ORIGINAL ARTICLE

Atezolizumab and Nab-Paclitaxel in Advanced Triple-Negative Breast Cancer

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ABSTRACT

BACKGROUND

Unresectable locally advanced or metastatic triple-negative (hormone-receptor–negative and human epidermal growth factor receptor 2 [HER2]–negative) breast cancer is an aggressive disease with poor outcomes. Nanoparticle albumin-bound (nab)–paclitaxel may enhance the anticancer activity of atezolizumab.

METHODS

In this phase 3 trial, we randomly assigned (in a 1:1 ratio) patients with untreated metastatic triple-negative breast cancer to receive atezolizumab plus nab-paclitaxel or placebo plus nab-paclitaxel; patients continued the intervention until disease progression or an unacceptable level of toxic effects occurred. Stratification factors were the receipt or nonreceipt of neoadjuvant or adjuvant taxane therapy, the presence or absence of liver metastases at baseline, and programmed death ligand 1 (PD-L1) expression at baseline (positive vs. negative). The two primary end points were progression-free survival (in the intention-to-treat population and PD-L1–positive subgroup) and overall survival (tested in the intention-to-treat population; if the finding was significant, then it would be tested in the PD-L1–positive subgroup).

RESULTS

Each group included 451 patients (median follow-up, 12.9 months). In the intention-to-treat analysis, the median progression-free survival was 7.2 months with atezolizumab plus nab-paclitaxel, as compared with 5.5 months with placebo plus nab-paclitaxel (hazard ratio for progression or death, 0.80; 95% confidence interval [CI], 0.69 to 0.92; P=0.002); among patients with PD-L1–positive tumors, the median progression-free survival was 7.5 months and 5.0 months, respectively (hazard ratio, 0.62; 95% CI, 0.49 to 0.78; P<0.001). In the intention-to-treat analysis, the median overall survival was 21.3 months with atezolizumab plus nab-paclitaxel and 17.6 months with placebo plus nab-paclitaxel (hazard ratio for death, 0.84; 95% CI, 0.69 to 1.02; P=0.08); among patients with PD-L1–positive tumors, the median overall survival was 25.0 months and 15.5 months, respectively (hazard ratio, 0.62; 95% CI, 0.45 to 0.86). No new adverse effects were identified. Adverse events that led to the discontinuation of any agent occurred in 15.9% of the patients who received atezolizumab plus nab-paclitaxel and in 8.2% of those who received placebo plus nab-paclitaxel.

CONCLUSIONS

Atezolizumab plus nab-paclitaxel prolonged progression-free survival among patients with metastatic triple-negative breast cancer in both the intention-to-treat population and the PD-L1–positive subgroup. Adverse events were consistent with the known safety profiles of each agent. (Funded by F. Hoffmann–La Roche/Genentech; IMpassion130 ClinicalTrials.gov number, NCT02425891.)

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*A complete list of the IMpassion130 trial investigators is provided in the Supplementary Appendix, available at NEJM.org.

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Triple-negative breast cancer is the term used to describe breast cancers that lack estrogen- and progesterone-receptor expression and do not overexpress human epidermal growth factor receptor 2 (HER2). Patients with triple-negative breast cancer have poor clinical outcomes.[1,2] Chemotherapy remains the primary systemic treatment, with international guidelines supporting the use of single-agent taxanes or anthracyclines as first-line therapy.[3-5] Estimates of the median overall survival vary but remain approximately 18 months or less.[6-8] In patients with triple-negative breast cancer, the expression of programmed death ligand 1 (PD-L1) occurs mainly on tumor-infiltrating immune cells rather than on tumor cells[9,10] and can inhibit anticancer immune responses.[11,12] Thus, the inhibition of programmed death 1 (PD-1) and PD-L1 may be a useful treatment strategy.

Atezolizumab selectively targets PD-L1 to prevent interaction with the receptors PD-1 and B7-1 (a costimulatory cell-surface protein), reversing T-cell suppression. Single-agent atezolizumab is approved for the treatment of metastatic urothelial carcinoma and non–small-cell lung cancer (NSCLC).[13,14] Atezolizumab has also been shown to have a good safety profile and clinical activity in patients with other solid tumors,[12] including triple-negative breast cancer.[15] Chemotherapy may enhance tumor-antigen release and antitumor responses to immune checkpoint inhibition. Taxanes in particular may additionally activate toll-like receptor activity and promote dendritic-cell activity.[16] Nanoparticle albumin-bound (nab)–paclitaxel was selected as a partner because, at the time that the trial was designed, the glucocorticoid premedication that is required with solvent-based paclitaxel (per the label) had been hypothesized to affect immunotherapy activity.[17]

The safety profile and activity of atezolizumab with nab-paclitaxel have been shown in patients with advanced NSCLC (in phase 1b and 3 studies) and those with triple-negative breast cancer (in a phase 1b study).[18-20] The phase 1b study involving patients with breast cancer showed that atezolizumab-mediated immunodynamic effects were not abrogated with concurrent administration of nab-paclitaxel.[20] Here we report the results of the IMpassion130 trial, an international, randomized, double-blind, placebo-controlled trial of first-line atezolizumab plus nab-paclitaxel, as compared with placebo plus nab-paclitaxel, in patients with locally advanced or metastatic triple-negative breast cancer.

Methods

Oversight

The trial sponsor, F. Hoffmann–La Roche/Genentech, provided atezolizumab and placebo and collaborated with an academic steering committee regarding the trial design and data collection, analysis, and interpretation. Celgene provided nab-paclitaxel; the company had no role in the trial design or data collection or analysis but did review the manuscript. The trial was conducted according to the guidelines of Good Clinical Practice and the principles of the Declaration of Helsinki. All the patients provided written informed consent. Protocol approval was obtained from independent review boards or ethics committees at each site. An independent data and safety monitoring committee reviewed unblinded safety and trial-conduct data every 6 months. All the authors verify that the trial was conducted according to the protocol and vouch for the accuracy and completeness of the data. All the drafts of the manuscript were prepared by the authors, with editorial assistance from professional medical writers funded by the sponsor.

Patients

Eligible patients were 18 years of age or older and had metastatic or unresectable locally advanced, histologically documented triple-negative breast cancer (lack of estrogen- and progesterone-receptor expression and no overexpression of HER2, according to American Society of Clinical Oncology–College of American Pathologists guideline criteria, as evaluated by local institutions).[21,22] Patients had a representative tumor specimen (formalin-fixed, paraffin-embedded archival or fresh pretreatment relapsed-disease tumor tissue) that could be evaluated for prospective central testing of PD-L1 expression (SP142 PD-L1 immunohistochemical assay, Ventana Medical Systems). Patients were eligible to receive taxane monotherapy and had received

no previous chemotherapy or targeted therapy for metastatic triple-negative breast cancer. Radiation therapy and previous chemotherapy (including taxanes) in the context of curative therapy (if treatment was completed ≥12 months before randomization) were allowed. Measurable disease according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1, an Eastern Cooperative Oncology Group performance-status score of 0 or 1 (on a 5-point scale, with higher numbers indicating greater disability), and adequate hematologic and organ function were also required.

Key exclusion criteria were untreated central nervous system (CNS) disease (patients with asymptomatic treated CNS metastases were permitted), a history of autoimmune disease, previous immune checkpoint–targeting therapies, recent treatment with a systemic immunostimulatory agent (received within the previous 4 weeks or 5 half-lives of the drug, whichever was shorter), and the use of systemic glucocorticoid or immunosuppressive medications. The full eligibility criteria (including exceptions to exclusions regarding glucocorticoid therapy) are provided in the protocol, available with the full text of this article at NEJM.org.

TRIAL DESIGN AND PROCEDURES

Patients were randomly assigned in a 1:1 ratio, with the use of a permuted block method and an interactive voice–Web response system, to receive atezolizumab plus nab-paclitaxel or placebo plus nab-paclitaxel. Stratification factors were the presence or absence of liver metastases, use or nonuse of neoadjuvant or adjuvant taxane treatment, and PD-L1 expression on tumor-infiltrating immune cells as a percentage of tumor area (<1% [PD-L1 negative] vs. ≥1% [PD-L1 positive]) according to immunohistochemical testing. Scoring regarding PD-L1 expression has been described previously[15,23] (see the Supplementary Methods section in the Supplementary Appendix, available at NEJM.org). The trial sponsor, site personnel, and patients were unaware of patients' PD-L1 status.

Patients received atezolizumab at a dose of 840 mg or placebo, administered intravenously, on days 1 and 15 and received nab-paclitaxel at a dose of 100 mg per square meter of body-surface area, administered intravenously, on days 1, 8, and 15 of every 28-day cycle. Patients received the trial intervention until progression, according to RECIST, version 1.1, or an unacceptable level of toxic effects occurred. In the absence of toxic effects, nab-paclitaxel was to be administered for six cycles or more. In the absence of disease progression, the discontinuation of atezolizumab or placebo or of nab-paclitaxel (owing to toxic effects) could occur independently. Dose reductions of atezolizumab or placebo were not permitted; prespecified modifications of the nab-paclitaxel dose were permitted in order to manage the toxic effects of chemotherapy. Tumor imaging occurred at baseline and every 8 weeks for 12 months and then every 12 weeks. Follow-up for survival occurred every 3 months after the discontinuation of the intervention.

The two primary efficacy end points, investigator-assessed progression-free and overall survival, were evaluated in both the intention-to-treat population, which included all the patients who had undergone randomization, and the subgroup of patients with PD-L1–positive tumors (expression on tumor-infiltrating immune cells ≥1% [PD-L1–positive subgroup]). Key secondary efficacy end points were the rate and duration of objective response, as assessed by the investigators according to RECIST, version 1.1. Safety was evaluated according to the Common Terminology Criteria for Adverse Events, version 4.0, of the National Cancer Institute. Additional details regarding the trial design, including key protocol amendments, are available with the protocol.

STATISTICAL ANALYSIS

The trial was initially designed to randomly assign approximately 350 patients for the evaluation of a primary end point of progression-free survival. During the course of the trial, enrollment was expanded to 900 patients to accommodate the addition of overall survival as a second primary end point. Definitive analyses of progression-free survival in the intention-to-treat population and in the PD-L1–positive subgroup were planned, at which time the first interim analysis of overall survival was also planned. The type I error (0.05) was controlled

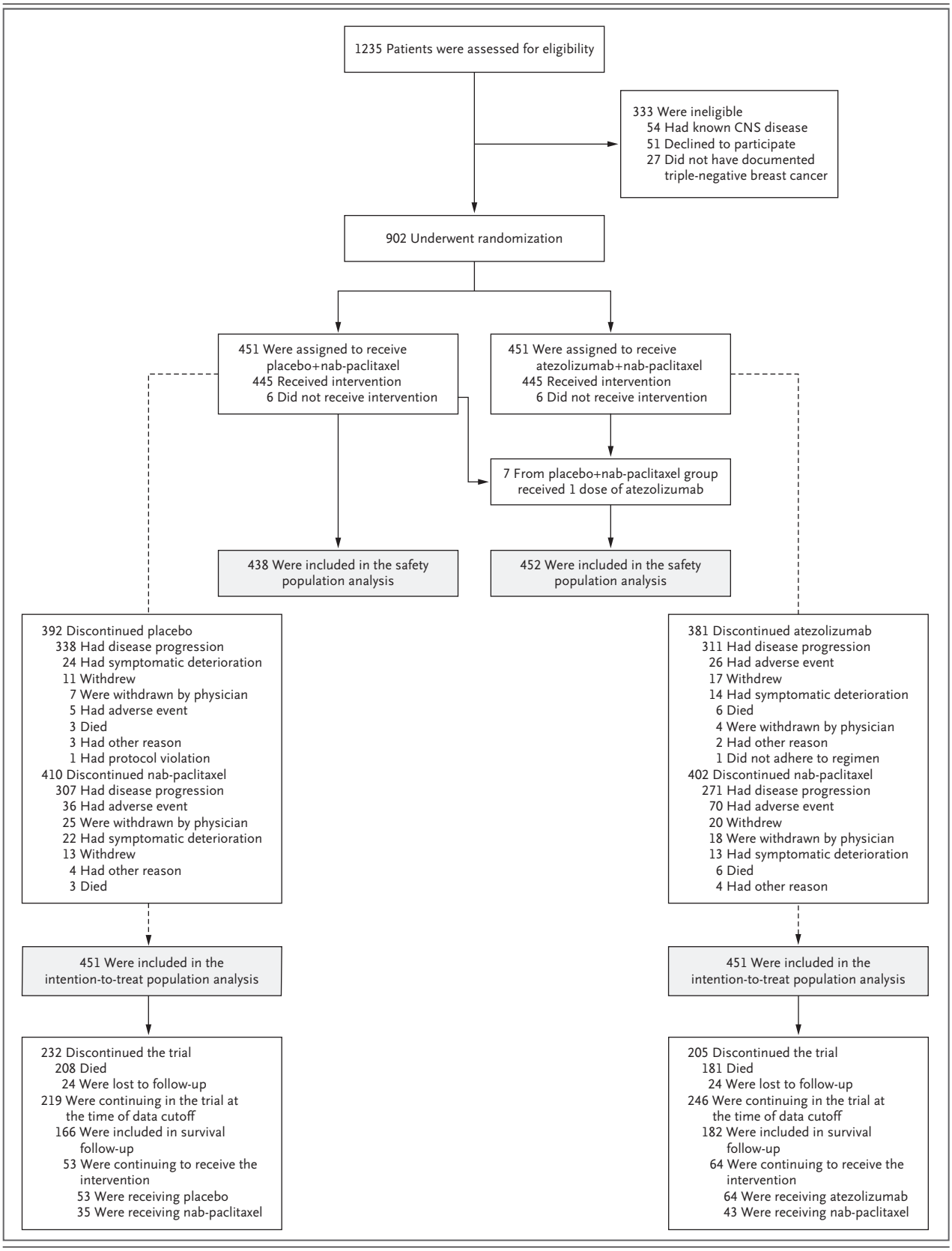


Figure 1 (facing page). Randomization, Trial Populations, and Follow-up.

Triple-negative breast cancer is breast cancer that does not express estrogen, progesterone, or human epidermal growth factor 2 (HER2) receptors. Patients may have been ineligible for inclusion in the trial for multiple reasons; the most common reasons are shown. The numbers of patients who were receiving the intervention on the data-cutoff date (April 17, 2018) are shown. CNS denotes central nervous system.

and split between the analyses of progression-free survival (0.01) and overall survival (0.04), with hierarchical testing for overall survival first in the intention-to-treat population and then in the PD-L1–positive subgroup (see the Supplementary Methods section in the Supplementary Appendix). The trial had 95% power for the primary analysis of progression-free survival among patients in the intention-to-treat population and 88% power for the analysis of overall survival.

Progression-free survival and overall survival were compared between the trial groups with the use of a stratified log-rank test, and hazard ratios for disease progression and death were estimated with the use of a stratified Cox proportional-hazards model. Kaplan–Meier analysis was applied to progression-free survival and overall survival, and the Brookmeyer–Crowley method was used to construct the 95% confidence interval for each median duration. Similar methods were applied to the duration of response for descriptive purposes, and the analysis was not stratified. The comparisons of the response rate between groups were made with the use of the stratified Cochran–Mantel–Haenszel test.

RESULTS

PATIENTS AND TRIAL INTERVENTIONS

From June 2015 through May 2017, a total of 902 patients (intention-to-treat population) were enrolled at 246 sites in 41 countries; a total of 348 patients (38.6%) were enrolled in Europe, 230 (25.5%) in the United States and Canada, 145 (16.1%) in Asia, 137 (15.2%) in Latin America, and 42 (4.7%) in Australia (see the Supplementary Appendix). A total of 451 patients were randomly assigned to each group (Fig. 1). The PD-L1–positive subgroup included 369 patients (40.9%; 185 patients in the atezolizumab–nab-paclitaxel group and 184 in the placebo–nab-paclitaxel group).

Overall, the characteristics of the patients at baseline were well balanced between the two trial groups, and the baseline characteristics of the patients in the PD-L1–positive subgroup appeared to be generally representative of the intention-to-treat population (Table 1). Approximately half the patients had been treated with neoadjuvant or adjuvant taxane or anthracycline chemotherapy (Table 1).

The numbers of patients who were still receiving the trial intervention at the time of analysis (data cutoff, April 17, 2018) are shown in Figure 1. For patients in the atezolizumab–nab-paclitaxel group, the median duration of atezolizumab treatment was 24.1 weeks and the median duration of nab-paclitaxel treatment was 22.1 weeks. For patients in the placebo–nab-paclitaxel group, the median duration that placebo was received was 22.1 weeks and the median duration of nab-paclitaxel treatment was 21.8 weeks. The mean (±SD) cumulative dose of nab-paclitaxel was 1980.0±1303.1 mg per square meter in the atezolizumab–nab-paclitaxel group and 1764.4±1238.3 mg per square meter in the placebo–nab-paclitaxel group. (Additional exposure and dose-intensity data are provided in Table S1 in the Supplementary Appendix.) Palliative radiation therapy was administered in 32 patients (7.1%) in the atezolizumab–nab-paclitaxel group and in 24 (5.3%) in the placebo–nab-paclitaxel group.

FINAL PROGRESSION-FREE SURVIVAL ANALYSIS

At the time of data cutoff, the median follow-up was 12.9 months in the intention-to-treat population (13.0 months in the atezolizumab–nab-paclitaxel group and 12.5 months in the placebo–nab-paclitaxel group). A total of 358 patients (79.4%) in the atezolizumab–nab-paclitaxel group and 378 (83.8%) in the placebo–nab-paclitaxel group had disease progression or died. Progression-free survival was significantly longer in the atezolizumab–nab-paclitaxel group than in the placebo–nab-paclitaxel group (median, 7.2 months vs. 5.5 months; stratified hazard ratio for progression or death, 0.80; 95% confidence interval [CI], 0.69 to 0.92; P=0.002) (Fig. 2A).

In the PD-L1–positive subgroup, 138 of 185 patients (74.6%) in the atezolizumab–nab-pacli-

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Intention-to-Treat Population		PD-L1–Positive Subgroup	
	Atezolizumab + Nab-Paclitaxel (N = 451)	Placebo + Nab-Paclitaxel (N = 451)	Atezolizumab + Nab-Paclitaxel (N = 185)	Placebo + Nab-Paclitaxel (N = 184)
Age				
Median (range) — yr	55 (20–82)	56 (26–86)	53 (26–82)	53 (28–85)
Distribution — no. (%)				
18–40 yr	63 (14.0)	51 (11.3)	31 (16.8)	24 (13.0)
41–64 yr	284 (63.0)	285 (63.2)	111 (60.0)	117 (63.6)
≥65 yr	104 (23.1)	115 (25.5)	43 (23.2)	43 (23.4)
Female sex — no. (%)	448 (99.3)	450 (99.8)	184 (99.5)	184 (100)
Race or ethnic group — no. (%)†				
White	308 (68.3)	301 (66.7)	125 (67.6)	129 (70.1)
Asian	85 (18.8)	76 (16.9)	38 (20.5)	28 (15.2)
Black	26 (5.8)	33 (7.3)	9 (4.9)	14 (7.6)
Native American	17 (3.8)	23 (5.1)	8 (4.3)	9 (4.9)
Hawaiian or other Pacific Islander	1 (0.2)	0	0	0
Multiple	2 (0.4)	3 (0.7)	0	0
Unknown	12 (2.7)	15 (3.3)	5 (2.7)	4 (2.2)
ECOG performance-status score — no./total no. (%)‡				
0	256/450 (56.9)	270/450 (60.0)	107/185 (57.8)	112/184 (60.9)
1	193/450 (42.9)	179/450 (39.8)	77/185 (41.6)	72/184 (39.1)
2	1/450 (0.2)	1/450 (0.2)	1/185 (0.5)	0
Metastatic disease — no./total no. (%)	404/450 (89.8)	408/450 (90.7)	162/185 (87.6)	159/183 (86.9)
No. of sites of metastatic disease — no./total no. (%)				
0–3	332/450 (73.8)	341/449 (75.9)	149/185 (80.5)	140/183 (76.5)
≥4	118/450 (26.2)	108/449 (24.1)	36/185 (19.5)	43/183 (23.5)
Site of metastatic disease				
Liver — no. (%)§	126 (27.9)	118 (26.2)	44 (23.8)	39 (21.2)
Bone — no. (%)	145 (32.2)	141 (31.3)	54 (29.2)	49 (26.6)
Brain — no. (%)	30 (6.7)	31 (6.9)	15 (8.1)	11 (6.0)
Lung — no. (%)	226 (50.1)	242 (53.7)	86 (46.5)	98 (53.3)
Lymph node only — no./total no. (%)	33/450 (7.3)	23/449 (5.1)	18/185 (9.7)	13/183 (7.1)
Previous therapy — no. (%)				
Neoadjuvant or adjuvant therapy	284 (63.0)	286 (63.4)	125 (67.6)	117 (63.6)
Taxane§	231 (51.2)	230 (51.0)	96 (51.9)	94 (51.1)
Anthracycline	243 (53.9)	242 (53.7)	109 (58.9)	101 (54.9)

* The summary statistics are based on the full population indicated in the column heading. If data regarding the baseline characteristic were not available for all patients, the total number of patients who could be evaluated for this characteristic is presented. The characteristics of the patients at baseline were well balanced between the two trial groups, and the baseline characteristics of the patients in the PD-L1–positive subgroup appeared to be generally representative of the intention-to-treat population. Percentages may not total 100 because of rounding. Nab-paclitaxel denotes nanoparticle albumin-bound paclitaxel.

† Race and ethnic group were reported by the patients.

‡ Eastern Cooperative Oncology Group (ECOG) performance-status scores are assessed on a 5-point scale, with higher numbers indicating greater disability. A score of 0 indicates no disability, a score of 1 that the patient is ambulatory and capable of light work but restricted in physically strenuous activity, and a score of 2 that the patient is ambulatory, awake and active more than 50% of waking hours, and capable of all self-care but unable to work. Two patients were enrolled with an ECOG performance-status score of 1 but had a score of 2 at the start of the trial intervention.

§ Data were from the case-report form.

taxel group and 157 of 184 patients (85.3%) in the placebo–nab-paclitaxel group had disease progression or died. A significantly lower risk of progression or death was observed with atezolizumab–nab-paclitaxel than with placebo–nab-paclitaxel (median progression-free survival, 7.5 months vs. 5.0 months; stratified hazard ratio for progression or death, 0.62; 95% CI, 0.49 to 0.78; P<0.001) (Fig. 2B). At 1 year, the rate of progression-free survival was higher in the atezolizumab–nab-paclitaxel group than in the placebo–nab-paclitaxel group (29.1% vs. 16.4%).

In sensitivity analyses, the assessments of progression-free survival were confirmed by means of central review (stratified hazard ratio for progression or death, 0.78 [95% CI, 0.67 to 0.91] in the intention-to-treat population and 0.63 [95% CI, 0.49 to 0.81] in the PD-L1–positive subgroup). The effects of treatment on progression-free survival in key subgroups are shown in Figure 3. The median progression-free survival was longer with atezolizumab–nab-paclitaxel than with placebo–nab-paclitaxel in the majority of subgroups, including subgroups that were defined on the basis of trial stratification factors and other baseline characteristics, in both the intention-to-treat population and the PD-L1–positive subgroup (Fig. S1 in the Supplementary Appendix).

INTERIM OVERALL SURVIVAL ANALYSIS

At the time of the data cutoff and first interim analysis of overall survival in the intention-to-treat population, 181 of 451 patients (40.1%) in the atezolizumab–nab-paclitaxel group and 208 of 451 (46.1%) in the placebo–nab-paclitaxel group had died. The median overall survival was 21.3 months in the atezolizumab–nab-paclitaxel group and 17.6 months in the placebo–nab-paclitaxel group (stratified hazard ratio for death, 0.84; 95% CI, 0.69 to 1.02; P=0.08 [not significant]) (Fig. 2C).

In the PD-L1–positive subgroup, 64 of 185 patients (34.6%) in the atezolizumab–nab-paclitaxel group and 88 of 184 (47.8%) in the placebo–nab-paclitaxel group died. Because of the hierarchical statistical analysis procedure, formal testing of overall survival in the PD-L1–positive subgroup was not conducted at this interim analysis. However, Kaplan–Meier analyses showed a median overall survival of 25.0 months in the atezolizumab–nab-paclitaxel group and 15.5 months in the placebo–nab-paclitaxel group (stratified hazard ratio for death, 0.62; 95% CI, 0.45 to 0.86) (Fig. 2D).

Subsequent anticancer therapy was administered to 242 patients (53.7%) in the atezolizumab–nab-paclitaxel group and to 272 (60.3%) in the placebo–nab-paclitaxel group and was generally balanced between the two groups. Most patients received chemotherapy during follow-up, and only a minority (<4%) received immunotherapy (Table S2 in the Supplementary Appendix).

RESPONSE RATE AND DURATION OUTCOMES

In the intention-to-treat population, the rate of objective response, as assessed by the investigator, was 56.0% in the atezolizumab–nab-paclitaxel group, as compared with 45.9% in the placebo–nab-paclitaxel group (Table 2). A total of 7.1% of the patients in the atezolizumab–nab-paclitaxel group had a complete response, as compared with 1.6% of those in the placebo–nab-paclitaxel group. In the PD-L1–positive subgroup, the response rate was 58.9% with atezolizumab–nab-paclitaxel and 42.6% with placebo–nab-paclitaxel; a total of 10.3% of the patients in the atezolizumab–nab-paclitaxel group had a complete response, as compared with 1.1% of those in the placebo–nab-paclitaxel group (Table 2).

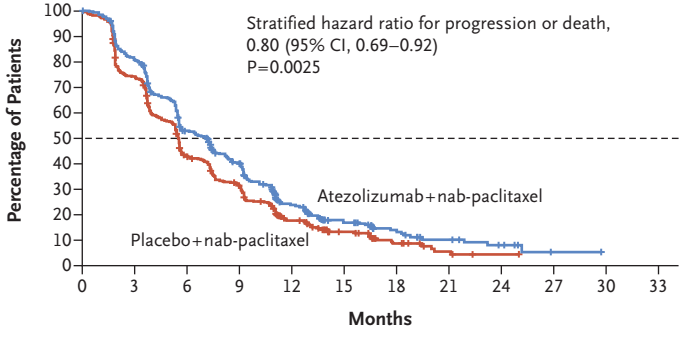
In the intention-to-treat population, the median duration of response was 7.4 months in the atezolizumab–nab-paclitaxel group and 5.6 months in the placebo–nab-paclitaxel group. In the PD-L1–positive subgroup, the median duration of response was 8.5 months with atezolizumab–nab-paclitaxel and 5.5 months with placebo–nab-paclitaxel (Table 2, and Fig. S2 in the Supplementary Appendix).

SAFETY

Among patients in the safety population, adverse events, regardless of attribution, occurred in 99.3% of 452 patients in the atezolizumab–nab-paclitaxel group and in 97.9% of 438 patients in the placebo–nab-paclitaxel group (Table 3, and Tables S3 and S4 in the Supplementary Appendix). The most common adverse events were similar in the two groups (Table 3, and Table S4 in the Supplementary Appendix), with no new adverse events identified. Alopecia was the most common event in each group. The fre-

A Progression-free Survival in the Intention-to-Treat Population

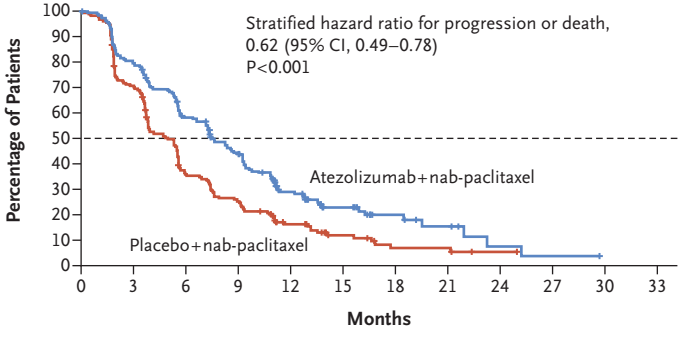
	No. of Events/ No. of Patients	Median Progression-free Survival (95% CI)	1-Yr Rate of Progression-free Survival (95% CI)
		mo	%
Atezolizumab+Nab-Paclitaxel	358/451	7.2 (5.6–7.5)	23.7 (19.6–27.9)
Placebo+Nab-Paclitaxel	378/451	5.5 (5.3–5.6)	17.7 (14.0–21.4)



No. at Risk												
Atezolizumab+ nab-paclitaxel	451	360	226	164	77	34	20	11	6	1	NE	NE
Placebo+ nab-paclitaxel	451	327	183	130	57	29	13	5	1	NE	NE	NE

B Progression-free Survival in the PD-L1–Positive Subgroup

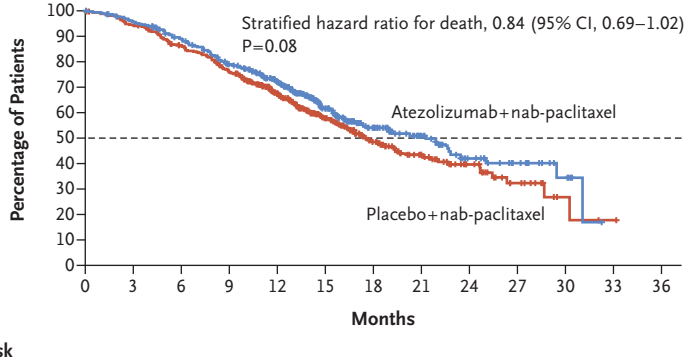
	No. of Events/ No. of Patients	Median Progression-free Survival (95% CI)	1-Yr Rate of Progression-free Survival (95% CI)
		mo	%
Atezolizumab+Nab-Paclitaxel	138/185	7.5 (6.7–9.2)	29.1 (22.2–36.1)
Placebo+Nab-Paclitaxel	157/184	5.0 (3.8–5.6)	16.4 (10.8–22.0)



No. at Risk												
Atezolizumab+ nab-paclitaxel	185	146	104	75	38	19	10	6	2	1	NE	NE
Placebo+ nab-paclitaxel	184	127	62	44	22	11	5	5	1	NE	NE	NE

C Overall Survival in the Intention-to-Treat Population

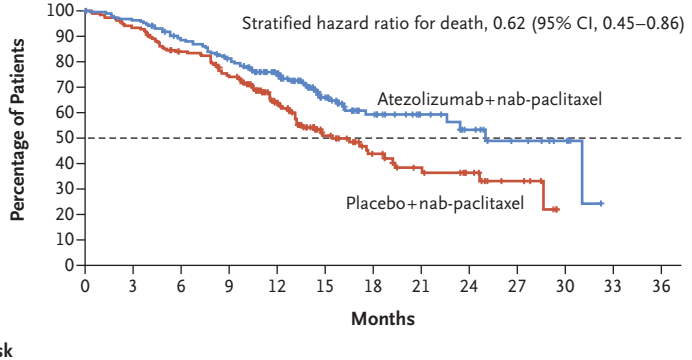
	No. of Events/ No. of Patients	Median Overall Survival (95% CI)	2-Yr Rate of Progression-free Survival (95% CI)
		mo	%
Atezolizumab+Nab-Paclitaxel	181/451	21.3 (17.3–23.4)	42.1 (34.3–49.9)
Placebo+Nab-Paclitaxel	208/451	17.6 (15.9–20.0)	39.7 (33.2–46.3)



No. at Risk												
Atezolizumab+ nab-paclitaxel	451	426	389	337	271	146	82	48	26	15	6	NE	NE
Placebo+ nab-paclitaxel	451	419	375	328	246	145	89	52	27	12	3	1	NE

D Overall Survival in the PD-L1–Positive Subgroup

	No. of Events/ No. of Patients	Median Overall Survival (95% CI)	2-Yr Rate of Progression-free Survival (95% CI)
		mo	%
Atezolizumab+Nab-Paclitaxel	64/185	25.0 (22.6–NE)	53.5 (42.3–64.6)
Placebo+Nab-Paclitaxel	88/184	15.5 (13.1–19.4)	36.6 (26.4–46.7)



No. at Risk												
Atezolizumab+ nab-paclitaxel	185	177	160	142	113	61	36	22	15	9	5	NE	NE
Placebo+ nab-paclitaxel	184	170	147	129	89	44	27	19	13	6	NE	NE	NE

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Figure 2 (facing page). Kaplan–Meier Analysis of Progression-free Survival and Overall Survival.

Shown are Kaplan–Meier estimates of progression-free-survival, according to the Response Evaluation Criteria in Solid Tumors, version 1.1, as assessed by the investigators, among patients in the intention-to-treat population (Panel A) and among patients whose tumors were positive for programmed death ligand 1 (PD-L1) expression (≥1% PD-L1 expression on tumor-infiltrating immune cells [PD-L1–positive subgroup]) (Panel B). Also shown are the Kaplan–Meier estimates of overall survival in the intention-to-treat population (Panel C) and the PD-L1–positive subgroup (Panel D). Stratified hazard ratios for disease progression or death (in analyses of progression-free survival) or for death (in analyses of overall survival) are reported along with P values. Tick marks indicate censored data, and the dashed line indicates the median. NE denotes could not be estimated.

quencies of nausea, cough, neutropenia, pyrexia, and hypothyroidism were at least 5 percentage points greater in the atezolizumab–nab-paclitaxel group than in the placebo–nab-paclitaxel group. The rate of adverse events of grade 3 or 4 was 48.7% in the atezolizumab–nab-paclitaxel group and 42.2% in the placebo–nab-paclitaxel group, and the most common events in these groups (as assessed by the investigator) were neutropenia, decreased neutrophil count, peripheral neuropathy, fatigue, and anemia (Table 3). The frequency of peripheral neuropathy of grade 3 or 4 was higher in the atezolizumab–nab-paclitaxel group (25 patients [5.5%]) than in the placebo–nab-paclitaxel group (12 patients [2.7%]). Serious adverse events occurred in 103 patients (22.8%) in the atezolizumab–nab-paclitaxel group and in 80 (18.3%) in the placebo–nab-paclitaxel group (Table S3 in the Supplementary Appendix).

A total of 259 patients (57.3%) in the atezolizumab–nab-paclitaxel group and 183 (41.8%) in the placebo–nab-paclitaxel group had an adverse event of special interest, which was suggestive of a potential immune-related cause (Tables S3 and S5 in the Supplementary Appendix). Grade 3 or 4 adverse events of special interest occurred in 34 patients (7.5%) in the atezolizumab–nab-paclitaxel group and in 19 (4.3%) in the placebo–nab-paclitaxel group. Two grade 5 adverse events of special interest occurred (autoimmune hepatitis in 1 patient in the atezolizumab–nab-paclitaxel group and hepatic failure in 1 patient in the placebo–nab-paclitaxel group). Immune-related hypothyroidism occurred at a higher frequency in the atezolizumab–nab-paclitaxel group than in the placebo–nab-paclitaxel group (17.3% vs. 4.3%); all the events were of grade 1 or 2, and none led to the discontinuation of the trial regimen. Pneumonitis was infrequent, occurring in 3.1% of the patients in the atezolizumab–nab-paclitaxel group and in 0.2% of those in the placebo–nab-paclitaxel group; only 1 patient (in the atezolizumab–nab-paclitaxel group) had an event of grade 3 or 4.

Adverse events that were attributed to the trial regimen by the investigators are reported in Table S6 in the Supplementary Appendix. Fatal adverse events occurred in 6 patients (1.3%) in the atezolizumab–nab-paclitaxel group and in 3 (0.7%) in the placebo–nab-paclitaxel group (Table S3 in the Supplementary Appendix); three deaths in the atezolizumab–nab-paclitaxel group (from autoimmune hepatitis, mucosal inflammation, and septic shock, in 1 patient each) and one death in the placebo–nab-paclitaxel group (from hepatic failure) were considered by the investigators to be related to the trial regimen (Table S6 in the Supplementary Appendix). Adverse events that led to withdrawal of any agent occurred in 15.9% of the patients who received atezolizumab–nab-paclitaxel group and in 8.2% of those who received placebo–nab-paclitaxel group. A total of 29 patients (6.4%) had adverse events that led to the discontinuation of atezolizumab, and 6 (1.4%) had adverse events that led to the discontinuation of placebo (Table S3 in the Supplementary Appendix).

DISCUSSION

We report here the primary results from IMpassion130, a phase 3 trial of an anti–PD-L1 or anti–PD-1 antibody in patients with metastatic triple-negative breast cancer. Administered as first-line treatment, the combination of atezolizumab with nab-paclitaxel led to significantly longer progression-free survival than was seen with placebo plus nab-paclitaxel in both the intention-to-treat population and the subgroup of patients with PD-L1–positive tumors. Although the boundary for declaring a statistical advantage for atezolizumab–nab-paclitaxel in the intention-to-treat population at

Subgroup	No. of Patients	Median Progression-free Survival		Hazard Ratio for Progression or Death (95% CI)
		Atezolizumab+ Nab-Paclitaxel	Placebo+ Nab-Paclitaxel	
		mo		
All	902	7.2	5.5	0.81 (0.70–0.93)
PD-L1 status				
Positive	369	7.5	5.0	0.64 (0.51–0.80)
Negative	533	5.6	5.6	0.95 (0.79–1.15)
Age				
18–40 yr	114	3.7	3.6	0.79 (0.53–1.16)
41–64 yr	569	6.7	5.5	0.84 (0.70–1.01)
≥65 yr	219	9.1	6.2	0.69 (0.51–0.94)
Race				
White	609	7.2	5.5	0.78 (0.65–0.93)
Asian	161	7.2	5.5	0.76 (0.54–1.08)
Black	59	6.8	3.9	0.79 (0.44–1.42)
ECOG performance-status score				
0	526	7.4	5.7	0.78 (0.64–0.94)
1	372	5.6	4.5	0.82 (0.66–1.03)
Baseline disease status				
Locally advanced	88	9.6	5.5	0.66 (0.40–1.09)
Metastatic	812	6.6	5.5	0.82 (0.71–0.96)
No. of metastatic sites				
0–3	673	8.2	5.6	0.76 (0.64–0.91)
>3	226	4.0	3.7	0.89 (0.67–1.17)
Brain metastases				
Yes	61	4.9	4.4	0.86 (0.50–1.49)
No	841	7.2	5.5	0.80 (0.69–0.93)
Bone metastases				
Yes	286	5.7	5.2	1.02 (0.79–1.31)
No	616	7.2	5.5	0.73 (0.61–0.87)
Liver metastases				
Yes	244	5.3	3.7	0.80 (0.62–1.04)
No	658	7.5	5.6	0.79 (0.66–0.94)
Lung metastases				
Yes	468	5.7	5.5	0.87 (0.72–1.07)
No	434	8.2	5.5	0.74 (0.60–0.91)
Lymph node–only disease				
Yes	56	12.7	5.5	0.44 (0.24–0.83)
No	843	6.4	5.5	0.84 (0.73–0.98)
Previous neoadjuvant or adjuvant chemotherapy				
Yes	570	7.2	5.6	0.85 (0.71–1.03)
No	332	7.0	5.4	0.72 (0.57–0.92)
Previous taxane treatment				
Yes	461	5.7	5.5	0.80 (0.65–0.97)
No	441	7.2	5.5	0.81 (0.66–1.00)
Previous anthracycline treatment				
Yes	485	6.4	5.5	0.90 (0.74–1.10)
No	417	7.3	5.5	0.70 (0.56–0.87)

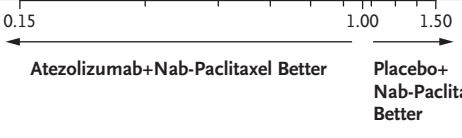

Figure 3 (facing page). Forest-Plot Analyses of Progression-free Survival in Key Subgroups.

An exploratory forest-plot analysis of progression-free survival according to baseline characteristics is shown for the intention-to-treat population. The dashed line represents the value in the intention-to-treat population. Unstratified hazard ratios for progression or death are shown. The analyses in the subgroups of race, disease status at baseline, and status of disease involving only the lymph nodes excluded patients with unknown or other values for the indicated categories. PD-L1–positive status was defined as PD-L1 expression on tumor-infiltrating immune cells of 1% or more. Race was reported by the patients. Eastern Cooperative Oncology Group (ECOG) performance-status scores are assessed on a 5-point scale, with higher numbers indicating greater disability; data are not shown for two patients with an ECOG performance-status score of 2 (a score of 2 indicates that the patient was ambulatory, awake and active >50% of waking hours, and capable of all self-care but unable to work).

this first interim analysis of overall survival was not crossed, and formal testing was not performed in the PD-L1–positive subgroup, numerical increases in median overall survival were observed in both the intention-to-treat population and the PD-L1–positive subgroup.

A clinical benefit with atezolizumab–nab-paclitaxel was particularly notable in the PD-L1–positive subgroup, as shown by a median progression-free survival that was significantly longer by 2.5 months (7.5 months with atezolizumab–nab-paclitaxel vs. 5.0 months with placebo–nab-paclitaxel; hazard ratio for progression or death, 0.62), by a median overall survival that was 10 months longer at this interim analysis (25.0 months vs. 15.5 months; hazard ratio for death, 0.62 [not statistically tested]), and a numerically higher objective response rate (58.9% vs. 42.6%). These data confirm phase 1 observations of improved outcomes in patients with high PD-L1 expression who were receiving treatment with atezolizumab,[15] pembrolizumab,[24] or avelumab.[25] As has been found regarding existing chemoimmunotherapy data from patients with other solid tumors who received atezolizumab plus chemotherapy[26] or pembrolizumab plus chemotherapy,[27] this trial establishes the benefit of adding a checkpoint inhibitor to standard chemotherapy for the first-line treatment of metastatic triple-negative breast cancer, with most of the benefit realized in the PD-L1–positive subgroup.

Combination therapy with atezolizumab plus nab-paclitaxel had a safety profile that was consistent with the known toxic effects of each agent. Consistent with observations from other atezolizumab–chemotherapy combination trials,[19,26] no new adverse-event signals were observed. The incidence of grade 3 or 4 adverse events of special interest was higher in the atezolizumab–nab-paclitaxel group than in the placebo–nab-paclitaxel group (7.5% vs. 4.3%). Discontinuations of either agent were higher in the atezolizumab–nab-paclitaxel group than in the placebo–nab-paclitaxel group; however, atezolizumab did not compromise the dose intensity of nab-paclitaxel.

This trial has a number of strengths. The trial groups were well balanced with respect to clinical characteristics at baseline and subsequent post-protocol therapies, which suggests that the observed improvements with regard to efficacy were not confounded by these factors. The unique spectrum of adverse events that are associated with immune checkpoint blockade does necessitate supplementary monitoring and treatment practices beyond those that are required for chemotherapy.[28] The trial showed activity for the combination of atezolizumab and nab-paclitaxel in patients with metastatic triple-negative breast cancer; it remains to be determined whether these findings extend to other chemoimmunotherapy combinations. Previous data have shown that tumor-infiltrating lymphocytes were associated with clinical benefit in patients with triple-negative breast cancer.[15,29-31] Similarly, improved clinical benefit was observed in patients with immune-enriched molecular subtypes of metastatic triple-negative breast cancer.[32]

A benefit with atezolizumab–nab-paclitaxel in patients with PD-L1–positive tumors that was shown in our trial provides evidence of the efficacy of immunotherapy in at least a subset of patients. It is important for patients' PD-L1

Table 2. Secondary Efficacy Outcomes.*

Variable	Atezolizumab + Nab-Paclitaxel	Placebo + Nab-Paclitaxel	Difference (95% CI)	P Value	Odds or Hazard Ratio (95% CI)
			percentage points		
Response					
Intention-to-treat population — no. of patients†	450	449			
Objective response					
No. of patients	252	206			
% of patients (95% CI)	56.0 (51.3–60.6)	45.9 (41.2–50.6)	10.1 (3.4–16.8)	0.002	1.52 (1.16–1.97)‡
Complete response					
No. of patients	32	7			
% of patients (95% CI)	7.1 (4.9–9.9)	1.6 (0.6–3.2)			
Partial response					
No. of patients	220	199			
% of patients (95% CI)	48.9 (44.2–53.6)	44.3 (39.7–49.1)			
Stable disease					
No. of patients	113	119			
% of patients (95% CI)	25.1 (21.2–29.4)	26.5 (22.5–30.8)			
Progressive disease					
No. of patients	69	104			
% of patients (95% CI)	15.3 (12.1–19.0)	23.2 (19.3–37.4)			
Patients who had missing data or could not be evaluated — no. (%)	16 (3.6)	20 (4.5)			
PD-L1–positive subgroup — no. of patients†	185	183			
Objective response					
No. of patients	109	78			
% of patients (95% CI)	58.9 (51.5–66.1)	42.6 (35.4–50.1)	16.3 (5.7–26.9)	0.002	1.96 (1.29–2.98)‡
Complete response					
No. of patients	19	2			
% of patients (95% CI)	10.3 (6.3–15.6)	1.1 (0.1–3.9)			
Partial response					
No. of patients	90	76			
% of patients (95% CI)	48.6 (41.3–56.1)	41.5 (34.3–49.0)			
Stable disease					
No. of patients	38	49			
% of patients (95% CI)	20.5 (15.0–27.1)	26.8 (20.5–33.8)			
Progressive disease					
No. of patients	31	46			
% of patients (95% CI)	16.8 (11.7–22.9)	25.1 (19.0–32.1)			
Patients who had missing data or could not be evaluated — no. (%)	7 (3.8)	10 (5.5)			
Duration of response§					
Intention-to-treat population — no. of patients	252	206			
Median duration of response (95% CI) — mo	7.4 (6.9–9.0)	5.6 (5.5–6.9)			0.78 (0.63–0.98)
Patients with ongoing response at data-cutoff date — no. (%)¶	78 (31.0)	52 (25.2)			
PD-L1–positive subgroup — no. of patients	109	78			
Median duration of response (95% CI) — mo	8.5 (7.3–9.7)	5.5 (3.7–7.1)			0.60 (0.43–0.86)
Patients with ongoing response at data-cutoff date — no. (%)¶	39 (35.8)	19 (24.4)			

* The objective response rate and duration of response were evaluated according to the Response Evaluation Criteria in Solid Tumors, version 1.1, as determined by the investigators. P values are for the difference analyses. Odds ratios are presented for analyses of response, and unstratified hazard ratios for progression or death, without P values, are shown for between-group analyses of duration of response.
† Data include only patients who had measurable disease at baseline.
‡ The result was not significant on the basis of an alpha level of 0.1%.
§ The duration of response was assessed among patients with an objective response.
¶ Patients who had an ongoing response at the data-cutoff date (April 17, 2018) were those who were alive and did not have progressive disease.

Table 3. Key Adverse Events.*

Event	Atezolizumab + Nab-Paclitaxel (N=452)		Placebo + Nab-Paclitaxel (N=438)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients with event (percent)			
Alopecia	255 (56.4)	3 (0.7)	252 (57.5)	1 (0.2)
Nausea	208 (46.0)	5 (1.1)	167 (38.1)	8 (1.8)
Cough	112 (24.8)	0	83 (18.9)	0
Peripheral neuropathy	98 (21.7)	25 (5.5)	97 (22.1)	12 (2.7)
Neutropenia	94 (20.8)	37 (8.2)	67 (15.3)	36 (8.2)
Pyrexia	85 (18.8)	3 (0.7)	47 (10.7)	0
Hypothyroidism	62 (13.7)	0	15 (3.4)	0

* Shown are the single most frequent adverse event of any grade, adverse events of any grade for which the rates differed by at least 5 percentage points between groups, and adverse events of grade 3 or 4 for which the rates differed by at least 2 percentage points between groups.

expression status on tumor-infiltrating immune cells to be taken into consideration to inform treatment choices for patients with metastatic triple-negative breast cancer.

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APPENDIX

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REFERENCES

1. den Brok WD, Speers CH, Gondara L, Baxter E, Tyldesley SK, Lohrisch CA. Survival with metastatic breast cancer based on initial presentation, de novo versus relapsed. Breast Cancer Res Treat 2017; 161:549-56.
2. Bonotto M, Gerratana L, Poletto E, et al. Measures of outcome in metastatic breast cancer: insights from a real-world scenario. Oncologist 2014;19:608-15.
3. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology — breast cancer. V1. 2018 (https://www.nccn.org/professionals/physician_gls/pdf/breast_blocks.pdf).
4. Cardoso F, Senkus E, Costa A, et al. 4th ESO-ESMO International Consensus Guidelines for advanced breast cancer (ABC 4). Ann Oncol 2018;29:1634-57.
5. Senkus E, Kyriakides S, Ohno S, et al. Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2015;26: Suppl 5:v8-v30.
6. Gobbini E, Ezzalfani M, Dieras V, et al. Time trends of overall survival among metastatic breast cancer patients in the real-life ESME cohort. Eur J Cancer 2018; 96:17-24.
7. Yardley DA, Coleman R, Conte P, et al. nab-Paclitaxel plus carboplatin or gemcitabine versus gemcitabine plus carboplatin as first-line treatment of patients with triple-negative metastatic breast cancer: results from the tnAcity trial. Ann Oncol 2018;29:1763-70.
8. Miles DW, Diéras V, Cortés J, Duenne AA, Yi J, O'Shaughnessy J. First-line bevacizumab in combination with chemotherapy for HER2-negative metastatic breast cancer: pooled and subgroup analyses of data from 2447 patients. Ann Oncol 2013; 24:2773-80.
9. Sabatier R, Finetti P, Mamessier E, et al. Prognostic and predictive value of PDL1 expression in breast cancer. Oncotarget 2015;6:5449-64.
10. Mittendorf EA, Philips AV, Meric-

Bernstam F, et al. PD-L1 expression in triple-negative breast cancer. Cancer Immunol Res 2014;2:361-70.
11. Chen DS, Mellman I. Oncology meets immunology: the cancer-immunity cycle. Immunity 2013;39:1-10.
12. Herbst RS, Soria JC, Kowanetz M, et al. Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients. Nature 2014;515:563-7.
13. Tecentriq (atezolizumab): summary of product characteristics. Welwyn Garden City, United Kingdom: Roche Registration, 2018.
14. Tecentriq (atezolizumab). South San Francisco, CA: Genentech, 2018 (package insert).
15. Emens LA, Cruz C, Eder JP, et al. Long-term clinical outcomes and biomarker analyses of atezolizumab therapy for patients with metastatic triple-negative breast cancer: a phase 1 study. JAMA Oncol 2018 September 13 (Epub ahead of print).
16. Emens LA, Middleton G. The interplay of immunotherapy and chemotherapy: harnessing potential synergies. Cancer Immunol Res 2015;3:436-43.
17. Soliman HH. *nab*-Paclitaxel as a potential partner with checkpoint inhibitors in solid tumors. Onco Targets Ther 2016;10:101-12.
18. Liu SV, Camidge DR, Gettinger SN, et al. Atezolizumab (atezo) plus platinum-based chemotherapy (chemo) in non-small cell lung cancer (NSCLC): update from a phase Ib study. J Clin Oncol 2017;35:Suppl:9092. abstract.
19. Jotte RM, Cappuzzo F, Vynnychenko I, et al. IMpower131: Primary PFS and safety analysis of a randomized phase III study of atezolizumab + carboplatin + paclitaxel or nab-paclitaxel vs carboplatin + nab-paclitaxel as 1L therapy in advanced squamous NSCLC. J Clin Oncol 2018;36:Suppl:LBA9000. abstract.
20. Adams S, Diamond JR, Hamilton E, et al. Atezolizumab plus nab-paclitaxel in the treatment of metastatic triple-negative breast cancer with 2-year survival follow-up: a phase 1b clinical trial. JAMA Oncol (in press).
21. Wolff AC, Hammond ME, Hicks DG, et al. Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline update. J Clin Oncol 2013;31:3997-4013.
22. Hammond ME, Hayes DF, Dowsett M, et al. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. J Clin Oncol 2010;28:2784-95.
23. Vennapusa B, Baker B, Kowanetz M, et al. Development of a PD-L1 complementary diagnostic immunohistochemistry assay (SP142) for atezolizumab. Appl Immunohistochem Mol Morphol 2018 January 16 (Epub ahead of print).
24. Adams S, Loi S, Toppmeyer D, et al. KEYNOTE-086 cohort B: pembrolizumab monotherapy for PD-L1–positive, previously untreated, metastatic triple-negative breast cancer (mTNBC). Cancer Res 2018;78:Suppl:PD6-10. abstract.
25. Dirix LY, Takacs I, Jerusalem G, et al. Avelumab, an anti-PD-L1 antibody, in patients with locally advanced or metastatic breast cancer: a phase 1b JAVELIN Solid Tumor study. Breast Cancer Res Treat 2018;167:671-86.
26. 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.
27. 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.
28. Brahmer JR, Lacchetti C, Schneider BJ, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol 2018;36:1714-68.
29. Loi S, Sirtaine N, Piette F, et al. Prognostic and predictive value of tumor-infiltrating lymphocytes in a phase III randomized adjuvant breast cancer trial in node-positive breast cancer comparing the addition of docetaxel to doxorubicin with doxorubicin-based chemotherapy: BIG 02-98. J Clin Oncol 2013;31:860-7.
30. Adams S, Gray RJ, Demaria S, et al. Prognostic value of tumor-infiltrating lymphocytes in triple-negative breast cancers from two phase III randomized adjuvant breast cancer trials: ECOG 2197 and ECOG 1199. J Clin Oncol 2014;32:2959-66.
31. Loi S, Adams S, Schmid P, et al. Relationship between tumor infiltrating lymphocyte (TIL) levels and response to pembrolizumab (pembro) in metastatic triple-negative breast cancer (mTNBC): results from KEYNOTE-086. Ann Oncol 2017;28:Suppl:LBA13. abstract.
32. Molinero L, Chang C, Udyavar A, et al. Molecular characterization of tumors from metastatic TNBC patients treated with atezolizumab (atezo). Cancer Res 2018;78:Suppl:P2-09-13. abstract.