ONLINE APPENDIX

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

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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)

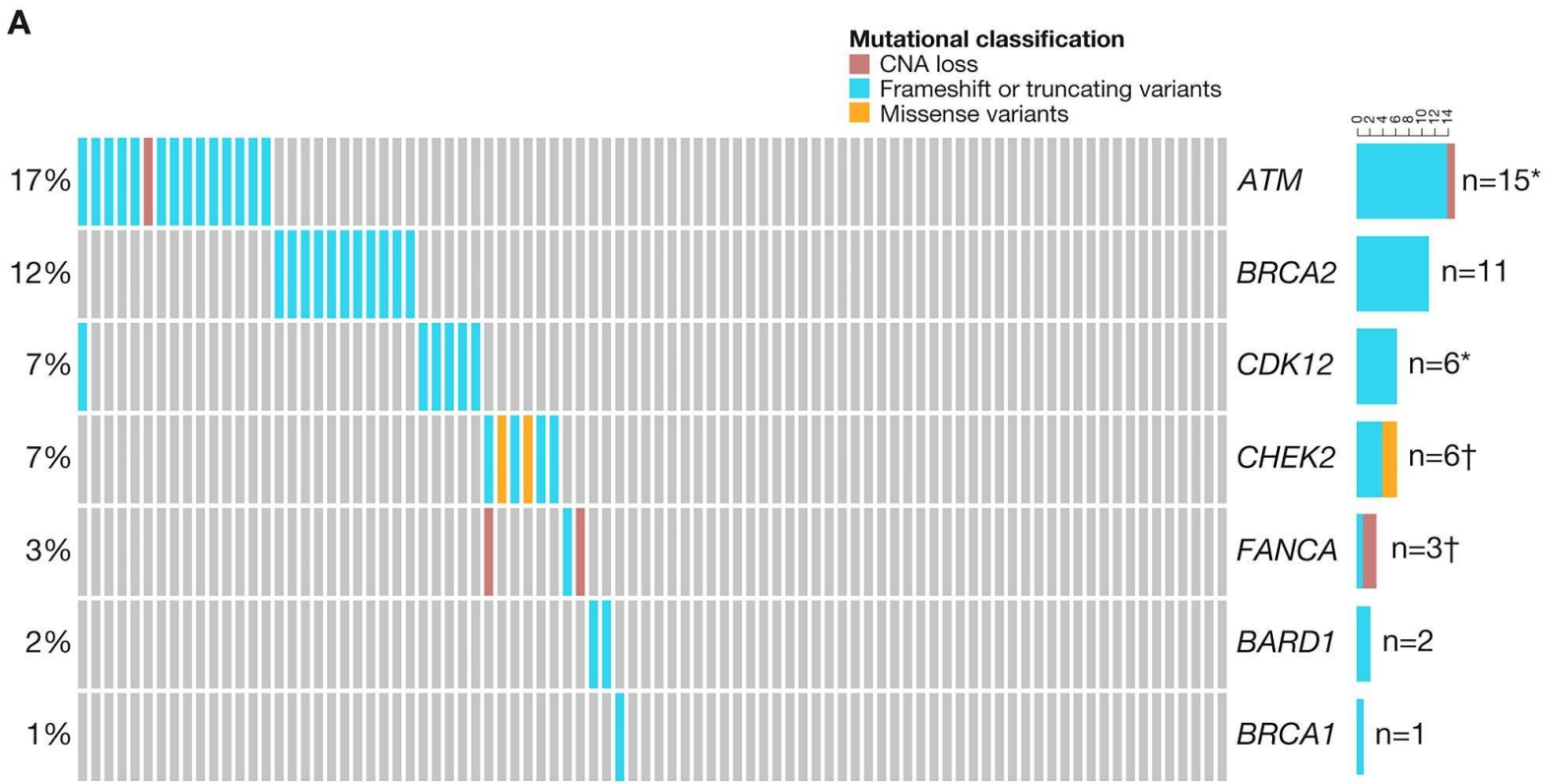
*Represents a treatment-related AE that led to permanent discontinuation of nivolumab and/or rucaparib; includes individual any-grade treatment-related AEs reported between first dose of nivolumab plus rucaparib and 30 days after the last dose of study drug that led to discontinuation and occurred in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

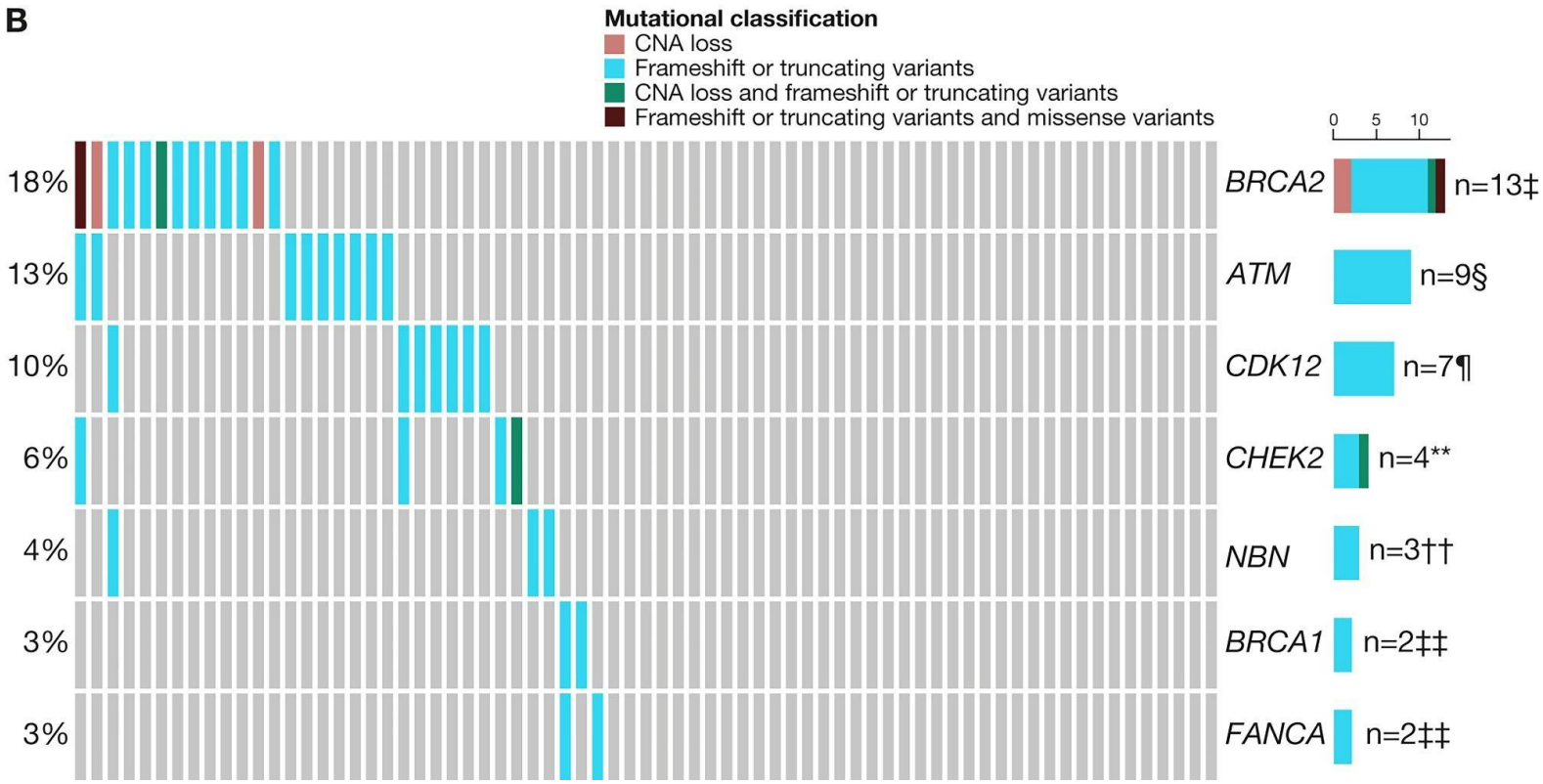
Supplemental Table 8 Summary of immune-mediated AEs* in cohorts A1 and A2

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.