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ORIGINAL REPORT

# Phase II Trial of Atezolizumab As First-Line or Subsequent Therapy for Patients With Programmed Death-Ligand 1–Selected Advanced Non–Small-Cell Lung Cancer (BIRCH)

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## ABSTRACT

### Purpose

BIRCH was designed to examine the efficacy of atezolizumab, a humanized anti–programmed death-ligand 1 (PD-L1) monoclonal antibody, in advanced non–small-cell lung cancer (NSCLC) across lines of therapy. Patients were selected on the basis of PD-L1 expression on tumor cells (TC) or tumor-infiltrating immune cells (IC).

### Patients and Methods

Eligible patients had advanced-stage NSCLC, no CNS metastases, and zero to two or more lines of prior chemotherapy. Patients whose tumors expressed PD-L1 using the SP142 immunohistochemistry assay on ≥ 5% of TC or IC (TC2/3 or IC2/3 [TC or IC ≥ 5% PD-L1–expressing cells, respectively]) were enrolled. Atezolizumab 1,200 mg was administered intravenously every 3 weeks. Efficacy-evaluable patients (N = 659) comprised three cohorts: first line (cohort 1; n = 139); second line (cohort 2; n = 268); and third line or higher (cohort 3; n = 252). The primary end point was independent review facility–assessed objective response rate (ORR; Response Evaluation Criteria in Solid Tumors [RECIST] version 1.1). Secondary end points included median duration of response, progression-free survival, and overall survival (OS).

### Results

BIRCH met its primary objective of demonstrating a significant ORR versus historical controls. With a minimum of 12 months of follow-up, the independent review facility–assessed ORR was 18% to 22% for the three cohorts, and 26% to 31% for the TC3 or IC3 subgroup; most responses are ongoing. Responses occurred regardless of *EGFR* or *KRAS* mutation status. The median OS from an updated survival analysis (minimum of 20 month follow up) for cohort 1 was 23.5 months (26.9 months for TC3 or IC3 patients); the median OS in cohorts 2 and 3 was 15.5 and 13.2 months, respectively. The safety profile was similar across cohorts and consistent with previous atezolizumab monotherapy trials.

### Conclusion

BIRCH demonstrated responses with atezolizumab monotherapy in patients with PD-L1–selected advanced NSCLC, with good tolerability. PD-L1 status may serve as a predictive biomarker for identifying patients most likely to benefit from atezolizumab.

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## INTRODUCTION

Patients with advanced non–small-cell lung cancer (NSCLC) have only modest improvements in survival with systemic therapies. First-line (1L) treatment with platinum-based chemotherapy generally results in median overall survival (mOS) of 8 to 10 months.[1] Combining antiangiogenic therapy with chemotherapy can improve response rates and survival in patients with nonsquamous histology.[2] Second-line (2L) chemotherapy results in small increases in survival (median survival approximately 9 months).[3,4] Patients with tumors that harbor epidermal growth factor receptor (*EGFR*) and anaplastic lymphoma kinase (*ALK*) driver alterations have high responses and improvements in survival when treated upfront with tyrosine kinase inhibitors; however, more effective treatments are needed for most patients with NSCLC.

ASSOCIATED CONTENT

See accompanying Editorial on page 2735

Appendix

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Immune checkpoint inhibitors have demonstrated efficacy and improved survival in various cancers, including advanced NSCLC,[5-8] and agents targeting programmed death-ligand 1 (PD-L1) and/or programmed death 1 (PD-1)—atezolizumab, nivolumab, and pembrolizumab—have been approved for use in NSCLC.[5,7,9-12] PD-L1 is an immune checkpoint protein expressed on tumor cells (TC) and tumor-infiltrating immune cells (IC).[13] Binding of PD-L1 to its receptors, PD-1 and B7.1 (CD80), on activated T cells can dampen the T-cell immune response and promote tumor immune escape.[14-16] Targeting PD-L1 and PD-1 can relieve this inhibition and increase tumor-specific T-cell immunity.

Atezolizumab is an engineered humanized anti–PD-L1 immunoglobulin G1 monoclonal antibody that binds PD-L1 and inhibits PD-L1–mediated signaling. It has demonstrated clinical efficacy in various solid tumors and is approved in ≥ 2L urothelial bladder cancer, 1L cisplatin-ineligible urothelial bladder cancer, and NSCLC.[12,17-21] Atezolizumab is the first anti–PD-L1 antibody to demonstrate efficacy in both chemotherapy-naïve and previously treated advanced NSCLC.[21-24] Studies suggested that PD-L1 expression on TC and IC was an independent predictor of response to atezolizumab, and that its efficacy increased with PD-L1 expression.[21,23] The phase II trial presented herein, BIRCH, was designed to assess the efficacy and safety of single-agent atezolizumab in patients with PD-L1–selected stage IIIB/IV NSCLC, across multiple lines of therapy.

## PATIENTS AND METHODS

### Study Design and Patients

BIRCH is a phase II, global, multicenter, single-arm trial of atezolizumab in patients with PD-L1–selected locally advanced or metastatic NSCLC. All patients were tested at enrollment for PD-L1 positivity on TC and IC using the SP142 immunohistochemistry assay (Ventana Medical Systems, Tucson, AZ) on archival or freshly collected tumor specimens, as determined in a central laboratory. This assay is sensitive and specific for PD-L1 expression on TC and IC.[17] PD-L1 TC expression was scored as a percentage of PD-L1–positive TC (TC3 ≥ 50% or TC2 ≥ 5% but < 50%). PD-L1 IC expression was scored as a percentage of tumor area stained positive (IC3 ≥ 10% or IC2 ≥ 5% but < 10%; Appendix Table A1, online only).

BIRCH comprised three patient cohorts (Fig 1): cohort 1 (no prior chemotherapy for advanced NSCLC [1L]); cohort 2 (progression during or following no more than one prior platinum-based regimen for advanced NSCLC [2L]); and cohort 3 (progression during or following at least two prior chemotherapy regimens for advanced disease [≥ 3L {third line}]).

The study protocol and amendments were approved by institutional review boards or ethics committees. BIRCH was conducted in accordance with the Declaration of Helsinki and International Conference on Harmonisation Guidelines for Good Clinical Practice. All patients provided written informed consent. BIRCH was sponsored by Genentech Inc. (a member of the Roche Group) which provided the study drug, atezolizumab (ClinicalTrials.gov identifier: NCT02031458).

### Study Assessments

The primary efficacy outcome measure was independent review facility (IRF)–assessed objective response rate (ORR) per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Secondary efficacy outcome measures included IRF-assessed progression-free survival (PFS) and duration of response (DOR); investigator-assessed ORR, PFS, and DOR; OS; and safety. IRF-assessed ORR, DOR, PFS, and OS as well as safety analyses were on the basis of a data cutoff of December 1, 2015. An updated OS analysis was also conducted on the basis of an August 1, 2016, data cutoff (minimum 20-month follow-up). Alterations in *EGFR*, *KRAS*, and *ALK* were determined by the FoundationOne panel (Foundation Medicine, Cambridge, MA)[25] and/or local tests. Tumors were considered *EGFR* or *KRAS* mutant if the mutation was detected by either testing method; those without either test result were considered missing.

### Patients

Key eligibility criteria included histologically or cytologically confirmed stage IIIB/IV or recurrent NSCLC, age ≥ 18 years, tumor PD-L1 expression (TC2/3 or IC2/3 [TC or IC ≥ 5% PD-L1–expressing cells,

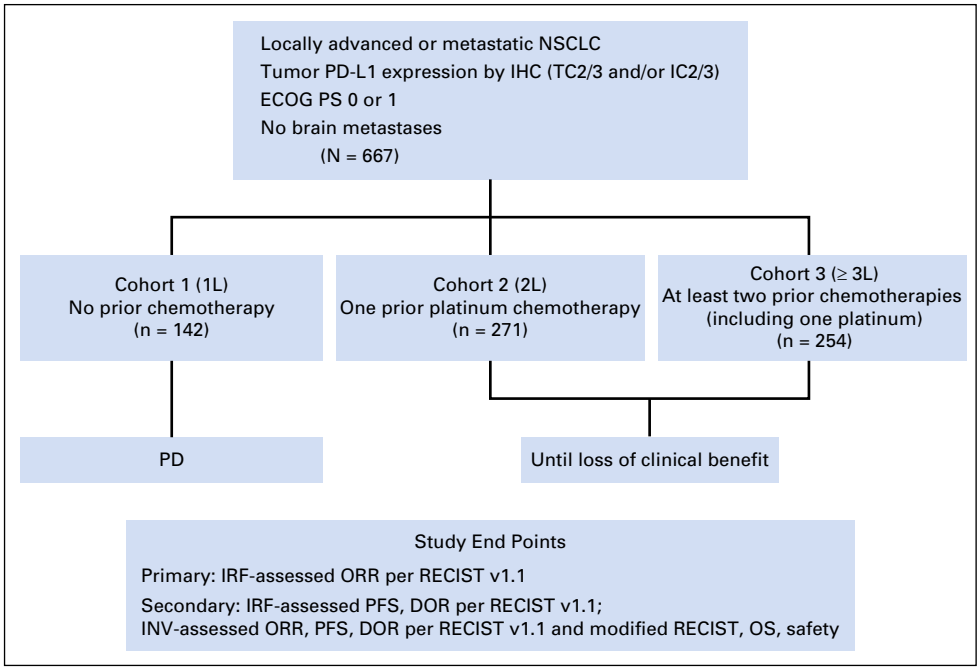


**Fig 1.** Atezolizumab was administered at a fixed dose of 1,200 mg intravenously on day 1 every 3 weeks in all cohorts. TC3 or IC3 = TC ≥ 50% or IC ≥ 10% PD-L1–expressing cells, respectively; TC2/3 or IC2/3 = TC or IC ≥ 5% PD-L1–expressing cells, respectively. 1L, first line; 2L, second line; 3L, third line; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; IC, tumor-infiltrating immune cells; IHC, immunohistochemistry; INV, investigator; IRF, independent review facility; NSCLC, non–small-cell lung cancer; ORR, objective response rate; OS, overall survival; PD, progressive disease; PD-L1, programmed death-ligand 1; PFS, progression-free survival; PS, performance status; RECIST, Response Evaluation Criteria in Solid Tumors; TC, tumor cells.

  

respectively]), Eastern Cooperative Oncology Group performance status 0 or 1, measurable disease per RECIST version 1.1, and adequate hematologic and end-organ function. Key exclusion criteria were CNS metastases, history of pneumonitis, autoimmune diseases, or chronic viral diseases, and prior treatment with CD137 agonists or immune checkpoint inhibitors (prior anti–cytotoxic T-cell lymphocyte antigen-4 treatment was allowed if it was ≥ 6 weeks from the last dose). Patients with a sensitizing *EGFR* or *ALK* mutation must have had disease progression or intolerance to an EGFR or ALK tyrosine kinase inhibitor approved for NSCLC, respectively.

### Treatments

For all cohorts, atezolizumab 1,200 mg was administered by intravenous infusion every 3 weeks. Patients in cohorts 2 and 3 could continue treatment as long as they received clinical benefit according to investigator assessment (absence of both unacceptable toxicity and symptomatic deterioration attributed to disease progression). Patients in cohort 1 were required to discontinue atezolizumab at disease progression per RECIST version 1.1. Dose reductions were not allowed.

### Study Assessments

Radiologic tumor assessments were performed every 6 weeks for 12 months, then every 9 weeks thereafter regardless of treatment delays until disease progression, loss of clinical benefit (patients in cohorts 2 and 3 only), withdrawal of consent, death, or study termination. This included patients who discontinued for reasons other than disease progression. All patients evaluable for safety and efficacy (per RECIST version 1.1) had measurable disease at baseline and received at least one dose of atezolizumab.

Adverse events (AEs) and laboratory data were summarized and graded per National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.

### Exploratory Outcome Measures and Biomarkers

Disease control rate was defined as the rate of complete response or partial response as best confirmed response, or stable disease maintained for ≥ 24 weeks. PD-L1 status and exploratory biomarkers such as driver mutation status were measured in archival and/or freshly obtained tumor tissues.

### Statistics

Estimated ORRs in all treated patients (all cohorts) and 95% CIs were calculated using the Clopper-Pearson method. No formal statistical comparison of response rates between cohorts was planned. Time-to-event outcomes (ie, DOR, PFS, and OS) were estimated by the Kaplan-Meier method. The 95% CIs for median DOR, PFS, and OS were calculated using the nonparametric Brookmeyer and Crowley method.

The primary efficacy analysis (May 28, 2015) compared IRF-assessed ORR in prespecified subgroups with prespecified historical control ORRs in a stepwise fashion using a hierarchical fixed-sequence procedure (Appendix Table A2, online only; $\alpha = 0.05$ for each test). Prespecified chemotherapy historical (2013) control ORRs for previously treated metastatic NSCLC, used for comparison purposes only, were 5% for ≥ 3L, 7% for ≥ 2L, 15% to 20% for 1L, and 15% across all lines.[2,26,27]

## RESULTS

### Patients and Treatment

Between January 16, 2014, and December 4, 2014, 3,914 patients were screened for PD-L1 status (36% were PD-L1 TC2/3 or IC2/3), and 667 patients were enrolled from 106 sites in 19 countries. Patient demographic data and baseline characteristics were similar across cohorts (Table 1). The median age was 64 years (range, 28 to 88 years). More than 70% of patients had nonsquamous tumors. Overall, 46% of patients had TC3 or IC3 tumor PD-L1 status, distributed similarly across cohorts.

A total of 659 patients (99%) received atezolizumab. The median duration of treatment was 4.2 months (range, 0 to 21 months) and the median number of doses was seven (range, one to 30 doses). Atezolizumab was discontinued in 520 patients (79%), due to progressive disease (65%), AE (7%), patient decision (3%), protocol deviation (2%), or physician decision (1%).

### Efficacy: ORR, DOR, and PFS

Results from the efficacy analysis performed with a follow-up of ≥ 12 months (data cutoff, December 1, 2015) are described in the following paragraphs. This analysis generally supports the results from the primary analysis (Appendix Table A2), which was performed with a minimum 6-month follow-up (data cutoff, May 28, 2015).

The IRF-assessed ORR was 22%, 19%, and 18% for cohorts 1, 2, and 3, respectively (Table 2, Appendix Fig A1 [online only, waterfall plots], and Appendix Table A3 [TC2 or IC2 subgroup]), with complete responses in 1%, 2%, and 2% for cohorts 1, 2, and 3, respectively. For those in the TC3 or IC3 subgroup, the IRF-assessed ORR was 31%, 26%, and 27% for cohorts 1, 2, and 3, respectively. The IRF-assessed ORR was generally higher in smokers and in patients with nonsquamous NSCLC (Appendix Fig A2, online only). Among responders, the median DOR was 9.8 months, not estimable (NE), and 11.8 months for cohorts 1, 2, and 3, respectively. For the TC3 or IC3 subgroup, median DOR values were 10.0 months, NE, and 7.2 months for cohorts 1, 2, and 3, respectively. Investigator-assessed efficacy results were generally similar to IRF data (data not shown).

The median PFS was higher for cohort 1 (5.4 months; 95% CI, 3.0 to 6.9 months) than cohort 2 (2.8 months; 95% CI, 1.5 to 3.9 months) and cohort 3 (2.8 months; 95% CI, 2.7 to 3.0 months; Table 2 and Appendix Fig A3, online only [by TC/IC subgroups]). Per PFS landmark analysis, 12-month PFS rates were 20%, 17%, and 14% for cohorts 1, 2 and 3, respectively.

### Efficacy: OS

The median duration of survival follow-up for all treated patients was 14.6 months (95% CI, 14.3 to 14.7 months), on the basis of a data cutoff of December 1, 2015. The mOS was highest in cohort 1 at 20.1 months (95% CI, 20.1 months to NE) compared with 15.5 months (95% CI, 12.3 months to NE) and 13.2 months (95% CI, 10.3 to 17.5 months) for cohorts 2 and 3, respectively (Table 2). The median OS for patients with nonsquamous tumors was 20.1, 16.3, and 14.7 months in cohorts 1, 2, and 3, respectively, versus NE, 12.3, and 9.2 months for those with squamous tumors.

In an updated OS analysis (data cutoff, August 1, 2016), with a median duration of survival follow-up of 22.5 months, mOS continued to improve. The mOS for cohort 1 was 23.5 months (95% CI, 18.1 months to NE), and for cohorts 2 and 3 the mOS was 15.5 months (95% CI, 12.3 to 19.3 months) and 13.2 months (95% CI, 10.3 to 17.5 months), respectively (Table 2 and Fig 2). The mOS was highest in cohort 1 for the TC3 or IC3 subgroup at 26.9 months (95% CI, 12.0 months to NE). Estimated 12-month OS rates per landmark analysis for all patients were 66.4%, 58.1%, and 52.3% for cohorts 1, 2, and 3, respectively. Survival rates for the TC3 or IC3 subgroup were comparable (Table 2), with

**Table 1.** Patient Demographic Data and Baseline Characteristics (all treated patients [TC2/3 or IC2/3])

| Variable | Cohort 1: 1L | Cohort 2: 2L | Cohort 3: ≥ 3L | All Patients |
|---|---|---|---|---|
| No. of patients | 139 | 268 | 252 | 659 |
| Median age, years (range) | 67 (35-88) | 63 (28-83) | 64 (38-84) | 64 (28-88) |
| Male, % | 51 | 61 | 61 | 59 |
| Race, % | | | | |
| Asian | 9 | 10 | 16 | 12 |
| Black | 1 | 1 | 2 | 2 |
| White | 88 | 85 | 79 | 84 |
| Other/unknown | 2 | 4 | 3 | 3 |
| Ethnicity, % | | | | |
| Hispanic/Latino | 1 | 2 | 2 | 2 |
| Not Hispanic/Latino | 91 | 95 | 94 | 94 |
| Not reported/unknown | 8 | 3 | 4 | 5 |
| ECOG PS 1, % | 57 | 63 | 68 | 64 |
| Current/previous tobacco use, % | 84 | 82 | 83 | 83 |
| Nonsquamous histology, % | 77 | 69 | 72 | 72 |
| Mutation/tested, No. (%) | | | | |
| *EGFR**† | 13/117 (11) | 18/219 (8) | 14/207 (7) | 45/543 (8) |
| *KRAS** | 33/100 (33) | 50/200 (25) | 54/188 (29) | 137/488 (28) |
| *ALK** | 3/79 (4) | 2/151 (1) | 4/146 (3) | 9/376 (2) |
| TC3 or IC3 status, % | 47 | 46 | 46 | 46 |

NOTE. TC3 or IC3 = TC ≥ 50% or IC ≥ 10% PD-L1–expressing cells, respectively; TC2/3 or IC2/3 = TC or IC ≥ 5% PD-L1–expressing cells, respectively.
Abbreviations: 1L, first line; 2L, second line; 3L, third line; ALK, anaplastic lymphoma kinase; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; IC, tumor-infiltrating immune cells; PS, performance status; TC, tumor cells.
*Mutational status was not required at enrollment; limited data available.
†Patients were considered *EGFR* mutant for the analysis if their tumor tested positive for at least one of the following mutations: exon 19 deletions or insertions, L858R, exon 20 insertion, G719X, L861Q, or S768I. Three patients with a T790M mutation were not included in this analysis; two of these patients also had an exon 19 deletion.
On the basis of a data cutoff of December 1, 2015.

12-month OS rates ranging from 57.5% to 61.5% for the cohorts exhibiting increased PD-L1 expression.

### Safety

Overall, 94% of patients experienced at least one AE, of which 65% were treatment related (Tables 3 and 4). All-cause grade 3 to 4 AEs occurred in 42% of patients (12% treatment related), with a similar incidence across cohorts. The AE profile for the TC3 or IC3 subgroup was generally similar to that for the TC2/3 or IC2/3 patients. Treatment-related AEs (TRAEs) in ≥ 10% of treated patients were fatigue (19%), diarrhea (11%), nausea (11%), and pruritus (10%). The most common serious AEs (SAEs, any grade) were pneumonia (4%), dyspnea (3%), pyrexia (3%), and pneumonitis (2%). One SAE of treatment-related pneumonia was fatal. AEs of special interest are listed in Table 4.

Forty-three patients (7%) withdrew from treatment due to an AE (15 [2%] were grade 3 to 4). AEs (any grade; grade 3 to 4) resulting in withdrawal among all cohorts (≥ 0.5%) were pneumonitis (1%; 1%) and pneumonia (1%; 0%). Fifteen patients (2%) withdrew as the result of TRAEs.

There were 305 deaths (46% of patients in the study), 234 of which occurred ≥ 30 days after the last administration of atezolizumab; most deaths (90%) were due to disease progression. The leading cause of death not resulting from progressive disease was pneumonia (1%).

### Exploratory Biomarker Analyses

Tumor tissue was analyzed for *EGFR* mutations in 543 patients (82%) and for *KRAS* mutations in 488 patients (74%; Table 1). Of those with available results, *EGFR* mutations were detected in 8% of patients (11%, 8%, and 7% in cohorts 1, 2, and 3, respectively), and *KRAS* mutations in 28% of patients (33%, 25%, and 29% in cohorts 1, 2, and 3, respectively). PD-L1 expression was comparable among TC3 or IC3 patients with *EGFR* mutations (range, 21% to 31% for the three cohorts). In subgroup analyses, responses occurred across lines of therapy regardless of *EGFR* status (ORRs for mutant/wild-type tumors in cohorts 1, 2, and 3 were 23%/19%, 0%/21%, and 7%/18%, respectively) or *KRAS* status (27%/16%, 32%/16%, and 19%/18% in cohorts 1, 2, and 3, respectively; Table 2). There was an insufficient number of patients with rearranged *ALK* (n = 2) to assess efficacy in this subgroup.

On the basis of a subgroup analysis (data cutoff, December 1, 2015), mOS for *EGFR*-mutant/ wild-type tumors in cohorts 1, 2, and 3 was 20.1 months/NE, 9.8/16.3 months, and 7.4/14.7 months, respectively; mOS for *KRAS*-mutant/wild-type tumors in cohorts 1, 2, and 3 was NE/20.1 months, 17.7/15.1 months, and 12.1/13.8 months, respectively (Table 2).

## DISCUSSION

On the basis of preliminary atezolizumab data suggesting that ORR may correlate with PD-L1 expression levels, BIRCH was designed to evaluate ORR in patients with tumors that expressed PD-L1 on ≥ 5% of TC or IC (TC2/3 or IC2/3). BIRCH met its primary objective of demonstrating efficacy with atezolizumab monotherapy in PD-L1–selected patients with advanced NSCLC. Results from BIRCH demonstrated clinically meaningful efficacy and safety of atezolizumab in all lines of therapy. With a minimum follow-up of 12 months, the ORR in ≥ 2L patients (cohorts 2 and 3) was 18% to 19% and in 1L (cohort 1) was 22%. The mOS in ≥ 2L patients, at 14.6 months, was consistent with prior atezolizumab ≥ 2L survival results.[21,28] An updated survival analysis

  

**Table 2.** Atezolizumab Efficacy by Cohort and Mutation Status

| PD-L1 Status, Mutation Status, and Cohort | No. of Patients | ORR per IRF, No. (%; 95% CI)[a] | Median DOR per IRF, months (95% CI)[a] | Median PFS per IRF, months (95% CI)[a] | Median OS, months (95% CI) |
|---|---|---|---|---|---|
| All treated patients (TC2/3 or IC2/3) | | | | | |
| Cohort | | | | | |
| 1 | 139 | 30 (22; 15 to 29) | 9.8 (5.6 to NE) | 5.4 (3.0 to 6.9) | 20.1 (20.1 to NE) |
| 2 | 268 | 52 (19; 15 to 25) | NE (8.3 to NE) | 2.8 (1.5 to 3.9) | 15.5 (12.3 to NE) |
| 3 | 252 | 45 (18; 13 to 23) | 11.8 (6.9 to NE) | 2.8 (2.7 to 3.0) | 13.2 (10.3 to 17.5) |
| PD-L1 TC3 or IC3 subgroup | | | | | |
| Cohort | | | | | |
| 1 | 65 | 20 (31; 20 to 43) | 10.0 (6.9 to NE) | 5.6 (2.7 to 8.3) | NE (12.0 to NE) |
| 2 | 122 | 32 (26; 19 to 35) | NE (8.3 to NE) | 4.0 (1.5 to 5.5) | 15.1 (12.0 to NE) |
| 3 | 115 | 31 (27; 19 to 36) | 7.2 (5.6 to NE) | 4.1 (2.8 to 5.6) | 17.5 (11.1 to NE) |
| *EGFR* mutation status[b] | | | | | |

| Cohort | | Mutant | WT | Mutant | WT | Mutant | WT | Mutant | WT |
|---|---|---|---|---|---|---|---|---|---|
| 1[c] | 117 | 3 (23; 5 to 54) | 20 (19; 12 to 28) | NE (5.6 to NE) | 8.5 (5.6 to 12.3) | 5.5 (2.6 to 8.3) | 5.5 (3.0 to 6.9) | 20.1 (NE to NE) | NE (15.5 to NE) |
| 2[d] | 219 | 0 (0; 0 to 19) | 43 (21; 16 to 28) | NE (NE to NE) | NE (8.3 to NE) | 1.3 (1.2 to 1.6) | 2.8 (1.4 to 4.0) | 9.8 (6.8 to NE) | 16.3 (13.6 to NE) |
| 3[e] | 207 | 1 (7; 0 to 34) | 35 (18; 13 to 24) | NE (NE to NE) | 16.4 (6.9 to NE) | 1.4 (1.3 to 2.9) | 2.8 (2.6 to 3.7) | 7.4 (3.4 to 12.7) | 14.7 (11.0 to NE) |
| *KRAS* mutation status | | | | | | | | | |
| Cohort | | | | | | | | | |
| 1[f] | 100 | 9 (27; 13 to 46) | 11 (16; 8 to 27) | 10.0 (6.9 to NE) | 7.1 (5.2 to 12.3) | 8.3 (1.6 to 12.7) | 4.8 (2.8 to 6.9) | NE (NE to NE) | 20.1 (14.1 to 20.1) |
| 2[g] | 200 | 16 (32; 20 to 47) | 24 (16; 11 to 23) | 11.3 (6.9 to NE) | NE (8.3 to NE) | 4.1 (2.6 to 7.1) | 1.4 (1.4 to 2.8) | 17.7 (13.7 to NE) | 15.1 (12.1 to NE) |
| 3[h] | 188 | 10 (19; 9 to 31) | 24 (18; 12 to 25) | NE (NE to NE) | 16.4 (5.7 to NE) | 2.6 (1.4 to 2.8) | 2.8 (1.9 to 3.0) | 12.1 (6.9 to NE) | 13.8 (10.6 to NE) |

| Atezolizumab updated efficacy analysis[i] | | ORR per INV, No. (%; 95% CI)[j] | Median OS (95% CI) | 12-Month OS Rate (95% CI) |
|---|---|---|---|---|
| All Treated Patients (TC2/3 or IC2/3) | | | | |
| Cohort | | | | |
| 1 | 138[k] | 35 (25; 18 to 33) | 23.5 (18.1 to NE) | 66.4 (58.1 to 74.6) |
| 2 | 269[k] | 53 (20; 15 to 25) | 15.5 (12.3 to 19.3) | 58.1 (52.1 to 64.1) |
| 3 | 252 | 50 (20; 15 to 25) | 13.2 (10.3 to 17.5) | 52.3 (46.1 to 58.6) |
| PD-L1 TC3 or IC3 Subgroup | | | | |
| Cohort | | | | |
| 1 | 65 | 22 (34; 23 to 47) | 26.9 (12.0 to NE) | 61.5 (49.0 to 74.0) |
| 2 | 122 | 32 (26; 19 to 35) | 16.6 (12.0 to NE) | 58.7 (49.8 to 67.6) |
| 3 | 115 | 36 (31; 23 to 41) | 17.5 (11.1 to 21.4) | 57.5 (48.4 to 66.6) |

NOTE. On the basis of a data cutoff of December 1, 2015.

Abbreviations: DOR, duration of response; EGFR, epidermal growth factor receptor; INV, investigator; IRF, independent review facility; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; NE, not estimable; TC2/3 or IC2/3 = TC or IC ≥ 5% PD-L1–expressing cells, respectively; TC3 or IC3 = TC ≥ 50% or IC ≥ 10% PD-L1–expressing cells, respectively; WT, wild type.

[a]Assessed by IRF per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.

[b]Patients were considered *EGFR* mutant for the analysis if their tumor tested positive for at least one of the following mutations: exon 19 deletions or insertions, L858R, exon 20 insertion, G719X, L861Q, or S768I. Three patients with a T790M mutation were not included in this analysis; two of these patients also had an exon 19 deletion.

[c]Number of patients tested: mutant (n = 13), WT (n = 104).

[d]Number of patients tested: mutant (n = 18), WT (n = 201).

[e]Number of patients tested: mutant (n = 14), WT (n = 193).

[f]Number of patients tested: mutant (n = 33), WT (n = 67).

[g]Number of patients tested: mutant (n = 50), WT (n = 150).

[h]Number of patients tested: mutant (n = 54), WT (n = 134).

[i]On the basis of an updated data cutoff of August 1, 2016; median duration of follow-up 22.5 months. Fewer than 50% of survival events had occurred at the time of data cutoff.

[j]Assessed by INV per RECIST version 1.1.

[k]One patient was mistakenly assigned to cohort 2 at the time of the August 1, 2016, data cutoff.

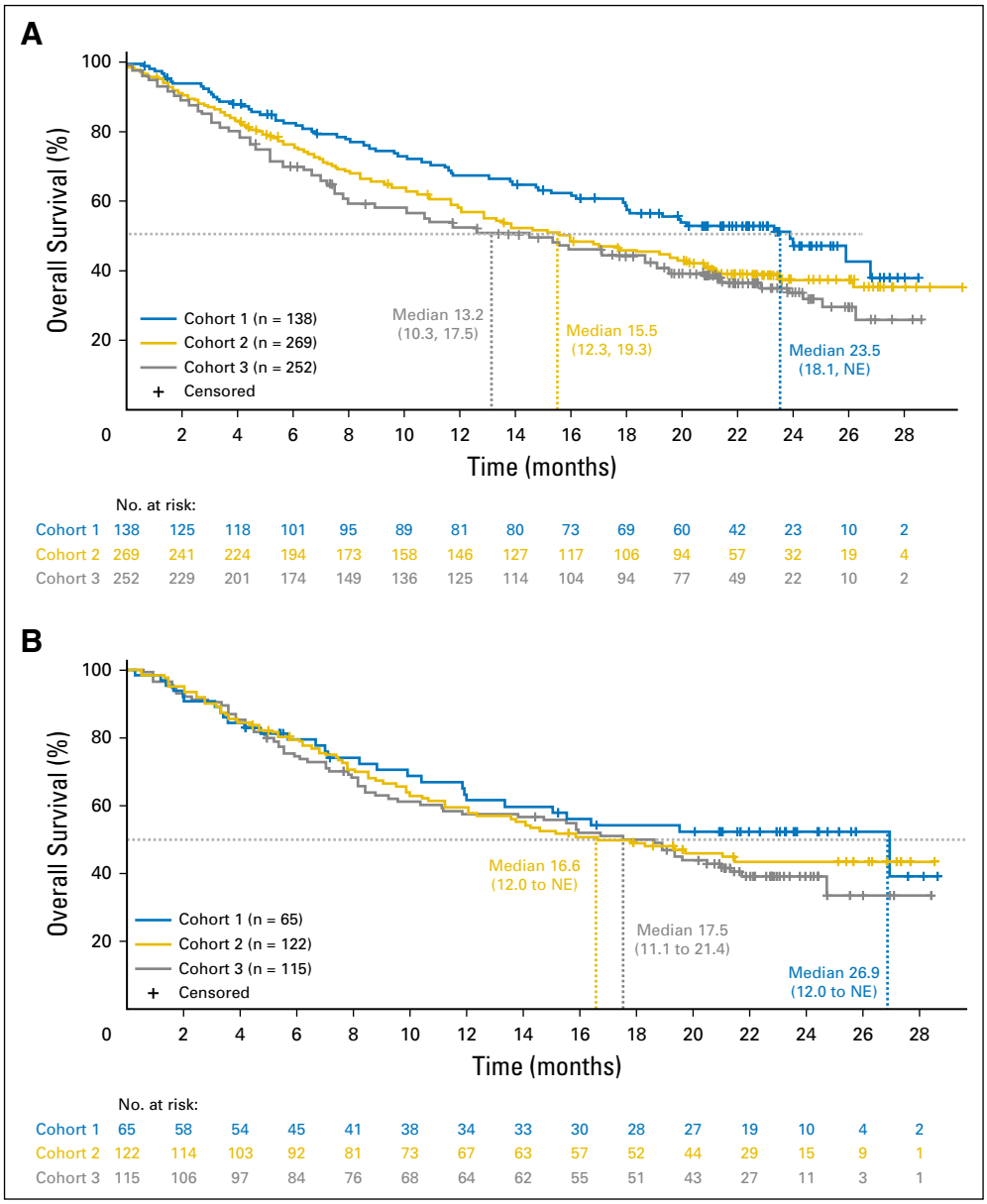


**Fig 2.** Estimated Kaplan-Meier overall survival for patients with advanced non–small-cell lung cancer treated with atezolizumab in the BIRCH trial, by cohort. (A) TC2/3 or IC2/3 group (intent-to-treat population), and (B) TC3 or IC3 subgroup. TC3 or IC3 = TC ≥ 50% or IC ≥ 10% PD-L1–expressing cells, respectively; TC2/3 or IC2/3 = TC or IC ≥ 5% PD-L1–expressing cells, respectively. Cohort 1 = 1L; cohort 2 = 2L; cohort 3 = ≥ 3L. On the basis of an updated data cutoff of August 1, 2016. IC, tumor-infiltrating immune cells; NE, not estimable; TC, tumor cells.

(minimum 20-month follow-up) showed that OS data continue to mature, with an mOS of 23.5 months for 1L patients (26.9 months for the TC3 or IC3 subgroup), which compares favorably to historical data with combination chemotherapy. A minority of patients (1.1%) received immunotherapy after atezolizumab, making subsequent immunotherapy an unlikely factor for influencing OS results.

Subgroup analyses conducted by varying PD-L1 levels support the hypothesis that atezolizumab treatment results in improvement in radiographic end points (eg, ORR) in patients with tumors that have the highest levels of PD-L1 expression (TC3 or IC3).[21,23,24] ORR was higher in the TC3 or IC3 subgroup for both 1L and ≥ 2L (Table 2), although in 1L patients it was comparable to chemotherapy.[1,2] PFS was greatest in 1L patients (cohort 1) but similar between TC3 or IC3 and TC2/3 or IC2/3 patients (5.6 and 5.4 months, respectively). In previously treated patients (cohorts 2 and 3), PFS was modestly higher in TC3 or IC3 patients versus TC2/3 or IC2/3 patients.

Unlike ORR and PFS, the OS benefit seemed to be independent of PD-L1 status. For both the TC2/3 or IC2/3 patients and TC3 or IC3 subgroup, atezolizumab treatment seemed to result in a clinically meaningful OS improvement relative to chemotherapy historical controls (23.5 months *v* 10 to 12 months with platinum-based chemotherapy for patients who received 1L treatment).[2,26,27] Similar results were seen in the POPLAR (ClinicalTrials.gov identifier: NCT01903993) and OAK (ClinicalTrials.gov identifier: NCT02008227) trials, in which investigator-assessed ORR and median PFS results underestimated the broad OS benefit seen with atezolizumab versus docetaxel.[21,28] In these studies, PD-L1 status can enrich for clinical efficacy with radiographic end points such as ORR, but may play less of a role with OS. Efforts are underway to compare different PD-L1 immunohistochemistry assays and to identify additional predictive biomarkers across various efficacy end points.

To our knowledge, BIRCH was among the first trials to show, with a robust sample size, the clinical benefit of atezolizumab in 1L

  

**Table 3.** Safety Summary (all treated patients)

| Variable | No. of Patients (%) | | | |
|---|---|---|---|---|
| | Cohort 1 | Cohort 2 | Cohort 3 | All Patients |
| No. of patients | 139 | 268 | 252 | 659 |
| Total No. of patients with at least one AE | 127 (91) | 247 (92) | 244 (97) | 618 (94) |
| Adverse events | | | | |
| Total No. of AEs | 1,291 | 2,512 | 2,575 | 6,378 |
| Grade 3 or 4 | 56 (40) | 108 (40) | 111 (44) | 275 (42) |
| Grade 5 | 2 (1) | 10 (4) | 9 (4) | 21 (3) |
| TRAEs | | | | |
| All grades | 81 (58) | 173 (65) | 175 (69) | 429 (65) |
| Grade 3 or 4 | 13 (9) | 35 (13) | 33 (13) | 81 (12) |
| Grade 5 | 0 | 0 | 1 (0.4) | 1 (0.2) |
| SAEs | 46 (33) | 101 (38) | 105 (42) | 252 (38) |
| AEs leading to withdrawal from atezolizumab* | 8 (6) | 20 (8) | 15 (6) | 43 (7) |
| AEs leading to dose interruption | 36 (26) | 68 (25) | 83 (33) | 187 (28) |
| TRAEs leading to withdrawal from atezolizumab | 5 (4) | 4 (2) | 6 (2) | 15 (2) |

NOTE. On the basis of a data cutoff of December 1, 2015.
Abbreviations: AE, adverse event; SAE, serious adverse event; TRAE, treatment-related adverse event.
*Causes of atezolizumab withdrawal (any grade; grade 3 to 4) occurring at an incidence ≥ 0.5% were pneumonitis (1%; 1%) and pneumonia (1%; 0%).

patients with NSCLC. These results seem to confirm the preliminary 1L activity seen in the FIR trial (ClinicalTrials.gov identifier: NCT01846416), which reported a similar ORR (26%) and 1-year OS rate of 73% in a small 1L cohort.[22]

Study limitations are similar to those of other single-arm phase II trials. Although BIRCH was an open-label trial, the primary efficacy end point was assessed by an IRF that was blinded to all clinical data except prior cancer treatment/surgery information, which minimized potential bias. Historical ORRs with chemotherapy were used for comparison with atezolizumab because chemotherapy was the standard of care for advanced NSCLC when BIRCH was initiated.

**Table 4.** Adverse Events

| Type of Adverse Event | Any Grade, No. (%) | Grade 3 to 4, No. (%) |
|---|---|---|
| TRAE (≥ 5% of treated patients)*,† | | |
| Fatigue | 122 (19) | 7 (1) |
| Diarrhea | 71 (11) | 2 (0) |
| Nausea | 73 (11) | 4 (1) |
| Pruritus | 65 (10) | 0 |
| Pyrexia | 54 (8) | 1 (0) |
| Decreased appetite | 53 (8) | 1 (0) |
| Asthenia | 50 (8) | 3 (1) |
| Rash | 50 (8) | 9 (1) |
| Arthralgia | 39 (6) | 2 (0) |
| AE of special interest (> 1% of treated patients) | | |
| Rash | 70 (11) | 3 (1) |
| Hypothyroidism | 30 (5) | 2 (0) |
| AST increased | 26 (4) | 5 (1) |
| ALT increased | 23 (4) | 2 (0) |
| Pneumonitis | 26 (4) | 11 (2) |
| Rash maculopapular | 13 (2) | 2 (0) |
| Colitis | 10 (2) | 3 (1) |
| Peripheral neuropathy | 15 (2) | 0 |

NOTE. On the basis of a data cutoff of December 1, 2015.
Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TRAE, treatment-related adverse event.
*TRAEs that occurred within 30 days from last day of atezolizumab administration.
†Grade 5 all-cause AEs: pneumonia (0.5%), lung infection, acute coronary syndrome, cardiac arrest, cardiac failure, cerebrovascular accident, hepatic failure, internal hemorrhage, pneumonia aspiration, pneumonitis, respiratory distress, septic shock, cerebral infarction, and respiratory failure (all < 0.3%).

Subgroup analyses found no clear association between response to atezolizumab and tumor histology. Efficacy was seen with both squamous and nonsquamous tumors, similar to POPLAR results.[21] Although mutational data were limited (particularly for *ALK*), results presented herein indicate that atezolizumab had activity in both wild-type and mutated tumors; however, atezolizumab seems less active in *EGFR*-mutated tumors. This is consistent with other data suggesting that *EGFR*-mutated NSCLC may have lower response to PD-L1/PD-1 inhibitors.[29]

Atezolizumab was well tolerated in all patients in BIRCH. The safety profile was consistent with previous atezolizumab monotherapy trials.[21-23] Treatment-related toxicities were generally manageable and consistent across multiple lines of therapy, with grade 3 to 4 TRAEs in 9% of patients in cohort 1 and in 13% of patients in both cohorts 2 and 3. No unexpected safety signals or significant differences in AEs or SAEs were seen across cohorts. The incidence of AEs resulting in atezolizumab withdrawal (≤ 8% across all cohorts) was similar to that in POPLAR (8%).[20] The TRAE profile noted in this and in other single-agent atezolizumab trials[21-23] is distinct from that seen with chemotherapy. The incidence of atezolizumab-related pneumonitis (3.3%) was consistent with prior studies.[21,22] In NSCLC trials of other PD-L1/PD-1 inhibitors, pneumonitis (all grades) occurred at an incidence of 1% to 6%.[6-8,11]

Results of 1L phase III trials were recently reported for PD-1 inhibitors. A significant benefit in ORR (45% *v* 28%), PFS (median, 10.3 *v* 6.0 months; hazard ratio, 0.50), and OS (median not reached; hazard ratio, 0.60) was demonstrated with pembrolizumab versus chemotherapy in PD-L1–selected patients (≥ 50% TC staining for PD-L1).[11] In contrast, a randomized phase III trial of single-agent nivolumab versus investigator's-choice chemotherapy in PD-L1–selected patients (≥ 1% PD-L1 tumor staining) did not meet its primary end point of improved PFS or OS, even in patients with higher PD-L1 staining (≥ 50% TC

staining).[30] Ongoing phase III trials are evaluating 1L atezolizumab versus chemotherapy in PD-L1–selected patients or atezolizumab with chemotherapy in PD-L1–unselected patients.

In conclusion, data from BIRCH confirmed that single-agent atezolizumab provided clinical benefit in patients with advanced NSCLC, with an mOS of approximately 2 years in 1L patients. Efficacy was also observed in ≥ 2L patients and in patients with or without driver mutations. For patients with PD-L1–expressing tumors, response rates were higher with atezolizumab versus historical chemotherapy, and patients with TC3 or IC3 tumors had numerically higher ORRs versus those with TC2/3 or IC2/3 tumors. Ongoing randomized phase III trials are comparing atezolizumab monotherapy with combination chemotherapy or comparing chemotherapy with and without atezolizumab in patients with chemotherapy-naïve advanced NSCLC.

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Disclosures provided by the authors are available with this article at jco.org.

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## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

**Phase II Trial of Atezolizumab As First-Line or Subsequent Therapy for Patients With Programmed Death-Ligand 1–Selected Advanced Non–Small-Cell Lung Cancer (BIRCH)**

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## *Appendix*

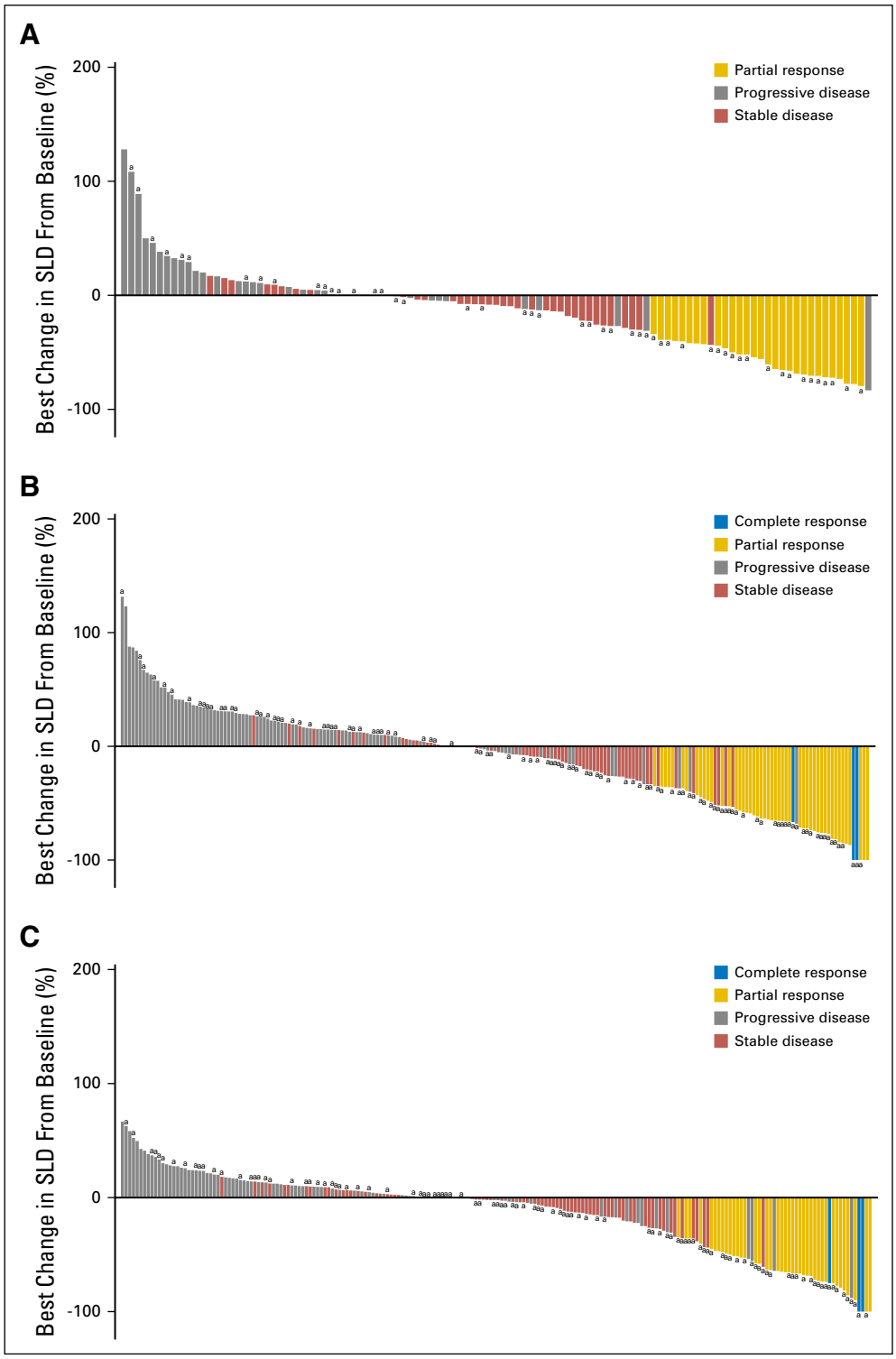


**Fig A1.** Best change in sum of the longest diameters (SLD) from baseline by cohort, on the basis of an independent review facility assessment. (A) Cohort 1 (1L), (B) cohort 2 (2L), and (C) cohort 3 (≥ 3L). Complete responders are indicated in blue, partial responders in gold, patients with stable disease in red, and patients experiencing disease progression in gray. [a]Patients with TC3 or IC3 PD-L1 immunohistochemistry status. On the basis of a data cutoff of December 1, 2015. 1L, first line; 2L, second line; 3L, third line; IC, tumor-infiltrating immune cells; PD-L1, programmed death-ligand 1; TC, tumor cells; TC3 or IC3 = TC ≥ 50% or IC ≥ 10% PD-L1–expressing cells, respectively.

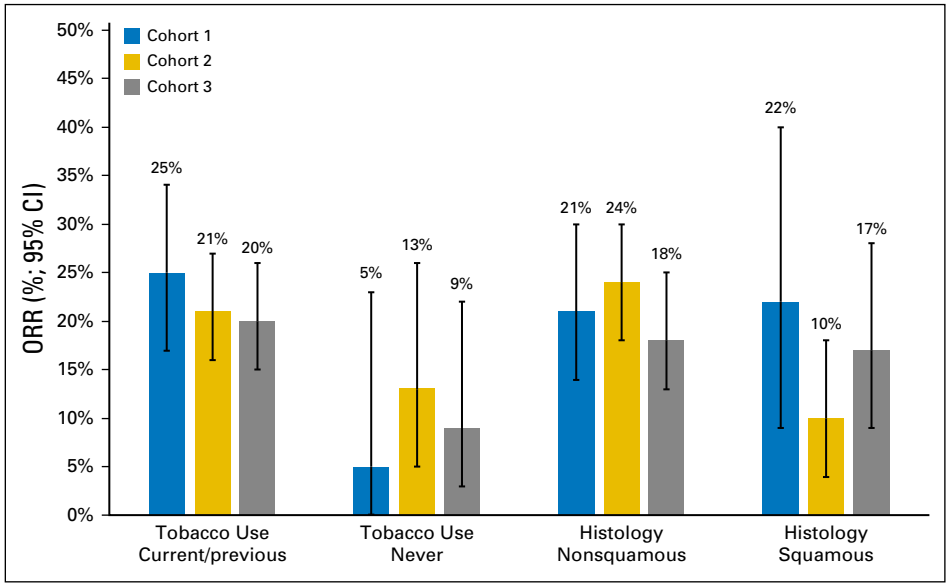


**Fig A2.** Objective response rates (ORR) for tobacco use and histology patient subgroups shown by cohort as determined by an independent review facility (Response Evaluation Criteria in Solid Tumors [RECIST] version 1.1). Error bars represent 95% CIs. On the basis of a data cutoff of December 1, 2015.

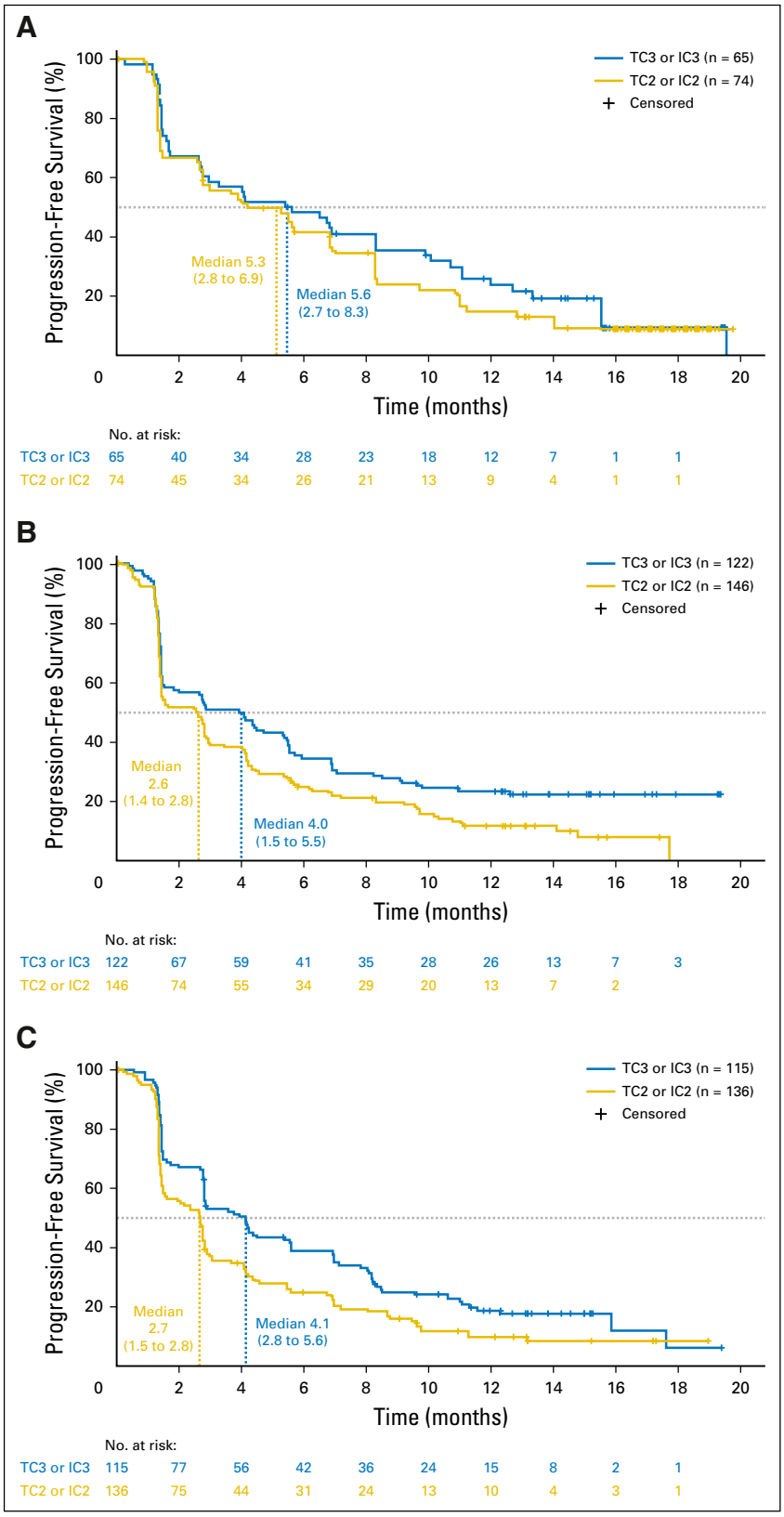


**Fig A3.** Estimated Kaplan-Meier progression-free survival (by independent review facility) curves by PD-L1 status for patients with advanced non–small-cell lung cancer treated with atezolizumab in the BIRCH trial. TC2 or IC2 patients were determined by excluding TC3 or IC3 patients from TC2/3 or IC2/3 patients. (A) Cohort 1 (1L), (B) cohort 2 (2L), and (C) cohort 3 (≥ 3L). On the basis of a data cutoff of December 1, 2015. 1L, first line; 2L, second line, 3L, third line; IC, tumor-infiltrating immune cells; PD-L1, programmed death-ligand 1; TC, tumor cells; TC2/3 or IC2/3 = TC or IC ≥ 5% PD-L1–expressing cells, respectively; TC3 or IC3 = TC ≥ 50% or IC ≥ 10% PD-L1–expressing cells, respectively.

**Table A1.** Programmed Death-Ligand 1 Tumor Cells and Tumor-Infiltrating Immune Cells Scoring Criteria

| | PD-L1 TC Scoring Criteria | PD-L1 IC Scoring Criteria | |
|---|---|---|---|
| TC Score | % of PD-L1–Expressing TC | IC Score | % of Tumor Area |
| TC3 | ≥ 50% | IC3 | ≥ 10% |
| TC2 | ≥ 5% and < 50% | IC2 | ≥ 5% and < 10% |
| TC1 | ≥ 1% and < 5% | IC1 | ≥ 1% and < 5% |
| TC0 | < 1% | IC0 | < 1% |

Abbreviations: IC, tumor-infiltrating immune cells; PD-L1, programmed death-ligand 1; TC, tumor cells.

**Table A2.** Independent Review Facility–Assessed Objective Response Rates (per Response Evaluation Criteria in Solid Tumors [RECIST] version 1.1) Versus Historical Data for All Subgroups

| Line of Therapy (ordered by testing procedure) | PD-L1 Status* | No. of Treated Patients | Prespecified Historical Control Response Rate (%)† | ORR, % (95% CI)‡ |
|---|---|---|---|---|
| ≥ 3L | TC2/3 or IC2/3 | 253 | 5 | 17 (13 to 23) |
| ≥ 3L | TC3 or IC2/3 | 236 | 5 | 18 (14 to 24) |
| ≥ 3L (cohort 3) | TC3 or IC3 | 115 | 5 | 27 (19 to 36) |
| ≥ 2L | TC2/3 or IC2/3 | 520 | 7 | 17 (14 to 21) |
| ≥ 2L | TC3 or IC2/3 | 483 | 7 | 18 (15 to 22) |
| ≥ 2L (cohorts 2/3) | TC3 or IC3 | 237 | 7 | 25 (20 to 31) |
| All lines (all three cohorts) | TC3 or IC3 | 302 | 15 | 26 (21 to 31) |

NOTE. On the basis of a data cutoff of May 28, 2015. Data analysis was performed approximately 6 months after the last patient was enrolled. Objective response rates (ORRs) were 17% to 19% for patients with TC2/3 or IC2/3 tumors and 26% to 27% for the TC3 or IC3 subgroup. The median overall survival (95% CI) for patients with TC2/3 or IC2/3 tumors was 14.0 months (14.0 months to NE), NE (11.2 months to NE), and NE (8.4 months to NE) for cohorts 1, 2, and 3, respectively, with 6-month cumulative survival rates of 82%, 76%, and 71%, respectively. (The median survival was immature for the TC3 or IC3 subgroup.)

Abbreviations: 2L, second line; 3L, third line; IC, tumor-infiltrating immune cells; NE, not estimable; PD-L1, programmed death-ligand 1; TC, tumor cells; TC2/3 or IC2/3 = TC or IC ≥ 5% PD-L1–expressing cells, respectively; TC3 or IC3 = TC ≥ 50% or IC ≥ 10% PD-L1–expressing cells, respectively.

*PD-L1–expressing TC: TC3 = ≥ 50%; TC2 = ≥ 5% and < 50%. Percentage of PD-L1–expressing IC in tumor microenvironment: IC3 = ≥ 10%; IC2 = ≥ 5% and < 10%.

†Prespecified historical control response rates shown were solely on the basis of prior lines of chemotherapy received.

‡$P < .001$ for each ORR value compared with respective historical chemotherapy control rates.

**Table A3.** Atezolizumab Efficacy by TC2 or IC2 Programmed Death-Ligand 1 Status

| Cohort | No. of Patients | ORR, No. (%; 95% CI)* | Median DOR, Months (95% CI) | Median PFS, Months (95% CI)* | Median OS, Months (95% CI) |
|---|---|---|---|---|---|
| 1 | 74 | 10 (14; 6 to 23) | 5.6 (4.6 to NE) | 5.3 (2.8 to 6.9) | 20.1 (NE to NE) |
| 2 | 146 | 20 (14; 9 to 20) | 11.3 (6.9 to NE) | 2.6 (1.4 to 2.8) | 15.5 (11.9 to NE) |
| 3 | 136 | 14 (10; 6 to 17) | 11.8 (8.4 to NE) | 2.7 (1.5 to 2.8) | 11.0 (7.5 to 14.9) |

NOTE. On the basis of a data cutoff of December 1, 2015. TC2/3 or IC2/3 excluding TC3 or IC3.

Abbreviations: DOR, duration of response; IC, tumor-infiltrating immune cells; IC2 = ≥ 5% and < 10%; PFS, progression-free survival; NE, not estimable; ORR, objective response rate; OS, overall survival; TC, tumor cells; TC2 = ≥ 5% and < 50%; TC2/3 or IC2/3 = TC or IC ≥ 5% PD-L1–expressing cells, respectively; TC3 or IC3 = TC ≥ 50% or IC ≥ 10% PD-L1–expressing cells, respectively.

*Assessed by an independent review facility per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.