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Atezolizumab + Chemotherapy in Older Patients With Lung Cancer in Japan

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ABSTRACT

Pivotal phase 3 trials leading to the approvals of atezolizumab—chemotherapy combinations for non-small cell and extensive-stage small cell lung cancer (NSCLC and ES-SCLC) had strict eligibility criteria. J-TAIL-2 was a prospective, observational study in Japan that evaluated atezolizumab regimens for advanced NSCLC/ES-SCLC, including patients ineligible for global trials. The primary endpoint was 12-month overall survival (OS); safety and efficacy in subgroups defined by age, ECOG PS and/or G8 score, and creatinine clearance were key secondary endpoints. As of February 3, 2023, 1217 patients were treated in clinical practice based on Japanese labeling/treatment guidelines. Patients received atezolizumab with either carboplatin and nab-paclitaxel (atezo + CnP), carboplatin/cisplatin and pemetrexed (atezo + PP), or bevacizumab and carboplatin and paclitaxel (atezo + bev + CP) in the NSCLC cohort ($n = 814$) or with carboplatin and etoposide (atezo + CE) in the ES-SCLC cohort ($n = 403$). Overall, 53.5% were ≥ 70 years old, and 11.8% had ECOG PS ≥ 2; median G8 scores were 13 (NSCLC cohort) and 12 (ES-SCLC). Patients < 70 and ≥ 70 years had similar median (m)OS and progression-free survival (mPFS) across treatment regimens. Patients with ECOG PS < 2 and G8 score ≥ median had the highest mOS/PFS vs. patients with ECOG PS ≥ 2 and G8 score<median. Patients ≥ 70 years had higher incidence of Grade ≥ 3 adverse events with atezo + CnP and atezo + PP than patients < 70 years;

Abbreviations: AE, adverse event; atezo + bev + CP, atezolizumab plus bevacizumab plus carboplatin and paclitaxel; atezo + CE, atezolizumab plus carboplatin and etoposide; atezo + CnP, atezolizumab plus carboplatin and nab-paclitaxel; atezo + PP, atezolizumab plus carboplatin or cisplatin plus pemetrexed; CI, confidence interval; CrCl, creatinine clearance; ECOG PS, Eastern Cooperative Oncology Group performance status; ES-SCLC, extensive-stage small-cell lung cancer; G8, Geriatric 8; HR, hazard ratio; ICI, immune checkpoint inhibitor; ILD, interstitial lung disease; ITT, intention to treat; mOS, median overall survival; mPFS, median progression-free survival; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival.

incidences were similar between groups for other regimens. Older vs. younger patients also had higher incidence of interstitial lung disease. Overall, these results suggest that atezolizumab-containing regimens remain effective in older patients, with no new safety signals.
Trial Registration: ClinicalTrials.gov: NCT04501497

1 | Introduction

Several global Phase 3 trials led to the approvals of first-line atezolizumab plus chemotherapy combinations for the treatment of advanced or recurrent nonsquamous non-small cell lung cancer (NSCLC; IMpower130 [1], IMpower132 [2], and IMpower150 [3]) and extensive-stage small-cell lung cancer (ES-SCLC; IMpower133 [4]). In IMpower130, atezolizumab plus carboplatin and nab-paclitaxel (atezo + CnP) significantly improved overall survival (OS) and progression-free survival (PFS) vs. chemotherapy alone [1]. IMpower132 showed a significant improvement in PFS and numerical improvement in OS with atezolizumab plus carboplatin or cisplatin plus pemetrexed (atezo + PP) vs. PP alone [2]. In IMpower150, atezolizumab added to bevacizumab plus carboplatin and paclitaxel (atezo + bev + CP) significantly improved PFS and OS [3]. IMpower133 demonstrated OS and PFS benefit with atezolizumab plus carboplatin and etoposide (atezo + CE) vs. chemotherapy alone [4]. These trials excluded patients with common, real-world baseline factors such as Eastern Cooperative Oncology Group performance status (ECOG PS) ≥ 2, active or untreated metastases in the central nervous system, autoimmune diseases, or interstitial lung disease (ILD). Given the incidence of these factors in older patients, the IMpower trial eligibility criteria resulted in a low proportion of older patients. In IMpower130, IMpower133, and IMpower150, respectively, 11.8%, 10.2%, and 9.8% of patients were aged ≥ 75 years [1, 3, 4], and in IMpower132, 44.5% were aged ≥ 65 years [2]. Additionally, there is a risk of adverse events (AEs) for older patients with lung cancer who receive chemotherapy plus immune checkpoint inhibitor (ICI) treatment [5, 6]. The J-TAIL-2 study (NCT04501497) was conducted to evaluate the real-world efficacy and safety of atezolizumab plus chemotherapy combinations for patients with NSCLC or ES-SCLC, including those who could have been excluded from clinical trials.

Almost half (46.1%) of patients with lung cancer worldwide are ≥ 70 years old [7]. The rapidly aging proportion of the global population has led to an urgent need to identify which older patients with cancer are suitable to receive the same treatment as younger patients. The International Society of Geriatric Oncology recommends the use of geriatric assessments to guide cancer treatment of older patients as chronological age alone is unable to accurately reflect the heterogeneity of aging [8]. The Geriatric 8 (G8) screening tool (Table S1), which was developed to identify older patients with cancer who would benefit from geriatric assessment, comprises 8 items that evaluate the older patient's physical and cognitive functions, number of prescribed drugs, and awareness of their own health [9]. A low G8 score indicates poor health status [9]. Previous studies have investigated the relationship between the G8 score and OS in older patients with various cancers [10–12]. However, the relationship between G8 score and prognosis of ICI treatment remains unclear, and the adoption of G8 in clinical practice is limited.

Here, we report the efficacy and safety of atezolizumab plus chemotherapy combinations in older patients (≥ 70 years) in the J-TAIL-2 study, including the results of their functional assessment using the G8 score.

2 | Materials and Methods

2.1 | Study Design and Patient Population

J-TAIL-2 is a noninterventional, prospective observational study that enrolled 2 patient cohorts across 150 institutions in Japan: patients with NSCLC and patients with ES-SCLC. Patients were eligible if they were ≥ 20 years old, diagnosed with NSCLC or ES-SCLC, and scheduled to receive atezolizumab in combination with chemotherapy (atezo + CnP, atezo + PP, atezo + bev + CP, or atezo + CE) in clinical practice, based on the latest prescribing information for atezolizumab in Japan and the latest guidelines for the promotion of optimal use. The dosage, schedule, criteria for dose reduction, interruption, discontinuation, and the timing of radiological evaluation were not specified and were based on clinical practice within the approved label. The study was conducted in accordance with the Declaration of Helsinki (Japan Medical Association translation), 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 details of this 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 participate in the study. Additional study details were previously reported [13, 14].

2.2 | Assessments and Endpoints

The primary endpoint was 12-month OS rate. Secondary endpoints included OS, PFS, and safety, as well as efficacy and safety analyses in select subgroups by age (≥ 70 and < 70 years, ≥ 75 and < 75 years), G8 score (≥ median and < median), and/or ECOG PS (≥ 2 and < 2), and creatinine clearance (CrCl) (≥ 60 mL/min, 45 to < 60 mL/min, < 45 mL/min). The G8 questionnaire, scored from 0 to 17, was conducted in patients ≥ 70 years old before the start of treatment [9]. Medical decisions were not based on G8 results. The median scores were used as the cutoff values for subgroup analysis in this study (13 in the NSCLC cohort and 12 in the ES-SCLC cohort).

2.3 | Statistical Analysis

The target enrollment of this study was 800 patients with NSCLC and 400 with ES-SCLC. Further details have been previously reported for each cohort [13, 14]. Efficacy endpoints were calculated in the efficacy analysis population, defined as all treated patients who met the eligibility criteria. Median OS (mOS) and median PFS (mPFS), as well as OS rate at 12 months were estimated using Kaplan–Meier methodology; 95% confidence intervals (CIs) for 12-month OS rate were estimated using Greenwood's formula, 95% CIs for mOS and mPFS were calculated using the Brookmeyer-Crowley method, and 95% CIs for hazard ratios (HRs) were calculated using the Cox proportional-hazards model. Safety was evaluated in the safety analysis population, which included all enrolled patients who received ≥1 dose of atezolizumab (or bevacizumab for patients receiving the atezo + bev + CP regimen only). Incidence and severity of AEs were summarized using the National Cancer Institute Common Terminology Criteria for Adverse Events v5.0.

3 | Results

3.1 | Patients and Baseline Characteristics

Between August 21, 2020, and February 3, 2022, 1217 patients were enrolled (intention-to-treat [ITT] population) in the study, including 814 patients with NSCLC and 403 patients with ES-SCLC (Figure S1). The NSCLC cohort consisted of 217 patients in the atezo + CnP group, 211 in the atezo + PP group, and 386 in the atezo + bev + CP group. In patients aged ≥70 years who were treated with atezo + bev + CP, 91.4% had an initial <200 mg/m^2-dose of paclitaxel. Patients in the ES-SCLC cohort were to receive atezo + CE. Baseline characteristics of the ITT population by treatment regimen and age (≥70 years) are summarized in Table 1. The overall proportion of patients ≥70 years old was 53.5%. Among patients ≥70 years, 89.1% had a G8 score. The distribution of G8 scores in both cohorts is summarized in Figure S2.

In the overall population vs. patients aged ≥70 years, the proportion of patients with ECOG PS <2 and ≥2 was similar (88.2% and 11.8% vs. 88.3% and 11.7%). The proportion of patients ≥70 years with low CrCl (<45 mL/min) was generally similar between regimens (17.9% [n = 22] atezo + CnP, 9.8% [n = 13] atezo + PP, 21.3% [n = 30] atezo + bev + CP, and 13.6% [n = 33] atezo + CE). Baseline characteristics of the ITT population by treatment regimen for additional subgroups based on age (≥75 years) and G8 score are summarized in Tables S2 and S3. Among patients with a G8 score, 88.8% had an ECOG PS <2. In patients with an ECOG PS <2 and G8 score ≥ median vs. <median, the average proportion with ECOG PS 0 was 48.6% vs. 30.2% in the NSCLC cohort and 36.6% vs. 22.6% in the ES-SCLC cohort.

3.2 | Effectiveness

The efficacy analysis population (n = 1190) comprised 791 patients with NSCLC and 399 patients with ES-SCLC. The median observation time was 14.1 months (range, 0.1–28.3) for the NSCLC cohort and 13.7 months (range, 0.3–28.6) for the ES-SCLC cohort. We previously reported the 12-month OS rates for NSCLC with atezo + CnP, atezo + PP and atezo + bev + CP as 62.9%, 72.1%, and 68.3%, respectively, and for ES-SCLC with atezo + CE as 63.7% [13, 14]. OS and PFS outcomes by treatment regimen and age (≥70 vs. <70 years) are shown in Figure 1. mOS in patients ≥70 vs. <70 years was 18.3 vs. 22.3 months (HR 1.15; 95% CI: 0.78, 1.70) with atezo + CnP, 24.0 vs. 18.5 months (HR 0.95; 95% CI: 0.62, 1.47) with atezo + PP, 17.7 vs. 17.0 months (HR 0.94; 95% CI: 0.70, 1.26) with atezo + bev + CP, and 16.4 vs. 17.9 months (HR 1.18; 95% CI: 0.90, 1.55) with atezo + CE (Figure 1A–D). mPFS in patients ≥70 vs. <70 years was 5.6 vs. 5.6 months (HR 1.05; 95% CI: 0.77, 1.43) with atezo + CnP, 7.1 vs. 6.6 months (HR 0.86; 95% CI: 0.62, 1.19) with atezo + PP, 6.2 vs. 6.5 months (HR 0.94; 95% CI: 0.75, 1.17) with atezo + bev + CP, and 5.1 vs. 5.1 months (HR 1.07; 95% CI: 0.86, 1.33) with atezo + CE (Figure 1E–H).

OS and PFS outcomes by G8 score (≥ median vs. <median) and ECOG PS (<2 vs. ≥2) are shown in Figure 2. In patients with ECOG PS <2, mOS was higher for patients with a G8 score ≥median vs. <median (22.3 vs. 12.1 months with atezo + CnP, NE vs. 16.3 months with atezo + PP, 22.3 vs. 15.3 months with atezo + bev + CP, and 18.5 vs. 12.1 months with atezo + CE).

A similar, but less pronounced, trend was found in mPFS among patients with ECOG PS <2 and G8 score ≥ median vs. <median (8.2 vs. 5.1 months with atezo + CnP, 10.6 vs. 5.8 months with atezo + PP, 6.4 vs. 6.1 months with atezo + bev + CP, and 5.2 vs. 5.1 months with atezo + CE). Further efficacy summaries by regimen for age, G8 score, and CrCl are shown in Figures S3–S5.

3.3 | Safety

The safety analysis population (n = 1200) included 800 patients with NSCLC and 400 patients with ES-SCLC. This population was analyzed for AEs by age, G8 score and ECOG PS, and CrCl. In patients aged ≥70 vs. <70 years, the incidence of Grade ≥3 AEs was higher with the atezo + CnP (65.3% vs. 54.3%) and atezo + PP (51.5% vs. 42.5%) regimens, but similar with atezo + bev + CP (67.9% vs. 66.1%) and atezo + CE (66.3% vs. 66.2%; Table 2). Patients aged ≥70 years had a higher ILD incidence than patients <70 years with atezo + CnP (15.3% vs. 6.5%) and atezo + PP (13.6% vs. 8.2%) regimens. Independent of age, ILD incidence was similar in patients receiving atezo + bev + CP and atezo + CE. The incidence of Grade ≥3 AEs in patients with an ECOG PS <2 and G8 score ≥ median vs. <median was 72.7% vs. 68.0% with atezo + CnP, 45.5% vs. 63.4% with atezo+PP, 62.3% vs. 75.4% with atezo + bev + CP, and 63.6% vs. 71.0% with atezo + CE (Table 3). ILD incidence was similar across patients with an ECOG PS <2 and G8 score ≥ median vs. <median except in patients receiving atezo + CnP (11.4% vs. 24.0%). Patients with CrCl ≥60 vs. 45 to <60 vs. <45 mL/min had a similar any-grade AE incidence except in the atezo + PP regimen where AE incidence tended to increase as CrCl decreased (78.9% vs. 88.1% vs. 93.3%; Table S6). Patients with CrCl ≥60 vs. 45 to <60 vs. <45 mL/min had a similar incidence of Grade ≥3 AEs except with the atezo + PP

TABLE 1 | Baseline characteristics in the ITT population by treatment regimen and age (≥70 and <70 years).

	Atezo + CnP		Atezo + PP		Atezo + bev + CP		Atezo + CE	
	≥70 years (*n* = 125)	<70 years (*n* = 92)	≥70 years (*n* = 137)	<70 years (*n* = 74)	≥70 years (*n* = 144)	<70 years (*n* = 242)	≥70 years (*n* = 245)	<70 years (*n* = 158)
Age, median (range), years	74 (70–83)	63 (42–69)	75 (70–85)	62 (41–69)	73 (70–83)	62 (32–69)	74 (70–91)	65 (39–69)
≥75 years	55 (44.0)	—	77 (56.2)	—	43 (29.9)	—	113 (46.1)	—
Male, *n* (%)	108 (86.4)	77 (83.7)	100 (73.0)	49 (66.2)	92 (63.9)	142 (58.7)	201 (82.0)	122 (77.2)
ECOG PS, *n* (%)								
0	43 (34.4)	33 (35.9)	54 (39.4)	33 (44.6)	48 (33.3)	104 (43.0)	66 (26.9)	61 (38.6)
1	63 (50.4)	48 (52.2)	72 (52.6)	33 (44.6)	92 (63.9)	114 (47.1)	137 (55.9)	72 (45.6)
2	16 (12.8)	10 (10.9)	10 (7.3)	7 (9.5)	2 (1.4)	18 (7.4)	32 (13.1)	16 (10.1)
3	3 (2.4)	1 (1.1)	1 (0.7)	1 (1.4)	2 (1.4)	4 (1.7)	10 (4.1)	9 (5.7)
4	0	0	0	0	0	2 (0.8)	0	0
Tobacco use, *n* (%)								
Never	14 (11.2)	8 (8.7)	29 (21.2)	22 (29.7)	51 (35.4)	85 (35.1)	12 (4.9)	5 (3.2)
Current	19 (15.2)	22 (23.9)	16 (11.7)	18 (24.3)	6 (4.2)	26 (10.7)	67 (27.3)	50 (31.6)
Former	92 (73.6)	62 (67.4)	92 (67.2)	34 (45.9)	87 (60.4)	131 (54.1)	166 (67.8)	103 (65.2)
Staging, *n* (%)								
IIIA/B/C	7 (5.6)	8 (8.7)	11 (8.0)	1 (1.4)	7 (4.9)	6 (2.5)	21 (8.6)	46 (29.1)
IV	95 (76.0)	68 (73.9)	94 (68.6)	58 (78.4)	101 (70.1)	193 (79.8)	196 (80.0)	93 (58.9)
Recurrence after operation/ chemotherapy/radiotherapy	23 (18.4)	16 (17.4)	32 (23.4)	15 (20.3)	36 (25.0)	43 (17.8)	28 (11.4)	19 (12.0)
Brain metastasis, *n* (%)	23 (18.4)	21 (22.8)	22 (16.1)	23 (31.1)	43 (29.9)	90 (37.2)	57 (23.3)	51 (32.3)
Complicated interstitial lung disease, *n* (%)	10 (8.0)	9 (9.8)	4 (2.9)	1 (1.4)	2 (1.4)	8 (3.3)	16 (6.5)	12 (7.6)
History of autoimmune disease, *n* (%)	8 (6.4)	6 (6.5)	6 (4.4)	3 (4.1)	2 (1.4)	15 (6.2)	12 (4.9)	9 (5.7)
Creatinine clearance[a]	*n* = 123	*n* = 90	*n* = 133	*n* = 72	*n* = 141	*n* = 239	*n* = 242	*n* = 157
≥60 mL/min, *n* (%)	58 (47.2)	74 (82.2)	82 (61.7)	66 (91.7)	64 (45.4)	192 (80.3)	139 (57.4)	139 (88.5)
45 to <60 mL/min, *n* (%)	43 (35.0)	12 (13.3)	38 (28.6)	4 (5.6)	47 (33.3)	38 (15.9)	70 (28.9)	13 (8.3)

(Continues)

TABLE 1 | (Continued)

	Atezo + CnP		Atezo + PP		Atezo + bev + CP		Atezo + CE	
	≥ 70 years (*n* = 125)	< 70 years (*n* = 92)	≥ 70 years (*n* = 137)	< 70 years (*n* = 74)	≥ 70 years (*n* = 144)	< 70 years (*n* = 242)	≥ 70 years (*n* = 245)	< 70 years (*n* = 158)
< 45 mL/min, *n* (%)	22 (17.9)	4 (4.4)	13 (9.8)	2 (2.8)	30 (21.3)	9 (3.8)	33 (13.6)	5 (3.2)
Completed induction therapy[b]	*n* = 123	*n* = 90	*n* = 133	*n* = 71	*n* = 141	*n* = 241	*n* = 243	*n* = 157
≥ 4 cycles, *n* (%)	68 (55.3)	39 (43.3)	86 (64.7)	42 (59.2)	86 (61.0)	143 (59.3)	182 (74.9)	117 (74.5)
Initial dose of paclitaxel	—	—	—	—	*n* = 140	*n* = 239	—	—
< 200 mg/m^2, *n* (%)	—	—	—	—	128 (91.4)	211 (88.3)	—	—
Completed G8, *n* (%)[c]	111 (88.8)	NA	120 (87.6)	NA	125 (86.8)	NA	224 (91.4)	NA
G8 score, median (range)	12 (4–17)		13 (4–17)		13 (4.5–17)		12 (3–17)	
EGFR mutation[d]	*n* = 109	*n* = 80	*n* = 127	*n* = 66	*n* = 136	*n* = 230	NA	NA
Positive, *n* (%)	6 (5.5)	9 (11.3)	11 (8.7)	17 (25.8)	74 (54.4)	122 (53.0)	NA	NA
PD-L1 expression[e,f]	*n* = 107	*n* = 79	*n* = 122	*n* = 59	*n* = 112	*n* = 193	NA	NA
< 1% of TCs, *n* (%)	39 (36.4)	26 (32.9)	46 (37.7)	19 (32.2)	41 (36.6)	71 (36.8)	NA	NA
1% to < 50% of TCs, *n* (%)	36 (33.6)	19 (24.1)	53 (43.4)	20 (33.9)	42 (37.5)	74 (38.3)	NA	NA
≥ 50% of TCs, *n* (%)	32 (29.9)	34 (43.0)	23 (18.9)	20 (33.9)	29 (25.9)	48 (24.9)	NA	NA

Note: Median G8 score in patients with NSCLC was 13. Median G8 score for patients with ES-SCLC was 12.

Abbreviations: atezo, atezolizumab; bev, bevacizumab; CnP, carboplatin + nab-paclitaxel; CP, carboplatin + paclitaxel; CE, carboplatin +toposide; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; G8, Geriatric 8; ITT, intention to treat; NA, not available; PD-L1, programmed death-ligand 1; PP, carboplatin or cisplatin + pemetrexed; TC, tumor cell.

[a]Calculated using age at the start of treatment; missing values were excluded.

[b]Percentages were calculated using the number of patients who underwent induction therapy.

[c]G8 assessment was conducted in patients ≥ 70 years at the time of informed consent.

[d]Percentages were calculated using the number of patients with available *EGFR* mutation status.

[e]Per 22C3 immunohistochemistry assay.

[f]Percentages were calculated using the number of patients with available PD-L1 expression.

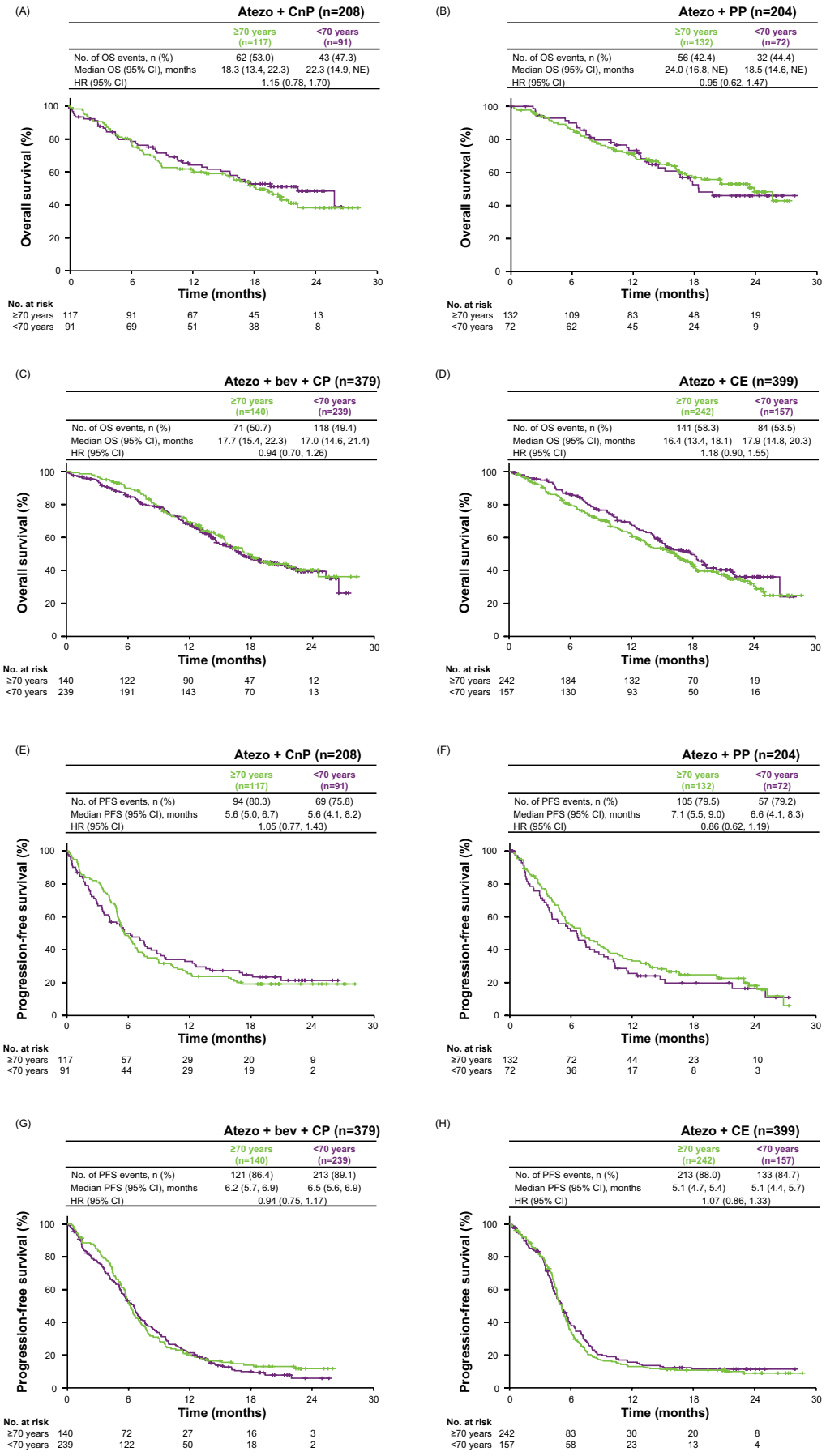

FIGURE 1 | Legend on next page.

FIGURE 1 | OS (A–D) and PFS (E–H) in patients receiving (A/E) Atezo + CnP, (B/F) Atezo + PP, (C/G) Atezo + bev + CP, and (D/H) Atezo + CE[a] by age (≥ 70 years and < 70 years). [a]Saito R, et al. Presented at the 2024 American Society of Clinical Oncology Annual Meeting. Abstract 8092. Adapted with permission by the author. Atezo, atezolizumab; bev, bevacizumab; CE, carboplatin + etoposide; CI, confidence interval; CnP, carboplatin + nab-paclitaxel; CP, carboplatin + paclitaxel; HR, hazard ratio; NE, not estimable; OS, overall survival; PFS, progression-free survival; PP, carboplatin or cisplatin + pemetrexed. 95% CIs evaluated using the Brookmeyer-Crowley method for medians, and Wald CIs for HRs.

(44.2% vs. 52.4% vs. 73.3%). ILD incidence was highest in patients with CrCl < 45 mL/min receiving atezo + CnP (26.9%). Further safety summaries by regimen for age, G8 score, and CrCl are shown in Tables S4–S6.

4 | Discussion

This prospective observational study suggests that the use of atezolizumab combined with chemotherapy is beneficial to older patients with NSCLC and ES-SCLC. J-TAIL-2 aimed to evaluate the efficacy and safety of atezolizumab combined with chemotherapy in real-world clinical practice, including in patients who could have been excluded from pivotal Phase 3 trials [1–4].

J-TAIL-2 enrolled 1217 patients, of whom 53.5% were ≥ 70 years old and 23.7% were ≥ 75 years old. The median age of patients in J-TAIL-2 was 69 years in the NSCLC cohort and 71 years in the ES-SCLC cohort, which is higher than the median ages of 64 years in IMpower130 [1], IMpower132 [2], and IMpower133 [4] and 63 years in IMpower150 [3]. The age cutoffs of 70 and 75 years were selected to reflect international oncology guidelines describing older patient sub-analyses, geriatric assessment-based evaluations, and disease-specific definitions for older patients with cancer in Japan [9, 15–18]. The mOS and mPFS were 18.6 and 7.0 months in IMpower130, 17.5 and 7.6 months in IMpower132, 19.2 and 8.3 months in IMpower150, and 12.3 and 5.2 months in IMpower133 [1–4, 19–22]. These study results suggest that an atezolizumab-containing regimen remains effective in older patients, as both the mOS and mPFS of patients aged ≥ 70 and ≥ 75 years were comparable to those of the results of each regimen's clinical trial with younger patients [1–4]. However, AE incidence tended to increase with age, particularly in patients ≥ 75 years old. The ILD incidence was over 10% for patients ≥ 75 years for all regimens in the NSCLC cohort. Furthermore, Grade ≥ 3 ILD incidence in patients aged ≥ 75 years was 4.7% and 2.7% for the NSCLC and ES-SCLC cohorts, respectively (Table S4). Although cross-trial comparisons are made with caution due to study design and population differences, multiple studies from Japan report the incidence of ILD in patients with NSCLC aged ≥ 75 years is approximately 25% with pembrolizumab-containing regimens and approximately 10% with atezolizumab-containing regimens. This is similar to our findings and supports the general tolerability of atezolizumab in older patients [5, 23–25]. The ILD incidence was 6.8% in the ES-SCLC cohort, which is consistent with reported ILD incidence in patients aged ≥ 70 years with SCLC in Japan [26]. There are several explanations for the higher incidence of ILD in patients ≥ 70 across regimens. Older lung tissues have high levels of oxidative stress that lead to chronic, low-grade inflammation and impaired proteostasis, both risk factors associated with respiratory disease [27, 28]. Our findings of higher ILD incidence in older patients is consistent with other studies including a long-term study in Korea that found people aged ≥ 70 years were 6.9 times more likely to develop ILD than a person in their 40s [29]. In a global study, ILD prevalence peaked in people aged 75–79 years [30]. Clinicians must consider the risk–benefit ratio during treatment selection for older patients.

This study of 580 patients evaluated by the G8 Questionnaire provides insight into the previously limited evidence of the utility of the G8 assessment and ICI treatment efficacy [19–22]. The median G8 scores for the NSCLC and ES-SCLC cohorts were 13 and 12, respectively. Although a G8 score of 14 has been used in other geriatric oncology studies, there is no established G8 score cutoff for immunotherapy. Consistent with previous studies reporting on prognosis and ICI treatment outcomes, we used the median G8 values for each cohort [10–12, 19–22]. In patients with a G8 score < median, mOS was generally shorter than in patients with a G8 score ≥ median. The tendency for shorter mPFS in patients with a G8 score < median was only observed in the atezo + CnP and atezo + PP groups. With the atezo + bev + CP and atezo + CE regimens, mPFS in patients with a G8 score < median vs. ≥ median was similar. Due to the varying PFS results yet consistent OS results across regimens, these results suggest that G8 score could be considered a prognostic factor and is consistent with previous reports [19–22]. However, further study is needed to standardize the G8 score threshold to evaluate immunotherapy efficacy.

Among patients with a G8 score < median, there was a tendency for the incidence of Grade ≥ 3 AEs to increase compared with patients with a G8 score ≥ median except in patients receiving atezo + CnP. However, the frequency of ILD was higher (18.5%), but not severe, in patients with a G8 score < median in the atezo + CnP regimen compared with other regimens. Beyond well-recognized nonspecific risk factors for drug-induced ILD, such as age and pre-existing lung abnormalities including baseline ILD, other factors such as impaired renal function and smoking history have also been reported as risk factors [31]. In this study, patients who received atezo + CnP had a higher proportion of patients with baseline ILD, CrCl < 60 mL/min and smoking history compared with patients treated with other regimens. We speculate that these baseline characteristics may have contributed to the higher incidence of ILD observed in the atezo + CnP group compared with other treatment groups. Overall, clinicians should be aware of the increased AE incidence across regimens during treatment selection for patients with a G8 score < median.

Similarly, when evaluating patients with ECOG PS < 2, those with a G8 score < median tended to have shorter mOS and mPFS. About 50% of patients with an ECOG PS 0/1 and a G8 score ≥ median had an ECOG PS 1 but had similar or better mOS compared with the ECOG PS 0 group in the overall population, including those < 70 years. About 30% of the ECOG PS 0/1

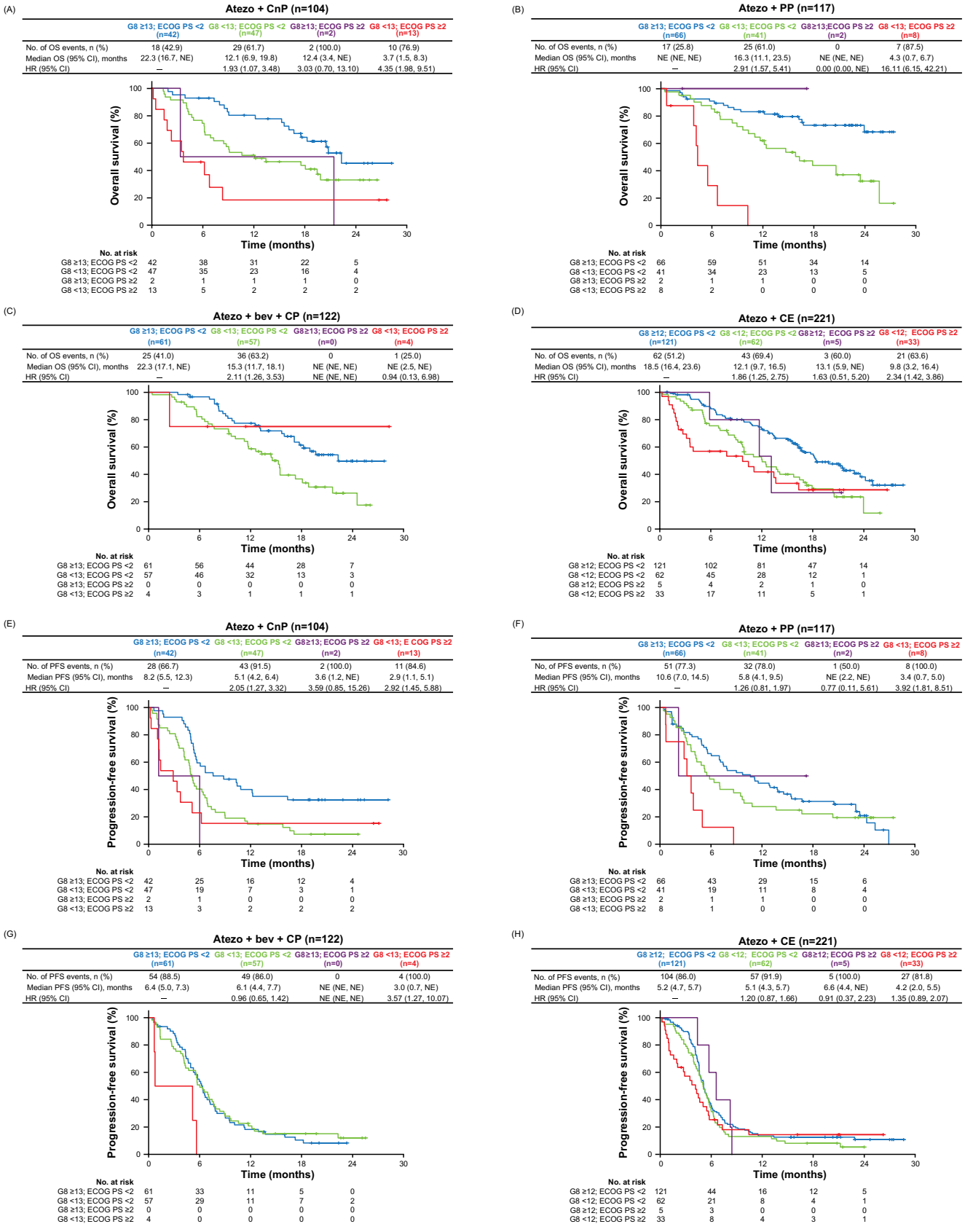

FIGURE 2 | Legend on next page.

group with a G8 score < median had ECOG PS 0 but had worse mOS than that of the ECOG PS 1 group in the overall population. These results suggest that using the G8 score could potentially stratify the prognosis of the ECOG PS 0/1 group with a better prognosis more effectively. Similar trends for mPFS were only observed with the atezo + CnP and atezo + PP regimens. In the

FIGURE 2 | OS (A–D) and PFS (E–H) in patients receiving (A/E) Atezo + CnP, (B/F) Atezo + PP, (C/G) Atezo + bev + CP, and (D/H) Atezo + CE with ECOG PS (< 2 and ≥ 2) and G8 score (≥ median and < median). Median G8 score in patients with NSCLC was 13. Median G8 score for patients with ES-SCLC was 12. Atezo, atezolizumab; bev, bevacizumab; CE, carboplatin + etoposide; CI, confidence interval; CnP, carboplatin + nab-paclitaxel; CP, carboplatin + paclitaxel; ECOG PS, Eastern Cooperative Oncology Group Performance Status; HR, hazard ratio; NE, not estimable; OS, overall survival; PFS, progression-free survival; PP, carboplatin or cisplatin + pemetrexed. 95% CIs evaluated using the Brookmeyer-Crowley method for medians, and Wald CIs for HRs.

TABLE 2 | Safety summary by treatment regimen and age (≥ 70 years and < 70 years).

	Atezo + CnP		Atezo + PP		Atezo + bev + CP		Atezo + CE[a]	
	≥ 70 years (*n* = 124)	< 70 years (*n* = 92)	≥ 70 years (*n* = 132)	< 70 years (*n* = 73)	≥ 70 years (*n* = 140)	< 70 years (*n* = 239)	≥ 70 years (*n* = 243)	< 70 years (*n* = 157)
Any grade AE, *n* (%)	112 (90.3)	76 (82.6)	109 (82.6)	59 (80.8)	132 (94.3)	213 (89.1)	207 (85.2)	135 (86.0)
Grade ≥ 3 AE	81 (65.3)	50 (54.3)	68 (51.5)	31 (42.5)	95 (67.9)	158 (66.1)	161 (66.3)	104 (66.2)
AE leading to death	2 (1.6)	0	1 (0.8)	0	2 (1.4)	5 (2.1)	8 (3.3)	3 (1.9)
Serious AE	46 (37.1)	29 (31.5)	37 (28.0)	21 (28.8)	43 (30.7)	97 (40.6)	75 (30.9)	39 (24.8)
AE leading to study treatment discontinuation	21 (16.9)	18 (19.6)	23 (17.4)	8 (11.0)	11 (7.9)	25 (10.5)	21 (8.6)	17 (10.8)
Immune-related AE	36 (29.0)	22 (23.9)	32 (24.2)	21 (28.8)	32 (22.9)	88 (36.8)	52 (21.4)	42 (26.8)
ADR associated with atezolizumab, *n* (%)[b]	54 (43.5)	35 (38.0)	48 (36.4)	25 (34.2)	53 (37.9)	118 (49.4)	83 (34.2)	61 (38.9)
Grade ≥ 3 ADR	27 (21.8)	17 (18.5)	17 (12.9)	5 (6.8)	21 (15.0)	41 (17.2)	36 (14.8)	19 (12.1)
ADR leading to death	1 (0.8)	0	1 (0.8)	0	0	1 (0.4)	2 (0.8)	0
Serious ADR	23 (18.5)	12 (13.0)	15 (11.4)	4 (5.5)	16 (11.4)	35 (14.6)	23 (9.5)	10 (6.4)
ADR leading to atezolizumab discontinuation	18 (14.5)	9 (9.8)	19 (14.4)	9 (12.3)	14 (10.0)	24 (10.0)	25 (10.3)	15 (9.6)
ADR leading to atezolizumab interruption	19 (15.3)	10 (10.9)	13 (9.8)	12 (16.4)	17 (12.1)	32 (13.4)	29 (11.9)	18 (11.5)
AE applicable to interstitial lung disease, *n* (%)	19 (15.3)	6 (6.5)	18 (13.6)	6 (8.2)	7 (5.0)	8 (3.3)	17 (7.0)	10 (6.4)
Grade ≥ 3	7 (5.6)	2 (2.2)	5 (3.8)	0	1 (0.7)	3 (1.3)	7 (2.9)	0
Grade 5	1 (0.8)	0	0	0	0	1 (0.4)	0	0

Abbreviations: ADR, adverse drug reaction; AE, adverse event; atezo, atezolizumab; bev, bevacizumab; CnP, carboplatin + nab-paclitaxel; CP, carboplatin + paclitaxel; CE, carboplatin + etoposide; NA, not available; PP, carboplatin or cisplatin + pemetrexed.
[a]Saito R, et al. Presented at the 2024 American Society of Clinical Oncology Annual Meeting. Abstract 8092. Adapted with permission by the author.
[b]ADRs are AEs for which a causal relationship cannot be ruled out.

overall population, there was no significant difference in the incidence of AEs and immune-related AEs between the ECOG PS 0 and 1 groups. However, in patients with an ECOG PS 0/1 with a G8 score < median, Grade ≥ 3 AEs incidence increased compared with a G8 ≥ median, except in patients receiving atezo + CnP where Grade ≥ 3 AEs by median G8 score was similar. These results are consistent with those of previous studies that showed G8 score can predict the prognosis of lung cancer and other cancers and that similar results can be obtained even when limiting a patient population to an ECOG PS 0/1 [22, 32].

TABLE 3 | Safety summary in patients with ECOG PS < 2 by treatment regimen and median G8 score. Median G8 score in patients with NSCLC was 13. Median G8 score for patients with ES-SCLC was 12.

	Atezo + CnP		Atezo + PP		Atezo + bev + CP		Atezo + CE	
	G8 ≥ 13; ECOG PS < 2 (*n* = 44)	G8 < 13; ECOG PS < 2 (*n* = 50)	G8 ≥ 13; ECOG PS < 2 (*n* = 66)	G8 < 13; ECOG PS < 2 (*n* = 41)	G8 ≥ 13; ECOG PS < 2 (*n* = 61)	G8 < 13; ECOG PS < 2 (*n* = 57)	G8 ≥ 12; ECOG PS < 2 (*n* = 121)	G8 < 12 ECOG PS < 2 (*n* = 62)
Any grade AE, *n* (%)	41 (93.2)	46 (92.0)	56 (84.8)	33 (80.5)	56 (91.8)	55 (96.5)	104 (86.0)	56 (90.3)
Grade ≥ 3 AE	32 (72.7)	34 (68.0)	30 (45.5)	26 (63.4)	38 (62.3)	43 (75.4)	77 (63.6)	44 (71.0)
AE leading to death	1 (2.3)	1 (2.0)	1 (1.5)	0	0	2 (3.5)	1 (0.8)	4 (6.5)
Serious AE	18 (40.9)	20 (40.0)	15 (22.7)	14 (34.1)	18 (29.5)	17 (29.8)	29 (24.0)	22 (35.5)
AE leading to study treatment discontinuation	8 (18.2)	8 (16.0)	8 (12.1)	8 (19.5)	1 (1.6)	7 (12.3)	9 (7.4)	8 (12.9)
Immune-related AE	13 (29.5)	18 (36.0)	17 (25.8)	9 (22.0)	13 (21.3)	13 (22.8)	28 (23.1)	15 (24.2)
ADR associated with atezolizumab, *n* (%)[a]	20 (45.5)	23 (46.0)	24 (36.4)	12 (29.3)	22 (36.1)	21 (36.8)	46 (38.0)	23 (37.1)
Grade ≥ 3 ADR	9 (20.5)	12 (24.0)	5 (7.6)	8 (19.5)	9 (14.8)	8 (14.0)	16 (13.2)	12 (19.4)
ADR leading to death	0	1 (2.0)	1 (1.5)	0	0	0	1 (0.8)	1 (1.6)
Serious ADR	10 (22.7)	9 (18.0)	5 (7.6)	6 (14.6)	6 (9.8)	6 (10.5)	11 (9.1)	8 (12.9)
ADR leading to atezolizumab discontinuation	4 (9.1)	9 (18.0)	6 (9.1)	8 (19.5)	7 (11.5)	5 (8.8)	9 (7.4)	11 (17.7)
ADR leading to atezolizumab interruption	8 (18.2)	8 (16.0)	9 (13.6)	1 (2.4)	7 (11.5)	5 (8.8)	16 (13.2)	8 (12.9)
AE applicable to interstitial lung disease, *n* (%)	5 (11.4)	12 (24.0)	9 (13.6)	5 (12.2)	3 (4.9)	3 (5.3)	11 (9.1)	4 (6.5)

Abbreviations: ADR, adverse drug reaction; AE, adverse event; atezo, atezolizumab; bev, bevacizumab; CnP, carboplatin + nab-paclitaxel; CP, carboplatin + paclitaxel; CE, carboplatin + etoposide; ECOG PS, Eastern Cooperative Oncology Group performance status; G8, Geriatric 8; NA, not available; PP, carboplatin or cisplatin + pemetrexed.

[a]ADRs are AEs for which a causal relationship cannot be ruled out.

Many clinical trials for lung cancer have excluded patients with CrCl < 60 mL/min [33]. These study results suggest that an atezolizumab combination regimen was effective even in patients with CrCl < 60 mL/min. Although approximately 80% of patients with low CrCl were ≥ 70 years old, the differences in mOS and mPFS between CrCl subgroups were comparable. Among patients receiving atezo + PP, mOS and mPFS of all CrCl subgroups were comparable between J-TAIL-2 and an integrated analysis of IMpower130 and IMpower132. Among patients receiving atezo + CnP, mOS for patients with CrCl < 45 mL/min and mPFS for patients in all CrCl subgroups are higher in the integrated analysis [34]. The incidence of serious AEs and AEs leading to study treatment discontinuation tended to increase as CrCl decreased in patients receiving atezo + CnP and atezo + PP. The incidence of Grade ≥ 3 AEs tended to increase as CrCl decreased with atezo + PP, and the incidence of ILD tended to increase as CrCl decreased with atezo + CnP. These safety results indicate that patients with low CrCl receiving atezo + CnP or atezo + PP have an increased risk of AEs.

This study has several limitations. As an observational study, J-TAIL-2 lacks a control group and does not specify dosage or treatment intervals. Additionally, the median observation period (14.1 months for the NSCLC cohort; 13.7 months for the ES-SCLC cohort) was not long enough to evaluate "long-tail effects." Further observation, updates of survival, and longer-term safety data are needed.

In conclusion, these subgroup analyses of J-TAIL-2, a large-scale observational study conducted in real-world clinical settings, showed that the efficacy and safety of atezolizumab with chemotherapy in older patients with lung cancer were comparable to the findings of each of the regimens' clinical trials. There were no new safety signals identified in this study. G8 score could be a useful tool to predict prognosis and safety when selecting treatment in older adults with an ECOG PS 0/1.

Author Contributions

Junichi Shimizu: writing – review and editing, writing – original draft, investigation. **Makoto Nishio:** investigation, writing – review and editing. **Kadoaki Ohashi:** investigation, writing – review and editing. **Atsushi Osoegawa:** investigation, writing – review and editing. **Eiki Kikuchi:** investigation, writing – review and editing. **Hideharu Kimura:** investigation, writing – review and editing. **Yasushi Goto:** methodology, writing – review and editing. **Eisaku Miyauchi:** investigation, writing – review and editing. **Hiroshige Yoshioka:** investigation, writing – review and editing. **Ichiro Yoshino:** writing – review and editing, investigation. **Toshihiro Misumi:** investigation, writing – review and editing. **Kozo Yoshimori:** investigation, writing – review and editing. **Kazuhiko Shibata:** investigation, writing – review and editing. **Takeshi Tsuda:** writing – review and editing, resources. **Masahiro Seike:** writing – review and editing, investigation. **Takahiro Ota:** writing – review and editing, resources. **Koichi Samata:** writing – review and editing, visualization, writing – original draft. **Yuki Kobayashi:** visualization, writing – review and editing. **Misa Tanaka:** writing – review and editing, methodology. **Akihiko Gemma:** investigation, data curation, writing – review and editing, supervision, project administration, funding acquisition.

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Ethics Statement

J-TAIL-2 was conducted in accordance 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. The Ethics Review Committee of each study site approved the study protocol and the informed consent form prior to study initiation at the site.

Consent

Enrolled patients received a full explanation of the clinical research and provided written consent to participate.

Conflicts of Interest

All authors declare editorial support from Chugai Pharmaceutical Co. Ltd. Junichi Shimizu has received honoraria for speakers' bureaus from Amgen, AstraZeneca, Chugai Pharmaceutical Co., MSD, Novartis, Pfizer, Taiho Pharmaceutical, and Takeda Pharmaceutical Ltd. Makoto Nishio has received payment or honoraria for lectures from AbbVie, AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Chugai Pharmaceutical Co. Ltd., Daiichi Sankyo, Janssen, Lilly, Nippon Kayaku, Merck, MSD, Novartis, Ono Pharmaceuticals, Pfizer, Taiho Pharmaceutical, and Takeda Pharmaceutical. Kadoaki Ohashi has received grants or contracts and honoraria from Chugai Pharmaceutical Co. Ltd. Atsushi Osoegawa has received grants from Chugai Pharmaceutical and Taiho Pharmaceutical; and has received honoraria from AstraZeneca, Bristol Myers Squibb, Chugai Pharmaceutical Co. Ltd., MSD, and Ono Pharmaceutical. Eiki Kikuchi has received honoraria from Chugai Pharmaceutical Co. Ltd. Hideharu Kimura has received honoraria and grants from Chugai Pharmaceutical Co. Ltd. Yasushi Goto is an Editorial Board member (Associate Editor) at *Cancer Science*; declares grants (to institution) from AbbVie, Bristol Myers Squibb, Daiichi Sankyo, Eli Lilly, Kyorin, Novartis, Ono Pharmaceutical, Pfizer, and Preferred Networks; has received payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing, or educational events from Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly, Merck, MSD, Novartis, Ono Pharmaceutical, Pfizer, Taiho Pharmaceutical, and Thermo Fisher; has participated on a data safety monitoring or advisory board for AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Chugai Pharmaceuticals Co. Ltd. Daiichi Sankyo, Eli Lilly, Guardant Health, Illumina, MSD, Novartis, Ono Pharmaceutical, Pfizer, and Taiho Pharmaceutical; has held leadership or fiduciary roles for Cancer Net Japan and JAMT; and has received honoraria from Chugai Pharmaceuticals Co. Ltd. Eisaku Miyauchi has received grants from Chugai Pharmaceutical Co. Ltd.; has received honoraria from Amgen, AstraZeneca K.K., Boehringer Ingelheim Japan, Bristol Myers Squibb, Chugai Pharmaceutical Co. Ltd., Daiichi Sankyo K.K., Eli Lilly Japan K.K., Kyowa Kirin, Merck Biopharma, MSD K.K., Nippon Kayaku, Novartis Pharma K.K., Ono Pharmaceutical, Pfizer, Sysmex Co, Taiho Pharmaceutical, Takeda Pharmaceutical,

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Data Availability Statement

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Figure S1:** Patient flow and analysis populations from J-TAIL-2 NSCLC and SCLC cohorts. **Figure S2:** G8 score distribution by NSCLC (A) and SCLC (B) cohorts. **Figure S3:** OS (A–D) and PFS (E–H) in patients receiving (A/E) Atezo + CnP, (B/F) Atezo + PP, (C/G) Atezo + bev + CP, and (D/H) Atezo + CE by age (≥ 75 years and < 75 years). **Figure S4:** OS (A–D) and PFS (E–H) in patients receiving (A/E) Atezo + CnP, (B/F) Atezo + PP, (C/G) Atezo + bev + CP, and (D/H) Atezo + CE by G8 score (≥ median and < median). **Figure S5:** OS (A–D) and PFS (E–H) in patients receiving (A/E) Atezo + CnP, (B/F) Atezo + PP, (C/G) Atezo + bev + CP, and (D/H) Atezo + CE by creatinine clearance (mL/min). **Table S1:** The G8 questionnaire. **Table S2:** Baseline characteristics in the ITT population by treatment regimen and age (≥ 75 years and < 75 years). **Table S3:** Baseline characteristics in the ITT population by treatment regimen and G8 score (≥median and <median). **Table S4:** Safety summary by treatment regimen and age (≥ 75 years and < 75 years). **Table S5:** Safety summary by treatment regimen and G8 score (≥ median and < median). **Table S6:** Safety summary by treatment regimen and creatinine clearance (≥ 60 mL/min, 45 to < 60 mL/min, and < 45 mL/min).