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Nivolumab plus rucaparib for metastatic castration-resistant prostate cancer: results from the phase 2 CheckMate 9KD trial

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ABSTRACT

Background CheckMate 9KD (NCT03338790) is a non-randomized, multicohort, phase 2 trial of nivolumab plus other anticancer treatments for metastatic castration-resistant prostate cancer (mCRPC). We report results from cohorts A1 and A2 of CheckMate 9KD, specifically evaluating nivolumab plus rucaparib.

Methods CheckMate 9KD enrolled adult patients with histologically confirmed mCRPC, ongoing androgen deprivation therapy, and an Eastern Cooperative Oncology Group performance status of 0–1. Cohort A1 included patients with postchemotherapy mCRPC (1–2 prior taxane-based regimens) and ≤2 prior novel hormonal therapies (eg, abiraterone, enzalutamide, apalutamide); cohort A2 included patients with chemotherapy-naïve mCRPC and prior novel hormonal therapy. Patients received nivolumab 480 mg every 4 weeks plus rucaparib 600 mg two times per day (nivolumab dosing ≤2 years). Coprimary endpoints were objective response rate (ORR) per Prostate Cancer Clinical Trials Working Group 3 and prostate-specific antigen response rate (PSA_{50}-RR; ≥50% PSA reduction) in all-treated patients and patients with homologous recombination deficiency (HRD)-positive tumors, determined before enrollment. Secondary endpoints included radiographic progression-free survival (rPFS), overall survival (OS), and safety.

Results Outcomes (95% CI) among all-treated, HRD-positive, and *BRCA1/2*-positive populations for cohort A1 were confirmed ORR: 10.3% (3.9–21.2) (n=58), 17.2% (5.8–35.8) (n=29), and 33.3% (7.5–70.1) (n=9); confirmed PSA_{50}-RR: 11.9% (5.9–20.8) (n=84), 18.2% (8.2–32.7) (n=44), and 41.7% (15.2–72.3) (n=12); median rPFS: 4.9 (3.7–5.7) (n=88), 5.8 (3.7–8.4) (n=45), and 5.6 (2.8–15.7) (n=12) months; and median OS: 13.9 (10.4–15.8) (n=88), 15.4 (11.4–18.2) (n=45), and 15.2 (3.0–not estimable) (n=12) months. For cohort A2 they were confirmed ORR: 15.4% (5.9–30.5) (n=39), 25.0% (8.7–49.1) (n=20), and 33.3% (7.5–70.1) (n=9); confirmed PSA_{50}-RR: 27.3% (17.0–39.6) (n=66), 41.9 (24.5–60.9) (n=31), and 84.6% (54.6–98.1) (n=13); median rPFS: 8.1 (5.6–10.9) (n=71), 10.9 (6.7–12.0) (n=34), and 10.9 (5.6–12.0) (n=15) months; and median OS: 20.2 (14.1–22.8) (n=71), 22.7 (14.1–not estimable) (n=34), and 20.2 (11.1–not estimable) (n=15) months. In cohorts A1 and A2, respectively, the most common any-grade and grade 3–4 treatment-related adverse events (TRAEs) were nausea (40.9% and 40.8%) and anemia (20.5% and 14.1%). Discontinuation rates due to TRAEs were 27.3% and 23.9%, respectively.

Conclusions Nivolumab plus rucaparib is active in patients with HRD-positive postchemotherapy or chemotherapy-naïve mCRPC, particularly those harboring *BRCA1/2* mutations. Safety was as expected, with no new signals identified. Whether the addition of nivolumab incrementally improves outcomes versus rucaparib alone cannot be determined from this trial.

Trial registration number NCT03338790.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Efficacy of single-agent immunotherapy for patients with metastatic castration-resistant prostate cancer (mCRPC) has been suboptimal, leading to the recent investigation of combination therapy approaches for this patient population.

WHAT THIS STUDY ADDS

⇒ Nivolumab plus rucaparib has clinical activity in patients with homologous recombination deficiency-positive mCRPC, particularly those harboring *BRCA1/2* mutations, with an acceptable safety profile.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These results contribute to our understanding of the efficacy and safety of combined PD-1/PD-L1 and poly(ADP-ribose) polymerase inhibition for postchemotherapy and chemotherapy-naïve mCRPC.

BACKGROUND

Over the past two decades, therapeutic advances have improved outcomes for

patients with metastatic castration-resistant prostate cancer (mCRPC), with the approval of various chemotherapies, hormonal therapies, poly(ADP-ribose) polymerase (PARP) inhibitors, and the immunotherapy sipuleucel-T.[1–3] Despite the emergence of these treatment options, mCRPC remains an incurable, fatal malignancy; thus, additional therapeutic strategies continue to be evaluated.

One such strategy, investigated in several clinical trials, involves combining immune checkpoint inhibitors with other anticancer treatments that have the potential to stimulate an increasingly immune-responsive prostate cancer microenvironment, testing the hypothesis that the immunotherapeutic effects will be augmented and outcomes improved.[4–7] This combination approach is necessary because treatment with single-agent immune checkpoint inhibitors targeting the anti-programmed death-1 (PD-1)/programmed death ligand 1 (PD-L1) pathway does not appear to elicit clinically impactful antitumor responses in unselected mCRPC populations.[8–11] Although pivotal trials of ipilimumab (a cytotoxic T-lymphocyte antigen-4 checkpoint inhibitor) monotherapy originally failed to show improvements in overall survival (OS) versus placebo for unselected patients with mCRPC,[12 13] an excess of long-term survivors versus placebo has since been reported in this clinical setting.[14] Preliminary studies of nivolumab combined with ipilimumab have shown clinical activity in patients with mCRPC,[15 16] supporting the concept of immunotherapy-based combinatorial strategies for this patient population.

PARP inhibitors have demonstrated encouraging clinical activity in patients with mCRPC who carry alterations in DNA damage repair genes, including those associated with homologous recombination deficiency (HRD),[17–19] leading to regulatory approvals in Europe and the United States. For example, one such PARP inhibitor, rucaparib, has shown antitumor activity as monotherapy for post-chemotherapy mCRPC in the TRITON2 trial, with a reported objective response rate (ORR) per independent radiology review of 43.5% and a prostate-specific antigen (PSA) response rate of 54.8% among patients harboring deleterious *BRCA1* or *BRCA2* mutations.[19] PARP inhibitors act by further limiting DNA damage repair in tumor cells that carry DNA damage repair mutations, resulting in tumor cell death; this produces tumor neoantigens and increases immunogenicity, thus promoting a more immune-responsive tumor microenvironment.[20 21] Indeed, in preclinical studies across various tumor types, PARP inhibitors have been shown to synergize with PD-1/PD-L1 checkpoint blockade and potentiate antitumor efficacy.[22–25] As such, there is a compelling therapeutic rationale for clinical investigations into the combination of immune checkpoint inhibitors and PARP inhibitors for patients with mCRPC.

Here, we report final analysis results from cohorts A1 and A2 of the multicohort, phase 2 CheckMate 9KD trial, which evaluated the efficacy and safety of the anti-PD-1 immune checkpoint inhibitor nivolumab combined with rucaparib in men with either chemotherapy-naïve or postchemotherapy mCRPC.

METHODS

Study design and participants

CheckMate 9KD is a non-randomized, open-label, multicohort, phase 2 trial of nivolumab combined with rucaparib (cohorts A1 and A2), docetaxel (cohort B), or enzalutamide (cohort C) for mCRPC. Methods for the overall study and specific to cohort B have previously been described.[26] In brief, the CheckMate 9KD study population comprises adult patients (≥18 years of age) with histological confirmation of adenocarcinoma of the prostate with radiologic evidence of stage IV disease (N1 and/or M1), ongoing androgen deprivation therapy or bilateral orchiectomy (confirmed by testosterone level ≤1.73 nmol/L at screening), and documented progressive disease per Prostate Cancer Clinical Trials Working Group 3 (PCWG3) criteria. Eligible patients were also required to have an Eastern Cooperative Oncology Group performance status of 0 or 1 and sufficient tumor tissue obtained within 5 years before enrollment from a metastatic or primary tumor lesion not previously irradiated. Exclusion criteria included active brain metastases, conditions requiring systemic treatment with corticosteroids (>10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of start of study treatment, and prior therapy specifically targeting T-cell costimulation or immune checkpoint pathways.

Cohort assignment was based on prior systemic treatment received in the castration-resistant setting and eligibility to begin immediate chemotherapy. For assignment to cohort A1, patients must have received 1–2 prior taxane-based chemotherapy regimens in the castration-resistant setting, and prior treatment with up to two novel hormonal therapies (eg, abiraterone, enzalutamide, or apalutamide) for castration-resistant disease was allowed. For assignment to cohort A2, patients must have been chemotherapy-naïve for mCRPC, have received prior abiraterone, enzalutamide, and/or apalutamide for castration-resistant disease up to 28 days before cohort assignment, and not be candidates for or have refused immediate chemotherapy. Although patients were excluded from cohort A2 if they had received prior chemotherapy for mCRPC, prior treatment with docetaxel for metastatic hormone-sensitive prostate cancer was allowed if at least 12 months had elapsed from the last dose. Patients in cohort A2 were also required to be asymptomatic or minimally symptomatic according to the Brief Pain Inventory-Short Form performed at screening. Patients were excluded from both cohorts A1 and A2 if they had myelodysplastic syndrome/acute myeloid leukemia, gastrointestinal disorders likely to interfere with absorption of study treatment, and/or had received previous treatment with a PARP inhibitor, mitoxantrone, cyclophosphamide, or platinum-based chemotherapy.

Treatment

Patients in cohorts A1 and A2 received a combination of intravenous nivolumab 480 mg every 4 weeks and oral rucaparib 600 mg two times per day. Nivolumab dosing was limited to at most 2 years from the date of first nivolumab dose in the absence of disease progression; rucaparib was administered continuously until disease progression. Treatment with either nivolumab or rucaparib could also be prematurely discontinued due to unacceptable toxicity, withdrawal of patient consent, or the end of the trial, whichever occurred first.

Endpoints and assessments

As previously described,[26] the co-primary endpoints for CheckMate 9KD were ORR (defined as the proportion of patients achieving a confirmed complete or partial response as assessed by the investigator using PCWG3 criteria) and PSA response rate (PSA_{50}-RR; defined as the proportion of patients with a ≥50% decrease in PSA from baseline). Secondary endpoints included time to and duration of objective response, time to PSA progression, investigator-assessed radiographic progression-free survival (rPFS), OS, and safety. Time to and duration of objective response, time to PSA progression, and rPFS were evaluated using PCWG3 criteria. For cohorts A1 and A2, all efficacy endpoints were assessed prospectively in the all-treated population (all patients receiving at least one dose of nivolumab and/or rucaparib) and in subgroups based on HRD status (positive versus negative/not evaluable). As previously described,[26] HRD status was determined before cohort assignment using the validated next-generation sequencing-based FoundationOne CDx and FoundationACT tests (Foundation Medicine Inc, Cambridge, MA, USA) for tissue-based and plasma-based assessment, respectively. HRD positivity from tissue was defined as the presence of a gene alteration that included protein truncating mutations, protein truncating rearrangements, splice site mutations, homozygous deletions, or deleterious missense mutations in *ATM*, *BARD1*, *BRCA1*, *BRCA2*, *BRIP1*, *CDK12*, *CHEK2*, *FANCA*, *NBN*, *PALB2*, *RAD51*, *RAD51B*, *RAD51C*, *RAD51D*, or *RAD54L*. HRD positivity from plasma was defined as the presence of a gene alteration that included protein truncating mutations, protein truncating rearrangements, splice site mutations, or deleterious missense mutations in *ATM*, *BRCA1*, *BRCA2*, *CDK12*, *CHEK2*, or *PALB2*. All testing for HRD was performed within Foundation Medicine Inc's College of American Pathologists-accredited, Clinical Laboratory Improvement Amendments-certified laboratory. A patient was considered HRD-positive if one of the two assays described (tissue based or plasma based) detected an alteration as defined above. Objective responses and related endpoints were determined only in patients with measurable disease at baseline; PSA responses and related endpoints were determined only in patients with a baseline and at least one postbaseline PSA assessment (PSA-evaluable patients).

Post hoc exploratory endpoints included the time to and duration of PSA response, and associations between efficacy outcomes and specific HRD-related genetic alterations or tumor mutational burden (TMB). TMB was measured using the FoundationOne CDx assay (Foundation Medicine, Cambridge, MA, USA), counting all synonymous and nonsynonymous mutations present within 1.1 Mb of coding genome and filtering out potential germline variants. Analyses were conducted based on the median TMB for all treated patients with available TMB data across all cohorts in the CheckMate 9KD trial, which was 6.7 mutations per Mb.

Adverse events (AEs), graded per National Cancer Institute Common Terminology Criteria for Adverse Events V.4.03, were assessed continuously and are reported from first dose of nivolumab plus rucaparib up to 30 days after last dose of study drug. Treatment-related AEs (TRAEs) were defined as events considered by the investigator to be related to any study treatment (ie, nivolumab, rucaparib, or both); no data are available on assignment of an event to a specific treatment. For CheckMate 9KD, immune-mediated AEs (ie, events consistent with an immune-mediated mechanism or component for which noninflammatory etiologies were excluded, eg, infection or tumor progression) are reported from first dose up to 100 days after last dose of study drug.[26]

As outlined in the prior publication from this study,[26] assessment of tumors by CT or MRI and radionuclide bone scans were performed at screening, every 8 weeks (±7 days) after the first dose for the first 24 weeks, then every 12 weeks (±7 days) until disease progression or treatment discontinuation (whichever occurred later). Objective responses and progressive disease were confirmed by repeat scans. For cohorts A1 and A2, PSA was assessed locally at screening, on day 1 of cycles 1–4, then on day 1 of every subsequent even-numbered cycle (cycle 6, cycle 8, cycle 10, etc). PSA responses were confirmed by a second consecutive assessment performed at least 3 weeks later.

Statistical analyses

Planned sample sizes for cohorts A1 and A2 were calculated using the precision approach for the dual primary endpoints with respective planned enrollment of 48 and 60 patients with baseline measurable disease evaluable for ORR and 80 and 100 patients evaluable for PSA_{50}-RR. Power calculations were assessed for each primary endpoint using the one-cohort binomial test, with the planned number of treated patients expected to provide adequate power for detecting an increase of 15% in ORR and an increase of 10% in PSA_{50}-RR compared with standard-of-care reference rates. Estimates of reference ORR and PSA response rates are described in online supplemental methods 1. Response rates and corresponding two-sided exact 95% CIs were calculated using Clopper–Pearson methodology.[27] The Kaplan-Meier method was used to estimate time to and duration of objective response, time to PSA progression, rPFS, and OS.[28] Median values and corresponding 95%

Table 1 Baseline demographic and clinical characteristics in cohorts A1 and A2

Characteristic	Cohort A1 (postchemotherapy) (N=88)	Cohort A2 (chemotherapy-naïve) (N=71)
Median age (range), years	66 (46–85)	73 (51–87)
Age categories, n (%)		
<70 years	53 (60.2)	29 (40.8)
≥70 years	35 (39.8)	42 (59.2)
Race, n (%)		
White	72 (81.8)	64 (90.1)
Black or African American	4 (4.5)	1 (1.4)
Asian	2 (2.3)	1 (1.4)
Other	10 (11.4)	5 (7.0)
Geographic region, n (%)		
Europe	33 (37.5)	22 (31.0)
Rest of the world*	38 (43.2)	28 (39.4)
USA	17 (19.3)	21 (29.6)
ECOG PS, n (%)		
0	39 (44.3)	30 (42.3)
1	48 (54.5)	41 (57.7)
Not reported	1 (1.1)	0
Gleason score, n (%)		
≤7	24 (27.3)	29 (40.8)
>7	60 (68.2)	39 (54.9)
Not reported	4 (4.5)	3 (4.2)
Median time since diagnosis (range), years	5.2 (1.1–25.1)	4.1 (0.4–19.6)
Bone lesions, n (%)		
0	7 (8.0)	9 (12.7)
1–4	17 (19.3)	13 (18.3)
>4	63 (71.6)	46 (64.8)
Not reported	1 (1.1)	3 (4.2)
Visceral metastases, n (%)		
Yes	30 (34.1)	17 (23.9)
No	56 (63.6)	48 (67.6)
Not reported	2 (2.3)	6 (8.5)
Measurable disease, n (%)	58 (65.9)	39 (54.9)
Average daily worst pain intensity, n (%)		
<4	66 (75.0)	57 (80.3)
≥4	19 (21.6)	13 (18.3)
Not reported	3 (3.4)	1 (1.4)
Median PSA (range), ng/mL	95.8 (0.1–4816.0)	37.8 (0.6–5807.0)
HRD status, n (%)		
Positive	45 (51.1)	34 (47.9)
Negative	40 (45.5)	36 (50.7)
Not evaluable†	3 (3.4)	1 (1.4)
Hemoglobin, n (%)		
<110 g/L	22 (25.0)	11 (15.5)
≥110 g/L	66 (75.0)	60 (84.5)
Alkaline phosphatase, n (%)		
<1.5 × ULN	66 (75.0)	57 (80.3)
≥1.5 × ULN	22 (25.0)	14 (19.7)
Prior cancer surgery, n (%)	42 (47.7)	30 (42.3)
Prior radiotherapy, n (%)	57 (64.8)	35 (49.3)

Continued

Table 1 Continued

Characteristic	Cohort A1 (postchemotherapy) (N=88)	Cohort A2 (chemotherapy-naïve) (N=71)
Prior taxane chemotherapy regimens in the castration-resistant setting, n (%)		
1	62 (70.5)	0
2	26 (29.5)	0
Prior novel hormonal therapy, n (%)	65 (73.9)	70 (98.6)§
Abiraterone only	19 (21.6)‡	43 (60.6)
Enzalutamide only	19 (21.6)	17 (23.9)§
Abiraterone and enzalutamide	27 (30.7)	10 (14.1)

*Represents Australia, Canada and South America.
†Represents patients with missing values for HRD using the assays described in the Methods section; reasons for missing values include, for example, missing or inadequate sample material or methodology/assay failures.
‡Notification of prior treatment with apalutamide in one patient recorded as receiving abiraterone alone was received after database lock; in total 18 patients (20.5%) in cohort A1 received prior abiraterone alone and one patient (1.1%) received prior treatment with both abiraterone and apalutamide.
§Notification of prior treatment with enzalutamide in one additional patient was received after database lock; in total 18 patients (25.4%) in cohort A2 received prior enzalutamide alone and all 71 (100.0%) received prior treatment with 1–2 novel hormonal therapies per protocol.
ECOG PS, Eastern Cooperative Oncology Group performance status; HRD, homologous recombination deficiency; PSA, prostate-specific antigen; ULN, upper limit of normal.

CIs for duration of objective response, rPFS, and OS were constructed based on a log-log transformed CI for the survivor function.[29]

RESULTS

Patients

Overall, 88 and 71 eligible patients with mCRPC received treatment with nivolumab plus rucaparib in cohorts A1 and A2, respectively. Baseline demographic and clinical characteristics are shown in table 1.

In cohorts A1 and A2, respectively, median age (range) was 66 (46–85) and 73 (51–87) years, 30 (34.1%) and 17 (23.9%) patients had visceral metastases, 58 (65.9%) and 39 (54.9%) had measurable disease at baseline, and 45 (51.1%) and 34 (47.9%) had HRD-positive tumors. Per the cohort-specific inclusion criteria, all 88 patients in cohort A1 had received one or two prior taxane-based chemotherapy regimens (docetaxel and/or cabazitaxel); 62 (70.5%) had received one prior regimen and 26 (29.5%) had received two prior regimens. Of the 26 patients receiving two prior taxane-based chemotherapy regimens, two had not received a prior novel hormonal therapy, 11 had also received one prior novel hormonal therapy, and 13 had also received two prior novel hormonal therapies. Patient disposition is shown in online supplemental table 1; at database lock (July 17, 2020, for cohort A1; March 12, 2021, for cohort A2), 83 (94.3%) patients in cohort A1 and 65 (91.5%) patients in cohort A2 had discontinued all study treatment, mostly because of disease progression (65 (73.9%) and 43 (60.6%) patients, respectively) or study drug toxicity (9 (10.2%) and 8 (11.3%) patients, respectively). One patient in cohort A1 (1.1%) and one in cohort A2 (1.4%) discontinued due to death.

Study drug exposure

Overall median duration of nivolumab plus rucaparib combination therapy (range) was 4.4 (0.3–17.9) months in cohort A1 and 5.8 (0.1–30.9) months in cohort A2. Treatment exposure data for the individual components are summarized in online supplemental table 2. Median duration of treatment (range) for nivolumab was 3.7 (0.0–17.8) months in cohort A1 and 4.6 (0.0–23.2) months in cohort A2, and for rucaparib was 4.0 (0.3–17.9) months in cohort A1 and 5.5 (0.0–30.9) months in cohort A2. The median number of administered nivolumab doses (range) was 4.5 (1–19) and 6.0 (1–25) in cohorts A1 and A2, respectively. Median duration of follow-up was 11.9 and 17.5 months, respectively.

Efficacy, cohort A1 (postchemotherapy)

Among 58 treated patients with baseline measurable disease in cohort A1, the confirmed ORR (95% CI) was 10.3% (3.9% to 21.2%), comprising six patients who achieved partial responses (table 2). Median time to objective response (range) was 1.9 (1.6–3.7) months and median duration of objective response (95% CI) was 6.5 (3.5 to not estimable) months. In 84 PSA-evaluable patients, the confirmed PSA_{50}-RR (95% CI) was 11.9% (5.9% to 20.8%; table 2). Median time to PSA response (range) was 1.0 (0.9–3.0) month and median duration of PSA response (95% CI) was 6.6 (5.6 to 9.5) months. Median time to PSA progression (95% CI) was 3.8 (2.8 to 6.5) months. In all 88 treated patients, median rPFS (95% CI) was 4.9 (3.7 to 5.7) months (figure 1A) and median OS (95% CI) was 13.9 (10.4 to 15.8) months (figure 1B).

The confirmed ORR (95% CI) among subpopulations of patients in cohort A1 with baseline measurable disease and HRD-positive (n=29) versus HRD-negative/

Table 2 Objective and PSA response outcomes in cohort A1 and A2

	Cohort A1 (postchemotherapy) (N=88)			Cohort A2 (chemotherapy-naïve) (N=71)		
	Overall	HRD-positive	HRD-negative/not evaluable	Overall	HRD-positive	HRD-negative/not evaluable
Objective response*						
Evaluable patients, n†	58	29	29	39	20	19
Confirmed ORR (95% CI), %	10.3 (3.9 to 21.2)	17.2 (5.8 to 35.8)	3.4 (0.1 to 17.8)	15.4 (5.9 to 30.5)	25.0 (8.7 to 49.1)	5.3 (0.1 to 26.0)
BOR, n (%)						
Complete response	0	0	0	0	0	0
Partial response	6 (10.3)	5 (17.2)	1 (3.4)	6 (15.4)	5 (25.0)	1 (5.3)
Stable disease	31 (53.4)	16 (55.2)	15 (51.7)	26 (66.7)	11 (55.0)	15 (78.9)
Progressive disease	18 (31.0)	5 (17.2)	13 (44.8)	5 (12.8)	3 (15.0)	2 (10.5)
Unable to determine	3 (5.2)	3 (10.3)	0	2 (5.1)	1 (5.0)	1 (5.3)
PSA response‡						
Evaluable patients, n§	84	44	40	66	31	35
Confirmed PSA_{50}-RR (95% CI), %	11.9 (5.9 to 20.8)	18.2 (8.2 to 32.7)	5.0 (0.6 to 16.9)	27.3 (17.0 to 39.6)	41.9 (24.5 to 60.9)	14.3 (4.8 to 30.3)
Confirmed or unconfirmed PSA_{50}-RR (95% CI), %	19.0 (11.3 to 29.1)	29.5 (16.8 to 45.2)	7.5 (1.6 to 20.4)	31.8 (20.9 to 44.4)	48.4 (30.2 to 66.9)	17.1 (6.6 to 33.6)

*Confirmed complete or partial response per PCWG3.
†Patients with measurable disease at baseline.
‡A decrease in PSA from baseline to the lowest postbaseline PSA result of ≥50%; a second consecutive value obtained at least 3 weeks later was required for confirmation of PSA responses.
§Patients with a baseline and at least one postbaseline PSA assessment.
BOR, best overall response; HRD, homologous recombination deficiency; ORR, objective response rate; PCWG3, Prostate Cancer Clinical Trials Working Group 3; PSA, prostate-specific antigen; PSA_{50}-RR, PSA response rate.

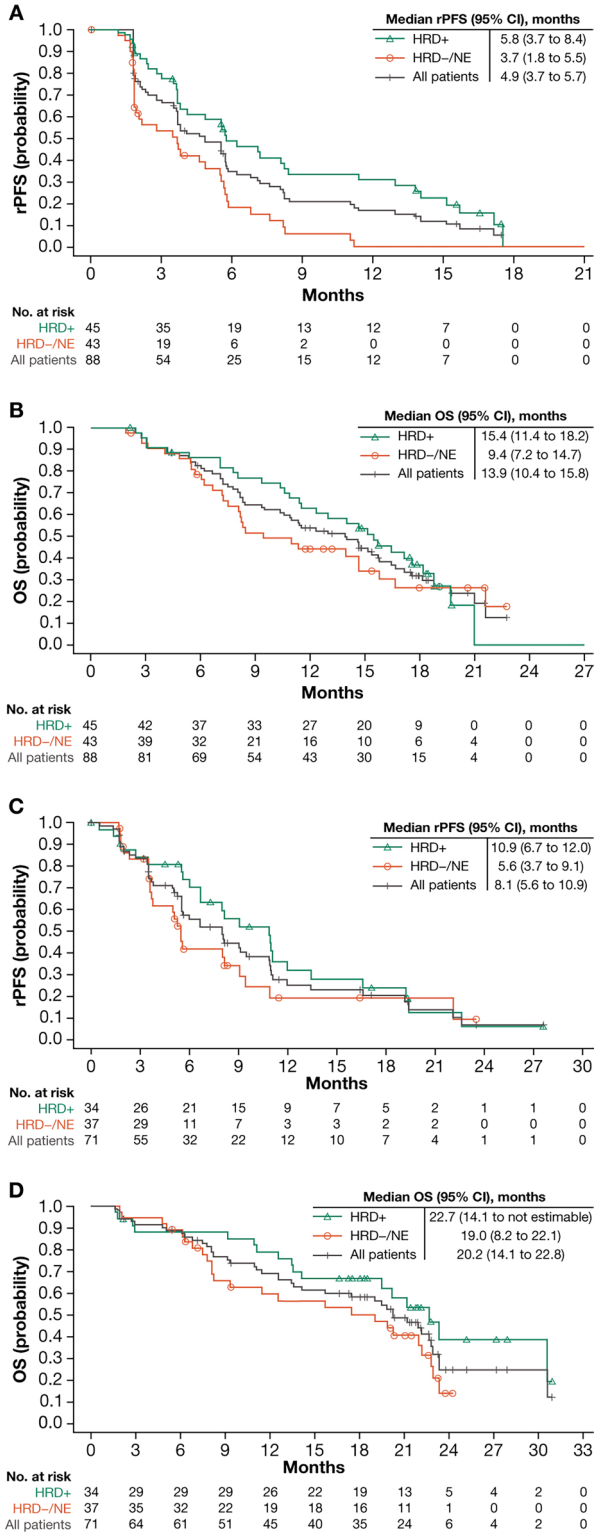

Figure 1 Kaplan-Meier plots of rPFS and OS in all treated patients and based on HRD status for cohort A1 (A, B) and cohort A2 (C, D). HRD, homologous recombination deficiency; NE, not evaluable; OS, overall survival; rPFS, radiographic progression-free survival.

not evaluable (n=29) tumors was 17.2% (5.8% to 35.8%) versus 3.4% (0.1% to 17.8%), respectively (table 2). The confirmed PSA_{50}-RR (95% CI) among subpopulations of PSA-evaluable patients in cohort A1 with HRD-positive (n=44) versus HRD-negative/not evaluable (n=40) tumors was 18.2% (8.2% to 32.7%) versus 5.0% (0.6% to 16.9%; table 2). Among all treated patients in cohort A1 with HRD-positive (n=45) versus HRD-negative/not evaluable (n=43) tumors, median rPFS (95% CI) was 5.8 (3.7 to 8.4) versus 3.7 (1.8 to 5.5) months, and median OS (95% CI) was 15.4 (11.4 to 18.2) versus 9.4 (7.2 to 14.7) months (figure 1A,B).

Efficacy, cohort A2 (chemotherapy-naïve)

Among 39 treated patients with baseline measurable disease in cohort A2, the confirmed ORR (95% CI) was 15.4% (5.9% to 30.5%), comprising six patients who achieved partial responses (table 2). Median time to objective response (range) was 2.0 (1.8–11.0) months and median duration of objective response (95% CI) was 7.1 (3.8 to not estimable) months. In 66 PSA-evaluable patients, the confirmed PSA_{50}-RR (95% CI) was 27.3% (17.0% to 39.6%; table 2). Median time to PSA response (range) was 1.8 (0.9–7.3) months and median duration of PSA response (95% CI) was 12.9 (4.1 to not estimable) months. Median time to PSA progression (95% CI) was 3.5 (2.8 to 6.2) months. In all 71 treated patients, median rPFS (95% CI) was 8.1 (5.6 to 10.9) months (figure 1C) and median OS (95% CI) was 20.2 (14.1 to 22.8) months (figure 1D).

The confirmed ORR (95% CI) among subpopulations of patients in cohort A2 with baseline measurable disease and HRD-positive (n=20) versus HRD-negative/not evaluable (n=19) tumors was 25.0% (8.7% to 49.1%) versus 5.3% (0.1% to 26.0%), respectively (table 2). The confirmed PSA_{50}-RR (95% CI) among subpopulations of PSA-evaluable patients in cohort A2 with HRD-positive (n=31) versus HRD-negative/not evaluable (n=35) tumors was 41.9% (24.5% to 60.9%) versus 14.3% (4.8% to 30.3%; table 2). Among all treated patients in cohort A2 with HRD-positive (n=34) versus HRD-negative/not evaluable (n=37) tumors, median rPFS (95% CI) was 10.9 (6.7 to 12.0) versus 5.6 (3.7 to 9.1) months, and median OS (95% CI) was 22.7 (14.1 to not estimable) versus 19.0 (8.2 to 22.1) months (figure 1C,D).

Biomarker analyses, cohorts A1 (postchemotherapy) and A2 (chemotherapy-naïve)

Data on specific HRD-related genetic mutations were available for 42 patients with HRD-positive tumors in cohort A1 and 33 patients with HRD-positive tumors in cohort A2. In both cohorts, the most frequent mutations were in the *BRCA1/2* (n=12 and n=15, respectively) or *ATM* (n=15 and n=9, respectively) genes, with the vast majority being frameshift or truncating variants (online supplemental figure 1).

Maximum changes in tumor size and PSA are shown based on HRD gene mutation(s) in figures 2 and 3, with related gene-specific outcomes summarized in online supplemental tables 3 and 4. The most noteworthy response outcomes were observed in patients carrying *BRCA1/2* mutations. In cohort A1, among nine patients

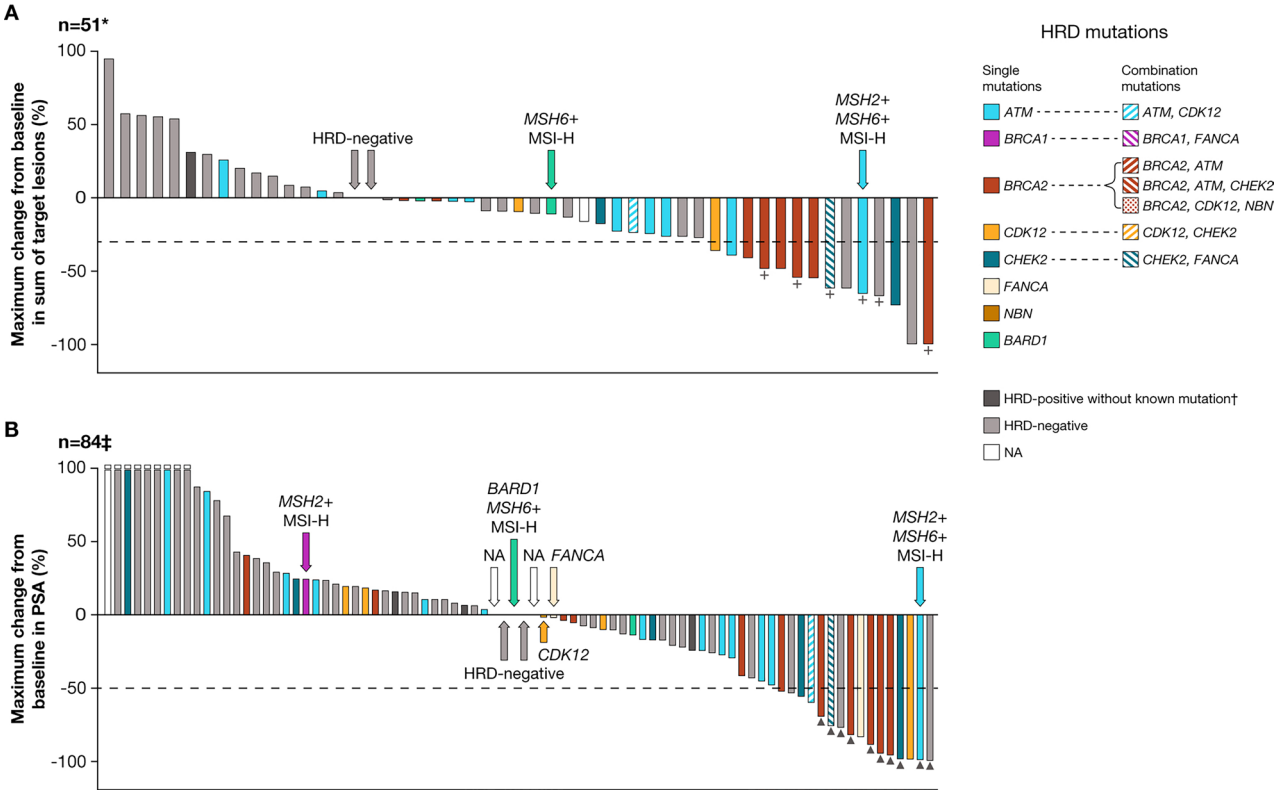

Figure 2 Waterfall plots of maximum change from baseline in tumor size (A) and PSA (B) based on HRD-related genetic mutations for cohort A1. *Patients with a measurable target lesion at baseline and at least one on-treatment tumor assessment; seven patients did not have available tumor change data. †Represents patients categorized as HRD-positive but with missing information on the specific genetic mutation(s). ‡Patients with baseline PSA and at least one postbaseline PSA assessment. Horizontal reference lines indicate a 30% reduction consistent with a PCWG3 response (A) or a 50% reduction consistent with a PSA response (B). Open squares indicate truncation of percent change at +100%. +Symbol represents a confirmed objective response; ▲ Symbol represents a confirmed PSA response. HRD, homologous recombination deficiency; MSI-H, microsatellite instability-high; NA, not available; PCWG3, Prostate Cancer Clinical Trials Working Group 3; PSA, prostate-specific antigen.

with baseline measurable disease and *BRCA1/2* mutations (all *BRCA2* alone), six (66.7%) had a ≥30% reduction in target lesions, with three (33.3%) achieving a confirmed objective response (figure 2A, table 3). Among 12 PSA-evaluable patients with *BRCA1/2* mutations (11 *BRCA2* alone, 1 *BRCA1* alone), 6 (50.0%) had a ≥50% reduction in PSA, with 5 (41.7%) achieving a confirmed PSA response (figure 2B, table 3).

In cohort A2, among nine patients with baseline measurable disease and *BRCA1/2* mutations (four *BRCA2* alone, three *BRCA2* with other HRD gene mutations, one *BRCA1* alone, and one *BRCA1* with other HRD gene mutations), three (33.3%) had a ≥30% reduction in target lesions and all three achieved a confirmed objective response (figure 3A, table 3). Among 13 PSA-evaluable patients with *BRCA1/2* mutations (9 *BRCA2* alone, 3 *BRCA2* with other HRD gene mutations, and 1 *BRCA1* with other HRD gene mutations), all 13 (100.0%) had a ≥50% reduction in PSA, with 11 (84.6%) achieving a confirmed PSA response (figure 3B, table 3). Median rPFS and OS for patients with *BRCA1/2* mutations are shown in table 3 and were relatively consistent with median observed for the overall HRD-positive subgroups (figure 1A–D). Figures 2 and 3 also show that a small number of patients had microsatellite instability-high disease and/or were carrying *MSH2* and/or *MSH6* structural rearrangements, although there were too few patients to assess any associations with changes in tumor size or PSA.

Eighty-two of 88 patients in cohort A1 and 60 of 71 in cohort A2 had available TMB data. As shown in online supplemental table 5, clinical activity was observed regardless of TMB status. However, there were no consistent trends in efficacy outcomes among subgroups of patients with TMB at or above versus below the median (6.7 mutations per Mb).

Safety, cohorts A1 (postchemotherapy) and A2 (chemotherapy-naïve)

Any-grade TRAEs occurred in 93.2% and 90.1% of all treated patients in cohorts A1 and A2, respectively (table 4). The most common any-grade treatment-related events were nausea (40.9%), fatigue (33.0%), anemia (26.1%), and decreased appetite (26.1%) in cohort A1, and nausea (40.8%), anemia (32.4%), fatigue (28.2%), and increased alanine aminotransferase (ALT; 28.2%) in cohort A2. Grade 3–4 TRAEs occurred in 54.5% and 50.7% of patients, respectively, with the most common events being anemia (20.5%) and neutropenia (10.2%)

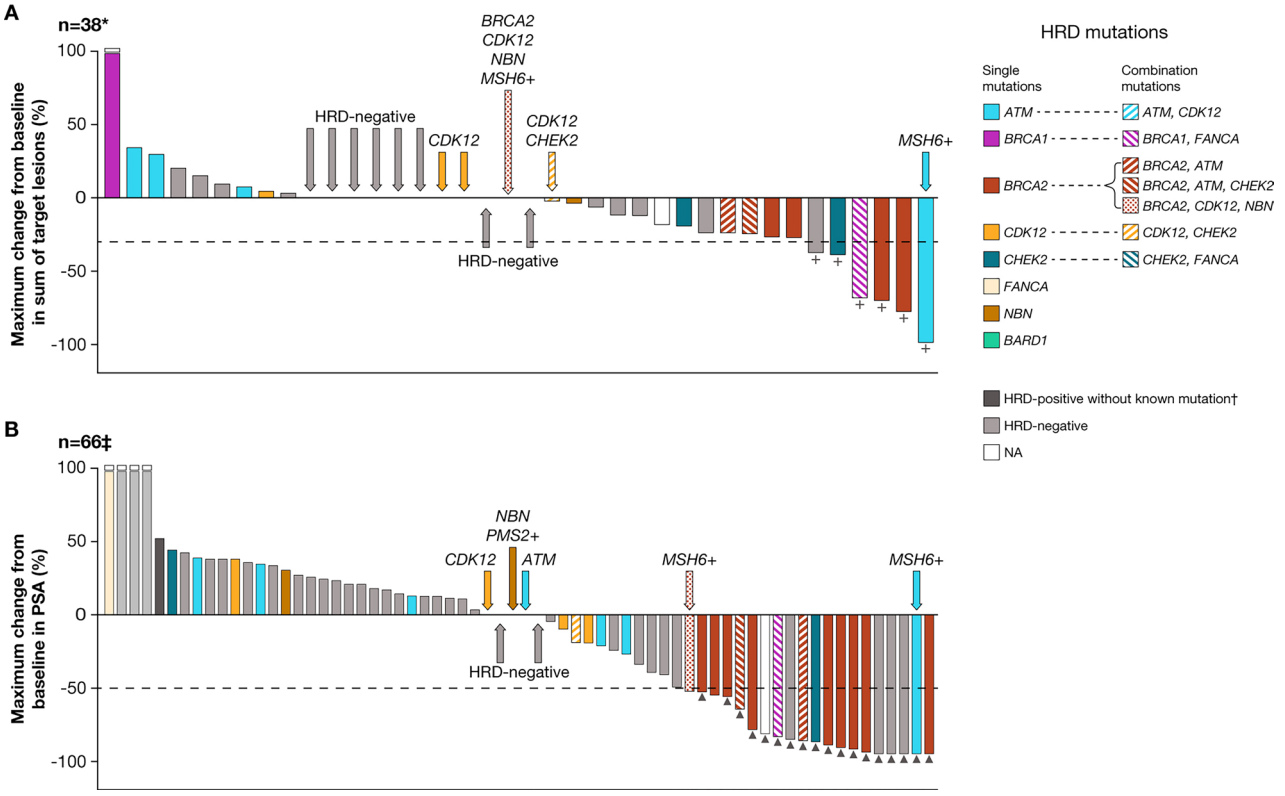

Figure 3 Waterfall plots of maximum change from baseline in tumor size (A) and PSA (B) based on HRD-related genetic mutations for cohort A2. *Patients with a measurable target lesion at baseline and at least one on-treatment tumor assessment; one patient did not have available tumor change data. †Represents patients categorized as HRD-positive but with missing information on the specific genetic mutation(s). ‡Patients with baseline PSA and at least one postbaseline PSA assessment. Horizontal reference lines indicate a 30% reduction consistent with a PCWG3 response (A) or a 50% reduction consistent with a PSA response (B). Open squares indicate truncation of percent change at +100%. +Symbol represents a confirmed objective response; ▲ Symbol represents a confirmed PSA response. HRD, homologous recombination deficiency; NA, not available; PCWG3, Prostate Cancer Clinical Trials Working Group 3; PSA, prostate-specific antigen.

in cohort A1 and anemia (14.1%) and increased ALT (12.7%) in cohort A2.

Any-grade treatment-related serious AEs were reported in 28.4% and 19.7% of patients in cohorts A1 and A2, with grade 3–4 treatment-related serious AEs reported in 27.3% and 18.3%, respectively (online supplemental table 6). The most common grade 3–4 treatment-related serious AEs were anemia in cohort A1 (6.8%), and increased ALT and aspartate aminotransferase in cohort A2 (2.8% each). Any-grade TRAEs led to discontinuation of one or both study drugs in 27.3% and 23.9% of patients in cohorts A1 and A2, respectively (online supplemental table 7). The most common grade 3–4 events leading to discontinuation were febrile neutropenia and neutropenia in cohort A1 (2.3% each) and anemia in cohort A2 (4.2%).

The most commonly reported individual any-grade immune-mediated AE in both cohorts was hypothyroidism (8.0% and 7.0% in cohorts A1 and A2, respectively; online supplemental table 8). Hepatic immune-mediated AEs comprised the most frequent grade 3–4 immune-mediated events, reported in 5.7% of patients in cohort A1 and 7.0% of patients in cohort A2.

In cohort A1, one on-study death was considered related to study treatment. Specifically, a patient with a preexisting meningioma had a stroke, for which a relationship to rucaparib could not be excluded by the investigator, after 28 days on rucaparib and two doses of nivolumab and died 2 months later due to postthrombolysis hematoma. There were no treatment-related deaths in cohort A2.

DISCUSSION

Based on the suboptimal efficacy of nivolumab monotherapy in unselected populations of patients with mCRPC, the phase 2 CheckMate 9KD trial was designed to investigate the hypothetical clinical benefits of combining nivolumab with other anticancer treatments that could potentially stimulate a more immune-responsive tumor microenvironment, namely rucaparib, docetaxel, or enzalutamide. Results for the cohort of patients treated with nivolumab plus docetaxel (cohort B) have been reported in a separate publication and showed encouraging clinical activity of this combination in men with chemotherapy-naïve mCRPC.[26] Here, we report results

Table 3 Efficacy outcomes in patients with *BRCA1/2* mutations in cohorts A1 and A2

	Cohort A1 (postchemotherapy) (N=12)	Cohort A2 (chemotherapy-naïve) (N=15)
Objective response*		
Evaluable patients, n†	9‡	9
Confirmed ORR (95% CI), %	33.3 (7.5 to 70.1)	33.3 (7.5 to 70.1)
BOR, n (%)		
Complete response	0	0
Partial response	3 (33.3)	3 (33.3)
Stable disease	4 (44.4)	5 (55.6)
Progressive disease	1 (11.1)	1 (11.1)
Unable to determine	1 (11.1)	0
PSA response§		
Evaluable patients, n¶	12	13
Confirmed PSA_{50}-RR (95% CI), %	41.7 (15.2 to 72.3)	84.6 (54.6 to 98.1)
Survival outcomes		
Evaluable patients**	12	15
Median rPFS (95% CI), months	5.6 (2.8 to 15.7)	10.9 (5.6 to 12.0)
Median OS (95% CI), months	15.2 (3.0 to not estimable)	20.2 (11.1 to not estimable)

*Confirmed complete or partial response per PCWG3.
†Patients with measurable disease at baseline and *BRCA1/2* mutations.
‡Includes one patient with measurable disease at baseline and a *BRCA2* mutation, but with no on-treatment tumor assessment; this patient is omitted from the associated waterfall plot (figure 2A).
§A decrease in PSA from baseline to the lowest postbaseline PSA result of ≥50%; a second consecutive value obtained at least 3 weeks later was required for confirmation of PSA responses.
¶Patients with a baseline and at least one postbaseline PSA assessment and *BRCA1/2* mutations.
**All treated patients with *BRCA1/2* mutations.
BOR, best overall response; ORR, objective response rate; OS, overall survival; PCWG3, Prostate Cancer Clinical Trials Working Group 3; PSA, prostate-specific antigen; PSA_{50}-RR, PSA response rate; rPFS, radiographic progression-free survival.

from cohorts A1 and A2 of CheckMate 9KD, which showed that the clinical antitumor activity of nivolumab plus rucaparib was limited in the overall (unselected) chemotherapy-naïve and postchemotherapy mCRPC cohorts, and that no new safety signals were observed with the combination regimen.

Although nivolumab plus rucaparib had minimal clinical activity in the unselected mCRPC populations, noteworthy efficacy differences were observed when patients were analyzed by HRD mutational status. Among patients with HRD-positive tumors, encouraging response rates and survival outcomes were observed, regardless of whether the patients had received prior chemotherapy for mCRPC. Moreover, despite small sample sizes, subgroups of patients harboring *BRCA1/2* mutations had further improved objective and PSA response rates, although survival outcomes in these subgroups were similar to those reported for the overall HRD-positive subpopulations. In both cohorts, most patients carrying *BRCA1/2* mutations had an alteration in the *BRCA2* gene; as such, any differences in the relative influence of *BRCA1* versus *BRCA2* mutations on response to nivolumab plus rucaparib could not be determined from this patient population. Of note, in a prior study of the combination of durvalumab and olaparib for mCRPC,[4] most responders to treatment carried *BRCA* mutations, and in a recent study of pembrolizumab plus olaparib,[30] patients with mCRPC carrying *BRCA* mutations showed higher objective and PSA response rates versus those not carrying these mutations, results that support the findings reported here. These observations might be somewhat expected as several studies have shown improved responses to PARP inhibitor monotherapy in patients with mCRPC and *BRCA1/2* mutations compared with patients carrying other DNA damage repair mutations and/or unselected populations,[17 19 31 32] and preliminary small-scale analyses have suggested that patients carrying DNA damage repair mutations (including in *BRCA1/2* or *ATM*) are more responsive to PD-1/PD-L1 checkpoint inhibitor therapy than those without these mutations.[10 15 16] Interestingly, in some of the prior studies of PARP inhibitor monotherapy, PFS and/or OS were improved among patients with *BRCA* mutations versus those with non-*BRCA* DNA damage repair mutations[31 32]—an outcome that was not seen in the CheckMate 9KD cohorts. It is unclear why the higher response rates in patients with *BRCA*-positive tumors versus the overall HRD-positive subpopulations observed in our study did not translate into observable survival advantages. In contrast to the patients in cohorts A1 and A2 with HRD-positive tumors, those with

Table 4 Treatment-related AEs in all treated patients in cohorts A1 and A2

	Cohort A1 (postchemotherapy) (N=88)		Cohort A2 (chemotherapy-naïve) (N=71)	
Treatment-related AEs, n (%)*	**Any grade**	**Grade 3–4**	**Any grade**	**Grade 3–4**
Any treatment-related AE	82 (93.2)	48 (54.5)	64 (90.1)	36 (50.7)
Nausea	36 (40.9)	4 (4.5)	29 (40.8)	0
Fatigue	29 (33.0)	5 (5.7)	20 (28.2)	2 (2.8)
Anemia	23 (26.1)	18 (20.5)	23 (32.4)	10 (14.1)
Decreased appetite	23 (26.1)	2 (2.3)	13 (18.3)	3 (4.2)
Diarrhea	21 (23.9)	3 (3.4)	14 (19.7)	3 (4.2)
Vomiting	20 (22.7)	2 (2.3)	13 (18.3)	1 (1.4)
Asthenia	19 (21.6)	3 (3.4)	7 (9.9)	1 (1.4)
Alanine aminotransferase increased	16 (18.2)	6 (6.8)	20 (28.2)	9 (12.7)
Neutropenia	14 (15.9)	9 (10.2)	3 (4.2)	3 (4.2)
Aspartate aminotransferase increased	13 (14.8)	2 (2.3)	18 (25.4)	5 (7.0)
Dysgeusia	10 (11.4)	0	9 (12.7)	0
Thrombocytopenia	9 (10.2)	4 (4.5)	6 (8.5)	2 (2.8)
Pruritus	9 (10.2)	0	11 (15.5)	1 (1.4)
Acute kidney injury	6 (6.8)	3 (3.4)	1 (1.4)	1 (1.4)
Rash	6 (6.8)	1 (1.1)	8 (11.3)	1 (1.4)
Blood alkaline phosphatase increased	5 (5.7)	3 (3.4)	3 (4.2)	0
Leukopenia	4 (4.5)	3 (3.4)	1 (1.4)	0
Blood creatinine increased	4 (4.5)	0	15 (21.1)	0
Hepatoxicity	4 (4.5)	2 (2.3)	1 (1.4)	1 (1.4)
Febrile neutropenia	3 (3.4)	3 (3.4)	0	0
Muscular weakness	2 (2.3)	2 (2.3)	2 (2.8)	0
Hepatitis	2 (2.3)	2 (2.3)	1 (1.4)	0
Lymphopenia	2 (2.3)	2 (2.3)	1 (1.4)	1 (1.4)
Gamma-glutamyl transferase increased	2 (2.3)	2 (2.3)	0	0
Hypophosphatemia	1 (1.1)	1 (1.1)	4 (5.6)	3 (4.2)
Neutrophil count decreased	0	0	3 (4.2)	2 (2.8)

*Includes individual any-grade treatment-related AEs reported between first dose of nivolumab plus rucaparib and 30 days after the last dose of study drug and occurring in >10% of all treated patients and/or grade 3–4 treatment-related AEs reported between first dose of nivolumab plus rucaparib and 30 days after the last dose of study drug and occurring in >2% of all treated patients in either cohort.
AE, adverse event.

HRD-negative tumors showed infrequent responses and appear to derive limited benefit from the nivolumab plus rucaparib combination.

As this trial did not include nivolumab and/or rucaparib monotherapy control arms, determining the contribution of each component to the observed outcomes is challenging. In the TRITON2 trial of rucaparib monotherapy for postchemotherapy mCRPC, an investigator-assessed ORR of 50.8%, a PSA_{50}-RR of 54.8%, and a median investigator-assessed rPFS of 8.5 months were reported among patients with *BRCA1/2* mutations,[19] which might suggest, considering the findings from cohort A1 in this study, that nivolumab contributes little additional benefit over rucaparib alone. However, cross-study comparisons should be treated cautiously due to the inherent influence of various factors (eg, study design and methodology and/or population characteristics) on the respective trial outcomes. For example, whereas patients in TRITON2 had received only one prior taxane regimen in the castration-resistant setting per the study inclusion criteria,[19] almost a third of the patients in cohort A1 had received two prior taxane regimens for mCRPC, a distinction that might have influenced the clinical efficacy reported for each study. Data from the ongoing TRITON3 trial (NCT02975934) might provide a benchmark against which to further hypothesize on the potential clinical benefits of dual PD-1/PD-L1 and PARP inhibition in chemotherapy-naïve mCRPC populations. Nevertheless, based on results from cohort A1 of CheckMate 9KD, along with the recent early discontinuation

for futility of the KEYLYNK-010 trial of pembrolizumab plus olaparib in postchemotherapy mCRPC,[33] further investigation of combination treatment with anti-PD-1/PD-L1 immune checkpoint inhibitors plus PARP inhibitors in unselected mCRPC populations appears to be unwarranted.

Although sample sizes were small, data from this trial showed clinical activity of nivolumab plus rucaparib in patients carrying non-*BRCA* HRD mutations. In the postchemotherapy setting (cohort A1), confirmed objective and/or PSA responses were observed in patients with mutations in *ATM* alone, *CHEK2* alone, and both *CHEK2* and *FANCA*. In the chemotherapy-naïve setting (cohort A2), confirmed responses were observed in patients with mutations in *ATM* or *CHEK2* alone. This observation aligns with data from other studies of PARP inhibitors for mCRPC. For example, the TALAPRO-1 trial showed objective and/or PSA responses to monotherapy with the PARP inhibitor talazoparib in a small number of patients with mCRPC carrying only *ATM* or *PALB2* mutations.[32] Likewise, the TRITON2 trial showed both objective and PSA responses to rucaparib monotherapy in patients with mCRPC and single *ATM, FANCA, BRIP1, PALB2,* and *RAD51B* mutations, although cohorts of patients carrying these mutations were very small.[18] Interestingly, in TRITON2, responders with *CHEK2* mutations also carried mutations in *ATM* or *BRCA2*, leading the authors to suggest that *CHEK2* alteration alone might not be sufficient to render tumor cells responsive to rucaparib monotherapy.[18] As with the overall HRD-positive and *BRCA*-positive populations, determining whether the addition of nivolumab incrementally improves responses rates over rucaparib alone in patients with non-*BRCA* HRD mutations is beyond the scope of the current study.

The role of TMB in antitumor responses to immune checkpoint inhibitors among patients with mCRPC remains uncertain, with some preliminary studies suggesting a positive relationship with 'high' TMB,[16] and others suggesting that 'high' TMB does not predict improved response.[34 35] Moreover, unlike in some other tumor types, there is no established threshold for 'high' TMB in patients with mCRPC and no standardized methodology for assessing TMB (eg, whole exome sequencing versus next-generation sequencing), further challenging the interpretation of results from these preliminary studies. Results from the current analyses did not demonstrate a clear association between 'high' or 'low' TMB and efficacy with combined nivolumab plus rucaparib. Additional prospective investigations would be required to determine the influence of TMB on response to immunotherapy and whether that influence is maintained with novel immunotherapy-based combination regimens.

The safety and tolerability profile of nivolumab plus rucaparib was as anticipated based on prior studies of the single agents in mCRPC or other tumors.[18 19 36 37] Moreover, the types of TRAEs observed and their relative incidence was similar to that recently reported for a study of pembrolizumab combined with olaparib in docetaxel-pretreated mCRPC.[38] Across both cohorts, there was only one treatment-related death. Furthermore, although this death was considered possibly related to rucaparib treatment by the study investigator, the patient had a preexisting condition (meningioma) that possibly contributed to the sequence of events leading to the fatal event.

In conclusion, the combination of nivolumab and rucaparib showed clinical efficacy in patients with HRD-positive chemotherapy-naïve or postchemotherapy mCRPC, particularly in those harboring *BRCA1/2* mutations. Safety of the combination was as expected, with no new signals identified. However, the modest activity observed as compared with historic single-agent therapy, the lack of study comparator arms, and the relatively short follow-up for these cohorts prevent adequate assessment of the clinical benefits of adding nivolumab to rucaparib.

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Ethics approval The CheckMate 9KD study protocol was approved by an institutional review board or independent ethics committee at each site before activation. The study was conducted in accordance with consensus ethical principles derived from international guidelines including the Declaration of Helsinki, Council for International Organizations of Medical Sciences, and Good Clinical Practice, as defined by the International Conference on Harmonisation. All patients provided written informed consent. Participants gave informed consent to participate in the study before taking part.

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ONLINE APPENDIX

Nivolumab plus rucaparib for metastatic castration-resistant prostate cancer: results from the phase 2 CheckMate 9KD trial

Karim Fizazi, *et al*.

This online appendix has been developed to provide readers with relevant supplemental information.

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Supplemental Methods 1 Estimates of reference response rates for sample size determinations

Estimates of reference PSA and objective response rates for cohorts A1 and A2 were based on the standard of care for the respective metastatic castration-resistant prostate cancer populations at the time of protocol preparation.

For patients enrolled into cohort A1 (ie, those with 1–2 prior taxane-based regimens), standard of care would have been second-line cabazitaxel for those with one prior taxane-based regimen, and best supportive care for those with two prior taxane-based regimens. PSA and objective response rate estimates for second-line cabazitaxel were 30% and 14%, respectively. According to studies conducted in the postchemotherapy setting, patients receiving placebo (assumed equivalent to best supportive care) had PSA and objective response rates of 2%–6% and 3%–4%, respectively (Scher HI, et al. *N Engl J Med* 2012;367:1187–97; de Bono JS, et al. *N Engl J Med* 2011;364:1995–2005). On this basis, reference PSA and objective response rates for cohort A1 were 20% and 10%, respectively.

For patients enrolled into cohort A2 (ie, chemotherapy-naïve and having failed prior abiraterone, enzalutamide, and/or apalutamide), standard of care would have been docetaxel chemotherapy. Estimates of PSA and objective response rates for docetaxel were extrapolated from the FIRSTANA clinical trial of docetaxel versus cabazitaxel as first-line therapy for mCRPC (Oudard S, et al. J Clin Oncol 2017;35:3189–97). However, considering that (1) the administration of docetaxel after one or more novel hormonal therapies might have less activity than in the pivotal trials (Mezynski J, et al. Ann Oncol 2012;23:2943–47), (2) only ~3% of participants in the FIRSTANA trial had received prior abiraterone or enzalutamide, and (3) all patients in cohort A2 had received prior abiraterone, enzalutamide, and/or apalutamide, the estimates based on the FIRSTANA trial were considered too optimistic. As such, the estimate of reference PSA response rate was modified based on data from the COU-AA-302 post hoc analysis, in which post-abiraterone docetaxel treatment led to a PSA response rate of 27% (de Bono JS, et al. *Eur Urol* 2017;71:656–64). A reference PSA response rate of 47%, which is between those obtained in the FIRSTANA trial (68%) and COU-AA-302 post hoc analysis (27%), was chosen. Since the COU-AA-302 post hoc analysis did not report on objective responses, a reference objective response rate of 21% was chosen, taking into account the response rates from the FIRSTANA trial (31%) and from a retrospective evaluation of the activity of docetaxel in patients previously treated with abiraterone (11%; Mezynski J, et al. *Ann Oncol* 2012;23:2943–47).

Supplemental Table 1 Patient disposition in cohorts A1 and A2

	Cohort A1 (postchemotherapy) (N=88)	Cohort A2 (chemotherapy-naïve) (N=71)
On study treatment, n (%)	4 (4.5)	4 (5.6)
Completing study treatment, n (%)	1 (1.1)*	2 (2.8)†
Not completing study treatment, n (%)	83 (94.3)	65 (91.5)
Reasons for treatment discontinuation, n (%)		
Disease progression	65 (73.9)	43 (60.6)
Study drug toxicity	9 (10.2)	8 (11.3)
Adverse event unrelated to study drug	4 (4.5)	4 (5.6)
Patient request to discontinue study drug	3 (3.4)	3 (4.2)
Death	1 (1.1)	1 (1.4)
Patient withdrew consent	1 (1.1)	0
Poor/non-compliance	0	1 (1.4)
Other	0	5 (7.0)

*Case represents a site data entry error; notification was received after database lock that the patient discontinued treatment due to disease progression.
†One case represents a site data entry error; notification was received after database lock that the patient discontinued treatment due to disease progression. The other case represents a protocol misinterpretation where site investigators stopped treatment of both nivolumab and rucaparib after 2 years (the protocol mandated that only nivolumab treatment should be stopped after a maximum of 2 years and rucaparib treatment could continue beyond this point).

Supplemental Table 2 Treatment exposure in cohorts A1 and A2

	Cohort A1 (postchemotherapy) (N=88)		Cohort A2 (chemotherapy-naïve) (N=71)	
	Nivolumab	**Rucaparib**	**Nivolumab**	**Rucaparib**
Median duration of therapy (range), months	3.7 (0.0–17.8)	4.0 (0.3–17.9)	4.6 (0.0–23.2)	5.5 (0.0–30.9)
Relative dose intensity, n (%)				
≥110%	0	2 (2.3)	0	0
90% to <110%	68 (77.3)	46 (52.3)	52 (73.2)	37 (52.1)
70% to <90%	20 (22.7)	24 (27.3)	17 (23.9)	19 (26.8)
50% to <70%	0	6 (6.8)	1 (1.4)	13 (18.3)
<50%	0	10 (11.4)	1 (1.4)	2 (2.8)
Median no. of doses (range)	4.5 (1–19)	NA	6.0 (1–25)	NA
Patients with dose delays, n (%)	40 (45.5)	7 (8.0)	34 (47.9)	5 (7.0)
Dose delays per patient, n (%)				
0	48 (54.5)	81 (92.0)	37 (52.1)	66 (93.0)
1	29 (33.0)	4 (4.5)	21 (29.6)	3 (4.2)
2	8 (9.1)	0	7 (9.9)	0
3	2 (2.3)	1 (1.1)	5 (7.0)	0
≥4	1 (1.1)	2 (2.3)	1 (1.4)	2 (2.8)
Total no. of dose delays	55	24	55	13
Length of dose delays, n (%)*				
≤7 days	25 (45.5)	3 (12.5)	16 (29.1)	1 (7.7)
8 to ≤14 days	15 (27.3)	8 (33.3)	18 (32.7)	3 (23.1)
15 to ≤42 days	13 (23.6)	9 (37.5)	17 (30.9)	8 (61.5)
>42 days	2 (3.6)	1 (4.2)	4 (7.3)	1 (7.7)

*Displayed as a proportion of the total number of dose delays per study treatment.
NA, not applicable.

Supplemental Table 3 Number of patients with target lesion and PSA changes by HRD gene mutation(s) in cohort A1

	Target lesion change*				PSA change†			
Mutated gene(s)	**n**	**Any reduction**	**≥30% reduction**	**Confirmed objective response‡**	**n**	**Any reduction**	**≥50% reduction**	**Confirmed PSA response§**
ATM alone	9	7	2	1	13	7	1	1
BRCA2 alone	8	8	6	3	11	9	6	5
CDK12 alone	2	2	1	0	5	3	1	0
CHEK2 alone	2	2	1	0	5	3	2	1
BARD1 alone	2	2	0	0	2	1	0	0
ATM; CDK12	1	1	0	0	1	1	1	0
CHEK2; FANCA	1	1	1	1	2	1	1	1
FANCA alone	0	–	–	–	2	2	1	0
BRCA1 alone	0	–	–	–	1	0	0	0

*In patients with a measurable target lesion at baseline and at least one on-treatment tumor assessment.
†In patients with a baseline and at least one postbaseline PSA assessment.
‡Confirmed complete or partial response per PCWG3.
§A decrease in PSA from baseline to the lowest postbaseline PSA result of ≥50%; a second consecutive value obtained at least 3 weeks later was required for confirmation of PSA responses.
HRD, homologous recombination deficiency; PCWG3, Prostate Cancer Clinical Trials Working Group 3; PSA, prostate-specific antigen.

Supplemental Table 4 Number of patients with target lesion and PSA changes by HRD gene mutation(s) in cohort A2

	Target lesion change*				PSA change†			
Mutated gene(s)	**n**	**Any reduction**	**≥30% reduction**	**Confirmed objective response‡**	**n**	**Any reduction**	**≥50% reduction**	**Confirmed PSA response§**
BRCA2 alone	4	4	2	2	9	9	9	8
ATM alone	4	1	1	1	7	4	1	1
CDK12 alone	3	1	0	0	4	2	0	0
CHEK2 alone	2	2	1	1	2	1	1	1
NBN alone	1	1	0	0	2	0	0	0
BRCA1 alone	1	0	0	0	0	–	–	–
FANCA alone	0	–	–	–	1	0	0	0
BRCA2; ATM	1	1	0	0	1	1	1	1
BRCA1; FANCA	1	1	1	1	1	1	1	1
CDK12; CHEK2	1	1	0	0	1	1	0	0
BRCA2; ATM; CHEK2	1	1	0	0	1	1	1	1
BRCA2; CDK12; NBN	1	1	0	0	1	1	1	0

*In patients with a measurable target lesion at baseline and at least one on-treatment tumor assessment.
†In patients with a baseline and at least one postbaseline PSA assessment.
‡Confirmed complete or partial response per PCWG3.
§A decrease in PSA from baseline to the lowest postbaseline PSA result of ≥50%; a second consecutive value obtained at least 3 weeks later was required for confirmation of PSA responses.
HRD, homologous recombination deficiency; PCWG3, Prostate Cancer Clinical Trials Working Group 3; PSA, prostate-specific antigen.

Supplemental Table 5 Efficacy outcomes based on TMB status (< median vs ≥ median*) in cohorts A1 and A2

	Cohort A1 (postchemotherapy)		Cohort A2 (chemotherapy-naïve)	
	< Median	**≥ Median**	**< Median**	**≥ Median**
Objective response†				
Evaluable patients, n‡	25	31	17	16
Confirmed ORR (95% CI), %	8.0 (1.0 to 26.0)	12.9 (3.6 to 29.8)	29.4 (10.3 to 56.0)	6.3 (0.2 to 30.2)
PSA response§				
Evaluable patients, n¶	38	40	28	28
Confirmed PSA_{50}-RR (95% CI), %	7.9 (1.7 to 21.4)	17.5 (7.3 to 32.8)	25.0 (10.7 to 44.9)	32.1 (15.9 to 52.4)
Survival outcomes				
Evaluable patients, n**	40	42	28	32
Median rPFS (95% CI), months	3.7 (2.1 to 5.7)	5.6 (3.5 to 6.8)	8.2 (5.6 to 11.0)	8.1 (3.8 to 11.1)
Median OS (95% CI), months	15.7 (10.6 to 21.6)	11.0 (7.8 to 15.2)	22.9 (15.7 to NE)	12.6 (8.2 to 20.2)

*Median TMB (6.7 mutations per Mb) was based on all treated patients with available TMB data across all cohorts in the CheckMate 9KD trial.
†Confirmed complete or partial response per PCWG3.
‡Patients with measurable disease at baseline and available TMB data.
§A decrease in PSA from baseline to the lowest postbaseline PSA result of ≥50%; a second consecutive value obtained at least 3 weeks later was required for confirmation of PSA responses.
¶Patients with a baseline and at least one postbaseline PSA assessment and available TMB data.
**All treated patients with available TMB data.
NE, not estimable; ORR, objective response rate; OS, overall survival; PCWG3, Prostate Cancer Clinical Trials Working Group 3; PSA, prostate-specific antigen; PSA_{50}-RR, PSA response rate; rPFS, radiographic progression-free survival; TMB, tumor mutational burden.

Supplemental Table 6 Summary of treatment-related serious AEs* in cohorts A1 and A2

	Cohort A1 (postchemotherapy) (N=88)		Cohort A2 (chemotherapy-naïve) (N=71)	
	Any grade	**Grade 3–4**	**Any grade**	**Grade 3–4**
Any treatment-related serious AE, n (%)	25 (28.4)	24 (27.3)	14 (19.7)	13 (18.3)
Anemia	6 (6.8)	6 (6.8)	1 (1.4)	1 (1.4)
Neutropenia	4 (4.5)	4 (4.5)	0	0
Acute kidney injury	4 (4.5)	3 (3.4)	1 (1.4)	1 (1.4)
Febrile neutropenia	3 (3.4)	3 (3.4)	0	0
Diarrhea	2 (2.3)	2 (2.3)	0	0
Fatigue	2 (2.3)	2 (2.3)	0	0
Hepatitis	2 (2.3)	2 (2.3)	0	0
Alanine aminotransferase increased	0	0	2 (2.8)	2 (2.8)
Aspartate aminotransferase increased	0	0	2 (2.8)	2 (2.8)
Autoimmune nephritis	0	0	2 (2.8)	1 (1.4)

*Includes individual any-grade treatment-related serious AEs reported between first dose of nivolumab plus rucaparib and 30 days after the last dose of study drug and occurring in >2% of all treated patients in either cohort.
AE, adverse event.

Supplemental Table 7 Summary of treatment-related AEs leading to discontinuation* in cohorts A1 and A2

	Cohort A1 (postchemotherapy) (N=88)		Cohort A2 (chemotherapy-naïve) (N=71)	
	Any grade	**Grade 3–4**	**Any grade**	**Grade 3–4**
Any treatment-related AE leading to discontinuation, n (%)	24 (27.3)	19 (21.6)	17 (23.9)	11 (15.5)
Febrile neutropenia	2 (2.3)	2 (2.3)	0	0
Neutropenia	2 (2.3)	2 (2.3)	1 (1.4)	1 (1.4)
Diarrhea	2 (2.3)	1 (1.1)	1 (1.4)	0
Hepatotoxicity	2 (2.3)	1 (1.1)	0	0
Decreased appetite	2 (2.3)	0	0	0
Nausea	2 (2.3)	0	0	0
Anemia	1 (1.1)	1 (1.1)	3 (4.2)	3 (4.2)
Alanine aminotransferase increased	1 (1.1)	1 (1.1)	3 (4.2)	2 (2.8)
Aspartate aminotransferase increased	0	0	2 (2.8)	2 (2.8)

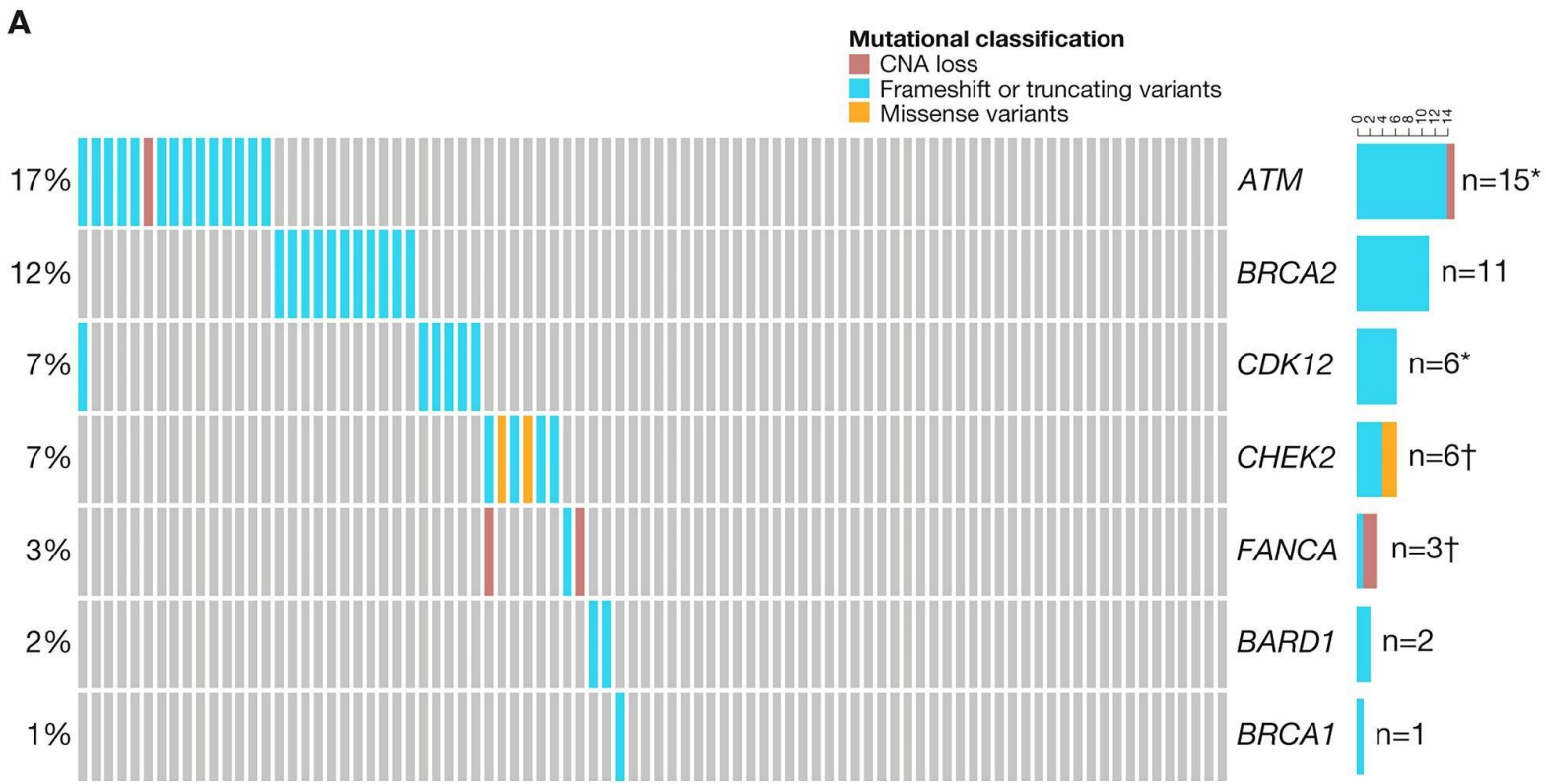
*Represents a treatment-related AE that led to permanent discontinuation of nivolumab and/or rucaparib; includes individual any-grade treatment-related AEs reported between first dose of nivolumab plus rucaparib and 30 days after the last dose of study drug that led to discontinuation and occurred in >2% of all treated patients in either cohort.
AE, adverse event.

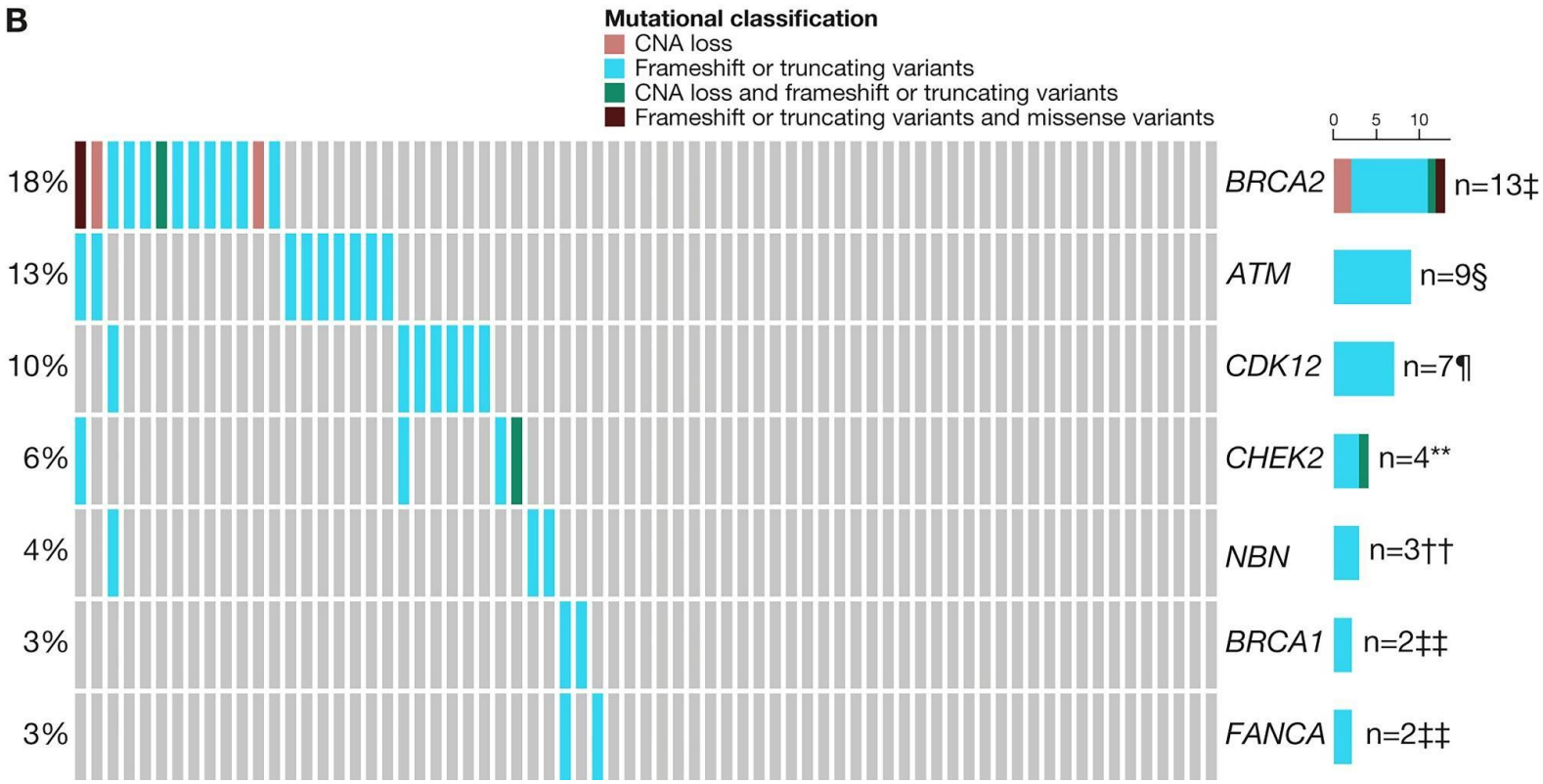
Supplemental Table 8 Summary of immune-mediated AEs* in cohorts A1 and A2

n (%)	Cohort A1 (postchemotherapy) (N=88)		Cohort A2 (chemotherapy-naïve) (N=71)	
	Any grade	Grade 3–4	Any grade	Grade 3–4
Endocrine				
Adrenal insufficiency	2 (2.3)	1 (1.1)	0	0
Hypothyroidism	7 (8.0)	0	5 (7.0)	1 (1.4)
Hyperthyroidism	2 (2.3)	0	1 (1.4)	0
Autoimmune thyroiditis	0	0	1 (1.4)	0
Diabetes mellitus	0	0	1 (1.4)	0
Gastrointestinal				
Diarrhea	3 (3.4)	1 (1.1)	4 (5.6)	2 (2.8)
Colitis/colitis ulcerative	1 (1.1)	1 (1.1)	2 (2.8)	0
Immune-mediated enterocolitis	1 (1.1)	1 (1.1)	0	0
Hepatic				
Hepatotoxicity	4 (4.5)	2 (2.3)	1 (1.4)	1 (1.4)
Hepatitis	2 (2.3)	2 (2.3)	1 (1.4)	0
ALT increased	1 (1.1)	1 (1.1)	3 (4.2)	3 (4.2)
Transaminases increased	1 (1.1)	0	1 (1.4)	0
AST increased	0	0	3 (4.2)	1 (1.4)
Autoimmune hepatitis	0	0	2 (2.8)	1 (1.4)
Drug-induced liver injury	0	0	1 (1.4)	1 (1.4)
Hyperbilirubinemia	0	0	1 (1.4)	1 (1.4)
Hypersensitivity				
Hypersensitivity	0	0	1 (1.4)	1 (1.4)
Pulmonary				
Pneumonitis	1 (1.1)	0	2 (2.8)	0
Renal				
Renal failure	1 (1.1)	1 (1.1)	0	0
Tubulointerstitial nephritis	1 (1.1)	0	0	0
Autoimmune nephritis	0	0	2 (2.8)	1 (1.4)
Immune-mediated nephritis	0	0	1 (1.4)	1 (1.4)
Skin				
Rash	5 (5.7)	2 (2.3)	4 (5.6)	1 (1.4)
Rash pustular	0	0	1 (1.4)	0

*Includes immune-mediated AEs reported between first dose of nivolumab plus rucaparib and 100 days after the last dose of study drug and occurring in >1% of all treated patients. Endocrine events listed represent all reported immune-mediated endocrine AEs; non-endocrine events listed are those resulting in initiation of immune-modulating medication.
AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Supplemental Figure 1 Oncoprints for HRD gene mutations in all treated patients in cohorts A1 (**A**; N=88) and A2 (**B**; N=71)





*Includes one patient with mutations in *ATM* and *CDK12*.
†Includes one patient with mutations in *CHEK2* and *FANCA*.
‡Includes one patient with mutations in *BRCA2*, *ATM*, and *CHEK2*; one with mutations in *BRCA2* and *ATM*; and one with mutations in *BRCA2*, *CDK12*, and *NBN*.
§Includes one patient with mutations in *BRCA2*, *ATM*, and *CHEK2*, and one patient with mutations in *BRCA2* and *ATM*.
¶Includes one patient with mutations in *BRCA2*, *CDK12*, and *NBN* and one patient with mutations in *CDK12* and *CHEK2*.
**Includes one patient with mutations in *BRCA2*, *ATM*, and *CHEK2* and one patient with mutations in *CDK12* and *CHEK2*.
††Includes one patient with mutations in *BRCA2*, *CDK12*, and *NBN*.
‡‡Includes one patient with mutations in *BRCA1* and *FANCA*.
CNA, copy number alteration.