What Clinicians Want to Know: Addressing Current Questions and Controversies in the Management of Prostate Cancer

Saturday, June 1, 2024

7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)

Faculty

Neeraj Agarwal, MD, FASCO

Emmanuel S Antonarakis, MD

Tanya B Dorff, MD

Matthew R Smith, MD, PhD

Moderator

Andrew J Armstrong, MD, ScM

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Faculty

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Director, Genitourinary Malignancies Program
Massachusetts General Hospital Cancer Center
Boston, Massachusetts

Moderator

Andrew J Armstrong, MD, ScM
Professor of Medicine, Surgery, Pharmacology and Cancer Biology
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Dr Agarwal — Disclosures
Faculty

No relevant conflicts of interest to disclose.

Dr Antonarakis — Disclosures
Faculty

Advisory Committees	Aadi Bioscience, Amgen Inc, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Blue Earth Diagnostics, Curium, Janssen Biotech Inc, Merck, Pfizer Inc, Sanofi, Tango Therapeutics, Tempus
Consulting Agreements	EcoR1 Capital LLC, Hookipa Pharma Inc, Lilly, Menarini Silicon Biosystems, Z-Alpha
Contracted Research	Astellas, Bayer HealthCare Pharmaceuticals, Bristol Myers Squibb, Clovis Oncology, MacroGenics Inc, Merck, Novartis, Orion Corporation, Seagen Inc
Patent Holder	QIAGEN

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Dr Dorff — Disclosures
Faculty

Advisory Committees	Astellas, AstraZeneca Pharmaceuticals LP, Janssen Biotech Inc, Sanofi
Consulting Agreement	Bayer HealthCare Pharmaceuticals

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Dr Smith — Disclosures
Faculty

Advisory Committees	Bayer HealthCare Pharmaceuticals, Janssen Biotech Inc, Lilly, Pfizer Inc
Consulting Agreements	Ambrx, Bayer HealthCare Pharmaceuticals, Janssen Biotech Inc, Lilly, Pfizer Inc
Contracted Research (to Institution)	Bayer HealthCare Pharmaceuticals, Janssen Biotech Inc, Lilly, Pfizer Inc
Stock Options/Ownership—Public Company	Ambrx

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Dr Armstrong — Disclosures
Moderator

Advisory Committees	AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Bristol Myers Squibb, Clovis Oncology, Exelixis Inc, GoodRx, Merck, Myovant Sciences, Novartis, Pfizer Inc, Z-Alpha
Consulting Agreements	Astellas, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Bristol Myers Squibb, Celgene Corporation, Clovis Oncology, Dendreon Pharmaceuticals Inc, Epic Sciences, Exact Sciences Corporation, Exelixis Inc, Forma Therapeutics, GoodRx, Janssen Biotech Inc, Merck, Myovant Sciences, Novartis, Pfizer Inc, Z-Alpha
Contracted Research	Amgen Inc, Astellas, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Bristol Myers Squibb, Celgene Corporation, Dendreon Pharmaceuticals Inc, Forma Therapeutics, Janssen Biotech Inc, Merck, Novartis, Pfizer Inc
Nonrelevant Financial Relationships	National Cancer Institute, National Institutes of Health, Prostate Cancer Foundation/Movember, US Department of Defense

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Dr Love — Disclosures

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Friday May 31	**Hepatobiliary Cancers** 11:45 AM – 12:45 PM CT (12:45 PM – 1:45 PM ET)
	Non-Small Cell Lung Cancer with an EGFR Mutation 6:30 PM – 8:30 PM CT (7:30 PM – 9:30 PM ET)
Saturday June 1	**Antibody-Drug Conjugates in the Treatment of Lung Cancer** 6:45 AM – 7:45 AM CT (7:45 AM – 8:45 AM ET)
	Prostate Cancer 7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)
Sunday June 2	**Multiple Myeloma** 6:45 AM – 7:45 AM CT (7:45 AM – 8:45 AM ET)
	Ovarian and Endometrial Cancer 7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)
Monday June 3	**Colorectal Cancer (Webinar)** 7:00 AM – 8:00 AM CT (8:00 AM – 9:00 AM ET)
	Metastatic Breast Cancer 7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)
Tuesday June 4	**Bispecific Antibodies in the Management of Lymphoma (Webinar)** 7:00 AM – 8:00 AM CT (8:00 AM – 9:00 AM ET)

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Exciting CME Events in Chicago You Do Not Want to Miss

A CME Hybrid Symposium Series Held in Conjunction with the 2024 ASCO® Annual Meeting

Hepatobiliary Cancers

Friday, May 31, 2024

11:45 AM – 12:45 PM CT (12:45 PM – 1:45 PM ET)

Faculty

Robin K (Katie) Kelley, MD
Edward Kim, MD
Arndt Vogel, MD, PhD

Antibody-Drug Conjugates in Lung Cancer

Saturday, June 1, 2024

6:45 AM – 7:45 AM CT (7:45 AM – 8:45 AM ET)

Faculty

Rebecca S Heist, MD, MPH
Luis Paz-Ares, MD, PhD
Jacob Sands, MD

Non-Small Cell Lung Cancer with an EGFR Mutation

Friday, May 31, 2024

6:30 PM – 8:30 PM CT (7:30 PM – 9:30 PM ET)

Faculty

Jonathan W Goldman, MD
Corey J Langer, MD
Joel W Neal, MD, PhD
Zofia Piotrowska, MD, MHS
Joshua K Sabari, MD
Helena Yu, MD

Prostate Cancer

Saturday, June 1, 2024

7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)

Faculty

Neeraj Agarwal, MD, FASCO
Emmanuel S Antonarakis, MD
Andrew J Armstrong, MD, ScM
Tanya B Dorff, MD
Matthew R Smith, MD, PhD

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Multiple Myeloma

Sunday, June 2, 2024

6:45 AM – 7:45 AM CT (7:45 AM – 8:45 AM ET)

Faculty

Rafael Fonseca, MD
María-Victoria Mateos, MD, PhD
Elizabeth O'Donnell, MD

LIVE WEBCAST

Colorectal Cancer

Monday, June 3, 2024

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

Faculty

Scott Kopetz, MD, PhD
John Strickler, MD

Ovarian and Endometrial Cancer

Sunday, June 2, 2024

7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)

Faculty

Floor J Backes, MD
Mansoor Raza Mirza, MD
Ritu Salani, MD, MBA
Angeles Alvarez Secord, MD, MHSc
Brian M Slomovitz, MD

Metastatic Breast Cancer

Monday, June 3, 2024

7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)

Faculty

Aditya Bardia, MD, MPH
Harold J Burstein, MD, PhD
Professor Giuseppe Curigliano, MD, PhD
Sara A Hurvitz, MD, FACP
Joyce O'Shaughnessy, MD
Hope S Rugo, MD

Exciting CME Events in Chicago You Do Not Want to Miss

A CME Hybrid Symposium Series Held in Conjunction with the 2024 ASCO® Annual Meeting

LIVE WEBCAST

Bispecific Antibodies in Lymphoma

Tuesday, June 4, 2024

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

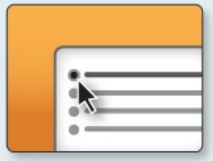
Faculty

Joshua Brody, MD
Ian W Flinn, MD, PhD
Tycel Phillips, MD

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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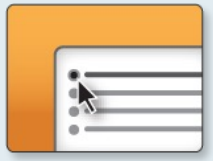
Clinicians Attending via Zoom

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 video/PowerPoint 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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Moderator

Andrew J Armstrong, MD, ScM

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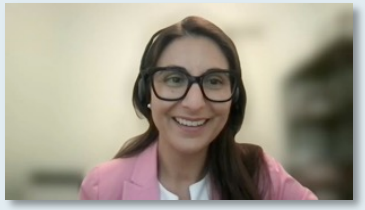
Consulting Oncologists

Neil Love, MD
Research To Practice
Miami, Florida



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Lynn Cancer Institute
Boca Raton, Florida

Warren S Brenner, MD
Lynn Cancer Institute
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Gigi Chen, MD
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Lecanto, Florida

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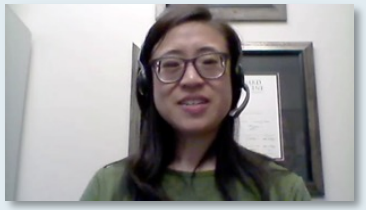
Lake Worth, Florida



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Estelamari Rodriguez, MD, MPH
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Erik Rupard, MD
Intermountain Health
St George, Utah

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Agenda

Module 1: Optimizing the Management of Nonmetastatic Prostate Cancer — Dr Dorff

Module 2: Evidence-Based Selection of Treatment for Metastatic Hormone-Sensitive Prostate Cancer — Dr Smith

Module 3: New Considerations with the Use of PARP Inhibitors for Metastatic Castration-Resistant Prostate Cancer (mCRPC) — Dr Agarwal

Module 4: Role of Novel Radiopharmaceuticals for mCRPC — Dr Armstrong

Module 5: Promising Investigational Approaches for Patients with Prostate Cancer — Dr Antonarakis

Agenda

Module 1: Optimizing the Management of Nonmetastatic Prostate Cancer — Dr Dorff

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Module 4: Role of Novel Radiopharmaceuticals for mCRPC — Dr Armstrong

Module 5: Promising Investigational Approaches for Patients with Prostate Cancer — Dr Antonarakis

Consulting Faculty Comments

Management of very high-risk localized prostate cancer

Dr Kimberly Ku (Bloomington, Illinois)

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QUESTIONS FOR THE FACULTY

In what situations are you considering treatment intensification for patients with newly diagnosed high-risk nonmetastatic hormone-sensitive prostate cancer?

How do you define high risk?

Are you always using abiraterone in this situation, or will you consider other AR pathway inhibitors?

Consulting Faculty Comments

Androgen receptor (AR) inhibitors in the localized (M0) setting

Dr Spencer Bachow
(Boca Raton, Florida)

Dr Kimberly Ku
(Bloomington, Illinois)

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QUESTIONS FOR THE FACULTY

How have findings from the EMBARK trial changed your practice?

For which patients with biochemical recurrence are you now offering androgen deprivation therapy (ADT) with enzalutamide?

QUESTIONS FOR THE FACULTY

How do you view findings from the PRESTO trial?

Would you find clinical equipoise in employing apalutamide instead of enzalutamide for a patient with biochemical recurrence for whom you wished to intensify treatment using an AR pathway inhibitor?

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Non-metastatic (BCR) prostate cancer

Tanya Dorff, MD
Professor of Medicine
Section Chief, Genitourinary Cancer Program

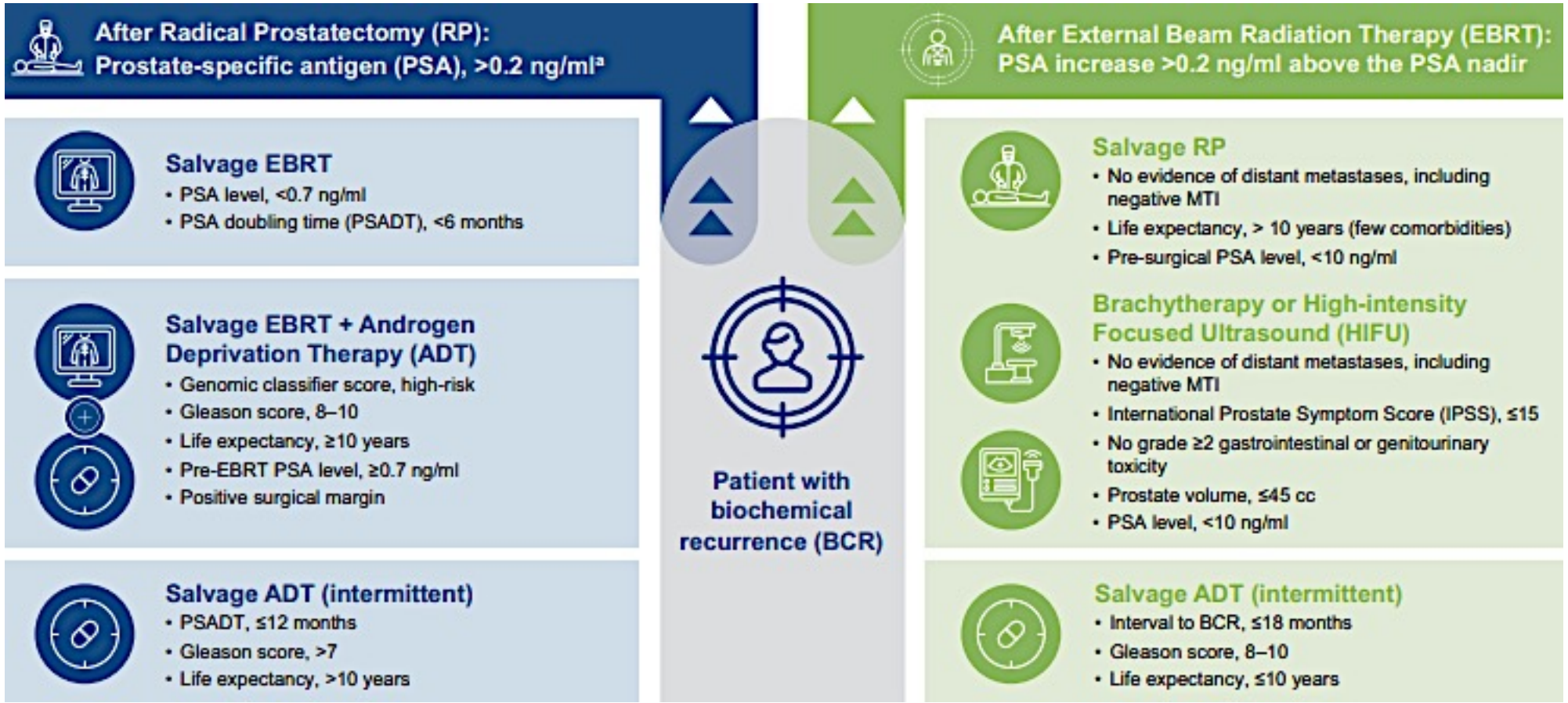
Biochemical Recurrence of Prostate Cancer: New Data

- EMBARK
  - Data: Doublet (ADT + Enza) moves to high risk BCR
  - Novel: Enzalutamide monotherapy
  - Controversies: PET imaging and recategorization
- PRESTO
  - Data: Doublet (ADT + Apa) may be useful in BCR
  - Confirms: AR antag + CYP17 inhib not beneficial
  - Controversies: time to PSA rise as meaningful endpoint
- nmCRPC: long term data from SPARTAN, ARAMIS and PROSPER
- Ongoing trials
  - ARASTEP

Taking a step back… BCR patients need to be contextualized

Initial disease characteristics and PSA DT are strong predictors

Newer technologies: Decipher ArteraAI



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Shore ND et al. Prost Ca Prost Dis 2024; 27:192-201

EMBARK and PRESTO at a glance

	EMBARK (n=1068)	PRESTO (n=503)
Inclusion	PSA DT ≤9 mo PSA ≥2 post RT or ≥1 post RRP	PSA DT ≤9 months PSA >0.5
Arms	A) Leuprolide B) Leuprolide + Enzalutamide C) Enzalutamide	A) Degarelix (or LHRH agonist) B) Degarelix + Apalutamide C) Degarelix + Apalutamide + Abiraterone
Treatmt duration	36 weeks (stop if PSA <0.2)	1 year
Baseline PSA	Median 5-5.5 (1-308) 50% had RRP + salvage RT 30% had prior ADT	Median 1.8 (1-3.6) 100% had RRP, 85% salvage RT 42% had prior ADT
Primary Endpt result	5 year MFS (A vs B) 87.3% vs 71.4% HR 0.42 (0.30-0.61)	PSA PFS (incr by 25%, >2 ng/dL) A vs B 24.9 mo vs 20.3 HR 0.52 (0.35-0.77)

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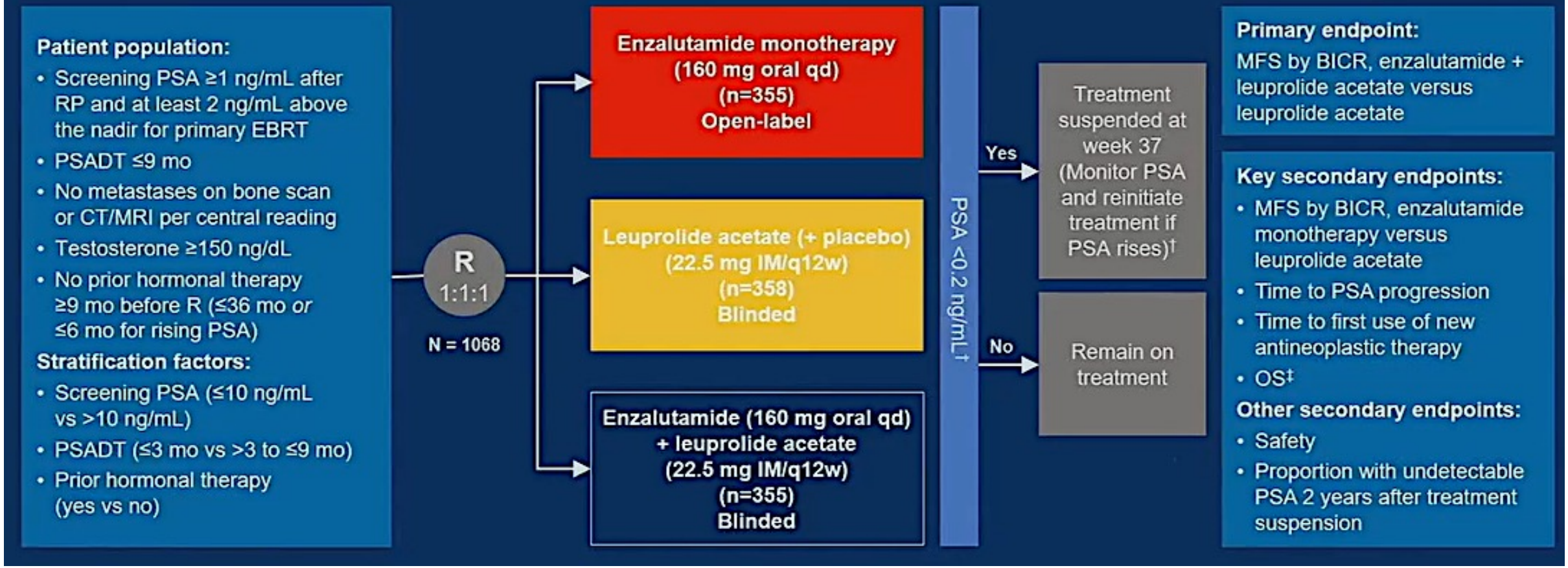
EMBARK Study Design



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Shore ND et al. ASCO GU 2024;Abstract 15.

EMBARK

Doublet superior to LHRH agonist except for
- Deterioration in FACT-P

Enza monotherapy superior to LHRH agonist except for
- time off treatment
- Deterioration in FACT-P

91% on doublet got treatment break
68% on LHRH agonist
86% on Enza monotx

Freedland SJ et al. *N Engl J Med*. 2023;389(16):1453-1465.

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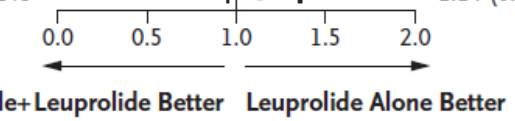
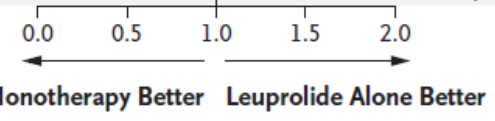
A Secondary End Points, Enzalutamide plus Leuprolide vs. Leuprolide Alone

End Point	Enzalutamide+ Leuprolide (no. of patients)	Leuprolide Alone (no. of patients)	Enzalutamide+ Leuprolide (no. of events)	Leuprolide Alone (no. of events)	Hazard Ratio (95% CI)	Two-Sided P Value
Metastasis-free survival (primary end point)	355	358	45	92	0.42 (0.30–0.61)	<0.001
Overall survival	355	358	33	55	0.59 (0.38–0.91)	0.02
PSA progression	355	358	8	93	0.07 (0.03–0.14)	<0.001
First use of new antineoplastic therapy	355	358	58	140	0.36 (0.26–0.49)	<0.001
Distant metastasis	355	358	30	59	0.44 (0.28–0.69)	
Resumption of any hormonal therapy	321	240	256	217	0.69 (0.58–0.83)	
Castration resistance	355	358	14	120	0.09 (0.05–0.16)	
Symptomatic progression	355	358	104	169	0.55 (0.43–0.70)	
First symptomatic skeletal event	355	358	9	32	0.26 (0.13–0.55)	
First deterioration in FACT-P total score	355	358	257	248	1.14 (0.95–1.36)	



B Secondary End Points, Enzalutamide Monotherapy vs. Leuprolide Alone

End Point	Enzalutamide Monotherapy (no. of patients)	Leuprolide Alone (no. of patients)	Enzalutamide Monotherapy (no. of events)	Leuprolide Alone (no. of events)	Hazard Ratio (95% CI)	Two-Sided P Value
Metastasis-free survival	355	358	63	92	0.63 (0.46–0.87)	0.005
Overall survival	355	358	42	55	0.78 (0.52–1.17)	0.23
PSA progression	355	358	37	93	0.33 (0.23–0.49)	<0.001
First use of new antineoplastic therapy	355	358	84	140	0.54 (0.41–0.71)	<0.001
Distant metastasis	355	358	40	59	0.61 (0.41–0.92)	
Resumption of any hormonal therapy	304	240	279	217	1.66 (1.38–1.98)	
Symptomatic progression	355	358	117	169	0.62 (0.49–0.79)	
First symptomatic skeletal event	355	358	14	32	0.42 (0.23–0.79)	
First deterioration in FACT-P total score	355	358	263	248	1.17 (0.98–1.39)	



EMBARK

Adverse events

Event	Enzalutamide + Leuprolide (N = 353)		Leuprolide Alone (N = 354)		Enzalutamide Monotherapy (N = 354)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Adverse event leading to permanent discontinuation of treatment	73 (20.7)	31 (8.8)	36 (10.2)	19 (5.4)	63 (17.8)	34 (9.6)
Adverse event leading to death†	6 (1.7)	—	3 (0.8)	—	8 (2.3)	—
Most common adverse events‡						
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)	7 (2.0)	75 (21.2)	1 (0.3)	81 (22.9)	2 (0.6)
Hypertension	82 (23.2)	24 (6.8)	69 (19.5)	18 (5.1)	67 (18.9)	19 (5.4)
Fall	74 (21.0)	4 (1.1)	51 (14.4)	4 (1.1)	56 (15.8)	7 (2.0)
Back pain	60 (17.0)	3 (0.8)	54 (15.3)	1 (0.3)	62 (17.5)	3 (0.8)
Diarrhea	49 (13.9)	2 (0.6)	31 (8.8)	1 (0.3)	46 (13.0)	1 (0.3)
Constipation	46 (13.0)	1 (0.3)	31 (8.8)	0	34 (9.6)	1 (0.3)
Hematuria	42 (11.9)	8 (2.3)	44 (12.4)	4 (1.1)	45 (12.7)	9 (2.5)
Insomnia	42 (11.9)	2 (0.6)	37 (10.5)	0	25 (7.1)	0
Nausea	42 (11.9)	1 (0.3)	29 (8.2)	1 (0.3)	54 (15.3)	2 (0.6)
Pain in arm or leg	41 (11.6)	3 (0.8)	36 (10.2)	2 (0.6)	40 (11.3)	1 (0.3)
Asthenia	39 (11.0)	2 (0.6)	21 (5.9)	1 (0.3)	39 (11.0)	3 (0.8)
Dizziness	39 (11.0)	2 (0.6)	37 (10.5)	2 (0.6)	41 (11.6)	3 (0.8)
Headache	39 (11.0)	3 (0.8)	32 (9.0)	0	41 (11.6)	1 (0.3)
Urinary incontinence	34 (9.6)	4 (1.1)	28 (7.9)	3 (0.8)	36 (10.2)	6 (1.7)
Gynecomastia	29 (8.2)	0	32 (9.0)	0	159 (44.9)§	3 (0.8)
Coronavirus disease 2019	27 (7.6)	2 (0.6)	36 (10.2)	4 (1.1)	44 (12.4)	2 (0.6)
Peripheral edema	27 (7.6)	1 (0.3)	37 (10.5)	1 (0.3)	31 (8.8)	1 (0.3)
Urinary tract infection	27 (7.6)	1 (0.3)	26 (7.3)	2 (0.6)	37 (10.5)	7 (2.0)
Weight decreased	24 (6.8)	1 (0.3)	12 (3.4)	0	39 (11.0)	1 (0.3)
Nipple pain	11 (3.1)	0	4 (1.1)	0	54 (15.3)	0
Breast tenderness	5 (1.4)	0	4 (1.1)	0	51 (14.4)	0

Freedland SJ et al. *N Engl J Med*. 2023;389(16):1453-1465.

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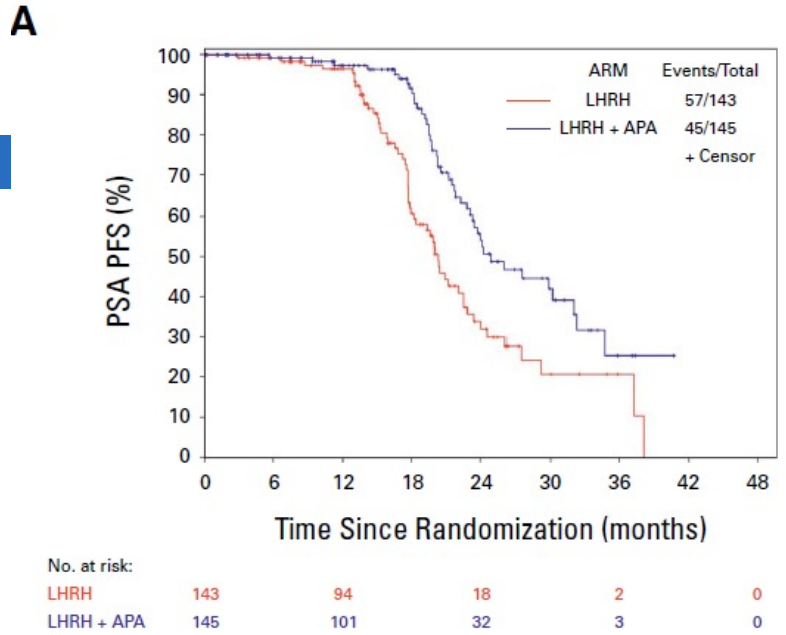
PRESTO primary endpoint

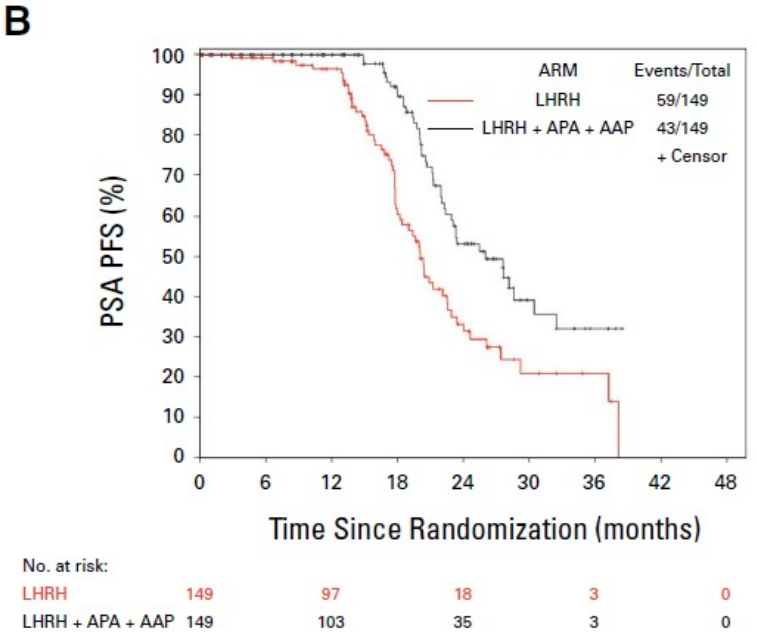
PSA PFS for ADT + Apa vs ADT (A) and triplet vs ADT (B)

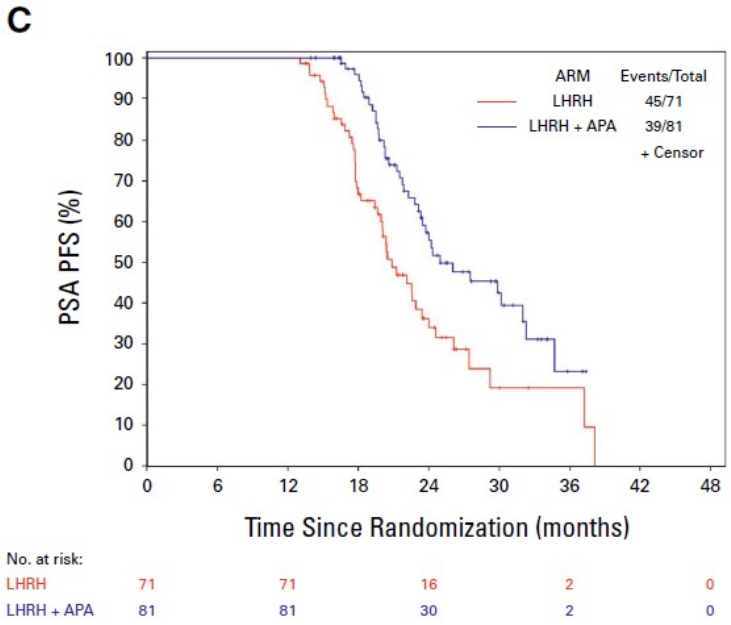
Time to testosterone recovery >150

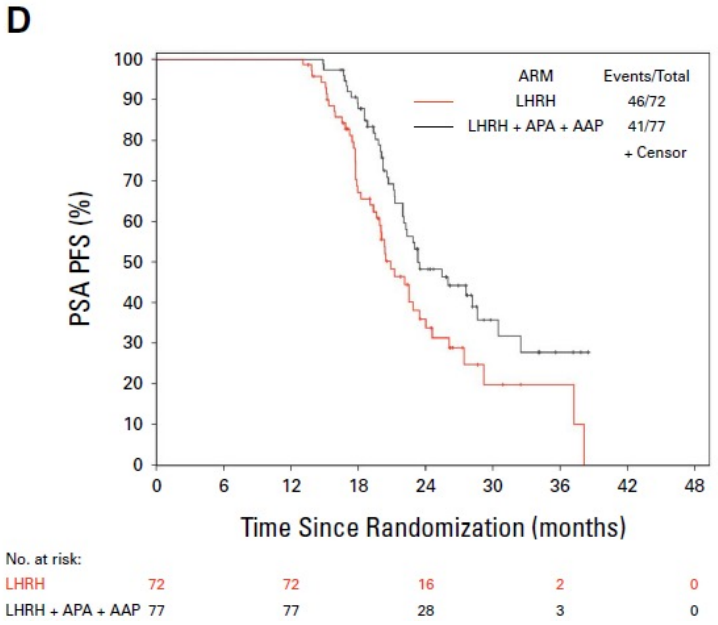
- ADT + Apa (5.7 mo) vs ADT (5.1 months)
- Longer with triplet (6.9 months)

Aggarwal R et al. J Clin Onc 2024; 42:1114-23









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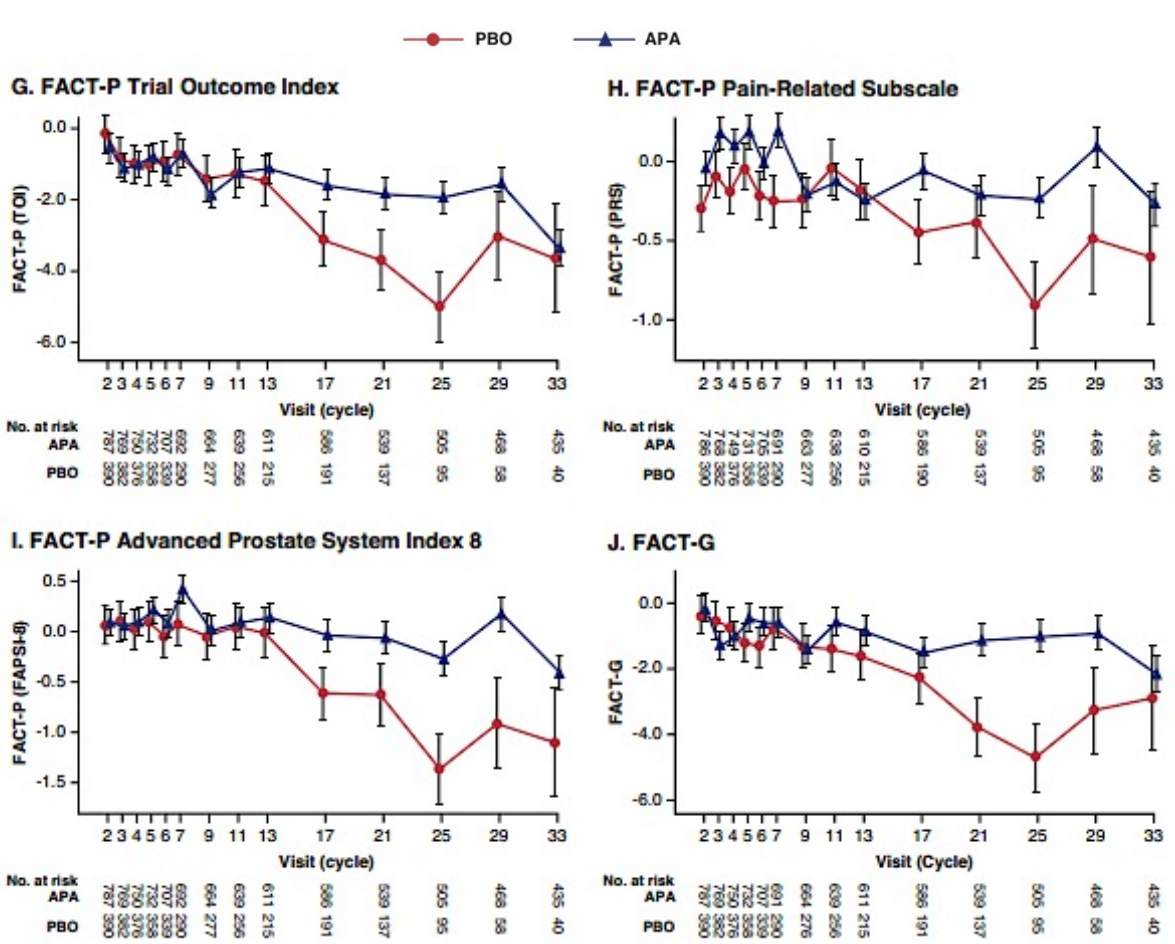
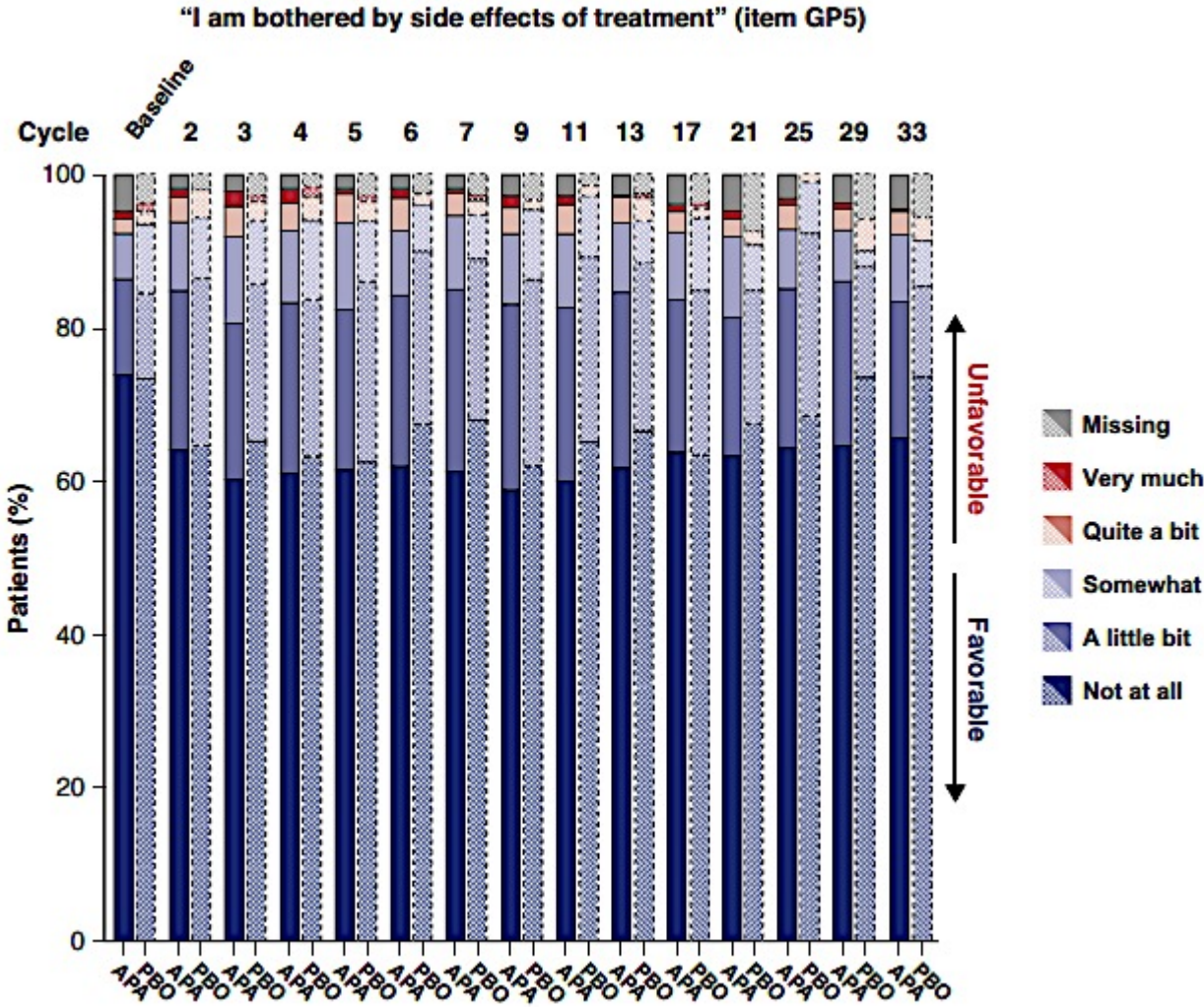
Treatment options in m0 CRPC

Study Name Agent	SPARTAN Apalutamide 240 mg daily	PROSPER Enzalutamide 160 mg daily	ARAMIS Darolutamide 600 mg BID
Design	2:1 apa/placebo	2:1 enza/placebo	2:1 daro/placebo
Number of pts	1207	1401	1509
Inclusion:	PSA DT <10 mo Pelvic LN <2 cm OK	PSA DT ≤10 mo -- bPSA ≥2	PSA DT ≤10 mo Pelvic LN <2cm OK bPSA ≥2
Met Free Surv	40.5 mo vs 16.2 placebo (HR 0.28)	36.6 mo vs 14.7 placebo (HR 0.29)	40.4 mo vs 18.4 placebo (HR 0.41)
Discontinuation	10.6% apa, 7.0% placebo	9% enza, 6% placebo	8.9% daro, 8.7% placebo

1. Smith MR et al. NEJM 2018; 378:1408-1418
2. Hussain M et al. NEJM 2018; 378:2465-74
3. Fizazi K et al. NEJM 2019; 380:1235-46

Long-term results from nmCRPC trials: SPARTAN (apalutamide)





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Oudard S et al. Eur Urol Focus 2022; 8:958-67

Long-term safety and tolerability of darolutamide: ARAMIS

Table 1. Treatment-emergent adverse events during long-term darolutamide treatment.

Treatment-emergent adverse events (TEAEs),[a] *n* (%)	Total: Darolutamide >2 years (*n* = 13)	Darolutamide >2 and ≤4 years (*n* = 7)	Darolutamide >4 years (*n* = 6)
Any TEAE	13 (100)	7 (100)	6 (100)
Worst grade			
1 or 2	7 (54)	6 (86)	1 (17)
3	6 (46)	1 (14)	5 (83)
Serious TEAE	6 (46)	2 (29)	4 (67)
TEAE leading to discontinuation of darolutamide	1 (8)	1 (14)	0
Any drug-related TEAE	5 (38)	3 (43)	2 (33)
Worst grade			
1 or 2	5 (38)	3 (43)	2 (33)
3	0	0	0
Serious drug-related TEAE	0	0	0
Drug-related TEAE leading to discontinuation of darolutamide	0	0	0
Most common TEAEs (occurring in ≥3 patients)[b]			
Diarrhea	5 (38)	2 (29)	3 (50)
Abdominal pain	4 (31)	2 (29)	2 (33)
Nausea	4 (31)	2 (29)	2 (33)
Arthralgia	3 (23)	1 (14)	2 (33)
Fatigue	3 (23)	2 (29)	1 (17)
Hematuria	3 (23)	1 (14)	2 (33)
Influenza	3 (23)	1 (14)	2 (33)

[a]Treatment-emergent adverse events were assessed according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.
[b]All TEAEs were grade 1 or 2 except 1 event each of grade 3 nausea and grade 3 hematuria.

Very small subset of patients

No new safety signals emerged

No DEXA data

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Jones RH et al. Prost Ca Prost Dis 2023; 1-4

Bone health in nmCRPC

Table 1 Falls, fractures, and other bone-related AEs in phase 3 trials for ARIs.

Study	Drug	Treatment arm			Placebo arm		
		Falls[a] *n* (%)	Fractures *n* (%)	Other[b] *n* (%)	Falls[a] *n* (%)	Fractures *n* (%)	Other[b] *n* (%)
SPARTAN (*N* = 1207) [15]	Apalutamide	125 (15.6)	94 (11.7)	NR	36 (9.0)	26 (6.5)	NR
ARAMIS (*N* = 1509) [17]	Darolutamide	40 (4.2)	40 (4.2)	139 (14.6)	26 (4.7)	20 (3.6)	68 (12.2)
PROSPER (*N* = 1401) [16, 28]	Enzalutamide	106 (11)	91 (10)	73 (8)	19 (4)	23 (5)	33 (7)

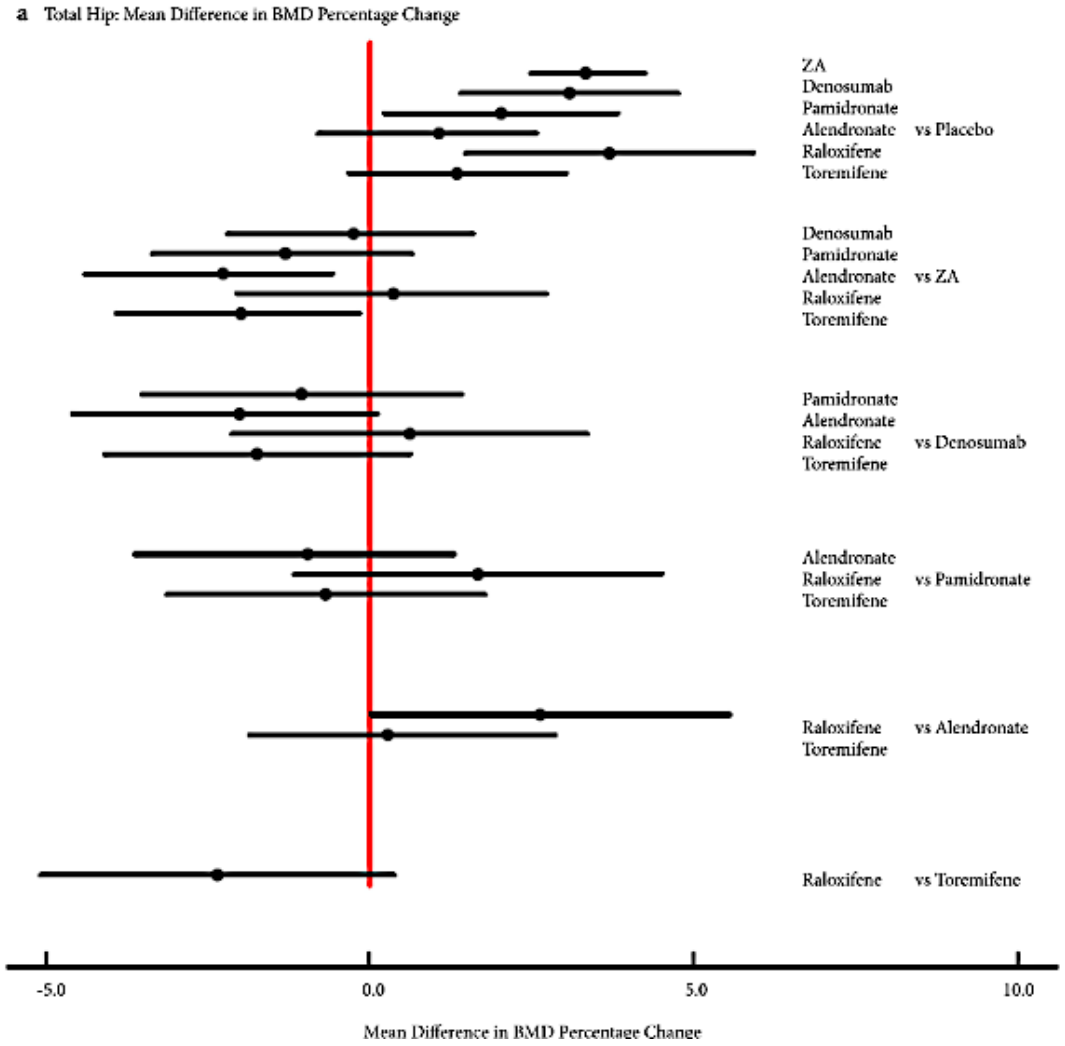
AE adverse event, *ARI* androgen receptor inhibitor, *NR* not reported.

[a]In SPARTAN, falls were deemed treatment-related by the investigators. In ARAMIS, falls included events recorded as accidents, and were determined to have been accidental falls.

[b]Other includes back pain in PROSPER, and back pain or pain in an extremity in ARAMIS.

Management strategies:
- Vitamin D +/- Calcium
- Exercise
- Regular screening by DEXA
- Bone support agents

Hussain A et al. PCAN 2021; 24:290-300



Poon Y et al. BJUI 2018; 121:17-28

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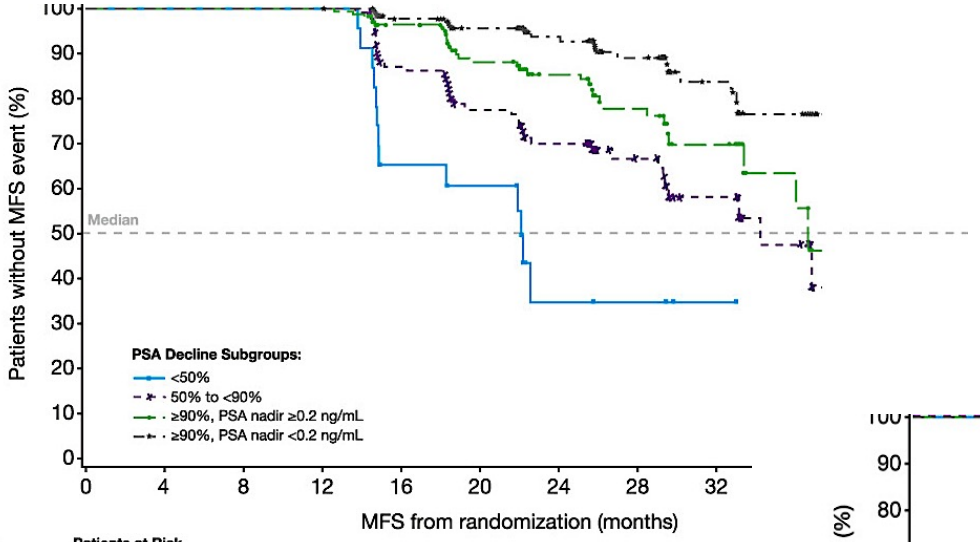
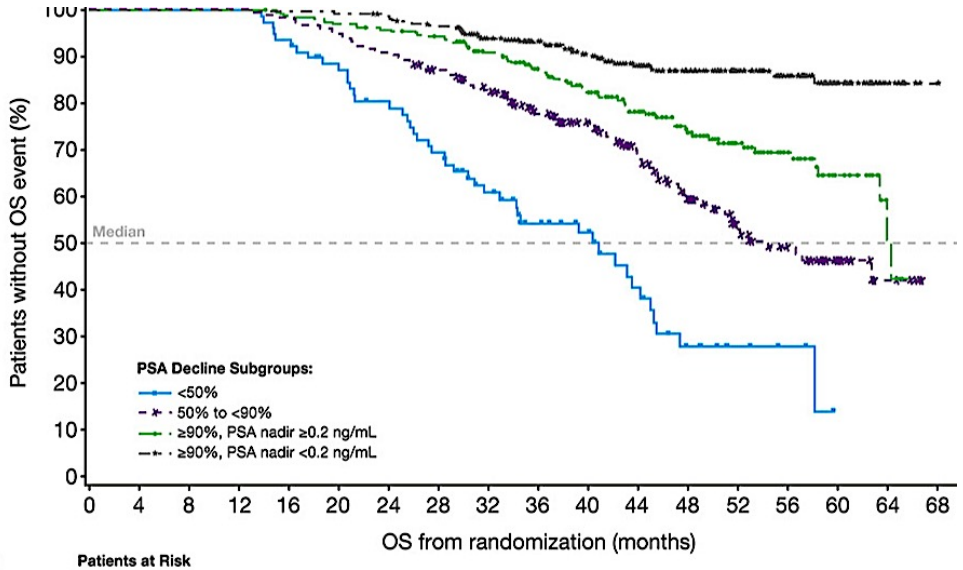
Long-term analysis from PROSPER: PSA nadir associated with benefit

Other nmCRPC trials have also shown this

No known intervention for those with inadequate PSA nadir



Subgroup	Patients at Risk								
<50%:	23	23	23	23	14	12	4	3	1
50% to <90%:	113	113	113	113	90	65	51	34	17
≥90%, PSA nadir ≥0.2 ng/mL:	172	172	172	172	146	107	76	51	27
≥90%, PSA nadir <0.2 ng/mL:	190	190	190	190	151	127	96	67	37



Subgroup	Patients at Risk																
<50%:	78	78	78	78	73	65	59	51	10	30	25	17	9	6	3	0	0
50% to <90%:	196	196	196	196	193	186	178	167	151	127	110	87	64	45	35	18	8
≥90%, PSA nadir ≥0.2 ng/mL:	266	266	266	266	261	257	251	245	225	194	168	141	108	77	53	27	6
≥90%, PSA nadir <0.2 ng/mL:	287	287	287	287	286	285	281	273	244	224	188	158	128	103	72	39	15

Hussain M et al. J Urol 2023; 209:532-9

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Alternative approaches to systemic management: use PSMA PET → MDT

No OS benefit

For some men delaying ADT is a goal

Surveillance or Metastasis-Directed Therapy for Oligometastatic PCa Recurrence: A Prospective, Randomized, Multicenter Phase II Trial.

- Primary endpoint: ADT-free survival; the indication to start ADT being symptomatic progression, progression to more than three metastases, or local progression of baseline-detected metastases.

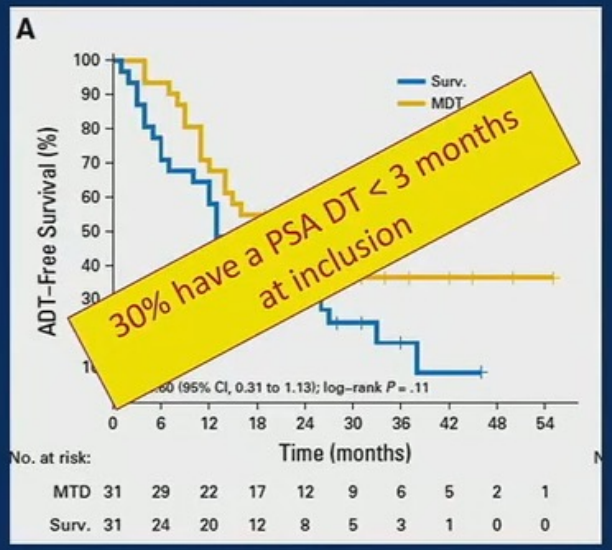

Table 2. Indications for Starting Androgen Deprivation Therapy

Indication	Surveillance (n = 31)	Metastasis-Directed Therapy (n = 31)
Not started yet	6 (19)	12 (39)
Polymetastatic progression	16 (55)	19 (61)
Local progression	6 (23)	0 (0)
Symptomatic progression	3 (10)*	0 (0)

NOTE. Data are presented as No. (%).
*Two patients with symptomatic progression also showed local and poly-metastatic progression.

Ost P. et J Clin Oncol. 2018 Feb 10;36(5):446-453.

ASCO Genitourinary Cancers Symposium #GU24 PRESENTED BY: Bertrand Tombal

ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY KNOWLEDGE CONQUERS CANCER

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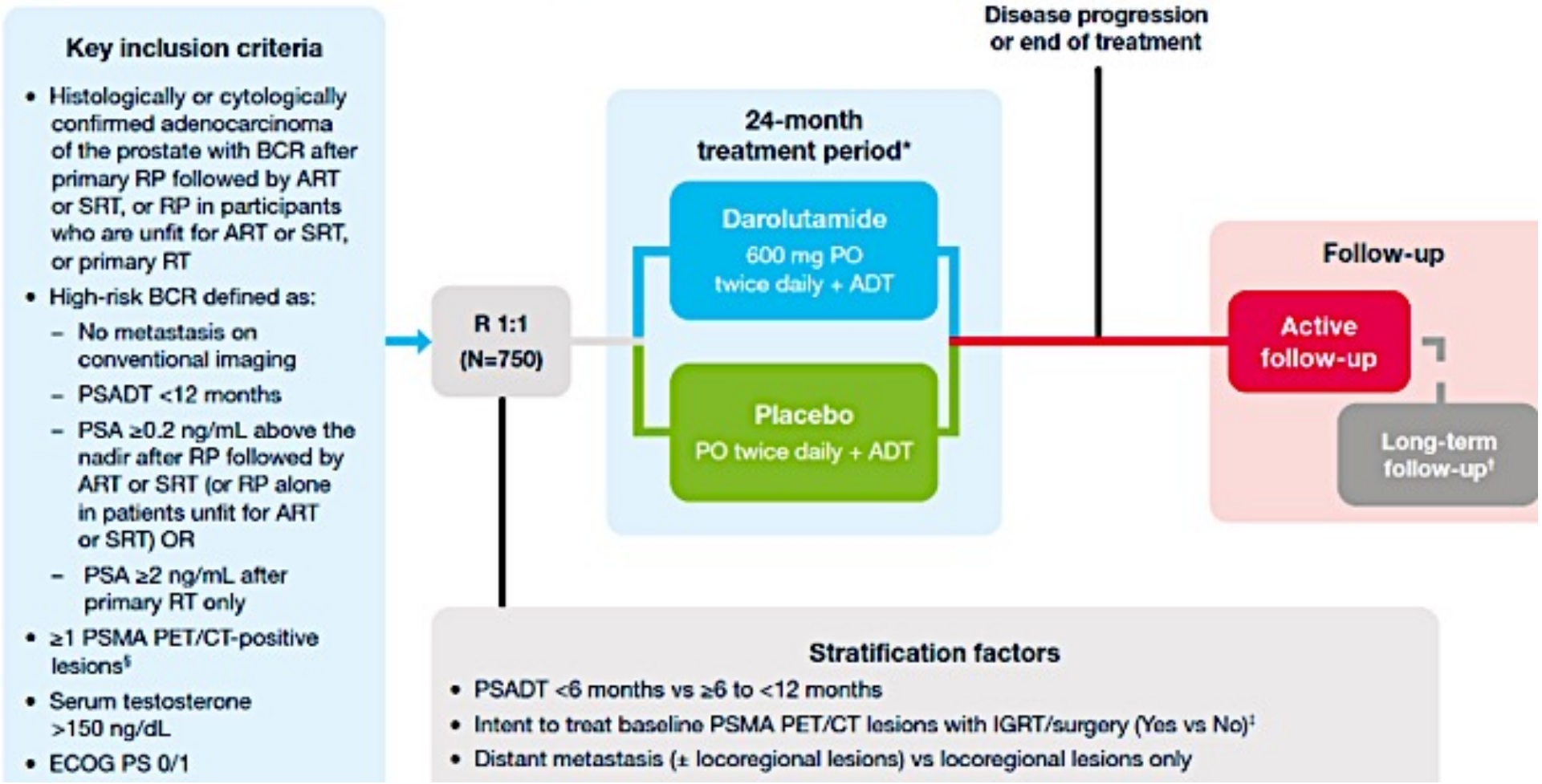
Ongoing phase 3 trials: ARASTEP



Addresses the unmet need of PSMA PET+

TiP poster ASCO 2024 Chehrazi-Raffle et al

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Ongoing trials in the BCR space

NCT05478239	N=30	ArtemiCoffee in patients with rising PSA	PSA 50% decline in 24 weeks	Kentucky
NCT03753334	N=40	EPA (LCn3 supp)	Change in PSA DT	Quebec
NCT04519879	N=66	White button mushroom supplement	Change in PSA during 48 weeks	COH (S. Calif)
NCT04114825	N=180	RV001V (BRaVac)	Time to PSA progression	Completed accrual, awaiting results

Agenda

Module 1: Optimizing the Management of Nonmetastatic Prostate Cancer — Dr Dorff

Module 2: Evidence-Based Selection of Treatment for Metastatic Hormone-Sensitive Prostate Cancer — Dr Smith

Module 3: New Considerations with the Use of PARP Inhibitors for Metastatic Castration-Resistant Prostate Cancer (mCRPC) — Dr Agarwal

Module 4: Role of Novel Radiopharmaceuticals for mCRPC — Dr Armstrong

Module 5: Promising Investigational Approaches for Patients with Prostate Cancer — Dr Antonarakis

RTP RESEARCH TO PRACTICE

Consulting Faculty Comments

Optimal selection of initial therapy for patients with metastatic hormone-sensitive prostate cancer and integration of triplet therapy

Dr Shaachi Gupta
(Lake Worth, Florida)

Dr Neil Morganstein
(Summit, New Jersey)

Dr Gigi Chen
(Pleasant Hill, California)

QUESTIONS FOR THE FACULTY

Given they have never been evaluated head to head, is there any evidence that ADT/docetaxel/darolutamide is superior to ADT with an AR pathway inhibitor alone?

For which types of patients are you prioritizing the triplet of ADT/docetaxel/darolutamide over other available options?

QUESTIONS FOR THE FACULTY

When using ADT in combination with an AR pathway inhibitor in the hormone-sensitive metastatic setting, which agent are you most frequently utilizing?

Are you comfortable using ADT/darolutamide without docetaxel?

Consulting Faculty Comments

Initial treatment options for older patients; durability of responses observed with AR inhibitors and with relugolix

Dr Erik Rupard (St George, Utah)

RTP
RESEARCH
TO PRACTICE

Cancer care in the Amish community

To view, visit https://www.ResearchToPractice.com/ASCO24Clip

RTP RESEARCH TO PRACTICE

QUESTIONS FOR THE FACULTY

Do you approach patients who present de novo with metastatic disease any differently than those who experience relapse after localized therapy?

How important is volume of disease in making these decisions?

Evidence-Based Selection of Treatment for Metastatic Castration-Sensitive Prostate Cancer (mCSPC)

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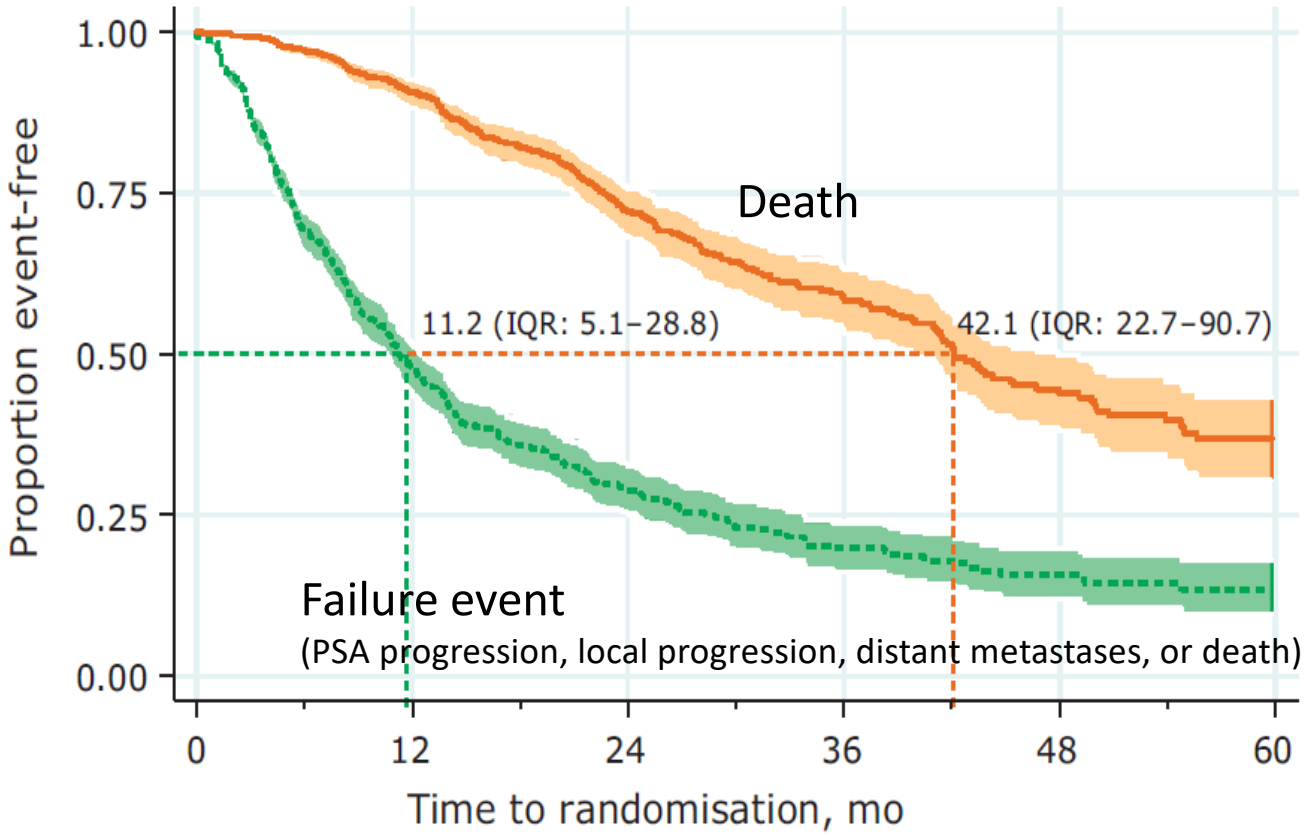
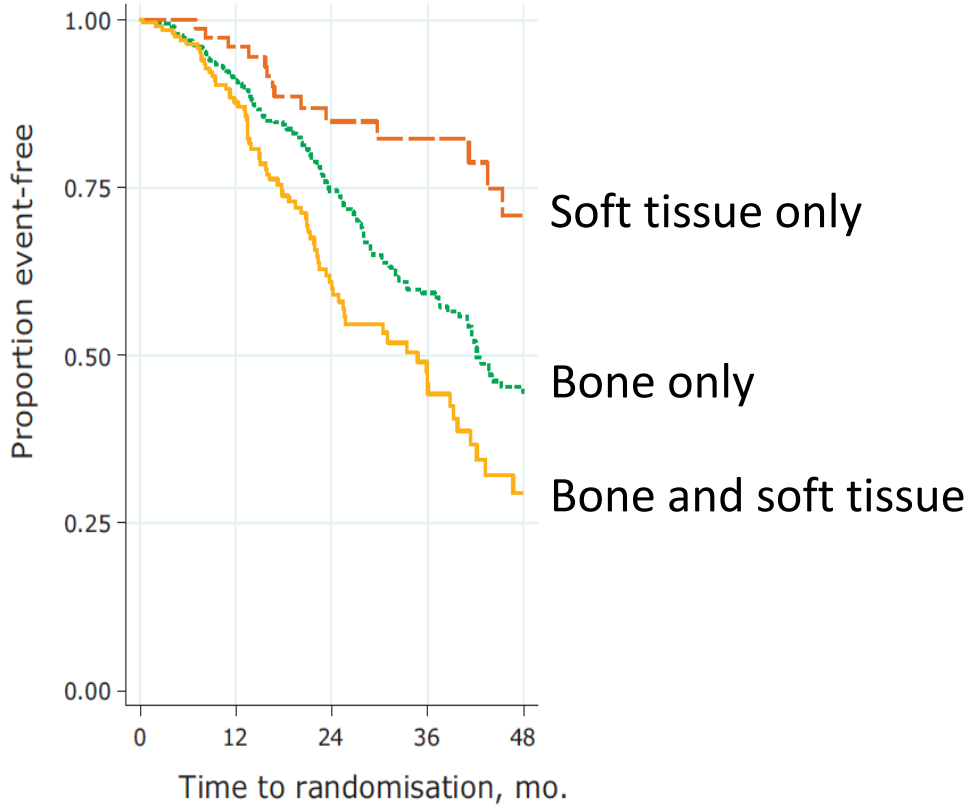
HARVARD MEDICAL SCHOOL

Matthew R. Smith, M.D.,Ph.D.
Professor of Medicine, Harvard Medical School
Director, MGH Genitourinary Malignancies Program

Clinical Outcomes in Metastatic Prostate Cancer: STAMPEDE Experience with ADT





STAMPEDE Control Arm
- Metastatic disease
- Accrued 10/2005-1/2014
- N=917

James ND *et al* (2015) Eur Urol 67: 1028-1038

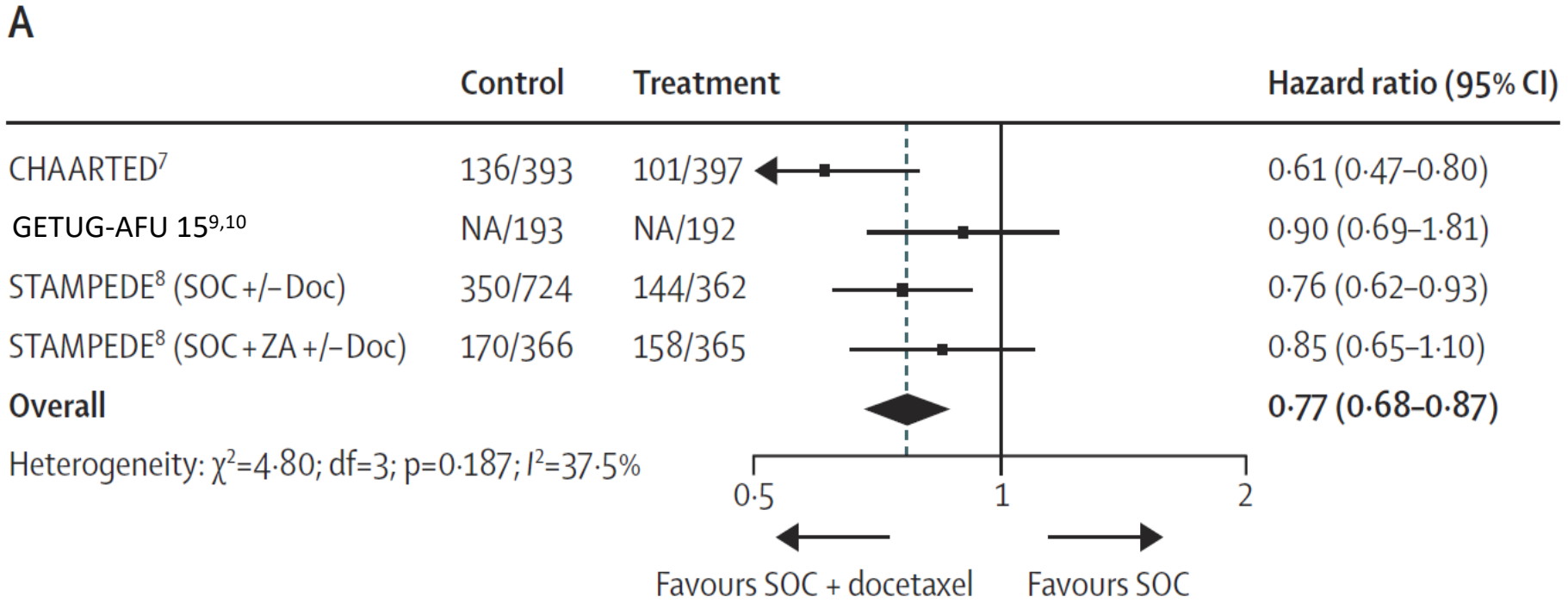
Level 1 Evidence for Improved Overall Survival in mCSPC

Studies	Intervention	Control	Comments
GETUG-AFU 15 CHAARTED STAMPEDE-C	Docetaxel + ADT	ADT	Benefit in high-volume subgroup
LATITUDE STAMPEDE-G	Abiraterone + ADT	ADT	Similar benefits by risk group
ARCHES ENZAMET	Enzalutamide + ADT	ADT	Similar benefits by risk group
TITAN	Apalutamide + ADT	ADT	Similar benefits by risk group
ARASENS	Darolutamide + ADT + docetaxel	ADT + docetaxel	Similar benefits for recurrent and de novo metastatic disease
PEACE-1	Abiraterone +ADT + docetaxel (+/- prostate radiation)	ADT + docetaxel (+/- prostate radiation)	Subgroup analysis

Gravis et al Lancet Oncol 2013; Sweeney et al NEJM 2015; James N et al Lancet 2015; Attard G et al Lancet Oncol 2023; Fizazi K et al NEJM 2017; James et al NEJM 2017; Armstrong et al JCO 2021; Davis et al NEJM 2019; Chi KN et al NEJM 2019; Smith MR et al NEJM 2022; Fizazi K et al Lancet 2022

Meta-Analysis of RCTs of Docetaxel in mCSPC

Overall Survival



- Results based on 2993 men/2198 events
- 9% absolute improvement in survival at 4 years

Vale et al. Lancet Oncol 2016; 17(2):243-56

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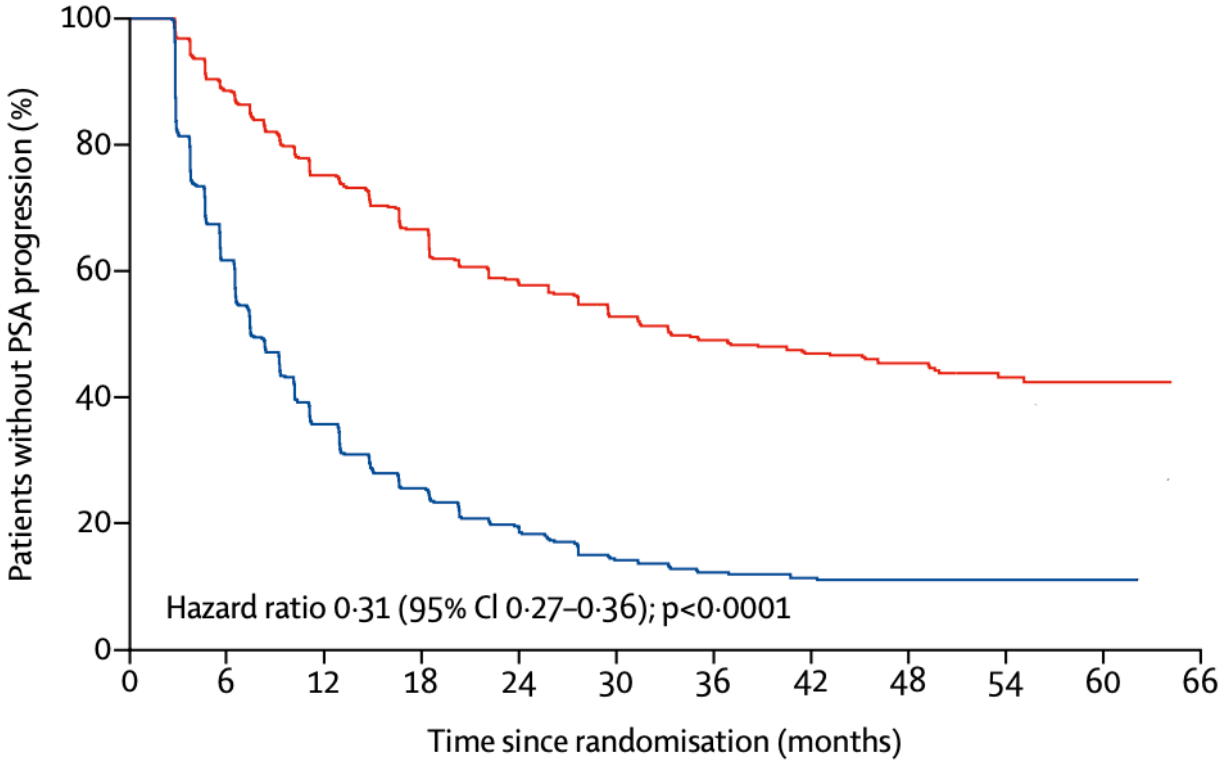
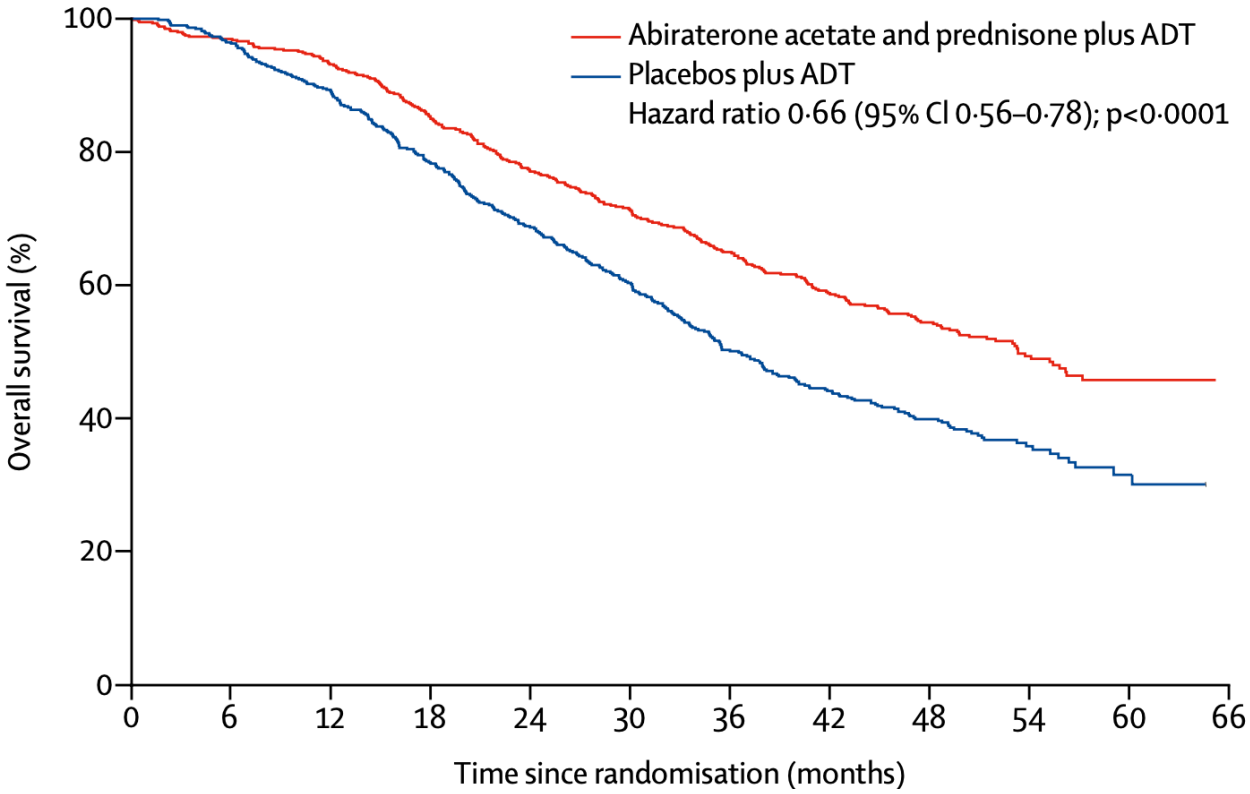
LATITUDE: Abiraterone Acetate for mCSPC

Radiographic Progression-Free Survival



Overall Survival



Fizazi K et al. *Lancet Oncol* 2019; 20: 686–700

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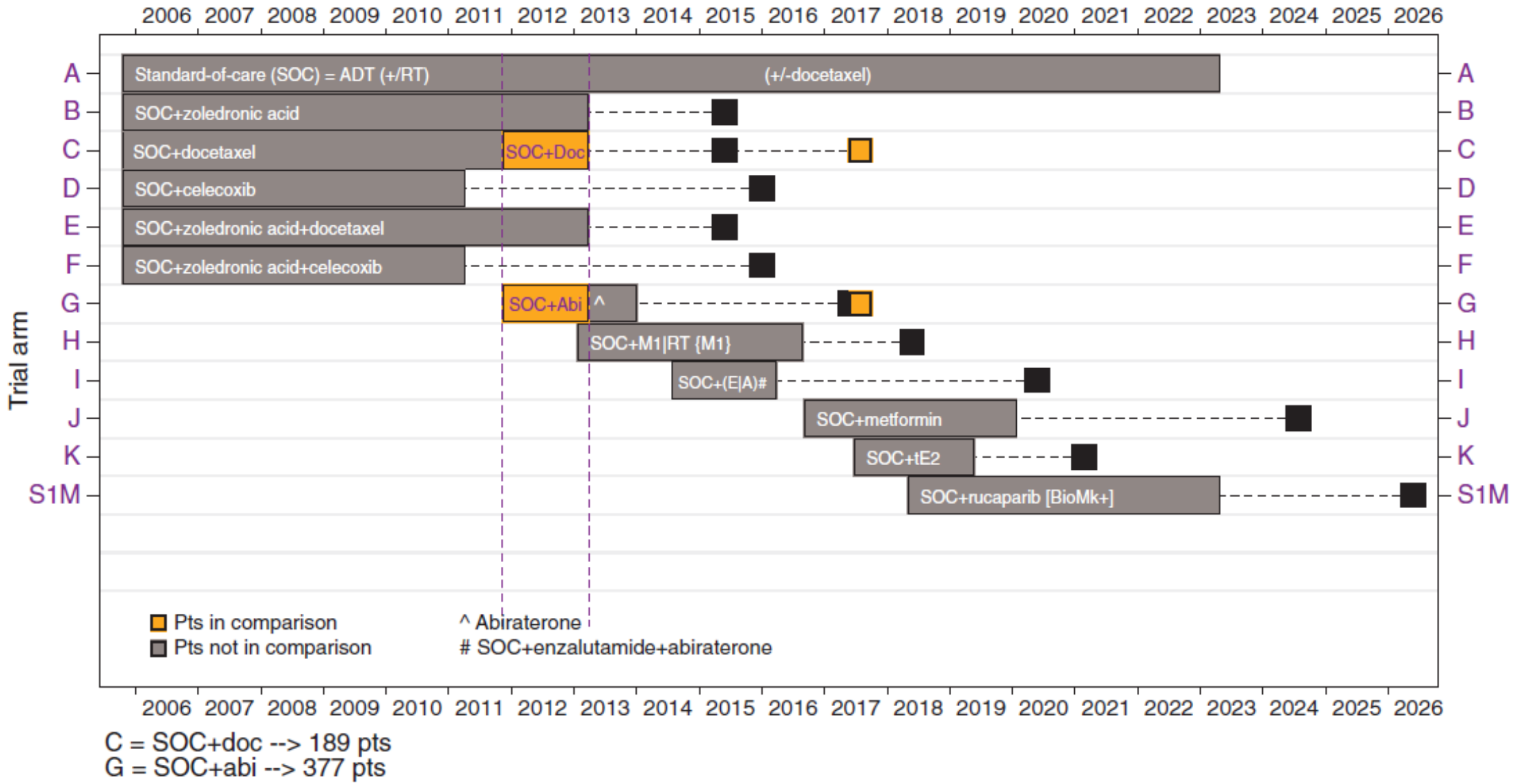
STAMPEDE: Docetaxel vs Abiraterone Comparison



Sydes et al (2018) *Annals of Oncology* 29:1235-1248

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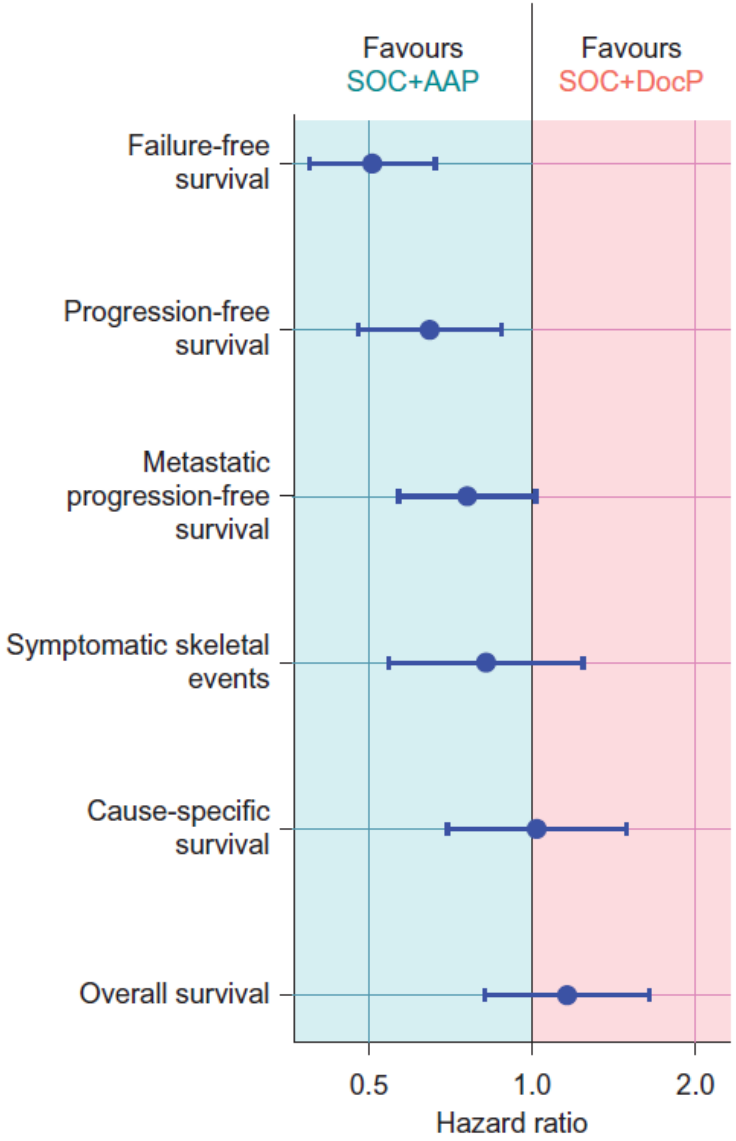
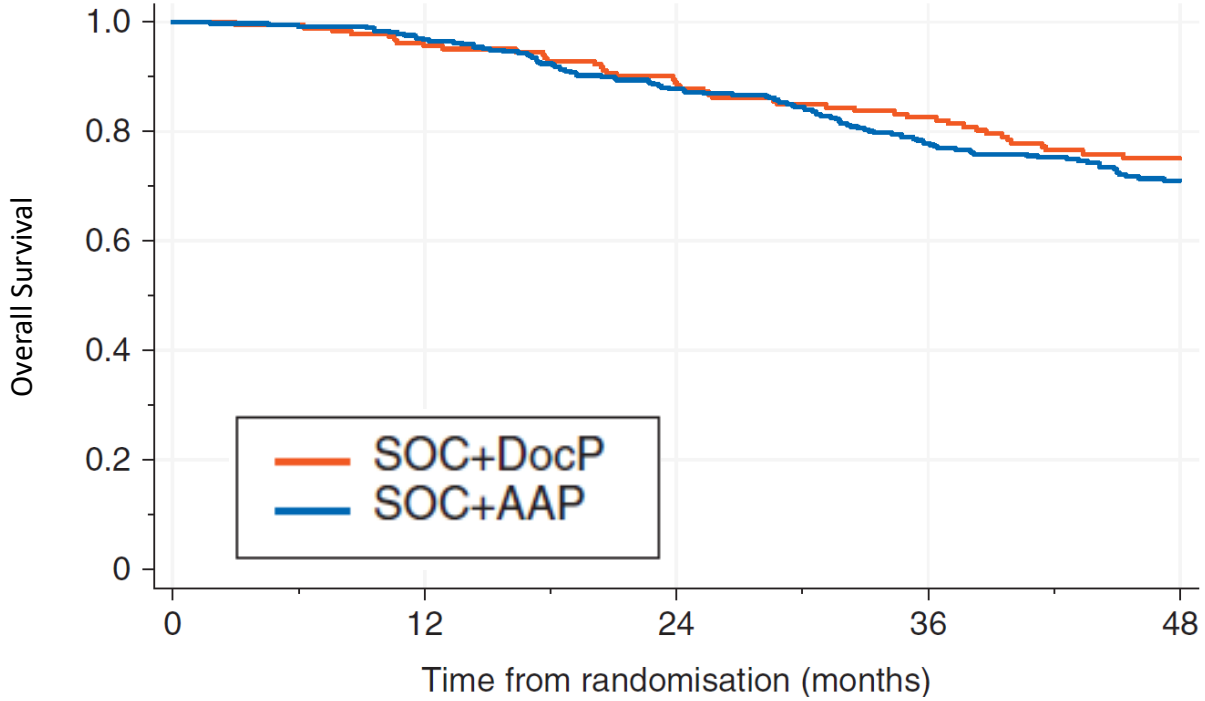
STAMPEDE: Docetaxel vs Abiraterone Comparison



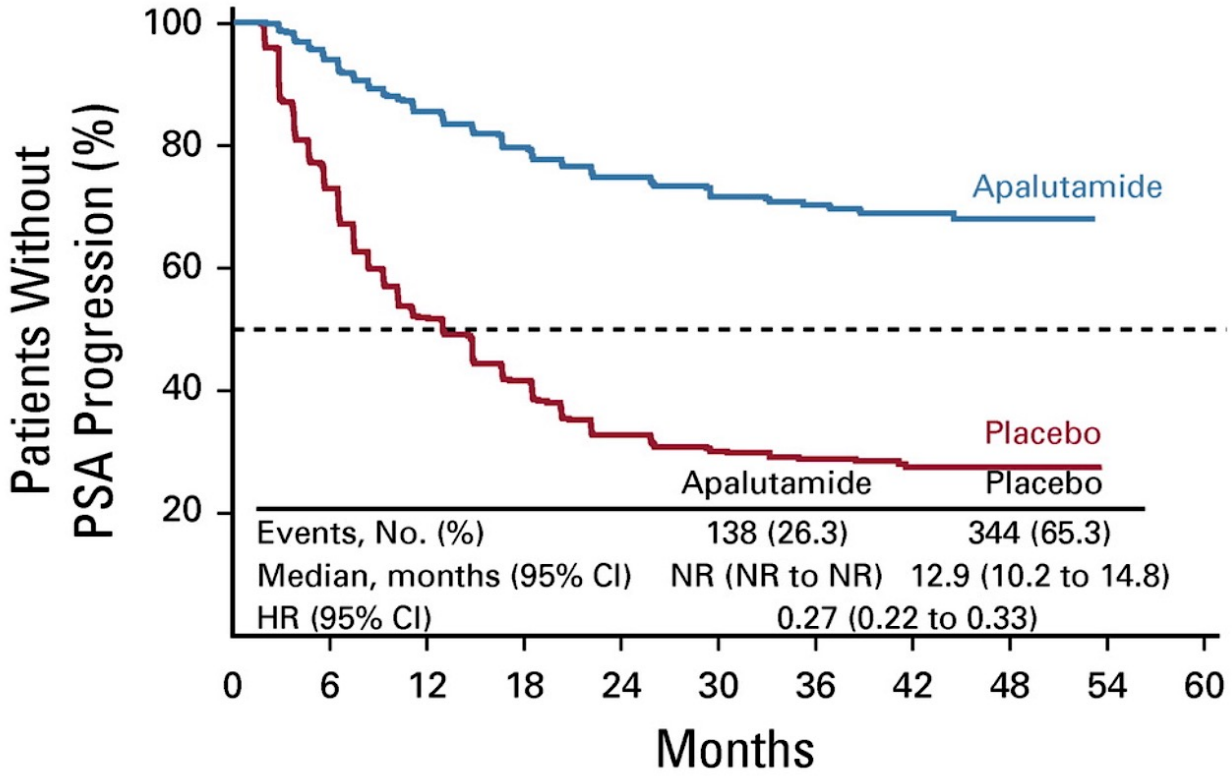
Overall Survival



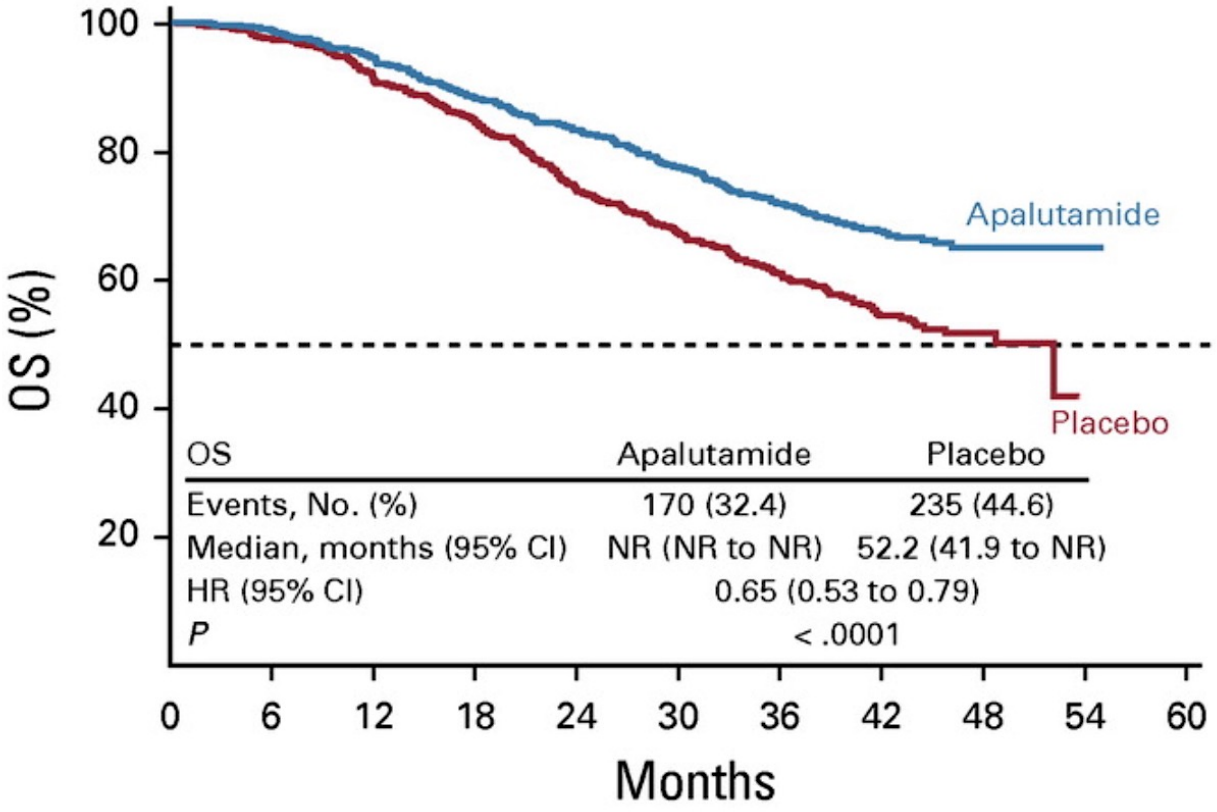
Sydes et al (2018) *Annals of Oncology* 29:1235-1248

TITAN: Apalutamide for mCSPC

Radiographic Progression-Free Survival



Overall Survival



Chi KN, Chowdhury S, Bjartell A, et al. J Clin Oncol. 2021;39(20):2294-2303.

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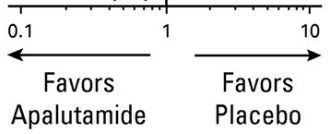
TITAN Subgroup Analyses

Overall Survival

Subgroup	Events/No. Apalutamide	Events/No. Placebo	Median OS (months) Apalutamide	Median OS (months) Placebo	HR (95% CI)
All patients	170/525	235/527	NR	52.2	0.65 (0.53 to 0.79)
Baseline ECOG performance status					
0	94/328	134/348	NR	52.2	0.68 (0.52 to 0.89)
1	76/197	101/178	NR	32.3	0.56 (0.42 to 0.76)
Geographic region					
EU/NA	53/173	66/173	NR	52.2	0.75 (0.52 to 1.07)
Other	117/352	169/354	NR	44.0	0.62 (0.49 to 0.78)
Bone metastasis only at baseline					
Yes	70/289	115/269	NR	NR	0.50 (0.37 to 0.67)
No	100/236	120/258	NR	48.7	0.85 (0.65 to 1.11)
Visceral disease at baseline					
Yes	27/56	43/72	40.8	30.1	0.76 (0.47 to 1.23)
No	143/469	192/455	NR	52.2	0.65 (0.52 to 0.80)
Gleason score at baseline					
≤ 7	48/174	63/169	NR	NR	0.67 (0.46 to 0.98)
> 7	122/351	172/358	NR	43.7	0.64 (0.51 to 0.81)
Prior docetaxel use					
Yes	21/58	17/55	NR	NR	1.12 (0.59 to 2.12)
No	149/467	218/472	NR	48.7	0.61 (0.50 to 0.76)
Age (years)					
< 65	49/149	90/182	NR	41.7	0.57 (0.40 to 0.80)
65-74	81/243	95/232	NR	NR	0.74 (0.55 to 0.99)
≥ 75	40/133	50/113	NR	52.2	0.65 (0.43 to 0.99)
Baseline PSA above median					
Yes	115/286	126/240	NR	38.9	0.67 (0.52 to 0.86)
No	55/239	109/287	NR	NR	0.54 (0.39 to 0.75)
Baseline LDH above ULN					
Yes	34/60	34/60	38.2	28.4	0.91 (0.57 to 1.47)
No	128/443	188/442	NR	52.2	0.61 (0.49 to 0.77)
Baseline ALP above ULN					
Yes	79/177	119/180	NR	28.7	0.55 (0.42 to 0.74)
No	90/346	115/345	NR	52.2	0.72 (0.55 to 0.95)
Disease volume					
High	134/325	175/335	NR	38.7	0.70 (0.56 to 0.88)
Low	36/200	60/192	NR	NR	0.52 (0.35 to 0.79)
No. of bone lesions					
≤ 10	76/318	108/331	NR	NR	0.69 (0.52 to 0.93)
> 10	94/207	127/196	NR	26.9	0.54 (0.42 to 0.71)
Metastasis stage at diagnosis					
M0	20/85	29/59	NR	41.2	0.39 (0.22 to 0.69)
M1	140/411	199/441	NR	48.7	0.68 (0.55 to 0.85)
Disease risk					
Low	58/236	75/241	NR	NR	0.76 (0.54 to 1.07)
High	112/289	160/286	NR	34.0	0.57 (0.45 to 0.73)



Chi KN, Chowdhury S, Bjartell A, et al. J Clin Oncol. 2021;39(20):2294-2303.

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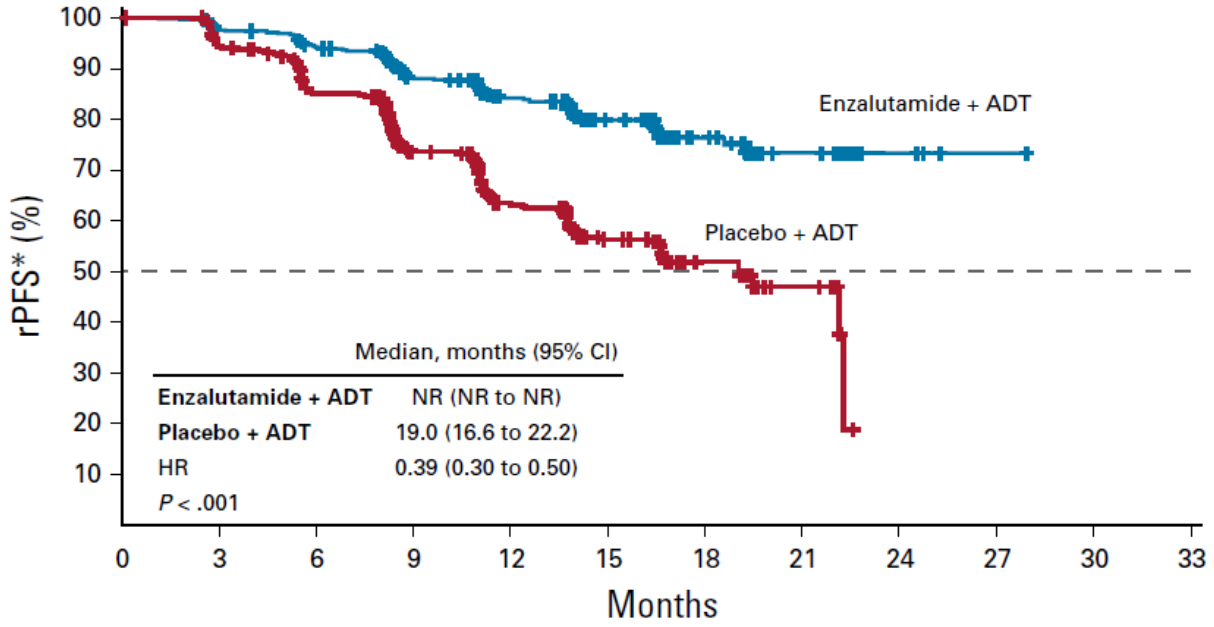
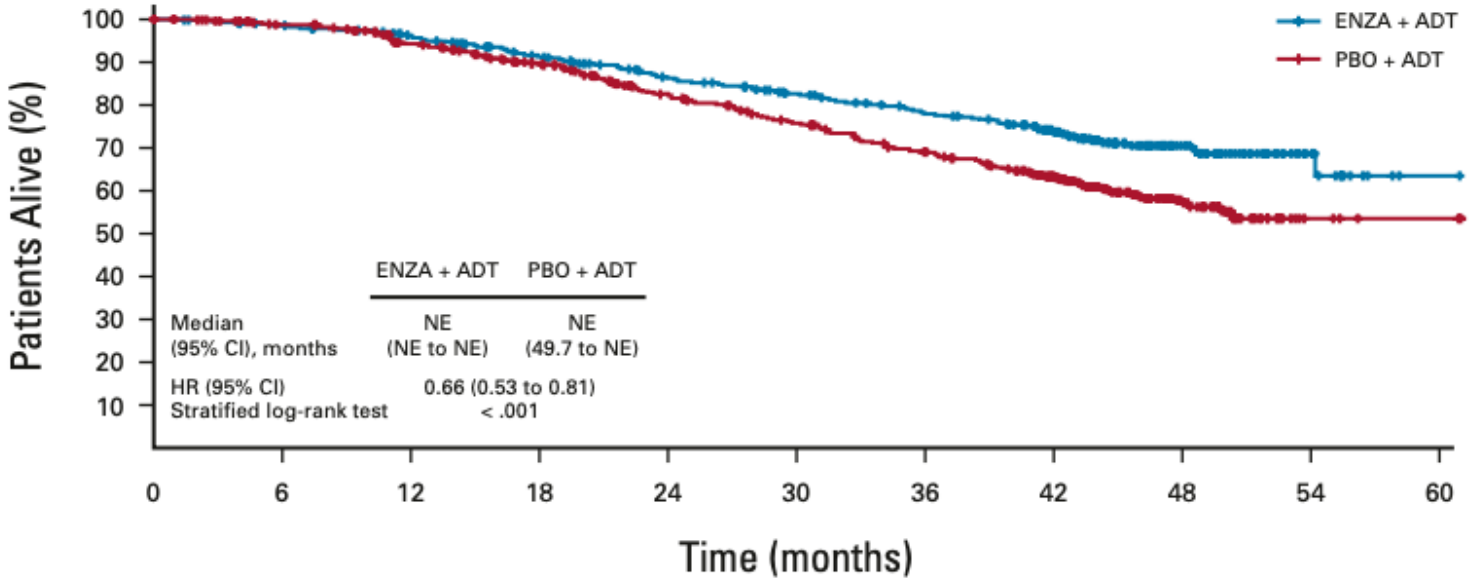
ARCHES: Enzalutamide for mCSPC

rPFS



OS



Armstrong et al (2019) *J Clin Oncol 37:* 2974-2986; Armstrong et al (2022) *J Clin Oncol* DOI: 10.1200/JCO.22.00193

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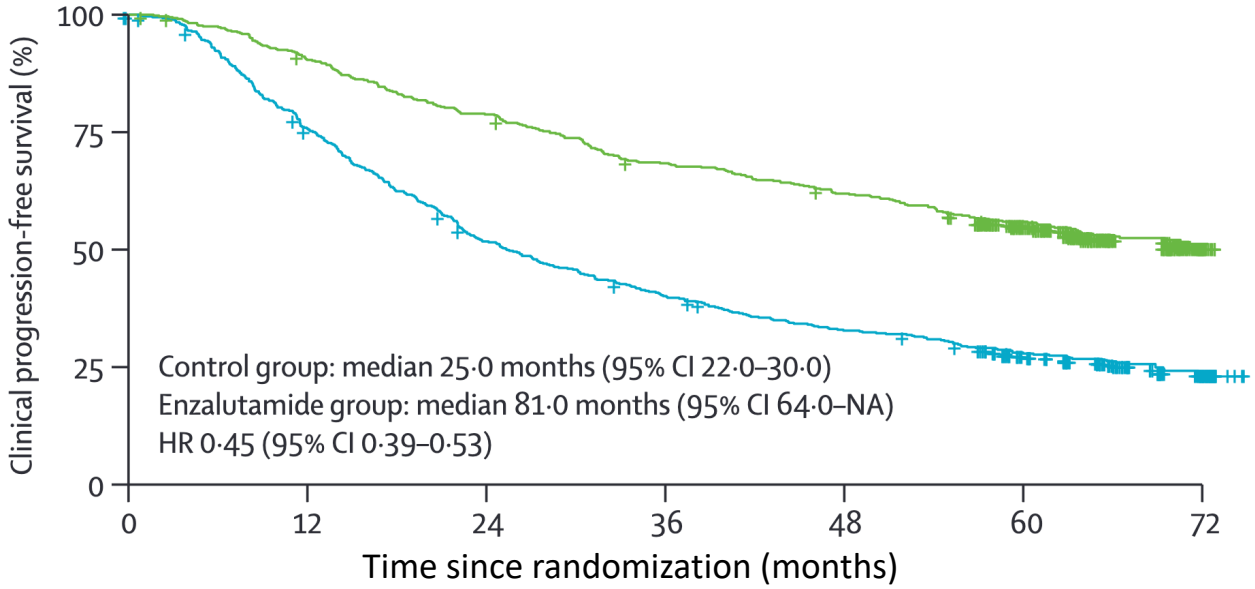
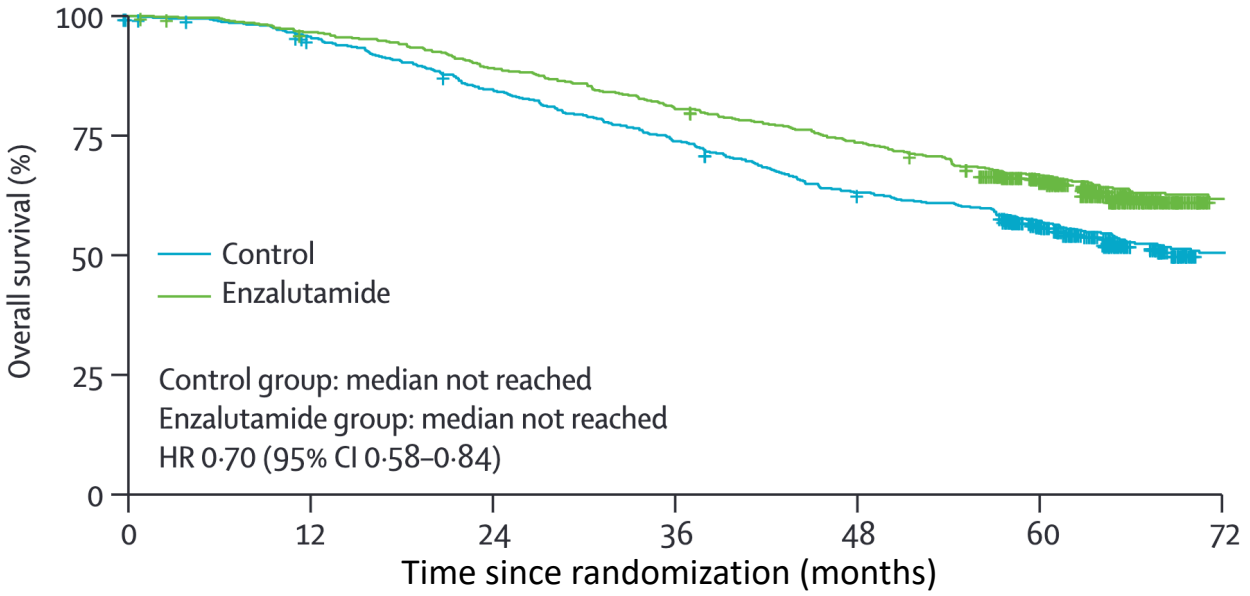
ENZAMET: Enzalutamide for mCSPC

Clinical Progression-Free Survival



Overall Survival



Sweeney CJ, Martin AJ, Stockler MR, et al. *Lancet Oncol*. 2023;24(4):323-334

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ARASENS Study Design

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

Patients (N=1306)
- mHSPC
- ECOG PS 0 or 1
- Candidates for ADT and docetaxel

Stratification
- Extent of disease: M1a vs M1b vs M1c
- ALP < vs ≥ ULN

Docetaxel × 6

→ **Darolutamide 600 mg twice daily + ADT**

→ **Placebo twice daily + ADT**

Docetaxel × 6

FPFV: Nov 2016
LPFV: June 2018

Data cut-off
Oct 25, 2021

Endpoints

Primary: OS

Secondary
- Time to CRPC
- Time to pain progression
- SSE-free survival
- Time to first SSE
- Time to initiation of subsequent systemic antineoplastic therapy
- Time to worsening of disease-related physical symptoms
- Time to initiation of opioid use for ≥7 consecutive days
- Safety

- The primary analysis was planned to occur after ~509 deaths
- Secondary efficacy endpoints were tested hierarchically

***One enrolled patient was excluded from all analysis sets because of Good Clinical Practice violations. ALP, alkaline phosphatase; CRPC, castration-resistant prostate cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; FPFV, first patient first visit; LPFV, last patient first visit; M1a, nonregional lymph node metastases only; M1b, bone metastases ± lymph node metastases; M1c, visceral metastases ± lymph node or bone metastases; Q3W, every 3 weeks; SSE, symptomatic skeletal event; ULN, upper limit of normal.**

Smith *et al* (2022) N Engl J Med DOI: 10.1056/NEJMoa2119115

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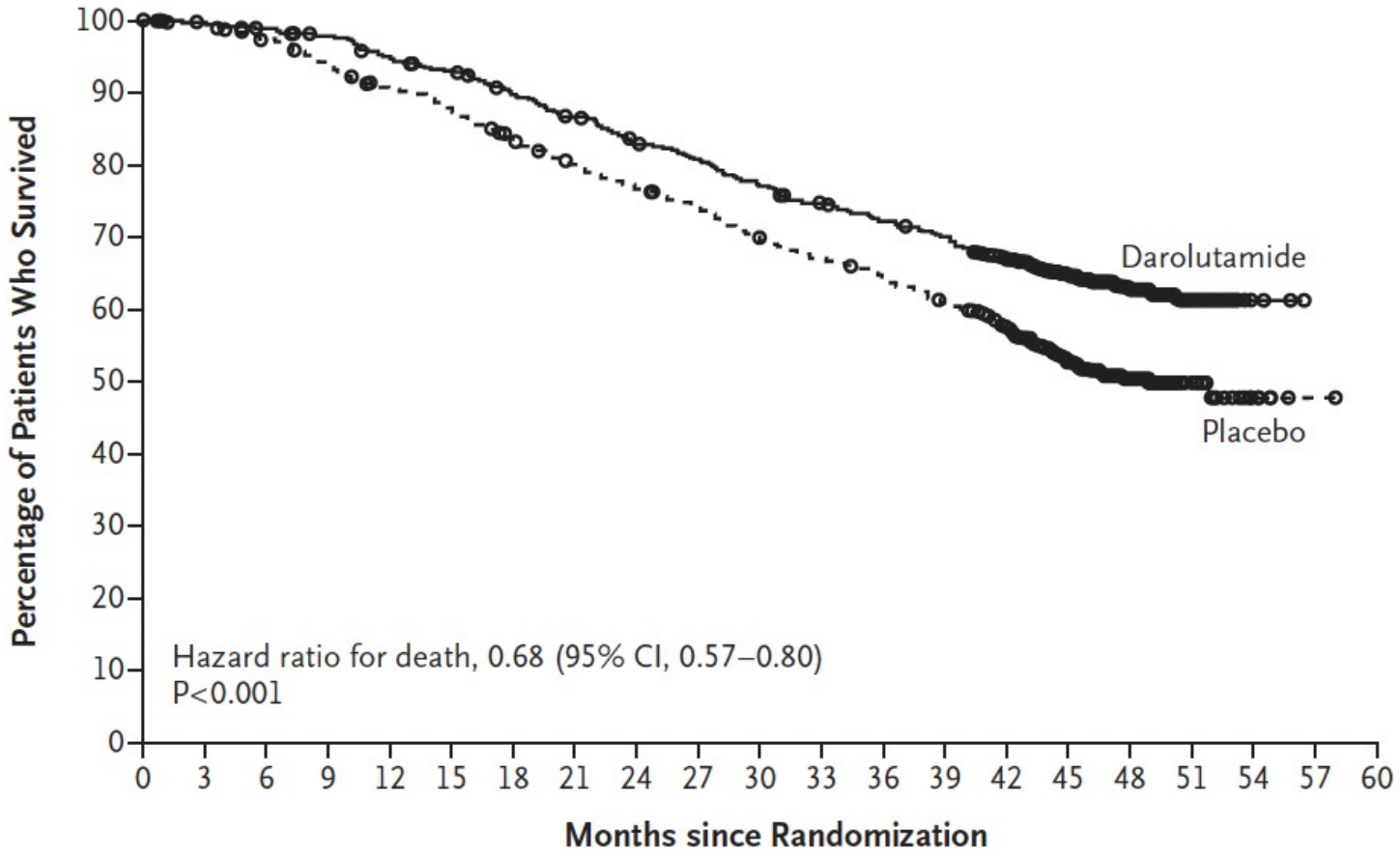
ARASENS Primary Endpoint: Overall Survival



	Median Survival (95% CI) *mo*
Darolutamide	NE
Placebo	48.9 (44.4–NE)

No. at Risk

Darolutamide	651	645	637	627	608	593	570	548	525	509	486	468	452	436	402	267	139	56	9	0	0
Placebo	654	646	630	607	580	565	535	510	488	470	441	424	402	383	340	218	107	37	6	1	0

Smith *et al* (2022) N Engl J Med DOI: 10.1056/NEJMoa2119115

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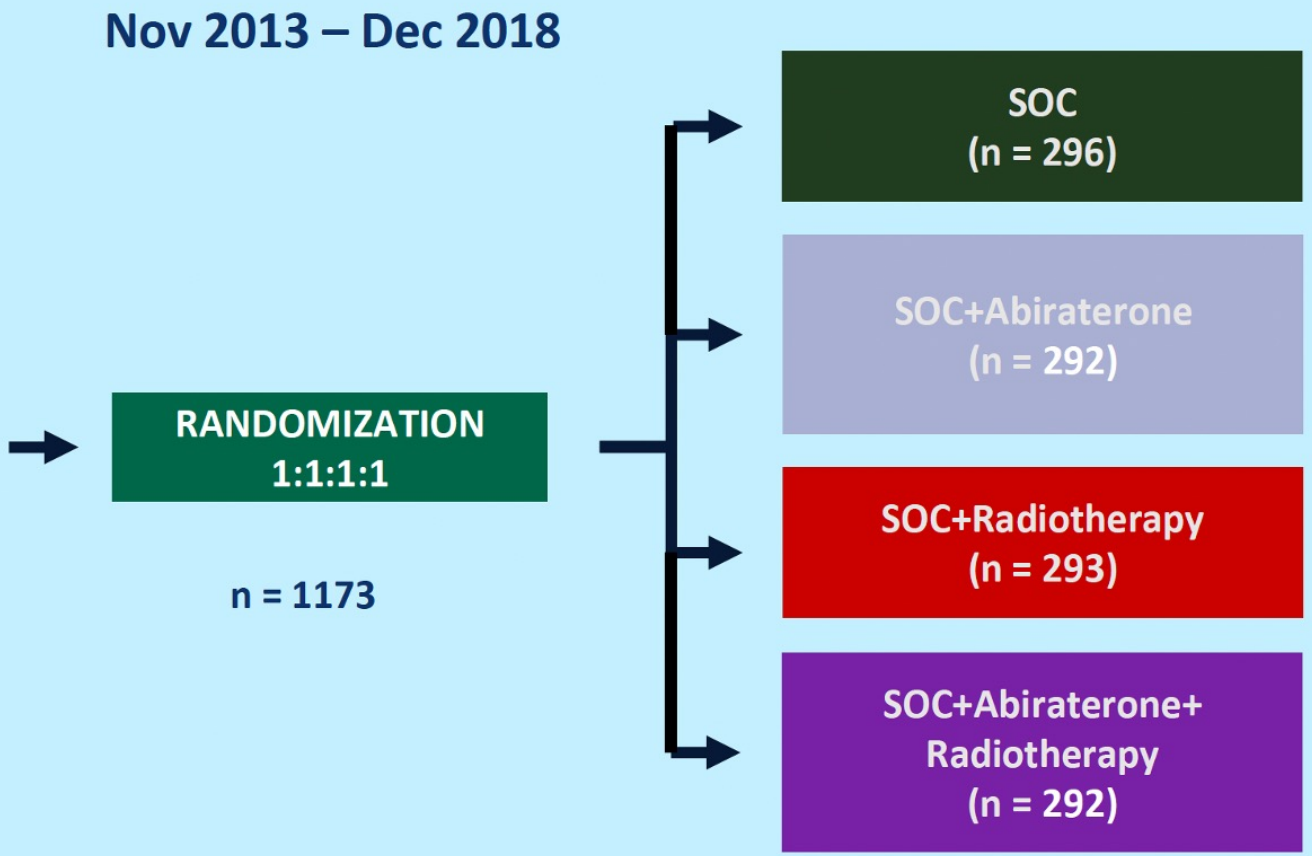
PEACE-1 Study Design

Key Eligibility Criteria
De novo mCSPC
Distant metastatic disease by ≥ 1 lesion on bone scan and/or CT scan
ECOG PS 0 -2

On-Study Requirement
Continuous ADT

Permitted
ADT ≤ 3 months

Stratification
ECOG PS (0 vs 1-2)
Metastatic sites (LN vs bone vs visceral)
Type of castration (orchidectomy vs LHRH agonist vs LHRH antagonist)
Docetaxel (yes vs no)



ECOG PS, Eastern Cooperative Oncology Group performance status

2021 ESMO congress

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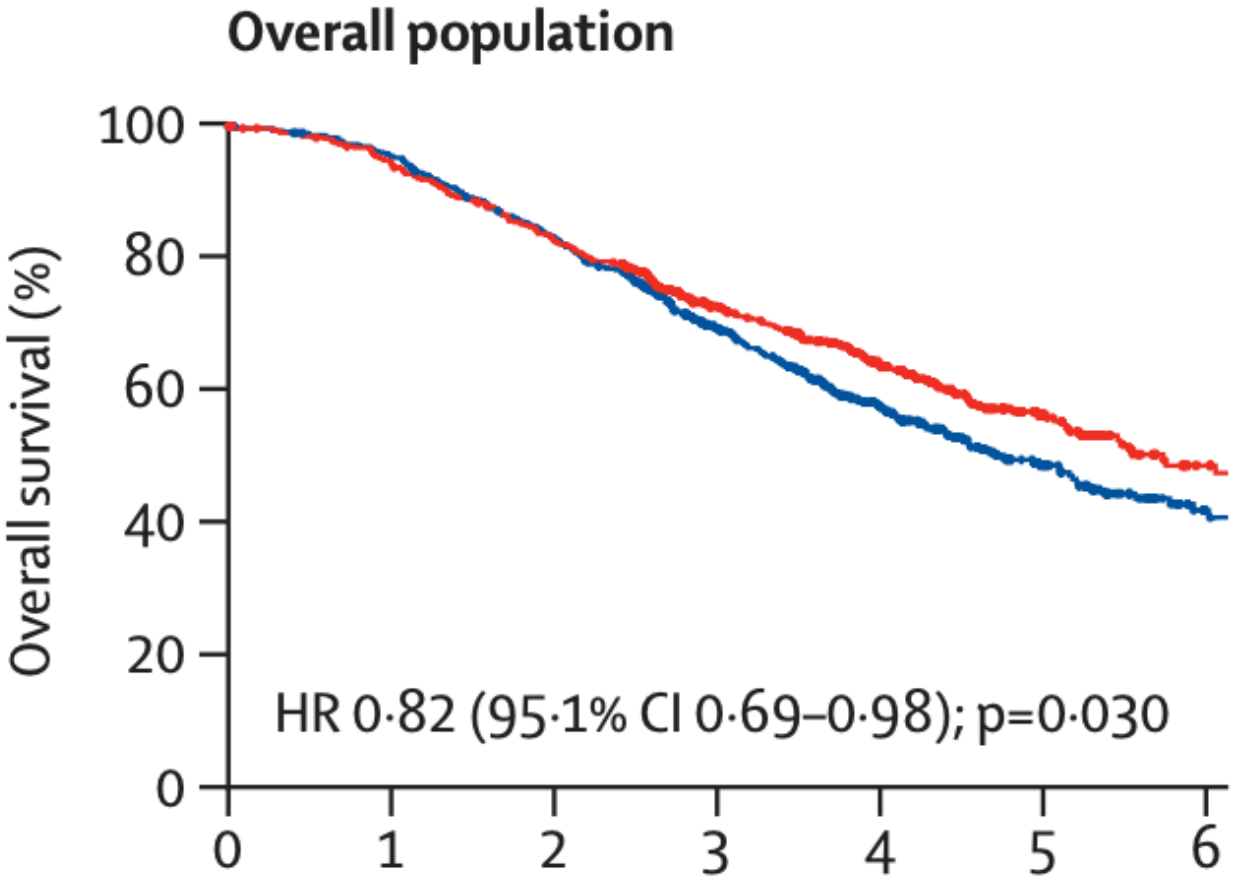
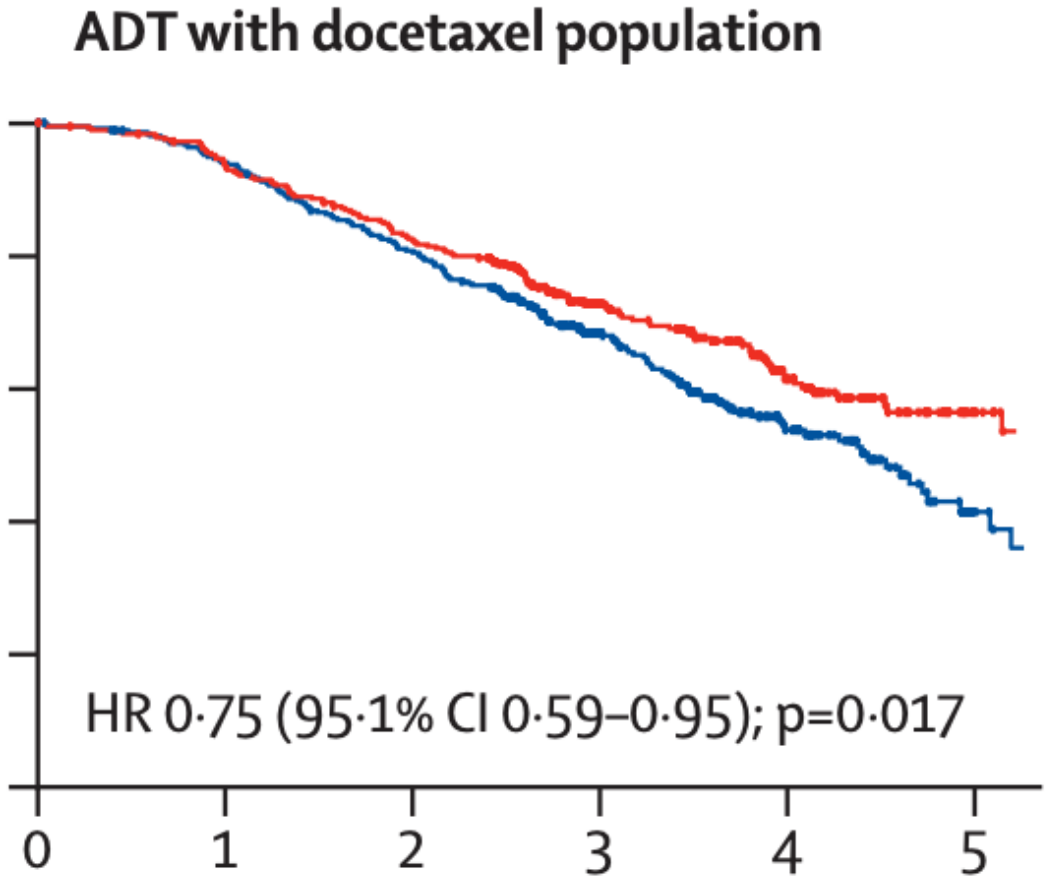
PEACE-1: Overall Survival





Fizazi et al (2022) *Lancet* https://doi.org/10.1016/ S0140-6736(22)00367-1

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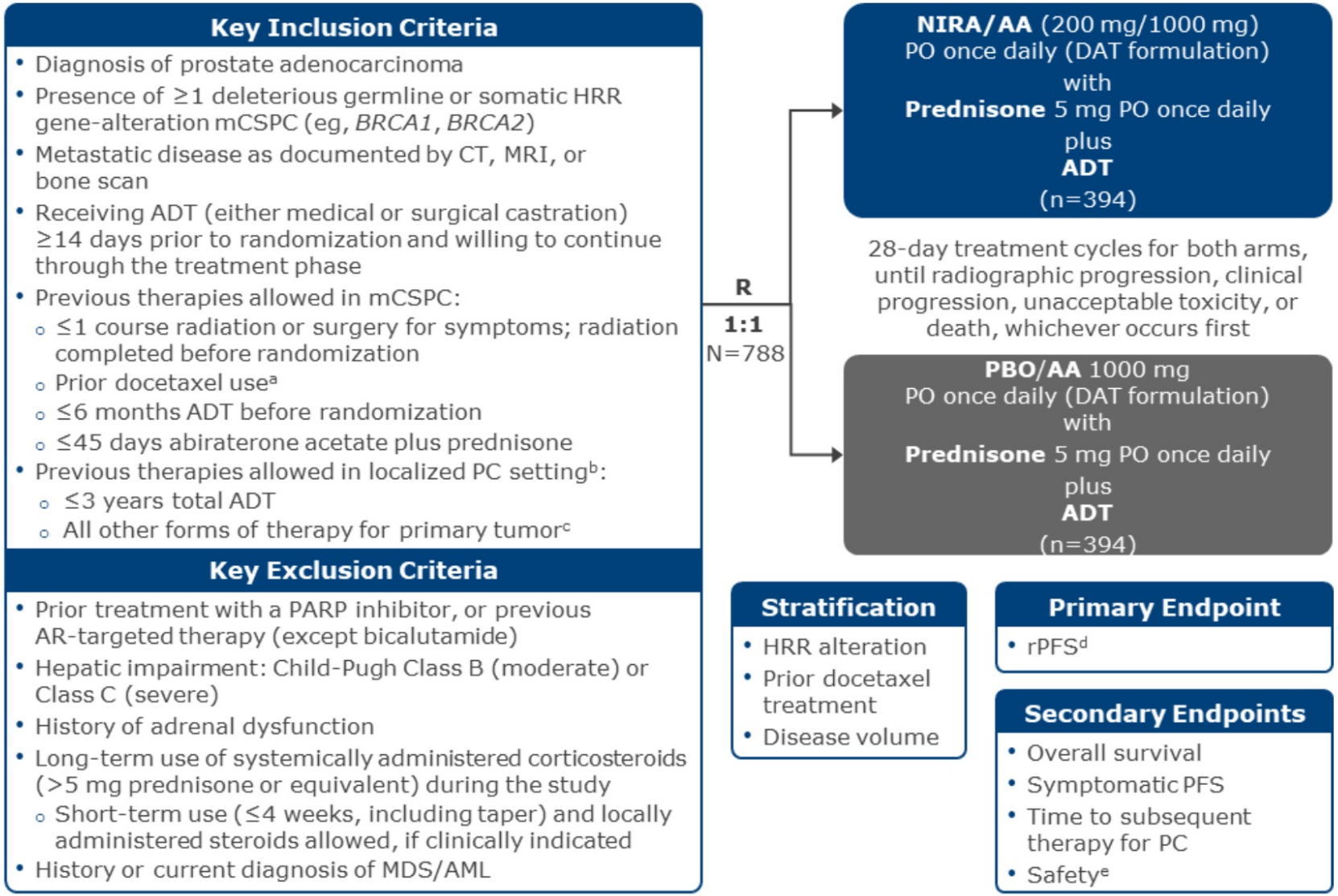
AMPLITUDE Study Design



ClinicalTrials.gov NCT04497844

MASSACHUSETTS GENERAL HOSPITAL
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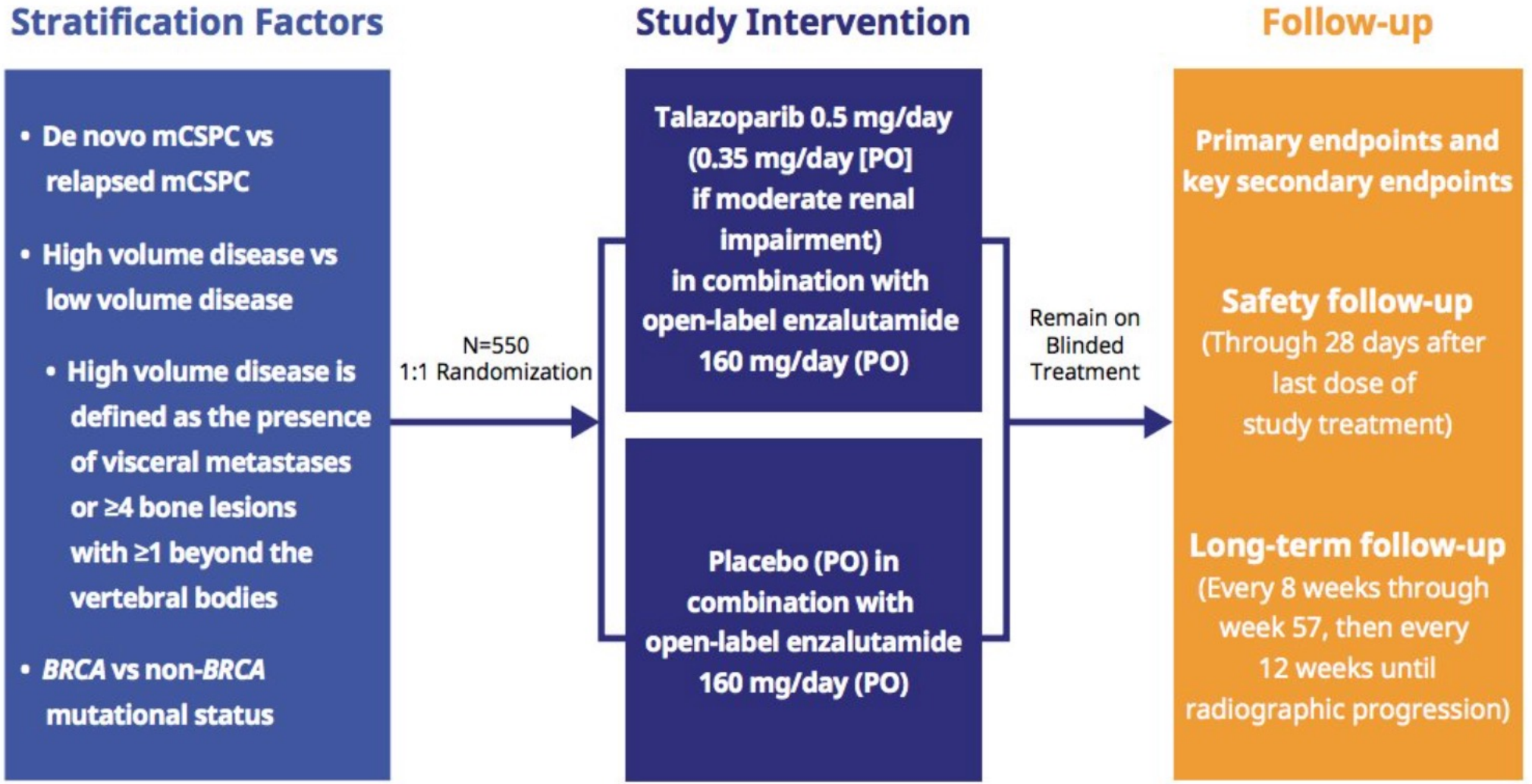
TALAPRO-3 Study Design



ClinicalTrials.gov NCT04821622

MASSACHUSETTS GENERAL HOSPITAL
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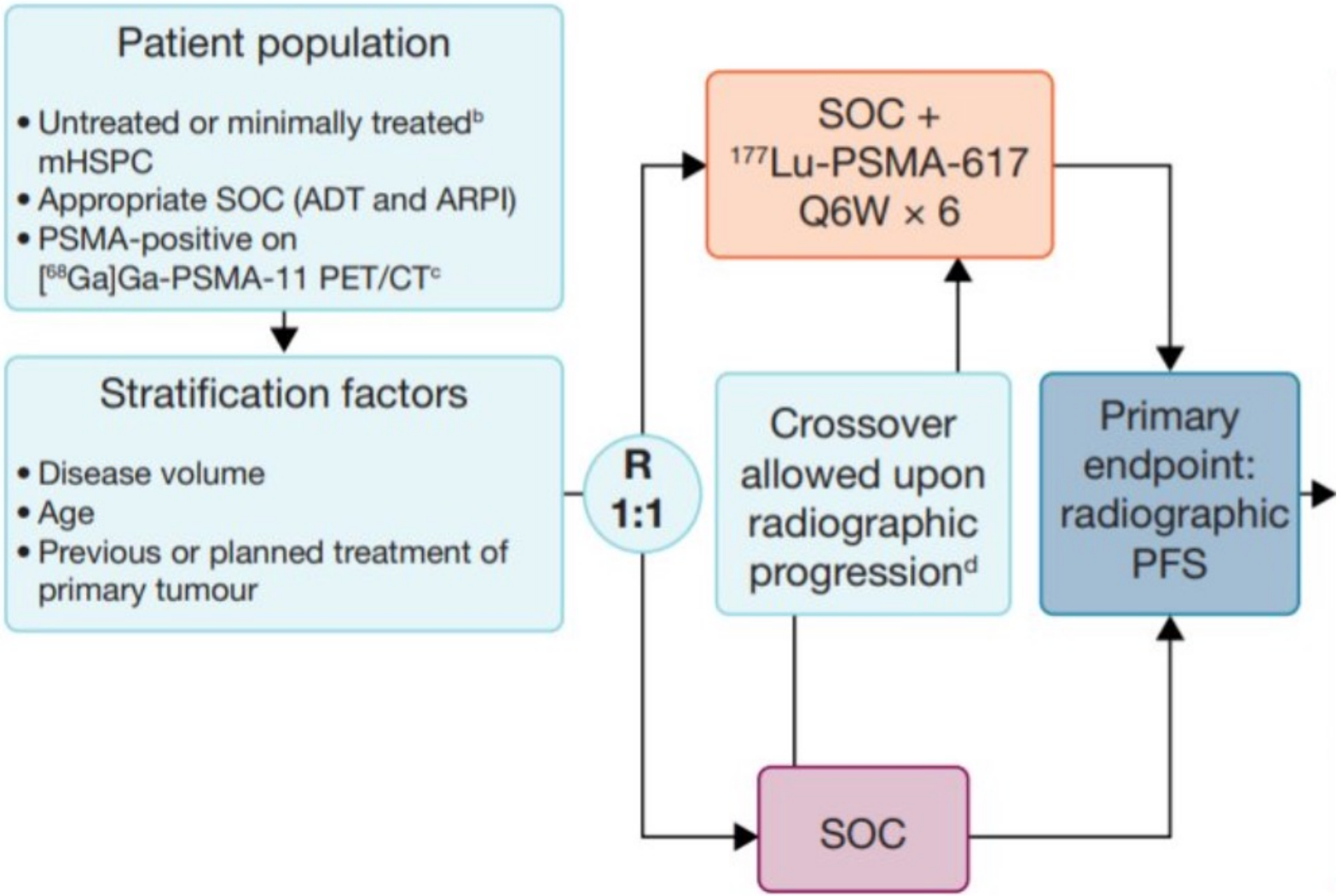
PSMAddition: Phase 3 Trial of ^{177}Lu-PSMA-617 in mCSPC



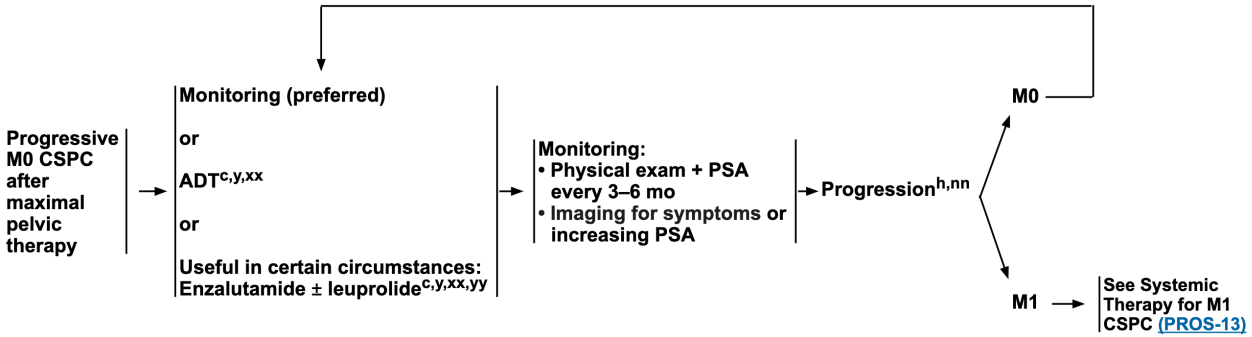
ClinicalTrials.gov NCT04720157

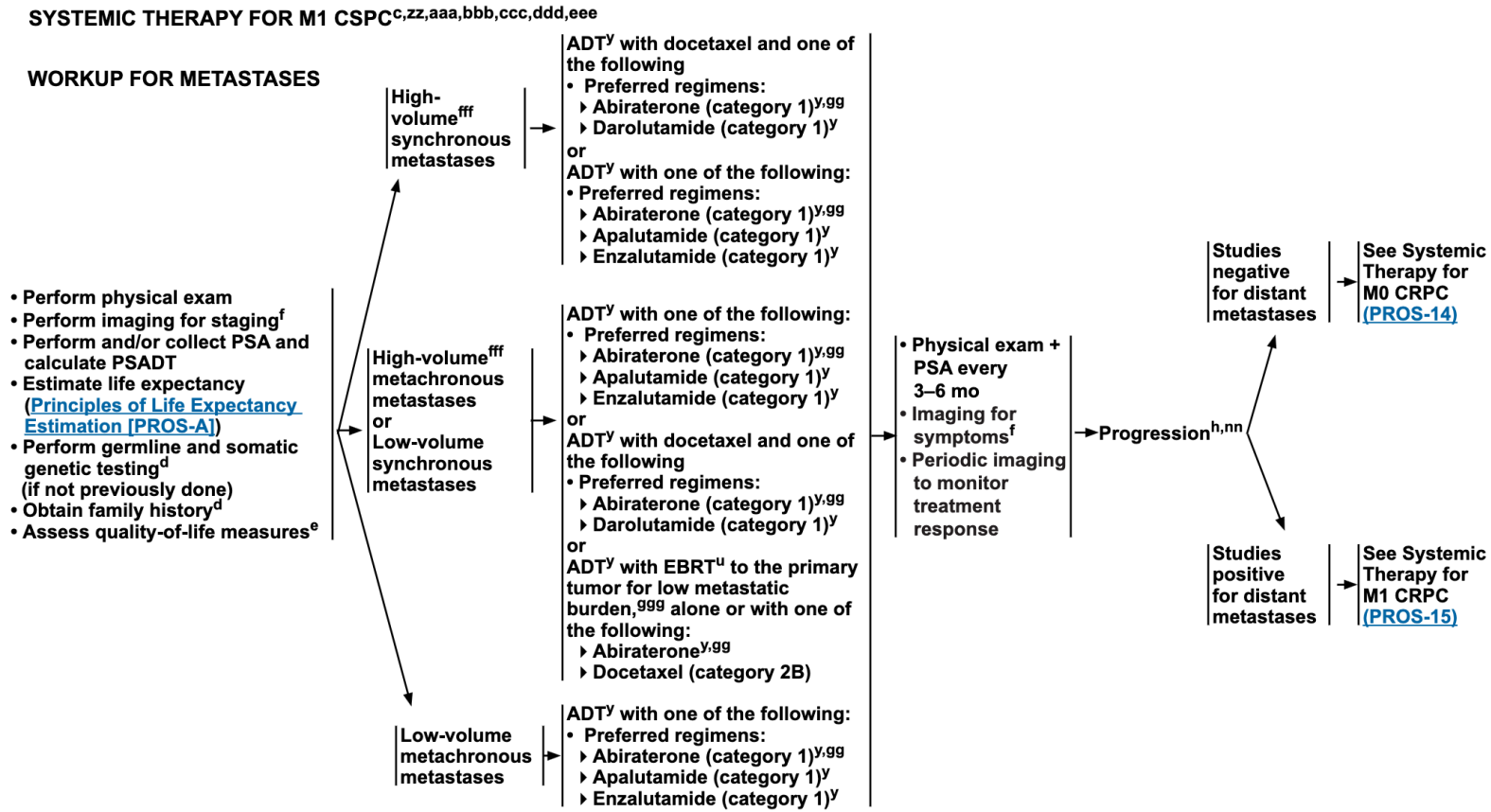
Conclusions

- ADT alone is *not* a standard of care for most patients with mCSPC
- Treatment intensification improves overall survival in mCSPC
  - ADT + docetaxel > ADT alone
  - ADT + ARPI >ADT alone
  - ADT + docetaxel + darolutamide > ADT + docetaxel
  - ADT + docetaxel + abiraterone > ADT + docetaxel
- Most/all patients with mCSPC should receive an ARPI:
  - ADT +ARPI
  - ADT + docetaxel + ARPI (darolutamide or abiraterone)
- Ongoing phase 3 clinical trials will evaluate the role of PARPi and PSMA RLT in mCSPC

NCCN Guidelines Version 4.2024
Prostate Cancer

NCCN Guidelines Index
Table of Contents
Discussion





Agenda

Module 1: Optimizing the Management of Nonmetastatic Prostate Cancer — Dr Dorff

Module 2: Evidence-Based Selection of Treatment for Metastatic Hormone-Sensitive Prostate Cancer — Dr Smith

Module 3: New Considerations with the Use of PARP Inhibitors for Metastatic Castration-Resistant Prostate Cancer (mCRPC) — Dr Agarwal

Module 4: Role of Novel Radiopharmaceuticals for mCRPC — Dr Armstrong

Module 5: Promising Investigational Approaches for Patients with Prostate Cancer — Dr Antonarakis

Consulting Faculty Comments

Role of liquid biopsies; selection of PARP inhibitor for patients with mCRPC and risk of myelodysplasia with these agents

Dr Neil Morganstein
(Summit, New Jersey)

Dr Kimberly Ku
(Bloomington, Illinois)

Dr Sunil Gandhi
(Lecanto, Florida)

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

Do you believe there is therapeutic synergy between PARP inhibitors and AR pathway inhibitors?

Is combination therapy really better than sequential single agents in this case?

QUESTIONS FOR THE FACULTY

When combining a PARP inhibitor with an AR pathway inhibitor, do you have a preference for abiraterone or enzalutamide, and if so, why?

Consulting Faculty Comments

Use of PARP inhibitors in combination with ADT and AR inhibitors for patients with mCRPC; PARP inhibitor combination therapy for patients without BRCA or HRR gene mutations

Dr Kimberly Ku
(Bloomington, Illinois)

Dr Spencer Bachow
(Boca Raton, Florida)

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

Do you make a clinical distinction among the various HRD pathway abnormalities? Do you view certain alterations as truly sensitive to PARP inhibition and others as only marginal in terms of their relevance?

QUESTIONS FOR THE FACULTY

For a patient who has received an AR pathway inhibitor in an earlier disease setting, do you generally favor PARP-inhibitor monotherapy or will you combine the PARP inhibitor with an alternate AR pathway inhibitor?

New Considerations with the Use of PARP Inhibitors for mCRPC

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)

Learning Objectives

- **Incidence of *BRCA1/2* and other HRR abnormalities in patients with prostate cancer**
- Long-term data with PARPi monotherapy in patients with mCRPC
- Biologic rationale for combining PARP inhibitors with ARPIs in patients with prostate cancer
- Key efficacy and safety results from phase 3 studies combining PARPi with ARPIs

Germline HRR Mutations in Metastatic Prostate Cancer

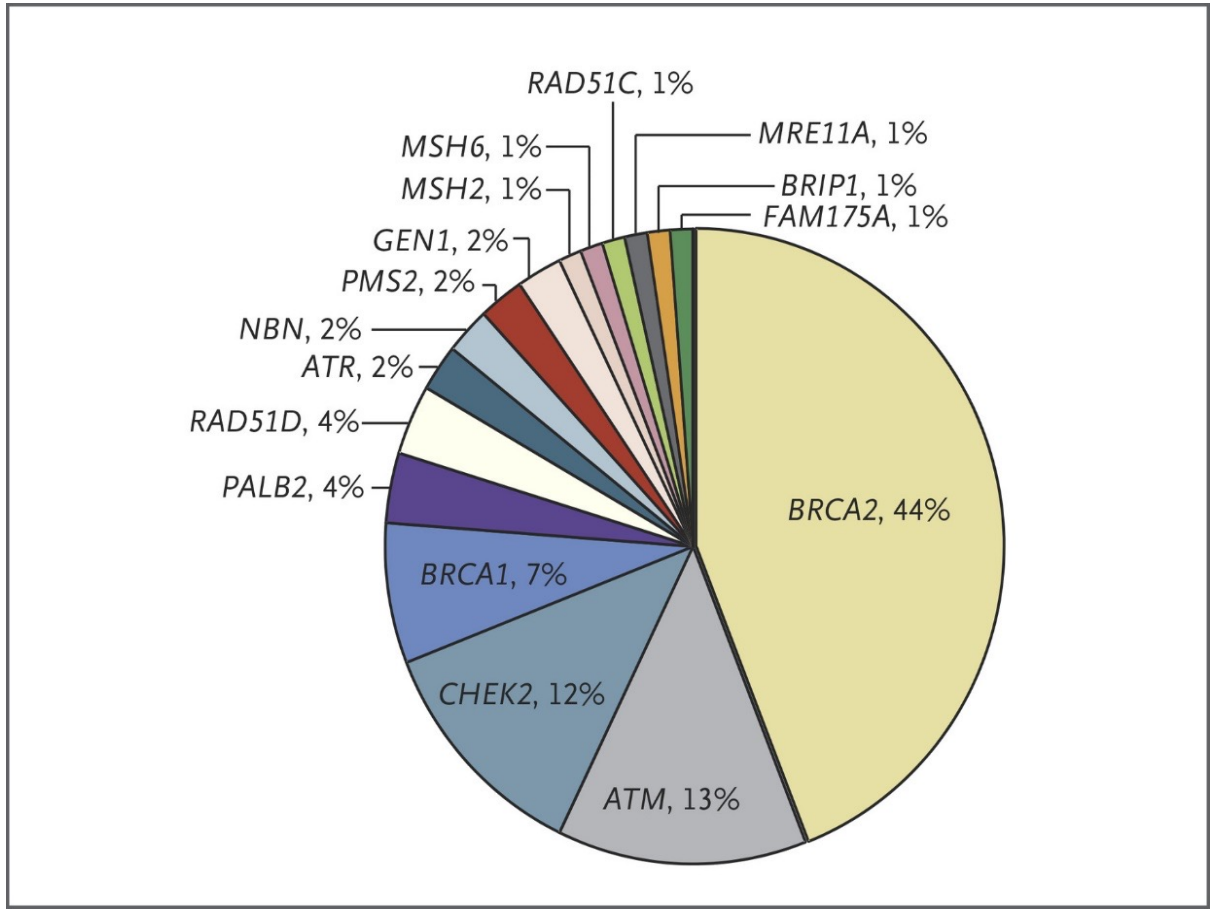
The NEW ENGLAND JOURNAL of MEDICINE

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

Germline mutations in DNA repair genes: 11.8%



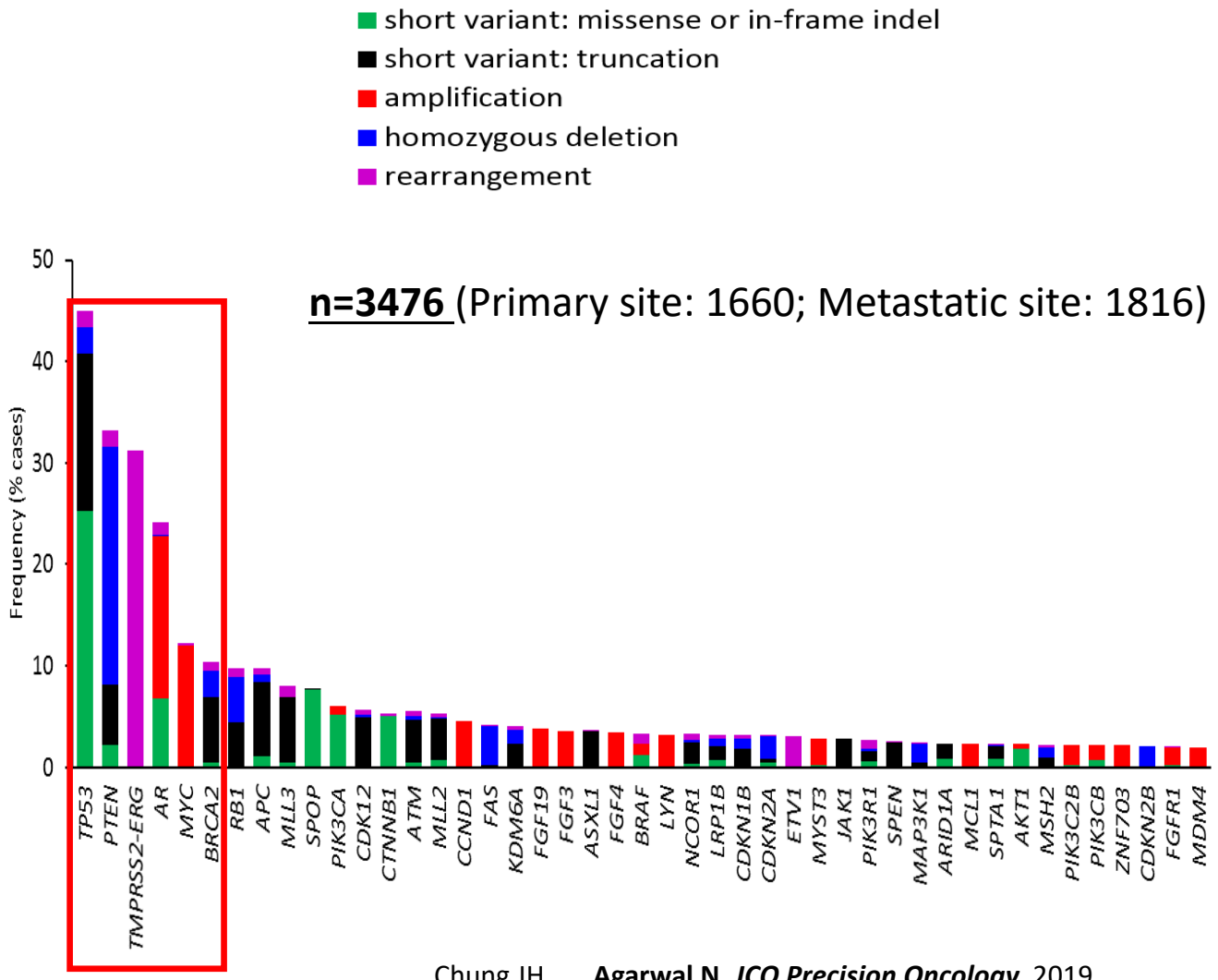
Pritchard et al. NEJM 2016

Genomic Landscape in Advanced Prostate Cancer (Tissue DNA)

JCO® Precision Oncology
An American Society of Clinical Oncology Journal

Prospective Comprehensive Genomic Profiling of Primary and Metastatic Prostate Tumors

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



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

HRR pathway alterations: 23.4%.
Other DNA repair pathway alterations (FA/ICL): 4.8%,
CDK12 **(5.6%),**

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

Learning Objectives

- Incidence of *BRCA1/2* and other HRR abnormalities in patients with prostate cancer
- **Long-term data with PARPi monotherapy in patients with mCRPC**
- Biologic rationale for combining PARP inhibitors with ARPIs in patients with prostate cancer
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Efficacy of PARPi Monotherapy in mCRPC

Table 1
Overview of clinical trials assessing single-agent PARP inhibitors in mCRPC [19–25].

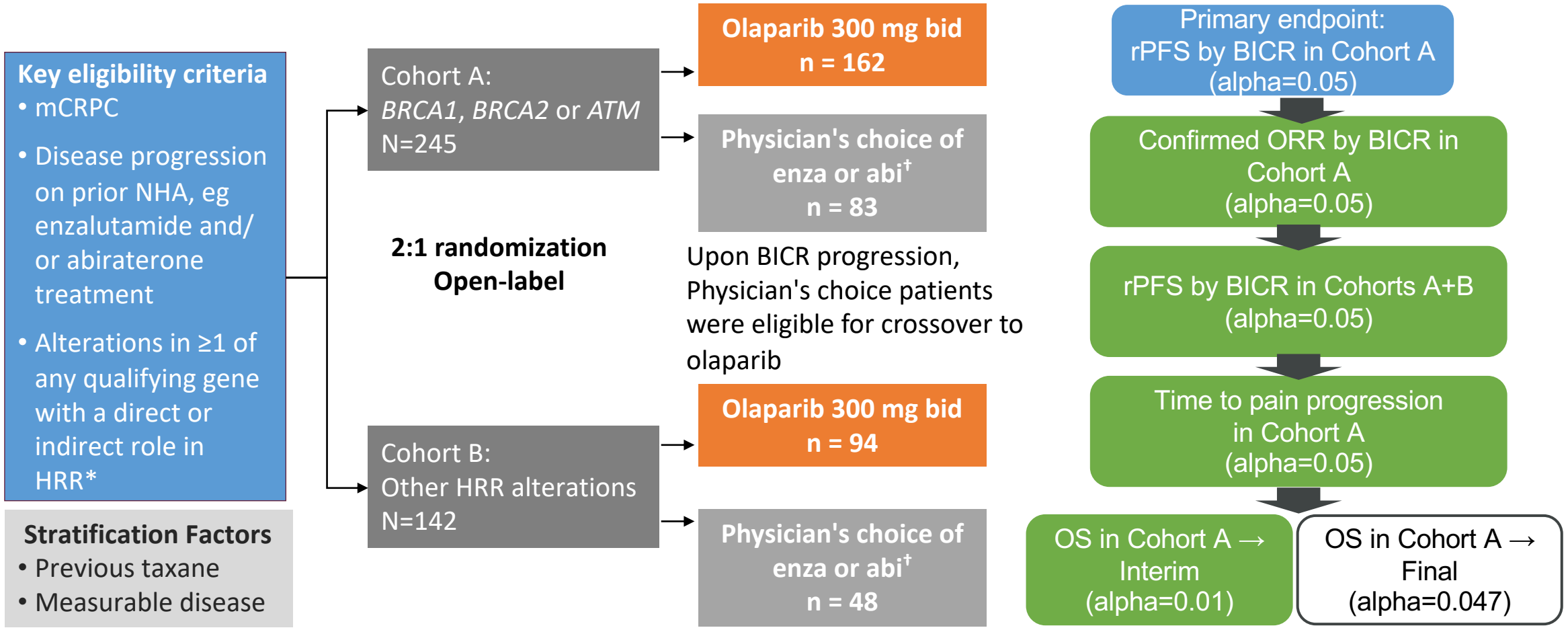
PARP Inhibitor	Clinical Study	Median rPFS	Single-Agent FDA Approval for mCRPC	Single-Agent EMA Approval for mCRPC
Olaparib	TOPARP-A (phase 2)	• 12 HRR gene panel-positive: 9.8 months • 12 HRR gene panel-negative: 2.7 months	Adult patients with deleterious or suspected deleterious germline or HRR gene-mutated mCRPC who have progressed following prior treatment with enzalutamide or abiraterone	Monotherapy for the treatment of adult patients with mCRPC and BRCA1/2 mutations (germline and/or somatic) who have progressed following prior therapy that included a new hormonal agent.
	PROfound (phase 3)	BRCA1/2 or ATM alteration: HR 0.34 – Olaparib 7.4 months – Physician's choice 3.6 months 15 HRR gene panel (including BRCA1/2): HR 0.49 – Olaparib 5.8 months – Physician's choice 3.5 months		
Rucaparib	TRITON2 (phase 2)	BRCA1/2 alteration 9.0 months	Adult patients with a deleterious BRCA mutation (germline and/or somatic)-associated mCRPC who have been treated with androgen receptor–directed therapy and a taxane-based chemotherapy	-
	TRITON3 (phase 3)	BRCA1/2 or ATM alteration: HR 0.61 – Rucaparib 10.2 months – Physician's choice 6.4 months		
Niraparib	GALAHAD (Phase 2)	• BRCA1/2 alteration: 8 months • Non-BRCA 6 HRR gene panel: 3.7 months	-	-
Talazoparib	TALAPRO-1 (phase 2)	• BRCA1/2 alteration: 11.2 months • 11 HRR gene panel (incl.BRCA1/2): 5.6 months	-	-

EMA, European Medicines Agency; FDA, US Food and Drug Administration; HRR, homologous recombination repair; mCRPC, metastatic castration-resistant prostate cancer; rPFS, radiographic progression-free survival; HR, hazard ratio

N. Agarwal et al. / European Journal of Cancer 192 (2023) 113249

Agarwal N. Fizazi K. European Journal of Cancer, 2023.

PROfound Trial: Phase 3 Trial Design



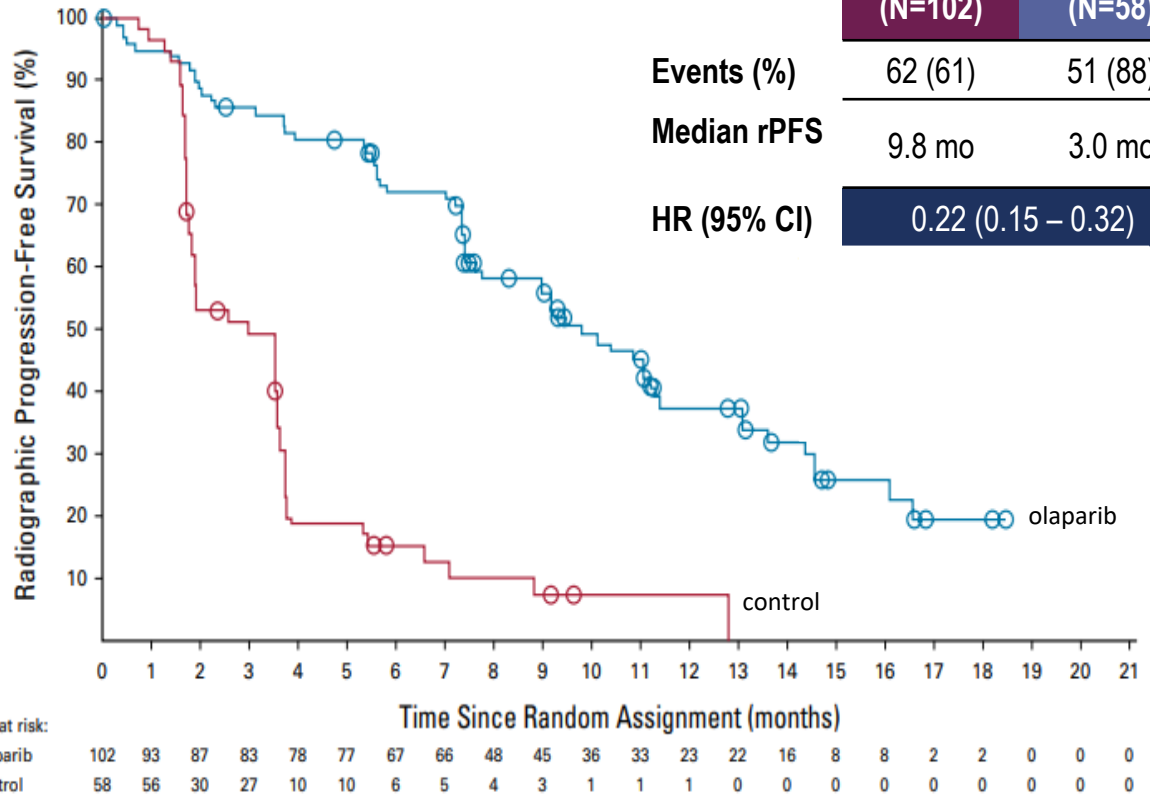
Statistical assumption for primary endpoint: Target hazard ratio = 0.53 (assumed 9.5 vs 5 months), 95% power, 2-sided 5% alpha (60% maturity, 143 events)

*_BRCA1_, _BRCA2_, _ATM_, _BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANC, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D RAD54L;_ †Physician choice of either enzalutamide (160 mg qd) or abiraterone (1000 mg qd plus prednisone [5 mg bid]); BICR, blinded independent central review; bid, twice daily; ORR, objective response rate; OS, overall survival; rPFS, radiographic progression free survival.

1. de Bono J *et al. N Engl J Med* 2020;382:2091–102

Post-hoc Analysis of PROfound Trial: Olaparib Efficacy in Patients with *BRCA* Alterations

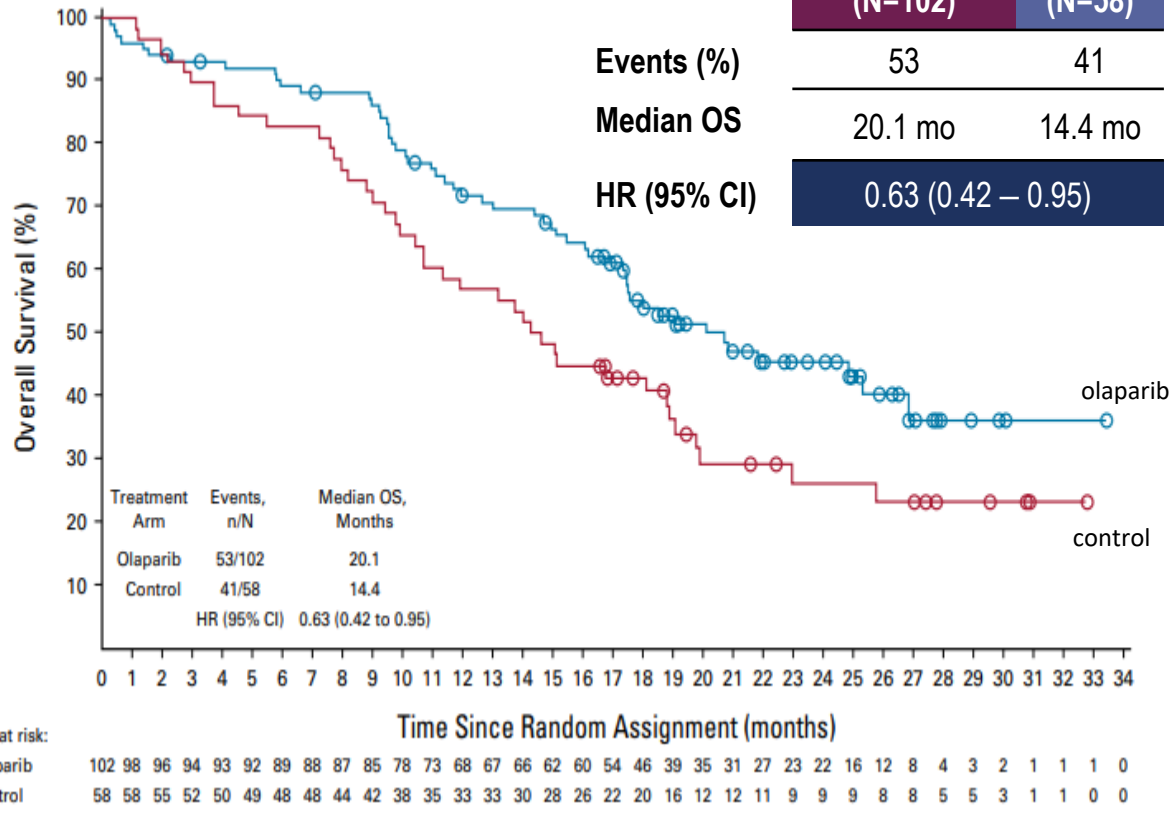
A



	Olaparib (N=102)	Control (N=58)
Events (%)	62 (61)	51 (88)
Median rPFS	9.8 mo	3.0 mo
HR (95% CI)	0.22 (0.15 – 0.32)	

rPFS

B



	Olaparib (N=102)	Control (N=58)
Events (%)	53	41
Median OS	20.1 mo	14.4 mo
HR (95% CI)	0.63 (0.42 – 0.95)	

OS

Data cutoff date: March 2020
Median follow-up 21.9 mo (olaparib group) and 21.0 mo (control group)

Mateo *et al.*, JCO, 2023

Post-hoc Analysis of PROfound Trial: Olaparib Safety in Patients with *BRCA* Alterations

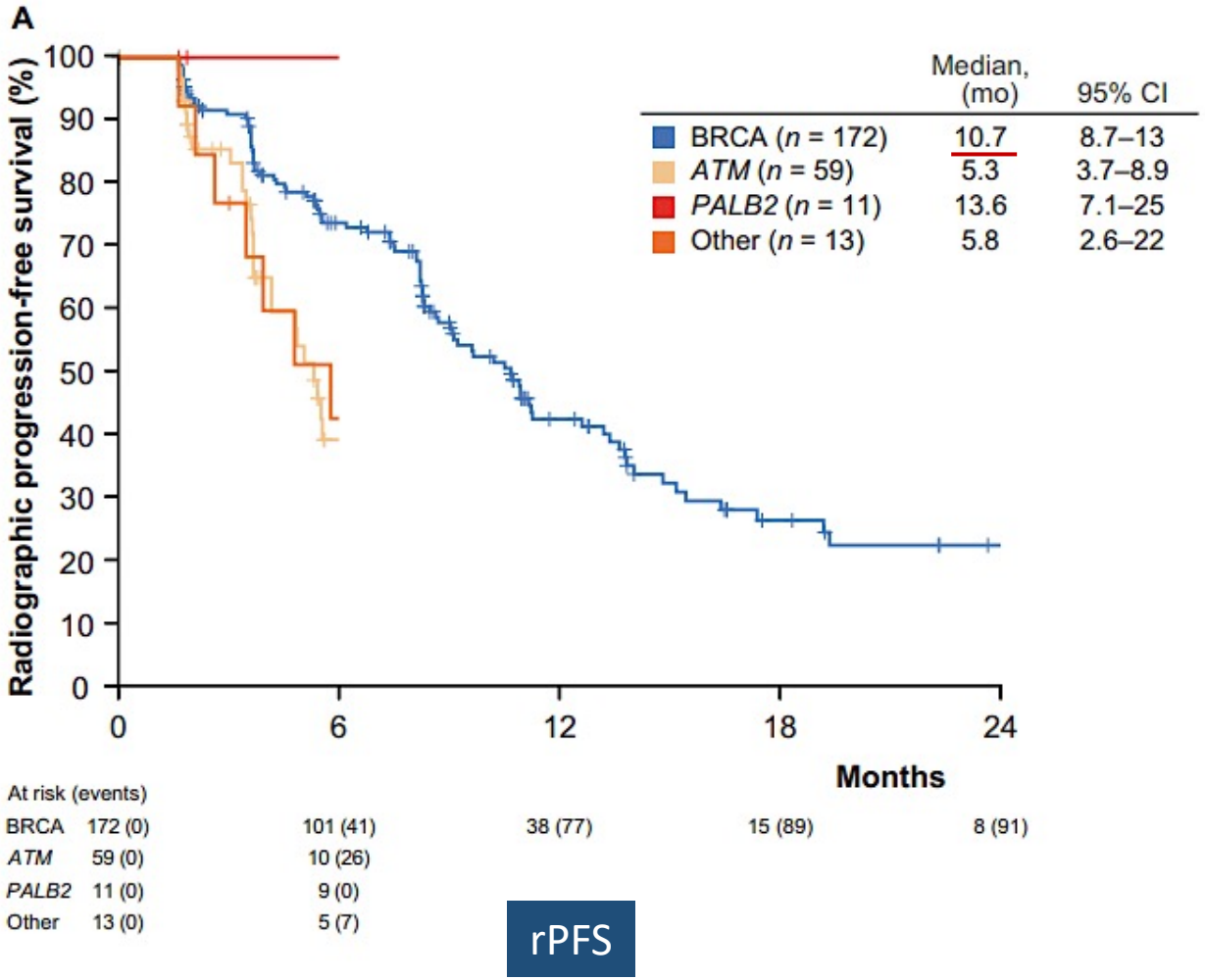
Category	Olaparib (n = 102)	Control (n = 58)
Any AE, No. (%)	99 (97.1)	52 (89.7)
Any AE of CTCAE grade ≥3	56 (54.9)	23 (39.7)
Any AE with outcome of death	6 (5.9)	4 (6.9)
Any serious AE (including with outcome of death)	38 (37.3)	14 (24.1)
Any AE leading to discontinuation of treatment	19 (18.6)	6 (10.3)
AE of anemia	52 (51.0)	8 (13.8)

AEs in patients with *BRCA* alterations

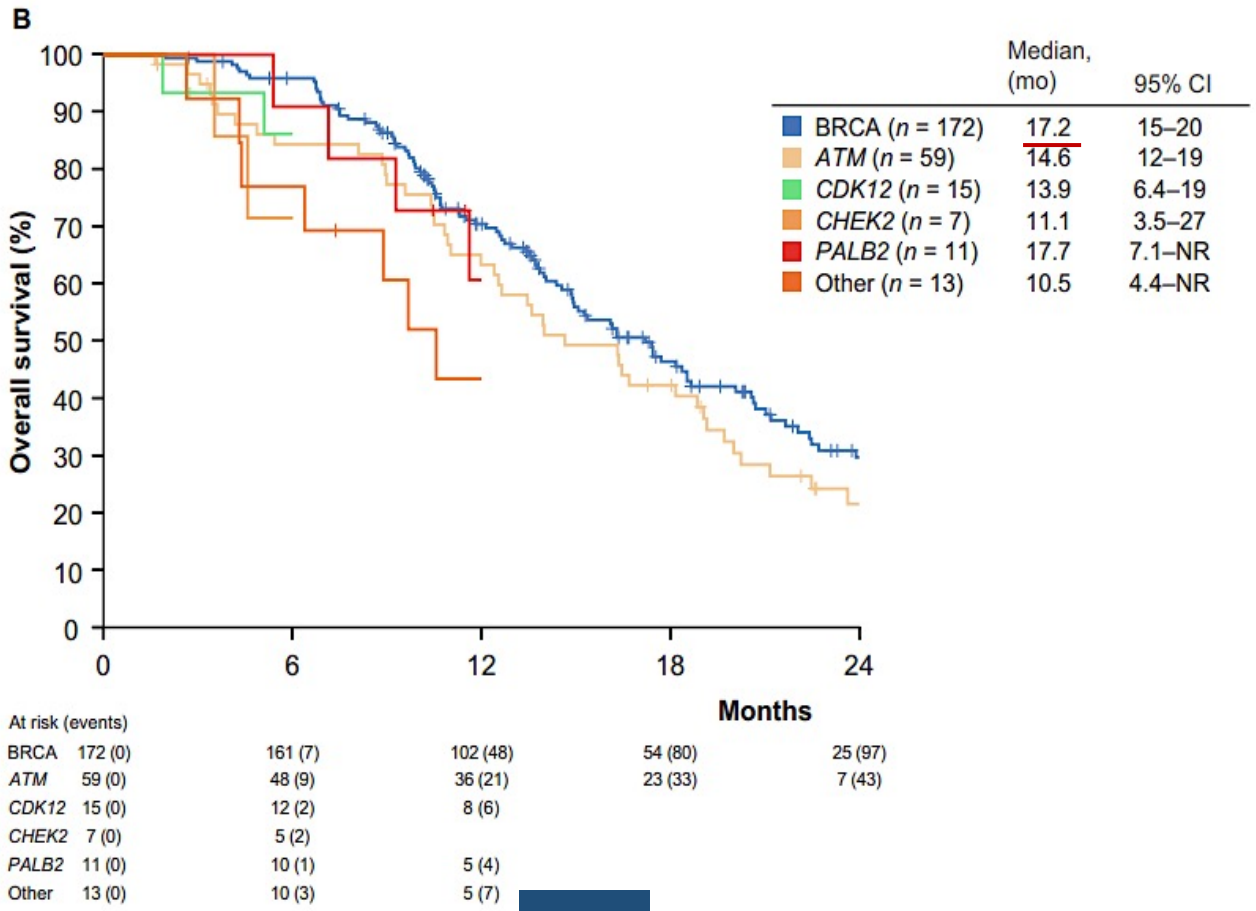
Data cutoff date: March 2020
Median follow-up 21.9 mo (olaparib group) and 21.0 mo (control group)

Mateo *et al*., JCO, 2023

Long-term Data with Rucaparib (TRITON2): Efficacy



rPFS



OS

Median follow-up 23.7 mo (*BRCA* group) and 25.8 mo (non-*BRCA* group)

Abida *et al*, EU, 2023

Long-term Data with Rucaparib (TRITON2): Safety

Table 2 – Most commonly reported TEAEs in the safety population

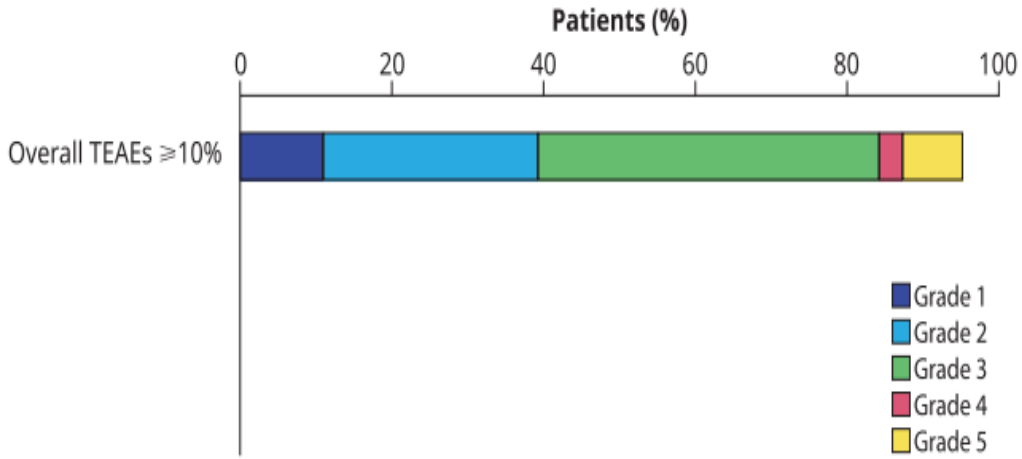
TEAEs, *n* (%)	Overall safety population (*N* = 277)	
	Any grade	Grade ≥3
Number of patients with ≥1 TEAE	274 (99)	178 (64)
Asthenia or fatigue	164 (59)	31 (11)
Nausea	140 (51)	7 (2.5)
Anemia or decreased hemoglobin	133 (48)	80 (29)
Decreased appetite	96 (35)	5 (1.8)
ALT or AST increased	82 (30)	16 (5.8)
Constipation	76 (27)	2 (0.72)
Vomiting	70 (25)	5 (1.8)
Diarrhea	66 (24)	3 (1.1)
Rash	64 (23)	4 (1.4)
Thrombocytopenia or decreased platelet count	61 (22)	22 (7.9)

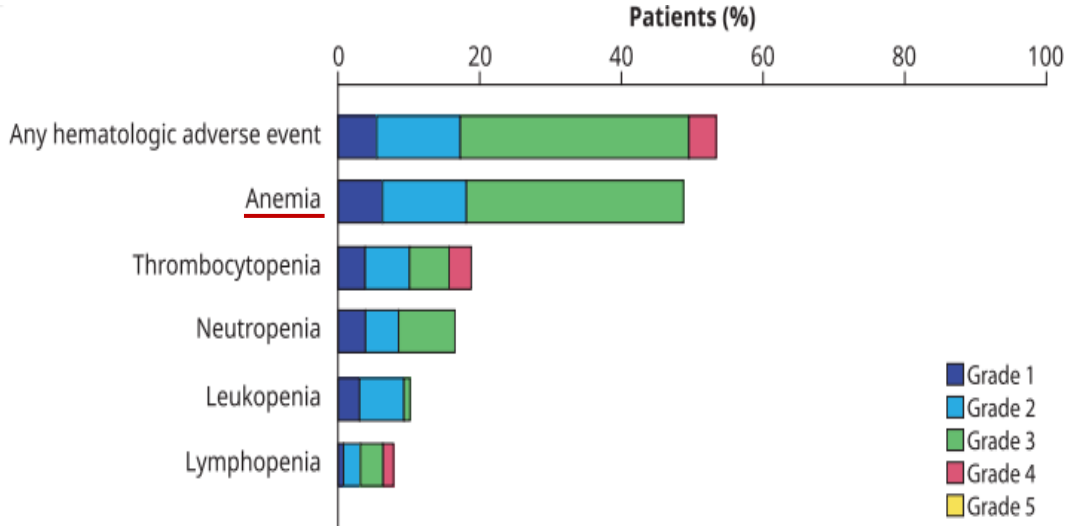
ALT = alanine aminotransferase; AST = aspartate aminotransferase; TEAE = treatment-emergent adverse event.
MedDRA preferred terms are combined for the following adverse events: asthenia or fatigue, anemia or decreased hemoglobin, ALT or AST increased, rash, and thrombocytopenia or decreased platelet count.
Any-grade TEAEs were reported in ≥20% of patients, as well as corresponding grade ≥≥3 TEAEs.

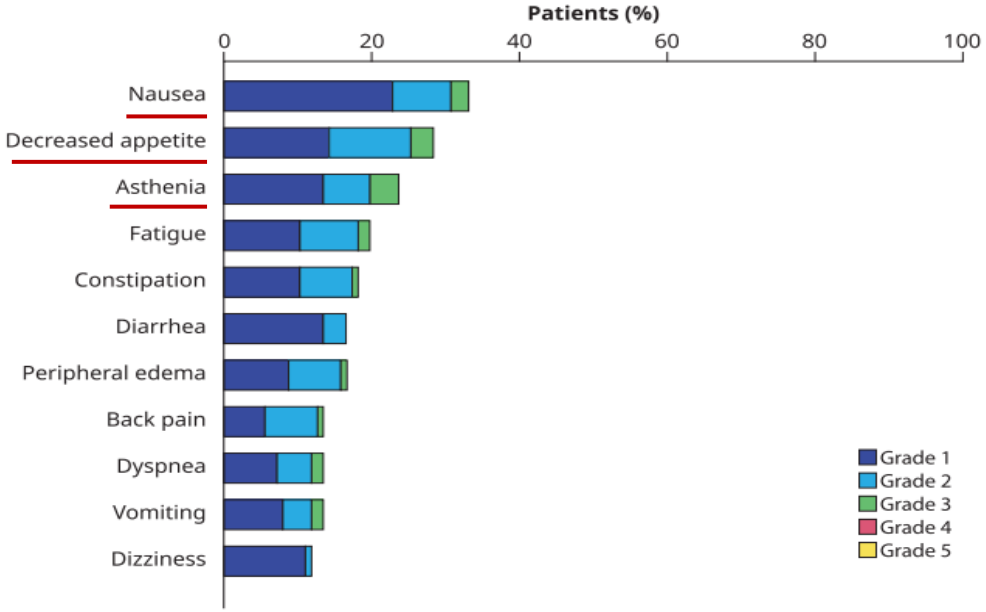
Median follow-up 23.7 mo (*BRCA* group) and 25.8 mo (non-*BRCA* group)

Abida *et al.*, EU, 2023

Long-term Data with Talazoparib (TALAPRO-1): Safety







Data cutoff date: September 2020
Median follow-up: 16.1 mo

Mehra *et al,* The Oncologist, 2022

Learning Objectives

- Incidence of *BRCA1/2* and other HRR abnormalities in patients with prostate cancer
- Long-term data with PARPi monotherapy in patients with mCRPC
- **Biologic rationale for combining PARP inhibitors with ARPIs in patients with prostate cancer**
- Key efficacy and safety results from phase 3 studies combining PARPi with ARPIs

The rationale for combining PARPi with ARPI

ARPIs induce a phenotype resembling HRR deficiency

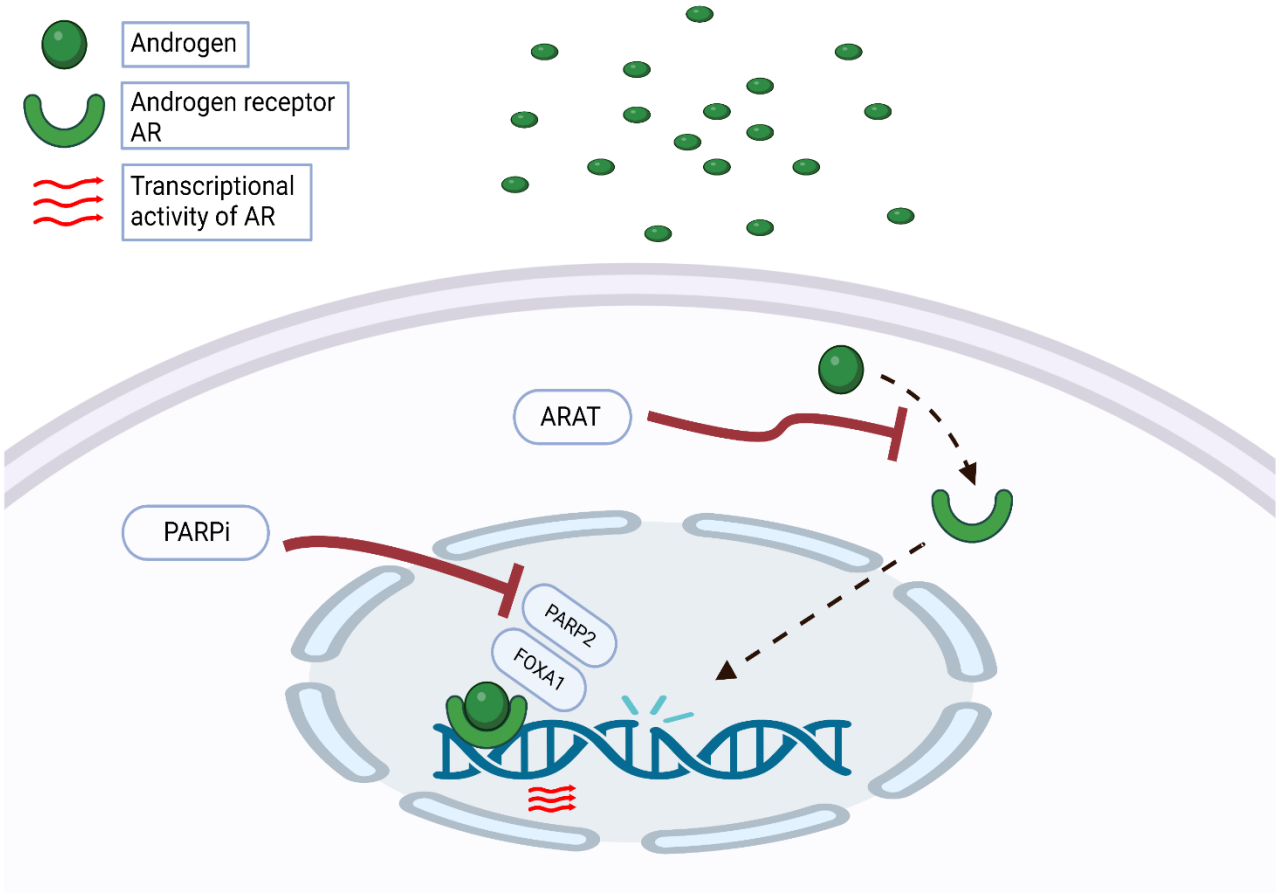
Suppressed AR function causes an upregulation of PARP

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.

Learning Objectives

- Incidence of *BRCA1/2* and other HRR abnormalities in patients with prostate cancer
- Long-term data with PARPi monotherapy in patients with mCRPC
- Biologic rationale for combining PARP inhibitors with ARPIs in patients with prostate cancer
- **Key efficacy and safety results from phase 3 studies combining PARPi with ARPIs**

Phase 3 trials of PARPi + AR pathway inhibitor in 1st line mCRPC setting

PROpel: Abiraterone + Olaparib [1]	Published
MAGNITUDE: Abiraterone + Niraparib [2]	Published
TALAPRO-2: Enzalutamide + Talazoparib[3]	Published
CASPAR: Enzalutamide + Rucaparib	Terminated

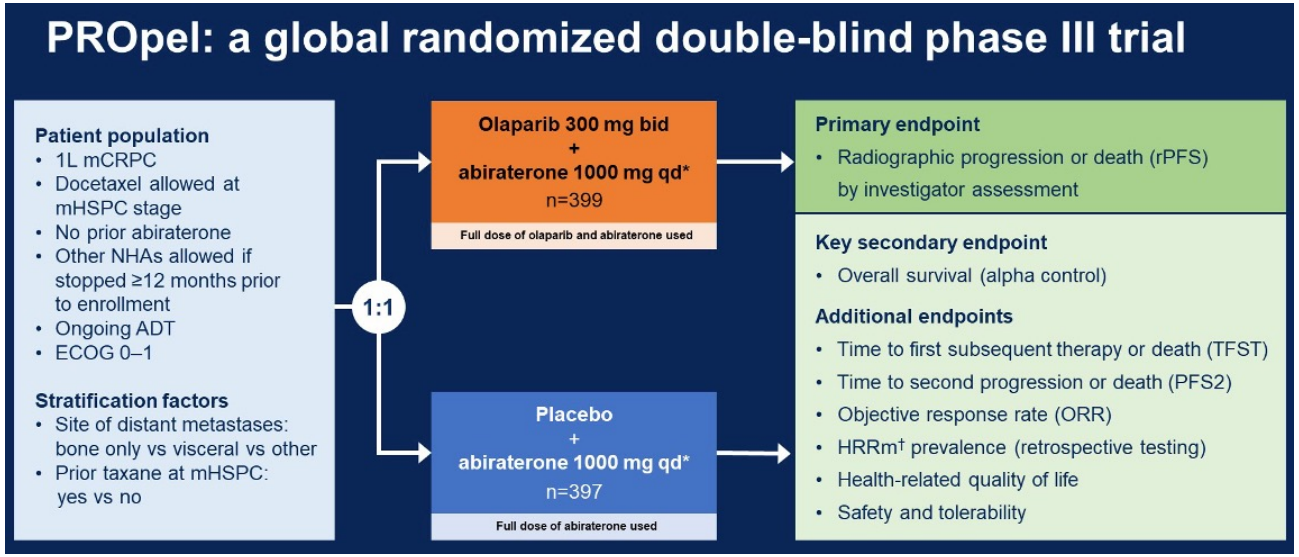
1- Clarke NW et al., NEJM Evidence. 2022 Aug 23

2- Chi KN et al., JCO. 2022 Feb 20;40(6_suppl):12–12. Kim Chi, (2022 Genitourinary Cancers Symposium (ASCO GU). Abstract #12)

3- Agarwal N et al., The Lancet. 2023 June 4

Phase 3 PARPi + ARPI Trials Design

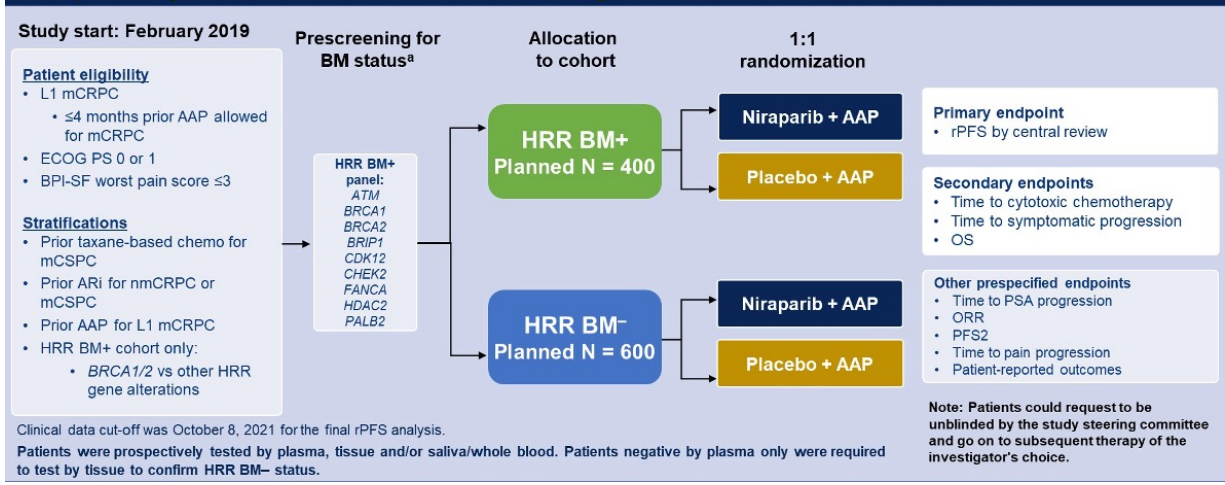
PROpel: a global randomized double-blind phase III trial



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

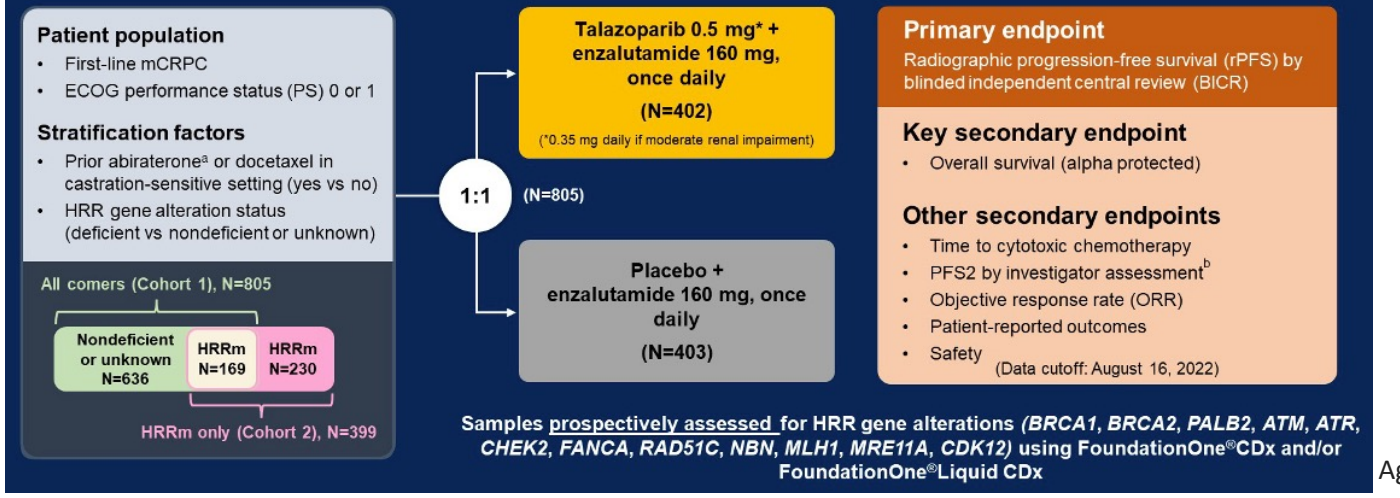
MAGNITUDE: Randomized, Double-Blind, Placebo-Controlled Study

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

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 randomization Abiraterone + olaparib (n = 399) vs abiraterone + placebo (n = 397)	Cohort 1: HRR cohort 1 : 1 randomization abiraterone + niraparib (n = 212) vs abiraterone + placebo (n = 211) Cohort 2: non-HRR cohort (closed prematurely because of futility)	All-comer population 1 : 1 randomization Enzalutamide + talazoparib (n = 402) vs enzalutamide + placebo (n = 403)	HRR cohort 1 : 1 randomization 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 0.76 (0.60-0.97)**	**HR 0.46 (0.30-0.70)**	**HR 0.45 (0.33-0.61)**
BRCA+	**HR 0.23 (0.12-0.43)**	**HR 0.55 (0.39-0.78)**	**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 0.82 (0.60-1.10) (only for HRR+ pts)	Immature HR 0.89 (0.69-1.14)	Immature HR 0.69 (0.46-1.03)
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.…Chi K Annals Oncol, 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

Baseline Characteristics

- 165 eligible pts were registered & underwent somatic & germline testing.
- 61 pts with qualifying alteration(s) were randomized to Arms I-III.

	Arm I (n = 19)	Arm II (n = 21)	Arm III (n = 21)
Age (Years), Median (IQR)	**63** (60-69)	**68** (66-72)	**69** (62-74)
Race, N (%)			
Black / African American	2 (11%)	2 (9.5%)	2 (9.5%)
Hispanic or Latino	0 (0%)	0 (0%)	1 (4.8%)
Non-Hispanic White	17 (89%)	19 (90%)	18 (86%)
ECOG Performance Status, N (%)			
0	10 (53%)	15 (71%)	16 (76%)
1	9 (47%)	6 (29%)	5 (24%)
Baseline PSA (ng/mL), Median (IQR)	**14** (3.7-133)	**14** (7.7-33)	**15** (6.3-39)
Sites of Metastatic Disease, N (%)[1]			
Bone	**16 (84%)**	**12 (57%)**	**16 (76%)**
Lymph node	9 (47%)	12 (57%)	10 (48%)
Visceral[2]	**2 (11%)**	**3 (14%)**	**7 (33%)**
Other[3]	1 (5.3%)	2 (9.5%)	0 (0%)
Measurable Disease, N (%)	8 (42%)	11 (52%)	9 (43%)
Genetic Alteration, N (%)			
Germline	**9 (47%)**	**13 (62%)**	**11 (52%)**
Somatic	10 (53%)	8 (38%)	10 (48%)
Genetic Mutation Type, N (%)[1]			
ATM	4 (21%)	3 (14%)	5 (24%)
BRCA1	2 (11%)	0 (0%)	1 (4.8%)
BRCA2	**13 (68%)**	**19 (90%)**	**15 (71%)**
Previous Treatments, N (%)[1,4]			
Docetaxel	8 (42%)	4 (19%)	4 (19%)
Darolutamide/Enzalutamide	1 (5.3%)	0 (0%)	1 (4.8%)
Sipuleucel-T	3 (16%)	4 (19%)	2 (9.5%)
Other Agent(s)[5]	2 (11%)	2 (9.5%)	0 (0%)

[1] Sites of metastatic disease, genetic mutation type, and previous treatment frequencies may not add up to the total number of patients because some patients had multiple disease sites, co-mutations, or multiple prior treatments.

[2] Visceral disease includes lung (n = 7), liver (n = 2), lung and liver (n = 2), and adrenal gland (n = 1).

[3] Other disease includes prostate gland (n = 2) and right pelvic sidewall mass (n = 1).

[4] Given in the mHSPC or m0CRPC setting.

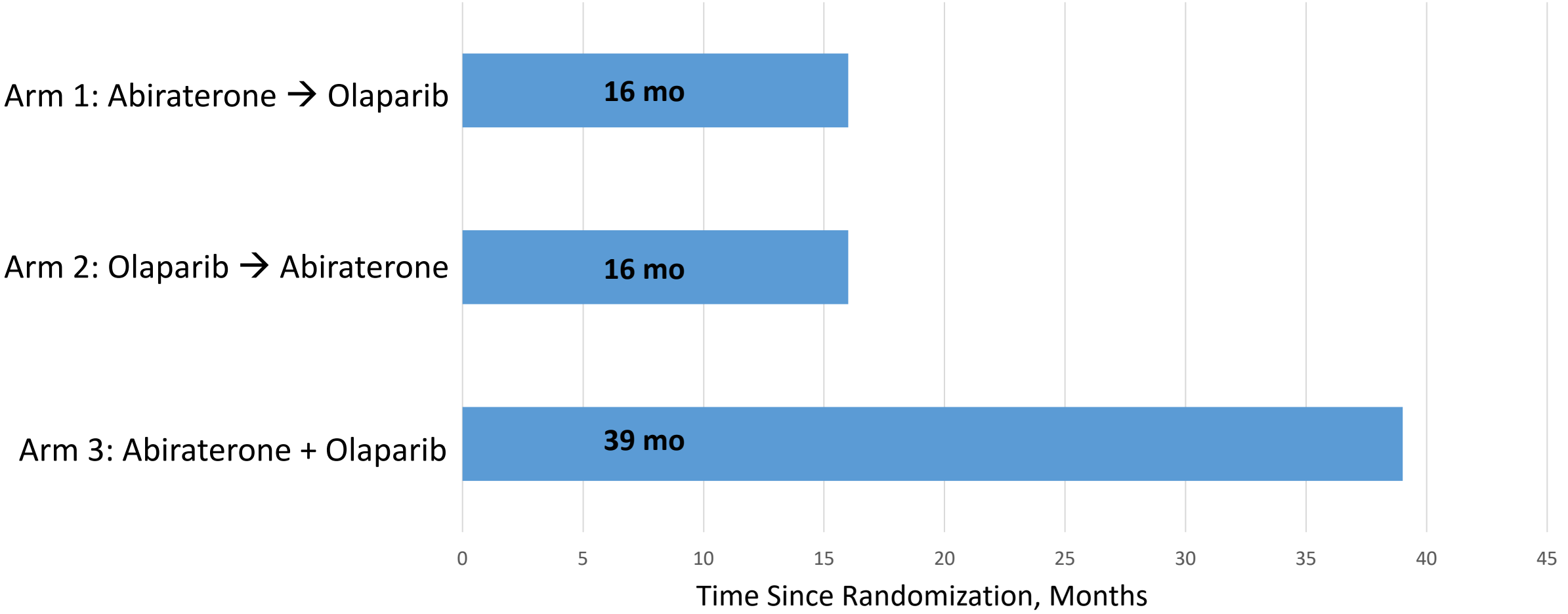
[5] Other agent(s) include Pembrolizumab, pTVG-HP/rhGM-CSF, Radium-223, Testosterone, or Nivolumab.

Efficacy Summary

	Arm I (n = 19)	Arm II (n = 21)	Arm III (n = 21)
Median PFS, months (95% CI)	**8.4 (2.9, 17)**	**14 (8.4, 20)**	**39 (22, NR)**
Objective RR, % (95% CI)	**22** (6.4, 48)	**14** (3, 36)	**33** (15, 57)
PSA RR, % (95% CI)	**61** (36, 83)	**67** (43, 85)	**95** (76, 100)
Undetectable PSA RR, % (95% CI)	**17** (3.6, 41)	**14** (3, 36)	**33** (15, 57)

NR, Not Reached

Median PFS from Randomization to End of Crossover Treatment



Hussain M., ASCO GU 2024

My take on PARPi plus ARPI in mCRPC

- In 2023, only ~34% of patients with new mCRPC had prior exposure to ARPI (Swami, 2024 AUA, Abs:24-7158)

- How I select a given combination:
  - For new mCRPC with BRCA1/2 mutations, I use the PARPi combinations based on my selection of the partner ARPI;
  - 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, and
  - Mechanism of resistance to PARPi

Agenda

Module 1: Optimizing the Management of Nonmetastatic Prostate Cancer — Dr Dorff

Module 2: Evidence-Based Selection of Treatment for Metastatic Hormone-Sensitive Prostate Cancer — Dr Smith

Module 3: New Considerations with the Use of PARP Inhibitors for Metastatic Castration-Resistant Prostate Cancer (mCRPC) — Dr Agarwal

Module 4: Role of Novel Radiopharmaceuticals for mCRPC — Dr Armstrong

Module 5: Promising Investigational Approaches for Patients with Prostate Cancer — Dr Antonarakis

RTP RESEARCH TO PRACTICE

Consulting Faculty Comments

Integrating radiopharmaceutical agents alone or in combination with other treatment modalities

Dr Gigi Chen
(Pleasant Hill, California)

Dr Kimberly Ku
(Bloomington, Illinois)

Dr Spencer Bachow
(Boca Raton, Florida)

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

When might we see some new data with Radium 223, and why haven't we seen more?

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

Where in your therapeutic algorithm have you typically been employing lutetium Lu 177 vipivotide tetraxetan, and do you generally recommend this approach first before docetaxel-based chemotherapy?

QUESTIONS FOR THE FACULTY

For patients eligible for both lutetium Lu 177 vipivotide tetraxetan and radium-223, do you have a preference for one over the other?

Do any available data suggest that the sequence of these agents matters?

QUESTIONS FOR THE FACULTY

Do you find any of the emerging radiopharmaceuticals to be particularly exciting in that they might replace or unseat lutetium Lu 177 vipivotide tetraxetan in your therapeutic algorithm?

Radiopharmaceuticals in Men with mCRPC

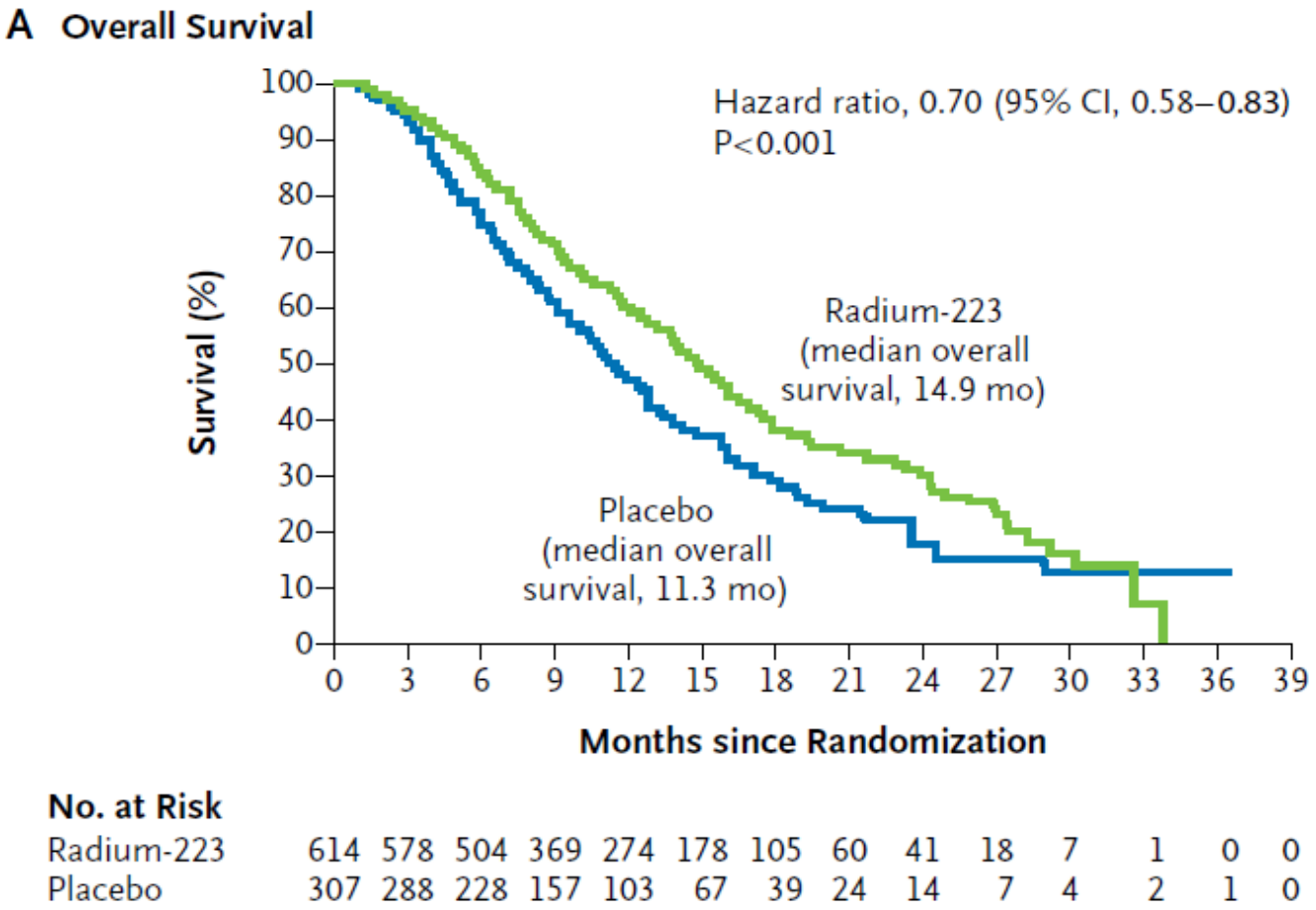
ASCO 2024 Updates

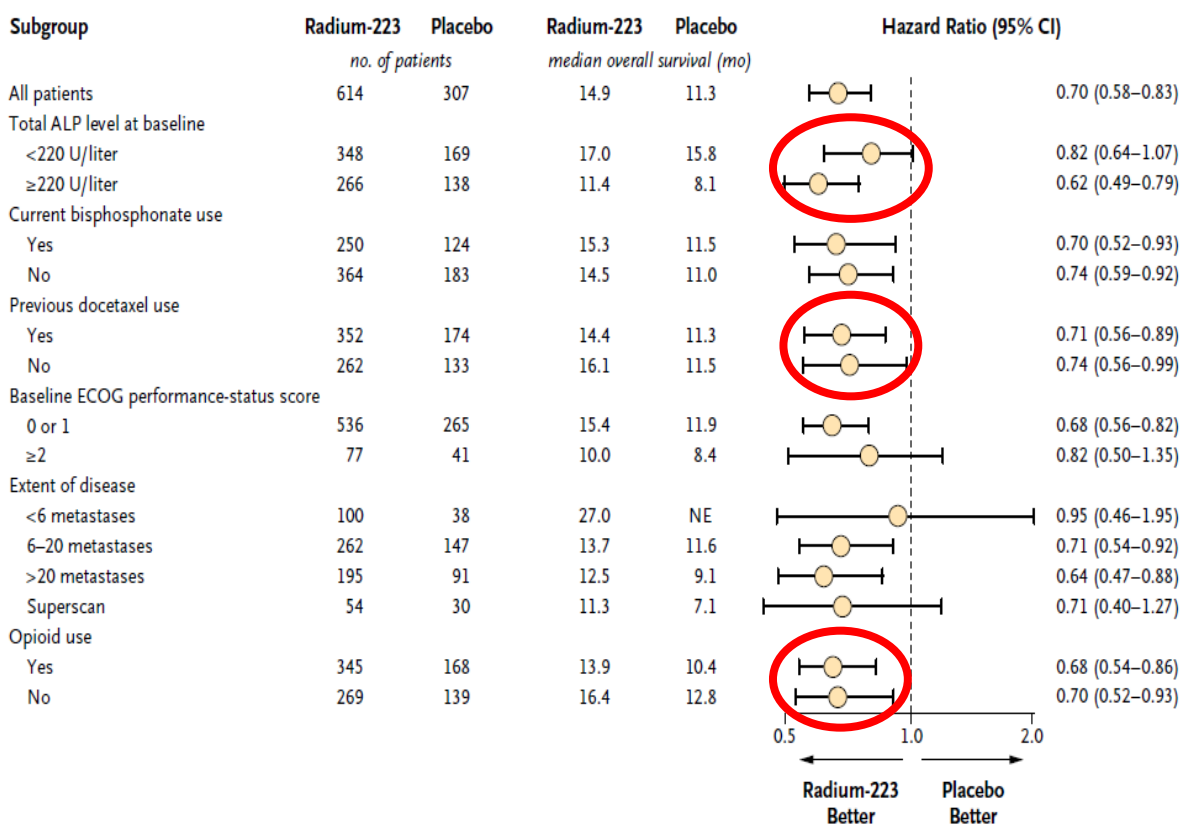
Andrew J Armstrong MD ScM FACP

Professor of Medicine, Surgery, Pharmacology and Cancer Biology

Duke Cancer Institute Center for Prostate and Urologic Cancers

ALSYMPCA: α-Emitter Radium 223 and Survival in mCRPC





- Parker C, et al. N Engl J Med. 2013;369:213-223.

ALSYMPCA: Safety

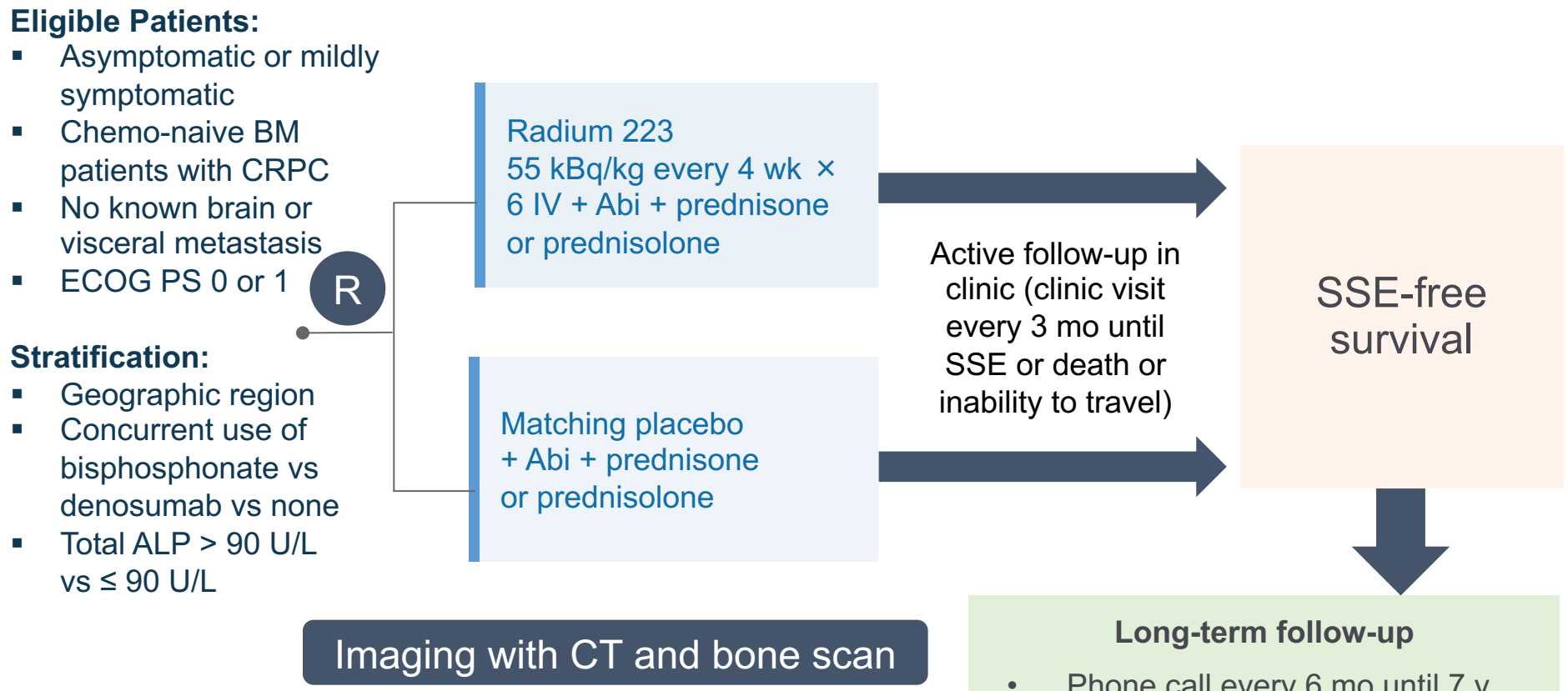
AEs that occurred in ≥ 5% of patients in the safety population

Adverse Event	Radium-223 (N=600)				Placebo (N=301)			
	All Grades	Grade 3	Grade 4	Grade 5*	All Grades	Grade 3	Grade 4	Grade 5*
	number of patients (percent)							
Hematologic								
Anemia	187 (31)	65 (11)	11 (2)	0	92 (31)	37 (12)	2 (1)	1 (<1)
Thrombocytopenia	69 (12)	20 (3)	18 (3)	1 (<1)	17 (6)	5 (2)	1 (<1)	0
Neutropenia	30 (5)	9 (2)	4 (1)	0	3 (1)	2 (1)	0	0
Nonhematologic								
Constipation	108 (18)	6 (1)	0	0	64 (21)	4 (1)	0	0
Diarrhea	151 (25)	9 (2)	0	0	45 (15)	5 (2)	0	0
Nausea	213 (36)	10 (2)	0	0	104 (35)	5 (2)	0	0
Vomiting	111 (18)	10 (2)	0	0	41 (14)	7 (2)	0	0
Asthenia	35 (6)	5 (1)	0	0	18 (6)	4 (1)	0	0
Fatigue	154 (26)	21 (4)	3 (1)	0	77 (26)	16 (5)	2 (1)	0
Deterioration in general physical health	27 (4)	9 (2)	2 (<1)	5 (1)	21 (7)	8 (3)	2 (1)	2 (1)
Peripheral edema	76 (13)	10 (2)	0	0	30 (10)	3 (1)	1 (<1)	0
Pyrexia	38 (6)	3 (1)	0	0	19 (6)	3 (1)	0	0
Pneumonia	18 (3)	9 (2)	0	4 (1)	16 (5)	5 (2)	2 (1)	0
Urinary tract infection	47 (8)	7 (1)	0	0	28 (9)	4 (1)	1 (<1)	1 (<1)
Weight loss	69 (12)	4 (1)	0	0	44 (15)	5 (2)	0	0
Anorexia	102 (17)	9 (2)	0	0	55 (18)	2 (1)	0	0
Decreased appetite	35 (6)	2 (<1)	0	0	13 (4)	0	0	0
Bone pain	300 (50)	120 (20)	5 (1)	0	187 (62)	74 (25)	3 (1)	0
Muscular weakness	9 (2)	2 (<1)	1 (<1)	0	17 (6)	6 (2)	0	0
Pathologic fracture	22 (4)	13 (2)	0	0	15 (5)	8 (3)	1 (<1)	0
Progression of malignant neoplasm	77 (13)	9 (2)	4 (1)	55 (9)	44 (15)	4 (1)	1 (<1)	33 (11)
Dizziness	43 (7)	2 (<1)	0	0	26 (9)	2 (1)	0	0
Spinal cord compression	25 (4)	14 (2)	6 (1)	1 (<1)	23 (8)	16 (5)	1 (<1)	0
Insomnia	27 (4)	0	0	0	21 (7)	1 (<1)	0	0
Hematuria	30 (5)	7 (1)	0	0	15 (5)	3 (1)	0	0
Urinary retention	25 (4)	9 (2)	0	0	18 (6)	6 (2)	0	0
Dyspnea	49 (8)	10 (2)	1 (<1)	1 (<1)	26 (9)	7 (2)	0	3 (1)

- AE, adverse event.
- Parker C, et al. N Engl J Med. 2013;369:213-223.

ERA-223: Abi + Prednisone or Prednisolone ± Radium 223

- **Patient population**
  - Different from ALSYMPCA
    - Asymptomatic
    - Chemo naive
- **Radium 223**
  - Combined with Abi plus prednisone or prednisolone
- **Locations**
  - Conducted in North America, Europe, Asia, Australia, Brazil, and Israel at 168 sites

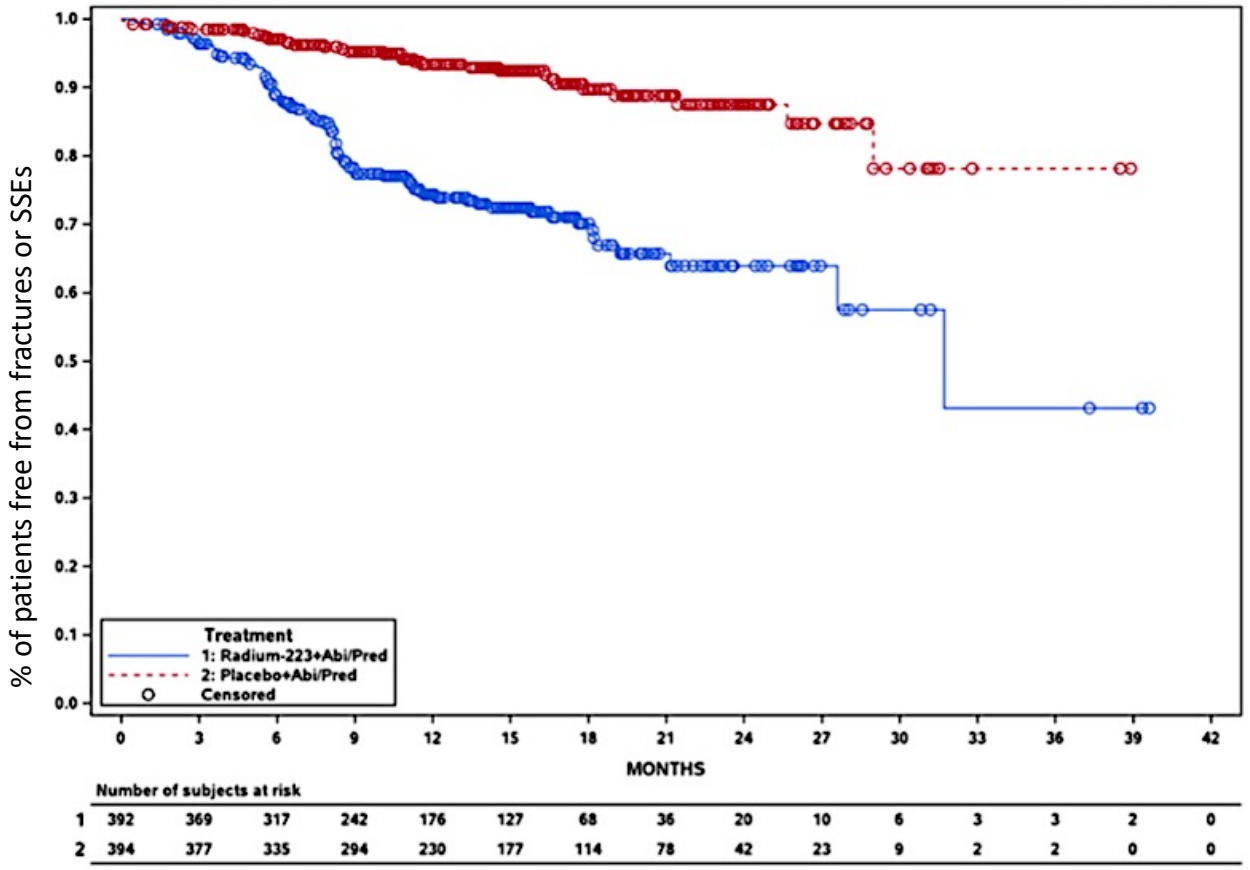


- BM, bone metastasis; IV, intravenous; SSE, symptomatic skeletal events.
- Smith MR, et al. Lancet Oncol. 2019;20:408-419.

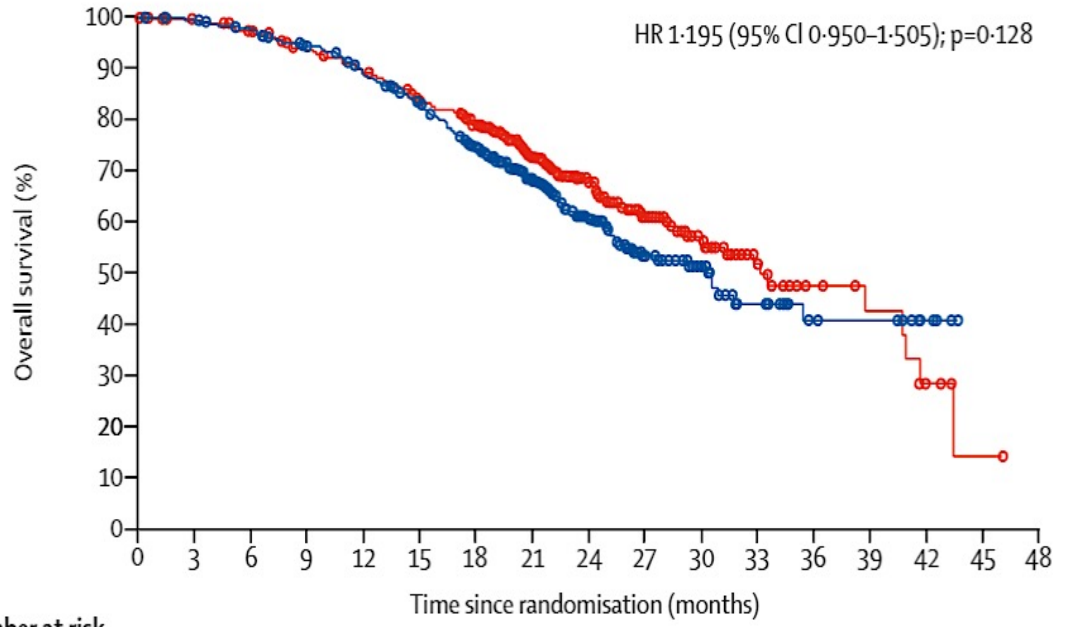
ERA-223 Stopped Early by IDMC for Adverse Findings: Fracture

Smith MR, et al. Lancet Oncol. 2019;20:408-419.

KM Curve of Time to First Fracture



KM Estimates of OS in ITT Population



Number at risk (number censored)

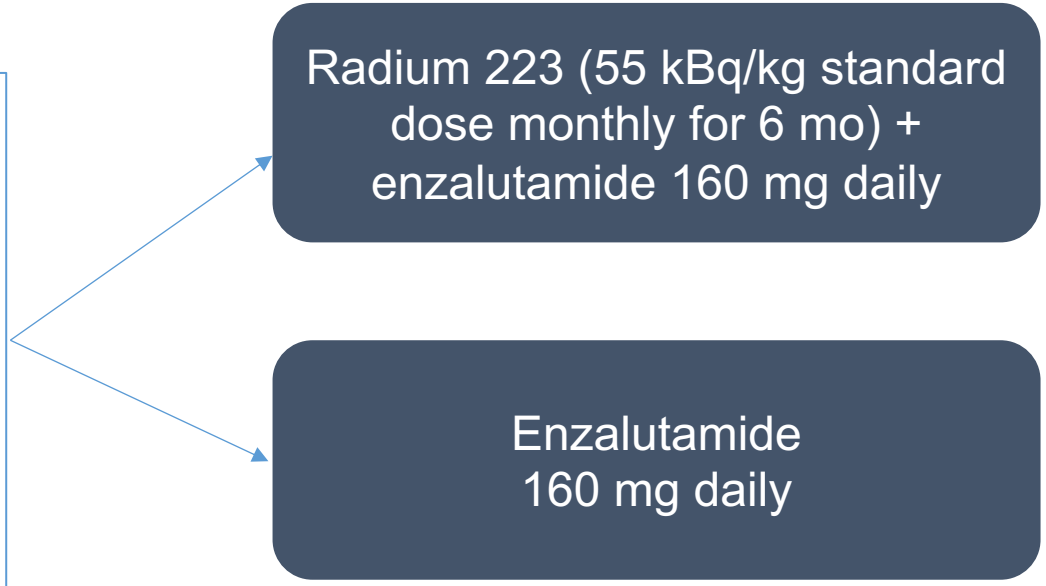
AAP plus radium-223 group	401 (0)	397 (2)	387 (6)	368 (11)	343 (15)	317 (20)	268 (37)	192 (93)	126 (141)	71 (184)	42 (210)	21 (226)	12 (234)	11 (235)	4 (242)	0 (246)	0 (246)
AAP plus Placebo group	405 (0)	397 (7)	385 (10)	366 (15)	348 (16)	323 (20)	291 (33)	218 (87)	145 (148)	90 (190)	52 (223)	27 (245)	12 (257)	9 (259)	5 (260)	1 (263)	0 (264)

- IDMC, independent data monitoring committee; KM, Kaplan-Meier; SSE, symptomatic skeletal events
- EMA. March 13, 2018. Accessed November 7, 2022. https://www.ema.europa.eu/en/documents/referral/xofigo-article-20-procedure-assessment-report-provisional-measures_en.pdf

PEACE III: Phase 3 Trial to Assess Whether Upfront Enzalutamide and Radium 223 Improves rPFS1 vs Enzalutamide Alone in Patients With CRPC Metastatic to Bone

Eligibility Criteria:

- Histologically confirmed diagnosis of prostate adenocarcinoma
- Progressive CRPC
- Asymptomatic or mildly symptomatic
- Metastatic to bone with ≥ 4 bone mets ± additional lymph node mets
- WHO PS 0-1
- Patients with visceral mets not allowed
- Patients with multifocal bone lesions allowed, whereas patients with diffuse confluent bone lesions not allowed



Primary outcomes: rPFS1, event of progression (objective progression of disease, appearance of ≥ 2 new bone lesions and for the first follow-up assessment only)

Secondary outcomes: OS, prostate cancer-specific survival, first SSE, time and incidence of first skeletal PFS, time from entry to initiation of next systemic antineoplastic therapy, treatments elected after first disease progression, second PFS in sequential regimen, patient self-rating scale assessing pain associated with cancer, time to pain progression, occurrence of AEs, time to opiate use, QoL, rate of skeletal fractures

- QoL, quality of life; rPFS1, radiological progression-free survival;
- WHO, World Health Organization.
- ClinicalTrials.gov. Accessed November 28, 2022. https://clinicaltrials.gov/ct2/show/NCT02194842

PEACE III: Updated Analysis

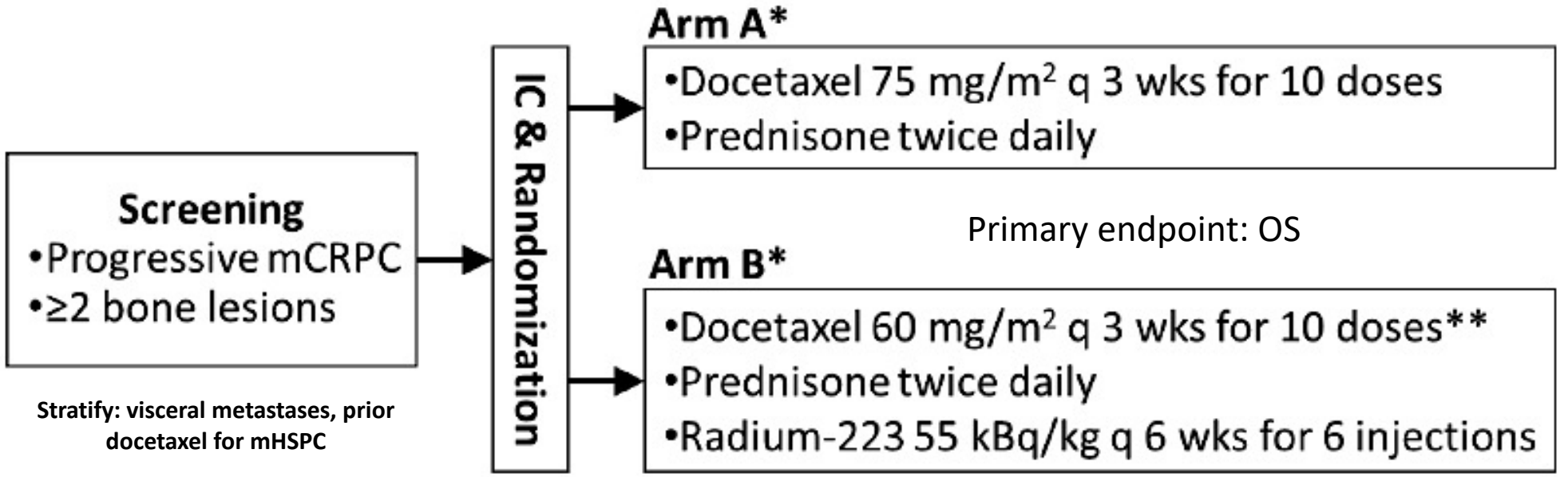
- Decreased fracture rate by mandating BPAs in the EORTC 1333/PEACE III trial combining radium 223 and Enza vs Enza alone: an updated safety analysis

- **Bone Fractures and Cumulative Incidence: Safety Population**

Time point	Without BPA		With BPA	
	Enza+Rad (N=35)	Enza (N=32)	Enza+Rad (N=87)	Enza (N=97)
	Cum Incidence (95% CI)	Cum Incidence (95% CI)	Cum Incidence (95% CI)	Cum Incidence (95% CI)
9 months	25.7 (12.6-41.0)	9.4 (2.3-22.5)	2.7 (0.5-8.5)	1.3 (0.1-6.1)
12 months	**37.1 (21.3-53.0)**	**15.6 (5.6-30.3)**	**2.7 (0.5-8.5)**	**2.6 (0.5-8.3)**
15 months	42.9 (26.1-58.6)	21.9 (9.5-37.5)	4.3 (1.1-10.9)	2.6 (0.5-8.3)
18 months	**45.9 (28.6-61.6)**	**21.9 (9.5-37.5)**	**4.3 (1.1-10.9)**	**2.6 (0.5-8.3)**
21 months	52.0 (33.8-67.5)	21.9 (9.5-37.5)	4.3 (1.1-10.9)	2.6 (0.5-8.3)

- BPA, bone-protecting agent; Cum, cumulative; Enza, enzalutamide; EORTC, European Organisation for Research and Treatment of Cancer; Rad, radium.
- Gillessen S, et al. J Clin Oncol. 2021;39(suppl 15):5002.

DORA Phase 3 Trial Schema



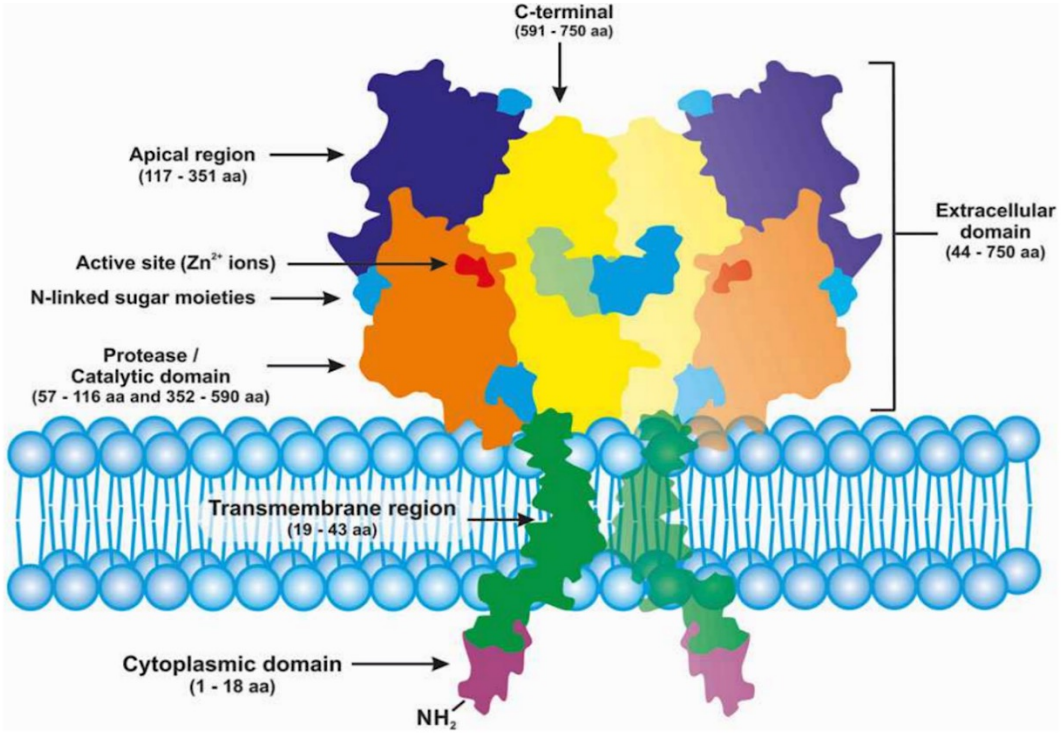
**Dexamethasone will be given per institutional practice. Growth factor support may be used per ASCO guidelines, but use as primary prophylaxis should be avoided. Pegfilgrastim, if given, should be given 24 hours after the last study drug(s) are given.*

***Docetaxel to precede Radium-223 and both treatments should be given on the same day, if feasible. If not, Radium-223 can be given the day after docetaxel.*

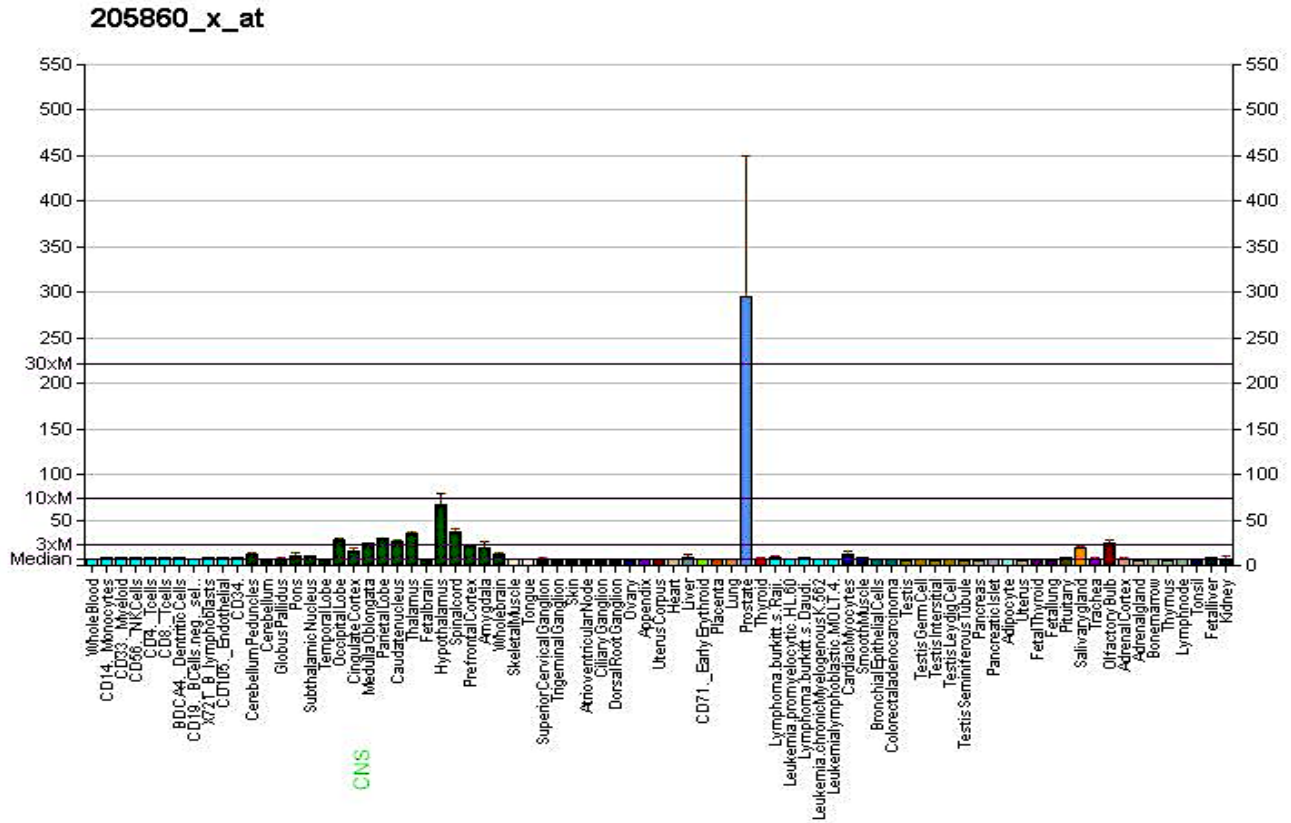
Morris MJ et al. ASCO 2021;Abstract TPS5091.

PSMA: Transmembrane Protein

Schematic Representation of PSMA/GCPII Transmembrane Protein[a]

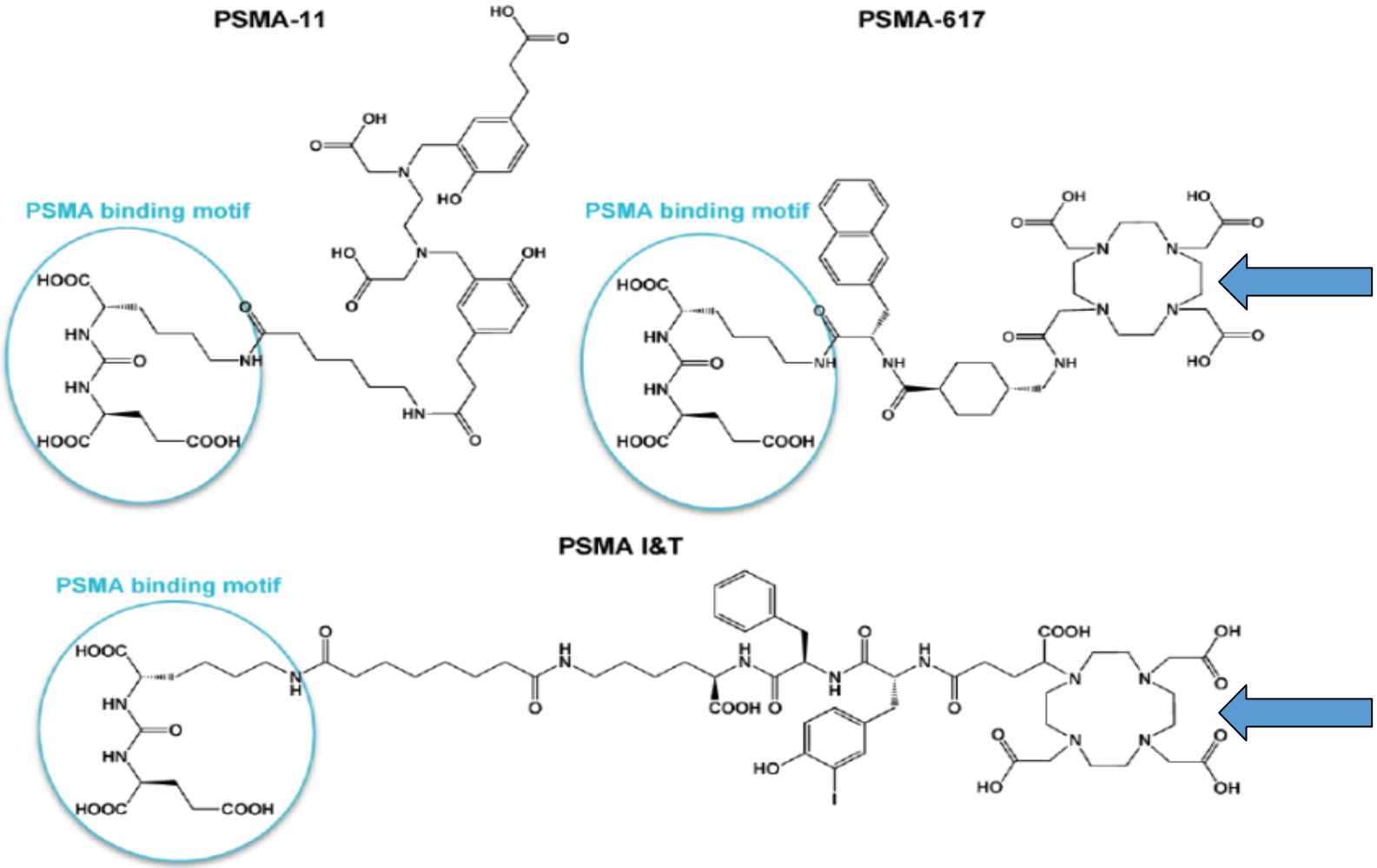


PSMA: Gene Expression High in the Prostate[b]



a. Evans JC, et al. Br J Pharmacol. 2016;173:3041-3079; b. O'Keefe DS, et al. Prostate. 2004;58:200-210.

PSMA Binding Ligands Can Be Linked to Therapeutic Agents via a Chelator



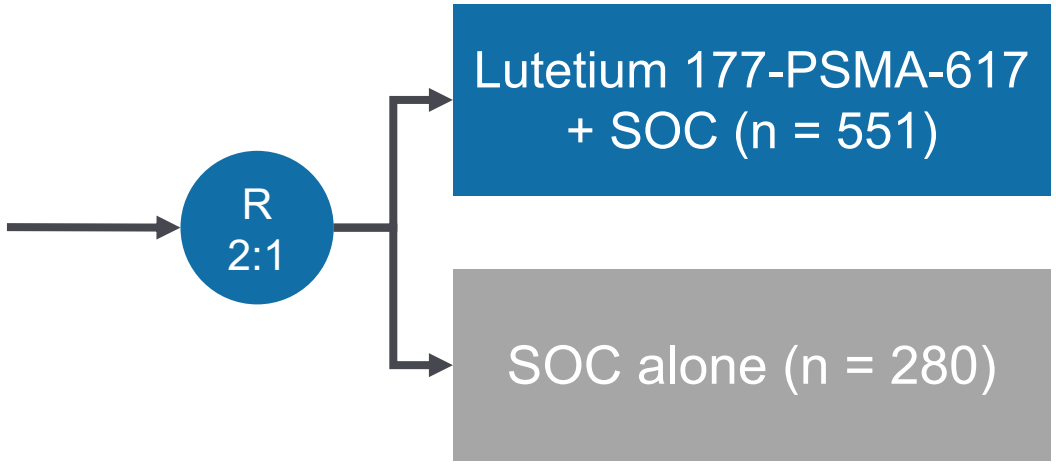
- Chatalic K, et al. Theranostics. 2016;6:849-861.

Phase 3 VISION Trial: Study Design

Patients selected based on PSMA-PET and CT scan

Eligibility Criteria

- Progressive mCRPC
- PSMA positive with gallium 68-PSMA-11 PET/CT scan (per predefined criteria)
- Previous taxane (≤ 2 regimens) therapy and previous Abi/Enza (≥ 1 regimen)
- ECOG PS 0-2
- Life expectancy > 6 mo



Trial fully enrolled (N = 831)

Primary endpoints:
OS, imaging-based PFS

Secondary endpoints: ORR and DCR per RECIST response, time to SSE, safety

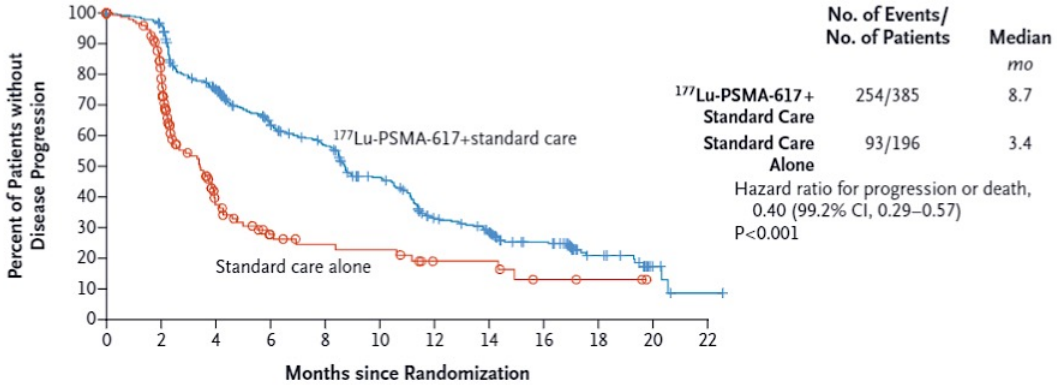
- Results published: 6/23/21
- FDA approved: 3/23/22
- Supply chain problems: 5/5/22

DCR, disease control rate; FDA, Food and Drug Administration; ORR, objective response rate; RECIST, Response Evaluation Criteria in Solid Tumors.

Sartor O, et al. N Engl J Med. 2021;385:1091-1103.

Phase 3 VISION Trial: Primary Endpoints OS and rPFS Were Met

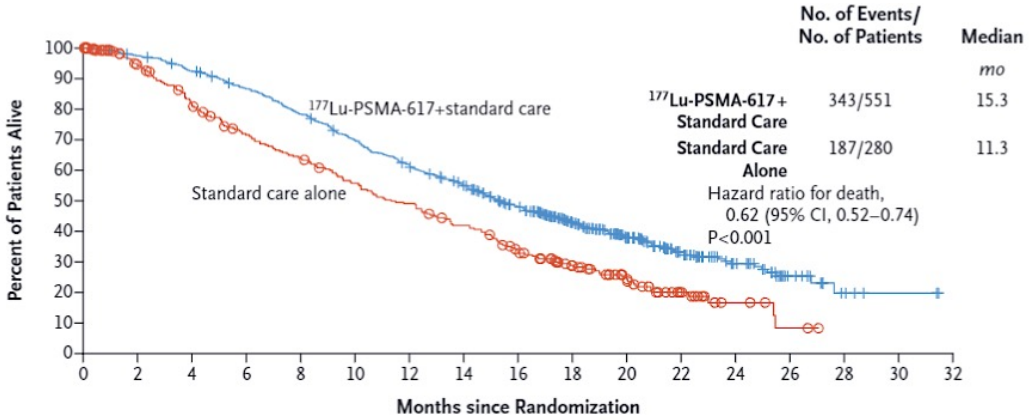
rPFS: HR 0.40 (99.2% CI, 0.29, 0.57)



No. at Risk

177Lu-PSMA-617+standard care	385	362	272	215	182	137	88	71	49	21	6	1
Standard care alone	196	119	36	19	14	13	7	7	3	2	0	0

OS: HR 0.62 (95% CI, 0.52, 0.74)



No. at Risk

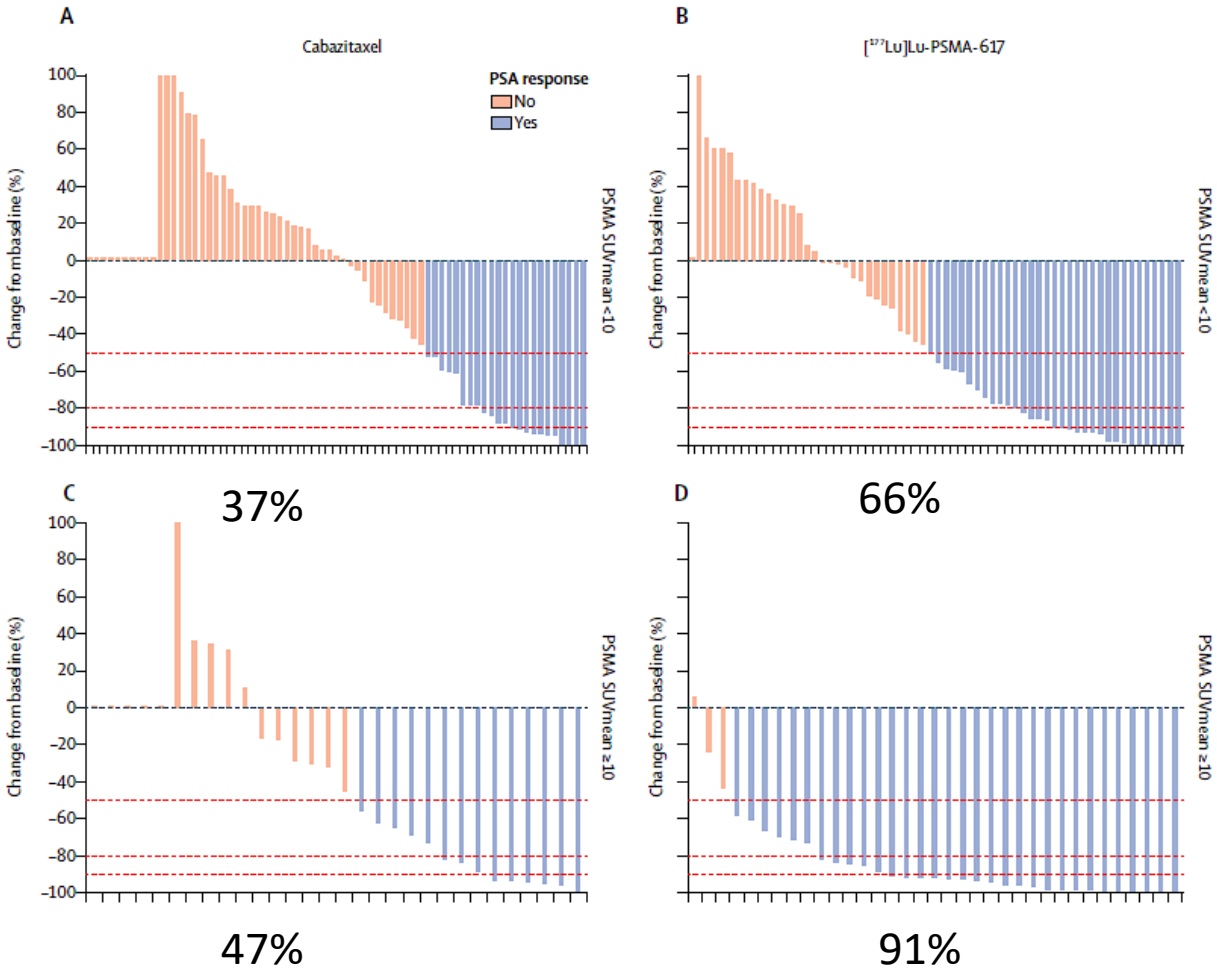
177Lu-PSMA-617+standard care	551	535	506	470	425	377	332	289	236	166	112	63	36	15	5	2	0
Standard care alone	280	238	203	173	155	133	117	98	73	51	33	16	6	2	0	0	0

Note: OS positive (HR 0.63) in rPFS subset and rPFS positive (HR 0.43) in OS subset

FDA Approved March 23, 2022!

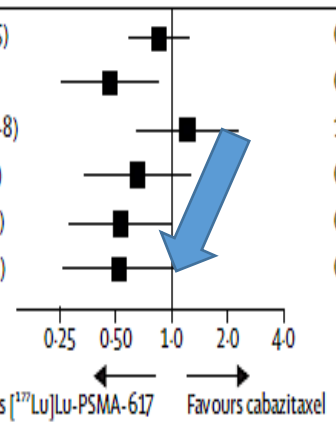
Sartor O, et al. N Engl J Med. 2021;385:1091-1103.

PSMA-Lu177 vs Cabazitaxel: TheraP Trial



B Radiographic progression-free survival

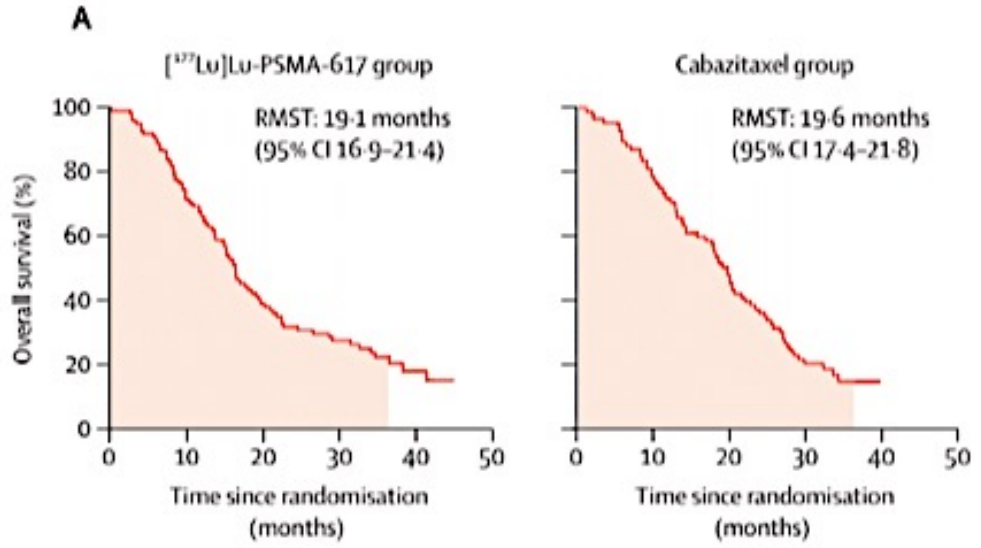
	Cabazitaxel (n/N)	Cabazitaxel, median, months (95% CI)	[177Lu]Lu-PSMA-617 (n/N)	[177Lu]Lu-PSMA-617, median, months (95% CI)	HR (95% CI)
PSMA SUVmean <10	57/71	7·6 (6·4–8·6)	57/64	6·0 (4·3–9·5)	0·85 (0·59–1·24)
PSMA SUVmean ≥10	23/30	9·4 (8·1–11·2)	23/35	12·7 (11–NE)	0·46 (0·25–0·84)
Q1: PSMA SUVmean <6·9	23/28	8·1 (6·4–10·6)	19/21	5·6 (3·8–10·8)	1·21 (0·65–2·26)
Q2: PSMA SUVmean ≥6·9 to <8·5	15/20	5·7 (4·3–NE)	27/29	8·5 (5·6–11)	0·65 (0·34–1·26)
Q3: PSMA SUVmean ≥8·5 to <10·8	24/30	7·5 (6·8–9·5)	18/22	8·9 (6–13·8)	0·53 (0·28–1·00)
Q4: PSMA SUVmean ≥10·8	18/23	9·6 (8·1–12·4)	16/27	14·2 (8·3–NE)	0·52 (0·26–1·04)



PSMA SUVmean<10: PSA50 32% vs 52% still favored PSMA-Lu177

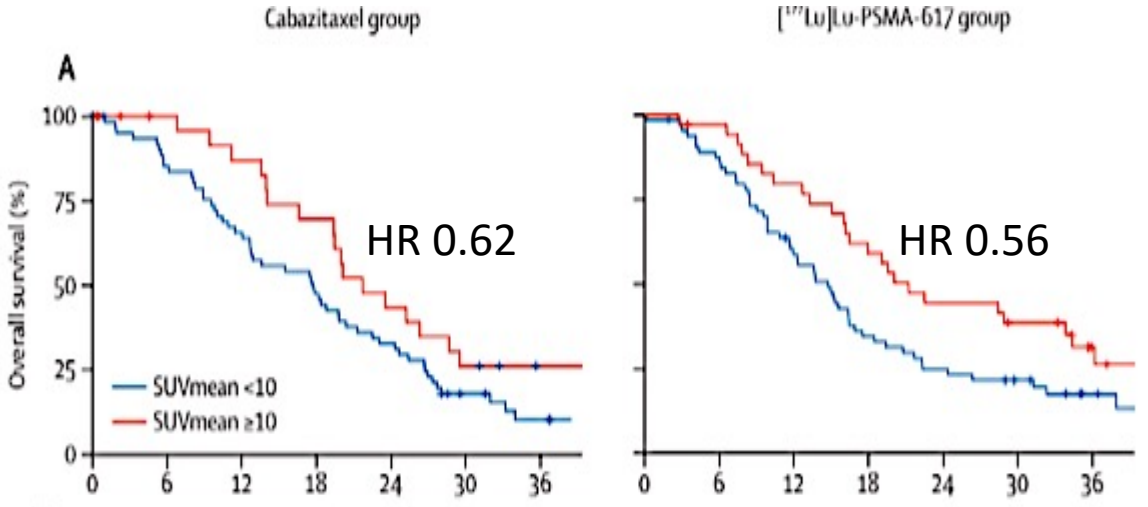
Hofman MS et al Lancet 2021
Burton JP et al Lancet Oncol 2022

Lu177-PSMA-617 Updates: TheraP



Number at risk (number censored)							
Cabazitaxel group	101	75	60	45	30	14	6
	(0)	(17)	(17)	(17)	(17)	(20)	(25)
[177Lu]Lu-PSMA-617 group	99	88	63	41	30	23	11
	(0)	(2)	(3)	(3)	(3)	(6)	(14)

Hofman MS et al Lancet Oncol 2024



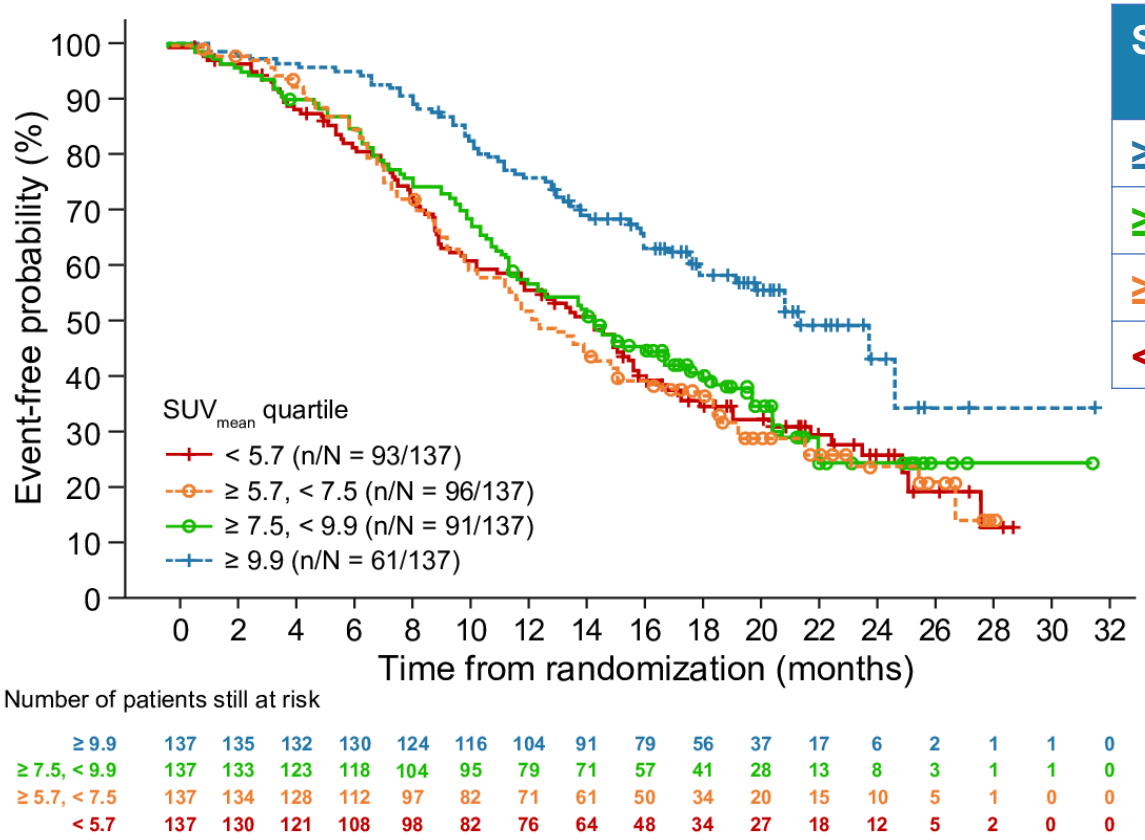
Conclusion: SUVmean ≥10 is prognostic for survival with both cabazitaxel and 177-PSMA-617 therapy but not predictive (similar for FDG PET and adverse prognosis)

High SUV OS HR 0.96 vs 1.07 for low SUV mCRPC patients

P(interaction)=0.70 not significant

Overall Survival by whole-body SUV_{mean} quartiles

- **Higher whole-body SUV_{mean} was associated with improved OS**



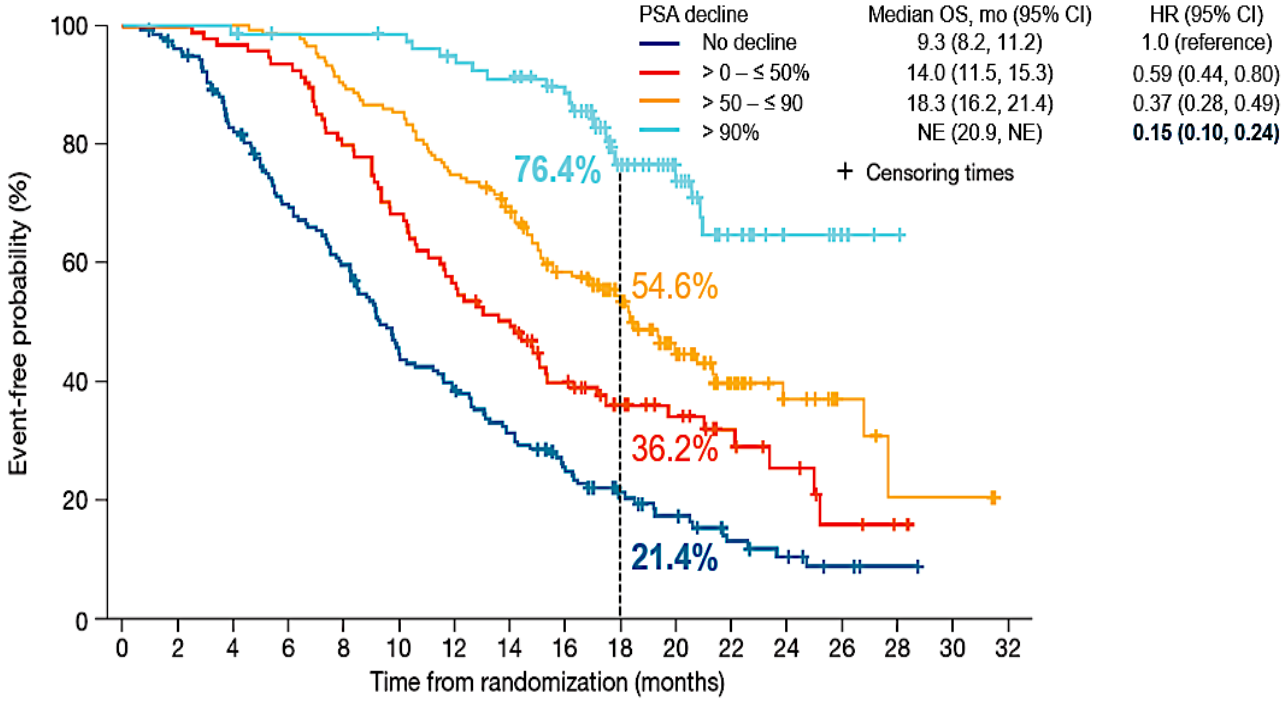
SUV_{mean} quartile	Median OS (months)
≥ 9.9 (highest)	21.4
≥ 7.5, < 9.9	14.6
≥ 5.7, < 7.5	12.6
< 5.7 (lowest)	14.5

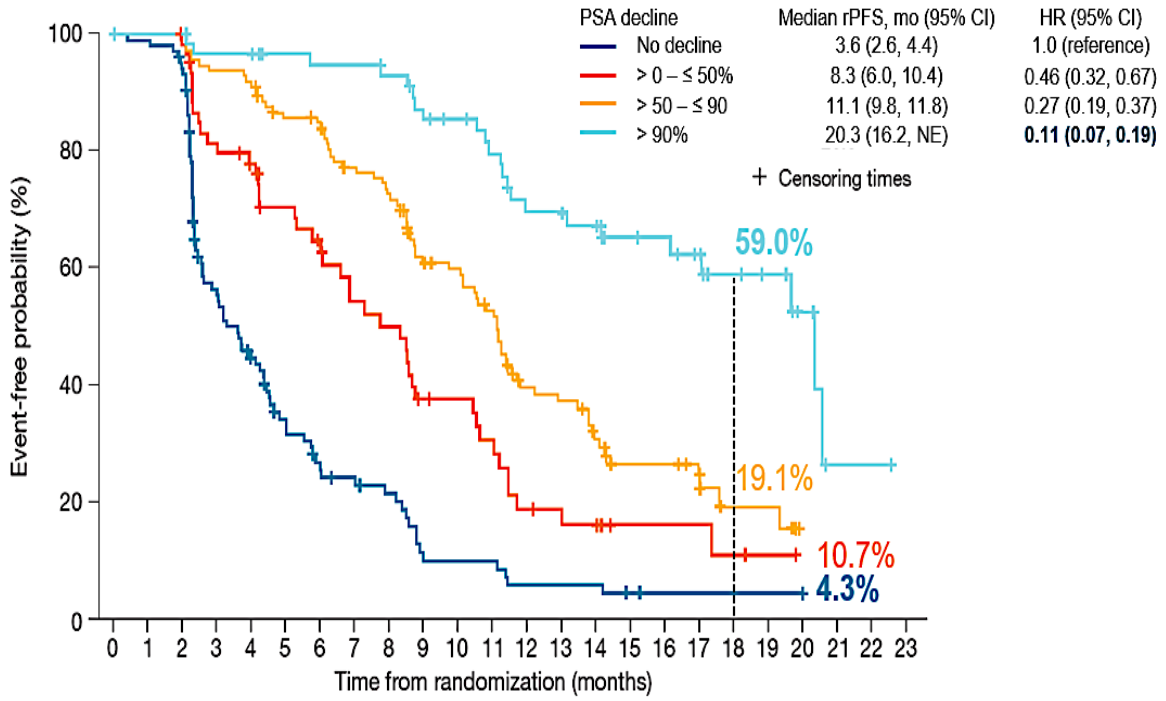
All SUV subgroups had better rPFS and OS than a second/third ARSI thus prognostic but NOT predictive!

SUV_{mean}	OS HR [95% CI], *p* value
Univariate analysis	**0.92** [0.89, 0.95], < 0.001
Multivariate analysis	**0.88** [0.84, 0.91], < 0.001

CI, confidence interval; HR, hazard ratio; FAS, full-analysis set; OS, overall survival; SUV, standardized uptake value

PSA decline is associated with improved overall and progression-free survival with PSMA-Lu177

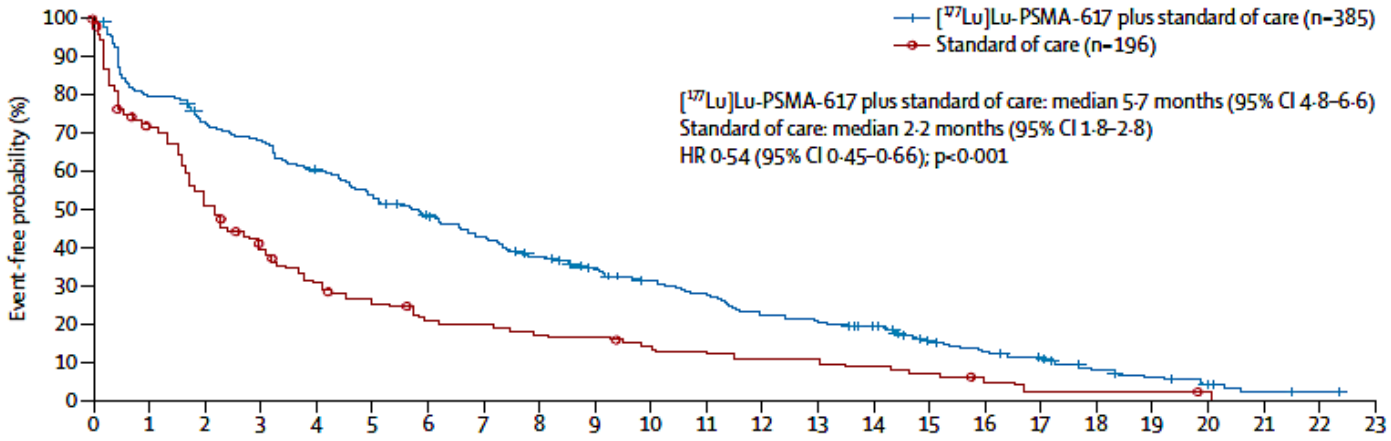




Armstrong et al ESMO 2022;Abstract 1372P

Lu177-PSMA-617 Updates: VISION and QOL

	Prespecified analyses		
	[^{177}Lu]Lu-PSMA-617 plus standard of care (n=385)	Standard of care (n=196)	Hazard ratio (95% CI)
FACT-P			
Total score	5·7 (4·8–6·6)	2·2 (1·8–2·8)	0·54 (0·45–0·66)
Pain-related subscale	4·6 (3·4–5·0)	1·8 (1·6–2·1)	0·55 (0·45–0·66)
Trial outcome index	6·0 (5·0–6·9)	2·2 (1·8–2·9)	0·56 (0·46–0·68)
Prostate cancer subscale	3·9 (3·3–4·6)	1·8 (1·6–2·3)	0·62 (0·51–0·76)
Physical wellbeing	4·7 (3·9–6·1)	1·8 (1·6–2·3)	0·51 (0·42–0·62)
Social or family wellbeing	5·9 (5·1–6·9)	2·9 (2·3–3·5)	0·55 (0·45–0·67)
Emotional wellbeing	6·6 (5·7–7·3)	2·4 (1·9–3·0)	0·52 (0·43–0·63)
Functional wellbeing	4·6 (3·3–5·2)	2·0 (1·6–2·6)	0·61 (0·51–0·74)
BPI-SF			
Pain intensity	6·9 (6·0–7·7)	2·6 (2·1–3·1)	0·52 (0·42–0·63)
Pain interference	5·9 (5·0–6·8)	2·9 (2·3–3·5)	0·62 (0·51–0·75)
Worst pain intensity	5·0 (4·2–5·9)	2·0 (1·7–2·2)	0·51 (0·42–0·63)
EQ-5D-5L			
Utility score	1·0 (0·7–1·8)	0·5 (0·4–1·0)	0·65 (0·54–0·78)



	[^{177}Lu]Lu-PSMA-617 plus standard of care (n=385)	Standard of care (n=196)	Hazard ratio (95% CI)
Bone-targeted agents			
Symptomatic skeletal event or death	115/175 (66%)	66/96 (69%)	..
Median time to event, months	12·0 (10·0–14·2)	7·2 (5·6–10·2)	0·49 (0·36–0·68)
Median follow-up time, months	17·1 (14·6–17·7)	16·6 (11·0–NE)	..
No bone-targeted agents			
Symptomatic skeletal event or death	141/210 (67%)	71/100 (71%)	..
Median time to event, months	11·5 (9·8–13·7)	5·8 (4·1–9·2)	0·50 (0·37–0·68)
Median follow-up time, months	17·0 (15·6–17·4)	19·8 (11·5–NE)	..
Overall			
Symptomatic skeletal event or death	256/385 (66%)	137/196 (70%)	..
Median time to event, months	11·5 (10·3–13·2)	6·8 (5·2–8·5)	0·50 (0·40–0·62)
Median follow-up time, months	17·0 (15·9–17·3)	16·9 (11·5–NE)	..

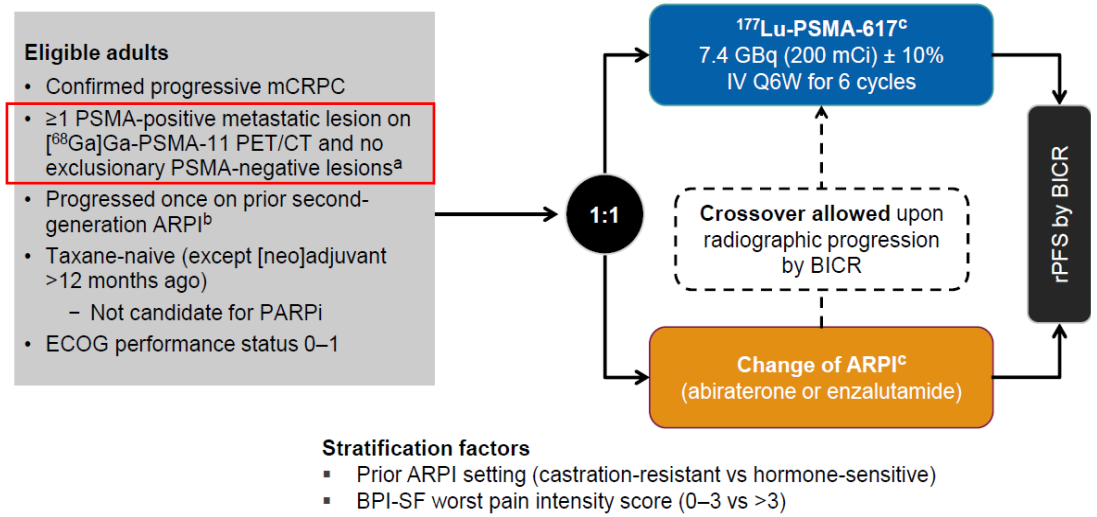
Fizazi K Lancet Oncol 2023

PSMAfore: Ph 3 evaluating ^{177}Lu-PSMA-617 vs change in NHA in chemo-naïve, NHA-exposed mCRPC

Baseline characteristics were as expected for a chemo-naïve mCRPC patient population

PSMAfore: Study Design

An international, multicenter, randomized, open-label Phase III study



Stratification factors

- Prior ARPI setting (castration-resistant vs hormone-sensitive)
- BPI-SF worst pain intensity score (0–3 vs >3)

Note that 505/547 (92%) of patients meet ^{68}Ga-PSMA-11 screening criteria (see below)

PSMAfore: Baseline Patient and Disease Characteristics

	^{177}Lu-PSMA-617 N=234	Change of ARPI N=234
Age, median (range), years	71 (43–94)	72 (53–91)
White, n (%)	211 (90.2)	214 (91.5)
ECOG performance status, n (%)		
0	146 (62.4)	115 (49.1)
1	86 (36.8)	114 (48.7)
Gleason score 8–10, n (%)	136 (58.1)	107 (45.7)
PSA, median (range), µg/L	18.4 (0–1197)	14.9 (0–4224)
Hemoglobin, median (range), g/L	128.0 (88–155)	129.0 (88–156)
Alkaline phosphatase, median (range), IU/L	100.0 (36–1727)	103.5 (28–1319)
Site of disease, n (%)		
Liver	13 (5.6)	7 (3.0)
Lymph node	76 (32.5)	74 (31.6)
Bone	205 (87.6)	203 (86.8)
Prior ARPI, n (%)		
Abiraterone	119 (50.9)	130 (55.6)
Enzalutamide	94 (40.2)	84 (35.9)
Other	21 (9.0)	20 (8.5)

^{68}Ga PSMA +ve based on whether soft tissue or bone only disease: centrally determined visually based on a lesion showing greater intensity compared to background liver;

soft tissue disease (with or without bone disease), all of the following 5 requirements must be met for eligibility [68Ga]Ga-PSMA-11 PET positivity in:

1) ≥1 lesion (osseous or extraosseous) irrespective of size;
2) all lymph nodes that measure ≥25 mm in short axis;
3) all bone metastases with a soft tissue component ≥10 mm in the longest diameter (PSMA-negative bone metastases without a soft tissue component do not exclude pts);
4) all solid organ metastases ≥10 mm in the longest diameter;
5) all intraprostatic lesions regardless of size.

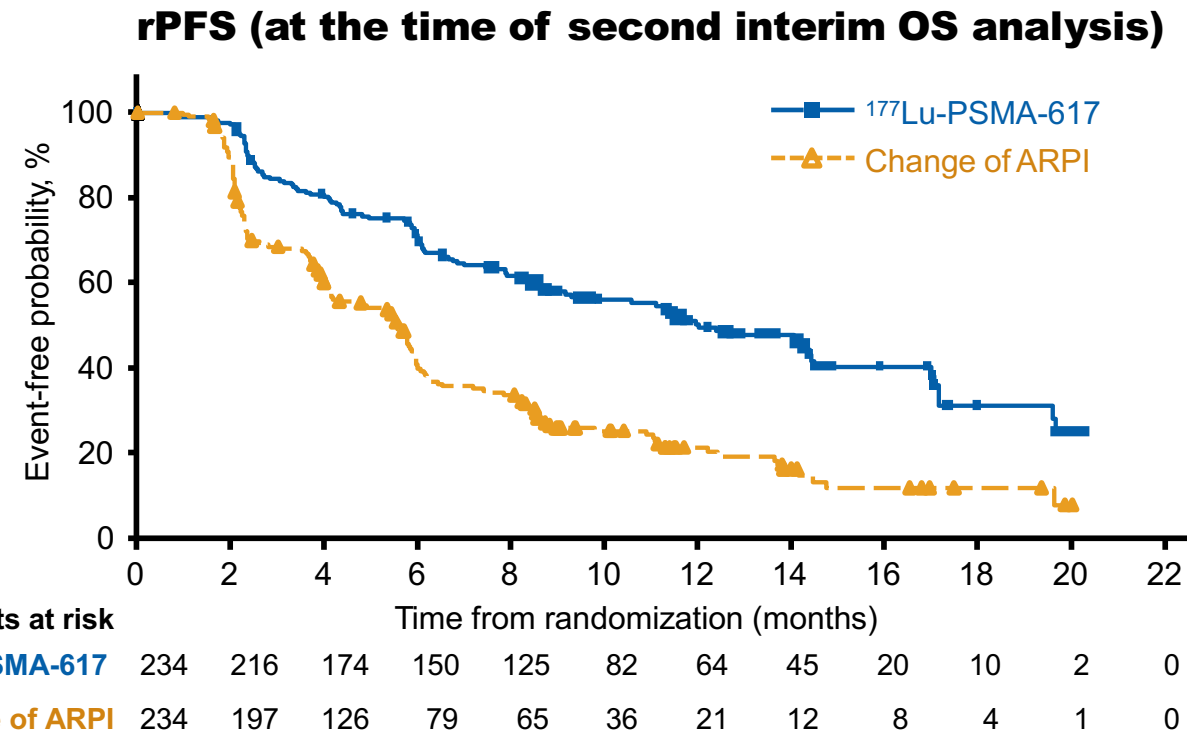
bone-only disease: ≥1 site of bone involvement must be [68Ga]Ga-PSMA-11 PET positive.

Sartor O, et al. Abstract presented at: ESMO Congress 2023; October 20-24, 2023; Madrid, Spain, Abstract LBA13

PSMAfore study met primary endpoint of rPFS

Primary endpoint was met:

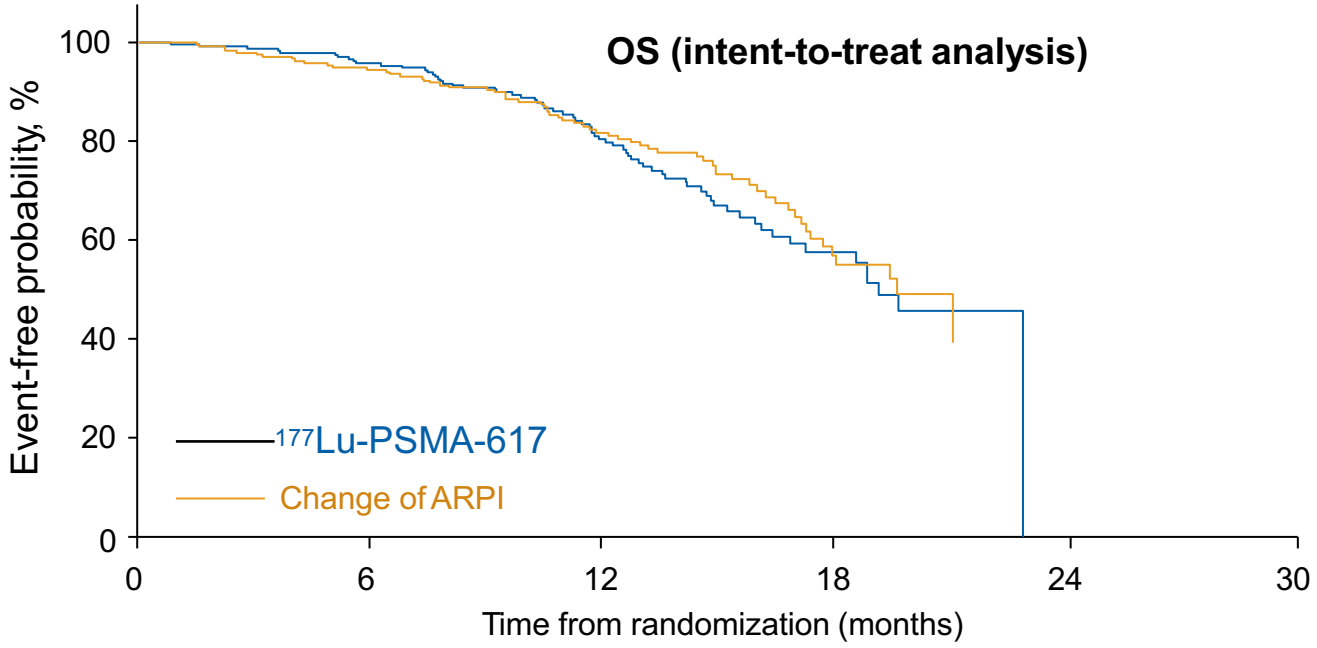
- **At the time of primary analysis** (DCO October 2, 2022): **HR was 0.41** (95% CI: 0.29, 0.56); *P* < .0001
- At the time of second interim OS analysis (DCO June 21, 2023): HR was 0.43 (95% CI: 0.33, 0.54)



	^{177}Lu-PSMA-617 (N=234)	Change of ARPI (N=234)
Events, n (%)	115 (49)	168 (72%)
Median rPFS , months (95% CI)	12.0 (9.30, 14.42)	5.6 (4.2, 5.9)
HR (95% CI)	**0.41** (0.29-0.56)	
P-value	< 0.0001	

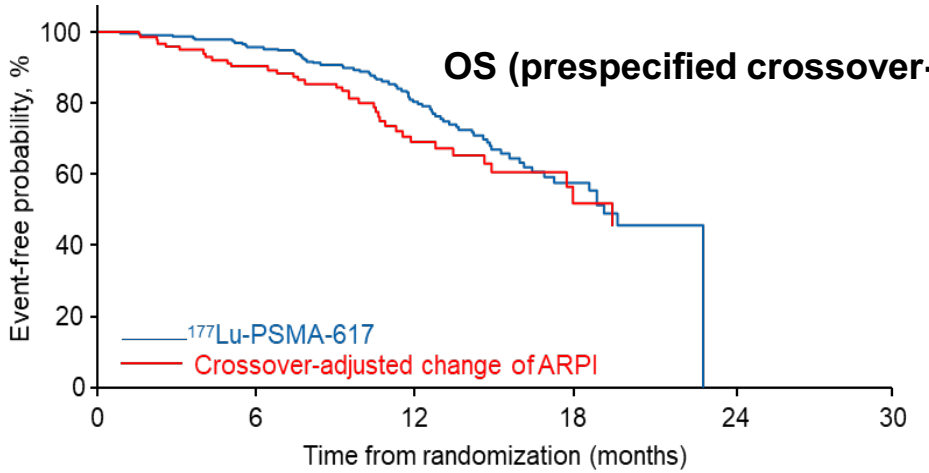
Sartor O, et al. Abstract presented at: ESMO Congress 2023; October 20-24, 2023; Madrid, Spain, Abstract LBA13

PSMAfore did not show an OS advantage at IA2



ITT analysis

	^{177}Lu-PSMA-617 (N=234)	Change of ARPI (N=234)
Events, n (%)	69 (29)[a]	65 (28)
Median OS , months (95% CI)	**19.2** (16.9-NE)	**19.7** (17.8-NE)
HR (95% CI)	**1.16** (0.83-1.64)	
P-value	--	



Crossover: 123/146 (84%)
patients with radiographic progression crossed over

	^{177}Lu-PSMA-617 (N=234)	Change of ARPI (N=234)
Median OS , months (95% CI)	**19.2** (16.9-NE)	**19.5** (14.9-NE)
HR (95% CI)	**0.80** (0.48-1.33)	

[a]Three patients died before receiving ^{177}Lu-PSMA-617.

Sartor O, et al. Abstract presented at: ESMO Congress 2023; October 20-24, 2023; Madrid, Spain, Abstract LBA13

^{177}Lu–PSMA–I&T: The ECLIPSE Ph3 Trial

Patient population

- mCRPC with progression per PCWG3 guidelines
- Only one prior ARAT (abiraterone, enzalutamide, darolutamide, apalutamide)
- No prior chemo treatment
- No prior radioligands
- ECOG PS 0–2
- Positive PSMA-PET scan

R 2:1

^{177}Lu-PSMA-I&T 200 mCi every 6 weeks x 6
(n=266)

Alternative ARAT
(n=133)

Enrollment completed

Primary endpoint

- rPFS

Key secondary endpoints

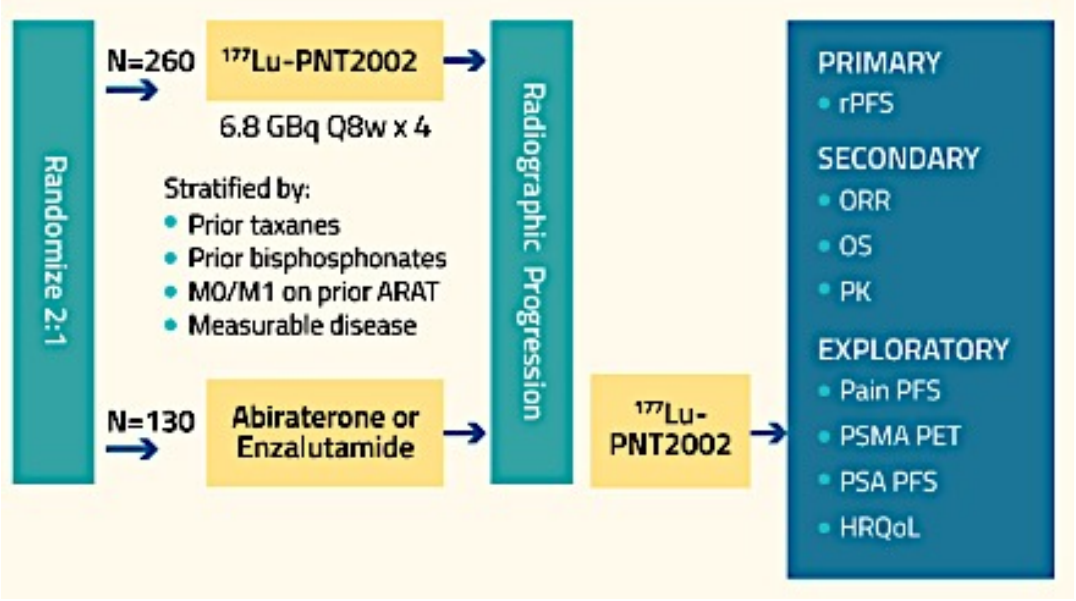
- OS
- Overall PFS
- PFS-2 (second PFS)
- PSA response rate
- Time to first SSE
- QOL (EORTC QLQ-C30)

Key correlative endpoint

- Dosimetry
- PKs (pharmacokinetics)

ClinicalTrials.gov Identifier: NCT05204927

Phase 3 SPLASH study of 177Lu-PNT2002 demonstrated statistically significant improvement in radiographic progression-free survival (rPFS)



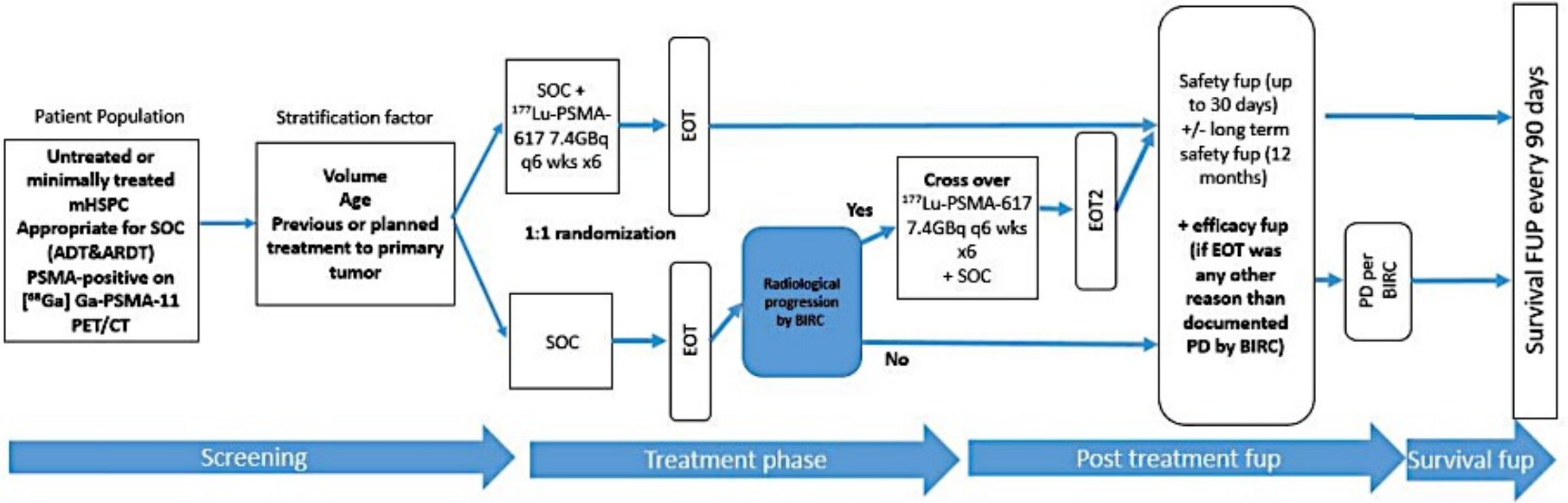
84.6% cross-over at progression on control (does not count commercial cross-over)

The SPLASH trial met its primary endpoint, improved rPFS per BICR of 9.5 mo for patients treated with ^{177}Lu-PNT2002, compared to 6.0 months for patients treated with ARPI in the control arm, a statistically significant 29% reduction in the risk of radiographic progression or death (hazard ratio [HR] 0.71; *p*=0.0088).

At the time of the analysis, interim overall survival (OS) results were immature (46% of protocol-specified target OS events reached), the HR was 1.11.

	^{177}Lu-PNT2002 Arm	ARPI Arm
TEAEs of CTCAE Grade ≥3	30.1%	36.9%
Serious TEAEs	17.1%	23.1%
TEAEs Leading to Discontinuation	1.9%	6.2%

PSMAddition: Benefits of PSMA RLT in the mHSPC Setting



N=1144

NCT04720157
Enrollment completed

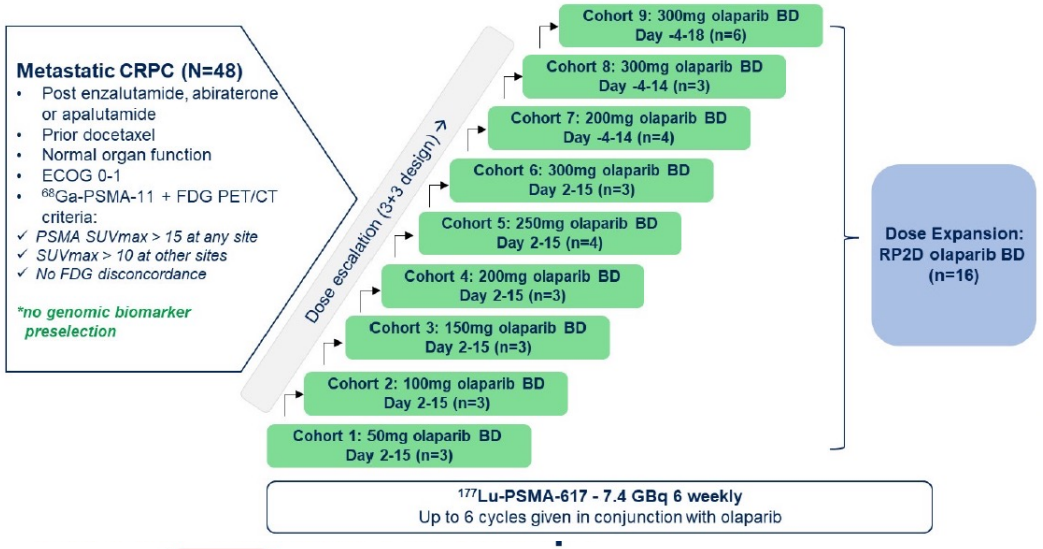
Tagawa ST et al. ASCO 2023;Abstract TPS5116.

Sandhu GU 2023 abstract 5005

177Lu-PSMA-617 Combination Therapy: LuPARP

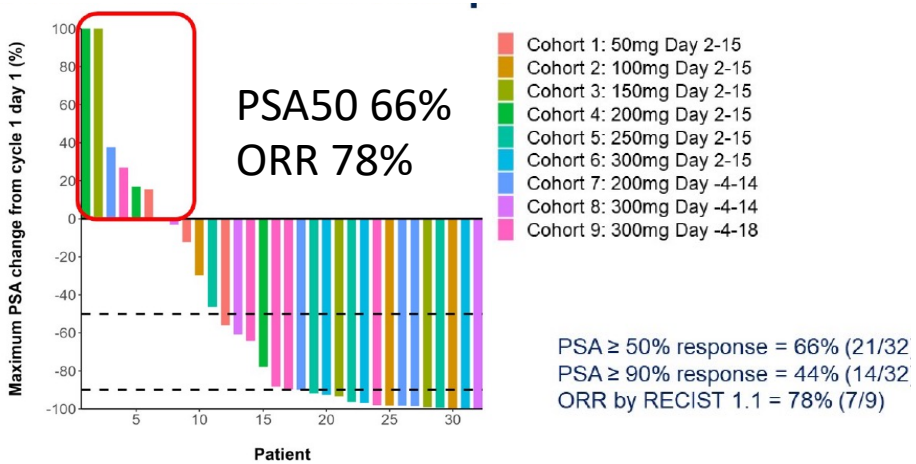
No DLTs, RP2D is olaparib 300 mg BID days -4 to +18 of each 6-weekly cycle

LuPARP: Phase 1 Trial Schema



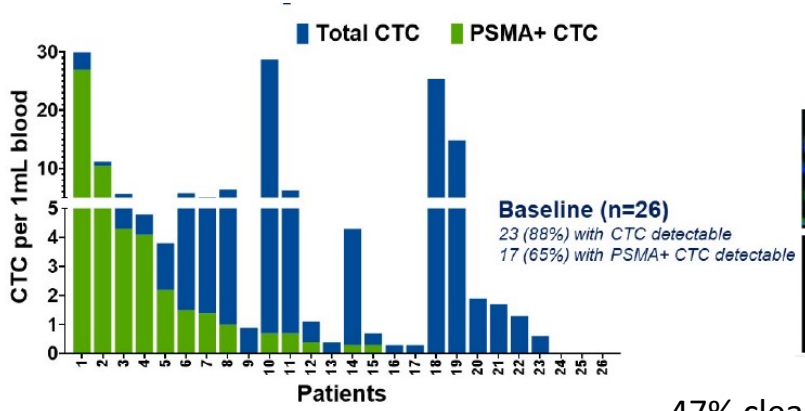
LuPARP results: Treatment Related AEs >5%

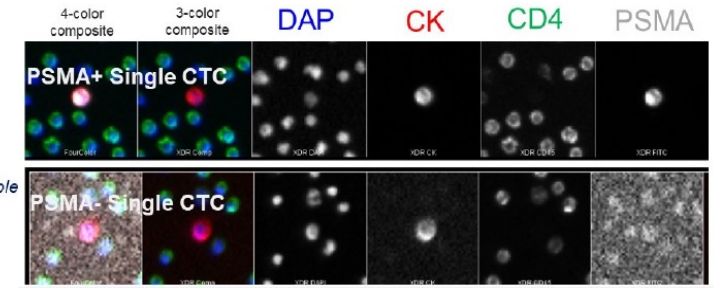
	N=3 Cohort 1 177Lu-PSMA & 50mg olaparib BD Day 2-15			N=3 Cohort 2 177Lu-PSMA & 100mg olaparib BD Day 2-15			N=3 Cohort 3 177Lu-PSMA & 150 olaparib BD Day 2-15			N=3 Cohort 4 177Lu-PSMA & 200mg olaparib BD Day 2-15			N=4 Cohort 5 177Lu-PSMA & 250mg olaparib BD Day 2-15			N=3 Cohort 6 177Lu-PSMA & 300 olaparib BD Day 2-15			N=4 Cohort 7 177Lu-PSMA & 200mg olaparib BD Day -4-14			N=3 Cohort 8 177Lu-PSMA & 300mg olaparib BD Day -4-14			N=6 Cohort 9 177Lu-PSMA & 300mg olaparib BD Day -4-18			Total (n=32)		
No. cycles of treatment Median (range)	4 (4-5)			6 (5-6)			6 (2-6)			3 (2-4)			6 (4-6)			6 (5-6)			5.5 (3-6)			4 (3-6)			3 (2-5)			5 (2-6)		
Adverse Event (AE) Grade (G)	**G1**	**G2**	**G3**	**G1**	**G2**	**G3**	**G1**	**G2**	**G3**	**G1**	**G2**	**G3**	**G1**	**G2**	**G3**	**G1**	**G2**	**G3**	**G1**	**G2**	**G3**	**G1**	**G2**	**G3**	**G1**	**G2**	**G3**	**G1**	**G2**	**G3**
Anemia	1	-	-	2	1	-	-	-	-	-	-	-	1	1	1	-	-	1	1	-	-	-	-	-	-	1	-	5	3	2
Neutropenia	-	-	-	1	-	-	-	-	-	-	-	-	-	-	1*	-	-	1	-	-	-	-	-	-	-	-	-	1	-	2
Thrombocytopenia	-	1	-	1	-	-	1	-	-	1	-	-	1	-	1	-	1	-	-	-	-	-	-	-	1	-	-	5	2	1
Nausea	1	2	-	3	-	-	1	1	-	2	-	-	1	1	-	1	1	-	2	1	-	-	-	-	2	-	-	13	6	-
Dry Mouth	3	-	-	3	-	-	3	-	-	2	-	-	3	1	-	2	1	-	1	1	-	2	-	-	3	-	-	22	3	-
Constipation	-	-	-	-	-	-	-	1	-	2	-	-	-	-	-	1	-	-	1	1	-	1	-	-	2	-	-	7	2	-
Vomiting	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	-	-	-	1	-	1	-	-	1	-	-	3	1	-
Gastroesophageal Reflux	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	1	-	-	-	-	-	-	-	1	-	-	2	1	-
Diarrhea	-	-	-	-	-	-	-	-	-	-	-	-	1	-	-	1	-	-	1	-	-	-	-	-	-	-	-	3	-	-
Weight Loss	-	-	-	-	-	-	-	-	-	-	-	-	-	1	-	1	-	-	-	-	-	-	-	-	-	-	-	1	1	-
Anorexia	1	-	-	2	-	-	1	-	-	-	-	-	-	-	-	1	-	-	-	-	-	-	-	-	1	-	-	6	-	-
Dry Eye	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	-	-	-	-	-	1	-	-	2	-	-
Fatigue	-	-	-	1	-	-	1	-	-	2	-	-	1	-	-	2	-	-	1	-	-	1	-	-	6	-	-	15	-	-



PSA50 66%
ORR 78%

PSA ≥ 50% response = 66% (21/32
PSA ≥ 90% response = 44% (14/32
ORR by RECIST 1.1 = 78% (7/9)





47% cleared all CTCs; 87% cleared all PSMA+ CTCs

ENZA-p: Synergy with ARSI Therapy?

ENZA-p schema

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

R 1:1

Enzalutamide 160 mg

Enzalutamide 160 mg
+ **Lu-PSMA** 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)
Radiographic PFS
PSA response rate
Pain response and PFS
Clinical PFS
HRQOL
Adverse events
Overall survival
Health economic analyses
Translational/correlative

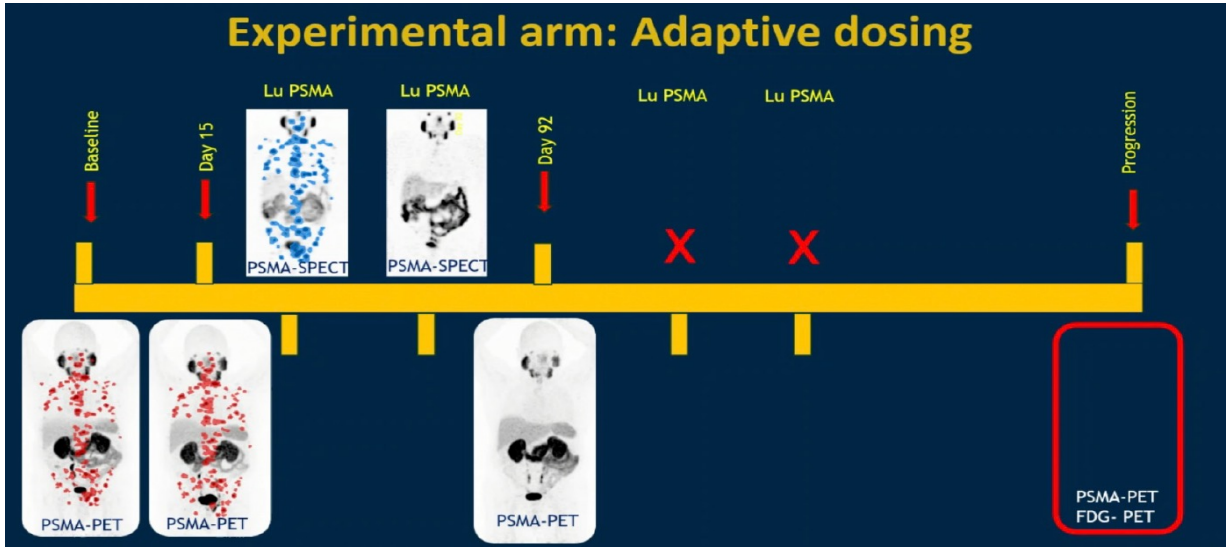
Risk Factors for Early Treatment Failure on Enzalutamide

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

SUVmax>15 at one site, >10 at all sites PLUS 2 adverse prognostic factors

Patient population:
11-14% prior abiraterone
52-58% de novo M1
53-56% prior docetaxel for mHSPC

Emmett L et al ESMO 2023 LBA84



2-4 doses given adaptively based on PSMA PET response, with further dosing only for those with PSMA-avid persistent disease

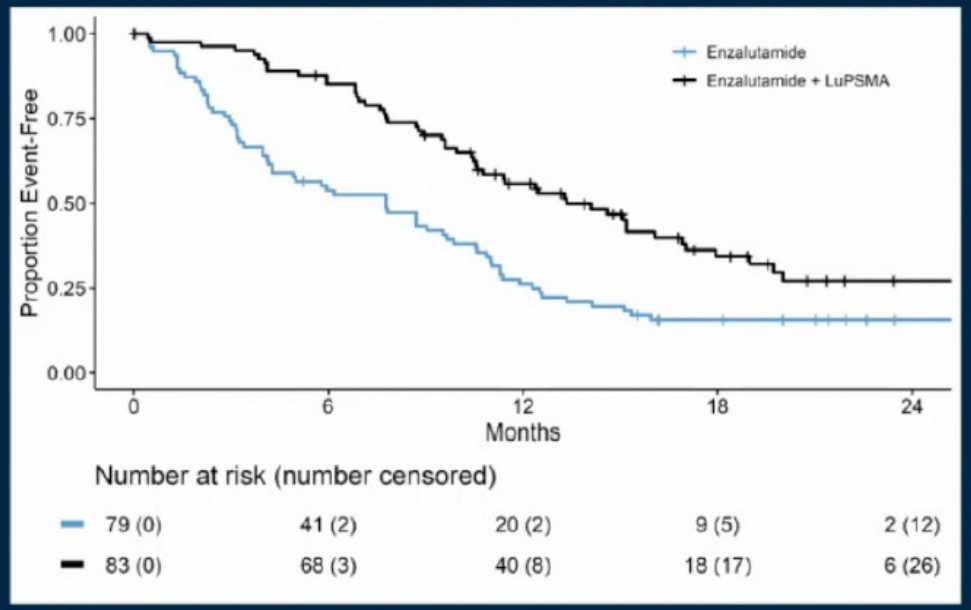
ENZA-p Results

PSA50 93% (combo) vs 68% (enza alone)
Similar adverse event profile except slightly more dry mouth (40% vs 10%) and anemia (14% vs 3%)

Progression Free Survival

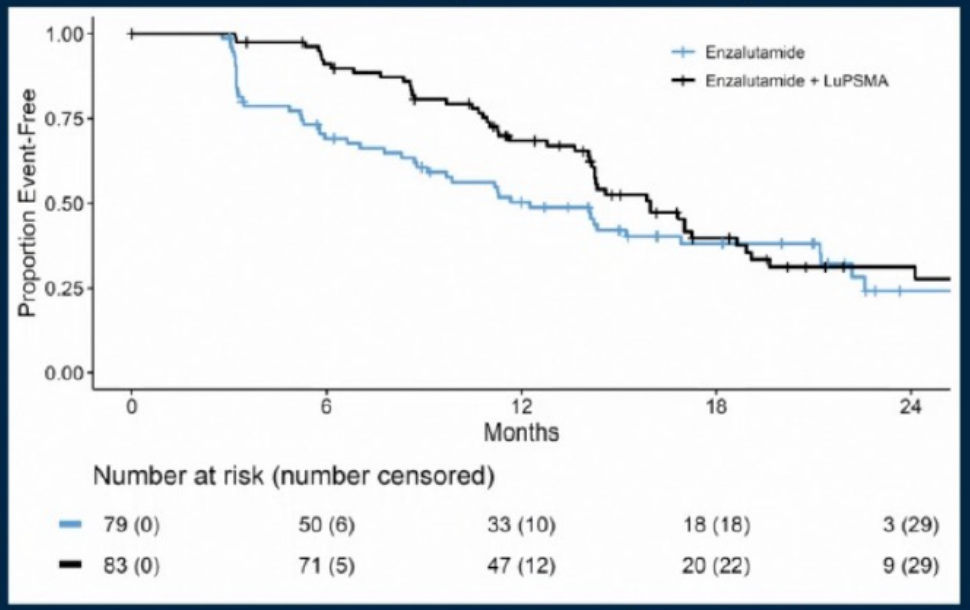
PSA-PFS

HR 0.43 (95%CI 0.29-0.63) p=0.00001



R-PFS

HR 0.67 (95% CI 0.44-1.01)



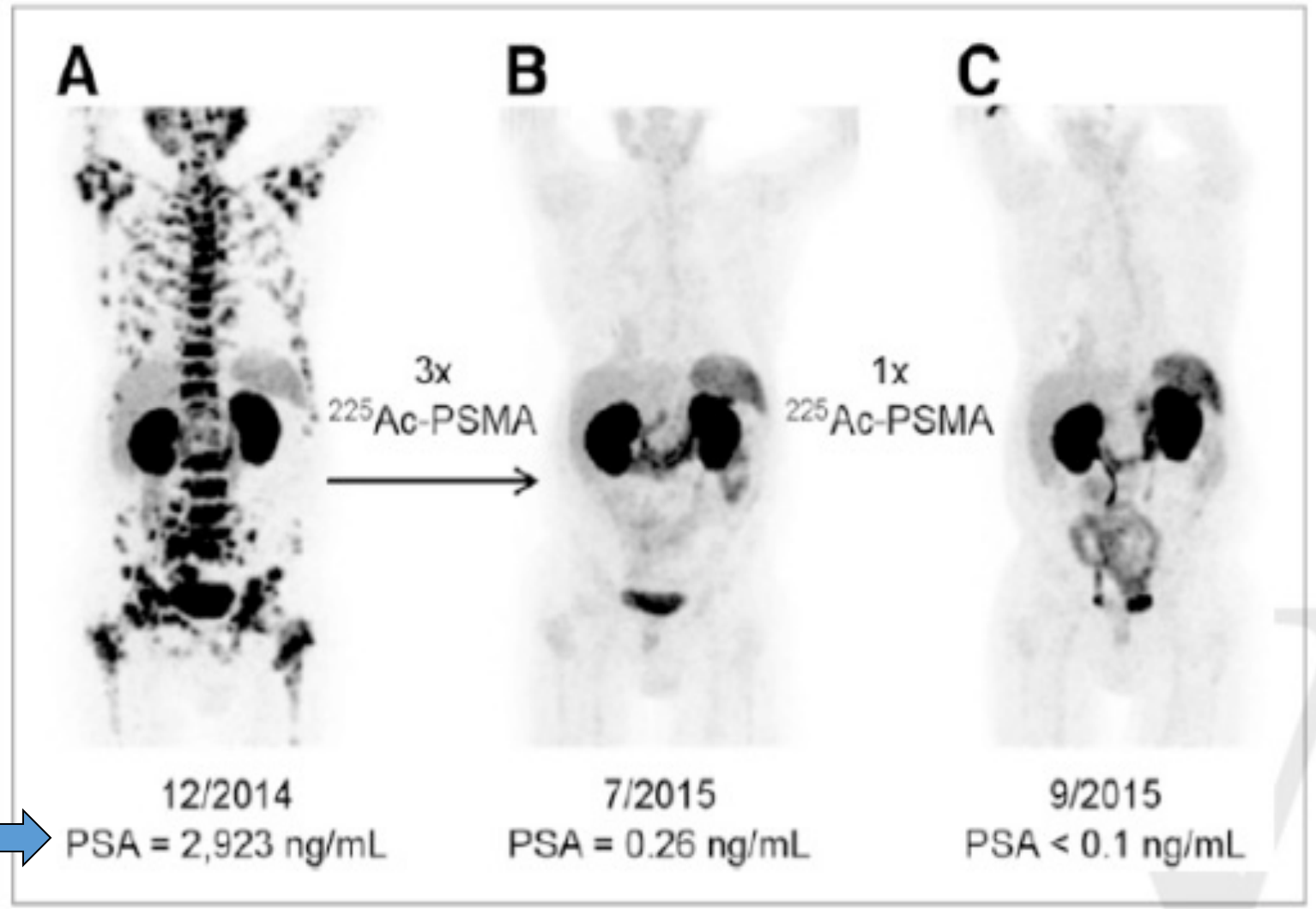
PSA-PFS	Participants	Events	Censored	Median Months
Enzalutamide	79	65	14	7.8
Enzalutamide + Lu-PSMA	83	52	31	13

Radiographic-PFS	Participants	Events	Censored	Median Months
Enzalutamide	79	47	35	12
Enzalutamide + Lu-PSMA	83	48	32	16

Radio-conjugates: PSMA targeted alpha emitters (Actinium-225) as 9th line treatment

Kratochwil et a. J Nuc Med 57: 1-4, 2016

Patient A
Leuprorelin
Zoledronate
Docetaxel (50 cycles)
Carmustine/epirubicin in hyperthermia
Abiraterone
Enzalutamide
^{223}Ra (6 cycles)
Abiraterone reexposition
Estramustine



Current CRPC Alpha Programs

Antibodies

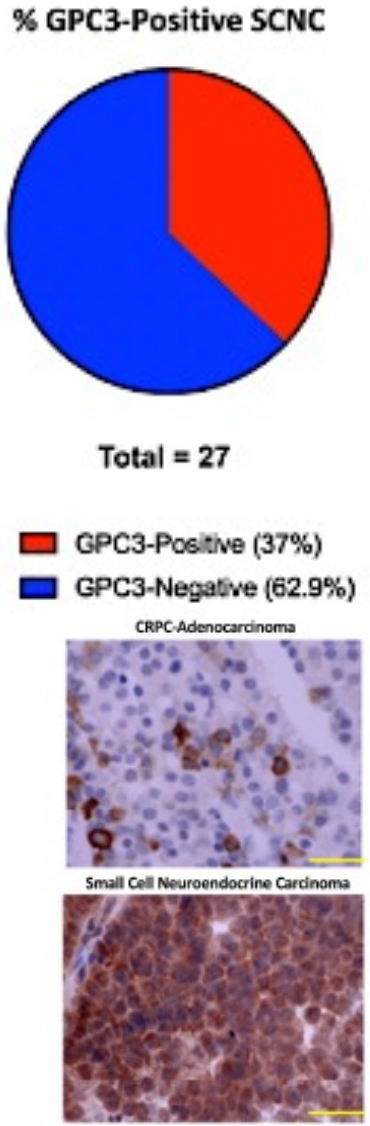
- J591-single dose phase I complete and “underway”
- PSMA TTC antibody-Th-227 complete
- Anti-HK2-Ac-225 Phase I underway
- IGF1R-Ac-225 Phase I underway
- J592 PSMA (Cu-64 imaging lead in)
- PSMA TTC Antibody-Ac-225 close

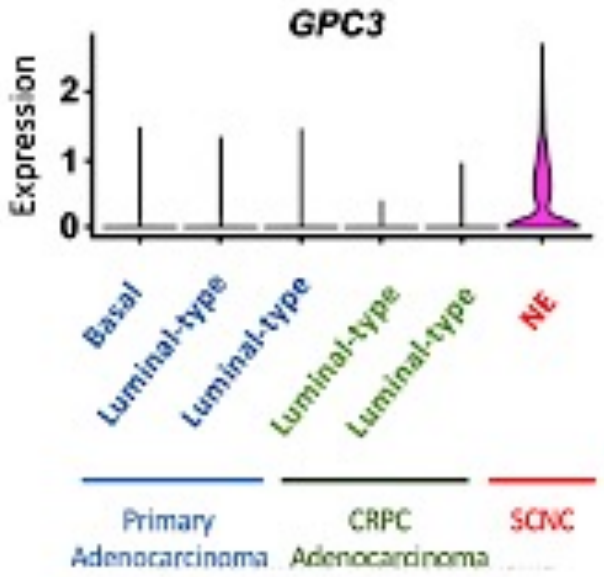
Small molecules

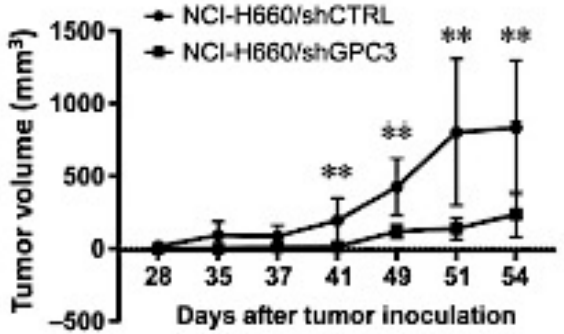
- PSMA-617-Ac-225 underway
- “PSMA I&T”-Ac-225 Phase I underway
- “PSMA albumin binder”-Ac-225 underway
- PNT2001 PSMA-Ac-225 close
- “PSMA albumin binder”-Ac-225 close
- PSMA NRG-001-Pb-212 close
- ADVC001-Pb-212 close
- PMI21-At-211 close

Radionuclide	Chelate	Half life	Total alpha	"Long lived" Intermediate	Final
Terbium-149	DOTA	4.1 hours	1 alpha		Nd-145
Astatine-211	Halogen chemistry	7.2 hours	1 alpha		Pb-207
Bismuth-212	C-DEPA/ DTPA/DOTA	61 minutes	1 alpha 1 beta		Pb-208
Lead-212	TCMC and more	10.6 hours	1 alpha 2 beta		Pb-208
Bismuth-213	C-DEPA/ DTPA/DOTA	46 minutes	1 alpha 2 beta		Bi-209
Radium-224	None	3.6 days	4 alpha	Lead-212	Pb-208
Actinium-225	DOTA and macropa, more	10.0 days	4 alpha 2 beta	Bismuth-213	Bi-209
Radium-223	None	11.4 days	4 alpha 2 beta		Pb-207
Thorium-227	DOTA	18.7 days	5 alpha	Radium-223	Pb-207

GPC3 as a novel target in NEPC





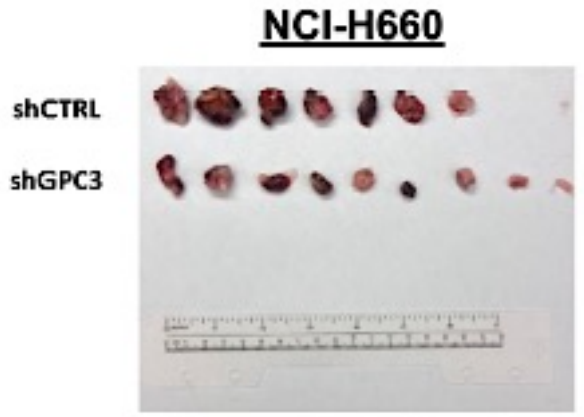


Journal of Pathology
J Pathol May 2023; **260**: 43–55
Published online 14 March 2023 in Wiley Online Library (wileyonlinelibrary.com) DOI: 10.1002/path.6063

ORIGINAL ARTICLE

Oncofetal protein glypican-3 is a biomarker and critical regulator of function for neuroendocrine cells in prostate cancer

William Butler[1], Lingfan Xu[1], Yinglu Zhou[2], Qing Cheng[3], J. Spencer Hauck[1], Yiping He[1,4], Robert Marek[1], Zachary Hartman[3,4,5], Liang Cheng[6], Qing Yang[7], Mu-En Wang[1], Ming Chen[1,4], Hong Zhang[1], Andrew J Armstrong[8,9] and Jiaoti Huang[1,9*]



PROSTATE CANCER FOUNDATION
PCF
CURING TOGETHER

2024 PCF Challenge:

Develop α-RLT vs GPC3 for NEPC!

Agenda

Module 1: Optimizing the Management of Nonmetastatic Prostate Cancer — Dr Dorff

Module 2: Evidence-Based Selection of Treatment for Metastatic Hormone-Sensitive Prostate Cancer — Dr Smith

Module 3: New Considerations with the Use of PARP Inhibitors for Metastatic Castration-Resistant Prostate Cancer (mCRPC) — Dr Agarwal

Module 4: Role of Novel Radiopharmaceuticals for mCRPC — Dr Armstrong

Module 5: Promising Investigational Approaches for Patients with Prostate Cancer — Dr Antonarakis

Consulting Faculty Comments

Use of novel hormonal agents with ADT or as monotherapy

Dr Spencer Bachow (Boca Raton, Florida)

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

What other novel therapies under development for metastatic prostate cancer do you believe hold the most therapeutic promise?

QUESTIONS FOR THE FACULTY

To what degree are you optimistic that immune checkpoint inhibition will play a role in the care of patients with metastatic prostate cancer beyond the small population with microsatellite instability-high disease?

Do you think the atezolizumab/cabozantinib regimen will be the one to cross the finish line?

QUESTIONS FOR THE FACULTY

Based on what we know from previous research efforts, do you believe capivasertib will eventually enter the treatment armamentarium for metastatic prostate cancer?

If so, do you anticipate that this agent will ultimately prove to be effective exclusively in patients with PTEN deficiency, or do you believe it will more likely demonstrate antitumor activity in a broader patient population?

Research To Practice

June 1, 2024

Promising Investigational Agents for Patients with Advanced Prostate Cancer

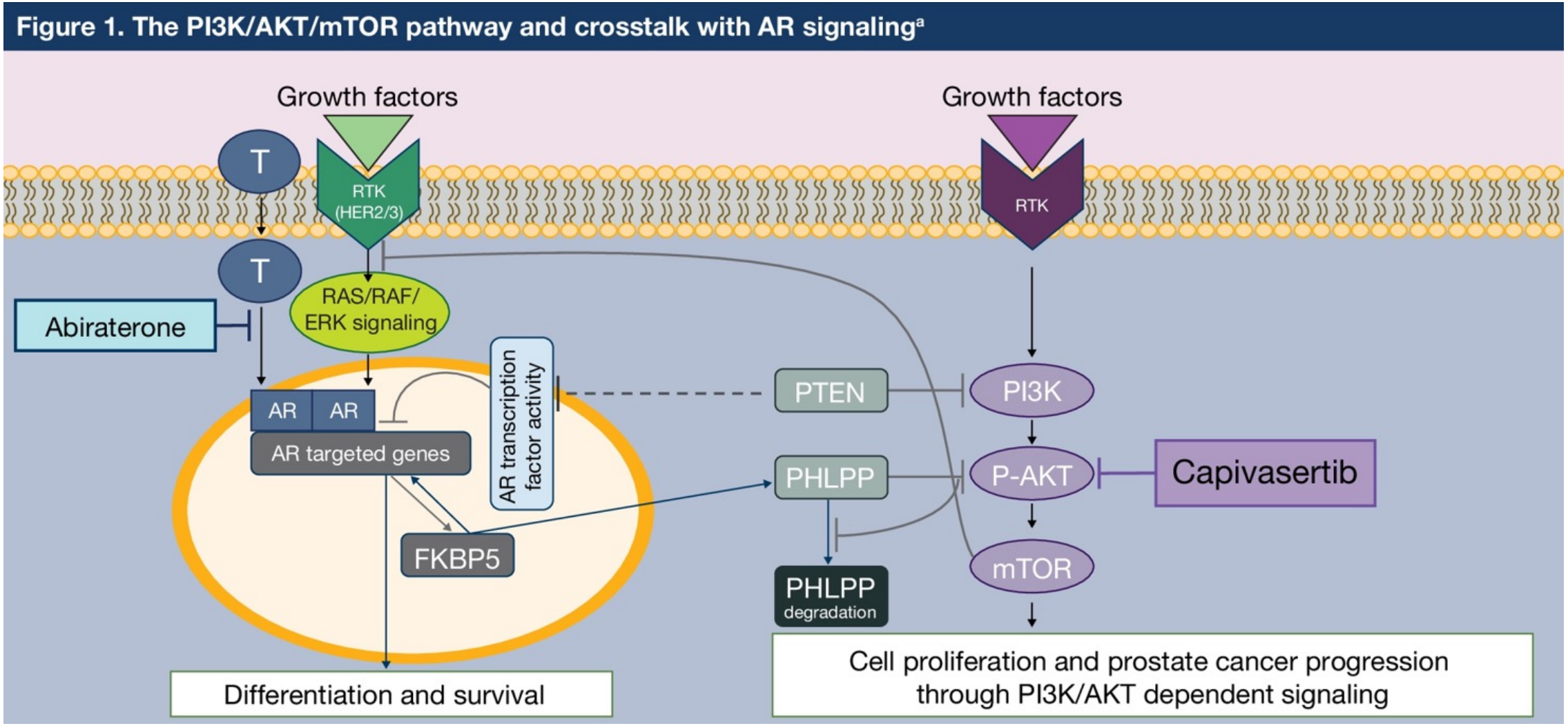
Emmanuel S. Antonarakis, M.D.
Clark Endowed Professor of Medicine
Division of Hematology/Oncology & Transplantation, University of Minnesota
Associate Director of Translation, Masonic Cancer Center

Outline

- PI3K-AKT-mTOR pathway: Ipatasertib and capivasertib
- TKI/IO combinations: Cabozantinib plus atezolizumab
- CYP11 inhibition: Opevesostat
- AR-targeting PROTACs: Bavdegalutamide, ARV-766, BMS-986365
- Antibody-drug conjugates (ADCs): Vobramitamab duocarmazine
- Bispecific immune engagers: Xaluritamig

PI3K-AKT-mTOR pathway: Ipatasertib and capivasertib

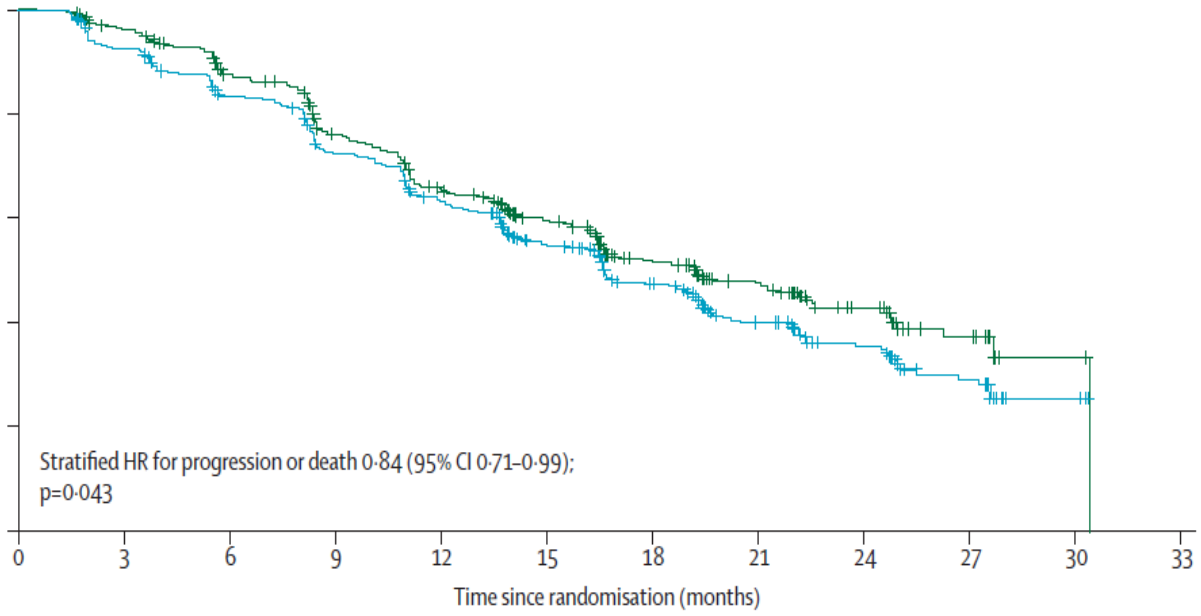
Reciprocal pathways: AR and PI3K



Ph-3 IPATential150 trial: Abi +/- Ipatasertib

PFS – Intention to Treat

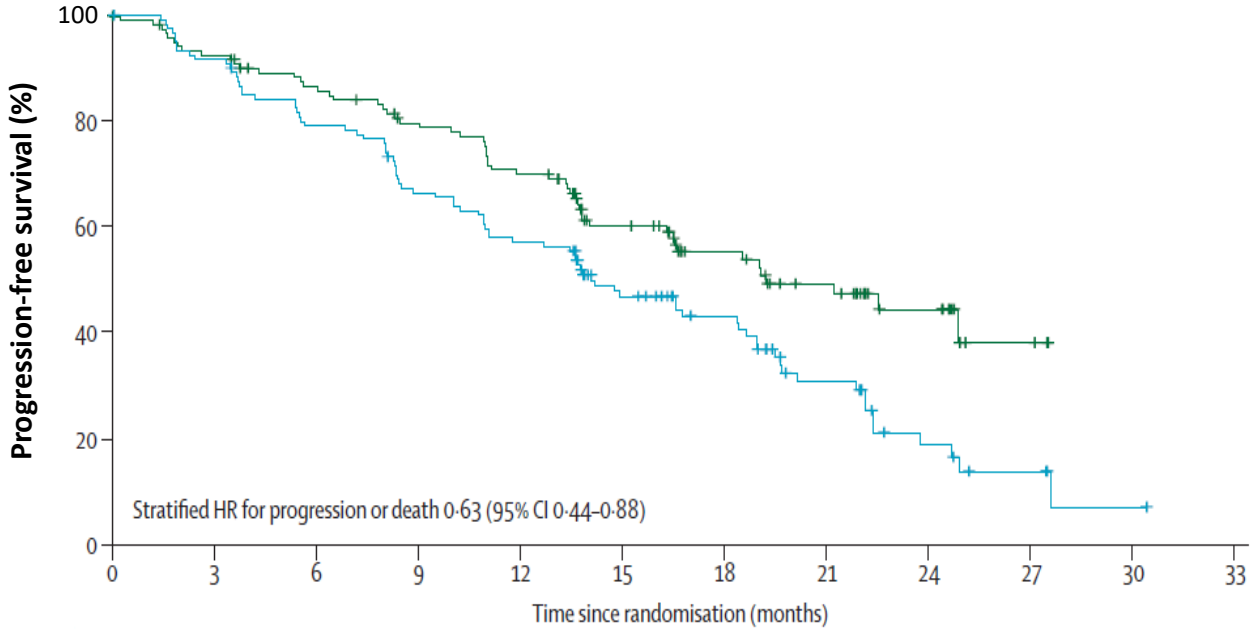
	Events, n	Patients, N	Median progression-free survival, months (95% CI)	Progression-free survival at 1 year since randomisation, % (95% CI)
Placebo–abiraterone group	306	554	16·6 (15·6–19·1)	63·0% (58·9–67·1)
Ipatasertib–abiraterone group	252	547	19·2 (16·5–22·3)	65·3% (61·1–69·5)



PFS – *PIK3CA/AKT/PTEN* altered

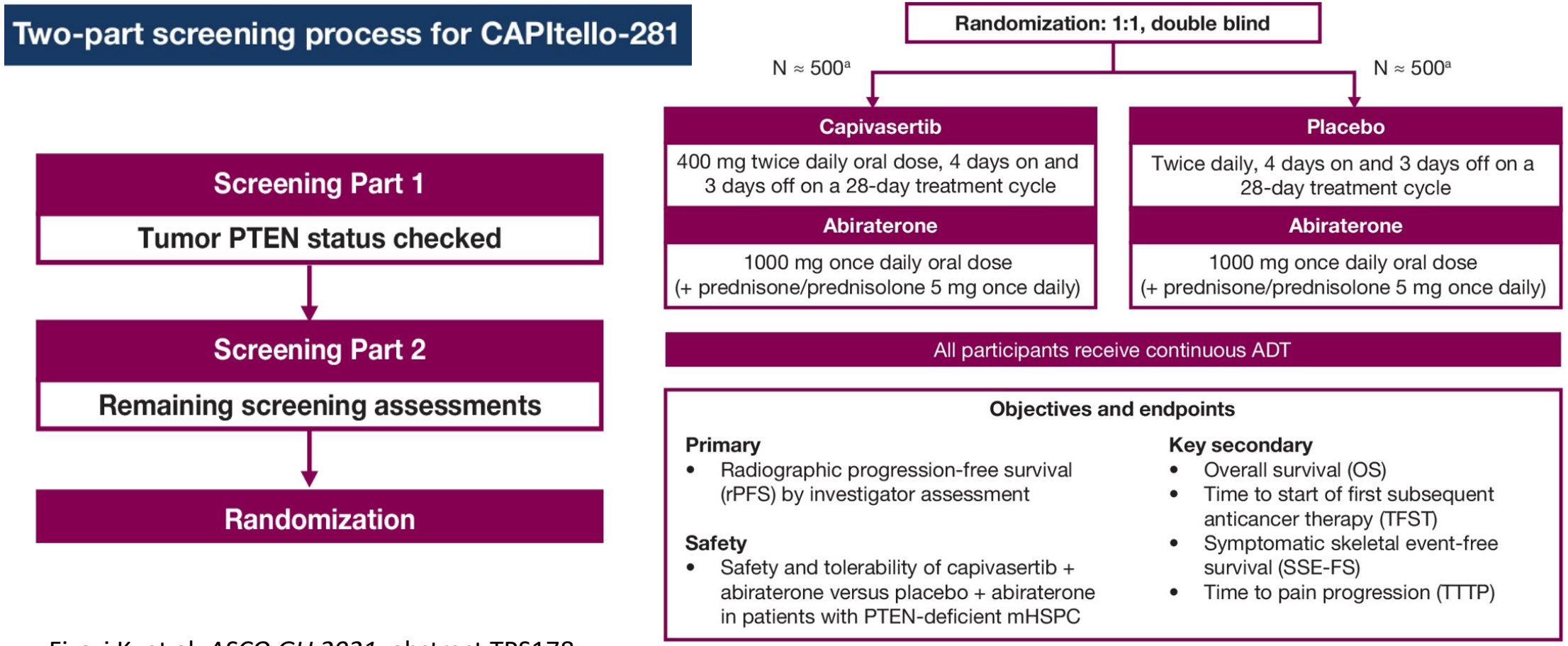
B

	Events, n	Patients, N	Median progression-free survival, months (95% CI)
Placebo–abiraterone group	83	122	14·1 (11·1–18·4)
Ipatasertib–abiraterone group	56	128	19·3 (16·4–NE)



Sweeney C, et al. *Lancet 2021*; 398:131-142.

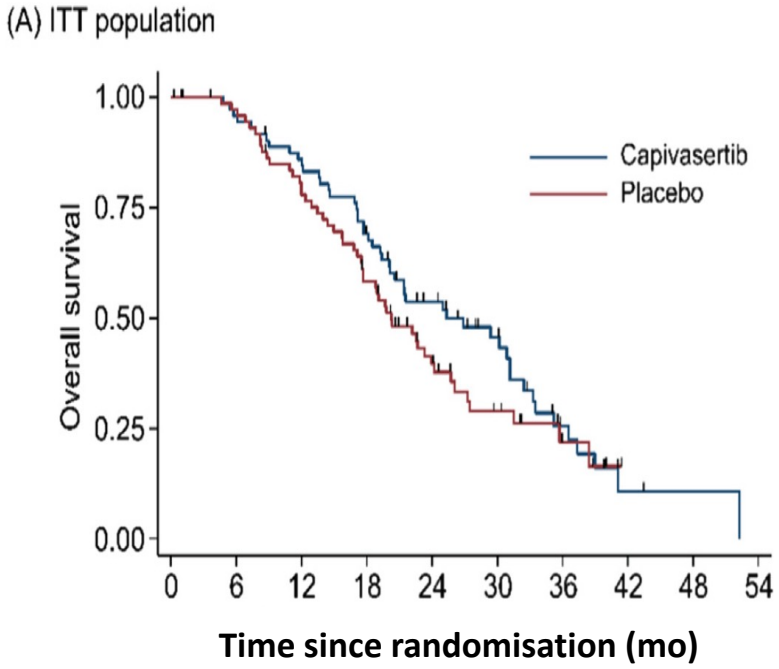
Ph3 CAPItello-281: Abi +/- Capivasertib (mHSPC)



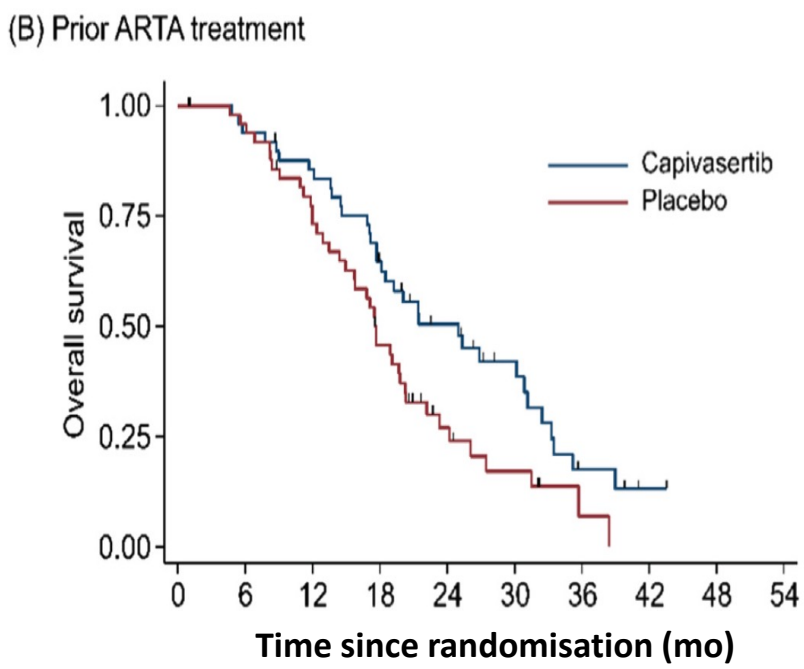
Fizazi K, et al. *ASCO GU 2021*; abstract TPS178.

Ph-2 ProCAID trial: Doce +/- Capivasertib

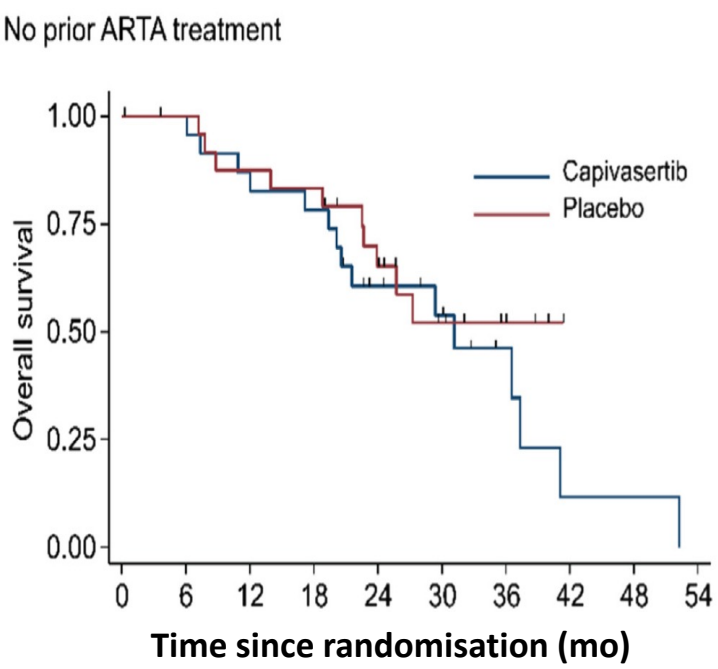
OS – ITT



OS – *Prior* ARPI



OS – *No prior* ARPI



Crabb SJ, et al. *European Urology 2022*; 82: 512-515.

Ph3 CAPItello-280: Doce ± Capivasertib (mCRPC)

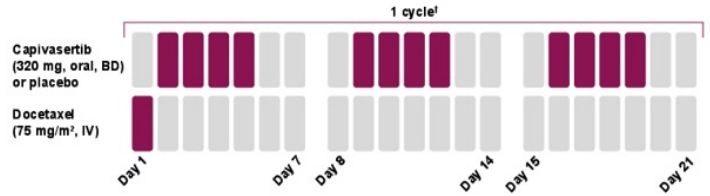
Key inclusion criteria

- Adults ≥18 years of age with metastatic CRPC
- No prior chemotherapy for metastatic CRPC
- Prior ARTA (abiraterone, enzalutamide, apalutamide, or darolutamide) for HSPC or CRPC for at least 3 months and evidence of disease progression (radiological or via PSA assessment) whilst on treatment
- Serum testosterone level ≤50 ng/dL
- Eligible for docetaxel treatment (investigator assessment)
- Ongoing ADT
- ECOG PS 0 or 1

N≈790 randomized 1:1*

Capivasertib (320 mg orally, BD, 4 days on, 3 days off) plus docetaxel (75 mg/m² IV on Day 1 of each 21-day cycle for 6–10 cycles)†

Schedule of each 21-day dosing cycle



Matching placebo (320 mg orally, BD, 4 days on, 3 days off) plus docetaxel (75 mg/m² IV on Day 1 of each 21-day cycle for 6–10 cycles)†

Study endpoints

Primary

- **OS** defined as the time from randomization until the date of death due to any cause

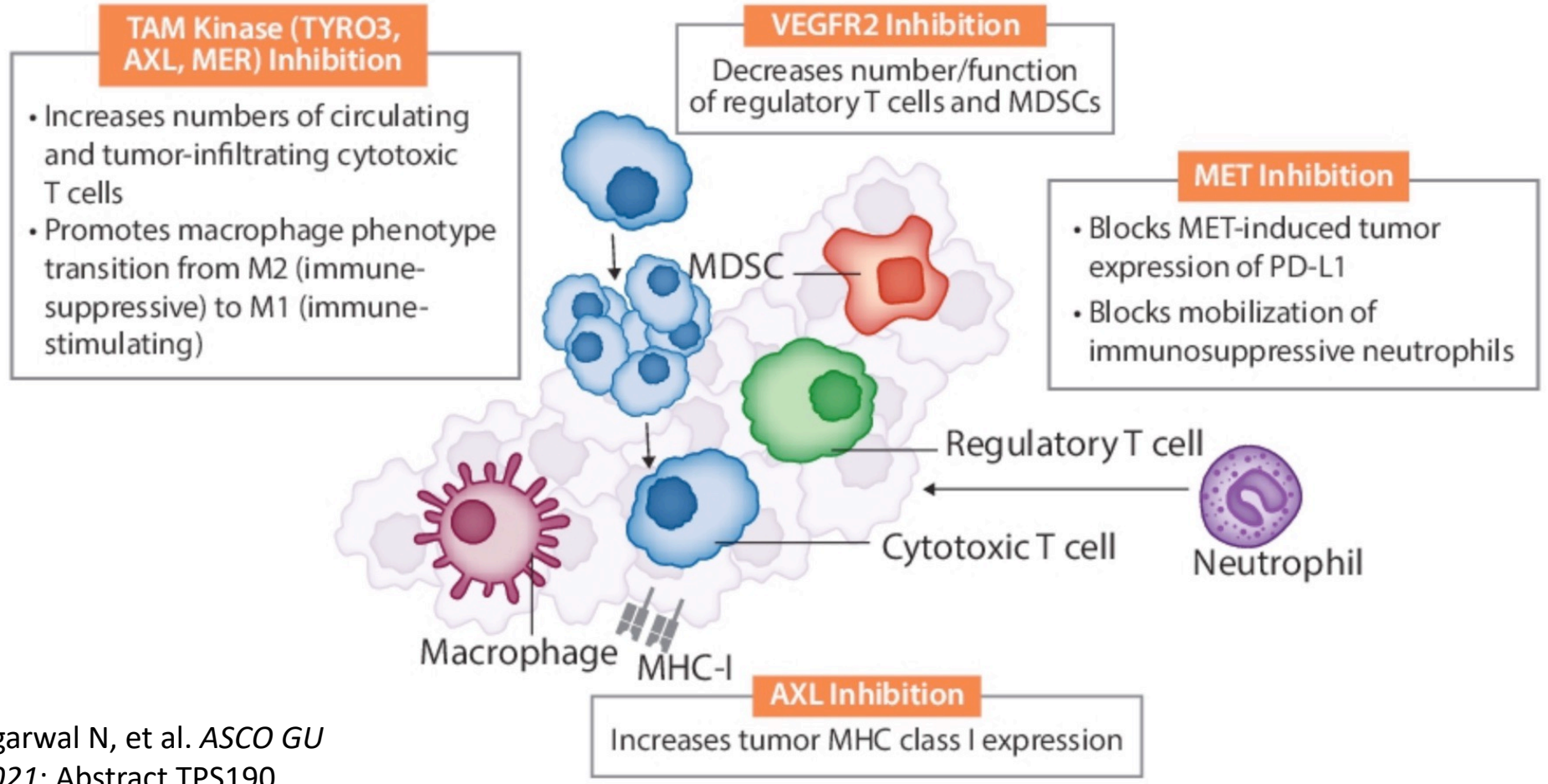
Secondary

- **rPFS** defined as the time from randomization to radiographic progression according to RECIST v1.1 or PCWG3 criteria (investigator-assessed)
- **TTPP** defined as the time from randomization to clinically meaningful pain progression (2-point increase from baseline in BPI-SF Item 3 'worst pain' and/or the initiation of, or increase in, opioid use)
- **SSRE** defined as the time from randomization to use of radiation therapy for skeletal symptoms, new symptomatic pathological bone fractures, spinal cord compression, or surgical intervention for bone metastasis
- **Safety and tolerability**
- **Patient-reported outcomes** including physical functioning, urinary symptoms, pain, and HRQoL
- **Pharmacokinetic analysis**

Crabb SJ, et al. *ASCO GU 2023*; abstract TPS287.

TKI/IO combinations: Cabozantinib plus atezolizumab

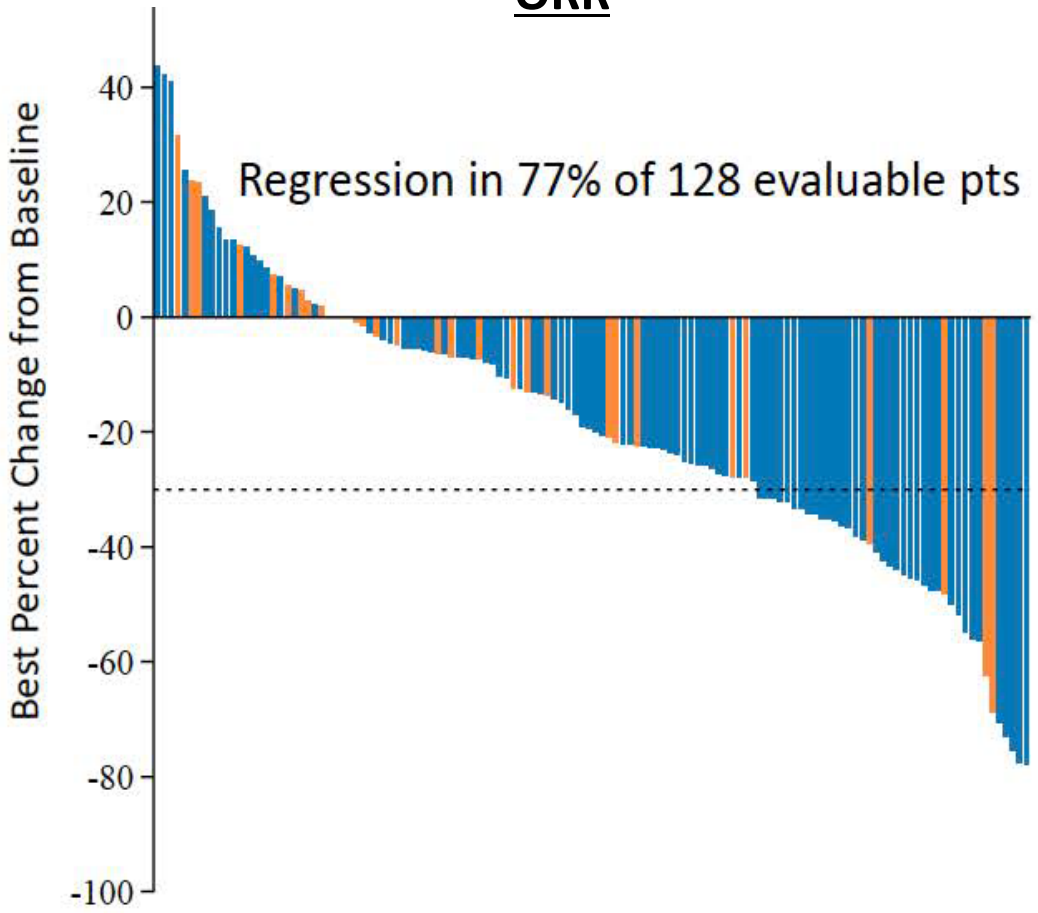
Cabozantinib + Atezo: *Rationale*



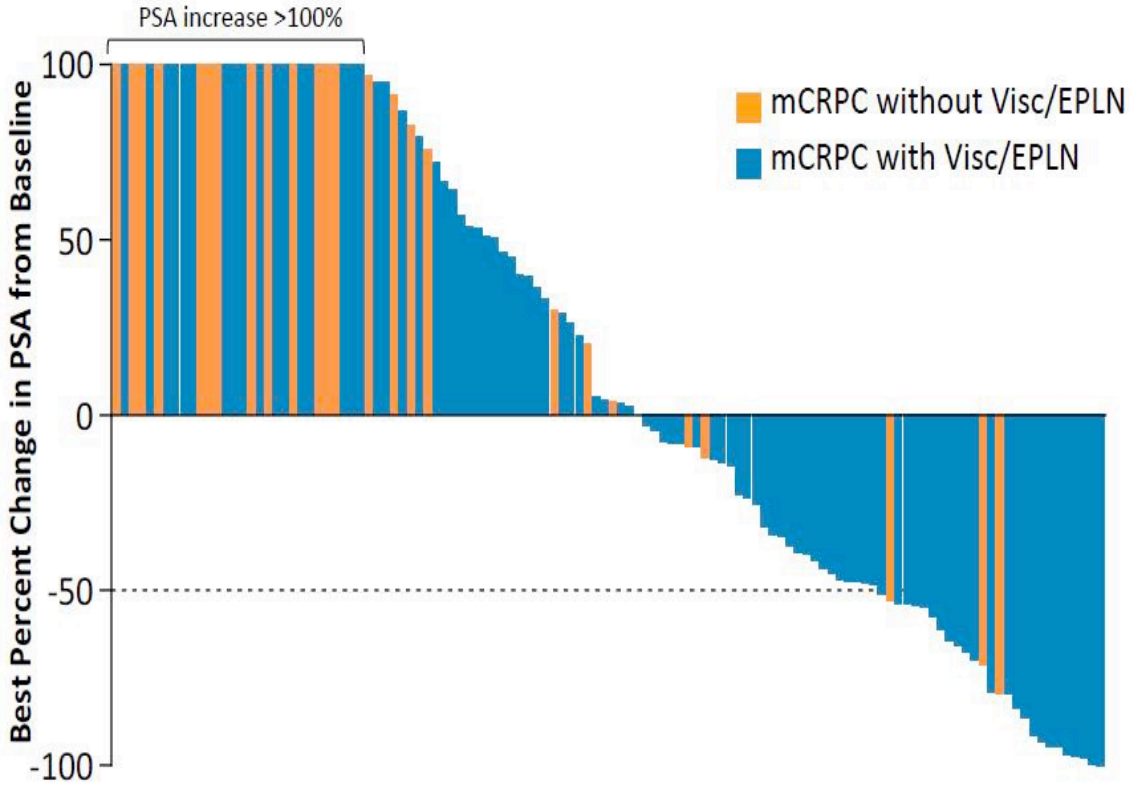
Agarwal N, et al. *ASCO GU 2021*; Abstract TPS190.

COSMIC-021: ORR and PSA response

ORR

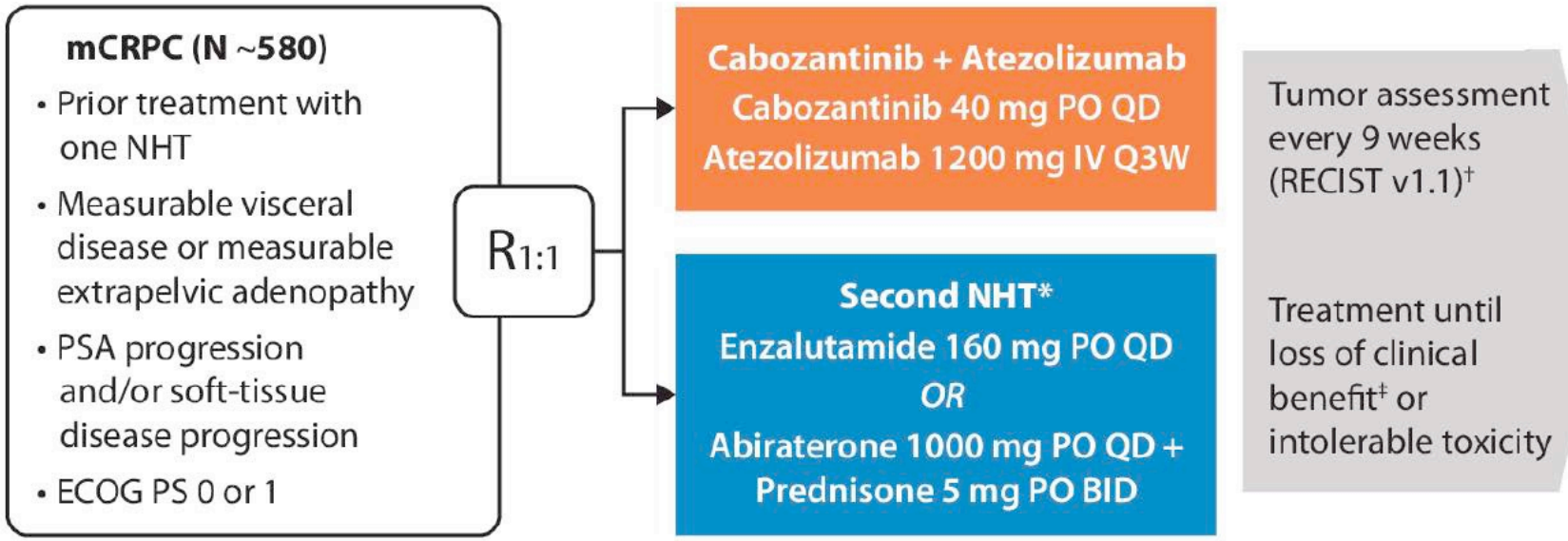


PSA_{50} Response



Agarwal N, et al. *ESMO 2021*; Abstract LBA24; Agarwal N, et al. *Lancet Oncol* 2022;23:899-909.

CONTACT-02: Phase III Trial Schema



Stratification

- Liver metastasis (yes, no)
- Prior docetaxel treatment for mCSPC (yes, no)
- Disease stage for which the first NHT was given (mCSPC, M0 CRPC, mCRPC)

Primary Endpoints:

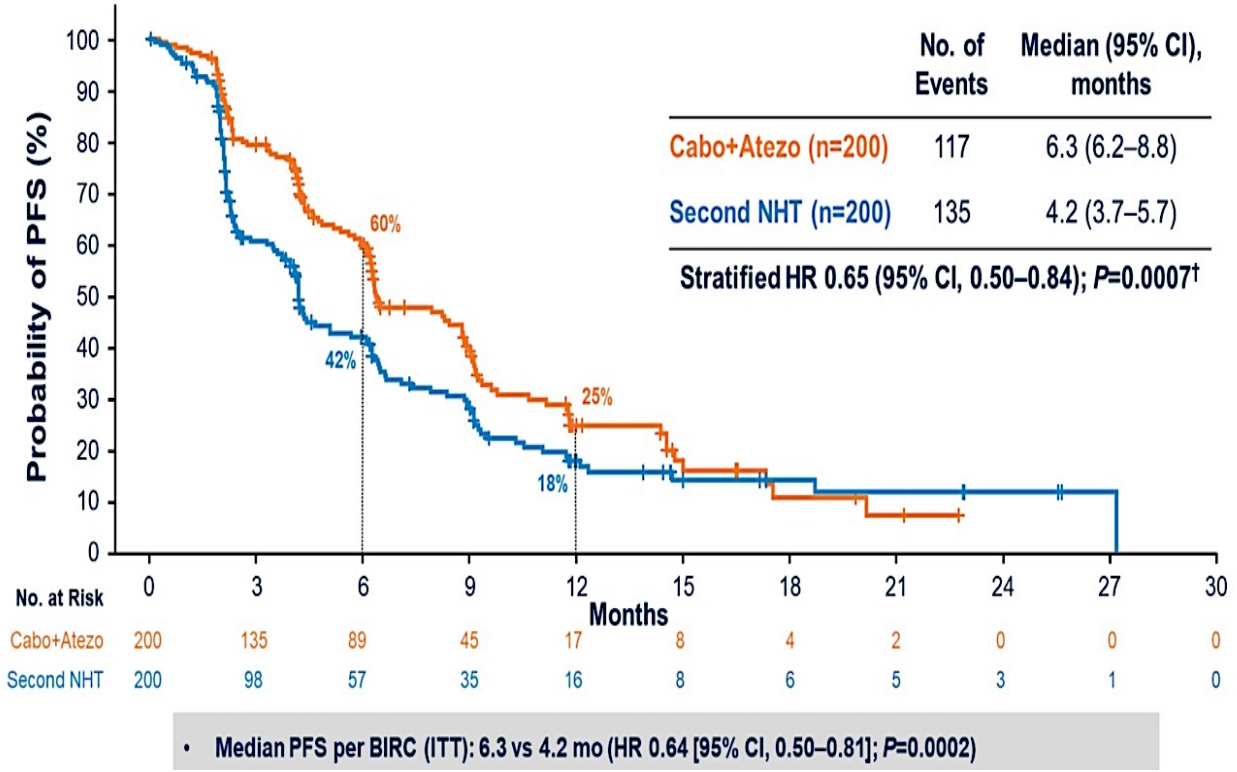
- PFS per RECIST v1.1 by BIRC
- OS

Secondary Endpoint:

- ORR per RECIST v1.1 by BIRC

Agarwal N, et al. *ASCO GU Symposium 2021*; Abstract TPS190.

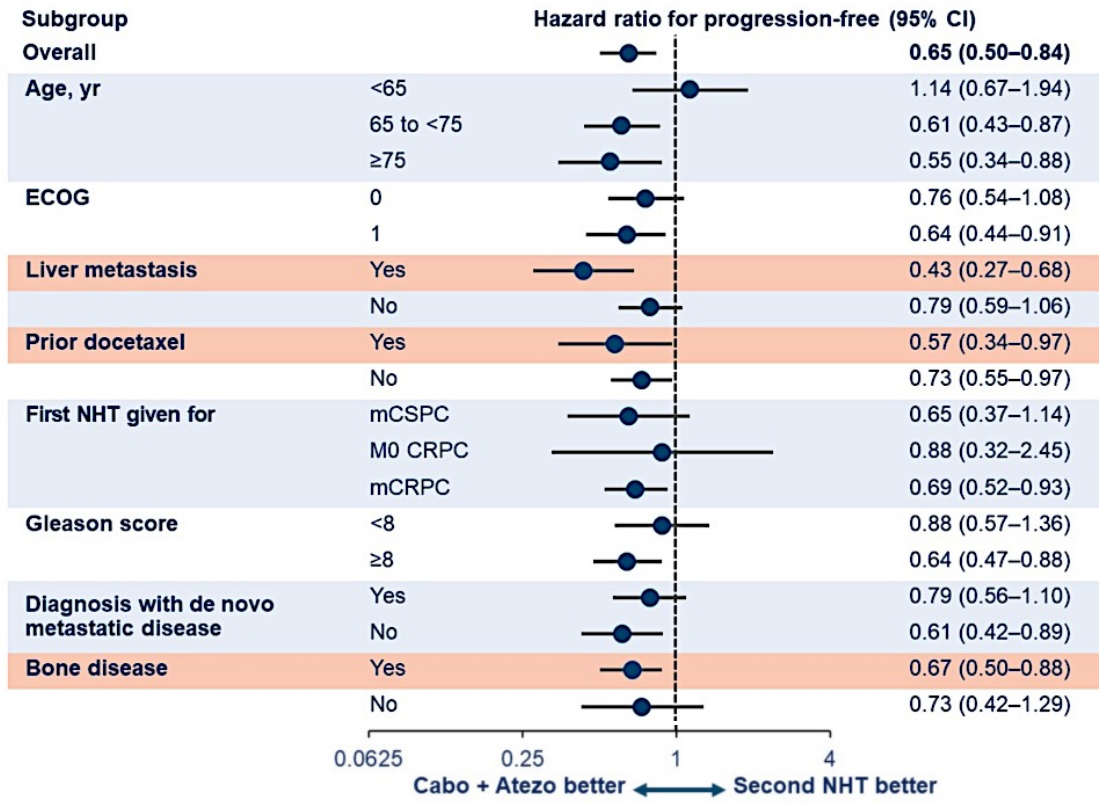
CONTACT-02: PFS Results (OS immature)



	No. of Events	Median (95% CI), months
Cabo+Atezo (n=200)	117	6.3 (6.2–8.8)
Second NHT (n=200)	135	4.2 (3.7–5.7)

Stratified HR 0.65 (95% CI, 0.50–0.84); *P*=0.0007†

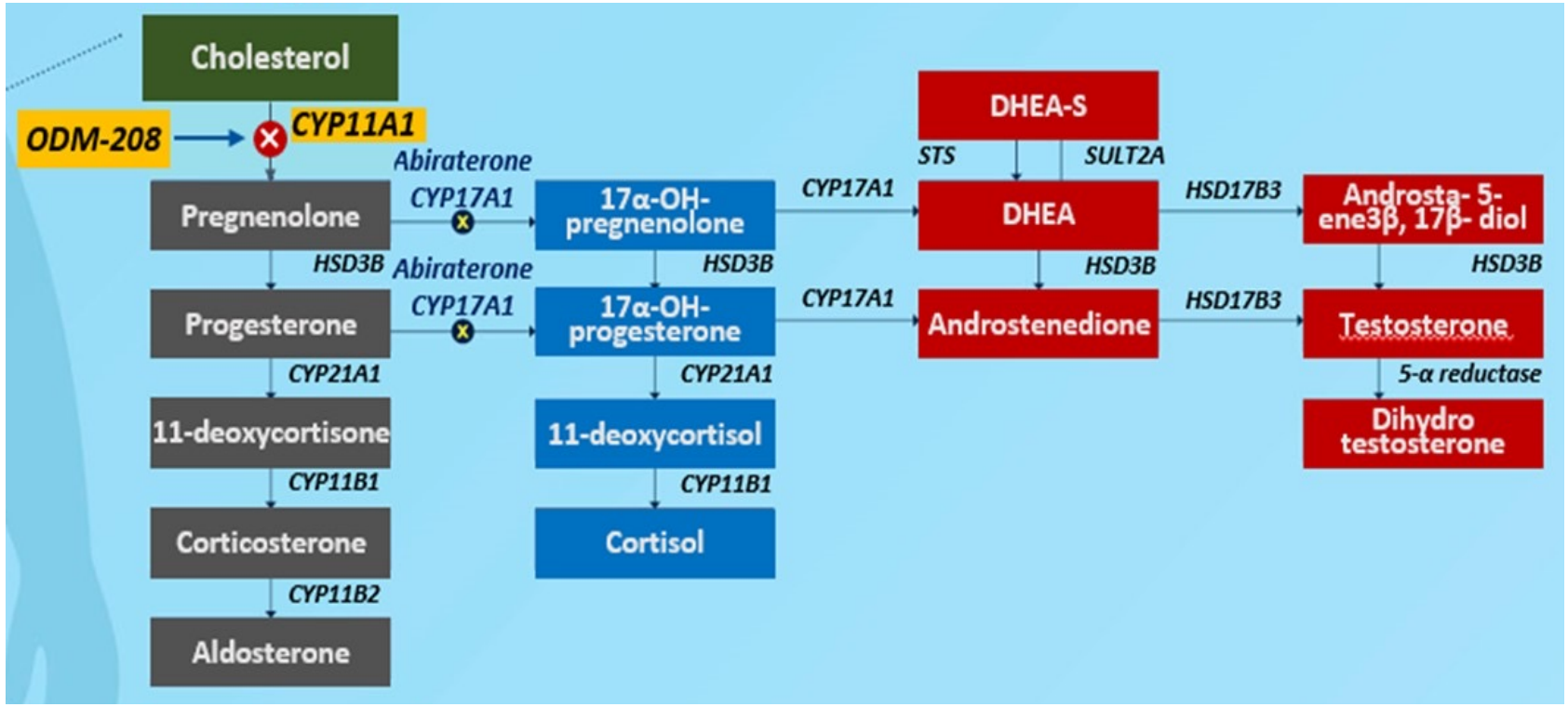
- Median PFS per BIRC (ITT): 6.3 vs 4.2 mo (HR 0.64 [95% CI, 0.50–0.81]; *P*=0.0002)

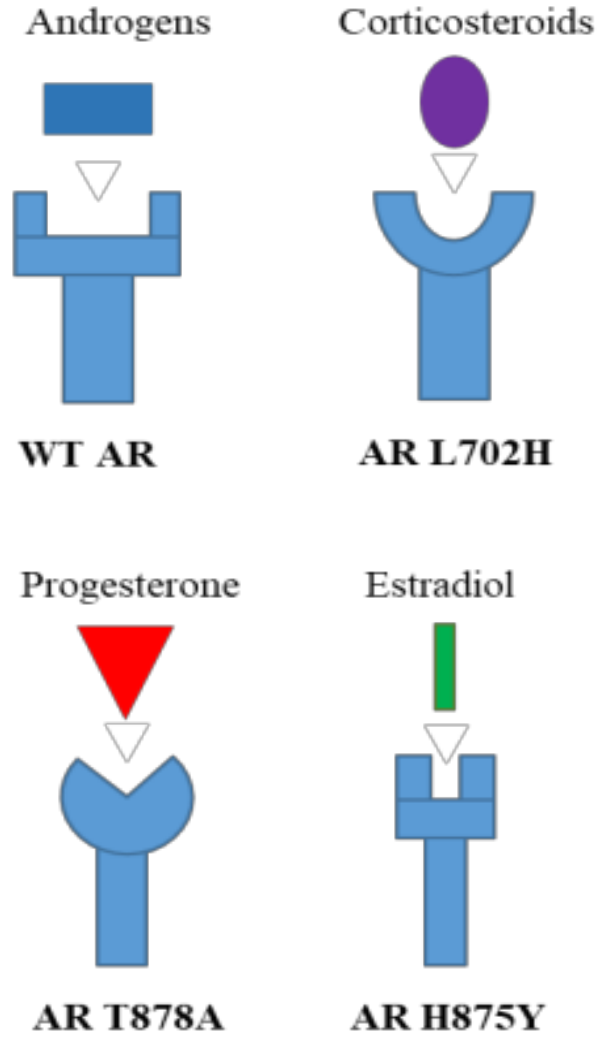


Agarwal N, et al. *ASCO GU Symposium 2024*; Abstract 18.

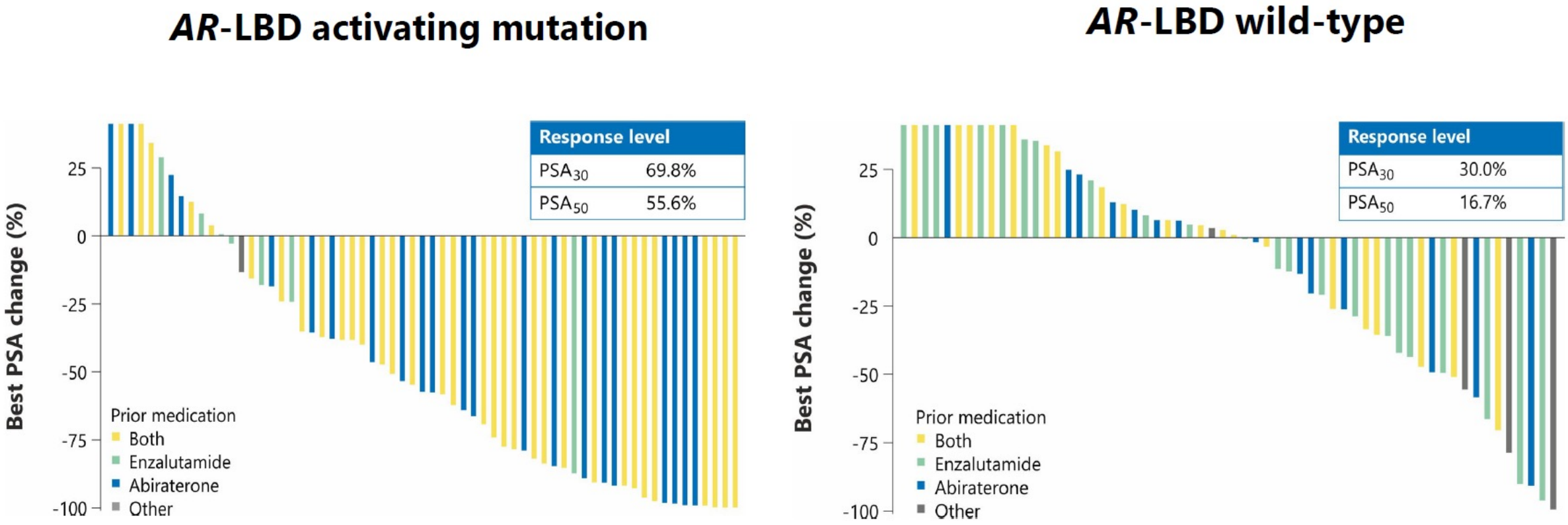
CYP11 inhibition: Opevesostat

ODM-208 → MK-5684 → Opevesostat



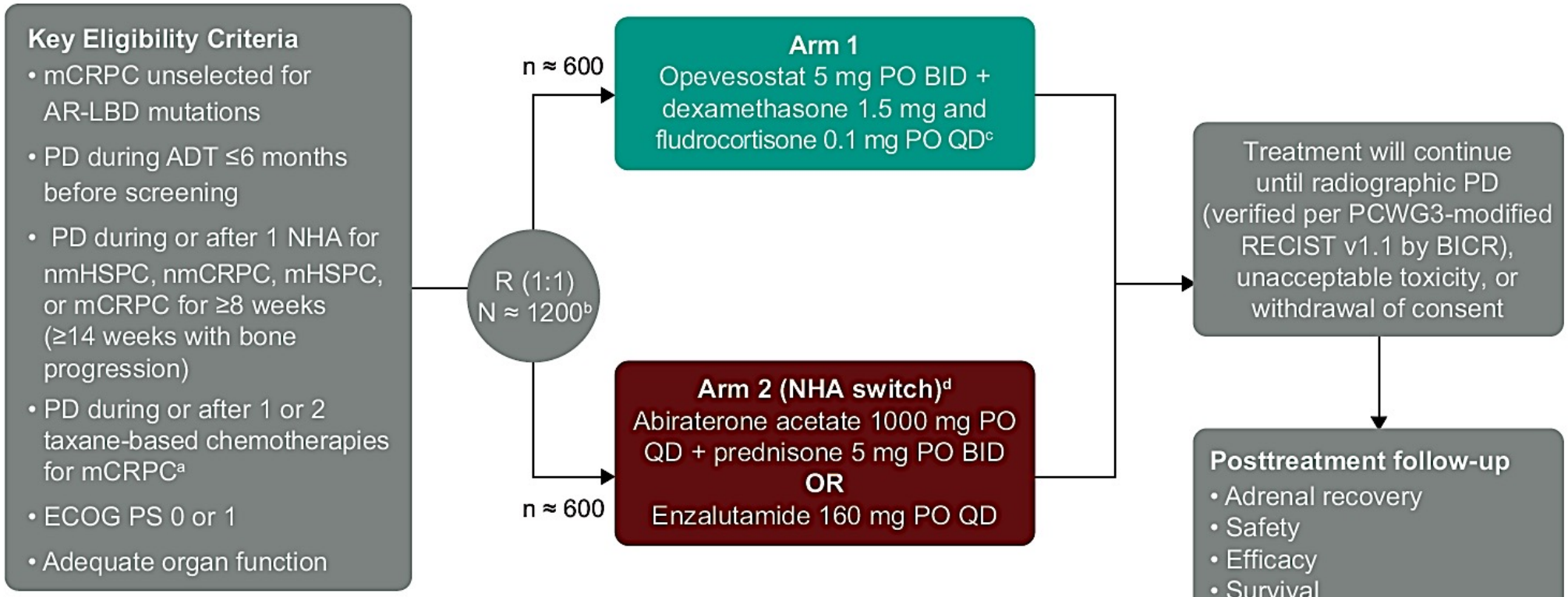


Opevesostat: Phase 2 CYPIDES trial



Fizazi K, et al. *NEJM Evid.* 2024;3:EVIDoa2300171; Fizazi K, et al. ASCO GU 2024; abstract 159.

Opevesostat (MK-5684): Phase 3 trial

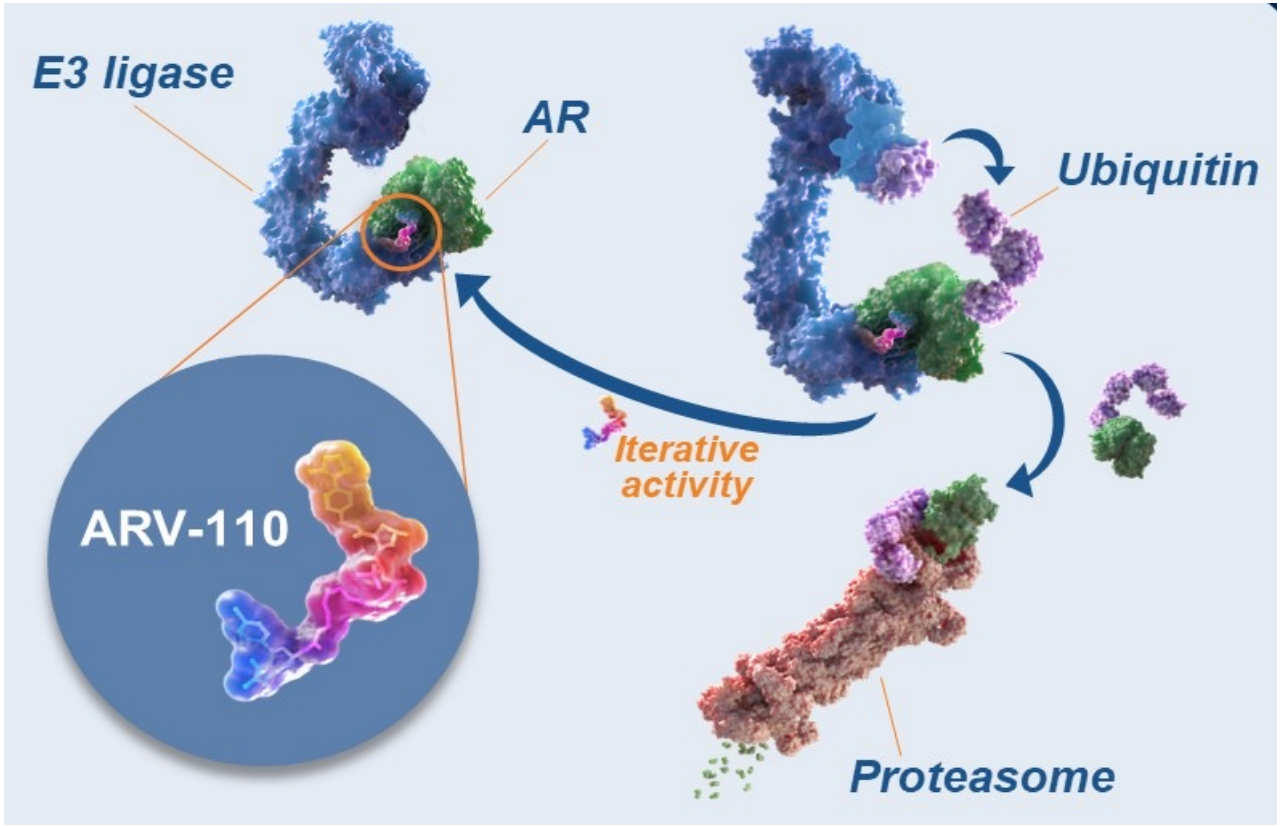


Stratification
- Measurable disease (yes vs no)
- AR-LBD mutation status[e] (positive vs negative)
- Prior cabazitaxel use (yes vs no)

Yu EY, et al. ASCO 2024; abstract TPS5113.

AR-targeting PROTACs: Bavdegalutamide, ARV-766, BMS-986365

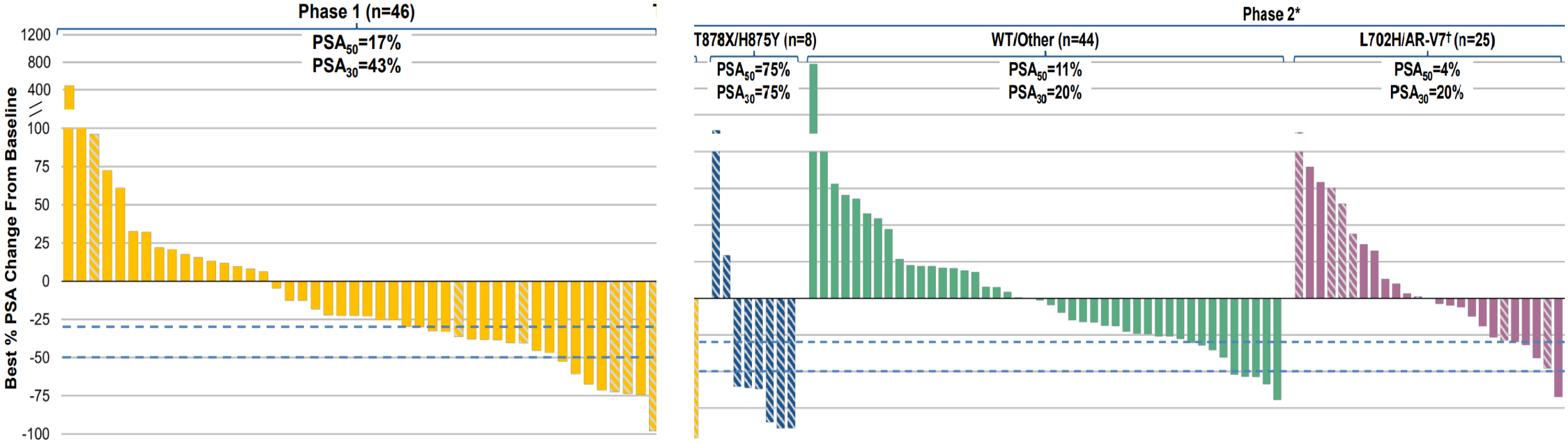
ARV-110: AR-directed PROTAC (*Bavdegalutamide*)



Gao X, et al. *ASCO GU 2022*; Abstract 17.

Phase 1 trial

Phase 2 trial



Gao X, et al. *ASCO GU 2022*; Abstract 17.

ARV-766: Phase 2 trial

Figure 2: Trial schema

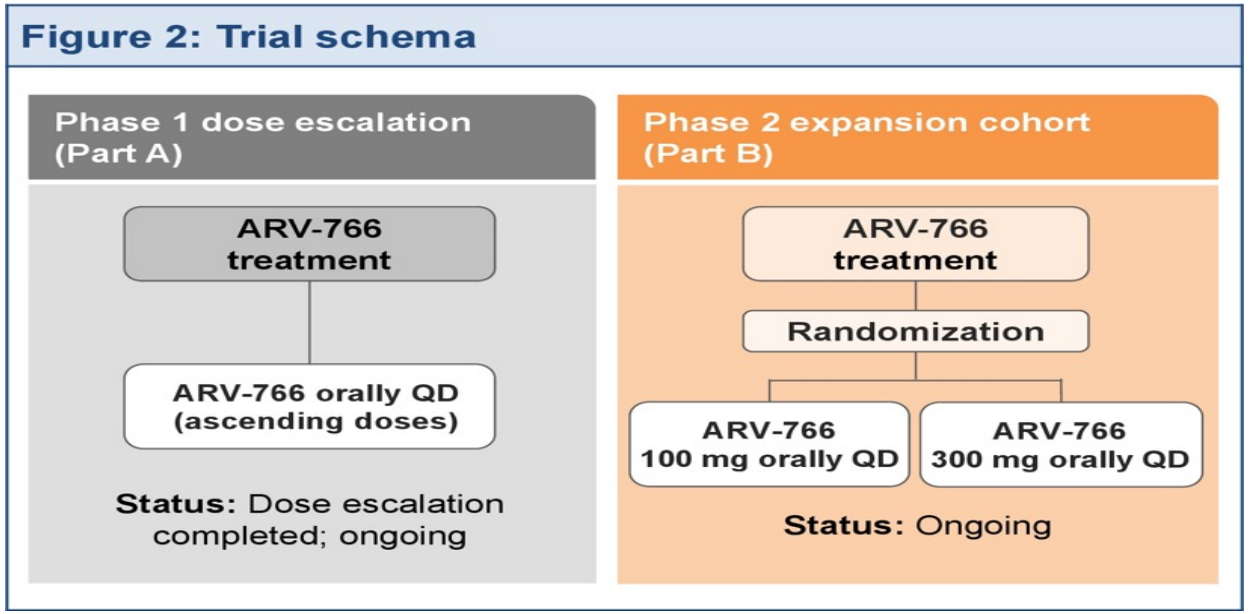


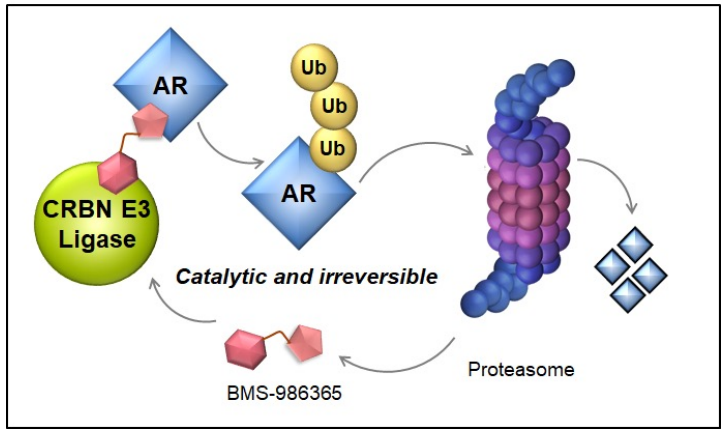
Table 2: Outcome measures[a]

Primary objective	Endpoints
• Evaluate the antitumor activity of ARV-766	• ORR (RECIST) • PSA_{30} rate • PSA_{50} rate
Secondary objective	**Endpoint**
• Evaluate the safety and tolerability of ARV-766	• Frequency and severity of adverse events and laboratory abnormalities

Petrylak D, et al. *ASCO 2023*, abstract TPS290; Petrylak D, et al. *ASCO 2024*, abstract 5011.

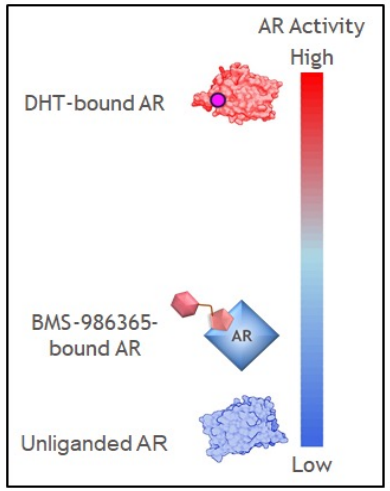
BMS-986365: Phase 1 trial

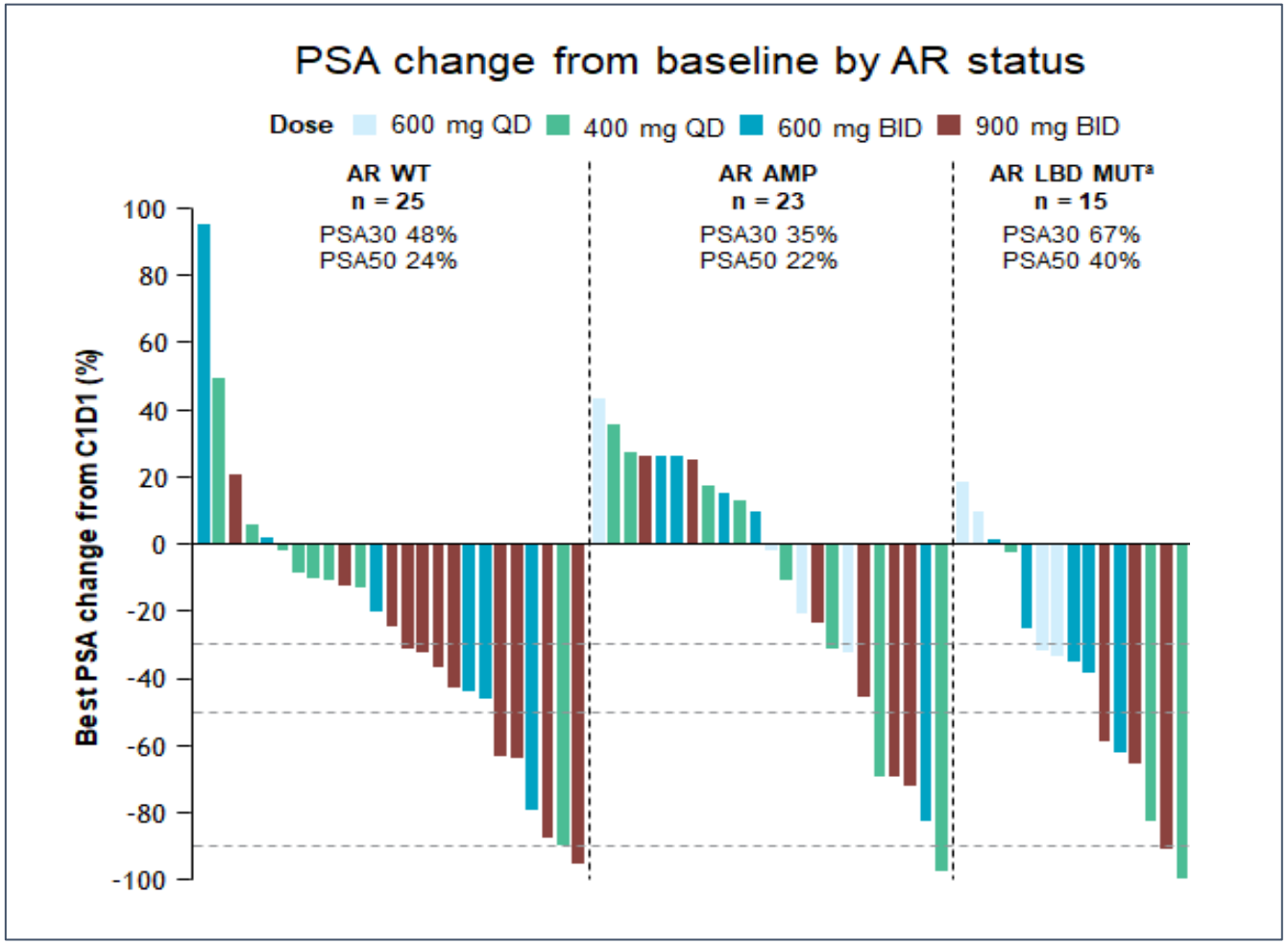
AR degradation
Primary driver of efficacy



+

AR antagonism
Important additional MoA



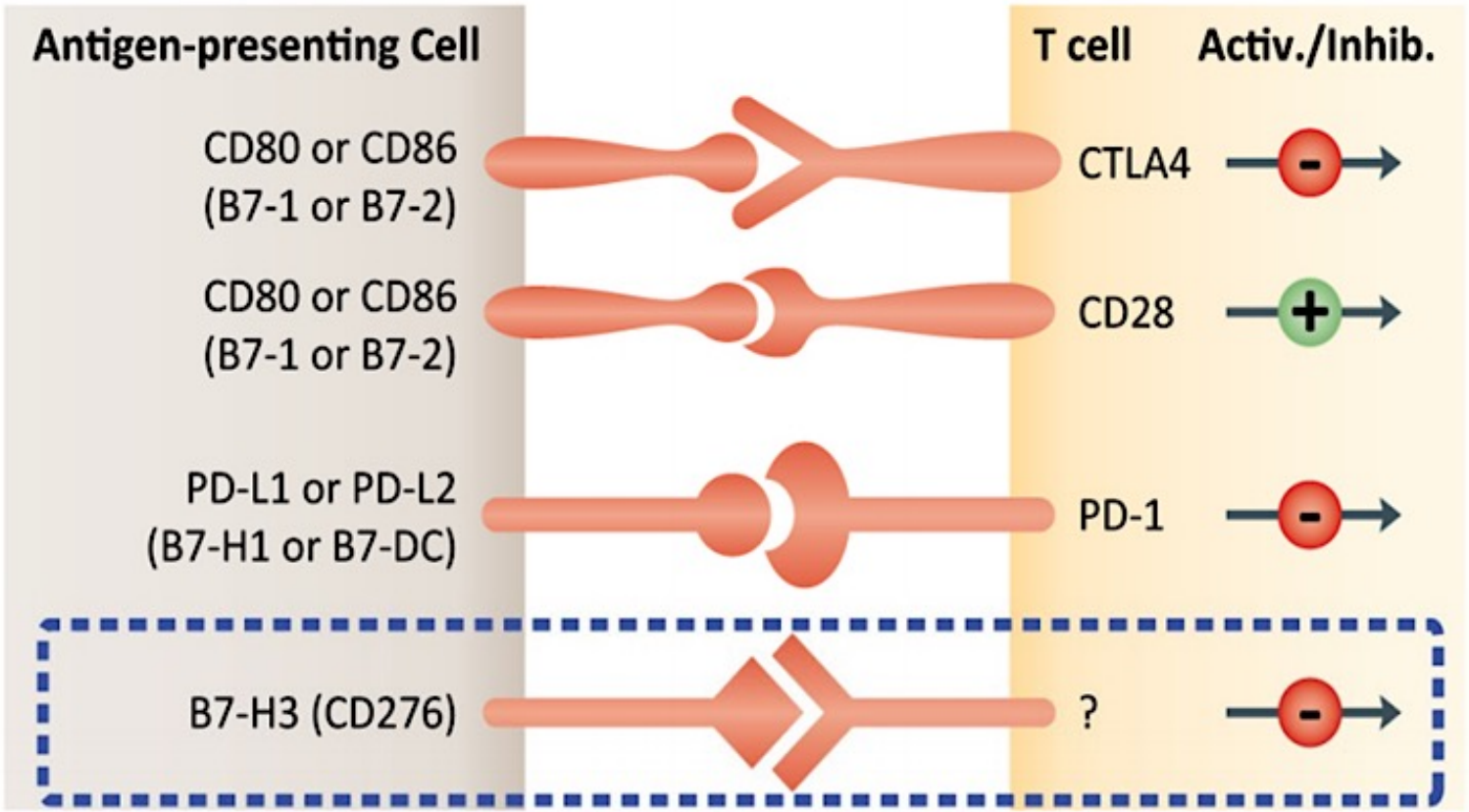


Rathkopf D, et al. *ASCO GU 2024*, abstract 134.

Antibody-drug conjugates (ADCs):

e.g. Vobramitamab duocarmazine

B7-H3: Member of B7 family of checkpoints

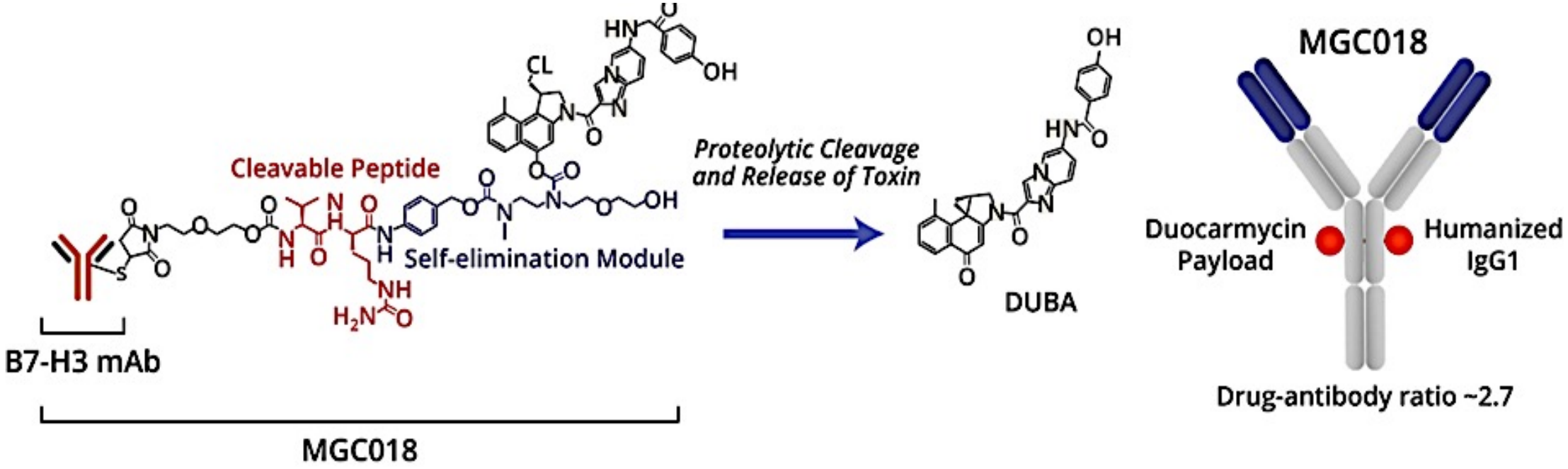


Expressed by 85-90% of prostate cancers (higher expression in mCRPC than in localized PCa).

Pardoll D, *et al. Nature 2012*.

MGC018 is a B7-H3–directed ADC

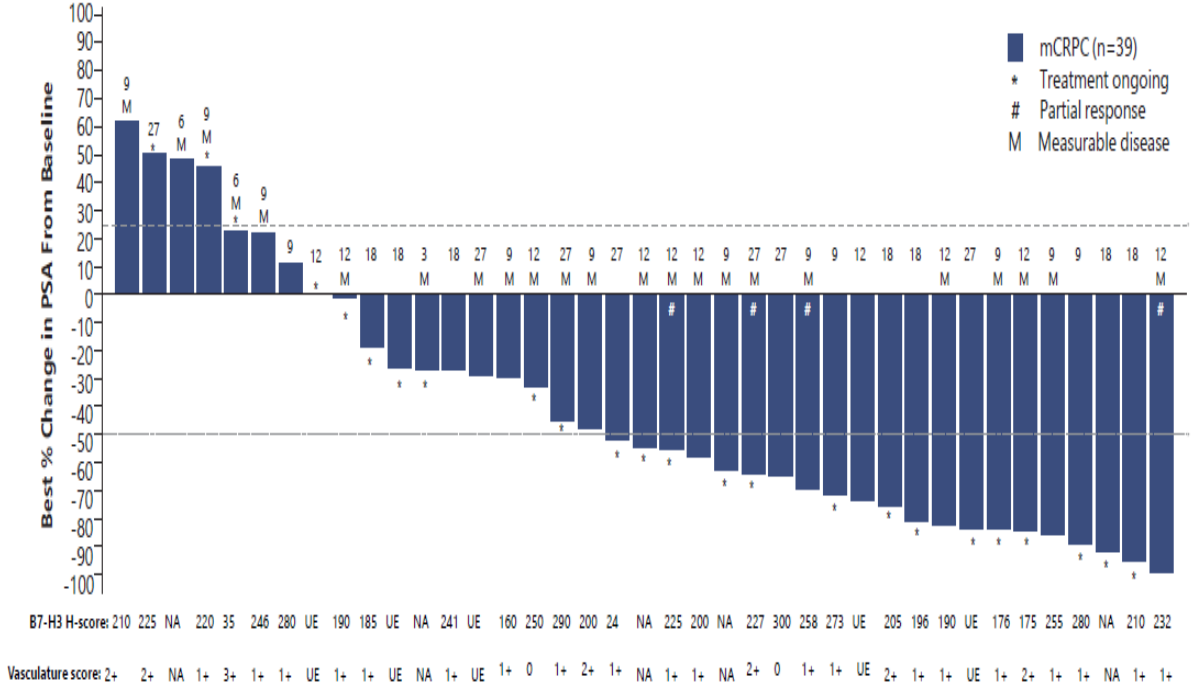
Vobramitamab duocarmazine

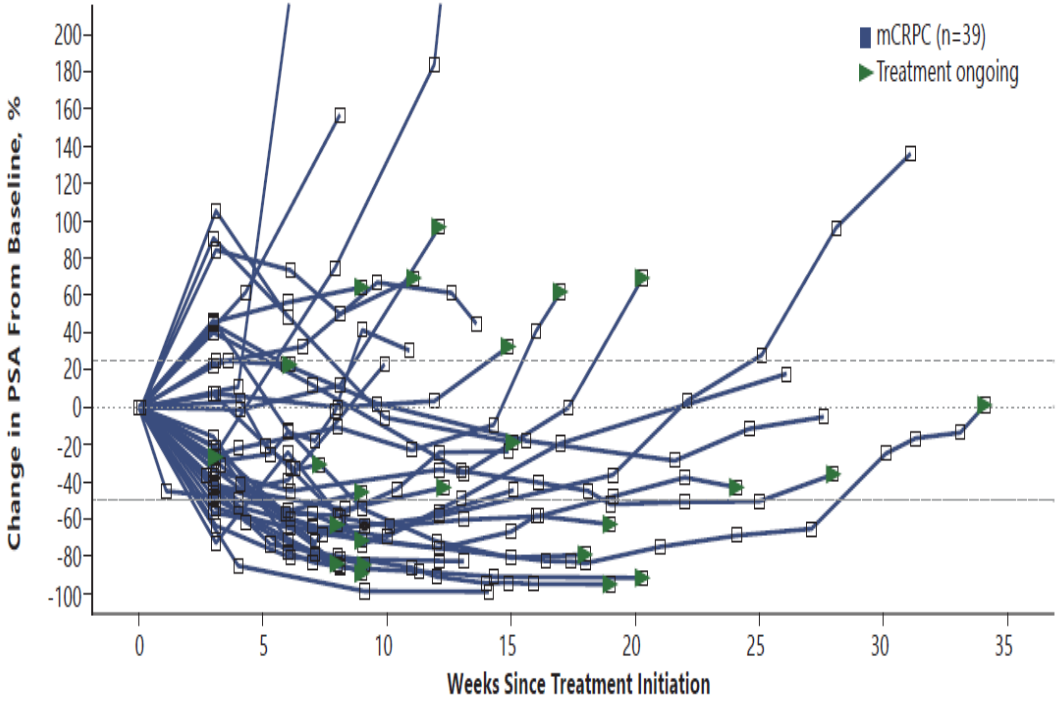


Jang S, *et al.* J Clin Oncol 39; 2021 (ASCO abstract 2631).

MGC018 clinical trial: Phase 2a Expansion

- In mCRPC cohort, 39 patients were evaluable for PSA response:
  - Twenty-one of 39 patients (53.8%) had reductions in PSA from baseline of more than 50%
  - Twenty-four of 39 patients (61.5%) remained on treatment



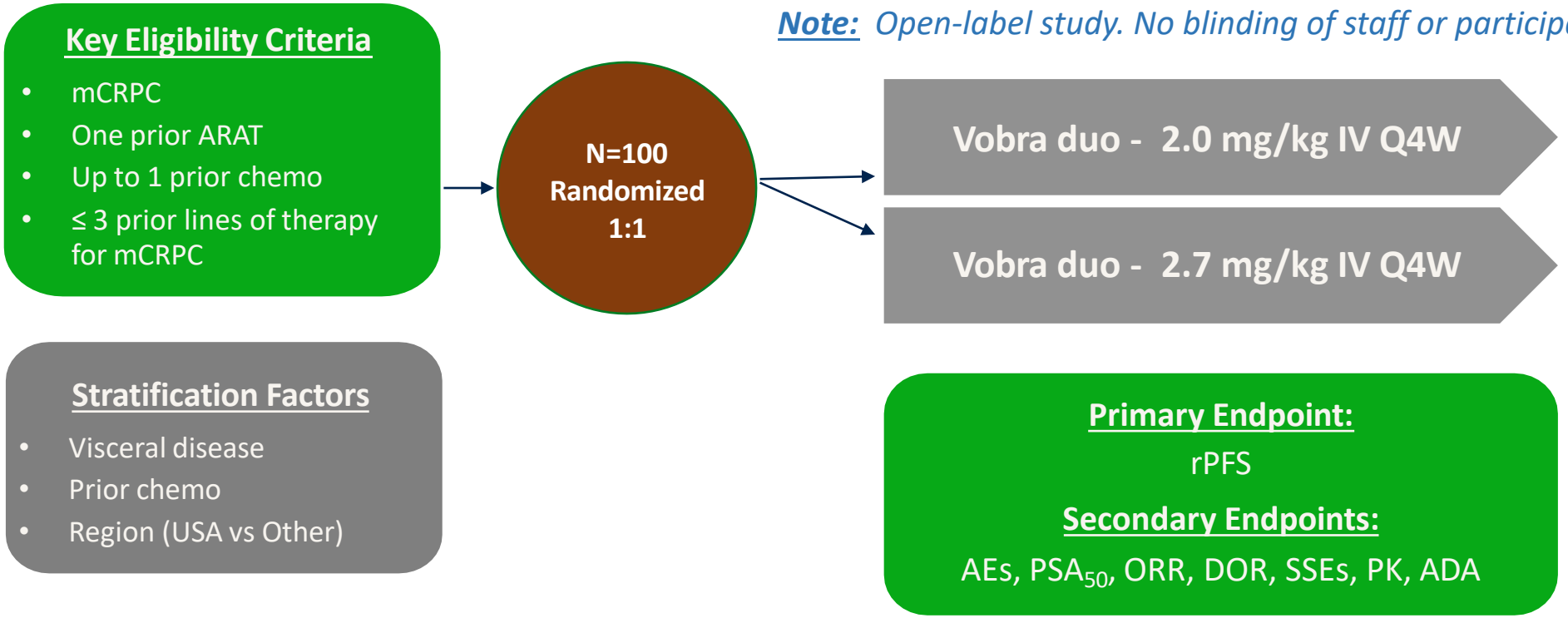


Shenderov E, *et al.* ESMO 2021 (abstract #620P).

TAMARACK trial: *Vobramitamab duocarmazine*

CP-MGC018-03: Phase 2, Randomized, Open-Label Study of Two Dose Levels of Vobramitamab Duocarmazine in Men with Metastatic Castration-Resistant Prostate Cancer

Note: *Open-label study. No blinding of staff or participants.*

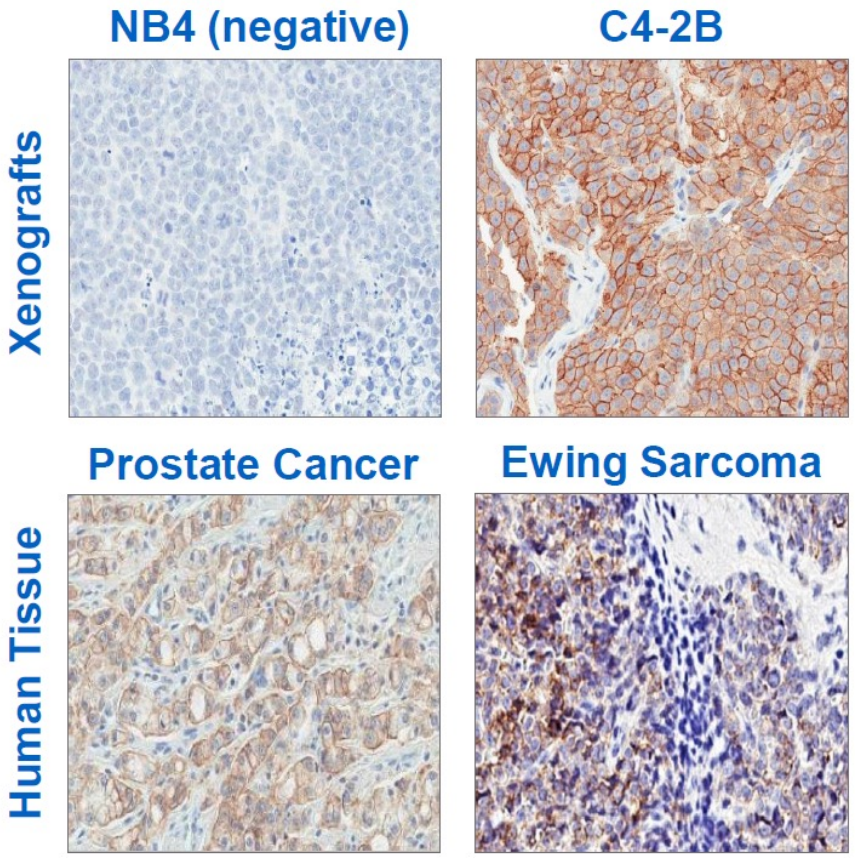


De Bono JS, *et al.* ESMO 2023 (abstract 1842TiP).

Bispecific immune engagers:

e.g. Xaluritamig

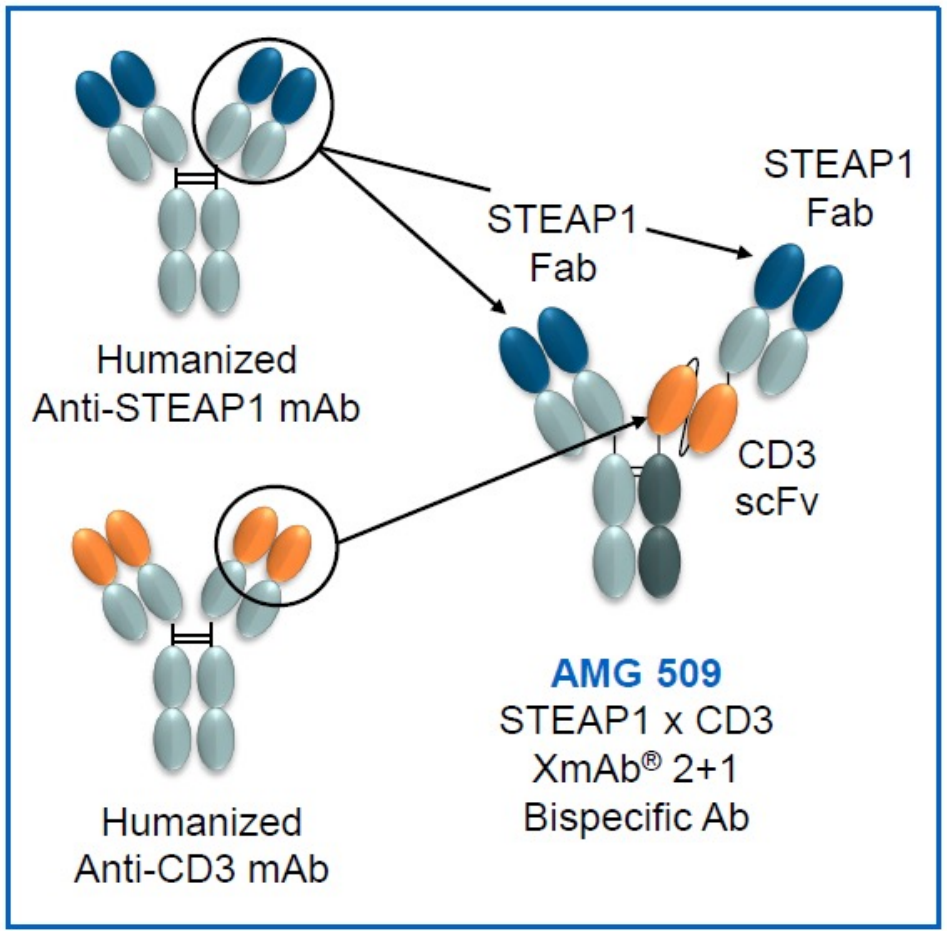
STEAP1 membrane expression in mCRPC

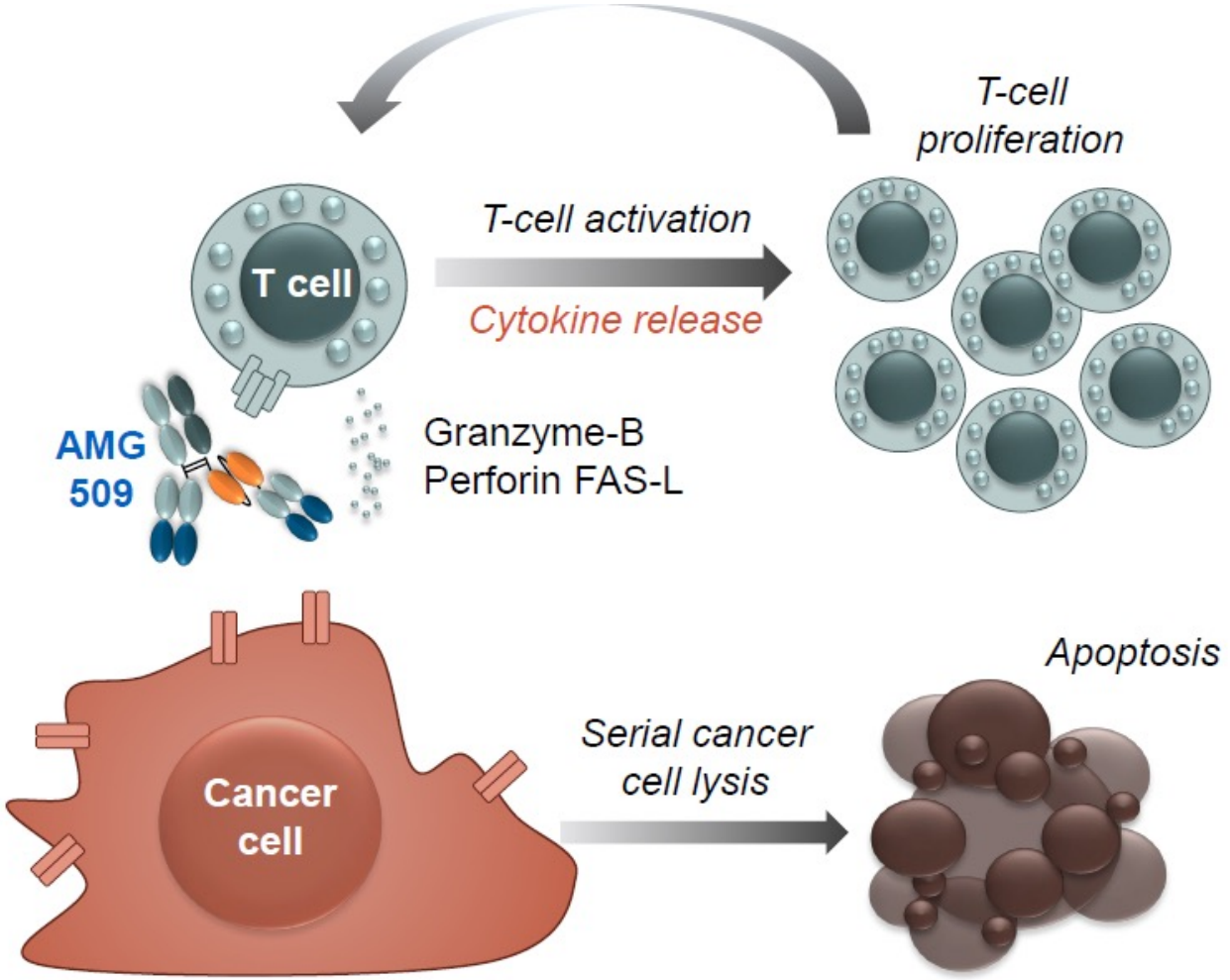


Samples	STEAP1 % Positive	PSMA % Positive
Primary Prostate Tumors (n = 88)	80	66–95*
mCRPC Bone Metastases (n = 25)†	84	72
mCRPC Liver Metastases (n = 27)†	81	63
Other mCRPC Metastases (n = 62)†	94	76

Mhawech-Fauceglia P, et al. *Histopathology*; 2017; 50: 472-483.

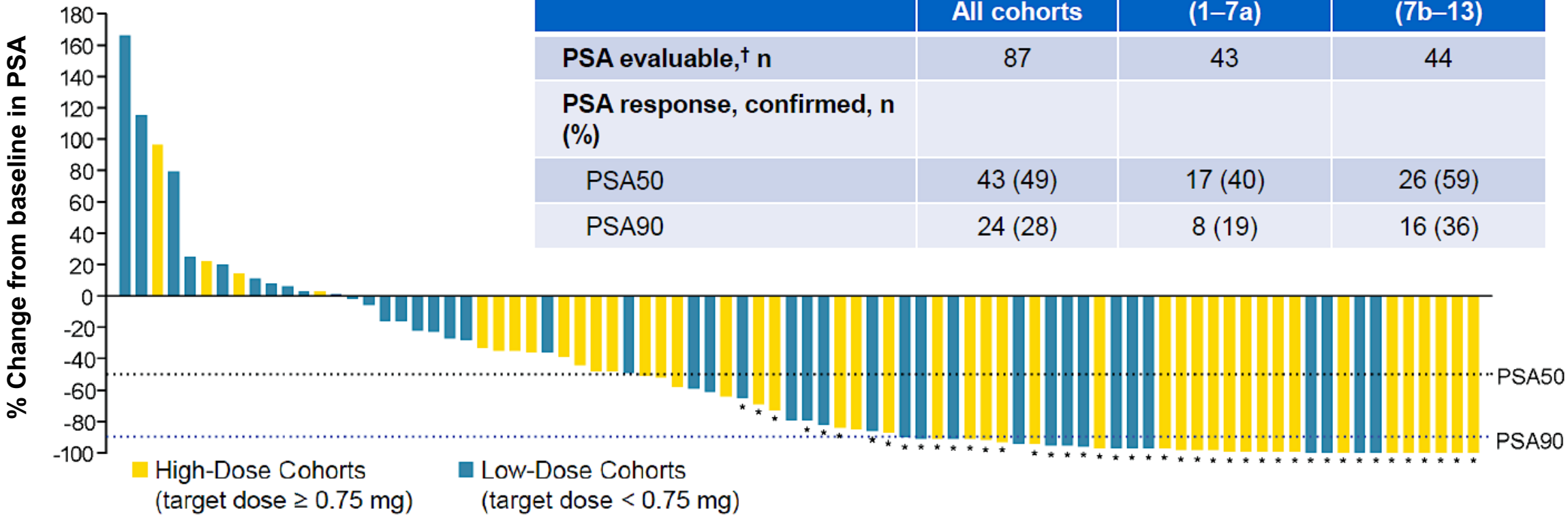
Xaluritamig (AMG 509)





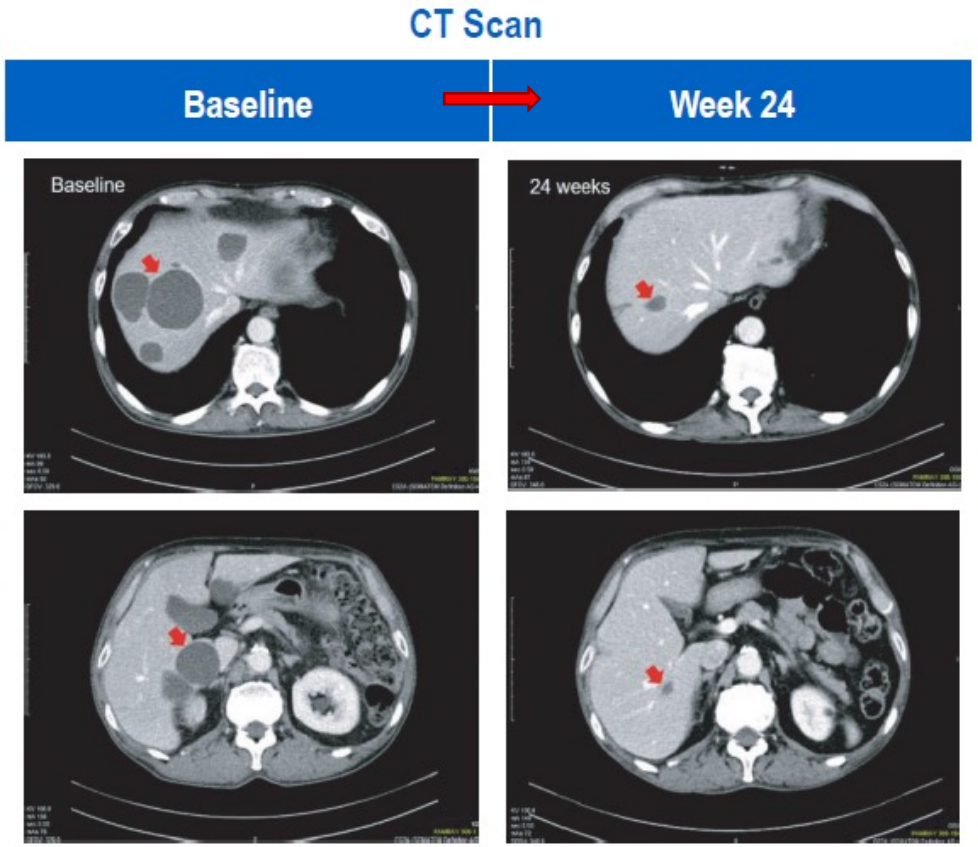
Xaluritamig: Clinical activity (Phase I trial)

	All cohorts	Low-dose cohorts (1–7a)	High-dose cohorts (7b–13)
PSA evaluable,† n	87	43	44
PSA response, confirmed, n (%)			
PSA50	43 (49)	17 (40)	26 (59)
PSA90	24 (28)	8 (19)	16 (36)

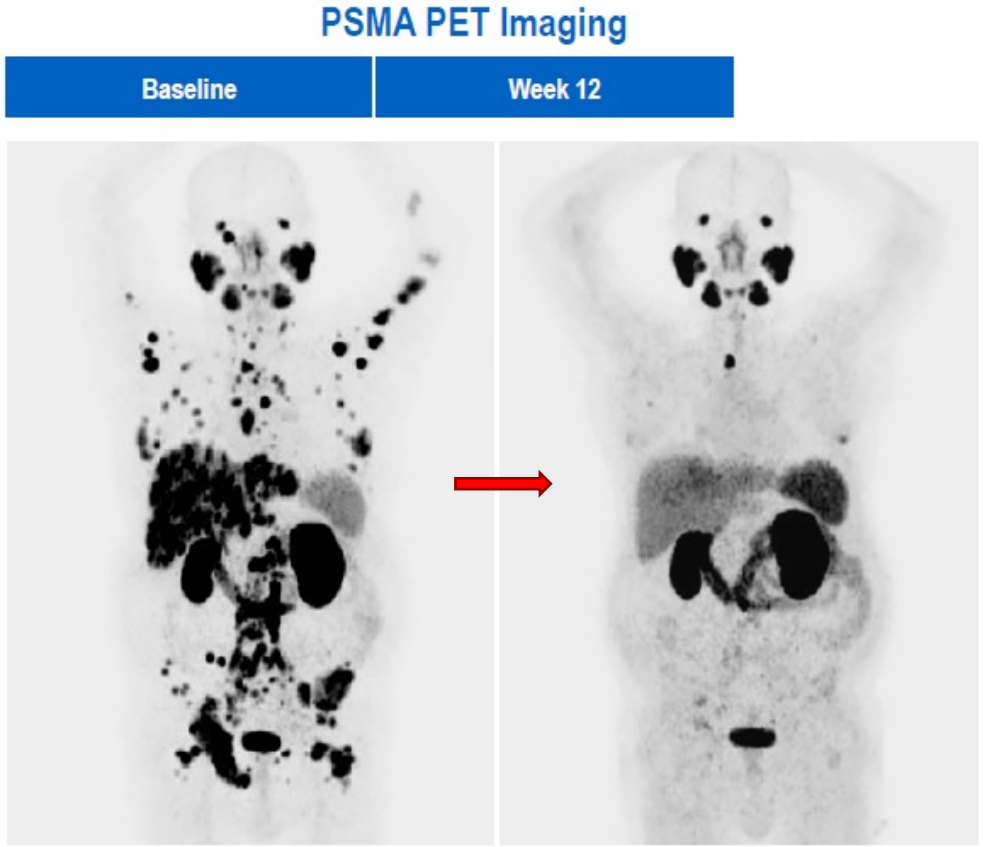


Kelly WK, et al. *Cancer Discovery*; 2024; 14: 76-89.

Xaluritamig: Clinical activity (Phase I trial)



65-year-old heavily pre-treated patient with mCRPC. Patient was enrolled in cohort 11 and achieved a confirmed RECIST and PSA90 response.



56-year-old heavily pre-treated patient with mCRPC. Patient was enrolled in cohort 12 and achieved a confirmed PSA90 response

Kelly WK, et al. *Cancer Discovery*; 2024; 14: 76-89.

Summary

- PI3K-AKT-mTOR pathway: Ipatasertib and capivasertib
- TKI/IO combinations: Cabozantinib plus atezolizumab
- CYP11 inhibition: Opevesostat
- AR-targeting PROTACs: Bavdegalutamide, ARV-766, BMS-986365
- Antibody-drug conjugates (ADCs): Vobramitamab duocarmazine
- Bispecific immune engagers: Xaluritamig

Breakfast with the Investigators: New Advances in Multiple Myeloma

A CME Symposium Held in Conjunction with the 2024 ASCO® Annual Meeting

Sunday, June 2, 2024

6:45 AM – 7:45 AM CT (7:45 AM – 8:45 AM ET)

Faculty

Rafael Fonseca, MD

María-Victoria Mateos, MD, PhD

Moderator

Elizabeth O'Donnell, MD

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