Prostate Cancer Updates

Neeraj Agarwal, MD

Professor of Medicine
Senior Director for Clinical Research Innovation, Huntsman Cancer Institute (HCI)
HCI Presidential Endowed Chair of Cancer Research
Director, Center of Investigational Therapeutics
Director, Genitourinary Oncology Program
Huntsman Cancer Institute, University of Utah (NCI-CCC)

ASCO Genitourinary Cancers Symposium

Efficacy and Safety of Darolutamide in Combination With Androgen-Deprivation Therapy and Docetaxel by Disease Volume and Risk in the Phase 3 ARASENS Study

Maha Hussain, MD, FACP, FASCO,[1] Bertrand Tombal, MD, PhD,[2] Fred Saad, MD,[3] Karim Fizazi, MD, PhD,[4] Cora N. Sternberg, MD,[5] E. David Crawford, MD,[6] Neal Shore, MD,[7] Evgeny Kopyltsov, MD,[8] Arash Rezazadeh Kalebasty, MD,[9] Martin Bögemann, MD,[10] Dingwei Ye, MD,[11] Felipe Cruz, MD,[12] Hiroyoshi Suzuki, MD, PhD,[13] Shivani Kapur, MD,[14] Shankar Srinivasan, PhD,[15] Frank Verholen, MD,[16] Iris Kuss, MD,[17] Heikki Joensuu, MD,[18] Matthew R. Smith, MD, PhD[19]

[1]Northwestern University, Feinberg School of Medicine, Chicago, IL; [2]Division of Urology, IREC, Cliniques Universitaires Saint Luc, UCLouvain, Brussels, Belgium; [3]University of Montreal Hospital Center, Montreal, Quebec, Canada; [4]Institut Gustave Roussy, University of Paris-Saclay, Villejuif, France; [5]Englander Institute for Precision Medicine, Weill Cornell Department of Medicine, Meyer Cancer Center, New York-Presbyterian Hospital, New York, NY; [6]UC San Diego School of Medicine, San Diego, CA; [7]Carolina Urologic Research Center/Genesis Care, Myrtle Beach, SC; [8]Clinical Oncological Dispensary of Omsk Region, Omsk, Russian Federation; [9]University of California Irvine, Division of Hematology/Oncology, Orange, CA; [10]Department of Urology, Münster University Medical Center, Münster, Germany; [11]Fudan University Shanghai Cancer Center, Xuhui District, Shanghai, China; [12]Núcleo de Pesquisa e Ensino da Rede São Camilo, São Paulo, Brazil; [13]Toho University Sakura Medical Center, Chiba, Japan; [14]Bayer SEA, Singapore; [15]Bayer HealthCare Pharmaceuticals Inc., Whippany, NJ; [16]Bayer Consumer Care AG, Basel, Switzerland; [17]Bayer AG, Berlin, Germany; [18]Orion Corporation, Espoo, Finland; [19]Massachusetts General Hospital Cancer Center, Boston, MA

ASCO Genitourinary Cancers Symposium

#GU23

PRESENTED BY: Maha Hussain, MD, FACP, FASCO

ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY
KNOWLEDGE CONQUERS CANCER

Introduction

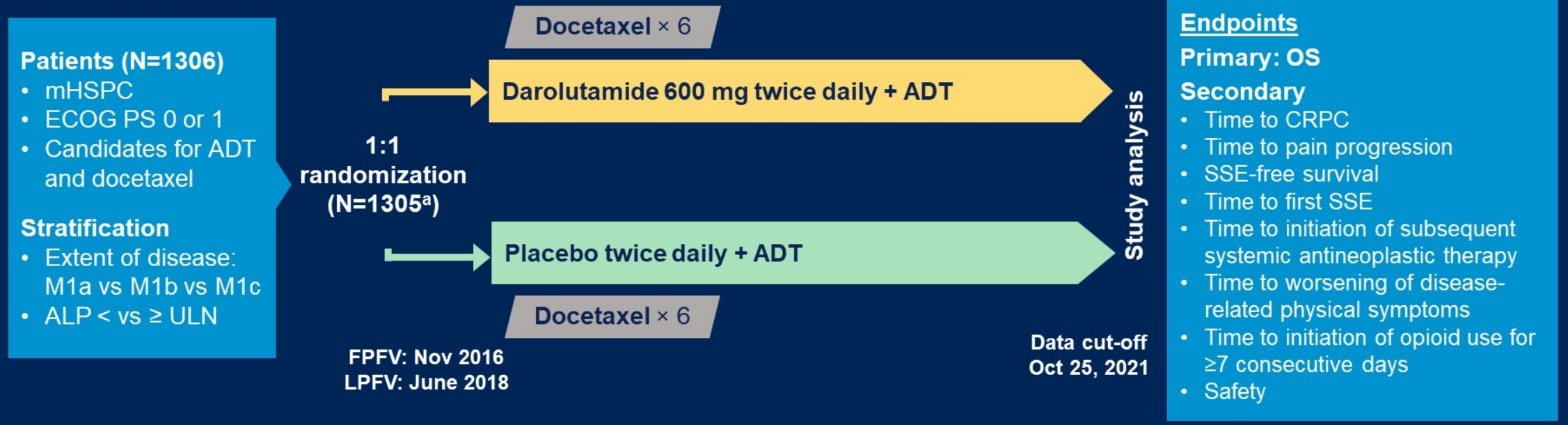
- In ARASENS, darolutamide + androgen-deprivation therapy (ADT) + docetaxel significantly improved survival (HR 0.68; 95% CI: 0.57–0.80; *P*<0.0001) vs ADT + docetaxel + placebo in patients with metastatic hormone-sensitive prostate cancer (mHSPC)[1]
  - The incidence of treatment-emergent adverse events (TEAEs) was similar between groups
- In patients with mHSPC, metastatic disease burden is a prognostic factor[2,3]
- Here we present a post hoc analysis of the ARASENS study reporting the impact of disease burden and risk on efficacy and safety outcomes

HR, hazard ratio.

1. Smith MR, et al. *N Engl J Med*. 2022;386:1132-1142; 2. Sweeney CJ, et al. *N Engl J Med*. 2015; 373:737-746; 3. Fizazi K, et al. *N Engl J Med*. 2017;377:352-360.

ARASENS Study Design

Global, randomized, double-blind, placebo-controlled phase III study (NCT02799602)[1]



1. Smith MR, et al. *N Engl J Med*. 2022;386:1132-1142.
[a]One enrolled patient was excluded from all analysis sets because of Good Clinical Practice violations.
ALP, alkaline phosphatase; CRPC, castration-resistant prostate cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; FPFV, first patient first visit; LPFV, last patient first visit; M1a, nonregional lymph node metastases only; M1b, bone metastases ± lymph node metastases; M1c, visceral metastases ± lymph node or bone metastases; SSE, symptomatic skeletal event; ULN, upper limit of normal.

Definition of Disease Volume and Risk Subgroups

High-Volume Disease: CHAARTED Criteria[1]	High-Risk Disease: LATITUDE Criteria[2]
• Visceral metastases • ≥4 bone metastases with ≥1 beyond the vertebral column/pelvis[a]	• ≥2 risk factors: ▪ Gleason score ≥8 ▪ ≥3 bone metastases[a] ▪ Visceral metastases
Low-volume and low-risk disease were defined as not meeting the respective high-volume and high-risk criteria [a]Including those with diffusely increased skeletal metastases with superscan[3]	

- Of 1305 patients in the ARASENS full analysis set
  - **1005 (77%) had high-volume disease and 300 (23%) had low-volume disease**
  - **912 (70%) had high-risk disease and 393 (30%) had low-risk disease**

1. Sweeney CJ, et al. *N Engl J Med*. 2015; 373:737-746; 2. Fizazi K, et al. *N Engl J Med*. 2017;377:352-360; 3. Manohar PR, et al. *World J Nucl Med*. 2017;16:39-44.

ARASENS VOLUME Subgroups: Select Baseline Demographics and Disease Characteristics

Characteristic at Baseline	High Volume		Low Volume	
	Darolutamide (n=497)	Placebo (n=508)	Darolutamide (n=154)	Placebo (n=146)
Age, median (range), y	67.0 (41–89)	67.0 (44–86)	67.0 (41–84)	67.5 (42–81)
Gleason score at initial diagnosis ≥8, n (%)	381 (76.7)	403 (79.3)	124 (80.5)	113 (77.4)
Metastasis stage at initial diagnosis, n (%)[a]				
De novo	**432 (86.9)**	**445 (87.6)**	**126 (81.8)**	**121 (82.9)**
Recurrent	58 (11.7)	59 (11.6)	28 (18.2)	23 (15.8)
Metastasis stage at screening, n (%)				
M1a (nonregional LN only)	0	0	23 (14.9)	15 (10.3)
M1b (bone ± LN)	386 (77.7)	390 (76.8)[b]	131 (85.1)	131 (89.7)
M1c (visceral ± LN or bone)	111 (22.3)	118 (23.2)	0	0
Serum PSA, median (range), ng/mL[c]	38.7 (0–9219.0)	27.9 (0–11,947.0)	11.7 (0–3771.0)	14.5 (0–3372.9)

[a]Data on distant metastases were missing for 13 patients; [b]One patient had lymph node metastasis alone per direct entry in case report form but was categorized as M1b in the high-volume subgroup using detailed tumor data; [c]These values were centrally assessed. Samples were obtained while patients were receiving ADT. LN, lymph node; PSA, prostate-specific antigen.

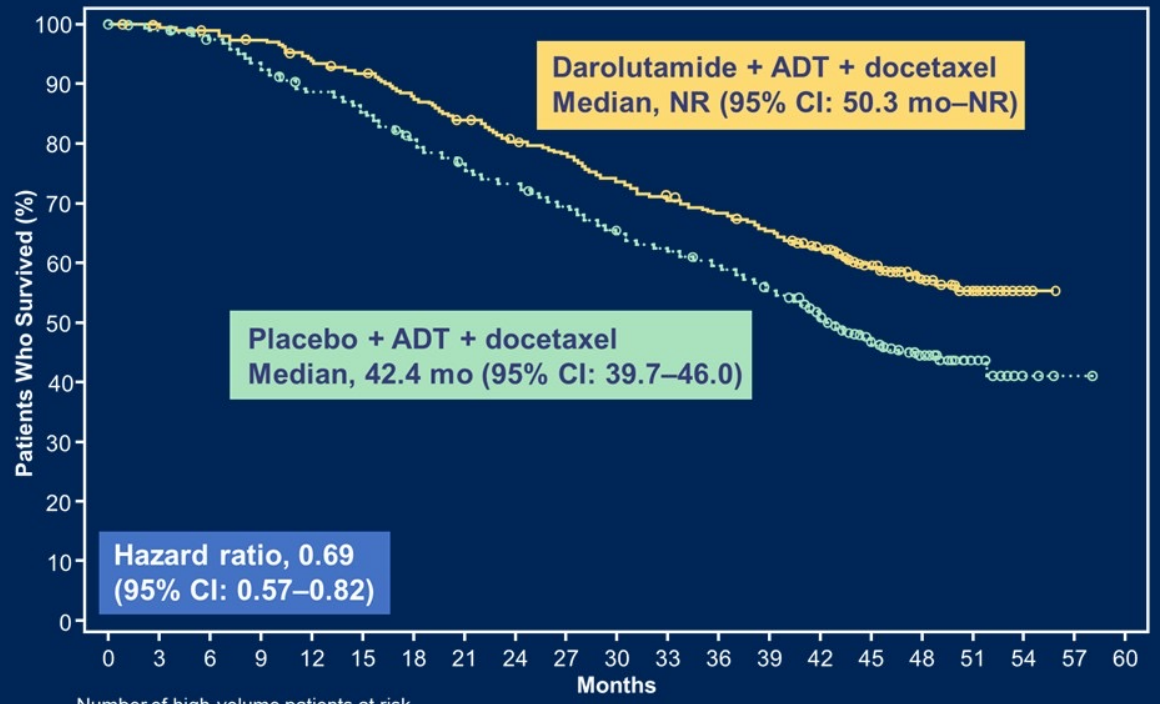
ARASENS RISK Subgroups: Select Baseline Demographics and Disease Characteristics

Characteristic at Baseline	High Risk		Low Risk	
	Darolutamide (n=452)	Placebo (n=460)	Darolutamide (n=199)	Placebo (n=194)
Age, median (range), y	67.0 (41–86)	67.0 (44–86)	67.0 (41–89)	67.0 (42–85)
Gleason score at initial diagnosis ≥8, n (%)	428 (94.7)	440 (95.7)	77 (38.7)	76 (39.2)
Metastasis stage at initial diagnosis, n (%)[a]				
De novo	**416 (92.0)**	**419 (91.1)**	**142 (71.4)**	**147 (75.8)**
Recurrent	33 (7.3)	39 (8.5)	53 (26.6)	43 (22.2)
Metastasis stage at screening, n (%)				
M1a (nonregional LN only)	0	0	23 (11.6)	15 (7.7)
M1b (bone ± LN)	345 (76.3)	354 (77.0)[b]	172 (86.4)	167 (86.1)
M1c (visceral ± LN or bone)	107 (23.7)	106 (23.0)	4 (2.0)	12 (6.2)
Serum PSA, median (range), ng/mL[c]	34.0 (0–9219.0)	30.0 (0–11,947.0)	19.2 (0–4173.0)	12.4 (0–3372.9)

[a]Data on distant metastases were missing for 13 patients; [b]One patient had lymph node metastasis alone per direct entry in case report form but was categorized as M1b in the high-risk subgroup using detailed tumor data; [c]These values were centrally assessed. Samples were obtained while patients were receiving ADT. LN, lymph node; PSA, prostate-specific antigen.

ARASENS VOLUME Subgroups: Overall Survival

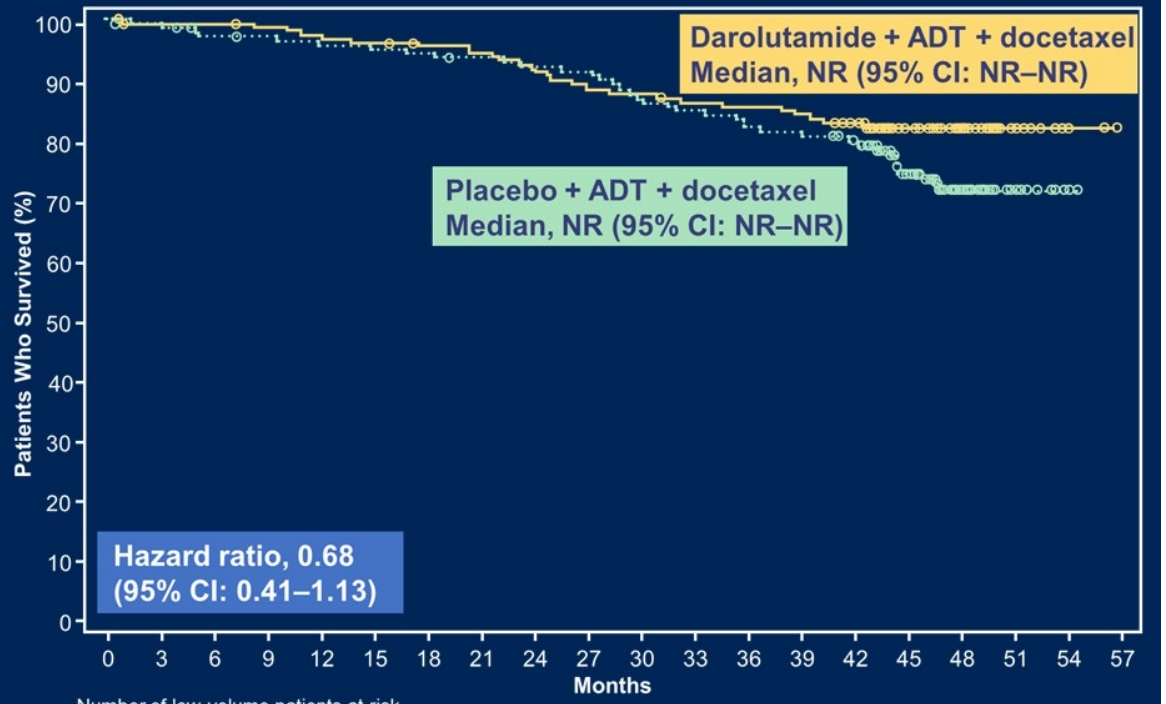
High-volume mHSPC



Number of high-volume patients at risk

Darolutamide	497	494	486	479	462	449	429	408	389	378	356	341	326	312	285	193	103	43	6	0	0
Placebo	508	502	491	469	444	430	401	378	358	341	319	304	286	269	233	153	72	23	4	1	0

Low-volume mHSPC



Number of low-volume patients at risk

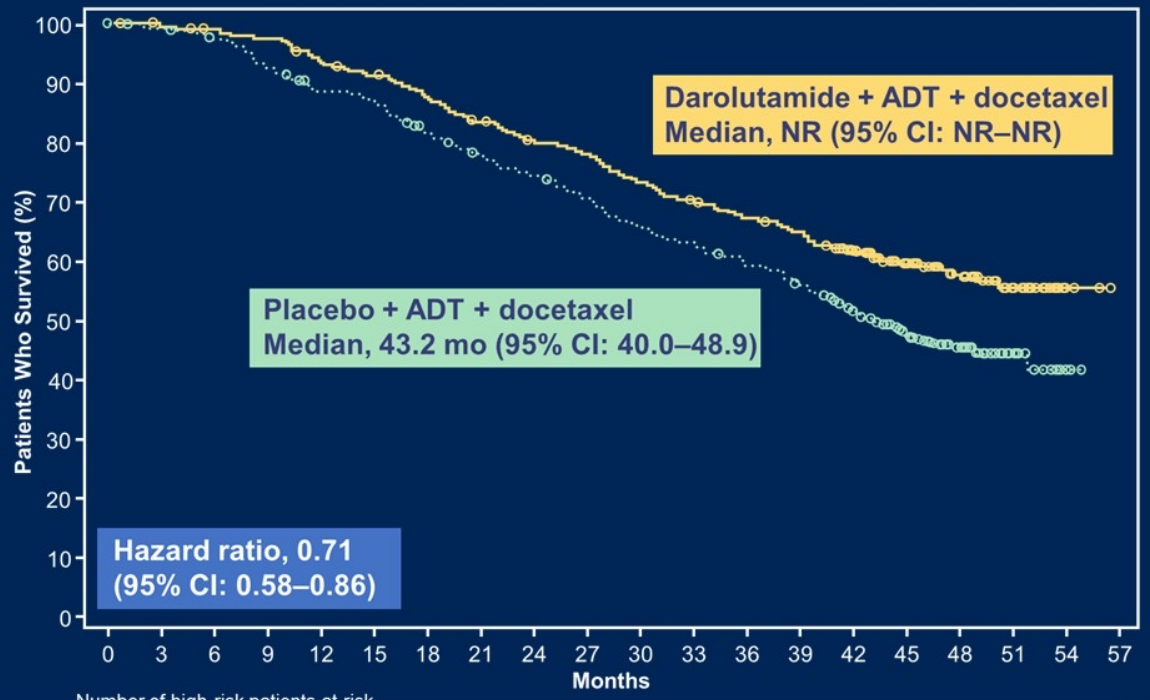
Darolutamide	154	151	151	148	146	144	141	140	136	131	130	127	126	124	117	74	36	13	3	0
Placebo	146	144	139	138	136	135	134	132	130	129	122	120	116	114	107	65	35	14	2	0

Analysis by unstratified Cox regression model. CI, confidence interval; NR, not reached.

PRESENTED BY: Maha Hussain, MD, FACP, FASCO

ARASENS RISK Subgroups: Overall Survival

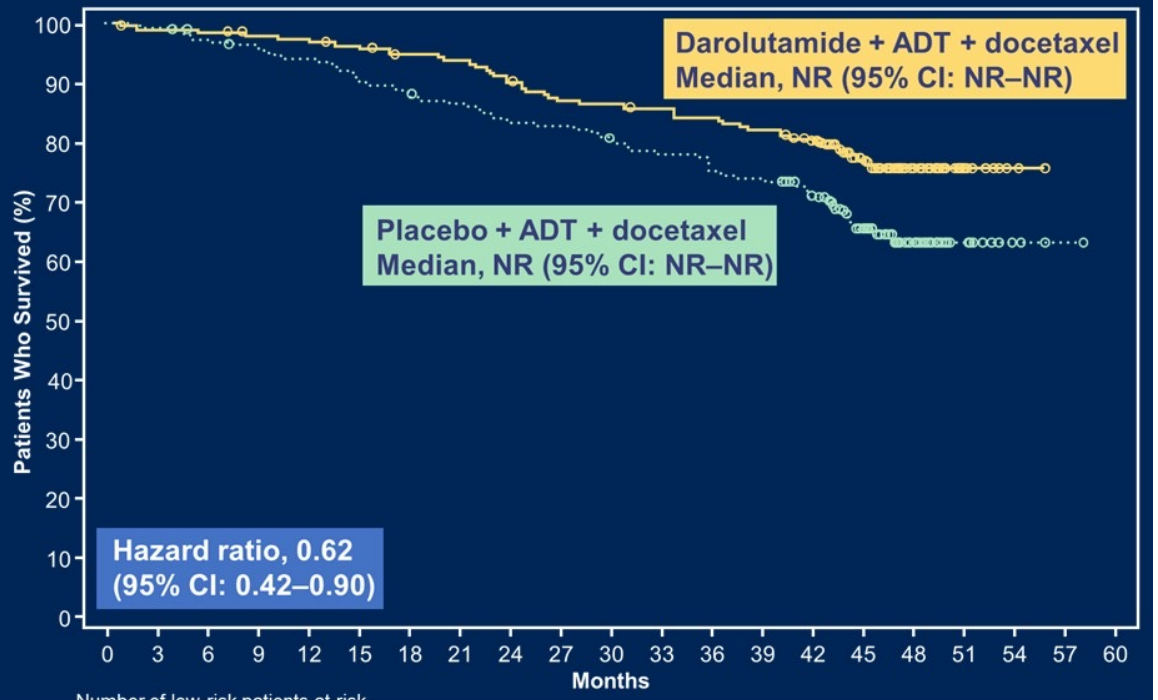
High-risk mHSPC



Number of high-risk patients at risk

Darolutamide	452	450	443	437	419	407	389	369	352	344	322	308	294	282	257	177	99	42	6	0
Placebo	460	453	443	423	400	392	367	346	330	313	290	277	261	245	215	148	72	24	3	0

Low-risk mHSPC

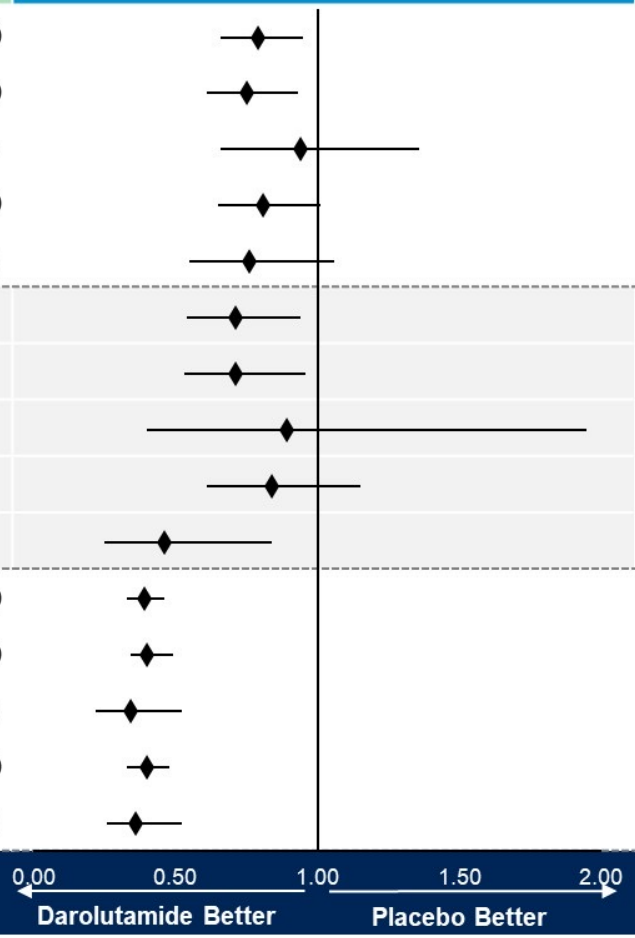


Number of low-risk patients at risk

Darolutamide	199	195	194	190	189	186	181	179	173	165	164	160	158	154	145	90	40	14	3	0	0
Placebo	194	193	187	184	180	173	168	164	158	157	151	147	141	138	125	70	35	13	3	1	0

ARASENS VOLUME and RISK Subgroups: Other Key Secondary Efficacy Endpoints

Secondary endpoint	Patient subgroups	Number of events/ Number of patients		Median (95% CI), months		HR (95% CI)[a]
		DARO	PBO	DARO	PBO	
Time to pain progression	All patients[b]	222/651	248/654	NE (30.5–NE)	27.5 (22.0–36.1)	0.79 (0.66–0.95)
	High volume	161/497	192/508	NE (26.7–NE)	24.4 (16.8–33.3)	0.75 (0.61–0.93)
	Low volume	61/154	56/146	46.1 (25.0–NE)	39.5 (24.6–NE)	0.94 (0.66–1.36)
	High risk	155/452	173/460	35.4 (25.0–NE)	25.0 (18.2–35.9)	0.81 (0.65–1.01)
	Low risk	67/199	75/194	NE (39.2–NE)	28.8 (19.3–NE)	0.76 (0.55–1.06)
Time to first symptomatic skeletal event	All patients[b]	95/651	108/654	NE (NE–NE)	NE (NE–NE)	0.71 (0.54–0.94)
	High volume	82/497	96/508	NE (NE–NE)	NE (NE–NE)	0.71 (0.53–0.96)
	Low volume	13/154	12/146	NE (NE–NE)	NE (NE–NE)	0.89 (0.40–1.95)
	High risk	78/452	79/460	NE (NE–NE)	NE (NE–NE)	0.84 (0.61–1.15)
	Low risk	17/199	29/194	NE (51.2–NE)	NE (NE–NE)	0.46 (0.25–0.84)
Time to initiation of subsequent systemic antineoplastic therapy	All patients[b]	219/651	395/654	NE (NE–NE)	25.3 (23.1–28.8)	0.39 (0.33–0.46)
	High volume	187/497	324/508	NE (49.6–NE)	22.7 (19.6–25.1)	0.40 (0.34–0.49)
	Low volume	32/154	71/146	NE (NE–NE)	42.5 (34.0–NE)	0.34 (0.22–0.52)
	High risk	173/452	299/460	NE (49.6–NE)	21.3 (19.2–24.0)	0.40 (0.33–0.48)
	Low risk	46/199	96/194	NE (NE–NE)	39.0 (31.8–NE)	0.36 (0.26–0.52)



[a]Based on unstratified Cox regression model.
[b]Includes all randomized patients according to planned treatment.

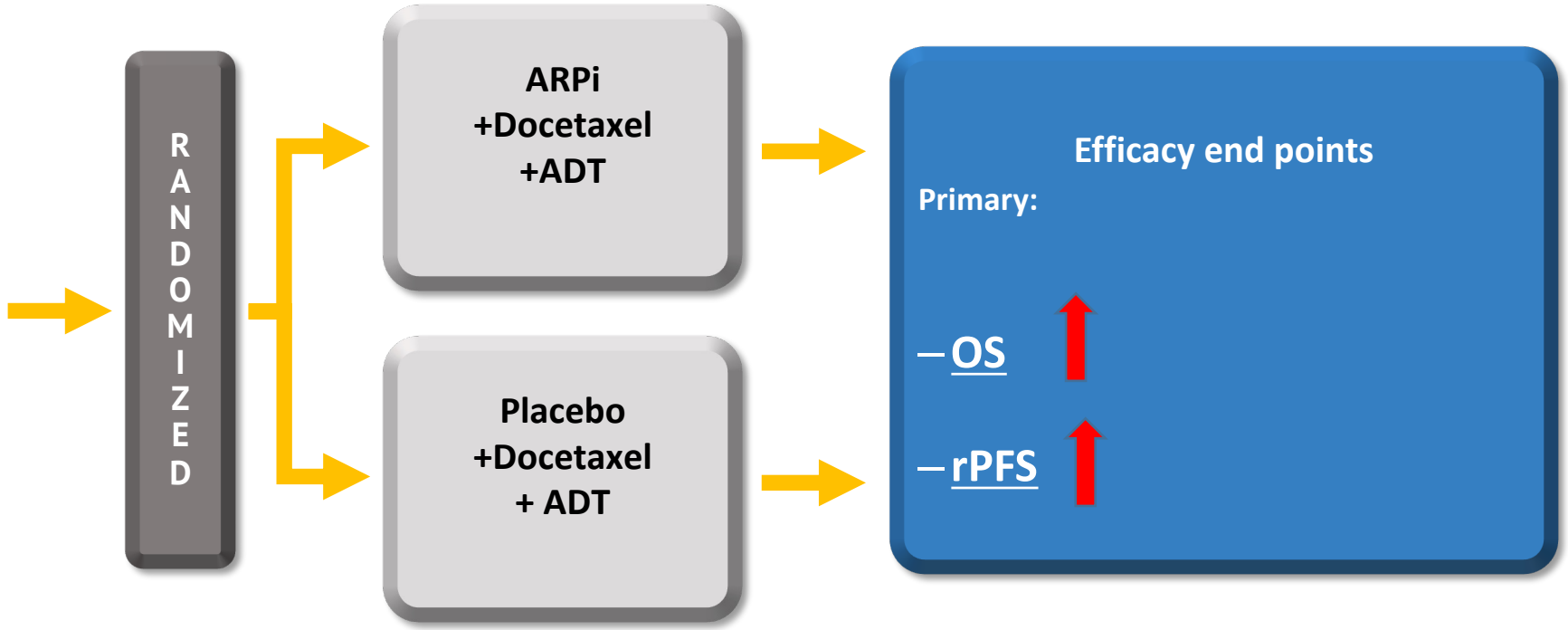
Phase III Trial: Triplets (ARPi+ Docetaxel + ADT) vs. Docetaxel + ADT

Key Eligibility Criteria
Castration sensitive
Distant metastatic disease by ≥ 1 lesion on bone scan
ECOG PS 0 or 1

On-Study Requirement
Continuous ADT

Permitted
ADT ≤ 6 mo for mCSPC or ≤ 3 yr for local disease
Local treatment completed ≥ 1 yr prior

Stratification
Gleason score at diagnosis (≤ 7 vs ≥ 8)
Volume of disease
Region (NA and EU vs all other countries)



ECOG PS, Eastern Cooperative Oncology Group performance status; ARPi, Androgen receptor pathway inhibitor; NA, North America; PSA, prostate-specific antigen; OS, Overall survival; rPFS, radiographic progression-free survival.

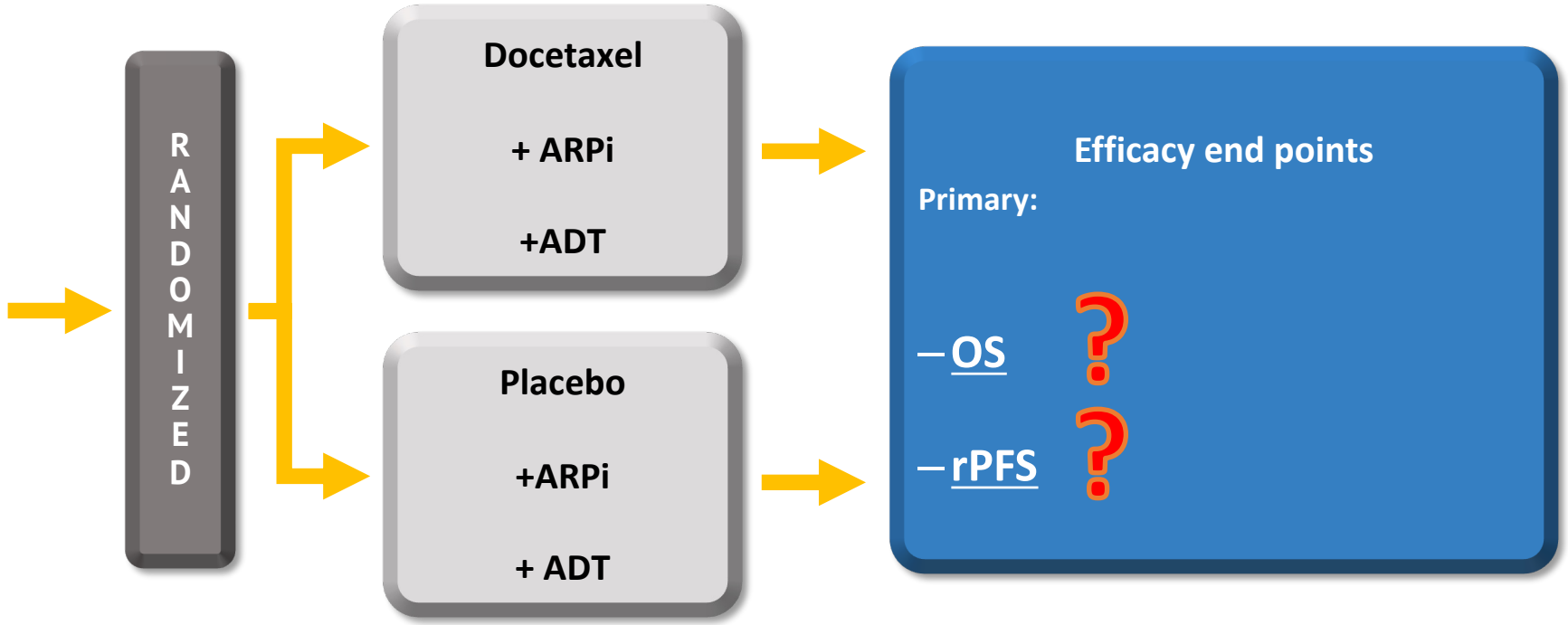
Need this trial:
Triplet (Docetaxel + ARPi + ADT) versus ARPi + ADT

Key Eligibility Criteria
Castration sensitive
Distant metastatic disease by ≥ 1 lesion on bone scan
ECOG PS 0 or 1

On-Study Requirement
Continuous ADT

Permitted
ADT ≤ 6 mo for mCSPC or ≤ 3 yr for local disease
Local treatment completed ≥ 1 yr prior

Stratification
Gleason score at diagnosis (≤ 7 vs ≥ 8)
Volume of disease
Region (NA and EU vs all other countries)



ECOG PS, Eastern Cooperative Oncology Group performance status; ARPi, Androgen receptor pathway inhibitor; NA, North America; PSA, prostate-specific antigen; OS, Overall survival; rPFS, radiographic progression-free survival.

Trials of Doublet Therapy in mHSPC

Trial	Experimental arm	Control arm	Number of enrolled patients (experimental vs control)	Population characteristics	Median follow-up (mo)	OS		
						Experimental	Control	HR, 95% CI; P
LATITUDE	Abiraterone + prednisone + ADT	ADT + placebo	1,199 (597 vs 602)	Newly diagnosed mCSPC ≥ 2 of following high-risk factors: Gleason score ≥ 8, ≥ 3 bone lesions, and measurable visceral metastasis	51.8	53.3 mo	36.5 mo	0.66 [0.56, 0.78]; P < .0001
STAMPED	Abiraterone + prednisolone + ADT	ADT	1,917 (960 vs 957)	Newly diagnosed metastatic, node-positive, or high-risk locally advanced (N0M0, ≥ 2 of following: T3 or T4, Gleason score ≥ 8, and PSA ≥ 40 ng/ml), or recurrent disease after local therapy with high-risk features or metastasis	40.0	—	—	0.61 [0.49, 0.75]; P < .001
TITAN	Apalutamide + ADT	ADT + placebo	1,052 (525 vs 527)	Prior docetaxel or ADT were allowed	44.0	NR	52.2 mo	0.65 [0.53, 0.79]; P < .0001
ENZAMET	Enzalutamide + testosterone suppression	Testosterone suppression + standard nonsteroidal antiandrogen therapy	1,125 (563 vs 562)	Testosterone suppression initiated up to 12 weeks before randomization; administration of docetaxel was allowed	68.0	OS at 5 years: 67%	OS at 5 years: 57%	0.7 [0.58, 0.84]; P < .0001
ARCHES	Enzalutamide + ADT	ADT + placebo	1,150 (574 vs 576)	Prior docetaxel or ADT were allowed	44.6	NR	NR	0.66 [0.53, 0.81]; P < .001

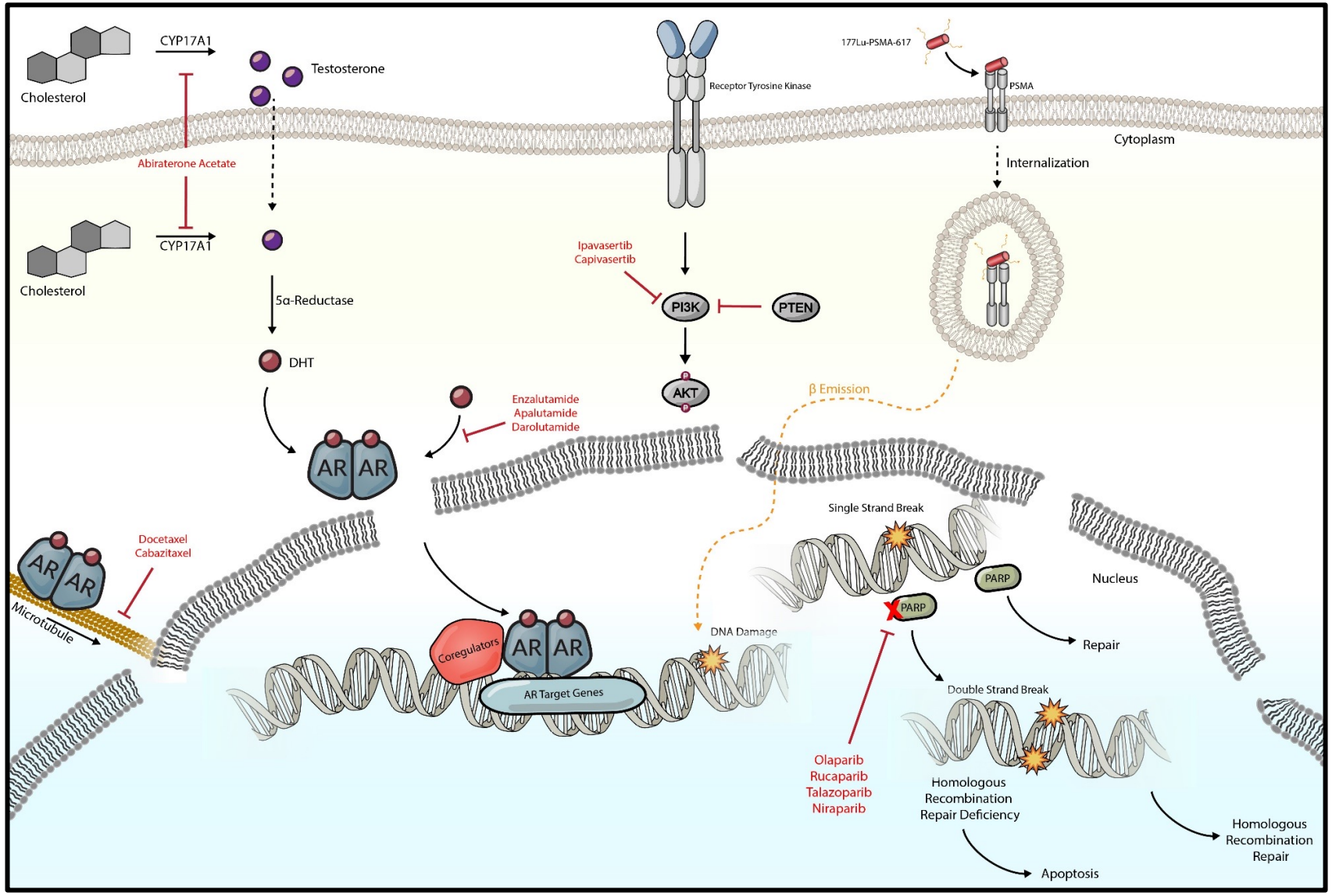
Trials of Triplet Therapy in mHSPC

Trial	Experimental arm	Control arm	Number of enrolled patients (experimental vs control)	Population characteristics	Median follow-up (mo)	OS		
						Experimental	Control	HR, 95% CI; P value
ARASENS	Darolutamide + docetaxel + ADT	ADT + docetaxel	1,306 (651 vs 655)	Synchronous disease: 86% High-volume disease: 77%	43.7	NR	48.9	0.68 [0.57, 0.8]; P < .001
						High-volume disease OS HR: 0.69 (0.57, 0.82)		
						Low-volume disease OS HR: 0.68 (0.41, 1.13)		
						Synchronous disease OS HR: 0.71 (0.59, 0.85)		
						Metachronous disease OS HR: 0.61 (0.35, 1.05)		
PEACE-1	Abiraterone + prednisone + docetaxel + ADT	ADT + docetaxel	710 (355 vs 355)	Only patients with synchronous disease were included; high-volume disease: 64%	45.6	NR	52.8	0.75 [0.59, 0.95]; P = .017
						High-volume disease OS HR: 0.72 [0.55, 0.95]		
						Low-volume disease OS HR: 0.83 [0.5, 1.39]		

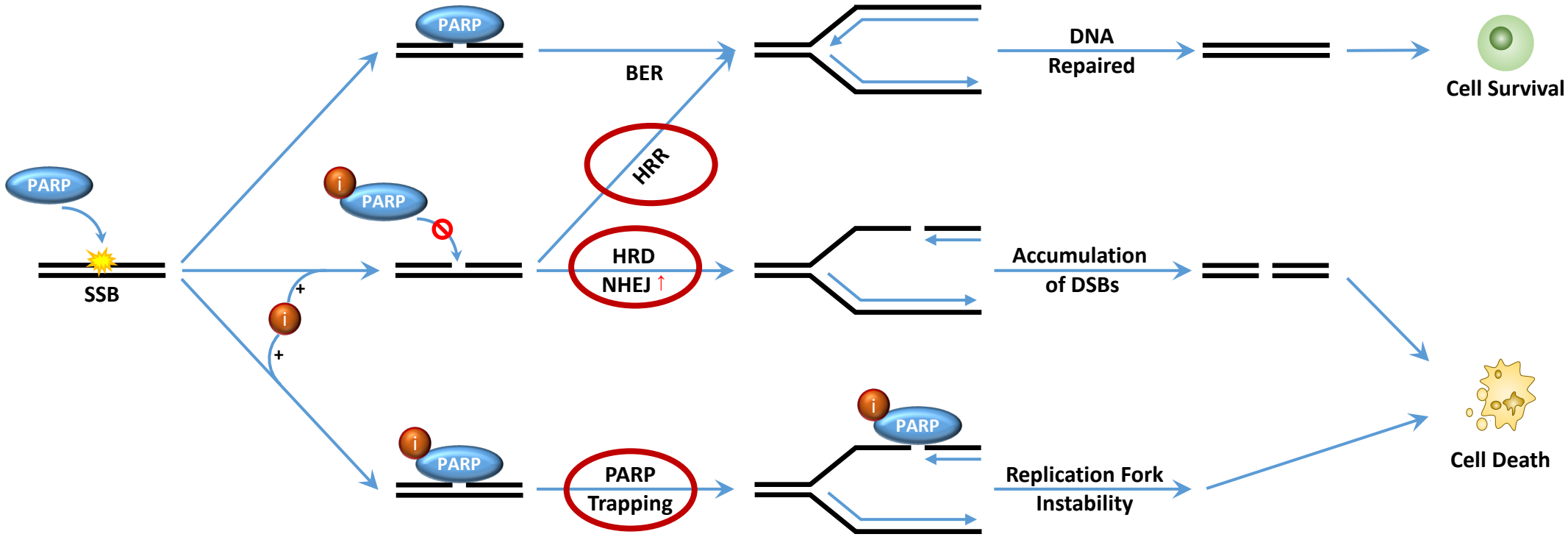
Treatment selection in mHSPC

- No role for ADT alone (except in exceptional cases e.g. life expectancy < 2 yrs)
- Doublets of ADT+ARAT (NHT) are applicable to all (except those with visceral (liver) metastasis)
- No role of ADT+ docetaxel doublet anymore (give superiority of ADT +docetaxel + ARAT triplets). Triplets replace only ADT+ docetaxel
- Patients are living longer with the diagnosis of mPC
- Given many options, its's time to optimize survival while maintaining the quality of life
- The art of medicine is more important than ever

Therapeutic targets of systemic therapies for advanced prostate cancer



PARP Inhibitors: Mechanism of Action



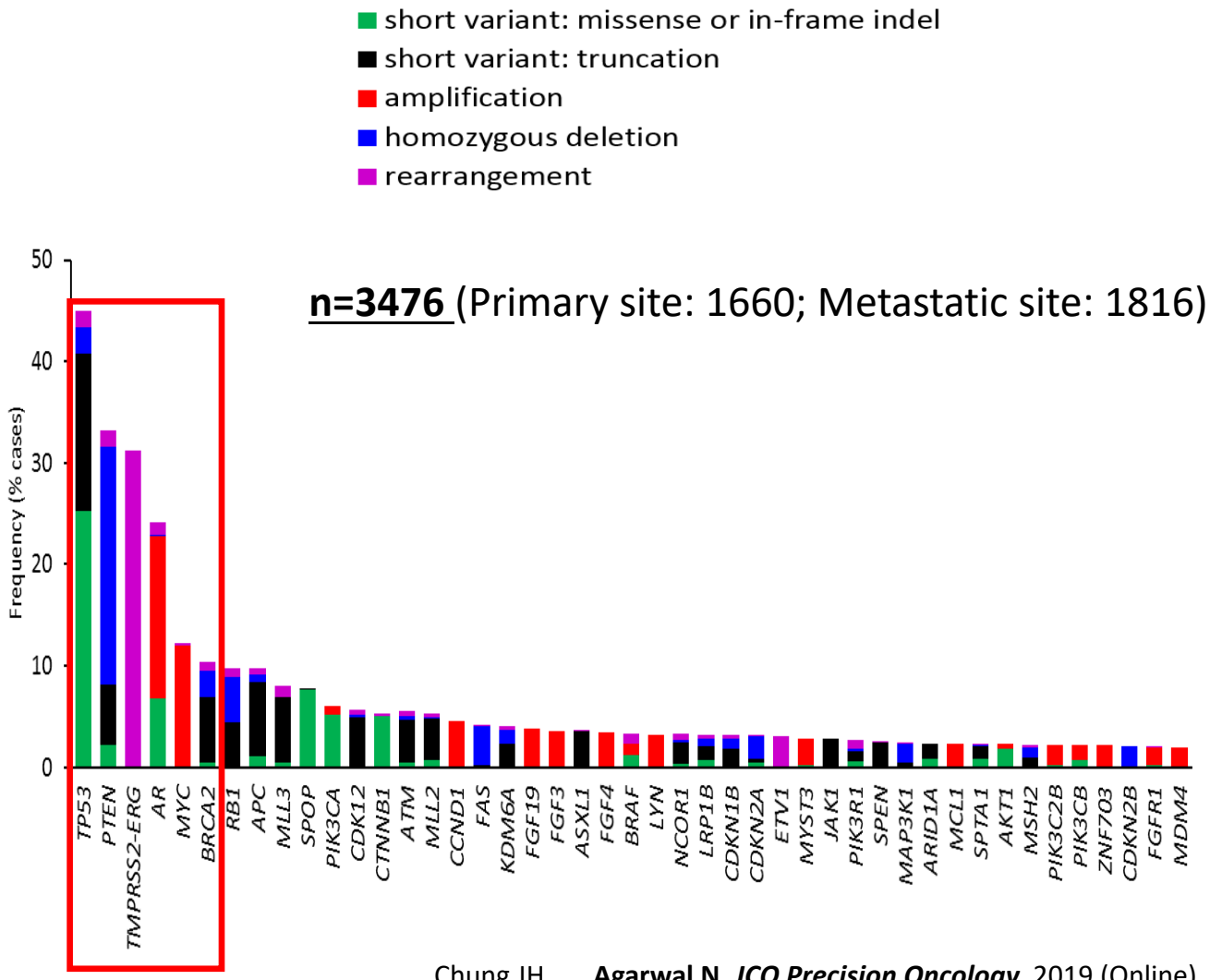
Abbreviations: PARP = poly(ADP-ribose) polymerase; SSB = single strand break; DSB = double strand break; i = PARP inhibitor; BER = base excision repair; HRR = homologous recombination repair; HRD = homologous recombination deficiency; NHEJ = non-homologous end joining.

Genomic Landscape in Advanced Prostate Cancer (Tissue DNA)

JCO® Precision Oncology
An American Society of Clinical Oncology Journal

Prospective Comprehensive Genomic Profiling of Primary and Metastatic Prostate Tumors

Jon H. Chung, PhD[1]; Ninad Dewal, PhD[1]; Ethan Sokol, PhD[1]; Paul Mathew, MD[2]; Robert Whitehead, MD[3]; Sherri Z. Millis, PhD[1]; Garrett M. Frampton, PhD[1]; Gennady Bratslavsky, MD[4]; Sumanta K. Pal, MD[5]; Richard J. Lee, MD, PhD[6]; Andrea Necchi, MD[7]; Jeffrey P. Gregg, MD[8]; Primo Lara Jr, MD[8]; Emmanuel S. Antonarakis, MD[9]; Vincent A. Miller, MD[1]; Jeffrey S. Ross, MD[1,4]; Siraj M. Ali, MD, PhD[1]; and Neeraj Agarwal, MD[10]



n=3476 (Primary site: 1660; Metastatic site: 1816)

Chung JH, …, **Agarwal N.** ***JCO Precision Oncology*** 2019 (Online)

TRITON3 Study Design

Key eligibility criteria

- Chemotherapy-naïve mCRPC
- BRCA or *ATM* alteration[a]
- 1 prior second-generation ARPI 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 (n=270)
600 mg BID

Physician's choice (n=135)[c]

Docetaxel (n=75)

or

Second-generation ARPI (n=60)

Abiraterone acetate or **Enzalutamide**

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

Endpoints[d]

Primary:
- rPFS by IRR

Key secondary:
- OS
- ORR by IRR

Subgroup analyses:
- OS and rPFS for rucaparib vs docetaxel or second-generation ARPI

Visit cutoff date: 25 August 2022. [a]Determined by Foundation Medicine testing of tissue or plasma. [b]Protocol amendment 19 June 2018: patients' qualifying second-generation ARPI could be in any setting. [c]If chosen, patients received whichever second-generation ARPI had not yet been received. Docetaxel: 75 mg/m^2 Q21D, 10 cycles max; Abiraterone acetate: 1000 mg QD; Enzalutamide: 160 mg QD; [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. [e]84 patients had IRR-confirmed progression, including 3 who were later re-evaluated as having non-progressive disease by IRR. ARPI, androgen receptor 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; OS, overall survival; Q21D, every 21 days; QD, daily; rPFS, radiographic progression-free survival.

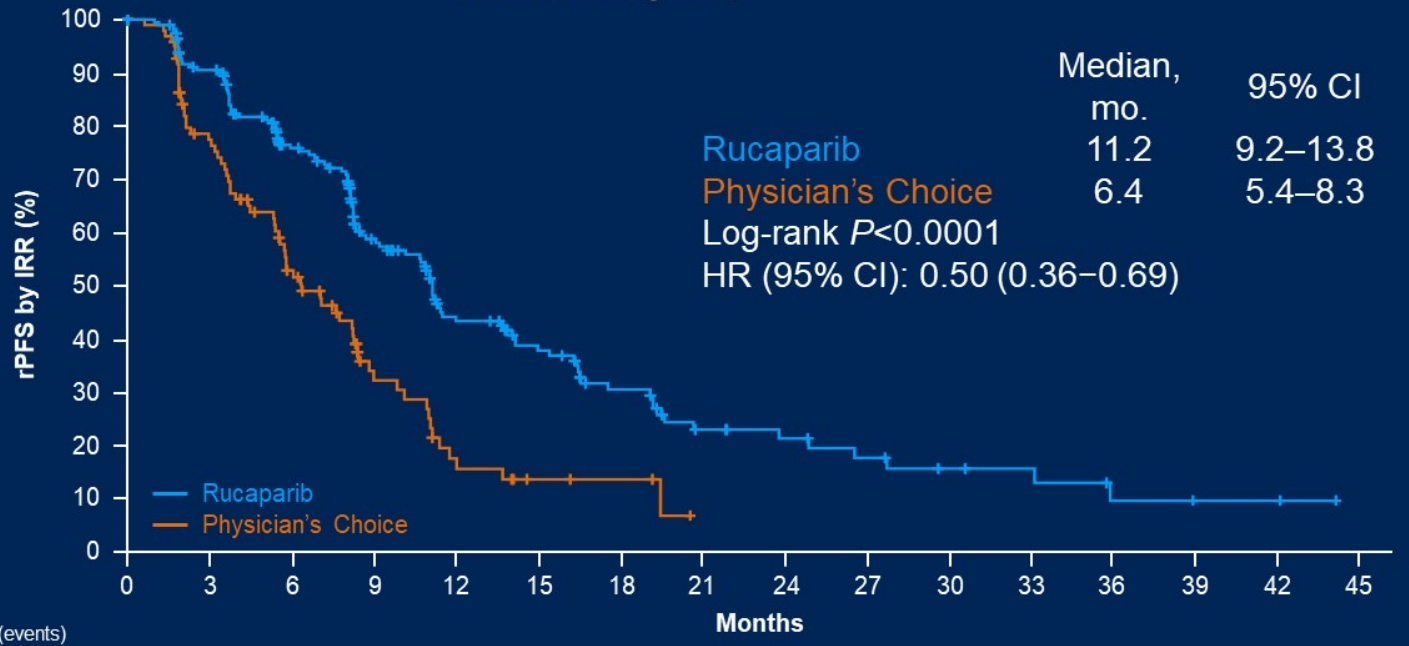
Baseline Characteristics in the ITT Population (1)

	Rucaparib (n=270)	Physician's Choice		
		Docetaxel (n=75)	Second-Generation ARPI (n=60)	Total (n=135)
Median age, years (range)	70 (45–90)	70 (47–88)	72 (54–92)	71 (47–92)
ECOG PS 0, n (%)	132 (49)	35 (47)	33 (55)	68 (50)
Alteration, (%)				
BRCA1	29 (11)	9 (12)	6 (10)	15 (11)
BRCA2	172 (64)	51 (68)	35 (58)	86 (64)
ATM	69 (26)	15 (20)	19 (32)	34 (25)
Baseline PSA, ng/mL, median (range)	27 (0.1–1247)	29 (0.2–1031)	29 (0–1039)	29 (0–1039)
Gleason score ≥8 at diagnosis, n (%)	173 (64)	59 (79)	37 (62)	96 (71)
Measurable disease per IRR, n (%)	106 (39)	34 (45)	21 (35)	55 (41)
Metastases per IRR, n (%)				
Bone	235 (87)	65 (87)	49 (82)	114 (84)
Bone-only	117 (43)	31 (41)	22 (37)	53 (39)
Nodal	118 (44)	36 (48)	24 (40)	60 (44)
Visceral	74 (27)	21 (28)	25 (42)	46 (34)

ARPI, androgen receptor pathway inhibitor; CRPC, castration-resistant prostate cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; HSPC, hormone-sensitive prostate cancer; IRR, independent radiology review; ITT, intent to treat; PSA, prostate-specific antigen.

Radiographic PFS

BRCA subgroup[1]



	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)								

ITT population[1]

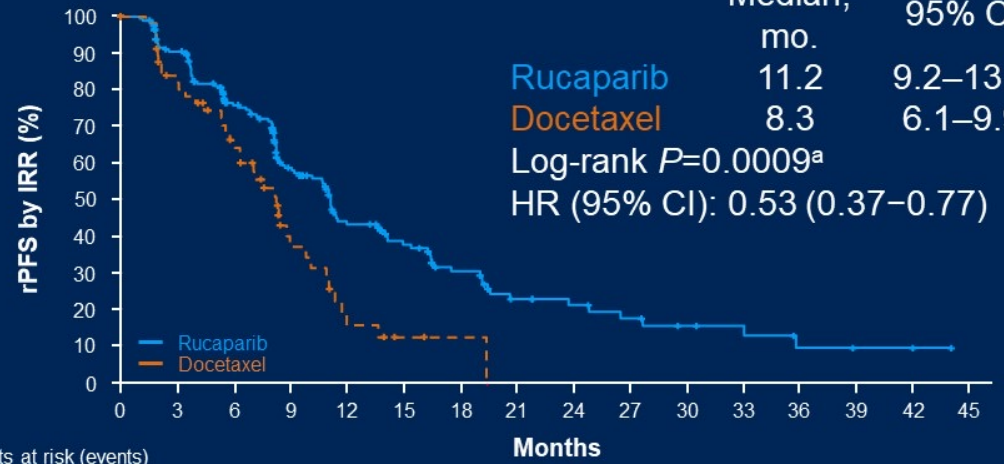
	Rucaparib (n=270)	Physician's Choice (n=135)
Median rPFS, mos (95% CI)	10.2 (8.3–11.2)	6.4 (5.6–8.2)
Log-rank *P*	0.0003	
HR (95% CI)	0.61 (0.47–0.80)	

Visit cutoff date: 25 August 2022. BRCA subgroup data maturity (rucaparib vs physician's choice): 182/302 (60.3%). 1. Bryce et al. Presented at the 2022 PCF Annual Retreat.
BRCA, *BRCA1* and *BRCA2*; HR, hazard ratio; IRR, independent radiology review; ITT, intent to treat; PFS, progression-free survival; rPFS, radiographic progression-free survival.

Radiographic PFS: Physician's Choice Subgroups

BRCA subgroup

Rucaparib vs Docetaxel

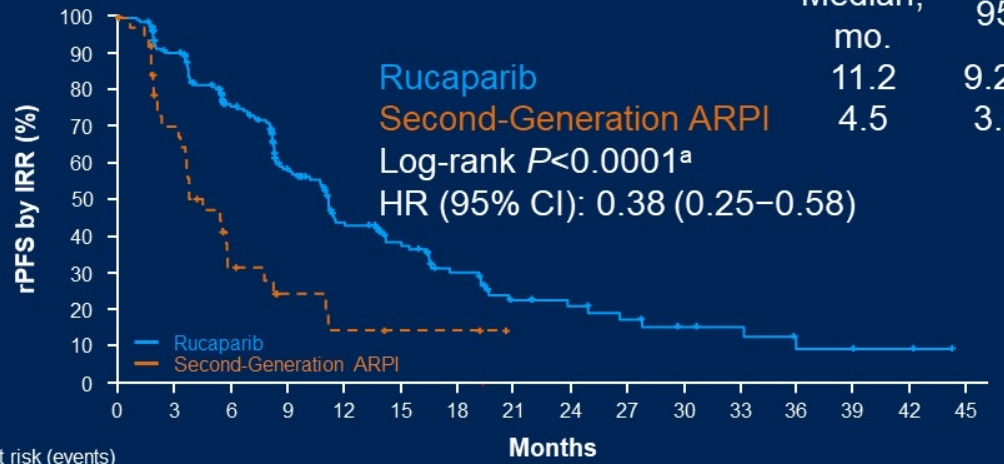


	Median, mo.	95% CI
Rucaparib	11.2	9.2–13.8
Docetaxel	8.3	6.1–9.9

Log-rank *P*=0.0009[a]
HR (95% CI): 0.53 (0.37−0.77)

Patients at risk (events)								
Rucaparib	201 (0)	124 (44)	55 (89)	27 (103)	13 (110)	7 (113)	3 (115)	2 (115)
Docetaxel	60 (0)	32 (18)	6 (36)	1 (38)	0 (39)			

Rucaparib vs Second-Generation ARPI



	Median, mo.	95% CI
Rucaparib	11.2	9.2–13.8
Second-Generation ARPI	4.5	3.3–5.8

Log-rank *P*<0.0001[a]
HR (95% CI): 0.38 (0.25−0.58)

Patients at risk (events)								
Rucaparib	201 (0)	124 (44)	55 (89)	27 (103)	13 (110)	7 (113)	3 (115)	2 (115)
Second-Generation ARPI	41 (0)	10 (24)	3 (28)	2 (28)	0 (28)			

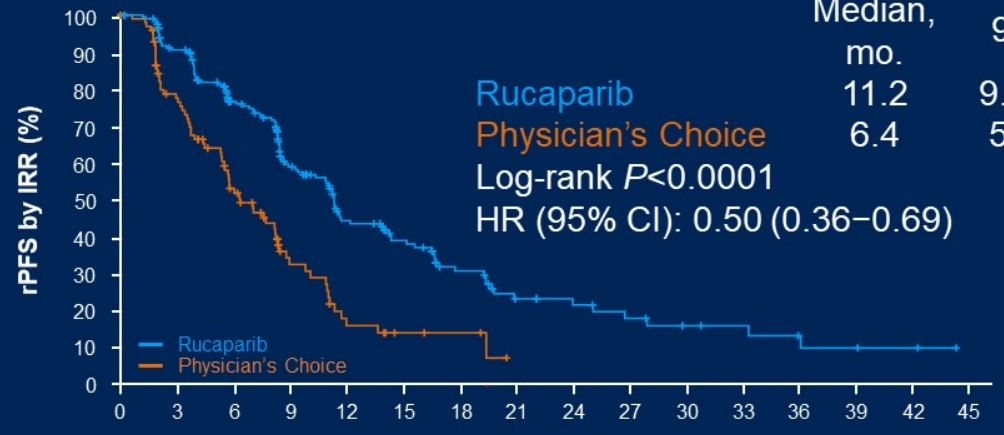
ITT population	Rucaparib (n=270)	Docetaxel (n=75)	Second-Generation ARPI (n=60)
rPFS, mos (95% CI)	10.2 (8.3–11.2)	8.3 (6.1–10.1)	4.5 (3.7–5.8)
Log-rank *P*	–	0.0066[a]	<0.0001[a]
HR (95% CI)	–	0.64 (0.46–0.88)	0.47 (0.34–0.66)

[a]Nominal. Visit cutoff date: 25 August 2022.
ARPI, androgen receptor pathway inhibitor; BRCA, *BRCA1* and *BRCA2*; HR, hazard ratio; IRR, independent radiology review; ITT, intent to treat; PFS, progression-free survival; rPFS, radiographic progression-free survival.

PRESENTED BY: Dr. Alan H. Bryce

Radiographic PFS: BRCA and *ATM* Subgroups

BRCA subgroup[1]



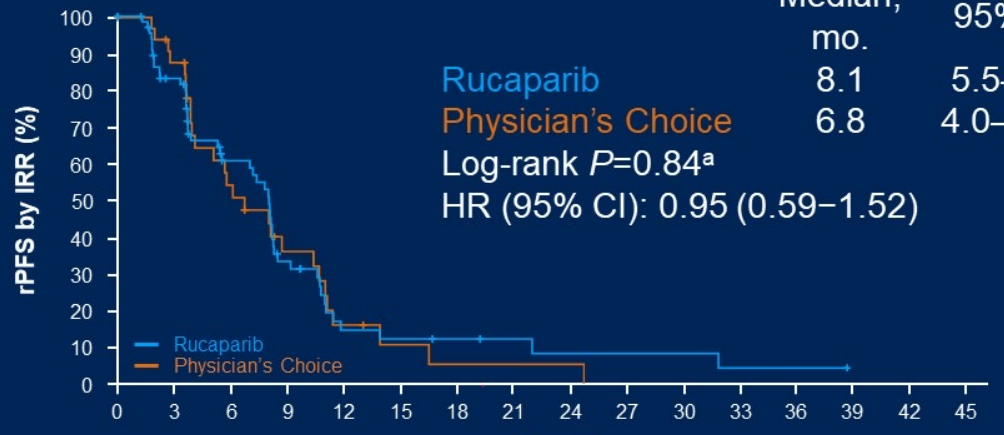
	Median, mo.	95% CI
Rucaparib	11.2	9.2–13.8
Physician's Choice	6.4	5.4–8.3

Log-rank $P<0.0001$

HR (95% CI): 0.50 (0.36–0.69)

Patients at risk (events)								
Rucaparib	201 (0)	124 (44)	55 (89)	27 (103)	13 (110)	7 (113)	3 (115)	2 (115)
Physician's Choice	101 (0)	42 (42)	9 (64)	3 (66)	0 (67)			

ATM subgroup[1]



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

Log-rank $P=0.84$[a]

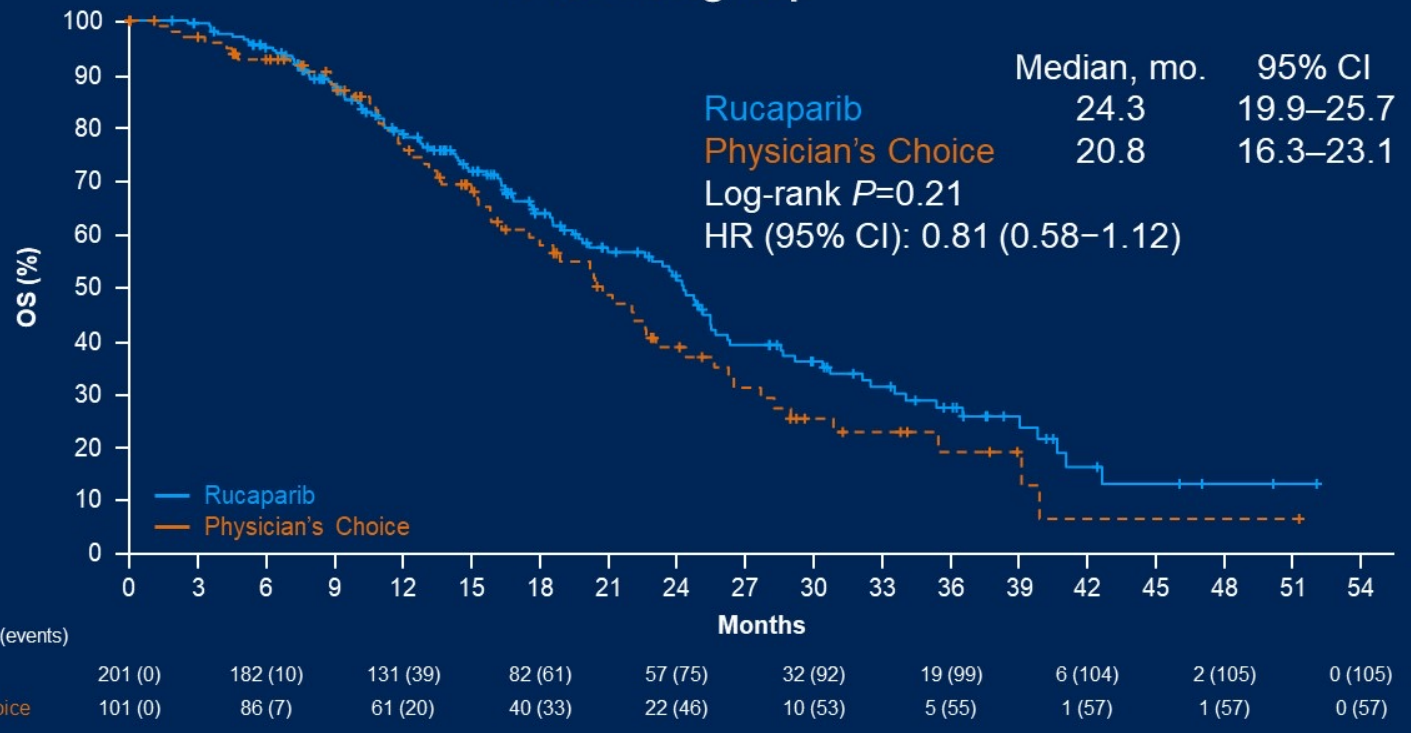
HR (95% CI): 0.95 (0.59–1.52)

Patients at risk (events)								
Rucaparib	69 (0)	31 (24)	6 (46)	4 (47)	2 (48)	2 (48)	1 (49)	0 (49)
Physician's Choice	34 (0)	16 (14)	4 (24)	1 (26)	1 (26)	0 (27)		

[a]Nominal. Visit cutoff date: 25 August 2022. 1. Bryce et al. Presented at the 2022 PCF Annual Retreat.
BRCA, *BRCA1* and *BRCA2*; HR, hazard ratio; IRR, independent radiology review; PFS, progression-free survival; rPFS, radiographic progression-free survival.

Interim OS

BRCA subgroup



Patients at risk (events)

Rucaparib	201 (0)	182 (10)	131 (39)	82 (61)	57 (75)	32 (92)	19 (99)	6 (104)	2 (105)	0 (105)
Physician's Choice	101 (0)	86 (7)	61 (20)	40 (33)	22 (46)	10 (53)	5 (55)	1 (57)	1 (57)	0 (57)

ITT population

	Rucaparib (n=270)	Physician's Choice (n=135)
Median OS, mos (95% CI)	23.6 (19.7–25.0)	20.9 (17.5–24.4)
Log-rank *P*	0.67[a]	
HR (95% CI)	0.94 (0.72–1.23)	

- BRCA subgroup data maturity (rucaparib vs physician's choice): 162/302 (53.6%)
- Target maturity for final analysis: 70%

[a]Nominal. Visit cutoff date: 25 August 2022. BRCA, *BRCA1* and *BRCA2*; HR, hazard ratio; ITT, intent to treat; OS, overall survival.

Safety Summary

n (%)	Rucaparib (n=270)	Physician's Choice					
		Docetaxel (n=71)		Second-Generation ARPI (n=59)		Total (n=130)	
At least 1 any-grade TEAE	270 (100)	71 (100)		58 (98)		129 (99)	
At least 1 grade ≥3 TEAE	161 (60)	43 (61)		26 (44)		69 (53)	
Dose reductions due to TEAEs	104 (39)	21 (30)		11 (19)		32 (25)	
Dose interruptions due to TEAEs	142 (53)	19 (27)		12 (20)		31 (24)	
Discontinuations due to TEAEs	40 (15)	23 (32)		5 (8)		28 (22)	
Death due to TEAEs	5 (2)	0		3 (5)		3 (2)	
Most frequently reported TEAEs	**Any grade**	**Grade ≥3**	**Any grade**	**Grade ≥3**	**Any grade**	**Grade ≥3**	**Any grade**	**Grade ≥3**
Asthenia/fatigue	165 (61)	19 (7)	48 (68)	7 (10)	34 (58)	5 (8)	82 (63)	12 (9)
Nausea	134 (50)	7 (3)	11 (15)	1 (1)	14 (24)	0	25 (19)	1 (1)
Anemia/hemoglobin decreased	126 (47)	64 (24)	10 (14)	1 (1)	13 (22)	0	23 (18)	1 (1)
Neuropathy[a]	25 (9)	0	34 (48)	4 (6)	2 (3)	0	36 (28)	4 (3)

- At visit cutoff, 33 (12%) patients were ongoing on rucaparib vs 1 (1%) patient on docetaxel and 4 (7%) patients on second-generation ARPI
- 29% of rucaparib-arm patients received ≥1 blood transfusion vs 2% of those receiving physician's choice
- No reported cases of MDS and/or AML

Visit cutoff date: 25 August 2022. [a]Neuropathy includes neurotoxicity, paresthesia, peripheral motor neuropathy, peripheral neuropathy, peripheral sensory neuropathy, and polyneuropathy.
AML, acute myeloid leukemia; ARPI, androgen receptor pathway inhibitor; MDS, myelodysplastic syndrome; TEAE, treatment-emergent adverse event.

Conclusions

- TRITON3 met its primary endpoint of improving rPFS by the use of rucaparib vs physician's choice of therapy
  - Rucaparib reduced risk of imaging-based progression or death by half in patients with BRCA alterations
  - Rucaparib improved rPFS vs both docetaxel and second-generation ARPI therapy in the BRCA subgroup and ITT population
- Three quarters of patients in the physician's choice arm who had progressive disease crossed over to rucaparib upon progression
  - OS results are immature (54% in the BRCA subgroup)
- In all treatment groups, the most frequent TEAE was asthenia/fatigue
  - No cases of MDS and/or AML were reported

AML, acute myeloid leukemia; ARPI, androgen receptor pathway inhibitor; BRCA, *BRCA1* and *BRCA2*; ARPI, androgen receptor pathway inhibitor; ITT, intent to treat; MDS, myelodysplastic syndrome; OS, overall survival; rPFS, radiographic progression-free survival; TEAE, treatment-emergent adverse event.

The rationale for combining PARPi with NHT

NHTs induce a phenotype resembling HRR deficiency

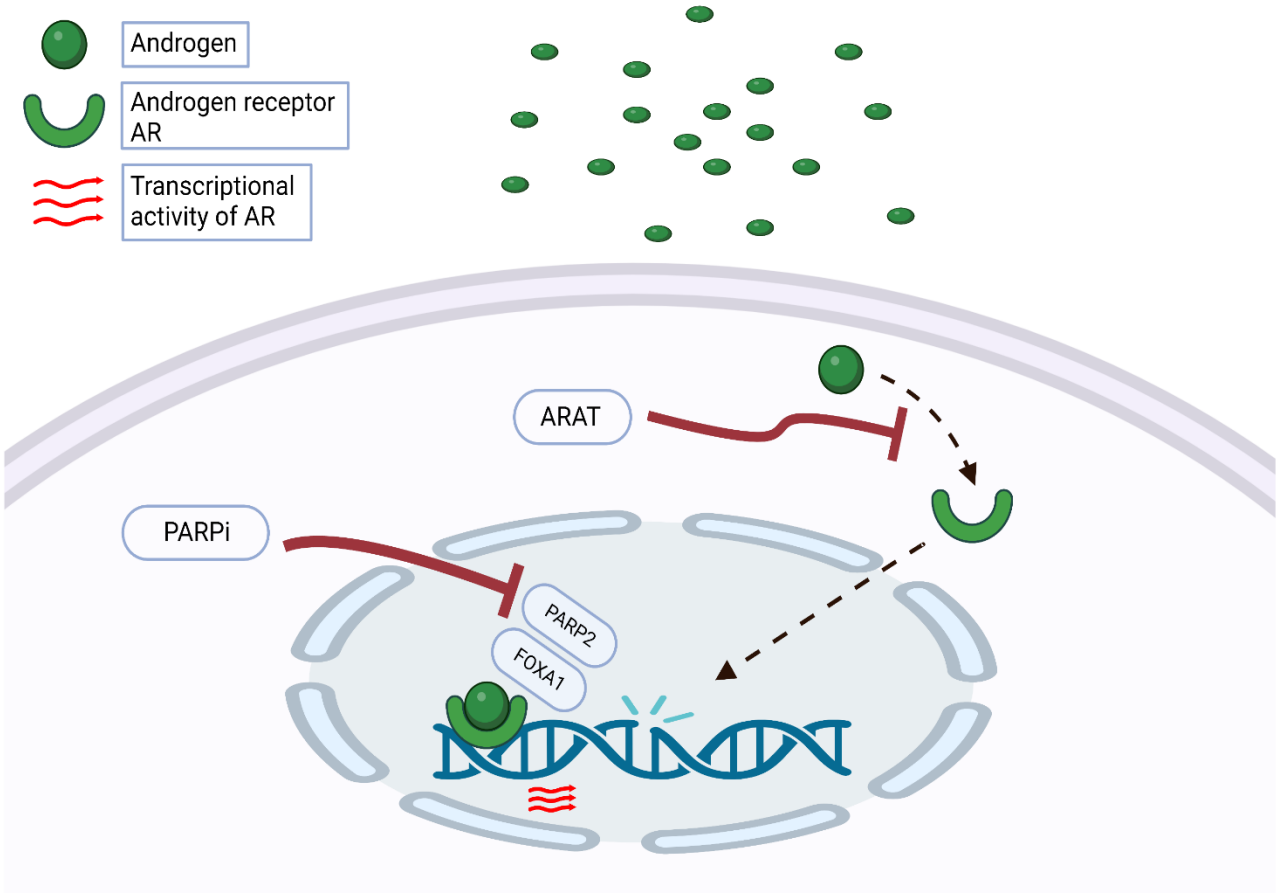
Suppressed AR function causes an upregulation of PARP

NHTs prime tumor cells for PARP inhibition

PARP augments AR activity

PARP inhibitors may attenuate resistance to NHTs

PARP inhibitors extend the benefits of NHTs



Adapted from Bin Gui et al., *PNAS* 2019 June,
DOI https://doi.org/10.1073/pnas.1908547116

PROpel and MAGNITUDE Revealed Conflicting Results

PROpel (1)		MAGNITUDE (2)
olaparib + abiraterone All-comers study		niraparib + abiraterone 2 seperate cohorts: HRR-pos. and HRR-neg.
HR **0.66**	rPFS all-comers	N/A
HR **0.76**	rPFS HRR-negative	HR **1.09**
HR **0.5**	rPFS HRR-positive	HR **0.73**
Not reported	rPFS BRCA-positive	HR **0.53**
Not reported	rPFS non-BRCA HRR-positive	HR **0.99**

DATA SUPPORT ALL-COMERS APPROACH

DATA SUPPORT TARGETED APPROACH

TALAPRO-2: TIEBREAKER ?

1 Saad et al., 2022, ABSTRACT 11 ASCO-GU
2 Kim N. Chi et al., 2022. ABSTRACT 12 ASCO-GU

Presentation number LBA17

ASCO Genitourinary Cancers Symposium

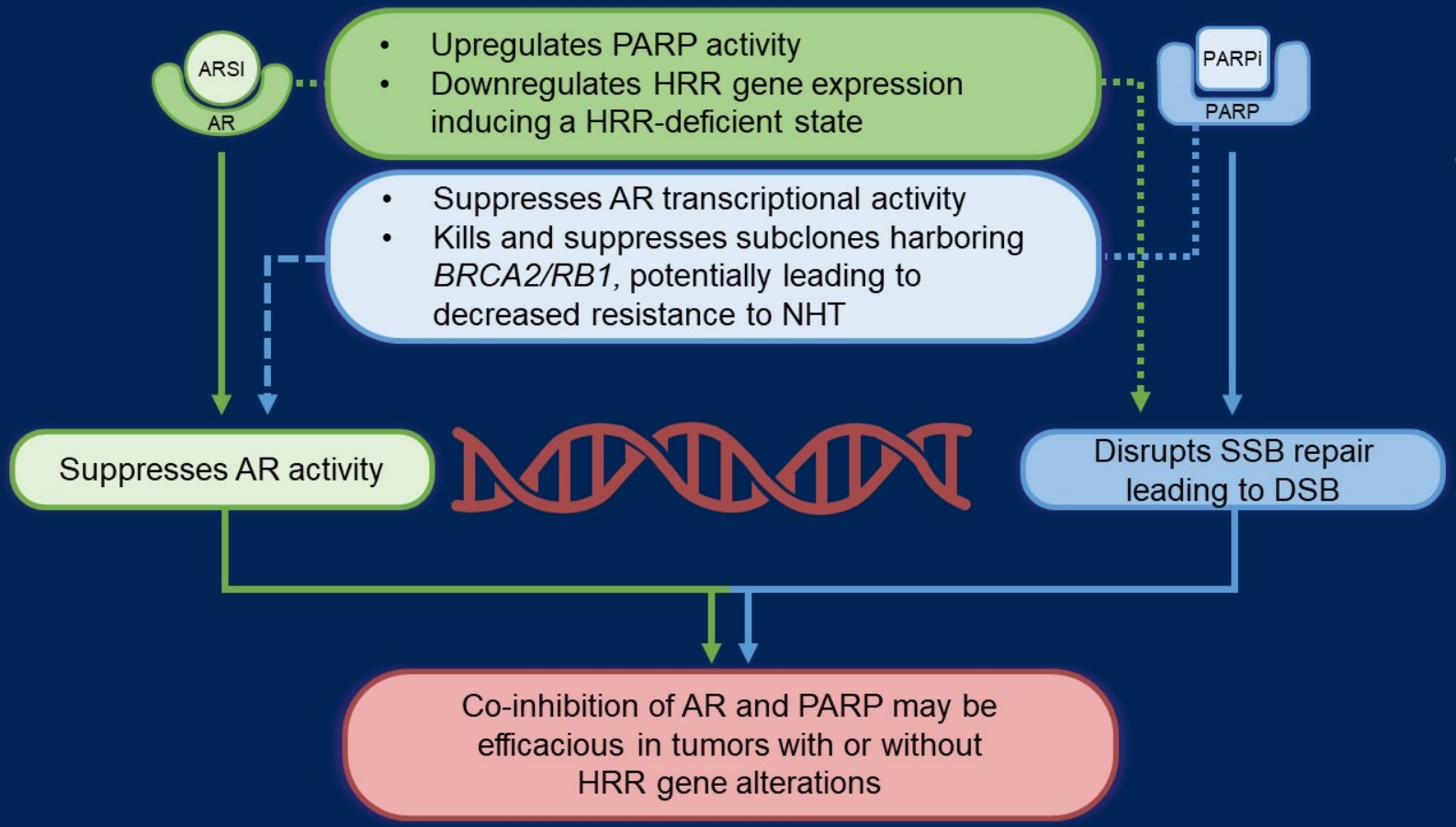
TALAPRO-2: Phase 3 study of talazoparib plus enzalutamide versus placebo plus enzalutamide as first-line treatment in patients with metastatic castration-resistant prostate cancer

Neeraj Agarwal,[1] Arun A. Azad,[2] Joan Carles,[3] Andre P. Fay,[4] Nobuaki Matsubara,[5] Daniel Heinrich,[6] Cezary Szczylik,[7] Ugo De Giorgi,[8] Jae Young Joung,[9] Peter C. Fong,[10] Eric Voog,[11] Robert J. Jones,[12] Neal D. Shore,[13] Curtis Dunshee,[14] Stefanie Zschäbitz,[15] Jan Oldenburg,[16] Xun Lin,[17] Cynthia G. Healy,[18] Nicola Di Santo,[19] Fabian Zohren,[17] Karim Fizazi[20]

[1]Huntsman Cancer Institute (NCI-CCC), University of Utah, Salt Lake City, UT, USA; [2]Peter MacCallum Cancer Centre, Melbourne, Australia; [3]Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; [4]PUCRS School of Medicine, Porto Alegre, Brazil; [5]National Cancer Center Hospital East, Chiba, Japan; [6]Innlandet Hospital Trust, Gjøvik, Norway; [7]Department of Oncology European Health Center, Otwock, Poland, and Postgraduate Medical Education Center, Warsaw, Poland; [8]IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) Dino Amadori, Meldola, Italy; [9]National Cancer Center, Goyang, Republic of Korea; [10]Auckland City Hospital and University of Auckland, Auckland, New Zealand; [11]Clinique Victor Hugo Centre Jean Bernard, Le Mans, France; [12]School of Cancer Sciences, University of Glasgow, Beatson West of Scotland Cancer Centre, Glasgow, UK; [13]Carolina Urologic Research Center, Myrtle Beach, SC, USA; [14]Arizona Urology Specialists, Tucson, AZ, USA; [15]National Center for Tumor Diseases (NCT), Heidelberg University Hospital, Heidelberg, Germany; [16]Akershus University Hospital (Ahus), Lørenskog, Norway; [17]Pfizer Inc., La Jolla, CA, USA; [18]Pfizer Inc., Collegeville, PA, USA; [19]Pfizer Inc., Durham, NC, USA; [20]Institut Gustave Roussy, University of Paris-Saclay, Villejuif, France

ClinicalTrials.gov identifier: NCT03395197
This study was sponsored by Pfizer Inc. Astellas Pharma Inc. provided enzalutamide

TALAPRO-2: Rationale for Combining Talazoparib and Enzalutamide[1-8]



- TALAPRO-2 is the first phase 3 trial evaluating talazoparib plus enzalutamide in patients with mCRPC unselected for HRR status[9]
  - An initial nonrandomized open-label run-in determined the starting dose as talazoparib 0.5 mg daily (0.35 mg daily if moderate renal impairment) plus enzalutamide 160 mg daily

1. Asim M, et al. *Nat Commun*. 2017;8:374; **2.** Li L, et al. *Sci Signal*. 2017;10:eaam7479; **3.** Polkinghorn WR, et al. *Cancer Discov*. 2013;3:1245-1253; **4.** Sun R, et al. *Proc Natl Acad Sci U.S.A*. 2022;119:e2205509119; **5.** Kounatidou E, et al. *Nucleic Acids Res*. 2019;47:5634-5647; **6.** Schiewer MJ, et al. *Cancer Discov*. 2012;2:1134-1149; **7.** Chakraborty G, et al. *Clin Cancer Res*. 2020;26:2047-2064; **8.** Rao A, et al. *Cancers (Basel)*. 2022;14:801; **9.** Agarwal N, et al. *Future Oncol*. 2022;18:425-436.

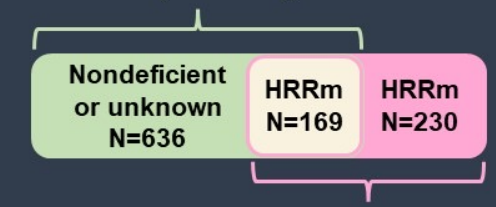
TALAPRO-2: A Randomized, Double-blind, Placebo-Controlled Study

Patient population

- First-line mCRPC
- ECOG performance status (PS) 0 or 1

Stratification factors

- Prior abiraterone[a] or docetaxel in castration-sensitive setting (yes vs no)
- HRR gene alteration status (deficient vs nondeficient or unknown)



1:1 (N=805)

Talazoparib 0.5 mg* + enzalutamide 160 mg, once daily

(N=402)

(*0.35 mg daily if moderate renal impairment)

Placebo + enzalutamide 160 mg, once daily

(N=403)

Primary endpoint

Radiographic progression-free survival (rPFS) by blinded independent central review (BICR)

Key secondary endpoint

- Overall survival (alpha protected)

Other secondary endpoints

- Time to cytotoxic chemotherapy
- PFS2 by investigator assessment[b]
- Objective response rate (ORR)
- Patient-reported outcomes
- Safety

(Data cutoff: August 16, 2022)

Samples prospectively assessed for HRR gene alterations *(BRCA1, BRCA2, PALB2, ATM, ATR, CHEK2, FANCA, RAD51C, NBN, MLH1, MRE11A, CDK12)* using FoundationOne®CDx and/or FoundationOne®Liquid CDx

We report results only from the all-comers cohort of men unselected for HRR gene alterations

To maintain the overall type I error at or below 1-sided 0.025, alpha for rPFS by BICR was split equally between the all-comers and forthcoming molecularly selected cohort (1-sided alpha of 0.0125 for each). If the rPFS showed statistically significant improvement, overall survival was tested in a hierarchical stepwise procedure to preserve the overall type I error.

[a]Two patients in each treatment arm received prior orteronel. [b]Time from randomization to the date of documented progression on the first subsequent antineoplastic therapy or death from any cause, whichever occurred first.

TALAPRO-2: Baseline Demographics and Disease Characteristics

These were well-balanced between treatment arms

	Talazoparib + Enzalutamide (N=402)	Placebo + Enzalutamide (N=403)
Age, median (range), years	71 (41–90)	71 (36–91)
Prostate-specific antigen (PSA), median (range), ng/mL	18.2 (0.1–2796.0)	16.2 (0.1–2285.1)
Disease site, n (%)		
Bone	349 (86.8)	342 (84.9)
Lymph node	147 (36.6)	167 (41.4)
Visceral (lung)	45 (11.2)	61 (15.1)
Visceral (liver)	12 (3.0)	16 (4.0)
ECOG PS 0/1, n (%)	259 (64.4)/143 (35.6)	271 (67.2)/132 (32.8)
Prior abiraterone[a] or docetaxel, n (%)	109 (27.1)	110 (27.3)
Abiraterone	21 (5.2)	25 (6.2)
Docetaxel	86 (21.4)	93 (23.1)
HRR gene alteration status (for prospective stratification), n (%)		
Deficient	85 (21.1)	84 (20.8)
Nondeficient or unknown	317 (78.9)	319 (79.2)

[a]Two patients in each treatment arm received prior orteronel.

TALAPRO-2: Source of Tumor DNA for Assessment and Baseline HRR Gene Status

Biomarker status was prospectively informed by tumor tissue for 99.9% of patients

Tissue source for prospective HRR gene alteration testing, n (%)	Talazoparib + Enzalutamide (N=402)	Placebo + Enzalutamide (N=403)
Tumor tissue	347 (86.3)	347 (86.1)
Tumor tissue and blood (circulating tumor DNA)	57 (14.2)	57 (14.1)
Blood (circulating tumor DNA) only	0	1 (0.2)

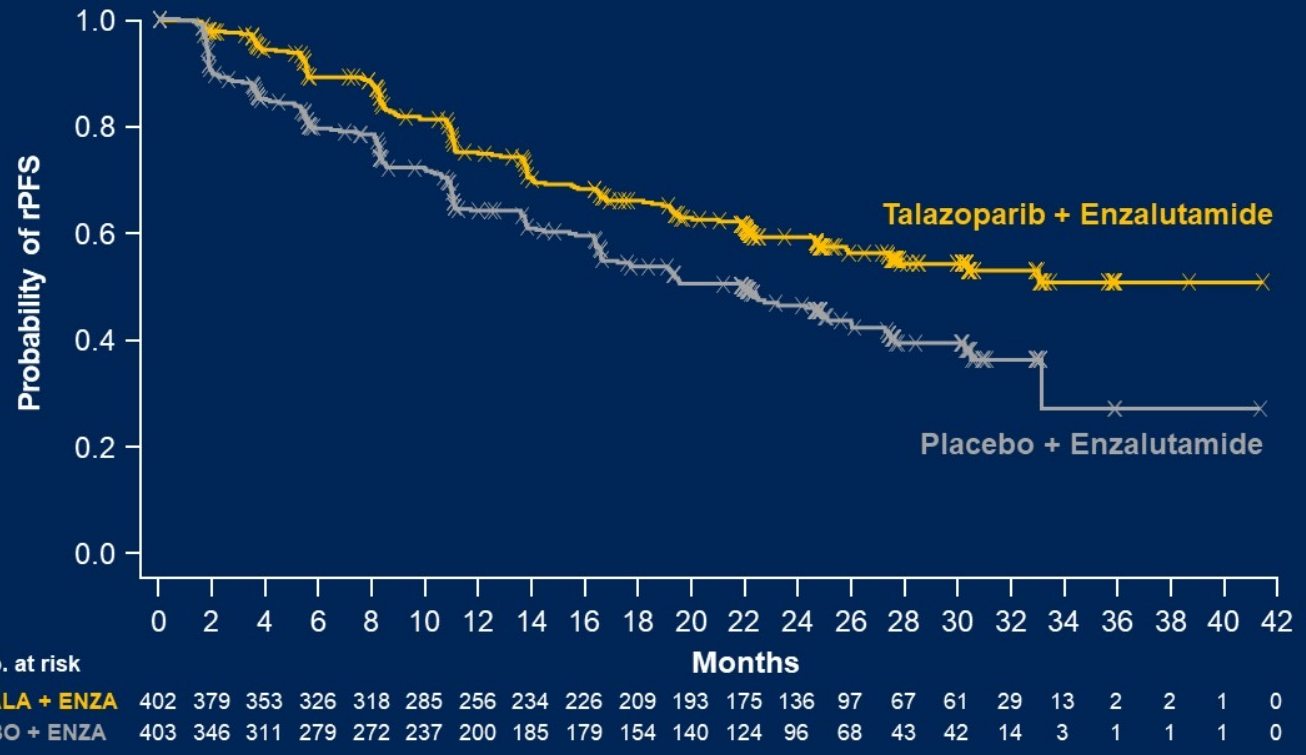
HRR gene alterations were well-balanced between treatment arms and consistent with prior reports[1,2]

Number of participants with HRR gene alterations, n (%)	Talazoparib + Enzalutamide (N=402)	Placebo + Enzalutamide (N=403)
1 or more alterations in the corresponding gene	85 (21.1)	82 (20.3)
CDK12	23 (5.7)	29 (7.2)
BRCA2	23 (5.7)	28 (6.9)
ATM	23 (5.7)	14 (3.5)
CHEK2	6 (1.5)	5 (1.2)
BRCA1	5 (1.2)	4 (1.0)
Other (*ATR*, *FANCA*, *MLH1*, *MRE11A*, *NBN*, *PALB2*, *RAD51C*)	14 (3.5)	13 (3.2)

1. Sigorski D, et al. *Target Oncol*. 2020;15:709-722; **2.** Abida W, et al. *JCO Precis Oncol*. 2017;2017:PO.17.00029.

TALAPRO-2 Primary Endpoint: rPFS by BICR

Treatment with talazoparib plus enzalutamide resulted in a 37% reduced risk of progression or death



	TALA + ENZA (N=402)	PBO + ENZA (N=403)
Events, n	151	191
Median (95% CI), months	Not reached (NR) (27.5–NR)	21.9 (16.6–25.1)
HR (95% CI)	0.63 (0.51–0.78); *P* < 0.001	

Median follow-up for rPFS was 24.9 and 24.6 months, respectively

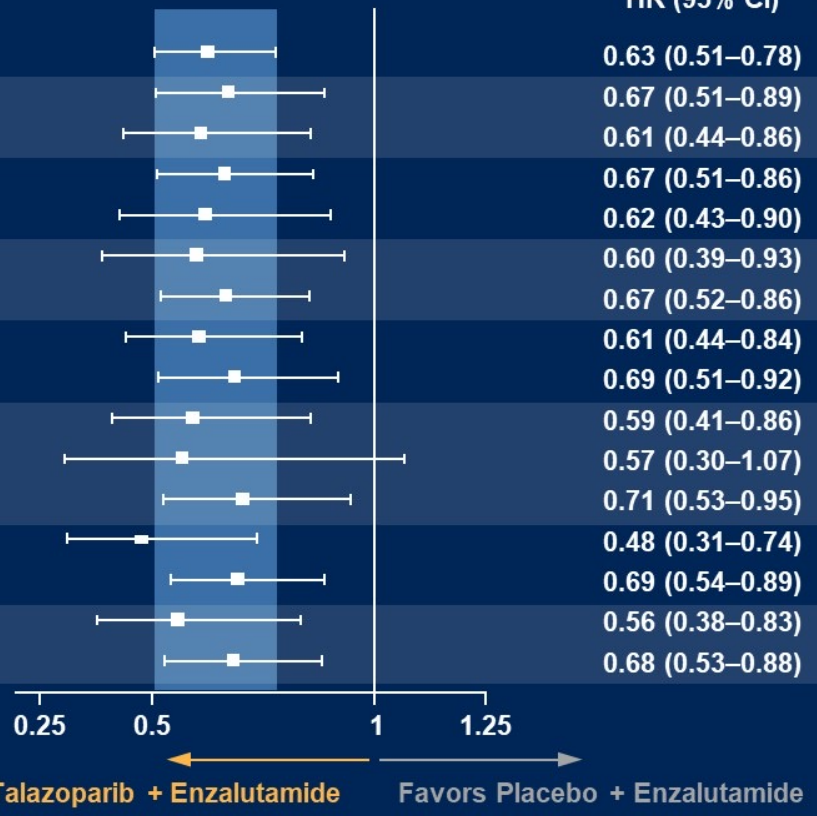
A consistent treatment effect was seen for investigator-assessed rPFS: HR 0.64 (95% CI, 0.50–0.81); *P* < 0.001

Stratified hazard ratios (HRs) and 2-sided *P* values are reported throughout this presentation unless otherwise stated.

TALAPRO-2: Subgroup Analysis of rPFS by BICR

A consistent treatment effect with talazoparib plus enzalutamide was seen in prespecified subgroups

Subgroup		Talazoparib + Enzalutamide Events/N	Placebo + Enzalutamide Events/N	HR (95% CI)	2-Sided *P* Value
Overall		151/402	191/403	0.63 (0.51–0.78)	< 0.001
Age, years	≥70	93/240	109/240	0.67 (0.51–0.89)	0.005
	<70	58/162	82/163	0.61 (0.44–0.86)	0.004
ECOG PS	0	100/259	130/271	0.67 (0.51–0.86)	0.002
	1	51/143	61/132	0.62 (0.43–0.90)	0.01
Gleason score	<8	34/117	49/113	0.60 (0.39–0.93)	0.02
	≥8	115/281	137/283	0.67 (0.52–0.86)	0.001
Stage at diagnosis	M0	64/172	92/185	0.61 (0.44–0.84)	0.002
	M1	86/226	98/215	0.69 (0.51–0.92)	0.01
Site of metastasis	Bone only	52/169	63/154	0.59 (0.41–0.86)	0.005
	Soft tissue only	15/48	29/57	0.57 (0.30–1.07)	0.07
	Bone and soft tissue	82/180	98/188	0.71 (0.53–0.95)	0.02
HRR status	Deficient	37/85	49/84	0.48 (0.31–0.74)	< 0.001
	Nondeficient/unknown	114/317	142/319	0.69 (0.54–0.89)	0.004
Prior abiraterone[a] or docetaxel	Yes	42/109	58/110	0.56 (0.38–0.83)	0.004
	No	109/293	133/293	0.68 (0.53–0.88)	0.003



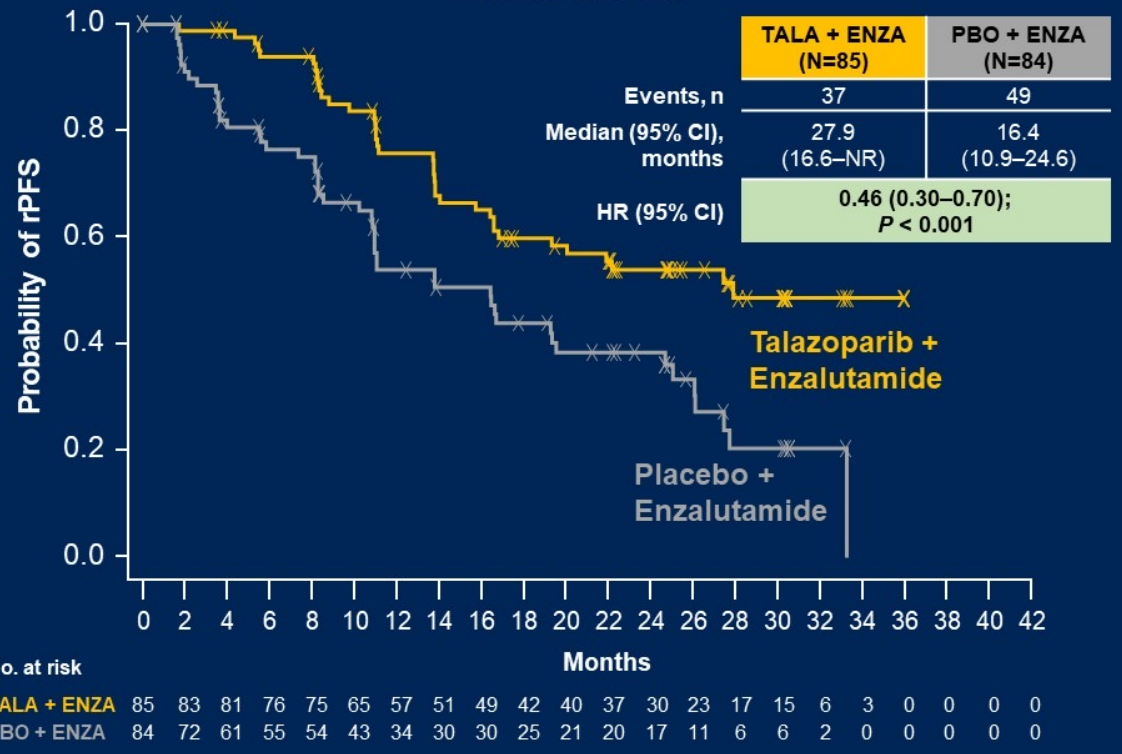
The HR for all patients was based on a Cox model stratified by the randomization stratification factors. For all subgroups, the HR was based on an unstratified Cox model with treatment as the only covariate.

[a]Includes two patients in each treatment arm who received prior orteronel.

TALAPRO-2: rPFS by BICR by HRR Status

A clinically meaningful reduction in risk of progression or death was seen regardless of HRR status

HRR-deficient

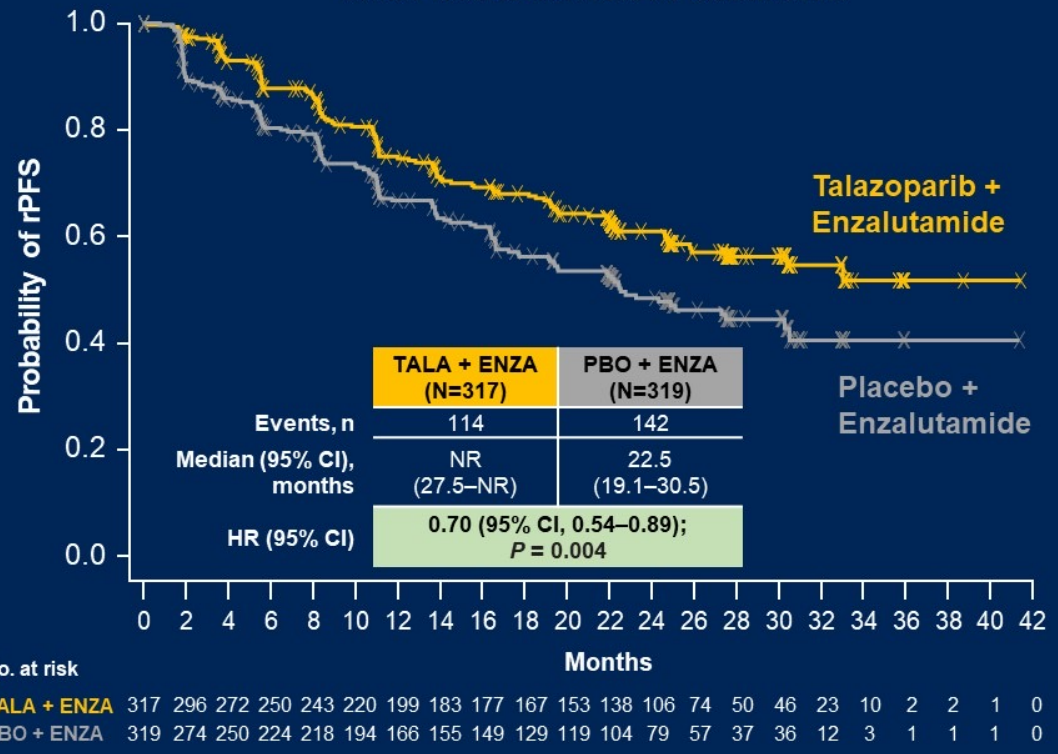


	TALA + ENZA (N=85)	PBO + ENZA (N=84)
Events, n	37	49
Median (95% CI), months	27.9 (16.6–NR)	16.4 (10.9–24.6)
HR (95% CI)	0.46 (0.30–0.70); *P* < 0.001	

No. at risk

TALA + ENZA	85	83	81	76	75	65	57	51	49	42	40	37	30	23	17	15	6	3	0	0	0	0
PBO + ENZA	84	72	61	55	54	43	34	30	30	25	21	20	17	11	6	6	2	0	0	0	0	0

HRR-nondeficient or unknown



	TALA + ENZA (N=317)	PBO + ENZA (N=319)
Events, n	114	142
Median (95% CI), months	NR (27.5–NR)	22.5 (19.1–30.5)
HR (95% CI)	0.70 (95% CI, 0.54–0.89); *P* = 0.004	

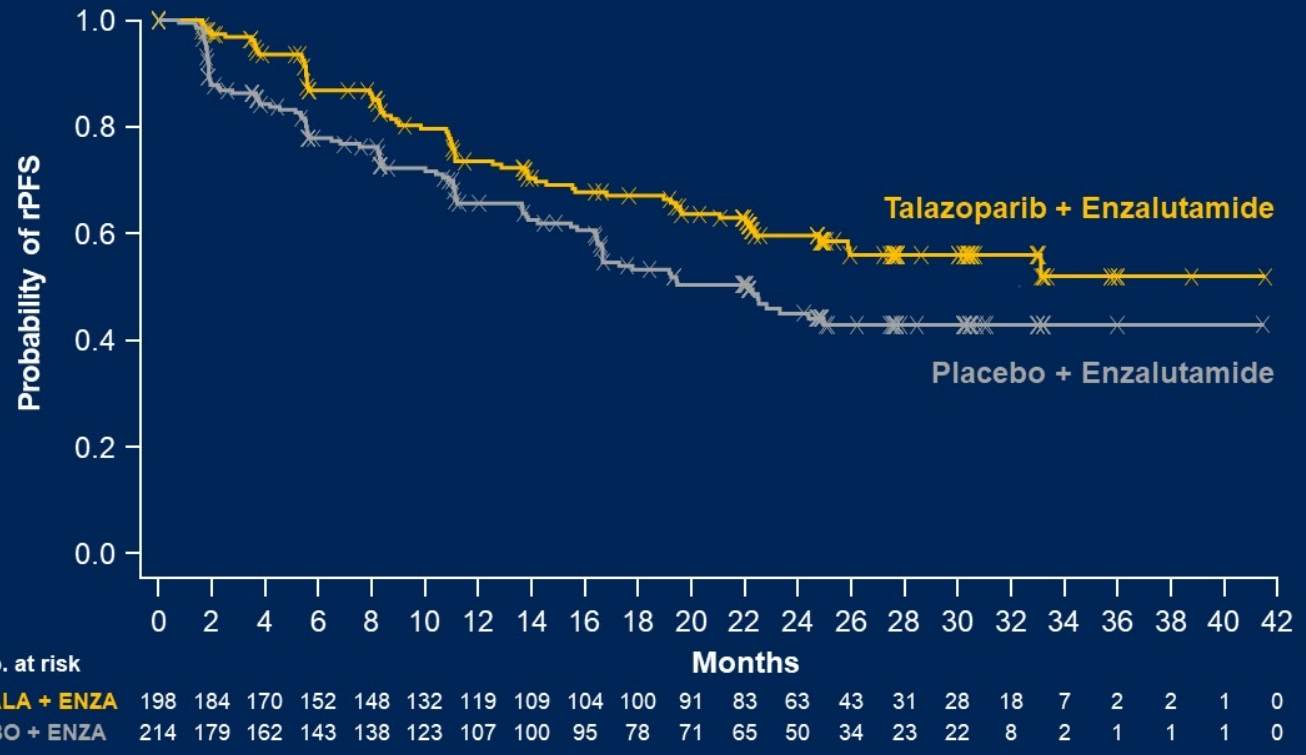
No. at risk

TALA + ENZA	317	296	272	250	243	220	199	183	177	167	153	138	106	74	50	46	23	10	2	2	1	0
PBO + ENZA	319	274	250	224	218	194	166	155	149	129	119	104	79	57	37	36	12	3	1	1	1	0

HRR gene alteration status (deficient vs nondeficient or unknown) as a stratification factor.

TALAPRO-2: rPFS by BICR in HRR-nondeficient by Prospective Tumor Tissue Testing

A 34% risk reduction was seen in patients without HRR gene alterations detected by prospective tumor tissue testing

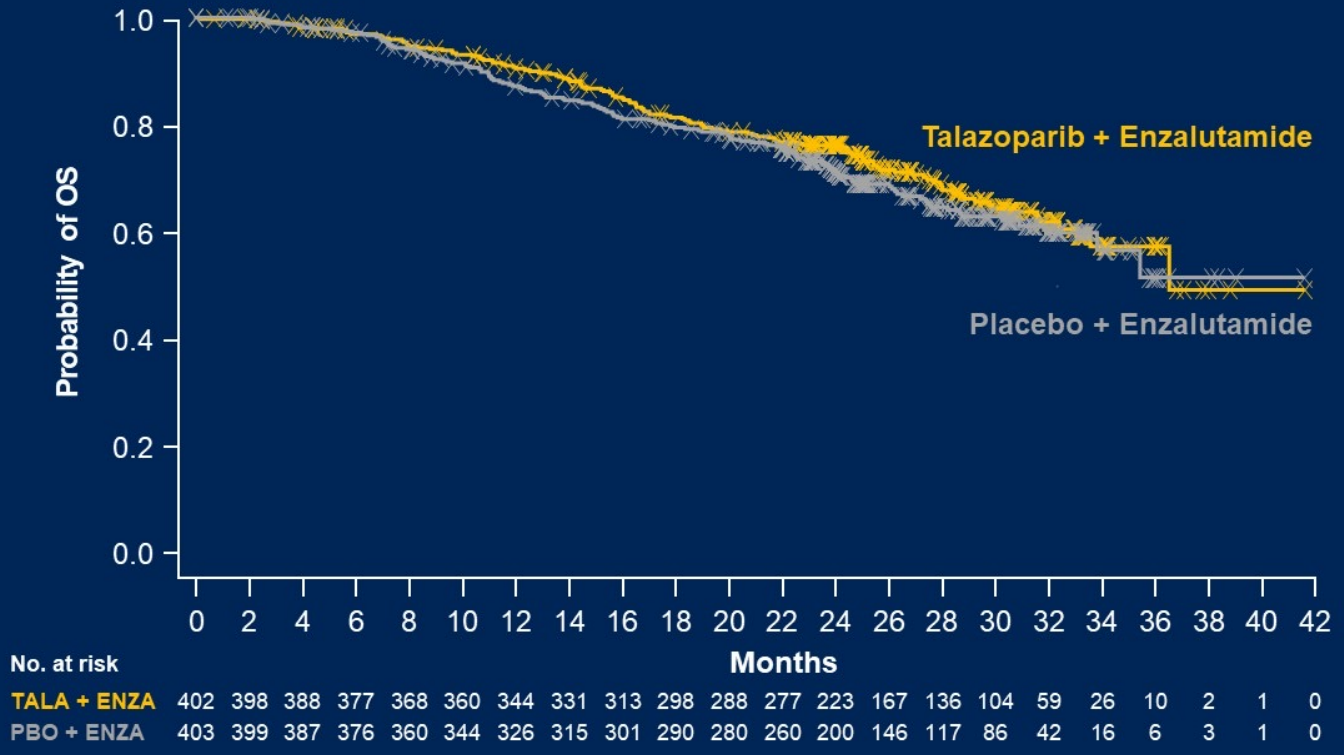


	TALA + ENZA (N=198)	PBO + ENZA (N=214)
Events, n	70	96
Median (95% CI), months	NR (25.8–NR)	22.1 (16.6–NR)
HR (95% CI)	HR 0.66 (95% CI, 0.49–0.91) *P* = 0.009	

Exploratory endpoint analysis based on HRR gene alteration status derived from the clinical database (unstratified analysis).

TALAPRO-2: Overall Survival (Interim Analysis)

Overall survival data are immature: 31% maturity

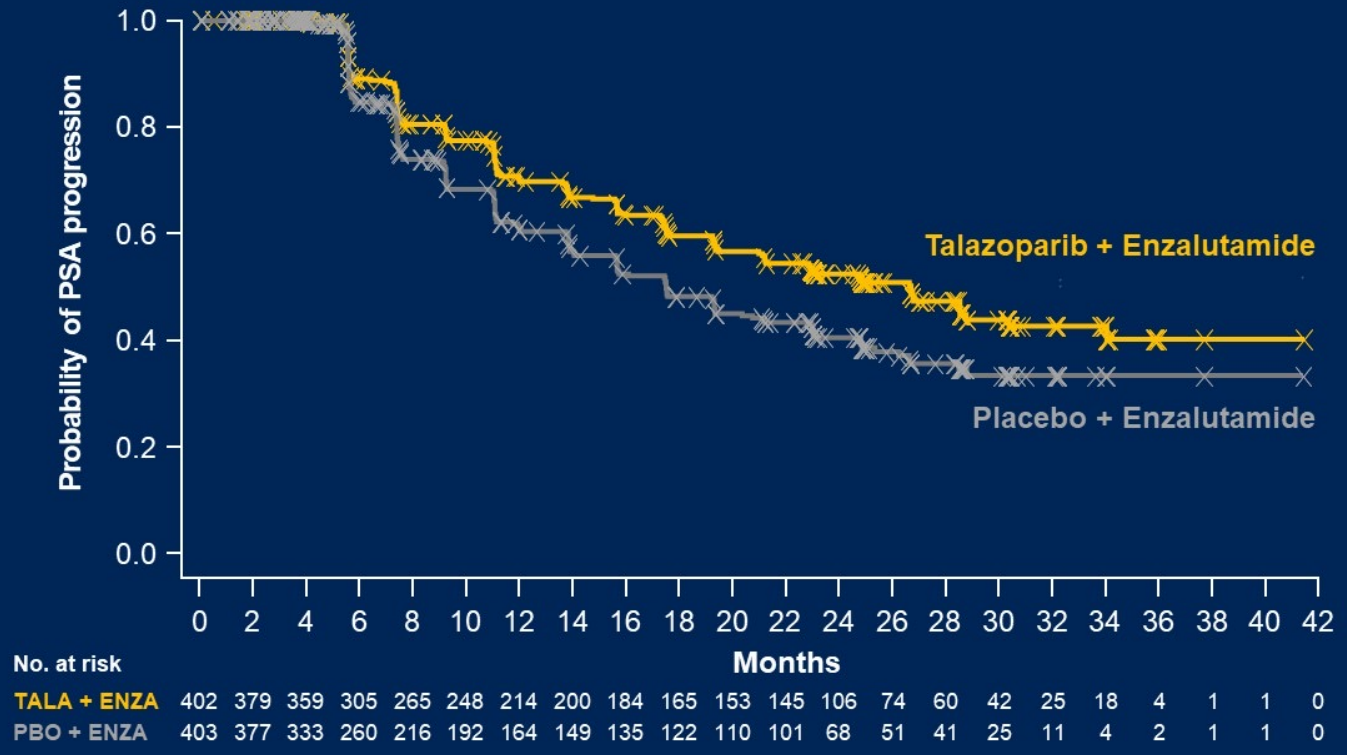


	TALA + ENZA (N=402)	PBO + ENZA (N=403)
Events, n	123	129
Median (95% CI), months	36.4 (33.5–NR)	NR (33.7–NR)
HR (95% CI)	HR 0.89 (95% CI, 0.69–1.14) *P* = 0.35	

PRESENTED BY: Dr Neeraj Agarwal @neerajaiims

TALAPRO-2: Time to PSA Progression

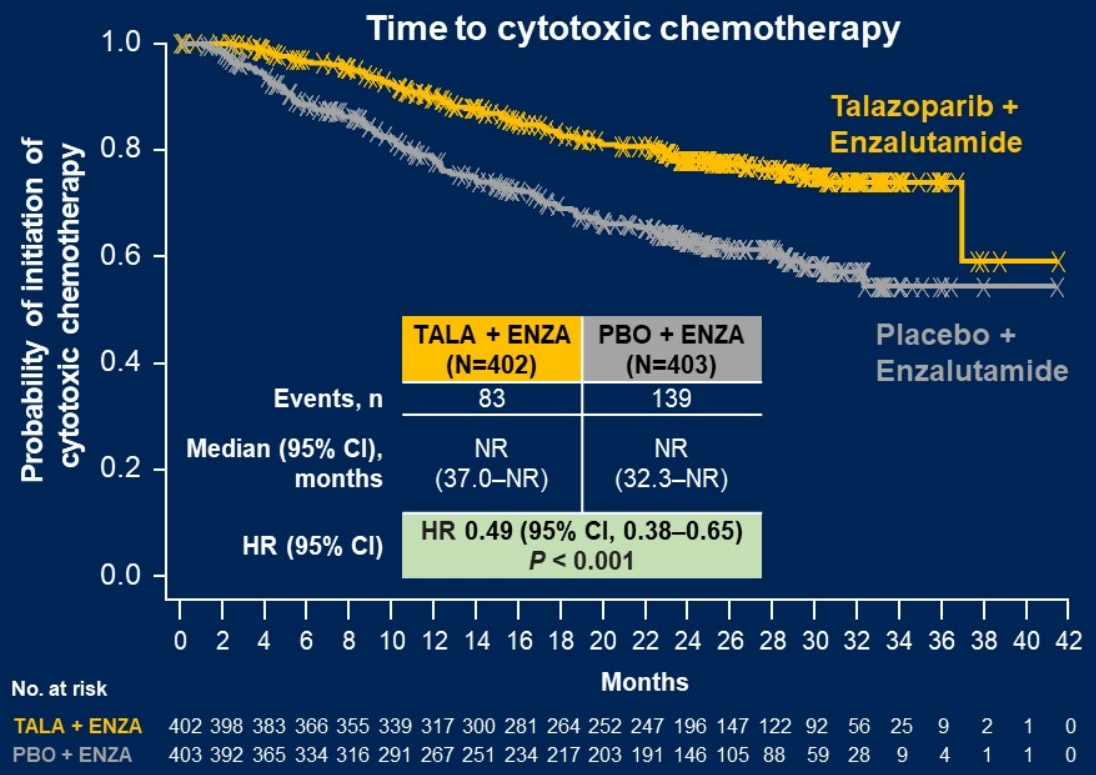
Treatment with talazoparib plus enzalutamide prolonged time to PSA progression

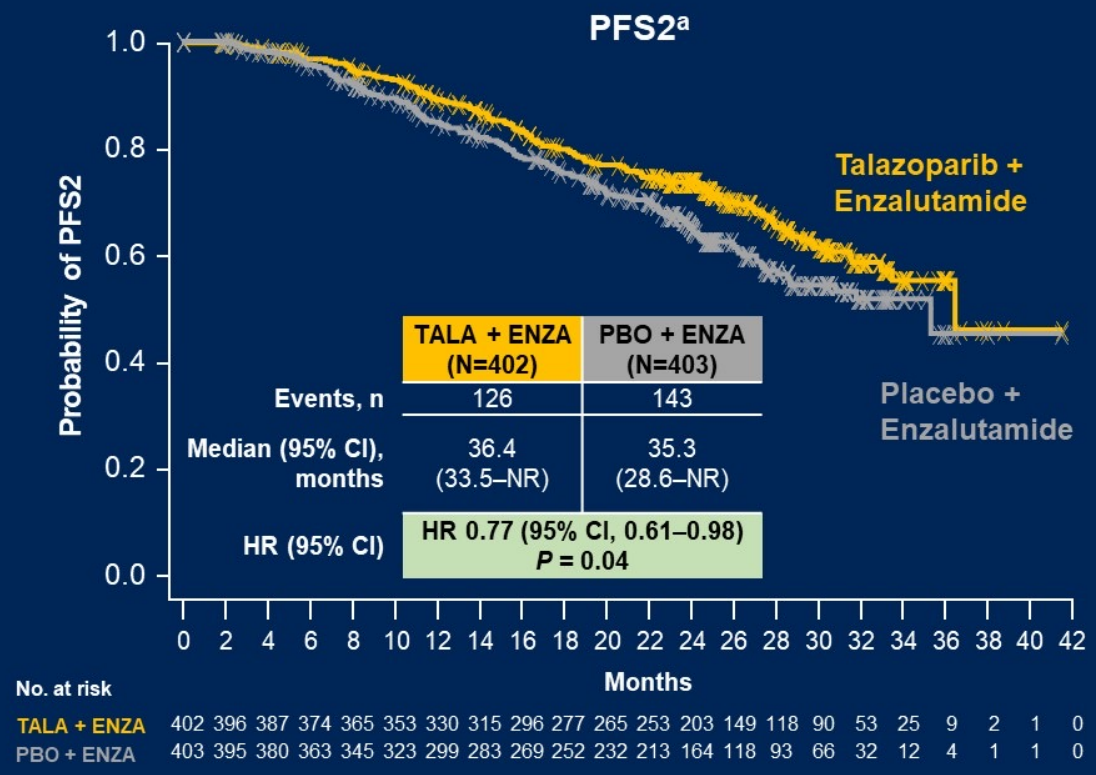


	TALA + ENZA (N=402)	PBO + ENZA (N=403)
Events, n	164	177
Median (95% CI), months	26.7 (21.2–30.4)	17.5 (14.1–20.8)
HR (95% CI)	HR 0.72 (95% CI, 0.58–0.89) *P* = 0.002	

TALAPRO-2: Time to Cytotoxic Chemotherapy and PFS2

Benefits of talazoparib plus enzalutamide were consistently observed across other secondary endpoints

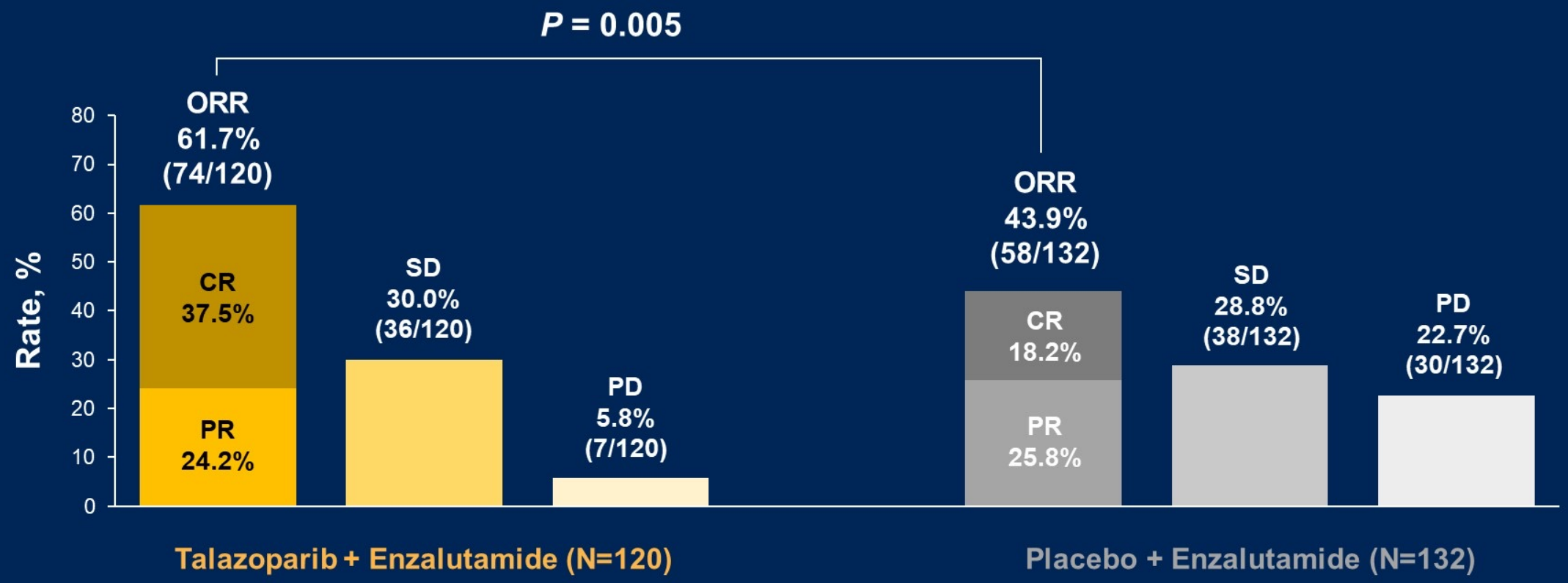




[a]PFS2 based on investigator assessment (time from randomization to the date of documented progression on the first subsequent antineoplastic therapy or death from any cause, whichever occurred first).

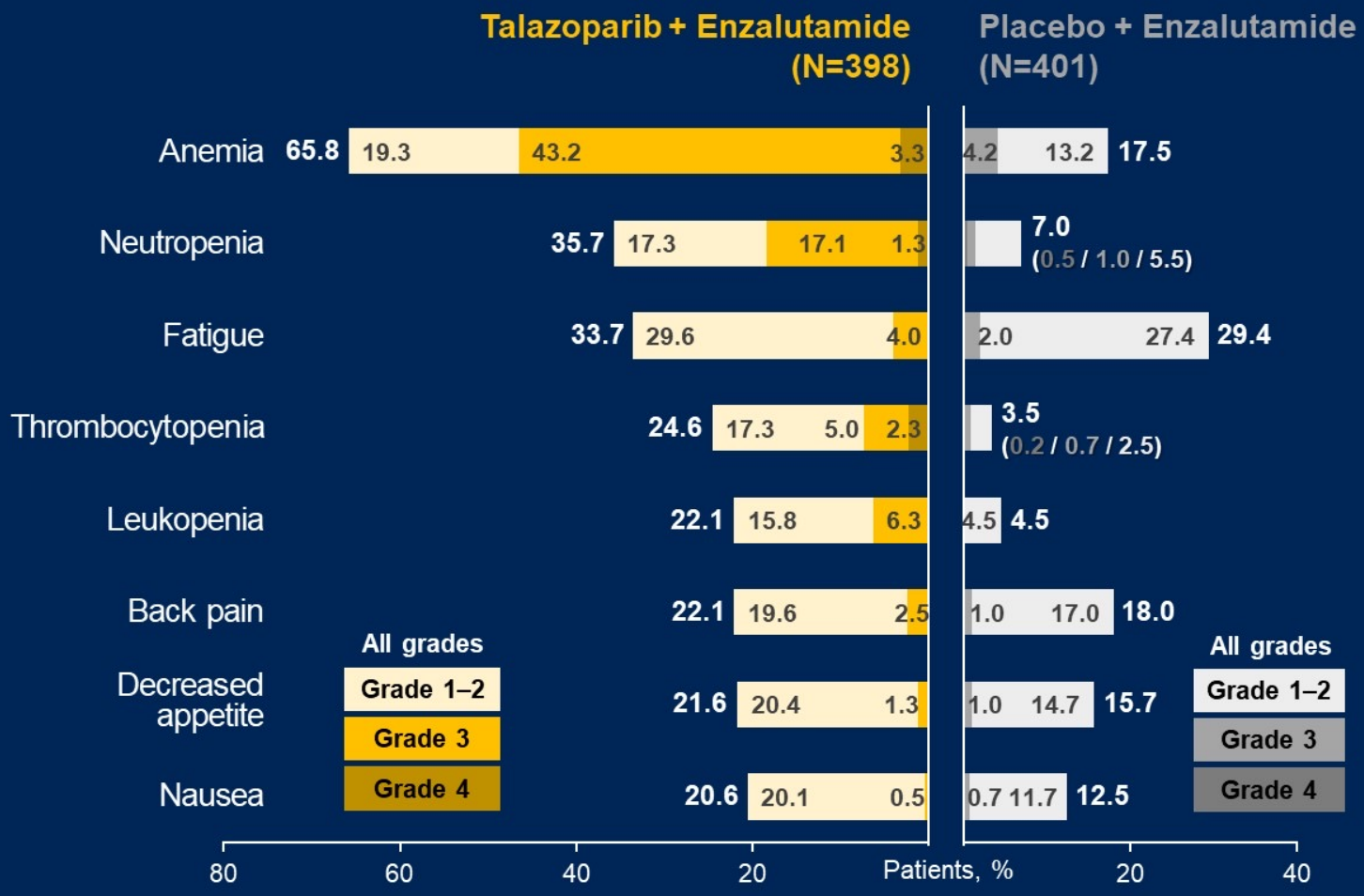
TALAPRO-2: Objective Response by BICR

Higher rates of complete response (CR) suggest a cooperative effect of talazoparib plus enzalutamide treatment



PD=progressive disease; PR=partial response; SD=stable disease.

TALAPRO-2: Most Common All-cause TEAEs

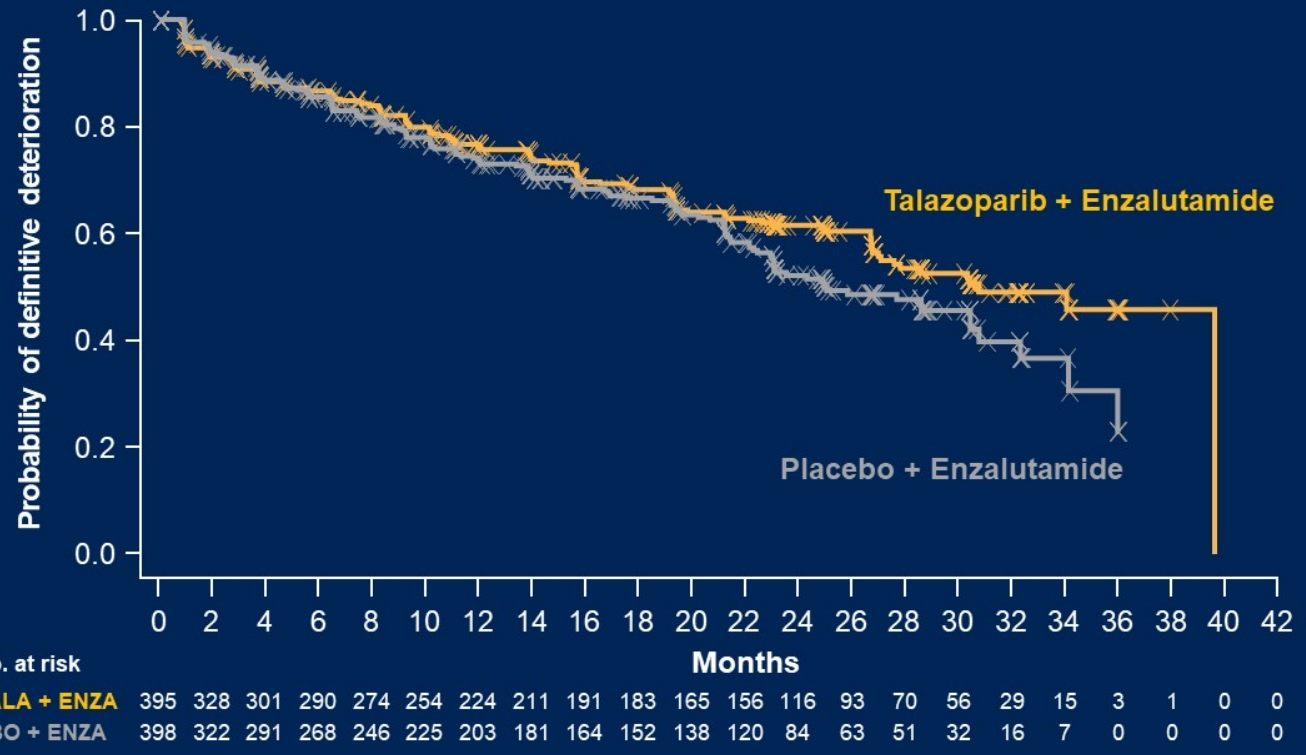


In the talazoparib arm:

- Most common TEAEs leading to a dose reduction of talazoparib were:
  - Anemia (43.2%)
  - Neutropenia (15.1%)
  - Thrombocytopenia (5.5%)
- 49.0% had grade 1–2 anemia at baseline
- Grade 3–4 anemia
  - Median time to onset was 3.3 months
  - Reported in 46.5% of men
- 8.3% discontinued talazoparib due to anemia
- The median relative dose intensity of talazoparib remained >80%

TALAPRO-2: Patient-Reported Global Health Status (GHS)/QoL per EORTC QLQ-C30

Talazoparib plus enzalutamide significantly prolonged time to definitive clinically meaningful deterioration in GHS/QoL[a]



	TALA + ENZA (N=395)	PBO + ENZA (N=398)
Events, n	138	146
Median (95% CI), months	30.8 (27.0–39.6)	25.0 (22.9–30.4)
HR (95% CI)	HR 0.78 (95% CI, 0.62–0.99) *P* = 0.04	

EORTC QLQ-C30=European Organisation for Research and Treatment of Cancer cancer-specific global health questionnaire.
[a]Definitive clinically meaningful deterioration defined as a ≥10-point decrease from baseline and no subsequent observations with <10-point decrease from baseline assessed by the EORTC QLQ-C30.[1]

1. Gamper EM, et al. *BMC Cancer*. 2021;21:1083.

TALAPRO-2: Conclusions

- Talazoparib plus enzalutamide resulted in a statistically significant and clinically meaningful improvement in rPFS by BICR over placebo plus enzalutamide across the all-comers population and prespecified subgroups in the first-line mCRPC setting
  - Benefit was consistent irrespective of HRR gene alteration status
  - Benefit was also seen in patients without HRR gene alterations detected by prospective tumor tissue testing
- The safety profile of talazoparib plus enzalutamide was consistent with individual profiles, and TEAEs were generally managed through dose modifications and supportive measures
- Time to definitive clinically meaningful deterioration in GHS/QoL was significantly longer with talazoparib plus enzalutamide versus placebo plus enzalutamide

Results from the primary analysis of the TALAPRO-2 trial support the use of talazoparib plus enzalutamide as a first-line treatment in patients with mCRPC regardless of HRR gene alteration status

	PROpel*	MAGNITUDE*	TALAPRO-2**
Primary endpoint	rPFS (investigator view)	rPFS (central view)	rPFS (central view)
Prior NHA in mCSPC	Only after 12 mo of interruption (abiraterone not allowed)	Yes (except abiraterone)	Yes (abiraterone only)
Prior Docetaxel in mCSPC	Yes	Yes	Yes (if discontinued in the 28 days prior to randomization)
Stratification by HRR status	No	Yes	Yes
HRR analysis	Tissue or ctDNA/retrospective	100% tissue/prospective	Primarily tissue (99.9%)/prospective
Patients who received NHT/Docetaxel in mCSPC in experimental arm (%)	0.3/22.6	3.8/19.3**	5.4/21.2
rPFS			
All commers	+ (HR 0.66)	Not reported	+ (HR 0.63)
HRR -ve	+ (HR 0.76)	No benefit	+ (HR 0.66)
HRR +ve	+ (HR0.50)	+ (HR 0.53 for BRCA+/0.73 for all HRR genes)	+ (HR 0.46)
ORR	58 vs 48%	60% vs 28% (only HRR+ pts)	61.7 vs 43.9%
HRQol	Maintained	Maintained	Prolonged time to clinically meaningful deterioration
OS	Immature	Immature	Immature

*ASCO GU 2022 **nmCRPC and mHSPC/23.6% received prior abiraterone in mCRPC setting **ASCO GU 2023 (LBA17).

Phase 3 Studies of PARPi+NHT combinations in 1L mCRPC – Can study design affect the results?

	TALAPRO-2[1]	PROpel[2]	MAGNITUDE[3]
INVESTIGATIONAL TREATMENT	Talazoparib + enzalutamide	Olaparib + abiraterone	Niraparib + abiraterone
STUDY POPULATION	(1a) all-comers (1b) DDR positive (fall-back)	all-comers (N=796)	(1) DDR positive (n=423) (2) DDR negative (n=233)
PRIMARY ENDPOINT	rPFS (BICR*)	rPFS (by investigator)	rPFS (BICR*)
ALLOWED PRIOR TREATMENTS FOR mCSPC	• Docetaxel for mCSPC • Abiraterone for mCSPC	• Docetaxel for mCSPC • Prior NHT allowed if stopped ≥ 12 months of enrollment (No prior abiraterone)	• Taxane for mCSPC • Any NHT (except AAP) in mCSPC • ≤4 months AAP for mCRPC
STRATIFICATION FACTORS	• DDR status • Prior docetaxel / NHT in CSPC	• Bone only vs visceral vs other • Prior docetaxel / NHT in CSPC	• Prior taxane for mCSPC • Prior NHT in nmCRPC or mCSPC • Prior AAP for 1L mCRPC • BRCA1/2 vs other HRR
BIOMARKERS	• 12 gene panel ATM, ATR, BRCA1, BRCA2, CDK12, CHEK2, FANCA, MRE11A, MLH1, NBN, PALB2, RAD51C	• 14 gene panel ATM, BARD1, BRCA1, BRCA2, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, RAD54L	• 9 gene panel, to inform study group ATM, BRCA1, BRCA2, BRIP1, CDK12, CHEK2, FANCA, HDAC2, PALB2

1. Agarwal N et al, Future Oncology, 2022;18:425-436; 2- Clarke NW et al., NEJM Evidence. 2022 Aug 23;1(9):EVIDoa2200043. 3- Chi KN et al., JCO. 2022 Feb 20;40(6_suppl):12–12. Kim Chi, (2022 Genitourinary cancers symposium (ASCO GU). Abstract #12)

Phase 3 trial of PARPi + NHT in 1st line mCRPC and mCSPC

mCRPC

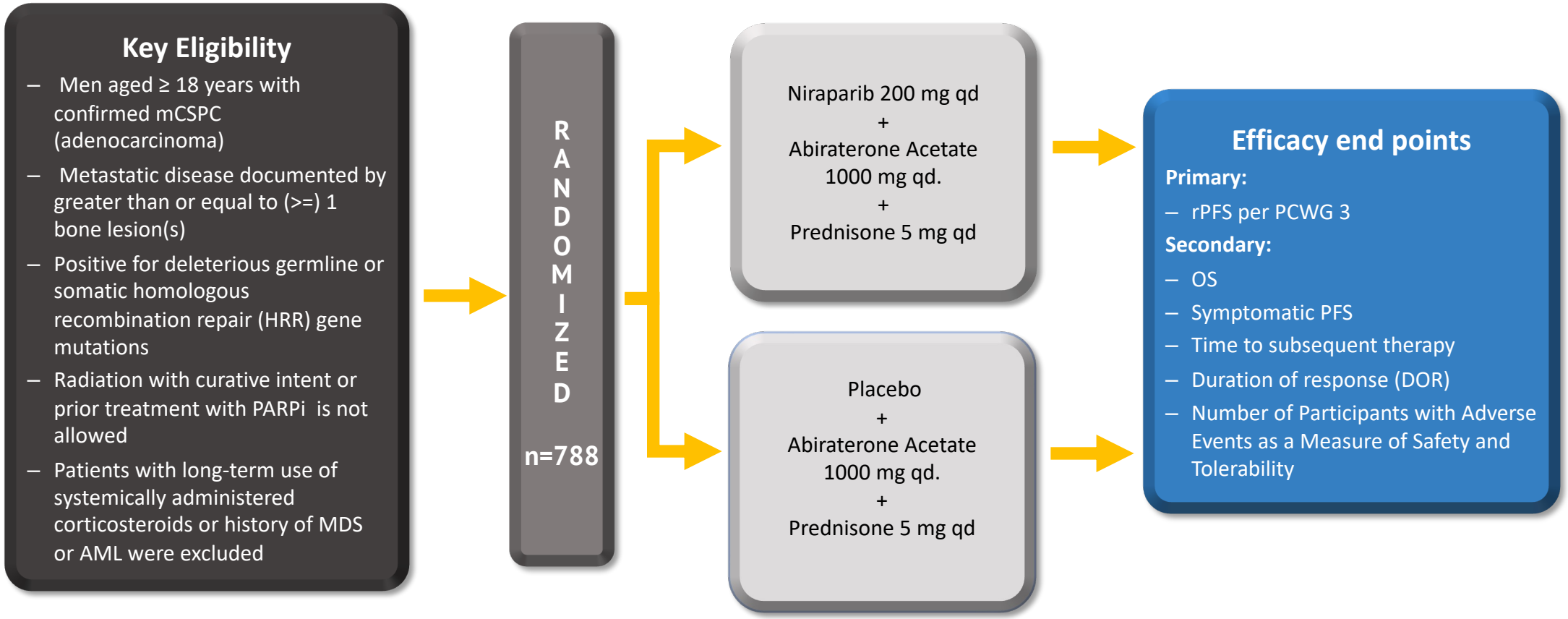
- PROpel: Abiraterone + Olaparib[1] — Published
- MAGNITUDE: Abiraterone + Niraparib[2] — Presented
- TALAPRO-2: Enzalutamide + Talazoparib — Press release October 2022
- CASPAR: Enzalutamide + Rucaparib — Enrolling

mCSPC

- TALAPRO-3: Enzalutamde + Talazoparib — Enrolling
- Amplitutde: Abiraterone + Niraparib — Enrolling

1- Clarke NW et al., NEJM Evidence. 2022 Aug 23;1(9):EVIDoa2200043; 2-2022 Genitourinary cancers symposium (ASCO GU). Abstract #12

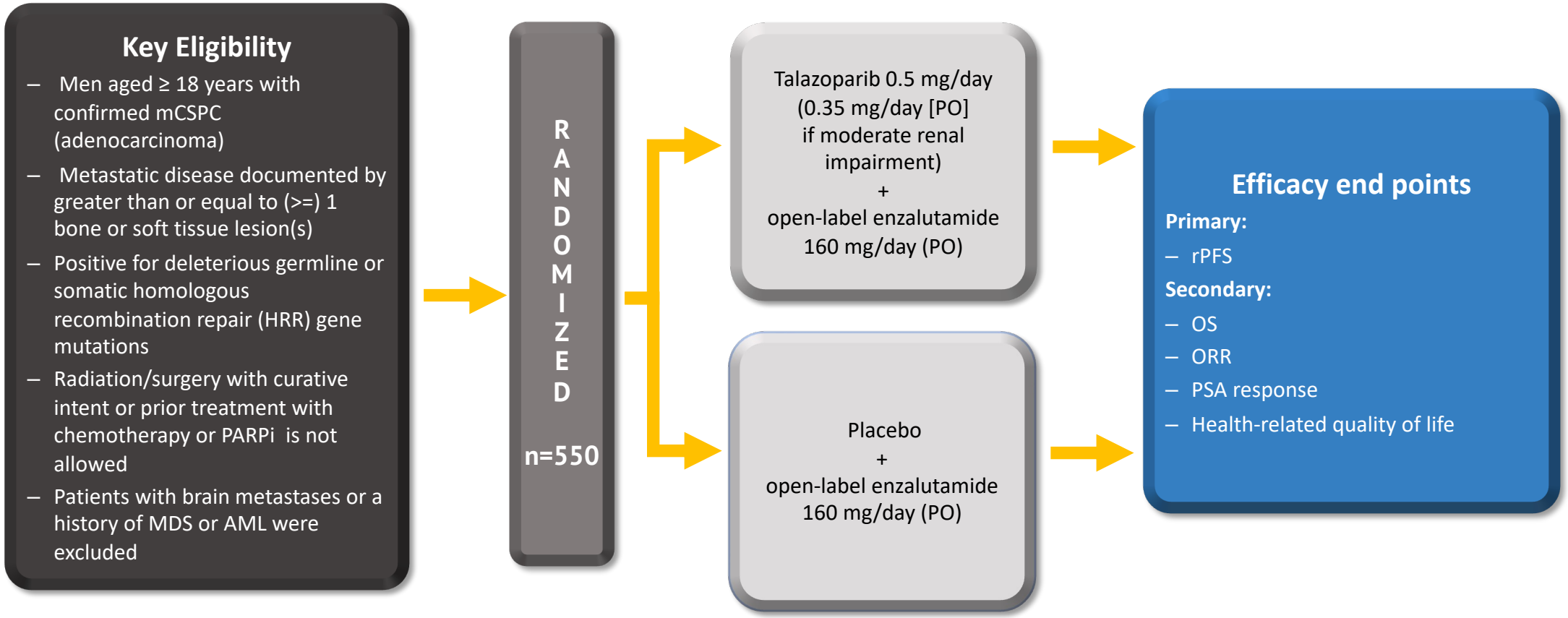
AMPLITUDE (Niraparib) : Phase 3 Trial Design (mCSPC)



www.clinicaltrials.gov: (NCT04497844)

Rathkopf et al., 2021, ABSTRACT TPS 176 ASCO-GU

TALAPRO-3 (Talazoparib) : Phase 3 Trial Design (mCSPC)



www.clinicaltrials.gov: (NCT04821622)

1 Agarwal et al., 2022, ABSTRACT TPS 221 ASCO-GU

Select Studies in mCRPC of PARP Inhibitors in Combination With Agents Targeting Potentially Synergistic Pathways

	AR Therapy	Immunotherapy		Cotargeting Other Pathways		
Olaparib	Ph III PROpel *Met primary endpoint* **Abiraterone**	Ph III KEYLYNK-010 **Pembrolizumab**	Ph II NCT03810105 **Durvalumab**	Ph I/II COMRADE* NCT03317392 **Radium-223**	Ph I LuPARP* NCT03874884 **^{177}Lu-PSMA-617**	Ph II NCT02893917 **Cediranib (VEGFRi)**
Talazoparib	Ph III TALAPRO-2 *Met primary endpoint* **Enzalutamide**			Ph II† NCT04824937 **Telaglenastat (GLSi)**	Ph I* NCT04846478 **Tazemetostat (EZH2i)**	Ph I* NCT04703920 **Belinostat (HDACi)**
Rucaparib	Ph III CASPAR* NCT04455750 **Enzalutamide**	Ph II CheckMate 9KD NCT03338790 **Nivolumab**		Ph II PLATI-PARP NCT03442556 **Chemotherapy**	Phase I/II NCT04253262 **Copanlisib (PI3Ki)**	
Niraparib	Ph III MAGNITUDE *Met primary endpoint* **Abiraterone**	Ph I/II QUEST NCT03431350 **Cetrelimab**		Ph I NiraRad NCT03076203 **Radium-223**		

Phase III

Early phase

Trials active as of February 2023. *Recruiting. †Not yet recruiting.

Conclusions

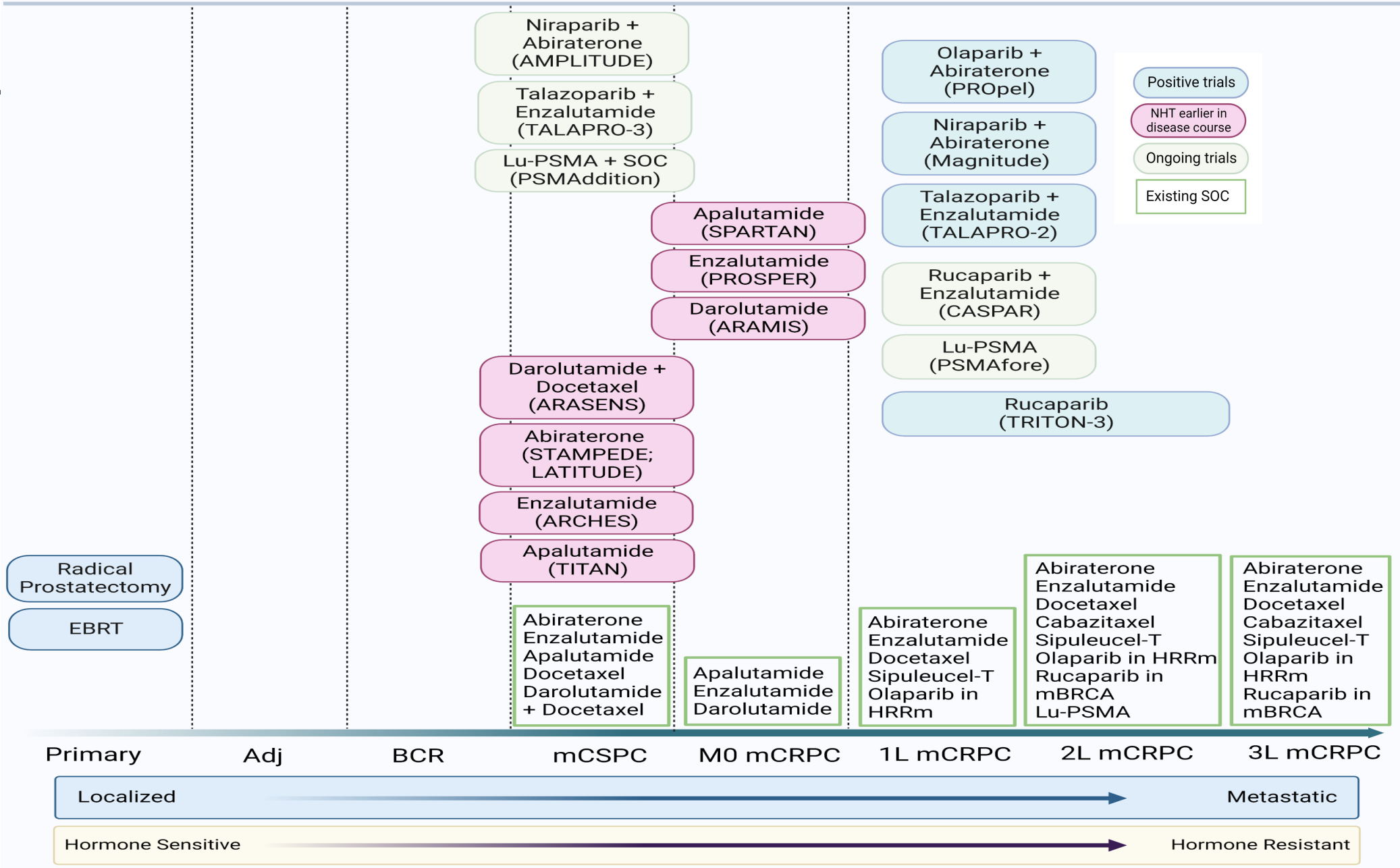
- Phase 3 trials (Magnitude and Propel) in the 1st line mCRPC showed improved rPFS in HRRm positive patients with the combination of NHT+PARPi, but conflicting results in HRRm negative patients

- All PARPi, and even combinations are not created equal.

- Phase 3 TALAPRO-2 trial in the 1st line mCRPC: Talazoparib + enzalutamide (vs. enzalutamide) improves rPFS in patients with or without HRRm

- Multiple PARPi studies ongoing in various settings of prostate cancer.

The Prostate Cancer CONTINUUM



Adj=Adjuvant; BCR=biochemical recurrence; mCSPC=metastatic castrate sensitive prostate cancer; mCRPC=metastatic castrate resistant prostate cancer; SOC=standard of care; NHT=novel hormonal therapy; EBRT=external beam radiation therapy; M0=non metastatic

Conclusion

- *Treatment of metastatic prostate cancer has undergone a revolution in the last decade leading to the approval of multiple novel agents*
- *In the absence of head-to-head comparison and biomarkers (for most agents), the art of medicine will continue to play a significant role in the sequencing of agents*
- *Eventual goal is to maximize receipt of life-prolonging agents while maintaining the quality of life*

@neerajaiims

Acknowledgements

- Umang Swami, MD
- Benjamin Louis Maughan, MD
- Nicolas Sayegh, MD
- Georges Gebrael, MD
- Nishita Tripathi, MD
- Beverly Chigarira, BS
- Roberto Nussenzveig, PhD

@neerajaiims

Thank you!

@neerajaiims