Beyond The Guidelines: Urologic Oncology Investigators Provide Perspectives on the Optimal Management of Prostate Cancer

Part 2 of a 2-Part CME Satellite Symposium Series Held in Conjunction with the American Urological Association Annual Meeting 2023 (AUA2023)

Sunday, April 30, 2023

6:00 PM – 8:00 PM

Faculty

Himisha Beltran, MD

Stephen J Freedland, MD

Fred Saad, MD

Neal D Shore, MD

Moderator

Matthew R Smith, MD, PhD

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Faculty

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

Stephen J Freedland, MD
Staff Physician, Durham VA Medical Center
Durham, North Carolina
Professor of Urology
Warschaw, Robertson, Law Families Chair in Prostate Cancer
Director, Center for Integrated Research on Cancer and Lifestyle (CIRCL)
Associate Director for Education and Training
Samuel Oschin Comprehensive Cancer Institute
Cedars-Sinai Medical Center
Los Angeles, California

Fred Saad, MD
Professor and Chief of Urology
Director of GU Oncology
Raymond Garneau Chair in Prostate Cancer
University of Montreal Hospital Center (CHUM)
Director, Prostate Cancer Research
Montreal Cancer Institute/CRCHUM
Montréal, Québec, Canada

Neal D Shore, MD
Director, CPI
Carolina Urologic Research Center
Chief Medical Officer, Surgery/Urology
GenesisCare
Medical Director, CUSP: Clinical Research Consortium
Myrtle Beach, South Carolina

Moderator
Matthew R Smith, MD, PhD
Claire and John Bertucci Endowed Chair
in Genitourinary Cancers
Professor of Medicine
Harvard Medical School
Director, Genitourinary Malignancies Program
Massachusetts General Hospital Cancer Center
Boston, Massachusetts

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Dr Beltran — Disclosures

Advisory Committee	Amgen Inc, Bayer HealthCare Pharmaceuticals, Blue Earth Diagnostics, Curie Therapeutics, Daiichi Sankyo Inc, Foundation Medicine, Loxo Oncology Inc, a wholly owned subsidiary of Eli Lilly & Company, Merck, Oncorus, Pfizer Inc, Sanofi
Contracted Research	Bristol-Myers Squibb Company, Circle Pharma, Daiichi Sankyo Inc, Novartis
Data and Safety Monitoring Board/Committee	AstraZeneca Pharmaceuticals LP

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Dr Freedland — Disclosures

Consulting Agreements	Astellas, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Janssen Biotech Inc, Merck, Myovant Sciences, Pfizer Inc, Sanofi
Speakers Bureau	AstraZeneca Pharmaceuticals LP, Sanofi

Dr Saad — Disclosures

Consultant	AbbVie Inc, Advanced Accelerator Applications, Astellas, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Janssen Biotech Inc, Lilly, Merck, Myovant Sciences, Novartis, Pfizer Inc, Tolmar
Grant/Research Support (Institution)	Advanced Accelerator Applications, Astellas, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Bristol-Myers Squibb Company, Exelixis Inc, Janssen Biotech Inc, Merck, Novartis, Pfizer Inc, Sanofi

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Dr Shore — Disclosures

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Dr Smith — Disclosures

Advisory Committee and Consulting Agreements	Bayer HealthCare Pharmaceuticals, Janssen Biotech Inc, Lilly, Pfizer Inc
Contracted Research (to Institution)	Bayer HealthCare Pharmaceuticals, Janssen Biotech Inc, Lilly, Pfizer Inc

Commercial Support

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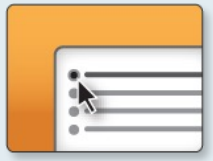
Research To Practice CME Planning Committee Members, Staff and Reviewers

Planners, scientific staff and independent reviewers for Research To Practice have no relevant conflicts of interest to disclose.

Clinicians in the Meeting Room

Networked iPads are available.

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



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

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

Complete Your Evaluation: Tap the CME 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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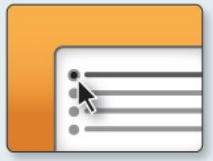
Clinicians Attending via Zoom

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 pre- and postmeeting surveys.

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

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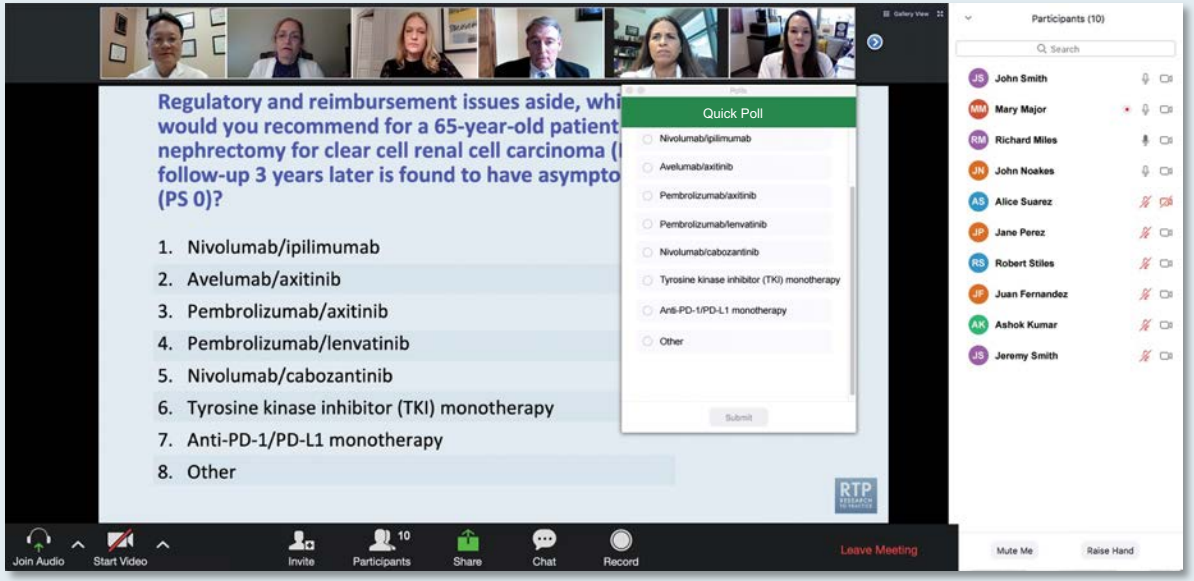
Clinicians, Please Complete the Pre- and Postmeeting Surveys



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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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Matthew R Smith, MD, PhD

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Agenda

Module 1 – Management Approaches for Nonmetastatic Prostate Cancer — Dr Freedland

Module 2 – Optimizing the Care of Patients with Metastatic Hormone-Sensitive Prostate Cancer (mHSPC) — Dr Saad

Module 3 – Therapeutic Considerations for Patients with Newly Diagnosed Metastatic CRPC (mCRPC) — Dr Shore

Module 4 – Contemporary Management of mCRPC in Patients Harboring an HRR Gene Alteration — Dr Smith

Module 5 – Current and Emerging Strategies in the Treatment of Recurrent mCRPC — Dr Beltran

Prostate Cancer Survey Respondents

Faculty

Himisha Beltran, MD
Stephen J Freedland, MD
Fred Saad, MD
Neal D Shore, MD
Matthew R Smith, MD, PhD

Clinical Investigators

Michael Ahdoot, MD
Brian F Chapin, MD
Raoul S Concepcion, MD
E David Crawford, MD
Sia Daneshmand, MD
Leonard G Gomella, MD
Jason Hafron, MD
Gautam Jayram, MD
Ashish M Kamat, MD, MBBS
Vitaly Margulis, MD
Joshua J Meeks, MD, PhD
Anirban P Mitra, MD, PhD
David S Morris, MD
Mark Preston, MD, MPH
Robert Svatek, MD
Stephen B Williams, MD, MS
Alfred Witjes, MD, PhD

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MODULE 1: Management Approaches for Nonmetastatic Prostate Cancer

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Cases from Contributing Urologists

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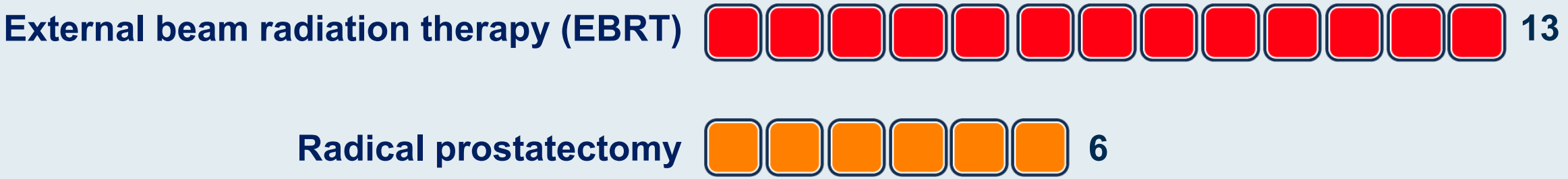
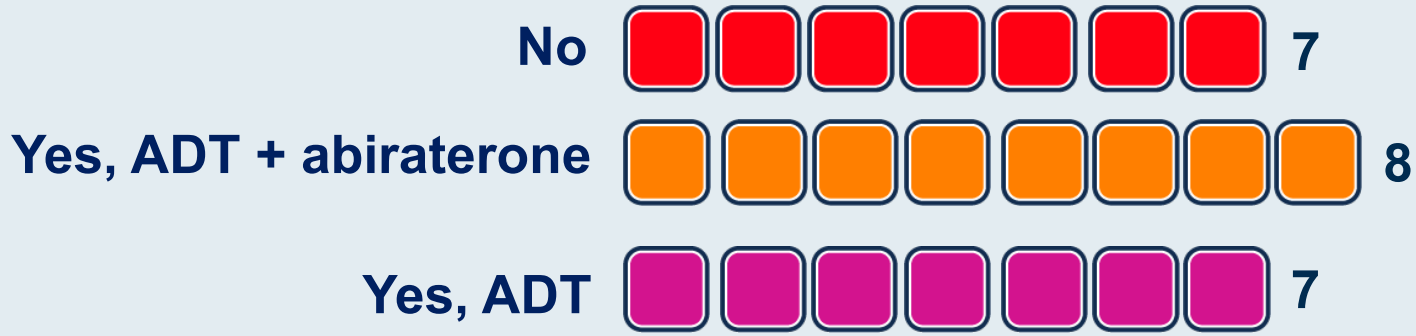
A 66-year-old man presents with Gleason 8 (4 + 4) prostate adenocarcinoma (PSA 12.7 ng/mL). A bone scan is negative. CT imaging reveals uptake in the pelvic nodes. What approach to primary therapy would you most likely recommend for this patient?



FROM THE PRACTICES OF DRS HAFRON AND MORRIS

Survey of urologic oncology clinical investigators

A 61-year-old man presents with Gleason 8 (4 + 4) prostate adenocarcinoma (PSA 8 ng/mL) and undergoes RALP (robotically assisted laparoscopic prostatectomy). Final pathology reveals T3bN1 disease with 2/10 positive lymph nodes. Regulatory and reimbursement issues aside, would you recommend hormonal therapy at this point?



How long would you continue the hormonal therapy?

- 6 months
- 12 months
- 18 months
- 24 months
- 24 months
- 24 months
- 24 months
- 24 months
- 24 months
- 24 months
- 24 months
- 24 months
- 24 months minimum
- At least 24 months
- 24-36 months

Survey of urologic oncology clinical investigators

A 64-year-old man underwent a radical prostatectomy 5 years ago for Gleason 9 (4 + 5) prostate adenocarcinoma (PSA 4.8 ng/mL). Pathology showed T2N0 disease with negative margins. His postsurgical PSA was initially undetectable but rose to 0.2 ng/mL. He undergoes salvage EBRT (45 Gray in 25 fractions) to the pelvic and prostate fossa and receives 6 months of ADT. His PSA rises to 0.23 ng/mL. Bone and CT scans are negative. PSMA PET reveals a lesion in the right anterior first rib. In addition to radiation therapy, regulatory and reimbursement issues aside, what would be your most likely treatment recommendation?

Survey of urologic oncology clinical investigators

Management Approaches for Nonmetastatic Prostate Cancer

Stephen J. Freedland, MD
Professor of Urology
Director, Center for Integrated Research on Cancer and Lifestyle
Cedars-Sinai Medical Center
Los Angeles, CA USA

Outline

- ADT
  - When and how
- NHTs in nmCSPC
- NHTs in nmCRPC
- Summary

ADT – WHEN AND HOW

Key unanswered questions for ADT

- When to start ADT
- How to deliver ADT
  - Intermittent vs. continuous
  - Combined androgen blockade vs. ADT alone
  - GnRH agonist vs. antagonist

Agonist vs. Antagonist

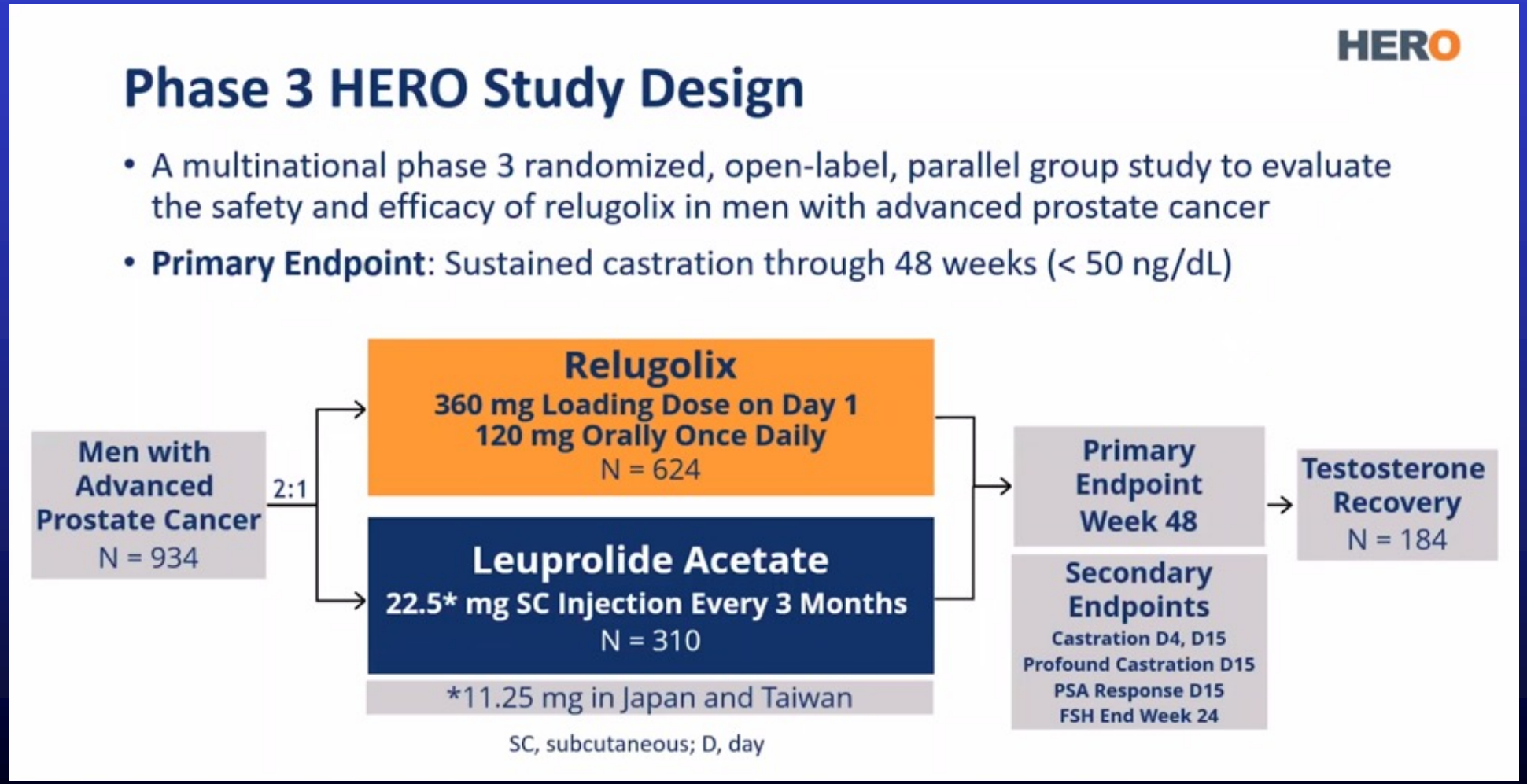
Agonist

- Pros
  - Convenience (once every 3-6 months shot)
  - Cost effective
  - Tradition
  - Works well
- Cons
  - No oral option
  - T surge
  - Time to T nadir
  - CV risk
  - Occasional T escape

Antagonist

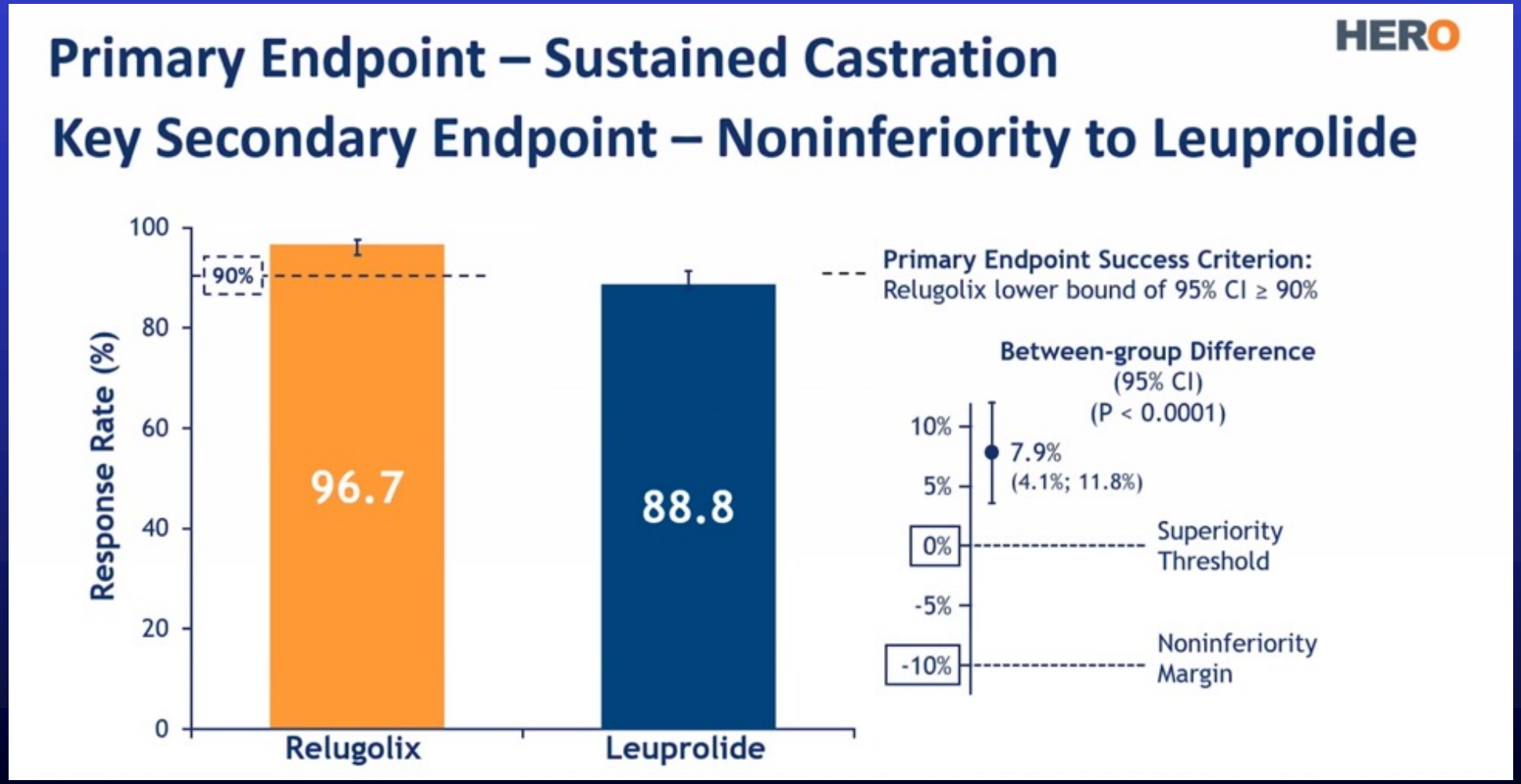
- Pros
  - Rapid T suppression
  - Rapid T return
  - Reduced CV risk?
  - Oral
  - Better T suppression
- Cons
  - Expensive
  - Logistically harder

Phase 3 HERO Trial: Relugolix vs. Leuprolide



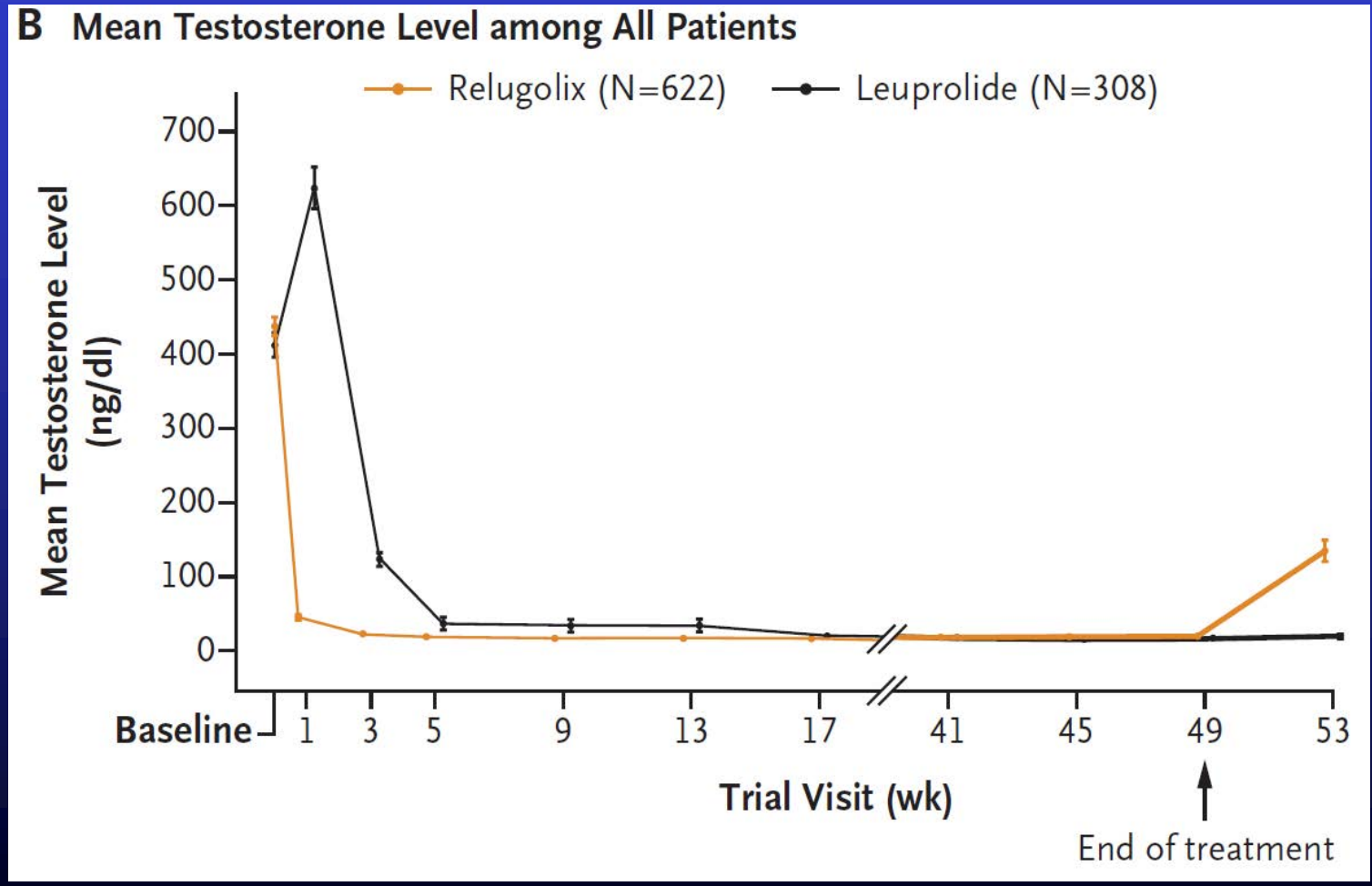
Shore, et al. NEJM, 2020

Phase 3 HERO Trial: Relugolix vs. Leuprolide



Shore, et al. NEJM, 2020

Phase 3 HERO Trial: Relugolix vs. Leuprolide



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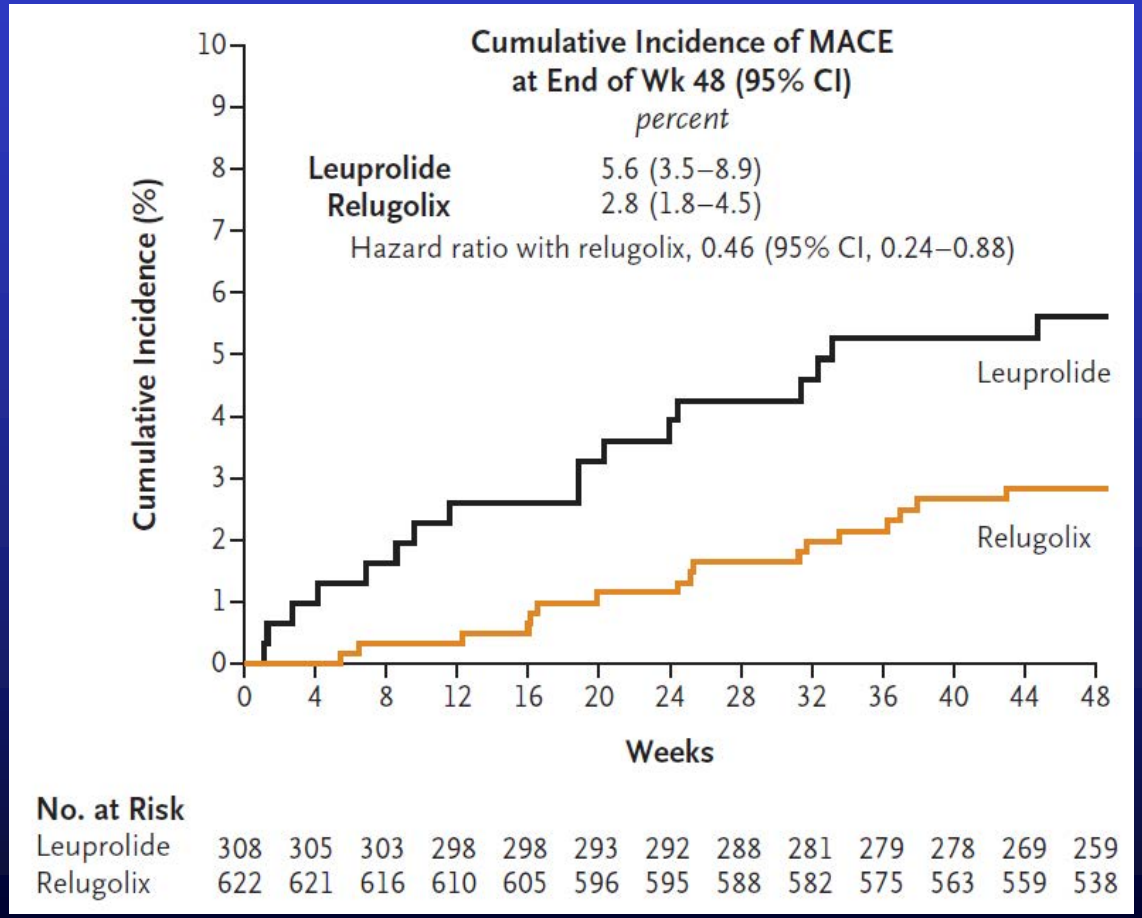
Phase 3 HERO Trial: Relugolix vs. Leuprolide



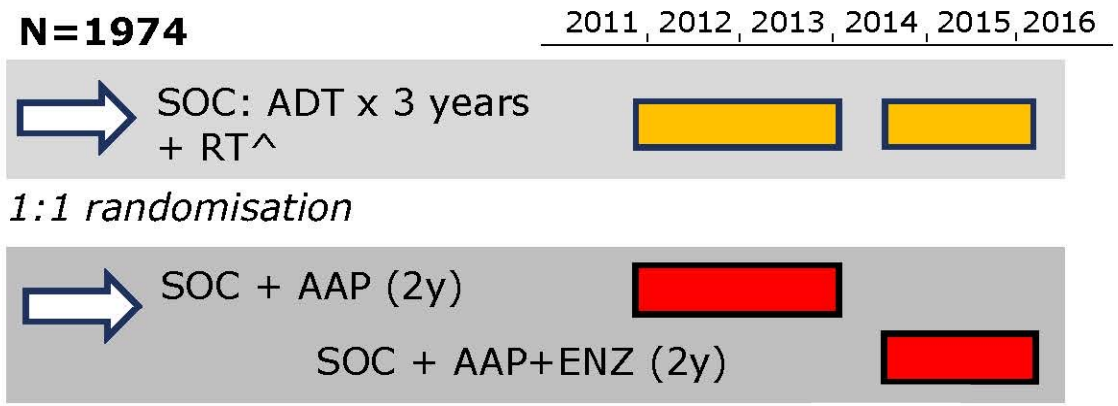
Shore, et al. NEJM, 2020

NOVEL HORMONAL THERAPIES FOR nmCSPC

STAMPEDE: Abiraterone ± Enzalutamide in nmCSPC

Study design

- M0 pts in AAP comparison: continued FU with **no further** efficacy inspections
- 2019 – amended the reporting plan* to split M1 & M0, power the primary end-point on MFS, meta-analyse with new data from AAP+ENZ comparison



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

Attard, et al. Lancet, 2022

STAMPEDE: Abiraterone ± Enzalutamide in nmCSPC

Patient population

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

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

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

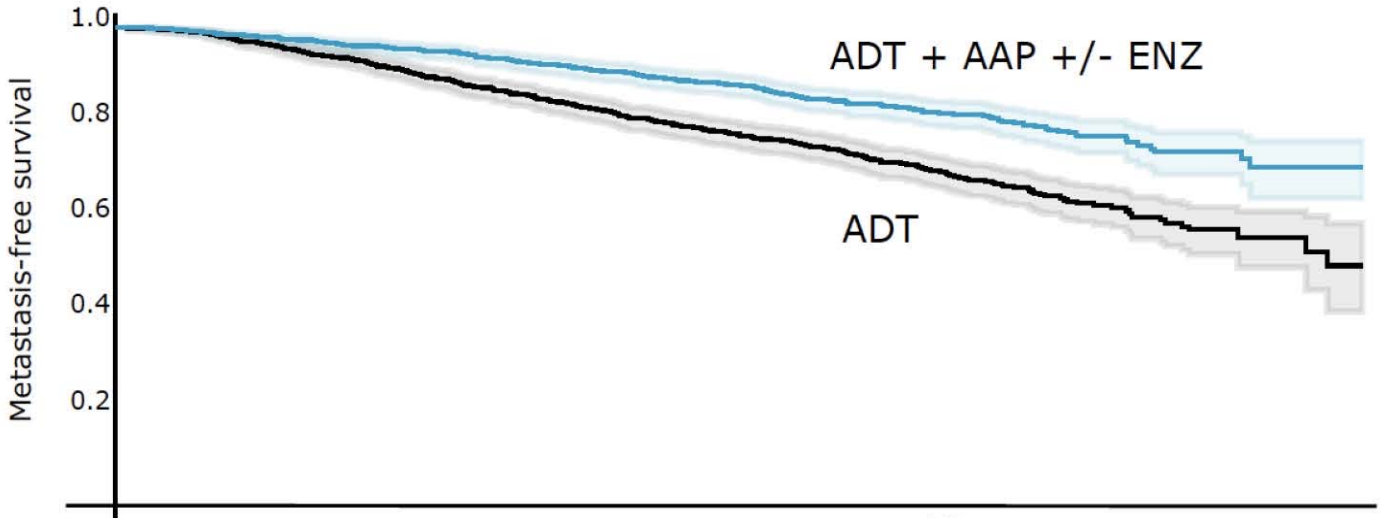
All patients
Written informed consent
Fit for all protocol treatment
Fit for follow-up

Full criteria: www.stampedetrial.org

Attard, et al. Lancet, 2022

STAMPEDE: Abiraterone ± Enzalutamide in nmCSPC

Metastasis-free survival



ADT										
At-risk	988	950	894	836	767	550	329	172	53	9
Censored	0	8	11	14	26	201	387	522	632	673
Event	0	30	83	138	195	237	272	294	303	306
ADT+AAP+/-ENZ										
At-risk	986	948	917	884	839	622	369	198	71	14
Censored	0	21	28	31	45	225	460	615	737	792
Event	0	17	41	71	102	139	157	173	178	180

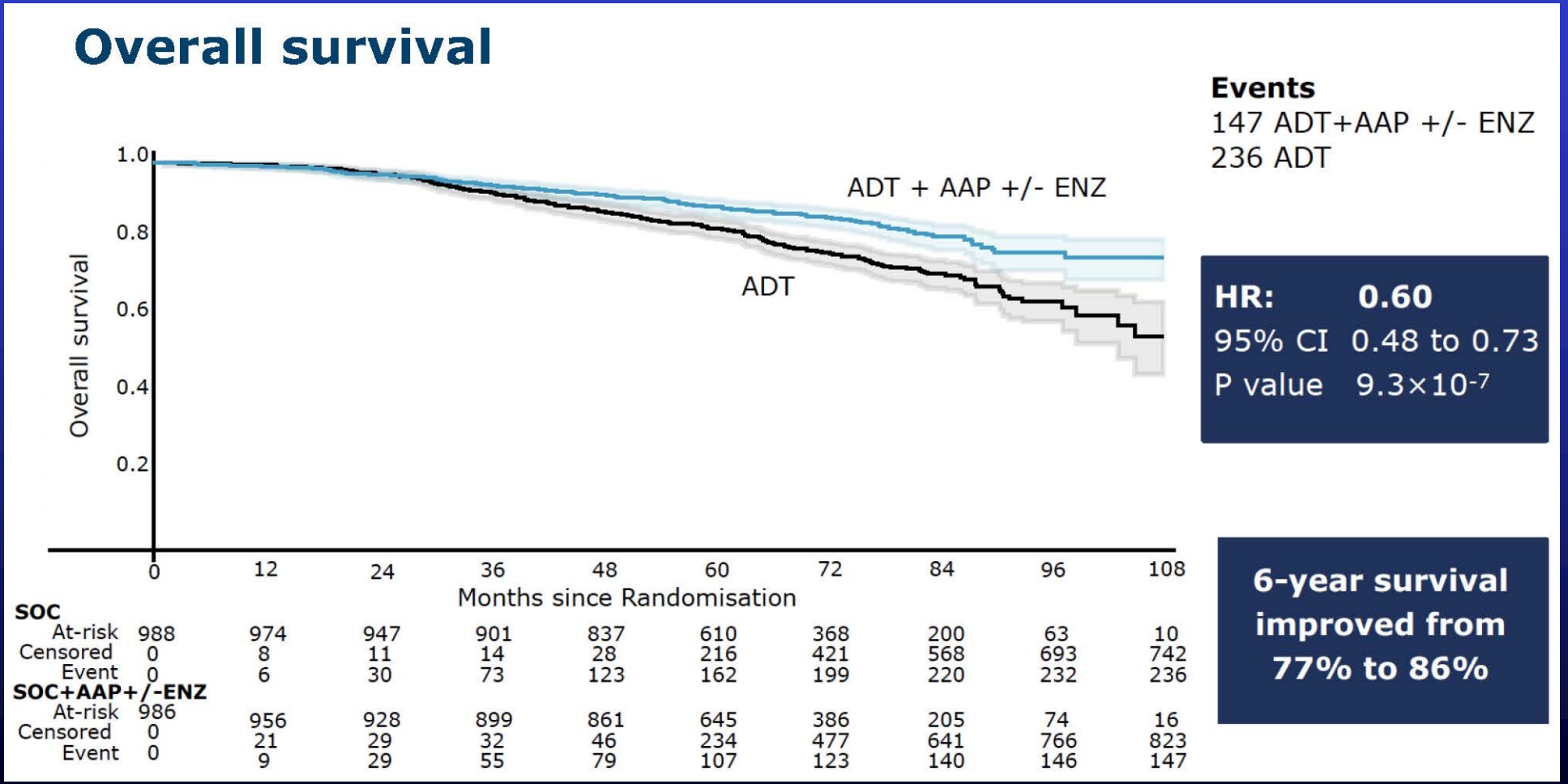
Events
180 ADT+ AAP +/- ENZ
306 ADT

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

6-year MFS improved from 69% to 82%

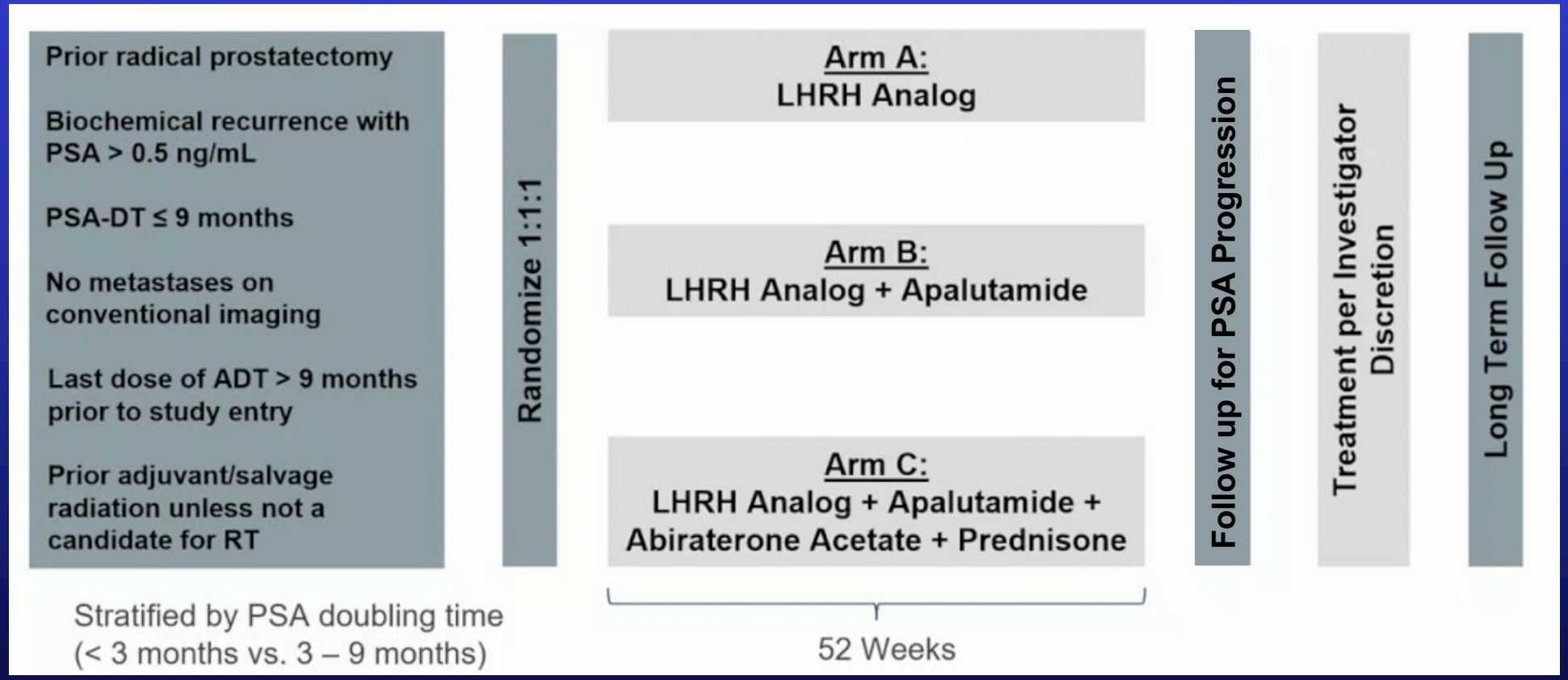
Attard, et al. Lancet, 2022

STAMPEDE: Abiraterone ± Enzalutamide in nmCSPC



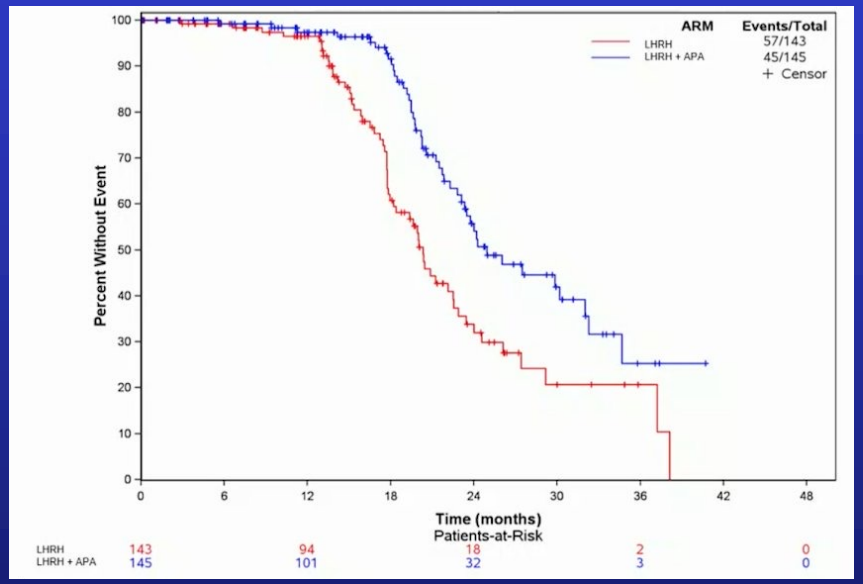
Attard, et al. Lancet, 2022

PRESTO: Apalutamide for high-risk BCR

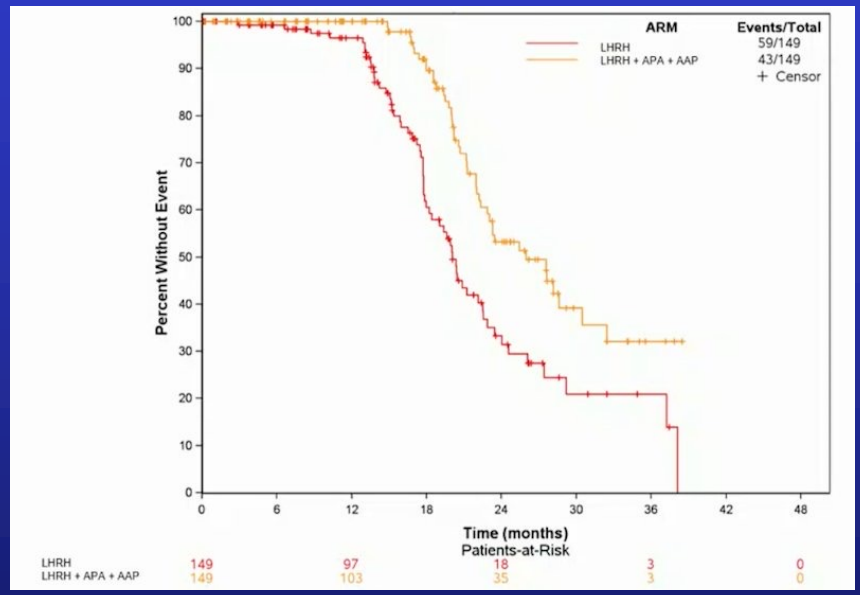


Aggarwal, et al. ESMO, 2022

PRESTO: Apalutamide for high-risk BCR



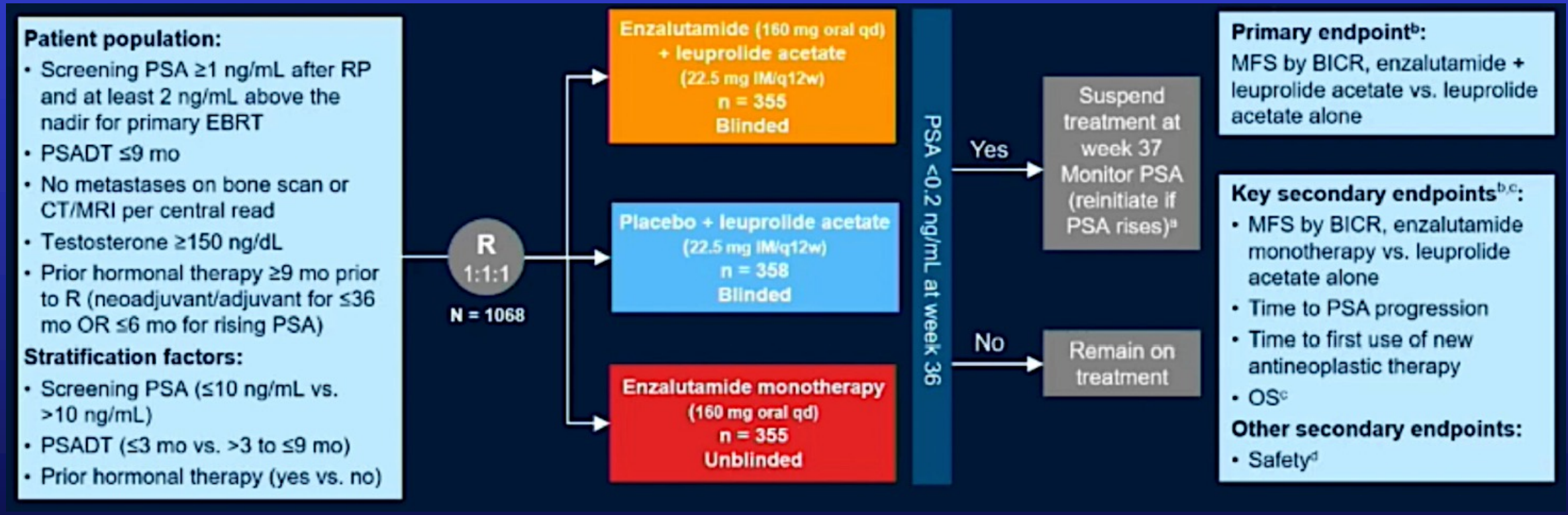
HR = 0.52 (95% CI 0.35-0.77)



HR = 0.48 (95% CI 0.32-0.71)

Aggarwal, et al. ESMO, 2022

EMBARK: Enzalutamide for high-risk BCR



BCR = biochemical recurrence

Shore, et al. AUA, 2023

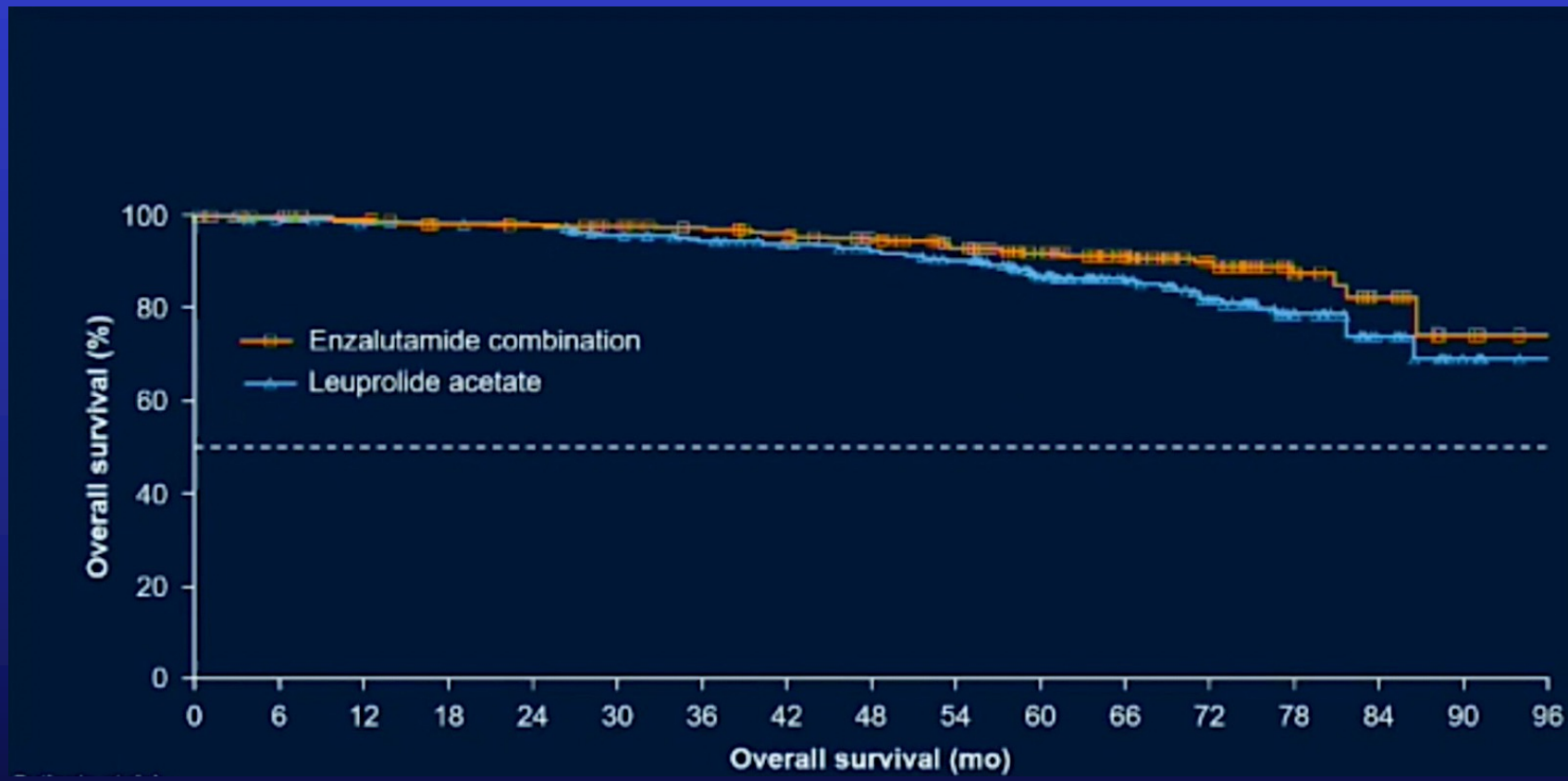
EMBARK: MFS with Enza Combination vs. Leuprolide

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

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

Shore, et al. AUA, 2023

EMBARK: Interim OS for Enza combination vs leuprolide



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

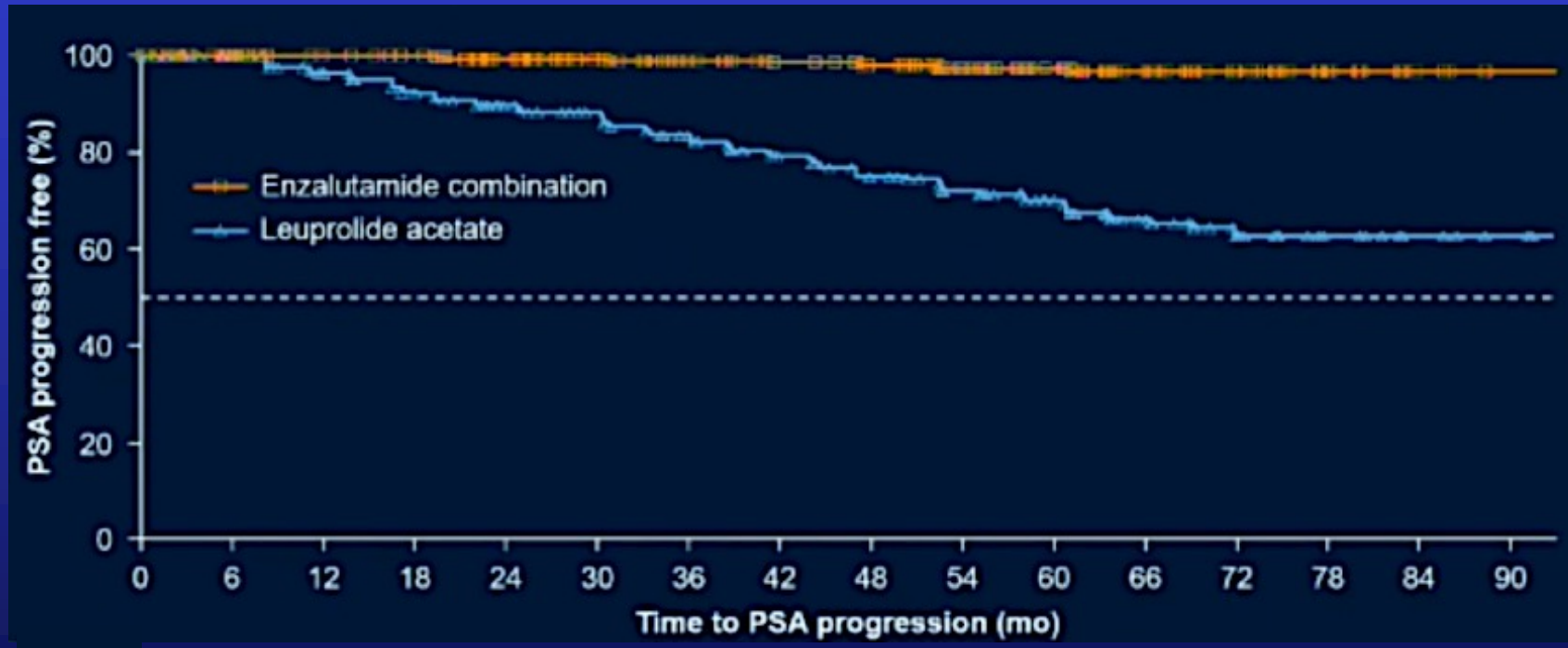
HR (95% CI): 0.59 (0.38–0.90) *P*=0.0142[a]

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

Final analysis at 271 deaths across all treatment groups.

Shore, et al. AUA, 2023

EMBARK: Time to PSA Progression with Enza Combination vs. Leuprolide

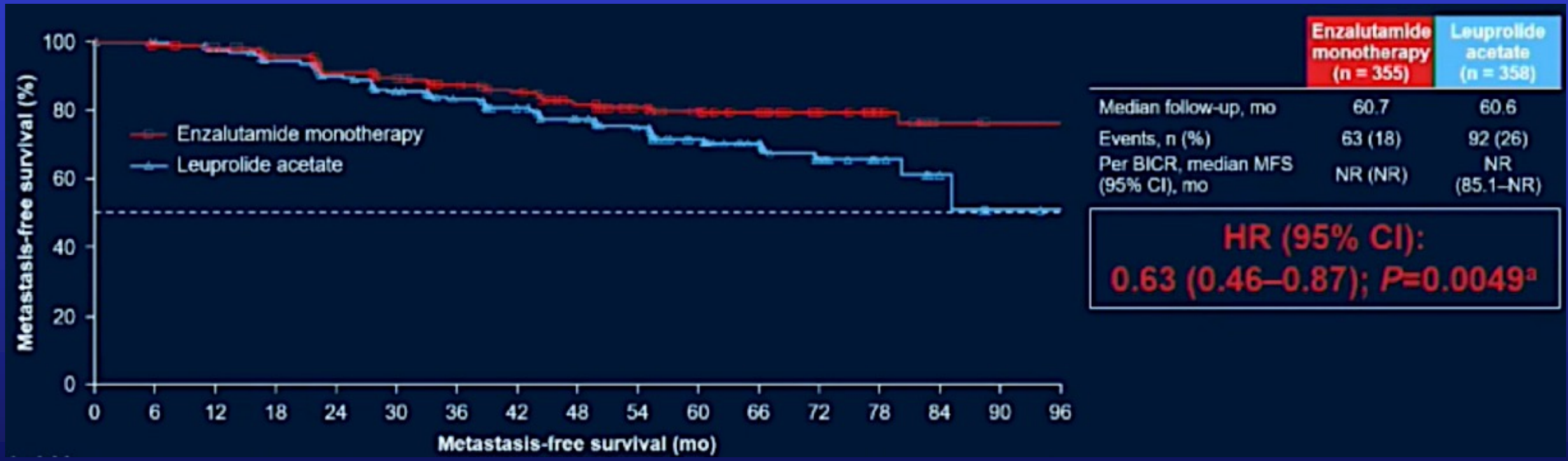


	Enzalutamide combination (n = 355)	Leuprolide acetate (n = 358)
Events, n (%)	8 (2)	93 (26)
Median time to PSA progression (95% CI), mo	NR (NR)	NR (NR)

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

Shore, et al. AUA, 2023

EMBARK: MFS with Enza Monotherapy vs. Leuprolide

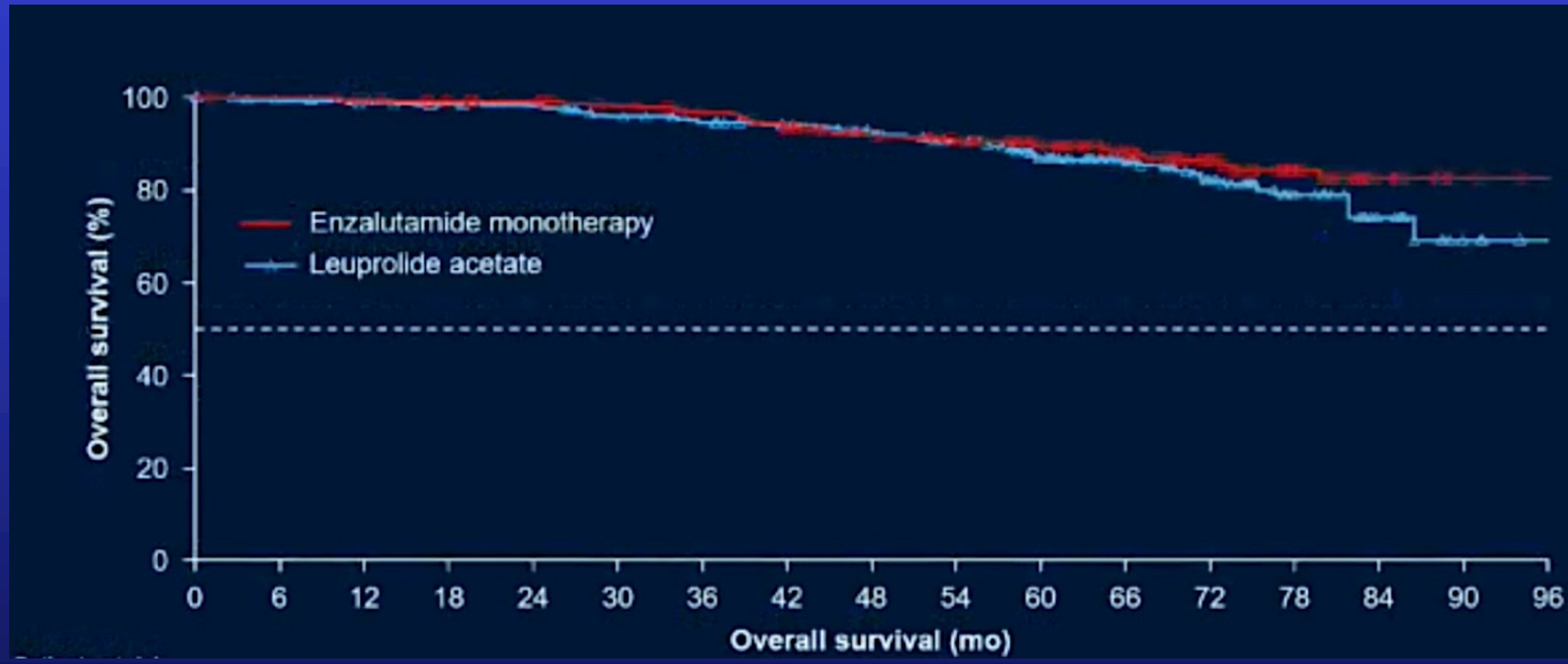


	Enzalutamide monotherapy (n = 355)	Leuprolide acetate (n = 358)
Median follow-up, mo	60.7	60.6
Events, n (%)	63 (18)	92 (26)
Per BICR, median MFS (95% CI), mo	NR (NR)	NR (85.1–NR)

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

Shore, et al. AUA, 2023

EMBARK: Interim OS of Enza monotherapy vs leuprolide



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

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

Final analysis at 271 deaths across all treatment groups.

Shore, et al. AUA, 2023

EMBARK: Most Common Treatment-Emergent Adverse Events

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

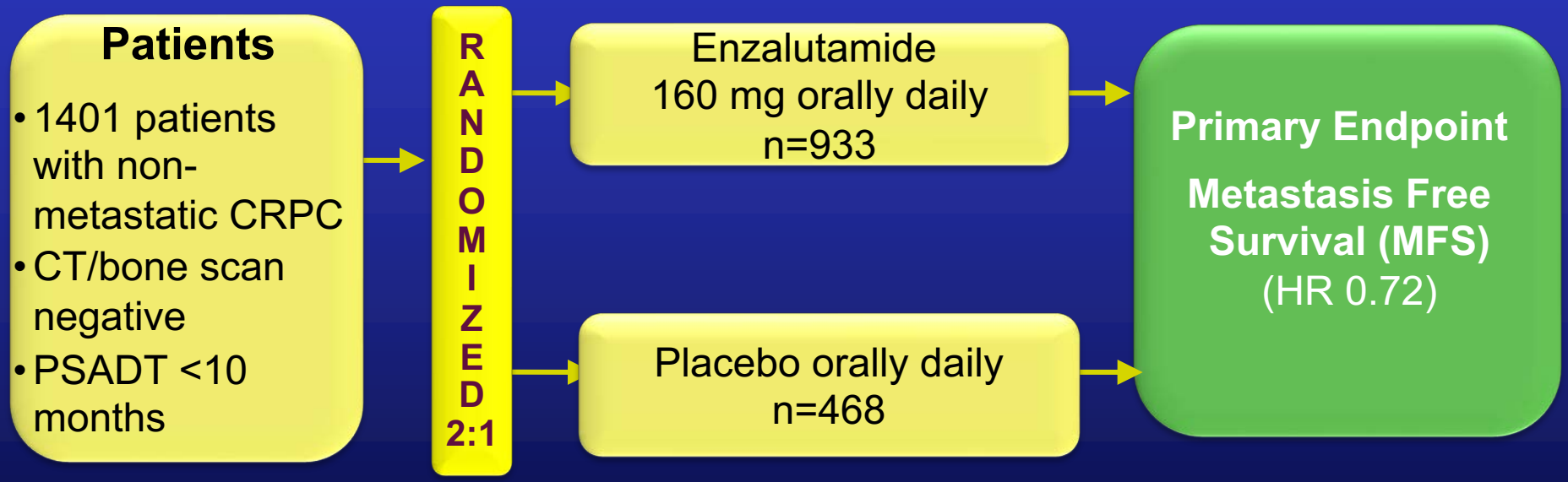
- The most common AEs (>15% of patients) for all treatment cohorts were hot flash, fatigue; plus gynecomastia in the enzalutamide monotherapy cohort; most were grade <3.

Shore, et al. AUA, 2023

NOVEL HORMONAL THERAPIES FOR nmCRPC

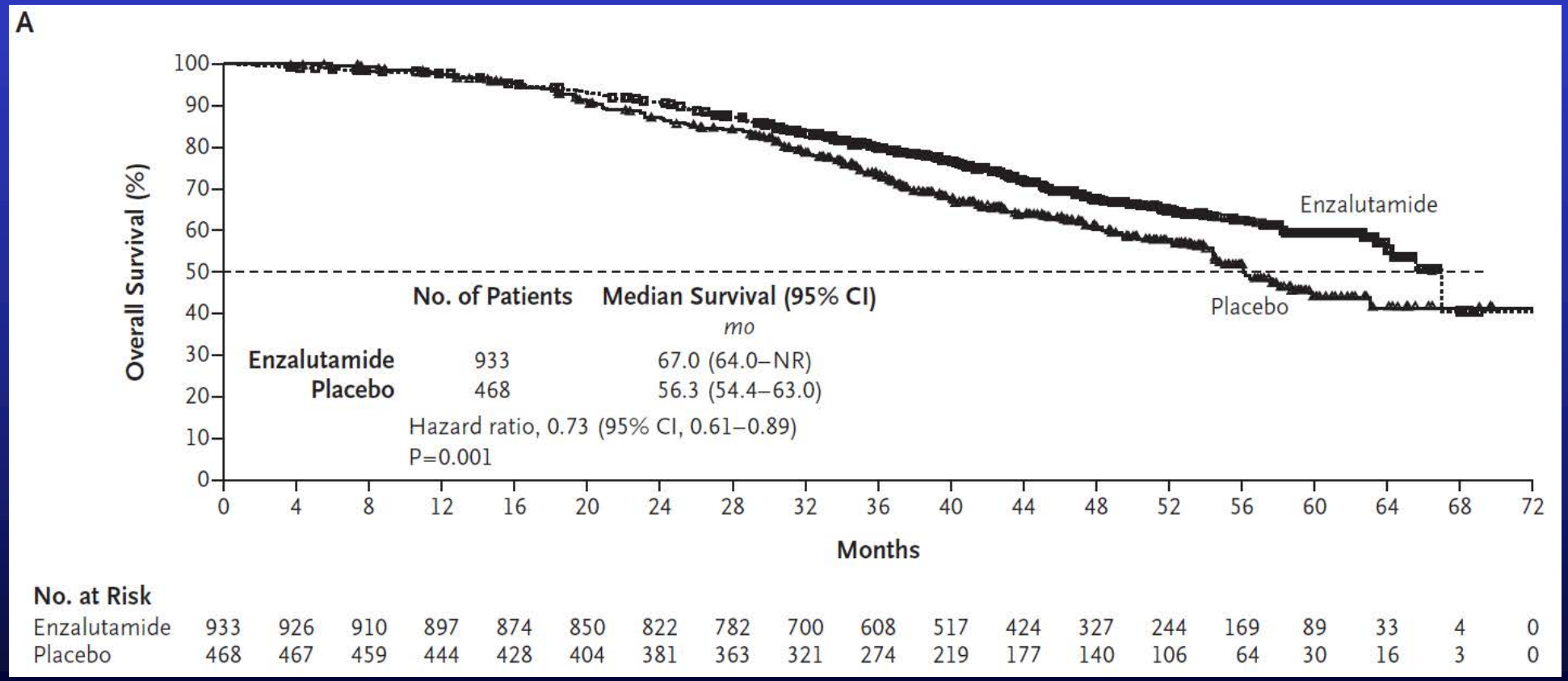
PROSPER: Enzalutamide for nmCRPC

- Phase III, multicenter, randomized, double-blind, placebo-controlled study



Sternberg et al, NEJM 2020

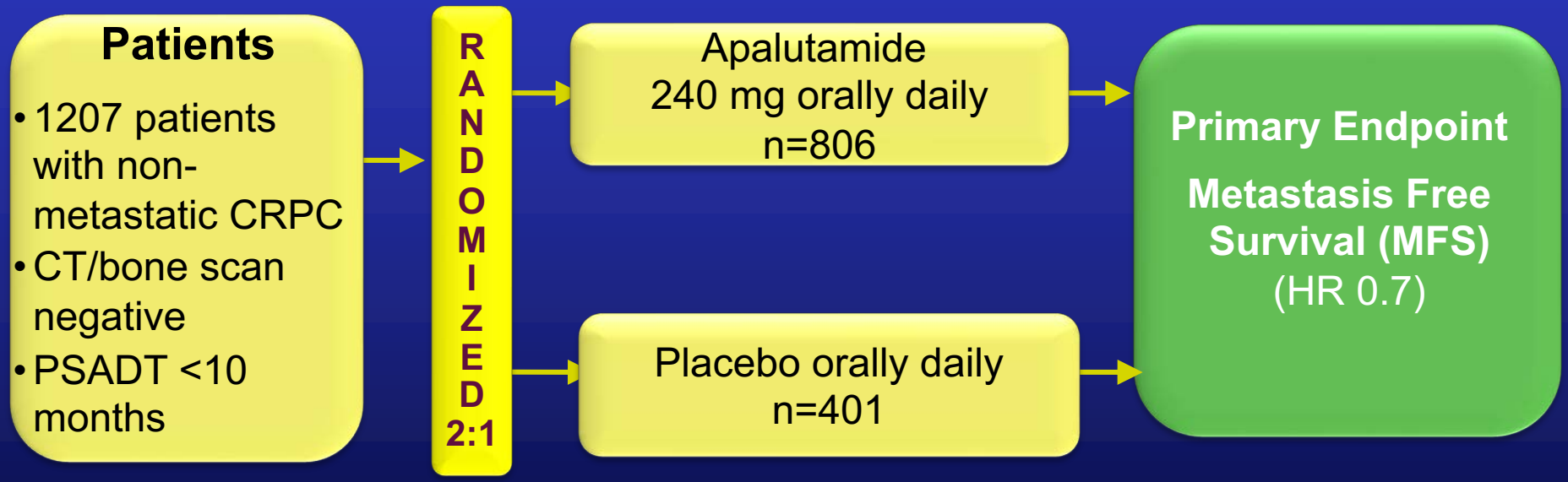
PROSPER: Enzalutamide for nmCRPC — OS



Sternberg et al, NEJM 2020

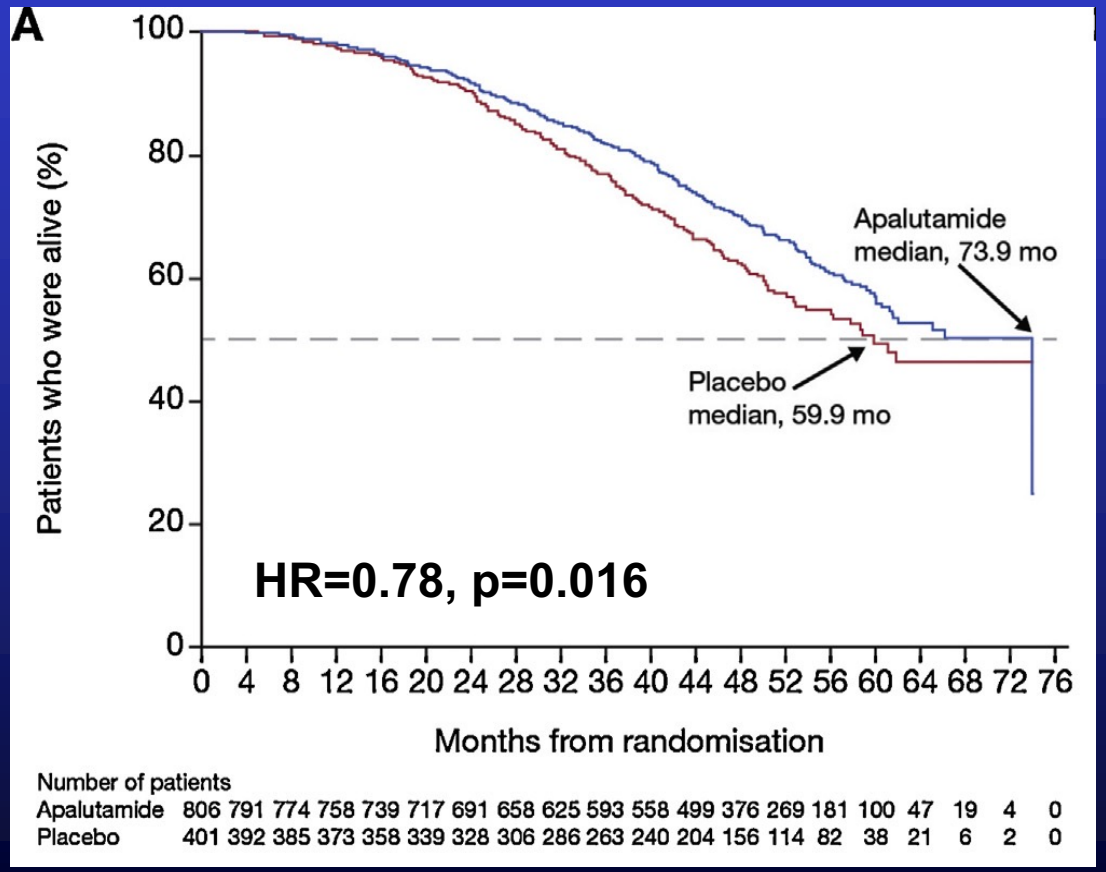
SPARTAN: Apalutamide for nmCRPC

- Phase III, multicenter, randomized, double-blind, placebo-controlled study



Smith et al, Eur Urol 2021

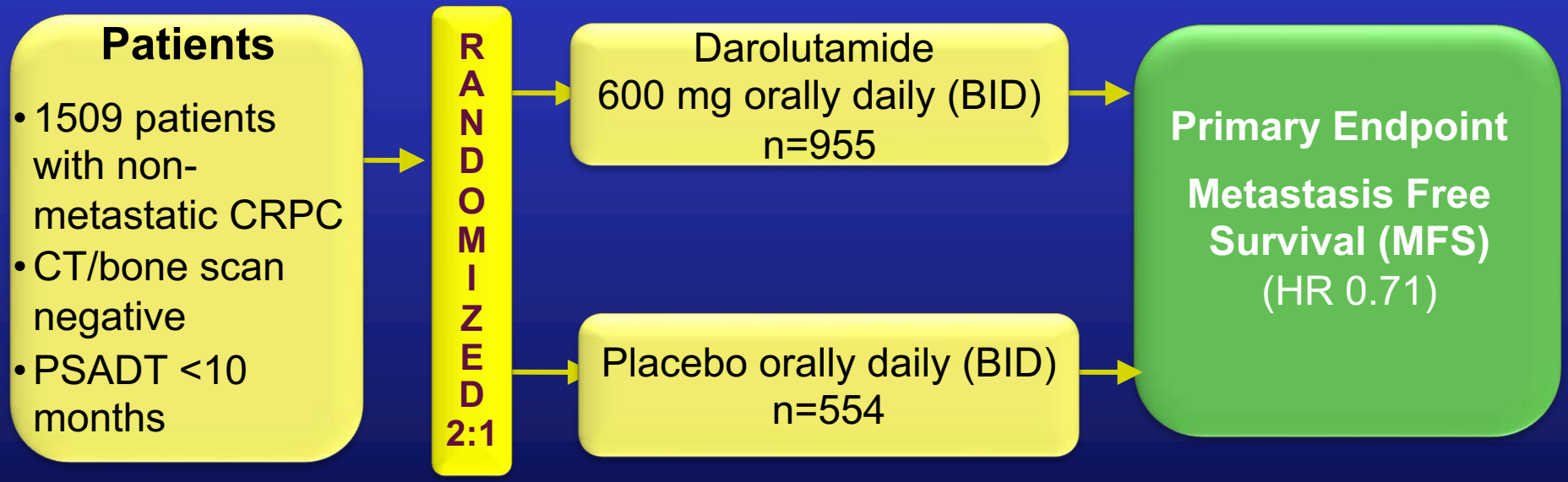
SPARTAN: Apalutamide for nmCRPC — OS



Smith et al, Eur Urol 2021

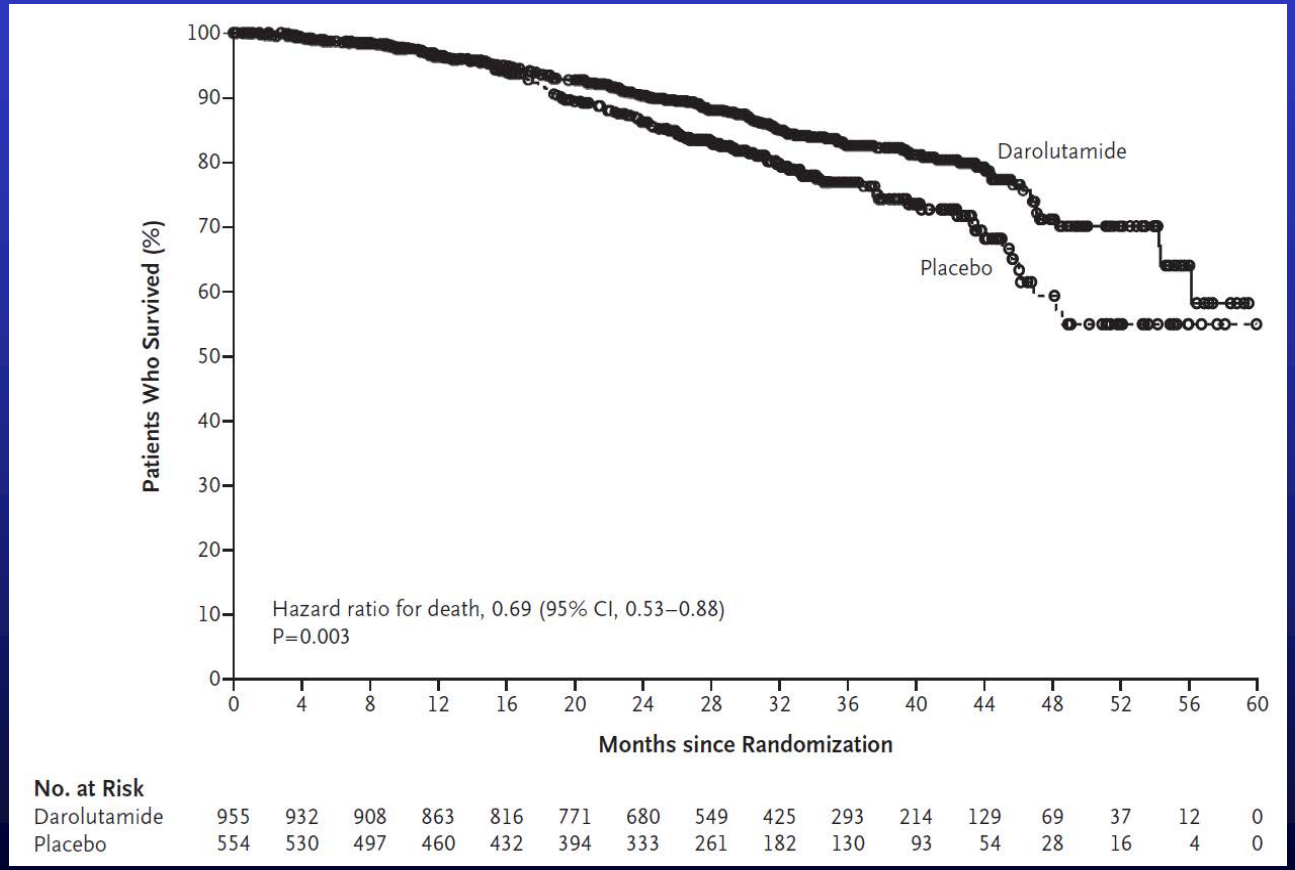
ARAMIS: Darolutamide for nmCRPC

- Phase III, multicenter, randomized, double-blind, placebo-controlled study



Fizazi et al, NEJM 2020

ARAMIS: Darolutamide for nmCRPC — OS



Fizazi et al, NEJM 2020

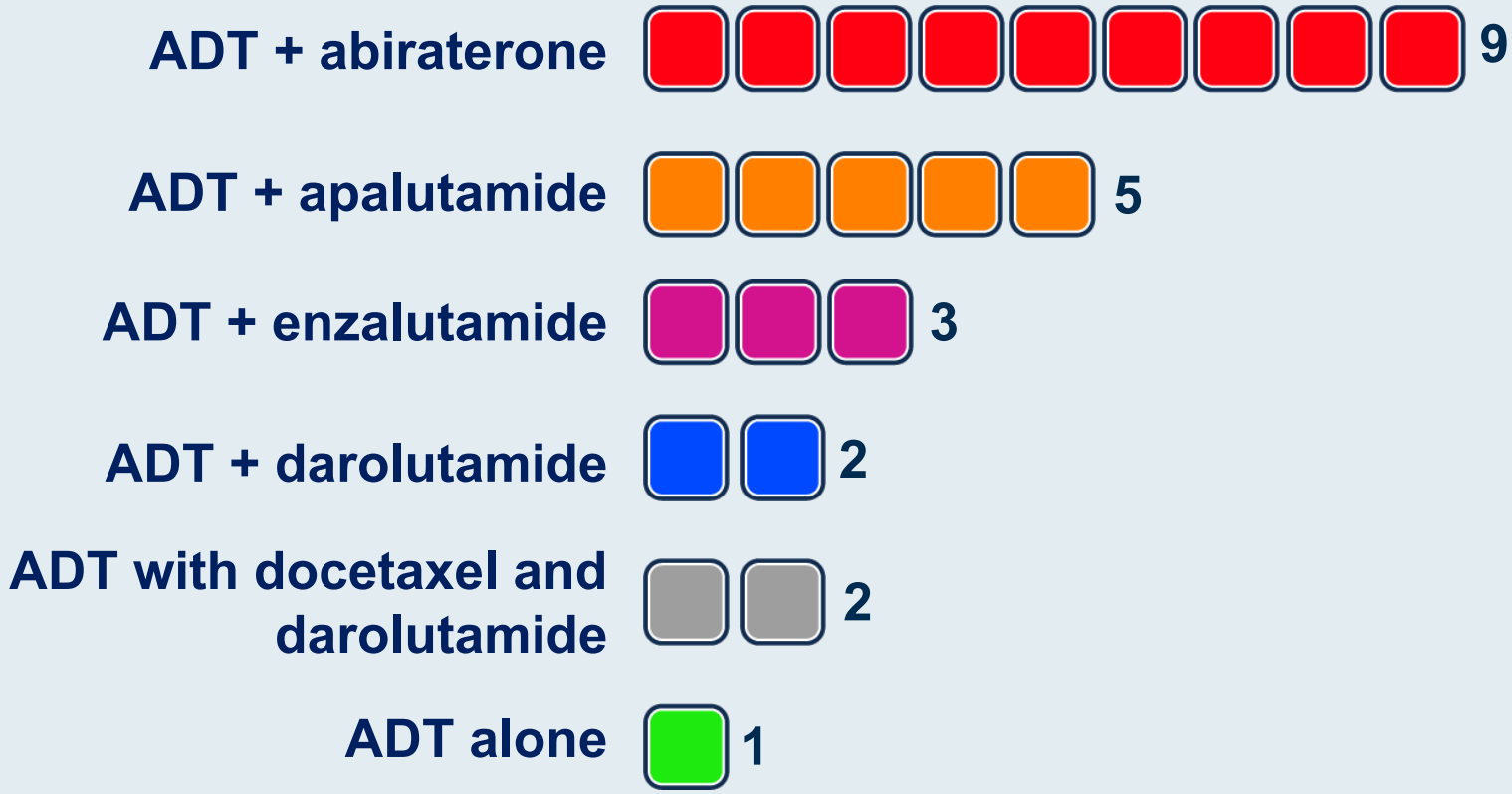
Summary

- For men requiring ADT, relugolix is a new SOC option
- In patients with high-risk BCR, EMBARK establishes a new SOC of ADT + enzalutamide
- In patients with high-risk nmCRPC, treatment with NHTs are SOC and improve MFS and OS
- The field of advanced PC is rapidly changing

MODULE 2: Optimizing the Care of Patients with Metastatic Hormone-Sensitive Prostate Cancer (mHSPC)

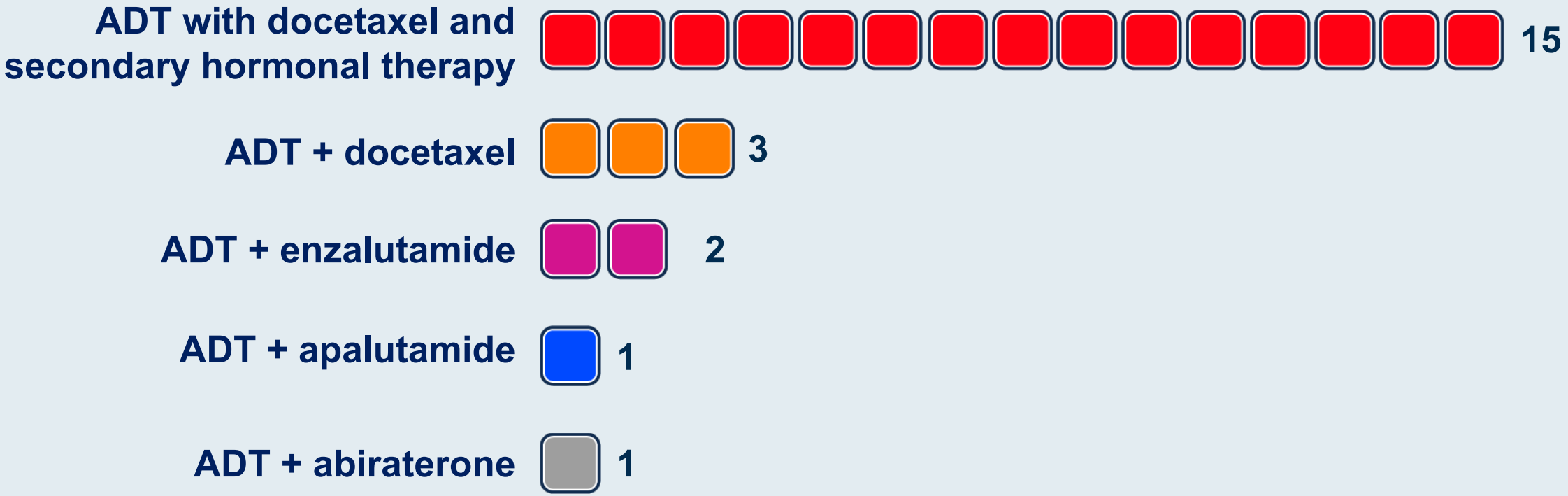
RTP
RESEARCH
TO PRACTICE

In general, which systemic therapy would you recommend for a 65-year-old patient presenting de novo with Gleason 8 prostate cancer and 3 asymptomatic bone metastases?



Survey of urologic oncology clinical investigators

In general, which systemic therapy would you recommend for a 65-year-old patient presenting de novo with Gleason 8 prostate cancer and multiple bone and liver metastases?



Survey of urologic oncology clinical investigators

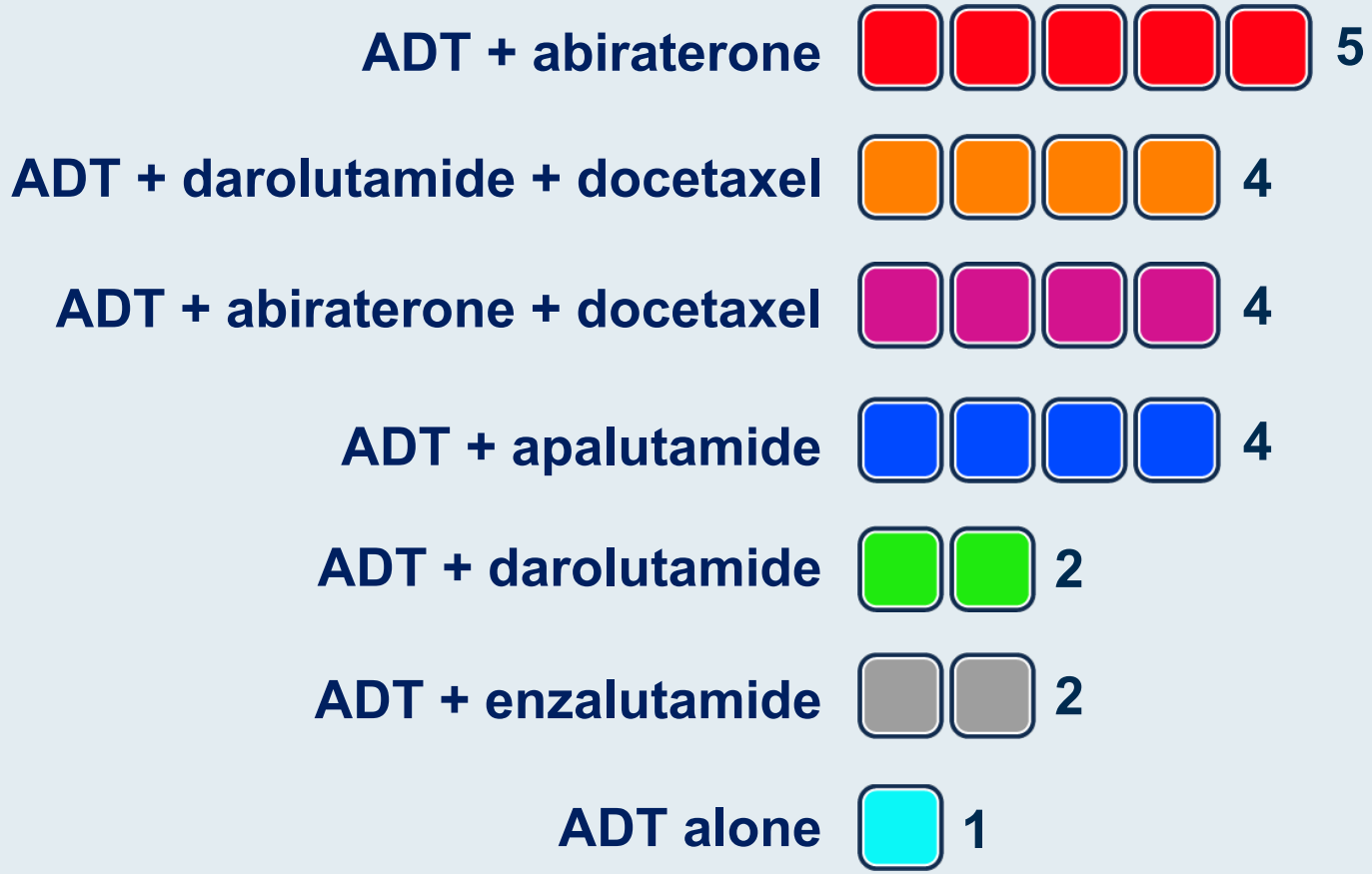
For a patient with metastatic castration-sensitive prostate cancer (CSPC) for whom you have elected to use a novel antiandrogen therapy in combination with ADT (without docetaxel), do you have a preferred agent?

Survey of urologic oncology clinical investigators

A 79-year-old man presents with high-volume metastatic CSPC. His pretreatment PSA is 173.2 ng/mL. CT and bone scans show widespread osseous metastases involving the skull, thoracic spine, proximal humerus, ribs, sternum and lumbar spine. Regulatory and reimbursement issues aside, what would be your most likely treatment recommendation?

Survey of urologic oncology clinical investigators

An 84-year-old man underwent robotic prostatectomy 11 years ago for pT3b, N0, Gleason 9 (4 + 5) prostate cancer. The patient was lost to follow-up and returned to the office several years later with a PSA of 80.82 ng/mL. CT scan reveals thoracolumbar and pelvic bone metastases. A bone scan shows additional extensive bony metastases. Regulatory and reimbursement issues aside, what would be your most likely treatment recommendation?



Survey of urologic oncology clinical investigators

Optimizing the Care of Patients with Metastatic Hormone-Sensitive Prostate Cancer (mHSPC)

Fred Saad MD FRCS

Professor and Chairman of Urology

Director of GU Oncology

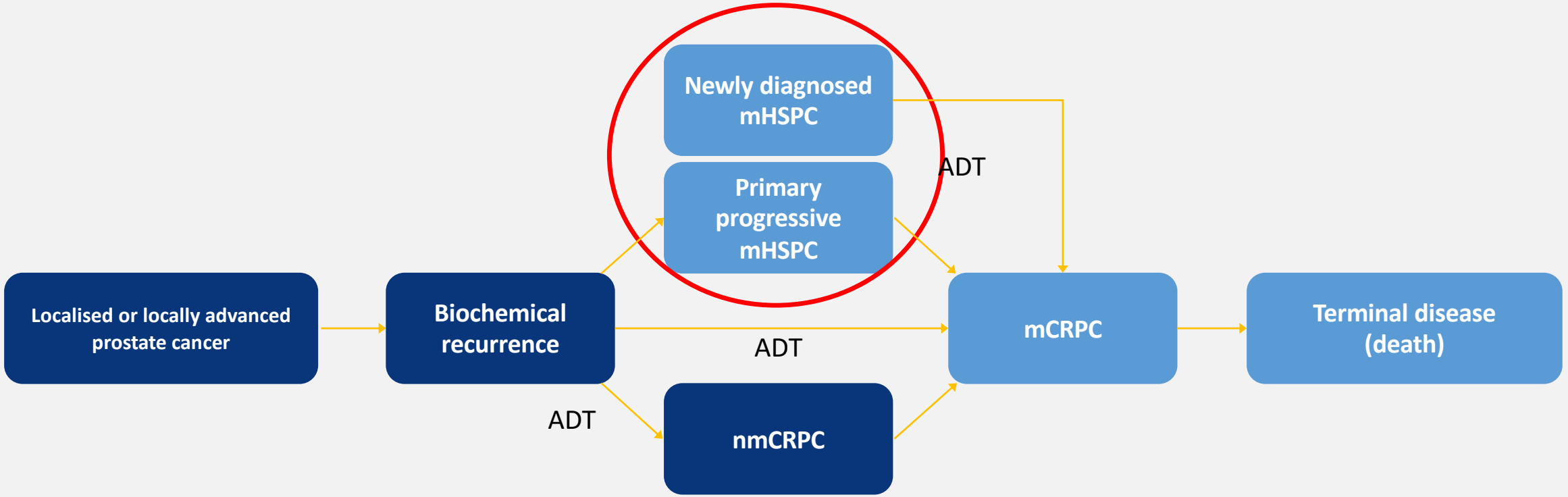
Raymond Garneau Chair in Prostate Cancer

University of Montreal Hospital Center

Montreal, QC, Canada

CHUM

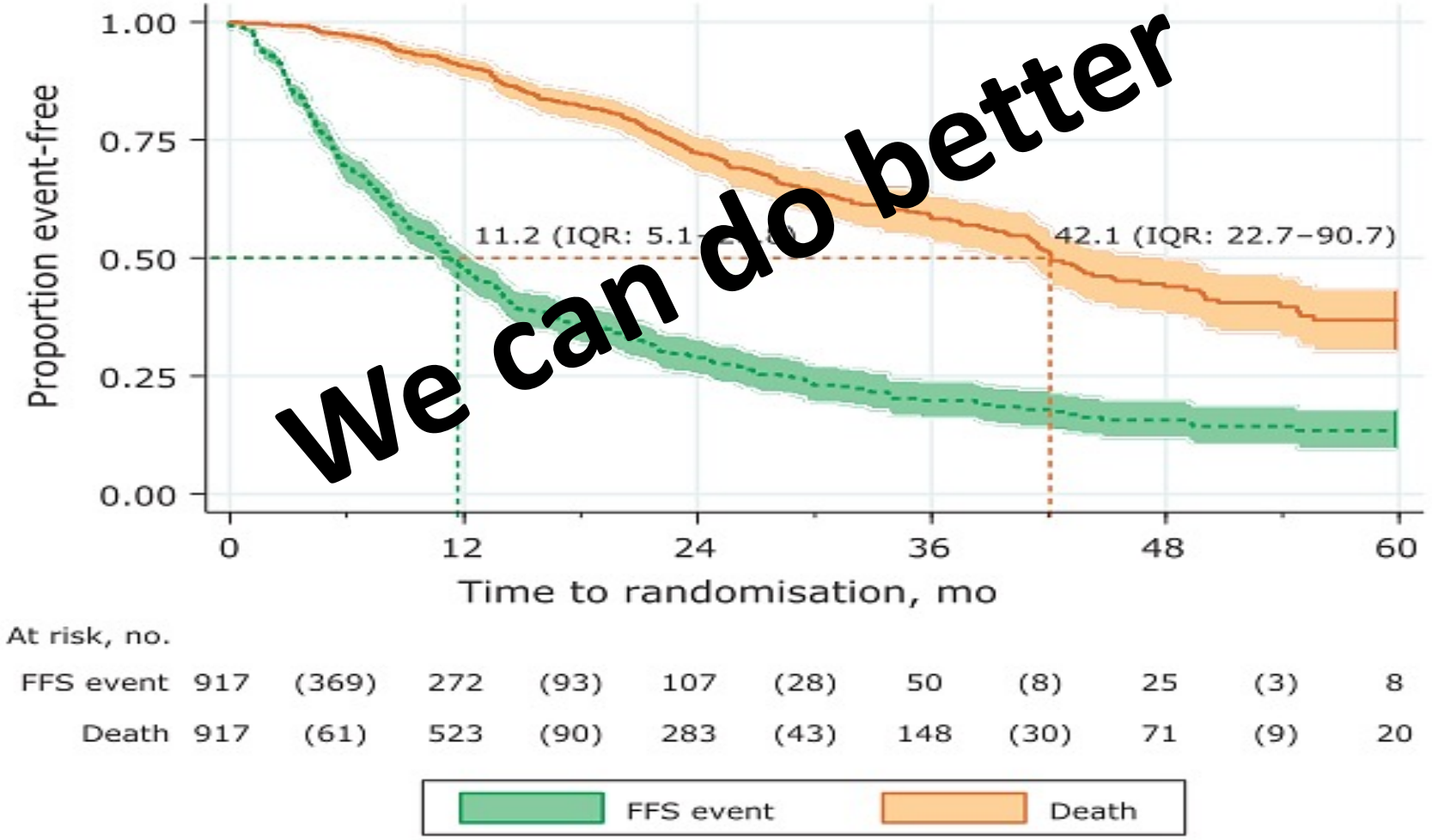
The prostate cancer landscape

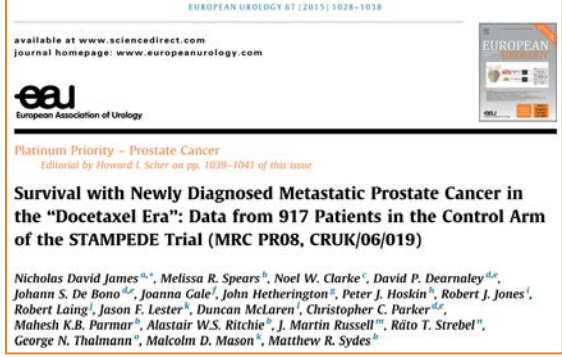


Almost all will progress to mCRPC and die of prostate cancer

CHUM

STAMPEDE control arm (ADT)
FFS and OS




EUROPEAN UROLOGY 67 (2015) 1028–1038
available at www.sciencedirect.com
journal homepage: www.europeanurology.com
European Association of Urology
Platinum Priority – Prostate Cancer
Editorial by Howard I. Scher on pp. 1039–1041 of this issue

Survival with Newly Diagnosed Metastatic Prostate Cancer in the "Docetaxel Era": Data from 917 Patients in the Control Arm of the STAMPEDE Trial (MRC PR08, CRUK/06/019)

Nicholas David James[a,], Melissa R. Spears[b], Noel W. Clarke[c], David P. Dearnaley[d,e], Johann S. De Bono[d,e], Joanna Gale[f], John Hetherington[g], Peter J. Hoskin[h], Robert J. Jones[i], Robert Laing[f], Jason F. Lester[h], Duncan McLaren[f], Christopher C. Parker[d,e], Mahesh K.B. Parmar[b], Alastair W.S. Ritchie[b], J. Martin Russell[m], Rätо T. Strebel[n], George N. Thalmann[o], Malcolm D. Mason[b], Matthew R. Sydes[b]*

James ND et al. *Eur Urol*. 2015;67:1028-38.

CHUM

Local control does make a difference (in some)

CHUM

STAMPEDE: Prostate Radiotherapy for mCSPC

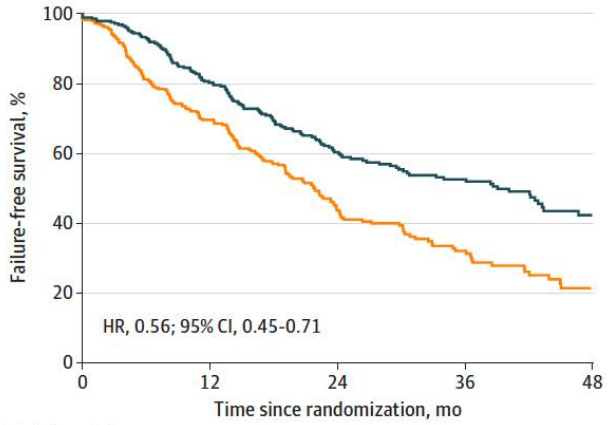
Failure Free Survival

Overall Survival

< 4 bone metastases

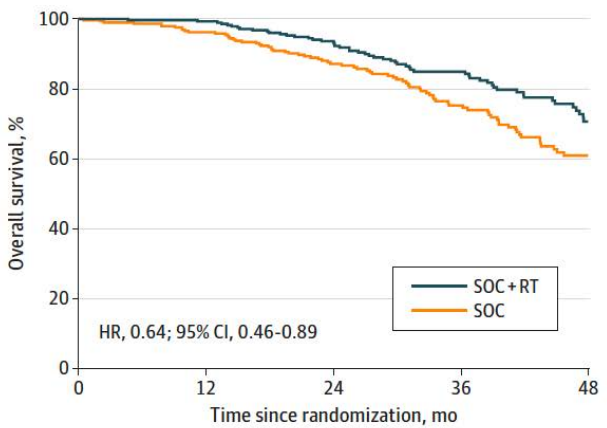
≥ 4 bone metastases

B Failure-free survival in ≤3 bone metastases (±NRLN) subcohort



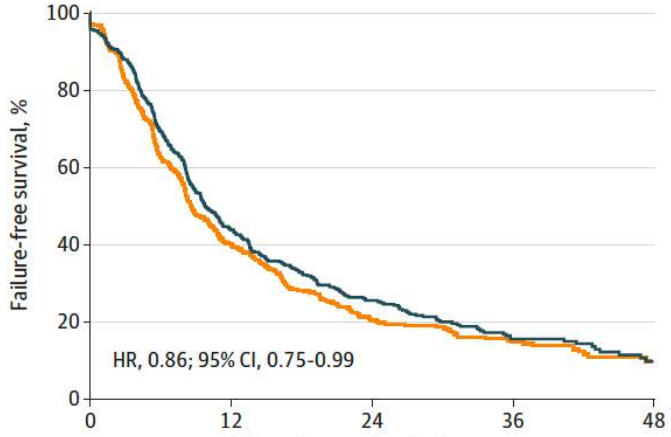
No. at risk (events)									
SOC	290	(87)	195	(66)	86	(19)	41	(11)	12
SOC+RT	287	(56)	228	(52)	129	(15)	86	(12)	26

A Overall survival in ≤3 bone metastases (±NRLN) subcohort



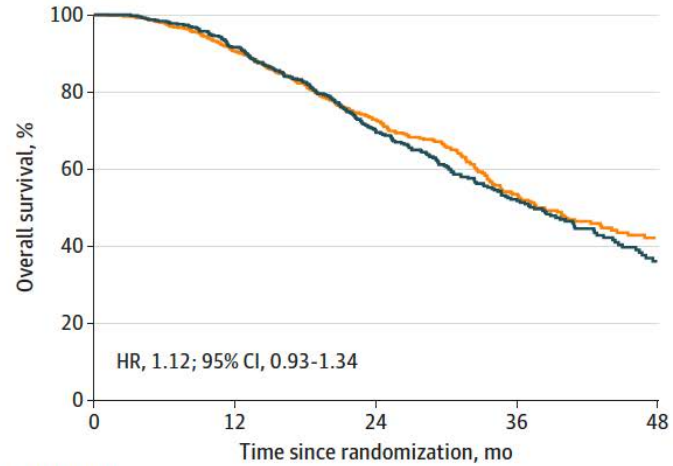
No. at risk (events)									
SOC	290	(11)	274	(24)	188	(22)	116	(19)	50
SOC+RT	287	(2)	281	(15)	212	(18)	145	(18)	59

D Failure-free survival in ≥4 bone metastases (±NRLN) subcohort



No. at risk (events)									
SOC	512	(301)	201	(90)	69	(15)	36	(8)	8
SOC+RT	498	(276)	212	(84)	89	(28)	34	(8)	9

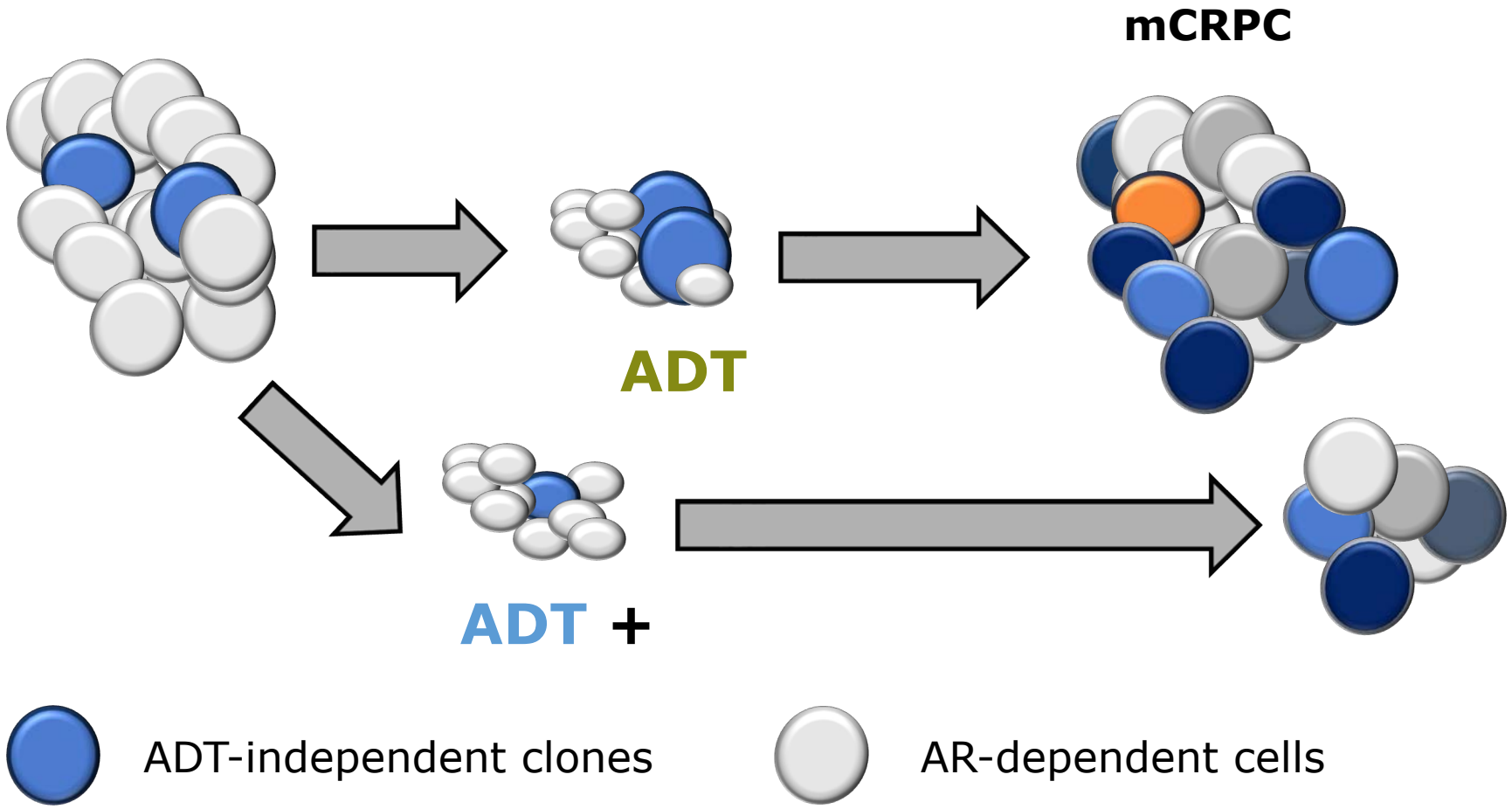
C Overall survival in ≥4 bone metastases (±NRLN) subcohort



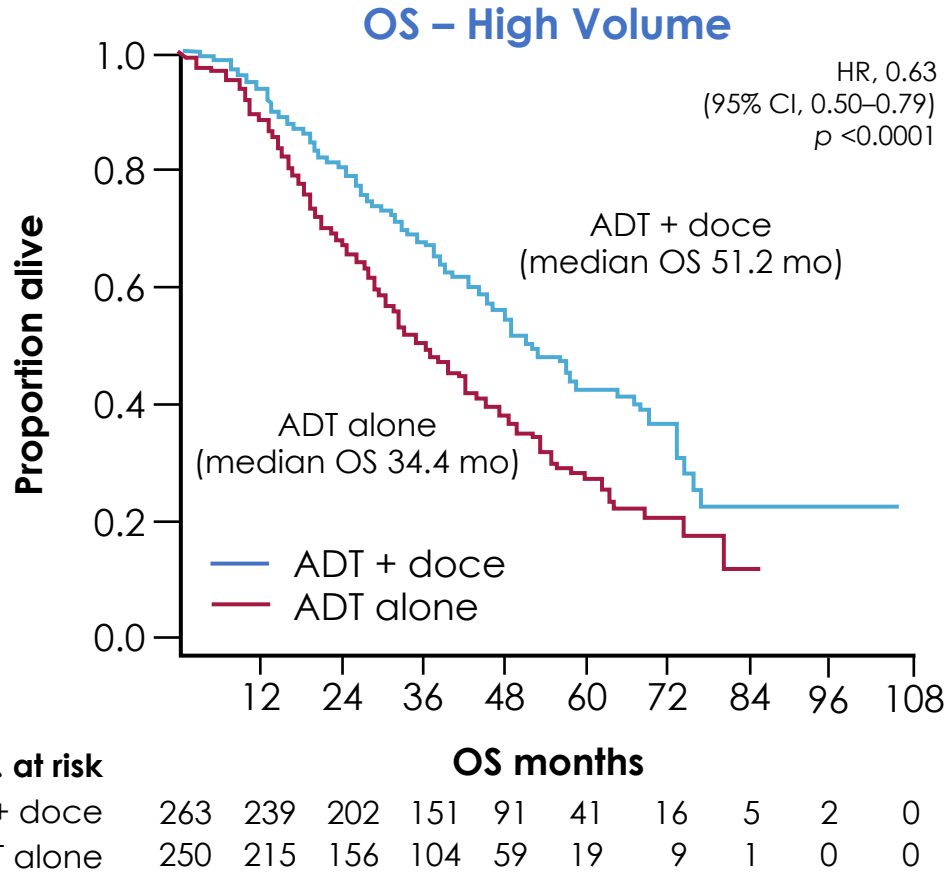
No. at risk (events)									
SOC	512	(47)	452	(83)	281	(64)	147	(25)	45
SOC+RT	498	(41)	441	(96)	260	(58)	136	(30)	38

Adnan A et al. JAMA Oncol. doi:10.1001/jamaoncol.2
Published online February 18, 2021.

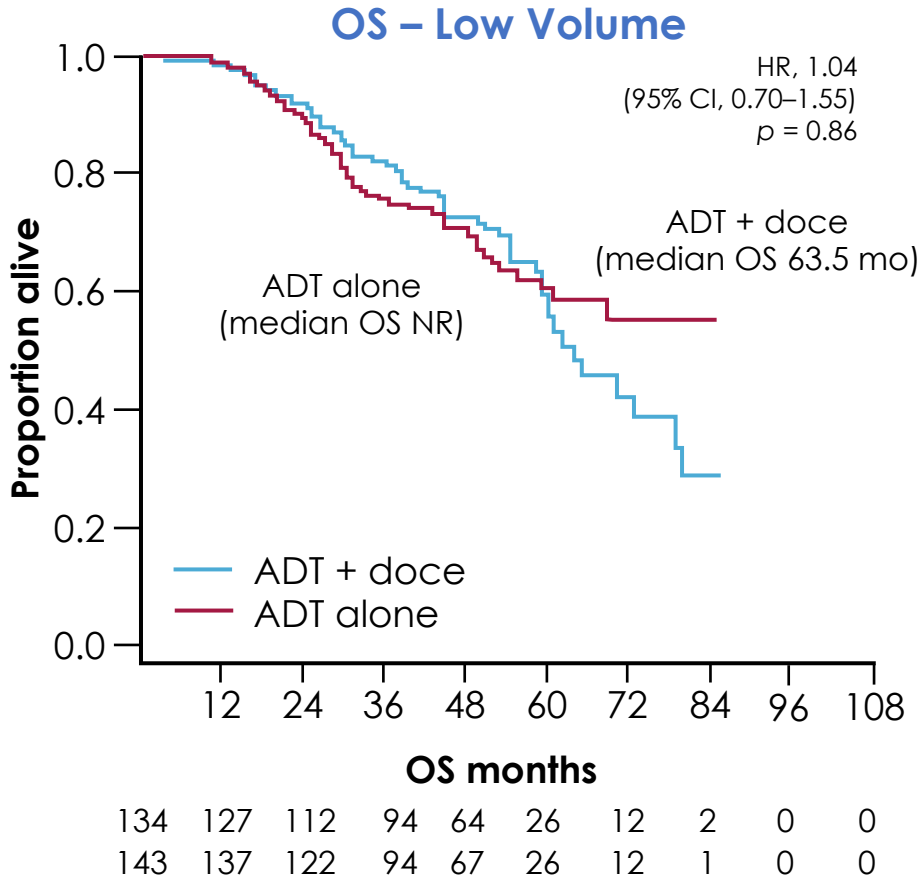
Role of Effective Systemic Therapy



CHAARTED: Docetaxel in mHSPC



16.8 months

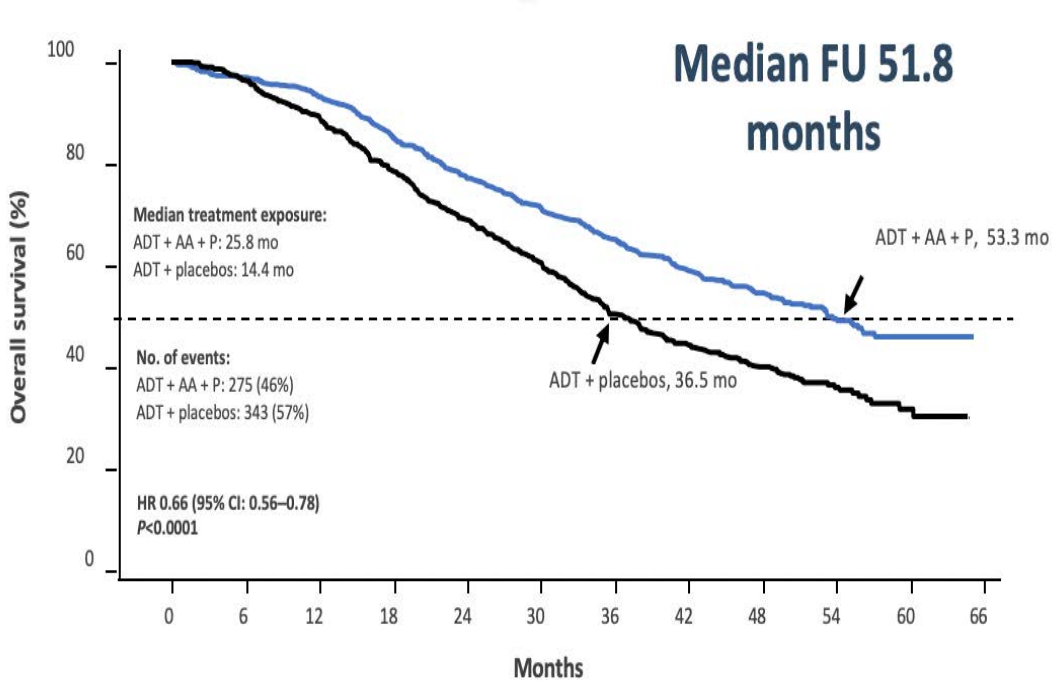


0 months

Kyriakopoulos CE, et al. *J Clin Oncol* 2018;36:1080-1087.

CHUM

LATITUDE: Abiraterone in high risk mCNPC



	Abiraterone acetate and prednisone plus ADT (n=597)		Placebos plus ADT (n=602)		Hazard ratio (95% CI)	p value
	Events	Median, months	Events	Median, months		
Primary endpoint						
Overall survival	275 (46%)	53·3 (48·2–NR)	343 (57%)	36·5 (33·5–40·0)	0·66 (0·56–0·78)	<0·0001
Secondary endpoints						
Pain progression	245 (41%)	47·4 (33·2–NR)	292 (49%)	16·6 (11·1–24·0)	0·72 (0·61–0·86)	0·00024
Skeletal-related event*	132 (22%)	NR (NR–NR)	150 (25%)	NR (NR–NR)	0·75 (0·60–0·95)	0·0181
Chemotherapy initiation†	150 (25%)	NR (62·6–NR)	218 (36%)	57·6 (38·2–NR)	0·51 (0·41–0·63)	<0·0001
Subsequent prostate cancer therapy	248 (42%)	54·9 (45·4–NR)	355 (59%)	21·2 (18·6–23·5)	0·45 (0·38–0·53)	<0·0001
Prostate-specific antigen progression	273 (46%)	33·3 (29·4–46·1)	448 (74%)	7·4 (7·2–9·2)	0·31 (0·27–0·36)	<0·0001
Exploratory endpoint						
Secondary progression-free survival‡	267 (45%)	53·3 (44·7–58·1)	336 (56%)	30·1 (26·2–33·4)	0·58 (0·49–0·68)	<0·0001

1. Fizazi K, et al. *Lancet Oncol* 2019;20:686;

CHUM

Why I prefer NOT to use abiraterone in mHSPC
Even if 'only' 5mg prednisone in mHSPC

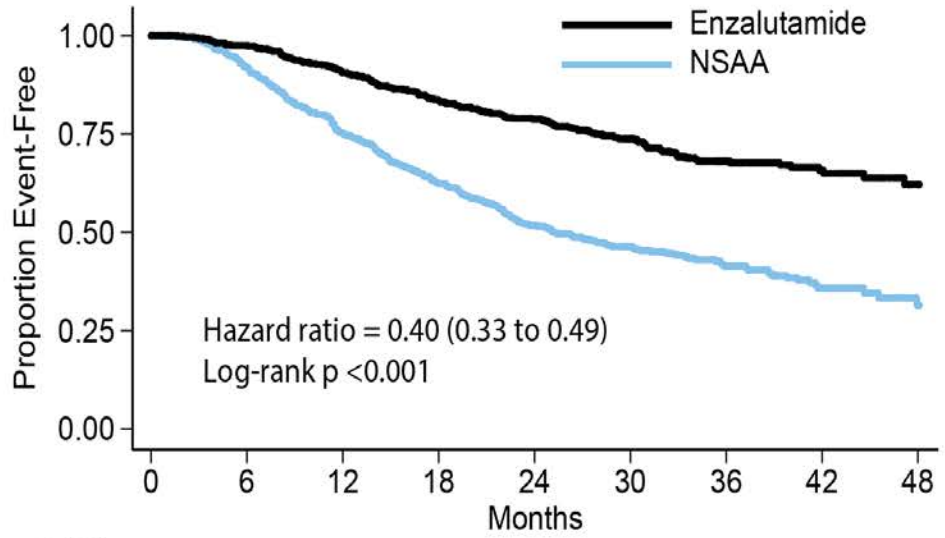
Graded adverse events	ADT + AA+P n=597		ADT+ Placebos n=602		Placebo cross over to AA+P n=72	
	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4
Hypertension	22%	<1%	10%	<1%	4%	0
Hepatotoxicity	8%	1%	4%	0	4%	0
ALT increased	5%	<1%	1%	0	3%	0
AST increased	4%	<1%	2%	0	1%	0
Hypokalemia	11%	1%	2%	<1%	3%	0
Cardiac Disorders	3%	1%	1%	0	0	0
Fluid retention/edema	1%	0	1%	0	0	0
Osteoporosis including osteoporosis-related fractures	2%	0	2%	<1%	0	0
Cataract	1%	0	<1%	0	0	0

1. Fizazi K, et al. *Lancet Oncol* 2019;20:686;

CHUM

ENZAMET: Enzalutamide in all-comers

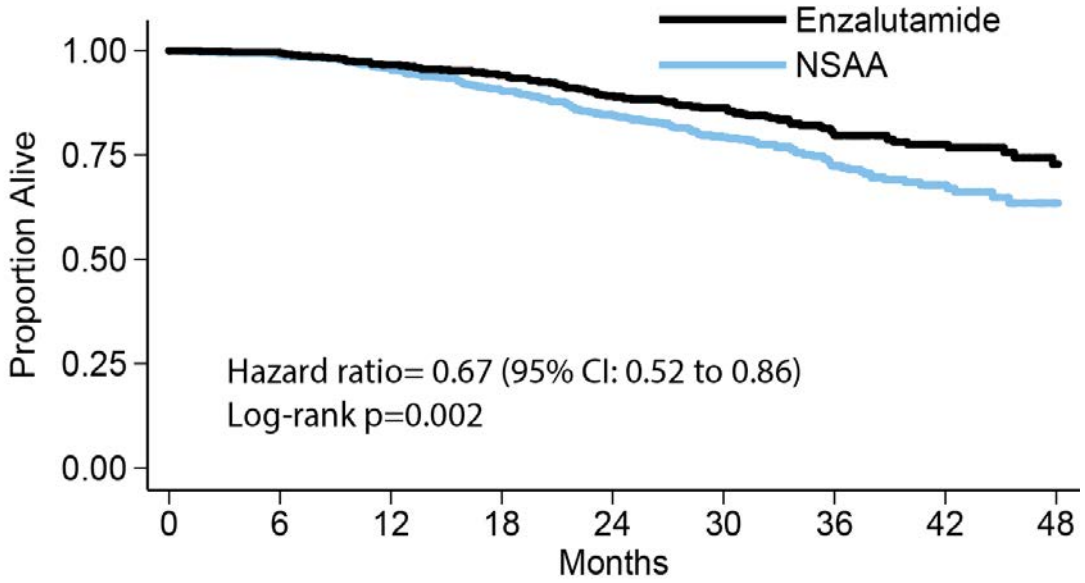
Progression free survival



Number at risk

NSAA	562	512	418	346	272	182	96	50	17
Enzalutamide	563	547	507	468	424	284	156	84	36

Overall survival



Number at risk

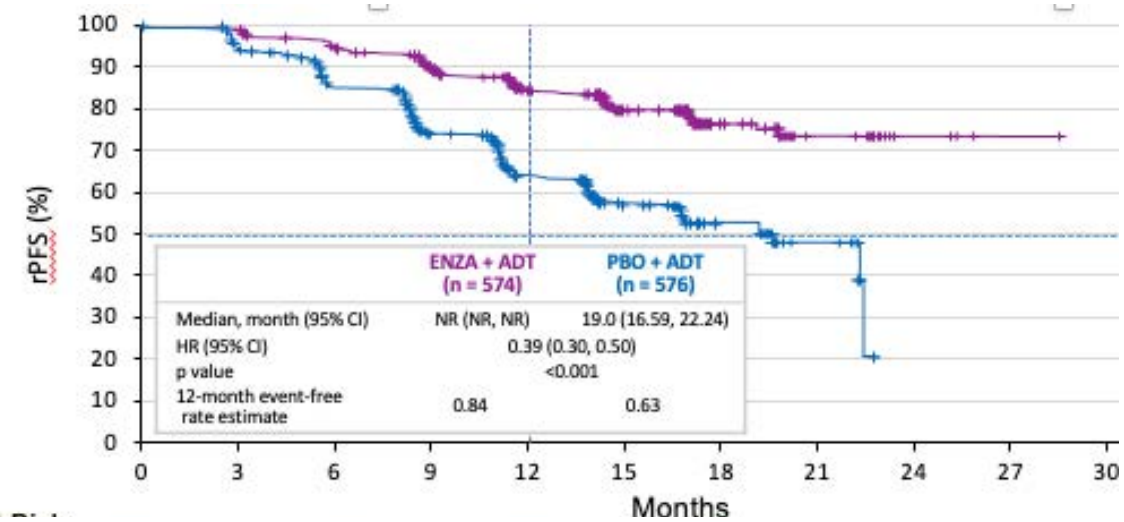
NSAA	562	551	531	501	452	311	174	86	32
Enzalutamide	563	558	541	527	480	340	189	106	45

Davis, I et al. Engl J Med. 2019 Jul 11;381(2):121-131.

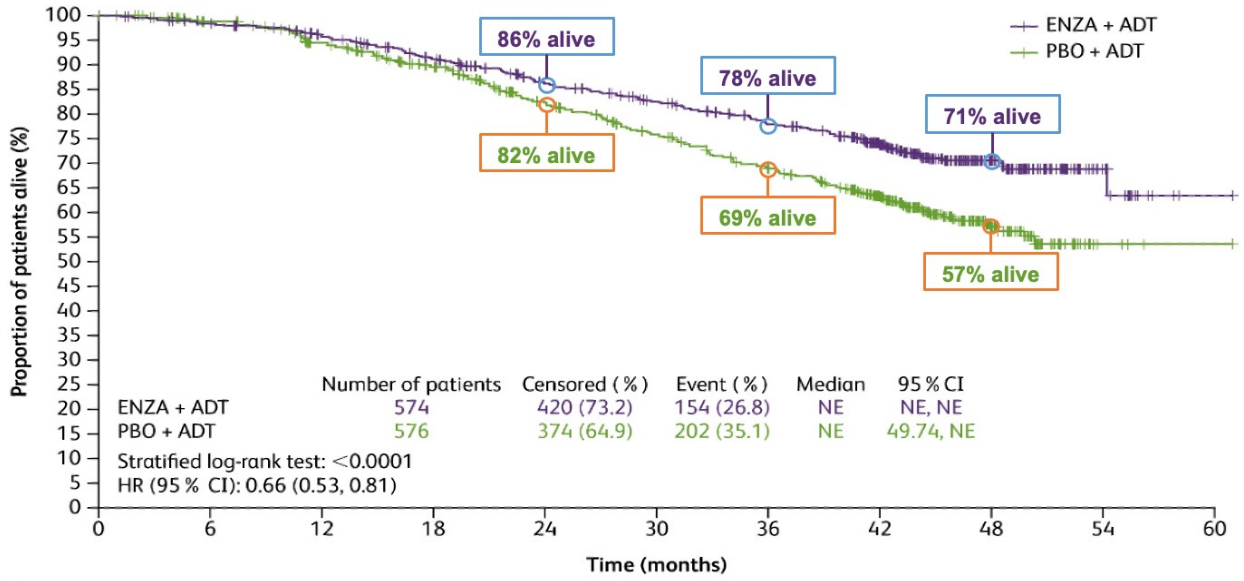
CHUM

ARCHES: Enzalutamide in all-comers mCSPC

Progression free survival



Overall survival

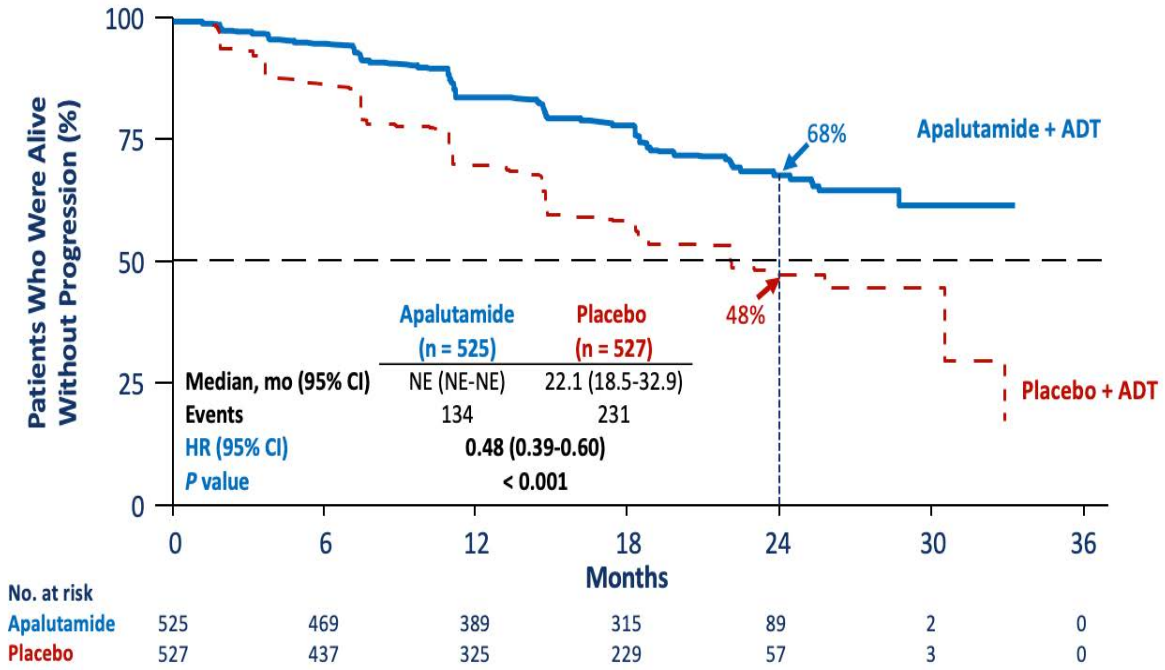


Low volume of disease	220 (35)/203 (46)	NR/NR		0.66 (0.43, 1.03)
High volume of disease	354 (119)/373 (156)	NR/45.9		0.66 (0.52, 0.83)

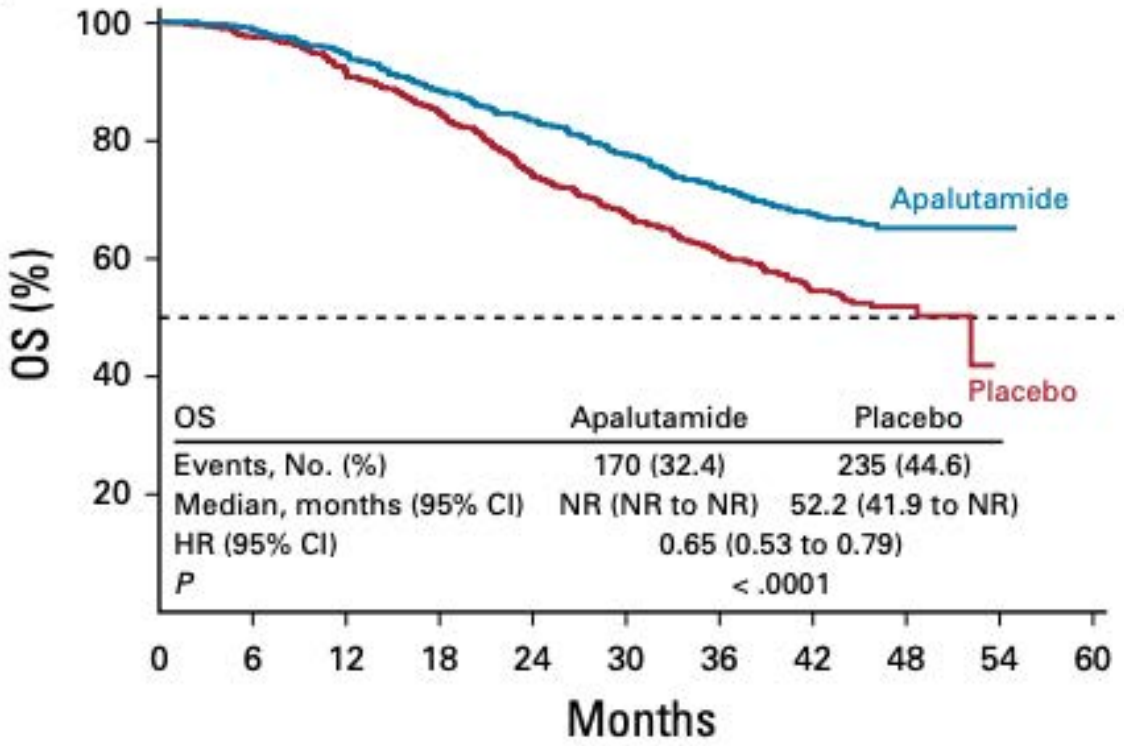
CHUM

TITAN: Apalutamide in all-comers mCSPC

Progression free survival



Overall survival



Disease volume	High	0.68 (0.50-0.92)	69/325	97/335
	Low	0.67 (0.34-1.32)	14/200	20/192

Chi K et al. N Engl J Med. 2019 Jul 4;381(1):13-24. Chi K et al. J Clin Oncol 2021 Apr 29;JCO2003488.

CHUM

PSA Responses Over Time

PSA Responses Over Time						
Decline	3 months		6 months		12 months	
	APA*	PBO	APA*	PBO	APA*	PBO
PSA ≥50% ↓	89%	41%	90%	49%	90%	52%
PSA ≥90% ↓	58%	13%	67%	18%	71%	22%
PSA ≤0.2 ng/mL	51%	18%	61%	21%	65%	23%

*P < 0.0001 for APA vs. PBO.

Data from the TITAN study: Chi K et al. N Engl J Med. 2019 Jul 4;381(1):13-24.

Chowdhury et al. AUA 2020. Oral Presentation PD10.

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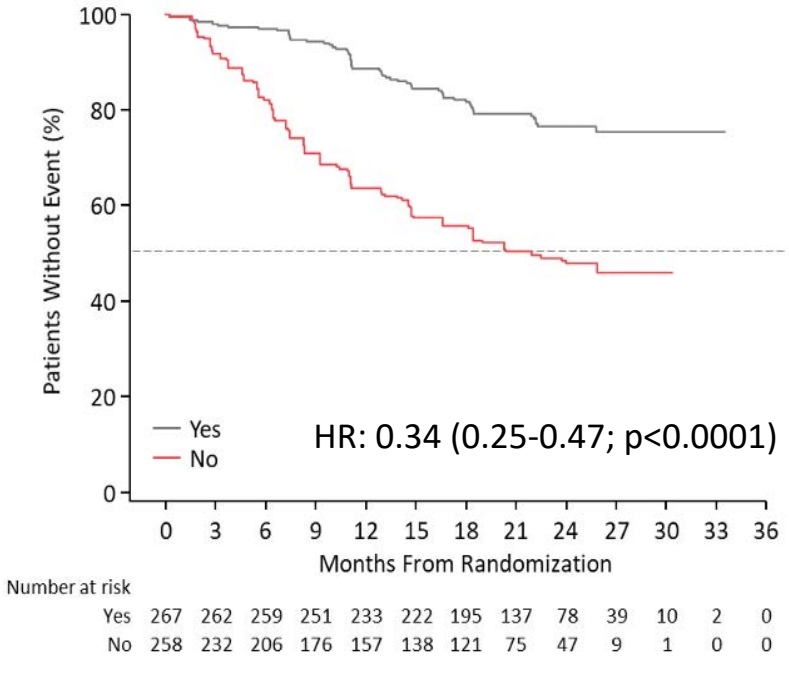
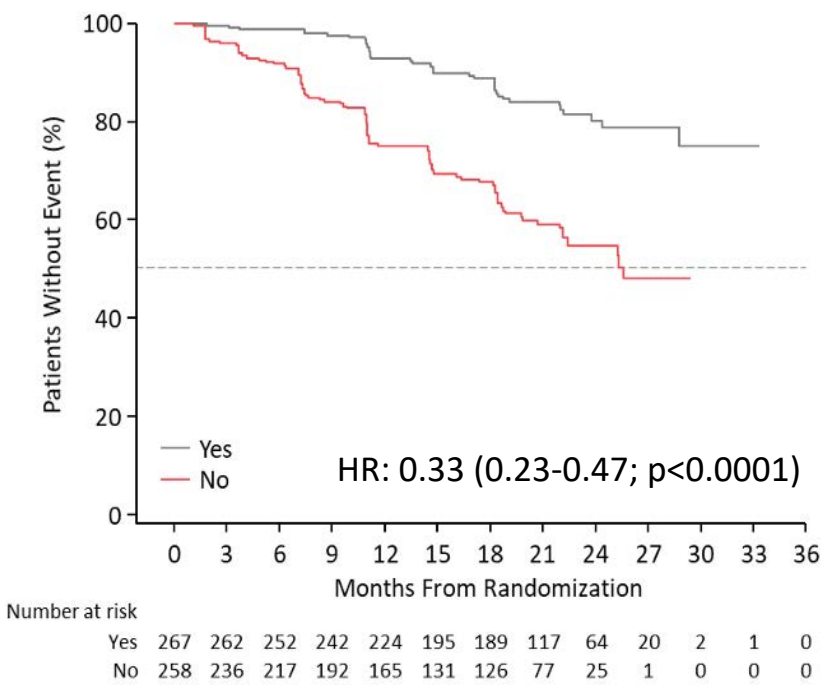
Patients who achieved reduction of PSA ≤0.2 ng/mL by 3 months

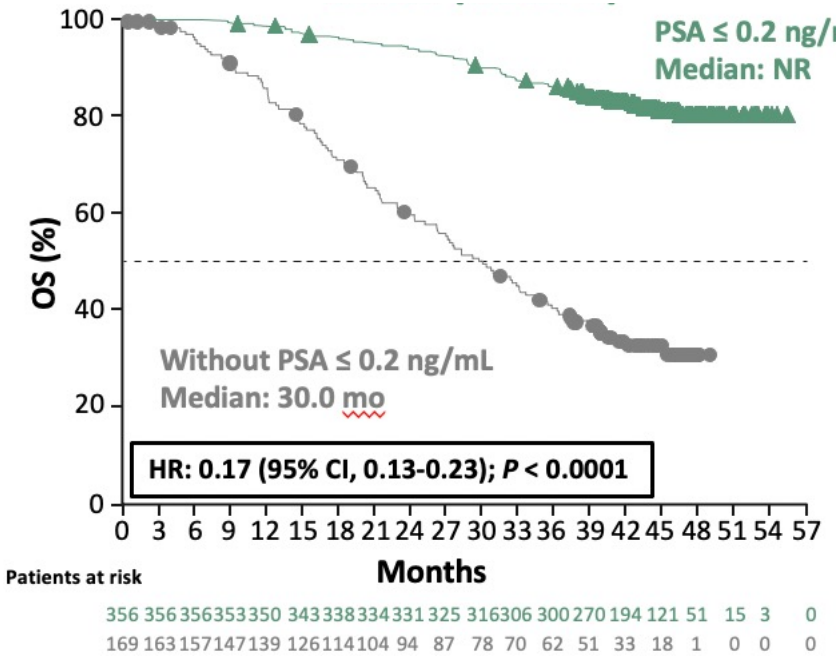
Time to mCRPC



Time to Radiographic progression



Overall survival



Data from the TITAN study: Chi K et al. N Engl J Med. 2019 Jul 4;381(1):13-24.

Chi KN, et al. Oral presentation at AUA Annual Meeting (Virtual), September 10-13, 2021

CHUM

Can combinations further improve outcome?

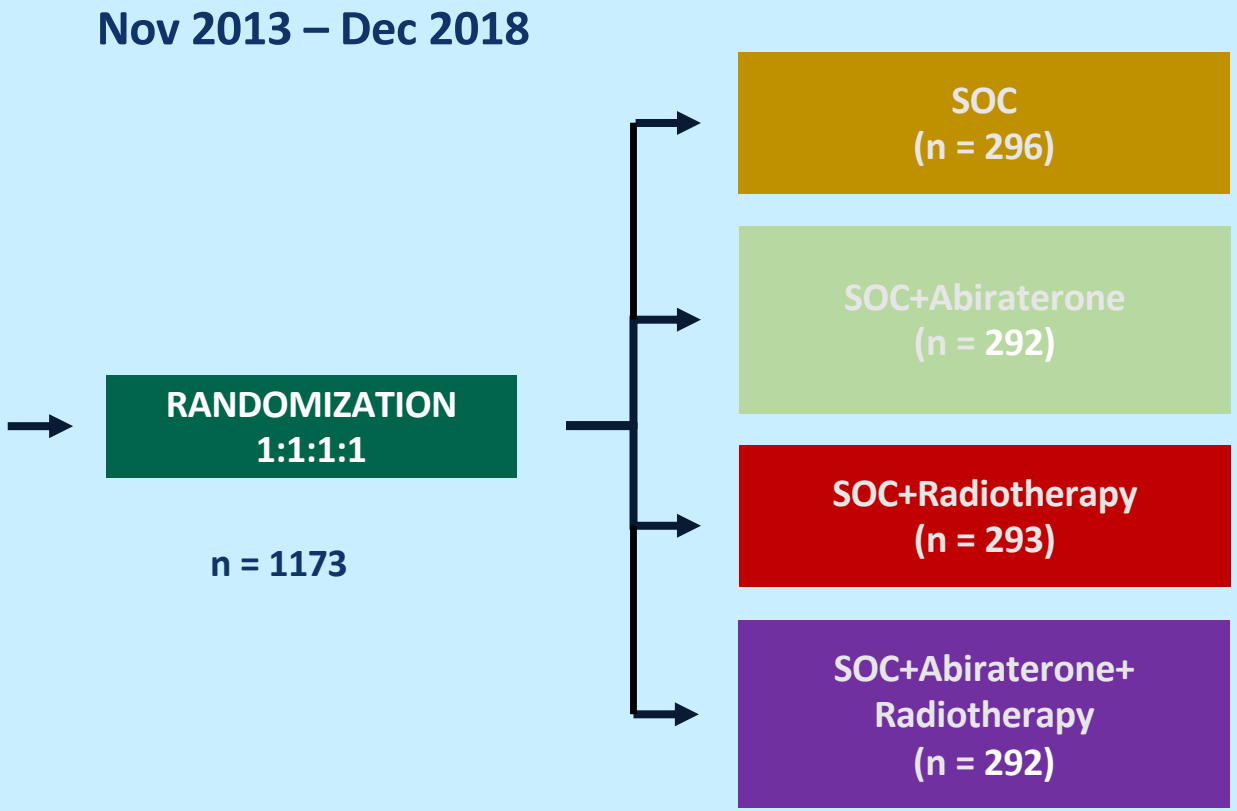
Design of PEACE-1 (2x2)

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

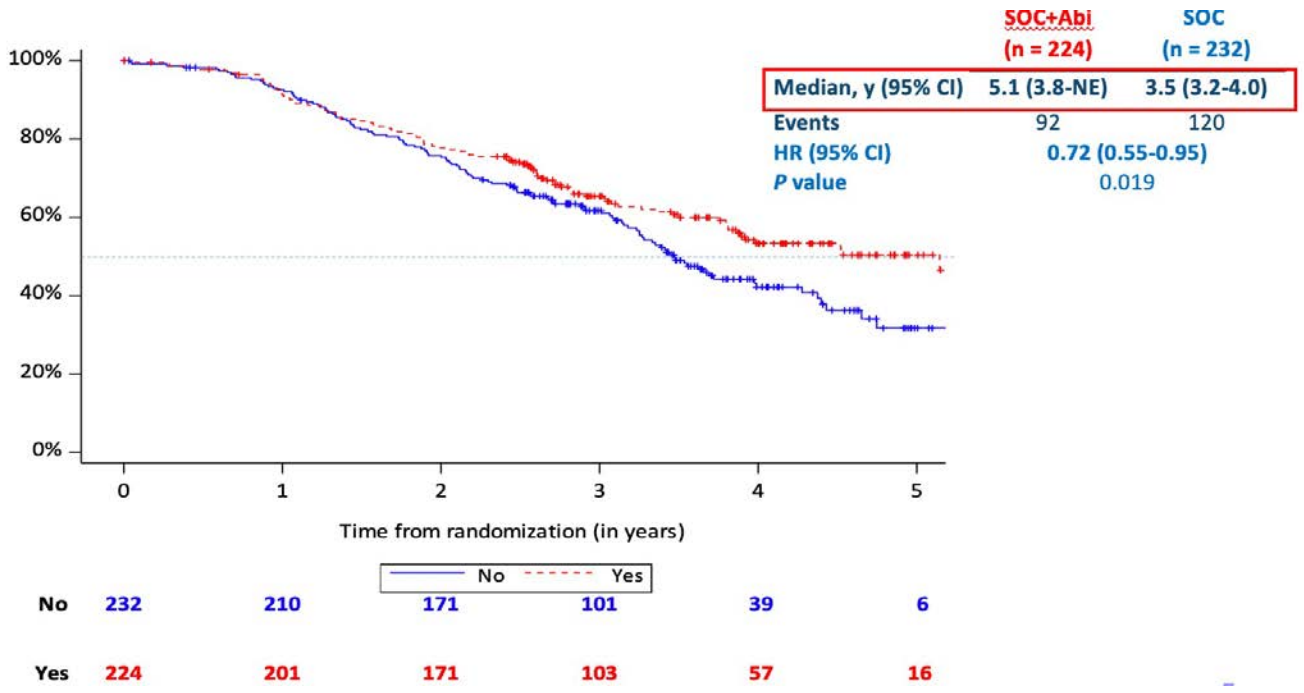
Stratification
ECOG PS (0 vs 1-2)
Metastatic sites (LN vs bone vs visceral)
Type of castration (orchidectomy vs LHRH agonist vs LHRH antagonist)
Docetaxel (yes vs no)



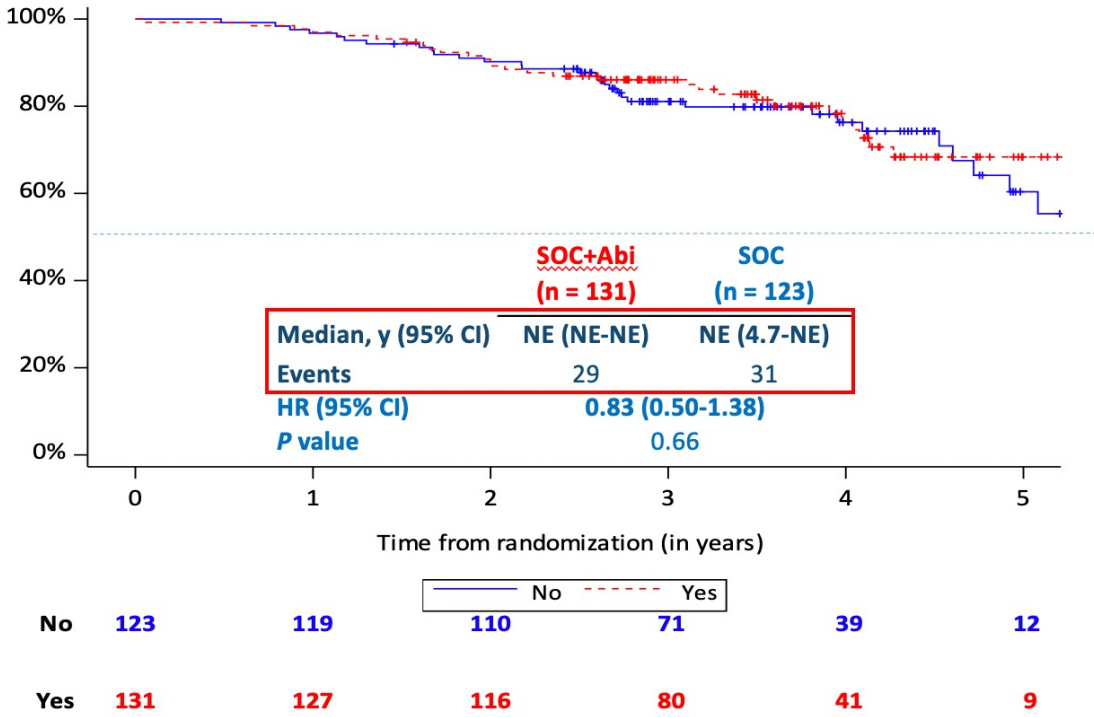
ECOG PS, Eastern Cooperative Oncology Group performance status

ADT/docetaxel +/- abiraterone population

High-volume patients



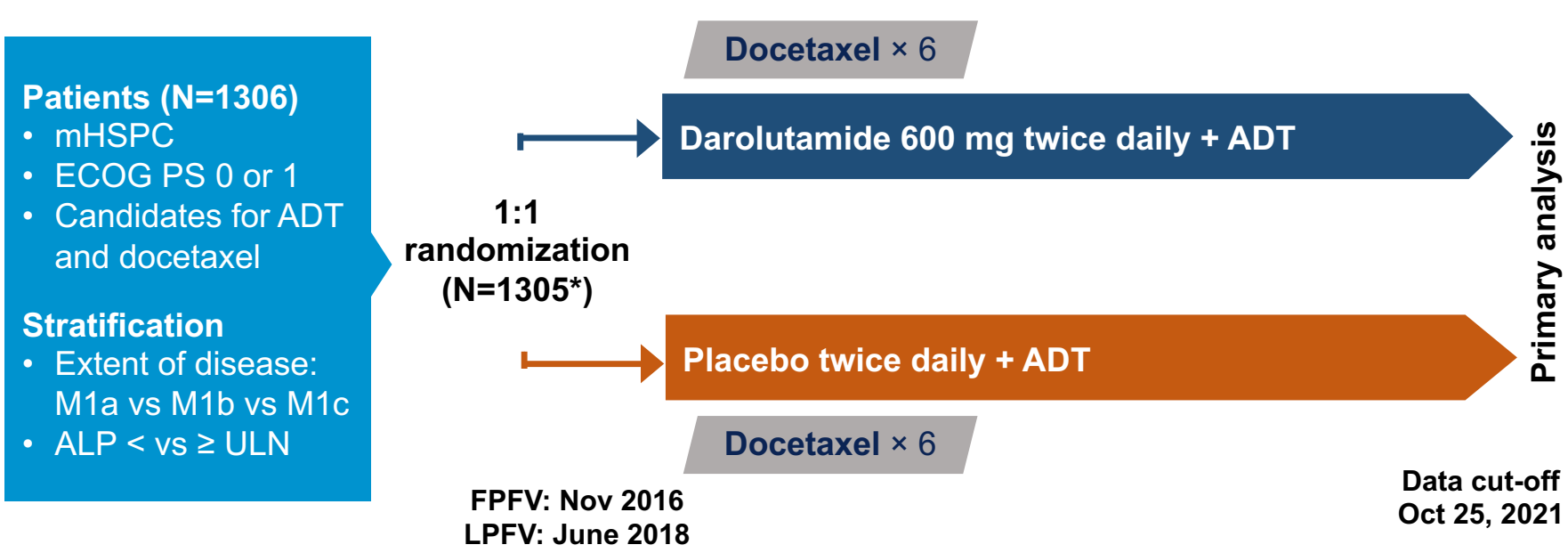
Low-volume patients



CHUM

ARASENS Study Design

- Global, randomized, double-blind, placebo-controlled, phase 3 study (NCT02799602)



Endpoints

Primary: Overall Survival

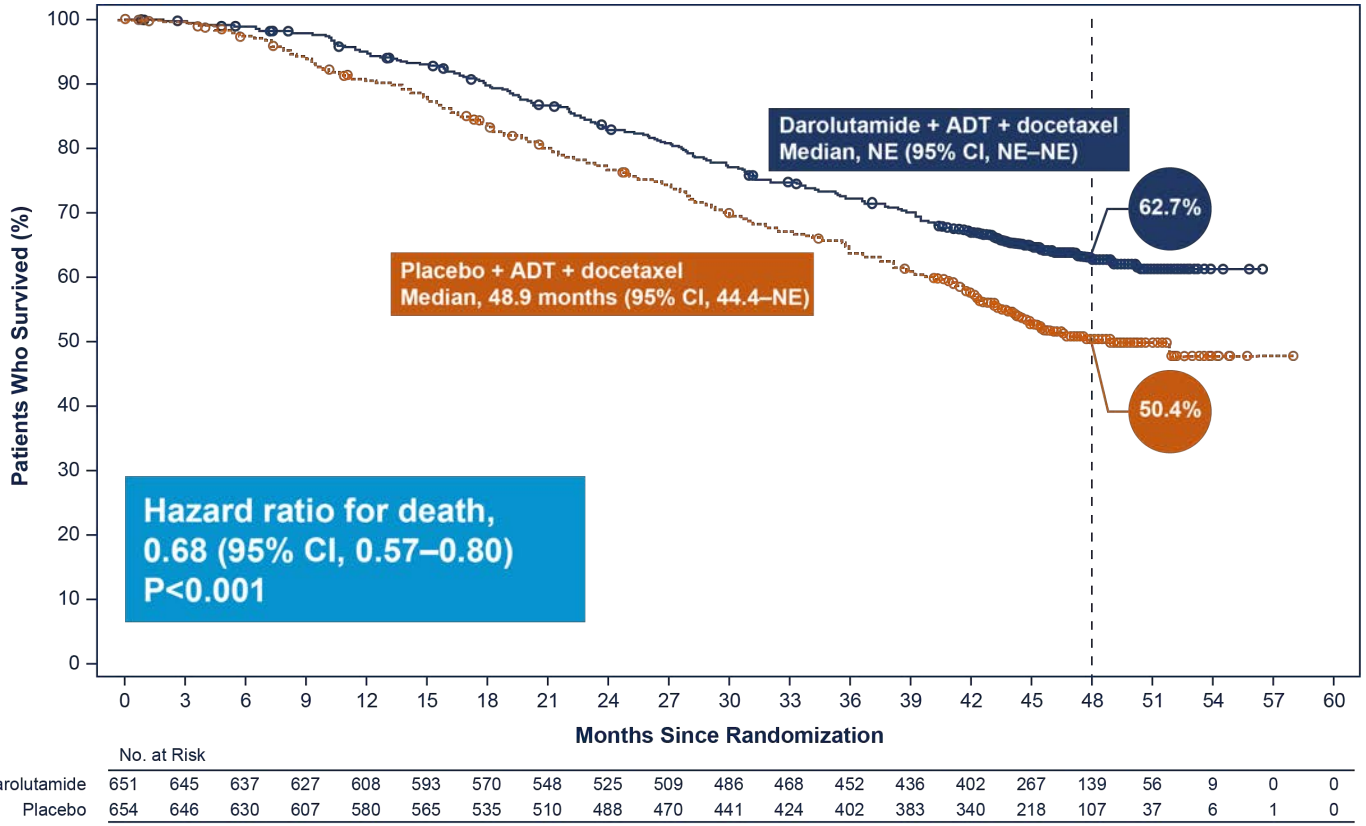
Secondary

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

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

CHUM

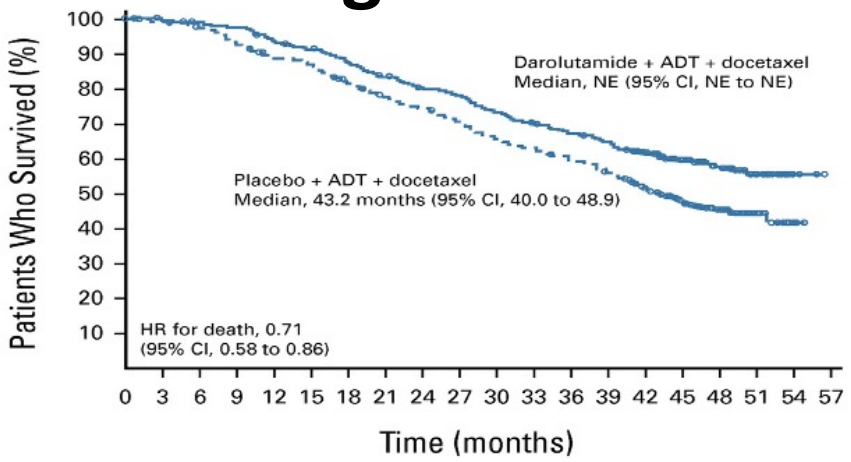
ARASENS: Overall Survival



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

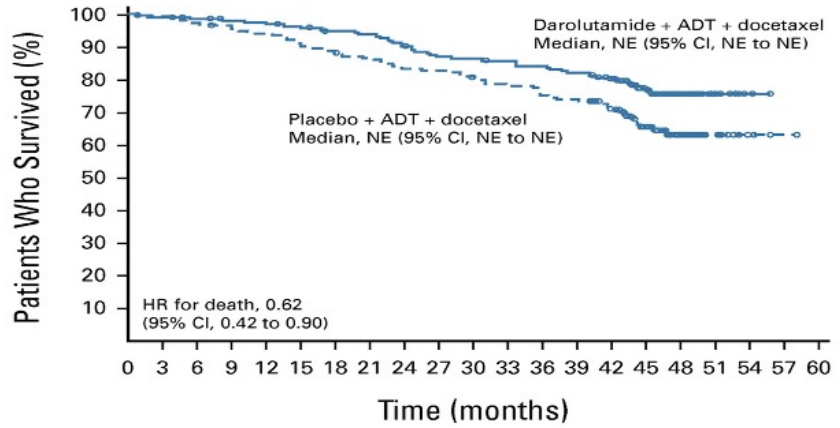
High Risk



No. of high-risk patients at risk:

Darolutamide	452	450	443	437	419	407	389	369	352	344	322	308	294	282	257	177	99	42	6	0
Placebo	460	453	443	423	400	392	367	346	330	313	290	277	261	245	215	148	72	24	3	0

Low Risk



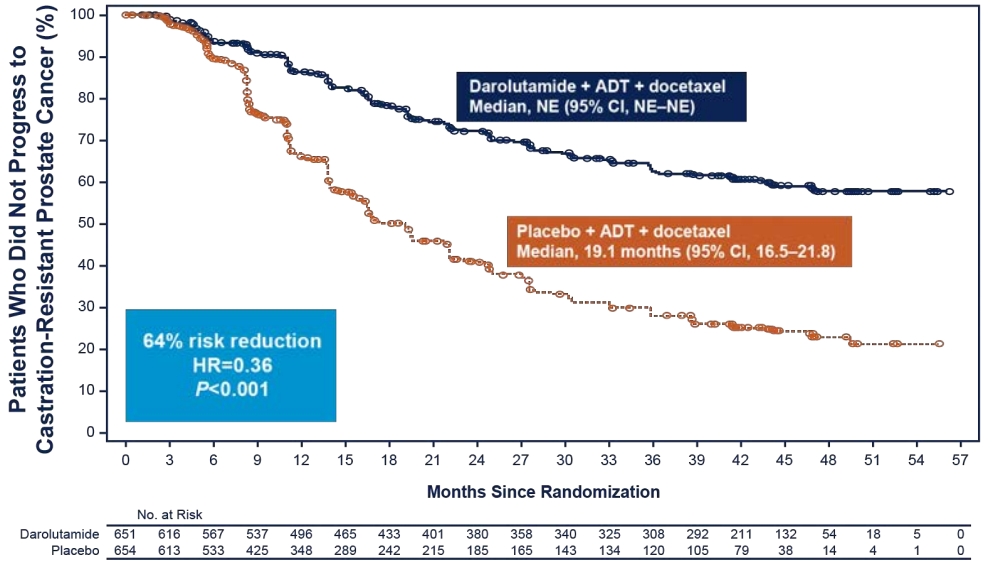
No. of low-risk patients at risk:

Darolutamide	199	195	194	190	189	186	181	179	173	165	164	160	158	154	145	90	40	14	3	0	0
Placebo	194	193	187	184	180	173	168	164	158	157	151	147	141	138	125	70	35	13	3	1	0

CHUM

Darolutamide significantly improved key secondary efficacy endpoints

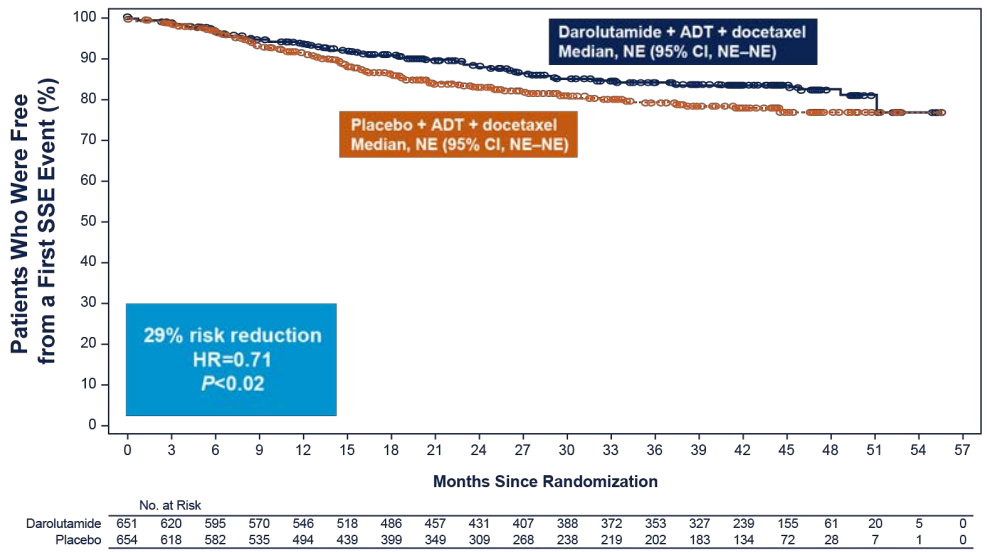
Time to CRPC



No. at Risk

Darolutamide	651	616	567	537	496	465	433	401	380	358	340	325	308	292	211	132	54	18	5	0
Placebo	654	613	533	425	348	289	242	215	185	165	143	134	120	105	79	38	14	4	1	0

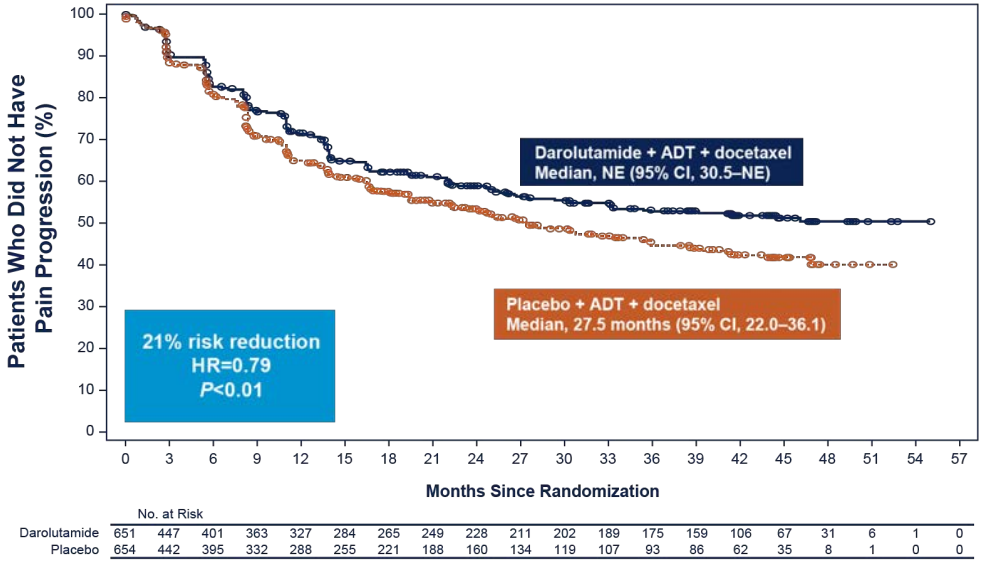
Time to first SSE



No. at Risk

Darolutamide	651	620	595	570	546	518	486	457	431	407	388	372	353	327	239	155	61	20	5	0
Placebo	654	618	582	535	494	439	399	349	309	268	238	219	202	183	134	72	28	7	1	0

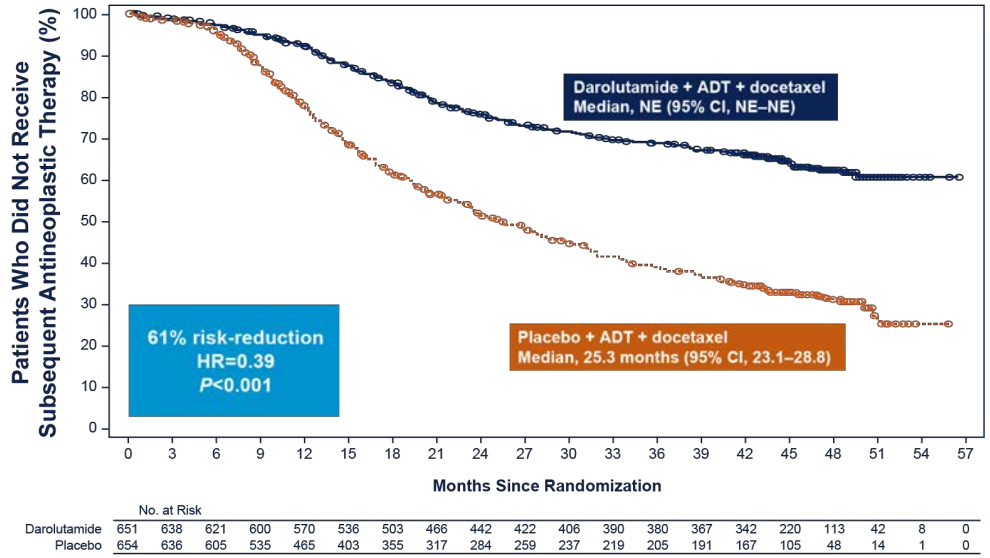
Time to pain progression



No. at Risk

Darolutamide	651	447	401	363	327	284	265	249	228	211	202	189	175	159	106	67	31	6	1	0
Placebo	654	442	395	332	288	255	221	188	160	134	119	107	93	86	62	35	8	1	0	0

Time to first subsequent antineoplastic therapy



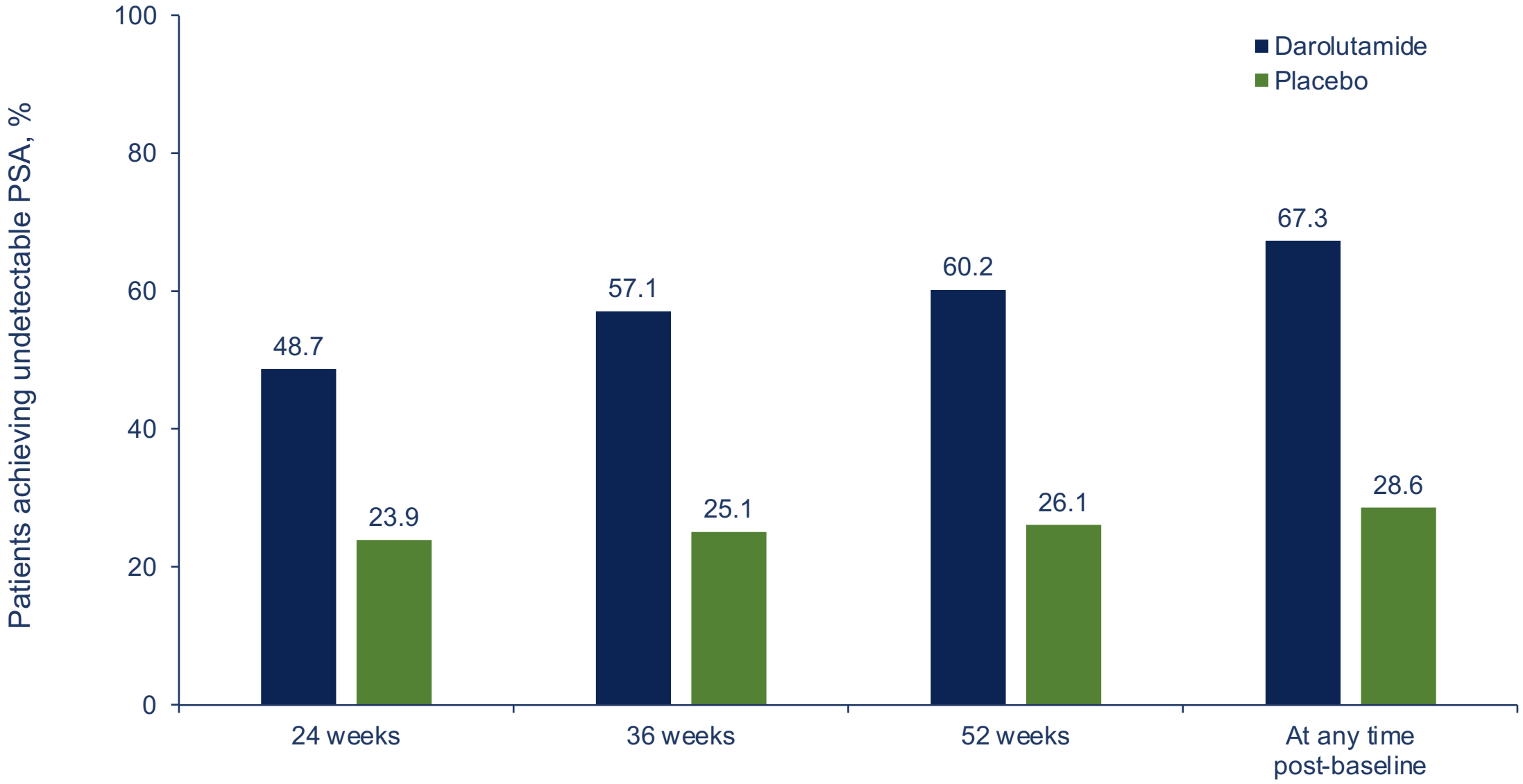
No. at Risk

Darolutamide	651	638	621	600	570	536	503	466	442	422	406	390	380	367	342	220	113	42	8	0
Placebo	654	636	605	535	465	403	355	317	284	259	237	219	205	191	167	105	48	14	1	0

Two-sided P values are presented.

CHUM

Objective: Undetectable (≤0.2) PSA Levels



Saad et al. AUA 2022

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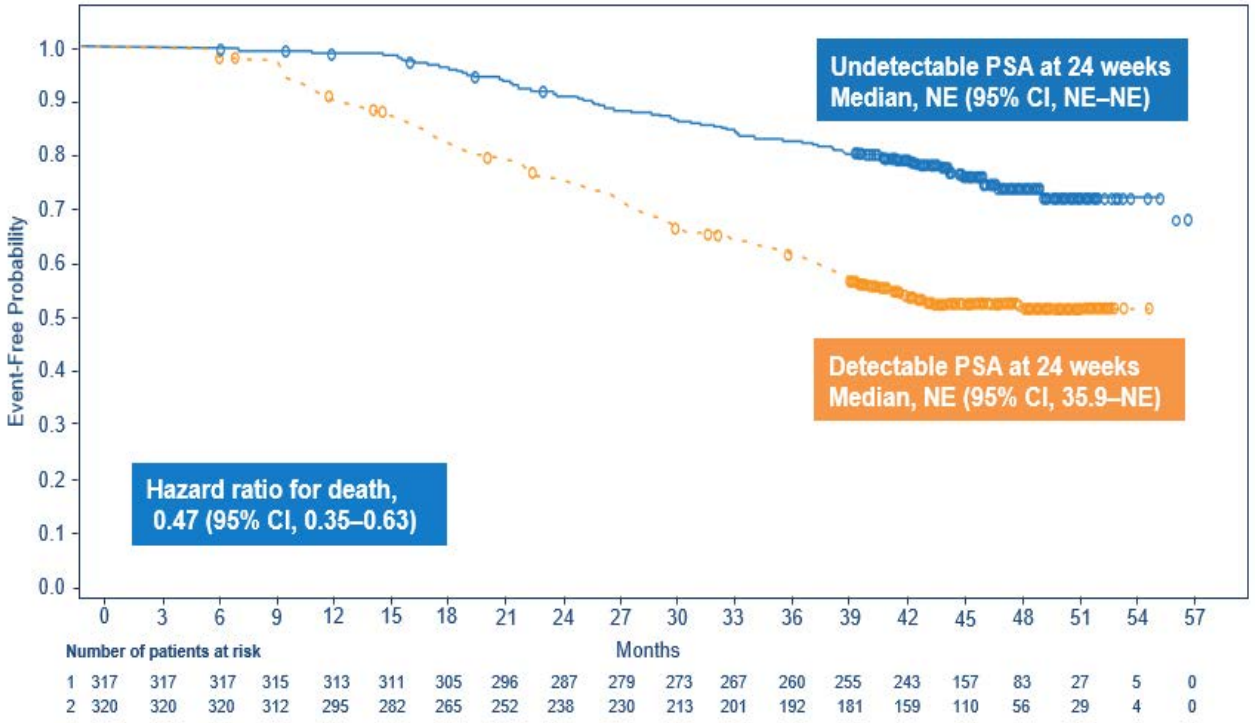
Results: Overall Survival

Undetectable PSA at 24 and 36 weeks was associated with a

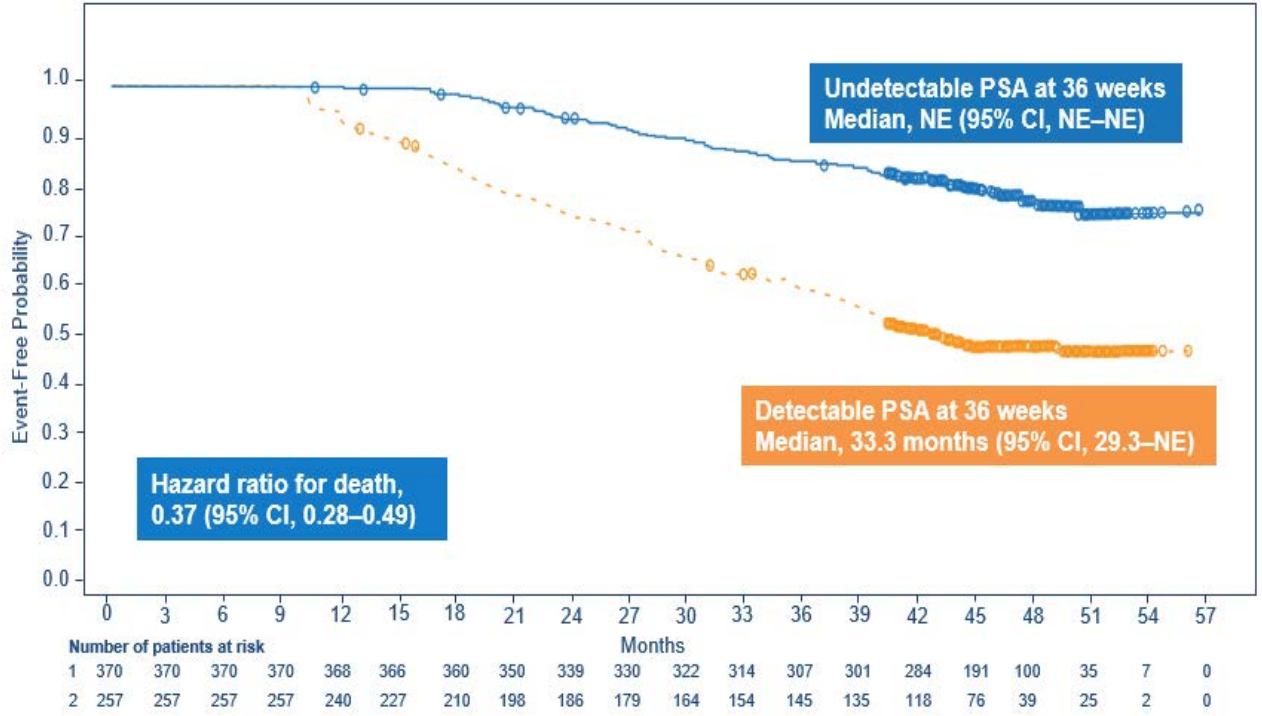
53% and 63% reduction in the risk of death

Darolutamide + ADT + docetaxel

Undetectable vs detectable PSA at 24 weeks



Undetectable vs detectable PSA at 36 weeks



Saad et al. AUA 2022

CHUM

Future and more questions

- Patients with mCSPC are at high risk of rapid progression to mCRPC and early death
  - Treatment beyond ADT is recommended in **all** patients
  - Adding NHT **must** be considered in patients who receive ADT + docetaxel

- Further intensification in some (trials ongoing)
  - Role of PARPi, radioligand therapy, immunotherapy etc.

- BUT De-intensification may make sense in some patients
  - Back to the concept of intermittant (but more intensive) therapy

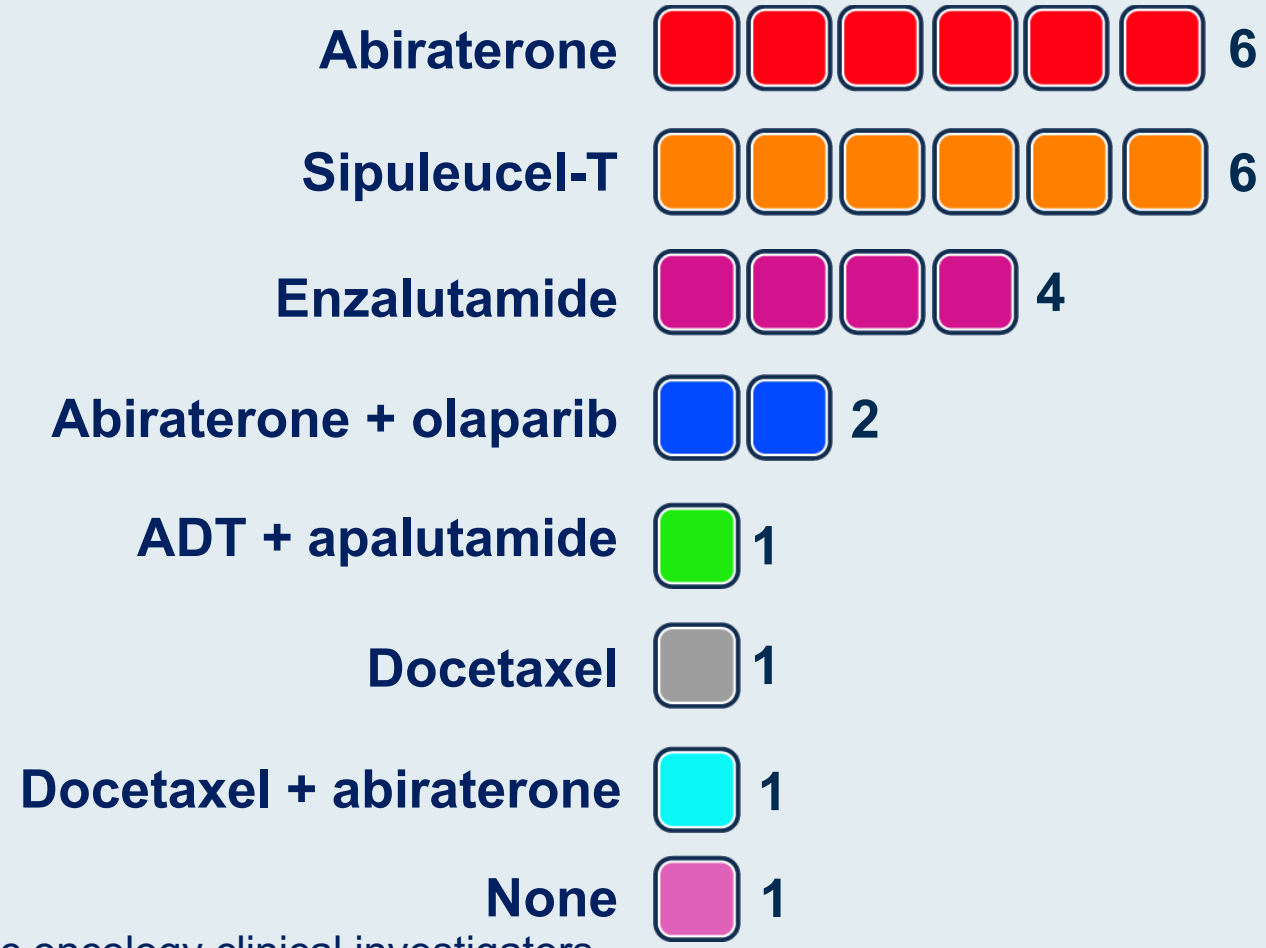
A multi D approach and research should be considered in all patients

CHUM

MODULE 3: Therapeutic Considerations for Patients with Newly Diagnosed Metastatic CRPC (mCRPC)

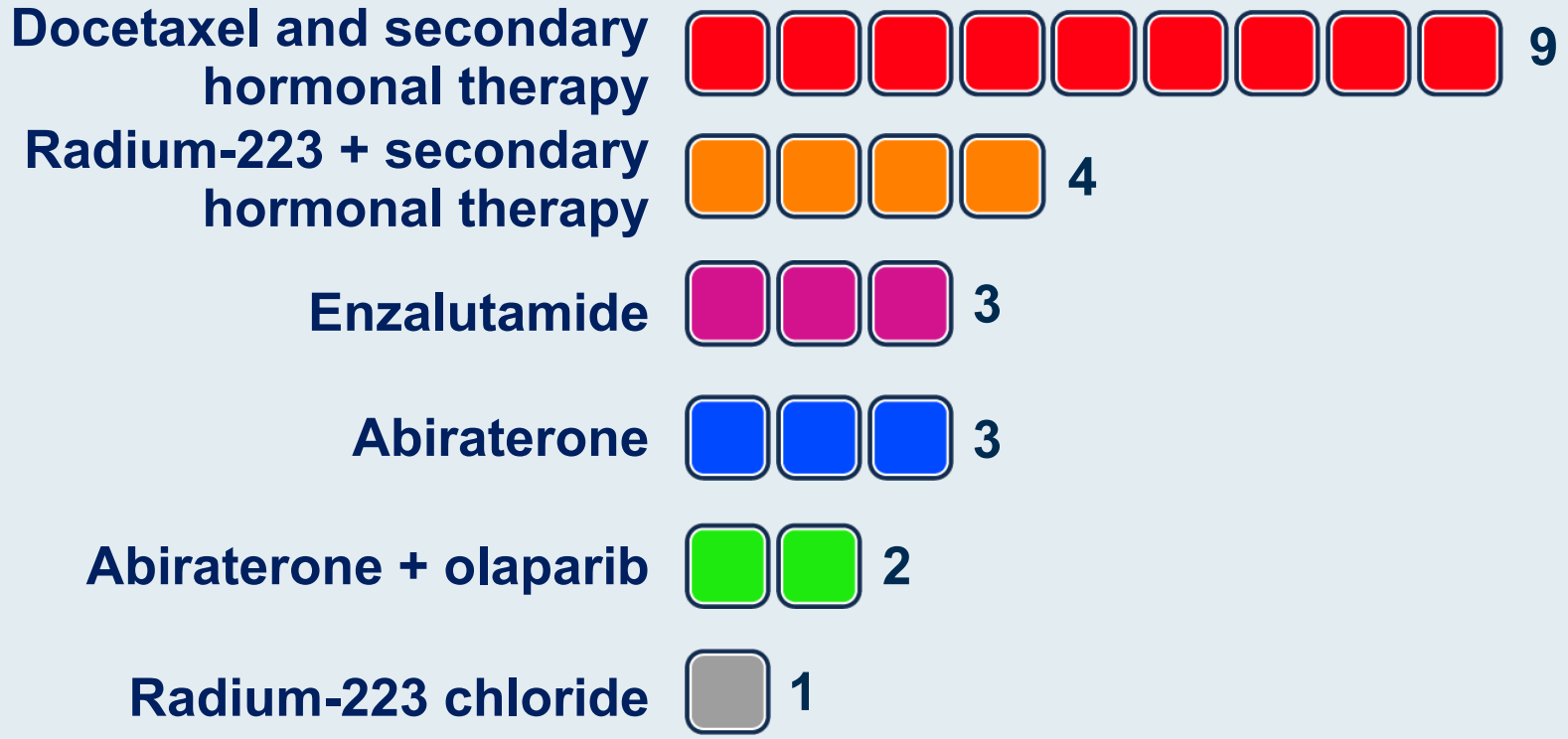
RTP
RESEARCH
TO PRACTICE

A 65-year-old man receiving ADT for M0 disease after radical prostatectomy is found to have asymptomatic bone metastases. Genetic testing is negative for homologous recombination repair (HRR) mutations. Regulatory and reimbursement issues aside, which systemic treatment would you most likely recommend?



Survey of urologic oncology clinical investigators

A 65-year-old man receiving ADT for M0 disease after radical prostatectomy is found to have widespread, moderately symptomatic bone metastases. Genetic testing is negative for HRR mutations. Regulatory and reimbursement issues aside, which systemic treatment would you most likely recommend?



Survey of urologic oncology clinical investigators

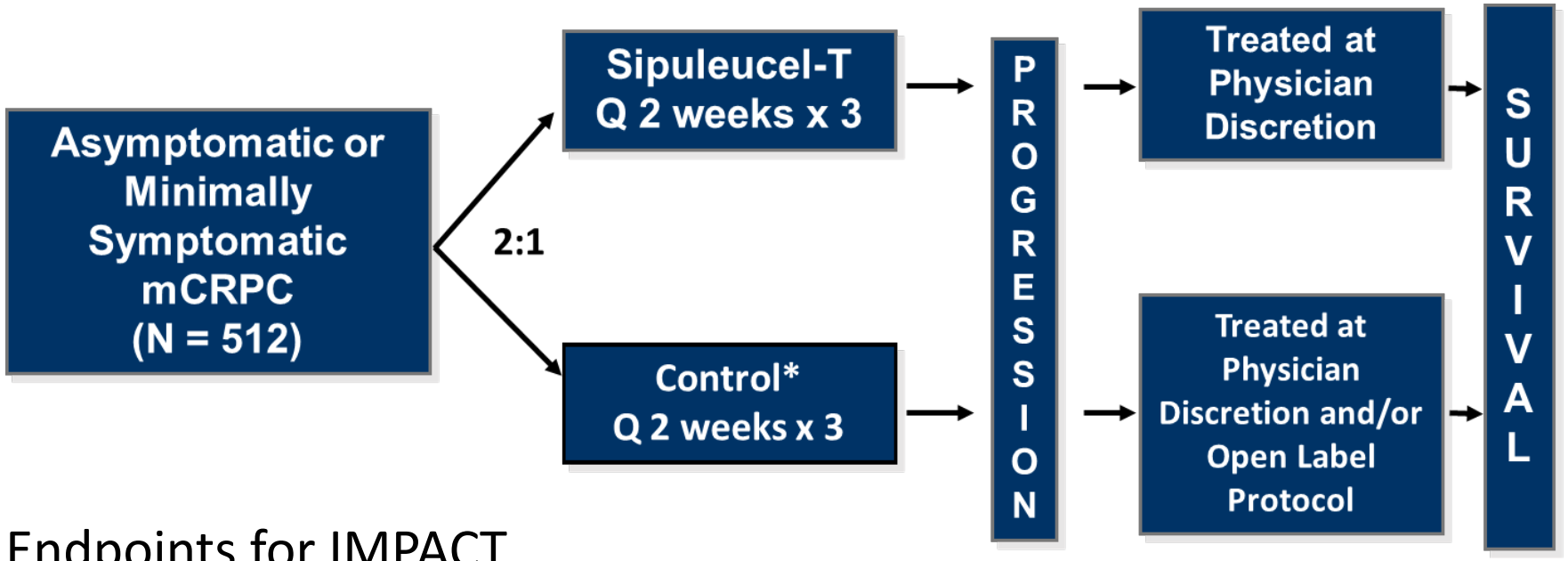
Therapeutic Considerations for Patients with Newly Diagnosed Metastatic CRPC (mCRPC)

Neal Shore, MD,FACS
GenesisCare,US
Carolina Urologic Research Center
Myrtle Beach, South Carolina

Overview

- Key efficacy and safety findings with sipuleucel-T
- Biologic basis for combining PARP inhibitors with ARSI for PCa
- Data with combination therapy (PARPi/ARSI): PROpel, MAGNITUDE and TALAPRO-2 studies *(<u>without</u> HRR gene mutations)*
- Biologic rationale for CDK4/6 inhibitors in PCa
- Study Design – CYCLONE 2 trial: abi/pred with or without abemaciclib

IMPACT, Phase 3 Study, NCT00065442
(Immunotherapy Prostate Adenocarcinoma Treatment)



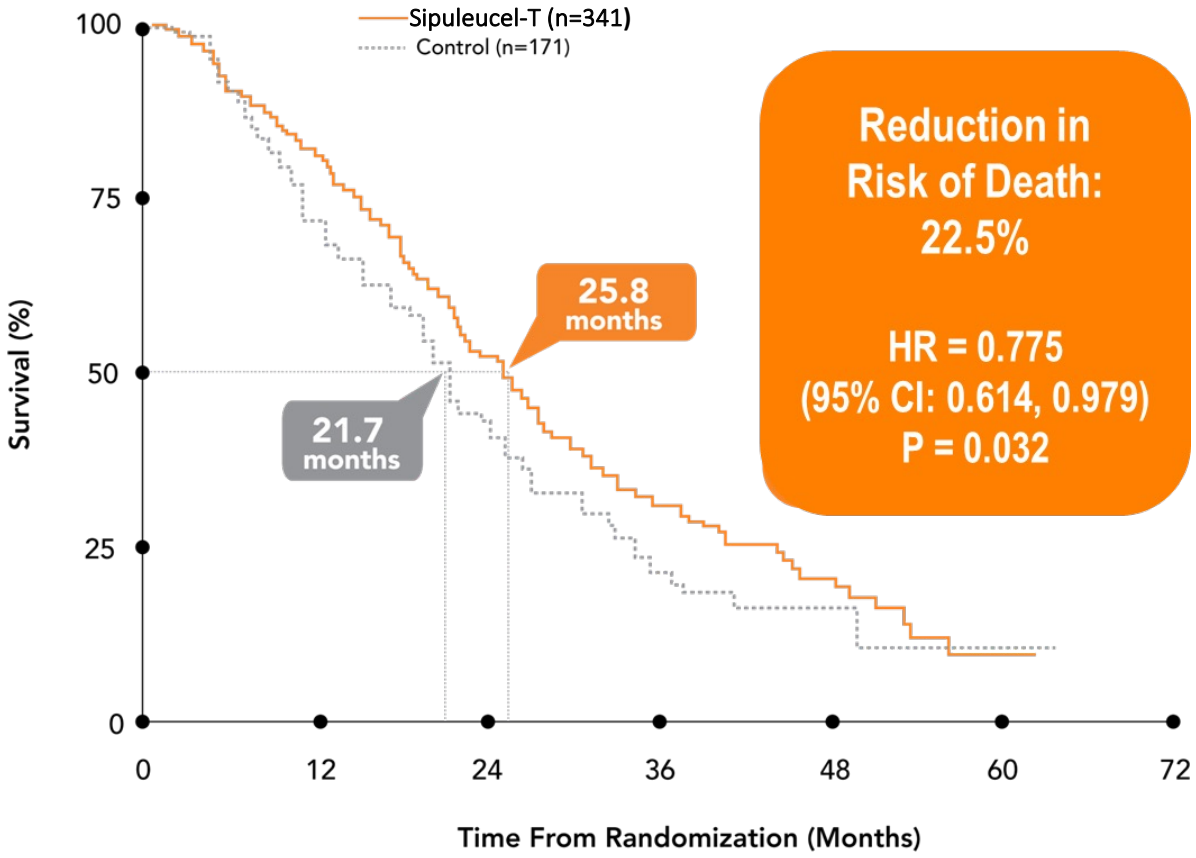
Endpoints for IMPACT

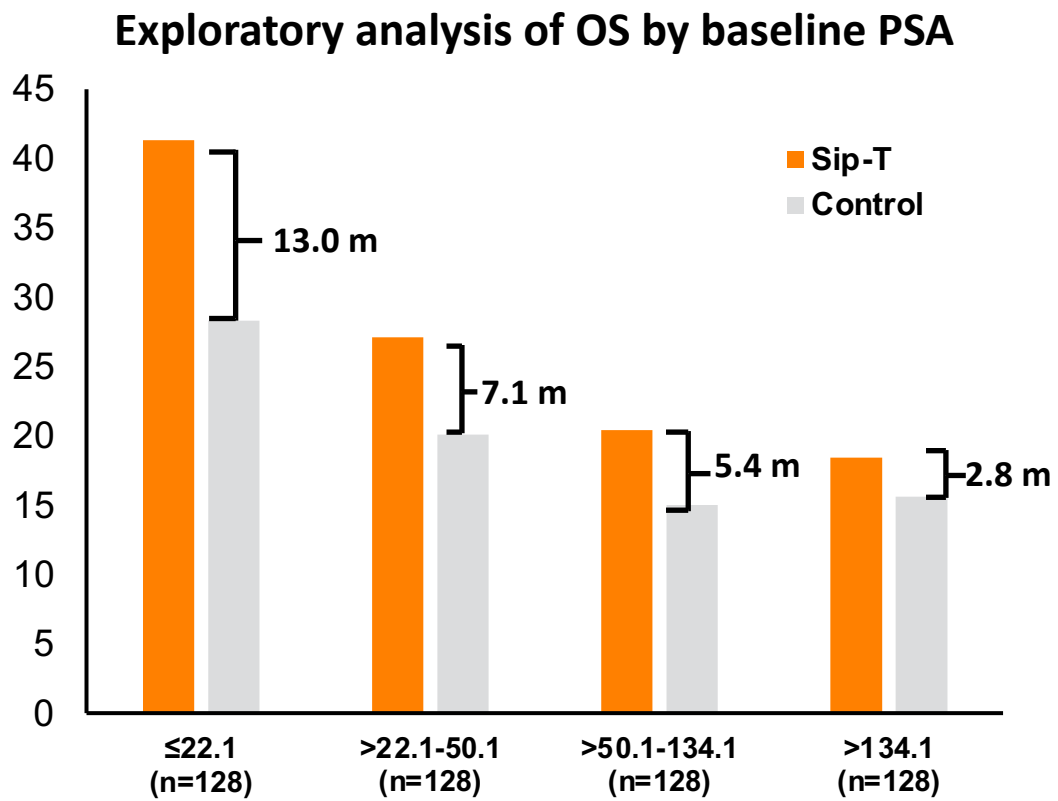
- *Primary endpoint*: Overall Survival
- *Secondary endpoint*: Time to Objective Disease Progression

* Control was nonactivated, autologous peripheral blood mononuclear cell
Note: Open label protocol: Control patients could have opted to receive active treatment with cryopreserved product

Kantoff PW, Higano CS, Shore ND, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. *N Engl J Med.* 2010;363(5):411-422. https://doi.org/10.1056/NEJMoa1001294.

IMPACT Primary Endpoint: Overall Survival





Kantoff PW, Higano CS, Shore ND, et al. *N Engl J Med.* 2010;363(5):411-422. https://doi.org/10.1056/NEJMoa1001294.

Schellhammer PF, Chodak G, Whitmore JB, et al. *Urology.* 2013;81(6):1297-1302. https://doi.org/10.1016/j.urology.2013.01.061.

IMPACT: Safety Profile

Most Common AEs (≥15%) in the sipuleucel-T Group*

	Chills	Fatigue	Fever	Back pain	Nausea	Joint ache	Headache
Sip-T (n=601)	53.1%	41.1%	31.3%	29.6%	21.5%	19.6%	18.1%
Control (n=303)	10.9%	34.7%	9.6%	28.7%	14.9%	20.5%	6.6%

The majority of adverse events reported with sipuleucel-T (67.4%) were mild to moderate and consistent with a response to immunotherapy

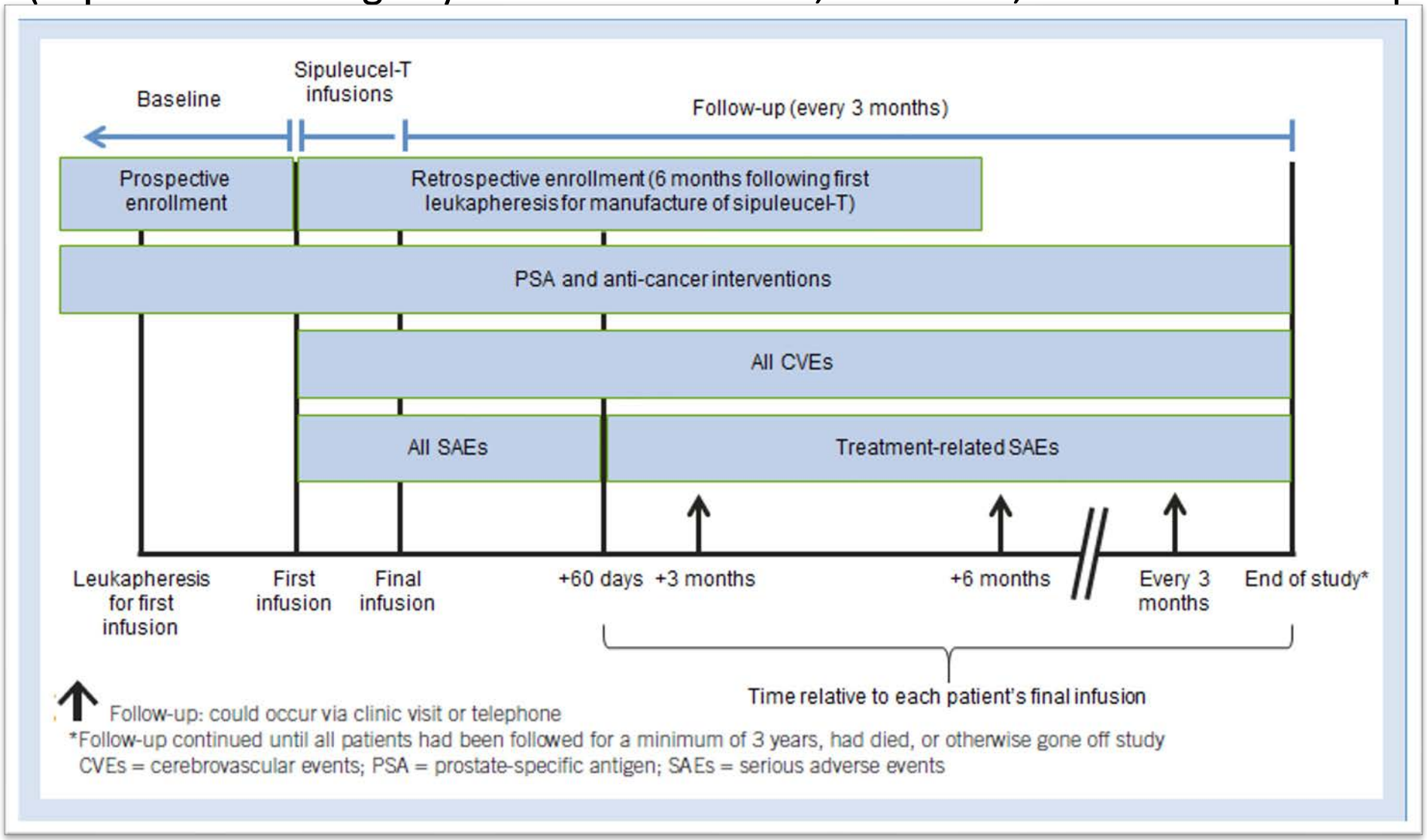
Sipuleucel-T does not require dosage adjustments, monitoring of liver/kidney function, or concomitant steroids

- 1.5% of patients in the pivotal trial discontinued treatment with sipuleucel-T due to adverse events
- 91.8% of patients in the sipuleucel-T group received a complete course of therapy

*All grades reported in ≥15% of patients randomized to Sipuleucel-t; the safety analysis is based on 601 patients with prostate cancer in the Sipuleucel-t group who underwent at least 1 leukapheresis procedure in Phase 3 clinical trials.
AE=adverse events.

PROCEED: Commitment Study, NCT0136890

(Sipuleucel-T Registry for the Observation, Collection, and Evaluation of Experience Data)



Primary Endpoint: Subject Incidence of Cerebrovascular Events

Secondary Endpoint: Overall Survival

Higano CS, Armstrong AJ, Sartor AO, et al. *Cancer.* 2019;125:4172-4180. https://doi.org/10.1002/cncr.32445.

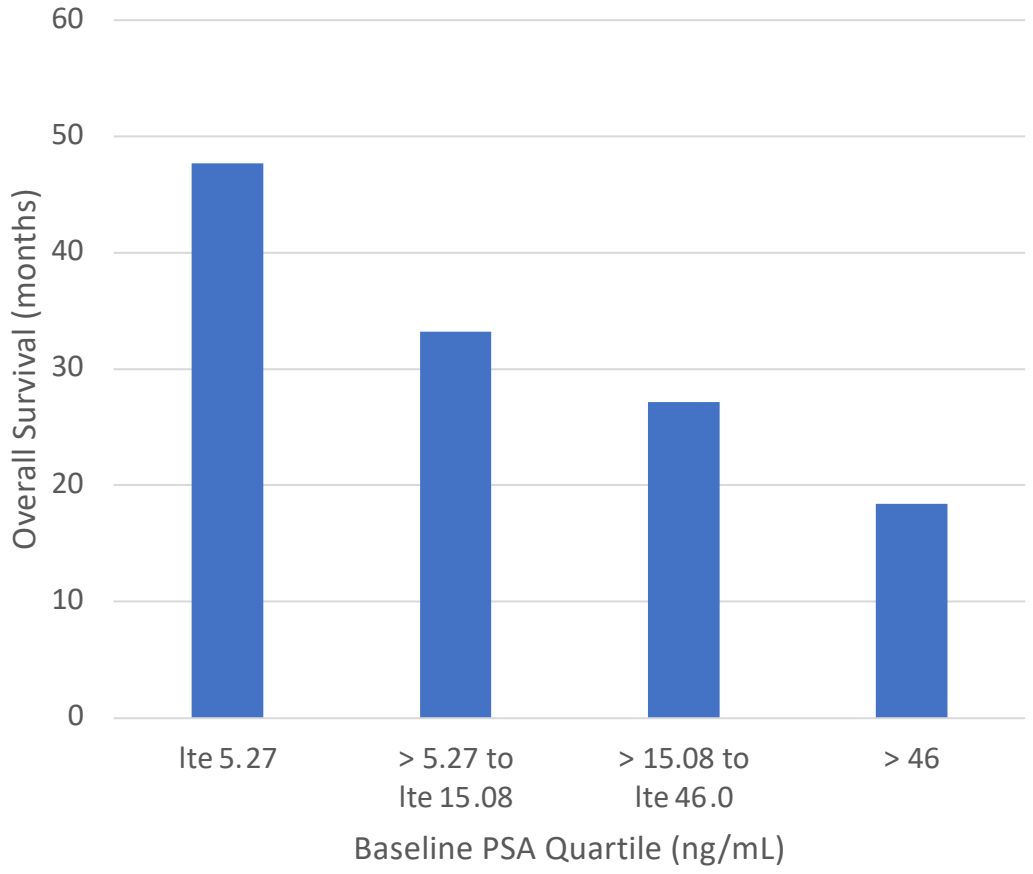
PROCEED: Serious Adverse Events

SAEs	Total population (n = 1902) Regardless of causality n (%)	
	All-grade	Grade 3–5
Any SAE	260 (13.7)	175 (9.2)
Disease progression	28 (1.5)	25 (1.3)
Cerebrovascular accident	16 (0.8)	11 (0.6)
Chills	13 (0.7)	0
Syncope	12 (0.6)	7 (0.4)
Device-related infection	10 (0.5)	7 (0.4)
Acute kidney injury	8 (0.4)	7 (0.4)
Deep vein thrombosis	8 (0.4)	2 (0.1)
Pulmonary embolism	8 (0.4)	7 (0.4)
Anemia	7 (0.4)	2 (0.1)
Dyspnea	7 (0.4)	6 (0.3)
Chest pain	6 (0.3)	2 (0.1)
Myocardial infarction	6 (0.3)	5 (0.3)
Pyrexia	6 (0.3)	2 (0.1)
Subdural hematoma	6 (0.3)	6 (0.3)
TIA	6 (0.3)	1 (0.1)
Cerebral hemorrhage	5 (0.3)	5 (0.3)
Pneumonia	5 (0.3)	3 (0.2)
Cerebral infarction	4 (0.2)	4 (0.2)

The most common SAEs were disease progression, cerebrovascular accident, chills, syncope and device-related infection, pulmonary embolism and pyrexia

Higano CS, Armstrong AJ, Sartor AO, et al. Real-world outcomes of sipuleucel-T treatment in PROCEED, a prospective registry of men with metastatic castration-resistant prostate cancer. *Cancer.* 2019;125:4172-4180. https://doi.org/10.1002/cncr.32445.

PROCEED: Overall Survival by Baseline PSA Quartile

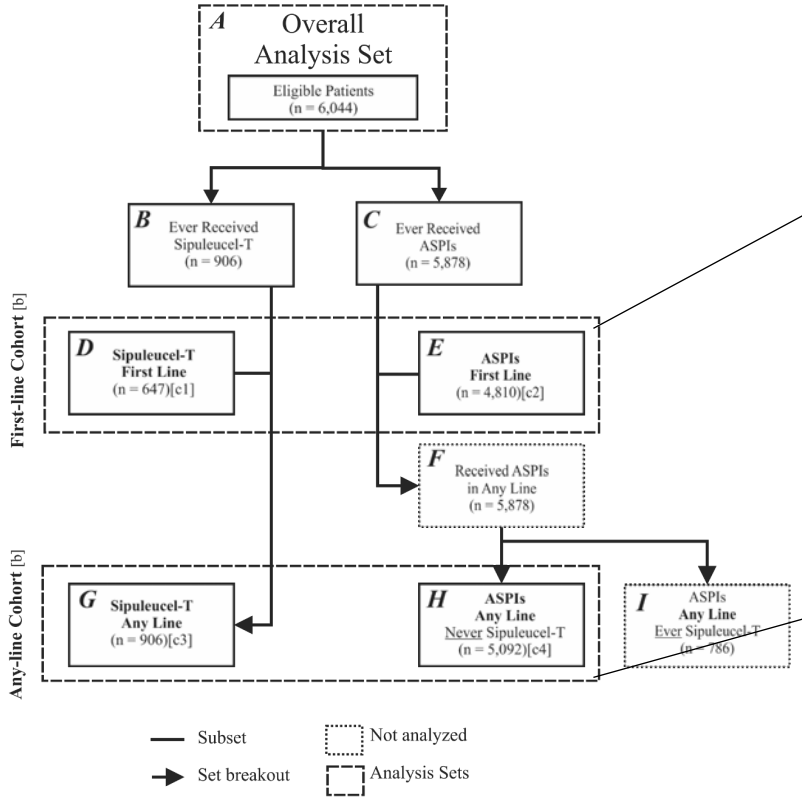


- The hazard ratios for each quartile versus the lowest quartile were:
  - Q2 vs Q1, 1.6 (95% CI, 1.3-1.9)
  - Q3 vs Q1, 2.0 (95% CI, 1.7-2.4)
  - Q4 vs Q1, 3.0 (95% CI, 2.6-3.6)

Abbreviations: CI, confidence interval; lte, less than or equal to; PSA: prostate-specific antigen; Q#, #th quartile;

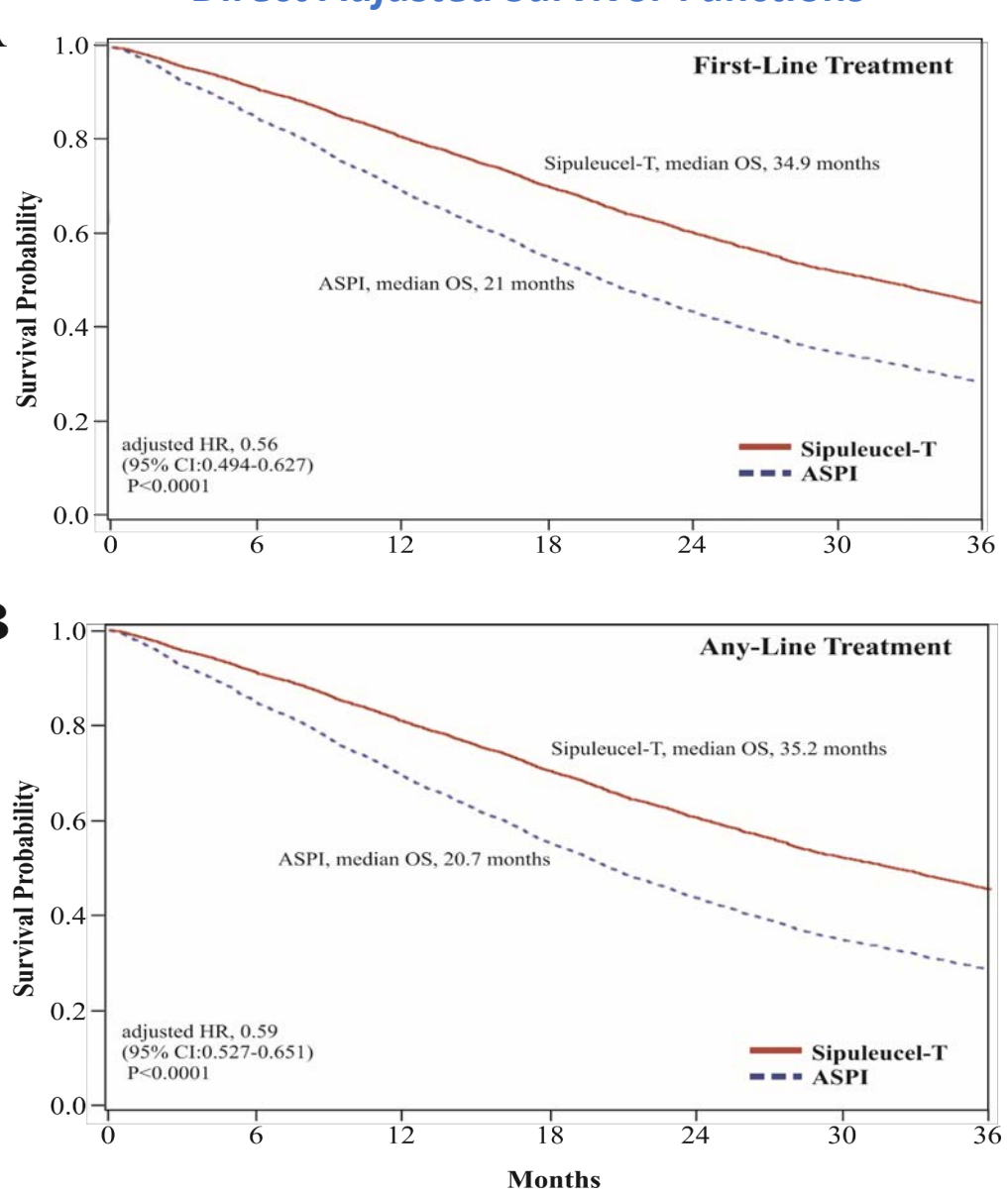
Higano CS, Armstrong AJ, Sartor AO, et al. Real-world outcomes of sipuleucel-T treatment in PROCEED, a prospective registry of men with metastatic castration-resistant prostate cancer. *Cancer.* 2019;125:4172-4180. https://doi.org/10.1002/cncr.32445.

McKay et al: Overall Survival



[a] **ASPI** treatments include abiraterone or enzalutamide.
[b] Analysis sets within each cohort are exclusive of one another.
[c] Number of men excluded due to missing data (each was missing data about race; c1<11; c2=34; c3=11; c4=35)

Direct Adjusted Survivor Functions



McKay RR, Hafron JM, Ferro C, et al. A Retrospective Observational Analysis of Overall Survival with Sipuleucel-T in Medicare Beneficiaries Treated for Advanced Prostate Cancer. *Adv Ther.* 2020;37(12):4910-4929. https://doi.org/10.1007/s12325-020-01509-5.

McKay et al: Medicare Analyses *Top-Line Results*

- We analyzed data from male Medicare beneficiaries who started mCRPC treatment in 2014 and received either sipuleucel-T or androgen-receptor signaling pathway inhibitors (ASPIs) and who either had 3 years of data available or died during that time.
- We observed that sipuleucel-T use was independently associated with longer overall survival (OS), after controlling for known confounders, regardless of line of use.

    - Comparing first-line use, we observed a **13.9-month difference in OS**
        - *34.9 months* of OS with sipuleucel-T (n=647) and
        - *21.0 months* of OS with ASPIs (n=4,810)
        - Adjusted hazard ratio, 0.56 (95%CI: 0.494-0.627)

    - Comparing any-line use, we observed a **14.5-month difference in OS**
        - *35.2 months* of OS in patients who ever received sipuleucel-T (n=906) and
        - *20.7 months* of OS in patients who received ASPIs and never sipuleucel-T (n=5,092)
        - Adjusted hazard ratio, 0.59 (95%CI: 0.527-0.651)

McKay RR, Hafron JM, Ferro C, et al. Adv Therapy.
https://doi.org/10.1007/s12325-020-01509-5

Phase 3 trial of PARPi + AR signaling inhibitor in 1st line mCRPC setting

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

1- Clarke NW et al., NEJM Evidence. 2022 Aug 23;1(9):EVIDoa2200043.

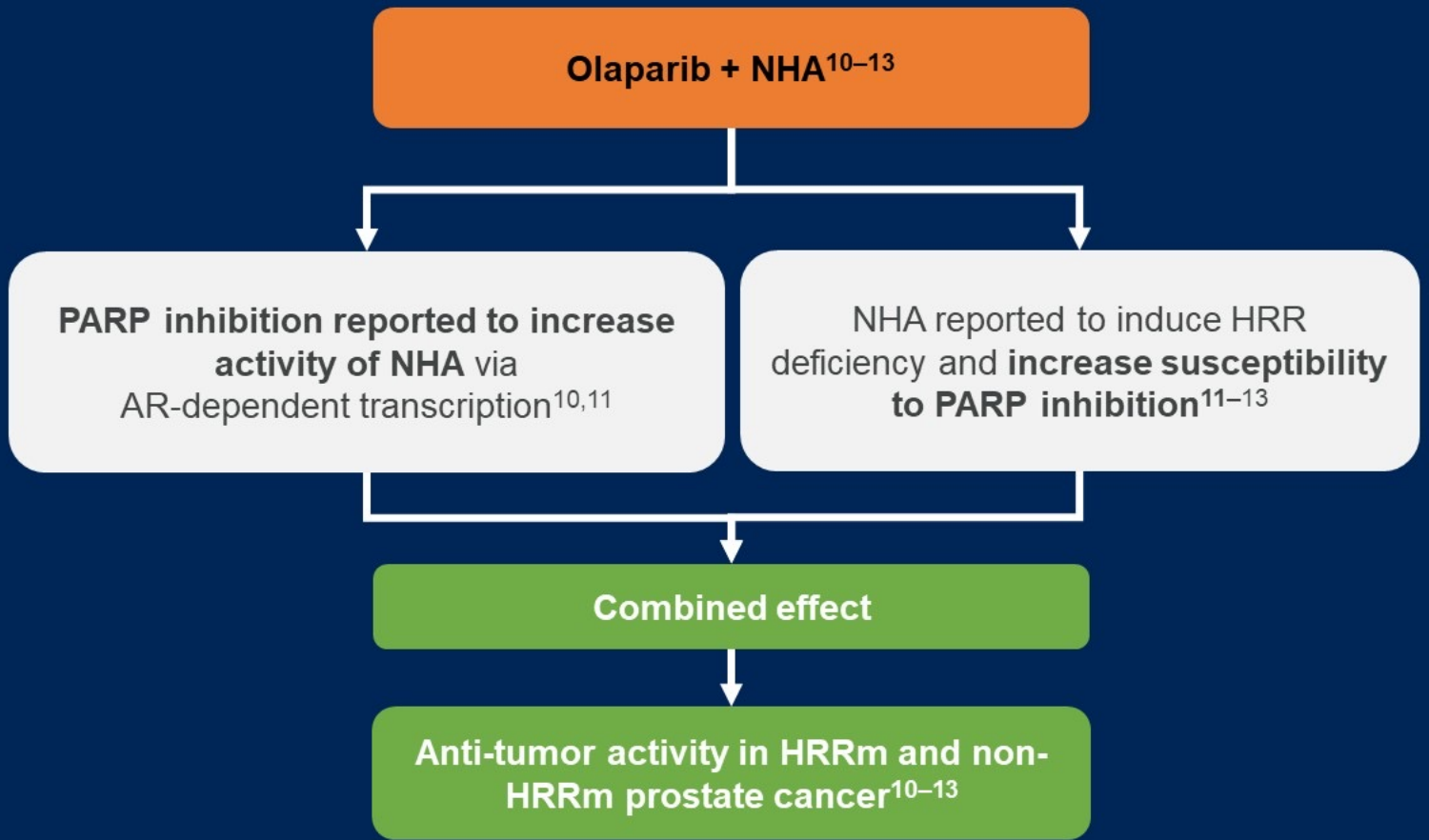
2- Chi KN et al., JCO. 2022 Feb 20;40(6_suppl):12–12. Kim Chi, (2022 Genitourinary cancers symposium (ASCO GU). Abstract #12)

ASCO® Genitourinary Cancers Symposium

PROpel: phase III trial of olaparib and abiraterone versus placebo and abiraterone as first-line therapy for patients with metastatic castration-resistant prostate cancer

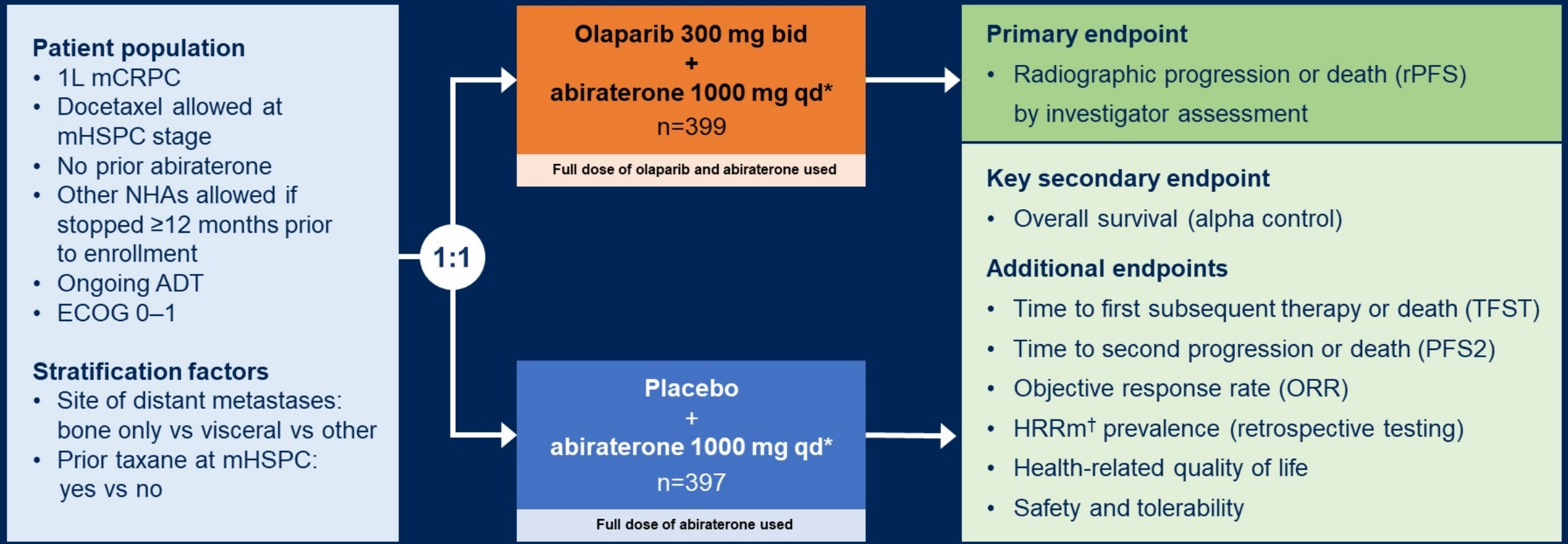
Fred Saad, Andrew J. Armstrong, Antoine Thiery-Vuillemin, Mototsugu Oya, Eugenia Loredo, Giuseppe Procopio, Juliana de Menezes, Gustavo Girotto, Cagatay Arslan, Niven Mehra, Francis Parnis, Emma Brown, Friederike Schlürmann, Jae Young Joung, Mikio Sugimoto, Christian Poehlein, Elizabeth A. Harrington, Chintu Desai, Jinyu Kang, and Noel Clarke

PROpel: rationale for combining olaparib and abiraterone



AR, androgen receptor; HRR, homologous recombination repair; NHA, next-generation hormonal agent; PARP, poly (ADP-ribose) polymerase.

PROpel: a global randomized double-blind phase III trial

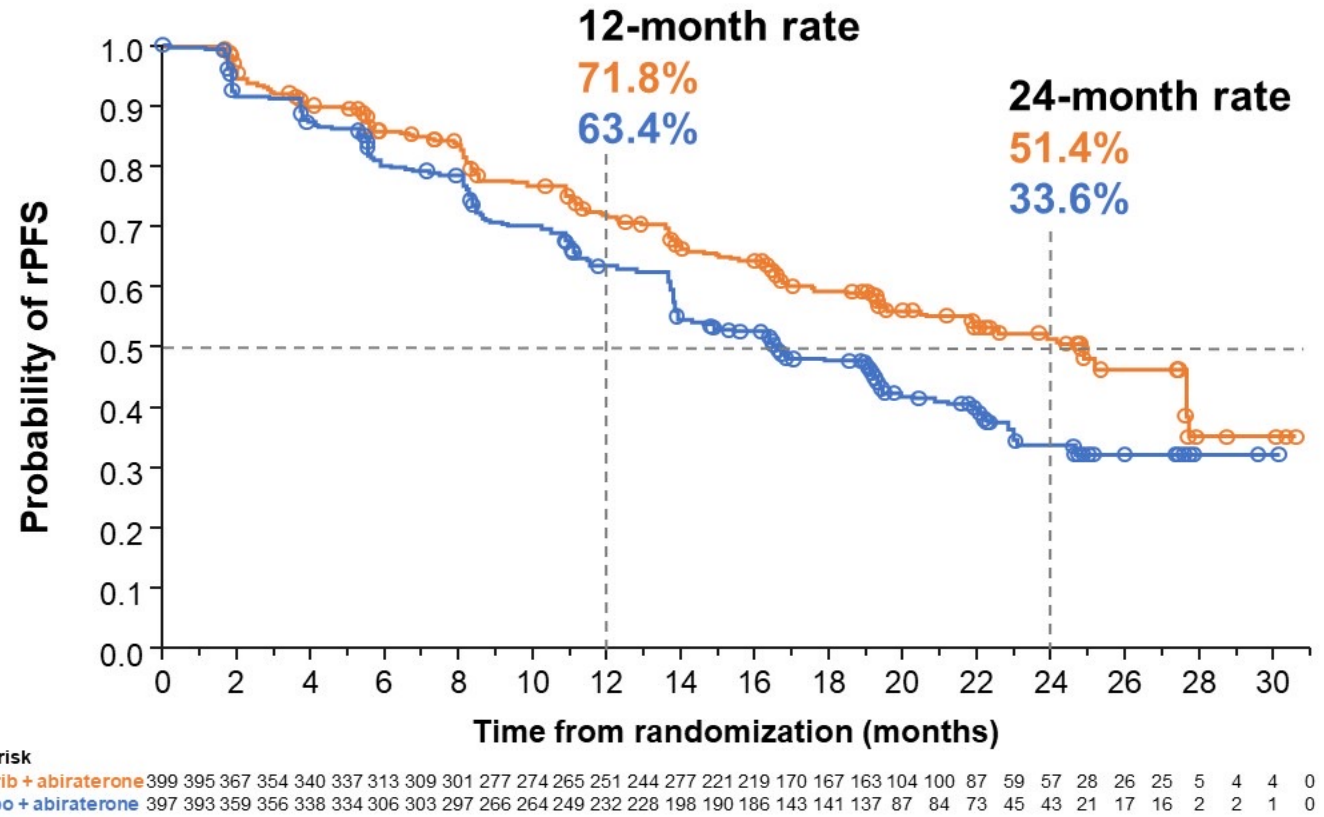


First patient randomized: Nov 2018; Last patient randomized: Mar 2020; DCO1: July 30, 2021, for interim analysis of rPFS and OS.
Multiple testing procedure is used in this study: 1-sided alpha of 0.025 fully allocated to rPFS. If the rPFS result is statistically significant, OS to be tested in a hierarchical fashion with alpha passed on to OS.

*In combination with prednisone or prednisolone 5 mg bid. †HRRm, homologous recombination repair mutation, including 14 genes panel.
ADT, androgen deprivation therapy; bid, twice daily; ECOG, Eastern Cooperative Oncology Group; mHSPC, metastatic hormone sensitive prostate cancer; qd, daily

PROpel primary endpoint: rPFS by investigator assessment

34% risk reduction of progression or death with olaparib + abiraterone



	Olaparib + abiraterone (n=399)	Placebo + abiraterone (n=397)
Events, n (%)	168 (42.1)	226 (56.9)
Median rPFS (months)	24.8	16.6
HR (95% CI)	0.66 (0.54–0.81); *P*<0.0001	

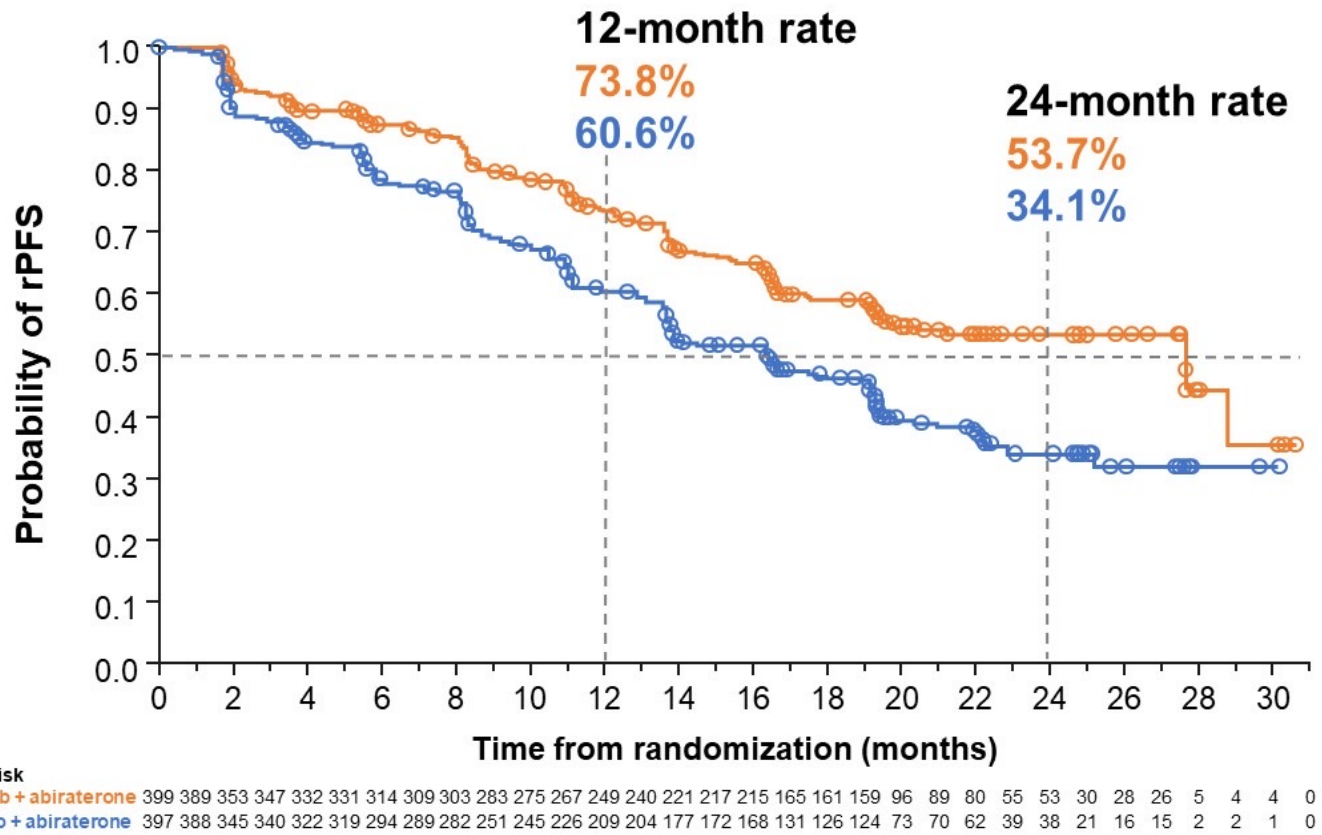
Pre-specified 2-sided alpha: 0.0324

Median rPFS improvement of 8.2 months favors olaparib + abiraterone*

Events: 394; Maturity 49.5%
*In combination with prednisone or prednisolone
CI, confidence interval; HR, hazard ratio.

PROpel: rPFS by blinded independent central review*

39% risk reduction of progression or death with olaparib + abiraterone
Highly consistent with the primary analysis



	Olaparib + abiraterone (n=399)	Placebo + abiraterone (n=397)
Events, n (%)	157 (39.3)	218 (54.9)
Median rPFS (months)	27.6	16.4
HR (95% CI)	0.61 (0.49–0.74) *P*<0.0001†	

Median rPFS improvement of 11.2 months favors olaparib + abiraterone‡

*Predefined sensitivity analysis. †Nominal. ‡In combination with prednisone or prednisolone

PROpel: conclusions

- **PROpel met its primary endpoint demonstrating a statistically significant and clinically meaningful rPFS benefit in the ITT population of patients with mCRPC treated with abiraterone + olaparib versus abiraterone + placebo**
  - Median 24.8 months vs 16.6 months, HR 0.66 (95% CI 0.54–0.81); *P*<0.0001
- **OS trend observed with abiraterone + olaparib versus abiraterone was sustained at final pre-specified analysis**
  - Abiraterone + olaparib prolonged OS by >7 months versus standard-of-care abiraterone
  - Median OS of >42 months is the longest reported to date in a Phase III trial in 1L mCRPC
- **rPFS and OS benefit was observed across subgroups**
- **The safety profile remained consistent over time, with no new signals observed**
- **Overall results support combination treatment with abiraterone + olaparib as an important new 1L treatment option for patients with mCRPC**

ASCO® Genitourinary Cancers Symposium

Phase 3 MAGNITUDE study: First results of niraparib (NIRA) with abiraterone acetate and prednisone (AAP) as first-line therapy in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) with and without homologous recombination repair (HRR) gene alterations

Kim N. Chi,[1] Dana E. Rathkopf,[2] Matthew R. Smith,[3] Eleni Efstathiou,[4] Gerhardt Attard,[5] David Olmos,[6] Ji Youl Lee,[7] Eric J. Small,[8] Andrea J. Pereira de Santana Gomes,[9] Guilhem Roubaud,[10] Marniza Saad,[11] Bogdan Zurawski,[12] Valerii Sakalo,[13] Gary E. Mason,[14] Adam del Corral,[15] George Wang,[14] Daphne Wu,[16] Brooke Diorio,[17] Angela Lopez-Gitlitz,[16] Shahneen Sandhu[18]

[1]University of British Columbia, BC Cancer – Vancouver Center, Vancouver, BC, Canada; [2]Memorial Sloan Kettering Cancer Center and Weill Cornell Medicine, New York, NY, USA; [3]Massachusetts General Hospital Cancer Center and Harvard Medical School, Boston, MA, USA; [4]Houston Methodist Cancer Center, Houston, TX, USA; [5]University College London, London, UK; [6]Department of Medical Oncology, Hospital Universitario 12 de Octubre, Instituto de Investigación Sanitaria Hospital 12 de Octubre (imas12), Madrid, Spain; [7]Department of Urology Cancer Center, Seoul St. Mary's Hospital, The Catholic University of Korea, Seoul, South Korea; [8]Helen Diller Family Comprehensive Cancer Center, University of California San Francisco, San Francisco, CA, USA; [9]Liga Norte Riograndense Contra o Câncer, Natal, Brazil; [10]Department of Medical Oncology, Institut Bergonié, Bordeaux, France; [11]Department of Clinical Oncology, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia; [12]Department of Outpatient Chemotherapy, Professor Franciszek Lukaszczyk Oncology Center, Bydgoszcz, Poland; [13]Institute of Urology named after Academician OF Vozianov of NAMS of Ukraine, Kyiv, Ukraine; [14]Janssen Research & Development, Spring House, PA, USA; [15]Janssen Research & Development, Bridgewater, NJ, USA; [16]Janssen Research & Development, Los Angeles, CA, USA; [17]Janssen Research & Development, Titusville, NJ, USA; [18]Peter MacCallum Cancer Center and the University of Melbourne, Melbourne, Australia

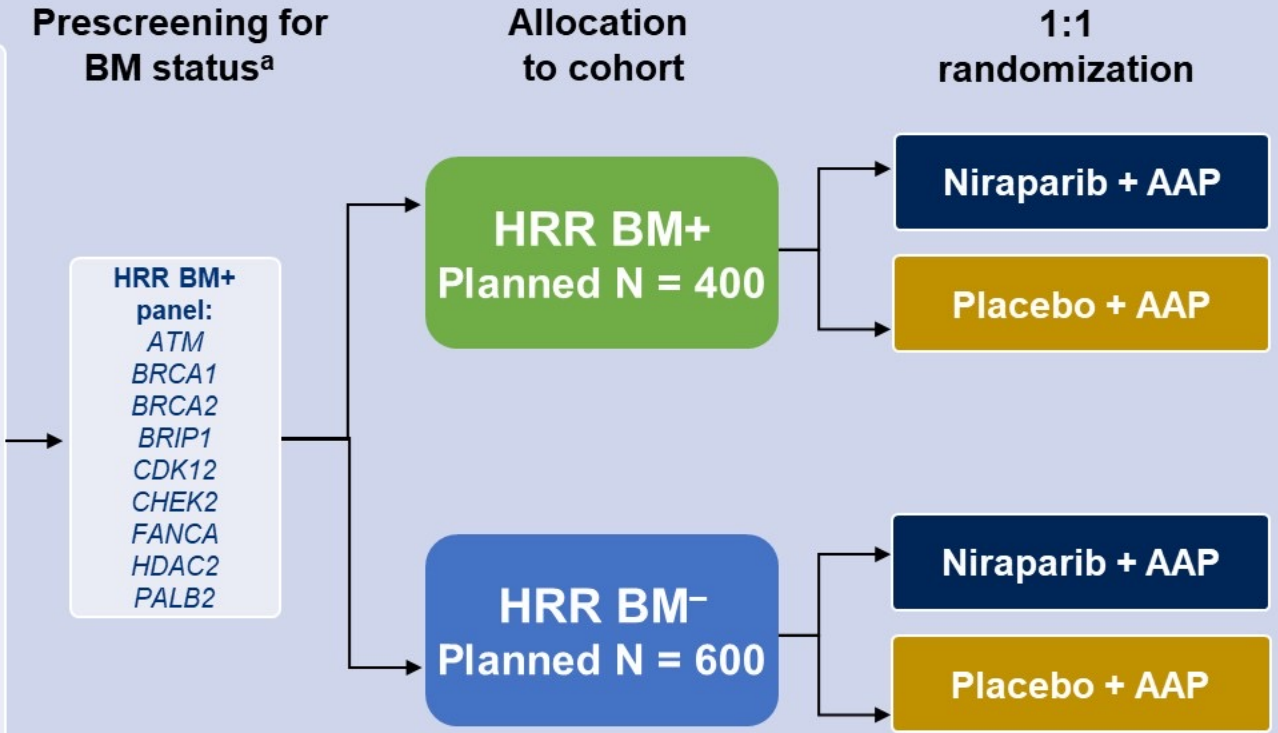
MAGNITUDE: Randomized, Double-Blind, Placebo-Controlled Study

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

Study start: February 2019

Patient eligibility
- L1 mCRPC
  - ≤4 months prior AAP allowed for mCRPC
- ECOG PS 0 or 1
- BPI-SF worst pain score ≤3

Stratifications
- Prior taxane-based chemo for mCSPC
- Prior ARi for nmCRPC or mCSPC
- Prior AAP for L1 mCRPC
- HRR BM+ cohort only:
  - *BRCA1/2* vs other HRR gene alterations



Primary endpoint
- rPFS by central review

Secondary endpoints
- Time to cytotoxic chemotherapy
- Time to symptomatic progression
- OS

Other prespecified endpoints
- Time to PSA progression
- ORR
- PFS2
- Time to pain progression
- Patient-reported outcomes

Note: Patients could request to be unblinded by the study steering committee and go on to subsequent therapy of the investigator's choice.

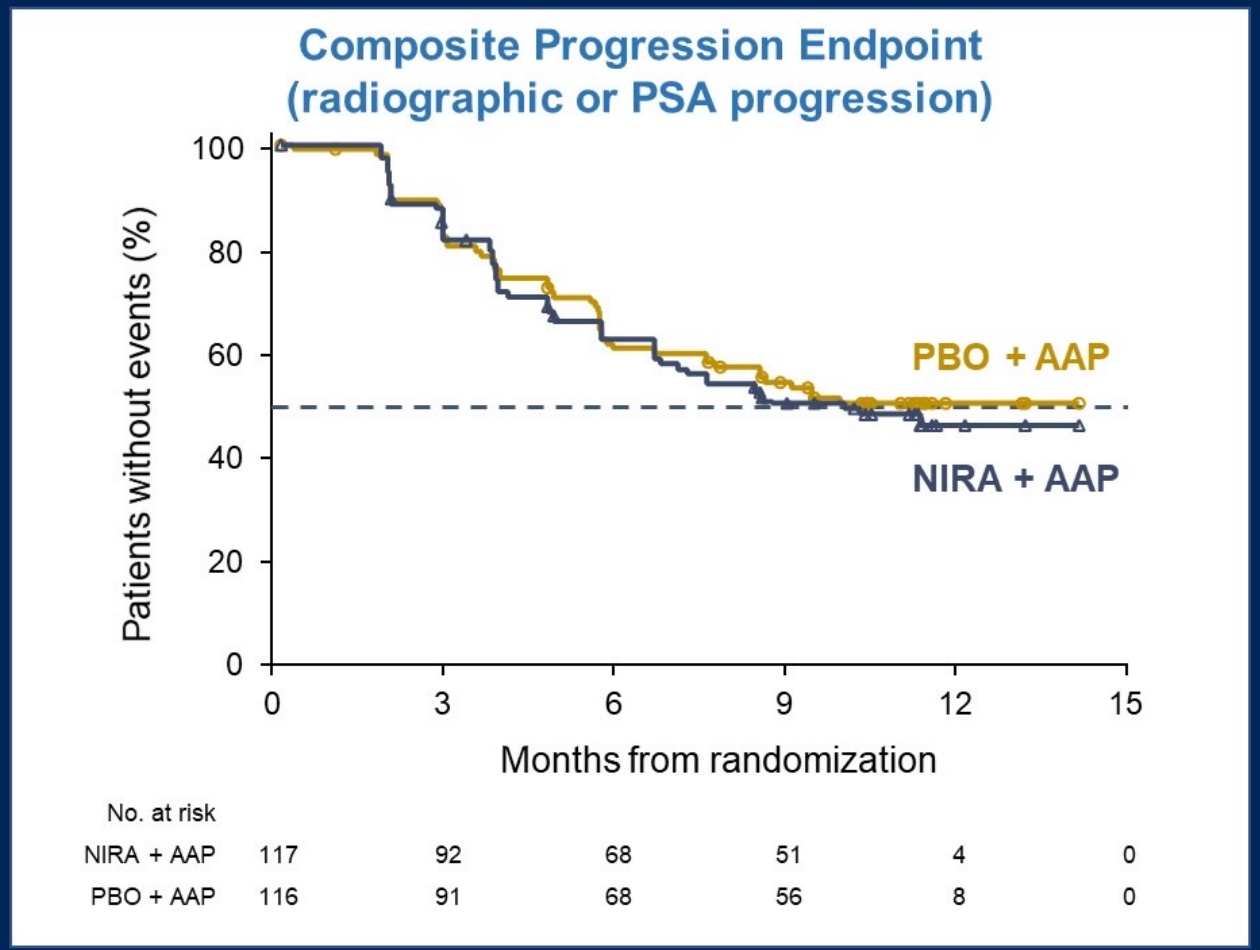
Clinical data cut-off was October 8, 2021 for the final rPFS analysis.

Patients were prospectively tested by plasma, tissue and/or saliva/whole blood. Patients negative by plasma only were required to test by tissue to confirm HRR BM– status.

AAP, abiraterone acetate + prednisone/prednisolone; AR, androgen receptor; ARi, androgen receptor inhibitor; BM, biomarker; BPI-SF, Brief Pain Inventory–Short Form; ctDNA, circulating tumor deoxyribonucleic acid; ECOG PS, Eastern Cooperative Oncology Group performance status; HRR, homologous recombination repair; L1, first line; mCRPC, metastatic castration-resistant prostate cancer; mCSPC, metastatic castration-sensitive prostate cancer; nmCRPC, nonmetastatic castration-resistant prostate cancer; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PFS2, progression-free survival on first subsequent therapy; PSA, prostate-specific antigen; rPFS, radiographic progression-free survival.

[a]Tissue and Plasma assays: FoundationOne tissue test (FoundationOne®CDx), Resolution Bioscience liquid test (ctDNA), AmoyDx blood and tissue assays, Invitae germline testing (blood/saliva), local lab biomarker test results demonstrating a pathogenic germline or somatic alteration listed in the study biomarker gene panel.

MAGNITUDE HRR BM⁻: Prespecified Early Futility Analysis
No Benefit of NIRA + AAP in HRR BM⁻ Patients



- Composite endpoint[a] (N = 233)
  HR = 1.09[b] (95% CI 0.75-1.59)
  [futility was defined as ≥1]
- Additional grade 3/4 toxicity was observed using NIRA + AAP vs PBO + AAP
- With added toxicity and no added efficacy in patients with HRR BM⁻ mCRPC, the IDMC recommend stopping enrollment in this cohort

[b]Breakdown of composite endpoint events
83 PSA events (HR = 1.03, 95% CI 0.67-1.59)
65 rPFS events (HR = 1.03, 95% CI 0.63-1.67)

[a]rPFS or PSA progression, whichever occurred first.
AAP, abiraterone acetate + prednisone/prednisolone; AE, adverse event; BM, biomarker; CI, confidence interval; HR, hazard ratio; HRR, homologous recombination repair; IDMC, independent data monitoring committee; mCRPC, metastatic castration-resistant prostate cancer; NIRA, niraparib; PBO, placebo; PSA, prostate specific antigen, rPFS, radiographic progression free survival

ASCO Genitourinary Cancers Symposium

TALAPRO-2: Phase 3 study of talazoparib plus enzalutamide versus placebo plus enzalutamide as first-line treatment in patients with metastatic castration-resistant prostate cancer

Neeraj Agarwal,[1] Arun A. Azad,[2] Joan Carles,[3] Andre P. Fay,[4] Nobuaki Matsubara,[5] Daniel Heinrich,[6] Cezary Szczylik,[7] Ugo De Giorgi,[8] Jae Young Joung,[9] Peter C. Fong,[10] Eric Voog,[11] Robert J. Jones,[12] Neal D. Shore,[13] Curtis Dunshee,[14] Stefanie Zschäbitz,[15] Jan Oldenburg,[16] Xun Lin,[17] Cynthia G. Healy,[18] Nicola Di Santo,[19] Fabian Zohren,[17] Karim Fizazi[20]

[1]Huntsman Cancer Institute (NCI-CCC), University of Utah, Salt Lake City, UT, USA; [2]Peter MacCallum Cancer Centre, Melbourne, Australia; [3]Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; [4]PUCRS School of Medicine, Porto Alegre, Brazil; [5]National Cancer Center Hospital East, Chiba, Japan; [6]Innlandet Hospital Trust, Gjøvik, Norway; [7]Department of Oncology European Health Center, Otwock, Poland, and Postgraduate Medical Education Center, Warsaw, Poland; [8]IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) Dino Amadori, Meldola, Italy; [9]National Cancer Center, Goyang, Republic of Korea; [10]Auckland City Hospital and University of Auckland, Auckland, New Zealand; [11]Clinique Victor Hugo Centre Jean Bernard, Le Mans, France; [12]School of Cancer Sciences, University of Glasgow, Beatson West of Scotland Cancer Centre, Glasgow, UK; [13]Carolina Urologic Research Center, Myrtle Beach, SC, USA; [14]Arizona Urology Specialists, Tucson, AZ, USA; [15]National Center for Tumor Diseases (NCT), Heidelberg University Hospital, Heidelberg, Germany; [16]Akershus University Hospital (Ahus), Lørenskog, Norway; [17]Pfizer Inc., La Jolla, CA, USA; [18]Pfizer Inc., Collegeville, PA, USA; [19]Pfizer Inc., Durham, NC, USA; [20]Institut Gustave Roussy, University of Paris-Saclay, Villejuif, France

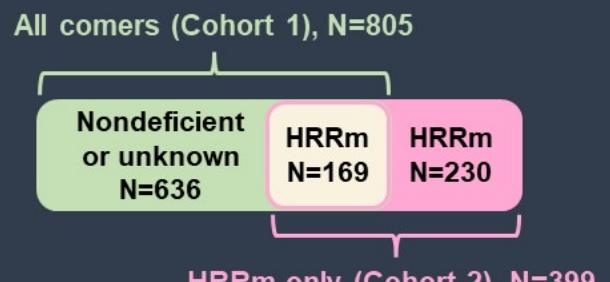
TALAPRO-2: A Randomized, Double-blind, Placebo-Controlled Study

Patient population

- First-line mCRPC
- ECOG performance status (PS) 0 or 1

Stratification factors

- Prior abiraterone[a] or docetaxel in castration-sensitive setting (yes vs no)
- HRR gene alteration status (deficient vs nondeficient or unknown)



1:1 (N=805)

Talazoparib 0.5 mg* + enzalutamide 160 mg, once daily

(N=402)

(*0.35 mg daily if moderate renal impairment)

Placebo + enzalutamide 160 mg, once daily

(N=403)

Primary endpoint

Radiographic progression-free survival (rPFS) by blinded independent central review (BICR)

Key secondary endpoint

- Overall survival (alpha protected)

Other secondary endpoints

- Time to cytotoxic chemotherapy
- PFS2 by investigator assessment[b]
- Objective response rate (ORR)
- Patient-reported outcomes
- Safety

(Data cutoff: August 16, 2022)

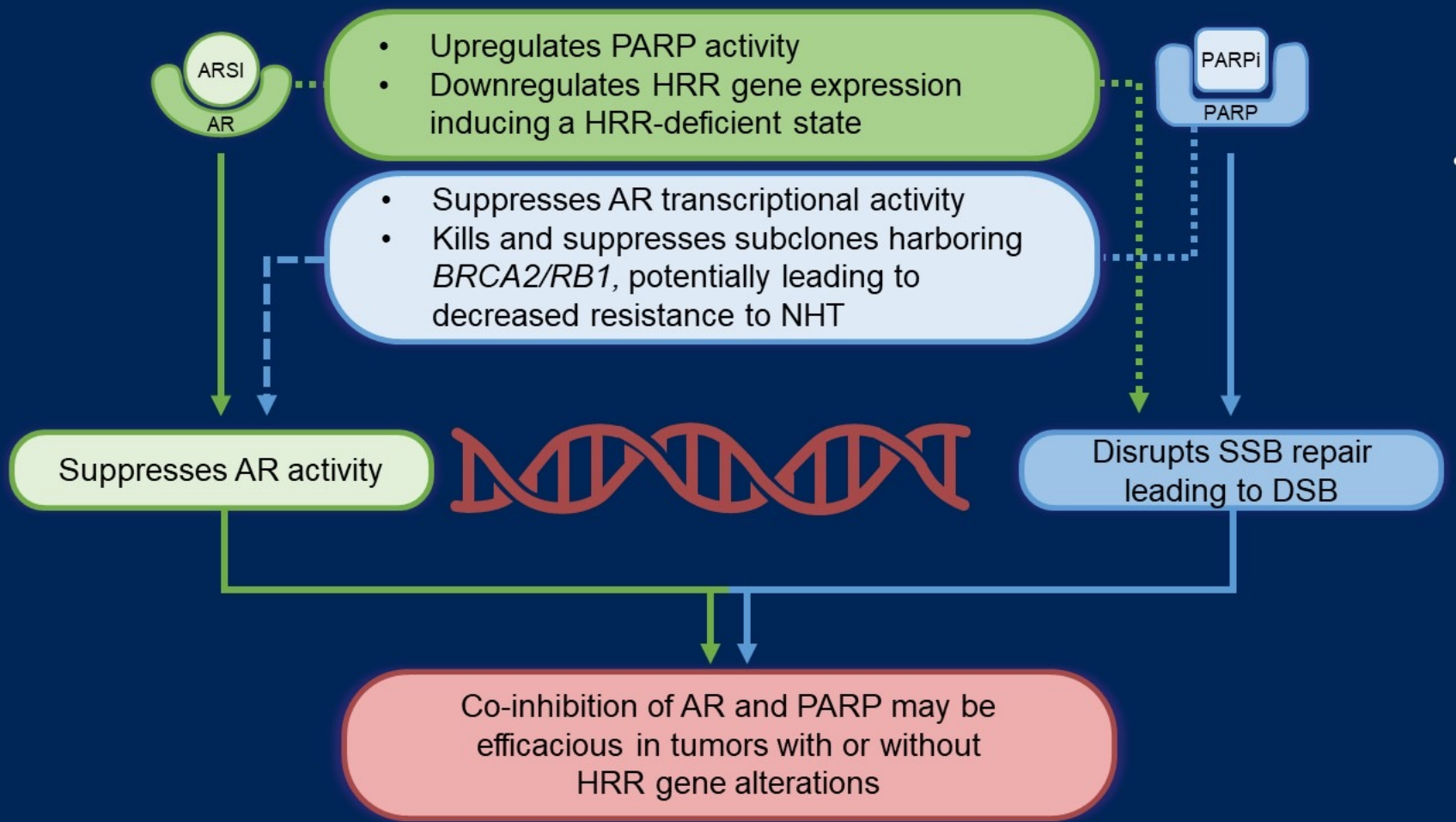
Samples prospectively assessed for HRR gene alterations *(BRCA1, BRCA2, PALB2, ATM, ATR, CHEK2, FANCA, RAD51C, NBN, MLH1, MRE11A, CDK12)* using FoundationOne®CDx and/or FoundationOne®Liquid CDx

We report results only from the all-comers cohort of men unselected for HRR gene alterations

To maintain the overall type I error at or below 1-sided 0.025, alpha for rPFS by BICR was split equally between the all-comers and forthcoming molecularly selected cohort (1-sided alpha of 0.0125 for each). If the rPFS showed statistically significant improvement, overall survival was tested in a hierarchical stepwise procedure to preserve the overall type I error.

[a]Two patients in each treatment arm received prior orteronel. [b]Time from randomization to the date of documented progression on the first subsequent antineoplastic therapy or death from any cause, whichever occurred first.

TALAPRO-2: Rationale for Combining Talazoparib and Enzalutamide[1-8]

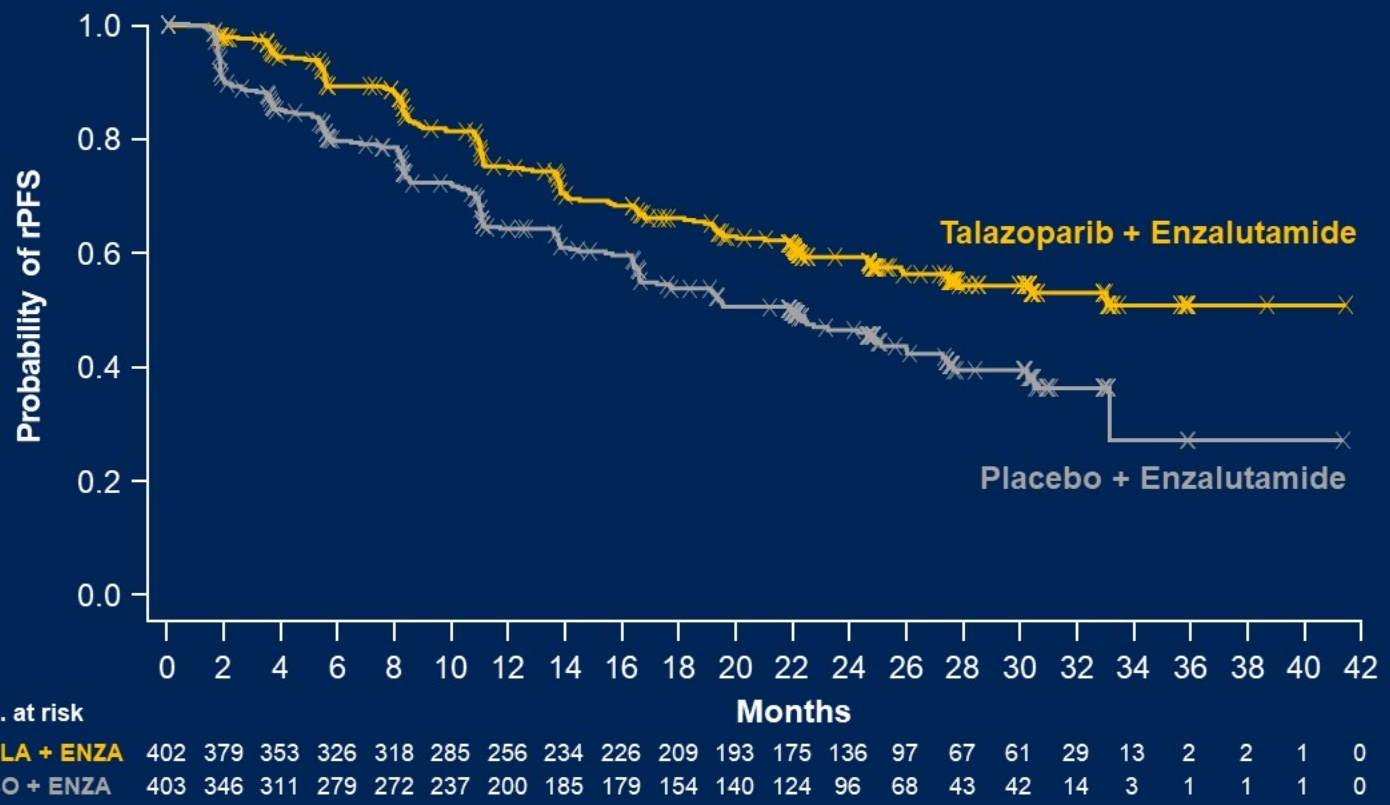


- TALAPRO-2 is the first phase 3 trial evaluating talazoparib plus enzalutamide in patients with mCRPC unselected for HRR status[9]
  - An initial nonrandomized open-label run-in determined the starting dose as talazoparib 0.5 mg daily (0.35 mg daily if moderate renal impairment) plus enzalutamide 160 mg daily

1. Asim M, et al. *Nat Commun.* 2017;8:374; **2.** Li L, et al. *Sci Signal.* 2017;10:eaam7479; **3.** Polkinghorn WR, et al. *Cancer Discov.* 2013;3:1245-1253; **4.** Sun R, et al. *Proc Natl Acad Sci U.S.A.* 2022;119:e2205509119; **5.** Kounatidou E, et al. *Nucleic Acids Res.* 2019;47:5634-5647; **6.** Schiewer MJ, et al. *Cancer Discov.* 2012;2:1134-1149; **7.** Chakraborty G, et al. *Clin Cancer Res.* 2020;26:2047-2064; **8.** Rao A, et al. *Cancers (Basel).* 2022;14:801; **9.** Agarwal N, et al. *Future Oncol.* 2022;18:425-436.

TALAPRO-2 Primary Endpoint: rPFS by BICR

Treatment with talazoparib plus enzalutamide resulted in a 37% reduced risk of progression or death



	TALA + ENZA (N=402)	PBO + ENZA (N=403)
Events, n	151	191
Median (95% CI), months	Not reached (NR) (27.5–NR)	21.9 (16.6–25.1)
HR (95% CI)	0.63 (0.51–0.78); *P* < 0.001	

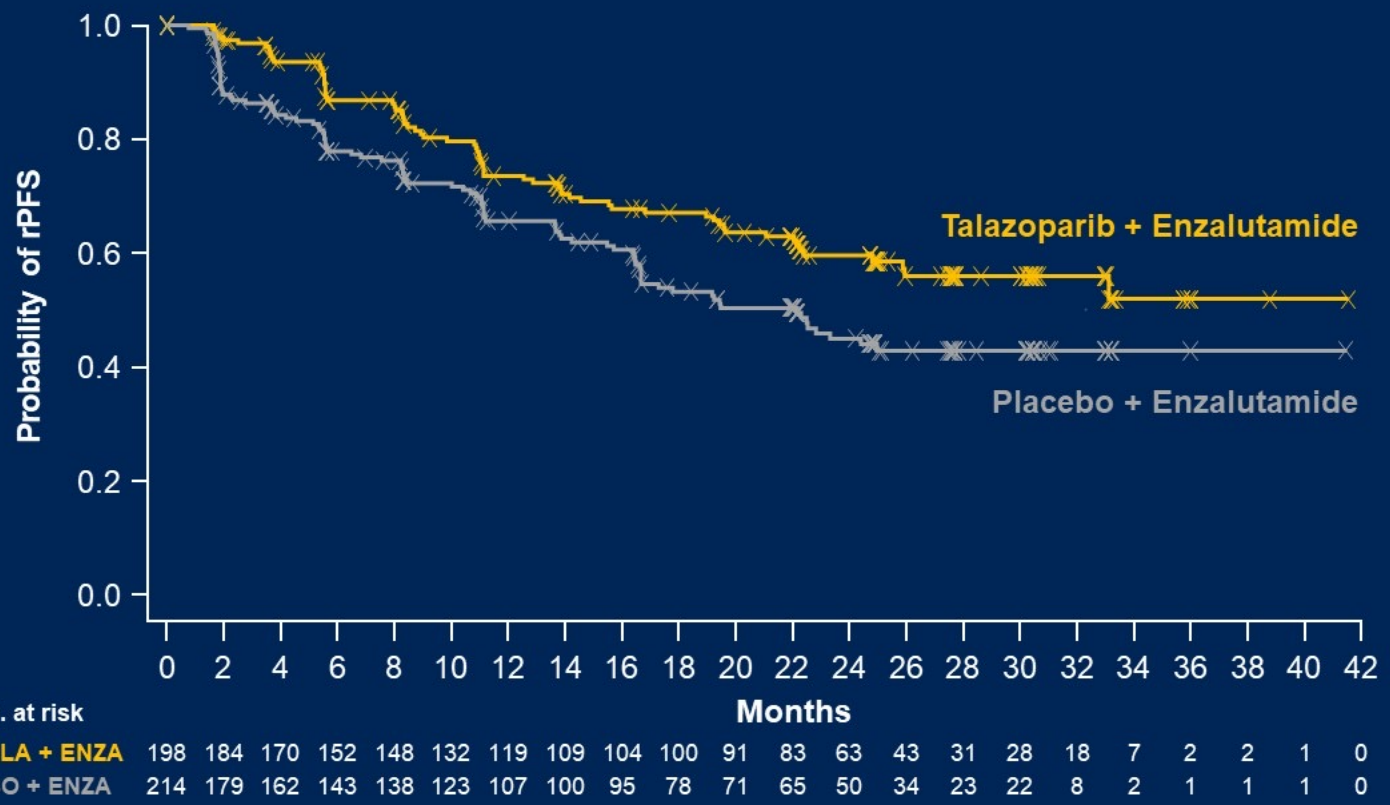
Median follow-up for rPFS was 24.9 and 24.6 months, respectively

A consistent treatment effect was seen for investigator-assessed rPFS: HR 0.64 (95% CI, 0.50–0.81); *P* < 0.001

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

TALAPRO-2: rPFS by BICR in HRR-nondeficient by Prospective Tumor Tissue Testing

A 34% risk reduction was seen in patients without HRR gene alterations detected by prospective tumor tissue testing



	TALA + ENZA (N=198)	PBO + ENZA (N=214)
Events, n	70	96
Median (95% CI), months	NR (25.8–NR)	22.1 (16.6–NR)
HR (95% CI)	HR 0.66 (95% CI, 0.49–0.91) *P* = 0.009	

Exploratory endpoint analysis based on HRR gene alteration status derived from the clinical database (unstratified analysis).

CYCLONE 1: Results of a Phase II Trial of Abemaciclib for Patients with Heavily Pretreated mCRPC

	Abemaciclib monotherapy (n = 44)
Overall response rate without concurrent bone progression	6.8%
Stable disease	40.9%
Disease control rate	47.7%
Median radiographic progression-free survival	2.7 months
Median time to PSA progression	6.5 months
Median overall survival	7.6 months

- Treatment-related adverse events (TRAEs) experienced by ≥50% of patients: Diarrhea (79.5%), decreased appetite (52.3%) and fatigue (50%)
- Grade 3 TRAEs in ≥5% of patients: Neutropenia (22.7%), anemia (6.8%), fatigue (6.8%) and diarrhea (6.8%)

Author Conclusions: *Abemaciclib demonstrated modest but objective single-agent clinical activity in heavily pretreated progressive mCRPC. The safety profile of abemaciclib was consistent with the experience in breast cancer. Although the primary endpoint was not formally met, the single agent activity observed in this late line mCRPC setting validates CDK4/6 as a therapeutic target in advanced PC.*

Agarwal N et al. AACR 2023;Abstract CT159.

Rationale to Study Abemaciclib in Metastatic Prostate Cancer

1

- The Androgen Receptor (AR) signaling pathway plays a pivotal role in normal prostate gland development as well as prostate carcinogenesis (4).
- Preclinical and human models suggest a relationship between the cellular AR level in both primary and metastatic disease and disease progression to castration resistant PCa (CRPC) (5-7).
- The transition from clinically localized prostate cancer to castration resistance (CRPC) involves a complex interplay of molecules and is attributed to aberrant AR signaling (4).

2

- Abemaciclib is a potent and selective oral inhibitor of CDK4&6 that is approved for the treatment of early and advanced/metastatic HR+/HER2- breast cancer (1).
- As with estrogen receptor signaling pathway in breast cancer, evidence exists that the AR signaling pathway activates the CDK4 & 6-cyclin D1 axis to sustain prostate cancer cell proliferation and survival (2,3).

3

- In both hormone sensitive and castration resistance prostate cancer cell models, Abemaciclib has demonstrated in vitro activity, as single agent and in combination with AR blocker agents, limiting cellular proliferation (Lilly/ICOS, file data).
- HYPOTHESIS: dual inhibition of the AR axis and cell cycle entry with the coadministration of abiraterone and Abemaciclib may inhibit the proliferation of prostate cancer cells and delay progression of anti-androgen resistant disease.

References: 1. Verzenio package insert, 2021; 2. Knudsen et al. 1998; 3. Xu et al. 2006; 4. Lonergan et al. 2011; 5, Hershall et al. 2001; 6. Ricciardelli et. al, 2005; 7. Chen CD et. al. 2004

CYCLONE 2: A Phase 2/3, Randomized, Double-Blind, Placebo-Controlled Study of Abiraterone Acetate plus Prednisone with or without Abemaciclib in Patients with mCRPC

Study Design

Population
mCRPC 1L

- ❑ **Exclusionary :** Prior CDK4/6i, NHA, Radiopharmaceuticals, and chemotherapy for mCRPC
- ❑ **Stratification Factors:** Radiographic progression Measurable disease docetaxel for mHSPC

PART 1 N=30

- ABEMACICLIB 150 mg BID
- ABEMACICLIB 200 mg BID
- PLACEBO 150 mg BID
- PLACEBO 200 mg BID

All arms: **Abiraterone + Prednisone**

PART 2 N=150

- ABEMACICLIB RP2D BID ABIRATERONE/PRED
- PLACEBO RP2D BID ABIRATERONE/PRED

Adaptive Interim Analysis

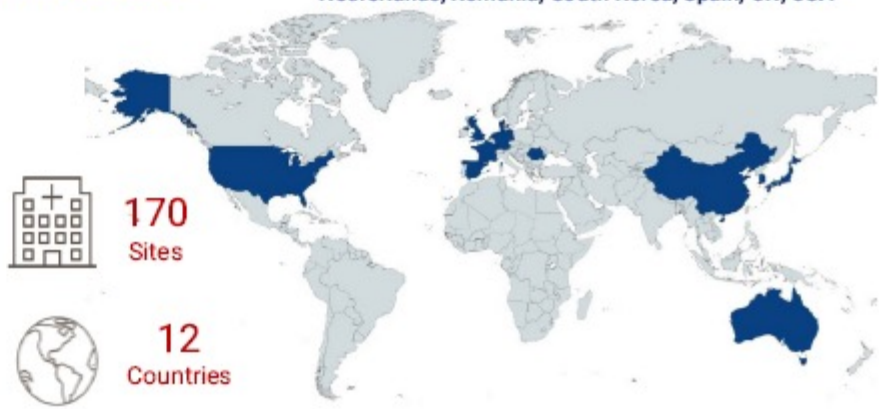
PART 3 N=170

- Prespecified adaptive expansion criteria were met at an Adaptive Interim Analysis conducted by the IDMC
- Part 3 was opened in June 2021
- Part 3 completed enrollment

Study Status

Participation

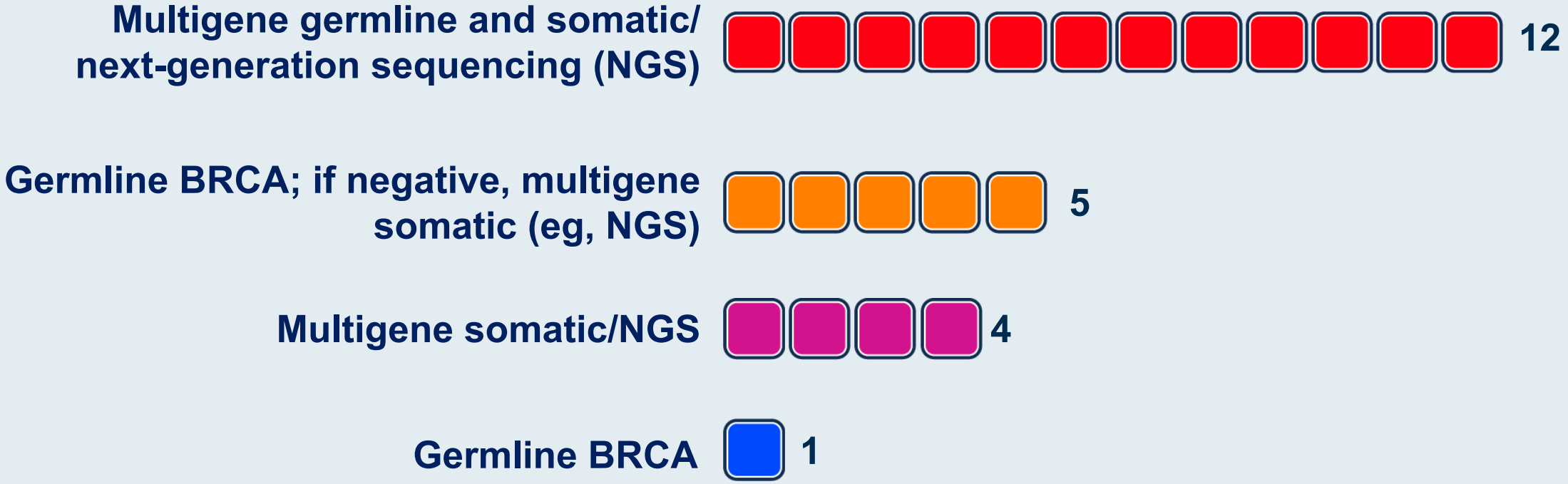
Australia, China, Denmark, France, Germany, Japan, Netherlands, Romania, South Korea, Spain, UK, USA



MODULE 4: Contemporary Management of mCRPC in Patients Harboring an HRR Gene Alteration

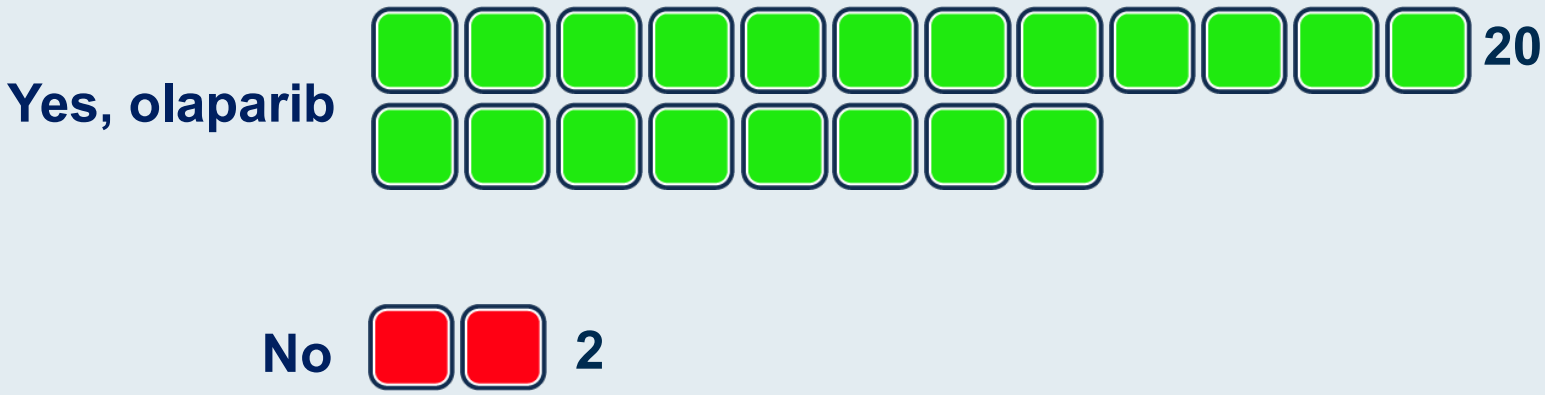
RTP
RESEARCH
TO PRACTICE

In general, what is the optimal approach to mutation testing for possible use of a PARP inhibitor for a patient with mCRPC?



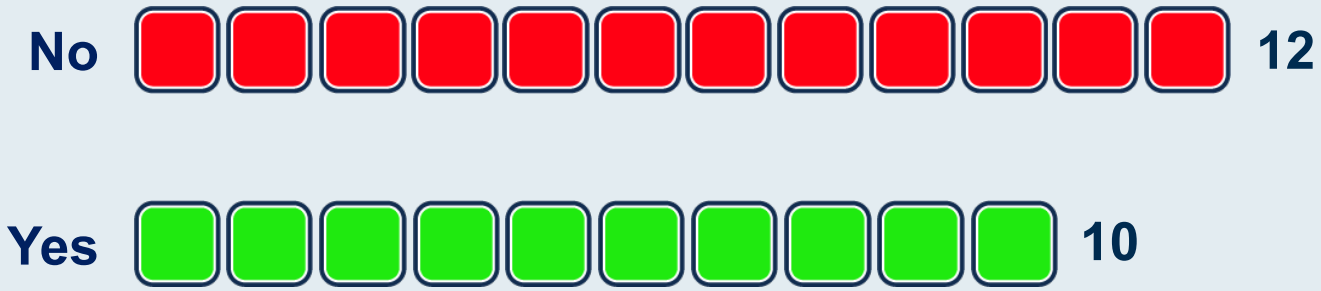
Survey of urologic oncology clinical investigators

Regulatory and reimbursment issues aside, for patients with mCRPC and a germline BRCA mutation to whom you are planning to administer a PARP inhibitor, do you have a preference as to which one?



Survey of urologic oncology clinical investigators

In general, when adminstering a PARP inhibitor to a patient with metastatic prostate cancer, do you use prophylactic antiemetic/gastrointestinal medication?

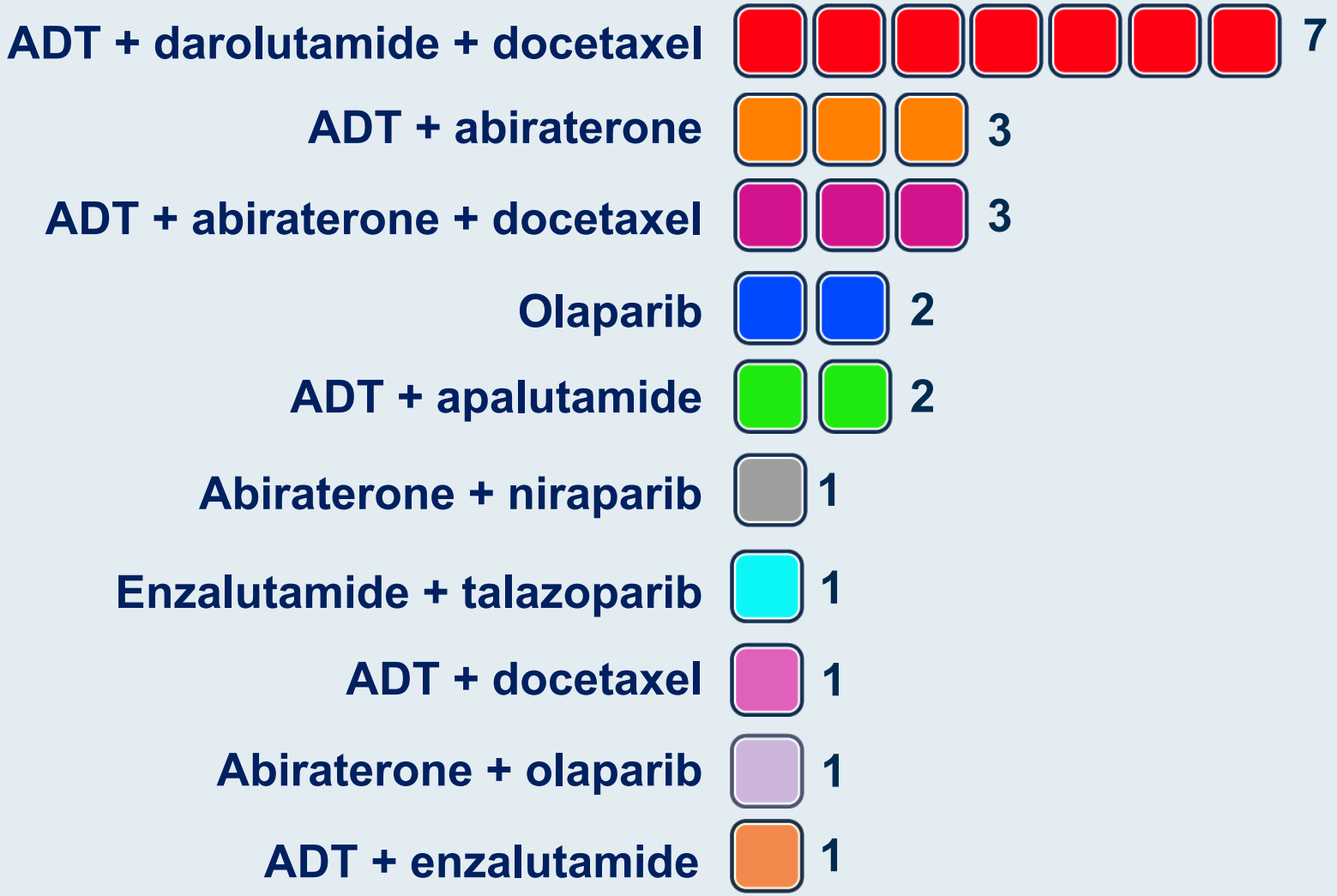


Survey of urologic oncology clinical investigators

A 72-year-old man presented with Gleason 8 (4 + 4) prostate adenocarcinoma 2 years ago. CT and bone scans were negative. He underwent proton beam therapy with 2 years of ADT planned. The PSA nadir was 0.1 ng/mL, and PSA rose to 11 ng/mL 1 year later. CT scan shows uptake in a lung nodule, a retroperitoneal node and sclerosis in bones. A bone scan is negative. Genetic testing reveals a BRCA2 germline mutation. Family history is negative for other cancers. Regulatory and reimbursement issues aside, which systemic treatment would you most likely recommend?

Survey of urologic oncology clinical investigators

A 67-year-old man presents with Gleason 9 (5 + 4) prostate adenocarcinoma (PSA 12 ng/mL). CT and bone scans show spine and pelvis lesions and small positive lymph nodes in the pelvis. Germline testing is negative, but somatic testing from biopsy reveals a BRCA1 mutation. Family history includes the patient's mother having breast cancer. Regulatory and reimbursement issues aside, what would be your most likely treatment recommendation?



Survey of urologic oncology clinical investigators

Research To Practice
April 30, 2023

Management of mCRPC Patients Harboring HRR Gene Alterations

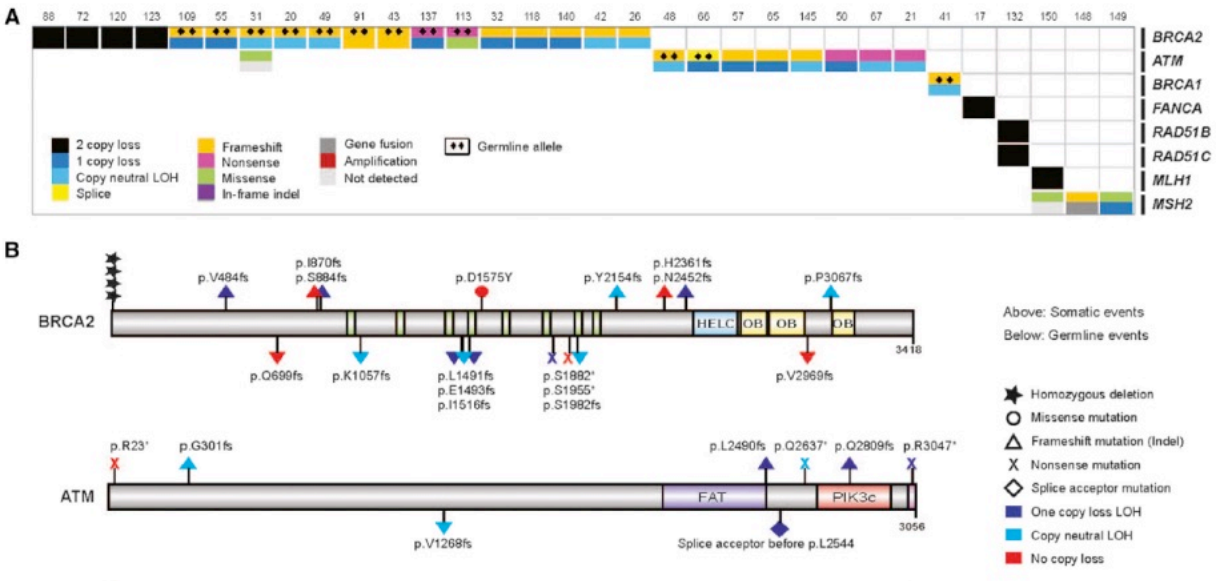
Matthew R. Smith, M.D., Ph.D.
Professor of Medicine, Harvard Medical School
Director, MGH Genitourinary Malignancies Program
Claire and John Bertucci Endowed Chair in Genitourinary Oncology

Incidence of HRR Gene Mutations in Prostate Cancer and Indications for Testing

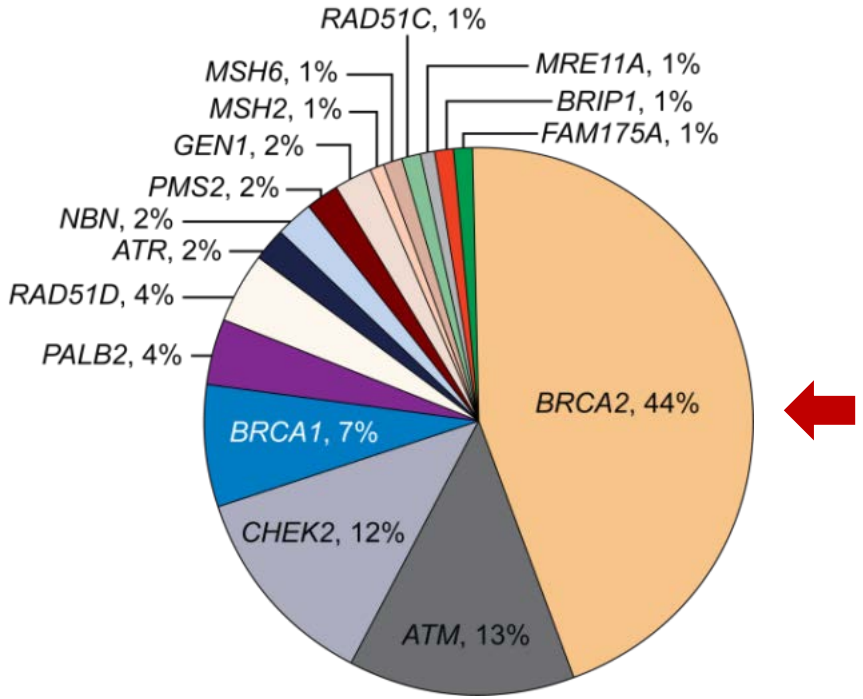
HRR Genes and Metastatic Prostate Cancer

Somatic

- **23%** of metastatic castration-resistant prostate cancers harbor DNA repair alterations
- The frequency of DNA repair alterations **increases in metastatic disease vs. localized disease**



Germline



- **12%** of men with metastatic prostate cancer have a germline DNA repair defect

1. Robinson D, et al. Cell. 2015;161:1215-28. **2.** Pritchard CC, et al. N Engl J Med. 2016;375:443-53.

Prostate NCCN Guidelines v 1.2023

Germline Testing

Germline testing is recommended in patients with a personal history of prostate cancer who:

- Have metastatic, regional (N+), very-high-risk localized, or high-risk localized prostate cancer
- Have family history and/or ancestry with:
  - ≥1 first, second, or third degree relative with
    - Breast cancer at age ≤50 years
    - Colorectal or endometrial cancer at age ≤50 years
    - Male breast cancer at any age
    - Ovarian cancer at any age
    - Pancreatic cancer at any age
    - Metastatic, regional, very-high-risk, or high-risk prostate cancer at any age
  - ≥1 first degree relative with prostate cancer at age ≤60 years
  - ≥2 first, second, or third degree relatives with:
    - Breast cancer at any age
    - Prostate cancer at any age
  - ≥3 first or second degree relatives with:
    - Lynch syndrome-related cancers, especially if diagnosed at age <50 years
    - A known family history of a familial cancer risk mutation
    - Ashkenazi Jewish ancestry
  - Personal history of male breast cancer

Germline testing may be considered in patients with a personal history of PCa who:

- Have intermediate-risk prostate cancer with intraductal/cribriform histology
- Have a personal history of pancreatic, colorectal, gastric, melanoma, upper tract urothelial, glioblastoma, biliary tract, or small intestinal cancer

Germline multigene testing that includes at least BRCA1, BRCA2, ATM, PALB2, CHEK2, HOXB13, MLH1, MSH2, MSH6, and PMS2 is recommended; additional genes may be appropriate based on clinical context

Somatic Tumor Testing

Tumor testing for alterations in HRR DNA repair genes such as ***BRCA1, BRCA2, ATM, PALB2, FANCA, RAD51D, CHEK2,*** and ***CDK12*** is recommended in patients with metastatic prostate cancer, and may be considered for patients with regional (N+) prostate cancer

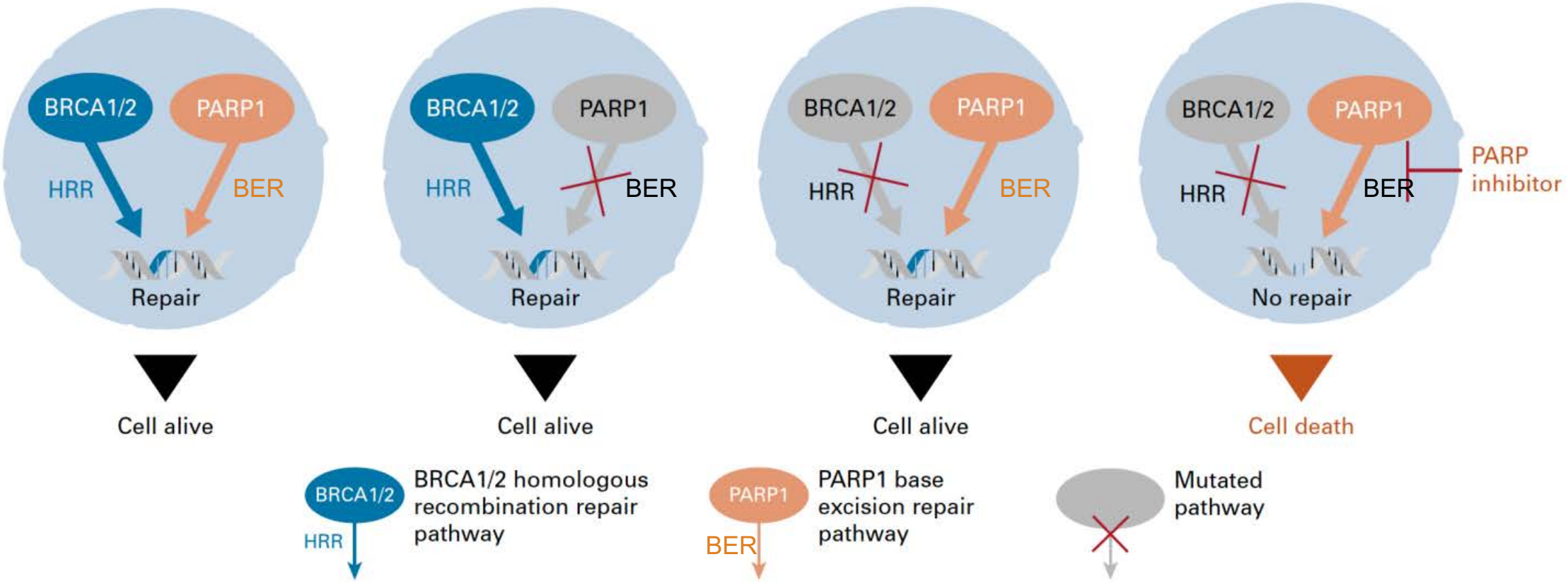
Tumor testing for MSI-H or dMMR is recommended in patients with mCRPC, and may be considered for patients with mCSPC

TMB testing may be considered in patients with mCRPC

NCCN Practice Guidelines: Prostate Cancer. Version 1.2023. https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf.

PARP Inhibitors for HRR-Deficient mCRPC

PARP Inhibition: “Synthetic Lethality”



PARP is required for single-strand break repair (e.g. via BER)

MOA – inhibiting SSB/BER is synthetic lethal with HRD

Comparison of Different PARP Inhibitors

Properties of PARP Inhibitors

	Olaparib	Talazoparib	Niraparib	Rucaparib
Mol. Weight	434.5	380.8	320.4	323.4
PARP1 IC_{50}	5 nM	0.56 nM	3.8 nM	0.65 nM
PARP2 IC_{50}	1 nM	0.15 nM	2.1 nM	0.08 nM
Trapping	++	++++	+++	++

Carney B, et al. *Nat Commun* 2018; 9: 176.

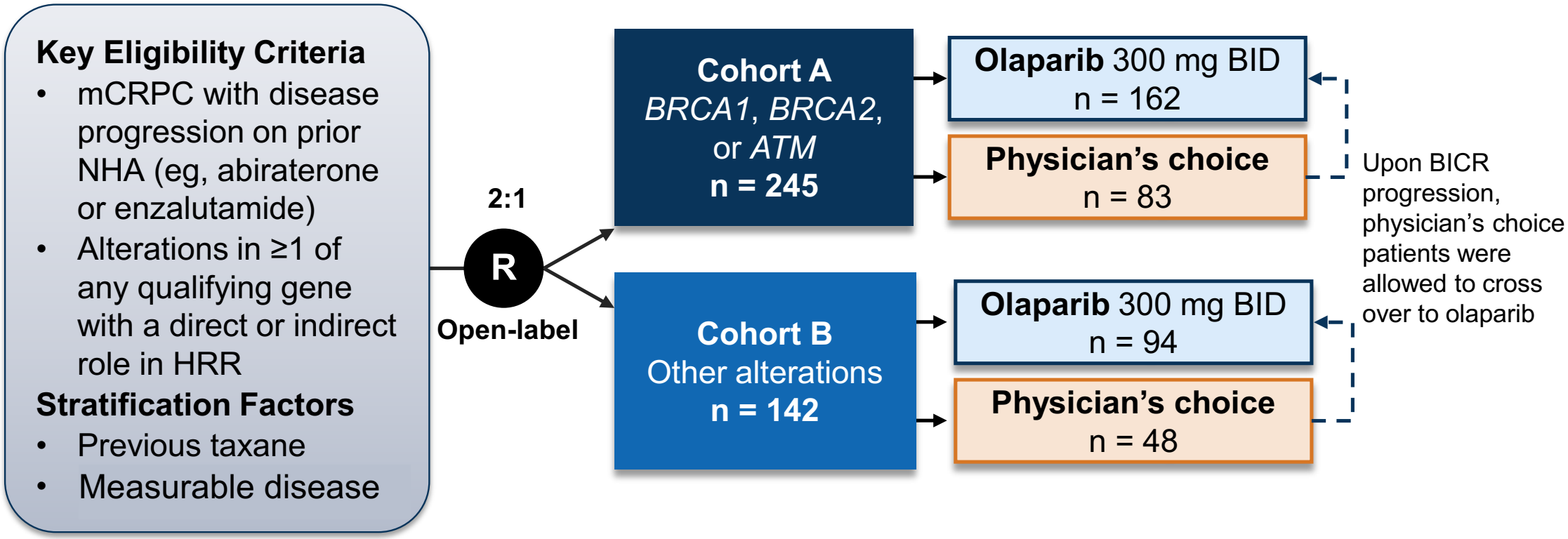
Summary of PARPi *Monotherapy* Trials in mCRPC

Study and treatment	Prior therapy	HRR status criteria; Sample type	Primary endpoint	Results
TOPARP-A[1] **Olaparib** 400 mg BID (N=50)	1–2 taxane CT regimens; 98% had prior NHT	Deficiency not required; tumor	Composite response rate	**33%** overall; 88% (14 of 16) with DDR gene alterations
TOPARP-B[2] **Olaparib** 300 mg or 400 mg BID, randomized 1:1 (N=98)	1–2 taxane CT regimens; 88%–92% had prior NHT	Deleterious germline or somatic DDR gene alterations; tumor	Composite response rate	**39.1%** 300-mg cohort; **54.3%** 400-mg cohort
TRITON2[3] **Rucaparib** 600 mg BID (N=115)	1 taxane and 1–2 NHT	Deleterious germline or somatic *BRCA1/2* alteration; tumor or plasma	ORR by blinded independent radiology review	**43.5%** (27 of 62)
GALAHAD[4] **Niraparib** 300 mg QD (N=289)	≥1 taxane and ≥1 NHT	Deleterious germline or somatic alteration in ≥1 of 8 prespecified DDR genes; tumor or plasma	ORR in patients with *BRCA* mutation and measurable disease	**34.2%** (26 of 76 measurable *BRCA* cohort) 10.6% (5 of 47 measurable non-*BRCA* cohort)
TALAPRO-1[5] **Talazoparib** 1 mg QD (N=128)	1–2 CT regimens (≥1 taxane) and ≥1 NHT	Deleterious germline or somatic alterations in ≥1 of 11 prespecified DDR-HRR genes; tumor or plasma	ORR by blinded independent review	**29.8%** (31 of 104)

1. Mateo J et al. *N Engl J Med.* 2015;373:1697-708; **2.** Mateo J et al. *Lancet Oncol.* 2020;21:162-174; **3.** Abida W et al. *J Clin Oncol.* 2020;38:3763-3772; **4.** Smith MR et al. *Lancet Oncol.* 2022;23:362-373; **5.** de Bono JS et al. *Lancet Oncol.* 2021;22:1250-1264.

Pivotal Trials of PARPi *Monotherapy*

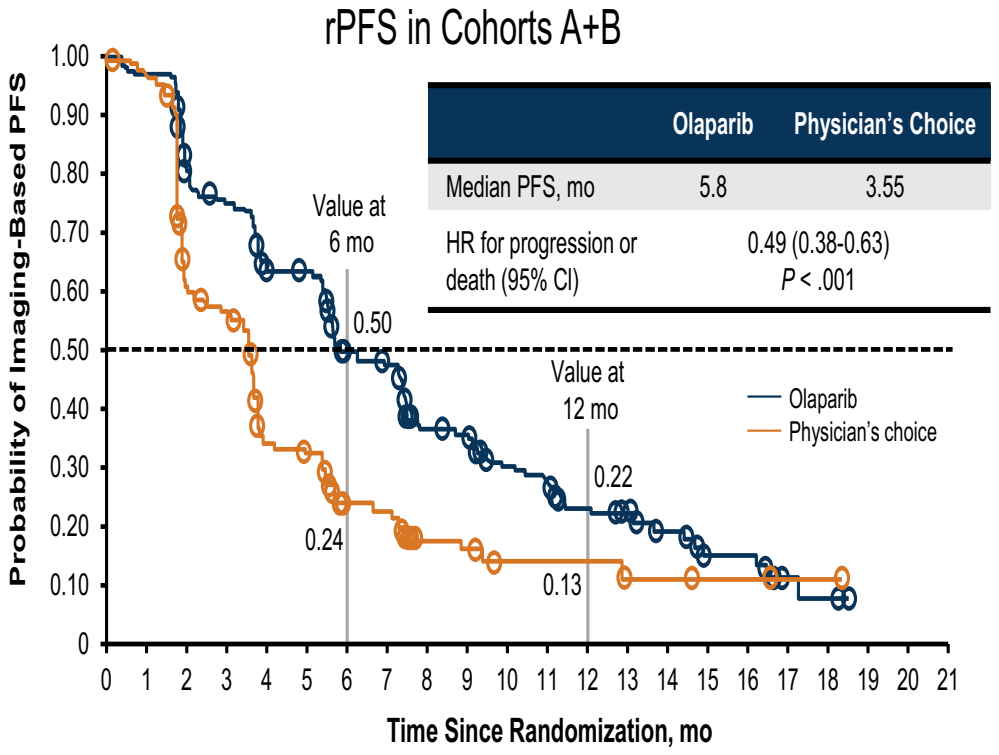
Olaparib: PROfound, Randomized Phase 3 Study



- Primary endpoint: rPFS in cohort A (RECIST 1.1 and PCWG3 by BICR)
- Key secondary endpoints: rPFS (cohorts A+B); confirmed radiographic ORR in cohort A; time to pain progression in cohort A; OS in cohort A

1. de Bono J et al. *N Engl J Med*. 2020;382:2091-2102.

PROfound: rPFS and OS in Whole Population (A+B)

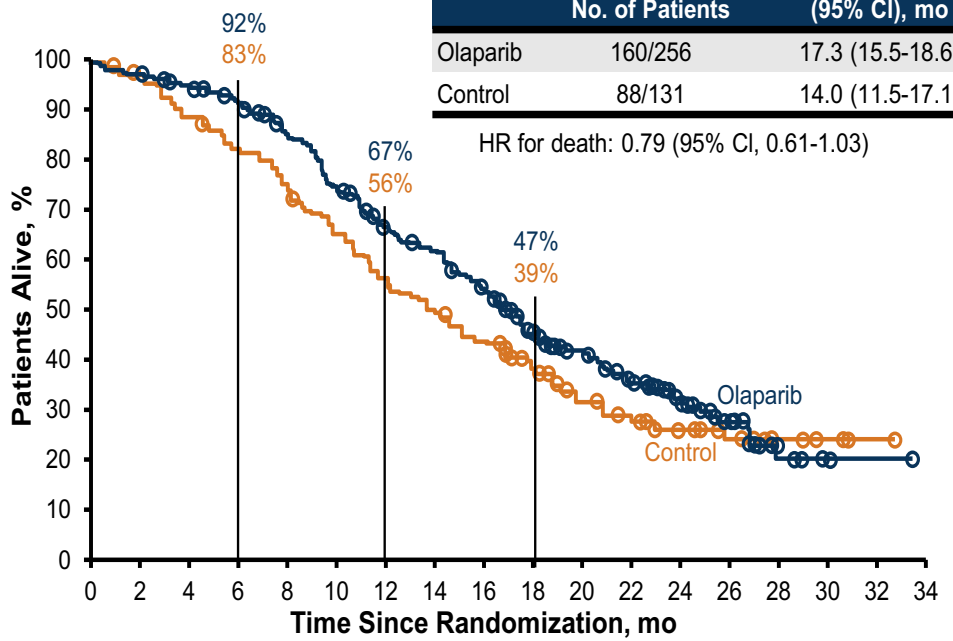


	Olaparib	Physician's Choice
Median PFS, mo	5.8	3.55
HR for progression or death (95% CI)	0.49 (0.38-0.63) $P < .001$	

No. at Risk

Olaparib	256	239	188	176	145	143	106	100	67	63	48	43	31	28	21	11	11	3	2	0	0	0
Control	131	123	73	67	38	35	20	19	9	8	5	5	5	3	3	2	2	1	1	0	0	0

OS in the Overall Population (Cohorts A + B)



	No. of Deaths/ No. of Patients	Median OS (95% CI), mo
Olaparib	160/256	17.3 (15.5-18.6)
Control	88/131	14.0 (11.5-17.1)

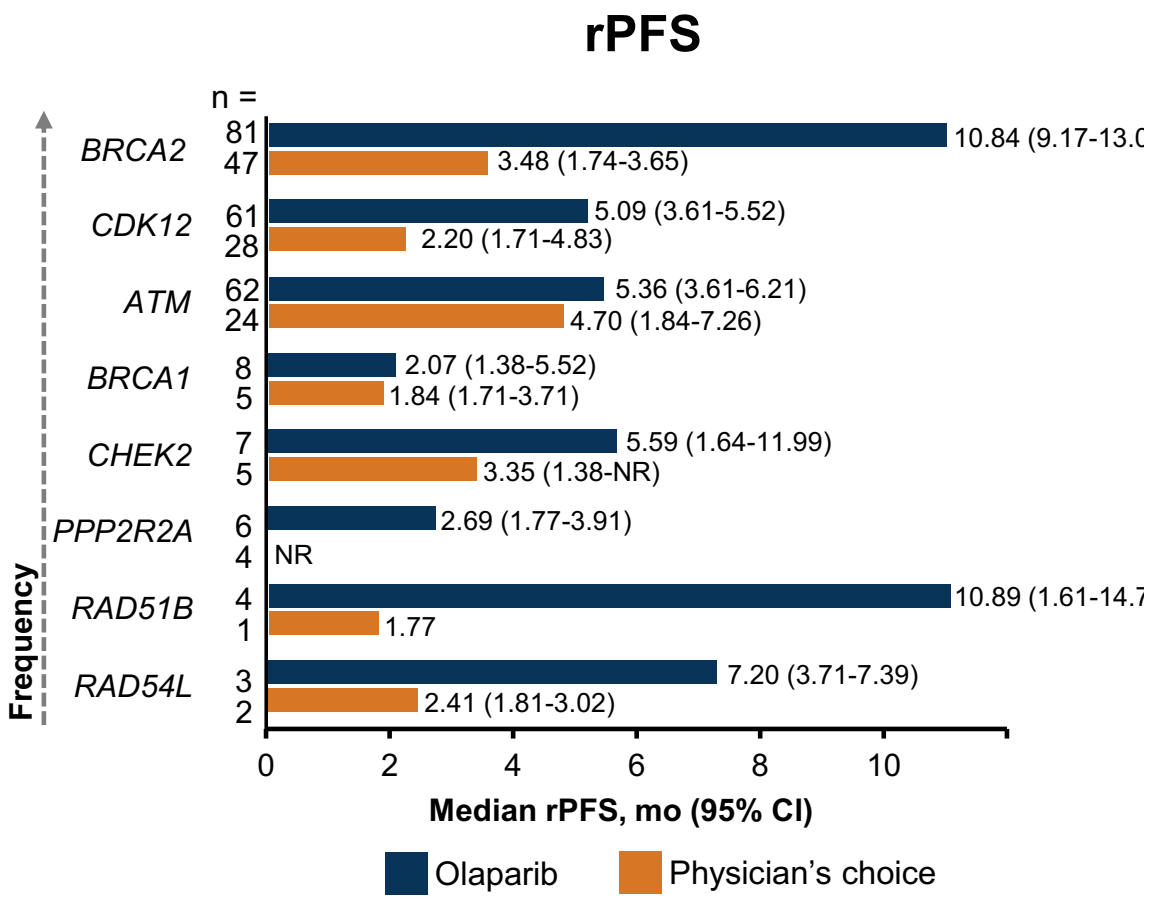
HR for death: 0.79 (95% CI, 0.61-1.03)

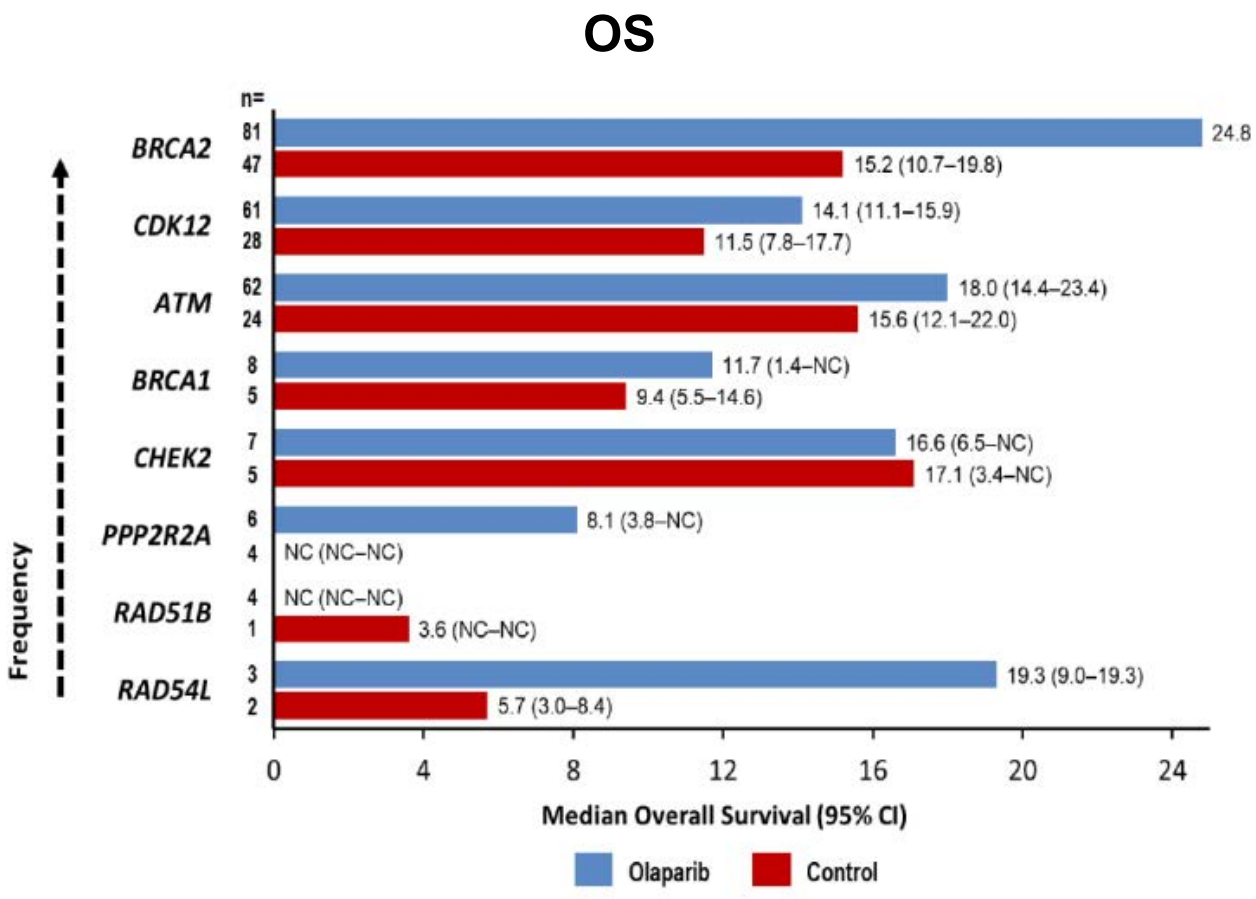
No. at Risk

Olaparib	256	249	240	228	209	182	157	146	126	96	73	56	39	22	7	2	1	0		
Control	131	125	115	106	96	83	71	63	55	37	27	22	15	11	6	3	1	0		

1. de Bono J et al. *N Engl J Med*. 2020;382:2091-2102. 2. Hussain M et al. *N Engl J Med*. 2020.

PROfound: Gene-by-Gene, rPFS and OS Analyses





1. de Bono J et al. *N Engl J Med*. 2020;382:2091-2102. 2. Hussain M et al. *N Engl J Med*. 2020.

Olaparib for HRR-Mutated mCRPC

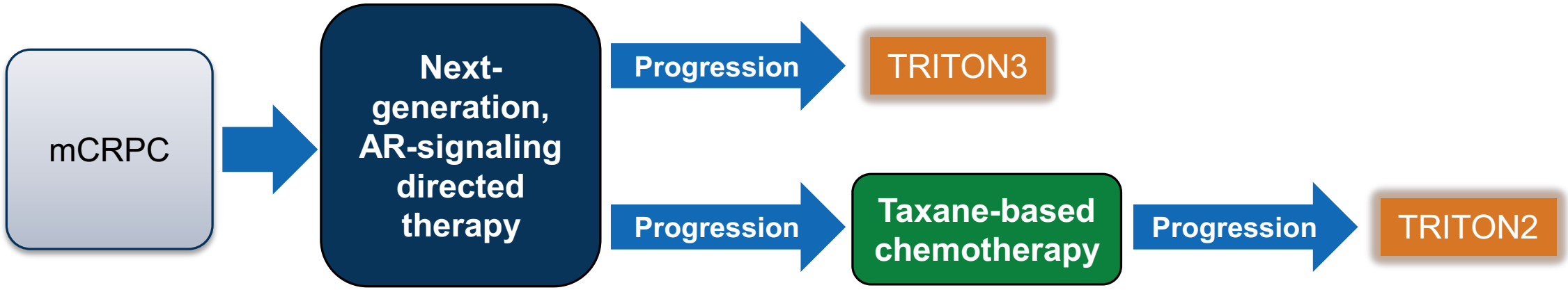
OLAPARIB: In **May 2020,** based on data from the **PROfound study,** the FDA granted **full approval to olaparib** for the treatment of patients with deleterious or suspected **germline or somatic HRR[a] gene-mutated mCRPC, who have progressed following prior treatment with enzalutamide or abiraterone[1,b]**

[a]***BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, RAD54L***.

[b]Select patients for therapy based on two FDA-approved companion diagnostic tests: BRACAnalysis CDx and FoundationOne CDx.

1. https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-olaparib-hrr-gene-mutated-metastatic-castration-resistant-prostate-cancer.

Rucaparib: TRITON2 and TRITON3 Studies



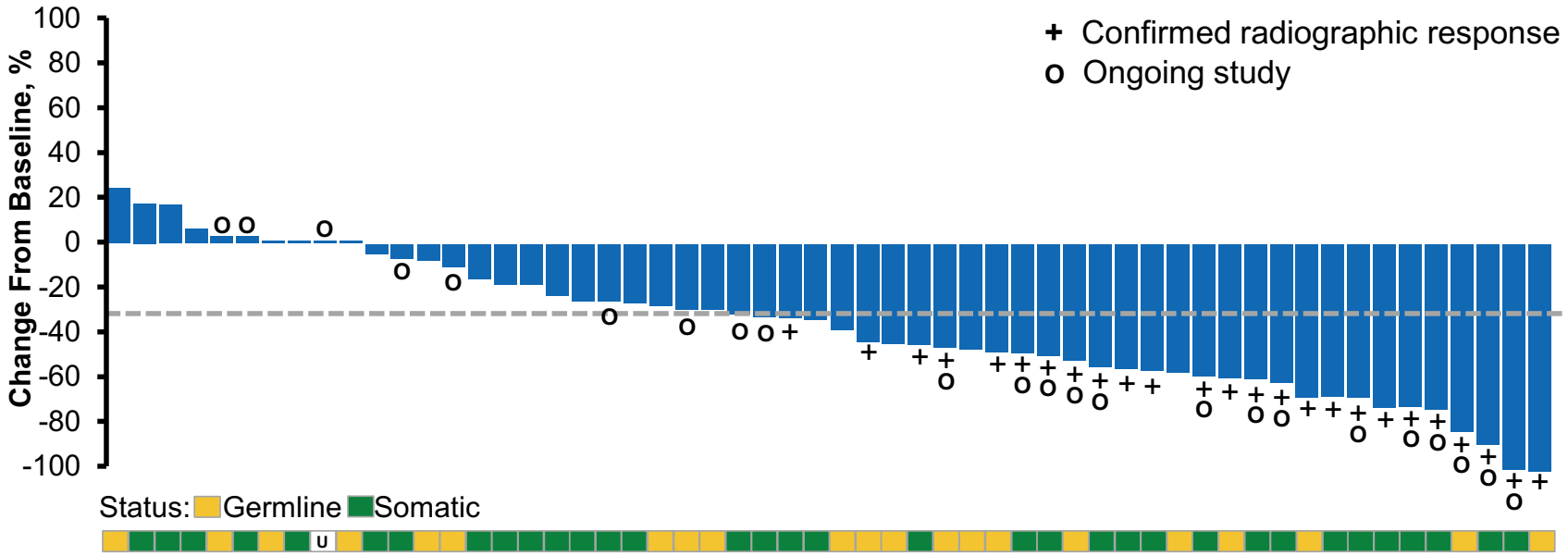
HRR-deficiency is defined by a deleterious alteration in *BRCA1*, *BRCA2*, *ATM*, or 12 other HRR genes (*BARD1, BRIP1, CDK12, CHEK2, FANCA, NBN, PALB2, RAD51, RAD51B, RAD51C, RAD51D, RAD54L)*

1. Abida W et al. *Annals Onc*. 2018:29(Suppl 8):viii271-viii302.

TRITON2: Objective Response Rate (ORR)

	DDR Gene				
	***BRCA* 1/2 (n = 57)**	***ATM* (n = 21)**	***CDK12* (n = 9)**	***CHEK2* (n = 5)**	**Other (n = 13)**
ORR, n (%) [95% CI]	25 (43.9) [30.7-57.6]	2 (9.5) [1.2-30.4]	0 [0.0-33.6]	0 [0.0-52.2]	5 (38.5) [13.9-68.4]
CR, n (%)	3 (5.3)	0	0	0	1 (7.7)
PR, n (%)	22 (38.6)	2 (9.5)	0	0	4 (30.8)
SD, n (%)	26 (45.6)	10 (47.6)	5 (55.6)	3 (60.0)	6 (46.2)
PD, n (%)	5 (8.8)	8 (38.1)	3 (33.3)	2 (40.0)	1 (7.7)
N/E, n (%)	1 (1.8)	1 (4.8)	1 (11.1)	0	1 (7.7)

Best Change From Baseline in Sum of Target Lesions in Patients With *BRCA 1/2* Alteration (N = 56)



1. Abida W et al. ESMO 2019. Abstract 846PD. 2. Abida W et al. *Clin Cancer Res*. 2020 Feb 21

Rucaparib for *BRCA1/2*-Mutated mCRPC

RUCAPARIB: In **May 2020,** based on data from the **TRITON2 study,** the FDA granted **accelerated approval to rucaparib** for the treatment of patients with **deleterious *BRCA1/2* (germline and/or somatic)-associated mCRPC, who have been treated with an androgen receptor-directed therapy and a taxane-based chemotherapy.**[1]

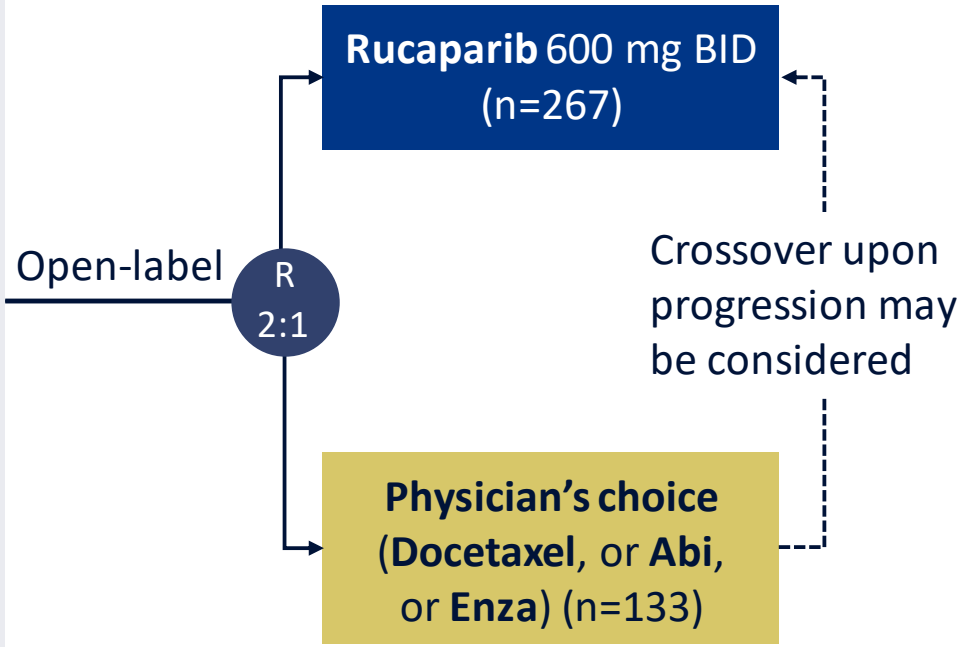
1. https://www.fda.gov/drugs/fda-grants-accelerated-approval-rucaparib-brca-mutated-metastatic-castration-resistant-prostate.

TRITON3: Randomized Phase III Trial

Patient population

- mCRPC with progression after 1 prior AR signaling-directed therapy (abiraterone, enzalutamide, or investigational agent)
- Deleterious germline or somatic alteration in ***BRCA1, BRCA2,*** or ***ATM****
- No prior PARP inhibitor
- No prior chemotherapy for mCRPC

Planned enrollment: 400



Primary endpoint

rPFS
(RECIST 1.1 and PCWG3 by IRR)

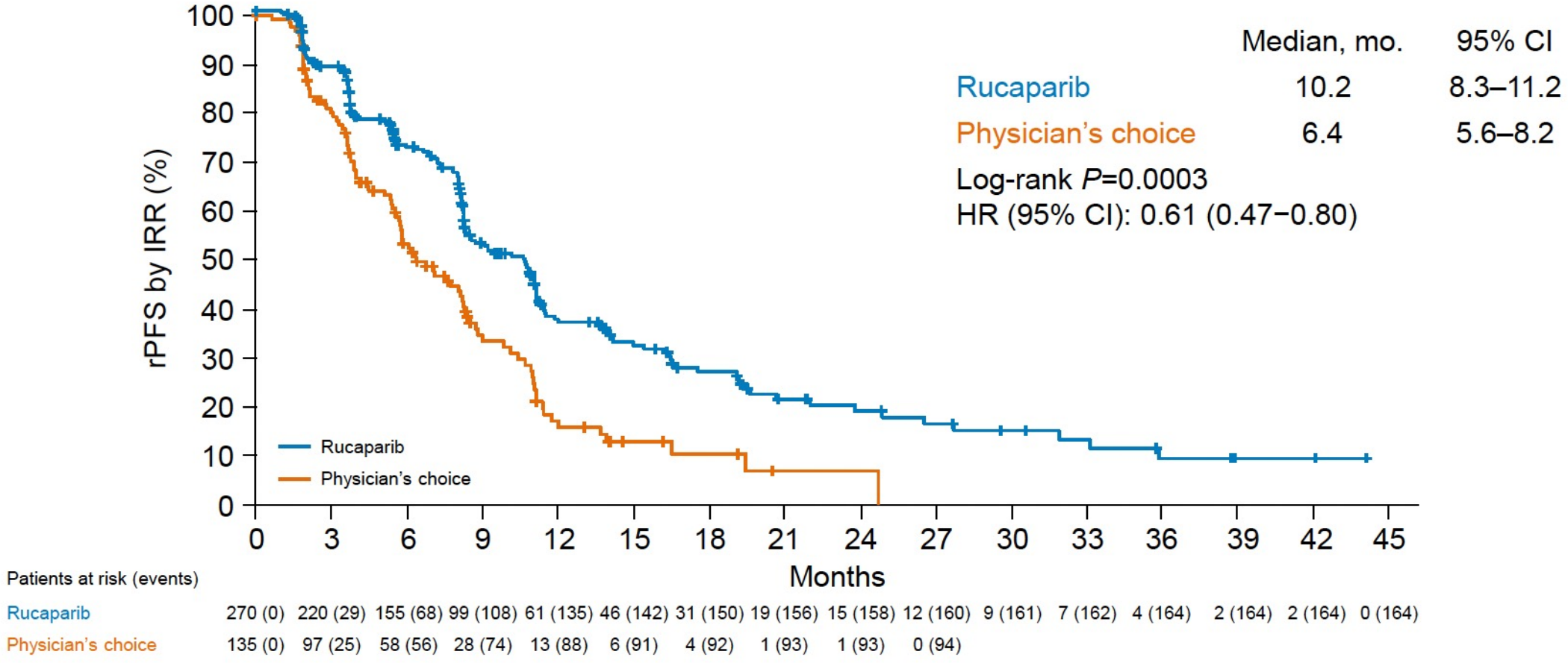
Key secondary endpoints

- ORR and DOR by modified RECIST criteria in patients with measurable nodal/visceral disease
- OS
- Clinical benefit rate
- PSA response of ≥50% and ≥90%
- Time to PSA progression
- Patient-reported outcomes
- Safety and tolerability

*Mutations identified in blood, archival tissue, or screening tumor tissue

Bryce A et al NEJM 2023; 388; 719-32. **NCT02975934**.

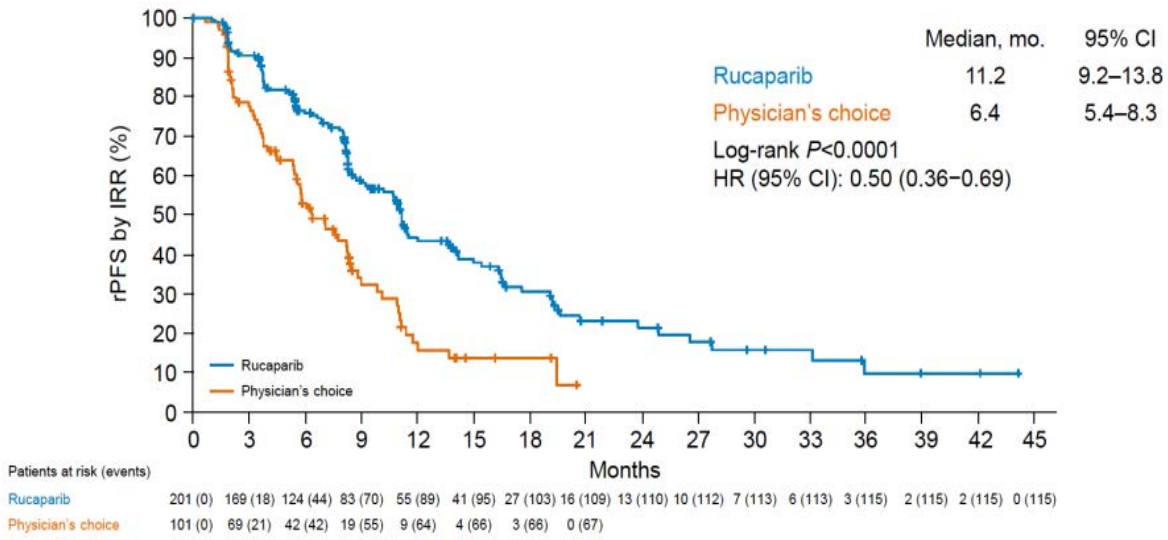
TRITON3: rPFS in ITT Population



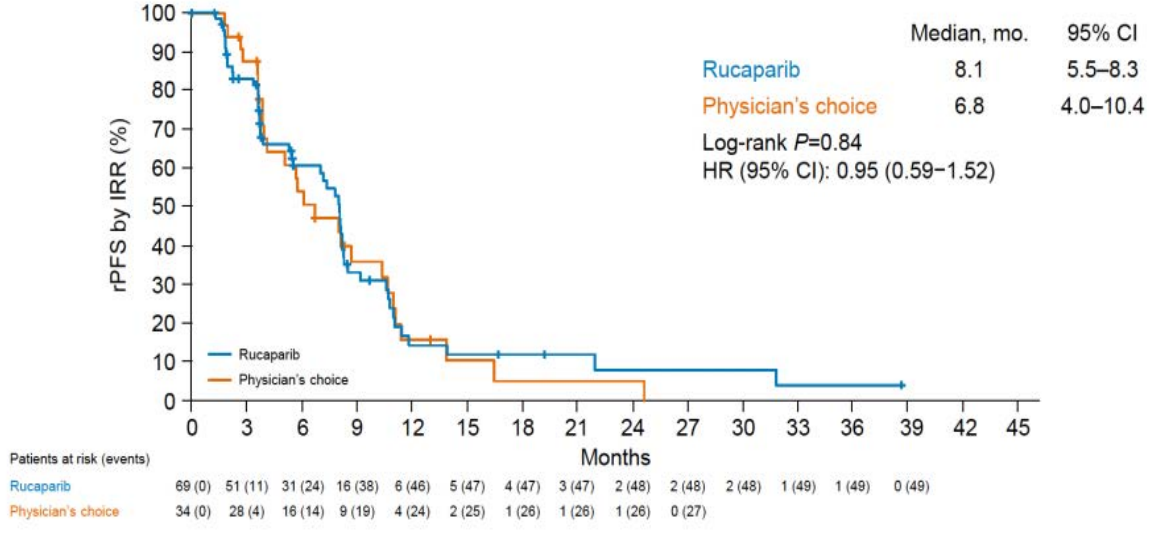
Bryce A et al NEJM 2023; 388; 719-32.

TRITON3: rPFS in *BRCA1/2* and *ATM* Subgroups

BRCA1/2 Subgroup

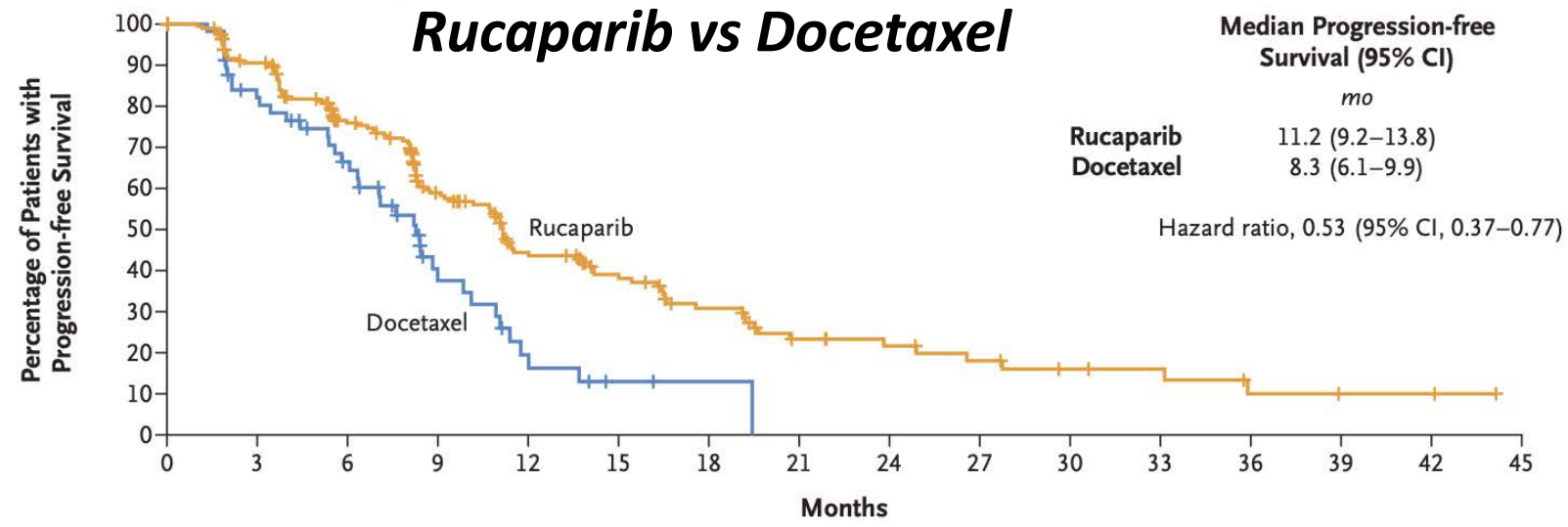


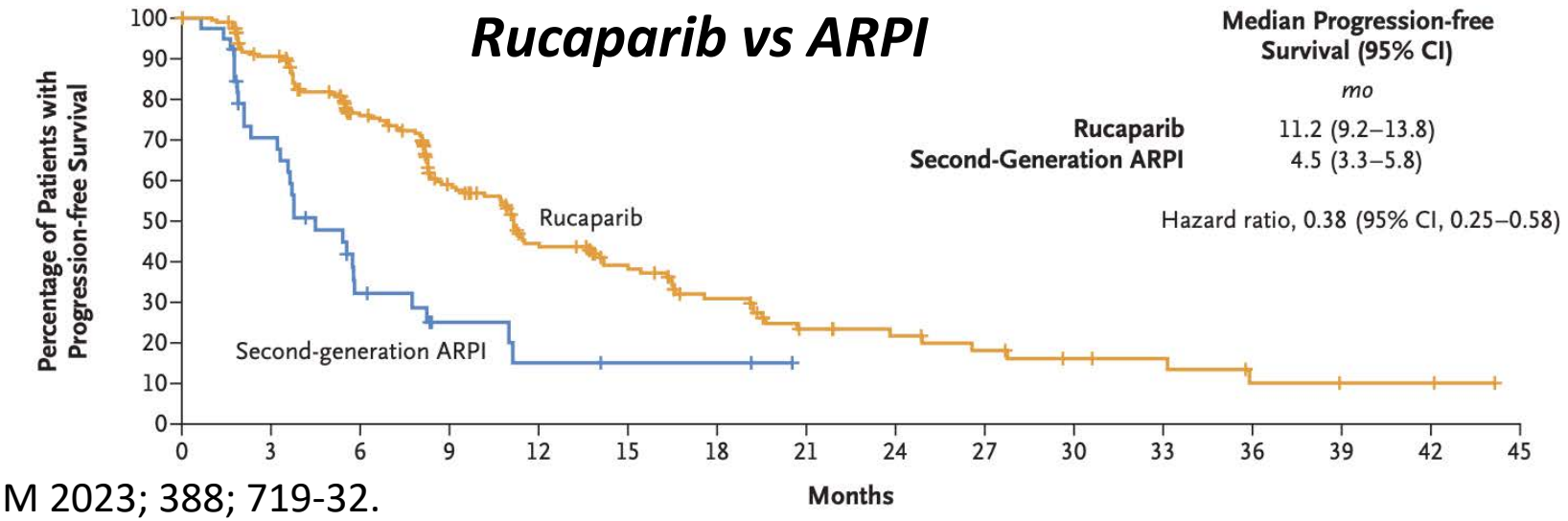
ATM Subgroup



Bryce A et al NEJM 2023; 388; 719-32.

TRITON3: rPFS by Control Treatment in *BRCA1/2* Subgroup





Bryce A et al NEJM 2023; 388; 719-32.

PARPi-Based *Combinations* (PROpel, MAGNITUDE, & TALAPRO-2)

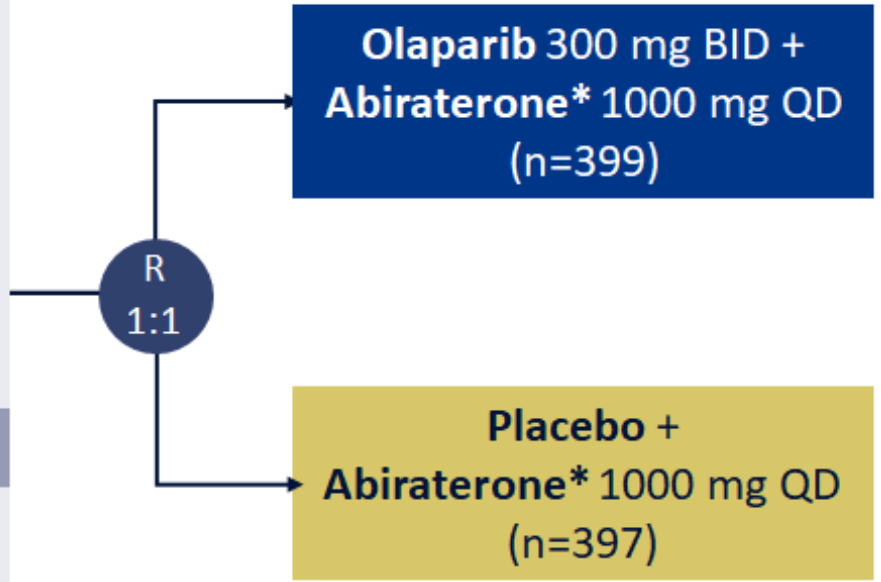
PROpel: Phase III Trial of Abiraterone +/– Olaparib

Patient population

- mCRPC
- Docetaxel for mCSPC allowed
- No prior abiraterone
- Other NHT allowed if stopped ≥12 months prior to enrollment
- Ongoing ADT
- ECOG PS 0–1

Stratification factors

- Site of distant metastases (bone only vs visceral vs other)
- Prior taxane for mCSPC



Primary endpoint

rPFS or death by investigator assessment

Key secondary endpoint

- OS

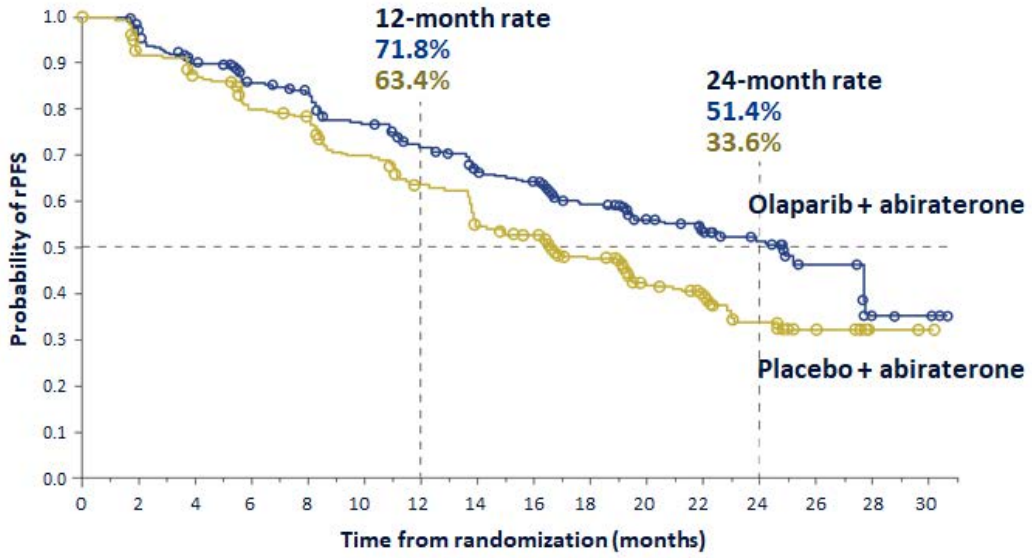
Additional endpoints

- TFST
- PFS2
- ORR
- HRR mutation prevalence (tested retrospectively)
- HRQOL
- Safety and tolerability

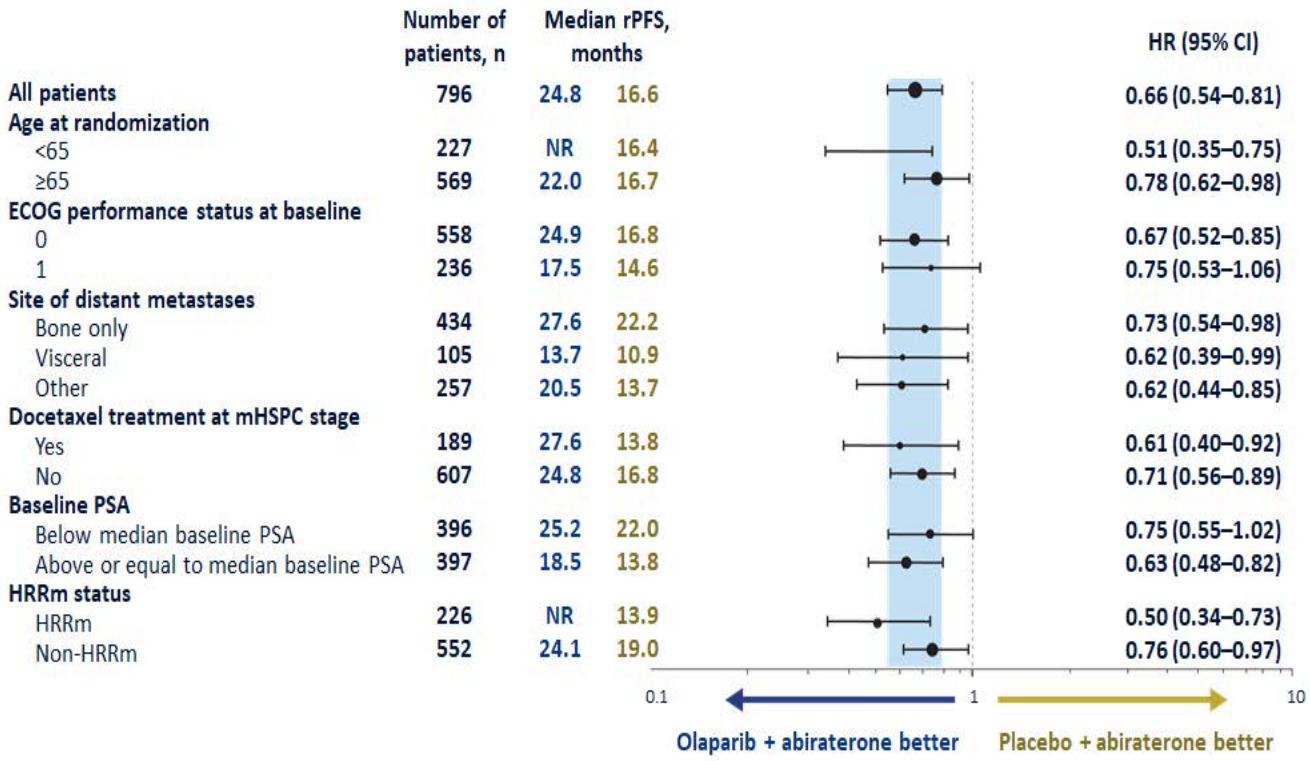
*Plus prednisone or prednisolone 5 mg BID

Saad F et al. *ASCO GU 2022*; abstr 11; **NCT03732820**.

PROpel: Radiographic Progression-Free Survival



	Olaparib + abiraterone (n=399)	Placebo + abiraterone (n=397)
rPFS by investigator assessment		
Events, n (%)	168 (42.1)	226 (56.9)
Median rPFS, months	24.8	16.6
HR (95% CI)	0.66 (0.54–0.81); *P*<0.0001	
rPFS by blinded independent central review		
HR (95% CI)	0.61 (0.49–0.74); *P*<0.0001	



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

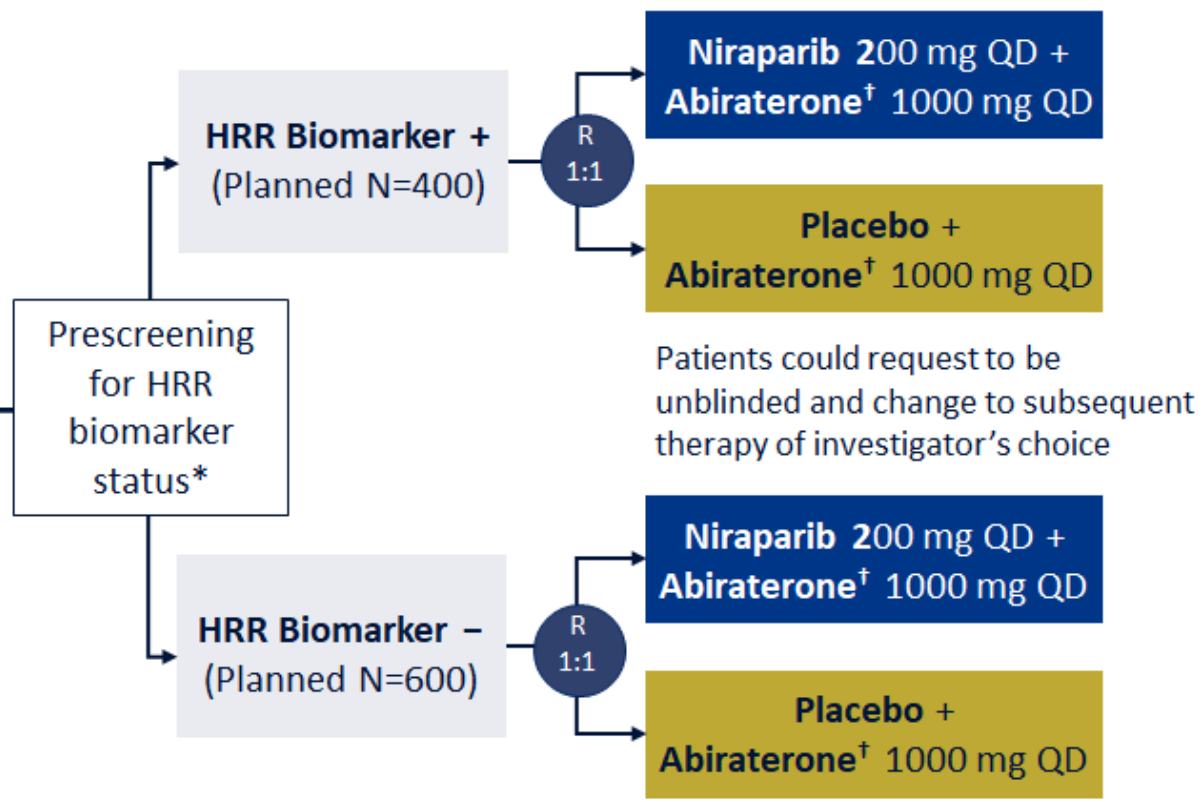
MAGNITUDE: Phase III Trial of Abi +/– Niraparib

Patient population

- mCRPC
- ≤4 months prior abiraterone for mCRPC allowed
- ECOG PS 0–1
- BPI-SF worst pain score ≤3

Stratification factors

- Prior taxane for mCSPC
- Prior NHT for nmCRPC or mCSPC
- Prior abiraterone for mCRPC
- *BRCA1/2* vs other HRR gene alterations (HRR biomarker+ cohort only)



Patients could request to be unblinded and change to subsequent therapy of investigator's choice

Primary endpoint

rPFS by central review

Key secondary endpoints

- Time to cytotoxic chemotherapy
- Time to symptomatic progression
- OS

Other prespecified endpoints

- Time to PSA progression
- ORR
- PFS2
- Time to pain progression
- Patient-reported outcomes

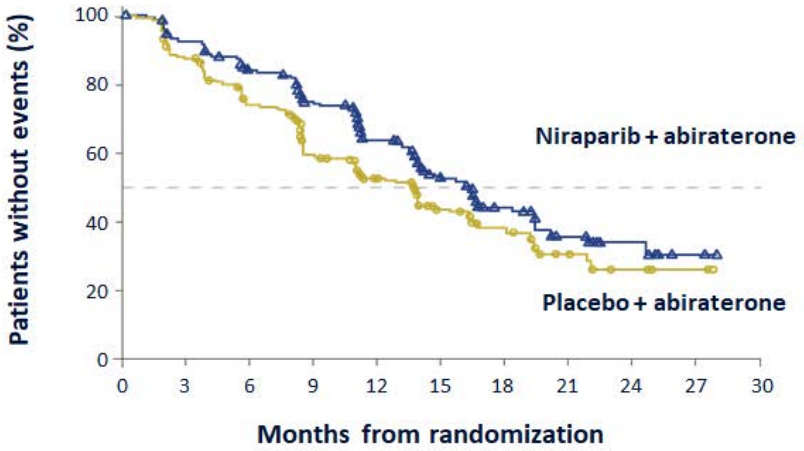
*HRR gene panel: ***ATM, BRCA1, BRCA2, BRIP1, CDK12, CHEK2, FANCA, HDAC2, PALB2***

†Plus prednisone 10 mg daily

Chi KN et al. *ASCO GU 2022*; abstr 12; **NCT03748641**.

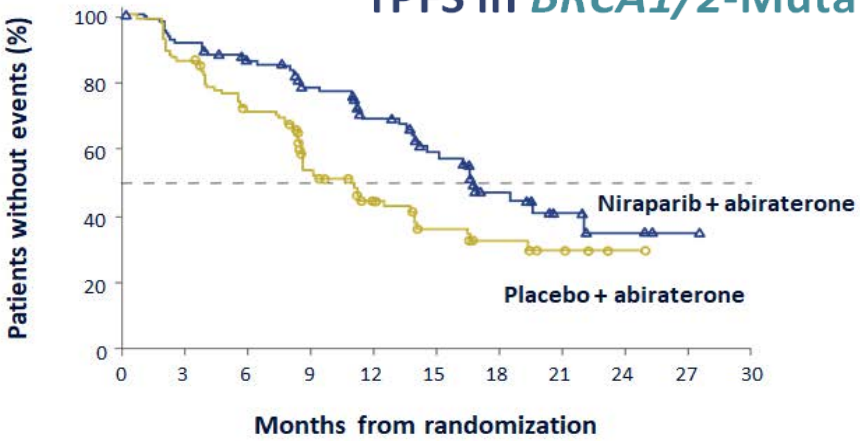
MAGNITUDE: Radiographic Progression-Free Survival

rPFS in All HRR BM+ Cohort



	Niraparib + abiraterone (n=212)	Placebo + abiraterone (n=211)
rPFS by central review		
Median rPFS, months	16.5	13.7
HR (95% CI)	0.73 (0.56–0.96); *P*=0.0217	
rPFS assessed by investigator		
Median rPFS, months	19.0	13.9
HR (95% CI)	0.64 (0.49–0.86); *P*=0.0022	

rPFS in *BRCA1/2*-Mutated Group



	Niraparib + abiraterone (n=113)	Placebo + abiraterone (n=112)
rPFS by central review		
Median rPFS, months	16.6	10.9
HR (95% CI)	0.53 (0.36–0.79); *P*=0.0014	
rPFS assessed by investigator		
Median rPFS, months	19.3	12.4
HR (95% CI)	0.50 (0.33–0.75); *P*=0.0006	

Chi KN et al. *ASCO GU 2022*; abstr 12.

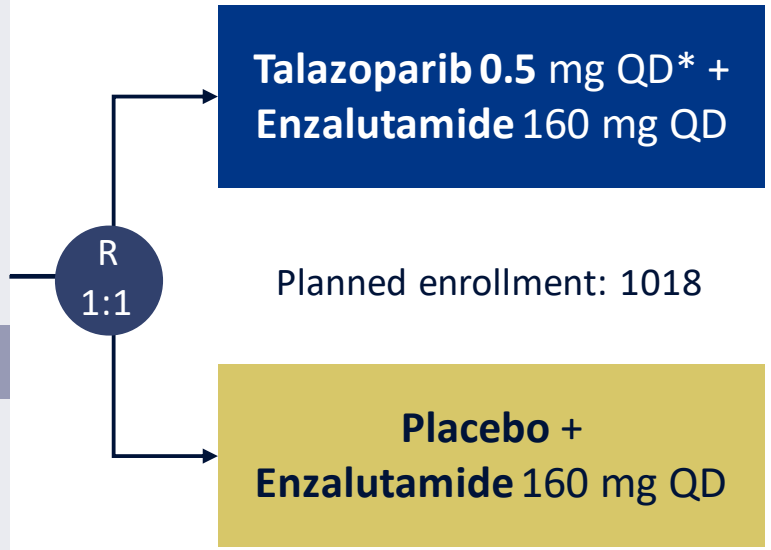
TALAPRO-2: Phase III Trial of Enza +/– Talazoparib

Patient population

- mCRPC with progression (PSA, bone, and/or soft tissue)
- Prior docetaxel and/or abiraterone in CSPC setting allowed
- Ongoing ADT or bilateral orchiectomy
- ECOG PS 0–1

Stratification factors

- Previous treatment with abiraterone or taxane-based chemotherapy for CSPC
- DDR# alteration status (deficient vs nondeficient/unknown)



Co-primary endpoints

- rPFS by BICR per RECIST 1.1 and PCWG3 in **All-comers (Cohort 1), n=804**
- rPFS by BICR in patients with **DDR# alterations (Cohort 2), n=214**

Key secondary endpoints (analyzed for both cohorts separately)

- OS
- OR per RESIST 1.1 (measurable disease)
- PSA response ≥50%
- Time to PSA progression
- Time to initiation of cytotoxic CT or antineoplastic therapy
- Time to first symptomatic skeletal event
- PFS2
- Safety
- Patient-reported outcomes

*0.35 mg QD if moderate renal impairment

DDR alterations (*BRCA1/2, PALB2, ATM, ATR, CHEK2, FANCA, RAD51C, NBN, MLH1, MRE11A, CDK12*).

Agarwal N et al. *Future Oncol.* 2022;18:425-436; **NCT03395197**.

TALAPRO-2: Phase III Trial of Enza +/– Talazoparib

All-comers cohort	rPFS 21.9 mo → NR	HR 0.63 (0.51-0.78)	*P* <0.001
HRR *mutated*	rPFS 16.4 → 27.9 mo	HR 0.46 (0.30-0.70)	*P* <0.001
HRR *wild-type*	rPFS 16.6 → 25.8 mo	HR 0.66 (0.49-0.91)	*P* = 0.009

Agarwal N et al. *ASCO GU 2023*; abstr LBA17.

Conclusions

- Germline and somatic DNA-repair mutations are common in mCRPC patients, and should be assayed
- Olaparib is approved for HRR-mutated mCRPC, and Rucaparib is approved for *BRCA1/2*-mutated mCRPC
- PROpel (Abi + Olap) improved rPFS in unselected mCRPC; MAGNITUDE (Abi + Nira) improved rPFS only in HRRm mCRPC
- TALAPRO-2 (Enza + Tala) improved rPFS in unselected mCRPC pts, and in HRRm as well as HRRwt subgroups
- No PARP inhibitor–based combination is FDA approved yet in prostate cancer

FDA Advisory Committee Supports the Approval of First-Line Olaparib plus Abiraterone and Prednisone for *BRCA*-Mutated mCRPC

Press Release: April 28, 2023

The US FDA Oncologic Drugs Advisory Committee (ODAC), by a vote of 11 to 1 with one abstention, supported FDA approval of olaparib plus abiraterone and prednisone or prednisolone (abi/pred) for the first-line treatment of adult patients with BRCA-mutated (BRCAm) metastatic castration-resistant prostate cancer (mCRPC). The committee voted that FDA should restrict use of olaparib plus abi/pred to these BRCAm mCRPC patients, recommending against approval beyond this patient population.

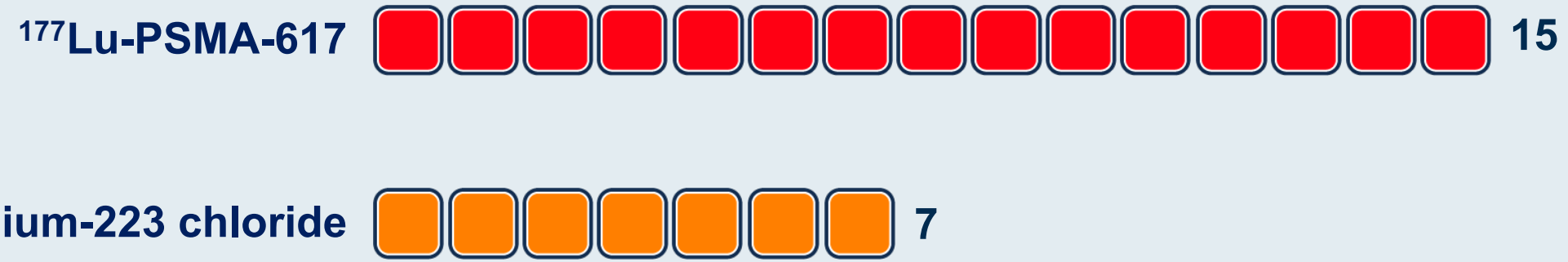
In August 2022, the FDA accepted the supplemental New Drug Application for olaparib plus abi/pred for priority review based on positive results from the pivotal Phase 3 PROpel trial.

https://finance.yahoo.com/news/fda-advisory-committee-vote-lynparza-213000796.html

MODULE 5: Current and Emerging Strategies in the Treatment of Recurrent mCRPC

RTP
RESEARCH
TO PRACTICE

For a 71-year-old man with PSMA-positive bone-only mCRPC who has experienced disease progression on multiple lines of systemic therapy, including ADT, enzalutamide and sipuleucel-T, which of the following therapies would you generally recommend first?



Survey of urologic oncology clinical investigators

To what extent do you believe the dry mouth associated with ^{177}Lu-PSMA-617 is problematic for patients?

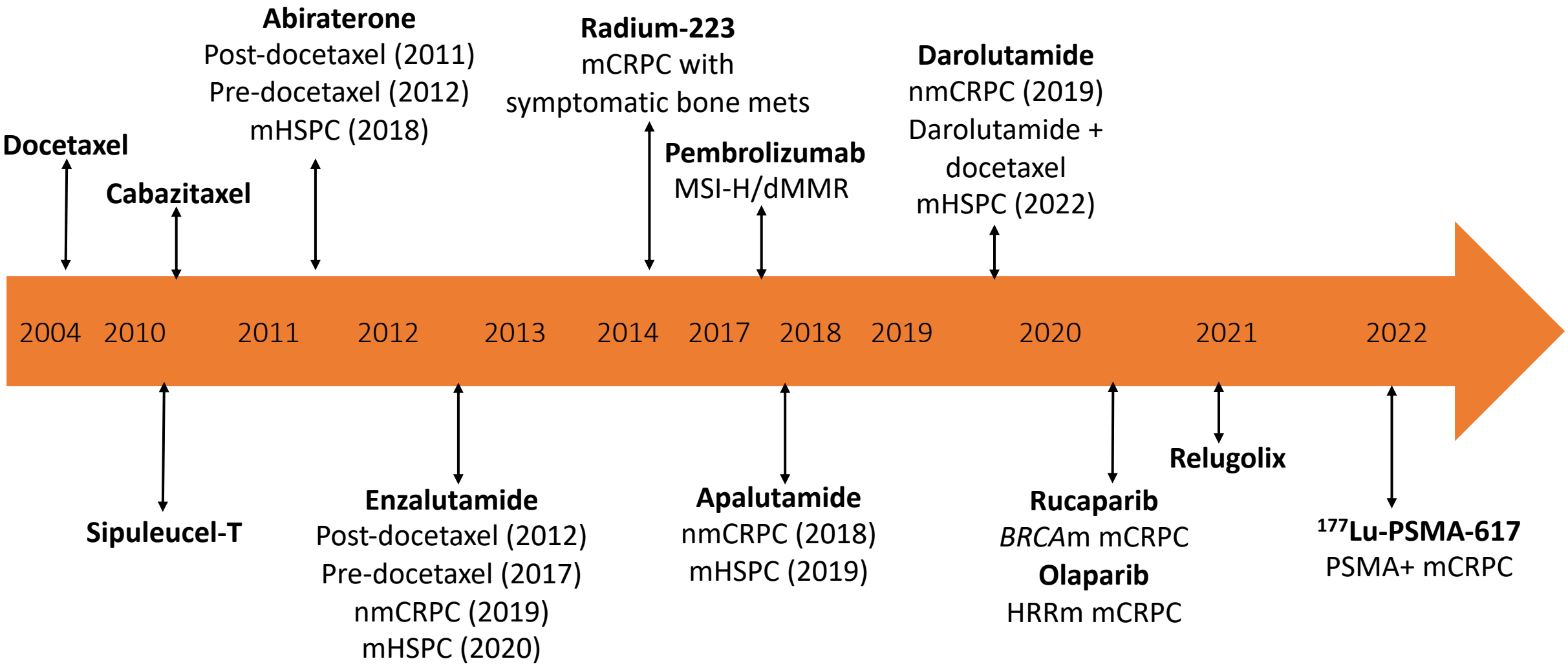
Survey of urologic oncology clinical investigators

Current and Emerging Strategies in the Treatment of Recurrent mCRPC

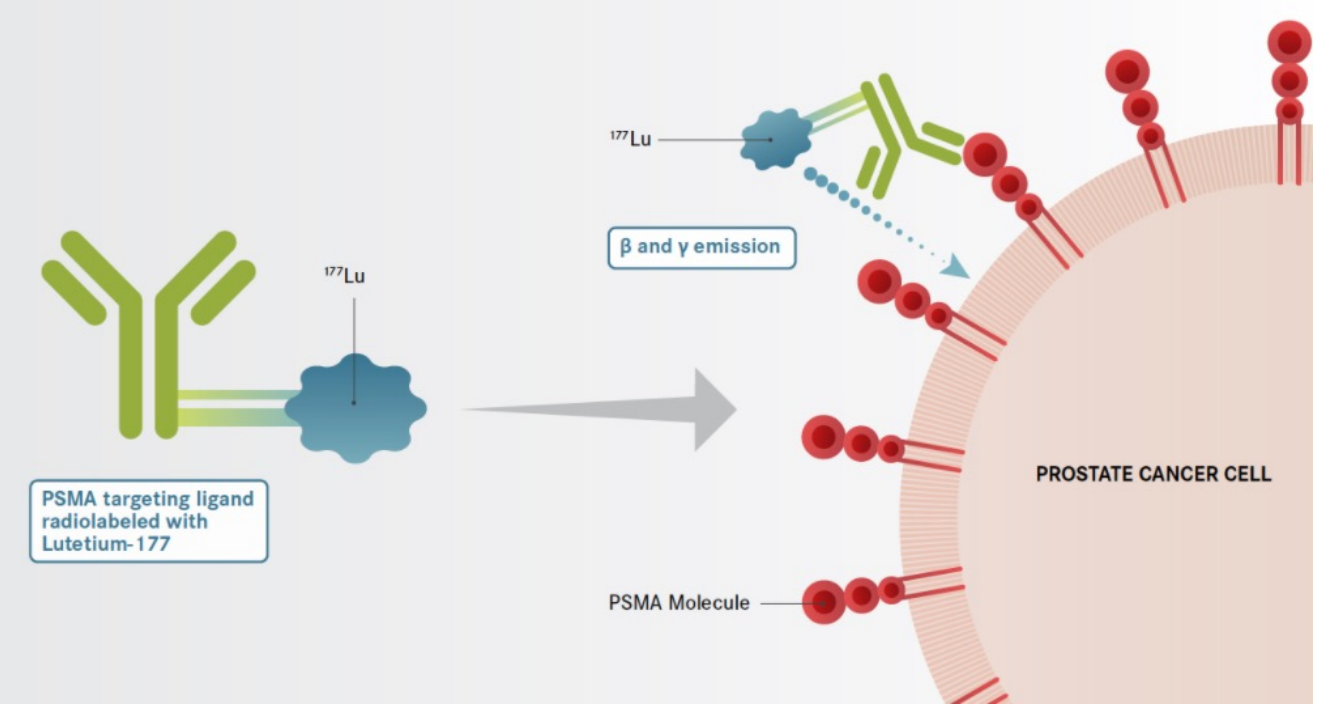
Himisha Beltran, MD

Dana Farber Cancer Institute

Treatment Landscape of mCRPC continues to evolve



^{177}Lu-PSMA-617



PSMA (prostate-specific membrane antigen): cell surface receptor involved in folate uptake and cell migration, proliferation, and survival

Overexpressed in nearly all HSPC and ~80% of mCRPC

Also expressed in normal prostate, proximal renal tubules, small intestine, salivary glands

177Lu-PSMA-617: β-emitting radioligand conjugated to small peptide that binds to PSMA

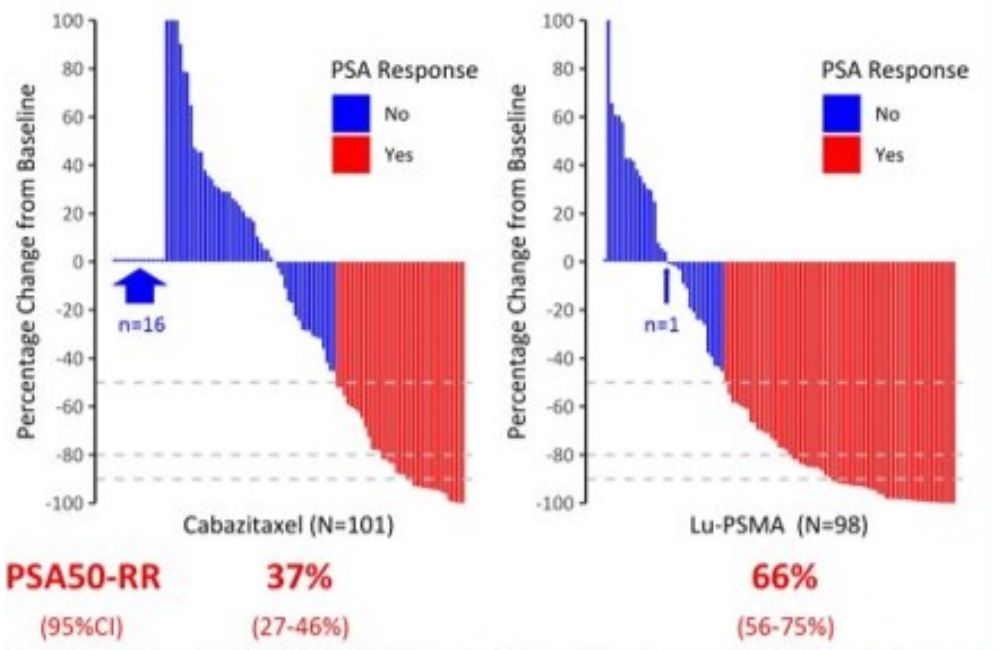
FDA approved for PSMA-positive mCRPC previously treated with AR pathway inhibition and taxane

- Select patients using gallium GA 68 PSMA PET
- 7.4 GBq (200 mCi) IV Q6W for up to 6 doses or until PD/unacceptable toxicity

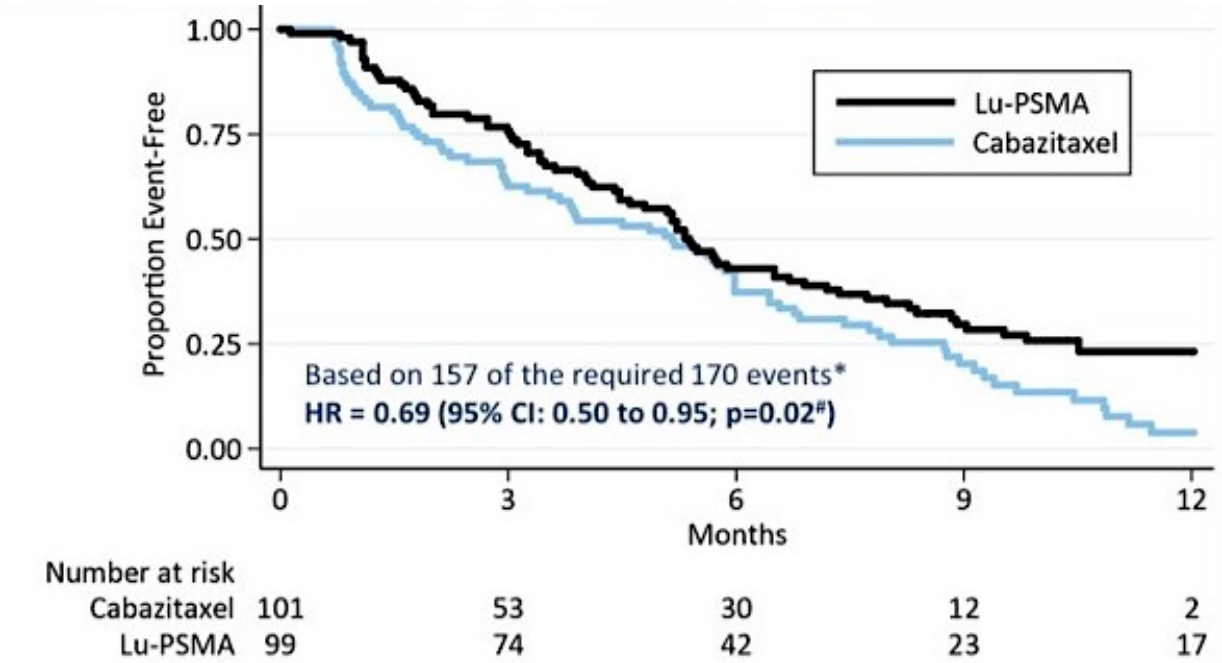
TheraP Trial- Phase 2 study ^{177}*Lu-PSMA-617 vs Cabazitaxel*

- PSA response
  - ^{177}Lu-PSMA = 66%
  - Cabazitaxel = 37%

Primary endpoint: PSA ≥ 50% response

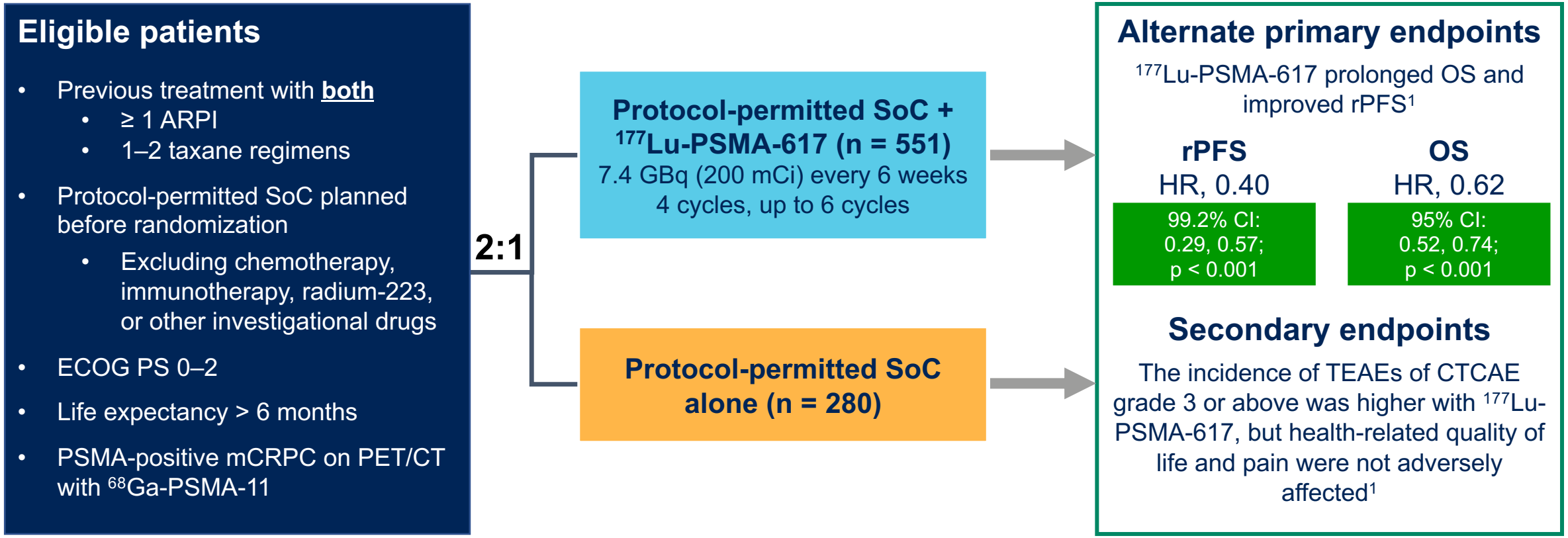


Secondary endpoint: PSA PFS



- Hofman M, et al. ASCO® 2020. Presentation 5500.

Phase 3 VISION trial (Lu-PSMA-617)



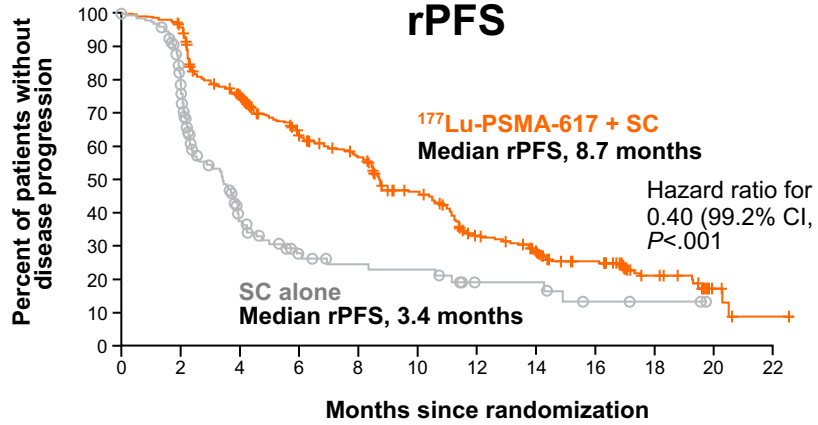
Required ^{68}Ga—PSMA-11 PET-CT with
at least one PSMA-positive lesion and no PSMA-negative soft tissue or visceral lesions ≥1cm or lymph nodes ≥2.5cm

Sartor et al NEJM 2021

^{177}Lu-PSMA-617: Phase 3 VISION Trial of ^{177}Lu-PSMA-617 in Patients With PSMA+ mCRPC With Prior AR Pathway Inhibitor and Taxane-Based Chemotherapy

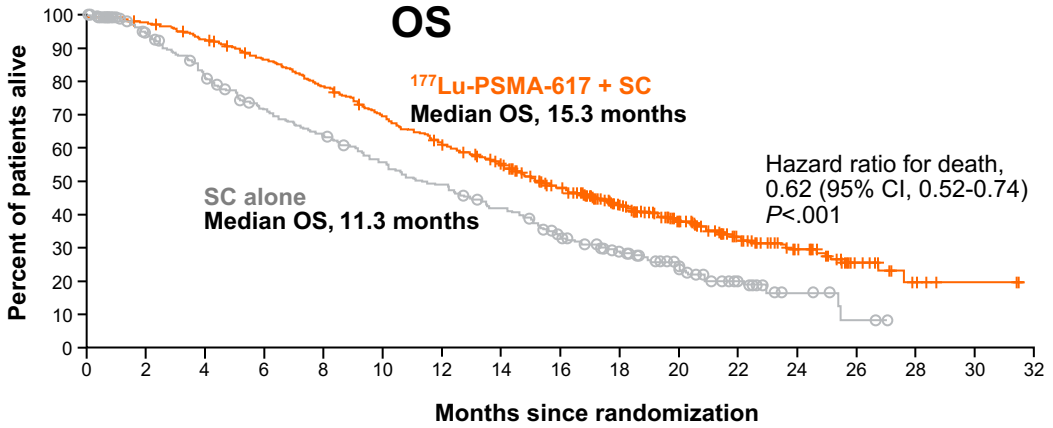
	^{177}Lu-PSMA-617 + SC (N=551)	SC alone (N=280)
Demographics		
Median age (range), years	70 (48-94)	71.5 (40-89)
Prior AR pathway inhibitor, %		
1	54	46
2	39	46
>2	7	9
Prior taxane therapy, %		
1	59	56
2	40	44
Safety	**(n=529)**	**(n=205)**
Most common (>25%) AEs, %	Fatigue (43), dry mouth (39), nausea (35), anemia (32)	
Most common (>5%) grade 3/4 AEs, %	Anemia (13), thrombocytopenia (8%), lymphopenia (8%), fatigue (6%)	
AEs leading to dose reduction or discontinuation		
Dose reductions due to AEs, %	6 (grade ≥3, 2)	Not applicable
Discontinuations due to AEs, %	12 (grade ≥3, 7)	Not applicable

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



No. at Risk

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



No. at Risk

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

- Median time to the first skeletal event was also longer with ^{177}Lu-PSMA-617 than standard care (SC; 11.5 vs 6.8 months; *P*<.001)

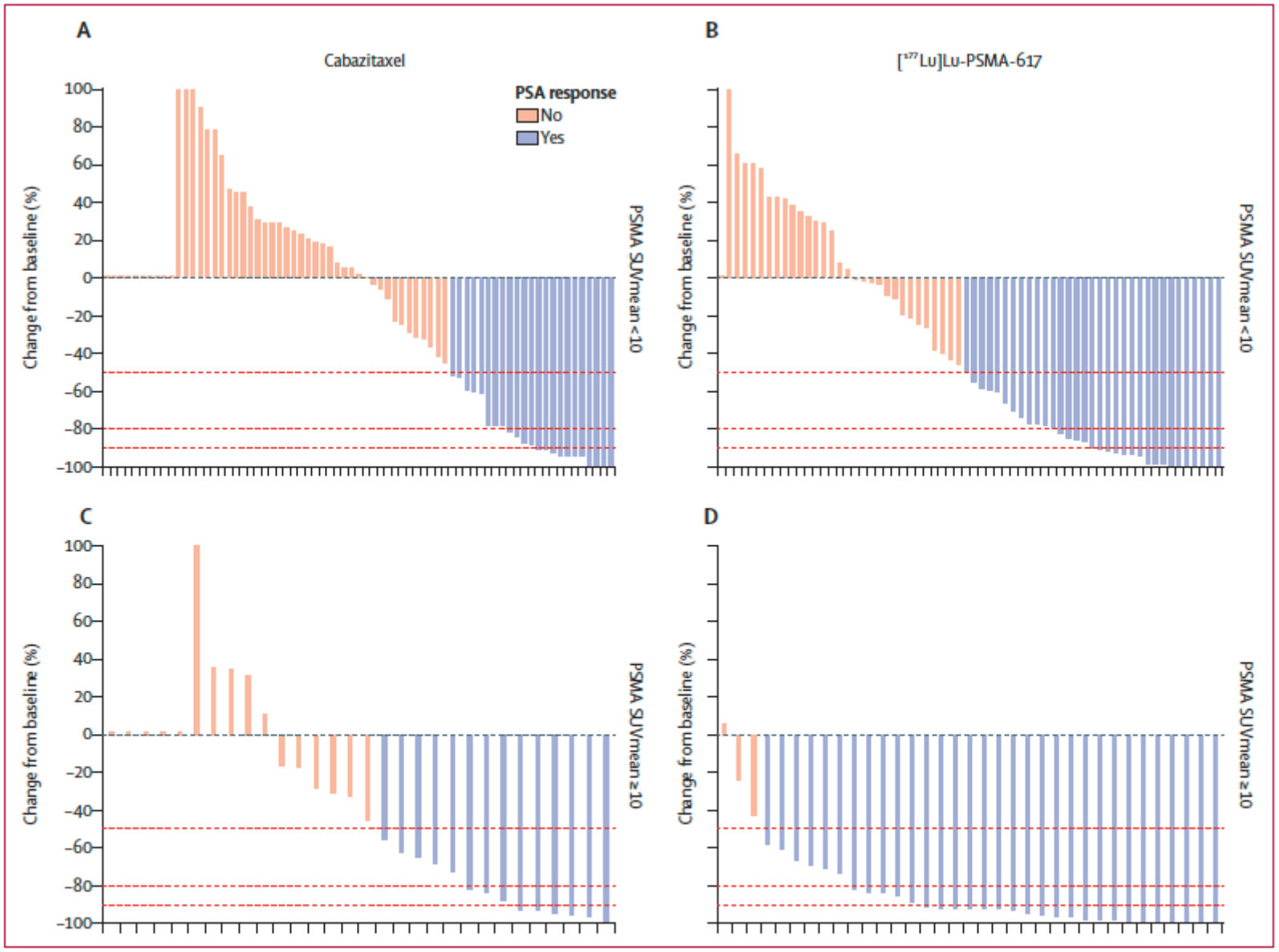
PSMA and FDG-PET as predictive and prognostic biomarkers in patients given [^{177}Lu]Lu-PSMA-617 versus cabazitaxel for metastatic castration-resistant prostate cancer (TheraP): a biomarker analysis from a randomised, open-label, phase 2 trial

*James P Buteau, Andrew J Martin, Louise Emmett, Amir Iravani, Shahneen Sandhu, Anthony M Joshua, Roslyn J Francis, Alison Y Zhang, Andrew M Scott, Sze-Ting Lee, Arun A Azad, Margaret M McJannett, Martin R Stockler, Scott G Williams, Ian D Davis, Michael S Hofman, for the TheraP Trial Investigators and the Australian and New Zealand Urogenital and Prostate Cancer Trials Group**

- TheraP trial -- ^{177}Lu-PSMA-617 improved PSA response rate and progression-free survival compared with cabazitaxel in men with mCRPC. Used both PSMA and FDG for eligibility. ~70% of screened pts were PSMA positive.

- PSMA and FDG imaging parameters were evaluated as predictive and prognostic biomarkers in this patient population.

Buteau et al, Lancet Oncol 2022



Buteau et al, Lancet Oncol 2022

Odds of PSA response to ^{177}Lu-PSMA-617 versus cabazitaxel significantly higher for SUVmean of 10 or higher compared with those with SUVmean of less than 10 (odds ratio [OR] 12·19 [95% CI 3·42. –58·76] vs 2·22 [1·11–4·51].

SUVmean also correlates with outcomes in VISION (*Kuo et al, ASCO 2022)*

** Of note: Quantitative PET parameters used for SUVmean calculation require specialised software and are not yet routinely available in most clinics*

FDG volume in TheraP prognostic

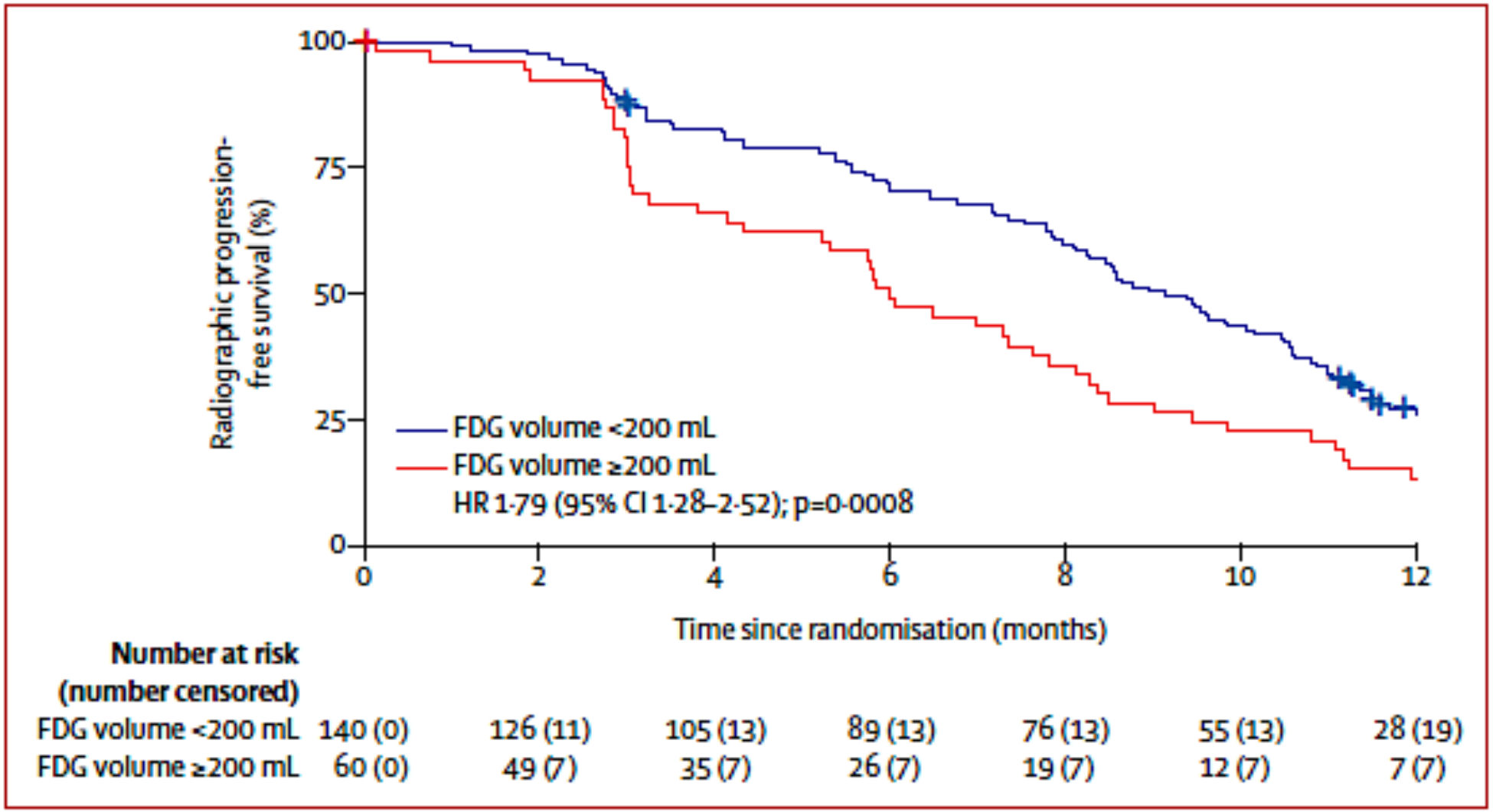
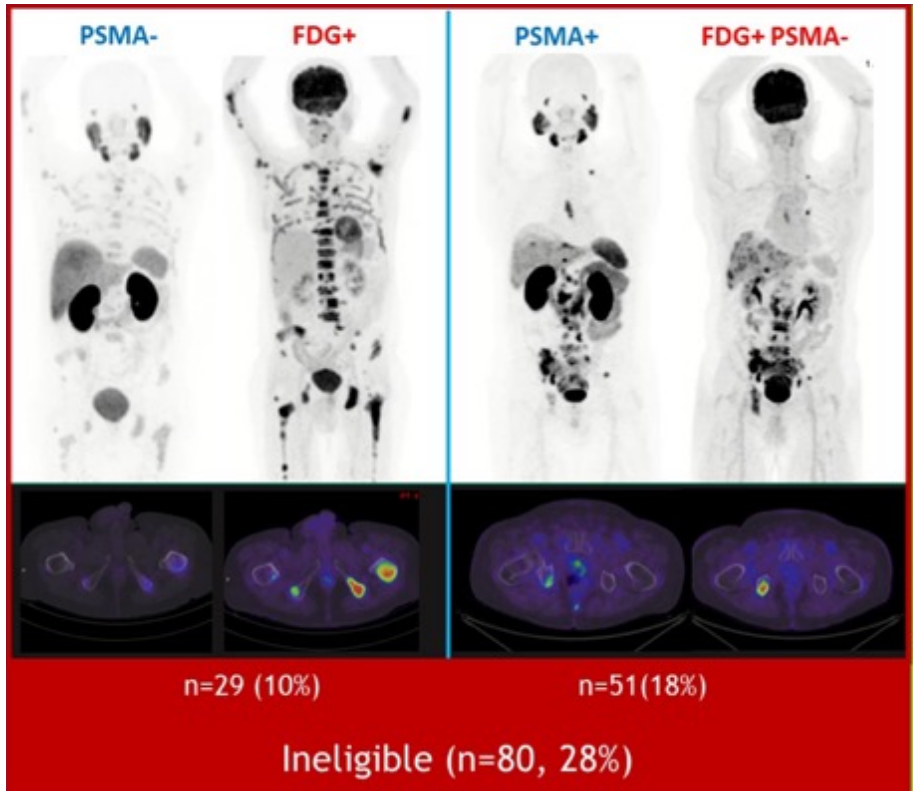


***Figure 5*: Radiographic progression-free survival according to FDG-PET MTV**
FDG=2-[18F]fluoro-2-deoxy-D-glucose. MTV=metabolic tumour volume.

Buteau et al, Lancet Oncol 2022

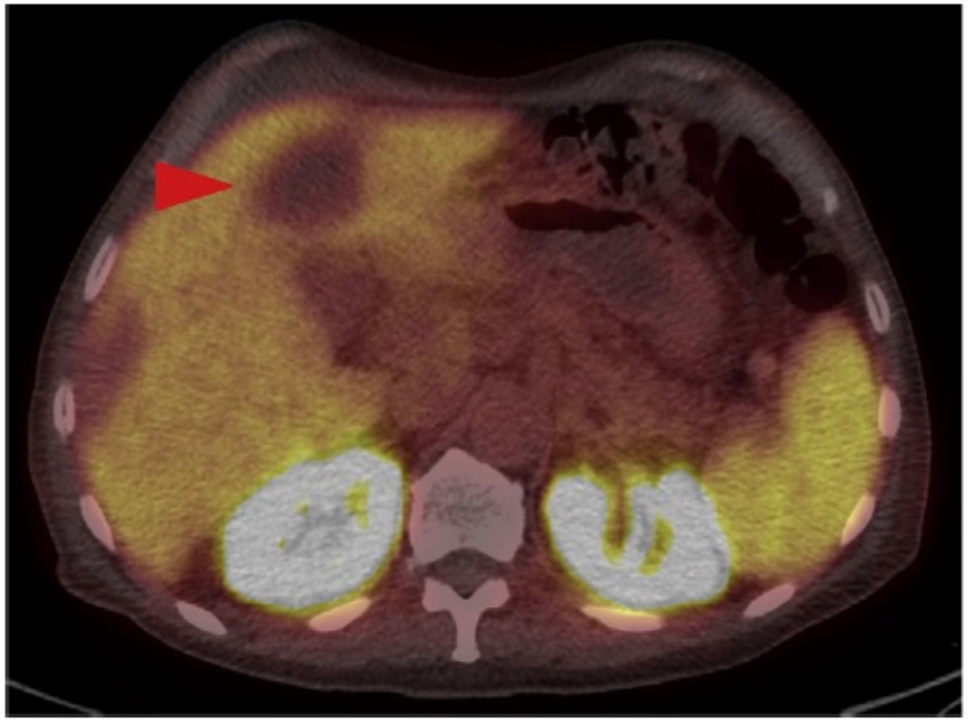
Loss of PSMA Expression in a Subset of CRPC

12.6% (VISION) + 28% (TheraP) were not eligible for Lu-PSMA due to PSMA-negative disease



Hofman et al. Lancet Oncol 2018, Thang et al, Eur Urol Oncol 2018

PSMA-low biopsies may reveal NEPC



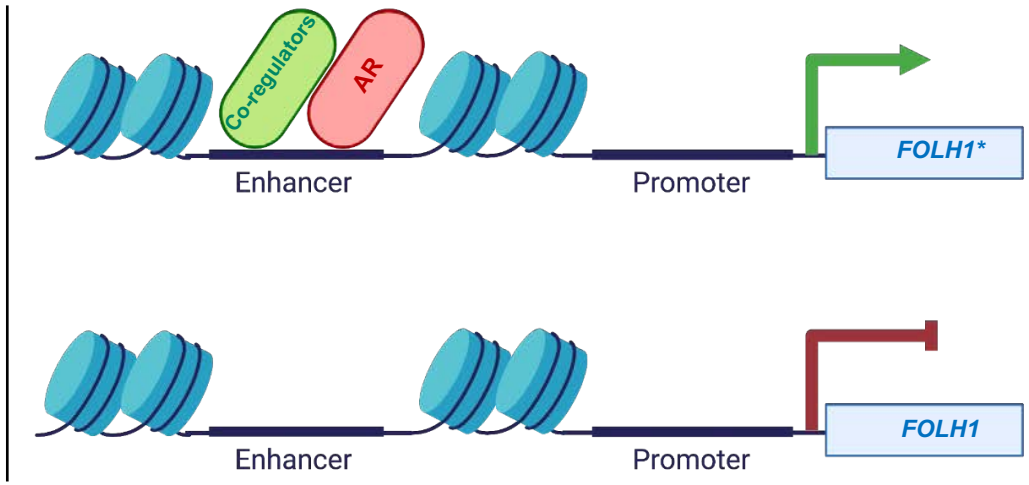
Tosoian et al, 2016

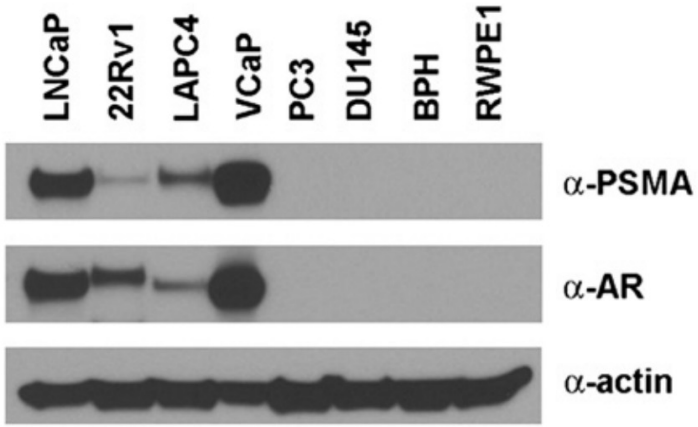
Bakht et al, Nat Cancer 2023

PSMA negative disease associated with poor prognosis (median OS 2.5 mo in TheraP)

AR Regulation of PSMA

Projected PSMA regulation models





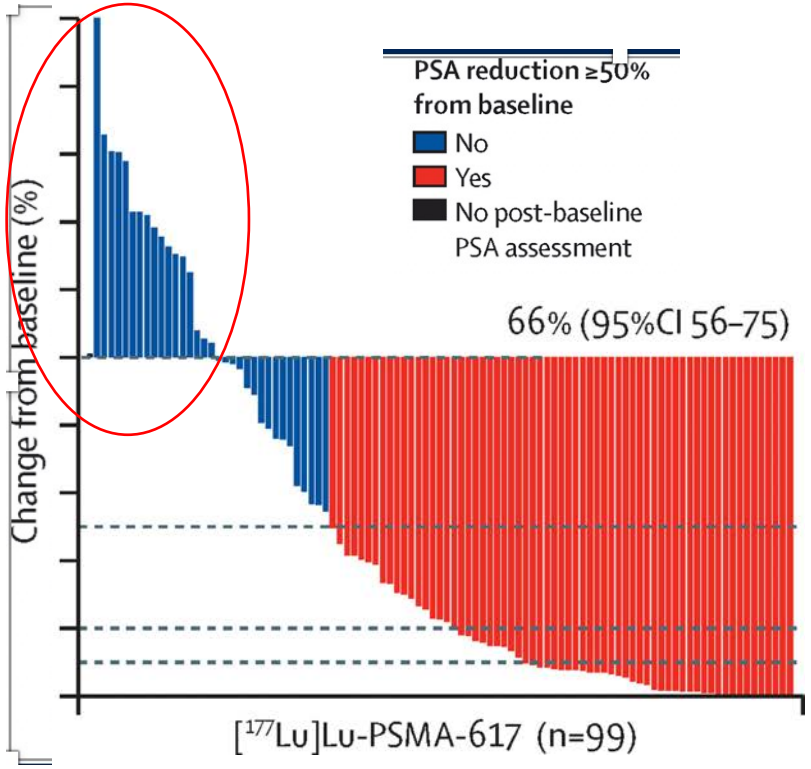
**FOLH1* gene encodes PSMA protein*

*Evans et al **PNAS 2011***

AR negative prostate cancer associates with loss of PSMA expression

But there are exceptions to this rule

Bakht et al, Nat Cancer 2023



TheraP trial--Hofman et al, Lancet 2021

Patient selection for PSMA-directed therapy

- Expression of the target (PSMA)
- Other biomarkers of response (tumor features, drug features, drug mechanism)
- Mechanisms of resistance (guide next therapy)

Other drugs that target PSMA

- Radionuclide therapies
  - ^{225}Ac-PSMA-617, ^{177}Lu-J591, ^{225}Ac-J591, ^{90}Y, others
- Bispecific T Cell Engager-- AMG160, BAY2010112, REGN5678
- CAR-T –CART-PSMA-TGFβRDN, P-PSMA-101
- PSMA-ADC
- **Is there cross resistance between drugs?**
- **Optimal combination therapies?**

Phase III PMSAfore Trial Meets Primary Endpoint with ^{177}Lu-PSMA-617 for PSMA-Positive mCRPC

Press Release: December 5, 2022

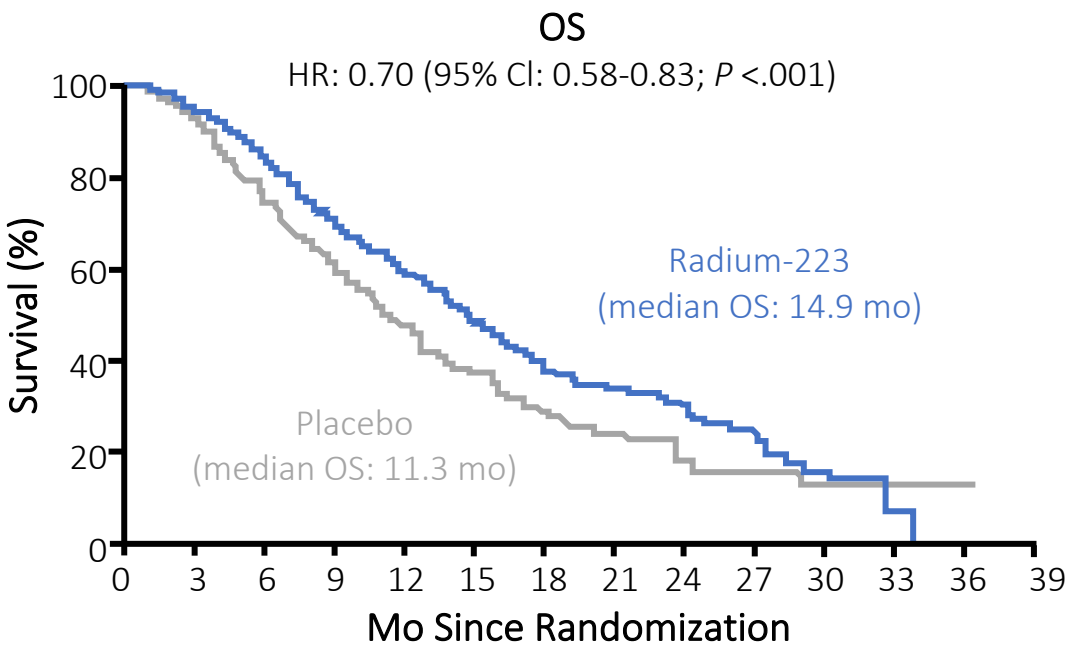
"Today, [it was announced that] the pivotal Phase III PSMAfore study with ^{177}Lu-PSMA-617, a prostate-specific membrane antigen (PSMA)-targeted radioligand therapy, met its primary endpoint. ^{177}Lu-PSMA-617 demonstrated a statistically significant and clinically meaningful improvement in radiographic progression-free survival (rPFS) in patients with PSMA-positive metastatic castration-resistant prostate cancer (mCRPC) after treatment with androgen-receptor pathway inhibitor (ARPI) therapy, compared to a change in ARPI. No unexpected safety findings were observed in PSMAfore; data are consistent with the already-well established safety profile of ^{177}Lu-PSMA-617.

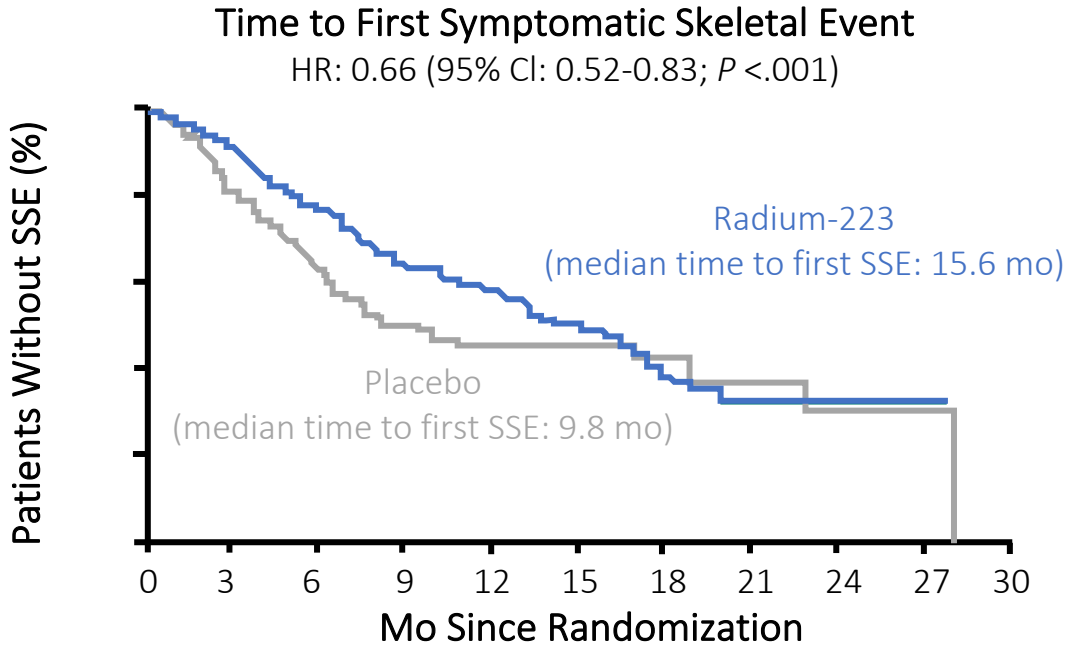
This is the second positive read-out for ^{177}Lu-PSMA-617 in a Phase III trial following the VISION study, where patients with PSMA-positive mCRPC who received ^{177}Lu-PSMA-617 plus standard of care after being treated with ARPI and taxane-based chemotherapy had a statistically significant reduction in risk of death. The PSMAfore results continue to support the important role of ^{177}Lu-PSMA-617 in treating patients with prostate cancer. The Phase III data will be presented at an upcoming medical meeting and discussed with the US Food and Drug Administration (FDA) in 2023 for regulatory approval."

https://www.globenewswire.com/en/news-release/2022/12/05/2567028/0/en/Novartis-PluvictoTM-shows-statistically-significant-and-clinically-meaningful-radiographic-progression-free-survival-benefit-in-patients-with-PSMA-positive-metastatic-castration-re.html

Radiopharmaceuticals: Radium-223 (α-emitting isotope, bone targeted)

ALSYMPCA: Symptomatic mCRPC With Bone Metastases

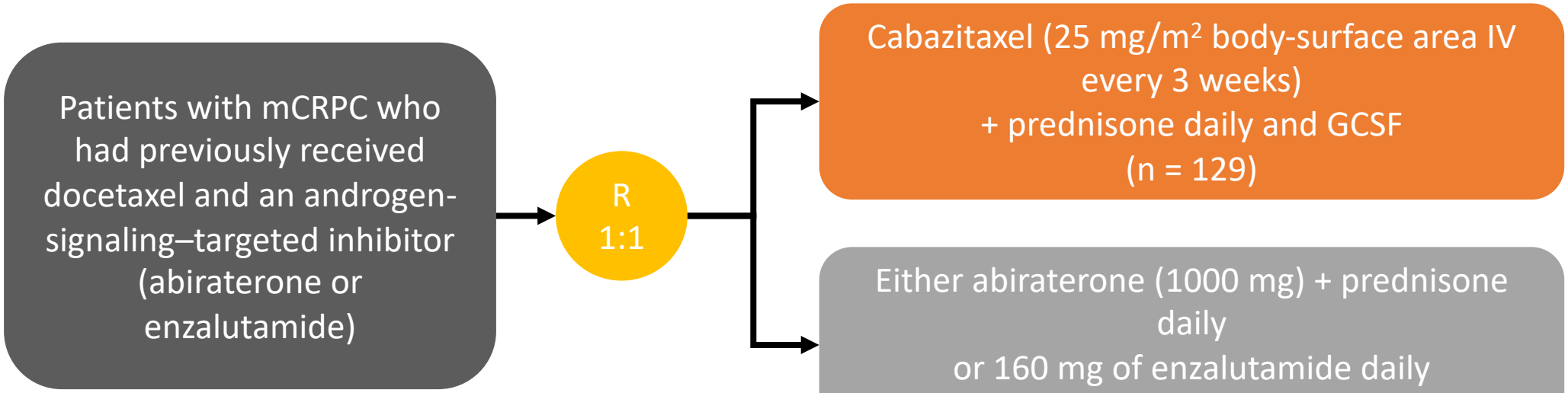




- FDA approved for CRPC with symptomatic bone metastases and no known visceral metastases
- Most common AEs: bone pain, nausea, anemia (no between-group differences)
- Seems feasible to give ^{177}Lu-PSMA-617 after Radium-223 – 1/3 pts in VISION had radium 223 (must have been >6 mo prior). Also supported by retrospective RALU study (Rahbar et al)- both safety and efficacy data

Parker. NEJM. 2013;369:213; Rahbar et al, J Nucl Med 2023

Cabazitaxel vs Abiraterone or Enzalutamide for mCRPC: *CARD Study*



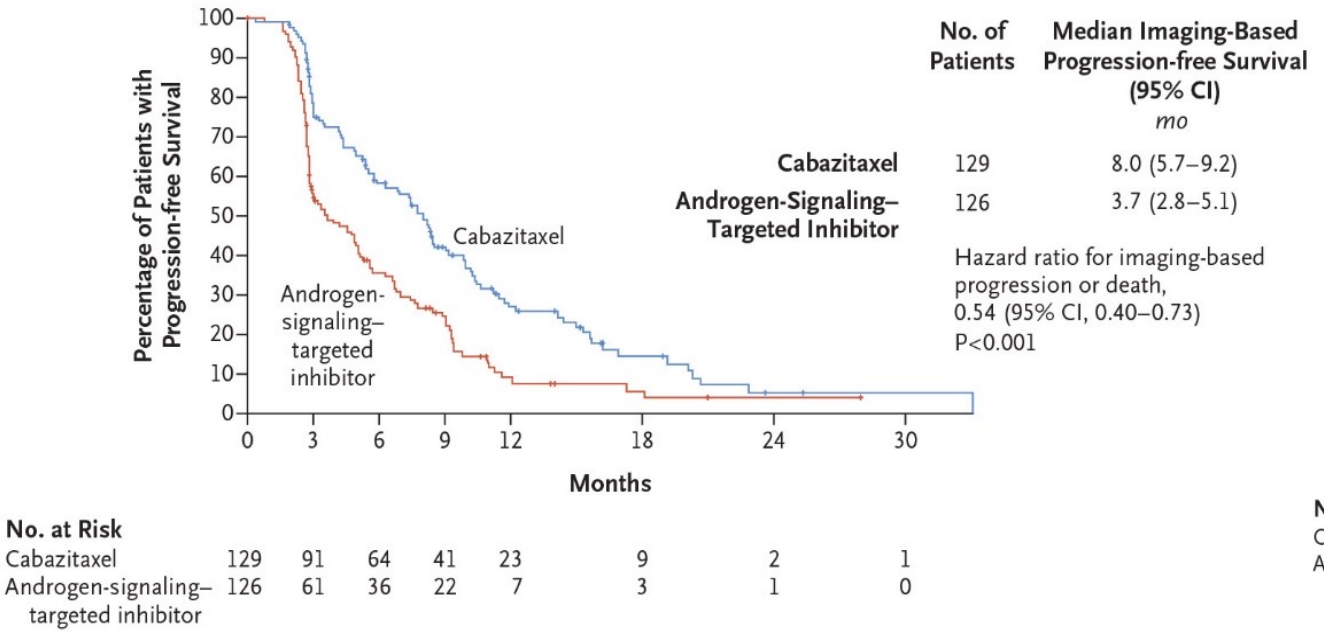
- *Abiraterone or docetaxel for mCSPC allowed*
- *Progression ≤12 mo on abiraterone or enzalutamide, before or after docetaxel*

Primary endpoint: imaging-based PFS
Secondary endpoints: survival, response, and safety

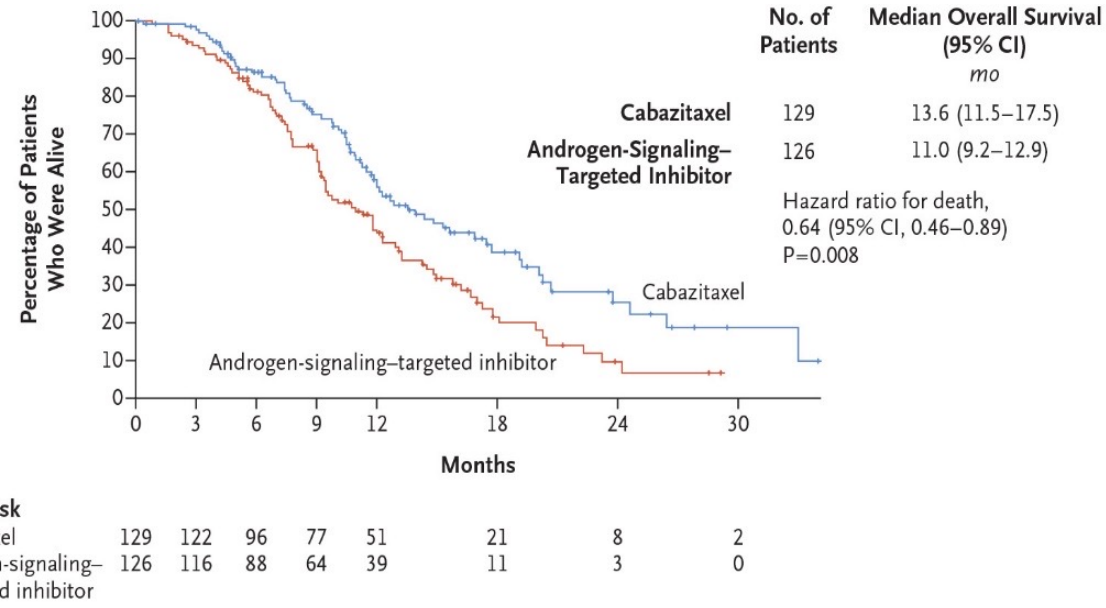
de Wit R, et al. *N Engl J Med*. 2019;381:2506-2518.

Cabazitaxel vs Abiraterone or Enzalutamide for mCRPC *Imaging-Based PFS and OS*

Imaging-based PFS



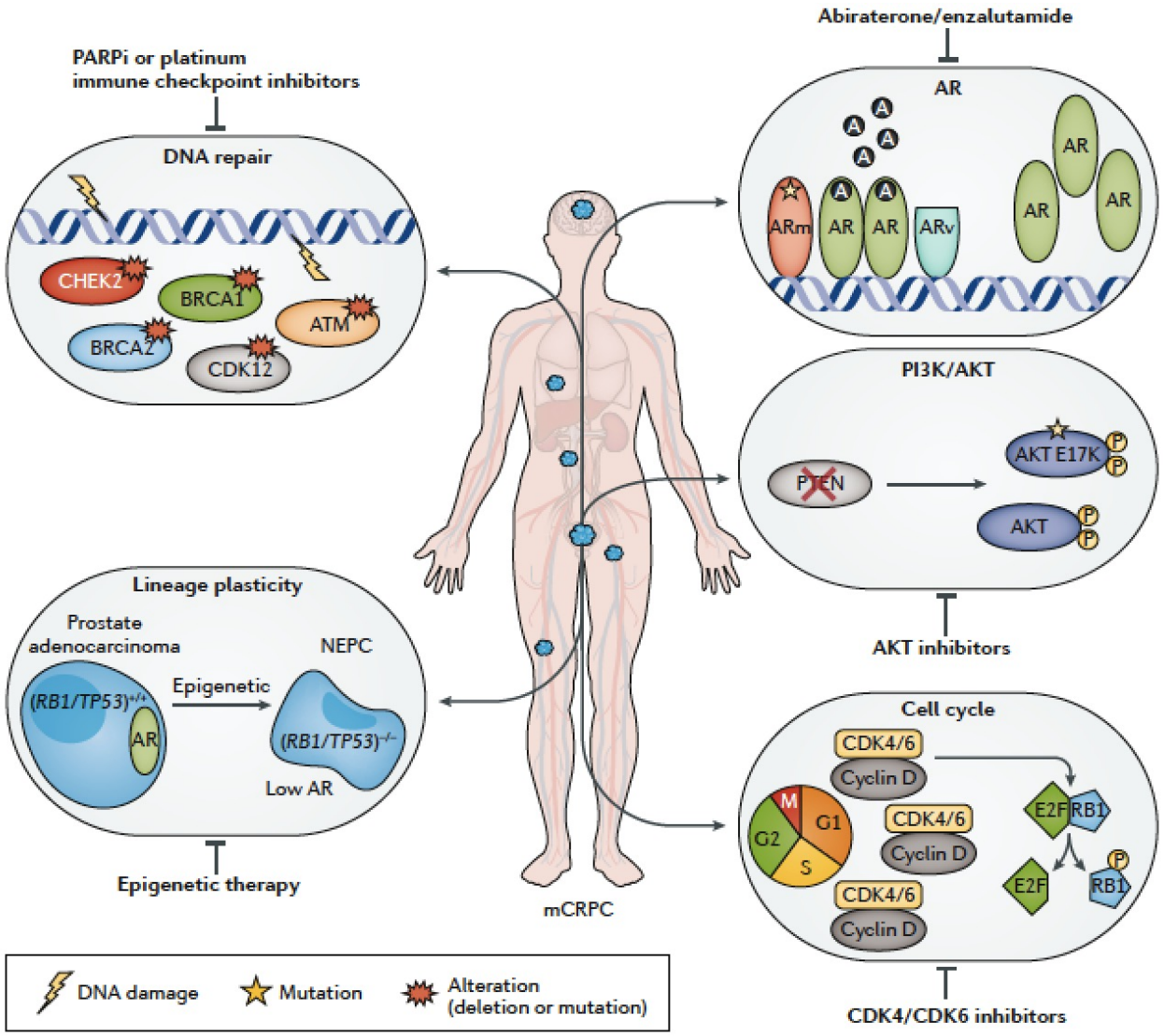
Median OS



Confirmed limited efficacy when sequencing ARPI (cross resistance)

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

Precision Medicine in Advanced Prostate Cancer



Ku et al., *Nat Rev Urol,* 2019

Genomic Testing Considerations

Primary tumor
- Advantages: non-invasive, HRD alterations tend to be early events
- Disadvantages: tissue quality (in PROfound, quality control failures in 31%), heterogeneity

Metastatic tumor
- Advantages: captures acquired alterations and tissue phenotype
- Disadvantages: invasive, bone metastatic biopsies for NGS are challenging

Liquid biopsy (ctDNA)
- Advantages: non-invasive, reflects matched tumor biopsy
- Disadvantages: dependent on tumor content, deletions (eg, *BRCA2*) not as robust as mutations, misses complex structural rearrangements, can be confounded by clonal hematopoiesis (particularly for *ATM*)

Germline testing (blood/saliva)
- Noninvasive, family implications, somatic testing should not replace germline

Mateo et al Nat Cancer 2020

Immunotherapy: Pembrolizumab

Response to Pembrolizumab Across 5 Trials in MSI-H Solid Tumors

Solid Tumors	N	ORR, %
CRC	124	34
Non-CRC	380	33
▪ Endometrial	94	50
▪ Biliary	22	41
▪ Gastric/GEJ	51	39
▪ Pancreatic	22	18
▪ Small intestine	27	59
▪ Breast	13	8
▪ Prostate	**8**	**13**

- PSA50 rates of 44-65% in small real-world cohorts with dMMR PCa

- FDA approved for:
  - Unresectable or metastatic solid tumors with PD after prior tx and no satisfactory alternatives that are either
    - **MSI-H or dMMR** *or*
    - **TMB high (≥10 mut/Mb)***
- dMMR rare in prostate cancer
  - 2%-5% of mCRPC cases

*Accelerated approval for TMB high.

Pembrolizumab PI. NCCN. Prostate cancer. v.1.2023. Graham. Prostate. 2022;82 Suppl 1:S37.

Identification of patients for pembrolizumab

57 yo with mCRPC s/p abiraterone, sip-T, docetaxel, enzalutamide, ARV110, with POD. No response to darolutamide

4/7/21; PSA 39.79 ng/ml, pembrolizumab #1

4/28/21: PSA 104.7 ng/ml, pembrolizumab #2

5/19/21: PSA 91.13 ng/ml

6/2/21: PSA 56.73

6/23/21: PSA 45.54

7/14/21: PSA 11.8 ng/ml

8/2021: PSA 5.18 ng/ml

Biomarker Findings

Blood Tumor Mutational Burden - 23 Muts/Mb
Microsatellite status - MSI-High Not Detected
Tumor Fraction - 17%

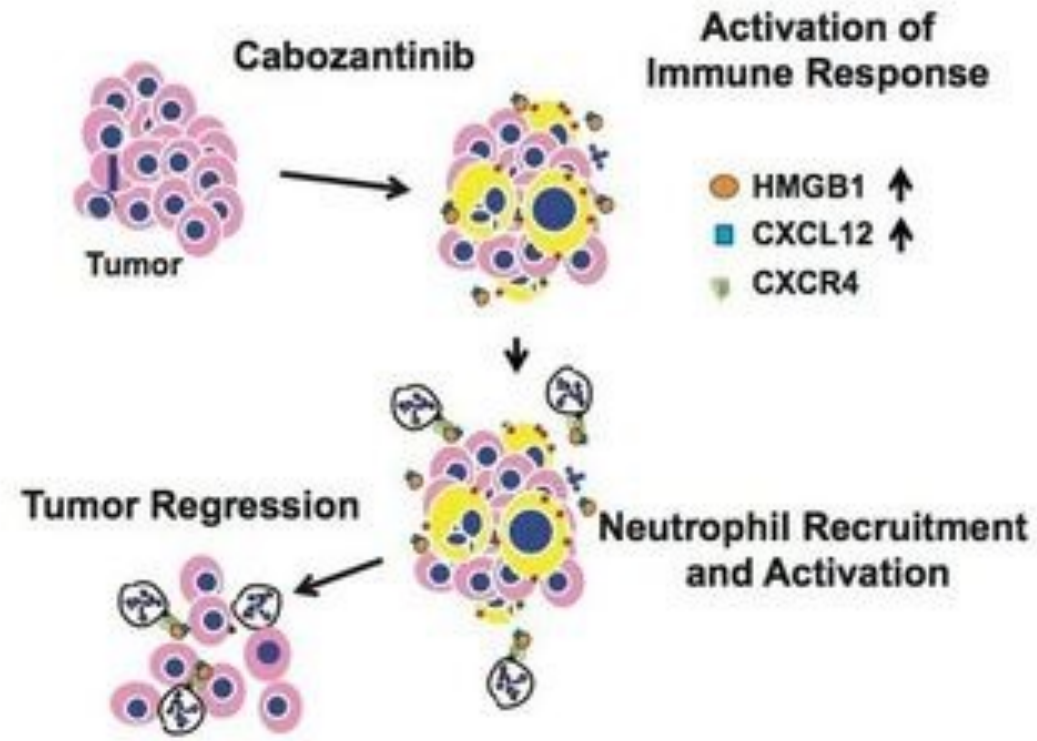
Genomic Findings

For a complete list of the genes assayed, please refer to the Appendix.

AR L702H, W742C, T878A
CDK12 splice site 2610-1G>A
BRAF SND1-BRAF fusion
PTEN loss
CTNNB1 S45P
RET R813W
MSH6 F1088fs*2
SPEN R1403*
TP53 R181C, C277G, R342*

PD-L1: Combined Positive Score (CPS) --- Negative
Genomic testing of metastatic bx failed
Primary tumor bx unsuccessful

Cabozantinib + Atezolizumab (COSMIC-021)



IO for biomarker unselected mCRPC has limited activity. Multiple IO combos have been investigated

Tumor Response per Investigator by RECIST v1.1

	CRPC Cohort (N=44)
Objective response rate (80% CI), %	32 (23–42)
Best overall response, n (%)	
Confirmed complete response	2 (4.5)
Confirmed partial response	12 (27)
Stable disease	21 (48)
Progressive disease	8 (18)*
Missing	1 (2.3)
Disease control rate, n (%)	35 (80)
Duration of objective response, median (range), mo	8.3 (2.8–9.8+)
Time to objective response, median (range), mo	1.6 (1–7)

Disease control rate = complete response + partial response + stable disease
*One patient with progressive disease had a subsequent immune-related partial response per irRECIST.

- ORR was 32% among all 44 CRPC patients and 33% among 36 patients with high-risk clinical features (visceral and/or extra-pelvic lymph node metastases)
- The disease control rate among all 44 CRPC pts was 80%

- Patnaik A, et al. Cancer Discov. 2017;7:750-765. Agarwal N, et al. GU ASCO 2020

New and Emerging Therapies for mCRPC

- Targeting the AR – e.g., AR-degraders, ODM-208, BAT
  - AR is still key driver of mCRPC
- PSMA therapies – e.g., Ac-PSMA, T-cell engagers, CAR-T
  - PSMA may still be expressed in patients post-^{177}Lu-PSMA-617
- Other cell surface targets – e.g., TROP2, B7-H3, DLL3
  - Potential role for biomarkers selection/molecular imaging
- Targeting non-AR driven disease – e.g, NEPC
- Targeting other genomic alterations – e.g, PTEN (AKTi)
- Rationale combination strategies
  - mCRPC is a biologically heterogeneous disease

Beyond The Guidelines: Urologic Oncology Investigators Provide Perspectives on the Optimal Management of Prostate Cancer

Part 2 of a 2-Part CME Satellite Symposium Series Held in Conjunction with the American Urological Association Annual Meeting 2023 (AUA2023)

Sunday, April 30, 2023

6:00 PM – 8:00 PM

Faculty

Himisha Beltran, MD

Stephen J Freedland, MD

Fred Saad, MD

Neal D Shore, MD

Moderator

Matthew R Smith, MD, PhD

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