ORIGINAL ARTICLE

Atezolizumab for First-Line Treatment of PD-L1–Selected Patients with NSCLC

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N Engl J Med 2020;383:1328-39.
DOI: 10.1056/NEJMoa1917346

ABSTRACT

BACKGROUND

The efficacy and safety of the anti–programmed death ligand 1 (PD-L1) monoclonal antibody atezolizumab, as compared with those of platinum-based chemotherapy, as first-line treatment for patients with metastatic non–small-cell lung cancer (NSCLC) with PD-L1 expression are not known.

METHODS

We conducted a randomized, open-label, phase 3 trial involving patients with metastatic nonsquamous or squamous NSCLC who had not previously received chemotherapy and who had PD-L1 expression on at least 1% of tumor cells or at least 1% of tumor-infiltrating immune cells as assessed by the SP142 immunohistochemical assay. Patients were assigned in a 1:1 ratio to receive atezolizumab or chemotherapy. Overall survival (primary end point) was tested hierarchically according to PD-L1 expression status among patients in the intention-to-treat population whose tumors were wild-type with respect to *EGFR* mutations or *ALK* translocations. Within the population with *EGFR* and *ALK* wild-type tumors, overall survival and progression-free survival were also prospectively assessed in subgroups defined according to findings on two PD-L1 assays as well as by blood-based tumor mutational burden.

RESULTS

Overall, 572 patients were enrolled. In the subgroup of patients with *EGFR* and *ALK* wild-type tumors who had the highest expression of PD-L1 (205 patients), the median overall survival was longer by 7.1 months in the atezolizumab group than in the chemotherapy group (20.2 months vs. 13.1 months; hazard ratio for death, 0.59; P=0.01). Among all the patients who could be evaluated for safety, adverse events occurred in 90.2% of the patients in the atezolizumab group and in 94.7% of those in the chemotherapy group; grade 3 or 4 adverse events occurred in 30.1% and 52.5% of the patients in the respective groups. Overall and progression-free survival favored atezolizumab in the subgroups with a high blood-based tumor mutational burden.

CONCLUSIONS

Atezolizumab treatment resulted in significantly longer overall survival than platinum-based chemotherapy among patients with NSCLC with high PD-L1 expression, regardless of histologic type. (Funded by F. Hoffmann–La Roche/Genentech; IMpower110 ClinicalTrials.gov number, NCT02409342.)

Inhibitors of programmed death 1 (PD-1) and its ligand PD-L1, either as monotherapy or combined with chemotherapy, with or without bevacizumab, have emerged as a new standard of care for the first-line treatment of patients with advanced non–small-cell lung cancer (NSCLC) without mutations of epidermal growth factor receptor (*EGFR*) or translocations of anaplastic lymphoma kinase (*ALK*).[1-7] Pembrolizumab monotherapy has been approved as a first-line treatment for patients with tumors with high PD-L1 expression (tumor proportion score [the fraction of tumor cells expressing PD-L1], ≥50%) in the United States and European Union.[6,7] In the United States, this approval has been extended to patients with advanced NSCLC with a tumor proportion score of at least 1%; however, most of the clinical benefit appears to be limited to the subgroup with the highest PD-L1 expression.[8] The phase 2 BIRCH and POPLAR trials as well as the phase 3 OAK trial showed an overall survival benefit with atezolizumab, an anti–PD-L1 monoclonal antibody,[9] as a monotherapy in patients with NSCLC with high PD-L1 expression (as assessed by the SP142 PD-L1 immunohistochemical assay) across multiple lines of therapy.[10-12]

Despite advances in the landscape of first-line treatment for metastatic NSCLC, additional treatment options are needed. IMpower110 is a global, randomized, open-label, phase 3 trial designed to evaluate the efficacy and safety of atezolizumab as compared with platinum-based chemotherapy in PD-L1–selected patients (positive for PD-L1 on the SP142 assay) with *EGFR* and *ALK* wild-type metastatic NSCLC who had not previously received chemotherapy.

Currently, several PD-L1 immunohistochemical assays are routinely used to guide decisions about immune-checkpoint inhibitor treatment.[13] We performed prespecified efficacy analyses of subgroups defined with the use of other frequently used PD-L1 immunohistochemical assays (22C3 and SP263),[14,15] allowing for their evaluation within the enrolled population. In addition, we performed efficacy analyses in subgroups defined according to blood-based tumor mutational burden, which is a noninvasive approach for identifying patients who may benefit from immunotherapy.[16-19] Here, we report primary efficacy and safety results of the interim analysis of overall survival among patients with high PD-L1 expression as assessed by the SP142 immunohistochemical assay, as well as efficacy in subgroups defined according to additional biomarkers.

Methods

Patients

Eligible patients were 18 years of age or older; had stage IV nonsquamous or squamous NSCLC, measurable by Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1; had a baseline Eastern Cooperative Oncology Group (ECOG) performance-status score of 0 or 1 (on a 5-point scale in which higher scores indicate greater disability); and had not previously received chemotherapy. PD-L1 expression on at least 1% of tumor cells or tumor-infiltrating immune cells covering at least 1% of the tumor area as determined by the SP142 assay was required.[20] Immunohistochemical analyses were conducted by a central laboratory on archival tumor tissue or tissue obtained through biopsy at the time of screening. Full details on eligibility are provided in the protocol, available with the full text of this article at NEJM.org. Initially, patients with a known sensitizing *EGFR* mutation or *ALK* translocation were eligible provided they had received previous targeted therapy. The protocol was subsequently amended to exclude these patients from the analysis (18 patients) because emerging data suggested that they may not benefit from immune-checkpoint inhibitor monotherapy.[21-23] All the patients were evaluated for central nervous system (CNS) metastasis at the time of screening with the use of computed tomography, magnetic resonance imaging, or both; patients with active or untreated CNS metastases were ineligible for enrollment in the trial.

Trial Design and Oversight

Patients were randomly assigned in a 1:1 ratio to receive atezolizumab (1200 mg intravenously) or platinum-based chemotherapy (4 or 6 cycles) once every 3 weeks. In the chemotherapy group, patients with nonsquamous NSCLC received either cisplatin (75 mg per square meter of body-surface area) or carboplatin (area under the concentration–time curve [AUC], 6) in addition to pemetrexed (500 mg per square meter) intravenously; patients with squamous NSCLC received a regimen of cisplatin (75 mg per square meter) plus gemcitabine (1250 mg per square meter) or a regimen of carboplatin (AUC, 5) plus gemcitabine (1000 mg per square meter) intravenously. Randomization was stratified according to sex (male vs. female), ECOG performance-status score (0 vs. 1), histologic type

(nonsquamous vs. squamous), and PD-L1 status (≥1% PD-L1 expression on tumor cells and any level of PD-L1 expression on tumor-infiltrating immune cells vs. <1% PD-L1 expression on tumor cells and ≥1% PD-L1 expression on tumor-infiltrating immune cells). Continuation of atezolizumab after disease progression was allowed in patients who had continued clinical benefit. No crossover to the atezolizumab group was permitted.

Genentech (a member of the Roche Group) funded the trial, provided the trial treatments, and collaborated with the academic authors on the design of the trial and the collection, analysis, and interpretation of the data. The trial was conducted in full accordance with Good Clinical Practice guidelines and the Declaration of Helsinki or the laws and regulations of the country in which the research was conducted, whichever afforded the most protection. Written informed consent was obtained from all the patients. Safety data were regularly reviewed by an independent data monitoring committee. The committee was also responsible for evaluating efficacy data at the prespecified interim analysis of overall survival. The protocol was approved by independent ethics committees for each site. All the authors vouch for the accuracy and completeness of the data and for the adherence of the trial to the protocol. Earlier versions of the manuscript were developed by the authors, with editorial and writing assistance funded by the sponsor.

END POINTS AND ASSESSMENTS

Overall survival was the primary end point in the PD-L1–selected population that excluded patients with *EGFR* mutations or *ALK* translocations. Secondary efficacy end points included investigator-assessed progression-free survival according to RECIST, version 1.1; the occurrence and duration of a response; and overall and investigator-assessed progression-free survival according to RECIST, version 1.1, in prespecified subgroups with respect to PD-L1 expression (defined by the SP263 immunohistochemical assay) and blood-based tumor mutational burden. Safety was assessed in all the patients who received a trial agent regardless of PD-L1 expression status or status with respect to *EGFR* or *ALK* alterations. Exploratory end points included overall and investigator-assessed progression-free survival according to RECIST, version 1.1, in prespecified subgroups with respect to PD-L1 expression defined by the 22C3 immunohistochemical assay.

Tumor assessments were conducted at baseline, every 6 weeks for 48 weeks, and every 9 weeks thereafter, until radiographic disease progression (or loss of clinical benefit for patients in the atezolizumab group who were treated beyond disease progression), withdrawal of consent, or death, whichever occurred first. Adverse events were reported according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0, and coded according to the *Medical Dictionary for Regulatory Activities*, version 22.0.

The scoring algorithm of the SP142 immunohistochemical assay (Ventana) measures PD-L1 expression on tumor cells and tumor-infiltrating immune cells; the algorithms of the 22C3 assay (Dako) and SP263 assay (Ventana) specifically measure PD-L1 expression on tumor cells.[13-15,20] The cutoffs of a tumor proportion score of at least 1% and at least 50% were evaluated for the 22C3 assay, and the cutoffs of at least 1% of tumor cells and at least 50% of tumor cells were evaluated for the SP263 assay. The blood-based tumor mutational burden assay (Foundation Medicine) identifies single-nucleotide variants at a variant allele fraction of at least 0.5% across 394 genes and estimates the tumor fraction according to maximum somatic allele frequency, filters out germline events, and counts nondriver somatic mutations to generate a score.[18] The cutoff scores for blood-based tumor mutational burden that were evaluated were at least 10, at least 16, and at least 20. A score of 16 (16 mutations per 1.1 megabases) equates to approximately 14.5 mutations per megabase.[18,24]

STATISTICAL ANALYSIS

Full details of the statistical analyses, including sample size and power, are provided in the protocol. To control for the overall type I error rate at a two-sided significance level of 0.05, the primary end point of overall survival was tested hierarchically in the population with *EGFR* and *ALK* wild-type tumors: high PD-L1 expression (≥50% of tumor cells or ≥10% of tumor-infiltrating immune cells), then combined high and intermediate PD-L1 expression (≥5% of tumor cells or tumor-infiltrating immune cells), and then any PD-L1 expression (≥1% of tumor cells or tumor-infiltrating immune cells; intention-to-treat population) (Fig. S1 in the Supplementary Appendix, available at NEJM.org). If the results for the primary end point of overall survival were significant in all three primary analysis populations, a

two-sided significance level of 0.05 would be passed down to compare progression-free survival between the atezolizumab and control groups.

An interim analysis of overall survival was conducted when approximately 96 deaths and an event–patient ratio of 45% had occurred among patients with *EGFR* and *ALK* wild-type tumors who had high PD-L1 expression. Analyses of overall and progression-free survival were performed with the use of a stratified log-rank test. Hazard ratios and 95% confidence intervals were estimated with a stratified Cox regression model. The Kaplan–Meier method was used to estimate medians, and the Brookmeyer–Crowley method was used to generate 95% confidence intervals for the medians. The percentages of patients with a response and 95% confidence intervals were calculated with the Clopper–Pearson method. Response duration was estimated with the Kaplan–Meier method. We performed prespecified subgroup analyses to assess the consistency of the treatment effect using unstratified hazard ratios that were estimated from a Cox proportional-hazards model.

RESULTS

PATIENTS

Between July 21, 2015, and February 20, 2018, a total of 572 patients underwent randomization at 144 centers in 19 countries, with 285 patients assigned to receive atezolizumab and 287 assigned to receive chemotherapy (Fig. S2). The population with *EGFR* and *ALK* wild-type tumors comprised 554 patients (277 patients in each group). A total of 18 patients with an *EGFR* mutation or *ALK* translocation were enrolled and were excluded from the primary analysis population but were included in the safety population.

The baseline characteristics of the patients were generally balanced between the treatment groups (Table 1 and Table S1). Overall in the population with *EGFR* and *ALK* wild-type tumors, 107 patients (38.6%) in the atezolizumab group and 98 (35.4%) in the chemotherapy group had high expression of PD-L1; 166 patients (59.9%) in the atezolizumab group and 162 (58.5%) in the chemotherapy group had high or intermediate PD-L1 expression (Table 1, Table S1, and Fig. S3).

INTERIM ANALYSIS OF OVERALL SURVIVAL

At the data cutoff date (September 10, 2018), the median follow-up times for survival among patients with *EGFR* and *ALK* wild-type tumors who had high PD-L1 expression, high or intermediate PD-L1 expression, and any PD-L1 expression were 15.7 months (range, 0 to 35), 15.2 months (range, 0 to 35), and 13.4 months (range, 0 to 35), respectively. In the specified population, 101 of 205 patients (49.3%) who had high PD-L1 expression, 154 of 328 patients (47.0%) who had high or intermediate PD-L1 expression, and 253 of 554 patients (45.7%) who had any PD-L1 expression had died.

Among patients with *EGFR* and *ALK* wild-type tumors who had high PD-L1 expression, the median overall survival was significantly longer — by 7.1 months — in the atezolizumab group than in the chemotherapy group (20.2 months vs. 13.1 months; stratified hazard ratio for death, 0.59; 95% confidence interval [CI], 0.40 to 0.89; P=0.01) (Fig. 1A). The effect of the treatment in patient subgroups is shown in Figure S4.

The results for overall survival among patients with *EGFR* and *ALK* wild-type tumors who had high or intermediate PD-L1 expression did not cross the prespecified alpha boundary (median, 18.2 months in the atezolizumab group and 14.9 months in the chemotherapy group; stratified hazard ratio for death, 0.72; 95% CI, 0.52 to 0.99; P=0.04) (Fig. 1B); therefore, in accordance with the statistical analysis plan, overall survival among patients with *EGFR* and *ALK* wild-type tumors who had any PD-L1 expression was not formally tested. The median overall survival among these patients was 17.5 months with atezolizumab and 14.1 months with chemotherapy (stratified hazard ratio for death, 0.83; 95% CI, 0.65 to 1.07) (Fig. 1C). The results of an exploratory sensitivity analysis of overall survival with adjustment for patients whose data were censored owing to early withdrawal are shown in Table S2.

Among patients with *EGFR* and *ALK* wild-type tumors who had high PD-L1 expression, 2 patients (1.9%) in the atezolizumab group and 29 patients (29.6%) in the chemotherapy group received subsequent immunotherapy (Table S3). Across subgroups with respect to PD-L1 expression, the percentage of patients receiving different classes of subsequent anticancer therapies was similar.

ANALYSIS OF PROGRESSION-FREE SURVIVAL

At data cutoff, 146 of 205 patients (71.2%) with *EGFR* and *ALK* wild-type tumors who had high PD-L1 expression had had disease progression or had died. Progression-free survival was 8.1 months in the atezolizumab group and 5.0 months in the chemotherapy group (stratified hazard ratio

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline (Population with *EGFR* and *ALK* Wild-Type Tumors).*

Characteristic	Any PD-L1 Expression		High or Intermediate PD-L1 Expression		High PD-L1 Expression	
	Atezolizumab (N=277)	Chemotherapy (N=277)	Atezolizumab (N=166)	Chemotherapy (N=162)	Atezolizumab (N=107)	Chemotherapy (N=98)
Median age (range) — yr	64 (30–81)	65 (30–87)	63 (33–81)	65 (33–87)	63 (33–79)	66 (33–87)
Male sex — no. (%)	196 (70.8)	193 (69.7)	122 (73.5)	107 (66.0)	79 (73.8)	64 (65.3)
Race — no. (%)†						
White	227 (81.9)	240 (86.6)	133 (80.1)	139 (85.8)	87 (81.3)	82 (83.7)
Asian	45 (16.2)	30 (10.8)	31 (18.7)	20 (12.3)	20 (18.7)	15 (15.3)
Black	2 (0.7)	2 (0.7)	1 (0.6)	0	0	0
Unknown	2 (0.7)	5 (1.8)	1 (0.6)	3 (1.9)	0	1 (1.0)
ECOG performance-status score — no. (%)‡						
0	97 (35.0)	102 (36.8)	60 (36.1)	62 (38.3)	35 (32.7)	38 (38.8)
1	180 (65.0)	175 (63.2)	106 (63.9)	100 (61.7)	72 (67.3)	60 (61.2)
History of tobacco use — no. (%)						
Never	37 (13.4)	35 (12.6)	21 (12.7)	17 (10.5)	9 (8.4)	15 (15.3)
Current	74 (26.7)	81 (29.2)	38 (22.9)	52 (32.1)	20 (18.7)	29 (29.6)
Previous	166 (59.9)	161 (58.1)	107 (64.5)	93 (57.4)	78 (72.9)	54 (55.1)
Histologic type at diagnosis — no. (%)						
Nonsquamous	192 (69.3)	193 (69.7)	122 (73.5)	116 (71.6)	80 (74.8)	75 (76.5)
Squamous	85 (30.7)	84 (30.3)	44 (26.5)	46 (28.4)	27 (25.2)	23 (23.5)

* This population comprised the patients whose tumors were wild-type with respect to *EGFR* mutations or *ALK* translocations. Any programmed death ligand 1 (PD-L1) expression indicates PD-L1 expression on at least 1% of tumor cells or tumor-infiltrating immune cells as assessed by the SP142 assay. High or intermediate PD-L1 expression indicates PD-L1 expression on at least 5% of tumor cells or tumor-infiltrating immune cells. High PD-L1 expression indicates PD-L1 expression on at least 50% of tumor cells or at least 10% of tumor-infiltrating immune cells. Percentages may not total 100 because of rounding.

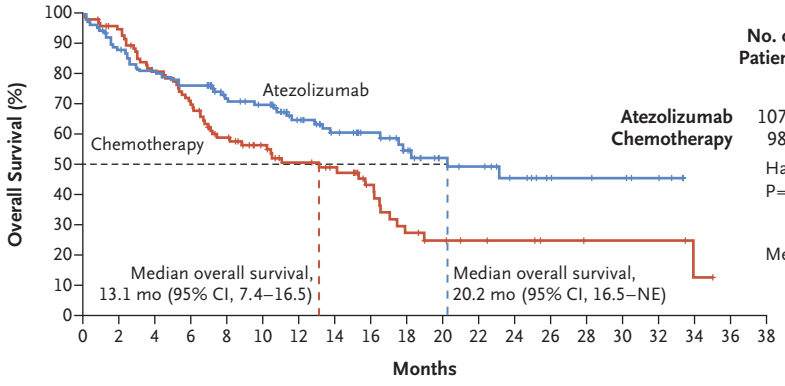
† Race was reported by the patients. One patient in the atezolizumab group with any PD-L1 expression was categorized as having multiple races (not shown).

‡ Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with 0 indicating no symptoms and higher scores indicating greater disability.

Figure 1 (facing page). Overall Survival in the Atezolizumab Group and the Chemotherapy Group.

Shown are Kaplan–Meier estimates of overall survival among the patients whose tumors were wild-type with respect to *EGFR* mutations or *ALK* translocations. High expression of programmed death ligand 1 (PD-L1) indicates PD-L1 expression on at least 50% of tumor cells or at least 10% of tumor-infiltrating immune cells as assessed by the SP142 immunohistochemical assay (Panel A). High or intermediate PD-L1 expression indicates PD-L1 expression on at least 5% of tumor cells or tumor-infiltrating immune cells (Panel B). Any PD-L1 expression indicates PD-L1 expression on at least 1% of tumor cells or tumor-infiltrating immune cells. Stratified hazard ratios are given according to the level of PD-L1 expression. Treatment comparisons (atezolizumab vs. platinum-based chemotherapy) for the primary end point of overall survival were based on a stratified log-rank test. Medians were estimated with the use of the Kaplan–Meier method. A stratified Cox regression model was used to estimate hazard ratios, and 95% confidence intervals (CIs) were calculated with the use of the Brookmeyer–Crowley method. The results for overall survival among patients who had high or intermediate PD-L1 expression did not cross the prespecified alpha boundary, so overall survival among patients who had any PD-L1 expression was not formally tested. Tick marks indicate censored data. NE denotes could not be estimated.

A High PD-L1 Expression



	No. of Patients	6-Mo Overall Survival (95% CI)	12-Mo Overall Survival (95% CI)
		percent	
Atezolizumab	107	76.3 (68.2–84.4)	64.9 (55.4–74.4)
Chemotherapy	98	70.1 (60.8–79.4)	50.6 (40.0–61.3)

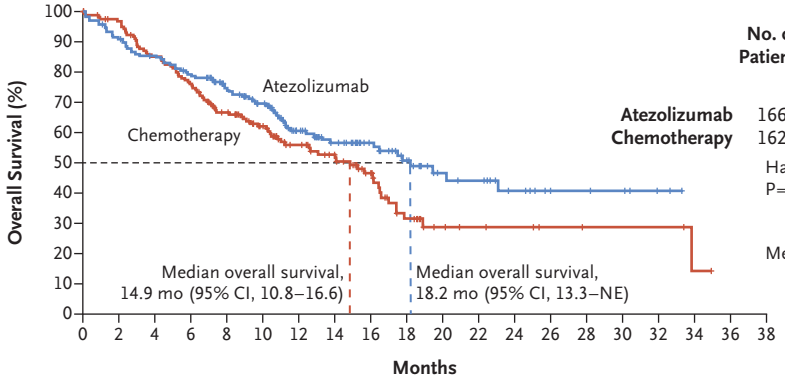
Hazard ratio for death, 0.59 (95% CI, 0.40–0.89)
P=0.01

Median follow-up, 15.7 mo (range, 0–35)

No. at Risk

Atezolizumab	107	94	85	80	66	61	48	40	34	25	18	16	11	7	6	5	2
Chemotherapy	98	89	75	65	50	40	33	28	19	12	9	7	6	4	3	3	3	1

B High or Intermediate PD-L1 Expression



	No. of Patients	6-Mo Overall Survival (95% CI)	12-Mo Overall Survival (95% CI)
		percent	
Atezolizumab	166	79.3 (73.1–85.5)	60.7 (52.6–68.7)
Chemotherapy	162	76.1 (69.3–82.8)	56.0 (47.7–64.3)

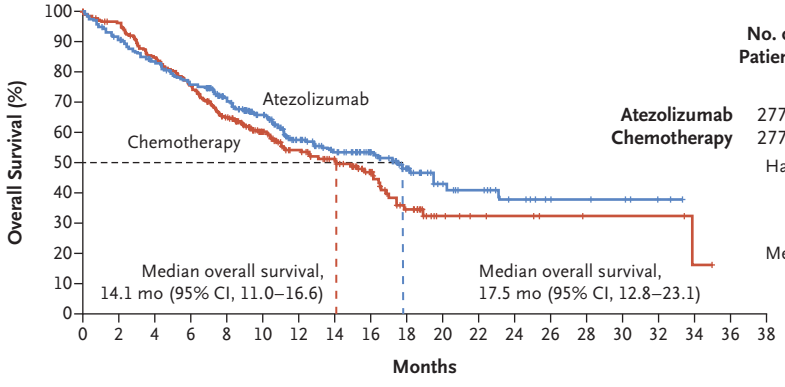
Hazard ratio for death, 0.72 (95% CI, 0.52–0.99)
P=0.04

Median follow-up, 15.2 mo (range, 0–35)

No. at Risk

Atezolizumab	166	151	139	128	108	92	66	54	42	30	19	17	11	7	6	5	2
Chemotherapy	162	150	131	117	95	75	57	46	32	17	9	7	6	4	3	3	3	1

C Any PD-L1 Expression



	No. of Patients	6-Mo Overall Survival (95% CI)	12-Mo Overall Survival (95% CI)
		percent	
Atezolizumab	277	76.2 (71.1–81.3)	57.6 (51.2–64.0)
Chemotherapy	277	75.7 (70.5–80.9)	54.3 (47.7–60.8)

Hazard ratio for death, 0.83 (95% CI, 0.65–1.07)

Median follow-up, 13.4 mo (range, 0–35)

No. at Risk

Atezolizumab	277	252	226	204	170	134	93	74	58	37	22	17	11	7	6	5	2
Chemotherapy	277	254	223	199	153	108	79	63	43	24	10	7	6	4	3	3	3	1

for disease progression or death, 0.63; 95% CI, 0.45 to 0.88) (Fig. S5A). Among patients with *EGFR* and *ALK* wild-type tumors who had high or intermediate PD-L1 expression, progression-free survival was 7.2 months in the atezolizumab group and 5.5 months in the chemotherapy group (stratified hazard ratio for disease progression or death, 0.67; 95% CI, 0.52 to 0.88) (Fig. S5B).

OCCURRENCE AND DURATION OF RESPONSE

Among patients with *EGFR* and *ALK* wild-type tumors who had high PD-L1 expression, the percentage of patients who had an investigator-assessed confirmed response was 38.3% in the atezolizumab group and 28.6% in the chemotherapy group (Table S4). At data cutoff, confirmed responses were ongoing in 68.3% of the patients in the atezolizumab group and 35.7% of those in the chemotherapy group. Among patients with *EGFR* and *ALK* wild-type tumors who had high or intermediate PD-L1 expression, the percentage of patients who had an investigator-assessed confirmed response was 30.7% in the atezolizumab group and 32.1% in the chemotherapy group, with confirmed responses ongoing in 70.6% of the patients in the atezolizumab group and 34.6% of those in the chemotherapy group. Among patients with *EGFR* and *ALK* wild-type tumors who had any PD-L1 expression, the percentage of patients who had an investigator-assessed confirmed response was 29.2% in the atezolizumab group and 31.8% in the chemotherapy group, with confirmed responses ongoing in 70.4% of the patients in the atezolizumab group and 33.0% of those in the chemotherapy group.

PD-L1 IMMUNOHISTOCHEMICAL ANALYSES

Of the 554 patients with *EGFR* and *ALK* wild-type tumors who had any PD-L1 expression, 534 could be evaluated by the 22C3 assay and 546 by the SP263 assay. Key baseline characteristics for each biomarker subgroup were consistent with those for the patients with *EGFR* and *ALK* wild-type tumors who had any PD-L1 expression (Table S5). The prevalence of PD-L1 expression as determined by the 22C3 and SP263 assays was similar (Fig. S6). High overlap was observed between the subgroup with a tumor proportion score of at least 50% on the 22C3 assay and the subgroup with PD-L1 expression on at least 50% of tumor cells on the SP263 assay (Fig. 2A). In addition, approximately 30% of the patients with *EGFR* and *ALK* wild-type tumors who had high PD-L1 expression as assessed by the SP142 assay were encompassed within the subgroup with a tumor proportion score of at least 50% on the 22C3 or the subgroup with PD-L1 expression on at least 50% of tumor cells on the SP263 assay (Fig. 2A).

Among patients with high PD-L1 expression as assessed by the SP142 assay, the median overall survival was 20.2 months in the atezolizumab group and 13.1 months in the chemotherapy group (stratified hazard ratio for death, 0.59; 95% CI, 0.40 to 0.89) (Fig. 1A). Patients with a tumor proportion score of at least 50% on the 22C3 assay had an overall survival of 20.2 months in the atezolizumab group and 11.0 months in the chemotherapy group (unstratified hazard ratio for death, 0.60; 95% CI, 0.42 to 0.86) (Fig. 2B), and patients with PD-L1 expression on at least 50% of tumor cells on the SP263 assay had values of 19.5 months and 16.1 months, respectively (unstratified hazard ratio for death, 0.71; 95% CI, 0.50 to 1.00) (Fig. 2C).

In the population of patients who could be evaluated for biomarker levels, those who were PD-L1–positive as assessed by the SP142 assay had a median overall survival of 17.5 months in the atezolizumab group and 14.1 months in the chemotherapy group (stratified hazard ratio for death, 0.83; 95% CI, 0.65 to 1.07). Patients who had a tumor proportion score of at least 1% on the 22C3 assay had an overall survival of 17.8 months in the atezolizumab group and 14.0 months in the chemotherapy group (unstratified hazard ratio for death, 0.73; 95% CI, 0.55 to 0.97), and patients who had PD-L1 expression on at least 1% of tumor cells on the SP263 assay had values of 17.8 months and 14.0 months, respectively (unstratified hazard ratio for death, 0.77; 95% CI, 0.58 to 1.02) (Fig. S7). Among patients who had intermediate or low PD-L1 expression as assessed by the SP142 assay, the median overall survival was 12.9 months in the atezolizumab group and 14.9 months in the chemotherapy group (unstratified hazard ratio for death, 1.04; 95% CI, 0.76 to 1.44). Patients with a tumor proportion score of 1 to 49% on the 22C3 assay had an overall survival of 16.5 months in the atezolizumab group and 15.7 months in the chemotherapy group (unstratified hazard ratio for death, 1.00; 95% CI, 0.63 to 1.58), and patients with PD-L1 expression on 1 to 49% of tumor cells on the SP263 assay had values of 13.3 months and 10.6 months, respectively (unstratified hazard ratio for death, 0.94; 95% CI, 0.58 to 1.53) (Fig. S8). Progression-free survival with atezolizumab as

compared with chemotherapy across subgroups of patients who could be evaluated for PD-L1 biomarker levels is shown in Figure S9.

ANALYSES OF BLOOD-BASED TUMOR MUTATIONAL BURDEN

Of the 554 patients with *EGFR* and *ALK* wild-type tumors who had any PD-L1 expression, 389 could be evaluated for blood-based tumor mutational burden. Baseline characteristics were consistent between the patients with *EGFR* and *ALK* wild-type tumors who had any PD-L1 expression and those who could be evaluated for blood-based tumor mutational burden (Table S6). A total of 22.4% of the patients with *EGFR* and *ALK* wild-type tumors who could be evaluated for mutational burden had a blood-based tumor mutational burden score of at least 16, and this burden level appeared to identify a distinct population as compared with the population identified as having high PD-L1 expression on the SP142 or 22C3 immunohistochemical assay (Fig. 3A). The median overall survival among patients with a blood-based tumor mutational burden score of at least 16 was 13.9 months in the atezolizumab group and 8.5 months in the chemotherapy group (unstratified hazard ratio for death, 0.75; 95% CI, 0.41 to 1.35) (Fig. S10). The median progression-free survival among patients with a blood-based tumor mutational burden score of at least 16 was 6.8 months in the atezolizumab group and 4.4 months in the chemotherapy group (unstratified hazard ratio for disease progression or death, 0.55; 95% CI, 0.33 to 0.92) (Fig. 3B).

SAFETY

Safety analysis was performed in all the patients who received a trial agent, including patients who received any amount of atezolizumab (286 patients) and those who received chemotherapy only (263 patients). The median treatment duration for atezolizumab was 5.3 months. In the chemotherapy group, the median treatment duration was 2.1 months for cisplatin, 2.3 months for carboplatin, 2.6 months for gemcitabine, and 3.5 months for pemetrexed.

Adverse events occurred in 90.2% of the patients receiving atezolizumab and in 94.7% of those receiving chemotherapy (Table 2 and Tables S7 and S8). Adverse events with a 5-percentage-point difference in incidence between the treatment groups are described in Figure S11. Grade 3 or 4 adverse events occurred in 30.1% of the patients in the atezolizumab group and in 52.5% of those in the chemotherapy group (Table 2), with the most common (≥5% in either group) being anemia, neutropenia, and thrombocytopenia (all with chemotherapy). Serious adverse events occurred in 28.3% of the patients in the atezolizumab group and in 28.5% of those in the chemotherapy group (Table S7). A total of 11 patients (3.8%) in the atezolizumab group and 11 patients (4.2%) in the chemotherapy group had a grade 5 adverse event (Table 2 and Table S7).

Immune-mediated adverse events, which were defined according to a list of sponsor-specified terms, regardless of whether these events led to use of systemic glucocorticoids, endocrine therapy, or other immunosuppressants, occurred in 40.2% of the patients in the atezolizumab group and in 16.7% of those in the chemotherapy group; grade 3 or 4 immune-mediated adverse events occurred in 6.6% and 1.5% of the patients in the respective groups (Table S9). No grade 5 immune-mediated adverse events were noted. Hepatic laboratory abnormalities, rash, and hypothyroidism were the most commonly reported immune-mediated adverse events (≥5% in either group) (Table S9). Immune-mediated adverse events that resulted in systemic glucocorticoid treatment are reported in Table S10.

DISCUSSION

We conducted a phase 3 trial of atezolizumab monotherapy as a first-line treatment in patients with nonsquamous or squamous metastatic NSCLC who had not previously received chemotherapy. The median overall survival was significantly longer — by 7.1 months — with atezolizumab than with chemotherapy among patients with *EGFR* and *ALK* wild-type tumors who had high PD-L1 expression. The observed safety profile was consistent with that observed in previous studies of atezolizumab monotherapy across indications, histologic type, and lines of therapy.

The testing boundary for overall survival was not crossed among patients with *EGFR* and *ALK* wild-type tumors who had high or intermediate PD-L1 expression; therefore, patients with *EGFR* and *ALK* wild-type tumors who had any PD-L1 expression could not be formally tested. The trial is ongoing to provide data on the final analysis of overall survival. Among patients with *EGFR* and *ALK* wild-type tumors who received atezolizumab, observed results for overall survival according to level of PD-L1 expression were

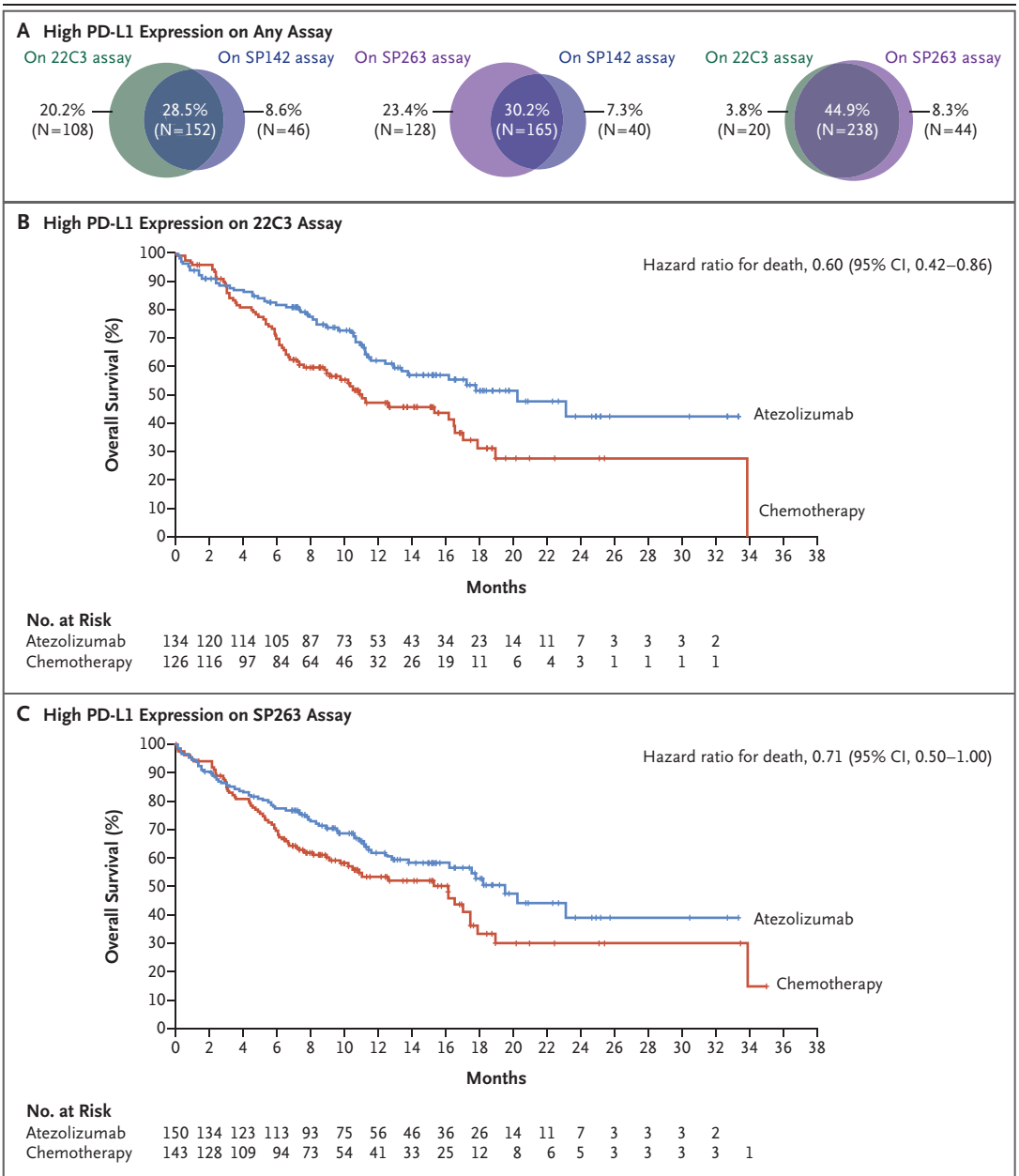
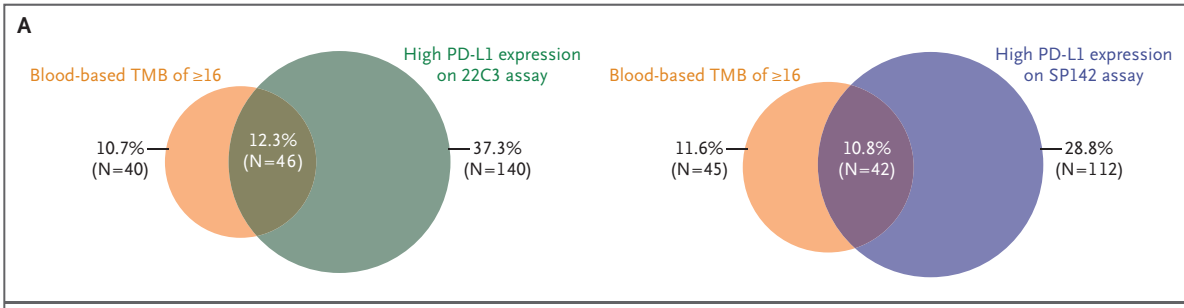


Figure 2. Overall Survival among Patients with High PD-L1 Expression, According to Immunohistochemical Assay.

Panel A shows the overlap among patients with a tumor proportion score of at least 50% as assessed by the 22C3 assay, patients with PD-L1 expression on at least 50% of tumor cells as assessed by the SP263 assay, and patients with PD-L1 expression on at least 50% of tumor cells or at least 10% of tumor-infiltrating immune cells as assessed by the SP142 assay. Each percentage in the Venn diagrams reflects the percentage of that specific subgroup out of the total population of patients who could be evaluated for biomarker levels: 534 patients for the 22C3 and SP142 overlap, 546 for the SP263 and SP142 overlap, and 530 for the 22C3 and SP263 overlap. Panel B shows Kaplan–Meier estimates of overall survival among patients with a tumor proportion score of at least 50% on the 22C3 assay, and Panel C shows Kaplan–Meier estimates of overall survival among patients with PD-L1 expression on at least 50% of tumor cells on the SP263 assay. Medians were estimated with the use of the Kaplan–Meier method. Unstratified hazard ratios are shown for 22C3 and SP263 subgroup analyses. Tick marks indicate censored data.



B

Subgroup	No. of Patients/ Total No. (%)	Median Progression-free Survival (mo) Atezolizumab	Chemotherapy	Hazard Ratio for Disease Progression or Death (95% CI)
Any PD-L1 expression	554/554 (100)	5.7	5.5	0.77 (0.63–0.94)
Could be evaluated for blood-based TMB				
No	165/554 (29.8)	9.3	5.7	0.53 (0.36–0.79)
Yes	389/554 (70.2)	5.5	5.4	0.88 (0.70–1.11)
Blood-based TMB				
≥10	175/389 (45.0)	5.5	4.3	0.74 (0.53–1.05)
≥16	87/389 (22.4)	6.8	4.4	0.55 (0.33–0.92)
≥20	56/389 (14.4)	6.8	5.2	0.56 (0.30–1.06)
<10	214/389 (55.0)	5.5	5.7	1.03 (0.76–1.39)
<16	302/389 (77.6)	4.5	5.5	1.00 (0.78–1.29)
<20	333/389 (85.6)	4.9	5.4	0.95 (0.74–1.21)

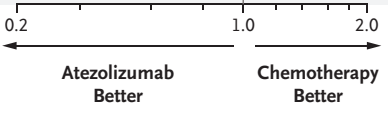


Figure 3. Progression-free Survival in Subgroups Defined According to Blood-Based Tumor Mutational Burden (TMB).

Panel A shows the overlap between patients with a blood-based TMB of at least 16 (16 mutations per 1.1 megabase, equivalent to approximately 14.5 mutations per megabase) and patients with high PD-L1 expression. Each percentage in the Venn diagrams reflects the percentage of that specific subgroup out of the total population of patients who could be evaluated for biomarker levels: 375 patients for the 22C3 assay and blood-based TMB overlap and 389 for the SP142 assay and blood-based TMB overlap. Panel B shows progression-free survival in subgroups defined according to blood-based TMB. Any PD-L1 expression was defined as PD-L1 expression on at least 1% of tumor cells or tumor-infiltrating immune cells as assessed by the SP142 assay. A total of 165 patients could not be evaluated for blood-based TMB: 88 patients had a blood-based TMB result with a maximum somatic allele frequency of less than 1%, 39 patients had a sample that failed quality control at the testing vendor or had a median exon coverage of less than 800, and 38 patients had not provided a baseline plasma sample. A stratified hazard ratio is shown for any PD-L1 expression, and unstratified hazard ratios are shown for the other subgroups.

similar to those seen in the phase 3 KEYNOTE-042 trial comparing pembrolizumab with chemotherapy; in both trials, the patients with high PD-L1 expression had the most benefit.[8]

Our trial evaluated as exploratory end points how different PD-L1 scoring methods perform to predict the activity of atezolizumab as compared with chemotherapy. The analytic performance and concordance of the different assays were evaluated previously[13,25]; these analyses have shown that the 22C3 and SP263 PD-L1 assays were highly concordant, whereas the SP142 assay was less sensitive for staining of both tumor cells and tumor-infiltrating immune cells. In the clinical setting, the 22C3 and SP263 assays evaluate PD-L1 expression on tumor cells only, whereas the SP142 assay evaluates expression on both tumor cells and tumor-infiltrating immune cells.[13-15,20] Our trial selected patients who had any level of PD-L1 expression as assessed by the SP142 assay. Hence, the assessment of additional biomarkers provided results from a double-selected patient population, which is a limitation of the analysis. A benefit favoring atezolizumab

Table 2. Reported Adverse Events (Safety Population).*

Adverse Event	Atezolizumab (N=286)			Chemotherapy (N=263)		
	All Grades	Grade 3 or 4	Grade 5	All Grades	Grade 3 or 4	Grade 5
	number (percent)					
Any adverse event	258 (90.2)	86 (30.1)	11 (3.8)	249 (94.7)	138 (52.5)	11 (4.2)
Anemia	44 (15.4)	5 (1.7)	0	125 (47.5)	48 (18.3)	0
Decreased appetite	44 (15.4)	2 (0.7)	0	50 (19.0)	0	0
Nausea	39 (13.6)	1 (0.3)	0	89 (33.8)	5 (1.9)	0
Asthenia	37 (12.9)	2 (0.7)	0	46 (17.5)	5 (1.9)	0
Fatigue	37 (12.9)	2 (0.7)	0	46 (17.5)	6 (2.3)	0
Constipation	35 (12.2)	3 (1.0)	0	57 (21.7)	2 (0.8)	0
Hyponatremia	17 (5.9)	6 (2.1)	0	12 (4.6)	6 (2.3)	0
Pneumonia	14 (4.9)	7 (2.4)	0	17 (6.5)	9 (3.4)	1 (0.4)
Hyperkalemia	12 (4.2)	6 (2.1)	0	8 (3.0)	3 (1.1)	0
Thrombocytopenia	7 (2.4)	1 (0.3)	0	44 (16.7)	19 (7.2)	0
Neutropenia	4 (1.4)	2 (0.7)	0	74 (28.1)	46 (17.5)	0
Death	2 (0.7)	0	2 (0.7)	3 (1.1)	0	3 (1.1)
Decreased platelet count	1 (0.3)	0	0	22 (8.4)	11 (4.2)	0
Decreased neutrophil count	0	0	0	19 (7.2)	10 (3.8)	0
Febrile neutropenia	0	0	0	9 (3.4)	9 (3.4)	0

* The safety population comprised all the patients who received atezolizumab or chemotherapy, regardless of PD-L1 expression or *EGFR* and *ALK* alterations. Shown are adverse events with an incidence of at least 15% in any group, events of grade 3 or 4 severity with an incidence of at least 2% in any group, and events of grade 5 severity with an incidence of at least 1% in any group.

was observed in patients with high PD-L1 expression across all three assays, despite different analytic sensitivities and scoring algorithms.

The role of tumor mutational burden (in blood and tissue) as a predictive biomarker of response to cancer immunotherapy in patients with metastatic NSCLC remains uncertain. Although the predictive value of tumor mutational burden in patients receiving the cancer immunotherapy–chemotherapy combination appears to be limited,[26] recent data suggest its predictive value in the context of immunotherapy without chemotherapy. Various cutoffs (≥20 and ≥10 mutations per megabase and ≥175 mutations per exome) have been used retrospectively across cancer immunotherapy studies and have been shown to be predictive of overall survival, progression-free survival, or both in this context.[17,19,27-29] It is difficult to compare results across trials owing to differences in the assays and cutoffs used. The prospective, phase 2 B-F1RST trial examined blood-based tumor mutational burden as a potential biomarker in patients with metastatic NSCLC receiving atezolizumab monotherapy as a first-line treatment. The median progression-free survival was 5.0 months among patients with a blood-based tumor mutational burden score of at least 16 and 3.5 months among those with a blood-based tumor mutational burden score of less than 16 (unstratified hazard ratio for disease progression or death, 0.80; 90% CI, 0.54 to 1.18), and the median overall survival was 23.9 months and 13.4 months, respectively (unstratified hazard ratio for death, 0.66; 90% CI, 0.40 to 1.10).[24] In our trial, outcomes also favored atezolizumab, with an apparent plateau of clinical benefit in the subgroup with a blood-based tumor mutational burden score of at least 16; the greatest magnitude of benefit was seen for progression-free survival, a finding consistent with those of previous trials.[18] The ongoing randomized, phase 3 Blood-First Assay Screening Trial (BFAST; ClinicalTrials.gov number, NCT03178552) is prospectively evaluating first-line treatment with atezolizumab monotherapy as compared with platinum-based chemotherapy in patients with advanced or metastatic NSCLC who have a positive blood-based tumor mutational burden score.

We found that atezolizumab monotherapy resulted in longer overall survival than platinum-based combination chemotherapy among patients with previously untreated metastatic NSCLC with high expression of PD-L1. Toxic effects were consistent with those that have been reported previously.

Supported by F. Hoffmann–La Roche/Genentech, a member of the Roche Group.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

We thank See Phan of Genentech for clinical expertise and guidance, Eugene Kim of Genentech and Kosei Tajima of Chugai Pharmaceutical for biostatistical analysis, Maureen Peterson of Genentech for biomarker operations, Hina Patel and Monette Villalobos of Genentech for guidance and support for the trial, and Kia C.E. Walcott of Health Interactions for medical writing assistance with an earlier version of the manuscript.

REFERENCES

1. Socinski MA, Jotte RM, Cappuzzo F, et al. Atezolizumab for first-line treatment of metastatic nonsquamous NSCLC. N Engl J Med 2018;378:2288-301.
2. Reck M, Mok TSK, Nishio M, et al. Atezolizumab plus bevacizumab and chemotherapy in non-small-cell lung cancer (IMpower150): key subgroup analyses of patients with EGFR mutations or baseline liver metastases in a randomised, open-label phase 3 trial. Lancet Respir Med 2019;7:387-401.
3. Gandhi L, Rodríguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus chemotherapy in metastatic non–small-cell lung cancer. N Engl J Med 2018;378:2078-92.
4. Paz-Ares L, Luft A, Vicente D, et al. Pembrolizumab plus chemotherapy for squamous non–small-cell lung cancer. N Engl J Med 2018;379:2040-51.
5. West H, McCleod M, Hussein M, et al. Atezolizumab in combination with carboplatin plus nab-paclitaxel chemotherapy compared with chemotherapy alone as first-line treatment for metastatic non-squamous non-small-cell lung cancer (IMpower130): a multicentre, randomised, open-label, phase 3 trial. Lancet Oncol 2019;20:924-37.
6. Reck M, Rodríguez-Abreu D, Robinson AG, et al. Pembrolizumab versus chemotherapy for PD-L1–positive non–small-cell lung cancer. N Engl J Med 2016;375:1823-33.
7. Reck M, Rodríguez-Abreu D, Robinson AG, et al. Updated analysis of KEYNOTE-024: pembrolizumab versus platinum-based chemotherapy for advanced non-small-cell lung cancer with PD-L1 tumor proportion score of 50% or greater. J Clin Oncol 2019;37:537-46.
8. Mok TSK, Wu Y-L, Kudaba I, et al. Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial. Lancet 2019;393:1819-30.
9. Herbst RS, Soria J-C, Kowanetz M, et al. Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients. Nature 2014;515:563-7.
10. Peters S, Gettinger S, Johnson ML, et al. 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). J Clin Oncol 2017;35:2781-9.
11. Fehrenbacher L, Spira A, Ballinger M, et al. Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial. Lancet 2016;387:1837-46.
12. Rittmeyer A, Barlesi F, Waterkamp D, et al. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. Lancet 2017;389:255-65.
13. Hirsch FR, McElhinny A, Stanforth D, et al. PD-L1 immunohistochemistry assays for lung cancer: results from phase 1 of the Blueprint PD-L1 IHC assay comparison project. J Thorac Oncol 2017;12:208-22.
14. Roach C, Zhang N, Corigliano E, et al. Development of a companion diagnostic PD-L1 immunohistochemistry assay for pembrolizumab therapy in non-small-cell lung cancer. Appl Immunohistochem Mol Morphol 2016;24:392-7.
15. Rebelatto MC, Midha A, Mistry A, et al. Development of a programmed cell death ligand-1 immunohistochemical assay validated for analysis of non-small cell lung cancer and head and neck squamous cell carcinoma. Diagn Pathol 2016;11:95.
16. Greillier L, Tomasini P, Barlesi F. The clinical utility of tumor mutational burden in non-small cell lung cancer. Transl Lung Cancer Res 2018;7:639-46.
17. Hellmann MD, Ciuleanu T-E, Pluzanski A, et al. Nivolumab plus ipilimumab in lung cancer with a high tumor mutational burden. N Engl J Med 2018;378:2093-104.
18. Gandara DR, Paul SM, Kowanetz M, et al. Blood-based tumor mutational burden as a predictor of clinical benefit in non-small-cell lung cancer patients treated with atezolizumab. Nat Med 2018;24:1441-8.
19. Rizvi NA, Cho BC, Reinmuth N, et al. Blood tumor mutational burden (bTMB) and tumor PD-L1 as predictive biomarkers of survival in MYSTIC: first-line durvalumab (D) ± tremelimumab (T) versus chemotherapy (CT) in metastatic (m) NSCLC. J Clin Oncol 2019;37:Suppl 15:9016. abstract.
20. Vennapusa B, Baker B, Kowanetz M, et al. Development of a PD-L1 complementary diagnostic immunohistochemistry assay (SP142) for atezolizumab. Appl Immunohistochem Mol Morphol 2019;27:92-100.
21. Barlesi F, Nishio M, Cobo M, et al. IMpower132: efficacy of atezolizumab (atezo) carboplatin (carbo)/cisplatin (cis) + pemetrexed (pem) as 1L treatment in key subgroups with stage IV non-squamous non-small cell lung cancer (NSCLC). Ann Oncol 2018;29:Suppl 8:LBA54. abstract.
22. Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus docetaxel in advanced nonsquamous non–small-cell lung cancer. N Engl J Med 2015;373:1627-39.
23. Herbst RS, Baas P, Kim D-W, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. Lancet 2016;387:1540-50.
24. Socinski M, Velcheti V, Mekhail T, et al. Final efficacy results from B-F1RST, a prospective phase II trial evaluating blood-based tumour mutational burden (bTMB) as a predictive biomarker for atezolizumab (atezo) in 1L non-small cell lung cancer (NSCLC). Ann Oncol 2019;30:Suppl 5: LBA83. abstract.
25. Tsao MS, Kerr KM, Kockx M, et al. PD-L1 immunohistochemistry comparability study in real-life clinical samples: results of Blueprint phase 2 project. J Thorac Oncol 2018;13:1302-11.
26. Garassino M, Rodriguez-Abreu D, Gadgeel S, et al. Evaluation of TMB in KEYNOTE-189: pembrolizumab plus chemotherapy vs placebo plus chemotherapy for nonsquamous NSCLC. J Thorac Oncol 2019;14:Suppl:OA04.6. abstract.
27. Peters S, Cho BC, Reinmuth N, et al. Tumor mutational burden (TMB) as a biomarker of survival in metastatic non-small cell lung cancer (mNSCLC): blood and tissue TMB analysis from MYSTIC, a Phase III study of first-line durvalumab ± tremelimumab vs chemotherapy. Cancer Res 2019;79:Suppl 13:CT074. abstract.
28. Hellmann MD, Paz-Ares L, Bernabe Caro R, et al. Nivolumab plus ipilimumab in advanced non–small-cell lung cancer. N Engl J Med 2019;381:2020-31.
29. Herbst RS, Lopes G, Kowalski DM, et al. Association between tissue TMB (tTMB) and clinical outcomes with pembrolizumab monotherapy (pembro) in PD-L1-positive advanced NSCLC in the KEYNOTE-010 and -042 trials. Ann Oncol 2019;30:Suppl 5:v916-v917. abstract.