Metastatic Castration Resistant Prostate Cancer: Sequencing the Treatment

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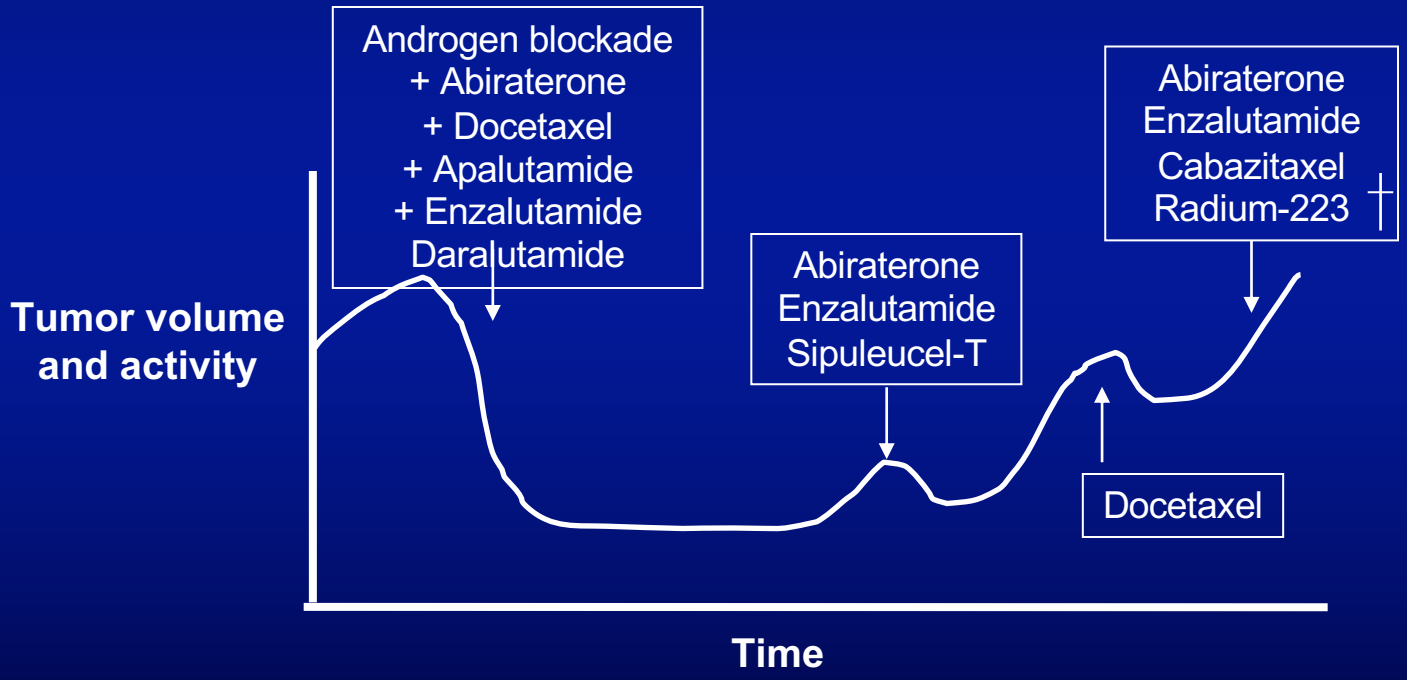
Treatment of Metastatic Prostate Cancer

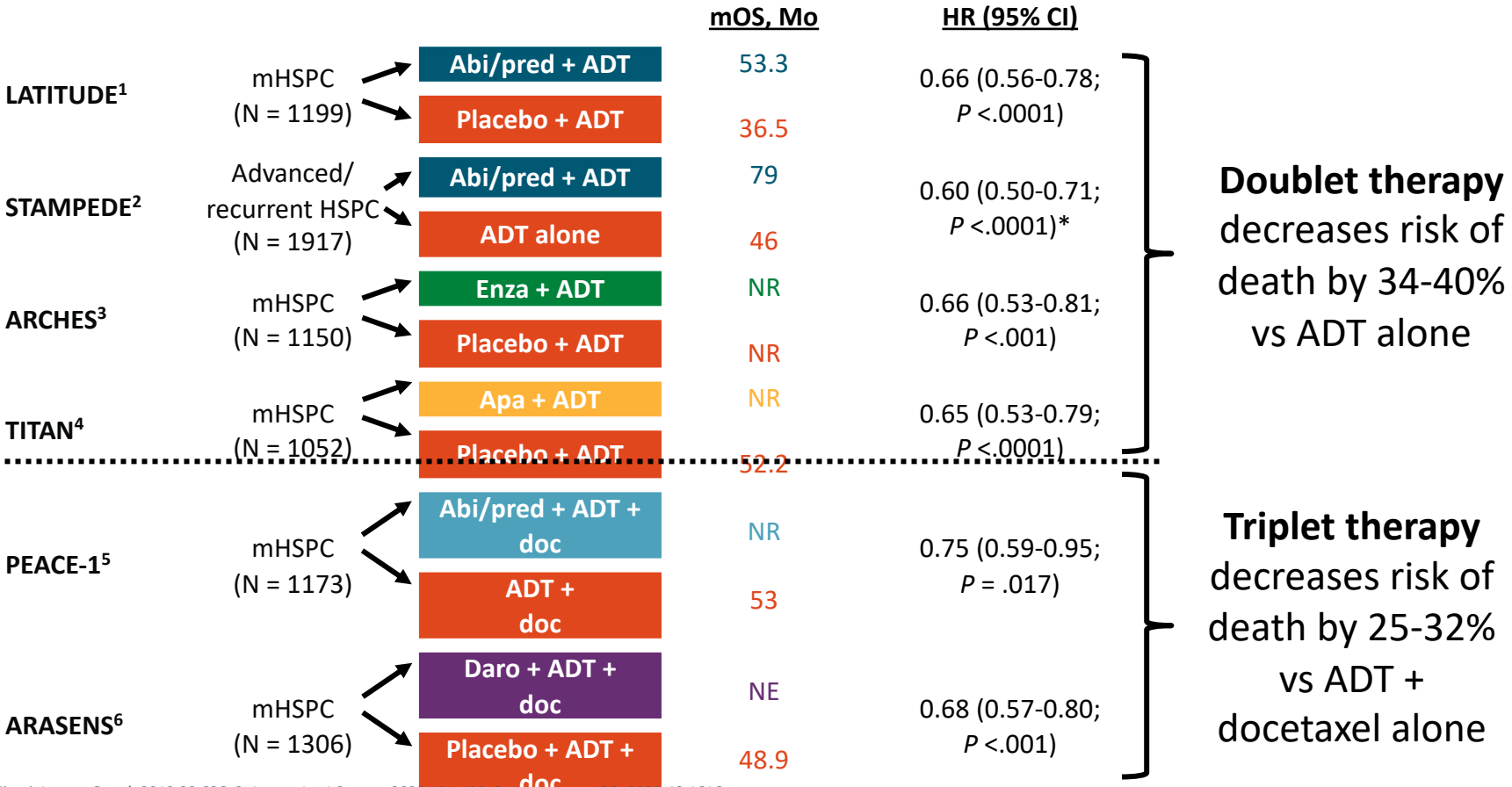


Metastatic HSPC: Many Treatment Options

- 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.

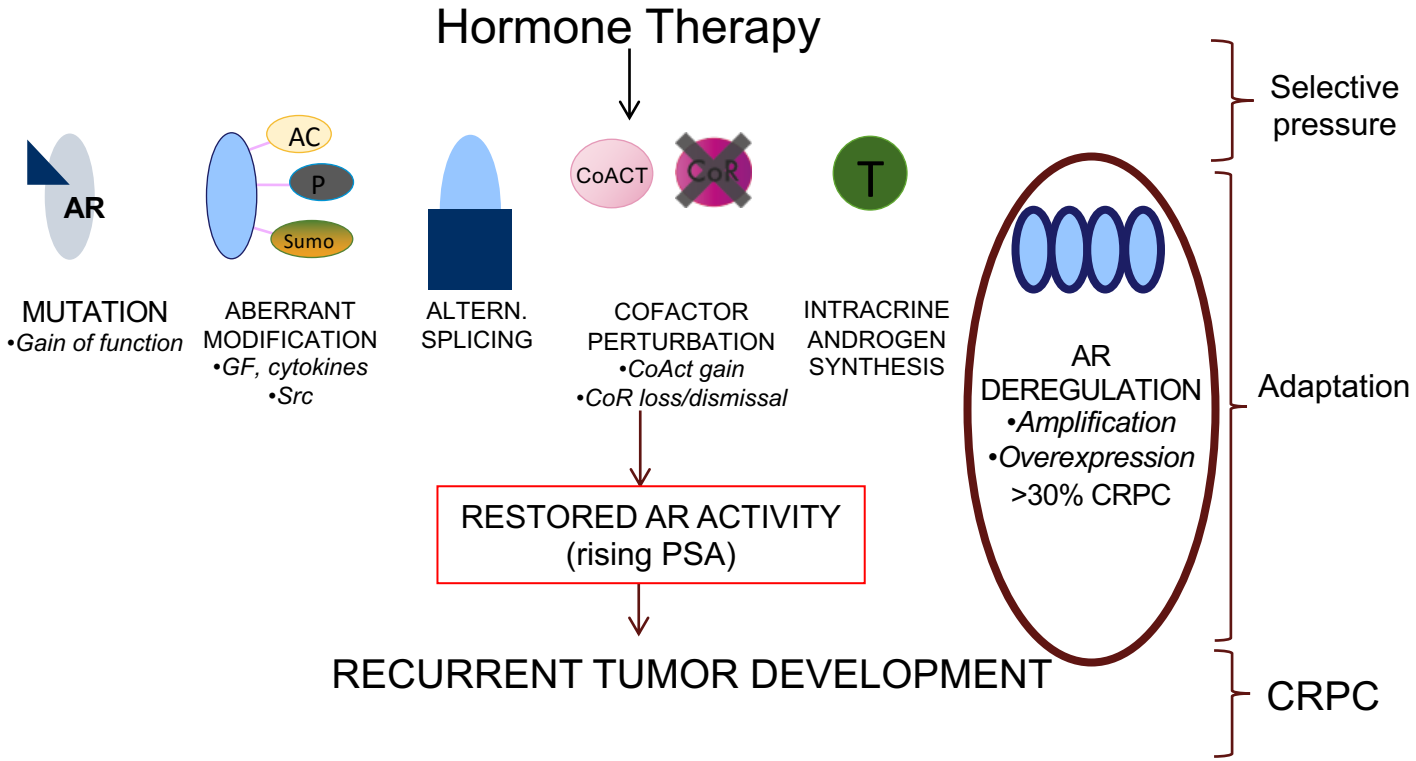
OS With Doublet and Triplet Therapy in mHSPC



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.

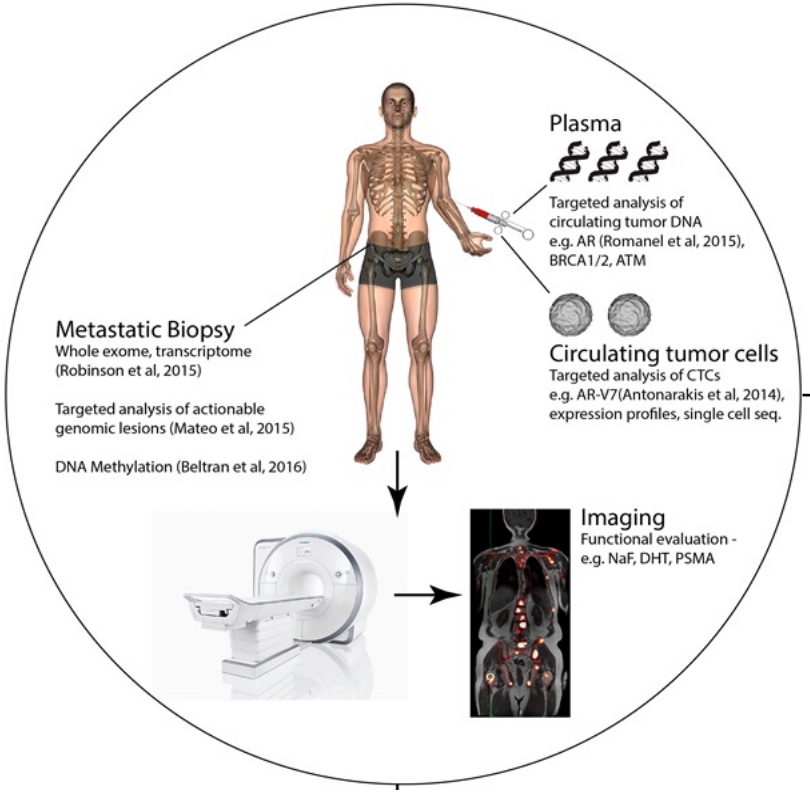
*In subgroup with metastatic disease.

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.

How Do We Sequence These Agents?

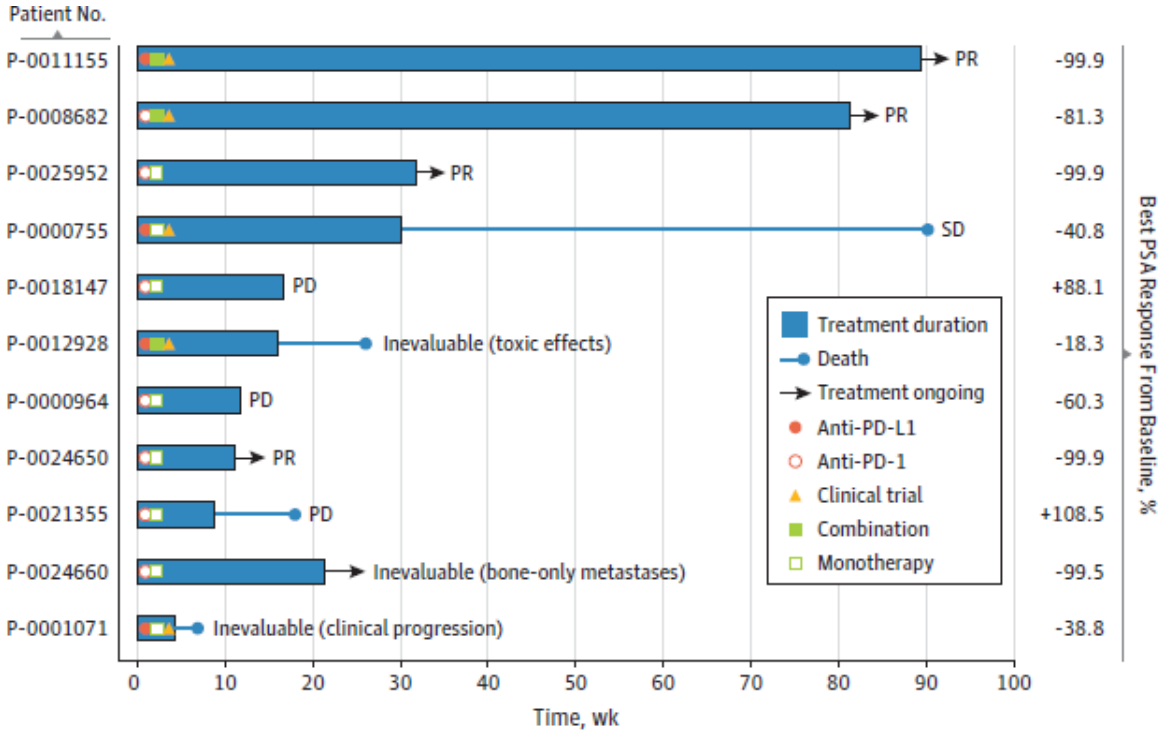
- Clinical characteristics
  - Symptomatic vs asymptomatic
  - Visceral vs nonvisceral
  - Pre- vs postdocetaxel
  - HSPCA vs CRPC
- Biologic markers
  - Immune markers: MSI
  - Androgen receptor mutations
  - DNA repair

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)

Mechanisms of Resistance

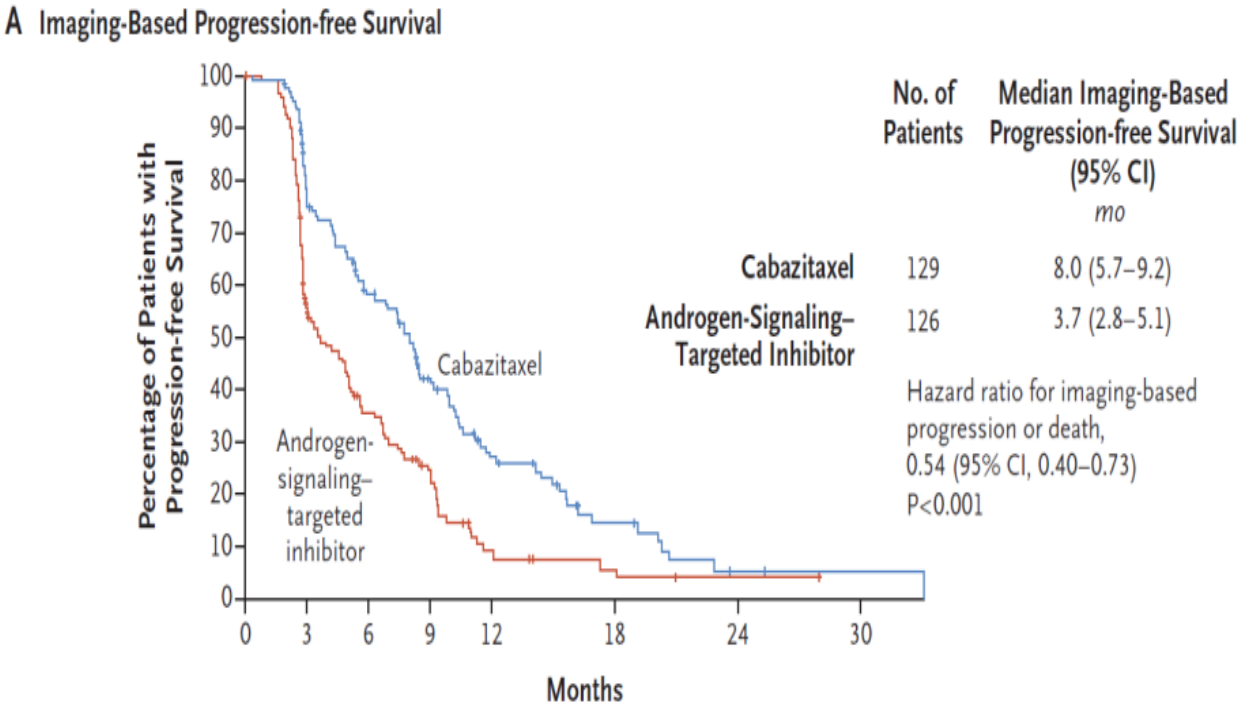
Abiraterone

- Upregulation CYP17
- Upregulation AR
- GC-activated AR mutations (*L702H*)
- Progesterone-activated AR mutations (*T878A*)
- AR splice variants
- AI AR independent mechanisms

Enzalutamide

- Upregulation of AR
- Enzalutamide-activated AR mutations (*F877L*)
- Induction GR expression
- AR splice variants
- AI AR independent mechanisms

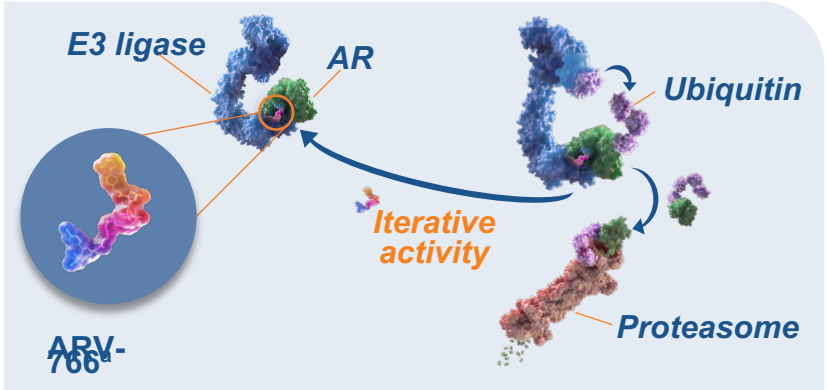
CARD



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

Background

- Patients with mCRPC inevitably develop resistance to available therapies, including NHAs, and experience disease progression[1]
- ≈20%–25% of men with mCRPC will develop mutations in the *AR* LBD (amino acids 671–920)
  - L702H, H875Y, and T878A are the most common *AR* mutations and are associated with poor prognosis[2–4]
- ARV-766 is a novel, potent, oral PROTAC AR degrader that targets wild-type *AR* and clinically relevant *AR* LBD mutants, including *AR* L702H, H875Y, and T878A

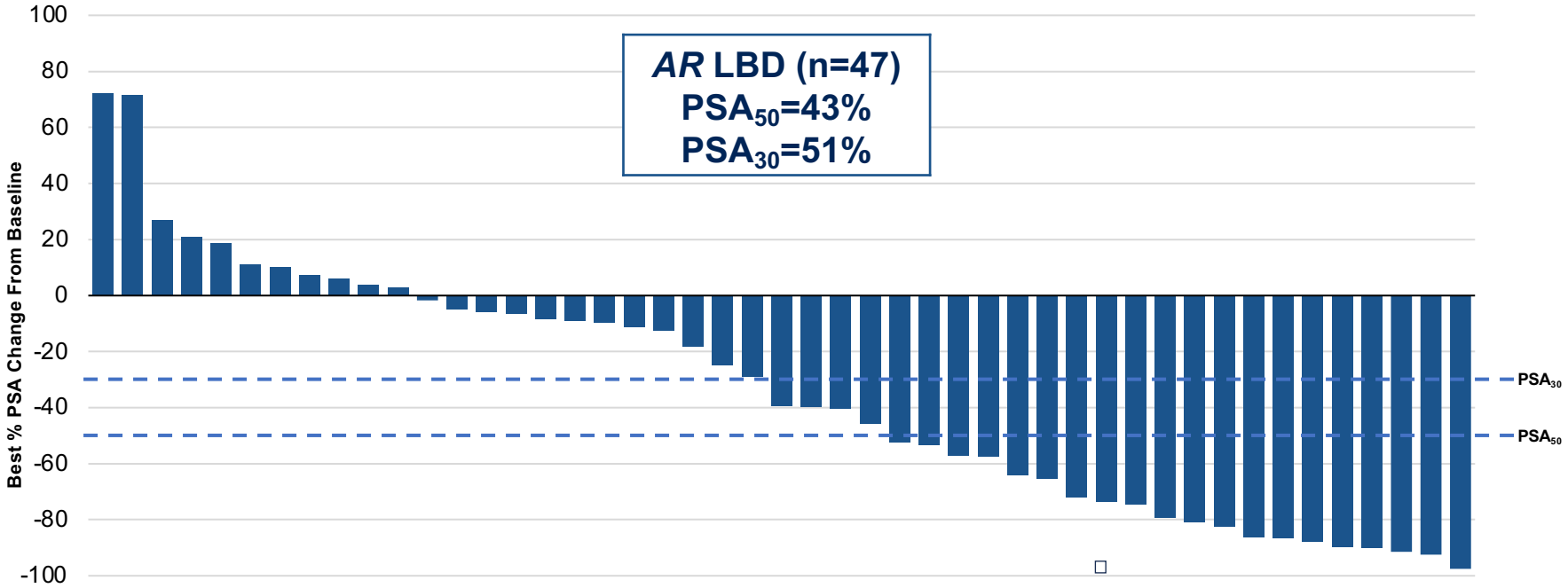


[a]General PROTAC protein degrader is shown.

AR=androgen receptor; LBD=ligand-binding domain; mCRPC=metastatic castration-resistant prostate cancer; NHA=novel hormonal agent; PROTAC=PROteolysis TArgeting Chimera.

1. Boudadi K and Antonarakis ES. *Clin Med Insights Oncol*. 2016;10(Suppl 1):1-9.
2. Snaterse G, et al. Prostate Cancer Prostatic Dis. 2023;26(2):293-301.
3. Lallous N, et al. Genome Biol. 2016;17:10.
4. Shiota M, et al. Endocr Relat Cancer. 2022;29(10):R143-R155..

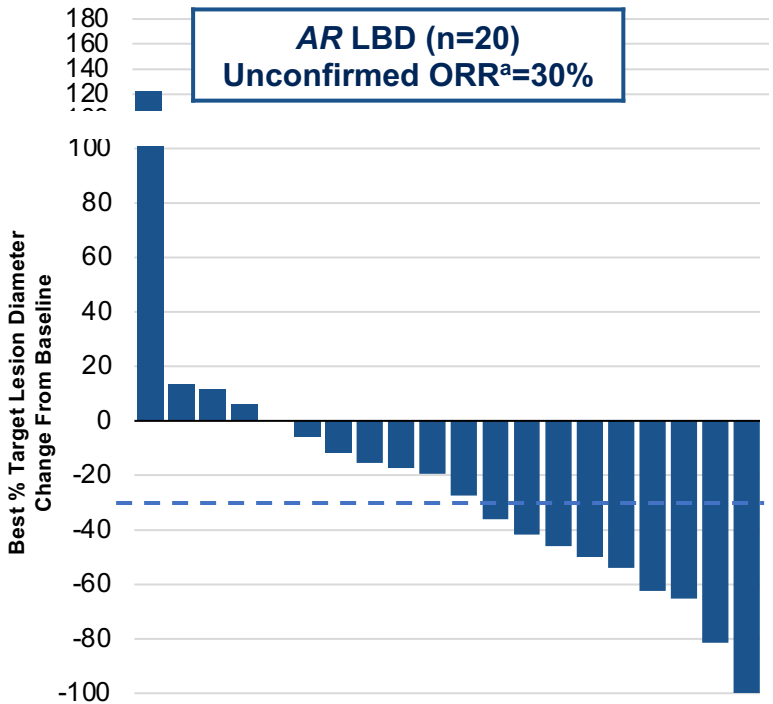
ARV-766 Monotherapy: Best Declines in PSA in Patients With *AR* LBD Mutations[a]

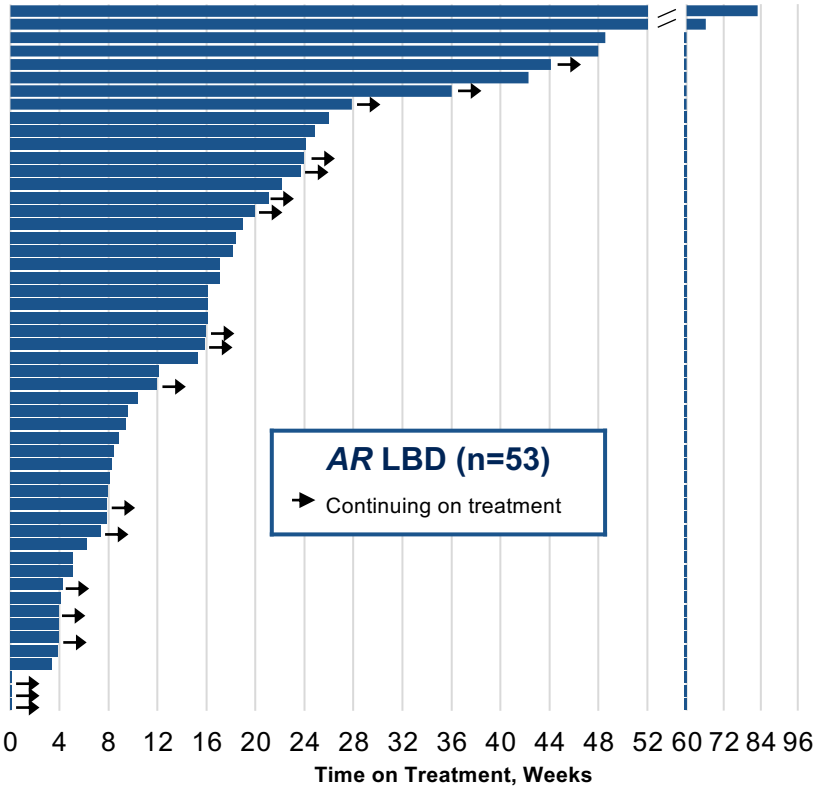


[a]Includes patients with ≥1 month of PSA follow-up.

AR=androgen receptor; LBD=ligand-binding domain; PSA=prostate-specific antigen; PSA_{30}=best PSA declines ≥50%; PSA_{50}=best PSA declines ≥50%

ARV-766 Monotherapy: Tumor Response and Treatment Duration in Patients With *AR* LBD Mutations

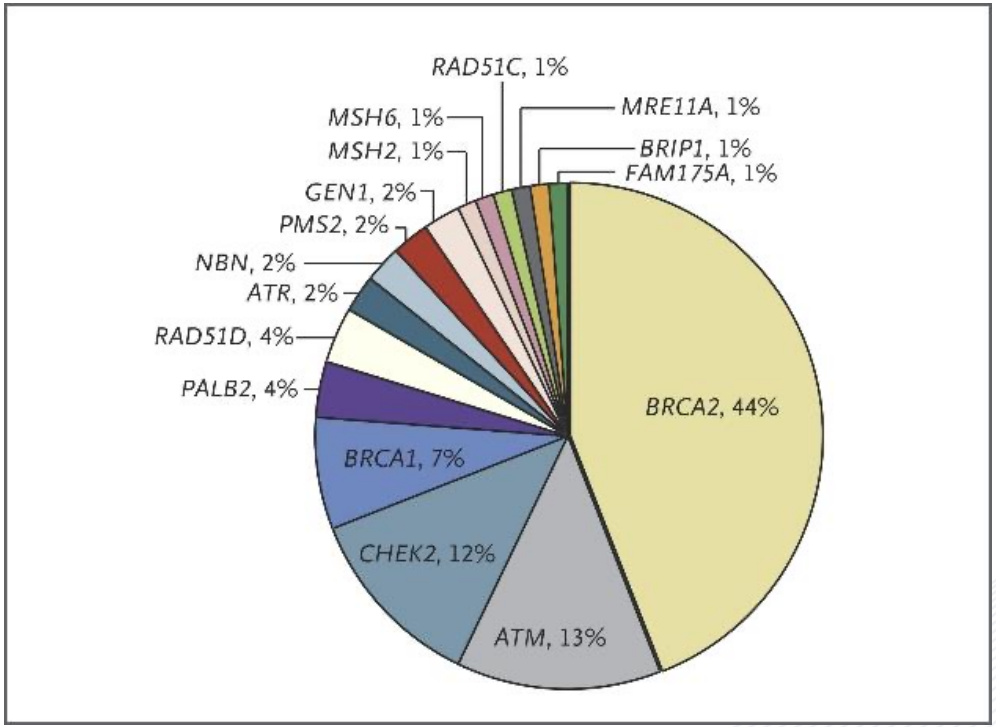




[a]Per PCWG3/RECIST; includes patients with measurable disease at baseline and ≥1 on-treatment scan.

AR=androgen receptor; LBD=ligand-binding domain; ORR=objective response rate; PCWG3=Prostate Cancer Working Group 3; RECIST=Response Evaluation Criteria in Solid Tumors

Distribution of Presumed Pathogenic Germline Mutations



The NEW ENGLAND JOURNAL of MEDICINE

FDA Indications and NCCN Recommendations for PARP Inhibitor Monotherapy in Prostate Cancer

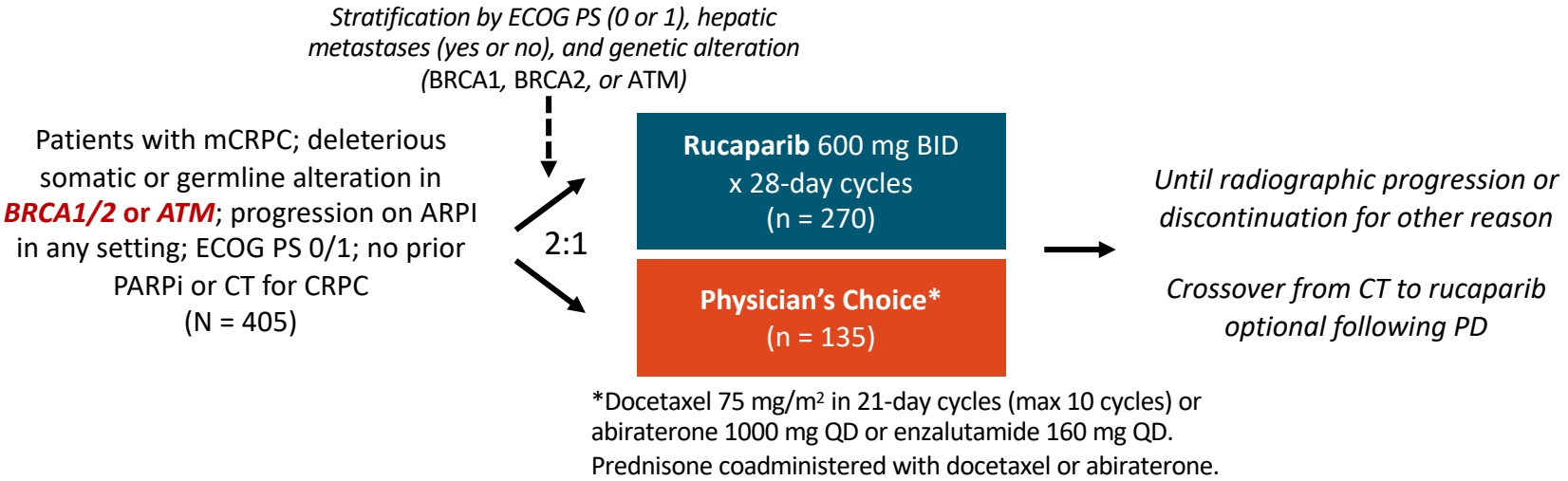
	Olaparib	Rucaparib
FDA	Deleterious/suspected deleterious germline or somatic **HRR gene–mutated mCRPC** that progressed following prior enzalutamide or abiraterone	Deleterious ***BRCA* mutation–associated mCRPC** treated with AR-directed tx and taxane-based CT *(accelerated approval)*
NCCN	Useful in certain circumstances for M1 mCRPC adenocarcinoma: ▪ With **HRRm** after prior NHT, no prior docetaxel ▪ With **HRRm** after prior NHT and prior docetaxel	Useful in certain circumstances for M1 mCRPC adenocarcinoma: ▪ With ***BRCA*m** after prior NHT, no prior docetaxel ▪ With ***BRCA*m** after prior NHT and prior docetaxel

- Patients on PARPi should also receive GnRH analog or had bilateral orchiectomy
- Continue PARPi until PD or unacceptable toxicity

Olaparib PI. Rucaparib PI. NCCN. Prostate cancer. v.4.2023.

TRITON3: Study Design

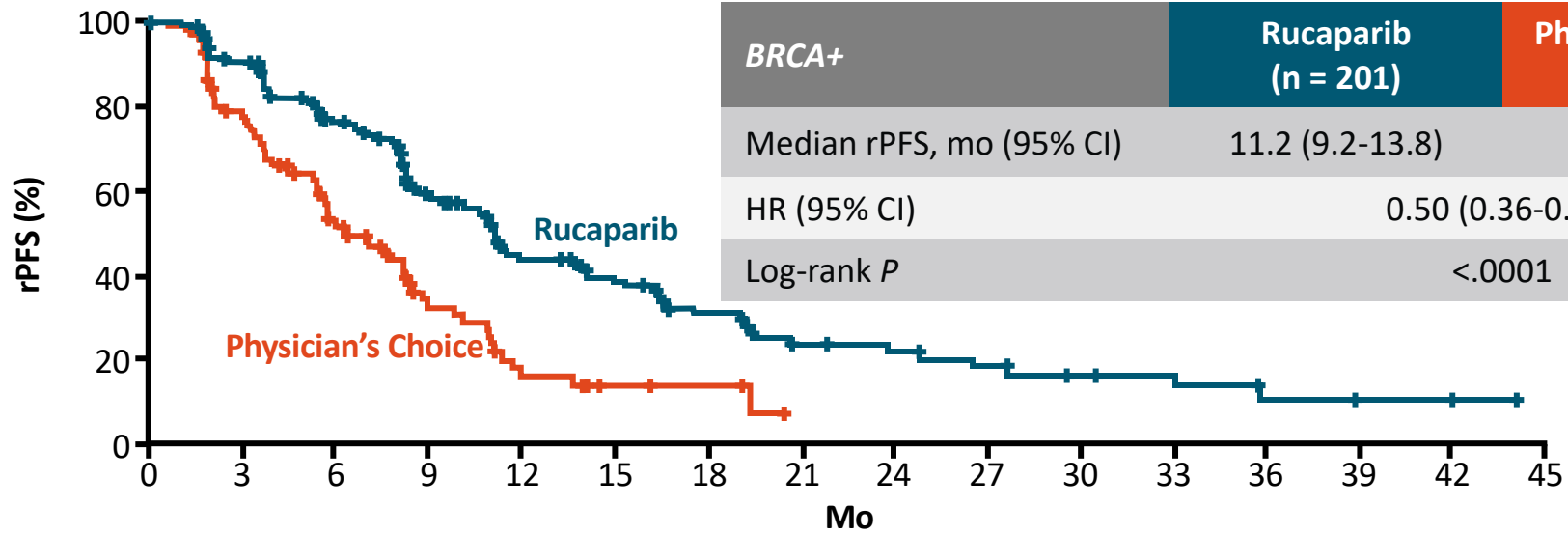
- Randomized, ongoing, multicenter, open-label phase III study



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

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

TRITON3: rPFS (*BRCA*-Altered Subgroup)



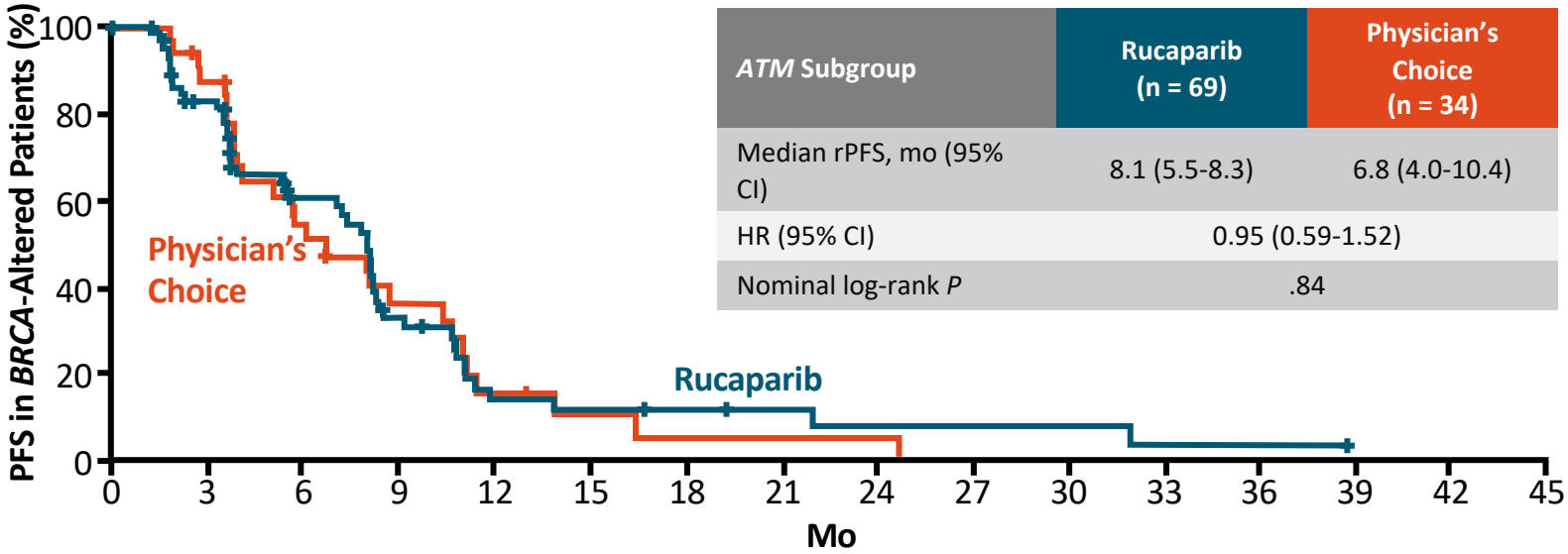
BRCA+	Rucaparib (n = 201)	Physician (n =
Median rPFS, mo (95% CI)	11.2 (9.2-13.8)	6.4 (5
HR (95% CI)	0.50 (0.36-0.69)	
Log-rank *P*	<.0001	

Patients at Risk, n

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)								

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

TRITON3: rPFS (*ATM*-Altered Subgroup)



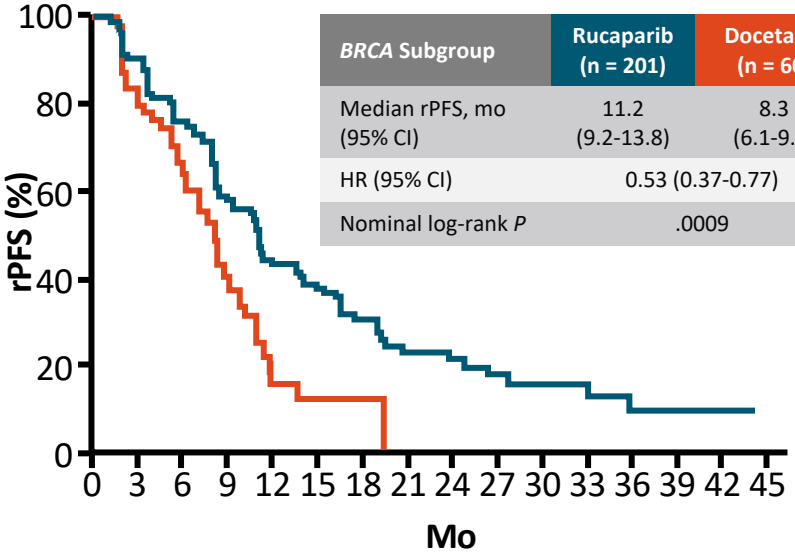
ATM Subgroup	Rucaparib (n = 69)	Physician's Choice (n = 34)
Median rPFS, mo (95% CI)	8.1 (5.5-8.3)	6.8 (4.0-10.4)
HR (95% CI)	0.95 (0.59-1.52)	
Nominal log-rank *P*	.84	

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.

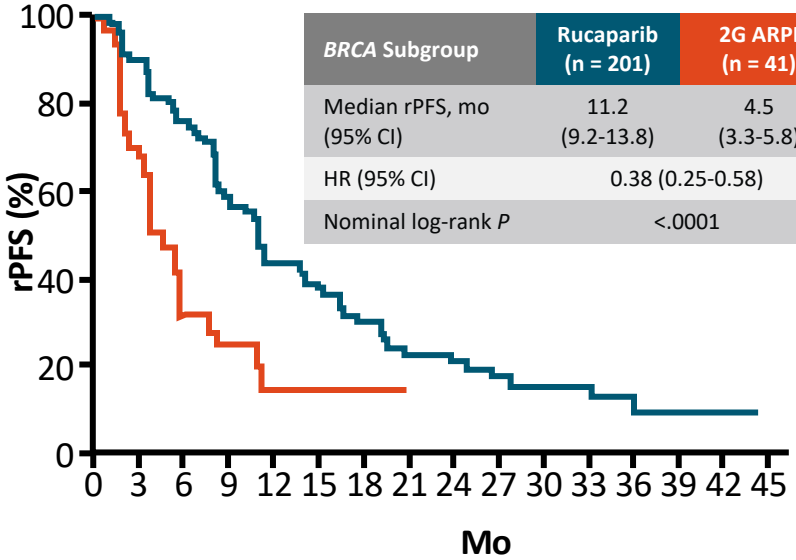
TRITON3: rPFS (*BRCA* Subgroup) by Physician's Choice Treatment

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.

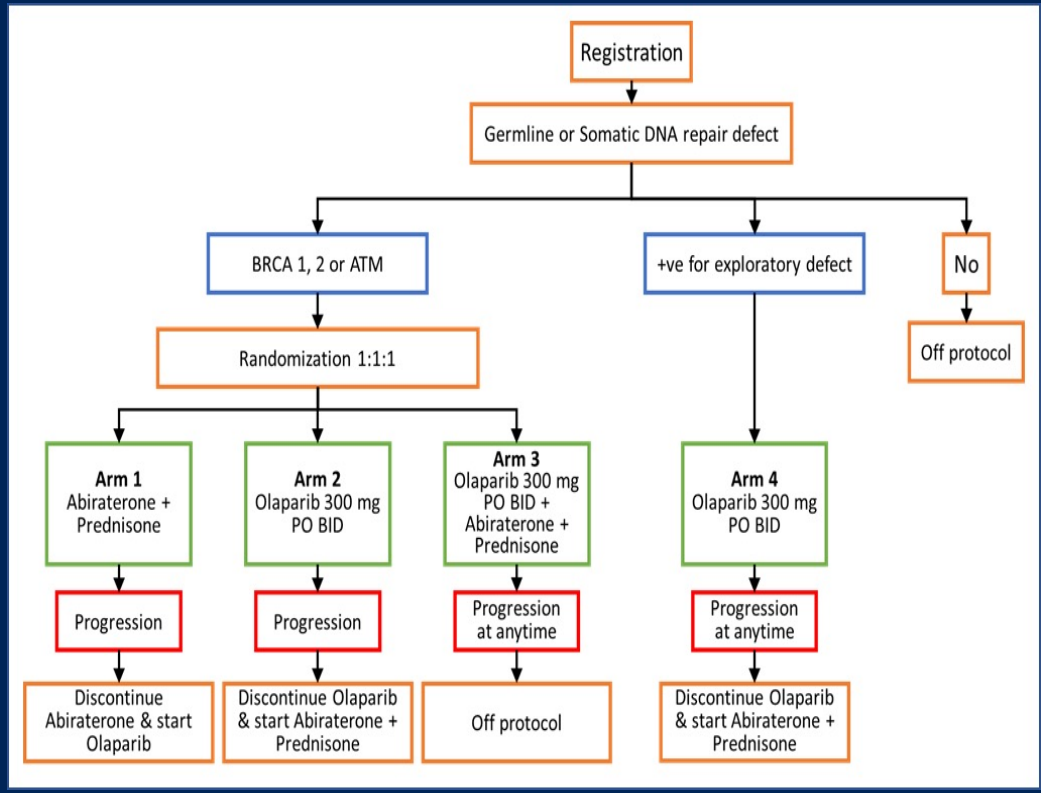
FDA Indications, EMA Indications, and NCCN Recommendations for PARP Inhibitor Combinations

	Niraparib + AAP	Olaparib + AAP	Talazoparib + Enzalutamide
FDA	Adults with deleterious or suspected deleterious ***BRCA*-mutated mCRPC**	Adults with deleterious or suspected deleterious ***BRCA*-mutated mCRPC**	Adults with **HRR gene–mutated mCRPC**
EMA	Adults with **mCRPC and *BRCA1/2* mutations** (germline and/or somatic) in whom **chemotherapy is not clinically indicated**	Adults with **mCRPC** in whom **chemotherapy is not clinically indicated**	Adults with **mCRPC** in whom **chemotherapy is not clinically indicated**
NCCN	Useful in certain circumstances for M1 mCRPC adenocarcinoma: ▪ With ***BRCA*m**, no prior docetaxel/no prior NHT ▪ With ***BRCA*m**, prior docetaxel/ no prior NHT ▪ With ***BRCA*m**, prior NHT/ no prior docetaxel	Useful in certain circumstances for M1 mCRPC adenocarcinoma: ▪ With ***BRCA*m**, no prior docetaxel/no prior NHT ▪ With ***BRCA*m**, prior docetaxel/ no prior NHT	Useful in certain circumstances for M1 mCRPC adenocarcinoma: ▪ With **HRRm**, no prior docetaxel/no prior NHT ▪ With **HRRm**, prior docetaxel/ no prior NHT ▪ With **HRRm**, prior NHT/ no prior docetaxel

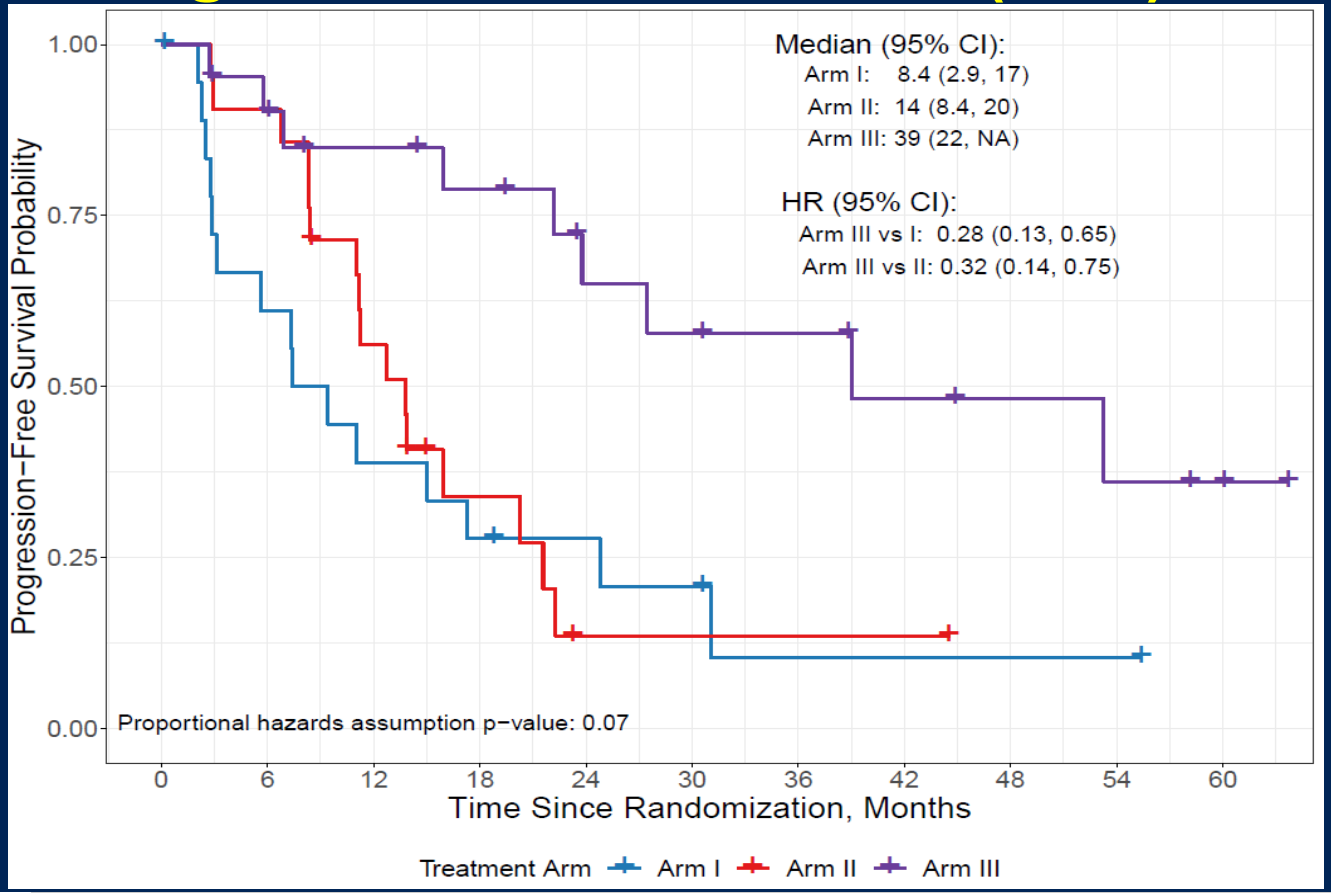
Niraparib and abiraterone acetate PI. Niraparib and abiraterone acetate: EPAR – product information.
Olaparib PI. Olaparib: EPAR – product information. Talazoparib PI. Talazoparib: EPAR – product information.

Methods & Study Design

- **Eligibility:** mCRPC, no prior exposure to PARP-I, AR-I, or chemotherapy for mCRPC, washout of antiandrogen (for mHSPC), radiation, and other investigational agents.
- Eligible pts underwent tumor next-generation sequencing (NGS) & germline testing; pts with inactivating BRCA1/2 and/or ATM alterations were randomized 1:1:1 to:
  - Arm I: abiraterone (1000 mg qd) + prednisone (5mg bid),
  - Arm II: olaparib (300 mg bid)
  - Arm III: olaparib + abiraterone/prednisone
- Arm I and II pts could cross over at progression



Progression-Free Survival (PFS)



PFS: time from randomization until first progression or death.

Proportional hazards assumption was not met for Arm I versus II comparison.

Crossover

- At progression 8/19 pts crossed over from abiraterone/prednisone to olaparib and 8/21 pts vice versa.

	Crossover to Olaparib (n = 8)	Crossover to Abiraterone (n = 8)
Median PFS from crossover, months (95% CI)	**8.3 (5.5, 15)**	**7.2 (2.8, NR)**
Median PFS from randomization, months (95% CI)	**16 (7.8, 25)**	**16 (11, NR)**

NR = Not Reached

- RR to crossover treatment: olaparib 38% and abiraterone 25%.
- PSA RR to crossover treatment: olaparib 50% and abiraterone 63%.

PSMA PET Takes Advantage of Prostate Cancer-Specific Markers

- PSMA is a membrane protein shown to have significant overexpression in prostatic tissues and low expression in normal tissues[1,2]
  - PSMA PET agents include ^{68}Ga PSMA and PyLARIFY PSMA that are approved by the FDA
- High image quality is achieved by uptake of ligand-binding PSMA into tumor cells[1]

Uptake of PSMA Into Tumor Cells*

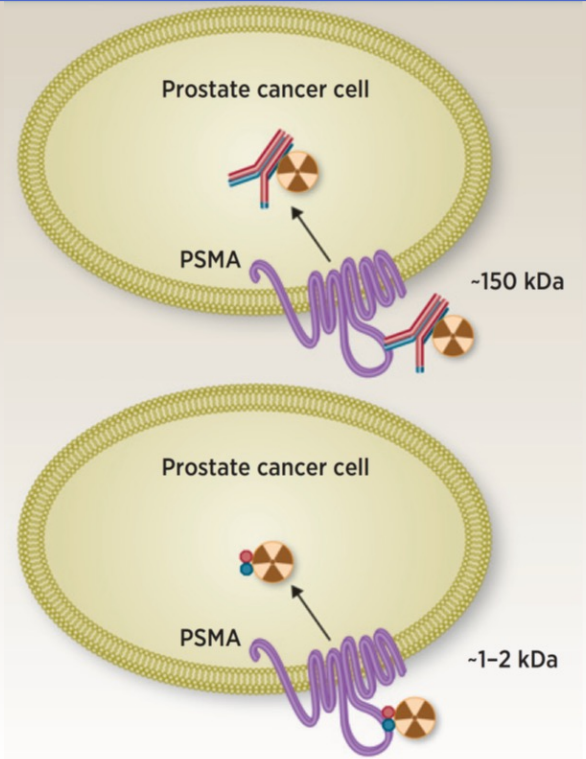


Image from Haberkorn 2016.

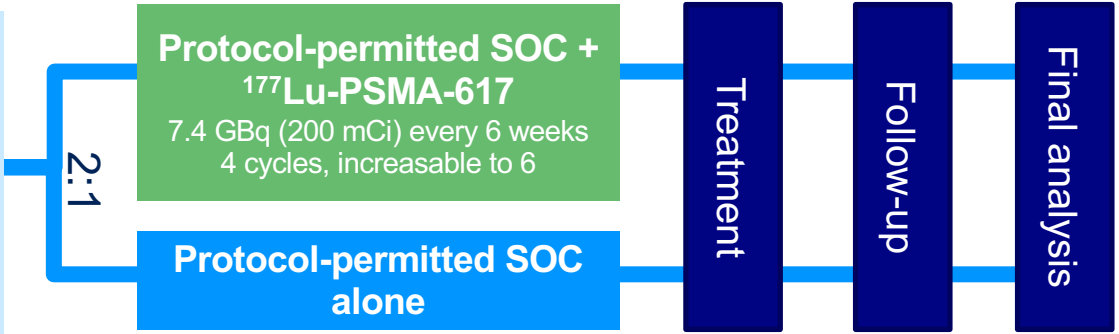
*This is for illustrative purposes only. PSMA crosses the plasma membrane only once.

1. Haberkorn U et al. *Clin Cancer Res*. 2016;22(1):9-15.
2. Lenzo NP et al. *Diagnostics* (Basel). 2018;8(1):pii:E16.

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

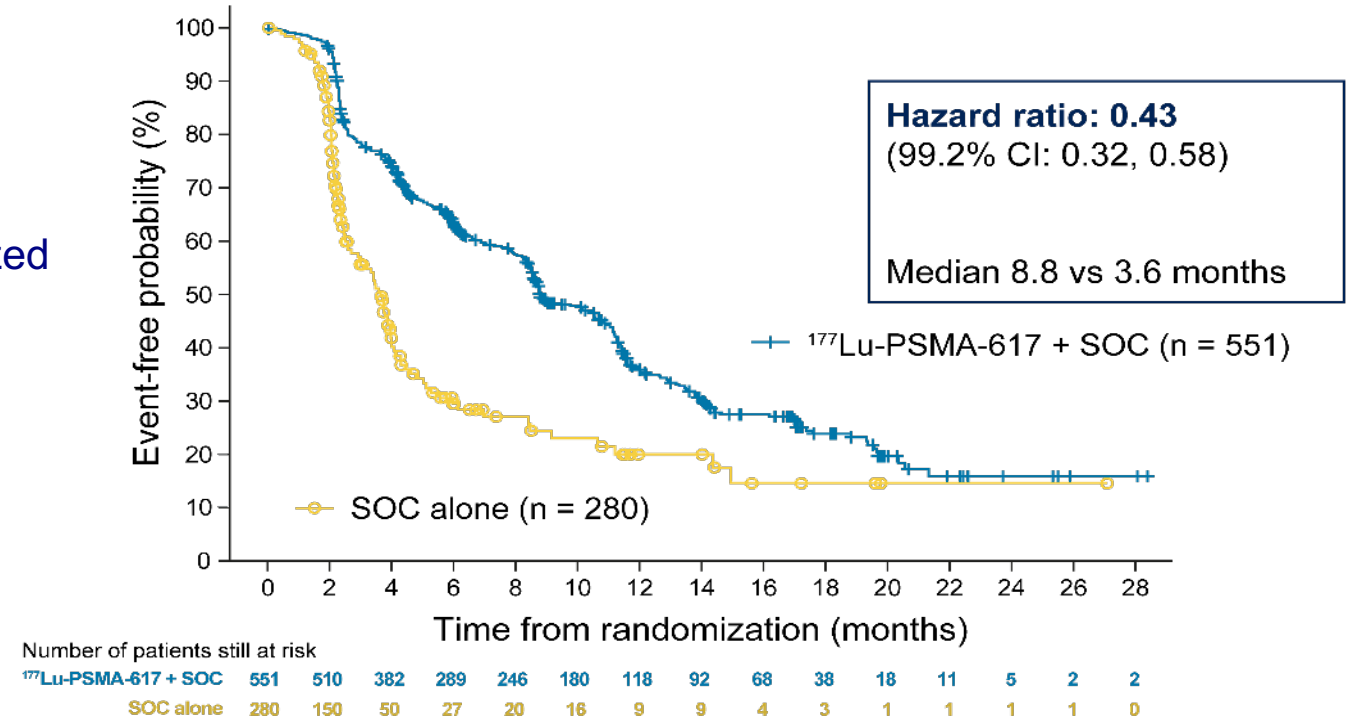
Morris MJ, et al. ASCO 2021. Abstract LBA4.

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

Additional analysis

- All randomized patients

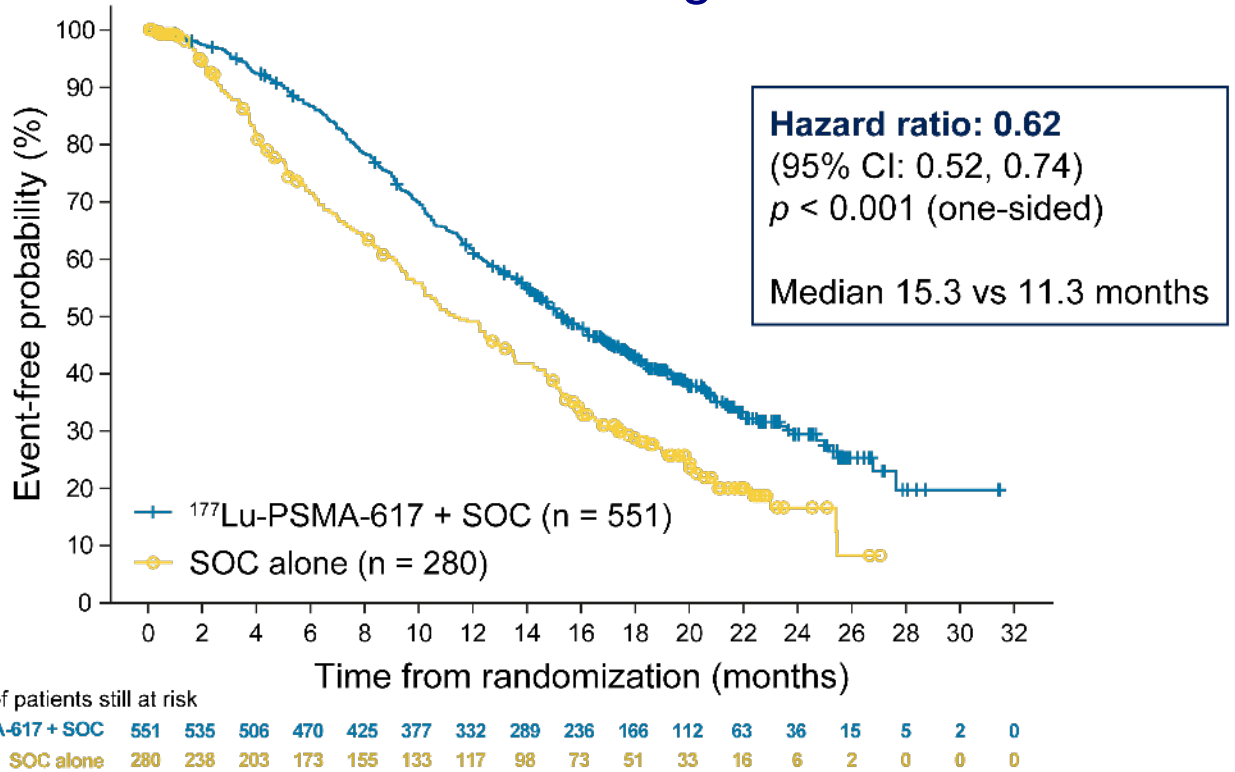
(N = 831)



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

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

Primary analysis
All randomized patients
(N = 831)

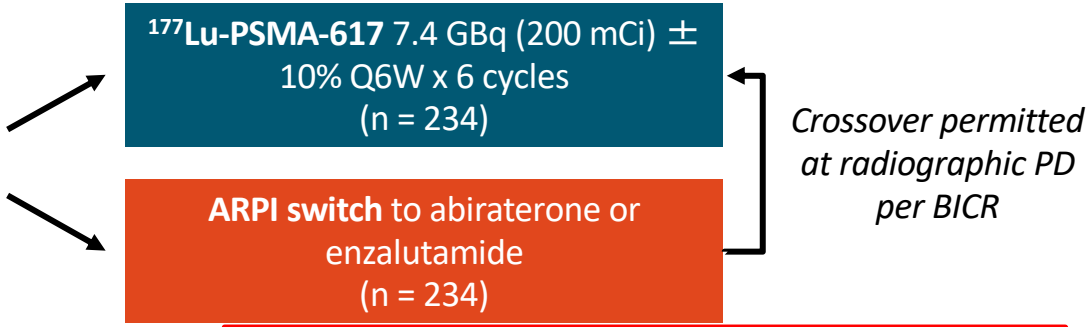


Morris MJ, et al. ASCO 2021. Abstract LBA4.

PSMAfore: Baseline ctDNA and Outcomes With ^{177}Lu-PSMA-617 vs ARPI Switch in Taxane-Naive mCRPC

- International, randomized, open-label phase III trial

Adults with taxane-naive confirmed mCRPC that progressed once on prior ARPI; ≥1 PSMA+ metastasis on ^{68}Ga-PSMA-11 PET/CT with no exclusionary PET- lesions; ineligible for PARP inhibitor; ECOG PS 0/1
(N = 468)



- **Primary endpoint:** rPFS per BICR
- **Selected secondary endpoints:** OS (key), PSA50

*Plasma ctDNA assessed with customized 585-gene sequencing assay. ctDNA fraction examined in all samples that passed quality control.

- Lutetium met its primary endpoint with a statistically significant benefit in rPFS (12 months) compared with ARPI (5.59 months), with a hazard ratio of 0.43
- Secondary and exploratory endpoints, including PSA response, objective response rate, time to symptomatic skeletal events, and time to worsening in health related quality of life and pain, also favored ^{177}Lu-PSMA-617

de Bono. ASCO 2024. Abstr 5008. NCT04689828. Sartor. ESMO 2023. Abstr LBA13.

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