Advanced Prostate Cancer – Castration-Sensitive and Castration-Resistant

Pedro C. Barata, MD, MSc, FACP

Miggo Family in Cancer Research

Co-Leader GU Disease Team

Director of GU Medical Oncology Research Program

University Hospitals Seidman Cancer Center

Associate Professor of Medicine

Case Western Reserve University

Disclosures

Consultant: Astellas; AstraZeneca; BMS; Bayer; Caris Life Sciences Eisai; Exelixis; Ipsen; JNJ, Dendreon; Pfizer, Seattle Genetics, Guardant Health; Novartis; MJH; Medscape; UroToday

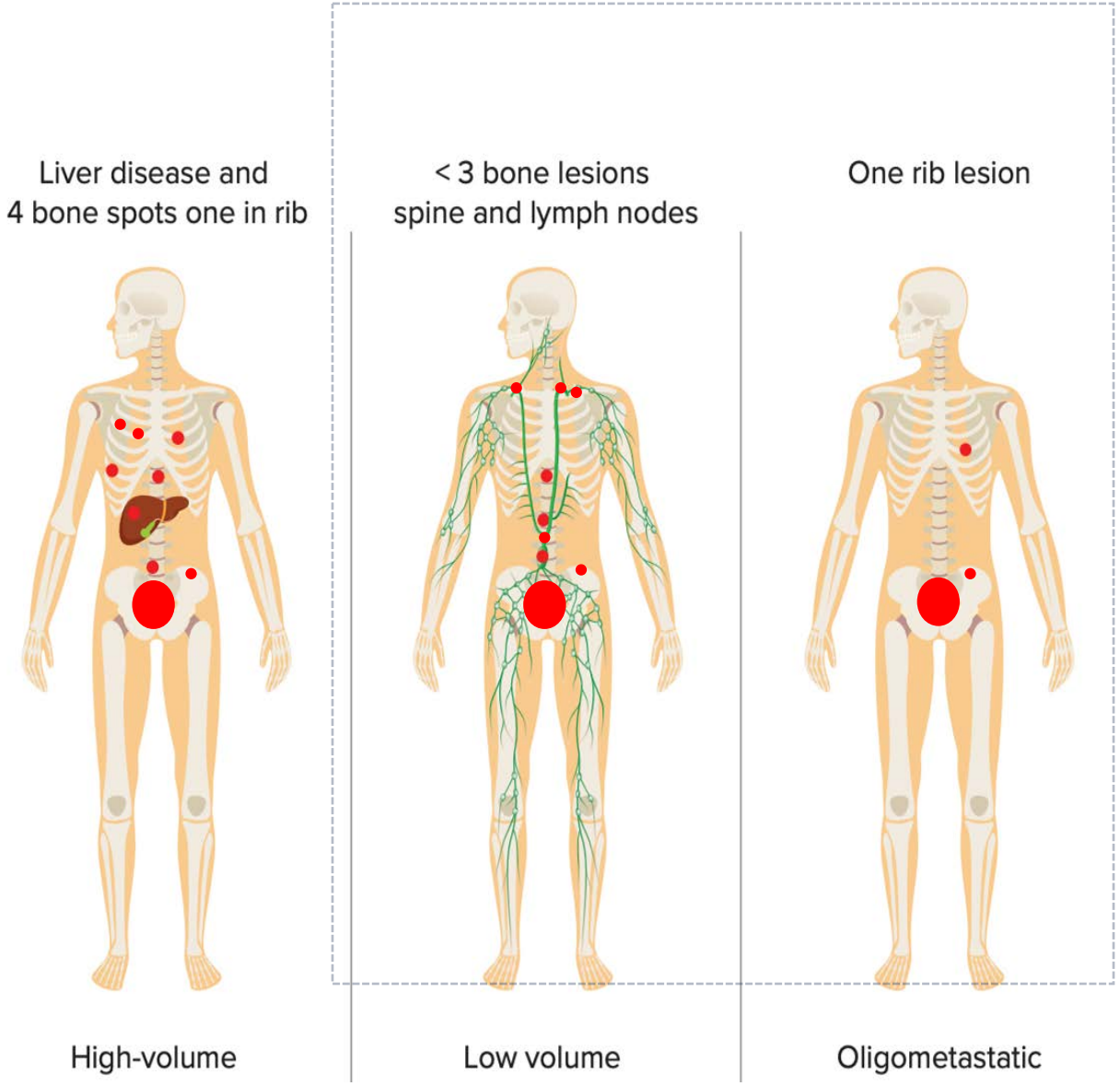
Contracted Research: AstraZeneca, Merck, BlueEarth Diagnostics, Merck, Exelixis
Caris Life Sciences, ESSA Pharma

Equity: Luminate

Metastatic Disease is Heterogenous

1. Newly diagnosed

- 5%-8%
- ↑ with PSMA PET

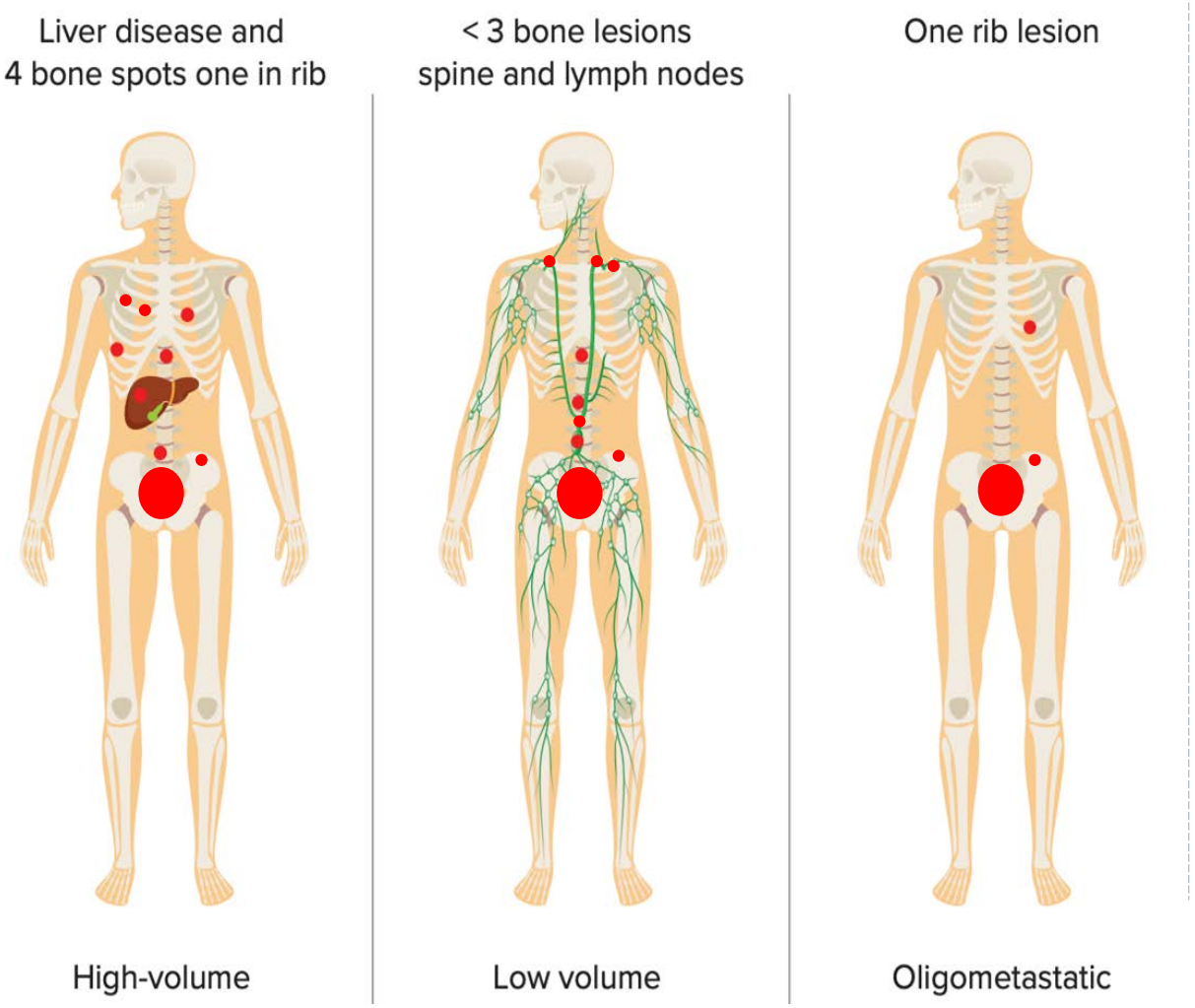


Barata P et al, Cancer 2019; Sorce et al, Prostate 2022; cancer.gov access 2023

Metastatic Disease is Heterogenous

2. Recurrent

- More frequent > *de novo*
- ↑ with PSMA PET

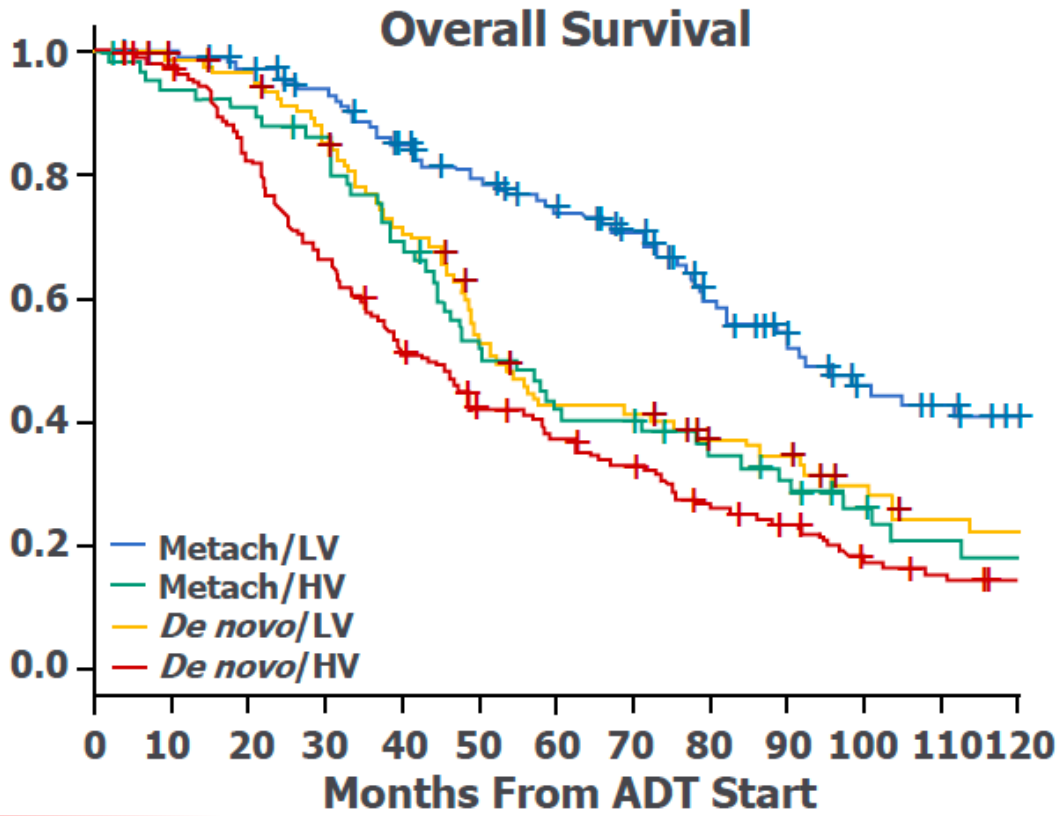


Barata P et al, Cancer 2019; Sorce et al, Prostate 2022; cancer.gov access 2023

Prognosis according to volume and presentation at diagnosis

High-volume de Novo Metastatic Disease Is Associated With the Poorest Prognosis

Groups	N (% events)	mOS, years (95% CI)
Metach/ Low Vol	125 (50)	7.7 (6.7, 10.6)
Metach/ High Vol	67 (75)	4.6 (3.7, 6.7)
De novo/ Low Vol	96 (70)	4.3 (4.0, 6.5)
De novo/ High vol	148 (84)	3.6 (3.1, 4.7)



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@PBarataMD

American Urological Association Education & Research, Inc.

SUO Society of Urologic Oncology, Inc.

The Standard of Care in mHSPC

DOCETAXEL	CHAARTED	Median f-up: 9.7 years, 8y OS rate: 34.9 vs 28.9%	HR=0.77
	STAMPEDE-C+E	Median f-up: 78.2 months, median OS: 59.1 vs 43.1 months	HR=0.81
ABIRATERONE	LATITUDE	Median f-up: 51.8 mo, median OS: 53.3 vs 36.5 months	HR=0.66
	STAMPEDE-G	Median f-up: 73 mo, median OS: 79 vs 46 months	HR=0.60
ENZALUTAMIDE	ENZAMET	Median f-up: 68 mo, median OS: NR vs 73.2 months	HR=0.70
	ARCHES	Median f-up: 44.6 mo, median OS: NR vs NR	HR=0.66
APALUTAMIDE	TITAN	Median f-up: 44.0 mo, median OS: NR vs 52.2 months	HR=0.65
DOCETAXEL + NHA	PEACE-01 (Abi)	Median f-up: 3.8 years, median OS: NR vs 4.43 years	HR=0.75
	ARASENS (Daro)	Median f-up: 43.7 mo, median OS: NR vs 48.9 months	HR=0.68

Tripathi A et al. ASCO 2022. Clarke N, et al, Ann Onc 2019. Fizazi K, et al. Lancet Oncol 2019. James ND et al, Int J Cancer 2022. Davis ID, et al, ASCO 2022 . Armstrong AJ, et al. JCO 2022. Chi KN et al, JCO 2021. Fizazi K et al, Lancet 2022. Smith MR, et al. NEJM 2022

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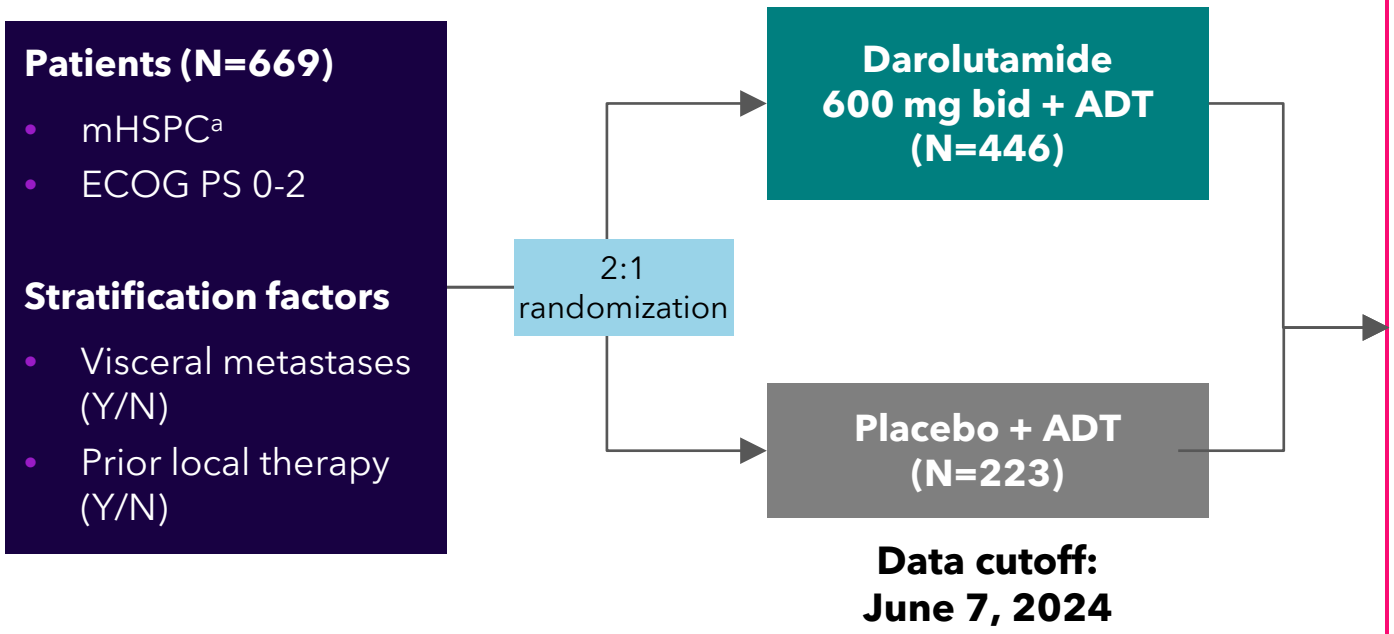
@PBarataMD

ARANOTE Study Design

Global, randomized, double-blind, placebo-controlled, phase 3 study



Endpoints

Primary

- rPFS by central blinded review

Secondary

- OS
- Time to initiation of subsequent anticancer therapy
- Time to mCRPC
- Time to PSA progression
- Rates of undetectable PSA (<0.2 ng/mL)
- Time to pain progression (BPI-SF)
- Safety

ClinicalTrials.gov: NCT04736199

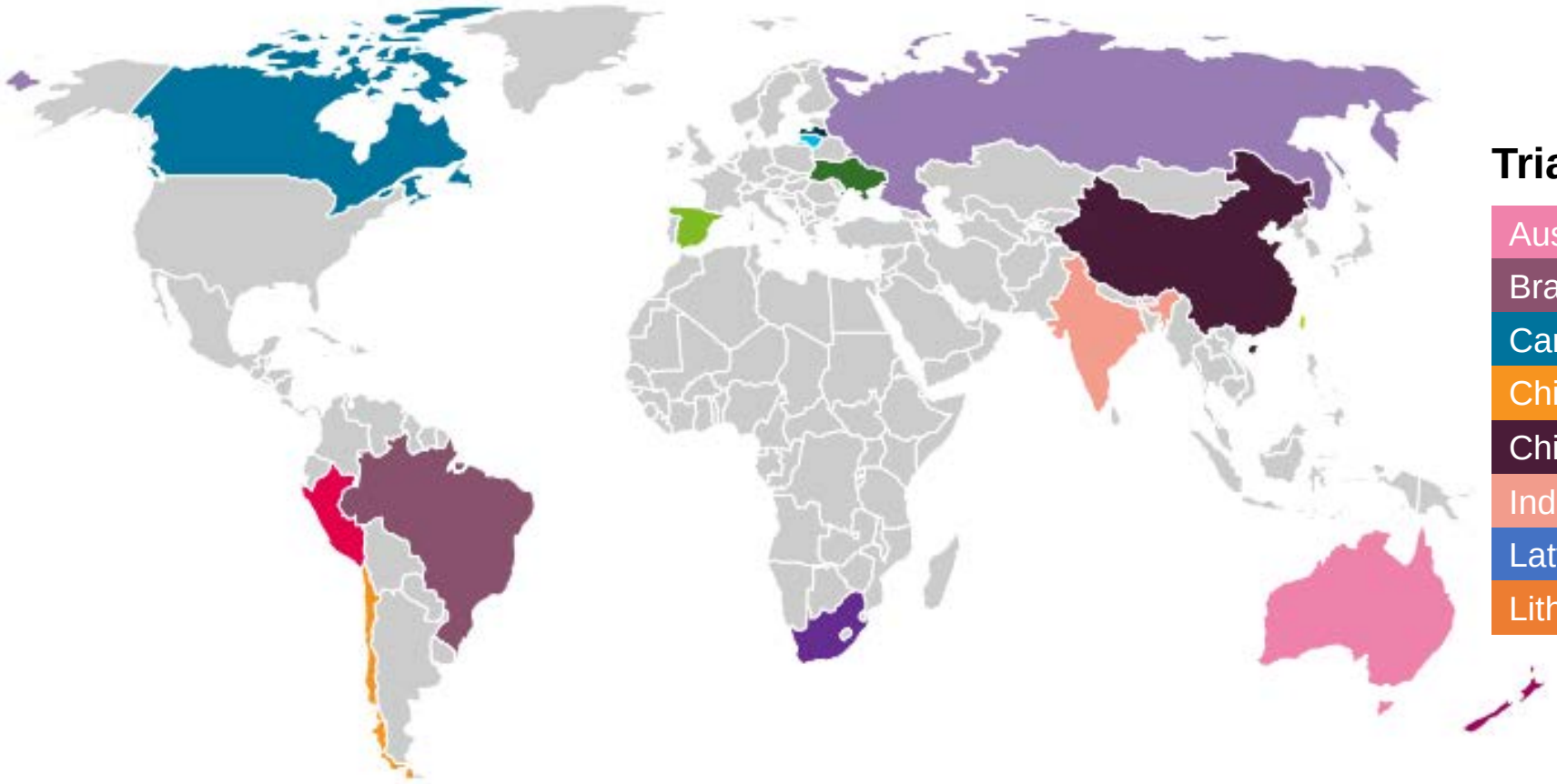
The combination of darolutamide + ADT has not been approved in Latin America

[a]Metastatic disease confirmed by conventional imaging method as a positive ^{99m}Tc-phosphonate bone scan or soft tissue/visceral metastases on contrast-enhanced abdominal/pelvic/chest CT or MRI scan, assessed by central review.

Saad F, et al. Presented at the European Society for Medical Oncology Congress; September 13-17, 2024; Barcelona, Spain. Abstract LBA68.

ARANOTE

Brazil 25% of Accrual



Trial Sites

Australia	New Zealand
Brazil	Peru
Canada	Russian Federation
Chile	South Africa
China	Spain
India	Taiwan
Latvia	Ukraine
Lithuania	

Hafeez KP, et al. Poster presented at: American Society of Clinical Oncology Genitourinary Cancers Symposium; February 17-19, 2022. Abstract TPS200.

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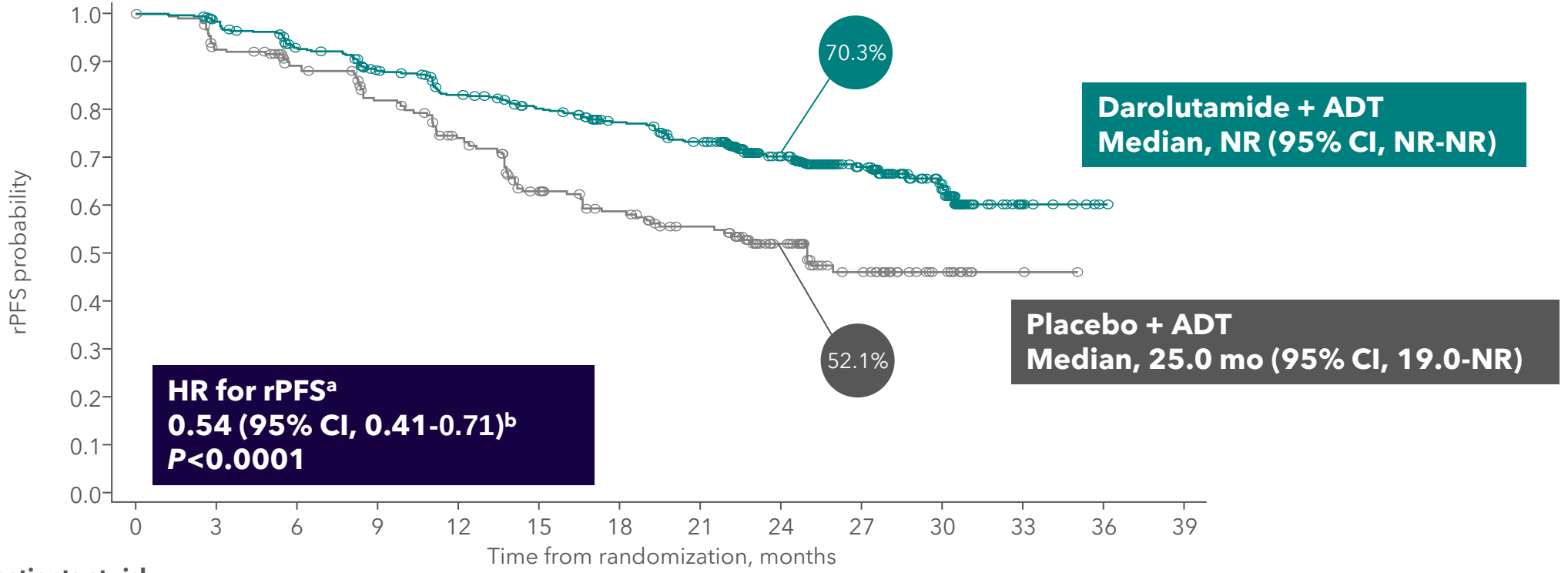
@PBarataMD

ARANOTE Primary Endpoint: rPFS[a]

Darolutamide significantly reduced the risk of radiological progression or death by 46%



No. of patients at risk

Darolutamide	446	422	388	358	330	309	285	262	186	113	54	9	1	0
Placebo	223	197	178	158	137	109	96	83	58	32	12	2	0	0

Median follow-up: darolutamide group 25.3 months; placebo group 25.0 months

The combination of darolutamide + ADT has not been approved in latin america.

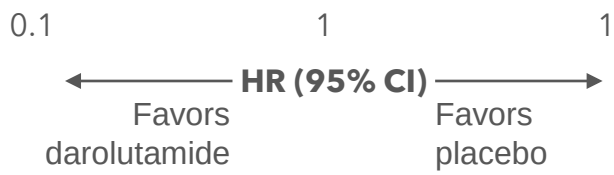
[a]Primary analysis occurred after 222 events (darolutamide 128, placebo 94); [b]HR and 95% CI were calculated using the Cox model stratified on visceral metastases (Y/N) and prior therapy (Y/N).

ADT, androgen deprivation therapy; CI, confidence interval; HR, hazard ratio; NR, not reached; rPFS, radiological progression-free survival.

Saad F, et al. Presented at the European Society for Medical Oncology Congress; September 13-17, 2024; Barcelona, Spain. Abstract LBA68.

ARANOTE: Darolutamide Showed a Benefit Across All Secondary Endpoints

Endpoint	Darolutamide (n=446)		Placebo (n=223)		Stratified HR (95% CI)
	n (%)	Median, months	n (%)	Median, months	
OS	103 (23.1)	NR	60 (26.9)	NR	0.81 (0.59-1.12)
Time to mCRPC	154 (34.5)	NR	143 (64.1)	13.8	0.40 (0.32-0.51)
Time to PSA progression	93 (20.9)	NR	108 (48.4)	16.8	0.31 (0.23-0.41)
Time to initiation of subsequent systemic therapy for prostate cancer	68 (15.2)	NR	74 (33.2)	NR	0.40 (0.29-0.56)
Time to pain progression	124 (27.8)	NR	79 (35.4)	29.9	0.72 (0.54-0.96)



At the time of primary analysis, OS data are immature

The combination of darolutamide + ADT has not been approved in Latin America.

Saad F, et al. Presented at the European Society for Medical Oncology Congress; September 13-17, 2024; Barcelona, Spain. Abstract LBA68.

Pedro C. Barata, MD MSc FACP
@PBarataMD

Significance of PSA responses in mHSPC

Deep prostate-specific antigen response and overall survival in patients with metastatic castration-sensitive prostate cancer: A systematic review and meta-analysis.

Authors: Syed Arsalan Ahmed Naqvi, Irbaz Bin Riaz, Manal Imran, Muhammad Daim Bin Zafar, Kunwer Sufyan Faisal, Zaryab Bin Riaz, Parminder Singh, and Alan Haruo Bryce | AUTHORS INFO & AFFILIATIONS

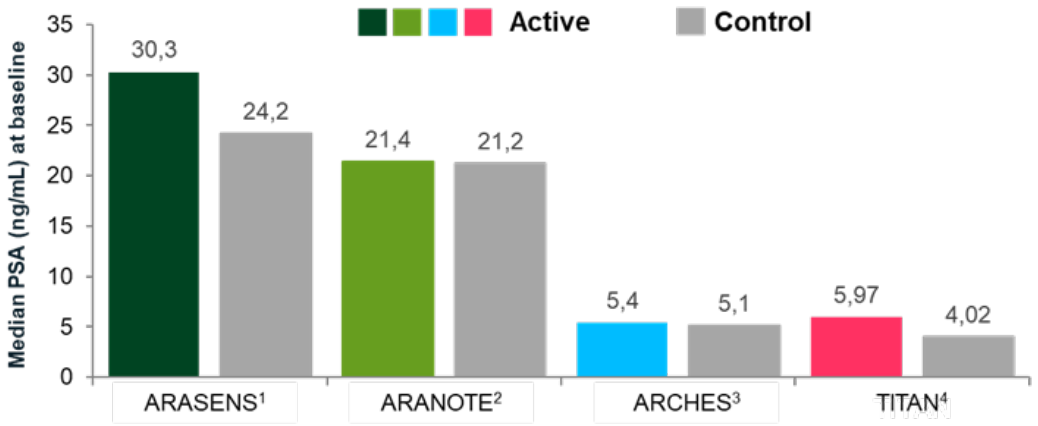
Publication: Journal of Clinical Oncology • Volume 41, Number 6_suppl • https://doi.org/10.1200/JCO.2023.41.6_suppl.195

			Anticipated absolute effects	
Outcome	Participants (trials)	Hazard ratio (95% CrI)	Risk of death without deep PSA response within 8 months	Survival benefit with deep PSA response within 8 months
Overall survival	1980 (4 trials)	**0.41** (0.31 to 0.53)	347 deaths per 1,000	187 fewer deaths per 1,000; (223 fewer to 145 fewer)

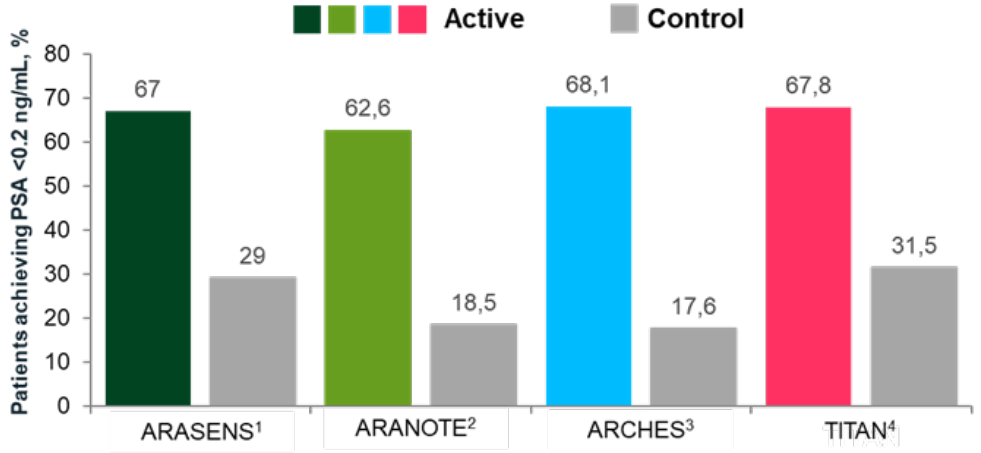
Meta-analysis from: CHAARTED, LATITUDE , TITAN, PEACE1 and ARASENS

Baseline PSA should be considered when assessing PSA outcomes

Median baseline PSA



Proportion of Patients With Undetectable PSA (<0.2 ng/mL) at Any Time



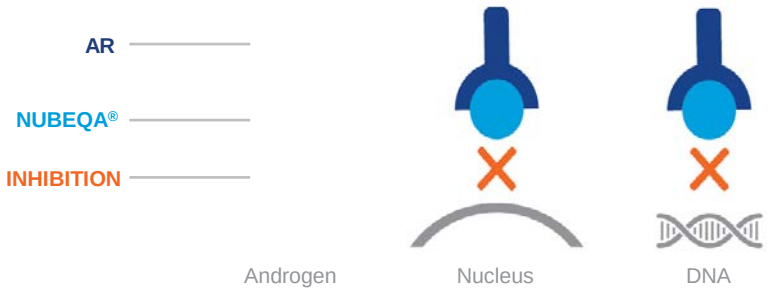
1. Smith MR, et al. N Engl J Med. 2022;386:1132–42. 2. Saad F, et al. J Clin Onol. 2024;42:4271–81. 3. Armstrong AJ, et al. J Clin Oncol. 2019;37:2974–86. 4. Chowdhury S, et al. Ann Oncol. 2023;34:477–85.

Pedro C. Barata, MD MSc FACP
@PBarataMD

Darolutamide has a unique structure with a distintic safety profile[1-4]

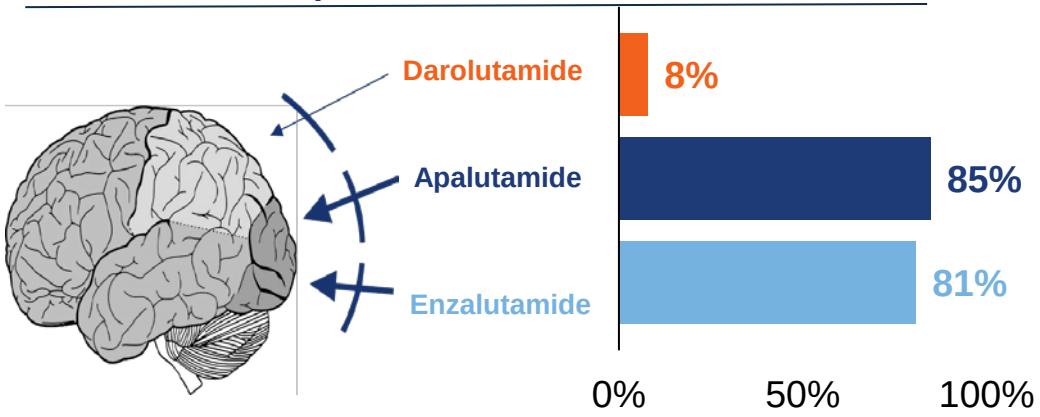
Mechanism of action

Darolutamide inhibits the androgen receptor (AR)



** Adapted from Moilanen 2015*

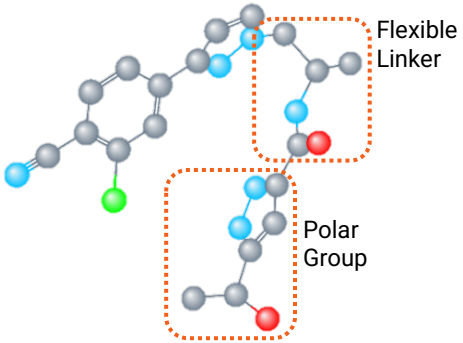
Ratio of brain/blood concentration[2]



** Preclinical study data*

Unique molecular structure

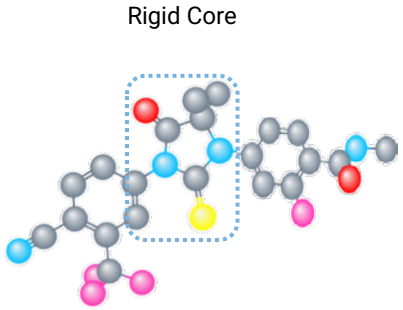
Darolutamide[3,4]



Interacts with **45** drugs while

12 with major severity

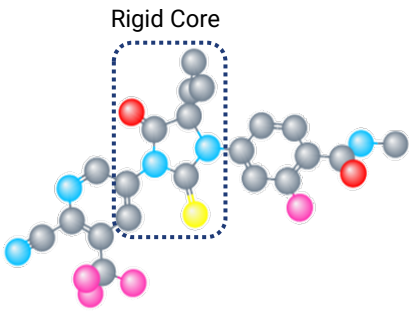
Enzalutamide[5]



Interacts with **426** drugs whille

143 with major severity

Apalutamide[6]



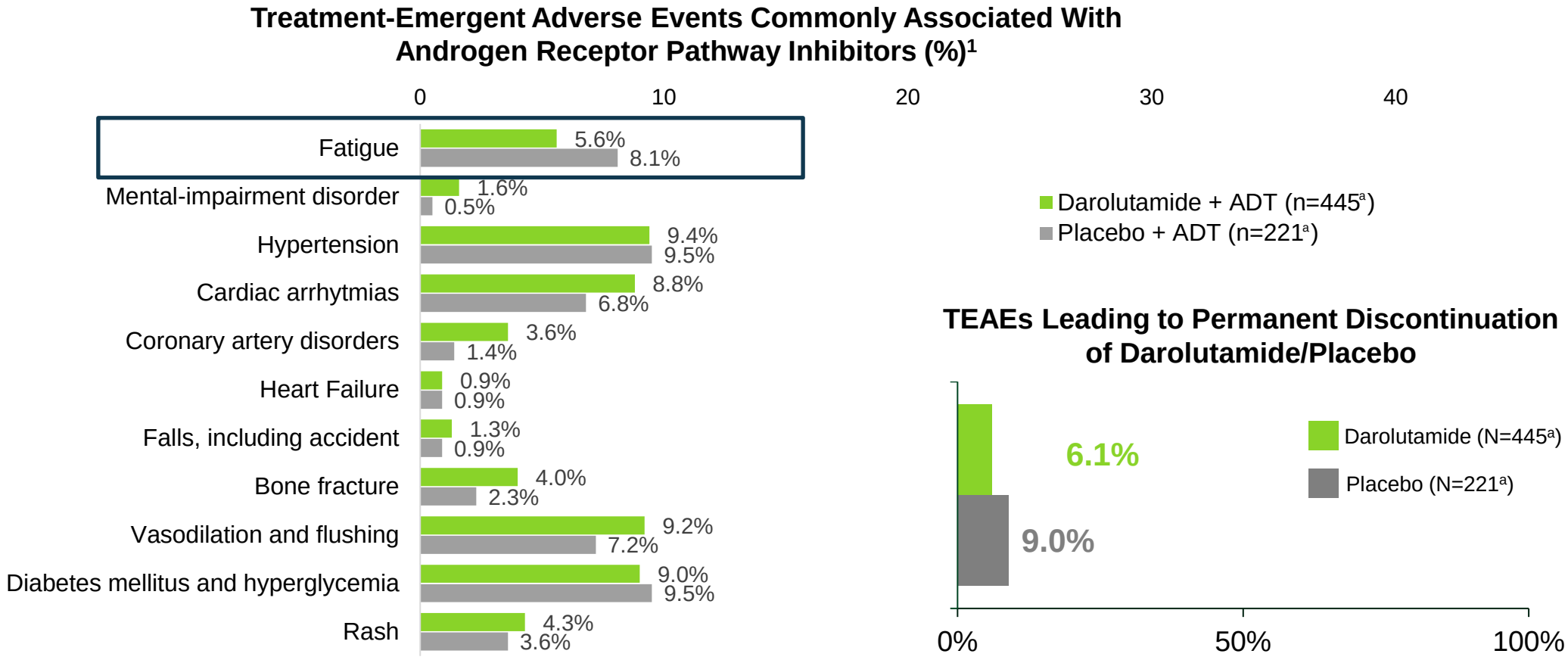
Interacts with **428** drugs while

160 with major severity

Individual information for each molecule, without comparative value.

1.Darolutamida. [Bula]. Finlândia: Bayer. Disponível em: <https://consultas.anvisa.gov.br/#/bulario/q/?nomeProduto=NUBEQA>. Acesso em: 20/01/2023; 2. Zurth et al. Higher blood–brain barrier penetration of [14c]apalutamide and [14c]enzalutamide compared to [14c]darolutamide in rats using wholebody autoradiography. Asco. 2019. Disponível em: https://ascopubs.Org/doi/10.1200/jco.2019.37.7_suppl.156. Acesso em: 23/01/20232. *3. Moilanen A, et al. Sci Rep. 2015;5:12007; 4. PubChem. Compound ID: 67171867. Acessado em 31 de Janeiro de 2019; 5. Pubchem. Compound ID: 15951529. Acessado em 31 de janeiro de 2019; 6. PubChem. Compound ID: 24872560. Acessado em 31 de janeiro de 2019;*

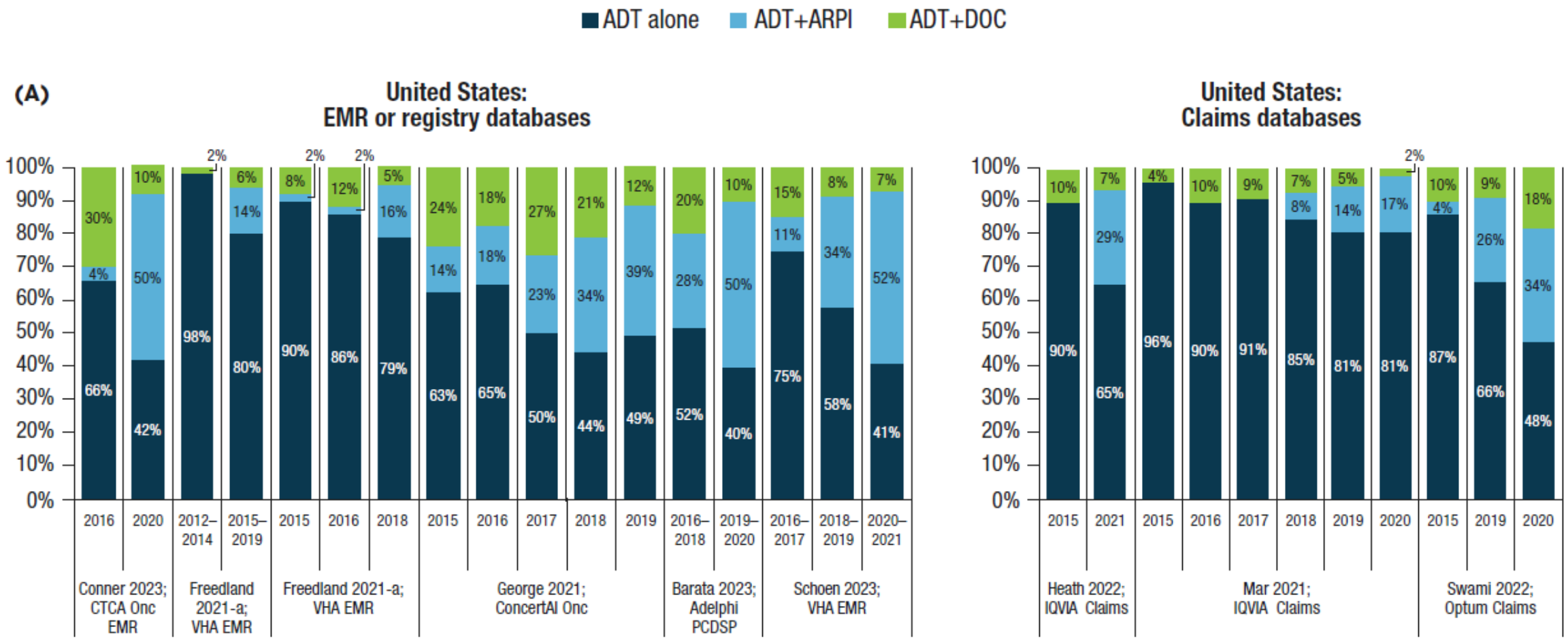
Rates of AEs Associated With Darolutamide Are Low and Similar Between Treatment Arms



ADT, androgen deprivation therapy; AEs, Adverse Events;TEAEs, Treatment-Emergent Adverse Events;
[a]Two patients who were randomized to the placebo group but received darolutamide are analyzed in the darolutamide group for the safety analysis set. The safety analysis set included all randomized patients who received at least one dose of study drug and are analyzed according to the treatment they received.[2]

1. Saad F, et al. Presented at: European Society for Medical Oncology Congress 2024. September 13-17, 2024; Barcelona, Spain. Abstract LBA68. 2. Saad F, et al. *J Clin Oncol*. 2024. doi:10.1200/JCO-24-01798.

ADT Alone Usage in mHSPC in US[1]



ADT, androgen deprivation therapy; ARPI, Androgen Receptor Pathway Inhibitor; DOC, Docetaxel; EMR, Electronic Medical Records; mHSPC, metastatic Hormonessensitive Prostate Cancer;

1. Amit D. Raval et al BJU Int 2024 doi:10.1111/bju.16577

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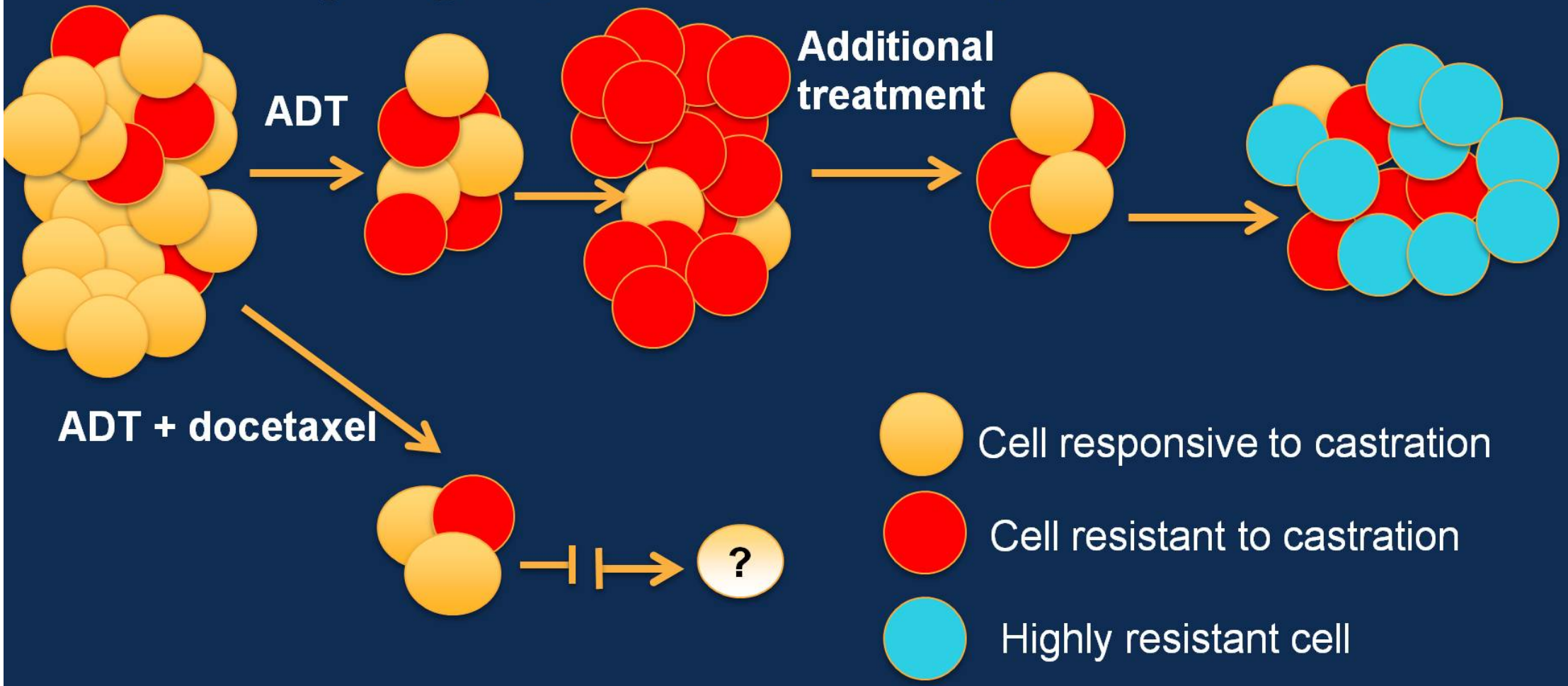
@PBarataMD

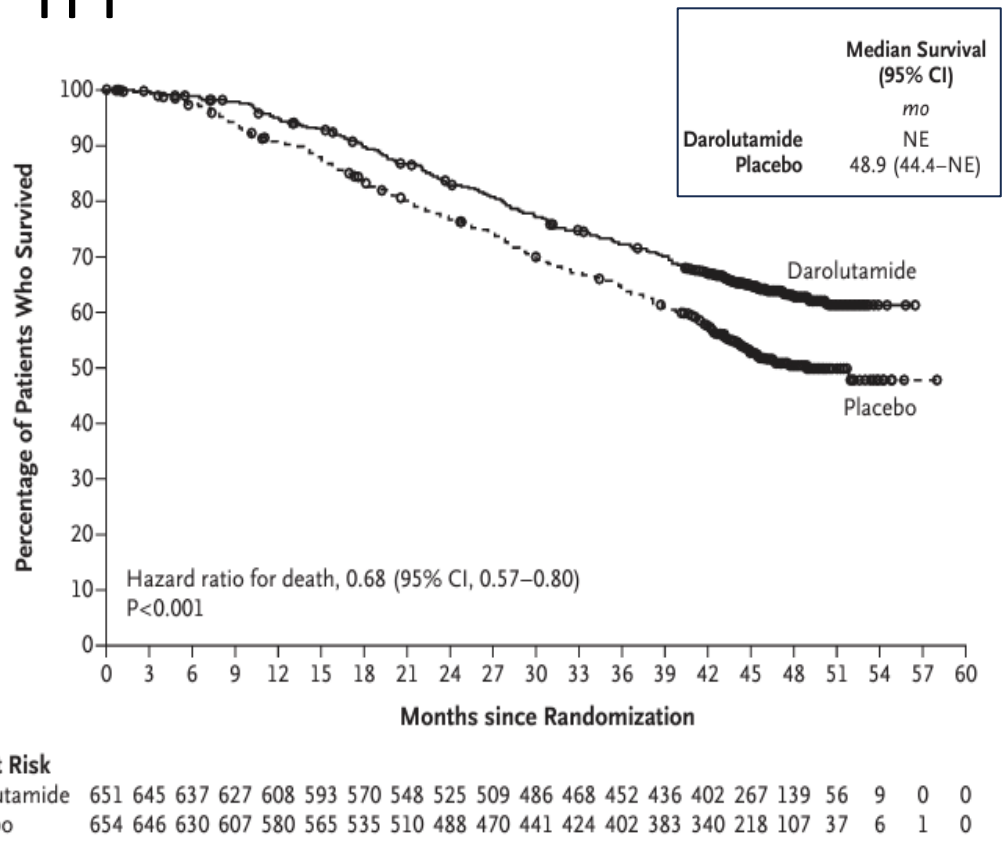
Intensifying up-front tx for prostate CA



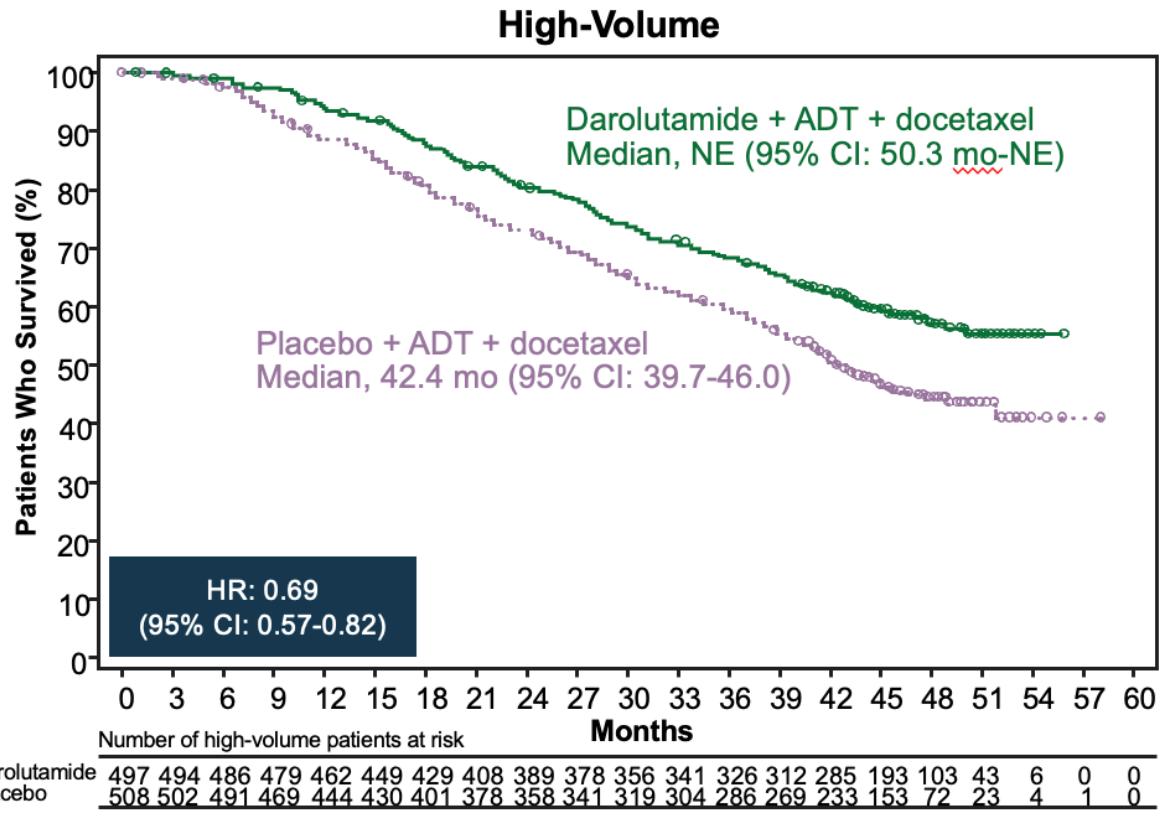
ARASENS Doc +- Daro (77% High-Volume / 86% *de novo*)

OS

ITT



High-Volume



Hussain M, et al. *J Clin Oncol.* 2023. doi:10.1200/JCO.23.00041.

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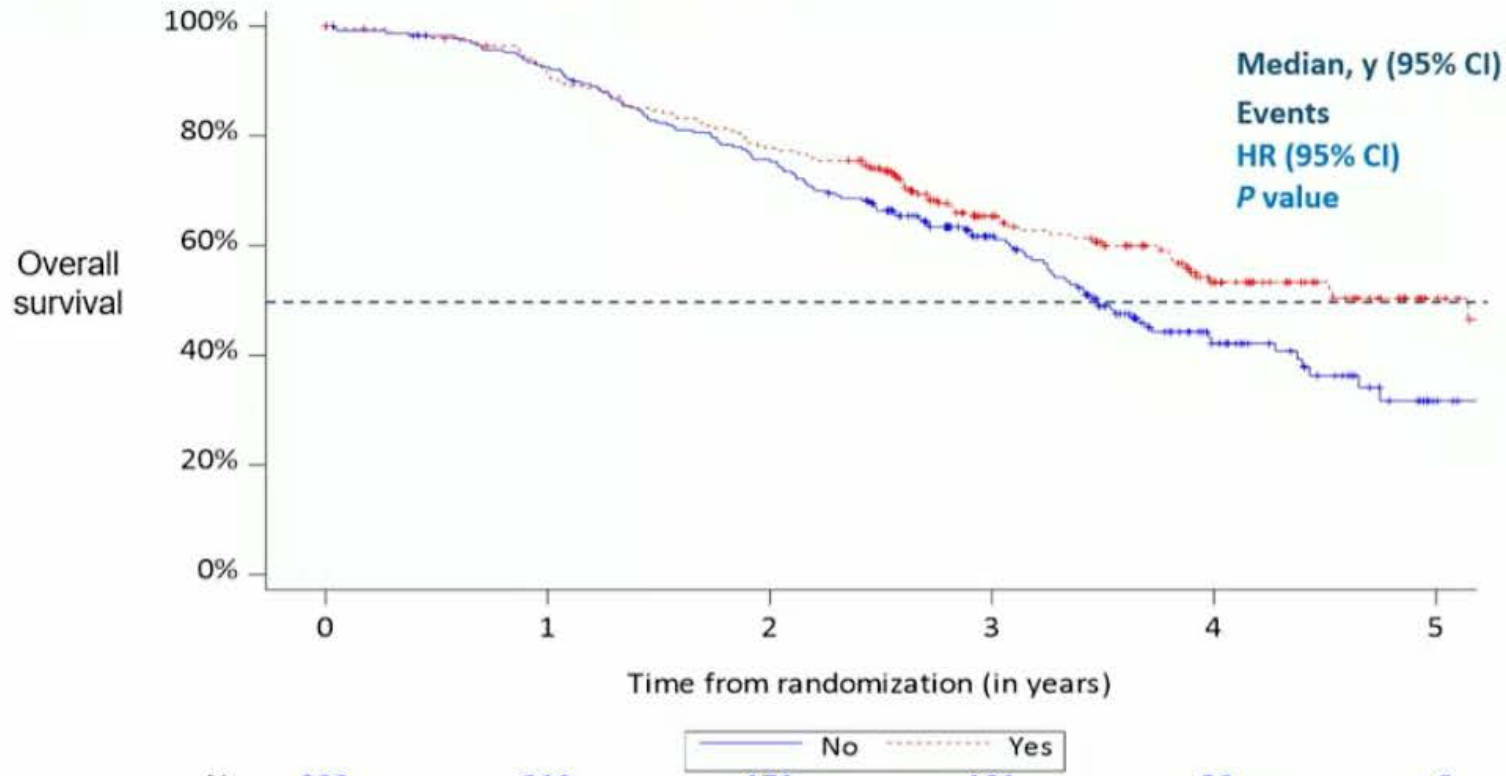
@PBarataMD

PEACE-1

OS with Abiraterone in the ADT+docetaxel (+/-RXT): High-volume patients



	SOC+Abi (n = 224)	SOC (n = 232)
Median, y (95% CI)	5.1 (3.8-NE)	3.5 (3.2-4.0)
Events	92	120
HR (95% CI)	0.72 (0.55-0.95)	
P value	0.019	

OS ADT+Docetaxel
HR 0.75 (0.59-0.95)
p = 0.017

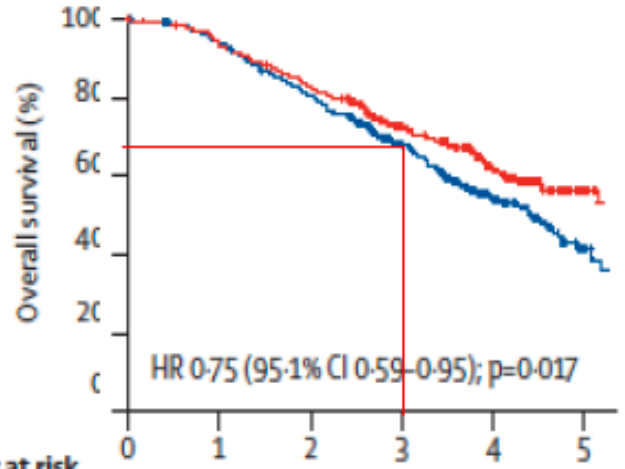
2021 ESMO congress

Karim Fizazi

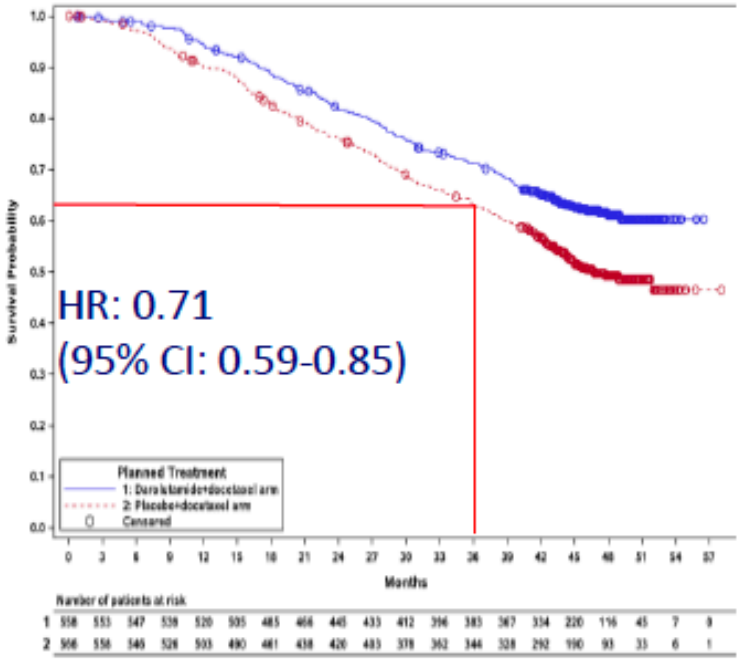
Pedro C. Barata, MD MSc FACP
@PBarataMD

Adding an ARPI to Docetaxel in Synchronous mHSPC Consistently Improves OS

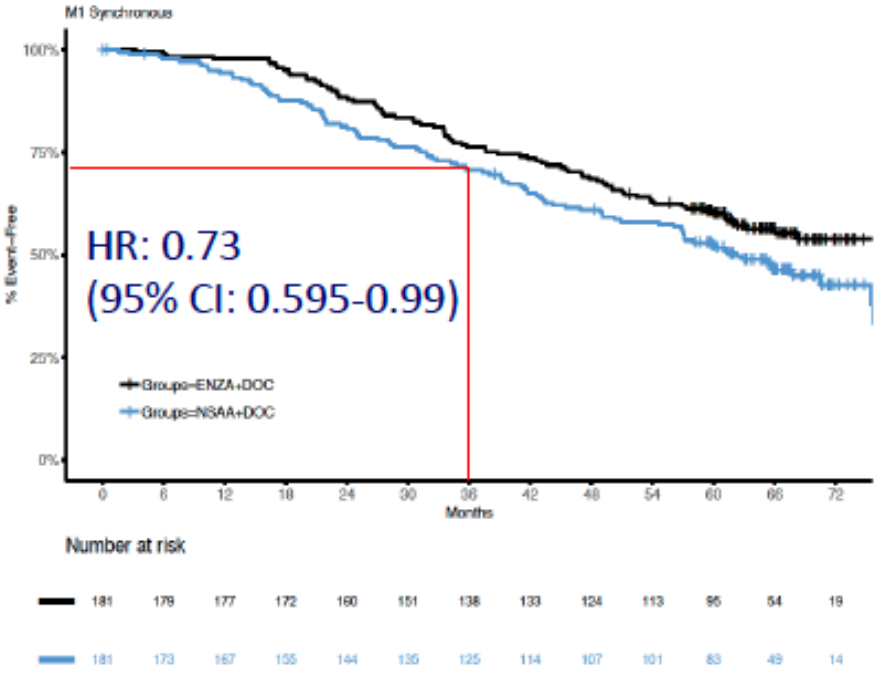
ADT + Doc + Abi > ADT + Doc
PEACE-1[1] (All De novo)



ADT + Doc + Daro > ADT + Doc
ARASENS[2] (All De novo)



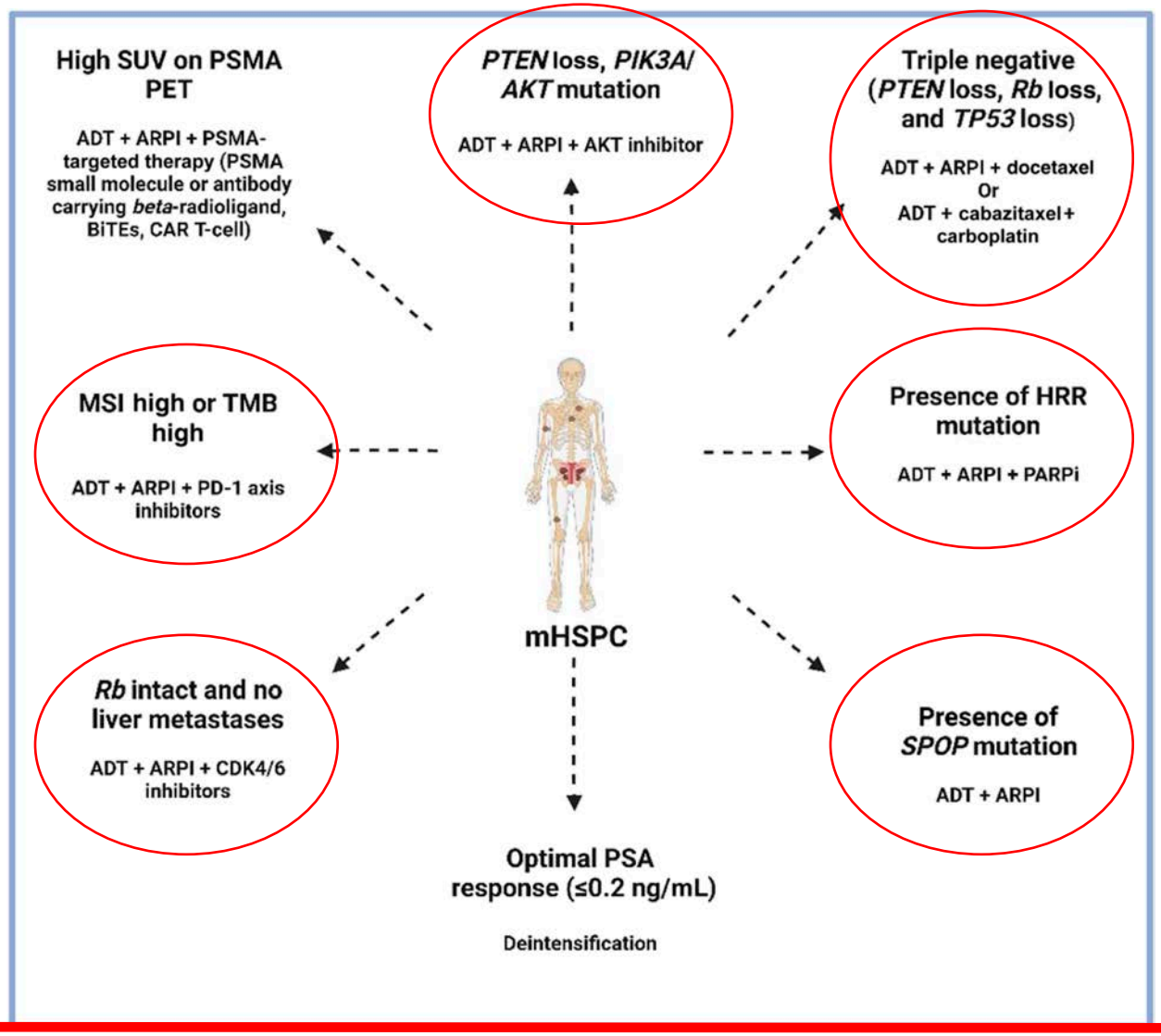
ADT + Doc + Enza > ADT + Doc
ENZAMET[3] (All De novo)



Fizazi Et al. Lancet 2022; Smith et al. NEJM 2022; Sweeney et al .Lancet Oncol 2023

Pedro C. Barata, MD MSc FACP
@PBarataMD

Personalizing treatment of mHSPC



- Many include molecular characterization of tumors

Hamid, ASCO Ed Book 2023

AMPLITUDE: Randomized, Double-Blind, Placebo-Controlled Trial in HRRm mCSPC

First and final rPFS analysis and first interim analysis of time to symptomatic progression and overall survival. Median follow-up: 30.8 months

Key inclusion criteria:

- mCSPC[a]
- Alteration in ≥1 HRR eligible gene: *BRCA1*, *BRCA2*, *BRIP1*, *CDK12*, *CHEK2*, *FANCA*, *PALB2*, *RAD51B*, *RAD54L*[b]
- ECOG PS 0-2

Key exclusion criteria:

- Any prior
  - PARPi
  - ARPI other than AAP

Prior allowed treatments in mCSPC:

- ADT ≤6 months
- Docetaxel ≤6 cycles[c]
- AAP ≤45 days
- Palliative RT

Randomized 1:1 (N=696)

Nira (200 mg QD) + **AAP** (1000 mg QD + 5 mg QD) + **ADT** (n=348)

PBO + **AAP** (1000 mg QD + 5 mg QD) + **ADT** (n=348)

Primary end point

- rPFS by investigator review

Key secondary end points

- Time to symptomatic progression
- OS
- Safety

Stratification factors:

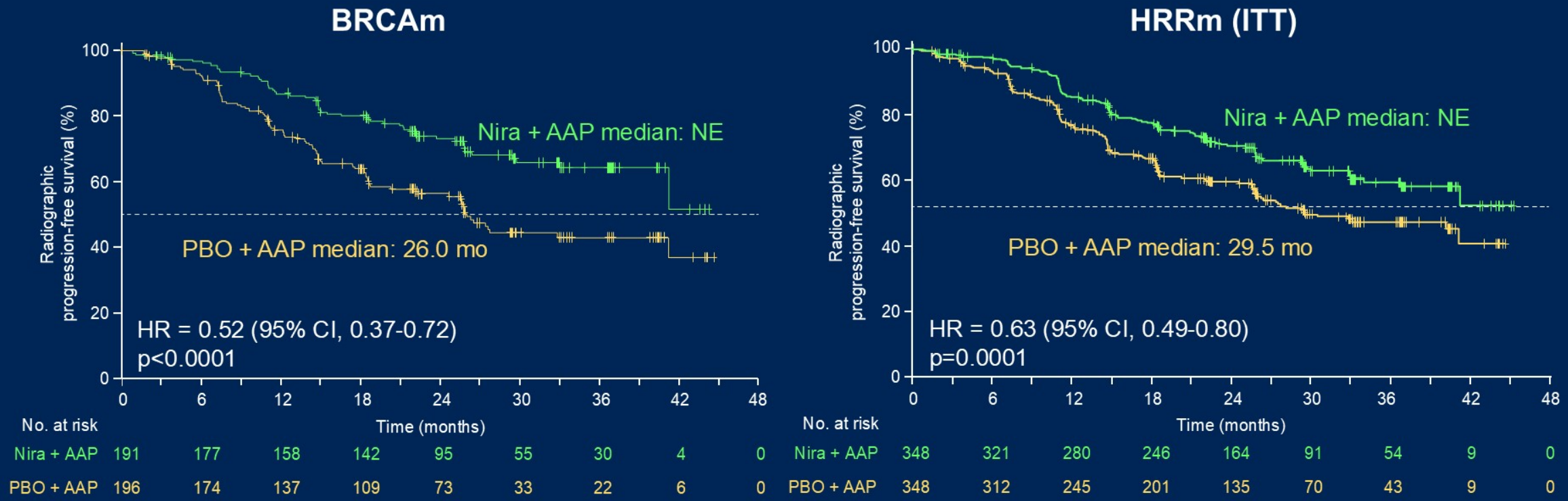
- *BRCA2* vs *CDK12* vs all other alterations
- Prior docetaxel (yes vs no)
- Disease volume (high vs low)

Clinical data cutoff: January 7, 2025

[a]Patients with lymph node–only disease are not eligible. [b]HRR gene panel was fixed prior to trial initiation based on MAGNITUDE trial and external data from the published literature. [c]Last dose ≤3 months prior to randomization.
ECOG PS, Eastern Cooperative Oncology Group performance status; Nira, niraparib; OS, overall survival; PBO, placebo; RT, radiotherapy; QD, once daily.

PRESENTED BY: Prof. Gerhardt Attard, MD, FRCP, PhD

Primary End Point: Radiographic Progression-Free Survival



AMPLITUDE met the primary end point: Nira + AAP significantly reduced the risk of radiographic progression[a] or death by 48% in BRCAm group and by 37% in HRRm population

[a]rPFS by investigator review; rPFS improvement by blinded independent central review was as large: HR = 0.51 (95% CI, 0.37-0.72) for BRCAm group and 0.61 (95% CI, 0.47-0.79) for HRRm group.
NE, not estimable.

Future…. More Ph. 3 Triplet Trials

- PSMAddition – ADT + **ARPI** +- 177Lu-PSMA-617 

- TALAPRO-3 – (HRR+) ADT + **enzalutamide** ± talazoparib

- CAPItello-281 – (PTENdef) ADT + **Abiraterone** ± capivasertib

Pedro C. Barata, MD MSc FACP
@PBarataMD

CCTG-PR26: Phase 3 TRIPLE-SWITCH

KEY ELIGIBILITY
- mCSPC (any volume/risk)
- Androgen Deprivation 6-12 months
- AR Pathway Inhibitor* >/= 4 months
  (any of Abiraterone acetate, Enzalutamide, Apalutamide, or Darolutamide)
- PSA ≥ 0.2 at enrolment
- Docetaxel naïve / eligible
- No evidence of progression by PSA, radiographic, or clinical since ADT

mCSPC
ADT 6-12 mo
ARPI* ≥ 4 mo
PSA ≥ 0.2

ctDNA at registration

RANDOMIZE

1:1

Arm A: Docetaxel
75mg/m² IV q3wk x6
+ ADT + ARPI

Arm B: Standard
ADT + ARPI

ctDNA C2, post C6, PD

PRIMARY ENDPOINT:
- Overall Survival

SECONDARY ENDPOINTS:
- Time to CRPC, PSA 50/90/<0.2/<0.02
- ctDNA

STRATIFICATION:
- PSA 0.2-4 vs >4
- ARPI class
- Liver metastases
- De novo vs Recurrent

SAMPLE SIZE:
- n=830, target HR 0.75

Study Chairs: Michael Ong (CCTG) and Alexandra Sokolova (SWOG)

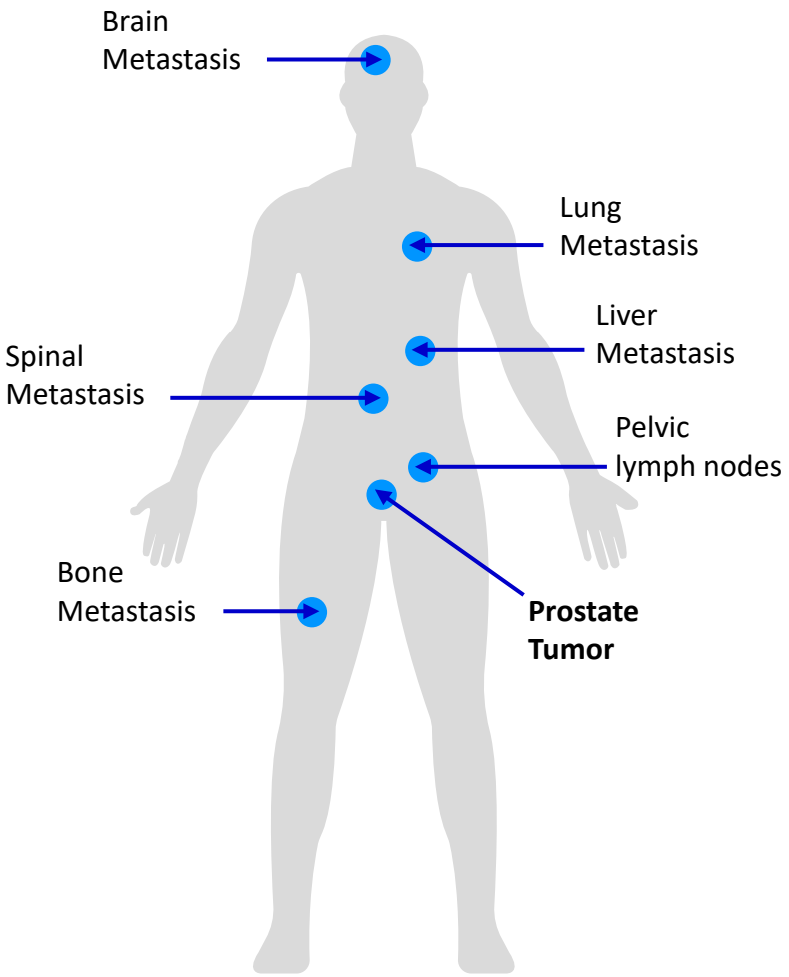
CIHR IRSC

Canadian Cancer Trials Group | Groupe canadien des essais sur le cancer

SWOG CANCER RESEARCH NETWORK

Pedro C. Barata, MD MSc FACP
@PBarataMD

mCRPC is an Aggressive and Fatal Disease



Potential metastatic sites	Common (≥80%): Pelvic lymph nodes and bone Uncommon (≤11%): Distant lymph nodes, liver, lungs, brain and dura[1]
Disease symptoms	Urinary incontinence, decreased libido, bone pain, fatigue, weight loss, and weakness[1]
Quality of life	Depression, anxiety, decreased physical and emotional functioning[2,3]
Probability of being alive 5 years after diagnosis	<40%[4]
Treatment priorities	Delay disease progression, delay decline in QoL, prolong survival[5]

QoL=quality of life.

1. Rebello RJ, et al. *Nat Rev Dis Primers*. 2021;7(1):9; 2. Rönningås U, et al. *BMC Palliat Care*. 2024;23(1):80; 3. Fallowfield L, et al. *Nat Rev Clin Oncol.* 2016;13:643-650; 4. American Cancer Society. Cancer Facts & Figures 2025;
5. George DJ, et al. *Cancer Med.* 2023;(5):6040-6055.

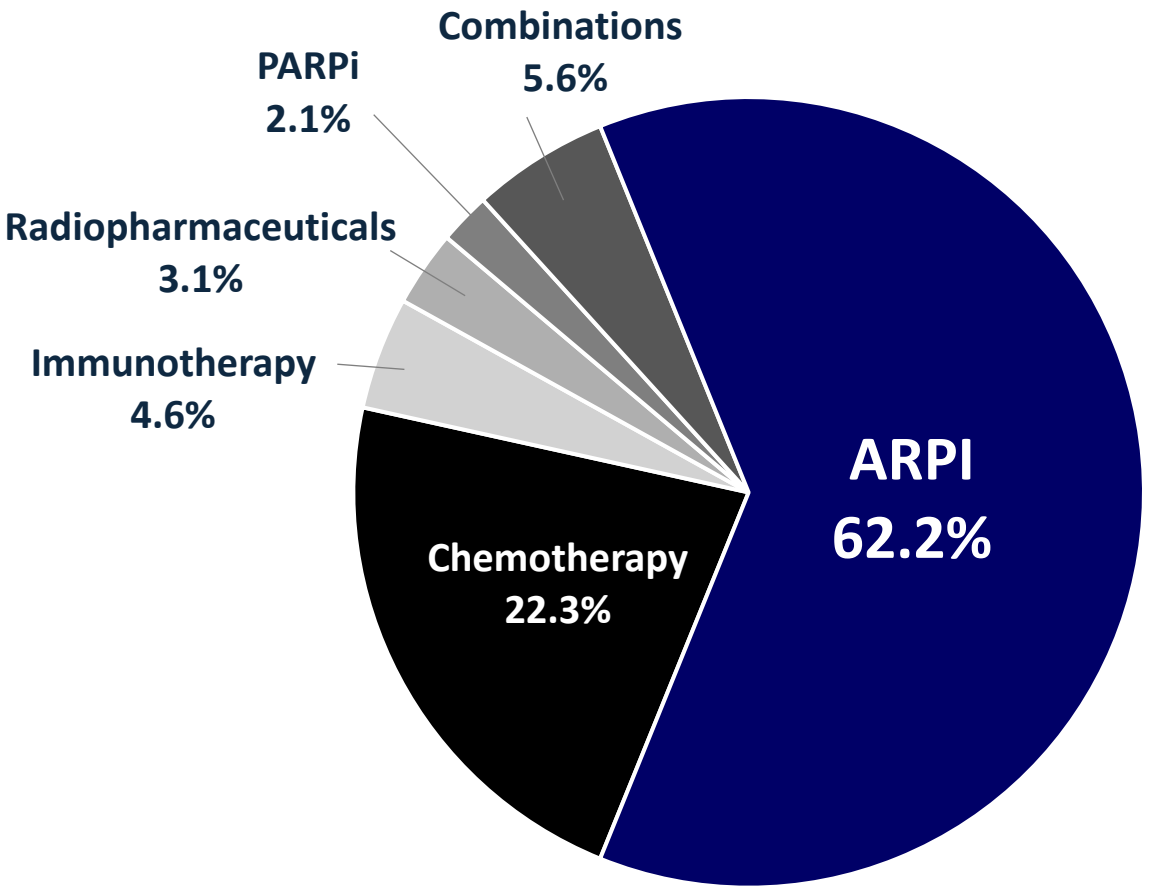
FDA-Approved Therapies for mCRPC

Approved Therapies for mCRPC in the United States[a]

	2004	2007	2010	2013	2016	2019	2022	2023
1L	**Docetaxel**[1] TAX327: 18.9 mo[b] KEYNOTE-921:17.5 mo		**Sipuleucel-T**[1] IMPACT: 25.8 mo[b] **Abiraterone acetate**[1] COU-AA-301: 34.7 mo[b]	**Radium-223**[1] ALSYMPCA: 14.9 mo[b] **Enzalutamide**[1] AFFIRM: 35.5 mo[b]			**Olaparib + abiraterone**[2] PROpel rPFS: not reached[c] **Talazoparib + Enzalutamide**[2] TALAPRO-2 rPFS: not reached[c] **Niraparib + abiraterone**[3] MAGNITUDE rPFS: 16.6 mo[c]	
2L			**Cabazitaxel**[1] TROPIC: 15.1 mo[b] **Abiraterone acetate**[1] COU-AA-301: 14.8 mo[b]	**Radium-223**[1] ALSYMPCA: 14.9 mo[b] **Enzalutamide**[1] AFFIRM: 18.4 mo[b]		**Olaparib**[1] PROfound: 17.3 mo[b]		**^{177}Lu-PSMA-617** PSMAfore: 19.25 mo
3L and beyond							**^{177}Lu-PSMA-617**[1] VISION: 15.3 mo[b]	

[a]Including trial leading to initial approval; [b]median overall survival (OS), unless otherwise noted; [c]study primary endpoint.
1L, first line; 2L, second line; 3L, third line; FDA, US Food and Drug Administration; mCRPC, metastatic CRPC; rPFS, radiographic progression-free survival.
1. Barata, PC. American Society of Clinical Oncology 2023. Presentation; 2. Olaparib [PI]. Approved 2014. Revised May 2023; 3. Talazoparib [PI]. Approved 2018. Revised June 2023; 4. Niraparib and abiraterone [PI]. Approved 2023. Revised August 2023.

Common First-Line Therapies for mCRPC



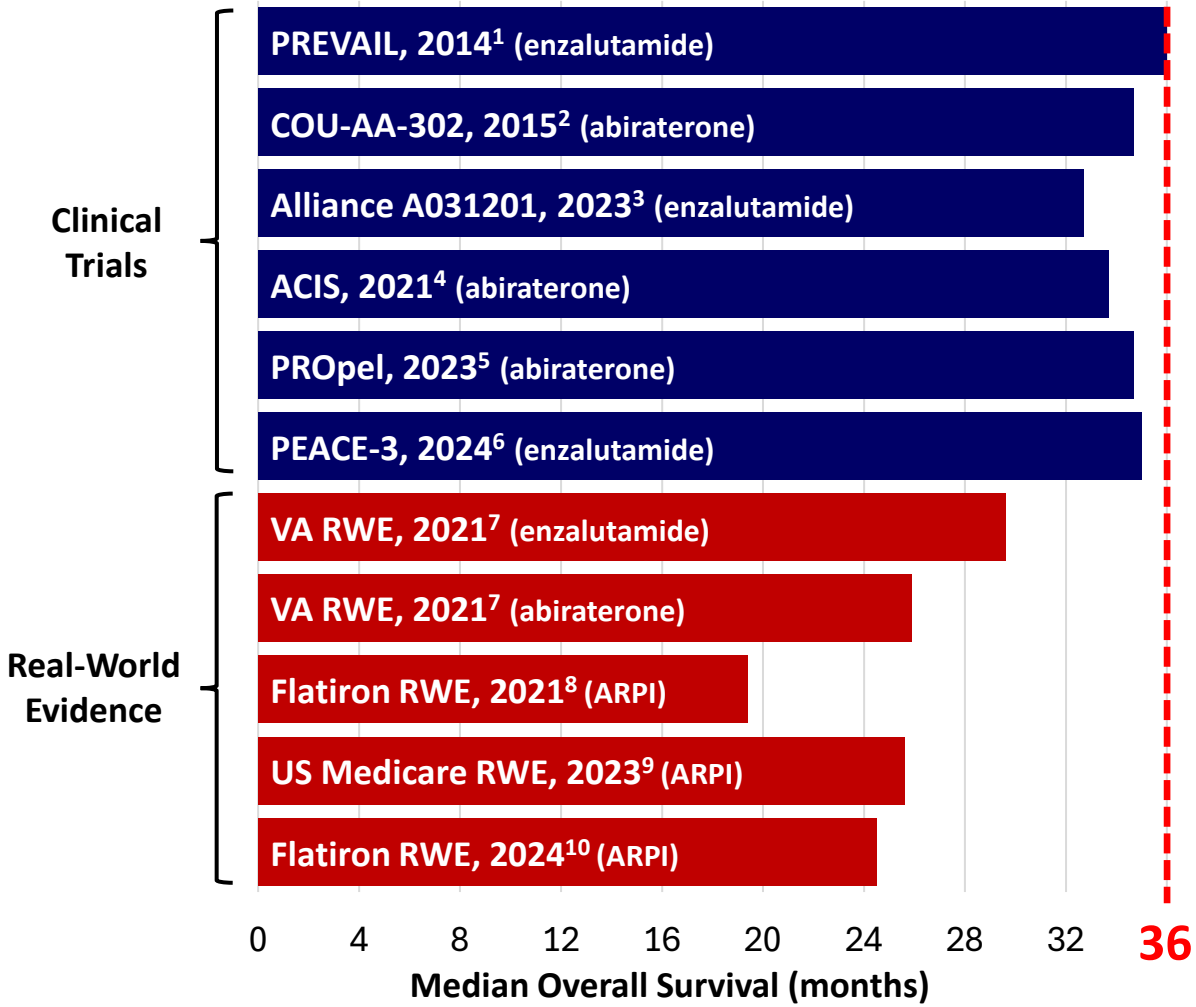
- Genetic testing identifies important biomarkers in subpopulations of patients with predictive and prognostic value (eg, HRRm[1,2]; TP53/Rb1/PTEN[3]; MSI/dMMR[4,5])
- Most mCRPC patients do not have a known predictive biomarker and are commonly treated with ARPIs[6]

ARPI=androgen receptor pathway inhibitor.

1. Azad AA, et al. *Eur J Cancer*. 2024;213:115078; 2. Hussain M, et al. *N Engl J Med*. 2020;383(24):2345-2357; 3. Corn PG, et al. *Lancet Oncol*. 2019;20(10):1432-1443; 4. Abida W, et al. *JAMA Oncol*. 2019;5(4):471-478; 5. Barata P, et al. *J Immunotherapy Cancer*. 2020;8(2):e001065; 6. Data from Raval AD, et al. *J Clin Oncol.* 2025;43(5),99-99.

Pedro C. Barata, MD MSc FACP
@PBarataMD

Survival Outcomes of Patients with mCRPC Receiving ARPIs



- Clinical trials over the past decade consistently show median OS **<36 months**[1-6]
- Real-world median OS is **lower**[7-10]

1. Armstrong AJ, et al. *Eur Urol*. 2020;78(3):347-357; 2. Ryan CJ, et al. *Lancet Oncol*. 2015;16(2):152-160; 3. Morris MJ, et al. *J Clin Oncol*. 2023;41(18):3352-3362; 4. Saad F, et al. *J Clin Oncol*. 2021;39(15 suppl). Abst 5037; 5. Saad F, et al. *Lancet Oncol*. 2023;24(10):1094-1108; 6. Gillessen S, et al. ESMO Congress 2024. Abstract LBA1. Presented September 13, 2024; 7. Tagawa ST, et al. *Prostate Cancer Prostatic Dis*. 2021;24(4):1032-1040; 8. Shore ND, et al. *Adv Ther.* 2021;38(8):4520-4540; 9. Freedland SJ, et al. *Prostate Cancer Prostatic Dis*. 2024;27(2):327-333; 10. Swami U, et al. *J Urol*. 2024;211(5S):e1115.

Pedro C. Barata, MD MSc FACP
@PBarataMD

Combination Therapy Is Changing the mCRPC Treatment Paradigm in 1L mCRPC

	Study	Arms	Prior Treatment	**mOS** (months)	**mPFS** (months)
Radiopharmaceutical + ARI	PEACE-III (2024)[1]	Ra-223 + enza vs enza	• Abi (for mHSPC): <5% • Docetaxel (for mHSPC): 30%	**42.3** vs 35.0 HR 0.69, *P*=0.0031	**19.4** vs 16.4 (rPFS) HR 0.69, *P*=0.0009
PARPi + ARPI	PROpel (2023)[2]	Olaparib + abi/pred vs placebo + abi/pred	• NHA (prior abi excluded): 0.1% • Docetaxel (before mCRPC): 24%	**42.1** vs 34.7 HR 0.81, *P*=0.054	**24.8** vs 16.6 (rPFS) HR 0.66, *P*<0.001
	TALAPRO-2 (2023)[34]	Talazoparib + enza vs placebo + enza	• Abi/orteronel (for HSPC): 6% abi, <1% orteronel • Docetaxel (for HSPC): 22%	**45.8** vs 37.0 HR 0.796 *P*=0.0155	**33.1** vs 19.5 (rPFS) HR 0.667, *P*<0.0001

1L, firstline; Abi, abiraterone; ARI, androgen receptor inhibitor; ARPI, androgen receptor pathway inhibitor; enza, enzalutamide; HR, hazard ratio; mCRPC, metastatic castration-resistant prostate cancer; mHSPC, metastatic hormone-sensitive prostate cancer; mOS, median overall survival; mPFS, median progression-free survival; NHA, next-generation hormonal agent; PARPi, polyADP-ribose polymerase inhibitor; Ra-223, radium-223; rPFS, radiographic progression free survival.

1. Gillessen S, et al. Presented at: European Society for Medical Oncology Congress; September 13-17, 2024; Barcelona, Spain. Abstract LBA1. 2. Saad F, et al. *Lancet Oncol*. 2023;24(10):1094-1108. 3. Agarwal N, et al. Presented at ASCO Genitourinary Cancers SympoBsium; February 13–15, 2025; San Francisco, CA, USA. Presentation LBA18. 4. Agarwal N, et al. Lancet. 2023;402(10398):291-303.

Pedro C. Barata, MD MSc FACP
@PBarataMD

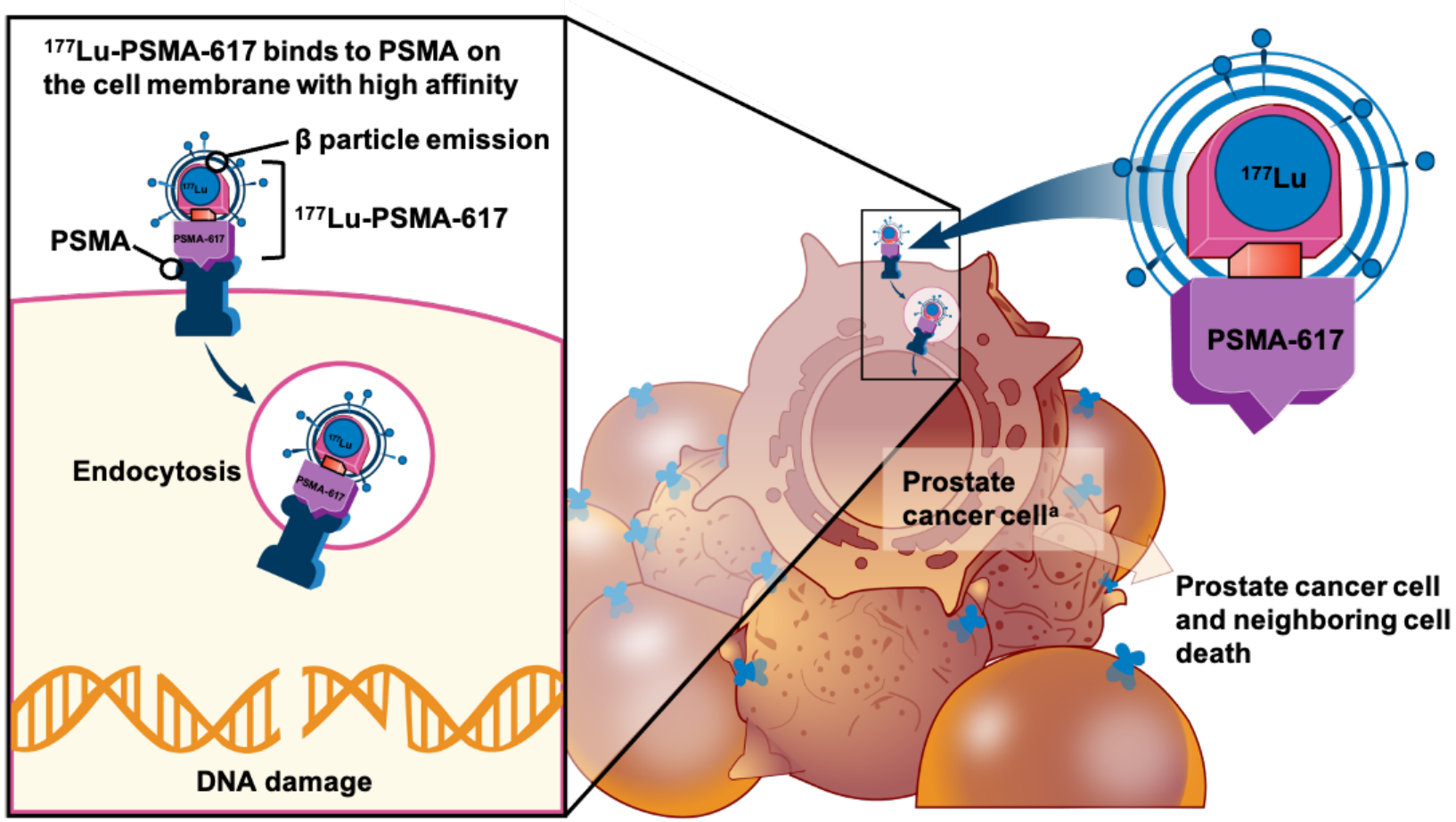
Radiopharmaceuticals Have Different Mechanisms of Action

	Radium-223 Alpha	^{177}Lu-PSMA-617 Beta
Radiation energy	**High LET**: fewer hits are required for cell killing[1-3]	**Lower LET**: less energy to the tumor results in lower potency[1-3]
Range of penetration	**Short penetration range**: limits exposure to nearby healthy tissue[1-3]	**Long penetration range**: potential exposure to nearby healthy tissue[1,2]
Type of DNA damage	**Complex clustered DNA double-strand breaks** are difficult to repair, leading to cell-cycle arrest and cell death[2-5]	**Single-strand DNA breaks** more likely, which are repaired by DNA ligase[3-5]

LET, linear energy transfer.

1. Marcu L, et al. Crit Rev Oncol Hematol. 2018;123:7-20; 2. Brechbiel MW. Dalton Trans. 2007;21:4918-4928; 3. Shore ND, et al. J Urology. 2015;193(4 Suppl.):e1088-e1089; 4. Kratochwil C, et al. Eur J Nucl Med Mol Imaging. 2014;41:2106-2119; 5. Lomax ME, et al. Clin Oncol (R Coll Radiol). 2013;25:578-585.

^{177}Lu-PSMA-617 Radioligand Therapy[1,2]



VISION Eligibility Criteria

- mCRPC
  - Prior treatments:
    - ≥1 NAAD
    - 1 or 2 taxane
  - PS of 0-2
  - PSMA PET/CT+

N = 831 **2:1** **R**

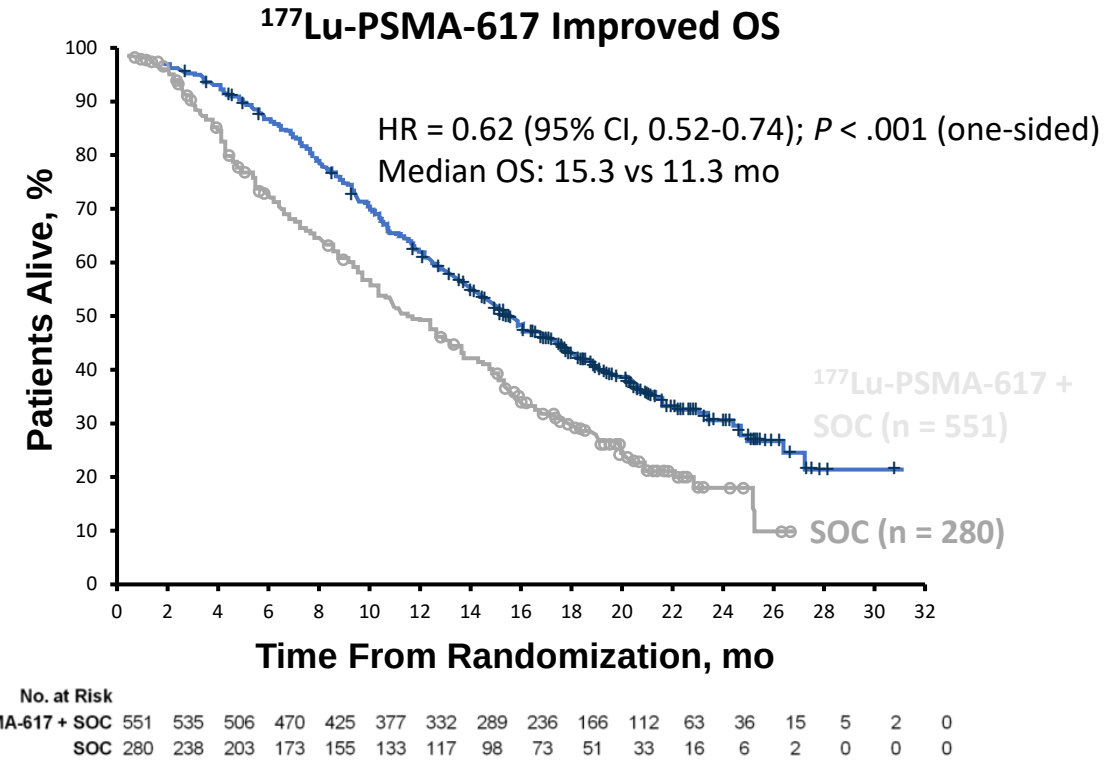
Best SOC ^{177}Lu-PSMA-617 (7.4 GBq Q6W x 4-6 cycles)	Best SOC

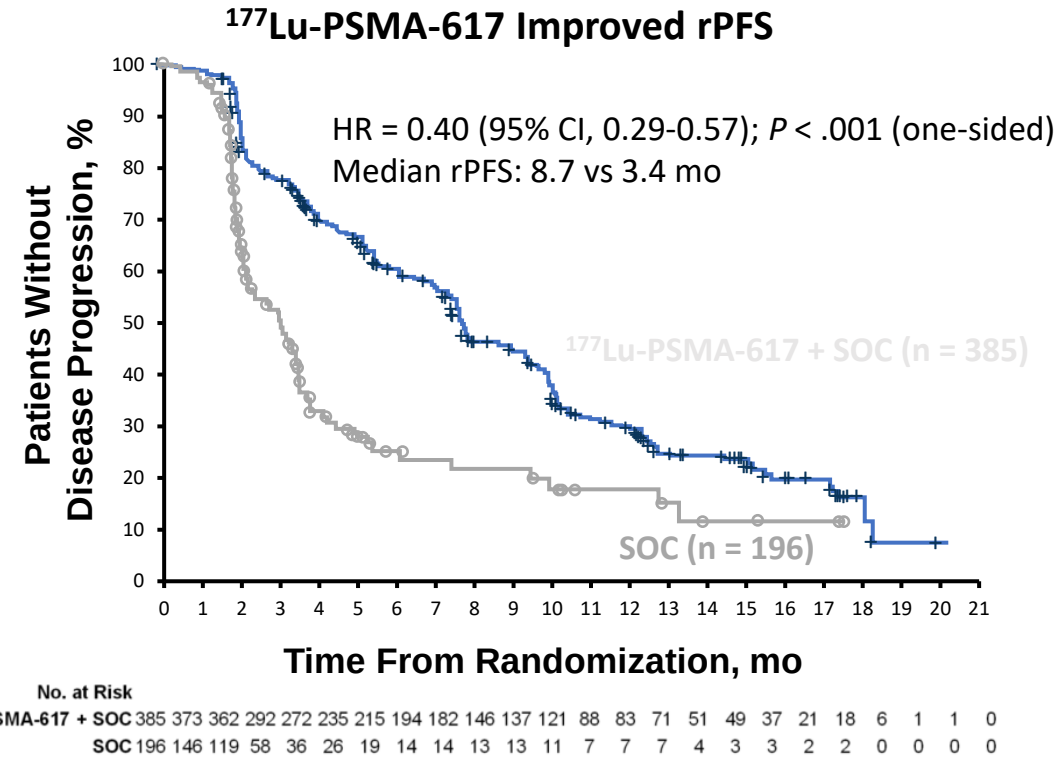
- **Primary endpoint:** rPFS, OS

[a] Reduced binding in the kidneys, spleen, liver, salivary glands, lacrimal glands, submandibular glands, and bone marrow is expected.

1. Morris MJ et al. ASCO 2021. Abstract LBA4. 2. https://clinicaltrials.gov/study/NCT03511664.

Phase 3 VISION: ^{177}Lu-PSMA-617 Plus Best SOC in mCRPC[1-4]



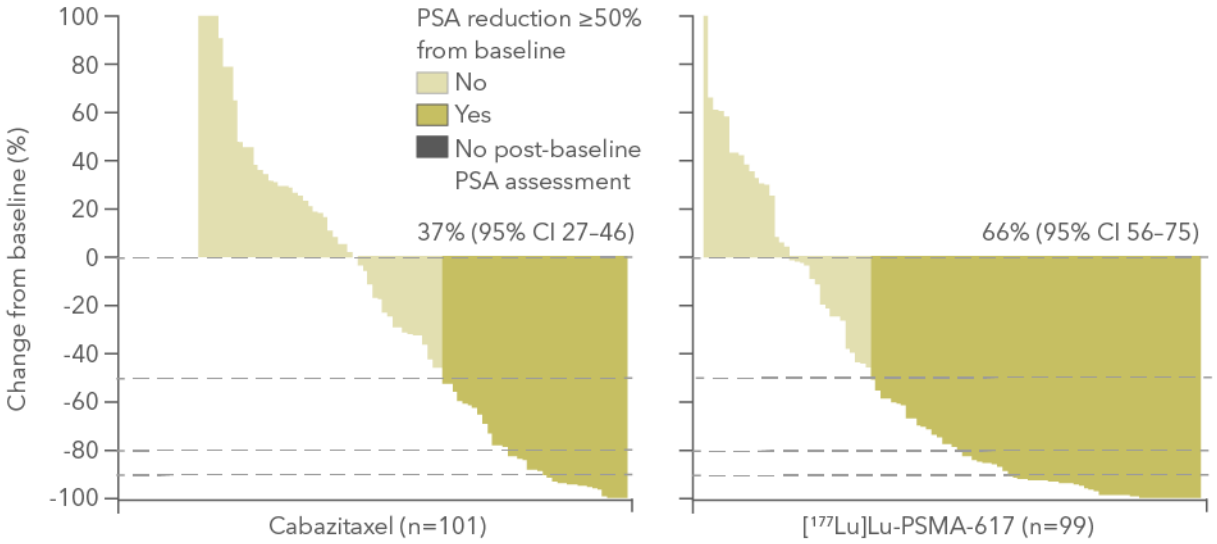


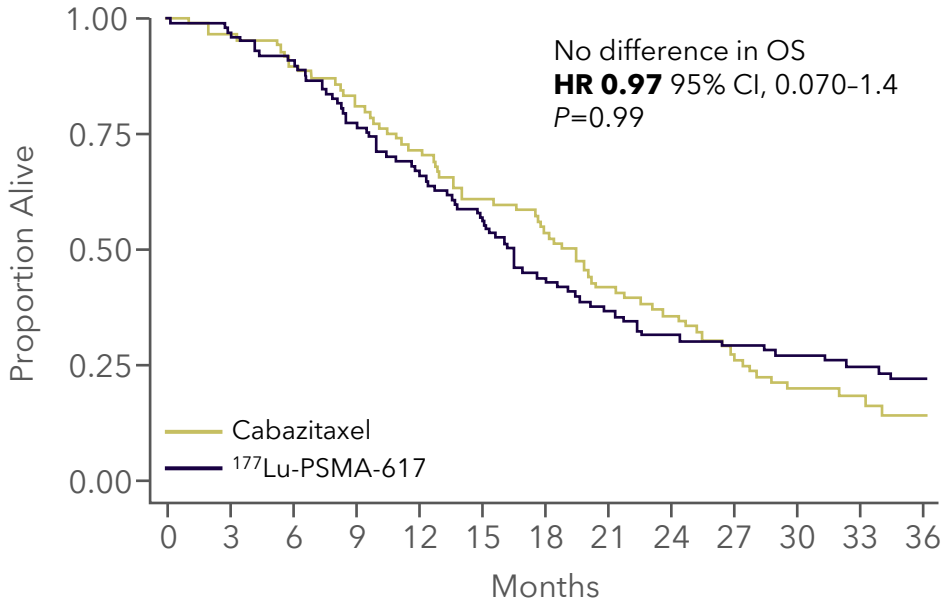
- Both primary endpoints met: improved OS and rPFS in patients receiving ^{177}Lu-PSMA-617 + best SOC compared with those receiving best SOC alone
- Higher incidence of TEAEs with ^{177}Lu-PSMA-617 + SOC vs SOC, but treatment exposure was ≥3 times longer in the ^{177}Lu-PSMA-617 + SOC arm; exposure-adjusted safety analyses showed comparable findings for both arms
- FDA approved on March 23, 2022

1. Sartor O et al. *N Engl J Med.* 2021;385:1091-1103. 2. Chi KN et al. ASCO GU 2022. Abstract 85. 3. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-pluvicto-metastatic-castration-resistant-prostate-cancer. 4. Kuo P et al. ASCO 2022. Abstract 5002.

TheraP: Despite Differences in PSA Response Rates, No Clinically Meaningful OS Benefit of ^{177}Lu-PSMA-617 Over Cabazitaxel Was Observed

PSA response was significantly greater with ^{177}Lu-PSMA-617 than with cabazitaxel





No. at Risk													
Cabazitaxel	101	82	75	68	60	51	45	35	30	22	17	9	6
Lu-PSMA	307	211	117	56	63	54	41	35	30	28	23	20	11

CI, confidence interval; HR, hazard ratio; OS, overall survival; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen.

Hofman MS, et al. Presented at: American Society of Clinical Oncology Annual Meeting; June 3-7, 2022; Chicago, IL, USA. Abstract 5000.

In RaLu, 177Lu-PSMA Was Efficacious and Well Tolerated in Patients Who Had Previously Received Ra-223[1,2]

mCRPC diagnosis

Median time from diagnosis to first dose of ^{177}Lu-PSMA: 37.8 mo

Baseline

Median duration of ^{177}Lu-PSMA: 3.5 mo

38% received ≥4 injections of ^{177}Lu-PSMA

Pre-baseline period | **^{177}Lu-PSMA treatment** | **Follow-up period**

Life-prolonging therapies:

75% received taxanes

60% received both abiraterone and enzalutamide

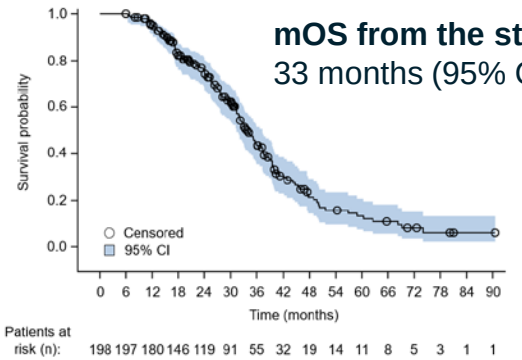
58% received ≥4 life-prolonging therapies

69% received ≥5 injections of radium-223

25%
grade 3–4 TEAEs

Grade 3–4 laboratory abnormalities:
- 32% anaemia
- 17% thrombocytopenia
- 4% neutropenia

mOS from the start of ^{177}Lu-PSMA
12 months (95% CI 11–15)

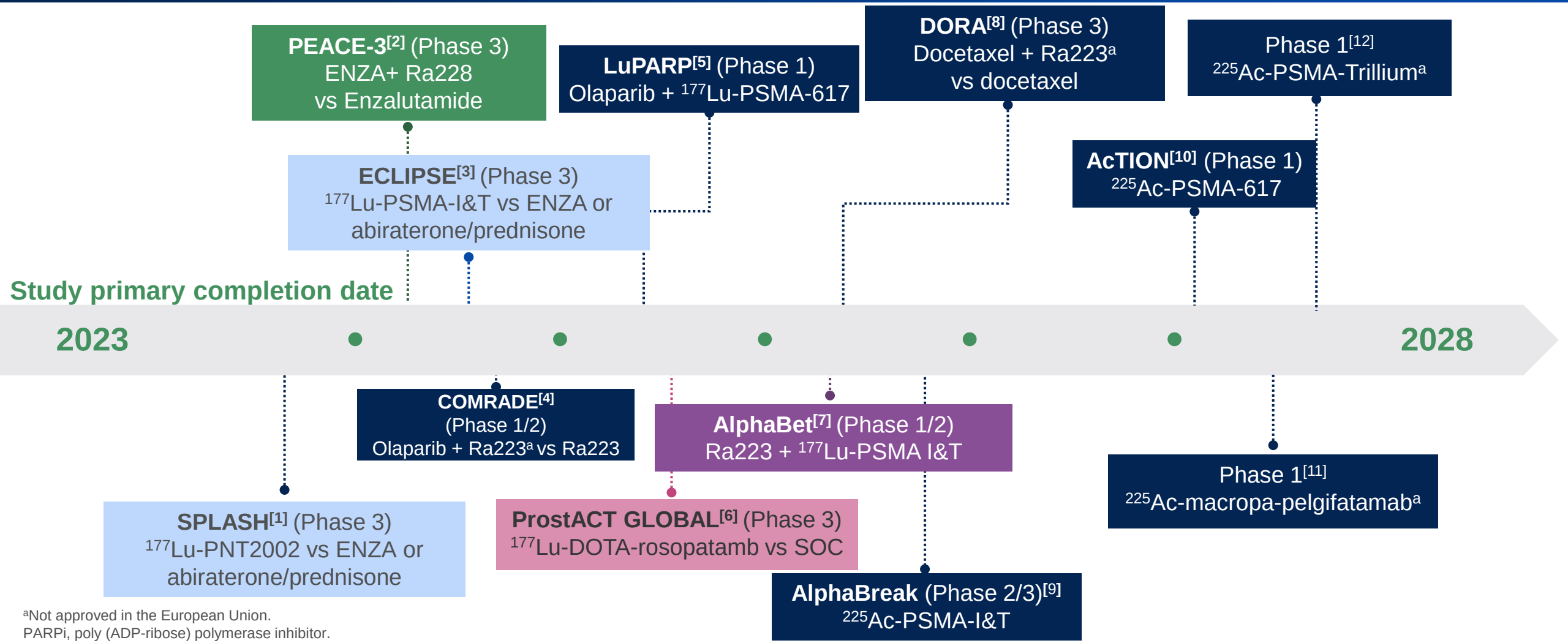


mOS from the start of ^{233}Ra
33 months (95% CI 31–37)

CI, confidence interval; mCRPC, metastatic castration-resistant prostate cancer; mOS, median overall survival; PSMA, prostate-specific membrane antigen; TEAE, treatment-emergent adverse event.

1. Rahbar K, et al. *J Nucl Med*. 2023;64(12):1925–1931. 2. Rahbar K, et al. Presented at: European Society for Medical Oncology Congress; September 13–17, 2024; Barcelona, Spain. Abstract 1629P.

Novel Combinations and New Radiopharmaceuticals Under Investigation in mCRPC



[a]Not approved in the European Union.
PARPi, poly (ADP-ribose) polymerase inhibitor.

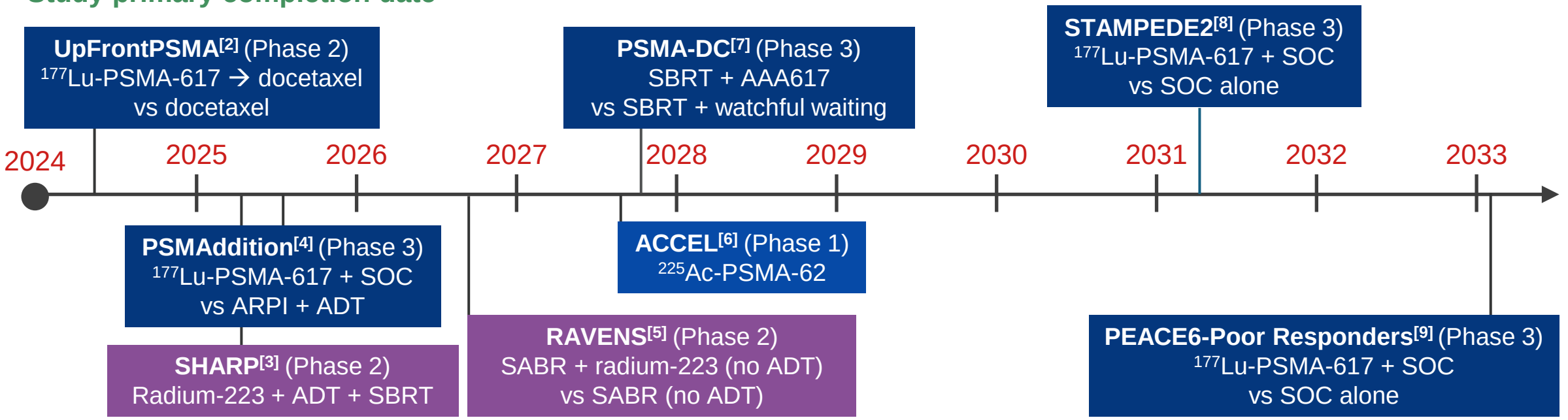
1. ClinicalTrials.gov. NCT04647526. Accessed February 11, 2025; 2. ClinicalTrials.gov. NCT02194842. Accessed February 11, 2025; 3. ClinicalTrials.gov. NCT05204927. Accessed February 11, 2025; 4. ClinicalTrials.gov. NCT03317392. Accessed February 11, 2025; 5. ClinicalTrials.gov. NCT03874884. Accessed February 11, 2025; 6. ClinicalTrials.gov. NCT04876651. Accessed February 11, 2025. 7. ClinicalTrials.gov. NCT05383079. Accessed February 11, 2025; 8. ClinicalTrials.gov. NCT03574571. Accessed February 11, 2025; 9. ClinicalTrials.gov. NCT06402331. Accessed February 11, 2025; 10. ClinicalTrials.gov. NCT04597411. Accessed February 11, 2025; 11. ClinicalTrials.gov. NCT06052306. Accessed February 11, 2025; 12. ClinicalTrials.gov. NCT06217822. Accessed February 11, 2025.

Investigative Radiopharmaceuticals in mHSPC

Completed study

RROPE [1] (Phase 2)
Radium-223

Study primary completion date



Completion date not reported

DUET [10] (Phase 1/2)
Radium-223 + ^{177}Lu-PSMA-617

SABR, stereotactic ablative body radiotherapy; SBRT, stereotactic body radiation therapy.

1. ClinicalTrials.gov. NCT03304418. Accessed February 11, 2025; 2. ClinicalTrials.gov. NCT04343885. Accessed February 11, 2025; 3. ClinicalTrials.gov. NCT03361735. Accessed February 11, 2025; 4. ClinicalTrials.gov. NCT04720157. Accessed February 11, 2025; 5. Clinicaltrials.gov. NCT04037358. Accessed February 11, 2025; 6. ClinicalTrials.gov. NCT06229366. Accessed February 11, 2025; 7. Clinicaltrials.gov. NCT05939414. Accessed February 11, 2025; 8. ClinicalTrials.gov. NCT06320067. Accessed February 11, 2025; 9. Clinicaltrials.gov. NCT06496581. Accessed February 11, 2025; 10. Vis A, et al. J Clin Oncol. 2023;41(suppl 16): Abstract TPS5113.

Cell-Surface Targets and MOAs in m(CR)PC

Target	Therapeutic Strategy	MOA
PSMA	RLT, ADC, CAR-T, bispecifics	Radiation-induced DNA damage, cytotoxicity, immune-mediated killing
B7-H3	ADCs, radiolabeled Abs, immunotherapy	Cytotoxicity via payload, immune activation/blockade
HK2	ADCs, metabolic inhibitors (early stage)	Inhibit glycolysis, deliver toxins or radiation
STEAP1	ADCs, bispecifics, radiolabeled Abs	Cytotoxicity, T-cell recruitment, radiation

Thank you!

Pedro.barata@UHhospitals.org

+1 216-262-1214