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Assessment of Combined Nivolumab and Bevacizumab in Relapsed Ovarian Cancer
A Phase 2 Clinical Trial

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IMPORTANCE To date, single-agent programmed cell death 1 protein 1 (PD-1)/programmed death ligand 1 (PD-L1) immune checkpoint blockade has shown limited activity in recurrent epithelial ovarian cancer. Combination strategies of PD-1/PD-L1 inhibition with antiangiogenic therapy have the potential for synergistic activity through modulation of the microenvironment and represent a potential therapeutic opportunity in this disease.

OBJECTIVE To evaluate the activity of combined nivolumab and bevacizumab in women with relapsed ovarian cancer.

DESIGN, SETTING, AND PARTICIPANTS A single-arm, phase 2 study enrolled patients between February 8, 2017, and December 29, 2017, at 2 sites in the United States; the primary data analysis was completed July 27, 2018. Thirty-eight women with relapsed epithelial ovarian cancer were enrolled in this study. Participants had disease recurrence within 12 months of their last platinum-based therapy and had received between 1 and 3 lines of prior therapy.

INTERVENTIONS Participants received intravenous nivolumab and intravenous bevacizumab once every 2 weeks.

MAIN OUTCOME AND MEASURES The primary end point was objective response rate (ORR) as measured by Response Evaluation Criteria in Solid Tumors 1.1. Secondary end points included evaluation of the ORR by platinum sensitivity, assessment of progression-free survival, assessment of safety data, and investigation of the association of tumor PD-L1 with response to therapy.

RESULTS Of the 38 women enrolled, 18 had platinum-resistant and 20 had platinum-sensitive disease; mean (SD) age was 63.0 (9.1) years. Eleven patients experienced a confirmed response to nivolumab with bevacizumab (ORR, 28.9%; 95% exact binomial CI, 15.4%-45.9%), with 1 additional unconfirmed response. The ORR was 40.0% (19.1%-64.0%) in platinum-sensitive and 16.7% (95% CI 3.6%-41.4%) in platinum-resistant participants. Thirty-four participants (89.5%) experienced at least 1 treatment-related adverse event; 9 participants (23.7%) experienced a grade 3 or higher treatment-related adverse event. Median progression-free survival was 8.1 months (95% CI, 6.3-14.7 months). In 36 histologic samples for which PD-L1 testing could be performed, 22 samples (61.1%) had a PD-L1 tumoral percentage less than 1, and 14 samples (38.9%) had a PD-L1 tumoral percentage of 1 or greater. Ten responses occurred in patients with PD-L1 tumor percentage less than 1, and 2 in patients with PD-L1 tumor percentages of 1 or greater.

CONCLUSIONS AND RELEVANCE The nivolumab with bevacizumab combination appeared to show activity in patients with relapsed ovarian cancer, with greater activity in the platinum-sensitive setting. Alternative combinational strategies may be necessary in the platinum-resistant setting.

Supplemental content

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Immune checkpoint inhibitor therapies have transformed cancer treatment in certain solid malignant tumors, such as melanoma and renal cell carcinomas. Studies performed in archival epithelial ovarian cancer specimens support the notion that the immune system is actively involved in ovarian cancer control. An early observation published in 2003 reported that the presence of $CD3^+$ tumor-infiltrating lymphocytes correlated with markedly improved overall survival in patients with stage III and IV ovarian cancer in the setting of both optimal and suboptimal cytoreductive surgery.[1] Subsequent studies have confirmed this finding, and a meta-analysis of 10 studies suggested that the presence of tumor-infiltrating lymphocytes correlated with improved overall survival with a hazard ratio of greater than 2.[2] Similarly, increased programmed death ligand 1 (PD-L1) or programmed cell death 1 ligand 2 (PD-L2) expression has also been reported to correlate with poorer overall survival in ovarian cancer, supporting the hypothesis that signaling via the PD-1/PD-L1 immune checkpoint is a mechanism of immune evasion in these tumors.[3]

Despite these findings supporting a role for immunotherapy in ovarian cancer, results thus far from trials of single-agent PD-1/PD-L1 inhibitors in this disease have demonstrated limited activity. An initial proof-of-concept trial reported a response rate of 15% to nivolumab monotherapy in 20 women with relapsed platinum-resistant ovarian cancer.[4] Subsequent trials of single-agent pembrolizumab (KEYNOTE-100)[5] and avelumab (JAVELIN Solid Tumor Trial)[6] have reported overall response rates of 8.0% and 9.6%, respectively.

Although the activity of PD-1/PD-L1 inhibitors as single agents in ovarian cancer is limited, it is possible that their effect could be potentiated through combinations with other agents. For example, signaling through the vascular endothelial growth factor (VEGF) pathway has been reported to confer immunomodulatory effects.[7] In particular, signaling through VEGFR-1, mediated by VEGF-A, can suppress dendritic cell maturation, and signaling through VEGFR-2 can increase the Treg population and stimulate the growth of myeloid-derived suppressor cells, contributing to a more immunosuppressive tumor microenvironment.[7] Studies of immunotherapy with antiangiogenic agents in other diseases, such as renal cell carcinoma, have demonstrated activity, supporting the hypothesis of synergy between these agents in solid tumors.[8,9] We therefore conducted this single-arm, phase 2 trial to assess the activity of combination bevacizumab and nivolumab in relapsed ovarian cancer with a platinum-free interval of less than 12 months (NCT02873962).

Key Points

Question What is the clinical activity associated with the combination treatment of nivolumab and bevacizumab in women with relapsed epithelial ovarian cancer?

Findings In this single-arm, phase 2 trial of 38 women, 28.9% experienced an objective confirmed response after combination therapy with nivolumab and bevacizumab by Response Evaluation Criteria in Solid Tumors 1.1, meeting the threshold for further exploration of the combination in this setting. The response rate was 40.0% in platinum-sensitive patients and 16.7% in platinum-resistant patients.

Meaning Further exploration of the nivolumab with bevacizumab combination in relapsed ovarian cancer is warranted.

Methods

Patient Selection

Eligible patients for this study were enrolled from the Dana-Farber Cancer Institute and Massachusetts General Hospital, both in Boston, Massachusetts. The study was approved by the Dana-Farber/Harvard Cancer Center Institutional Review Board, and all patients provided written informed consent prior to initiating any study procedures. Participants did not receive financial compensation.

Eligibility criteria included recurrent epithelial ovarian cancer that had relapsed within 12 months of prior platinum-based therapy. All histologic types (serous, mucinous, endometrioid, clear cell, carcinosarcoma, or mixed) and all grades were eligible. Participants were defined as having platinum-resistant disease if they had experienced relapse within 6 months of platinum-based chemotherapy and as platinum-sensitive if they had experienced relapse within 6 to 12 months after platinum-based chemotherapy. Patients with primary platinum-refractory disease, defined as disease progression or relapse within 2 months of initial platinum-based chemotherapy, were not eligible. Up to 3 prior cytotoxic regimens were allowed. Previous bevacizumab therapy was allowed unless there was evidence of prior unacceptable bevacizumab-related toxic effects. Earlier treatment with an anti-PD1, anti-PD-L1, anti-PD-L2, anti-cytotoxic T-lymphocyte–associated protein 4 (CTLA-4), or any other drug specifically targeting T-cell costimulation or immune checkpoint pathways was not allowed. An archival sample obtained less than 20 months before study entry was necessary; if an archival sample was not available, participants were required to undergo pretreatment biopsy. Additional eligibility criteria are detailed in the eMethods in the Supplement.

Study Design

This was a single-arm, phase 2 trial of combination bevacizumab and nivolumab, both delivered intravenously. Each cycle was 14 days. Bevacizumab, 10 mg/kg, and nivolumab, 240-mg, were administered every 14 days. A single dose reduction of bevacizumab to 5 mg/kg was allowed for bevacizumab-related adverse events. No dose reductions were allowed for nivolumab. Treatment was continued until disease progression or adverse events prohibited further treatment; treatment beyond progression was allowed in the setting of clinical benefit, as determined by the treating investigator and in discussion with the principal investigator (J.F.L.). Patients were assessed radiographically by Response Evaluation Criteria in Solid Tumors 1.1 (RECIST 1.1) criteria using computed tomographic imaging or magnetic resonance imaging every

8 weeks (every 4 cycles) until disease progression was confirmed. Toxic effects were measured by Common Terminology Criteria for Adverse Events, version 4.0.[10]

The study had a 2-stage design based on Jung et al,[11] with an initial 6-patient safety lead-in incorporated in the first stage. If no dose-limiting toxic effects were observed, an additional 10 patients were accrued to complete accrual of 16 patients to the first stage of the study. Dose-limiting toxic effects are further described in the eMethods in the Supplement. Three or more responses were required to proceed to the second stage of the study, during which an additional 22 patients could be enrolled. A study flow diagram is shown in **Figure 1**.

Study End Points

The primary objective of the study was to investigate the objective response rate (ORR) to combination bevacizumab and nivolumab by RECIST 1.1 criteria. Secondary end points included assessment of progression-free survival (PFS), assessment of safety data, and investigation of the association of tumoral PD-L1 in archival or pretreatment tumor samples with response to therapy. Details regarding PD-L1 testing are included in the eMethods in the Supplement.

Statistical Analysis

With the planned total accrual of 38 patients, the study had an 80% power to detect an improvement in the response rate from 0.15 to 0.30, with an α level of 0.10. Therefore, the null hypothesis was rejected if 9 or more responses were observed in the overall study population. The null hypothesis of 0.15 was based on the presumed activity of single-agent bevacizumab in this population based on previous single-agent bevacizumab studies.[12,13]

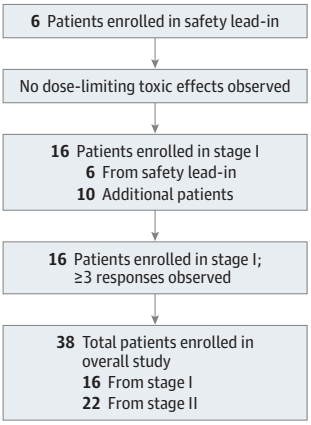
Analyses included all participants who initiated study treatment. The ORR was calculated as the combination of patients achieving a complete response or a partial response with a 95% CI estimated by exact binomial. Progression-free survival was defined as the time from registration in the study until documented disease progression or death without progression, whichever occurred first. Participants not experiencing a PFS event were censored at the last date of documented disease evaluation. Progression-free survival analyses were summarized using the Kaplan-Meier product-limit estimator with reported event rate and estimate of median survival using the Greenwood formula with 95% CIs. Safety data were described by the number and proportion of patients who had treatment-related adverse effects, using CTCAE, version 4.0 (National Cancer Institute). Two-sided *P* values were reported for all analyses. No multiple comparison adjustments were implemented. Findings were considered significant at $P < .05$. All analyses were conducted using SAS statistical software, version 9.1 (SAS Institute Inc) and R statistical software, version 3.3.1 (R Project for Statistical Computing).

Results

Patient Characteristics

Thirty-eight patients were enrolled between February 8, 2017, and December 29, 2017, and the cutoff date for primary analysis was July 27, 2018. Mean (SD) age was 63.0 (9.1) years; other patient characteristics are presented in **Table 1**. Most patients had a high-grade cancer, and most cancers were of serous histologic subtype. Germline *BRCA* status was known in 31 patients (81.6%), of whom 2 harbored a deleterious germline mutation. Eighteen patients (47.4%) had platinum-resistant and 20 individuals (52.6%) had platinum-sensitive disease. Participants with platinum-resistant disease tended to be more heavily pretreated (median, 2; range, 1-3) than those with platinum-sensitive disease (median, 1; range, 1-3); the rate of prior bevacizumab receipt was similar between platinum-sensitive and platinum-resistant patients (platinum-sensitive, 65.0%; in platinum-resistant, 66.7%) (Table 1).

Figure 1. Study Flow Diagram



Outcomes

Eleven patients experienced a confirmed response to the bevacizumab and nivolumab combination for an ORR of 28.9% (95% CI, 15.4%-45.9%). **Table 2** summarizes the best overall responses across the trial. There were 8 confirmed responses in patients with platinum-sensitive disease (ORR, 40.0%; 95% CI, 19.1%-64.0%) and 1 additional unconfirmed response. There were 3 confirmed responses in patients with platinum-resistant disease (ORR, 16.7%; 95% CI, 3.6%-41.4%); 2 of these patients had primary and 1 had secondary platinum resistance. In addition, 6 patients with platinum-sensitive disease (30.0%) and 3 patients with platinum-resistant disease (16.7%) had stable disease lasting at least 24 weeks. Overall, 27 patients (71.1%) experienced some degree of tumor decrease (**Figure 2**). In patients who experienced a response, the median duration of response was 6.0 months, with a duration of response of 5.6 months in the platinum-sensitive patients and 12.3 months in the platinum-resistant patients. The overall clinical benefit rate (response + stable disease >24 weeks) was 55.3% (75.0% in platinum-sensitive and 33.3% in platinum-resistant patients). **Figure 3** presents a swimmer plot of time receiving treatment across all patients. Seven patients were treated post progression, with a median time of treatment post progression of 3.1 (range, 0.7 to >5.8 months) months.

Table 1. Patient Characteristics, Overall and by Platinum Status

Characteristic	No. (%)			*P* Value
	Total (N = 38)	Platinum Sensitive (n = 20)	Platinum Resistant (n = 18)	
Age, y				.09
Median (IQR) [range]	64 (57-68) [36-76]	61 (55-68) [36-76]	66 (64-69) [54-76]	
Mean (SD)	63.0 (9.1)	60.1 (10.3)	66.1 (6.5)	
Race				
White	35 (92.1)	20 (100.0)	15 (83.3)	.16
Asian	2 (5.3)	0	2 (11.1)	
>1 Race	1 (2.6)	0	1 (5.6)	
Performance status				
00: Fully active	22 (57.9)	13 (65.0)	9 (50.0)	.51
01: Restricted	16 (42.1)	7 (35.0)	9 (50.0)	
Stage at diagnosis				
I	1 (2.6)	0	1 (5.6)	.74
II	3 (7.9)	2 (10.0)	1 (5.6)	
III	19 (50.0)	9 (45.0)	10 (55.6)	
IV	13 (34.2)	8 (40.0)	5 (27.8)	
Unknown	2 (5.3)	1 (5.0)	1 (5.6)	
Histologic subtype				
Serous	23 (60.5)	12 (60.0)	11 (61.1)	.50
Adenocarcinoma	10 (26.3)	4 (20.0)	6 (33.3)	
Carcinosarcoma	2 (5.3)	1 (5.0)	1 (5.6)	
Clear cell	2 (5.3)	2 (10.0)	0	
Mixed	1 (2.6)	1 (5.0)	0	
Grade				
Poorly differentiated	33 (86.8)	18 (90.0)	15 (83.3)	.78
Unknown	3 (7.9)	1 (5.0)	2 (11.1)	
Well differentiated	2 (5.3)	1 (5.0)	1 (5.6)	
Germline *BRCA* status				
Mutated	2 (5.3)	0	2 (11.1)	.23
Wild-type	29 (76.3)	17 (85.0)	12 (66.7)	
Unknown	7 (18.4)	3 (15.0)	4 (22.2)	
No. of prior lines				
1	16 (42.1)	11 (55.0)	5 (27.8)	.08
2	13 (34.2)	7 (35.0)	6 (33.3)	
3	9 (23.7)	2 (10.0)	7 (38.9)	
Prior receipt of bevacizumab				
No	25 (65.8)	13 (65.0)	12 (66.7)	>.99
Yes	13 (34.2)	7 (35.0)	6 (33.3)	

Abbreviation: IQR, interquartile range.

Median PFS, with progression events measured by RECIST 1.1 criteria, was 9.4 months (95% CI, 6.7 months to NA), with a median PFS of 12.1 months (95% CI, 8.4 months to NA) in platinum-sensitive patients and 7.7 months (95% CI, 4.7 months to NA) in platinum-resistant patients. When clinical progression, as determined by the treating investigator, was included as a progression event, the median PFS was 8.1 months (95% CI, 6.3-14.7 months), with a median PFS of 9.4 months (95% CI, 8.7 months to NA) in platinum-sensitive and 5.3 months (95% CI, 3.9 months to NA) in platinum-resistant patients.

In the 2 patients with clear-cell tumors, 1 patient experienced a best response of stable disease and stopped study treatment after 14 weeks of treatment for clinical progression. The second patient experienced a partial response and continued to receive study therapy. Both patients with known germline *BRCA* mutations experienced progressive disease with their first study assessment; 1 patient continued therapy post progression and had been receiving postprogression therapy for 5.8 months at the time of the data cut, with a best immune-related RECIST 1.1 response of stable disease.

Safety

Overall, 34 patients (89.5%) experienced at least 1 treatment-related adverse effect. Treatment-related adverse effects occurring in at least 10% of patients are reported in eTable 1 in the Supplement. Nine patients (23.7%) experienced grade 3 or higher treatment-related adverse effects. Three grade 4 events

were reported: 1 serum amylase level increase (likely due to disease progression) and 2 serum lipase level increases (likely related to nivolumab therapy). Both events related to nivolumab were asymptomatic; therapy was not interrupted and events resolved to grade 1 level without further intervention. No grade 5 events were observed. The most common adverse effects included fatigue (18 [47.4%]), headache (11 [28.9%]), myalgia (11 [28.9%]), serum amylase level increase (11 [28.9%]), aspartate aminotransferase level increase (10 [26.3%]), and hypertension (10 [26.3%]). Four events of pneumonitis (4 [10.5%]; 3 grade 2 and 1 grade 1) and 2 events of colitis (2 [5.3%]; 1 grade 2 level, likely related to and treated with budesonide, and 1 grade 1 level, possibly related to and self-resolved following diagnostic colonoscopy) were reported.

PD-L1 Assessment

In 36 of 38 patients (94.7%), PD-L1 assessment was performed successfully; in 1 patient, an insufficient number of slides was available for analysis, and in another patient, fewer than 100 cells were detected on hematoxylin-eosin staining and the sample was deemed insufficient for PD-L1 assessment. Twenty-two of the assessable tumors (61.1%) had a PD-L1 tumor percentage lower than 1, and 14 tumors (38.9%) had a percentage of 1 or more. There were 10 confirmed or unconfirmed responses in patients with a PD-L1 tumor percentage lower than 1 (ORR, 45.5%) and 2 in patients with a PD-L1 tumor percentage of 1 or more (ORR, 14.3%). Overall distribution of PD-L1 expression, using PD-L1 cutoffs of tumor percentage of 1, combined positive score of 1 or 10, and immune percentage of 5, are reported in eTable 2 in the Supplement.

Table 2. Best Responses, Overall and by Platinum Status

Best Response	No. (%)		
	Platinum Sensitive (n = 20)	Platinum Resistant (n = 18)	Overall (N = 38)
Unevaluable	0	1 (5.6)	1 (2.6)
Partial response			
Confirmed	8 (40.0)	3 (16.7)	11 (28.9)
Unconfirmed	1 (5.0)	0	1 (2.6)
Stable disease, wk			
≥24	6 (30.0)	3 (16.7)	9 (23.7)
<24	3 (15.0)	7 (38.9)	10 (26.3)
Progressive disease	2 (10.0)	4 (22.2)	6 (15.8)
Overall confirmed response rate	8 (40.0)	3 (16.7)	11 (28.9)
Total clinical benefit rate	15 (75.0)	6 (33.3)	21 (55.3)

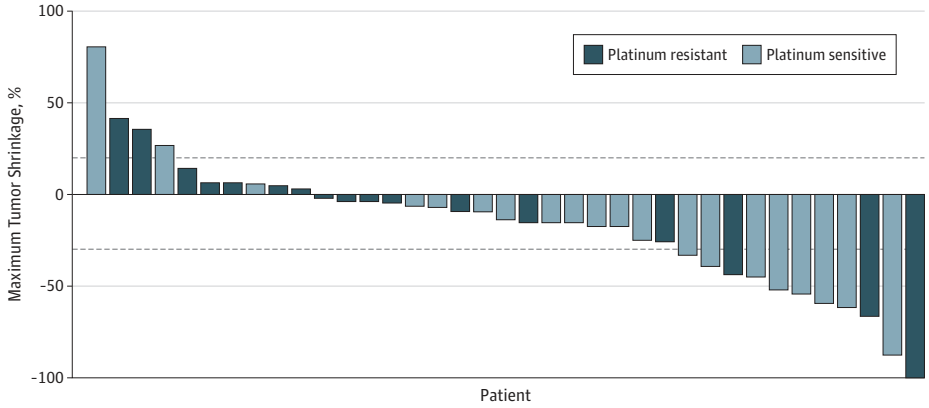
Discussion

This single-arm, phase 2 study met its predefined end point, with an ORR of 28.9% across all patients. The findings suggest that combination therapy with nivolumab and bevacizumab is safe and tolerable in women with relapsed ovarian cancer and may provide evidence of clinical activity. To allow exploration of this combination in a broader population, this study enrolled patients both with platinum-resistant and platinum-sensitive (up to 12-month platinum-free interval) disease. Within patients with platinum-resistant disease, the ORR remained low at 16.7%, although the median PFS accounting for both RECIST 1.1 and clinical progression was 5.3 months. Within patients with platinum-sensitive disease, the ORR rose to 40.0%, with a median PFS in these patients of 9.4 months. Although we did not have a control arm of either agent alone, our results suggest that increased benefits associated with these agents may exist within the platinum-sensitive population, given previously reported single-agent activities of bevacizumab and of immune checkpoint inhibitors.[4-6,12,13] In addition, in the 13 patients who had received bevacizumab previously, there were 2 confirmed responses and 1 unconfirmed response, suggesting some activity of this regimen even in patients with previous bevacizumab exposure. However, the results within the platinum-resistant patients raise the issue of whether this combination may have limited activity in this population.

Given the limited activity of single-agent PD-1/PD-L1-directed therapy in ovarian cancer, combination studies of immune checkpoint inhibitors with other agents are of growing interest in this disease. In a phase 1 study combining the PD-L1 inhibitor durvalumab with either cediranib or olaparib in women with relapsed or metastatic cancers (triple-negative breast, ovarian, cervical, or uterine), 6 of 12 women with evaluable disease receiving combination durvalumab and cediranib had a response measured by RECIST 1.1 criteria, including 3 women with platinum-sensitive ovarian cancer.[14] In a small, heavily pretreated population, less activity in women with platinum-resistant ovarian cancer appeared to be present in this study as well. A recent NRG Oncology study combining nivolumab with the CTLA-4 inhibitor ipilimumab, also in a population of patients with recurrent ovarian cancer with a platinum-free interval of 12 months with up to 3 prior lines of therapy, reported similar activity to the present study of the nivolumab with bevacizumab combination, with an ORR of 33.3% for combination nivolumab with ipilimumab compared with 12.2% with nivolumab alone, and a median PFS of 3.9 months for the combination compared with 2.0 months for nivolumab alone.[15]

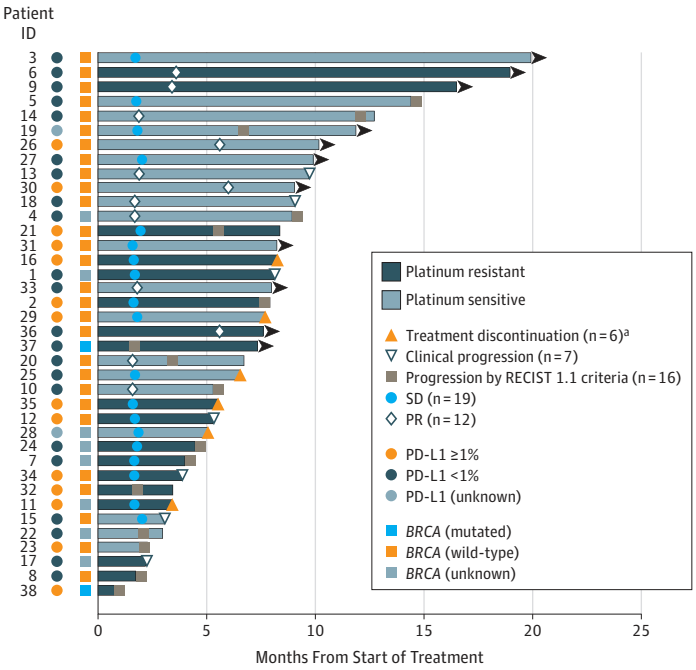
A subset of patients in this study receiving nivolumab and bevacizumab appeared to derive significant clinical benefit, with 6 patients (20%) at the time of the data cutoff continuing treatment for at least 12 months and several others still receiving therapy. The findings here and in other trials of immunotherapy highlight the importance of identifying a reproducible biomarker of response to these agents.[4-6] Expression of PD-L1 has been described as associated with response to immune checkpoint therapies.[16,17] In the current study, better response rates were observed in patients with PD-L1-negative tumors, in contrast to observations from other studies in ovarian cancer, which have reported either higher response rates in PD-L1 high cancers (KEYNOTE-100, as measured by combined positive score)[5] or no correlation of activity with PD-L1 expression (JAVELIN Solid Tumor Trial).[6] The findings in this study are difficult to interpret given the relatively small numbers of patients; however, the lack of consistent correlation between PD-L1 status and response to immu-

Figure 2. Best Responses in Evaluable Patients



Each bar represents an individual patient.

Figure 3. Time Receiving Treatment



ID indicates identification; PD-L1, programmed death ligand 1; PR, partial response; SD, stable disease.

[a] Six patients discontinued treatment for the following reasons: withdrawal of consent (n = 3); recurrent, grade 2 treatment-related pneumonitis (n = 1); grade 3 treatment-related transaminitis (n = 1); and increase in disease during treatment for treatment-related pneumonitis (n = 1).

notherapies in ovarian cancer reinforces the notion that PD-L1 expression may not be a reliable biomarker of immunotherapy activity in this disease. Similarly, activity in *BRCA* mutation carriers, where preclinical data have suggested the presence of higher tumor mutational burden and PD-L1 expression and therefore potentially a higher likelihood of response to immunotherapy,[18] was limited. Additional biomarkers of response to this combination are of interest. A number of biomarkers for response to antiangiogenics, such as plasma protein levels, circulating endothelial cells, and tumor microvessel density, have been reported[19,20] but have yet to be validated, and alternative biomarkers of response to immune checkpoint therapies, such as tumor-infiltrating lymphocytes and tumor mutational burden, have also been described.[21] Exploration of potential alternative biomarkers in patient samples obtained in this study is ongoing.

While the activity of this combination was higher in platinum-sensitive patients, it is not clear if this further activity could be related to increased sensitivity to bevacizumab in this population. To our knowledge, direct comparisons of bevacizumab activity in platinum-sensitive or -resistant ovarian cancers have not been performed; however, the response rates to bevacizumab monotherapy in 2 phase 2 studies were 15.9% in the study comprising only platinum-resistant patients[13] and 21% in the study in which the proportion of platinum-resistant patients was 58.1%.[12] Thus, it is possible that bevacizumab activity is slightly higher in platinum-sensitive patients. In contrast, subset analyses of the KEYNOTE-100 study did not demonstrate significantly different response rates between these 2 subsets to pembrolizumab.[5] The proportion of patients who had tumors with increased PD-L1 expression in this study was lower in the platinum-sensitive population;

therefore, PD-L1 positivity seems unlikely to underlie the higher activity in platinum-sensitive patients.

Given the observed activity of the nivolumab/bevacizumab combination and the current landscape of therapy in platinum-sensitive ovarian cancer, where higher response rates and longer PFS have been seen with platinum chemotherapy followed by poly (ADP-ribose) polymerase (PARP) inhibitor maintenance or combination platinum and bevacizumab therapy,[22-26] a nivolumab with bevacizumab combination as primary therapy for relapsed platinum-sensitive disease may not yield significant comparative clinical benefit. However, our data suggest that antiangiogenic and immunotherapy combinations are still worthy of exploration in this space, especially in conjunction with chemotherapy or other agents, and clinical trials are currently ongoing. The ATALANTE trial is comparing the combination of chemotherapy with bevacizumab and atezolizumab with chemotherapy and bevacizumab alone in platinum-sensitive relapsed disease,[27] while IMagyn050 is exploring this strategy in first-line treatment of newly diagnosed disease.[28] A phase 2 study is currently also examining the activity of the durvalumab and cediranib combination in recurrent ovarian cancer.[29]

Alternative combinations beyond antiangiogenic and PD-1/PD-L1 inhibitors may be necessary in platinum-resistant disease. Data exist for potential synergy between PARP inhibitors and immune checkpoint therapy, both in the preclinical[30,31] and clinical[32,33] settings, and trials of triplet combinations of PARP inhibitors, immune checkpoint agents, and antiangiogenics are now under way in a number of clinical settings, including in platinum-resistant disease. A recently presented trial reported a high response rate of 40% in platinum-resistant patients with recurrent ovarian cancer with the combination of bevacizumab, pembrolizumab, and metronomic oral cyclophosphamide, suggesting that further alteration of the tumor microenvironment via the immunomodulatory effects of cyclophosphamide might allow for significantly enhanced activity in the platinum-resistant setting.[34]

Limitations

Limitations of this study include a relatively small sample cohort, with a mixed population of platinum-sensitive and platinum-resistant patients. Because the study was designed as a single-arm study, a comparator arm is not available to understand whether the nivolumab and bevacizumab combination adds significantly when compared with single-agent activity of these agents.

Conclusions

The results of our trial suggest that a nivolumab and bevacizumab combination was feasible and well tolerated in patients with ovarian cancer. Although the study met its primary statistical end point for overall response, with an ORR of 28.9%, examination of the response rates by platinum status suggests that this combination strategy may have the greatest promise in platinum-sensitive disease, while alternative strategies to enhance immunotherapy may still be required in the platinum-resistant setting.

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