IMPORTANCE Preclinical data suggest that poly(ADP-ribose) polymerase (PARP) inhibitors have synergistic activity when combined with immune checkpoint inhibitors (ICIs); however, it is unknown which tumor types or molecular subtypes may benefit from this combination.

OBJECTIVE To investigate responses associated with the combination of avelumab and talazoparib in different tumor types and/or molecular subtypes.

DESIGN, SETTING, AND PARTICIPANTS In this phase 1b and 2 basket nonrandomized controlled trial, patients with advanced solid tumors were enrolled in the following cohorts: non–small cell lung cancer (NSCLC); DNA damage response (DDR)–positive NSCLC; triple-negative breast cancer (TNBC); hormone receptor–positive, human epidermal growth factor receptor 2 (ERBB2)–negative, DDR-positive breast cancer; recurrent, platinum-sensitive ovarian cancer (OC); recurrent, platinum-sensitive, BRCA1/2-altered OC; urothelial cancer; metastatic castration-resistant prostate cancer (mCRPC); DDR-positive mCRPC; and BRCA1/2- or ATM-altered solid tumors. Data were analyzed between June 17, 2021, and August 6, 2021.

INTERVENTIONS All patients in phases 1b and 2 received avelumab plus talazoparib.

MAIN OUTCOMES AND MEASURES The phase 1b primary end point was dose-limiting toxic effects. The phase 2 primary end point was objective response, measured as objective response rate (ORR). Secondary end points included safety, time to response, duration of response (DOR), progression-free survival, time to prostate-specific antigen progression and PSA response of 50% or greater (for mCRPC), cancer antigen 125 response (for OC), pharmacokinetics, immunogenicity, and biomarkers.

RESULTS A total of 223 patients (mean [SD] age, 63.2 [11.0] years; 117 [52.5%] men) were treated, including 12 patients in phase 1b and 211 patients in phase 2. The recommended phase 2 dose was avelumab 800 mg every 2 weeks plus talazoparib 1 mg once daily. In phase 2, the ORR was 18.2% (95% CI, 5.2%-40.3%) in patients with TNBC; 34.8% (95% CI, 16.4%-57.3%) in patients with HR-positive, ERBB2-negative, and DDR-positive BC; and 63.6% (95% CI, 30.8%-89.1%) in patients with platinum-sensitive, BRCA1/2-altered OC. Responses occurred more frequently in patients with BRCA1/2-altered tumors. Durable responses were observed in patients with TNBC (median [range] DOR, 11.1 [3.4-20.4] months); HR-positive, ERBB2-negative, and DDR-positive BC (median [range] DOR, 15.7 [3.9 to \( \geq 20.6 \) months]; and BRCA1/2-altered OC (median DOR not reached; range, 5.6 to \( \geq 18.4 \) months). The most common grade 3 or greater treatment-related adverse events were anemia (75 patients [33.6%]), thrombocytopenia (48 patients [21.5%]), and neutropenia (31 patients [13.9%]).

CONCLUSIONS AND RELEVANCE This nonrandomized controlled trial found that ORRs for avelumab plus talazoparib were comparable with those with PARP inhibitor or ICI monotherapy. Prolonged DOR in patients with TNBC; HR-positive, ERBB2-negative, and DDR-positive BC; and BRCA1/2-altered OC warrant further investigation in randomized clinical trials. These data highlight the importance of prospective patient selection in future studies of ICI and PARP-inhibitor combinations.

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immune checkpoint inhibitors (ICIs) are effective as monotherapy or in combination with other agents in multiple solid tumors.1–4 Avelumab (an anti–programmed cell death 1 ligand 1 [PD-L1] antibody) is approved as monotherapy for treating metastatic Merkel cell carcinoma and locally advanced or metastatic urothelial carcinoma (UC) as first-line maintenance and second-line therapy and in combination with axitinib as first-line treatment of advanced renal cell carcinoma.5

Poly(ADP-ribose) polymerase (PARP) inhibitors are an effective treatment option for patients with tumors containing DNA damage response (DDR) alterations, such as BRCA1/2 (OMIM 113705 and OMIM 600185) alterations.6 Talazoparib, an oral PARP inhibitor, is approved for the treatment of deleterious or suspected deleterious germline BRCA1/2-altered, human epidermal growth factor receptor 2 (ERBB2)-negative, locally advanced or metastatic breast cancer (BC).7 In a phase 3 trial of patients with advanced BC and germline BRCA1/2 alterations, talazoparib significantly improved progression-free survival (PFS) vs chemotherapy8–9; talazoparib has also shown clinical activity in metastatic castration-resistant prostate cancer (mCRPC) and pancreatic cancer with germline or tumor BRCA1/2 alterations.10–11

Preclinical data and early-phase clinical trials suggest that PARP inhibitors have synergistic activity when administered in combination with ICIs.6,12–14 However, it is unknown which tumor types or molecular subtypes may benefit from this combination. In this study, we report results from the JAVELIN PARP Medley trial that investigated the safety and efficacy of avelumab plus talazoparib in 10 prospectively defined tumor-selected and/or molecularly selected cohorts of patients, including those sensitive to PARP inhibition (BRCA-associated tumors and DDR-positive tumors) or those with ICI-sensitive tumors.

Methods

This nonrandomized controlled trial was conducted in accordance with the International Ethical Guidelines for Biomedical Research Involving Human Subjects, the International Conference on Harmonization 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 and is provided in Supplement 1. This study is registered on ClinicalTrials.gov (NCT03330405). This study is reported following the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline and Transparent Reporting of Evaluations With Nonrandomized Designs (TREND) reporting guideline.

Patients

Eligible patients (aged ≥18 years) had an Eastern Cooperative Oncology Group performance status of 0 or 1; histologically diagnosed, locally advanced (primary or recurrent) or metastatic solid tumor not amenable to treatment with curative intent; measurable disease by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, with at least 1 measurable lesion (not required for patients with mCRPC); and adequate hematologic, kidney, and liver function. Complete eligibility criteria are detailed in the eAppendix in Supplement 2.

Findings

This nonrandomized controlled trial including 223 patients found that avelumab plus talazoparib was safe and well tolerated. Objective responses were mostly observed in patients with BRCA-altered tumors, with limited activity seen in patients with non–BRCA-altered DNA damage response (DDR)-positive tumors; however, prolonged duration of response was observed in patients with triple-negative breast cancer; hormone receptor–positive, human epidermal growth factor receptor 2-negative, DDR-positive breast cancer; and BRCA-altered ovarian cancer.

Meaning

These findings suggest that treatment with avelumab plus talazoparib warrants further investigation in specific molecular and tumor subtypes in randomized clinical trials.

Key Points

Question Which tumor types and/or molecular subtypes are associated with response to the combination of avelumab plus talazoparib?

Findings This nonrandomized controlled trial including 223 patients found that avelumab plus talazoparib was safe and well tolerated. Objective responses were mostly observed in patients with BRCA-altered tumors, with limited activity seen in patients with non–BRCA-altered DNA damage response (DDR)-positive tumors; however, prolonged duration of response was observed in patients with triple-negative breast cancer; hormone receptor–positive, human epidermal growth factor receptor 2-negative, DDR-positive breast cancer; and BRCA-altered ovarian cancer.

Meaning These findings suggest that treatment with avelumab plus talazoparib warrants further investigation in specific molecular and tumor subtypes in randomized clinical trials.

Study Design and Treatment

JAVELIN PARP Medley is an open-label, multicenter, phase Ib and 2 basket trial of avelumab plus talazoparib in patients with prospectively selected, molecularly defined, locally advanced or metastatic solid tumors, including non–small-cell lung cancer (NSCLC); DDR-positive NSCLC; triple-negative BC (TNBC); hormone receptor (HR)-positive, ERBB2-negative, DDR-positive BC; recurrent platinum-sensitive ovarian cancer (OC); recurrent, platinum-sensitive, BRCA-altered OC; UC; mCRPC; DDR-positive mCRPC; and BRCA1/2- or ATM-altered (OMIM 607585) solid tumors. The NSCLC cohorts were recruited in parallel; however, the inclusion criteria for patients with DDR-positive NSCLC were revised in trial protocol amendment 3 on November 20, 2018 (Supplement 1). The inclusion criteria were revised such that patients with NSCLC were no longer required to have PD-L1-positive tumors and instead were required to have DDR-positive tumors and may have previously received prior anti–PD-L1 and anti–programmed cell death 1 (PD-1) treatment. The mCRPC cohorts were also run in parallel. The mCRPC cohort enrolled unselected patients with mCRPC with unknown DDR status at the time of enrollment, while the DDR-positive mCRPC cohort enrolled patients with previously known DDR-positive tumors at the time of enrollment. As the study used retrospective central testing for the presence of DDR alterations, it was possible that patients in the mCRPC cohort could have had DDR-positive tumors identified after enrollment.

In phase Ib, patients received avelumab 800 mg intravenously every 2 weeks plus talazoparib 1 mg orally once daily; talazoparib dose reductions to 0.75 or 0.5 mg or interruptions were allowed based on tolerability. In the phase 2 (dose-expansion) part, patients received the recommended phase 2
dose (RP2D) determined in the phase lb. To mitigate infusion-related reactions, patients received antihistamine or acetaminophen prior to the first 4 avelumab infusions. Dose interruptions and reductions (talazoparib only) were permitted. In the event of a grade 3 or 4 adverse event (AE), avelumab or talazoparib administration was delayed until resolution to grade 1 or baseline (eAppendix in Supplement 2). Treatment was continued until disease progression, unacceptable toxic effects, or patient withdrawal. Patients with progressive disease who had ongoing clinical benefit could continue treatment at the treating physician’s discretion.

### End Points and Assessments

The primary end point of the dose-finding part of phase lb was first-cycle (28 days) dose-limiting toxic effects (DLTs; defined in the eAppendix in Supplement 2). In phase 2, the primary end point was confirmed objective response (OR; defined as best overall response of complete response [CR] or partial response [PR] per RECIST 1.1, confirmed by a second assessment ≥4 weeks after initial documentation). Secondary end points included safety, time to response, duration of response (DOR), PFS, time to prostate-specific antigen (PSA) progression and PSA response of 50% or greater (for mCRPC), cancer antigen 125 (CA-125) response (for OC), pharmacokinetics, immunogenicity, and biomarkers; definitions of end points are provided in the eAppendix in Supplement 2.

Blood samples for pharmacokinetics, pharmacodynamics, immunogenicity, and biomarker analyses were collected from all patients. In all patients, archival tumor tissue collected no more than 12 months before treatment was mandatory at screening (<45 days before enrollment for the DDR-positive NSCLC; HR-positive, ERBB2-negative, and DDR-positive BC; and DDR-positive mCRPC cohorts). Optional fresh tumor biopsies were performed throughout treatment between day 15 of cycle 1 and day 1 of cycle 3. Biomarker methods are provided in the eAppendix, eTable 1, and eTable 2 in Supplement 2.

### Statistical Analysis

In the dose-finding phase, DLTs were assessed in all patients who received at least 1 dose of study treatment and experienced a DLT during the first treatment cycle or completed the DLT observation period (first treatment cycle). Efficacy and safety were assessed in all patients who received at least 1 dose of study treatment. Avelumab pharmacokinetics and immunogenicity and talazoparib pharmacokinetics were analyzed in all patients who provided at least 1 sample for analysis.

An adaptive modified toxic effects probability interval design was used in phase lb to identify the RP2D of talazoparib in combination with avelumab. Detailed information is provided in the trial protocol in Supplement 1 and eAppendix in Supplement 2.

Approximately 20 to 40 patients would be enrolled in each phase 2 cohort; detailed information is provided in the trial protocol in Supplement 1 and eAppendix in Supplement 2. Time to response was summarized using simple descriptive statistics. DOR and PFS were analyzed using the Kaplan-Meier method. We calculated 2-sided 95% CIs using the Clopper-Pearson method for ORR, and the Brookmeyer and Crowley method was used for DOR and PFS. No hypothesis was tested in this study. Biomarker data were analyzed using descriptive statistics. Analyses were conducted using SAS statistical software version 9.4 (SAS Institute). Data were analyzed between June 17, 2021, and August 6, 2021.

### Results

#### Patients and Treatment

Between October 31, 2017, and November 7, 2019, a total of 223 patients (mean [SD] age, 63.2 [11.0] years; 117 [52.5%] men) were enrolled and treated, including 12 patients in phase lb and 211 patients in phase 2 (Figure 1). Due to slow enrollment, the DDR-positive NSCLC and BRCA1/2- or ATM-altered solid tumor cohorts were stopped early. The data cutoff was September 21, 2020.

#### Dose-Finding Phase

Of 12 patients in phase lb, 9 (75.0%) had mCRPC, 2 (16.7%) had TNBC, and 1 (8.3%) had OC. Baseline characteristics are shown in Table 1. In total, 3 patients (25.0%) experienced DLTs, including 2 (16.7%) with grade 3 thrombocytopenia and 1 (8.3%) with grade 3 neutropenia. This led to interruption of both study drugs and, in 1 patient with neutropenia, permanent withdrawal of talazoparib. The RP2Ds were determined to be avelumab 800 mg intravenously every 2 weeks and talazoparib 1 mg orally once daily. One patient with advanced OC had a CR that was ongoing at data cutoff, with a DOR of 31.9 months, and 1 patient with mCRPC had a PR (Table 2).

#### Dose-Expansion Phase

Of 211 patients in phase 2, 20 patients (9.5%) were still receiving treatment at the data cutoff; the most common reason for treatment discontinuation of both avelumab and talazoparib was progressive disease (131 patients [62.1%]) (Figure 1; eTable 3 in Supplement 2). A total of 108 patients (51.2%) were men; the median (IQR) patient age was 65.0 (56.0-70.0) years. Baseline characteristics of each cohort are shown in Table 1, and duration of treatment is shown in eTable 3 in Supplement 2. Across all cohorts, the median (range) duration of treatment was 4.6 (0.46-24.4) months for avelumab and 4.4 (0.02-24.9) months for talazoparib.

#### Dose-Expansion Cohorts

The median DOR, median PFS, proportions of patients with a confirmed OR, and best percentage change in target lesion size from baseline by cohort are shown in Table 2, Figure 2, and eFigures 1 through 3 in Supplement 2. ORs and ORRs according to biomarker status are shown in eTables 4 and 5 in Supplement 2. CA-125 and PSA responses are shown in eTable 6 in Supplement 2, and biomarker status is shown in eTable 7 in Supplement 2.

In the NSCLC cohort, the ORR was 16.7% (95% CI, 7.0%-31.4%) (Table 2). The median (range) DOR was 17.5 (5.4-17.5) months (eFigure 4 in Supplement 2). Responses were only observed in 1 patient with a DDR-positive tumor and 6 patients...
In total, 3 patients in the phase 1b portion experienced dose-limiting toxic effects leading to dose interruption. Of them, 2 patients (with thrombocytopenia) continued therapy following talazoparib dose reductions and recovery of platelet counts. Both patients subsequently discontinued from study treatment because of progressive disease; 1 patient discontinued 2 months after the start of treatment, and 1 withdrew from the study after 10 months of treatment. Only 1 patient permanently discontinued talazoparib because of neutropenia (after approximately 3 months); however, this patient continued to receive avelumab for a total of 5 months before discontinuing because of progressive disease. DDR indicates DNA damage repair; ERBB2, human epidermal growth factor receptor 2; HR, hormone receptor; mCRPC, metastatic castration-resistant prostate cancer; NSCLC, non–small-cell lung cancer; and TNBC, triple-negative breast cancer.

Safety
The most common (experienced by ≥30% of patients) treatment-related AEs (TRAEs) of any grade were anemia (135 patients [60.5%]), thrombocytopenia (110 patients [49.3%]), neutropenia (77 patients [34.5%]), and fatigue (69 patients [30.5%]) (Table 3). Grade 3 or 4 TRAEs observed in more than 5% of patients were anemia (75 patients [33.6%]), thrombocytopenia (48 patients [21.5%]), and neutropenia (31 patients [13.9%]). Talazoparib dose reductions due to AEs (regardless of causality) occurred in 79 patients (34.5%) and were most frequently due to hematological toxic effects, including anemia.
### Table 1. Baseline Characteristics of Patients in the Dose-Finding Phase and Dose-Expansion Cohorts

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Dose-finding phase (n = 12)</th>
<th>NSCLC (n = 42)</th>
<th>DDR+ NSCLC (n = 5)</th>
<th>TNBC (n = 22)</th>
<th>HR+, ERBB2−, DDR+ BC (n = 23)</th>
<th>OC (n = 20)</th>
<th>BRCA-alt OC (n = 11)</th>
<th>UC (n = 40)</th>
<th>mCRPC (n = 21)</th>
<th>DDR+ mCRPC (n = 18)</th>
<th>BRCA/ATM alt (n = 9)</th>
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(continued)
### Table 1. Baseline Characteristics of Patients in the Dose-Finding Phase and Dose-Expansion Cohorts (continued)

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<th>Patients, No. (%):</th>
<th>Dose-finding phase (n = 12)</th>
<th>NSCLC (n = 42)</th>
<th>DDR+ NSCLC (n = 5)</th>
<th>HR+, ERBB2−, BRCA−-alt OC (n = 11)</th>
<th>mCRPC (n = 21)</th>
<th>DDR+ mCRPC (n = 20)</th>
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**Characteristics**
- **Prior anticancer therapies for advanced disease**: Includes regimens in the neoadjuvant, adjuvant, or advanced or metastatic setting. In patients with BC, disease was considered as advanced or metastatic if disease progression occurred during previous neoadjuvant or adjuvant treatment due to TRAEs was low.

**Abnormalities**
- *Defined from baseline tumor, circulating tumor DNA, and germline DDR alteration data.*
- *Includes regimens as advanced or metastatic if disease progression occurred during previous neoadjuvant or adjuvant treatment.*
- *Except for data in clinical trials.*
- *Pending data or missing sample.*
- *Defined subgroup with known biomarker (PD-L1 in inhibitor combination in patients with prospectively defined subgroups with known biomarker (BRCA1/2 and DDR) statuses.*
- *Except for data in clinical trials.*
- *Defined subgroup with known biomarker (PD-L1 in inhibitor combination in patients with prospectively defined subgroups with known biomarker (BRCA1/2 and DDR) statuses.*
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- *Except for data in clinical trials.*
- *Defined subgroup with known biomarker (PD-L1 in inhibitor combination in patients with prospectively defined subgroups with known biomarker (BRCA1/2 and DDR) statuses.*
- *Except for data in clinical trials.*

### Discussion

This nonrandomized controlled trial is the largest and most histologically diverse basket trial, to our knowledge, to assess the safety and clinical efficacy of a PARP inhibitor and PD-1 and PD-L1 inhibitor combination in patients with prospectively defined subgroups with known biomarker (BRCA1/2 and DDR) statuses. To identify molecular subtypes that may respond to avelumab and talazoparib, we used a panel of 34 genes to define DDR status. While alterations in genes implicated in homologous recombination are associated with sensitization to PARP inhibition, a large analysis by Hsiehchen et al reported that such alterations also are associated with benefit to ICIs independent of tumor mutation burden and tumor type, thus complicating attempts to attribute benefit to either of the respective single agents.

Avelumab 800 mg every 2 weeks plus talazoparib 1 mg once daily was generally well tolerated, and no new safety signals were identified compared with both drugs given as monotherapy. Toxic effects were manageable with dose modifications, and the proportion of patients who discontinued study treatment due to TRAEs was low.

In patients with NSCLC and UC, and with the caveat of cross-trial comparison, the clinical activity was similar to that seen in previous studies of ICI monotherapy. These cohorts included at least 1 prior line of therapy for advanced disease in more than 50% of patients, low or negative PD-L1 expression, and low tumor mutational burden (where known) in most patients. In the NSCLC cohort, responses were observed in three-fourths of patients with high PD-L1 expression. However, DDR-positive or BRCA-altered tumors were not associated with significantly increased antitumor activity in either the NSCLC cohort or the UC cohort, suggesting that DDR alterations, including some BRCA alterations, did not increase sensitivity to the combination. As previously reported, BRCA1/2 alterations are an indispensable founding event for certain cancers; however, in other tumors, they appear to be biologically neutral.

Disease control was achieved in all patients with confirmed BRCA-altered, platinum-sensitive OC; despite the small sample size, the findings are comparable with reports of patients treated with PARP-inhibitor monotherapy or PARP inhibitor plus ICI combination therapy. With the
Table 2. Best Overall Response, Confirmed Objective Response, and Progression-Free Survival in the Dose-Finding Phase and Dose-Expansion Cohorts

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Patients, No. (%)</th>
<th>Dose-finding phase (n = 12)</th>
<th>NSCLC (n = 42)</th>
<th>DDR+ NSCLC (n = 5)</th>
<th>TNBC (n = 22)</th>
<th>HR+, ERBB2+, BRCA-alt OC (n = 23)</th>
<th>DDR+ BC (n = 20)</th>
<th>OC (n = 20)</th>
<th>BRCA-alt OC (n = 11)</th>
<th>UC (n = 40)</th>
<th>mCRPC (n = 21)</th>
<th>DDR+ mCRPC (n = 18)</th>
<th>BRCA/ATM alt (n = 9)</th>
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<td>Best overall response</td>
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<td>CR</td>
<td>1 (8.3)</td>
<td>1 (8.3)</td>
<td>1 (4.5)</td>
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<td>2 (18.2)</td>
<td>1 (2.5)</td>
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<td>PR</td>
<td>1 (8.3)</td>
<td>7 (16.7)</td>
<td>1 (20.0)</td>
<td>3 (13.6)</td>
<td>7 (30.4)</td>
<td>4 (20.0)</td>
<td>5 (45.5)</td>
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<td>Stable disease</td>
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<td>Non-CR or non-PD</td>
<td>1 (8.0)</td>
<td>24 (57.1)</td>
<td>1 (20.0)</td>
<td>8 (36.4)</td>
<td>8 (34.8)</td>
<td>15 (75.0)</td>
<td>4 (36.4)</td>
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<td>7 (33.3)</td>
<td>5 (27.8)</td>
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<td>1 (11.1)</td>
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<td>PD</td>
<td>5 (41.7)</td>
<td>7 (16.7)</td>
<td>3 (60.0)</td>
<td>10 (45.5)</td>
<td>7 (30.4)</td>
<td>1 (5.0)</td>
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<td>Not evaluable</td>
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<td>4 (9.5)</td>
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<td>Patients with OR, % (95% CI)</td>
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<td>Time to response, median (mo)</td>
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<td>Duration of response, median (mo)</td>
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<td>PFS, median (95% CI), month</td>
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<td>Probability of no disease progression, % (95% CI)</td>
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<td>Avelumab</td>
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<td>Talazoparib</td>
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Abbreviations: −, negative; +, positive; alt, altered; BC, breast cancer; CR, complete response; DDR, DNA damage repair deficient; ERBB2, human epidermal growth factor receptor 2; HR, hormone receptor; mCRPC, metastatic castration-resistant prostate cancer; NA, not available; NC, not calculable; NE, not estimable; NR, not reached; NSCLC, non-small-cell lung cancer; OC, ovarian cancer; OR, objective response; PD, progressive disease; PFS, progression-free survival; PR, partial response; TNBC, triple-negative BC; UC, urothelial carcinoma.

a Assessed by investigators per Response Evaluation Criteria in Solid Tumors version 1.1 for patients with BRCA1/2.
b Assessed by investigators per Response Evaluation Criteria in Solid Tumors version 1.1 and Prostate Cancer Working Group 3 patients with BRCA1/2.

References:
Figure 2. Best Percentage Change in Size of Target Lesions Assessed by Investigators per RECIST v1.1 While Receiving Treatment in the Dose-Expansion Phase

The blue dashed lines represent the threshold for progressive disease (PD), defined as an increase of at least 20% in target lesion diameter from baseline. The lower dashed lines represent the threshold for a partial response, defined as a decrease of at least 30% in target lesion diameter from baseline. In patients with DNA damage repair–positive (DDR+) status but for whom a DDR alteration is not specified, DDR status was confirmed by germline loss of heterozygosity (gLOH) score. Presence of a germline DDR+ alteration (gDDR) alone did not confirm DDR+ status. In the absence of positive solid tumor or circulating tumor DNA alteration results, detection of a known or likely deleterious germline variant suggested that a patient had a DDR+ tumor, provided that solid tumor and circulating tumor DNA results did not both suggest DDR-negative (DDR−).

(Three patients were considered to have DDR+ tumors at enrollment, determined by a gLOH score above the predefined cutoff; however, their tumors were subsequently considered DDR− because of a change in gLOH assay specifications. Two patients were enrolled based on a local test result but received negative results centrally.) Arrows indicate ongoing treatment; bDDR, blood DDR; bTMB, blood tumor mutational burden; ERBB2, human epidermal growth factor receptor 2; HR, hormone receptor; PD-L1, programmed cell death 1 ligand 1; SD, stable disease; tDDR, tumor DDR. For some items, the genetic variation is written in vertical text above the bar, with black font indicating tDDR alteration and teal font, bDDR alteration.
caveat of cross-trial comparison, the median DOR among patients with BRCA-altered, platinum-sensitive OC compared favorably with that reported with olaparib monotherapy in a similar population. This is also supported by the observation that 55% of patients were alive and progression free at 18 months after treatment start, suggesting potentially improved efficacy compared with that seen with olaparib monotherapy (median PFS, 12.7 months in a study by Lieu et al26 and 13.2 months in the SOLO3 trial24). Overall, and with the limitations of small sample size and nonrandomized trial design, these results suggest improved response durability and PFS in patients with platinum-sensitive, BRCA1/2-altered OC. Lower ORRs were observed in patients with platinum-sensitive, unselected OC, since most patients (75%) in this cohort had DDR-negative disease; in patients with DDR-positive disease, only 1 had a BRCA-altered tumor. The difference in clinical outcomes between biomarker-unselected and biomarker-selected OC cohorts highlights the importance of appropriate patient selection using biomarkers associated with response to optimize patient benefit, even with combination approaches.

In the advanced BC cohorts (ie, TNBC and HR-positive, ERBB2-negative, and DDR-positive BC), clinical activity was primarily observed in patients with BRCA-altered tumors. While the number of patients with BRCA-altered tumors was a small proportion of the total population (3 of 22 patients with TNBC; 9 of 19 patients with HR-positive, ERBB2-negative, and DDR-positive BC), most responses were observed in patients with BRCA-altered tumors (3 of 4 patients with TNBC; 6 of 8 patients with HR-positive, ERBB2-negative, and DDR-positive BC). Despite the small sample size, the response rate in patients with BRCA-altered tumors (3 of 3 patients with TNBC; 6 of 9 patients with HR-positive, ERBB2-negative, and DDR-positive BC) was comparable with the phase 3 EMBRACA and phase 2 ABRAZO studies of talazoparib monotherapy in patients with germline BRCA-altered, advanced BC and the combination study of niraparib and pembrolizumab in patients with advanced or metastatic TNBC. The median DORs in patients with advanced TNBC (11.1 months) and HR-positive, ERBB2-negative, and DDR-positive BC (15.7 months) compare favorably with the DOR in the EMBRACA study (median DOR, 5.4 months), suggesting improved response durability with combination treatment.

The clinical activity of avelumab plus talazoparib in unselected patients with mCRPC and DDR-positive mCRPC was limited. In the mCRPC cohort, most patients (62%) had DDR-negative tumors, while in the DDR-positive mCRPC cohort, most patients with DDR-positive tumors (14 of 16 patients) had non-BRCA-altered tumors, and the efficacy was consistent with other studies of patients with mCRPC and BRCA wild-type tumors treated with PARP-inhibitor monotherapy.11,29,30 Overall, these data suggest that clinical benefit was limited for other DDR alterations, and the addition of ICIs did not extend clinical benefit to patients with mCRPC with BRCA1/2 wild-type tumors.

In several cohorts, no clear association of PD-L1 status, tumor mutational burden, CD8+ T-cell level, or DDR status with antitumor response was observed. However, in other cohorts (eg, DDR-positive mCRPC), the limited sample sizes and/or imbalances in distribution precluded these formal assessments.
Avelumab Plus Talazoparib in Advanced Solid Tumors

Limitations
This study has some limitations. Several of the patient groups have small numbers, which prevents us from drawing definitive conclusions. Furthermore, some of the analyses were retrospective and exploratory. Additionally, due to single-arm study design, the response rates for the combination of avelumab and talazoparib were compared with historical data for avelumab or talazoparib monotherapy in similar patient populations.

Conclusions
In this nonrandomized controlled trial, the combination of avelumab and talazoparib was generally well tolerated. The addition of talazoparib was not associated with significantly extending the clinical activity of avelumab in patients with DDR-positive NSCLC and unselected NSCLC or UC. In patients with PARP inhibitor–sensitive tumor types, most responses were observed in patients with BRCA-altered tumors, and activity was limited in patients with BRCA wild-type, DDR-positive tumors. A potential reason for this may have been receipt of prior chemotherapy, including prior platinum, which could have affected the response of BRCA wild-type DDR-positive tumors to talazoparib due to cross-resistance mechanisms, such as restoration of HR. Furthermore, a limitation of these data is that the association of response with individual BRCA wild-type DDR genes could not be assessed due to small sample sizes. Selection of patients via DDR status could guide future therapeutic strategies, eg, use of other DDR inhibitors, in combination with ICIs, perhaps tailored to specific tumor types.

Overall, these data highlight the importance of prospective patient selection in future studies of ICI and PARP inhibitors or other DDR inhibitor combinations. The addition of avelumab did not extend DOR across all tumor types; however, potential clinical benefit was observed in patients with TNBC, HR-positive, ERBB2-negative, and DDR-positive BC, and BRCA-altered OC, warranting further investigation in the context of an optimized patient selection strategy and randomized clinical trials.

Critical revision of the manuscript for important intellectual content: Yap, Bardia, Dvorkin, Galsky, Beck, Rubovszky, Kislov, Rohrberg, Telli, Schram, Conte, Chappey, Stewart, Stypinski, Michelon, Cesari, Konstantinopoulos.

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Obtained funding: Kislov.

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Supervision: Bardia, Beck, Karyakin, Rubovszky, Schram, Conte, Cesari.

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Dr Beck reported receiving grants from Pfizer during the conduct of the study. Dr Wise reported serving as a consultant for and receiving grants from Pfizer during the conduct of the study and serving as a consultant for Janssen, Leap Therapeutics, and Foundation Medicine outside the submitted work.

Dr Rubovszky reported receiving research support from Pfizer during the conduct of the study and personal fees from Pfizer, Eli Lilly, and Novartis outside the submitted work. Dr Kislov reported receiving grants from Pfizer during the conduct of the study and grants from Pfizer outside the submitted work. Dr Rohrberg reported receiving grants from Pfizer during the conduct of the study and grants from Eli Lilly, Roche/Genentech, Bristol Myers Squibb, Symphogen, Novartis, Loxo, Bayer, Alligator Bioscience, Incyte, Genmab, Monta BioScience, Bioinvent, Onconova, Cantagia, and personal fees from Bayer and Amgen outside the submitted work. Dr Joy reported receiving personal fees from Pfizer, AstraZeneca, Novartis, Bristol Myers Squibb, Roche, Seagen, and Gilead Sciences outside the submitted work. Dr Telli reported receiving grants and personal fees from Pfizer during the conduct of the study; personal fees from AstraZeneca, Merck, Genentech, Gilead Sciences, Blueprint Medicine, Novartis, ReFlexion, GI Therapeutics, Immunomedics, Guardant, Natera, Sanofi, OncoSec, Celgene, Eli Lilly, AbbVie, Daiichi Sankyo, and Aduro and grants from Bayer, Vertex, EMD Serono, Merck, Genentech, GlaxoSmithKline, OncoSec, AbbVie, Hummingbird, and Biothera outside the submitted work. Dr Schram reported receiving research support from AstraZeneca, ArQuile, BeGene, Black Diamond Therapeutics, Eli Lilly, Merus, Northern Biologics, Pfizer, Relay, Elevation Oncology, Kura Oncology, PMV Pharma, Revolution Medicine, Repare, and Surface Oncology and personal fees from Relay and Mersana outside the submitted work. Dr Conte reported being employed by Pfizer during the conduct of the study. Dr Chappey reported being employed by Pfizer during the conduct of the study. Dr Stewart reported being employed by Pfizer during the conduct of the study; owning stock in Pfizer and AstraZeneca and being employed by AstraZeneca outside the submitted work. Dr Michelon reported being employed by and owning stock in Pfizer during the conduct of the study. Dr Cesari reported being employed by Pfizer during the conduct of the study. Dr Konstantinopoulos reported receiving

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Author Contributions: Drs Yap and Konstantinopoulos had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Yap, Bardia, Conte, Stewart, Michelon, Cesari.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Yap, Bardia, Wise, Karyakin, Joy, Conte, Stypinski, Michelon, Cesari, Konstantinopoulos.
grants from Pfizer during the conduct of the study; serving as a consultant for Alkermes, Bayer, Merck, Merck KGaA, Pfizer, Kadmon, AstraZeneca, Bristol Myers Squibb, GlaxoSmithKline, and IMV outside the submitted work. No other disclosures were reported.

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Data Sharing Statement: See Supplement 3.

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REFERENCE


