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Pembrolizumab in patients with programmed death ligand 1–positive advanced ovarian cancer: Analysis of KEYNOTE-028☆

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HIGHLIGHTS

- Most patients with ovarian cancer eventually relapse and ultimately die of chemoresistant disease
- Sustained responses are less likely after second-line and subsequent therapies, suggesting a need for new treatment options
- Responses to pembrolizumab were modest but durable in patients with advanced ovarian cancer expressing PD-L1
- The safety profile of pembrolizumab was acceptable, with no deaths or treatment-related discontinuations
- Further evaluation of pembrolizumab is warranted to identify the tumors most likely to respond in this patient population

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ABSTRACT

Objective. To evaluate safety, tolerability, and antitumor activity of pembrolizumab monotherapy in patients with programmed death ligand 1 (PD-L1)–expressing advanced ovarian cancer enrolled in the multicohort, phase Ib KEYNOTE-028 trial.

Methods. Key inclusion criteria were age ≥18 years; advanced ovarian epithelial, fallopian tube, or primary peritoneal carcinoma; failure of previous therapy; and tumor PD-L1 positivity. Patients received pembrolizumab (10 mg/kg every 2 weeks) for ≤24 months or until disease progression/intolerable toxicity. Tumor response was assessed per RECIST v1.1 (investigator review). Adverse events (AEs) were graded using CTCAE version 4.0. Primary end point was confirmed objective response rate (ORR) per RECIST v1.1 (investigator review); data cutoff date was February 20, 2017.

Results. Twenty-six patients (median age, 57.5 years) with PD-L1–positive advanced metastatic ovarian cancer received pembrolizumab; 38.5% had metastatic disease, and 73.1% previously received ≥3 lines of therapy. Treatment-related AEs (TRAEs) occurred in 19 (73.1%) patients, most commonly arthralgia (19.2%), nausea (15.4%), and pruritus (15.4%). One grade 3 TRAE (increased plasma transaminase level) occurred. No deaths and no treatment discontinuations due to TRAEs occurred. After a median follow-up duration of 15.4 months, ORR was 11.5% (1 complete response, 2 partial responses); 7 patients (26.9%) achieved stable disease. Median progression-free and overall survival were 1.9 (95% CI, 1.8–3.5) and 13.8 (95% CI, 6.7–18.8) months, respectively.

Conclusion. Pembrolizumab conferred durable antitumor activity with manageable safety and toxicity in patients with advanced PD-L1–positive ovarian cancer and is under further investigation in an ongoing phase II trial, KEYNOTE-100.

☆ Clinical trial information: NCT02054806.

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1. Background

Ovarian cancer is the seventh most common cancer in women worldwide (sixth in the United States [1]) and ranks 18th overall. Of 239,000 patients who received diagnoses in 2012, almost two thirds (64%) died of the disease [2], largely because symptoms are vague and nonspecific and appear only when the disease is advanced and because effective screening strategies are lacking [3].

First-line treatment options include cytoreductive surgery followed by carboplatin plus paclitaxel or docetaxel [3]. Despite a response rate of 70% to 80% with these regimens, most women experience relapse or disease progression and ultimately develop chemotherapy-resistant disease [4,5]. Platinum-sensitive recurrence (active disease recurrence in a patient with documented response to initial platinum-based therapy but off therapy for an extended time [6]) is treated with platinum-based combination therapy such as carboplatin/paclitaxel and carboplatin/liposomal doxorubicin [3]. The mainstay of treatment for recurrent, platinum-resistant disease is nonplatinum-based monotherapy or bevacizumab-based combination therapy with paclitaxel, doxorubicin, or topotecan [3]. Response rates vary according to the interval between completion of first-line therapy and disease recurrence and are generally low (19% to 31%) [3,5,7]. It is thus clear that patients with advanced metastatic ovarian cancer represent a population in dire need of effective therapeutic strategies.

The immune system plays a significant role in ovarian cancer outcome, with intratumoral T cells conferring a survival benefit. In a study of 174 patients with varying responses to surgical debulking and adjuvant chemotherapy, intratumoral T cells were associated with prolonged progression-free survival (PFS) (22.4 months vs. 5.8 months in the absence of intratumoral T cells; $P < 0.001$), 5-year overall survival (OS) (38.0% vs. 4.5% in the absence of intratumoral T cells; $P < 0.001$), and delayed recurrence or death [8]. Complete response (CR) to adjuvant chemotherapy conferred an almost tenfold increase in the duration of PFS, and evidence showed immune activation with increased expression of immune cell-attracting chemokines [8]. Conversely, ovarian tumors can evade immune recognition through an array of suppressive factors and genetic changes [9]. In particular, CD4 regulatory T cells ($CD4^+$ Tregs), which block the function of activated T cells, are upregulated in the peripheral blood of patients with ovarian tumors [9,10]. Levels of intratumoral $CD4^+$ Treg infiltration are also prognostic. Increased levels of intratumoral $CD4^+$ Tregs in ovarian tumors are associated with poor patient survival; in one study, patients with the highest Tregs levels had a 25.1-fold higher mortality risk than those with the lowest Tregs levels [11]. Low intratumor levels of FOXP3 (forkhead box P3; expressed specifically by Tregs) are associated with significantly improved survival and delayed progression over high intratumoral levels (PFS [median ± SD], 57.5 ± 27.3 months vs. 18.0 ± 0.7 months) [12]. FOXP3 expression was independently prognostic of OS and PFS [12]. Tumor cells themselves, in addition to intratumoral macrophages, produce a Treg-attracting chemokine, CCL22, that promotes $CD4^+$ Treg accumulation within the tumor [11].

Overexpression of the immune-checkpoint receptor programmed death-1 (PD-1) ligand, PD-L1, can lead to inhibition of an effective antitumor immune response [13,14]. Upregulation of PD-1 limits T-cell activity during the inflammatory response to infection and autoimmunity and may confer immune resistance to tumors, contributing to their ability to escape attack by tumor-specific T cells [13,14]. The existence of an immunosuppressive environment in ovarian tumors is further evidenced by the reported association between high PD-L1 expression on ovarian cancer cells and reduced tumor infiltration of cytotoxic T lymphocytes (tumor infiltrating lymphocytes [TILs]) [15]. Activation of the PD-1 pathway also escalates Treg function [16]. The presence of PD-L1 in tumors thus presents a potential target toward counteracting tumor immune suppression mediated by the PD-1/PD-L1 pathway [17]. Indeed, blockade of the PD-1/PD-L1 axis has demonstrated antitumor activity in a wide spectrum of solid and hematologic malignancies (including recurrent and platinum-resistant ovarian cancer [18,19]), and PD-L1 expression has been correlated with a higher rate of response to this therapy [20,21]. Patients with high tumor cell PD-L1 expression had poorer outcomes, and multivariate analysis demonstrated that PD-L1 expression is an independent prognostic factor in ovarian cancer [15] and some other cancers [19,22]. PD-L1 can be expressed in a variety of cell types other than tumor cells [23]. In ovarian cancer, PD-L1 is expressed primarily by TILs, and PD-L1 expression on tumor cells and TILs is prognostic of survival [24]. Taken together, these findings suggest that immune checkpoint blockade using an anti-PD1/-PD-L1 therapy could be particularly beneficial for the subpopulation of patients with PD-L1–expressing ovarian tumors.

Pembrolizumab is a high-affinity, humanized monoclonal antibody targeting PD-1 that has demonstrated robust antitumor activity and a favorable safety profile in multiple tumor types and is approved worldwide for selected advanced malignancies [25,26]. The aim of the multicohort KEYNOTE-028 study (NCT02054806) was to evaluate the safety and efficacy of pembrolizumab in patients with advanced solid tumors selected for PD-L1 expression. Findings of the ovarian cancer cohort are presented here.

2. Methods

2.1. Study design and patient population

KEYNOTE-028 is a nonrandomized (open-label), multicohort, phase Ib trial of pembrolizumab in patients with PD-L1–positive advanced solid tumors. Key eligibility criteria for the present cohort were age ≥18 years; advanced ovarian epithelial, fallopian tube, or primary peritoneal carcinoma; failure of previous therapy (or disease for which no standard therapy exists or therapy is not considered appropriate by the patient and treating physician), measurable disease based on Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1), PD-L1 positivity, determined immunohistochemically and defined as membranous staining on ≥1% modified proportion score or interface pattern (QualTek Molecular Laboratories, Goleta, CA, USA) using the 22C3 antibody (Merck & Co., Inc., Kenilworth, NJ, USA) [27] and Eastern Cooperative Oncology Group performance status 0 or 1. Key exclusion criteria included diagnosis of immunodeficiency; anticancer monoclonal antibody therapy within 4 weeks or chemotherapy within 2 weeks before study day 1; known active CNS metastases or carcinomatous meningitis; active autoimmune disease; and interstitial lung disease. Histological subtypes of adenocarcinoma, MSI status and BRCA status were not collected because of the multicohort nature of the KEYNOTE-028 study.

The protocol and all amendments were approved by the relevant institutional review board or independent ethics committee at each study center. The study was conducted in accordance with the protocol, Good Clinical Practice guidelines, and the provisions of the Declaration of Helsinki. All patients provided written informed consent.

2.2. Treatment and assessments

All enrolled patients received pembrolizumab 10 mg/kg every 2 weeks for ≤24 months or until disease progression, intolerable toxicity, death, or withdrawal of consent. Tumor response was assessed every 8 weeks for the first 6 months and every 12 weeks thereafter per RECIST v1.1 by investigator review. Patients with radiographic progression who were clinically stable could remain on pembrolizumab until progression was confirmed on follow-up imaging performed ≥4 weeks later. Furthermore, patients who had confirmed radiographic progression but whose disease was clinically stable or improved were also able to remain on treatment at the discretion of the investigator. Doses were withheld because of predetermined toxicities; in these cases, pembrolizumab was resumed only upon resolution of that

toxicity to grade 0 to 1 or baseline within 12 weeks of the last infusion; otherwise treatment was discontinued. Adverse events (AEs) were assessed and graded using National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

2.3. End points

The primary efficacy end point was confirmed overall response rate (ORR; defined as the proportion of patients with a best overall response of CR or partial response [PR]) per RECIST v1.1 by investigator review. Secondary end points included safety, duration of response (DOR), PFS, and OS. Safety was assessed by recording toxicities and grades of AEs experienced by patients who received pembrolizumab.

2.4. Statistical analysis

A sequential monitoring procedure was used to evaluate for efficacy and futility simultaneously based on the number of patients with confirmed or unconfirmed response (six or more patients). Enrollment of approximately 22 subjects was planned, providing 80% power to demonstrate that the best ORR induced by pembrolizumab exceeds 10% (based on the assumption that the population is expected to consist of patients with incurable solid tumors for whom multiple lines of therapy have failed) at an overall one-sided 8% alpha level, if the true best ORR is 35%. Efficacy was assessed in all patients who received at least one dose of pembrolizumab and whose baseline scan showed measurable disease per RECIST v1.1 (full analysis set); DOR was assessed using data from all responders. ORR was analyzed using the truncated sequential probability ratio test; missing observations were counted as no responses. The Kaplan-Meier method was used to estimate PFS, OS, and DOR; PFS and DOR were also described using summary statistics. Safety and tolerability were assessed in the all-patients-as-treated population, comprising all patients who received at least one 1 dose of pembrolizumab. Safety and tolerability were evaluated by clinical review of all relevant parameters including AEs, laboratory test results, and vital signs, and were summarized using descriptive statistics. Immune-related AEs, defined as AEs (nonserious and serious) associated with drug exposure that were consistent with immune phenomena and that had a potentially immunologic etiology, were prespecified as events of interest and were summarized separately. All data were analyzed based on a database cutoff of February 20, 2017.

3. Results

3.1. Baseline patient characteristics

Of 90 screened patients with ovarian cancer, 26 had PD-L1–positive disease and were enrolled (Supplemental Fig. 1). The median age of this cohort was 57.5 years (range, 44 to 75 years). More than one third (38.5%) presented initially with metastatic disease, and more than half ($n = 15$; 58%) previously received more than three lines of therapy for recurrent/metastatic disease; ten patients (38.5%) previously received at least five lines (Table 1). Consistent with NCCN guidelines [3], all patients previously received therapies that included carboplatin (Table 1); other frequently reported previous chemotherapies were paclitaxel ($n = 25$; 96.2%), doxorubicin ($n = 22$; 84.6%), bevacizumab ($n = 16$; 61.5%), and gemcitabine ($n = 16$; 61.5%). The most common sites of metastases were the lymph nodes ($n = 19$; 73.1%), peritoneum ($n = 14$; 53.8%), and liver ($n = 14$; 53.8%). Of the 26 patients enrolled, 16 (61.5%) had PD-L1 expression in the tumor only, six (23.1%) had PD-L1 expression in the stroma only, and four (15.4%) had PD-L1 expression in the tumor and stroma. Median follow-up was 15.4 months (range, 2.3–33.9 months) as of the data cutoff date.

Table 1
Baseline characteristics.

Characteristic	Total $N = 26$
Age, median (range), years	57.5 (44.0–75.0)
Race, *n* (%)	
White	16 (61.5)
Asian	2 (7.7)
Not specified	8 (30.8)
ECOG performance status,[a] *n* (%)	
0	15 (57.7)
1	11 (42.3)
Adjuvant/neoadjuvant systemic therapy, *n* (%)	14 (53.8)
Metastatic stage (TNM), *n* (%)	
MX	6 (23.1)
M0	8 (30.8)
M1	10 (38.5)
Unknown	2 (7.7)
Tumor histology, *n* (%)	
Adenocarcinoma	12 (46.2)
High-grade serous	9 (34.6)
Papillary adenocarcinoma	3 (11.5)
Endometrioid carcinoma	1 (3.8)
Transitional cell carcinoma	1 (3.8)
Location of metastases, *n* (%)	
Lymph node	19 (73.1)
Peritoneum	14 (53.8)
Liver	14 (53.8)
Pelvis	5 (19.2)
Mediastinum	5 (19.2)
Spleen	4 (15.4)
Pleural cavity	4 (15.4)
Lung	3 (11.5)
Other[a]	14 (53.8)
Previous lines of therapy for advanced disease, *n* (%)	
0	3 (11.5)
2	4 (15.4)
3	4 (15.4)
4	5 (19.2)
≥5	10 (38.5)
Previous therapies, *n* (%)	
Carboplatin	26 (100.0)
Paclitaxel	25 (96.2)
Doxorubicin	22 (84.6)
Bevacizumab	16 (61.5)
Gemcitabine	16 (61.5)
Cisplatin	9 (34.6)
Cyclophosphamide	7 (26.9)
Topotecan	6 (23.1)
Sum of target lesions measurable at baseline, mm	
Subjects with data, *n*	26
Median (range)	77.5 (17.0–178.0)
Baseline lactate dehydrogenase	
Normal	18 (69.2)
Elevated	7 (26.9)
Not reported	1 (3.8)

ECOG, Eastern Cooperative Oncology Group.
[a] "Other" includes all others: kidney, inguinal, uterus ($n = 2$ for each), bone, skin, ovary, neck, retroperitoneum, adrenal, vaginal, rectum, iliac vein, anus, pancreas, peri-pancreas soft tissue, pleural effusion, abdomen, abdominal soft tissue, vaginal cuff implant, peritoneal, rectal implant, omentum, diaphragm, small bowel, abdominal wall, and periportal ($n = 1$ for each).

3.2. Safety

Treatment-related AEs (TRAEs) were observed in 19 (73.1%) patients; one TRAE (3.8%) was grade 3 or higher (increased plasma transaminase levels). The most commonly encountered TRAEs (occurring in >10% of patients) were arthralgia ($n = 5$; 19.2%), nausea ($n = 4$; 15.4%), pruritus ($n = 4$; 15.4%), diarrhea ($n = 3$; 11.5%), and rash ($n = 3$; 11.5%) (Table 2). No patients died during the study as a result of AEs, and none discontinued because of TRAEs. Eight immune-mediated AEs were observed in 7 (26.9%) patients (Table 2): hypothyroidism ($n = 3$; 11.5%), hyperthyroidism ($n = 2$; 7.7%), myositis ($n = 1$; 3.8%), pancreatitis ($n = 1$; 3.8%), and uveitis ($n = 1$; 3.8%). Pancreatitis was the only immune-mediated AE that was grade 3.

Table 2
TRAEs of any grade observed in ≥2 patients and immune-mediated AEs observed in any patient ($N = 26$).

	n (%)[a]
TRAE	19 (73.1)
Arthralgia	5 (19.2)
Nausea	4 (15.4)
Pruritus	4 (15.4)
Diarrhea	3 (11.5)
Rash	3 (11.5)
Abdominal pain (lower)	2 (7.7)
Asthenia	2 (7.7)
Fatigue	2 (7.7)
Hypothyroidism	2 (7.7)
Onychomadesis	2 (7.7)
Pyrexia	2 (7.7)
Thrombocytopenia	2 (7.7)
Grade 3 TRAE	
Transaminase levels increased	1 (3.8)
Immune-mediated AEs[b]	
Any	7 (26.9)
Hypothyroidism	3 (11.5)
Hyperthyroidism	2 (7.7)
Myositis	1 (3.8)
Pancreatitis	1 (3.8)
Uveitis	1 (3.8)

AEs, adverse events; TRAEs, treatment-related adverse events.
[a] Included patients who had received ≥1 dose of pembrolizumab.
[b] Defined as events with potentially drug-related immunologic causes that were consistent with an immune phenomenon, regardless of whether they were attributable to the study drug or to an immune response.

3.3. Antitumor activity

Data for all 26 patients were available for efficacy analysis. Best overall response was CR in one patient and PR in two patients, for an ORR of 11.5% (95% CI, 2.4–30.2%) (Table 3). All three responders completed 2 years of treatment (Fig. 1). Of the remaining 23 patients, seven (26.9%) had stable disease and 16 (61.5%) experienced disease progression. The clinical benefit rate (proportion of patients with a best overall response of CR, PR, or stable disease lasting ≥6 months) was 19.2% (95% CI, 6.6–39.4%). Median (range) time to response was 1.7 months (1.7–1.8 months), and the median DOR was not reached (range, 20.5 + to 30.4+ months) (Table 3).

Reductions in tumor size from baseline were observed in 7/26 (26.9%) patients; one patient experienced complete resolution of the target tumor (Fig. 2A). The decreases in tumor size of the three responders were maintained over time (Fig. 2B). The target lesions of these responders were in the liver and spleen, pelvis, and lymph node, respectively (Supplemental Table S1).

Table 3
Best overall response as assessed by investigator review according to RECIST v1.1 and duration of response.

	Total $N = 26$
Best overall response	
ORR,[a] n (%, [95% CI])[b]	3 (11.5 [2.4 to 30.2])
CR	1 (3.8 [0.1 to 19.6])
PR	2 (7.7 [0.9 to 25.1])
CBR (CR + PR + SD ≥6 months), n (% [95% CI])[b]	5 (19.2 [6.6 to 39.4])
SD, n (% [95% CI])[b]	7 (26.9 [11.6 to 47.8])
Progressive disease, n (% [95% CI])[b]	16 (61.5 [40.6 to 79.8])
Time to response, months	
n	3
Median (range)	1.7 (1.7 to 1.8)
Response duration, months	
n	3
Median (range)	NR (20.5+ to 30.4+)

CBR, clinical benefit rate; CI, confidence interval; CR, complete response; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease.
[a] Only confirmed responses were included. Patients who received at least one dose of pembrolizumab and had measurable disease at baseline as per RECIST v1.1 were included.
[b] Based on binomial exact CI method.

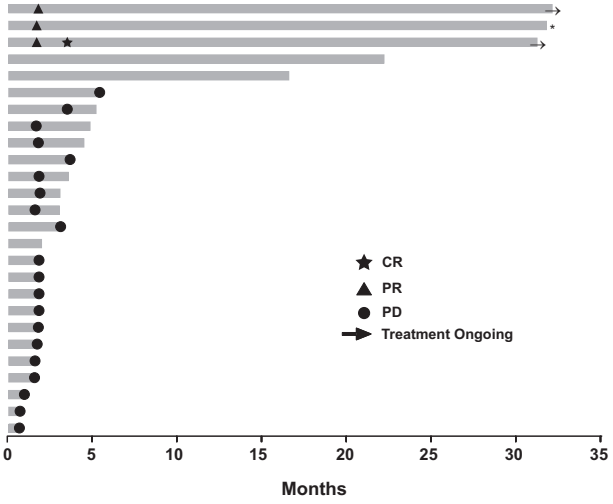

Fig. 1. Treatment exposure and duration of response in responders ($N = 26$). The length of the bars corresponds with time to the last tumor assessment. Only PR, CR, disease progression, and ongoing response are displayed for each subject. *Response presumed to be ongoing; patient had ≥2 consecutive missed assessments. CR, complete response; PD, progressive disease; PR, partial response.

Median (95% CI) PFS and OS were 1.9 months (1.8–3.5 months) and 13.8 months (6.7–18.8 months), respectively (Fig. 3A, B). The 6- and 12-month PFS rates were both 21.4%. The 6- and 12-month OS rates were 79.2% and 54.2%, respectively.

3.4. Tumor, disease, and treatment characteristics of the responders

Of the three responders, the one with CR had stage III transitional cell carcinoma, M0 disease, PD-L1–positive tumor and stroma and previously received no lines of therapy for recurrent/metastatic disease. Both patients who experienced PR had adenocarcinoma; one patient had stage IIIC, M0 disease, PD-L1–positive tumor and stroma and previously received two lines of therapy for recurrent/metastatic disease, and the other had stage IV, M1 disease, PD-L1–positive tumor cells only and previously received five lines of systemic therapy for recurrent/metastatic disease (Supplemental Table S1). Two responses were ongoing at the time of data analysis, with durations of 29.6+ and 30.4+, and one patient had at least two consecutive missed assessments but was presumed to be ongoing with a duration of 20.5+ months, respectively.

4. Discussion

The high rate of relapse or chemotherapy resistance after first-line treatment of ovarian cancer and the diminishing responses to currently recommended second-line or subsequent therapies [3–5] highlight an urgent need for an effective therapeutic strategy in this patient population. The role of PD-L1 selection for pembrolizumab in ovarian cancer has not been explored; however, the established success of pembrolizumab for the treatment of certain PD-L1–positive malignancies [28–30] (reflected by US Food and Drug Administration approval of pembrolizumab for the treatment of PD-L1–positive non-small cell lung carcinoma and gastric cancer [25]) suggests that consideration of only patients with PD-L1–expressing ovarian tumors may enrich for those more likely to respond to this immune checkpoint inhibitor.

Pembrolizumab was well tolerated and conferred promising antitumor activity in this cohort of patients with PD-L1–positive ovarian cancer, with an ORR of 11.5%. Notably, all responses were durable (≥20.5+

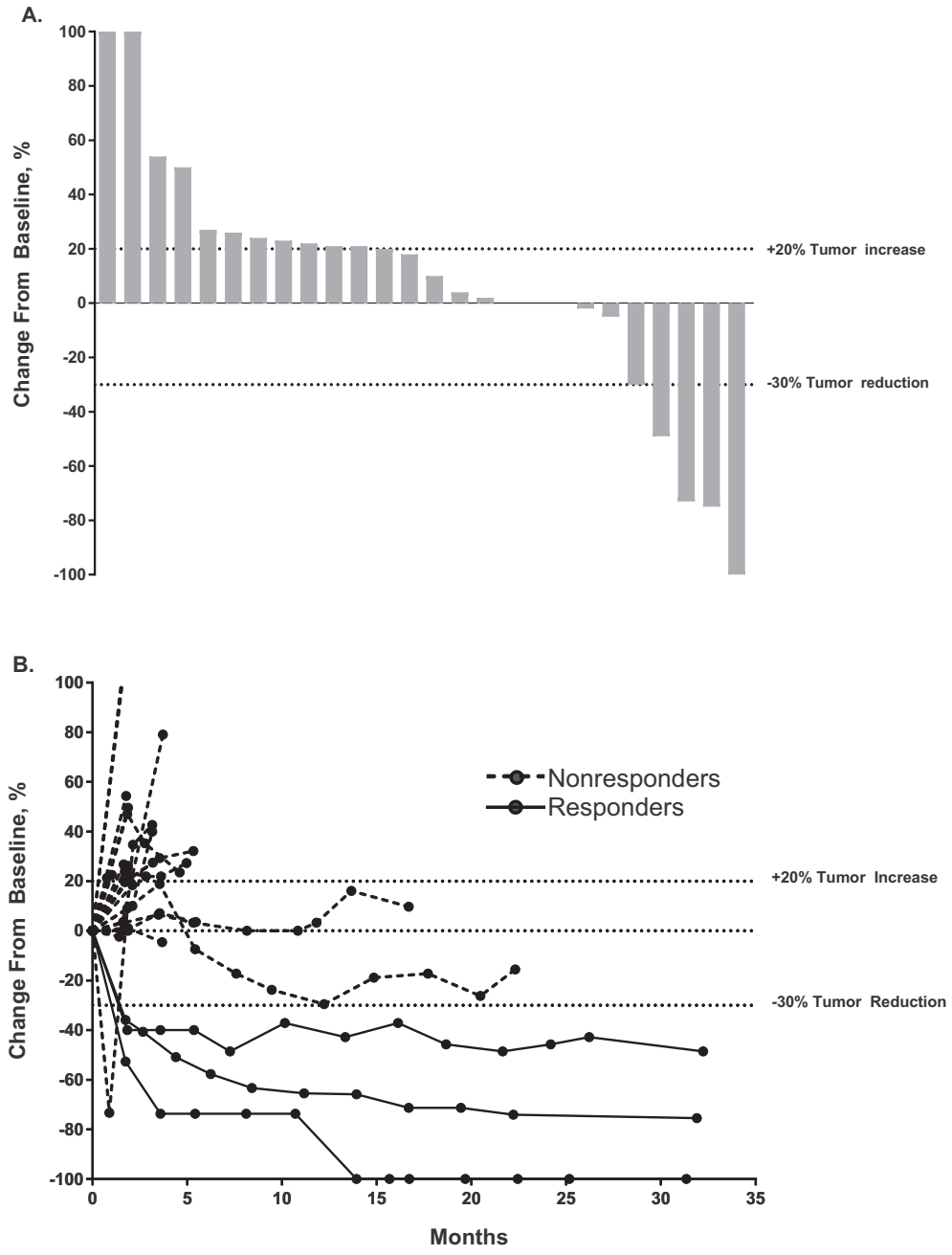

Fig. 2. Change in tumor size from baseline as assessed per RECIST v1.1 by investigator review. (A) Best percentage change from baseline ($N = 26$). (B) Longitudinal change from baseline ($N = 26$). Percentage changes >100% are truncated at 100%. RECIST v1.1, Response Evaluation Criteria in Solid Tumors, version 1.1.

months), and two were ongoing at the time of this analysis. The safety and toxicity profile of pembrolizumab in these patients was favorable, and no deaths or discontinuations occurred because of TRAEs. Although eight immune-mediated AEs were observed, they occurred infrequently ($n = 7/26$ patients) and were generally low grade; only one was grade 3 (grade 3 pancreatitis).

The weight-based dose of pembrolizumab administered in this study (10 mg/kg every 2 weeks [Q2W]), the highest dose tested in the open-label phase I KEYNOTE-001 trial [30], differs from the fixed-dose (in adults) of 200 mg every 3 weeks (Q3W) that is now recommended [25]. Exploration of weight-based (10 mg/kg Q2W or Q3W, 2 mg/kg Q3W) and fixed-dose (200 mg Q3W) schedules during the therapeutic development of pembrolizumab revealed no difference in efficacy or safety among the three weight-based doses [31] and comparable exposures with the 200-mg Q3W and 2-mg/kg Q3W schedules [32]. The fixed dose, now being applied in all ongoing trials of ovarian cancer, may further improve the tolerability of pembrolizumab.

The antitumor response observed with pembrolizumab (11.5%) was similar to that reported in a phase II clinical trial for a cohort of 20 patients with platinum-resistant ovarian cancer treated with another anti-PD-1 antibody, nivolumab. The ORR of all patients regardless of PD-L1 status was 15%, including two patients who experienced CR [18]. In addition, the ORR in a phase Ib study of avelumab in 124 patients with refractory or recurrent ovarian cancer was 9.7% [33,34], and the ORR in a phase II study of ipilimumab in 40 patients with recurrent platinum-sensitive ovarian cancer was 10.3% [33]. Toxicity was particularly problematic in the latter, with a rate of drug-related AEs of grade 3 or higher of 50%; 42.5% of patients discontinued because of drug-related toxicity [33].

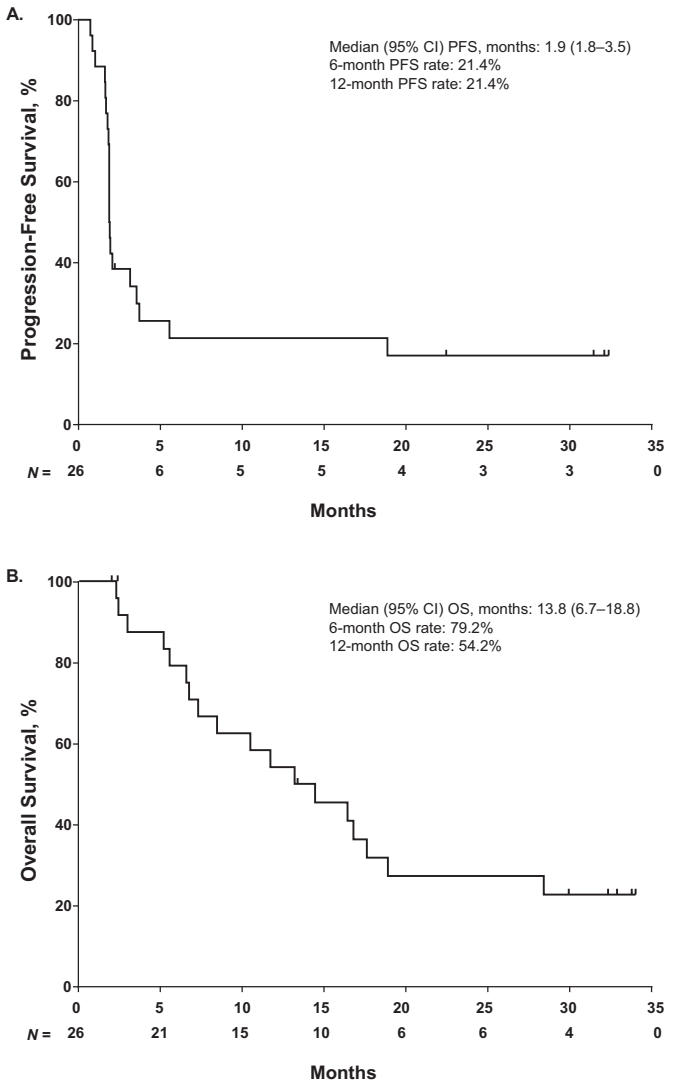

Fig. 3. Kaplan-Meier estimates. (A) PFS per RECIST v1.1 by investigator review ($N = 26$). (B) OS ($N = 26$). From product-limit (Kaplan–Meier) method for censored data. CI, confidence interval; OS, overall survival; PFS, progression-free survival; RECIST v1.1, Response Evaluation Criteria in Solid Tumors, version 1.1.

In addition, BMS-936559, a high-affinity, fully human, PD-L1–specific, immunoglobulin G4 monoclonal antibody that inhibits binding of PD-L1 to PD-1 and CD80, has also shown clinical activity in 17 patients with ovarian cancer whose disease progressed after at least one previous course of chemotherapy for advanced or metastatic disease, with ORRs of 6% (one patient with PR) and 18% (three patients with stable disease). Both rates were lower than those obtained in the present study with pembrolizumab monotherapy (11.5% and 26.9%, respectively) [35].

Combination therapies with pembrolizumab are being investigated in patients with ovarian cancer. The combination of pembrolizumab and the indoleamine 2,3-dioxygenase inhibitor epacadostat is being evaluated in patients with advanced tumors, including ovarian cancer, with encouraging safety and antitumor activity overall [36,37]. In advanced or metastatic triple-negative breast cancer or recurrent ovarian cancer, pembrolizumab is being evaluated in combination with the orally active small molecule poly(ADP-ribose)polymerase inhibitor niraparib (NCT02657889) [38]. This list is far from exhaustive but is indicative of the potential of combination therapy with pembrolizumab, possibly extending to patients with PD-L1–expressing, advanced ovarian cancer.

Although the ORR in this study was modest, future identification of biomarkers specific to subtypes of ovarian tumors may enable a tighter focus on those patients most likely to respond. Gene expression profiling analyses have revealed the existence of several distinct and clinically relevant high-grade molecular subtypes (e.g., C1, C2, C4, C5) associated with particular clinical outcomes [39–41]. Furthermore, the mutational load of specific tumor subtypes is also potentially relevant given that the presence of genetic alterations within a tumor is associated with clinical response to immune checkpoint inhibition through generation of neoantigens [33]. Many ovarian cancers have genetic alterations that encode neoantigens, and mismatched repair (MMR) deficiency (through somatic loss of expression) occurs in ≤29% of patients with ovarian cancer (pembrolizumab has recently received approval for the treatment of patients with MMR-deficient solid tumors [25,33]). Despite their elevated PD-L1 expression, it is possible that the tumors analyzed in this study constituted subtypes not particularly amenable to immunotherapy with respect to gene expression profile, predominant genetic alteration, or tumor mutational load. Assessment of the tumor gene expression profile/molecular microenvironment may help identify patients more likely to respond to treatment with pembrolizumab.

4.1. Limitations

Given the multicohort nature of the KEYNOTE-028 study, in which 20 different types of advanced, PD-L1–positive solid tumors were evaluated, details of the specific histological subtypes of ovarian cancer, MSI-H status and BRCA status were not collected in the database. It is possible that response to pembrolizumab may differ between histological subtypes of this disease. Indeed, an association has been demonstrated between high-grade serous ovarian cancers and favorable tumor-infiltrating lymphocyte response, which predisposes the response to PD-1 pathway inhibition [33]. Therefore, this study should be considered hypothesis generating.

The findings of this study are sufficiently promising to warrant further evaluation of pembrolizumab in patients with PD-L1–positive ovarian cancer, potentially refining the tumors most likely to be responsive in this patient population. Pembrolizumab monotherapy is being evaluated in KEYNOTE-100 (NCT02674061), a long-term, open-label, phase II study in which patients with advanced recurrent ovarian cancer will receive pembrolizumab (200 mg Q3W) for 2 years or less.

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Data availability

Merck & Co., Inc.'s data sharing policy, including restrictions, is available at http://engagezone.merck.com/ds_documentation.php. Requests for access to the clinical study data can be submitted through the EngageZone site or via email to dataaccess@merck.com.

Authors' disclosures of potential conflicts of interest

Andrea Varga: Principal/sub-Investigator of Clinical Trials - Abbvie, Aduro, Agios, Amgen, Argen-x, Astex, AstraZeneca, Aveo pharmaceuticals, Bayer, Beigene, Blueprint, BMS, Boeringer Ingelheim, Celgene, Chugai, Clovis, Daiichi Sankyo, Debiopharm, Eisai, Eos, Exelixis, Forma, Gamamabs, Genentech, Gortec, GSK, H3 biomedecine, Incyte, Innate Pharma, Janssen, Kura Oncology, Kyowa, Lilly, Loxo, Lysarc, Lytix Biopharma, Medimmune, Menarini, Merus, MSD, Nanobiotix, Nektar Therapeutics, Novartis, Octimet, Oncoethix, Oncopeptides AB, Orion, Pfizer, Pharmamar, Pierre Fabre, Roche, Sanofi, Servier, Sierra Oncology, Taiho, Takeda, Tesaro, Xencor. Teaching/ speaker activities for Astra Zeneca, MSD, Roche. Tavel, accomodations, expenses - AstraZeneca, Clovis, Boeringer Ingelheim, Roche.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2018.11.017.

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