ORIGINAL ARTICLE

J-TAIL-2: A Prospective, Observational Study of Atezolizumab Combined With Carboplatin and Etoposide in Patients With Extensive-Stage SCLC in Japan

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ABSTRACT

Introduction: On the basis of the IMpower133 trial, atezolizumab plus carboplatin and etoposide (CE) is approved as first-line treatment for extensive-stage (ES)-SCLC. The J-TAIL-2 study evaluated atezolizumab plus CE in routine clinical practice settings.

Methods: J-TAIL-2 was a prospective, multicenter observational study in Japan. Patients with ES-SCLC received atezolizumab plus CE in clinical practice. The primary end point was 12-month OS rate. Secondary end points included overall survival (OS), progression-free survival (PFS), and safety in select subgroups, including the IMpower133-unlike (i.e., Eastern Cooperative Oncology Group performance status 2 or more, interstitial lung disease, autoimmune disease) versus IMpower133-like groups.

Results: Overall, 403 patients were included; the median age was 71 years, 16.6% (n = 67) had an Eastern Cooperative Oncology Group performance status 2 or more, 26.8%

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(n = 108) had brain metastasis, 6.9% (n = 28) had interstitial lung disease, 4.0% (n = 16) had autoimmune disease, and 72.7% (n = 293) were IMpower133-unlike. In the efficacy population (n = 399), the 12-month OS rate was 63.7%, median OS was 16.5 months, and median PFS was 5.1 months. In IMpower133-unlike versus IMpower133-like subgroups, the 12-month OS rate was 58.5% versus 77.5%, median OS was 15.5 versus 19.1 months (hazard ratio, 1.32; 95% confidence interval: 0.98–1.77), and median PFS was 4.8 versus 5.4 months (hazard ratio, 1.14; 95% confidence interval: 0.90–1.45). No new safety signals were observed (safety population, n = 400); safety outcomes in the IMpower133-unlike and IMpower133-like subgroups were similar.

Conclusions: In J-TAIL-2, atezolizumab plus CE had efficacy in patients with ES-SCLC in clinical practice that was consistent with that in IMpower133. Taken together with the acceptable safety profile, these data support the use of atezolizumab plus CE in patients with ES-SCLC in Japan, including those who would have been ineligible for IMpower133.

Keywords: Extensive-stage small cell lung cancer; Atezolizumab; Immune checkpoint inhibitor; Observational study

Introduction

Extensive-stage SCLC (ES-SCLC) represents approximately two-thirds of SCLC diagnoses and is characterized by rapid progression, metastases, and poor prognosis.[1–3] For nearly 30 years, platinum-based chemotherapy represented the standard of care for ES-SCLC, despite 2-year survival rates of up to 10%.[4] Results from two phase 3 trials evaluating immune checkpoint inhibitors in combination with platinum-based chemotherapy, IMpower133 (NCT02763579) and CASPIAN (NCT03043872), established a new standard of care for ES-SCLC.[5–8] IMpower133, a multinational, double-blind, placebo-controlled, phase 3 trial that enrolled patients with previously untreated ES-SCLC, revealed overall survival (OS) and progression-free survival (PFS) benefit in patients receiving atezolizumab plus carboplatin and etoposide (CE) compared with chemotherapy.[5,6] On the basis of the results of IMpower133, atezolizumab was the first immune checkpoint inhibitor approved for the first-line treatment of adult patients with ES-SCLC in combination with CE in several countries and regions globally, including in North America, Europe, and countries such as China and Japan in Asia. Nevertheless, only 20 Japanese patients with ES-SCLC were enrolled in the atezolizumab combination arm of the IMpower133 trial,[9] and many patients with frequently occurring demographic-related factors in the real-world setting were excluded from IMpower133 based on its eligibility criteria (i.e., history of autoimmune disease or Eastern Cooperative Oncology Group performance status [ECOG PS] $\geq$ 2).

J-TAIL-2 was a prospective observational study conducted in Japan to collect real-world clinical information on patients with NSCLC or ES-SCLC treated with atezolizumab combination therapy. We report the results from the ES-SCLC cohort of J-TAIL-2, which evaluated the effectiveness and safety of atezolizumab plus CE in patients treated in clinical practice, including patients who would have been excluded from IMpower133 because they did not meet the eligibility criteria.

Methods

Study Design and Patients

This multicenter, noninterventional, prospective observational study enrolled two cohorts of patients: those with NSCLC and those with ES-SCLC across 150 sites in Japan. Eligible patients from the ES-SCLC cohort were at least 20 years of age and scheduled to begin atezolizumab plus CE to treat ES-SCLC in clinical practice. Each drug was administered based on the dosage and schedule in their local labels. Subsequent therapy after discontinuation of study treatment and the criteria for dose reduction, interruption, or discontinuation were not specified. The study was conducted in compliance with the Declaration of Helsinki, the Act on the Protection of Personal Information, and the Ethical Guidelines for Medical and Health Research Involving Human Subjects. All enrolled patients received a full explanation of the contents of the clinical research and provided written consent to participate. The Ethics Review Committee of each study site approved the study protocol and Informed Consent Form before the site could take part in the study. This study was registered at UMIN-CTR under the identifier number UMIN000041263 and at ClinicalTrials.gov under the identifier number NCT04501497.

End Points

The primary end point was 12-month OS rate, defined as the proportion of patients alive at 12 months among the estimated OS rates at each time point, taking censoring into account. OS was defined as the time from the start date of study treatment to death from any cause. Patients without post-baseline information were censored on the date study treatment was started, and patients lost to follow-up were censored on the last known date they were alive before the loss to follow-up.

Surviving patients were censored on the date of last confirmation of survival. Secondary end points included OS, PFS, objective response rate, incidence of adverse events (AEs), and effectiveness and safety analyses in select subgroups based on characteristics at enrollment: IMpower133-unlike versus IMpower133-like, ECOG PS of 2 or more versus less than 2, with versus without brain metastasis, with versus without liver metastasis, with versus without pleural effusion, with versus without history or complication of autoimmune disease, with versus without complication of interstitial lung disease (ILD), large cell neuroendocrine carcinoma versus SCLC, and with versus without immune-related AEs (irAEs). Patients were defined as IMpower133-like if they met eligibility criteria based on IMpower133 and as IMpower133-unlike if they would not have been eligible for IMpower133 due to any of the following: ECOG PS of 2 to 4, inadequate hematologic or end-organ function, brain metastases (without post-treatment loss or scarring), double cancer, history or complication of autoimmune disease, history or complication of ILD, lack of target lesions, previous treatment with immune checkpoint inhibitors, study treatment started within 6 months after completion of chemoradiotherapy, or previous treatment for ES-SCLC (Supplementary Table 1).

Statistics

The target sample size for the ES-SCLC cohort was 400 patients based on feasibility, considering factors such as the enrollment period and number of enrollment sites. On the basis of the difference in 12-month OS rates between the phase 3 OAK trial and the real-world TAIL study and the 12-month OS rate of the IMpower133 trial, the 12-month OS rate for this study was assumed to be 45.2% (95% confidence interval [CI]: 40.4–50.1).[5,10,11] Under these assumptions, the recruitment of 400 patients would enable a reasonably accurate estimation of the 12-month OS rate in a patient population that reflects the real-world clinical setting in Japan.

Kaplan-Meier methodology was used for estimation of median time points and the primary end point of 12-month OS rate. The Brookmeyer-Crowley method was used to calculate the 95% CI for median OS and PFS. The Greenwood formula was used to provide the 95% CI for time point survival. The efficacy analysis population consisted of all treated patients who met the eligibility criteria. Safety analyses included the incidence and severity of AEs, which were summarized using National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 grades. The safety analysis population included all patients who received at least 1 dose of atezolizumab.

Results

Patient Characteristics

Between August 21, 2020, and February 3, 2022, 403 patients were enrolled (intent-to-treat [ITT] population). A total of 400 patients comprised the safety analysis population, and 399 patients comprised the efficacy analysis population (Supplementary Fig. 1). Baseline characteristics of the ITT population are found in Table 1. The median age was 71 (range, 39–91) years, 60.8% (n = 245) of patients were aged 70 years or older, 80.1% (n = 323) were male, and 95.8% (n = 386) were former or current smokers. Within the ITT population, 16.6% (n = 67) of patients had an ECOG PS of 2 or more, 26.8% (n = 108) had brain metastasis, 6.9% (n = 28) had ILD, 1.2% (n = 5) had a history of autoimmune disease, and 4.0% (n = 16) had a complication of autoimmune disease (Table 1). Detailed information on patients with history and complications of autoimmune disease is available in Supplementary Table 2. The most common complications of autoimmune disease were endocrine disorders (2.3%, n = 9). In the ITT population, 72.7% (n = 293) would not have met IMpower133 eligibility criteria (Supplementary Table 3). The most common reasons for not meeting IMpower133-like eligibility criteria were liver function abnormalities (30.8%), brain metastasis (23.3%), and ECOG PS 0 or 1 (16.6%). Overall, 61.9% of patients received at least 1 subsequent cancer therapy (efficacy analysis population; Table 2). A similar proportion of patients in the IMpower133-unlike and IMpower133-like groups received at least 1 post-treatment regimen (61.6% and 62.7%, respectively) (Table 2).

Effectiveness

The median observation time was 13.7 (range, 0.3–28.6) months. OS and PFS outcomes in the efficacy analysis population and the IMpower133-unlike and -like subgroups are summarized in Table 2. In the efficacy analysis population, the 12-month OS rate was 63.7% (95% CI: 58.6–68.3) and median OS (mOS) was 16.5 months (95% CI: 14.9–18.2) (Fig. 1*A*; Table 2). The 12-month PFS rate was 13.9% (95% CI: 10.7–17.6) and median PFS (mPFS) was 5.1 months (95% CI: 4.7–5.3) (Fig. 1*B*; Table 2). Among the efficacy analysis population with measurable lesions, the objective response rate was 66.1% (95% CI: 61.1–70.9). In the IMpower133-unlike subgroup (n = 289) versus the IMpower133-like subgroup (n = 110), mOS was 15.5 months versus 19.1 months (hazard ratio [HR], 1.32; 95% CI: 0.98–1.77), the 12-month OS rate was 58.5% versus 77.5% (Fig. 2*A*; Table 2), mPFS was 4.8 months versus 5.4 months (HR, 1.14; 95% CI: 0.90–1.45), and the 12-month PFS rate was 12.8% versus 16.8%

Table 1. Patient Characteristics of the ITT Population

Patient Characteristics	ITT Population (N = 403)
Age	
Median (range), y	71 (39-91)
≥70 y, n (%)	245 (60.8)
Sex, n (%)	
Male	323 (80.1)
ECOG PS, n (%)	
0	127 (31.5)
1	209 (51.9)
2	48 (11.9)
3	19 (4.7)
4	0
Tobacco use history, n (%)	
Previous	269 (66.7)
Current	117 (29.0)
Never	17 (4.2)
Histology, n (%)	
Small cell carcinoma	392 (97.3)
LCNEC	11 (2.7)
Stage at diagnosis, n (%)	
IIIA	6 (1.5)
IIIB	10 (2.5)
IIIC	12 (3.0)
IV	325 (80.6)
Postoperative recurrence	20 (5.0)
Recurrence after chemoradiation	27 (6.7)
Recurrence after radiation monotherapy	3 (0.7)
Brain metastasis, n (%)	108 (26.8)
Liver metastasis, n (%)	118 (29.3)
Pleural effusion, n (%)	86 (21.3)
Complication of ILD, n (%)	28 (6.9)
History of autoimmune disease, n (%)	5 (1.2)
Complication autoimmune disease, n (%)	16 (4.0)
IMpower133-unlike, n (%)[a]	293 (72.7)
History of surgery for primary disease, n (%)	36 (8.9)
History of irradiation, n (%)	84 (20.8)
Induction therapy completion rate, n (%)[a]	
1-3 cycles	101 (25.3)
≥4 cycles	299 (74.8)

[a]Percentages were calculated based on the safety analysis set (patients who received ≥1 dose of atezolizumab; n = 400).
ECOG PS, Eastern Cooperative Oncology Group performance status; ILD, interstitial lung disease; ITT, intent-to-treat; LCNEC, large cell neuroendocrine carcinoma.

(Fig. 2*B*; Table 2). OS and PFS outcomes for additional select subgroups are summarized in Supplementary Table 4 and depicted in Figure 3*A* and *B* and Supplementary Figures 2 to 9. In patients with ECOG PS of 2 or more (n = 66) versus less than 2 (n = 333), mOS was 11.1 months versus 17.9 months (HR, 2.00; 95% CI: 1.43–2.80; Supplementary Fig. 2A) and mPFS was 4.2 versus 5.2 months (HR, 1.44; 95% CI: 1.08–1.91; Supplementary Fig. 2B). In patients with (n = 108) versus without (n = 280) brain metastasis, mOS was 18.4 months versus 16.2 months (HR, 0.82; 95% CI: 0.60–1.12; Supplementary Fig. 3A) and mPFS was 4.9 months versus 5.2 months (HR, 1.14; 95% CI: 0.90–1.45; Supplementary Fig. 3B). In patients with (n = 94) versus without (n = 305) an irAE, mOS was 21.5 months versus 15.3 months (HR, 0.64; 95% CI: 0.46–0.89; Supplementary Fig. 9A), and mPFS was 6.5 months versus 4.8 months (HR, 0.57; 95% CI: 0.44–0.74; Supplementary Fig. 9B).

Safety

In the safety analysis population, the incidence of all-cause AEs was 85.5% (n = 342; Supplementary Table 5). The most frequently reported AEs of any grade are found in Supplementary Table 6. Grade 3 or higher AEs occurred in 66.3% (n = 265) of patients, with the most frequent being decreased neutrophil count (n = 154; 38.5%), decreased white blood cell count (n = 50; 12.5%), febrile neutropenia (n = 33; 8.3%), decreased platelet count (n = 33; 8.3%), and neutropenia (n = 30; 7.5%) (Table 3). Grade 5 AEs were reported in 2.8% (n = 11) of patients (Supplementary Table 7). These events were pneumonia (n = 3), aspiration pneumonia, bacterial pneumonia, ILD, pneumonitis, febrile neutropenia, peripheral arterial occlusive disease, gastrointestinal hemorrhage, and death (n = 1 each). Any-grade irAEs occurred in 23.5% (n = 94) of patients and were grade 3 or higher in 7.8% of patients (Table 3 and Supplementary Table 8). Two patients (0.5%) had grade 5 irAEs (ILD and pneumonitis [n = 1 each]).

In the IMpower133-unlike (n = 290) versus IMpower133-like (n = 110) subgroups, safety outcomes, including the incidences of AEs of any-grade, grade 3 or higher AEs, and AEs leading to discontinuation of study treatment, were similar (Supplementary Table 5). Safety outcomes in additional select subgroups are found in Supplementary Table 9. Differences in AE incidences of 10% or more within subgroups were found across several groups. In patients with an ECOG PS of 2 or more (n = 67) versus less than 2 (n = 333), SAEs occurred in 43.3% versus 25.5% of patients and irAEs occurred in 13.4% versus 25.5% of patients. In patients with (n = 20) versus without (n = 380) a history or complications of autoimmune disease, irAEs occurred in 40.0% versus 22.6% of patients, adverse drug reactions (ADRs) leading to atezolizumab discontinuation occurred in 10.0% of patients in both groups, and ADRs leading to atezolizumab interruption occurred in 11.3% versus 20.0% of patients. In patients with ILD excluding radiation pneumonitis (n = 17) versus radiation pneumonitis (n = 8) versus without ILD (n = 375), incidences of irAEs (29.4%, 12.5%, 23.5%), AEs applicable to ILD (0%, 12.5%, 6.9%), grade 3 or higher ADRs associated with atezolizumab (23.5%, 12.5%, 13.3%), and ADRs leading to

Table 2. Effectiveness in the Efficacy Analysis, IMpower133-Unlike, and IMpower133-Like Populations

End Points	Efficacy Analysis Population (n = 399)	IMpower133-Unlike Population (n = 289)	IMpower133-Like Population (n = 110)	HR (95% CI) IMpower 133-Unlike vs. -Like
OS events, n	225	164	61	
Median OS (95% CI), mo	16.5 (14.9-18.2)	15.5 (12.6-17.8)	19.1 (16.2-21.8)	1.32 (0.98-1.77)
12-mo OS rate (95% CI), %	63.7 (58.6- 68.3)	58.5 (52.4- 64.1)	77.5 (68.0- 84.4)	
24-mo OS rate (95% CI), %	32.7 (26.9-38.6)	33.4 (26.6- 40.4)	32.9 (22.3- 43.9)	
PFS events, n	346	251	95	
Median PFS, mo (95% CI)	5.1 (4.7-5.3)	4.8 (4.6-5.3)	5.4 (4.9-5.9)	1.14 (0.90-1.45)
12-mo PFS rate (95% CI), %	13.9 (10.7-17.6)	12.8 (9.2-17.0)	16.8 (10.5-24.5)	
24-mo PFS rate (95% CI), %	9.9 (7.0-13.3)	10.0 (6.8-14.0)	9.8 (4.7-17.2)	
Objective response rate (95% CI), %	66.1 (61.1-70.9)	64.9 (58.9-70.6)	69.1 (59.6-77.6)	
Received subsequent treatment, n (%)	247 (61.9)	178 (61.6)	69 (62.7)	

CI, confidence interval; OS, overall survival; PFS, progression-free survival.

atezolizumab discontinuation (5.9%, 0%,10.4%) differed between groups.

AEs related to ILD occurred in 6.8% (n = 27) of patients overall and were grade 3 or higher in 1.8% (n = 7) (Supplementary Table 10). In patients with (n = 86) versus without (n = 314) pleural effusion, grade 3 or higher AEs occurred in 81.4% versus 62.1% of patients, serious AEs occurred in 37.2% versus 26.1% of patients, and grade 3 or higher ADRs associated with atezolizumab occurred in 22.1% versus 11.5% of patients. In patients with (n = 108) versus without (n = 281) brain metastases, grade 3 or higher ADRs associated with atezolizumab occurred in 4.6% versus 16.0% of patients, respectively.

Discussion

To our knowledge, J-TAIL-2 is the largest prospective observational study evaluating atezolizumab use in ES-SCLC in Japanese clinical practice to date. Results from J-TAIL-2 support the use of atezolizumab plus CE in patients with ES-SCLC in routine clinical practice. The patient population in J-TAIL-2 was distinct from a trial population due to various factors, and most patients treated in this clinical practice setting exhibited baseline characteristics that were different from those in IMpower133.[5] For example, patients in J-TAIL-2 had a greater median age (J-TAIL-2: 71 y; IMpower133: 64 y) and 72.7% would have been ineligible for IMpower133 due to various factors such as liver function

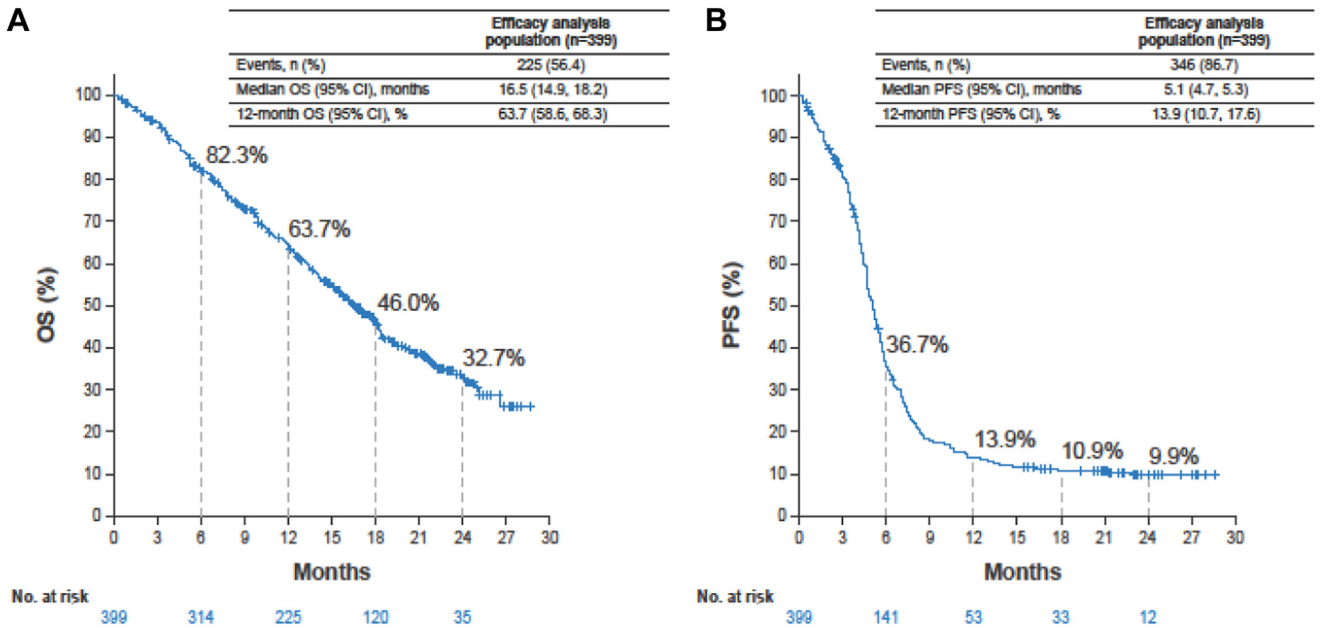

Figure 1. (*A*) OS and (*B*) PFS in the efficacy analysis population. CI, confidence interval; OS, overall survival; PFS, progression-free survival.

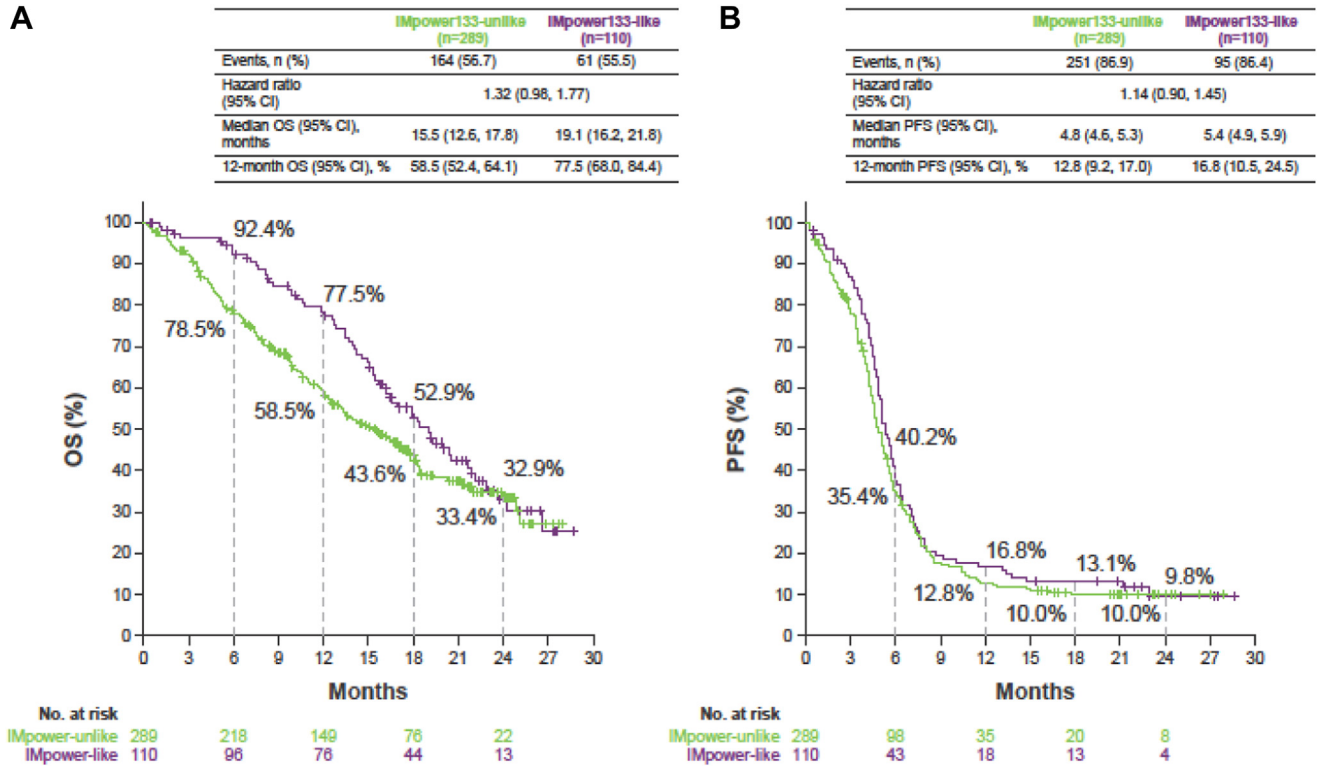

Figure 2. (*A*) OS and (*B*) PFS in IMpower133-unlike versus IMpower133-like subgroups of the efficacy analysis population. CI, confidence interval; OS, overall survival; PFS, progression-free survival.

abnormalities, ECOG PS of 2 or more, or a history or complication of ILD or autoimmune disease. It also should be noted that although the IMpower133-like subgroup is defined as a population similar to that of the IMpower133 trial, it is a distinct trial population. Although crosstrial comparisons should be made with caution given differences in study design and populations, it appeared that effectiveness in J-TAIL-2 was similar to or better than that in IMpower133 (J-TAIL-2: 12-mo OS rate, 63.7%; mOS, 16.5 mo; mPFS, 5.1 mo; IMpower133: 12-mo OS rate, 51.7%; mOS, 12.3 mo; mPFS, 5.2 mo).[5] Because the proportion of patients who received at least 1 post-treatment regimen was 61.9% in J-TAIL-2 compared with 51.7% in the atezolizumab arm of IMpower133, one possibility is that the higher proportion of patients receiving post-treatment therapy may have contributed to OS outcomes in this study. No new safety signals were observed in the safety analysis population of J-TAIL-2, which included elderly patients and those with various disease characteristics and comorbidities often excluded from clinical trials.

Although reduced OS and PFS outcomes, including 12-month rates, were found in the IMpower133-unlike when compared with the IMpower133-like subgroup, results were still favorable in the IMpower133-unlike group and were comparable to the IMpower133 trial results. Similar 24-month OS and PFS rates between the two groups suggest that the proportion of patients who can achieve long-term survival may not change even in the IMpower133-unlike population. Of note, a similar proportion of patients received at least 1 subsequent cancer therapy in the IMpower133-unlike and IMpower133-like groups (61.6% and 62.7%, respectively), which may have contributed to OS outcomes as mentioned previously. Other subgroups also revealed efficacy in clinical practice. Although mOS and mPFS tended to be shorter in the subgroup with ECOG PS more than or equal to 2 than in the subgroup with ECOG PS less than 2, OS and PFS rates were similar at 24 months, suggesting that a similar percentage of patients in each subgroup may achieve long-term response. In addition, improvement in ECOG PS has been found to occur with treatment in patients with an ECOG PS of 2 or more at baseline.[12] In the subgroup of patients with irAEs, the 24-month PFS rate was 19.5% versus 6.8% in the group without irAEs, suggesting a relationship between the occurrence of irAEs and long-term response. Although the relationship between irAEs and atezolizumab efficacy has been reported in NSCLC,[13] it is also important to monitor for and appropriately manage these events.[14,15]

Safety outcomes were similar between the IMpower133-unlike and IMpower133-like groups, and similar safety signals were found in subgroups with

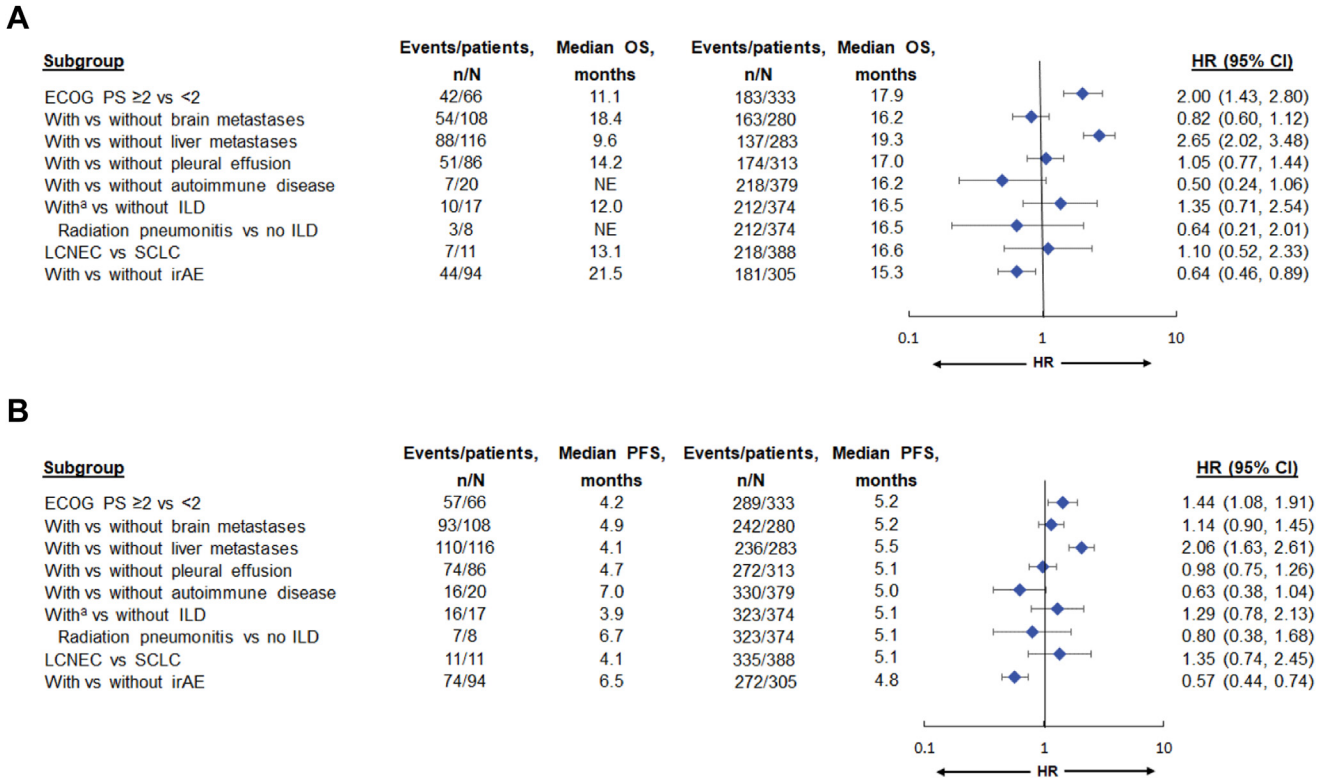

Figure 3. (*A*) OS and (*B*) PFS in select subgroups of the efficacy analysis population. CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; ILD, interstitial lung disease; irAE, immune-related adverse event; OS, overall survival; PFS, progression-free survival. [a]Excluding radiation pneumonitis.

other characteristic baseline factors. Nevertheless, analyses highlighted some safety differences between groups. For example, serious AEs were more common in patients with an ECOG PS of 2 or more versus less than 2 (43.3% versus 25.5%), with versus without pleural effusion (37.2% versus 26.1%), and with versus without autoimmune disease (45.0% versus 27.6%). Although long-term efficacy outcomes were encouraging in the ECOG PS of 2 or more subgroup, the incidence of SAEs may be increased in those patients versus patients with an ECOG PS less than 2; thus, the risk-benefit ratio should be considered in clinical practice. Among the patients with pleural effusion, AEs were generally more common, and the incidences and grades of hematologic toxicities, such as neutropenia, were higher than in patients without pleural effusion. Patients with a history or complication of autoimmune disease had a higher incidence of irAEs than patients without a history or complication of autoimmune disease. As such, and although efficacy was similar between the two subgroups, caution is needed when administering atezolizumab plus CE to these patients.[16]

ILD did not occur in patients with a complication of ILD before the initiation of study treatment (excluding radiation pneumonitis), and grade 2 ILD occurred in one patient with radiation pneumonitis as a complication. Although these data are informative, baseline ILD imaging and other related details were not obtained; thus, continued caution is required when treating these patients.[17] On the basis of the safety data, the risk-benefit ratio should be considered when treating select subgroups in clinical practice. Indeed, the safety and efficacy outcomes from this analysis suggest that administration of atezolizumab plus CE should not necessarily be prohibited, even in patients with a history of ILD or autoimmune disease. Furthermore, the encouraging 12- and 24-month survival rates observed in select subgroups, even those with ECOG PS of 2 or more, suggest that long-term responses may be achieved in patients with various baseline factors not necessarily permitted in clinical trials.

Limitations of the study include the observational nature of the trial under real clinical conditions, the lack of a control group, and the small sample size of some of the subgroups. Furthermore, the frequency of testing for PFS assessment was not specified and may have varied among participating centers, affecting PFS outcomes (secondary end point). In addition to baseline ILD imaging, details of baseline autoimmune disease status and detailed information on baseline brain metastases (stable brain metastases that had been treated or active brain metastases that had not been treated) were not

Table 3. The Most Common Grade 3 or Higher AEs (in ≥1% of patients) and irAEs (in ≥1% of patients) in the Safety Analysis Population

n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
AE, by grade	23 (5.8)	54 (13.5)	108 (27.0)	146 (36.5)	11 (2.8)
Neutrophil count decreased	2 (0.5)	14 (3.5)	44 (11.0)	110 (27.5)	0
White blood cell count decreased	8 (2.0)	18 (4.5)	32 (8.0)	18 (4.5)	0
Febrile neutropenia	0	0	25 (6.3)	7 (1.8)	1 (0.3)
Platelet count decreased	35 (8.8)	21 (5.3)	21 (5.3)	12 (3.0)	0
Neutropenia	0	2 (0.5)	12 (3.0)	18 (4.5)	0
Anemia	20 (5.0)	30 (7.5)	17 (4.3)	0	0
Decreased appetite	21 (5.3)	17 (4.3)	10 (2.5)	0	0
Pneumonia	0	4 (1.0)	5 (1.3)	1 (0.3)	3 (0.8)
Thrombocytopenia	2 (0.5)	1 (0.3)	5 (1.3)	0	0
Hyponatremia	1 (0.3)	6 (1.5)	5 (1.3)	0	0
Interstitial lung disease	2 (0.5)	4 (1.0)	2 (0.5)	1 (0.3)	1 (0.3)
irAE, by grade	15 (3.8)	48 (12.0)	19 (4.8%)	10 (2.5)	2 (0.5)
Hypothyroidism	2 (0.5)	11 (2.8)	0	0	0
Rash	3 (0.8)	4 (1.0)	0	0	0
Pneumonitis	2 (0.5)	3 (0.8)	1 (0.3)	0	1 (0.3)
Interstitial lung disease	0	2 (0.5)	1 (0.3)	1 (0.3)	1 (0.3)
Hyperthyroidism	3 (0.8)	1 (0.3)	0	0	0
Decreased appetite	2 (0.5)	1 (0.3)	1 (0.3)	0	0
Diarrhea	1 (0.3)	2 (0.5)	1 (0.3)	0	0
Neutrophil count decreased	0	0	2 (0.5)	2 (0.5)	0
Platelet count decreased	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)	0

AE, adverse event; irAE, immune-related adverse event.

collected; thus, results in these subgroups should be interpreted with caution. Given the median observation time of 13.7 months, longer follow-up is needed to assess long-term OS outcomes and improve the robustness of the study finding. In addition, AEs of lower severity may not be as frequently recorded in real clinical practice as they are in clinical trials,[18] so the incidence of these AEs may have been lower in this study compared with the IMpower133 trial.

In conclusion, the J-TAIL-2 study was a large observational study conducted in patients with ES-SCLC in Japanese real-world clinical practice which revealed that the effectiveness of atezolizumab plus CE was comparable to that of the IMpower133 trial. Subgroup analyses revealed an acceptable benefit-risk profile in patients who were ineligible for the IMpower133 trial. There were no new safety signals, and data suggest that the regimen may be suitable in patients with comorbidities based on a risk-benefit evaluation.

CRediT Authorship Contribution Statement

Eisaku Miyauchi: Investigation, Writing - review and editing.

Makoto Nishio: Conceptualization, Methodology, Writing - review and editing, Supervision, Project Administration.

Kadoaki Ohashi: Resources, Writing - review and editing.

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Eiki Kikuchi: Investigation, Writing - review and editing.

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Yuki Kobayashi: Visualization, Writing - original draft, Writing - review and editing.

Asako Miwa: Project administration, Writing - review and editing.

Misa Tanaka: Methodology, Visualization, Writing - review and editing.

Akihiko Gemma: Conceptualization, Investigation, Data Curation, Writing - review and editing, Supervision, Project administration, Funding acquisition.

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Data Sharing Statement

The data sets generated or analyzed during the current study are available from the corresponding author on reasonable request.

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.2024.100783.

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