

ORIGINAL ARTICLE

Antitumor activity and safety of pembrolizumab in patients with advanced recurrent ovarian cancer: results from the phase II KEYNOTE-100 study

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Background: Advanced recurrent ovarian cancer (ROC) is the leading cause of gynecologic cancer-related death in developed countries and new treatments are needed. Previous studies of immune checkpoint blockade showed low objective response rates (ORR) in ROC with no identified predictive biomarker.

Patients and methods: This phase II study of pembrolizumab (NCT02674061) examined two patient cohorts with ROC: cohort A received one to three prior lines of treatment with a platinum-free interval (PFI) or treatment-free interval (TFI) between 3 and 12 months and cohort B received four to six prior lines with a PFI/TFI of ≥ 3 months. Pembrolizumab 200 mg was administered intravenously every 3 weeks until cancer progression, toxicity, or completion of 2 years. Primary end points were ORR by Response Evaluation Criteria in Solid Tumors version 1.1 per blinded independent central review by cohort and by PD-L1 expression measured as combined positive score (CPS). Secondary end points included duration of response (DOR), disease control rate (DCR), progression-free survival (PFS), overall survival (OS), and safety.

Results: Cohort A enrolled 285 patients; the first 100 served as the training set for PD-L1 biomarker analysis. Cohort B enrolled 91 patients. ORR was 7.4% for cohort A and 9.9% for cohort B. Median DOR was 8.2 months for cohort A and not reached for cohort B. DCR was 37.2% and 37.4%, respectively, in cohorts A and B. Based on the training set analysis, CPS 1 and 10 were selected for evaluation in the confirmation set. In the confirmation set, ORR was 4.1% for CPS < 1 , 5.7% CPS ≥ 1 , and 10.0% for CPS ≥ 10 . PFS was 2.1 months for both cohorts. Median OS was not reached for cohort A and was 17.6 months for cohort B. Toxicities were consistent with other single-agent pembrolizumab trials.

Conclusions: Single-agent pembrolizumab showed modest activity in patients with ROC. Higher PD-L1 expression was correlated with higher response.

Clinical Trial Number: Clinicaltrials.gov, NCT02674061

Key words: ovarian cancer, pembrolizumab, immunotherapy, combined positive score

Introduction

Advanced recurrent ovarian cancer (ROC), the leading cause of gynecologic cancer-related death in the developed world, is responsible for over 184 000 deaths annually worldwide [1]. Most women are diagnosed at a later stage and, despite response to initial platinum-based chemotherapy, the majority will develop recurrent cancer and die of their cancer [2, 3].

Treatment of ROC has traditionally been decided based on platinum sensitivity; platinum-sensitive recurrence is defined as cancer progression ≥ 6 months, and platinum-resistant recurrence is < 6 months, after platinum-based chemotherapy. As patients with ROC receive more lines of treatment, the platinum-free interval (PFI) shortens for those with platinum-sensitive recurrence, and the treatment response is usually < 3 months for those with platinum-resistant cancer. Defining platinum sensitivity based on PFI lacks precision and it is therefore preferable to consider alternate factors that might predict response to treatment, such as biomarkers, histology, *BRCA* status, and the number of prior lines of treatment [4, 5]. Additionally, the introduction of targeted agents such as bevacizumab and poly (ADP ribose) polymerase (PARP) inhibitors into ovarian cancer treatment may confound the interpretation of platinum sensitivity.

The importance of the immune system in ovarian cancer has been demonstrated by favorable prognostic implications, such as the presence of tumor-infiltrating lymphocytes (TILs), but contradictory outcomes have been reported with increased PD-L1 expression on ovarian cancer cells [6–8]. Different immunotherapy approaches for the treatment of ROC are underway, including immune checkpoint blockade, autologous T-cell infusions, vaccines, combinations of biologic and immunotherapy agents, and others [9–15]. Single-agent immune checkpoint blockade trials in small patient populations with ROC have demonstrated a low objective response rate (ORR) of $< 15\%$ [9, 10, 15]. To date, no predictive biomarkers have been identified in these studies. The present KEYNOTE-100 clinical trial examined the antitumor activity and safety of pembrolizumab monotherapy in a large population of patients with advanced ROC.

Methods

Study design and participants

This phase II, open-label, multi-center study evaluated the efficacy and safety of pembrolizumab monotherapy in patients with epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer who demonstrated recurrent disease following primary or interval cytoreductive/debulking surgery and standard front-line, platinum-based combination therapy. The study enrolled two cohorts of patients: cohort A received one to three prior lines of treatment and had a PFI or treatment-free interval (TFI) of 3–12 months based on the last regimen received, and cohort B received four to six prior lines of treatment and had a PFI/TFI ≥ 3 months based on the last regimen received. PFI was defined as the time elapsed between the last dose of platinum and documented evidence of disease progression per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST1.1). TFI was defined as the time elapsed between the last dose of the regimen received and documented evidence of disease progression per RECIST1.1. The 3-month minimal PFI and TFI were

mandated in order to only include patients who experienced disease stabilization from their last treatment.

Eligible patients were ≥ 18 years of age and had histologically confirmed ROC, received a platinum-based regimen as front-line treatment and cytoreductive surgery, documented evidence of clinical response or disease stabilization to the last treatment regimen received, measurable disease based on RECIST1.1, life expectancy of ≥ 16 weeks, access to formalin-fixed paraffin-embedded block specimens, and normal organ function.

Key exclusion criteria included active autoimmune disease, mucinous histology, active central nervous system metastases and/or carcinomatous meningitis, other malignancies that progressed or required active treatment within 5 years, bowel obstruction within 3 months, history of pneumonitis, or prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent, or with an agent directed to another co-inhibitory T cell.

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.

Procedures

Pembrolizumab 200 mg was administered intravenously every 3 weeks. Imaging-based disease assessment via CT or MRI and serum CA 125 were carried out every 9 weeks for the first 54 weeks, and every 12 weeks thereafter until disease progression, unacceptable toxicities, investigator decision, noncompliance, patient withdrawal of consent, or the patient received 35 administrations of pembrolizumab (~ 2 years). Patients with a complete response (CR) before 24 months could stop pembrolizumab at the discretion of the investigator. Patients who stopped pembrolizumab after receiving 35 administrations for reasons other than disease progression or intolerability or patients who attained a CR and stopped trial treatment were eligible for up to 17 additional administrations of pembrolizumab (~ 1 year) after experiencing disease progression.

Toxicities were assessed every 3 weeks per Common Toxicity Criteria for Adverse Events, version 4.0. Specific immune-mediated adverse events (AEs) and infusion reactions based on a list specified by the sponsor and considered regardless of attribution to study treatment or immune relatedness by the investigator were also collected.

Outcomes

The primary outcome was the ORR assessed per RECIST1.1 by blinded independent central review (BICR) in both cohorts and by PD-L1 expression level using a cut point that was established in the training set, as described below. Secondary end points (defined in [supplementary material S1](#), available at *Annals of Oncology* online) included progression-free survival (PFS), overall survival (OS), disease control rate (DCR), duration of response (DOR), and safety.

Statistical analyses

PD-L1 analysis. The PD-L1 IHC 22C3 pharmDx assay, Dako North America, was used to assess PD-L1 expression from archival tumor tissue biopsy. The first 100 patients in cohort A were designated the ‘training set’ to identify the PD-L1 scoring cut points. An interim analysis was carried out after 100 patients in cohort A were enrolled and followed for at least 4 months to determine the PD-L1 expression cut point based on PD-L1 biomarker and tumor response data (see [supplementary material S2](#), available at *Annals of Oncology* online). The measure of expression was the combined positive score (CPS), defined as the number of PD-L1 staining cells (tumor cells, lymphocytes, macrophages) divided by the total number of viable tumor cells $\times 100$ [16]. Remaining patients in cohort A (excluding the training set) along with patients in cohort B served as the ‘confirmation set’ for the identified PD-L1 cut points. This independent confirmation set was used to avoid overfitting bias; this analysis

validated that the response rate above the cut point was consistent with predictions made based on the training set data and the association of higher PD-L1 expression with increased clinical activity with pembrolizumab.

Other analyses. All efficacy and safety analyses were carried out in the all-subjects-as-treated population. For ORR, the point estimate and 95% CI were estimated using an exact binomial distribution. Patients without response data were considered non-responders. For PFS and OS, Kaplan–Meier (KM) curves, median estimates, and survival at 6, 12, and 18 months based on the KM curves (95% CI based on Greenwood's formula) were provided. Patients without efficacy or survival data were censored at day 1. Safety and tolerability were assessed by clinical review of all relevant parameters including AEs, laboratory tests, and vital signs.

Results

Overall, 376 patients with ROC were enrolled, and their treatment disposition is shown in [supplementary Figure S2](#), available at *Annals of Oncology* online. The analysis population included 97 patients in the training set with clinical efficacy data available, of whom, 93 patients had CPS data available. Follow-up duration was 16.9 months (range 8.5–18.5 months). At data cut-off on 2 February 2018, 15 patients in cohort A and 6 patients in cohort B were still receiving study treatment.

Baseline characteristics of the patients are listed in [supplementary Table S1](#), available at *Annals of Oncology* online. The ORR was 7.4% in cohort A, 9.9% in cohort B, and 8.0% in the combined cohorts (Table 1). The DCR was ~37% in both cohorts (Table 1). Overall, 36.7% of patients experienced a decrease in their target lesions (Figure 1A). The characteristics of the 30 responses are shown in Figure 1B. The median time to response was 2.1 months in both cohorts, and the median DOR was 8.2 months in cohort A and not reached in cohort B; 65.5% of responses lasted ≥ 6 months (Table 1). At data cut-off, 9 of the 30 responses were ongoing. Median PFS was 2.1 months for both cohorts (Figure 1C). Median OS was not reached in cohort A and was 17.6 months in cohort B (Figure 1D). The 82 patients with CPS ≥ 10 had an ORR of 17.1%; however, neither age, number of prior lines of treatment, PFI/TFI, level of platinum sensitivity, nor ovarian cancer histology impacted the ORR (Figure 1E).

Based on the training set analysis, CPS 1 and 10 were selected for evaluation in the confirmation set (see [supplementary material S2](#), available at *Annals of Oncology* online). The ORR was higher in CPS ≥ 10 patients, both in cohorts A and B (Table 1). For the entire cohort A (training and confirmation sets), which enrolled less heavily pretreated patients, the ORR was 3.7% for CPS < 1 , 10.2% for CPS ≥ 1 , and 16.7% for CPS ≥ 10 patients. The ORR in cohort B followed similar trends: 8.8% for CPS < 1 , 10.0% for CPS ≥ 1 , and 18.2% for CPS ≥ 10 patients. For the combined cohorts A and B, the ORR was 5.0% for CPS < 1 , 10.2% for CPS ≥ 1 , and 17.1% for CPS ≥ 10 patients. Other biomarkers are discussed in [supplementary section S3](#), available at *Annals of Oncology* online.

Overall, 73.1% patients experienced ≥ 1 treatment-related AE, including 19.7% who experienced ≥ 1 grade 3–5 event (Table 2). The most common grade 3–5 toxicity was fatigue (2.7%), which was also the most common overall toxicity. At the time of the data cut-off, 5.1% had discontinued because of a treatment-related AE, and two deaths were attributed to a treatment-related

AE (one Stevens-Johnson syndrome and one hypoaldosteronism). Immune-mediated AEs occurred in 22.6% patients; the most common were hypothyroidism (11.2%) and hyperthyroidism (6.6%) and the most common of grade 3–5 severity were severe skin reaction (1.9%) and colitis (1.6%) (Table 2).

Discussion

Single-agent pembrolizumab in ROC showed an 8% ORR in KEYNOTE-100, the largest study to date of single-agent immune checkpoint for ROC. This study identified a biomarker which was able to predict a higher ORR; higher PD-L1 expression using a CPS of ≥ 10 resulted in a higher ORR compared with a CPS score of ≥ 1 or < 1 . Number of lines of prior treatment, ovarian cancer histology, and the degree of platinum sensitivity were not predictive of response. The responses to pembrolizumab were quite durable in a subset of patients with ROC. No new safety signals of pembrolizumab were demonstrated compared with other trials of single-agent pembrolizumab.

Other phase II studies of single-agent immune checkpoint blockade in ROC have been carried out, including avelumab, nivolumab, and pembrolizumab [9, 10, 15]. In each study, PD-L1 was examined either retrospectively or prospectively as an eligibility requirement. In the largest of these studies, avelumab showed an ORR of 9.7%, with a median PFS of 11.3 weeks and a median OS of 10.8 months. In this study, tumor PD-L1 expression (positive or negative) was assessed using a proprietary IHC assay (Dako; clone 73-10) using various cut points based on quantity and level of staining intensity; 59.7% of samples were available for PD-L1 expression analysis. In patients who had tumor PD-L1 expression measured, ORR was 12.3% for PD-L1-positive cancers (i.e. $\geq 1\%$ threshold in tumor cells) versus 5.9% of PD-L1-negative cancers. This ORR difference was not statistically significant, nor were median PFS and median OS. Single-agent nivolumab was tested in 20 patients unselected for PD-L1 status, and PD-L1 expression was analyzed on tumor cells retrospectively. PD-L1 expression was scored from 0 to 3+ and did not correlate with ORR, which was 15% in the total population; interestingly, one of the two patients with a CR had clear cell carcinoma. In KEYNOTE-028, single-agent pembrolizumab tested in 26 patients with PD-L1-positive (i.e. CPS ≥ 1 determined by membranous staining using the 22C3 antibody) ROC resulted in an ORR of 11.3%, a median PFS of 1.9 months, and a median OS of 13.8 months. In KEYNOTE-028, 38.5% of patients received five or more lines of therapy and histological type was not reported.

KEYNOTE-100 tested the PD-L1 biomarker, and more convincingly showed that, compared with previously reported single-agent checkpoint inhibitors, the level of PD-L1 expression as measured by CPS was predictive of ORR, both in less heavily pretreated (cohort A) and more heavily pretreated (cohort B) patients. This study is unique in that the PD-L1 expression level cut points were carried out within the trial using an established PD-L1 antibody. The first 100 patients enrolled into cohort A were designated the 'training set' and all enrolled and treated patients excluding the training set represented the 'confirmation set' to assess the correlation between PD-L1 expression and ORR. Since the CPS cut-off was selected based on the training set, the

Table 1. Confirmed objective response rates based on RECIST1.1 per BICR

		Cohort A N = 285		Cohort B N = 91		Cohorts A + B N = 376	
		ORR % (95% CI)	n	ORR % (95% CI)	n	ORR % (95% CI)	n
Best overall response		37.2 (31.6–43.1)		37.4 (27.4–48.1)		37.2 (32.3–42.3)	
Complete response n (%)		5 (1.7)		2 (2.2)		7 (1.9)	
Partial response n (%)		16 (5.6)		7 (7.7)		23 (6.1)	
Stable disease n (%)		85 (10.5)		25 (27.5)		110 (29.3)	
Progressive disease n (%)		166 (58.2)		49 (53.8)		215 (57.2)	
Responders (n)		21		9		30	
Time to response, median months (range)		2.1 (1.9–6.3)		2.1 (1.8–12.3)		2.1 (1.8–12.3)	
Duration of response, median months (range)		8.2 (3.9–18.6)		NR (3.3+–15.2+)		8.2 (3.3+–18.6)	

		All Cohort A ^a N = 285				Cohort B N = 91				Cohorts A + B ^a N = 376				
		CPS <1 n = 34	CPS ≥1 n = 59	CPS ≥10 n = 20	CPS <1 n = 73	CPS ≥1 n = 88	CPS ≥10 n = 40	CPS <1 n = 107	CPS ≥1 n = 147	CPS <1 n = 34	CPS ≥1 n = 50	CPS <1 n = 141	CPS ≥1 n = 197	CPS <10 n = 22
ORR % (95% CI)		2.9 (0.1–15.3)	16.9 (8.4–29.0)	30.0 (11.9–54.3)	4.1 (0.9–11.5)	5.7 (1.9–12.8)	10.0 (2.8–23.7)	10.2 (5.8–16.3)	8.8 (1.9–23.7)	10.0 (3.3–21.8)	5.0 (2.0–10.0)	10.2 (6.3–15.2)	18.2 (5.2–40.3)	17.1 (9.7–27.0)
DCR % (95% CI)		29.4 (15.1–47.5)	39.0 (26.5–52.6)	50.0 (27.2–72.8)	31.5 (21.1–43.4)	37.5 (27.4–48.5)	30.8 (22.3–40.5)	38.1 (30.2–46.5)	38.2 (22.2–56.4)	38.0 (24.7–52.8)	32.6 (25.0–41.0)	38.1 (31.3–45.2)	45.5 (24.4–67.8)	41.5 (30.7–52.9)
Best overall response, n (%)		0 (0.0)	3 (5.1)	3 (15.0)	0 (0.0)	2 (2.3)	2 (5.0)	5 (3.4)	0 (0.0)	2 (4.0)	0 (0.0)	7 (3.6)	2 (9.1)	7 (8.5)
Complete response		1 (2.9)	7 (11.9)	3 (15.0)	3 (4.1)	3 (3.4)	2 (5.0)	10 (6.8)	3 (8.8)	3 (6.0)	7 (5.0)	13 (6.6)	2 (9.1)	7 (8.5)
Partial response		9 (26.5)	13 (22.0)	4 (20.0)	20 (27.4)	28 (31.8)	10 (25.0)	41 (27.9)	10 (29.4)	14 (28.0)	39 (27.7)	55 (27.9)	6 (27.3)	20 (24.4)
Stable disease		23 (67.6)	35 (59.3)	10 (50.0)	46 (63.0)	49 (55.7)	22 (55.0)	84 (57.1)	18 (52.9)	29 (58.0)	87 (61.7)	113 (57.4)	12 (54.5)	44 (53.7)
Progressive disease														

^aCPS cut-off was selected based on results from the training set. Results in CPS ≥1 and CPS ≥10 among participants in the combined training set and confirmation set tend to overestimate efficacy and should be interpreted with caution. Database cut-off date: 2 February 2018.

RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; BICR, Blinded Independent Central Review; DCR, CR+PR+SD.

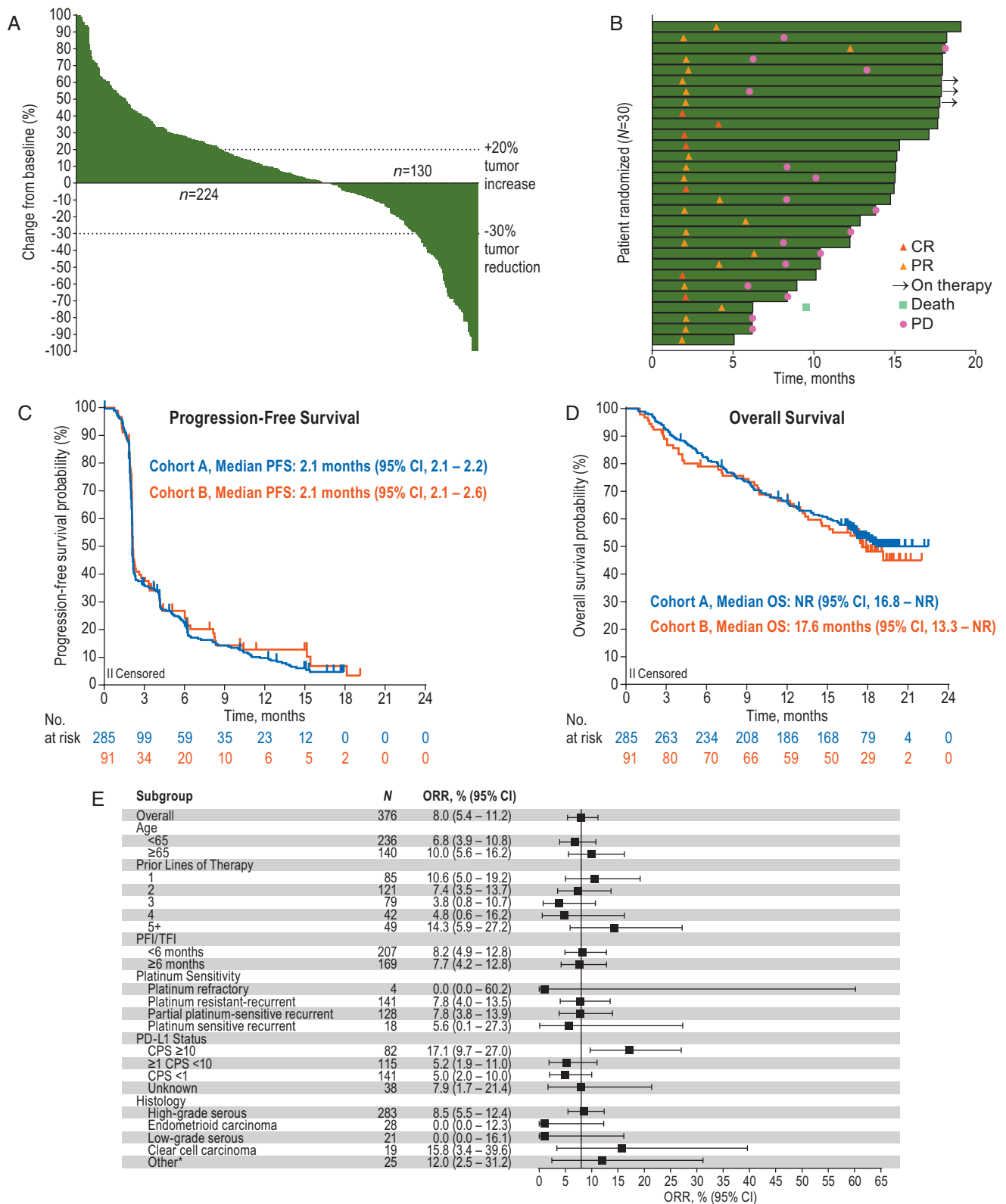


Figure 1. Antitumor activity of pembrolizumab in the total population. (A) Best change from baseline in target lesion size assessed by RECIST1.1 per independent central review in patients with ≥ 1 evaluable post-baseline imaging assessment ($N = 354$). (B) Time to response and response duration assessed by RECIST1.1 per independent central review. (C) Progression-free survival assessed by RECIST1.1 per independent central review in cohort A (blue) and cohort B (red). (D) Overall survival for cohort A (blue) and cohort B (red). (E) Objective response rate assessed by RECIST1.1 per independent central review in subgroups of the efficacy population ($N = 376$).

Table 2. Summary of adverse events in the total population (N = 376)

Adverse event	Any grade, N (%)	Grade 3–5, N (%)
Treatment-related AEs of any grade that occurred in $\geq 5\%$ of patients or of grade 3–5 that occurred in ≥ 3 patients		
Any	275 (73.1)	74 (19.7)
Fatigue	127 (33.8)	10 (2.7)
Nausea	58 (15.4)	2 (0.5)
Decreased appetite	40 (10.6)	1 (0.3)
Hypothyroidism	40 (10.6)	1 (0.3)
Diarrhea	38 (10.1)	3 (0.8)
Pruritus	31 (8.2)	0
Rash	27 (7.2)	2 (0.5)
Vomiting	21 (5.6)	2 (0.5)
Arthralgia	20 (5.3)	1 (0.3)
Anemia	18 (4.8)	5 (1.3)
Colitis	6 (1.6)	5 (1.3)
Amylase increased	7 (1.9)	4 (1.1)
Blood alkaline phosphatase increased	12 (3.2)	4 (1.1)
Ascites	4 (1.1)	3 (0.8)
	Grades 1–2	Grades 3–5
Immune-mediated AEs and infusion reactions that occurred in ≥ 1 patient		
Hypothyroidism	41 (10.9)	1 (0.3)
Hyperthyroidism	25 (6.6)	0
Severe skin reaction	3 (0.8)	7 (1.9)
Infusion reactions	6 (1.6)	1 (0.3)
Colitis	2 (0.5)	6 (1.6)
Pneumonitis	5 (1.3)	1 (0.3)
Thyroiditis	3 (0.8)	0
Hypophysitis	0	2 (0.5)
Type 1 diabetes mellitus	0	2 (0.5)
Adrenal insufficiency	1 (0.3)	0
Hepatitis	0	1 (0.3)
Myasthenic syndrome	0	1 (0.3)
Myositis	1 (0.3)	0
Nephritis	0	1 (0.3)
Pancreatitis	0	1 (0.3)
Sarcoidosis	1 (0.3)	0
Uveitis	1 (0.3)	0

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.

results in CPS ≥ 1 and CPS ≥ 10 among participants in the combined training set and confirmation set tend to overestimate efficacy and should therefore be interpreted with caution.

It is important to note that across studies of different checkpoint inhibitors, PD-L1 assays use different antibodies with a variety of cut points, each with unique and different thresholds for defining PD-L1 positivity [17, 18]. Additionally, which cells express PD-L1 may impact the PD-L1 score and complicate the interpretation of PD-L1 expression levels; positive expression may occur on non-cancer immune cells and some may have different significance [17, 18]. In our study, PD-L1 expression was determined on tumor cells, lymphocytes, and macrophages as the CPS using the IHC 22C3 pharmDx assay [16], whereas earlier studies measured expression on tumor cells only.

Importantly, as identified in KEYNOTE-100, other clinical features, such as the number of lines of prior treatment and level of platinum sensitivity, did not appear to influence the ORR of single-agent pembrolizumab; however, the heterogeneous population of patients leading to small subgroups limits the interpretation of these results. In addition, cohort A included platinum-partial-sensitive patients with < 3 lines of prior therapy, who typically have a more favorable prognosis than platinum-resistant patients. Further analysis of specific histological subtypes also did not identify an ovarian cancer pathology that helped predict response to single-agent pembrolizumab, although there was a trend toward improved response rate in clear cell carcinoma. Other trials have also identified clear cell histology as potentially being more responsive to checkpoint blockade [10, 19].

Other potential biomarkers for response to immune checkpoint blockade include *BRCA* status, mutational burden, and microsatellite status. Several studies have reported that ovarian cancers harboring *BRCA* mutations are associated with higher PD-L1 expression and mutational burden [20, 21], potentially making these cancers better candidates for checkpoint blockade therapy; further biomarker analyses are ongoing in our trial and will be reported at a later date. Strickland et al. [20] showed that two distinct groups of high-grade serous ovarian cancers exist, one with a poor prognosis characterized by homologous recombination proficiency and low number of TILs and another with *BRCA*-mutated cancers and a high number of TILs. Wieser et al. [21] also showed that PD-1 and PD-L1 mRNA-expression is controlled by interferon gamma and is affected by both *TP53* and *BRCA* mutations. Other mechanisms of response to single-agent checkpoint blockade have also been identified such as mutations within the PD-L1 gene [22].

Clinical trials are underway to test combinations of checkpoint blockade and other therapies, such as chemotherapy, PARP inhibitors, antivascular agents, and other biologic agents to enhance the effectiveness of checkpoint blockade in a variety of settings. Recent negative results have been reported for JAVELIN 100 and 200 [23, 24], which tested the addition of avelumab to treatment of patients with newly diagnosed ovarian cancer and platinum-resistant recurrence, respectively; final results are pending. Other trials have reported results of the addition of checkpoint blockade and PARP inhibitors, with some enhancement of activity of the combination in these single-arm studies [11, 12]. Checkpoint blockade has been added to bevacizumab in at least two studies (NCT02873962 and NCT02659384), along with planned studies of triplet therapies that include checkpoint blockade. Also, combinations of checkpoint blockade with other unique agents are being tested [25–27].

In conclusion, single-agent pembrolizumab showed durable activity in a subset of patients with advanced ROC. Clinical features, such as the number of lines of prior treatment and the degree of platinum sensitivity, did not appear to influence the ORR of pembrolizumab. The present results signal a patient population defined by CPS ≥ 10 who may benefit from single-agent pembrolizumab after treatment with standard chemotherapies.

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Disclosure

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