Atezolizumab in Japanese Patients With Previously Treated Advanced Non–Small-Cell Lung Cancer: A Subgroup Analysis of the Phase 3 OAK Study

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Abstract

Atezolizumab is effective and well tolerated in pretreated advanced/metastatic non–small-cell lung cancer (NSCLC). We examined atezolizumab's efficacy and safety in 64 Japanese patients with NSCLC in the same setting via a subanalysis of the phase 3 OAK study. Atezolizumab improved overall survival versus docetaxel and was generally well tolerated, thus offering a potential NSCLC treatment for Japanese patients.

Introduction: Atezolizumab, an anti–programmed death-ligand 1 (PD-L1) agent, is effective and well tolerated in patients with pretreated advanced non–small-cell lung cancer (NSCLC). We assessed its efficacy and safety in Japanese patients through subgroup analyses of the phase 3 OAK study (NCT02008227). **Patients and Methods:** Key eligibility criteria of this randomized, controlled, open-label, international study include locally advanced/metastatic NSCLC, $\geq$ 1 prior platinum-based chemotherapy, age $\geq$ 18 years, measurable disease (Response Evaluation Criteria in Solid Tumors v1.1), and Eastern Cooperative Oncology Group performance status 0 or 1. Atezolizumab 1200 mg or docetaxel 75 mg/m^2 was provided intravenously every 3 weeks. Co-primary end points were overall survival (OS) in the intention-to-treat (ITT) population and those with $\geq$ 1% PD-L1 expression on tumor cells (TC) or tumor-infiltrating immune cells (IC; TC1/2/3 or IC1/2/3). **Results:** Sixty-four ITT patients were Japanese; 19 had TC1/2/3 or IC1/2/3 status. In Japanese ITT patients, median OS in the atezolizumab arm (n = 36) was longer than the docetaxel arm (n = 28; 21.3 months [95% confidence interval (CI), 11.0-not estimable (NE)] versus 17.0 months [95% CI, 12.5-NE], respectively; hazard ratio 0.80 [95% CI, 0.41-1.57]). In the TC1/2/3 or IC1/2/3 population, median OS was 21.3 months (95% CI, 15.0-NE) and NE in the atezolizumab (n = 11) and docetaxel (n = 8) groups, respectively (hazard ratio, 0.81 [95% CI, 0.22-3.05]). Atezolizumab was generally well tolerated, with no treatment-related deaths. **Conclusion:** Atezolizumab was effective and well tolerated in pretreated Japanese patients with NSCLC. Results are consistent with the primary analysis of OAK.

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Introduction

Lung cancer is the leading cause of cancer death in Japan, with an estimated 77,300 deaths due to this disease in 2016 and an estimated 133,800 individuals projected to develop lung cancer in same year.[1] Notably, non–small-cell lung cancer (NSCLC) is the predominant subtype of lung cancer, accounting for approximately 87% of all lung cancers; approximately 65% of patients with NSCLC present with locally advanced or metastatic disease.[2]

Treatment strategies for patients with NSCLC have evolved over recent years. The standard of care had been docetaxel for patients with locally advanced or metastatic NSCLC that progressed after first-line therapy, including for Japanese patients.[3,4] The introduction of targeted therapies for patients with genetic aberrations led to the rapid adaptation of treatment recommendations between 2010 to 2015 by the Japan Lung Cancer Society, supporting the use of targeted therapies in patients with activating mutations in the epidermal growth factor receptor (*EGFR*) gene, rearrangements of the gene encoding anaplastic lymphoma kinase (*ALK*), or *ROS1*.[4,5] In recent years, positive results from clinical trials investigating the efficacy and safety of agents targeting the programmed death-ligand 1 (PD-L1)/programmed death-1 (PD-1) pathway led to the inclusion of the PD-1 inhibitors pembrolizumab and nivolumab in the Japanese guidelines for the treatment of NSCLC in the second line and beyond.[5-11]

Atezolizumab (TECENTRIQ; F. Hoffmann-La Roche Ltd) is an anti–PD-L1 monoclonal antibody that selectively inhibits PD-L1 interacting with its receptors PD-1 and B7.1, thereby reinvigorating and enhancing anticancer immunity.[6,8] It also leaves the PD-L2/PD-1 interaction intact, potentially preserving immune homeostasis.[6] Atezolizumab has demonstrated efficacy and safety in a broad range of cancer types, including NSCLC.[8,12-16] Results from the phase 2 POPLAR and phase 3 OAK studies, both in PD-L1-unselected patients with NSCLC, showed significant survival benefits with atezolizumab compared with docetaxel.[13,16] Furthermore, atezolizumab was well tolerated and had a favorable safety profile in these studies.[13,16]

In the first 850 patients of the OAK study, the median overall survival (OS) was 13.8 months (95% confidence interval [CI], 11.8-15.7) in the atezolizumab arm compared with 9.6 months (95% CI, 8.6-11.2) in the docetaxel arm in the intention-to-treat (ITT) population (hazard ratio [HR], 0.73 [95% CI, 0.62-0.87]).[16] In patients with tumor cells (TC) or tumor-infiltrating immune cells (IC) expressing PD-L1 (TC1/2/3 or IC1/2/3 [PD-L1 expression on $\geq$ 1% of TC or IC]), significant survival benefit was reported with atezolizumab versus docetaxel (15.7 months [95% CI, 12.6-18.0] vs. 10.3 months [95% CI, 8.8-12.0], respectively; HR, 0.74 [95% CI, 0.58-0.93]).[16] Patients with low or undetectable PD-L1 expression (TC0 and IC0 [PD-L1 expression on $<$ 1% of TC and IC]) also showed improvement in OS with atezolizumab compared with those receiving docetaxel (12.6 months [95% CI, 9.6-15.2] vs. 8.9 months [95% CI, 7.7-11.5], respectively; HR, 0.75 [95% CI, 0.59-0.96]).[16]

Several studies have shown differences between Asian/Japanese and global populations in the way established treatments for NSCLC, such as docetaxel, irinotecan-based regimens, and gefitinib, work. Docetaxel monotherapy has been associated with a significantly higher risk of grade 3/4 neutropenia in Southeast Asian patients.[17] In addition, although not a head-to-head comparison, studies of irinotecan-based regimens suggest an apparent disparity in survival and hematologic toxicity between the Japanese and US populations.[18,19] In the context of targeted therapy, the incidence of interstitial lung disease caused by gefitinib was higher in Japanese patients compared with a global population.[20,21] Further, the prevalence of *EGFR* mutations has been reported to be higher in Asian versus Caucasian patients; in Japanese patients, the rate was approximately 64.8% in a multicenter diagnostic survey.[22] In the OAK study, patients with *EGFR* mutations have previously been reported to experienced a reduced benefit with atezolizumab compared with the overall population.[16] It is therefore of interest to assess whether the efficacy and tolerability of atezolizumab differs between Asian patients, particularly Japanese patients, and the global population, and to further explore the efficacy in Japanese patients with driver mutations.

This subgroup analysis of the OAK study aims to assess the efficacy and safety of atezolizumab in the Japanese subpopulation.

Methods

Study Design

OAK (ClinicalTrials.gov NCT02008227) is a randomized, controlled, open-label, international, phase 3 trial investigating atezolizumab monotherapy versus docetaxel in previously treated patients with locally advanced or metastatic NSCLC. The overall study design, including method of randomization and masking, was previously reported.[16] PD-L1 expression was assessed prospectively using archival or fresh tissue via a central laboratory. Baseline PD-L1 expression was evaluated using the VENTANA SP142 immunohistochemistry assay (Ventana Medical Systems, Inc., Tucson, AZ). PD-L1 expression was scored on TC as a percentage of PD-L1–expressing TC: TC1/2/3 ($\geq$ 1%), TC2/3 ($\geq$ 5%), TC3 ($\geq$ 50%), and TC0 ($<$ 1%); PD-L1 expression was scored on IC as a percentage of tumor area: IC1/2/3 ($\geq$ 1%), IC2/3 ($\geq$ 5%), IC3 ($\geq$ 10%), and IC0 ($<$ 1%). Patients were stratified by PD-L1 expression (IC0 vs. IC1 vs. IC2 vs. IC3 level), number of previous chemotherapy regimens (1 vs. 2), and histology (nonsquamous vs. squamous).

This study was conducted in accordance with good clinical practice and the Helsinki Declaration and was approved by local institutional review boards.

Patients

Patients were enrolled regardless of PD-L1 expression. The key eligibility criteria included squamous or nonsquamous locally advanced or metastatic NSCLC, disease progression during or after a platinum-based regimen, age $\geq$ 18 years, measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and tumor sample available for evaluation of PD-L1 expression. Patients with treated asymptomatic supratentorial central nervous system metastases were also eligible. Patients with *EGFR* mutations or an *ALK* rearrangement were required to have received previous tyrosine kinase inhibitor or *ALK* inhibitor therapy for inclusion in the study. Further, patients were included in the study only if they had received $\leq$ 2 prior chemotherapy regimens.

Patients with a history of autoimmune disease and those who had received prior therapy with docetaxel, CD137 agonists, anti–cytotoxic T-lymphocyte–associated antigen 4, or anti–PD-L1/PD-1 therapies were excluded. All patients provided written informed consent.

Treatments

Patients in the atezolizumab group received atezolizumab intravenously every 3 weeks at a 1200 mg fixed dose. Those in the docetaxel group received docetaxel intravenously every 3 weeks at 75 mg/m^2. Treatment was provided until unacceptable toxicity or disease progression, as determined by the investigator. Continuation of treatment beyond progression was allowed for patients receiving atezolizumab until loss of clinical benefit, as assessed by the investigator. Crossover to the atezolizumab group was not allowed.

Assessments

Tumors were assessed at baseline, then every 6 weeks until week 36, and every 9 weeks thereafter until disease progression, regardless of treatment discontinuation. Tumor assessments were continued until treatment discontinuation for patients receiving atezolizumab after disease progression. Survival follow-up was conducted throughout the study and every 3 months after treatment discontinuation.

The incidence of adverse events (AEs) and laboratory abnormalities and their severity were graded per the National Cancer Institute Common Terminology Criteria for Adverse Events, v4.0. All patients who received atezolizumab or docetaxel were evaluable for safety. AEs of special interest were collected based on conditions suggestive of autoimmune disorders such as colitis, hepatitis, endocrinopathies, meningoencephalitis, myocarditis, neuropathies, pancreatitis and pneumonitis, and infusion-related reactions.

Outcomes

The study co-primary end points were OS in the ITT population and the TC1/2/3 or IC1/2/3 population. The secondary end points were investigator-assessed progression-free survival (PFS), objective response rate and duration of response per RECIST v1.1, and safety.

In this subgroup analysis, we report the co-primary end points in Japanese patients compared against results previously reported for the ITT population.[16] We also evaluate the secondary end points in the Japanese subpopulation.

Statistical Analysis

Details on the statistical analysis were previously described in the primary analysis of OAK.[16] Briefly, the study was initially designed to enroll 850 patients, and the sample size was subsequently increased (up to 1300 patients) to power for a comparison of OS in patients with high PD-L1 expression (TC3 or IC3); 1225 patients were ultimately enrolled onto the study. On the basis of external data, the planned primary efficacy analysis was updated to be conducted on the first 850 ITT patients because this number ensured that the comparisons of OS in the ITT and TC1/2/3 or IC1/2/3 populations were sufficiently powered. The primary analysis of OS was planned to occur when 70% of the first 850 ITT patients had died.

For both the primary analysis and the current Japanese subgroup analysis, OS was estimated by the Kaplan-Meier method, with 95% CIs estimated using the Brookmeyer-Crowley method. HR was estimated with a stratified Cox regression analysis. In exploratory subgroup analyses and analyses of specific subgroups with potentially small sample sizes, HR was estimated with an unstratified Cox regression analysis. Patients who were still alive at the time of analysis were censored at the date they were last known to be alive, while those without postbaseline information were censored at the randomization date plus 1 day. PFS was analyzed with similar methods as described for OS. The overall response rates and corresponding 95% CIs were calculated by the Clopper-Pearson method. Safety was assessed descriptively.

The Japanese subgroup analysis was conducted based on the same data set as the primary analysis of OAK.

Results

Patients and Treatments

The first 850 ITT patients, including Japanese patients, were enrolled between March 11, 2014, and November 28, 2014, from 194 sites across 31 countries in North America, South America, Europe, and Asia (including Japan). Among the first 850 ITT patients, 425 were randomized to receive atezolizumab and 425 were randomized to receive docetaxel, as previously described.[16] Of the first 850 ITT patients, 64 (8%) of 850 were enrolled from centers in Japan and included in the current efficacy subgroup analysis.

Thirty-six (56%) of 64 patients were randomized to the atezolizumab group, while 28 (44%) received docetaxel. Nineteen Japanese patients (30%) were in the TC1/2/3 or IC1/2/3 subgroup, of whom 11 (58%) of 19 were in the atezolizumab group and 8 (42%) of 19 were in the docetaxel group. Forty-five (70%) of 64 Japanese patients were in the TC0 and IC0 subgroup, of whom 25 (56%) of 45 were in the atezolizumab group and 20 (44%) of 45 were in the docetaxel group (Supplemental Table 1 in the online version).

The remaining 375 patients were subsequently enrolled until April 29, 2015. Of the final 1225 patients (safety population), 101 (8%) were from Japan and were evaluable for safety in this subgroup analysis; of these, 56 (55%) received atezolizumab and 45 (45%) received docetaxel.

The minimum follow-up duration was 19.4 months for Japanese patients, with median follow-up durations of 21.0 months (range, 1.5-25.2 months) and 23.4 months (range, 2.8-24.5 months), respectively, in the atezolizumab and docetaxel groups. The median duration of treatment was 2.3 months (range, 0 to > 19.9 months) in the atezolizumab group and 3.5 months (range, 0 to > 24.0 months) in the docetaxel group. The demographic and baseline characteristics of the Japanese subpopulation were largely balanced between both treatment groups apart from age, sex, and ECOG performance status (Table 1).

Efficacy

The overall median OS of patients in the atezolizumab group was longer (21.3 months [95% CI, 11.0-not estimable [NE]) compared with that in the docetaxel group (17.0 months [95% CI, 12.5-NE]) in the ITT Japanese subpopulation. In the TC1/2/3 or IC1/2/3 subgroup, Japanese patients in the atezolizumab group had a

Table 1 Demographic and Baseline Characteristics of the Japanese Subpopulation

Characteristic	Atezolizumab (n = 36)	Docetaxel (n = 28)	All Patients (N = 64)
Age, y			
Median (range)	63.5 (33-77)	58.5 (34-79)	63.0 (33-79)
≥ 65, n (%)	17 (47.2)	11 (39.3)	28 (43.8)
Sex, n (%)			
Male	19 (52.8)	19 (67.9)	38 (59.4)
Female	17 (47.2)	9 (32.1)	26 (40.6)
ECOG Performance Status, n (%)			
0	12 (33.3)	15 (53.6)	27 (42.2)
1	24 (66.7)	13 (46.4)	37 (57.8)
History of Tobacco Use, n (%)			
Never	13 (36.1)	9 (32.1)	22 (34.4)
Current	3 (8.3)	1 (3.6)	4 (6.3)
Previous	20 (55.6)	18 (64.3)	38 (59.4)
***EGFR* Mutation Status, n (%)**			
Positive	8 (22.2)	9 (32.1)	17 (26.6)
Negative	28 (77.8)	18 (64.3)	46 (71.9)
Unknown	0	1 (3.6)	1 (1.6)
***EML4-ALK* Rearrangement Status, n (%)**			
Positive	0	0	0
Negative	31 (86.1)	19 (67.9)	50 (78.1)
Unknown	5 (13.9)	9 (32.1)	14 (21.9)
***KRAS* Mutation Status, n (%)**			
Positive	0	0	0
Negative	6 (16.7)	7 (25.0)	13 (20.3)
Unknown	30 (83.3)	21 (75.0)	51 (79.7)
Histology, n (%)			
Nonsquamous	28 (77.8)	22 (78.6)	50 (78.1)
Squamous	8 (22.2)	6 (21.4)	14 (21.9)
PD-L1 Subgroups, n (%)			
TC3 or IC3	5 (13.9)	3 (10.7)	8 (12.5)
TC2/3 or IC2/3	8 (22.2)	6 (21.4)	14 (21.9)
TC1/2/3 or IC1/2/3	11 (30.6)	8 (28.6)	19 (29.7)
TC0 and IC0	25 (69.4)	20 (71.4)	45 (70.3)
No. of Prior Therapies, n (%)			
1	27 (75.0)	23 (82.1)	50 (78.1)
2	9 (25.0)	5 (17.9)	14 (21.9)

Abbreviations: *ALK* = anaplastic lymphoma kinase; ECOG = Eastern Cooperative Oncology Group; *EGFR* = epidermal growth factor receptor; *EML4* = echinoderm microtubule-associated protein–like 4; IC = tumor-infiltrating immune cells; *KRAS* = Kirsten rat sarcoma virus; PD-L1 = programmed death-ligand 1; TC = tumor cells.

median OS of 21.3 months (95% CI, 15.0-NE), while the median OS for those receiving docetaxel during the study was not reached. In the TC0 and IC0 subgroup, Japanese patients in the atezolizumab group had a longer median OS (20.9 months [95% CI 7.8-NE]) than patients in the docetaxel group (17.0 months [95% CI, 12.0-NE]). The OS of the Japanese subpopulation was consistent with that of the overall OAK patient population, wherein patients who received atezolizumab had an increased OS versus those who received docetaxel (Japanese subpopulation: HR, 0.80 [95% CI, 0.41-1.57]; overall OAK population: HR, 0.73 [95% CI, 0.62-0.87][16]; Figure 1).

Patients with *EGFR* driver mutations had an OS HR of 1.79 (95% CI, 1.28-2.52) with atezolizumab versus docetaxel, with a median OS of 6.4 months versus 14.8 months, respectively. Patients without *EGFR* mutation had an OS HR of 0.78 (95% CI, 0.64-0.95), with a median OS of 8.4 months versus 7.0 months, respectively. Furthermore, no Japanese patients with *ALK* translocation or *KRAS* (Kirsten rat sarcoma viral oncogene) mutations were enrolled.

PFS was similar between both treatment groups in the ITT Japanese subpopulation (HR, 1.37 [95% CI, 0.81-2.31]; Table 2), with median PFS in patients in the atezolizumab group at 4.2 months (95% CI, 2.8-4.4) and 4.4 months (95% CI, 4.1-5.7) in those in the docetaxel group. Thirty-five (97.2%) of 36 patients in the atezolizumab group had disease progression, and 25 (89.3%) of 28 patients receiving docetaxel had disease progression. There was also no difference in PFS between both treatment groups for the TC1/2/3 or IC1/2/3 subgroup (HR, 1.18 [95% CI, 0.44-3.16]; Table 2), with median PFS at 4.2 months (95% CI, 2.9-10.2 months) with atezolizumab and 5.6 months (95% CI, 4.2-8.8 months) with docetaxel. The proportions of patients with PFS events in the atezolizumab and docetaxel groups were 90.9% (10/11 patients) and 87.5% (7/8 patients), respectively.

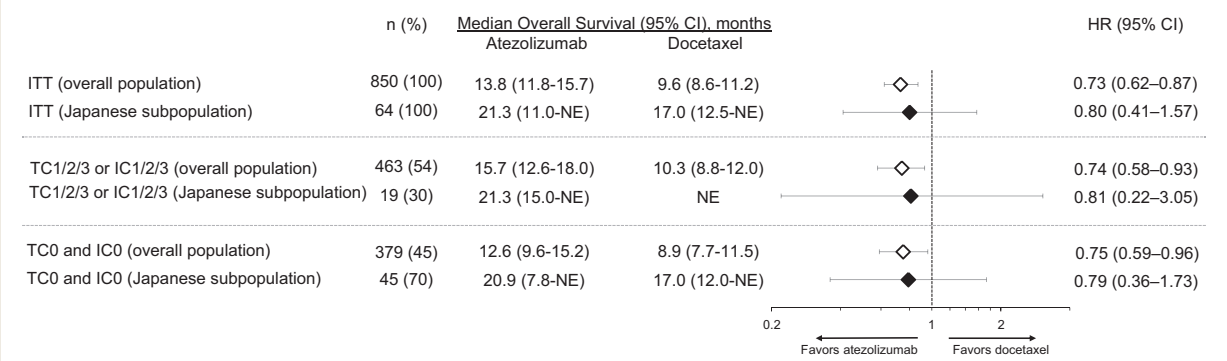
The proportion of patients with an objective response was 11.1% (4/36) with atezolizumab; 1 patient had a complete response, and 3 had partial responses (Table 3). This proportion was lower than that of patients in the docetaxel group (9/28, 32.1%), in which all responders had partial responses. On the contrary, more patients in the atezolizumab group had stable disease (21/36, 58.3%) than those in the docetaxel group (13/28, 46.4%). The duration of responses between the atezolizumab and docetaxel groups in the ITT Japanese population were comparable (HR, 1.22 [95% CI, 0.30-4.92]). Only 4 patients in the atezolizumab group and 9 in the docetaxel group were evaluable for duration of response, thus limiting our analysis.

Safety

In Japanese patients, the rates of all-grade treatment-related AEs reported for both treatment groups were similar, wherein 49 patients (87.5%) in the atezolizumab group and 44 patients (97.8%) in the docetaxel group experienced an AE of any grade. However, there were fewer grade 3/4 treatment-related AEs with atezolizumab (13/56, 23.2%) compared with docetaxel (41/45, 91.1%). The most common all-grade atezolizumab-related AEs reported in patients who received atezolizumab (incidence ≥ 10%; n = 56) were pyrexia (28.6%), rash (16.1%), diarrhea (14.3%), fatigue and headache (12.5% each), arthralgia, decreased appetite, malaise, and stomatitis (10.7% each; Table 4).

Compared with non-Japanese patients, Japanese patients had a generally higher incidence of any-grade treatment-related AEs (Japanese vs. non-Japanese: atezolizumab, 87.5% vs. 61.7%;

Figure 1 Comparison of OS in the Japanese Subpopulation Versus the Overall Population. Forest Plot Illustrating OS HRs and 95% CI for Both the Japanese Subpopulation (Solid Diamond) and the Overall Population (Open Diamond)



Abbreviations: CI = confidence interval; HR = hazard ratio; IC = tumor-infiltrating immune cells; ITT = intention-to-treat; NE = not estimable; OS = overall survival; PD-L1 = programmed death-ligand 1; TC = tumor cells.

docetaxel, 97.8% vs. 84.8%) and grade 3/4 treatment-related AEs (Japanese vs. non-Japanese: atezolizumab, 23.2% vs. 13.9%; docetaxel, 91.1% vs. 38.6%). However, this increase was not observed with serious AEs, regardless of study treatment (Table 5). A comparison of all-cause AEs in Japanese versus non-Japanese patients is shown in Supplemental Table 2 in the online version.

All-grade AEs of special interest occurred in 46 patients (82.1%) in the atezolizumab group and 39 patients (86.7%) in the docetaxel group (Table 6). The most frequently occurring all-grade AE of special interest in patients who received atezolizumab were rash (44.6%), infusion reaction (39.3%), pyrexia (35.7%), and hepatitis (17.9%). Most AEs of special interest were grade 1/2, regardless of treatment (only 1 patient in the atezolizumab group had grade 4 meningitis).

AEs leading to treatment discontinuation occurred in 10 patients (17.9%) in the atezolizumab group and 3 (6.7%) in the docetaxel group. There were no treatment-related deaths in the Japanese subpopulation.

Discussion

Despite being the historical mainstay for patients with locally advanced or metastatic NSCLC that progressed after first-line therapy, docetaxel has been associated with toxicities such as neutropenia, particularly in Asian patients,[17] limiting treatment options and highlighting the need for applying and/or identifying better therapeutic solutions. The current subgroup analysis of the phase 3 OAK trial is to our knowledge the first investigation of the efficacy and safety of atezolizumab in Japanese patients with NSCLC that could help broaden therapeutic options for these patients.

Comparisons on the primary end point, OS, showed that the efficacy of atezolizumab in ITT Japanese patients was consistent with that reported in the ITT overall population from the primary analysis.[16] Atezolizumab monotherapy provided a survival benefit over docetaxel in the Japanese subpopulation of OAK. Nishio et al[10] reported a median OS of 16.3 months in a phase 2 study of nivolumab in the second-line setting in patients with NSCLC.

Table 2 PFS in All Japanese Patients and in the TC1/2/3 or IC1/2/3 Subgroup

Population	n	Atezolizumab Median (95% CI), mo	Docetaxel Median (95% CI), mo	HR (95% CI)	*P*
ITT					
Overall population[a,b]	850	2.8 (2.6-3.0)	4.0 (3.3-4.2)	0.95 (0.82-1.10)	.49
Japanese subpopulation[c]	64	4.2 (2.8-4.4)	4.4 (4.1-5.7)	1.37 (0.81-2.31)	.23
TC1/2/3 or IC1/2/3					
Overall population[a,b]	137	2.8 (2.6-4.0)	4.1 (2.9-4.3)	0.91 (0.74-1.12)	.38
Japanese subpopulation[c]	19	4.2 (2.9-10.2)	5.6 (4.2-8.8)	1.18 (0.44-3.16)	.74
TC0 and IC0					
Overall population[a,b]	379	2.6 (1.7-2.9)	4.0 (3.1-4.2)	1.00 (0.80-1.25)	.99
Japanese subpopulation[c]	45	4.0 (1.5-4.4)	4.2 (2.9-5.8)	1.45 (0.78-2.69)	.24

Abbreviations: HR = hazard ratio; IC = tumor-infiltrating immune cells; ITT = intention-to-treat; PD-L1 = programmed death-ligand 1; PFS = progression-free survival; TC = tumor cells.
[a]Distribution of patients in the atezolizumab and docetaxel group: ITT (n = 425 each for atezolizumab and docetaxel); TC1/2/3 or IC1/2/3 subgroup (n = 241 for atezolizumab and n = 222 for docetaxel); TC0 and IC0 subgroup (n = 180 for atezolizumab and n = 199 for docetaxel).
[b]The overall population refers to the first 850 randomized patients in the OAK study.
[c]Distribution of patients in the atezolizumab and docetaxel groups: ITT (n = 36 for atezolizumab and n = 28 for docetaxel); TC1/2/3 or IC1/2/3 subgroup (n = 11 for atezolizumab and n = 8 for docetaxel); TC0 and IC0 subgroup (n = 25 for atezolizumab and n = 20 for docetaxel).

Table 3 Response in Japanese Patients

Response	Atezolizumab (n = 36)	Docetaxel (n = 28)
ORR, n (%)	4 (11.1)	9 (32.1)
CR	1 (2.8)	0
PR	3 (8.3)	9 (32.1)
SD	21 (58.3)	13 (46.4)
PD	11 (30.6)	6 (21.4)

Abbreviations: CR = complete response; ORR = objective response rate; PD = progressive disease; PR = partial response; SD = stable disease.

However, direct comparisons to the current analysis cannot be made due to differences in study treatment, the nature of the study, and the lack of planned head-to-head comparison.

The median OS in patients in the TC1/2/3 or IC1/2/3, and TC0 and IC0 subgroups in the Japanese subpopulation was similar to that in the global population in the OAK primary analysis.[16] Patients in this subgroup analysis still received a survival benefit from atezolizumab compared with docetaxel regardless of PD-L1 expression, with a longer survival associated with patients who had high PD-L1 expression versus those with low or undetectable PD-L1 expression. Previous studies of the PD-1 inhibitors pembrolizumab and nivolumab have also reported similar patterns in survival benefit associated with the level of PD-L1 expression.[9,23] This is expected because low PD-L1 expression has been linked to weak or no preexisting anticancer immunity.[13] However, the current observation that patients with no to low PD-L1 expression still derived OS benefit appears to be exclusive to atezolizumab, consistent with the OAK primary analysis[16]; patients with no to low PD-L1 expression had no survival benefit with nivolumab versus docetaxel.[9] Furthermore, the OS benefit with atezolizumab versus docetaxel has been observed in OAK patients categorized as PD-L1−negative by an alternative immunohistochemistry assay (22C3),[24] demonstrating the consistency of this observation. Together, these data support the use of atezolizumab in an all-comer setting.

PFS and the proportions of patients with an objective response were similar between the atezolizumab and docetaxel arms in

Table 4 Any-Grade Treatment-Related AEs Occurring in ≥ 10% of Japanese Patients

AE	Atezolizumab (n = 56)		Docetaxel (n = 45)	
	Any Grade in ≥ 10% of Patients, n (%)	Grade 3 or Higher, n (%)[a]	Any Grade in ≥ 10% of Patients, n (%)	Grade 3 or Higher, n (%)[a]
Patients with ≥ 1 AE	49 (87.5)	13 (23.2)	44 (97.8)	41 (91.1)
Pyrexia	16 (28.6)	0	10 (22.2)	0
Rash	9 (16.1)	0	13 (28.9)	0
Diarrhea	8 (14.3)	0	7 (15.6)	1 (2.2)
Fatigue	7 (12.5)	2 (3.6)	9 (20.0)	0
Headache	7 (12.5)	0	4 (8.9)	0
Arthralgia	6 (10.7)	0	14 (31.1)	0
Decreased appetite	6 (10.7)	0	25 (55.6)	3 (6.7)
Malaise	6 (10.7)	0	24 (53.3)	0
Stomatitis	6 (10.7)	0	20 (44.4)	2 (4.4)
Constipation	5 (8.9)	0	14 (31.1)	0
Anemia	4 (7.1)	0	8 (17.8)	1 (2.2)
White blood cell count decreased	4 (7.1)	0	13 (28.9)	12 (26.7)
Leukopenia	3 (5.4)	0	13 (28.9)	12 (26.7)
Nausea	3 (5.4)	0	18 (40.0)	0
Neutropenia	3 (5.4)	1 (1.8)	16 (35.6)	16 (35.6)
Myalgia	2 (3.6)	0	9 (20.0)	0
Dysgeusia	1 (1.8)	0	13 (28.9)	0
Edema	1 (1.8)	0	5 (11.1)	0
Neutrophil count decreased	1 (1.8)	0	22 (48.9)	22 (48.9)
Peripheral edema	1 (1.8)	0	16 (35.6)	0
Alopecia	0	0	28 (62.2)	0
Face edema	0	0	5 (11.1)	0
Febrile neutropenia	0	0	16 (35.6)	16 (35.6)
Nail discoloration	0	0	8 (17.8)	0
Nail disorder	0	0	5 (11.1)	0
Peripheral sensory neuropathy	0	0	14 (31.1)	0

AEs were assessed in 101 safety-evaluable patients. Multiple occurrences of same AE in one individual were counted once at the highest grade. AE incidences collected after the first treatment and within 30 days from the last treatment were included for analysis, unless the AE occurred after the start of nonprotocol cancer therapy within the 30-day posttreatment period.
Abbreviation: AE = adverse event.
[a]No grade 5 AEs were reported.

Table 5 Summary of AEs in Japanese and Non-Japanese Patients

Characteristic	Japanese (n = 101)		Non-Japanese (n = 1086)	
	Atezolizumab (n = 56), n (%)	Docetaxel (n = 45), n (%)	Atezolizumab (n = 553), n (%)	Docetaxel (n = 533), n (%)
All-cause AEs	52 (92.9)	45 (100)	521 (94.2)	510 (95.7)
Treatment-related AEs	49 (87.5)	44 (97.8)	341 (61.7)	452 (84.8)
All-cause grade 3/4 AEs	15 (26.8)	41 (91.1)	212 (38.3)	269 (50.5)
Treatment-related grade 3/4 AEs	13 (23.2)	41 (91.1)	77 (13.9)	206 (38.6)
All deaths	0	0	10 (1.8)	14 (2.6)
Treatment-related deaths	0	0	0	1 (0.2)
Serious AEs	11 (19.6)	9 (20.0)	183 (33.1)	172 (32.3)
AEs leading to withdrawal from treatment	10 (17.9)	3 (6.7)	36 (6.5)	105 (19.7)

Abbreviation: AE = adverse event.
Summary of AEs were assessed in the Japanese and the non-Japanese subgroups of overall OAK population.

Japanese patients. Furthermore, no survival benefit with atezolizumab was observed for patients with *EGFR* driver mutations. These results were consistent with data presented on the overall OAK population.[16] These data were also aligned with previous clinical trials of pembrolizumab, nivolumab, and atezolizumab[9,13,16,23]; a short median PFS (2.7 months) with a relatively long median OS (16.3 months) was also previously observed in a phase 2 study with nivolumab in pretreated Japanese patients with NSCLC.[10] Lack of improvement in PFS, as reported with PD-L1/PD-1 inhibitors, may be attributed to a delay in antitumor activity, an increase in tumor size that typically indicates disease progression but could also be a result of increased immune infiltration, or the initiation of antitumor activity after disease progression due to continued treatment.[25] The lack of improvement in the proportion of patients with objective response and the contrasting subsequent OS benefit observed in this subgroup analysis and in the original primary analysis of OAK[16] provide further support for these potential explanations.

Atezolizumab monotherapy was generally well tolerated in Japanese patients, with a similar safety profile as previously reported in the primary analysis of OAK.[16] There were, however, notable increases in the incidence of any-grade all-cause pyrexia (Japanese

Table 6 Summary of AEs of Special Interest in Japanese Patients

AE	Atezolizumab (n = 56)		Docetaxel (n = 45)	
	Any Grade, n (%)	Grade 3 or Higher, n (%)[a]	Any Grade, n (%)	Grade 3 or Higher, n (%)[a,b]
Any AE	46 (82.1)	8 (14.3)	39 (86.7)	1 (2.2)
Rash	25 (44.6)	2 (3.6)	35 (77.8)	0
Infusion reaction	22 (39.3)	0	20 (44.4)	0
Pyrexia	20 (35.7)	0	11 (24.4)	0
Hepatitis	10 (17.9)	2 (3.6)	5 (11.1)	0
Pneumonitis	5 (8.9)	1 (1.8)	1 (2.2)	1 (2.2)
Pneumonitis	2 (3.6)	1 (1.8)	1 (2.2)	1 (2.2)
Radiation pneumonitis	2 (3.6)	0	0	0
Interstitial lung disease	1 (1.8)	0	0	0
Hypothyroidism	3 (5.4)	0	1 (2.2)	0
Hyperthyroidism	2 (3.6)	0	1 (2.2)	0
Meningoencephalitis	4 (7.1)	3 (5.4)	0	0
Meningitis	3 (5.4)	2 (3.6)	0	0
Encephalitis	1 (1.8)	1 (1.8)	0	0
Guillain-Barré syndrome	1 (1.8)	1 (1.8)	0	0
Henoch-Schönlein purpura nephritis	1 (1.8)	1 (1.8)	0	0
Diabetes mellitus	1 (1.8)	0	0	0

AEs were assessed in 101 safety-evaluable patients.
Abbreviation: AE = adverse event.
[a]No grade 5 AEs of special interest were reported.
[b]Most incidences were grade 3 AEs of special interest; one grade 4 AE of special interest occurred in 1 patient, who experienced grade 4 meningitis.

[35.7%] vs. overall population [17.7%][16]), nasopharyngitis (Japanese [19.6%] vs. overall population [5.1%]), and stomatitis (Japanese [12.5%] vs. overall population [3.1%][16]). Nevertheless, no difference was observed between Japanese patients and the overall population for these AEs at higher grades (grade 3/4). Treatment-related pneumonitis is of particular interest in Japan. In this analysis, the incidence of pneumonitis in Japanese patients (3.6%), when assessed as an AE of special interest, was higher than that in the overall population (0.8%); however, the incidence was similar to that observed in Japanese patients (2.2%) who received docetaxel.

This was a subgroup analysis with a small number of Japanese patients and therefore limits direct comparisons between Japanese and non-Japanese subpopulations and the overall OAK population. Further, a high rate of patients with TC0 and IC0 status was observed in this analysis, but because of small patient numbers, these data warrant further study. The current analysis was also not powered for formal efficacy comparisons in the Japanese subpopulation. Furthermore, although the 75 mg/m^2 dose of docetaxel used here is considered a standard of care, it is a higher dose than that recommended by the Japan Cancer Society, which recommends 60 mg/m^2. The rate of grade 3/4 AEs in the docetaxel arm was higher than expected. This observation could be due to the small patient population or the higher dose of docetaxel used in this study. Nonetheless, the current analysis provides useful insights into the efficacy and safety of atezolizumab in Japanese patients. Further, the type and grade of AEs observed in the overall safety population were similar to those in the Japanese subpopulation, despite numerical differences.

In conclusion, despite notable differences in the incidences of pyrexia, nasopharyngitis, and stomatitis between Japanese patients and the global population, no difference was seen in these grade 3/4 AEs between the 2 patient groups. The overall efficacy and safety profile of atezolizumab in this subgroup analysis of Japanese patients treated in the OAK trial was consistent with that observed in the global ITT population of OAK, the latter of which supported the use of atezolizumab in pretreated patients with NSCLC.

Clinical Practice Points

- Atezolizumab improved OS and was well tolerated in pretreated patients with NSCLC, regardless of PD-L1 status.
- Differences between the Asian (and Japanese) and global population have been demonstrated for established NSCLC treatments.
- The current subgroup analysis provides support for the efficacy of atezolizumab in Japanese patients, which is consistent with results reported for the global population in the phase 3 OAK study for atezolizumab.
- The safety profile in this subgroup was also comparable to that in the global population in OAK, and despite increases in the incidences of pyrexia, nasopharyngitis, and stomatitis observed in Japanese patients, no differences were seen in the incidences of these AEs at grade 3/4 compared with non-Japanese patients.
- Atezolizumab may offer a potential treatment for Japanese patients with NSCLC who had disease progression after first-line therapy.

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Supplemental Data

Supplemental tables accompanying this article can be found in the online version at https://doi.org/10.1016/j.cllc.2018.01.004.

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Supplemental Table 1 Distribution of Patients Between Treatment Arms

Characteristic	All Patients, n/N (%)	Atezolizumab, n/N (%)	Docetaxel, n/N (%)
ITT			
Overall population	850/850 (100)	425/850 (50)	425/850 (50)
Japanese subpopulation	64/64 (100)	36/64 (56)	28/64 (44)
TC1/2/3 or IC1/2/3			
Overall population	463/850 (54)	241/463 (52)	222/463 (48)
Japanese subpopulation	19/64 (30)	11/19 (58)	8/19 (42)
TC0 and IC0			
Overall population	379/850 (45)	180/379 (47)	199/379 (53)
Japanese subpopulation	45/64 (70)	25/45 (56)	20/45 (44)

Abbreviations: IC = tumor-infiltrating immune cells; ITT = intention-to-treat; TC = tumor cells.

Supplemental Table 2 Any-Grade All-Cause AEs Occurring in ≥ 10% of Japanese and Non-Japanese Patients

	Japanese (n = 101)				Non-Japanese (n = 1086)			
	Atezolizumab, n (%) (n = 56)		Docetaxel, n (%) (n = 45)		Atezolizumab, n (%) (n = 553)		Docetaxel, n (%) (n = 533)	
AE[a]	Any Grade[b]	Grade 3 or Higher[c]	Any Grade[b]	Grade 3 or Higher[c]	Any Grade[b]	Grade 3 or Higher[c]	Any Grade[b]	Grade 3 or Higher[c]
Patients with ≥ 1 event	52 (92.9)	15 (26.8)	45 (100)	41 (91.1)	521 (94.2)	222 (40.1)	510 (95.7)	283 (53.1)
Pyrexia	20 (35.7)	0	11 (24.4)	0	88 (15.9)	1 (0.2)	65 (12.2)	1 (0.2)
Nasopharyngitis	11 (19.6)	0	6 (13.3)	0	20 (3.6)	0	14 (2.6)	0
Rash	9 (16.1)	0	13 (28.9)	0	49 (8.9)	2 (0.4)	36 (6.8)	0
Decreased appetite	8 (14.3)	0	26 (57.8)	3 (6.7)	135 (24.4)	2 (0.4)	110 (20.6)	6 (1.1)
Constipation	8 (14.3)	0	15 (33.3)	0	99 (17.9)	2 (0.4)	67 (12.6)	1 (0.2)
Diarrhea	8 (14.3)	0	11 (24.4)	1 (2.2)	86 (15.6)	4 (0.7)	130 (24.4)	10 (1.9)
Headache	8 (14.3)	0	5 (11.1)	0	49 (8.9)	2 (0.4)	41 (7.7)	1 (0.2)
Fatigue	7 (12.5)	2 (3.6)	9 (20.0)	0	156 (28.2)	15 (2.7)	196 (36.8)	23 (4.3)
Insomnia	7 (12.5)	0	6 (13.3)	0	42 (7.6)	1 (0.2)	36 (6.8)	3 (0.6)
Stomatitis	7 (12.5)	0	20 (44.4)	2 (4.4)	12 (2.2)	1 (0.2)	43 (8.1)	9 (1.7)
Arthralgia	6 (10.7)	0	14 (31.1)	0	67 (12.1)	3 (0.5)	44 (8.3)	1 (0.2)
Malaise	6 (10.7)	0	24 (53.3)	0	6 (1.1)	0	5 (0.9)	0
Nausea	5 (8.9)	0	19 (42.2)	0	103 (18.6)	4 (0.7)	112 (21.0)	2 (0.4)
Vomiting	5 (8.9)	0	4 (8.9)	0	69 (12.5)	2 (0.4)	58 (10.9)	4 (0.8)
Pruritus	5 (8.9)	0	5 (11.1)	0	45 (8.1)	3 (0.5)	13 (2.4)	0
Anemia	4 (7.1)	0	8 (17.8)	1 (2.2)	66 (11.9)	14 (2.5)	128 (24.0)	32 (6.0)
White blood cell count decreased	4 (7.1)	0	13 (28.9)	12 (26.7)	1 (0.2)	0	16 (3.0)	9 (1.7)
Back pain	3 (5.4)	0	6 (13.3)	0	64 (11.6)	7 (1.3)	36 (6.8)	4 (0.8)
Neutropenia	3 (5.4)	1 (1.8)	16 (35.6)	16 (35.6)	7 (1.3)	2 (0.4)	74 (13.9)	59 (11.1)
Leukopenia	3 (5.4)	0	13 (28.9)	12 (26.7)	1 (0.2)	0	12 (2.3)	10 (1.9)
Myalgia	2 (3.6)	0	9 (20.0)	0	37 (6.7)	1 (0.2)	82 (15.4)	4 (0.8)
Dysgeusia	2 (3.6)	0	13 (28.9)	0	16 (2.9)	0	45 (8.4)	0
Neutrophil count decreased	2 (3.6)	1 (1.8)	22 (48.9)	22 (48.9)	0	0	33 (6.2)	30 (5.6)
Cough	1 (1.8)	0	1 (2.2)	0	140 (25.3)	2 (0.4)	104 (19.5)	1 (0.2)
Dyspnea	1 (1.8)	0	1 (2.2)	0	117 (21.2)	16 (2.9)	111 (20.8)	15 (2.8)
Musculoskeletal pain	1 (1.8)	0	0	0	63 (11.4)	4 (0.7)	25 (4.7)	1 (0.2)
Peripheral edema	1 (1.8)	0	16 (35.6)	0	53 (9.6)	1 (0.2)	66 (12.4)	3 (0.6)
Dry skin	1 (1.8)	0	7 (15.6)	0	26 (4.7)	0	27 (5.1)	1 (0.2)
Edema	1 (1.8)	0	5 (11.1)	0	5 (0.9)	0	9 (1.7)	0
Asthenia	0	0	0	0	116 (21.0)	8 (1.4)	114 (21.4)	13 (2.4)
Neuropathy peripheral	0	0	1 (2.2)	0	24 (4.3)	0	64 (12.0)	7 (1.3)
Peripheral sensory neuropathy	0	0	14 (31.1)	0	6 (1.1)	0	29 (5.4)	5 (0.9)
Alopecia	0	0	28 (62.2)	0	3 (0.5)	0	174 (32.6)	1 (0.2)
Face edema	0	0	5 (11.1)	0	3 (0.5)	0	6 (1.1)	0
Febrile neutropenia	0	0	16 (35.6)	16 (35.6)	1 (0.2)	1 (0.2)	46 (8.6)	46 (8.6)
Nail discoloration	0	0	8 (17.8)	0	1 (0.2)	0	18 (3.4)	0
Nail disorder	0	0	5 (11.1)	0	0	0	25 (4.7)	1 (0.2)

Summary of AEs was assessed in Japanese and non-Japanese subgroups of overall OAK population.
Abbreviation: AE = adverse event.
[a]AEs that occurred within 30 days from the last study treatment were included in the analysis.
[b]Only incidences of AEs occurring in ≥ 10% of patients.
[c]No grade 5 AEs of special interest were reported.