Year in Review: Clinical Investigator Perspectives on the Most Relevant New Data Sets and Advances in Oncology

A Multitumor CME/MOC-Accredited Live Webinar Series

Prostate Cancer

Wednesday, March 6, 2024
5:00 PM – 6:00 PM ET

Faculty

Andrew J Armstrong, MD, ScM
Maha Hussain, MD, FACP, FASCO

Moderator

Neil Love, MD

RTP Year in Review 2024

Faculty

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

Maha Hussain, MD, FACP, FASCO
Genevieve Teuton Professor of Medicine
Division of Hematology/Oncology
Deputy Director
Robert H Lurie Comprehensive Cancer Center
Northwestern University Feinberg School of Medicine
Chicago, Illinois

MODERATOR
Neil Love, MD
Research To Practice
Miami, Florida

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Commercial Support

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Dr Love — Disclosures

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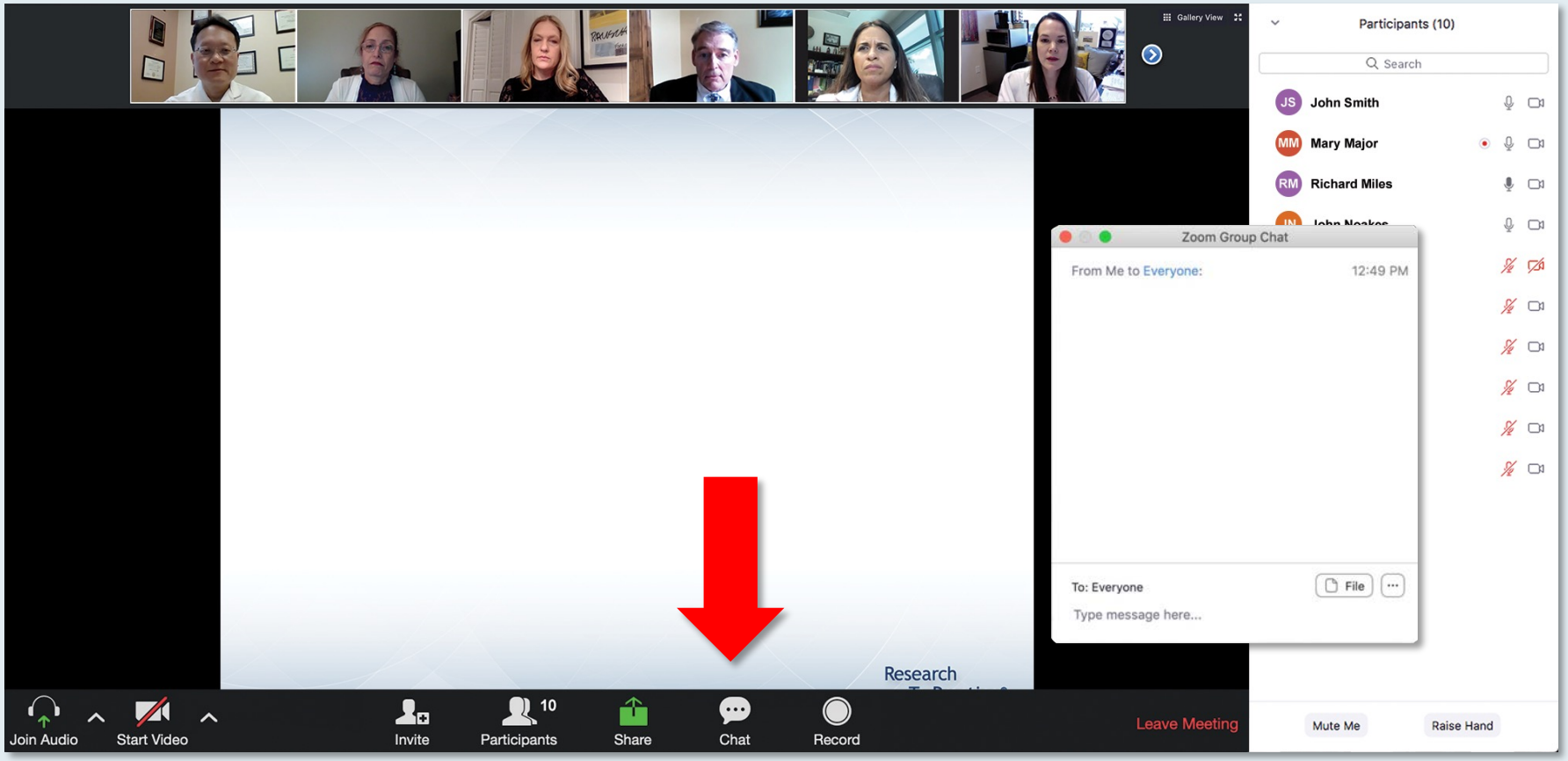
We Encourage Clinicians in Practice to Submit Questions



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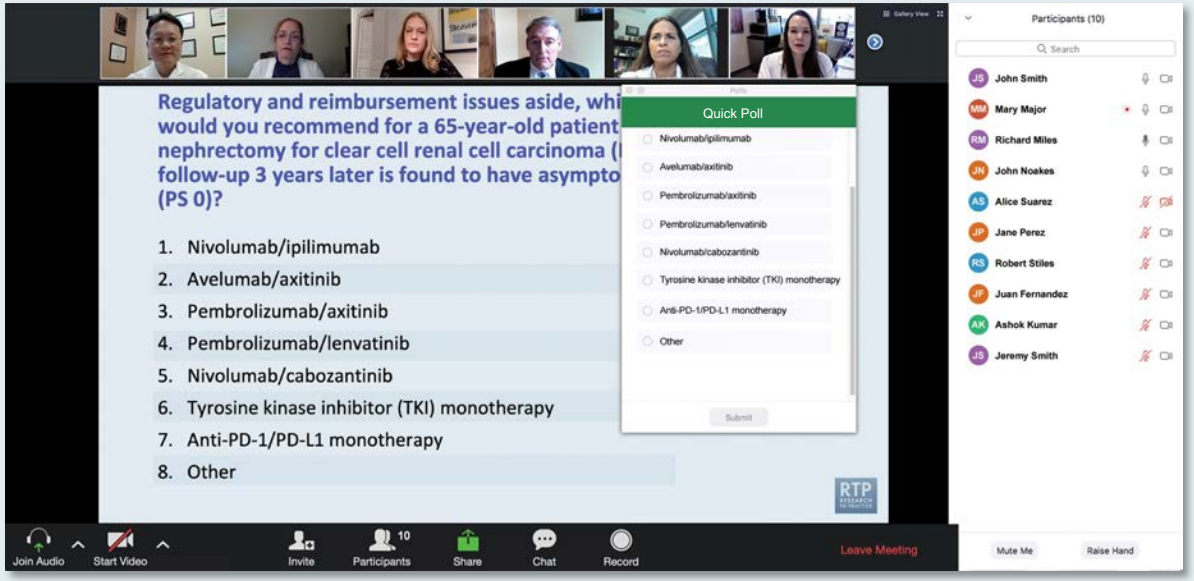

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ONCOLOGY TODAY

WITH DR NEIL LOVE

Exploring the Current and Future Management of High-Risk, Hormone-Sensitive Nonmetastatic Prostate Cancer

DR NEAL SHORE
CAROLINA UROLOGIC RESEARCH CENTER

DR MARY-ELLEN TAPLIN
DANA-FARBER CANCER INSTITUTE

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

Part 1 of a 2-Part CME Symposium Series Held in Conjunction with the 2024 Society of Gynecologic Oncology (SGO) Annual Meeting on Women's Cancer®

Monday, March 18, 2024

6:30 AM – 8:00 AM PT (9:30 AM – 11:00 AM ET)

Faculty

Joyce F Liu, MD, MPH

Mansoor Raza Mirza, MD

David M O'Malley, MD

Moderator

Kathleen N Moore, MD, MS

RTP RESEARCH TO PRACTICE

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

Part 2 of a 2-Part CME Symposium Series Held in Conjunction with the 2024 Society of Gynecologic Oncology (SGO) Annual Meeting on Women's Cancer®

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JW Marriott Miami Turnberry

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Meet The Professor

Optimizing the Management of Myelofibrosis

Wednesday, April 3, 2024
5:00 PM – 6:00 PM ET

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Ruben A Mesa, MD

Moderator

Neil Love, MD

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Agenda

INTRODUCTION: Carpool Karaoke – RTP Style

MODULE 1: Hormonal Therapy

- Intensification
  - Localized and locally recurrent disease
  - PSA-only recurrence, high risk – PRESTO, EMBARK trials
- Metastatic disease – role of docetaxel, choice of AR inhibitor
- New approaches – CDK4/6 and AKT inhibitors

MODULE 2: Other Treatment Approaches

- Lutetium Lu 177 vipivotide tetraxetan
- Radium-223 chloride
- PARP inhibitors
- Neuroendocrine differentiation

Thank you for joining us!

CME and MOC credit information will be emailed to each participant within 5 business days.

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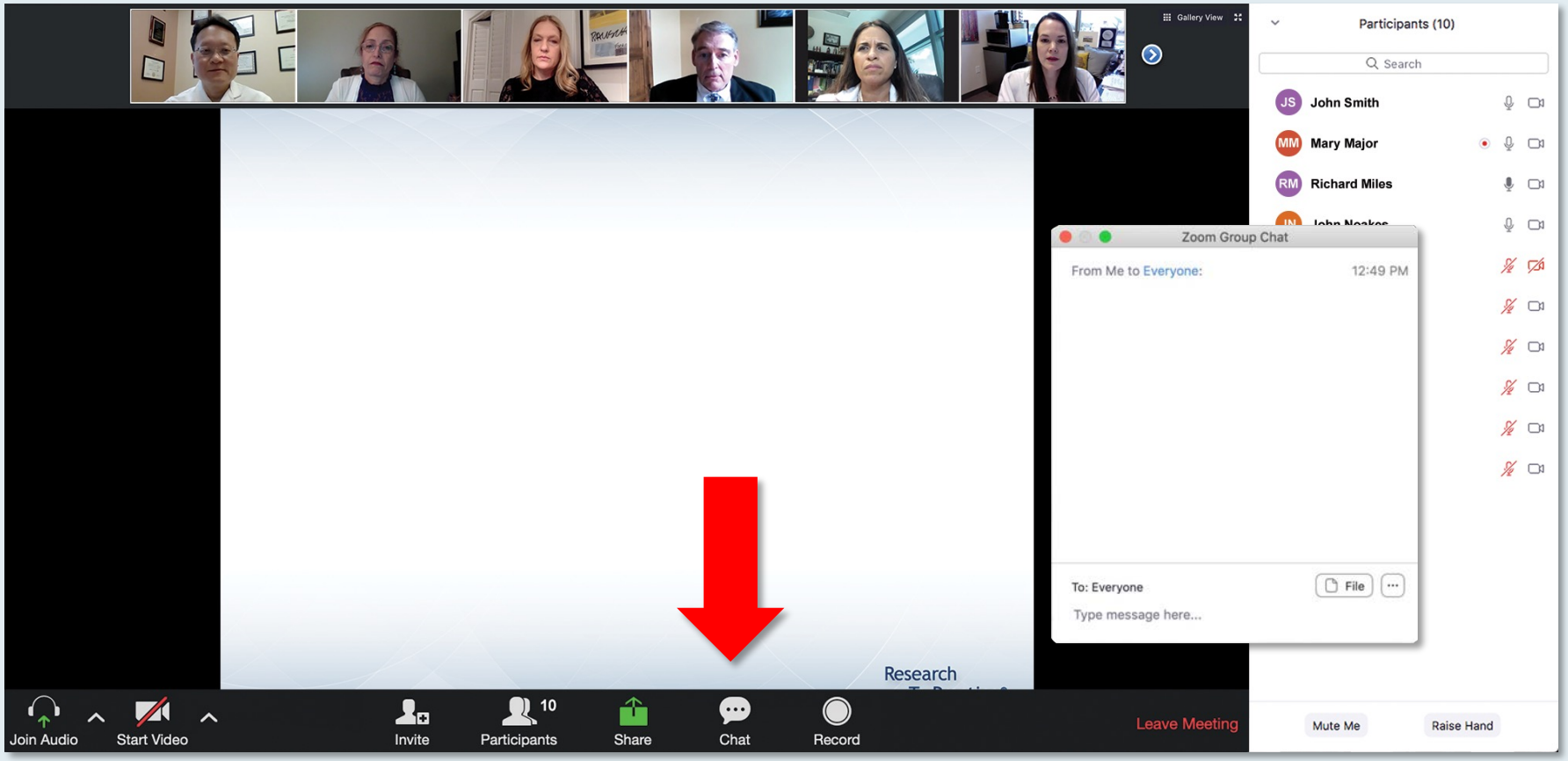

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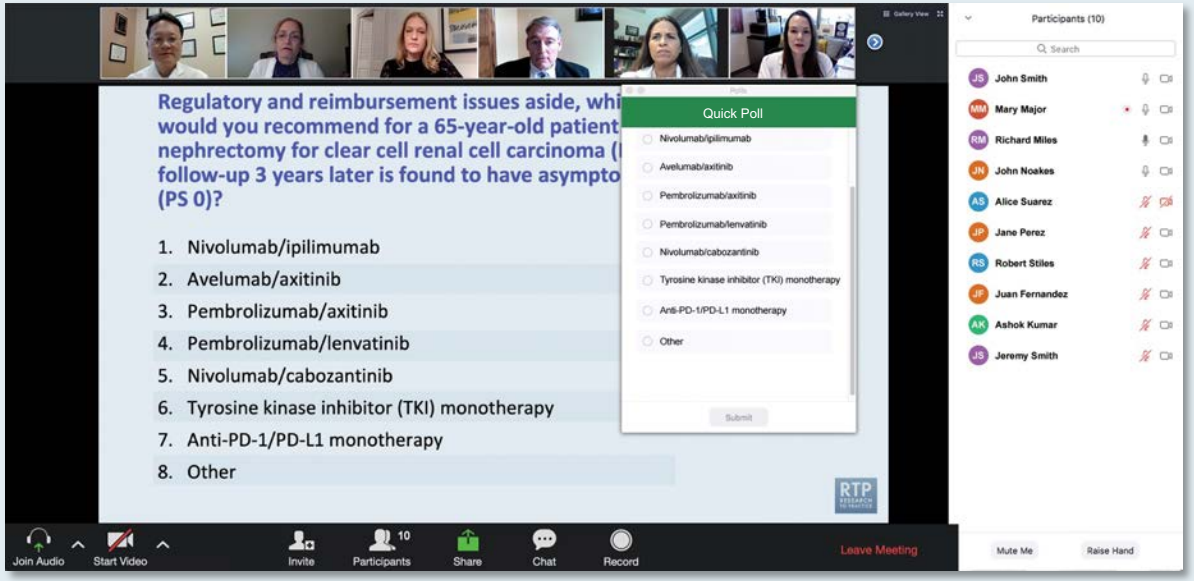

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Third Annual **National General Medical Oncology Summit**

Friday, March 22, 2024

6:30 PM – 7:00 PM

Welcome Reception

7:00 PM – 9:00 PM

Keynote Session: ER-Positive Metastatic Breast Cancer

Erika Hamilton, MD
Kevin Kalinsky, MD, MS
Joyce O'Shaughnessy, MD
Hope S Rugo, MD

Special Feature: Clinicians with Breast Cancer

Third Annual **National General Medical Oncology Summit**

Saturday, March 23, 2024

7:30 AM – 9:10 AM

Hodgkin and Non-Hodgkin Lymphoma

Ann S LaCasce, MD, MMSc
Matthew Lunning, DO
Kami Maddocks, MD
Andrew D Zelenetz, MD, PhD

9:30 AM – 10:20 AM

Gynecologic Cancers

Bradley J Monk, MD
David M O'Malley, MD

10:20 AM – 11:10 AM

Localized Breast Cancer; SABCS 2023 Review

Virginia Kaklamani, MD, DSc
Kevin Kalinsky, MD, MS
Joyce O'Shaughnessy, MD

11:10 AM – 12:00 PM

Metastatic Breast Cancer, Triple-Negative Breast Cancer, HER2-Positive Breast Cancer; SABCS 2023 Review

Erika Hamilton, MD
Virginia Kaklamani, MD, DSc
Hope S Rugo, MD

Third Annual **National General Medical Oncology Summit**

Saturday, March 23, 2024

12:30 PM – 1:20 PM

Prostate Cancer

Emmanuel S Antonarakis, MD

Rana R McKay, MD

1:20 PM – 2:10 PM

Urothelial Bladder Cancer

Matthew D Galsky, MD

Jonathan E Rosenberg, MD

2:10 PM – 3:00 PM

Renal Cell Carcinoma

Eric Jonasch, MD

Brian Rini, MD

3:20 PM – 4:10 PM

Targeted Therapy for Non-Small Cell Lung Cancer

Ibiayi Dagogo-Jack, MD

Helena Yu, MD

4:10 PM – 5:00 PM

Nontargeted Treatments for Lung Cancer

Edward B Garon, MD, MS

Corey J Langer, MD

Third Annual **National General Medical Oncology Summit**

Sunday, March 24, 2024

7:30 AM – 8:20 AM

Multiple Myeloma

Natalie S Callander, MD
Paul G Richardson, MD

8:20 AM – 9:10 AM

Gastroesophageal Cancers

Yelena Y Janjigian, MD
Samuel J Klempner, MD

9:30 AM – 10:20 AM

Hepatobiliary Cancers

Ghassan Abou-Alfa, MD, MBA
Richard S Finn, MD

10:20 AM – 11:10 AM

Colorectal Cancer

Kristen K Ciombor, MD, MSCI
John Strickler, MD

11:10 AM – 12:00 PM

Pancreatic Cancer

Andrew H Ko, MD
Eileen M O'Reilly, MD

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Optimizing The Role of Hormonal Therapy and Novel Therapeutic Strategies for Patients with Prostate Cancer

Maha Hussain, MD, FACP, FASCO
Genevieve Teuton Professor of Medicine
Division of Hematology/Oncology
Deputy Director
Robert H Lurie Comprehensive Cancer Center
Northwestern University Feinberg School of Medicine
Chicago, Illinois

Other Available and Emerging Therapeutic Approaches in Prostate Cancer

Andrew J Armstrong MD ScM FACP
Professor of Medicine, Surgery, Pharmacology and Cancer Biology
Duke Cancer Institute Center for Prostate and Urologic Cancers

Duke Cancer Institute
Center For Prostate & Urologic Cancers

Key Data Sets

Maha Hussain, MD, FACP, FASCO

- Shore ND et al. Impact of **concomitant cardiovascular therapies** on efficacy and **safety of relugolix** vs leuprolide: **Subgroup analysis from HERO study** in advanced prostate cancer. *Adv Ther* 2023;40(11):4919-27.
- Freedland SJ et al. Improved outcomes with **enzalutamide in biochemically recurrent prostate cancer**. *N Engl J Med* 2023;389(16):1453-65.
- Aggarwal R et al. **Updated progression-free survival from PRESTO**: A phase 3 randomized study of **androgen annihilation for high-risk biochemically relapsed prostate cancer** (AFT-19). AUA 2023;Abstract LBA02-11.
- Hussain M et al. **Nadir prostate-specific antigen as an independent predictor of survival outcomes**: A **post hoc analysis of the PROSPER** randomized clinical trial. *J Urol* 2023;209(3):532-9.
- Bögemann M et al. Efficacy and safety of **darolutamide** in patients with nonmetastatic castration-resistant prostate cancer **stratified by prostate-specific antigen doubling time**: **Planned subgroup analysis of the phase 3 ARAMIS trial**. *Eur Urol* 2023;83(3):212-21.

Key Data Sets

Maha Hussain, MD, FACP, FASCO (continued)

- Attard G et al. **Abiraterone acetate plus prednisolone with or without enzalutamide** for patients with metastatic prostate cancer starting androgen deprivation therapy: **Final results from two randomised phase 3 trials of the STAMPEDE platform protocol**. *Lancet Oncol* 2023;24(5):443-56.
- Chowdhury S et al. Deep, rapid, and durable prostate-specific antigen decline with **apalutamide plus androgen deprivation therapy** is associated with longer survival and improved clinical outcomes in **TITAN patients with metastatic castration-sensitive prostate cancer**. *Ann Oncol* 2023;34(5):477-85.
- Armstrong AJ et al. The efficacy of **enzalutamide plus androgen deprivation therapy** in oligometastatic hormone-sensitive prostate cancer: **A post hoc analysis of ARCHES**. *Eur Urol* 2023;84(2):229-41.
- Sweeney CJ et al. **Testosterone suppression plus enzalutamide** versus testosterone suppression plus standard antiandrogen therapy for **metastatic hormone-sensitive prostate cancer (ENZAMET)**: An international, open-label, randomised, phase 3 trial. *Lancet Oncol* 2023;24(4):323-34.
- Hussain M et al. **Darolutamide plus androgen-deprivation therapy and docetaxel** in metastatic hormone-sensitive prostate cancer by disease volume and risk subgroups in the phase III **ARASENS** trial. *J Clin Oncol* 2023;41(20):3595-607.

Key Data Sets

Maha Hussain, MD, FACP, FASCO (continued)

- Bossi A et al. **Prostate irradiation** in men with de novo, low-volume, metastatic, castration-sensitive prostate cancer (mCSPC): **Results of PEACE-1**, a phase 3 randomized trial with a 2x2 design. ASCO 2023;Abstract LBA5000.
- Agarwal N et al. **CYCLONE 1**: **Abemaciclib** in men with **heavily pretreated metastatic castration-resistant prostate cancer (mCRPC)**. AACR 2023;Abstract CT159.
- Matsubara N et al. **CYCLONE 3**: A **phase III**, randomized, double-blind, placebo-controlled study of **abemaciclib in combination with abiraterone plus prednisone** in men with **high-risk metastatic hormone-sensitive prostate cancer**. ESMO Asia 2023;Abstract 284TiP.
- Shore N et al. A phase I study of **capivasertib in combination with abiraterone acetate** in patients with metastatic castration-resistant prostate cancer. *Clin Genitourin Cancer* 2023;21(2):278-85.

Key Data Sets

Andrew J Armstrong, MD, ScM

- Saad F et al. **Olaparib plus abiraterone** versus placebo plus abiraterone in metastatic castration-resistant prostate cancer **(PROpel)**: **Final prespecified overall survival results** of a randomised, double-blind, phase 3 trial. *Lancet Oncol* 2023;24(10):1094-108.
- Shore ND et al. Efficacy of **olaparib (O) plus abiraterone (A)** versus placebo (P) plus A in patients (pts) with **metastatic castration-resistant prostate cancer (mCRPC)** with **single homologous recombination repair gene mutations (HRRm) in the PROpel trial**. Genitourinary Cancers Symposium 2024;Abstract 165.
- Chi KN et al. **Niraparib (NIRA) with abiraterone acetate plus prednisone (AAP)** as **first-line (1L)** therapy in patients (pts) with **metastatic castration-resistant prostate cancer (mCRPC)** and homologous recombination repair (HRR) gene alterations: **Three-year update and final analysis (FA) of MAGNITUDE**. ESMO 2023;Abstract LBA85.
- Agarwal N et al. **Talazoparib plus enzalutamide** in men with **first-line metastatic castration-resistant prostate cancer (TALAPRO-2)**: A randomised, placebo-controlled, phase 3 trial. *Lancet* 2023;402(10398):291-303.
- Fizazi K et al. **First-line talazoparib with enzalutamide** in HRR-deficient metastatic castration-resistant prostate cancer: The phase 3 **TALAPRO-2** trial. *Nat Med* 2024;30(1):257-64.

Key Data Sets

Andrew J Armstrong, MD, ScM (continued)

- Fizazi K et al. **Rucaparib** or physician's choice in **metastatic prostate cancer**. *N Engl J Med* 2023;388(8):719-32.
- Hofman MS et al. **Overall survival** with **[^{177}Lu]Lu-PSMA-617** versus cabazitaxel in metastatic castration-resistant prostate cancer **(TheraP)**: **Secondary outcomes** of a randomised, open-label, phase 2 trial. *Lancet Oncol* 2024;25(1):99-107.
- Fizazi K et al. **Health-related quality of life and pain outcomes** with **[^{177}Lu]Lu-PSMA-617 plus standard of care** versus standard of care in patients with metastatic castration-resistant prostate cancer **(VISION)**: A multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol* 2023;24(6):597-610.
- Sartor O et al. Phase III trial of **[^{177}Lu]Lu-PSMA-617** in **taxane-naive patients** with metastatic castration-resistant prostate cancer **(PSMAfore)**. ESMO 2023;Abstract LBA13.
- Sandhu S et al. LuPARP: **Phase 1 trial of ^{177}Lu-PSMA-617 and olaparib** in patients with metastatic castration resistant prostate cancer (mCRPC). ASCO 2023;Abstract 5005.
- Emmett L et al. **Enzalutamide and ^{177}Lu-PSMA-617** in poor-risk, metastatic, castration-resistant prostate cancer (mCRPC): A randomised, phase II trial**: ENZA-p (ANZUP 1901)**. ESMO 2023;Abstract LBA84.

Key Data Sets

Andrew J Armstrong, MD, ScM (continued)

- Rahbar K et al. Safety and survival outcomes of ^{177}**Lu-prostate-specific membrane antigen therapy** in patients with metastatic castration-resistant prostate cancer with **prior** ^{223}**Ra treatment**: **The RALU study**. *J Nucl Med* 2023;64(4):574-8.
- Lantheus and POINT Biopharma announce positive **topline results** from **pivotal SPLASH trial** in metastatic castration-resistant prostate cancer [press release]. December 18, 2023. https://lantheusholdings.gcs-web.com/news-releases/news-release-details/lantheus-and-point-biopharma-announce-positive-topline-results.
- Agarwal N et al. **CONTACT-02**: **Phase 3 study of cabozantinib (C) plus atezolizumab (A)** vs second novel hormonal therapy (NHT) in patients (pts) with **metastatic castration-resistant prostate cancer (mCRPC)**. Genitourinary Cancers Symposium 2024;Abstract 18.

Agenda

INTRODUCTION: Carpool Karaoke – RTP Style

MODULE 1: Hormonal Therapy

- Intensification
  - Localized and locally recurrent disease
  - PSA-only recurrence, high risk – PRESTO, EMBARK trials
- Metastatic disease – role of docetaxel, choice of AR inhibitor
- New approaches – CDK4/6 and AKT inhibitors

MODULE 2: Other Treatment Approaches

- Lutetium Lu 177 vipivotide tetraxetan
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4 years ago…

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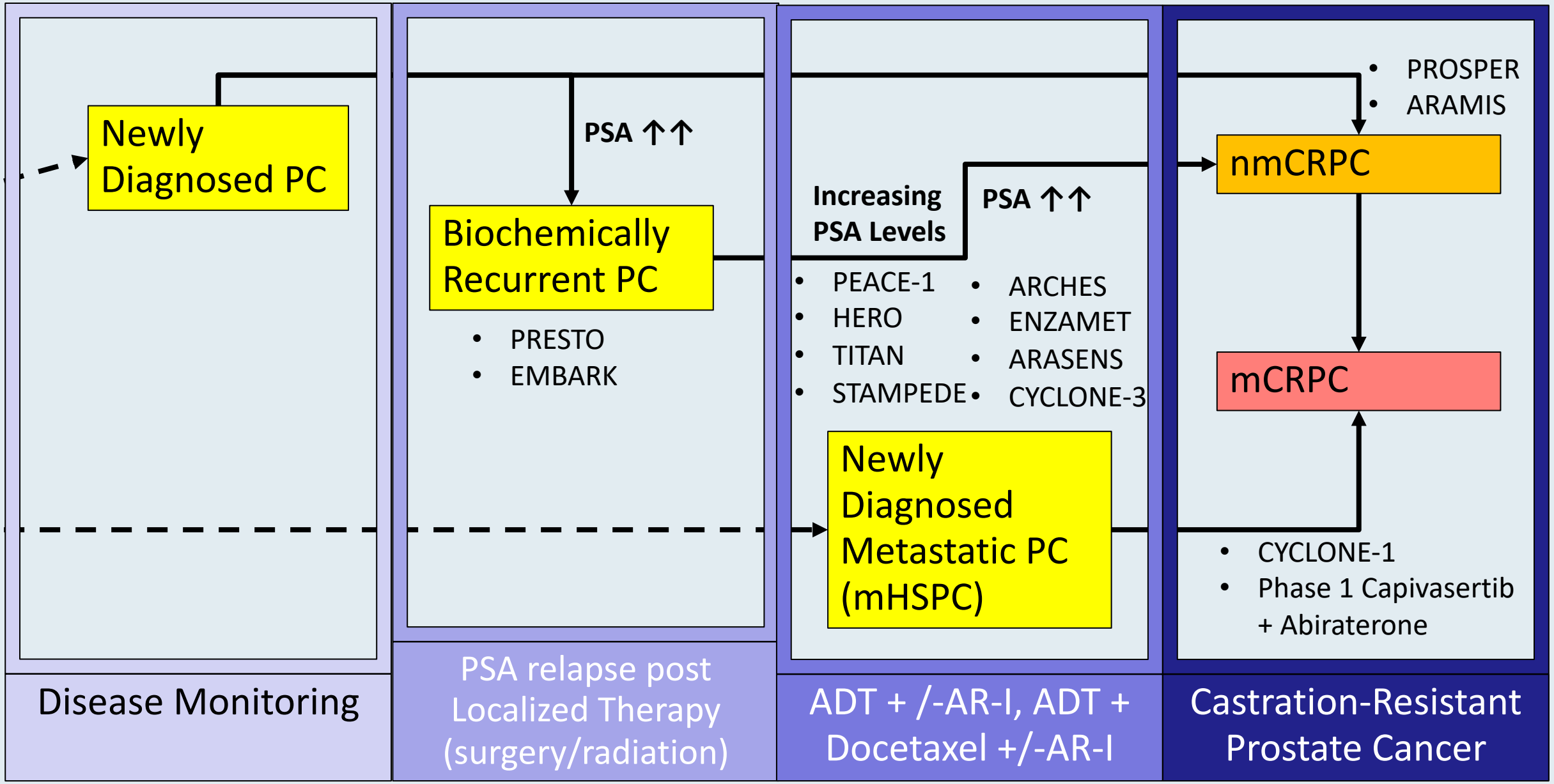
Prostate Cancer Disease States



Scher HI et al. *PLoS One* 2015

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- Aggarwal R et al. **Updated progression-free survival from PRESTO**: A phase 3 randomized study of **androgen annihilation for high-risk biochemically relapsed prostate cancer** (AFT-19). AUA 2023;Abstract LBA02-11.
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- Bögemann M et al. Efficacy and safety of **darolutamide** in patients with nonmetastatic castration-resistant prostate cancer **stratified by prostate-specific antigen doubling time**: **Planned subgroup analysis of the phase 3 ARAMIS trial**. *Eur Urol* 2023;83(3):212-21.

Key Clinical Questions/Issues Related to Systemic Management/Research in Prostate Cancer

Androgen deprivation therapy intensification of localized disease treated with surgery/radiation therapy:

- **When, how, how long?**

PSA relapse after radical prostatectomy: Radiation therapy alone or with endocrine therapy?

Key Clinical Questions/Issues Related to Systemic Management/Research in Prostate Cancer

M0 disease

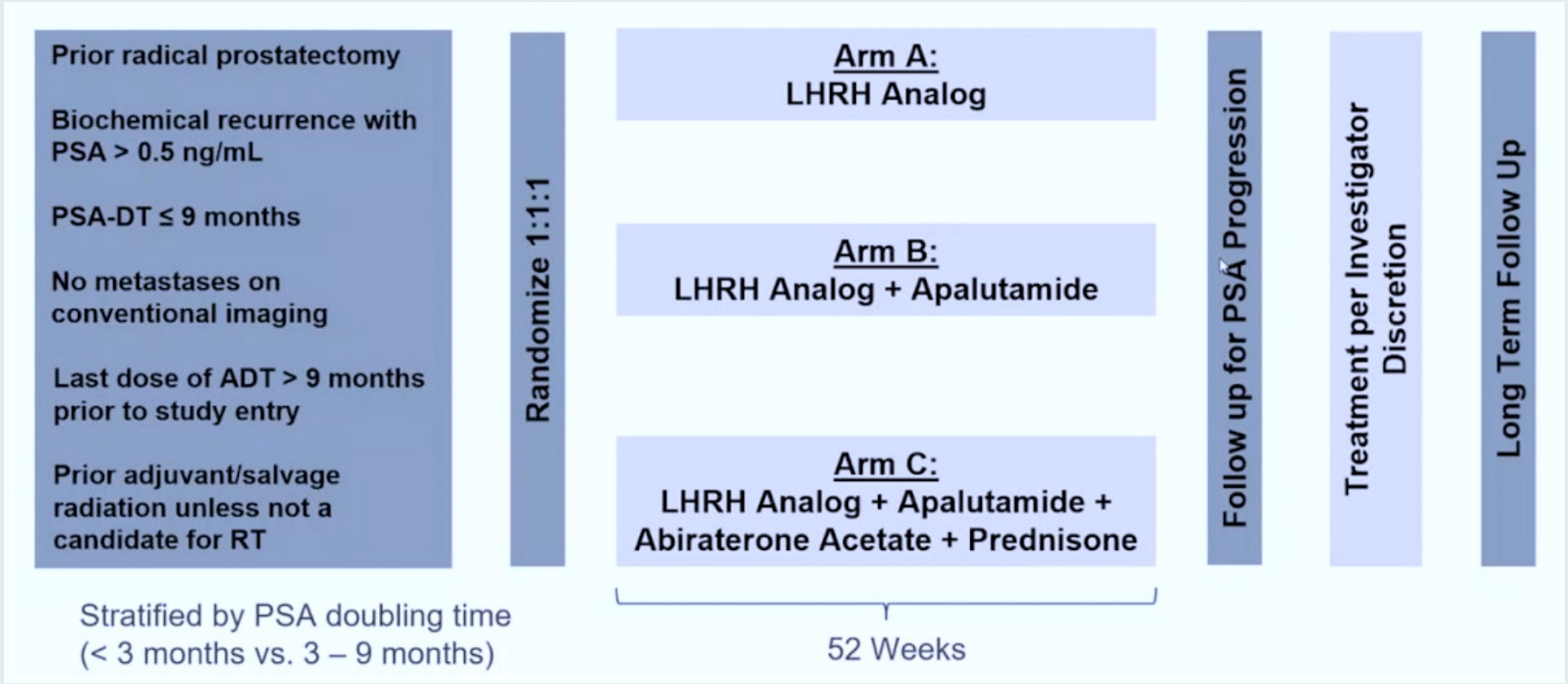
- **PRESTO versus EMBARK**
- **Defining high-risk disease**

Enzalutamide monotherapy: Present or not?

- **Gynecomastia**
- **Sexual function QoL**

M0 progression on LHRH — choice of AR (androgen receptor) blocker, toxicity profile

PRESTO: A Phase III Randomized Study of Androgen Annihilation for High-Risk Biochemically Relapsed Prostate Cancer



ADT = androgen deprivation therapy

https://www.urotoday.com/conference-highlights/esmo-2022/esmo-2022-prostate-cancer/139400-esmo-2022-discussion-of-presto-and-propel.html

PRESTO: Updated PFS

	Apa + ADT vs ADT	Apa + AAP + ADT vs ADT	Apa + ADT vs Apa + AAP + ADT
PSA-PFS	24.9 vs 20.3 months **HR = 0.52** [95% CI, 0.35 to 0.77]	26.0 vs 20.0 months **HR = 0.48** [95% CI, 0.32 to 0.71]	24.9 vs 26.0 months **HR = 0.95** (95% CI: 0.62-1.45)
	ADT	**Apa + ADT**	**Apa + AAP + ADT**
Median Time to Testosterone Recovery (months)	3.9	3.8	4.7

AAP = abiraterone acetate with prednisone

- **In patients with high-risk BCR following radical prostatectomy, intensified ADT with addition of apalutamide or apalutamide plus abiraterone prolonged biochemical PFS without new safety concerns identified. Follow up is ongoing to determine the impact on longer term endpoints including MFS and time to castration resistance.**

Aggarwal R et al. AUA 2023;Abstract LBA02-11.

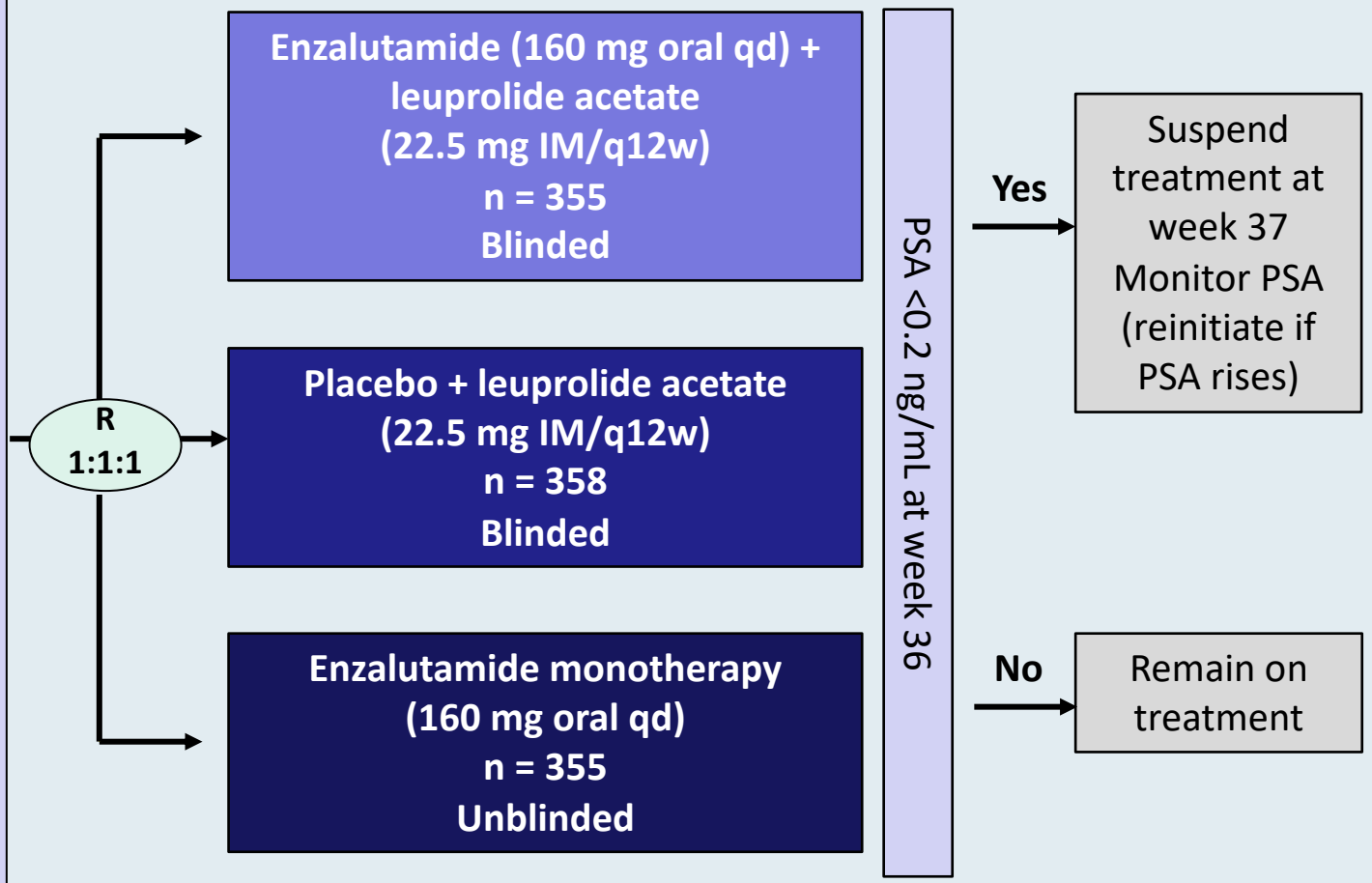
EMBARK: A Phase III Randomized Study of Enzalutamide or Placebo with Leuprolide Acetate and Enzalutamide Monotherapy for High-Risk Biochemically Recurrent Prostate Cancer

Patient population

- Screening PSA ≥1 ng/mL after RP and at least 2 ng/mL above nadir for primary EBRT
- **PSADT ≤9 mo**
- **No metastases on bone scan or CT/MRI** per central read
- Testosterone ≥150 ng/dL
- Prior hormonal therapy ≥9 mo prior to randomization (neoadjuvant/adjuvant for ≤36 mo OR ≤6 mo for rising PSA)

Stratification factors

- Screening PSA (≤10 ng/mL vs >10 ng/mL)
- PSADT (≤3 mo vs >3 to ≤9 mo)
- Prior hormonal therapy (yes vs no)



Primary endpoint:
MFS by BICR, enzalutamide + leuprolide acetate vs leuprolide acetate alone

Key secondary endpoints:

- MFS by BICR, enzalutamide monotherapy vs leuprolide acetate alone
- Time to PSA progression
- Time to first use of new antineoplastic therapy
- OS

Other secondary endpoints:

- Safety

RP = radical prostatectomy; EBRT = external beam radiation therapy; PSADT = PSA doubling time; MFS = metastasis-free survival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AUA 2023
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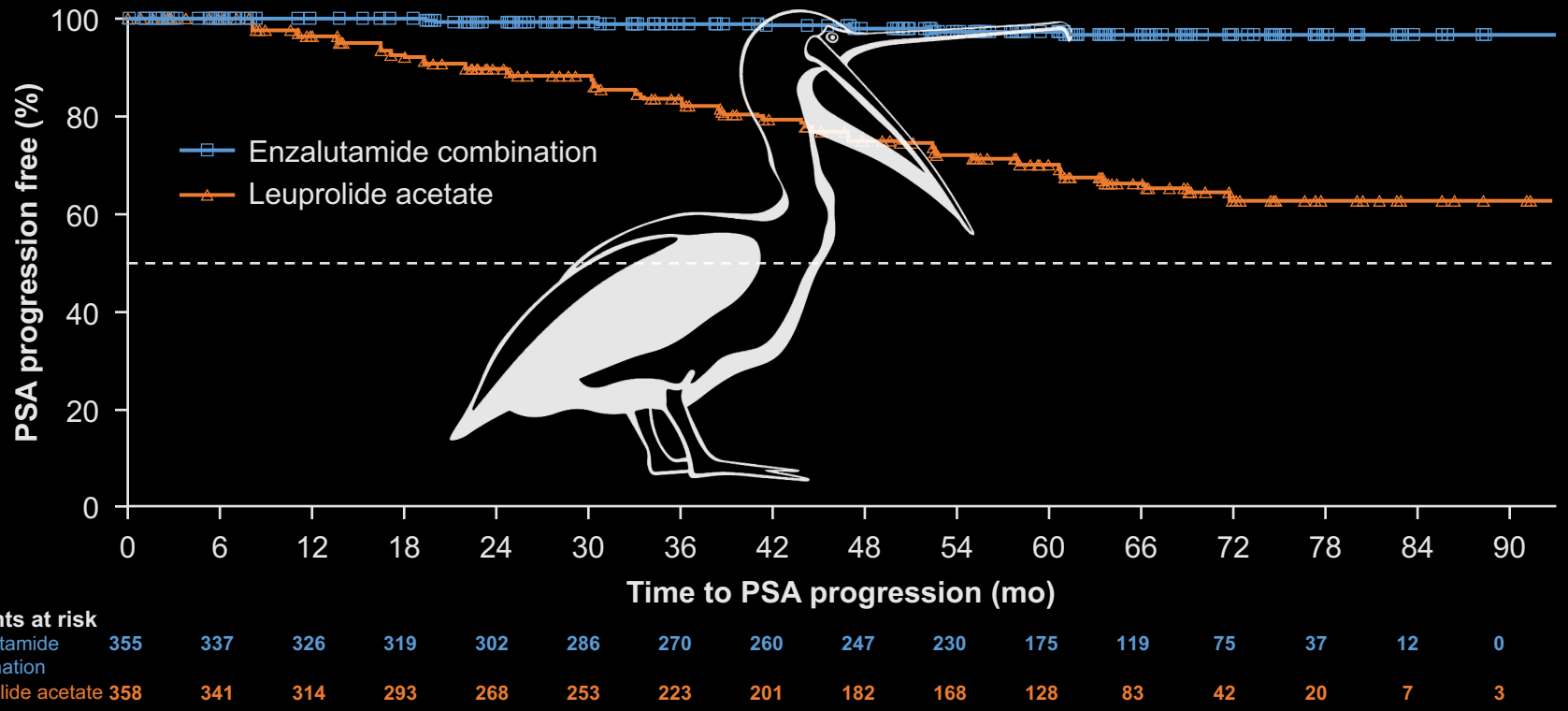
Key secondary endpoint — Time to PSA progression for enzalutamide combination vs. leuprolide acetate



Patients at risk

Enzalutamide combination	355	337	326	319	302	286	270	260	247	230	175	119	75	37	12	0
Leuprolide acetate	358	341	314	293	268	253	223	201	182	168	128	83	42	20	7	3

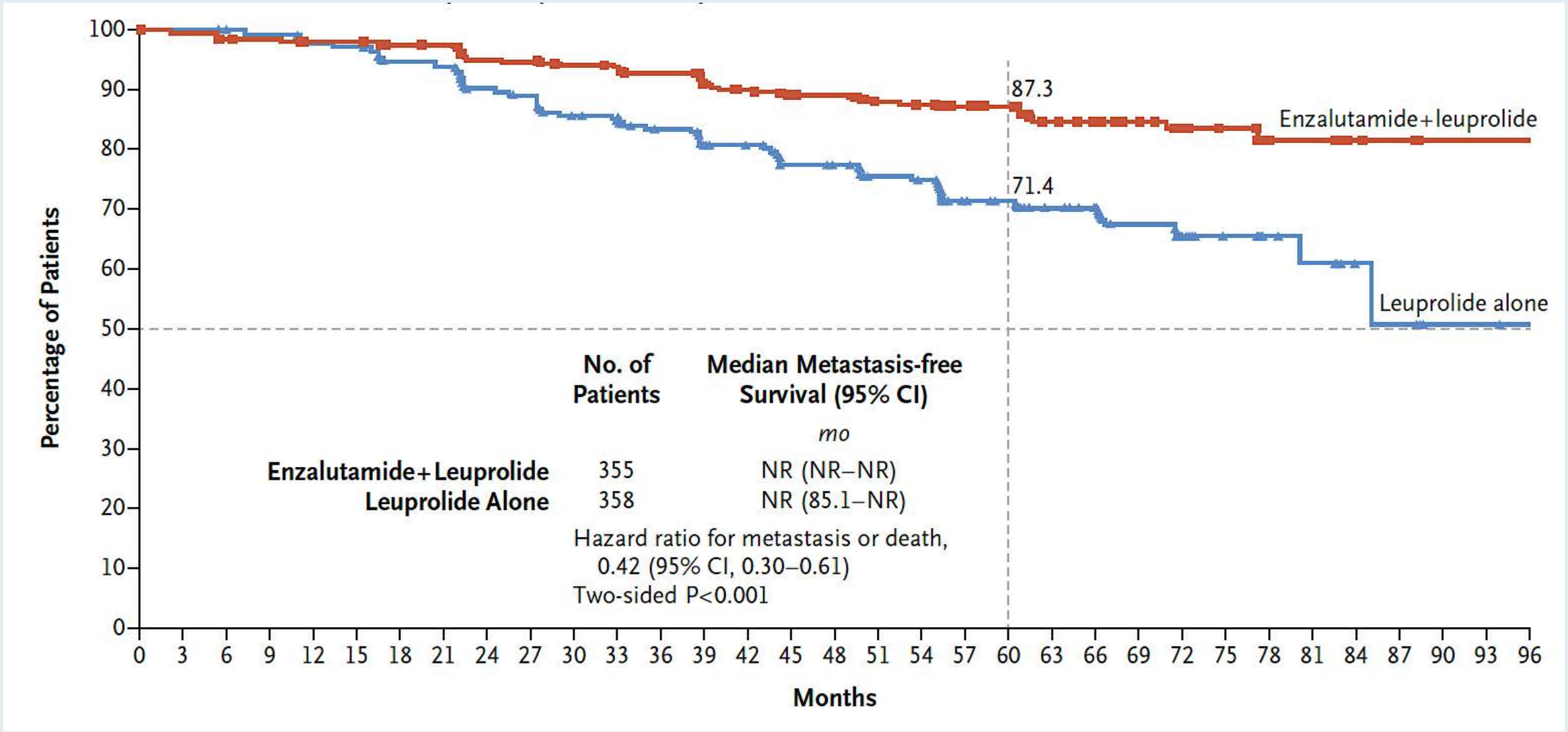
	Enzalutamide combination (n = 355)	Leuprolide acetate (n = 358)
Events, n (%)	8 (2)	93 (26)
Median time to PSA progression (95% CI), mo	NR (NR)	NR (NR)

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

Data cutoff: January 31, 2023. Symbols indicate censored data. [a]The HR was based on a Cox regression model with treatment as the only covariate stratified by screening PSA, PSADT, and prior hormonal therapy as reported in the IWRS; relative to leuprolide acetate <1 favoring enzalutamide combination; the two-sided *P*-value is based on a stratified log-rank test.

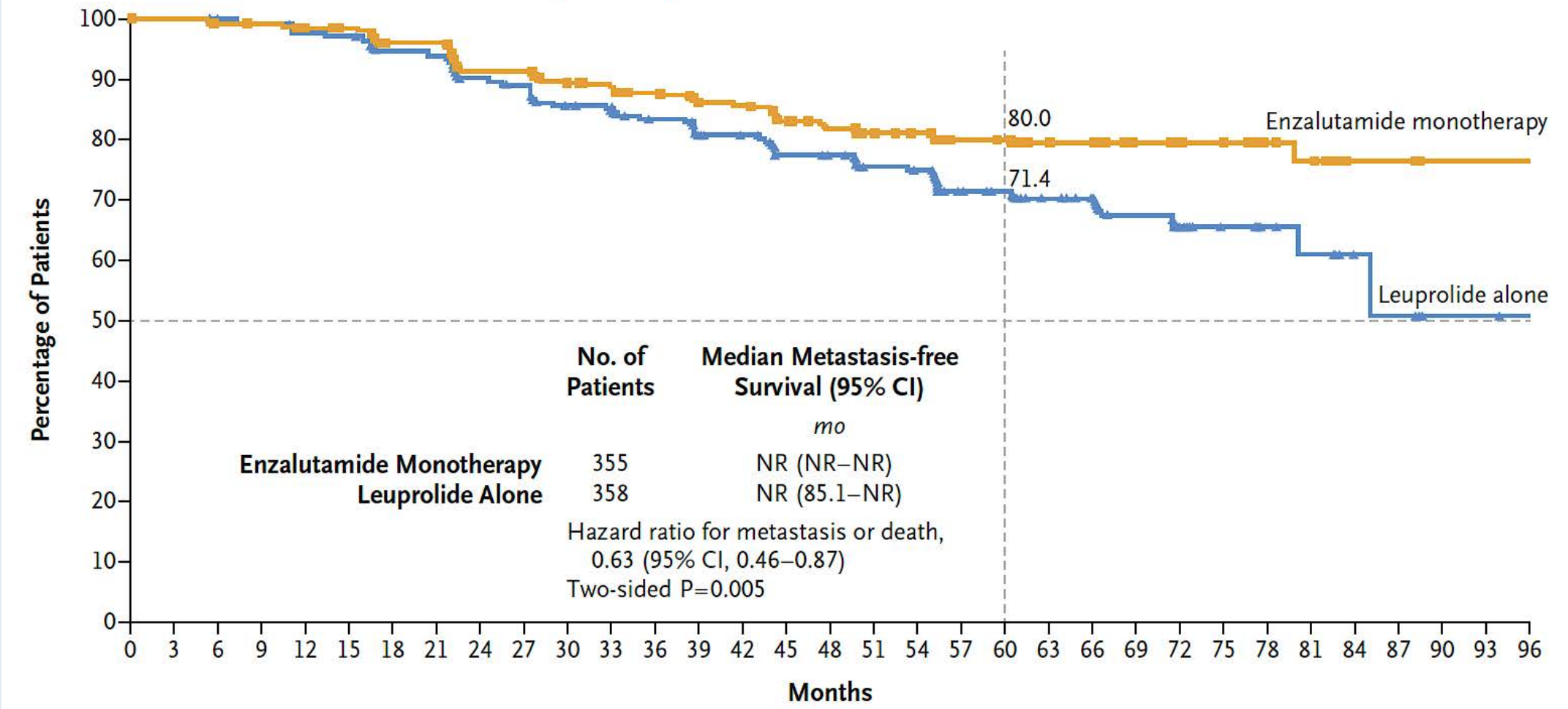
Shore N et al. AUA 2023;Abstract LBA02-09.

EMBARK: Metastasis-Free Survival with Enzalutamide and Leuprolide versus Leuprolide Alone



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

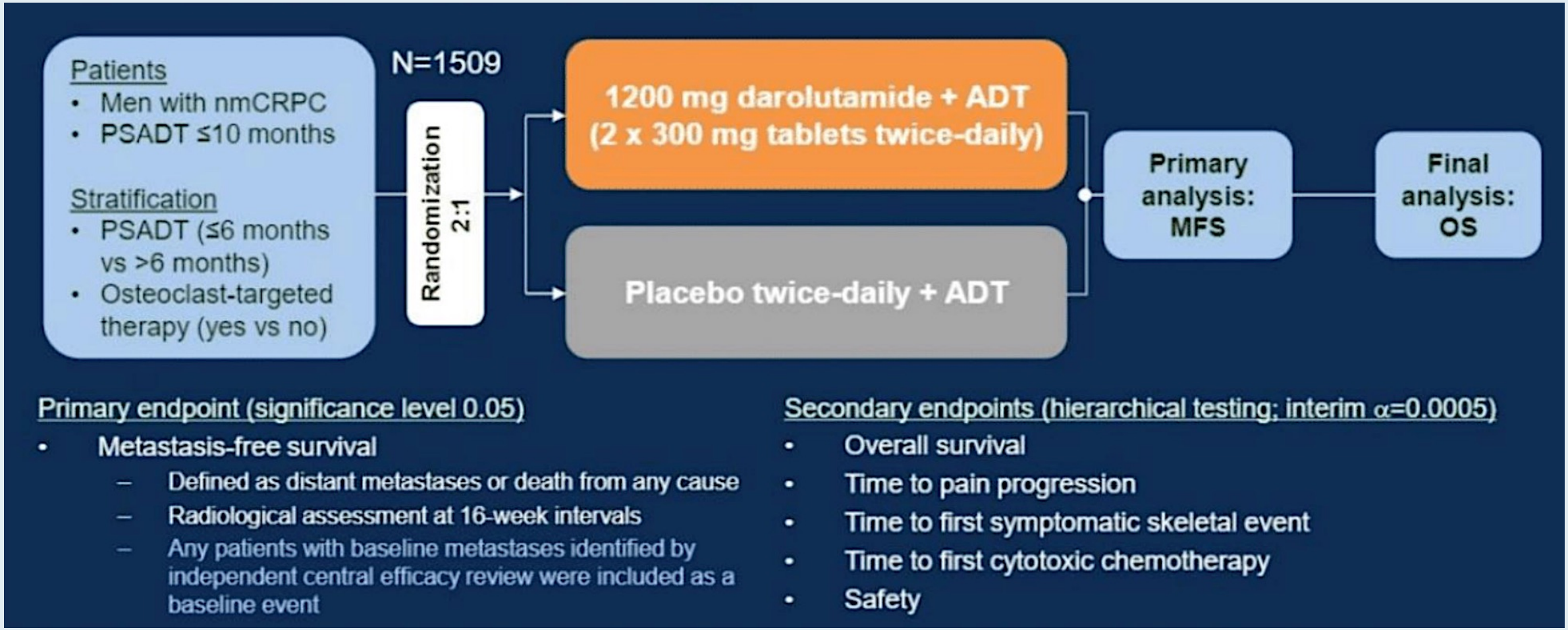
EMBARK: MFS with Enzalutamide Monotherapy versus Leuprolide Alone



- **Data on overall survival were immature at the time of publication.**
- **The safety profile of enzalutamide was consistent with that shown in previous clinical studies, with no apparent detrimental effect on quality of life.**

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

ARAMIS: Darolutamide for Nonmetastatic Castration-Resistant Prostate Cancer (nmCRPC) – Study Design



https://www.urotoday.com/conference-highlights/asco-gu-2019/asco-gu-2019-prostate-cancer/110279-sco-gu-2019-efficacy-and-safety-data-of-the-aramis-study-darolutamide-in-nonmetastatic-castration-resistant-prostate-cancer-patients.html

Metastatic Hormone-Sensitive Prostate Cancer (mHSPC)

- Bossi A et al. **Prostate irradiation** in men with de novo, low-volume, metastatic, castration-sensitive prostate cancer (mCSPC): **Results of PEACE-1**, a phase 3 randomized trial with a 2x2 design. ASCO 2023;Abstract LBA5000.
- Chowdhury S et al. Deep, rapid, and durable prostate-specific antigen decline with **apalutamide plus androgen deprivation therapy** is associated with longer survival and improved clinical outcomes in **TITAN patients with metastatic castration-sensitive prostate cancer**. *Ann Oncol* 2023;34(5):477-85.
- Attard G et al. **Abiraterone acetate plus prednisolone with or without enzalutamide** for patients with metastatic prostate cancer starting androgen deprivation therapy: **Final results from two randomised phase 3 trials of the STAMPEDE platform protocol**. *Lancet Oncol* 2023;24(5):443-56.
- Armstrong AJ et al. The efficacy of **enzalutamide plus androgen deprivation therapy** in oligometastatic hormone-sensitive prostate cancer: **A post hoc analysis of ARCHES**. *Eur Urol* 2023;84(2):229-41.
- Sweeney CJ et al. **Testosterone suppression plus enzalutamide** versus testosterone suppression plus standard antiandrogen therapy for **metastatic hormone-sensitive prostate cancer (ENZAMET)**: An international, open-label, randomised, phase 3 trial. *Lancet Oncol* 2023;24(4):323-34.
- Hussain M et al. **Darolutamide plus androgen-deprivation therapy and docetaxel** in metastatic hormone-sensitive prostate cancer by disease volume and risk subgroups in the phase III **ARASENS** trial. *J Clin Oncol* 2023;41(20):3595-607.

Key Clinical Questions/Issues Related to Systemic Management/Research in Prostate Cancer

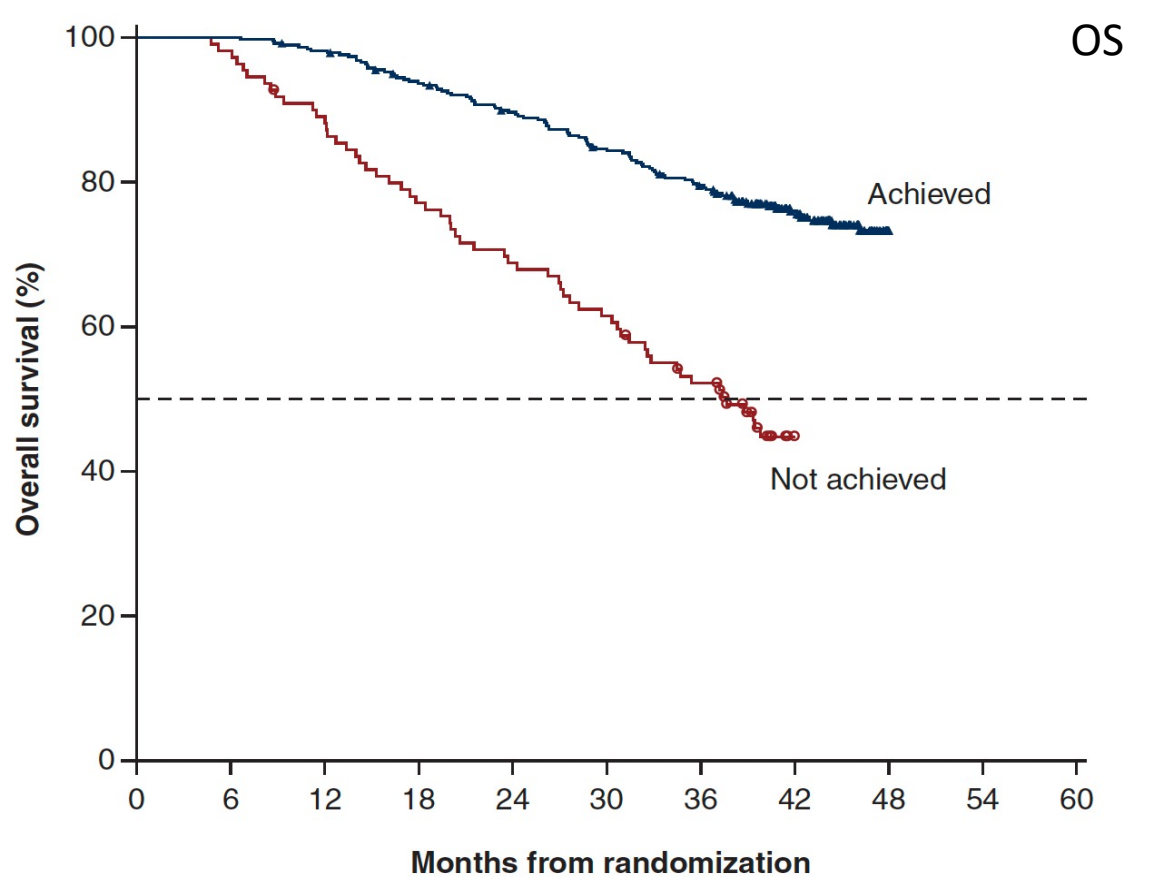
Metastatic hormone-sensitive prostate cancer — synchronous or recurrent

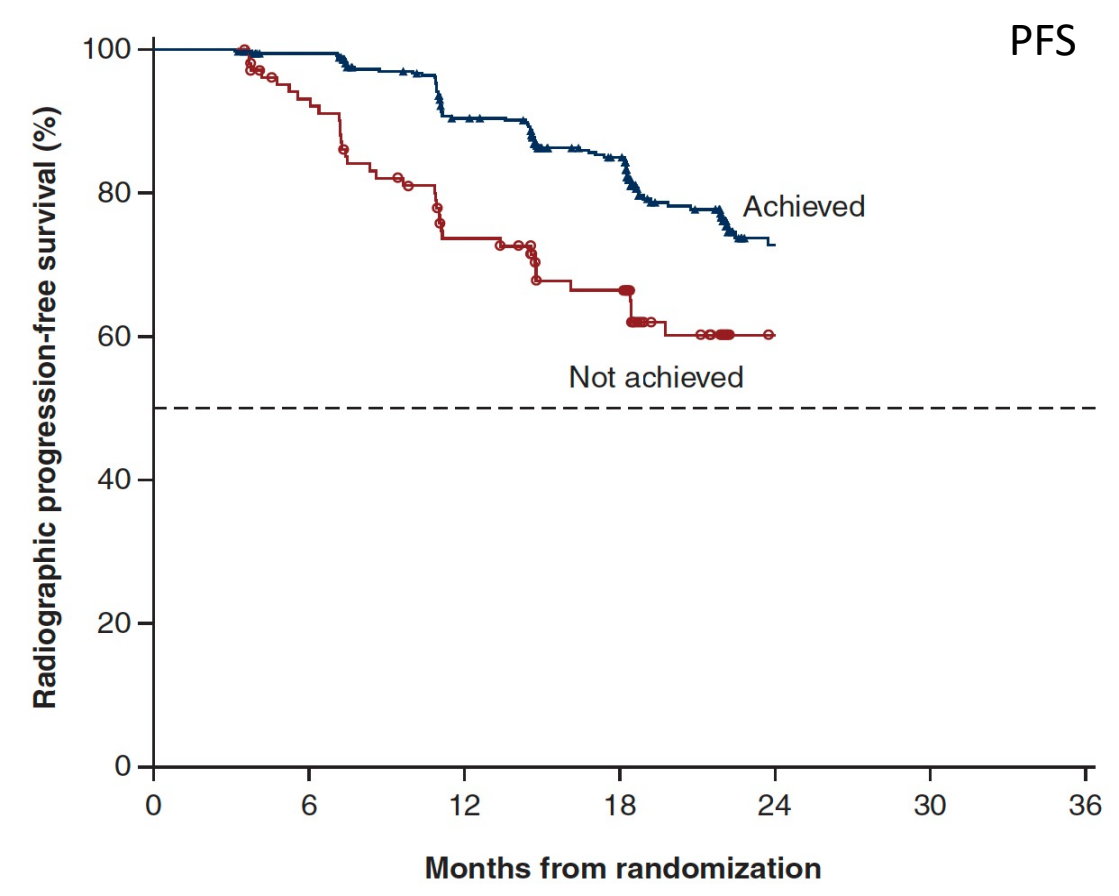
Role of radiation of the prostate (PEACE-1)

Use of docetaxel in combination with ADT/darolutamide (ARASENS)

Selection of AR pathway inhibitor – relative benefit versus toxicity

TITAN: Outcomes by Achievement of Deep PSA Decline (≥90% PSA Decline or PSA ≤0.2 ng/ml) at 3 Months of Apalutamide Treatment

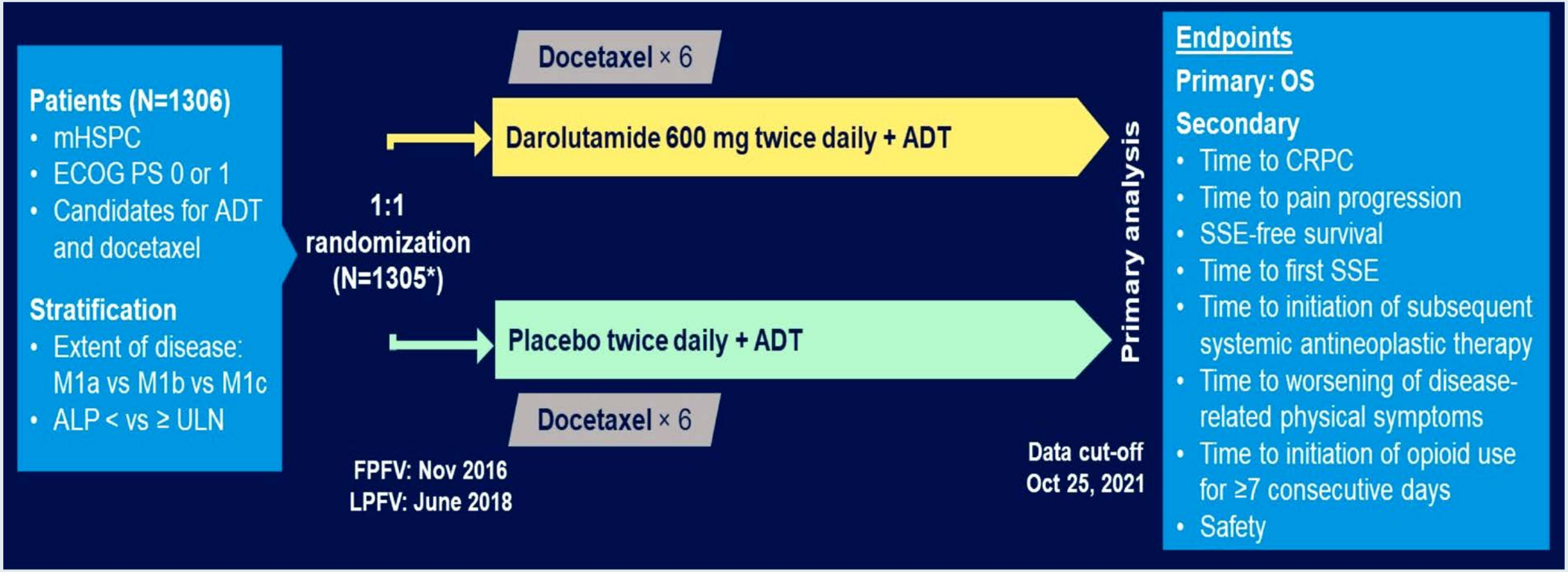




- **Apalutamide plus ADT demonstrated a robust (rapid, deep, and durable) PSA decline that was associated with improved clinical outcomes, including long-term survival.**

Chowdhury S et al. *Ann Oncol* 2023;34(5):477-85.

ARASENS: A Randomized Phase III Trial of Darolutamide versus Placebo for Metastatic Hormone-Sensitive Prostate Cancer (mHSPC) – Study Design



Smith MR et al. Genitourinary Cancers Symposium 2022;Abstract 13.

Novel Management Approaches for Patients with Advanced PC

- Agarwal N et al. **CYCLONE 1**: **Abemaciclib** in men with **heavily pretreated metastatic castration-resistant prostate cancer (mCRPC)**. AACR 2023;Abstract CT159.
- Matsubara N et al. **CYCLONE 3**: A **phase III**, randomized, double-blind, placebo-controlled study of **abemaciclib in combination with abiraterone plus prednisone** in men with **high-risk metastatic hormone-sensitive prostate cancer**. ESMO Asia 2023;Abstract 284TiP.
- Shore N et al. A phase I study of **capivasertib in combination with abiraterone acetate** in patients with metastatic castration-resistant prostate cancer. *Clin Genitourin Cancer* 2023;21(2):278-85.

Key Clinical Questions/Issues Related to Systemic Management/Research in Prostate Cancer

New approaches to endocrine therapy

- **CDK4/6 inhibitors abemaciclib and palbociclib**
- **AKT inhibitor capivasertib**

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 demonstrated in vitro activity, as single agent and in combination with AR blocker agents, limiting cellular proliferation.
- **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. Abemaciclib 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 1 Study Design

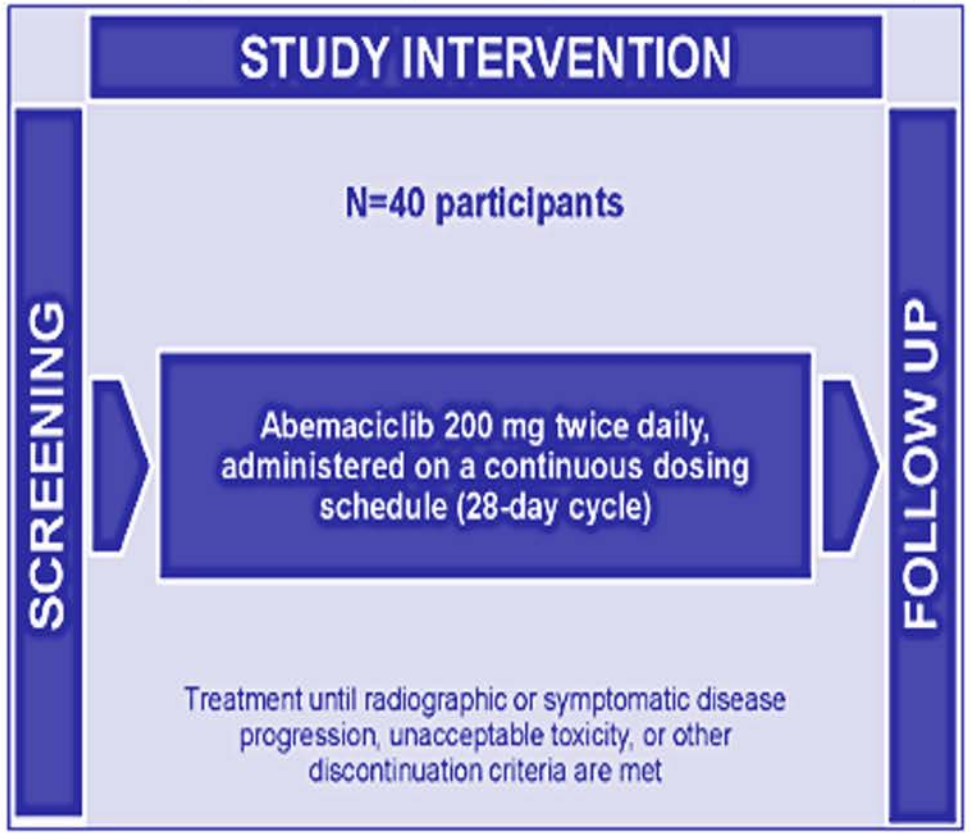
Key eligibility criteria *Additional screening criteria will be assessed prior to trial enrollment*

- mCRPC with at least 1 measurable lesion per RECIST v1.1
- Progressive disease at study entry in the setting of medical or surgical castration, defined as at least one of the following:
  - PSA progression (per PCWG3)
  - Radiographic progression (per RECIST v1.1 for soft tissue and/or PCWG3 for bone)
- Prior treatments:
  - ≥1 NHA (abiraterone acetate, apalutamide, darolutamide or enzalutamide, in any setting)
  - 2 taxane regimens[b] (docetaxel and cabazitaxel, ≥2 cycles each, in any setting)
  - ≤3 prior systemic therapy regimens for mCRPC
- Amenable to metastatic biopsy or availability of adequate archival metastatic tissue
- No prior treatment with abemaciclib or any CDK4 and/or CDK6 inhibitors
- Participants with serious and/or uncontrolled preexisting medical condition(s) (e.g. interstitial lung disease/pneumonitis), known/suspected brain metastasis or untreated (or risk of) spinal cord compression are not eligible

[b] if a patient has received only 1 taxane regimen, he may eligible ONLY if the second taxane regimen is deemed unsuitable (e.g. intolerance or contraindication). This requires sponsor approval.

Study Design

Phase 2, open label, single-arm, global multi-center study



Agarwal N et al. ASCO 2021;Abstract TPS5086.

CYCLONE 1: Results

Metric	No. patients
ORR	3 (6.8%)
Stable disease	17 (38.6%)
Stable disease lasting ≥6 months	6 (13.6%)
DCR	45.5%
Median PFS	2.7 months (95% CI 1.9, 3.7)
6-month rPFS	24.9% (95% CI 12.4, 39.5)
Median OS	7.6 months (CI 5.6, NE)

- No Grade 4 or 5 AEs
- Discontinuation due to AEs was 13.6%
- Most common AEs (≥50% of pts): Diarrhea (79.5%), decreased appetite (52.3%) and fatigue (50%)
- Most common Grade 3 AEs (≥5% of pts): neutropenia (22.7%), anemia (6.8%), and fatigue (6.8%)

- Abemaciclib demonstrated modest but objective single-agent clinical activity in patients with very heavily pretreated progressive mCRPC.

ORR = objective response rate; DCR = disease control rate

Agarwal N et al. AACR 2023;Abstract CT159.

CYCLONE 3: A Phase III, Randomized, Double-Blind, Placebo-Controlled Study of Abemaciclib in Combination with Abiraterone for High Risk mHSPC

Inclusion:

- **High-risk mHSPC** defined as:

≥4 bone metastases by Tc99 bone scan

and/or

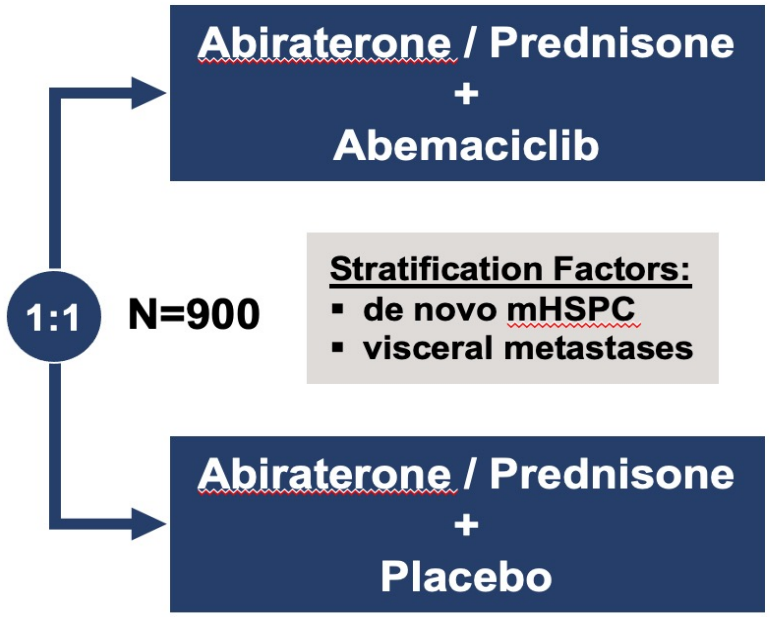
≥1 visceral metastases by CT/MRI

- ≤ 3 months of ADT (orchiectomy or LHRH ± anti-androgen)
- ECOG 0-1

Exclusion:

- Prior CDK4 & 6i
- Prior systemic therapy for metastatic prostate cancer (except for ADT/anti-androgen)
- Clinically significant cardiovascular disease, moderate/severe hepatic impairment

Study Schema



Endpoints

Primary Endpoint:

- Investigator-assessed rPFS

(per RECIST/adapted PCWG3 criteria)

Key Secondary Endpoints:

- rPFS by blinded independent central review
- Castration-resistant prostate cancer-free survival
- Overall Survival
- Time to pain progression
- Safety
- Pharmacokinetics

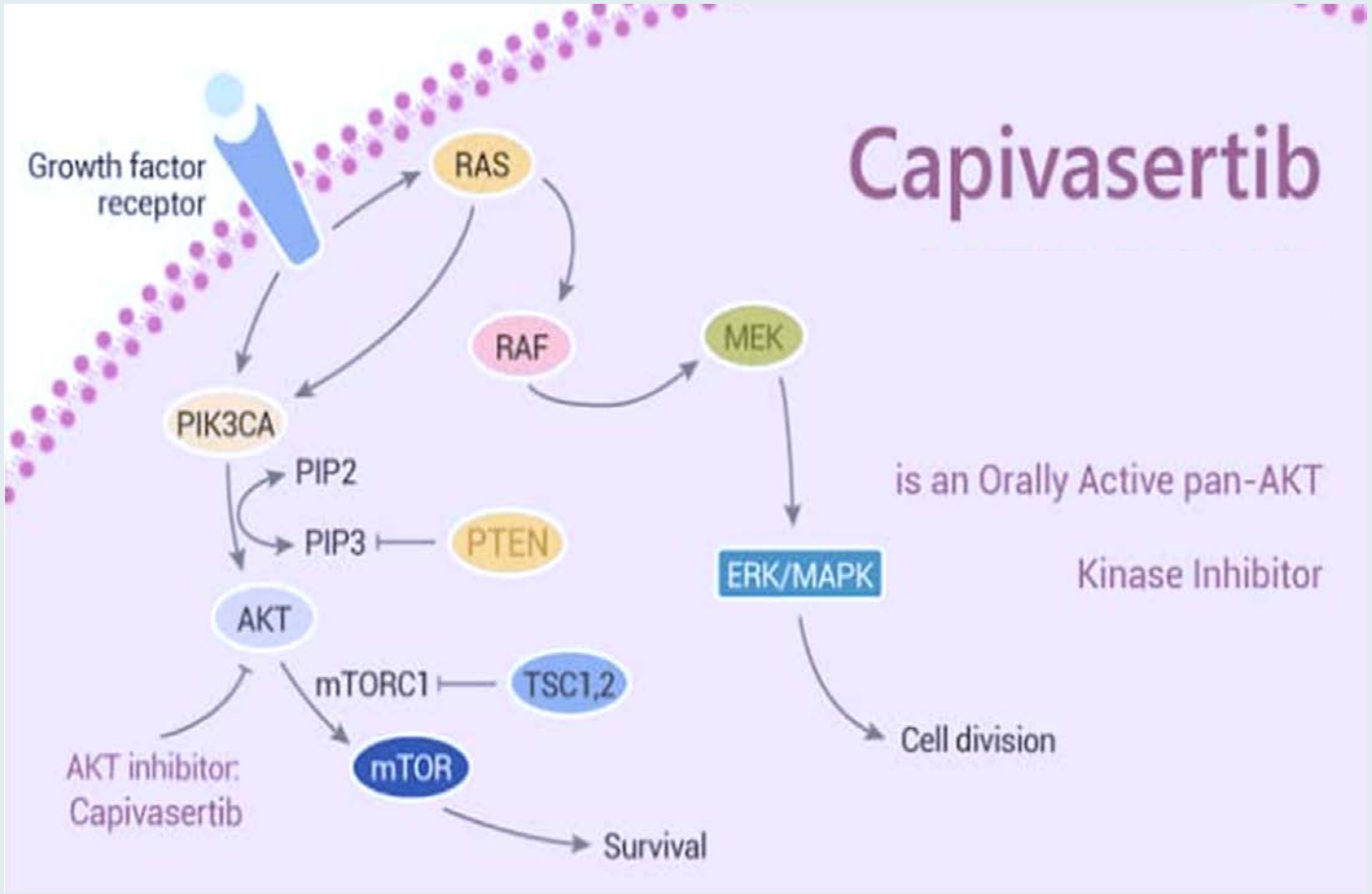
Smith MR et al. Genitourinary Cancers Symposium 2023;Abstract TPS289. Matsubara N et al. ESMO Asia 2023;Abstract 284TiP.

“**Phase 3 CYCLONE-2** results [demonstrated that] abemaciclib added to abiraterone did not meet the primary endpoint of improved radiographic progression-free survival in men with metastatic castration-resistant prostate cancer (mCRPC); the overall safety and tolerability profile was consistent with the known profiles of the medicines.”

https://investor.lilly.com/news-releases/news-release-details/lilly-reports-strong-fourth-quarter-2023-financial-results-and

Rationale to Study Capivasertib (Pan-AKT Inhibitor) in mHRPC

- Patients with metastatic prostate cancer can develop PI3K/AKT/PTEN pathway-associated resistance to andro-gen receptor-targeted therapy.
- In an open-label phase Ib study, 27 patients received abiraterone acetate + capivasertib, a potent, selective pan-AKT inhibitor.
- The combination demonstrated acceptable tolerability with no dose-limiting toxicity and pharmacokinetics consistent with monotherapy dosing. These data support further clinical evaluation in this patient population.

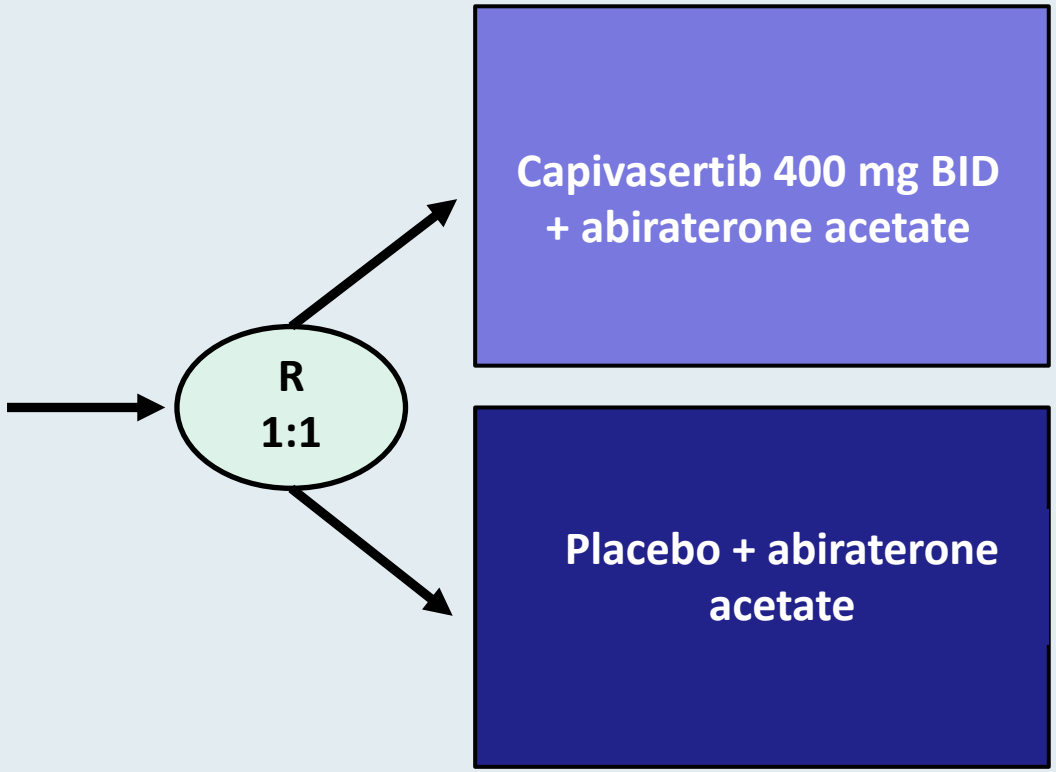


Shore N et al. *Clin Genitourin Cancer* 2023;21(2):278-85. Kyinno Biotechnology November 11, 2023.

Phase I Trial of Capivasertib with Abiraterone Acetate for Patients with mCRPC: Study Design

Key inclusion criteria

- Asymptomatic or mildly symptomatic histologically confirmed de novo hormone-sensitive prostate adenocarcinoma
- PTEN IHC result indicating PTEN deficiency
- Metastatic disease by clear evidence of ≥1 bone lesion and/or ≥1 soft tissue lesion
- Eligibility for abiraterone and steroid therapy
- Ongoing ADT with GnRH analog, or LHRH agonists or antagonist, or bilateral orchiectomy (regardless of method) from 0 days to a maximum of 93 days prior to randomization
- ECOG performance status 0 to 1



Primary Endpoint

- Radiographic PFS

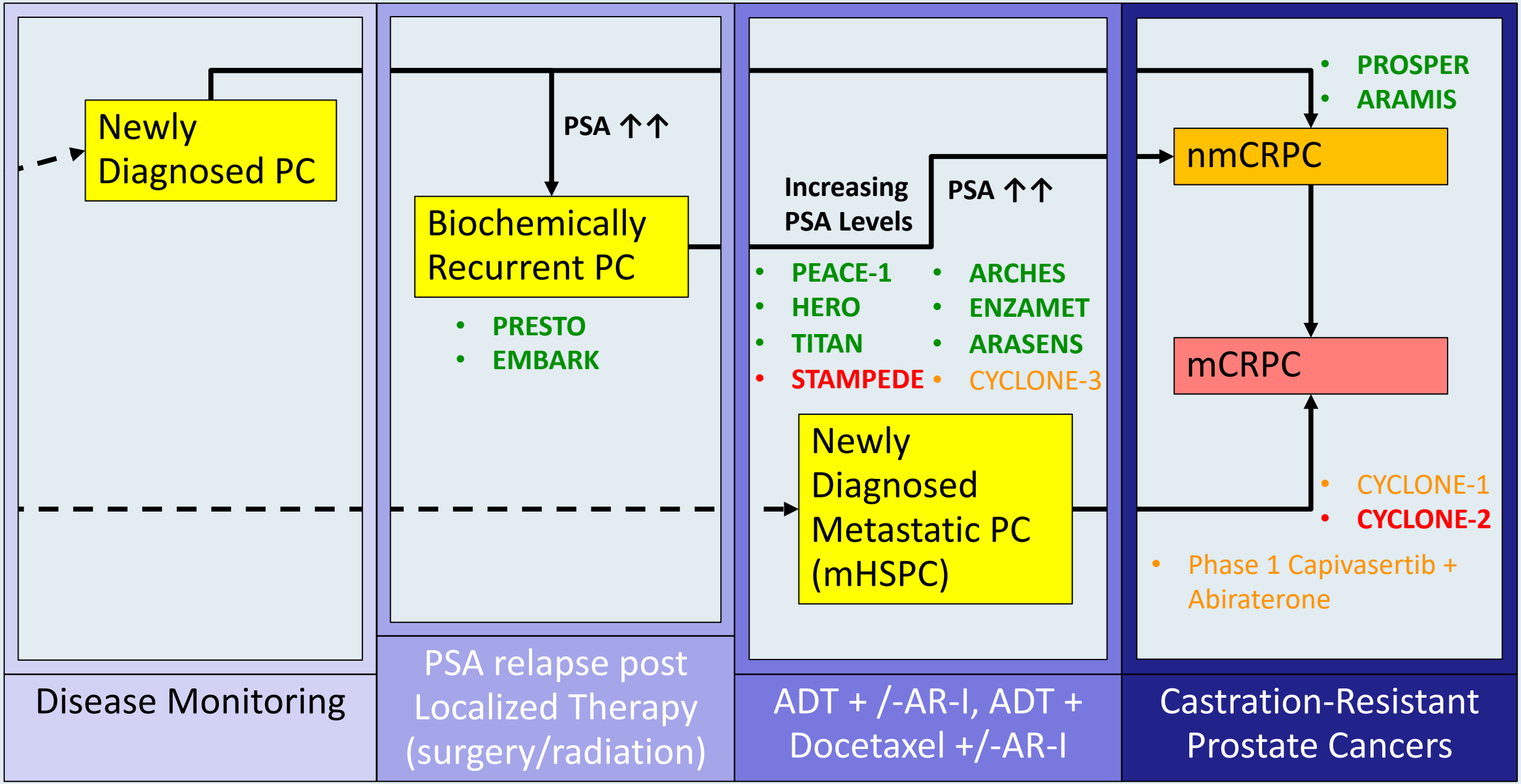
Secondary Endpoints

- OS
- TFST
- SSE-FS
- TTPP
- Time to PSA progression
- TTCR
- PFS2
- QoL Outcomes
- AEs

– Nine participants (33%) showed a 20% or greater decrease in PSA during study treatment.
– The combination of capivasertib/abiraterone had an acceptable tolerability profile consistent with the known profile of each agent.
– These data support further evaluation of capivasertib and abiraterone acetate in patients with advanced prostate cancer.

Shore N et al. *Clin Genitourin Cancer* 2023;21(2):278-85.

Prostate Cancer Disease States



Scher HI et al. *PLoS One* 2015.

Agenda

INTRODUCTION: Carpool Karaoke – RTP Style

MODULE 1: Hormonal Therapy

- Intensification
  - Localized and locally recurrent disease
  - PSA-only recurrence, high risk – PRESTO, EMBARK trials
- Metastatic disease – role of docetaxel, choice of AR inhibitor
- New approaches – CDK4/6 and AKT inhibitors

MODULE 2: Other Treatment Approaches

- Lutetium Lu 177 vipivotide tetraxetan
- Radium-223 chloride
- PARP inhibitors
- Neuroendocrine differentiation

Case from the Practice of Atif M Hussein, MD: 76-year-old man who presented with mHSPC with perineural invasion (Gleason 9) receives leuprolide and experiences disease progression almost 6 years later

- 04/24/2018: Needle core biopsy of prostate left lateral base — prostate adenocarcinoma Gleason score 9 (4 + 5). Grade Group 5. The tumor involves 80% of the tissue examined. Perineural invasion is present.
- 05/01/2018: PET scan — multiple lung lesions. No bone lesions.
- 05/03/2018: Received one dose of leuprolide 22.5 mg SC; PSA decreased from 71.8 on 02/06/2018 to 0.8 on 06/29/2018.
- 07/27/2018: Doing well. Unusual for lung mets without bone mets. Probably need to add abiraterone/prednisone or docetaxel.
- Patient refused to add any therapy to leuprolide since was doing well.
- 02/2024: Asymptomatic, progressive disease in lungs, still no bone disease. PSA increased, now around 10. PET scan now worse. Biopsy lung lesion done but awaiting results.

KEY ✓ Approved in indication ~ Approved in other indication ✗ Lack of response

Detected Alteration(s) / Biomarker(s)	Associated FDA-approved therapies	Clinical trial availability (see page 5)	% cfDNA or Amplification
AR T878A	✗ Abiraterone, Flutamide, Flutamide+goserelin, Niraparib+abiraterone, Olaparib+abiraterone	Yes	9.3%
AR V716M	✗ Bicalutamide, Flutamide	Yes	1.4%
BRCA2 F1216fs	✓ Olaparib, Rucaparib, Talazoparib+enzalutamide	Yes	0.2%
MSI-High	✓ Pembrolizumab ~ Dostarlimab, Nivolumab, Nivolumab+ipilimumab	Yes	DETECTED
PIK3CA R108H	~ Alpelisib, Capivasertib	Yes	4.1%
PIK3CA H1047R	~ Alpelisib, Capivasertib	Yes	0.2%
MTOR V2291I	None	Yes	4.4%
APC S678fs	None	Yes	5.2%

Variants of Uncertain Clinical Significance
ATM M2532V (6.4%), *MTOR* R1818C (5.1%), *ALK* R1347W (4.3%), *MSH6* R922Q (0.4%)
The functional consequences and/or clinical significance of alterations are unknown. Relevance of therapies targeting these alterations is uncertain.

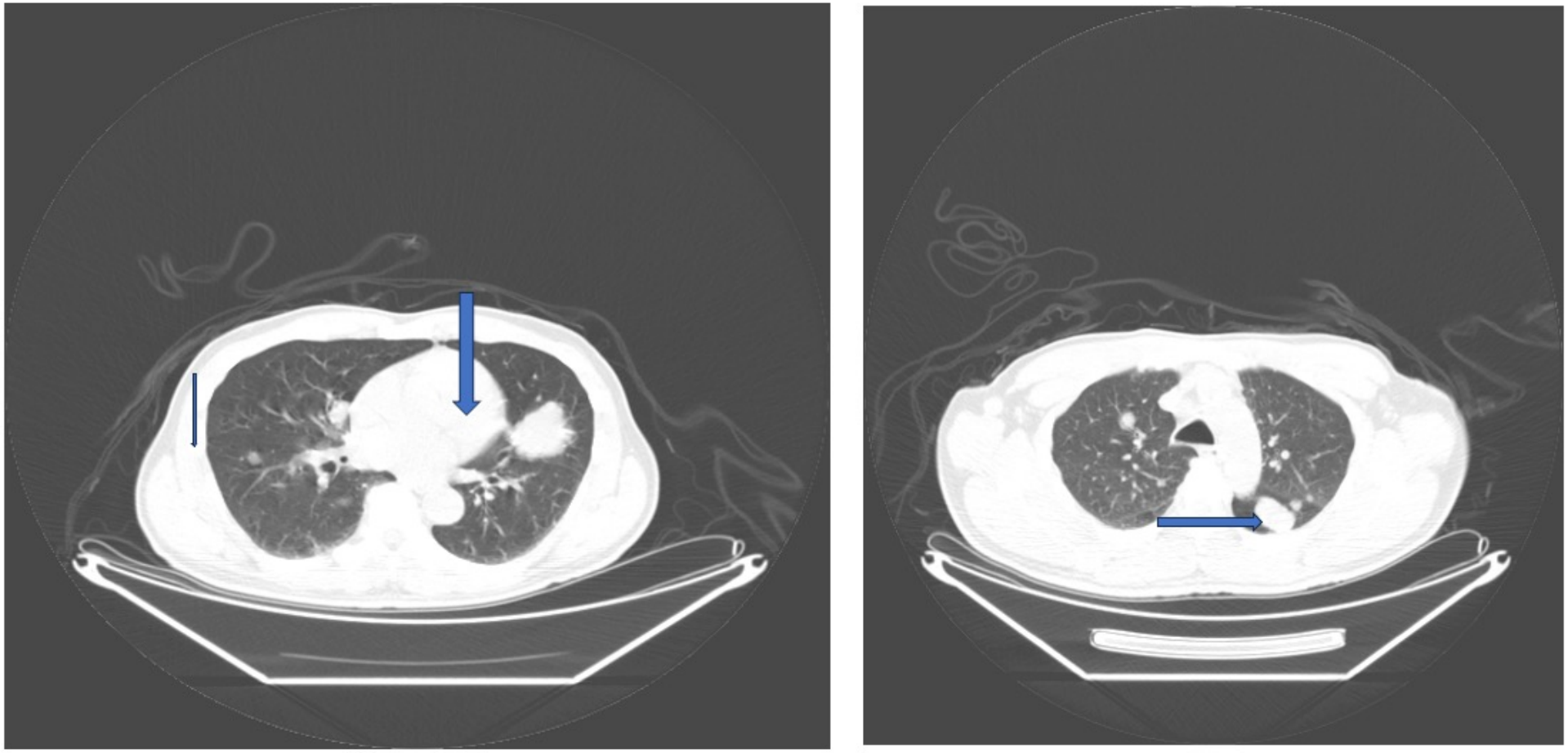
Synonymous Alterations
MPL L38L (0.2%)
This sequence change does not alter the amino acid at this position and is unlikely to be a therapeutic target. Clinical correlation is advised.

RTP RESEARCH TO PRACTICE

Additional Biomarkers

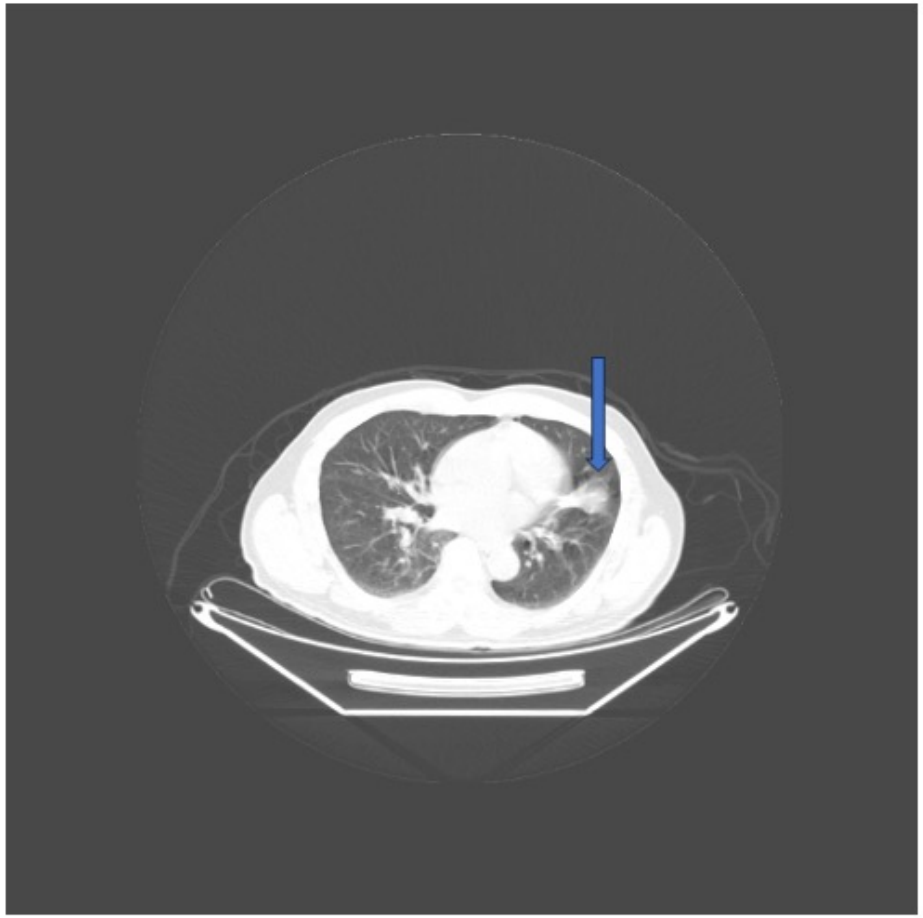
Biomarker	Additional Details
Tumor Mutational Burden (TMB)	42.16 mut/Mb
MSI-High	DETECTED

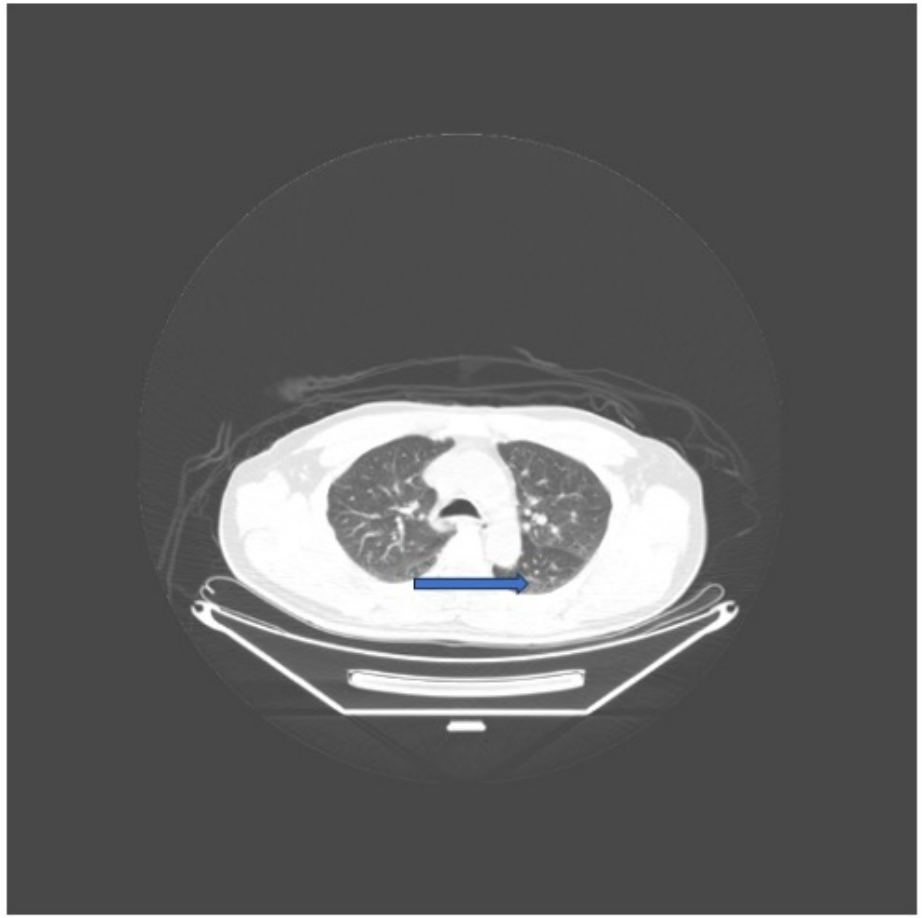
May 2018



August 2018 compared to May 2018

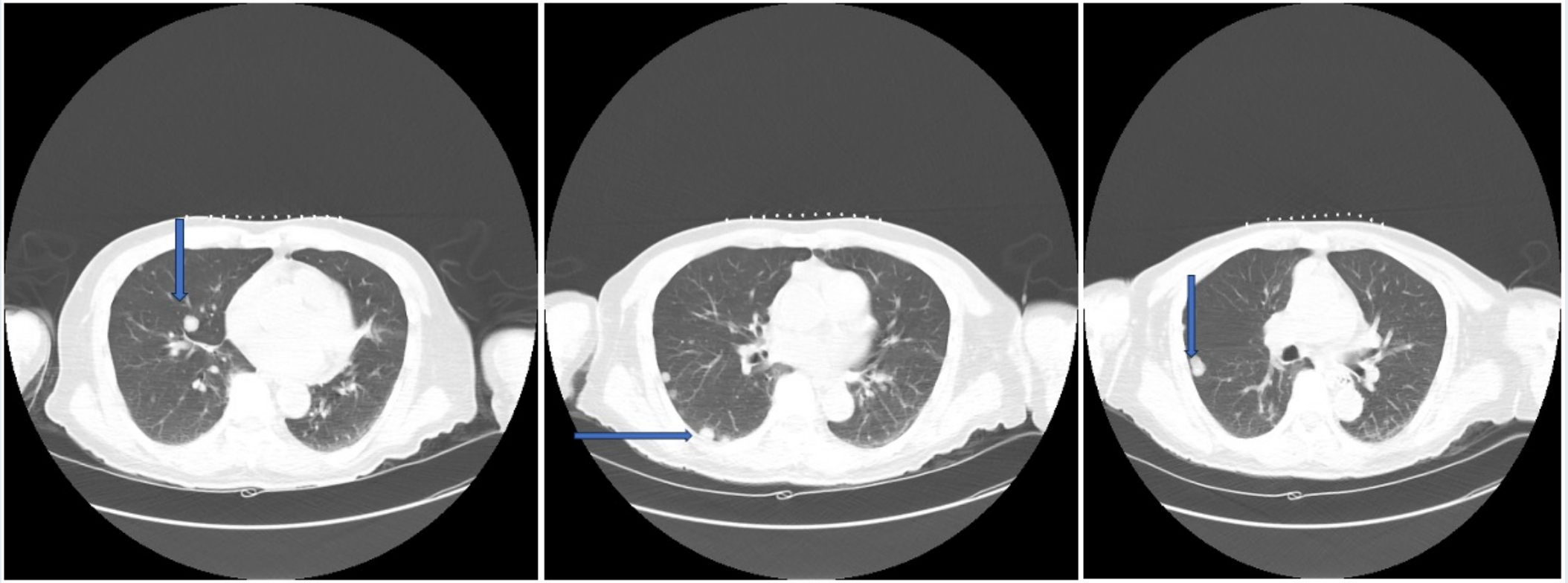
Marked decrease in the upper left lung mass and disappearance of the right lower mass





January 2024

New small bilateral pulmonary nodules



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- 07/27/2018: Doing well. Unusual for lung mets without bone mets. Probably need to add abiraterone/prednisone or docetaxel.
- Patient refused to add any therapy to leuprolide since was doing well.
- 02/2024: Asymptomatic, progressive disease in lungs, still no bone disease. PSA increased, now around 10. PET scan now worse. Biopsy lung lesion done but awaiting results.
- Guardant360® blood:
  - 2 AR mutations conferring resistance to anti-androgen therapy
  - BRCA2 somatic mutation
  - MSI-high
- Germline testing negative
- NGS pending

RTP RESEARCH TO PRACTICE

PSMA-Targeted Radioligand Therapy

- Hofman MS et al. **Overall survival** with **[^{177}Lu]Lu-PSMA-617** versus cabazitaxel in metastatic castration-resistant prostate cancer **(TheraP)**: **Secondary outcomes** of a randomised, open-label, phase 2 trial. *Lancet Oncol* 2024;25(1):99-107.
- Fizazi K et al**. Health-related quality of life and pain outcomes** with **[^{177}Lu]Lu-PSMA-617 plus standard of care** versus standard of care in patients with metastatic castration-resistant prostate cancer **(VISION)**: A multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol* 2023;24(6):597-610.
- Sartor O et al. Phase III trial of **[^{177}Lu]Lu-PSMA-617** in **taxane-naive patients** with metastatic castration-resistant prostate cancer **(PSMAfore)**. ESMO 2023;Abstract LBA13.
- Sandhu S et al. LuPARP: **Phase 1 trial of ^{177}Lu-PSMA-617 and olaparib** in patients with metastatic castration resistant prostate cancer (mCRPC). ASCO 2023;Abstract 5005.
- Emmett L et al. **Enzalutamide and ^{177}Lu-PSMA-617** in poor-risk, metastatic, castration-resistant prostate cancer (mCRPC): A randomised, phase II trial**: ENZA-p (ANZUP 1901)**. ESMO 2023;Abstract LBA84.

PSMA-Targeted Radioligand Therapy

- Rahbar K et al. Safety and survival outcomes of **^{177}Lu-prostate-specific membrane antigen therapy** in patients with metastatic castration-resistant prostate cancer with **prior ^{223}Ra treatment**: **The RALU study**. *J Nucl Med* 2023;64(4):574-8.
- Lantheus and POINT Biopharma announce positive **topline results** from **pivotal SPLASH trial** in metastatic castration-resistant prostate cancer [press release]. December 18, 2023. https://lantheusholdings.gcs-web.com/news-releases/news-release-details/lantheus-and-point-biopharma-announce-positive-topline-results.

Key Clinical Questions/Issues Related to Systemic Management/Research in Prostate Cancer

Lutetium Lu 177 vipivotide tetraxetan

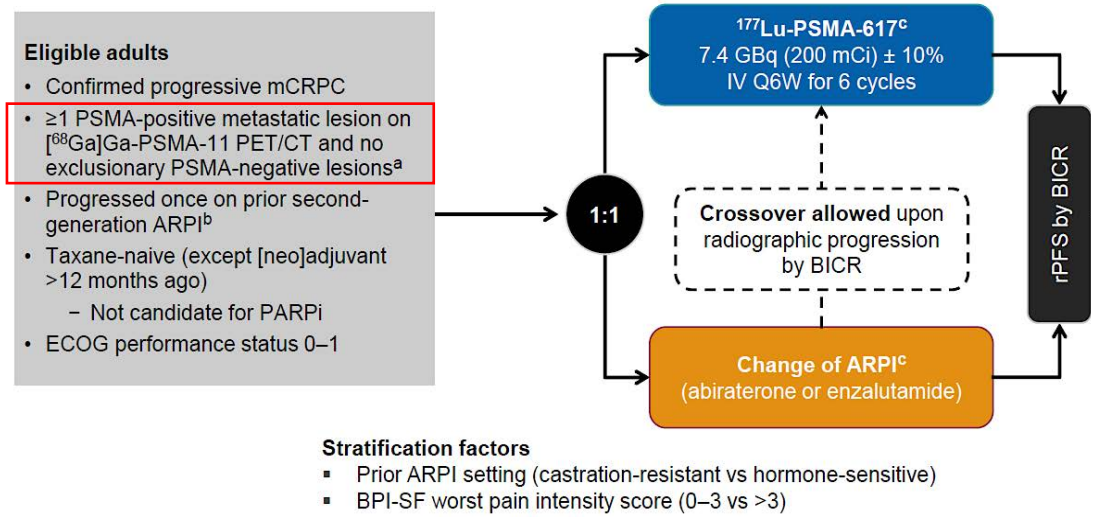
- **PSMA findings and treatment benefit**
- **Follow-up of patients – imaging**
- **Prevention and management of xerostomia and dry eye**
- **Radiation protection precautions**
- **Sequencing PSMA radioligand therapy and radium-223**
- **Re-treatment after initial progression**
- **Combining PSMA radioligand therapy with other systemic agents**

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

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

PSMAfore: Study Design

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



Stratification factors

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

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

PSMAfore: Baseline Patient and Disease Characteristics

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

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

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

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

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

Courtesy of Andrew J Armstrong, MD, ScM

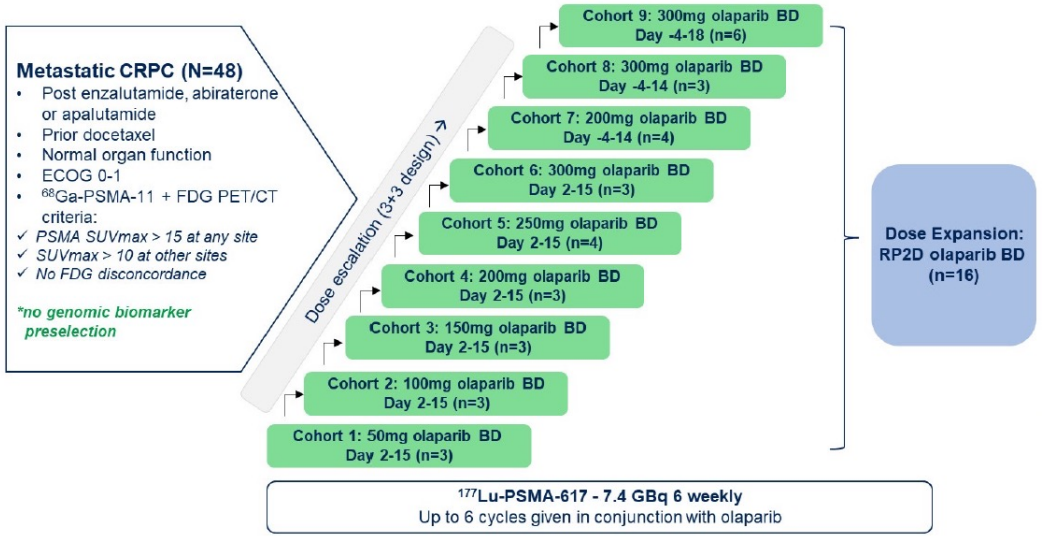
Sartor O, et al. Abstract presented at: ESMO Congress 2023; October 20-24, 2023; Madrid, Spain, Abstract LBA13

Sandhu GU 2023 abstract 5005

177Lu-PSMA-617 Combination Therapy: LuPARP

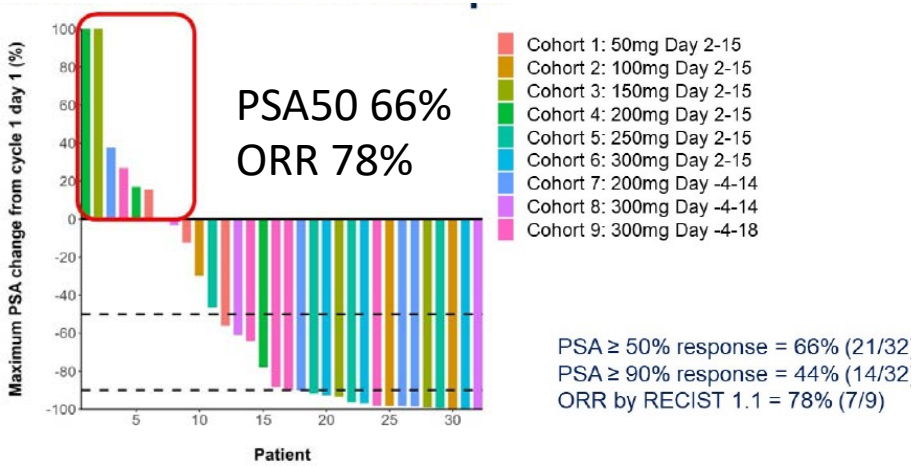
No DLTs, RP2D is olaparib 300 mg BID days -4 to +18 of each 6 weekly cycle

LuPARP: Phase 1 Trial Schema



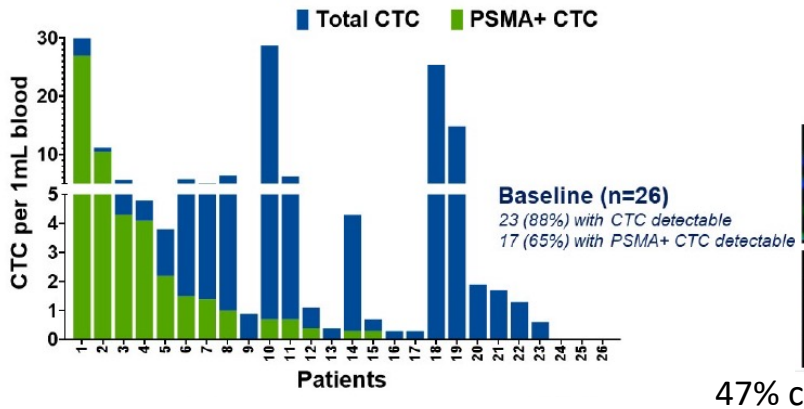
LuPARP results: Treatment Related AEs >5%

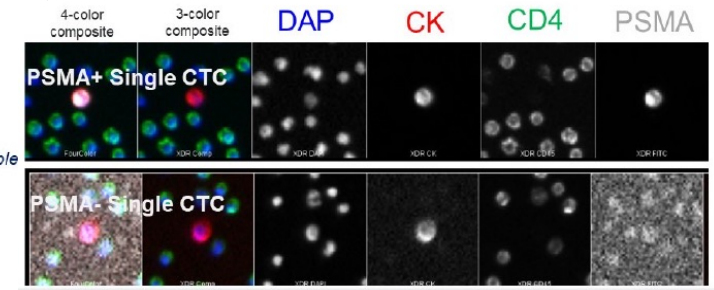
	N=3 Cohort 1 177Lu-PSMA & 50mg olaparib BD Day 2-15			N=3 Cohort 2 177Lu-PSMA & 100mg olaparib BD Day 2-15			N=3 Cohort 3 177Lu-PSMA & 150 olaparib BD Day 2-15			N=3 Cohort 4 177Lu-PSMA & 200mg olaparib BD Day 2-15			N=4 Cohort 5 177Lu-PSMA & 250mg olaparib BD Day 2-15			N=3 Cohort 6 177Lu-PSMA & 300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



PSA50 66%
ORR 78%

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

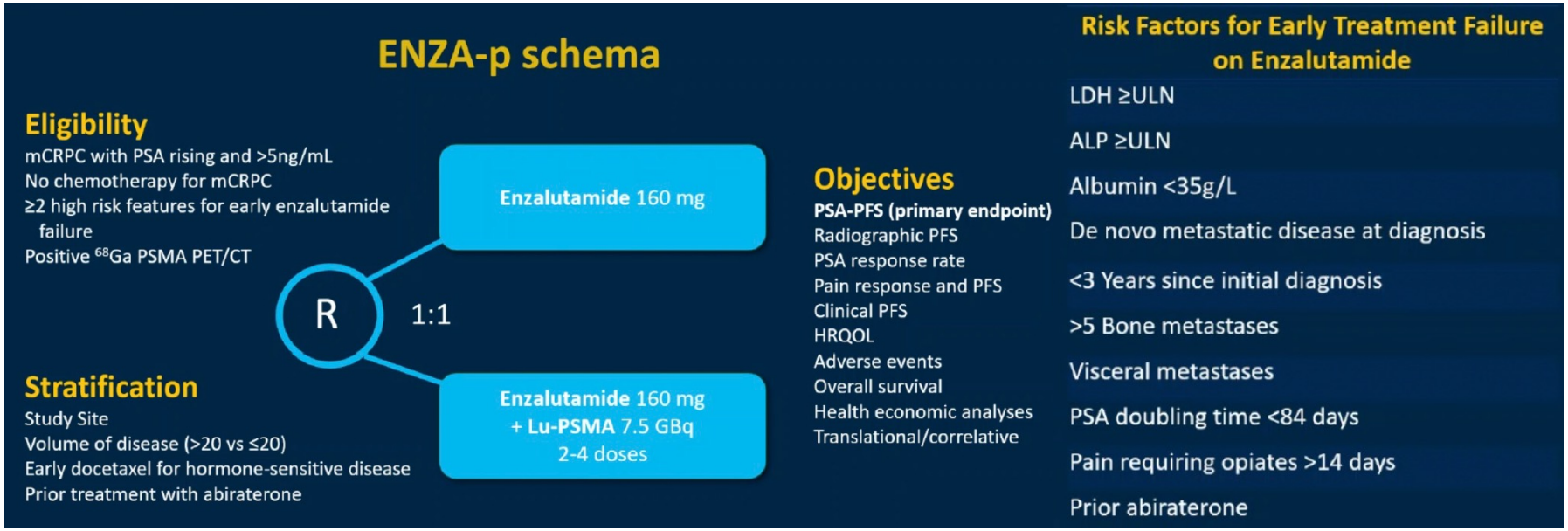




47% cleared all CTCs; 87% cleared all PSMA+ CTCs

Courtesy of Andrew J Armstrong, MD, ScM

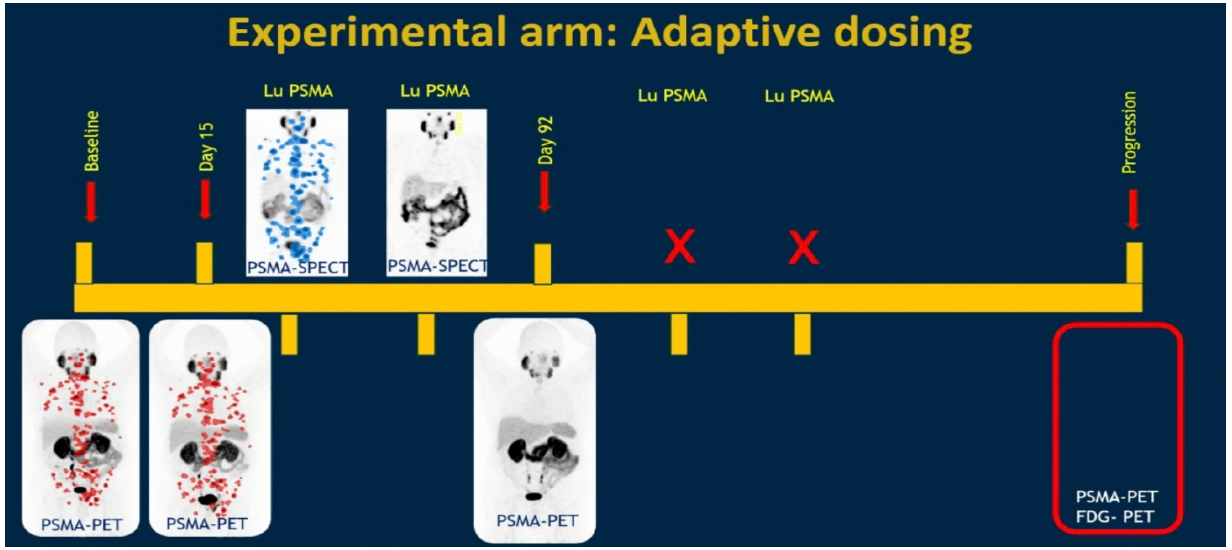
Enza-p: Synergy with ARSI Therapy?



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

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

Emmett L et al ESMO 2023 LBA84



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

Courtesy of Andrew J Armstrong, MD, ScM

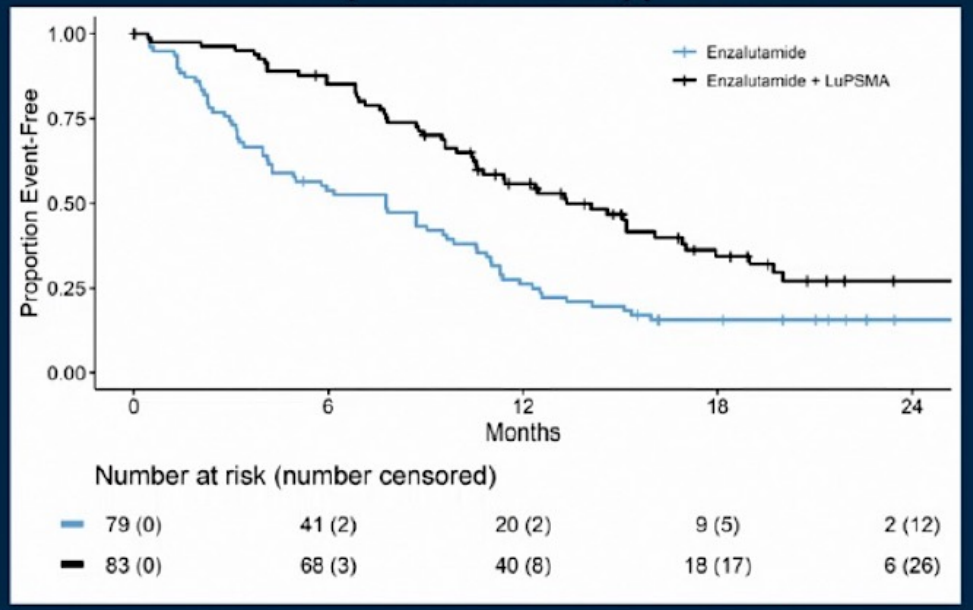
Enza-p Results

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

Progression Free Survival

PSA-PFS

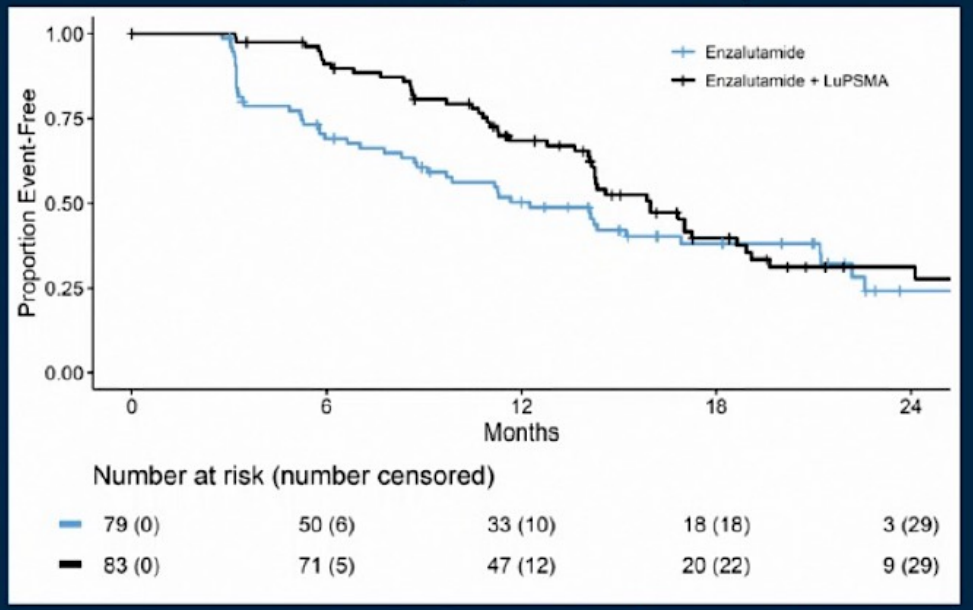
HR 0.43 (95%CI 0.29-0.63) p=0.00001



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

R-PFS

HR 0.67 (95% CI 0.44-1.01)

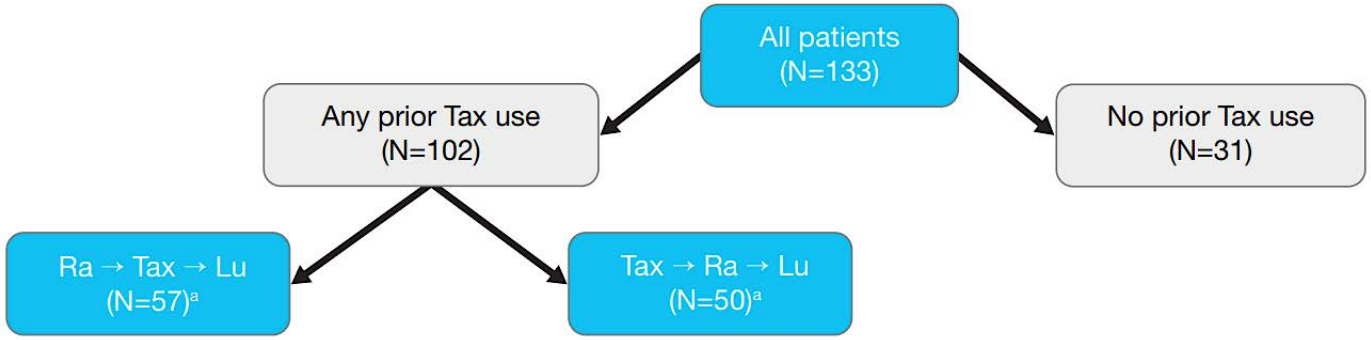


Radiographic-PFS	Participants	Events	Censored	Median Months
Enzalutamide	79	47	35	12
Enzalutamide + Lu-PSMA	83	48	32	16

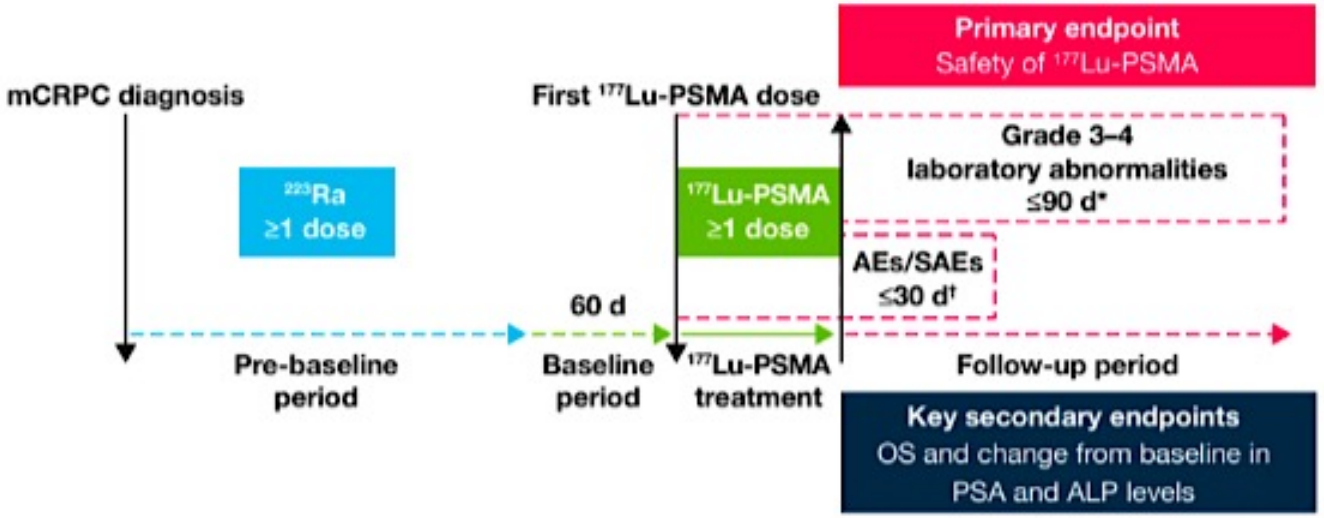
Emmett L et al ESMO 2023 LBA84

Courtesy of Andrew J Armstrong, MD, ScM

Is Lu177-PSMA-617 Safe After Radium-223? RALU phase 2 Study



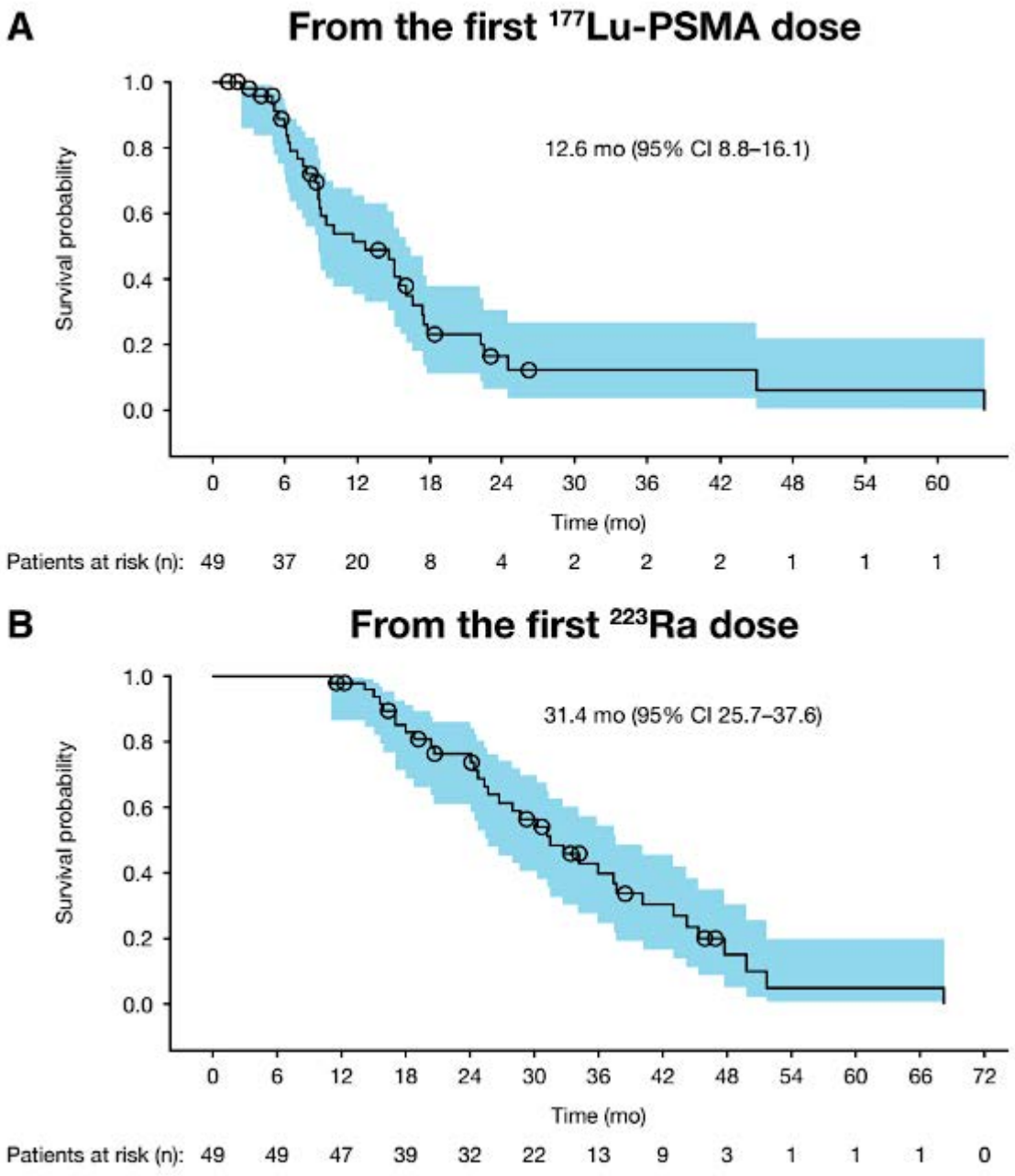
Groups highlighted in blue are included in these analyses
[a]13 patients who received Tax both before and after ^{223}Ra were included in both groups

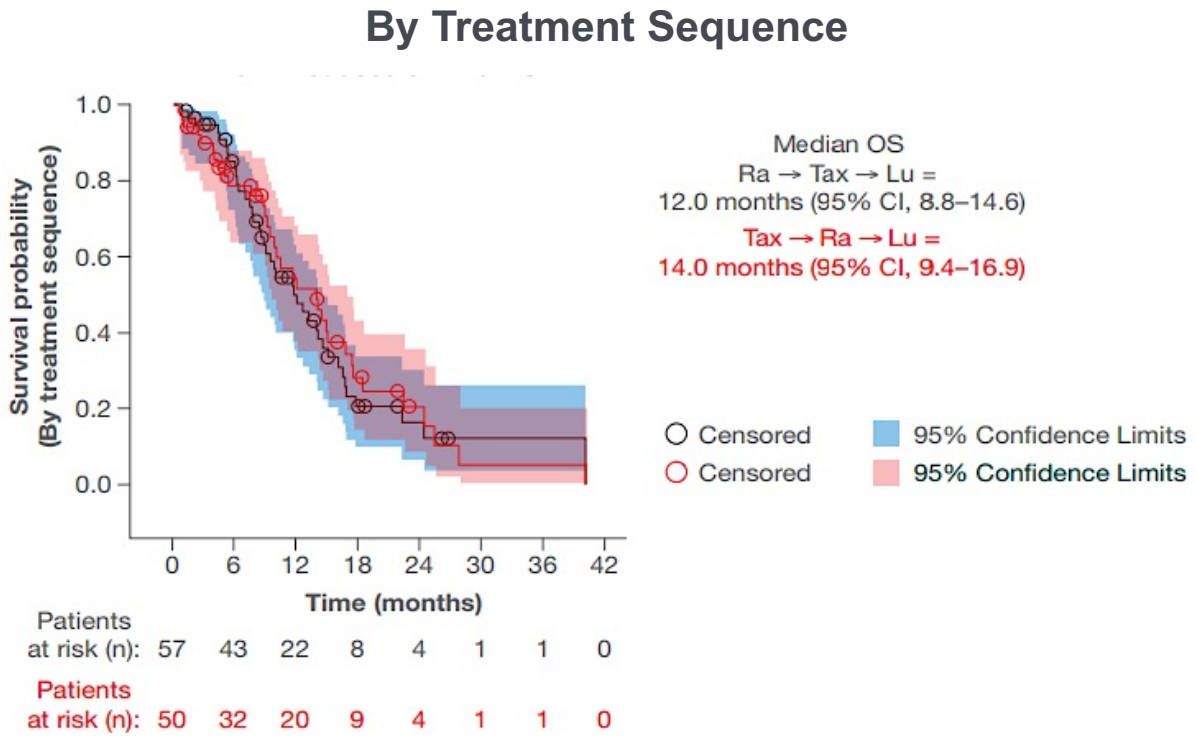


Baseline characteristics	All patients (N=133)	By treatment sequence[a]	
		Ra → Tax → Lu (N=57)	Tax → Ra → Lu (N=50)
Age, median (range) years	73 (49–90)	73 (53–90)	71 (49–84)
ECOG PS			
1	82 (62)	37 (65)	31 (62)
2	51 (38)	20 (35)	19 (38)
PSA (ng/mL), median (range)	286 (1–12,229)	329 (7–12,229)	500 (20–5,810)
ALP (U/L), median (range)	146 (23–973)	154 (23–973)	128 (51–532)
Extent of metastatic disease[b]			
Bone metastases with lymph node metastases	63 (47)	24 (42)	27 (54)
Bone metastases without lymph node metastases	33 (25)	10 (18)	9 (18)
Visceral metastases	36 (27)	23 (40)	14 (28)
Life-prolonging therapies			
≥4 Life-prolonging therapies[c]	75 (56)	44 (77)	35 (70)
Prior ^{233}Ra	133 (100)	57 (100)	50 (100)
Completed ^{223}Ra therapy (6 injections)	94 (71)	42 (74)	31 (62)
Second-generation antiandrogen therapies			
Abiraterone	95 (71)	43 (75)	36 (72)
Enzalutamide	92 (69)	45 (79)	30 (60)
Abiraterone and enzalutamide	71 (53)	-	-
Number of any Tax lines[d]			
0	31 (23)	0 (0)	0 (0)
1	67 (50)	33 (58)	27 (54)
≥2	35 (26)	24 (42)	23 (46)
Docetaxel	99 (74)	54 (95)	50 (100)
Number of cycles[e]			
1–4	27 (24)	17 (27)	15 (26)
≥5	59 (53)	32 (51)	28 (48)
Missing/unknown	26 (23)	14 (22)	15 (26)
Cabazitaxel	30 (23)	21 (37)	19 (38)
Number of cycles[f]			
1–4 cycles	7 (21)	11 (48)	4 (18)
≥5 cycles	14 (42)	6 (26)	10 (45)
Missing/unknown	12 (36)	6 (26)	8 (36)

Rahbar K, et al. Ann Oncol. 2022;33(suppl 7):S1180 and J Nucl Med 2023; 64: 574-78.

Courtesy of Andrew J Armstrong, MD, ScM



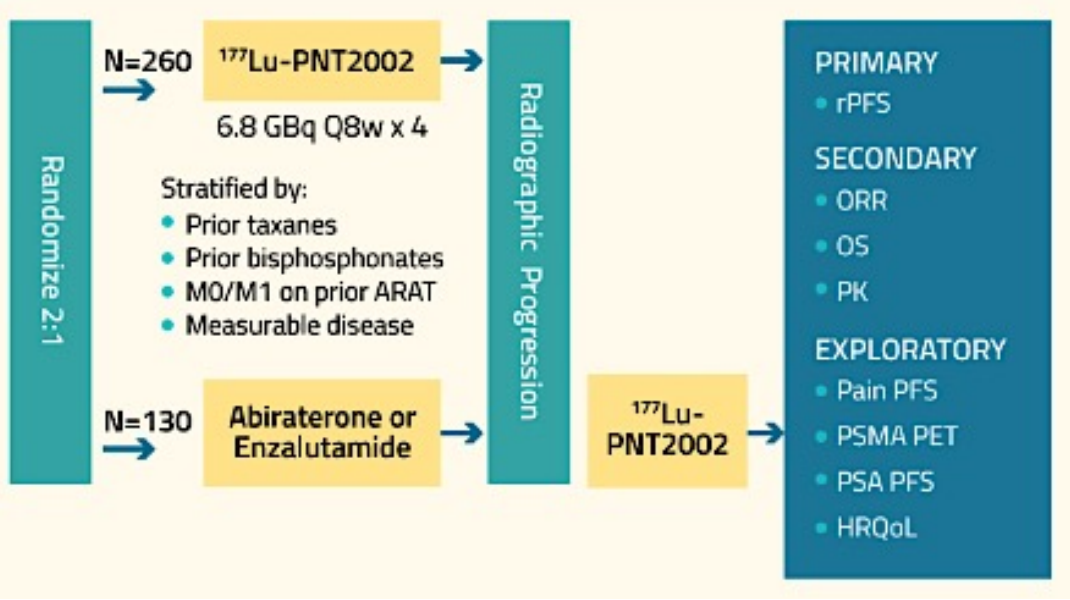


- In patients for whom radium 223 had been used as part of routine disease management, subsequent lutetium 177-PSMA therapy was clinically feasible and well tolerated, with acceptable myelosuppression rates
- Survival outcomes in patients who received the radium 223/lutetium 177-PSMA sequence were similar to those reported in previous real-world studies and the phase 3 VISION trial

Rahbar K, et al. Ann Oncol. 2022;33(suppl 7):S1180 and J Nucl Med 2023; 64: 574-78.

Courtesy of Andrew J Armstrong, MD, ScM

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



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

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

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

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

Courtesy of Andrew J Armstrong, MD, ScM

PARP Inhibitors for mCRPC

- Saad F et al. **Olaparib plus abiraterone** versus placebo plus abiraterone in metastatic castration-resistant prostate cancer **(PROpel)**: **Final prespecified overall survival results** of a randomised, double-blind, phase 3 trial. *Lancet Oncol* 2023;24(10):1094-108.
- Shore ND et al. Efficacy of **olaparib (O) plus abiraterone (A)** versus placebo (P) plus A in patients (pts) with **metastatic castration-resistant prostate cancer (mCRPC)** with **single homologous recombination repair gene mutations (HRRm) in the PROpel trial.** Genitourinary Cancers Symposium 2024;Abstract 165.
- Chi KN et al. **Niraparib (NIRA) with abiraterone acetate plus prednisone (AAP)** as **first-line (1L)** therapy in patients (pts) with **metastatic castration-resistant prostate cancer (mCRPC)** and homologous recombination repair (HRR) gene alterations: **Three-year update and final analysis (FA) of MAGNITUDE**. ESMO 2023;Abstract LBA85.
- Agarwal N et al. **Talazoparib plus enzalutamide** in men with **first-line metastatic castration-resistant prostate cancer (TALAPRO-2)**: A randomised, placebo-controlled, phase 3 trial. *Lancet* 2023;402(10398):291-303.
- Fizazi K et al. **First-line talazoparib with enzalutamide** in HRR-deficient metastatic castration-resistant prostate cancer: The phase 3 **TALAPRO-2** trial. *Nat Med* 2024;30(1):257-64.
- Fizazi K et al. **Rucaparib** or physician's choice in **metastatic prostate cancer**. *N Engl J Med* 2023;388(8):719-32.

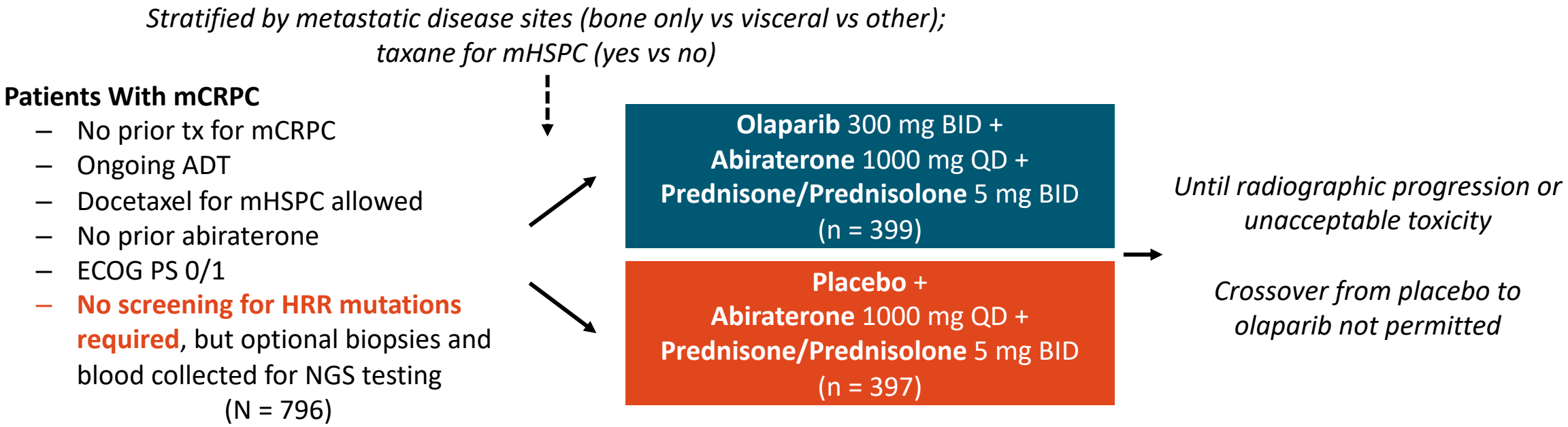
Key Clinical Questions/Issues Related to Systemic Management/Research in Prostate Cancer

PARP inhibitors

- **Appropriate germline and somatic workup**
  - **Alterations for which PARP inhibitors to consider**
- **PARP inhibitor/AR pathway inhibitor combinations for mCRPC**
  - **Olaparaib + abiraterone (PROpel)**
  - **Niraparib + abiraterone (MAGNITUDE)**
  - **Talazoparib + enzalutamide (TALAPRO-2)**
- **Toxicity profile of available agents; choice of treatment**
  - **Management of fatigue and anemia associated with PARP inhibitors**
  - **Risk of AML/MDS**

PROpel Trial: First-line Abiraterone/Prednisone ± Olaparib in mCRPC

- International, randomized, double-blind phase III study



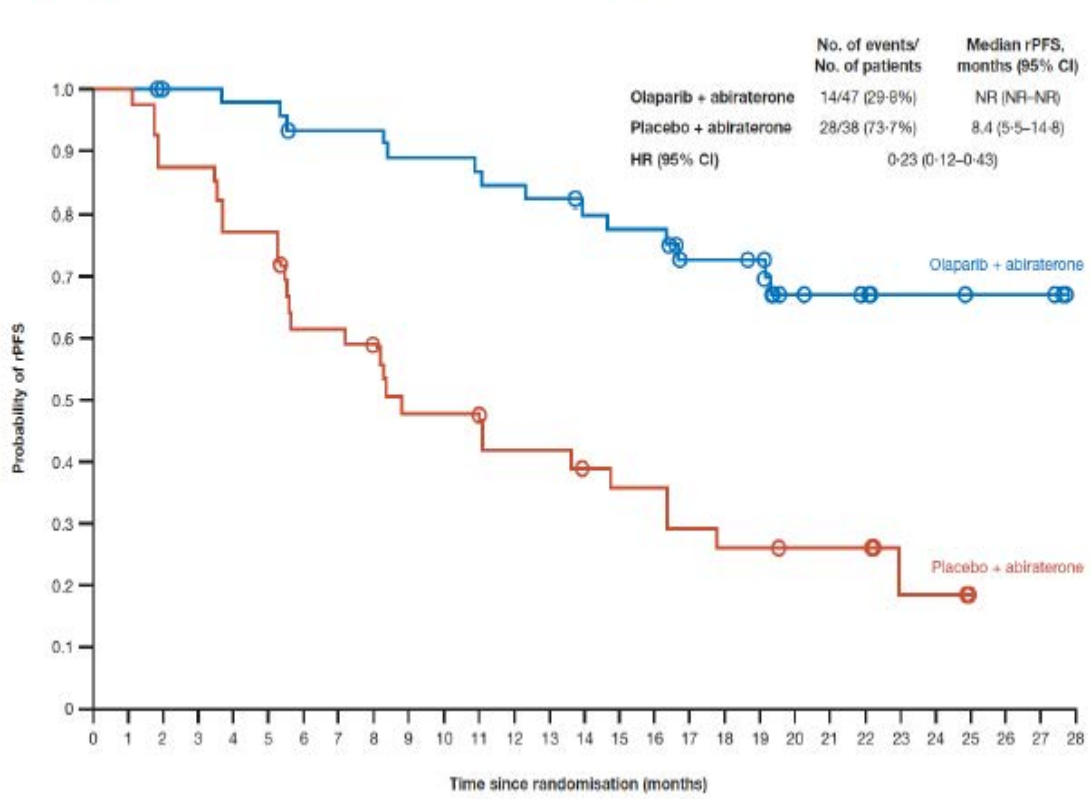
- **Primary endpoint**: rPFS by investigator
- **Key secondary endpoints**: OS, time to subsequent therapy or death, PFS2, ORR, HRR mutation prevalence (retrospectively assessed), HRQoL, safety

Clarke. NEJM Evid. 2022;1. Saad. Lancet Oncol. 2023;24:1094.

Courtesy of Andrew J Armstrong, MD, ScM

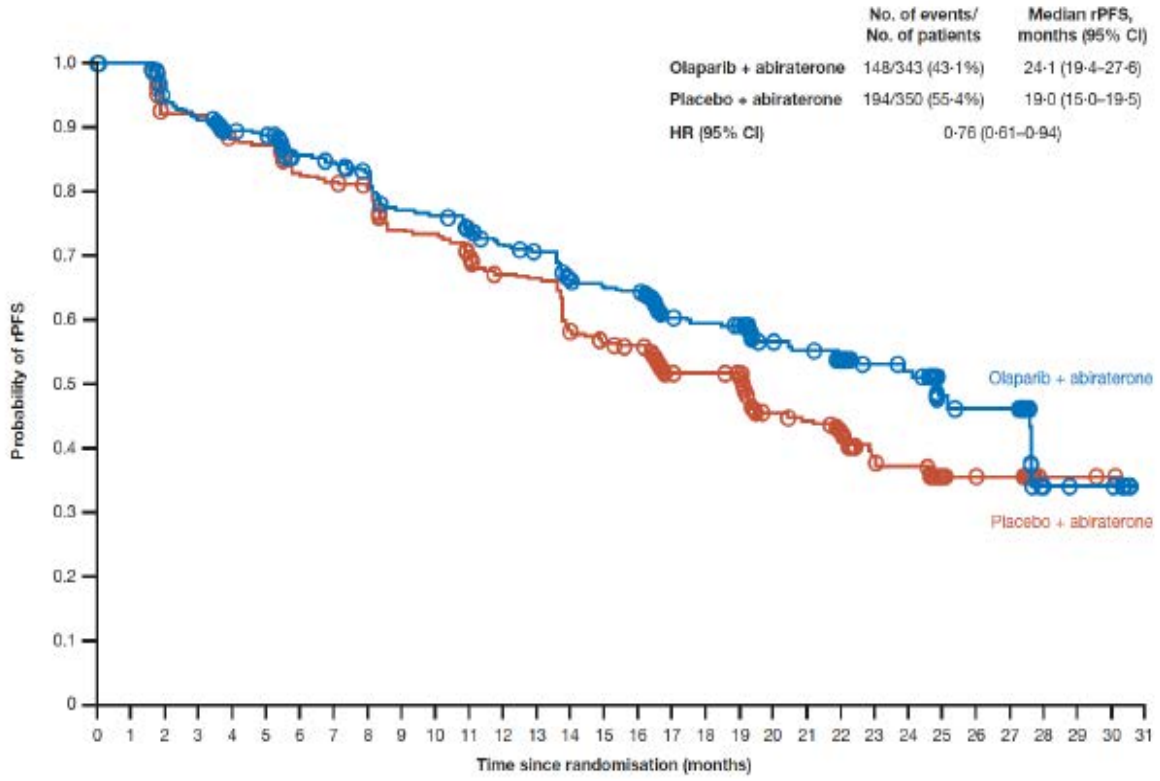
Updated rPFS in PROpel by BRCAm Status

A. Radiographic progression-free survival in the BRCAm subgroup



PSA PFS HR 0.14 (0.08-0.25)

Radiographic progression-free survival in the non-BRCAm subgroup



PSA PFS HR 0.67 (0.55-0.82)

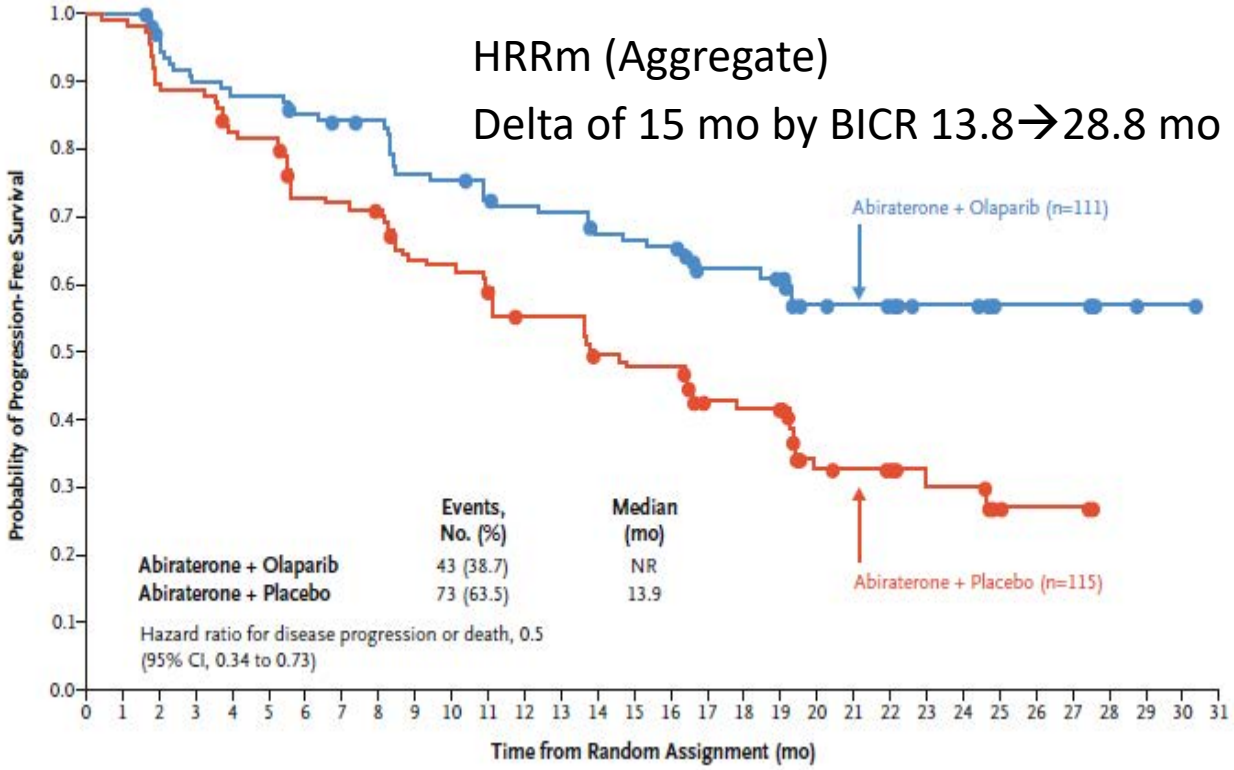
Saad. Armstrong. Lancet Oncol. 2023:24:1094.

Courtesy of Andrew J Armstrong, MD, ScM

Is there clinical utility in delaying rPFS by 8.5 months?

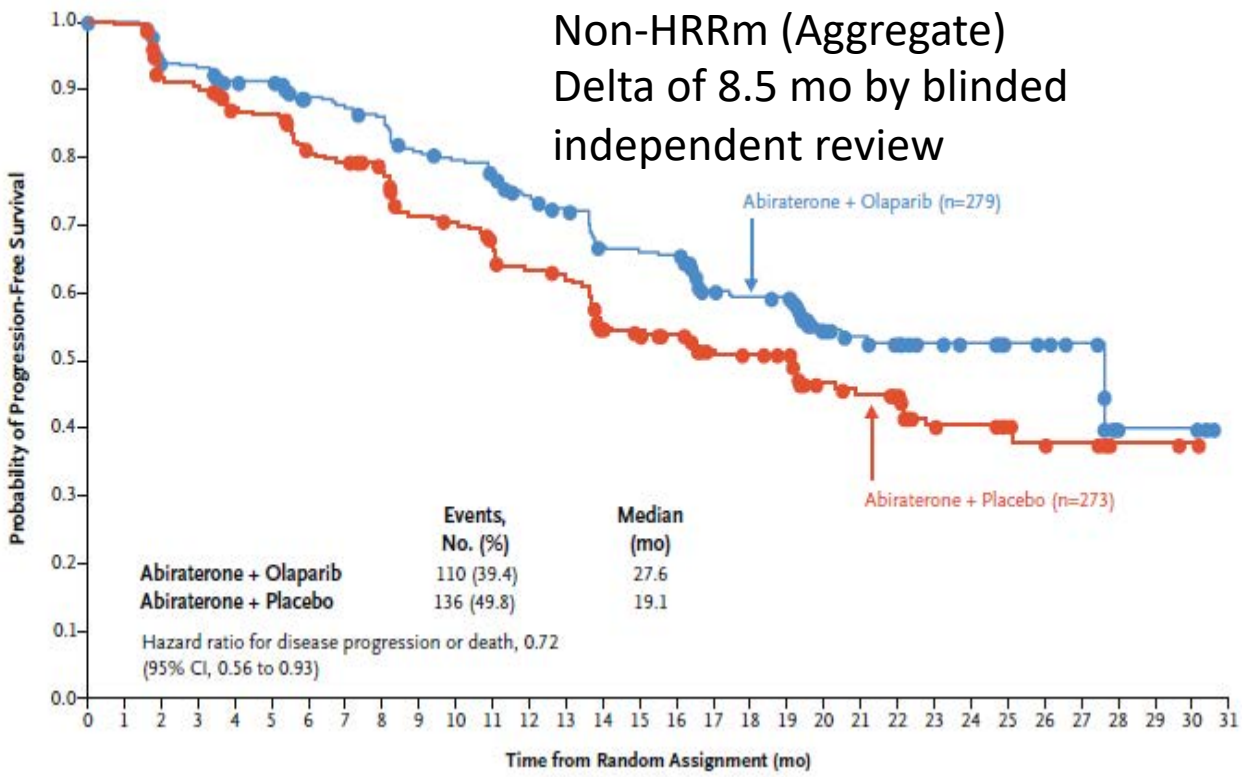
HRRm (Aggregate)

Delta of 15 mo by BICR 13.8→28.8 mo



Non-HRRm (Aggregate)

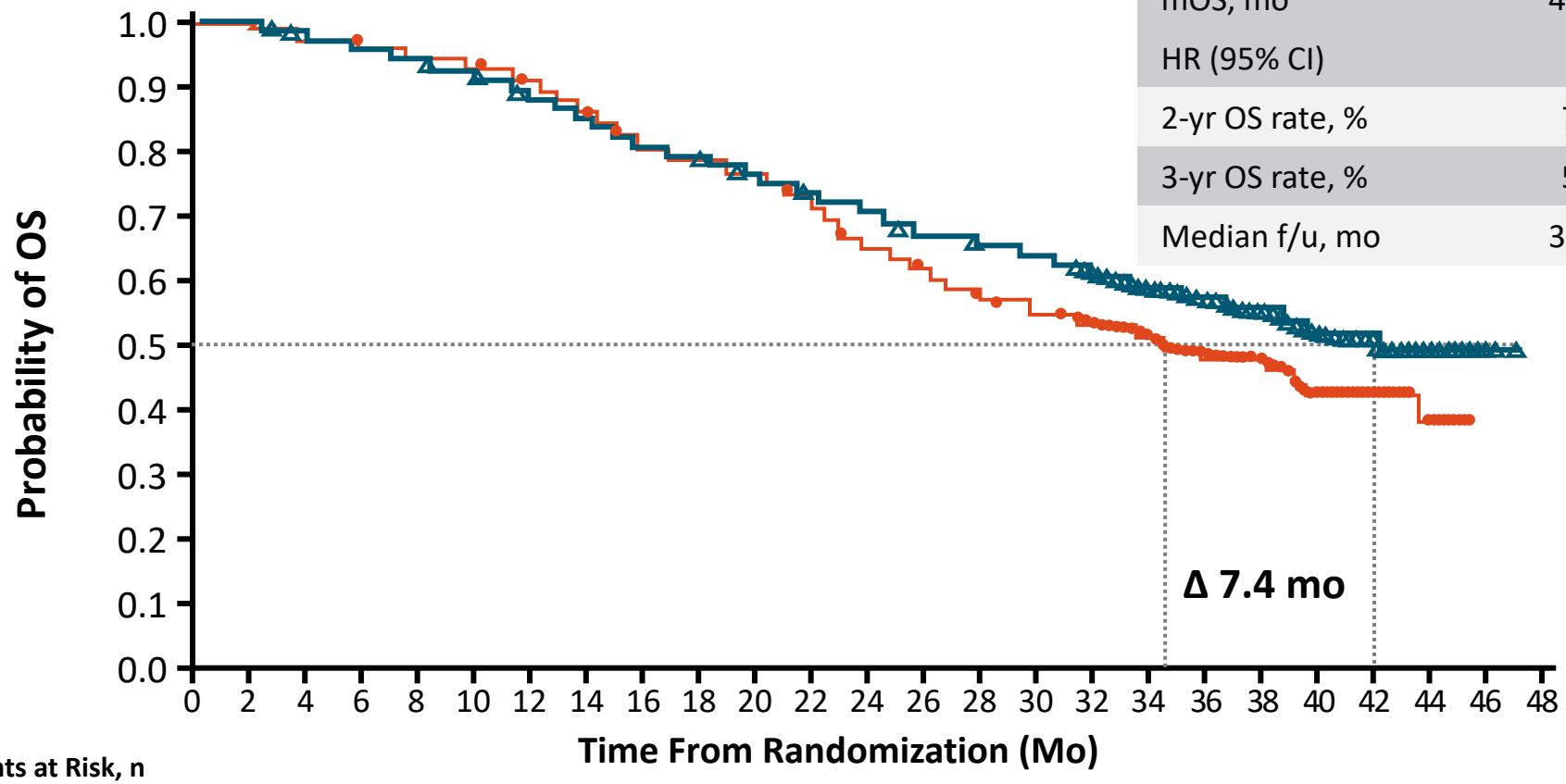
Delta of 8.5 mo by blinded independent review



Courtesy of Andrew J Armstrong, MD, ScM

PROpel: OS in ITT Population

Outcome	Ola + Abi (n = 399)	Placebo + Abi (n = 397)
mOS, mo	42.1	34.7
HR (95% CI)	0.81 (0.67-1.00; *P* = .054)	
2-yr OS rate, %	70	67
3-yr OS rate, %	57	50
Median f/u, mo	36.6	36.5



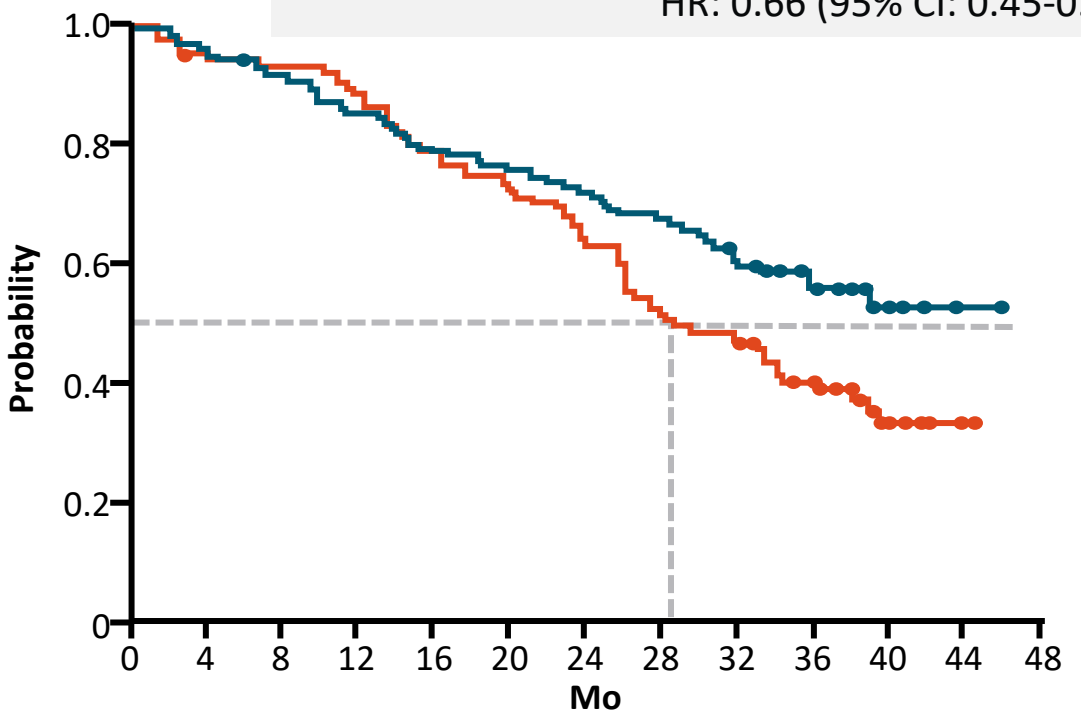
Clarke. ASCO GU 2023. Abstr LBA16. Saad. Lancet Oncol. 2023;24:1094.

Courtesy of Andrew J Armstrong, MD, ScM

PROpel: OS by HRR Status

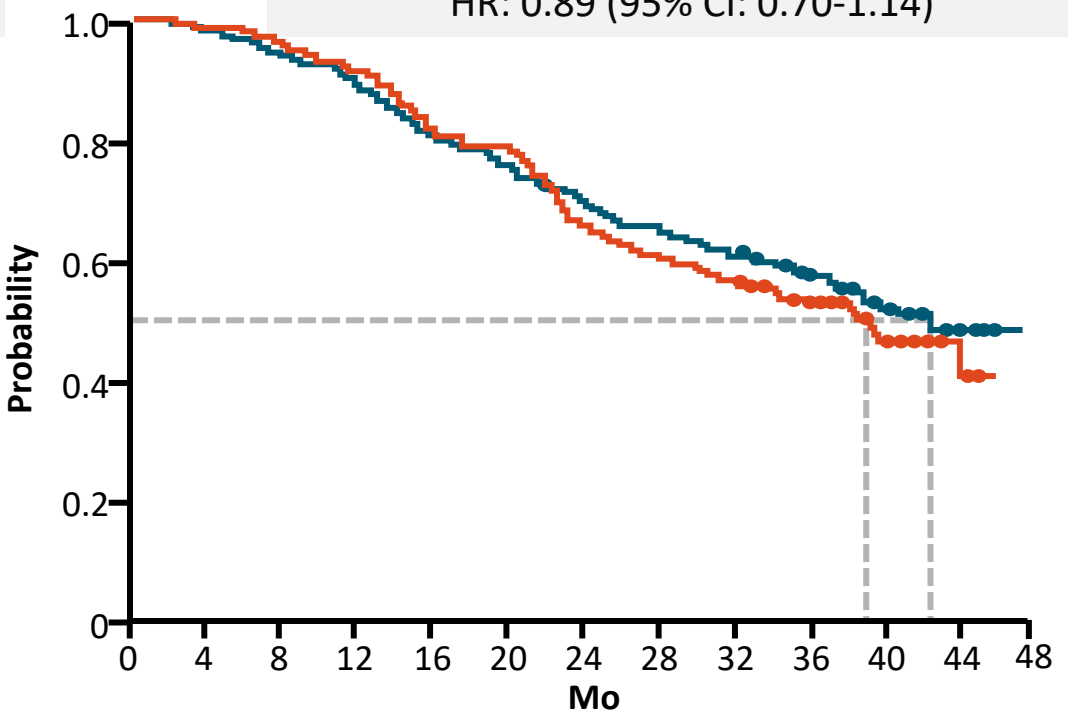
HRR Mutated
(28.4% of ITT population)

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



Not HRR Mutated
(69.3% of ITT population)

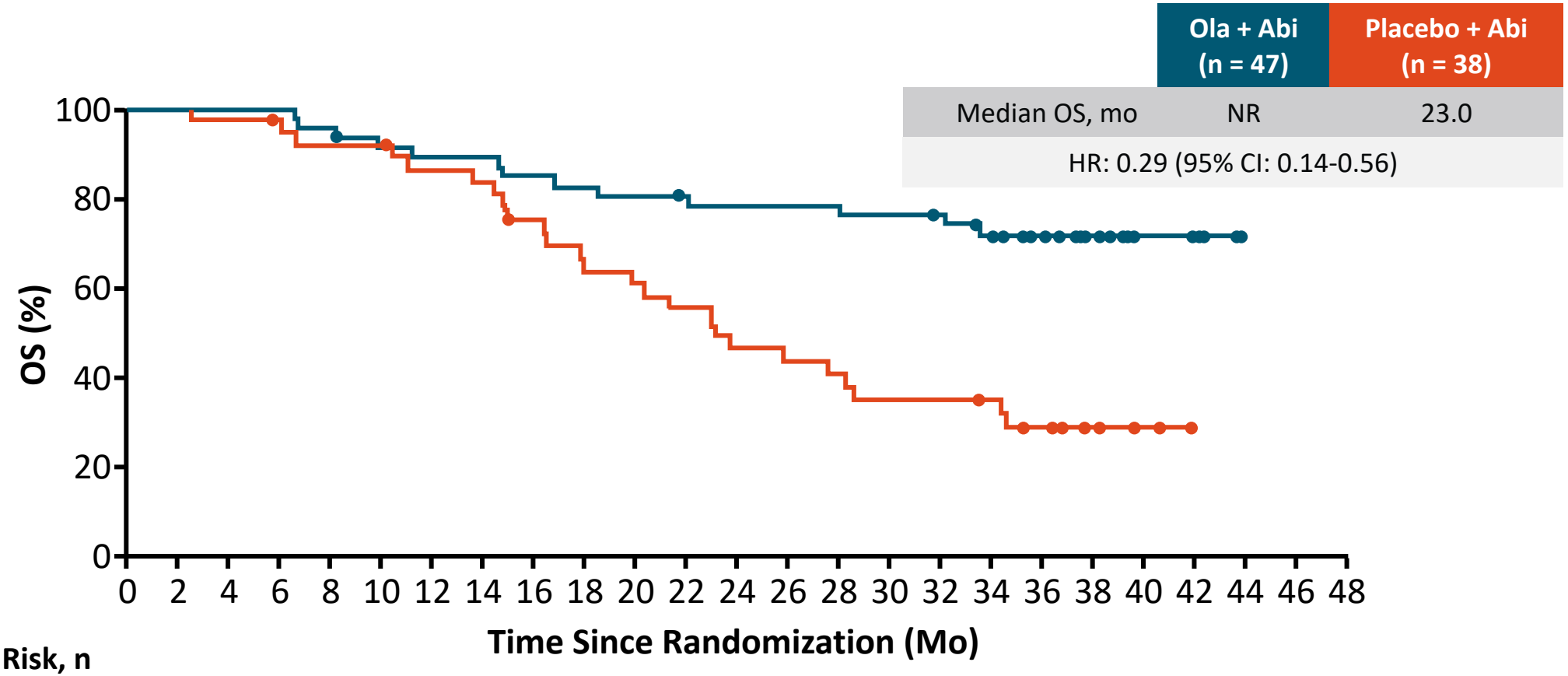
	Ola + Abi (n = 279)	Placebo + Abi (n = 273)
Median OS, mo	42.1	38.9
	HR: 0.89 (95% CI: 0.70-1.14)	



Saad. Lancet Oncol. 2023;24:1094.

Courtesy of Andrew J Armstrong, MD, ScM

PROpel: OS in *BRCAm*



Saad. Lancet Oncol. 2023:24:1094.

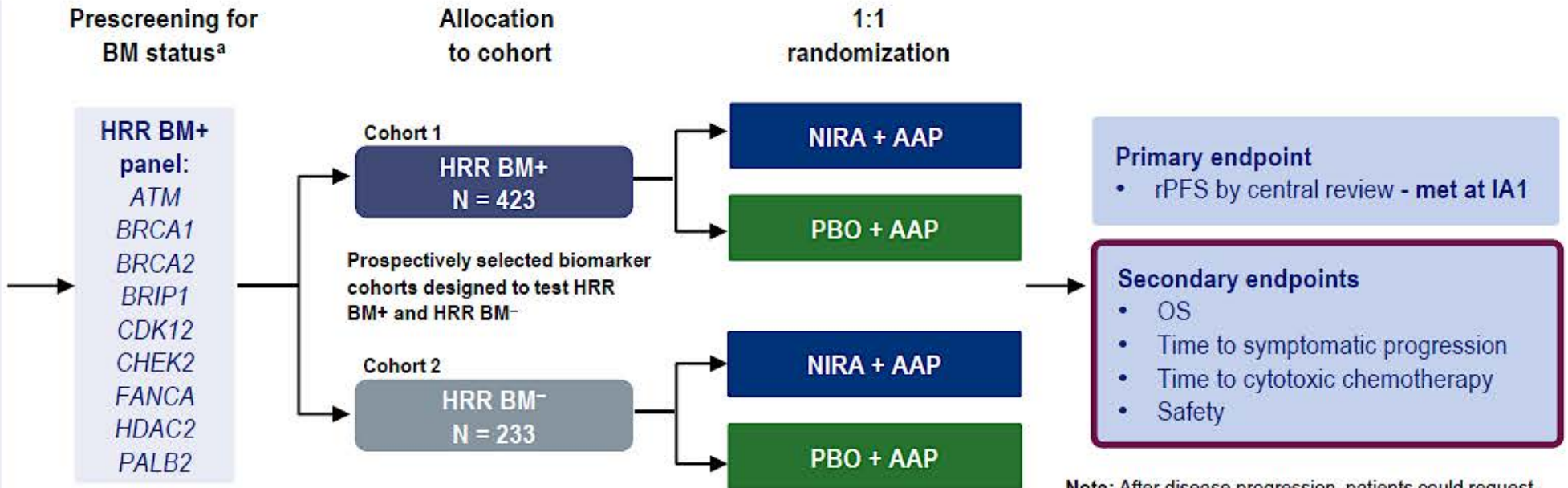
Courtesy of Andrew J Armstrong, MD, ScM

MAGNITUDE

Phase 3, randomized, double-blind, placebo-controlled study enrolling a population representative of patients treated in clinical practice today

Patient eligibility
- 1L 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 1L mCRPC
- *BRCA1/2* vs other HRR gene alterations (HRR BM+ cohort)



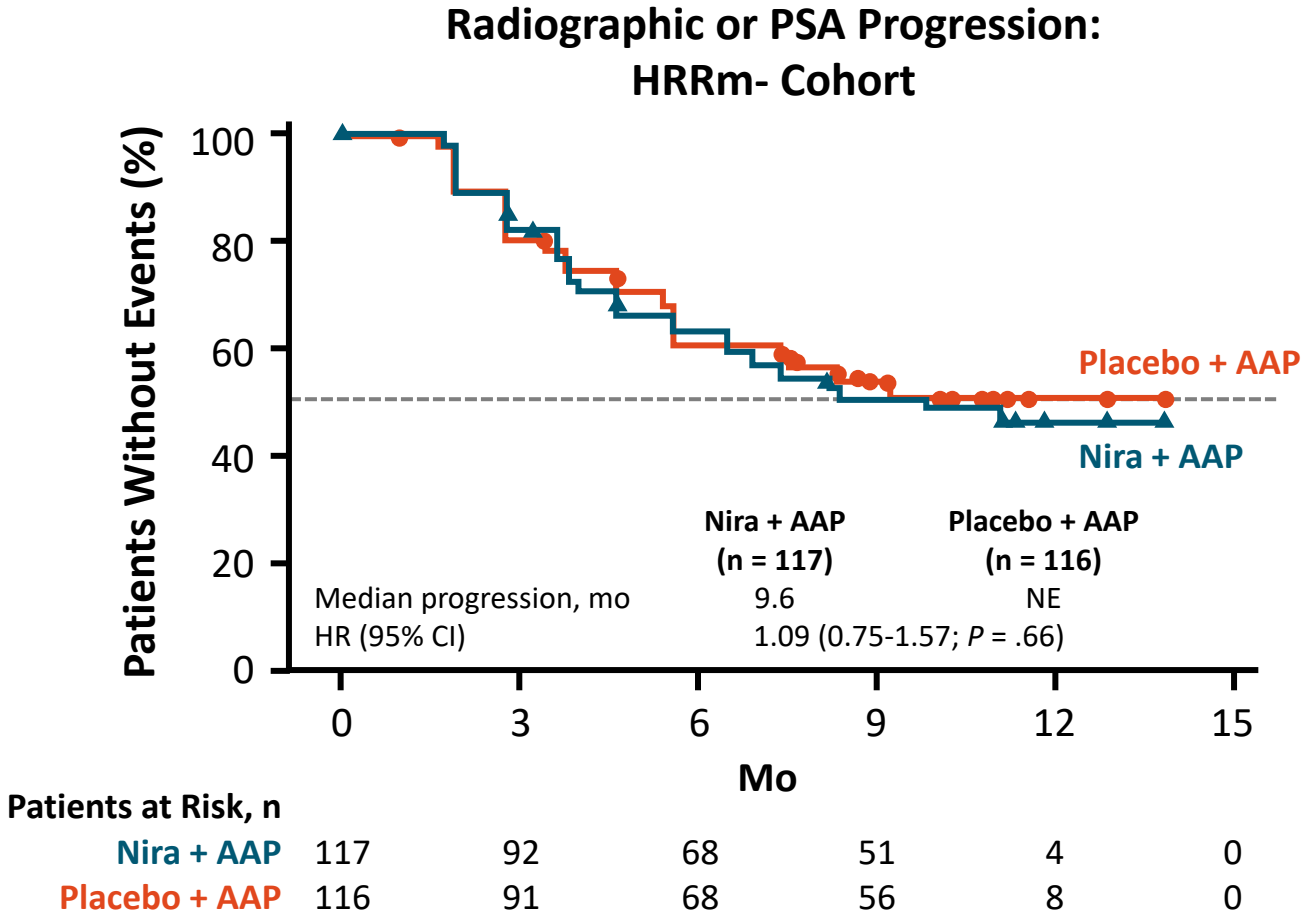
IA1 cutoff: October 8, 2021
IA2 cutoff: June 17, 2022
Final analysis cutoff: May 15, 2023

Note: After disease progression, patients could request to be unblinded by the study steering committee and go on to subsequent therapy of the investigator's choice.

[a]Tissue and plasma assays: FoundationOne tissue test (FoundationOne®CDx), Resolution Bioscience liquid test (circulating tumor [ct]DNA), 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 BM gene panel. AR, androgen receptor; ARi, androgen receptor inhibitor; BM, biomarker; BPI-SF, Brief Pain Inventory-Short Form; ECOG PS, Eastern Cooperative Oncology Group performance status; IA, interim analysis; mCSPC, metastatic castration-sensitive prostate cancer; nmCRPC, nonmetastatic castration-resistant prostate cancer.

Courtesy of Andrew J Armstrong, MD, ScM

MAGNITUDE: PSA Progression and/or rPFS in HRRm- Cohort (Prespecified Early Futility Analysis)

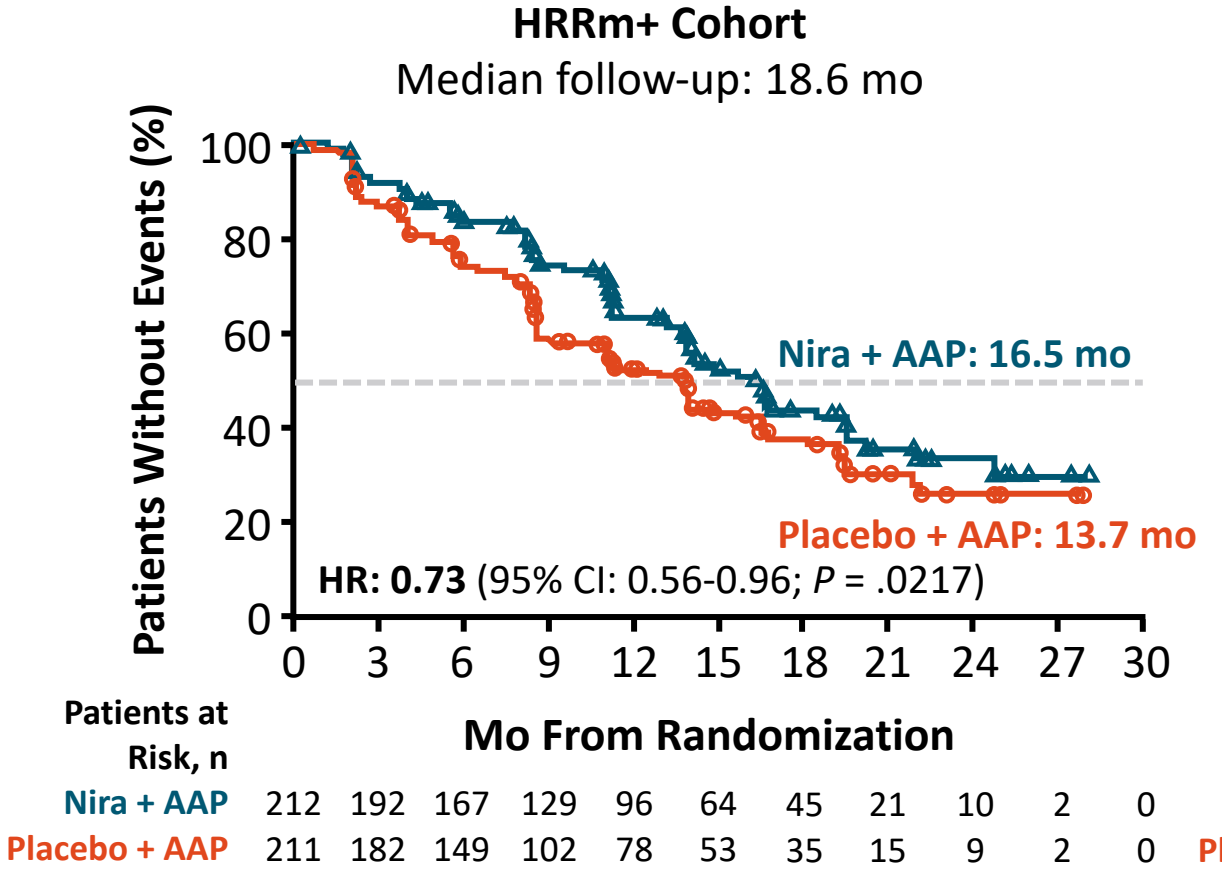


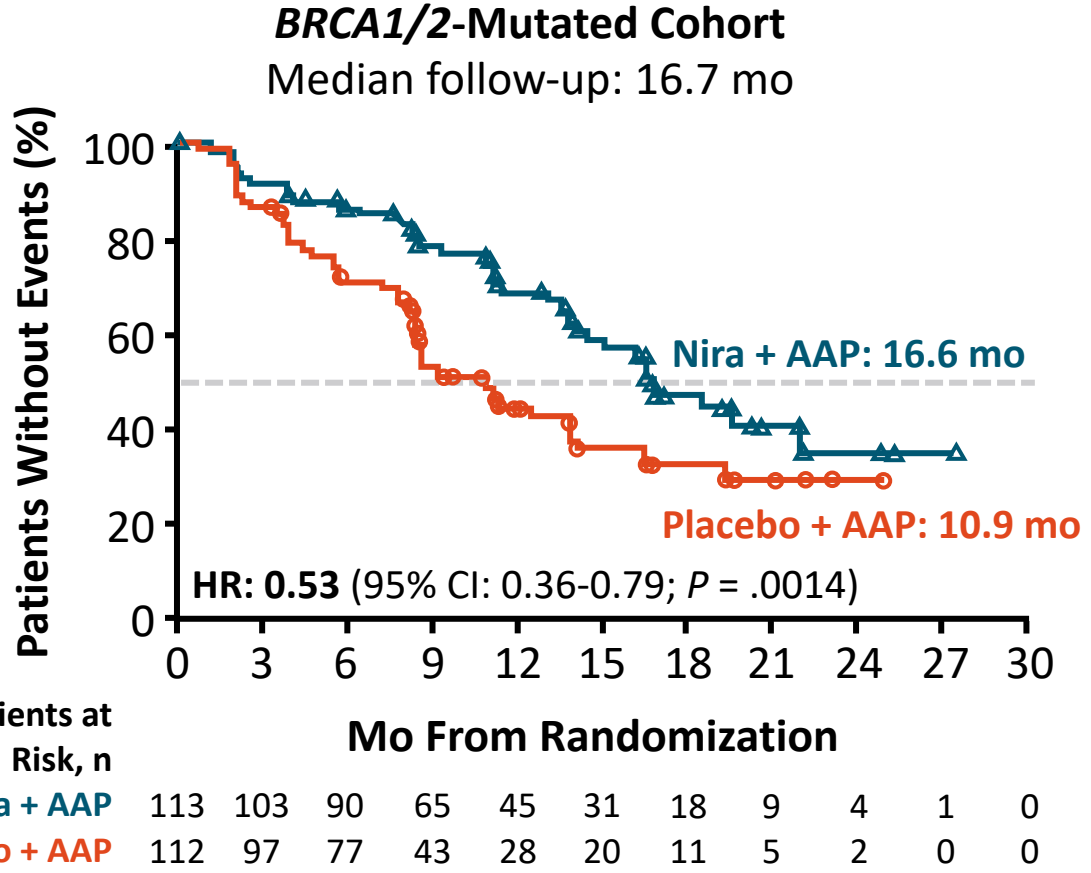
- Futility definition (HR ≥1) met in HRRm- cohort at time of preplanned analysis
  - Composite HR: 1.09 (95% CI: 0.75-1.59)
  - PSA HR: 1.03 (95% CI: 0.67-1.59)
  - rPFS HR: 1.03 (95% CI: 0.63-1.67)
- Grade 3/4 AEs higher in niraparib vs placebo arm
- HRRm- enrollment stopped in August 2020

Chi. JCO. 2023;41:3339. Chi. ASCO GU 2022. Abstr 12.

Courtesy of Andrew J Armstrong, MD, ScM

MAGNITUDE: Radiologic PFS by Central Review (Primary Endpoint)

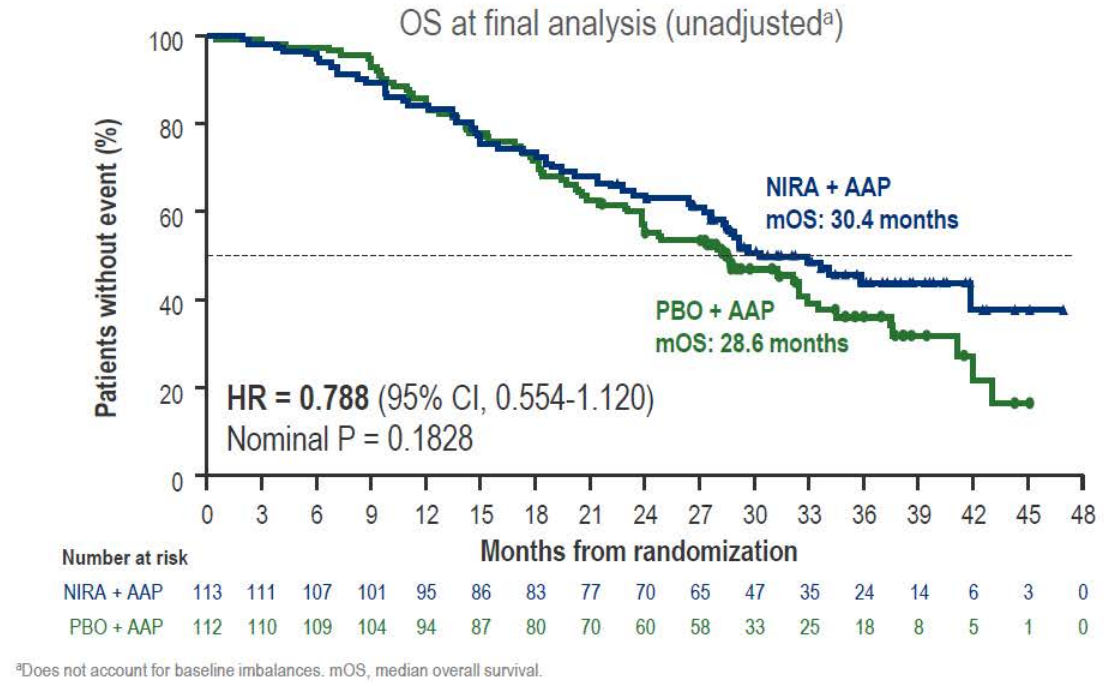




Chi. JCO. 2023;41:3339. Chi. ASCO GU 2022. Abstr 12.

Courtesy of Andrew J Armstrong, MD, ScM

Not as much MAGNITUDE of benefit…



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

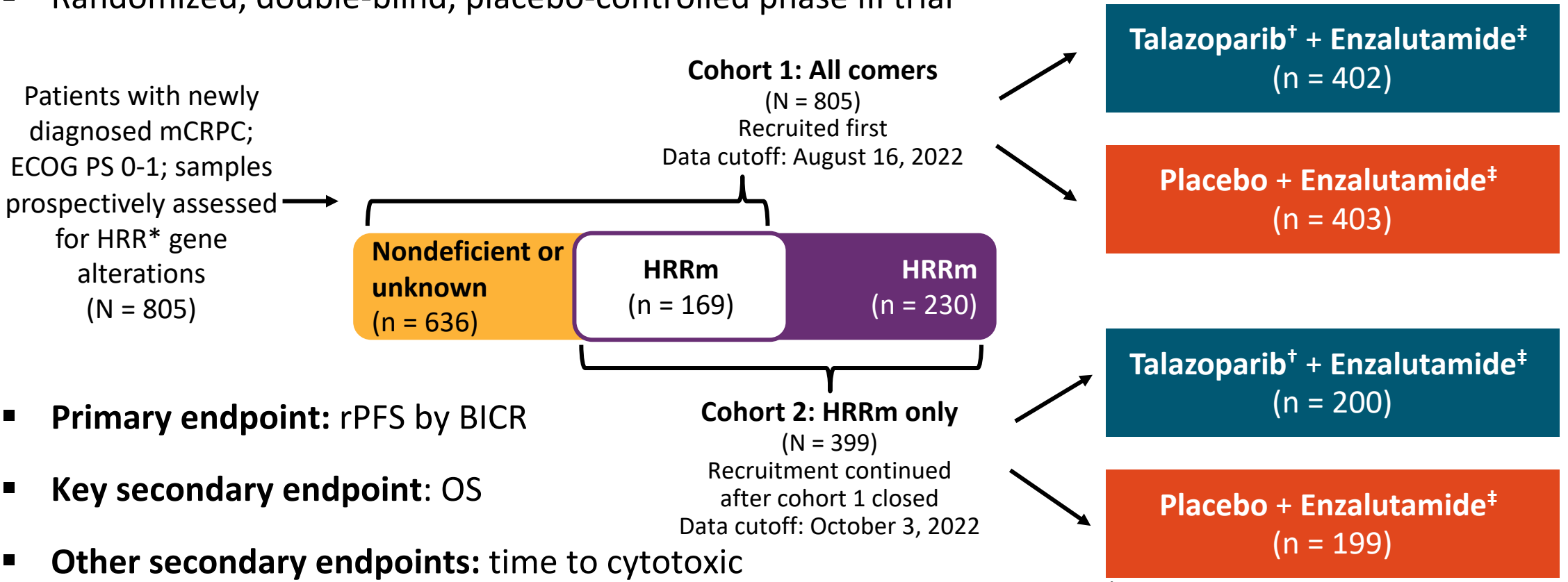
Chi et al ESMO 2023
LBA 85

TEAEs of special interest, n (%)	NIRA + AAP (N = 212)		PBO + AAP (N = 211)	
	All grade	Grade ≥ 3	All grade	Grade ≥ 3
Participants with ≥ 1 AESI	179 (84.4)	113 (53.3)	136 (64.5)	64 (30.3)
Anemia	111 (52.4)	65 (60.6)	48 (22.7)	18 (8.5)
Thrombocytopenia	51 (24.1)	18 (8.5)	20 (9.5)	5 (2.4)
Neutropenia	34 (16.0)	14 (6.6)	15 (7.1)	5 (2.4)
Pulmonary embolism	10 (4.7)	7 (3.3)	3 (1.4)	3 (1.4)
Acute myeloid leukemia	0	0	1 (0.5)	1 (0.9)

Courtesy of Andrew J Armstrong, MD, ScM

TALAPRO-2: Enzalutamide ± Talazoparib as First-Line Therapy for mCRPC

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



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

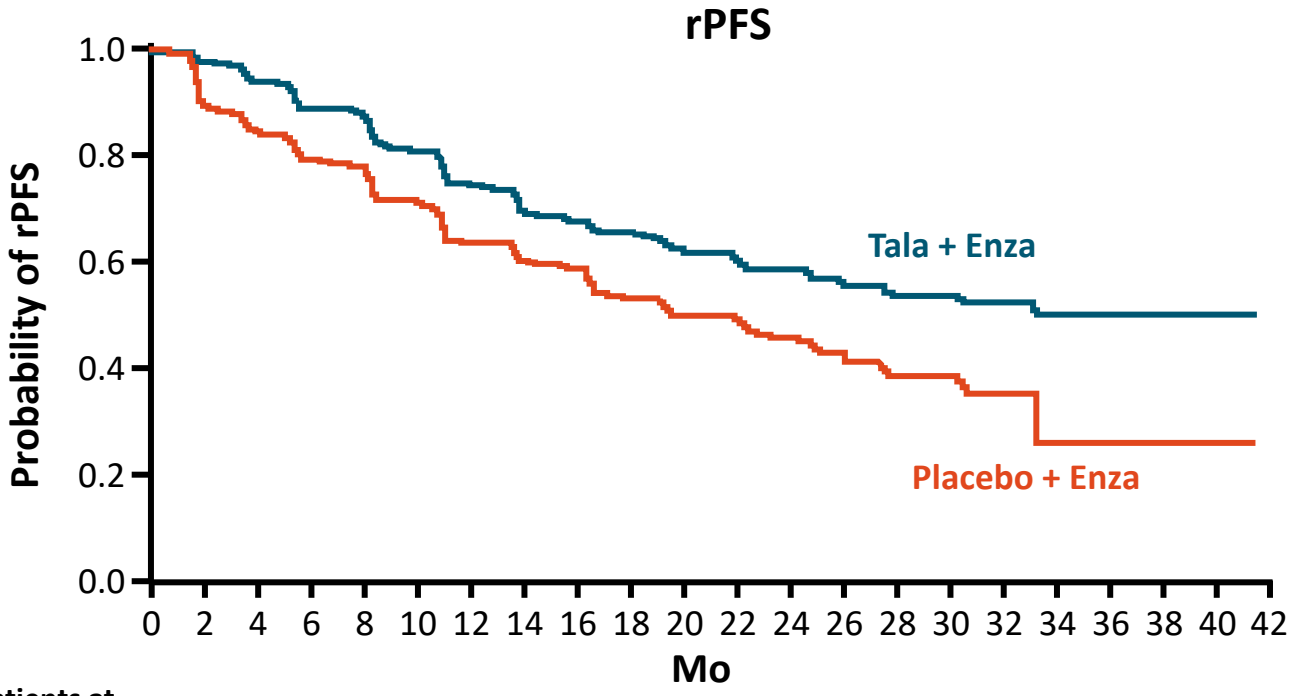
†0.5 mg QD; 0.35 mg if moderate renal impairment.
‡160 mg QD.

*HRR gene alterations: *BRCA1, BRCA2, PALB2, ATM, ATR, CHECK2, FANCA, RAD51C, NBN, MLH1, MRE11A, CDK12.*

Agarwal. ASCO GU 2023. Abstr LBA17. Agarwal. Lancet. 2023;204:291.
Fizazi. ASCO 2023. Abstr 5004. Fizazi. Nat Med. 2023;[Epub].

Courtesy of Andrew J Armstrong, MD, ScM

TALAPRO-2: rPFS by BICR in Cohort 1 All Comers (Primary Endpoint)



Patients at Risk, n																					
Tala + Enza	402	379	353	326	318	285	256	234	226	209	193	175	136	97	67	61	29	13	2	2	1	0
Pbo + Enza	403	346	311	279	272	237	200	185	179	154	140	124	96	68	43	42	14	3	1	1	1	0

	Tala + Enza (n = 402)	Placebo + Enza (n = 403)
Events, n	151	191
Median rPFS, mo (95% CI)	NR (27.5-NR)	21.9 (16.6-25.1)
Median f/u, mo	24.9	24.6

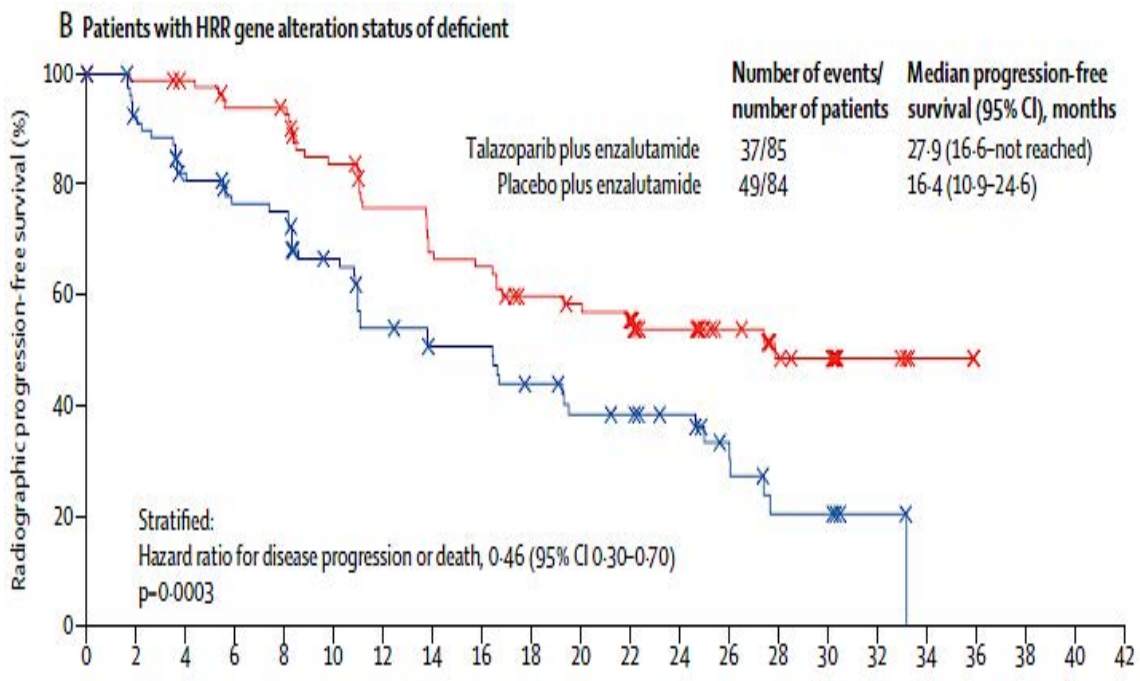
HR: 0.63 (95% CI: 0.51-0.73; *P* <.001)

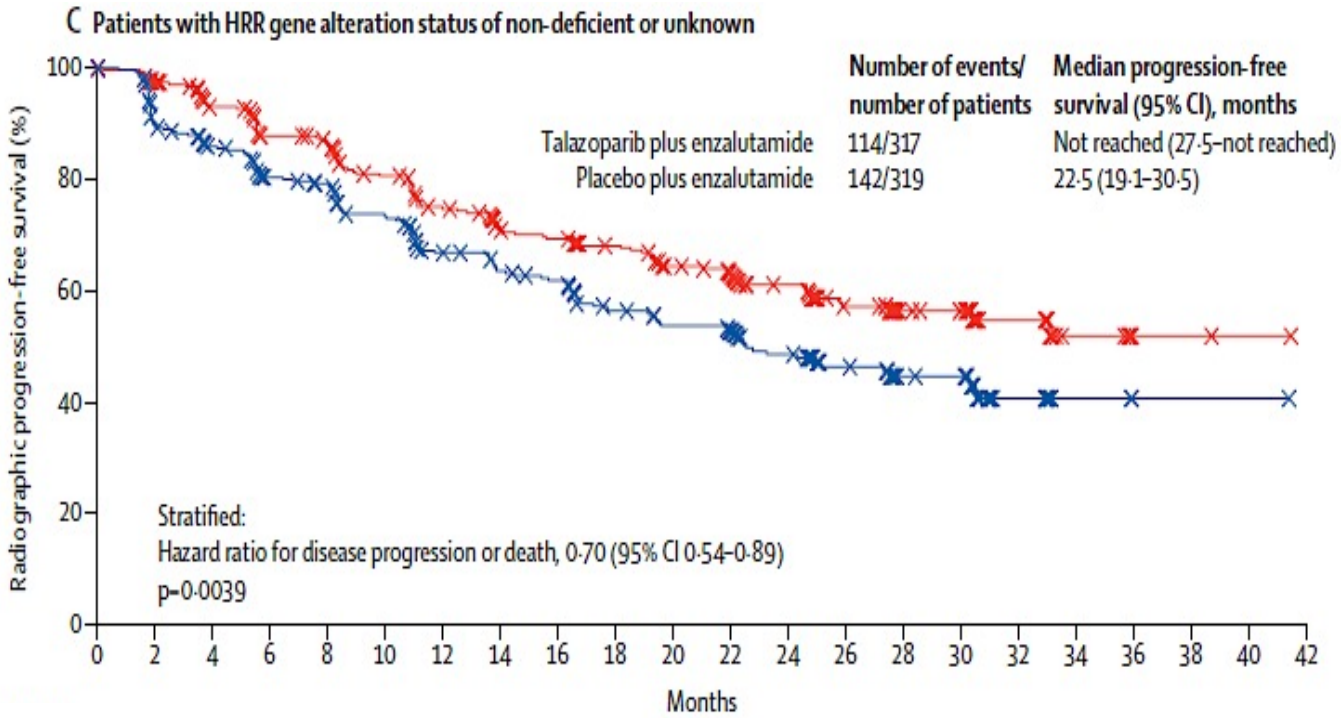
- Investigator-assessed rPFS HR: 0.64 (95% CI: 0.50-0.91; *P* <.001)

Agarwal. ASCO GU 2023. Abstr LBA17. Agarwal. Lancet. 2023;204:291.

Courtesy of Andrew J Armstrong, MD, ScM

Is there clinical utility in improving rPFS by 30%?

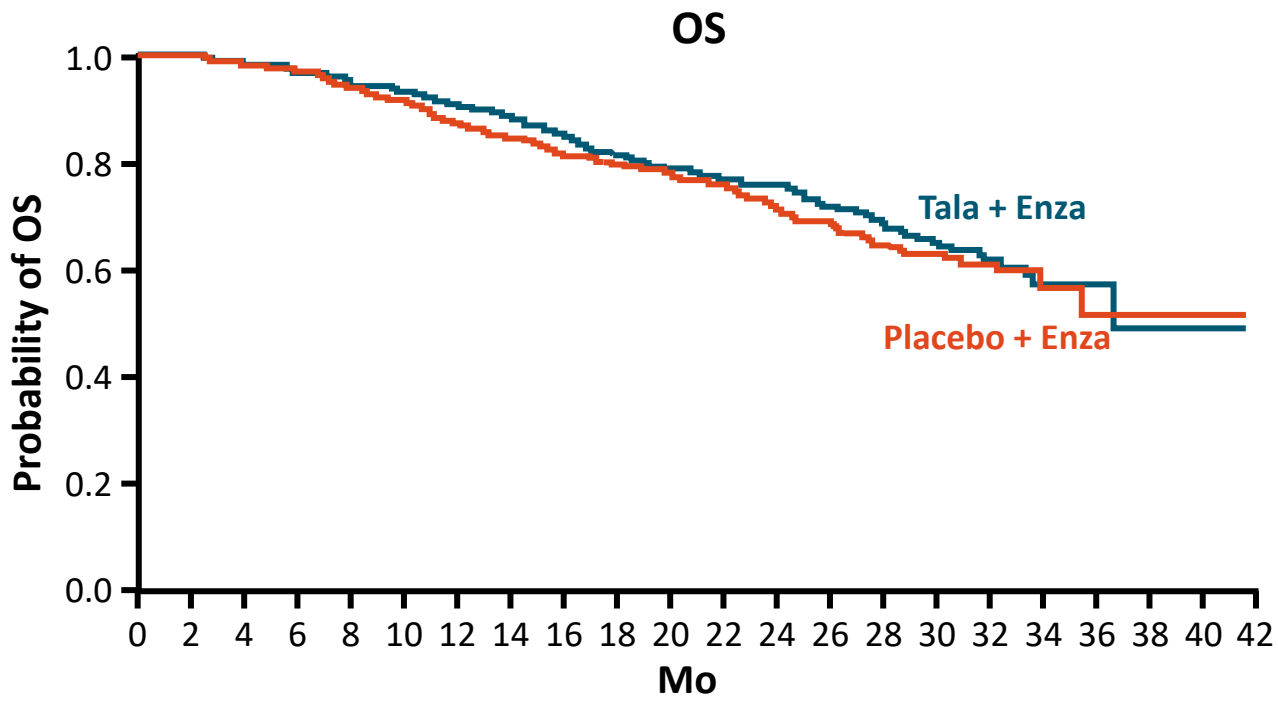




Agarwal N et al Lancet 2023

Courtesy of Andrew J Armstrong, MD, ScM

TALAPRO-2: Overall Survival in All-Comers Population



Patients at Risk, n																				
Tala + Enza	402	398	388	377	368	360	344	331	313	298	288	277	223	167	136	104	59	26	10	2	1	0
Pbo + Enza	403	399	387	376	360	344	326	315	301	290	280	260	200	146	117	86	42	16	6	3	1	0

	Tala + Enza (n = 402)	Placebo + Enza (n = 403)
Events, n	123	123
Median OS, mo (95% CI)	36.4 (33.5-NR)	NR (33.7-NR)

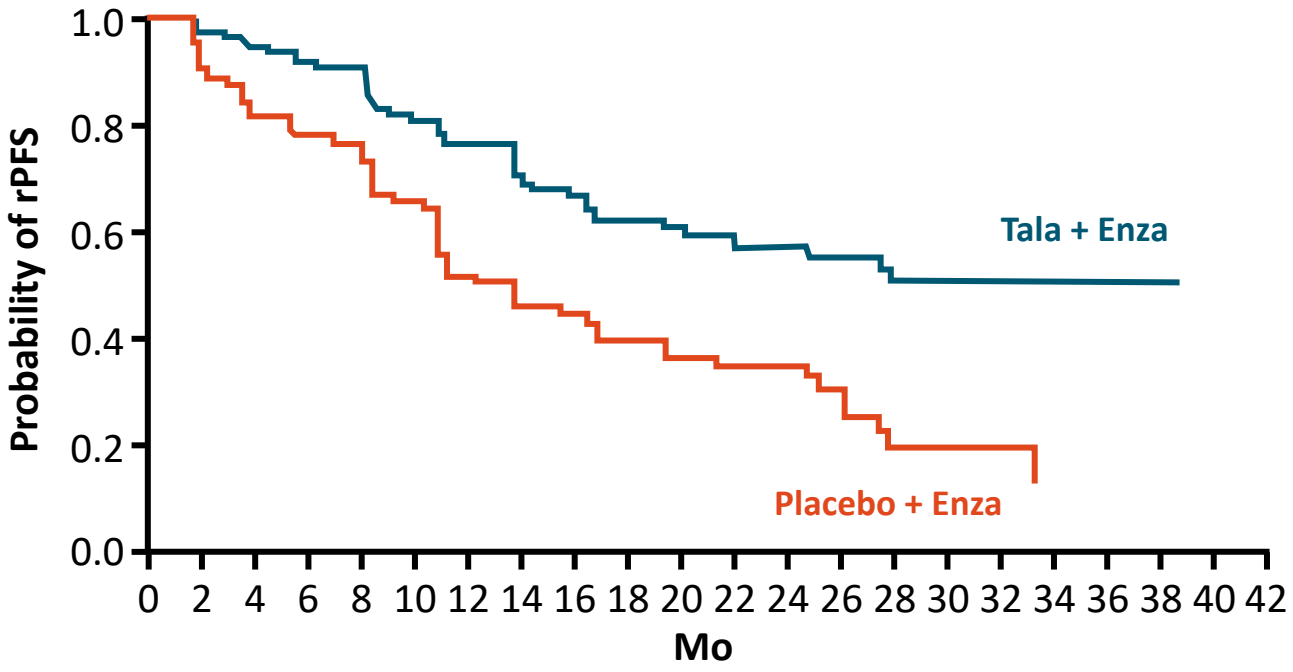
HR: 0.89 (95% CI: 0.69-1.14; *P* = .35)

- OS data at 31% mature; additional follow-up needed

Agarwal. ASCO GU 2023. Abstr LBA17. Agarwal. Lancet. 2023;204:291.

Courtesy of Andrew J Armstrong, MD, ScM

TALAPRO-2: rPFS by BICR in HRR-Deficient Cohort 2



Patients at Risk, n																				
Tala + Enza	200	191	180	168	163	131	107	86	82	60	49	45	34	26	21	19	9	4	2	1	0	0
Pbo + Enza	199	171	149	131	126	96	67	51	47	38	29	25	21	11	7	7	4	0	0	0	0	0

	Tala + Enza (n = 200)	Placebo + Enza (n = 199)
Events, n	66	104
Median rPFS, mo (95% CI)	NR (21.9-NR)	13.8 (11.0-16.7)
Median f/u, mo	17.5	16.8

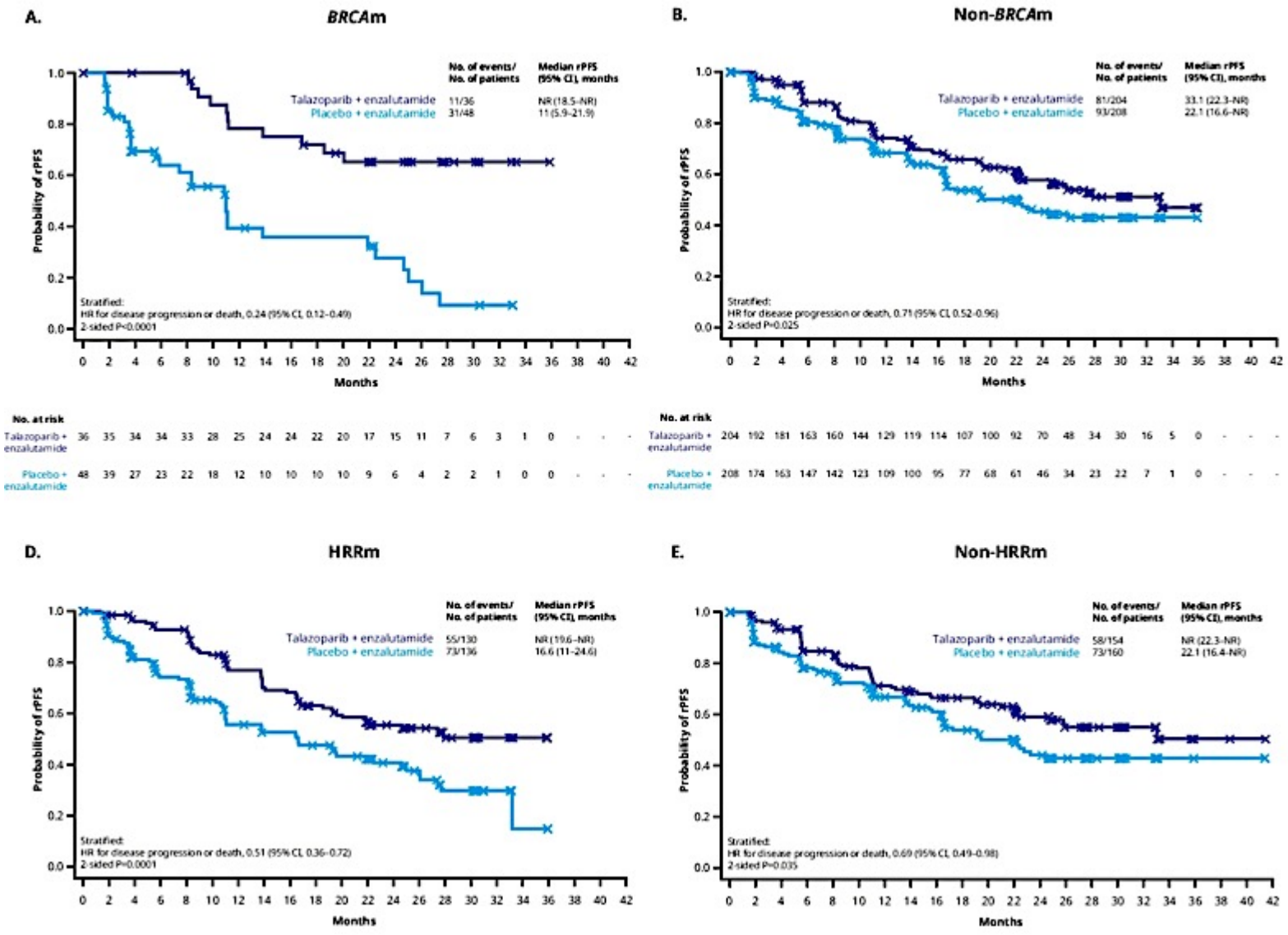
HR: 0.45 (95% CI: 0.33-0.61; *P* <.0001)

- Investigator-assessed rPFS HR: 0.48 (95% CI: 0.33-0.67; *P* <.0001)

Fizazi. ASCO 2023. Abstr 5004. Fizazi. Nat Med. 2023;[Epub].

Courtesy of Andrew J Armstrong, MD, ScM

TALAPRO-2 Updates from GU 2024



<u>Overall Survival Update</u>

BRCAm HR 0.53 (0.28-1.03) p=0.06

Non-BRCAm HR 0.76 (0.56-1.03) p=0.07

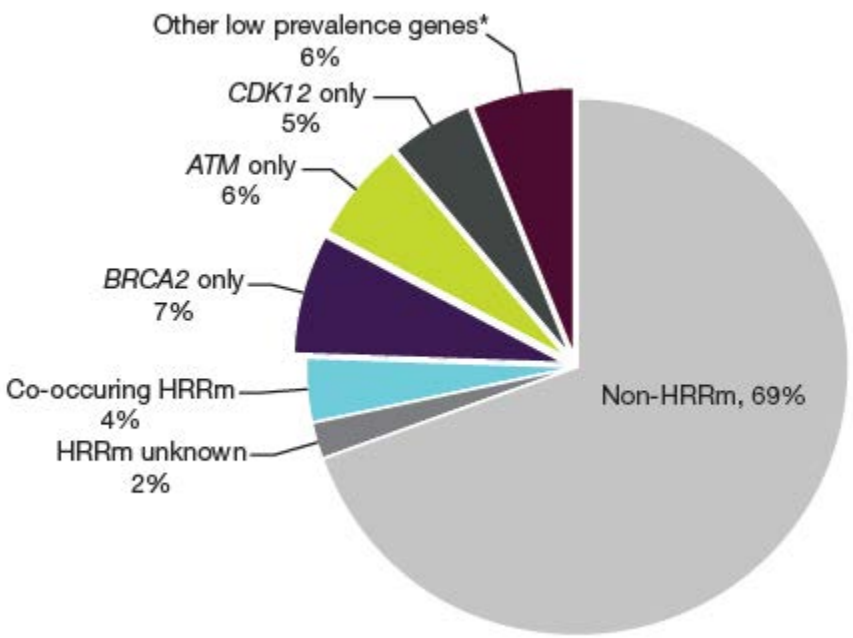
HRRm HR 0.68 (0.47-0.99) p=0.04

Non-HRRm HR 0.88 (0.63-1.23) p=0.45

Shore et al GU 2024 abstract 136

Courtesy of Andrew J Armstrong, MD, ScM

What about combination activity in non-BRCA2 HRRm mCRPC patients?



- In the *CHEK2* population, 5/7 (71%) patients in the olaparib plus abiraterone arm and 8/12 (67%) patients in the placebo plus abiraterone arm had an rPFS event; median rPFS was 5.7 months with olaparib plus abiraterone versus 13.8 months with placebo plus abiraterone

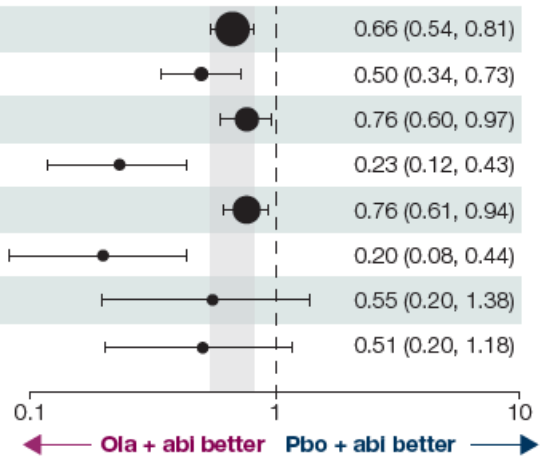
- In the *BRCA1* population, 0/6 (0%) patients in the olaparib plus abiraterone arm and 3/3 (100%) patients in the placebo plus abiraterone arm had an rPFS event; median rPFS was not reached with olaparib plus abiraterone versus 5.5 months with placebo plus abiraterone

- In the *PALB2* population, 1/3 (33%) patients in the olaparib plus abiraterone arm and 3/4 (75%) patients in the placebo plus abiraterone arm had an rPFS event; median rPFS was not reached with olaparib plus abiraterone versus 7.3 months with placebo plus abiraterone

Shore, Armstrong et al GU 2024 abstract 165

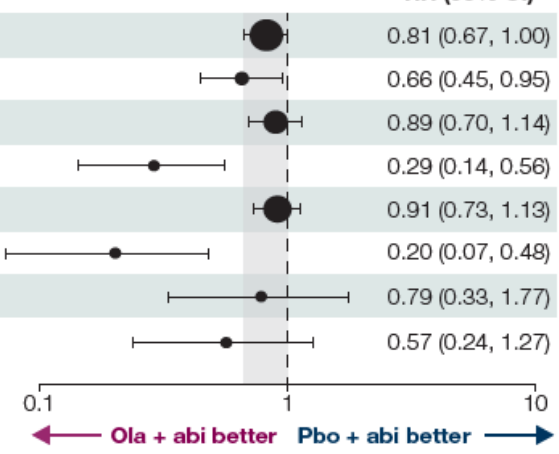
rPFS

	Events, n/N% Ola + abi	Events, n/N% Pbo + abi	Ola + abi Median rPFS, months	Pbo + abi Median rPFS, months	HR (95% CI)
All patients	168/399 (42)	226/397 (57)	24.8	16.6	0.66 (0.54, 0.81)
HRRm	43/111 (39)	73/115 (63)	NR	13.9	0.50 (0.34, 0.73)
Non-HRRm	119/279 (43)	149/273 (55)	24.1	19.0	0.76 (0.60, 0.97)
BRCAm	14/47 (30)	28/38 (74)	NR	8.4	0.23 (0.12, 0.43)
Non-BRCAm	148/343 (43)	194/350 (55)	24.1	19.0	0.76 (0.61, 0.94)
BRCA2 single gene	8/30 (27)	20/28 (71)	NR	8.4	0.20 (0.08, 0.44)
ATM single gene	6/21 (29)	14/28 (50)	NR	19.9	0.55 (0.20, 1.38)
CDK12 single gene	8/19 (42)	14/21 (67)	NR	16.6	0.51 (0.20, 1.18)



OS

	Events, n/N% Ola + abi	Events, n/N% Pbo + abi	Ola + abi Median OS, months	Pbo + abi Median OS, months	HR (95% CI)
All patients	176/399 (44)	205/397 (52)	42.1	34.7	0.81 (0.67, 1.00)
HRRm	48/111 (43)	69/115 (60)	NR	28.5	0.66 (0.45, 0.95)
Non-HRRm	123/279 (44)	132/273 (48)	42.1	38.9	0.89 (0.70, 1.14)
BRCAm	13/47 (28)	25/38 (66)	NR	23.0	0.29 (0.14, 0.56)
Non-BRCAm	158/343 (46)	176/350 (50)	39.6	38.0	0.91 (0.73, 1.13)
BRCA2 single gene	6/30 (20)	18/28 (64)	NR	23.6	0.20 (0.07, 0.48)
ATM single gene	9/21 (43)	15/28 (54)	NR	31.9	0.79 (0.33, 1.77)
CDK12 single gene	9/19 (47)	15/21 (71)	NR	33.7	0.57 (0.24, 1.27)



PSA50 was 93% in BRCA2m with combo vs 31% with abi; for ATMm was 76 vs 75%; for CDK12 was 83 vs 62%

Courtesy of Andrew J Armstrong, MD, ScM

The future:
Evaluation of PARPi Sensitivity Genomic Biomarkers

Non-Traditional HRD Genes: needs meta-analysis across trials!

PARP Sensitive Alterations

- MMS22L loss (5-15%), 6q16.1
  - Unless TP53 loss/mutation
- RNASEH2 loss (12%), 13q14.3
  - Unless RB1 loss/BRCA2 wt, higher BRCA levels
- WDR76 loss
- RAD54L loss
- MCM6 loss
- FANCI loss
- CHD1 loss or SPOP F133V

PARP Resistant Alterations

- PARP1 or PARP2 loss
- RB1 loss (BRCA wt)
- PARG loss
- ADPRHL2 loss
- TP53BP1 gain
- PPP2R2A loss
- CHEK2 loss (increases BRCA2, TP53→E2F7 dependent)

Courtesy of Andrew J Armstrong, MD, ScM

In conclusion

- The Europeans have it correct, by allowing physicians and patients to decide on the net risks and benefits for PARP/AR inhibitor combinations as per the original study designs of PROpel and TALAPRO-2
  - Large magnitude of benefit in rPFS delay ~6-11 mo over an ACTIVE control ARSI therapy, unlike many other failed mCRPC trials
  - European Commission approved both identically for first line mCRPC for patients where chemotherapy is not indicated

Courtesy of Andrew J Armstrong, MD, ScM

Additional Abstracts – Dr Armstrong

- Meyer HM et al. **Lurbinectedin** in **prostatic small cell and neuroendocrine carcinoma**. 2024 ASCO Genitourinary Cancers Symposium;Abstract 164.
- Beltran H et al. Interim results from **a phase 1/2 study of HPN328**, a tri-specific, half-life (T1/2) extended **DLL3-targeting T-cell engager**, in patients (pts) with **neuroendocrine prostate cancer (NEPC) and other neuroendocrine neoplasms (NEN)**. 2024 ASCO Genitourinary Cancers Symposium;Abstract 121.
- Rathkopf DE et al. First-in-human **phase 1 study of CC-94676**, a first-in-class **androgen receptor (AR) ligand-directed degrader (LDD)**, in patients (pts) with **metastatic castration-resistant prostate cancer (mCRPC)**. 2024 ASCO Genitourinary Cancers Symposium;Abstract 134.

Key Clinical Questions/Issues Related to Systemic Management/Research in Prostate Cancer

Neuroendocrine differentiation and small cell strategies

- **Lurbinectedin**
- **Tarlatamab**
- **Other agents under investigation**

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

Part 1 of a 2-Part CME Symposium Series Held in Conjunction with the 2024 Society of Gynecologic Oncology (SGO) Annual Meeting on Women's Cancer®

Monday, March 18, 2024

6:30 AM – 8:00 AM PT (9:30 AM – 11:00 AM ET)

Faculty

Joyce F Liu, MD, MPH

Mansoor Raza Mirza, MD

David M O'Malley, MD

Moderator

Kathleen N Moore, MD, MS

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Thank you for joining us!

CME and MOC credit information will be emailed to each participant within 5 business days.

RTP Year in Review 2024