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Atezolizumab Versus Docetaxel in Pretreated Patients With NSCLC: Final Results From the Randomized Phase 2 POPLAR and Phase 3 OAK Clinical Trials

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ABSTRACT

Introduction: The phase 2 POPLAR and phase 3 OAK studies of the anti-programmed death-ligand 1 (PD-L1) immunotherapy atezolizumab in patients with previously treated advanced NSCLC revealed significant improvements in survival versus docetaxel ($p = 0.04$ and 0.0003 , respectively). Longer follow-up permits evaluation of continued benefit of atezolizumab. This study reports the final overall survival (OS) and safety findings from both trials.

Methods: POPLAR randomized 287 patients (atezolizumab, 144; docetaxel, 143) and OAK randomized 1225 patients (atezolizumab, 613; docetaxel, 612). The patients received atezolizumab (1200 mg fixed dose) or docetaxel (75 mg/m²) every 3 weeks. Efficacy and safety outcomes were evaluated.

Results: A longer OS was observed in patients receiving atezolizumab versus docetaxel in POPLAR (median OS = 12.6 mo versus 9.7 mo; hazard ratio = 0.76,

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AstraZeneca, Merck Sharp & Dohme, and Boehringer Ingelheim outside of the submitted work. Dr. Barlesi reports receiving personal fees from AstraZeneca, Bayer, Bristol-Myers Squibb, Boehringer Ingelheim, Eli Lilly Oncology, F. Hoffmann-La Roche Ltd., Novartis, Merck, Merck Sharp & Dohme, Pierre Fabre, Pfizer, and Takeda outside of the submitted work. Drs. Yu, Matheny, and Ballinger report receiving grants from Genentech during the conduct of the study, personal fees from Genentech, and other fees from Roche outside of the submitted work. Dr. Park reports receiving other fees from Roche outside of the submitted work.

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95% confidence interval [CI]: 0.58–1.00) and OAK (median OS = 13.3 versus 9.8 mo; hazard ratio = 0.78, 95% CI: 0.68–0.89). The 4-year OS rates in POPLAR were 14.8% (8.7–20.8) and 8.1% (3.2–13.0) and those in OAK were 15.5% (12.4–18.7) and 8.7% (6.2–11.3) for atezolizumab and docetaxel, respectively. Atezolizumab had improved OS benefit compared with docetaxel across all PD-L1 expression and histology groups. Most 4-year survivors in the docetaxel arms received subsequent immunotherapy (POPLAR, 50%; OAK, 65%). Of the 4-year survivors, most had Eastern Cooperative Oncology Group performance status of 0 and nonsquamous histological classification and approximately half were responders (POPLAR: atezolizumab, seven of 15; docetaxel, three of four; OAK: atezolizumab, 24 of 43; docetaxel, 11 of 26). Treatment-related grade 3/4 adverse events occurred in 27% and 16% of atezolizumab 4-year survivors in POPLAR and OAK, respectively.

Conclusions: Long-term follow-up suggests a consistent survival benefit with atezolizumab versus docetaxel in patients with previously treated NSCLC regardless of PD-L1 expression, histology, or subsequent immunotherapy. Atezolizumab had no new safety signals, and the safety profile was similar to that in previous studies.

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Keywords: Non-small cell lung cancer; Atezolizumab; Docetaxel; Overall survival

Introduction

Before the availability of cancer immunotherapies, patients with advanced or metastatic NSCLC had a poor prognosis and poor outcomes with docetaxel chemotherapy.¹ Cancer immunotherapies, such as atezolizumab, pembrolizumab, and nivolumab, targeting the programmed death-ligand 1 (PD-L1) or programmed cell death-protein 1 pathway have since changed the approach to managing patients with progression after first-line treatment, providing additional options with sustained benefit.²⁻⁷

The efficacy and safety of the anti-PD-L1 cancer immunotherapy atezolizumab in patients with previously treated advanced NSCLC was investigated initially in a phase 2 study, POPLAR, and later with a confirmatory phase 3 study, OAK. Primary findings from the phase 2 POPLAR and phase 3 OAK studies have revealed significant improvements in survival outcomes ($p=0.04$ and $p=0.0003$, respectively) with an acceptable benefit-risk profile when compared with docetaxel.^{2,4} Primary analyses from both the POPLAR (intent-to-treat [ITT] population) and OAK (primary efficacy population,

$n = 850$, ITT850) trials have revealed longer overall survival (OS) with atezolizumab compared with docetaxel, regardless of PD-L1 expression, in patients who progressed after previous platinum therapy, with the greatest benefits observed among those with the highest PD-L1 expression.^{2,4} The updated analysis of the OAK study in the primary efficacy population (ITT850) (data cutoff, January 23, 2017; median follow-up, 28 mo) continued to reveal improved OS with atezolizumab, with a median OS of 13.8 versus 9.6 months (hazard ratio [HR] = 0.75, 95% confidence interval [CI]: 0.64–0.89 mo) in the atezolizumab arm and docetaxel arm, respectively; findings were similar in the secondary efficacy population (data cutoff, January 23, 2017; $n = 1225$, ITT1225; median follow-up, 26 mo), with a median OS of 13.3 versus 9.8 months (HR = 0.80, 95% CI: 0.70–0.92).³

Patients receiving atezolizumab had fewer grade 3 or 4 adverse events (AEs) and lower rates of discontinuation owing to AEs than those receiving docetaxel in both studies.^{2,4} Atezolizumab was associated with some low-grade toxicity and low frequencies of immune-mediated AEs, whereas docetaxel treatment was associated with common chemotherapy toxicities.

In clinical trials conducted with immunotherapy, the benefit to patients is usually sustained over time.^{3,7,8} However, response and progression-free survival (PFS) rates cannot give a complete picture of the full benefit of immunotherapy treatment or the entire patient journey. Thus, an analysis of long-term survival and other outcomes is needed to assess the benefit of these treatments in patients. The pivotal studies of OAK and POPLAR in pretreated patients support evaluation of the long-term benefits of atezolizumab, given the similarities in study design, patients, and objectives. This article reports the final OS from both studies (with a focus on 4-year outcomes) and the safety findings from the ITT population of the phase 2 POPLAR trial and the secondary efficacy population (ITT1225, i.e., ITT) of the phase 3 OAK trial.

Materials and Methods

Study Design and Participants

The design and methods of the POPLAR and OAK studies have been reported previously.^{2,4} POPLAR is a randomized, open-label phase 2 study (NCT01903993) conducted in Europe, Asia, and North America. OAK is a randomized, open-label phase 3 study (NCT02008227) conducted in Europe, Asia, North America, South America, and New Zealand. Both studies enrolled adults (≥ 18 y) with measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 and an Eastern Cooperative Oncology Group performance status of 0 or 1. Patients in both studies previously received

one to two cytotoxic chemotherapy regimens (≥ 1 platinum-based combination therapy) for stage IIIB or IV NSCLC. Furthermore, patients with *EGFR* mutations or an *ALK* fusion oncogene had to have received tyrosine kinase inhibitor treatment.

The patients in both studies were stratified by level of PD-L1 expression, number of previous chemotherapy lines, and squamous versus nonsquamous histological classification. PD-L1 expression groups were as follows: tumor cell (TC) 0 and immune cell (IC) 0 had PD-L1 expression on less than 1% of TCs or tumor-infiltrating ICs, respectively; TC1/2/3 or IC1/2/3 had PD-L1 expression on greater than or equal to 1% of TCs or tumor-infiltrating ICs; and TC3 or IC3 had PD-L1 expression on greater than or equal to 50% of TCs or greater than or equal to 10% of tumor-infiltrating ICs. PD-L1 expression was centrally assessed using the VENTANA SP142 immunohistochemistry assay (Ventana Medical Systems, Tucson, AZ).

Both study populations were randomized 1:1 to atezolizumab (1200 mg fixed dose) or docetaxel (75 mg/m²) every 3 weeks. Patients received atezolizumab or docetaxel until unacceptable toxicity or disease progression as assessed by the investigator. Atezolizumab treatment could be continued beyond disease progression if the investigator determined that the patient was receiving clinical benefit. Crossover from docetaxel to atezolizumab for either study was only allowed after the primary analysis of OAK revealed benefit with atezolizumab.^{3,4} Independent monitoring committees reviewed the safety outcomes. Both studies were conducted in full accordance with the Guidelines for Good Clinical Practice and the Declaration of Helsinki. The study sites obtained local ethics committee approvals; all participating patients provided informed consent.

Outcomes and Statistical Analysis

The primary end points of POPLAR and OAK were OS with atezolizumab versus docetaxel in the ITT population and PD-L1 subgroups. Patients not reported as having died at the time of the analysis were censored at the date they were last known to be alive. OS was compared between groups in the ITT population using a stratified log-rank test (by histology, number of previous chemotherapy lines, and level of PD-L1 expression) at a two-sided significance level. Owing to smaller sample sizes, OS in subgroups was compared using an unstratified log-rank test. Stratified and unstratified Cox regression models were used to estimate HRs and 95% CIs in the ITT population and subgroups. The Kaplan-Meier method was used to estimate median OS; the Brookmeyer-Crowley method was used to generate 95% CIs. OS rates at 3 and 4 years were estimated using Kaplan-Meier methodology for each treatment arm, with

95% CIs calculated using Greenwood's formula. The 95% CIs for the difference in OS rates between the treatment arms were estimated using the normal approximation method, with the SEs computed using Greenwood's method. Sample size and power calculations have been reported previously.²⁻⁴

Safety analyses were based on all patients who received any dose of the study drug during the study treatment period, with patients grouped according to whether any atezolizumab treatment was received. Patients who received any dose of atezolizumab were analyzed as part of the atezolizumab arm even if atezolizumab was given in error. Patients who were randomized to the study but did not receive any study drug were not included in the safety population. Statistical analyses were performed using SAS version 9.2 or higher.

Safety analyses of AEs with onset within or beyond 1 year were based on patients with more than or equal to 1 year of safety follow-up period, which was defined as the duration from the first treatment of atezolizumab until 3 months of follow-up after the last dose, last known alive date, or death, whichever occurs first.

Results

Patient Disposition and Characteristics

The primary findings from each study have been reported previously.²⁻⁴ POPLAR randomized 287 patients to atezolizumab (n = 144) or docetaxel (n = 143), all of whom were included in the ITT population. OAK randomized 1225 patients to atezolizumab (n = 613) or docetaxel (n = 612), all of whom were defined as the secondary analysis population (ITT1225 or ITT).³ For this final analysis, the median follow-up was 48.6 months for POPLAR (data cutoff, August 31, 2018) and 47.7 months for OAK (data cutoff, January 9, 2019). In the POPLAR study, there were 121 deaths (84.0%) in the atezolizumab arm and 120 deaths (83.9%) in the docetaxel arm. In the OAK study, there were 486 deaths (79.3%) in the atezolizumab arm and 496 deaths (81.0%) in the docetaxel arm. Patient demographics for the ITT population of POPLAR and ITT1225 population of OAK have been reported previously.^{2,3}

Overall Survival

Median OS and corresponding HRs after long-term follow-up were similar to results observed at earlier analyses, with a longer OS in patients receiving atezolizumab versus docetaxel in both POPLAR (median OS = 12.6 mo versus 9.7 mo; HR = 0.76, 95% CI: 0.58–1.00; Fig. 1A) and OAK (median OS = 13.3 mo versus 9.8 mo; HR = 0.78, 95% CI: 0.68–0.89; Fig. 1B).⁹ The 3-year OS rates in POPLAR were 18.7% (95% CI: 12.1%–25.3%) and 10.0% (95% CI: 4.7%–15.2%) and those in OAK

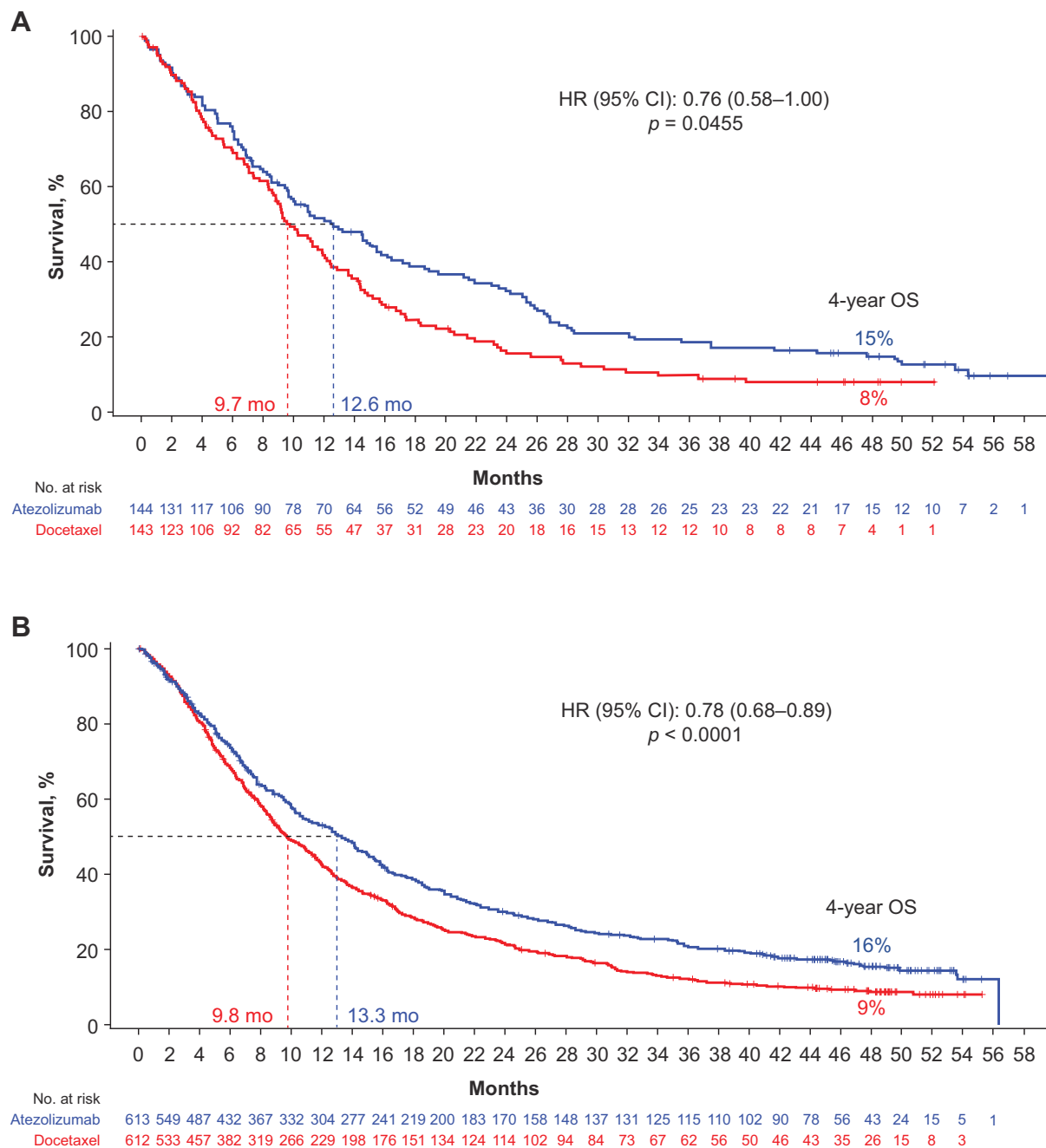


Figure 1. OS in the POPLAR and OAK ITT populations. (A) POPLAR ITT population (August 31, 2018; median follow-up, 48.6 mo); (B) OAK ITT population (ITT1225, January 9, 2019; median follow-up, 47.7 mo). CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; OS, overall survival.

were 21.0% (95% CI: 17.7%–24.4%) and 12.4% (95% CI: 9.6%–15.2%) for patients receiving atezolizumab or docetaxel, respectively (Table 1 and Fig. 1). The 4-year OS rates (including number of patients at risk) in POPLAR were 14.8% (95% CI: 8.7%–20.8%) and 8.1% (95% CI: 3.2%–13.0%) and those in OAK were 15.5% (95% CI: 12.4%–18.7%) and 8.7% (95% CI: 6.2%–11.3%) for patients receiving atezolizumab or docetaxel, respectively (Fig. 1).

Median OS was longest in the highest PD-L1 expression groups (expression on $\geq 50\%$ TCs or on 10% of ICs [TC3 or IC3]; Fig. 2A and B). Median OS was longer in patients with expression on less than 1% of TCs and ICs (TC0 and IC0 subgroups) compared with those receiving docetaxel in OAK, and the median OS in patients in the TC0 and IC0 subgroups was the same as in those receiving atezolizumab and docetaxel in POPLAR (Fig. 2C and D).

Table 1. The 3- and 4-Year OS Rates Overall and by PD-L1 Expression and Histology

Patient Population	POPLAR						OAK					
	Atezolizumab			Docetaxel			Atezolizumab			Docetaxel		
	n	3-Year OS, n (%) [95% CI]	4-Year OS, n (%) [95% CI]	n	3-Year OS, n (%) [95% CI]	4-Year OS, n (%) [95% CI]	n	3-Year OS, n (%) [95% CI]	4-Year OS, n (%) [95% CI]	n	3-Year OS, n (%) [95% CI]	4-Year OS, n (%) [95% CI]
ITT	144	25 (19) [12.1-25.3]	15 (15) [8.7-20.8]	143	12 (10) [4.7-15.2]	4 (8) [3.2-13.0]	613	115 (21) [17.7-24.4]	43 (16) [12.4-18.7]	612	62 (12) [9.6-15.2]	26 (9) [6.2-11.3]
TC3 or IC3	24	9 (38) [18.1-56.9]	6 (33) [14.5-52.2]	23	3 (15) [0.0-30.1]	1 (15) [0.0-30.1]	89	23 (29) [19.4-39.0]	10 (28) [18.1-37.5]	85	9 (12) [4.5-18.9]	4 (10) [2.8-16.7]
TC2/3 or IC2/3	50	10 (21) [9.6-32.9]	7 (19) [7.9-30.3]	55	5 (10) [1.7-18.0]	1 (8) [0.5-15.3]	168	42 (27) [20.4-34.3]	16 (20) [13.1-26.8]	182	23 (16) [10.0-21.5]	10 (12) [6.6-17.2]
TC1/2/3 or IC1/2/3	93	16 (18) [10.0-26.0]	10 (15) [7.3-22.0]	102	10 (11) [4.61-17.33]	2 (9) [2.7-14.3]	347	72 (23) [18.4-27.6]	27 (17) [12.4-21.1]	337	38 (15) [10.4-18.5]	20 (12) [7.9-15.7]
TC0 and IC0	51	9 (21) [8.8-32.3]	5 (15) [4.4-26.0]	41	2 (7) [0-15.8]	2 (7) [0-15.8]	260	42 (18) [13.4-23.3]	16 (14) [9.3-18.5]	271	24 (10) [6.3-13.9]	6 (5) [2.2-8.1]
Nonsquamous	95	21 (23) [14.6-32.0]	13 (19) [10.5-26.7]	95	10 (12) [5.3-19.6]	4 (10) [3.5-16.4]	452	99 (24) [19.9-28.1]	38 (18) [14.0-21.7]	452	52 (14) [10.8-17.8]	22 (10) [7.0-13.3]
Squamous	49	4 (9) [0.7-18.1]	2 (7) [0-14.7]	48	2 (5) [0-12.0]	NE ^a	161	16 (12) [6.9-17.7]	5 (9) [3.6-13.5]	160	10 (7) [2.9-11.5]	4 (5) [1.2-8.4]

^a4-Year OS was NE because too few patients were at risk.

CI, confidence interval; IC, immune cell; ITT, intent-to-treat; NE, not estimable; OS, overall survival; PD-L1, programmed death-ligand 1; TC, tumor cell.

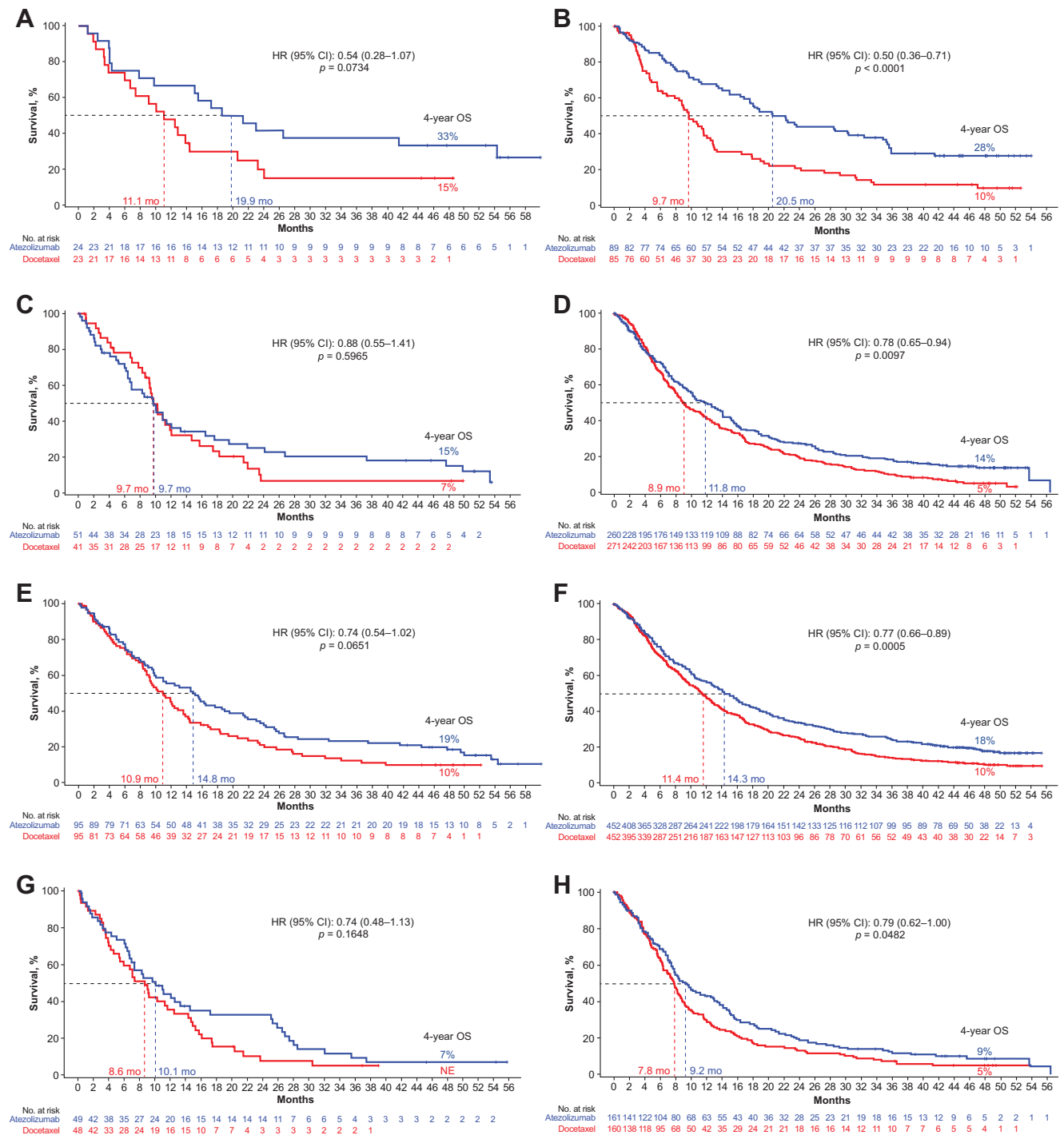


Figure 2. OS in the highest PD-L1 expression group (on $\geq 50\%$ TCs or on 10% of ICs [TC3 or IC3]). (A) POPLAR TC3 or IC3; (B) OAK TC3 or IC3. OS in the PD-L1-negative groups (expression on $< 1\%$ TC and IC [TC0 or IC0]). (C) POPLAR TC0 and IC0; (D) OAK TC0 and IC0. OS among nonsquamous and squamous histological classification. (E) POPLAR nonsquamous histological classification; (F) OAK nonsquamous histological classification; (G) POPLAR squamous histological classification; (H) OAK squamous histological classification. The p value is for descriptive purposes. CI, confidence interval; HR, hazard ratio; IC, immune cell; NE, not estimable; OS, overall survival; PD-L1, programmed death-ligand 1; TC, tumor cell.

Patients receiving atezolizumab had higher 3- and 4-year OS rates compared with those receiving docetaxel across PD-L1 expression subgroups (Table 1 and Supplementary Fig. 1). The 4-year OS rates in POPLAR

were 33.3% (95% CI: 14.5%–52.2%) and 14.9% (95% CI: 0%–30.1%) and those in OAK were 27.8% (95% CI: 18.1%–37.5%) and 9.8% (95% CI: 2.8%–16.7%) for the TC3 or IC3 patients receiving atezolizumab or docetaxel,

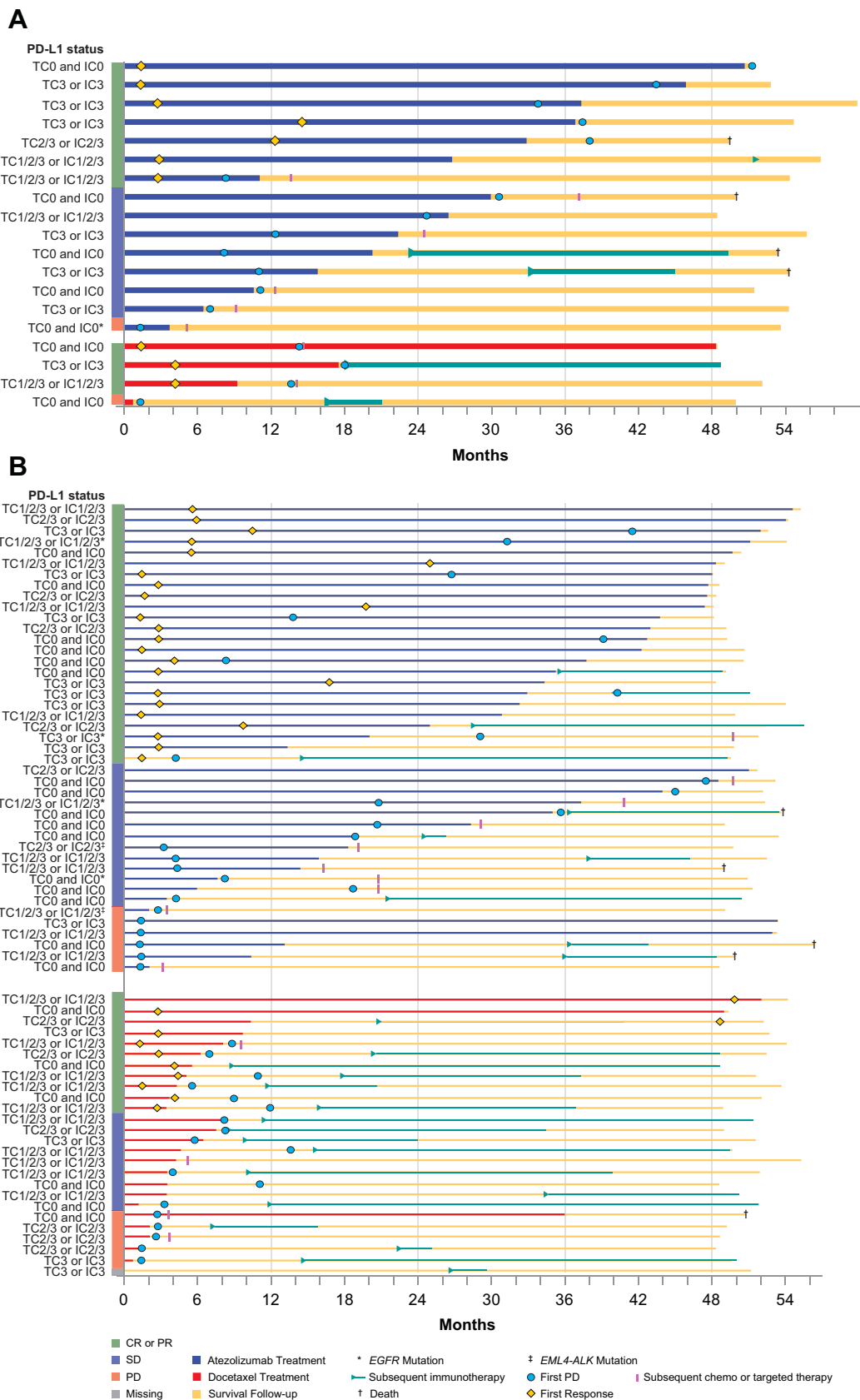


Figure 3. Treatment duration, response, and treatment beyond progression among patients who survived more than or equal to 4 years. (A) POPLAR; (B) OAK. Chemo, chemotherapy; CR, complete response; IC, immune cell; PD, progressive disease; PD-L1, programmed death-ligand 1; PR, partial response; TC, tumor cell.

Table 2. Best Overall Response Among Patients Who Survived More Than or Equal to 4 Years

Response	POPLAR		OAK	
	Atezolizumab (n = 15)	Docetaxel (n = 4)	Atezolizumab (n = 43)	Docetaxel (n = 26)
n (%)				
Responders	7 (47)	3 (75)	24 (56)	11 (42)
Complete response	0	0	4 (9)	1 (4)
Partial response	7 (47)	3 (75)	20 (47)	10 (39)
Stable disease	7 (47)	0	14 (33)	9 (35)
Progressive disease	1 (7)	1 (25)	5 (12)	5 (19)
Missing or unassessable	0	0	0	1 (4)

respectively (Table 1 and Fig. 2A and B). The 4-year OS rates in POPLAR were 15.2% (95% CI: 4.4%–26.0%) and 6.8% (95% CI: 0%–15.8%) and those in OAK were 13.9% (95% CI: 9.30%–18.45%) and 5.1% (95% CI: 2.2%–8.1%) for patients in the TC0 and IC0 subgroups receiving atezolizumab or docetaxel, respectively (Table 1 and Fig. 2C and D).

A longer median OS and higher 3- and 4-year OS rates were observed in patients with both nonsquamous and squamous histological classification with atezolizumab (Table 1 and Fig. 2E–H). The 4-year OS rates in POPLAR were 18.6% (95% CI: 10.5%–26.7%) and 10.0% (95% CI: 3.5%–16.4%) and those in OAK were 17.9% (95% CI: 14.0%–21.7%) and 10.1% (95% CI: 7.0%–13.3%) for nonsquamous patients receiving atezolizumab or docetaxel, respectively (Table 1 and Fig. 2E and F). In squamous patients, the 4-year OS rate in POPLAR was 7.0% (95% CI: 0.0%–14.7%) in patients receiving atezolizumab and not estimable (NE) in the docetaxel arm owing to its small sample size whereas the 3-year OS rates with atezolizumab and docetaxel were 9.4% (95% CI: 0.70%–18.06%) and 5.2% (95% CI: 0.0%–12.0%), respectively. In OAK, the 4-year OS rates were 8.5% (95% CI: 3.6%–13.5%) and 4.8% (95% CI: 1.2%–8.4%), respectively.

Crossover, Treatment Beyond Progression, and Subsequent Follow-Up Therapy

Crossover from docetaxel to atezolizumab was permitted for both studies after the primary analysis of OAK; two docetaxel patients (1%) in POPLAR and 12 (2%) in OAK crossed over to atezolizumab treatment. Nearly half of the atezolizumab patients in each study continued atezolizumab after progression (47% in POPLAR; 41% in OAK). Approximately half of all patients receiving atezolizumab or docetaxel in each study received subsequent nonprotocol therapy (Supplementary Table 1). More patients in the docetaxel than in the atezolizumab arms of each study received follow-up immunotherapy (15% in POPLAR and 26% in OAK compared with 4% in POPLAR and 8% in OAK, respectively; Supplementary Table 1).

Patients Who Survived More Than or Equal to 4 Years

A total of 19 patients in the POPLAR study and 69 patients in the OAK study were alive after 4 years (48 mo), of whom 15 and 4 in POPLAR and 43 and 26 in OAK were in the atezolizumab and docetaxel arms, respectively (Supplementary Table 2 and Fig. 3A and B). An increased number of patients in the atezolizumab arm survived 4 years, with an Eastern Cooperative Oncology Group performance status of 0 (POPLAR, 73%; OAK, 56%) and nonsquamous histological classification (POPLAR, 87%; OAK, 88%) in comparison with the ITT population (Supplementary Table 2). In addition, there was an increase of patients in the TC3 or IC3 PD-L1 subgroup (POPLAR, 40%; OAK, 23%); patients in the TC0 and IC0 PD-L1 subgroups were also represented (POPLAR, 33%; OAK, 37%). Of atezolizumab 4-year survivors with known *KRAS* status, two of five in POPLAR and three of 17 in OAK had *KRAS* mutations; one of eight in POPLAR and four of 38 in OAK had an *EGFR* mutation; and zero of nine in POPLAR and two of 28 in OAK had *EML4-ALK* mutations.

Approximately half of the 4-year survivors were responders. In POPLAR, seven of 15 patients in the atezolizumab arm and three of four in the docetaxel arm were responders (Table 2, and Fig. 3A). In OAK, 24 of 43 patients in the atezolizumab arm and 11 of 26 in the docetaxel arm were responders (Supplementary Table 2, and Fig. 3B). The median duration of response among the responders in the atezolizumab arms was longer, at 31.1 months (95% CI: 22.9–50.0 mo) in POPLAR and NE (95% CI: 36.3 mo–NE) in OAK, compared with that among those in the docetaxel arms, at 12.9 months (95% CI: 9.5–13.8 mo) in POPLAR and 7.6 months (95% CI: 4.9 mo–NE) in OAK.

Among the 4-year survivors in POPLAR, the PFS rate at 4 years was 13.3% (95% CI: 0%–30.5%) in the patients in the atezolizumab arm and NE in those in the docetaxel arm. Among the 4-year survivors in OAK, the PFS rate at 4 years was 34.6% (95% CI: 19.6%–49.6%) in the atezolizumab patients and 19.2% (95% CI: 2.4%–36.0%) in the docetaxel patients.

Approximately half of the atezolizumab patients who survived more than or equal to 4 years were treated

Table 3. Summary of AEs in the POPLAR and OAK Safety Populations

Patients ^a	POPLAR		OAK	
	Atezolizumab (n = 142)	Docetaxel (n = 135)	Atezolizumab (n = 609)	Docetaxel (n = 578)
Median treatment duration (range), mo	3.7 (0-51)	2.1 (0-18)	3.4 (0-55)	2.1 (0-52)
All-grade AEs, any cause	136 (96)	130 (96)	575 (94)	559 (97)
Treatment-related AEs, any cause	95 (67)	119 (88)	395 (65)	499 (86)
Grade 3 or 4, any causes	67 (47)	75 (56)	243 (40)	310 (54)
Treatment-related grade 3 or 4	21 (15)	54 (40)	93 (15)	245 (42)
Grade 5, any cause	7 (5)	5 (4)	11 (2)	14 (2)
Treatment-related grade 5	1 (1)	3 (2)	0	1 (0.2)
Serious AEs	53 (37)	46 (34)	200 (33)	182 (32)
AE leading to treatment withdrawal	13 (9)	30 (22)	54 (9)	107 (19)
AE leading to drug interruption/dose modification	39 (28)	43 (32)	164 (27)	214 (37)

^aAll values are n (%) unless noted.
AE, adverse event.

with atezolizumab after RECIST version 1.1 progression (POPLAR, 53%; OAK, 42%; [Supplementary Table 3](#)). More 4-year survivors in the docetaxel arms received subsequent therapy (POPLAR, 100% versus 67%, respectively; OAK, 85% versus 47%; [Supplementary Table 3](#) and [Fig. 3A](#) and [B](#)). Of the 4-year survivors in the docetaxel arms who received subsequent therapy, most received immunotherapy in both POPLAR (50%) and OAK (65%; [Supplementary Table 3](#)). All immunotherapy treatments received by docetaxel patients in OAK and POPLAR were anti-programmed cell death-protein 1 or PD-L1 antibodies, with the exception of a single immunotherapy treatment received by a patient in POPLAR ([Supplementary Table 3](#)).

Safety

The median treatment duration in the overall treated population of the atezolizumab arm was 3.7 months (range = 0–51 mo) and 3.4 months (range = 0–55 mo) in the POPLAR and OAK studies, respectively ([Table 3](#)). In both studies, fewer patients receiving atezolizumab experienced treatment-related grade 3 or 4 AEs and fewer discontinued treatment owing to AEs than did those receiving docetaxel ([Table 3](#)). AEs observed through 4 years in both treatment arms were consistent with the known safety profiles of atezolizumab and docetaxel.

The median treatment duration in atezolizumab patients who survived more than or equal to 4 years was 26.5 months (range = 3.7–50.6 mo) and 35.2 months (range = 0.0–54.6 mo) in the POPLAR and OAK studies, respectively ([Supplementary Table 4](#) and [Fig. 3](#)). Treatment-related grade 3 or 4 AEs occurred in 27% and 16% of atezolizumab 4-year survivors, AEs that led to drug interruptions occurred in 40% and 51% of the

patients, and AEs that led to withdrawal occurred in 13% and 16% of the patients, in POPLAR and OAK, respectively. No treatment-related grade 5 AEs led to death. Of new grade 3 or greater AEs with onset of more than or equal to 1 year in atezolizumab 4-year survivors, there were only grade 3 events (POPLAR, eight events; OAK, 21 events) and no grade 4 or 5 events ([Supplementary Table 5](#)). Onset of new grade 3 or greater immune-related AEs after 2 years of treatment was rare in atezolizumab 4-year survivors, with only one grade 3 immune-related AE reported in POPLAR (grade 3 myocarditis) and none reported in OAK.

Among the patients in the atezolizumab arms with at least 1 year of safety follow-up, most AEs occurred within the first year (POPLAR: 97.7%, OAK: 98.1%; [Supplementary Table 6](#)). Fewer AEs with onset of more than or equal to 1 year were observed in both studies in the patients with 1 year of safety evaluation (POPLAR: 53.5%, OAK: 67.9%), including treatment-related AEs and grade 3 or greater events ([Supplementary Table 6](#)).

Discussion

These final analyses of the POPLAR and OAK studies revealed consistent and sustained OS benefit with atezolizumab versus docetaxel in patients with previously treated NSCLC across PD-L1 expression and histology subgroups. Although the greatest benefit was observed in the highest PD-L1 expression subgroup (expression on $\geq 50\%$ TC or on 10% of IC [TC3 or IC3]), patients with tumors negative for PD-L1 expression (expression on $< 1\%$ TC and IC [TC0 and IC0]) also had a survival benefit with atezolizumab through 3 and 4 years, with more than double the 3- and 4-year OS rates compared with docetaxel. Although the overall OS benefit with

atezolizumab compared with docetaxel in the PD-L1-negative population was more clearly observed in OAK (HR = 0.78, 95% CI: 0.65–0.94) relative to POPLAR (HR = 0.88, 95% CI: 0.55–1.41), both studies revealed higher 3- and 4-year OS rates in the atezolizumab arm, and the 95% CI of the HRs overlapped. These differences between studies could be because of the smaller patient populations in POPLAR and therefore a reduced number of patients at risk in the TC0 and IC0 population. Furthermore, an OS benefit was observed in patients with nonsquamous or squamous histological classification. Although the 4-year OS rate was NE in the docetaxel arm in the patients with squamous histological classification, the 3-year OS rates in the patients with squamous histological classification for OAK and POPLAR were consistent between arms, and the 4-year OS rate in the atezolizumab arm was also consistent (8.5% and 7.0%, respectively).

Patients who survived more than or equal to 4 years had nonsquamous histological classification and better performance status when compared with the overall study populations. Only a low proportion of patients had mutations in *EGFR* or *KRAS* or *EML4-ALK* translocations. Atezolizumab 4-year survivors included patients from all PD-L1 subgroups, and although there was an increased number of patients with PD-L1 tumors with the highest PD-L1 expression (TC3 or IC3), patients with PD-L1-negative tumors (TC0 and IC0) were also included. These findings are consistent with those of a previous evaluation of 2-year survivors in the OAK study.¹⁰

Approximately half of the 4-year survivors were RECIST version 1.1 responders in each arm, and the 4-year survivors receiving atezolizumab who were responders had a longer duration of response than those who received docetaxel. Of the 4-year survivors in the docetaxel arms who were responders, one of three (POPLAR) and six of 11 (OAK) received subsequent immunotherapy.

In POPLAR and OAK, 53% and 45% of the 4-year survivors in the atezolizumab arms, respectively, were nonresponders, which included long-term survivors with stable or progressive disease as best overall response. In addition, approximately half of the atezolizumab patients who survived more than or equal to 4 years in either study received treatment beyond progression (including five in OAK and one in POPLAR who had progressive disease as best response). These observations, indicating radiographic response is not a requirement for long-term survival benefit, are consistent with previous reports describing discordance between radiographic end points and survival that may result in postprogression prolongation of survival.^{10,11}

More patients in the docetaxel arms received subsequent nonprotocol immunotherapy in each study (POPLAR, 15%; OAK, 26%) than in the atezolizumab arms,

and a minority of patients in the docetaxel arm crossed over to receive atezolizumab (POPLAR, 1%; OAK, 2%). Moreover, of the docetaxel patients who survived more than or equal to 4 years in either study, most (POPLAR, 50%; OAK, 65%) received subsequent immunotherapy. Despite subsequent use of immunotherapy in the docetaxel arm, a sustained benefit with atezolizumab versus docetaxel was observed. Subsequent immunotherapy use was larger than that observed in other immunotherapy clinical trials for patients with previously treated NSCLC. In the CheckMate (CHECKpoint pathway and nivolumab clinical Trial Evaluation) 057 and 017 studies, at 3 years, no docetaxel-treated patients remained on treatment and 4% of nivolumab and 10% of docetaxel patients received subsequent immunotherapy either during crossover or as subsequent therapy after the study.¹²

Long-term treatment with atezolizumab revealed a manageable safety profile consistent with previous reports from these trials.²⁻⁴ Within all safety-assessable patients, atezolizumab was well tolerated, with lower proportions of treatment-related grade 3 or 4 AEs than in the docetaxel arms, and less than half of treatment discontinuations were because of AEs in the atezolizumab arms compared with the docetaxel arms. AEs leading to dose interruptions or modifications and serious AEs appeared comparable between the atezolizumab and docetaxel arms. Among the 4-year survivors, the prevalence of treatment-related grade 3 or 4 AEs in the atezolizumab arm was similar to that of the ITT population. The prevalence of AEs that led to drug interruption in the atezolizumab arm was increased, which may have been because of the longer duration of treatment. Onset of new grade greater than or equal to 3 immune-related AEs after 2 years of treatment was rare in atezolizumab 4-year survivors, with only one grade 3 immune-related AE reported in POPLAR and none in OAK.

In conclusion, long-term follow-up from these two randomized phase 2 and 3 clinical trials suggests a consistently greater survival benefit with atezolizumab versus docetaxel in patients with previously treated NSCLC regardless of the level of PD-L1 expression or histology. Atezolizumab has been found to have a consistent and manageable safety profile with fewer treatment-related AEs and fewer treatment discontinuations owing to AEs than docetaxel. Most patients continued atezolizumab or received immunotherapy beyond progression, indicating the potential for long-term clinical benefit from these therapies.

Data Sharing Statement

Qualified researchers may request access to individual patient-level data through the clinical study data request platform (www.clinicalstudydatarequest.com).

Further details on Roche's criteria for eligible studies are available here (<https://clinicalstudydatarequest.com/Study-Sponsors/Study-Sponsors-Roche.aspx>). For further details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see here (https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm).

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Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org and at <https://doi.org/10.1016/j.jtho.2020.09.022>.

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