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Clinical Trials: Immunotherapy

Clinical Cancer Research

Safety and Antitumor Activity of Pembrolizumab in Patients with Estrogen Receptor–Positive/Human Epidermal Growth Factor Receptor 2–Negative Advanced Breast Cancer

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Abstract

Purpose: We investigated the safety and antitumor activity of the anti–programmed death 1 monoclonal antibody pembrolizumab in patients with estrogen receptor–positive (ER^+)/human epidermal growth factor receptor 2–negative ($HER2^-$) advanced breast cancer with programmed death ligand 1–positive (PD-L1–positive) tumors in the phase Ib open-label, multicohort KEYNOTE-028 (NCT02054806) study.

Patients and Methods: Patients with $ER^+/HER2^-$ advanced breast cancer with PD-L1–positive tumors (combined positive score $\geq$1) received pembrolizumab (10 mg/kg every 2 weeks) up to 2 years or until confirmed progression/intolerable toxicity. Primary endpoints were safety and overall response rate (ORR), based on Response Evaluation Criteria in Solid Tumors, version 1 (RECIST v1.1) as assessed by investigator review.

Results: Between April 2014 and January 2015, 25 patients were enrolled. Median number of prior therapies for breast cancer, including endocrine agents, was 9 (range, 3–15). Median follow-up was 9.7 months (range, 0.7–31.8 months). Three patients experienced partial response (PR) and none experienced complete response (CR), resulting in an ORR of 12.0% (95% CI, 2.5%–31.2%); 16% of patients had stable disease (SD) and clinical benefit rate (CR + PR + [SD for $\geq$24 weeks]) was 20% (95% CI, 7–41). Median duration of response was 12.0 months (range, 7.4–15.9 months). The incidence of treatment-related adverse events was 64%; nausea (20%) and fatigue (12%) were most common and were predominantly grade 1/2. No treatment-related discontinuations or deaths occurred.

Conclusions: Pembrolizumab was well tolerated with modest but durable overall response in certain patients with previously treated, advanced, PD-L1–positive, $ER^+/HER2^-$ breast cancer. *Clin Cancer Res; 24(12); 2804–11. ©2018 AACR.*

Introduction

Worldwide, breast cancer is the most common cancer in women, representing 14.6% of all new cancer cases in the United States. It is estimated that in 2017 there will be 252,710 new cases of breast cancer and 40,610 breast cancer–related deaths in the United States alone (1). Although the number of deaths is decreasing because of advances in diagnosis and therapy, distant

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Translational Relevance

Evidence in multiple tumor types indicates that PD-L1 expression is associated with increased response to pembrolizumab. We demonstrate here that, in a cohort of patients with previously treated, PD-L1–positive, ER$^+$/HER2$^-$ advanced breast cancer, treatment with pembrolizumab is well tolerated and results in durable overall responses in certain patients. These data support further investigation of pembrolizumab alone or in combination with other therapies in the treatment of breast cancer and identification of potentially prognostic and predictive biomarkers of response.

metastatic disease is expected to develop in approximately 20% to 30% of all patients with breast cancer (2).

Estrogen receptor–positive (ER$^+$)/human epidermal growth factor receptor 2–negative (HER2$^-$) breast cancer represents 60% to 65% of all breast malignancies, and the incidence increases with older age (3, 4). Therapeutic strategies for these generally endocrine-responsive tumors include aromatase inhibitors and selective estrogen receptor modulators and a selective estrogen receptor degrader, alone or in combination with CDK4/6 inhibitors or mammalian target of rapamycin inhibitors (5–10). Although endocrine therapy provides a clinical benefit ratio of 40% to 80%, metastatic breast cancers may develop endocrine resistance over time (3).

The programmed death 1 (PD-1) pathway is an immune checkpoint used by tumor cells to evade detection and attack by tumor-directed T cells (11). PD-1 is expressed on the surface of activated T cells where it interacts with its ligands, programmed death ligands 1 and 2 (PD-L1 and PD-L2, respectively), to attenuate T-cell signaling, resulting in downregulation of T-cell proliferation, activation, and antitumor immune response (12, 13). Although PD-L1 is rarely expressed in normal breast tissue, it can be expressed in some breast cancer cells and surrounding immune cells (14–16), where it can mediate the inhibition of tumor-infiltrating lymphocytes (TIL; ref. 17).

Pembrolizumab is a highly selective, humanized, monoclonal immunoglobulin G4-κ antibody targeting PD-1 (13). It has demonstrated robust antitumor activity and a favorable safety profile in multiple tumor types and is currently approved in more than 60 countries for 1 or more advanced malignancies (18–24). It is currently being investigated alone and in combination with other anticancer therapies in multiple tumor types.

Pembrolizumab has demonstrated antitumor activity as monotherapy for metastatic triple-negative breast cancer (mTNBC). In the phase Ib KEYNOTE-012 study (clinicaltrials.gov, NCT02447003), treatment with pembrolizumab resulted in an overall response rate (ORR) of 18.5% after a median follow-up of 10 months in patients with previously treated PD-L1–positive mTNBC (25). In the phase II KEYNOTE-086 study (clinicaltrials.gov, NCT02447003), after a median follow-up of 10.9 months, treatment with pembrolizumab resulted in an ORR of 5% (95% CI, 2.3%–9.2%) in a cohort of patients with previously treated mTNBC, regardless of PD-L1 expression (26). In a cohort of patients receiving pembrolizumab as first-line treatment for PD-L1–positive mTNBC in the same study, ORR was 23% (95% CI, 14%–36%; ref. 27). Responses to pembrolizumab were durable in both the KEYNOTE-012 study and the KEYNOTE-086 study (25–27).

KEYNOTE-028 is a phase Ib multicohort study conducted to evaluate the safety and efficacy of pembrolizumab monotherapy in 20 different types of advanced or recurrent PD-L1–positive cancers that progressed on prior standard therapies. Here, we examined the safety and antitumor activity of pembrolizumab in the ER$^+$/HER2$^-$ advanced breast cancer cohort of this study.

Patients and Methods

Study design and patient population

KEYNOTE-028 (clinicaltrials.gov, NCT02054806) is a nonrandomized, multicohort, open-label, phase Ib study designed to evaluate the safety, tolerability, and antitumor activity of pembrolizumab in 20 cohorts of patients with PD-L1–positive advanced solid tumors. For the breast cancer cohort, key eligibility requirements included age ≥18 years; ER$^+$/HER2$^-$ tumor status as defined by local pathology review; histologically or cytologically confirmed, locally advanced or metastatic disease that had progressed on or after prior standard therapy; measurable disease per Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST v1.1); any number of prior systemic treatments (including endocrine therapy); Eastern Cooperative Oncology Group performance status of 0 or 1; PD-L1–positive tumors; and adequate organ function (hematologic, renal, hepatic, and coagulation). PD-L1 expression was determined by combined positive score (CPS), defined as the number of PD-L1–positive cells (tumor cells, lymphocytes, and macrophages) divided by the total number of tumor cells, multiplied by 100. The specimen is considered to have positive PD-L1 expression when CPS ≥1.

Key exclusion criteria included use of investigational therapy or anticancer monoclonal antibody therapy within 4 weeks before the first pembrolizumab dose; use of systemic steroids within 7 days before study entry; chemotherapy within 2 weeks before the first pembrolizumab dose; active brain metastases (previously treated stable brain metastases were allowed) or carcinomatous meningitis; prior therapy with anti–PD-1, anti–PD-L1, or other immune checkpoint inhibitors; and active autoimmune disease that necessitated systemic treatment within the preceding 2 years.

The study was conducted at 11 investigational sites in Canada, France, the Netherlands, Republic of Korea, and the United States and was performed in accordance with the protocol, Good Clinical Practice standards, provisions outlined in the Declaration of Helsinki, and the US Department of Health and Human Services, where appropriate. The study protocol and all amendments were approved by the appropriate institutional review boards and ethics committees of the participating institutions. All patients provided written informed consent to participate.

Treatment

Patients received pembrolizumab 10 mg/kg intravenously over 30 minutes every 2 weeks for 2 years or until unacceptable toxicity, disease progression, patient withdrawal of consent, or investigator decision to withdraw the patient. Patients who were clinically stable with initial radiographic evidence of disease progression based on RECIST v1.1 were permitted to continue pembrolizumab treatment until confirmatory imaging was performed ≥4 weeks later. Patients who interrupted treatment because of toxicity could resume pembrolizumab after resolution of toxic effects to grade ≤1 or baseline level; if toxicity did not

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resolve within 12 weeks after the last pembrolizumab infusion, study treatment was discontinued. Patients experiencing stable disease (SD), partial response (PR), or complete response (CR) who discontinued pembrolizumab after 24 months of continuous treatment without evidence of disease progression were eligible for up to 1 year of additional pembrolizumab treatment after subsequent progression.

Assessments

An archival or newly obtained core or excisional biopsy specimen from a nonirradiated tumor lesion was collected from each patient for assessment of PD-L1 expression. Tumor PD-L1 expression was assessed by immunohistochemistry at a central laboratory using a prototype assay (QualTek Molecular Laboratories; ref. 28) and the 22C3 antibody (Merck & Co. Inc., ref. 29).

Imaging was performed every 8 weeks until month 6, and every 12 weeks thereafter for 2 years or until documented disease progression, start of new anticancer treatment, withdrawal of consent, death, or the end of the study. Response was based on RECIST v1.1, as assessed by the investigator. The primary efficacy endpoint was ORR, defined as the proportion of patients with a best overall response of CR or PR at any time during the study. Secondary efficacy endpoints were progression-free survival (PFS), defined as the time from enrollment to disease progression or death, whichever occurred first; overall survival (OS), defined as the time from enrollment to death from any cause; and duration of response, defined as the time from initial radiographic evidence of response based on RECIST v1.1 to disease progression in patients who experienced PR or CR.

Adverse events (AE) were graded per the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 during study treatment and for up to 30 days after the last dose of trial treatment; data on serious AEs were collected up to 90 days after the last pembrolizumab dose.

Analysis of tumor-infiltrating lymphocytes

An exploratory analysis to evaluate the percentage of stromal TIL infiltration in tumor samples was conducted using light microscopy on hematoxylin and eosin diagnostic sections per previously described methodology (30). Sections used were adjacent to those used for PD-L1 IHC quantification. Percentage stromal TIL evaluation was used as a surrogate for an antitumor host T-cell response (31). All but 3 samples were from archival primary tumors.

Statistical analysis

Antitumor activity was assessed in all patients who received $\geq$1 pembrolizumab dose and had measurable disease at baseline, based on RECIST v1.1 as assessed by investigator review. The safety population consisted of all patients who received $\geq$1 pembrolizumab dose. For each cohort included in KEYNOTE-028, a sequential monitoring approach was used to evaluate ORR after $\geq$6 patients had $\geq$1 postbaseline scan. Subsequently, cohorts not closed for futility enrolled a total of 22 evaluable patients per cohort. With 22 evaluable patients, the study had approximately 80% power to demonstrate that ORR exceeded 10% at a one-sided $\alpha = 8\%$, if the true ORR was 35%. For ORR, the point estimate, repeated CI, and adjusted *P* values were computed using a truncated sequential probability test (32). Patients without response data were counted as nonresponders. PFS, OS, and duration of response were estimated using the Kaplan–Meier method. The data cutoff date for all analyses presented herein was February 20, 2017.

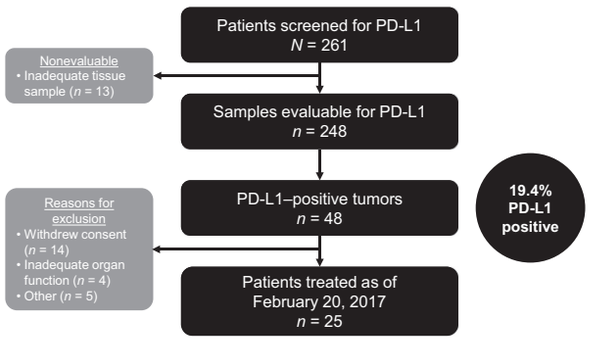

Figure 1.
Patient disposition.

Results

Study patients

Median follow-up was 9.7 months (range, 0.7–31.8 months). From the 261 patients screened for tumor PD-L1 expression, samples were evaluable for PD-L1 expression in 248 (95%; Fig. 1), of which 48 (19.4%) were PD-L1 positive. Of the patients with PD-L1–positive tumors, 23 (47.9%) were excluded from enrollment because of withdrawal of consent ($n = 14$), inadequate organ function ($n = 4$), and other reasons ($n = 5$). Between April 2014 and January 2015, 25 patients with PD-L1–positive tumors (52.1%) were enrolled and treated (Fig. 1). Median age was 53 years (range, 36–79 years); 13 (52%) patients had ductal carcinoma, 3 (12%) had lobular carcinoma, 3 (12%) had carcinoid/neuroendocrine tumors, and 6 (24%) had adenocarcinoma not otherwise specified; 11 (44%) had elevated lactate dehydrogenase (LDH) levels; 17 (68%) had prior (neo)adjuvant therapy; and 12 (48%) had received $\geq$5 lines of prior therapy (including endocrine treatments) for metastatic disease (Table 1). Baseline LDH levels were available for 22 patients, and values were calculated and reported as a ratio compared with the upper limit of normal (ULN) at the site of testing. The median baseline LDH levels were 1.10 (range, 0.61–4.30) for the 22 patients with available measurements, 1.06 (range, 0.61–1.81) for responders, and 0.95 (range, 0.61–1.81) for responders plus patients with SD $\geq$24 weeks. Sites of metastases included bone (19 patients); liver (16 patients); lymph node (13 patients); axilla (5 patients); peritoneum (4 patients); chest (4 patients); pleural cavity (3 patients); skin (2 patients); and adrenal gland, superior left orbit, abdomen, pancreas, thoracic wall, right gluteus medius, back, pelvis, trunk, and stomach in 1 patient each. The median number of prior therapies for breast cancer was 9 (range, 3–18). All patients had prior chemotherapy in the (neo)adjuvant and/or metastatic setting, 22 (88%) had prior endocrine therapy, and 7 (28%) had previously received other investigational therapy (Table 1).

Clinical activity

Based on RECIST v1.1 as assessed by investigator review, 3 of 25 patients had PR (no CR was observed) for an ORR of 12% (95% CI, 2.5–31.2; Table 2). Additionally, 4 (16%) patients had SD with a median duration of 20 weeks (range, 15.7–37.4 weeks);

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Table 1. Patient baseline characteristics

Characteristic	*N* = 25
Age, median (range), years	53.0 (36–79)
Female, *n* (%)	25 (100)
Race, *n* (%)	
White	16 (64)
Asian	4 (16)
Black or African American	1 (4)
Not specified	4 (16)
ECOG performance status, *n* (%)	
0	13 (52)
1	11 (44)
Unknown	1 (4)
Histology, *n* (%)	
Ductal carcinoma	13 (52)
Adenocarcinoma (NOS)	6 (24)
Lobular carcinoma	3 (12)
Carcinoid	2 (8)
Neuroendocrine	1 (4)
LDH level, *n* (%)	
Normal	11 (44)
Elevated	11 (44)
Null	3 (12)
Prior (neo)adjuvant therapy, *n* (%)	17 (68)
Prior systemic therapies for metastatic disease, *n* (%)	
0	2 (8)
1	1 (4)
2	2 (8)
3	4 (16)
4	4 (16)
≥5	12 (48)
Type of prior therapy, *n* (%)[a,b]	
Chemotherapy	25 (100)
Endocrine therapy	22 (88)
Tamoxifen	19 (76)
Fulvestrant	9 (36)
Aromatase inhibitor	17 (68)
Other investigational therapy	7 (28)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; NOS, not otherwise specified.
[a]Patients could have received ≥1 type of prior therapy.
[b]Not all prior therapies are listed.

2 of these patients experienced SD for ≥24 weeks. The clinical benefit rate [CR + PR + (SD for ≥24 weeks)] was 20% (95% CI, 6.8–40.7; Table 2). Three patients did not have postbaseline tumor assessments because of withdrawal of consent, progressive disease, and an AE ($n = 1$ each).

Table 2. Response in evaluable patients based on RECIST v1.1 assessed by investigator review[a]

	N = 25	95% CI
Overall response rate, *n* (%)	3 (12)	2.5–31.2
Clinical benefit rate[b], *n* (%)	5 (20)	6.8–40.7
Best overall response[c], *n* (%)		
CR	0 (0)	0.0–13.7
PR	3 (12)	2.5–31.2
SD	4 (16)	4.5–36.1
Progressive disease	15 (60)	38.7–78.9
No assessment[d]	3 (12)	2.5–31.2

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; RECIST, Response Evaluation Criteria in Solid Tumors.
[a]Includes patients with measurable disease at baseline based on RECIST v1.1 as assessed by investigator review who received ≥1 pembrolizumab dose.
[b]CR + PR + (SD for ≥24 weeks).
[c]All responses were confirmed.
[d]Signifies patients who did not have any postbaseline imaging studies.

Of the 22 patients with ≥1 postbaseline tumor assessment, 21 had evaluable tumor lesions. Of those patients with evaluable lesions, 8 (35%) experienced a decrease in the size of target lesions from baseline (Fig. 2A). The median time to response was 1.7 months (range, 1.7–1.9 months). Median duration of response was 12.0 months (range, 7.4–15.9 months; Fig. 2B and C).

All 3 patients who experienced PR had received ≥3 lines of chemotherapy for metastatic disease, and 2 had experienced progression with endocrine therapy in the metastatic setting. The first responder was a 40-year-old woman with stage IV ductal carcinoma with metastases to the liver, peritoneum, lymph nodes, and bone who had already been treated with 4 lines of chemotherapy (capecitabine plus vinorelbine, paclitaxel, eribulin, and carboplatin plus gemcitabine) for metastatic disease. She experienced PR in target lesions in the lymph nodes, 1 lung, and the peritoneum after 8 weeks of treatment with pembrolizumab. At the time of analysis, the patient had received 50 cycles of pembrolizumab, and PR was sustained for approximately 69.3 weeks. The second responder was a 65-year-old woman with stage IV lobular carcinoma with metastases to the breasts, orbit, axilla, peritoneum, and bone. She experienced progression of metastatic disease with everolimus plus exemestane, tamoxifen, capecitabine, gemcitabine plus paclitaxel, and, most recently, an investigational PI3 kinase inhibitor. She experienced PR in her left breast mass after 9 weeks of treatment with pembrolizumab. At the time of analysis, the patient had received 28 cycles of pembrolizumab, and PR was sustained for approximately 52.1 weeks. The third responder was a 68-year-old woman with stage IV lobular carcinoma with liver metastases who experienced progression of metastatic disease with letrozole, docetaxel plus cyclophosphamide, paclitaxel plus bevacizumab, and capecitabine. PR was observed after 8 weeks of treatment with pembrolizumab. At the time of analysis, the patient had received 22 cycles of pembrolizumab, and PR was sustained for approximately 32.3 weeks.

Median PFS was 1.8 months (95% CI, 1.4–2.0 months; Fig. 3A). The 6-month PFS rate was 16.7%. Median OS was 8.6 months (95% CI, 7.3–11.6 months; Fig. 3B). The 6-month OS rate was 73.6% and the 12-month OS rate was 29.5%.

In an exploratory analysis of stromal TIL levels that included 23 evaluable samples (2 from responders, 21 from nonresponders), the median TIL level was 10% [interquartile range (IQR): 5%–35%]. Because of the small number of samples and the limited number of responders, this analysis was greatly underpowered and did not yield meaningful results.

Safety

Overall, 16 (64%) patients experienced ≥1 treatment-related AE, most commonly nausea in 5 (20%) patients and fatigue in 3 (12%) patients and predominantly grade 1/2 (Table 3). Grade 3/4 treatment-related AEs occurred in 4 (16%) patients and included nausea, autoimmune hepatitis, septic shock, increased γ-glutamyltransferase, and muscular weakness. AEs of special interest with a potential immune-mediated cause (regardless of attribution to pembrolizumab by the investigator) were observed in 5 (20%) patients. These patients experienced grade 2 hypothyroidism, grade 2 hyperthyroidism, grade 3 autoimmune hepatitis, grade 2 infusion-related reaction, and grade 1 pneumonitis.

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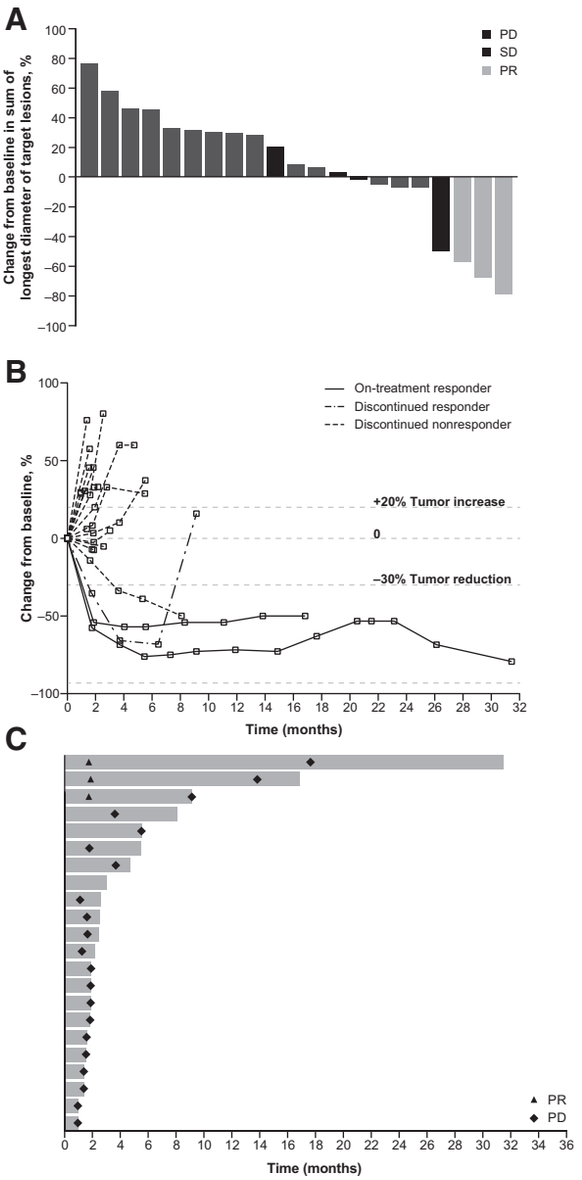

Figure 2.

Antitumor activity of pembrolizumab based on RECIST v1.1 assessed by investigator review in patients with ≥1 evaluable postbaseline tumor assessment ($n = 22$). **A,** Best percentage change from baseline in the sum of the longest diameters of target lesions. **B,** Longitudinal change from baseline in the sum of the longest diameters of target lesions. **C,** Time to and durability of response. In **A** and **B**, data are presented for 20 patients; 2 patients were excluded because of nonevaluable postbaseline lesions. In **C**, bar length is equivalent to the time to the last imaging assessment by investigator review. RECIST, Response Evaluation Criteria in Solid Tumors.

Of the 25 enrolled patients, 24 (96%) discontinued pembrolizumab treatment because of adverse events ($n = 5$), physician decision ($n = 1$), progressive disease ($n = 15$), withdrawal ($n = 3$), or unknown reasons ($n = 1$); none discontinued because of treatment-related toxicity. There were no treatment-related deaths.

Discussion

In this multicohort, open-label, phase Ib study, the safety and efficacy of pembrolizumab were assessed in patients with PD-L1–positive advanced solid tumors. Evidence in other tumor types suggested that PD-L1 expression was associated with higher antitumor activity of PD-1 blockade (33–35); therefore, tumor PD-L1 positivity was used as a selection criterion to improve the likelihood of identification of clinical benefit with PD-1 inhibition across multiple tumor types. The data presented herein show that, in the cohort of patients with previously treated, PD-L1–positive, $ER^+/HER2^-$ advanced breast cancer, treatment with pembrolizumab is well tolerated and provides durable overall response in some patients. Most treatment-related AEs were low grade and manageable.

The safety profile observed with pembrolizumab in this population is comparable with that reported in other studies (13, 20, 34). In this study, the most common AEs were nausea, fatigue, and rash, which were consistent with the AEs most commonly observed in the initial dose-expansion phase of the KEYNOTE-001 study of pembrolizumab in patients with advanced solid tumors (13). Grade 3/4 treatment-related AEs, namely, increased γ-glutamyltransferase and autoimmune hepatitis, were similar to those reported for patients with non–small cell lung cancer treated with pembrolizumab (34).

The observed ORR in this study is comparable with that reported in other cohorts of KEYNOTE-028 (11%–30%). Notably, all patients who experienced PR had received ≥3 lines of previous therapy because of metastatic disease. A durable clinical benefit of more than 24 weeks was observed in 20% of patients.

Only 19.4% of patients with evaluable $ER^+/HER2^-$ tumors were PD-L1 positive. By comparison, in the KEYNOTE-012 trial to investigate pembrolizumab in TNBC, 58.6% of the 111 patients screened were PD-L1 positive (25). The ORR of 12% is also lower than the ORR of 18.5% observed for PD-L1–positive TNBC in the KEYNOTE-012 study (25). This difference reflects the relatively low level of lymphocyte infiltration observed in $ER^+/HER2^-$ tumors compared with TNBC and $HER2^+$ tumors, a feature that has been termed as being immunologically "cold" and may predict nonresponsiveness to single-agent checkpoint inhibition (36). Further work is warranted to compare subsets of PD-L1–positive and PD-L1–negative $ER^+/HER2^-$ tumor responsiveness to pembrolizumab to establish the importance of PD-L1 expression.

Although only 3 (12%) of the patients in this trial had lobular histology, 2 of those 3 patients were among the 3 responders. This raises the question of whether lobular tumors are more responsive to immune checkpoint blockade. In addition, a small subset of lobular tumors contains greater immune infiltrate, raising the additional question of whether the lobular cancers that respond are part of this subset (37). The small size of this trial does not allow conclusions based on lobular disease as a signal for treatment response. The JAVELIN trial of avelumab in locally advanced or metastatic breast cancer included 6 patients (3.6% of the study population) with lobular histology. The histology of the responders (3% of the study population) was not reported. However, the authors did report that 3 responders had TNBC, and none of the patients with lobular tumors had TNBC (38). Investigation in larger trials of enrichment for lobular histology among ER^+ breast cancers that are responsive to immune checkpoint inhibition would be of interest.

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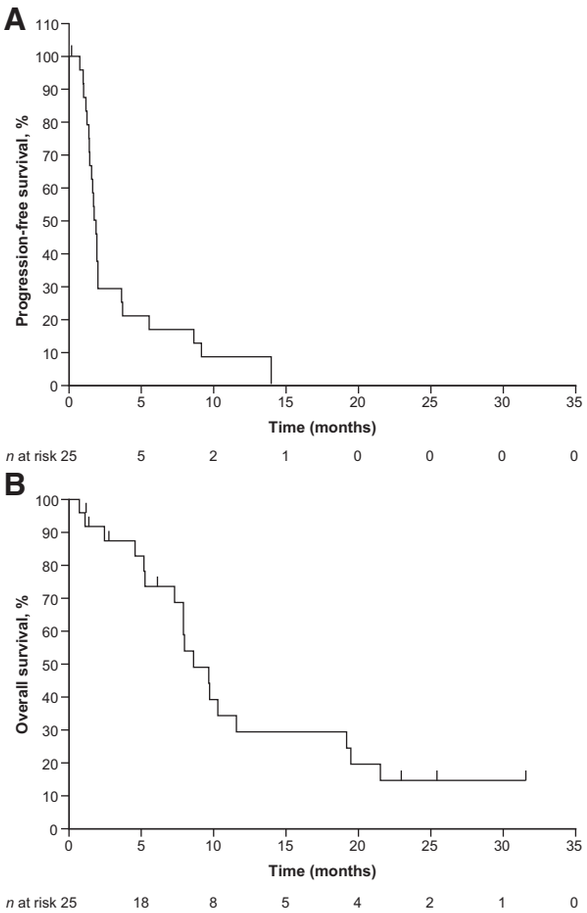

Figure 3.
Kaplan–Meier curves of (**A**) progression-free survival and (**B**) overall survival.

Because this was a "signal-finding" study, tumor PD-L1 expression was used as a selection criterion to enrich the patient population. Given the low rate of PD-L1 positivity, the relatively low response rate in this study, and the observation that, in other tumor types, patients with PD-L1–negative tumors may also respond to PD-1 inhibition, additional biomarkers such as TILs, interferon-γ gene expression signatures, and tumor mutational burden might be helpful in identifying responders in subsequent larger studies in advanced ER$^+$/HER2$^-$ breast cancer.

Table 3. Treatment-related adverse events

AEs	*N* = 25
Any-grade adverse events occurring in ≥2 patients, *n* (%)	
Nausea	5 (20)
Fatigue	3 (12)
Arthralgia	2 (8)
Decreased appetite	2 (8)
Mucosal inflammation	2 (8)
Pruritus	2 (8)
Rash	2 (8)
Grade 3/4 adverse events occurring in ≥1 patient, *n* (%)	
Autoimmune hepatitis (grade 3)	1 (4)
γ-Glutamyltransferase increased (grade 3)	1 (4)
Muscular weakness (grade 3)[a]	1 (4)
Nausea (grade 3)[a]	1 (4)
Septic shock (grade 4)	1 (4)

Abbreviation: AE, adverse event.
[a]Occurred in the same patient.

In a recent study (37), the relevance of TILs for chemotherapy response and prognosis in patients with TNBC, HER2$^+$ breast cancer, and luminal (hormone receptor positive [HR$^+$]) HER2$^-$ breast cancer was assessed. Increased TIL concentration was associated with a survival benefit in TNBC and HER2$^+$ breast cancer but was an adverse prognostic factor for survival in HR$^+$ HER2$^-$ breast cancer. It was proposed that this difference between HR$^+$ HER2$^-$ and TNBC might be the result of different immune cell composition of the infiltrates observed in the 2 tumor types. In TNBC, B cells, T cells, and macrophages were increased and linked to improved survival. In contrast, the presence of T cells was not prognostic of survival, and only B cells and myeloid dendritic cells were linked to survival in HR$^+$ HER2$^-$ breast cancer (37). These results indicate that, beyond TILs, the analysis of specific immune cell subtypes in immune infiltrates is of interest in identifying potential prognostic markers of response.

Limitations of the current study include small sample size and selective enrollment of patients with PD-L1–positive tumors. By excluding patients with PD-L1–negative tumors, this study did not allow for comparison of the response to pembrolizumab in patients with PD-L1–positive and PD-L1–negative tumors. Additionally, this study was constrained because a high proportion of patients received multiple lines of therapy.

Since the time this study was conducted, CDK4/6 inhibitors have emerged as first- and second-line treatments for ER$^+$/HER2$^-$ metastatic breast cancer (6, 9). Combining antihormone therapy with a CDK4/6 inhibitor and pembrolizumab is an interesting treatment to explore. Recent studies in a mouse model of breast carcinoma showed that selective CDK4/6 inhibitors not only induce tumor cell arrest, but also promote antitumor immunity in 2 ways (39). First, CDK/6 inhibitors activate tumor cell expression of endogenous retroviral elements, increasing intracellular double-stranded RNA, which stimulates production of type III interferons, which then enhance tumor antigen presentation. Second, CDK4/6 inhibitors suppress proliferation of regulatory T cells. Ultimately, these events promote T-cell–mediated tumor cell clearance. In this mouse model, CDK4/6 inhibition initially resulted in a decrease in tumor size, but growth resumed by day 21. However, when CDK4/6 inhibition was coupled with anti–PD-L1 combination therapy, tumors regressed to a greater degree, and tumor growth did not resume by day 35 (39). These results suggest that CDK4/6 inhibition combined with PD-L1 inhibition would be more effective than CDK4/6 inhibition alone. The combination of letrozole, palbociclib, and pembrolizumab is currently being investigated in clinical trials (40).

In conclusion, in patients with heavily pretreated, PD-L1–positive, advanced ER$^+$/HER2$^-$ breast cancer, pembrolizumab was well tolerated with durable overall responses in certain patients. Additional studies should be conducted to investigate the safety and efficacy of pembrolizumab in combination with other therapies and should investigate possible biomarkers, or other clinical characteristics that may be predictive of pembrolizumab response.

Disclosure of Potential Conflicts of Interest

S.-A. Im is a consultant/advisory board member for AstraZeneca, Hanmi, Novartis, and Roche/Genentech. P.A. Ott reports receiving other commercial

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