Data + Perspectives: Clinical Investigators Discuss the Current and Future Clinical Care of Patients with Prostate Cancer

Saturday, May 31, 2025
7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)

Faculty

Neeraj Agarwal, MD, FASCO
Andrew J Armstrong, MD, ScM
Himisha Beltran, MD
Fred Saad, MD

Moderator

Rana R McKay, MD

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Faculty

Neeraj Agarwal, MD, FASCO
Professor of Medicine
Senior Director for Clinical Research
Huntsman Cancer Institute Presidential Endowed Chair of Cancer Research
Director, Center of Investigational Therapeutics
Director, Genitourinary Oncology Program
Huntsman Cancer Institute, University of Utah (NCI-CCC)
Salt Lake City, Utah

Andrew J Armstrong, MD, ScM
Professor of Medicine, Surgery, Pharmacology and Cancer Biology
Director of Research
Duke Cancer Institute Center for Prostate and Urologic Cancers
Divisions of Medical Oncology and Urology
Duke University
Durham, North Carolina

Himisha Beltran, MD
Associate Professor of Medicine
Lank Center for Genitourinary Oncology and the Division of Molecular and Cellular Oncology
Director of Translational Research
Medical Oncology
Dana-Farber Cancer Institute
Boston, Massachusetts

Fred Saad, MD
Professor and Chairman, Department of Surgery
Raymond Garneau Chair in Prostate Cancer
University of Montreal
Director of GU Oncology
University of Montreal Hospital Center (CHUM)
Montréal, Québec, Canada

Moderator
Rana R McKay, MD
Professor of Medicine and Urology
Associate Director, Clinical Research
Co-Lead, Genitourinary Program
Moores Cancer Center
University of California San Diego
San Diego, California

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Dr Agarwal — Disclosures
Faculty

No relevant conflicts of interest to disclose

Dr Armstrong — Disclosures
Faculty

Advisory Committees	Astellas, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Cytogen Corporation, Janssen Biotech Inc, Merck, Myovant Sciences, Novartis, Pfizer Inc
Consulting Agreements	Astellas, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Curium, Janssen Biotech Inc, Merck, Novartis, Pfizer Inc
Contracted Research	Amgen Inc, Astellas, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Bristol Myers Squibb, Janssen Biotech Inc, Merck, Novartis, Pathos, Pfizer Inc

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Dr Beltran — Disclosures
Faculty

Advisory Committees	Amgen Inc, Astellas, Bayer HealthCare Pharmaceuticals, Daiichi Sankyo Inc, Merck, Novartis, Pfizer Inc
Contracted Research	Bristol Myers Squibb, Circle Pharma, Daiichi Sankyo Inc, Novartis
Data and Safety Monitoring Boards/Committees	AstraZeneca Pharmaceuticals LP

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Dr Saad — Disclosures
Faculty

Advisory Committees and Consulting Agreements	AbbVie Inc, Astellas, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, GSK, Janssen Biotech Inc, Merck, Novartis, Pfizer Inc, Tolmar
Contracted Research	AbbVie Inc, Astellas, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, GSK, Janssen Biotech Inc, Merck, Novartis, Pfizer Inc
Speakers Bureaus	AbbVie Inc, Astellas, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Janssen Biotech Inc, Merck, Novartis, Pfizer Inc, Tolmar

Dr McKay — Disclosures
Moderator

Advisor/Consultant	Ambrx, Arcus Biosciences, AstraZeneca Pharmaceuticals LP, Aveo Pharmaceuticals, Bayer HealthCare Pharmaceuticals, Blue Earth Diagnostics, Bristol Myers Squibb, Calithera Biosciences, Caris Life Sciences, Daiichi Sankyo Inc, Dendreon Pharmaceuticals Inc, Exelixis Inc, Johnson & Johnson Pharmaceuticals, Lilly, Merck, Myovant Sciences, Neomorph, Novartis, Pfizer Inc, Sanofi, Seagen Inc, Sorrento Therapeutics, Telix Pharmaceuticals Limited, Tempus
Institutional Research Funding	Artera, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Bristol Myers Squibb, Exelixis Inc, Oncternal Therapeutics, Tempus

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Dr Love — Disclosures

Dr Love is president and CEO of Research To Practice. Research To Practice receives funds in the form of educational grants to develop CME activities from the following companies: Aadi Bioscience, AbbVie Inc, ADC Therapeutics, Alexion Pharmaceuticals, Amgen Inc, Array BioPharma Inc, a subsidiary of Pfizer Inc, Arvinas, Astellas, AstraZeneca Pharmaceuticals LP, Aveo Pharmaceuticals, Bayer HealthCare Pharmaceuticals, BeiGene Ltd, Black Diamond Therapeutics Inc, Blueprint Medicines, Boehringer Ingelheim Pharmaceuticals Inc, Bristol Myers Squibb, Clovis Oncology, Coherus BioSciences, CTI BioPharma, a Sobi Company, Daiichi Sankyo Inc, Eisai Inc, Elevation Oncology Inc, Exact Sciences Corporation, Exelixis Inc, Genentech, a member of the Roche Group, Genmab US Inc, Geron Corporation, Gilead Sciences Inc, GSK, Hologic Inc, ImmunoGen Inc, Incyte Corporation, Ipsen Biopharmaceuticals Inc, Jazz Pharmaceuticals Inc, Johnson & Johnson, Karyopharm Therapeutics, Kite, A Gilead Company, Kura Oncology, Legend Biotech, Lilly, MEI Pharma Inc, Merck, Mersana Therapeutics Inc, Mirati Therapeutics Inc, Mural Oncology Inc, Natera Inc, Novartis, Novartis Pharmaceuticals Corporation on behalf of Advanced Accelerator Applications, Novocure Inc, Nuvalent, Pfizer Inc, Pharmacyclics LLC, an AbbVie Company, Puma Biotechnology Inc, Regeneron Pharmaceuticals Inc, Rigel Pharmaceuticals Inc, R-Pharm US, Sanofi, Seagen Inc, Servier Pharmaceuticals LLC, SpringWorks Therapeutics Inc, Stemline Therapeutics Inc, Syndax Pharmaceuticals, Taiho Oncology Inc, Takeda Pharmaceuticals USA Inc, TerSera Therapeutics LLC, and Tesaro, A GSK Company.

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Friday May 30	**Immunotherapy and Antibody–Drug Conjugates in Lung Cancer** 11:15 AM – 12:45 PM CT (12:15 PM – 1:45 PM ET)
	Colorectal Cancer 6:30 PM – 8:30 PM CT (7:30 PM – 9:30 PM ET)
	EGFR Mutation–Positive Non–Small Cell Lung Cancer 6:30 PM – 8:30 PM CT (7:30 PM – 9:30 PM ET)
Saturday May 31	**Urothelial Bladder Cancer** 6:45 AM – 7:45 AM CT (7:45 AM – 8:45 AM ET)
	Non–Hodgkin Lymphoma 7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)
	Prostate Cancer 7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)
Sunday June 1	**Chronic Lymphocytic Leukemia (Webinar)** 7:00 AM – 8:00 AM CT (8:00 AM – 9:00 AM ET)
	HER2–Positive Gastrointestinal Cancers 7:00 PM – 8:30 PM CT (8:00 PM – 9:30 PM ET)
	Ovarian and Endometrial Cancer 7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)
Monday June 2	**Renal Cell Carcinoma (Webinar)** 7:00 AM – 8:00 AM CT (8:00 AM – 9:00 AM ET)
	Multiple Myeloma (Webinar) 6:00 PM – 7:00 PM CT (7:00 PM – 8:00 PM ET)
	Metastatic Breast Cancer 7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)
Tuesday June 3	**Soft Tissue Sarcoma and Other Connective Tissue Neoplasms (Webinar)** 7:00 AM – 8:00 AM CT (8:00 AM – 9:00 AM ET)

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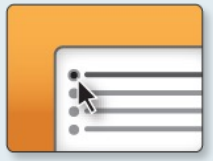
Clinicians in the Meeting Room

Networked iPads are available.

Review Program Slides: Tap the Program Slides button to review speaker presentations and other program content.



Answer Survey Questions: Complete the pre- and postmeeting surveys.

Ask a Question: Tap Ask a Question to submit a challenging case or question for discussion. We will aim to address as many questions as possible during the program.

For assistance, please raise your hand. Devices will be collected at the conclusion of the activity.

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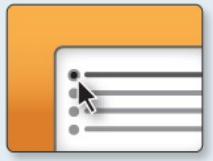
Clinicians Attending via Zoom

Review Program Slides: A link to the program slides will be posted in the chat room at the start of the program.



Answer Survey Questions: Complete the pre- and postmeeting surveys.

Ask a Question: Submit a challenging case or question for discussion using the Zoom chat room.

Get CME Credit: A CME credit link will be provided in the chat room at the conclusion of the program.

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About the Enduring Program

- The live meeting is being video and audio recorded.
- The proceedings from today will be edited and developed into an enduring web-based program. An email will be sent to all attendees when the activity is available.
- To learn more about our education programs, visit our website, **www.ResearchToPractice.com**

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Agenda

MODULE 1: Evolving Management of Nonmetastatic Hormone-Sensitive Prostate Cancer (HSPC) — Dr Saad

MODULE 2: Current Treatment for Metastatic HSPC — Dr Armstrong

MODULE 3: Role of PARP Inhibition in Metastatic Castration-Resistant Prostate Cancer (mCRPC) — Dr Agarwal

MODULE 4: Current and Future Use of Radiopharmaceuticals for mCRPC — Dr McKay

MODULE 5: Promising Novel Agents and Strategies Under Investigation for the Management of Prostate Cancer — Dr Beltran

Agenda

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Optimizing care in high risk nmHSPC

Fred Saad CQ MD FRCS FCAHS
Professor and Chairman, Department of Surgery,
Raymond Garneau Chair in Prostate Cancer
University of Montreal
Director of GU Oncology and Prostate Cancer Research
University of Montreal Hospital Center

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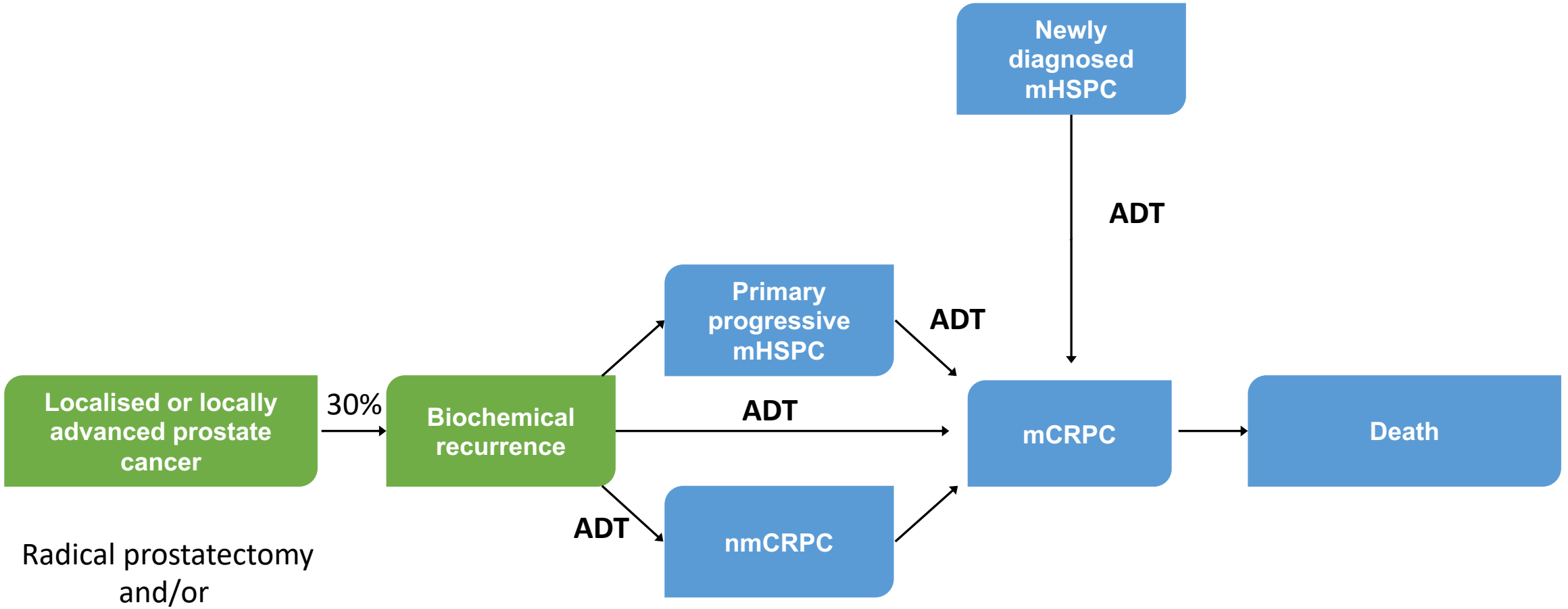
Spectrum of prostate cancer



mHSPC, metastatic hormone-sensitive prostate cancer; mCRPC, metastatic castration-resistant prostate cancer; nmCRPC, non-metastatic castration-resistant prostate cancer

Intensifying ADT in high risk prostate cancer

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Abiraterone acetate and prednisolone with or without enzalutamide for high-risk non-metastatic prostate cancer: a meta-analysis of primary results from two randomised controlled phase 3 trials of the STAMPEDE platform protocol

Gerhardt Attard, Laura Murphy, Noel W Clarke, William Cross, Robert J Jones, Christopher C Parker, Silke Gillessen, Adrian Cook, Chris Brawley, Claire L Amos, Nafisah Atako, Cheryl Pugh, Michelle Buckner, Simon Chowdhury, Zafar Malik, J Martin Russell, Clare Gilson, Hannah Rush, Jo Bowen, Anna Lydon, Ian Pedley, Joe M O'Sullivan, Alison Birtle, Joanna Gale, Narayanan Srihari, Carys Thomas, Jacob Tanguay, John Wagstaff, Prantik Das, Emma Gray, Mymoona Alzoueb, Omi Parikh, Angus Robinson, Isabel Syndikus, James Wylie, Anjali Zarkar, George Thalmann, Johann S de Bono, David P Dearnaley, Malcolm D Mason*, Duncan Gilbert, Ruth E Langley, Robin Millman, David Matheson, Matthew R Sydes†, Louise C Brown†, Mahesh K B Parmar†, Nicholas D James†, on behalf of the Systemic Therapy in Advancing or Metastatic Prostate cancer: Evaluation of Drug Efficacy (STAMPEDE) investigators‡*

Lancet 2022; 399: 447–60
Published Online
December 23, 2021
https://doi.org/10.1016/
S0140-6736(21)02437-5

Patient population

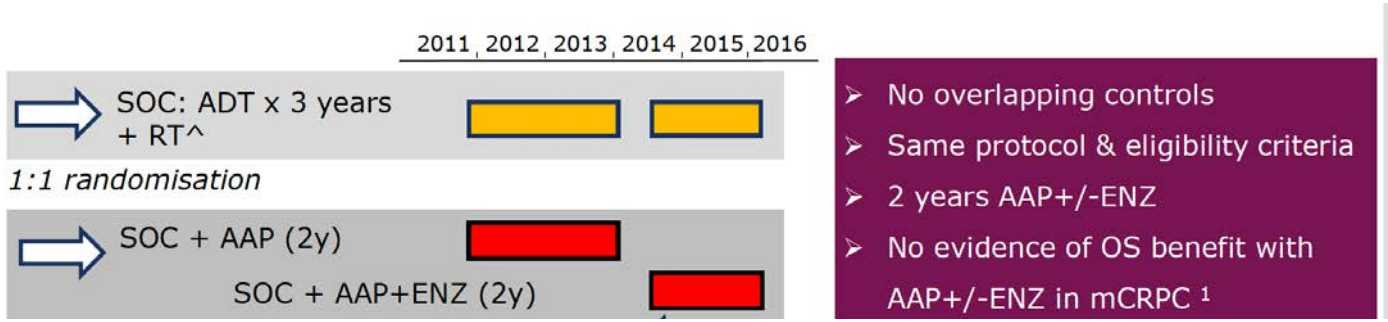
M0
No evidence of metastases on bone and CT scan of pelvis, abdo, chest
(pre-defined stratification criterion)

Newly-diagnosed
Any of:
- Node-Positive
- ≥2 of: Stage T3 or T4
  PSA≥40ng/ml
  Gleason 8, 9 or 10

Relapsing after previous RP or RT
Any of:
- Node-positive
- PSA≥4ng/ml, rising & doubling time <6m
- PSA≥20ng/ml

All patients
Written informed consent
Fit for all protocol treatment
Fit for follow-up

Full criteria: www.stampedetrial.org



- No overlapping controls
- Same protocol & eligibility criteria
- 2 years AAP+/-ENZ
- No evidence of OS benefit with AAP+/-ENZ in mCRPC [1]

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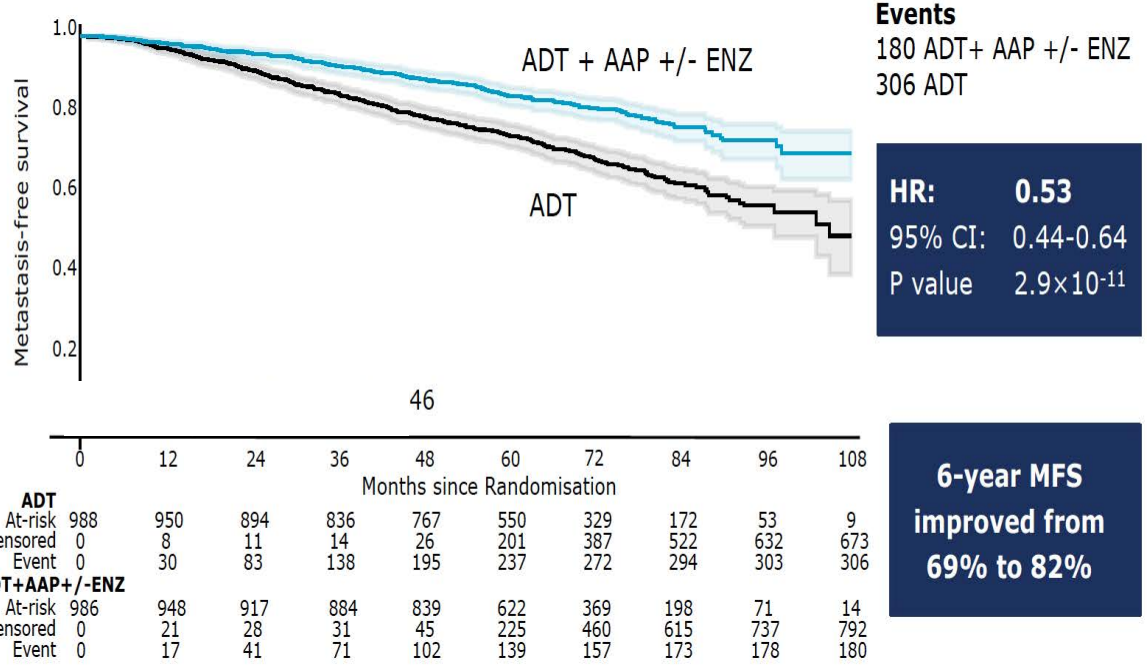
RESULTS

Metastasis-free survival

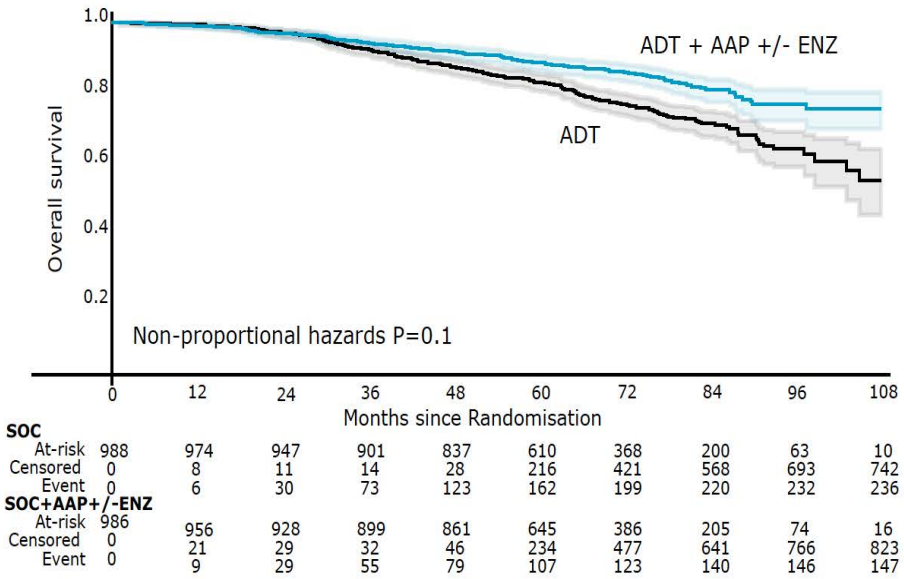


Events
180 ADT+ AAP +/- ENZ
306 ADT

HR:	**0.53**
95% CI:	0.44-0.64
P value	2.9×10^{-11}

6-year MFS improved from 69% to 82%

Overall survival



Events
147 ADT+AAP +/- ENZ
236 ADT

HR:	**0.60**
95% CI	0.48 to 0.73
P value	9.3×10^{-7}

6-year survival improved from 77% to 86%

Gerhardt Attard et al. Lancet 2022

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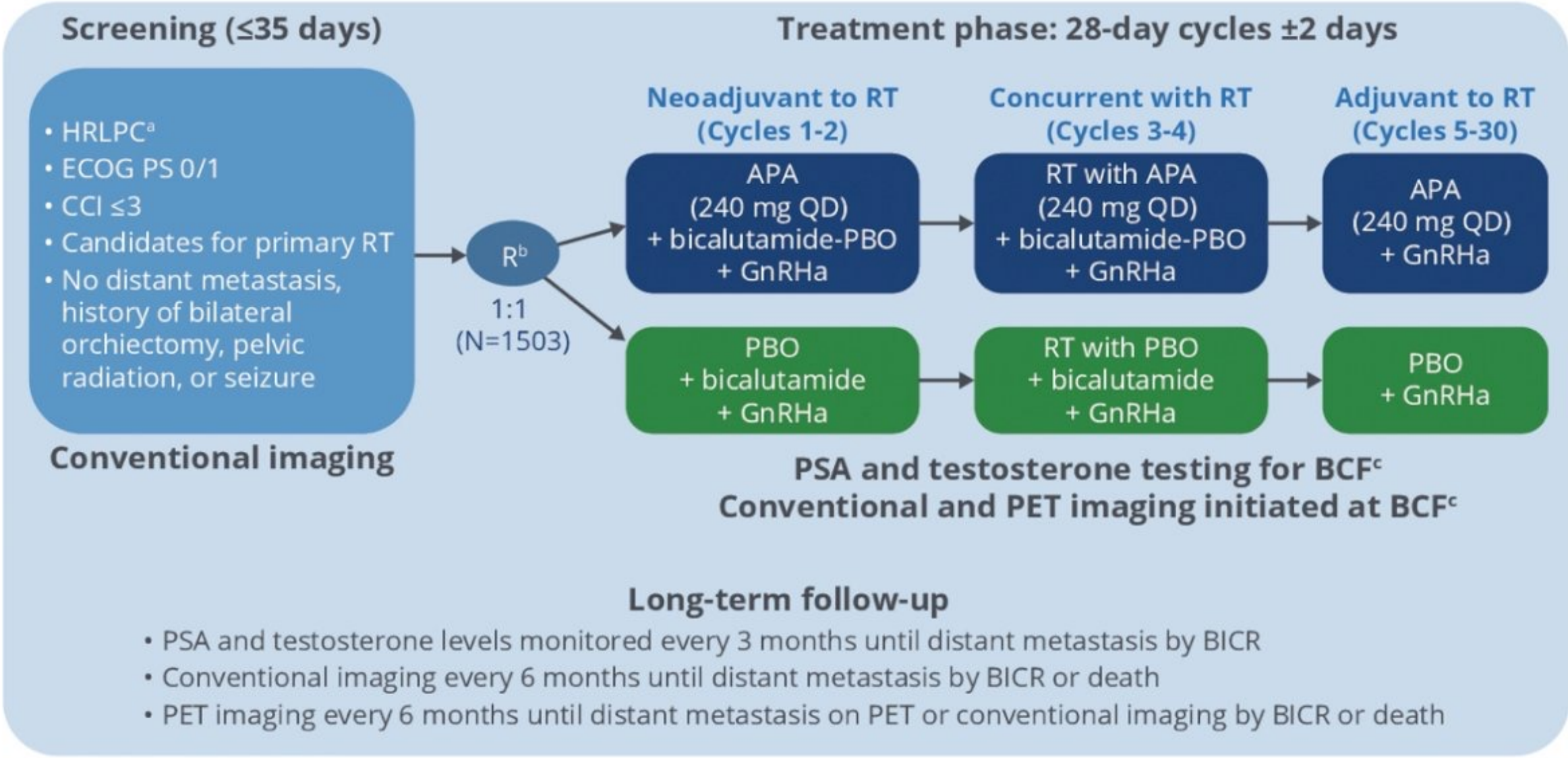
ATLAS



Sandler et al. ASCO 2022;Abstract 5084.

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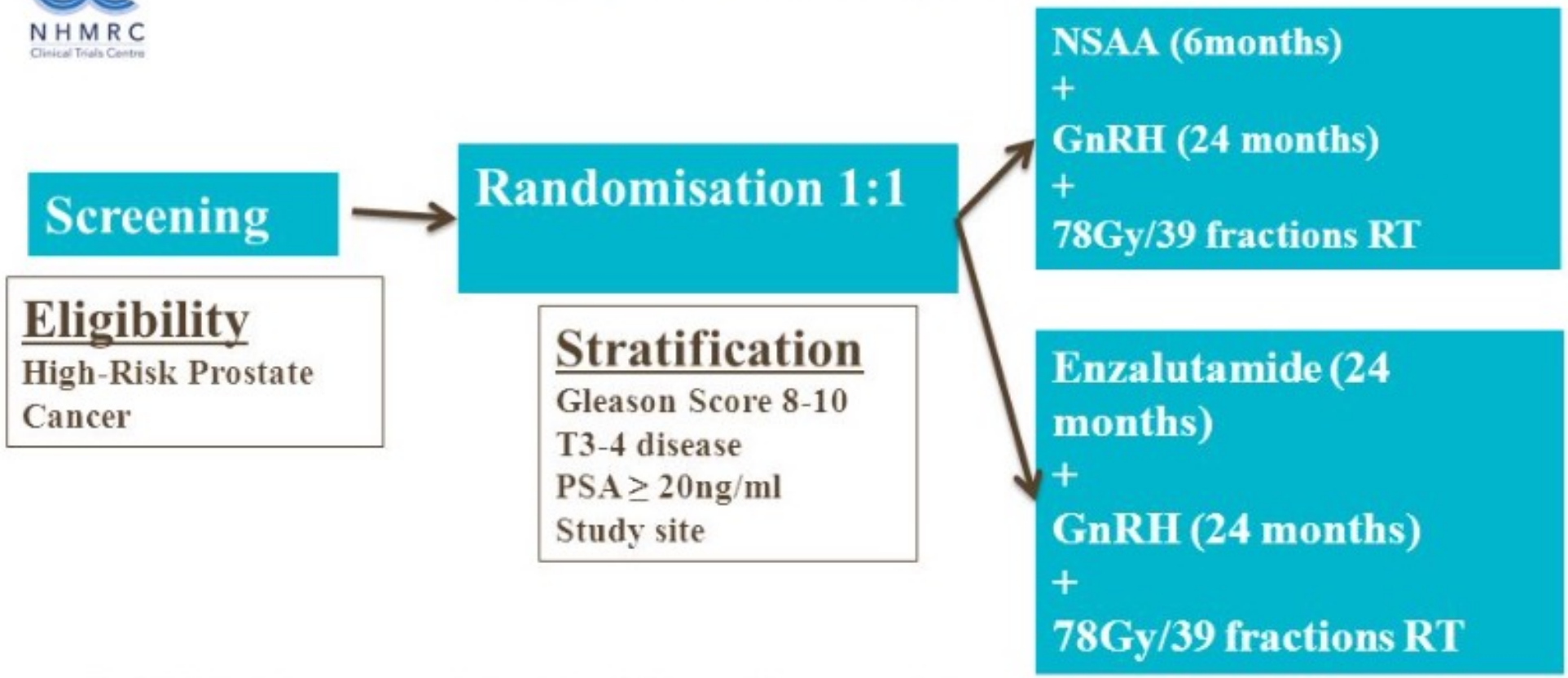
ENZARAD

TROG 14.01/ANZUP 1303



N=800, Primary Endpoint = Overall Survival

Participants: ANZUP, TROG, Dana-Farber, ICORG, UK

Williams et al. ASCO GU 2018;Abstract TPS156.

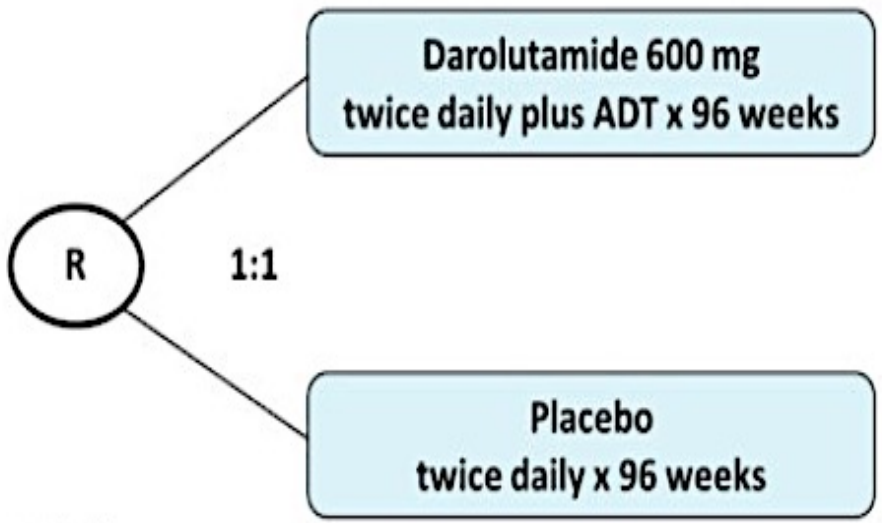
DASL HiCaP

All participants are also treated concurrently with an LHRHA for 96 weeks post randomization, plus RT starting at week 8-24 post randomization.

Eligibility

- Very high risk localized prostate cancer to be treated with definitive radiation, or

  Very high risk features + PSA persistence/rise within 12 months following radical prostatectomy (RP) to be treated with post RP radiation
- Suitable for EBRT with or without brachytherapy
- CT/MRI and bone scan negative for distant metastases (allow pelvic LN)



Endpoints

Primary

- Metastasis-free survival

Secondary

- Overall survival
- Prostate cancer-specific survival
- PSA-progression free survival
- Time to subsequent hormonal therapy
- Time to castration-resistance
- Frequency and severity of adverse events
- Health-related quality of life
- Fear of cancer recurrence

Exploratory

- Incremental cost-effectiveness
- Prognostic/predictive biomarkers

Statistical analysis

1100 participants:

- 3 years accrual + at least 4 years of additional follow up (until 130 events recorded)
- 80% power to detect: 40% reduction in the hazard for metastasis or death
  - assuming MFS rate at 5 years: 85% in the control group; 90.7% darolutamide group, allowing for interim analysis and missing data

Stratification

1. Previous radical prostatectomy (yes or no)
2. Planned docetaxel use (yes or no)
3. Clinical or pathological pelvic LN involvement (yes or no)

Niazi et al. ASCO GU 2023;Abstract TPS396.

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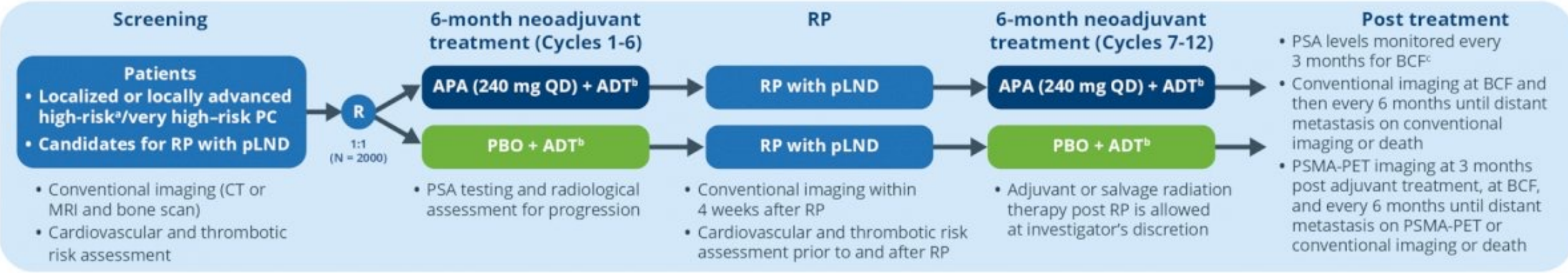
PROTEUS: ADT Intensification in Surgery



The primary endpoints are pCR rate and MFS on conventional imaging

MFS based on PSMA PET or conventional imaging will be assessed as a separate endpoint.

Kibel et al. ASCO GU 2022;Abstract TPS285.

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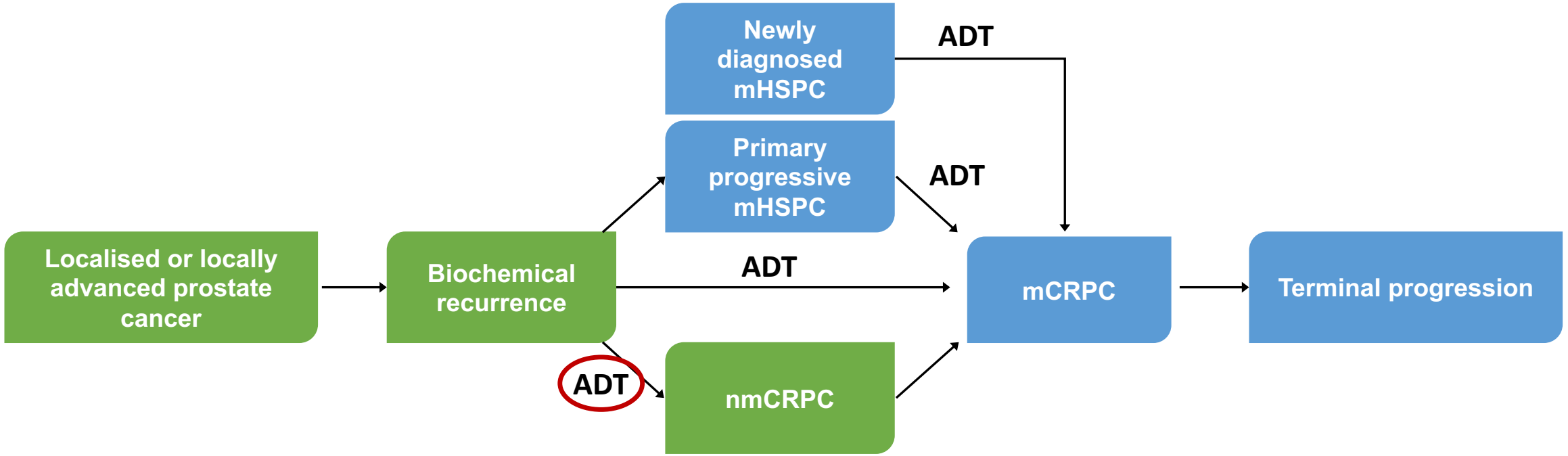
Biochemical recurrence



When to start in the biochemically recurrent non-metastatic patient?

Personal Slide Fred Saad
mHSPC, metastatic hormone-sensitive prostate cancer; mCRPC, metastatic castration-resistant prostate cancer; nmCRPC, non-metastatic castration-resistant prostate cancer

Natural History of Progression
After PSA Elevation Following Radical Prostatectomy

	Gleason 5-7				Gleason 8-10			
Year of Recurrence	>2 Years		≤2 Years		>2 Years		≤2 Years	
PSADT	>10 mo	≤10 mo	>10 mo	≤10 mo	>10 mo	≤10 mo	>10 mo	≤10 mo
3 years (%)	92	66	99	60	84	57	NA	52
5 years (%)	92	34	83	24	72	36	NA	27
7 years (%)	84	27	75	6	57	24	NA	7

- Probability of metastases-free progression after biochemical recurrence at 3, 5 and 7 years

1. Partin AW et al.

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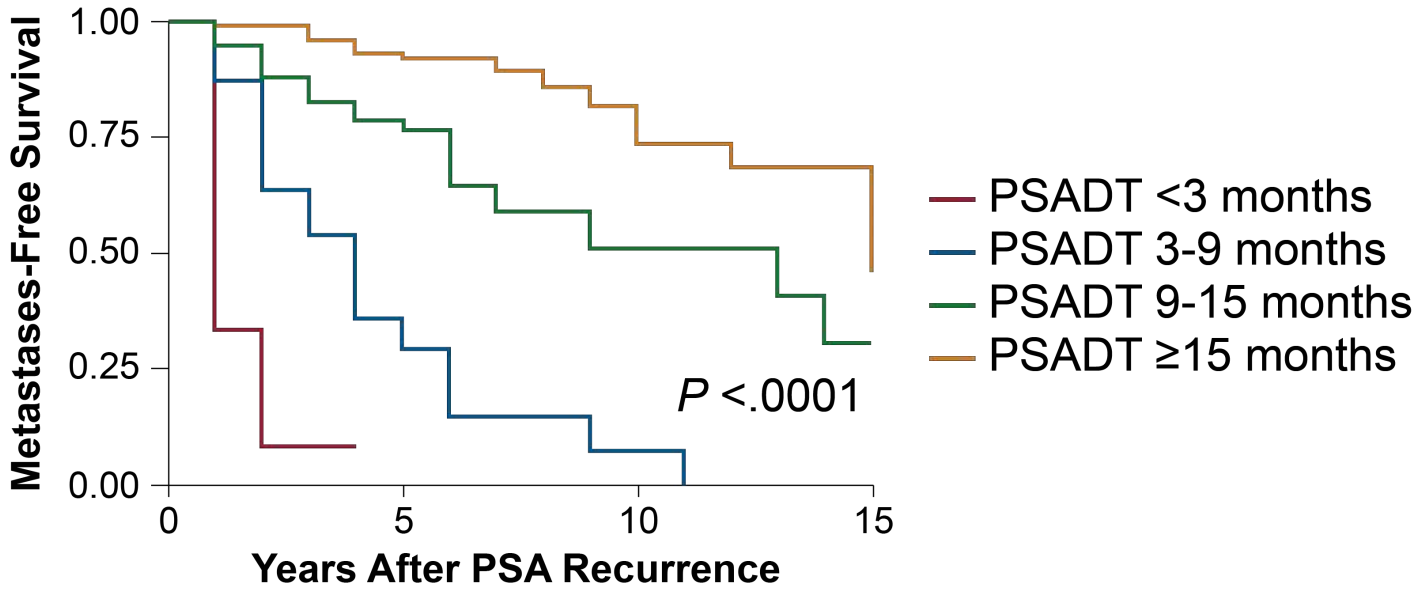
Metastases-Free Survival by PSADT[1]



No. at Risk				
PSADT <3 months	46	0	0	0
PSADT 3-9 months	106	16	2	0
PSADT 9-15 months	86	37	11	1
PSADT ≥15 months	212	86	30	3

1. Antonarakis et al. *BJU Int.* 2012;109: 32-39.

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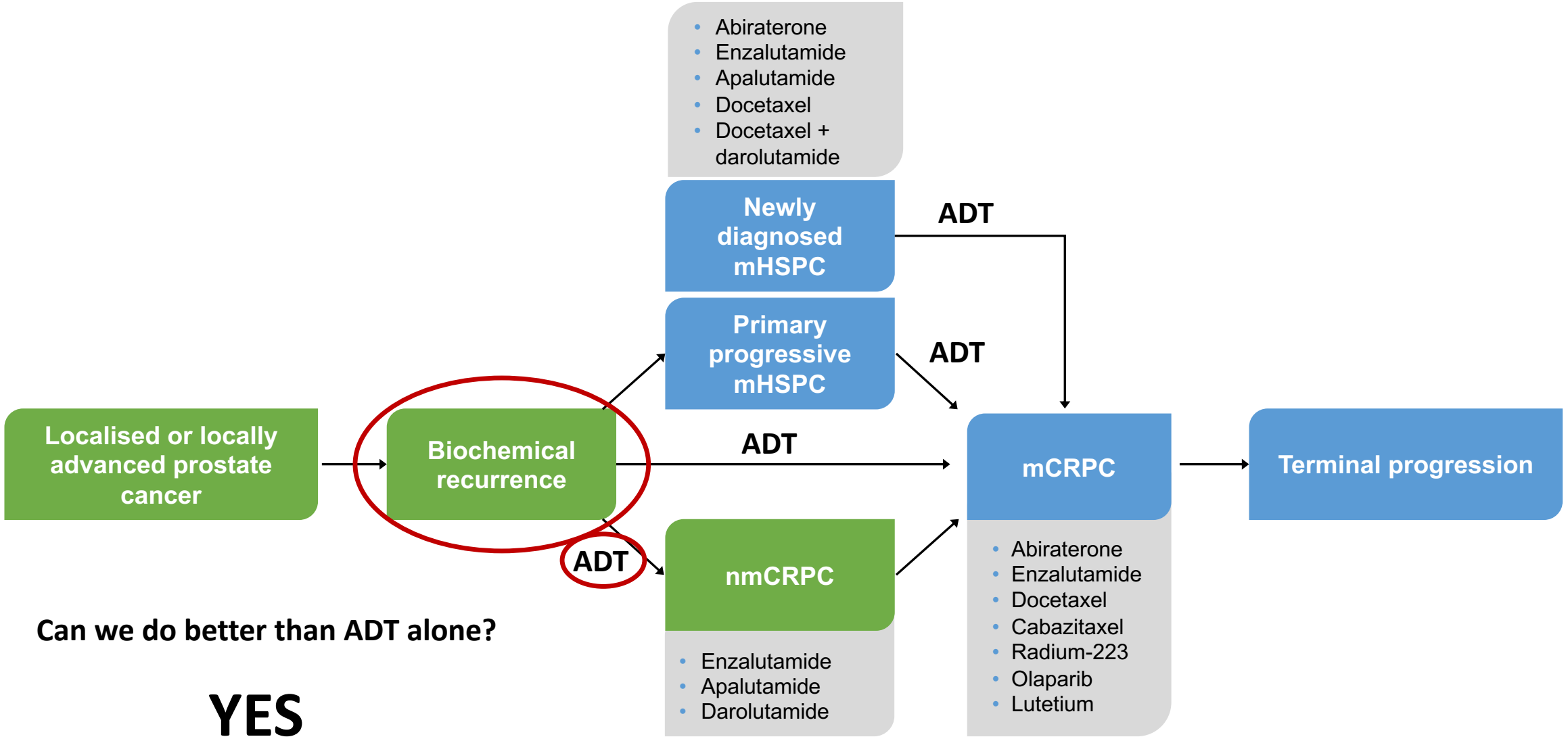
Systemic treatment options for prostate cancer



Can we do better than ADT alone?

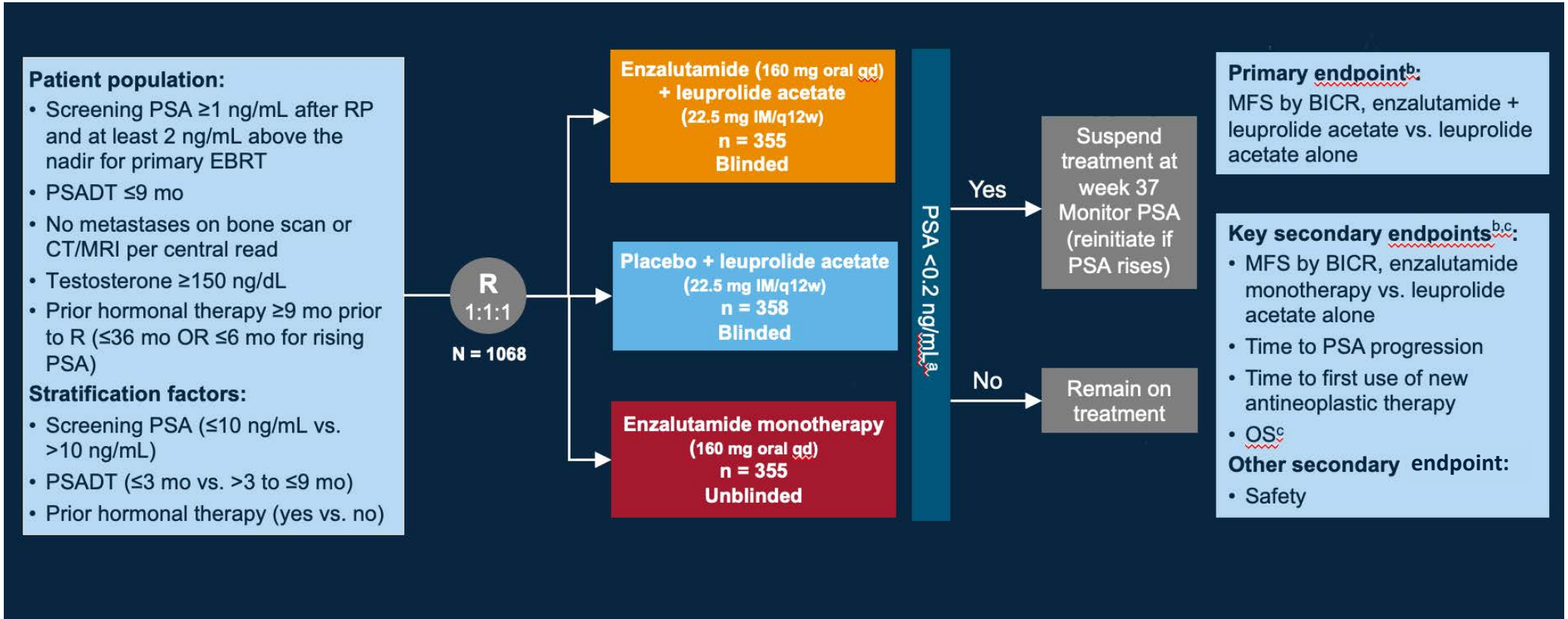
YES

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 19, 2023 VOL. 389 NO. 16

Improved Outcomes with Enzalutamide in Biochemically Recurrent Prostate Cancer

S.J. Freedland, M. de Almeida Luz, U. De Giorgi, M. Gleave, G.T. Gotto, C.M. Pieczonka, G.P. Haas, C.-S. Kim, M. Ramirez-Backhaus, A. Rannikko, J. Tarazi, S. Sridharan, J. Sugg, Y. Tang, R.F. Tutrone, Jr., B. Venugopal, A. Villers, H.H. Woo, F. Zohren, and N.D. Shore



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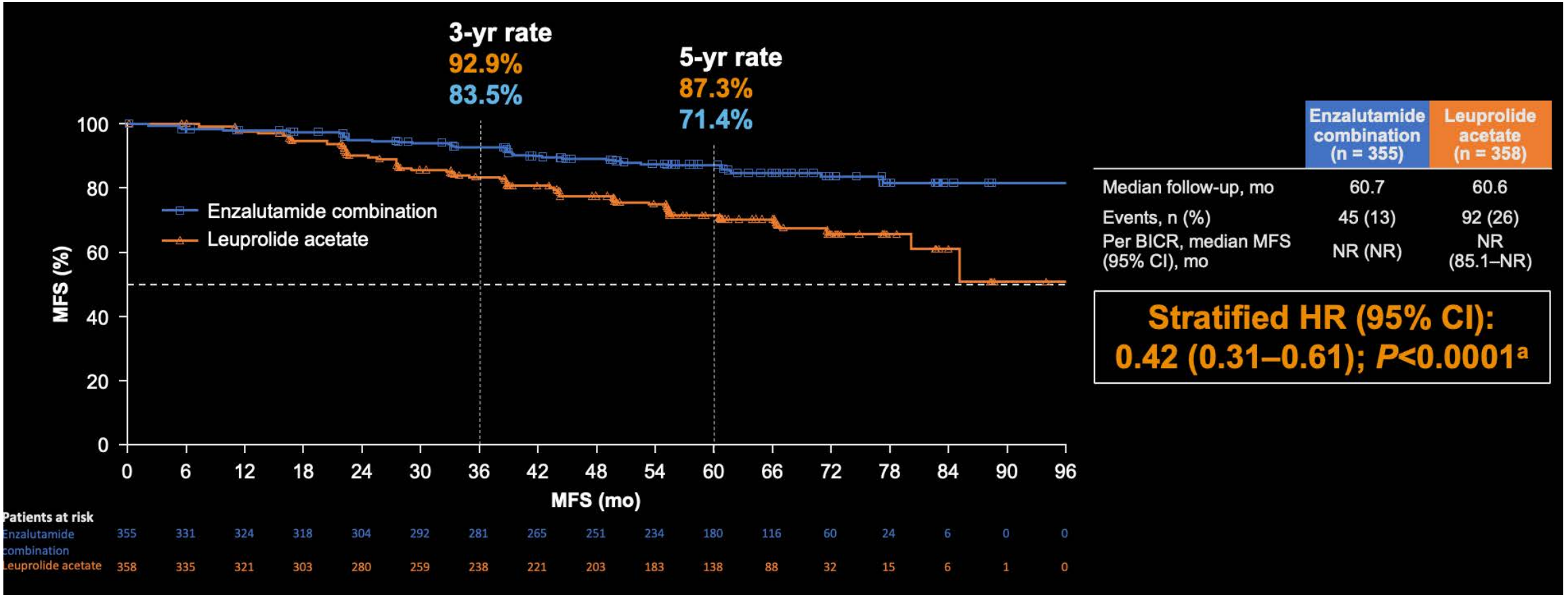
Primary endpoint — MFS for enzalutamide combination vs. leuprolide acetate



	Enzalutamide combination (n = 355)	Leuprolide acetate (n = 358)
Median follow-up, mo	60.7	60.6
Events, n (%)	45 (13)	92 (26)
Per BICR, median MFS (95% CI), mo	NR (NR)	NR (85.1–NR)

Stratified HR (95% CI): 0.42 (0.31–0.61); *P*<0.0001[a]

Freedland et al. NEJM Oct 2023

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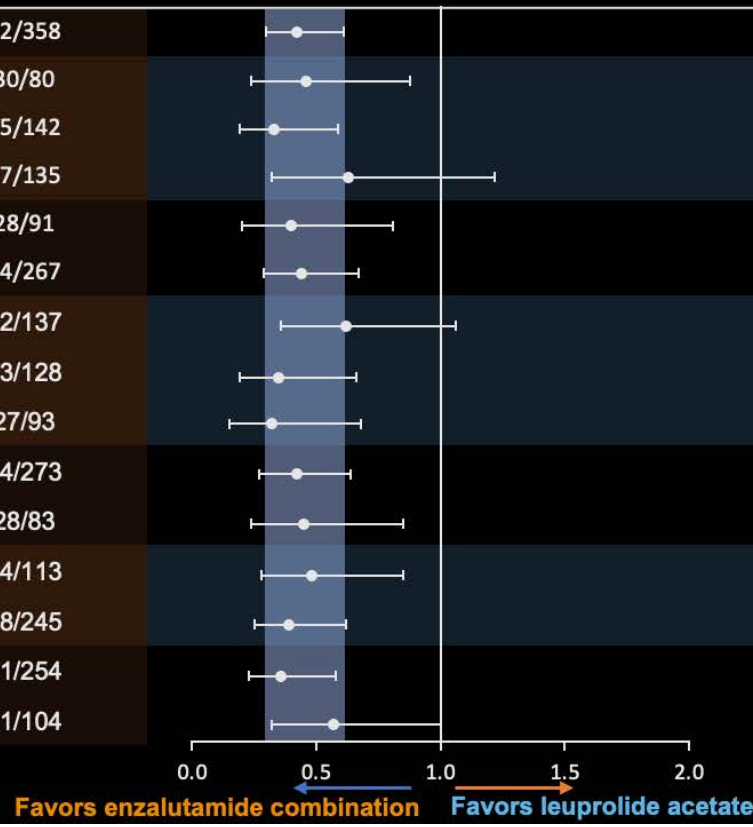
Subgroup analysis of MFS for enzalutamide combination vs. leuprolide acetate

Subgroup		Enzalutamide combination Events, n /patients, n	Leuprolide acetate Events, n /patients, n	MFS HR (95% CI)
All patients		45/355	92/358	0.42 (0.30–0.61)
PSADT	≤3 mo	14/69	30/80	0.46 (0.24–0.88)
	>3 to ≤6 mo	18/187	35/142	0.33 (0.19–0.59)
	>6 to ≤9 mo	13/98	27/135	0.63 (0.32–1.22)
Baseline age	≤65 years	11/81	28/91	0.40 (0.20–0.81)
	≥65 years	34/274	64/267	0.44 (0.29–0.67)
Geographic region	North America	22/144	32/137	0.62 (0.36–1.06)
	Europe	14/130	33/128	0.35 (0.19–0.66)
	ROW	9/81	27/93	0.32 (0.15–0.68)
Baseline PSA	≤10 ng/mL	31/278	64/273	0.42 (0.27–0.64)
	>10 ng/mL	14/77	28/83	0.45 (0.24–0.85)
Prior hormonal therapy	Yes	19/107	34/113	0.48 (0.28–0.85)
	No	26/248	58/245	0.39 (0.25–0.62)
Prior RP	Yes	26/269	61/254	0.36 (0.23–0.58)
	No	19/86	31/104	0.57 (0.32–1.00)



Freedland et al. NEJM Oct 2023

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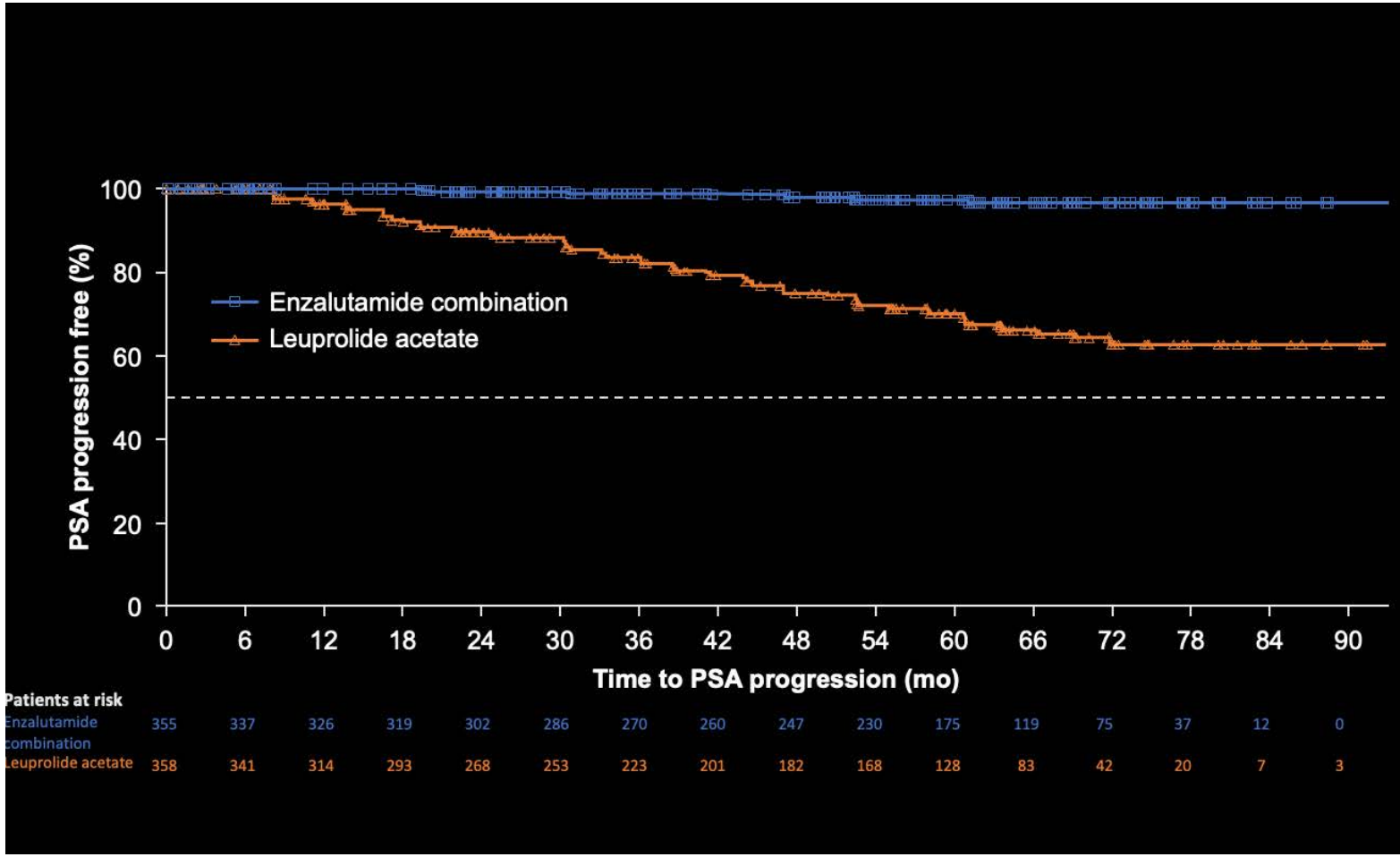
Key secondary endpoint — Time to PSA progression for enzalutamide combination vs. leuprolide acetate



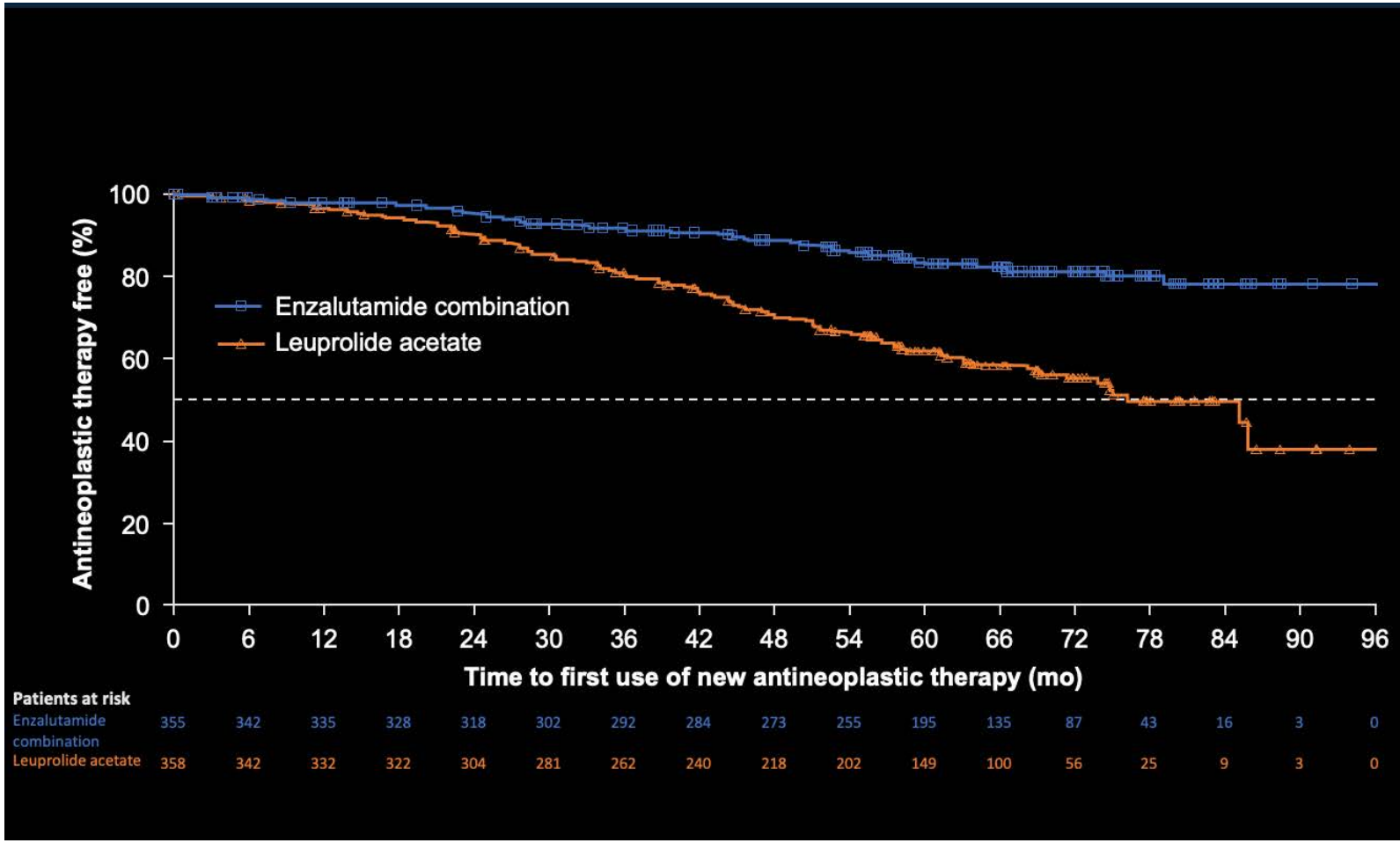
	Enzalutamide combination (n = 355)	Leuprolide acetate (n = 358)
Events, n (%)	8 (2)	93 (26)
Median time to PSA progression (95% CI), mo	NR (NR)	NR (NR)

Stratified HR (95% CI): 0.07 (0.03–0.14); *P*<0.0001[a]

Freedland et al. NEJM Oct 2023

CHUM

Key secondary endpoint — Time to first use of new antineoplastic therapy for enzalutamide combination vs. leuprolide acetate



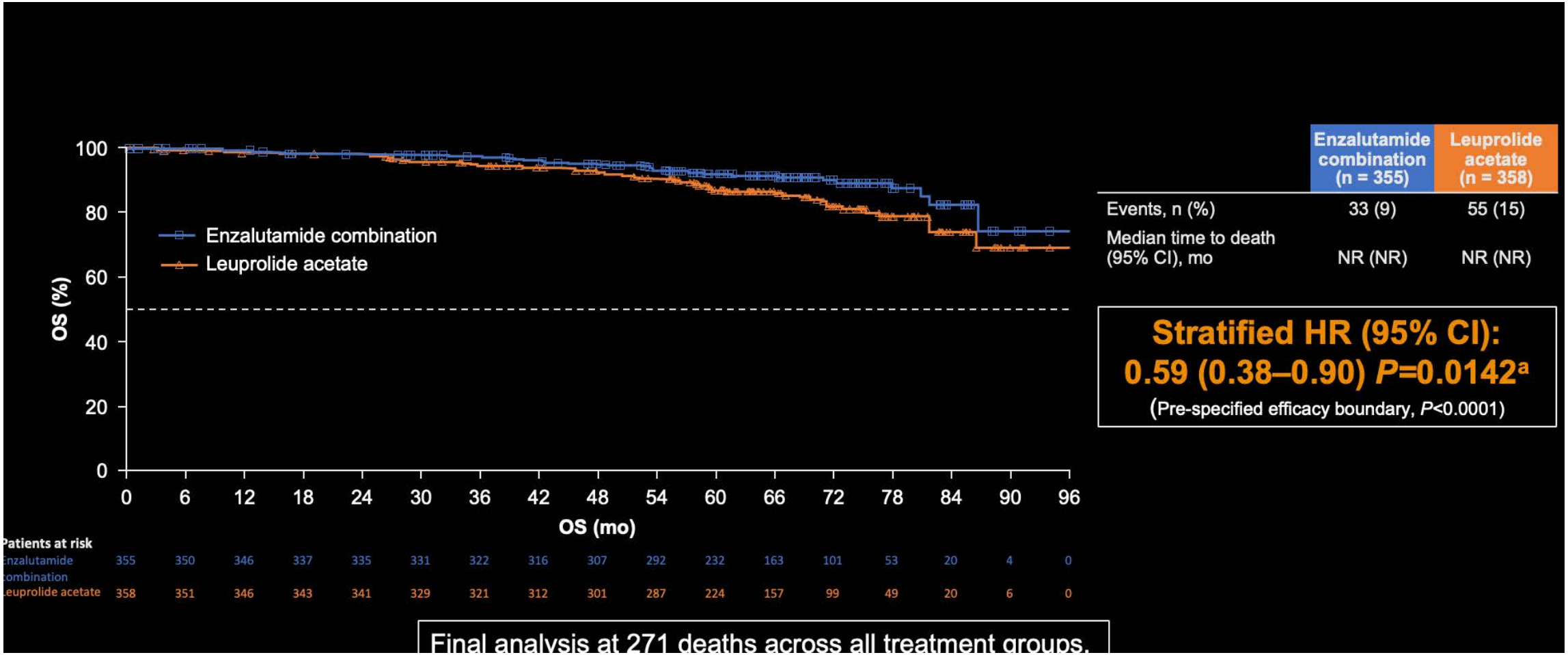
	Enzalutamide combination (n = 355)	Leuprolide acetate (n = 358)
Events, n (%)	58 (16)	140 (39)
Median time to first use of new antineoplastic therapy (95% CI), mo	NR (NR)	76.2 (71.3–NR)

Stratified HR (95% CI): 0.36 (0.26–0.49); *P*<0.0001[a]

Freedland et al. NEJM Oct 2023

CHUM

Key secondary endpoint — Interim OS for enzalutamide combination vs. leuprolide acetate



	Enzalutamide combination (n = 355)	Leuprolide acetate (n = 358)
Events, n (%)	33 (9)	55 (15)
Median time to death (95% CI), mo	NR (NR)	NR (NR)

Stratified HR (95% CI): 0.59 (0.38–0.90) *P*=0.0142[a]

(Pre-specified efficacy boundary, *P*<0.0001)

Final analysis at 271 deaths across all treatment groups.

Freedland et al. NEJM Oct 2023

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Safety

Event, n (%)[a]	Enzalutamide combination (n = 353)		Leuprolide acetate (n = 354)		Enzalutamide monotherapy (n = 354)	
	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
Any AE	343 (97.2)	164 (46.5)	345 (97.5)	151 (42.7)	347 (98.0)	177 (50.0)
Treatment-related AE	305 (86.4)	62 (17.6)	283 (79.9)	31 (8.8)	312 (88.1)	57 (16.1)
Serious AE	123 (34.8)	110 (31.2)	112 (31.6)	100 (28.2)	131 (37.0)	116 (32.8)
Treatment-related serious AE	26 (7.4)	22 (6.2)	8 (2.3)	7 (2.0)	17 (4.8)	17 (4.8)
AE leading to dose reduction	25 (7.1)	11 (3.1)	16 (4.5)	5 (1.4)	56 (15.8)	14 (4.0)
AE leading to permanent discontinuation	73 (20.7)	31 (8.8)	36 (10.2)	19 (5.4)	63 (17.8)	34 (9.6)
AE leading to death	–	6 (1.7)[b]	–	3 (0.8)[b]	–	8 (2.3)[b]

- Median treatment duration excluding treatment suspension was 32.4 mo (range, 0.1–83.4 mo) for enzalutamide combination, 35.4 mo (range, 0.7–85.7 mo) for leuprolide acetate, and 45.9 mo (0.4–88.9 mo) for enzalutamide monotherapy.
- The most common AE leading to study drug discontinuation was fatigue (enzalutamide combination, 3.4% [n = 12]; leuprolide acetate, 1.1% [n = 4]; enzalutamide monotherapy, 2.3% [n = 8]).

Freedland et al. NEJM Oct 2023

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Most common TEAEs

Most common TEAEs (>15% of patients), n (%)[a]	Enzalutamide combination (n = 353)		Leuprolide acetate (n = 354)		Enzalutamide monotherapy (n = 354)	
	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
Hot flash	243 (68.8)	2 (0.6)	203 (57.3)	3 (0.8)	77 (21.8)	1 (0.3)
Fatigue	151 (42.8)	12 (3.4)	116 (32.8)	5 (1.4)	165 (46.6)	14 (4.0)
Arthralgia	97 (27.5)	5 (1.4)	75 (21.2)	1 (0.3)	81 (22.9)	1 (0.3)
Hypertension	82 (23.2)	2 (0.6)	69 (19.5)	0	67 (18.9)	0
Fall	74 (21.0)	3 (0.8)	51 (14.4)	2 (0.6)	56 (15.8)	5 (1.4)
Back pain	60 (17.0)	1 (0.3)	54 (15.3)	0	62 (17.5)	1 (0.3)
Nausea	42 (11.9)	0	29 (8.2)	0	54 (15.3)	1 (0.3)
Gynecomastia	29 (8.2)	0	32 (9.0)	0	159 (44.9)	1 (0.3)
Nipple pain	11 (3.1)	0	4 (1.1)	0	54 (15.3)	0

- The most common AEs (>15% of patients) for all treatment cohorts were hot flash, fatigue; plus gynecomastia in the enzalutamide monotherapy cohort; most were grade <3.

Freedland et al. NEJM Oct 2023

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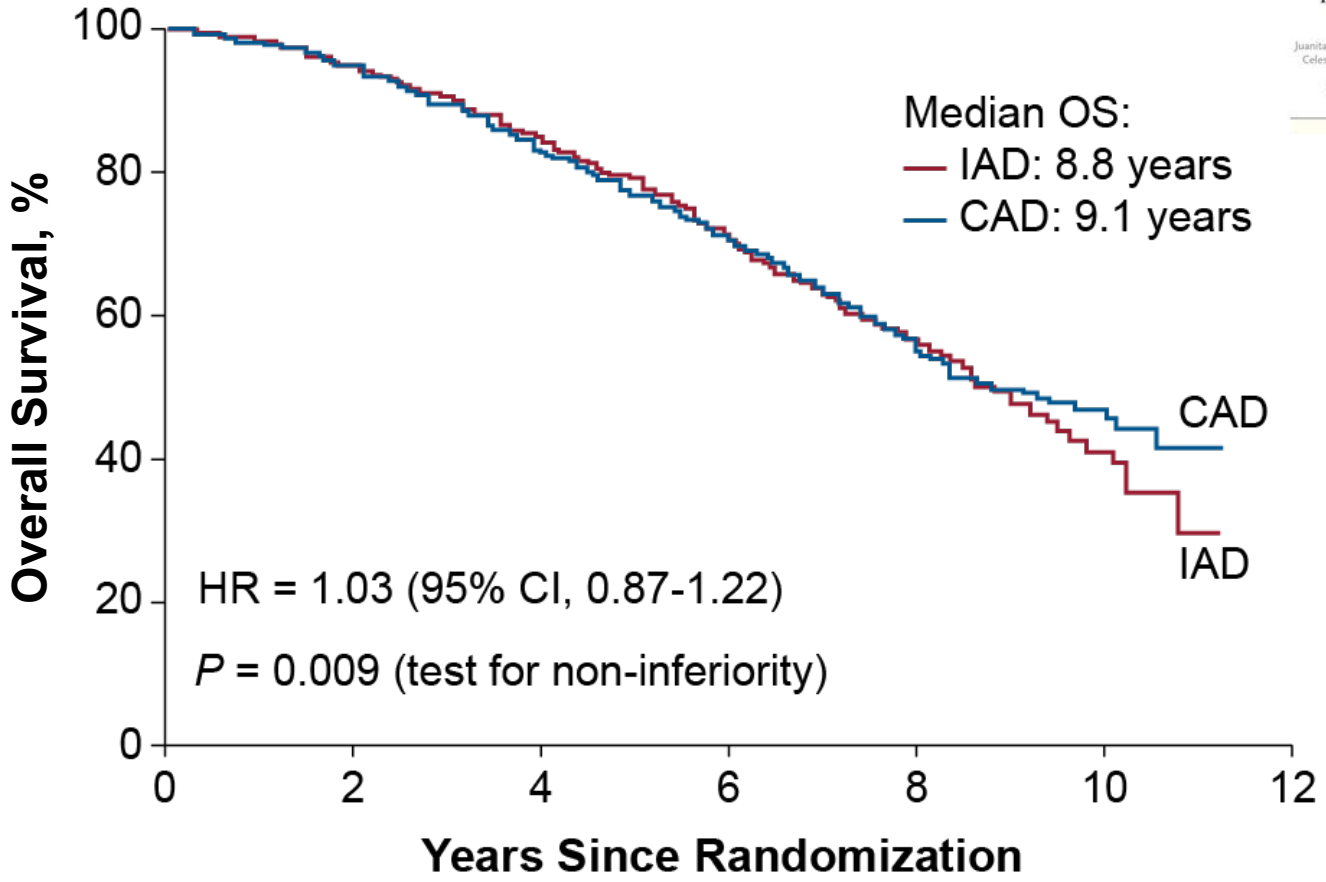
Intermittent vs Continuous?

Compromise between early vs delayed

PR.7 (non-metastatic): Overall Survival



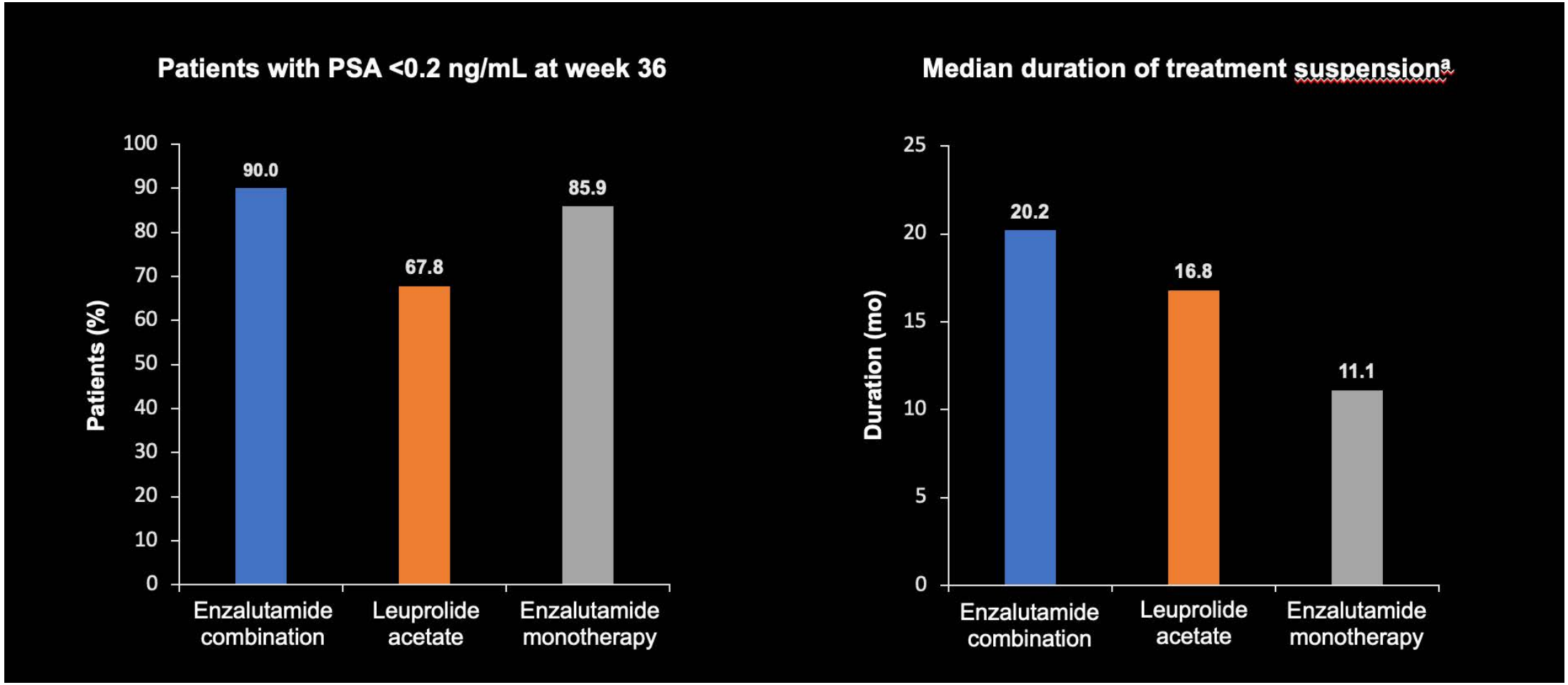
No. at Risk

CAD	696	652	561	319	125	35	0
IAD	690	651	571	327	140	34	0

Adapted from: Crook JM et al. *N Engl J Med.* 2012;367:895-903.

CHUM

Secondary endpoint
Undetectable PSA and Duration of suspension

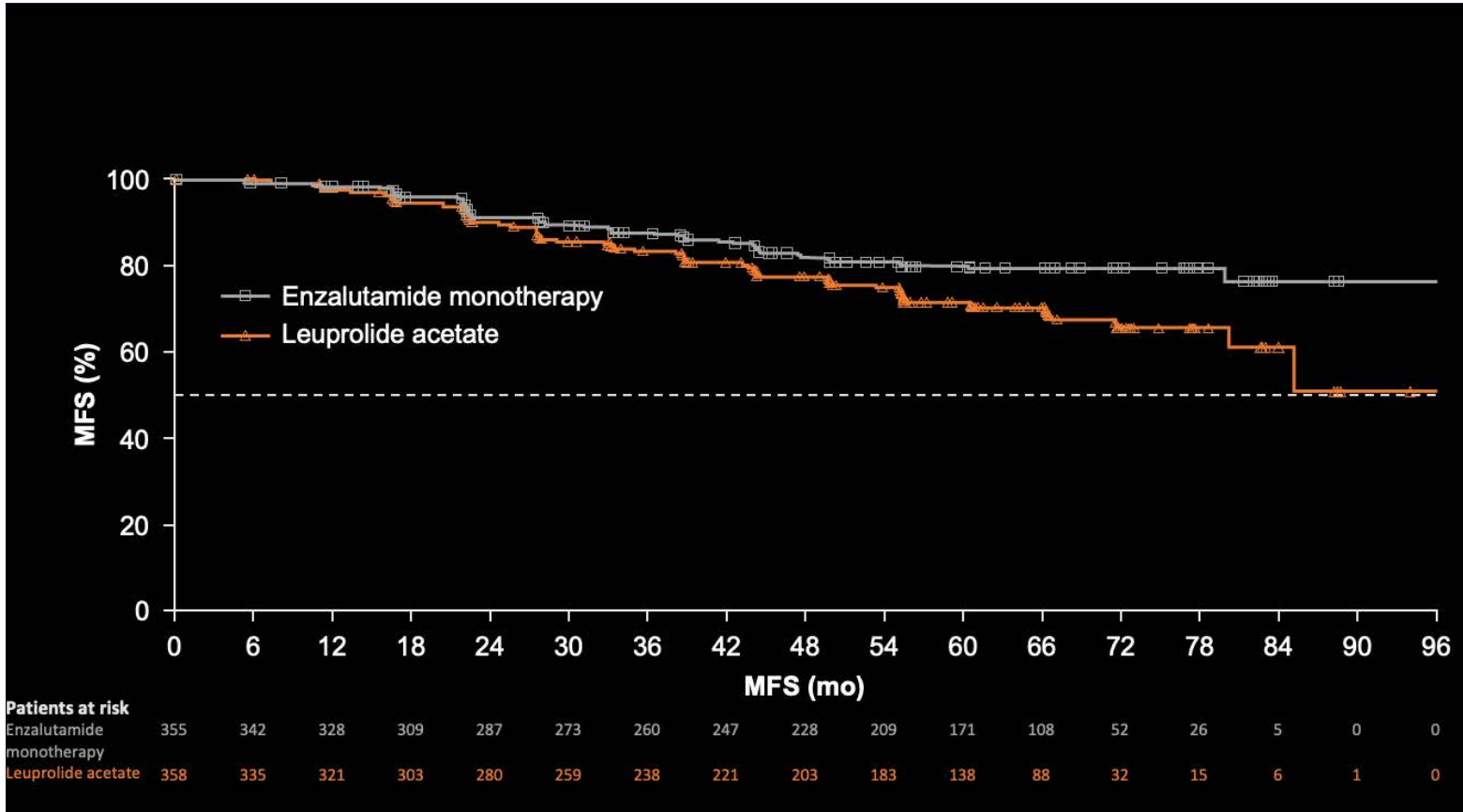


Freedland et al. NEJM Oct 2023

CHUM

Can enzalutamide be an effective alternative to ADT?

Key secondary endpoint — MFS for enzalutamide monotherapy vs. leuprolide acetate



	Enzalutamide monotherapy (n = 355)	Leuprolide acetate (n = 358)
Median follow-up, mo	60.7	60.6
Events, n (%)	63 (18)	92 (26)
Per BICR, median MFS (95% CI), mo	NR (NR)	NR (85.1–NR)

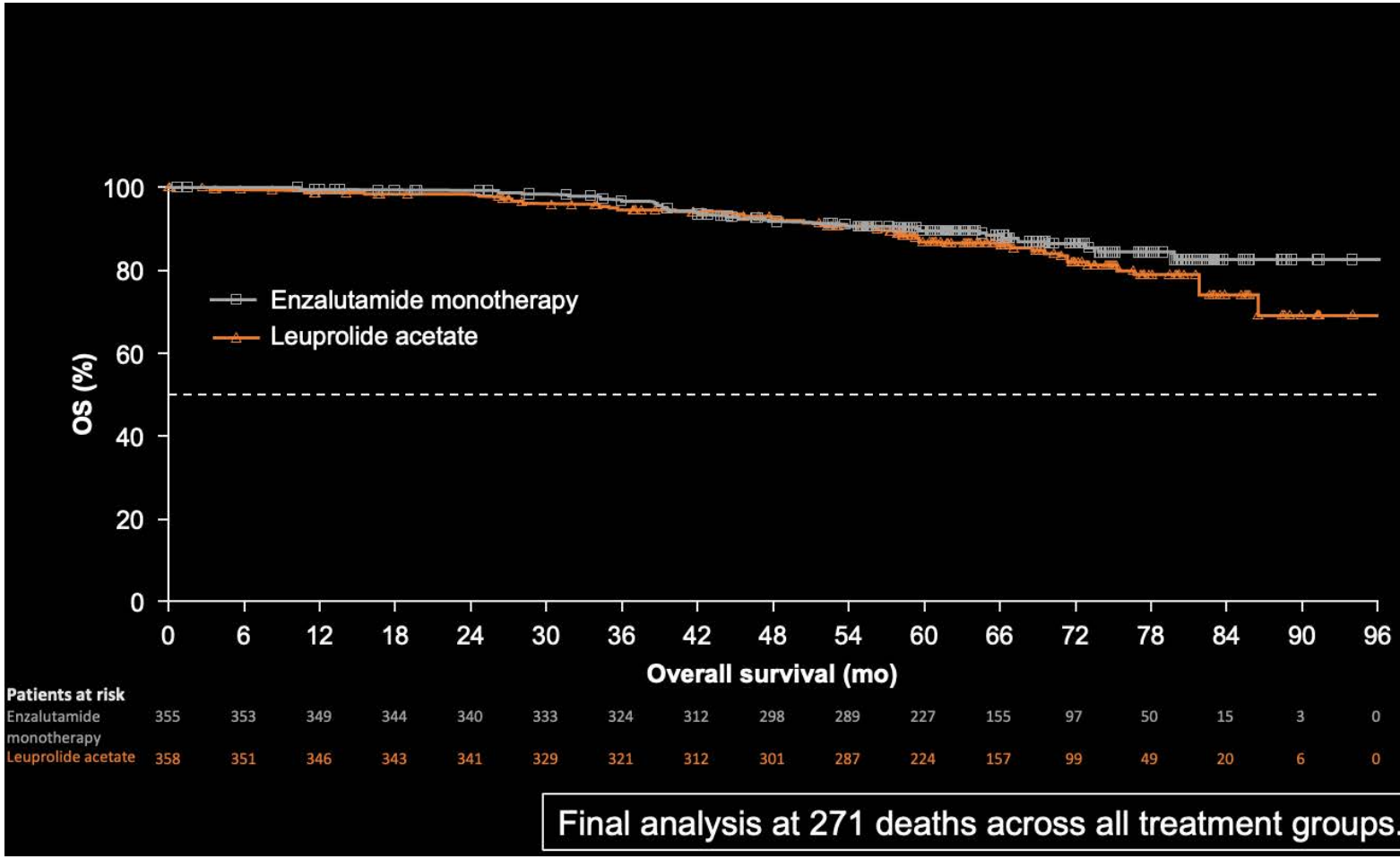
Stratified HR (95% CI): 0.63 (0.46–0.87); *P*=0.0049[a]

A consistent treatment effect was seen for investigator-assessed MFS: HR (95% CI): 0.56 (0.40–0.78); *P*=0.0006

Freedland et al. NEJM Oct 2023

CHUM

Key secondary endpoint — Interim OS of enzalutamide monotherapy vs. leuprolide acetate



	Enzalutamide monotherapy (n = 355)	Leuprolide acetate (n = 358)
Events, n (%)	42 (12)	55 (15)
Median time to death (95% CI), mo	NR (NR)	NR (85.1–NR)

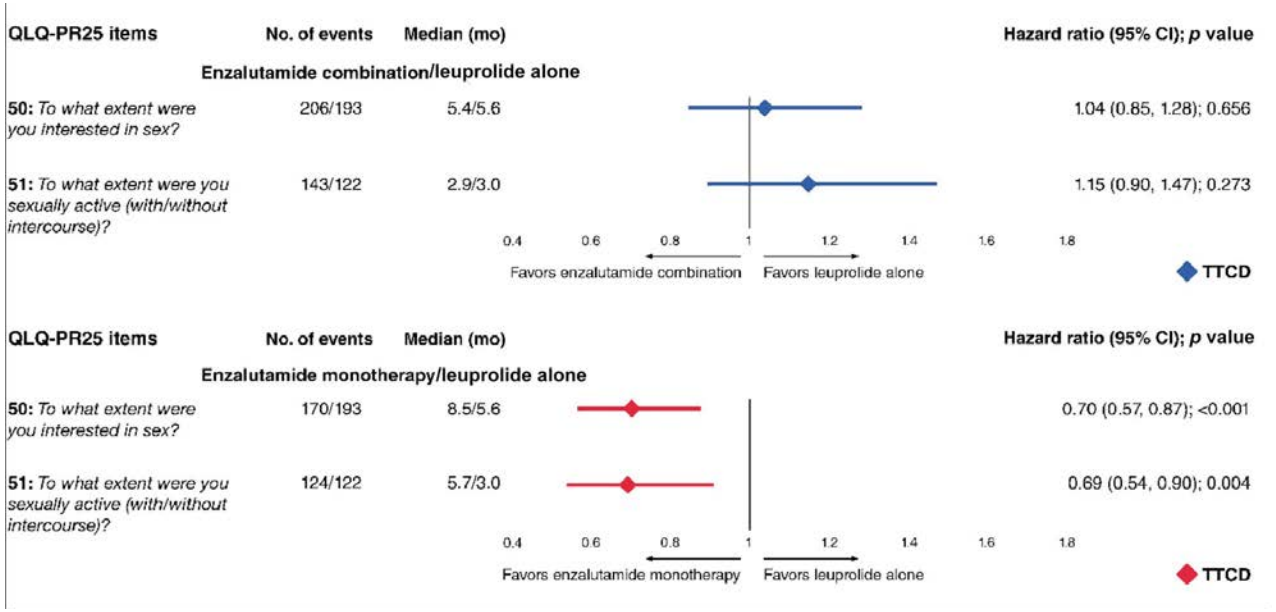
Stratified HR (95% CI): 0.77 (0.51–1.15); nominal *P*=0.1963[a]

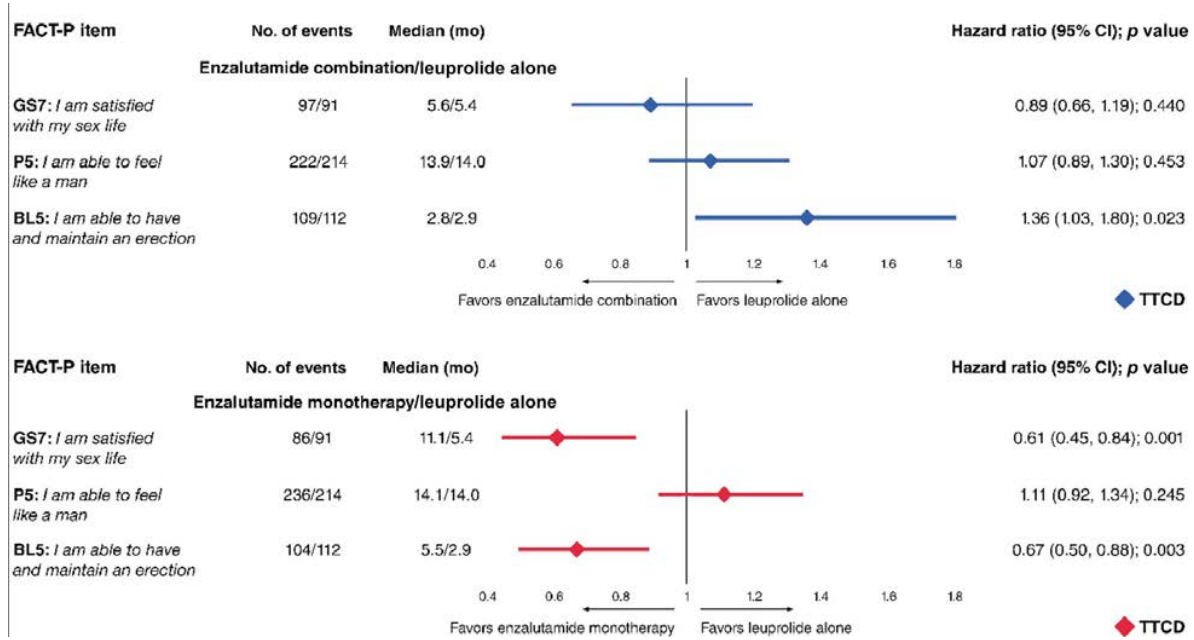
Final analysis at 271 deaths across all treatment groups.

Freedland et al. NEJM Oct 2023

CHUM

Sexual Quality of Life





Freedland et al. Eur Urol 2025

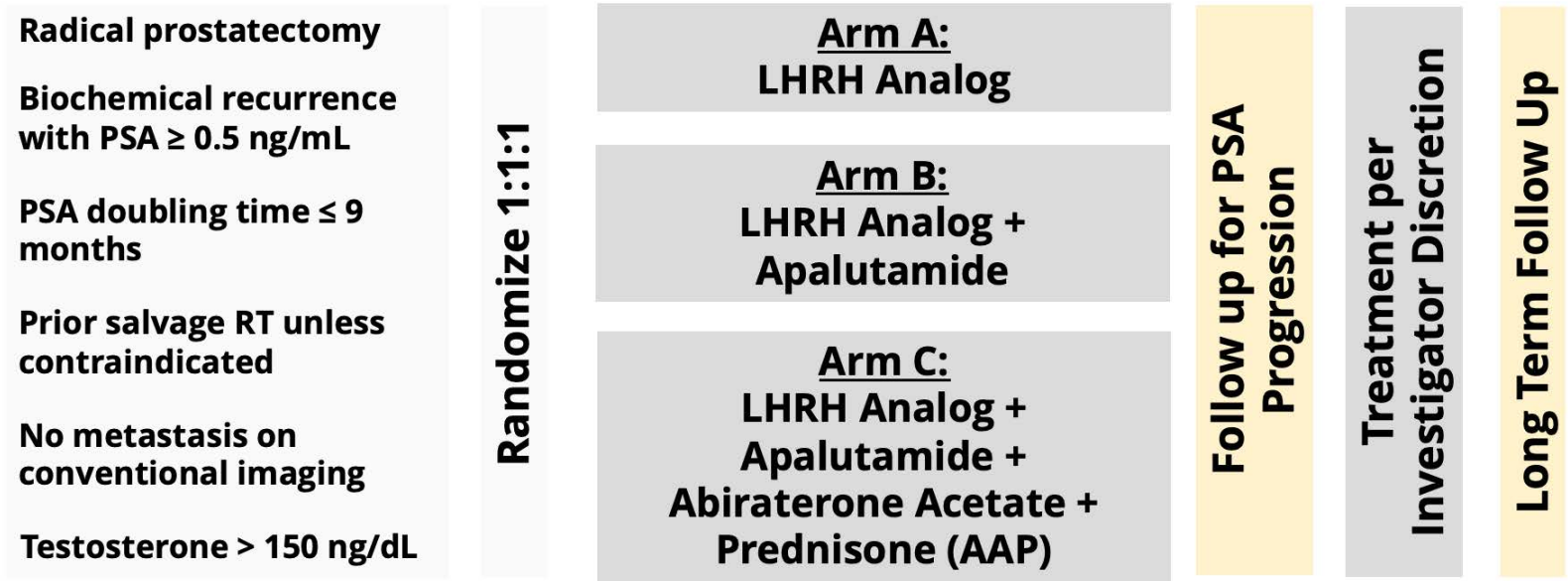
CHUM

PRESTO: A Phase III, Open-Label Study of Intensification of Androgen Blockade in Patients With High-Risk Biochemically Relapsed Castration-Sensitive Prostate Cancer (AFT-19)

Rahul Aggarwal, MD[1]; Glenn Heller, PhD[2]; David W. Hillman, MS[3]; Han Xiao, MD[2]; Joel Picus, MD[4]; Mary-Ellen Taplin, MD[5]; Tanya Dorff, MD[6]; Leonard Appleman, MD[7]; Douglas Weckstein, MD[8]; Akash Patnaik, MD[9]; Alan Bryce, MD[10]; Daniel Shevrin, MD[11]; James Mohler, MD[12]; Daniel Anderson, MD[13]; Arpit Rao, MD[14]; Scott Tagawa, MD[15]; Alan Tan, MD[16]; Susan Halabi, PhD[17]; Katharine Dooley, MPH[3]; Patrick O'Brien, BS[3]; Ronald Chen, MD, MPH[18]; Charles J. Ryan, MD[19]; Scott E. Eggener, MD[9] and Michael J. Morris, MD[2]; on behalf of the PRESTO Study Investigators

DOI https://doi.org/10.1200/JCO.23.01157

Study Schema (N=504)



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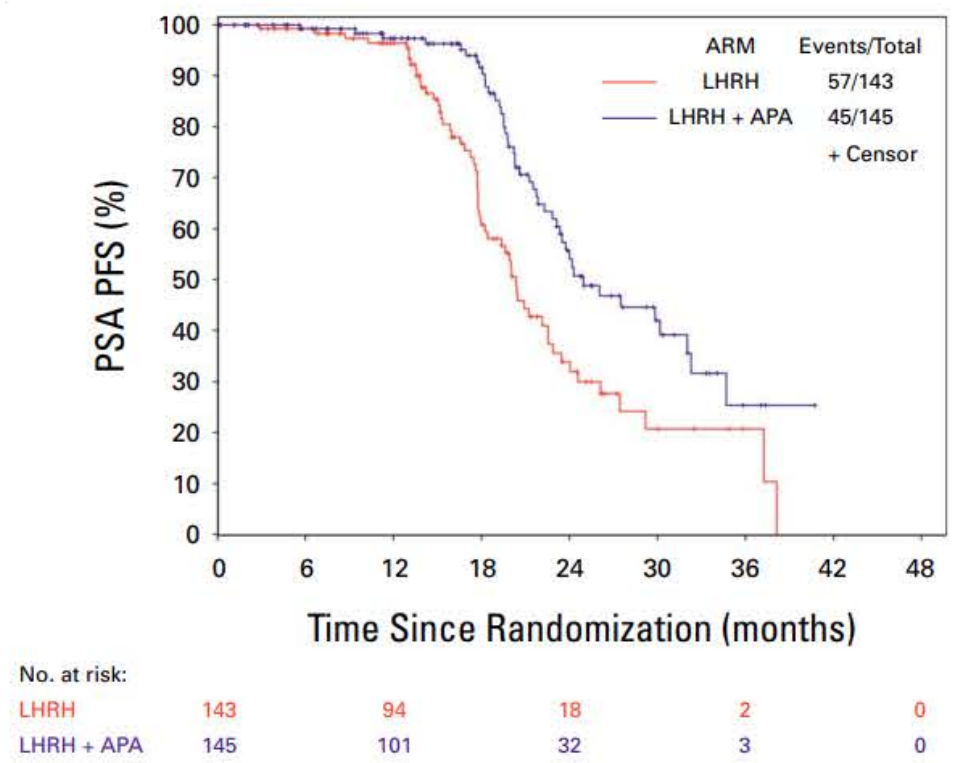
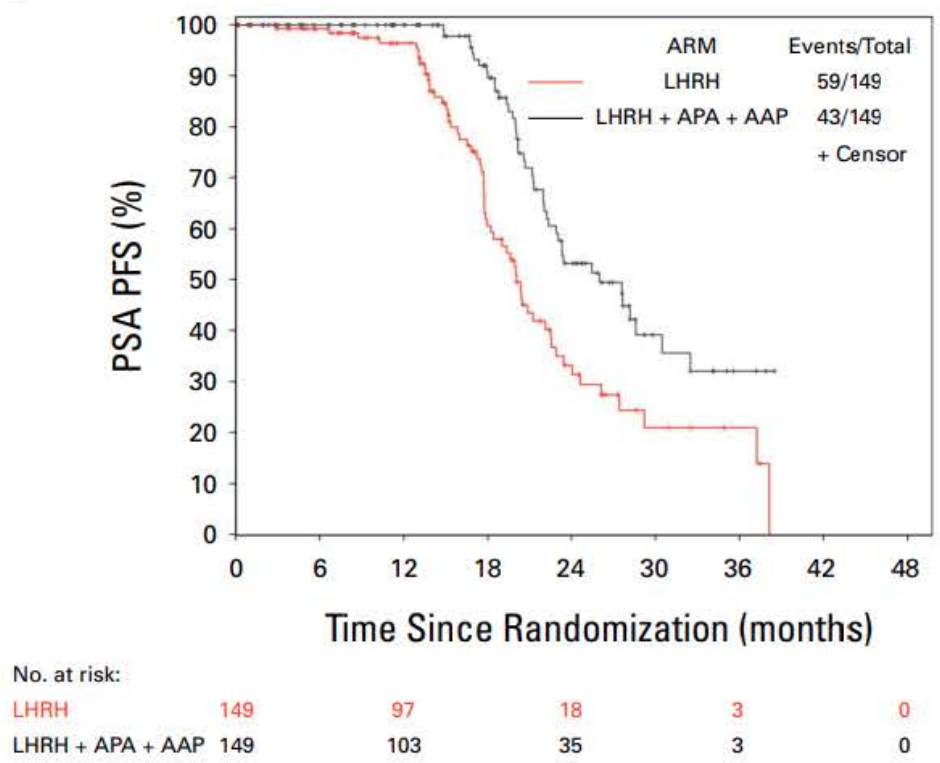
PRESTO (AFT-19): PSA-PFS





Median PSA-PFS

ADT: 20.3 months
ADT + apa: 24.9 months

ADT: 20.0 months
ADT + apa + AAP: 26.0 months

Aggarwal R, et al. JCO 42:1114-23, 2024.

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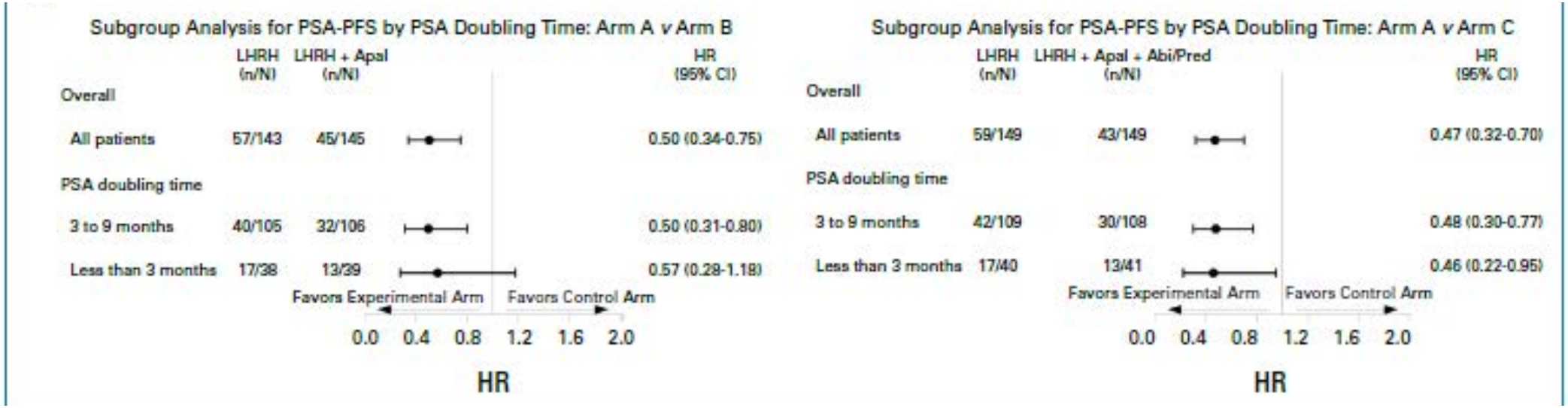
Subgroup analysis



	ADT	ADT + Apa	ADT + Apa + AAP
% Completed Therapy	87.7%	93.5%	91.9%
T recovery to >150 (mo)	5.1	5.7	6.9
Serious adverse events*	8%	9%	17%

*Most common: hypertension

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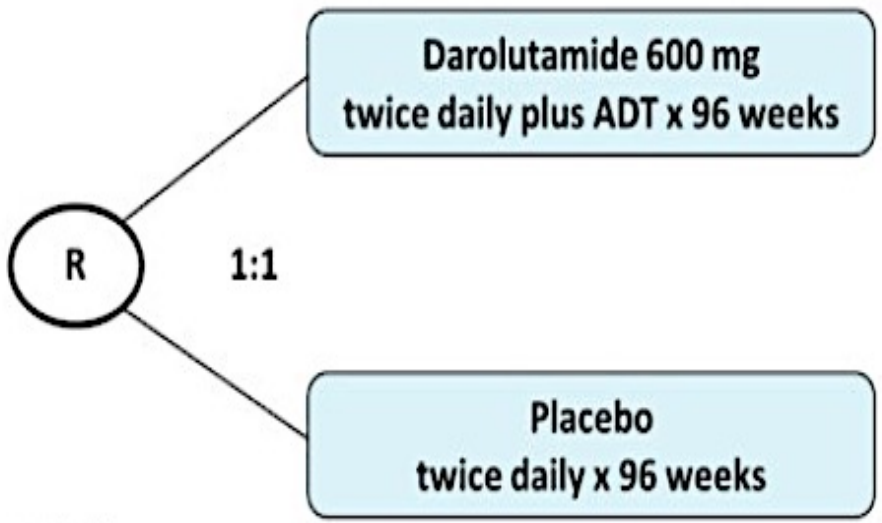
DASL HiCaP

All participants are also treated concurrently with an LHRHA for 96 weeks post randomization, plus RT starting at week 8-24 post randomization.

Eligibility

- Very high risk localized prostate cancer to be treated with definitive radiation, or

  Very high risk features + PSA persistence/rise within 12 months following radical prostatectomy (RP) to be treated with post RP radiation
- Suitable for EBRT with or without brachytherapy
- CT/MRI and bone scan negative for distant metastases (allow pelvic LN)



Endpoints

Primary

- Metastasis-free survival

Secondary

- Overall survival
- Prostate cancer-specific survival
- PSA-progression free survival
- Time to subsequent hormonal therapy
- Time to castration-resistance
- Frequency and severity of adverse events
- Health-related quality of life
- Fear of cancer recurrence

Exploratory

- Incremental cost-effectiveness
- Prognostic/predictive biomarkers

Statistical analysis

1100 participants:

- 3 years accrual + at least 4 years of additional follow up (until 130 events recorded)
- 80% power to detect: 40% reduction in the hazard for metastasis or death
  - assuming MFS rate at 5 years: 85% in the control group; 90.7% darolutamide group, allowing for interim analysis and missing data

Stratification

1. Previous radical prostatectomy (yes or no)
2. Planned docetaxel use (yes or no)
3. Clinical or pathological pelvic LN involvement (yes or no)

Niazi et al. ASCO GU 2023;Abstract TPS396.

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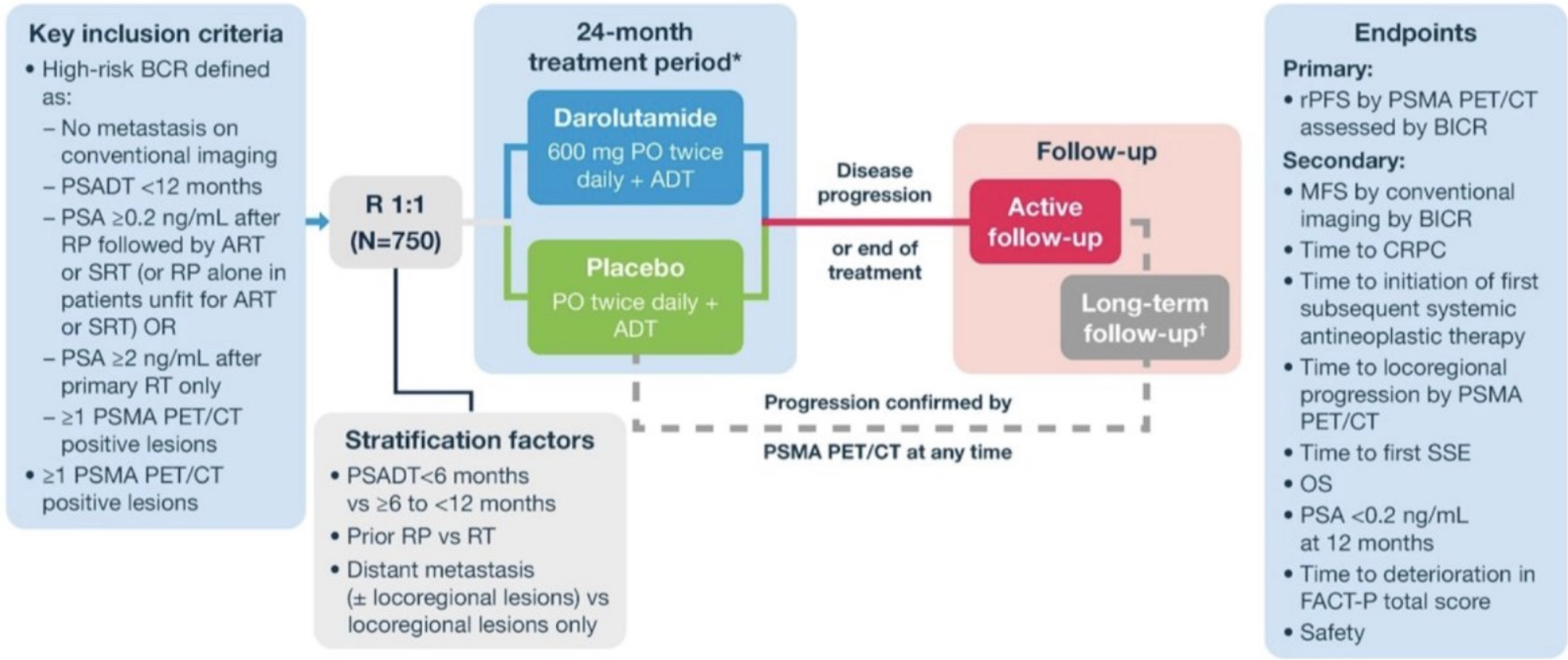
ARASTEP



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Conclusion

- Very high risk localized may benefit from ADT intensification
  - To reduce their risk of becoming metastatic and dying of prostate cancer
- BCR is concerning but not all patients are at the same risk of metastases and death
  - PSA doubling time allows us to evaluate risk
  - Lower risk can be followed or consider PSMA directed MDT +/- ADT
  - Higher risk patients (short PSADT) are in need of better treatment
    - To reduce their risk of becoming metastatic and dying of prostate cancer
  - Patients with optimal response may be safely given a treatment holiday thus reducing the cost and morbidity of treatment

Early and optimal hormonally based therapy is effective
in patients with potentially lethal prostate cancer

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Faculty Case Presentations

Case Presentation – Dr Armstrong: nmHSPC, enzalutamide monotherapy

- 56 yo AAM presented with a screening PSA of 8 at age 50, asymptomatic
- Biopsy showed GG4 in 12/12 cores, high volume disease
- Initial PSMA PET/CT normal other than uptake in prostate, no LAD, SVI
- Initially treated with radical prostatectomy, found to have pT3a GG4 bilateral disease, positive margins
- PSA persistence with PSA of 0.2 3 months post-op
- Completed early salvage RT to the prostate bed only, no ADT 6 mo post-op once urinary incontinence resolved, has return of sexual function despite radiation
- Despite radiation, PSA continues to rise. CT/bone scan are normal. PSA rises to 5.0 over a period of 12 months and repeat PSMA PET/CT shows multiple (4) SUV + tiny retroperitoneal and 2 pelvic lymph nodes, SUVs ranging from 6-12, size of 6-8 mm, no bone metastases
- PSADT is around 4-5 months
- Inquires about approaches to control disease while minimizing impact on quality of life and sexual health.
- Married since age 48, no children, works full time and active bicyclist and tennis player

Case Presentation – Dr Armstrong: nmHSPC, enzalutamide monotherapy (cont'd)

- Starts enzalutamide monotherapy, no ADT (patient preference to minimize sexual side effects)
- PSA drops to undetectable after 6 months and he stops therapy
- After 12 months, PSA has risen again quickly to 6.4
- He inquires if anything can be done to ensure a longer break from hormonal therapy
- Some breast tenderness but this resolved during the treatment break
- Reduced libido for about 7-8 months during enzalutamide monotherapy, but this resolved now.

QUESTIONS FOR THE FACULTY

Which patients with biochemical recurrence after definitive local treatment represent ideal candidates for ADT alone versus ADT in combination with enzalutamide versus enzalutamide alone?

How would you compare the global tolerability of enzalutamide monotherapy versus enzalutamide and ADT for patients with nmHSPC? How do they compare in terms of sexual side effects?

Do you have any tricks of the trade for managing the breast symptoms associated with enzalutamide monotherapy?

What would you recommend for this patient given his rising PSA?

Case Presentation – Dr McKay: nmHSPC

Patient Profile:

- 68-year-old male,
- Initial diagnosis: March 2021
  - PSA at diagnosis: 14.3 ng/mL
  - Digital rectal exam: Firm, irregular right base
  - MRI: PI-RADS 5 lesion in right peripheral zone, ECE suspected
  - Biopsy: Gleason 4+5=9 (Grade Group 5) in 6/12 cores, 80% maximum core involvement
  - Clinical stage: cT3a N0 M0
- Initial treatment:
  - Radical prostatectomy (May 2021)
  - Pathology: pT3b (SV+), N0, R1 (positive margin at apex)
  - Post-op PSA (8 weeks): 0.4 ng/mL
- Adjuvant treatment:
  - External beam radiation (66 Gy to prostate bed + pelvic lymph nodes)
  - Completed December 2020
  - PSA nadir after radiation: 0.1 ng/mL (May 2022)
- Biochemical recurrence:
  - PSA rise beginning September 2022
  - PSA trend: 0.3 ng/mL (Sep 2022) → 0.7 ng/mL (Dec 2022) → 1.4 ng/mL (Feb 2023) → 2.8 ng/mL (May 2023)
  - PSA doubling time: 4.2 months (high-risk)
  - Conventional imaging (CT/bone scan): Negative for metastases
  - PSMA PET/CT: Two small pelvic lymph nodes with mild PSMA uptake (SUVmax 4.2, equivocal)
  - Current status: Non-metastatic hormone-sensitive prostate cancer (nmHSPC) with biochemical recurrence

Case Presentation – Dr McKay: nmHSPC (cont'd)

Treatment Course:

- Started on ADT (leuprolide q3mo) + enzalutamide 160mg daily in July 2023
- PSA response:
  - 2.8 ng/mL (pre-treatment)
  - 0.4 ng/mL (1 month)
  - 0.08 ng/mL (2 months)
  - <0.01 ng/mL (3 months and maintained through present)
- Testosterone levels consistently <20 ng/dL
- Toxicity:
  - Grade 2 fatigue, managed with exercise program
  - Grade 1 hot flashes
  - Mild cognitive changes
- Current status:
  - 10 months into treatment (May 2024)
  - PSA remains undetectable (<0.01 ng/mL)
  - Baseline bone density scan showing osteopenia, now on calcium and vitamin D supplements

QUESTIONS FOR THE FACULTY

How do you approach treatment for patients such as this one who experience biochemical recurrence with a rapidly rising PSA after local therapy and have evidence of metastatic disease on PSMA PET but not on conventional imaging?

If this man's PSA remains undetectable, would you offer him a treatment break? Are you comfortable using intermittent therapy in this population despite their high-risk status? If so, when do you start measuring PSA levels after commencing hormonal therapy, and at what intervals do you do so? At what PSA level do you stop treatment, and when do you reinitiate it?

QUESTIONS FOR THE FACULTY

Outside of a clinical trial, would you currently employ an AR pathway inhibitor other than enzalutamide with or without ADT for patients with biochemically recurrent nmHSPC under any circumstances?

Agenda

MODULE 1: Evolving Management of Nonmetastatic Hormone-Sensitive Prostate Cancer (HSPC) — Dr Saad

MODULE 2: Current Treatment for Metastatic HSPC — Dr Armstrong

MODULE 3: Role of PARP Inhibition in Metastatic Castration-Resistant Prostate Cancer (mCRPC) — Dr Agarwal

MODULE 4: Current and Future Use of Radiopharmaceuticals for mCRPC — Dr McKay

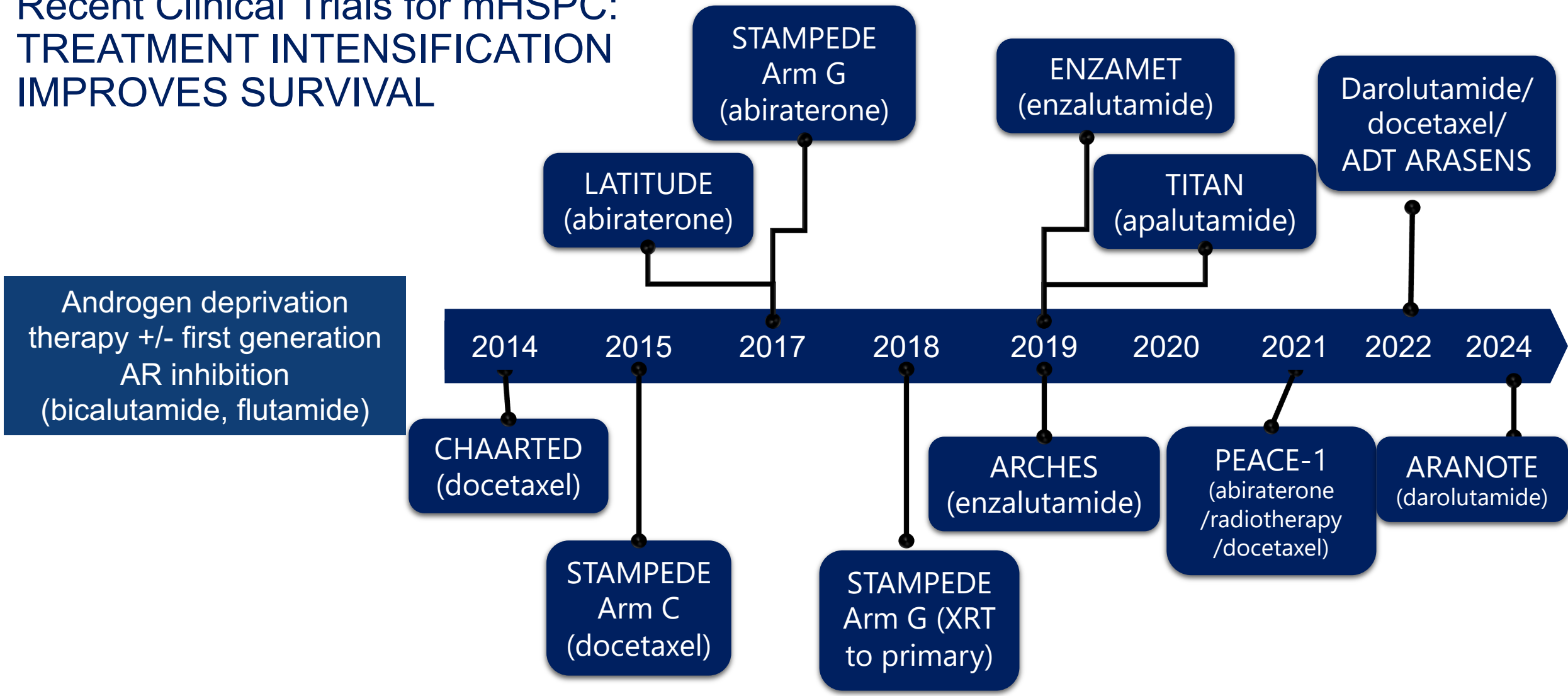
MODULE 5: Promising Novel Agents and Strategies Under Investigation for the Management of Prostate Cancer — Dr Beltran

Current Treatment for Metastatic HSPC (mHSPC)

Andrew J Armstrong MD ScM FACP
ASCO 2025
Professor of Medicine, Surgery, Pharmacology and Cancer Biology
Director of Research
Duke Cancer Institute's Center for Prostate and Urologic Cancers

Duke Cancer Institute
Center For Prostate & Urologic Cancers

Recent Clinical Trials for mHSPC: TREATMENT INTENSIFICATION IMPROVES SURVIVAL



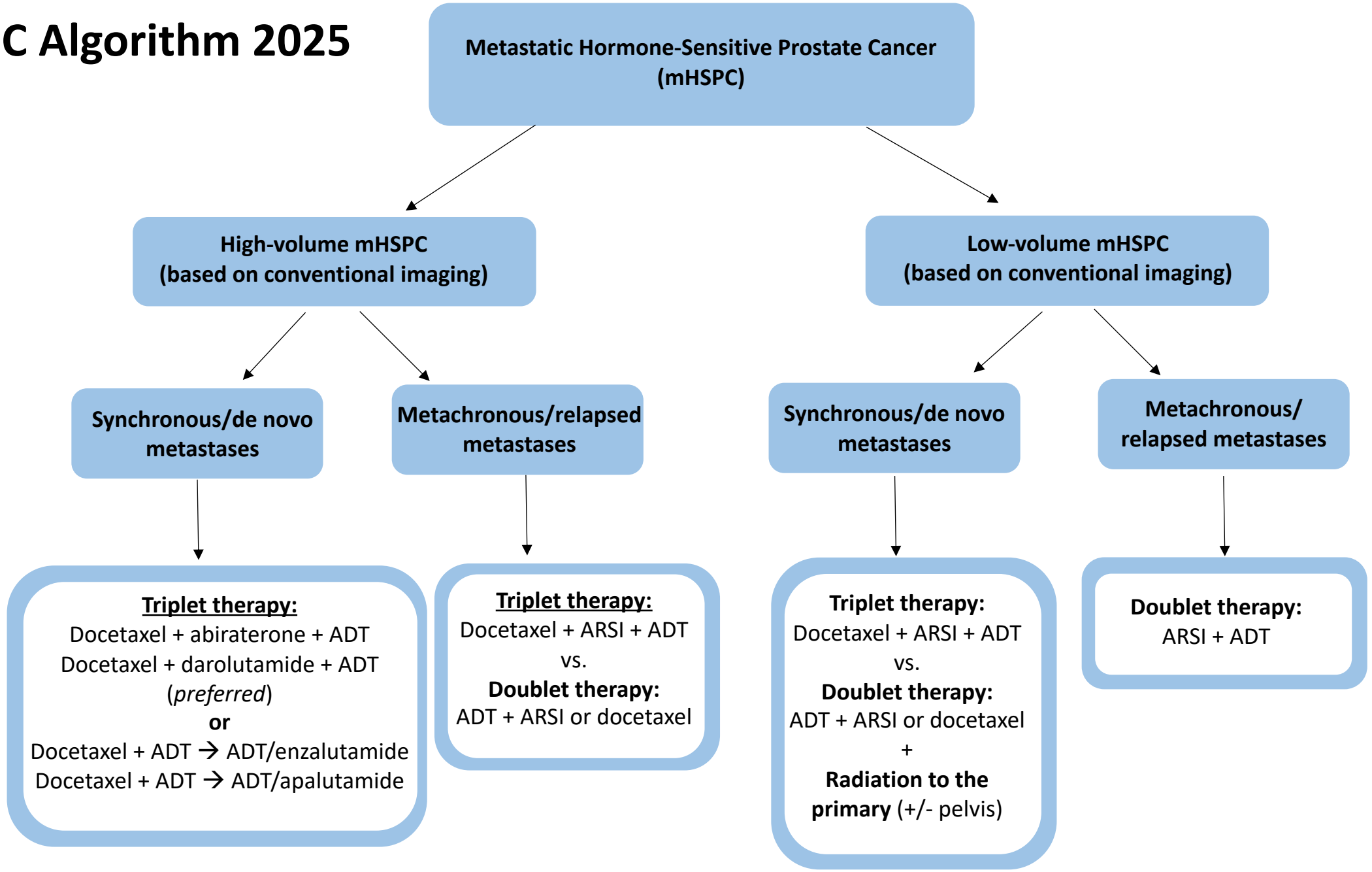
2025 ASCO: ARCHES 5 year updates and the AMPLITUDE study (abi +/- niraparib). Come on Tuesday!

mHSPC Therapies with Proven Survival Benefit

Therapy	Prior Docetaxel	Comparator	FFS/PFS benefit, HR, p-value	OS benefit, HR; p-value
Radiation to the Primary	No	No radiation, ADT alone +/- docetaxel	Yes: low volume HR 0.59 p<0.0001	Yes: low volume HR 0.68 p=0.007
Enzalutamide ARCHES ENZAMET	18% 44-45%	Placebo/ADT ADT/Bicalutamide	Yes HR 0.39 p<0.0001 Yes HR 0.39 p<0.0001	Yes HR 0.66 p<0.0001 all volumes Yes HR 0.67 p=0.002 all volumes
Docetaxel/prednisone: STAMPEDE	No	ADT	Yes HR 0.61 p<0.0001	Yes HR 0.76 p=0.005 all volumes
Docetaxel: CHAARTED	No	ADT	Yes HR 0.61 p<0.0001	Yes HR 0.63 p<0.001 high volume HR 1.04 low volume
Docetaxel/Abiraterone	Yes	Docetaxel/ADT	Yes HR 0.47-0.58 p=0.006, <0.0001	Yes HR 0.72 p=0.019 high volume de novo
Apalutamide	11%	Placebo/ADT	Yes HR 0.48 p<0.001	Yes HR 0.67 p=0.0053 all volumes
Abiraterone/Prednisone LATITUDE	No	Prednisone	Yes HR 0.47 p<0.0001	Yes HR 0.66 p<0.001 high risk
Abiraterone/Prednisone STAMPEDE	No	Prednisone	Yes HR 0.31 p<0.0001	Yes HR 0.61 p<0.001 all risk/volumes
Abiraterone/prednisone (PEACE-1)	100% (concurrent)	**ADT/Docetaxel**	Yes HR 0.50 p<0.0001	Yes HR 0.75 p=0.017; HV: HR 0.72 p=0.019
Darolutamide	100% (concurrent)	Placebo/ADT/ Docetaxel	Yes CRPC HR 0.35 p<0.0001	Yes HR 0.675 p<0.0001 de novo 86%

Parker et al Lancet 2018; Armstrong et al JCO 2019 and ESMO/JCO 2021; Davis et al NEJM 2019; James N et al Lancet 2015; Sweeney et al NEJM 2015; Chi KN et al NEJM 2019; Fizazi K et al NEJM 2017; James et al NEJM 2017; Smith MR et al NEJM 2022; Fizazi K et al Lancet 2022

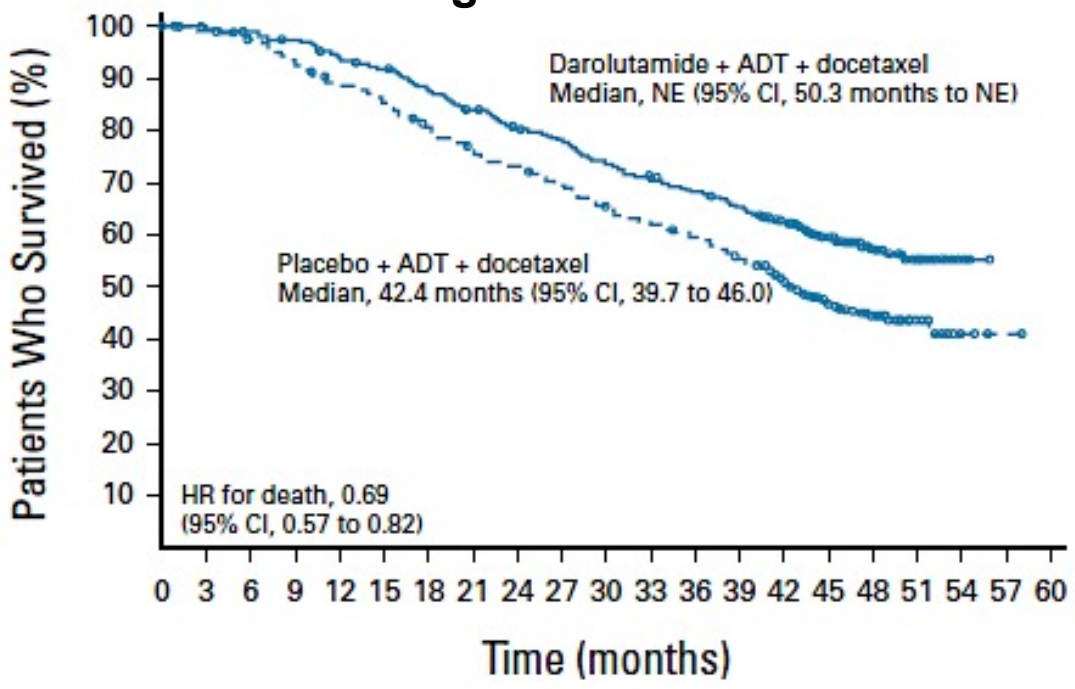
mHSPC Algorithm 2025



McManus and Armstrong, JCO 2023

ARASENS by Volume

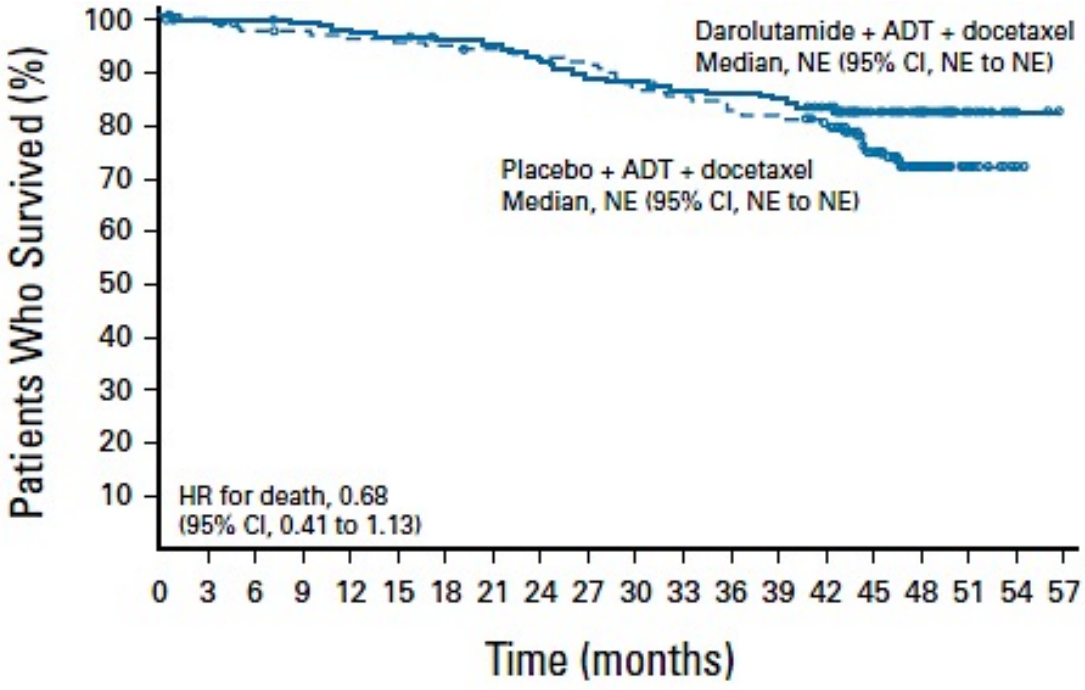
High-volume disease



No. of high-volume patients at risk:

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

Low-volume disease

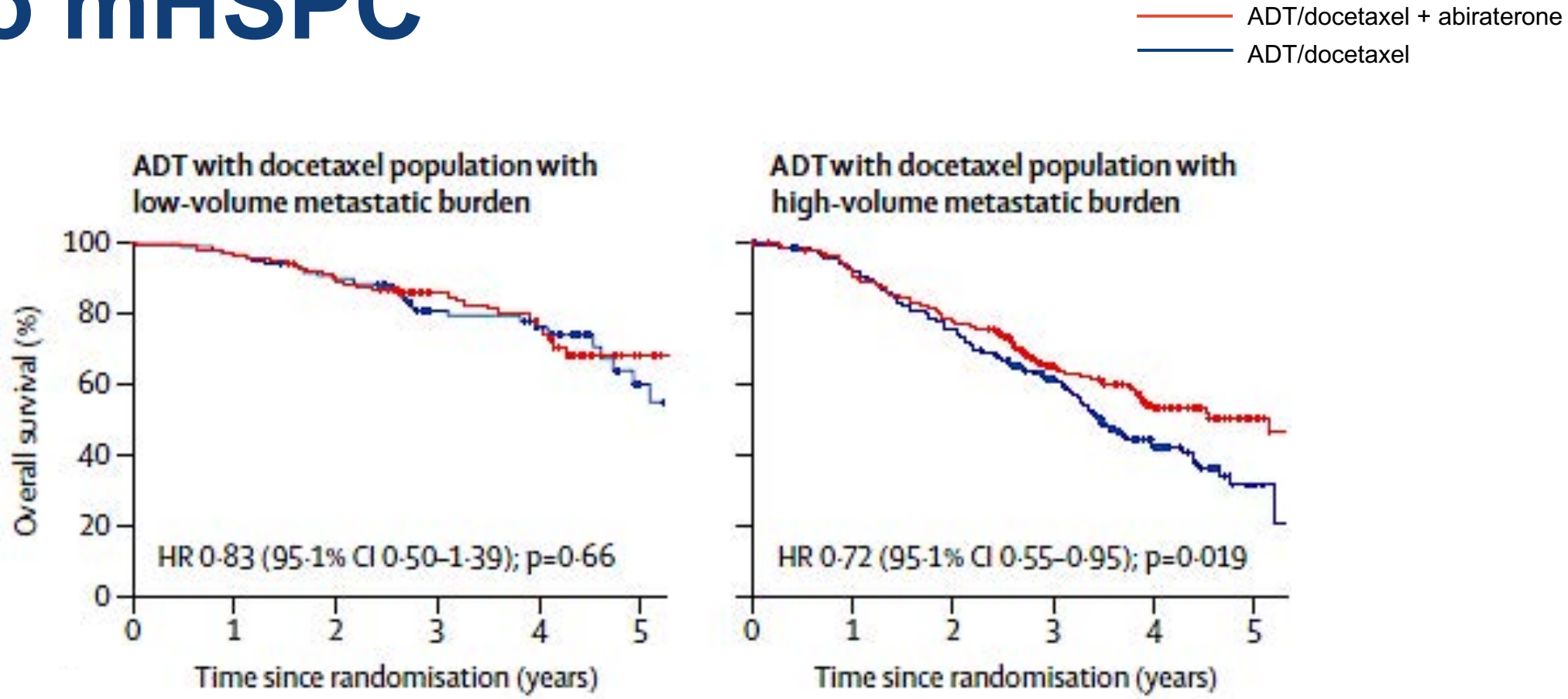


No. of low-volume patients at risk:

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

Hussain et al JCO 2023

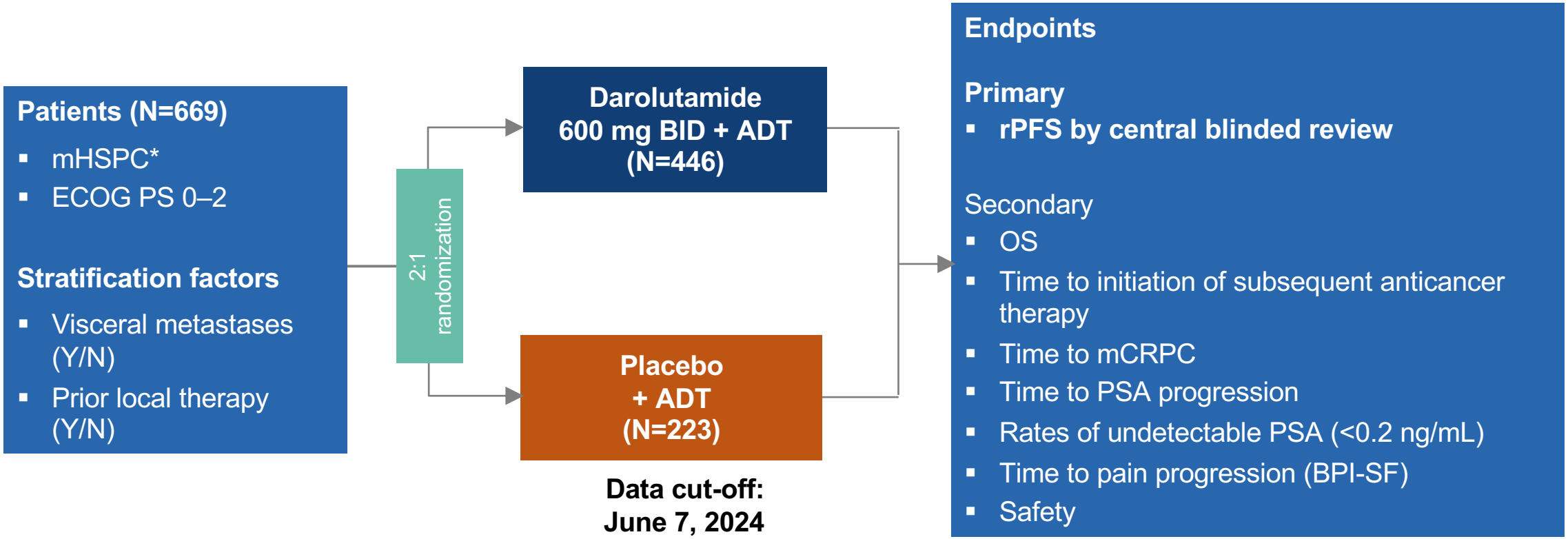
Triplet Therapy: High Volume De Novo mHSPC



Fizazi K et al Lancet 2023

ARANOTE Study Design

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



ClinicalTrials.gov: NCT04736199

*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.
BPI-SF, Brief Pain Inventory-Short Form.

Saad F et al. ESMO 2024; Abstract LBA68

ARANOTE: Study Design Darolutamide + ADT in mHSPC

KEY INCLUSION CRITERIA

- Histologically confirmed mHSPC (by central review)
- Started ADT w/in 12 weeks
- ECOG 0-2

N=669 R 2:1

Darolutamide 600 mg BID PO + ADT

Placebo + ADT

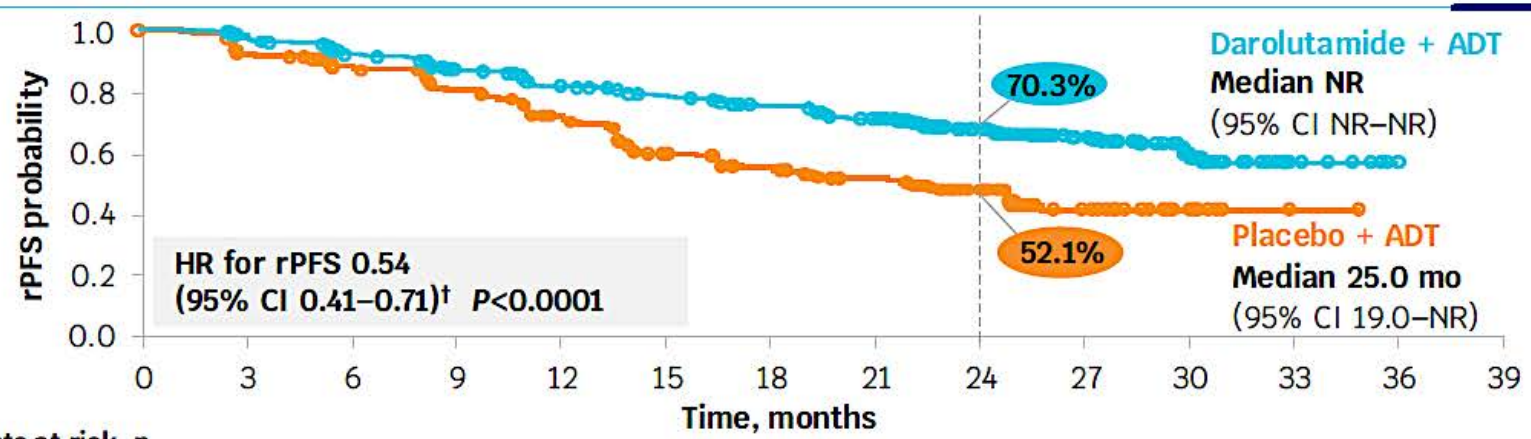
Stratification:

- Presence of visceral metastases assessed by central review
- Prior local therapy versus no local therapy

Primary endpoint: rPFS

Key Secondary Endpoint: OS

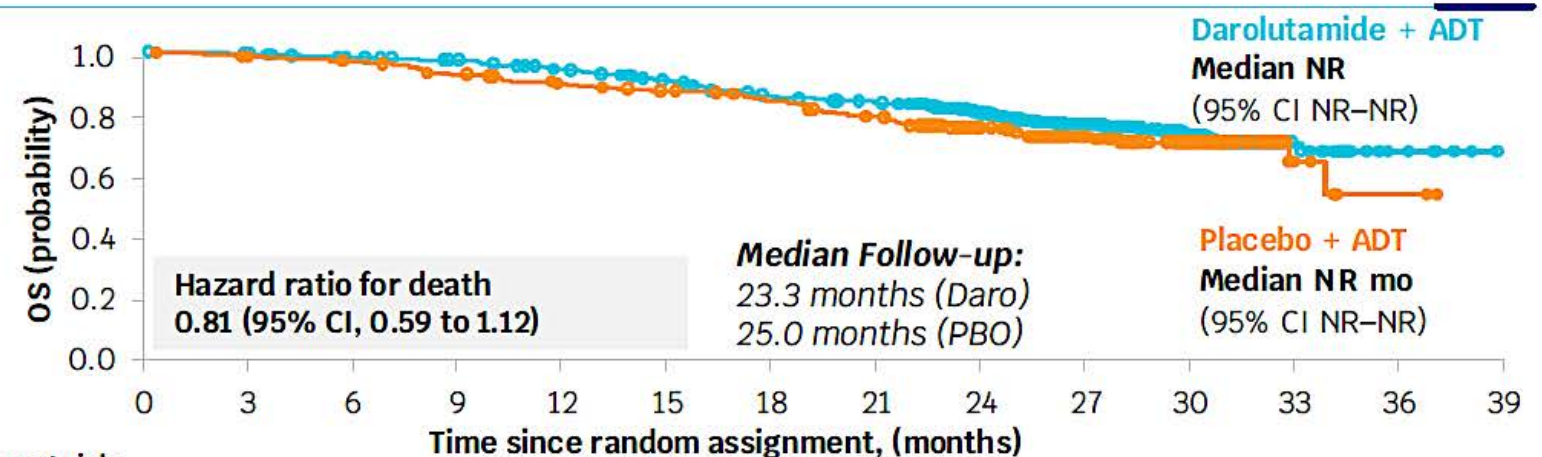
rPFS



Patients at risk, n

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

OS



Number at risk:

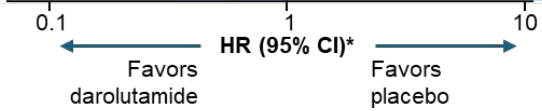
Darolutamide	446	440	429	417	399	374	346	332	269	169	91	26	7	0
Placebo	223	217	213	200	188	180	170	156	127	85	41	8	2	0

Saad F, et al. JCO 2024.

ARANOTE rPFS: Subgroup Analyses

Consistent benefit of darolutamide across all subgroups

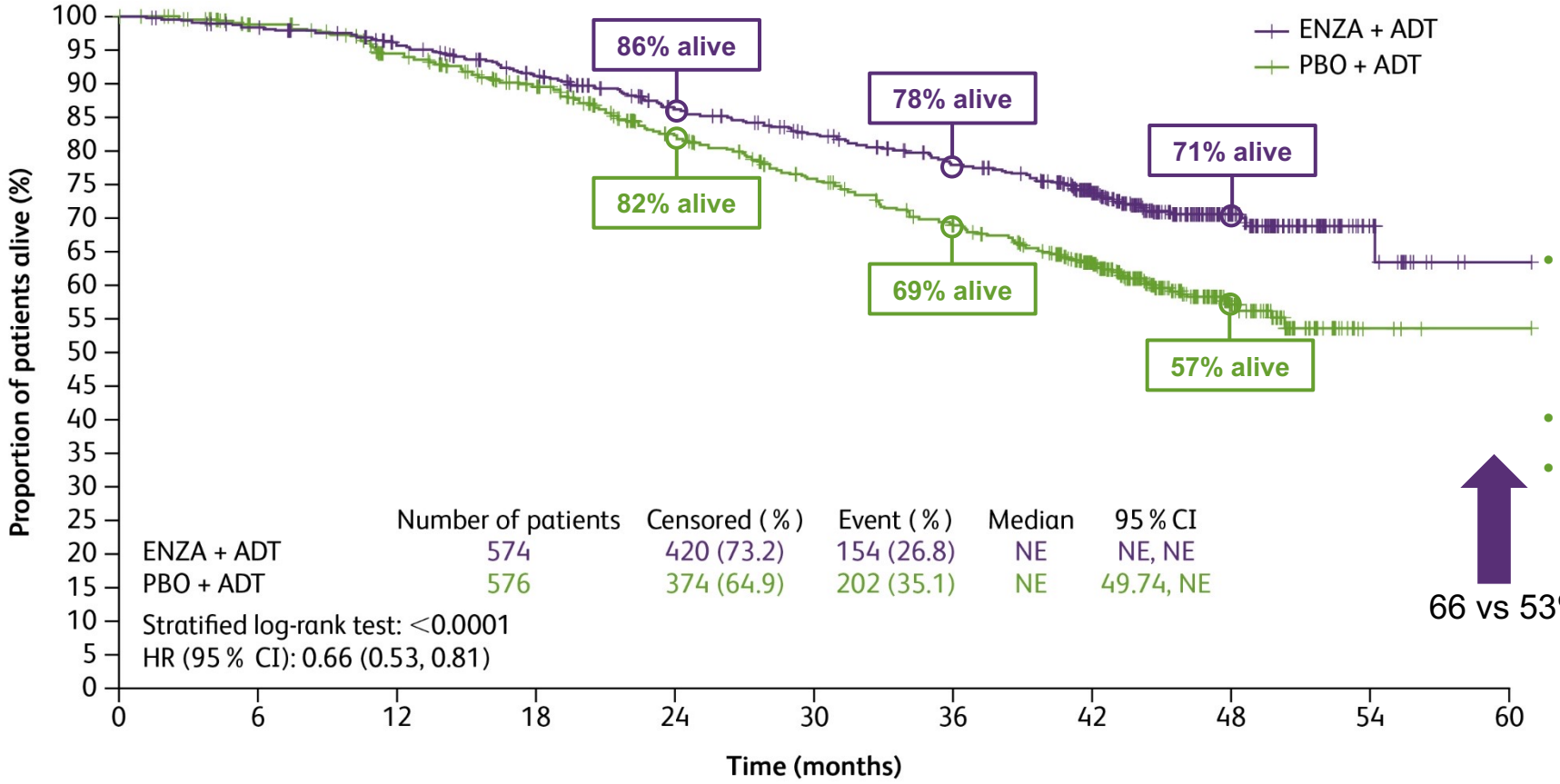
rPFS		Darolutamide (n=446) Events/Patients, n/N	Darolutamide (n=446) Median, months	Placebo (n=223) Events/Patients, n/N	Placebo (n=223) Median, months	HR (95% CI)*
Overall population		128/446	NR	94/223	25.0	0.54 (0.41–0.71)
Age subgroups, years	<65	37/118	NR	32/65	14.2	0.44 (0.27–0.71)
	65–74	53/193	NR	35/96	NR	0.64 (0.41–0.98)
	75–84	29/117	NR	22/52	NR	0.48 (0.27–0.83)
	≥85	9/18	27.4	5/10	19.2	0.51 (0.16–1.66)
Baseline PSA values	< median	58/216	NR	44/111	26.0	0.55 (0.37–0.81)
	≥ median	67/220	NR	47/108	22.9	0.55 (0.38–0.80)
ECOG PS at baseline	0	61/235	NR	37/98	NR	0.55 (0.37–0.83)
	≥1	67/211	NR	57/125	22.6	0.56 (0.39–0.79)
Gleason score at initial diagnosis	Missing/not assessed	5/13	NR	4/10	13.8	
	<8	32/122	NR	30/67	22.9	0.46 (0.28–0.75)
	≥8	91/311	NR	60/146	25.1	0.58 (0.42–0.81)
Disease volume	High volume	113/315	30.2	75/157	19.2	0.60 (0.44–0.80)
	Low volume	15/131	NR	19/66	NR	0.30 (0.15–0.60)
Race	White	76/251	NR	55/125	22.2	0.52 (0.36–0.73)
	Asian	38/144	NR	24/65	25.0	0.59 (0.35–0.98)
	Black	10/41	NR	10/24	NR	0.51 (0.21–1.23)
	Other	4/10	NR	5/9	13.7	
Geographic region	Europe and RoW	56/186	NR	39/88	22.6	0.50 (0.33–0.75)
	Asia	37/141	NR	23/63	25.0	0.60 (0.35–1.01)
	Latin America	35/119	NR	32/72	25.1	0.56 (0.35–0.90)
Visceral metastases	Yes	21/53	NR	13/27	25.0	0.71 (0.35–1.41)
	No	107/393	NR	81/196	25.0	0.52 (0.39–0.69)
Prior local therapy	Yes	19/80	NR	18/40	19.5	0.34 (0.17–0.66)
	No	109/366	NR	76/183	25.0	0.59 (0.44–0.79)



*HR and 95% CI were calculated from univariate analysis using unstratified Cox regression.

Saad F et al. JCO 2024

Overall survival with Enzalutamide (ARCHES): updated Tuesday!



- **As of May 28, 2021: 356 deaths (enzalutamide plus ADT, 154; placebo plus ADT, 202) were observed**
- **Median follow-up time: 44.6 mo**
- **Median treatment duration:**
  - **Enzalutamide plus ADT: 40.2 mo**
  - **Placebo plus ADT: 13.8 mo**
  - **Placebo plus ADT crossover: 23.9 mo**

Patients at risk

ENZA + ADT	574	559	535	498	457	427	396	316	120	17	1
PBO + ADT	576	548	511	468	404	363	322	232	80	4	1

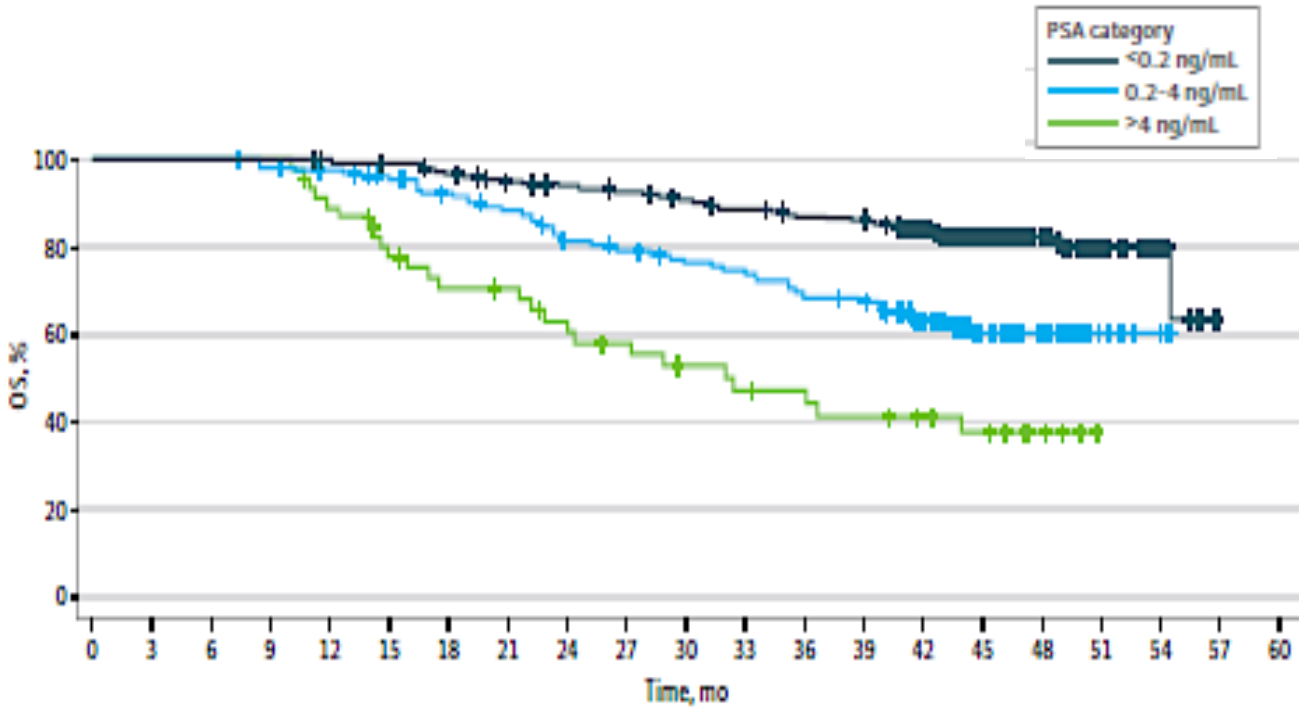
Armstrong AJ et al JCO 2022 and ASCO 2025

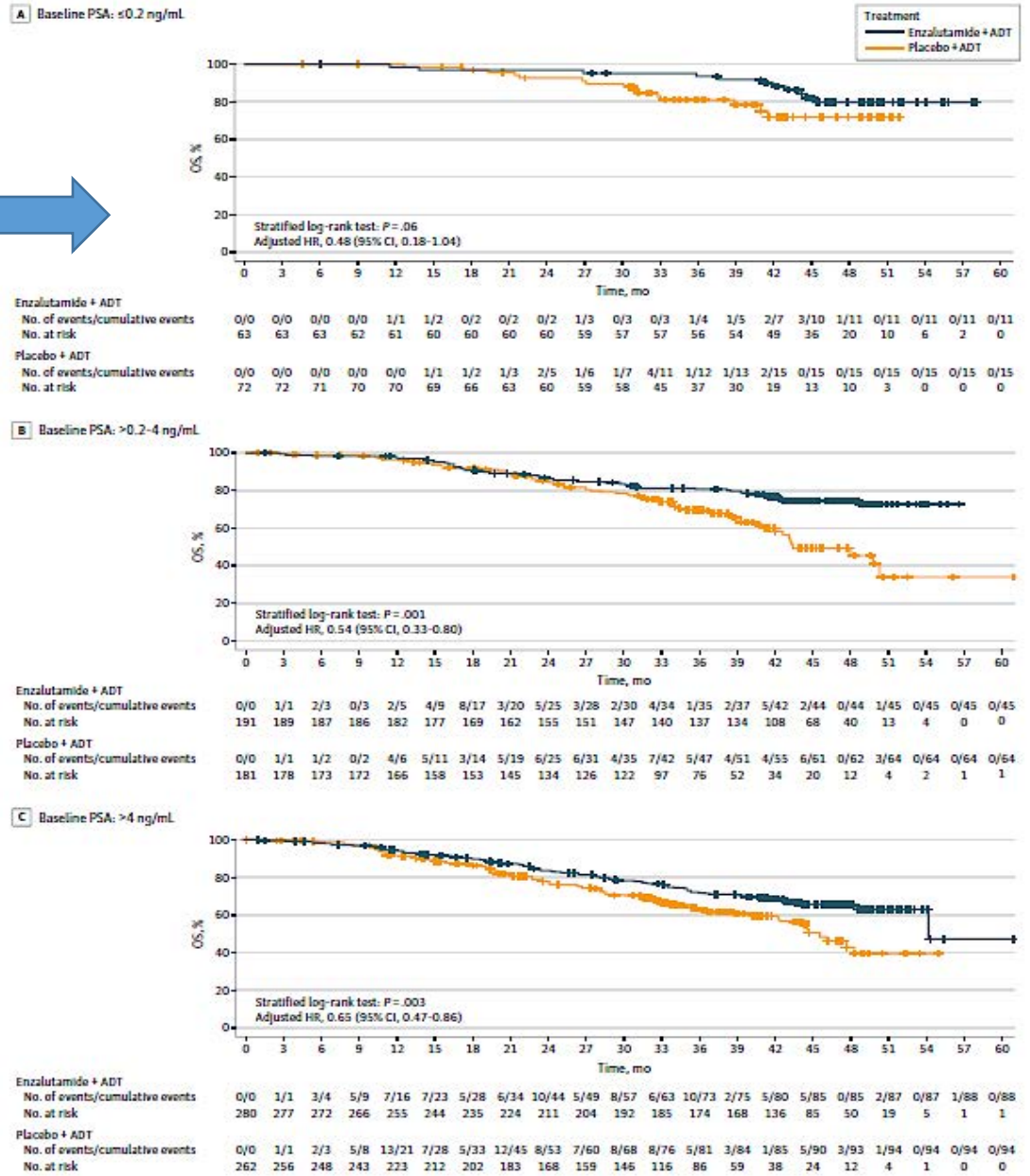
ADT=androgen deprivation therapy; CI=confidence interval; ENZA=enzalutamide; HR=hazard ratio; ITT=intent-to-treat; NE=not evaluable; PBO=placebo.

- **Enzalutamide plus ADT significantly improved overall survival by 34% vs placebo plus ADT**

Pre-treatment PSA and Long Term Survival with Doublet Therapy

Post-treatment PSA nadir and Long Term Survival with Doublet Therapy





Armstrong AJ et al JAMA Netw Open 2025

TITAN: Apalutamide in mHSPC

KEY ELIGIBILITY CRITERIA

- Castration sensitive
- Distant metastatic disease by >1 lesion on bone scan mHSPC
- ECOG PS 0 or 1

N = 1,052 **R**

Apalutamide 240mg QD + ADT

Placebo + ADT

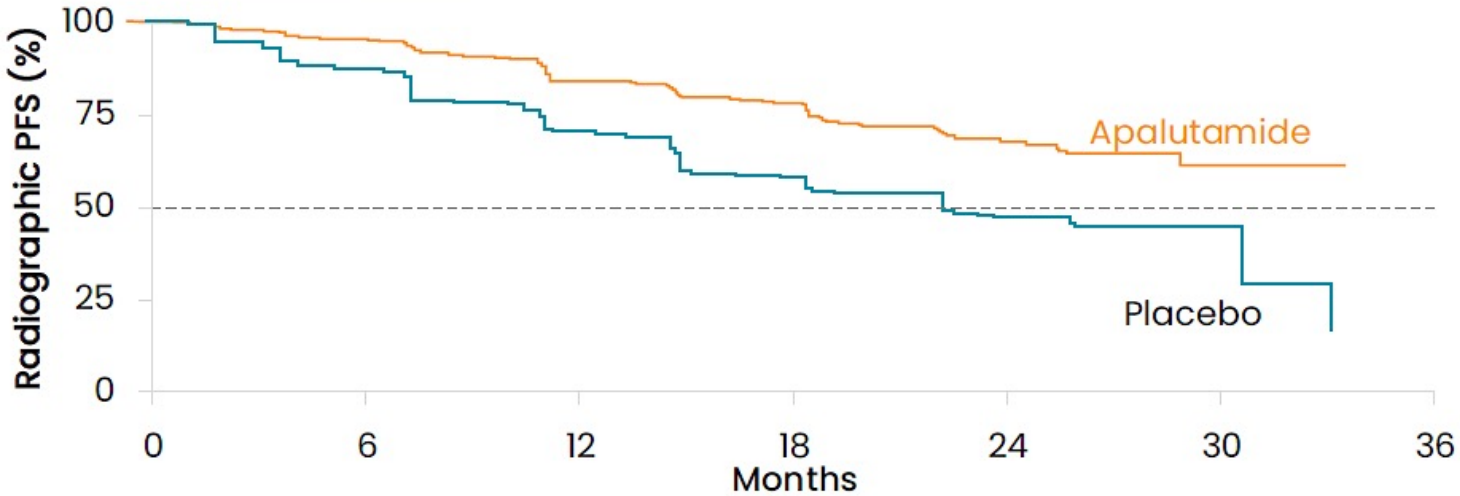
STRATIFICATION FACTORS

- Gleason score at baseline
- Region (NA and EU vs others)
- Prior docetaxel (yes or no)

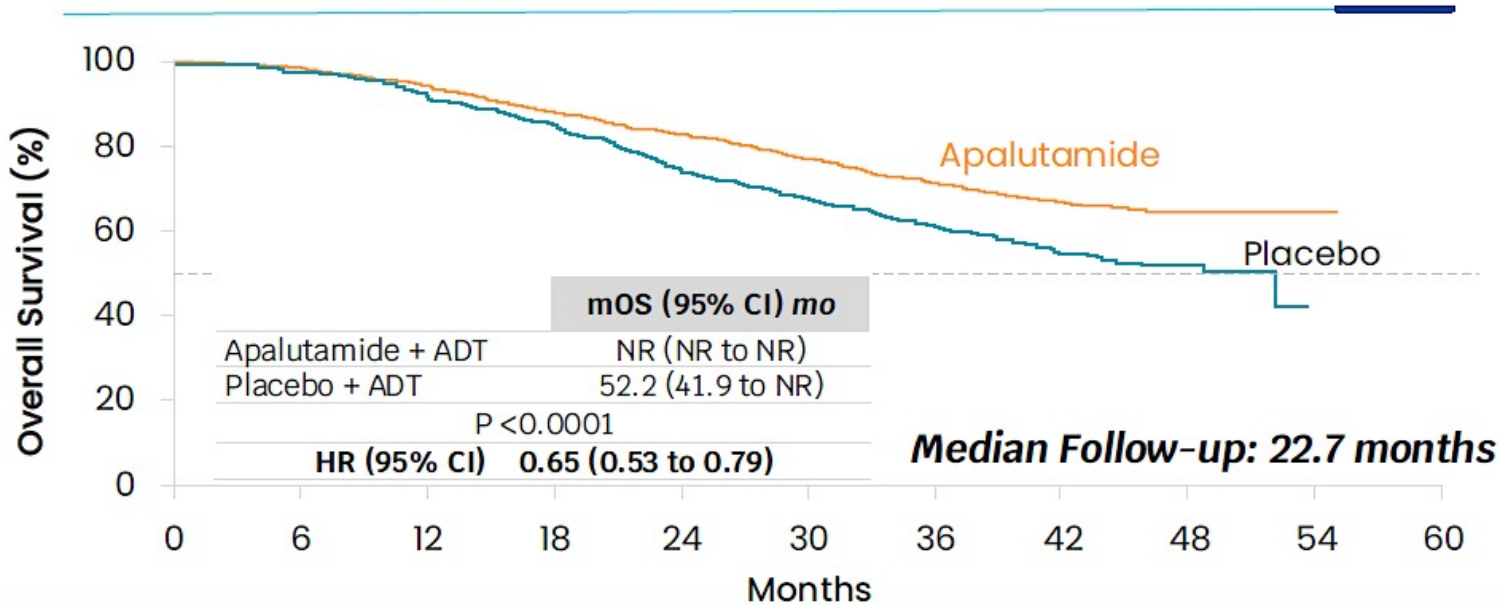
Primary endpoints:

- rPFS and OS

rPFS: Reduced risk of rPFS or death by 52%



OS: Reduced risk of death by 35%



Chi et al. JCO 2021.

Assessing risk: PSA decline

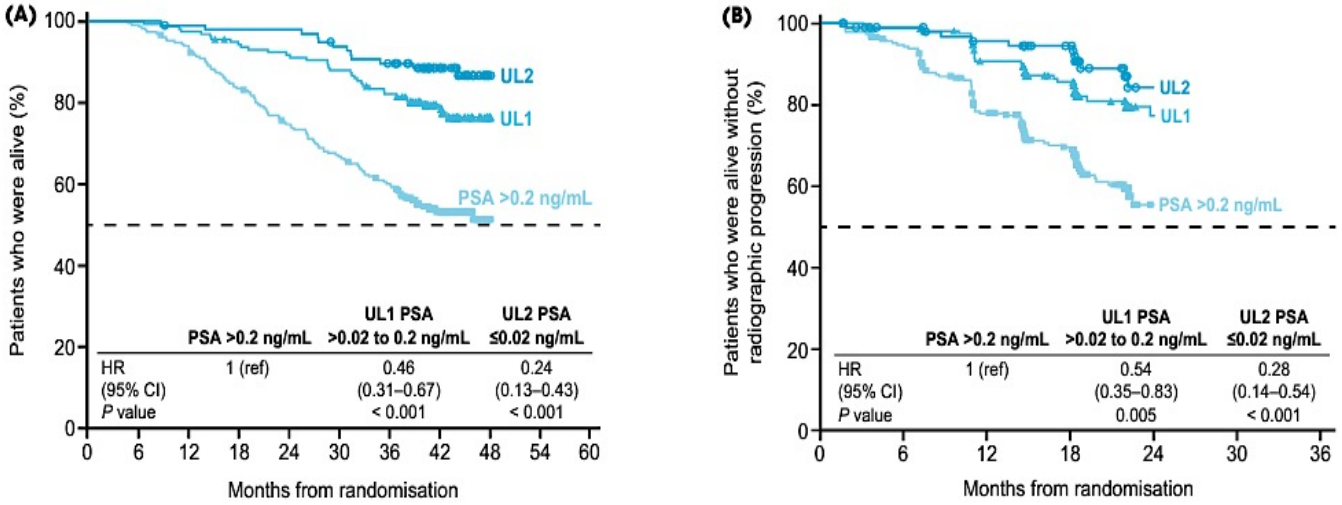
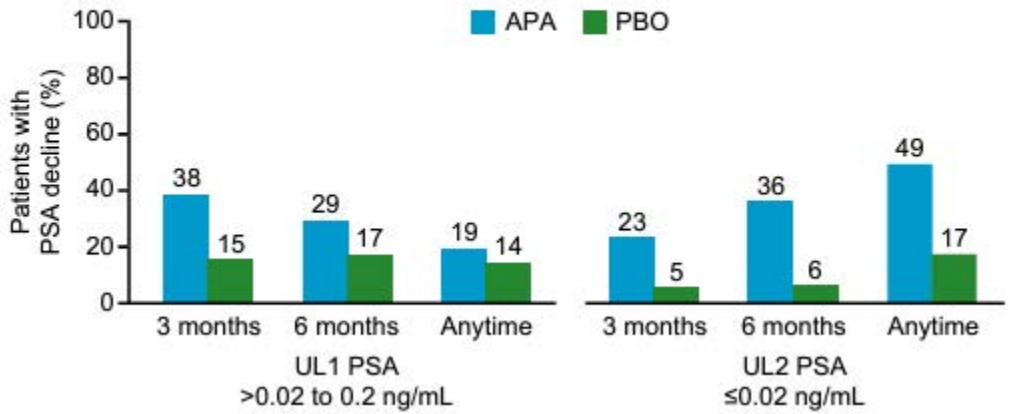
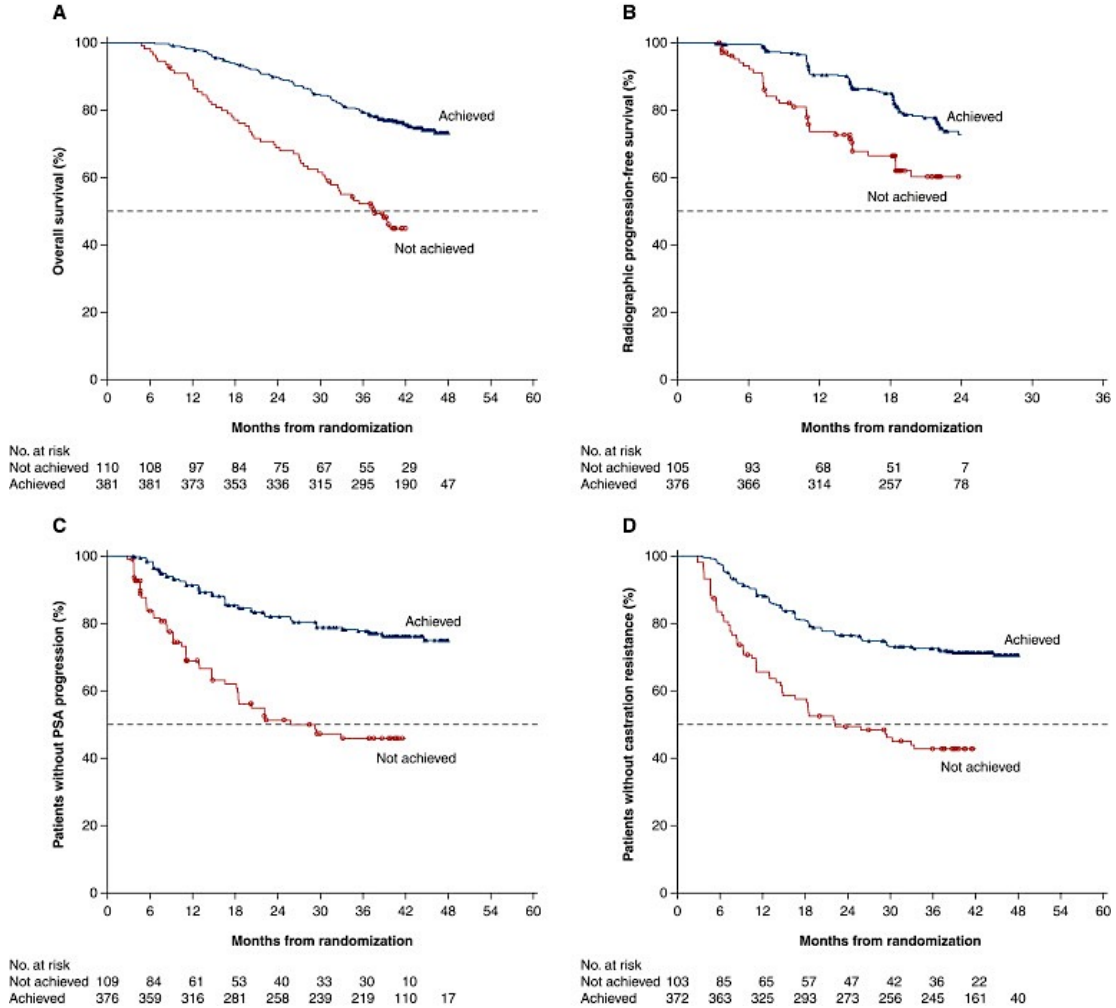


Fig. 1 The PSA decline to UL1 (>0.02 to 0.2 ng/mL) and UL2 (≤0.02 ng/mL) levels over time. APA, apalutamide; PBO, placebo.





TITAN (apalutamide)
Deep PSA decline (>90% decline or <0.2ng/mL) at 3 months

Merseburger AS et al BJUI Int 2024
Chowdhury S et al Ann Oncol 2023

Abiraterone vs. Enzalutamide vs. Apalutamide vs Darolutamide

Abiraterone acetate

- Requires prednisone
- Mineralocorticoid excess
- Liver and electrolyte monitoring required
- BP monitoring required
- Some CV risk (afib, others)
- Bone density monitoring recommended (fracture risk)
- Exercise recommended (fatigue, muscle loss)
- Beneficial in high and low volume/risk patients
- Can be safely given with RT

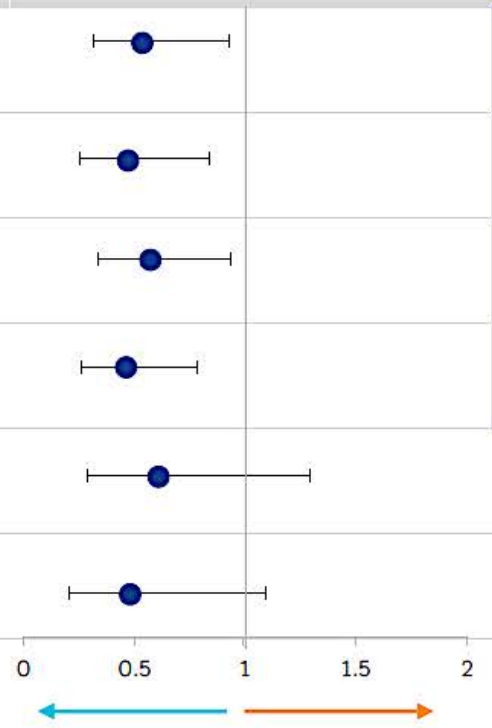
Enzalutamide, Apalutamide, Darolutamide

- No prednisone requirement
- No mineralocorticoid excess
- No liver/electrolyte monitoring required
- BP monitoring required
- Fatigue, fracture risk
- Bone density monitoring recommended (fracture risk)
- Exercise recommended (fatigue, muscle loss)
- Minimal seizure risk <1%, but careful in patients with h/o seizures, strokes
- Apalutamide rash in ~30% can be significant (not enzalutamide)
- Beneficial in high and low volume/risk patients
- Can be safely given with RT

Indirect Comparison: Enza + ADT vs Daro + ADT

Indirect treatment comparison of ENZA + ADT versus DARO + ADT

Outcome	Population	ESS	Matching-adjusted estimates, forest plot	Matching-adjusted estimates, HR (95% CI); *P*-value	Unadjusted Bucher estimate, HR (95% CI); *P*-value
rPFS	Total population	319		**0.54 (0.32 – 0.93); 0.03**	0.72 (0.50 – 1.05); 0.09
	DOC-naïve population	263		**0.47 (0.26 – 0.84); 0.01**	0.69 (0.49 – 1.01); 0.06
Time to castration resistance	Total population	319		**0.57 (0.34 – 0.94); 0.03**	0.70 (0.50 – 0.98); 0.04
	DOC-naïve population	263		**0.46 (0.27 – 0.79); 0.01**	0.63 (0.44 – 0.90); 0.01
Time to PSA progression	Total population	319		0.61 (0.29 – 1.30); 0.20	0.61 (0.39 – 0.96); 0.03
	DOC-naïve population	263		0.48 (0.21 – 1.10); 0.08	0.58 (0.37 – 0.91); 0.02



Azad et al. EAU 2025.

STOPCAP: Assessing benefit of ARPIs across large trials in mHSPC

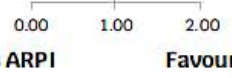
Trials

1. LATITUDE: M1, ADT +/- abiraterone
2. SWOT S1216: M1, ADT +/- TAK700 (orteronel)
3. ENZAMET: M1, ADT + bicalutamide vs ADT + enzalutamide
4. STAMPEDE: M1 or N1, arm G (abi)
5. STAMPEDE: M1 or N1, arm J (abi + enza)
6. TITAN: Apalutamide
7. PEACE-1: Abi, doce, RT

Majority of patients benefit (PFS and OS), impact less in oldest population. No clear difference by class of agent.

PFS in ARPI trials

Age Group	Control n /N	ARPI N /N	Haz.ratio (95% CI)
< 65	872 / 1124	627 / 1092	0.47 (0.43, 0.53)
65 to <75	1129 / 1502	805 / 1490	0.50 (0.45, 0.54)
75+	451 / 610	381 / 649	0.63 (0.54, 0.72)

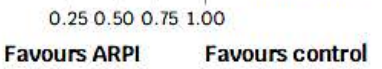


PFS in abiraterone trials

Age Group	Control n /N	ARPI N /N	Haz.ratio (95% CI)
< 65	533 / 647	394 / 626	0.49 (0.43, 0.56)
65 to <75	617 / 764	464 / 770	0.51 (0.45, 0.58)
75+	222 / 282	209 / 285	0.80 (0.66, 0.98)

OS across all trials

Class of agent and Study	ARPI n / N	Control n /N	Haz.ratio (95% CI)	% Weight
Abiraterone trials				
STAMPEDE	293 / 501	371 / 502	0.61 (0.52, 0.71)	19.97
LATITUDE	275 / 597	343 / 602	0.66 (0.56, 0.78)	18.76
PEACE-1, no RT	149 / 292	177 / 296	0.86 (0.69, 1.08)	9.74
PEACE-1, RT	138 / 291	175 / 293	0.72 (0.57, 0.90)	9.36
Subgroup	855 / 1681	1066 / 1693	0.68 (0.62, 0.75)	57.83
(Cochran Q = 6.66 on 3 d.f., p = 0.083)				
Other ARPI trials				
ENZAMET	208 / 563	268 / 562	0.67 (0.56, 0.81)	14.49
TITAN	170 / 525	235 / 527	0.59 (0.49, 0.73)	12.03
Subgroup	378 / 1088	503 / 1089	0.64 (0.56, 0.73)	26.51
(Cochran Q = 0.80 on 1 d.f., p = 0.37)				
Abiraterone + Other ARPI				
STAMPEDE	228 / 462	292 / 454	0.64 (0.54, 0.77)	15.66
Overall	**1461 / 3231**	**1861 / 3236**	**0.66 (0.62, 0.71)**	100.00
(Cochran Q = 8.33 on 6 d.f., p = 0.22)				



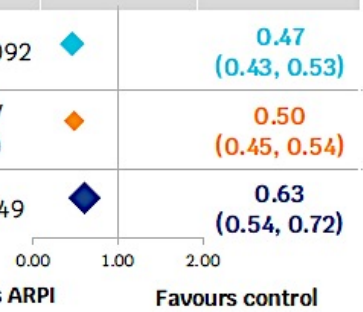
Adapted from Fisher D, et al. ASCO GU 2025

STOPCAP: Assessing benefit of ARPIs across large trials in mHSPC

Effect of ARPIs by Age Group

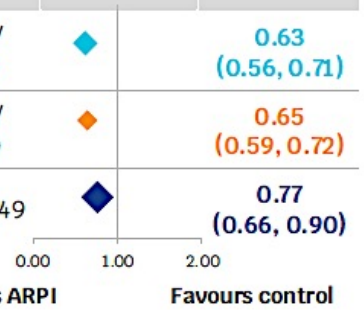
PFS in ARPI trials

Age Group	Control n /N	ARPI N /N	Haz.ratio (95% CI)
< 65	872 / 1124	627 / 1092	0.47 (0.43, 0.53)
65 to <75	1129 / 1502	805 / 1490	0.50 (0.45, 0.54)
75+	451 / 610	381 / 649	0.63 (0.54, 0.72)



OS in ARPI trials

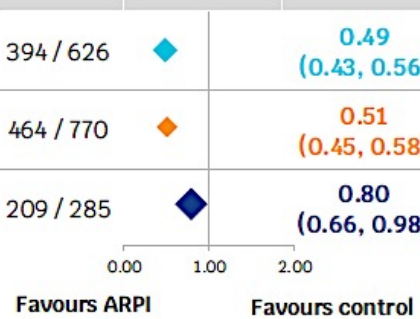
Age Group	Control n /N	ARPI N /N	Haz.ratio (95% CI)
< 65	645 / 1124	480 / 1092	0.63 (0.56, 0.71)
65 to <75	847 / 1502	658 / 1490	0.65 (0.59, 0.72)
75+	369 / 610	323 / 649	0.77 (0.66, 0.90)



Effect of ARPIs by Age Group: Abiraterone Trials

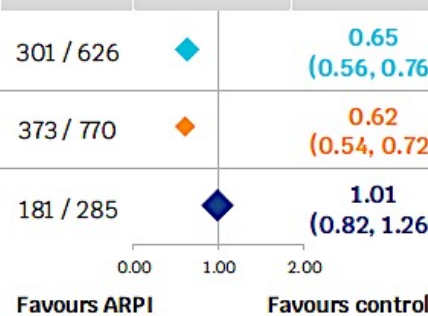
PFS in abiraterone trials

Age Group	Control n /N	ARPI N /N	Haz.ratio (95% CI)
< 65	533 / 647	394 / 626	0.49 (0.43, 0.56)
65 to <75	617 / 764	464 / 770	0.51 (0.45, 0.58)
75+	222 / 282	209 / 285	0.80 (0.66, 0.98)



OS in abiraterone trials

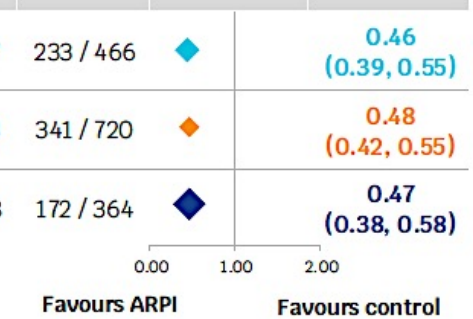
Age Group	Control n /N	ARPI N /N	Haz.ratio (95% CI)
< 65	399 / 647	301 / 626	0.65 (0.56, 0.76)
65 to <75	485 / 764	373 / 770	0.62 (0.54, 0.72)
75+	182 / 282	181 / 285	1.01 (0.82, 1.26)



Effect of ARPIs by Age Group: Amide Trials

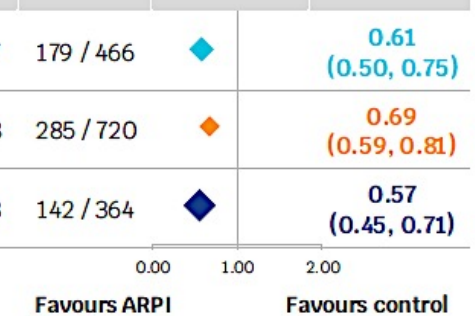
PFS in amide trials

Age Group	Control n /N	ARPI N /N	Haz.ratio (95% CI)
< 65	339 / 477	233 / 466	0.46 (0.39, 0.55)
65 to <75	512 / 738	341 / 720	0.48 (0.42, 0.55)
75+	229 / 328	172 / 364	0.47 (0.38, 0.58)



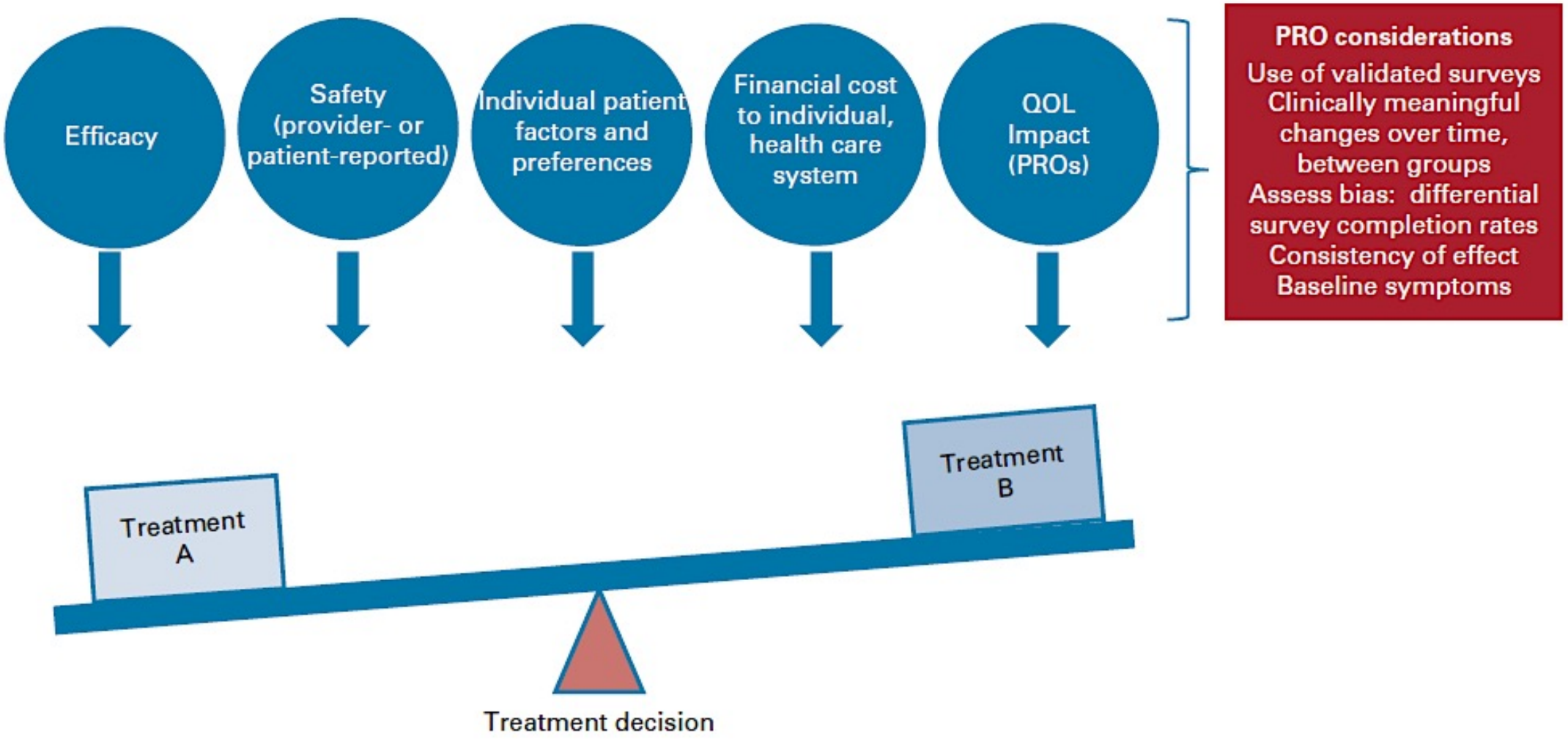
OS in amide trials

Age Group	Control n /N	ARPI N /N	Haz.ratio (95% CI)
< 65	246 / 477	179 / 466	0.61 (0.50, 0.75)
65 to <75	362 / 738	285 / 720	0.69 (0.59, 0.81)
75+	187 / 328	142 / 364	0.57 (0.45, 0.71)



Fisher D, et al. ASCO GU 2025

Making the Decision: mHSPC



Dzimitrowicz HE, Armstrong AJ. J Clin Oncol. 2022; 40:807-810

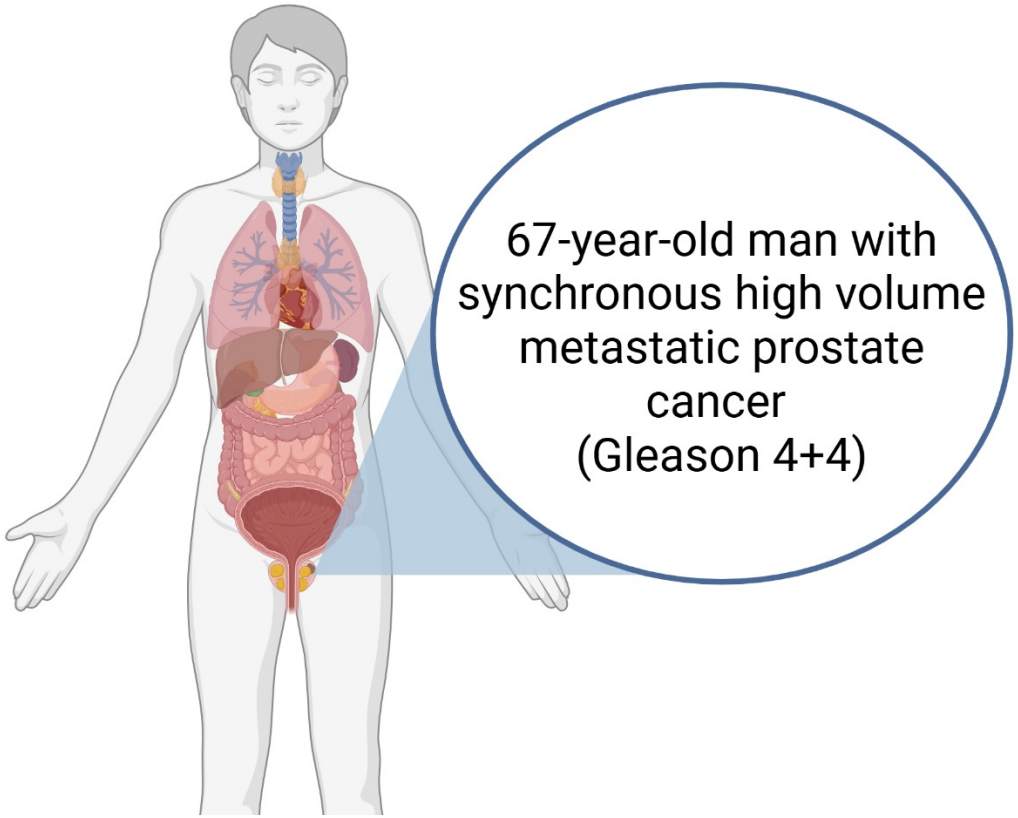
Conclusions

- The standard of care for low volume mHSPC based on conventional imaging is doublet ADT/ARPI (LEVEL 1 EVIDENCE, SURVIVAL BENEFIT)
  - Radiation to the primary for those with synchronous metastases
  - Radiation to metastatic sites may be beneficial but is presently under study!
  - STAMPEDE 2 Treatment Arm S: Stereotactic Ablative Body Radiotherapy (SABR), a type of radiotherapy to up to 5 PSMA PET + sites
  - Emerging/ongoing trials of ARPI/PARPIs (AMPLITUDE, TALAPRO-3, EVOPAR-02), Lu177-PSMA-617 (PSMAddition), AKTi (capivasertib in Capitello-281)
- Many patients would love to have a treatment holiday or to stop therapy altogether if remission is achieved in this setting
  - EMBARK, EXTEND trials establish this proof of concept
  - New trials are needed to test MDT in the setting of brief ADT/ARPI use in this oligomet HSPC setting with the goal of maintaining survival but extending treatment free intervals!

Faculty Case Presentations

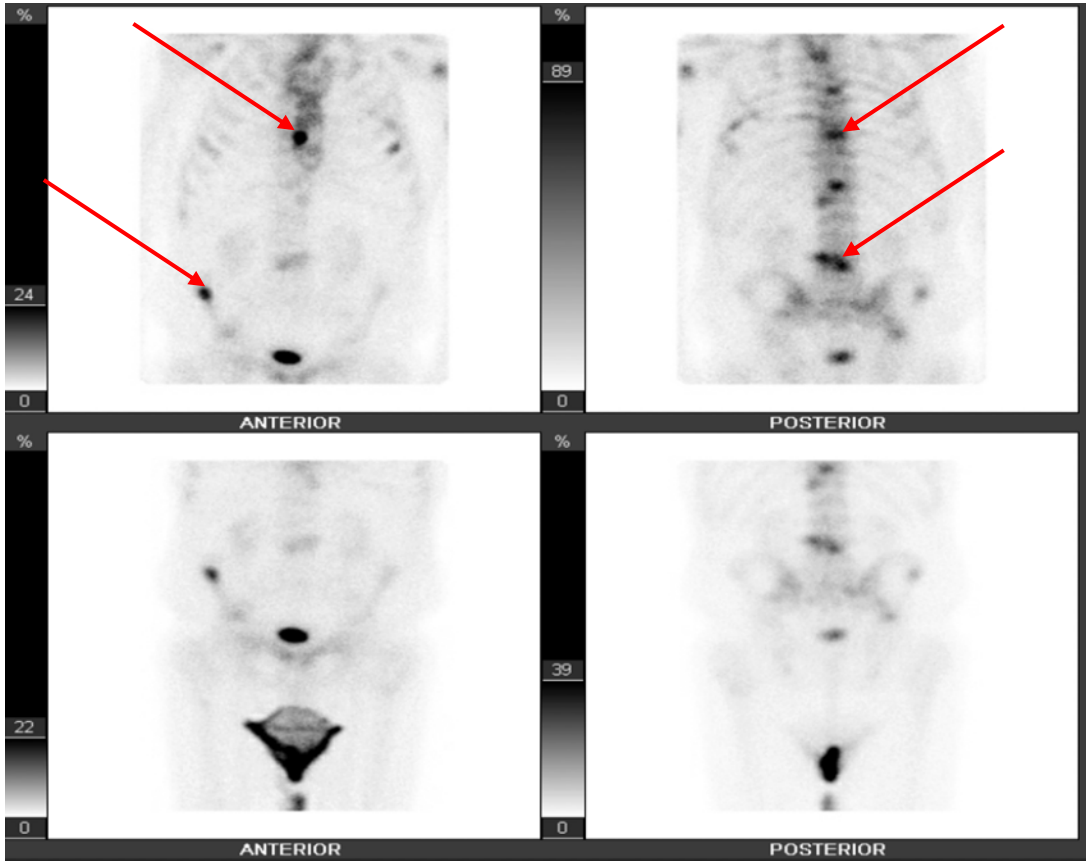
Case Presentation – Dr Agarwal: ADT + Apalutamide in mHSPC

June 2021



67-year-old man with synchronous high volume metastatic prostate cancer (Gleason 4+4)

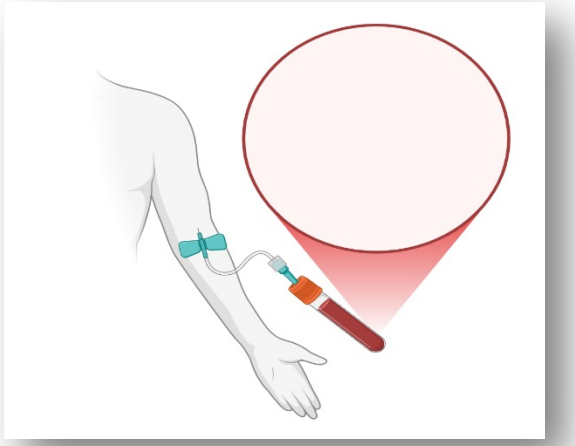
Bone scan showing high-volume disease



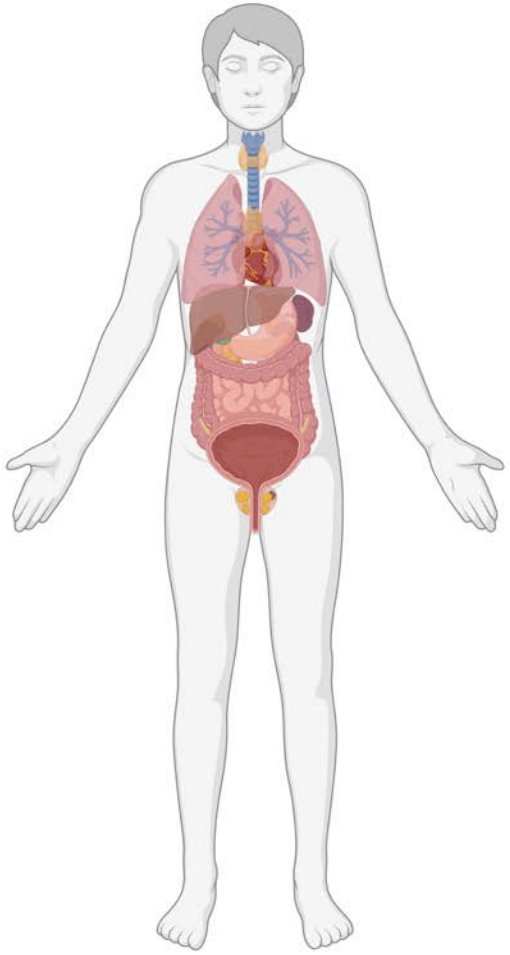
IMPRESSION:

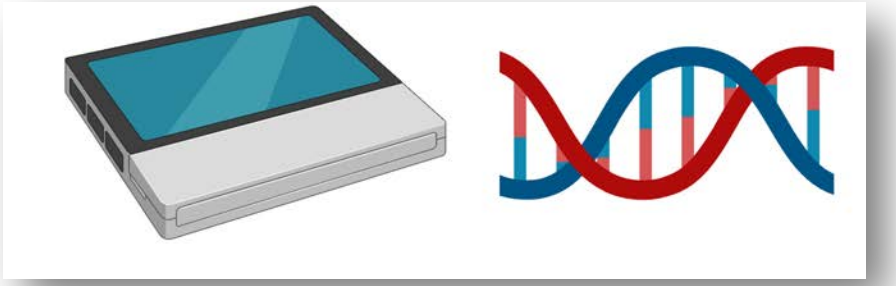
Widespread skeletal metastases throughout the axial and appendicular skeleton with some new foci of uptake in the spine and increased uptake in one focus of the sternum and one focus of the ileum

Case Presentation – Dr Agarwal: ADT + Apalutamide in mHSPC (cont'd)



June 2021
At the time of diagnosis





PSA, TOTAL

Status: **Final result** Dx: **Prostate cancer (HCC)**

Test Result Released: **Yes (seen)**

0 Result Notes

Component	
Ref Range & Units (hover)	
PSA	28.0 ▲

648 gene panel

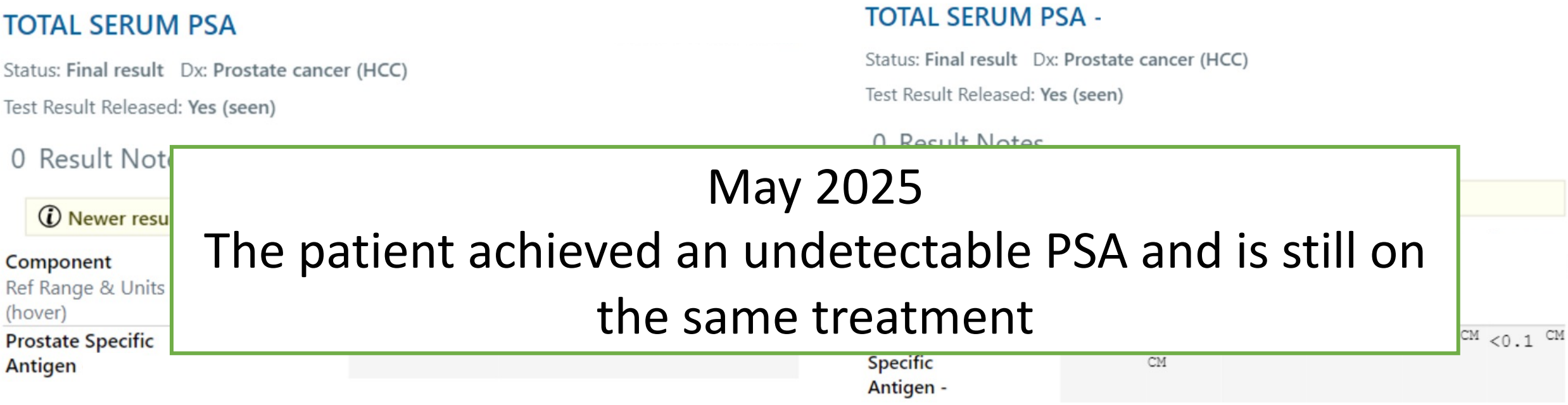
GENOMIC VARIANTS

Biologically Relevant		Variant Allele Fraction
SPOP	p.W131C Missense variant - LOF	25.8%
CDKN1B	p.D108fs Frameshift - LOF	20.0%

Case Presentation – Dr Agarwal: ADT + Apalutamide in mHSPC (cont'd)

July 2021

Patient started on ADT + Apalutamide



May 2025

The patient achieved an undetectable PSA and is still on the same treatment

QUESTIONS FOR THE FACULTY

When combining an AR pathway inhibitor with ADT for a patient with mHSPC, do you have a preference for a specific agent? How do you choose among them for individual patients?

Do recent findings suggesting that abiraterone may yield less benefit than enzalutamide or apalutamide for patients aged 75 years or older diminish your enthusiasm for that strategy in older patients?

Would you ever consider a treatment break (similar to the EMBARK strategy in nmHSPC) for a patient such as this with metastatic disease but an undetectable PSA on therapy?

Case Presentation – Dr Beltran: 55 yo gentleman

- Presented to PCP and had his first screening PSA.
  - PSA 664 ng/dL
- Feels well overall. Reports frequency and 2-3 x nocturia, no back pain, fatigue, wt changes or other symptoms
- Prostate biopsy: Gleason 4+4 prostate adenocarcinoma
- PSMA PET : enlarged pelvic and retroperitoneal lymph nodes and high volume of bone metastases and multiple subcm lung lesions
- Started on degarelix
- He is presenting to discuss additional treatment recommendations
  - His PSA is now 98 ng/mL with testosterone <10 ng/dL
- Otherwise healthy, hx of hypertension controlled on amlodipine and HCTZ

QUESTIONS FOR THE FACULTY

What would you most likely recommend for this patient at this time?

For which types of patients are you prioritizing the combination of ADT/docetaxel/darolutamide over available doublet options? Do you believe all patients with mHSPC who receive cytotoxic therapy should also receive secondary hormonal therapy? Is docetaxel/ADT still an acceptable strategy under any circumstances?

Would you attempt to combine any other secondary hormonal agents (enzalutamide, apalutamide or abiraterone) with docetaxel and ADT for a patient with mHSPC?

Agenda

MODULE 1: Evolving Management of Nonmetastatic Hormone-Sensitive Prostate Cancer (HSPC) — Dr Saad

MODULE 2: Current Treatment for Metastatic HSPC — Dr Armstrong

MODULE 3: Role of PARP Inhibition in Metastatic Castration-Resistant Prostate Cancer (mCRPC) — Dr Agarwal

MODULE 4: Current and Future Use of Radiopharmaceuticals for mCRPC — Dr McKay

MODULE 5: Promising Novel Agents and Strategies Under Investigation for the Management of Prostate Cancer — Dr Beltran

The Role of PARP Inhibition in Metastatic Castration-Resistant Prostate Cancer

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

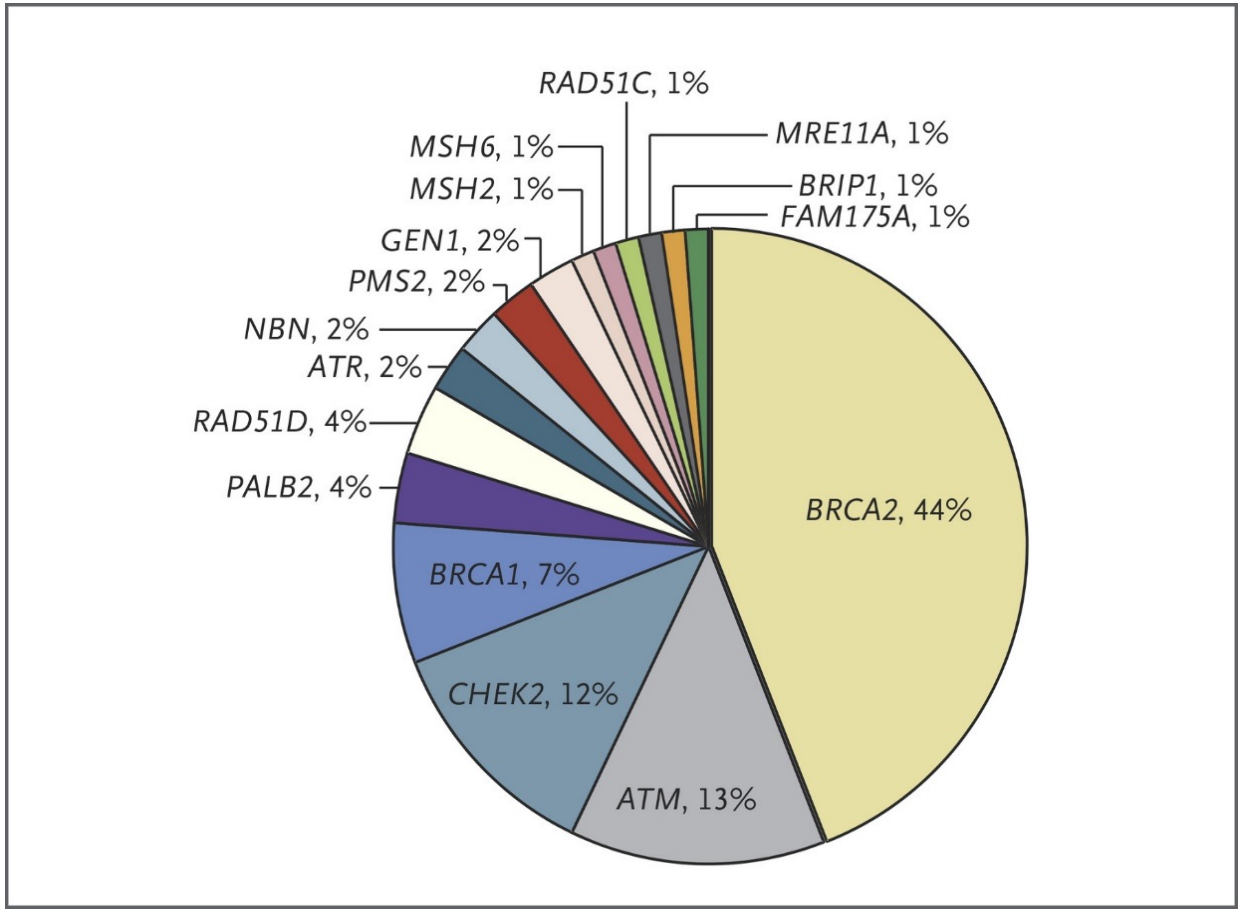
Germline HRR mutations in metastatic prostate cancer

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

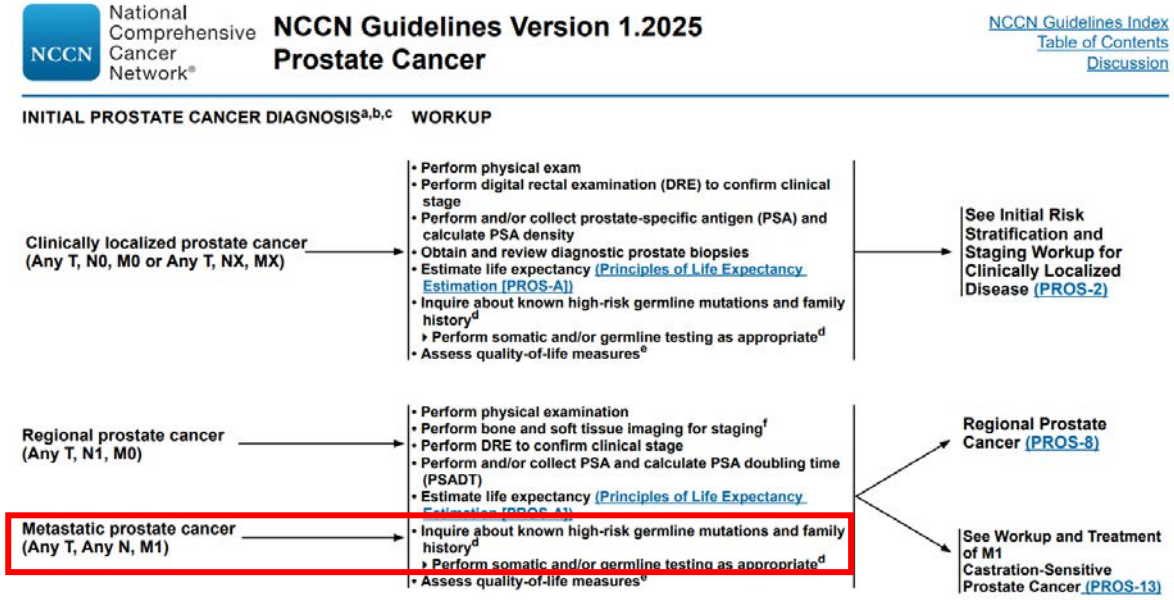
Inherited DNA-Repair Gene Mutations in Men with Metastatic Prostate Cancer

C.C. Pritchard, J. Mateo, M.F. Walsh, N. De Sarkar, W. Abida, H. Beltran, A. Garofalo, R. Gulati, S. Carreira, R. Eeles, O. Elemento, M.A. Rubin, D. Robinson, R. Lonigro, M. Hussain, A. Chinnaiyan, J. Vinson, J. Filipenko, L. Garraway, M.-E. Taplin, S. AlDubayan, G.C. Han, M. Beightol, C. Morrissey, B. Nghiem, H.H. Cheng, B. Montgomery, T. Walsh, S. Casadei, M. Berger, L. Zhang, A. Zehir, J. Vijai, H.I. Scher, C. Sawyers, N. Schultz, P.W. Kantoff, D. Solit, M. Robson, E.M. Van Allen, K. Offit, J. de Bono, and P.S. Nelson



Pritchard et al. NEJM 2016

Indications for and practical implementation of genetic testing



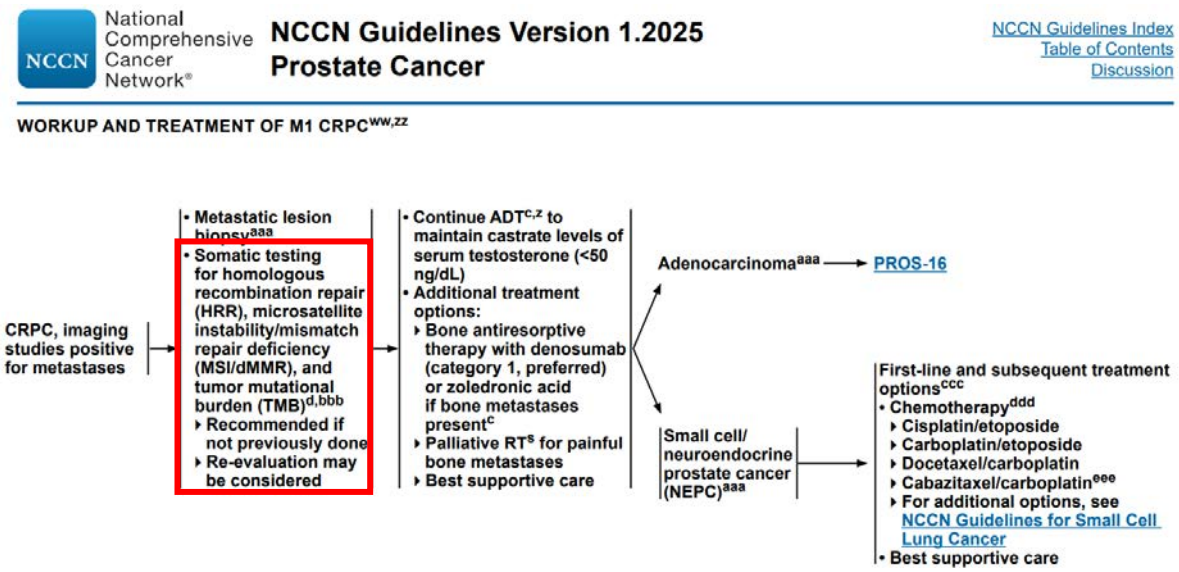


TABLE 1. Summary of All Recommendations

Clinical Question	Recommendation
General note. The following recommendations (strong or conditional/weak) and terminology (see Data Supplement) represent reasonable options for patients depending on clinical circumstances and in the context of individual patient preferences. Recommended care should be accessible to patients whenever possible	
Who should receive germline testing with NGS technologies?	1. All patients with metastatic prostate cancer should undergo germline genetic testing with next-generation sequencing technologies. (Evidence quality: High; Strength of recommendation: Strong)
Who should receive somatic testing with NGS technologies?	2. Those patients with metastatic prostate cancer (both CSPC and CRPC) who are being considered for biomarker-directed systemic treatment should undergo somatic testing with next-generation sequencing technologies. (Evidence quality: High; Strength of recommendation: Strong)
	Practical information for Recommendation 2: While there are no current FDA-approved biomarker-directed treatments following somatic testing for mCSPC, somatic testing may be warranted in the presence of high-volume disease or where there is a high likelihood the patient's disease will progress to CRPC, where the patient is a candidate for future treatment with a biomarker-directed therapy (PARP inhibitor or checkpoint inhibitor).
Who should receive sequential somatic testing with NGS technologies?	3. The panel recommends that sequential somatic testing may be offered when there has been a meaningful change in the patient's status or treatment plan, especially in cases where prior tests were negative or uninformative (eg, insufficient or low tumor content). (Evidence quality: Moderate; Strength of recommendation: Weak)

Yu et al, *JCO*, 2025

The rationale for combining PARPi with ARPI

ARPIs induce a phenotype resembling HRR deficiency

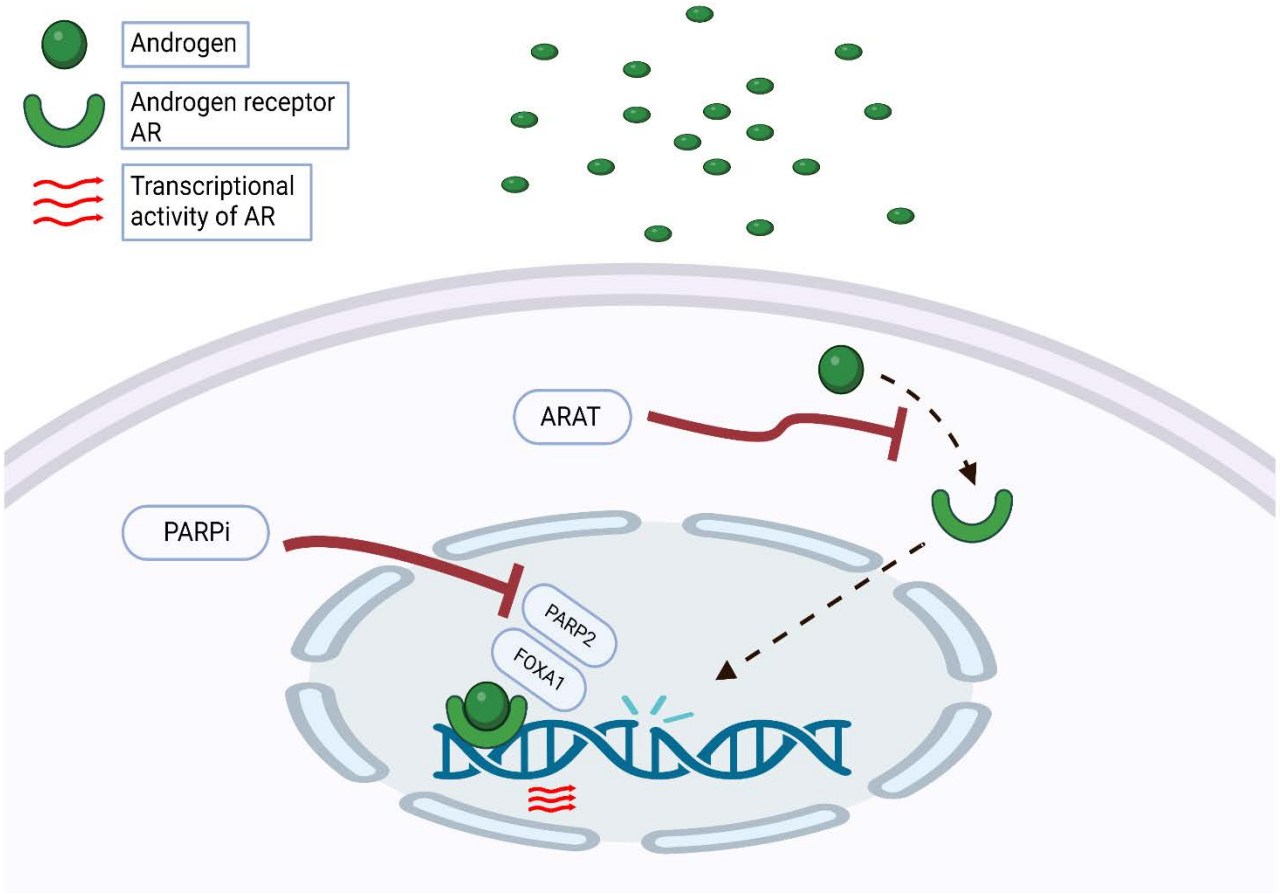
Suppressed AR function causes an upregulation of PARP

ARPIs prime tumor cells for PARP inhibition

PARP augments AR activity

PARP inhibitors may attenuate resistance to ARPIs

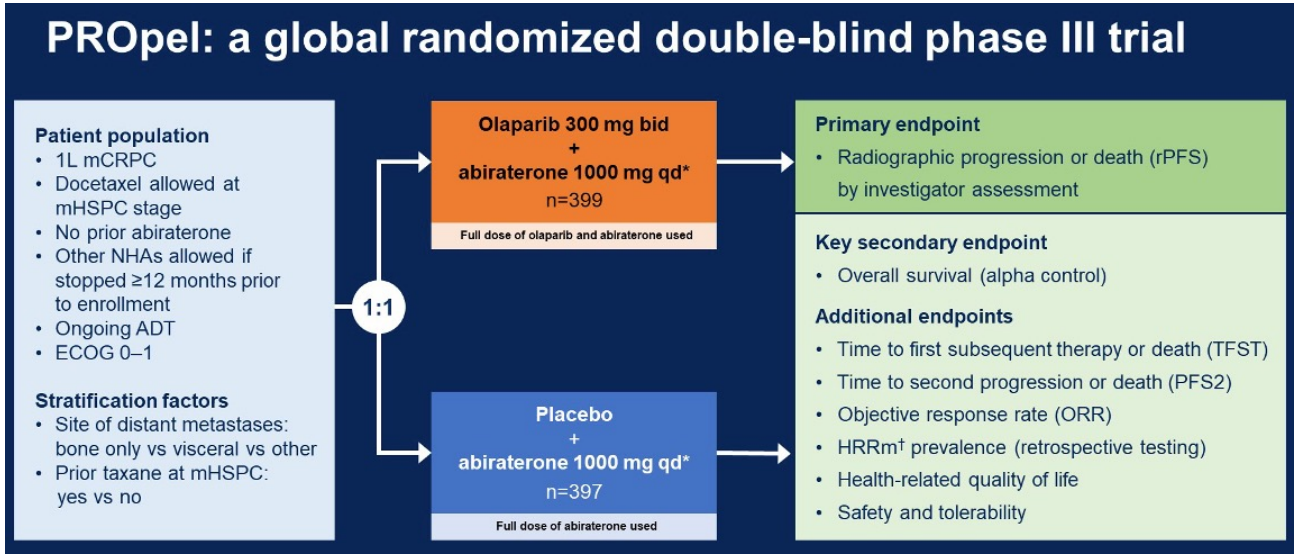
PARP inhibitors extend the benefits of ARPIs



1. Adapted from Bin Gui et al., *PNAS* 2019 June, DOI https://doi.org/10.1073/pnas.1908547116
2. **Agarwal N**, et al European Journal of Cancer, 2023.

Phase 3 PARPi + ARPI Trials Design

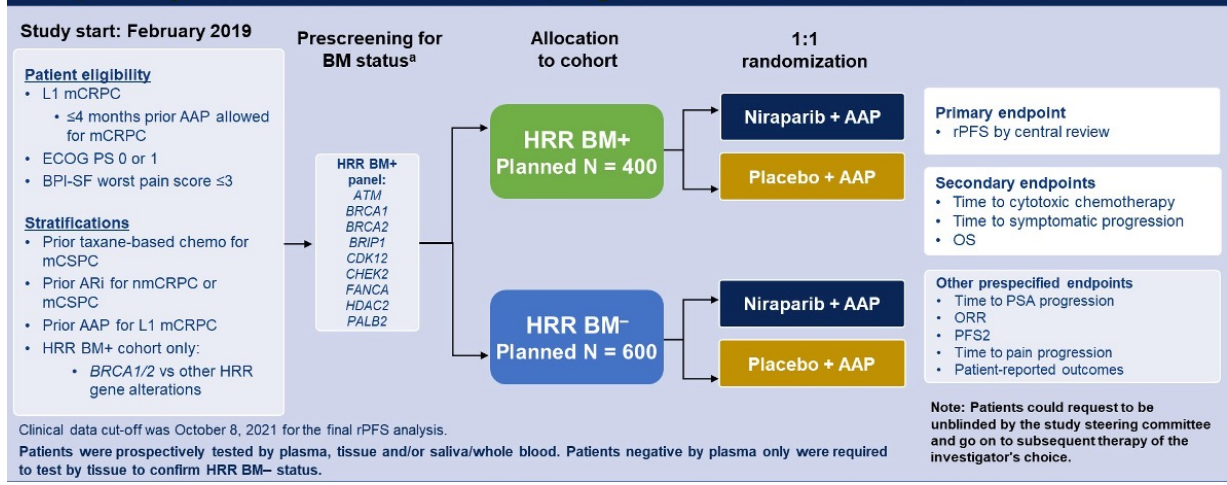
PROpel: a global randomized double-blind phase III trial



Clarke, NW. *et al.* ***NEJM Evidence,*** 2022

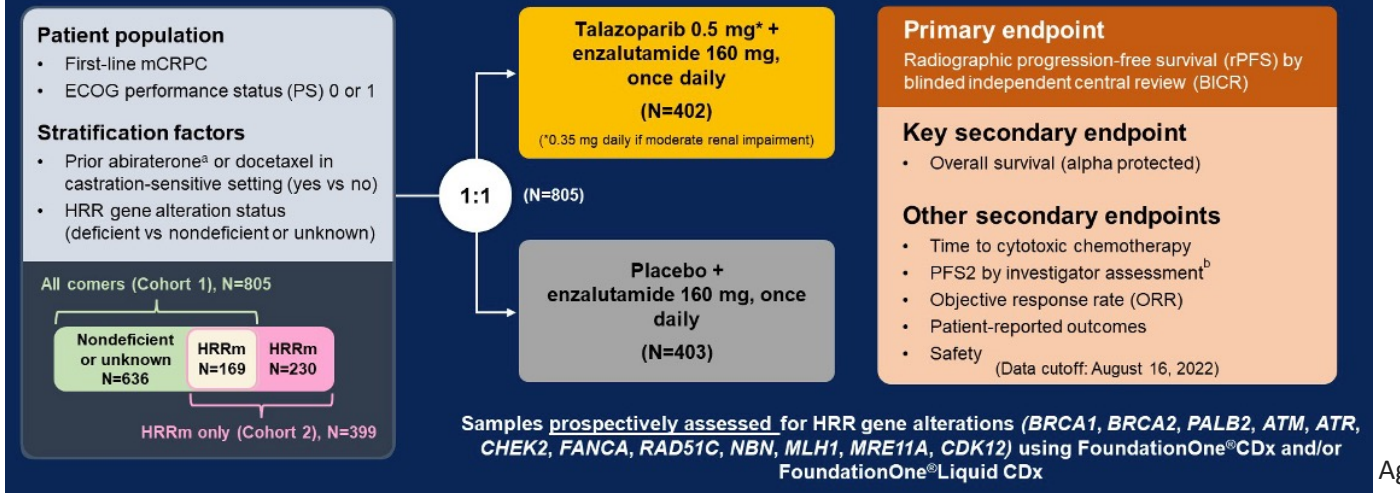
MAGNITUDE: Randomized, Double-Blind, Placebo-Controlled Study

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



Chi, KN. *et al*. ***JCO,*** 2022

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



Agarwal, N. *et al.* ***Lancet,*** 2023.

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

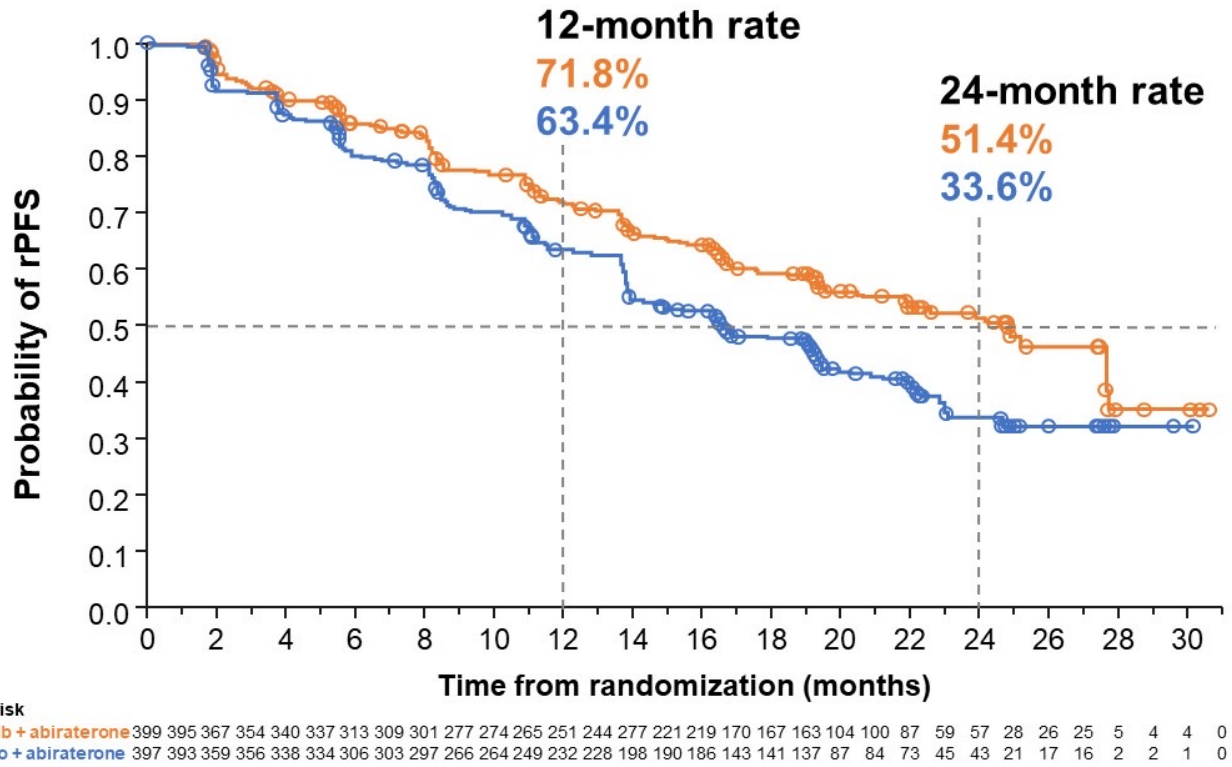
Key secondary endpoint
- Overall survival (alpha control)

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

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	

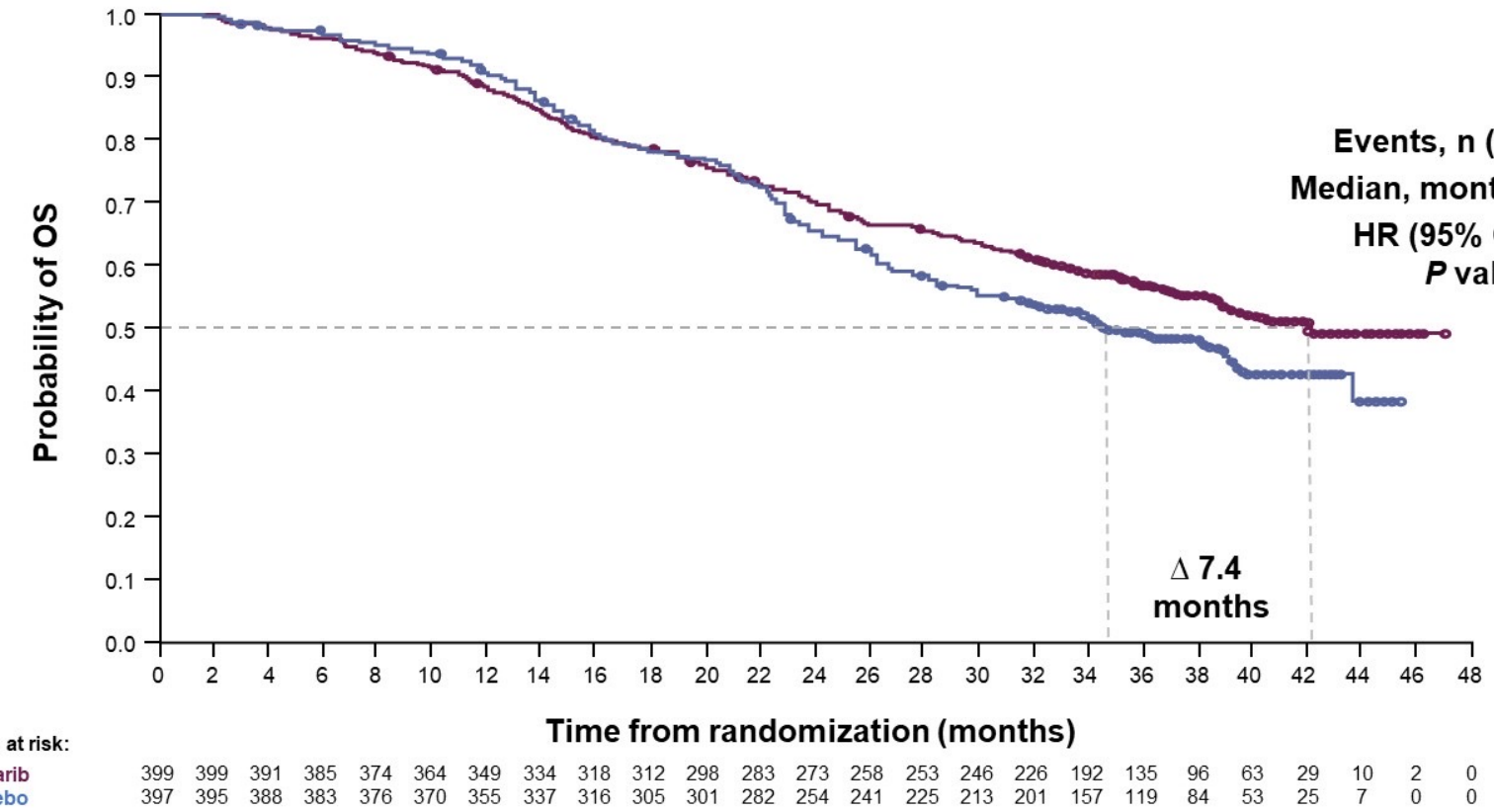
Pre-specified 2-sided alpha: 0.0324

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.

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

In the ITT population, median OS was >7 months longer in the abiraterone + olaparib arm



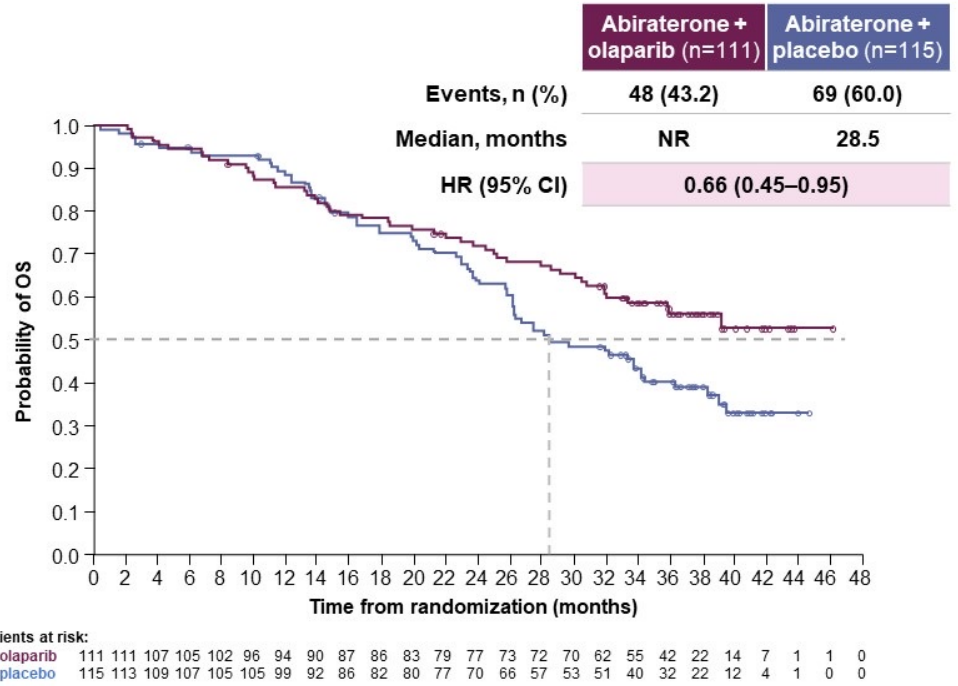
	Abiraterone + olaparib (n=399)	Abiraterone + placebo (n=397)
Events, n (%)	176 (44.1)	205 (51.6)
Median, months	42.1	34.7
HR (95% CI)	0.81 (0.67–1.00)	
P value	0.0544	
2-sided boundary for significance	0.0377	
	47.9% maturity	

DCO3: 12 October 2022.
Median (range) duration of follow-up for censored patients at DCO3 was 36.6 months (8.3–47.0) in the abiraterone + olaparib arm and 36.5 months (2.9–45.3) in the abiraterone + placebo arm.

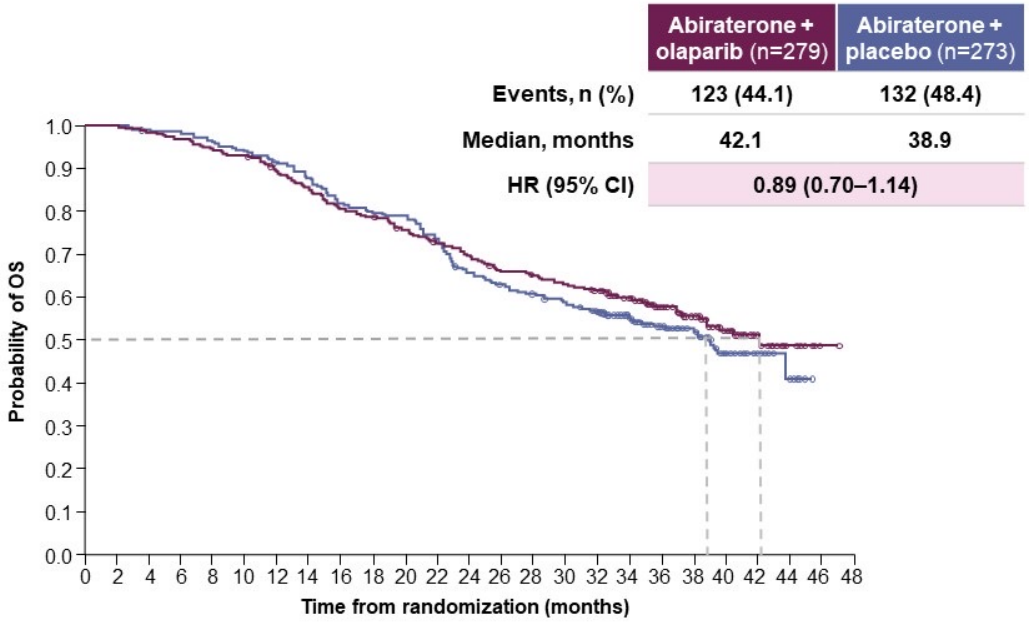
PROpel: OS in HRRm and non-HRRm subgroups (DCO3)

A trend towards OS benefit was observed across HRRm and non-HRRm subgroups

HRRm (28.4% of ITT population)



Non-HRRm (69.3% of ITT population)



DCO3: 12 October 2022.
The preplanned tumor tissue and plasma ctDNA testing was conducted after randomization and before primary analysis. Results from tumor tissue and plasma ctDNA were combined to determine patients HRRm status (see supplement for more details). 18 patients had unknown HRRm status.

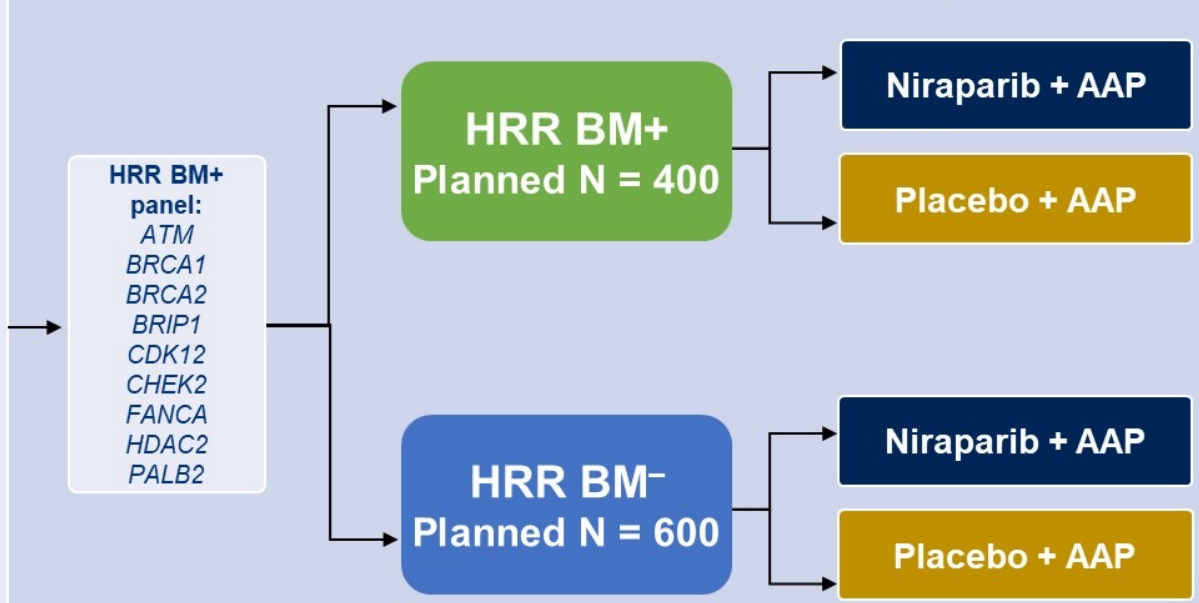
MAGNITUDE: Randomized, Double-Blind, Placebo-Controlled Study

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.

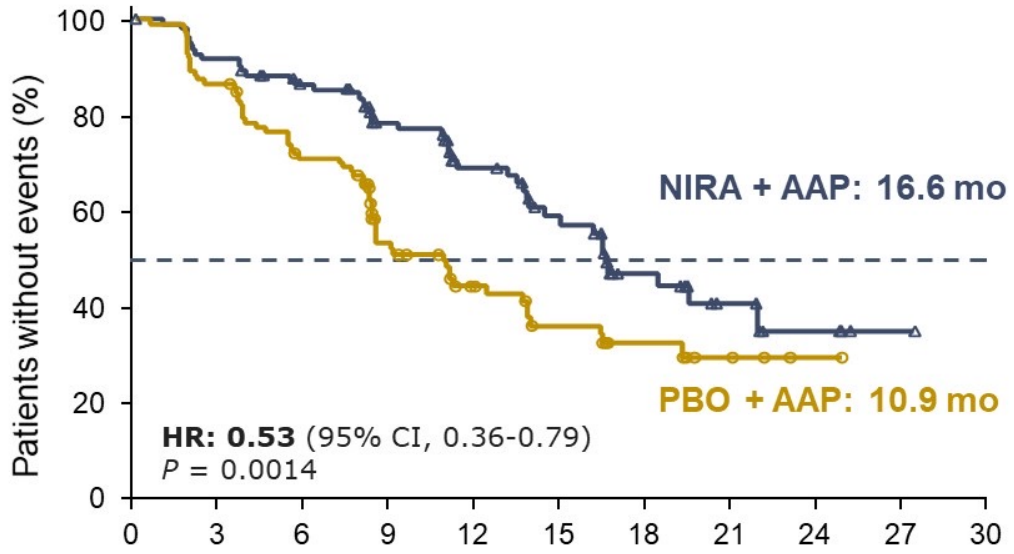
AAP, abiraterone acetate + prednisone/prednisolone; AR, androgen receptor; ARi, androgen receptor inhibitor; BM, biomarker; BPI-SF, Brief Pain Inventory–Short Form; ctDNA, circulating tumor deoxyribonucleic acid; ECOG PS, Eastern Cooperative Oncology Group performance status; HRR, homologous recombination 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.

MAGNITUDE *BRCA1/2-mutated*: Primary Endpoint

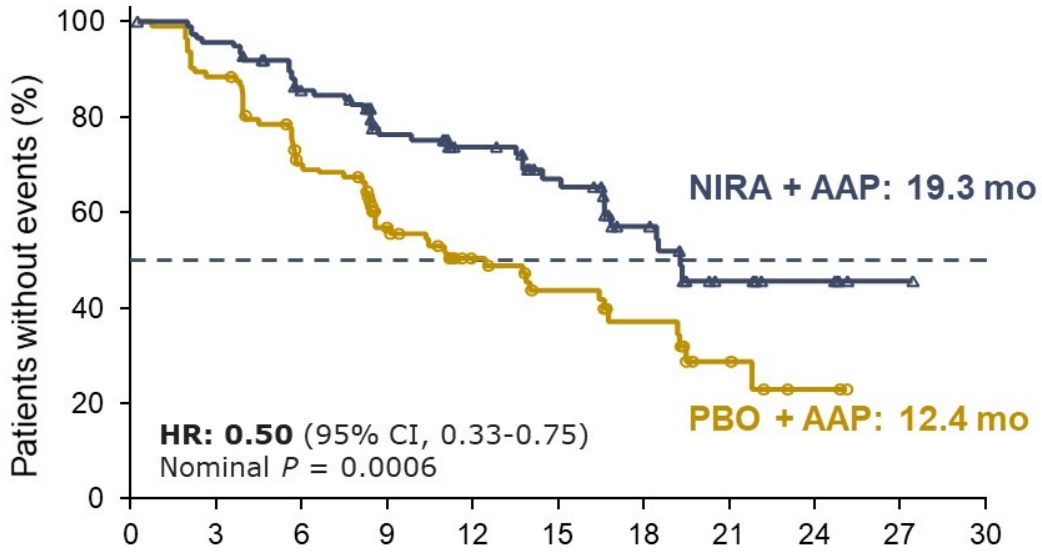
NIRA + AAP Significantly Reduced the Risk of Progression or Death by 47%

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

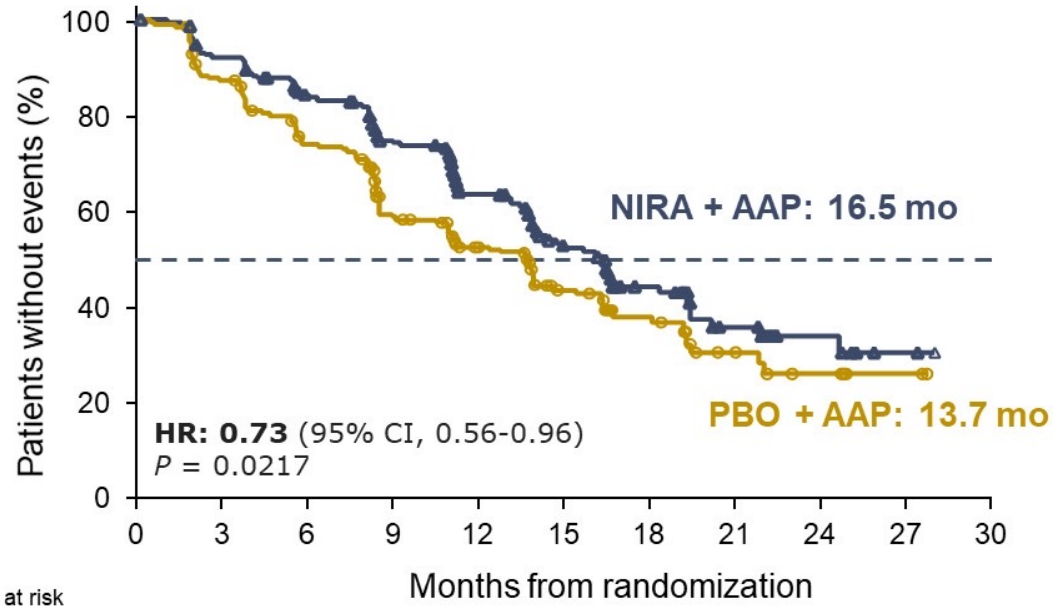
Median follow-up 16.7 months

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

MAGNITUDE All HRR BM+: Primary Endpoint

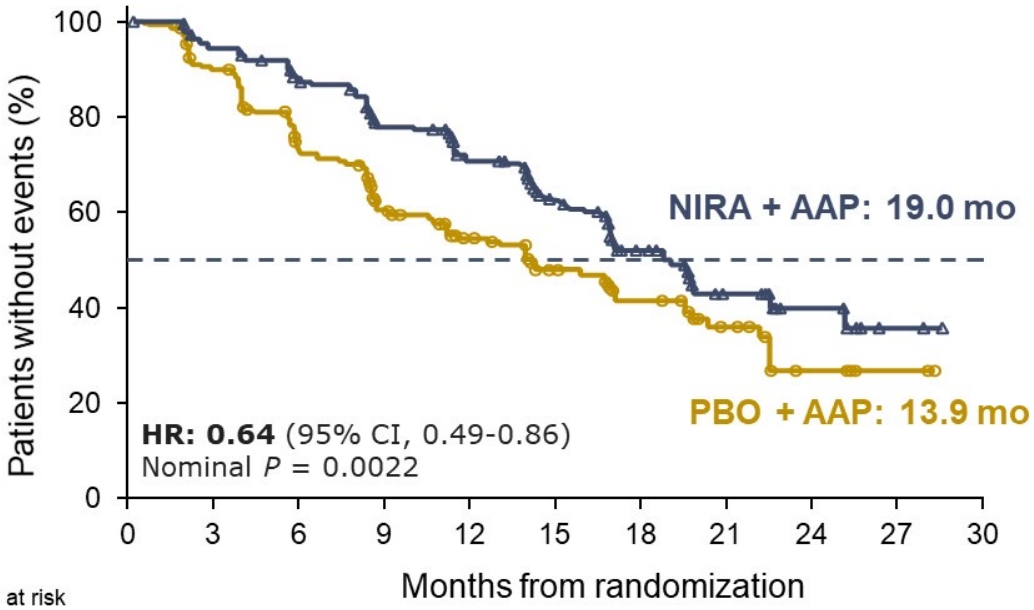
NIRA + AAP Significantly Reduced the Risk of Progression or Death by 27%

rPFS assessed by central review



No. at risk											
NIRA + AAP	212	192	167	129	96	64	45	21	10	2	0
PBO + AAP	211	182	149	102	78	53	35	15	9	2	0

rPFS assessed by investigator

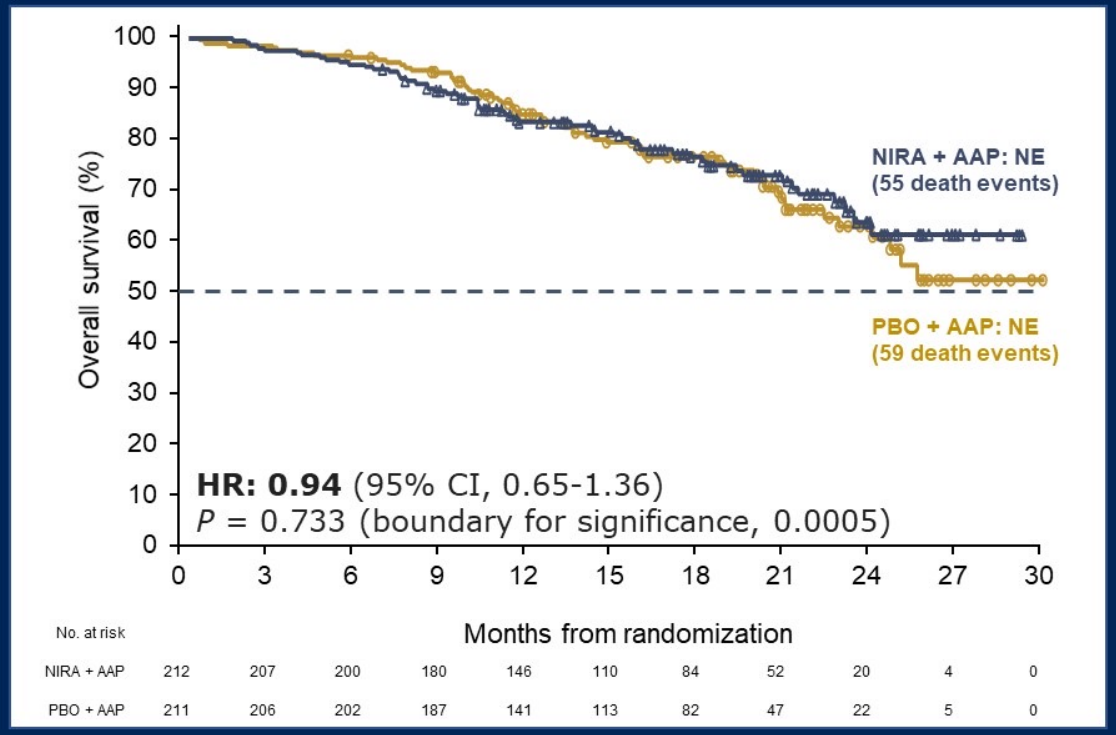


No. at risk											
NIRA + AAP	212	197	174	136	108	75	50	23	11	2	0
PBO + AAP	211	187	145	103	81	58	41	20	9	2	0

Median follow-up 18.6 months

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

MAGNITUDE All HRR BM+: Overall Survival
First Interim Analysis With Median Follow-up of 18.6 Months



Pre-specified Overall Survival Multivariate Analysis

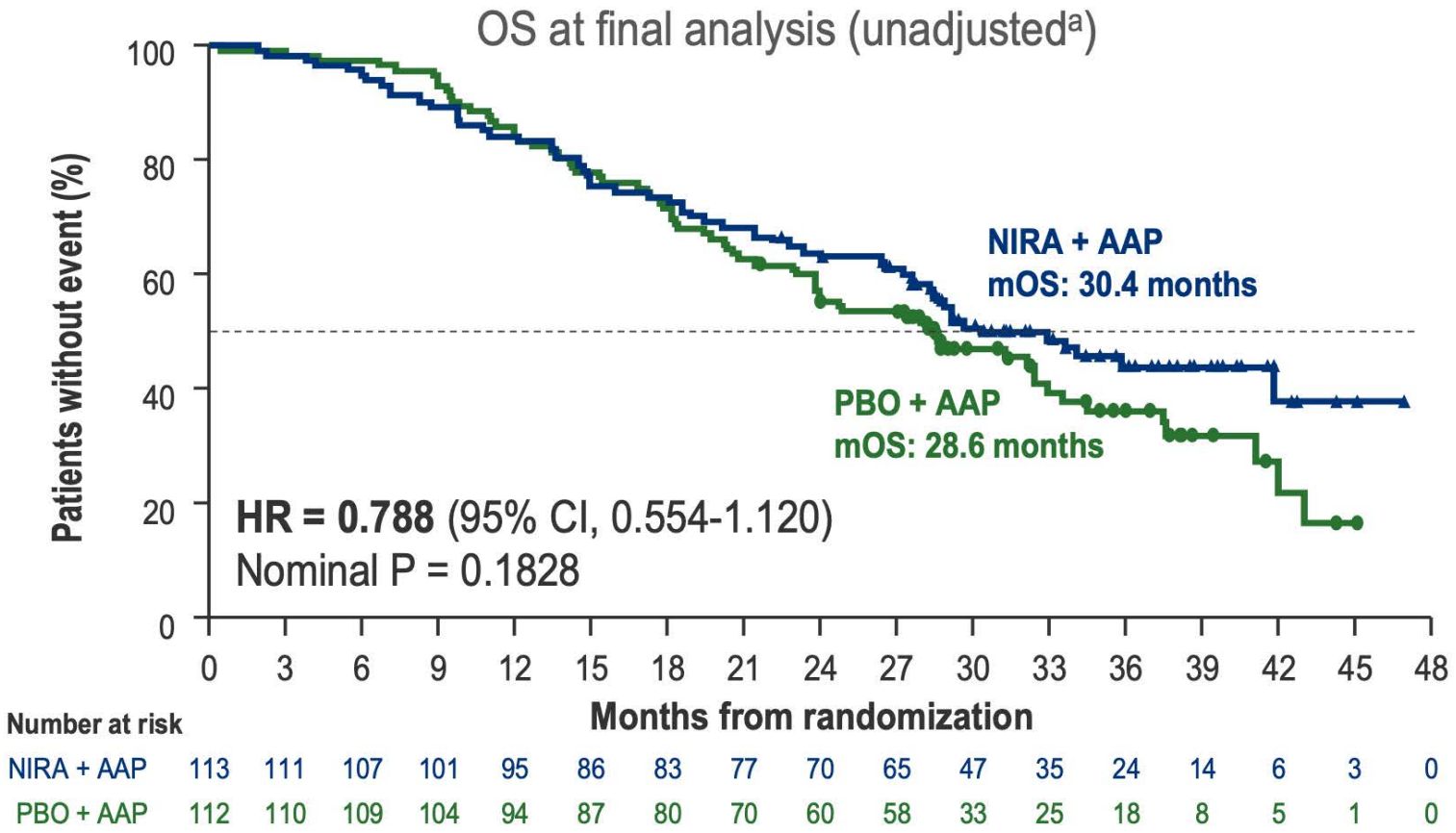
- A multivariate analysis accounting for baseline characteristics shows overall survival favors the NIRA + AAP arm
- Overall survival **HR = 0.767** (95% CI, 0.525-1.119; nominal *P* = 0.1682)

27% of deaths in the study population observed at overall survival interim analysis and thus these data are immature

AAP, abiraterone acetate + prednisone/prednisolone; BM, biomarker; CI, confidence interval; HR, hazard ratio; HRR, homologous recombination repair; NE, not estimable; NIRA, niraparib; PBO, placebo.

MAGNITUDE Final Analysis

Secondary endpoint: OS favored NIRA + AAP over PBO + AAP in *BRCA*+ patients



[a]Does not account for baseline imbalances. mOS, median overall survival.

Preplanned multivariate analysis (MVA) using prespecified prognostic factors supported an OS benefit of NIRA + AAP

MVA: HR = 0.663 (95% CI, 0.464-0.947); nominal P = 0.0237

MADRID 2023 ESMO congress

Dr Kim Chi

TALAPRO-2: Trial Design

Patient population

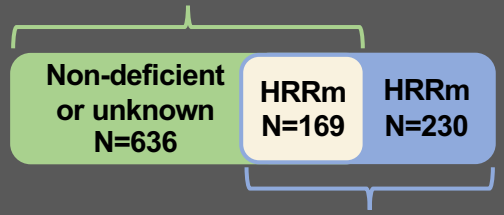
- 1L mCRPC
- ECOG 0 or 1
- Ongoing androgen deprivation therapy

Stratification factors

- Prior abiraterone[a] or docetaxel for CSPC (yes vs no)
- HRR gene alteration status (deficient vs non-deficient or unknown)[b]

Sequential enrollment in two cohorts:

Unselected (Cohort 1), N=805



1:1

Talazoparib + enzalutamide (N=402)

Unselected Cohort 1 (N=805)

Placebo + enzalutamide (N=403)

Primary endpoint

- rPFS by BICR

Key secondary endpoint

- OS (alpha protected)

Other secondary endpoints

- Time to cytotoxic chemotherapy
- PFS2
- ORR
- Patient-reported outcomes
- Safety

Samples **prospectively assessed** for HRR gene alterations
(ATM, ATR, BRCA1, BRCA2, CDK12, CHEK2, FANCA, NBN, MLH1, MRE11A, PALB2, RAD51C)

Analysis timeline: (unselected)

DCO1: Aug 16, 2022
rPFS (primary)

DCO2: March 28, 2023
OS (interim)

DCO3: Sept 3, 2024
OS (final) current

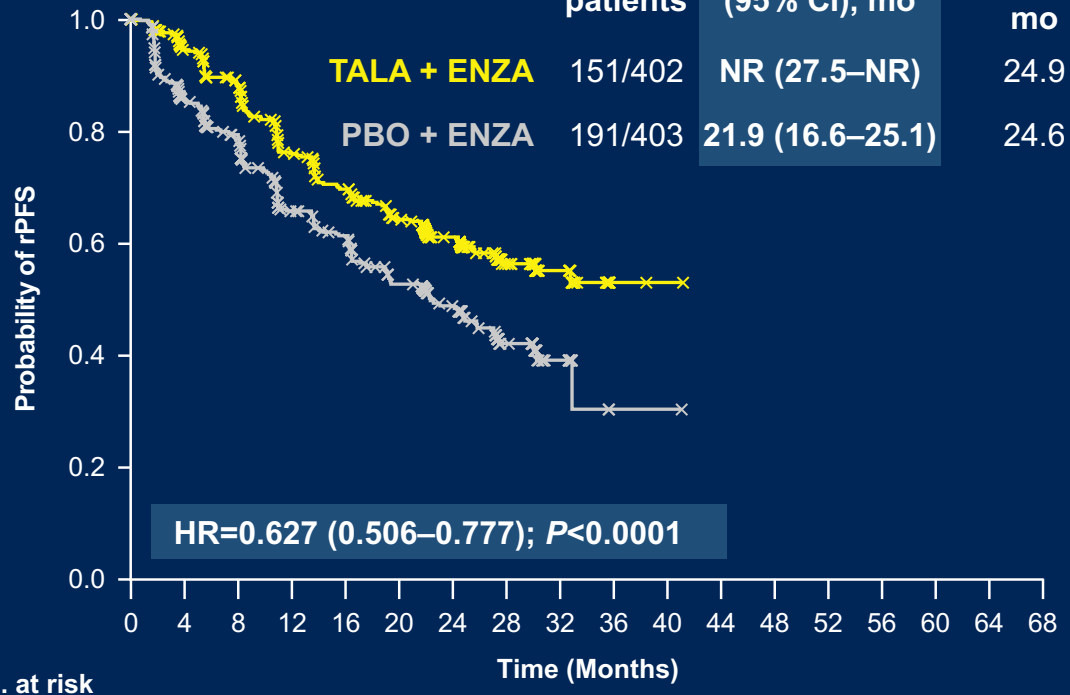
[a]**Prior orteronel was received by two patients in each treatment arm in Cohort 1 and one patient in each treatment arm in Cohort 2.** [b]**Unselected cohort only.**
BICR=blinded independent central review; CSPC=castration-sensitive prostate cancer; DCO=data cutoff; ORR=objective response rate; PFS2=time to second progression or death.

Primary Endpoint: rPFS by BICR

Statistically significant and clinically meaningful benefit maintained with ~2 years of additional follow-up

Primary analysis (DCO: Aug 16, 2022)[1]

	Events/ patients	Median rPFS (95% CI), mo	Median follow-up, mo
TALA + ENZA	151/402	NR (27.5–NR)	24.9
PBO + ENZA	191/403	21.9 (16.6–25.1)	24.6

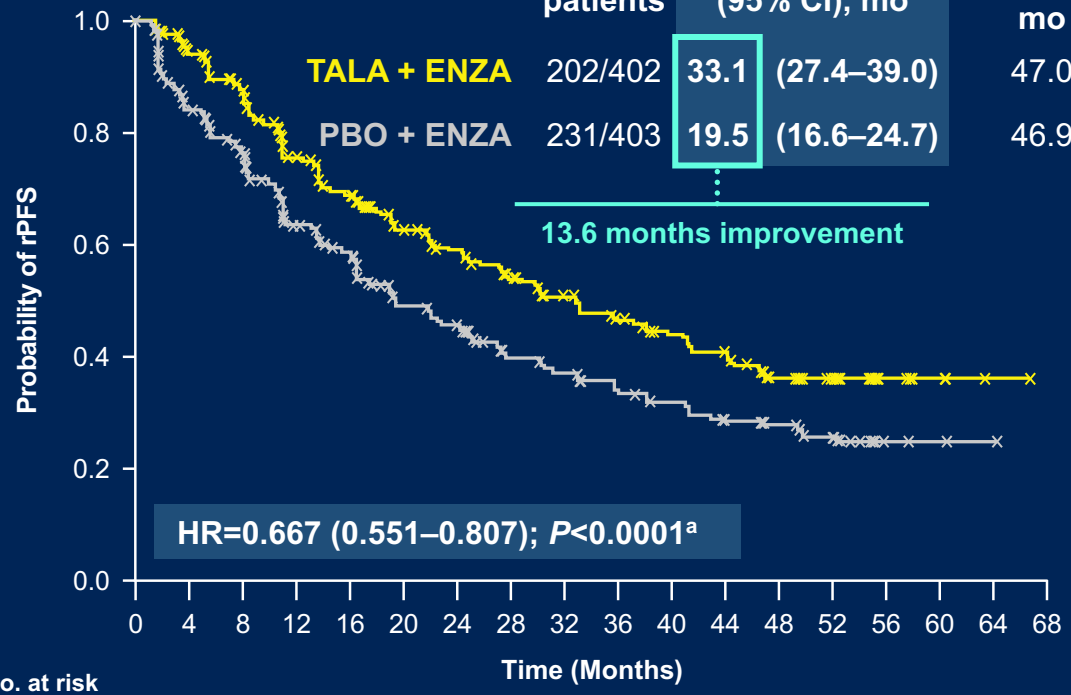


No. at risk

TALA + ENZA	402	353	318	256	226	193	136	67	29	2	1	0	0	0	0	0	0
PBO + ENZA	403	311	272	200	179	140	96	43	14	1	1	0	0	0	0	0	0

Update (DCO: Sept 3, 2024)

	Events/ patients	Median rPFS (95% CI), mo	Median follow-up, mo
TALA + ENZA	202/402	33.1 (27.4–39.0)	47.0
PBO + ENZA	231/403	19.5 (16.6–24.7)	46.9



No. at risk

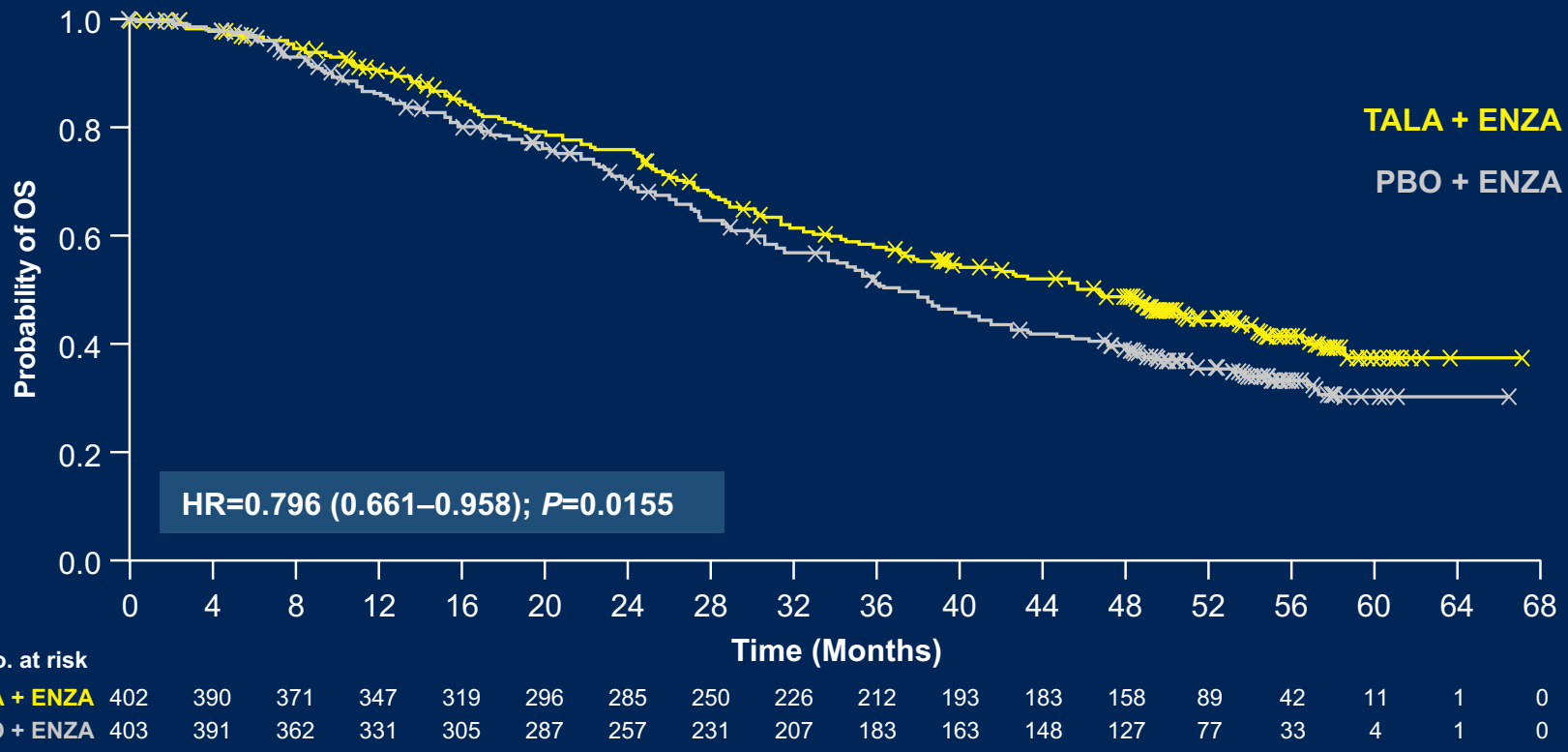
TALA + ENZA	402	353	318	257	228	196	180	155	138	122	108	101	63	50	13	7	1	0
PBO + ENZA	403	312	273	201	180	138	128	100	92	81	72	66	44	35	5	2	1	0

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

[a]**The updated rPFS data are descriptive.** DCO=data cutoff; ENZA=enzalutamide; NR=not reached; PBO=placebo; TALA=talazoparib. 1. **Reproduced with permission from** Agarwal N, et al. *Lancet.* 2023;402:291-303.

Overall Survival (Final Analysis)

20.4% reduction in risk of death, >8 months improvement in median OS



	Events/patients	Median OS (95% CI), mo	
TALA + ENZA	211/402	45.8	(39.4–50.8)
PBO + ENZA	243/403	37.0	(34.1–40.4)

8.8 months improvement

Median follow-up for OS was 52.5 months

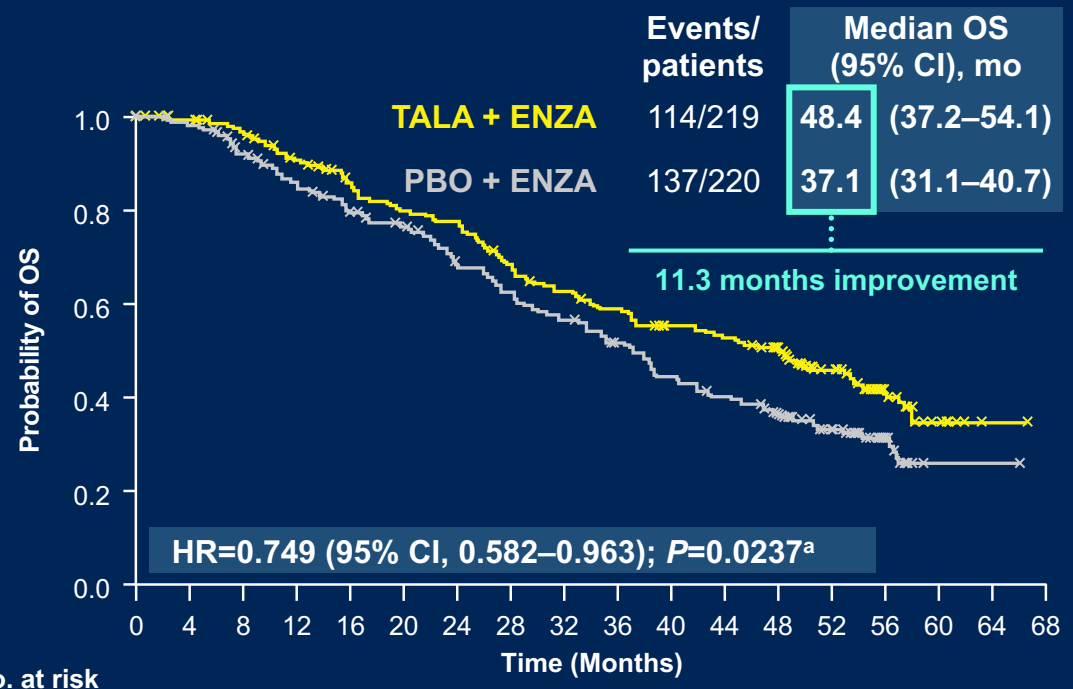
For statistical significance at the final overall survival analysis, the stratified log-rank 2-sided *P* value needed to be ≤0.022 based on a group sequential design with O'Brien-Fleming spending function.

Data cutoff: September 3, 2024.

Overall Survival in Subgroups With No Alterations Detected by Both ctDNA and Tumor Tissue

Clinically meaningful reduction in risk of death in patients without *BRCA* or HRR alterations

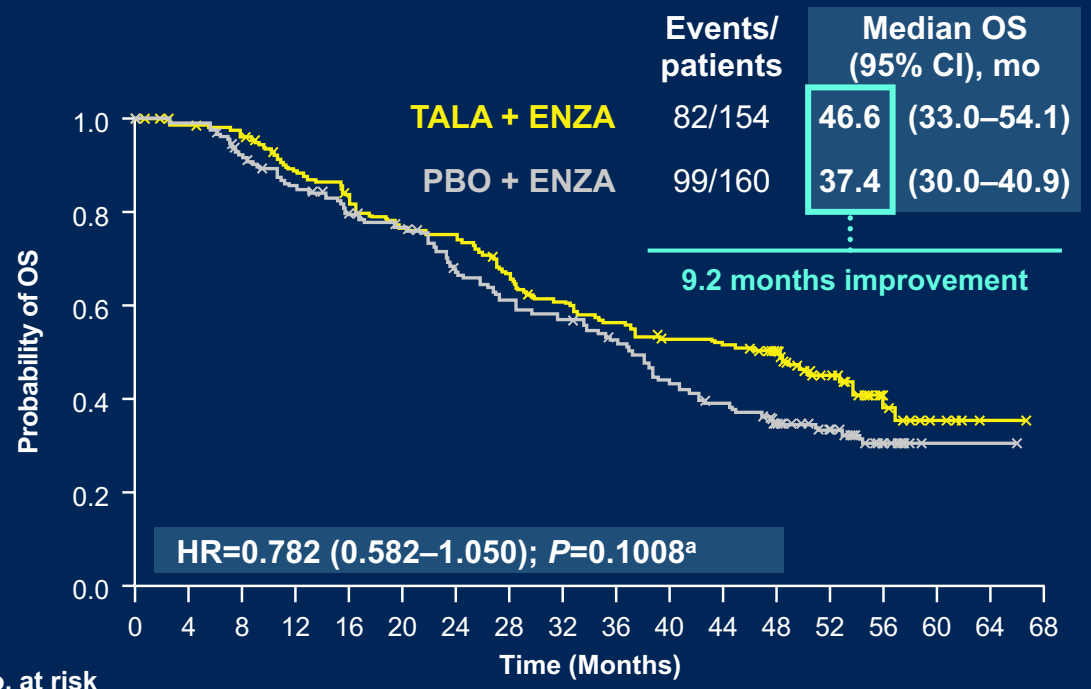
No *BRCA* alteration detected



No. at risk

TALA + ENZA	219	213	204	187	172	159	155	135	123	114	102	99	89	51	26	7	1	0
PBO + ENZA	220	214	196	179	164	155	135	121	110	98	84	75	63	39	20	1	1	0

No HRR alteration detected



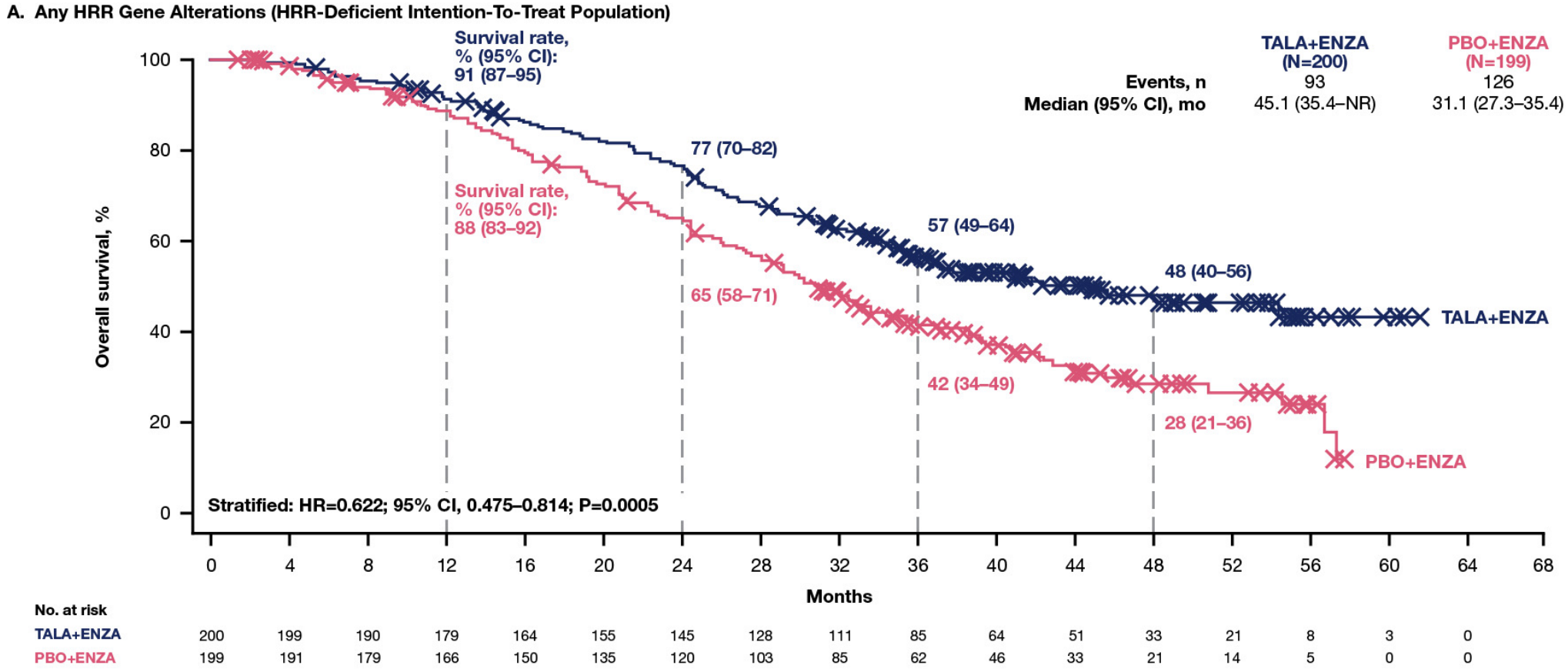
No. at risk

TALA + ENZA	154	148	142	128	120	110	108	95	85	79	72	71	64	36	19	5	1	0
PBO + ENZA	160	156	143	131	120	113	97	87	81	73	61	53	44	29	14	1	1	0

Post hoc analysis employing all available test results of prescreening/screening samples including both prospective and retrospective analyses.

Data cutoff: September 3, 2024. [a]Reported *P* values are nominal and descriptive.

Final Overall Survival Analysis in Patients with any HRR Gene Alterations (HRR-deficient Intention-to-Treat Population)



CI=confidence interval; ENZA=enzalutamide; HR=hazard ratio; HRR=homologous recombination repair; mo=months; NR=not reached; PBO=placebo; TALA=talazoparib

Fizazi, K et al. *J Clin Oncol*. 2025;43(suppl 5):Abstract LBA141.

FDA's Oncologic Drugs Advisory Group Unanimously Voted Against Broad Label Expansion for Talazoparib in Combination with Enzalutamide for Patients with mCRPC

On May 21, 2024, the FDA's Oncologic Drugs Advisory Committee unanimously voted that the data from TALAPRO-2 investigating talazoparib in combination with enzalutamide were not sufficient to conclude a favorable benefit-risk profile for patients with mCRPC not selected for homologous recombination repair (HRR) gene alterations.

The committee expressed concerns over the trial design and the toxicity of this regimen for this population.

The FDA previously approved talazoparib + enzalutamide combination therapy for patients with HRR-positive mCRPC on June 20, 2023. Approval for this therapy was supported with the data from the TALAPRO-2 trial (NCT03395197).

https://www.fda.gov/media/186563/download

Phase 3 Combination trials of PARP inhibitors with an ARPI

	PROpel (N = 796)	MAGNITUDE (N = 423)	TALAPRO-2 (Cohort 1: N = 805)	TALAPRO-2 (Cohort 2: N = 399)
Trial population mCRPC 1st line	Docetaxel / ARSI in mCSPC setting allowed (ARSI without progression and > 12 months ago)	Docetaxel / ARSI in mCSPC setting allowed ; Abiraterone in mCRPC allowed if given < 4 months	Docetaxel / Abiraterone in mCSPC setting allowed	
Design and randomization	1 : 1 randomisation Abiraterone + olaparib (n = 399) vs abiraterone + placebo (n = 397)	Cohort 1: HRR cohort 1 : 1 randomisation abiraterone + niraparib (n = 212) vs abiraterone + placebo (n = 211) Cohort 2: non-HRR cohort (closed prematurely because of futility)	All-comer population 1 : 1 randomisation Enzalutamide + talazoparib (n = 402) vs enzalutamide + placebo (n = 403)	HRR cohort 1 : 1 randomisation Enzalutamide + talazoparib (n = 200) vs enzalutamide + placebo (n = 199)
HRR analysis	Tissue or ctDNA / retrospective	100% tissue / prospective	100% tissue / prospective	99.5% tissue / prospective 0.5% ctDNA or unspecified tissue source / prospective
Primary endpoint	rPFS (investigator review)	rPFS (central review)	rPFS (central review)	rPFS (central review)
rPFS, HR (95% CI)				
All comers	HR 0.66 (0.54-0.81)	NR	HR 0.63 (0.51-0.78)	Not included
HRR -ve	HR 0.76 (0.6-0.97)	HR 1.09 (0.75-1.57)	HR 0.70 (0.54-0.89)	Not included
HRR +ve	HR 0.50 (0.34-0.73)	HR 0.73 (0.56-0.96)	HR 0.46 (0.30-0.70)	HR 0.45 (0.33-0.61)
BRCA+	HR 0.23 (0.12-0.43)	HR 0.53 (0.36-0.79)	HR 0.23 (0.10-0.53)	HR 0.20 (0.11-0.36)
ORR (all comers)	58% vs 48%	60% vs 28% (only HRR+ pts)	61.7% vs 43.9%	67% vs 40%
OS (all comers)	HR 0.81 (0.67-1)	HR 0.66 (0.46-0.95) (only for BRCA 1/2)	**HR 0.80 (0.66–0.96)**	**HR 0.62 (0.48–0.81)**
FDA approval; EMA approval	**mCRPC with BRCA1/2 mutations; mCRPC when chemotherapy is not indicated**	**mCRPC with BRCA1/2 mutations**	**mCRPC with any HRR mutations; mCRPC when chemotherapy is not clinically indicated**	
Publication	Clarke N….Saad F. ***NEJM Evidence***, 2022	Chi K….Sandhu S. ***JCO***, 2023	**Agarwal N**….Fizazi K. ***Lancet***, 2023	Fizazi K….**Agarwal N.** ***Nature medicine***, 2023

ASCO Genitourinary Cancers Symposium

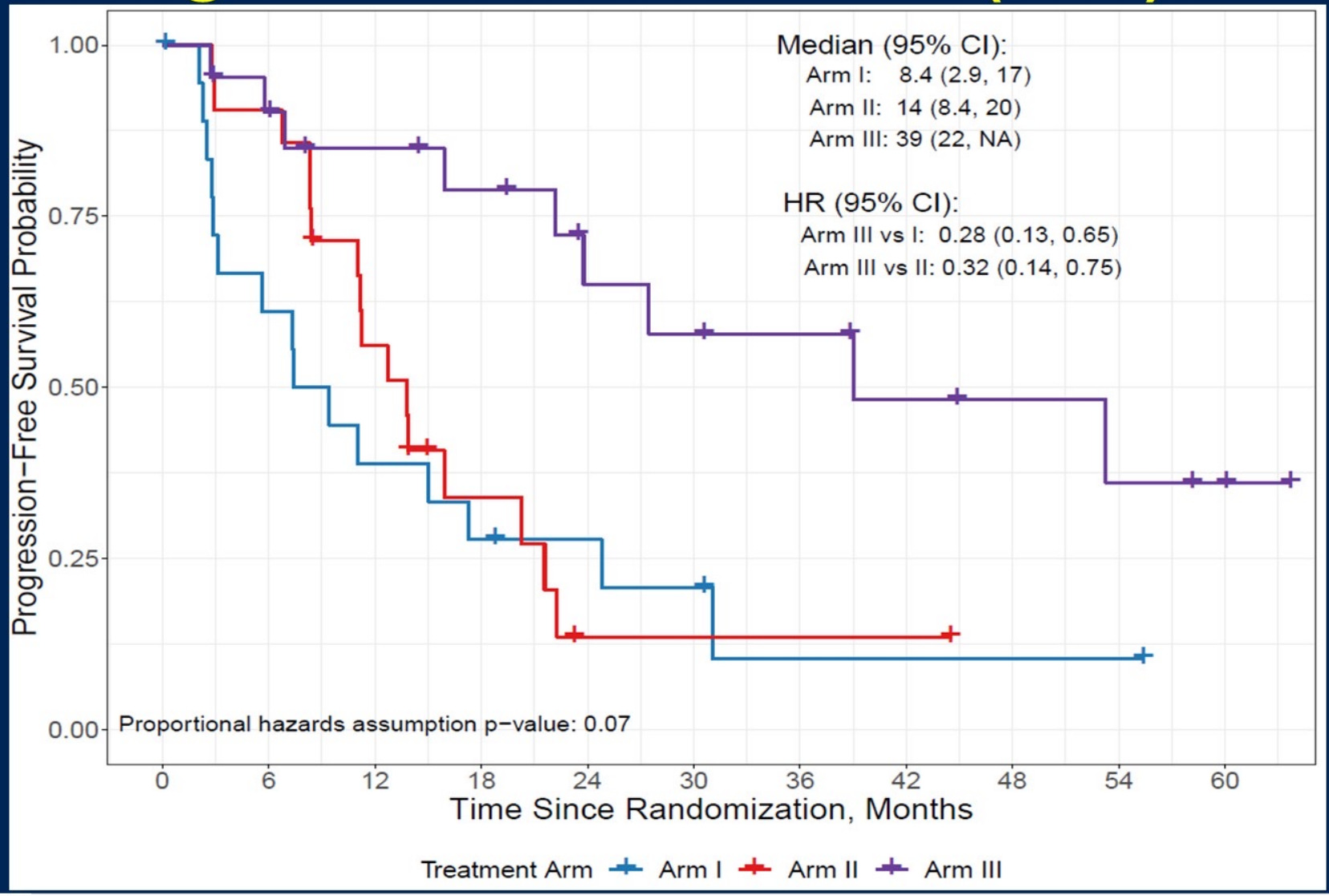
Abstract # 19

BRCAAway: A Randomized Phase 2 Trial of Abiraterone, Olaparib, or Abiraterone + Olaparib in Patients with Metastatic Castration-Resistant Prostate Cancer (mCRPC) bearing Homologous Recombination-Repair Mutations (HRRm)

Maha Hussain*, MD, FACP, FASCO, Masha Kocherginsky, PhD, Neeraj Agarwal, MD, Nabil Adra, MD, Jingsong Zhang, MD, PhD, Channing Judith Paller, MD, Joel Picus, MD, Zachery R Reichert, MD, PhD, Russell Zelig Szmulewitz, MD, Scott T. Tagawa, MD, Timothy Kuzel, MD, Latifa Bazzi, MPH, Stephanie Daignault-Newton, MS, Young E. Whang, MD, PhD, Robert Dreicer, MD, Ryan D. Stephenson, DO, Matthew Rettig, MD, Daniel H. Shevrin, MD, Arul Chinnaiyan, MD, PhD, Emmanuel S. Antonarakis, MD

pcctc
The Prostate Cancer Clinical Trials Consortium

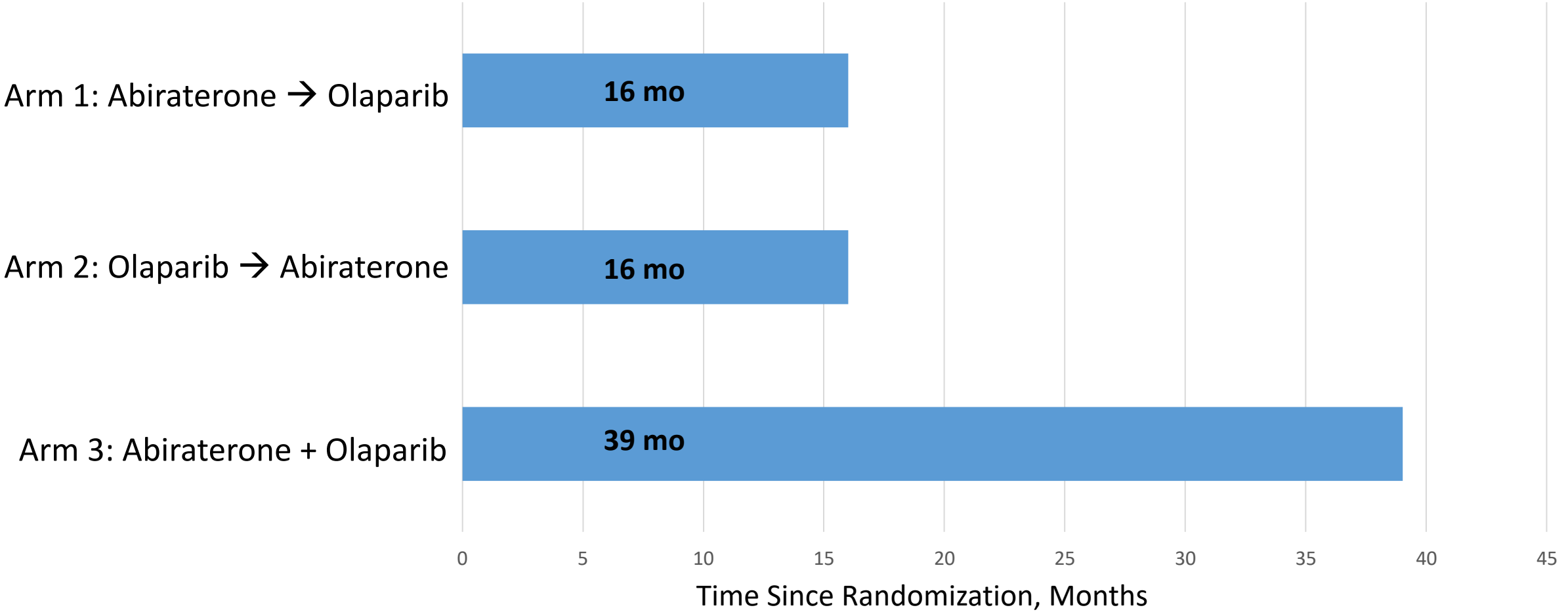
Progression-Free Survival (PFS)



PFS: time from randomization until first progression or death.

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

Median PFS from Randomization to End of Crossover Treatment



Hussain M., ASCO GU 2024

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

Key Eligib

- Men aged ≥ 18 yea
  confirmed mHSPC
  (adenocarcinoma)
- Metastatic disease
  greater than or equa
  bone lesion(s)
- Positive for deleteri
  somatic homologou
  recombination repa
  mutations
- Radiation with curat
  prior treatment with
  allowed
- Patients with long-t
  systemically adminis
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  or AML were exclud

Genitourinary Cancer—Prostate, Testicular, and Penile

Location

Live Stream | Hall D1

Time

June 3, 2025
9:45 AM – 12:45 PM CDT

11:45 AM – 11:57 AM CDT

ABSTRACT PRESENTATION 7

Phase 3 AMPLITUDE trial: Niraparib (NIRA) and abiraterone acetate plus prednisone (AAP) for metastatic castration-sensitive prostate cancer (mCSPC) patients (pts) with alterations in homologous recombination repair (HRR) genes.

Abstract LBA5006

Gerhardt Attard, MD, PhD
Cancer Institute, University College London

fficacy end points

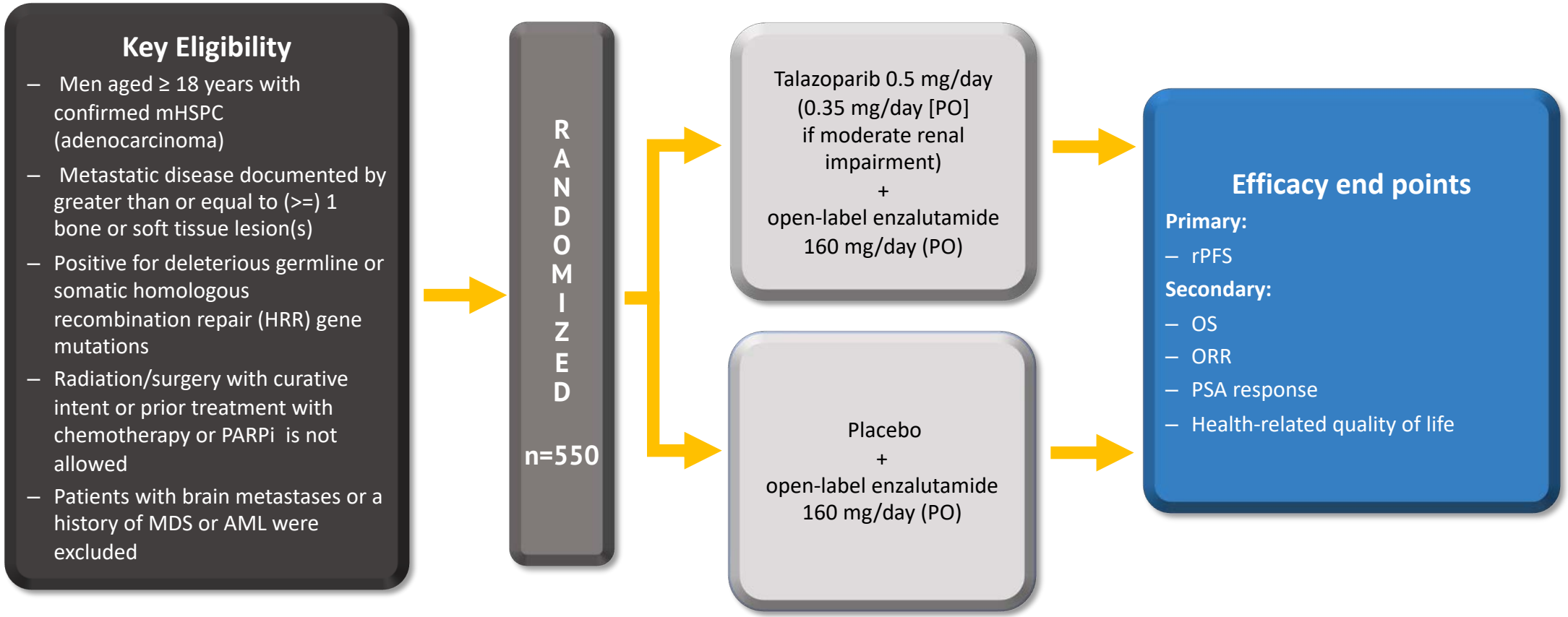
er PCWG 3
ry:

omatic PFS
o subsequent therapy
on of response (DOR)
er of Participants with Adverse
as a Measure of Safety and
bility

www.clinicaltrials.gov: (NCT04497844)

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

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



www.clinicaltrials.gov: (NCT04821622)

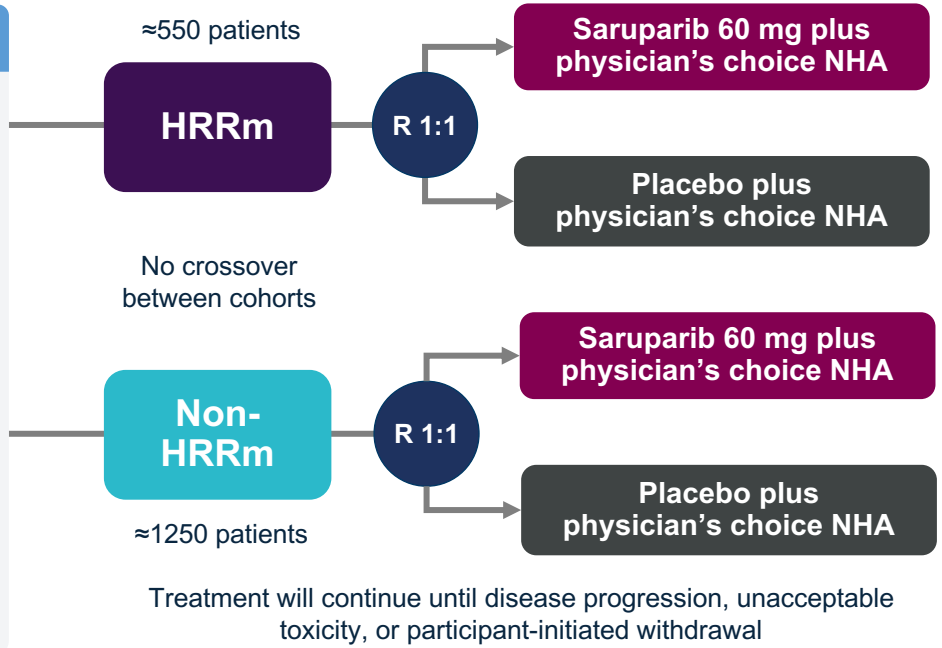
1 Agarwal et al., 2022, ABSTRACT TPS 221 ASCO-GU

EvoPAR-Prostate01: Phase 3 Trial Design (mHSPC)

A Phase III, 2-cohort, 2-arm, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of saruparib plus physician's choice of NHA (abiraterone, darolutamide, or enzalutamide) versus placebo plus physician's choice of NHA in participants with mCSPC

Eligibility criteria

- Aged ≥18 years
- Histologically confirmed mCSPC (*de novo* or recurrent low- or high-volume disease)
- ECOG PS 0–1
- Prospectively defined HRRm status*
- Must be receiving ADT throughout the study or have undergone bilateral orchiectomy, and must be suitable for treatment with NHAs
- No prior treatment with PARP inhibitors, CT, or NHAs in the metastatic setting†
- No suspected or prior history of myelodysplastic syndrome/acute myeloid leukemia



Treatment will continue until disease progression, unacceptable toxicity, or participant-initiated withdrawal

Select endpoints

HRRm cohort
- rPFS
- OS

Non-HRRm cohort
- rPFS
- OS

Statistical analyses

rPFS and OS will be tested for each cohort separately using a stratified log-rank test

www.clinicaltrials.gov: (NCT06120491)

Agarwal N. *et al*, ***AUA*** 2024

My take on PARPi plus ARPI in mCRPC

- Many patients with new mCRPC will not have disease progression on a prior ARPI in the next 5-7 years: 1) patients progressing from localized prostate cancer with BCR, 2) patients with locally advanced prostate cancer receiving limited duration ARPI, and 3) patients with mHSPC not receiving ARPI at all or until progression
- How I select a given combination: 1) For new mCRPC with BRCA1/2 mutations, I use the PARPi combinations based on my selection of the partner ARPI; 2) For new mCRPC with non-BRCA1/2 HRRm, I use enzalutamide plus talazoparib
- Based on the results of the BRCAAway trial, the upfront combination of an ARPI+PARPi seems more efficacious than the sequencing of ARPI followed by a PARPi
- All patients with advanced prostate cancer should undergo tumor genomic profiling and germline testing
- Next steps:
  - Elucidation of the mechanism of response in HRRm-negative patients
  - Mechanism of resistance to PARPi

Faculty Case Presentations

Case Presentation – Dr Beltran: 69 yo gentleman

- Diagnosed with T3aN0M0 Gleason 4+5 prostate adenocarcinoma 4 years ago, PSA 15ng/ml
- Treated with radiation plus 2 years of ADT , PSA nadir 0.3 , testo <3 ng/dL
- He came off ADT but was then lost to follow-up and has not had regular PSA checks
- Presents now with PSA 10 ng/ml, testosterone 10 ng/dL
- Imaging shows multiple bone metastases
- He feels well, asymptomatic
- PMH is notable for HTN, hyperlipidemia- well controlled
- Family history notable for a sister and maternal aunt with breast cancer in 50s
- Genetic testing identified a **pathogenic germline *BRCA2* mutation**

QUESTIONS FOR THE FACULTY

What would you recommend next for this patient?

Are there any situations in which you would currently attempt to access olaparib/abiraterone or niraparib/abiraterone outside of a clinical trial for a patient with mCRPC and an HRR mutation other than BRCA?

Outside of a clinical trial, would you currently administer a PARP inhibitor in combination with an AR pathway inhibitor for a patient with mCRPC without a documented HRR gene mutation?

QUESTIONS FOR THE FACULTY

How do you approach the use of PARP inhibitor-based combinations in patients with mCRPC who have already received a novel antiandrogen in an earlier disease setting? Would you consider a PARP inhibitor in combination with the same or an alternate secondary hormonal agent in such a scenario, or would you favor PARP inhibitor monotherapy?

Case Presentation – Dr Saad: 72-year-old patient

- In 2014 at age 61 diagnosed with cT3, Gleason 8 prostate cancer, PSA 42
- Treated with radiation therapy and 3 years of ADT
  - PSA undetectable in 2017

- In 2019 PSA was up to 4.5 with a PSADT of 6 months
  - Negative metastatic work-up
  - Put on ADT in 2019

- Did well until 2023 when PSA rose to 5.5
  - Imaging revealed metastases to lymph nodes and bone

- Lymph node biopsy revealed a BRCA2 mutation in May 2023

CHUM

Case Presentation – Dr Saad: Patient with newly diagnosed mCRPC with a BRCA mutation

- Patient well informed and accepted abiraterone + niraparib
- PSA decline from 8.1 to 2.3 after 1 month of treatment
- At week 8
  - Symptomatic anemia with HB declining from 12.2 to 8.7
- Niraparib suspended and transfused 1 unit
- 1 week later was put back on niraparib at reduced dose (100mg)

- Update April 2025
  - PSA is undetectable (< 0.02) and CR of measurable disease
  - Continues to do very well on treatment

CHUM

QUESTIONS FOR THE FACULTY

What outcomes from ongoing Phase III trials of PARP inhibitors in mHSPC would prompt you to employ them in that setting? What would you be looking for in terms of hazard ratios/advantages in PFS or OS?

If PARP inhibitors eventually reach the clinic for mHSPC, how would you select between this strategy and triplet therapy with an AR pathway inhibitor, docetaxel and ADT?

For how long would you likely administer the PARP inhibitor if these agents were available for mHSPC? How concerned are you about the risk of MDS/AML with prolonged use?

Agenda

MODULE 1: Evolving Management of Nonmetastatic Hormone-Sensitive Prostate Cancer (HSPC) — Dr Saad

MODULE 2: Current Treatment for Metastatic HSPC — Dr Armstrong

MODULE 3: Role of PARP Inhibition in Metastatic Castration-Resistant Prostate Cancer (mCRPC) — Dr Agarwal

MODULE 4: Current and Future Use of Radiopharmaceuticals for mCRPC — Dr McKay

MODULE 5: Promising Novel Agents and Strategies Under Investigation for the Management of Prostate Cancer — Dr Beltran

UC San Diego Health

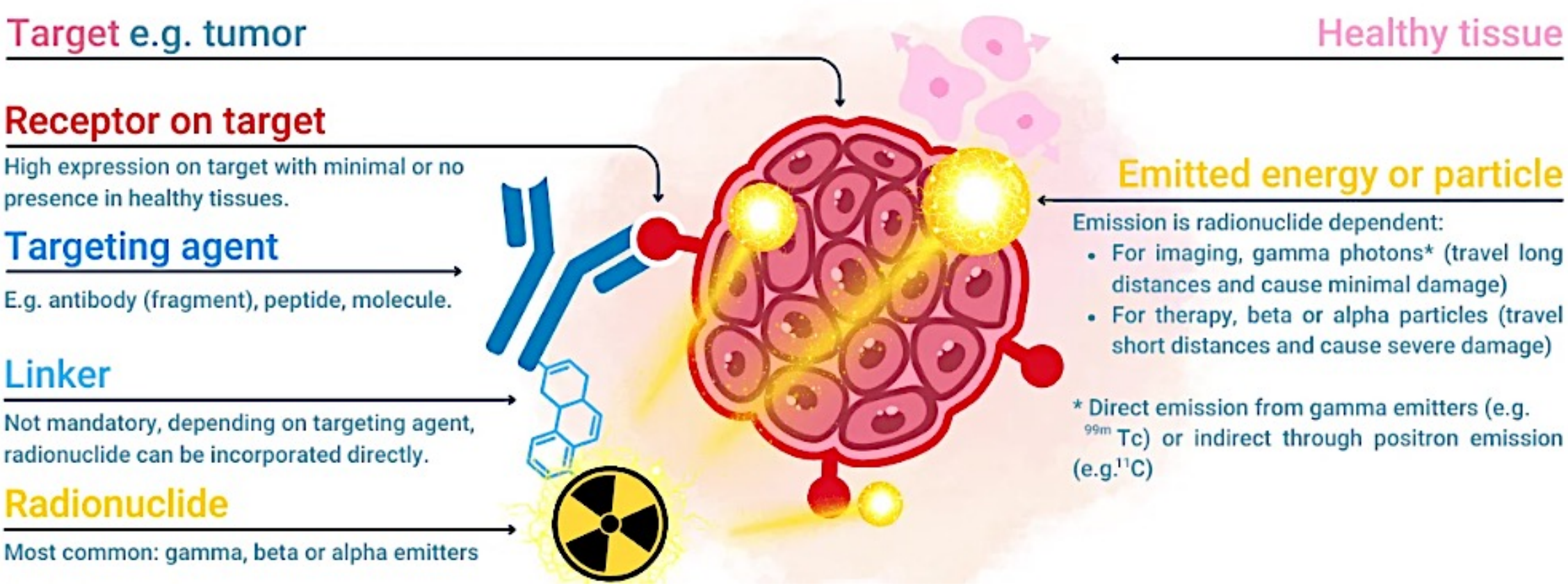
Current and Future Use of Radiopharmaceuticals in mCRPC

Rana R. McKay, MD, FASCO

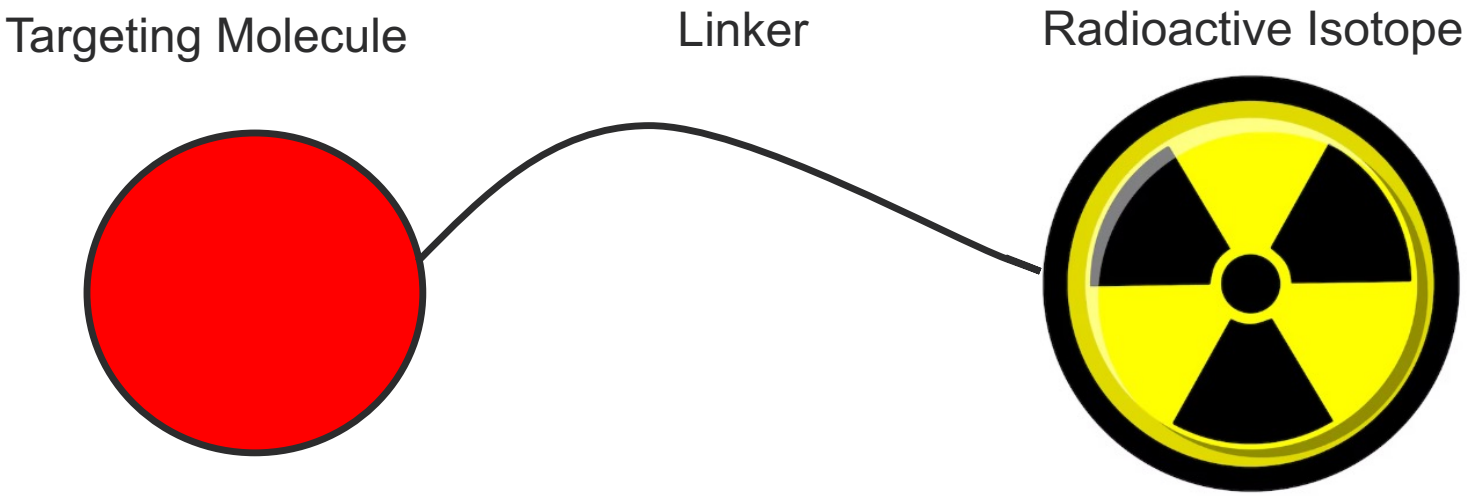
Professor of Medicine and Urology

Moores Cancer Center, University of California San Diego

Radiopharmaceuticals

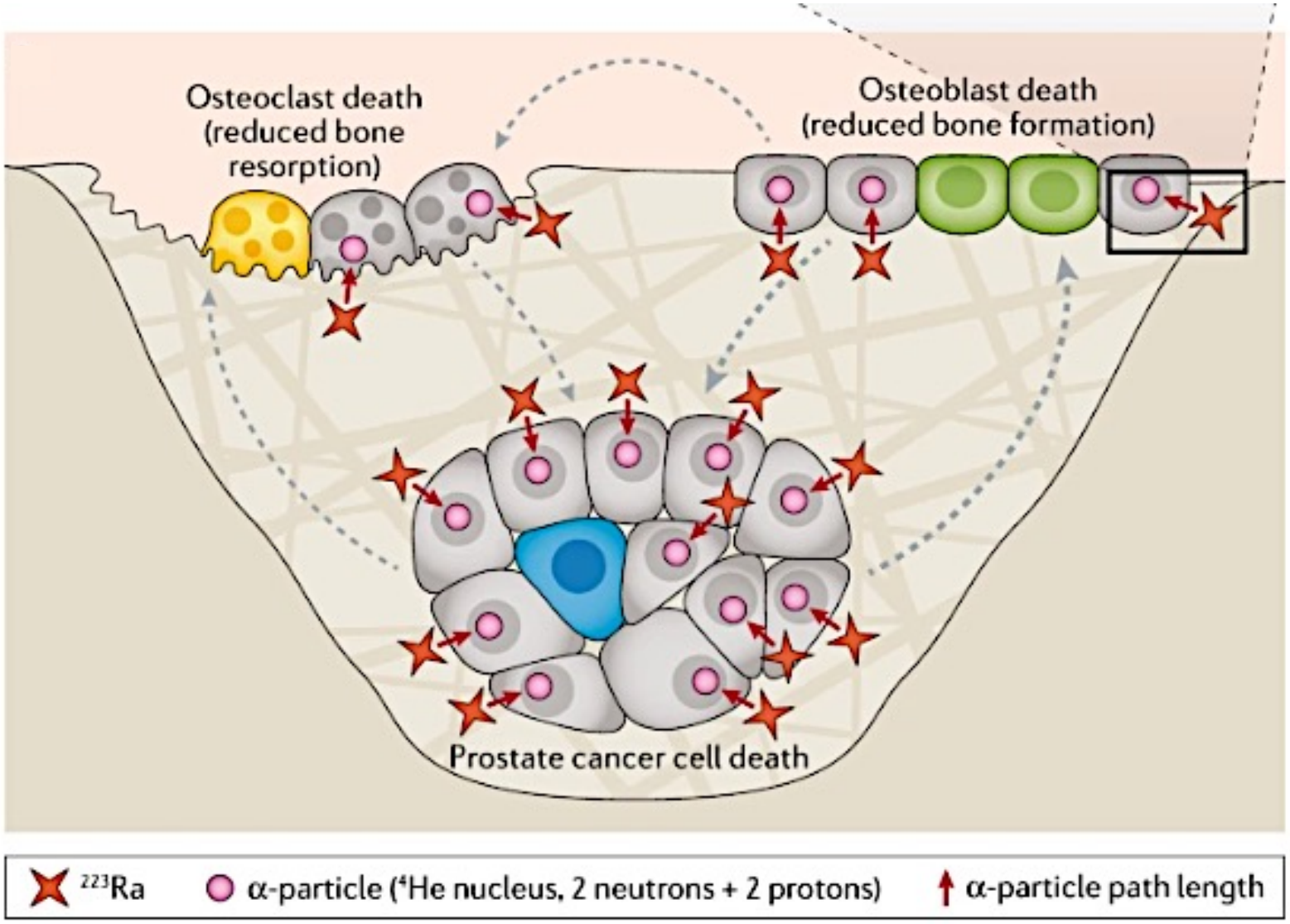


Heterogeneity of Agents



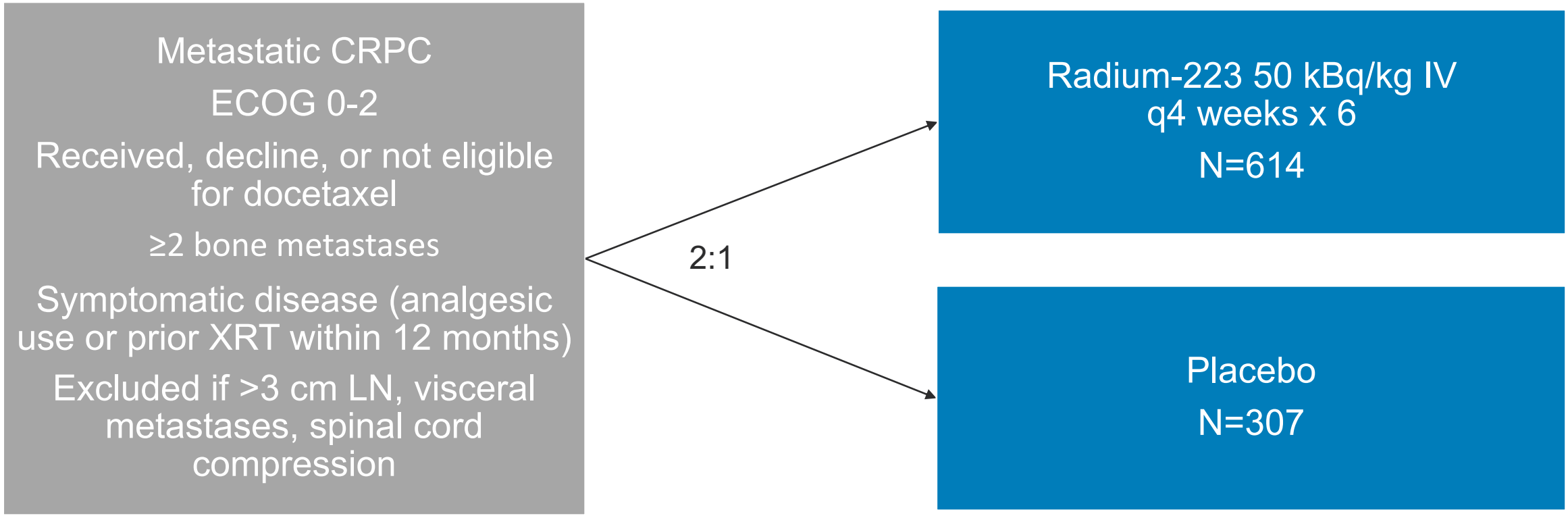
Target	Carrier Systems	Linkers	Radiation Types
PSMA	Small molecule	Chelators – DOTA, DOTAGA	β – Lu-177, I-131, Cu-67
KLK2	Peptides	Chemical – Hydrocarbon, PEG, Peptide, Cleavable	α – Ac-225, Ra-223, Th-227
STEAP 1/STEAP 2	Antibodies		
DLL3	Nucleic acid		
	Nanoparticles		

Mechanisms of Action of Radium-223



ALSYMPCA Trial

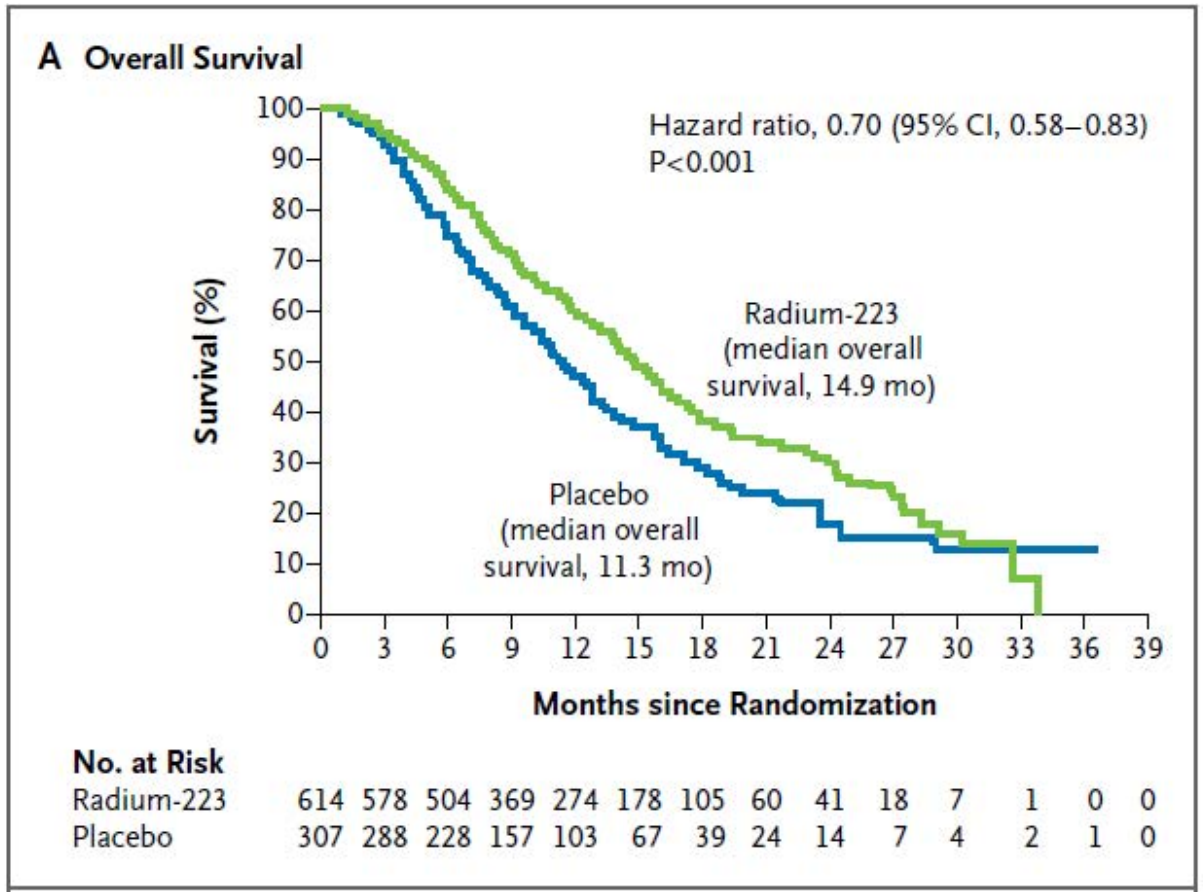
Double-Blind, Placebo-Controlled Randomized Phase III Study

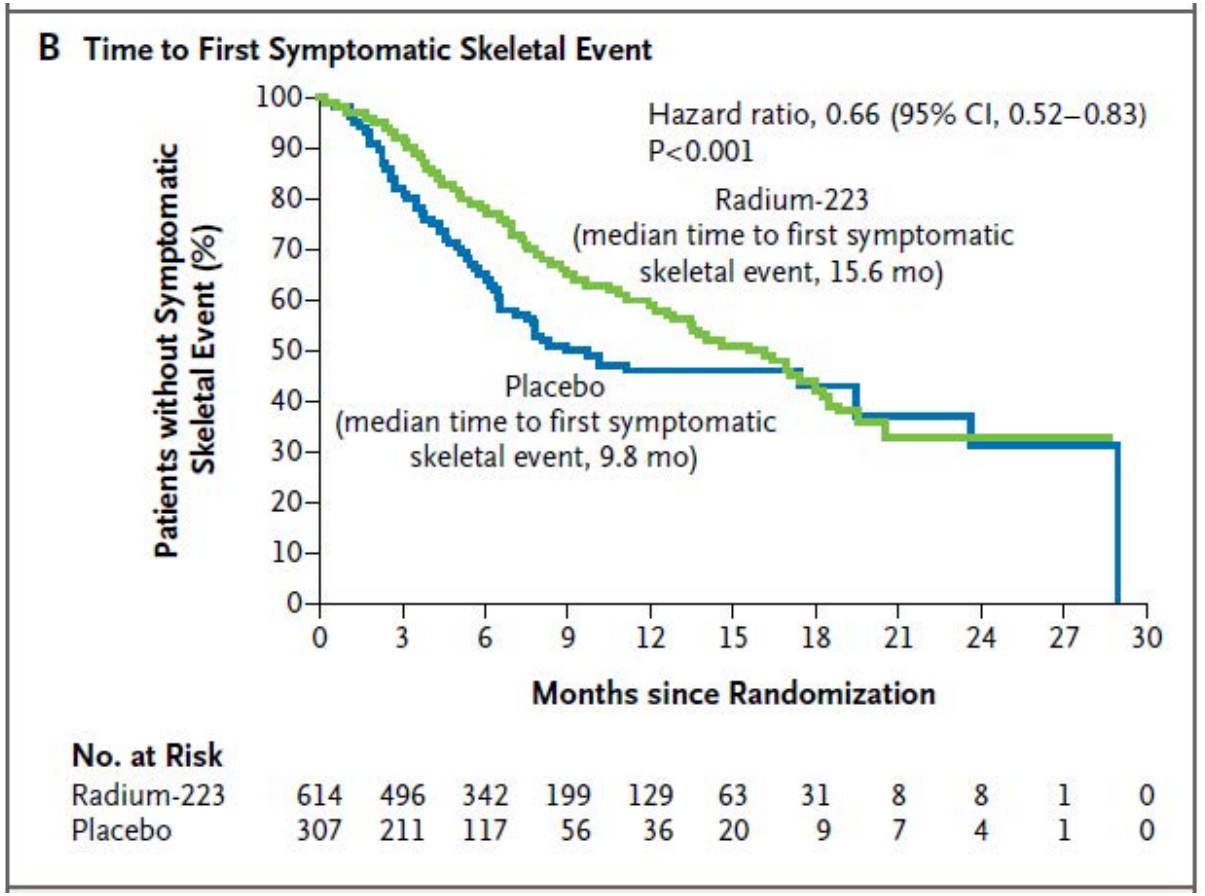


Primary Endpoint: Overall Survival

Parker et al, NEJM, 2013

ALSYMPCA Trial





Parker et al, NEJM, 2013

ALSYMPCA Secondary Endpoints

Table 2. Main Secondary Efficacy End Points in the Intention-to-Treat Population.

End Point	Radium-223 (N=614)	Placebo (N=307)	Hazard Ratio (95% CI)	P Value
Median time to first symptomatic skeletal event — mo	15.6	9.8	0.66 (0.52–0.83)	<0.001
Median time to increase in total alkaline phosphatase level — mo	7.4	3.8	0.17 (0.13–0.22)	<0.001
Median time to increase in PSA level — mo	3.6	3.4	0.64 (0.54–0.77)	<0.001
Patients with ≥30% reduction in total alkaline phosphatase response — no. /total no. (%)	233/497 (47)	7/211 (3)		<0.001
Patients with normalization of total alkaline phosphatase level — no./total no. (%)*	109/321 (34)	2/140 (1)		<0.001

* Only patients who had elevated total alkaline phosphatase levels at baseline are included.

Parker et al, NEJM, 2013

REASSURE – Real World Observational Study Radium-223

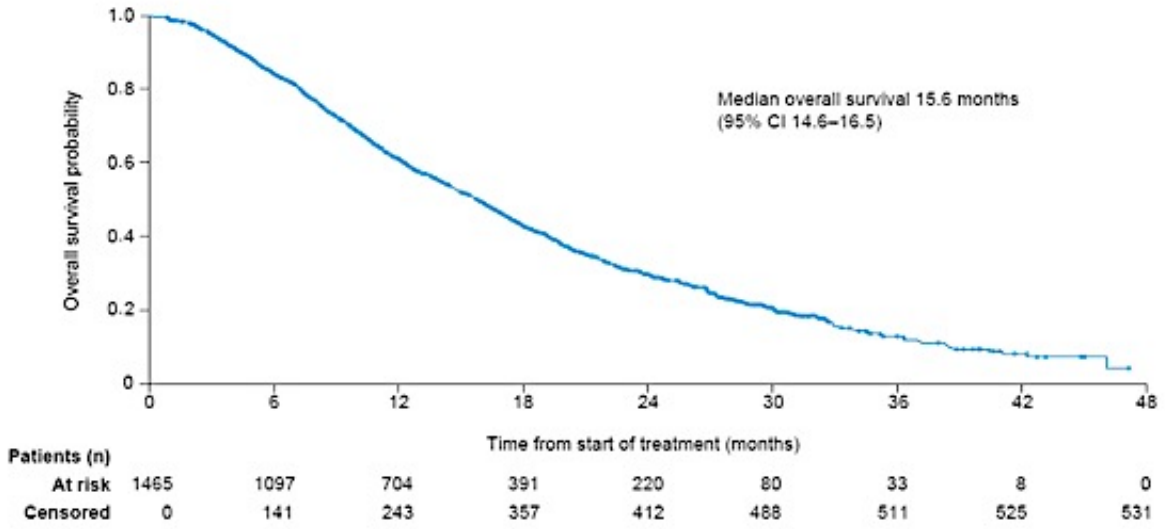


Fig. 3: Kaplan–Meier estimate of overall survival (n = 1465). Of the 531 censored patients at month 48, 171 were permanently lost to follow-up. CI = confidence interval.

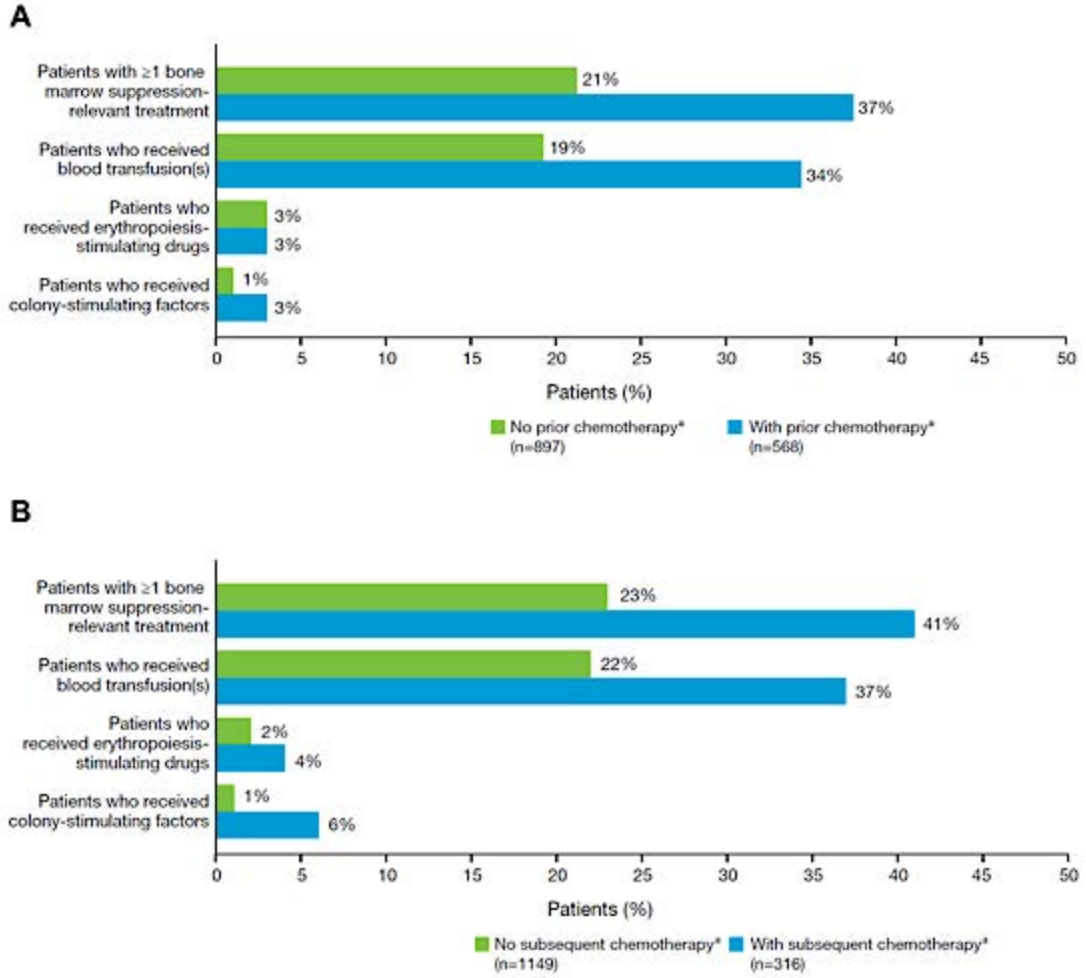
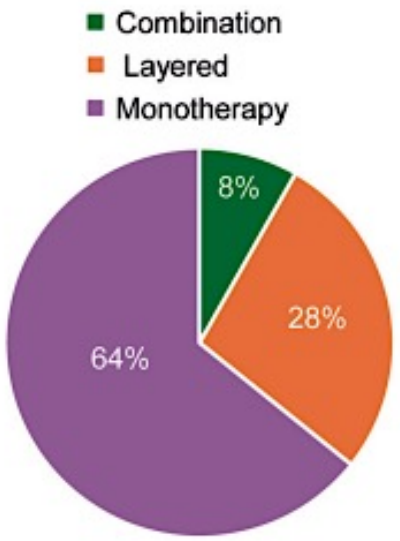


***Fig. 2:* Use of therapeutic or preventive treatments for bone-marrow suppression (n = 1465).** (A) After start of radium-223 treatment in patients who did or did not receive prior chemotherapy. (B) After completion of radium-223 treatment in patients who did or did not receive subsequent chemotherapy. *Patients may have received chemotherapy at other times.

Higano et al, Lancet, 2023

Real World Radium-223 Outcomes



Retrospective analysis of 1376 patients treated with radium-223

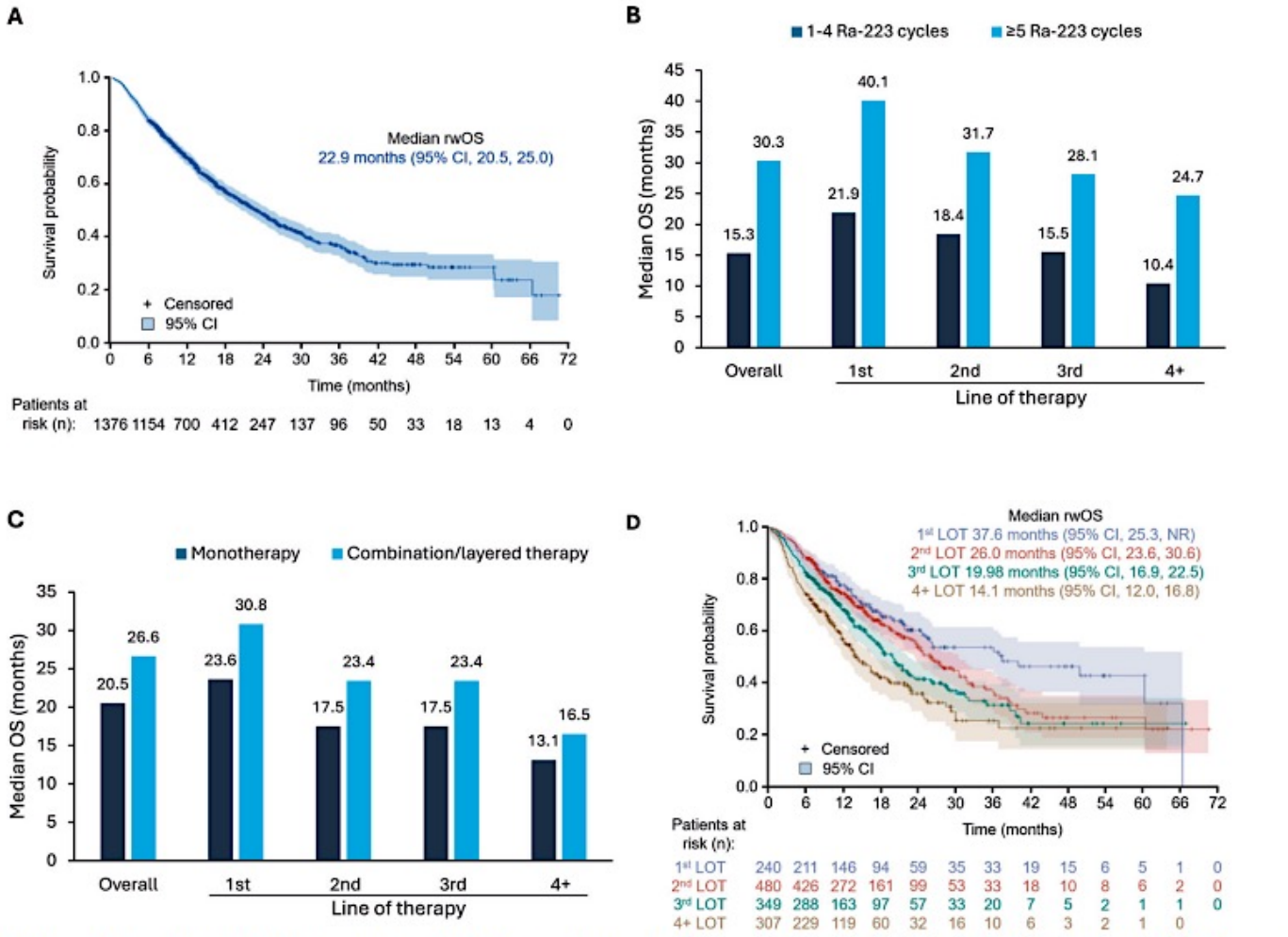
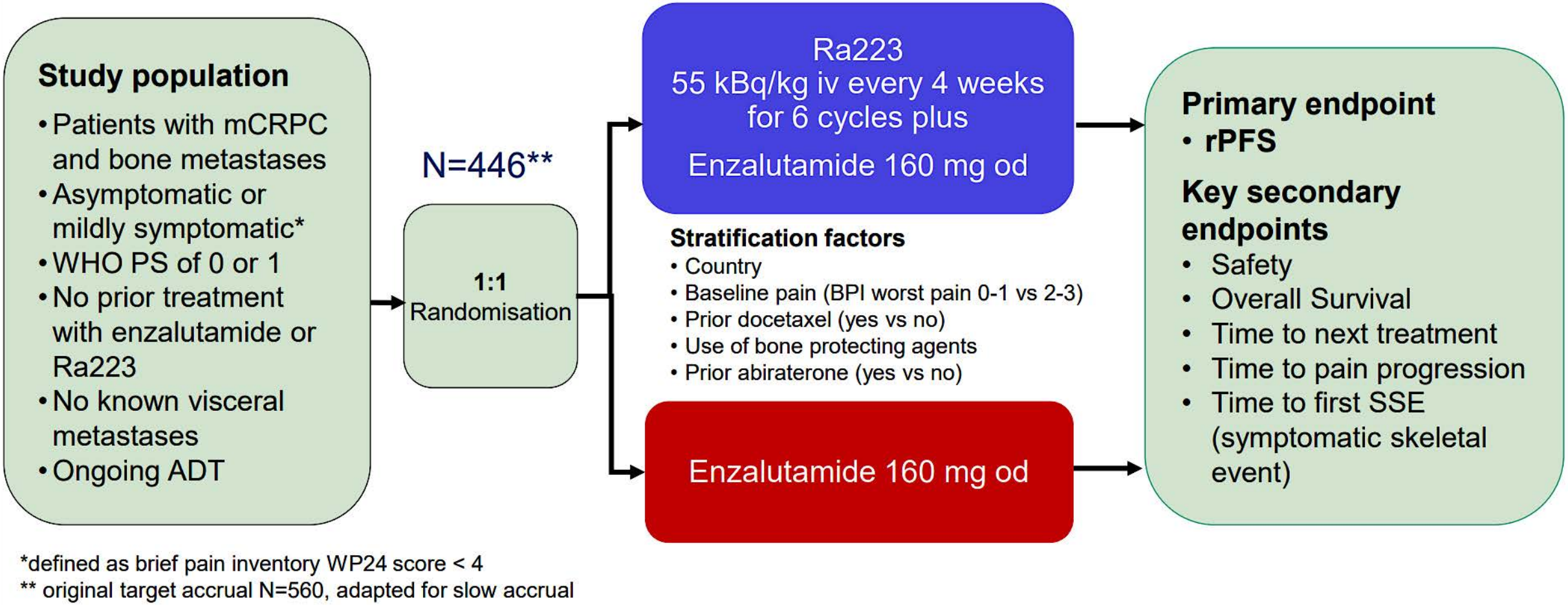


Fig. 3 Real-world overall survival. Data are shown for **A** the overall cohort, **B** by completion of 1–4 versus ≥5 Ra-223 cycles and LOT, **C** by use of Ra-223 monotherapy versus combination/layered and LOT, and **D** by LOT. CI confidence interval, LOT line of therapy, rwOS real-world overall survival.

Raval et al, PCPD, 2025

PEACE III Design



*defined as brief pain inventory WP24 score < 4
** original target accrual N=560, adapted for slow accrual

Gillessen et al, ESMO, 2024

PEACE III Baseline Characteristics

446 patients enrolled in 12 countries, 11/2015 to 03/2023, median follow-up: 42.2 months

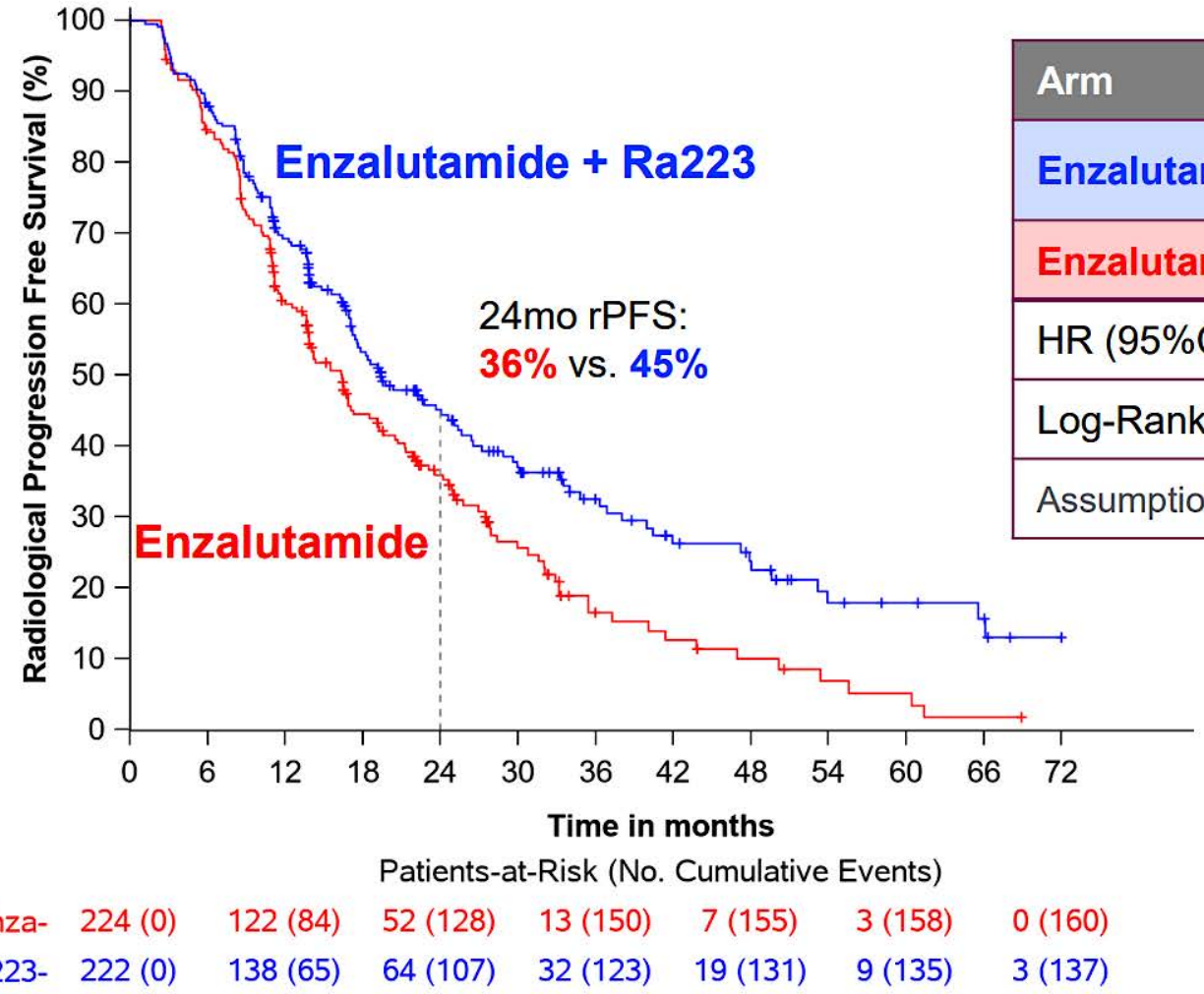
	Enza+Ra223 (N=222)	Enza (N=224)
	N (%)	N (%)
Age, Median (range) years	70.0 (43.0 - 90.0)	70.0 (47.0 - 90.0)
PSA, Median (Q25-Q75) ng/mL	25.3 (6.5 - 68.8)	23.0 (8.5 - 54.9)
WHO Performance status 0	152 (69)	154 (69)
Prior docetaxel(1)	67 (30.2)	66 (30)
Prior abiraterone(1)	4 (2)	7 (3)
Bone lesions(2)		
<10	109 (49)	105 (47)
≥10	93 (42)	99 (44)
Missing or diffuse lesions	20 (9)	20 (9)
Alkaline phosphatase		
≤ULN	127 (57)	107 (48)
>ULN	82 (37)	110 (49)
Missing	13 (6)	7 (3)
Extra-skeletal disease at baseline	77 (35)	73 (33)

(1) Prior docetaxel or abiraterone was allowed for mHSPC

(2) Per imaging guidelines, the type of bone lesions is reported by a radiologist and classified into focal, diffuse or equivocal. Only focal bone lesions can be counted.

Gillessen et al, ESMO, 2024

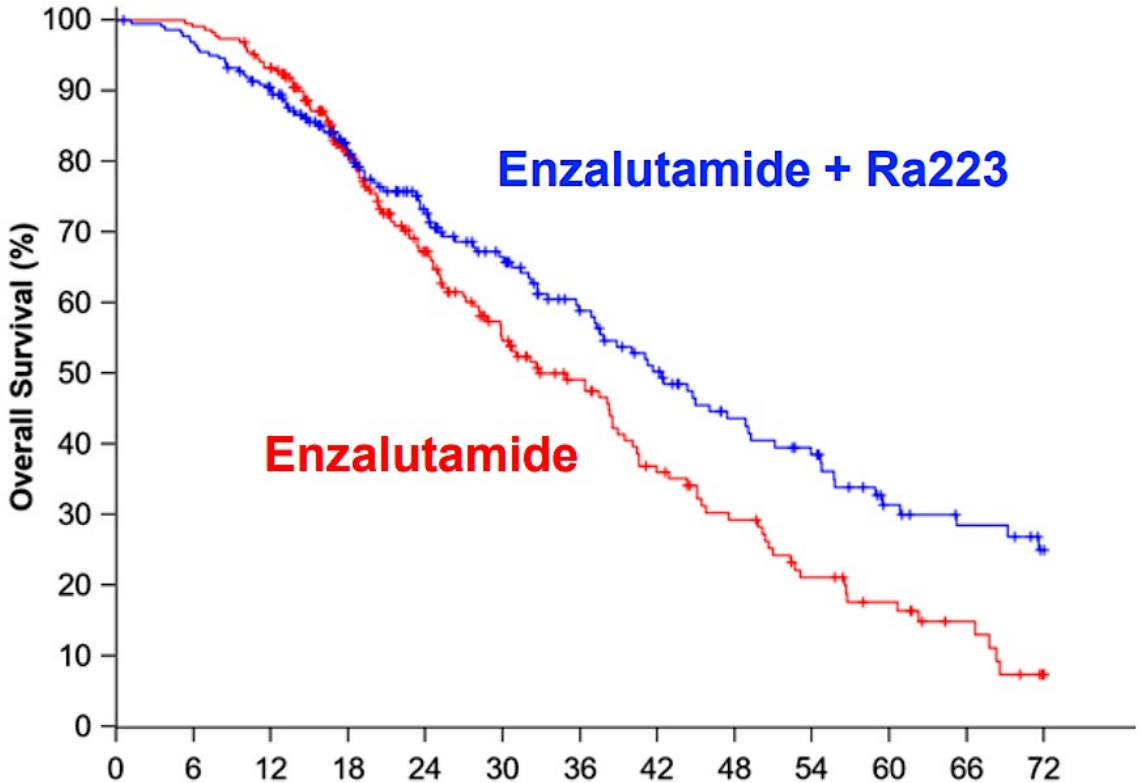
PEACE III Primary Endpoint rPFS



Arm	n/N	Median (95%CI)
Enzalutamide + Ra223	139/222	**19.4** (17.1-25.3) mo
Enzalutamide	160/224	**16.4** (13.8-19.2) mo
HR (95%CI)	**0.69** (0.54-0.87)	
Log-Rank p-value	**0.0009**	
Assumption of proportional hazard achieved		

Gillessen et al, ESMO, 2024

PEACE III Overall Survival



Patients-at-Risk (No. Cumulative Events)

Enza-	224 (0)	206 (15)	107 (64)	58 (90)	30 (112)	14 (123)	1 (129)
Enza+Ra223-	222 (0)	194 (21)	114 (53)	71 (73)	43 (90)	23 (101)	12 (105)

Arm	n/N	Median (95%CI)
Enzalutamide + Ra223	110/222	**42.3** (36.8-49.1) mo
Enzalutamide	129/224	**35.0** (28.8-38.9) mo
HR (95%CI)	**0.69** (0.52-0.90)	
Log-Rank p-value	**0.0031**	<0.0034

- Pre-set level of significance for interim analysis was ≤ 0.0034
- Due to non-proportional hazards plus lack of unequivocal significance for RMST (restricted mean survival time) sensitivity analysis, study will continue to final OS analysis

Gillessen et al, ESMO, 2024

PEACE III Adverse Events

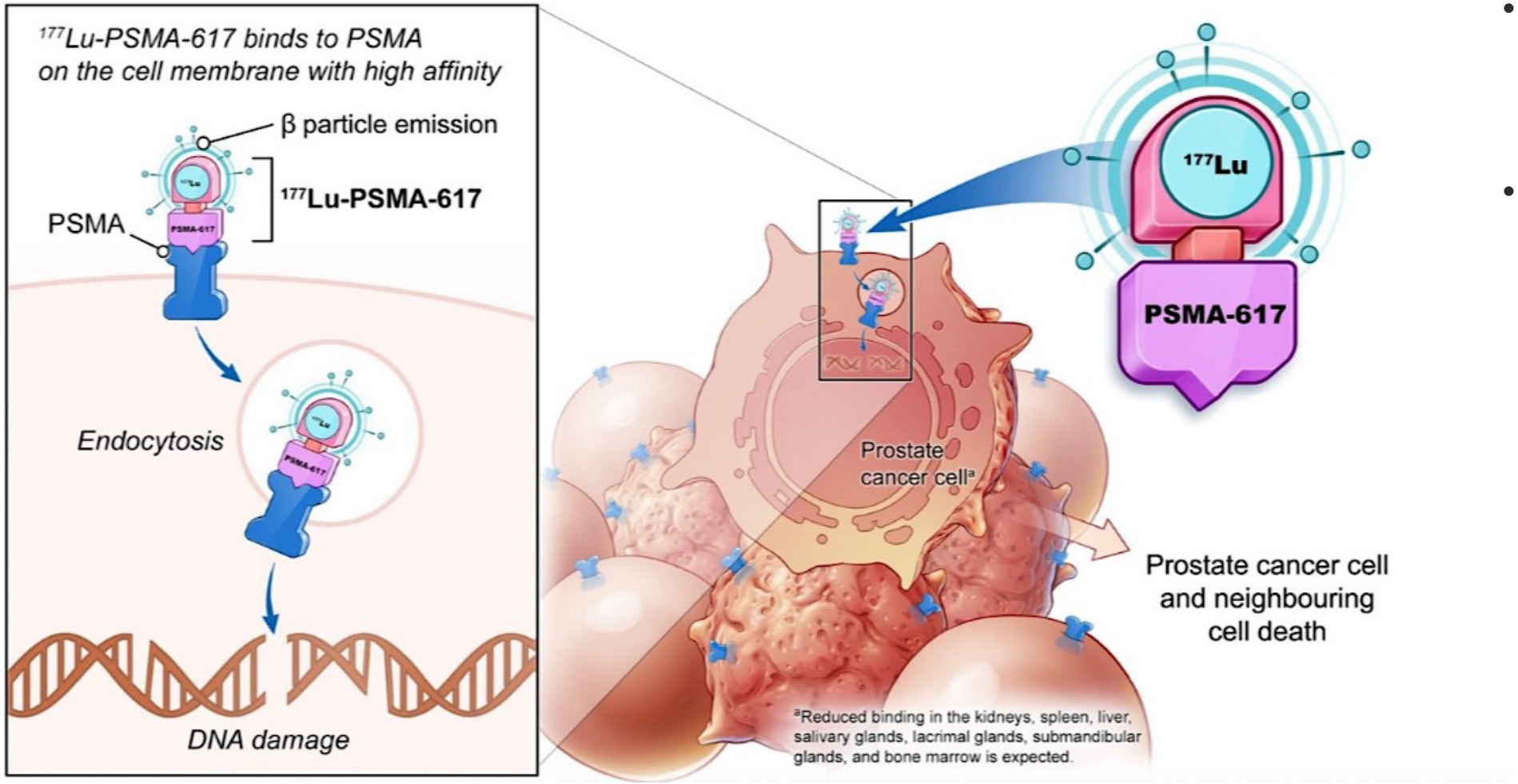
Patients	Enza+Ra223 (N=218) N (%)	Enza (N=224) N (%)
Adverse events (AEs)	218 (100)	216 (96)
Drug-related AEs	183 (84)	158 (71)
Serious AEs	93 (43)	66 (30)
Serious drug-related AEs	18 (8)	3 (1)
Grade 3-5 AEs	143 (66)	125 (56)
Grade 3-5 drug-related AEs	61 (28)	42 (19)
Death due to AE	7 (3)	4 (2)
Death due to a drug-related AE	0	0
Treatment discontinuation due to toxicity		
Enzalutamide	13 (8)	12 (7)
RA223	7 (3)	

Most common grade 3-5 treatment emergent AE (TEAE)	Enza+Ra223 (N=218) N (%)	Enza (N=224) N (%)
All		
Hypertension	73 (33.5)	77 (34.4)
Fatigue	12 (5.5)	4 (1.8)
Fracture	11 (5.1)	3 (1.3)
Anaemia	10 (4.6)	5 (2.2)
Neutropenia	10 (4.6)	0
Bone Pain	9 (4.1)	11 (4.9)
Weight Decreased	7 (3.2)	1 (0.4)
Spinal Cord Compression	6 (2.8)	8 (3.6)
Treatment related		
Hypertension	25 (11.5)	27 (12.1)
Fatigue	9 (4.1)	3 (1.3)
Anaemia	6 (2.8)	0
Neutropenia	7 (3.2)	0

Side effects of special interest: 1 MDS, 1 AML and 1 CML in the combination arm

Gillessen et al, ESMO, 2024

Mechanisms of Action of ^{177}Lu-PSMA-617



- ^{177}Lu-PSMA-617: β-emitting radioligand conjugated to PSMA-binding peptide
- PSMA (prostate-specific membrane antigen): Cell surface receptor involved in folate uptake and cell migration, proliferation, survival
  - Overexpressed in ~80% of mCRPC
  - Also expressed in normal prostate, proximal renal tubules, small intestine, salivary glands

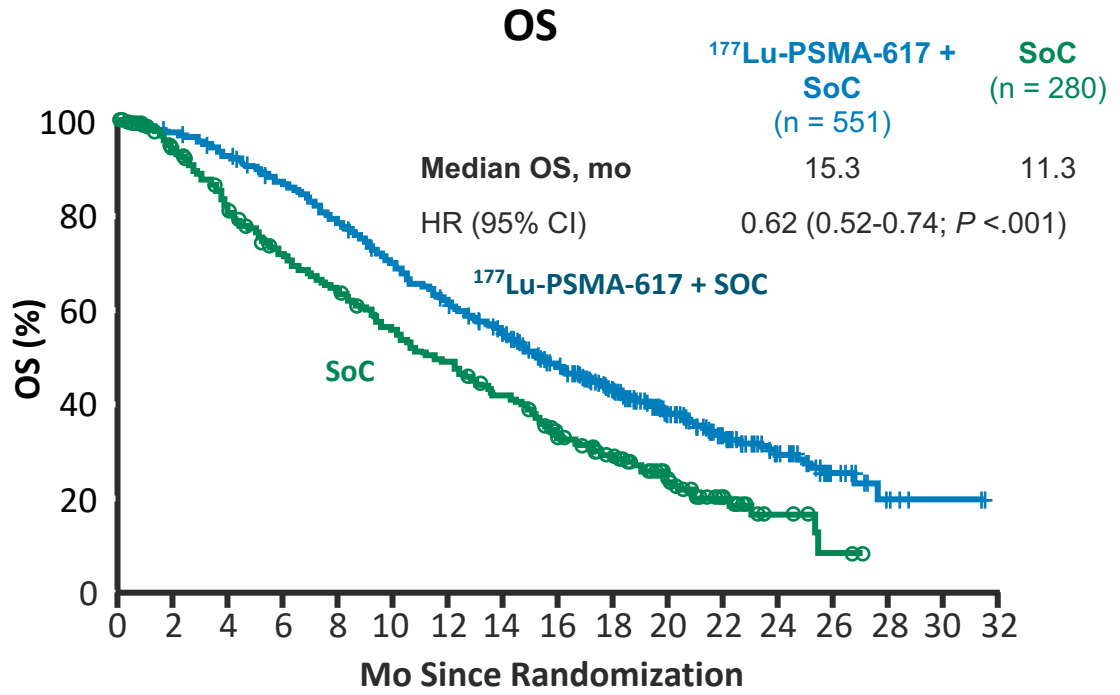
Phase III VISION: ^{177}Lu-PSMA-617 + SoC vs SoC

Patients with PSMA+ mCRPC on PET/CT with ^{68}Ga-PSMA-11; ≥1 prior AR pathway inhibitor and prior ≥1 taxane; ECOG PS 0-2
(N = 831)

→ ^{177}Lu-PSMA-617 7.4 GBq (200 mCi) Q6W x 4-6 cycles + Protocol-permitted SoC*
(n = 551)

→ Protocol-permitted SoC*
(n = 280)

*Excludes CT, immunotherapy, systemic radioisotopes, and investigational drugs.



- PSMA+ mCRPC defined as ≥1 PSMA+ metastatic lesion with ^{68}Ga uptake > liver *and* no PSMA- lesions in bone with soft tissue component ≥1 cm, lymph nodes ≥2.5 cm, or solid organ ≥1 cm
- Of 1003 patients who underwent scanning for VISION, 12.6% did not meet PSMA+ criteria

Sartor et al. NEJM. 2021;385:1091.

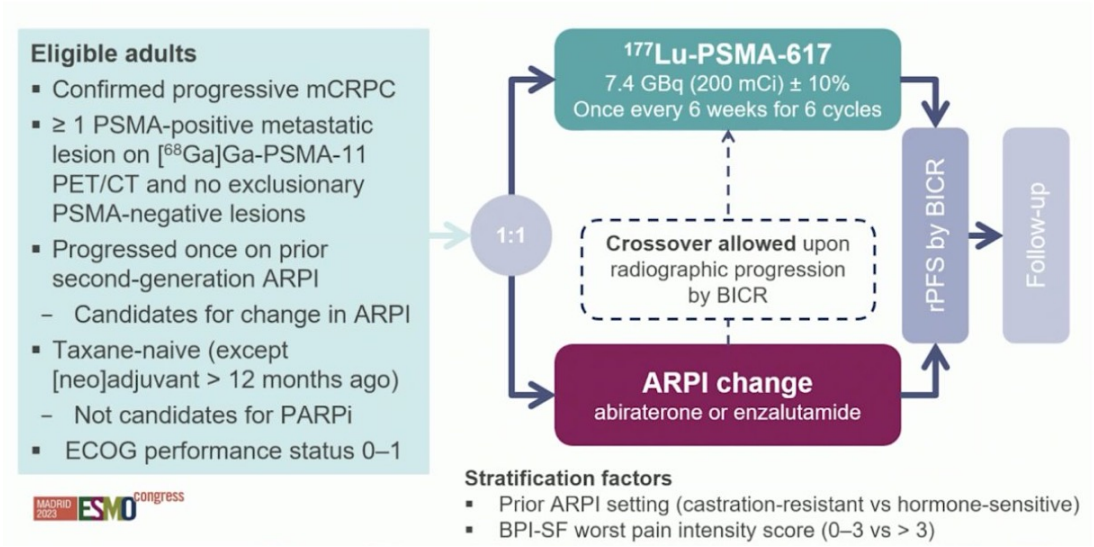
VISION: Safety

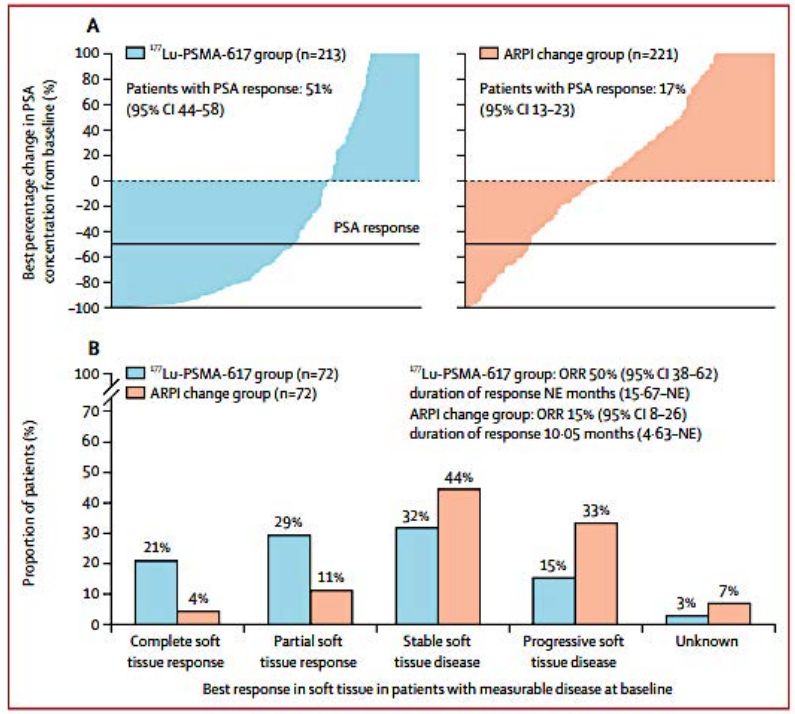
Patients, n (%)	All Grades		Grade 3-5	
	^{177}Lu-PSMA-617 + SoC (n = 529)	SoC Alone (n = 205)	^{177}Lu-PSMA-617 + SoC (n = 529)	SoC Alone (n = 205)
Fatigue	228 (43.1)	47 (22.9)	31 (5.9)	3 (1.5)
Dry mouth	205 (38.8)	1 (0.5)	0	0
Nausea	187 (35.3)	34 (16.6)	7 (1.3)	1 (0.5)
Anemia	168 (31.8)	27 (13.2)	68 (12.9)	10 (4.9)
Back pain	124 (23.4)	30 (14.6)	17 (3.2)	7 (3.4)
Arthralgia	118 (22.3)	26 (12.7)	6 (1.1)	1 (0.5)
Decreased appetite	112 (21.2)	30 (14.6)	10 (1.9)	1 (0.5)
Constipation	107 (20.2)	23 (11.2)	6 (1.1)	1 (0.5)
Diarrhea	100 (18.9)	6 (2.9)	4 (0.8)	1 (0.5)
Vomiting	100 (18.9)	13 (6.3)	5 (0.9)	1 (0.5)
Thrombocytopenia	91 (17.2)	9 (4.4)	42 (7.9)	2 (1.0)
Lymphopenia	75 (14.2)	8 (3.9)	41 (7.8)	1 (0.5)
Leukopenia	66 (12.5)	4 (2.0)	13 (2.5)	1 (0.5)

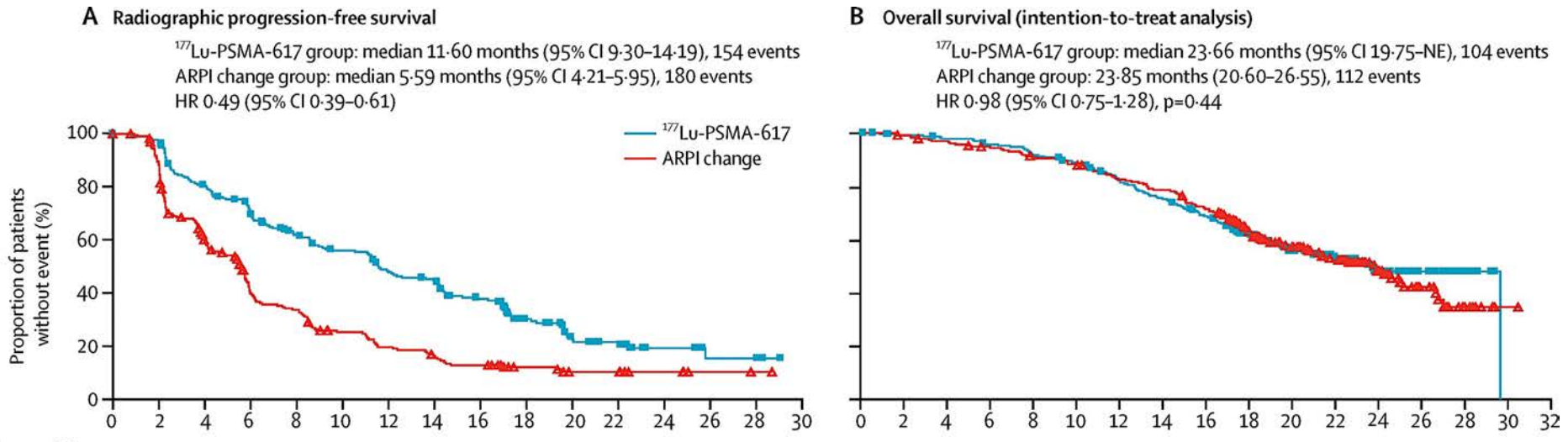
Sartor et al. NEJM. 2021;385:1091.

PSMAFore

Eligible adults
- Confirmed progressive mCRPC
- ≥ 1 PSMA-positive metastatic lesion on [^{68}Ga]Ga-PSMA-11 PET/CT and no exclusionary PSMA-negative lesions
- Progressed once on prior second-generation ARPI
  - Candidates for change in ARPI
- Taxane-naive (except [neo]adjuvant > 12 months ago)
  - Not candidates for PARPi
- ECOG performance status 0–1







Morris et al, Lancet, 2024

ENZA-P

ENZA-p Schema

Eligibility

mCRPC with PSA rising and >5ng/mL
No chemotherapy for mCRPC
≥2 risk features for early enzalutamide failure
Positive ^{68}Ga PSMA PET/CT

R

1:1

Enzalutamide 160 mg

Enzalutamide 160 mg + [^{177}Lu]Lu- PSMA-617 7.5 GBq 2-4 doses

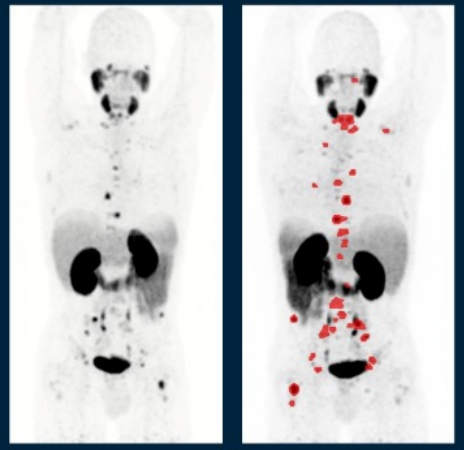
Stratification

Study Site
Volume of disease (>20 vs ≤20)
Early docetaxel for hormone-sensitive disease
Prior treatment with abiraterone

Objectives

PSA-PFS (primary endpoint)
Overall survival
Health-related Quality of Life
Radiographic PFS
PSA response rate
Pain response and PFS
Clinical PFS
Adverse events
Health economic analyses
Translational/correlative

Screening Criteria



PSMA-PET screening criteria

SUV_{max} ≥15 at one site AND ≥10 at all measurable sites
Mismatch on diagnostic CT not an exclusion

Risk Factors for Early Treatment Failure on Enzalutamide

LDH ≥ULN
ALP ≥ULN
Albumin <35g/L
De novo metastatic disease at diagnosis
<3 Years since initial diagnosis
>5 Bone metastases
Visceral metastases
PSA doubling time <84 days
Pain requiring opiates >14 days
Prior abiraterone

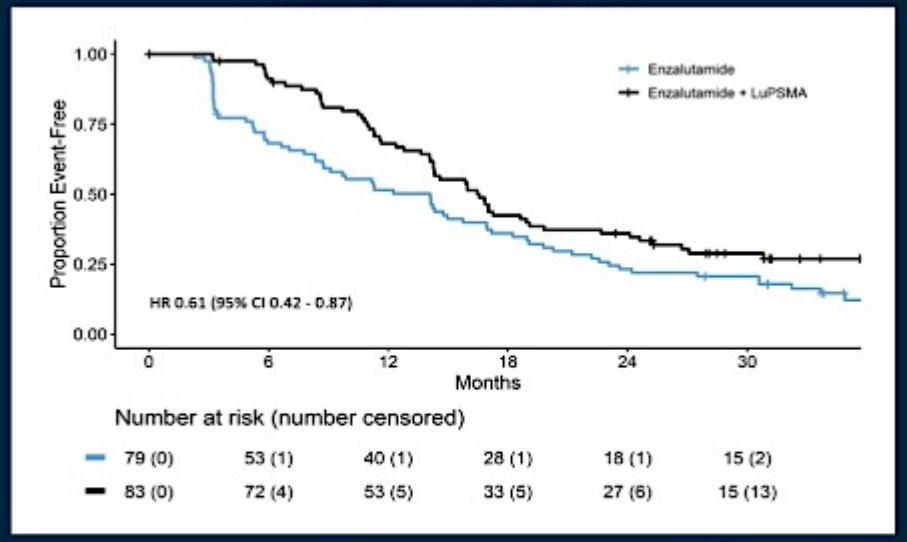
Imaging screen failure rate 18%

Emmett et al, GU ASCO, 2025

ENZA-P

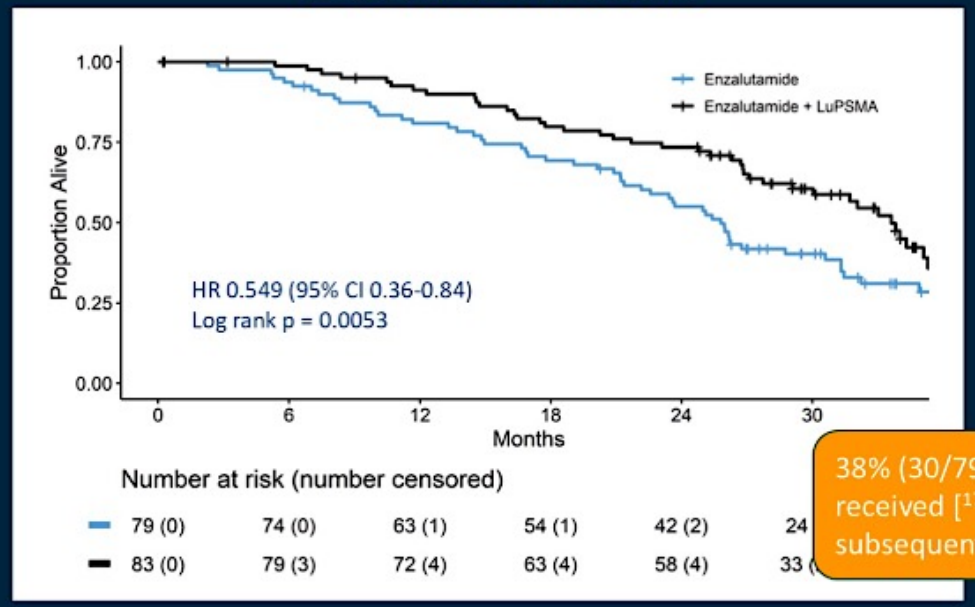
R-PFS

HR 0.61 (95% CI 0.42-0.87)



R-PFS	Participants	Events	Censored	Median Months
Enzalutamide	79	69	10	14
Enzalutamide+[^{177}Lu]LuPSMA617	83	56	27	17

Overall Survival

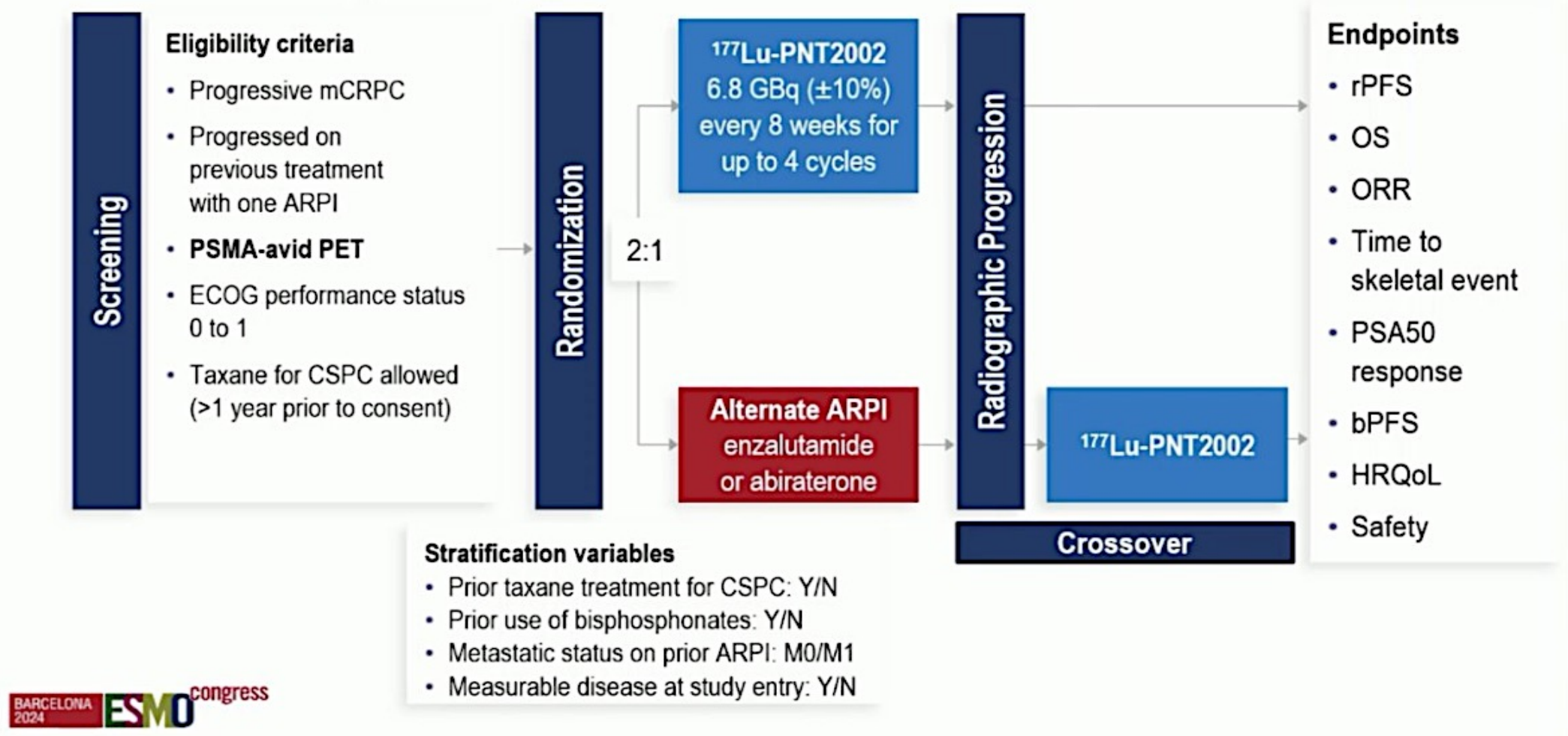


38% (30/79) on enzalutamide-alone received [^{177}Lu]Lu-PSMA 617 as subsequent treatment off protocol

Overall Survival	Participants	Events	Censored	Median Months
Enzalutamide	79	53	26	26 (C195% 23-31)
Enzalutamide + Lu-PSMA 617	83	43	40	34 (CI95% 30-37)

Emmett et al, GU ASCO, 2025

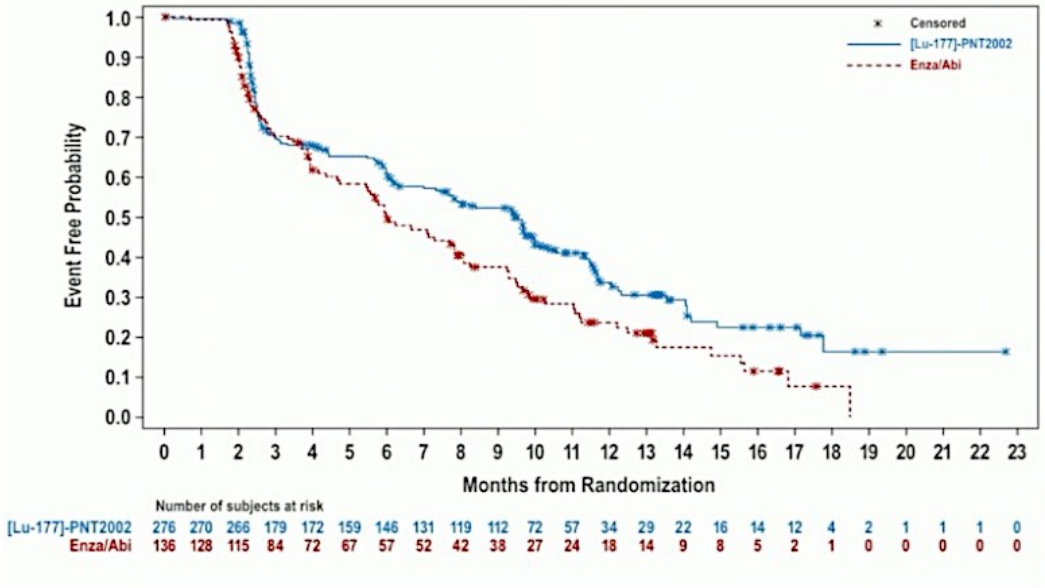
SPLASH Study Design



Sartor et al, ESMO, 2024

SPLASH – rPFS, ORR, PSA Response

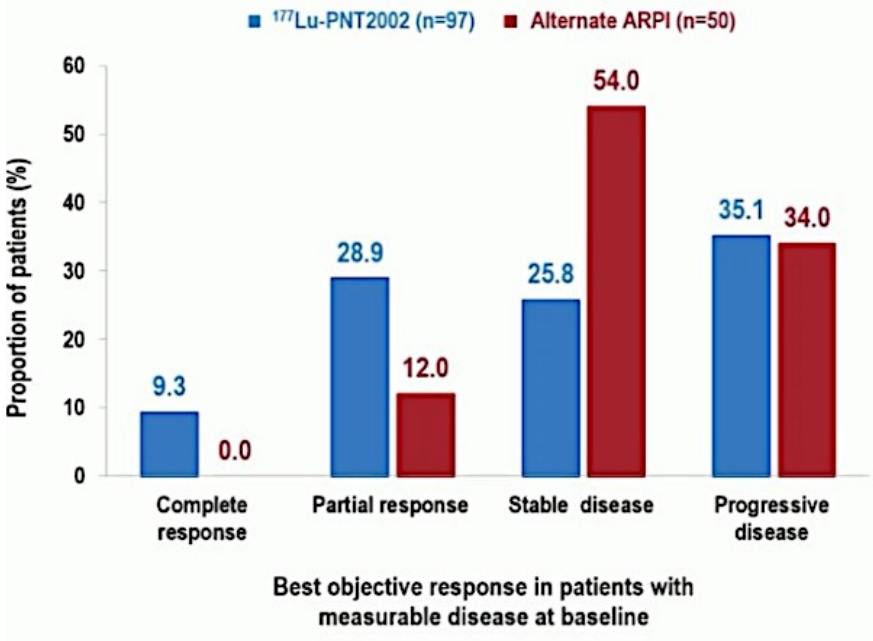
Primary Endpoint - rPFS: Primary Analysis



	^{177}Lu-PNT2002 (n = 276)	Alternate ARPI (n = 136)
Events, n	162 (58.7%)	96 (70.6%)
Median rPFS (95% CI)	9.5 months (7.4, 10.0)	6.0 months (4.7, 7.9)
Median follow-up (95% CI)	11.1 months (10.1, 11.6)	12.9 months (10.2, 15.9)

HR: 0.71 (95% CI: 0.55, 0.92)
p = 0.0088

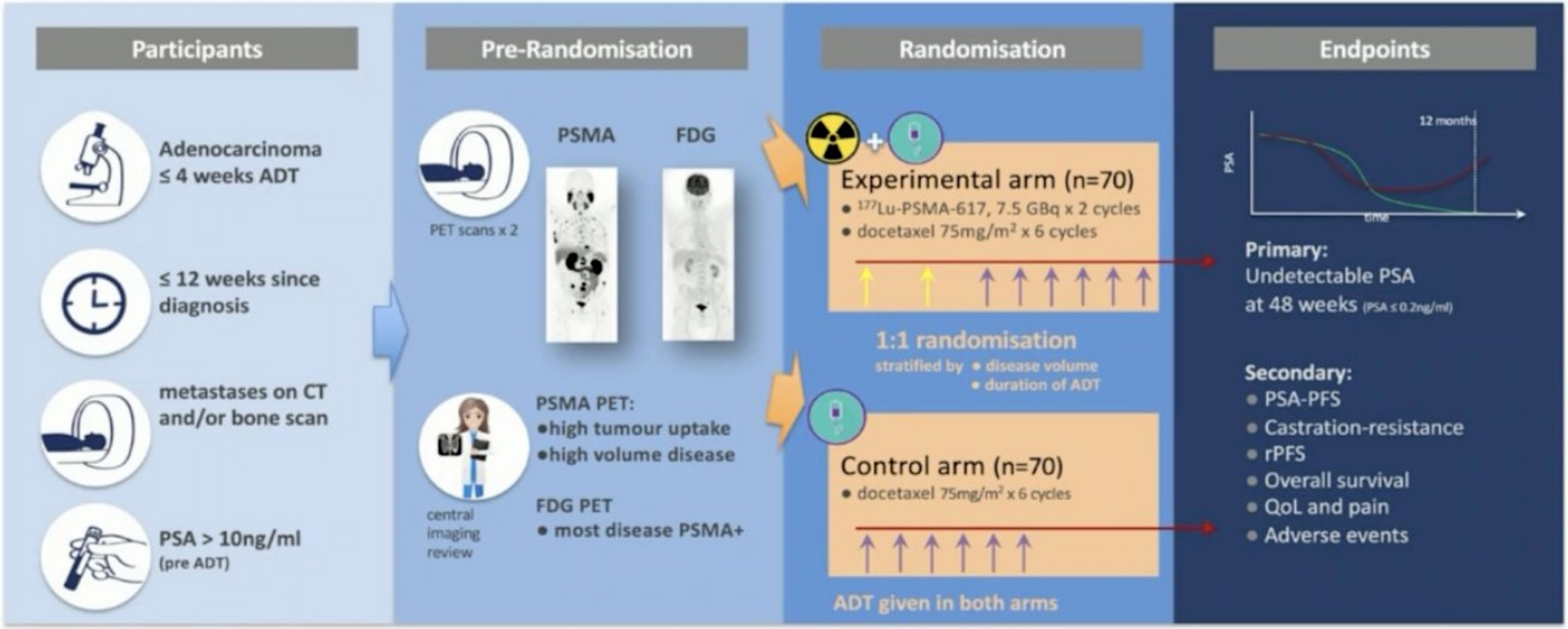
Overall Response Rate



PSA ≥50%: 35.7% vs. 14.6%

Sartor et al, ESMO, 2024

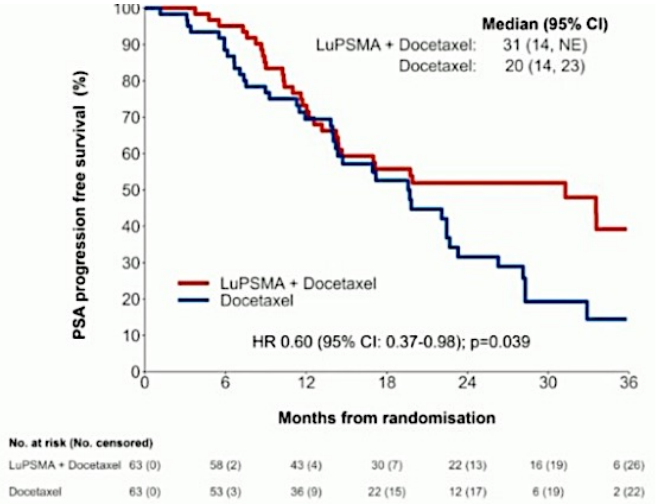
UpFrontPSMA

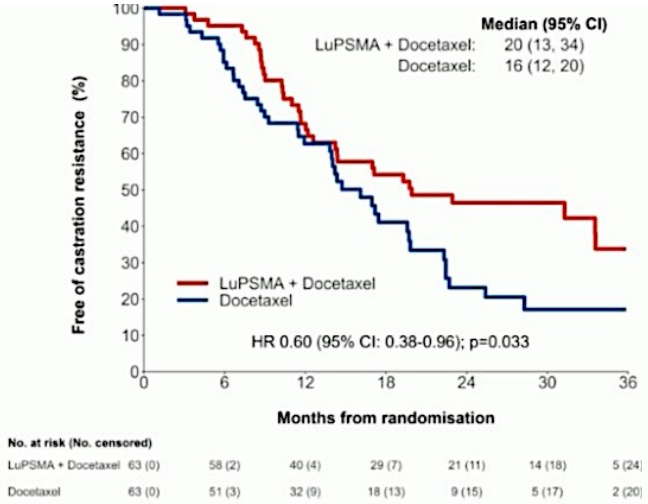


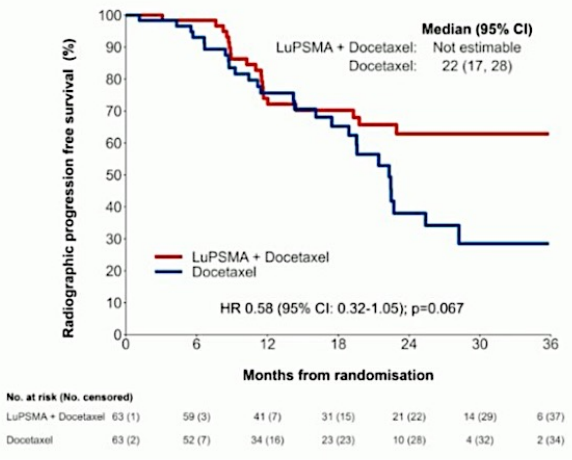
Azad et al, ESMO, 2024

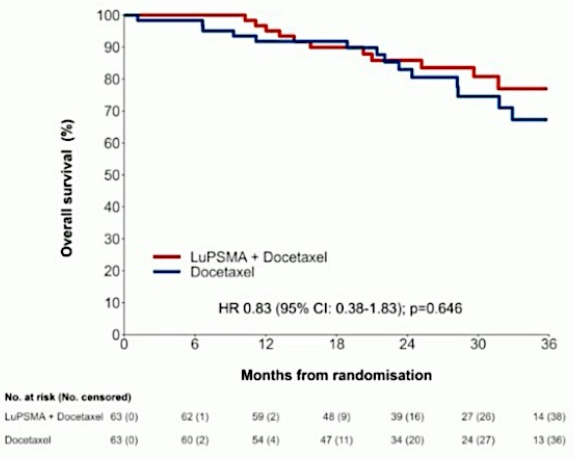
UpFrontPSMA

Treatment	Lu-PSMA + docetaxel (n=61)*	Docetaxel (n=61)*
Undetectable PSA at week 48, %	41% (95% CI 30-54)	16% (95% CI 9-28)
	OR 3.88 (95% CI 1.61-9.38); p=0.002	
Undetectable PSA at any time point, %	51% (95% CI 39-63)	32% (95% CI 22-45)
	OR 2.14 (95% CI 1.03-4.46); p=0.042	
Undetectable PSA at week 12, %	17% (95% CI 10-29)	18% (95% CI 10-29)
	OR 0.94 (95% CI 0.37-2.36); p=0.895	









Azad et al, ESMO, 2024

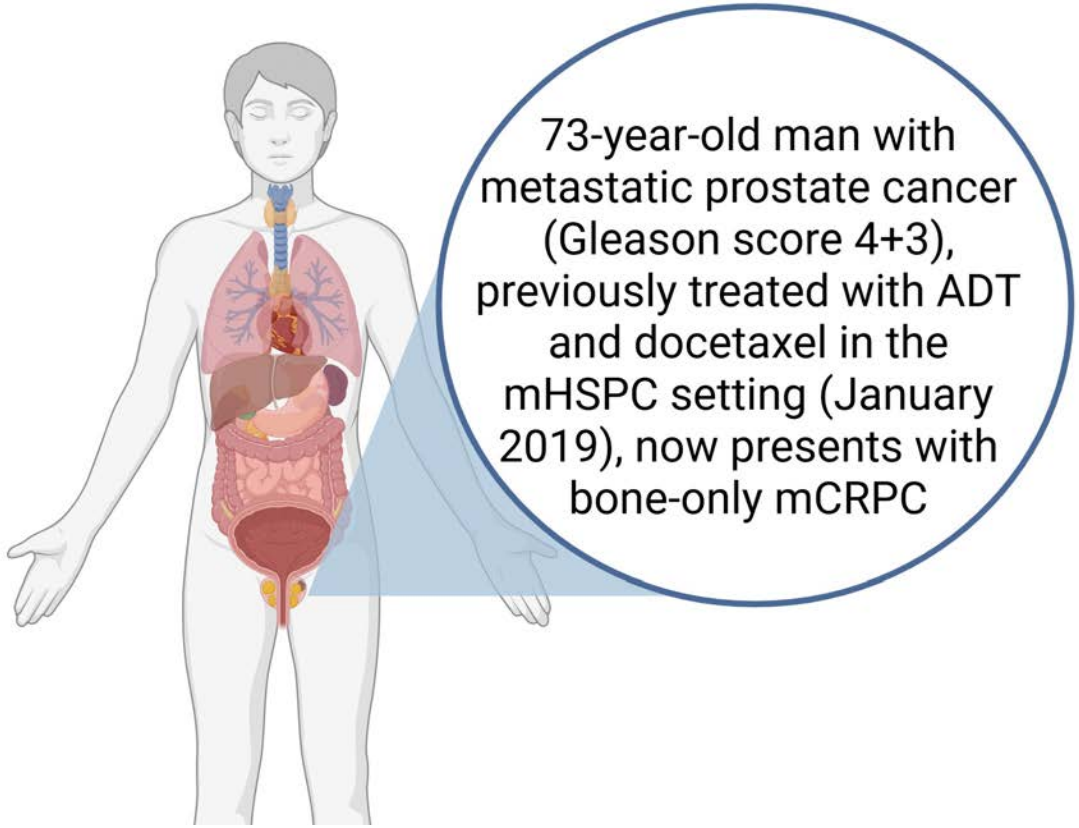
Conclusions

- **Radium-223**
  - First FDA-approved alpha-emitter (2013) with calcium-mimetic properties that specifically targets bone metastases, extending overall survival in the ALSYMPCA trial with a manageable safety profile, though effectiveness is limited to bone disease with minimal impact on PSA levels.
- **177Lu-PSMA-617**
  - First PSMA-targeted radiopharmaceutical (approved 2022) that demonstrated significant survival benefits in the VISION trial, effectively targeting PSMA-expressing metastatic sites with robust PSA responses, which received FDA approval expansion in March 2025 for pre-chemotherapy use based on the PSMAfore trial
- **Future Directions**
  - The field is rapidly evolving with numerous promising agents in development, including Actinium-225-PSMA (with higher energy alpha particles) and combination approaches

Faculty Case Presentations

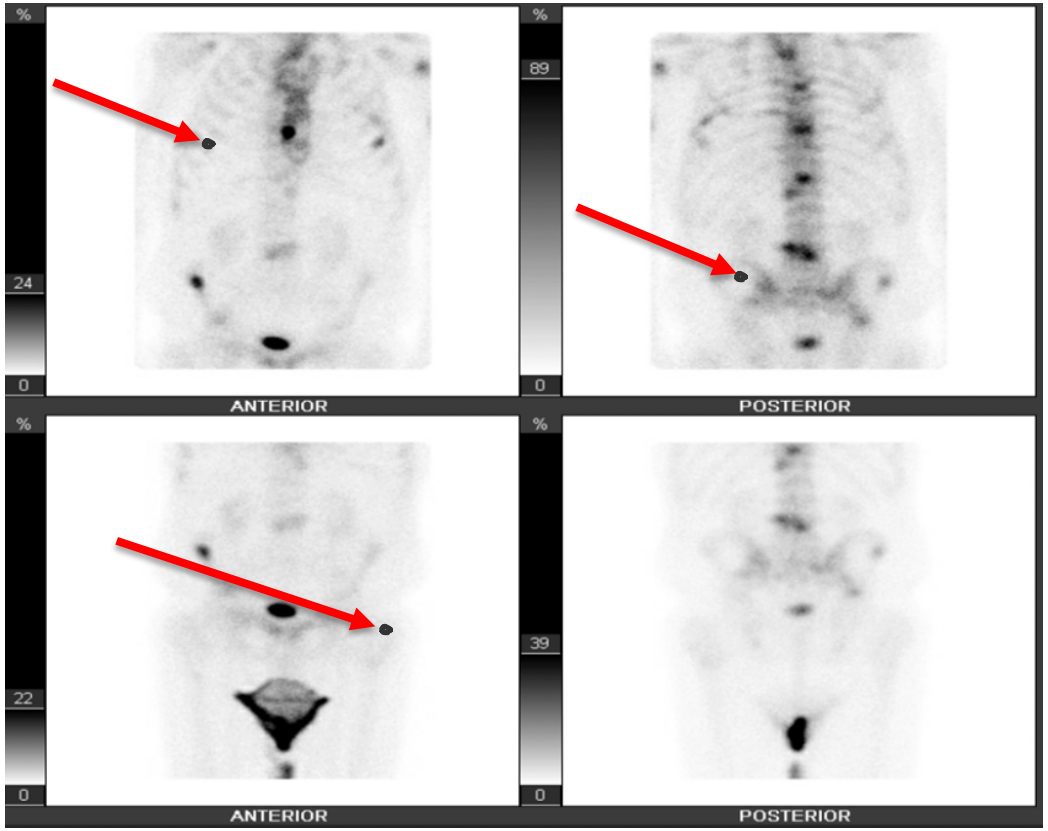
Case Presentation – Dr Agarwal: Enza + Radium-223 in mCRPC

May 2021



73-year-old man with metastatic prostate cancer (Gleason score 4+3), previously treated with ADT and docetaxel in the mHSPC setting (January 2019), now presents with bone-only mCRPC

Bone scan showing multiple bone metastases



IMPRESSION:

Widespread skeletal metastases throughout the axial and appendicular skeleton with some new foci of uptake in the spine and increased uptake in one focus of the sternum and one focus of the ileum

Case Presentation – Dr Agarwal: Enza + Radium-223 in mCRPC (cont'd)

TOTAL SERUM PSA -

Status: Final result Dx: Prostate ca

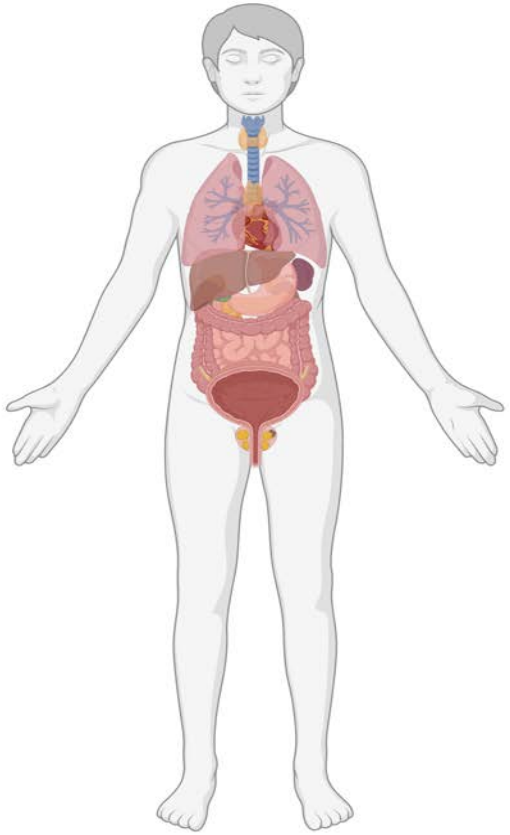
Test Result Released: No (inaccessi

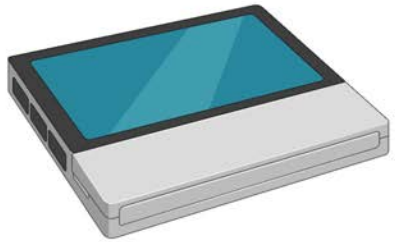
0 Result Notes

Newer results are available

Component		
Ref Range & Units (hover)		
Prostate Specific Antigen -	30.7 ▲	

May 2021
Onset of castration-resistant disease





648 gene panel

GENOMIC VARIANTS

Somatic - Potentially Actionable

AR	Copy number gain
TP53	Copy number loss
TMPRSS2 - ERG	Chromosomal rearrangement

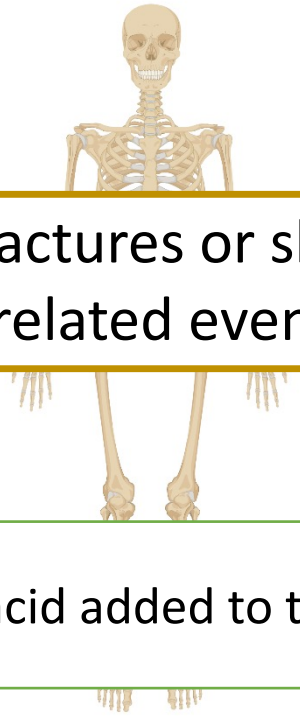
Somatic - Biologically Relevant

ZFHX3	Copy number loss

Case Presentation – Dr Agarwal: Enza + Radium-223 in mCRPC (cont'd)

June 2021

Patient started on Enzalutamide + Radium-223



No fractures or skeletal-related events

Zoledronic acid added to the regimen

TOTAL SERUM PSA

Status: Final result Dx: Prostate cancer metastatic to multipl...

Test Result Released: No (seen, inaccessible in MyChart)

0 Resul

Disease control for ~2 years

Component Ref Range & Units (hover)							
Prostate Specific Antigen -	2.6	2.8 CM	2.9 CM	2.5 CM	3.1 CM	3.9 CM	30.7 CM ^

QUESTIONS FOR THE FACULTY

Which patients with mCRPC do you feel are ideal candidates for radium-223?

What are the practical applications of the PEACE III trial for patients who have been exposed to AR pathway inhibitors in a prior line of therapy? Would you consider radium-223 in combination with enzalutamide in such a scenario? Would this depend at all on the specific AR pathway inhibitor the patient had received or how long ago they had received it?

How often do you see prolonged disease control with radium-223-based therapy as in this patient's case?

RTP
RESEARCH
TO PRACTICE

Case Presentation – Dr Saad: 70-year-old patient

- Treated with RoRx in 2018 for cT2 Gleason 4+3 prostate cancer
- Recurrence: mHSPC in 6-2021 treated with ADT + APALUTAMIDE
- Progression on APA with PSA 5.7 in 07-2023

- PLUDO trial randomized to lutetium 09-2023
- PSA post C1 3.76, C2 1.31, C3 0.29, C4 0.02
- Last seen May 2025 PSA remains 0.02 ECOG 0
- No radiographic progression

CHUM

QUESTIONS FOR THE FACULTY

How are you currently employing lutetium Lu 177 vipivotide tetraxetan for patients with mCRPC vis-à-vis other evidence-based options? Given the recent expansion of its indication, in which situations are you prioritizing it over taxane-based chemotherapy?

What other novel radiopharmaceuticals do you believe may soon enter the treatment armamentarium for patients with PSMA-expressing mCRPC? If these therapies become available, how will you select between them and lutetium Lu 177 vipivotide tetraxetan?

Agenda

MODULE 1: Evolving Management of Nonmetastatic Hormone-Sensitive Prostate Cancer (HSPC) — Dr Saad

MODULE 2: Current Treatment for Metastatic HSPC — Dr Armstrong

MODULE 3: Role of PARP Inhibition in Metastatic Castration-Resistant Prostate Cancer (mCRPC) — Dr Agarwal

MODULE 4: Current and Future Use of Radiopharmaceuticals for mCRPC — Dr McKay

MODULE 5: Promising Novel Agents and Strategies Under Investigation for the Management of Prostate Cancer — Dr Beltran

Promising Novel Agents and Strategies Under Investigation for the Management of Prostate Cancer

Himisha Beltran, MD

Dana-Farber Cancer Institute

Boston, Massachusetts, United States

New therapies across the disease continuum

- **Localized prostate cancer**: Phase III trial of CAN-2409+prodrug in combination with standard of care EBRT for newly diagnosed localized prostate cancer

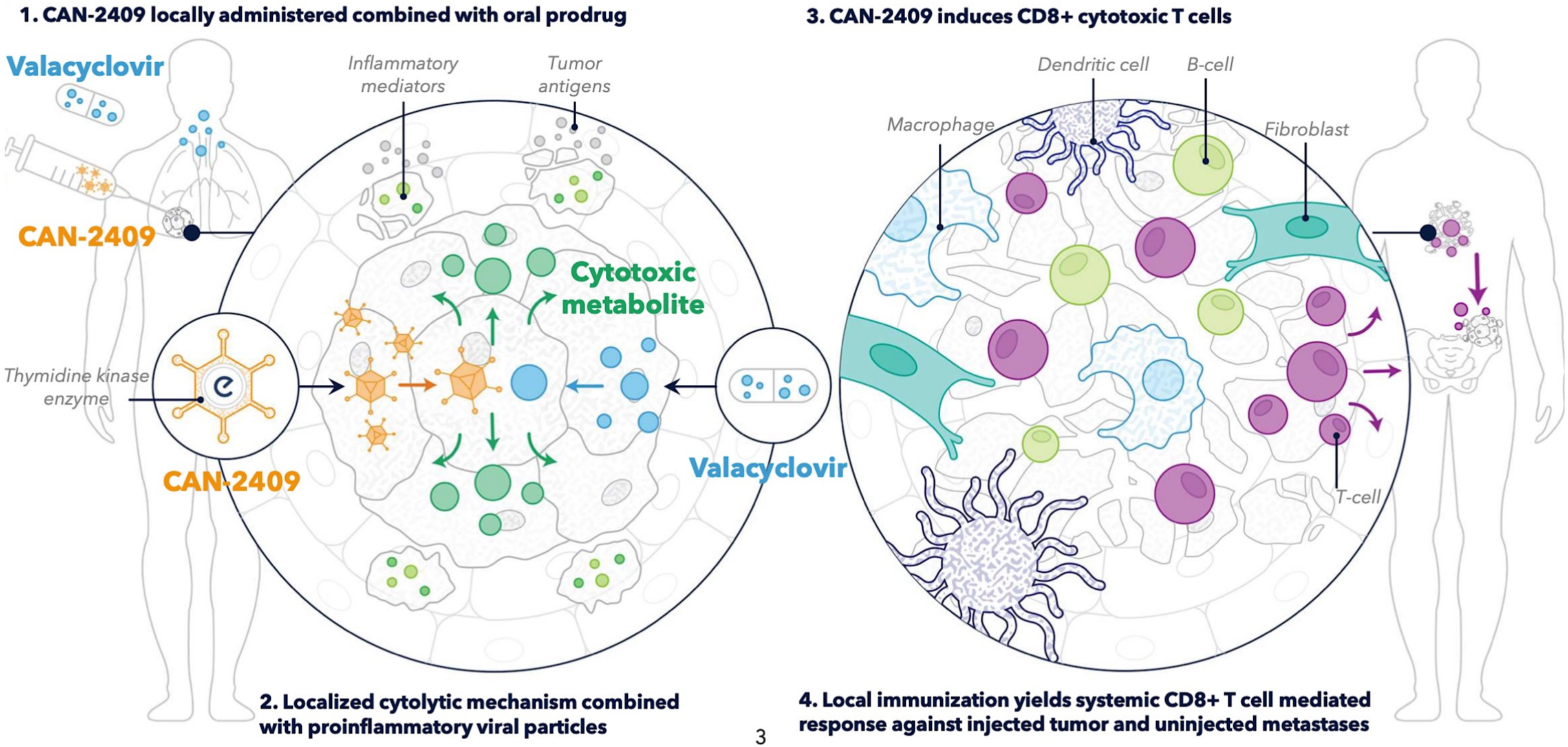
- **De novo metastatic hormone sensitive prostate cancer**: Phase III CAPItello-281 trial assessing capivasertib plus abiraterone/ADT in patients with PTEN deficiency

- **Metastatic CRPC**: Early phase data supporting mevrometostat in combination with enzalutamide

CAN-2409

- Locally delivered oncolytic therapy, results in vaccination against the injected tumor.
- Consists of a non-replicating adenovirus engineered to deliver gene encoding Herpes virus thymidine kinase in tumor cells
- Thymidine kinase converts oral valacyclovir into a phosphorylated nucleotide that is incorporated into the tumor cell's genome → termination of DNA synthesis and cell death
- Overall results in immunogenic cell death, release of tumor specific antigens recognized by immune system. Adenovirus itself recruits immune cells -> response in injected tumor + distant metastases

CAN-2409



CAN-2409 is an investigational product and its mechanism of action in humans has not been definitively established. This depiction of the CAN-2409 mechanism of action and the MoA video linked above are based on preclinical data and observations in clinical studies to date

Phase 3 clinical trial of CAN-2409 in patients with newly diagnosed, intermediate / high risk, localized prostate cancer

PIs: Dr. T. DeWeese (JHU) and Dr. P. Scardino (MSKCC)

NCT01436968

N=745
Fully enrolled
Newly diagnosed, intermediate / high risk, localized prostate cancer

2:1
Randomization

CAN-2409 + Valacyclovir
(3 injection courses + radiotherapy, with or without short course ADT)

Placebo + Valacyclovir
(3 injection courses + radiotherapy, with or without short course ADT)

Primary Endpoint

- Disease-free survival (time to cancer recurrence or death due to any cause)

Key secondary endpoints

- PSA freedom from biochemical failure[1]
- Prostate cancer specific outcomes[2]
- Overall survival[3]

- *Randomization stratified by NCCN[4] risk group and planned short course ADT*

Disease-free survival (DFS)

Date of randomization to date of recurrence proven by biopsy, clinical or radiographic evidence of local or regional failure, distant metastases, or death from any cause

- Local failure: includes increase in tumor size by 50%, reappearance of palpable tumor or biopsy revealing adenocarcinoma of the prostate at least 2 years after randomization
- Regional failure: clinical recurrence with radiographic evidence of tumor in the pelvis
- Distant metastases: clinical recurrence with radiographic evidence of disease beyond the pelvis

CAN-2409 in combination with SoC radiation +/-ADT was generally well tolerated

Treatment related AEs >5% in either arm

Preferred term	CAN-2409+prodrug (N=479)	Placebo+prodrug (N=232)	Total (N=711)
Chills	160 (33.4)	20 (8.6)	180 (25.3)
Influenza-like illness	146 (30.5)	32 (13.8)	178 (25.0)
Fever	120 (25.1)	9 (3.9)	129 (18.1)
Fatigue	87 (18.2)	35 (15.1)	122 (17.2)
Urinary frequency	58 (12.1)	34 (14.7)	92 (12.9)
Nausea	53 (11.1)	19 (8.2)	72 (10.1)
Headache	45 (9.4)	12 (5.2)	57 (8.0)
Diarrhoea	30 (6.3)	18 (7.8)	48 (6.8)
Malaise	28 (5.8)	5 (2.2)	33 (4.6)
Vomiting	26 (5.4)	3 (1.3)	29 (4.1)
Urinary urgency	19 (4.0)	16 (6.9)	35 (4.9)
Urinary tract pain	18 (3.8)	14 (6.0)	32 (4.5)

Chills, fever, flu-like symptoms were commonly mild to moderate and self limited

Incidence of treatment related SAEs lower on CAN-2409

- 1.7% on CAN-2409 + SoC
- 2.2% on placebo + SoC

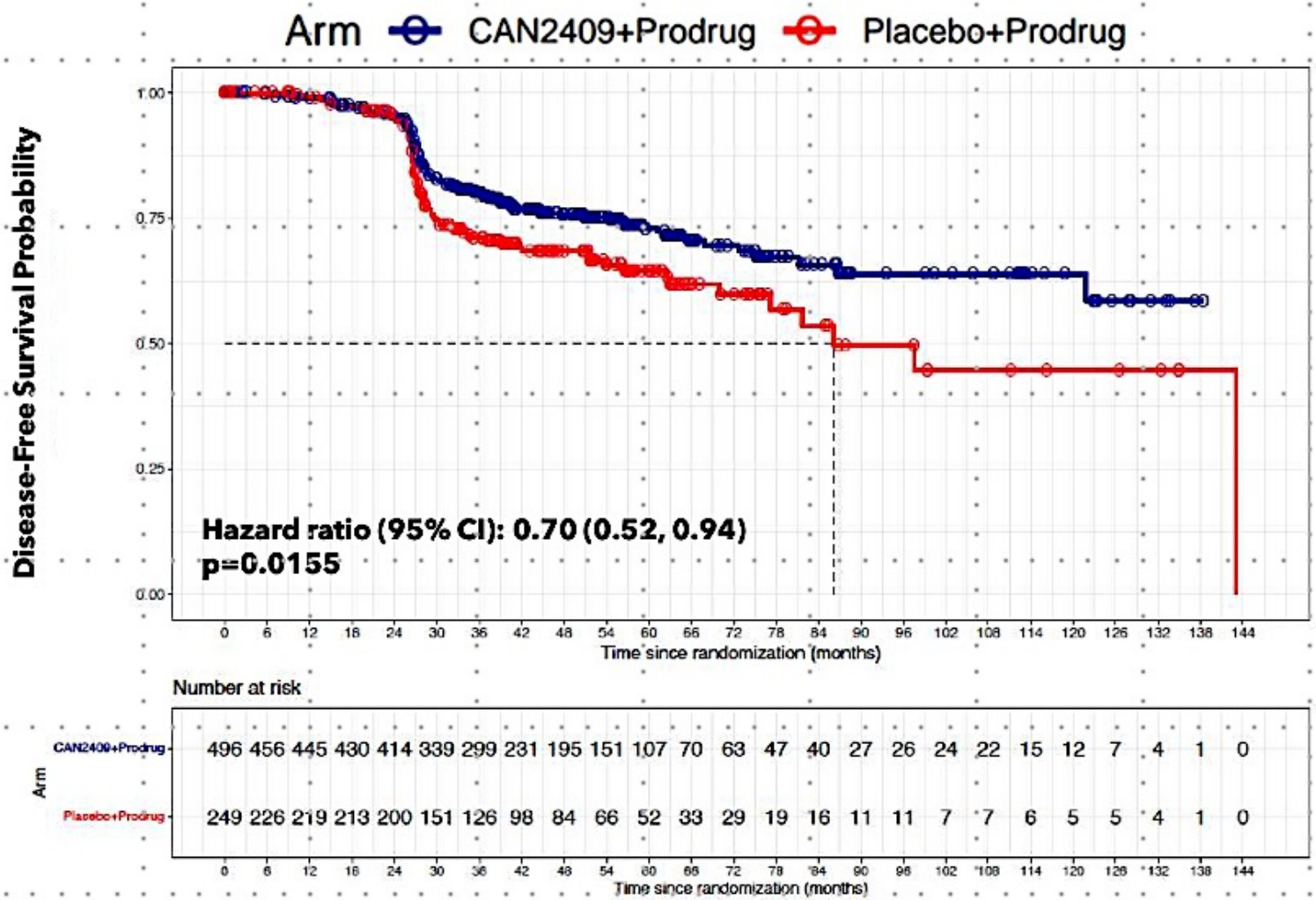
Incidence of SAEs lower on CAN-2409 arm

- 5.8% on CAN-2409 + SoC
- 7.3% on placebo + SoC

Incidence of treatment discontinuation due to AEs lower on CAN-2409 arm

- 5.4% on CAN-2409 + SoC
- 6.0% on placebo + SoC

CAN-2409 significantly improved DFS in newly diagnosed, intermediate/high-risk prostate cancer (ITT, N=745): 30% decrease in disease recurrence



median follow-up 50.3 months (CI 45.37, 51.29)

New therapies across the disease continuum

- **Localized prostate cancer**: Phase III trial of CAN-2409+prodrug in combination with standard of care EBRT for newly diagnosed localized prostate cancer

- **De novo metastatic hormone sensitive prostate cancer**: Phase III CAPItello-281 trial assessing capivasertib plus abiraterone/ADT in patients with PTEN deficiency

- **Metastatic CRPC**: Early phase data supporting mevrometostat in combination with enzalutamide

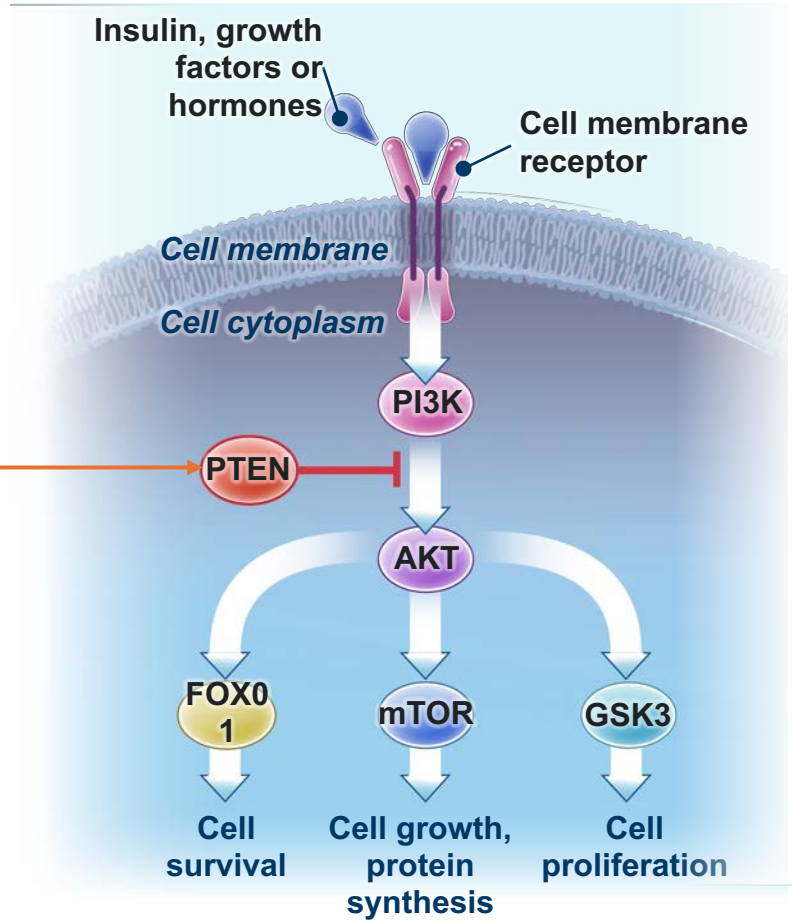
In mHSPC, PI3K/AKT dysregulation by deficiency of PTEN

PTEN deficiency, through gene deletion and other mechanisms, leads to unopposed PI3K/AKT signalling, contributing to tumour growth and progression, and development of treatment resistance

PTEN is a protein that modulates PI3K/AKT signalling by opposing AKT activation[2,4]

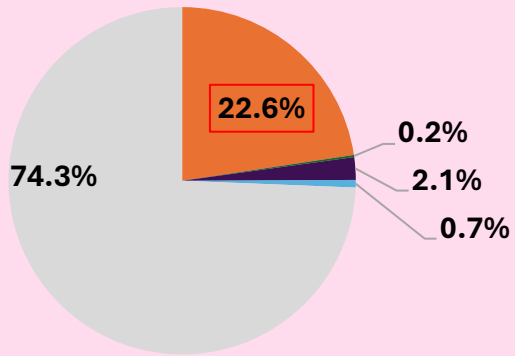
PTEN is a key tumour suppressor, and deficiency leads to unregulated PI3K/AKT signalling, which can contribute to tumour growth and progression and development of treatment resistance[1–6]

Deficiency of PTEN protein function or *PTEN* gene inactivation occurs in **~25% of patients with *de novo* mHSPC** and is associated with poor outcomes[2,4,7,8]



Alterations, such as *PTEN* rearrangements and deletions, are the predominant causes of PI3K/AKT pathway activation[7,9]

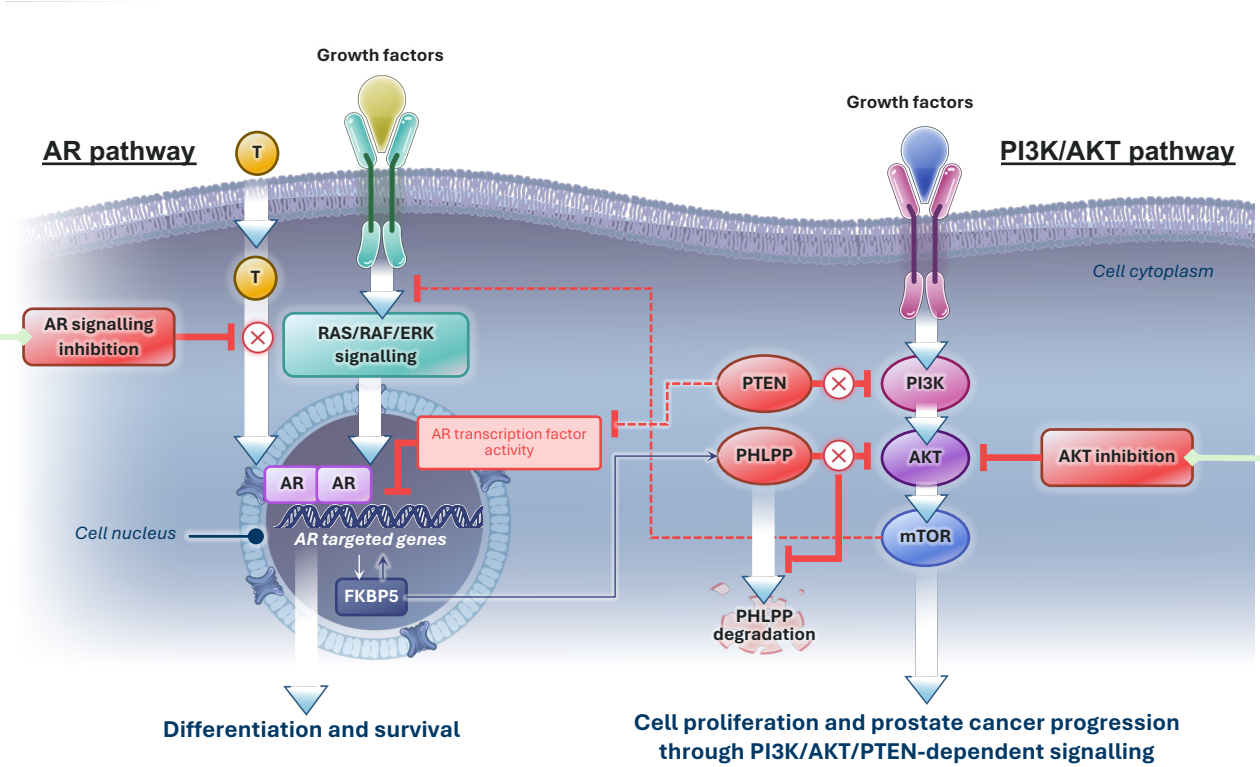
Spectrum of alterations in mHSPC[10]



1. Hoxhaj G and Manning BD. *Nat Rev Cancer* 2020;20:74–88; 2. Jamaspishvili T, et al. *Nat Rev Urol* 2018;15:222–234; 3. Brown JS and Banerji U. *Pharmacol Ther* 2017;172:101–115; 4. Marques RB, et al. *Eur Urol* 2015;67:1177–1185; 5. Glaviano A, et al. *Mol Cancer* 2023;22:138; 6. Manning BD and Toker A. *Cell* 2017;169:381–405; 7. Ferraldeschi R, et al. *Eur Urol.* 2015;67:795–802; 8. AstraZeneca Data on File. CAPItello-281 Screening Data; 9. Phin S, et al. Front Oncol 2013;3:240; 10. Stopsack KH, et al. *Clin Cancer Res* 2020;26:3230–3238; 11. Pompura SL, Dominguez-Villar M. *J Leukoc Biol* 2018;103:1065–1076.

The AR and PI3K/AKT pathways are reciprocally cross-regulated, so that inhibition of one leads to upregulation of the other

Inhibition of the AR pathway activates the PI3K/AKT pathway by reducing levels of the AKT phosphatase PHLPP, therefore increasing activation of AKT and its downstream targets



Conversely, treatment with a PI3K or AKT inhibitor results in increased levels of AR protein and increases AR target gene activity

Carver, et al. 2011 and Mulholland, et al. 2011

In PTEN-deficient prostate tumours, the PI3K/AKT and AR pathways cooperate to drive tumour progression

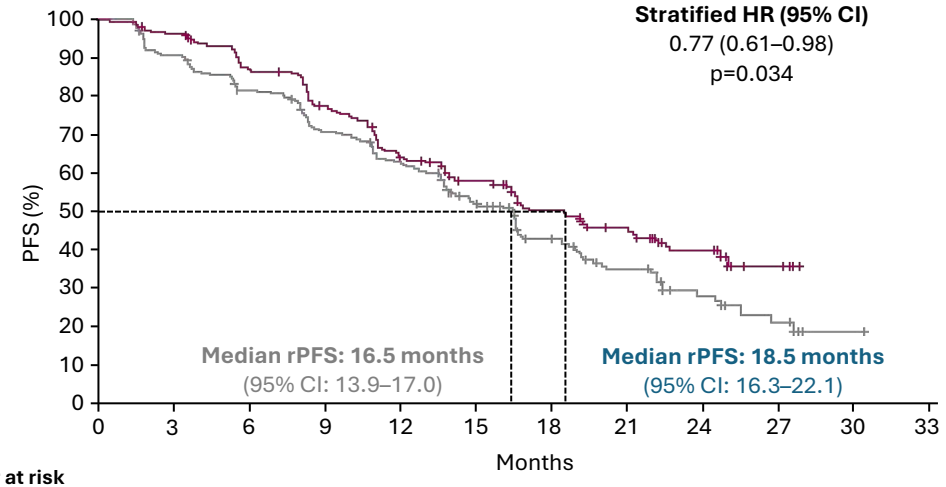
In mCRPC, co-inhibition of AR and AKT in patients with PTEN-deficient tumours

Ipatasertib + abiraterone significantly improved rPFS compared with placebo + abiraterone in patients with PTEN-deficient mCRPC. However, there was no statistically significant difference in the ITT population of the Phase III randomised IPATential150 trial

Co-primary endpoint:

rPFS in the PTEN-deficient population (IHC ≥50%)

	Placebo + Abi n=261	Ipatasertib + Abi n=260
Events, n (%)	154 (59)	124 (48)
rPFS at 1 year, % (95% CI)	63.3 (57.3–69.3)	64.4 (58.3–70.5)



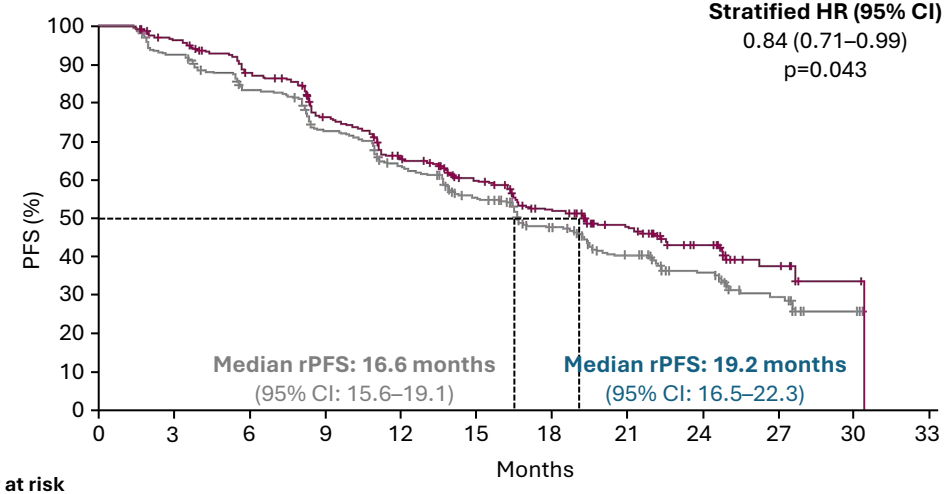
Number at risk

Pbo + Abi	261	233	206	175	151	105	71	41	22	10	3
Ipat + Abi	260	238	211	182	149	113	72	48	25	12	

Co-primary endpoint:

rPFS in the ITT population

	Placebo + Abi n=554	Ipatasertib + Abi n=547
Events, n (%)	306 (55)	252 (46)
PFS at 1 year, % (95% CI)	63.0 (58.9–67.1)	65.3 (61.1–69.5)



Number at risk

Pbo + Abi	554	501	443	377	322	237	165	98	60	29	5
Ipat + Abi	547	495	436	368	310	239	158	103	53	26	2

*PTEN loss by IHC was defined as ≥50% of the specimen's tumour area having no detectable PTEN staining with VENTANA PTEN [SP218] assay

Sweeney C, et al. *Lancet* 2021;398(10295):131–142; 2. Clinicaltrials.gov. NCT03072238

CAPItello-281

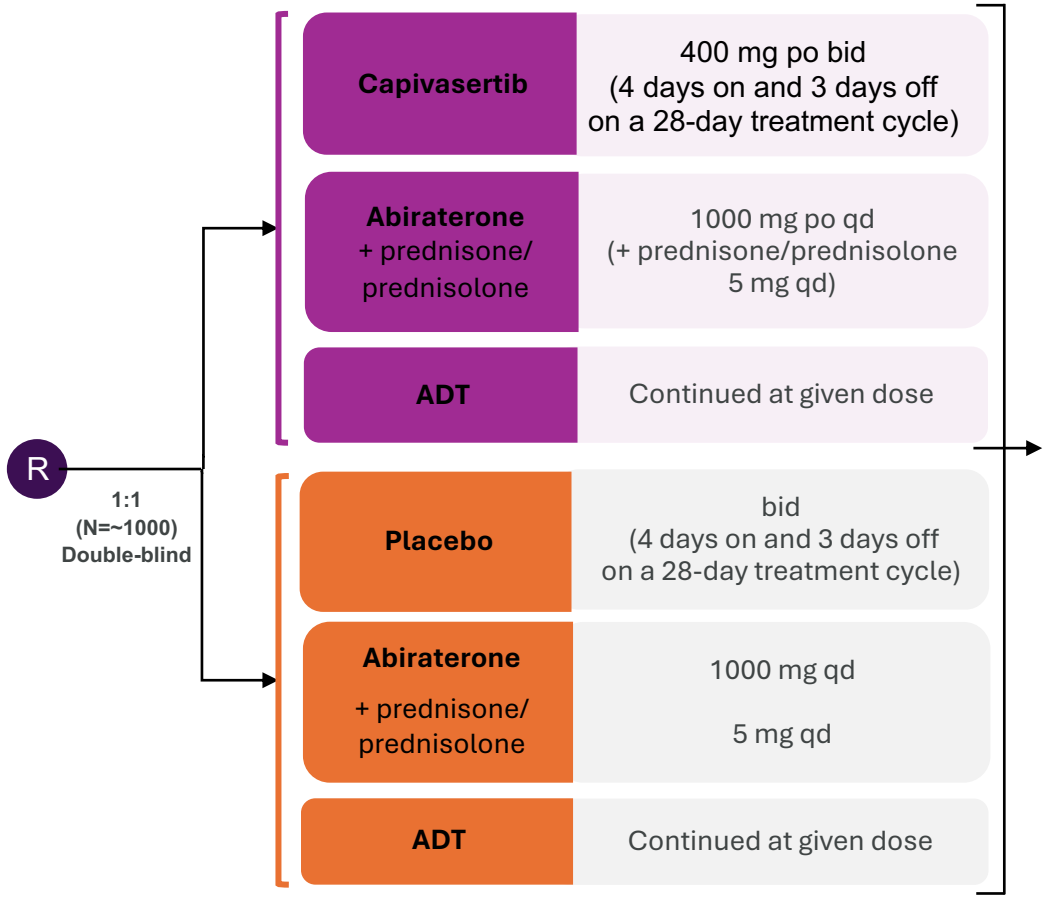
Phase III randomised trial assessing the combination of capivasertib + abiraterone vs placebo + abiraterone in patients with PTEN-deficient *de novo* mHSPC

Key eligibility criteria:[1]

- mHSPC and PTEN-deficient tumours
- Aged ≥18 years with asymptomatic or mildly symptomatic mHSPC
- ECOG PS 0–1
- Histologically confirmed *de novo* disease

Stratification factors:

- Volume of disease and visceral metastases (high volume with visceral metastases/high volume without visceral metastases/ low-volume disease)
- Geographical region



Primary endpoint

- rPFS

Secondary endpoints

- OS
- TFST
- SSE-FS
- TTPP
- Time to PSA progression
- TTCR
- PFS2
- PRO measures (BFI, BPI-SF, FACT-P)

ClinicalTrials.gov. NCT04493853

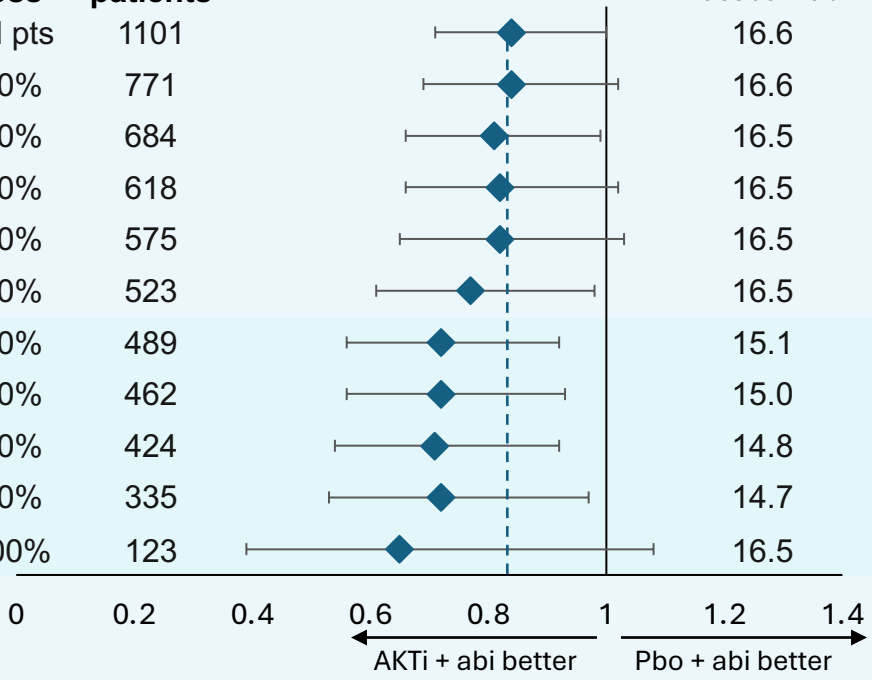
In CAPItello-281, the IHC cut-off for tumour PTEN deficiency was ≥90% (VENTANA assay)

This is equivalent to cytoplasmic PTEN staining in no more than 10% of viable malignant cells

An exploratory analysis of the IHC data in IPATential150 demonstrated that a **90% threshold resulted in an HR of 0.72 (95% CI: 0.53–0.97) and a median rPFS of 14.7 months vs 18.5 months,** which further substantiates the clinical relevance for the selected population[1–4]

IPATential150: rPFS by PTEN-deficient status by IHC % cut-off[1,2]

PTEN loss	No. of patients	Median PFS: Placebo + abi	Median PFS: AKTi + abi	HR for progression or death (95% CI)
All pts	1101	16.6	19.2	0.84 (0.71–1.00)
10%	771	16.6	17.7	0.84 (0.69–1.02)
20%	684	16.5	17.1	0.81 (0.66–0.99)
30%	618	16.5	17.1	0.82 (0.66–1.02)
40%	575	16.5	18.5	0.82 (0.65–1.03)
50%	523	16.5	19.1	0.77 (0.61–0.98)
60%	489	15.1	18.6	0.72 (0.56–0.92)
70%	462	15.0	18.6	0.72 (0.56–0.93)
80%	424	14.8	18.6	0.71 (0.54–0.92)
90%	335	14.7	18.5	0.72 (0.53–0.97)
100%	123	16.5	19.2	0.65 (0.39–1.08)



In IPATential150, PTEN deficiency by IHC was defined as ≥50% of the specimen's tumour area having no detectable PTEN staining with VENTANA® antibody clone SP218[1]

However, **consistent rPFS benefits were observed when more stringent IHC cut-offs were used**[1,3]

*Tumour PTEN status was centrally assessed by IHC using a validated assay (VENTANA PTEN [SP218] assay; Ventana Medical Systems, Oro Valley, AZ, USA). This assay prospectively describes the PTEN status of PC baseline tumour samples (archival or newly collected).[3]

Abi, abiraterone; AKTi, protein kinase B inhibitor; ARPI, androgen receptor pathway inhibitor; CI, confidence interval; HR, hazard ratio; IHC, immunohistochemistry; Pbo, placebo; PC, prostate cancer; PTEN, phosphatase and tensin homologue; pts, patients; rPFS, radiographic progression-free survival.

1. de Bono J, et al. Presented at ASCO Genitourinary Cancers Symposium 2021; 2. Sweeney C, et al. *Lancet* 2021;398:131–142; 3. Sweeney C, et al. Article and supplementary online content. *Lancet* 2021;398:131–142;
4. CAPItello-281 Study Protocol.

Capivasertib combination in PTEN-deficient metastatic hormone-sensitive prostate cancer demonstrated statistically significant and clinically meaningful improvement in radiographic progression-free survival in CAPItello-281 Phase III trial

Press release, November 2024

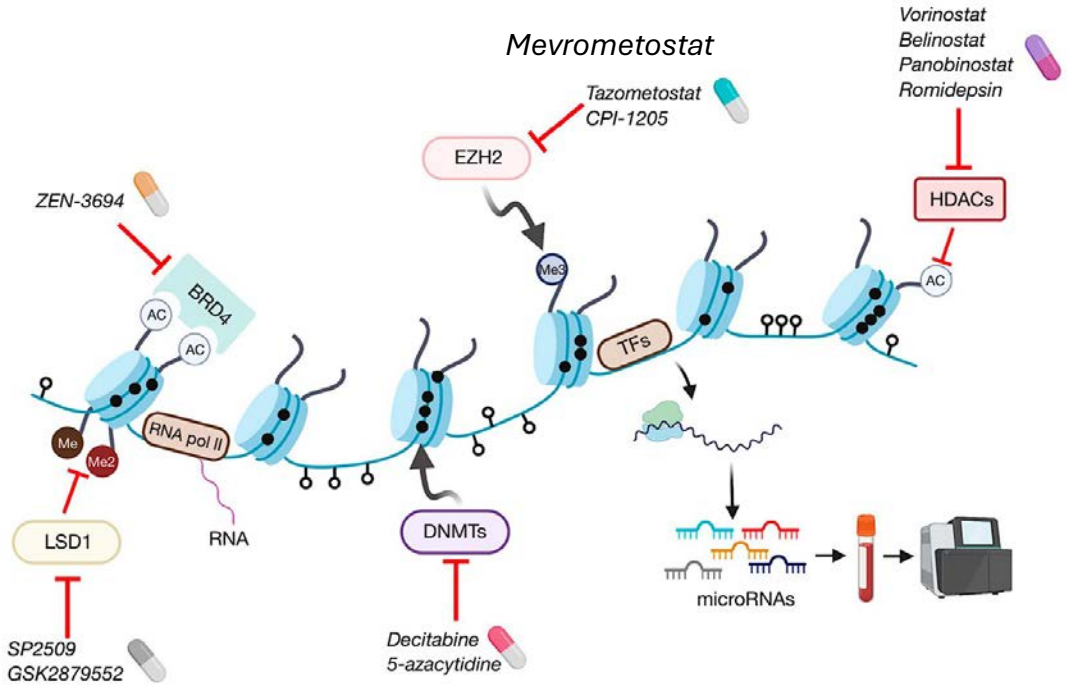
New therapies across the disease continuum

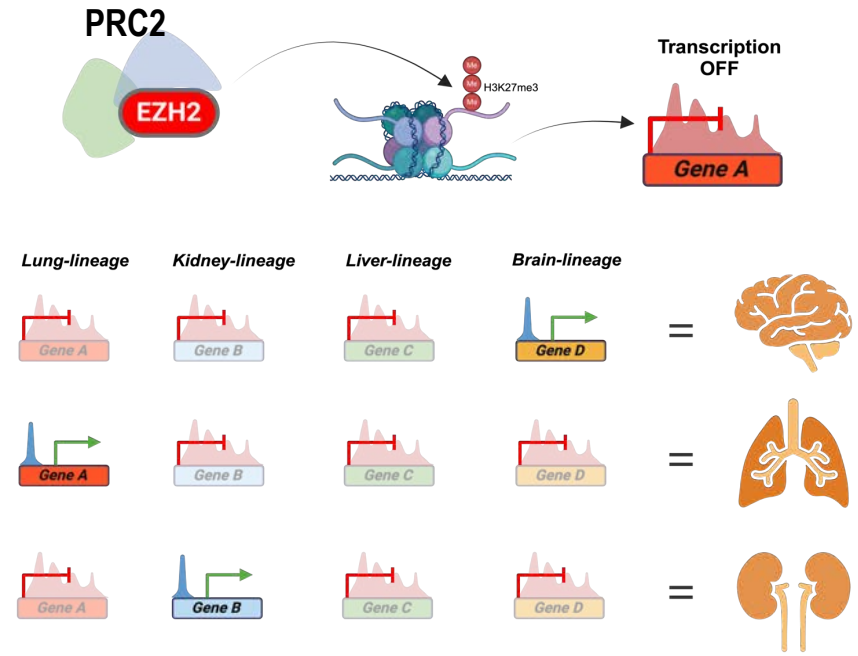
- **Localized prostate cancer**: Phase III trial of CAN-2409+prodrug in combination with standard of care EBRT for newly diagnosed localized prostate cancer

- **De novo metastatic hormone sensitive prostate cancer**: Phase III CAPItello-281 trial assessing capivasertib plus abiraterone/ADT in patients with PTEN deficiency

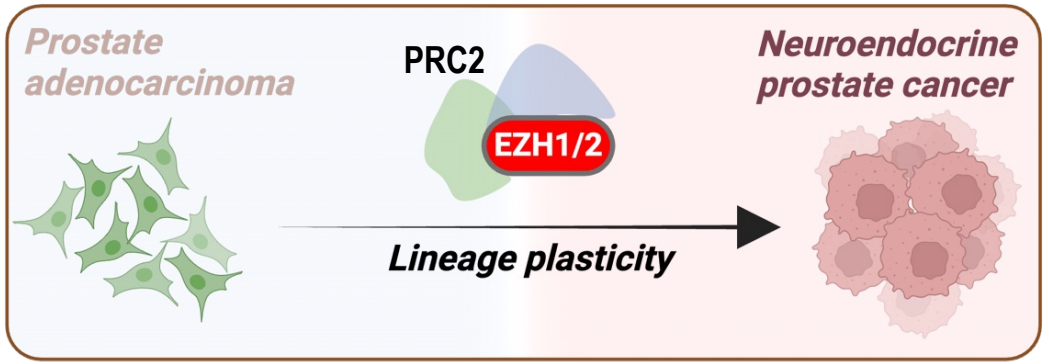
- **Metastatic CRPC**: Early phase data supporting mevrometostat in combination with enzalutamide

Targeting the epigenome in prostate cancer



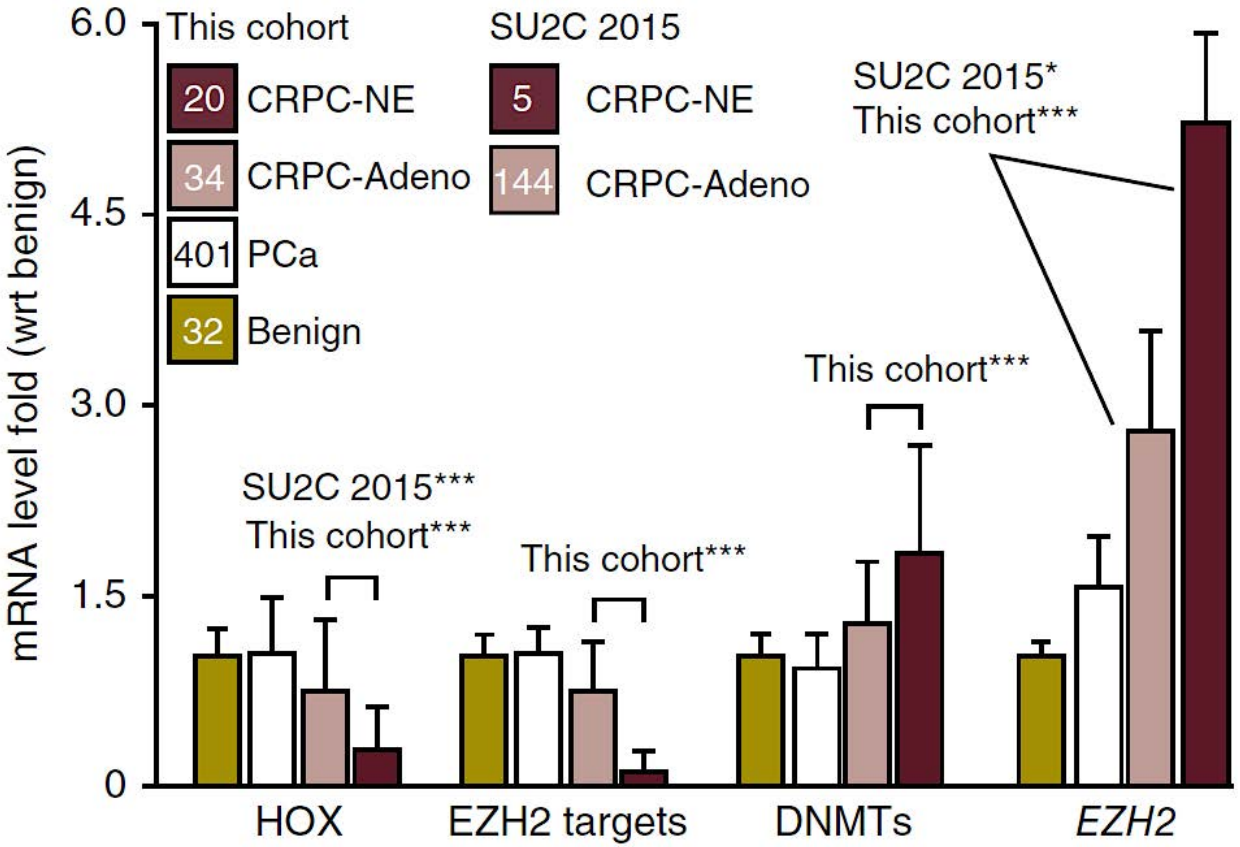


EZH2 (PRC2) Plays an Important Role in Lineage Specification

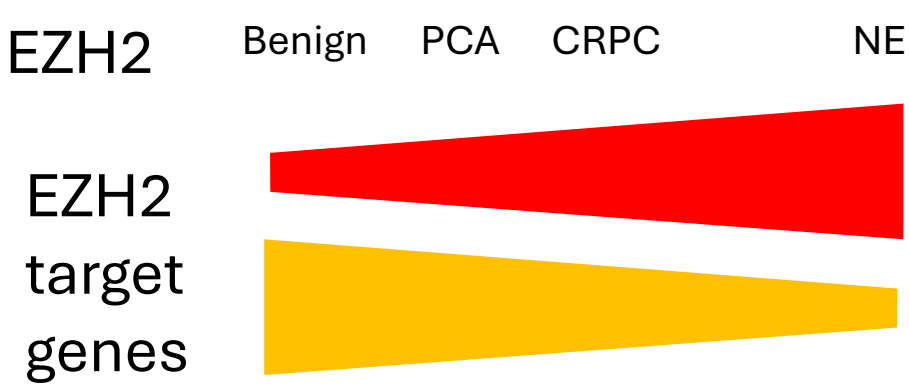


Conteduca V et al, 2021; Parreno V et al. *Nature* 2024; Ku et al 2016

Epigenetic Dysregulation in CRPC/NEPC

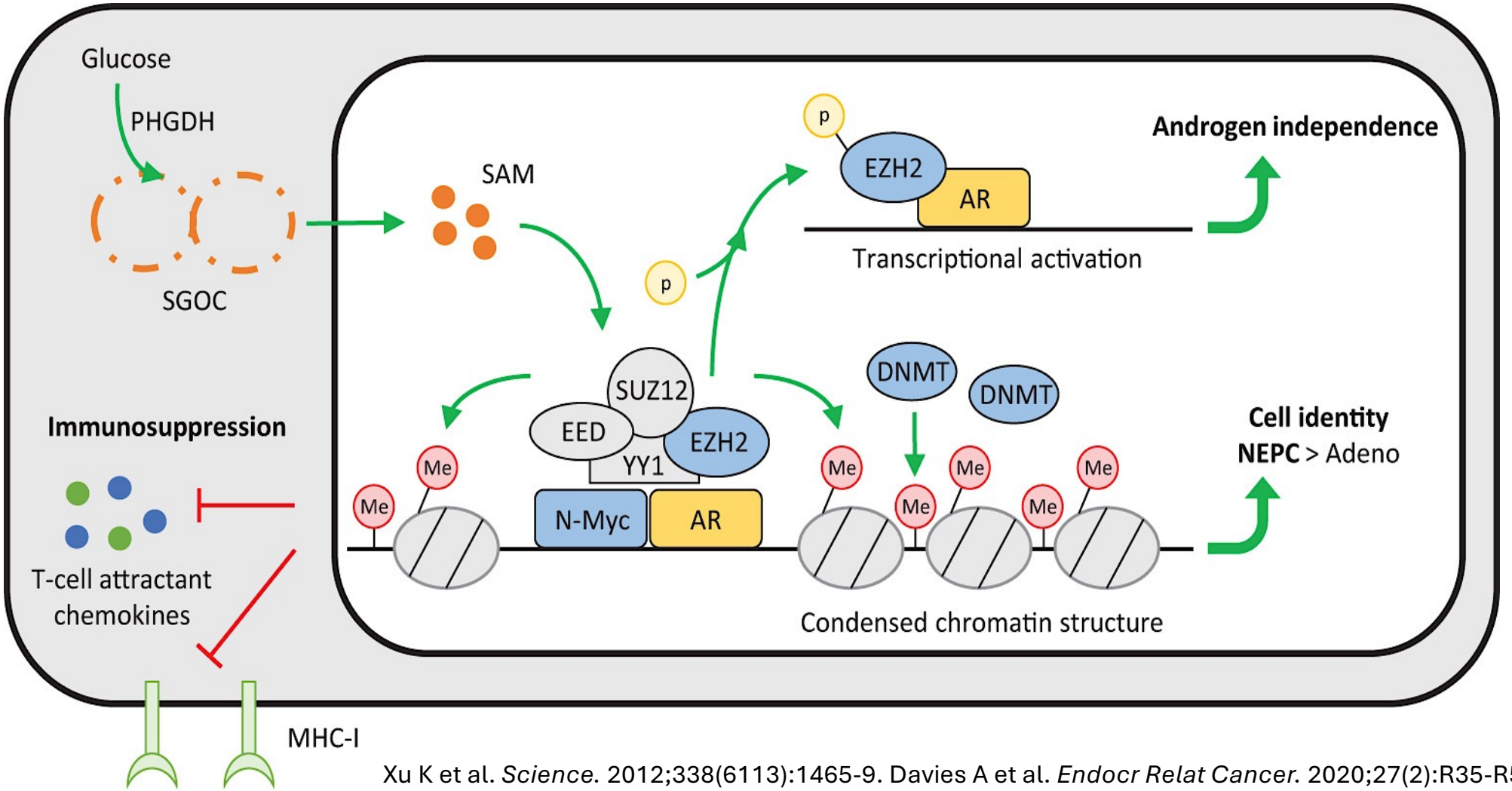


Progression of prostate cancer



Beltran H et al. *Nat Med*. 2016;22(3):298-305.

Beyond PRC2: Non-Canonical Function of EZH2

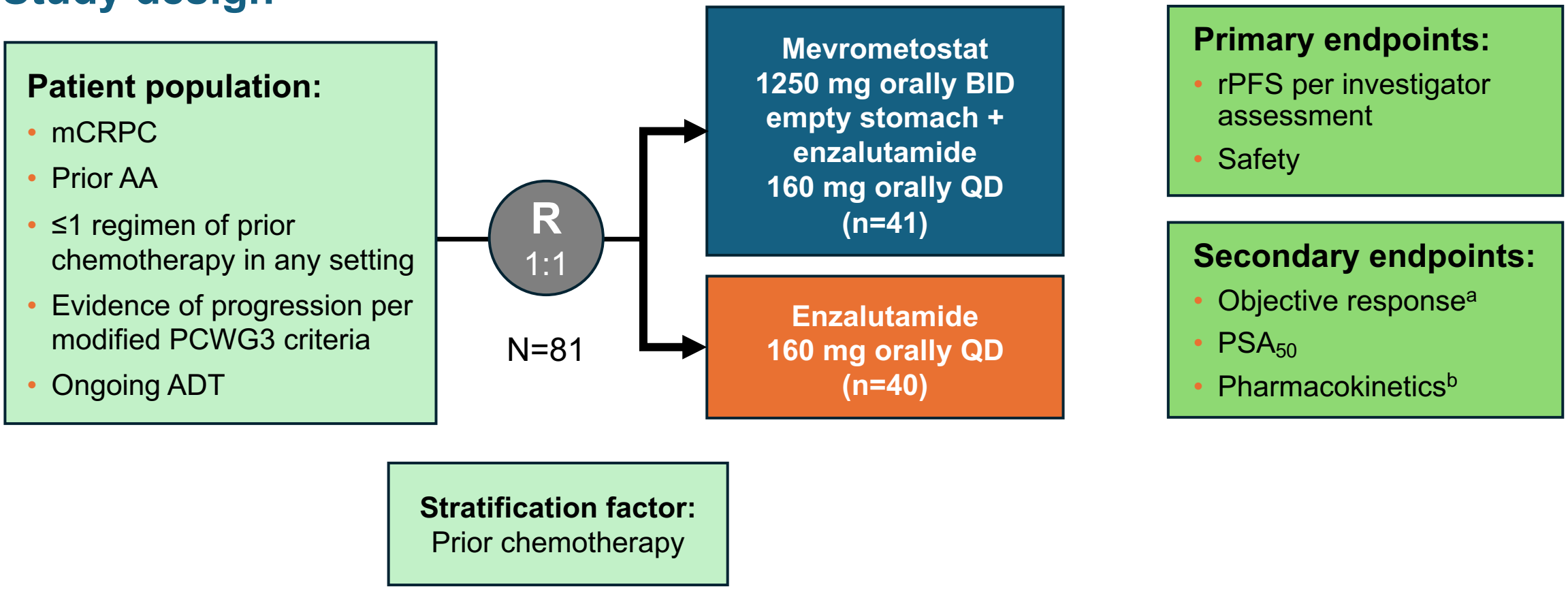


Xu K et al. *Science*. 2012;338(6113):1465-9. Davies A et al. *Endocr Relat Cancer*. 2020;27(2):R35-R50.

Mevrometostat + Enzalutamide

Open-label, Dose Expansion Study

Study design



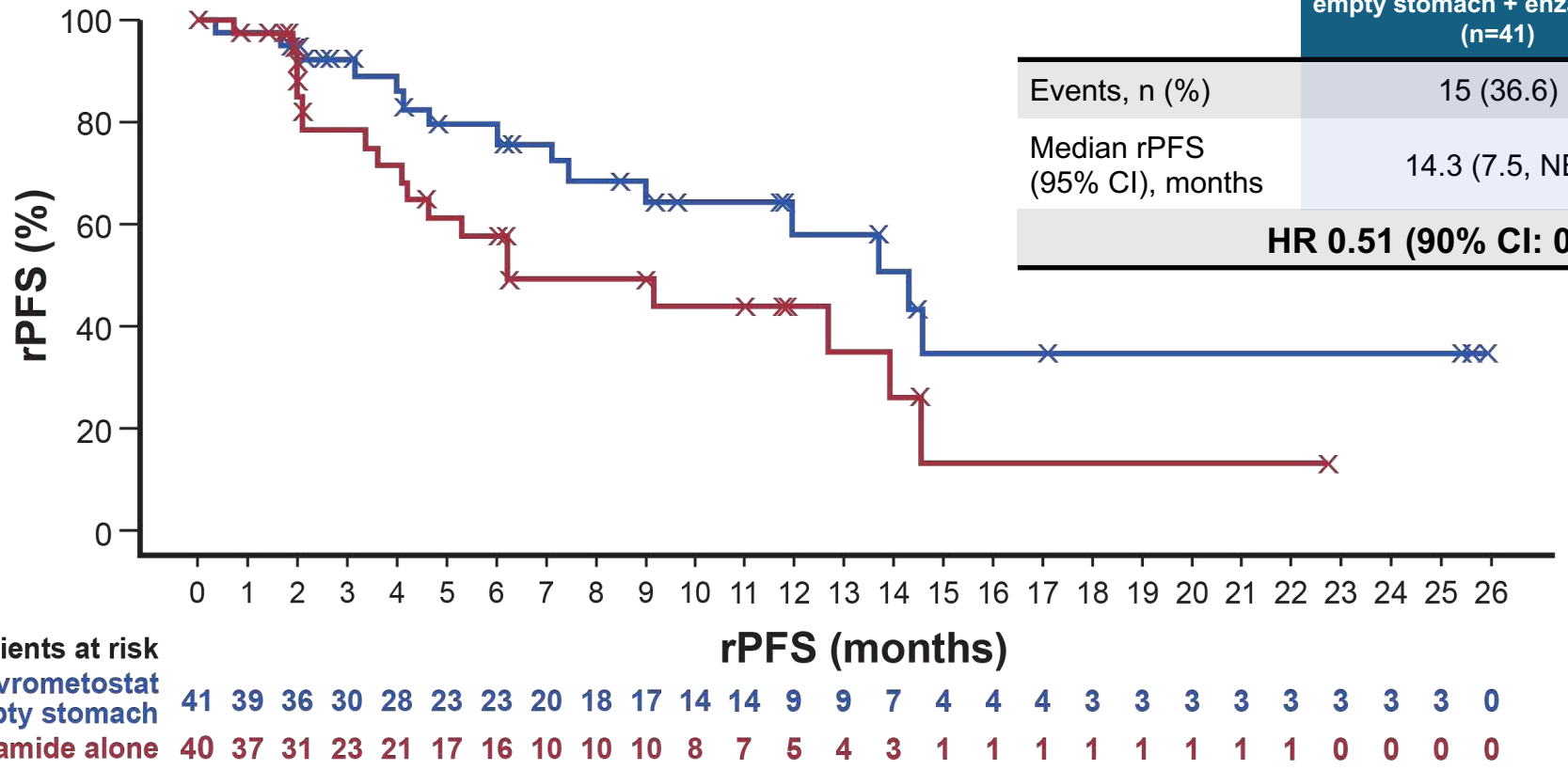
Schweizer MT, et al. ASCO GU 2025. Abstract LBA138.

Mevrometostat + Enzalutamide

Open-label, Dose Expansion Study (cont)

Primary endpoint: rPFS by investigator

49% reduction in the risk of progression or death and ~8-month improvement in median rPFS



	Mevrometostat 1250 mg BID empty stomach + enzalutamide (n=41)	Enzalutamide alone (n=40)
Events, n (%)	15 (36.6)	19 (47.5)
Median rPFS (95% CI), months	14.3 (7.5, NE)	6.2 (4.1, 13.9)
HR 0.51 (90% CI: 0.28, 0.95)		

Median (IQR) duration of follow-up for rPFS was 9.6 (3.1-14.5) months.

Data cutoff: September 2, 2024.

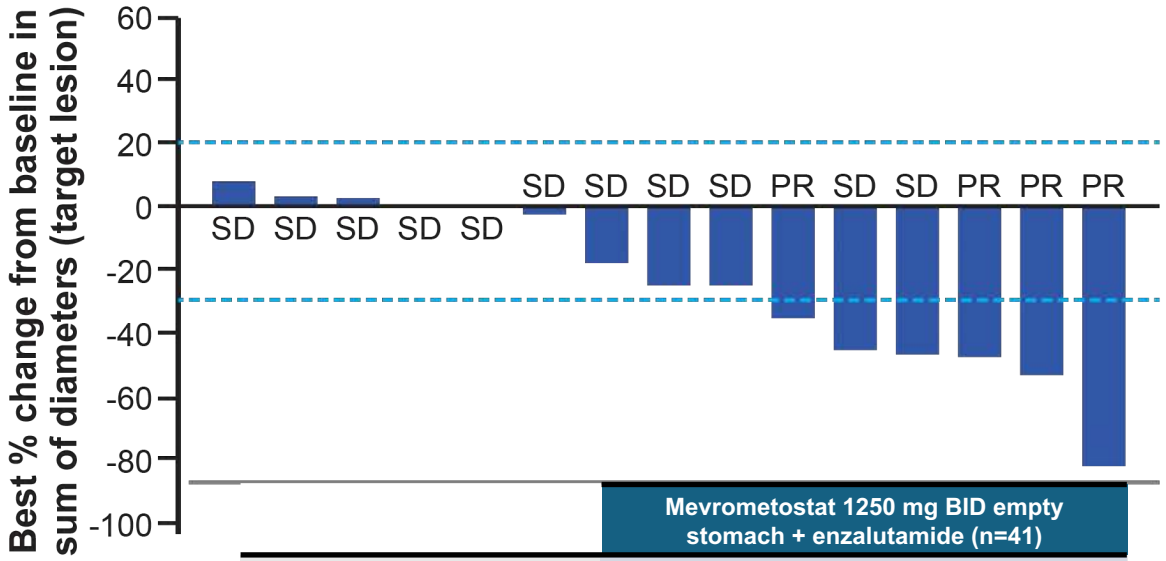
Schweizer MT, et al. ASCO GU 2025. Abstract LBA138.

Mevrometostat + Enzalutamide

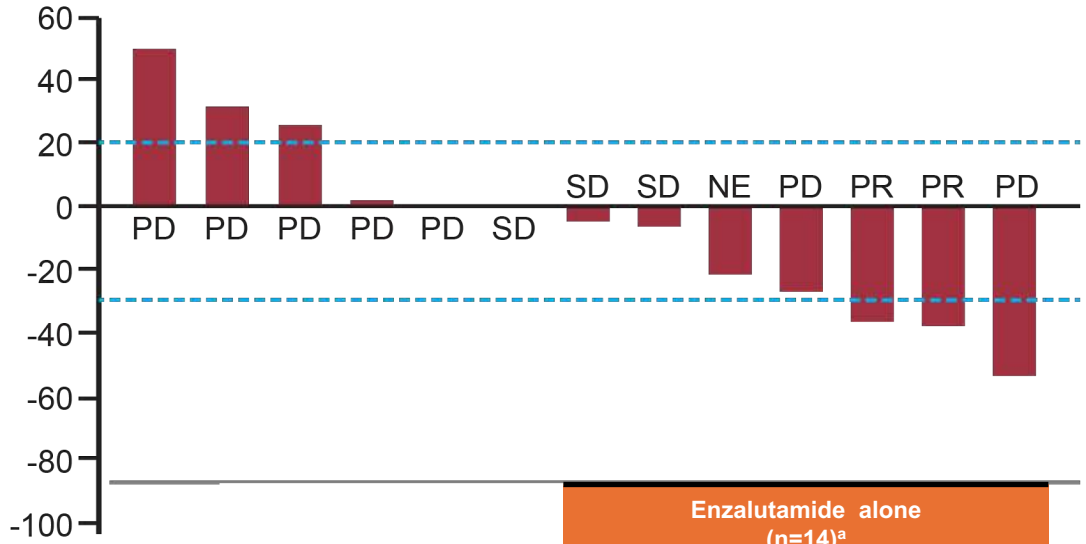
Open-label, Dose Expansion Study (cont)

ORR

Mevrometostat 1250 mg BID empty stomach + enzalutamide improved ORR vs enzalutamide



	Mevrometostat 1250 mg BID empty stomach + enzalutamide (n=41)
Confirmed BOR, n (%)	
PR	4 (26.7)
SD	11 (73.3)
PD	0
ORR (CR + PR), % (95% CI)	26.7 (7.8, 55.1)

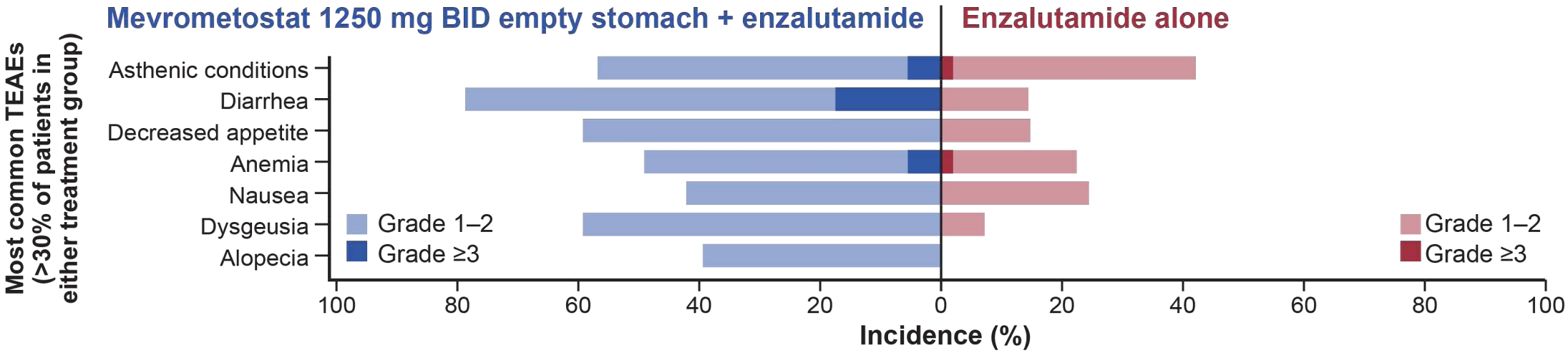


	Enzalutamide alone (n=14)[a]
Confirmed BOR, n (%)	
PR	2 (14.3)
SD	3 (21.4)
PD	7 (50.0)
ORR (CR + PR), % (95% CI)	14.3 (1.8, 42.8)

Schweizer MT, et al. ASCO GU 2025. Abstract LBA138.

Mevrometostat AE Data

	Mevrometostat 1250 mg BID empty stomach + enzalutamide (n=41)		Enzalutamide alone (n=40)	
Event, n (%)	All grades	Grade ≥3	All grades	Grade ≥3
Any TEAE	40 (97.6)	22 (53.7)	37 (92.5)	17 (42.5)
Treatment-related TEAE	39 (95.1)	20 (48.8)	33 (82.5)	9 (22.5)
Serious AE	14 (34.1)	13 (31.7)	11 (27.5)	10 (25.0)
Treatment-related serious TEAE[a]	10 (24.4)	10 (24.4)	1 (2.5)	1 (2.5)
TEAE leading to dose reduction	15 (36.6)	7 (17.1)	3 (7.5)	0
TEAE leading to study discontinuation	1 (2.4)	0	2 (5.0)	1 (2.5)



Schweizer MT, et al. ASCO GU 2025. Abstract LBA138.

Mevrometostat + Enzalutamide

Open-label, Dose Expansion Study (cont)

- Mevrometostat + enzalutamide was associated with a 49% reduction in risk of rPFS compared with enzalutamide
- Mevrometostat 1250 mg BID on empty stomach + enzalutamide has a manageable safety profile
- Plasma exposure with mevrometostat 875 mg with food was similar to 1250 mg empty stomach, with an improved safety profile
- Mevrometostat 875 mg with food is the recommended phase 3 dose

Schweizer MT, et al. ASCO GU 2025. Abstract LBA138.

Next steps
Mevrometostat + Enzalutamide

- **MEVPRO-1: Phase 3 Study**
  Mevrometostat + Enzalutamide vs Physician Choice (Docetaxel or Enzalutamide) in Patients With mCRPC Previously Treated With Abiraterone (rPFS)

- **MEVPRO-2 Phase 3 Study**
  Mevrometostat + Enzalutamide vs Placebo + Enzalutamide in ARPI-Naive Patients With mCRPC (rPFS)

Exciting new therapies with new mechanisms of action in late-stage clinical development across the disease continuum

- Phase III trial of CAN-2409+prodrug in combination with standard of care EBRT for newly diagnosed localized prostate cancer (ASCO 2025)
- Phase III CAPItello-281 trial assessing capivasertib plus abiraterone/ADT in patients with mHSPC and PTEN deficiency
- Promising early phase data supporting mevrometostat in combination with enzalutamide for mCRPC

Faculty Case Presentations

Case Presentation – Dr Armstrong: mHSPC, low volume disease

- 71 yo WM presented with back pain to the ER after a negative sports medicine physical, worse with activity, but still bothering him after 2 months at night
- PSA found to be 71 (first ever), alkaline phosphatase 220 (high), newly elevated from last year's wellness check. Never had PSA screening.
- PSMA PET/CT shows 4 bone metastases in his L-spine (2) and ribs, L ilium, PSMA Avid (SUV 14-20) and uptake in his prostate, no LAD
- Prostate biopsy confirms high grade GG5 disease in multiple cores, sent for Foundation CDX testing. Found to have PTEN loss and a TMPRSS2-ERG fusion, no HRD alterations, MSS, TMB 2.0 (low), PD-L1 negative
- Starts on ADT/abiraterone and inquires if there are other approaches that could improve his survival
- PMH significant for HTN and hyperlipidemia, well controlled. No heart disease and he is active but somewhat sedentary, retired. Married for 45 years, no family history of malignancy but does have 3 children

QUESTIONS FOR THE FACULTY

Should general medical oncologists in community-based practice be testing their patients with mHSPC for PTEN deficiency? If so, how would you recommend that they do so?

When will data from the CAPItello-281 study be available, and what would they need to demonstrate for you to enthusiastically employ capivasertib? For a patient with mHSPC and PTEN deficiency for whom you would normally recommend a triplet regimen based on clinical characteristics, how would you select between an AR pathway inhibitor/docetaxel/ADT and capivasertib/abiraterone/ADT if capivasertib becomes available?

Case Presentation – Dr McKay: mCRPC

Patient Profile:

- 65-year-old male
- Initial diagnosis: De novo metastatic disease (January 2022)
  - Presenting PSA: 125.6 ng/mL
  - Biopsy: Gleason 4+5=9 (Grade Group 5) in 8/12 cores
  - Imaging: Multiple bone metastases (spine, pelvis, ribs) on bone scan
  - No visceral metastases
  - Clinical stage: cT3b N1 M1b
  - Genomic testing on prostate biopsy: TP53 mutation identified, no HRR alterations
- Initial treatment for mHSPC:
  - ADT + abiraterone 1000mg daily + prednisone 5mg daily (Jan 2022-May 2024)
  - Initial PSA response: Declined to 0.2 ng/mL within 3 months
  - Maintained response for 28 months with castrate testosterone <20 ng/dL
- Recent progression to mCRPC (May 2024):
  - Rising PSA to 4.7 ng/mL despite castrate testosterone
  - CT scan and bone scan: New bone lesions, no visceral disease
  - Considered first-line mCRPC with progression on abiraterone
  - No prior enzalutamide exposure
  - No prior chemotherapy exposure
- Current status (June 2024):
  - PSA: 7.2 ng/mL (rising)
  - ECOG performance status: 1
  - Mild fatigue, intermittent bone pain well-controlled with NSAIDs
  - Laboratory: Hemoglobin 13.1 g/dL, WBC 5.8, platelets 245K, liver/renal function normal
  - PSMA PET/CT: Diffuse PSMA-avid bone metastases (SUVmax 14-38)
  - No hepatic metastases, no lymphadenopathy >1.5cm
- Treatment Course
  - Enrolled on Mevpro-1 trial

QUESTIONS FOR THE FACULTY

If mevrometostat were to eventually reach the clinic, how do you see it being sequenced relative to currently available therapies for mCRPC? Based on what we know so far, in which patient populations do you think mevrometostat might be particularly advantageous?

What other potential therapeutic targets are you most excited about in prostate cancer?

RTP
RESEARCH
TO PRACTICE

Consensus or Controversy? Clinical Investigators Provide Perspectives on the Current and Future Care of Patients with Chronic Lymphocytic Leukemia

A CME-Accredited Virtual Event Held in Conjunction with the 2025 ASCO® Annual Meeting

Sunday, June 1, 2025

7:00 AM – 8:00 AM CT (8:00 AM – 9:00 AM ET)

Faculty

Catherine C Coombs, MD

William G Wierda, MD, PhD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

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Please complete the survey currently up on the iPads for attendees in the room and on Zoom for those attending virtually. The survey will remain open up to 5 minutes after the meeting ends.

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