Abstract 80

Association of Co-Occurring Gene Alterations and Clinical Activity of Rucaparib in Patients With *BRCA1*- or *BRCA2*-Mutated Metastatic Castration-Resistant Prostate Cancer (mCRPC)

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Introduction

- The PARP inhibitor rucaparib was approved by the US FDA for patients with BRCA-mutated mCRPC based on phase 2 TRITON2 study results (NCT02952534)[1,2]
  - ORRs to rucaparib were similar in subgroups of germline and somatic alterations in these genes, as well as by type of alteration (approximately 40–50%).[2] It is not clear whether co-occurring genomic alterations impact responses
- Alterations in the *TP53*, *PTEN*, and *RB1* tumor suppressor genes are associated with poor prognosis in patients with prostate cancer[3-6]
  - *RB1* and *BRCA2* are located proximal to each other on chromosome 13q
  - Co-occurring loss of *RB1* and *BRCA2* conferred more aggressive behavior in models of CRPC[7]
- We present data on co-occurring alterations in *TP53*, *PTEN*, and *RB1* for patients with BRCA-mutated mCRPC treated with rucaparib in TRITON2

BRCA, *BRCA1* or *BRCA2*; CRPC, castration-resistant prostate cancer; FDA, Food and Drug Administration; mCRPC, metastatic castration-resistant prostate cancer; ORR, objective response rate; PARP, poly(ADP-ribose) polymerase.

1. Rubraca (rucaparib) tablets [prescribing information]. Boulder, CO: Clovis Oncology, Inc.; 2020. 2. Abida et al. *J Clin Oncol.* 2020;38(32):3763-72. 3. Abida et al. *Proc Natl Acad Sci U S A.* 2019;116(23):11428-36. 4. Hamid et al. *Eur Urol.* 2019;76(1):89-97. 5. Ferraldeschi et al. *Eur Urol.* 2015;67(4):795-802. 6. Aparicio et al. *Clin Cancer Res.* 2016;22(6):1520-30. 7. Chakraborty et al. *Clin Cancer Res.* 2020;26(8):2047-64.

Methods

- Patients had progressed on 1–2 lines of androgen receptor-directed therapy and 1 taxane-based chemotherapy and were treated with rucaparib 600 mg BID
- Tissue and/or cell-free DNA extracted from plasma samples were profiled for genomic alterations using Foundation Medicine, Inc., next-generation sequencing assays[1,2]
  - Germline testing for BRCA was performed by Color Genomics[3,4]
- ORR was assessed per modified RECIST/PCWG3 criteria by independent radiology review of patients with measurable disease
  - Duration of response was evaluated for patients achieving a radiographic response
- PSA response rate (≥50% decrease from baseline) was assessed in all patients

BID, twice daily; BRCA, *BRCA1* or *BRCA2;* ORR, objective response rate; PCWG3, Prostate Cancer Clinical Trials Working Group 3; PSA, prostate-specific antigen; RECIST, Response Evaluation Criteria In Solid Tumors, version 1.1.

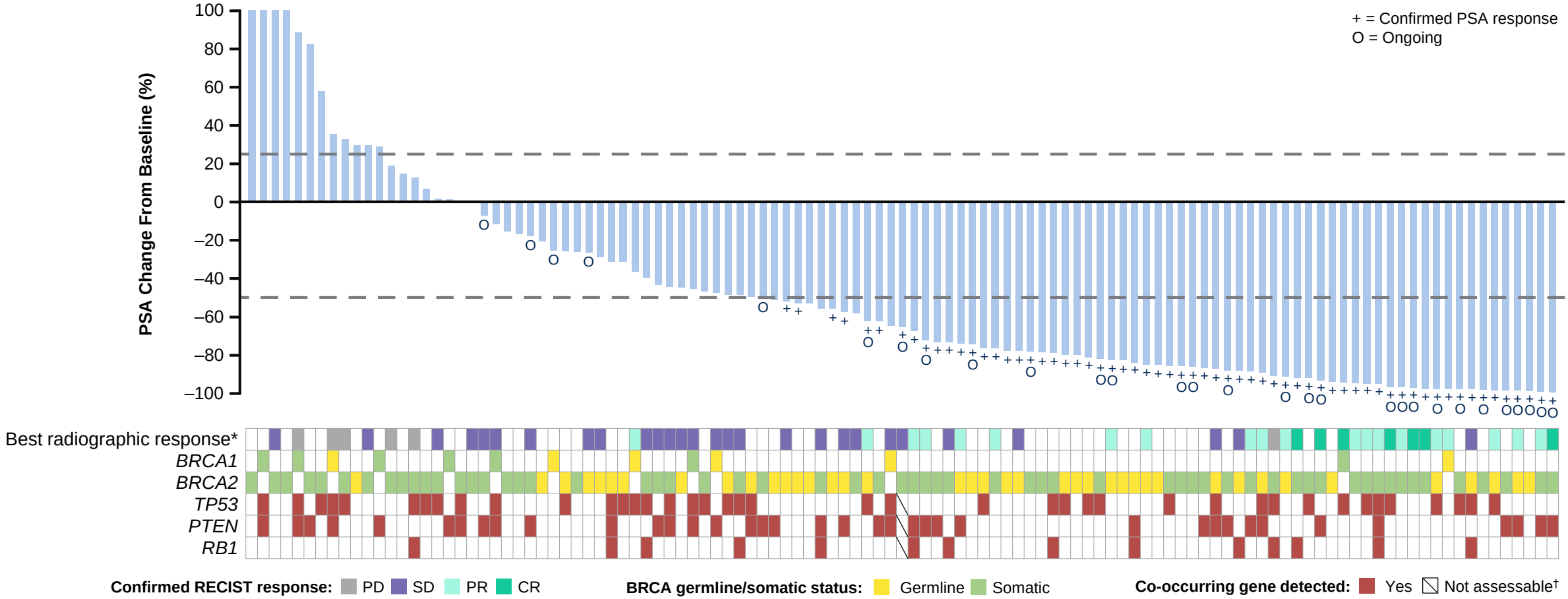
1. Frampton et al. *Nat Biotechnol.* 2013;31(11):1023-31. 2. Clark et al. *J Mol Diagn.* 2018;20(5):686-702. 3. Crawford et al. *Breast Cancer Res Treat.* 2017;163(2):383-90. 4. Neben et al. *J Mol Diagn.* 2019;21(4):646-57.

Baseline Characteristics in Rucaparib-Treated Patients With BRCA-Mutated mCRPC

Baseline characteristic	Co-Occurring Gene Alteration[a,b]						Overall BRCA^{mut} (N=115)
	TP53^{mut} (n=42)	*TP53*^{wt} (n=72)	*PTEN*^{mut} (n=39)	*PTEN*^{wt} (n=75)	*RB1*^{mut} (n=14)	*RB1*^{wt} (n=100)	
Age, median (range), yr	72.5 (52–86)	71.5 (50–88)	70.0 (56–87)	72.0 (50–88)	73.0 (54–88)	71.0 (50–87)	72.0 (50–88)
Time since cancer diagnosis, median (range), yr	3.8 (0.8–21.2)	5.65 (1.5–19.2)	4.7 (1.0–21.2)	4.3 (0.8–15.8)	3.95 (1.0–19.2)	4.65 (0.8–21.2)	4.6 (0.8–21.2)
ECOG PS, n (%)							
0	13 (31.0)	24 (33.3)	12 (30.8)	25 (33.3)	5 (35.7)	32 (32.0)	37 (32.2)
1	28 (66.7)	47 (65.3)	26 (66.7)	49 (65.3)	9 (64.3)	66 (66.0)	76 (66.1)
≥2	1 (2.4)	1 (1.4)	1 (2.6)	1 (1.3)	0	2 (2.0)	2 (1.7)
Baseline PSA, median (range), ng/mL	75.8 (3.5–3758.6)	51.3 (0.0–4782.0)	47.0 (1.8–4669.0)	82.8 (0.0–4782.0)	35.5 (3.7–348.0)	69.2 (0.0–4782.0)	61.1 (0.0–4782.0)
Gleason score ≥8, n (%)	24 (57.1)	53 (73.6)	26 (66.7)	51 (68.0)	9 (64.3)	68 (68.0)	77 (67.0)
Measurable disease (per blinded IRR), n (%)[c]							
Measurable disease							
Only measurable nodal disease	13 (31.0)	27 (37.5)	16 (41.0)	24 (32.0)	4 (28.6)	36 (36.0)	41 (35.7)
Measurable visceral ± nodal disease	12 (28.6)	9 (12.5)	8 (20.5)	13 (17.3)	7 (50.0)	14 (14.0)	21 (18.3)
No measurable disease							
Bone-only disease	11 (26.2)	25 (34.7)	11 (28.2)	25 (33.3)	1 (7.1)	35 (35.0)	36 (31.3)
Other	6 (14.3)	11 (15.3)	4 (10.3)	13 (17.3)	2 (14.3)	15 (15.0)	17 (14.8)
Disease status (per blinded IRR), n (%)[d]							
Bone	37 (88.1)	56 (77.8)	32 (82.1)	61 (81.3)	8 (57.1)	85 (85.0)	93 (80.9)
Nodal	23 (54.8)	37 (51.4)	23 (59.0)	37 (49.3)	10 (71.4)	50 (50.0)	61 (53.0)
Visceral	23 (54.8)	21 (29.2)	18 (46.2)	26 (34.7)	10 (71.4)	34 (34.0)	44 (38.3)
Lung	8 (19.0)	6 (8.3)	4 (10.3)	10 (13.3)	2 (14.3)	12 (12.0)	14 (12.2)
Hepatic	9 (21.4)	5 (6.9)	7 (17.9)	7 (9.3)	5 (35.7)	9 (9.0)	14 (12.2)

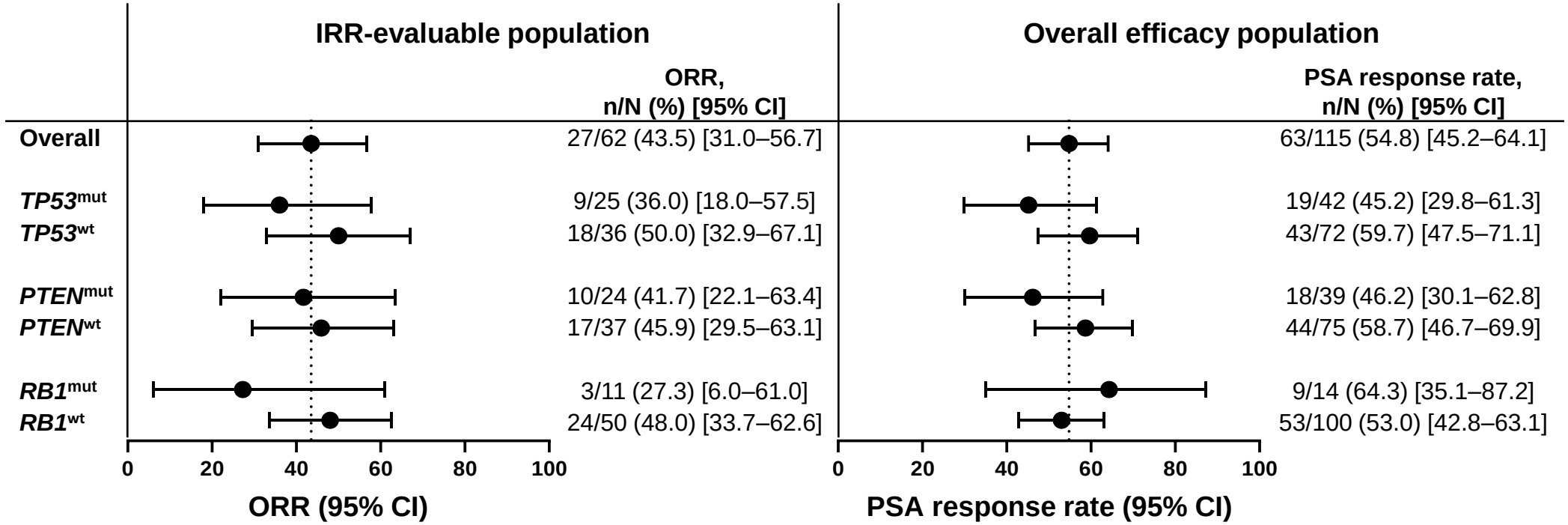
Visit cutoff date: December 23, 2019. [a]Subgroups are not mutually exclusive; patients may have more than one co-occurring gene alteration. [b]One patient had only local test results available; presence of co-occurring alterations could not be determined. [c]Based on modified RECIST/PCWG3. [d]Categories are not mutually exclusive. BRCA, *BRCA1* or *BRCA2*; ECOG PS, Eastern Cooperative Oncology Group performance status; IRR, independent radiology review; mCRPC, metastatic castration-resistant prostate cancer; mut, mutated; PCWG3, Prostate Cancer Clinical Trials Working Group 3; PSA, prostate-specific antigen; RECIST, Response Evaluation Criteria In Solid Tumors, version 1.1; wt, wild type.

Best PSA Change From Baseline in Rucaparib-Treated Patients With BRCA-Mutated mCRPC (n=113)



Visit cutoff date: December 23, 2019. Excludes 2 patients who were not evaluable for change in PSA. Bars were capped at 100% for visual clarity. PSA increases for the 4 leftmost patients were 689%, 231%, 183%, and 133%. *For patients with measurable disease; assessed by IRR per modified RECIST/PCWG3 criteria. †One patient had only local test results available; presence of co-occurring alterations could not be determined. BRCA, *BRCA1* or *BRCA2*; CR, complete response; IRR, independent radiology review; mCRPC, metastatic castration-resistant prostate cancer; PCWG3, Prostate Cancer Clinical Trials Working Group 3; PD, progressive disease; PR, partial response; PSA, prostate-specific antigen; RECIST, Response Evaluation Criteria In Solid Tumors, version 1.1; SD stable disease. Adapted from a figure originally published by the American Society of Clinical Oncology [Abida et al. *J Clin Oncol.* 2020;38(32):3763-72].

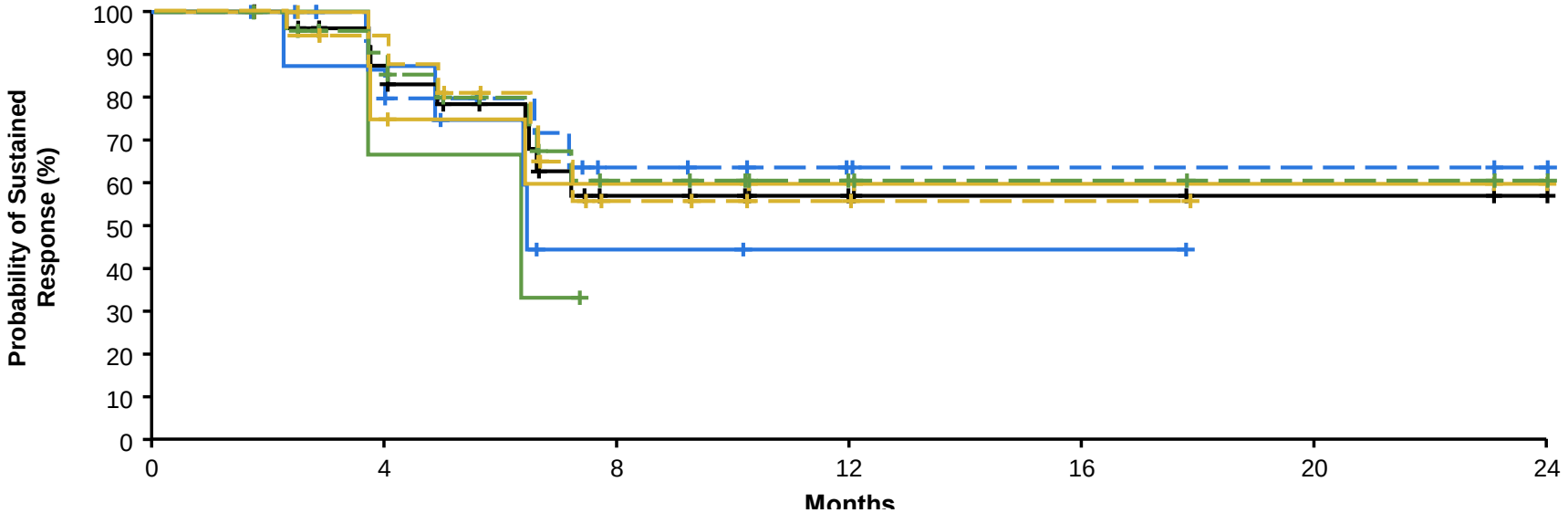
Response Rates to Rucaparib for Patients With BRCA-Mutated mCRPC



- Patients with BRCA-mutated mCRPC and co-occurring *TP53*, *PTEN*, or *RB1* alterations overall had similar objective and PSA response rates as those without co-occurring alterations
  - ORR for patients with BRCA-mutated mCRPC and co-occurring *RB1* alterations appeared numerically lower than *RB1*-wild-type cases, but there were insufficient cases to draw a definitive conclusion

Visit cutoff date: December 23, 2019. The vertical dotted line corresponds to the overall ORR or PSA response. One patient was enrolled based on BRCA status from a local test, but the presence of co-occurring alterations could not be determined; this patient is excluded from the co-occurring gene subgroups shown (n=61 or n=114). BRCA, *BRCA1* or *BRCA2*; IRR, independent radiology review; mCRPC, metastatic castration-resistant prostate cancer; mut, mutated; ORR, objective response rate; PSA, prostate-specific antigen; wt, wild type.

Duration of Radiographic Response to Rucaparib for Patients With BRCA-Mutated mCRPC



	Median, mo (95% CI)
Overall (n=27)	NR (6.4–NR)
TP53^{mut} (n=9)	6.4 (2.3–NR)
TP53^{wt} (n=18)	NR (4.0–NR)
PTEN^{mut} (n=10)	NR (3.7–NR)
PTEN^{wt} (n=17)	NR (6.4–NR)
RB1^{mut} (n=3)	6.4 (3.7–NR)
RB1^{wt} (n=24)	NR (6.4–NR)

No. at risk (events)							
Overall	27 (0)	20 (3)	8 (9)	4 (9)	3 (9)	2 (9)	0 (9)
TP53^{mut}	9 (0)	7 (1)	2 (4)	1 (4)	1 (4)	0 (4)	
TP53^{wt}	18 (0)	13 (2)	6 (5)	3 (5)	2 (5)	2 (5)	0 (5)
PTEN^{mut}	10 (0)	6 (2)	4 (3)	3 (3)	2 (3)	2 (3)	0 (3)
PTEN^{wt}	17 (0)	14 (1)	4 (6)	1 (6)	1 (6)	0 (6)	
RB1^{mut}	3 (0)	2 (1)	0 (2)				
RB1^{wt}	24 (0)	18 (2)	8 (7)	4 (7)	3 (7)	2 (7)	0 (7)

- Similar durations of response were observed in patients with BRCA-mutated mCRPC with or without a *TP53, PTEN,* or *RB1* alteration, with the same caveat for *RB1* as noted previously

Visit cutoff date: December 23, 2019. Response was assessed by IRR per modified RECIST/PCWG3 criteria. Subgroups are not mutually exclusive; patients may be included in more than one line.
BRCA, *BRCA1* or *BRCA2*; IRR, independent radiology review; mCRPC, metastatic castration-resistant prostate cancer; mut, mutated; NR, not reached; PCWG3, Prostate Cancer Clinical Trials Working Group 3; RECIST, Response Evaluation Criteria In Solid Tumors, version 1.1; wt, wild type. Adapted from a figure originally published by the American Society of Clinical Oncology [Abida et al. *J Clin Oncol.* 2020;38(32):3763-72].

Summary

- Although *TP53*, *PTEN*, or *RB1* alterations are associated with poor prognosis, results from TRITON2 showed antitumor activity for rucaparib in patients with BRCA-mutated mCRPC associated with or without co-occurring alterations in these genes
  - There was no clear difference in radiographic and PSA response rates for patients with or without co-occurring *TP53*, *PTEN*, or *RB1* alterations, but the low frequency of RB1 loss limited our conclusion for this gene
- At this time, patients with mCRPC associated with a BRCA alteration should be considered for treatment with rucaparib irrespective of the presence of co-occurring alterations in these tumor suppressor genes

BRCA, *BRCA1* or *BRCA2*; mCRPC, metastatic castration-resistant prostate cancer; PSA, prostate-specific antigen.