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Twenty-Ninth Annual
Prostate Cancer Foundation
SCIENTIFIC RETREAT

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TRITON3: A Phase 3 Study of Rucaparib vs Physician's Choice of Therapy in Metastatic Castration-Resistant Prostate Cancer Associated with Homologous Recombination Deficiency

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Disclosures

Company Name	*Honoraria/ expenses*	*Consulting/ advisory board*	*Funded research*	*Royalties/ patent*	*Stock options*	*Ownership/ equity position*	*Employee*	*Other (please specify)*
Clovis Oncology, Phosplatin Therapeutics								X (travel/accommodations/ expenses)
Advanced Accelerator Applications/Novartis, Astellas Pharma, AstraZeneca, Bayer, Castle Biosciences, Horizon CME, Myovant Sciences Pfizer, Research to Practice, Verity Pharmaceuticals	X							
Janssen			X					

Background

- The PARP inhibitor rucaparib received accelerated approval in the US for the treatment of mCRPC associated with a deleterious *BRCA1/2* (BRCA) mutation in patients previously treated with a second-generation API and taxane-based chemotherapy, based on data from the open-label, phase 2 TRITON2 study[1,2]
  - In TRITON2, patients with mCRPC and a BRCA alteration treated with rucaparib had an IRR-assessed ORR of 43.5% and a PSA response rate of 54.8%[1]
  - Investigator-assessed radiographic and PSA responses were observed in a limited number of patients with an *ATM* alteration (2/19 [10.5%] and 2/49 [4.1%], respectively)[3]
- TRITON3 is the confirmatory study for this accelerated approval
- We present top-line efficacy and safety data from TRITON3

API, androgen pathway inhibitor; IRR, independent radiology review; mCRPC, metastatic castration-resistant prostrate cancer; ORR, objective response rate; PARP, poly(ADP-ribose) polymerase; PSA, prostate specific antigen; US, United States.

1. Abida et al. *J Clin Oncol*. 2020;38:3763-72. 2. Rubraca® (rucaparib) tablets [prescribing information]. Boulder, CO: Clovis Oncology, Inc.; 2022.
3. Abida W, et al. *Clin Cancer Res.* 2020;26:2487–96.

TRITON3 Study Design

TRITON3
TRIAL OF RUCAPARIB IN PROSTATE INDICATIONS

Key eligibility criteria

- Chemotherapy-naïve mCRPC
- BRCA or *ATM* alteration[a]
- 1 prior second-generation API in any setting[b]

Prior docetaxel or other taxane chemotherapy for castration-sensitive disease was permitted

Randomization 2:1

Stratification:

- ECOG PS 0 vs 1
- Hepatic metastases yes vs no
- *BRCA1* vs *BRCA2* vs *ATM*

Rucaparib
600 mg BID

Physician's choice of[c]:

Docetaxel
75 mg/m^2 Q21D; 10 cycles max

or

Abiraterone acetate
1000 mg QD

or

Enzalutamide
160 mg QD

Endpoints[d]

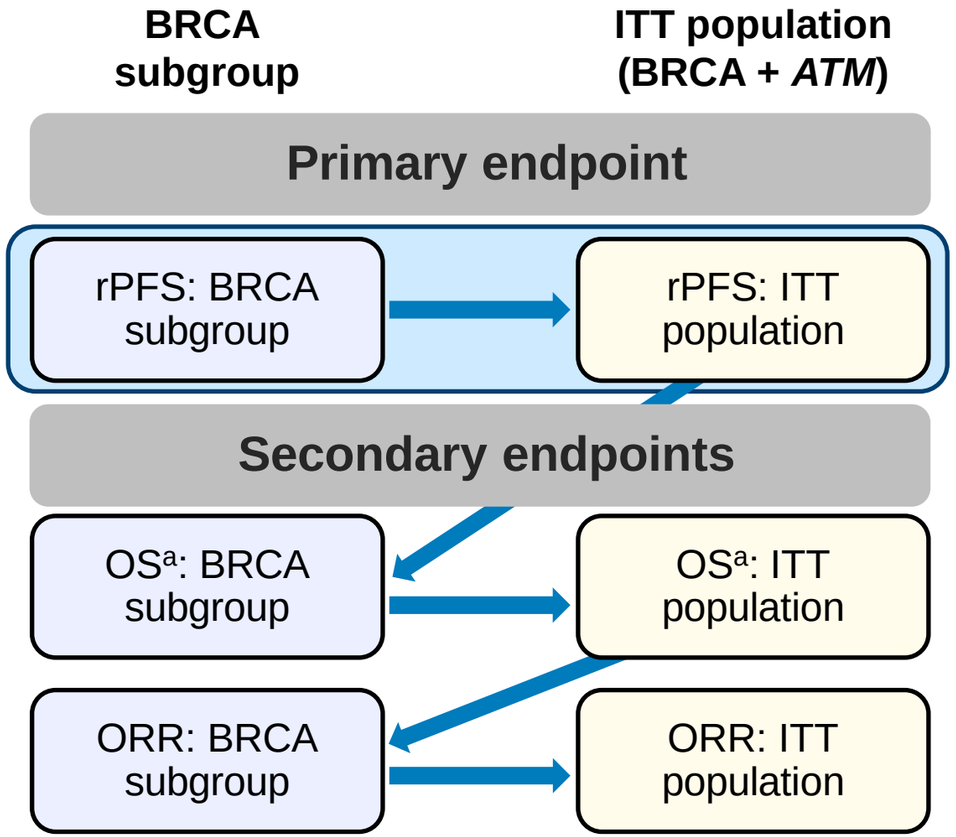
Primary:
- rPFS by IRR

Key secondary:
- OS
- ORR by IRR

Patients who progress on physician's choice of treatment may be considered for crossover to rucaparib

Visit cutoff date: 25 August 2022. [a]Determined by Foundation Medicine testing of tissue or plasma. [b]Protocol amendment June 19, 2018: patients' qualifying second-generation API could be in any setting. [c]If chosen, patients received whichever second-generation API had not yet been received. [d]Tumor assessments were conducted at baseline and every 8 weeks for 24 weeks, then every 12 weeks, via CT/MRI and technetium-bone scans. API, androgen pathway inhibitor; BID, twice daily; BRCA, *BRCA1* and *BRCA2*; CT, computed tomography; ECOG PS, Eastern Cooperative Oncology Group performance status; IRR, independent radiology review; mCRPC, metastatic castration-resistant prostrate cancer; MRI, magnetic resonance imaging; ORR, objective response rate; OS, overall survival; Q21D, every 21 days; QD, daily; rPFS, radiographic progression-free survival.

TRITON3 Ordered Step-Down Analysis



Sample size assumptions for rPFS (primary endpoint)

	Sample size	HR
BRCA	≈300 patients	0.60
ITT	≈400 patients (*ATM* ≈100 patients[b])	0.67

- The primary endpoint was first tested in the BRCA population and then, if statistically significant, in the ITT population
  - Analysis for secondary endpoints continued in the same manner

[a]Following a protocol amendment on 18 February 2022, OS was elevated to be the first secondary endpoint in the step-down analysis procedure.
[b]Enrollment capped at 100 patients. BRCA, *BRCA1* and *BRCA2*; HR, hazard ratio; ITT, intent-to-treat; ORR, objective response rate; OS, overall survival; rPFS, radiographic progression-free survival.

Baseline Characteristics (ITT Population)

	Rucaparib (n=270)	Physician's choice (n=135)
Median age, years (range)	70.0 (45–90)	71.0 (47–92)
Race, n (%)		
White	199 (73.7)	103 (76.3)
Black or African American	10 (3.7)	4 (3.0)
Asian	4 (1.5)	1 (0.7)
Other	4 (1.5)	0
Missing[a]	53 (19.6)	27 (20.0)
ECOG PS,[b] n (%)		
0	132 (48.9)	68 (50.4)
1	138 (51.1)	67 (49.6)
Alteration,[b] n (%)		
BRCA1	29 (10.7)	15 (11.1)
BRCA2	172 (63.7)	86 (63.7)
ATM	69 (25.6)	34 (25.2)

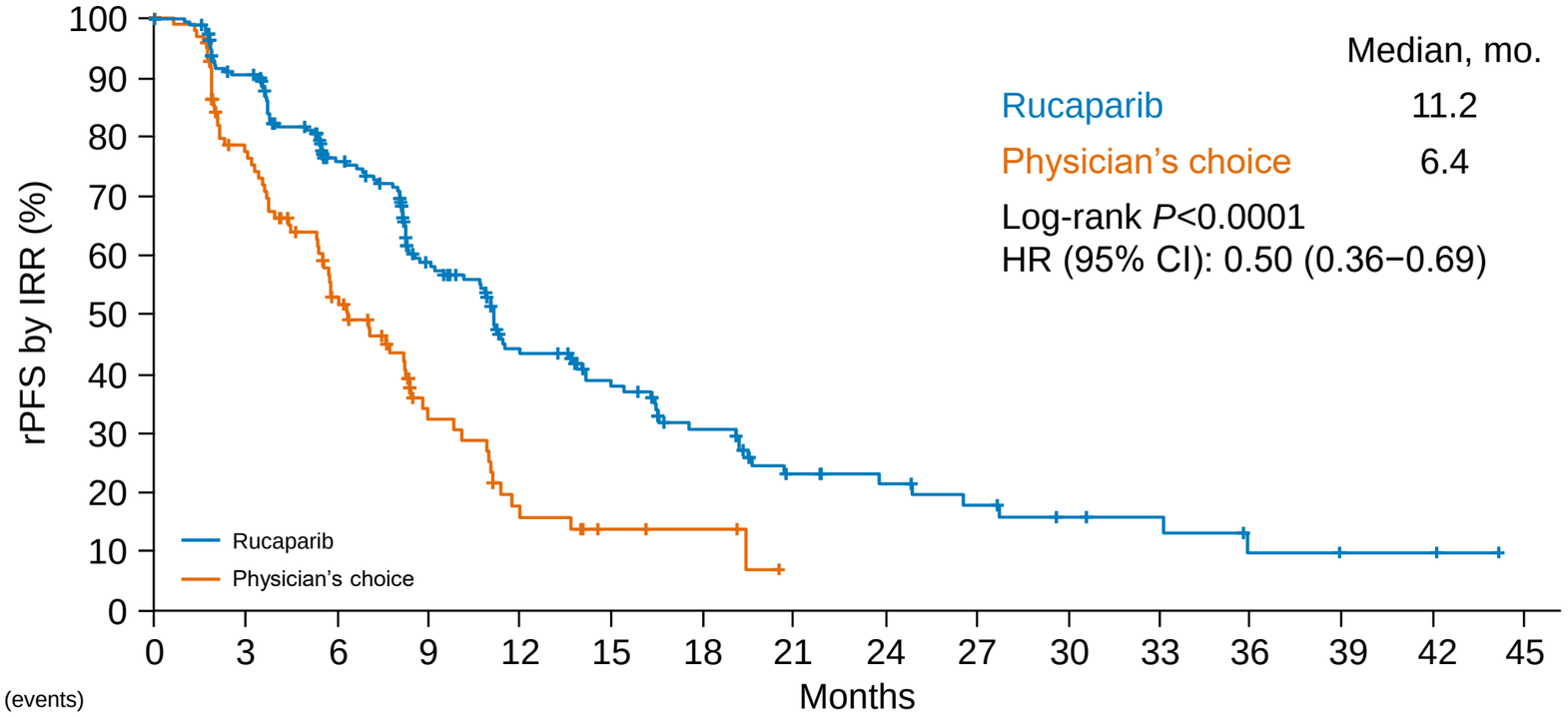
[a]Data may be missing due to region-specific privacy laws. [b]Randomization stratification factor.
ECOG PS, Eastern Cooperative Oncology Group performance status; ITT, intent-to-treat.

Baseline Characteristics (ITT Population), Cont.

	Rucaparib (n=270)	Physician's choice (n=135)
Baseline PSA, ng/mL, median (range)	26.9 (0.1–1247.0)	28.8 (0–1039.0)
Gleason score ≥8 at diagnosis, n (%)	173 (64.1)	96 (71.1)
Measurable disease per IRR, n (%)	106 (39.3)	55 (40.7)
Prior anticancer therapies, n (%)		
Second-generation API		
Enzalutamide	119 (44.1)	61 (45.2)
Abiraterone acetate	150 (55.6)	80 (59.3)
Apalutamide	8 (3.0)	1 (0.7)
Docetaxel for HSPC	63 (23.3)	28 (20.7)
Prior CRPC therapies, n (%)		
0	48 (17.8)	26 (19.3)
≥1	222 (82.2)	109 (80.7)
Physician's choice of treatment		
Docetaxel	–	75 (55.6)
Abiraterone acetate	–	28 (20.7)
Enzalutamide	–	32 (23.7)

API, androgen pathway inhibitor; CRPC, castration-resistant prostate cancer; HSPC, hormone-sensitive prostate cancer; ITT, intent-to-treat; IRR, independent radiology review; PSA, prostate specific antigen.

rPFS by IRR in the BRCA Subgroup



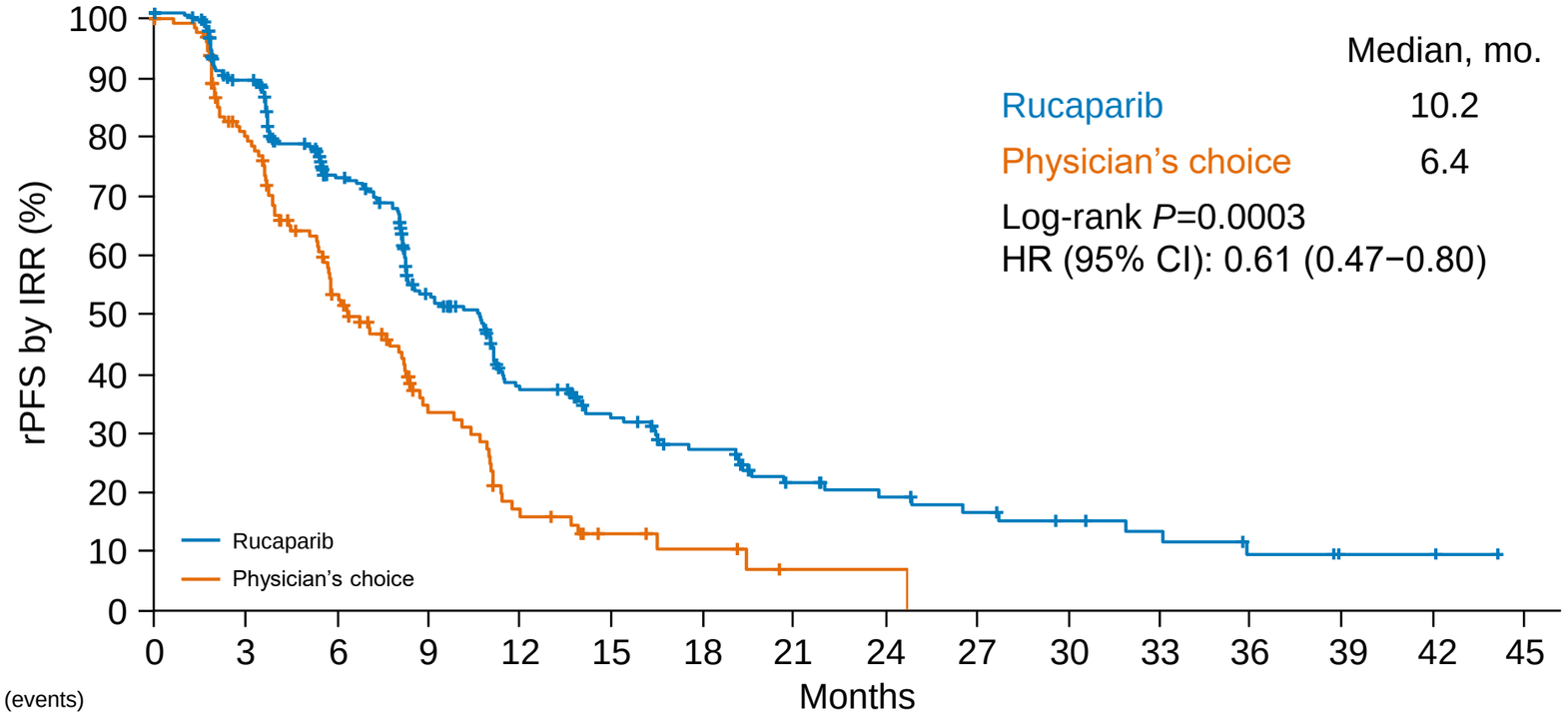
	Median, mo.	95% CI
Rucaparib	11.2	9.2–13.8
Physician's choice	6.4	5.4–8.3

Log-rank *P*<0.0001
HR (95% CI): 0.50 (0.36−0.69)

Patients at risk (events)																
Rucaparib	201 (0)	169 (18)	124 (44)	83 (70)	55 (89)	41 (95)	27 (103)	16 (109)	13 (110)	10 (112)	7 (113)	6 (113)	3 (115)	2 (115)	2 (115)	0 (115)
Physician's choice	101 (0)	69 (21)	42 (42)	19 (55)	9 (64)	4 (66)	3 (66)	0 (67)								

Data maturity: 60% (182/302).
BRCA, *BRCA1* and *BRCA2*; HR, hazard ratio; IRR, independent radiology review; rPFS, radiographic progression-free survival.

rPFS by IRR in the ITT Population



	Median, mo.	95% CI
Rucaparib	10.2	8.3–11.2
Physician's choice	6.4	5.6–8.2

Log-rank *P*=0.0003
HR (95% CI): 0.61 (0.47−0.80)

Patients at risk (events)																
Rucaparib	270 (0)	220 (29)	155 (68)	99 (108)	61 (135)	46 (142)	31 (150)	19 (156)	15 (158)	12 (160)	9 (161)	7 (162)	4 (164)	2 (164)	2 (164)	0 (164)
Physician's choice	135 (0)	97 (25)	58 (56)	28 (74)	13 (88)	6 (91)	4 (92)	1 (93)	1 (93)	0 (94)						

Data maturity: 64% (258/405). The *ATM* subgroup completed enrollment in December 2019.
HR, hazard ratio; IRR, independent radiology review; ITT, intent-to-treat; rPFS, radiographic progression-free survival.

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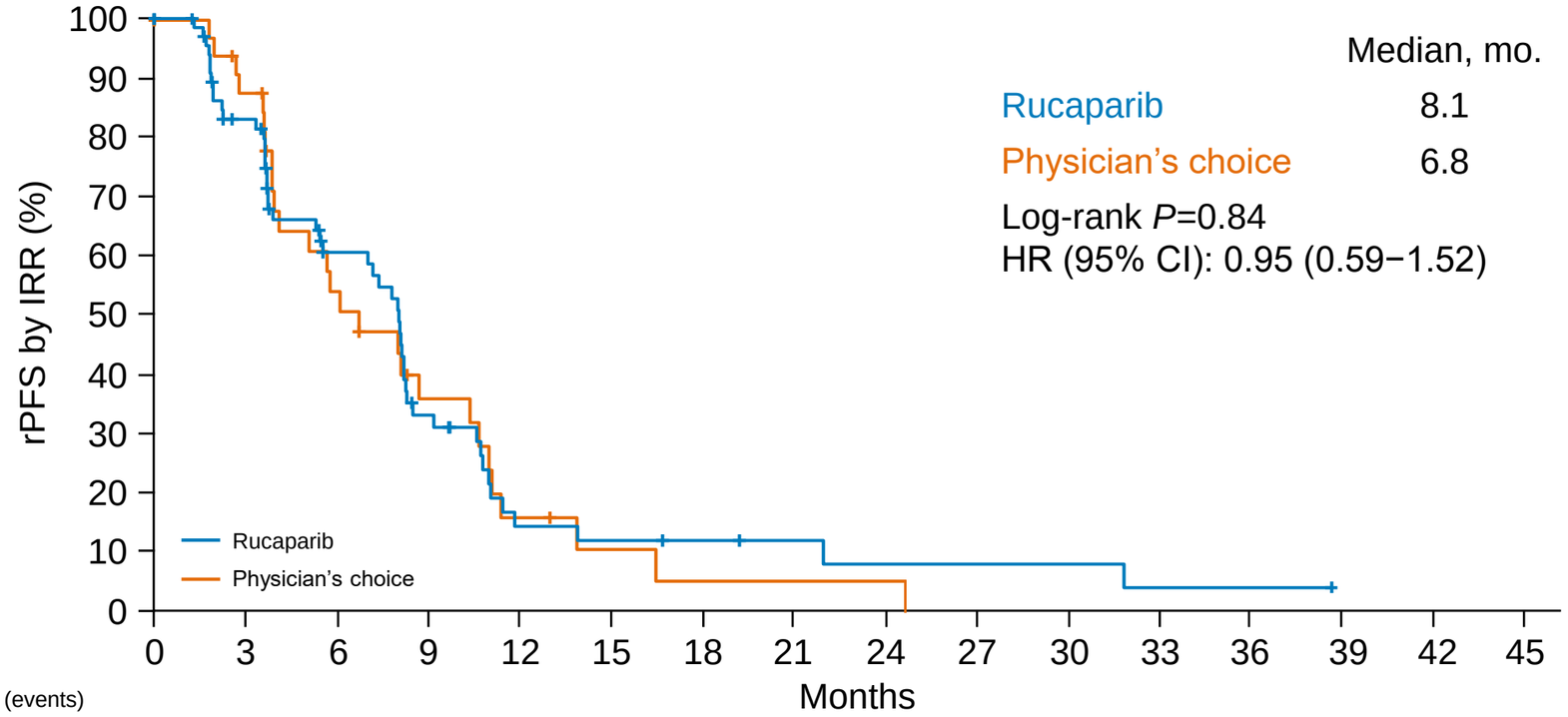
rPFS by IRR in the *ATM* Subgroup



	Median, mo.	95% CI
Rucaparib	8.1	5.5–8.3
Physician's choice	6.8	4.0–10.4

Log-rank *P*=0.84
HR (95% CI): 0.95 (0.59−1.52)

Patients at risk (events)														
Rucaparib	69 (0)	51 (11)	31 (24)	16 (38)	6 (46)	5 (47)	4 (47)	3 (47)	2 (48)	2 (48)	2 (48)	1 (49)	1 (49)	0 (49)
Physician's choice	34 (0)	28 (4)	16 (14)	9 (19)	4 (24)	2 (25)	1 (26)	1 (26)	1 (26)	0 (27)				

Exploratory subgroup analysis.
Data maturity: 74% (76/103). The *ATM* subgroup completed enrollment in December 2019.
HR, hazard ratio; IRR, independent radiology review; rPFS, radiographic progression-free survival.

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Safety Summary

TEAE, n (%)	Rucaparib (n=270)[a]	Physician's choice (n=130)[a]
At least 1 any-grade TEAE	270 (100)	129 (99.2)
At least 1 grade ≥3 TEAE	161 (59.6)	69 (53.1)
Dose reductions/interruptions due to TEAEs	160 (59.3)	50 (38.5)
Dose reductions due to TEAEs	104 (38.5)	32 (24.6)
Dose interruptions due to TEAEs	142 (52.6)	31 (23.8)
Discontinuations due to TEAEs	40 (14.8)	28 (21.5)
Death due to TEAEs	5 (1.9)	3 (2.3)

- At visit cutoff, 33 (12.2%) patients were ongoing on rucaparib treatment vs 5 (3.7%) on physician's choice
- The median treatment duration was 8.3 months (range, 0.2–46.0) for the rucaparib group and 5.1 months (range, 0.3–30.4) for the physician's choice group
- There were no reported cases of MDS and/or AML

[a]Safety population (all patients who received ≥1 dose of protocol-specified treatment).
AML, acute myeloid leukemia; MDS, myelodysplastic syndrome; TEAE, treatment-emergent adverse event.

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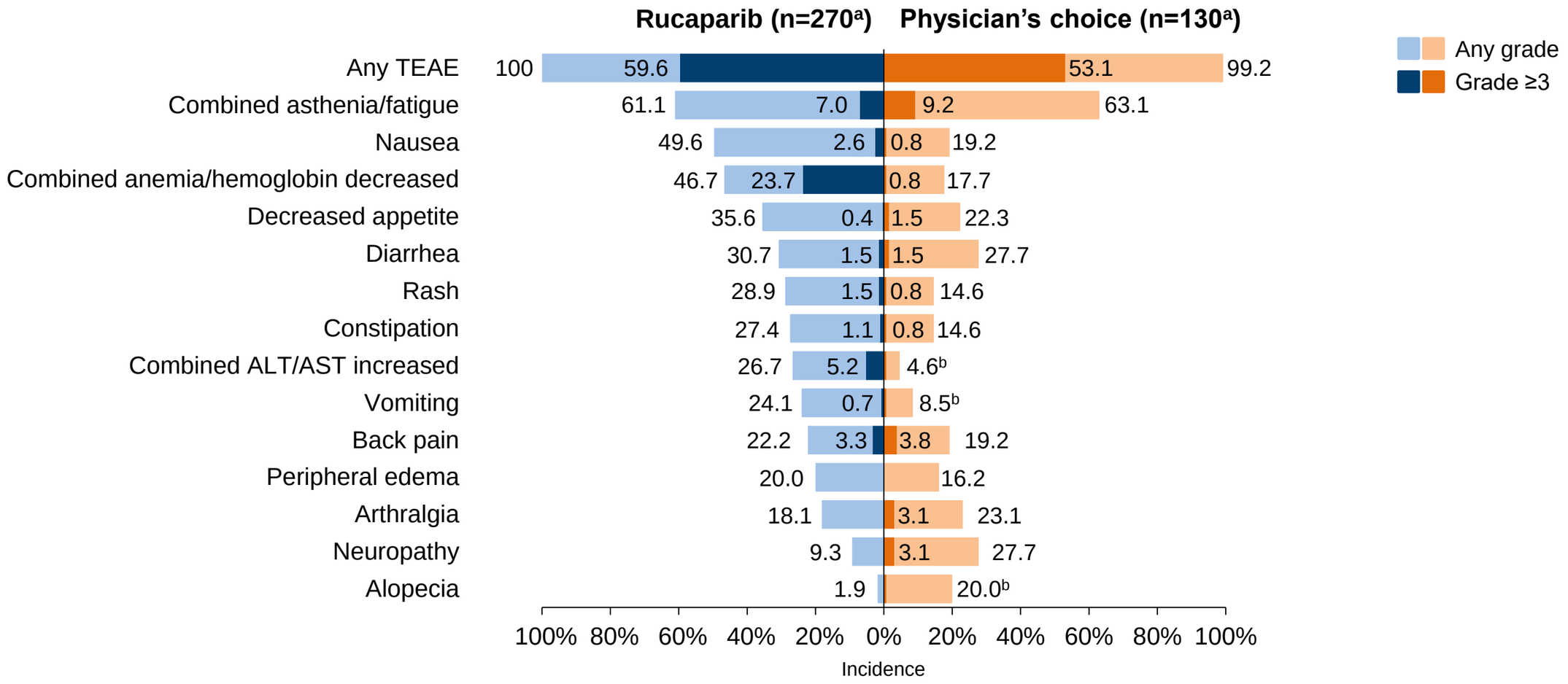
Most Common TEAEs (≥20% Any Grade)



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[a]Safety population (all patients who received ≥1 dose of protocol-specified treatment). [b]Grade ≥3, 0.8%.
Neuropathy includes neurotoxicity, paraesthesia, peripheral motor neuropathy, peripheral neuropathy, peripheral sensory neuropathy, and polyneuropathy.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; TEAE, treatment-emergent adverse event.

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Summary

- TRITON3 met its primary endpoint
  - Significant improvement in rPFS with rucaparib vs physician's choice of docetaxel or second-generation API in the BRCA subgroup and ITT population
- TRITON3 confirmed the efficacy and safety results from TRITON2[1]
- Full details of secondary endpoints – including OS, and efficacy and safety of rucaparib compared individually with either docetaxel or second-generation API – will be presented at a future meeting

API, androgen pathway inhibitor; BRCA, *BRCA1* and *BRCA2*; ITT, intent-to-treat; OS, overall survival; rPFS, radiographic progression-free survival.

1. Abida et al. *J Clin Oncol.* 2020;38:3763-72.

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TRITON3: Additional Perspective

- TRITON3 had a rigorous and patient-centric design:
  - First clinical study to compare a PARP inhibitor with docetaxel as one of the standards of care
  - First clinical study in mCRPC to demonstrate superiority to a docetaxel-containing control arm
  - Crossover from physician's choice of treatment to rucaparib was allowed in patients with confirmed radiographic progression

mCRPC, metastatic castration-resistant prostrate cancer; PARP, poly(ADP-ribose) polymerase.

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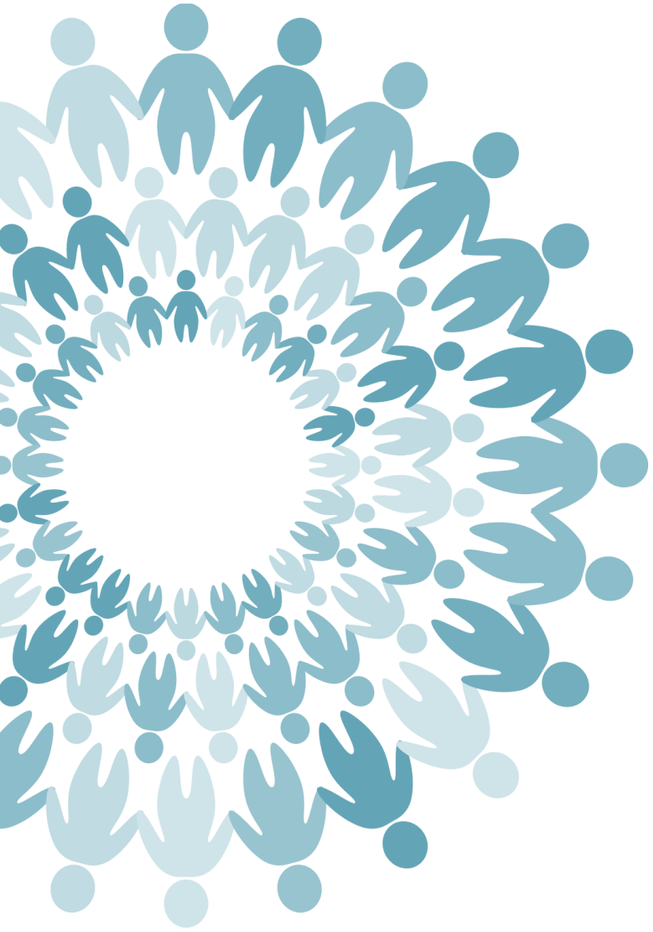
Thank you



We thank all the
PATIENTS, **FAMILIES**, **CAREGIVERS**
and **MANY MORE**
involved in the TRITON3 study

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TRITON3 Acknowledgments

Co-coordinating investigators: Alan Bryce, USA
Karim Fizazi, France

Past co-coordinating investigators: Charles Ryan, USA
Simon Chowdhury, UK

Australia
Patricia Bastick
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David Campbell
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Celestia Higano
Arif Hussain
John Keech
Mark Klein
Samith Kochuparambil
Alan Koletsky
Vadim Koshkin
Daniel Landau
Wes Lee
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David Lipsitz
Jamal Misleh
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Nicholas Vogelzang
Sunny Wang
Young Whang
Eddy Yang

We thank PCF for the opportunity to present these data, the TRITON3 principal investigators and steering committee, and Melanie Dowson and Owen Bowles (Clovis Oncology) for Clinical Operations support.

This research was sponsored by Clovis Oncology, Inc. Medical writing and editorial support funded by Clovis Oncology, Inc., were provided by Sachi Yim and Kathleen Blake of Ashfield MedComms, an Inizio company.