Consensus or Controversy? Clinical Investigators Provide Perspectives on the Current and Future Management of Prostate Cancer

Part 1 of a 2-Part CME Symposium Series Held in Conjunction with the 2024 ASCO Genitourinary Cancers Symposium

Thursday, January 25, 2024

6:15 PM – 8:15 PM PT (9:15 PM – 11:15 PM ET)

Faculty

Rahul Aggarwal, MD

Emmanuel S Antonarakis, MD

Elisabeth I Heath, MD

A Oliver Sartor, MD

Moderator

Alan H Bryce, MD

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Faculty

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Moderator
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Chief Clinical Officer
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Dr Aggarwal — 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, Janssen Biotech Inc, Merck, Pfizer Inc, Sanofi, Tango Therapeutics, Tempus
Consulting Agreements	Alkido Pharma Inc, Corcept Therapeutics, Foundation Medicine, HOOKIPA Pharma Inc, KeyQuest Health, Lilly, Menarini Silicon Biosystems, Z-Alpha
Contracted Research	Astellas, Bayer HealthCare Pharmaceuticals, Bristol Myers Squibb, MacroGenics Inc, Merck, Orion Corporation
Patent Holder	QIAGEN

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Dr Heath — Disclosures
Faculty

Advisory Committees	Astellas, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Sanofi
Consulting Agreements	Astellas, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Janssen Biotech Inc, Sanofi
Contracted Research	Arvinas, Astellas, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, BioXcel Therapeutics Inc, Bristol Myers Squibb, Calithera Biosciences, Caris Life Sciences, Corcept Therapeutics, Corvus Pharmaceuticals, Daiichi Sankyo Inc, Eisai Inc, Exelixis Inc, F Hoffmann-La Roche Ltd, Five Prime Therapeutics Inc, Fortis Therapeutics, Gilead Sciences Inc, GSK, Harpoon Therapeutics, Infinity Pharmaceuticals Inc, iTeosTherapeutics, Janssen Biotech Inc, Merck, Mirati Therapeutics Inc, Modra Pharmaceuticals, MSD, Novartis, Oncolys BioPharma, Peloton Therapeutics Inc, a wholly-owned subsidiary of Merck & Co Inc, Pfizer Inc, Pharmacyclics LLC, an AbbVie Company, POINT Biopharma, Seagen Inc
Honoraria/Paid Travel	Astellas, Bayer HealthCare Pharmaceuticals, Caris Life Sciences, Sanofi, Seagen Inc
Speakers Bureau	Sanofi
Nonrelevant Financial Relationship	Calibr

Dr Sartor — Disclosures
Faculty

Consulting Agreements	Fusion Pharmaceuticals, ITM Isotopen Technologien München AG, Janssen Biotech Inc, NorthStar Rx LLC, Novartis, Pfizer Inc, POINT Biopharma, Sanofi, Telix Pharmaceuticals Limited, TeneoBio
Consulting or Advisory Roles	Advanced Accelerator Applications, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Clarity Pharmaceuticals, Fusion Pharmaceuticals, ITM Isotopen Technologien München AG, Janssen Biotech Inc, NorthStar Rx LLC, Novartis, Pfizer Inc, POINT Biopharma, Sanofi, Telix Pharmaceuticals Limited, TeneoBio
Data and Safety Monitoring Boards/Committees	AstraZeneca Pharmaceuticals LP, Merck, Pfizer Inc
Research Funding to Institution	Advanced Accelerator Applications, Amgen Inc, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Invitae, Janssen Biotech Inc, Lantheus, Merck, Novartis, Progenics Pharmaceuticals Inc, TeneoBio
Stock Options/Ownership — Public Companies	Abbott Laboratories, AbbVie Inc, Fusion Pharmaceuticals, Johnson & Johnson Pharmaceuticals, Lantheus, Lilly, Pfizer Inc, Telix Pharmaceuticals Limited
Nonrelevant Financial Relationships	ARTBIO, Convergent Therapeutics Inc, Curadh, Ratio Therapeutics

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Dr Bryce — Disclosures
Moderator

Advisory Committees	AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Gilead Sciences Inc, Lantheus, Merck, Myovant Sciences, Novartis, Pfizer Inc
Consulting Agreement	MOMA therapeutics
Contracted Research	Astellas, Janssen Biotech Inc
Data and Safety Monitoring Board/Committee	Lantheus

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Dr Armstrong — Disclosures
Survey Participant

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

Dr McKay — Disclosures
Survey Participant

Consulting Agreements	AstraZeneca Pharmaceuticals LP, Aveo Pharmaceuticals, Bayer HealthCare Pharmaceuticals, Blue Earth Diagnostics, Bristol Myers Squibb, Calithera Biosciences, Caris Life Sciences, Dendreon Pharmaceuticals Inc, Eisai Inc, Exelixis Inc, Johnson & Johnson Pharmaceuticals, Lilly, Merck, Myovant Sciences, Novartis, Pfizer Inc, Sanofi, Seagen Inc, Sorrento Therapeutics, Telix Pharmaceuticals Limited, Tempus
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Commercial Support

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Consensus or Controversy? Clinical Investigators Provide Perspectives on the Current and Future Management of Urothelial Bladder Cancer

Part 2 of a 2-Part CME Symposium Series Held in Conjunction with the 2024 ASCO Genitourinary Cancers Symposium

Friday, January 26, 2024

7:00 PM – 9:00 PM PT (10:00 PM – 12:00 AM ET)

Faculty

Matthew Milowsky, MD, FASCO

Peter H O'Donnell, MD

Jonathan E Rosenberg, MD

Arlene Siefker-Radtke, MD

Moderator

Evan Y Yu, MD

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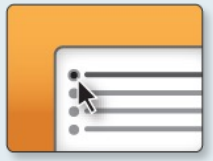
Clinicians in the Meeting Room

Networked iPads are available.

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



Answer Survey Questions: Complete the premeeting survey.

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.

Complete Your Evaluation: Tap the CME/NCPD Evaluation button to complete your evaluation electronically to receive credit for your participation.

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

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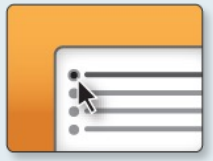
Clinicians Attending via Zoom

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 premeeting survey at the beginning of each module.

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

Get CME/NCPD Credit: CME and NCPD credit links will be provided in the chat room at the conclusion of the program. MOC and ONCC credit information will be emailed to attendees within the next 2-3 business days.

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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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Consensus or Controversy? Clinical Investigators Provide Perspectives on the Current and Future Management of Prostate Cancer

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Thursday, January 25, 2024

6:15 PM – 8:15 PM PT (9:15 PM – 11:15 PM ET)

Faculty

Rahul Aggarwal, MD

Emmanuel S Antonarakis, MD

Elisabeth I Heath, MD

A Oliver Sartor, MD

Moderator

Alan H Bryce, MD

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Agenda

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

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

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

Module 4: Role of Novel Radiopharmaceuticals in Therapy for mCRPC — Dr Sartor

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

Consulting Faculty

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

Rana R McKay, MD
Associate Professor of Medicine and Urology
Associate Director, Translational Sciences
Interim Associate Director, Clinical Sciences
Co-Lead, Genitourinary Oncology Program
University of California San Diego
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MODULE 1: Optimizing the Management of Nonmetastatic Prostate Cancer – Dr Aggarwal

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Consulting Faculty Questions

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

Neil Love, MD

Andrew J Armstrong, MD, ScM

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QUESTIONS FOR THE FACULTY

Andrew J Armstrong, MD, ScM

Would you extrapolate from the STAMPEDE data and substitute another AR pathway inhibitor (ie, apalutamide, darolutamide or enzalutamide) for abiraterone for a patient with high-risk localized prostate cancer?

What are your thoughts about ongoing trials evaluating AR pathway inhibitors for high-risk localized disease? Are you already employing any of these strategies in clinical practice while awaiting the results?

Consulting Faculty Questions

Management of biochemically recurrent prostate cancer; EMBARK data and integration of intermittent hormonal therapy

Neil Love, MD

Rana R McKay, MD

Andrew J Armstrong, MD, ScM

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QUESTIONS FOR THE FACULTY

Rana R McKay, MD

Andrew J Armstrong, MD, ScM

What would you recommend for a highly functional 90-year-old man with biochemical (M0) recurrence after radical prostatectomy and salvage radiation therapy (PSA 11-13 ng/mL, PSA doubling time 6 months)?

In which situations are you considering enzalutamide and ADT for patients with biochemical recurrence after definitive local therapy? What about enzalutamide monotherapy? Intermittent versus continuous?

What is your opinion about prophylactic breast radiation for patients receiving enzalutamide monotherapy?

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How would you approach the management of high-risk localized prostate cancer in a patient with negative CT imaging but PSMA PET suggesting metastatic disease?

 Dr Aggarwal	Systemic therapy with ADT + AR signaling inhibitor; treat primary tumor with radiation; MDT to PET-avid sites of disease if oligometastatic in select cases
 Dr Antonarakis	If oligometastatic, treat mets with MDT RT, add 12-24 months of ADT + AR signaling inhibitor, consider RT to the primary prostate gland
 Dr Bryce	Add radiation to metastatic sites
 Dr Heath	PSMA PET-positive data must be considered in the treatment plan; if possible, a tissue biopsy may be indicated to confirm metastatic disease
 Dr Sartor	Treat with SBRT and add abi for the duration of the ADT (typically 2 y)
 Dr Armstrong	Treat as metastatic low-volume mHSPC, still treat primary with RT, routine use of ADT/AR signaling inhibitors
 Dr McKay	If amenable to MDT then definitive radiation and ADT + abi with MDT; if not amenable to MDT, then definitive radiation and ADT + abi

MDT = metastasis-directed therapy; SBRT = stereotactic body radiation therapy; AR = androgen receptor; abi = abiraterone

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What was the age of the last patient in your practice with locally advanced prostate cancer? What was their PSA level?

	Age	PSA
 Dr Aggarwal	70 years	45 ng/mL
 Dr Antonarakis	58 years	19 ng/mL
 Dr Bryce	74 years	8.9 ng/mL
 Dr Heath	62 years	23 ng/mL
 Dr Sartor	72 years	8 ng/mL
 Dr Armstrong	68 years	5 ng/mL
 Dr McKay	70 years	15 ng/mL

For the patient in the previous scenario with locally advanced prostate cancer, what were their tumor characteristics? What specific treatment did the patient receive?

	Tumor characteristics	Treatment
 Dr Aggarwal	Gleason 4 + 5	ADT + abiraterone x 24 mo, RT to prostate + pelvis
 Dr Antonarakis	Gleason 5 + 4 = 9, cT3b, node-negative, PSMA PET-negative	ADT + abiraterone x 24 mo, primary prostatic RT
 Dr Bryce	Gleason 4 + 5	RT, ADT + abiraterone x 2 years
 Dr Heath	Gleason 8 (4 + 4), cT3b	RT, leuprolide, abiraterone
 Dr Sartor	Gleason 4 + 5 = 9, T3b	ADT + abiraterone and XRT
 Dr Armstrong	GG5 (Gleason 10) cT1c but PSMA PET with possible ECE/EVI, N0	ADT + abiraterone, RT to prostate and pelvic nodes
 Dr McKay	Gleason 4 + 5, cT3a	Abiraterone, ADT + EBRT to prostate and pelvic nodes

XRT = radiation therapy; EBRT = external beam radiation therapy

What was the age of the last patient in your practice who received systemic therapy for biochemical recurrence after local therapy for prostate cancer? What was their PSA level and PSA doubling time?

	Age	PSA	PSA doubling time
 Dr Aggarwal	65 years	0.6 ng/mL	3.4 months
 Dr Antonarakis	62 years	1.8 ng/mL	5.5 months
 Dr Bryce	68 years	3.5 ng/mL	7 months
 Dr Heath	70 years	4.8 ng/mL	8 months
 Dr Sartor	75 years	0.3 ng/mL	9 months
 Dr Armstrong	73 years	6 ng/mL	4 months
 Dr McKay	65 years	1.21 ng/mL	3 months

For the patient in the previous scenario who received systemic therapy for biochemical recurrence after local therapy for prostate cancer, what specific treatment did the patient receive? Did the patient receive intermittent or continuous therapy?

	Treatment	Intermittent or continuous
 Dr Aggarwal	MDT RT to PET-avid sites coupled with ADT x 3 mo	Intermittent
 Dr Antonarakis	Leuprolide + enza 160 mg (plan for 12 mo if complete PSA response)	Intermittent
 Dr Bryce	ADT	Intermittent
 Dr Heath	Leuprolide	Intermittent
 Dr Sartor	PSMA PET-directed SBRT with 6 mo of abiraterone monotherapy	—
 Dr Armstrong	ADT + enzalutamide	Intermittent
 Dr McKay	Relugolix + enzalutamide	Intermittent

MDT = metastasis-directed therapy

Outside of a clinical trial, are you offering enzalutamide monotherapy without ADT as an option to your patients with biochemical recurrence after definitive therapy for prostate cancer?

 Dr Aggarwal	No
 Dr Antonarakis	Yes, if patient asks
 Dr Bryce	No
 Dr Heath	Yes, if patient wants faster recovery from sexual dysfunction
 Dr Sartor	No (may discuss but not using yet)
 Dr Armstrong	Yes, but only for patients unable to tolerate ADT + enzalutamide
 Dr McKay	Yes, if patient prefers to avoid castration therapy

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UCSF Helen Diller Family Comprehensive Cancer Center

Optimizing the Management of Nonmetastatic Prostate Cancer

Rahul Aggarwal MD
Professor of Medicine
University of California San Francisco

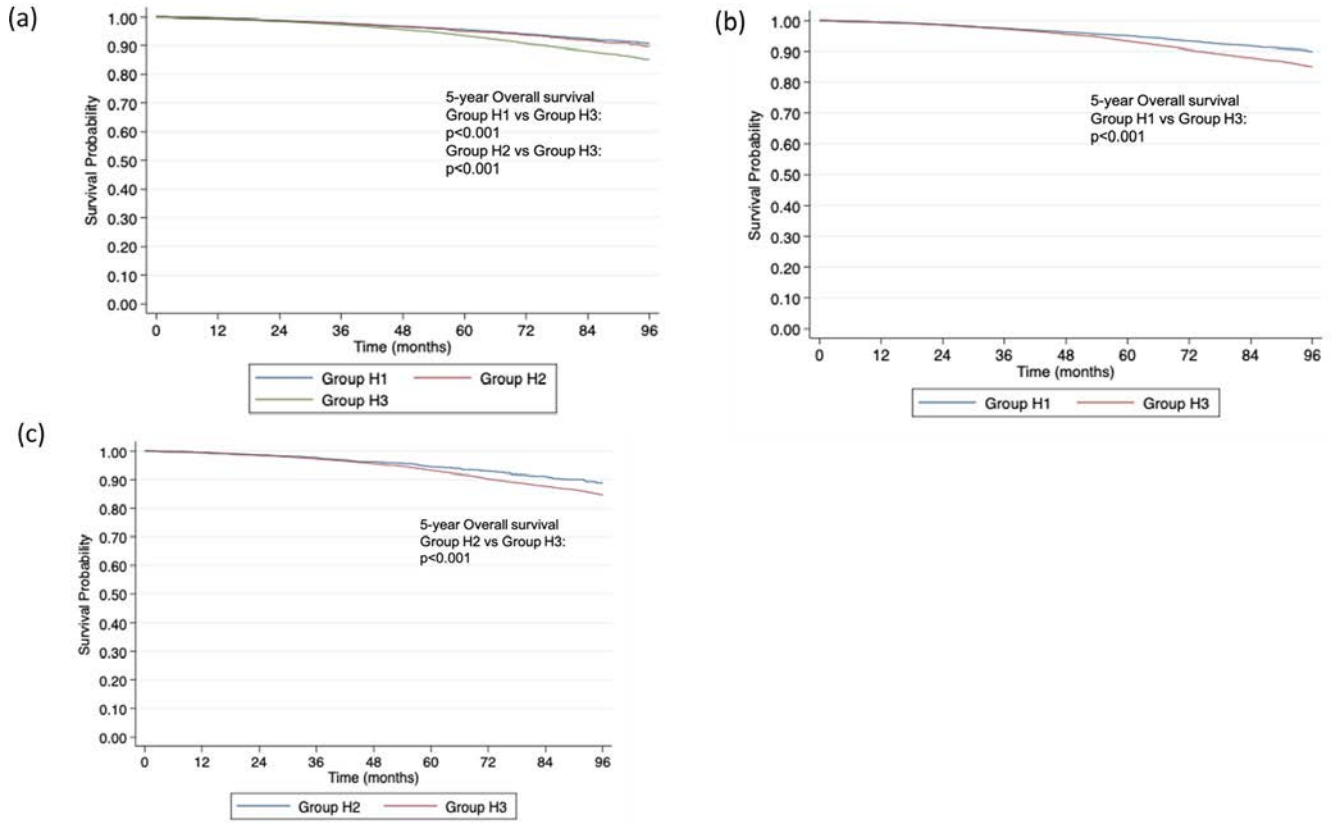
Outline

- Risk stratification and staging of patients with newly diagnosed prostate cancer
  - Molecular testing
  - Imaging
- High-risk nonmetastatic prostate cancer
- Biochemically recurrent castration-sensitive prostate cancer
- Nonmetastatic CRPC

Risk Stratification of Newly Diagnosed Prostate Cancer

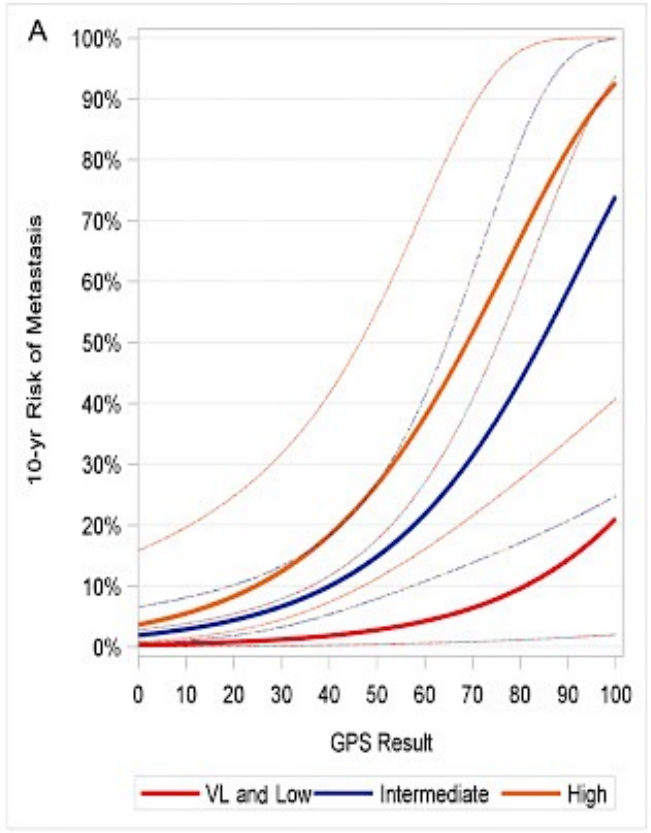
- NCCN criteria
  - Low
  - Favorable/unfavorable intermediate
  - High
  - Very high

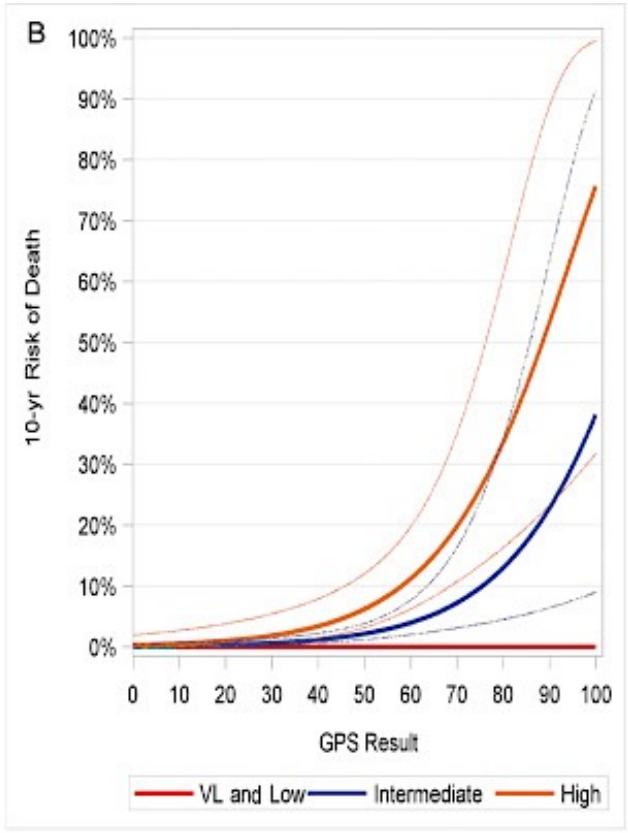
Outcomes by High Risk Criterion

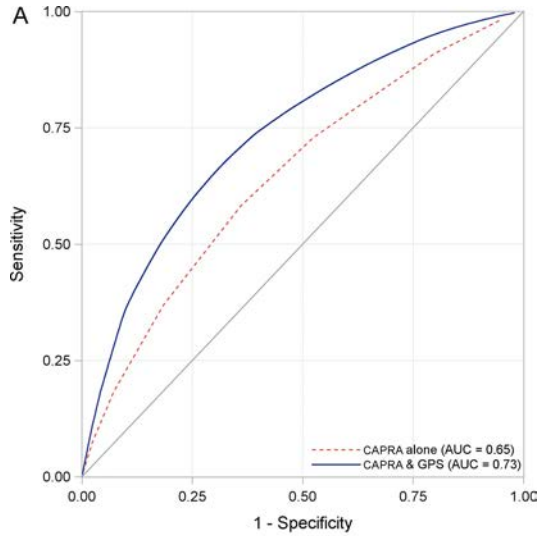


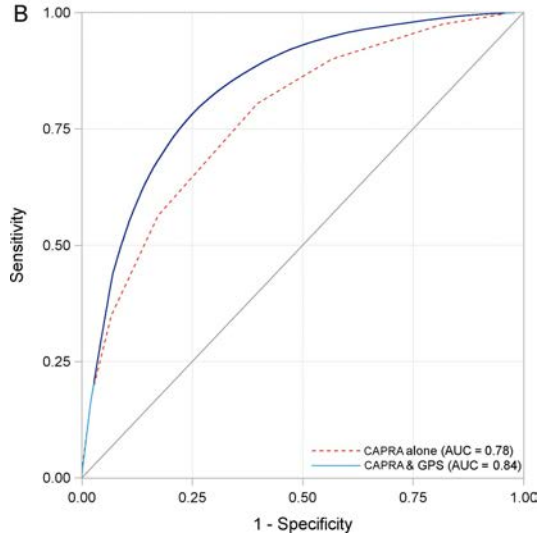
Garg H et al. Prostate Cancer Prostatic Disease 2023

Molecularly Guided Risk Stratification









Van Den Eeden SK et al. European Urology 2018

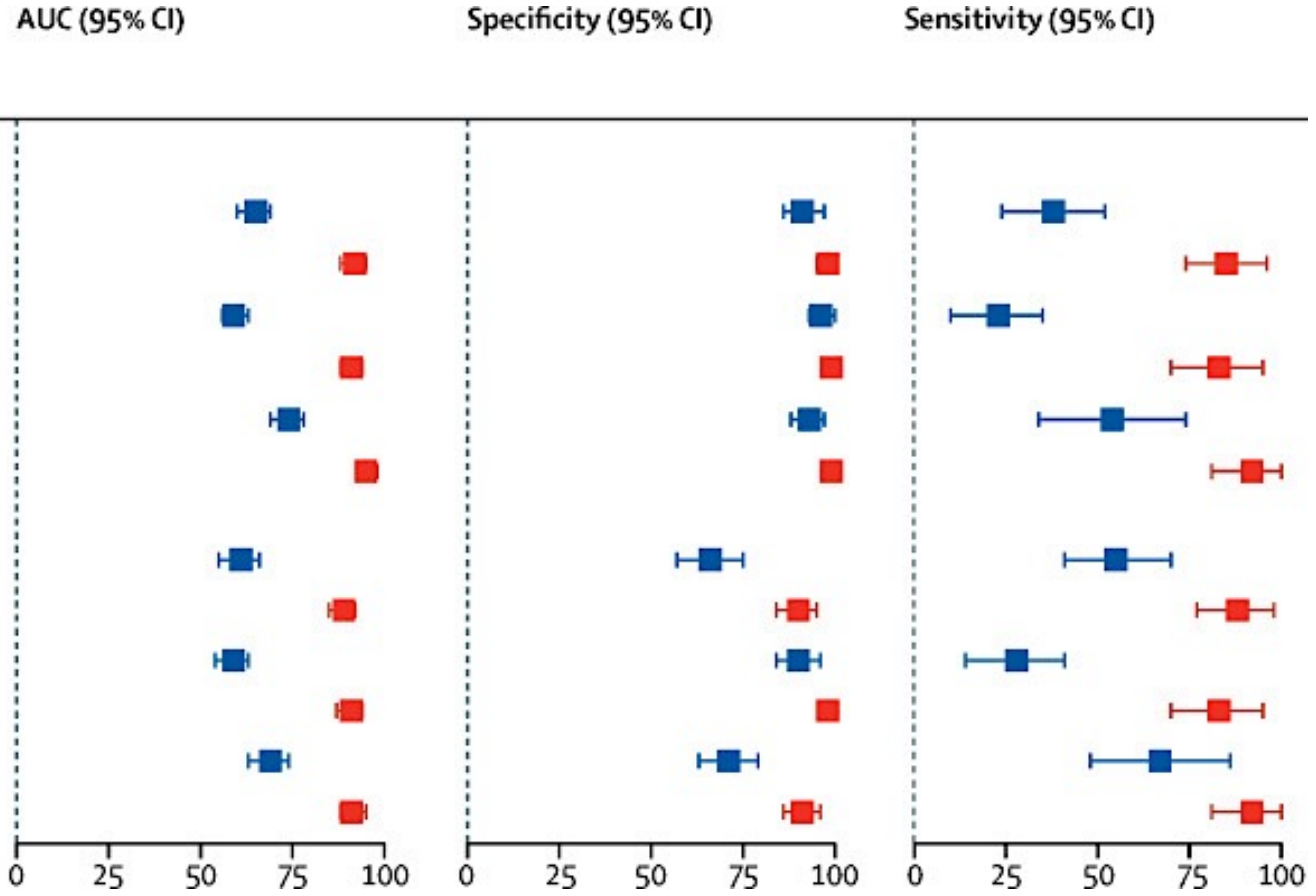
Molecularly Guided Risk Stratification

Table 1. Initial Risk Stratification for Clinically Localized Disease					
Category	Tool	Predictive	Prognostic	Endpoint Trained For[a]	Level of Evidence for Validation[b]
Clinical	NCCN	No	Yes	See note[c]	1
	STAR-CAP[2]	No	Yes	PCSM	3
	CAPRA[11,d]	No	Yes	BCR	3
	MSKCC[12]	No	Yes	BCR and PCSM[f]	3
AI	ArteraAI Prostate (category 2B)[5,e]	No	Yes	BCR, DM, PCSM[g]	1
Gene Expression Testing	Decipher[13]	No	Yes	DM	1
	Prolaris[14]	No	Yes	See note[h]	3
	Oncotype[15]	No	Yes	Adverse pathology	3
Germline	HRR	No	Uncertain	See note[i]	4

NCCN Guidelines Prostate Cancer version 4.2023

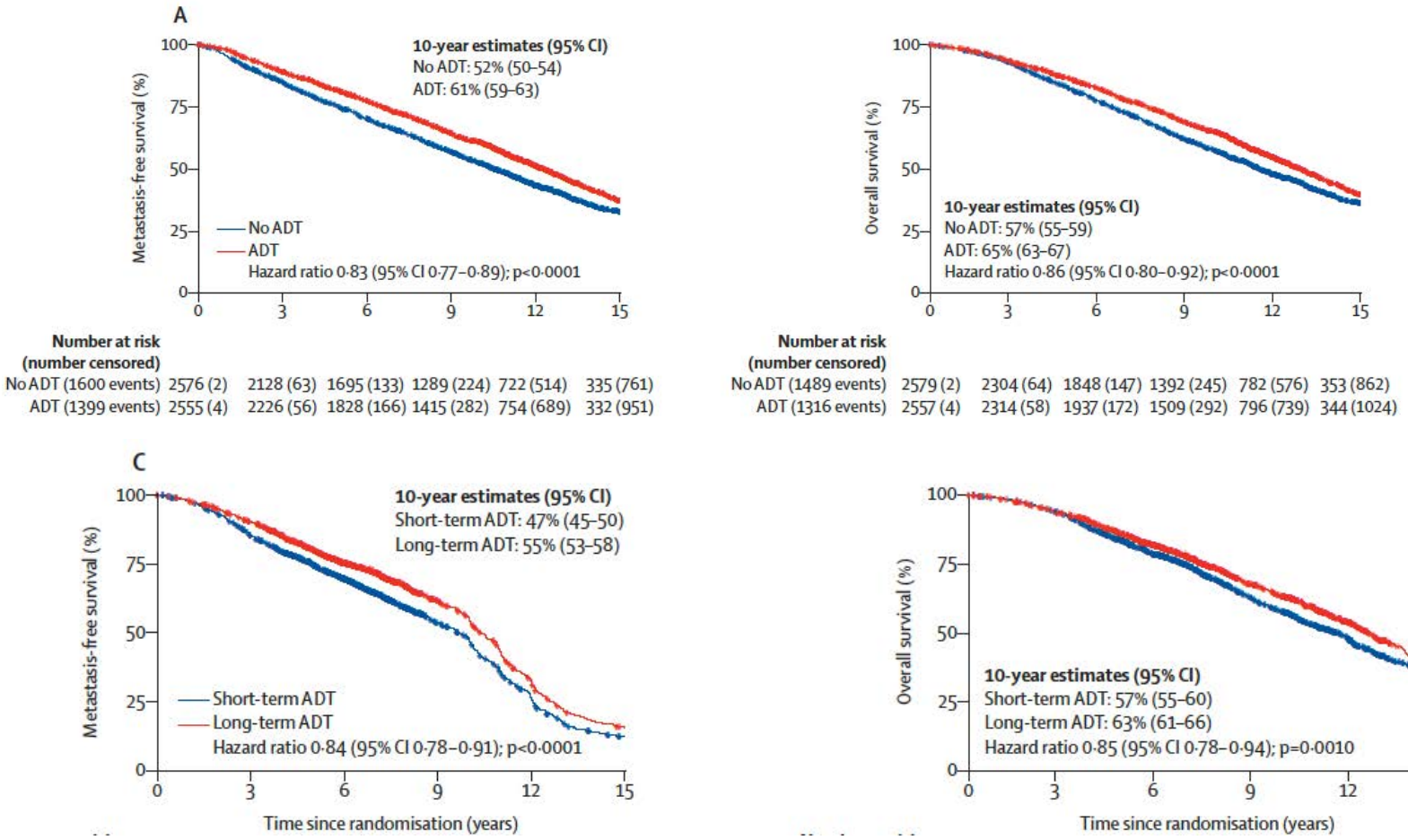
PSMA PET increases the accuracy of staging in high risk prostate cancer

	N	Positive True/False	Negative True/False
Primary analysis			
Any metastatic disease	150	18/9	94/29
	145	34/2	103/6
Pelvic nodal	150	9/4	106/31
	145	29/1	109/6
Distant metastases	150	13/9	117/11
	145	22/1	120/2
Sensitivity analysis: equivocal lesions treated as positive			
Any metastatic disease	150	26/35	68/21
	145	35/11	94/5
Pelvic nodal	150	11/11	99/29
	145	29/2	108/6
Distant metastases	150	16/37	89/8
	145	22/11	110/2



Hofman MS et al. Lancet Oncol 2020

Outcomes with ADT plus radiation: an individualized patient data meta-analysis

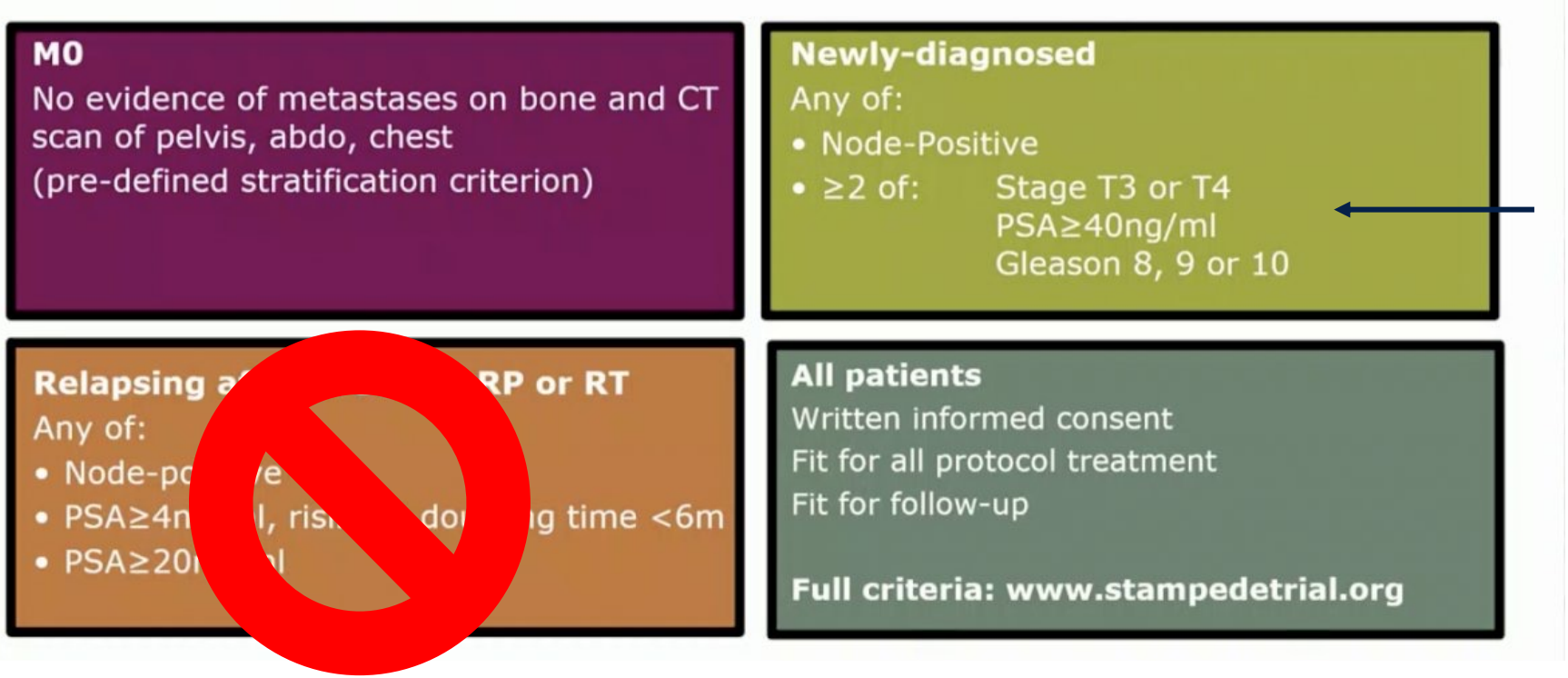


ADT versus no ADT

Short versus long term ADT

Kishan, AU et al. Lancet Oncol 2022

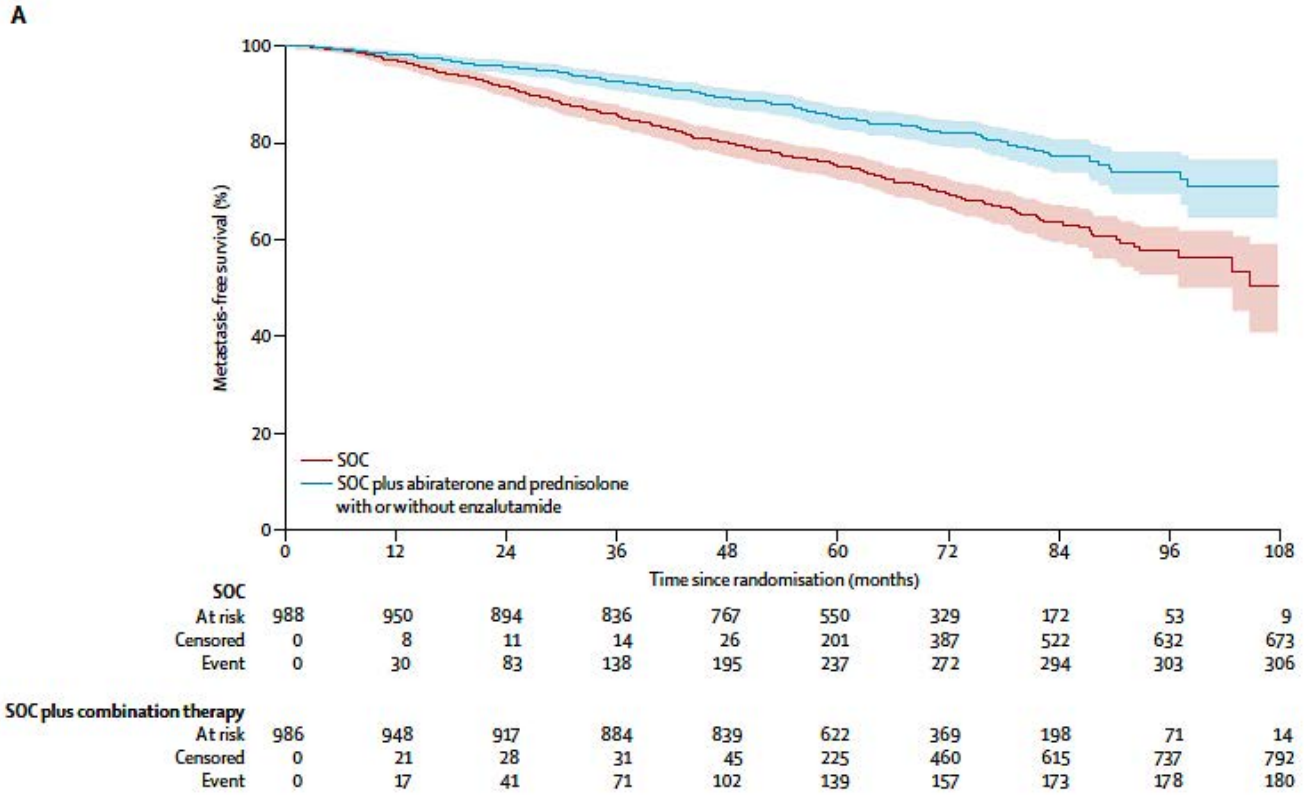
ADT intensification in very high risk non-metastatic prostate cancer: STAMPEDE

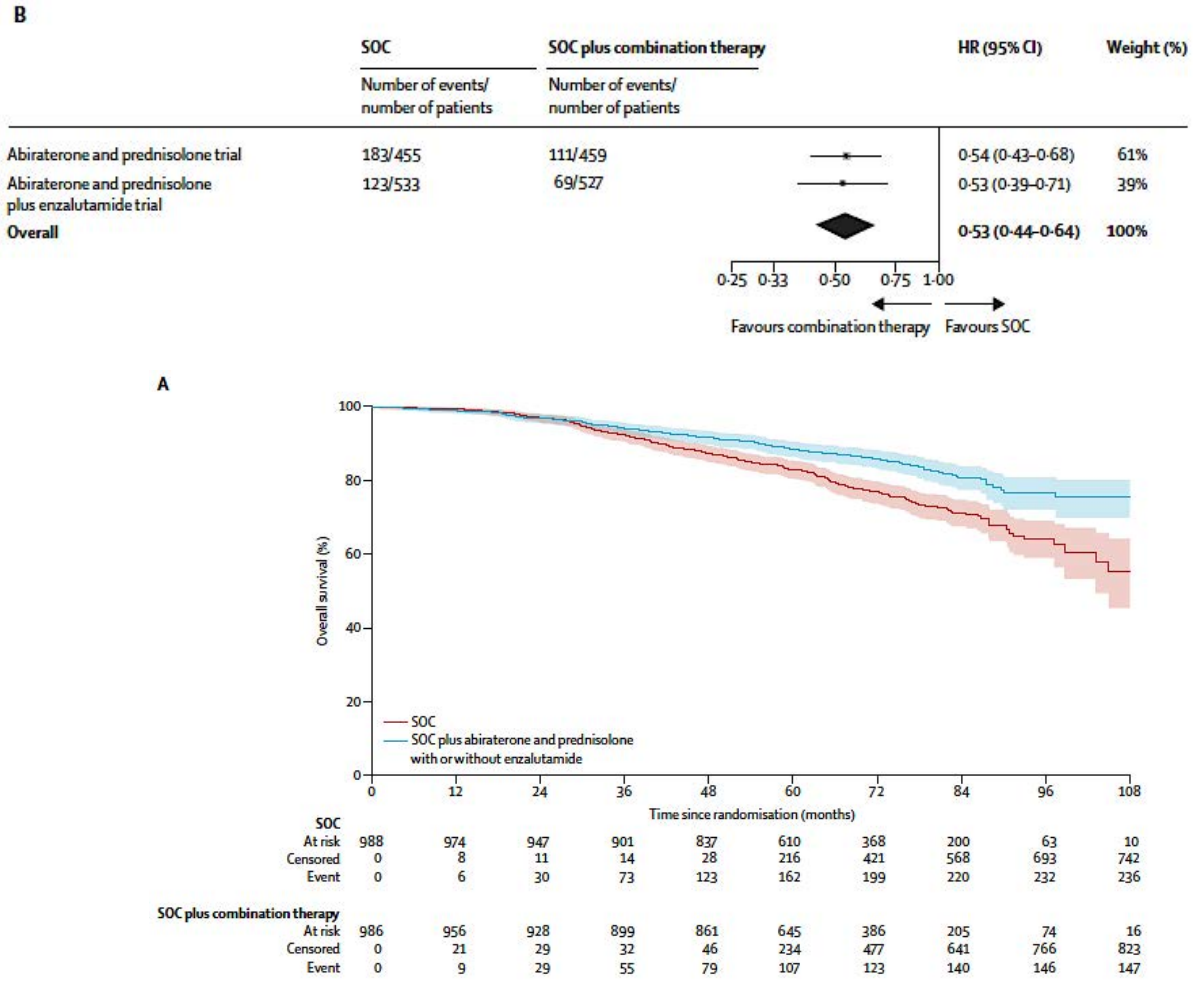


Very high risk (higher than NCCN)

Attard G et al. Lancet 2022

ADT intensification with abiraterone improves survival outcomes in newly diagnosed high risk non-metastatic prostate cancer





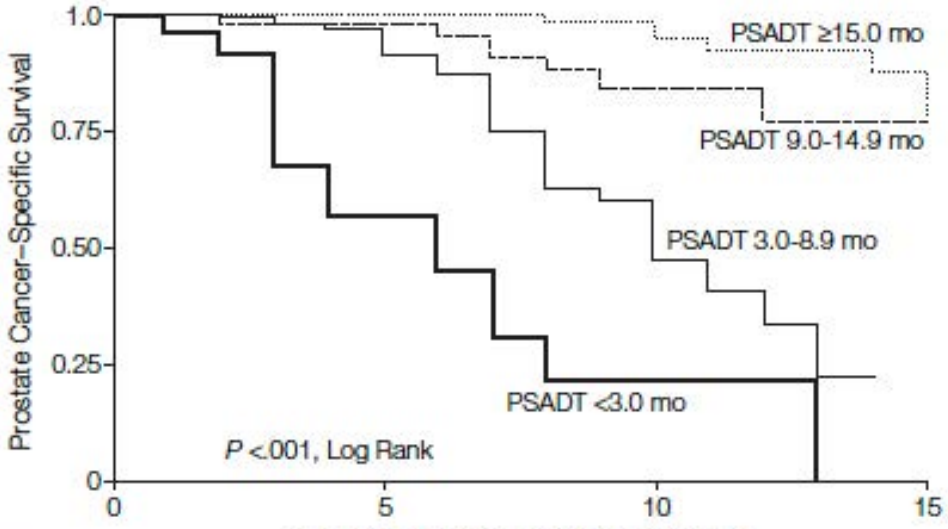
Attard G et al. Lancet 2022

Outline

- Risk stratification and staging of patients with newly diagnosed prostate cancer
  - Molecular testing
  - Imaging
- High-risk nonmetastatic prostate cancer
- Biochemically recurrent castration-sensitive prostate cancer
- Nonmetastatic CRPC

Risk stratification for non-metastatic biochemically recurrent CSPC

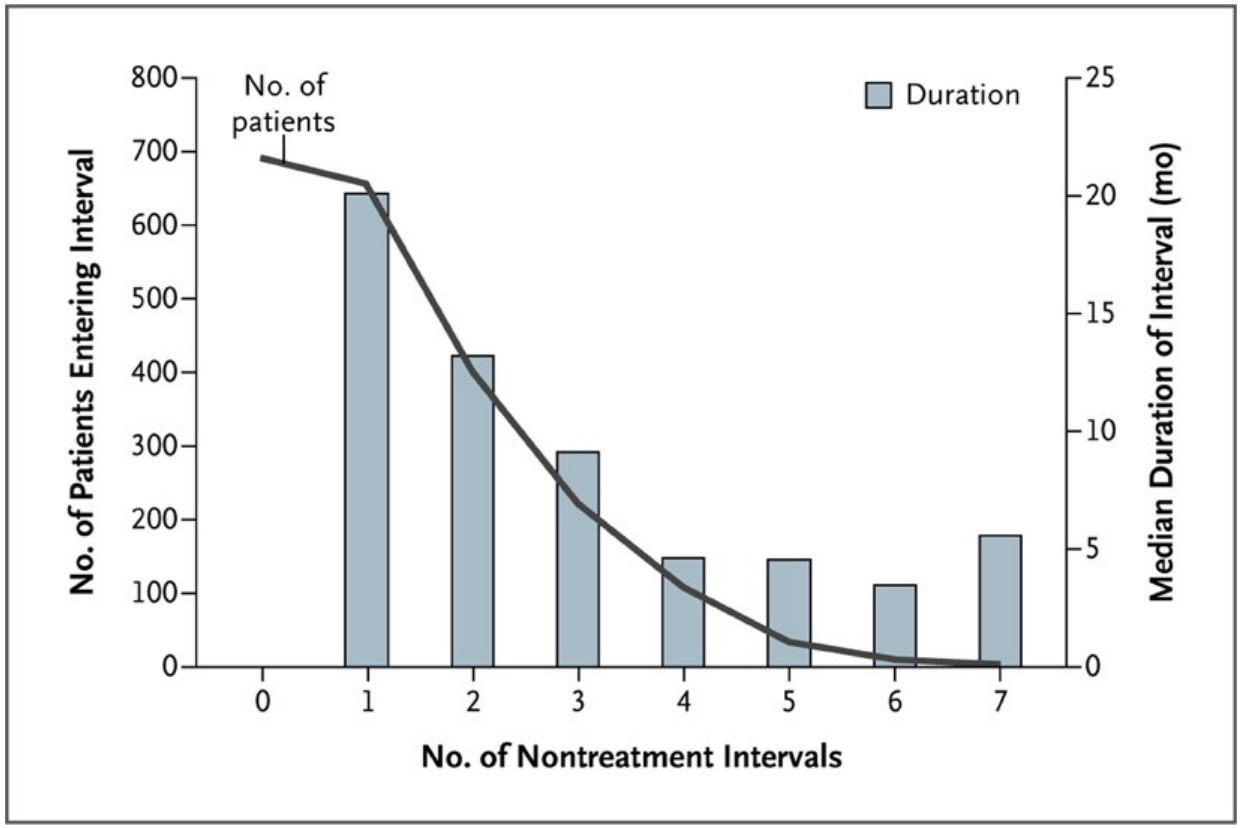
- PSA doubling time
- Gleason grade
- Time interval from definitive local tx to relapse
- Emerging factors
  - PSMA PET
  - Molecular features *(PTEN* loss)

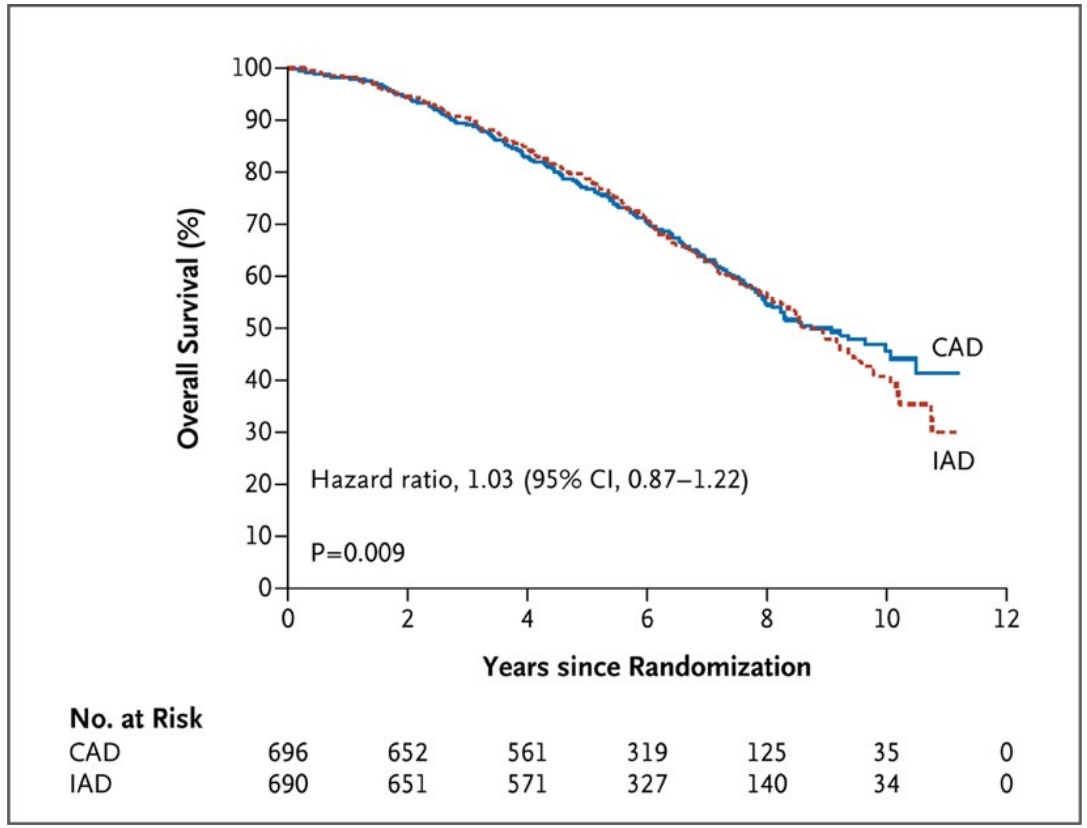


No. at Risk PSADT, mo				
<3.0	23	10	2	0
3.0-8.9	119	85	19	0
9.0-14.9	79	51	19	3
≤15	158	113	52	9

Freedland SJ, et al. JAMA 2005

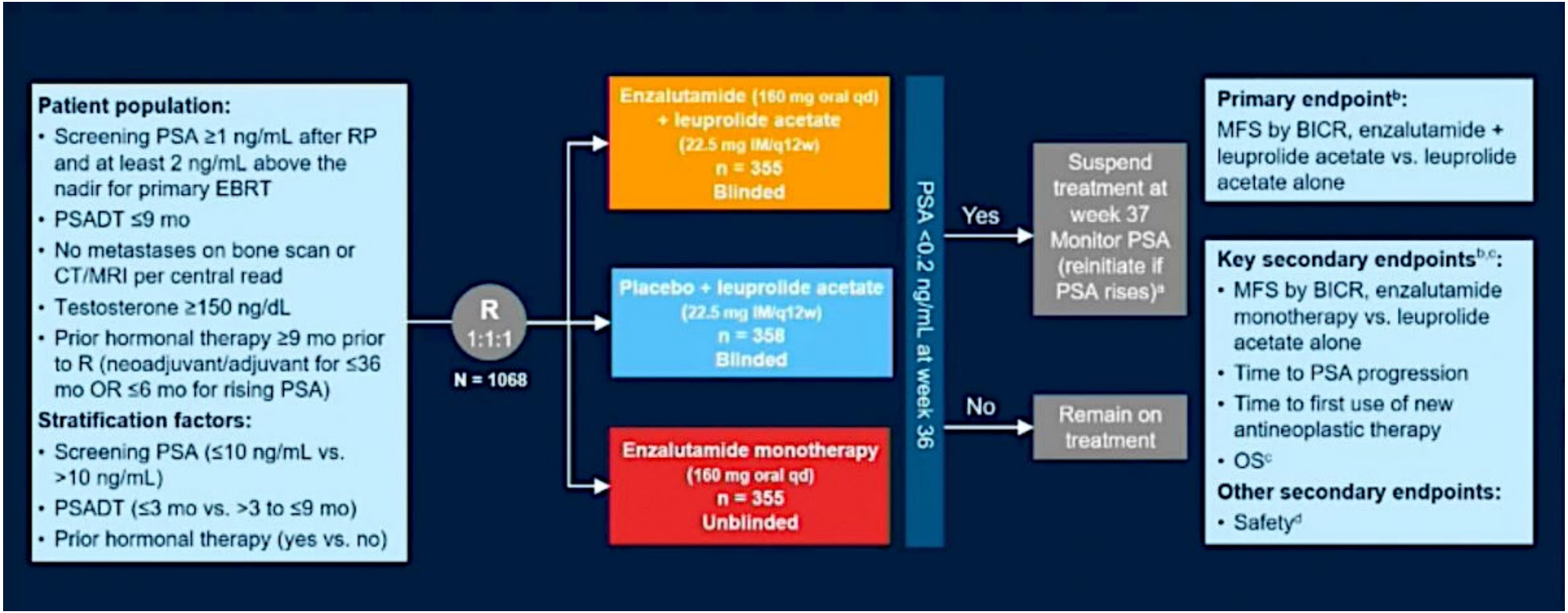
Intermittent ADT as a framework for the management of nmCSPC



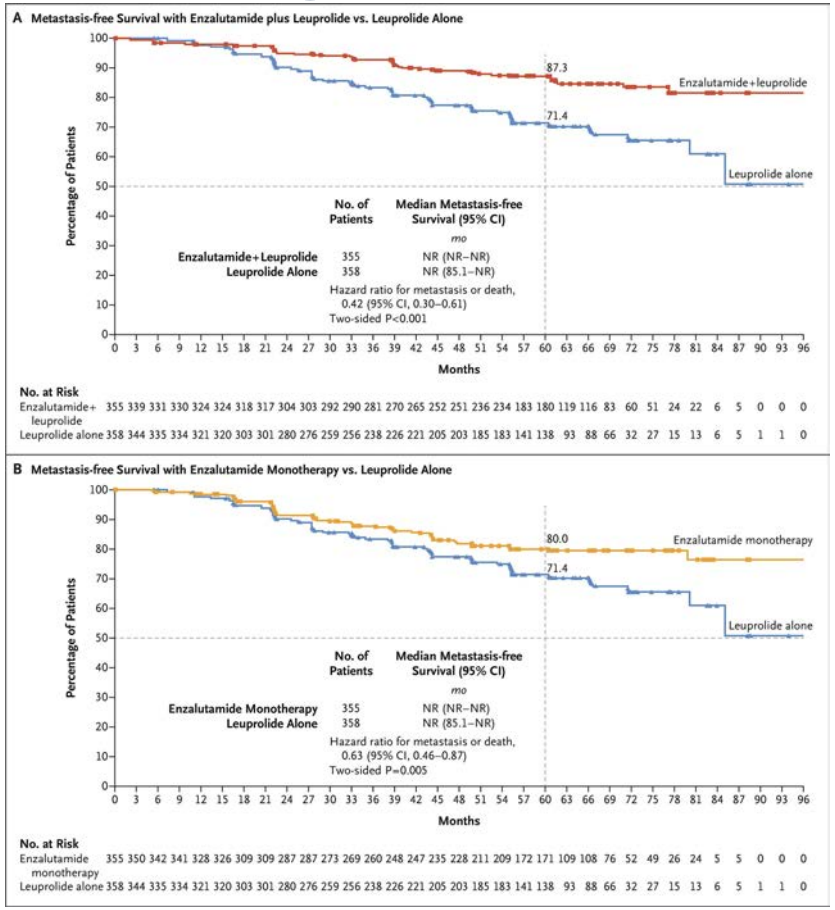


Crook JM, et al. New Engl J Med 2012

EMBARK Phase 3 Study



EMBARK: Metastasis-free survival prolonged with inclusion of enzalutamide



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)	

0.0 0.5 1.0 1.5 2.0

Enzalutamide+Leuprolide Better | Leuprolide Alone Better

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)	

0.0 0.5 1.0 1.5 2.0

Enzalutamide Monotherapy Better | Leuprolide Alone Better

Freedland SJ, et al. New Engl J Med 2023

EMBARK: Safety of Enzalutamide + Leuprolide

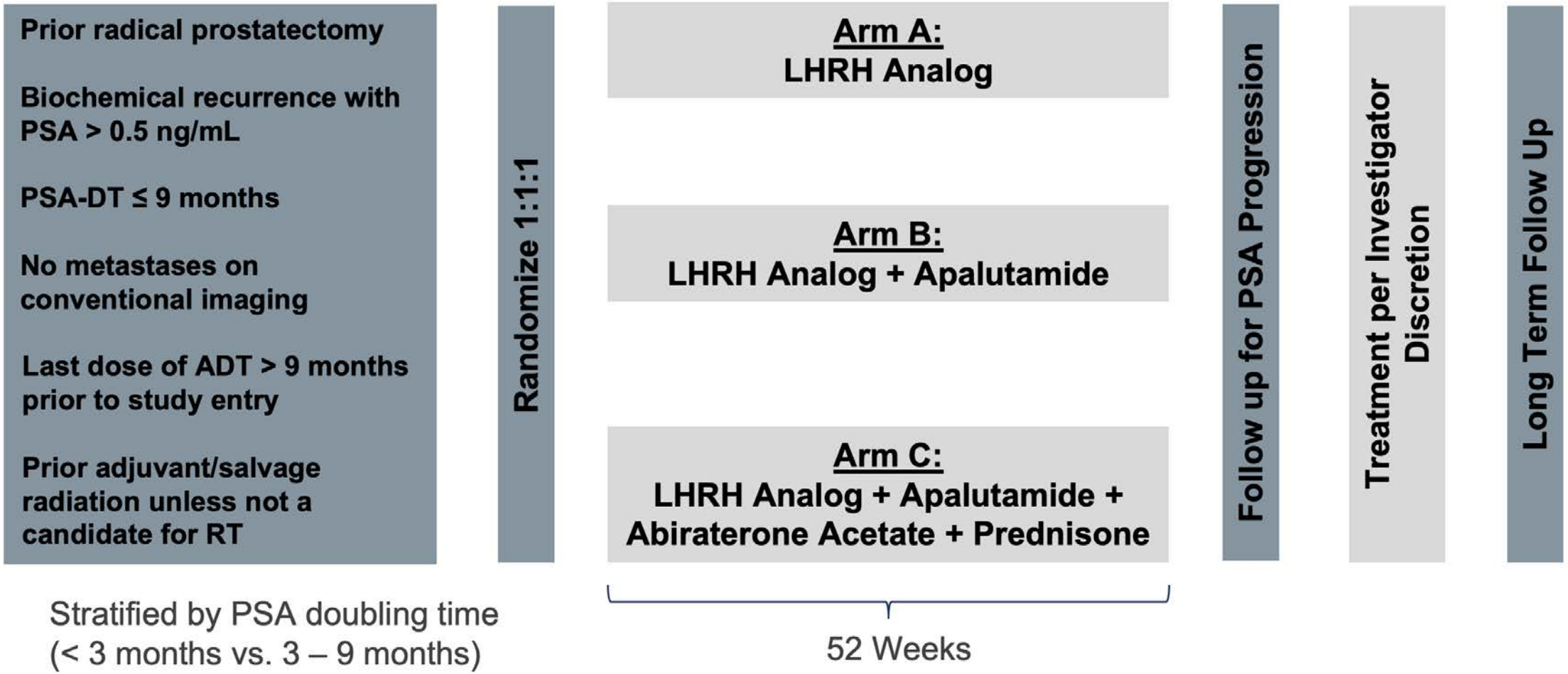
Table 2. Adverse Events (Safety Population).*

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
	number (percent)					
Any adverse event	343 (97.2)	164 (46.5)	345 (97.5)	151 (42.7)	347 (98.0)	177 (50.0)
Treatment-related adverse event	305 (86.4)	62 (17.6)	283 (79.9)	31 (8.8)	312 (88.1)	57 (16.1)
Serious adverse event	123 (34.8)	110 (31.2)	112 (31.6)	100 (28.2)	131 (37.0)	116 (32.8)
Treatment-related serious adverse event	26 (7.4)	22 (6.2)	8 (2.3)	7 (2.0)	17 (4.8)	17 (4.8)
Adverse event leading to dose reduction	25 (7.1)	11 (3.1)	16 (4.5)	5 (1.4)	56 (15.8)	14 (4.0)
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)	5 (1.4)	75 (21.2)	1 (0.3)	81 (22.9)	1 (0.3)
Hypertension	82 (23.2)	2 (0.6)	69 (19.5)	0	67 (18.9)	0
Fall	74 (21.0)	3 (0.8)	51 (14.4)	2 (0.6)	56 (15.8)	5 (1.4)
Back pain	60 (17.0)	1 (0.3)	54 (15.3)	0	62 (17.5)	1 (0.3)
Diarrhea	49 (13.9)	2 (0.6)	31 (8.8)	1 (0.3)	46 (13.0)	0
Constipation	46 (13.0)	0	31 (8.8)	0	34 (9.6)	1 (0.3)
Hematuria	42 (11.9)	7 (2.0)	44 (12.4)	3 (0.8)	45 (12.7)	6 (1.7)

Freedland SJ et al. *N Engl J Med* 2023;389(16):1453-65.

RTP RESEARCH TO PRACTICE

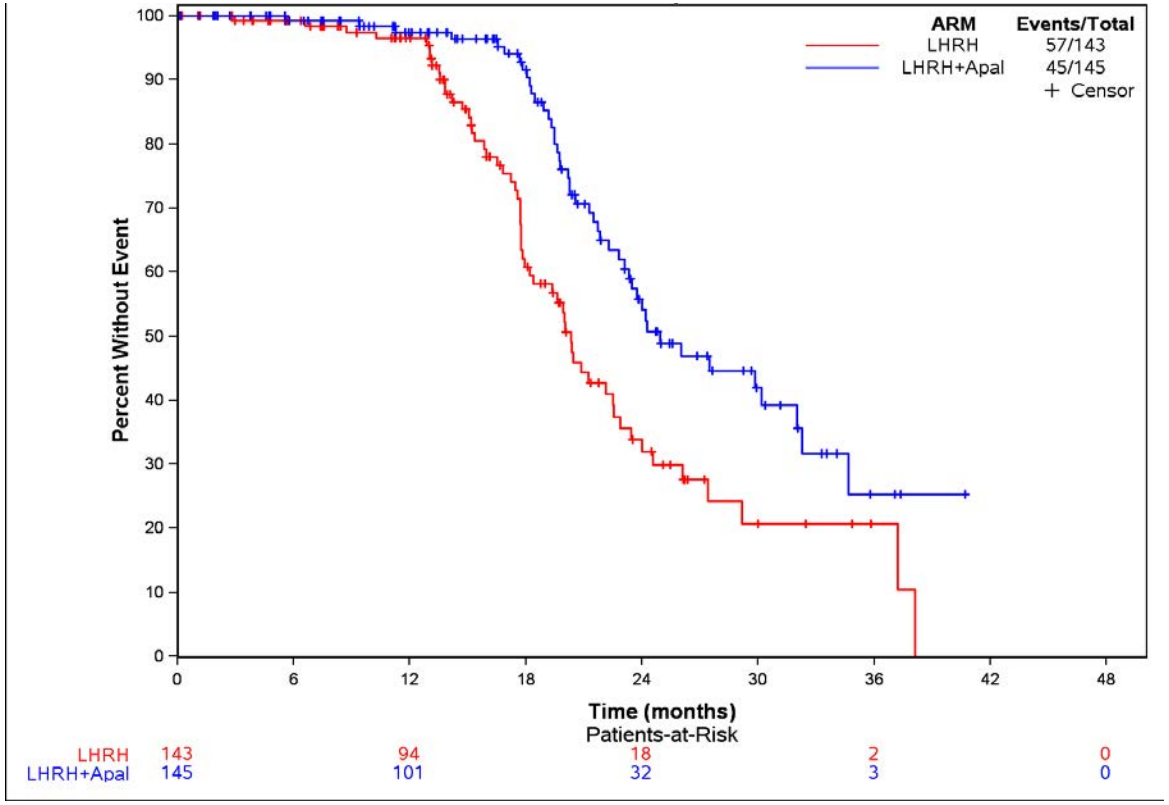
PRESTO Phase 3 Study



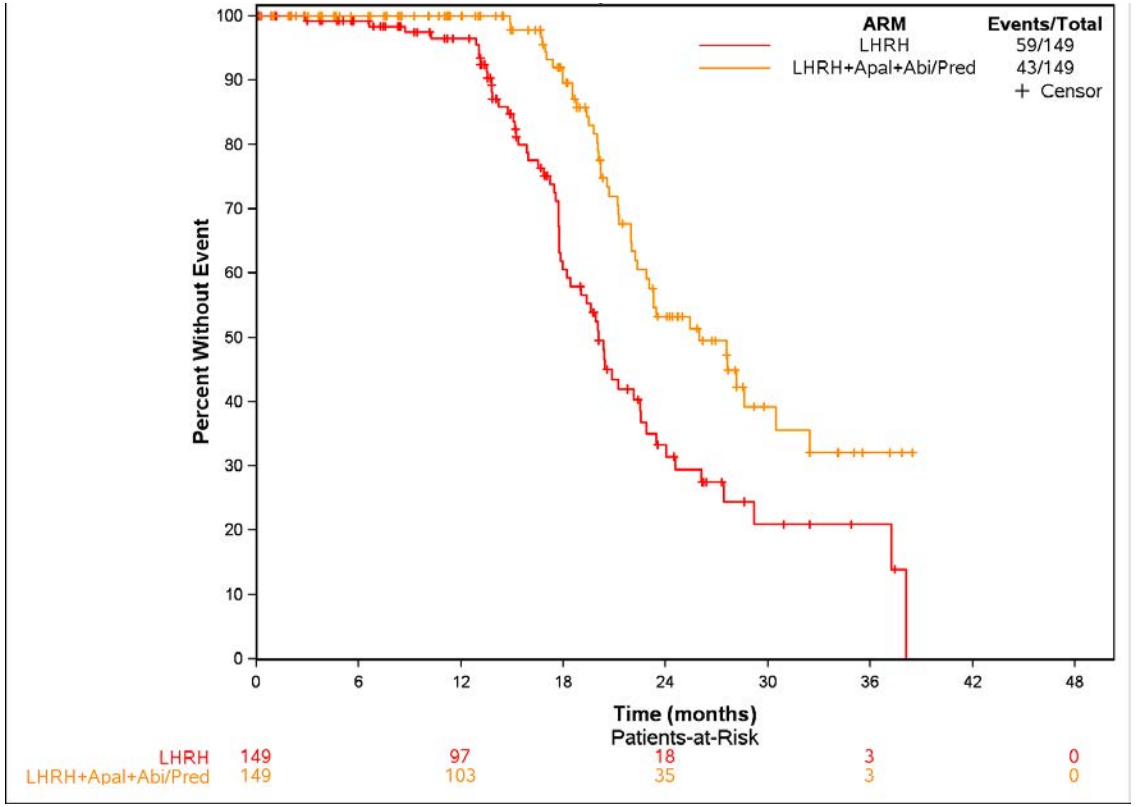
Aggarwal R et al. ESMO 2022

PRESTO: ADT intensification prolongs PSA progression-free survival

ADT + Apalutamide vs. ADT



ADT + Apa + AAP vs. ADT



Aggarwal R et al. ESMO 2022

PRESTO: Safety of ADT ± Apalutamide ± Abiraterone/Prednisone

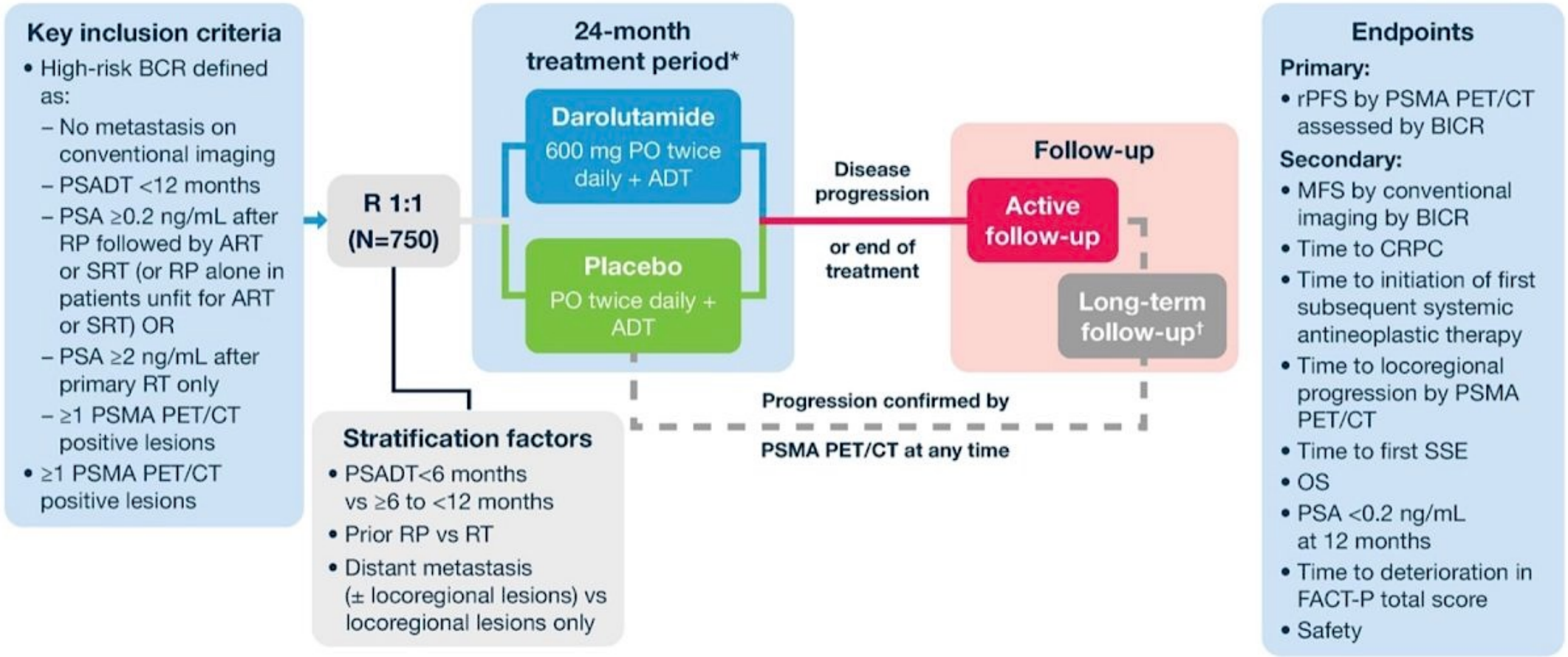
	Arm A ADT (n = 160)		Arm B ADT + APA (n = 163)		Arm C ADT + APA + AAP (n = 161)	
Adverse Events (AE)	**Grade 2**	**Grade ≥ 3**	**Grade 2**	**Grade ≥ 3**	**Grade 2**	**Grade ≥ 3**
	n (%)		n (%)		n (%)	
Hypertension	19 (12)	12 (8)	25 (15)	12 (7)	18 (11)	31 (19)
Hot flashes	19 (12)	1 (1)	8 (5)	0	23 (14)	0
Fatigue	14 (9)	0	8 (5)	3 (2)	16 (10)	2 (1)
Injection site reaction	9 (6)	0	10 (6)	0	11 (7)	0
Insomnia	9 (6)	0	5 (3)	0	8 (5)	0
Hyperglycemia	0	3 (2)	6 (4)	2 (1)	6 (4)	5 (3)
Rash	2 (1)	1 (1)	7 (4)	3 (2)	3 (2)	5 (3)
Erectile dysfunction	10 (6)	1 (1)	6 (4)	1 (1)	2 (1)	0
Arthralgia	4 (3)	1 (1)	6 (4)	1 (1)	3 (2)	2 (1)

Aggarwal R et al. ESMO 2022;Abstract LBA63.

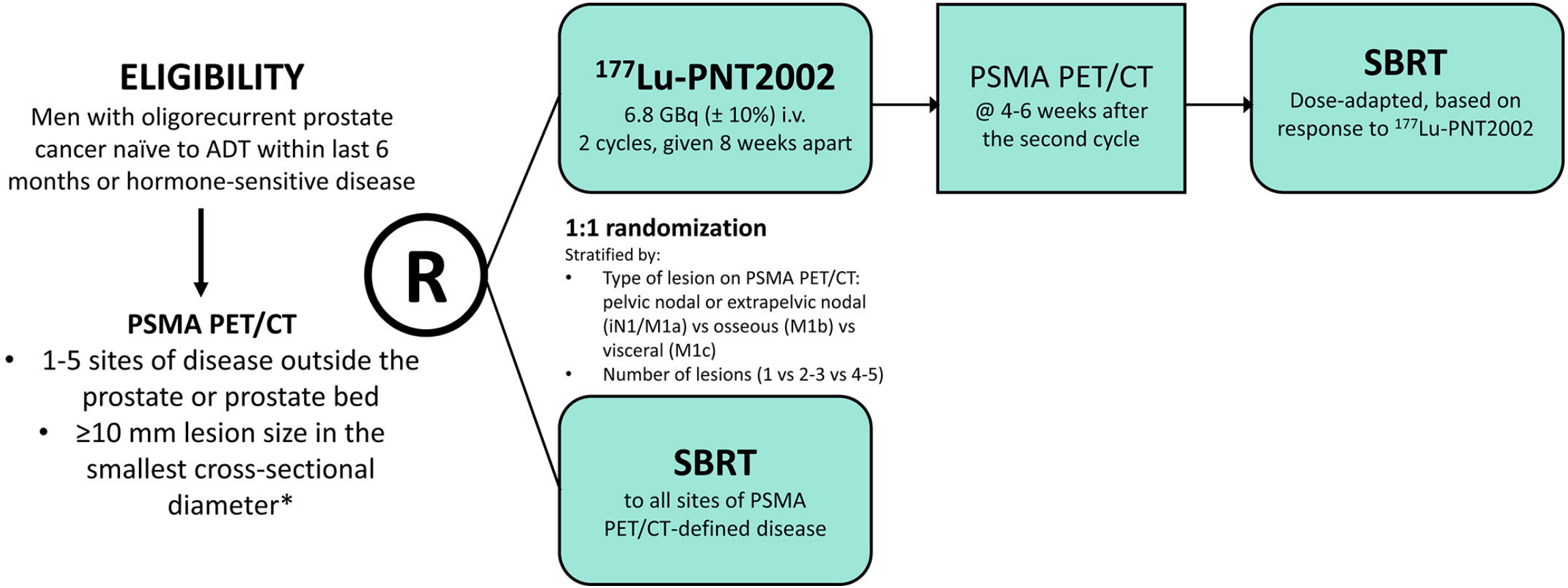
Current/Future Directions in nmCSPC

- Other secondary hormonal therapies for management of nmCSPC
- Role of metastasis-directed radiation based upon metabolic imaging
- Non-hormonal therapies (e.g. targeted radioligand therapy)
- Evolution of the MFS endpoint to incorporate metabolic imaging
- Molecularly defined risk stratification

ARASTEP: Phase 3 Trial of Darolutamide in nmCSPC



ADT-free treatment approach: Metastasis-directed radiation +/- radioligand therapy



Outline

- Risk stratification and staging of patients with newly diagnosed prostate cancer
  - Molecular testing
  - Imaging
- High-risk nonmetastatic prostate cancer
- Biochemically recurrent castration-sensitive prostate cancer
- Nonmetastatic CRPC

ADT intensification in nmCRPC

	PROSPER	SPARTAN	ARAMIS
Agents	Placebo vs. enzalutamide	Placebo vs. apalutamide	Placebo vs. darolutamide
Entry criteria	nmCRPC, N0, PSA-DT < 10 months, PSA > 2 ng/ml	nmCRPC, N0/N1, PSA-DT < 10 months, PSA > 2 ng/ml	nmCRPC, N0/N1, PSA-DT < 10 months, PSA > 2 ng/ml
Sample size	1401 (468/933)	1207 (401/806)	1509 (554/955)
Metastasis-free survival	14.7 (14.2–15.0) vs. 36.6 months (33.1–NR); HR: 0.29, CI: 0.24–0.35	16.2 vs. 40.5 months; HR: 0.30, CI: 0.24–0.36	18.4 (15.5–22.3) vs. 40.4 (34.3–NR);HR: 0.41, CI: 0.34–0.50
Overall survival	56.3 (54.5–63.0) vs. 67.0 (64.0–NR); HR: 0.73, CI: 0.61–0.89	59.9 (52.8–NR) vs. 73.9 months (61.2–NR); HR: 0.79, CI: 0.65–0.96	NR vs. NR; HR: 0.69, CI: 0.53–0.88
Grade ≥ 3 adverse event	27.0 vs. 48.0%	36.5 vs. 59.0%	25.1 vs. 30.3%

Wenzel M et al. Prostate Cancer Prostatic Diseases 2022

Current/future directions in nmCRPC and oligometastatic CRPC

- What is the optimal definition of oligometastatic/oligorecurrent disease by metabolic imaging?
- What is role of metastasis-directed treatment in CRPC?
- Is there a subset of patients for whom switch in ARSI is reasonable (e.g. low volume of disease by PET)?
- Molecular features to guide treatment sequencing/selection?
- Combination versus sequential treatment?
  - E.g. ARSI + PARPi phase 3 trial data

Take Home Points

- ADT intensification improves long term outcomes in high risk early stage prostate cancer
  - Very high risk localized newly diagnosed prostate cancer
  - High risk non-metastatic biochemically recurrent disease
- Risk stratification is critical to select patients appropriate for treatment intensification
  - Validation of predictive biomarkers is critical
- ADT-free treatment approaches including metastasis-directed radiation offer promise but require rigorous prospective validation

MODULE 2: Evidence-Based Selection of Treatment for Metastatic Hormone-Sensitive Prostate Cancer (mHSPC) – Dr Antonarakis

RTP
RESEARCH
TO PRACTICE

Consulting Faculty Questions

Current approaches to the treatment of mHSPC; PSMA-PET imaging as part of the armamentarium

Neil Love, MD

Rana R McKay, MD

RTP RESEARCH TO PRACTICE

QUESTIONS FOR THE FACULTY

Rana R McKay, MD

Is ADT intensification with an AR pathway inhibitor now standard of care? When combining an AR pathway inhibitor with ADT for a patient with mHSPC, do you have a preference for a specific agent?

In what situations do you utilize the ARASENS regimen of ADT/docetaxel/darolutamide?

How would you approach a patient with negative conventional imaging but a PSMA-PET suggestive of metastatic disease?

RTP RESEARCH TO PRACTICE

Consulting Faculty Questions

Real-world experience with side effects associated with AR inhibitors

Neil Love, MD

Andrew J Armstrong, MD, ScM

RTP RESEARCH TO PRACTICE

QUESTIONS FOR THE FACULTY

Andrew J Armstrong, MD, ScM

What has been your experience with the toxicities associated with AR pathway inhibitors (eg, cognitive effects with enzalutamide, rash with apalutamide, cardiovascular/hepatotoxicity and steroid toxicity with abiraterone)?

How do patient age and comorbidities affect your choice among these agents?

What are your usual criteria for using ADT with docetaxel and darolutamide for patients with mHSPC?

 Dr Aggarwal	Liver mets or other aggressive variant, clinical and/or genomic features, de novo metastatic disease, younger patient, good PS
 Dr Antonarakis	High-volume mets, symptomatic mets, visceral mets, de novo, mutation in TP53/RB1
 Dr Bryce	Never for metachronous low volume, occasionally for metachronous high volume, occasionally for de novo low volume, usually for de novo high volume
 Dr Heath	De novo presentation, high volume (visceral mets, >4 bone mets with >1 beyond vertebra/pelvis)
 Dr Sartor	High-volume disease and liver mets especially
 Dr Armstrong	High-volume disease by CHAARTED criteria, not solely based on PSMA PET (BS, CT/MRI), candidate for docetaxel
 Dr McKay	High volume, visceral mets, low PSA to tumor burden, TSG alterations

TSG = tumor suppressor gene

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Outside of a clinical trial, have you recommended ADT and darolutamide without docetaxel for a patient with mHSPC?

 Dr Aggarwal	Yes
 Dr Antonarakis	Yes
 Dr Bryce	Yes
 Dr Heath	No
 Dr Sartor	Yes
 Dr Armstrong	Yes
 Dr McKay	Yes

RTP RESEARCH TO PRACTICE

Globally, which comorbidities are likely to steer you away from choosing ADT and abiraterone?

 Dr Aggarwal	Poorly controlled diabetes or CHF
 Dr Antonarakis	Severe heart failure, severe diabetes, more than 2+ peripheral edema
 Dr Bryce	Diabetes
 Dr Heath	Brittle diabetes, history of ulcer
 Dr Sartor	Liver dysfunction
 Dr Armstrong	Diabetes, steroid intolerance, severe obesity, CHF, severe HTN uncontrolled, cardiac arrhythmias, hypokalemia
 Dr McKay	CHF, HTN, liver dysfunction

CHF = congestive heart failure; HTN = hypertension

RTP RESEARCH TO PRACTICE

Globally, which comorbidities are likely to steer you away from choosing ADT and apalutamide?

 Dr Aggarwal	History of seizure or multiple falls/gait instability
 Dr Antonarakis	Skin conditions (rash), ataxia/imbalance
 Dr Bryce	CNS disease, history of CVA
 Dr Heath	Uncontrolled hypertension
 Dr Sartor	Rash
 Dr Armstrong	Drug-drug interactions
 Dr McKay	Arrhythmias, falls

RTP RESEARCH TO PRACTICE

Globally, which comorbidities are likely to steer you away from choosing ADT and enzalutamide?

 Dr Aggarwal	History of seizure or multiple falls/gait instability, baseline cognitive dysfunction or situations where patient requires high cognitive function
 Dr Antonarakis	Seizure disorder, severe fatigue, severe diarrhea, ataxia/imbalance
 Dr Bryce	CNS disease, history of CVA
 Dr Heath	History of seizure
 Dr Sartor	Age, cognitive concerns, fatigue, fall risk
 Dr Armstrong	Drug-drug interactions, age >75 or severe frailty, cognitive concerns/memory loss
 Dr McKay	Falls, seizure, drug-drug interaction

RTP RESEARCH TO PRACTICE

Globally, which comorbidities are likely to steer you away from choosing ADT and darolutamide?

 Dr Aggarwal	None
 Dr Antonarakis	None
 Dr Bryce	None
 Dr Heath	None
 Dr Sartor	None
 Dr Armstrong	None
 Dr McKay	None

RTP RESEARCH TO PRACTICE

Research To Practice
January 25, 2024

Evidenced-Based Treatment for Metastatic Hormone-Sensitive Prostate Cancer (mHSPC)

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

Incidence of *de novo* mHSPC around the globe

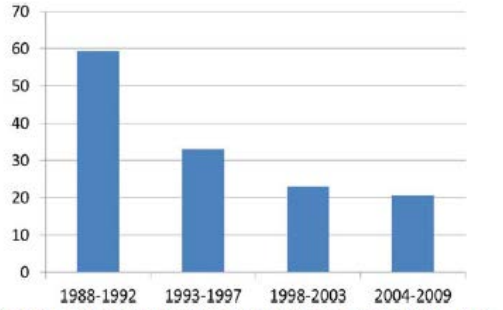
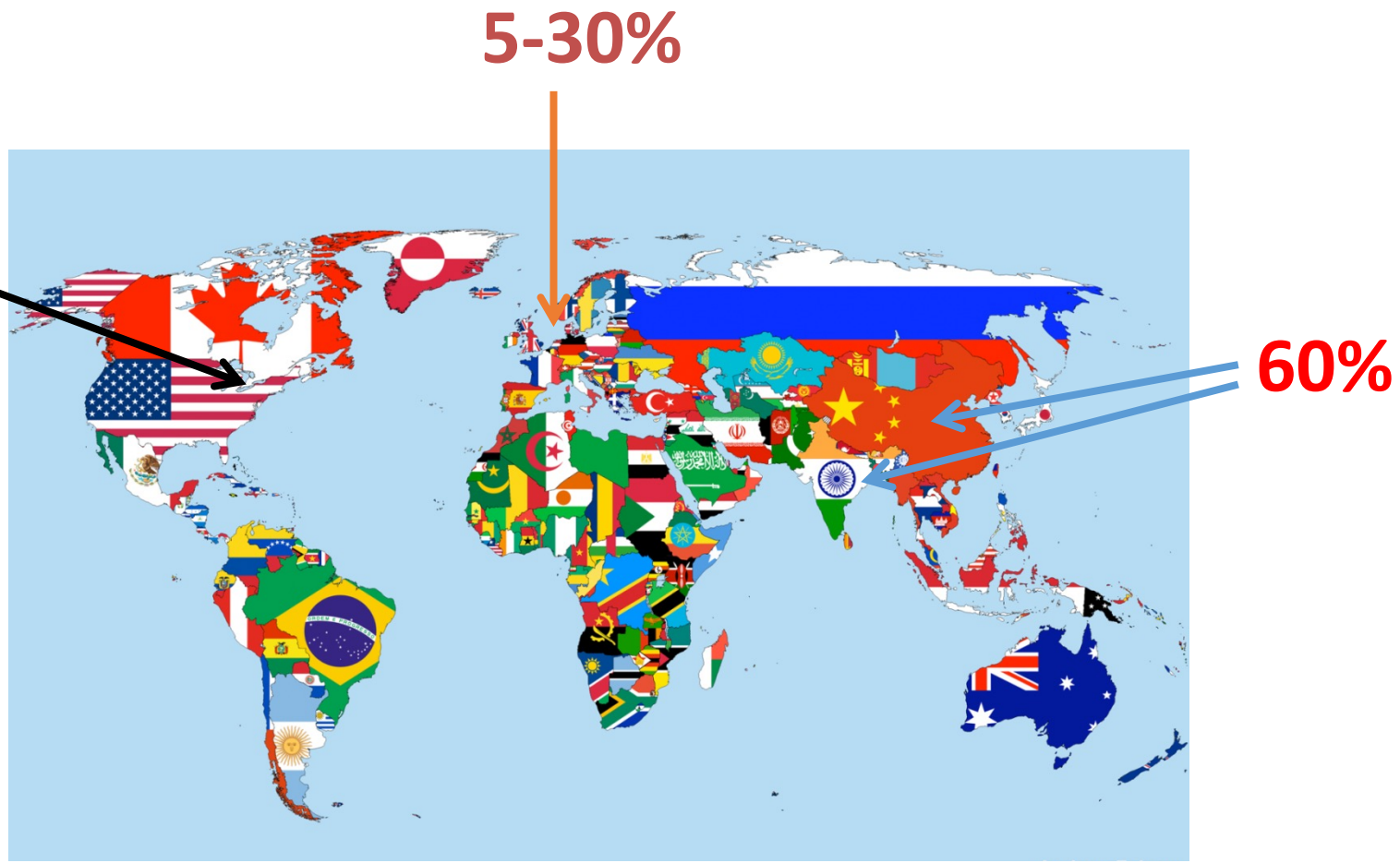
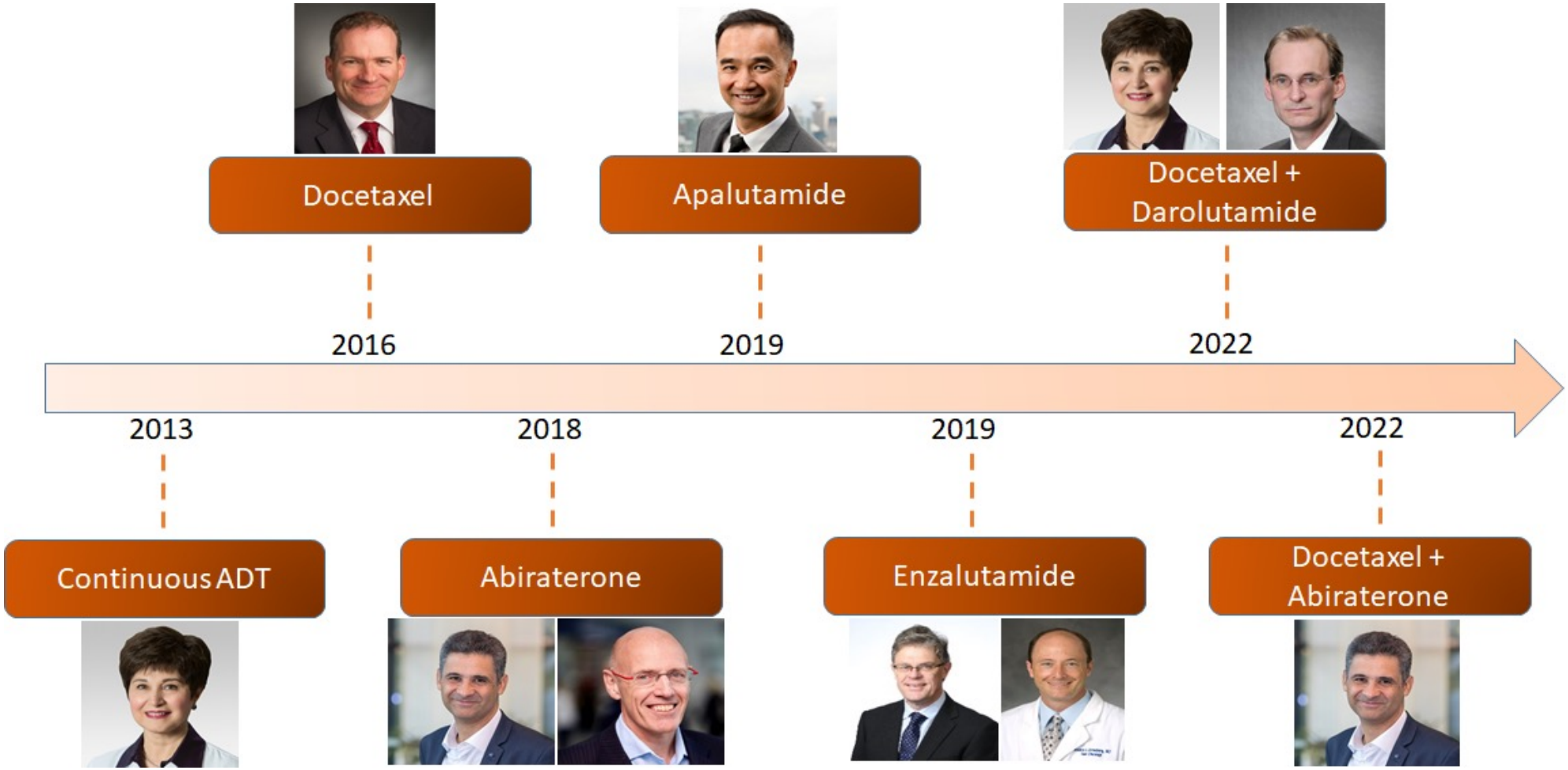


Figure 1. The age-adjusted incidence rates of newly diagnosed metastatic prostate cancer are shown by era of diagnosis.



Wu JN, *Cancer* 2014; 120: 818-823.

Evolving Paradigm of mHSPC Management



Hussein M. et al. *NEJM* 2013; Fizazi K et al. *NEJM* 2017; James N.D. et al. *NEJM* 2017; Davis I.D. et al. *NEJM* 2017; Armstrong A. et al. *JCO* 2019; Chi K.N. et al. *NEJM* 2019; Smith MR. et al *NEJM* 2022; Fizazi K. et al *Lancet* 2022.

Courtesy of Neeraj Agarwal

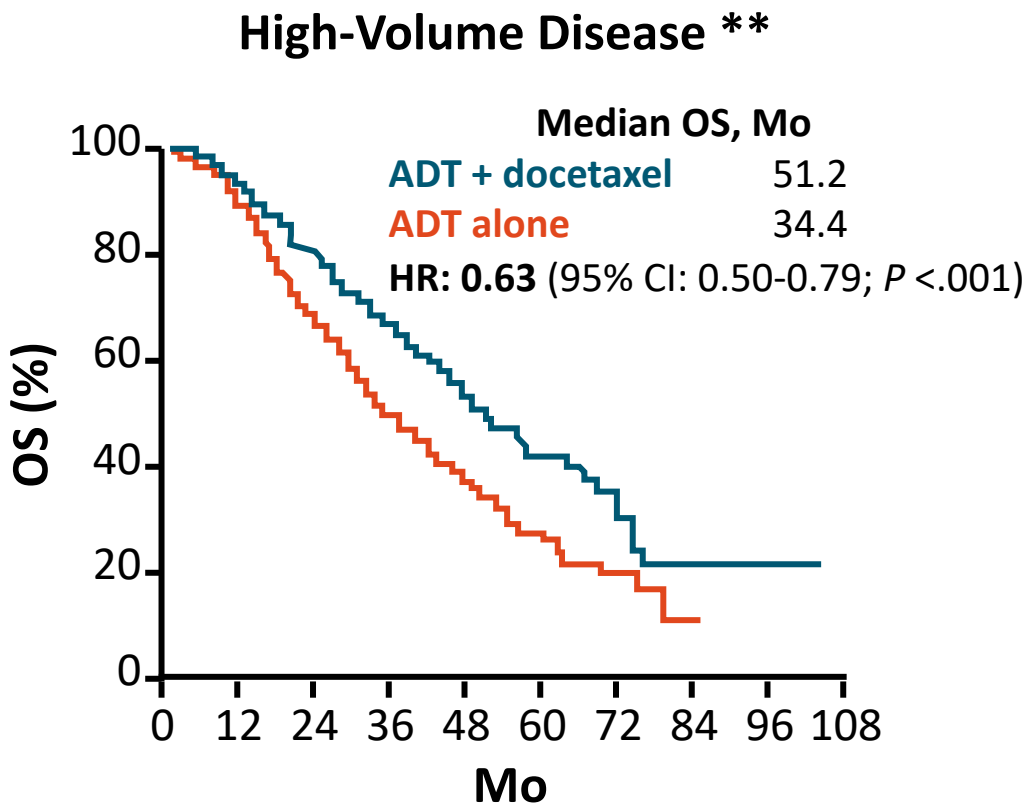
Metastatic HSPC: Overview of Treatment Options

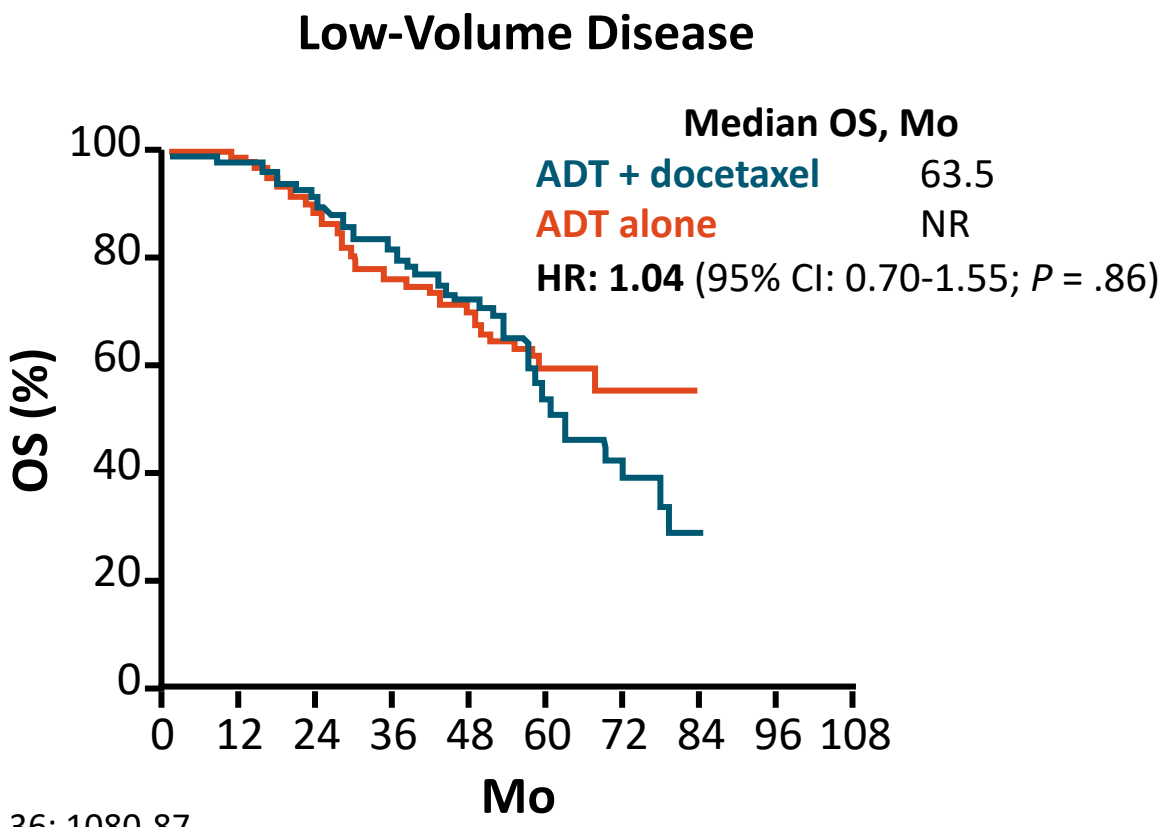
- Androgen-deprivation therapy is the mainstay of managing mHSPC
- Intensifying therapy beyond ADT alone is associated with improved OS
  - **Doublet therapy:** ADT + ARPI (abiraterone/prednisone, apalutamide, enzalutamide)
    - NOTE: **Doublet** of ADT + docetaxel is no longer recommended!
  - **Triplet therapy:** ADT + chemotherapy (docetaxel) + ARPI (abiraterone/pred, darolutamide, enzalutamide?)
  - **Radiation therapy** to the prostate in the setting of low-volume disease

NCCN. Prostate cancer. v 4.2023.

Historical data: CHAARTED, ADT ± Docetaxel in mHSPC: High-volume vs Low-volume

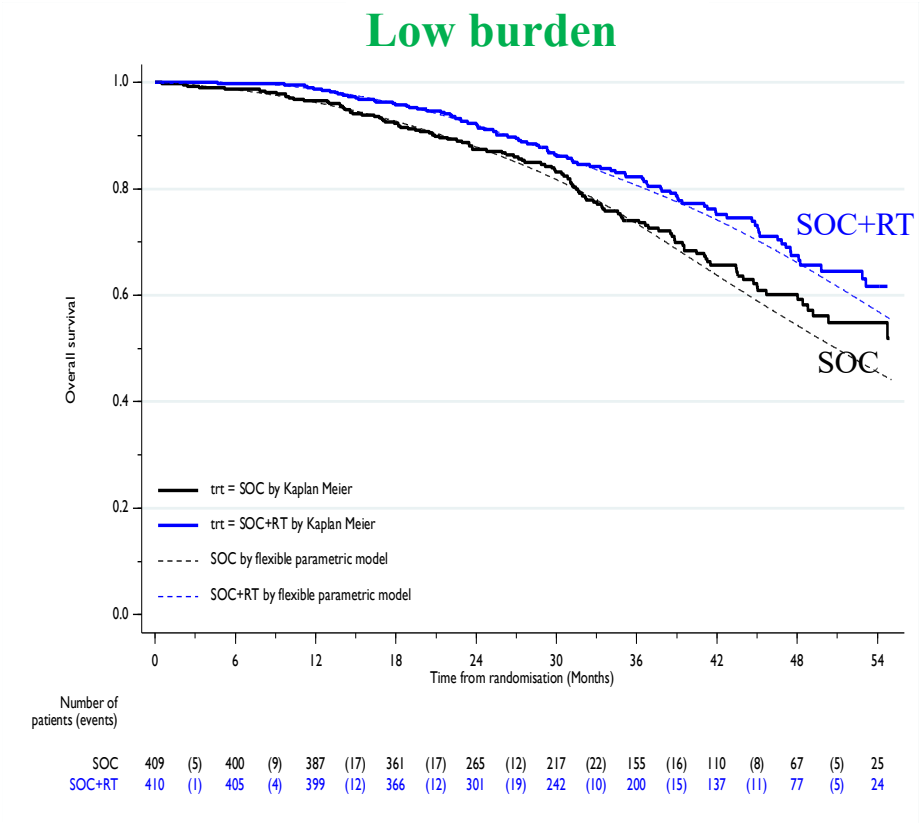
- Adding docetaxel to ADT showed greater benefit in high- (vs. low-) volume disease

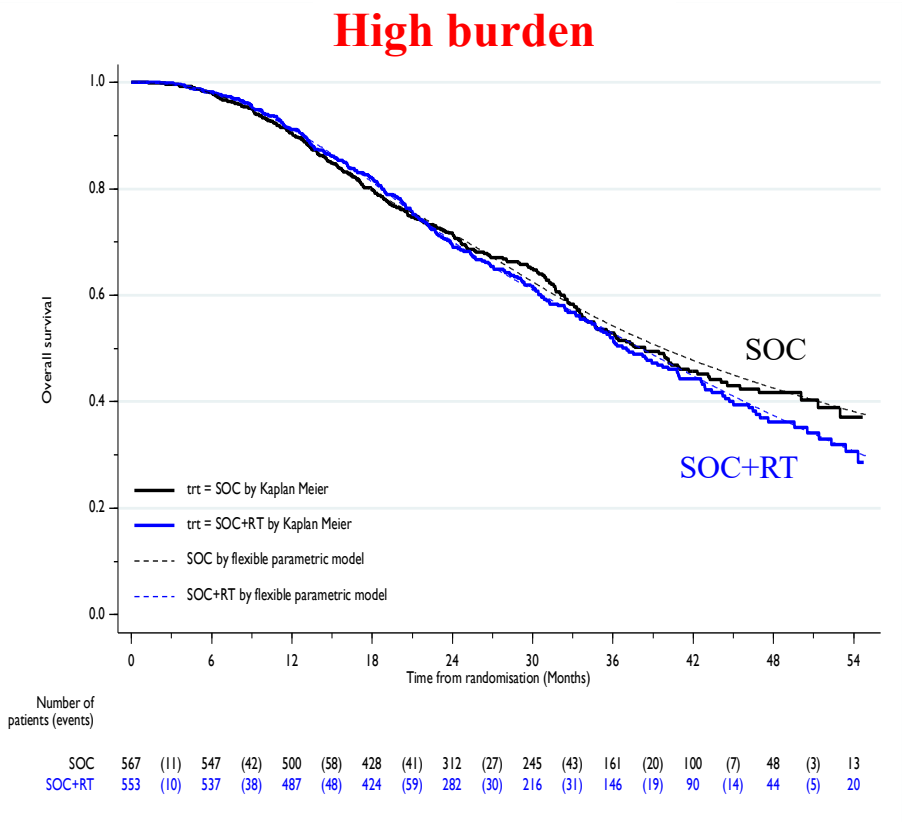




Kyriakopoulos CE, *JCO* 2018; 36: 1080-87.

Role of Prostate XRT: STAMPEDE – H



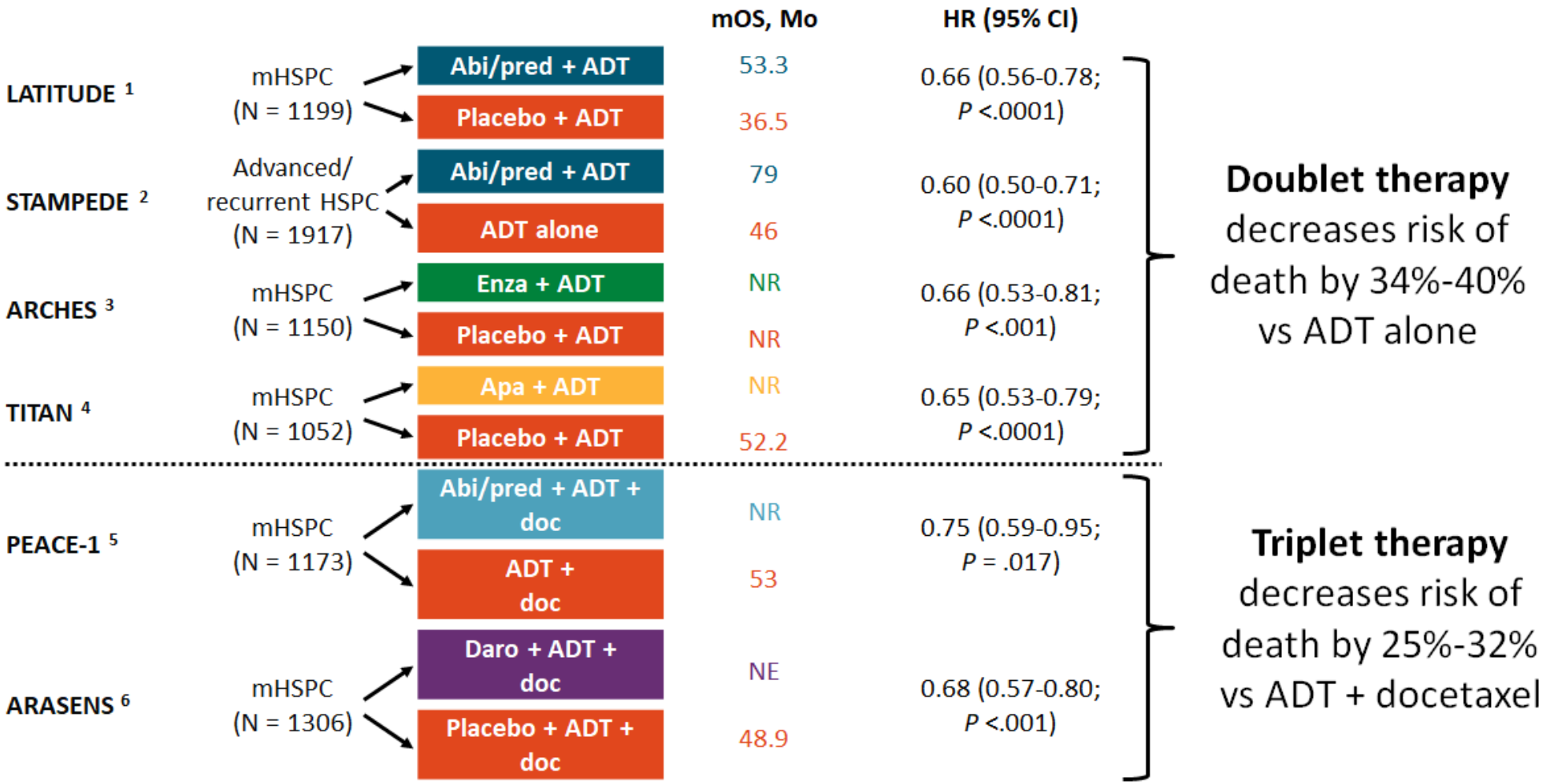


HR: 0.68 (95% CI 0.52-0.90); p=0.007
3 year OS (%):
SOC = 73%
SOC+RT = 81%

HR: 1.07 (95% CI 0.90-1.28); p=0.420
3 year OS (%):
SOC = 54%
SOC+RT = 53%

Parker C, *Lancet* 2018

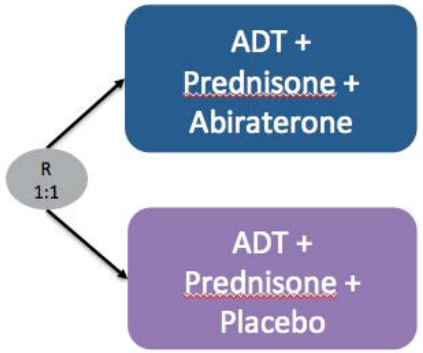
OS with Doublet and Triplet Therapy in mHSPC

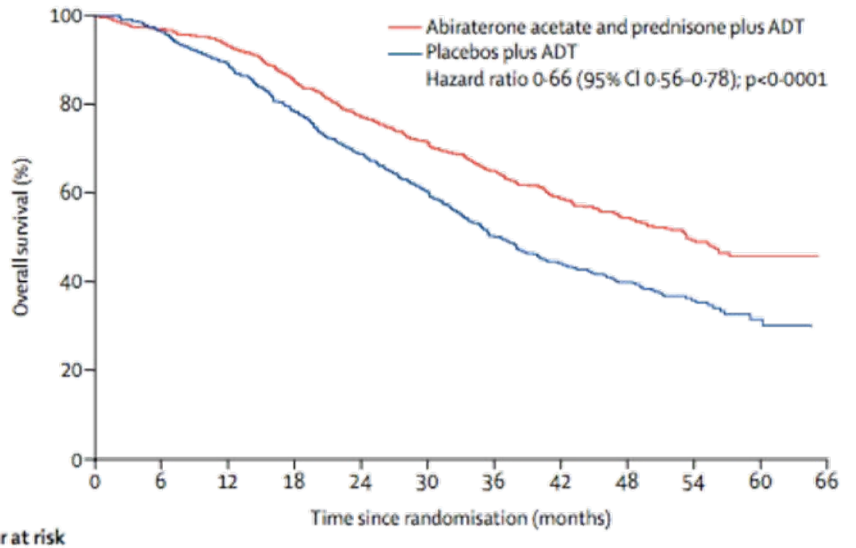


1. Fizazi. *Lancet Oncol.* 2019;20:686. 2. James. *Int J Cancer.* 2022;151:422. 3. *Armstrong. JCO.* 2022;40:1616. 4. Chi. *JCO.* 2021;39:2294. 5. Fizazi. *Lancet.* 2022;399:1695. 6. Smith. *NEJM.* 2022;386:1132.

ADT + Abiraterone > ADT alone in mHSPC

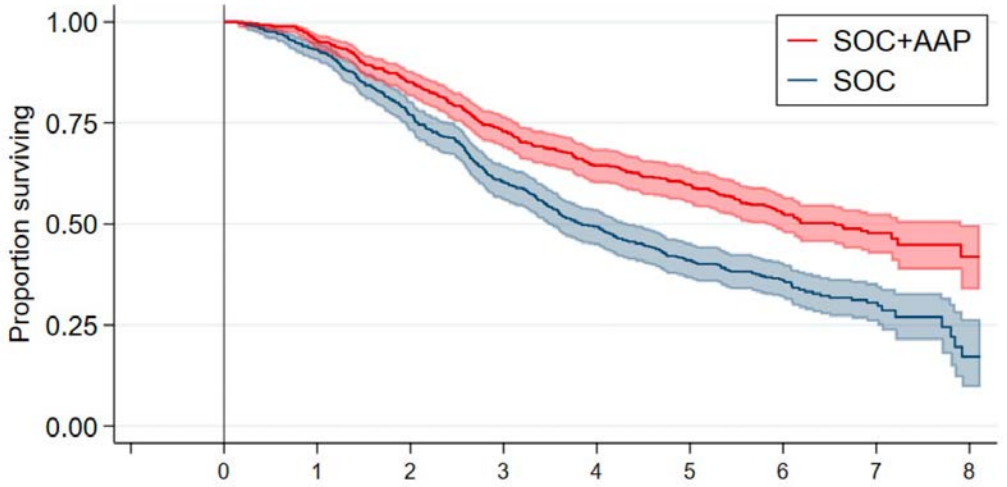
LATITUDE





Number at risk (number censored)												
Abiraterone acetate and prednisone plus ADT	597	565 (14)	529 (28)	479 (34)	425 (42)	389 (46)	351 (50)	311 (57)	240 (106)	124 (205)	40 (282)	0 (322)
Placebos plus ADT	602	564 (17)	505 (34)	432 (47)	368 (58)	315 (37)	256 (74)	220 (79)	165 (114)	69 (197)	23 (237)	0 (259)

STAMPEDE – G



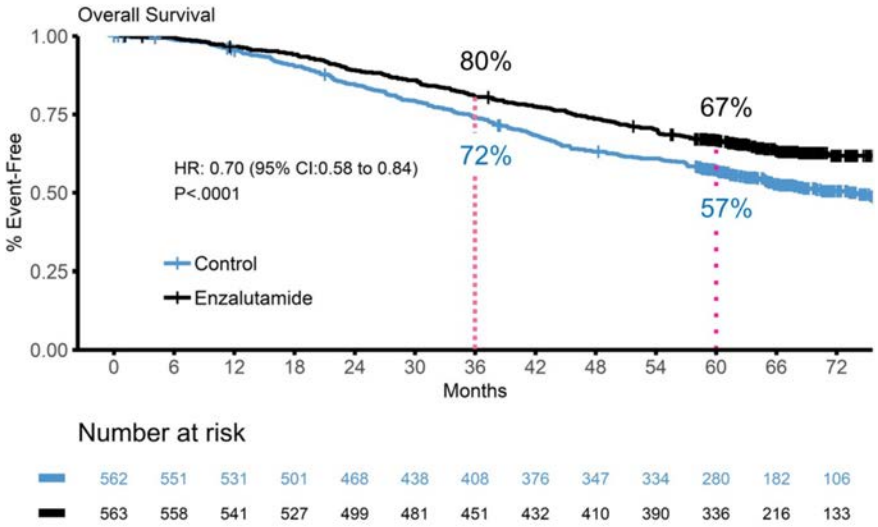
SOC									
At-risk	502	464	380	297	241	182	100	39	2
Censored	0	4	8	9	11	30	91	141	171
Died	0	34	114	196	250	290	311	322	329
SOC+AAP									
At-risk	501	474	421	357	314	284	176	56	6
Censored	0	4	6	10	12	19	95	204	251
Died	0	23	74	134	175	198	230	241	244

Study	N	Follow up	OS abiraterone	HR OS	95% CI
LATITUDE	1199	52 mo	53.3 mo	0.66	0.56-0.78
STAMPEDE	1003	72 mo	79 mo	0.60	0.50-0.71

Fizazi K, *N Engl J Med* 2017; 377: 352-60. James ND, *N Engl J Med* 2017; 377: 338-51. Fizazi K, et al. *Lancet Oncol* 2019; 20: 686-700. James ND, et al. *Ann Oncol* 2020; 31: S507-S549. Attard G et al. Lancet Oncol. 2023;24(5):443-456.

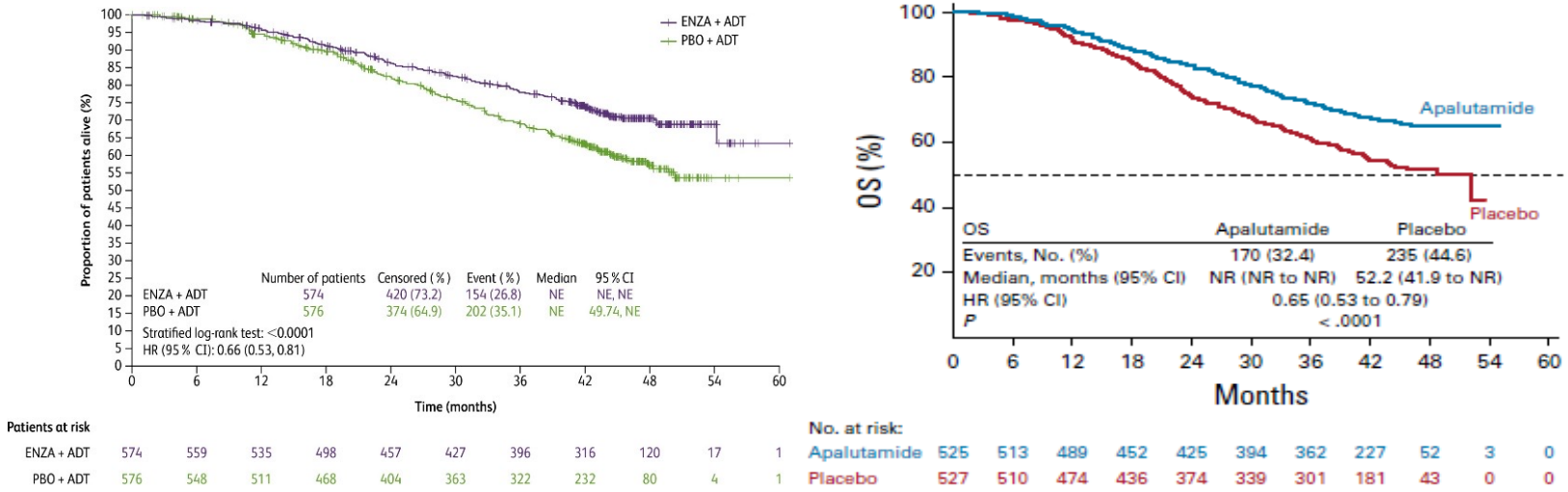
ADT + ARPI > ADT alone in mHSPC

ENZAMET (Enzalutamide)



Davis I et al. *NEJM* 2019;381:121-31.
Davis I et al. ASCO 2022; Abstract LBA5004.

ARCHES (Enzalutamide)



Armstrong A et al. ESMO 2021; Abstract LBA25.
Armstrong A et al. *J Clin Oncol* 2022;40(15):1616-22.

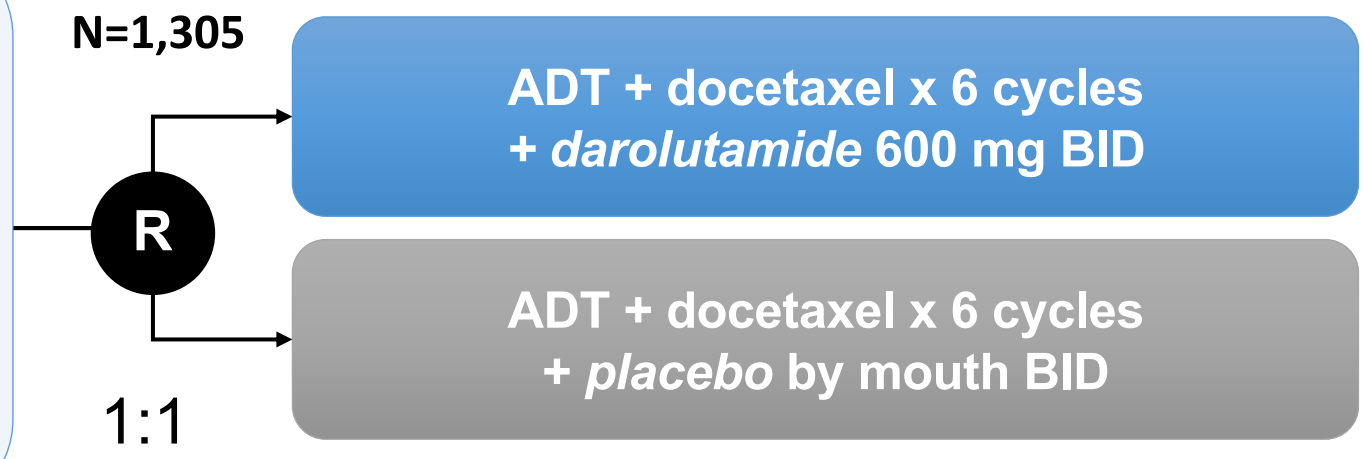
TITAN (Apalutamide)

Chi K et al. *J Clin Oncol* 2021;39(20):2294-303

Triplet Therapy: ARASENS trial (ADT/doce/daro)

Key Eligibility Criteria
- mHSPC
- ECOG 0 or 1
- Candidates for ADT + docetaxel

Stratification Factors
- Extent of disease (M1a vs 1b vs 1c)
- ALP level (< vs > ULN)

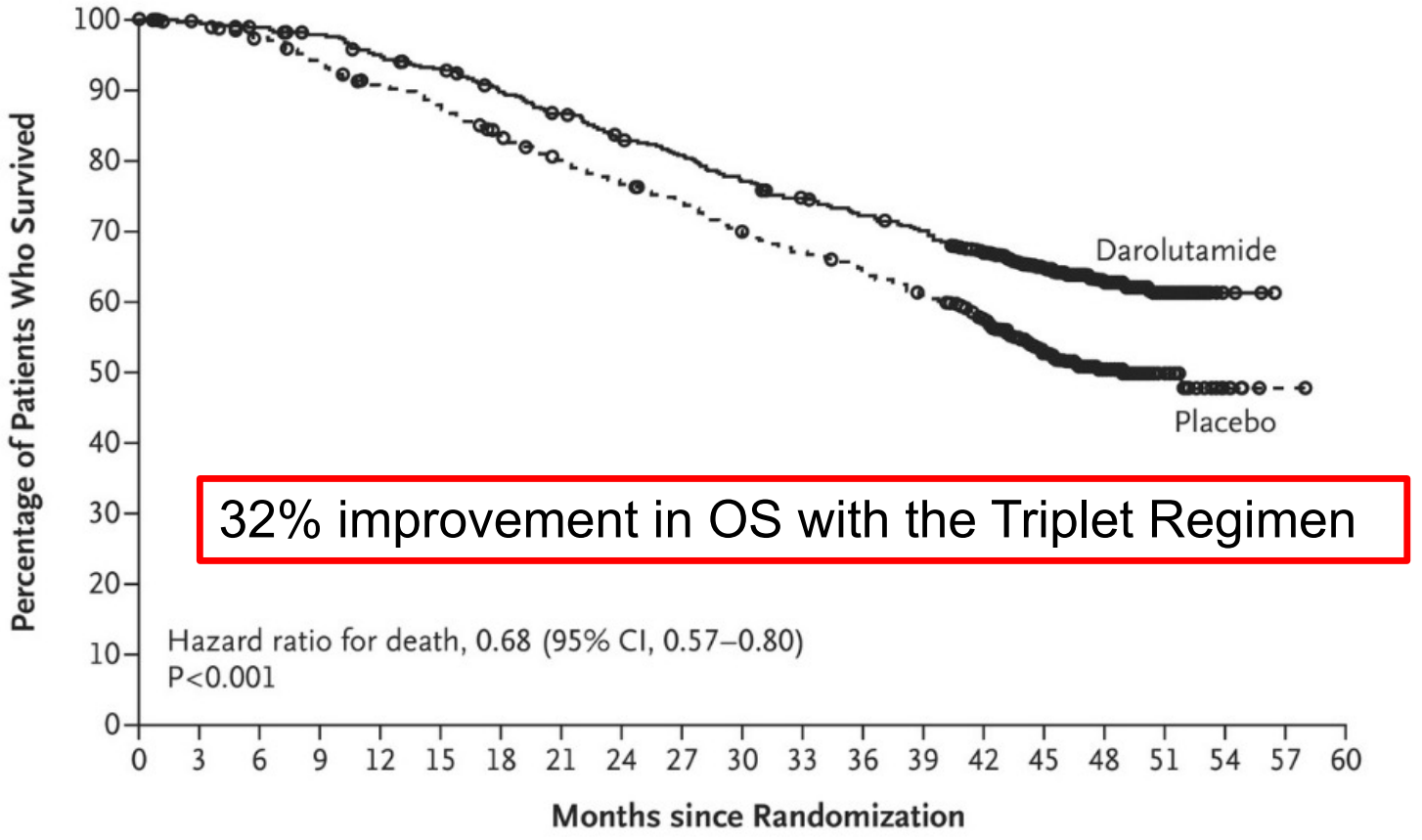


- **Primary endpoint:** OS
- **Key secondary endpoints:** time to mCRPC, time to initiation of subsequent anticancer therapy, time to SSE-free survival, time to first SSE, time initiation of subsequent RX, time to pain progression

Smith MR, et al. *N Engl J Med.* 2022 Mar 24;386(12):1132-1142.

ARASENS trial (ADT/doce ± darolutamide)

Overall Survival



32% improvement in OS with the Triplet Regimen

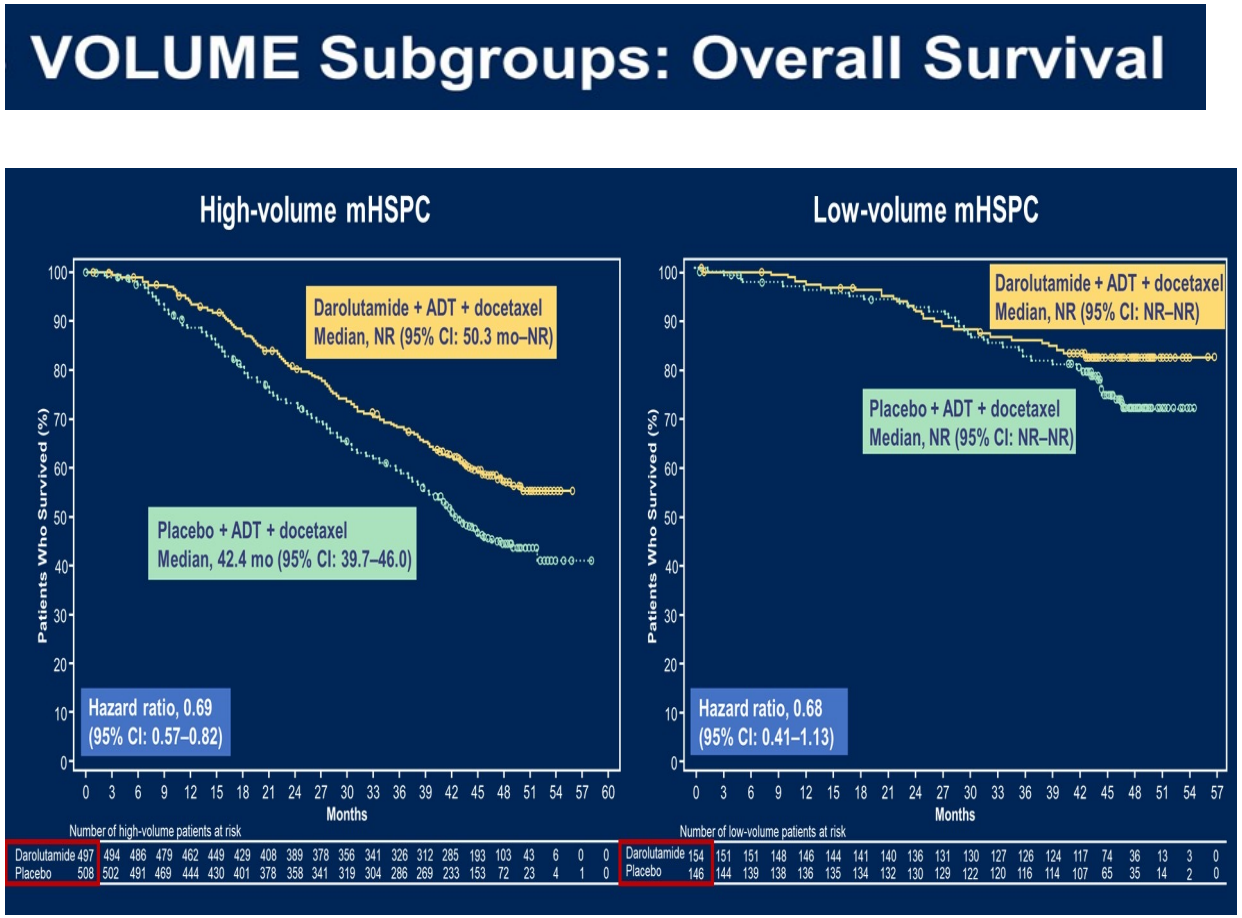
	Median Survival (95% CI)
	mo
Darolutamide	NE
Placebo	48.9 (44.4–NE)

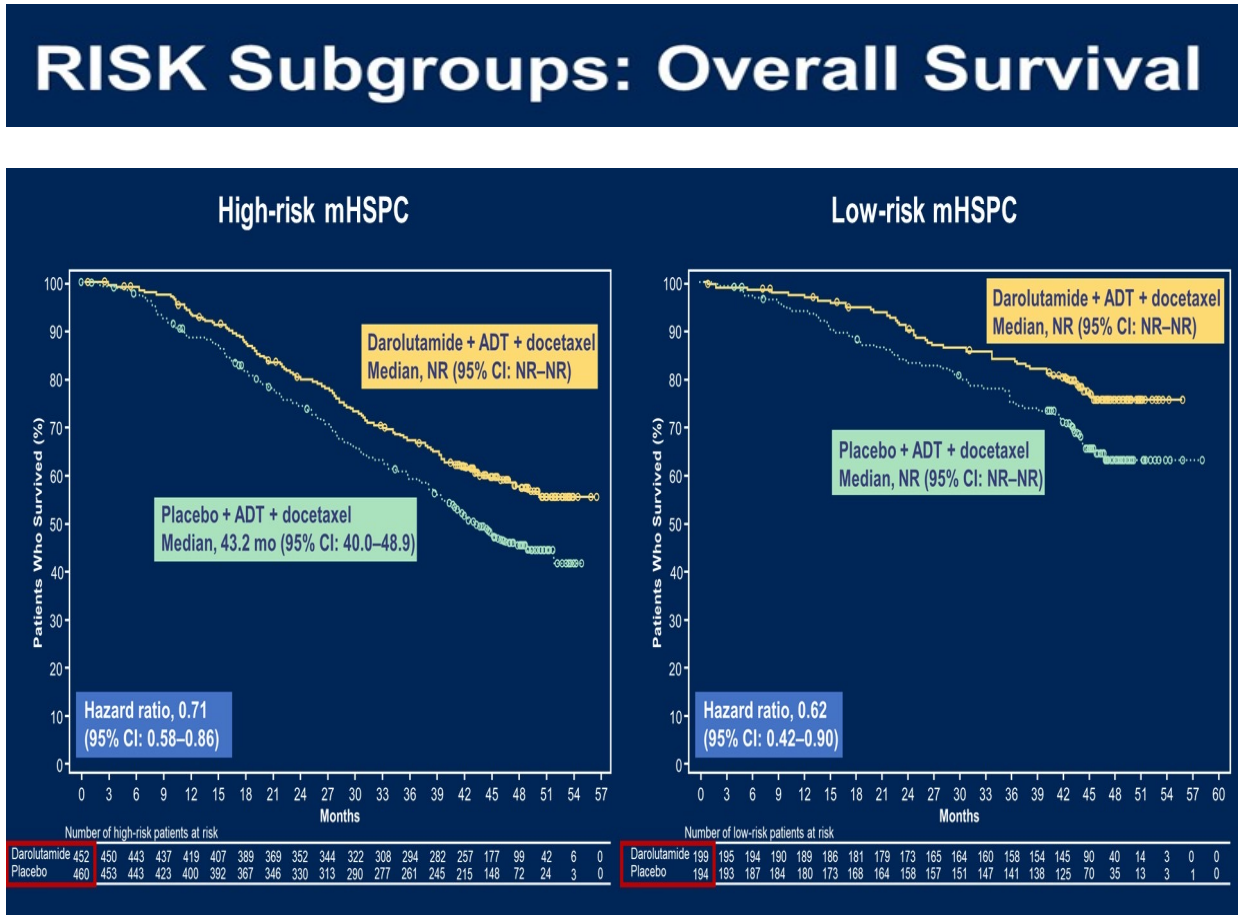
No. at Risk

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 MR, et al. *NEJM* 2022;386:1132-42.

ARASENS trial: Two important subsets





Hussain M, et al. *ASCO GU.* 2023. Hussain M et al. *J Clin Oncol* 2023;41(20):3595-3607.

Triplet Therapy: Design of PEACE-1 (2x2)

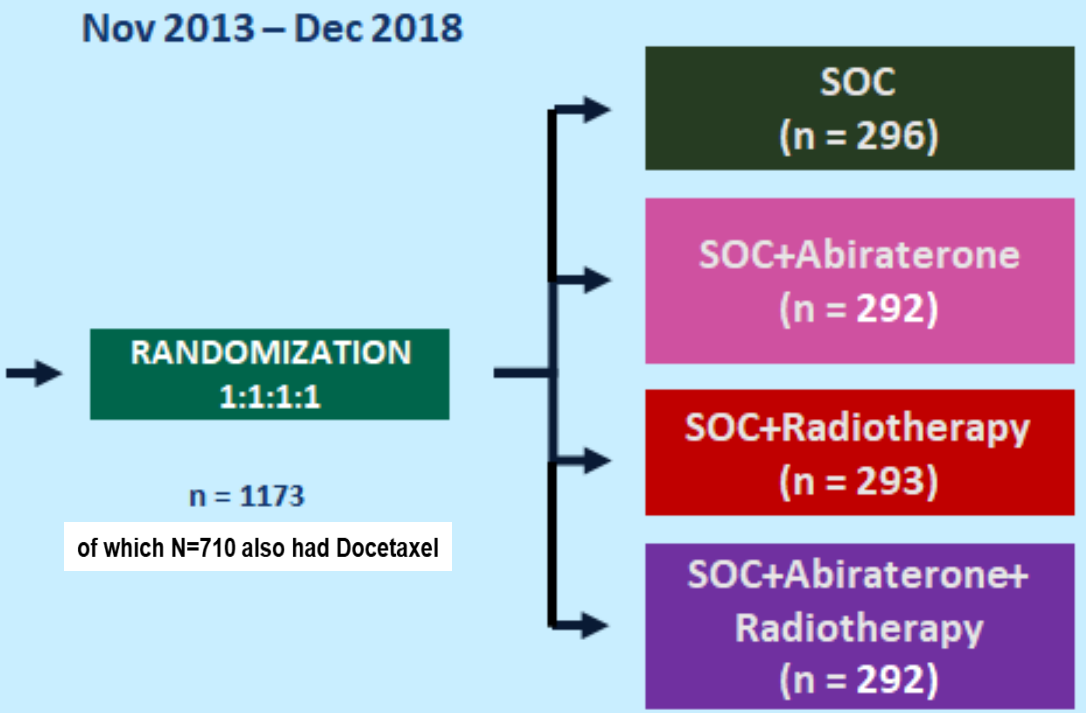
From 2017, accrual restricted to ADT + docetaxel as SOC

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

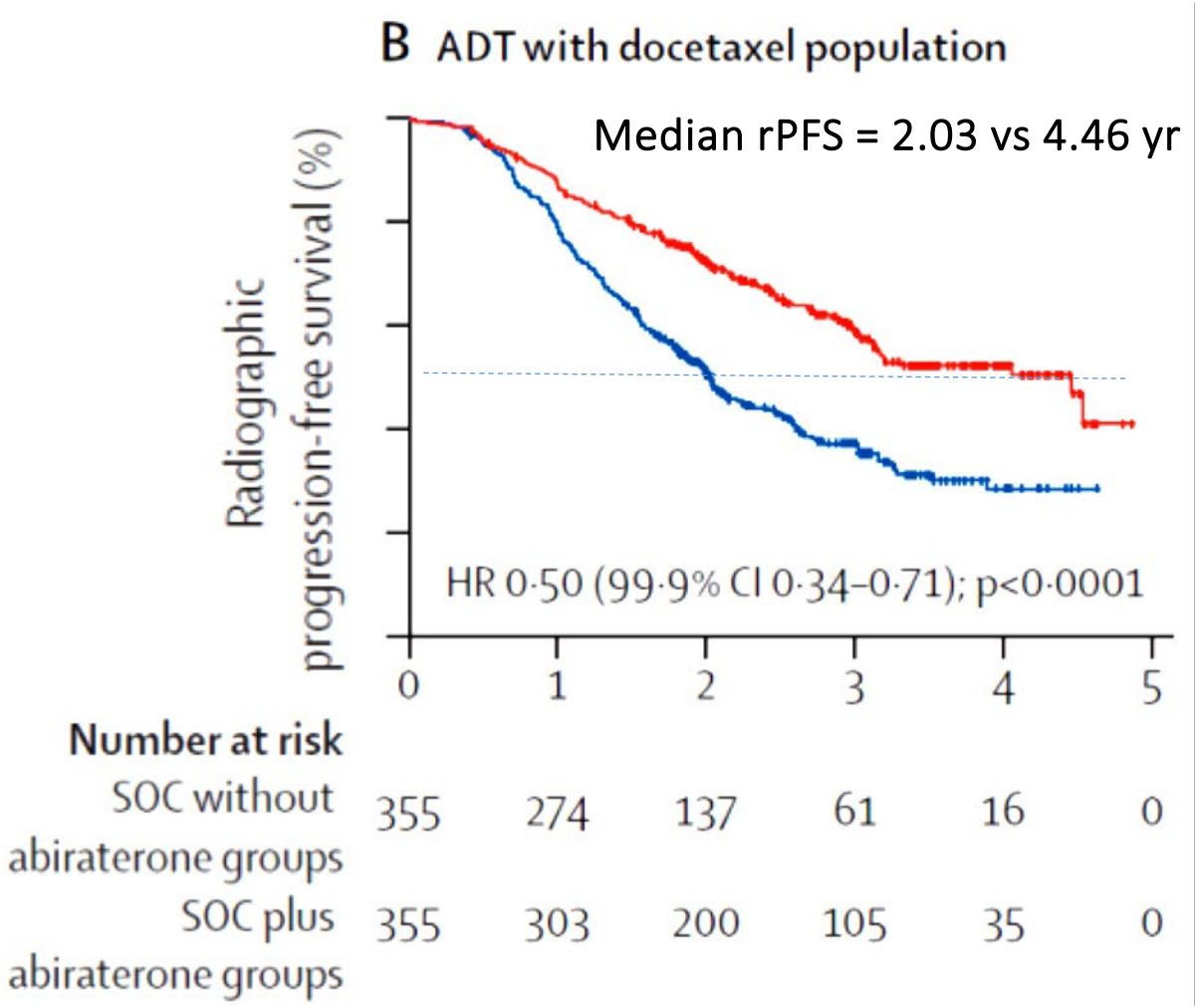
Stratification
ECOG PS (0 vs 1-2)
Metastatic sites (LN vs bone vs visceral)
Type of castration (orchidectomy vs LHRH agonist vs LHRH antagonist)
Docetaxel (yes vs no)

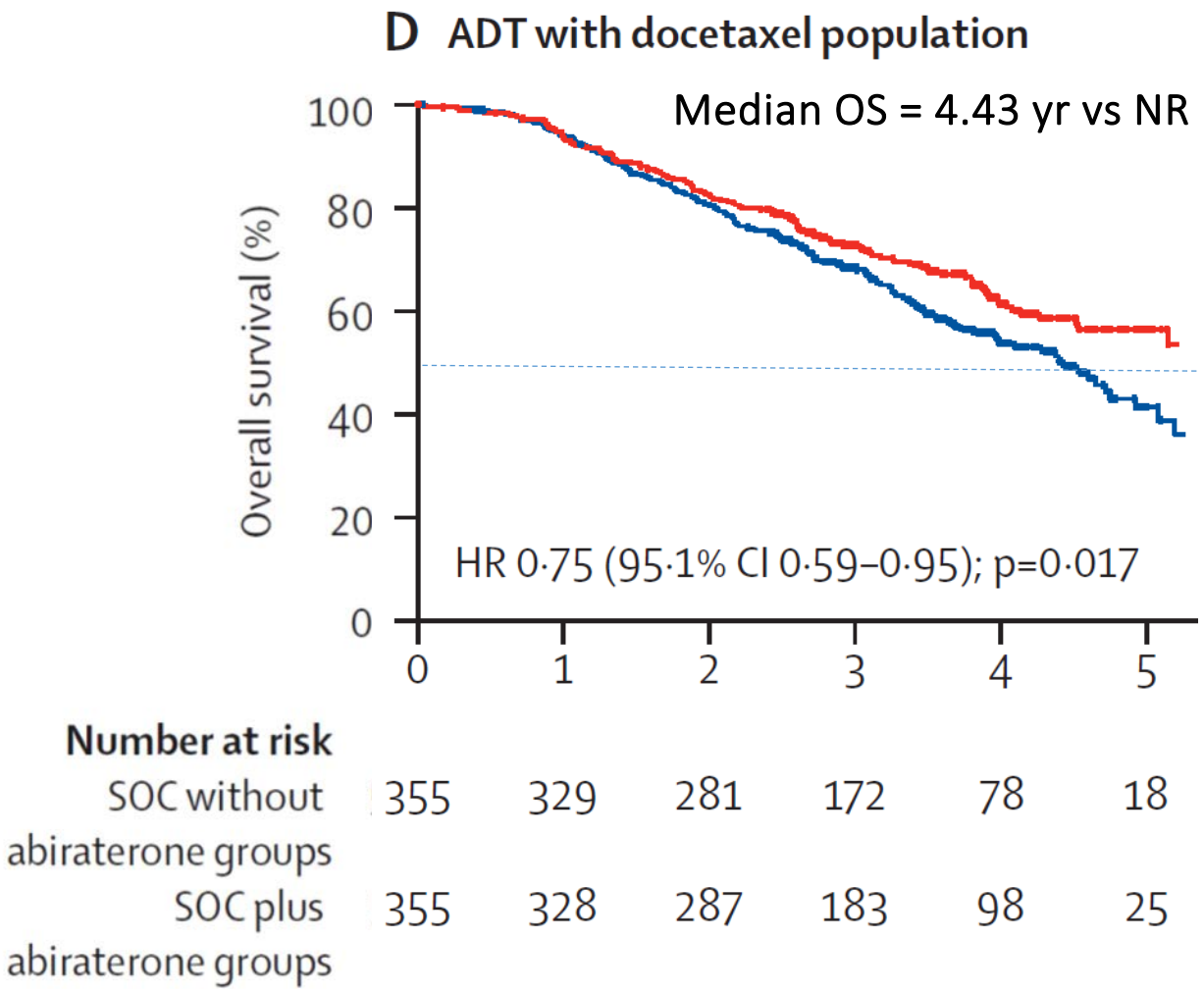


ECOG PS, Eastern Cooperative Oncology Group performance status

Bossi A, *ASCO Annual* 2023

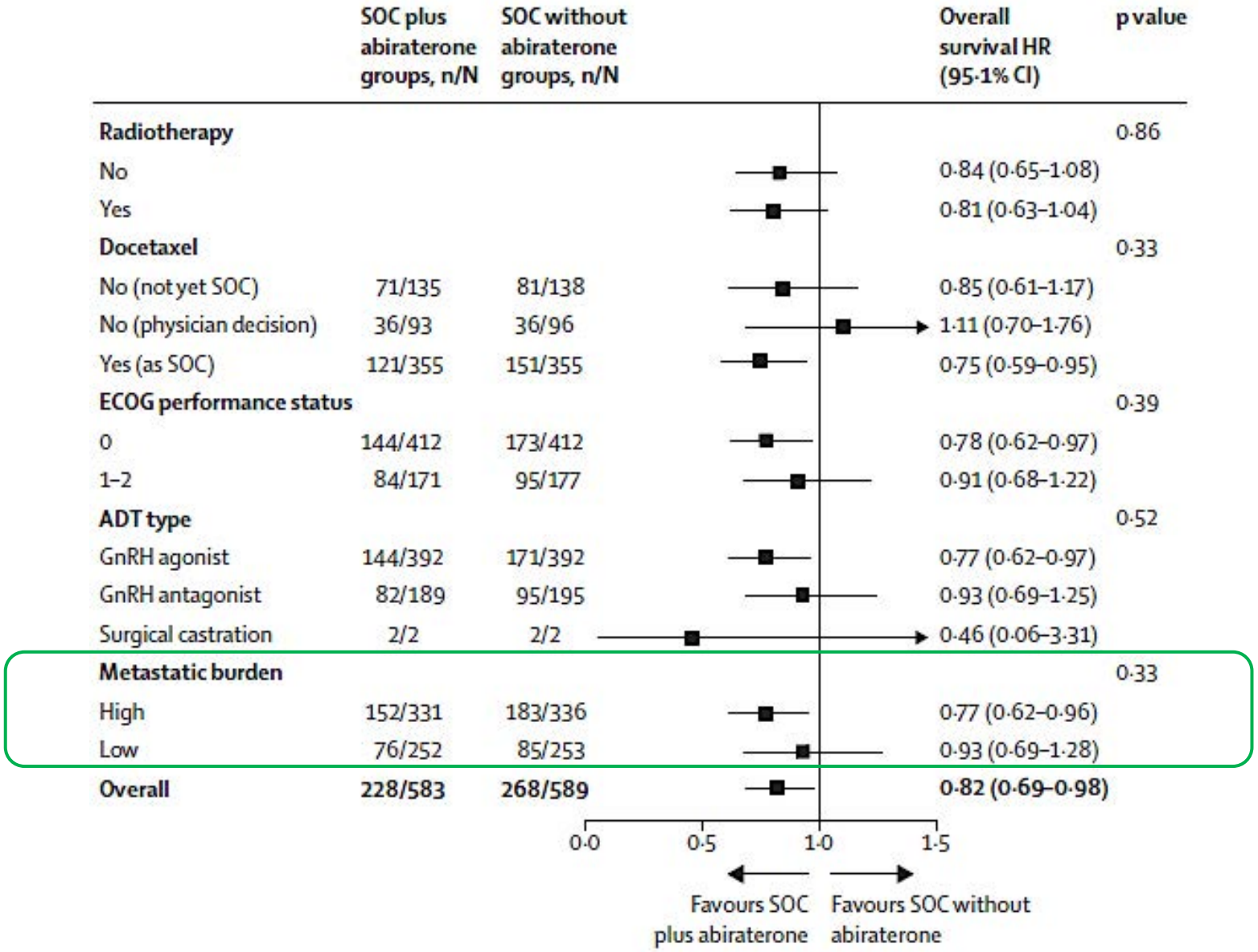
PEACE-1: ADT/doce + Abiraterone > ADT/doce





Fizazi K, *Lancet* 2022

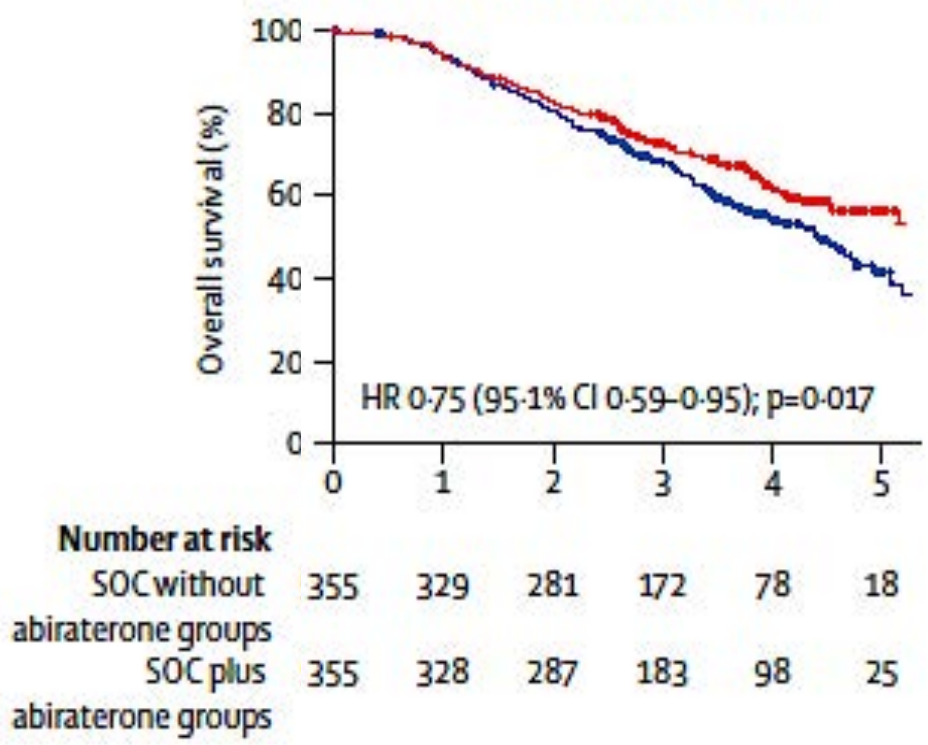
PEACE-1 (Abiraterone): OS Subsets



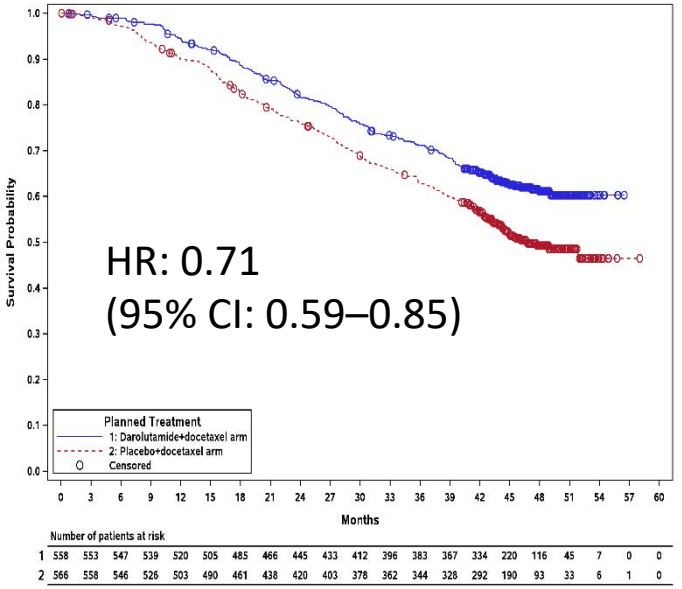
Fizazi K, *Lancet* 2022

Triplet: Consistent benefit in *de novo* mHSPC

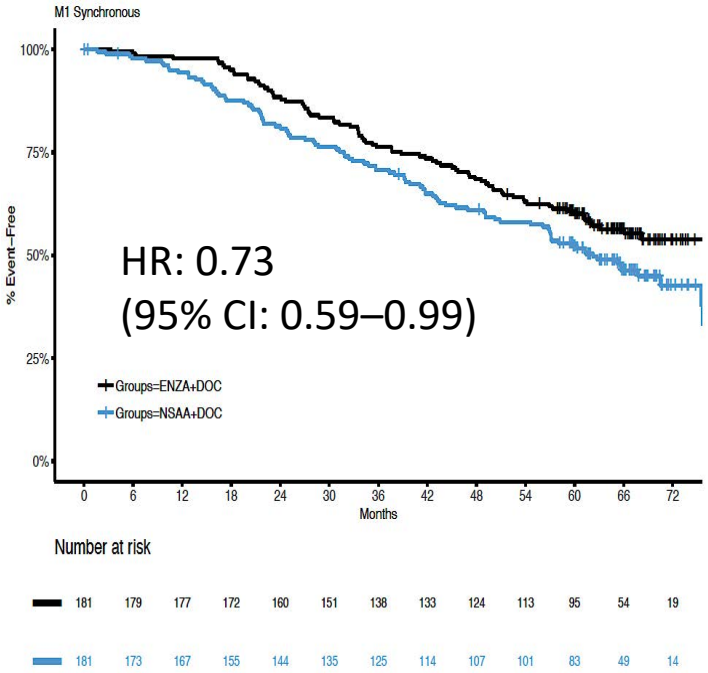
ADT + Doc + Abi > ADT + Doc
PEACE-1 (all *De novo*)



ADT + Doc + Daro > ADT + Doc
ARASENS (*De novo* subset)

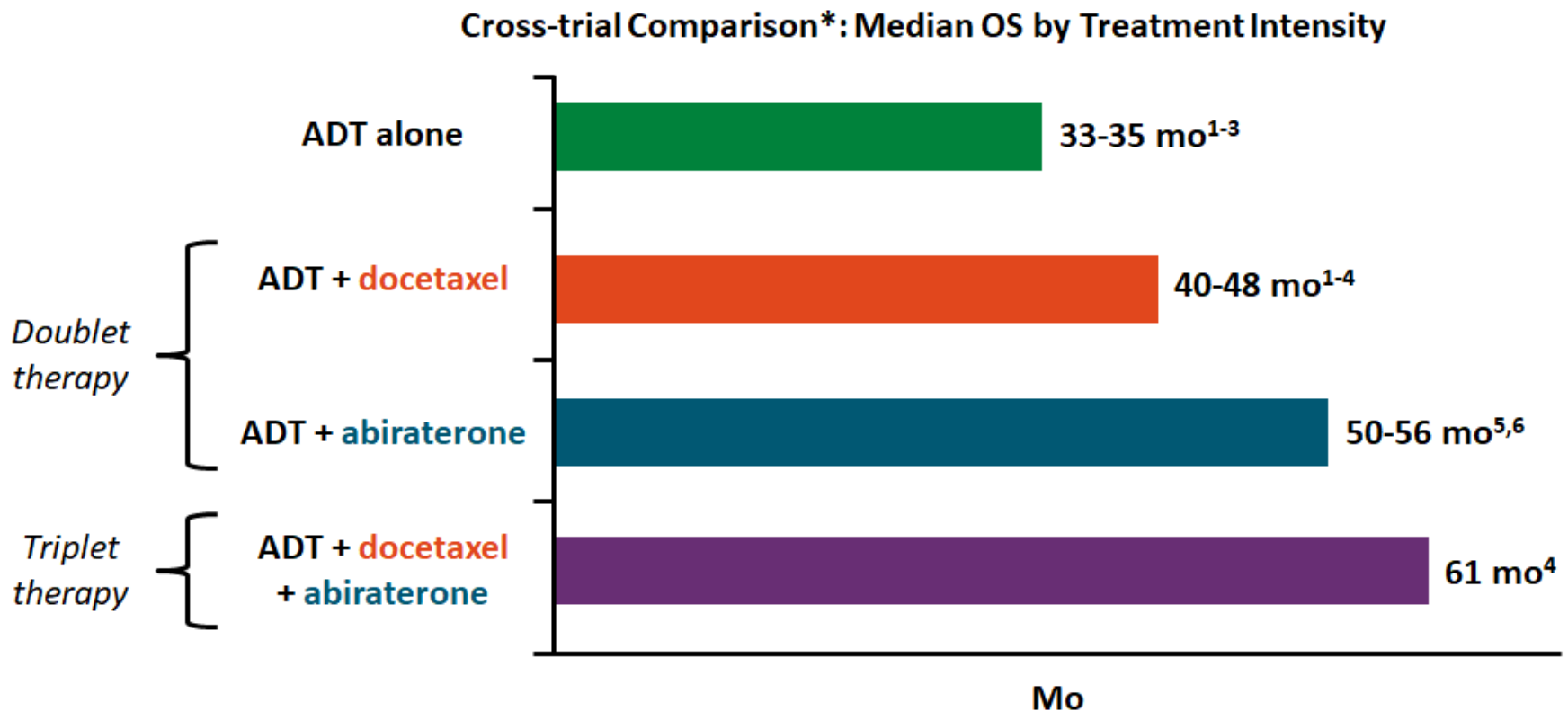


ADT + Doc + Enza > ADT + Doc
ENZAMET (*De novo* subset)



Fizazi K *Lancet* 2022; Smith M *NEJM* 2022; Davis I *ASCO* 2022

Median OS with Treatment Intensification in *de novo* High-Volume mHSPC



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

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

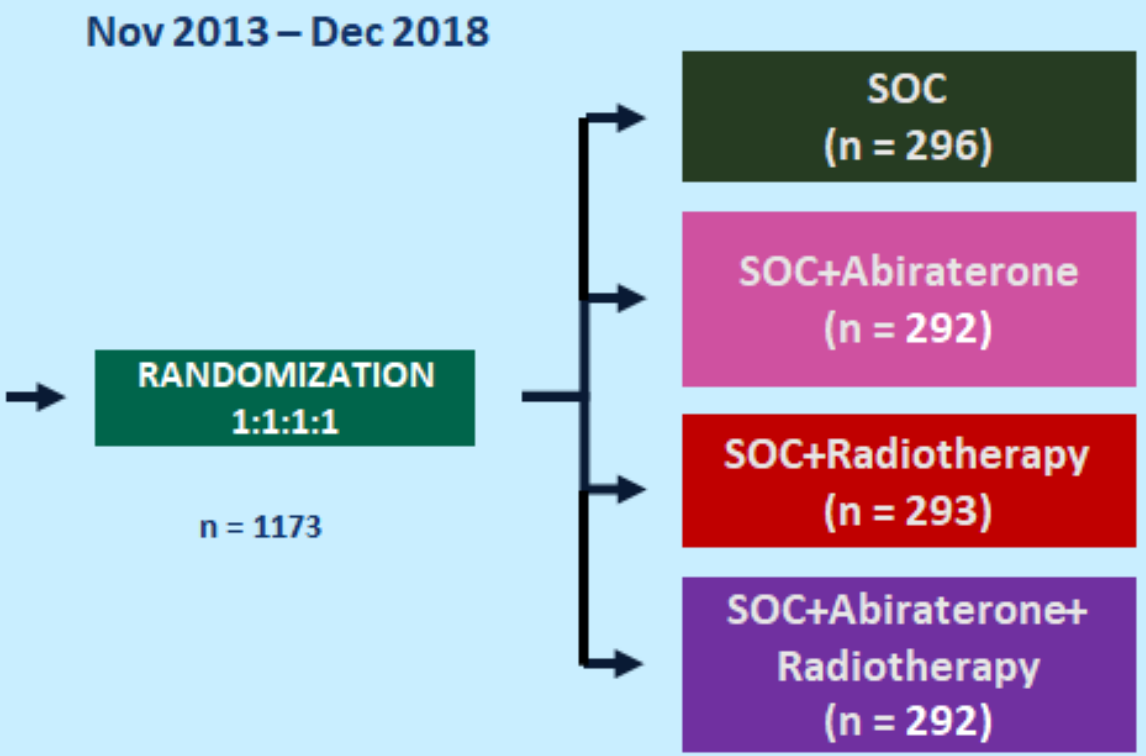
Role of Prostatic XRT: PEACE-1 (2x2)

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)

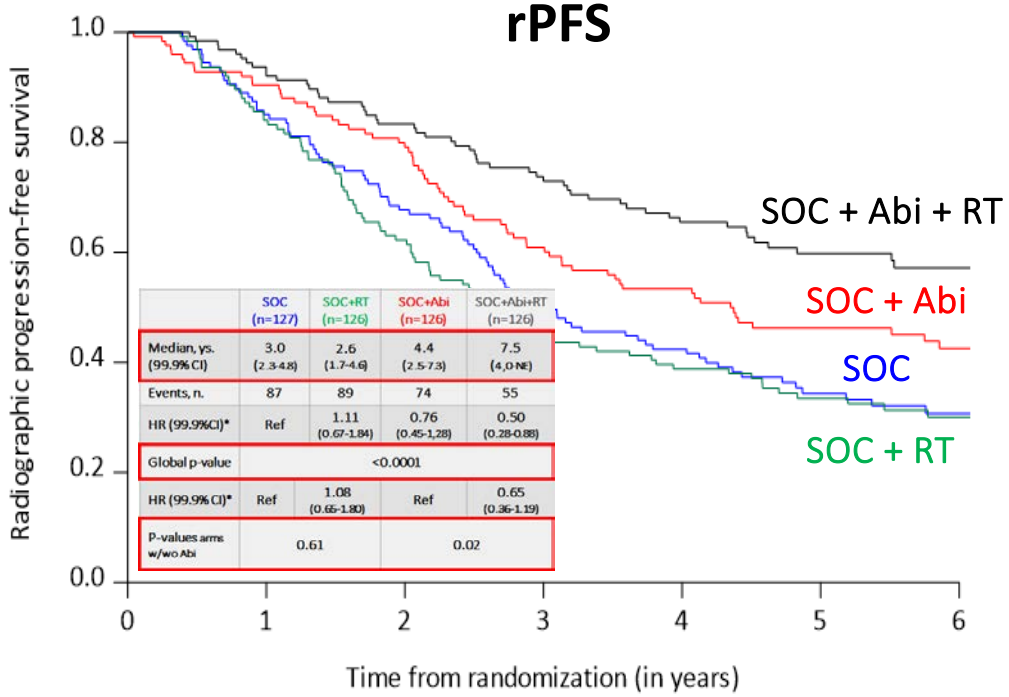


ECOG PS, Eastern Cooperative Oncology Group performance status

Bossi A, *ASCO Annual* 2023

Role of Prostate XRT: Efficacy outcomes

rPFS

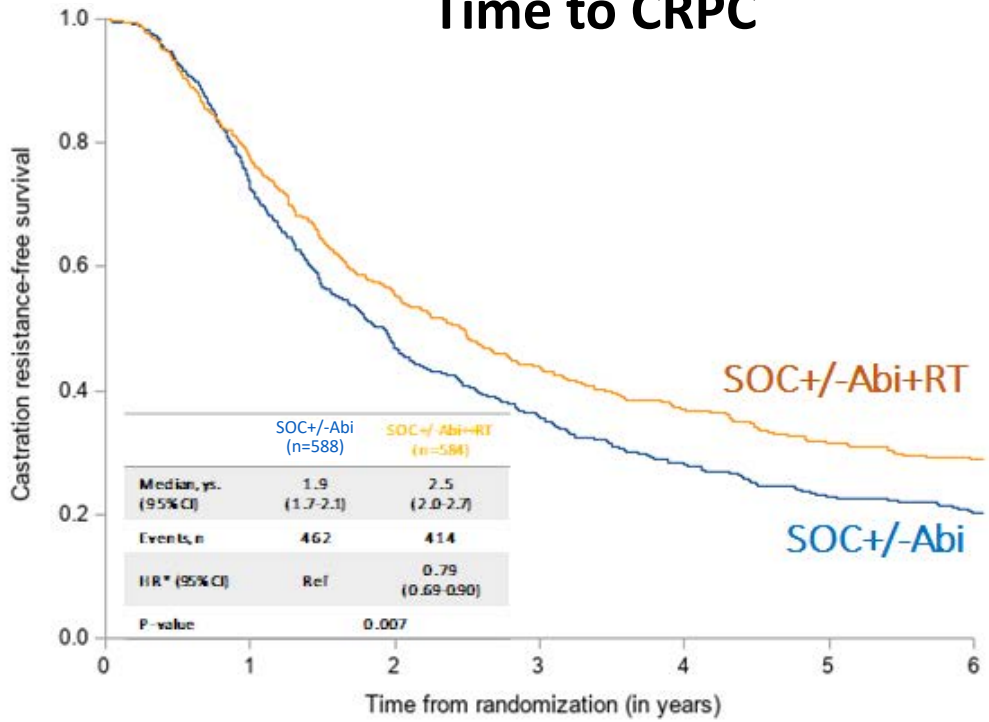


	SOC (n=127)	SOC+RT (n=126)	SOC+Abi (n=126)	SOC+Abi+RT (n=126)
Median, ys. (99.9% CI)	3.0 (2.3-4.8)	2.6 (1.7-4.6)	4.4 (2.5-7.3)	7.5 (4.0-NE)
Events, n.	87	89	74	55
HR (99.9%CI)*	Ref	1.11 (0.67-1.84)	0.76 (0.45-1.28)	0.50 (0.28-0.88)
Global p-value	<0.0001			
HR (99.9% CI)*	Ref	1.08 (0.66-1.80)	Ref	0.65 (0.36-1.19)
P-values arms w/wo Abi	0.61		0.02	

Number at risk (censored)

SOC 127(0)	108(0)	86(0)	64(0)	53(1)	34(11)	20(22)
SOC+Abi 126(0)	113(1)	96(4)	73(5)	64(5)	46(15)	31(27)
SOC+RT 126(0)	105(1)	77(2)	58(2)	48(2)	36(8)	23(18)
SOC+Abi+RT 126(0)	116(0)	105(0)	89(3)	79(4)	60(17)	34(41)

Time to CRPC



	SOC+/-Abi (n=588)	SOC+/-Abi+RT (n=584)
Median, ys. (95% CI)	1.9 (1.7-2.1)	2.5 (2.0-2.7)
Events, n	462	414
HR* (95% CI)	Ref	0.79 (0.69-0.90)
P-value	0.007	

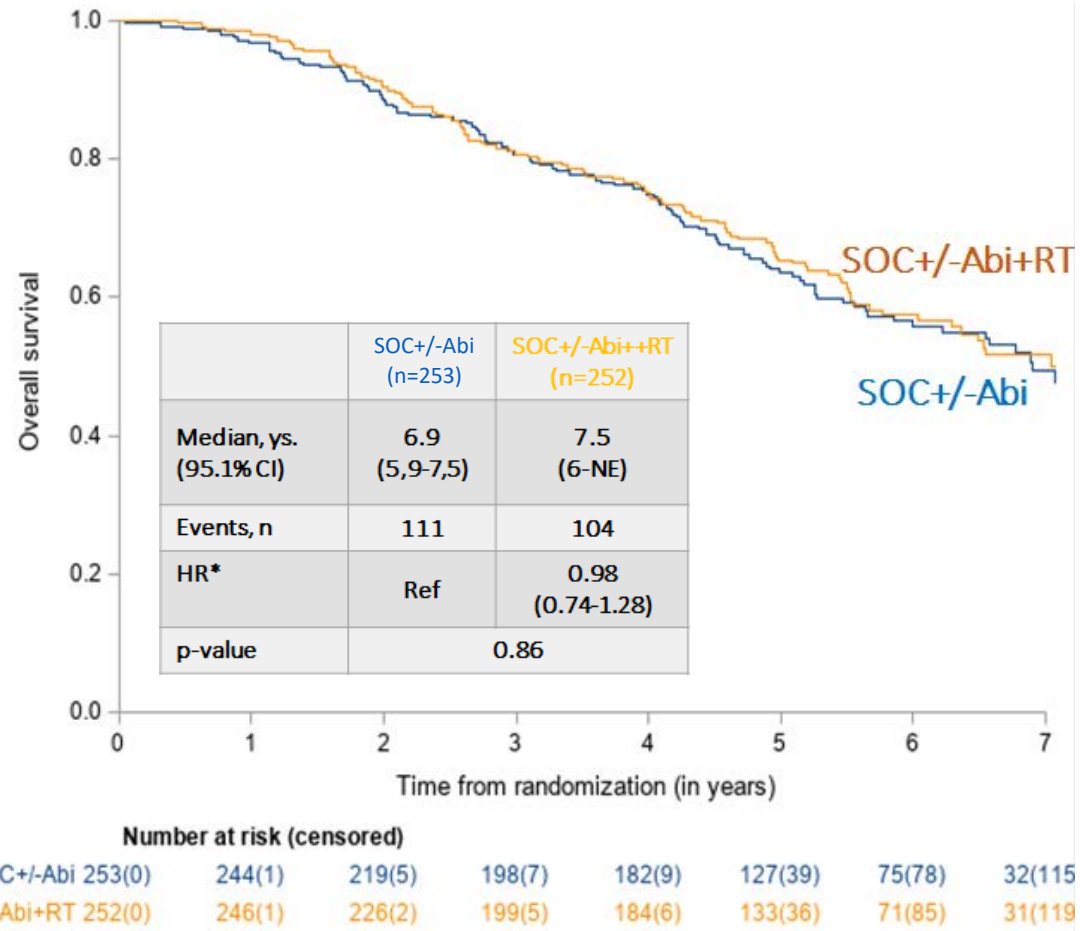
Number at risk (censored)

SOC+/-Abi 588(0)	424(5)	271(8)	204(10)	160(11)	107(37)	67(67
SOC+/-Abi+RT 584(0)	448(6)	320(7)	250(10)	210(11)	144(50)	81(10

Bossi A, *ASCO Annual* 2023

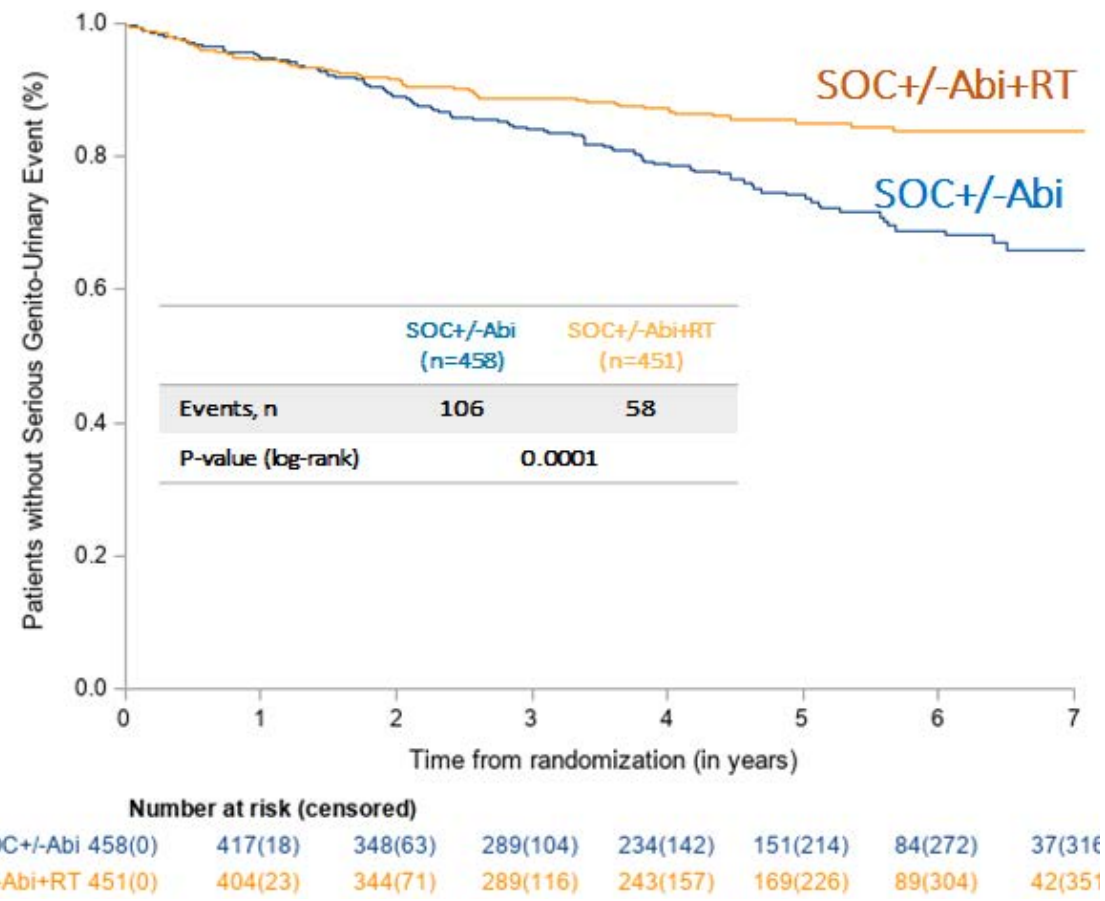
Role of Prostate XRT: OS, and GU events

OS (low-volume pts)



	SOC+/-Abi (n=253)	SOC+/-Abi++RT (n=252)
Median, ys. (95.1% CI)	6.9 (5,9-7,5)	7.5 (6-NE)
Events, n	111	104
HR*	Ref	0.98 (0.74-1.28)
p-value	0.86	

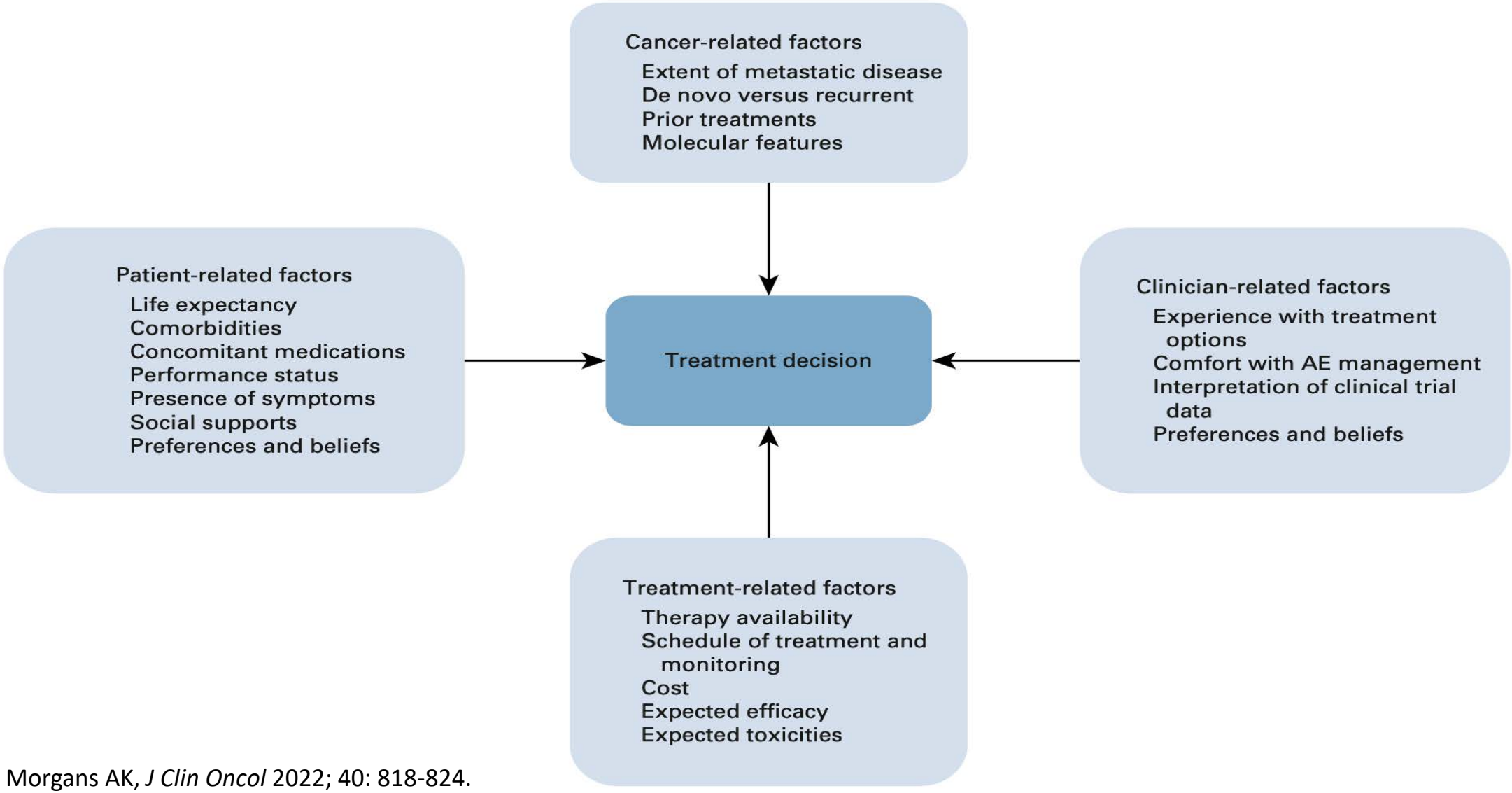
Time to serious GU event



	SOC+/-Abi (n=458)	SOC+/-Abi+RT (n=451)
Events, n	106	58
P-value (log-rank)	0.0001	

Bossi A, *ASCO Annual* 2023

Factors Contributing to Treatment Choice

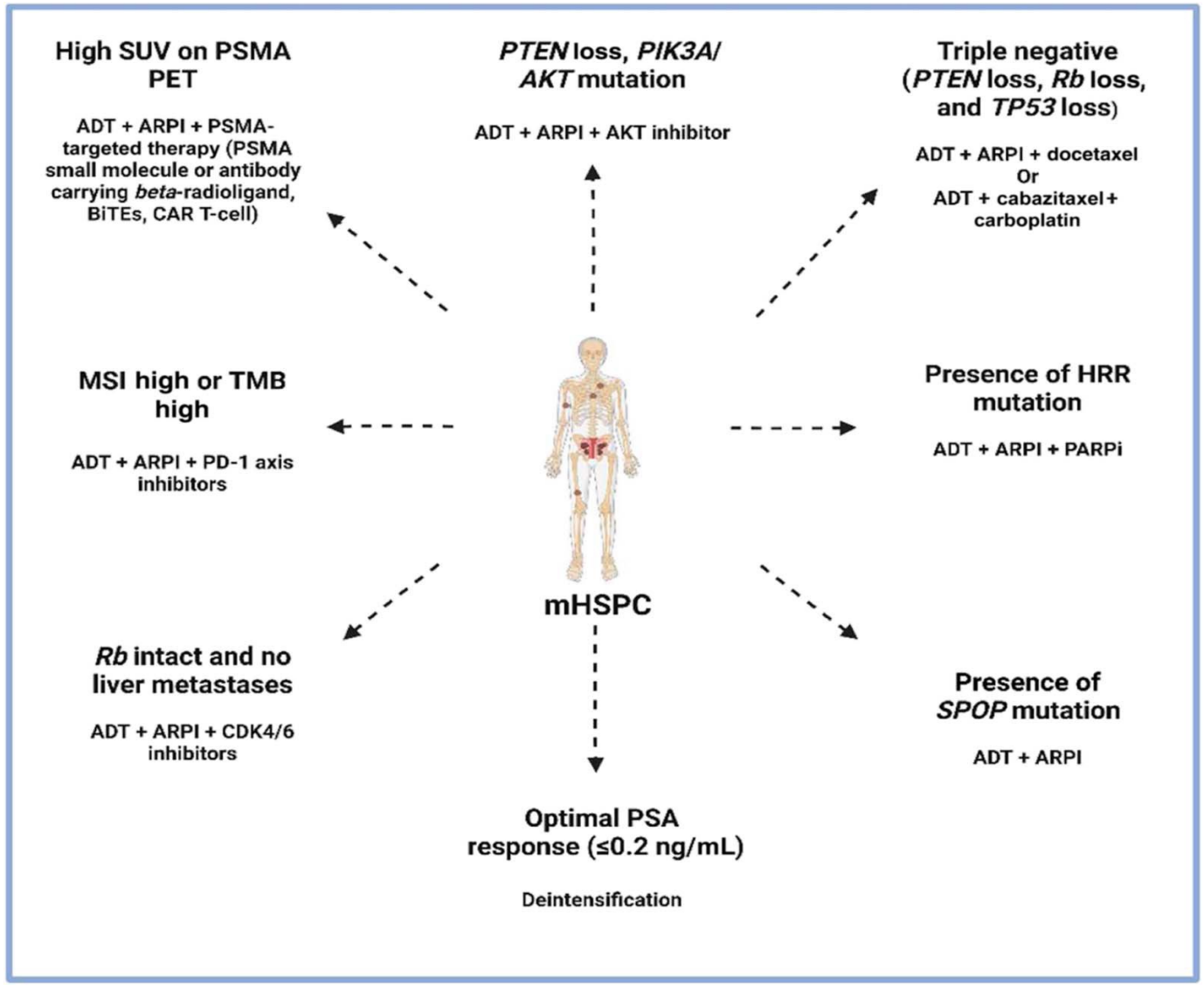


Morgans AK, *J Clin Oncol* 2022; 40: 818-824.

Selected Ongoing Phase III Trials in mHSPC

Trial	Regimens	Population
ARANOTE (NCT04736199)	ADT ± darolutamide (without docetaxel)	mHSPC, unselected (N = 662)
KEYNOTE-991 (NCT04191096)	ADT + enzalutamide ± pembrolizumab	mHSPC, unselected (N = 1,232)
CAPItello-281 (NCT04493853)	ADT + abiraterone acetate ± capivasertib	*De novo* mHSPC, PTEN loss on IHC (N = 1000)
CYCLONE 03 (NCT05288166)	ADT + abemaciclib + abiraterone/prednisone	High-risk mHSPC, unselected (N = 900)
TALAPRO-3 (NCT04821622)	Enzalutamide ± talazoparib	mHSPC, HRR gene mutation (N = 550)
AMPLITUDE (NCT04497844)	Abiraterone/prednisone ± niraparib	mHSPC, HRR gene mutation (N = 788)
PSMAddition (NCT04720157)	AR-directed tx + ADT ± ^{177}Lu-PSMA-617	mHSPC, PSMA-PET positive (N = 1,126)

The future of mHSPC treatment



Hamid A, et al. *Am Soc Clin Oncol Educ Book*, 2023, e390166.

Treatment of mHSPC: Conclusions

- Almost no role for ADT alone (except in exceptional cases *e.g.* life expectancy < 2 yrs)
- Doublets of ADT + ARPI are applicable to most (except those with visceral metastasis or other high-risk genomic or clinical features)
- No role of ADT + docetaxel doublet (given superiority of ADT+ doce + ARPI triplets). Triplets have replaced ADT+ docetaxel
- Clearest benefit of triplet: *De novo* high-volume mHSPC
- Prostate XRT may improve OS, delay GU events in low-volume HSPC
- Biomarkers may guide treatment decisions in the near future

MODULE 3: New Considerations with PARP Inhibitors for Metastatic Castration-Resistant Prostate Cancer (mCRPC) – Dr Bryce

RTP
RESEARCH
TO PRACTICE

Consulting Faculty Questions

Selection of optimal PARP inhibitor for mCRPC; use of PARP inhibitors for patients with non-BRCA mutations

Neil Love, MD

Andrew J Armstrong, MD, ScM

Rana R McKay, MD

RTP RESEARCH TO PRACTICE

QUESTIONS FOR THE FACULTY

Andrew J Armstrong, MD, ScM

Rana R McKay, MD

For a patient with BRCA-mutated mCRPC, how do you choose among the 3 approved PARP inhibitor-based combinations?

In which situations would you offer one of these combinations to a patient with mCRPC and an HRR mutation other than BRCA? What about patients without a documented HRR gene mutation?

RTP RESEARCH TO PRACTICE

Consulting Faculty Questions

PARP inhibitor-associated side effects; risk of second cancer with prolonged exposure to PARP inhibitors

Neil Love, MD

Rana R McKay, MD

QUESTIONS FOR THE FACULTY

Rana R McKay, MD

How do you typically manage the fatigue and anemia associated with PARP inhibitors? What is your threshold for dose reduction?

How do you integrate the increased risk of AML/MDS in clinical decision-making?

What is your usual approach to mutation testing for possible use of a PARP inhibitor for a patient with mCRPC?

 Dr Aggarwal	Multigene germline and somatic/NGS
 Dr Antonarakis	Multigene germline and somatic/NGS
 Dr Bryce	Multigene germline and somatic/NGS
 Dr Heath	Multigene germline and somatic/NGS
 Dr Sartor	Multigene germline and somatic/NGS
 Dr Armstrong	Multigene germline and somatic/NGS
 Dr McKay	Multigene germline and somatic/NGS

NGS = next-generation sequencing

RTP RESEARCH TO PRACTICE

In addition to BRCA1/2, what other homologous recombination repair (HRR) mutations will lead you to attempt to use a PARP inhibitor for mCRPC? What about LOH?

 Dr Aggarwal	PALB2, RAD51
 Dr Antonarakis	PALB2, RAD51B/C/D, RAD54L; perhaps CDK12 or really high gLOH (eg, >20%)
 Dr Bryce	PALB2, FANCA
 Dr Heath	CHEK2, CDK12, BARD1, BRIP1, PALB2, RAD51b, RAD51c, RAD51d
 Dr Sartor	PALB2, RAD54L, RAD51 family members
 Dr Armstrong	ATM, CDK12, CHEK2, PALB2, RAD51 family members
 Dr McKay	PALB2

RTP RESEARCH TO PRACTICE

What was the age of the last patient in your practice with mCRPC who received a PARP inhibitor in combination with ADT and a secondary hormonal agent? What HRR gene mutation did the patient have? Which specific regimen did the patient receive?

	Age	HRR gene mutation	Treatment
 Dr Aggarwal	73 years	gBRCA2	Talazoparib + enzalutamide
 Dr Antonarakis	62 years	BRCA2 (somatic)	Talazoparib + enzalutamide
 Dr Bryce	No patient	Not applicable	Not applicable
 Dr Heath	74 years	BRCA2	Talazoparib + enzalutamide
 Dr Sartor	59 years	BRCA2	Olaparib + abiraterone
 Dr Armstrong	63 years	BRCA2 (somatic)	Olaparib + abiraterone
 Dr McKay	65 years	PALB2	Talazoparib + enzalutamide

A 65-year-old man with a germline BRCA2 mutation presents with HSPC metastatic to the bone and receives docetaxel and ADT, experiencing response then progression (PSMA-positive). Regulatory and reimbursement issues aside, what systemic treatment would you most likely recommend?

 Dr Aggarwal	Olaparib + abiraterone
 Dr Antonarakis	Olaparib + abiraterone
 Dr Bryce	Talazoparib + enzalutamide
 Dr Heath	Lutetium Lu 177 vipivotide tetraxetan
 Dr Sartor	Olaparib + abiraterone
 Dr Armstrong	Olaparib + abiraterone
 Dr McKay	Talazoparib + enzalutamide

RTP RESEARCH TO PRACTICE

A 65-year-old man with a germline BRCA2 mutation presents with HSPC metastatic to the bone and receives enzalutamide and ADT, experiencing response then progression (PSMA-positive). Regulatory and reimbursement issues aside, what systemic treatment would you most likely recommend?

 Dr Aggarwal	Olaparib
 Dr Antonarakis	Olaparib
 Dr Bryce	Olaparib
 Dr Heath	Lutetium Lu 177 vipivotide tetraxetan
 Dr Sartor	Olaparib + abiraterone
 Dr Armstrong	Olaparib
 Dr McKay	Olaparib

RTP RESEARCH TO PRACTICE

New Considerations with the Use of PARP Inhibitors for Metastatic CRPC (mCRPC)

Research to Practice Prostate Cancer Symposium

GU ASCO 2024

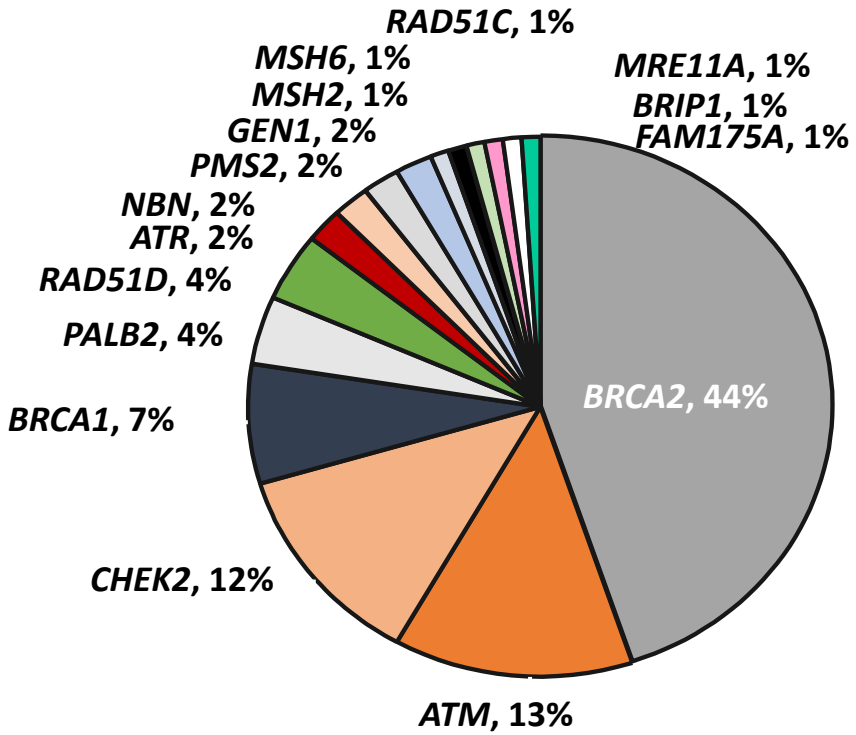
Alan H. Bryce, M.D.
Chief Clinical Officer, City of Hope Cancer Center, Phoenix
Clinical Professor, Department of Medical Oncology and Therapeutics Research
Professor of Molecular Medicine, TGen Research Institute

@AlanBryce9

Inherited DNA-repair gene mutations in men with metastatic prostate cancer

Case series of men with metastatic prostate cancer, unselected for family history of cancer or age at diagnosis

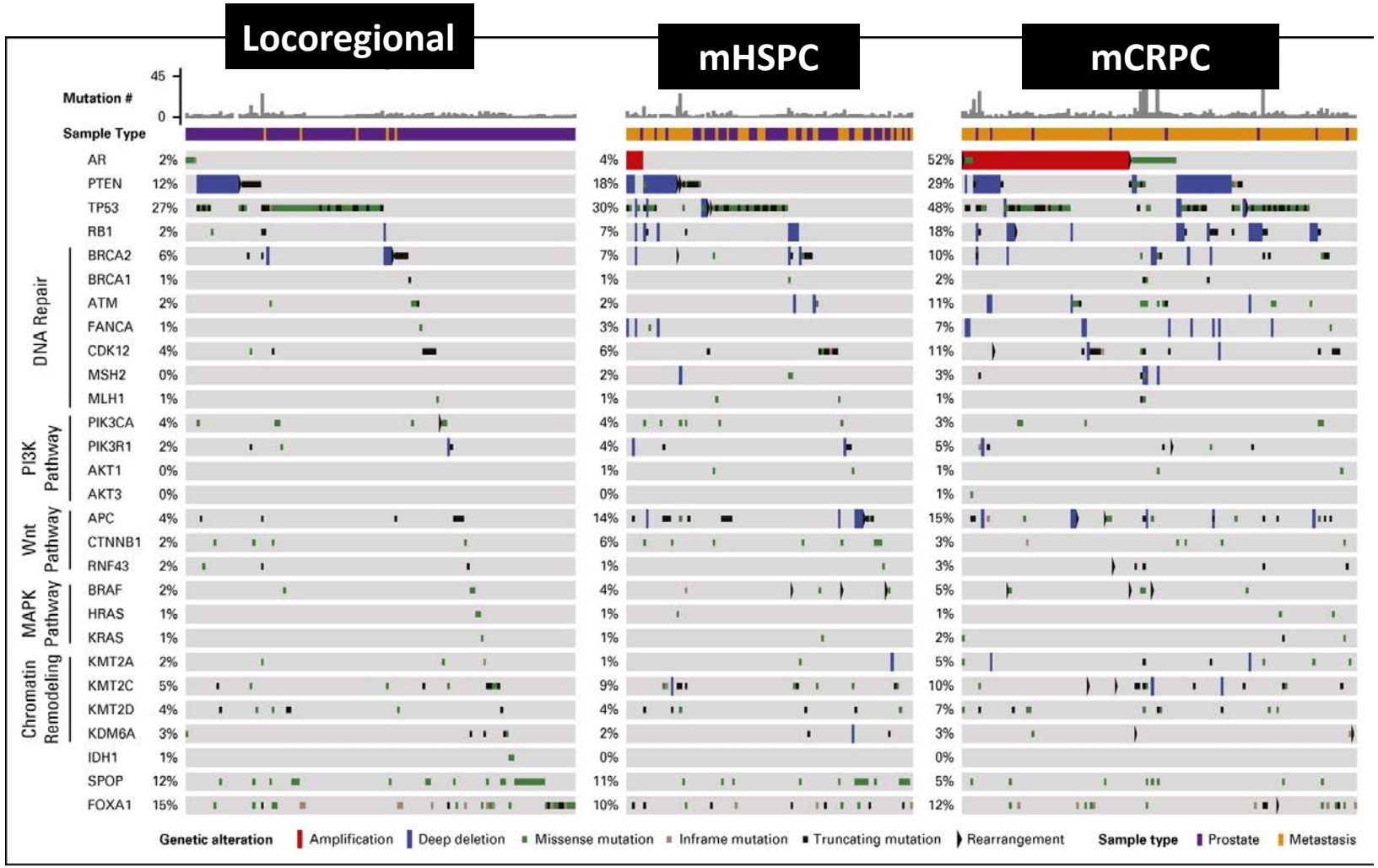
Case Series	Description	Patients, n	Patients With Mutations, n (%)
1	Stand Up to Cancer: Prostate Cancer Foundation discovery series	150	15 (10.0)
2	Stand Up to Cancer: Foundation validation series	84	9 (10.7)
3	Royal Marsden Hospital	131	16 (12.2)
4	University of Washington	91	8 (8.8)
5	Weill Cornell Medical College	69	7 (10.1)
6	University of Michigan	43	4 (9.3)
7	Memorial Sloan Kettering Cancer Center	124	23 (18.5)
Total		692	82 (11.8)



Pritchard. NEJM. 2016;375:443.

Cancer Evolution

Mutational Landscape By Disease State



Genomic progression from localized disease to mCRPC

- *BRCA*1: 1% to 2%
- *BRCA2*: 6% to 10%
- *FANCA*: 1% to 7%

Cumulative incidence of pathogenic DDR variants (excluding ATM) ~25%

- 10-15% germline
- 10-15% somatic

Abida. JCO Precision Oncol. 2017;PO.17.00029.

PARP Monotherapy
Overall survival

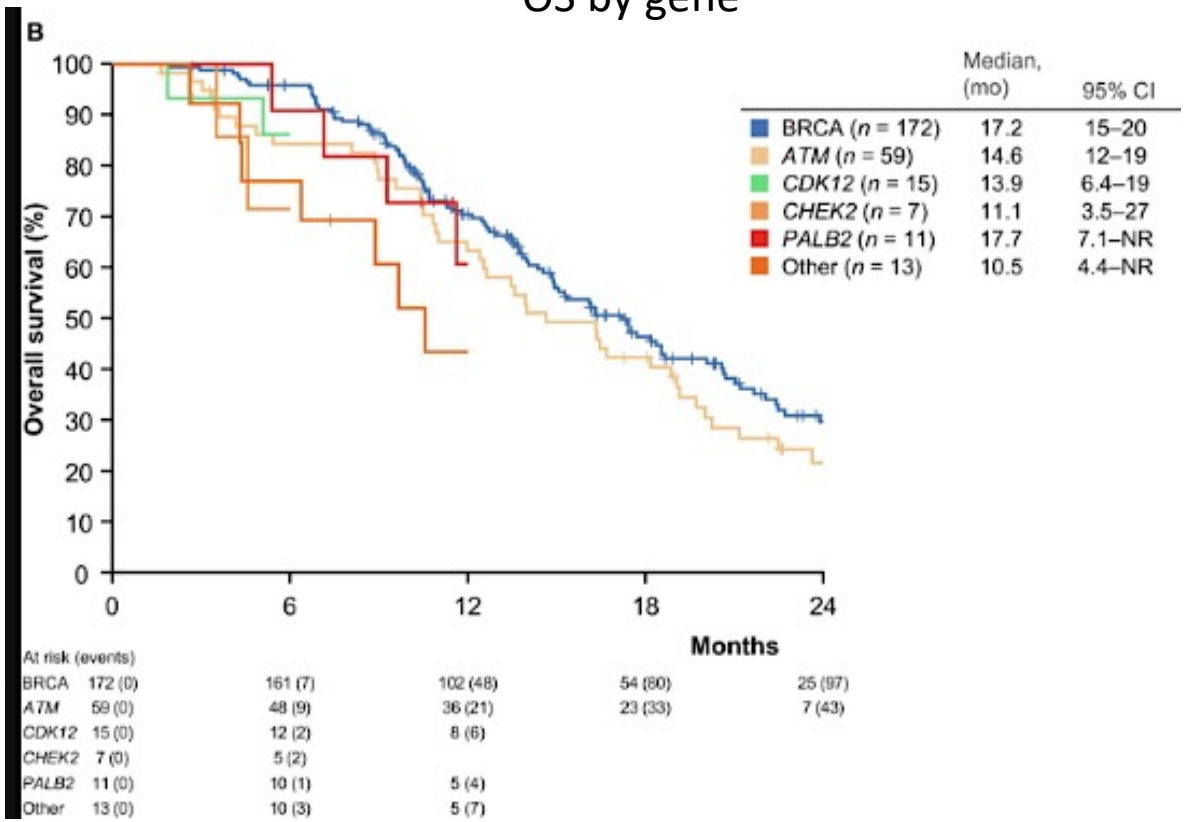
PROFOUND: Olaparib post ARPi, versus ARPi
Cohort A: *BRCA1, BRCA2, or ATM*

Table: 610O

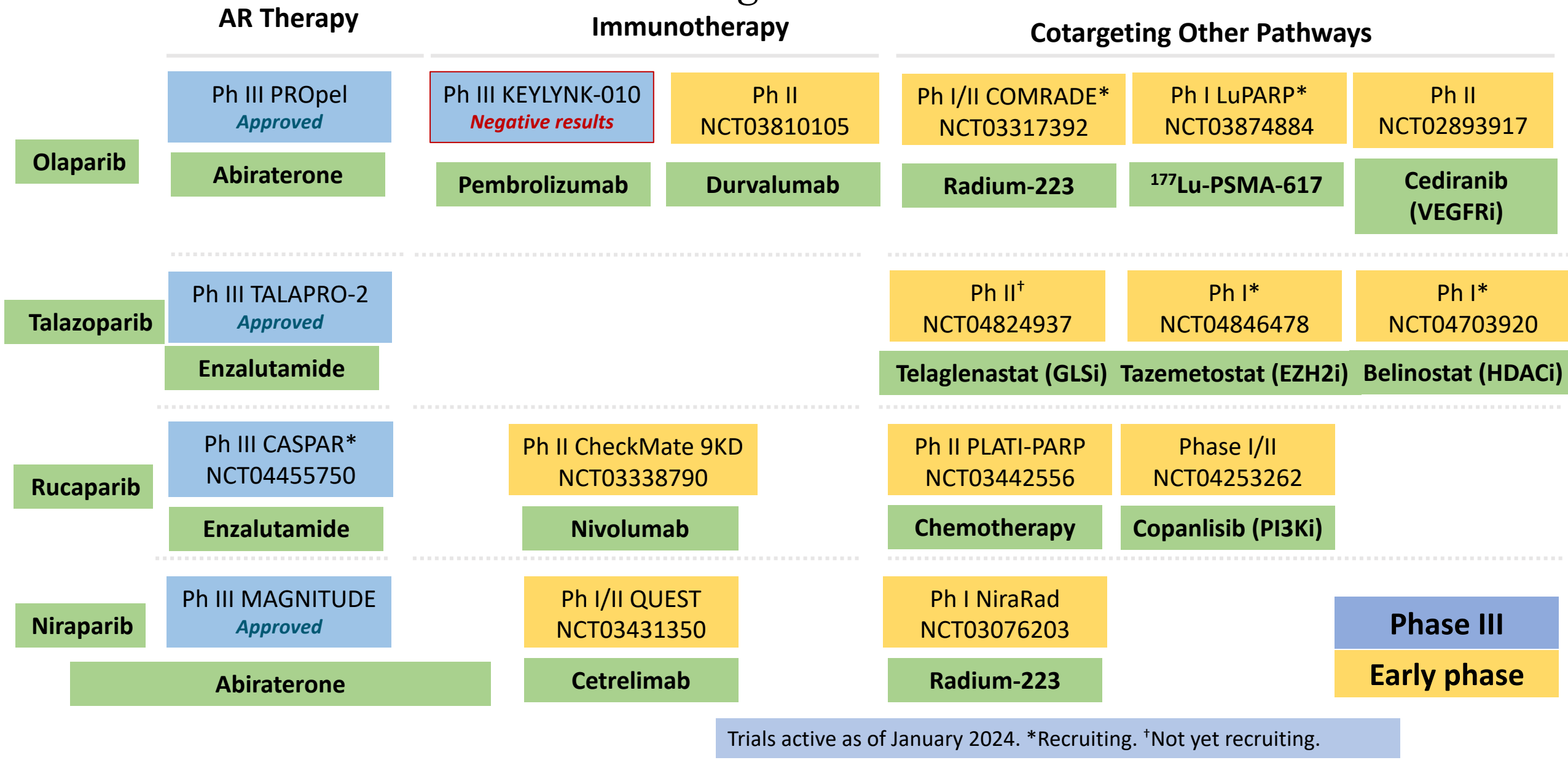
	Cohort A		Overall population	
	Olaparib n=162	Control n=83	Olaparib n=256	Control n=131
Events, n (%)	91 (56)	57 (69)	160 (63)	88 (67)
Median (95% CI) OS (months)	**19.1 (17.4, 23.4)**	**14.7 (11.9, 18.8)**	**17.3 (15.5, 18.6)**	**14.0 (11.5, 17.1)**
HR (95% CI)	**0.69 (0.50, 0.97)**		**0.79 (0.61, 1.03)**	
***P* value (2-sided)**	**0.0175***		**0.0515†**	
OS rate (%)				
12-month	73	61	67	56
18-month	54	42	47	39
Median follow-up (months)‡	21.9	21.0	20.7	20.5

*0.047 alpha spent at final OS analysis; †Nominal; ‡Censored pts. CI, confidence interval; HR, hazard ratio; OS overall survival

Triton 2: Rucaparib post ARPi and Docetaxel
OS by gene



Select studies combining PARP Inhibitors with other agents in mCRPC

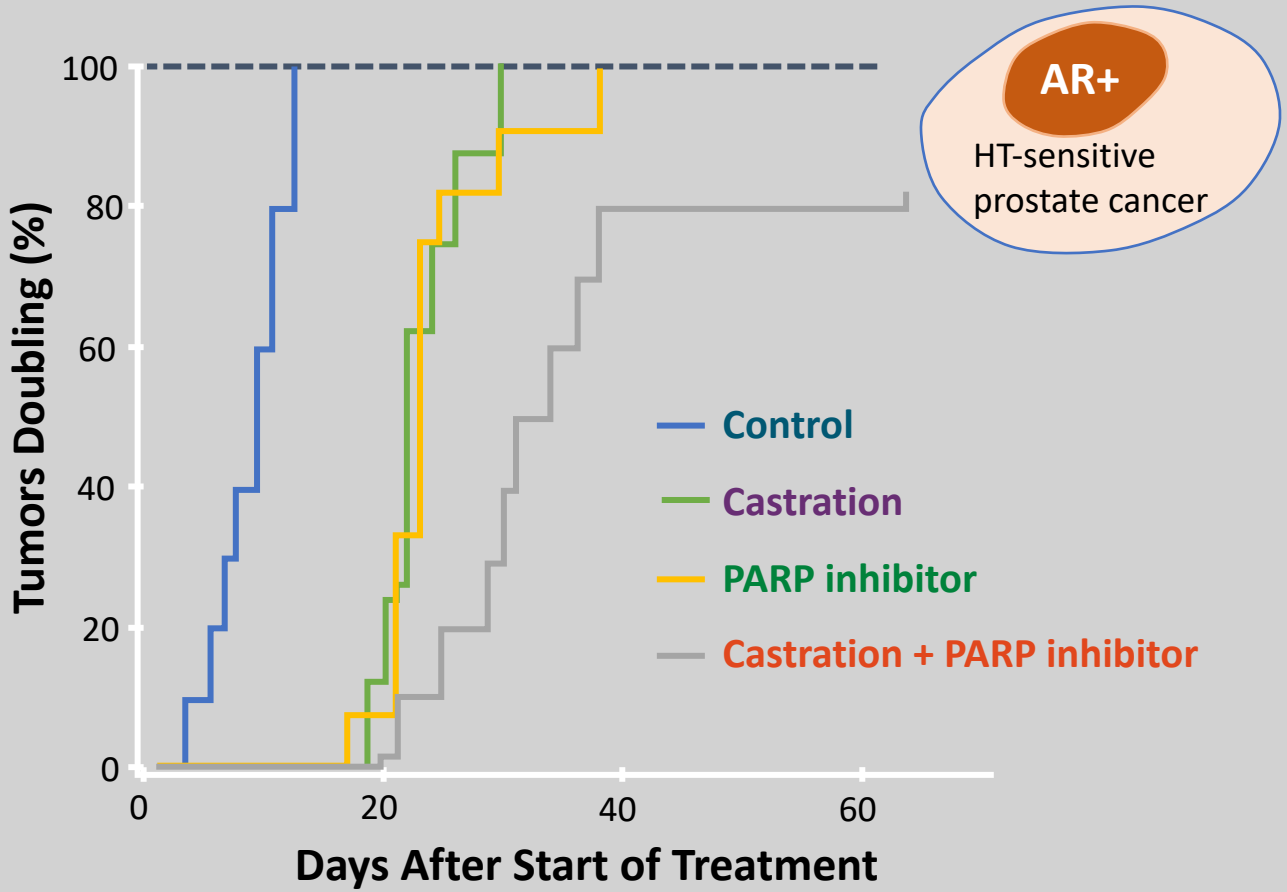


Trials active as of January 2024. *Recruiting. †Not yet recruiting.

Rationale for Cotargeting AR Signaling and PARP

- Preclinical evidence for potential synthetic lethality
- PARP-1 interacts with androgen signaling
- Castration-resistant tumor cells exhibit increased PARP-1 activity
- Preclinically, PARP-1–inhibition synergizes with AR-targeted therapy
- NHAs inhibit transcription of several HRR genes, inducing HRR deficiency and increasing sensitivity to PARP inhibition

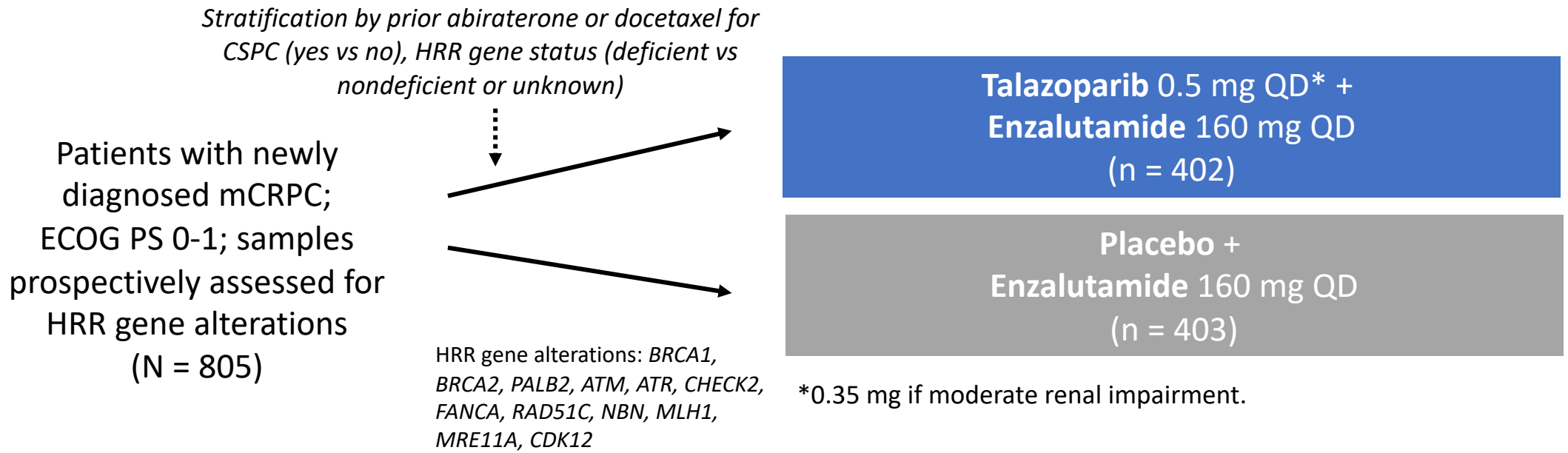
PARP Inhibitor Synergizes With Castration in Mouse Xenograft Models of Prostate Cancer



Polkinghorn. Cancer Discov. 2013;3:1245. Schiewer. Cancer Discov. 2012;2:1134.
Asim. Nat Commun. 2017;29:374. Li. Sci Signal. 2017;10:eaam7479. Schiewer. Cancer Discov. 2012;2:1134.

TALAPRO-2
First-Line Enzalutamide ± Talazoparib for mCRPC

- Randomized, double-blind, placebo-controlled phase III trial

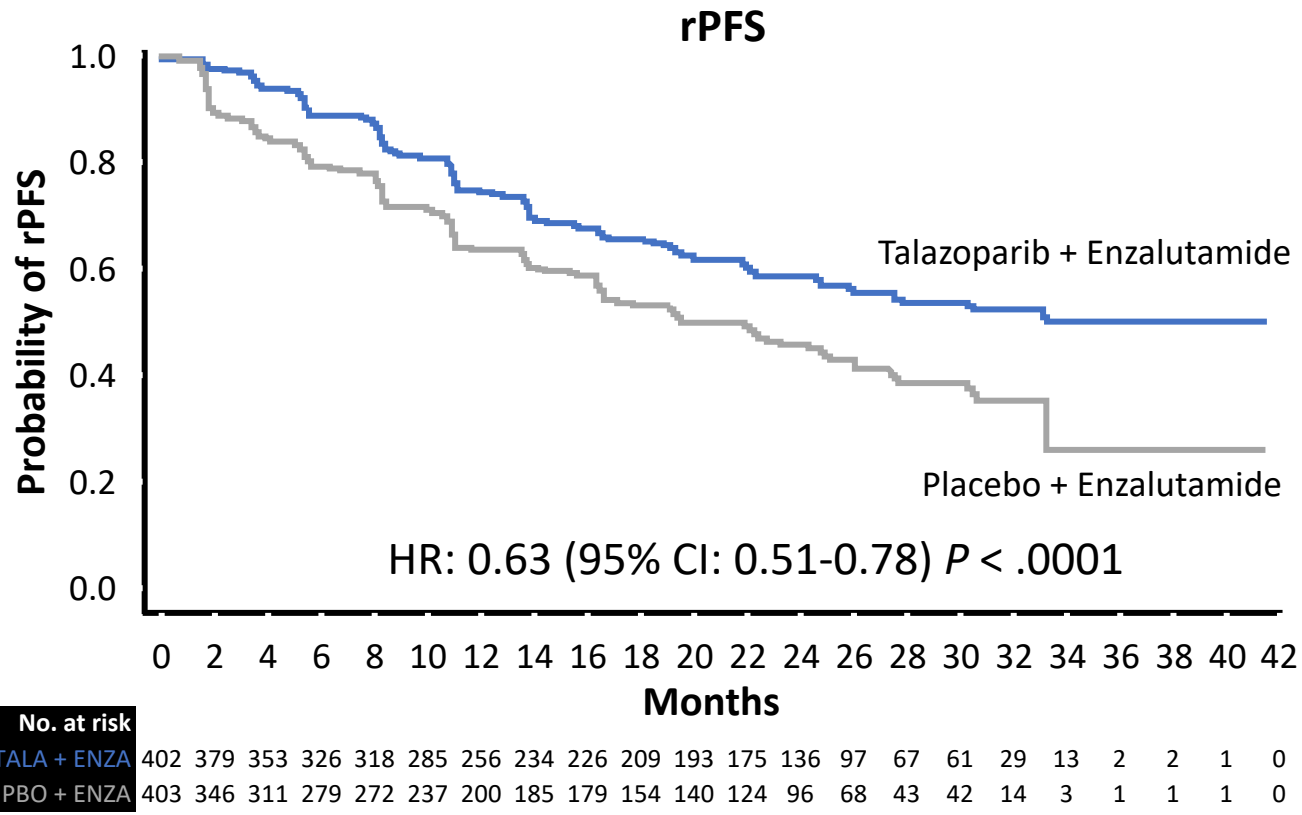


*0.35 mg if moderate renal impairment.

- **Primary endpoint:** rPFS by BICR
- **Key secondary endpoint**: OS
- **Other secondary endpoints:** time to cytotoxic chemotherapy, PFS2 (by investigator), ORR, PROs, safety

Agarwal. ASCO GU 2023. Abstr LBA17.

TALAPRO-2
rPFS by BICR

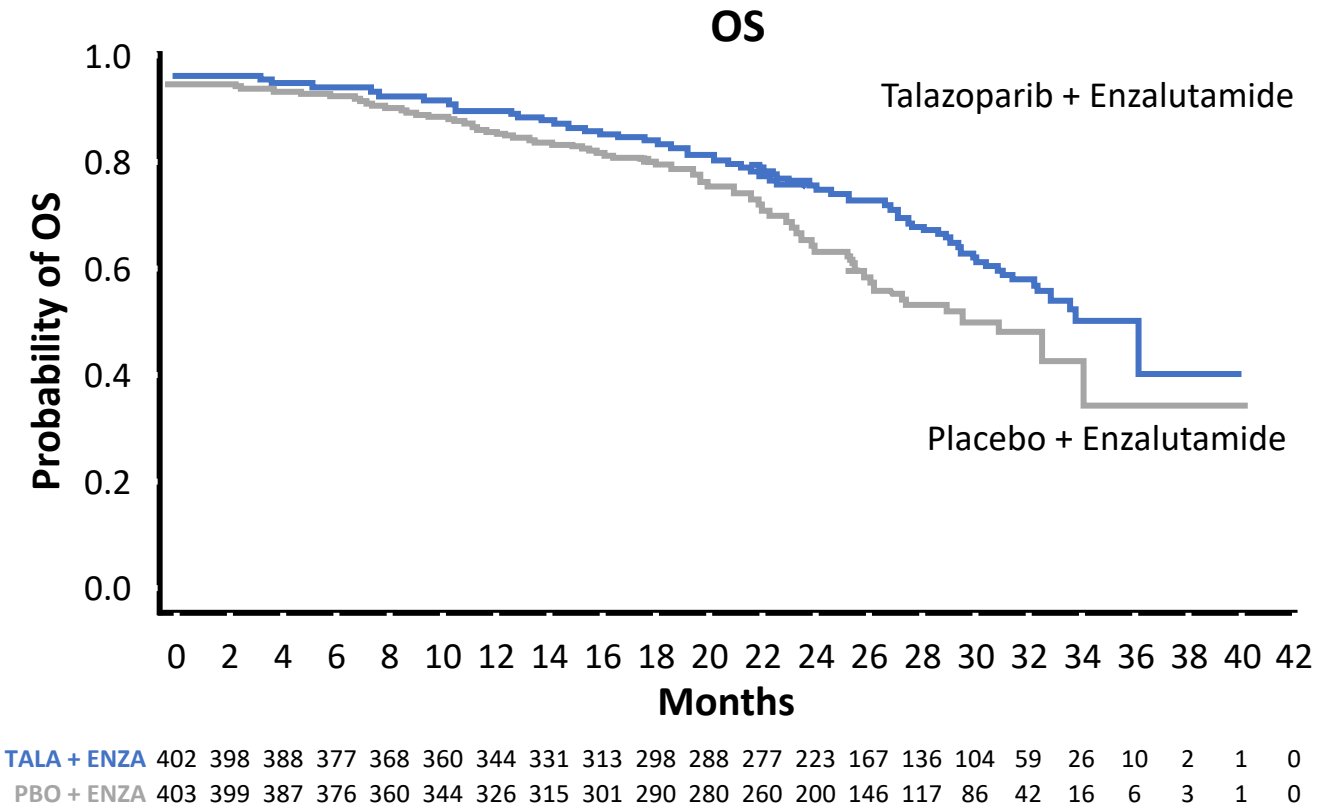


	Talazoparib + Enzalutamide (n = 402)	Placebo + Enzalutamide (n = 403)
Events, n	151	191
Median rPFS, mo	NR (27.5-NR)	21.9 (16.6-25.1)
Median f/u, mo	24.9	24.6

- Investigator assessed rPFS HR: 0.64 (95% CI: 0.50-0.91) *P* < .001

TALAPRO-2

Overall survival in HRR MUT+ subgroup



	Talazoparib + Enzalutamide (n = 200)	Placebo + Enzalutamide (n = 199)
Events, n	43	53
Median OS, mo	NR(36.4-NR)	33.7 (27.6-NR)

HR: 0.69 (95% CI: 0.46-1.03) *P* = .068

- OS data at 24% mature; additional follow-up is needed

Agarwal N et al. The Lancet. 2023. doi.org/10.1016/S0140-6736(23)01055-3

TALAPRO-2
Safety

TEAE, n (%)	Talazoparib + Enzalutamide (n = 398)	Placebo + Enzalutamide (n = 401)
Any TEAE ▪ Treatment related	392 (98.0) 357 (90.0)	379 (95.0) 279 (70.0)
Serious AE ▪ Treatment related	157 (39.0) 78 (20.0)	107 (27.0) 11 (3.0)
Any grade 3-4 TEAE	299 (75.0)	181 (45)
Any grade 5 TEAE ▪ Treatment related	13 (3.3) 0	18 (4.5) 2 (0.5)
Dose interruption of talazoparib or placebo due to AE	247 (62.0)	84 (21.0)
Dose reduction of talazoparib or placebo due to AE	210 (53.0)	27 (7.0)
Discontinuation of talazoparib or placebo due to AE	75 (19.0)	49 (12.0)

TEAEs of Special Interest

- **MDS**: 1 patient receiving talazoparib during safety reporting period
- **AML**: 1 patient receiving talazoparib during follow-up period
- **Pulmonary embolism**: 10 (3.0%) patients with talazoparib + enzalutamide and 3 (0.7%) patients with placebo + enzalutamide

- Median relative dose intensity remained >83.5% in dose-reduced patients
- Most common TEAEs leading to dose reduction: anemia (43.0%), neutropenia (15. 0%), thrombocytopenia

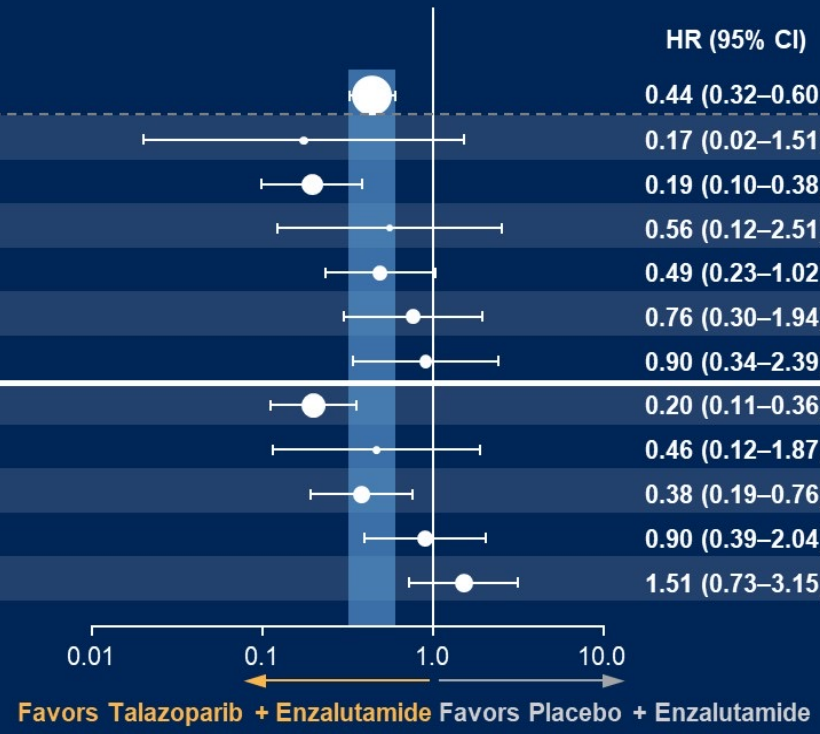
Agarwal. ASCO GU 2023. Abstr LBA17

TALAPRO-2 HRR-Deficient: rPFS by BICR by Selected Gene Subgroups

Broad treatment effect with talazoparib plus enzalutamide seen across gene subgroups

Subgroup	Talazoparib + Enzalutamide Events/N	Placebo + Enzalutamide Events/N	Median, mo	HR (95% CI)	2-Sided *P* Value
All HRR-deficient	65/198	104/197	NR/13.8	0.44 (0.32–0.60)	<0.0001
Only *BRCA1*	2/8	5/9	20.0/11.7	0.17 (0.02–1.51)	0.074
Only *BRCA2*	11/55	40/60	NR/11.0	0.19 (0.10–0.38)	<0.0001
Only *PALB2*	3/6	4/5	NR/8.6	0.56 (0.12–2.51)	0.44
Only *CDK12*	12/28	18/30	21.9/13.8	0.49 (0.23–1.02)	0.055
Only *ATM*	12/35	7/22	NR/27.7	0.76 (0.30–1.94)	0.58
Only *CHEK2*	8/24	8/24	22.1/NR	0.90 (0.34–2.39)	0.83
BRCA cluster	15/71	54/84	NR/11.0	0.20 (0.11–0.36)	<0.0001
PALB2 cluster	3/7	6/8	NR/8.3	0.46 (0.12–1.87)	0.27
CDK12 cluster	13/35	23/36	21.9/13.8	0.38 (0.19–0.76)	0.0045
ATM cluster	16/43	9/29	27.9/27.7	0.90 (0.39–2.04)	0.80
Other gene cluster	18/42	12/40	22.1/NR	1.51 (0.73–3.15)	0.26

Hierarchy



Gene clustering alteration dominance hierarchy is any *BRCA1/2* alteration (*BRCA cluster*), then any *PALB2* (*PALB2* cluster), then any *CDK12* (*CDK12* cluster), then any *ATM* (*ATM* cluster), then any of all other HRR12 genes (with each patient counted only once).

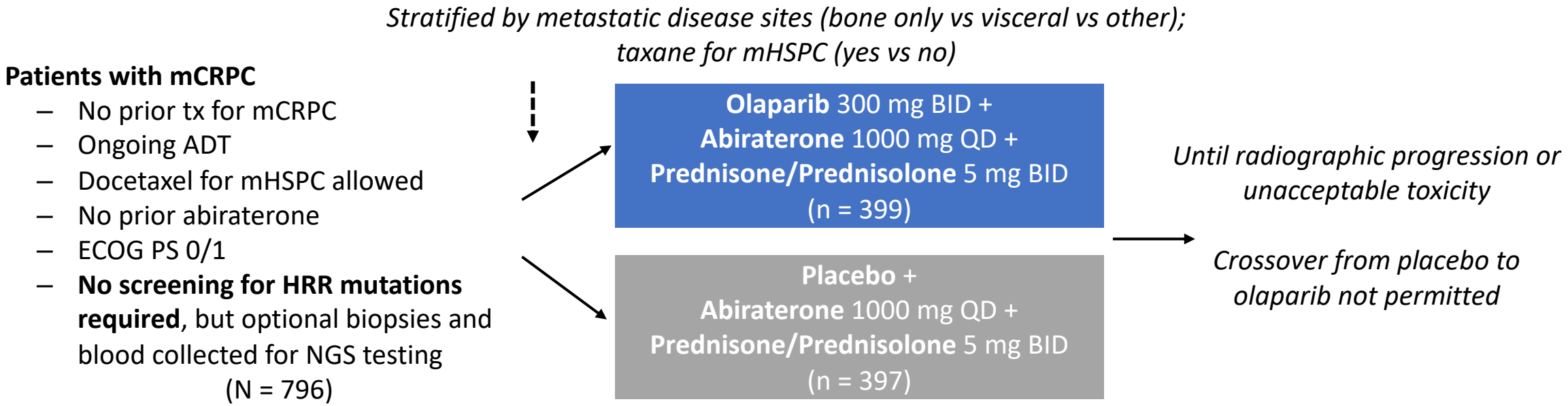
2023 ASCO ANNUAL MEETING #ASCO23

PRESENTED BY: Professor Karim Fizazi

ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY
KNOWLEDGE CONQUERS CANCER

PROpel
First-line Abiraterone/Prednisone ± Olaparib in mCRPC

- International, randomized, double-blind phase III study

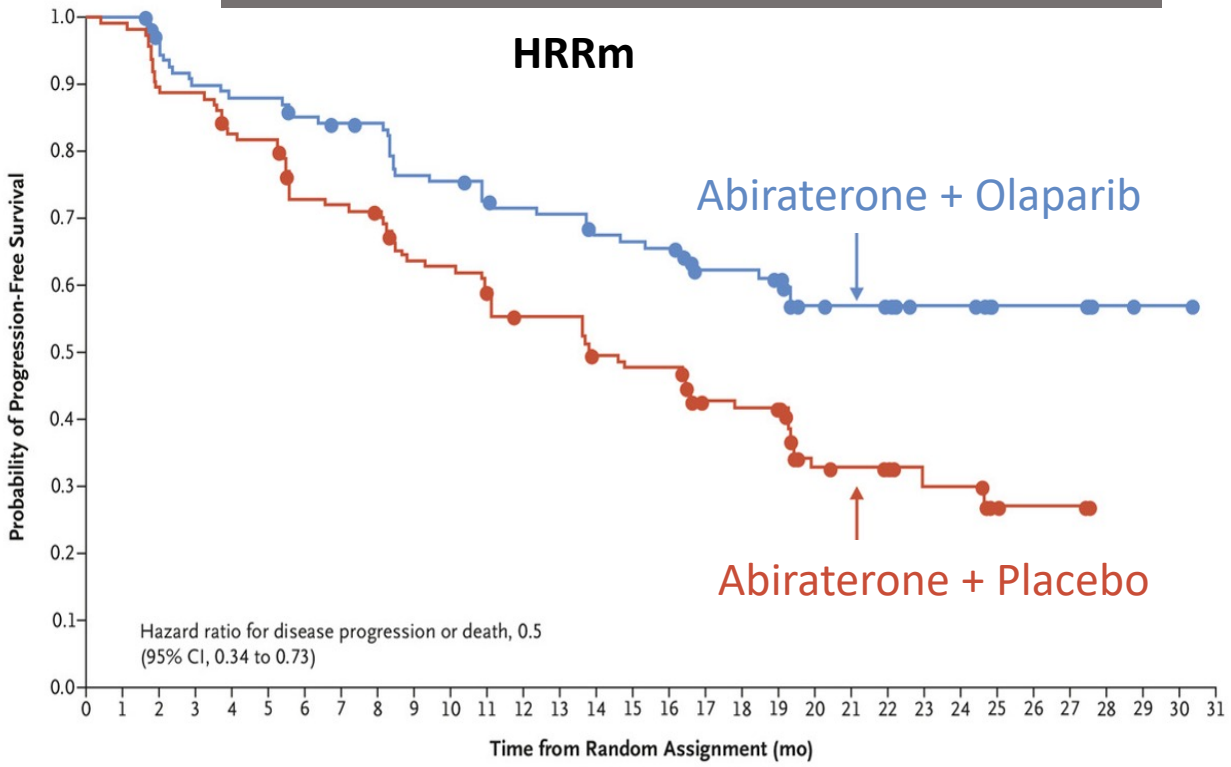


- **Primary endpoint**: rPFS by investigator
- **Key secondary endpoints**: OS, time to subsequent therapy or death, PFS2, ORR, HRRm prevalence (retrospectively assessed), HRQoL, safety

PROpel
rPFS by HRR status

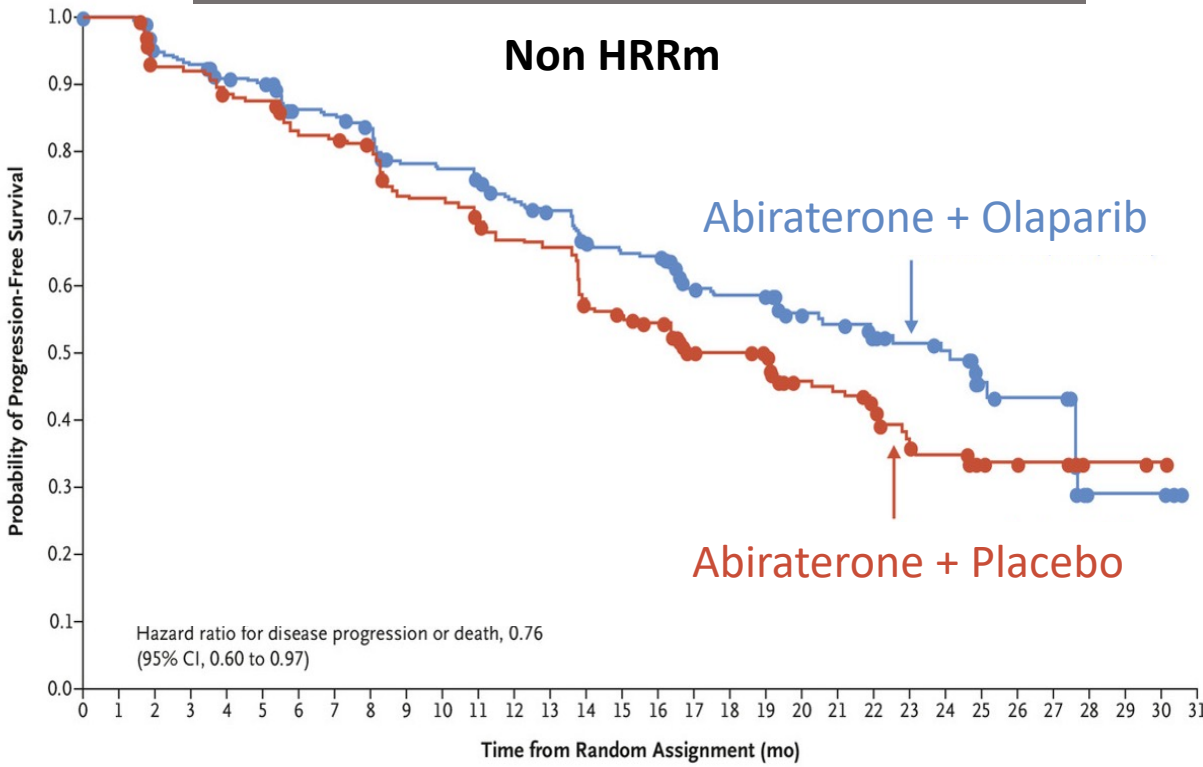
	Abi + Ola (n = 111)	Abi + Placebo (n = 115)
Events, n (%)	43 (38.7)	73 (63.5)
Median rPFS, mo	NR	13.9
	HR: 0.5 (95% CI: 0.34-0.73)	

HRRm



	Abi + Ola (n = 279)	Abi + Placebo (n = 273)
Events, n (%)	119 (42.7)	149 (54.6)
Median rPFS, mo	24.1	19.0
	HR: 0.76 (95% CI: 0.60-0.97)	

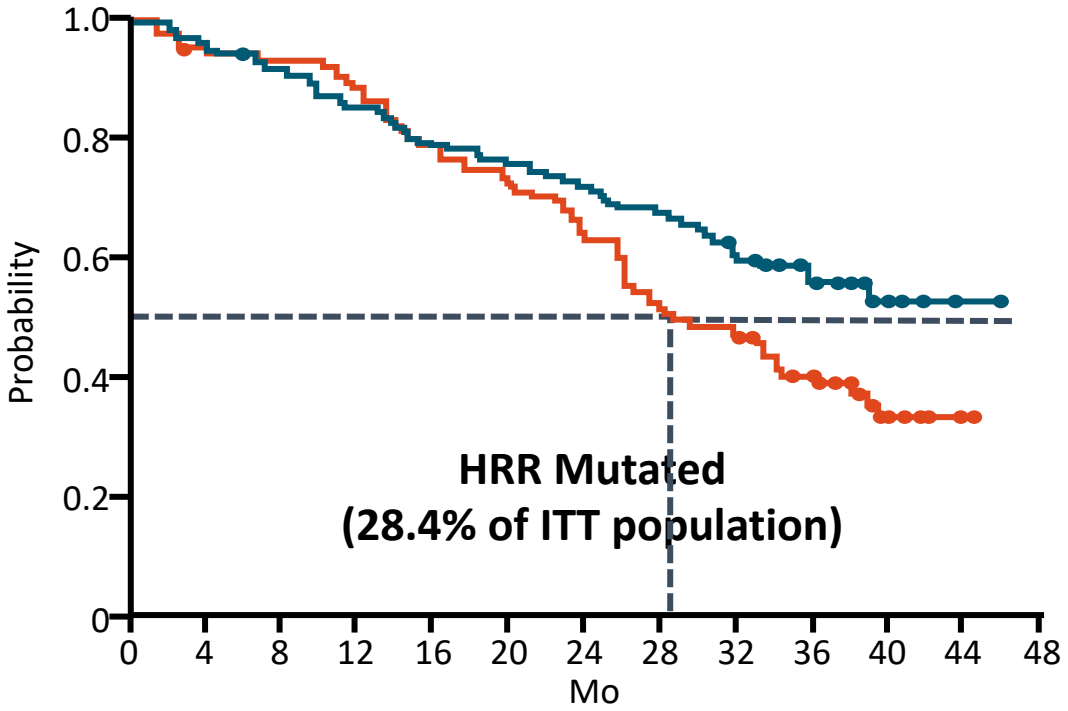
Non HRRm



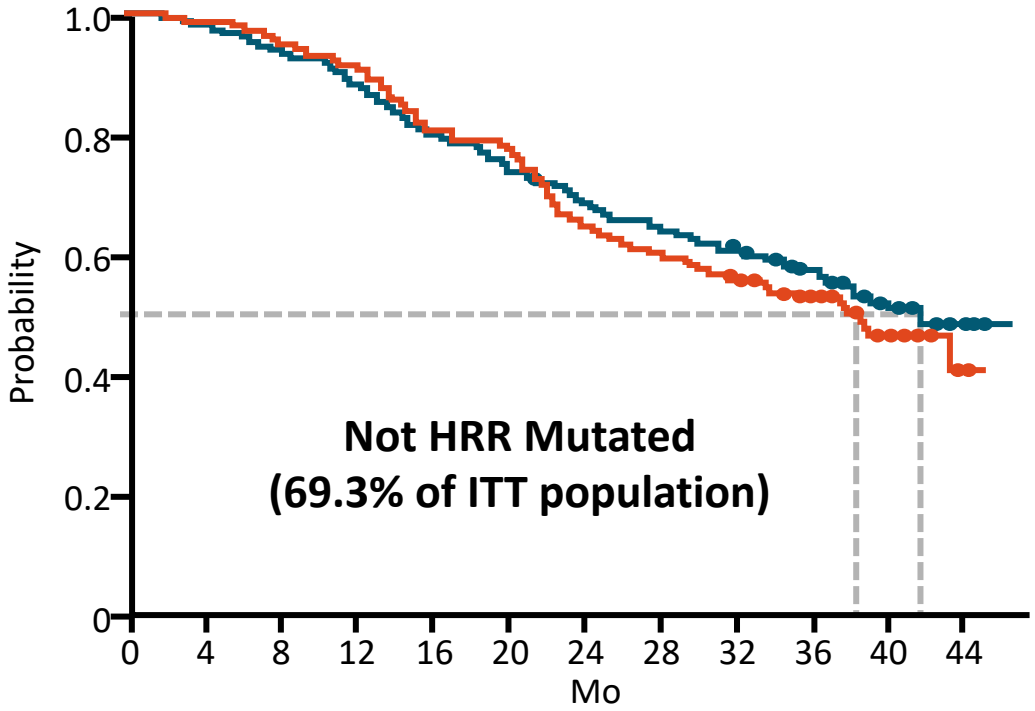
Clarke. NEJM Evid. 2022;1.

PROpel
OS by HRR status

	Abi + Ola (n = 111)	Abi + Placebo (n = 115)
Median OS, mo	NR	28.5
	HR: 0.66 (95% CI: 0.45-0.95)	



	Abi + Ola (n = 279)	Abi + Placebo (n = 273)
Median OS, mo	42.1	38.9
	HR: 0.89 (95% CI: 0.70-1.14)	



Clarke. ASCO GU 2023. Abstr LBA16.

PROpel
Safety

AE, n (%)	Abiraterone + Olaparib (n = 398)	Abiraterone + Placebo (n = 396)
Any AE	389 (97.7)	380 (96.0)
Any AE grade ≥3	222 (55.8)	171 (43.2)
Death due to AE	26 (6.5)	20 (5.1)
Any AE leading to:		
▪ Dose interruption of olaparib or placebo	195 (49.0)	112 (28.3)
▪ Dose reduction of olaparib or placebo	90 (22.6)	24 (6.1)
▪ Discontinuation of olaparib or placebo	69 (17.3)	34 (8.6)
▪ Discontinuation of abiraterone	45 (11.3)	37 (9.3)

2 cases of MDS/AML in abiraterone + olaparib arm

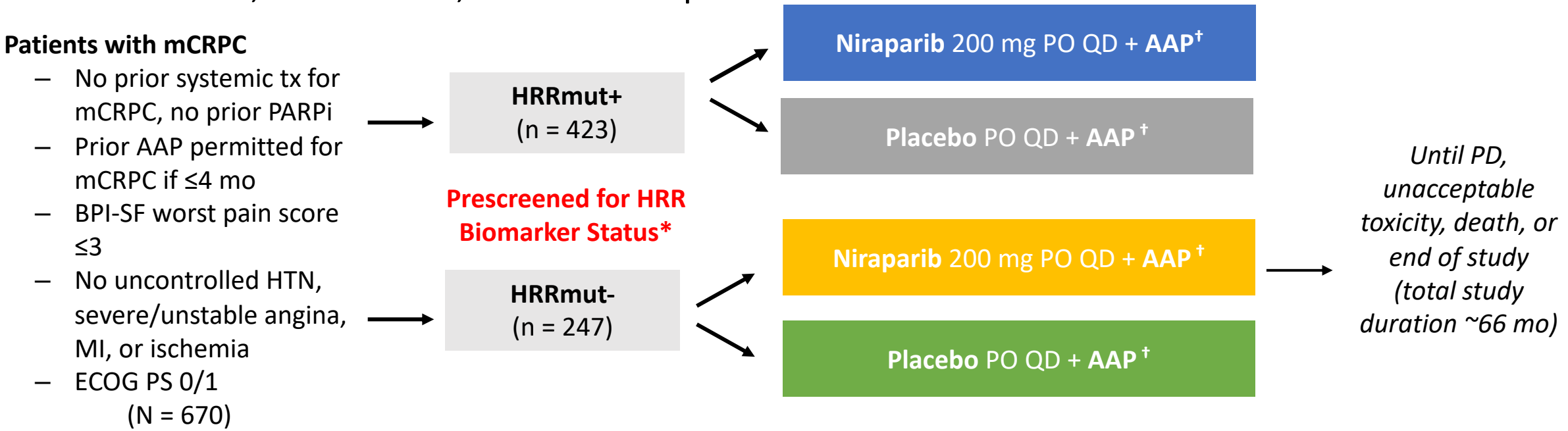
Incidence of new primary malignancies, pneumonitis balanced between treatment arms

HRQoL assessed by FACT-P was similar between treatment arms

Clarke. ASCO GU 2023. Abstr LBA16.

MAGNITUDE
First-line Abiraterone/Prednisone ± Niraparib in mCRPC

- International, randomized, double-blind phase III trial



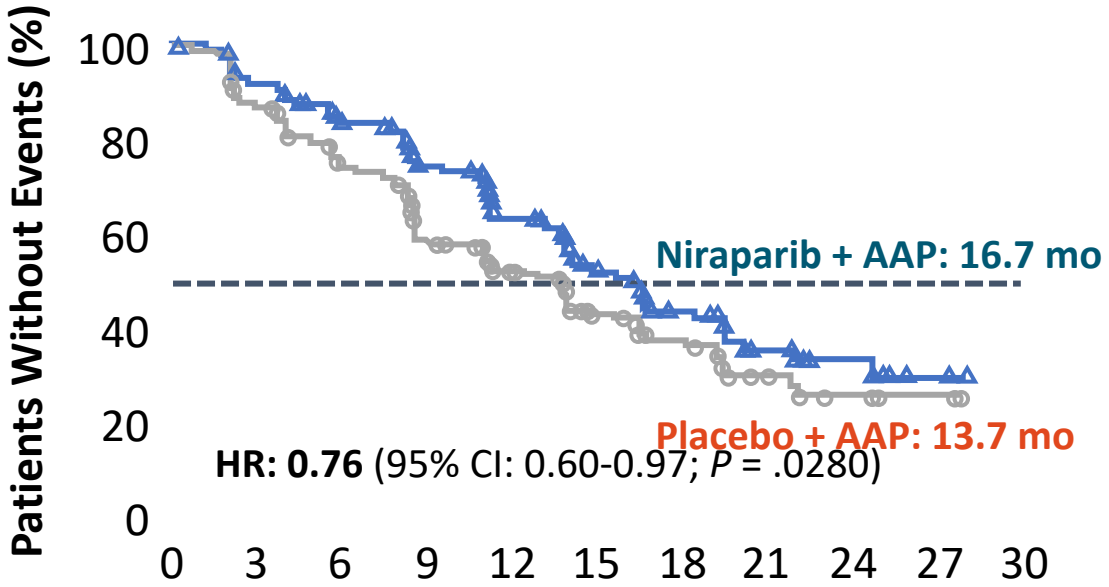
*HRRmut+ per tissue and/or plasma assays for ***ATM, BRCA1, BRCA2, BRIP1, CDK12, CHEK2, FANCA, HDAC2, PALB2***.
†AAP: abiraterone acetate 1000 mg PO QD + prednisone 10 mg PO QD.

- Primary endpoint: radiographic PFS by central review
- Secondary endpoints: OS, time to symptomatic progression, time to cytotoxic chemotherapy

Chi. ASCO GU 2022. Abstr 12. Chi. J Clin Oncol. 2023; JCO2201649.

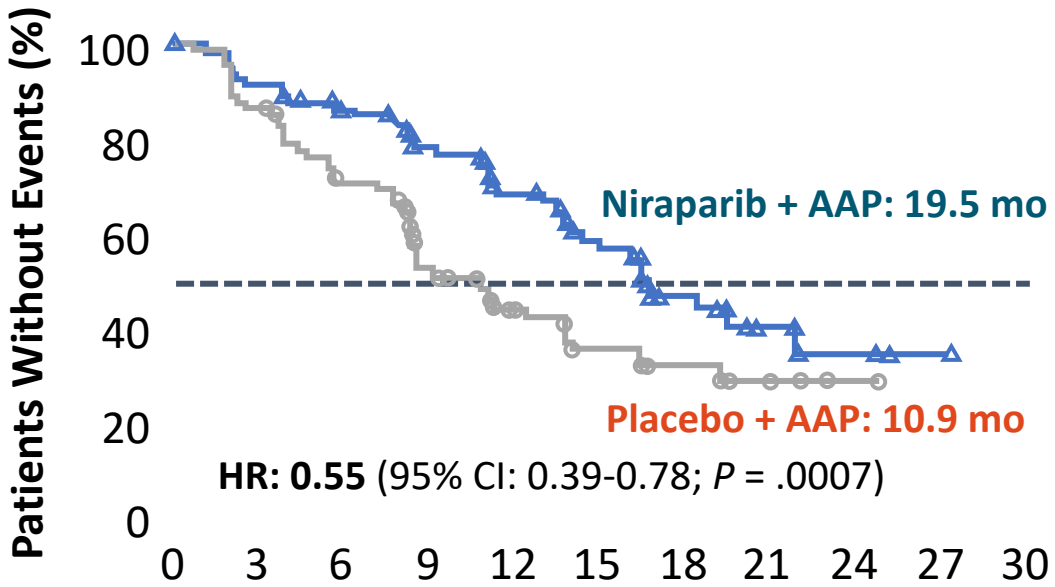
MAGNITUDE Primary Endpoint
rPFS by Central Review

HRRmut+ Cohort
Median follow-up: 26.8 mo



Patients at Risk, n											
Nira + AAP	212	192	167	129	96	64	45	21	10	2	0
Pbo + AAP	211	182	149	102	78	53	35	15	9	2	0

***BRCA1/2*-Mutated Cohort**
Median follow-up: 24.8 mo



Patients at Risk, n											
Nira + AAP	113	103	90	65	45	31	18	9	4	1	0
Pbo + AAP	112	97	77	43	28	20	11	5	2	0	0

Chi. J Clin Oncol. 2023; JCO2201649. Chi. ASCO GU 2022. Abstr 12.

MAGNITUDE
TEAEs in HRR MUT+ Cohort

Safety Outcome, n (%)	Niraparib + AAP (n = 212)	Placebo + AAP (n = 211)
All TEAEs ▪ Drug related	211 (99.5) 165 (77.8)	203 (96.2) 121 (57.3)
Grade 3/4 TEAEs	153 (72.1)	104 (49.2)
Serious AEs ▪ Drug related	93 (43.9) 24 (11.3)	61 (28.9) 6 (2.8)
Dose reduction due to AE	42 (20.3)	7 (3.8)
Discontinuation of niraparib/placebo due to AE	**23 (15.1)**	**10 (5.7)**
All deaths within 30 d of last dose ▪ Death due to prostate cancer ▪ AE	29 (13.7) 10 (4.7) 19 (9.0)	23 (10.9) 14 (6.6) 9(4.3)

- AEs most frequently leading to dose reduction in niraparib arm:
  - Anemia, 50%
  - Thrombocytopenia, 23.1%
- Median relative dose intensity in niraparib arm: 99%

Chi. J Clin Oncol. 2023; JCO2201649. Chi. ASCO GU 2022. Abstr 12.

MAGNITUDE: Common TEAEs of Clinical Interest in HRR MUT+ Cohort

TEAEs Occurring in >10% of Niraparib Arm or of Clinical Interest, n (%)	Niraparib + AAP (n = 212)		Placebo + AAP (n = 211)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Hematologic				
▪ Anemia	106 (50.0)	64 (30.1)	48 (22.7)	18 (8.5)
▪ Thrombocytopenia	49 (23.1)	16 (2.4)	20 (9.5)	5 (2.4)
▪ Neutropenia	32 (15.1)	14 (6.6)	15 (7.1)	5 (2.3)
▪ AML/MDS	0	0	1 (0.5)	1 (0.5)
Cardiovascular				
▪ Hypertension	70 (33.0)	33 (15.6)	47 (22.3)	26 (12.3)
▪ Arrhythmia	27 (12.7)	6 (2.8)*	12 (5.7)	3 (1.4)
▪ Cardiac failure	4 (1.9)	3 (1.4)*	4 (1.9)	1 (0.5)
▪ Ischemic heart disease	4 (1.9)	4 (1.9)	8 (3.8)	6 (2.8)†
General disorders				
▪ Fatigue	63 (29.7)	8 (3.7)	40 (19.0)	11(2.5)
Gastrointestinal				
▪ Constipation	70 (33.0)	1(0.5)	33 (15.6)	--
▪ Nausea	52 (24.5)	1 (0.5)	31 (14.7)	0
Hepatotoxicity	25 (11.8)	4 (1.9)	26 (12.3)	10 (4.7)
Cerebrovascular disorders	6 (2.8)	2 (0.9)	2 (0.9)	1 (0.5)*

Chi. J Clin Oncol. 2023; JCO2201649. Chi. ASCO GU 2022. Abstr 12.

Summary of Completed Trials with PARP Inhibitors and AR Signaling Inhibitors

	PROpel	MAGNITUDE	TALAPRO-2
Radiographic PFS			
All-comers, ITT population	24.8 vs 16.6 mo HR 0.66, 95% CI 0.54–0.81	Not assessed	NR vs 21.9 mo HR 0.63, 95% CI 0.51–0.78
HRR gene aberration present	NR vs 13.9 mo HR 0.50, 95% CI 0.34–0.73	HR 0.76, 95% CI 0.60–0.97	HR 0.46, 95% CI 0.30–0.70
HRR gene aberration absent/unknown	24.1 vs 19.0 mo HR 0.76, 95% CI 0.60–0.97	HR 1.09, 95% CI 0.75–1.57	HR 0.70, 95% CI 0.54–0.89
BRCA1/2 gene aberration	NR	HR 0.55, 95% CI 0.39–0.78	NR
Overall survival			
ITT population	47.9% at maturity 42.1 vs 34.7 mo HR 0.81, 95% CI 0.67–1.00	Not assessed	31% at maturity HR 0.89, 95% CI 0.69–1.14
HRR gene aberration present	NR vs 28.5 mo HR 0.66, 95% CI 0.45–0.95	27% at maturity HR 1.01, 95% CI 0.75–1.36	NR
HRR gene aberration absent	42.1 vs 38.9 mo HR 0.89, 95% CI 0.70–1.14	NR	NR

Beije. Eur Urol. 2023;S0302-2838(23)02716-1.

Safety Summary

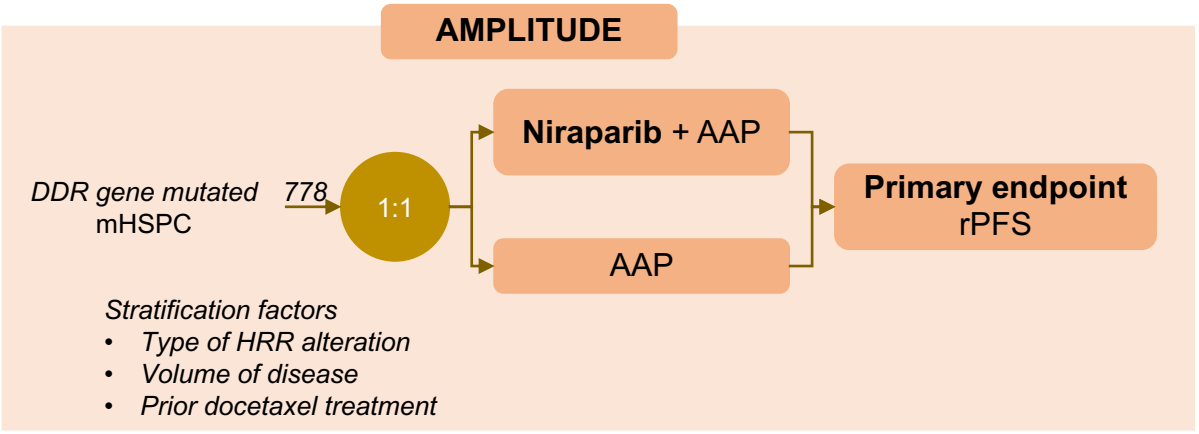
	PROPEL Olaparib + Abiraterone	MAGNITUDE Niraparib + Abiraterone	TALAPRO-2 Talazoparib + Enzaluatmide
Select G3-4 Toxicities % (all grades %)			
Anemia ---Transfusion Rate	16.3 (50) 18%	30.1 (50.0) 27.4%	46 (66) 39%
Fatigue	2.5 (39.0)	3.3 (29.7)	4 (34)
Nausea	0.3 (31.0)	0.5 (24.5)	<1 (21)
Hypertension	3.8 (15.0)	33 (15.6)	5 (14)
Pulmonary Embolism	7.3%	1.9%	2.5%
Outcomes			
PARP interruption	49%	49.1%	62.0%
PARP dose reduction	22.6%	20.3%	53.0%
PARP discontinuation	17.3%	15.1%	19.0%

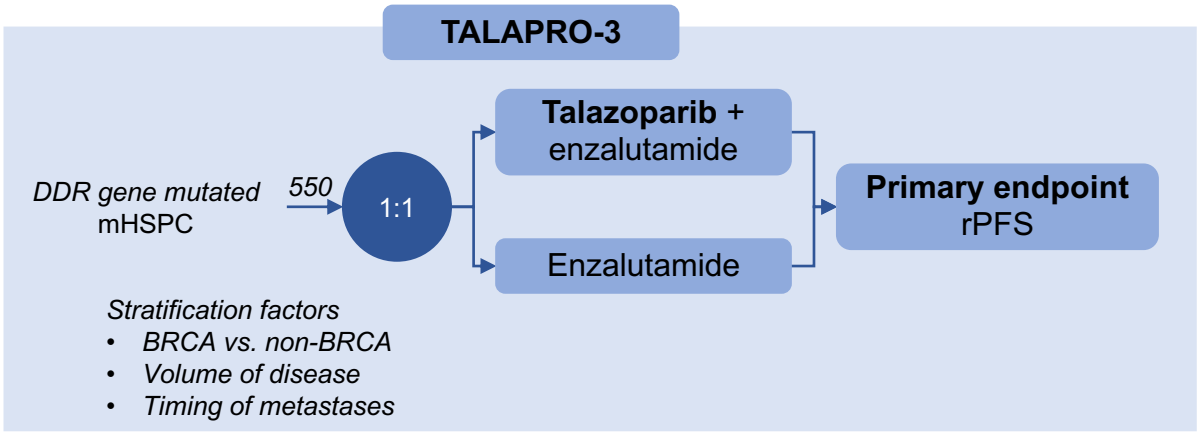
- Toxicities are largely a class effect of PARPi's. Myelosuppression and GI toxicity are most prominent.
- AE's of special interest include MDS/AML and PE.

Clarke. NEJM Evid. 2022;1. Chi. J Clin Oncol. 2023; JCO2201649. Fizazi. Lancet. 2023;402

Ongoing Ph3 studies of PARPi in mHSPC

Trial	Design	Treatment	Control	Setting	Primary endpoint	Estimated/actual enrollment
AMPLITUDE NCT04497844	Phase-III randomized controlled trial	**Niraparib** + Abiraterone Acetate + Prednisone	Abiraterone Acetate + Prednisone	mHSPC Deleterious germline or somatic homologous recombination repair gene mutations Previous docetaxel in mHSPC *allowed*	rPFS	778
TALAPRO-3 NCT04821622	Phase-III randomized controlled trial	**Talazoparib** + Enzalutamide	Enzalutamide	mHSPC Deleterious germline or somatic homologous recombination repair gene mutations Previous docetaxel in mHSPC *not allowed*	rPFS	550





Rathkopf DE, ASCO GU 2021. Agarwal N, ASCO GU 2022

EvoPAR-PR01: Phase III Study of AZD5305 vs Placebo in mHSPC Receiving Physician's Choice of New Hormonal Agents

Trial Identifier: NCT06120491

Key inclusion criteria

- mHSPC (≥1 bone lesion and/or ≥1 soft tissue lesion)
- Receiving ADT with GnRH analogue or bilateral orchiectomy
- ECOG PS 0-1

Key exclusion criteria

- Any prior prostate cancer pharmacotherapy or surgery
- History of arrythmia and cardiovascular disease
- History of MDS/AML
- Any predisposition to bleeding

N = 1800
550 HRRm
1250 non-HRRm
(1:1)

→ **AZD5305 + Abiraterone/Darolutamide/Enzalutamide**

→ **Placebo + Abiraterone/Darolutamide/Enzalutamide**

Outcomes

- Primary Endpoint: rPFS [up to 50 months]
- Key Secondary Endpoints: OS, time to first subsequent therapy or death (TFST), symptomatic skeletal event-free survival (SSE-FS) [up to 90 months]

mHSPC = metastatic hormone-sensitive prostate cancer; ADT = androgen deprivation therapy; GnRH = gonadotropin releasing hormone; ECOG PS = Eastern Cooperative Oncology Group Performance Status; HRRm = homologous recombination repair mutated; MDS = myelodysplastic syndrome; AML = acute myeloid leukemia; rPFS = radiographic progression-free survival OS = overall survival

www.clinicaltrials.gov; Accessed January 2024.

Summary

- PARP inhibitors continue to prove effective in patients with metastatic PC harboring HRR mutations
- Combinations with ARPi's are manageable and effective
- Toxicities vary across the different combinations and require careful management
- Data in earlier lines of therapy are expected in the near future

MODULE 4: Role of Novel Radiopharmaceuticals in Therapy for mCRPC – Dr Sartor

RTP
RESEARCH
TO PRACTICE

Consulting Faculty Questions

Optimal candidates for lutetium Lu 177 vipivotide tetraxetan (^{177}Lu-PSMA-617); monitoring disease and treatment options after ^{177}Lu-PSMA-617

Neil Love, MD

Andrew J Armstrong, MD, ScM

Rana R McKay, MD

RTP RESEARCH TO PRACTICE

QUESTIONS FOR THE FACULTY

Andrew J Armstrong, MD, ScM

Rana R McKay, MD

Do you use PSMA-PET characteristics to identify patients who may fare better with lutetium Lu 177 vipivotide tetraxetan than with cabazitaxel?

How do you approach follow-up imaging for patients receiving PSMA radioligand therapy? Do you follow with PSMA-PET or conventional imaging?

Is there any role for re-treatment with lutetium Lu 177 vipivotide tetraxetan? What about the combination of lutetium Lu 177 vipivotide tetraxetan with other systemic therapies?

RTP RESEARCH TO PRACTICE

Consulting Faculty Questions

Prevention and management of side effects associated with lutetium Lu 177 vipivotide tetraxetan

Neil Love, MD

Rana R McKay, MD

Andrew J Armstrong, MD, ScM

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

Andrew J Armstrong, MD, ScM

How do you approach radiation protection precautions for patients with external urine collection devices who are receiving lutetium Lu 177 vipivotide tetraxetan?

Rana R McKay, MD

What strategies do you use to prevent and manage the xerostomia and dry eye associated with lutetium Lu 177 vipivotide tetraxetan?

RTP
RESEARCH
TO PRACTICE

Consulting Faculty Questions

Sequencing lutetium Lu 177 vipivotide tetraxetan and radium Ra 223 dichloride

Neil Love, MD

Andrew J Armstrong, MD, ScM

Rana R McKay, MD

RTP RESEARCH TO PRACTICE

QUESTIONS FOR THE FACULTY

Andrew J Armstrong, MD, ScM

Rana R McKay, MD

In which clinical situations are you currently prioritizing radium-223 for patients with mCRPC?

Do you generally use lutetium Lu 177 vipivotide tetraxetan or radium-223 first for patients with PSMA-positive mCRPC and bone-only metastases?

What investigational radioligand therapies with targets beyond PSMA seem most promising?

RTP RESEARCH TO PRACTICE

What was the age of the last patient in your practice with mCRPC who received lutetium Lu 177 vipivotide tetraxetan? What prior treatment or treatments did the patient receive?

	Age	Prior treatment
 Dr Aggarwal	72 years	Abiraterone, docetaxel
 Dr Antonarakis	78 years	ADT, abi, docetaxel, daro
 Dr Bryce	78 years	ADT, abi, docetaxel
 Dr Heath	72 years	Enzalutamide, docetaxel
 Dr Sartor	62 years	ADT/abi/enza/docetaxel
 Dr Armstrong	66 years	Abi, enza, docetaxel, sip-T
 Dr McKay	83 years	Docetaxel

Daro = darolutamide; sip-T = sipuleucel-T

A 65-year-old man receiving ADT and abiraterone/prednisone for mHSPC develops new bone metastases (PSMA-positive). Genetic testing is negative for HRR mutations. Regulatory and reimbursement issues aside, what systemic treatment would you most likely recommend?

 Dr Aggarwal	Docetaxel
 Dr Antonarakis	Docetaxel
 Dr Bryce	Docetaxel
 Dr Heath	Lutetium Lu 177 vipivotide tetraxetan
 Dr Sartor	Lutetium Lu 177 vipivotide tetraxetan
 Dr Armstrong	Docetaxel or radium-223
 Dr McKay	Docetaxel

RTP RESEARCH TO PRACTICE

Regulatory and reimbursement issues aside, what would you generally recommend first for a patient with PSMA-positive mCRPC (chemotherapy or ^{177}Lu-PSMA-617)?

 Dr Aggarwal	Chemotherapy
 Dr Antonarakis	Lutetium Lu 177 vipivotide tetraxetan
 Dr Bryce	Lutetium Lu 177 vipivotide tetraxetan
 Dr Heath	Lutetium Lu 177 vipivotide tetraxetan
 Dr Sartor	Lutetium Lu 177 vipivotide tetraxetan
 Dr Armstrong	Lutetium Lu 177 vipivotide tetraxetan
 Dr McKay	Chemotherapy

RTP RESEARCH TO PRACTICE

Regulatory and reimbursement issues aside, what would you generally prefer for a patient with PSMA-positive mCRPC and bone-only metastases (radium-223 or ^{177}Lu-PSMA-617)?

 Dr Aggarwal	Lutetium Lu 177 vipivotide tetraxetan
 Dr Antonarakis	Lutetium Lu 177 vipivotide tetraxetan
 Dr Bryce	Lutetium Lu 177 vipivotide tetraxetan
 Dr Heath	Lutetium Lu 177 vipivotide tetraxetan
 Dr Sartor	Lutetium Lu 177 vipivotide tetraxetan
 Dr Armstrong	Lutetium Lu 177 vipivotide tetraxetan
 Dr McKay	Lutetium Lu 177 vipivotide tetraxetan

RTP RESEARCH TO PRACTICE

Based on current clinical trial data and your personal experience, to what extent do you believe the xerostomia associated with lutetium Lu 177 vipivotide tetraxetan is problematic for patients?

 Dr Aggarwal	Not very problematic
 Dr Antonarakis	Somewhat problematic
 Dr Bryce	Not very problematic
 Dr Heath	Not very problematic
 Dr Sartor	Not very problematic
 Dr Armstrong	Somewhat problematic
 Dr McKay	Not very problematic

RTP RESEARCH TO PRACTICE

What strategies do you use to prevent and manage the xerostomia associated with lutetium Lu 177 vipivotide tetraxetan?

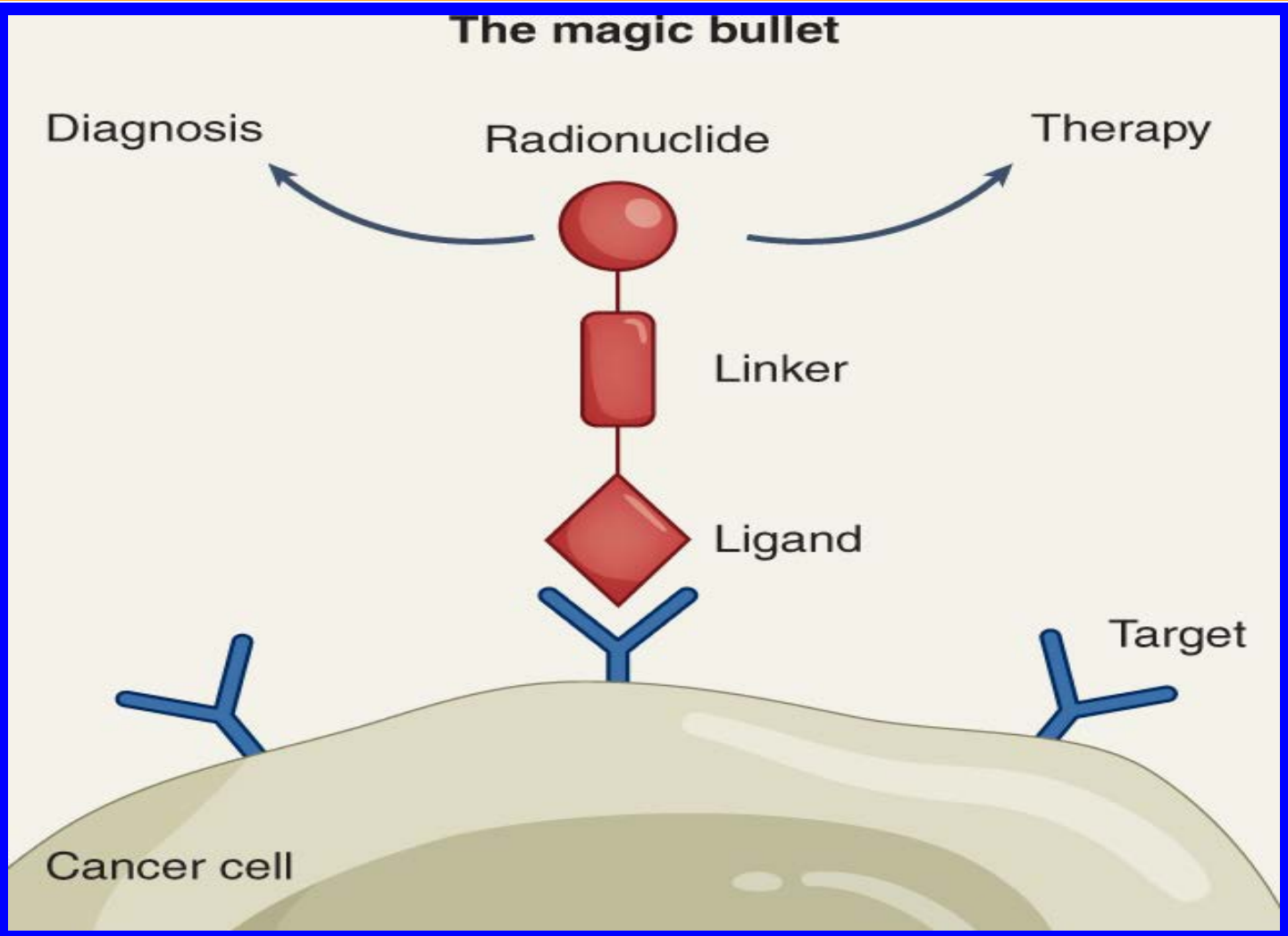
 Dr Aggarwal	Mouth rinse 3 to 4 times per day
 Dr Antonarakis	Saliva supplements, mouth rinse
 Dr Bryce	Hydration
 Dr Heath	Hydration, OTC medications for dry mouth
 Dr Sartor	Water and mints
 Dr Armstrong	Ice packs to salivary glands (preventive), hydration pre- and post-therapy and long term, chewing gum
 Dr McKay	Hydration, mouth rinse

RTP RESEARCH TO PRACTICE

Role of novel radiopharmaceuticals in prostate cancer

Oliver Sartor, MD
Chief, GU Cancers Disease Group
Director, Radiopharmaceutical Trials
Mayo Clinic

Theranostics:
See it…. Treat it…..Love it!



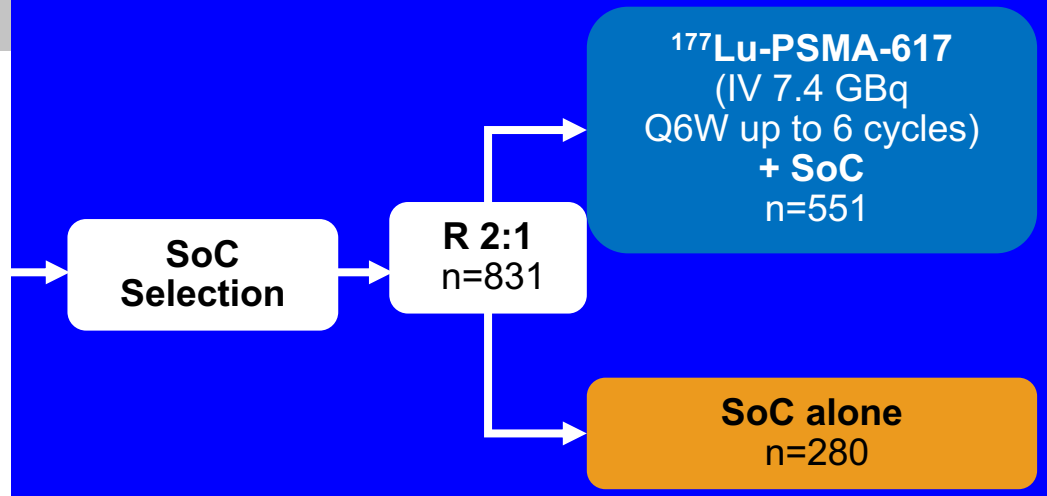
Cell surface target, a ligand, a linker, and an isotope

VISION: ^{177}Lu-PSMA-617 Phase III trial

Study Design

Population

- Progressive mCRPC
- PSMA-positive with ^{68}Ga-PSMA-11 PET/CT scan (uptake more than liver)
- Previous taxane (≤2 regimens) therapy and previous abiraterone/ enzalutamide[a] (≥1 regimen)
- ECOG PS 0–2
- Life expectancy >6 months



Alternate Primary Endpoints

- rPFS (per PCWG3)
- OS

Key Secondary Endpoints
(with α control)

- RECIST v1.1 response: ORR
- Time to first SSE

Stratification Factors

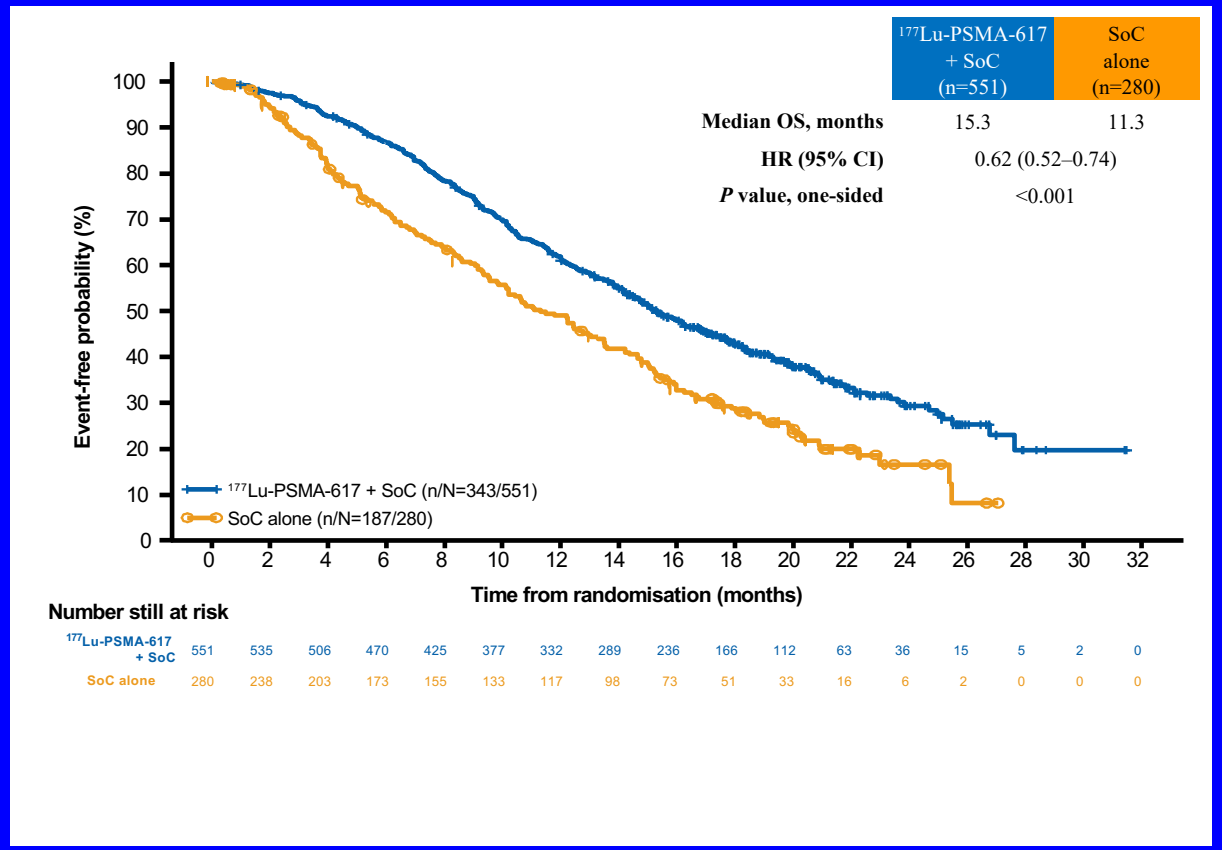
- Serum LDH (≤ 260 IU/L vs >260 IU/L)
- Presence of liver metastases (yes vs no)
- ECOG PS (0–1 vs 2)
- Inclusion of ARPI in SoC (yes vs no) at time of randomisation

VISION: ^{177}Lu-PSMA-617 Phase III trial

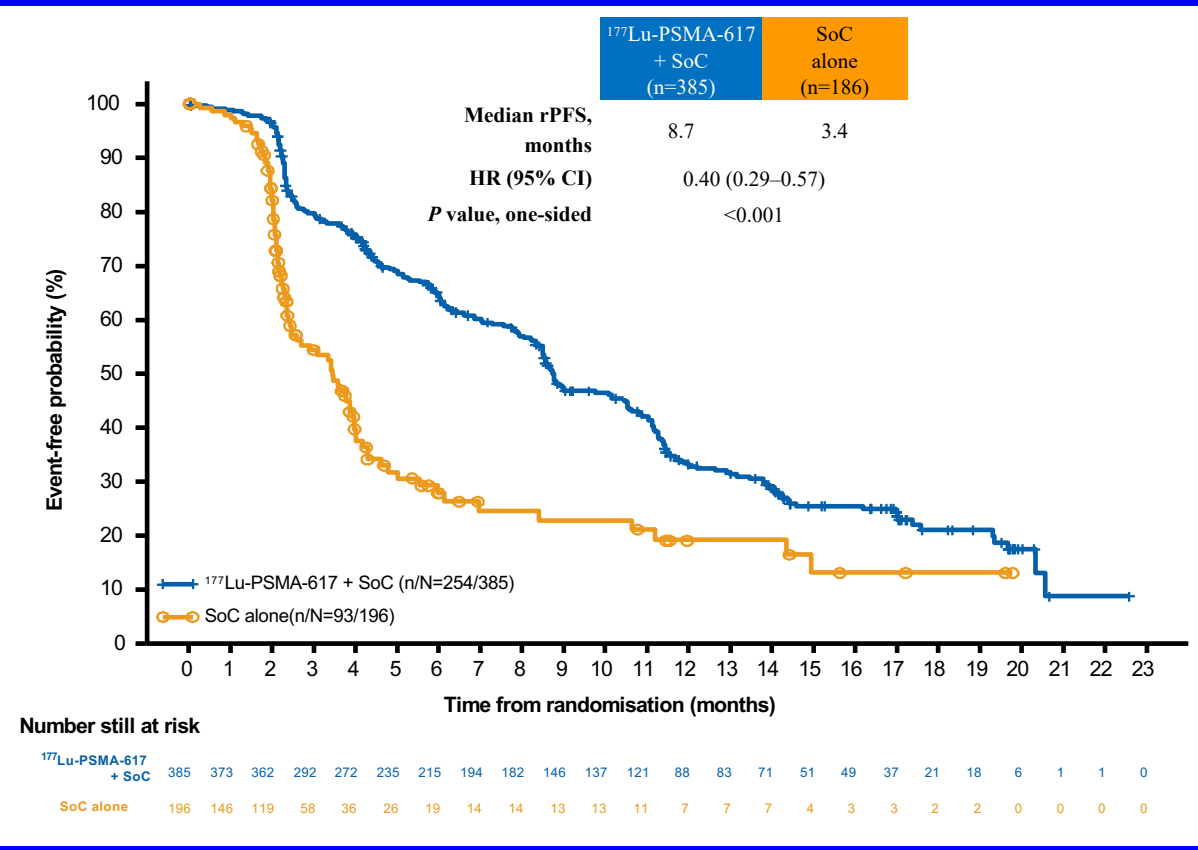
VISION met both primary endpoints of OS and rPFS

Sartor et al NEJM 2021

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

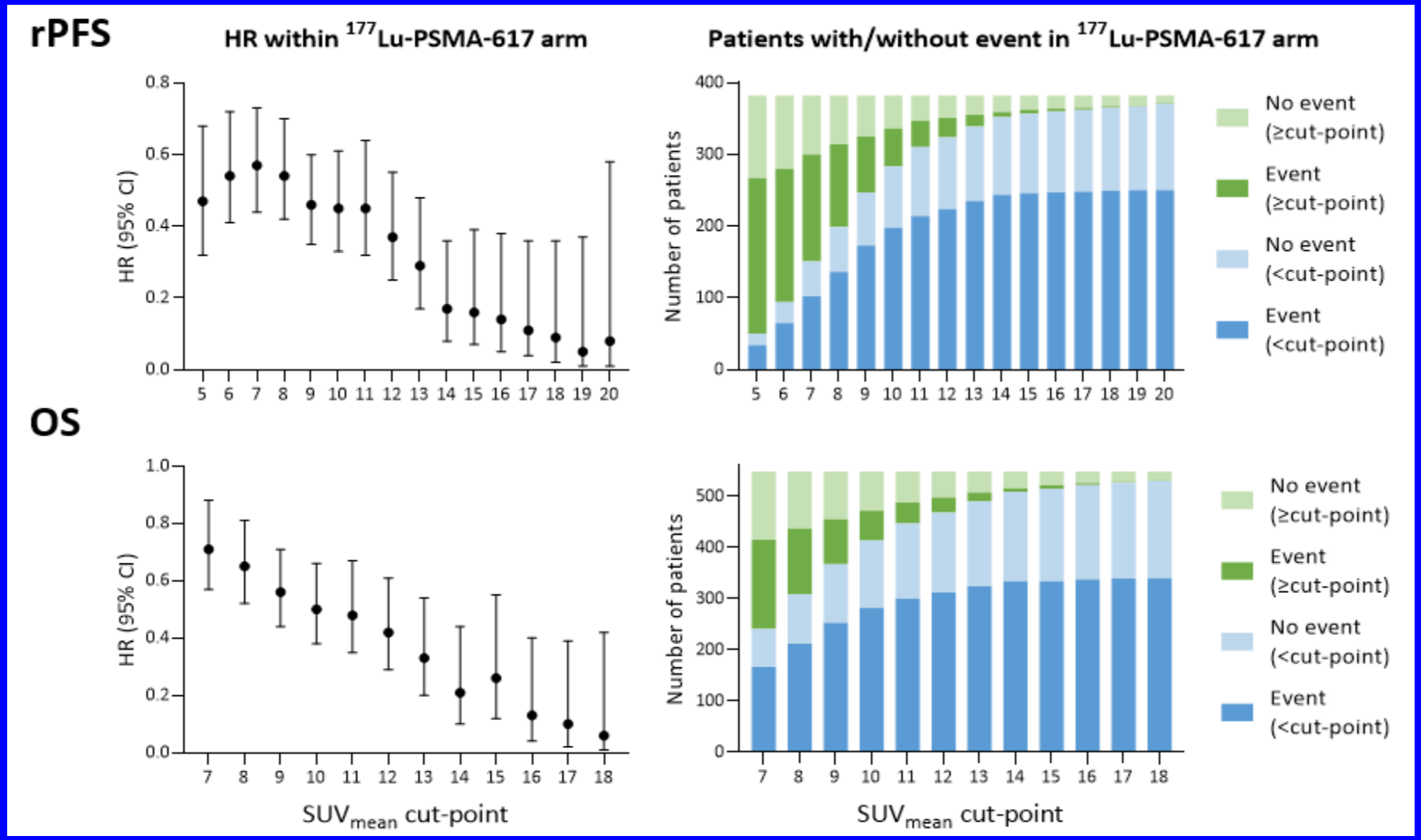


rPFS: HR 0.40 (95% CI 0.29-57)



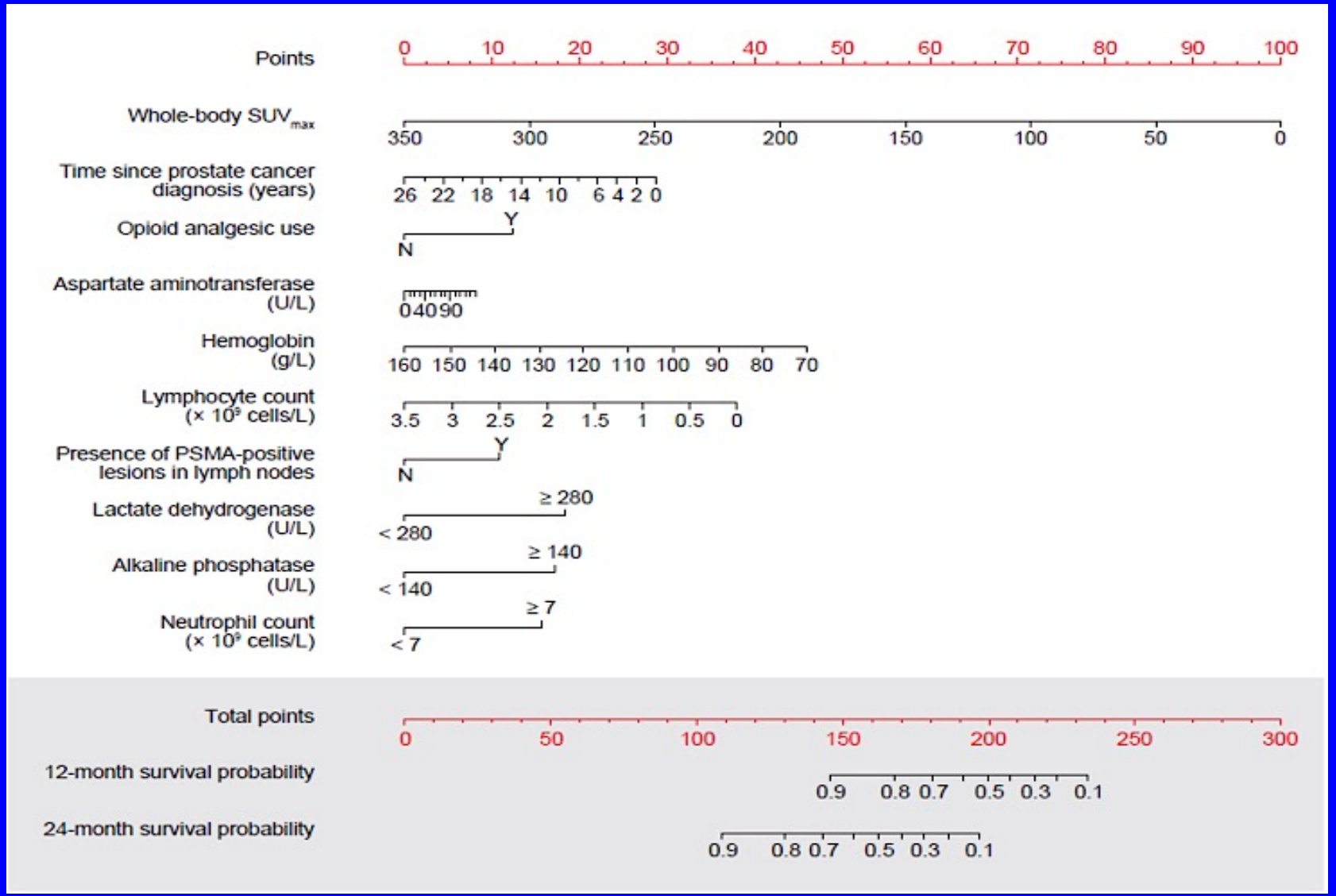
SUV^{mean} on baseline PSMA PET predicts rPFS and OS

Kuo et al. EANM 2023



Overall Survival Nomogram from VISION

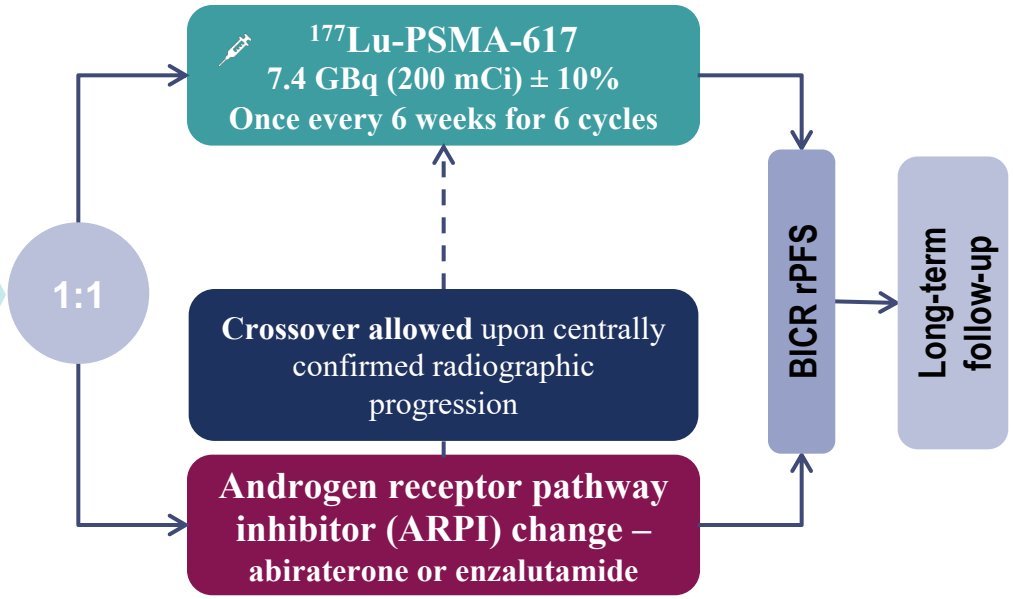
Herrmann et al. ASCO 2023



PSMAfore: phase 3, randomized, study of ^{177}Lu-PSMA-617 versus ARPI change in taxane-naive patients with PSMA-positive mCRPC

Eligible patients

- Adults with confirmed progressive mCRPC
- ≥ 1 PSMA-positive metastatic lesion on [^{68}Ga]Ga-PSMA-11 PET/CT and no PSMA-negative lesions that meet specific size exclusion criteria
- **Progressed once on prior second-generation ARPI**
  - Candidates for change in ARPI
- **Taxane-naive (except adjuvant/neoadjuvant > 12 months ago)**
  - No prior treatment with immunotherapy (except sipuleucel-T) or systemic radiotherapy (within 6 months)
  - Not candidates for PARP inhibition
- ECOG performance status 0–1

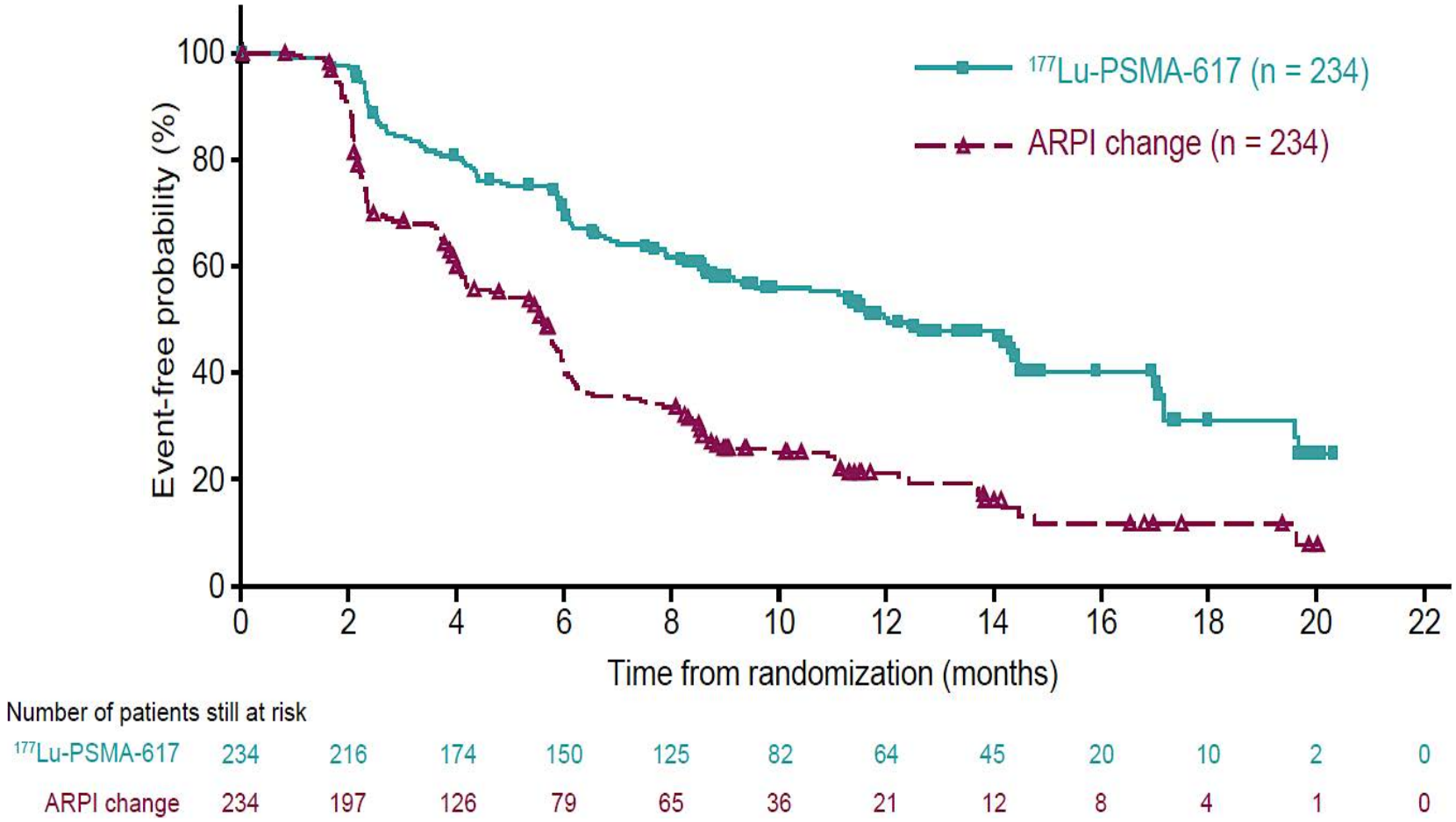


Randomization stratification factors

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

Updated rPFS analysis for PSMAfore

Sartor et al. ESMO 2023



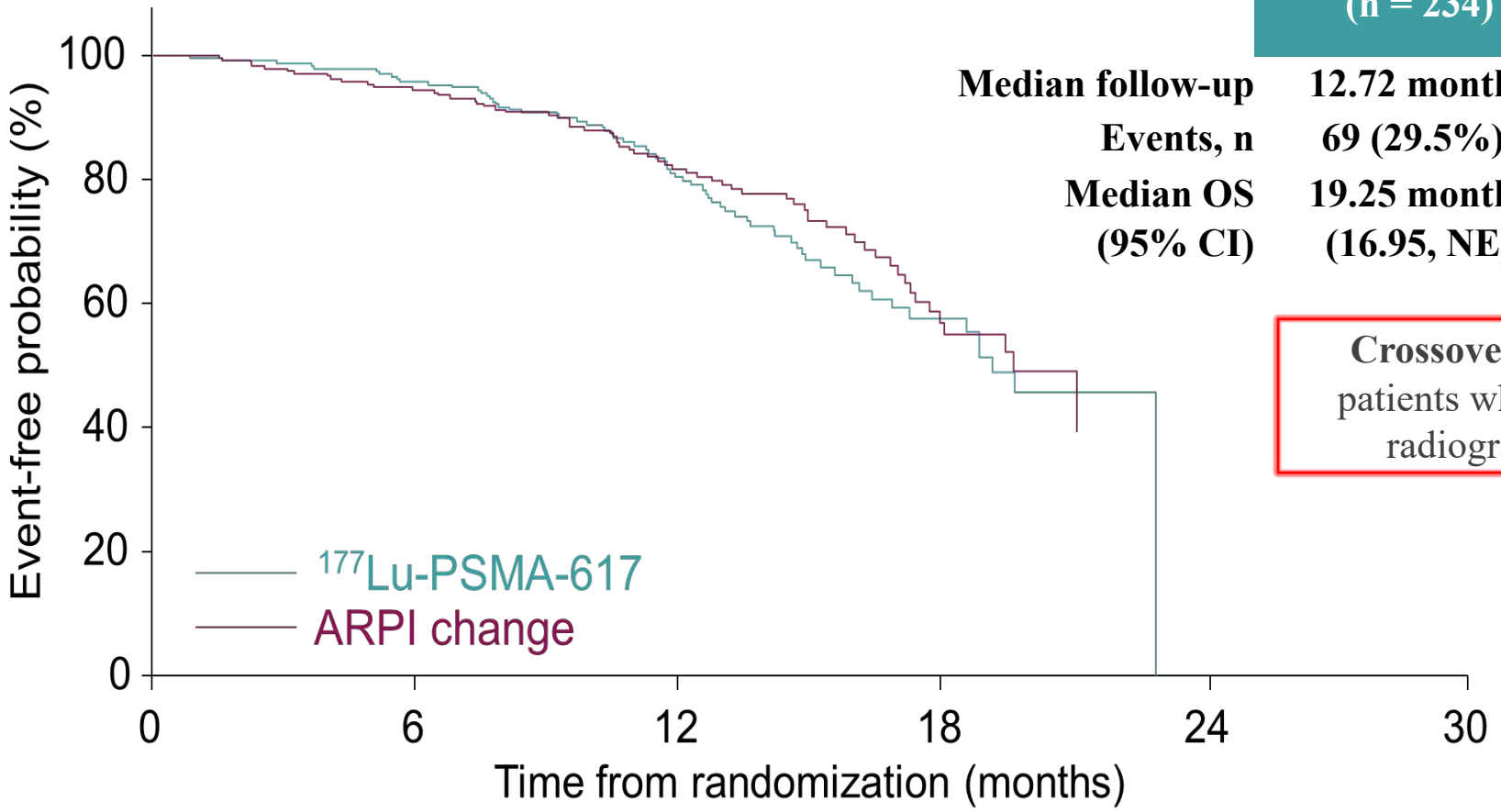
Median, months (95% CI):
12.02 (9.30, 14.42) vs 5.59 (4.17, 5.95)

HR: 0.43 (95% CI: 0.33,-0.54)

Intent-to-treat analysis OS for PSMAfore

Sartor et al. ESMO 2023

HR: 1.16 (95% CI: 0.83, 1.64)



	^{177}Lu-PSMA-617 (n = 234)	ARPI change (n = 234)
Median follow-up	12.72 months	13.08 months
Events, n	69 (29.5%)[a]	65 (27.8%)
Median OS (95% CI)	19.25 months (16.95, NE)	19.71 months (17.81, NE)

Crossover: 123/146 (84.2%)
patients who discontinued with radiographic progression

^{177}Lu-PNT2002 Demonstrates Initial Safety and Efficacy for mCRPC

Press Release: December 18, 2023

"Topline results from the phase 3 SPLASH trial (NCT04647526) show initial safety and efficacy of ^{177}Lu-PNT2002, an investigational prostate-specific membrane antigen (PSMA)-targeted radioligand therapy, in patients with metastatic castration-resistant prostate cancer (mCRPC) who have progressed following treatment with androgen receptor pathway inhibitor (ARPI).

The trial met its primary end point of radiographic progression-free survival (rPFS) per blinded independent central review and demonstrated a favorable safety profile in this patient population.

Overall, ^{177}Lu-PNT2002 demonstrated a median rPFS of 9.5 months, compared with 6.0 months among patients in the control arm, who were treated with an ARPI. This translates to a 29% reduction in the risk of radiographic progression or death with ^{177}Lu-PNT2002 (HR, 0.71; *P* = 0.0088)."

https://www.urologytimes.com/view/177lu-pnt2002-shows-initial-safety-and-efficacy-in-mcrpc

RTP RESEARCH TO PRACTICE

ENZA-p randomized phase II in mCRPC

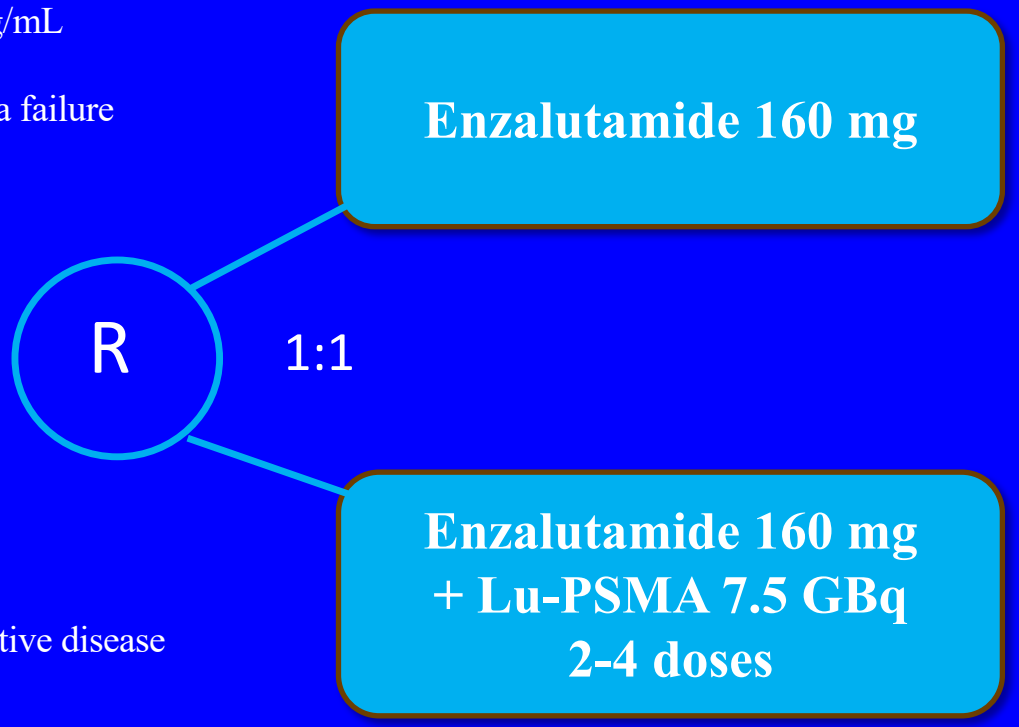
Emmett et al, ESMO 2023

Eligibility

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

Stratification

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



Objectives

PSA-PFS (primary)
Radiographic PFS
PSA response rate
Pain response and PFS
Clinical PFS
HRQOL
Adverse events
Overall survival
Health economics
Translational/correlative

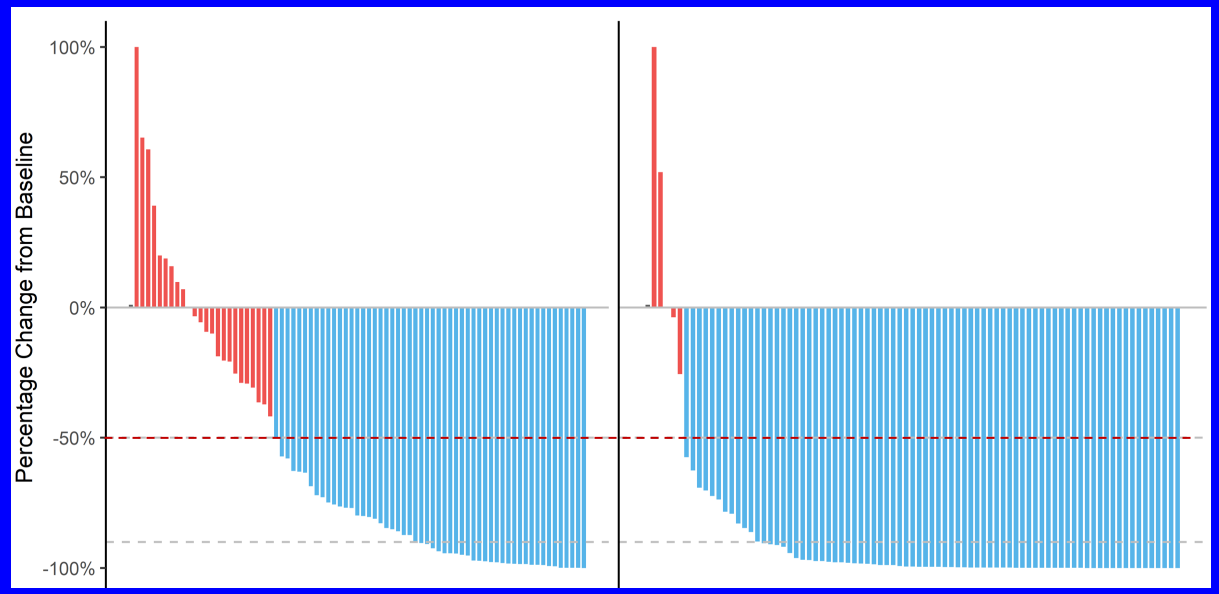
ENZA-p PSA Response Rates

Emmett et al. ESMO 2023

PSA 50% RR

Enzalutamide
68%

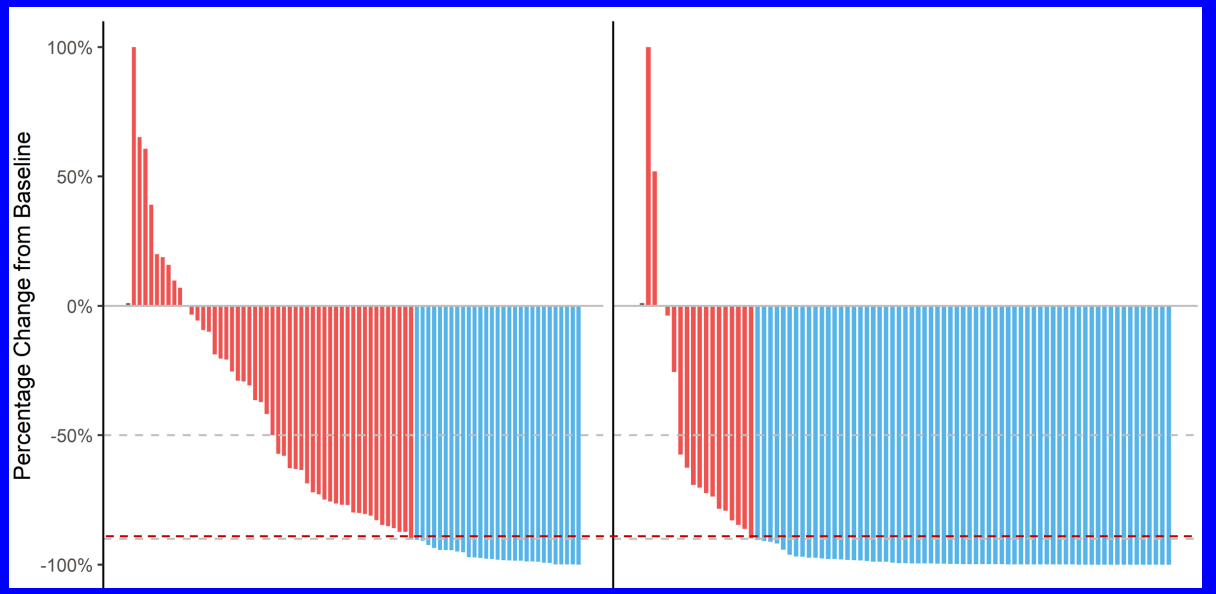
Enzalutamide + Lu-PSMA
93%



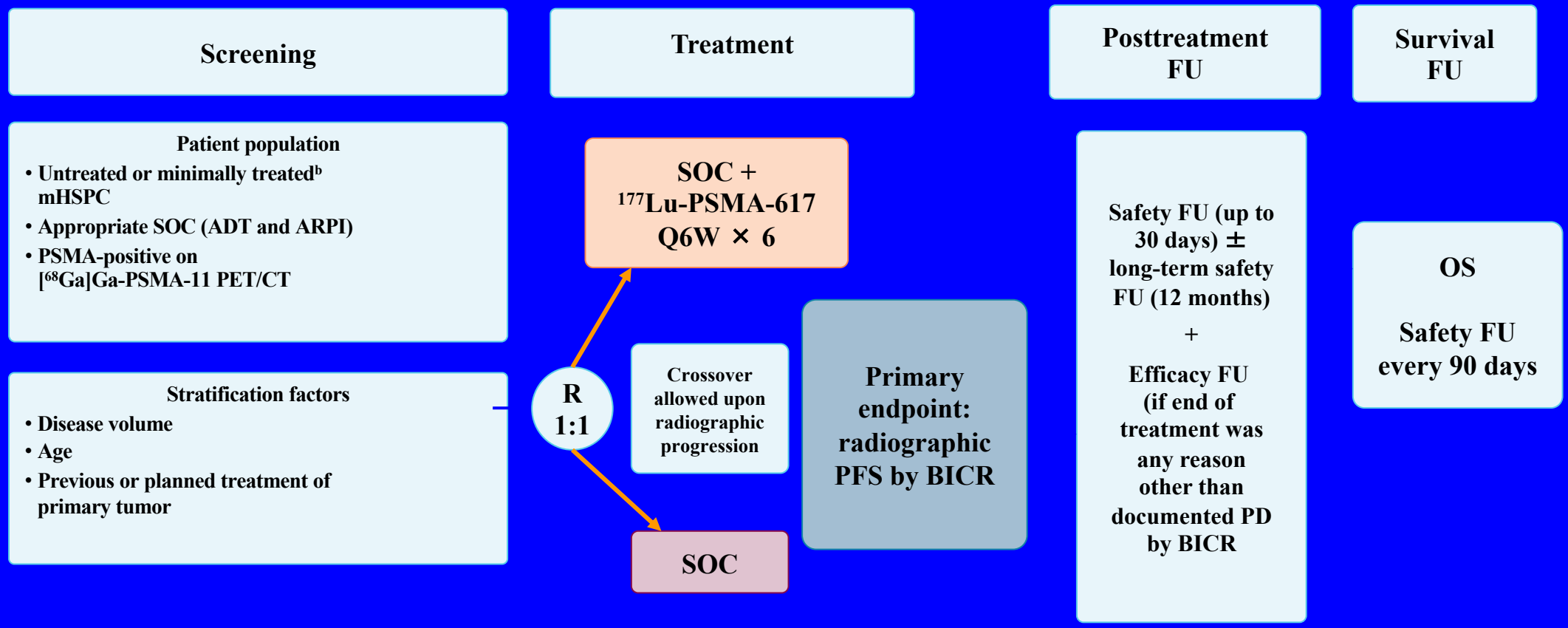
PSA 90% RR

Enzalutamide
37%

Enzalutamide + Lu-PSMA
78%



PSMAddition: Design for Metastatic Castrate-Sensitive Prostate Cancer

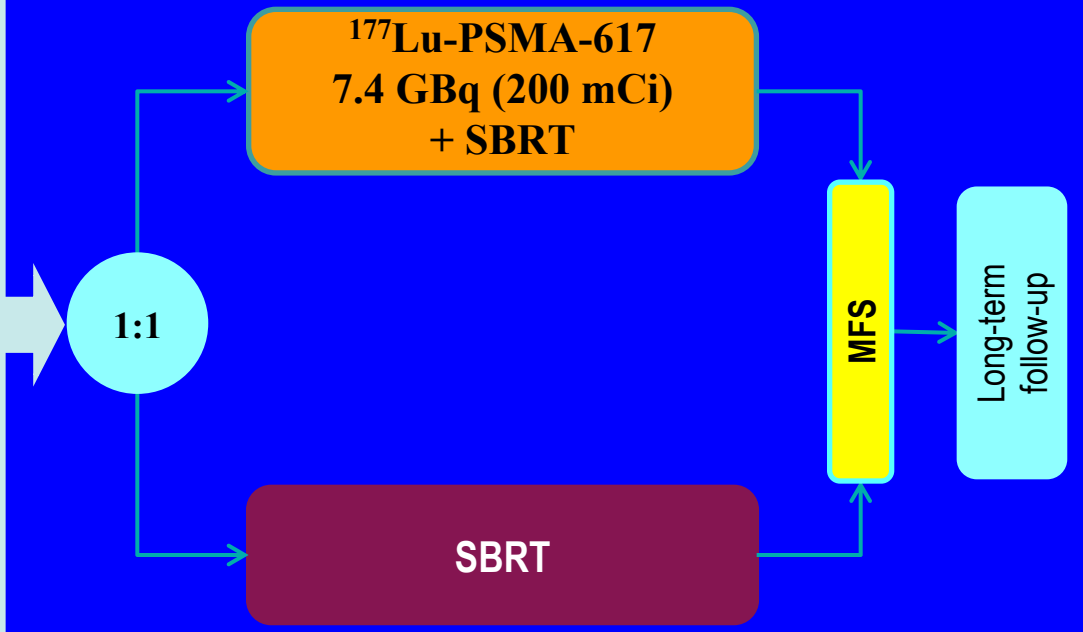


SOC =ADT and ARPI of choice (abiraterone or enzalutamide or apalutamide)

A Phase III Open-label Study Comparing Lutetium (177Lu) Vipivotide Tetraxetan Versus Observation in PSMA Positive Oligometastatic Prostate Cancer (PSMA-DC)

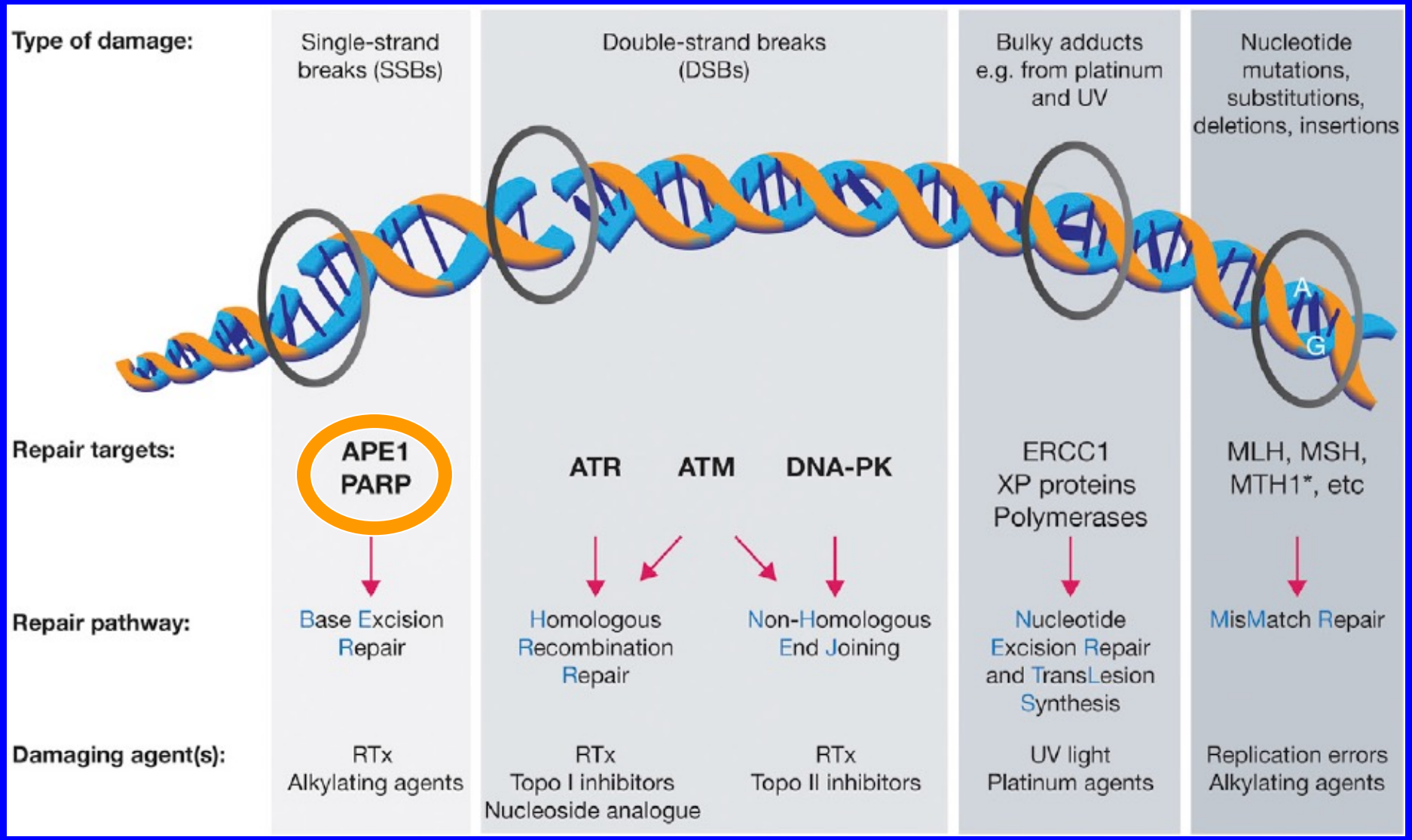
Eligible patients

- Adults with progressive castrate-sensitive prostate cancer
- 1-5 PSMA-positive M1 lesion on PSMA PET and negative conventional imaging
- All metastatic lesions amenable to SBRT
- PSADT ≤10 months
- Prior treatment of the prostate by RP or XRT
- Non-castrate T at baseline
- Prior adjuvant ADT allowed if ≥12 months in past
- ECOG performance status 0–1



MFS by conventional imaging primary endpoint makes it FDA approvable

Targeting DNA damage repair pathways in combination with radionuclides

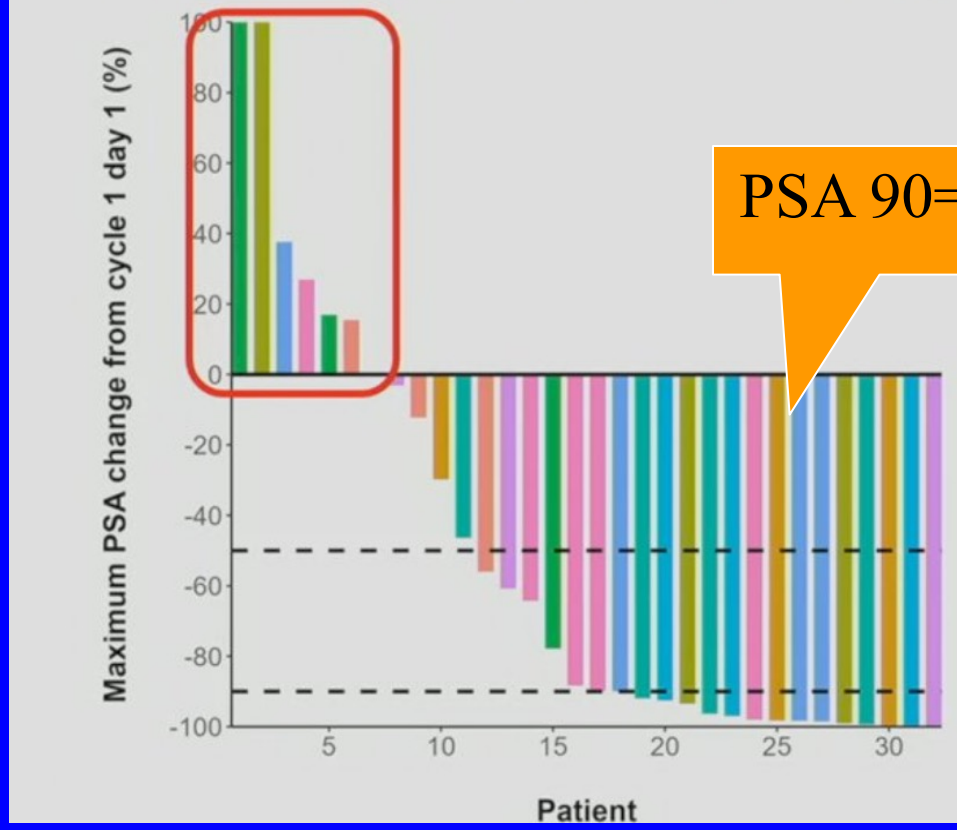


O'Connor, Molecular Cell 60, November 19, 2015

Phase I LuPARP study: ^{177}Lu-PSMA-617 and olaparib

Sandhu et al. ASCO 2023

LuPARP results: PSA Response



PSA 90=44%

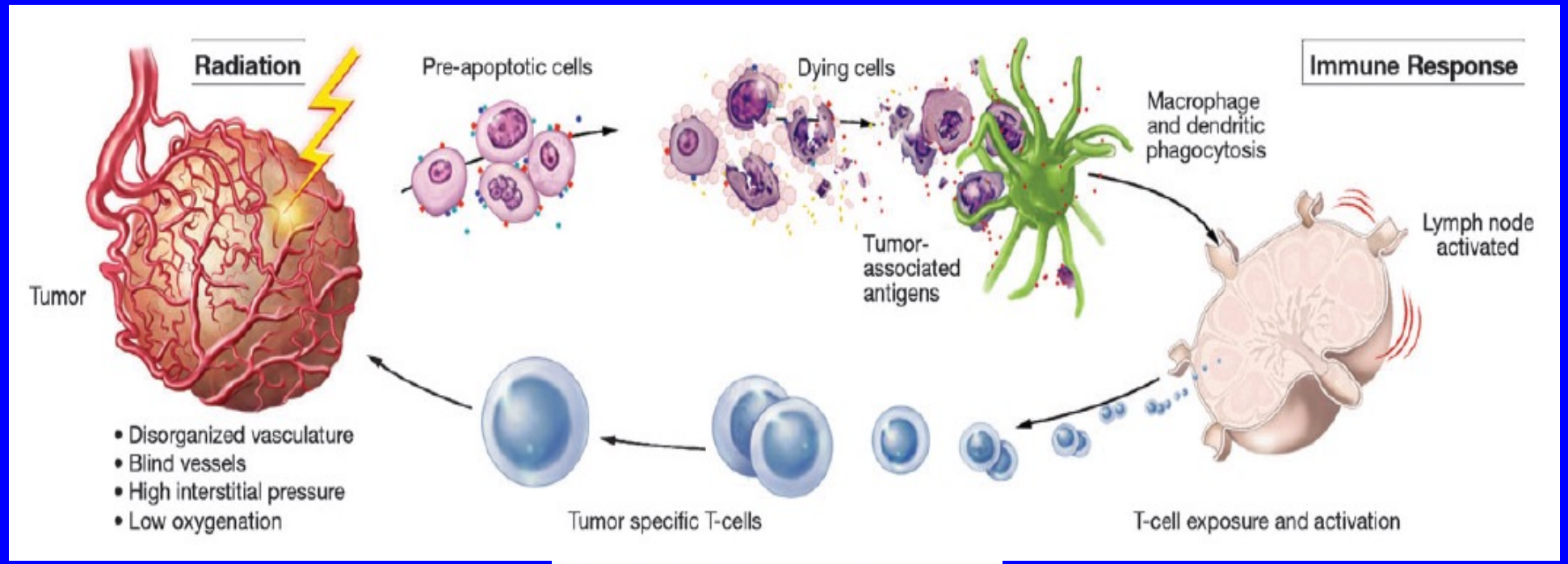
- Cohort 1: 50mg Day 2-15
- Cohort 2: 100mg Day 2-15
- Cohort 3: 150mg Day 2-15
- Cohort 4: 200mg Day 2-15
- Cohort 5: 250mg Day 2-15
- Cohort 6: 300mg Day 2-15
- Cohort 7: 200mg Day -4-14
- Cohort 8: 300mg Day -4-14
- Cohort 9: 300mg Day -4-18

	LuPARP	TheraP	VISION
PSMA SUVmax	>15	>20	> Liver
PSA50 response	66% (21/32)	66% (67/99)	46% (177/385)
PSA80 response	53% (17/32)	48% (48/99)	33% (127/385)
PSA90 response	44% (14/32)	38/99 (38%)	N/A
ORR by RECIST 1.1	78% (7/9)	49% (48/99)	30% (95/319)

1. Sartor O et al. N Engl J Med 2021;385(12):1091-1103.
2. Hofman MS et al. Lancet 2021;397(10276):797-804

Antigen release from radiated tumor: Synergy with immunotherapies?

Kamrava et al., Molecular Biosystems: 5:1249–1372, 2009



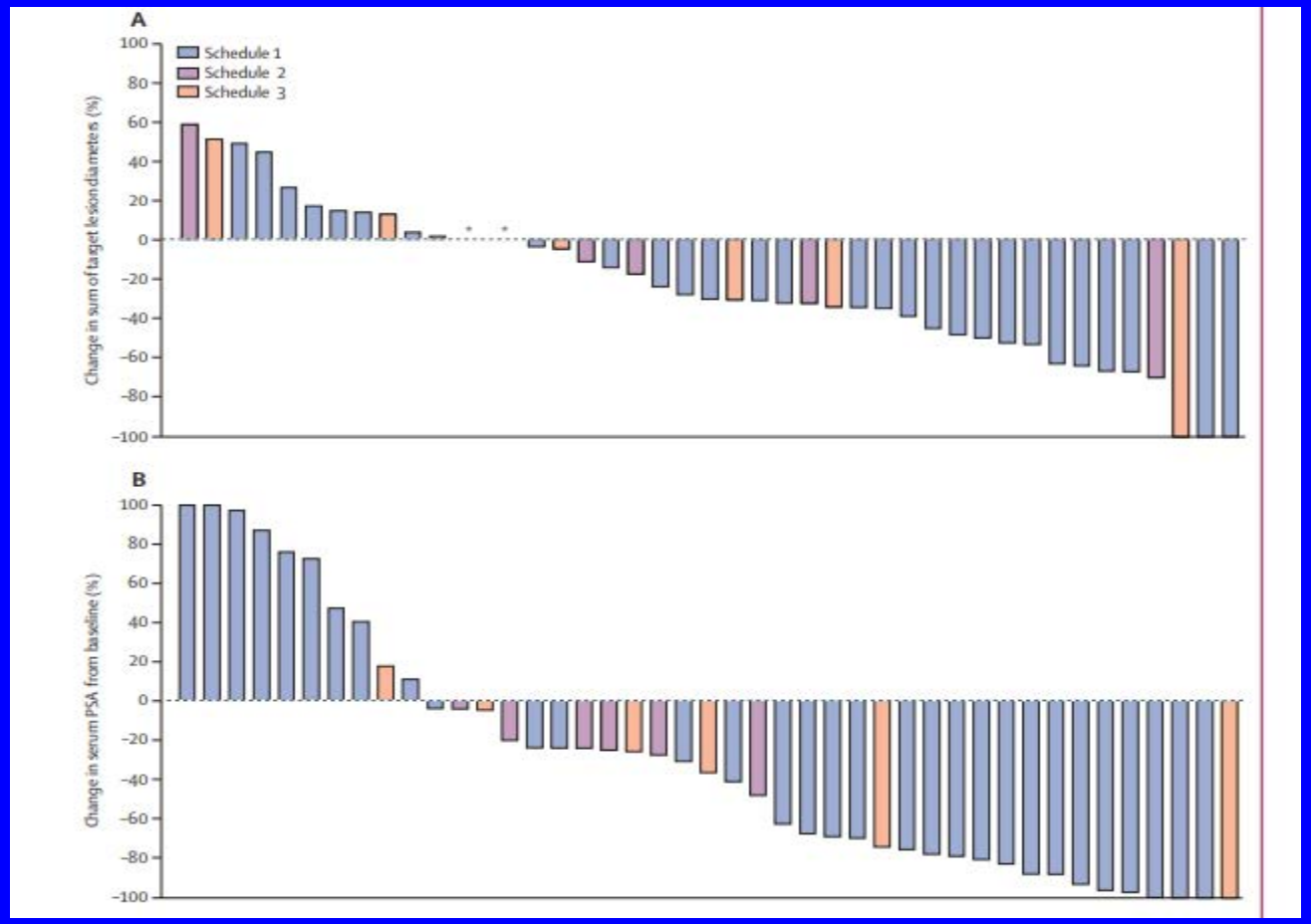
Systemic/local immune enhancement

- Vaccine
- Checkpoint inhibitors
  - Anti-CTLA-4
  - Anti-PD-1
  - Anti-PD-L1
  - Anti-TIM3
- Co-stimulatory agonists
  - Anti-OX40
  - Anti-4-1BB
  - Anti-GITR
  - Anti-CD27
  - Anti-CD40
- Exogenous cytokines
  - IL-2
  - IL-7
  - IL-12
  - IL-15
  - IL-21
  - GM-CSF

Single-dose ^{177}Lu-PSMA-617 followed by maintenance pembrolizumab in patients with metastatic castration-resistant prostate cancer: an open-label, dose-expansion, phase 1 trial

Rahul Aggarwal, Stephanie Starzinski, Ivan de Kouchkovsky, Vadim Koshkin, Rohit Bose, Jonathan Chou, Arpita Desai, Daniel Kwon, Samuel Kaushal, Lauren Trihy, Medini Rastogi, Robin Ippisch, Maya Aslam, Terence Friedlander, Felix Feng, David Oh, Alexander Cheung, Eric Small, Michael Evans, Lawrence Fong, Thomas A Hope**

Lancet Oncol 2023; 24: 1266–76



Alpha Particles

(Ra-223, Ac-225, Pb-212, At-211)

Critical differences in α and β Particles: Short range, high LET and lethal!

	α	β
Relative particle mass	7300	1
Speed of light	6%	98%
Initial energy (MeV) per particle	3–8	0.01–2.5
Range in tissue (μm)	40–100	50–5000
* LET (KeV/μm)	60–230	0.015–0.4
DNA hits to kill cells	1–10	100–1000

*LET, linear energy transfer adapted from Henriksen G, et al. J Nucl Med. 2003;44(2):252-9

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 18, 2013 VOL. 369 NO. 3

Alpha Emitter Radium-223 and Survival in Metastatic Prostate Cancer

C. Parker, S. Nilsson, D. Heinrich, S.I. Helle, J.M. O'Sullivan, S.D. Fosså, A. Chodacki, P. Wiechno, J. Logue, M. Seke, A. Widmark, D.C. Johannessen, P. Hoskin, D. Bottomley, N.D. James, A. Solberg, I. Syndikus, J. Kliment, S. Wedel, S. Boehmer, M. Dall'Oglio, L. Franzén, R. Coleman, N.J. Vogelzang, C.G. O'Bryan-Tear, K. Staudacher, J. Garcia-Vargas, M. Shan, Ø.S. Bruland, and O. Sartor, for the ALSYMPCA Investigators*

Radium-223 targets osteoblastic bone lesions

EORTC GUCG 1333 (PEACE III)

Study population

- Patients with bone-predominant mCRPC (≥2 bone metastases)
- Asymptomatic or mildly symptomatic
- WHO PS of 0 or 1
- No prior treatment with, cyp17 inhibitors, enzalutamide, Ra233, other radionucleotides, hemibody radiotherapy
- No known brain or visceral metastases

Target Accrual
N=560

1:1
Randomisation,

Enzalutamide 160 mg qd
Radium-223
55 kBq/kg IV every 4 weeks for 6 cycles

Stratification factors

- Country
- Baseline pain (BPI worst pain 0-1 vs 2-3)
- Prior docetaxel (yes vs no)
- Use of bone health agents*

Enzalutamide 160 mg qd

Primary endpoint

- rPFS

Secondary endpoints

- OS
- DSS
- SSE
- Time to initiation of next systemic anti-neoplastic therapy
- PFS2
- Brief Pain Inventory (BPI),
- (EQ-5D-5L)

The Prostate Cancer Clinical Trials Consortium

Phase III Trial of Docetaxel vs. Docetaxel and Radium-223 for Metastatic Castration-Resistant Prostate Cancer

AlphaBet: Combination of Radium-223 and ^{177}Lu-PSMA-I&T in men with metastatic castration-resistant prostate cancer

Kostos et al. Front Med
https://doi.org/10.3389/fmed.2022.1059122

NCT05383079

BAT-RAD
Bipolar Androgen Therapy (BAT) and Radium-223 (RAD) in Metastatic Castration-resistant Prostate Cancer (mCRPC)

NCT04704505

Metastatic Hormone-Sensitive Prostate Cancer with ^{225}Ac-PSMA-617 and No Hormones

Sathegke et al. EJNMMI 2023 https://doi.org/10.1007/s00259-023-06165-9

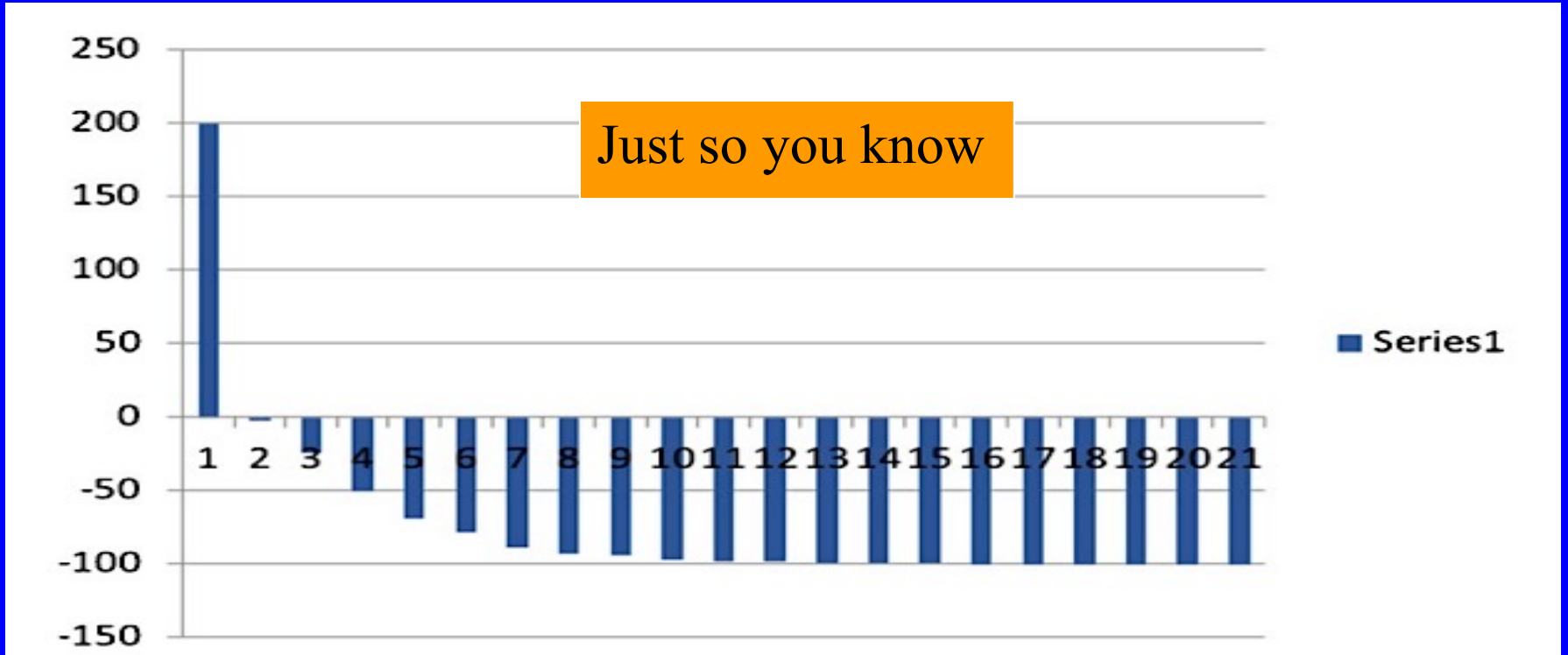
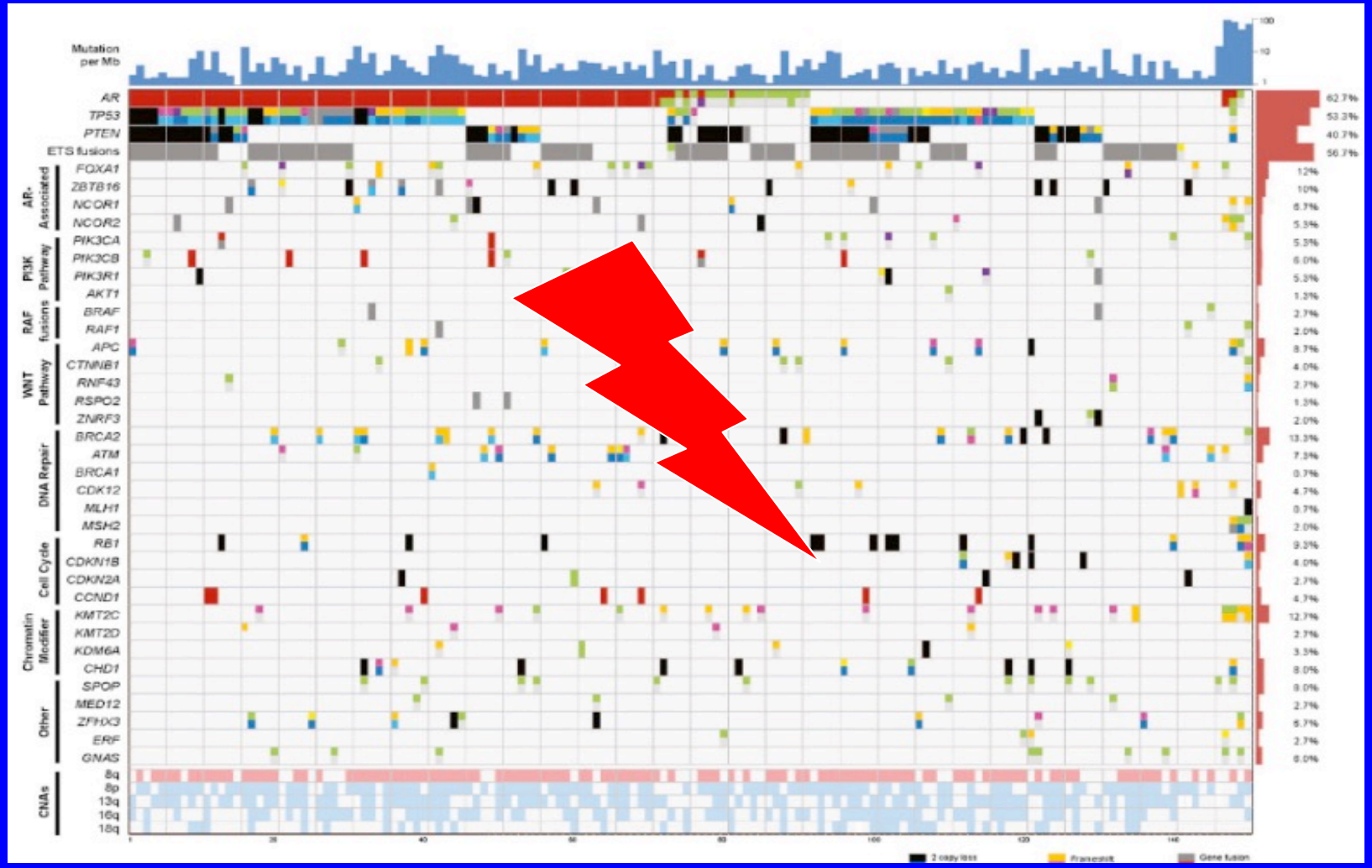


Fig. 1 Waterfall plot demonstrating percentage change in PSA levels after treatment with ^{225}Ac-PSMA-617 in studied patients (x-axis= number of patients, y-axis= percentage change)

Challenges: Metastatic prostate cancer is a genetically heterogeneous group of diseases but radiation can kill them all!



Robinson et al. Cell 161:1215, 2015

MODULE 5: Promising Investigational Approaches for Patients with Prostate Cancer – Dr Heath

RTP
RESEARCH
TO PRACTICE

Consulting Faculty Questions

Promising treatment strategies under investigation — immunotherapy, cabozantinib, abemaciclib and others

Neil Love, MD

Rana R McKay, MD

RTP RESEARCH TO PRACTICE

QUESTIONS FOR THE FACULTY

Rana R McKay, MD

What novel investigational strategies are you most excited about for patients with metastatic prostate cancer? What drug classes do you believe are most likely to be approved in the near future?

What are your thoughts about recent data on the combination of nivolumab and cabozantinib and on the use of CDK4/6 inhibitors (abemaciclib)?

RTP
RESEARCH
TO PRACTICE

Consulting Faculty Questions

Approach to endocrine therapy for patients with disease progression on prior AR inhibitor; potential role of targeted therapies

Neil Love, MD

Andrew J Armstrong, MD, ScM

RTP RESEARCH TO PRACTICE

QUESTIONS FOR THE FACULTY

Andrew J Armstrong, MD, ScM

Do you routinely offer a second AR pathway inhibitor after disease progression on one of these agents?

Does a change in AR pathway inhibitor after prior treatment with one of these drugs represent a reasonable control arm for future clinical trials?

Do you order AR-V7 testing for your patients experiencing disease progression on secondary hormonal therapy?

What are your thoughts about the future role of oral targeted agents such as capivasertib and cabozantinib in this disease?

RTP RESEARCH TO PRACTICE

What was the age of the last patient in your practice with metastatic prostate cancer who was enrolled on a clinical trial? On which clinical trial was the patient enrolled and what treatment did they receive?

	Age	Clinical trial treatment
 Dr Aggarwal	68 years	Lu-PSMA + pembrolizumab
 Dr Antonarakis	75 years	PSMA x CD3 + bispecific antibody
 Dr Bryce	64 years	Trial of PT-112
 Dr Heath	66 years	Darolutamide + AZD5305 on PETRANHA study
 Dr Sartor	72 years	About to enroll on trial of ^{225}Ac-PSMA-617
 Dr Armstrong	56 years	Ph II CHAMP trial of cabazitaxel, carboplatin, nivolumab and ipilimumab
 Dr McKay	63 years	Ph II single-arm trial of nivolumab + cabozantinib

Based on emerging positive findings from the Phase III CONTACT-02 study, in which situations, if any, would you use the combination of cabozantinib and atezolizumab?

 Dr Aggarwal	Need to see OS data first
 Dr Antonarakis	Not yet, I would wait for more mature OS data
 Dr Bryce	To be determined
 Dr Heath	In non-HRR mutated mCRPC
 Dr Sartor	Need to see data
 Dr Armstrong	None
 Dr McKay	After AR signaling inhibitor, after PSMA therapy

OS = overall survival

Do you believe one or more CDK4/6 inhibitors (eg, abemaciclib) will someday be endorsed for use in metastatic prostate cancer?

 Dr Aggarwal	No
 Dr Antonarakis	Yes
 Dr Bryce	Yes
 Dr Heath	No
 Dr Sartor	No
 Dr Armstrong	No
 Dr McKay	Yes

RTP
RESEARCH
TO PRACTICE

What type(s) of tolerability issues would you anticipate with CDK4/6 inhibitors in metastatic prostate cancer?

 Dr Aggarwal	Neutropenia, GI toxicities
 Dr Antonarakis	Myelosuppression, LFT abnormalities, small but scary risk of ILD
 Dr Bryce	Myelosuppression, GI toxicity
 Dr Heath	Neutropenia, anemia, fatigue, diarrhea
 Dr Sartor	GI side effects and low blood counts
 Dr Armstrong	Diarrhea and some marrow suppressive effects, nausea, fatigue
 Dr McKay	Diarrhea

ILD = interstitial lung disease

Which investigational approaches do you believe hold the most therapeutic promise in metastatic prostate cancer?

 Dr Aggarwal	Bispecific T-cell engagers (eg, xaluritamig [AMG 509]), emerging ADCs (B7-H3, ARX517)
 Dr Antonarakis	STEAP1-directed engagers (xaluritamig), alpha particle radioligands, B7-H3 targeting drugs
 Dr Bryce	BiTEs and RLT
 Dr Heath	Bicyclic peptides, PROTACs, BET inhibitors
 Dr Sartor	Targeted alpha particle therapies (both Ac-225 and Pb-212), novel ADCs (PSMA and beyond), STEAP1-targeted BiTEs, selected AR degraders
 Dr Armstrong	BiTEs, CAR T combinations, ADCs, alpha particle therapies, AR degraders, CBP/p300 inhibitors, EZH2 inhibitor combinations, combinations with dual checkpoint blockade
 Dr McKay	PSMA ADC, B7-H3 ADC, AR degraders, alternate radioligand

Prostate Cancer Treatment Updates

Elisabeth I. Heath, MD FACP
Professor of Oncology
Associate Center Director, Translational Sciences
Chair, Genitourinary Oncology Multidisciplinary Team
Detroit, MI

CONTACT-02: Scientific Rationale

- Prostate cancer associated with immune-suppressive tumor microenvironment (TME)
  - Tregs and immunosuppressive M2 macrophages recruited to TME, limited CD8+ T cells, and correlated with worse prognosis
  - Promotion of immune-permissive TME is potential therapeutic strategy
- Immune checkpoint inhibitors (ICI) alone has limited activity in prostate cancer
- ICI in combination with receptor tyrosine kinase (RTK) inhibitors against Tyro3, Axl, and Mer (TAM) kinases has increased efficacy in preclinical studies
- Cabozantinib, RTK inhibitor against TAM promotes an immune-permissive environment that consists of decreased Tregs and increased cytokines
- ICI in combination with RTK inhibitor effective in other cancers such as renal cell carcinoma

Lundholm M et al. Sci. Rep. 5, 15651(2015). Kiniwa Y et al. Clin Cancer Res. 13(23),6947-6958 (2007). Hansen AR et al. Ann. Oncol. 29(8), 1807-1813(2018). Davidsen K et al. Cancer Res. 78(suppl.13), abstract 3774(2018). Axelrod HD et al. Mol. Cancer Res. 17(2), 356-369(2019). Choueri TK et al. N. Engl. J. Med. 373(19), 1814-1823 (2015).

CONTACT-02: Clinical Background Data

- COMET-1
  - Phase III randomized, double-blind study of cabozantinib versus prednisone
  - No OS improvement in overall population (11 vs 9.8 months, HR=0.9, p=0.213)
  - Higher OS rate with cabozantinib with visceral metastasis
- COSMIC-021
  - Phase Ib open-label study of cabozantinib and atezolizumab in multiple solid tumors including renal and prostate cancer
  - Cohort 6 in mCRPC with prior NHT
    - 44 patients with ORR 32%, 2 patients (CR), 12 patients (PR), 50% with PSA decrease
    - 36 patients with visceral or extrapelvic lymph node metastasis, ORR 33%

Smith MR et al. J. Clin.Oncol. 34(25), 3005-2013 (2016). Paul SK et al. J. Clin. Oncol. 39(33), 3725-3736 (2021). Agarwal N et al. J. Clin. Oncol.8(suppl.15), abstract 5564 (2020).

Abstract #18

ASCO GU 2024

Cabozantinib Plus Atezolizumab vs Second Novel Hormonal Therapy in Patients With Metastatic Castration-Resistant Prostate Cancer (mCRPC): Primary Analyses From the Phase 3 CONTACT-02 Study

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CONTACT-02 Study Design

mCRPC

- Adenocarcinoma histology
- Progressed on one prior NHT*
  - No requirement for rapid progression on the first NHT
- Measurable extrapelvic soft tissue metastasis (visceral or lymph node) per RECIST v1.1
- Progressive mCRPC (PSA or soft-tissue progression)
- ECOG PS 0 or 1
- Age ≥18 years
- Allowed prior docetaxel for locally advanced or metastatic CSPC

R1:1

Cabo+Atezo

Cabo 40 mg PO QD
+ Atezo 1200 mg IV Q3W

Second NHT

Abiraterone 1000 mg PO QD
+ prednisone 5 mg PO BID
or
Enzalutamide 160 mg PO QD

Dual primary endpoints

- PFS in the PFS ITT population per RECIST v1.1 by BIRC (first 400 randomized patients)†
- OS in the ITT population

Secondary endpoint

- ORR per RECIST v1.1 by BIRC

Other key endpoints

- PFS in the ITT population
- rPFS per PCWG3 by BIRC
- PSA response rate
- Time to PSA progression, symptomatic skeletal event‡, chemotherapy, pain progression
- Safety

Stratification

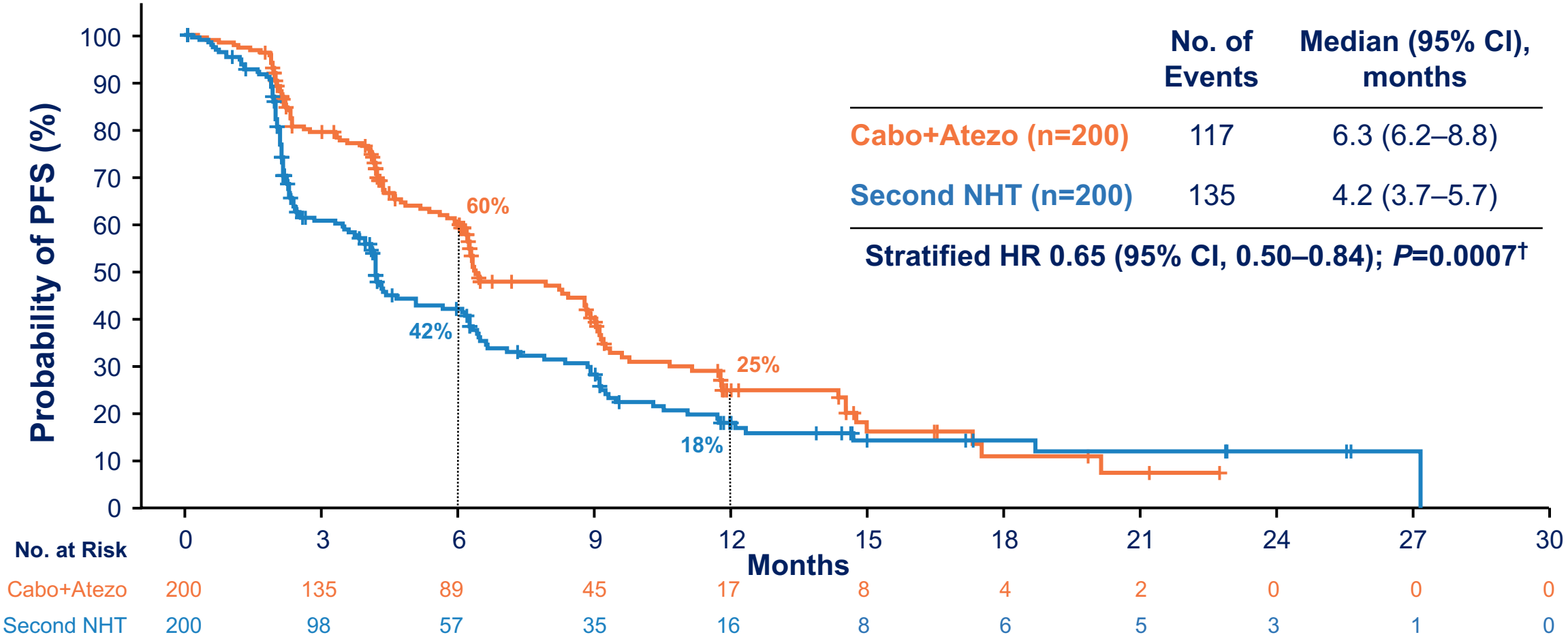
- Liver metastasis (yes / no)
- Prior docetaxel treatment for locally advanced or metastatic CSPC (yes / no)
- Disease stage for which the first NHT was given (mCSPC / M0 CRPC / mCRPC)

- Tumor assessments (RECIST v1.1) were performed at baseline, every 9 weeks for 28 weeks, then every 12 weeks thereafter
- Treatment was continued until loss of clinical benefit§ or intolerable toxicity

BID, twice daily; BIRC, Blinded Independent Radiology Committee; CSPC, castration-sensitive prostate cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; ITT, intention-to-treat; IV, intravenous; M0 CRPC, non-metastatic CRPC; mCSPC, metastatic CSPC; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PO, orally; PSA, prostate specific antigen; QD, once daily; Q3W, every 3 weeks; PCWG3, Prostate Cancer Working Group 3; RECIST, Response Evaluation Criteria in Solid Tumors.
*NHT for the treatment of mCSPC, M0 CRPC, or mCRPC. †Bone scan assessment not included in analysis. ‡Time to symptomatic skeletal event is defined as time from randomization to earliest of any of the following: radiation therapy to bone, surgery to bone, spinal cord compression, or symptomatic fracture. §Patients may be treated beyond progression if there is clinical benefit in the opinion of the investigator.

PFS per BIRC* (PFS ITT Population†)

Cabo+Atezo Reduced the Risk of Progression or Death by 35% vs Second NHT



	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†

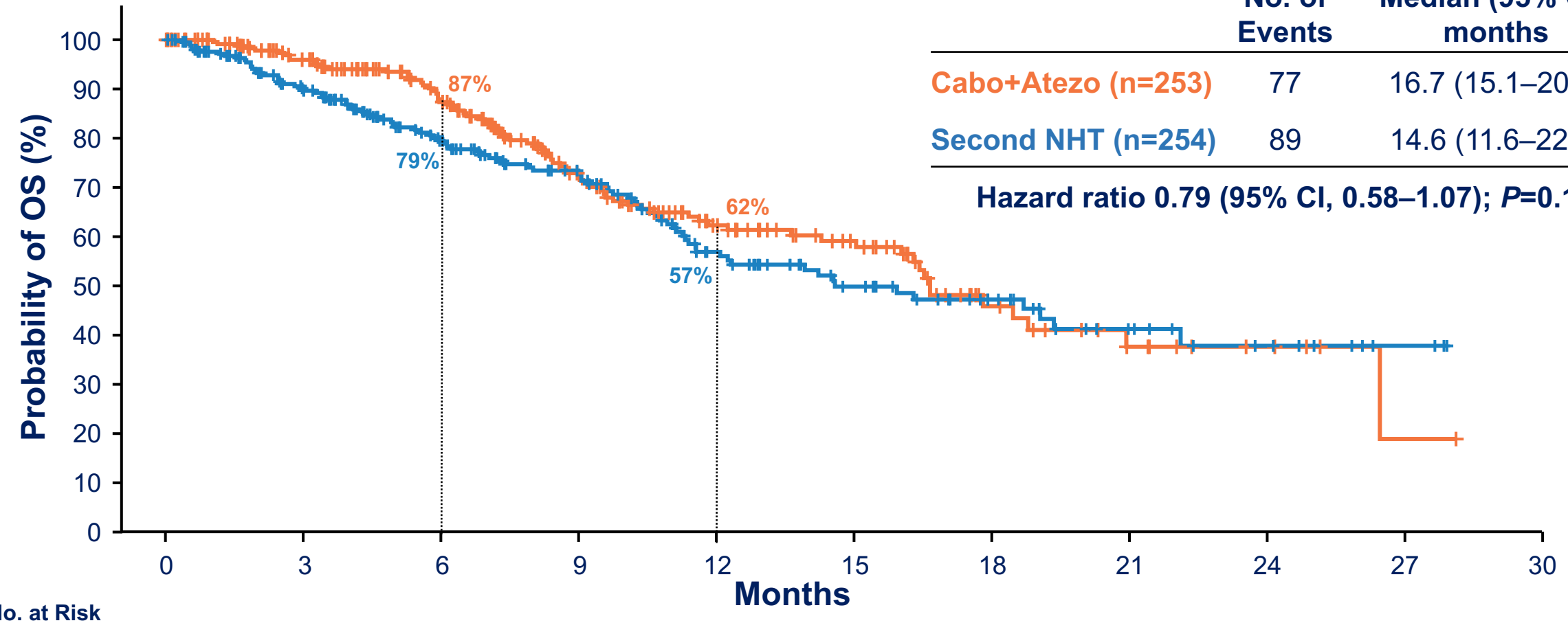
No. at Risk											
Cabo+Atezo	200	135	89	45	17	8	4	2	0	0	0
Second NHT	200	98	57	35	16	8	6	5	3	1	0

- **Median PFS per BIRC (ITT): 6.3 vs 4.2 mo (HR 0.64 [95% CI, 0.50–0.81]; *P*=0.0002)**
- Median rPFS per PCWG3 in PFS ITT population: 6.3 vs 4.1 mo (HR, 0.62 [95% CI, 0.48–0.81])

CI, confidence interval; HR, hazard ratio. *PFS per RECIST v1.1 by BIRC or death. †Critical *P* value=0.002. †First 400 randomized patients.

Interim OS (ITT Population)

49% of Target Number of Events



	No. of Events	Median (95% CI), months
Cabo+Atezo (n=253)	77	16.7 (15.1–20.9)
Second NHT (n=254)	89	14.6 (11.6–22.1)

Hazard ratio 0.79 (95% CI, 0.58–1.07); *P*=0.13

No. at Risk										
Cabo+Atezo	253	204	155	104	68	48	20	10	5	1	0
Second NHT	254	198	141	107	66	43	28	15	9	3	0

Critical *P* value for OS is 0.002675 at this interim analysis using a prespecified Lan-DeMets O'Brien-Fleming (LD-OF) alpha-spending function.

CYCLONE-1: Scientific Rationale

- Cyclin-dependent Kinases 4 and 6 (CDK4 and CDK6) are enzymes that primarily function in the transition from the G1 phase to the S phase of the cell cycle
- Kinases are activated when they bind to specific regulatory proteins called cyclins, particularly Cyclin D1
- Once activated, CDK4 and CDK6 phosphorylate the retinoblastoma protein (Rb)
- Phosphorylated Rb releases transcription factor E2F, activating genes necessary for DNA synthesis and progression into S phase
- Targeting CDK4 and CDK6 can prevent uncontrolled proliferation of cancer cells
- Three FDA approved CDK4/6 inhibitors for metastatic breast cancer
  - Palbociclib
  - Ribociclib
  - Abemaciclib

Comstock CES et al. Oncogene (2013) 32, 5481-5491. Kase AM et al. Onco Targets Ther 2020;13:10499-10513.

CYCLONE-1: Scientific Rationale

- AR acts as a master regulator of G1-S phase progression in prostate cancer
- AR activates CDK4 and CDK6
- CDK4 and CDK6 are direct transcriptional targets of c-Myc which is upregulated in mCRPC
- Resistance to AR signaling inhibitors have been associated with CDK6 and MYC amplifications and cyclin D1 upregulation
- Abemaciclib is oral selective inhibitor of CDK4 and CDK6

Balk SP et al. Nucl Recept Signal 2008 Feb 1;6: e001. Cho H et al. Cancer Discov 2014;4:318-33. Quigley DA et al. Cell 2018;174:758-69. Han GC et al. JCO Preci Oncol 2017;1-11. Pal SK et al. Cancer 2018:124:1216-24.

CYCLONE-1: Study Design

Patient Population
- mCRPC
- ECOG 0-1
- Progressed after ≥1 NHA
- Progressed after 2 taxanes

Treatment
- Abemaciclib 200 mg PO BID
- Cycle = 28 days
- Planned 40 patients

Treatment until unacceptable adverse events or disease progression

Endpoints and Assessments
- Primary Objective: ORR
- Secondary Objectives: safety, rPFS, OS, PSA response, Ki-67 expression

Agarwal N et al. 2021 ASCO Annual Meeting. TPS5086.

CYCLONE-1: Results

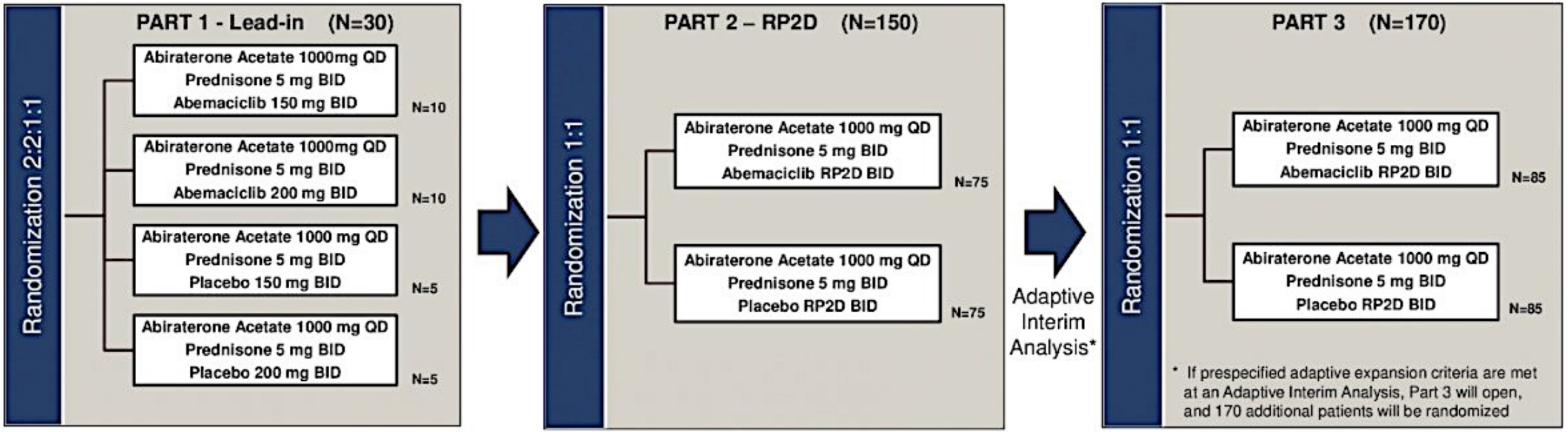
- 44 patients enrolled, median age 68, PS=1, at least 3 metastatic sites, 47% with visceral metastasis, 28% liver metastasis
- Primary endpoint of ORR NOT met (6.8% compared to target ORR of 12.5%)
- Disease control rate 45% with 38% of patients with stable disease
- Median rPFS 2.7 months, median OS 7.6 months
- Grade 3 treatment related AEs: neutropenia, anemia, fatigue, diarrhea
- Conclusion: Abemaciclib demonstrated modest but objective single agent activity in heavily pretreated mCRPC

Agarwal N et al. Cancer Res 2023 (83) 8-supplement):CT159.

CYCLONE-2: Study Design (mCRPC)

STUDY DESIGN

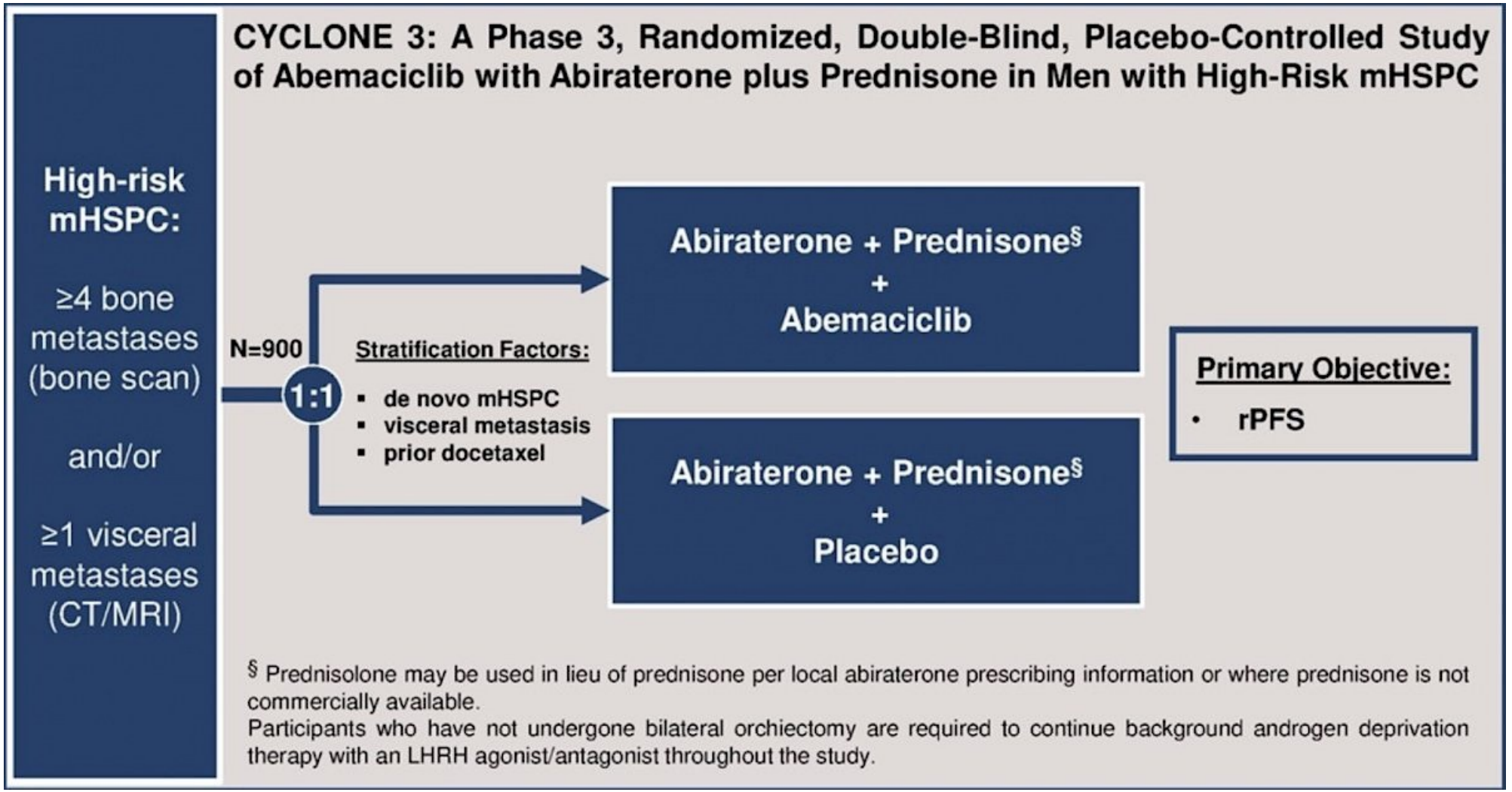
Phase 2/3, randomized, double blind, placebo-controlled study



Patients who have not undergone bilateral orchiectomy will continue ADT (LHRH agonist/antagonist) throughout the study.
Patients are stratified by radiographic progression at time of study entry, measurable disease and prior docetaxel for mHSCP
Prednisolone may be used in lieu of prednisone per local regulation. For sites in the USA, the fine-particle formulation of abiraterone (500 mg QD) can be used with methylprednisolone (4 mg BID)

DOI: 10.1200/JCO.2022.40.6_suppl.TPS198 *Journal of Clinical Oncology* 40, no. 6_suppl.

CYCLONE-3: Study Design (mHSPC)

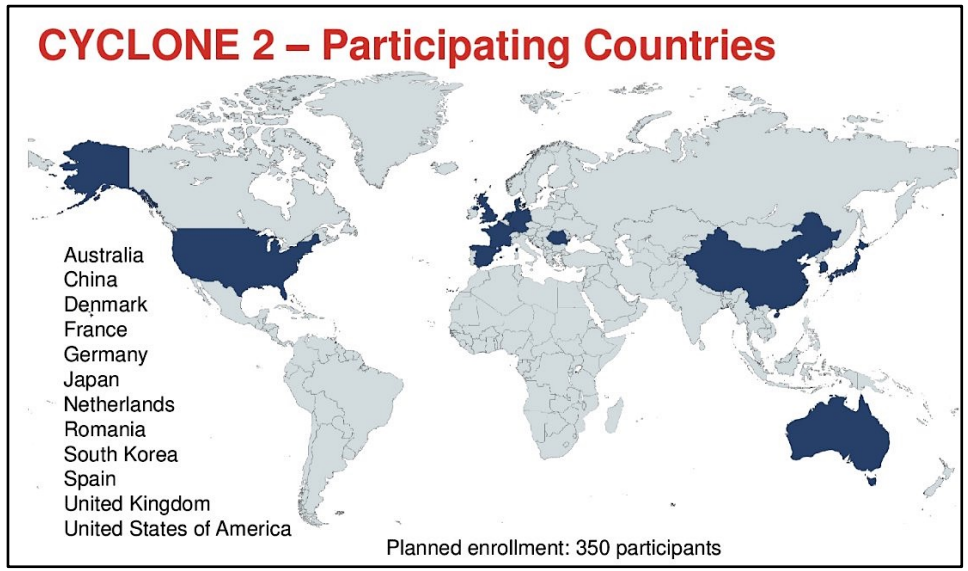


McKay R et al. 2022 ESMO Annual Meeting.

Study Design

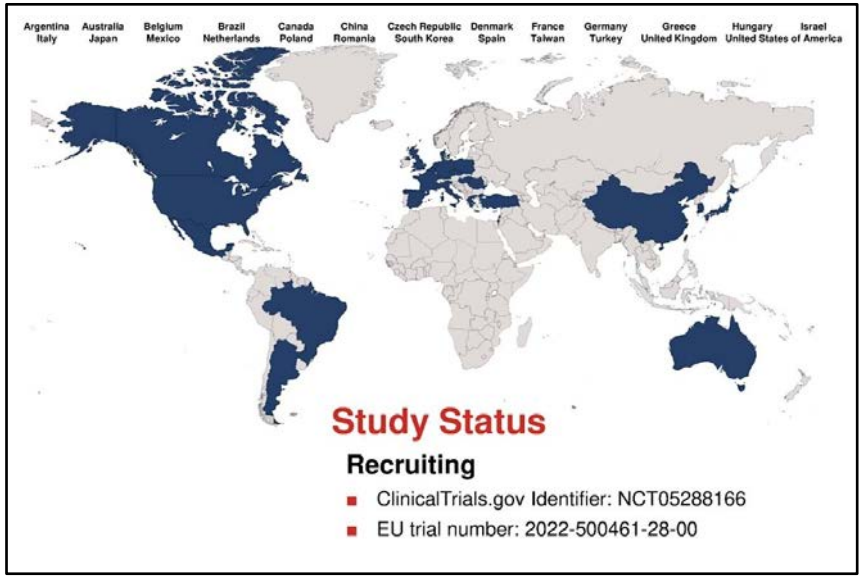
CYCLONE-2 (mCRPC)

- No prior NHA, chemotherapy, radiopharmaceuticals
- Primary Objective: rPFS
- Secondary Objectives: safety, ORR, OS



CYCLONE-3 (mHSPC)

- No prior ADT, NHA, chemotherapy
- Primary Objective: rPFS
- Secondary Objectives: safety, castration-resistant prostate cancer-free survival, OS

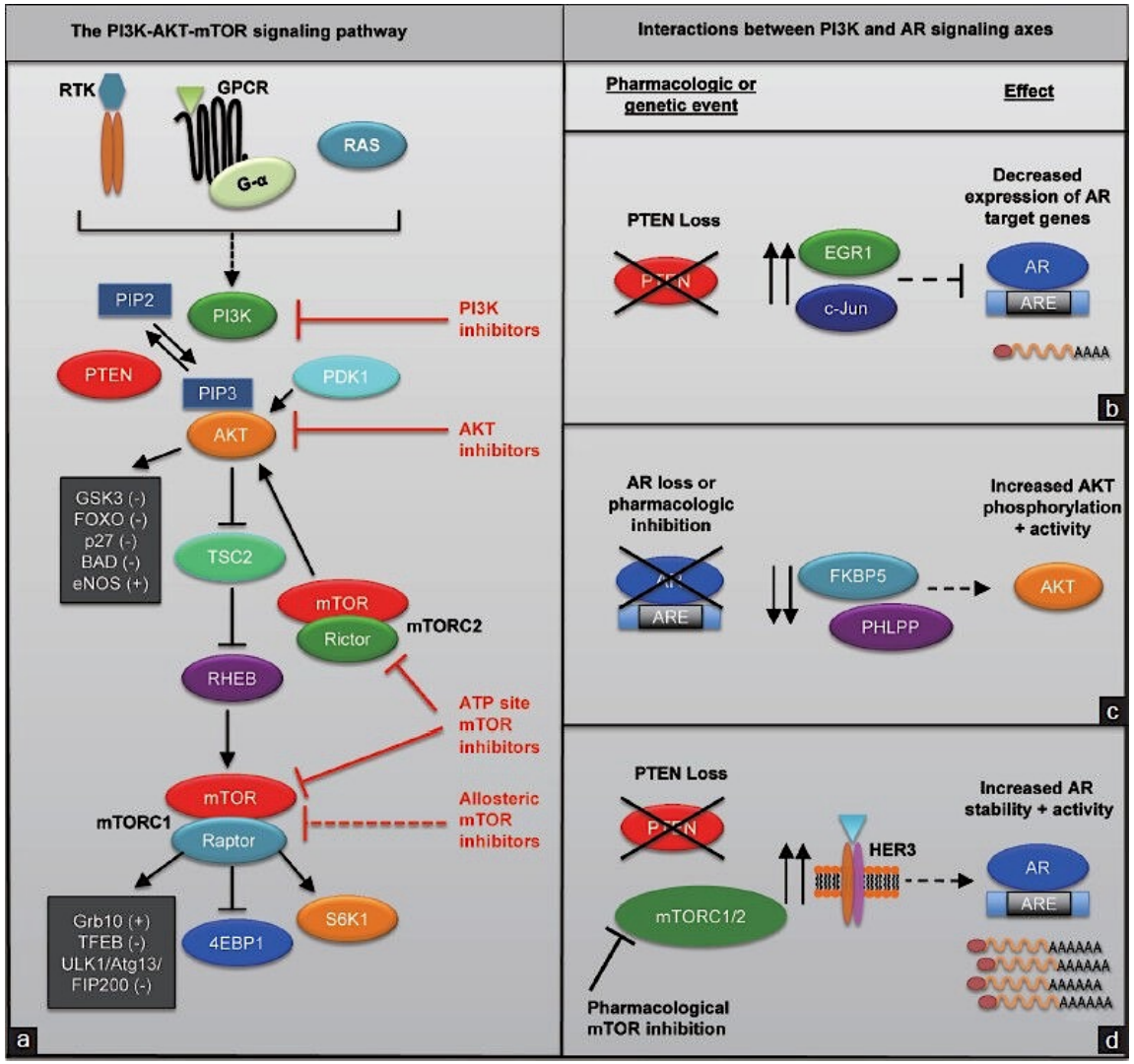


Additional Clinical Trials

- A Phase 1b Study of Abemaciclib Plus Darolutamide in Men With Metastatic Castration-Resistant Prostate Cancer (NCT05999968)
- Phase II Abemaciclib With or Without Atezolizumab for mCRPC (NCT04751929)
- Phase II Abemaciclib in Combination With Androgen Deprivation Therapy for Locally Advanced Prostate Cancer (RAD 1805) (NCT04298983)
- Phase I/II Neo-DAB: Darolutamide and Abemaciclib in Prostate Cancer (NCT05617885)
- Phase II Palbociclib in Patients With Metastatic Castration-Resistant Prostate Cancer (NCT02905318)
- Phase I/II Enzalutamide With and Without Ribociclib for Metastatic, Castrate-Resistant, Chemotherapy-Naive Prostate Cancer That Retains RB Expression (NCT02555189)

Capivasertib: Scientific Rationale

- AKT protein (protein kinase B, PKB) plays an important part in the PI3K/AKT/mTOR signaling pathway in prostate cancer
- Pathway becomes dysregulated leading to prostate cancer progression
- AKT plays a role in inhibiting apoptosis and overactivation of AKT has been linked to hormone resistance



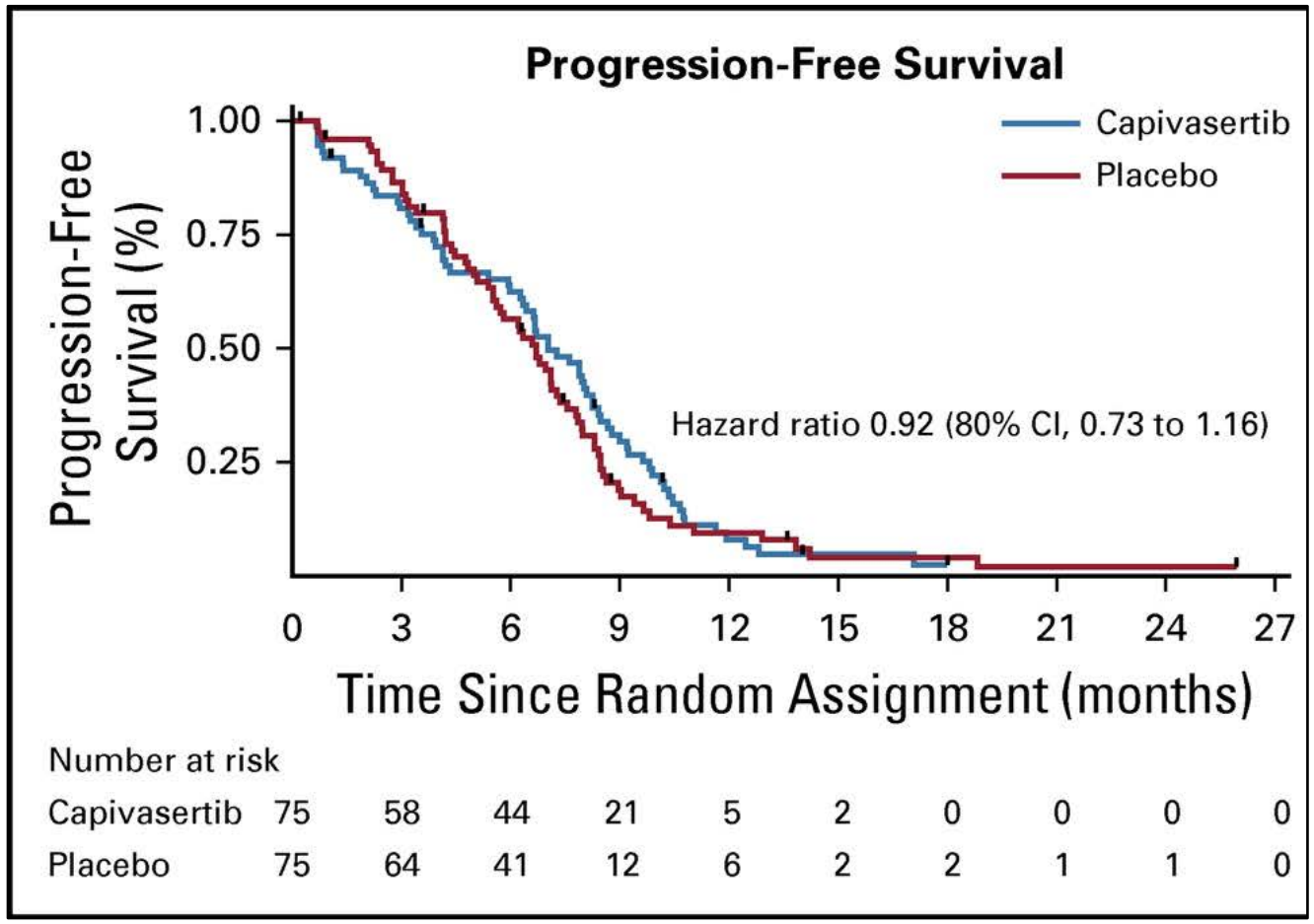
Shorning BY et al. Int. J.Mol.Sci.2020,21,4507. Edlind MP et al. Asian J Androl. 2014:16(3):378-386.

ProCAID: Results

- Capivasertib is a potent selective inhibitor of all three AKT isoforms (AKT1/2/3)
- Phase II, randomized, double-blind, placebo-controlled trial in mCRPC patients
- Eligibility: no restrictions on prior NHA but previous chemotherapy not allowed
- All patients received docetaxel and prednisolone
- Patients also received capivasertib 320 mg PO BID or matched placebo PO BID on a 4 days on/3 days off schedule
- Dose was determined based on Phase Ib portion of ProCAID
- Primary outcome: investigator-assessed composite PFS

Crabb SJ et al. Journal of Clinical Oncology 39, no. 3 (January 20, 2021) 190-201. Crabb SJ et al. Invest New Drugs 35:599-607, 2017.

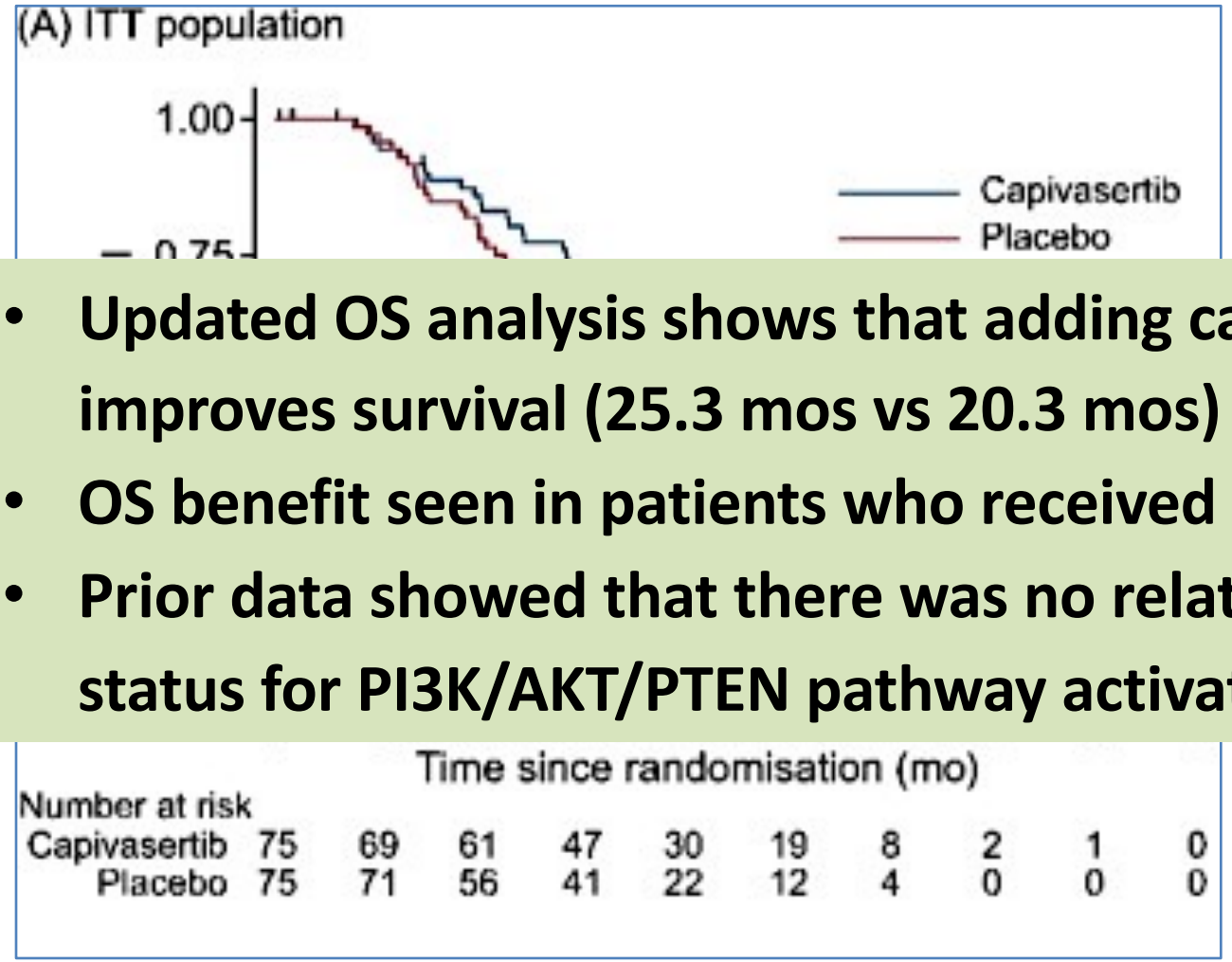
ProCAID: Results

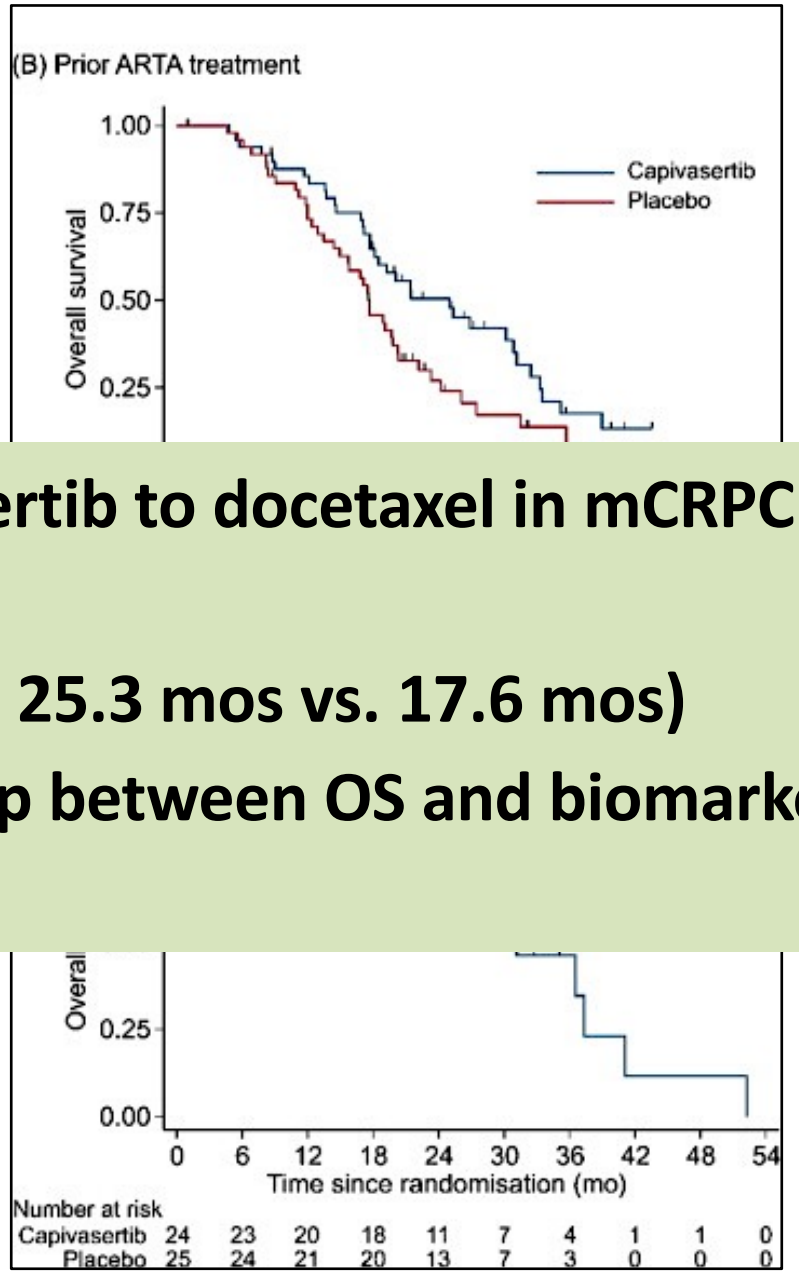


- 150 patients enrolled
- Median cPFS 7.03 months versus 6.7 months
- Addition of capivasertib to chemotherapy did not meet primary endpoint

Crabb SJ et al. Journal of Clinical Oncology 39, no. 3 (January 20, 2021) 190-201.

ProCAID: Results





- **Updated OS analysis shows that adding capivasertib to docetaxel in mCRPC improves survival (25.3 mos vs 20.3 mos)**
- **OS benefit seen in patients who received ARTA (25.3 mos vs. 17.6 mos)**
- **Prior data showed that there was no relationship between OS and biomarker status for PI3K/AKT/PTEN pathway activation**

Crabb SJ et al. Eur Urol. 2022 Nov;82(5):512-515. doi: 10.1016/j.eururo.2022.05.019. Epub 2022 Jun 7. Crabb et al. J Clin Oncol, 39(2021),pp190-201.

Additional Clinical Trials

- Phase III Study of Capivasertib + Docetaxel vs Placebo + Docetaxel as Treatment for Metastatic Castration Resistant Prostate Cancer (mCRPC) (CAPItello-280) (NCT05348577)
- Phase III Study Capivasertib + Abiraterone as Treatment for Patients With Metastatic Hormone-sensitive Prostate Cancer and PTEN Deficiency (CAPItello-281) (NCT04493853)
- A Single-Arm Phase II Study of Neoadjuvant Intensified Androgen Deprivation (Leuprolide and Abiraterone Acetate) in Combination With AKT Inhibition (Capivasertib) for High-Risk Localized Prostate Cancer With PTEN Loss (SNARE) (NCT05593497)

Novel Targets in Clinical Trials

- Chimeric antigen receptor (CAR) T cells, based on genetic engineering of the patient's own T cells for targeted tumor cell lysis
- Bromodomain (BET) inhibitors
- Androgen Receptor (AR) degraders (PROTAC)
- Bicyclic peptides or drug conjugates (synthetic short peptides that are chemically bonded to form a two-loop structure, resembling a bicycle)
- **877 interventional and accruing clinical trials for patients with prostate cancer**

Clinicaltrials.gov accessed 01/03/2024

Consensus or Controversy? Clinical Investigators Provide Perspectives on the Current and Future Management of Urothelial Bladder Cancer

Part 2 of a 2-Part CME Symposium Series Held in Conjunction with the 2024 ASCO Genitourinary Cancers Symposium

Friday, January 26, 2024

7:00 PM – 9:00 PM PT (10:00 PM – 12:00 AM ET)

Faculty

Matthew Milowsky, MD, FASCO

Peter H O'Donnell, MD

Jonathan E Rosenberg, MD

Arlene Siefker-Radtke, MD

Moderator

Evan Y Yu, MD

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