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Avelumab Plus Talazoparib in Patients With *BRCA1/2*- or *ATM*-Altered Advanced Solid Tumors

Results From JAVELIN BRCA/ATM, an Open-Label, Multicenter, Phase 2b, Tumor-Agnostic Trial

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IMPORTANCE Nonclinical studies suggest that the combination of poly(ADP-ribose) polymerase and programmed cell death 1/programmed cell death–ligand 1 inhibitors has enhanced antitumor activity; however, the patient populations that may benefit from this combination have not been identified.

OBJECTIVE To evaluate whether the combination of avelumab and talazoparib is effective in patients with pathogenic *BRCA1/2* or *ATM* alterations, regardless of tumor type.

DESIGN, SETTING, AND PARTICIPANTS In this pan-cancer tumor-agnostic phase 2b nonrandomized controlled trial, patients with advanced *BRCA1/2*-altered or *ATM*-altered solid tumors were enrolled into 2 respective parallel cohorts. The study was conducted from July 2, 2018, to April 12, 2020, at 42 institutions in 9 countries.

INTERVENTIONS Patients received 800 mg of avelumab every 2 weeks and 1 mg of talazoparib once daily.

MAIN OUTCOMES AND MEASURES The primary end point was confirmed objective response (OR) per RECIST 1.1 by blinded independent central review.

RESULTS A total of 200 patients (median [range] age, 59.0 [26.0-89.0] years; 132 [66.0%] women; 15 [7.5%] Asian, 11 [5.5%] African American, and 154 [77.0%] White participants) were enrolled: 159 (79.5%) in the *BRCA1/2* cohort and 41 (20.5%) in the *ATM* cohort. The confirmed OR rate was 26.4% (42 patients, including 9 complete responses [5.7%]) in the *BRCA1/2* cohort and 4.9% (2 patients) in the *ATM* cohort. In the *BRCA1/2* cohort, responses were more frequent (OR rate, 30.3%; 95% CI, 22.2%-39.3%, including 8 complete responses [6.7%]) and more durable (median duration of response: 10.9 months [95% CI, 6.2 months to not estimable]) in tumor types associated with increased heritable cancer risk (ie, *BRCA1/2*-associated cancer types, such as ovarian, breast, prostate, and pancreatic cancers) and in uterine leiomyosarcoma (objective response in 3 of 3 patients and with ongoing responses greater than 24 months) compared with non–*BRCA*-associated cancer types. Responses in the *BRCA1/2* cohort were numerically higher for patients with tumor mutational burden of 10 or more mutations per megabase (mut/Mb) vs less than 10 mut/Mb. The combination was well tolerated, with no new safety signals identified.

CONCLUSIONS AND RELEVANCE In this phase 2b nonrandomized controlled trial, neither the *BRCA1/2* nor *ATM* cohort met the prespecified OR rate of 40%. Antitumor activity for the combination of avelumab and talazoparib in patients with *BRCA1/2* alterations was observed in some patients with *BRCA1/2*-associated tumor types and uterine leiomyosarcoma; benefit was minimal in non–*BRCA*-associated cancer types.

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Poly(ADP-ribose) polymerase (PARP) inhibitor clinical development has focused on tumor types associated with pathogenic germline *BRCA1/2* alterations.[1] *BRCA1/2* alteration carriers have a heritable risk of breast, ovarian, prostate, and pancreatic tumors (termed *BRCA1/2*-associated cancer types), and PARP inhibitors are approved for these indications in the relapsed and/or maintenance settings. Germline alterations in other DNA damage repair genes, such as *ATM*, can also confer heritable cancer risk. Additionally, *BRCA1/2* and *ATM* alterations are present in other solid tumors with limited treatment options.[2] For example, homozygous somatic *BRCA2* deletions have been identified in uterine sarcomas, with anecdotal response to PARP inhibitors reported.[3-6]

Preclinical data suggest that immune checkpoint inhibitors (ICIs) may be effective in *BRCA1/2*-altered tumors and synergize with PARP inhibitors due to their complementary mechanisms of action.[7] Early-phase trials of PARP inhibitors combined with anti-programmed cell death 1/programmed cell death-ligand 1 (anti-PD-1/PD-L1) antibodies showed preliminary antitumor activity and tolerable safety in patients with selected cancers.[8,9] We therefore hypothesized that combining PARP inhibition with PD-L1 inhibition could represent a promising therapeutic strategy in *BRCA1/2*- and *ATM*-altered solid tumors.

Talazoparib is a potent oral PARP inhibitor that is approved for the treatment of patients with deleterious or suspected deleterious germline *BRCA1/2*-altered, ERBB2 (formerly HER2)-negative, locally advanced or metastatic breast cancer. Talazoparib has also shown clinical activity in ovarian, pancreatic, and prostate cancers, harboring germline and/or somatic *BRCA1/2* alterations.[10-14]

Avelumab is a human immunoglobin G1 anti-PD-L1 monoclonal antibody approved as monotherapy for metastatic Merkel cell carcinoma and advanced urothelial carcinoma (first-line maintenance or second-line therapy). It has been approved in combination with axitinib for first-line treatment of advanced renal cell carcinoma.[15-17] In this phase 2b tumor-agnostic trial (JAVELIN BRCA/ATM), we investigated avelumab plus talazoparib in patients with *BRCA1/2*- or *ATM*-altered cancers, regardless of tumor histology, to evaluate whether PD-L1 inhibitors enhanced the efficacy observed with PARP inhibitor monotherapy in *BRCA1/2*-associated tumor types and extended the clinical benefit to other *BRCA*- or *ATM*-altered tumors.

Key Points

Question Is the combination of avelumab and talazoparib effective in patients with pathogenic *BRCA1/2* or *ATM* alterations, regardless of tumor type?

Findings In this phase 2b nonrandomized controlled trial with 200 patients, neither the *BRCA1/2* nor *ATM* cohort met the prespecified target of an objective response rate of 40% across cancer types. Durable clinical activity was observed in patients with *BRCA1/2*-associated tumor types (eg, ovarian, breast, prostate, and pancreatic cancers) vs those with non–*BRCA*-associated cancer types; a notable exception were patients with *BRCA1/2*-altered uterine leiomyosarcoma, who had prolonged responses to treatment.

Meaning These findings suggest that a pan-cancer, tumor-agnostic approach with this combination is not an optimal clinical strategy for treating patients with *BRCA1/2*-altered tumors.

Methods

Patients

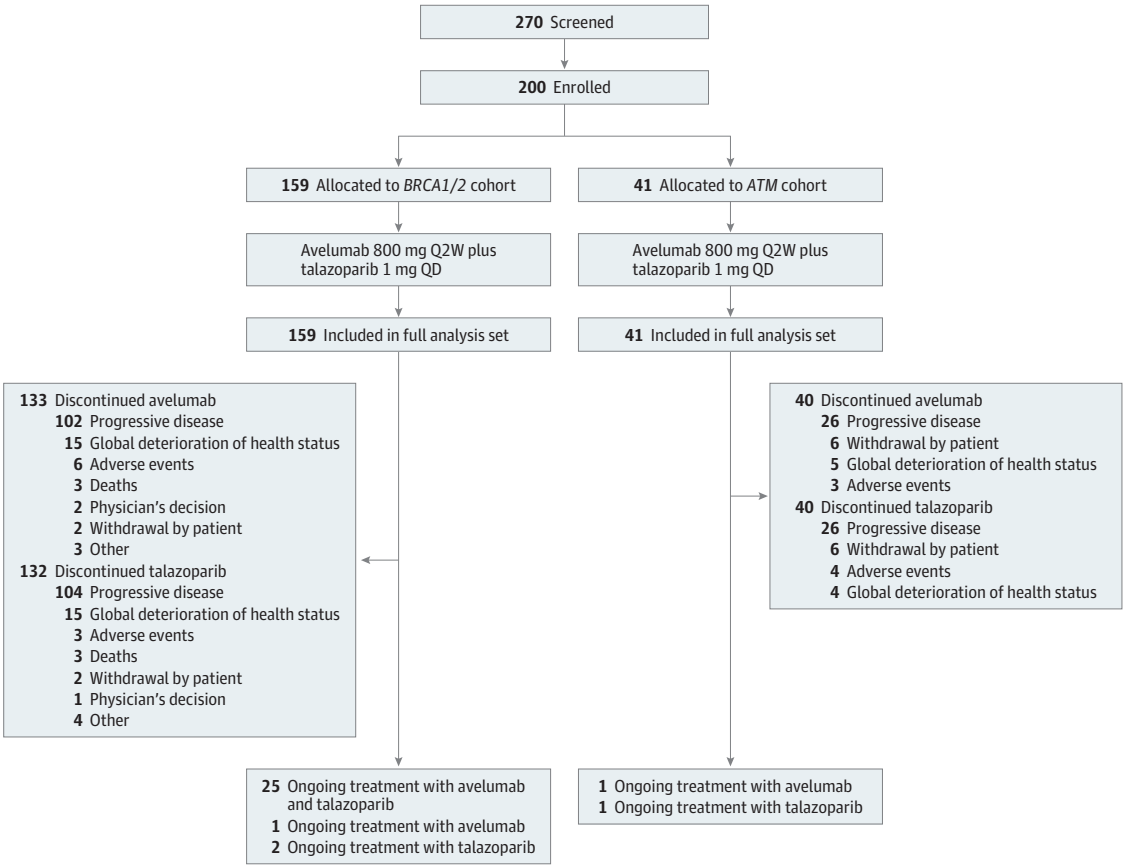
Eligible patients (aged ≥18 years; ≥20 years in Japan) had histologically diagnosed locally advanced or metastatic solid tumors not amenable to treatment with curative intent, had received at least 1 prior line of standard-of-care treatment for locally advanced or metastatic disease (unless otherwise specified), and had pathogenic or likely pathogenic germline or somatic alterations in *BRCA1*, *BRCA2*, or *ATM*, as determined by local testing in a College of American Pathologists/Clinical Laboratory Improvement Amendments-certified (or comparable locally or regionally certified) laboratory using either germline or tumor DNA. Prior treatment with ICIs and PARP inhibitors was not allowed. Except for patients with metastatic castration-resistant prostate cancer (mCRPC), patients were required to have investigator-assessed measurable disease per RECIST 1.1. Complete eligibility criteria are detailed in the trial protocol, which appears in Supplement 1. This study followed the Transparent Reporting of Evaluations With Nonrandomized Designs (TREND) reporting guideline.

The trial was performed in accordance with the International Ethical Guidelines for Biomedical Research Involving Human Subjects, the International Conference on Harmonisation Guidelines for Good Clinical Practice, and the Declaration of Helsinki. All patients provided written informed consent before enrollment. The protocol was approved by the institutional review board or independent ethics committee at each participating center.

Study Design and Treatment

JAVELIN BRCA/ATM is an open-label, multicenter, pan-cancer, phase 2b nonrandomized clinical trial investigating avelumab plus talazoparib in patients with *BRCA1/2*- or *ATM*-altered solid tumors. The study was conducted at 42 centers in 9 countries. Patients were enrolled into 1 of 2 cohorts based on their qualifying mutation: *BRCA1/2* or *ATM* alterations; patients with concurrent *BRCA1/2* and *ATM* alterations were enrolled in the *BRCA1/2* cohort. All patients received avelumab 800 mg as a 1-hour intravenous infusion every 2 weeks and talazoparib 1 mg orally once daily (0.75 mg for patients with moderate kidney impairment). To mitigate infusion-related reactions, patients received premedication with antihistamine and acetaminophen prior to the first 4 avelumab infusions. Treatment was continued until disease progression, unacceptable toxic effects, or patient withdrawal. For toxic effects, avelumab dosing could be delayed; talazoparib dosing could be delayed or reduced. Treatment could continue beyond initial disease progression if the investigator judged that the patient was experiencing clinical benefit from either study drug.

Figure 1. Study Flow Diagram



Q2W indicates every 2 weeks; QD, once daily.

End Points and Assessments

The primary end point was confirmed objective response (OR; best overall response of complete response or partial response) assessed by blinded independent central review (BICR) per RECIST 1.1; bone disease in patients with mCRPC was assessed per Prostate Cancer Clinical Trials Working Group 3. Secondary end points included time to response (TTR), duration of response (DOR), progression-free survival (PFS) by BICR and investigator assessments, confirmed OR by investigator, overall survival (OS), safety, and biomarker assessments. End point definitions and biomarker methods are provided in eAppendix 1 and eAppendix 2 in Supplement 2.

Statistical Analysis

Data analyses were conducted in SAS version 9.4 (SAS Institute). The planned sample size was 200 patients: 150 and 50 patients in the *BRCA1/2* and *ATM* cohorts, respectively. Assuming a beta distribution (0.5, 0.5) prior, the posterior probability of a true OR rate (ORR) of 40% or greater was 0.80 or greater with 66 responders of 150 patients (ORR, 44%) in the *BRCA1/2* cohort and with 23 responders of 50 patients (ORR, 46%) in the *ATM* cohort. An interim analysis for each cohort was planned after at least 20 patients had been treated and followed up for 24 weeks to allow early termination of enrollment for futility according to prespecified criteria (ie, if the probability of a true ORR ≥40% was ≤0.05, then the cohort would be stopped for futility). The ORR was calculated by cohort, with corresponding exact 2-sided 95% CIs using the Clopper-Pearson method. Median PFS, OS, and DOR were estimated using the Kaplan-Meier method.

Results

Patients and Treatment

Between July 2, 2018, and April 12, 2020, 200 patients were enrolled and treated: 159 patients in the *BRCA1/2* cohort and 41 patients in the *ATM* cohort (**Figure 1**). Median patient age was 59 (range, 26-89) years; 132 patients (66.0%) were women; there were 15 (7.5%) Asian, 11 (5.5%) African American, and 154 (77.0%) White participants; most patients were heavily pretreated (**Table 1**). The *BRCA1/2* and *ATM* cohorts included 23 and 16 different tumor types, respectively (Table 1). At data cutoff (October 12, 2020), combination treatment was ongoing for 27 patients (16.4%) in the *BRCA1/2* cohort and 1 patient (2.4%) in the *ATM* cohort (eTable 1 in Supplement 2). Median duration of treatment with avelumab and talazoparib was 5.3 (range, 0.5-26.7) months for both treatments in the *BRCA1/2* cohort

Table 1. Patient Demographic and Baseline Characteristics

Characteristic	No. (%)		
	BRCA1/2 cohort (n = 159)	*ATM* cohort (n = 41)	All patients (N = 200)
Age, median (range), y	57.0 (26.0-84.0)	61.0 (32.0-89.0)	59.0 (26.0-89.0)
Sex			
Female	108 (67.9)	24 (58.5)	132 (66.0)
Male	51 (32.1)	17 (41.5)	68 (34.0)
Race			
African American	8 (5.0)	3 (7.3)	11 (5.5)
American Indian or Alaska Native	1 (0.6)	0	1 (0.5)
Asian	15 (9.4)	0	15 (7.5)
White	117 (73.6)	37 (90.2)	154 (77.0)
Not reported	18 (11.3)	1 (2.4)	19 (9.5)
Pooled geographic region			
North America	89 (56.0)	37 (90.2)	126 (63.0)
Europe	61 (38.4)	4 (9.8)	65 (32.5)
Asia	9 (5.7)	0	9 (4.5)
ECOG PS			
0	76 (47.8)	13 (31.7)	89 (44.5)
1	81 (50.9)	28 (68.3)	109 (54.5)
2[a]	2 (1.3)	0	2 (1.0)
Primary tumor subgroup			
Breast cancer			
Any	51 (32.0)	6 (14.6)	57 (28.5)
HR+/ERBB2−	26 (16.4)	6 (14.6)	32 (16.0)
Triple negative	25 (15.7)	0	25 (12.5)
Ovarian cancer	26 (16.4)	3 (7.3)	29 (14.5)
mCRPC			
Any	26 (16.4)	5 (12.2)	31 (15.5)
Measurable disease (investigator)[b]	18 (69.2)	3 (60.0)	21 (67.7)
Pancreatic cancer	16 (10.1)	5 (12.2)	21 (10.5)
Colorectal cancer	8 (5.0)	9 (22.0)	17 (8.5)
Cholangiocarcinoma	8 (5.0)	1 (2.4)	9 (4.5)
Endometrial cancer	2 (1.3)	3 (7.3)	5 (2.5)
Gallbladder cancer	3 (1.9)	1 (2.4)	4 (2.0)
Uterine leiomyosarcoma	3 (1.9)	0	3 (1.5)
Other	16 (10.1)[c]	8 (19.5)[d]	24 (12.0)
TNM stage			
Stage III	3 (1.9)	0	3 (1.5)
Stage IV	156 (98.1)	41 (100)	197 (98.5)
BRCA status[e]			
Positive	159 (100)	0	159 (79.5)
Negative	0	24 (58.5)	24 (12.0)
Unknown	0	17 (41.5)	17 (8.5)
BRCA1 status[e]			
Positive	72 (45.3)	0	72 (36.0)
Negative	58 (36.5)	24 (58.5)	82 (41.0)
Unknown	29 (18.2)	17 (43.9)	46 (23.0)
BRCA2 status[e]			
Positive	88 (55.3)	0	88 (44.0)
Negative	47 (29.6)	23 (56.1)	70 (35.0)
Unknown	24 (15.1)	18 (43.9)	42 (21.0)

(continued)

Table 1. Patient Demographic and Baseline Characteristics (continued)

Characteristic	No. (%)		
	BRCA1/2 cohort (n = 159)	*ATM* cohort (n = 41)	All patients (N = 200)
ATM status[e]			
Positive	4 (2.5)	41 (100)	45 (22.5)
Negative	46 (28.9)	0	46 (23.0)
Unknown	109 (68.6)	0	109 (54.5)
Prior lines of therapy			
0	2 (1.3)	1 (2.4)	3 (1.5)
1	31 (19.5)	8 (19.5)	39 (19.5)
2	50 (31.4)	8 (19.5)	58 (29.0)
≥3	76 (47.8)	24 (58.5)	100 (50.0)
Prior lines of therapy in the advanced setting			
0	26 (16.4)	5 (12.2)	31 (15.5)
1	41 (25.8)	8 (19.5)	49 (24.5)
2	48 (30.2)	11 (26.8)	59 (29.5)
≥3	44 (27.7)	17 (41.5)	61 (30.5)
Breast cancer			
≥1 Prior cytotoxic therapy in the advanced setting	30 (58.8)	5 (83.3)	35 (61.4)
≥1 Prior platinum regimen	13 (25.5)	0	13 (22.8)
Ovarian cancer			
≥1 Prior platinum-containing regimen	26 (100)	3 (100)	29 (100)
≥2 Prior platinum regimens	18 (69.2)	2 (66.7)	20 (69.0)
≥3 Prior platinum regimens	7 (26.9)	0	7 (24.1)
Platinum sensitive	1 (3.8)	1 (33.3)	2 (6.9)
Platinum resistant	25 (96.2)	2 (66.7)	27 (93.1)
mCRPC			
≥1 Prior taxane-containing regimen	18 (69.2)	2 (40.0)	20 (64.5)
Measurable disease at baseline by BICR	126 (79)	30 (73)	156 (78)

Abbreviations: +, positive, −, negative; BICR, blinded independent central review; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hormone receptor; mCRPC, metastatic castration-resistant prostate cancer.

[a] Patients had an ECOG PS of 1 at screening and 2 at the time of enrollment.

[b] The percentage was calculated using the number of participants with mCRPC as the denominator.

[c] Other tumor types include esophageal cancer (n = 2), gastric cancer (n = 1), glial tumor (n = 2), malignant tumor, site unspecified (n = 1), non–small cell lung cancer (n = 2), urothelial cancer (n = 1), gastrointestinal stromal tumor (n = 1), leiomyosarcoma (n = 1), metastatic uveal melanoma (n = 1), sarcoma of the uterus (n = 1), testicular cancer (n = 1), uterine carcinoma (n = 1), and uvula squamous carcinoma (n = 1).

[d] Other tumor types include esophageal cancer (n = 1), gastric cancer (n = 1), malignant tumor, site unspecified (n = 1), urothelial cancer (n = 1), glomangiosarcoma of the lung (n = 1), high-grade neuroendocrine tumor (n = 1), papillary thyroid cancer (n = 1), and small bowel adenocarcinoma (n = 1).

[e] Local laboratory testing. Unknown includes uninformative or missing results.

and 3.7 and 3.8 months, respectively, (range for both, 0.5-18.6 months) in the *ATM* cohort (eTable 1 in Supplement 2). The median duration of follow-up for OS in the *BRCA1/2* and *ATM* cohorts was 13.5 (95% CI, 12-15.2) months and 16.7 (95% CI, 16-19.9) months, respectively.

Efficacy in the *BRCA1/2* Cohort

In the *BRCA1/2* cohort, 42 of 159 patients had a confirmed OR by BICR (ORR, 26.4%; 95% CI, 19.7%-34.0%) (**Table 2**); ORR by investigator was 33.3% (95% CI, 26.1%-41.2%) (eTable 2 in Supplement 2). In patients with measurable disease at baseline, the ORR by BICR was 32.5% (95% CI, 24.5%-41.5%), and many patients had some degree of tumor shrinkage (eFigure 4 in Supplement 2). In patients with *BRCA1/2*-dependent tumors, for *BRCA1/2* alterations under loss of heterozygosity (LOH), responses occurred in 14 of 47 patients (29.8%; 95% CI, 17.3%-44.9%) compared with 2 of 9 patients (22.2%; 95% CI, 2.8%-60.0%) with heterozygous *BRCA* alterations. In patients with *BRCA1/2*-dependent tumors, the response rate was 36.4% (95% CI, 22.4%-52.2%; 16 of 44 patients) for high genomic LOH (gLOH) tumors vs 31.6% (95% CI, 12.6%-56.6%; 6 of 19 patients) for low gLOH tumors. In patients with tumor mutational burden (TMB) of 10 or greater mutations per megabase (mut/Mb) vs less than 10 mut/Mb, responses occurred in 5 of 8 patients (ORR, 62.5%; 95% CI, 24.5%-91.5%) vs 22 of 92 (ORR, 23.9%; 95% CI, 15.6%-33.9%) (eTable 4 in the Supplement). According to BICR, median TTR was 1.8 (range, 1.5-3.6) months and median DOR was 10.9 months (95% CI, 6.2 months to not estimable) (**Figure 2**). Median PFS was 3.7 (95% CI, 3.1-5.3) months (eFigure 1 in Supplement 2). At data cutoff, responses were ongoing in 17 of 42 patients (40.5%) with a confirmed OR. Efficacy in tumor types with 5 or more patients is given in Table 2 and eTable 3 in Supplement 2.

Table 2. Best Overall Response and Confirmed Objective Response by BICR in *BRCA*-Dependent Tumors and in the *BRCA1/2* Cohort in Tumor Types With at Least 5 Patients

Best overall response by BICR	Patients in *BRCA1/2* cohort, No. (%)											*ATM* cohort, FAS (n = 41)
	FAS (n = 159)	*BRCA* categorization		*BRCA1/2* by tumor types with ≥5 patients								
		Dependent tumor (n = 122)[a]	Not dependent tumor (n = 37)	Breast (n = 51)[b]	HR+ and ERBB2– breast (n = 26)	TNBC (n = 25)	mCRPC (n = 26)[c]	Ovarian (n = 26)	Pancreatic (n = 16)	Colorectal (n = 8)	Cholangiocarcinoma or gallbladder (n = 10)	Other tumors (n = 22)[d]
CR	9 (5.7)	9 (7.4)	0	3 (5.9)	2 (7.7)	1 (4.0)	4 (15.4)	1 (3.8)	0	0	0	1 (4.5)	0
PR	33 (20.8)	30 (24.6)	3 (8.1)	21 (41.2)	12 (46.2)	9 (36.0)	1 (3.8)	4 (15.4)	2 (12.5)	0	0	5 (22.7)	2 (4.9)
SD	32 (20.1)	26 (21.3)	6 (16.2)	9 (17.6)	3 (11.5)	6 (24.0)	11 (42.3)	4 (15.4)	2 (12.5)	1 (12.5)	3 (30.0)	2 (9.1)	18 (43.9)
No CR, no PD	10 (6.3)	8 (6.6)	2 (5.4)	3 (5.9)	2 (7.7)	1 (4.0)	2 (7.7)	3 (11.5)	0	0	1 (10.0)	1 (4.5)	4 (9.8)
PD	55 (34.6)	33 (27.0)	22 (59.5)	8 (15.7)	3 (11.5)	5 (20.0)	3 (11.5)	11 (42.3)	11 (68.8)	7 (87.5)	4 (40.0)	11 (50.0)	14 (34.1)
NE	20 (12.6)	16 (13.1)	4 (10.8)	7 (13.7)	4 (15.4)	3 (12.0)	5 (19.2)	3 (11.5)	1 (6.3)	0	2 (20.0)	2 (9.1)	3 (7.3)
ORR, No. (%) [95% CI]	42 (26.4) [19.7-34.0]	39 (32.0) [23.8-41.0]	3 (8.1) [1.7-21.9]	24 (47.1) [32.9-61.5]	14 (53.8) [33.4-73.4]	10 (40.0) [21.1-61.3]	5 (19.2) [6.6-39.4]	5 (19.2) [6.6-39.4]	2 (12.5) [1.6-38.3]	0 [0.0-36.9]	0 [0.0-30.8]	6 (27.3) [10.7-50.2]	2 (4.9) [0.6-16.5]

Abbreviations: +, positive; –, negative; BICR, blinded independent central review; CR, complete response; FAS, full analysis set; HR, hormone receptor; mCRPC, metastatic castration-resistant prostate cancer; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease; TNBC, triple negative breast cancer; uLMS, uterine leiomyosarcoma.

[a] Defined as breast, ovarian, prostate, and pancreatic cancers and uLMS.

[b] Responders with breast cancer include patients with HR+/ERBB2– breast cancer and TNBC.

[c] ORR in patients with mCRPC and measurable disease by BICR was 30.8%.

[d] Responders with other tumors (with <5 patients) include 3 patients with uLMS (also included in the *BRCA*-dependent tumor types) and 1 patient each with uterine sarcoma, uterine carcinoma, and testicular cancer.

In the *BRCA1/2* cohort, 119 patients had *BRCA1/2*-associated tumor types (defined as breast, ovarian, prostate, and pancreatic cancers) and 40 patients had non-*BRCA1/2*-associated cancer types.[6] Within this *BRCA1/2* cohort, the ORR was 30.3% (95% CI, 22.2%-39.3%) for *BRCA1/2*-associated tumor types vs 15.0% (95% CI, 5.7%-29.8%) for patients with non-*BRCA1/2*-associated tumor types, including 3 of 3 responses in patients with advanced uterine leiomyosarcoma (uLMS) (Table 2). In an exploratory analysis, we combined the patients with uLMS with the patients with *BRCA1/2*-associated tumor types to form 1 subset, defined collectively as *BRCA1/2*-dependent cancer types.[6] In the *BRCA1*/2-dependent vs non-*BRCA1/2*-dependent groups (with 122 and 37 patients, respectively), ORRs were 32.0% (95% CI, 23.8%-41.0%) vs 8.1% (95% CI, 1.7%-21.9%), median DOR was 12.5 months (95% CI, 7.4 months to not estimable) vs 5.8 months (95% CI, 5.7 months to not estimable), and median PFS was 5.3 (95% CI, 3.7-7.3) months vs 1.9 (95% CI, 1.8-2.1) months, respectively (eFigure 1 in Supplement 2). The ORRs were 40.0% (95% CI, 30.1%-50.6%) vs 9.7% (95% CI, 2.0%-25.8%) in patients with BICR-assessed measurable disease, respectively (eTable 3 in Supplement 2).

Efficacy in the *ATM* Cohort

In June 2019, 41 patients had been rapidly enrolled and the interim analysis criteria had not yet been reached. At this time, clinical activity data for 19 patients followed up for 24 weeks was reviewed by the sponsor and the steering committee. The investigator-assessed ORR was 10.5% and was determined to be unlikely to surpass prespecified futility requirements. Further enrollment to this cohort was subsequently discontinued prior to the planned analysis. Final BICR-assessed ORR was 4.9% (Table 2).

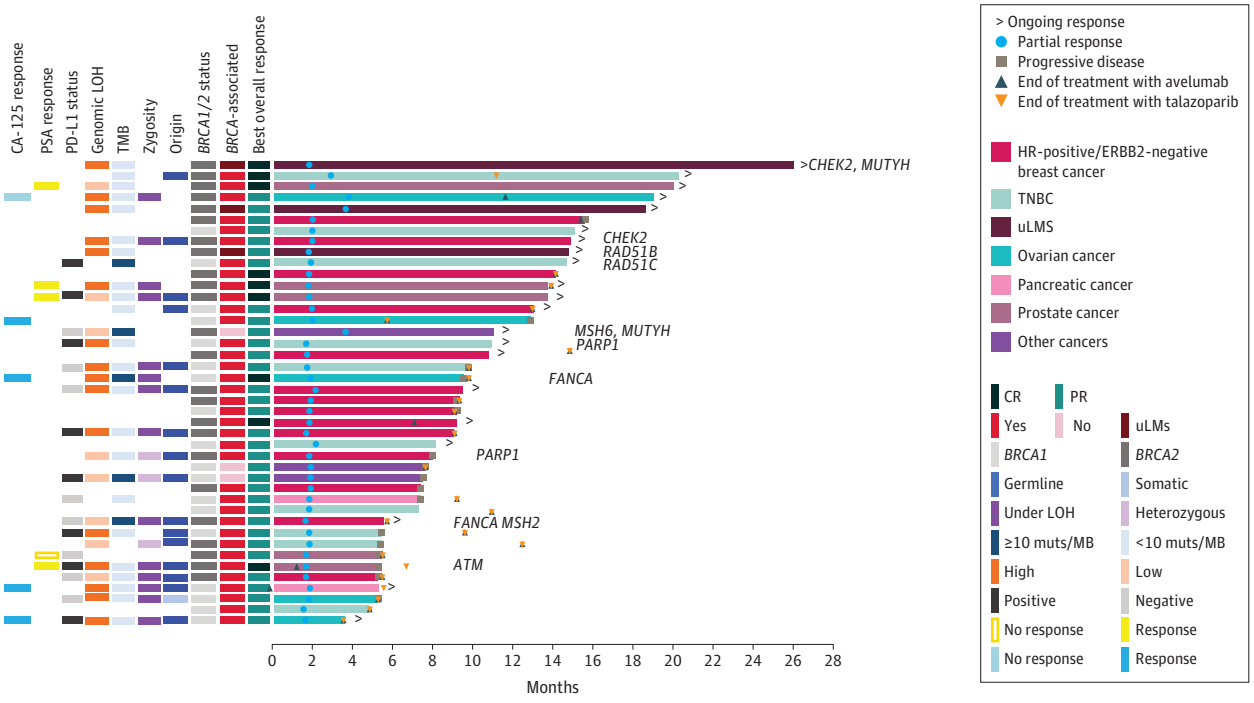
Biomarker Analyses

Central tumor sequencing was performed in 134 patients enrolled in the *BRCA1/2* cohort and 32 in the *ATM* cohort (eTable 4 in Supplement 2). The response rate was numerically higher for patients with germline vs somatic tumor alterations: 16 of 58 (27.6%; 95% CI, 16.7%-40.9%) vs 1 of 13 (7.7%; 95% CI, 0.2%-36.0%), respectively, although 95% CIs overlapped. We also investigated biallelic loss, TMB, whole-exome sequencing (WES) and whole-genome sequencing (WGS), and response to treatment. Results from these exploratory analyses are provided in eAppendix 3 and eFigures 2 and 3 in Supplement 2.

Safety

In total, 182 patients (98.1%) experienced at least 1 treatment-emergent adverse event (TEAE) (**Table 3**). The most common TEAEs were anemia (99 [49.5%]), nausea (93 [46.5%]), fatigue (66 [33.0%]), and thrombocytopenia (63 [31.5%]) (eTable 5 in Supplement 2). Treatment-related adverse events (TRAEs) of any grade occurred in 182 patients (91.0%), including grade 3 or greater TRAEs in 98 patients (49.0%) (Table 3). The most common grade 3 or greater TRAEs (≥5% of patients) were anemia (68 [34.0%]), thrombocytopenia (30 [15.0%]), and neutropenia (22 [11.0%]). TRAEs led to discontinuation of any study drug in 11 patients (5.5%) (eTable 6 in Supplement 2). The

Figure 2. Efficacy Summary in the *BRCA1/2* Cohort



Time to and duration of response in the full analysis set per blinded independent central review, for all patients in the *BRCA1/2* cohort and in *BRCA*-associated and non–*BRCA*-associated tumor types. Molecular analysis was based on results from central laboratories and supplemented by local laboratories when central results were not available. Patients with alterations in non-*BRCA* DNA damage response genes are indicated accordingly.

CA-125 indicates cancer antigen 125; CR, complete response; HR, hormone receptor; LOH, loss of heterozygosity; mCRPC, metastatic castration-resistant prostate cancer; mut/MB, mutations per megabase; PD-L1, programmed cell death–ligand 1; PR, partial response; PSA, prostate-specific antigen; TMB, tumor mutational burden; TNBC, triple-negative breast cancer; uLMS, uterine leiomyosarcoma.

talazoparib dose was reduced because of TRAEs in 65 patients (32.5%) (eTable 6 in Supplement 2). No TRAEs resulted in death. Immune-related adverse events (irAEs) occurred in 25 patients (12.5%); grade 3 or greater irAEs occurred in 5 patients (2.5%) (eTable 6 in Supplement 2).

Discussion

To our knowledge, this is the first trial to assess the combination of PARP and PD-L1 inhibitors as a pan-cancer tumor-agnostic treatment strategy in *BRCA1/2*- and *ATM*-altered cancers. Neither the *BRCA1/2* nor *ATM* cohort met the prespecified target ORR of 40%, indicating that a pan-cancer tumor-agnostic approach with this combination is not an optimal clinical strategy. Clinical activity within the *BRCA1/2* cohort was mainly observed in patients with *BRCA1/2*-associated tumor types (ovarian, breast, prostate, and pancreatic cancers) and uLMS; limited benefit was seen in patients with non-*BRCA1/2*-associated tumor types. These data are consistent with a recent large clinicogenomic analysis, which indicated that *BRCA1/2* alterations have pleiotropic effects that are tumor-lineage dependent, while most *BRCA1/2* alterations in non-*BRCA*-associated cancers may be unrelated to tumor pathogenesis and unlikely to be therapeutically actionable.[6] Further studies are required to determine the underlying mechanisms that mediate differences in tolerance to defects in homologous recombination across various tumor lineages. Our findings indicate that rather than a tumor-agnostic drug development strategy used with biomarkers such as *NTRK* fusions[18] and microsatellite instability,[19] future clinical trial approaches with PARP and anti-PD-1/PD-L1 inhibitor combinations should be focused on *BRCA*-associated tumors.

A notable exception in the non-*BRCA1/2*-associated tumors is uterine cancer, which comprised 5 of 6 patients who responded to therapy, none with the more common endometrioid histology. All 3 patients with uLMS had prolonged responses ongoing at the data cutoff. In contrast to *BRCA1/2*-associated tumor types, typified by their frequency of germline *BRCA1/2* alterations, patients with uLMS harbored somatic *BRCA2* homozygous deletions associated with a high gLOH phenotype. The prolonged clinical benefit may be attributable to the inability of tumors bearing *BRCA* large homozygous deletions to develop reversion alterations, a known mechanism of acquired resistance to PARP inhibitors.[6] Consistent with this hypothesis, patients with *BRCA1/2* homozygous deletions have been reported as extraordinary responders to PARP inhibitors.[10,20-24] Somatic biallelic *BRCA2* loss is present in 6.5% of all uterine sarcomas, and our data suggest that this tumor type may be *BRCA* dependent.[6]

When the *BRCA1/2* cohort was further explored for clinical activity by tumor type, the overall efficacy of avelumab plus

Table 3. Treatment-Related Adverse Events[a]

	Patients, No. (%) (n = 200)	
TRAE	Any grade	Grade ≥3
Any	182 (91.0)	98 (49.0)
Anemia[b]	92 (46.0)	68 (34.0)
Nausea	62 (31.0)	1 (0.5)
Thrombocytopenia[c]	58 (29.0)	30 (15.0)
Fatigue	45 (22.5)	3 (1.5)
Neutropenia[d]	40 (20.0)	22 (11.0)
Diarrhea	29 (14.5)	0
Asthenia	22 (11.0)	1 (0.5)
Decreased appetite	20 (10.0)	0
Alopecia	19 (9.5)	0
Vomiting	19 (9.5)	0
Headache	18 (9.0)	1 (0.5)
ALT increased	15 (7.5)	3 (1.5)
AST increased	15 (7.5)	4 (2.0)
Infusion-related reaction[e]	41 (20.5)	1 (0.5)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; TRAE, treatment-related adverse event.

[a] TRAEs of any grade occurring in 10% or more of patients or grade 3 or greater in 5% or more of patients are shown. Adverse events are reported as preferred terms, and some are grouped according to hematologic cluster terms.

[b] Anemia was defined as any event having the following preferred terms: anemia, hematocrit decreased, hemoglobin decreased, iron deficiency anemia, or red blood cell count decreased.

[c] Thrombocytopenia was defined as any event having the following preferred terms: immune thrombocytopenia, platelet count decreased, or thrombocytopenia.

[d] Neutropenia was defined as any event having the following preferred terms: autoimmune neutropenia, febrile neutropenia, neutropenia, or neutrophil count decreased.

[e] Infusion-related reactions were identified based on a list of prespecified Medical Dictionary for Regulatory Activities Terminology preferred terms and time of onset and resolution of the events in relation to the avelumab infusions, regardless of investigator-assessed causality.

talazoparib remained generally consistent with previous PARP inhibitor monotherapy and/or in combination with ICIs. The confirmed response rates in breast, ovarian, and pancreatic cancers were comparable with prior studies,[8,11,25-28] notwithstanding that these studies typically did not use central independent review of ORR and/or frequently included unconfirmed responses.

We also explored whether biallelic *BRCA1/2* loss or high gLOH scores were associated with efficacy. In patients with *BRCA1/2*-dependent tumors, the response rate was similar for tumors with *BRCA* alterations under LOH vs heterozygous tumors (29.8% vs 22.2%) and high gLOH vs low gLOH tumors (36.4% vs 31.6%). These results are consistent with prior reports suggesting that *BRCA1/2* zygosity and gLOH may not correlate with outcomes in *BRCA1/2*-altered, *BRCA1/2*-dependent tumors treated with PARP inhibitors.[6,29] In ovarian cancer, several studies have validated homologous recombination deficient positivity and/or high gLOH as a biomarker predictive of response to PARP inhibition, with 2 US Food and Drug Administration–approved companion diagnostics for this indication.[30] However, it is important to note that this testing was used to identify the subset of patients with *BRCA1/2* wild-type tumors more likely to benefit from PARP inhibitors, and *BRCA1/2* alteration status remains the strongest predictor of response.[25,31-34] Furthermore, in the *BRCA1/2* cohort, the ORR was numerically higher for germline vs somatic mutations (27.6% and 7.7%, respectively), although 95% CIs overlapped. This may partly reflect the higher rate of germline alterations in *BRCA1/2*-dependent tumors, likely due to intrinsic tumor characteristics and pre-enrichment due to increased germline testing in patients with these cancer types.

Response to therapy in the *BRCA1/2* cohort was numerically higher for patients with TMB of 10 or more mutations per megabase (mut/Mb) vs TMB of less than 10 mut/Mb tumors, which is consistent with data from KEYNOTE-158, which identified TMB of 10 or more mut/Mb as a predictive biomarker for response to PD-1/PD-L1 blockade.[35] However, few *BRCA1/2*-associated tumors were included. Although limited by small numbers of participants, responses in high TMB, non-*BRCA*-associated tumors (Figure 2) suggest that PD-L1 blockade is contributing to efficacy and support TMB as a potential predictive biomarker in this population. Patients enrolled in the *ATM* cohort had limited clinical benefit, leading to early closure of this cohort. The lack of efficacy observed in the *ATM* cohort has important implications for the development of PARP inhibitors.

Limitations

Study limitations include the single-group study design, which makes assessment of response rates for the combination challenging without comparing with historical data for avelumab or talazoparib monotherapy in similar patient populations. In addition, many of the subanalyses were retrospective and exploratory and often limited by small numbers of patients, which prevents us from drawing definitive conclusions.

Conclusions

In this nonrandomized controlled trial, we evaluated *BRCA1/2*- and *ATM*-altered cancers in a pan-cancer tumor-agnostic study of patients with a range of solid tumors, including rare cancers such as uLMS. The combination of avelumab and talazoparib was well tolerated, with no new safety signals identified. In *BRCA1/2*-altered cancers, efficacy for the combination was mainly observed in *BRCA1/2*-associated tumor types (ovarian, breast, prostate, and pancreatic) and uLMS and was comparable with that reported for PARP inhibitor monotherapy.

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