ORIGINAL ARTICLE

Pembrolizumab plus Chemotherapy in Advanced Triple-Negative Breast Cancer

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ABSTRACT

BACKGROUND

In an interim analysis of this phase 3 trial, the addition of pembrolizumab to chemotherapy resulted in longer progression-free survival than chemotherapy alone among patients with advanced triple-negative breast cancer whose tumors expressed programmed death ligand 1 (PD-L1) with a combined positive score (CPS; the number of PD-L1–staining tumor cells, lymphocytes, and macrophages, divided by the total number of viable tumor cells, multiplied by 100) of 10 or more. The results of the final analysis of overall survival have not been reported.

METHODS

We randomly assigned patients with previously untreated locally recurrent inoperable or metastatic triple-negative breast cancer in a 2:1 ratio to receive pembrolizumab (200 mg) every 3 weeks plus the investigator's choice of chemotherapy (nanoparticle albumin-bound paclitaxel, paclitaxel, or gemcitabine–carboplatin) or placebo plus chemotherapy. The primary end points were progression-free survival (reported previously) and overall survival among patients whose tumors expressed PD-L1 with a CPS of 10 or more (the CPS-10 subgroup), among patients whose tumors expressed PD-L1 with a CPS of 1 or more (the CPS-1 subgroup), and in the intention-to-treat population. Safety was also assessed.

RESULTS

A total of 847 patients underwent randomization: 566 were assigned to the pembrolizumab–chemotherapy group, and 281 to the placebo–chemotherapy group. The median follow-up was 44.1 months. In the CPS-10 subgroup, the median overall survival was 23.0 months in the pembrolizumab–chemotherapy group and 16.1 months in the placebo–chemotherapy group (hazard ratio for death, 0.73; 95% confidence interval [CI], 0.55 to 0.95; two-sided P=0.0185 [criterion for significance met]); in the CPS-1 subgroup, the median overall survival was 17.6 and 16.0 months in the two groups, respectively (hazard ratio, 0.86; 95% CI, 0.72 to 1.04; two-sided P=0.1125 [not significant]); and in the intention-to-treat population, the median overall survival was 17.2 and 15.5 months, respectively (hazard ratio, 0.89; 95% CI, 0.76 to 1.05 [significance not tested]). Adverse events of grade 3, 4, or 5 that were related to the trial regimen occurred in 68.1% of the patients in the pembrolizumab–chemotherapy group and in 66.9% in the placebo–chemotherapy group, including death in 0.4% of the patients in the pembrolizumab–chemotherapy group and in no patients in the placebo–chemotherapy group.

CONCLUSIONS

Among patients with advanced triple-negative breast cancer whose tumors expressed PD-L1 with a CPS of 10 or more, the addition of pembrolizumab to chemotherapy resulted in significantly longer overall survival than chemotherapy alone. (Funded by Merck Sharp and Dohme; KEYNOTE-355 ClinicalTrials.gov number, NCT02819518.)

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*A complete list of investigators in the KEYNOTE-355 trial is provided in the Supplementary Appendix, available at NEJM.org.

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Triple-negative breast cancer is an aggressive breast cancer subtype that lacks expression of estrogen and progesterone receptors and amplification or overexpression of human epidermal growth factor receptor 2 (HER2).[1] The absence of these receptors renders endocrine and HER2-targeted therapies ineffective, leaving cytotoxic chemotherapy as the standard treatment option.[2] However, chemotherapy results in suboptimal antitumor response rates and short overall survival and response durations.[3-5] New therapeutic strategies to improve outcomes are needed.

Pembrolizumab monotherapy has shown durable antitumor activity in advanced triple-negative breast cancer,[6-9] particularly as first-line therapy, with improved clinical responses observed among patients with higher programmed death ligand 1 (PD-L1) expression.[9] The phase 3 KEYNOTE-355 trial examined whether the addition of pembrolizumab would enhance the antitumor activity of chemotherapy, including taxanes and a non-taxane platinum-based regimen, in patients with previously untreated locally recurrent inoperable or metastatic triple-negative breast cancer. Data from a prespecified interim analysis showed that pembrolizumab plus chemotherapy resulted in significantly longer progression-free survival than placebo plus chemotherapy among patients with a PD-L1 combined positive score (CPS) of 10 or more.[10] The CPS is the number of PD-L1–staining cells (tumor cells, lymphocytes, and macrophages) divided by the total number of viable tumor cells, multiplied by 100. Here, we present the results of the protocol-specified final analysis of the KEYNOTE-355 trial, which assessed overall survival among patients treated with pembrolizumab plus chemotherapy as compared with those who received placebo plus chemotherapy.

Methods

Patients

As described previously,[10] adult patients eligible for enrollment had centrally confirmed, locally recurrent inoperable or metastatic triple-negative breast cancer defined according to American Society of Clinical Oncology–College of American Pathologists guidelines[11]; measurable disease according to the Response Evaluation Criteria in Advanced Solid Tumors (RECIST), version 1.1[12]; an Eastern Cooperative Oncology Group performance-status score of 0 or 1 (on a 5-point scale, with higher numbers indicating greater disability)[13]; and adequate organ function. Patients who completed treatment for stage I, II, or III breast cancer were eligible if at least 6 months had elapsed between completion of treatment with curative intent (e.g., the date of primary breast tumor surgery or the date of the last administration of adjuvant chemotherapy, including capecitabine, whichever occurred last) and the first documented (by biopsy or imaging) local or distant disease recurrence. Adjuvant radiation therapy was acceptable for use during the 6-month interval requirement. Patients with new metastatic triple-negative breast cancer at initial diagnosis were also eligible for the trial. Patients who received taxane, gemcitabine, or platinum agents as neoadjuvant or adjuvant therapy could be treated with the same class of chemotherapy (a taxane or gemcitabine–carboplatin) if at least 12 months had elapsed between the completion of treatment with curative intent and the first documented local or distant disease recurrence.

Exclusion criteria were treatment with an investigational agent within 4 weeks before randomization or previous therapy that targeted programmed death 1, PD-L1, programmed death ligand 2, or an agent directed at another coinhibitory T-cell receptor; active autoimmune disease warranting systemic treatment within the previous 2 years; immunosuppressive therapy or diagnosis of immunodeficiency within the previous 1 week; active central nervous system metastases or carcinomatous meningitis (previously treated stable brain metastases were permitted); a history of noninfectious pneumonitis warranting glucocorticoids or current pneumonitis; or any active infection warranting systemic therapy.

Trial Design and Interventions

In this phase 3, randomized, double-blind, international trial, eligible patients were randomly assigned in a 2:1 ratio to receive pembrolizumab (200 mg every 3 weeks) plus chemotherapy (investigator's choice of nanoparticle albumin-bound [nab]–paclitaxel at a dose of 100 mg per square meter of body-surface area on days 1, 8, and 15 of every 28-day cycle; paclitaxel at a dose of 90 mg per square meter on days 1, 8, and 15 of every 28-day cycle; or gemcitabine at a dose of 1000 mg per square meter plus carboplatin [area

under the concentration–time curve, 2] on days 1 and 8 of every 21-day cycle) or placebo plus chemotherapy for up to 35 intravenous administrations of pembrolizumab or placebo (chemotherapy was continued at the investigator's discretion) or until confirmed disease progression or unacceptable toxic effects had occurred or withdrawal of consent or physician's decision. Chemotherapy was administered on an open-label basis. A central interactive voice-response system with an integrated Web-response system was used for randomization. Stratification factors were the type of chemotherapy received during the trial (a taxane or gemcitabine–carboplatin), tumor PD-L1 expression (CPS ≥1 or CPS <1), and previous treatment with the same class of neoadjuvant or adjuvant chemotherapy as that received during the trial (yes or no).

ASSESSMENTS

As described previously,[10] response was assessed by imaging every 8 weeks until week 24, then every 9 weeks during the first year, and every 12 weeks thereafter on the basis of RECIST, version 1.1,[12] by blinded independent central review. After verified disease progression or initiation of new anticancer therapy, patients were monitored for survival status every 12 weeks. Baseline PD-L1 expression in archival or newly obtained formalin-fixed tumor samples was assessed at a central laboratory with the use of PD-L1 IHC 22C3 pharmDx (Agilent Technologies) and characterized according to the CPS.

Adverse events were monitored throughout the trial and for 30 days (90 days for serious adverse events) after discontinuation of the trial regimen and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.[14] Immune-mediated adverse events were determined on the basis of a prespecified list of *Medical Dictionary for Regulatory Activities* (MedDRA) terms, which was updated with each new version of MedDRA.

END POINTS

The primary end points were progression-free survival according to RECIST, version 1.1, as assessed by means of blinded independent central review, and overall survival among patients whose tumors expressed PD-L1 with a CPS of 10 or more (the CPS-10 subgroup), among patients whose tumors expressed PD-L1 with a CPS of 1 or more (the CPS-1 subgroup), and in the intention-to-treat population. Secondary efficacy end points included objective response, the duration of response, and disease control (complete response plus partial response plus stable disease for ≥24 weeks), all according to RECIST, version 1.1, and assessed by means of blinded independent central review. Safety was assessed among all patients who had received at least one dose of pembrolizumab, placebo, or chemotherapy.

TRIAL OVERSIGHT

The trial was developed by academic advisors and employees of the sponsor. An external, independent data and safety monitoring committee oversaw the trial, periodically assessed safety, and assessed efficacy at prespecified interim analyses. The trial protocol and all amendments were approved by the appropriate ethics body at each participating institution. All patients provided written informed consent before enrollment.

All authors attest that the trial was conducted in accordance with the protocol, its amendments, and standards of Good Clinical Practice. The first draft of the manuscript was written by the first author with editorial assistance provided by a medical writer employed by the sponsor. All authors approved the submitted manuscript and vouch for the accuracy and completeness of the data and the fidelity of the trial to the protocol (available with the full text of this article at NEJM.org).

STATISTICAL ANALYSIS

Details of the statistical analysis have been published previously.[10] In brief, efficacy was assessed in the intention-to-treat population, which included all patients who underwent randomization; safety was assessed among patients who underwent randomization and received at least one dose of pembrolizumab or placebo. The nonparametric Kaplan–Meier method was used to estimate progression-free survival, overall survival, and response curves in each group. The primary progression-free survival and overall survival hypotheses were tested with the use of the stratified log-rank test; hazard ratios and associated 95% confidence intervals were analyzed with the use of a stratified Cox proportional-hazards model with Efron's method of tie handling to assess the magnitude of the between-group difference. The confidence intervals reported

here are two-sided. The stratified Miettinen and Nurminen method[15] with strata weighting according to sample size was used to compare objective response and disease control between the two groups. The same stratification factors used for randomization were used in all stratified analyses.

The primary purpose of the final analysis was to perform formal statistical testing of overall survival. Formal statistical testing of other efficacy end points was completed at previous prespecified interim analyses, and updated descriptive analyses are provided. The familywise type I error rate across the primary and secondary hypotheses was strongly controlled at a two-sided alpha level of 0.05, which was split among the end points of progression-free survival (0.01), overall survival (0.036), and objective response (0.004) (see the Supplementary Appendix, available at NEJM.org). The group sequential method was used to allocate alpha between the interim and final analyses of overall survival, and alpha could be reallocated among hypotheses with the use of the graphical approach of Maurer and Bretz.[16] For the analysis of overall survival, the initial alpha was assigned to the CPS-10 subgroup and the CPS-1 subgroup; the prespecified statistical criteria for this final analysis were an alpha level of 0.0227 for the CPS-10 subgroup and an alpha level of 0.013 (if the results for overall survival in the CPS-10 subgroup were not significant) or 0.0344 (if the results for overall survival in the CPS-10 subgroup were significant) for the CPS-1 subgroup. Overall survival in the intention-to-treat population could be tested only if the criterion for success with respect to overall survival in the CPS-1 subgroup was met. With a target of 240 deaths in the CPS-10 subgroup, the trial had an overall power of 79% to show superiority with respect to overall survival of pembrolizumab plus chemotherapy as compared with placebo plus chemotherapy at an initial two-sided overall alpha level of 0.02022 (before alpha reallocation), with an underlying hazard ratio of 0.65. The final analysis of overall survival was planned to be performed after approximately 664 deaths had occurred among all patients, approximately 482 deaths had occurred in the CPS-1 subgroup, and approximately 240 deaths had occurred in the CPS-10 subgroup. The protocol stated that the trial groups would be compared with the use of one-sided P values; however, in accordance with *Journal* policy, two-sided P values are reported here. Therefore, the two-sided overall alpha level and two-sided alpha boundaries are provided. The full statistical analysis plan is available with the protocol.

RESULTS

PATIENTS AND INTERVENTIONS

From January 2017 through June 2018, a total of 847 patients from 209 sites in 29 countries underwent randomization: 566 patients were assigned to the pembrolizumab–chemotherapy group and 281 to the placebo–chemotherapy group (Fig. S1 in the Supplementary Appendix). At the data-cutoff date (June 15, 2021), the median time since randomization was 44.1 months (range, 36.1 to 53.2). As reported previously,[10] the baseline characteristics of the patients were well balanced between the two groups, and the baseline characteristics of the patients in the CPS-1 subgroup (636 patients [75.1%]) and the CPS-10 subgroup (323 patients [38.1%]) were similar to those of the intention-to-treat population (Table S1). Details regarding the representativeness of the trial patients are provided in Table S2. The median duration of exposure was 26.4 weeks in the pembrolizumab–chemotherapy group and 23.1 weeks in the placebo–chemotherapy group (Table S3).

OVERALL SURVIVAL

In the CPS-10 subgroup, 155 of 220 patients (70.5%) in the pembrolizumab–chemotherapy group and 84 of 103 patients (81.6%) in the placebo–chemotherapy group died. The median overall survival was 23.0 months (95% confidence interval [CI], 19.0 to 26.3) in the pembrolizumab–chemotherapy group and 16.1 months (95% CI, 12.6 to 18.8) in the placebo–chemotherapy group (hazard ratio for death, 0.73; 95% CI, 0.55 to 0.95; two-sided P=0.0185) (Fig. 1A). According to the prespecified criterion for statistical significance for the final analysis (an alpha level of 0.0227), the addition of pembrolizumab to chemotherapy resulted in significantly longer overall survival than chemotherapy alone. The estimated overall survival at 18 months was 58.3% (95% CI, 51.4 to 64.5) in the pembrolizumab–chemotherapy group and 44.7% (95% CI, 34.9 to 53.9) in the placebo–chemotherapy group.

In the CPS-1 subgroup, 336 of 425 patients (79.1%) in the pembrolizumab–chemotherapy group and 177 of 211 patients (83.9%) in the placebo–chemotherapy group died. The median overall survival was 17.6 months (95% CI, 15.5 to 19.5) in the pembrolizumab–chemotherapy group and 16.0 months (95% CI, 12.8 to 17.4) in the placebo–chemotherapy group (hazard ratio for death, 0.86; 95% CI, 0.72 to 1.04; two-sided P=0.1125) (Fig. 1B). No significant between-group difference in overall survival was observed according to the prespecified criterion (an alpha level of 0.0344). The estimated overall survival at 18 months was 48.4% (95% CI, 43.5 to 53.0) in the pembrolizumab–chemotherapy group and 41.4% (95% CI, 34.7 to 48.0) in the placebo–chemotherapy group.

In the intention-to-treat population, 460 of 566 patients (81.3%) in the pembrolizumab–chemotherapy group and 238 of 281 patients (84.7%) in the placebo–chemotherapy group died. The median overall survival was 17.2 months (95% CI, 15.3 to 19.0) in the pembrolizumab–chemotherapy group and 15.5 months (95% CI, 13.9 to 17.2) in the placebo–chemotherapy group (hazard ratio for death, 0.89; 95% CI, 0.76 to 1.05) (Fig. 1C). Significance was not tested because of the prespecified multiplicity strategy. The estimated overall survival at 18 months was 47.8% (95% CI, 43.6 to 51.9) in the pembrolizumab–chemotherapy group and 41.8% (95% CI, 36.0 to 47.5) in the placebo–chemotherapy group. Log–log survival plots are provided in Figure S2 to support the proportional-hazards assumption for overall survival.

The treatment effect of pembrolizumab on overall survival increased with higher PD-L1 expression, with similar treatment effects observed among patients whose tumors expressed PD-L1 with a CPS of 10 or more and among those whose tumors expressed PD-L1 with a CPS of 20 or more (Fig. 2). The exploratory analysis of overall survival according to additional CPS cutoffs showed similar overall survival in the pembrolizumab–chemotherapy group and the placebo–chemotherapy group among patients whose tumors expressed PD-L1 with a CPS of less than 1 (hazard ratio, 0.97; 95% CI, 0.72 to 1.32) and among patients whose tumors expressed PD-L1 with a CPS of 1 to 9 (hazard ratio, 1.09; 95% CI, 0.85 to 1.40). The relative benefit of adding pembrolizumab to chemotherapy was similar among patients whose tumors expressed PD-L1 with a CPS of 10 to 19 (hazard ratio, 0.71; 95% CI, 0.46 to 1.09) and among those whose tumors expressed PD-L1 with a CPS of 20 or more (hazard ratio, 0.72; 95% CI, 0.51 to 1.01) (Fig. S3). The results of the analysis of overall survival in prespecified subgroups are shown in Figure S4.

PROGRESSION-FREE SURVIVAL

The median progression-free survival in the CPS-10 subgroup was 9.7 months in the pembrolizumab–chemotherapy group and 5.6 months in the placebo–chemotherapy group (hazard ratio for progression or death, 0.66; 95% CI, 0.50 to 0.88). In the CPS-1 subgroup, the median progression-free survival was 7.6 months in the pembrolizumab–chemotherapy group and 5.6 months in the placebo–chemotherapy group (hazard ratio, 0.75; 95% CI, 0.62 to 0.91). In the intention-to-treat population, the median progression-free survival in the two groups was 7.5 and 5.6 months, respectively (hazard ratio, 0.82; 95% CI, 0.70 to 0.98) (Fig. S5).

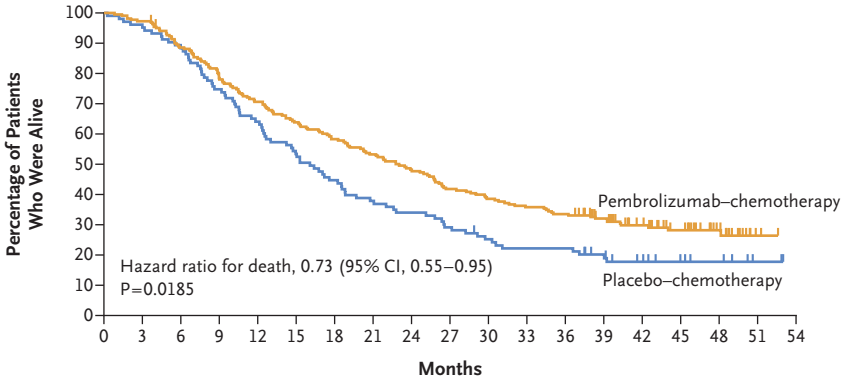
TUMOR RESPONSE

In the CPS-10 subgroup, a confirmed objective response occurred in 116 of 220 patients (52.7%) in the pembrolizumab–chemotherapy group and in 42 of 103 (40.8%) in the placebo–chemotherapy group. In the CPS-1 subgroup, a confirmed objective response occurred in 191 of 425 patients (44.9%) in the pembrolizumab–chemotherapy group and in 82 of 211 (38.9%) in the placebo–chemotherapy group. In the intention-to-treat population, a confirmed objective response occurred in 231 of 566 patients (40.8%) in the pembrolizumab–chemotherapy group and in 104 of 281 (37.0%) in the placebo–chemotherapy group (Table S4). Among patients with a confirmed objective response, the duration of response was longer in the pembrolizumab–chemotherapy group than in the placebo–chemotherapy group. In the CPS-10 subgroup, the median duration of response was 12.8 months in the pembrolizumab–chemotherapy group and 7.3 months in the placebo–chemotherapy group (Table S4 and Fig. S6).

SAFETY

Adverse events of any grade that were considered by the investigator to be related to the trial

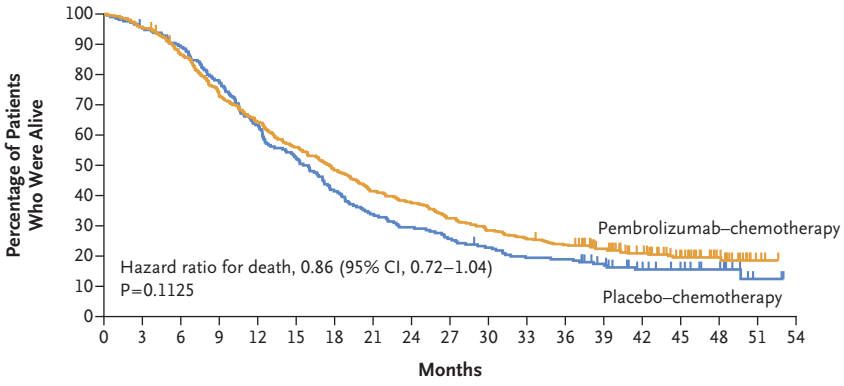
A Overall Survival in the CPS-10 Subgroup



No. at Risk

Pembrolizumab–chemotherapy	220	214	193	171	154	139	127	116	105	91	84	78	73	59	43	31	17	2	0
Placebo–chemotherapy	103	98	91	77	66	55	46	39	35	30	25	22	22	17	12	8	6	2	0

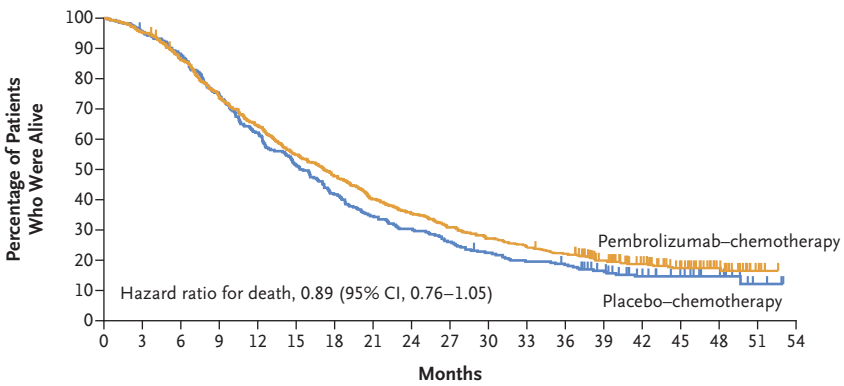
B Overall Survival in the CPS-1 Subgroup



No. at Risk

Pembrolizumab–chemotherapy	425	406	365	308	271	236	204	175	159	137	120	108	99	80	60	38	21	3	0
Placebo–chemotherapy	211	200	187	163	133	110	87	71	62	54	47	40	39	30	21	15	10	2	0

C Overall Survival in the Intention-to-Treat Population



No. at Risk

Pembrolizumab–chemotherapy	566	539	486	415	363	309	269	226	200	174	153	137	124	94	69	42	22	4	0
Placebo–chemotherapy	281	267	246	209	174	144	117	97	85	73	62	54	50	38	25	18	12	3	0

Figure 1 (facing page). Overall Survival.

Shown are Kaplan–Meier estimates of overall survival among patients whose tumors expressed programmed death ligand 1 (PD-L1) with a combined positive score (CPS) of 10 or more (CPS-10 subgroup) (Panel A), among patients whose tumors expressed PD-L1 with a CPS of 1 or more (CPS-1 subgroup) (Panel B), and in the intention-to-treat population (Panel C). The CPS is the number of PD-L1–staining cells (tumor cells, lymphocytes, and macrophages) divided by the total number of viable tumor cells, multiplied by 100. Tick marks represent data censored at the last time the patient was known to be alive. The hazard ratios and confidence intervals were analyzed on the basis of a Cox regression model with treatment group as a covariate, with stratification according to the randomization stratification factors of the type of chemotherapy received in the trial (a taxane or gemcitabine–carboplatin), tumor PD-L1 expression (CPS ≥1 or CPS <1), and previous treatment with the same class of neoadjuvant or adjuvant chemotherapy as that received in the trial (yes or no). The prespecified statistical criteria for significance for this final analysis were an alpha level of 0.0227 for the CPS-10 subgroup and an alpha level of 0.013 (if the results for overall survival in the CPS-10 subgroup were not significant) or 0.0344 (if the results for overall survival in the CPS-10 subgroup were significant) for the CPS-1 subgroup.

regimen occurred in 96.3% of 562 patients in the pembrolizumab–chemotherapy group and in 95.0% of 281 patients in the placebo–chemotherapy group. Anemia (in 49.1% of patients in the pembrolizumab–chemotherapy group and in 45.9% in the placebo–chemotherapy group), neutropenia (in 41.1% and 38.1%, respectively), and nausea (in 39.3% and 41.3%, respectively) were the most common adverse events (Table 1). Adverse events related to the trial regimen that were of grade 3 or higher occurred in 68.1% and 66.9% of the patients in the two groups, respectively. As reported previously,[10] adverse events related to the trial regimen led to death in 2 patients (0.4%) in the pembrolizumab–chemotherapy group (1 from acute kidney injury and 1 from pneumonia) and in no patients in the placebo–chemotherapy group.

Immune-mediated adverse events occurred in 26.5% of the patients in the pembrolizumab–chemotherapy group and in 6.4% in the placebo–chemotherapy group (Table 1); these events were of grade 3 or 4 in 5.3% of the patients in the pembrolizumab–chemotherapy group and in no patients in the placebo–chemotherapy group. No patients died due to immune-mediated adverse events. The most common immune-mediated adverse events were hypothyroidism (in 15.8% in the pembrolizumab–chemotherapy group and in 3.2% in the placebo–chemotherapy group) and hyperthyroidism (in 4.3% and 1.1%, respectively).

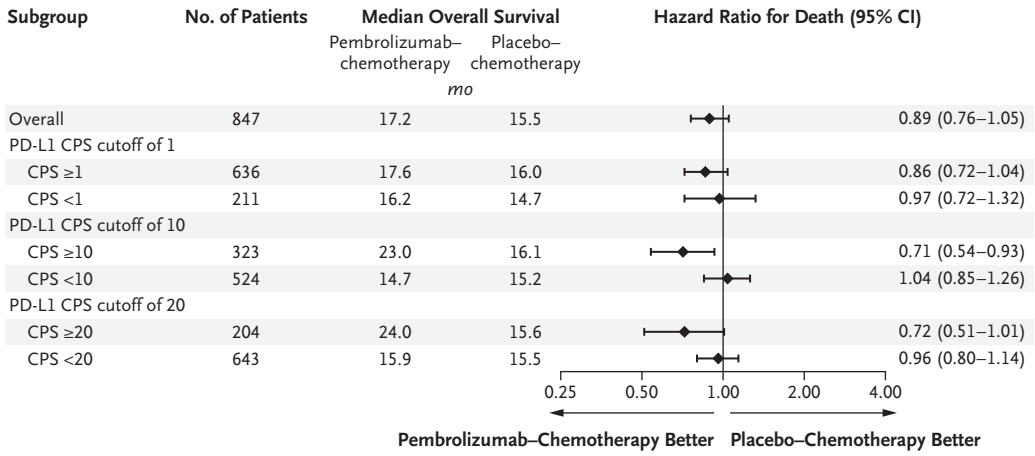


Figure 2. Overall Survival in Subgroups According to PD-L1 CPS Status at Baseline.

The analysis (hazard ratios and 95% confidence intervals) in the overall population used the stratified Cox regression model; the subgroup analyses used the unstratified Cox model.

Table 1. Adverse Events.*

Event	Pembrolizumab–Chemotherapy (N=562)		Placebo–Chemotherapy (N=281)	
	Any Grade	Grade 3, 4, or 5	Any Grade	Grade 3, 4, or 5
	number of patients (percent)			
Any adverse event	554 (98.6)	438 (77.9)	276 (98.2)	207 (73.7)
Adverse events that were attributed to the trial regimen†	541 (96.3)	383 (68.1)	267 (95.0)	188 (66.9)
Anemia	276 (49.1)	93 (16.5)	129 (45.9)	41 (14.6)
Neutropenia	231 (41.1)	167 (29.7)	107 (38.1)	84 (29.9)
Nausea	221 (39.3)	9 (1.6)	116 (41.3)	4 (1.4)
Alopecia	186 (33.1)	5 (0.9)	94 (33.5)	3 (1.1)
Fatigue	161 (28.6)	16 (2.8)	84 (29.9)	7 (2.5)
Neutrophil count decreased	126 (22.4)	98 (17.4)	74 (26.3)	57 (20.3)
Alanine aminotransferase increased	115 (20.5)	34 (6.0)	46 (16.4)	13 (4.6)
Immune-mediated adverse events‡	149 (26.5)	30 (5.3)	18 (6.4)	0
Hypothyroidism	89 (15.8)	2 (0.4)	9 (3.2)	0
Hyperthyroidism	24 (4.3)	1 (0.2)	3 (1.1)	0
Pneumonitis	14 (2.5)	6 (1.1)	0	0
Colitis	10 (1.8)	2 (0.4)	4 (1.4)	0
Severe skin reactions	10 (1.8)	10 (1.8)§	1 (0.4)	0

* Safety was assessed in all patients who had undergone randomization and received at least one dose of pembrolizumab, placebo, or chemotherapy. Listed are adverse events that occurred during the treatment period or within the 30 days thereafter (within 90 days for serious adverse events). Events are listed in descending order of frequency in the pembrolizumab–chemotherapy group. The severity of adverse events was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. Patients may have had more than one adverse event.

† Adverse events that were determined by the investigator to be related to the trial regimen and occurred in at least 20% of patients or events that were considered medically relevant are reported.

‡ Immune-mediated adverse events were those included in a list of terms specified by the sponsor and were assessed regardless of attribution to the trial regimen. Events that occurred in at least 10 patients are reported.

§ Severe skin reactions included pruritus (in 1 patient), rash (in 4 patients), and maculopapular rash (in 6 patients).

DISCUSSION

The results of the protocol-specified second interim analysis of this trial showed that pembrolizumab plus chemotherapy resulted in significantly longer progression-free survival than chemotherapy alone among patients whose tumors expressed PD-L1 with a CPS of 10 or more.[10] The results of this protocol-specified final analysis showed that pembrolizumab plus chemotherapy also resulted in significantly longer overall survival than chemotherapy alone among patients whose tumors expressed PD-L1 with a CPS of 10 or more. The significance boundary for an overall survival benefit of pembrolizumab plus chemotherapy in the CPS-1 subgroup was not crossed, and formal testing in the intention-to-treat population was not performed. The results of an exploratory analysis of overall survival according to additional CPS cutoffs showed a consistent benefit with the addition of pembrolizumab among patients whose tumors expressed PD-L1 with a CPS of 10 to 19 and among those whose tumors expressed PD-L1 with a CPS of 20 or more; this finding provides further support that a CPS of 10 or more is an appropriate criterion to define the population of patients with advanced triple-negative breast cancer who would be expected to derive benefit from pembrolizumab plus chemotherapy.

As in the interim analysis,[10] pembrolizumab plus chemotherapy provided a greater reduction in the risk of disease progression or death than chemotherapy alone; in the CPS-10 subgroup,

the percentage of patients with progression-free survival at 12 months was approximately 16 percentage points higher in the pembrolizumab–chemotherapy group than in the placebo–chemotherapy group. The updated results for progression-free survival in the CPS-1 subgroup and the intention-to-treat population are also consistent with the previous results.[10] Similarly, the percentage of patients with an objective response is consistent with the previous interim data[17] and remains higher with pembrolizumab plus chemotherapy than with chemotherapy alone in both subgroups and in the intention-to-treat population, with the greatest benefit observed in the CPS-10 subgroup. Responses in the pembrolizumab–chemotherapy group were durable over longer follow-up, with the longest duration of response observed in the CPS-10 subgroup.

Our results build on findings from earlier trials involving patients with metastatic triple-negative breast cancer that showed greater single-agent activity with pembrolizumab and other immune checkpoint inhibitors with increasing PD-L1 expression.[7,8,18-20] By contrast, the efficacy of neoadjuvant pembrolizumab plus chemotherapy followed by adjuvant pembrolizumab in early-stage triple-negative breast cancer was independent of PD-L1 expression.[21,22] Together with similar observations in studies of atezolizumab for metastatic and early triple-negative breast cancer,[23,24] these observations suggest a differential role of baseline tumor PD-L1 expression in the efficacy of immune checkpoint inhibition for early-stage as compared with late-stage disease.

Our findings are generally consistent with those of the phase 3 IMpassion130 trial, which showed that the addition of atezolizumab to nab-paclitaxel as first-line treatment of metastatic triple-negative breast cancer resulted in significantly longer progression-free survival than placebo plus nab-paclitaxel (hazard ratio for progression or death, 0.80; 95% CI, 0.69 to 0.92; P=0.002 [in the intention-to-treat population]; hazard ratio, 0.62; 95% CI, 0.49 to 0.78; P<0.001 [among patients with PD-L1–positive tumors, with the use of a different assay])[23] and numerically longer overall survival among patients with PD-L1–positive tumors than among patients with PD-L1–negative tumors (hazard ratio, 0.67; 95% CI, 0.53 to 0.86 [significance not formally tested]).[25] In the IMpassion131 trial, which evaluated a different chemotherapy backbone (paclitaxel rather than nab-paclitaxel),[26] combining atezolizumab with paclitaxel did not prolong progression-free survival or overall survival among patients with metastatic triple-negative breast cancer in either the PD-L1–positive or the intention-to-treat populations. In our trial, the benefit of pembrolizumab in the CPS-10 subgroup was observed with both paclitaxel and nab-paclitaxel, although these results should be interpreted with caution owing to the small number of patients who received paclitaxel.

After longer follow-up, the safety profile of pembrolizumab in combination with chemotherapy remained consistent with that in the previous analyses,[10] with no evidence of cumulative toxic effects. Adverse events were consistent with the known safety profiles of pembrolizumab and the chemotherapy regimens, with no new safety signals. The most frequent adverse events related to the trial regimen in both groups (anemia, neutropenia, and nausea) reflect toxic effects typically associated with chemotherapy, and the addition of pembrolizumab did not increase the incidence of these adverse events or compromise exposure to chemotherapy. As in the interim analysis,[10] the higher incidence of immune-mediated adverse events in the pembrolizumab–chemotherapy group than in the placebo–chemotherapy group was primarily driven by hypothyroidism and hyperthyroidism. Overall, these events were generally low grade and were manageable with dose interruptions and appropriate use of supportive care.

In this trial, first-line treatment with pembrolizumab–chemotherapy resulted in significantly longer overall survival than chemotherapy alone among patients with advanced triple-negative breast cancer whose tumors expressed PD-L1 with a CPS of 10 or more.

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APPENDIX

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