

ORIGINAL ARTICLE

Pembrolizumab monotherapy for previously treated metastatic triple-negative breast cancer: cohort A of the phase II KEYNOTE-086 study

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Background: Treatment options for previously treated metastatic triple-negative breast cancer (mTNBC) are limited. In cohort A of the phase II KEYNOTE-086 study, we evaluated pembrolizumab as second or later line of treatment for patients with mTNBC.

Patients and methods: Eligible patients had centrally confirmed mTNBC, ≥ 1 systemic therapy for metastatic disease, prior treatment with anthracycline and taxane in any disease setting, and progression on or after the most recent therapy. Patients received pembrolizumab 200 mg intravenously every 3 weeks for up to 2 years. Primary end points were objective response rate in the total and PD-L1–positive populations, and safety. Secondary end points included duration of response, disease control rate (percentage of patients with complete or partial response or stable disease for ≥ 24 weeks), progression-free survival, and overall survival.

Results: All enrolled patients ($N = 170$) were women, 61.8% had PD-L1–positive tumors, and 43.5% had received ≥ 3 previous lines of therapy for metastatic disease. ORR (95% CI) was 5.3% (2.7–9.9) in the total and 5.7% (2.4–12.2) in the PD-L1–positive populations. Disease control rate (95% CI) was 7.6% (4.4–12.7) and 9.5% (5.1–16.8), respectively. Median duration of response was not reached in the total (range, 1.2+–21.5+) and in the PD-L1–positive (range, 6.3–21.5+) populations. Median PFS was 2.0 months (95% CI, 1.9–2.0), and the 6-month rate was 14.9%. Median OS was 9.0 months (95% CI, 7.6–11.2), and the 6-month rate was 69.1%. Treatment-related adverse events occurred in 103 (60.6%) patients, including 22 (12.9%) with grade 3 or 4 AEs. There were no deaths due to AEs.

Conclusions: Pembrolizumab monotherapy demonstrated durable antitumor activity in a subset of patients with previously treated mTNBC and had a manageable safety profile.

Clinical trial registration: ClinicalTrials.gov, NCT02447003

Key words: anti-PD-1, immunotherapy, pembrolizumab, triple-negative breast neoplasms

Introduction

Treatment of metastatic triple-negative breast cancer TNBC (mTNBC) is challenging and survival, despite standard of care cytotoxic chemotherapy, is poor (median OS, 9–17 months) [1, 2]. Only a limited subset of patients with germline BRCA-related TNBC benefit from poly (ADP-ribose) polymerase (PARP) inhibitors, the only available targeted therapy [3, 4]. Current therapies are frequently associated with significant toxicity. The aggressive disease biology coupled with the suboptimal treatment outcomes underscore the urgent need for new therapies to effectively treat mTNBC.

The programmed death receptor 1 (PD-1) pathway is frequently co-opted by tumors to evade an immune response [5]. Pembrolizumab is a high-affinity, highly selective, humanized monoclonal IgG4- κ antibody against PD-1 that provides dual ligand blockade of programmed death-ligand 1 (PD-L1) and 2 (PD-L2). PD-L1 is not detected in normal breast tissue, but is expressed in approximately half of all breast cancers, with expression generally higher in TNBC [6–8]. The phase Ib KEYNOTE-012 study in patients with PD-L1-positive mTNBC ($N=27$) showed that pembrolizumab had manageable safety and durable antitumor activity in a subset of patients [9]. The present study examined the efficacy and safety of pembrolizumab monotherapy in a large cohort of patients with previously treated mTNBC, regardless of PD-L1 expression.

Methods

Study design and patients

KEYNOTE-086 (ClinicalTrials.gov, NCT02447003) was an international, open-label, multicohort, phase II study of pembrolizumab monotherapy in patients with mTNBC. Eligibility for cohort A was ≥ 1 prior systemic treatment for metastatic disease, treatment with anthracycline and taxane in the neoadjuvant, adjuvant, or metastatic setting, and documented disease progression on or after the most recent therapy. Men and women were eligible for enrollment if they were aged ≥ 18 years, had centrally confirmed TNBC [10], an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, baseline lactate dehydrogenase (LDH) levels $< 2.5 \times$ ULN, and measurable disease based on Response Evaluation Criteria in Advanced Solid Tumors, version 1.1 (RECIST v1.1) assessed by independent central radiology review. All patients were required to provide tumor tissue from a newly obtained (within 56 days of the first dose of study medication) core or excisional biopsy sample (preferred) or archival tumor sample of a nonirradiated lesion for central confirmation of TNBC status and determination of PD-L1 status.

Exclusion criteria included radiographically detectable central nervous system metastases, regardless of symptomatology or previous treatment; active autoimmune disease that required systemic treatment within the previous 2 years; history of noninfectious pneumonitis or interstitial lung disease; prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2 or another co-inhibitory T-cell receptor; an antineoplastic monoclonal antibody within the previous 4 weeks; chemotherapy, targeted small molecule therapy, or radiation therapy within the previous 2 weeks; or adverse events (AEs) from previous therapy that had not resolved to grade ≤ 1 or baseline.

All patients provided written, informed consent. The study protocol was approved by the independent ethics committee or review board at each participating institution. The study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization Guidelines for Good Clinical Practice.

Study treatment

Pembrolizumab 200 mg was administered intravenously over 30 min every 3 weeks for up to 2 years. Treatment was discontinued upon disease progression, intolerable toxicity, physician decision, or patient withdrawal of consent. Clinically stable patients with radiologic evidence of disease progression could continue treatment until radiologic progression was confirmed at the next imaging assessment ≥ 4 weeks later.

Assessments

PD-L1 expression was assessed during screening at a central laboratory (Q² Solutions, Valencia, CA) using the PD-L1 IHC 22C3 pharmDx kit (Agilent, Carpinteria, CA). The measure of expression was the combined positive score (CPS), defined as the ratio of PD-L1-positive cells (tumor cells, lymphocytes, and macrophages) out of the total number of tumor cells $\times 100$. PD-L1 positivity was defined as CPS ≥ 1 (previously reported as, and equivalent to, CPS $\geq 1\%$). Tumor imaging was performed by computed tomography (preferred) or magnetic resonance imaging at baseline, and every 9 weeks thereafter through 12 months, then every 12 weeks.

Physical examination and laboratory tests were performed and vital signs were assessed at baseline and regularly throughout study treatment. AEs were monitored throughout treatment and for 30 days thereafter (90 days for serious AEs) and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

Statistical analysis

Primary and secondary efficacy end points were assessed by independent central radiology review based on RECIST v1.1. Primary end points were objective response rate [ORR; the proportion of patients with complete response (CR) or partial response (PR)] in the total and PD-L1-positive populations, and safety. Secondary end points, evaluated in the total population and by PD-L1 status, included duration of response (the time from initial radiologic evidence of CR or PR to disease progression or death, whichever occurred first); disease control rate [DCR; the proportion of patients with CR or PR or stable disease (SD) for ≥ 24 weeks]; progression-free survival (PFS; the time from first dose of pembrolizumab to disease progression or death, whichever occurred first); and overall survival (OS; the time from first dose of pembrolizumab to death). Efficacy was assessed in all patients with measurable disease at baseline who received ≥ 1 dose of pembrolizumab. Safety was assessed in all patients who received ≥ 1 dose of pembrolizumab.

For ORR, the point estimate 95% Agresti-Coull confidence interval (CI) was provided based on normal approximation for the binomial distribution. Participants without response data were counted as nonresponders. For DCR, similar estimation methods used for ORR were applied. For duration of response, PFS, and OS, Kaplan–Meier curves, median estimates, and survival at 6 and 12 months based on the Kaplan–Meier curves (95% CI based on Greenwood's formula) were provided, as appropriate. Participants without efficacy evaluation or survival data were censored at day 1. Summary statistics were provided for baseline demographics, disease characteristics, and AEs. The target sample size was approximately 160 patients. The current analysis was based on the data cut-off date of 10 November 2017.

Results

Patients

Of 388 patients screened, 170 patients, including 105 (61.8%) with PD-L1-positive tumors, were allocated between 17 July 2015 and 29 January 2016 at 48 sites in 13 countries (supplementary Table S1, available at *Annals of Oncology* online). The most

Table 1. Baseline demographics and disease characteristics in the total, PD-L1–positive and PD-L1–negative populations

Characteristic	Total population N = 170 ^a	PD-L1–positive population N = 105	PD-L1–negative population N = 64
Female	170 (100)	105 (100)	64 (100)
Age, years, median (range)	53.5 (28–85)	53.0 (30–85)	55.0 (28–80)
Postmenopausal	140 (82.4)	85 (81.0)	54 (84.4)
ECOG performance status			
0	90 (52.9)	51 (48.6)	38 (59.4)
1	80 (47.1)	54 (51.4)	26 (40.6)
LDH concentration			
<1 × ULN	82 (48.2)	53 (50.5)	28 (43.8)
≥1 × ULN to <2.5 × ULN	85 (50.0)	50 (47.6)	35 (54.7)
≥2.5 × ULN	2 (1.2)	1 (1.0)	1 (1.6)
Unknown	1 (0.6)	1 (1.0)	0 (0.0)
Sum of the size of target lesions, ^b mm, median (range)	51.0 (10–531)	56.0 (10–531)	44.0 (11–178)
No. of metastatic organ sites			
1	46 (27.1)	29 (27.6)	17 (26.6)
2	68 (40.0)	40 (38.1)	27 (42.2)
≥3	56 (32.9)	36 (34.3)	20 (31.3)
Visceral ± nonvisceral disease	125 (73.5)	74 (70.5)	50 (78.1)
Prior taxane and anthracycline therapy	163 (95.9)	102 (97.1)	60 (93.8)
Previous (neo)adjuvant therapy	141 (82.9)	86 (81.9)	54 (84.4)
No. of previous lines of therapy for recurrent/metastatic disease			
1	53 (31.2)	37 (35.2)	16 (25.0)
2	43 (25.3)	26 (24.8)	16 (25.0)
3	31 (18.2)	20 (19.0)	11 (17.2)
4	22 (12.9)	10 (9.5)	12 (18.8)
≥5	21 (12.4)	12 (11.4)	9 (14.1)

Data are presented as *n* (%) unless otherwise noted.

^aIncludes one patient with unknown PD-L1 status.

^bDefined as the sum of the longest diameters of target lesions measurable by central radiology review.

ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; ULN, upper limit of normal.

common reasons for nonenrollment were the presence of radiographically detectable central nervous system metastases [*N* = 64 (29.4%)] and inadequate organ function [*N* = 55 (25.2%)]. All enrolled patients received ≥1 dose of pembrolizumab. After a median follow-up of 9.6 months (range, 0.1–25.7), 165 (97.1%) patients discontinued pembrolizumab, most commonly for disease progression [*N* = 153 (90.0%)] (supplementary Figure S1, available at *Annals of Oncology* online). Median duration of exposure to pembrolizumab was 57 days (range, 1–740), and the median number of pembrolizumab doses was 3 (range, 1–35).

All patients were women, median age was 53.5 years (range, 28–85), and 51.2% had elevated serum LDH (Table 1). The population was heavily pretreated, with 82.9% having received neoadjuvant/adjuvant chemotherapy, and 43.5% having received ≥3 previous lines of therapy for metastatic disease.

Antitumor activity

All patients were evaluable for efficacy. In the total population, two patients had a CR and seven patients had a PR, for an ORR of 5.3% (95% CI, 2.7–9.9) (Table 2). In the PD-L1–positive

population, two patients had a CR and four patients had a PR, for an ORR of 5.7% (95% CI, 2.4–12.2) (Table 2). In the PD-L1–negative population, zero patients had a CR and three patients had a PR, for an ORR of 4.7% (95% CI, 1.1–13.4) (Table 2). Four patients, all with PD-L1–positive disease, had SD ≥24 weeks, leading to DCRs of 7.6% (95% CI, 4.4–12.7) in the total, 9.5% (95% CI, 5.1–16.8) in the PD-L1–positive, and 4.7% (95% CI, 1.1–13.4) in the PD-L1–negative populations (Table 2). Examination of subgroups in the total population revealed that although ORR was numerically higher in patients with normal versus elevated LDH, <3 versus ≥3 metastatic organ sites, lymph node metastases-only versus other, and nonvisceral-only versus visceral (with or without nonvisceral) disease, all confidence intervals overlapped, except for subgroups based on lymph node metastases (Figure 1A). There were no responses in patients with liver metastases. At the time of data cut-off, 6/9 responders in the total population (5/6 PD-L1–positive and 1/3 PD-L1–negative patients) did not experience subsequent disease progression or death. The median duration of response was not reached in the total (1.2+–21.5+ months) or PD-L1–positive populations (6.3–21.5+ months), and was 4.4 months (1.2+–4.6) in the PD-L1–

Table 2. Antitumor activity assessed by RECIST v1.1 per independent central review in the total, PD-L1–positive, and PD-L1–negative efficacy populations

Antitumor activity	Total population N = 170	PD-L1–positive population N = 105	PD-L1–negative population N = 64
ORR, n (%) [95% CI]	9 (5.3) [2.7–9.9]	6 (5.7) [2.4–12.2]	3 (4.7) [1.1, 13.4]
DCR ^a , n (%) [95% CI]	13 (7.6) [4.4–12.7]	10 (9.5) [5.1–16.8]	3 (4.7) [1.1–13.4]
Best overall response, n (%)			
Complete response	2 (1.2)	2 (1.9)	0 (0.0)
Partial response	7 (4.1)	4 (3.8)	3 (4.7)
Stable disease	34 (20.0)	21 (20.0)	12 (18.8)
Progressive disease	103 (60.6)	66 (62.9)	37 (57.8)
Not able to be evaluated ^b	6 (3.5)	3 (2.9)	3 (4.7)
Not able to be assessed ^c	18 (10.6)	9 (8.6)	9 (14.1)
Time to response, ^d months, median (range)	3.9 (1.9–8.1)	3.1 (1.9–6.2)	3.9 (1.9–8.1)
Duration of response, ^{d,e} months, median (range)	NR (1.2+ to 21.5+)	NR (6.3 to 21.5+)	4.4 (1.2+ to 4.6)
Estimated rate of response duration ≥6 months, ^{d,e} %	6 (75.0)	6 (100.0)	0 (NR)
Estimated rate of response duration ≥12 months, ^{d,e} %	3 (62.5)	3 (83.3)	0 (NR)
Progression-free survival events, n (%)	158 (92.9)	95 (90.5)	62 (96.9)
Progression-free survival, months, median (95% CI) ^e	2.0 (1.9–2.0)	2.0 (1.9–2.1)	1.9 (1.7–2.0)
Progression-free survival at 6 months, % ^e	14.9	14.3	16.4
Progression-free survival at 12 months, % ^e	8.1	8.7	7.3
Death, n (%)	136 (80.0)	82 (78.1)	53 (82.8)
Overall survival, months, median (95% CI) ^e	9.0 (7.6, 11.2)	8.8 (7.1, 11.2)	9.7 (6.2, 12.6)
Overall survival at 6 months, % ^e	69.1	71.1	65.4
Overall survival at 12 months, % ^e	39.8	39.0	40.2

Total population includes the one patient who had disease that was not evaluable for PD-L1 expression. '+' indicates there is no progressive disease by the time of last disease assessment.

^aDCR = the proportion of patients with complete or partial response or stable disease for ≥24 weeks.

^bPatients who had ≥1 postbaseline tumor assessment, none of which were evaluable.

^cPatients who had no postbaseline tumor assessment because of death, withdrawal of consent, loss to follow-up, or start of new anticancer therapy.

^dEvaluated in patients who had a complete or partial response (n = 9 for the total population, n = 6 for the PD-L1–positive population, n = 3 for the PD-L1–negative population).

^eEstimated using the Kaplan–Meier method.

NR, not reached; RECIST, Response Evaluation Criteria in Solid Tumors.

negative population (Table 2). Overall, 75.0% and 62.5% of responders had response duration ≥6 months and ≥12 months, respectively (Table 2). Best percentage change from baseline in target lesion size for the 146 patients with ≥1 evaluable post-baseline imaging assessment is shown in Figure 1B.

By data cut-off, 158 (92.9%) patients had disease progression or died. Median PFS was 2.0 months (95% CI, 1.9–2.0), and the estimated 6- and 12-month PFS rates were 14.9% and 8.1%, respectively; similar PFS was observed despite PD-L1 expression status (Table 2, Figure 1C). Overall, 136 (80.0%) patients had died. Median OS was 9.0 months (95% CI, 7.6–11.2), and the 6- and 12-month OS rates were 69.1% and 39.8%, respectively; similar OS was observed despite PD-L1 expression status (Table 2, Figure 1D).

Safety

All patients were evaluable for safety. One hundred and three (60.6%) patients experienced ≥1 treatment-related AE, including 22 (12.9%) with ≥1 grade 3 or 4 event. No AEs led to death. Seven (4.1%) patients discontinued pembrolizumab because of

treatment-related AEs. The most common treatment-related AEs were fatigue (20.6%) and nausea (11.2%) (Table 3). The only treatment-related AEs of grade 3 or 4 severity that occurred in ≥2 patients were diarrhea [N = 3 (1.8%)] and increased alanine aminotransferase [N = 2 (1.2%)].

Immune-mediated AEs, considered regardless of attribution to treatment by the investigator, occurred in 33 (19.4%) patients. The most common immune-mediated AEs were hypothyroidism (11.8%) and hyperthyroidism (5.3%) (Table 3). The only immune-mediated AEs of grade 3 or 4 severity were one case of grade 4 type 1 diabetes mellitus and one case of grade 3 pneumonitis.

Discussion

Pembrolizumab monotherapy demonstrated antitumor activity in a subset of patients with previously treated mTNBC. Although the ORR of 5.3% is lower than single-agent chemotherapy in this setting, pembrolizumab avoided common chemotherapy toxicities and responses were quite durable. At database cut-off, the

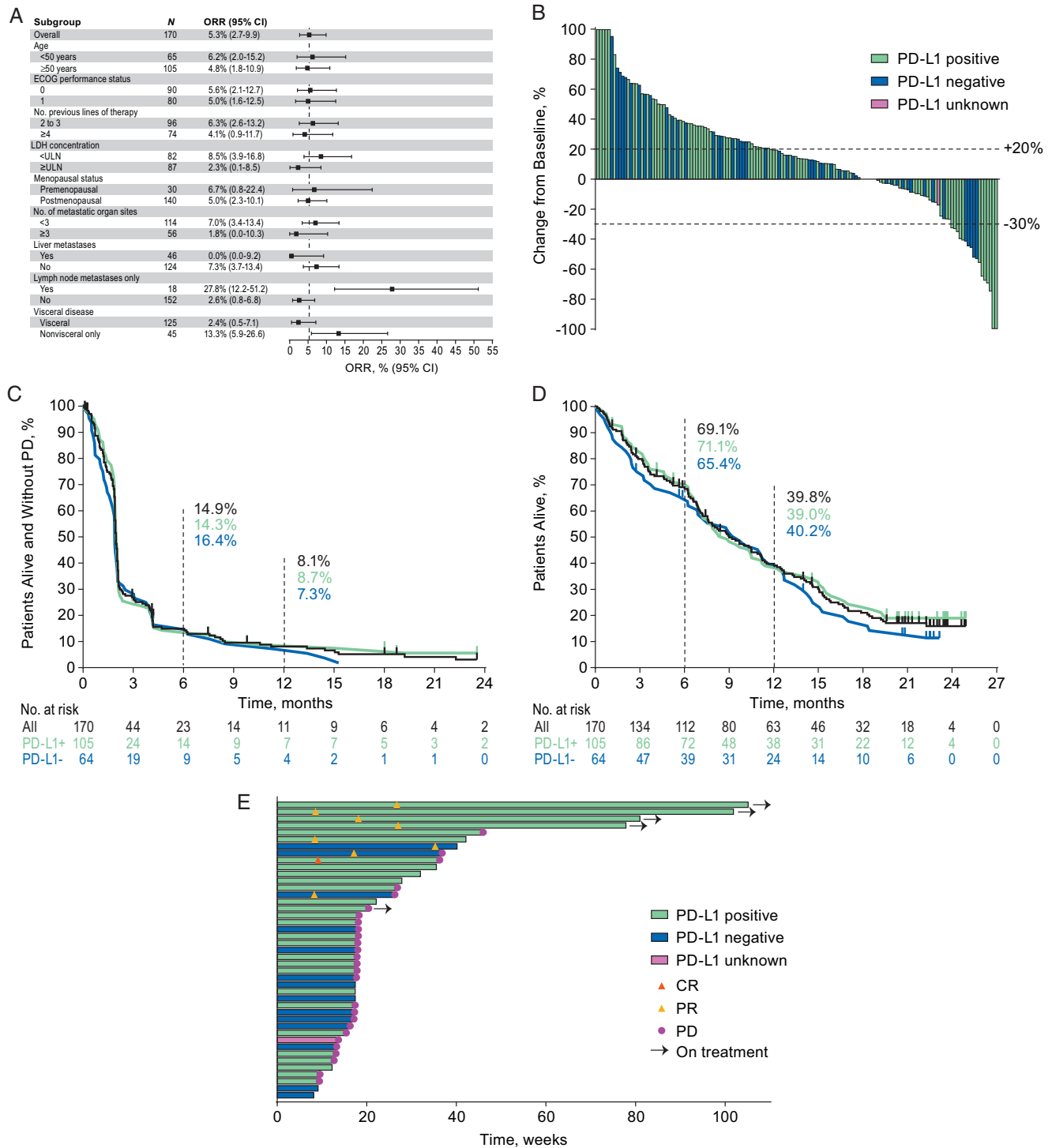


Figure 1. Antitumor activity of pembrolizumab in the total population. (A) Objective response rate assessed by RECIST v1.1 per independent central review in subgroups of the efficacy population ($N=170$). Prespecified subgroups include age, menopausal status, previous lines of therapy, and liver metastases; all other subgroups are exploratory. (B) Best change from baseline in target lesion size assessed by RECIST v1.1 per independent central review in patients with ≥ 1 evaluable post-baseline imaging assessment ($N=146$). (C) Progression-free survival assessed by RECIST v1.1 per independent central review in the efficacy population ($N=170$). (D) Overall survival in the efficacy population ($N=170$). (E) Time to response and response duration assessed by RECIST v1.1 per independent central review. CR, complete response; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; ULN, upper limit of normal.

Table 3. Adverse events in the total treated population (N = 170)

Adverse event	Any grade	Grade 3–4
Treatment related, incidence $\geq 5\%$		
Any	103 (60.6)	22 (12.9)
Fatigue	35 (20.6)	1 (0.6)
Nausea	19 (11.2)	1 (0.6)
Hypothyroidism	14 (8.2)	0
Decreased appetite	13 (7.6)	0
Diarrhea	12 (7.1)	3 (1.8)
Asthenia	11 (6.5)	0
Pruritus	11 (6.5)	0
Arthralgia	10 (5.9)	0
Hyperthyroidism	9 (5.3)	0
Immune mediated, incidence $>0\%$		
Hypothyroidism	20 (11.8)	0
Hyperthyroidism	9 (5.3)	0
Pneumonitis	7 (4.1)	1 (0.6)
Infusion-related reaction	3 (1.8)	0
Colitis	2 (1.2)	0
Myocarditis	1 (0.6)	0
Type 1 diabetes mellitus	1 (0.6)	1 (0.6)

Data are presented as *n* (%), where *n* is the number of patients who experienced ≥ 1 episode of a given event. Relatedness to treatment was determined by the investigator. Immune-mediated events were based on a list of terms specified by the sponsor and considered regardless of attribution to treatment or immune relatedness by the investigator; related terms were included.

duration of response was not reached, and 75.0% and 62.5% of responders had a response duration of ≥ 6 and ≥ 12 months, respectively. These results are encouraging compared with the typical duration of response (1–3 months) to standard chemotherapy in the mTNBC setting [11]. The DCR was 9.5% in the PD-L1–positive population and 4.7% in the PD-L1–negative population. Taken together, these data support the durable effect of pembrolizumab in patients who achieved a response, and possibly signal a greater benefit in the subset of patients with PD-L1–positive tumors.

The study population was heavily pretreated, with 82.9% having received neoadjuvant/adjuvant therapy, and 43.5% having received ≥ 3 previous lines of therapy for metastatic disease. The response to pembrolizumab may have been attenuated due to the heavily pretreated population studied. Data from cohort B of the present trial evaluating the antitumor activity of pembrolizumab as first-line therapy for patients with PD-L1–positive mTNBC show an ORR of 21.4% (95% CI, 13.9%–31.4%) [12], suggesting an improved response with earlier line of treatment.

Pembrolizumab demonstrated a numerically lower ORR in patients with poor prognostic factors, including elevated LDH, a greater number of metastatic sites, and visceral disease. No responses were observed in patients with liver metastases. Previous studies in patients with melanoma and non-small-cell lung cancer have also shown reduced response to immunotherapies with liver metastases, coinciding with reduced antigen-

specific T-cell infiltration [13]. Patients with poor prognostic factors should be considered for alternative strategies, including combination of immune checkpoint inhibitors with cytotoxic agents.

These results supplement findings from smaller trials of pembrolizumab and other immune checkpoint inhibitors for the treatment of TNBC. In the phase Ib KEYNOTE-012 trial of pembrolizumab as first line or greater treatment for patients with mTNBC selected by PD-L1 expression ($N = 32$), ORR was 18.5% in 27 evaluable patients [9]. In a phase Ib study of avelumab in patients with metastatic breast cancer ($N = 168$), the confirmed ORR was 5.2% in patients with TNBC ($N = 58$), with higher ORR in PD-L1–positive versus PD-L1–negative TNBC (22.2% versus 2.6%) [14]. Single-agent atezolizumab in patients with mTNBC ($N = 116$) produced an ORR of 10% in the overall population, which was higher in first-line ($N = 21$; 24%) versus second-line or greater treatment ($N = 94$; 6%) [15]. In addition to monotherapy studies, combinations of different immune checkpoint inhibitors and immune checkpoint inhibition with chemotherapy for TNBC are being evaluated, and preliminary data suggest increased response rates with the combinations versus their respective single-agent components [16–18].

Pembrolizumab demonstrated an acceptable safety profile. Treatment-related AEs were common; however, the incidence of grade 3 or 4 treatment-related AEs was low and similar to earlier anti-PD-L1/PD-1 monotherapy studies for the treatment of breast cancer [9, 15]. Few patients discontinued due to treatment-related AEs, and no deaths due to AEs were reported.

This study had several limitations. The small number of responders precludes definitive identification of patient subgroups with mTNBC who would most likely derive clinical benefit from pembrolizumab. Additionally, the modest response to pembrolizumab in this heavily pretreated population is not generalizable to patients with less advanced disease. Indeed, available results with pembrolizumab in the first-line setting demonstrate a higher ORR than that observed here [12], and studies of pembrolizumab as monotherapy and in combination with chemotherapy are ongoing in less heavily treated or previously untreated mTNBC, and in the neoadjuvant and adjuvant settings. Finally, the use of PD-L1 as a predictive biomarker to compare results across studies of different immunotherapies is limited by differences in detection antibodies and IHC cut-offs [19]. Additional studies of immune biomarkers to identify patients most likely to benefit from immunotherapies are critical. Early findings from the present study suggest that tumor infiltrating lymphocyte (TIL) levels can identify patients with mTNBC who have a greater chance of achieving response to pembrolizumab monotherapy [20].

In conclusion, pembrolizumab monotherapy showed durable antitumor activity in a small subset of patients with heavily pretreated mTNBC and had a manageable safety profile, with most AEs of low grade. Survival was promising, particularly in patients with CR, PR, or SD. Whereas clinical features (normal LDH, absence of liver metastases, etc.) and the presence of TILs can enrich for a TNBC population with higher response rate, further elucidation of the molecular or immunologic features of responders may identify a subset of patients who have excellent outcomes with pembrolizumab monotherapy. Randomized studies of pembrolizumab monotherapy and pembrolizumab-based combination therapy for the treatment of TNBC are ongoing.

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