Prostate Cancer: Targeted, Hormonal & Novel Pathways in mCRPC

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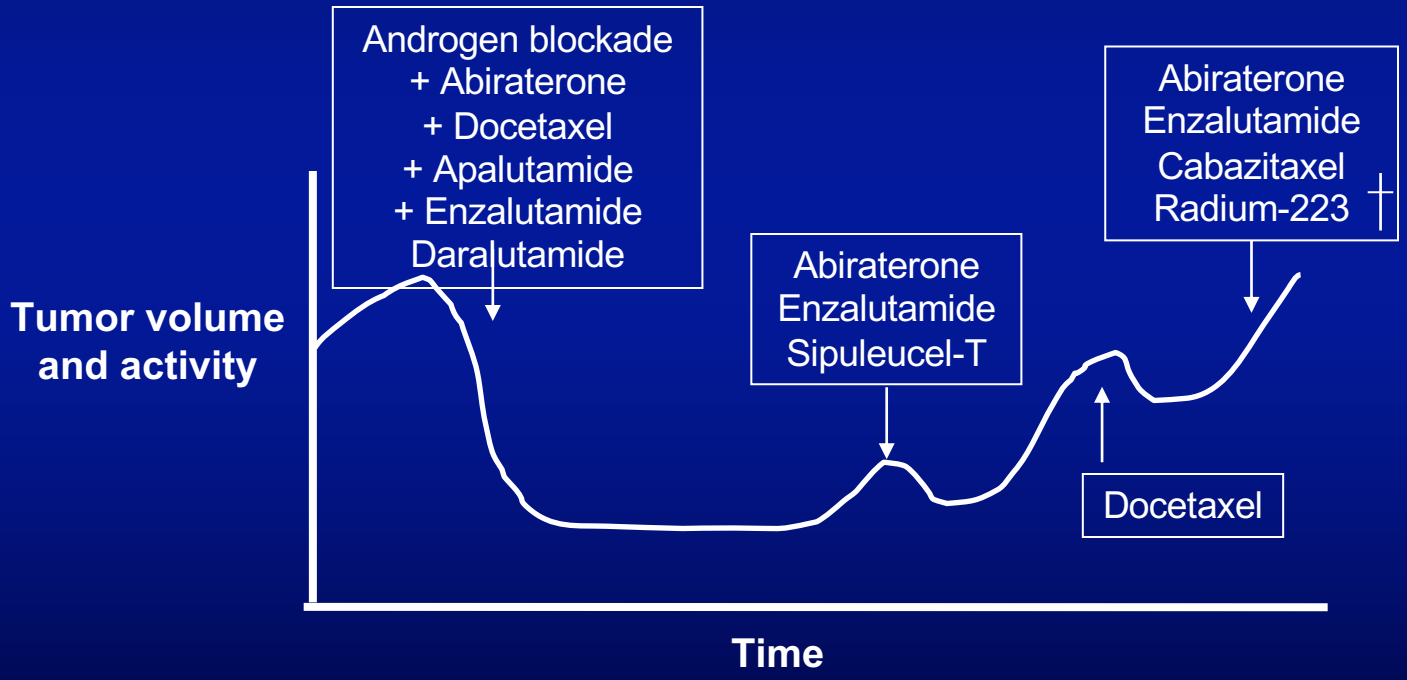
Treatment of Metastatic Prostate Cancer



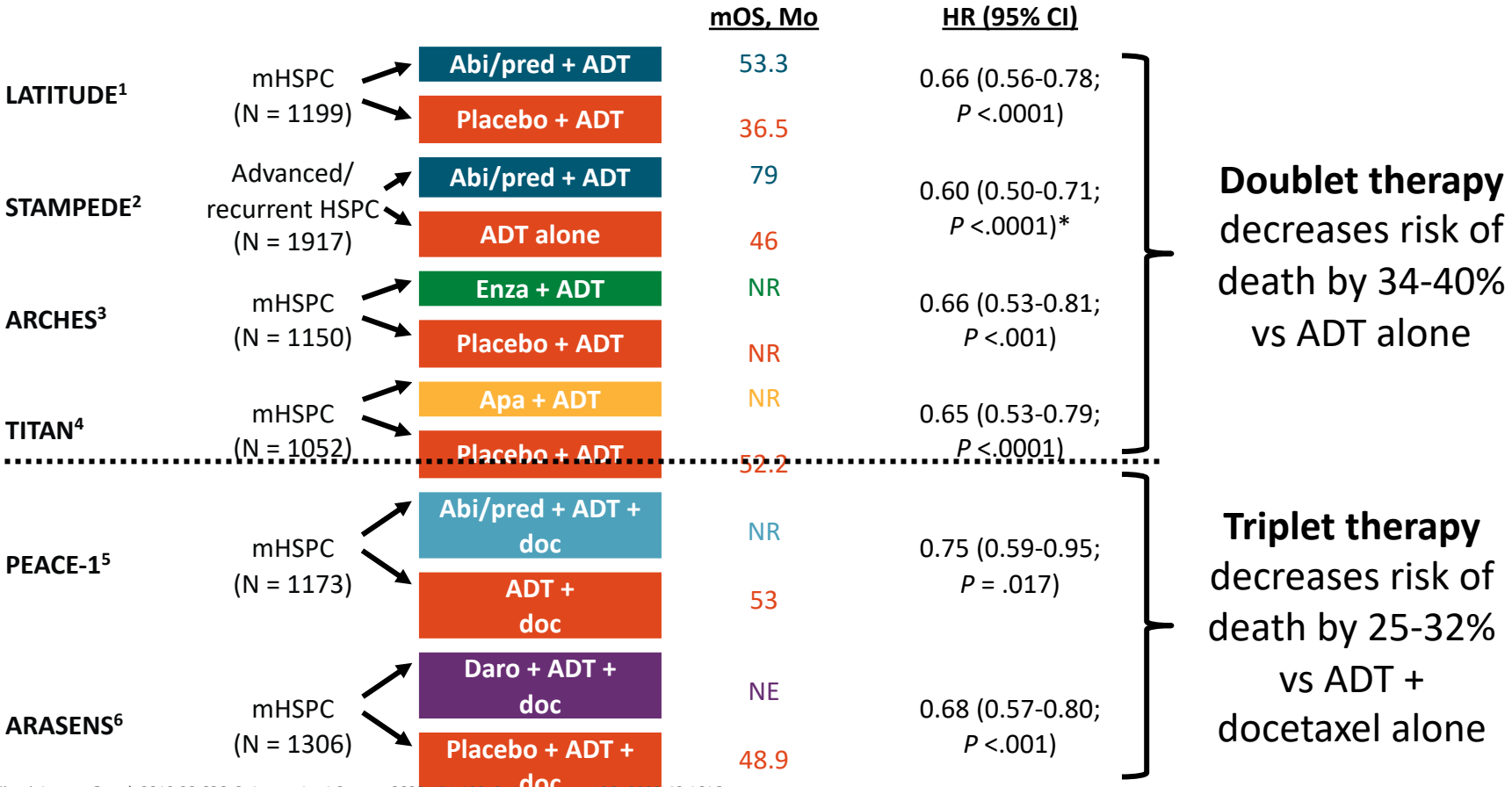
Does the Earlier Use of Chemotherapy or Next Generation AR Targeting Agents Improve Survival?

Metastatic HSPC: Many Treatment Options

- Androgen-deprivation therapy (ADT) is the mainstay of managing mHSPC
- Intensifying therapy beyond ADT alone has shown improved survival
  - **Doublet therapy:** AR-directed therapy (abiraterone/prednisone, apalutamide, enzalutamide) + ADT
  - **Triplet therapy:** Chemotherapy (docetaxel) + AR-directed therapy (abiraterone/prednisone, darolutamide) + ADT
  - **Radiation therapy** to the prostate in the setting of low-volume disease

NCCN. Clinical practice guidelines in oncology: prostate cancer. v.1.2023.

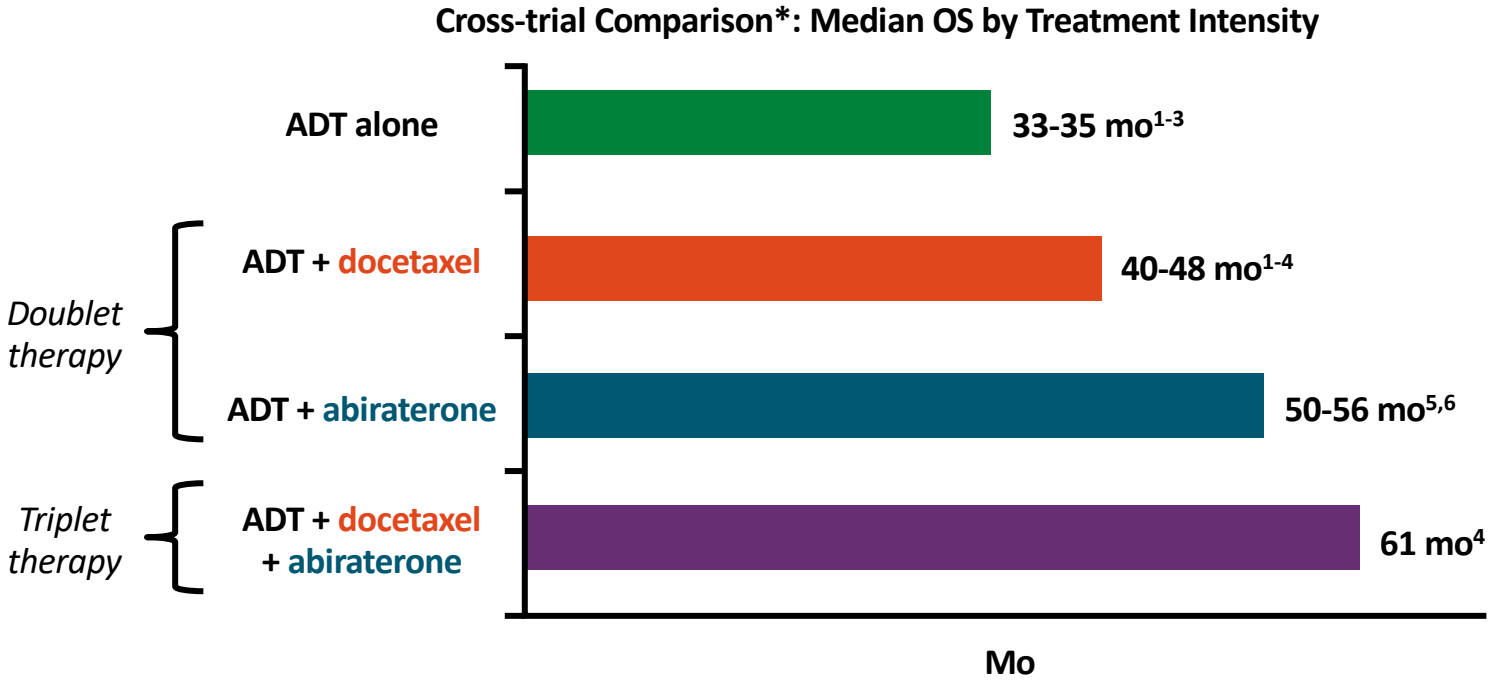
OS With Doublet and Triplet Therapy in mHSPC



1. Fizazi. Lancet Oncol. 2019;20:686. 2. James. Int J Cancer. 2022;151:422. 3. Armstrong. JCO. 2023;40:1616.
4. Chi. JCO. 2021;39:2294. 5. Fizazi. Lancet. 2022;399:1695. 6. Smith. NEJM. 2022;386:1132.

*In subgroup with metastatic disease.

Median OS With Treatment Intensification in De Novo High-Volume mHSPC



*Cross-trial comparisons have significant limitations. Data are shown here to generate discussion, not directly compare between trials.

1. Kyriakopoulos. JCO. 2018;36:1080. 2. Gravis. Eur Urol. 2018;73:847. 3. Clarke. Ann Oncol. 2019;30:1992.
4. Fizazi. Lancet. 2022;399:1695. 5. Fizazi. Lancet Oncol. 2019;20:686. 6. James. Int J Cancer. 2022;151:422.

Treatment Selection for mHSPC

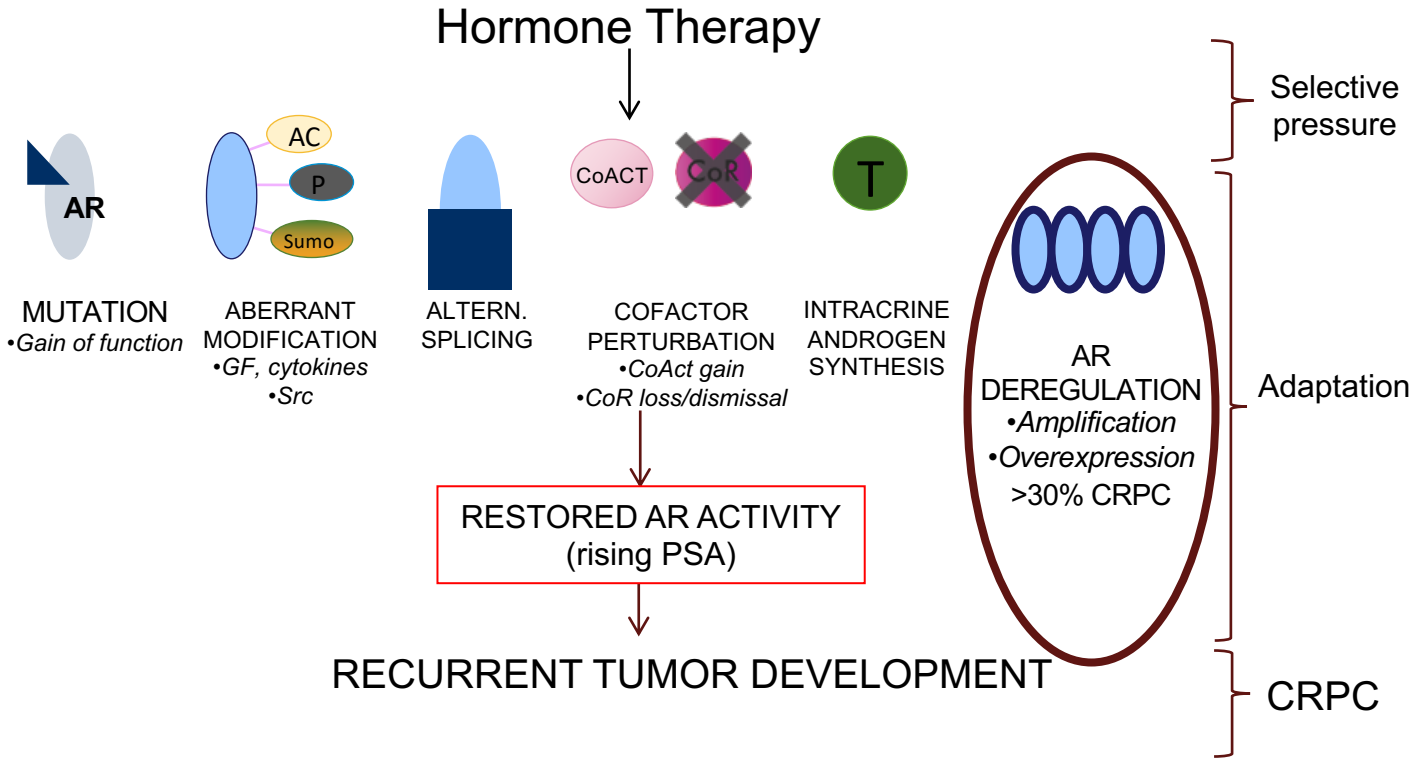
- Choice of agent depends on cost, safety profile, patient comorbidities

Abiraterone	Enzalutamide	Apalutamide	Darolutamide	Docetaxel
▪ Generic ▪ Requires K+/LFT/BP monitoring ▪ Concern for long-term HTN and prednisone ▪ Less fatigue than AR antagonists ▪ **Can intensify to triplet therapy**	▪ Less monitoring ▪ Concern for neurocognitive issues	▪ Less monitoring ▪ Concern for rash and neurocognitive issues	▪ Less monitoring ▪ **Can intensify to triplet therapy**	▪ Least expensive ▪ Completed after 6 cycles ▪ Offer while chemo fit ▪ Potential for new/worsened neuropathy ▪ Can consider stopping early if exceptional responder/not tolerating chemo

- **Triplet therapy** often used in fit patients with aggressive disease or features suggesting less dependence on AR (high volume of metastatic disease, low PSA given volume of disease, high grade/poorly differentiated)

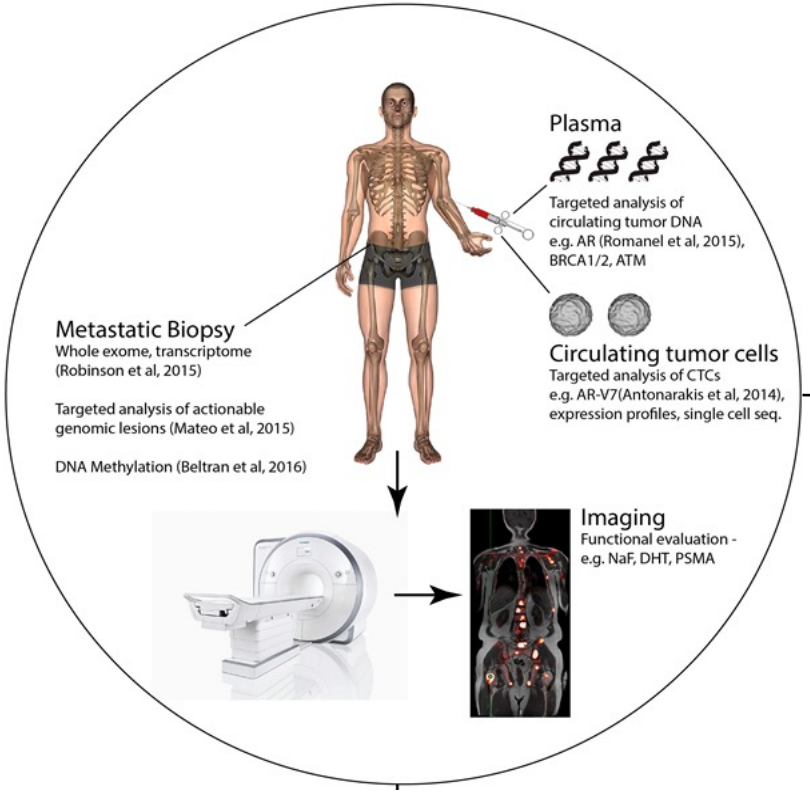
Abiraterone PI. Shpilsky. Expert Opin Pharmacother. 2021;22:1227. Fizazi. Lancet. 2022;399:1695. Enzalutamide PI. Ryan. Prostate Cancer Prostatic Dis. 2020;23:207. Apalutamide PI. Schulte. Am Soc Clin Oncol Educ Book. 2020;40:1. Darolutamide PI. Smith. NEJM. 2022;386:1132. Docetaxel PI. Thomas. Cancers. 2022;14:8. NCCN Clinical Practice Guidelines in Oncology: Prostate Cancer. v.1.2023. Maluf. JCO Glob Oncol. 2021;7:559.

Development of Castrate-Resistant Prostate Cancer



Penning and Knudsen. *Trends Endocrinol Metab*. 2010;21(5):315-324.

Molecular Biomarkers Under Investigation: Improving Clinical Decision Making for Patients With Advanced Prostate Cancer



Treatment decision

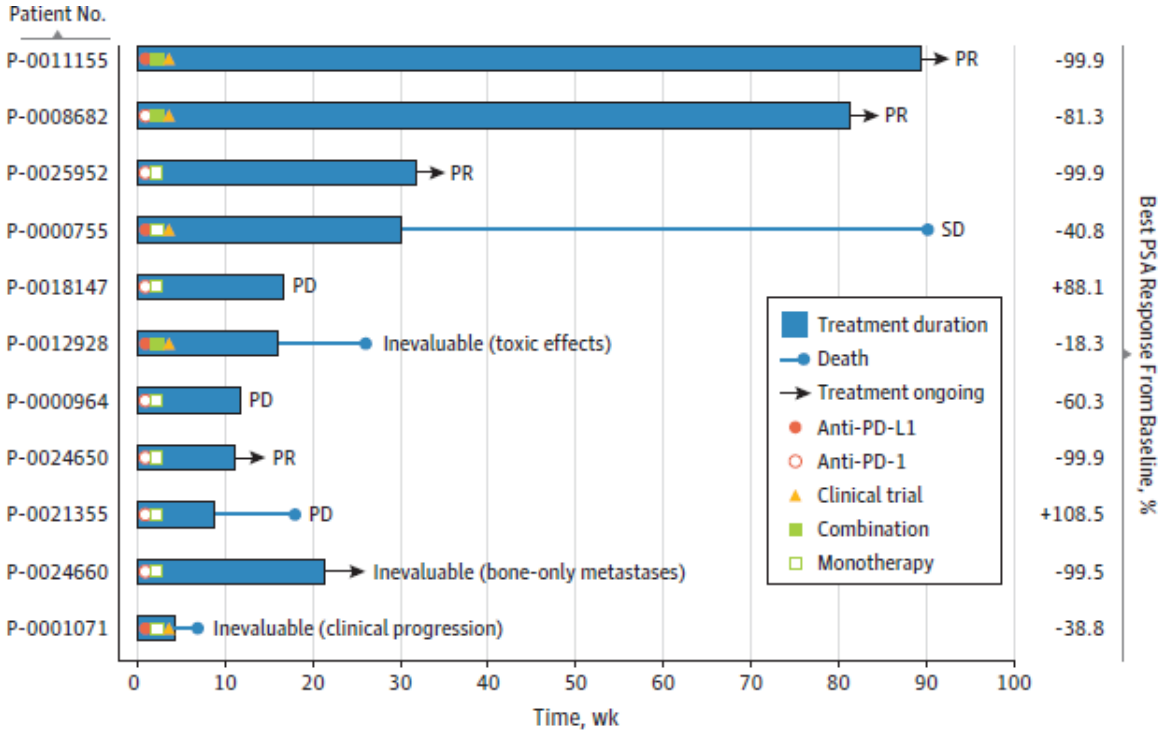
Image from Bertran H, et al. 2016 ASCO Educational Book. Presented June 4, 2016.

MSI in Prostate Cancer

- 1033 patients who had adequate tumor quality for MSI sensor analysis; 32 (3.1%) had MSI-H/dMMR prostate cancer
- 23 of 1033 patients (2.2%) had tumors with high MSI sensor scores, and an additional 9 had indeterminate scores with evidence of dMMR
- 7 of the 32 MSI-H/dMMR patients (21.9%) had a pathogenic germline mutation in a Lynch syndrome-associated gene
- 6 patients had more than 1 tumor analyzed; 2 of these patients displayed an acquired MSI-H phenotype later in their disease course

Abida W, et al. *JAMA Oncol*. 2019;5(4):471-478.

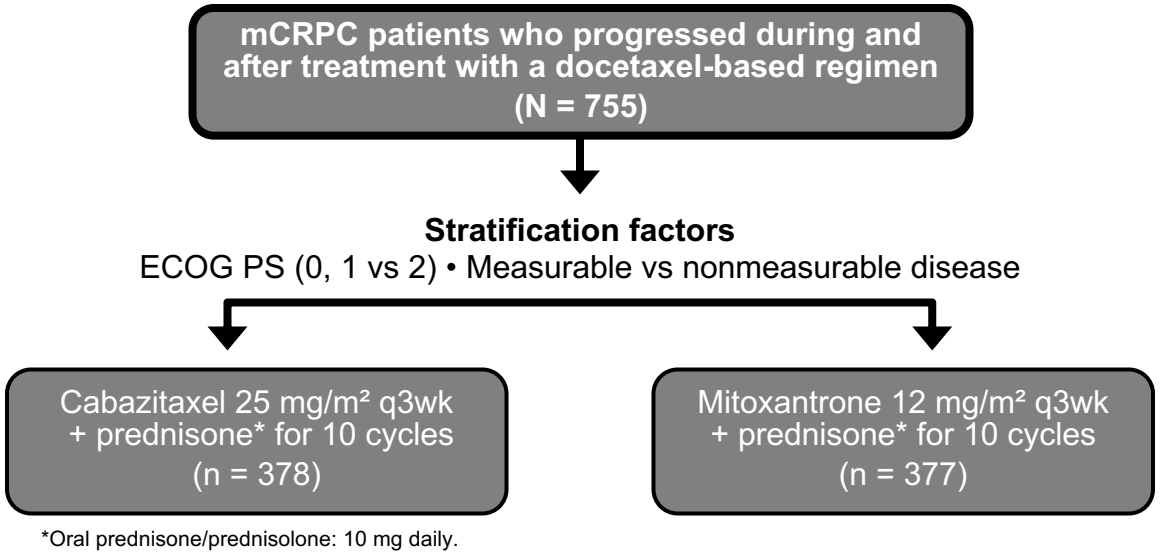
MSI in Castration-Resistant Prostate Cancer



Abiraterone and Enzalutamide

- There is clinical evidence of cross-resistance between Abi and Enza
- PSA responses to Abi/Enza after prior Enza/Abi are 10-20% and rPFS is 3-4 months (Noonan KL, et al. *Ann Oncol.* 2013; 24:1802-1807; Loriot Y, et al. *Ann Oncol.* 2013;24:1807-1812; Schrader AJ, et al. *Eur Urol.* 2014;65:30-36; Badrising S, et al. *Cancer.* 2014;120:968-975; Cheng HH, et al. *Prostate Cancer Prostatic Dis.* 2015;18:122-127)
- There is evidence of cross-resistance between Abi/Enza and taxanes
- Abi/Enza are less effective after taxanes (deBono JS, et al. *N Engl J Med.* 2011;364:1995-2005; Scher HI, et al. *N Engl J Med.* 2012;367:1187-1197; Nadal R, et al. *Prostate.* 2014;74:1560-1568), and taxanes are less effective after Abi/Enza (Schweizer MT, et al. *Eur Urol.* 2014;66:646-652; Mezynski J, et al. Ann Oncol. 2012;23:2943-2947)

TROPIC: Phase III Registration Study – 146 Sites in 26 Countries



*Oral prednisone/prednisolone: 10 mg daily.

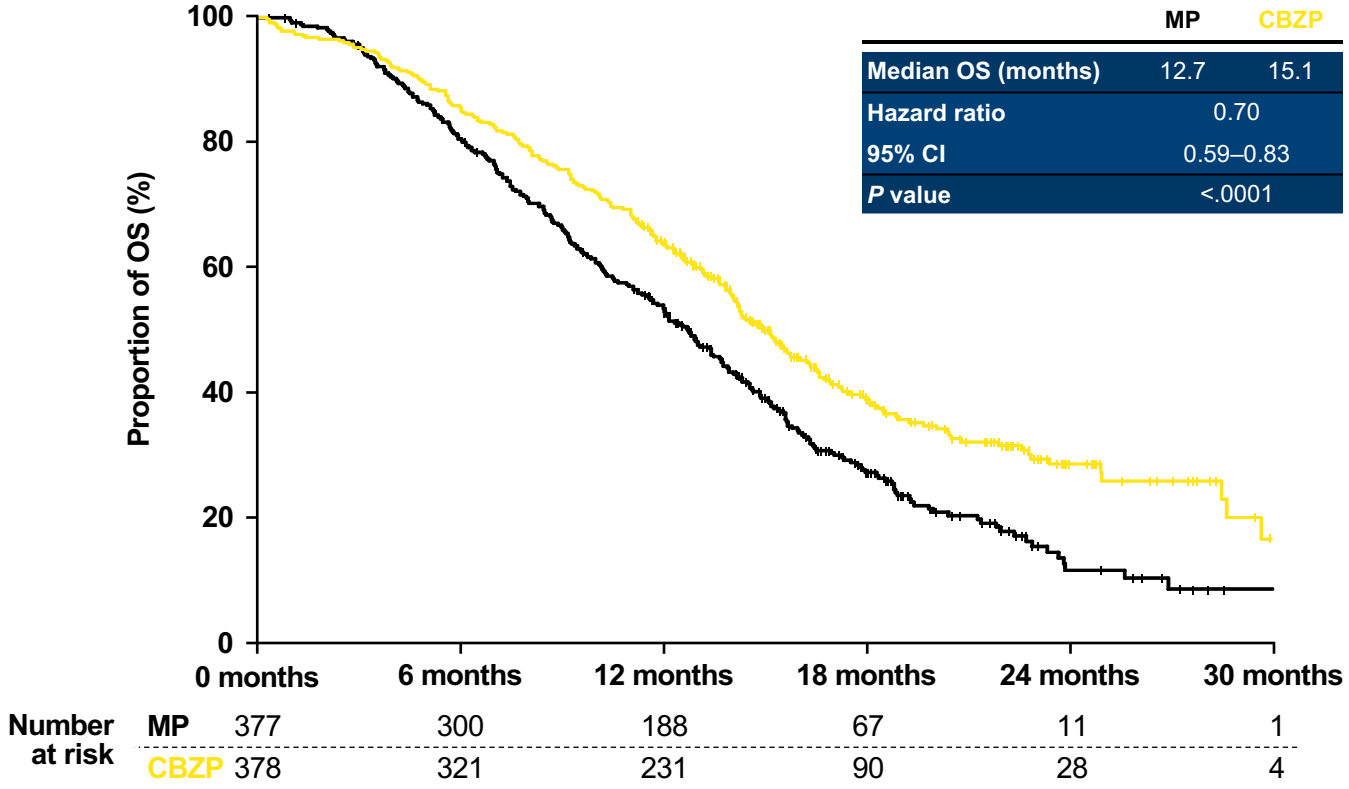
Primary endpoint: OS

Secondary endpoints: progression-free survival (PFS), response rate, and safety

Inclusion: Patients with measurable disease must have progressed by RECIST; otherwise, must have had new lesions or PSA progression

de Bono JS, et al. *Lancet*. 2010;376(9747):1147-1154.

Primary Endpoint: Overall Survival (ITT Analysis)



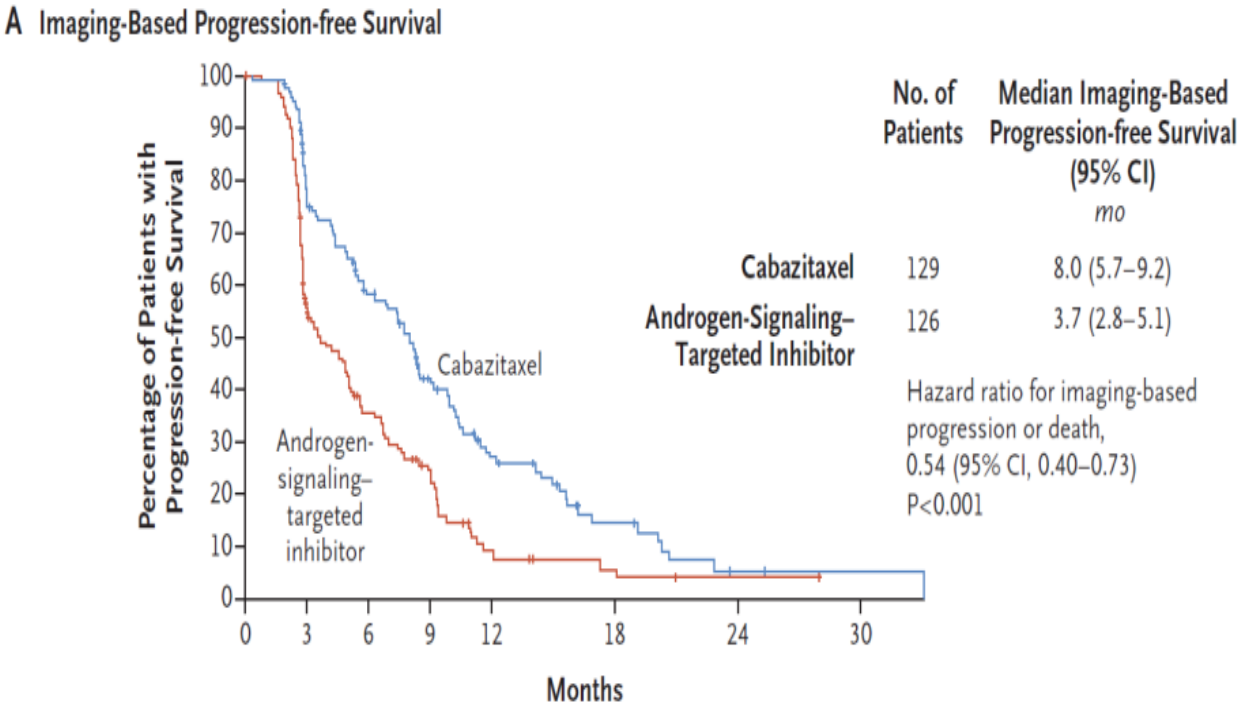
de Bono JS, et al. *Lancet*. 2010;376(9747):1147-1154.

Cabazitaxel versus Abiraterone or Enzalutamide in Metastatic Prostate Cancer

R. de Wit, J. de Bono, C.N. Sternberg, K. Fizazi, B. Tombal, C. Wülfing, G. Kramer, J.-C. Eymard, A. Bamias, J. Carles, R. Iacovelli, B. Melichar, Á. Sverrisdóttir, C. Theodore, S. Feyerabend, C. Helissey, A. Ozatilgan, C. Geffriaud-Ricouard, and D. Castellano, for the CARD Investigators*

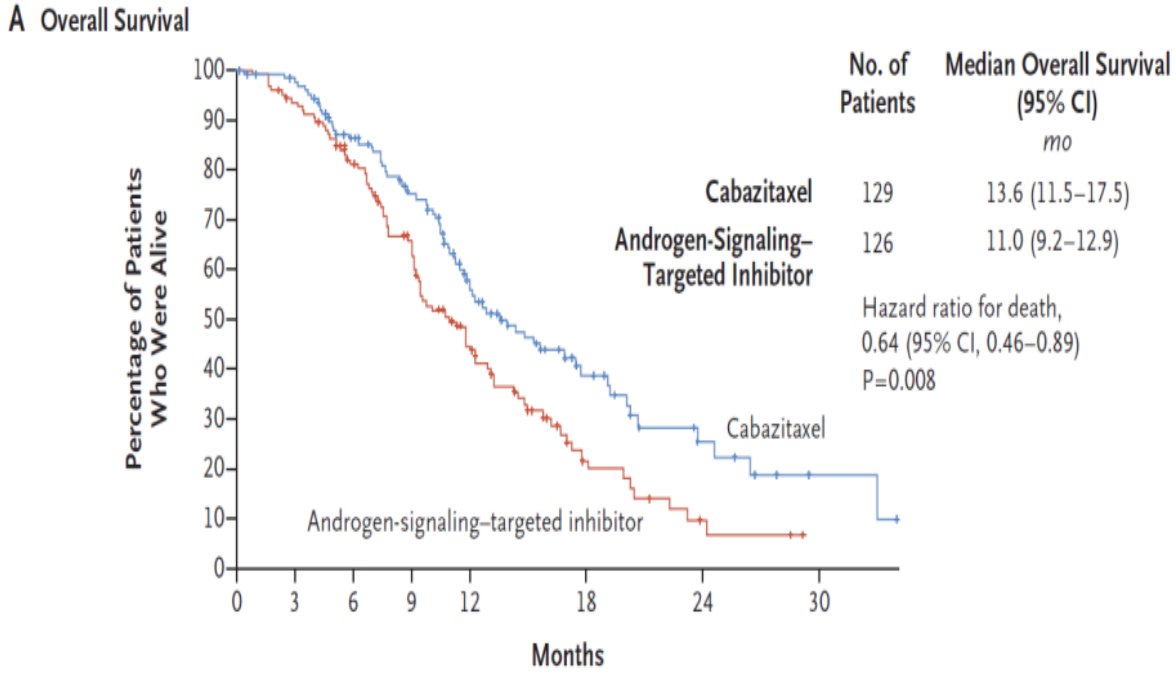
de Wit R, et al. *N Engl J Med*. 2019;381(26):2506-2518.

CARD



de Wit R, et al. *N Engl J Med*. 2019;381(26):2506-2518.

CARD



de Wit R, et al. *N Engl J Med*. 2019;381(26):2506-2518.

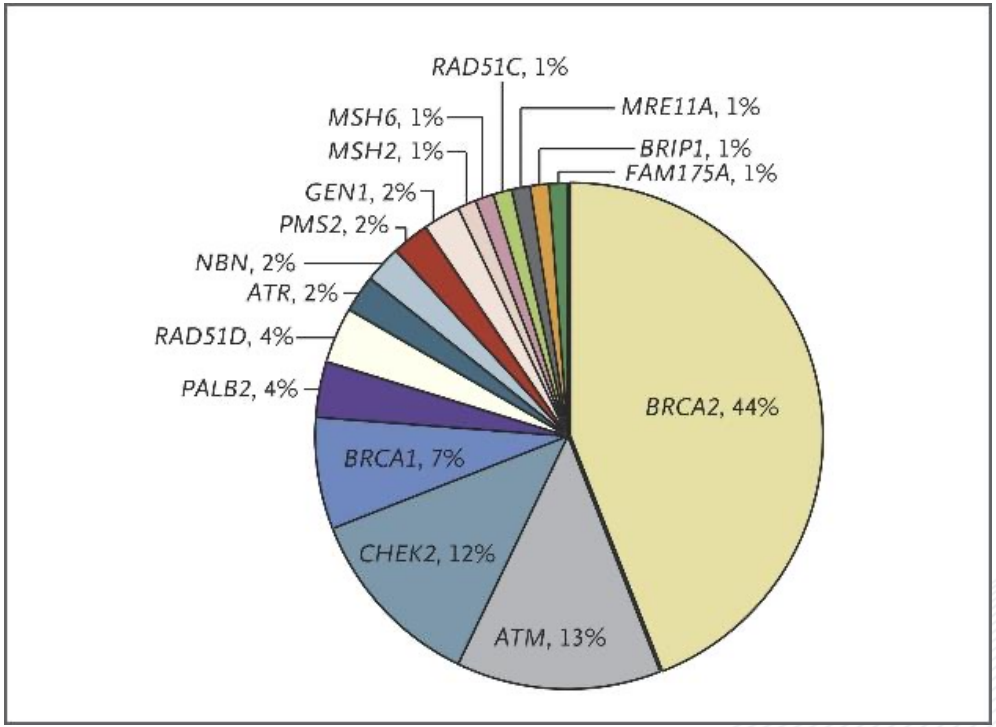
Germline DNA-Repair Gene Mutations in 7 Metastatic Prostate Cancer Case Series

Table 3. Germline DNA-Repair Gene Mutations in Seven Metastatic Prostate Cancer Case Series.

Case Series	Description	Patients	Patients with Mutations
		no.	*no. (%)*
1	Stand Up To Cancer–Prostate Cancer Foundation discovery series	150	15 (10.0)
2	Stand Up To Cancer–Prostate Cancer Foundation validation series	84	9 (10.7)
3	Royal Marsden Hospital	131	16 (12.2)
4	University of Washington	91	8 (8.8)
5	Weill Cornell Medical College	69	7 (10.1)
6	University of Michigan	43	4 (9.3)
7	Memorial Sloan Kettering Cancer Center	124	23 (18.5)
Total		692	82 (11.8)

Pritchard CC, et al. *N Engl J Med.* 2016;375:443-453.

Distribution of Presumed Pathogenic Germline Mutations



The NEW ENGLAND JOURNAL of MEDICINE

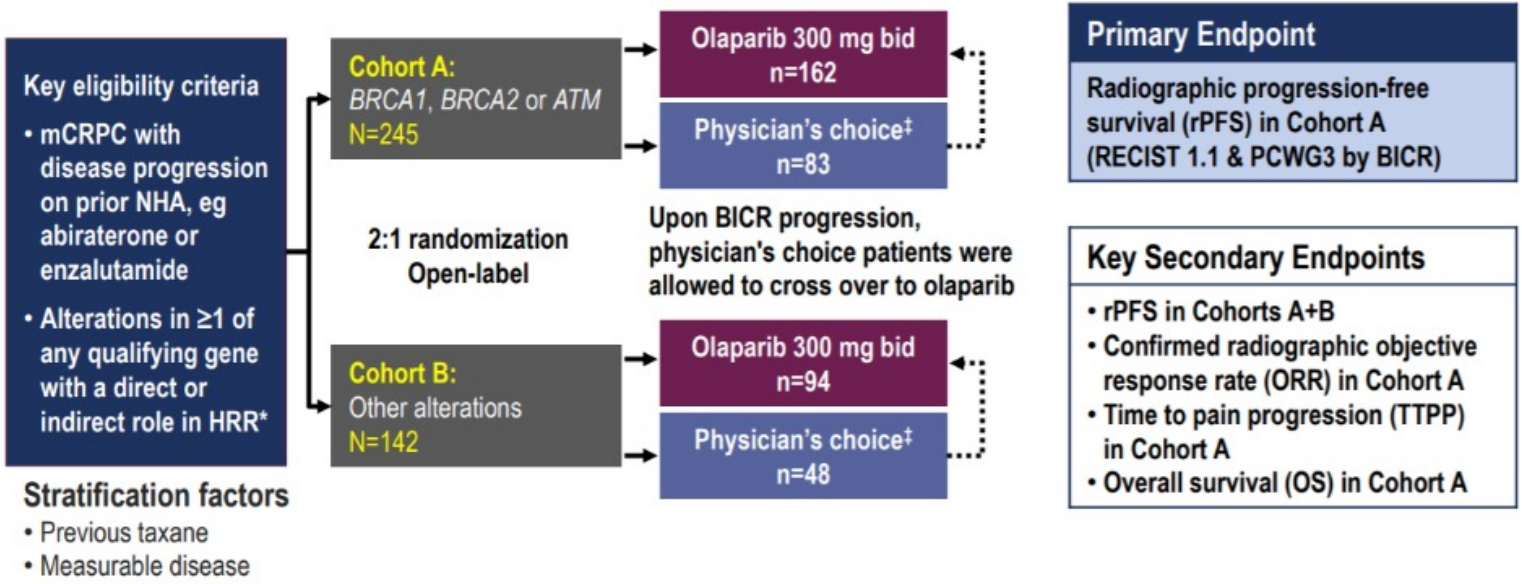
Olaparib in Prostate Cancer

- **TOPARP study: n = 49 patients with mCRPC who are docetaxel pretreated** (Mateo et al. 2015)
  - **32.7% (16/49**) response rate in “unselected” mCRPC patients
  - Genomic analysis of their prospectively obtained tumor samples
    - **16 (33%)** had mutations in DNA repair pathway (*ATM, BRCA2,* and others*;* biomarker positive)

      14 of these patients responded
    - **33 (67%)** had no such mutations (biomarker negative);

      2 of these patients responded

Phase III PROfound Study: Study Design

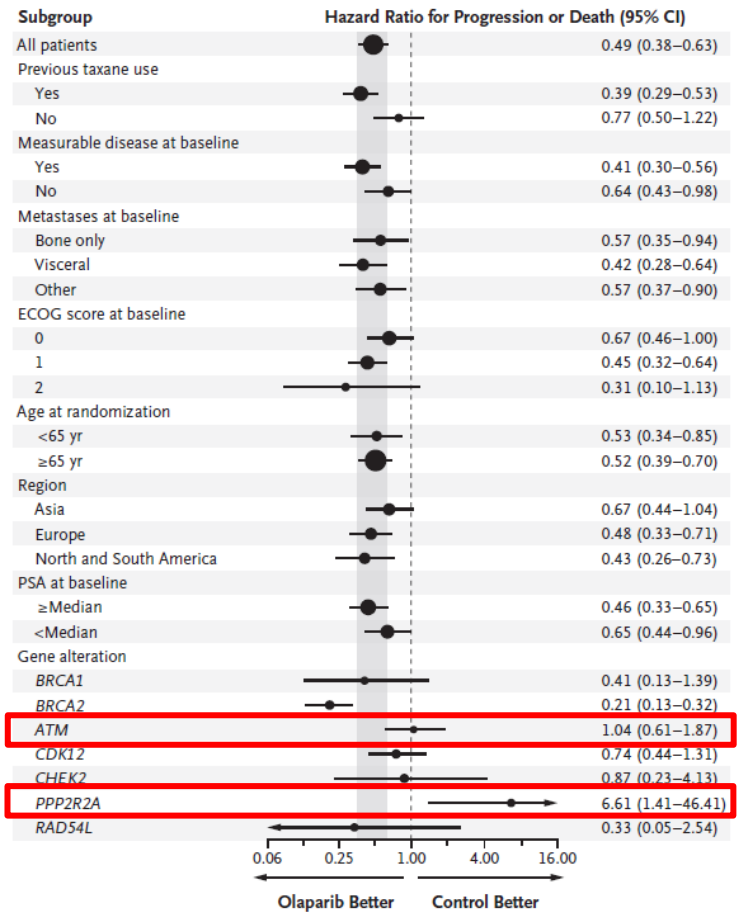


*An investigational Clinical Trial Assay, based on the FoundationOne® CDx next-generation sequencing test

Developed in partnership with Foundation Medicine Inc, and used to prospectively select patients harboring alterations in *BRCA1*, *BRCA2*, *ATM*, *BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *PPP2R2A*, *RAD51B*, *RAD51C*, *RAD51D* and/ or *RAD54L* in their tumor tissue

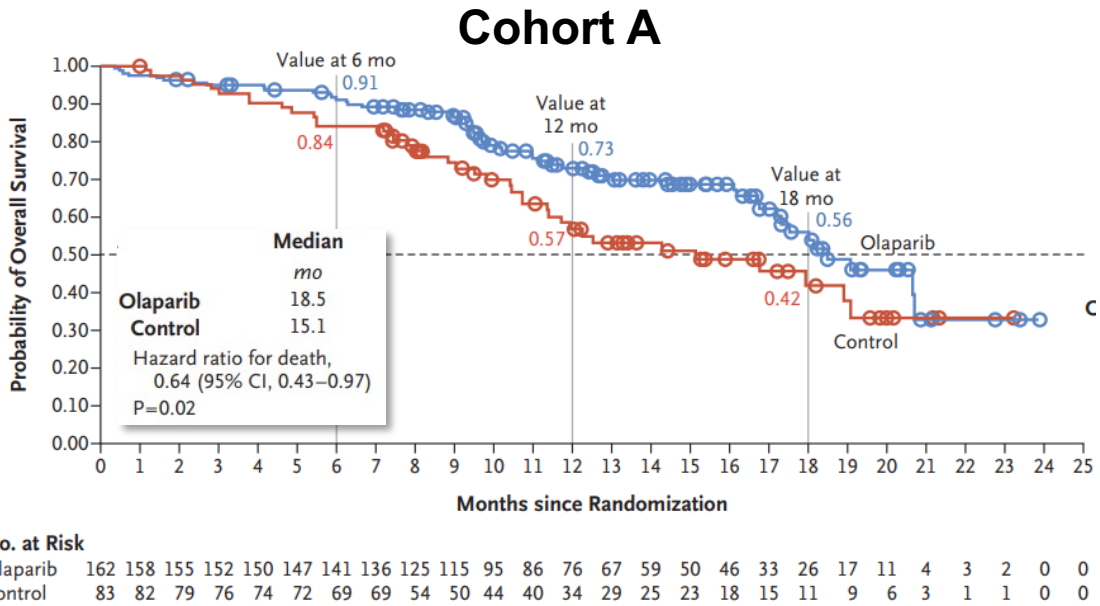
Hussain M, et al. ESMO 2019. Abstract LBA12.

PROfound: PFS by Subgroup (Overall Population)



de Bono J, et al. *N Engl J Med*. 2020;382:2091-2102.

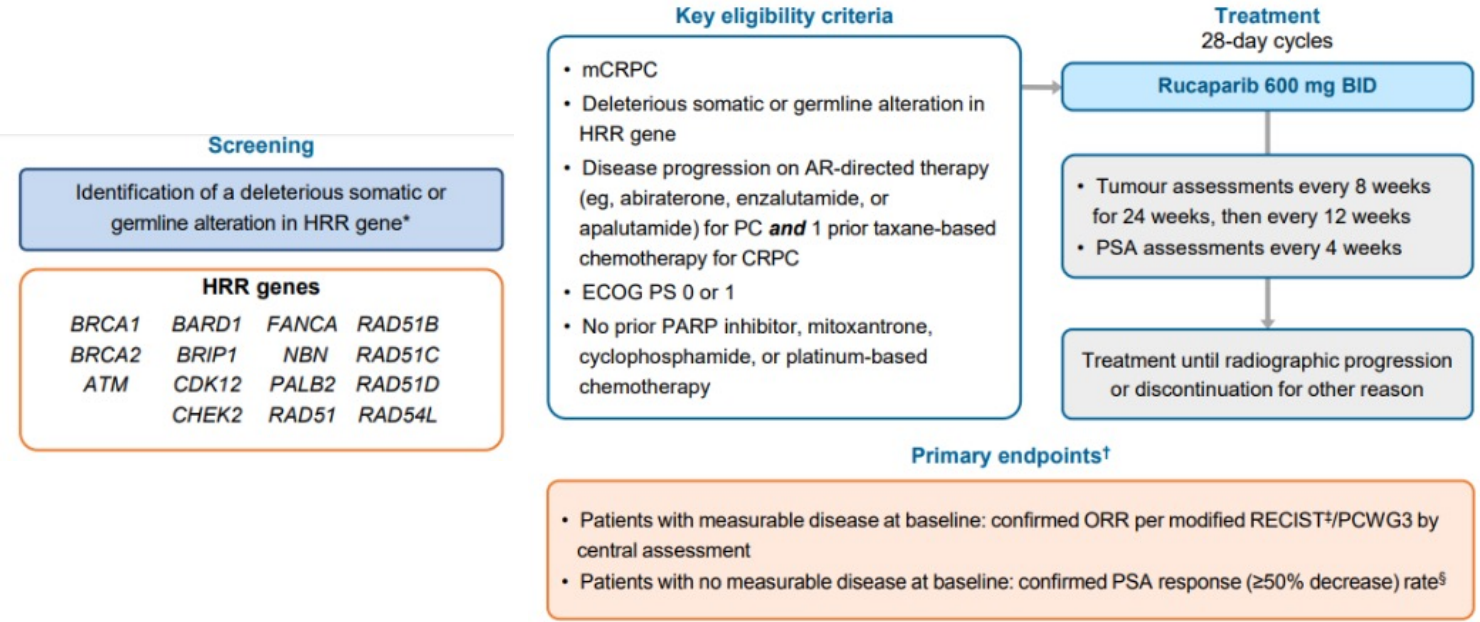
Phase III PROfound Study: Interim OS



Overall population, median OS: 17.5 mo vs 14.3 mo (HR, 0.67; 95% CI, 0.49-0.93; *P* =.0063)

de Bono J, et al. *N Engl J Med*. 2020;382:2091-2102.

Phase II TRITON2 Trial of Rucaparib for mCRPC: Study Design

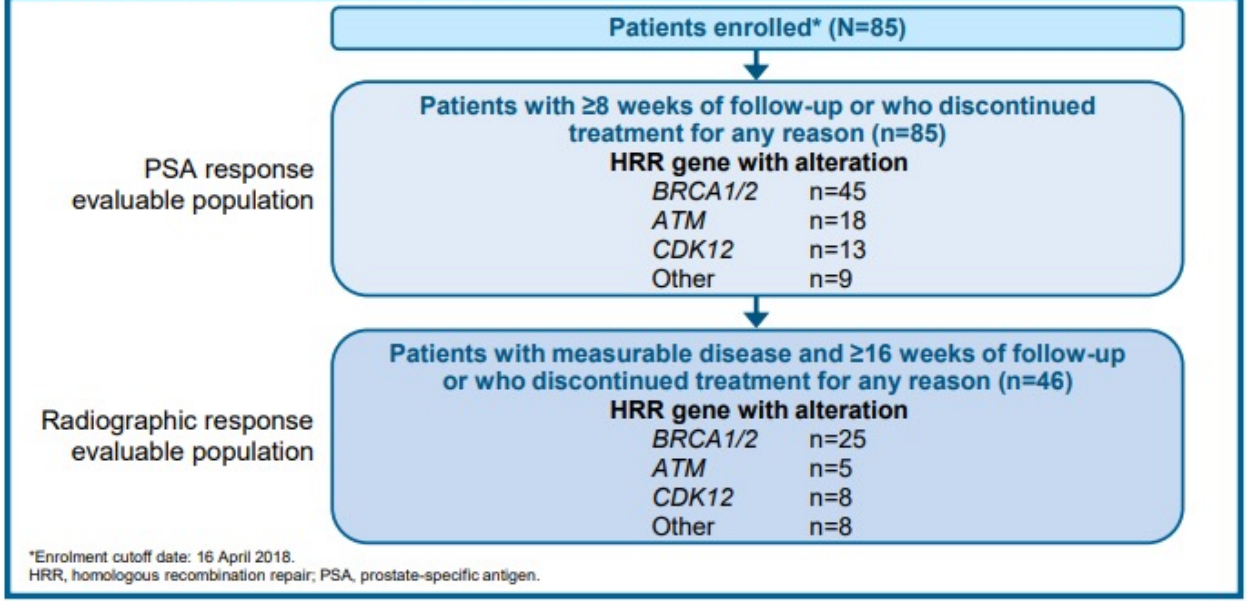


Abida W, et al. *J Clin Oncol*. 2018;36(6 suppl): abstractTPS388.

Phase II TRITON2: Population

- As of 16 April 2018, 85 patients were enrolled in TRITON2 (**Figure 2**; **Table 1**)
  - At the visit cutoff date (29 June 2018), median duration of follow-up was 5.7 months (range, 2.6–16.4 months)

Figure 2. Efficacy Populations



*Enrolment cutoff date: 16 April 2018.
HRR, homologous recombination repair; PSA, prostate-specific antigen.

Abida W, et al. *Clin Cancer Res*. 2020;26(11):2487-2496.

Phase II TRITON2: Radiographic Response

Investigator-confirmed objective response in patients with measurable disease

Radiographic response in patients with measurable disease

- 44% (11/25)
- 1 patient with a *BRIP1* alteration and 1 patient with a *FANCA* alteration

Table 2. Confirmed Investigator-Assessed ORR in Evaluable Patients

Characteristic	By HRR gene with alteration			
	BRCA1/2 (n=25)	*ATM* (n=5)	*CDK12* (n=8)	Other (n=8)
ORR, n (%) [95% CI][a]	11 (44.0%) [24.4–65.1]	0 [0.0–52.2]	0 [0.0–36.9]	2 (25.0%) [3.2–65.1]
Complete response, n (%)	0	0	0	0
Partial response, n (%)	11 (44.0%)	0	0	2 (25.0%)[b]
Stable disease, n (%)	9 (36.0%)	4 (80.0%)	5 (62.5%)	5 (62.5%)
Progressive disease, n (%)	4 (16.0%)	1 (20.0%)	2 (25.0%)	1 (12.5%)
Not evaluable, n (%)	1 (4.0%)	0	1 (12.5%)	0

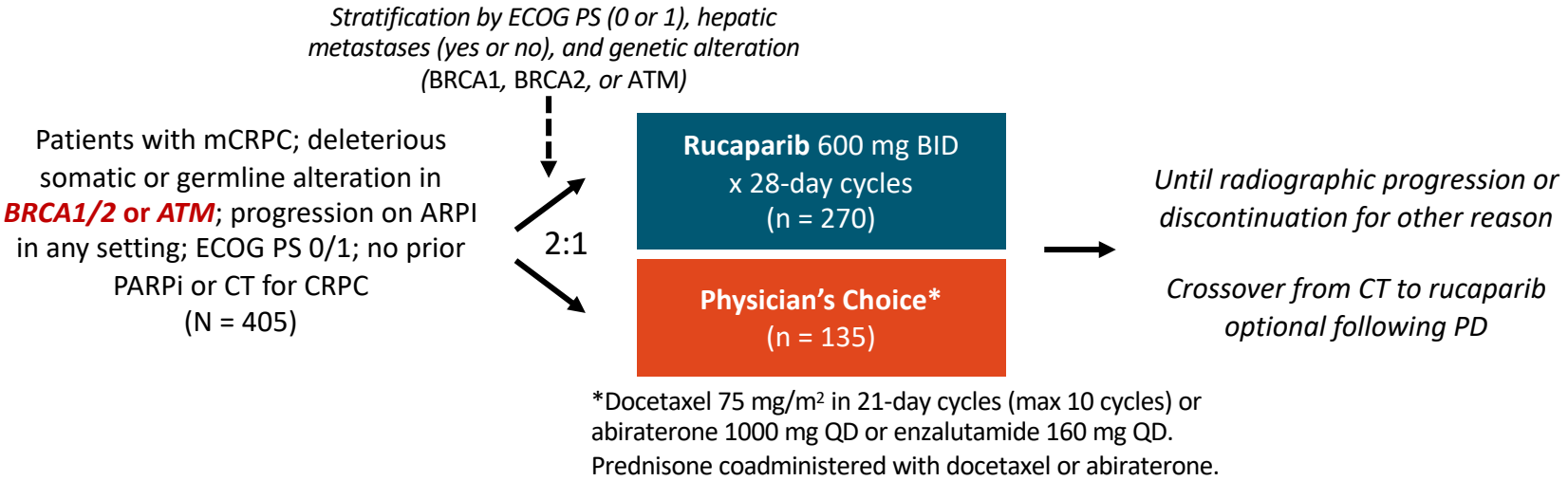
Abida W, et al. *Clin Cancer Res*. 2020;26(11):2487-2496.

PARP Inhibitor Toxicities

- Hematologic: anemia, thrombocytopenia, neutropenia
- Nausea
- Fatigue, asthenia
- Liver enzyme elevations
- Most AEs low-grade except anemia
- Grade 3-4 AEs leading to treatment interruption, dose reduction, or discontinuation more common in PARP arms than controls
- Often these toxicities are tolerable after dose tailoring and wane over time, allowing continued long-term dosing

TRITON3: Study Design

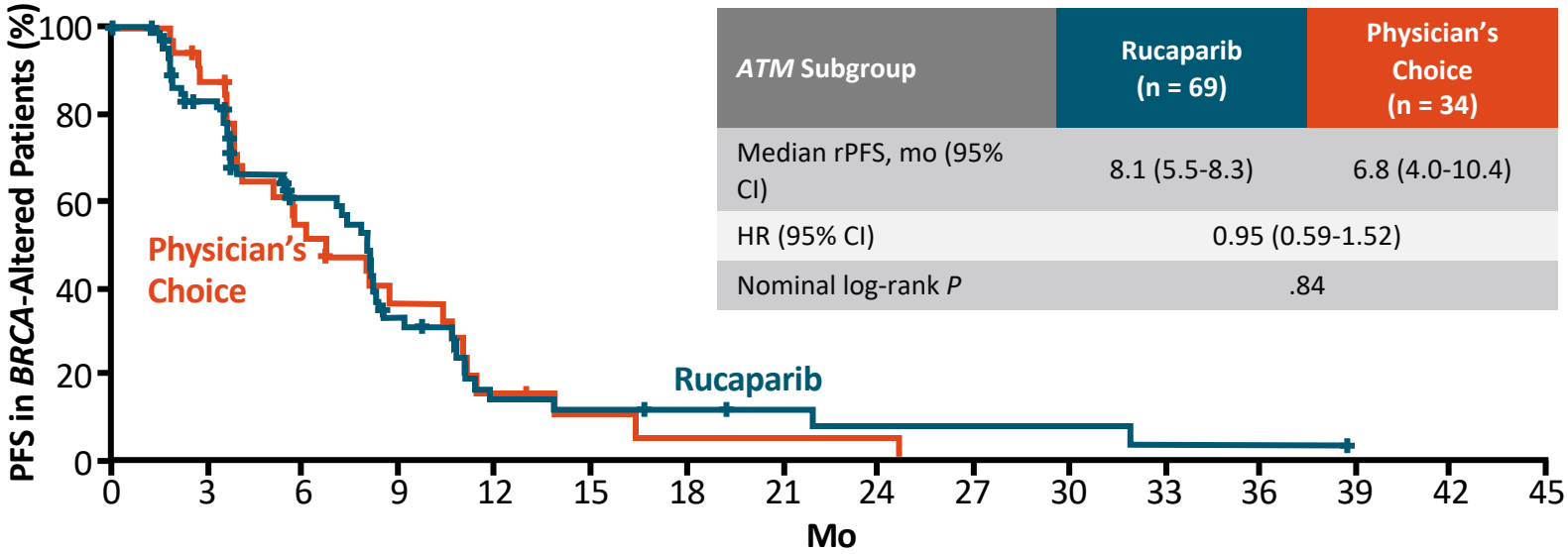
- Randomized, ongoing, multicenter, open-label phase III study



- **Primary endpoint:** rPFS by IRR
- **Key secondary endpoints:** OS, ORR by IRR

Fizazi. NEJM. 2023;[Epub]. Bryce. ASCO GU 2023. Abstr 18.

TRITON3: rPFS (*ATM*-Altered Subgroup)



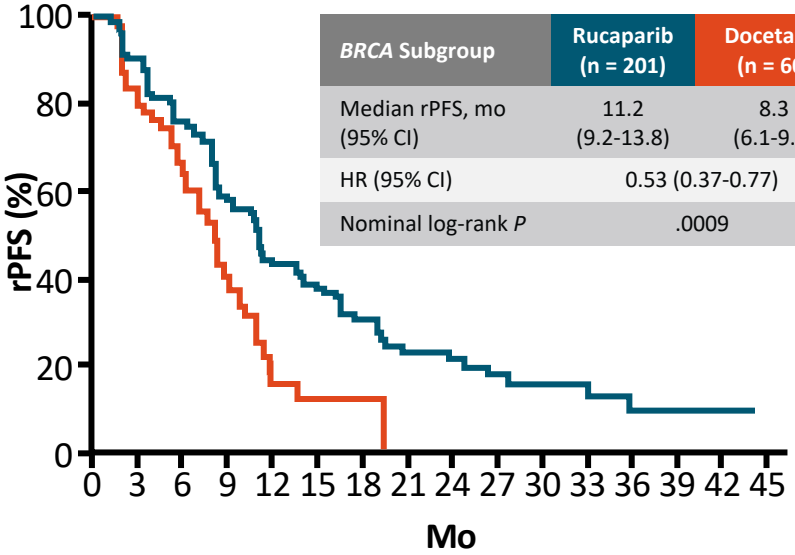
ATM Subgroup	Rucaparib (n = 69)	Physician's Choice (n = 34)
Median rPFS, mo (95% CI)	8.1 (5.5-8.3)	6.8 (4.0-10.4)
HR (95% CI)	0.95 (0.59-1.52)	
Nominal log-rank *P*	.84	

No. at Risk														
Rucaparib	69 (0)	51 (11)	31 (24)	16 (38)	6 (46)	5 (47)	4 (47)	3 (47)	1 (48)	2 (48)	2 (48)	1 (49)	1 (49)	0 (49)
Physician's Choice	34 (0)	28 (4)	16 (12)	9 (19)	4 (24)	2 (25)	1 (26)	1 (26)	1 (26)	0 (27)				

Fizazi. NEJM. 2023;[Epub]. Bryce. ASCO GU 2023. Abstr 18.

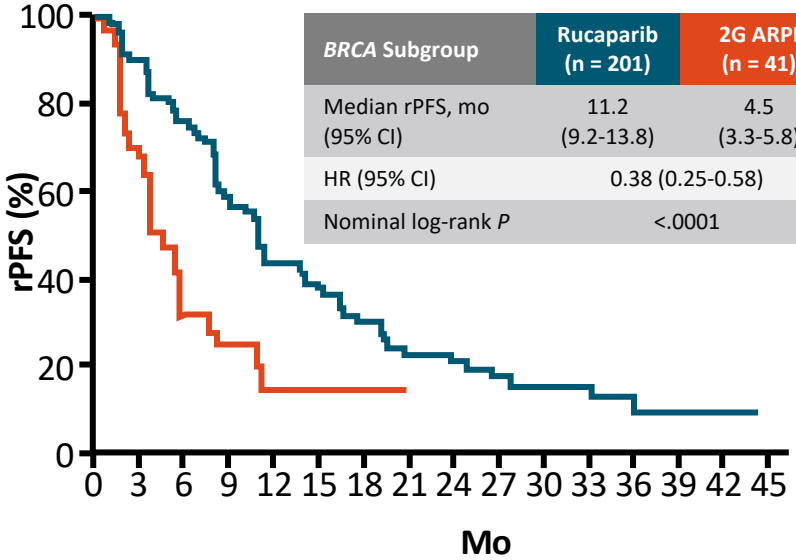
TRITON3: rPFS (*BRCA* Subgroup) by Physician's Choice Treatment

Rucaparib vs Docetaxel



BRCA Subgroup	Rucaparib (n = 201)	Docetaxel (n = 60)
Median rPFS, mo (95% CI)	11.2 (9.2-13.8)	8.3 (6.1-9.9)
HR (95% CI)	0.53 (0.37-0.77)	
Nominal log-rank *P*	.0009	

Rucaparib vs Second-Generation ARPI



BRCA Subgroup	Rucaparib (n = 201)	2G ARPI (n = 41)
Median rPFS, mo (95% CI)	11.2 (9.2-13.8)	4.5 (3.3-5.8)
HR (95% CI)	0.38 (0.25-0.58)	
Nominal log-rank *P*	<.0001	

- Improved rPFS also was demonstrated in ITT population with rucaparib vs docetaxel (HR: 0.64; nominal log-rank *P* = .0066) or second-generation ARPI (HR: 0.47; nominal log-rank *P* <.0001)

Fizazi. NEJM. 2023;[Epub]. Bryce. ASCO GU 2023. Abstr 18.

Dual Mode of Synergy With Olaparib Plus Second-Generation Antiandrogens[1-4]

- Enhance blockade of AR signaling
  - Failure of AR-dependent localization of PARP to target genes
  - PARP-mediated nucleosome remodeling at targets abolished
  - Transcriptional downregulation of AR targets
- Inducing "*BRCA*ness"
  - Decreased HRR gene expression
  - Decreased DSB repair
  - Radiosensitivity

SGA, second-generation antiandrogen.

1. Polkinghorne WR, et al. *Cancer Discov.* 2013;3(11):1245-1253; 2. Tarish FL, et al. *Sci Transl Med.* 2015;7(312):312re11; 3. Li L, et al. *Sci Signal.* 2017;10(480); 4. Asim M, et al. *Nat Commun.* 2017;8(1):374.

ASCO Genitourinary Cancers Symposium

Phase 3 MAGNITUDE study: First results of niraparib (NIRA) with abiraterone acetate and prednisone (AAP) as first-line therapy in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) with and without homologous recombination repair (HRR) gene alterations

Kim N. Chi,[1] Dana E. Rathkopf,[2] Matthew R. Smith,[3] Eleni Efstathiou,[4] Gerhardt Attard,[5] David Olmos,[6] Ji Youl Lee,[7] Eric J. Small,[8] Andrea J. Pereira de Santana Gomes,[9] Guilhem Roubaud,[10] Marniza Saad,[11] Bogdan Zurawski,[12] Valerii Sakalo,[13] Gary E. Mason,[14] Adam del Corral,[15] George Wang,[14] Daphne Wu,[16] Brooke Diorio,[17] Angela Lopez-Gitlitz,[16] Shahneen Sandhu[18]

[1]University of British Columbia, BC Cancer – Vancouver Center, Vancouver, BC, Canada; [2]Memorial Sloan Kettering Cancer Center and Weill Cornell Medicine, New York, NY, USA; [3]Massachusetts General Hospital Cancer Center and Harvard Medical School, Boston, MA, USA; [4]Houston Methodist Cancer Center, Houston, TX, USA; [5]University College London, London, UK; [6]Department of Medical Oncology, Hospital Universitario 12 de Octubre, Instituto de Investigación Sanitaria Hospital 12 de Octubre (imas12), Madrid, Spain; [7]Department of Urology Cancer Center, Seoul St. Mary's Hospital, The Catholic University of Korea, Seoul, South Korea; [8]Helen Diller Family Comprehensive Cancer Center, University of California San Francisco, San Francisco, CA, USA; [9]Liga Norte Riograndense Contra o Câncer, Natal, Brazil; [10]Department of Medical Oncology, Institut Bergonié, Bordeaux, France; [11]Department of Clinical Oncology, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia; [12]Department of Outpatient Chemotherapy, Professor Franciszek Lukaszczyk Oncology Center, Bydgoszcz, Poland; [13]Institute of Urology named after Academician OF Vozianov of NAMS of Ukraine, Kyiv, Ukraine; [14]Janssen Research & Development, Spring House, PA, USA; [15]Janssen Research & Development, Bridgewater, NJ, USA; [16]Janssen Research & Development, Los Angeles, CA, USA; [17]Janssen Research & Development, Titusville, NJ, USA; [18]Peter MacCallum Cancer Center and the University of Melbourne, Melbourne, Australia

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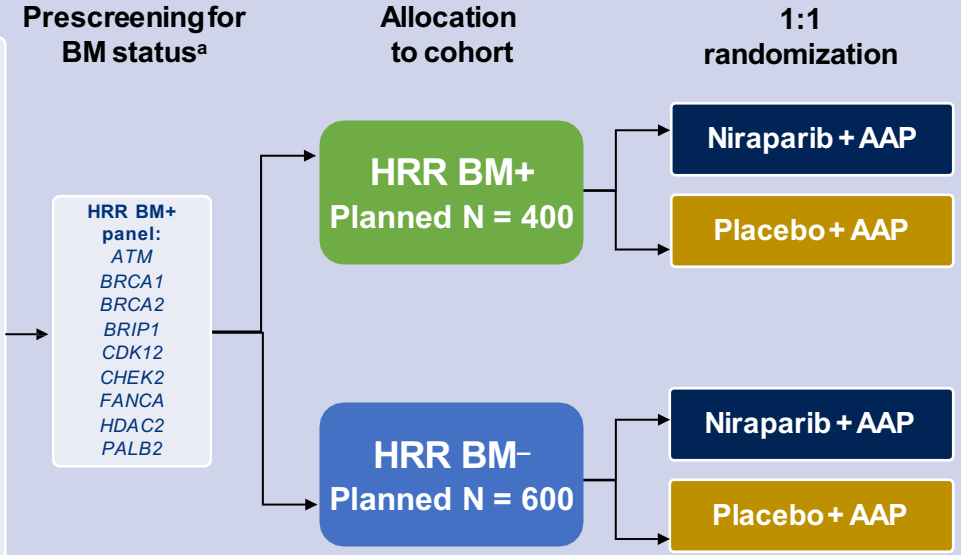
MAGNITUDE: Randomized, Double-Blind, Placebo-Controlled Study

Prospectively selected biomarker cohorts designed to test HRR BM+ and HRR BM–

Study start: February 2019

Patient eligibility
- L1 mCRPC
  - ≤4 months prior AAP allowed for mCRPC
- ECOG PS 0 or 1
- BPI-SF worst pain score ≤3

Stratifications
- Prior taxane-based chemo for mCSPC
- Prior ARi for nmCRPC or mCSPC
- Prior AAP for L1 mCRPC
- HRR BM+ cohort only:
  - *BRCA1/2* vs other HRR gene alterations



Primary endpoint
- rPFS by central review

Secondary endpoints
- Time to cytotoxic chemotherapy
- Time to symptomatic progression
- OS

Other prespecified endpoints
- Time to PSA progression
- ORR
- PFS2
- Time to pain progression
- Patient-reported outcomes

Note: Patients could request to be unblinded by the study steering committee and go on to subsequent therapy of the investigator's choice.

Clinical data cut-off was October 8, 2021 for the final rPFS analysis.

Patients were prospectively tested by plasma, tissue and/or saliva/whole blood. Patients negative by plasma only were required to test by tissue to confirm HRR BM– status.

AAP, abiraterone acetate + prednisone/prednisolone; AR, androgen receptor; ARi, androgen receptor inhibitor; BM, biomarker; BPI-SF, Brief Pain Inventory–Short Form; ctDNA, circulating tumor deoxyribonucleic acid; ECOG PS, Eastern Cooperative Oncology Group performance status; HRR, homologous recombination repair; L1, first line; mCRPC, metastatic castration-resistant prostate cancer; mCSPC, metastatic castration-sensitive prostate cancer; nmCRPC, nonmetastatic castration-resistant prostate cancer; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PFS2, progression-free survival on first subsequent therapy; PSA, prostate-specific antigen; rPFS, radiographic progression-free survival.

[a]Tissue and Plasma assays: FoundationOne tissue test (FoundationOne®CDx), Resolution Bioscience liquid test (ctDNA), AmoyDx blood and tissue assays, Invitae germline testing (blood/saliva), local lab biomarker test results demonstrating a pathogenic germline or somatic alteration listed in the study biomarker gene panel.

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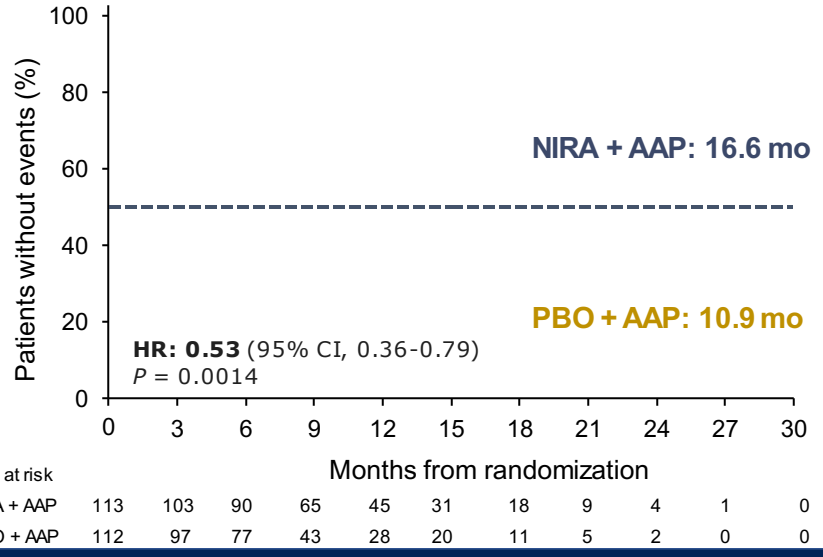
MAGNITUDE *BRCA1/2*-mutated: Primary Endpoint

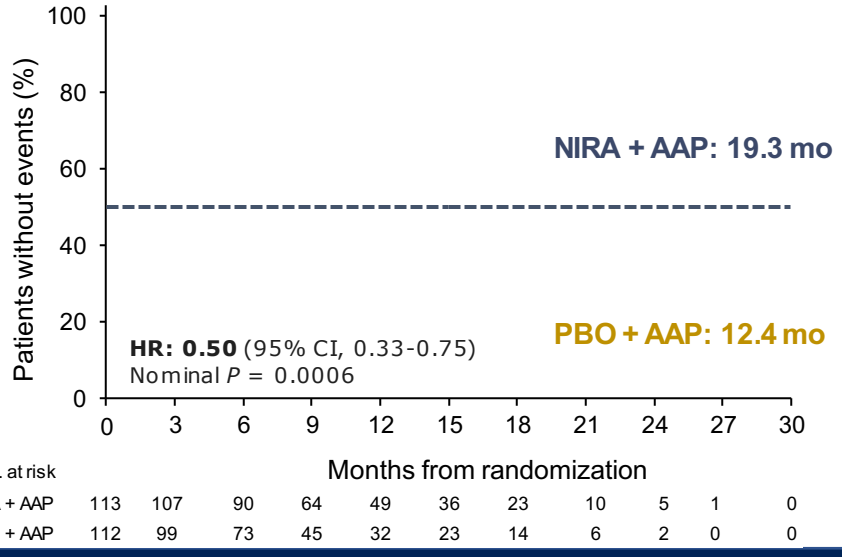
NIRA + AAP Significantly Reduced the Risk of Progression or Death by 47%

rPFS assessed by central review



No. at risk											
NIRA + AAP	113	103	90	65	45	31	18	9	4	1	0
PBO + AAP	112	97	77	43	28	20	11	5	2	0	0

rPFS assessed by investigator



No. at risk											
NIRA + AAP	113	107	90	64	49	36	23	10	5	1	0
PBO + AAP	112	99	73	45	32	23	14	6	2	0	0

Median follow-up 16.7 months

AAP, abiraterone acetate + prednisone/prednisolone; CI, confidence interval; HR, hazard ratio; NIRA, niraparib; PBO, placebo; rPFS, radiographic progression-free survival.

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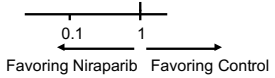
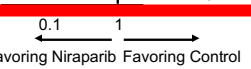
MAGNITUDE All HRR BM+: Prespecified Subgroup Analysis of rPFS Showed Consistency of Effect

Variable	Subgroup	Median (months) niraparib	Median (months) control	HR (95% CI)	Events/N niraparib	Events/N control
All HRR+ patients	All	16.5	13.7	0.74 (0.57–0.97)	100/212	117/211
Age group	<65	13.9	13.9	1.01 (0.61–1.66)	32/61	30/62
	≥65-74	19.4	13.6	0.58 (0.38–0.89)	34/88	57/100
	≥75	16.4	10.9	0.76 (0.46–1.24)	34/63	30/49
Race group	Asian	22.0	10.9	0.48 (0.22–1.05)	9/29	22/41
	White	14.4	13.8	0.83 (0.61–1.13)	82/160	83/153
	Other	18.4	9.0	0.47 (0.20–1.14)	9/23	12/17
Baseline ECOG performance status	0	19.5	13.9	0.65 (0.46–0.92)	53/130	76/146
	1	13.1	10.5	0.84 (0.55–1.28)	47/82	41/65
Baseline BPI-SF#3 Score	0	16.7	16.8	0.75 (0.51–1.12)	47/108	53/103
	1 to 3	13.9	10.5	0.78 (0.52–1.17)	46/88	50/86
	>3	13.7	13.7	0.68 (0.26–1.79)	6/14	14/22
Region	Asia Pacific	19.5	13.8	0.64 (0.35–1.17)	17/43	27/52
	Europe	14.4	13.7	0.82 (0.58–1.14)	68/128	71/120
	North and South America	16.6	16.4	0.60 (0.30–1.18)	15/41	19/39



Variable	Subgroup	Median (months) niraparib	Median (months) control	HR (95% CI)	Events/N niraparib	Events/N control
Past taxane–based chemotherapy	Yes	13.4	10.9	0.89 (0.48–1.66)	20/40	21/41
	No	16.6	13.8	0.71 (0.53–0.96)	80/172	96/170
Past androgen receptor-targeted therapy[a]	Yes	NE	4.3	0.19 (0.03–1.23)	2/8	3/4
	No	16.5	13.8	0.76 (0.58-1.00)	98/204	114/207
Prior AAP use[b]	Yes	13.9	14.6	0.95 (0.54–1.67)	23/47	26/45
	No	16.7	12.7	0.71 (0.52–0.96)	77/165	91/166
Presence of visceral metastases	Yes	11.0	8.1	1.03 (0.60–1.77)	34/51	22/39
	No	19.4	13.8	0.64 (0.47–0.87)	66/161	95/172
Bone only metastasis at entry	Yes	19.4	15.4	0.72 (0.45–1.14)	32/78	41/85
	No	14.8	10.9	0.73 (0.53–1.02)	68/134	76/126
Number of bone lesions at baseline	≤10	19.4	15.4	0.76 (0.53–1.10)	54/127	65/128
	>10	13.8	8.4	0.69 (0.47–1.04)	46/85	52/83
Baseline PSA above median	Yes	15.7	8.3	0.58 (0.40–0.82)	56/110	66/101
	No	16.7	18.2	0.93 (0.62–1.40)	44/102	51/110
Gene mutation type	BRCA	16.6	10.9	0.55 (0.38–0.81)	45/113	64/112
	Other HRR	14.8	16.4	0.99 (0.68–1.45)	55/99	53/99



AAP, abiraterone acetate + prednisone/prednisolone; AR, androgen receptor; BM, biomarker; BPI-SF, Brief Pain Inventory–Short Form; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; HRR, homologous recombination repair; NE, not estimable; PSA, prostate-specific antigen; rPFS, radiographic progression-free survival.

[a]Past AR-targeted therapy was considered prior novel anti-androgen therapy, such as enzalutamide, apalutamide, or darolutamide.

[b]Prior AAP use was up to 4 months prior to study start.

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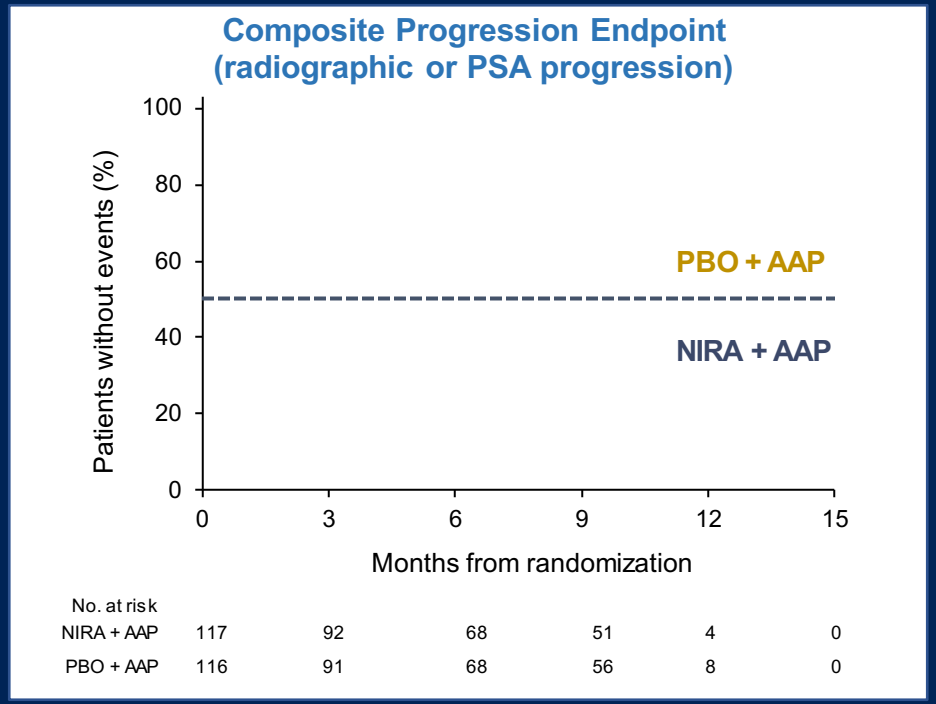
MAGNITUDE HRR BM⁻ : Prespecified Early Futility Analysis

No Benefit of NIRA + AAP in HRR BM⁻ Patients



- Composite endpoint[a] (N = 233)
  HR = 1.09[b] (95% CI 0.75-1.59)
  [futility was defined as ≥1]
- Additional grade 3/4 toxicity was observed using NIRA + AAP vs PBO + AAP
- With added toxicity and no added efficacy in patients with HRR BM⁻ mCRPC, the IDMC recommend stopping enrollment in this cohort

[b]Breakdown of composite endpoint events
83 PSA events (HR = 1.03, 95% CI 0.67-1.59)
65 rPFS events (HR = 1.03, 95% CI 0.63-1.67)

[a]rPFS or PSA progression, whichever occurred first.
AAP, abiraterone acetate + prednisone/prednisolone; AE, adverse event; BM, biomarker; CI, confidence interval; HR, hazard ratio; HRR, homologous recombination repair; IDMC, independent data monitoring committee; mCRPC, metastatic castration-resistant prostate cancer; NIRA, niraparib; PBO, placebo; PSA, prostate specific antigen, rPFS, radiographic progression free survival

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ASCO Genitourinary Cancers Symposium

PROpel: phase III trial of olaparib and abiraterone versus placebo and abiraterone as first-line therapy for patients with metastatic castration-resistant prostate cancer

Fred Saad, Andrew J. Armstrong, Antoine Thiery-Vuillemin, Mototsugu Oya, Eugenia Loredo, Giuseppe Procopio, Juliana de Menezes, Gustavo Girotto, Cagatay Arslan, Niven Mehra, Francis Parnis, Emma Brown, Friederike Schlürmann, Jae Young Joung, Mikio Sugimoto, Christian Poehlein, Elizabeth A. Harrington, Chintu Desai, Jinyu Kang, and Noel Clarke

ClinicalTrials.gov identifier: NCT03732820..

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PROpel: a global randomized double-blind phase III trial

Patient population
- 1L mCRPC
- Docetaxel allowed at mHSPC stage
- No prior abiraterone
- Other NHAs allowed if stopped ≥12 months prior to enrollment
- Ongoing ADT
- ECOG 0–1

Stratification factors
- Site of distant metastases: bone only vs visceral vs other
- Prior taxane at mHSPC: yes vs no

1:1

Olaparib 300 mg bid + abiraterone 1000 mg qd*
n=399

Full dose of olaparib and abiraterone used

Placebo + abiraterone 1000 mg qd*
n=397

Full dose of abiraterone used

Primary endpoint
- Radiographic progression or death (rPFS) by investigator assessment

Key secondary endpoint
- Overall survival (alpha control)

Additional endpoints
- Time to first subsequent therapy or death (TFST)
- Time to second progression or death (PFS2)
- Objective response rate (ORR)
- HRRm† prevalence (retrospective testing)
- Health-related quality of life
- Safety and tolerability

First patient randomized: Nov 2018; Last patient randomized: Mar 2020; DCO1: July 30, 2021, for interim analysis of rPFS and OS.
Multiple testing procedure is used in this study: 1-sided alpha of 0.025 fully allocated to rPFS. If the rPFS result is statistically significant, OS to be tested in a hierarchical fashion with alpha passed on to OS.
Please access the ***Supplement*** via the QR code at the end of this presentation for more details.
*In combination with prednisone or prednisolone 5 mg bid. †HRRm, homologous recombination repair mutation, including 14 genes panel.
ADT, androgen deprivation therapy; bid, twice daily; ECOG, Eastern Cooperative Oncology Group; mHSPC, metastatic hormone sensitive prostate cancer; qd, daily

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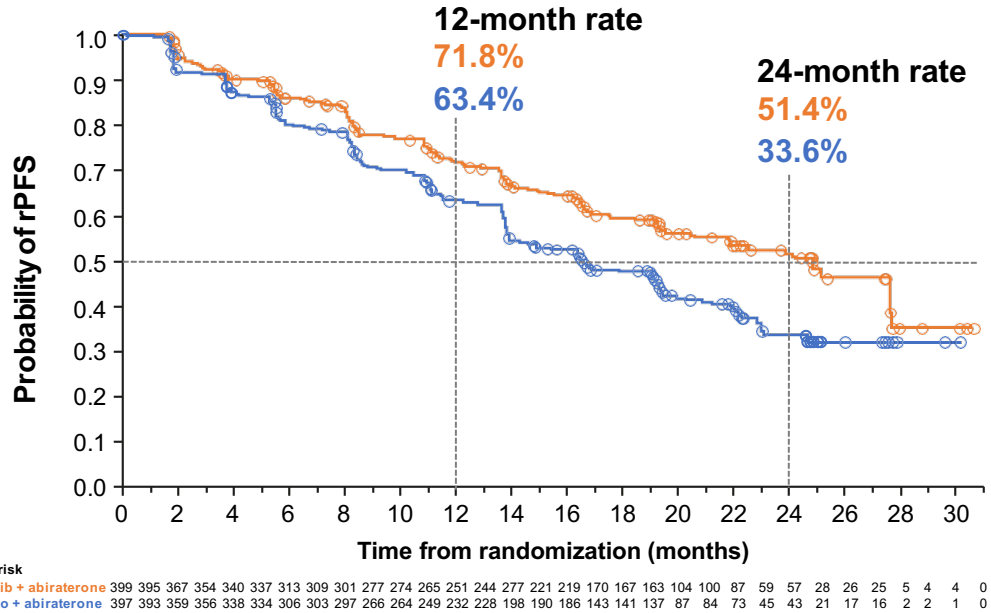
PROpel primary endpoint: rPFS by investigator-assessment

34% risk reduction of progression or death with olaparib + abiraterone



	Olaparib + abiraterone (n=399)	Placebo + abiraterone (n=397)
Events, n (%)	168 (42.1)	226 (56.9)
Median rPFS (months)	24.8	16.6
HR (95% CI)	0.66 (0.54–0.81); P<0.0001	

Pre-specified 2-sided alpha: 0.0324

Median rPFS improvement of 8.2 months favors olaparib + abiraterone*

Events: 394; Maturity 49.5%
*In combination with prednisone or prednisolone
CI, confidence interval; HR, hazard ratio.

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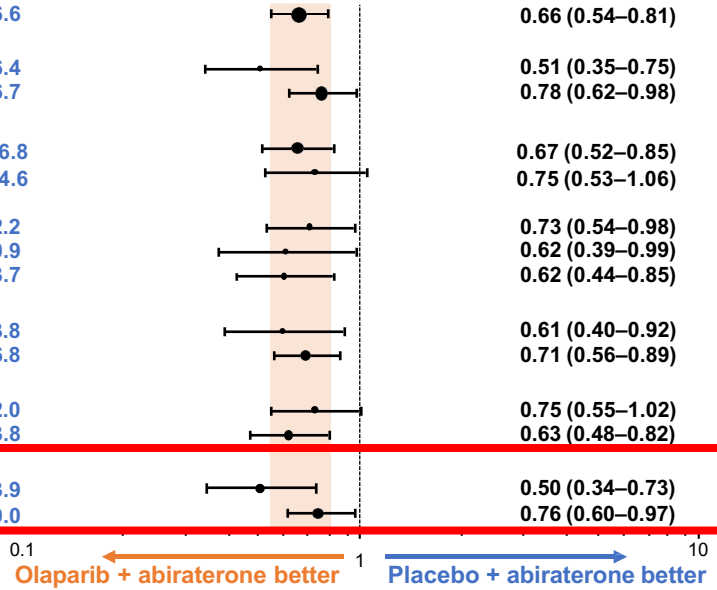
PROpel: subgroup analysis of rPFS

rPFS benefit observed across all pre-specified subgroups

	Number of patients, n	Median rPFS, months		HR (95% CI)
All patients	796	24.8	16.6	0.66 (0.54–0.81)
Age at randomization				
<65	227	NR	16.4	0.51 (0.35–0.75)
≥65	569	22.0	16.7	0.78 (0.62–0.98)
ECOG performance status at baseline				
0	558	24.9	16.8	0.67 (0.52–0.85)
1	236	17.5	14.6	0.75 (0.53–1.06)
Site of distant metastases				
Bone only	434	27.6	22.2	0.73 (0.54–0.98)
Visceral	105	13.7	10.9	0.62 (0.39–0.99)
Other	257	20.5	13.7	0.62 (0.44–0.85)
Docetaxel treatment at mHSPC stage				
Yes	189	27.6	13.8	0.61 (0.40–0.92)
No	607	24.8	16.8	0.71 (0.56–0.89)
Baseline PSA				
Below median baseline PSA	396	25.2	22.0	0.75 (0.55–1.02)
Above or equal to median baseline PSA	397	18.5	13.8	0.63 (0.48–0.82)
HRRm status*				
HRRm	226	NR	13.9	0.50 (0.34–0.73)
Non-HRRm	552	24.1	19.0	0.76 (0.60–0.97)



Global interaction test not significant at 10% level

Global interaction test not significant at 10% level. *The HRRm status of patients in PROpel was determined retrospectively using results from tumor tissue and plasma ctDNA HRRm tests. Patients were classified as HRRm if (one or more) HRR gene mutation was detected by either test; patients were classified as non-HRRm patients if no HRR gene mutation was detected by either test; patients were classified as unknown HRRm if no valid HRR test result from either test was achieved. 18 patients did not have a valid HRR testing result from either a tumor tissue or ctDNA test and were excluded from the subgroup analysis. This subgroup analysis is post hoc exploratory analysis. Please access the Supplement via the QR code at the end of this presentation for more details. NR, not reached.

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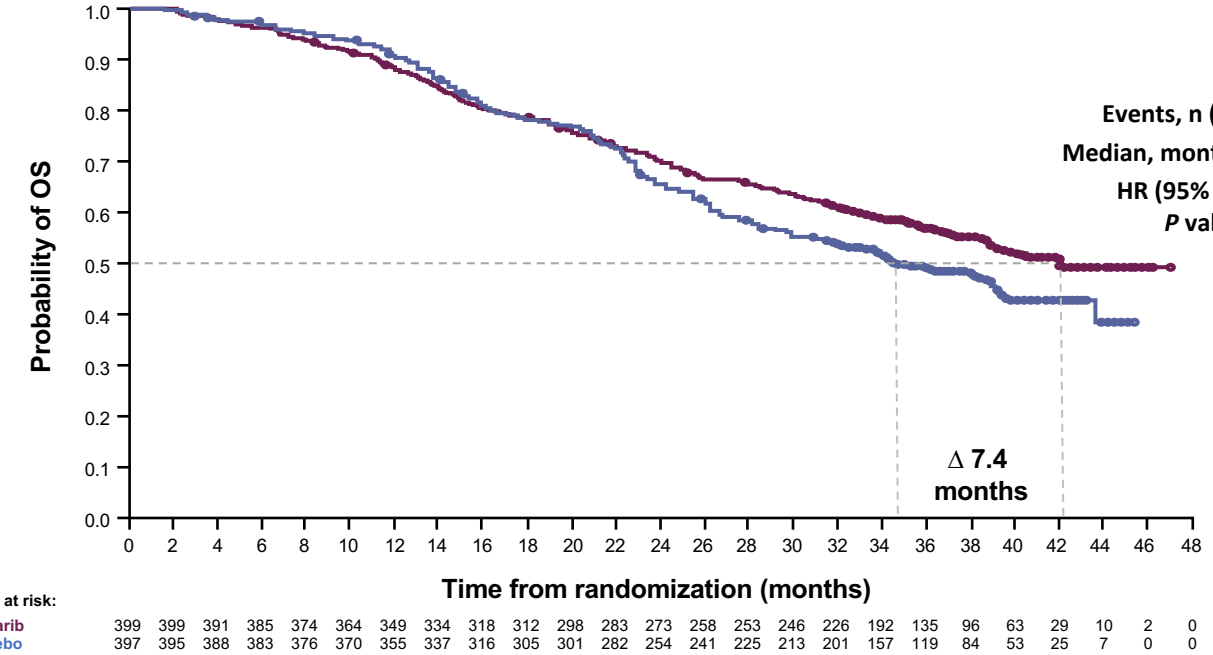
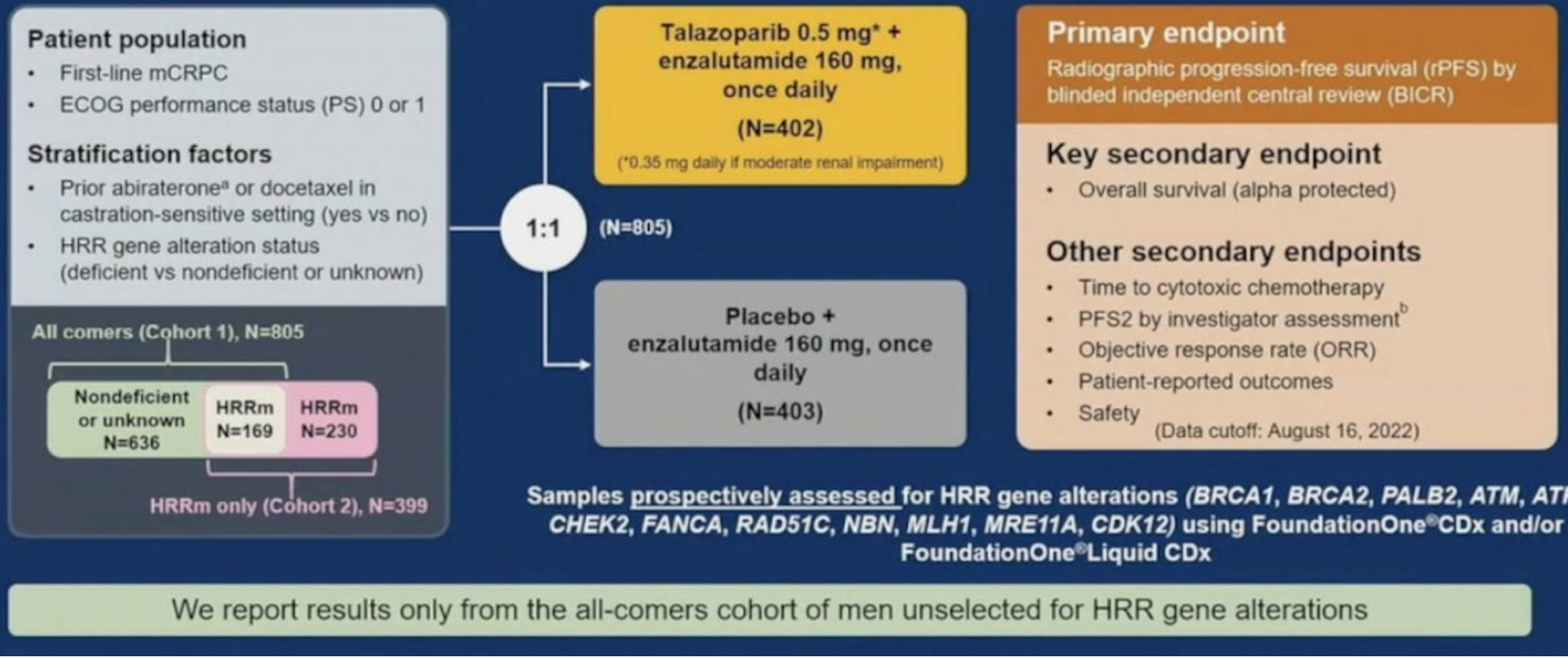
PROpel: OS at final pre-specified analysis (DCO3)



	Abiraterone + olaparib (n=399)	Abiraterone + placebo (n=397)
Events, n (%)	176 (44.1)	205 (51.6)
Median, months	42.1	34.7
HR (95% CI)	0.81 (0.67–1.00)	
P value	0.0544	
2-sided boundary for significance	0.0377	
47.9% maturity		

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

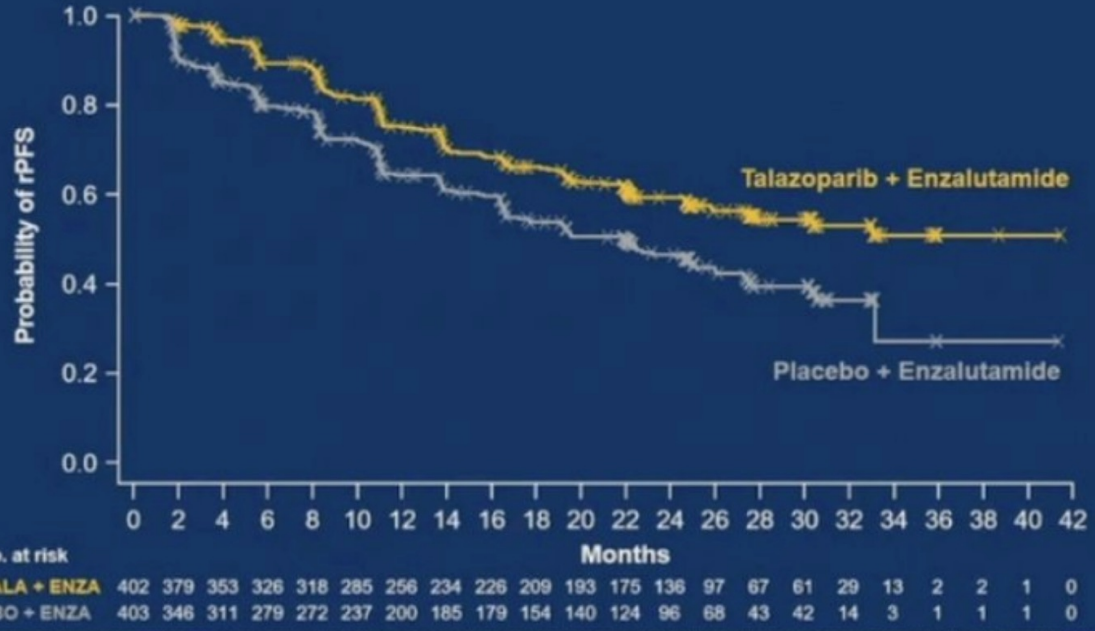


We report results only from the all-comers cohort of men unselected for HRR gene alterations

Presented by Dr. Neeraj Agarwal

TALAPRO-2 Primary Endpoint: rPFS by BICR

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

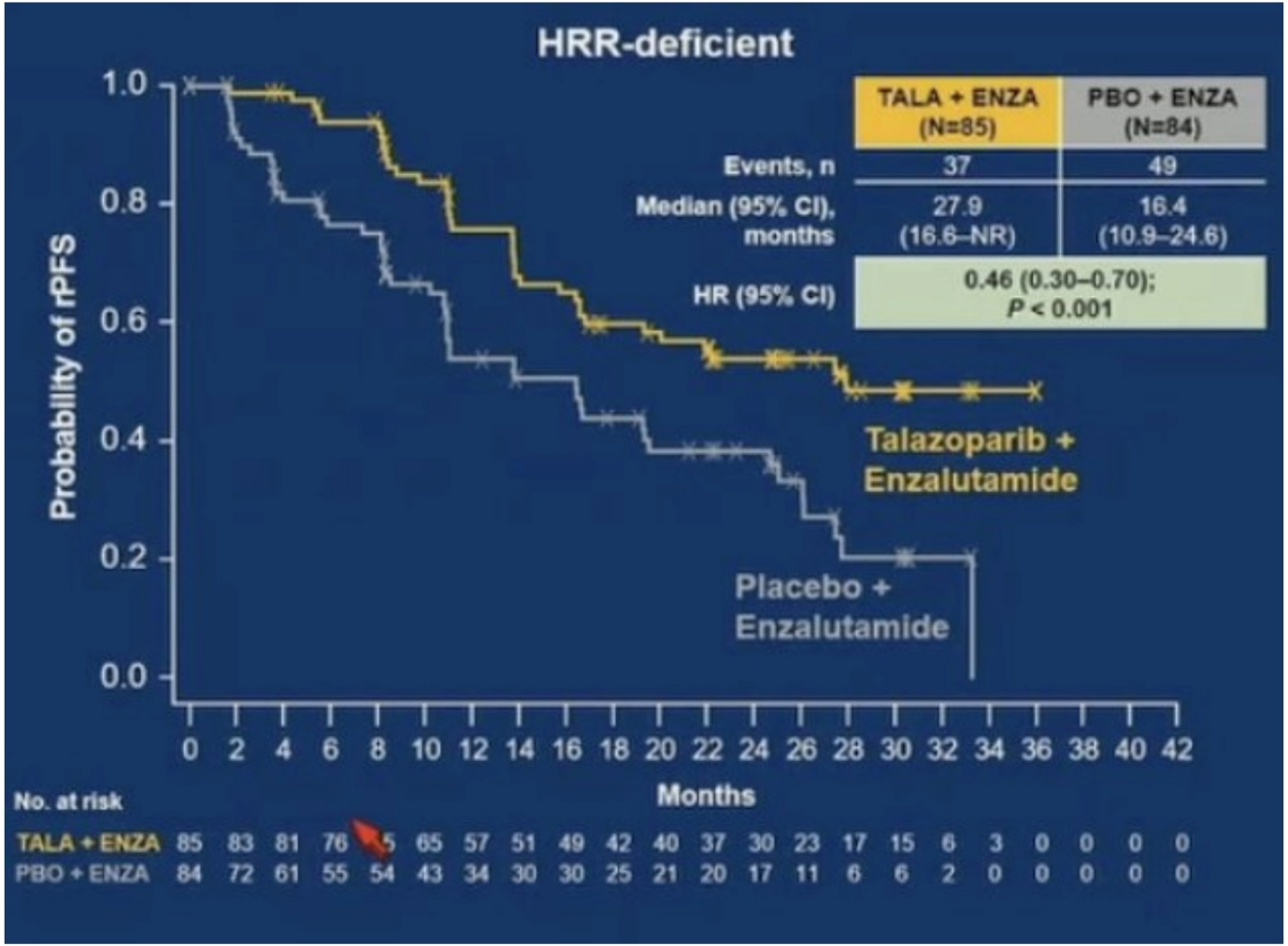


	TALA + ENZA (N=402)	PBO + ENZA (N=403)
Events, n	151	191
Median (95% CI), months	Not reached (NR) (27.5–NR)	21.9 (16.6–25.1)
HR (95% CI)	0.63 (0.51–0.78); $P < 0.001$	

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.


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
Probability of rPFS
1.0
0.8
0.6
0.4
0.2
0.0
Talazoparib + Enzalutamide
Placebo + Enzalutamide
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 38 40 42
Months
No. at risk
TALA + ENZA 85 83 81 76 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

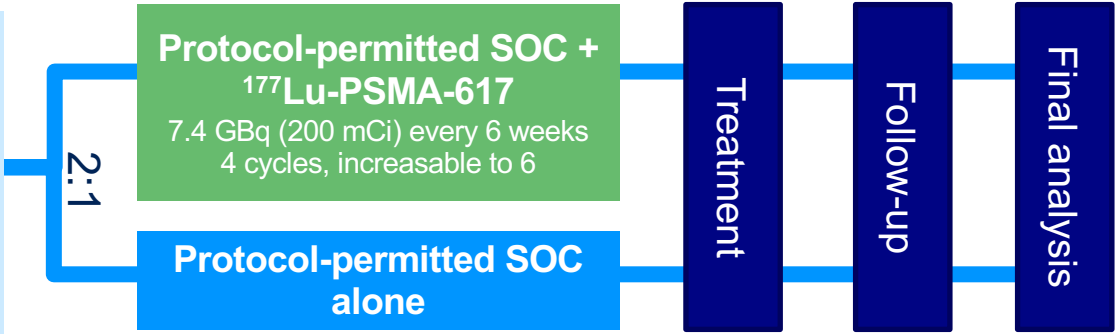
What Do We Know About Combination Therapy for 1L mCRPC?

- To date, rPFS is improved with the combination of PARPi and abiraterone in PROpel and MAGNITUDE
- OS improved in all comers in PROpel, but not mature in MAGNITUDE
- MAGNITUDE and PROpel appear to have conflicting outcomes:
  - PROpel: rPFS and OS advantage for “all-comers”
  - MAGNITUDE: no advantage for HRR-, rPFS advantage only for HRR+, especially *BRCA1/2*
- TALAPRO-2 rPFS seen with combination talazoparib and enzalutamide, especially HRRm
  - OS pending (rPFS is not a surrogate for OS for PARPi’s)

Open-Label Study of Protocol-Permitted Standard of Care ± ^{177}Lu-PSMA-617 in Adults with PSMA-Positive mCRPC

Eligible patients

- Previous treatment with both
  - ≥1 androgen receptor pathway inhibitor
  - 1 or 2 taxane regimens
- Protocol-permitted standard of care (SOC) planned before randomization
  - Excluding chemotherapy immunotherapy, radium-223, investigational drugs
- ECOG performance status 0-2
- Life expectancy >6 months
- PSMA-positive mCRPC on PET/CT with ^{68}Ga-PSMA-11



Randomization stratified by

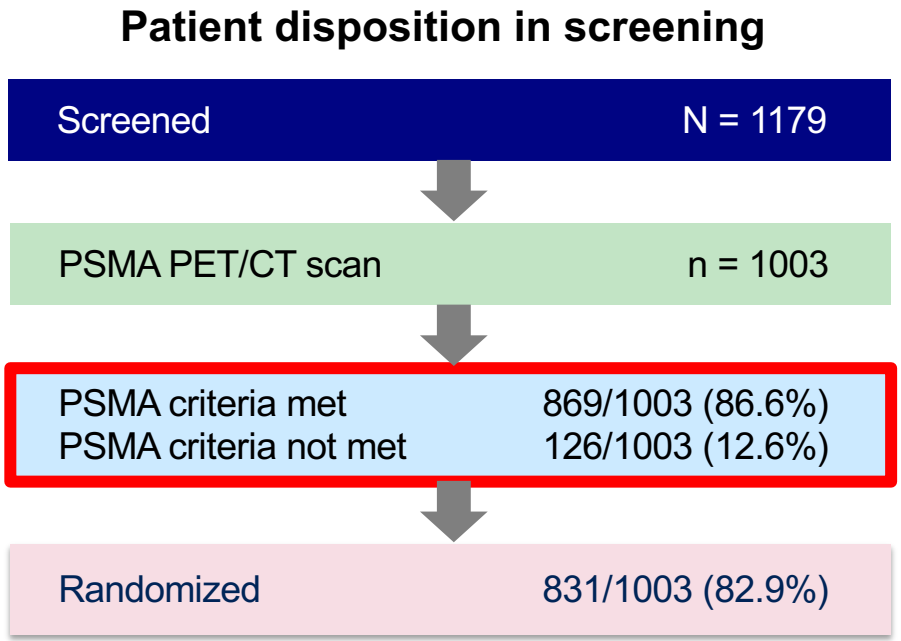
- ECOG status (0-1 or 2)
- LDH (high or low)
- Liver metastases (yes or no)
- Androgen receptor pathway inhibitors in SOC (yes or no)

CT/MRI/bone scans

- Every 8 weeks (treatment)
- Every 12 weeks (follow-up)
- Blinded independent central review

Morris MJ, et al. ASCO 2021. Abstract LBA4.

^{68}Ga-PSMA-11 PET/CT: ~87% of Patients Scanned Met the VISION Imaging Criteria for PSMA-Positive mCRPC



95% with at least 1 lesion > liver
Of those, 8.7% with at least 1 lesion < liver

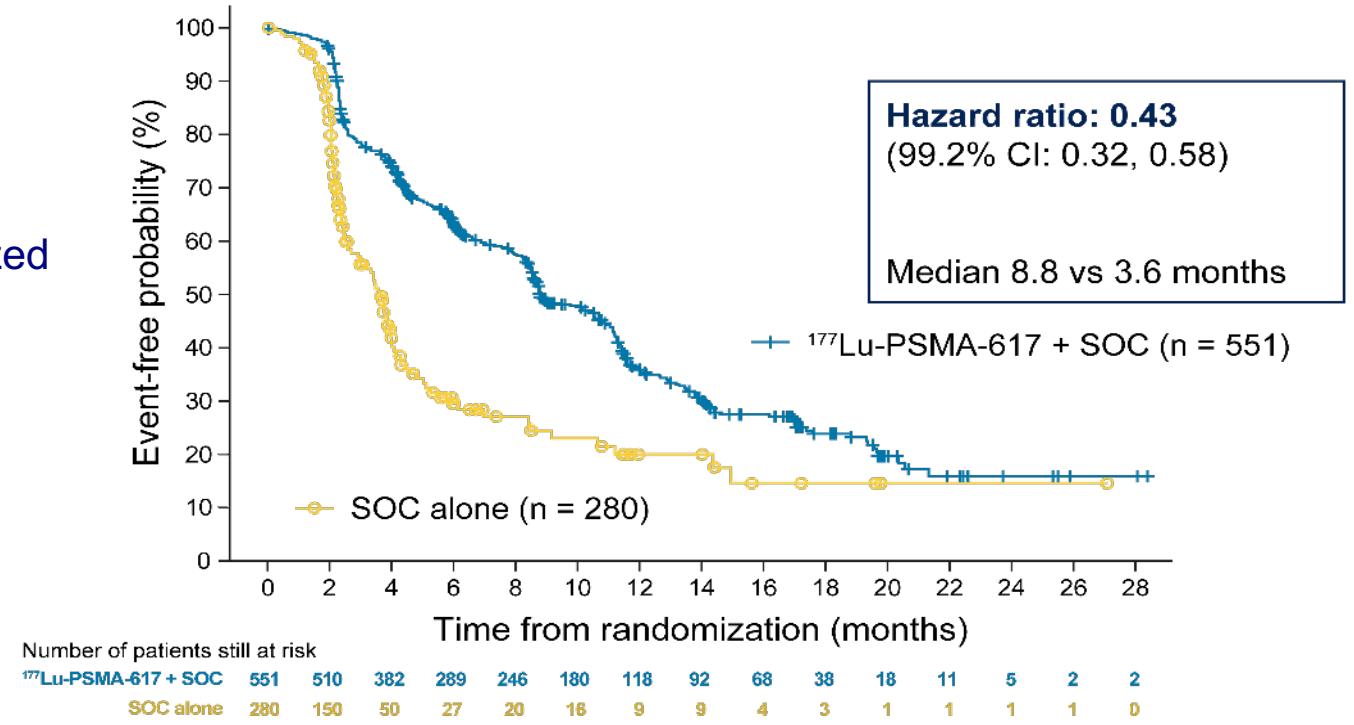
Morris MJ, et al. ASCO 2021. Abstract LBA4.

^{177}Lu-PSMA-617 Improved rPFS in the OS Analysis Set

Additional analysis

- All randomized patients

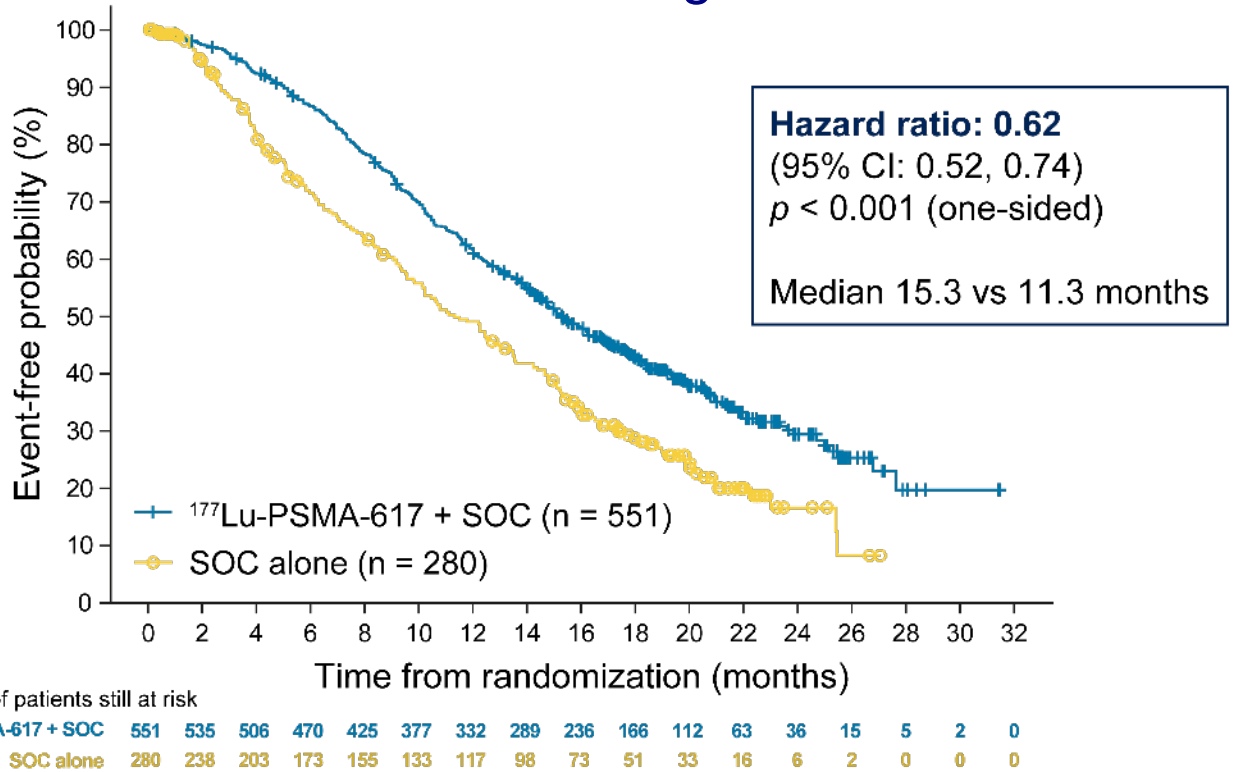
(N = 831)



Morris MJ, et al. ASCO 2021. Abstract LBA4.

Primary Endpoints: ^{177}Lu-PSMA-617 Prolonged OS

Primary analysis
All randomized patients
(N = 831)



Morris MJ, et al. ASCO 2021. Abstract LBA4.

Conclusions

- In the hormone sensitive prostate cancer, intensification of treatment with either doublet or triplet therapy is standard treatment
- All prostate cancer patients should be tested for MSI, mutational burden, and DDR mutations
- Checkpoint inhibition therapy is an appropriate treatment for those patients who have MSI
- PARP inhibition is appropriate for those patients with DNA repair mutations
- Sequential androgens does not improve survival in mCRPC

Conclusions and Clinical Implications

- PARP inhibition is effective in patients with DNA repair mutations
- PARP inhibition appears to be less effective in those patients with *ATM* mutations
- Olaparib is FDA approved in CRPC patients with HRR gene mutations who have been treated with enzalutamide or abiraterone
- Rucaparib is FDA approved in *BRCA*-mutated patients who have received abiraterone or enzalutamide and docetaxel chemotherapy
- Lu177 PSMA is FDA approved for patients who have been treated with prior antiandrogen therapy and taxanes