



IMpower132: Atezolizumab plus platinum-based chemotherapy vs chemotherapy for advanced NSCLC in Japanese patients

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Abstract

IMpower132 explored the safety and efficacy of atezolizumab plus pemetrexed and platinum-based chemotherapy as first-line treatment for advanced non-small-cell lung cancer (NSCLC). Key eligibility criteria for the phase 3, open-label, IMpower132 study included age ≥ 18 y, histologically or cytologically confirmed advanced non-squamous NSCLC per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, Eastern Cooperative Oncology Group performance status of 0/1, and no prior systemic treatment for stage IV NSCLC. Patients received atezolizumab (1200 mg) plus pemetrexed (500 mg/m²) and cisplatin (75 mg/m²) or carboplatin (area under the concentration curve, 6 mg/mL/min) (APP arm) or chemotherapy alone (PP arm). The co-primary study endpoints were overall survival (OS) and investigator-assessed progression-free survival (PFS) per RECIST 1.1 in the intention-to-treat population. A subgroup analysis was conducted in Japanese patients. In the Japanese subgroup (n = 101), median OS was 30.8 (95% CI, 24.3 to not estimable) mo in the APP arm (n = 48) and 22.2 (95% CI, 15.7-30.8) mo in the PP arm (n = 53; hazard ratio [HR], 0.63 [95% CI, 0.36-1.14]). PFS was 12.8 (95% CI, 8.6-16.6) mo in the APP arm vs 4.5 (95%

Abbreviations: AE, adverse event; AESI, adverse event of special interest; ALK, anaplastic lymphoma kinase; APP, atezolizumab plus platinum-based chemotherapy plus pemetrexed; DOR, duration of response; EGFR, epidermal growth factor receptor; EML4, echinoderm microtubule-associated protein-like 4; HR, hazard ratio; IC, tumor-infiltrating immune cells; ITT, intention-to-treat; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PD-1, programmed death-1; PD-L1, programmed death-ligand 1; PFS, progression-free survival; PP, platinum-based chemotherapy plus pemetrexed; TC, tumor cells; TRAE, treatment-related adverse event.

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CI, 4.1-6.7) mo in the PP arm (HR, 0.33 [95% CI, 0.21-0.58]). Grade 3/4 treatment-related adverse events (TRAEs) occurred in 68.8% of APP arm patients and 44.2% of PP arm patients. Consistent with global study results, atezolizumab plus pemetrexed and platinum-based chemotherapy improved efficacy and was well tolerated in Japanese patients with advanced NSCLC despite a higher incidence of grade 3/4 TRAEs.

KEYWORDS

atezolizumab, checkpoint inhibitors, IMpower132, Japan, programmed death-ligand 1

1 | INTRODUCTION

Lung cancer is one of the most common forms of malignancy and a leading cause of cancer-related deaths worldwide,^{1,3} accounting for the highest number of diagnosed cases (11.6%) and the highest mortality rate (18.4%) among all cancers, in both sexes combined.^{2,3} NSCLC is the most dominant form of lung cancer, accounting for more than 80% of all lung cancers. The incidence and mortality of lung cancer are significantly higher in Asian populations, particularly in Japanese patients,^{1,3} compared with in other demographics.³ Treatment strategies for advanced or metastatic NSCLC (stage IV) are limited to systemic therapies such as chemotherapy, targeted therapy, and immunotherapy, or their combinations.⁴⁻⁸ The standard first-line treatment for patients with metastatic NSCLC without EGFR or ALK gene alterations, having tumors with high expression of programmed death-ligand 1 (PD-L1; tumor proportion score, $\geq 50\%$) and no contraindications for the use of immunotherapy, irrespective of histology, is anti-programmed death-1 (PD-1) monotherapy with pembrolizumab.^{4-6,9} Additionally, chemo-immunotherapy combinations of pembrolizumab plus carboplatin or cisplatin and pemetrexed,¹⁰ carboplatin plus paclitaxel plus bevacizumab and atezolizumab,¹¹ and carboplatin plus *nab*-paclitaxel and atezolizumab¹² are approved first-line treatments for advanced non-squamous NSCLC, irrespective of PD-L1 expression levels, in the USA, Europe, and other countries worldwide.⁴⁻⁶

The humanized anti-PD-L1 monoclonal antibody atezolizumab inhibits the interaction of PD-L1 with PD-1 and B7.1, thereby reinvigorating tumor-specific T-cell immunity.¹³ Second-line atezolizumab monotherapy in patients with advanced or metastatic NSCLC who previously received platinum-based chemotherapy showed improved OS compared with those who received docetaxel in the phase 3 OAK¹⁴ clinical trial. Phase 3 trials evaluating the efficacy of atezolizumab combined with carboplatin and *nab*-paclitaxel (IMpower130)¹² or atezolizumab combined with bevacizumab and carboplatin plus paclitaxel (IMpower150)¹¹ in first-line treatment of metastatic non-squamous NSCLC also achieved their co-primary endpoints of OS and PFS. In the IMpower130 study, a median OS benefit of 4.7 mo (stratified HR, 0.79; 95% confidence interval [CI], 0.64-0.98) and a PFS benefit of 1.5 mo (stratified HR 0.64; 95% CI, 0.54-0.77) were observed with the addition of atezolizumab to carboplatin plus *nab*-paclitaxel. Median OS with atezolizumab plus bevacizumab and chemotherapy treatment in the IMpower150 study was 19.2 mo vs 14.7 mo with bevacizumab

plus chemotherapy treatment (stratified HR, 0.78; 95% CI, 0.64-0.96), and the median PFS was 8.3 mo with atezolizumab vs 6.8 mo without atezolizumab (stratified HR, 0.62; [95% CI, 0.52-0.74]). Atezolizumab in combination with chemotherapy with or without bevacizumab is approved for the first-line treatment of non-squamous stage IV NSCLC.^{4-6,11} Atezolizumab plus pemetrexed and platinum-based chemotherapy is approved in Japan alone for the first-line treatment of advanced non-squamous NSCLC.

Previous studies have demonstrated differences between Asian and non-Asian populations in their clinical responses and AEs with systemic therapy.¹⁵⁻¹⁷ Japanese populations in particular have shown greater clinical benefit with some targeted therapies and immunotherapies.¹⁵⁻¹⁷ However, a higher incidence of treatment-related pneumonitis and risk of hepatotoxicities has also been observed in Japanese patients.¹⁶ Anti-PD-1/PD-L1 treatments are associated with a greater risk of immune-related pneumonitis compared with chemotherapy or placebo,^{18,19} particularly in patients with NSCLC.^{16,19-21} For example, the Japanese subpopulation in the OAK study had a survival benefit similar to that of the non-Japanese population, but these patients had a higher incidence of pneumonitis as an AESI (Japanese patients, 3.6%; overall population, 0.8%).²² In addition, the clinical study data in the Japanese patients on anti-PD-1/PD-L1 treatment plus carboplatin or cisplatin and pemetrexed are limited.

Therefore, it is of interest to analyze the clinical outcomes and safety risks with immunotherapy specifically in Asian populations, particularly Japanese patients, in order to study demographic-specific clinical responses and toxicities and further help to tailor treatment strategies.¹⁶

The global phase 3 IMpower132 study (NCT02657434) compared the safety and efficacy of atezolizumab in combination with PP with those of PP in chemotherapy-naïve patients with stage IV NSCLC. Here we describe the efficacy and safety results for the Japanese subpopulation of the IMpower132 study.

2 | PATIENTS AND METHODS

2.1 | Study design and treatment

IMpower132 (NCT02657434) is a multicenter, randomized, open-label, phase 3 trial in which the safety and efficacy of atezolizumab

plus pemetrexed and carboplatin or cisplatin were compared with those of pemetrexed and carboplatin or cisplatin as first-line treatment in chemotherapy-naïve patients with stage IV non-squamous NSCLC.

Eligible patients were randomized in a 1:1 ratio through an interactive voice/web response system into the atezolizumab plus platinum-based chemotherapy plus pemetrexed (APP) arm or the platinum-based chemotherapy PP arm. The study was conducted in 2 phases: induction and maintenance. Patients in the APP arm received atezolizumab (1200 mg) plus pemetrexed (500 mg/m²) and, based on the investigator's choice, either cisplatin (75 mg/m²) or carboplatin (area under the curve of 6 mg/mL/min) on day 1 of a 3-wk cycle, for 4 or 6 cycles. All drugs were administered intravenously. Patients in the PP arm received identical doses of pemetrexed and carboplatin or cisplatin. The number of cycles in the induction phase was determined and documented by the investigator prior to randomization. Induction treatment was administered until completion of 4 or 6 cycles, as determined by the investigator, or until unacceptable toxicity or disease progression. Participants in either arm who experienced clinical benefit during the induction phase proceeded to the maintenance phase, in which APP patients received atezolizumab (1200 mg) plus pemetrexed (500 mg/m²) and PP patients received pemetrexed alone on day 1 of every 3-wk cycle until disease progression, loss of clinical benefit, or unacceptable toxicity.

The trial was conducted in accordance with Good Clinical Practice guidelines and the principles of the Declaration of Helsinki. Ethics approval was obtained from the Institutional Review Board or Ethics Committees of each participating institution. To participate in the trial, all patients provided written informed consent.

2.2 | Patients

Japanese patients, both male and female and aged ≥ 18 y, were eligible for enrollment in the trial if they had histologically or cytologically confirmed stage IV NSCLC in accordance with the Union Internationale contre le Cancer/American Joint Committee on Cancer staging system (7th edition)²³ with measurable disease as defined by RECIST version 1.1. Patients with tumors of mixed non-small-cell histology (ie, squamous and non-squamous) were eligible if the major histological component appeared to be non-squamous. Eligibility criteria also included no prior treatment for stage IV non-squamous NSCLC and an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1. A treatment-free interval of at least 6 mo before randomization since the last dose of chemotherapy and/or radiotherapy was required for patients who had received any systemic treatment with curative intent for non-metastatic disease. The anti-PD-L1 SP142 immunohistochemistry assay (Ventana Medical Systems Inc) was used to determine PD-L1 status for investigational purposes. PD-L1 expression on TC or tumor-infiltrating IC was scored as: TC1/2/3 or IC1/2/3, defined as PD-L1 expression on $\geq 1\%$ TCs or ICs; TC2/3 or IC2/3, defined as PD-L1 expression on

$\geq 5\%$ TCs or ICs; and TC3 or IC3, defined as PD-L1 expression on $\geq 50\%$ TCs or $\geq 10\%$ ICs.

Patients were excluded from the study if they had a sensitizing *EGFR* mutation or an *ALK* fusion oncogene. Patients with unknown *EGFR/ALK* status were required to be tested before enrolling. Other exclusion criteria were active or untreated central nervous system metastases, prior treatment with *EGFR* or *ALK* inhibitors, CD137 agonist or immune checkpoint blockade therapies and treatment with systemic immunosuppressants or immunostimulatory agents within 4 wk prior to randomization.

2.3 | Assessments and endpoints

The co-primary efficacy endpoints of this study were investigator-assessed PFS based on RECIST 1.1 and OS. Tumor assessment was conducted at baseline and every 6 wk for the first 48 wk after day 1 of cycle 1 of a 21-d cycle, followed by assessment every 9 wk until radiographic disease progression, consent withdrawal, death, or study termination by sponsor, whichever occurred first. Key secondary efficacy endpoints included investigator-assessed objective response rates (ORR) and the DOR in accordance with RECIST 1.1 and the OS rate at 12 and 24 mo. Stratification factors for randomization were sex (male vs female), ECOG PS (0 vs 1), smoking status (never vs current and/or former), and chemotherapy regimen (carboplatin vs cisplatin).

2.4 | Safety

The safety and tolerability of PP with or without atezolizumab were evaluated by monitoring the incidence, nature, and severity of AEs graded in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events v4.0 (NCI CTCAE) in all randomized patients who received any amount of study drug, with patients grouped based on whether a full or partial dose of any amount of atezolizumab was received, including cases where atezolizumab was administered by error. From initiation of study drug, all serious AEs and AESIs were reported until 90 d after the last dose of study drug or initiation of non-protocol systemic therapy after the last dose of study treatment, whichever occurred first. All other AEs were reported until 30 d after the last dose of study drug or initiation of new anti-cancer therapy after the last dose of study drug.

2.5 | Statistical analysis

Detailed statistical methods for the global IMpower132 study have been previously described (Nishio et al *J Thorac Oncol* in preparation). Briefly, primary PFS analysis for the global ITT population was conducted at 458 PFS events, along with interim efficacy analysis of OS. Final OS analysis was conducted when 389 OS events in the ITT population occurred. Primary PFS and final OS results are reported

here. Comparisons of PFS and OS between the treatment and control arms in the ITT population were tested based on a stratified log-rank test, using sex (male vs female), ECOG PS (0 vs 1), and chemotherapy regimen (carboplatin vs cisplatin) as stratification factors. HRs including 95% CIs were estimated using a stratified Cox regression model. Kaplan-Meier methodology was used to estimate median PFS and OS for each treatment arm, and the 95% CI for the median PFS and OS was constructed using the Brookmeyer-Crowley methodology.

The Japanese subpopulation, which included patients enrolled at sites in Japan during the global enrollment phase, was analyzed using the same statistical methods as described for the global population. The Japanese ITT population included all patients in the Japanese subgroup, with patients grouped based on the treatment assigned at randomization, regardless of whether they received any assigned study drug. Safety was evaluated in all Japanese patients who received any amount of any study drug.

3 | RESULTS

3.1 | Patients

In total, 578 patients were enrolled globally in the IMpower132 study, of which 101 patients from 20 sites in Japan enrolled between

July 22, 2016, and April 14, 2017 (Figure 1). Among the Japanese subpopulation, 48 patients were randomized to the APP arm and 53 to the PP arm. Baseline characteristics were similar between the 2 treatment arms in the Japanese subpopulation, with the exception of PD-L1 expression. High PD-L1 expression (TC3 or IC3) was observed in a higher proportion of patients in the APP arm ($n = 7$, 14.6%) compared with in the PP arm ($n = 1$, 1.9%, Table 1). However, only 49.5% of the Japanese subpopulation was evaluable for exploratory PD-L1 biomarker analysis. Baseline characteristics were similar between the Japanese and the global ITT populations in both treatment arms (Nishio et al *J Thorac Oncol* in preparation).

3.2 | Efficacy

The cutoff dates were May 22, 2018, for the primary PFS analysis and July 18, 2019, for the OS final analysis. In the Japanese subpopulation, the median duration of survival follow-up for PFS at primary analysis was 17.5 (range, 0.8-21.6) mo in the APP arm and 15.9 (range, 0-21.5) mo in the PP arm. The median PFS in the APP arm was 12.8 (95% CI, 8.6-16.6) mo compared with 4.5 (95% CI, 4.1-6.7) mo in the PP arm (stratified HR, 0.35 [95% CI, 0.21-0.58]) (Figure 2A). At the time of the OS final analysis, the updated median PFS in the Japanese subpopulation was 13.3 (95% CI, 9.5-17.4) mo with APP

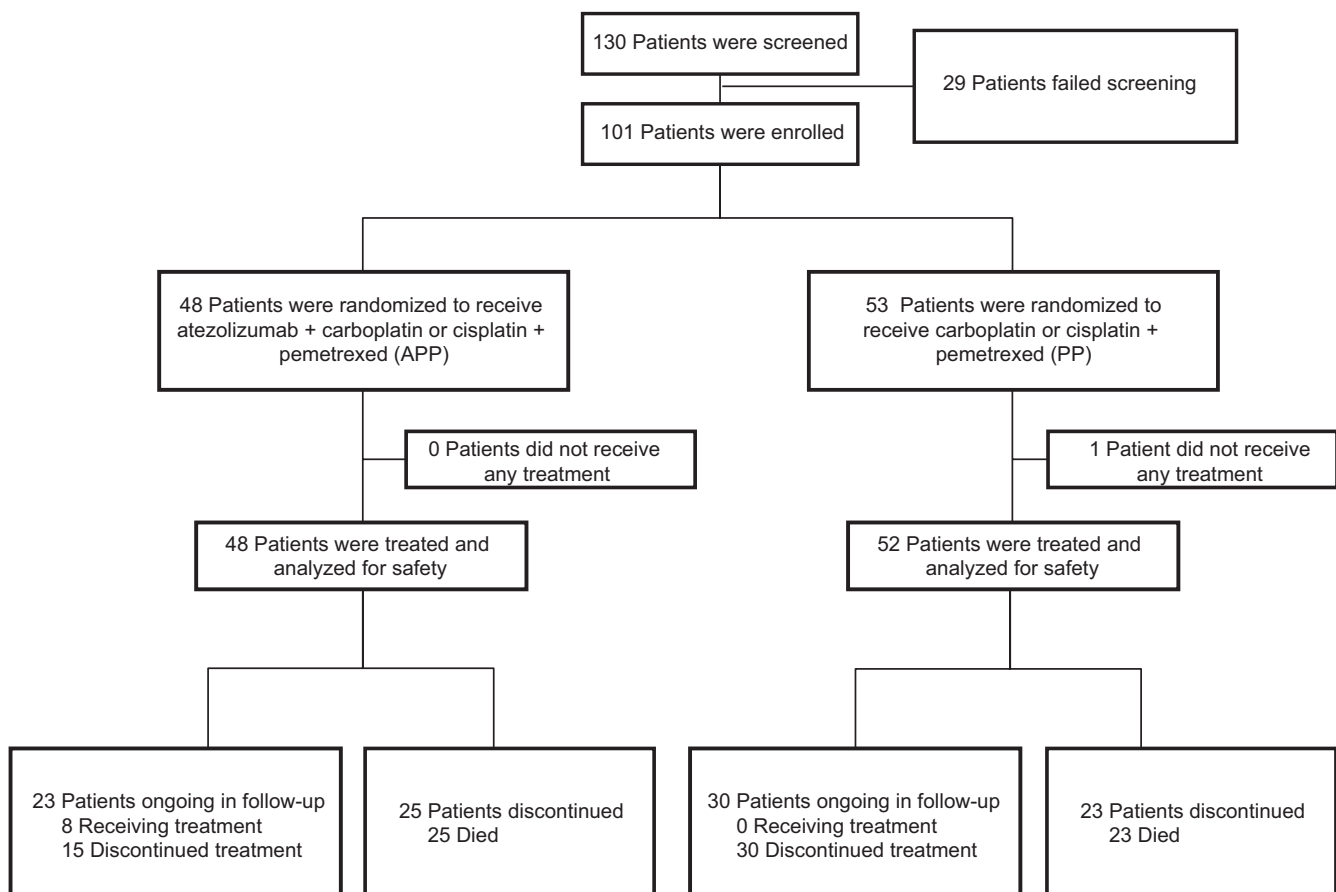


FIGURE 1 CONSORT diagram in Japanese patients

TABLE 1 Demographics and baseline characteristics of the Japanese patients

	APP (n = 48)	PP (n = 53)	All patients (N = 101)
Age			
Median (range)	65 (37-83)	66 (44-78)	65 (37-83)
≥65 y, n (%)	29 (60.4)	29 (54.7)	58 (57.4)
Age group, y, n (%)			
<65	19 (39.6)	24 (45.3)	43 (42.6)
65-74	22 (45.8)	26 (49.1)	48 (47.5)
75-84	7 (14.6)	3 (5.7)	10 (9.9)
Sex, n (%)			
Male	31 (64.6)	39 (73.6)	70 (69.3)
Female	17 (35.4)	14 (26.4)	31 (30.7)
Baseline ECOG, n (%)			
0	21 (43.8)	22 (41.5)	43 (42.6)
1	27 (56.3)	31 (58.5)	58 (57.4)
Tobacco use history, n (%)			
Never	9 (18.8)	5 (9.4)	14 (13.9)
Current or former	39 (81.3)	48 (90.6)	87 (86.1)
Liver metastasis at enrollment			
Yes	3 (6.3)	3 (5.7)	6 (5.9)
No	45 (93.8)	50 (94.3)	95 (94.1)
EGFR mutation status, n (%)			
Positive	0	0	0
Negative	48 (100)	53 (100)	101 (100)
EML4-ALK			
Rearrangement status, n (%)			
Positive	0	0	0
Negative	48 (100)	53 (100)	101 (100)
KRAS mutation status, n (%)			
Positive	0	0	0
Negative	0	2 (3.8)	2 (2.0)
Unknown	48 (100)	51 (96.2)	99 (98.0)
Creatinine clearance, n (%)^a			
<60 mL/min	9 (18.8)	8 (15.4)	17 (17.0)
>60 mL/min	39 (81.3)	44 (84.6)	83 (83.0)
PD-L1 subgroups, n (%)			
TC3 or IC3	7 (14.6)	1 (1.9)	8 (7.9)
TC2/3 or IC2/3	11 (22.9)	2 (3.8)	13 (12.9)
TC1/2/3 or IC1/2/3	14 (29.2)	9 (17.0)	23 (22.8)
TC0 and IC0	13 (27.1)	14 (26.4)	27 (26.7)
Unknown	21 (43.8)	30 (56.6)	51 (50.5)

Abbreviations: ALK, anaplastic lymphoma kinase; APP, atezolizumab + carboplatin or cisplatin + pemetrexed; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; EML4, echinoderm microtubule-associated protein-like 4; IC, tumor-infiltrating immune cells; PD-L1, programmed death-ligand 1; PP, carboplatin or cisplatin + pemetrexed; TC, tumor cells.

^aWeight for 1 patient in the PP arm could not be measured and hence was not evaluable for creatinine clearance.

compared with 4.5 (95% CI, 4.1-6.7) mo in the PP patients (stratified HR, 0.33; [95% CI, 0.20-0.54]) (Figure S1).

At the OS final analysis, the median follow-up duration for Japanese patients was 31.7 (range, 0.8-35.7) mo in the APP arm and 29.3 (range, 0-35.2) mo in the PP arm. The median OS in the APP arm was 30.8 (95% CI, 24.3-not estimable [NE]) mo compared with 22.2 (95% CI, 15.7-30.8) mo in the PP arm (stratified HR, 0.63; [95% CI, 0.36-1.14]) (Figure 2B). The OS rate at 12 mo was 82.6% (95% CI, 71.7%-93.6%) in the APP arm and 77.6% (95% CI, 65.9%-89.3%) in the PP arm and at 24 mo was 65.2% (95% CI, 51.5%-79.0%) in the APP arm and 46.1% (95% CI, 32.0%-60.2%) in the PP arm. Exploratory subgroup analyses in Japanese patients have been shown as a reference (Figure S2).

Confirmed investigator-assessed ORR was 64.6% with APP compared with 28.3% with PP treatment (Table 2). Median DOR was 15.2 (95% CI, 7.9-NE) mo with APP and 5.6 (95% CI, 4.3-11.8) mo with PP. Ongoing response at the data cutoff for final analysis was observed in 11 of the 31 evaluable patients (35.5%) in the APP arm and in none of the 15 evaluable patients in the PP arm.

3.3 | Safety

At the time of final OS analysis, 32 Japanese patients (66.7%) received more than 6 doses of atezolizumab (Table S1), and 22 (42.3%) and 29 patients (60.4%) received more than 6 pemetrexed doses in the APP and PP arms, respectively. The median duration of treatment was 7.9 (range, 0-34) mo and 3.7 (range, 0-31) mo with APP and PP, respectively.

Both treatment arms in the Japanese population reported the same rates of all-cause AEs (100% in both arms) and treatment-related AEs (TRAEs) (100% in both arms) (Table 3). Higher incidences of all-cause and treatment-related grade 3/4 AEs were observed with APP (Table 3; all-cause, 72.9%; treatment related, 68.8%) compared with taking PP (all-cause, 50.0%; treatment related, 44.2%). The most-frequent all-grade AEs were nausea (APP, 62.5%; PP, 51.9%), decreased appetite (APP, 56.3%; PP, 48.1%), and constipation (APP, 45.8%; PP, 46.2%) (Table 4). The most frequently reported grade 3/4 AEs were neutrophil count decreased (APP, 22.9%; PP, 19.2%), white blood cell decreased (APP, 14.6%; PP, 9.6%), and lymphocyte count decreased (APP, 14.6%; PP, 1.9%). More serious AEs were reported with APP (52.1%) compared with taking PP (23.1%), with a higher incidence of treatment-related serious AEs with APP (35.4%) compared with taking PP (21.2%). Two deaths occurred in each arm (APP, 4.2%; PP, 3.8%) and they were both deemed treatment related.

In the APP arm, a higher incidence of respiratory, thoracic, and mediastinal disorders (69.0%) and renal and urinary disorders (24.1%) were reported in patients >65 y (n = 29) compared with in patients <65 y of age (n = 19; respiratory, thoracic, and mediastinal disorders, 42.1%; renal and urinary disorders, 5.3%; Table 5). Further analysis of reported AEs based on advanced age (<75 or ≥75 y; Table S2) showed an 85.7% incidence of respiratory, thoracic, and mediastinal disorders, and a 28.6% incidence of renal and urinary

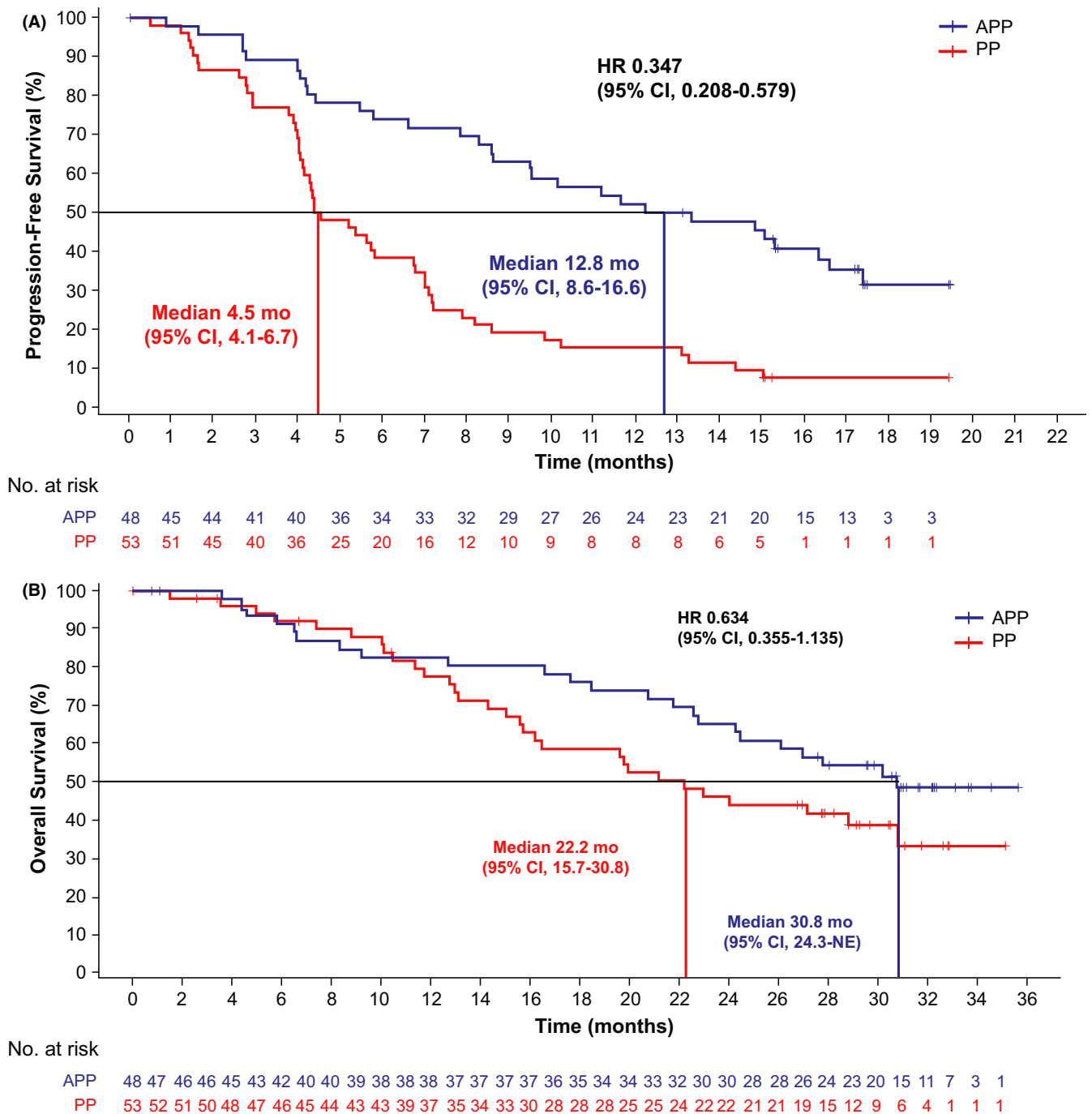


FIGURE 2 In Japanese patients, (A) investigator-assessed progression-free survival at primary analysis and (B) overall survival at final analysis. APP, atezolizumab + carboplatin or cisplatin + pemetrexed; HR, hazard ratio; NE, not estimable; PP, carboplatin or cisplatin + pemetrexed

disorders in patients >75 y of age in the APP arm ($n = 7$), compared with a 53.7% incidence of respiratory, thoracic, and mediastinal disorders, and a 14.6% incidence of renal and urinary disorders in patients <75 y of age ($n = 41$).

In the Japanese subpopulation, AEs led to withdrawal from any treatment in 20 (41.7%) patients in the APP arm (Table 3), which included 3 out of 7 patients (42.9%) who were aged ≥ 75 y and 17 of 41 patients who were aged <75 y. AEs led to withdrawal from any treatment in 63 (25.9%) patients in the PP arm, with all 3 patients

(100%) with advanced age (≥ 75 y) and 12 (41.5%) out of 49 patients aged <75 y withdrawing from any treatment.

A higher incidence of TRAEs was observed with the atezolizumab combination in Japanese patients (100%) compared with in the non-Japanese IMpower132 population (89.7%). The Japanese subpopulation also had a higher incidence of all-cause AEs (Japanese, 72.9%; non-Japanese, 61.7%) and treatment-related grade 3-4 AEs (Japanese, 68.8%; non-Japanese, 51.9%) with APP. In the Japanese and non-Japanese populations treated with APP, similar rates of

TABLE 2 Treatment response in Japanese patients

	APP (n = 48)	PP (n = 53)
Objective confirmed response	31 (64.6)	15 (28.3)
Complete response	0	0
Partial response	31 (64.6)	15 (28.3)
Stable disease	11 (22.9)	29 (54.7)
Progressive disease	4 (8.3)	8 (15.1)
Missing or unevaluable	2 (4.2)	1 (1.9)
Duration of response		
Median (95% CI), mo	15.2 (7.9-NE)	5.6 (4.3-11.8)
Ongoing response at data cutoff		
No. of patients with response/total number of patients (%) ^a	11/31 (35.5)	0/15 (0)

Abbreviations: APP, atezolizumab + carboplatin or cisplatin + pemetrexed; NE, not estimable; PP, carboplatin or cisplatin + pemetrexed.

^aThe total number of patients here corresponds to the number of patients demonstrating ongoing response at data cutoff.

treatment-related deaths (Japanese, 4.2%; non-Japanese, 3.7%) and serious AEs (Japanese, 52.1%; non-Japanese, 49.8%) were observed. A higher percentage of patients withdrew from atezolizumab treatment in the Japanese subpopulation (29.2%) compared with in the non-Japanese population (13.6%).

All-grade AESIs were reported in 47 Japanese patients (97.9%) treated with APP and in 42 patients (80.8%) treated with PP (Table S3). The most-frequent AESIs were alanine aminotransferase increased (APP, 45.8%; PP, 15.4%), aspartate aminotransferase increased (APP, 43.8%; PP, 15.4%), and neutrophil count decreased (APP, 39.6%; PP, 38.5%). The most commonly reported grade ≥ 3 AESI was neutrophil count decreased (APP, 22.9%; PP, 19.2%).

In the Japanese subpopulation, 65 of 101 patients (64.4%) received 1 or more subsequent cancer treatments, and 43 patients (42.6%) received 1 or more subsequent immunotherapy (Table S4). More patients in the PP arm compared with in the APP arm received ≥ 1 subsequent treatment (APP, 50.0%; PP, 77.4%) or ≥ 1 immunotherapy (APP, 8.3%; PP, 73.6%). However, the proportions of patients who received subsequent chemotherapy (APP, 50.0%; PP, 47.2%) or targeted therapy (APP, 33.3%; PP, 32.1%) were similar between the treatment arms.

4 | DISCUSSION

The global IMpower132 study met its co-primary PFS endpoint at primary analysis, with a median PFS of 7.6 mo in the APP arm and 5.2 mo in the PP arm (stratified HR, 0.60; [95% CI, 0.49-0.72]). However, the co-primary OS endpoint was not met at final analysis in the ITT population, with a median OS of 17.5 mo in the APP arm and 13.6 mo in the PP arm (stratified HR, 0.86, 95% CI, 0.71-1.06) (Nishio et al, *J Thorac Oncol* in preparation). Consistent with the results

TABLE 3 Summary of adverse events in Japanese and non-Japanese patients

Event, n (%)	Japanese (n = 100)		Non-Japanese (n = 465)	
	APP (n = 48)	PP (n = 52)	APP (n = 243)	PP (n = 222)
All-cause AEs	48 (100)	52 (100)	239 (98.4)	214 (96.4)
All-cause grade 3/4 AEs	35 (72.9)	26 (50.0)	150 (61.7)	125 (56.3)
TRAEs	48 (100)	52 (100)	218 (89.7)	188 (84.7)
Grade 3/4 TRAEs	33 (68.8)	23 (44.2)	126 (51.9)	87 (39.2)
All deaths	2 (4.2)	2 (3.8)	21 (8.6)	13 (5.9)
Treatment-related deaths	2 (4.2)	2 (3.8)	9 (3.7)	6 (2.7)
Serious AEs	25 (52.1)	12 (23.1)	121 (49.8)	77 (34.7)
Serious TRAEs	17 (35.4)	11 (21.2)	83 (34.2)	37 (16.7)
AEs leading to withdrawal from any treatment	20 (41.7)	15 (28.8)	63 (25.9)	35 (15.8)
AEs leading to withdrawal from atezolizumab	14 (29.2)	–	33 (13.6)	–
AEs leading to withdrawal from cisplatin	2 (4.2)	3 (5.8)	9 (3.7)	10 (4.5)
AEs leading to withdrawal from carboplatin	2 (4.2)	6 (11.5)	11 (4.5)	14 (6.3)
AEs leading to withdrawal from pemetrexed	15 (31.3)	9 (17.3)	53 (21.8)	23 (10.4)

Abbreviations: AEs, adverse events; APP, atezolizumab + carboplatin or cisplatin + pemetrexed; PP, carboplatin or cisplatin + pemetrexed; TRAE, treatment-related AEs.

obtained in the global population, the Japanese subpopulation had a longer median PFS of 13.3 mo in the APP arm, a significant PFS benefit over chemotherapy alone (PP, 4.5 mo; stratified HR, 0.33 [95% CI, 0.20-0.54]). The Japanese subgroup also showed a longer median OS in the APP arm (30.8 mo) compared with the PP arm (24.3 mo; stratified HR, 0.63 [95% CI, 0.36-1.1]). In these Japanese patients, the ORR was 64.6% with APP compared with 28.3% with PP, and the median DOR was 15.2 mo with APP vs 5.6 mo with PP.

Japanese patients have had better clinical response with immunotherapy compared with non-Japanese patients in second-line treatment of advanced non-squamous NSCLC, as seen in studies of atezolizumab and the anti-PD-1 nivolumab.^{14,22,24,25} In the Japanese subgroup analysis of the IMpower132 study, survival rates were largely consistent with those in patients in the global study. It should be noted that in the Japanese subgroup of the IMpower132 study, the proportion of patients with high PD-L1 expression (TC3 or IC3)

TABLE 4 Adverse events occurring in $\geq 10\%$ of patients in either treatment arm in the Japanese safety-evaluable subgroup

	APP (n = 48)		PP (n = 52)	
	Any grade	Grade ≥ 3	Any grade	Grade ≥ 3
Patients with ≥ 1 event, n (%)	48 (100)	37 (77.1)	52 (100)	28 (53.8)
Nausea	30 (62.5)	1 (2.1)	27 (51.9)	1 (1.9)
Decreased appetite	27 (56.3)	3 (6.3)	25 (48.1)	1 (1.9)
Constipation	22 (45.8)	1 (2.1)	24 (46.2)	0
Pyrexia	22 (45.8)	1 (2.1)	9 (17.3)	0
Alanine aminotransferase increased	22 (45.8)	1 (2.1)	8 (15.4)	1 (1.9)
Aspartate aminotransferase increased	21 (43.8)	0	8 (15.4)	2 (3.8)
Neutrophil count decreased	19 (39.6)	11 (22.9)	20 (38.5)	10 (19.2)
Anemia	18 (37.5)	3 (6.3)	17 (32.7)	7 (13.5)
Platelet count decreased	17 (35.4)	4 (8.3)	17 (32.7)	4 (7.7)
Stomatitis	16 (33.3)	1 (2.1)	9 (17.3)	0
White blood cell count decreased	15 (31.3)	7 (14.6)	17 (32.7)	5 (9.6)
Hiccups	12 (25.0)	0	13 (25.0)	0
Rash	12 (25.0)	1 (2.1)	4 (7.7)	0
Malaise	11 (22.9)	0	14 (26.9)	0
Diarrhea	10 (20.8)	2 (4.2)	8 (15.4)	1 (1.9)
Vomiting	10 (20.8)	1 (2.1)	7 (13.5)	0
Edema peripheral	10 (20.8)	0	5 (9.6)	0
Lymphocyte count decreased	9 (18.8)	7 (14.6)	2 (3.8)	1 (1.9)
Neutropenia	9 (18.8)	7 (14.6)	4 (7.7)	0
Rash, maculopapular	9 (18.8)	2 (4.2)	3 (5.8)	0
Dysgeusia	8 (16.7)	0	5 (9.6)	0
Weight decreased	8 (16.7)	1 (2.1)	2 (3.8)	0
Blood creatinine increased	7 (14.6)	0	3 (5.8)	0
Pneumonitis	6 (12.5)	1 (2.1)	3 (5.8)	1 (1.9)

(Continues)

TABLE 4 (Continued)

	APP (n = 48)		PP (n = 52)	
	Any grade	Grade ≥ 3	Any grade	Grade ≥ 3
Upper respiratory tract infection	6 (12.5)	0	2 (3.8)	0
Headache	6 (12.5)	0	2 (3.8)	0
Lung infection	6 (12.5)	2 (4.2)	1 (1.9)	1 (1.9)
Edema	6 (12.5)	0	1 (1.9)	0
Arthralgia	6 (12.5)	0	0	0
Insomnia	5 (10.4)	0	4 (7.7)	0
Dry skin	5 (10.4)	0	3 (5.8)	0
Myalgia	5 (10.4)	1 (2.1)	1 (1.9)	0
Dehydration	5 (10.4)	0	1 (1.9)	0
Fatigue	4 (8.3)	0	6 (11.5)	0

Abbreviations: APP, atezolizumab + carboplatin or cisplatin + pemetrexed; PP, carboplatin or cisplatin + pemetrexed.

was higher in the APP (14.6%) arm compared with in the PP arm (1.9%). Additionally, in the Japanese subgroup of the IMpower132 study, a relatively smaller proportion of patients received subsequent therapy following APP treatment (50.0%) compared with those who received PP treatment (77.4%), with only 8.3% patients in the APP arm receiving subsequent immunotherapy vs. 73.6% in the PP arm (Table S4), which was higher compared with the proportion of patients receiving immunotherapy following PP treatment, in the global study (PP, 45.8%; APP, 5.5%; Nishio et al *J Thorac Oncol* in preparation). This underscores the potential of this regimen for first-line use in Japanese patients with advanced NSCLC.

The safety profile of the atezolizumab combination in the Japanese subpopulation was generally consistent with that in the non-Japanese IMpower132 population, although higher rates of all-cause and treatment-related grade 3/4 AEs were observed in Japanese patients. A higher incidence of any-grade pneumonitis was reported in the APP arm (12.5%) compared with in the PP arm (5.8%) of the Japanese subpopulation. Any-grade pneumonitis in the APP arm was higher in the Japanese population compared with in the global population (6.2%). Previous studies of immunotherapies have also reported higher rates of immune-associated pneumonitis in Japanese patients compared with in non-Japanese patients.^{16,19,20}

Although higher incidences of respiratory, thoracic, and mediastinal disorders as well as renal and urinary disorders were reported in Japanese patients >75 y in the APP arm (Table S2), the small size of this age-specific subgroup (n = 7) precludes any implications for administration of the APP treatment in elderly Japanese patients (age >75 y).

The safety profile of the atezolizumab combination was consistent with the known risks of the individual components and in line with the findings from other NSCLC studies involving first-line atezolizumab and platinum-based chemotherapy combinations.^{11,12} No new safety signals were identified.

	APP (n = 48)		PP (n = 52)	
	<65 (n = 19)	≥65 (n = 29)	<65 (n = 24)	≥65 (n = 28)
Total number of patients with at least 1 AE, n (%)	19 (100.0)	29 (100.0)	24 (100.0)	28 (100.0)
MedDRA System Organ Class				
Gastrointestinal disorder	19 (100.0)	25 (86.2)	20 (83.3)	23 (82.1)
Investigations ^a	15 (78.9)	21 (72.4)	19 (79.2)	19 (67.9)
General disorders and administration site conditions	16 (84.2)	22 (75.9)	12 (50.0)	17 (60.7)
Metabolism and nutrition disorders	14 (73.7)	19 (65.5)	12 (50.0)	15 (53.6)
Blood and lymphatic system disorders	11 (57.9)	17 (58.6)	7 (29.2)	14 (50.0)
Respiratory, thoracic, and mediastinal disorders	8 (42.1)	20 (69.0)	9 (37.5)	11 (39.3)
Skin and subcutaneous tissue disorders	12 (63.2)	19 (65.5)	4 (16.7)	13 (46.4)
Infections and infestations	12 (63.2)	18 (62.1)	5 (20.8)	12 (42.9)
Nervous system disorders	11 (57.9)	12 (41.4)	5 (20.8)	7 (25.0)
Musculoskeletal and connective tissue disorders	9 (47.4)	7 (24.1)	3 (12.5)	5 (17.9)
Vascular disorders	4 (21.1)	6 (20.7)	4 (16.7)	0
Eye disorders	2 (10.5)	6 (20.7)	1 (4.2)	3 (10.7)
Psychiatric disorders	2 (10.5)	4 (13.8)	2 (8.3)	2 (7.1)
Renal and urinary disorders	1 (5.3)	7 (24.1)	1 (4.2)	1 (3.6)
Ear and labyrinth disorders	3 (15.8)	3 (10.3)	3 (12.5)	0
Hepatobiliary disorders	2 (10.5)	3 (10.3)	2 (8.3)	0
Injury, poisoning, and procedural complications	3 (15.8)	4 (13.8)	0	0
Endocrine disorders	4 (21.1)	1 (3.4)	0	0
Cardiac disorders	1 (5.3)	2 (6.9)	1 (4.2)	0
Immune system disorders	2 (10.5)	1 (3.4)	1 (4.2)	0
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	2 (10.5)	1 (3.4)	0	1 (3.6)
Reproductive system and breast disorders	0	3 (10.3)	0	0
Congenital, familial, and genetic disorders	0	1 (3.4)	0	0

Abbreviations: AEs, adverse events; APP, atezolizumab + carboplatin or cisplatin + pemetrexed; MedDRA, Medical Dictionary for Regulatory Activities; PP, carboplatin or cisplatin + pemetrexed.

^aAbnormal laboratory tests.

The strengths of this phase 3 study include its randomized nature and the consistency of the efficacy findings between these Japanese patients and the relatively large, global, non-Japanese population.

In conclusion, combining atezolizumab with pemetrexed and platinum-based chemotherapy was tolerable and improved OS and PFS compared with chemotherapy alone in Japanese patients with chemotherapy-naïve, advanced, or metastatic non-squamous NSCLC. The safety profile of the atezolizumab combination was consistent with the known safety profile of the individual treatment components, and with the findings from other NSCLC studies involving first-line atezolizumab and platinum-based chemotherapy combinations. No new safety signals were identified. Although the incidence of grade 3/4 TRAEs in the APP arm of the Japanese population was

higher compared with that in the global population, the overall improvement in efficacy with the addition of atezolizumab to chemotherapy was similar to that observed in the global ITT population.

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TABLE 5 Adverse events by age (≥65 y vs <65 y) in Japanese patients

analysis, and gave approval to submit for this publication. Chugai Pharmaceutical Co, Ltd was involved in the data collection for the IMpower132 analysis, data analysis, data interpretation, and writing of the report for the Japanese subgroup analysis of IMpower132 and gave approval to submit for publication. Makoto Nishio had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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DATA AVAILABILITY STATEMENT

Qualified researchers may request access to individual patient level data through the clinical study data request platform (www.clinicalstudydatarequest.com). Please visit www.chugai-pharm.co.jp/english/profile/rd/ctds_request.html for further details on Chugai's Data Sharing Policy and how to request access to related clinical study documents.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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