-year OS rate in our study were similar to the results of the PACIFIC-KR study (median rwPFS: 25.9 mo, 3-y OS rate: 69.2%) conducted in South Korea.²¹ The current study included three times more patients than the PACIFIC-KR study, providing a more robust validation of the effectiveness of the PACIFIC regimen in Asian patients. Our survival data were also aligned with the PACIFIC-R study data reported from European countries.^{14,15} Although the PACIFIC-R^{14,15} and PACIFIC-KR²¹ were observational studies conducted in patients who participated in an EAP, the present study confirmed the findings of previous reports by prospective follow-up.

The AYAME study found no substantial difference in rwPFS between patients who started durvalumab within 14 days or more than or equal to 14 days after CRT, aligning with a database study revealing no PFS benefit from earlier initiation.²² However, a subgroup analysis from the PACIFIC trial suggested improved PFS and OS with durvalumab initiated within 14 days of CRT compared with placebo,^{5,6} and other studies, including a phase 2 study and a retrospective analysis, indicated improved effectiveness with immediate initiation.^{15,23} Because the optimal timing of durvalumab

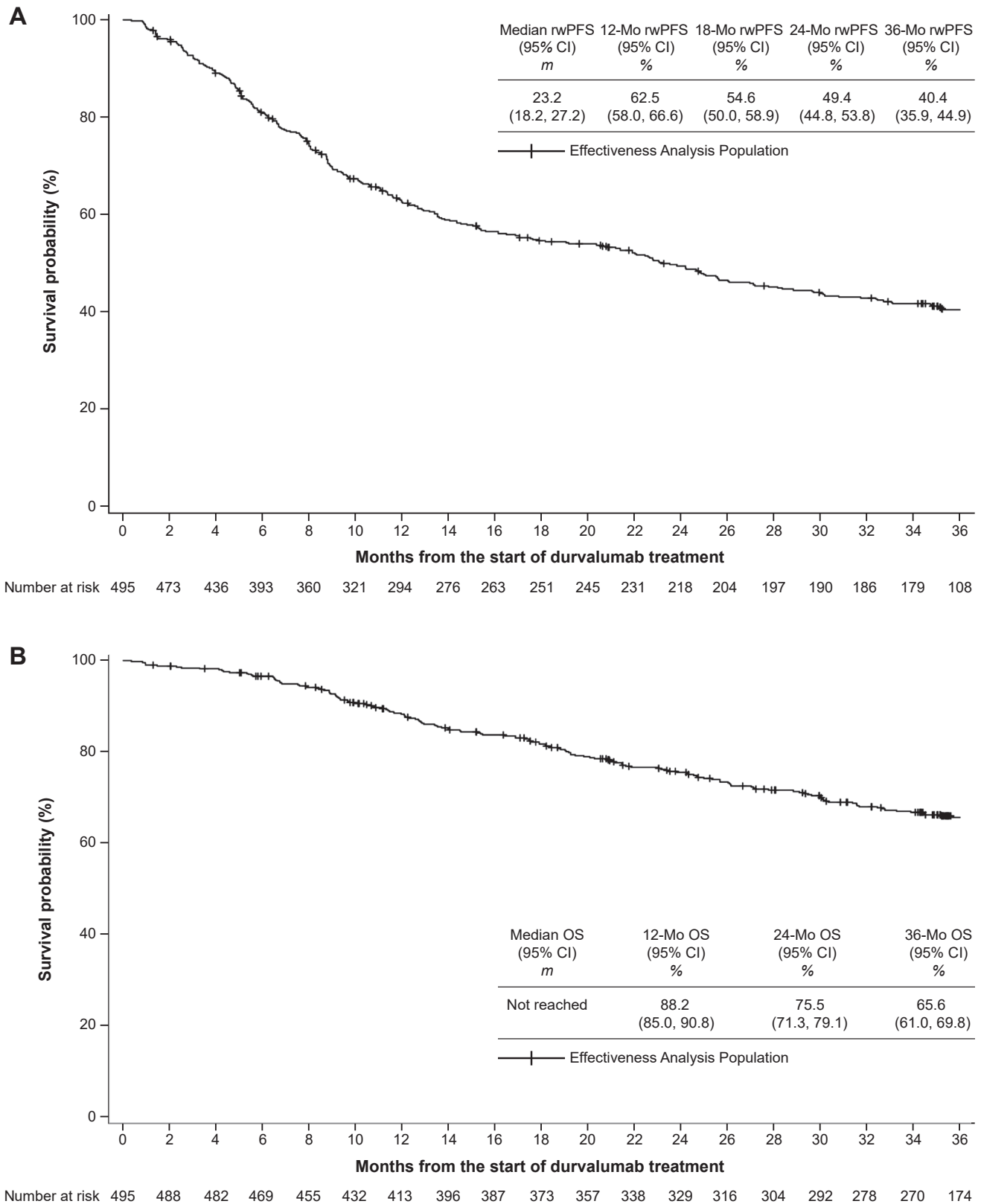
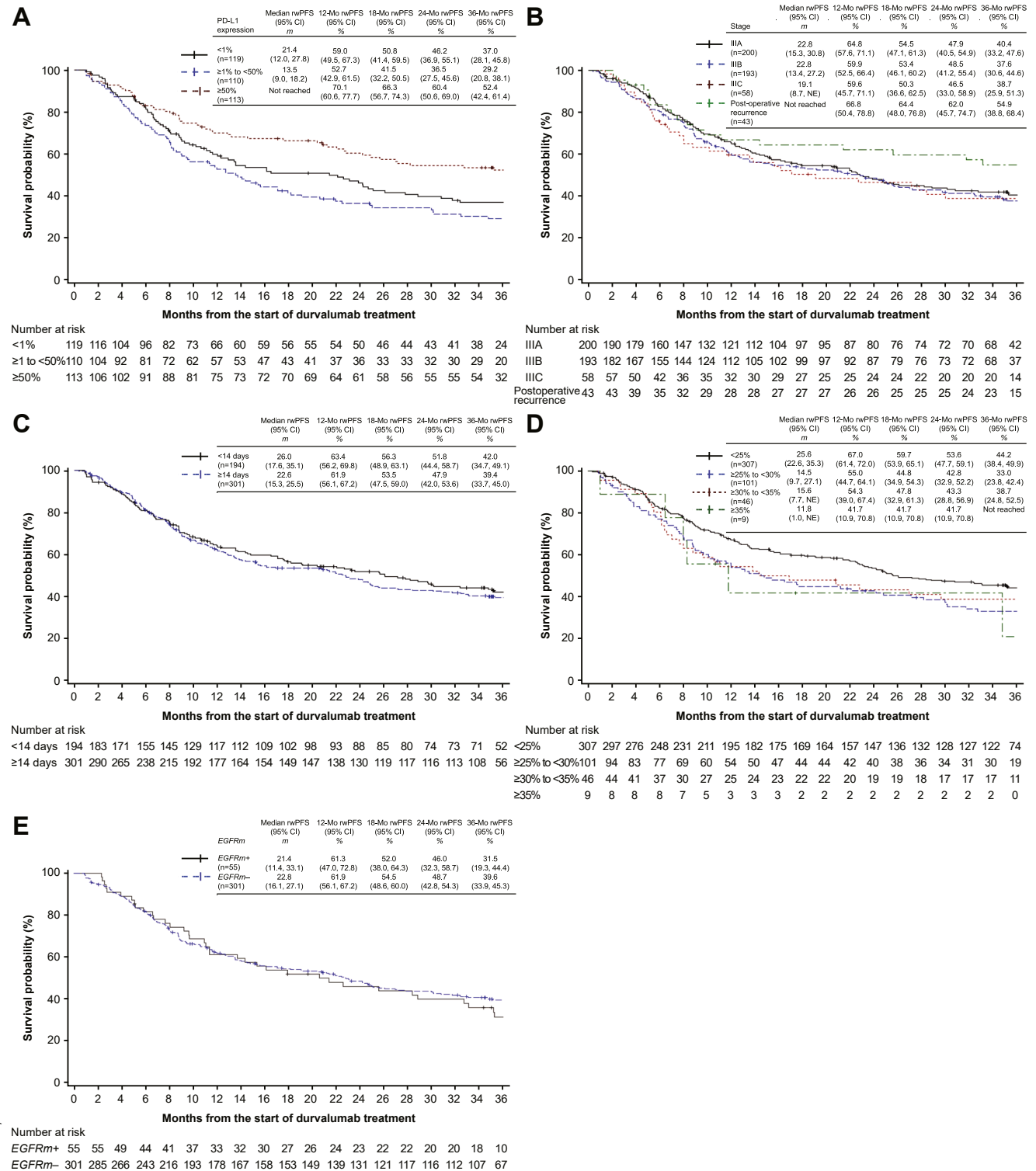


Figure 2. Kaplan-Meier plot of (A) rwPFS and (B) OS during the 3-year study period (effectiveness analysis population). CI, confidence interval; m, months; OS, overall survival; rwPFS, real-world progression-free survival.



after CRT remains controversial, it should be determined based on a careful assessment of the patient's condition. Regarding the influence of PD-L1 expression status, the

rwPFS rates in patients with PD-L1 more than or equal to 50% were consistently numerically higher throughout the study period than those in patients with PD-L1 less

than 1% and PD-L1 more than or equal to 1% to less than 50% in the AYAME study, and these results are consistent with those reported in a previous study.²⁴ In the AYAME study, the median rwPFS in patients with PD-L1 less than 1% tended to be longer than that in patients with PD-L1 more than or equal to 1% to less than 50%. Similar results were reported in a previous study.²⁴ The relationship between PD-L1 expression and PFS in cases with PD-L1 less than 50% is controversial²⁵; this could be attributed to changes in PD-L1 expression rates after CRT²⁶ or differences in patient backgrounds other than PD-L1 expression.

The results of the AYAME study suggested that there is no numerical difference in survival among patients in stages IIIA, IIIB, and IIIC before CRT with the PACIFIC regimen. However, longer survival was observed in the postoperative recurrence group than in other stage III groups, which could be attributable to the previous findings that postoperative recurrence tends to have better survival.²⁷ A recent retrospective study reporting improved PFS in patients with locoregional recurrence of NSCLC (after complete resection) treated with CRT followed by durvalumab versus those treated with CRT alone²⁸ confirmed the benefit of durvalumab in this segment.

In this study, rwPFS was numerically comparable among patients with and without *EGFRm*. Patients with *EGFRm* experienced an rwPFS of 21.4 months when treated with durvalumab after CRT. The phase 3 LAURA trial²⁹ indicated that patients with *EGFRm* had a median PFS of 39.1 months with osimertinib after CRT, suggesting that the findings from the LAURA trial could expand treatment options for patients with *EGFRm* in clinical practice.

Our additional analysis demonstrated that patients experiencing AESIs had improved rwPFS compared with those without AESI, which is consistent with the findings from several studies in the context of NSCLC.^{30–33} A study conducted in Japan found that the development of mild irAEs in patients with unresectable stage III NSCLC was associated with better survival outcomes when treated with durvalumab after CRT.³⁰ In addition, several studies have reported an association between irAEs and the efficacy of nivolumab in advanced NSCLC.^{31,32} A meta-analysis further supports this finding, indicating that the occurrence of irAEs is linked to the efficacy of PD-1 or PD-L1 inhibitors in NSCLC treatment.³³ Although AESIs in our study are defined differently from irAEs, the occurrence of AESIs after durvalumab treatment may reflect an active immune response. This immune activation could potentially enhance antitumor activity and lead to improved clinical outcomes in patients with NSCLC receiving immunotherapy.

A retrospective observational study¹⁰ conducted in Japan evaluated 127 patients who progressed after the PACIFIC regimen and received initial subsequent treatment (chemotherapy [platinum + non-platinum]: 94 patients [74.0%]; platinum + ICI: 18 patients [14.2%]; TKI: eight patients [6.3%]; and ICI: seven patients [5.5%]). In the present study, the same tendency was observed as in a previous study¹⁰ regarding the choice of subsequent treatment regimen after the PACIFIC regimen. Findings from both studies indicate that a certain number of patients can receive treatment including platinum-based chemotherapy even after the PACIFIC regimen.

This study has several limitations. First, because this was an observational study, there were no requirements regarding the timing or method of evaluating the treatment effect of durvalumab; hence, rwPFS may have been affected. Second, ILD and AESI assessments were not centrally evaluated, and there is a possibility of variability among the assessments. However, it is important to note that we were able to detect serious toxicities because this study was conducted in a prospective setting.

In conclusion, the results of this large cohort study prospectively demonstrated and strengthened the evidence for the long-term safety, including the post-durvalumab treatment period and effectiveness of durvalumab after CRT in a real-world clinical setting. There are no new safety concerns associated with the PACIFIC regimen in clinical practice, including during the post-durvalumab period, and evaluations of subset populations have demonstrated its effectiveness in a variety of cases.

CRediT Authorship Contribution Statement

Hirotsugu Kenmotsu: Conceptualization, Investigation, Methodology, Project administration, Resources, Supervision, Writing - review & editing.

Yoshinobu Saito: Conceptualization, Methodology, Investigation, Resources, Writing - review & editing, Supervision, Project administration.

Kiichiro Ninomiya: Conceptualization, Methodology, Investigation, Resources, Writing - review & editing, Supervision, Project administration.

Shinya Uematsu: Methodology, Writing - original draft, Writing - review & editing, Project administration.

Burak Akdemir: Methodology, Writing - original draft, Writing - review & editing, Project administration.

Ayako Fukui: Methodology, Writing - original draft, Writing - review & editing, Supervision, Project administration.

Ryo Koto: Methodology, Writing - original draft, Writing - review & editing, Project administration.

Masakazu Fujiwara: Methodology, Writing - original draft, Writing - review & editing, Project administration.

Chikako Iwao: Conceptualization, Methodology, Writing - original draft, Writing - review & editing, Supervision, Project administration.

Hiroshi Kitagawa: Methodology, Writing - original draft, Writing - review & editing, Supervision, Project administration.

Ichiro Yoshino: Conceptualization, Methodology, Investigation, Resources, Writing - review & editing, Supervision, Project administration.

Akihiko Gemma: Conceptualization, Methodology, Investigation, Resources, Writing - review & editing, Supervision, Project administration.

Tetsuya Mitsudomi: Conceptualization, Methodology, Investigation, Resources, Writing - review & editing, Supervision, Project administration.

Nobuyuki Yamamoto: Conceptualization, Investigation, Methodology, Project administration, Resources, Supervision, Writing - review & editing.

All authors approve the final manuscript.

Disclosure

Dr. Kenmotsu has received grants for his institution from Ono Pharmaceutical Co., Ltd., Novartis Pharma K.K., Eli Lilly K.K., AstraZeneca K.K., and Loxo Oncology, and personal fees from Amgen Inc., AstraZeneca K.K., Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Chugai Pharmaceutical Co., Ltd., Daiichi Sankyo Co., Ltd., Eli Lilly K.K., Kyowa Hakko Kirin Co., Ltd., Merck, MSD, Novartis Pharma K.K., Ono Pharmaceutical Co., Ltd., Pfizer, Taiho Pharma, and Takeda Pharmaceutical Co., Ltd., in the past 36 months. Dr. Saito has received support for the present manuscript from AstraZeneca K.K. since the initial planning of the work and payment or honoraria from AstraZeneca K.K., MSD K.K., Daiichi Sankyo Co., Ltd., Nippon Boehringer Ingelheim Co., Ltd., Teijin Healthcare Limited, and Insmed Inc. in the past 36 months. Dr. Ninomiya has received personal fees from AstraZeneca, Boehringer Ingelheim, Kyowa Kirin, Eli Lilly Japan, Chugai Pharmaceutical, Nippon Kayaku, Taiho Pharmaceutical, MSD K.K., Ono Pharmaceutical, Takeda Pharmaceutical, Pfizer Inc., Bristol Myers Squibb, Elekta K.K., Janssen Pharma, Daiichi Sankyo, and Amgen K.K. in the past 36 months. Dr. Uematsu, Ms. Fukui, Mr. Koto, Dr. Fujiwara, Dr. Iwao, Dr. Kitagawa, and Dr. Akdemir are employees of AstraZeneca K.K. Dr. Yoshino has received personal fees from AstraZeneca, Covidien Japan, Takeda, Chugai Pharmaceutical, and Johnson & Johnson in the past 36 months. Dr. Gemma has received support for the present manuscript from

Chugai since the initial planning of the work; payment or honoraria from Chugai and Nippon Kayaku in the past 36 months; and personal fees for participating in a Data Safety Monitoring Board or an Advisory Board from Daiichi Sankyo and AstraZeneca. Dr. Mitsudomi has received funding for the present manuscript from AstraZeneca since the initial planning of the work and personal fees from AstraZeneca in the past 36 months. Dr. Yamamoto has received support for the present manuscript from AstraZeneca K.K. since the initial planning of the work; grants for his institution from A2 Healthcare Corporation, Amgen K.K., AstraZeneca K.K., Eli Lilly Japan K.K., Mebix, Inc., AbbVie GK, Janssen Pharmaceutical K.K., Bristol Myers Squibb, RPM Co., Ltd., Pfizer R&D Japan G.K., Chugai Pharmaceutical Co., Ltd., MSD K.K., Nippon Boehringer Ingelheim Co., Ltd., PRIME-R, Inc., IQVIA Solutions Japan G.K., Novartis Japan, EPS Corporation, Medpace Japan K.K., and Syneos Health Clinical K.K. in the past 36 months; fees for participation on a Data Safety Monitoring Board or Advisory Board from MSD K.K., Amgen K.K., Daiichi Sankyo, Inc., USACO Corporation, AstraZeneca K.K., Ono Pharmaceutical Co., Ltd., and Novartis Japan in the past 36 months; and payment or honoraria for self from Amgen K.K., AstraZeneca K.K., Chugai Pharmaceutical Co., Ltd., AbbVie GK, Janssen Pharmaceutical K.K., Accuray Japan K.K., Guardant Health Japan Corp., Taiho Oncology, Inc., Tsumura & Co., Nippon Kayaku Co., Ltd., Merck Biopharma Co., Ltd., Otsuka Pharmaceutical Co., Ltd., Miyarisan Pharmaceutical Co., Ltd., Kyowa Kirin Co., Ltd., ShiftZero K.K., MSD K.K., Nippon Boehringer Ingelheim Co., Ltd., Eli Lilly Japan K.K., Novartis Japan, Bristol Myers Squibb, Ono Pharmaceutical Co., Ltd., Daiichi Sankyo, Inc., Takeda Pharmaceutical Co., Ltd., Terumo Corporation, Pfizer Japan Inc., USACO Corporation, Kyorin Pharmaceutical Co., Ltd., Medical Review Co., Ltd., and Kowa Company Ltd. in the past 36 months.

Acknowledgments

The authors thank the patients, their families, and all the collaborators and coordinators for their participation. Medical writing support was provided by Annirudha Chillar, MD, PhD, of Cactus Life Sciences (part of Cactus Communications) and was funded by AstraZeneca K.K., Osaka, Japan. This work was funded by AstraZeneca K.K.

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.2025.08.010>.

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