Supplemental Online Content

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This supplemental material has been provided by the authors to give readers additional information about their work.

eAppendix. Supplementary Data

Definitions of Select Terms and Endpoints

- **Dose-limiting toxicities (DLTs)** were defined as an adverse event (AE) occurring within the first treatment cycle (28 days) and assessed as related to one or both study drugs, including any grade 3 or higher nonhematological event (excluding nausea, vomiting, or diarrhea lasting <72 hours; fatigue lasting <5 days; hypertension controlled with therapy; increase in bilirubin indicative of Gilbert syndrome; grade 3 serum lipase or amylase for <7 days and without pancreatitis; grade 3 endocrinopathies controlled with hormonal therapy; and grade 3 or higher laboratory abnormalities without a clinical correlate); hematological events including febrile neutropenia, grade 4 neutropenia, neutropenic infection, grade 3 thrombocytopenia with bleeding, grade 4 thrombocytopenia, and grade 4 anemia; inability to take ≥75% of the planned dose of talazoparib; any AE resulting in talazoparib dose reduction; and any grade 3 nonhematological toxicity that delayed either study drug for >2 weeks

In patients with solid tumors (all cohorts except E1 and E2):

- **Objective response (OR)** was defined as a complete response (CR) or partial response (PR) per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) by investigator assessment from the first dose of study treatment until disease progression or death due to any cause. Both CR and PR were required to be confirmed by repeat assessments performed no less than 4 weeks after the criteria for response were first met
- **Objective response rate (ORR)** was defined as the proportion of patients with a confirmed CR or PR per investigator assessment according to RECIST 1.1. Confirmed responses were those that persisted on repeat tumor assessments for ≥4 weeks after initial documentation or response. Otherwise, the patient was counted as a nonresponder in the assessment of ORR. Additionally, patients with inadequate data for tumor assessment (eg, no baseline assessment or no follow-up assessments) were considered nonresponders in the assessment of ORR

- **Time to response (TTR)** was defined for patients with confirmed OR (CR or PR) as the time from the first dose of study treatment to the first documentation of objective tumor response
- **Duration of response (DOR)** was defined for patients with confirmed OR (CR or PR) as the time from the first documentation of objective tumor response to the first documentation of objective tumor progression or to death due to any cause, whichever occurred first
- **Progression-free survival (PFS)** was defined as the time from the first dose of study treatment to the date of disease progression per RECIST 1.1 or death due to any cause, whichever occurred first
- **Overall survival (OS)** was defined as the time from the first dose of study treatment to the date of death

In patients with metastatic castration-resistant prostate cancer (mCRPC; cohorts E1 and E2):

- **OR** was defined as a best overall soft tissue response of CR or PR per RECIST 1.1 by investigator assessment from the first dose of study treatment until disease progression or death due to any cause. Soft tissue responses were required to be confirmed by a follow-up radiographic assessment performed ≥4 weeks later with repeated computed tomography (CT) or magnetic resonance imaging (MRI) with no evidence of confirmed bone disease progression per Prostate Cancer Working Group 3 (PCWG3) criteria by investigator assessment. The radiographic assessment of soft tissue disease was performed using RECIST 1.1, and bone disease was evaluated per PCWG3
- **TTR** was defined as the time from the first dose of study treatment to the first objective evidence of soft tissue response with no evidence of confirmed bone disease progression on a bone scan per PCWG3. Soft tissue response was defined as a CR or PR as assessed by the investigator using RECIST 1.1. The response was required to be confirmed ≥4 weeks later with repeated CT/MRI
- **DOR** was defined for patients with confirmed OR (CR or PR) as the time from the first objective evidence of soft tissue response (confirmed subsequently) as assessed by the investigator using RECIST 1.1 and no evidence of confirmed bone disease progression by PCWG3 to the first subsequent objective evidence of radiographic progression or death due to any cause, whichever occurred first. Radiographic progression was defined as soft tissue progression as assessed by the investigator using RECIST 1.1 or bone disease progression as assessed by the investigator using PCWG3

- **PFS** was defined as the time from the first dose of study treatment to documentation of radiographic progression in soft tissue as assessed by the investigator using RECIST 1.1, in bone as assessed by the investigator using PCWG3, or death, whichever occurred first
- **Prostate-specific antigen (PSA) response** was defined as a confirmed PSA level decline ≥50% compared with baseline. PSA response will be calculated as a decrease from baseline PSA (ng/mL) to the maximal PSA response with a threshold of ≥50%. A PSA response was required to be confirmed by a second consecutive value ≥3 weeks later
- **Time to PSA progression** was defined as the time from the first dose to the date that a ≥25% increase in PSA level with an absolute increase of ≥2 µg/L (2 ng/mL) above the nadir (or baseline for patients with no PSA decline) was documented, confirmed by a second consecutive PSA value obtained ≥3 weeks (21 days) later
- **OS** was defined as the time from the first dose of study treatment to the date of death

In patients with ovarian cancer (OC; cohorts C1 and C2):

- **Cancer antigen 125 (CA-125)** response was defined as a ≥50% reduction in CA-125 level from baseline. The response was required to be confirmed and maintained for ≥28 days

Supplementary Methods

Statistical analyses

In the dose-finding phase, patients were to be treated with 1 of up to 3 different doses of talazoparib (0.5 mg, 0.75 mg, or 1 mg once daily) administered orally in combination with a fixed dose of avelumab 800 mg IV Q2W. The starting regimen was talazoparib 1 mg once daily plus avelumab 800 mg Q2W. Phase 1b dose finding was deemed complete when 12 DLT-evaluable patients had been treated at the highest dose associated with a DLT rate <0.33 or if the combination was deemed too toxic.

For the phase 2 cohorts, with 20 patients per cohort, the OR rate (ORR) could be estimated with a maximum standard error of 0.112. With 40 patients per cohort, the ORR could be estimated with a maximum standard error of 0.079. Sample sizes were determined empirically and driven also by strategic priorities. The study was initiated to be efficacy signal finding and to support stepwise decision making for the clinical development for the talazoparib plus avelumab combination. If no efficacy signal was identified in that respective cohort, we considered this as justification to conduct no further investigation and expansion of that particular indication.

Biomarker analyses

Tumor tissue samples collected at screening were stained for programmed cell death 1 ligand 1 (PD-L1; SP263 analytical IHC assay on Ventana Benchmark ULTRA) and CD8 (clone C8/144B on Ventana Benchmark XT) at Hematogenix Laboratory Services (Tinley Park, IL, USA). The PD-L1 scoring algorithm by tumor type is shown in **Supplementary Table 1**. For mutational profiling, tumor tissue was assessed using FoundationOne (Foundation Medicine, Cambridge, MA, USA). Circulating tumor DNA (ctDNA) and germline DNA (gDNA) were analyzed using the Guardant Omni and CancerNEXT assays, respectively (Guardant Health, Redwood City, CA, USA; Ambry Genetics, Aliso Viejo, CA, USA). FoundationOne and CancerNEXT pipeline calls were used in variant calling for tumor tissue and gDNA, respectively. For ctDNA, known or likely pathogenic variants (ie, alterations) were defined as variants resulting in frameshifts, rearrangements, or ≥1 of a prespecified list of nucleotide changes, protein changes, or both. Tumors were considered DNA damage repair deficient (DDR)+ if ≥1 of the following criteria were met: a pretreatment tumor tissue sample, ctDNA sample, or both contained a likely or known pathogenic or deleterious mutation in ≥1 of 34 genes (*ATM, ATR, BRCA1, BRCA2,*

BRIP1, CDK12, CHEK1, CHEK2, ERCC4, FANCA, FANCC, FANCG, FANCL, MLH1, MRE11A, MSH2, MSH6, MUTYH, NBN, PALB2, PARP1, PARP2, PARP3, PMS2, POLD1, POLE, RAD51, RAD51B, RAD51C, RAD51D, RAD52, RAD54L, XRCC2, or *XRCC3; PARP3* was represented in the tumor tissue panel only), tumor tissue (triple-negative breast cancer, hormone receptor–positive breast cancer, OC, or mCRPC), or both and had a genomic loss of heterozygosity score ≥16% (≥22% for mCRPC). The background and rationale for the 34 tumor DDR genes, including genes implicated in homologous recombination, base excision repair, nucleotide excision repair, mismatch repair, and polymerase proof-reading, is summarized in **Supplementary Table 2**.

gDNA DDR profiling was based on a panel of 17 genes (subset of the 34 above): *ATM, BRCA1, BRCA2, BRIP1, CHEK2, MLH1, MRE11A, MSH2, MSH6, MUTYH, NBN, PALB2, PMS2, POLD1, POLE, RAD51C,* and *RAD51D*. In the absence of positive tumor tissue or ctDNA mutational results, detection of a known or likely deleterious germline variant resulted in a tumor being considered DDR+, provided tumor tissue and ctDNA results were not both DDR negative. In practice, application of this rule only excluded 3 tumors (1 each in cohorts A1, C1, and E2) with gDDR alterations from DDR+ status.

Tumor mutational burden (TMB) was assessed in pretreatment tumor tissue and ctDNA; samples were considered TMB high, medium, or low if they presented with ≥20, ≥10 to <20, or <10 mutations/megabase of DNA, respectively.

Supplementary Results

Pharmacokinetics and immunogenicity

At steady state, the observed median (percentage coefficient of variation) and maximum (maximum concentration–steady state) avelumab concentrations during co-administration with talazoparib were 26.4 µg/mL (57.58%) and 250.3 µg/mL (23.0%), respectively; concentrations were similar to those previously reported following avelumab 10 mg/kg Q2W monotherapy and those predicted for 800-mg flat dosing (**Supplementary Figure 5**).[1,2] Likewise, talazoparib steady-state predose concentrations during coadministration (geometric mean [GM] range, 4.06-4.54 ng/mL) were within the range of those previously reported following talazoparib 1 mg once daily monotherapy (GM range, 3.53-4.95 ng/mL).[3,4] Two patients (0.9%) developed antibodies to avelumab while receiving combination treatment. This incidence is lower than the 15% to 19% incidence previously reported for avelumab.[5]

References

1. Novakovic AM, Wilkins JJ, Dai H, et al. Changing body weight-based dosing to a flat dose for avelumab in metastatic Merkel cell and advanced urothelial carcinoma. *Clin Pharmacol Ther.* 2020;107(3):588-596.
2. Heery CR, O'Sullivan-Coyne G, Madan RA, et al. Avelumab for metastatic or locally advanced previously treated solid tumours (JAVELIN Solid Tumor): a phase 1a, multicohort, dose-escalation trial. *Lancet Oncol.* 2017;18(5):587-598.
3. Hoffman J, Chakrabarti J, Plotka A, et al. Talazoparib has no clinically relevant effect on QTc interval in patients with advanced solid tumors. *Anticancer Drugs.* 2019;30(5):523-532.
4. Yu Y, Durairaj C, Shi H, Wang DD. Population pharmacokinetics of talazoparib in patients with advanced cancer. *J Clin Pharmacol.* 2020;60(2):218-228.
5. Bavencio (avelumab). Prescribing information. EMD Serono; 2020.

eTable 1. PD-L1 Scoring By Indication

Cohort	Scoring Algorithm	PD-L1 Subgroup			
		High, %	Low, %	Positive, %	Negative, %
NSCLC	TPS like[a]	TC ≥50	TC ≥1 and <50	NA	TC <1
Breast, ovarian	PTA[b]	NA	NA	IC ≥5	IC <5
Urothelial	PIC[c]	NA	NA	TC ≥25 or IC ≥25	TC <25 and IC <25
Prostate, other	PTA[c]	NA	NA	TC ≥1 or IC ≥5	TC <1 and IC <5

IC, immune cell; NA, not applicable; NSCLC, non-small cell lung cancer; PD-L1, programmed cell death 1 ligand 1; PIC, proportion of immune cell; PTA, proportion of tumor area; TC, tumor cell; TPS, tumor proportion score.

[a] TPS like: percentage of tumor cells demonstrating membranous PD-L1 expression.

[b] PTA-based algorithm: percentage of tumor area populated by PD-L1–expressing ICs.

[c] PIC-based algorithm: percentage of all PD-L1–expressing ICs.

eTable 2. Rationale for DDR Gene Testing

Gene altered	Primary function in DDR	Rationale
ATM, ATR, BRCA1, BRCA2, BRIP1, CHEK1, CHEK2, PALB2, RAD51C, RAD51D, MLH1, MRE11A, NBN, FANCA, FANCC, FANCG, FANCL, RAD51, RAD51B, RAD52, RAD54L, XRCC2, or XRCC3	Homologous recombination (direct or indirect)/ DNA checkpoints	Sensitization to PARP inhibitors
PARP1, PARP2, PARP3, MUTYH	Base excision repair	Potentially altered sensitivity to PARP inhibitors or anti–PD-1/L1
ERCC4	Nucleotide excision repair	Potential sensitization to anti–PD-1/L1
MSH2, MSH6, PMS2	Mismatch repair	Sensitization to anti–PD-1/L1
POLD1, POLE	Polymerase proof-reading	Potential sensitization to anti–PD-1/L1
CDK12	Multiple, not fully defined, including indirect regulation of HR; defects associated with tandem duplicator phenotype	Potential sensitization to PARP inhibitors or anti–PD-1/L1

Alterations in genes involved directly or indirectly in homologous recombination are known to predict response to PARP inhibitors, while alterations in genes involved in DNA mismatch repair predict response to immune checkpoint inhibitors.

References. 1. Hsiehchen D, et al. *Cell Rep Med*. 2020;1(3):100034; 2. Baxter JS, et al. *Mol Oncol*. 2022 May 14, Online ahead of print; 3. Yap TA, et al. Am Soc Clin Oncol Educ Book. 2019;39:185-195; 4. Westphalan CB, et al. Clin Cancer Res. 2022;28(7):1412-1421; 5. Kutuzov MM, et al. Adv Exp Med Biol. 2020;1241:47-57; 6. Heeke AL, et al. JCO Precis Oncol. 2018;2018:PO.17.00286; 7. Wu Y-M, et al. Cell. 2018;173(7):1770-1782.e14; 9. Keshinro A, et al. JCO Precis Oncol. 2021;5:PO.20.00456.

eTable 3. Treatment Disposition of Patients in the Dose-Finding and Dose-Expansion Cohorts

No. (%)	Dose finding (n=12)	A1: NSCLC (n=42)	A2: DDR+ NSCLC (n=5)	B1: TNBC (n=22)	B2: HR+, HER2−, DDR+ BC (n=23)	C1: OC (n=20)	C2: *BRCA*-mut OC (n=11)	D: UC (n=40)	E1: mCRPC (n=21)	E2: DDR+ mCRPC (n=18)	F: *BRCA*/ *ATM* mut (n=9)
Avelumab treatment discontinued	11 (91.7)	37 (88.1)	4 (80.0)	22 (100.0)	20 (87.0)	18 (90.0)	7 (63.6)	36 (90.0)	21 (100.0)	17 (94.4)	9 (100.0)
Reason for discontinuation											
Adverse event	0	0	0	1 (4.5)	1 (4.3)	1 (5.0)	2 (18.2)	3 (7.5)	2 (9.5)	2 (11.1)	2 (22.2)
Death	0	4 (9.5)	0	0	0	1 (5.0)	0	2 (5.0)	0	1 (5.6)	0
Progressive disease	8 (66.7)	25 (59.5)	4 (80.0)	18 (81.8)	15 (65.2)	12 (60.0)	5 (45.5)	28 (70.0)	9 (42.9)	10 (55.6)	5 (55.6)
Patient withdrawal	1 (8.3)	4 (9.5)	0	1 (4.5)	1 (4.3)	1 (5.0)	0	1 (2.5)	2 (9.5)	0	1 (11.1)
Global deterioration of health status	2 (16.7)	3 (7.1)	0	2 (9.1)	3 (13.0)	3 (15.0)	0	2 (5.0)	8 (38.1)	4 (22.2)	1 (11.1)
Other	0	1 (2.4)	0	0	0	0	0	0	0	0	0
Avelumab treatment ongoing	1 (8.3)	5 (11.9)	1 (20.0)	0	3 (13.0))	2 (10.0)	4 (36.4)	4 (10.0)	0	1 (5.6)	0
Talazoparib treatment discontinued	11 (91.7)	38 (90.5)	4 (80.0)	22 (100.0)	20 (87.0)	18 (90.0)	7 (63.6)	36 (90.0)	21 (100.0)	17 (94.4)	9 (100.0)
Reason for discontinuation											
Adverse event	1 (8.3)	3 (7.1)	0	2 (9.1)	1 (4.3)	0	2 (18.2)	5 (12.5)	1 (4.8)	0	2 (22.2)
Death	0	4 (9.5)	0	0	0	1 (5.0)	0	2 (5.0)	0	1 (5.6)	0
Physician decision	0	0	0	0	0	0	0	0	0	1 (5.6)	0
Progressive disease	7 (58.3)	24 (57.1)	4 (80.0)	17 (77.3)	15 (65.2)	13 (65.0)	5 (45.5)	26 (65.0)	9 (42.9)	11 (61.1)	5 (55.6)
Patient withdrawal	1 (8.3)	3 (7.1)	0	1 (4.5)	1 (4.3)	1 (5.0)	0	1 (2.5)	2 (9.5)	0	1 (11.1)
Global deterioration of health status	2 (16.7)	3 (7.1)	0	2 (9.1)	3 (13.0)	3 (15.0)	0	2 (5.0)	9 (42.5)	4 (22.2)	1 (11.1)
Other	0	1 (2.4)	0	0	0	0	0	0	0	0	0
Talazoparib treatment ongoing	1 (8.3)	4 (9.5)	1 (20.0)	0	3 (13.0)	2 (10.0)	4 (36.4)	4 (10.0)	0	1 (5.6)	0

The denominator to calculate percentages is n, ie, the number of subjects in the full analysis set within each cohort.

BC, breast cancer; DDR, DNA damage repair; HER, human epidermal growth factor receptor; HR, hormone receptor;; mCRPC, metastatic castration-resistant prostate cancer; mut, mutated; NSCLC, non-small cell lung cancer; OC, ovarian cancer; TNBC, triple-negative breast cancer; UC, urothelial carcinoma.

eTable 4. Objective Response Rate by Investigators Per RECIST 1.1 According to Biomarker Status in the Dose-Expansion Cohorts

	A1: NSCLC (n=42)	**A2: DDR+ NSCLC (n=5)**	**B1: TNBC (n=22)**	**B2: HR+, HER2−, DDR+ BC (n=23)**	**C1: OC (n=20)**	**C2: *BRCA*-mut OC (n=11)**	**D: UC (n=40)**	**E1: mCRPC (n=21)**	**E2: DDR+ mCRPC (n=18)**
PD-L1 status									
High, no.	**3**	**1**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
ORR (95% CI), %	33.3 (0.8, 90.6)	100.0 (2.5, 100)	NA	NA	NA	NA	NA	NA	NA
Low, no.	**8**	**1**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
ORR (95% CI), %	25.0 (3.2, 65.1)	0 (0, 97.5)	NA	NA	NA	NA	NA	NA	NA
Positive, no.	**0**	**0**	**8**	**3**	**5**	**5**	**13**	**1**	**2**
ORR (95% CI), %	NA	NA	25.0 (3.2, 65.1)	66.7 (9.4, 99.2)	20.0 (0.5, 71.6)	60.0 (14.7, 94.7)	15.4 (1.9, 45.4)	0 (0, 97.5)	0 (0, 84.2)
Negative, no.	**22**	**2**	**6**	**16**	**13**	**4**	**19**	**12**	**12**
ORR (95% CI), %	4.5 (0.1, 22.8)	0 (0, 84.2)	0 (0, 45.9)	25.0 (7.3, 52.4)	23.1 (5.0, 53.8)	50.0 (6.8, 93.2)	15.8 (3.4, 39.6)	0 (0, 26.5)	8.3 (0.2, 8.5)
Unknown, no.	**9**	**1**	**8**	**4**	**2**	**2**	**8**	**8**	**4**
ORR (95% CI), %	33.3 (7.5, 70.1)	0 (0, 97.5)	25.0 (3.2, 65.1)	50.0 (6.8, 93.2)	0 (0, 84.2)	100.0 (15.8, 100)	12.5 (0.3, 52.7)	0 (0, 36.9)	25.0 (0.6, 80.6)
DDR status, no.									
Positive, no.	**12**	**3**	**11**	**19**	**5**	**10**	**18**	**7**	**16**
ORR (95% CI), %	0 (0, 26.5)	0 (0, 70.8)	27.3 (6.0, 61.0)	42.1 (20.3, 66.5)	20.0 (0.5, 71.6)	70.0 (34.8, 93.3)	11.1 (1.4, 34.7)	0 (0, 41.0)	12.5 (1.6, 38.3)
Negative, no.	**30**	**2**	**11**	**4**	**15**	**1**	**22**	**13**	**2**
ORR (95% CI), %	23.3 (9.9, 42.3)	50.0 (1.3, 98.7)	9.1 (0.2, 41.3)	0 (0.0, 60.2)	20.0 (4.3, 48.1)	0 (0.0, 97.5)	18.2 (5.2, 40.3)	0 (0.0, 24.7)	0 (0.0, 84.2)
Unknown, no.	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**1**	**0**
ORR (95% CI), %	NA	NA	NA	NA	NA	NA	NA	0 (0.0, 97.5)	NA

The denominator to calculate percentages is n, ie, the number of subjects in the full analysis set within each cohort.

BC, breast cancer; DDR, DNA damage repair; HER, human epidermal growth factor receptor; HR, hormone receptor; mCRPC, metastatic castration-resistant prostate cancer; mut, mutated; NA, not applicable; NSCLC, non-small cell lung cancer; OC, ovarian cancer; ORR, objective response rate; PD-L1, programmed cell death 1 ligand 1; RECIST 1.1, Response Evaluation Criteria in Solid Tumors version 1.1; TNBC, triple-negative breast cancer; UC, urothelial carcinoma.

eTable 5. Objective Response Assessed by the Investigator Per RECIST 1.1 by Alteration Status in the Dose-Expansion BC Cohorts

Gene	A1: NSCLC		A2: DDR+ NSCLC		B1: TNBC		B2: HR+, HER2−, DDR+ BC		C1: OC		C2: *BRCA*-mut OC		D: UC		F: *BRCA*/ *ATM* mut	
	n	CR/PR, no. (%)	No.	CR/PR, no. (%)	No.	CR/PR, no. (%)	No.	CR/PR, no. (%)	No.	CR/PR, n (%)	No.	CR/PR, no. (%)	No.	CR/PR, no. (%)	No.	CR/PR, no. (%)
ATM	5	1 (20.0)	1	0	3	1 (33.3)[a]	4	1 (25.0)[a]	1	0	0	0	6	0	4	0
ATR	0	0	0	0	0	0	0	0	0	0	0	0	2	0	0	0
BRCA1	1	0	1	0	2	2 (100.0)	4	2 (50.0)	1	0	6	4 (66.7)	1	0	1	0
BRCA2	5	0	0	0	1	1 (100.0)	5	4 (80.0)	0	0	4	3 (75.0)	3	1 (33.3)	4	1 (25.0)
BRIP1	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0
CDK12	0	0	0	0	0	0	0	0	0	0	0	0	3	0	1	0
CHEK2	2	0	0	0	0	0	0	0	0	0	1	0	2	0	1	0
FANCA	1	0	0	0	1	1 (100.0[a]	0	0	1	0	0	0	2	0	0	0
FANCC	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0
FANCG	1	0	0	0	0	0	0	0	0	0	0	0	1	1 (100.0)	0	0
MLH1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
MSH2	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0
MSH6	0	0	1	0	1	1 (100.0)[a]	0	0	0	0	0	0	2	1 (50.0)	0	0
MUTYH	1	0	0	0	1	1 (100.0)[a]	0	0	0	0	0	0	1	0	0	0
PALB2	1	0	1	0	0	0	2	1 (50.0)	0	0	0	0	0	0	0	0
PSM2	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
POLD1	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0
POLE	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
RAD51B	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
RAD54L	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0

eTable 5 (cont)

Gene	E1: mCRPC		E2: DDR+ mCRPC	
	No.	CR/PR, no. (%)	No.	CR/PR, no. (%)
ATM	4	0	9	1 (11.1)[a]
ATR	1	0	1	0
BRCA2	1	0	2	1 (50.0)
CDK12	2	0	3	0
CHEK1	0	0	1	0
CHEK2	0	0	2	0
FANCC	0	0	1	0
MRE11	0	0	1	0
MSH2	0	0	1	0
MSH6	0	0	3	0
MUTYH	0	0	1	0
NBN	0	0	1	0
PALB2	1	0	0	0
PARP1	0	0	1	0
POLD1	1	0	1	0
RAD54L	0	0	1	0

The denominator to calculate percentages is n, ie, the number of patients with corresponding gene mutations in the biomarker analysis set within each treatment group.

BC, breast cancer; CR, complete response; DDR, DNA damage repair; HER, human epidermal growth factor receptor; HR, hormone receptor; mCRPC, metastatic castration-resistant prostate cancer; mut, mutated; NSCLC, non-small cell lung cancer; OC, ovarian cancer; PR, partial response; RECIST 1.1, Response Evaluation Criteria in Solid Tumors version 1.1; TNBC, triple-negative breast cancer; UC, urothelial carcinoma.

[a] Patient also had mutations in *BRCA1* or *BRCA2*.

eTable 6. Summary of CA-125 and PSA Response in the Dose-Expansion Cohorts

	C1: OC (n=20)	**C2: *BRCA*-mut OC (n=11)**	**E1: mCRPC (n=21)**	**E2: DDR+ mCRPC (n=18)**
CA-125 response, % (95% CI)	40.0 (19.1, 63.9)	63.6 (30.8, 89.1)	NA	NA
PSA response, % (95% CI)	NA	NA	9.5 (1.2, 30.4)	5.6 (0.1, 27.3)

The denominator to calculate percentages is n, ie, the number of subjects in the full analysis set within each cohort. CIs were determined using the Clopper-Pearson method.

CA-125, cancer antigen 125; DDR, DNA damage repair; mCRPC, metastatic castration-resistant prostate cancer; mut, mutated; NA, not applicable; OC, ovarian cancer; PSA, prostate-specific antigen.

eTable 7. Summary of Biomarker Status of Patients in the Dose-Expansion Cohorts

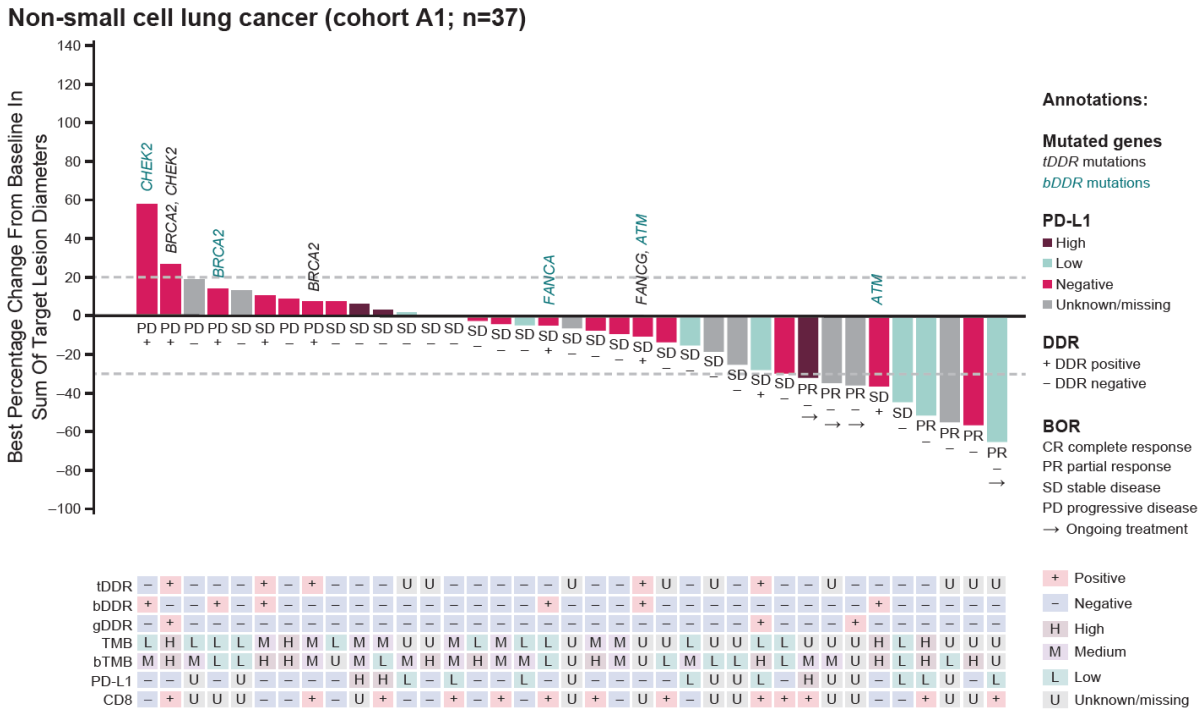
	A1: NSCLC (n=42)	**A2: DDR+ NSCLC (n=5)**	**B1: TNBC (n=22)**	**B2: HR+, HER2−, DDR+ BC (n=23)**	**C1: OC (n=20)**	**C2: *BRCA*-mut OC (n=11)**	**D: UC (n=40)**	**E1: mCRPC (n=21)**	**E2: DDR+ mCRPC (n=18)**	**F: *BRCA*/ *ATM* mut (n=9)**
bDDR, n (%)										
Positive	9 (21.4)	1 (20.0)	4 (18.2)	3 (13.0)	2 (10.9)	3 (27.3)	14 (35.0)	5 (23.8)	10 (55.6)	6 (66.7)
Negative	33 (78.6)	4 (80.0)	18 (81.8)	20 (87.0)	18 (90.0)	8 (72.7)	23 (57.5)	15 (71.4)	8 (44.4)	3 (33.3)
Unknown[a]	0	0	0	0	0	0	3 (7.5)	1 (4.8)	0	0
tDDR, n (%)										
Positive	5 (11.9)	3 (60.0)	9 (40.9)	19 (82.6)	3 (15.0)	8 (72.7)	10 (25.0)	4 (19.0)	14 (77.8)	5 (55.6)
Negative	26 (61.9)	2 (40.0)	6 (27.3)	4 (17.4)	11 (55.0)	2 (18.2)	24 (60.0)	8 (38.1)	1 (5.6)	3 (33.3)
Unknown[a]	11 (26.2)	0	7 (31.8)	0	6 (30.0)	1 (9.1)	6 (15.0)	9 (42.9)	3 (16.7)	1 (11.1)
gDDR, n (%)										
Positive	4 (9.5)	0	3 (13.6)	6 (26.1)	1 (5.0)	2 (18.2)	1 (2.5)	2 (9.5)	5 (27.8)	3 (33.3)
Negative	37 (88.1)	5 (100.0)	19 (86.4)	17 (73.9)	18 (90.0)	9 (81.8)	39 (97.5)	18 (85.7)	13 (72.2)	6 (66.7)
Unknown[a]	1 (2.4)	0	0	0	1 (5.0)	0	0	1 (4.8)	0	0
bTMB, n (%)										
High	13 (31.0)	2 (40.0)	4 (18.2)	6 (26.1)	0	0	12 (30.0)	3 (14.3)	3 (16.7)	3 (33.3)
Medium	13 (31.0)	1 (20.0)	8 (36.4)	4 (17.4)	7 (35.0)	3 (27.3)	11 (27.5)	4 (19.0)	5 (27.8)	3 (33.3)
Low	10 (23.8)	1 (20.0)	8 (36.4)	9 (39.1)	9 (45.0)	6 (54.5)	12 (30.0)	10 (47.6)	8 (44.4)	3 (33.3)
Unknown[a]	6 (14.3)	1 (20.0)	2 (9.1)	4 (17.4)	4 (20.0)	2 (18.2)	5 (12.5)	4 (19.0)	2 (11.1)	0
TMB, n (%)										
High	4 (9.5)	1 (20.0)	0	0	0	0	5 (12.5)	0	2 (11.1)	0
Medium	9 (21.4)	1 (20.0)	3 (13.6)	2 (8.7)	1 (5.0)	2 (18.2)	4 (10.0)	0	0	0
Low	13 (31.0)	3 (60.0)	12 (54.5)	20 (87.0)	12 (60.0)	6 (54.5)	22 (55.0)	11 (52.4)	13 (72.2)	8 (88.9)
Unknown[a]	16 (38.1)	0	7 (31.8)	1 (4.3)	7 (35.0)	3 (27.3)	9 (22.5)	10 (47.6)	3 (16.7)	1 (11.1)
CD8, n (%)										
Positive	14 (33.3)	2 (40.0)	7 (31.8)	9 (39.1)	8 (40.0)	5 (45.5)	14 (35.0)	6 (28.6)	6 (33.3)	2 (22.2)
Negative	14 (33.3)	2 (40.0)	7 (31.8)	9 (39.1)	8 (40.0)	4 (36.4)	14 (35.0)	5 (23.8)	6 (33.3)	1 (11.1)
Unknown[a]	14 (33.3)	1 (20.0)	8 (36.4)	5 (21.7)	4 (20.0)	2 (18.2)	12 (30.0)	10 (47.6)	6 (33.3)	6 (66.7)

The denominator to calculate percentages is n, ie, the number of subjects in the full analysis set within each cohort.
BC, breast cancer; bDDR, baseline DNA damage repair; bTMB, blood tumor mutational burden; DDR, DNA damage repair; gDDR, germline DNA damage repair; HER, human epidermal growth factor receptor; HR, hormone receptor; mCRPC, metastatic castration-resistant prostate cancer; mut, mutated; NSCLC, non-small cell lung cancer; OC, ovarian cancer; tDDR, tumoral DNA damage repair; TMB, tumor mutational burden; TNBC, triple-negative BC; UC, urothelial carcinoma.
[a] Includes nonanalyzable or missing samples.

eFigure 1. Best Percentage Change in Size of Target Lesions Among Patients Receiving Treatment Assessed by Investigators Per RECIST v1.1 in the Dose-Expansion Phase
Patients with (A) non-small cell lung cancer (cohort A1; n=37) by PD-L1 and DDR status; or (B) urothelial carcinoma (cohort D; n=36) by PD-L1 status.

The upper dashed lines represent the threshold for PD, defined as a ≥20% increase in target lesion diameter from baseline. The lower dashed lines represent the threshold for a PR, defined as a ≥30% decrease in target lesion diameter from baseline. In patients with DDR+ status but for whom a DDR mutation is not specified, DDR+ status was confirmed by germline loss of heterozygosity (gLOH) score. Presence of a gDDR+ mutation alone did not confirm DDR+ status. In the absence of positive solid tumor or circulating tumor DNA mutational 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−. (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.)

A



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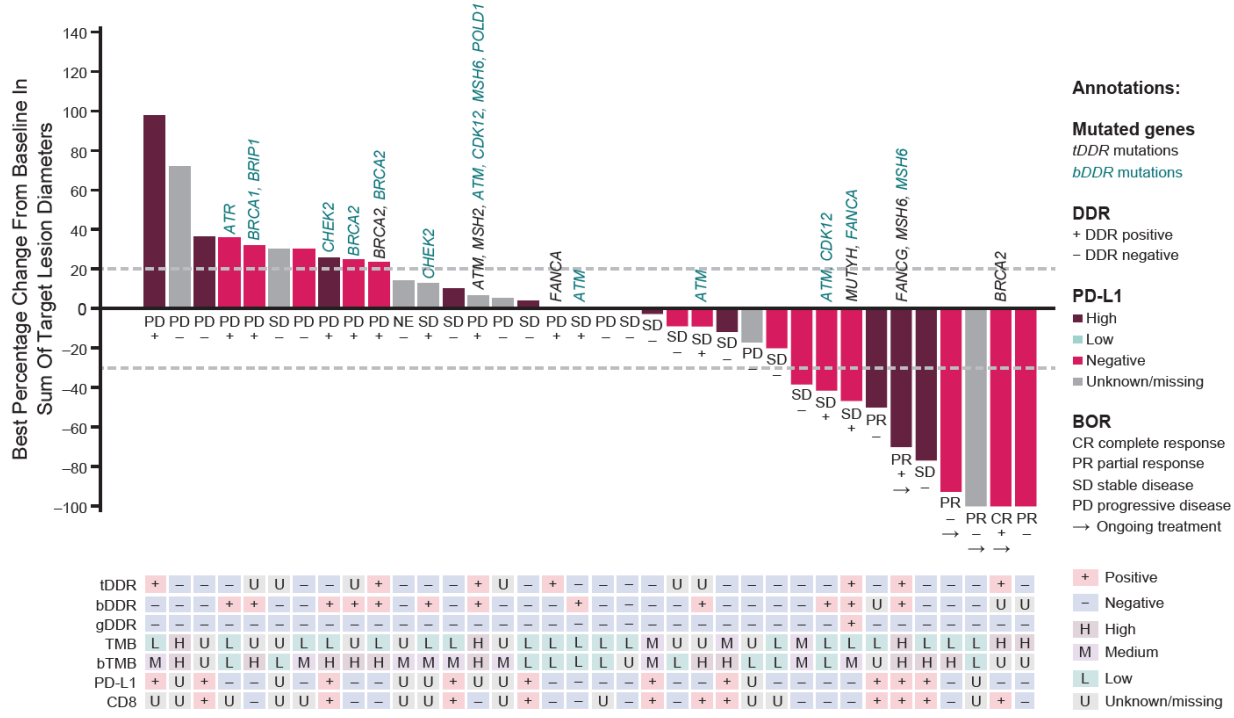
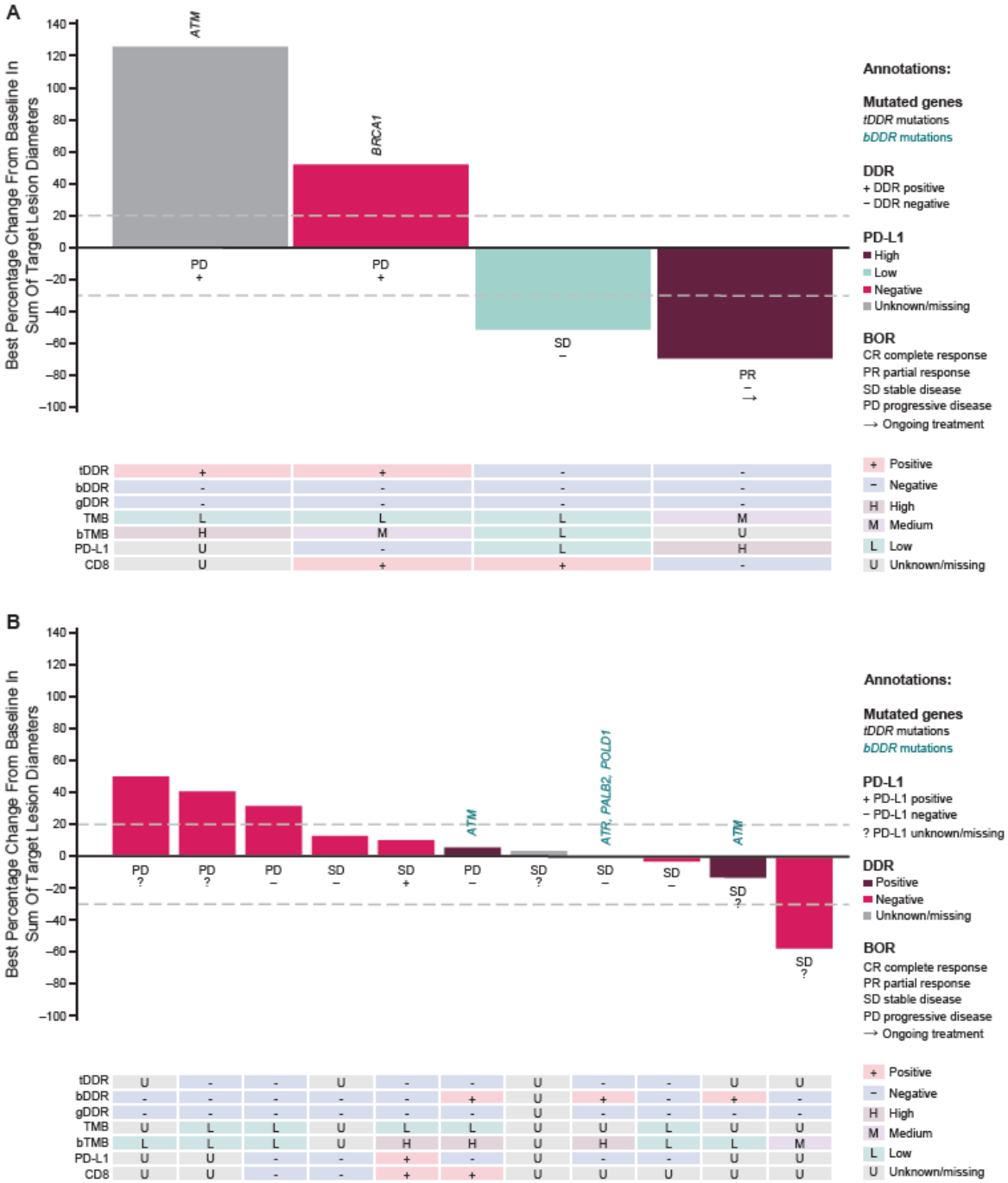
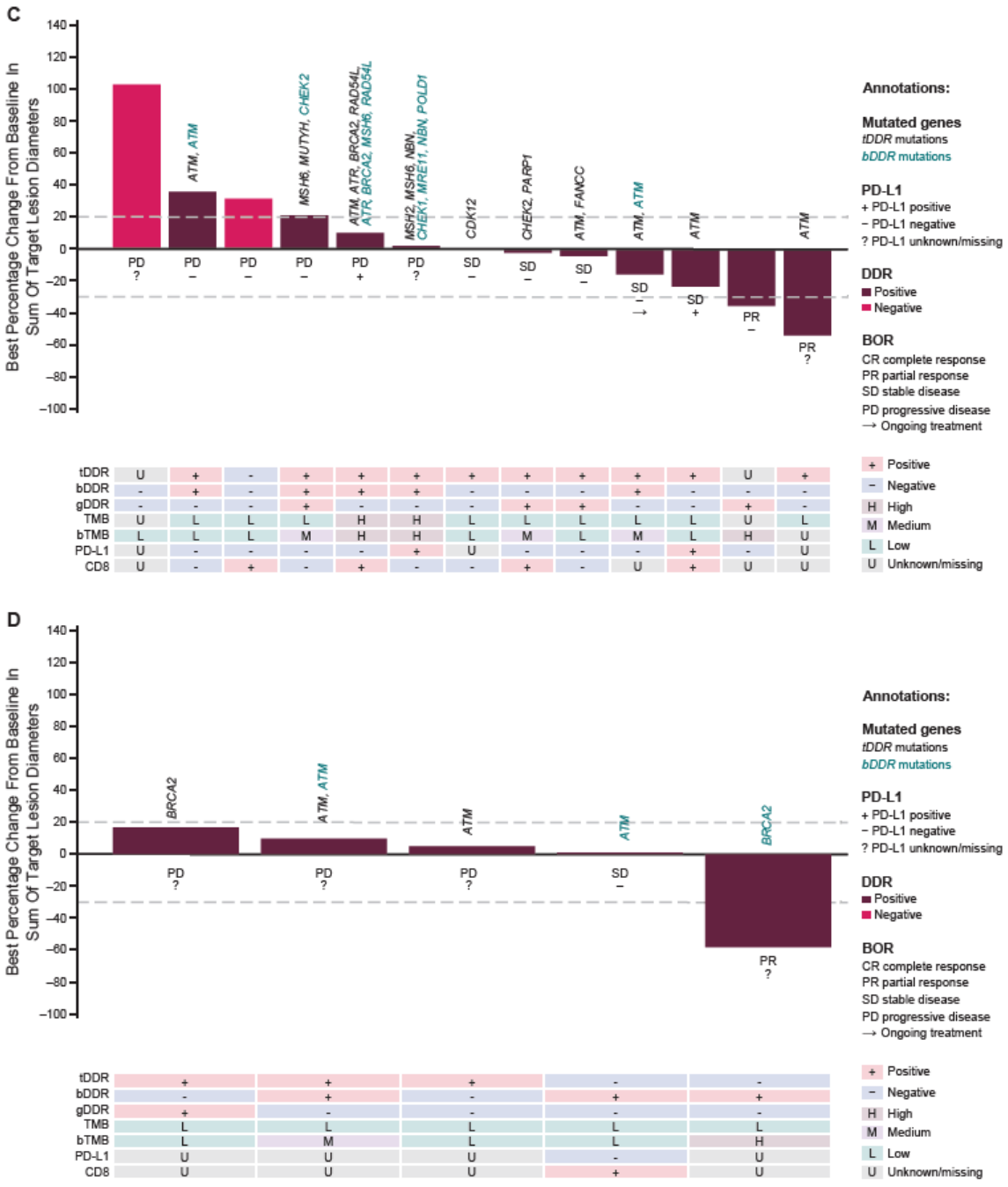


eFigure 2. BOR[a] in Patients in the Dose-Expansion Phase

Patients with (A) DDR+ non-small cell lung cancer (cohort A2; n=4) by PD-L1 and DDR status, (B) metastatic castration-resistant prostate cancer (cohort E1; n=11) by DDR and PD-L1 status, (C) DDR+ metastatic castration-resistant prostate cancer (cohort E2; n=13) by DDR and PD-L1 status, and (D) *BRCA/ATM*-mutated solid tumors (cohort F; n=5) by DDR and PD-L1 status.



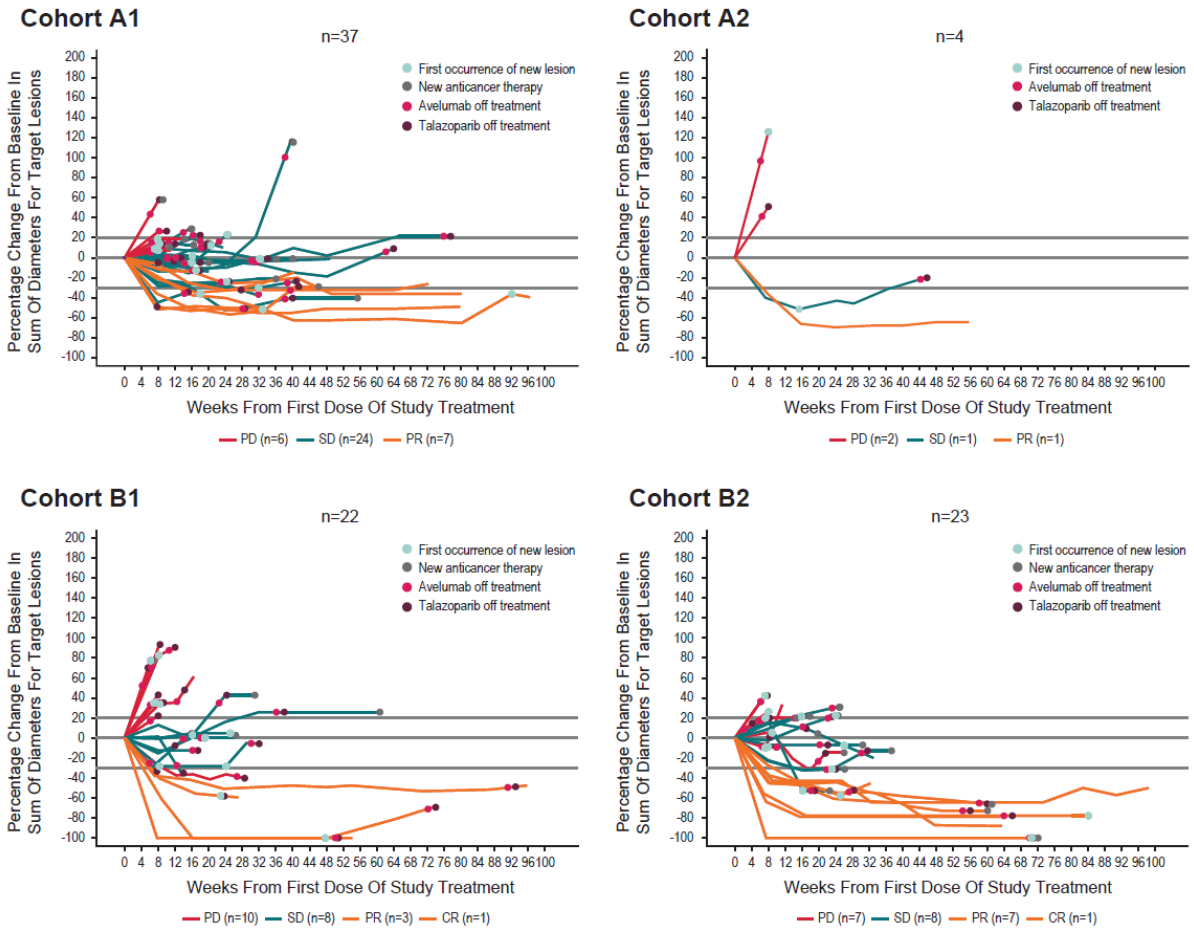


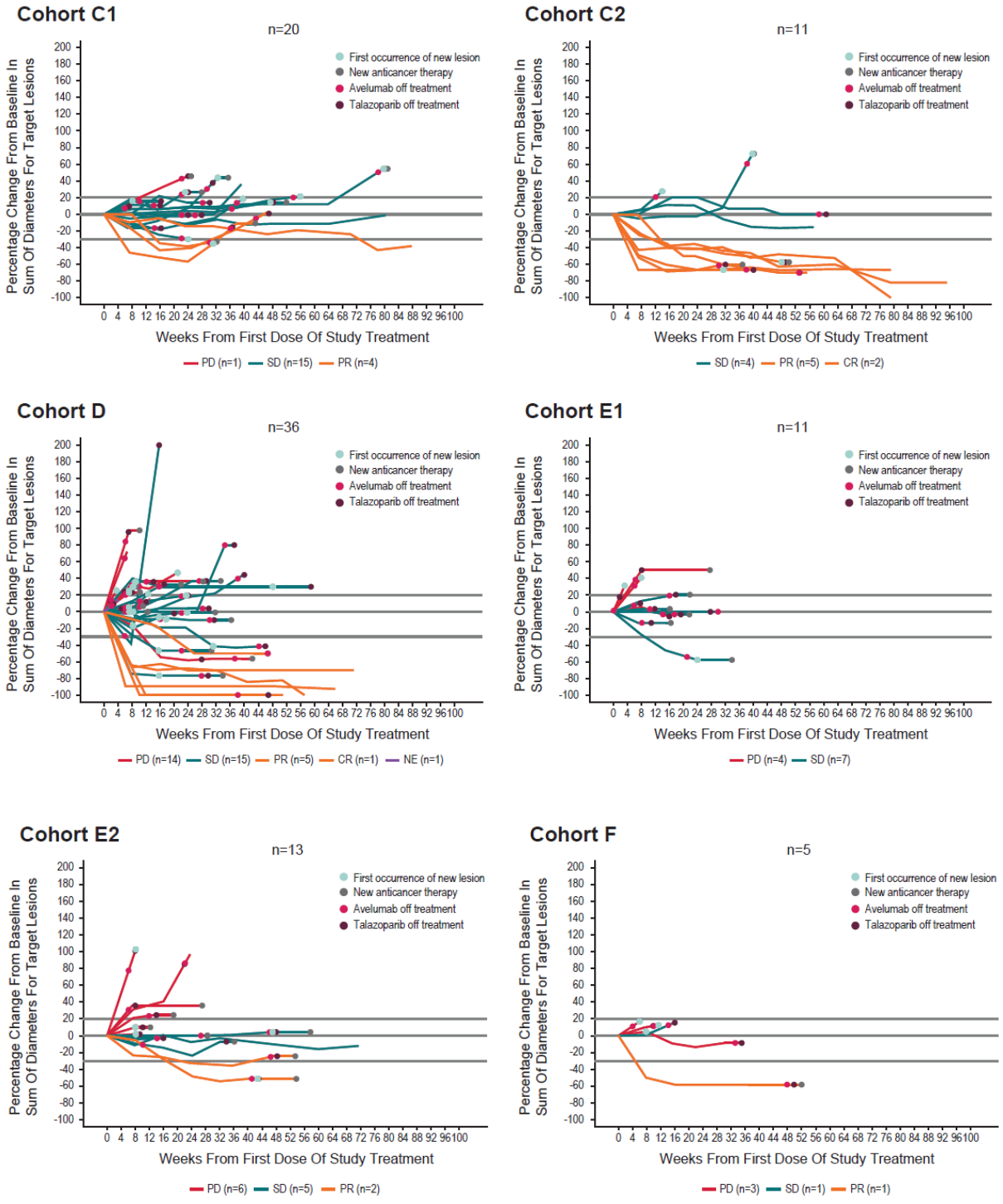
bDDR, blood DNA damage repair; BOR, best overall response; bTMB, blood tumor mutational burden; DDR, DNA damage repair; gDDR, germline DNA damage repair; NSCLC, non-small cell lung cancer; PCWG3, Prostate Cancer Working Group 3; PD-L1, programmed cell death 1 ligand 1; RECIST 1.1, Response Evaluation Criteria in Solid Tumors version 1.1; tDDR, tumor DNA damage repair; TMB, tumor mutational burden.

[a] Assessed by investigators per RECIST 1.1 (cohort A2 and F) and RECIST 1.1 and PCWG3 (cohorts E1 and E2).

eFigure 3. Percentage Change in Sum of Diameters of Target Lesions From Baseline

In patients with non-small cell lung cancer (A; cohort A1); DNA damage repair–positive (DDR+) NSCLC (B; cohort A2); triple-negative breast cancer (C; cohort B1); hormone receptor positive–, human epidermal growth factor receptor–negative, DDR+ breast cancer (D; cohort B2); ovarian cancer (E; cohort C1); *BRCA*-mutated ovarian cancer (F; cohort C2); urothelial cancer (G; cohort D); metastatic castration-resistant prostate cancer (H; cohort E1); DDR+ metastatic castration-resistant prostate cancer (I; cohort E2); and *BRCA/ATM*-mutated tumor (J; cohort F).

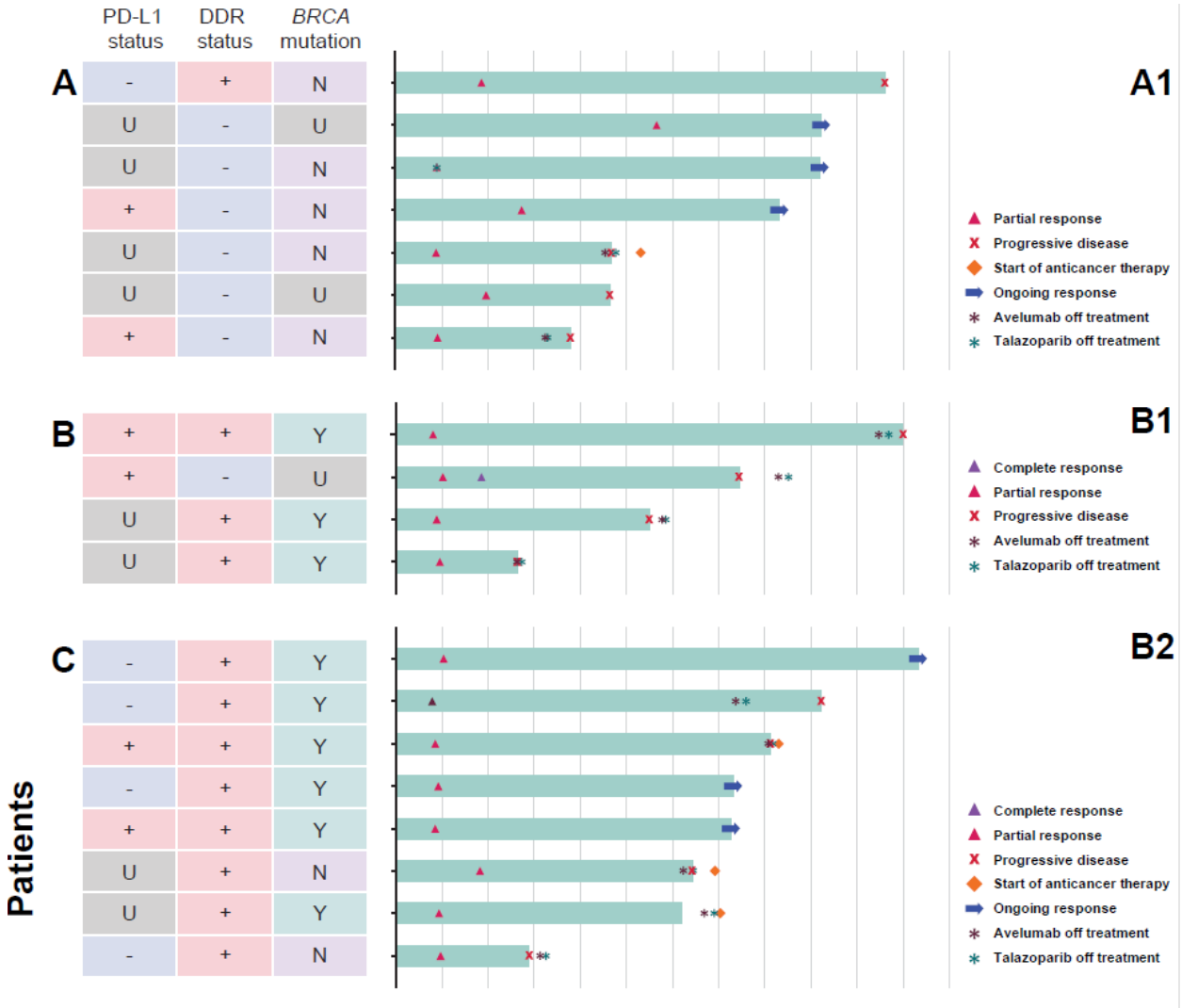


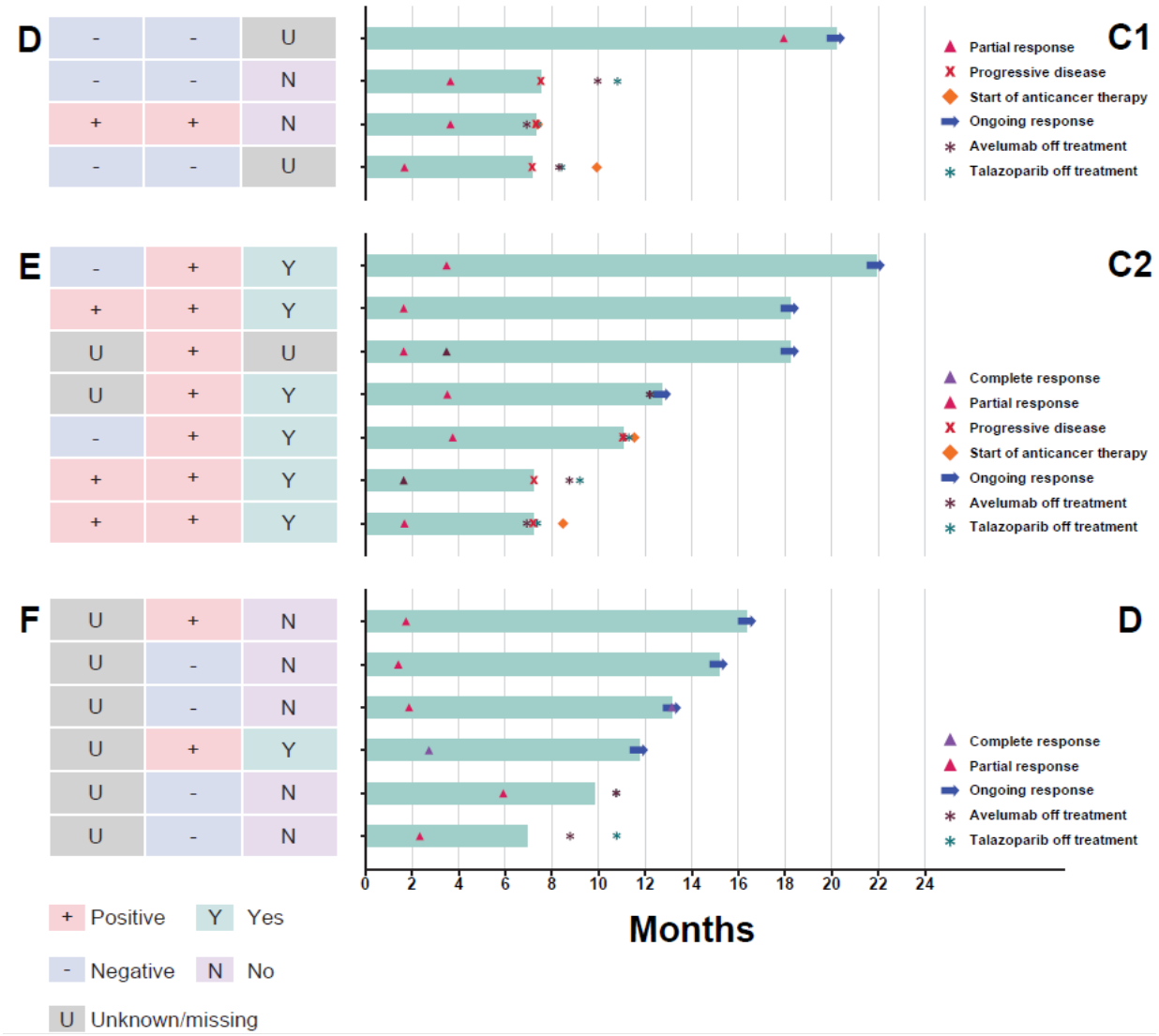


NE, not estimable; PD, progressive disease; PR, partial response; SD, stable disease.

eFigure 4. Time to and Duration of Response by Investigators Per Response Evaluation Criteria in Solid Tumors Version 1.1

Patients in the dose-expansion phase with a confirmed objective response with (A) non-small cell lung cancer (cohort A1; n=7); (B) triple-negative breast cancer with DDR+ status (cohort B1; n=4); (C) hormone receptor positive–, human epidermal growth factor receptor–negative, DDR+ breast cancer (cohort B2; n=8); (D) ovarian cancer (cohort C1; n=4); (E) *BRCA*-mutated ovarian cancer (cohort C2; n=7); or (F) urothelial carcinoma (cohort D; n=6).

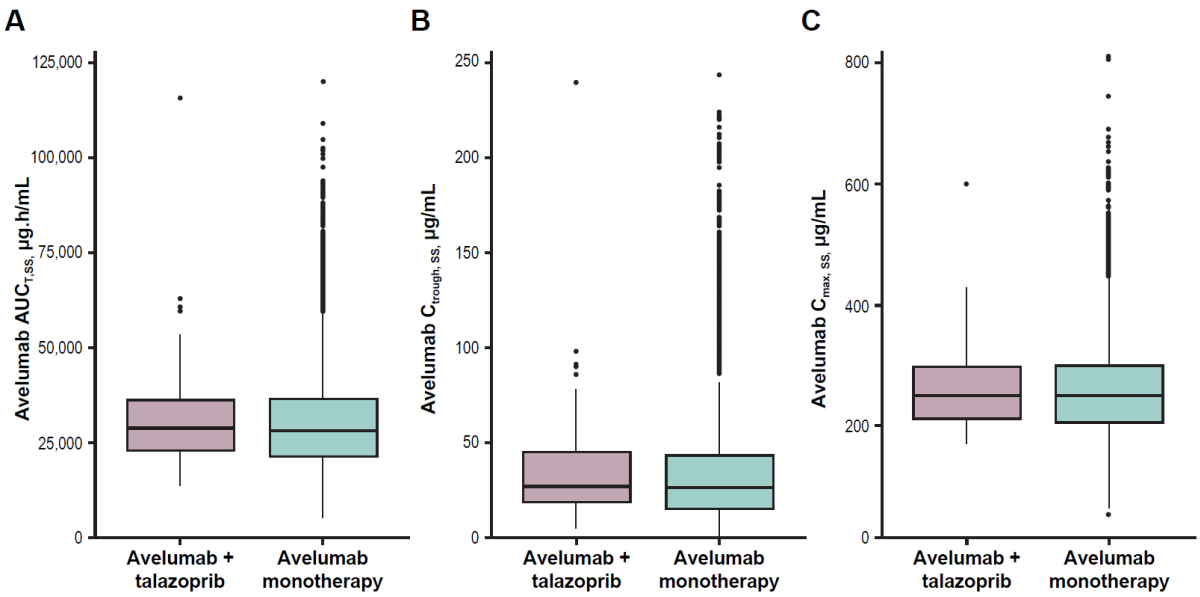




DDR, DNA damage repair; PD-L1, programmed cell death 1 ligand 1.

eFigure 5. Avelumab Steady-State Exposures Following 800 mg Intravenous Infusion Every 2 Weeks Coadministered With Oral Talazoparib 1 mg Once Daily vs Avelumab 10 mg/kg Every 2 Weeks Monotherapy

Avelumab + talazoparib box plots in (A) $AUC_{T,SS}$, (B) $C_{trough\ SS}$ (predose, 0-hour, minimum exposure at steady state), and (C) $C_{max,SS}$ (1-hour end of infusion, corresponding to maximum exposure at steady state) are based on observed data from this study. Corresponding avelumab monotherapy box plots have been generated from the final steady state avelumab monotherapy population pharmacokinetic model.[1]



Horizontal line in box interior represents the median. Upper and lower box lines represent the first and third quantiles, respectively. End of vertical lines represent 1 SD above or below the arithmetic mean. Symbols outside the box represent measurements outside 1 SD from the arithmetic mean. Arithmetic mean: SD below 0 is set to 0. AUC_T, area under the concentration-time curve; C_{max}, maximum concentration; C_{trough}, trough concentration; SS, steady state.