Original Article

IMpower210: A phase III study of second-line atezolizumab *vs.* docetaxel in East Asian patients with non-small cell lung cancer

Yi-Long Wu[1*], Shun Lu[2*], Gongyan Chen[3], Jianxing He[4], Jifeng Feng[5], Yiping Zhang[6], Liyan Jiang[7], Hongming Pan[8], Jianhua Chang[9], Jian Fang[10], Amy Cai[11], Lilian Bu[11], Jane Shi[11], Jinjing Xia[11]

[1]Guangdong Lung Cancer Institute, Guangdong Provincial Key Laboratory of Translational Medicine in Lung Cancer, Guangdong Provincial People's Hospital & Guangdong Academy of Medical Sciences, Southern Medical University, Guangzhou 510080, China; [2]Shanghai Lung Cancer Center, Shanghai Chest Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai 200025, China; [3]Department of Respiration, Harbin Cancer Hospital, Harbin Medical University, Harbin 150081, China; [4]Department of Thoracic Oncology and Surgery, the First Affiliated Hospital of Guangzhou Medical University, Guangzhou 510120, China; [5]Department of Medical Oncology, Jiangsu Cancer Hospital, Nanjing 210009, China; [6]Department of Medical Oncology, Zhejiang Cancer Hospital, Hangzhou 330022, China; [7]Department of Pulmonary Medicine, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai 200030, China; [8]Department of Medical Oncology, Sir Run Run Shaw Hospital, Zhejiang University School of Medicine, Hangzhou 310016, China; [9]Department of Medical Oncology, Shenzhen Hospital, Cancer Hospital of Chinese Academy of Medical Sciences, Shenzhen 518116, China; [10]Department of Thoracic Oncology, Beijing Cancer Hospital, Beijing 100142, China; [11]Product Development, Shanghai Roche Pharmaceutical Ltd, Shanghai 201203, China

*These authors contributed equally to this work.

Correspondence to: Yi-Long Wu. Guangdong Lung Cancer Institute, Guangdong Provincial Key Laboratory of Translational Medicine in Lung Cancer, Guangdong Provincial People's Hospital & Guangdong Academy of Medical Sciences, Southern Medical University, No. 106 Zhongshan Er Road, Guangzhou 510080, China. Email: syylwu@live.cn.

Abstract

Objective: IMpower210 (NCT02813785) explored the efficacy and safety of single-agent atezolizumab *vs.* docetaxel as second-line treatment for advanced non-small cell lung cancer (NSCLC) in East Asian patients.

Methods: Key eligibility criteria for this phase III, open-label, randomized study included age ≥18 years; histologically documented advanced NSCLC per the Union for International Cancer Control/American Joint Committee on Cancer staging system (7th edition); Eastern Cooperative Oncology Group performance status of 0 or 1; and disease progression following platinum-based chemotherapy for advanced or metastatic NSCLC. Patients were randomized 2:1 to receive either atezolizumab (1,200 mg) or docetaxel (75 mg/m^2). The primary study endpoint was overall survival (OS) in the intention-to-treat (ITT) population with wild-type epidermal growth factor receptor expression (ITT *EGFR*-WT) and in the overall ITT population.

Results: Median OS in the ITT *EGFR*-WT population (n=467) was 12.3 [95% confidence interval (95% CI), 10.3–13.8] months in the atezolizumab arm (n=312) and 9.9 (95% CI, 7.8–13.9) months in the docetaxel arm [n=155; stratified hazard ratio (HR), 0.82; 95% CI, 0.66–1.03]. Median OS in the overall ITT population was 12.5 (95% CI, 10.8–13.8) months with atezolizumab treatment and 11.1 (95% CI, 8.4–14.2) months (n=377) with docetaxel treatment (n=188; stratified HR, 0.87; 95% CI, 0.71–1.08). Grade 3/4 treatment-related adverse events (TRAEs) occurred in 18.4% of patients in the atezolizumab arm and 50.0% of patients in the docetaxel arm.

Conclusions: IMpower210 did not meet its primary efficacy endpoint of OS in the ITT *EGFR*-WT or overall ITT populations. Atezolizumab was comparatively more tolerable than docetaxel, with a lower incidence of grade 3/4 TRAEs.

Keywords: Atezolizumab; East Asia; non-small cell lung cancer; programmed death-ligand 1 inhibitors; monoclonal antibody

Submitted Dec 21, 2023. Accepted for publication Mar 28, 2024.
doi: 10.21147/j.issn.1000-9604.2024.02.01

View this article at: https://doi.org/10.21147/j.issn.1000-9604.2024.02.01

Introduction

Non-small cell lung cancer (NSCLC) accounts for more than 80% of all lung cancers, with most patients presenting with advanced or metastatic disease (1). Lung cancer incidence is particularly high among Asians, who constitute approximately 50% of the global cases (2). In China, lung cancer incidence has increased primarily due to air pollution and high rates of cigarette smoking (3). Anti-programmed death-ligand 1 (PD-L1)/programmed death-1 (PD-1) agents administered as monotherapy or in combination with platinum-based chemotherapy, with or without bevacizumab for non-squamous NSCLC, are standard first-line treatments for advanced NSCLC tumors with no sensitizing epidermal growth factor receptor (*EGFR*) mutations or anaplastic lymphoma kinase (*ALK*) rearrangements (4,5).

Prior to the approval of immune checkpoint inhibitors, disease progression frequently occurred following first-line treatment with platinum-based chemotherapy for advanced NSCLC. In recent years, standard second-line treatment for metastatic NSCLC has shifted from docetaxel to monotherapy with the anti-PD-1 agents nivolumab or pembrolizumab, or the anti-PD-L1 atezolizumab (4,5).

Atezolizumab is an engineered, humanized anti-PD-L1 monoclonal antibody that reinvigorates anticancer immunity by inhibiting the interactions between PD-1 and B7-1 with PD-L1 (6). The global, randomized phase III OAK study evaluated the efficacy and safety of single-agent atezolizumab *vs.* docetaxel (N=1,225; atezolizumab, n=613; docetaxel, n=612) in patients with advanced NSCLC who experienced disease progression with platinum-based chemotherapy (7). Primary analysis (n=850) showed median overall survival (OS) of 13.8 months in the atezolizumab arm (n=425) and 9.6 months in the docetaxel arm [n=425; hazard ratio (HR), 0.73; 95% confidence interval (95% CI), 0.62–0.87] in the intention-to-treat (ITT) population (8). Median OS in patients with ≥1% PD-L1 expression on tumor cells (TC) or tumor-infiltrating immune cells (IC; TC1/2/3 or IC1/2/3) was 15.7 months and 10.3 months in the atezolizumab and docetaxel arms, respectively (HR, 0.74; 95% CI, 0.58–0.93) (7,8). Atezolizumab was more tolerable than docetaxel, with fewer grade ≥3 adverse events (AEs) and lower treatment discontinuation rates reported in both analyses (7,8).

A Japanese subgroup analysis of the OAK study (n=64) showed OS results consistent with those observed in the global study (9), with median OS in the ITT population of 21.3 months in the atezolizumab arm (n=36) and 17.0 months in the docetaxel arm (n=28; HR, 0.80; 95% CI, 0.41–1.57) (9). However, no Chinese patients were enrolled in the global OAK study.

The current IMpower210 study (No. NCT02813785) was initiated in 2016 to provide data on the safety and efficacy of atezolizumab for the second-line treatment of advanced NSCLC in East Asian patients. Although immunotherapy was the standard of care for second-line treatment of metastatic NSCLC in 2016, checkpoint inhibitors including atezolizumab were not yet approved in China or most East Asian countries at that time, and chemotherapy remained the standard of care. Data demonstrating the efficacy and safety of checkpoint inhibitor monotherapy in the Asian population were also limited, especially in Chinese patients. Therefore, without access to immune checkpoint inhibitor therapy, an unmet medical need existed for the East Asian population, particularly the Chinese population.

Here we report the results from the phase III IMpower210 study, which compared the efficacy and safety of atezolizumab monotherapy with those of docetaxel in East Asian patients with advanced or metastatic NSCLC who had experienced disease progression with platinum-based chemotherapy.

Materials and methods

Study design and participants

IMpower210 is a multicenter, randomized, open-label, phase III trial comparing the efficacy and safety of atezolizumab with those of docetaxel in patients with advanced or metastatic NSCLC who demonstrated disease progression with platinum-based chemotherapy. Eligible patients were randomized 2:1 to receive either atezolizumab 1,200 mg intravenously (IV) until loss of clinical benefit or docetaxel 75 mg/m^2 IV until disease progression, both on d 1 of a 21-d cycle.

Eligible participants were aged ≥18 years; had histologically documented advanced or metastatic NSCLC, measurable per the Union for International Cancer Control/American Joint Committee on Cancer staging

system, 7th edition; and had an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1. Patients were required to have experienced disease progression during or following platinum-based chemotherapy for locally advanced, unresectable, inoperable or metastatic NSCLC or disease recurrence within ≤6 months of platinum-based adjuvant and/or neoadjuvant treatment with curative intent. Patients with NSCLC harboring a sensitizing *EGFR* mutation or an *ALK* fusion oncogene must have received prior tyrosine kinase inhibitor treatment. Representative tumor specimens for prospective central testing of tumor PD-L1 expression and *EGFR* mutation status were required prior to enrollment. PD-L1 expression was assessed using the VENTANA SP142 immunohistochemical assay (Ventana Medical Systems, Inc, Tucson, AZ, USA) as the percentage of PD-L1-expressing TC or IC (as a percentage of the tumor area). TC3 or IC3 was defined as PD-L1 expression on ≥50% of TC or ≥10% of IC; TC2/3 or IC2/3 was defined as PD-L1 expression on ≥5% of TC or IC; TC1/2/3 or IC1/2/3 was defined as PD-L1 expression on ≥1% of TC or IC; and TC0 or IC0 was defined as PD-L1 expression on ≤1% of TC or IC.

Key exclusion criteria included the known absence of PD-L1 expression (e.g., patients whose PD-L1 expression status was determined for enrollment in a study involving anti-PD-1/PD-L1 agents), previous docetaxel treatment, active or untreated central nervous system metastases, and treatment with systemic immunomodulators within 4 weeks or 5 drug half-lives, whichever is shorter, or with systemic corticosteroids 2 weeks prior to randomization. Stratification factors were the number of prior chemotherapy regimens received (1 *vs.* 2), histology in combination with *EGFR* mutation status (non-squamous with *EGFR* mutations *vs.* non-squamous without *EGFR* mutations *vs.* squamous), and PD-L1 expression status (TC1/2/3 or IC1/2/3 *vs.* TC0 and IC0).

The trial was conducted in accordance with Good Clinical Practice guidelines and the principles of the Declaration of Helsinki. The major quality control measurements being taken in study include standard operating procedures (SOPs), training and certification, site monitoring, data validation and cleaning, data management, regular communication and collaboration, as well as an independent data monitoring committee. Ethics approval was obtained from the Institutional Review Board or Ethics Committee of participating institutions (*Supplementary Table S1*). Informed consent was required from all patients.

Randomization

After written informed consent was obtained and eligibility was established (including determination of tumor PD-L1 status and *EGFR* mutation status), the study site entered demographic and baseline characteristics in the interactive voice/web response system (IxRS) and obtained the patient's randomization number and treatment assignment. Permuted block randomization was applied to ensure an approximately 2:1 randomization ratio within each stratum. Randomization was stratified by PD-L1 expression on TCs and ICs by immunohistochemistry (TC1/2/3 or IC1/2/3 *vs.* TC0 and IC0); number of prior chemotherapy regimens (1 *vs.* 2); and histology and *EGFR* status (non-squamous with *EGFR* mutation *vs.* non-squamous without *EGFR* mutation *vs.* squamous). An IxRS vendor was responsible for the conduct of randomization, including randomization specification preparation, randomization code generation, and overall system implementation. The sponsor had no access to the randomization list until unblinding after study completion.

Assessments and endpoints

The primary study endpoint was OS in the ITT population with wild-type *EGFR* expression (ITT *EGFR*-WT) and in the overall ITT population. Secondary efficacy endpoints included investigator-assessed progression-free survival (PFS), objective response rate (ORR), and duration of response (DOR) per Response Evaluation Criteria in Solid Tumors 1.1 in the ITT *EGFR*-WT and ITT populations. Tumor assessments were performed at baseline and every 6 weeks for 36 weeks and every 9 weeks thereafter, until radiographic disease progression, withdrawal of consent, death, or study termination by sponsor, whichever occurred first. Follow-up data capture, including subsequent anti-cancer therapies, continued for each patient until death, loss of follow-up, withdrawal of consent, or study termination by sponsor, whichever occurred first.

Safety was evaluated for all patients who received any amount of study drug by monitoring the incidence, nature, and severity of AEs, graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCICTCAE) version 4.0. All AEs were reported until 30 d after the last dose of study drug or start of a new anticancer therapy after the last dose of study drug. Serious AEs and AEs of special interest (AESIs) were

recorded from the study start until 90 d after the last dose of study drug or initiation of non-protocol therapy. No crossover from the docetaxel arm to the atezolizumab arm was allowed. All AEs were followed up by the investigator until the event resolved to baseline grade or better, was assessed as stable by the investigator, loss of follow-up, or withdrawal of consent. For serious AEs, AESIs, and pregnancies, the sponsor or a designee was followed up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

Statistical analysis

The study was designed to randomize approximately 563 patients from East Asian countries, aiming to enroll at least 507 *EGFR*-WT patients and at least 450 patients from mainland China. OS was tested hierarchically in the ITT *EGFR*-WT population, followed by analysis in the ITT population, with a one-sided significance level of 0.025. The overall type I error rate for co-primary statistical testing of OS in the *EGFR*-WT and ITT populations was controlled (10) at the one-sided 0.025 level. OS in the *EGFR*-WT population was first tested at a one-sided α level of 0.025. Further statistical testing was performed for OS in the ITT population only if the hypothesis testing of OS in the *EGFR*-WT population was statistically significant. The sample size considerations for the co-primary testing of OS in *EGFR*-WT and ITT populations were: 1) 86.5% power to detect an HR of 0.69, corresponding to an improvement in median OS from 12 months in the docetaxel arm to 17.4 months in the atezolizumab arm in the *EGFR*-WT population (11-14); 2) 78.5% power to detect an HR of 0.73, corresponding to an improvement in median OS from 12 months in the docetaxel arm to 16.4 months in the atezolizumab arm, in the ITT population (11-14); 3) One interim analysis after 82% of the total OS events required for the final analysis have occurred, with use of the Lan-DeMets approximation to the Pocock boundary; and 4) Randomization ratio 2:1 (atezolizumab arm *vs.* docetaxel arm).

With these assumptions, final OS analysis was planned at approximately 335 and 376 OS events in the ITT *EGFR*-WT and ITT populations, respectively. Sample size was estimated using EAST version 6.0.

HRs for the OS analysis were estimated by the stratified Cox regression model method, including 95% CIs, with treatment arms compared based on a stratified log-rank test. Median OS was estimated by the Kaplan-Meier method, with the 95% CIs being estimated by the Brookmeyer-Crowley method. All AEs, including serious AEs, AESIs, and AEs leading to study drug discontinuation or interruption occurring during or after the first study drug dose, were summarized by treatment arm and according to the NCICTCAE version 4.0 grade.

Results

A total of 565 patients (*Supplementary Figure S1*) were enrolled from 40 sites in 5 East Asian countries (China, n=469; Republic of Korea, n=45; Thailand, n=29; Malaysia, n=16; and Singapore, n=6) between July 1, 2016, and May 31, 2017. The ITT population comprised 377 patients randomized to the atezolizumab arm and 188 to the docetaxel arm. The ITT *EGFR*-WT population comprised 312 patients in the atezolizumab arm and 155 patients in the docetaxel arm.

Baseline characteristics were similar between the two treatment arms (*Table 1*) in the ITT *EGFR*-WT and ITT populations. Baseline characteristics were generally similar between Chinese patients and patients from other countries in the ITT *EGFR*-WT populations, except for the percentage of patients in the PD-L1 TC1/2/3 or IC1/2/3 subgroup and the percentage of patients who had previous tobacco use history (*Supplementary Table S2*).

Efficacy

At the data cutoff of August 1, 2019, the median survival follow-up duration in the ITT *EGFR*-WT population was 30.2 (95% CI, 29.1–31.0) months in atezolizumab arm and 27.7 (95% CI, 26.9–29.9) months in docetaxel arm. In the ITT population, the median survival follow-up duration was 30.4 (95% CI, 29.4–31.6) months and 27.8 (95% CI, 26.9–29.9) months in atezolizumab and docetaxel arms, respectively.

Median OS in the ITT *EGFR*-WT population was 12.3 (95% CI, 10.3–13.8) months in the atezolizumab arm and 9.9 (95% CI, 7.8–13.9) months in the docetaxel arm (stratified HR, 0.82; 95% CI, 0.66–1.03) (*Figure 1A*). Median OS in the ITT population was 12.5 (95% CI, 10.8–13.8) months and 11.1 (95% CI, 8.4–14.2) months in the atezolizumab and docetaxel arms, respectively (stratified HR, 0.87; 95% CI, 0.71–1.08) (*Figure 1B*).

Table 1 Demographics and baseline characteristics of study populations

Variables	n (%)			
	ITT		ITT *EGFR*-WT	
	Atezolizumab (N=377)	Docetaxel (N=188)	Atezolizumab (N=312)	Docetaxel (N=155)
Age<65 years	257 (68.2)	131 (69.7)	215 (68.9)	108 (69.7)
Male	273 (72.4)	135 (71.8)	239 (76.6)	116 (74.8)
Baseline ECOG				
0	71 (18.8)†	44 (23.4)	63 (20.2)‡	36 (23.2)
1	304 (80.6)	144 (76.6)	248 (79.5)	119 (76.8)
Tobacco use history				
Never	147 (39.0)	78 (41.5)	105 (33.7)	57 (36.8)
Previous	187 (49.6)	86 (45.7)	169 (54.2)	75 (48.4)
Current	43 (11.4)	24 (12.8)	38 (12.2)	23 (14.8)
Metastatic disease	329 (87.3)	164 (87.2)	311 (99.7)	155 (100)
Prior chemotherapy regimens				
1	308 (81.7)	153 (81.4)	258 (82.7)	129 (83.2)
2	69 (18.3)	35 (18.6)	54 (17.3)	26 (16.8)
Histology combined with *EGFR* mutation status (central laboratory testing)				
Squamous	129 (34.2)	62 (33.0)	120 (38.5)	56 (36.1)
Nonsquamous with *EGFR* mutation	52 (13.8)	26 (13.8)	–	–
Nonsquamous without *EGFR* mutation	196 (52.0)	100 (53.2)	192 (61.5)	99 (63.9)
PD-L1 subgroups				
TC3 or IC3	40 (10.6)	20 (10.6)	36 (11.5)	17 (11.0)
TC2/3 or IC2/3	94 (24.9)	40 (21.3)	85 (27.2)	36 (23.2)
TC1/2/3 or IC1/2/3	146 (38.7)	71 (37.8)	131 (42.0)	61 (39.4)
TC0 and IC0	231 (61.3)	117 (62.2)	181 (58.0)	94 (60.6)

ECOG, Eastern Cooperative Oncology Group; *EGFR*, epidermal growth factor receptor; PD-L1, programmed death-ligand 1; TC, tumor cell; IC, tumor-infiltrating immune cell; ITT, intention to treat; WT, wild type. †, Number of evaluable patients is 375; ‡, Number of evaluable patients is 311.

Median OS in the PD-L1 TC1/2/3 or IC1/2/3 subgroup of the ITT *EGFR*-WT population was 15.8 (95% CI, 10.8–20.4) months in the atezolizumab arm *vs.* 8.3 (95% CI, 5.7–12.8) months in the docetaxel arm (unstratified HR, 0.68; 95% CI, 0.47–0.97) (*Figure 1C*). In the PD-L1 TC0 and IC0 subgroup of the ITT *EGFR*-WT population, median OS was 11.5 (95% CI, 8.1–13.2) months in the atezolizumab arm and 12.4 (95% CI, 8.4–15.8) months in the docetaxel arm (unstratified HR, 0.95; 95% CI, 0.71–1.27) (*Supplementary Figure S2*).

In the ITT *EGFR*-WT population, median OS among patients recruited in China was 12.6 (95% CI, 10.8–15.1) months in the atezolizumab arm and 8.9 (95% CI, 7.2–13.1) months in the docetaxel arm (unstratified HR, 0.74; 95% CI, 0.58–0.95) (*Figure 1D*, *Supplementary Figure S3*). In the ITT *EGFR*-WT population, median OS among patients recruited from countries other than China was 10.4 (95% CI, 8.0–16.2) months and 19.6 (95% CI, 8.3–31.9) months in the atezolizumab and docetaxel arms, respectively (unstratified HR, 1.43; 95% CI, 0.79–2.56) (*Supplementary Figure S4*).

Investigator-assessed ORR in ITT *EGFR*-WT population was 15.1% and 6.5% in atezolizumab and docetaxel arms, respectively (*Table 2*), and 12.8% and 10.1% in ITT population. The median DOR with atezolizumab in ITT *EGFR*-WT population was 19.8 [95% CI, 11.7–not estimable (NE)] months *vs.* 4.4 (4.0–6.9) months with docetaxel and 18.4 (11.7–NE) months and 4.6 (4.1–8.8) months in ITT population (*Table 2*).

Median PFS in the ITT *EGFR*-WT population was 2.9

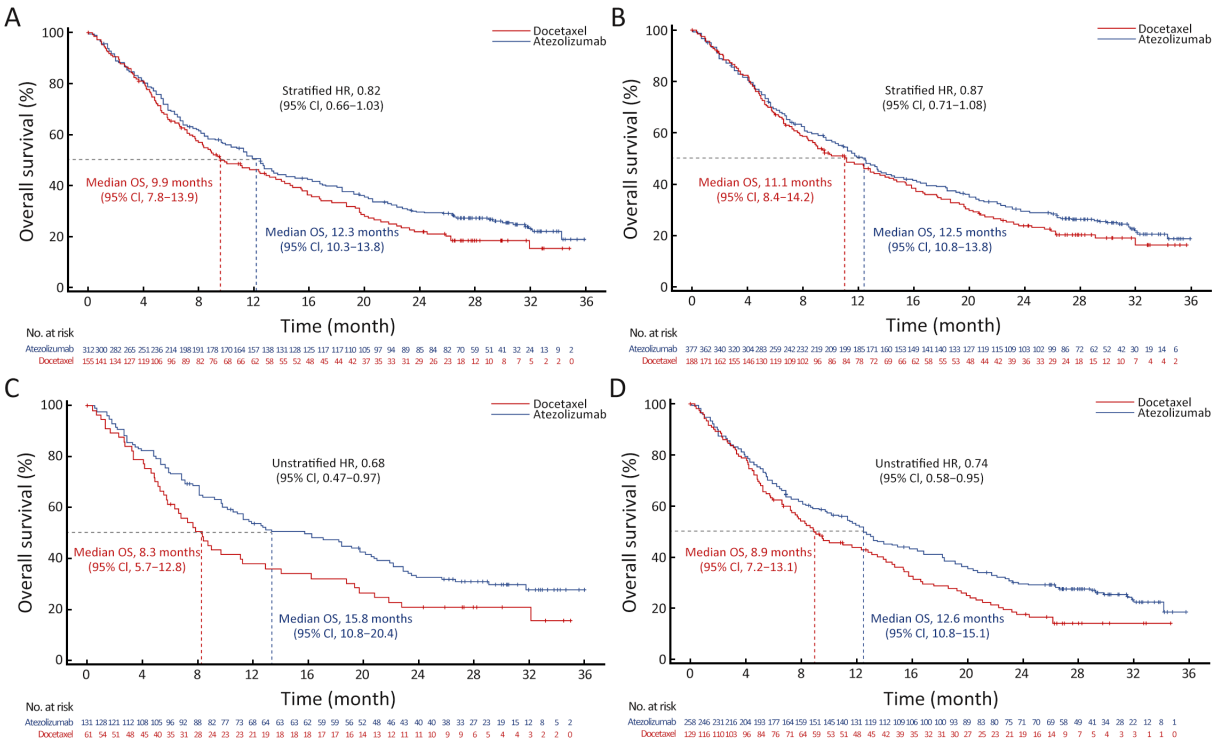

Figure 1 OS in ITT *EGFR*-WT population (A), ITT population (B), PD-L1 TC1/2/3 or IC1/2/3 subgroup of the ITT *EGFR*-WT population (C), and among Chinese patients in the ITT *EGFR*-WT population (D). OS, overall survival; ITT, intention to treat; *EGFR*, epidermal growth factor receptor; WT, wild type; PD-L1, programmed death-ligand 1; TC, tumor cell; IC, tumor-infiltrating immune cell; HR, hazard ratio; 95% CI, 95% confidence interval.

Table 2 Investigator-assessed treatment response in ITT and ITT *EGFR*-WT populations†

Response	n (%)			
	ITT		ITT *EGFR*-WT	
	Atezolizumab (N=375)	Docetaxel (N=188)	Atezolizumab (N=311)	Docetaxel (N=155)
Responders	48 (12.8)	19 (10.1)	47 (15.1)	10 (6.5)
Complete response	1 (0.3)	0 (0)	1 (0.3)	0 (0)
Partial response	47 (12.5)	19 (10.1)	46 (14.8)	10 (6.5)
Stable disease	162 (43.2)	66 (35.1)	131 (42.1)	61 (39.4)
Progressive disease	133 (35.5)	59 (31.4)	105 (33.8)	48 (31.0)
DOR (month)	48	19	47	10
Median	18.4	4.6	19.8	4.4

ITT, intention to treat; *EGFR*, epidermal growth factor receptor; WT, wild type; DOR, duration of response. †, Patients with measurable diseases at baseline.

(95% CI, 2.8–4.1) months with atezolizumab and 2.9 (95% CI, 2.7–4.1) months with docetaxel (unstratified HR, 0.83; 95% CI, 0.68–1.03) (*Figure 2A*). In the ITT population, median PFS was 2.8 (95% CI, 2.8–3.4) months with atezolizumab and 2.8 (95% CI, 2.7–4.1) months with docetaxel (unstratified HR, 0.89; 95% CI, 0.74–1.08) (*Figure 2B*). Among Chinese patients in the ITT *EGFR*-WT population, median PFS was 2.8 (95% CI, 2.8–4.1) months in the atezolizumab arm and 2.8 (95% CI, 1.7–3.2) months in the docetaxel arm (unstratified HR, 0.74; 95% CI, 0.59–0.93) (*Supplementary Figure S5*).

The OS trend was consistent across most patient subgroups in the overall ITT *EGFR*-WT population (*Supplementary Figure S6*) and in the Chinese ITT *EGFR*-

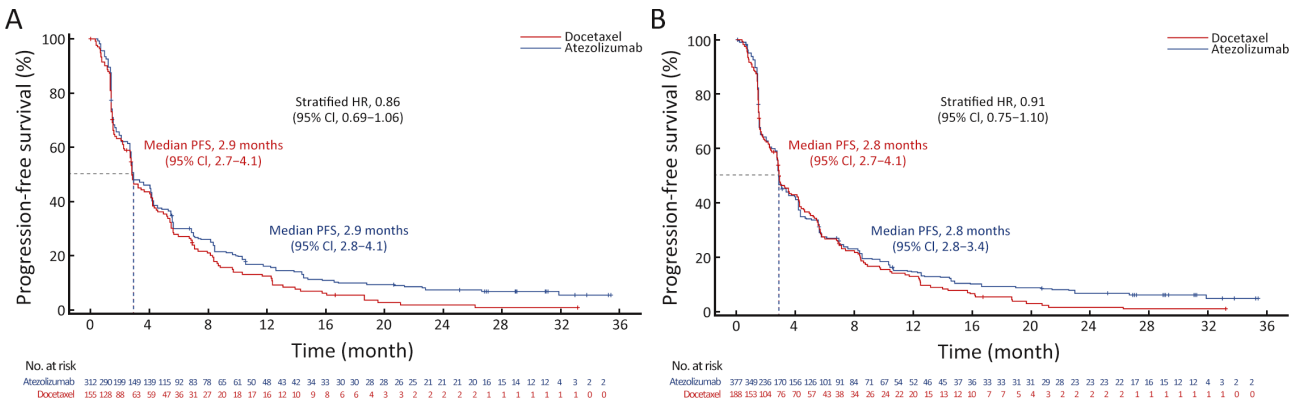

Figure 2 PFS in ITT *EGFR*-WT (A) and ITT populations (B). PFS, progression-free survival; ITT, intention to treat; *EGFR*, epidermal growth factor receptor; WT, wild type; HR, hazard ratio; 95% CI, 95% confidence interval.

WT population (*Supplementary Figure S7*). A more favorable improvement in OS was observed in patients in the atezolizumab arm who had an ECOG PS of 0 and with tumors expressing PD-L1 *vs.* patients in the docetaxel arm in both the overall and the Chinese ITT *EGFR*-WT populations.

Subsequent non-protocol treatment was administered to 54.0% of the patients (atezolizumab arm, 50.0%; docetaxel arm, 61.9%) in the ITT *EGFR*-WT population (*Supplementary Table S3*); these non-protocol treatments included chemotherapy (36.8%), targeted therapy (25.3%), and immunotherapy (3.6%). Six (1.9%) patients in the atezolizumab arm and 11 patients (7.1%) in the docetaxel arm received subsequent immunotherapy. Among Chinese patients in the ITT *EGFR*-WT population, 55.3% received subsequent anticancer treatment (atezolizumab, 50.8%; docetaxel, 64.3%), including chemotherapy (35.7%), targeted therapy (28.4%), and immunotherapy (3.6%). Six (2.3%) patients in the atezolizumab arm received subsequent immunotherapy compared with 8 (6.2%) patients in the docetaxel arm (*Supplementary Table S3*).

Safety

The median treatment duration was 3.5 months in the atezolizumab arm and 1.5 months in the docetaxel arm (*Supplementary Table S4*). In the safety-evaluable population, 96.0% of patients in the atezolizumab arm and 95.9% of patients in the docetaxel arm experienced all-cause AEs, with 75.1% and 87.8% of patients, respectively, experiencing treatment-related AEs (*Table 3*). Grade 3/4 AEs were experienced by 37.2% and 58.1% of patients in the atezolizumab and docetaxel arms, respectively (*Table 3*). Grade≥3 AEs reported in ≥5% of evaluable patients in the atezolizumab and docetaxel arms were lung infection,

Table 3 Summary of AEs in safety-evaluable group

AEs	n (%)	
	Atezolizumab (N=374)	Docetaxel (N=172)
All-cause any grade AEs	359 (96.0)	165 (95.9)
Treatment-related AEs	281 (75.1)	151 (87.8)
All-cause grade 3/4 AEs	139 (37.2)	100 (58.1)
Treatment-related grade 3/4 AEs	69 (18.4)	86 (50.0)
Grade 5 AEs	19 (5.1)	11 (6.4)
Treatment-related grade 5 AEs	11 (2.9)	9 (5.2)
Serious AEs	119 (31.8)	57 (33.1)
Any grade AESIs	154 (41.2)	55 (32.0)
AEs leading to withdrawal from any treatment	18 (4.8)	20 (11.6)
AEs leading to dose modification or interruption	75 (20.1)	55 (32.0)

AE, adverse event; AESI, AE of special interest.

anemia, neutropenia, decreased neutrophil count, and decreased white blood cell count. Treatment-related grade 3/4 AEs were experienced by 18.4% of patients in the atezolizumab arm and 50.0% of patients in the docetaxel arm (*Table 3*). The most frequent all-grade AEs that were observed at a difference of ≥5% between the treatment arms were pyrexia, cough, anemia, decreased weight, and increased alanine aminotransferase (*Table 4*).

All-grade AESIs were reported in 154 (41.2%) patients in the atezolizumab arm and 55 (32.0%) patients in the docetaxel arm. The most frequent AESIs were hepatic laboratory abnormalities, rash, and pneumonitis (*Supplementary Table S5*). Two patients in the atezolizumab arm reported grade 5 pneumonitis. The most commonly reported grade 3/4 AESI was hepatic laboratory abnormality.

Discussion

The IMpower210 study is one of the few cancer immunotherapy trials to have enrolled patients only from Asia and explored the clinical benefit of PD-1/PD-L1 inhibitors in patients with NSCLC in this ethnic demographic. The study did not meet its primary efficacy endpoint of OS in the ITT *EGFR*-WT population, although the longer median OS observed in the atezolizumab arm compared with the docetaxel arm (12.3 *vs.* 9.9 months) and an estimated HR of 0.82 are suggestive of clinical benefit in this population.

The clinically meaningful OS improvement observed in the Chinese patients in the atezolizumab arm of the ITT *EGFR*-WT population (3.7 months; HR, 0.74; 95% CI, 0.58–0.95) was consistent with that observed in the global OAK study (4.2 months; HR, 0.73; 95% CI, 0.62–0.87). Longer median OS with docetaxel treatment was observed in patients enrolled from countries other than China (docetaxel, 19.6 months; atezolizumab, 10.4 months), which is inconsistent with the results observed among Chinese patients in this study and in previous pivotal studies conducted in a global population (7,8,15). Median

Table 4 AEs occurring with a difference of ≥5% of patients between treatment arms in safety-evaluable subgroup

AEs	n (%)	
	Atezolizumab (N=374)	Docetaxel (N=172)
Pyrexia	83 (22.2)	20 (11.6)
Cough	76 (20.3)	18 (10.5)
Anemia	72 (19.3)	45 (26.2)
Decreased weight	55 (14.7)	11 (6.4)
Increased alanine aminotransferase	54 (14.4)	14 (8.1)
Increased aspartate aminotransferase	49 (13.1)	13 (7.6)
Fatigue	35 (9.4)	28 (16.3)
Musculoskeletal pain	34 (9.1)	7 (4.1)
Increased γ-glutamyl transferase	31 (8.3)	3 (1.7)
Asthenia	29 (7.8)	23 (13.4)
Diarrhea	21 (5.6)	23 (13.4)
Increased white blood cell count	21 (5.6)	48 (27.9)
Myalgia	17 (4.5)	17 (9.9)
Peripheral oedema	14 (3.7)	18 (10.5)
Decreased neutrophil count	10 (2.7)	41 (23.8)
Alopecia	8 (2.1)	60 (34.9)
Neutropenia	4 (1.1)	23 (13.4)
Leukopenia	4 (1.1)	17 (9.9)
Stomatitis	3 (0.8)	10 (5.8)
Bone marrow failure	0 (0)	10 (5.8)
Peripheral neuropathy	0 (0)	9 (5.2)

AE, adverse event.

OS observed with docetaxel for the second-line treatment of advanced NSCLC is typically 5.7 to 10.0 months (7,16-19). This anomalous result in this patient subgroup could not be explained with the currently available data but may have had an impact on the absence of a clinically meaningful OS benefit in the atezolizumab arm in the overall ITT *EGFR*-WT population in this study.

Most patients enrolled in this study were Chinese (83%), and the study population was similar to that of the phase III CheckMate 078 trial exploring the efficacy and safety of nivolumab in patients with advanced NSCLC who were previously treated with platinum-based chemotherapy (20). The CheckMate 078 trial demonstrated a similar OS trend in the nivolumab and docetaxel treatment arms (12.0 *vs.* 9.6 months; HR, 0.68; 97.7% CI, 0.52–0.90). However, the phase III KEYNOTE-033 study, which compared pembrolizumab and docetaxel for the second-line treatment of advanced NSCLC in PD-L1-positive Chinese patients, also did not reach its primary OS endpoint (21).

Longer median OS was reported in the atezolizumab arm than in the docetaxel arm in the PD-L1 subgroups (TC3 or IC3, TC2/3 or IC2/3, and TC1/2/3 or IC1/2/3) of the ITT *EGFR*-WT population, consistent with the global study and the OAK Japanese subgroup analysis (7,9). The proportion of PD-L1-positive patients in the atezolizumab arm of the ITT *EGFR*-WT population in this study (42%) was lower than that in the global OAK population (54%) (8) or in other comparable studies, such as the nivolumab arm of CheckMate 078 (50%) (19) in which PD-L1 expression was assessed by the Dako PD-L1 immunohistochemical 28-8 pharmDx assay (Agilent Technologies, Inc, Santa Clara, CA, USA) (19). This may have contributed to the lack of significant OS benefit with atezolizumab treatment in the overall ITT *EGFR*-WT population. However, OS benefit in the atezolizumab arm in subgroups with PD-L1 expression was consistent with that of other PD-1/PD-L1 inhibitors (17,19). The global study population and the OAK Japanese subgroup showed OS benefit with atezolizumab treatment in the PD-L1-negative subgroup, which was not observed in the current study (7,9).

The ORR in the ITT *EGFR*-WT population in this study was significantly higher with atezolizumab treatment than with docetaxel treatment (15.1% *vs.* 6.5%) compared with that observed in the global study population (14.6% *vs.* 13.4%), implying a potential benefit of atezolizumab treatment in this patient population. Durable response in this study, as evidenced by a longer median DOR in the atezolizumab arm (19.8 months) than in the docetaxel arm (4.4 months) in the ITT *EGFR*-WT population, is consistent with the sustained antitumor immune checkpoint blockade inhibition by anti-PD-1/PD-L1 agents observed in other studies (7,22-24).

Treatment discontinuation or disruption in fewer patients in the atezolizumab arm shows that atezolizumab was better tolerated than docetaxel in the safety-evaluable population. A higher proportion of patients receiving docetaxel reported grade 3/4 AEs than those receiving atezolizumab. Although the frequency of grade 5 AEs was comparable between treatment arms, treatment-related grade 5 AEs were less frequent in the atezolizumab arm. The safety profile of atezolizumab observed in this study was consistent with the known risks of atezolizumab monotherapy, with atezolizumab demonstrating more favorable tolerability than docetaxel. No new safety signals were identified in the safety-evaluable population.

Study strengths include the large population (N=565), the randomized design, and the consistent efficacy findings between the Chinese patients in this population and the large, global population.

Although a clinically meaningful OS benefit was observed among Chinese patients in the atezolizumab arm of the ITT *EGFR*-WT population, the statistical significance boundary for OS was not crossed in the overall ITT *EGFR*-WT population, signifying a key limitation of this study. This result precluded an analysis of the potential OS benefit provided by atezolizumab treatment in the overall East Asian demographic.

Conclusions

Although the primary study endpoint of OS in the ITT *EGFR*-WT population was not met, second-line atezolizumab treatment in patients with advanced NSCLC who had experienced disease progression with platinum-based chemotherapy showed a numerical OS improvement compared with docetaxel treatment. A clinically meaningful improvement in OS was observed in the atezolizumab arm of the China subgroup and in patients with tumors expressing PD-L1. Atezolizumab was well tolerated in the safety-evaluable population, with a favorable safety profile compared with that of docetaxel.

Acknowledgements

This study was funded by F. Hoffmann-La Roche Ltd. F.

Hoffmann-La Roche Ltd sponsored the IMpower210 study, provided study drugs, was involved in the study design, data collection, analysis, and interpretation, and approved this submission for publication.

Footnote

Conflicts of Interest: Yi-Long Wu has received honoraria from AstraZeneca, Biogen, Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly, Merck Sharpe and Dohme, Novartis, Pfizer, Roche, and Sanofi; is an advisor or consultant to AstraZeneca, Boehringer Ingelheim, Novartis, Takeda, and Merck Sharpe and Dohme; and has received research grant or funding to institution from AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Hengrui, and Roche. Shun Lu has received research support from AstraZeneca, Hutchison MediPharma, Bristol Myers Squibb, Hengrui, Beigene, Roche, and Hansoh; has received speaker fees from AstraZeneca, Roche, Hansoh, and Hengrui; is an advisor and consultant to AstraZeneca, Pfizer, Boehringer Ingelheim, Hutchison MediPharma, Simcere, Zai Lab, GenomiCare, Yuhan Corporation, PrIME Oncology, Menarini, and Roche. Lilian Bu, Jane Shi, Jinjing Xia, and Amy Cai are employees of F. Hoffmann-La Roche Ltd (China). The other authors have no conflicts of interest to declare.

References

1. Bareschino MA, Schettino C, Rossi A, et al. Treatment of advanced non-small cell lung cancer. J Thorac Dis 2011;3:122-33.
2. International Agency for Research on Cancer. Globocan Worldwide Fact Sheet 2020 (Lung). Available online: https://gco.iarc.fr/today/data/factsheets/cancers/15-Lung-fact-sheet.pdf
3. Cheng TYD, Cramb SM, Baade PD, et al. The international epidemiology of lung cancer: latest trends, disparities, and tumor characteristics. J Thorac Oncol 2016;11:1653-71.
4. Hanna NH, Schneider BJ, Temin S, et al. Therapy for stage IV non-small-cell lung cancer without driver alterations: ASCO and OH (CCO) joint guideline update. J Clin Oncol 2020;38:1608-32.
5. Planchard D, Popat S, Kerr K, et al. Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2018;29(Suppl 4):iv192-237.
6. Herbst RS, Soria JC, Kowanetz M, et al. Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients. Nature 2014;515:563-7.
7. Mazieres J, Rittmeyer A, Gadgeel S, et al. Atezolizumab versus docetaxel in pretreated patients with NSCLC: final results from the randomized phase 2 POPLAR and phase 3 OAK clinical trials. J Thorac Oncol 2021;16:140-50.
8. Rittmeyer A, Barlesi F, Waterkamp D, et al. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. Lancet 2017;389:255-65.
9. Hida T, Kaji R, Satouchi M, et al. Atezolizumab in Japanese patients with previously treated advanced non-small-cell lung cancer: a subgroup analysis of the phase 3 OAK study. Clin Lung Cancer 2018;19:e405-15.
10. Bretz F, Maurer W, Brannath W, et al. A graphical approach to sequentially rejective multiple test procedures. Stat Med 2009;28:586-604.
11. Shepherd FA, Dancey J, Ramlau R, et al. Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. J Clin Oncol 2000;18:2095-103.
12. Fossella FV, DeVore R, Kerr RN, et al. Randomized phase III trial of docetaxel versus vinorelbine or ifosfamide in patients with advanced non-small cell lung cancer previously treated with platinum-containing chemotherapy regimens. The TAX 320 Non-Small Cell Lung Cancer Study Group. J Clin Oncol 2000;18:2354-63.
13. Hanna N, Shepherd FA, Fossella FV, et al. Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small cell lung cancer previously treated with chemotherapy. J Clin Oncol 2004;22:1589-97.
14. Ramlau R, Gorbunova V, Ciuleanu TE, et al. Aflibercept and docetaxel versus docetaxel alone after platinum failure in patients with advanced or metastatic non-small-cell lung cancer: a randomized, controlled phase III trial. J Clin Oncol 2012;30:3640-7.

15. Fehrenbacher L, Spira A, Ballinger M, et al. Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial. Lancet 2016;387: 1837-46.
16. Schuette W, Nagel S, Blankenburg T, et al. Phase III study of second-line chemotherapy for advanced non-small-cell lung cancer with weekly compared with 3-weekly docetaxel. J Clin Oncol 2005;23:8389-95.
17. Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. N Engl J Med 2015;373:1627-39.
18. Herbst RS, Baas P, Kim DW, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. Lancet 2016;387:1540-50.
19. Morabito A. Second-line treatment for advanced NSCLC without actionable mutations: is immunotherapy the 'panacea' for all patients. BMC Med 2018;16:24.
20. Wu YL, Lu S, Cheng Y, et al. Nivolumab versus docetaxel in a predominantly Chinese patient population with previously treated advanced NSCLC: CheckMate 078 randomized phase III clinical trial. J Thorac Oncol 2019;14:867-75.
21. Zhou C, Feng J, Ma S, et al. Randomized, open-label phase III study of pembrolizumab (pembro) *vs* docetaxel (doce) in patients (pts) with previously treated NSCLC with PD-L1 tumour proportion score (TPS) ≥1%: KEYNOTE-033. Ann Oncol 2020;31(Suppl 4):S816.
22. Antonia SJ, Borghaei H, Ramalingam SS, et al. Four-year survival with nivolumab in patients with previously treated advanced non-small-cell lung cancer: a pooled analysis. Lancet Oncol 2019;20: 1395-408.
23. Zimmermann S, Peters S, Owinokoko T, et al. Immune checkpoint inhibitors in the management of lung cancer. Am Soc Clin Oncol Educ Book 2018; 38:682-95.
24. Mortezaee K, Majidpoor J. Anti-PD-(L)1 therapy of non-small cell lung cancer — A summary of clinical trials and current progresses. Heliyon 2023;9:e14566.

Cite this article as: Wu YL, Lu S, Chen G, He J, Feng J, Zhang Y, Jiang L, Pan H, Chang J, Fang J, Cai A, Bu L, Shi J, Xia J. IMpower210: A phase III study of second-line atezolizumab *vs*. docetaxel in East Asian patients with non-small cell lung cancer. Chin J Cancer Res 2024;36(2):103-113. doi: 10.21147/j.issn.1000-9604.2024.02.01

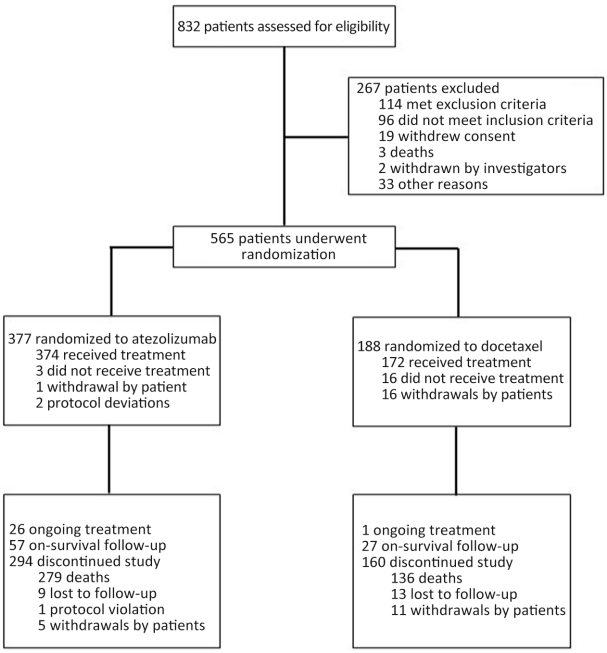

Figure S1 Consort diagram.

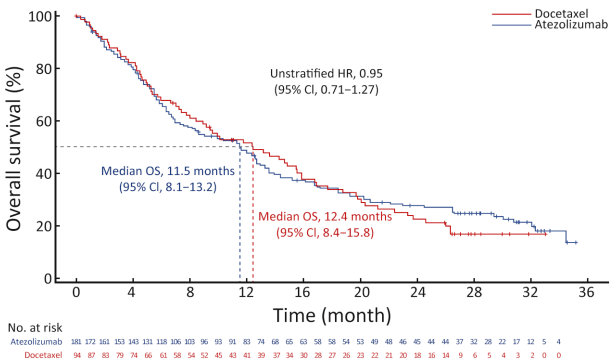

Figure S2 OS in PD-L1 TC0 and IC0 subgroup in ITT *EGFR*-WT population. OS, overall survival; PD-L1, programmed death-ligand 1; TC, tumor cell; IC, tumor-infiltrating immune cell; ITT, intention to treat; *EGFR*, epidermal growth factor receptor; WT, wild type; HR, hazard ratio; 95% CI, 95% confidence interval.

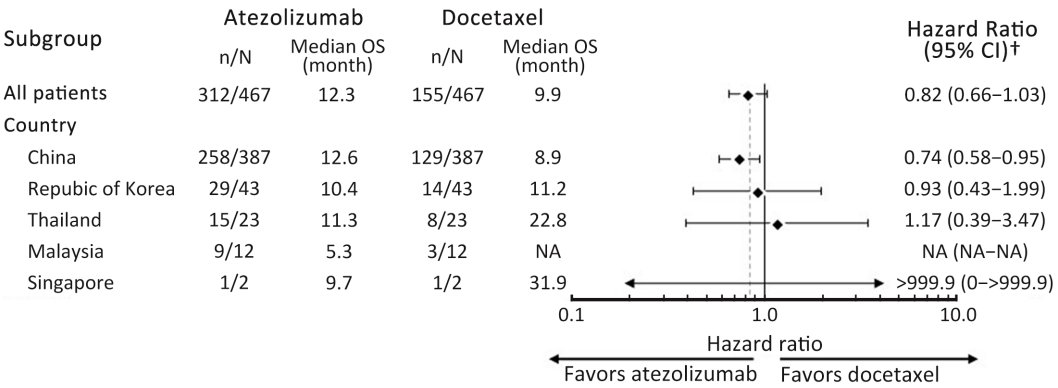

Figure S3 Subgroup analysis of OS in ITT *EGFR*-WT population according to country. OS, overall survival; ITT, intention to treat; *EGFR*, epidermal growth factor receptor; WT, wild type; NA, not applicable; HR, hazard ratio; 95% CI, 95% confidence interval. †, Stratified HR for ITT *EGFR*-WT population; unstratified HR for all other subgroups.

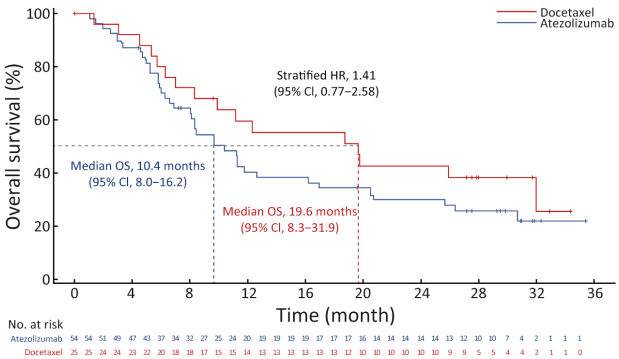

Figure S4 OS in patients in ITT *EGFR*-WT population from countries other than China. OS, overall survival; ITT, intention to treat; *EGFR*, epidermal growth factor receptor; WT, wild type; HR, hazard ratio; 95% CI, 95% confidence interval.

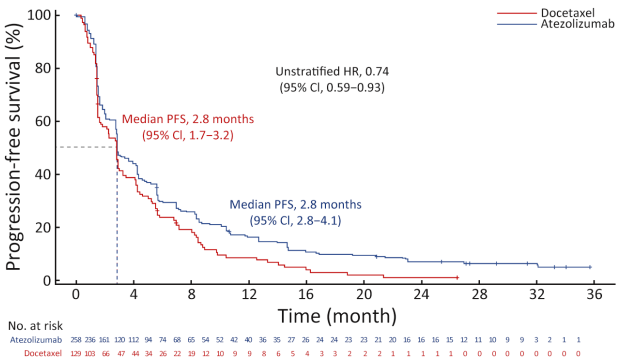

Figure S5 PFS in Chinese ITT *EGFR*-WT population. PFS, progression-free survival; ITT, intention to treat; *EGFR*, epidermal growth factor receptor; WT, wild type; HR, hazard ratio; 95% CI, 95% confidence interval.

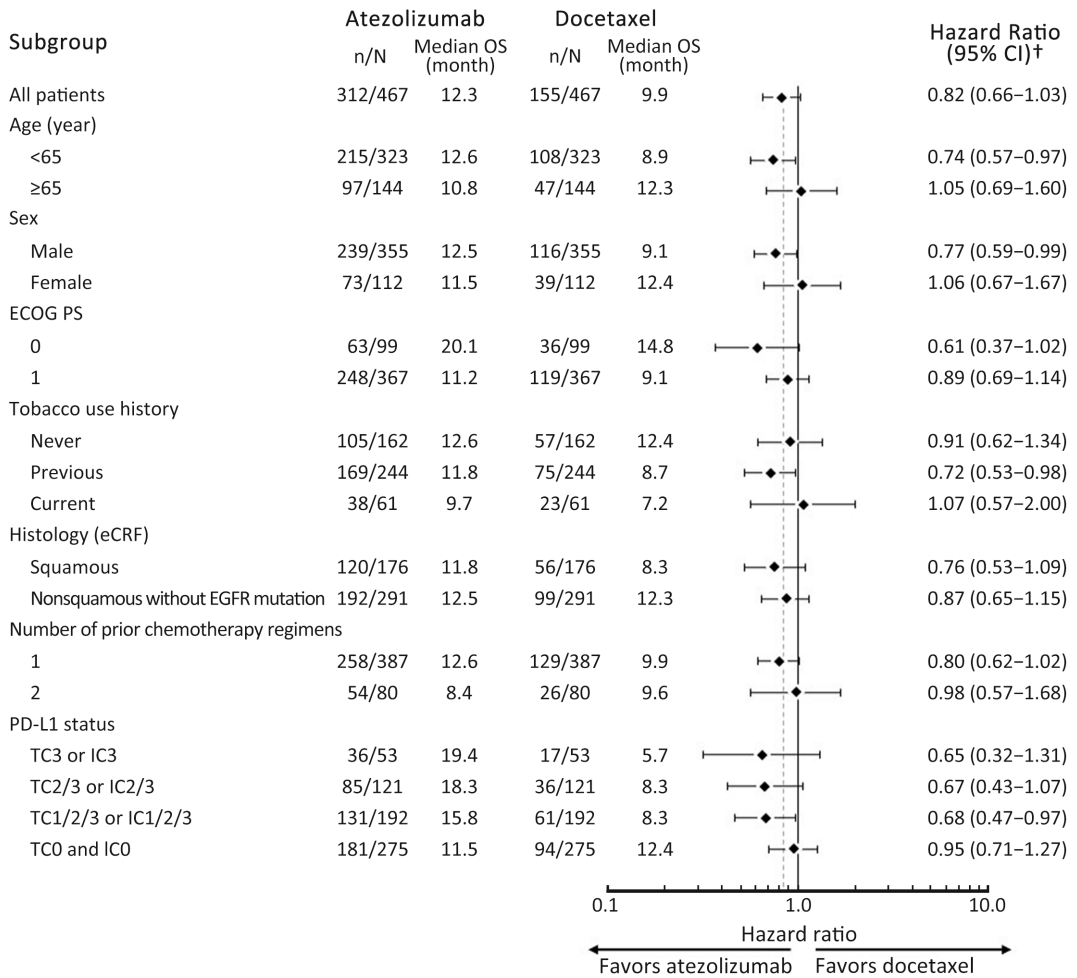

Figure S6 Subgroup analysis of OS in ITT *EGFR*-WT population. OS, overall survival; ITT, intention to treat; *EGFR*, epidermal growth factor receptor; WT, wild type; ECOG PS, Eastern Cooperative Oncology Group performance status; eCRF, electronic case report form; PD-L1, programmed-death-ligand 1; TC, tumor cell; IC, tumor-infiltrating immune cell; HR, hazard ratio; 95% CI, 95% confidence interval. †, Stratified HR for ITT *EGFR*-WT population; unstratified HR for all other subgroups.

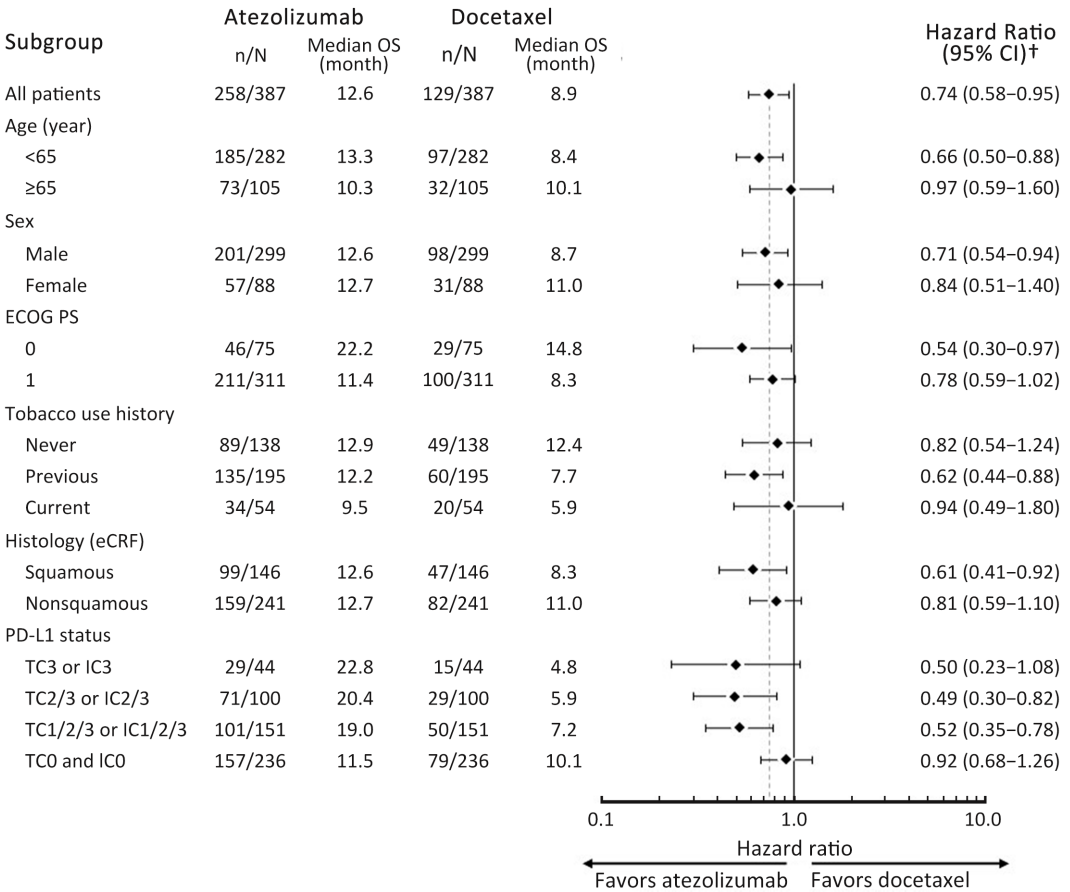

Figure S7 Subgroup analysis of OS in Chinese ITT *EGFR*-WT population. OS, overall survival; ITT, intention to treat; *EGFR*, epidermal growth factor receptor; WT, wild type; ECOG PS, Eastern Cooperative Oncology Group performance status; eCRF, electronic case report form; PD-L1, programmed death-ligand 1; TC, tumor cell; IC, tumor-infiltrating immune cell; HR, hazard ratio; 95% CI, 95% confidence interval. †, All HRs are unstratified.

Table S1 List of participating institutions

Country	Participating institutions
China	
	Beijing Cancer Hospital, Thoracic Oncology First Department
	Beijing Cancer Hospital, Thoracic Oncology Second Department
	Beijing Chest Hospital Oncology Department
	Cancer Hospital, Chinese Academy of Medical Sciences
	Changzhou First People's Hospital
	Fudan University Shanghai Cancer Center
	Guangdong General Hospital
	Harbin Medical University Cancer Hospital
	Henan Cancer Hospital
	Jiangsu Cancer Hospital
	Jilin Cancer Hospital
	Liaoning Cancer Hospital & Institute
	Shanghai Chest Hospital, Oncology Department
	Shanghai Chest Hospital, Respiratory Department
	Sir Run Run Shaw Hospital
	Sun Yet-Sen University Cancer Center
	The Affiliated Hospital of Bengbu Medical College
	The Affiliated Hospital of Medical College Qingdao University
	The First Affiliated Hospital of College of Medicine, Zhejiang University
	The First Affiliated Hospital of Guangzhou Medical University
	The First Affiliated Hospital of Xi'an Jiao Tong University
	The First Hospital of Jilin University
	The Second Affiliated Hospital of Third Military Medical University
	The Third Affiliated Hospital of Third Military Medical University
	Tianjin Medical University General Hospital
	West China Hospital, Sichuan University
	Zhejiang Cancer Hospital
	Zhongshan Hospital Fudan University
Republic of Korea	
	Chonnam National University Hwasun Hospital
	Chungnam National University Hospital
	Korea University Guro Hospital
	Kyungpook National University Medical Center
Malaysia	
	Hospital Kuala Lumpur
	Hospital Sultan Ismail
	Sarawak General Hospital
Singapore	
	National Cancer Center
Thailand	
	Chiang Mai University Hospital
	Chulalongkorn Hospital
	Ramathibodi Hospital
	Siriraj Hospital

Table S2 Demographics and baseline characteristics of Chinese and non-Chinese ITT *EGFR*-WT populations

Variables	n (%)			
	ITT *EGFR*-WT (China)		ITT *EGFR*-WT (other countries)	
	Atezolizumab (N=258)	Docetaxel (N=129)	Atezolizumab (N=54)	Docetaxel (N=26)
Age<65 years	185 (71.7)	97 (75.2)	30 (55.6)	11 (42.3)
Male	201 (77.9)	98 (76.0)	38 (70.4)	18 (69.2)
Baseline ECOG				
0	46† (17.8)	29 (22.5)	17 (31.5)	7 (26.9)
1	211 (81.8)	100 (77.5)	37 (68.5)	19 (73.1)
Tobacco use history				
Never	89 (34.5)	49 (38.0)	16 (29.6)	8 (30.8)
Previous	135 (52.3)	60 (46.5)	34 (63.0)	15 (57.7)
Current	34 (13.2)	20 (15.5)	4 (7.4)	3 (11.5)
Metastatic disease	257 (99.6)	129 (100)	54 (100)	26 (100)
Prior chemotherapy regimens				
1	212 (82.2)	106 (82.2)	46 (85.2)	23 (88.5)
2	46 (17.8)	23 (17.8)	8 (14.8)	3 (11.5)
Histology combined with *EGFR* mutation status (central laboratory testing)				
Squamous	99 (38.4)	47 (36.4)	21 (38.9)	9 (34.6)
Nonsquamous with *EGFR* mutation	–	–	–	–
Nonsquamous without *EGFR* mutation	159 (61.6)	82 (63.6)	33 (61.1)	17 (65.4)
PD-L1 subgroups				
TC3 or IC3	29 (11.2)	15 (11.6)	7 (13.0)	2 (7.7)
TC2/3 or IC2/3	71 (27.5)	29 (22.5)	14 (25.9)	7 (26.9)
TC1/2/3 or IC1/2/3	101 (39.1)	50 (38.8)	30 (55.6)	11 (42.3)
TC0 and IC0	157 (60.9)	79 (61.2)	24 (44.4)	15 (57.7)

ITT, intention to treat; *EGFR*, epidermal growth factor receptor; WT, wild type; ECOG, Eastern Cooperative Oncology Group; PD-L1, programmed death-ligand 1; TC, tumor cell; IC, tumor-infiltrating immune cell. †, Number of evaluable patients is 257.

Table S3 Subsequent non-protocol anticancer therapy received by patients in ITT *EGFR*-WT and Chinese ITT *EGFR*-WT populations

Variables	n (%)			
	ITT *EGFR*-WT		ITT *EGFR*-WT (Chinese)	
	Atezolizumab (N=312)	Docetaxel (N=155)	Atezolizumab (N=258)	Docetaxel (N=129)
≥1 treatment	156 (50.0)	96 (61.9)	131 (50.8)	83 (64.3)
Chemotherapy	120 (38.5)	52 (33.5)	97 (37.6)	41 (31.8)
Targeted therapy	67 (21.5)	51 (32.9)	63 (24.4)	47 (36.4)
Immunotherapy	6 (1.9)	11 (7.1)	6 (2.3)	8 (6.2)
Unknown	26 (8.3)	21 (13.5)	26 (10.1)	21 (16.3)
Other	2 (0.6)	7 (4.5)	2 (0.8)	7 (5.4)

ITT, intention to treat; *EGFR*, epidermal growth factor receptor; WT, wild type.

Table S4 Study drug exposure in safety-evaluable population

Treatment duration (month)	n (%)	
	Atezolizumab (N=374)	Docetaxel (N=172)
Median	3.5	1.5
0<Duration≤3	181 (48.4)	120 (69.8)
3<Duration≤6	62 (16.6)	31 (18.0)
6<Duration≤12	66 (17.6)	18 (10.5)
Duration>12	65 (17.4)	3 (1.7)
Median dose intensity (%)	97.7	95.5
Median doses received (n)	5.5	3.0

Table S5 Summary of AESI occurring in safety-evaluable subgroup

AEs	n (%)			
	Atezolizumab (N=374)		Docetaxel (N=172)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Hepatitis (laboratory abnormal)	110 (29.4)	17 (4.5)	29 (16.9)	3 (1.7)
Rash	44 (11.8)	4 (1.1)	24 (14.0)	0 (0)
Pneumonitis†	12 (3.2)	2 (0.5)	4 (2.3)	1 (0.6)
Hypothyroidism	12 (3.2)	1 (0.3)	0 (0)	0 (0)
Hepatitis (diagnosis)	4 (1.1)	0 (0)	2 (1.2)	0 (0)
Infusion-related reactions	2 (0.5)	1 (0.3)	2 (1.2)	0 (0)
Pancreatitis	4 (1.1)	3 (0.8)	0 (0)	0 (0)
Hyperthyroidism	2 (0.5)	0 (0)	0 (0)	0 (0)
Diabetes mellitus	2 (0.5)	1 (0.3)	0 (0)	0 (0)
Ocular inflammatory toxicity	1 (0.3)	0 (0)	0 (0)	0 (0)
Vasculitis	0 (0)	0 (0)	1 (0.6)	0 (0)
Severe cutaneous reactions	1 (0.3)	1 (0.3)	0 (0)	0 (0)

AESI, adverse event of special interest; AE, adverse event. †, Two patients in the atezolizumab arm had grade 5 pneumonitis.