Year in Review:
Management of Prostate Cancer

A CME/MOC-Accredited Live Webinar

Thursday, April 17, 2025
5:00 PM – 6:00 PM ET

Faculty

Emmanuel S Antonarakis, MD
Professor Karim Fizazi, MD, PhD

Moderator

Neil Love, MD

RTP Year in Review 2025

Faculty

Emmanuel S Antonarakis, MD
Clark Endowed Professor of Medicine
Division of Hematology, Oncology and Transplantation
University of Minnesota
Minneapolis, Minnesota

Professor Karim Fizazi, MD, PhD
Head of Service and Full Professor
Institut Gustave Roussy
University of Paris Saclay
Villejuif, France

MODERATOR
Neil Love, MD
Research To Practice
Miami, Florida

RTP Year in Review 2025

Commercial Support

This activity is supported by educational grants from Astellas and Pfizer Inc, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Janssen Biotech Inc, administered by Janssen Scientific Affairs LLC, and Merck.

Dr Love — Disclosures

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

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.

Dr Antonarakis — Disclosures

Advisory Committees	Abeona Therapeutics Inc, AstraZeneca Pharmaceuticals LP, Blue Earth Diagnostics, Boundless Bio, Curium, Forbion, Sanofi, Tango Therapeutics
Consulting Agreements	Acerand Therapeutics, Clarity Pharmaceuticals, Curium, EcoR1 Capital LLC, Health Monitor, Lilly, LinKinVax, Vir Biotechnology Inc, Z-Alpha
Contracted Research	Bayer HealthCare Pharmaceuticals, Bristol Myers Squibb, MacroGenics Inc, Novartis, Orion Corporation, pharmaand GmbH, Seagen Inc

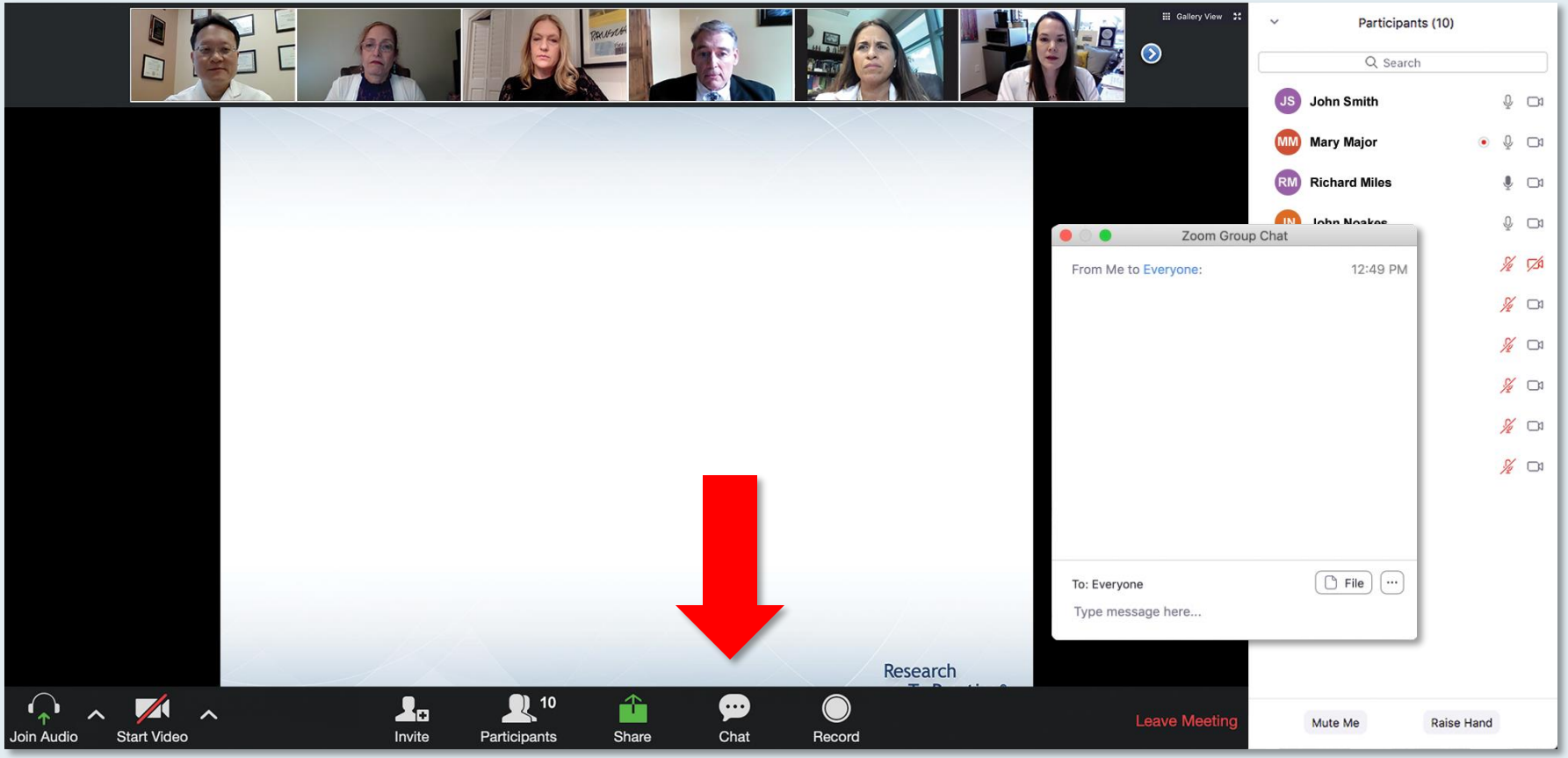
Prof Fizazi — Disclosures

Institutional Honoraria	Advanced Accelerator Applications, Amgen Inc, Astellas, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Daiichi Sankyo Inc, Janssen Biotech Inc, Merck, MSD, Novartis, Pfizer Inc

This educational activity contains discussion of non-FDA-approved uses of agents and regimens. Please refer to official prescribing information for each product for approved indications.

RTP
RESEARCH TO PRACTICE

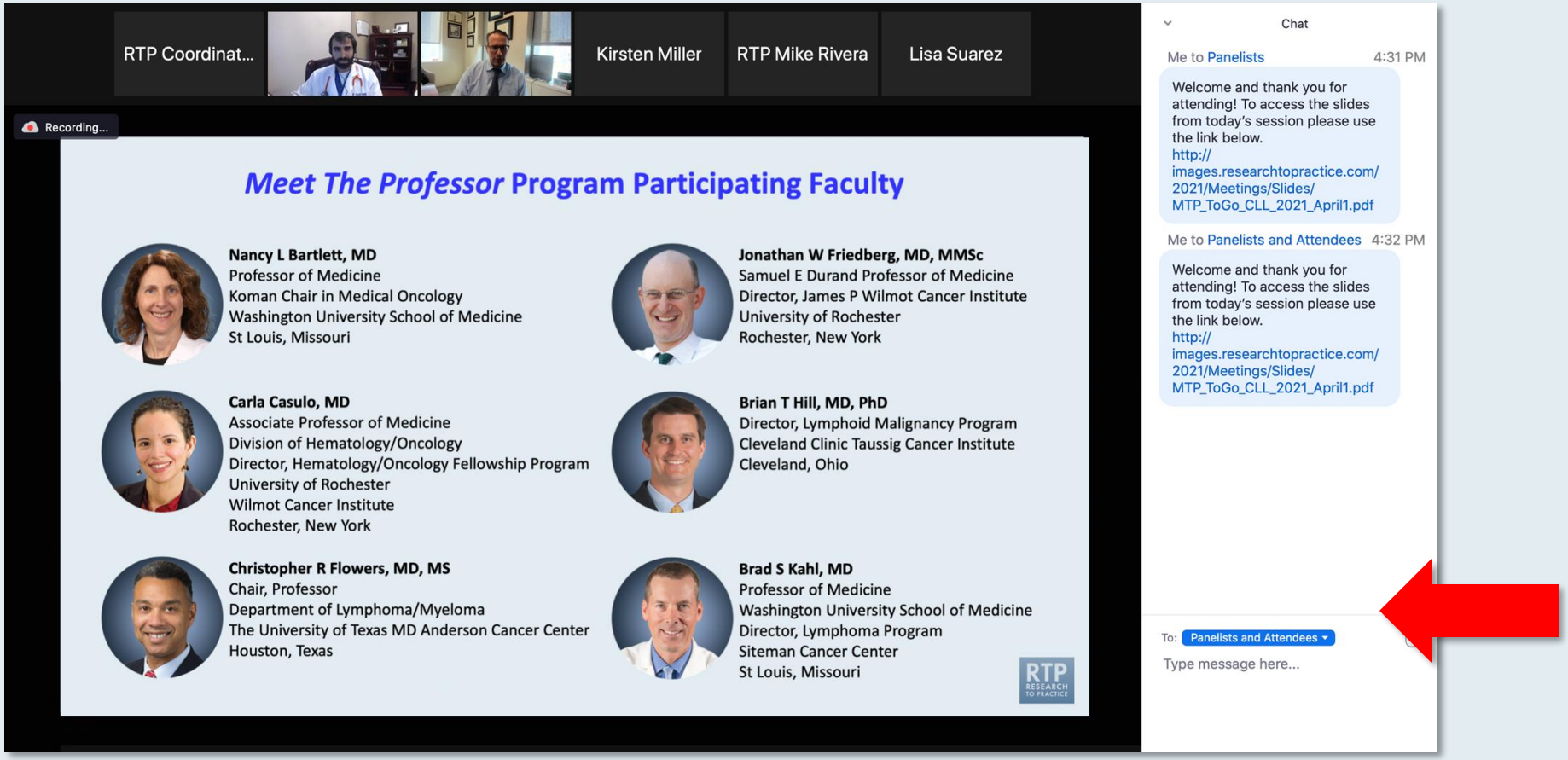
We Encourage Clinicians in Practice to Submit Questions



Feel free to submit questions now before the program begins and throughout the program.

Familiarizing Yourself with the Zoom Interface

Expand chat submission box

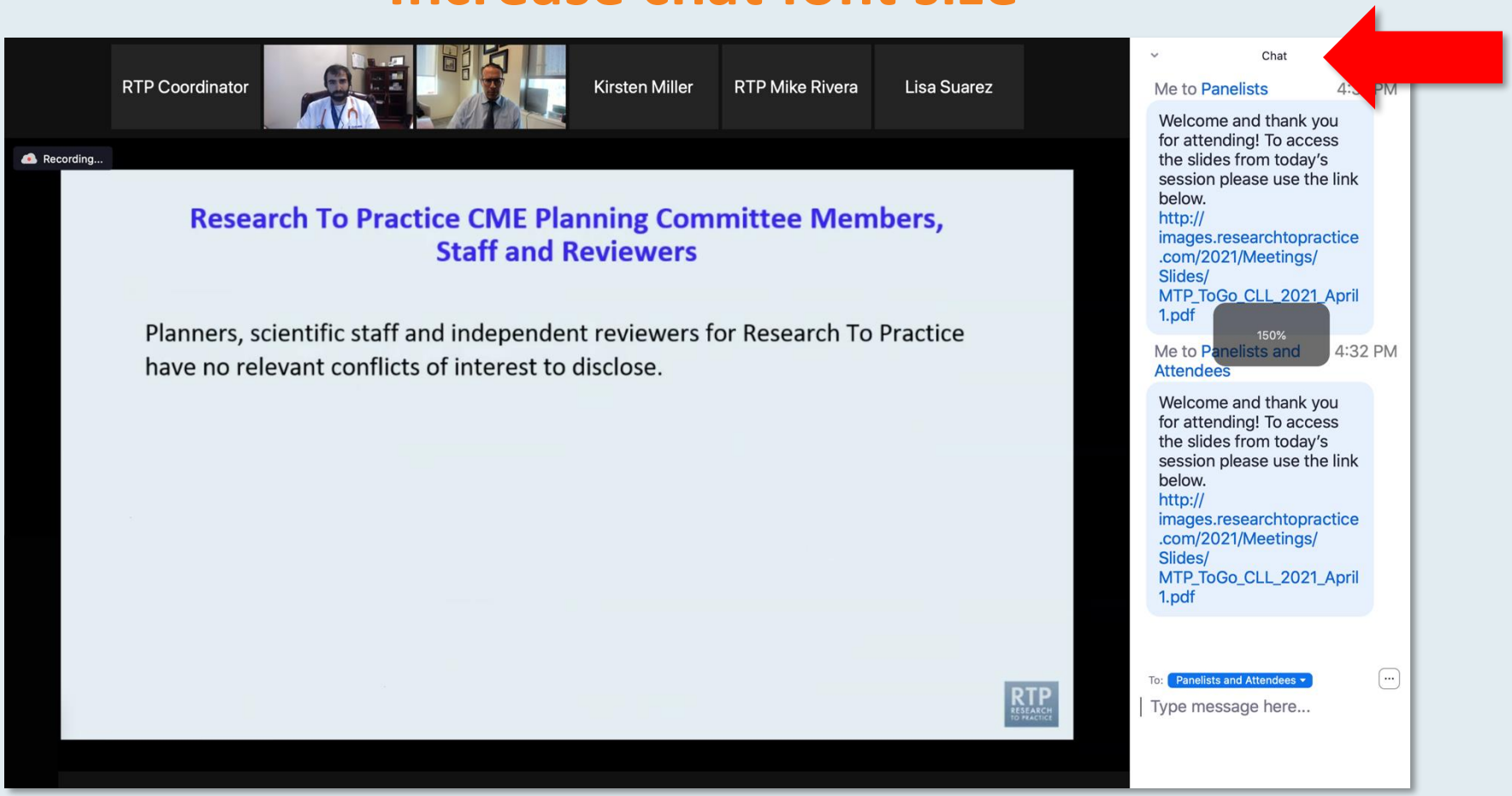


Drag the white line above the submission box up to create more space for your message.

RTP RESEARCH TO PRACTICE

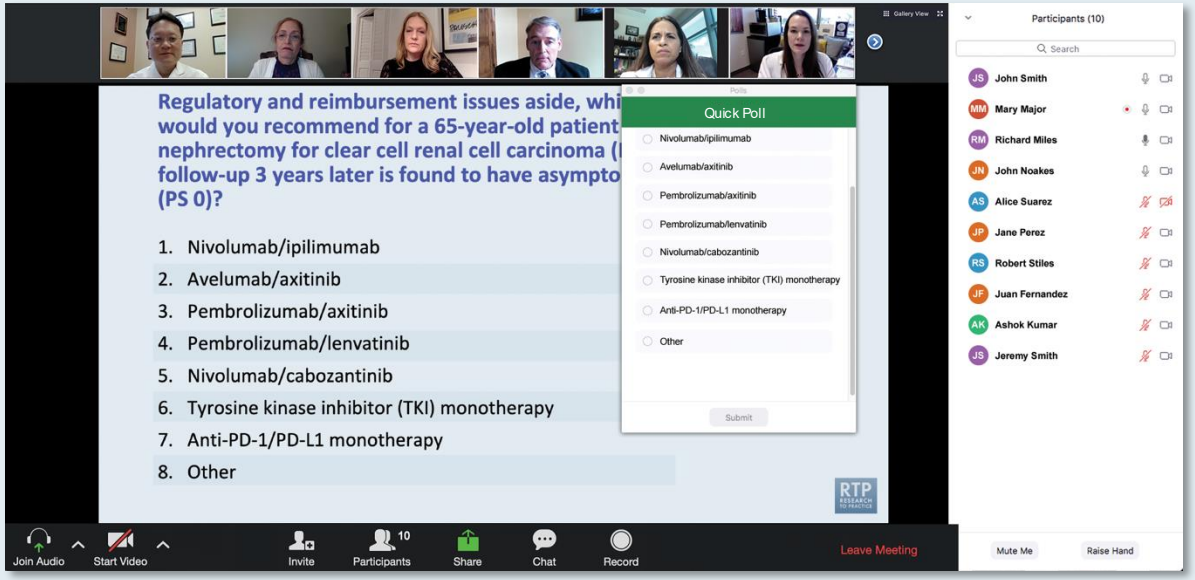
Familiarizing Yourself with the Zoom Interface

Increase chat font size



Press Command (for Mac) or Control (for PC) and the + symbol.
You may do this as many times as you need for readability.

Clinicians in the Audience, Please Complete the Pre- and Postmeeting Surveys



Urothelial Bladder Cancer and Prostate Cancer — Proceedings from a Session Held in Conjunction with the 2025 ASCO Genitourinary Cancers Symposium (ASCO GU)

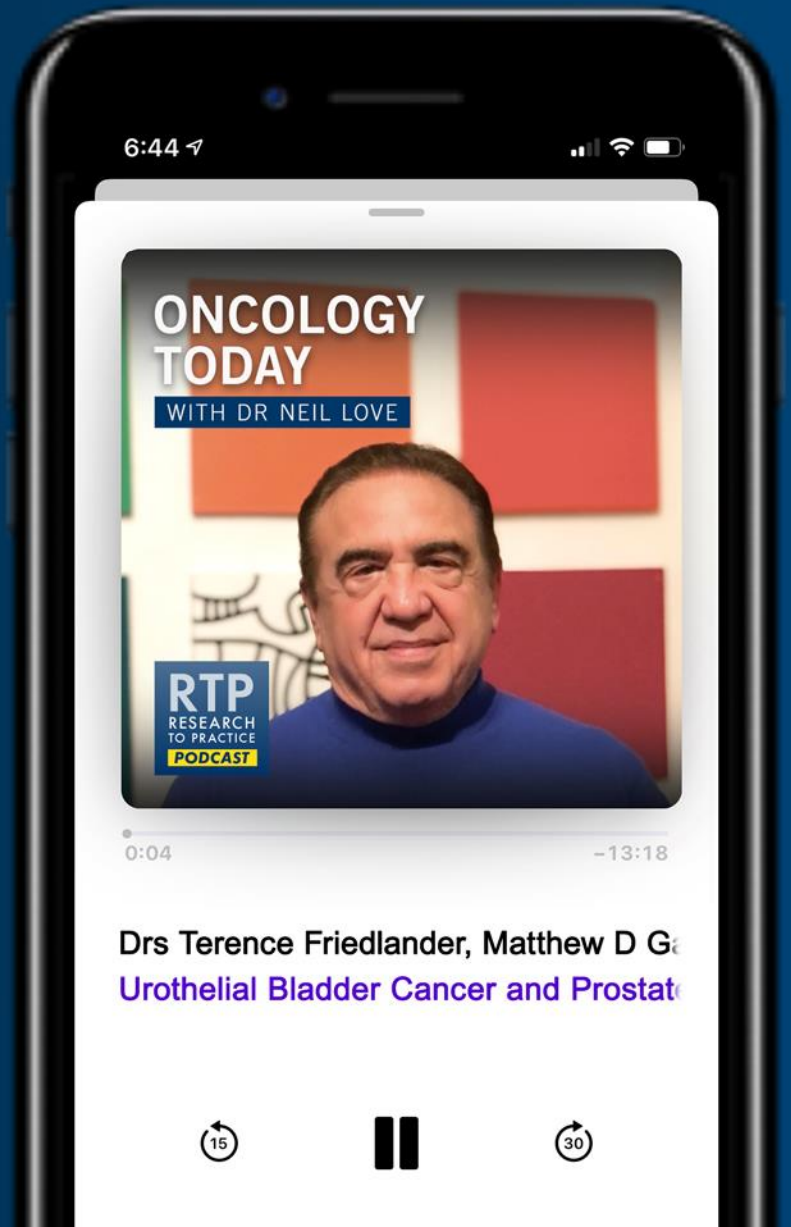
DR NEERAJ AGARWAL
UNIVERSITY OF UTAH HUNTSMAN CANCER INSTITUTE

DR TERENCE FRIEDLANDER
UCSF HELEN DILLER FAMILY COMPREHENSIVE CANCER CENTER

DR ANDREW J ARMSTRONG
DUKE CANCER INSTITUTE

DR MATTHEW D GALSKY
THE TISCH CANCER INSTITUTE

MODERATOR
DR ELISABETH I HEATH
MAYO CLINIC



Listen on Apple Podcasts

Spotify

Listen on Google Podcasts

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

Management of Non-Hodgkin Lymphoma

A CME/MOC-Accredited Live Webinar

Tuesday, April 22, 2025

5:00 PM – 6:00 PM ET

Faculty

Stephen M Ansell, MD, PhD

Brian T Hill, MD, PhD

Moderator

Neil Love, MD

RTP Year in Review 2025

Data + Perspectives: Clinical Investigators Discuss the Emerging Role of AKT Inhibitors in the Care of Patients with Prostate Cancer

A CME Satellite Symposium Held in Conjunction with the American Urological Association Annual Meeting 2025 (AUA2025)

Saturday, April 26, 2025

8:00 AM – 9:30 AM PT (11:00 AM – 12:30 PM ET)

Faculty

Leonard G Gomella, MD

Evan Y Yu, MD

Moderator

Daniel George, MD

RTP RESEARCH TO PRACTICE

Year in Review: Management of Prostate Cancer

INTRODUCTION: Quality of Life

MODULE 1: PARP Inhibition (PARPi)

- Mutations that predict PARPi sensitivity
- Endocrine therapy and PARPi synergy
- Ongoing PARPi trials in metastatic hormone-sensitive prostate cancer

MODULE 2: M0 Disease

- PRESTO; EMBARK

MODULE 3: Metastatic Hormone-Sensitive Prostate Cancer

- De novo versus recurrent
- PTEN deficiency – CAPItello-281

MODULE 4: Radiopharmaceuticals

- Radium-223
- ^{177}Lu-PSMA-617; ^{177}Lu-PNT2002 – SPLASH

MODULE 5: Other Novel Investigational Approaches for Metastatic Castration-Resistant Prostate Cancer

- CYP11A1 inhibition – Opevesostat
- EZH2 inhibition – Mevrometostat

RTP Year in Review 2025

Thank you for joining us!

Please take a moment to complete the survey currently up on Zoom.
Your feedback is very important to us.

Information on how to obtain CME, ABIM MOC and ABS credit will be provided in the Zoom chat room.
Attendees will also receive an email in 1 to 3 business days with these instructions.

RTP Year in Review 2025

Year in Review:
Management of Prostate Cancer

A CME/MOC-Accredited Live Webinar

Thursday, April 17, 2025
5:00 PM – 6:00 PM ET

Faculty

Emmanuel S Antonarakis, MD
Professor Karim Fizazi, MD, PhD

Moderator

Neil Love, MD

RTP Year in Review 2025

Faculty

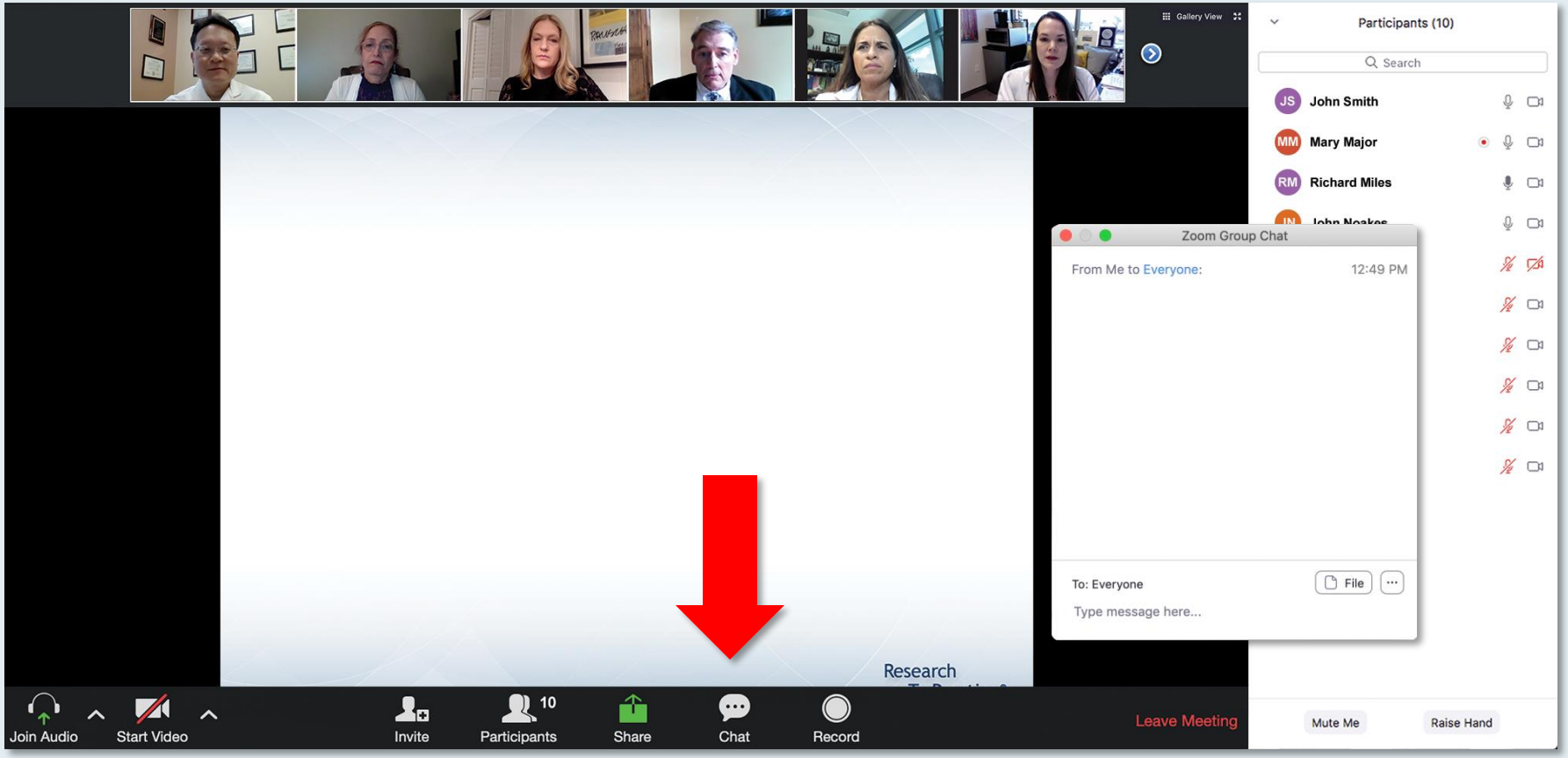
Emmanuel S Antonarakis, MD
Clark Endowed Professor of Medicine
Division of Hematology, Oncology and Transplantation
University of Minnesota
Minneapolis, Minnesota

Professor Karim Fizazi, MD, PhD
Head of Service and Full Professor
Institut Gustave Roussy
University of Paris Saclay
Villejuif, France

MODERATOR
Neil Love, MD
Research To Practice
Miami, Florida

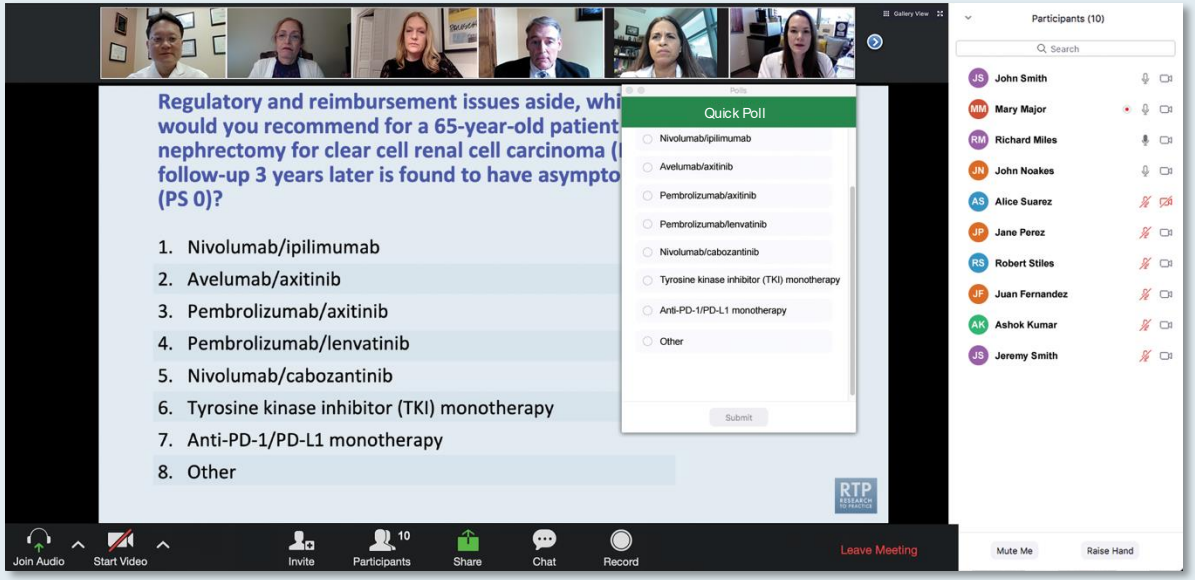
RTP Year in Review 2025

We Encourage Clinicians in Practice to Submit Questions



Feel free to submit questions now before the program begins and throughout the program.

Clinicians in the Audience, Please Complete the Pre- and Postmeeting Surveys



Urothelial Bladder Cancer and Prostate Cancer — Proceedings from a Session Held in Conjunction with the 2025 ASCO Genitourinary Cancers Symposium (ASCO GU)

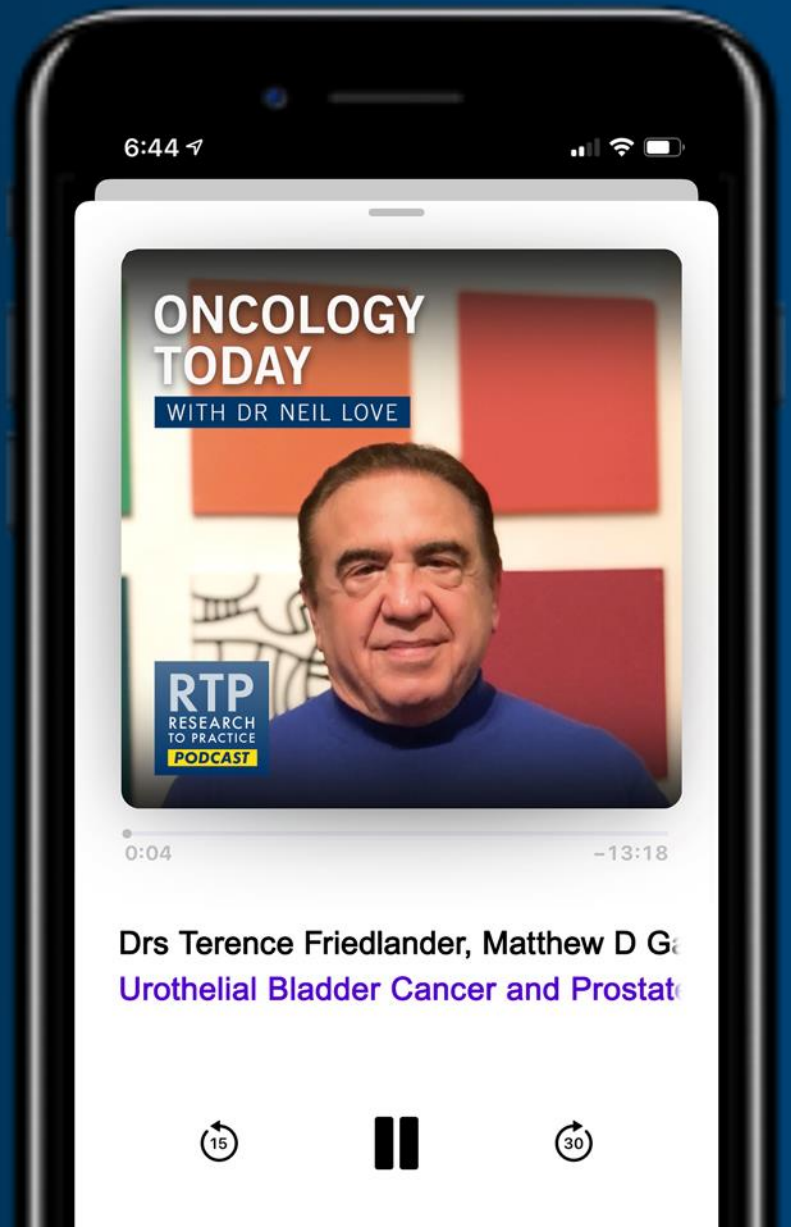
DR NEERAJ AGARWAL
UNIVERSITY OF UTAH HUNTSMAN CANCER INSTITUTE

DR TERENCE FRIEDLANDER
UCSF HELEN DILLER FAMILY COMPREHENSIVE CANCER CENTER

DR ANDREW J ARMSTRONG
DUKE CANCER INSTITUTE

DR MATTHEW D GALSKY
THE TISCH CANCER INSTITUTE

MODERATOR
DR ELISABETH I HEATH
MAYO CLINIC



Listen on Apple Podcasts

Spotify

Listen on Google Podcasts

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

Management of Non-Hodgkin Lymphoma

A CME/MOC-Accredited Live Webinar

Tuesday, April 22, 2025

5:00 PM – 6:00 PM ET

Faculty

Stephen M Ansell, MD, PhD

Brian T Hill, MD, PhD

Moderator

Neil Love, MD

RTP Year in Review 2025

Data + Perspectives: Clinical Investigators Discuss the Emerging Role of AKT Inhibitors in the Care of Patients with Prostate Cancer

A CME Satellite Symposium Held in Conjunction with the American Urological Association Annual Meeting 2025 (AUA2025)

Saturday, April 26, 2025

8:00 AM – 9:30 AM PT (11:00 AM – 12:30 PM ET)

Faculty

Leonard G Gomella, MD

Evan Y Yu, MD

Moderator

Daniel George, MD

RTP RESEARCH TO PRACTICE

Year in Review:
Management of Prostate Cancer

A CME/MOC-Accredited Live Webinar

Thursday, April 17, 2025
5:00 PM – 6:00 PM ET

Faculty

Emmanuel S Antonarakis, MD
Professor Karim Fizazi, MD, PhD

Moderator

Neil Love, MD

RTP Year in Review 2025

Commercial Support

This activity is supported by educational grants from Astellas and Pfizer Inc, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Janssen Biotech Inc, administered by Janssen Scientific Affairs LLC, and Merck.

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.

Dr Antonarakis — Disclosures

Advisory Committees	Abeona Therapeutics Inc, AstraZeneca Pharmaceuticals LP, Blue Earth Diagnostics, Boundless Bio, Curium, Forbion, Sanofi, Tango Therapeutics
Consulting Agreements	Acerand Therapeutics, Clarity Pharmaceuticals, Curium, EcoR1 Capital LLC, Health Monitor, Lilly, LinKinVax, Vir Biotechnology Inc, Z-Alpha
Contracted Research	Bayer HealthCare Pharmaceuticals, Bristol Myers Squibb, MacroGenics Inc, Novartis, Orion Corporation, pharmaand GmbH, Seagen Inc

Prof Fizazi — Disclosures

Institutional Honoraria	Advanced Accelerator Applications, Amgen Inc, Astellas, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Daiichi Sankyo Inc, Janssen Biotech Inc, Merck, MSD, Novartis, Pfizer Inc

This educational activity contains discussion of non-FDA-approved uses of agents and regimens. Please refer to official prescribing information for each product for approved indications.

Research To Practice
April 7, 2025

Available and Emerging Therapeutic Approaches for Metastatic CRPC

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

GUSTAVE ROUSSY
CANCER CAMPUS GRAND PARIS

Discussing recent data about Advanced prostate cancer

Karim Fizazi, MD, PhD
Institut Gustave Roussy
Villejuif, France

Key Datasets

Professor Karim Fizazi, MD, PhD

- Parker CC et al. Randomised trial of no, **short-term, or long-term androgen deprivation therapy with postoperative radiotherapy** after radical prostatectomy: Results from the three-way comparison of **RADICALS-HD** (NCT00541047). *Eur Urol* 2024;86(5):422-30.
- Tutrone R et al. **Testosterone recovery for relugolix versus leuprolide** in men with advanced prostate cancer: Results from the **Phase 3 HERO study**. *Eur Urol Oncol* 2024;7(4):906-13.
- Shore N et al. **Apalutamide for high-risk localized prostate cancer** following radical prostatectomy **(Apa-RP)**. *J Urol* 2024;212(5):682-91.
- Shore ND et al. **Enzalutamide (enza) with or without leuprolide** in patients (pts) with high-risk biochemically recurrent (hrBCR) prostate cancer (PC): **EMBARK post hoc analysis** by age. ESMO 2024;Abstract 1638P.
- Freedland SJ et al. **Effects of enzalutamide on the sexual activity** of patients with biochemically recurrent prostate cancer: A post hoc analysis of **patient-reported outcomes in the EMBARK study**. *Eur Urol* 2025;[Online ahead of print].
- Aggarwal R et al. **PRESTO**: A phase III, open-label study of **intensification of androgen blockade** in patients with high-risk biochemically relapsed castration-sensitive prostate cancer (AFT-19). *J Clin Oncol* 2024;42(10):1114-23.

Key Datasets

Professor Karim Fizazi, MD, PhD (continued)

- Morgans AK et al. **Darolutamide plus androgen-deprivation therapy (ADT)** in patients with high-risk biochemical recurrence (BCR) of prostate cancer: A phase 3, randomized, double-blind, placebo-controlled study (**ARASTEP**). Genitourinary Cancers Symposium 2025;Abstract TPS432.
- Roy S et al. **Early prostate-specific antigen response by 6 months** is predictive of treatment effect in metastatic hormone sensitive prostate cancer: **An exploratory analysis of the TITAN trial.** *J Urol* 2024;212(5):672-81.
- Gomez-Veiga F et al. Clinical outcomes of **enzalutamide** in metastatic hormone-sensitive prostate cancer **in patients aged <75 and 75 years: ARCHES post hoc analysis**. *Eur Urol Oncol* 2024;7(4):860-9.
- Saad F et al. **Darolutamide in combination with androgen-deprivation therapy** in patients with metastatic hormone-sensitive prostate cancer from the **phase III ARANOTE trial.** *J Clin Oncol* 2024;42(36):4271-81.
- Saad F et al. Deep and durable prostate-specific antigen response to **darolutamide with androgen deprivation therapy and docetaxel**, and association with clinical outcomes for patients with high- or low-volume metastatic hormone-sensitive prostate cancer: Analyses of the randomized **phase 3 ARASENS study**. *Eur Urol* 2024;86(4):329-39.

Key Datasets

Emmanuel S Antonarakis, MD

- Saad F et al. Efficacy of **olaparib (ola) plus abiraterone (abi)** versus placebo (pbo) plus abi in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) with a germline or somatic BRCA mutation in the **PROpel trial**. Genitourinary Cancers Symposium 2025;Abstract 219.
- Roubaud G et al. Adjustment for imbalances in baseline characteristics in the **MAGNITUDE phase 3 study** confirms the clinical benefit of **niraparib in combination with abiraterone** acetate plus prednisone in patients with metastatic prostate cancer. *Eur J Cancer* 2024;209:114183.
- Agarwal N et al. Final overall survival (OS) with **talazoparib (TALA) + enzalutamide (ENZA)** as first-line treatment in unselected patients with metastatic castration-resistant prostate cancer (mCRPC) in the **phase 3 TALAPRO-2 trial**. Genitourinary Cancers Symposium 2025;Abstract LBA18.
- Hussain MH et al. **Abiraterone, olaparib, or abiraterone + olaparib** in first-line metastatic castration-resistant prostate cancer with **DNA repair defects (BRCAAway)**. *Clin Cancer Res* 2024;30(19):4318-28.
- Azad A et al. Phase III, double-blind, placebo-controlled, 2-cohort, randomized study of **saruparib (AZD5305) in combination with androgen receptor pathway inhibitors** in patients with metastatic hormone-sensitive prostate cancer with and without homologous recombination repair mutation **(EvoPAR-Prostate01)**. Genitourinary Cancers Symposium 2025;Abstract TPS279.
- Gillessen S et al. A randomized multicenter open label phase III trial comparing **enzalutamide vs a combination of radium-223 (Ra223) and enzalutamide** in asymptomatic or mildly symptomatic patients with bone metastatic castration-resistant prostate cancer (mCRPC): First results of EORTC-GUCG 1333/**PEACE-3**. ESMO 2024;Abstract LBA1.

Key Datasets

Emmanuel S Antonarakis, MD (continued)

- Morris MJ et al. **177Lu-PSMA-617 versus a change of androgen receptor pathway inhibitor therapy** for taxane-naive patients with progressive metastatic castration-resistant prostate cancer (**PSMAfore**): A phase 3, randomised, controlled trial. *Lancet* 2024;404(10459):1227-39.
- Emmett L et al. Overall survival and quality of life with **[(177)Lu]Lu-PSMA-617 plus enzalutamide versus enzalutamide alone** in metastatic castration-resistant prostate cancer (**ENZA-p**): Secondary outcomes from a multicentre, open-label, randomised, phase 2 trial. *Lancet Oncol* 2025;26(3):291-9.
- Sartor O et al. Efficacy of **177Lu-PNT2002** in PSMA-positive mCRPC following progression on an androgen-receptor pathway inhibitor (ARPI) (**SPLASH**). ESMO 2024;Abstract LBA65.
- Agarwal N et al. **Cabozantinib (C) plus atezolizumab (A) versus 2nd novel hormonal therapy (NHT)** in patients (Pts) with metastatic castration-resistant prostate cancer (mCRPC): Final overall survival (OS) results of the phase III, randomized, **CONTACT-02 study**. ESMO 2024;Abstract LBA67.
- Schweizer MT et al. **Mevrometostat** (PF-06821497), an enhancer of zeste homolog 2 (EZH2) inhibitor, **in combination with enzalutamide** in patients with metastatic castration-resistant prostate cancer (mCRPC): A randomized dose-expansion study. Genitourinary Cancers Symposium 2025;Abstract LBA138.
- Gratzke CJ et al. **Phase 3 OMAHA-004 study** of CYP11A1 inhibitor **opevesostat versus next-generation hormonal agent (NHA) switch** in patients with metastatic castration-resistant prostate cancer (mCRPC) after 1 prior NHA. Genitourinary Cancers Symposium 2025;Abstract TPS301.
- Yu EY et al. OMAHA-003: A **phase 3 study** of CYP11A1 inhibitor **opevesostat versus next-generation hormonal agent (NHA) switch** in metastatic castration-resistant prostate cancer (mCRPC) after NHA and taxane-based chemotherapy. Genitourinary Cancers Symposium 2025;Abstract TPS286.

Year in Review: Management of Prostate Cancer

INTRODUCTION: Quality of Life

MODULE 1: PARP Inhibition (PARPi)

- Mutations that predict PARPi sensitivity
- Endocrine therapy and PARPi synergy
- Ongoing PARPi trials in metastatic hormone-sensitive prostate cancer

MODULE 2: M0 Disease

- PRESTO; EMBARK

MODULE 3: Metastatic Hormone-Sensitive Prostate Cancer

- De novo versus recurrent
- PTEN deficiency – CAPItello-281

MODULE 4: Radiopharmaceuticals

- Radium-223
- ^{177}Lu-PSMA-617; ^{177}Lu-PNT2002 – SPLASH

MODULE 5: Other Novel Investigational Approaches for Metastatic Castration-Resistant Prostate Cancer

- CYP11A1 inhibition – Opevesostat
- EZH2 inhibition – Mevrometostat

RTP Year in Review 2025

Year in Review: Management of Prostate Cancer

INTRODUCTION: Quality of Life

MODULE 1: PARP Inhibition (PARPi)

- Mutations that predict PARPi sensitivity
- Endocrine therapy and PARPi synergy
- Ongoing PARPi trials in metastatic hormone-sensitive prostate cancer

MODULE 2: M0 Disease

- PRESTO; EMBARK

MODULE 3: Metastatic Hormone-Sensitive Prostate Cancer

- De novo versus recurrent
- PTEN deficiency – CAPItello-281

MODULE 4: Radiopharmaceuticals

- Radium-223
- ^{177}Lu-PSMA-617; ^{177}Lu-PNT2002 – SPLASH

MODULE 5: Other Novel Investigational Approaches for Metastatic Castration-Resistant Prostate Cancer

- CYP11A1 inhibition – Opevesostat
- EZH2 inhibition – Mevrometostat

RTP Year in Review 2025

50TH ANNUAL

ONS™ Congress

CELEBRATING YESTERDAY TRANSFORMING TOMORROW

CELEBRATING 50 YEARS

Welcome ONS Members!

RTP RESEARCH TO PRACTICE

Understanding the Current Paradigm and New Approaches in the Care of Patients with Cancer

A Complimentary NCPD Hybrid Symposium Series Held During the 50th Annual ONS Congress

Prostate Cancer

Thursday, April 10, 2025

12:15 PM – 1:45 PM

Faculty

Rahul Aggarwal, MD
Monica Averia, MSN, AOCNP, NP-C
Kathleen D Burns, RN, MSN, AGACNP-BC, OCN
William K Oh, MD

Moderator

Neil Love, MD

RTP Year in Review 2025

Faculty

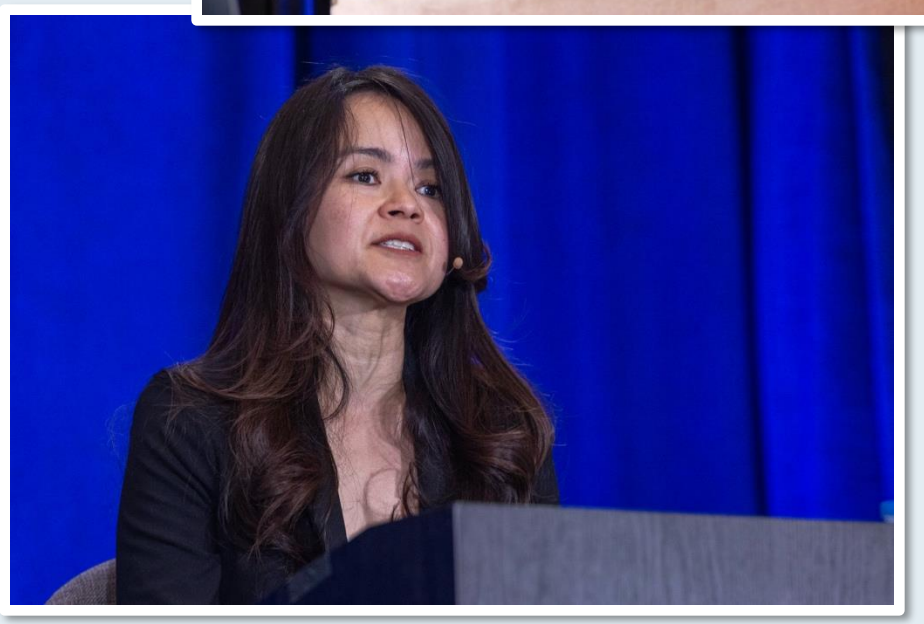
Monica Averia, MSN, AOCNP, NP-C
Oncology Nurse Practitioner
Clinical Instructor of Medicine
USC Norris Cancer Center
Los Angeles, California

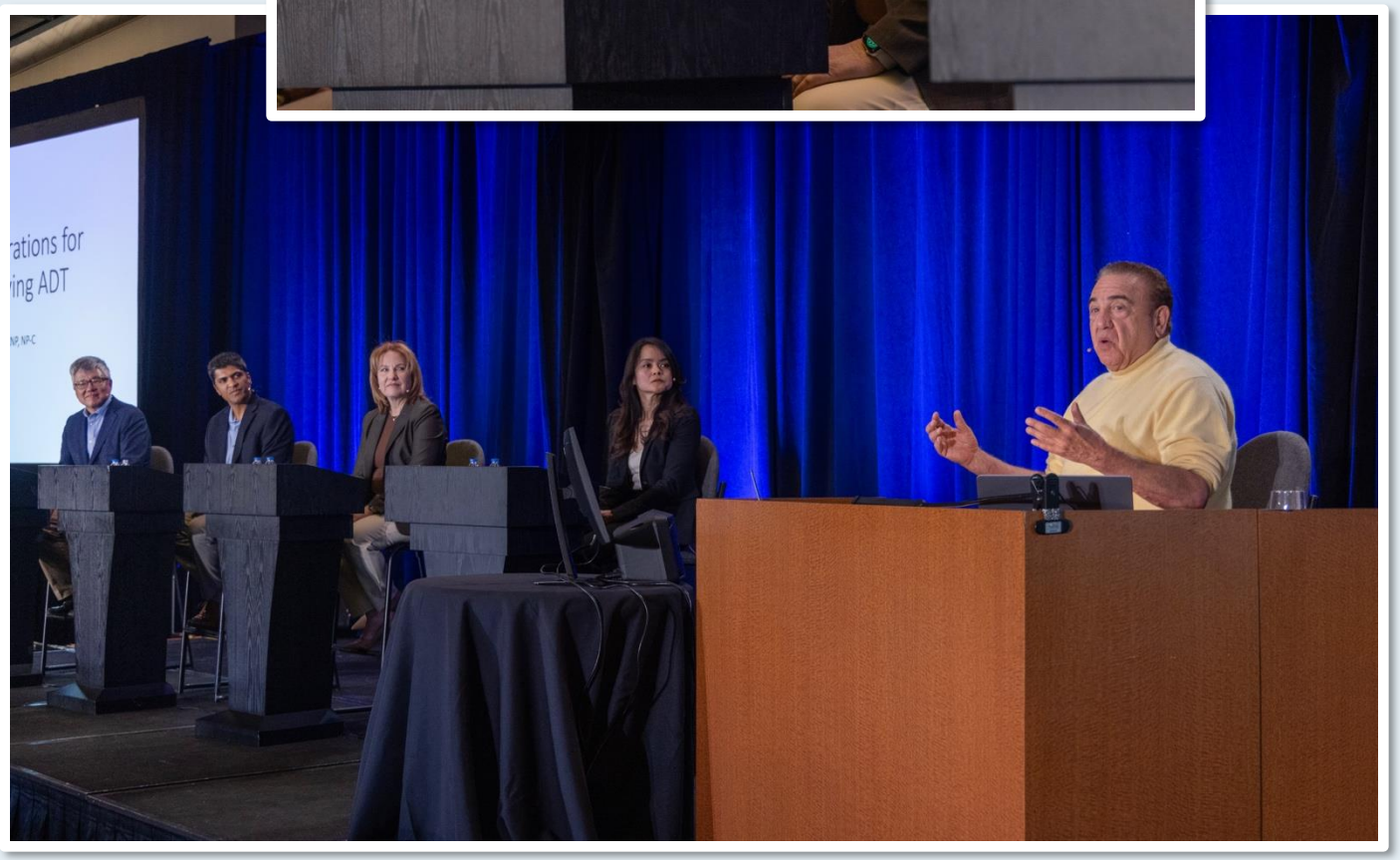
Rahul Aggarwal, MD
Professor of Medicine and Thomas Perkins
Distinguished Professor of Cancer Research
Director, Genitourinary Medical Oncology
University of California, San Francisco
Department of Medicine
Division of Hematology/Oncology
Associate Director for Clinical Research
UCSF Helen Diller Family Comprehensive Cancer Center
San Francisco, California

Kathleen D Burns, RN, MSN, AGACNP-BC, OCN
Genitourinary Medical Oncology
City of Hope Comprehensive Cancer Center
Duarte, California

William K Oh, MD
Director of Precision Medicine
Yale Cancer Center
Professor of Medicine
Division of Medical Oncology
Yale School of Medicine
Medical Director, Service Line
Smilow Cancer Hospital at Greenwich Hospital
New Haven, Connecticut

RTP
RESEARCH TO PRACTICE




rations for
ring ADT

Year in Review: Management of Prostate Cancer

INTRODUCTION: Quality of Life

MODULE 1: PARP Inhibition (PARPi)

- Mutations that predict PARPi sensitivity
- Endocrine therapy and PARPi synergy
- Ongoing PARPi trials in metastatic hormone-sensitive prostate cancer

MODULE 2: M0 Disease

- PRESTO; EMBARK

MODULE 3: Metastatic Hormone-Sensitive Prostate Cancer

- De novo versus recurrent
- PTEN deficiency – CAPItello-281

MODULE 4: Radiopharmaceuticals

- Radium-223
- ^{177}Lu-PSMA-617; ^{177}Lu-PNT2002 – SPLASH

MODULE 5: Other Novel Investigational Approaches for Metastatic Castration-Resistant Prostate Cancer

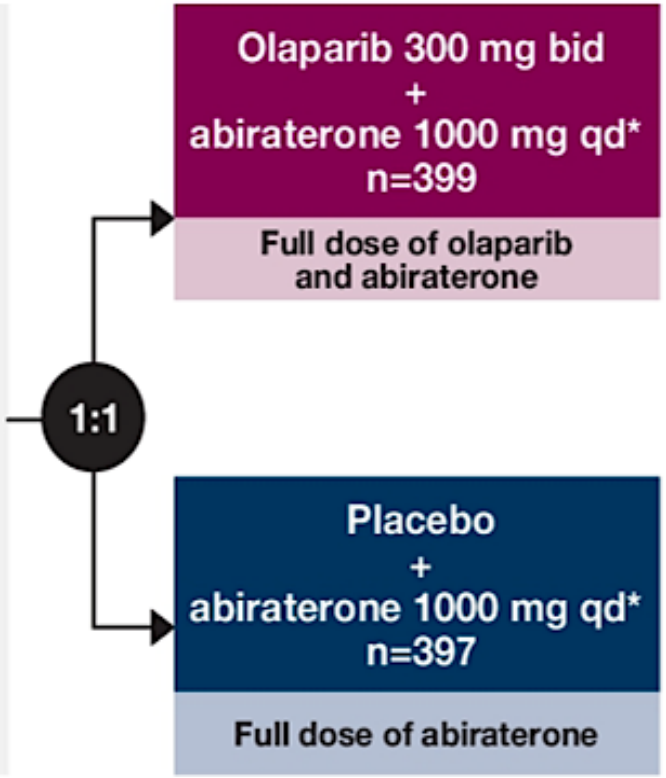
- CYP11A1 inhibition – Opevesostat
- EZH2 inhibition – Mevrometostat

RTP Year in Review 2025

Olap + Abi: Phase 3 PROpel trial design

Patient population
- 1L mCRPC
- Asymptomatic, mildly symptomatic, symptomatic
- No prior abiraterone
- Other NHAs allowed if stopped ≥12 months prior to enrollment
- ECOG 0/1

Stratification factors
- Site of distant metastases: bone only versus visceral versus other
- Prior taxane at mHSPC: yes versus no



Primary endpoint
- rPFS by investigator assessment (sensitivity analysis by BICR)

Key secondary endpoint
- OS (alpha control)

Additional planned analyses
- TFST
- PSA progression
- PFS2
- Confirmed PSA_{50} response
- HRQoL
- ORR
- HRRm status (germline, tissue and ctDNA after randomization and before primary analysis)
- Safety and tolerability

Saad F, et al. *ASCO GU Symposium* 2025; Abstract 219.

Courtesy of Emmanuel S Antonarakis, MD

PFS/OS results by germline or somatic *BRCA*m

Figure 4. An rPFS benefit was observed with olaparib + abiraterone versus placebo + abiraterone for patients with a germline or somatic BRCAm

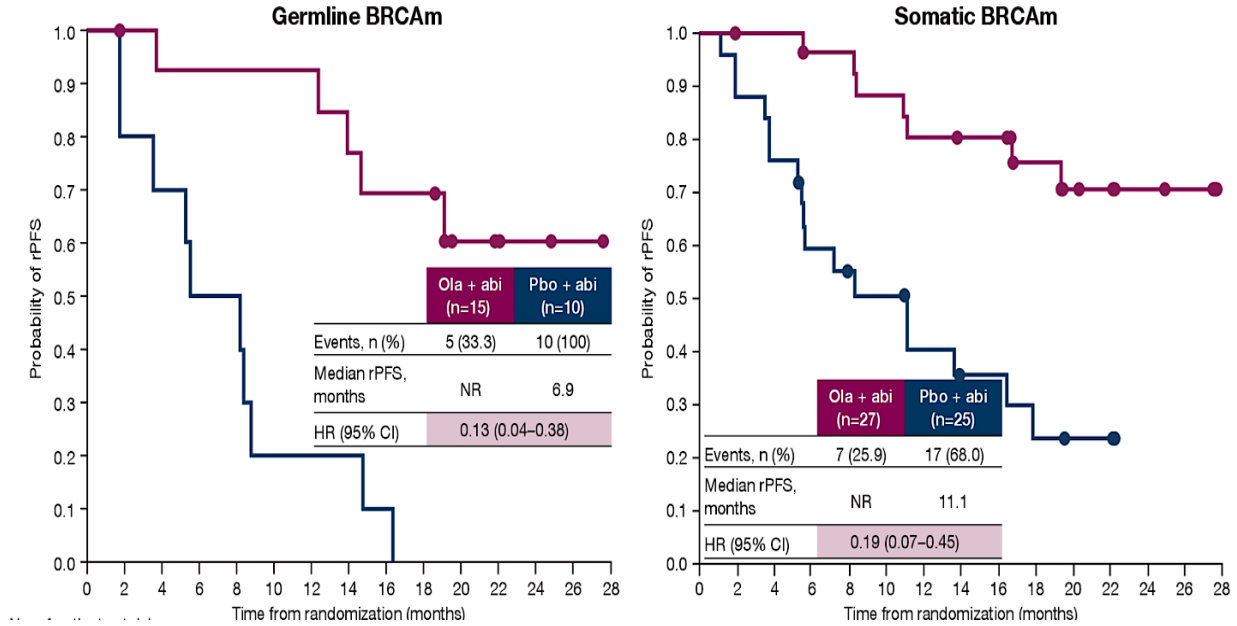
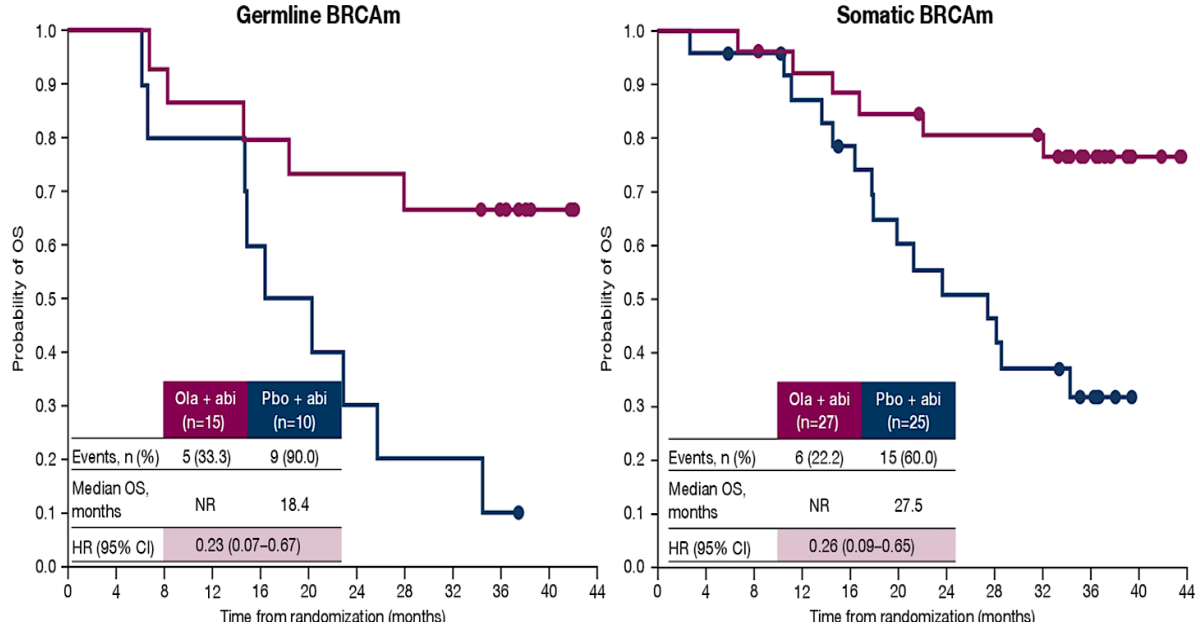


Figure 5. An OS benefit with olaparib + abiraterone was observed for patients with a germline or somatic BRCAm



Saad F, et al. *ASCO GU Symposium* 2025; Abstract 219.

Courtesy of Emmanuel S Antonarakis, MD

PFS/OS results by germline or somatic *BRCA*m

Figure 4. An rPFS benefit was observed with olaparib + abiraterone versus placebo + abiraterone for patients with a germline or somatic BRCAm

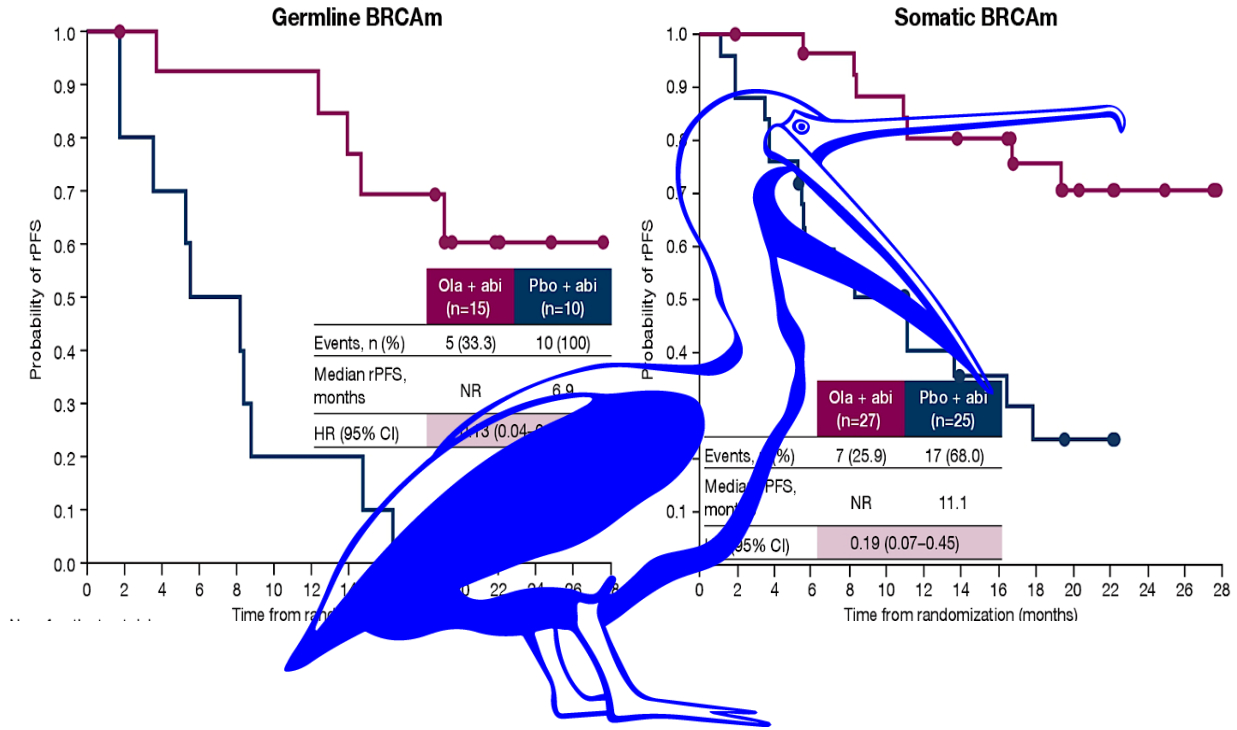
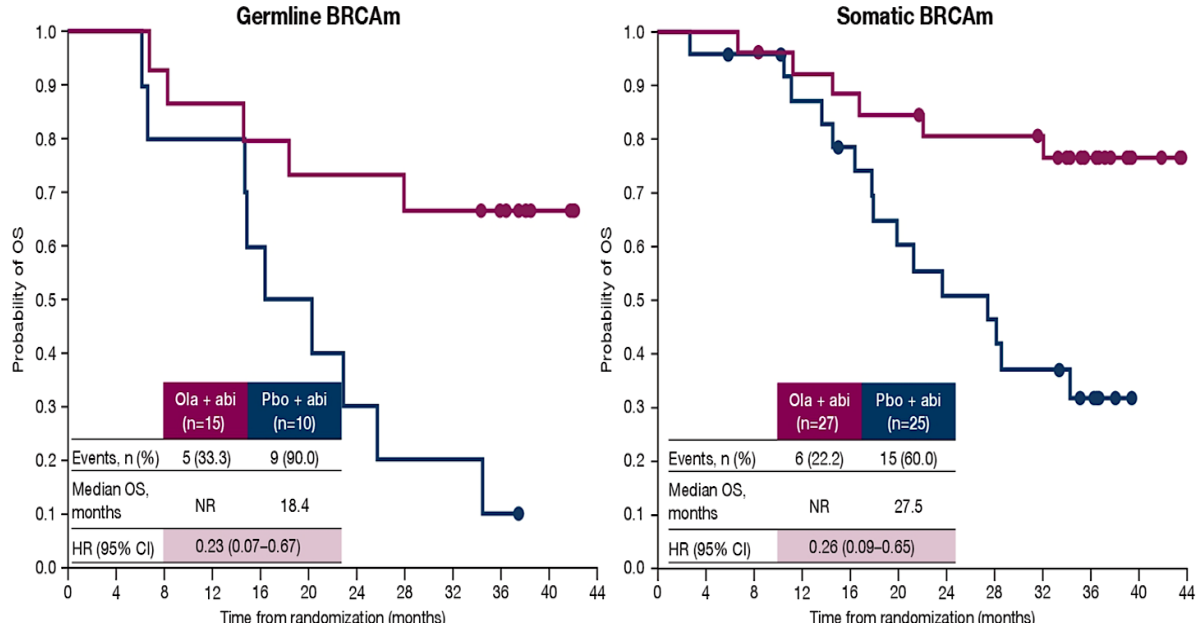


Figure 5. An OS benefit with olaparib + abiraterone was observed for patients with a germline or somatic BRCAm



Saad F, et al. *ASCO GU Symposium* 2025; Abstract 219.

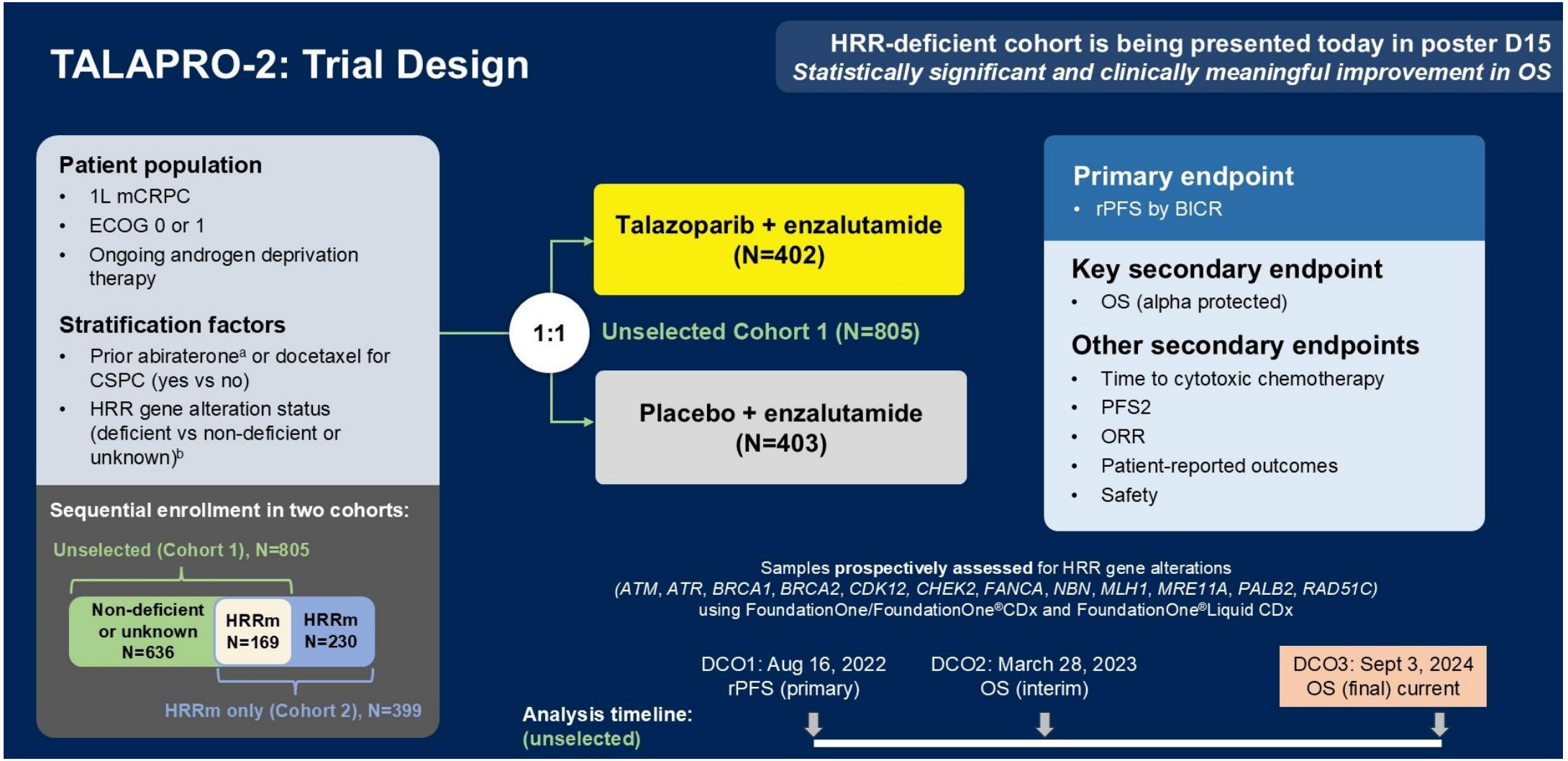
Courtesy of Emmanuel S Antonarakis, MD

Conclusions

- In first-line mCRPC patients with *BRCA*m, both germline and somatic muts derive similar benefit to olaparib + abiraterone
- The natural history of germline *BRCA*m may be worse than somatic *BRCA*m in terms of PFS and OS
- Since about 50% of *BRCA* mutations are of somatic-only origin, relying on germline testing alone will miss half of *BRCA*m cases
- Germline *and* somatic testing are needed for all mCRPC patients
- Somatic testing: tissue biopsy (primary, mets) or ctDNA assay

Courtesy of Emmanuel S Antonarakis, MD

Talazop + Enza: Phase 3 TALAPRO-2 trial



Agarwal N, et al. *ASCO GU Symposium* 2025; Abstract LBA18.

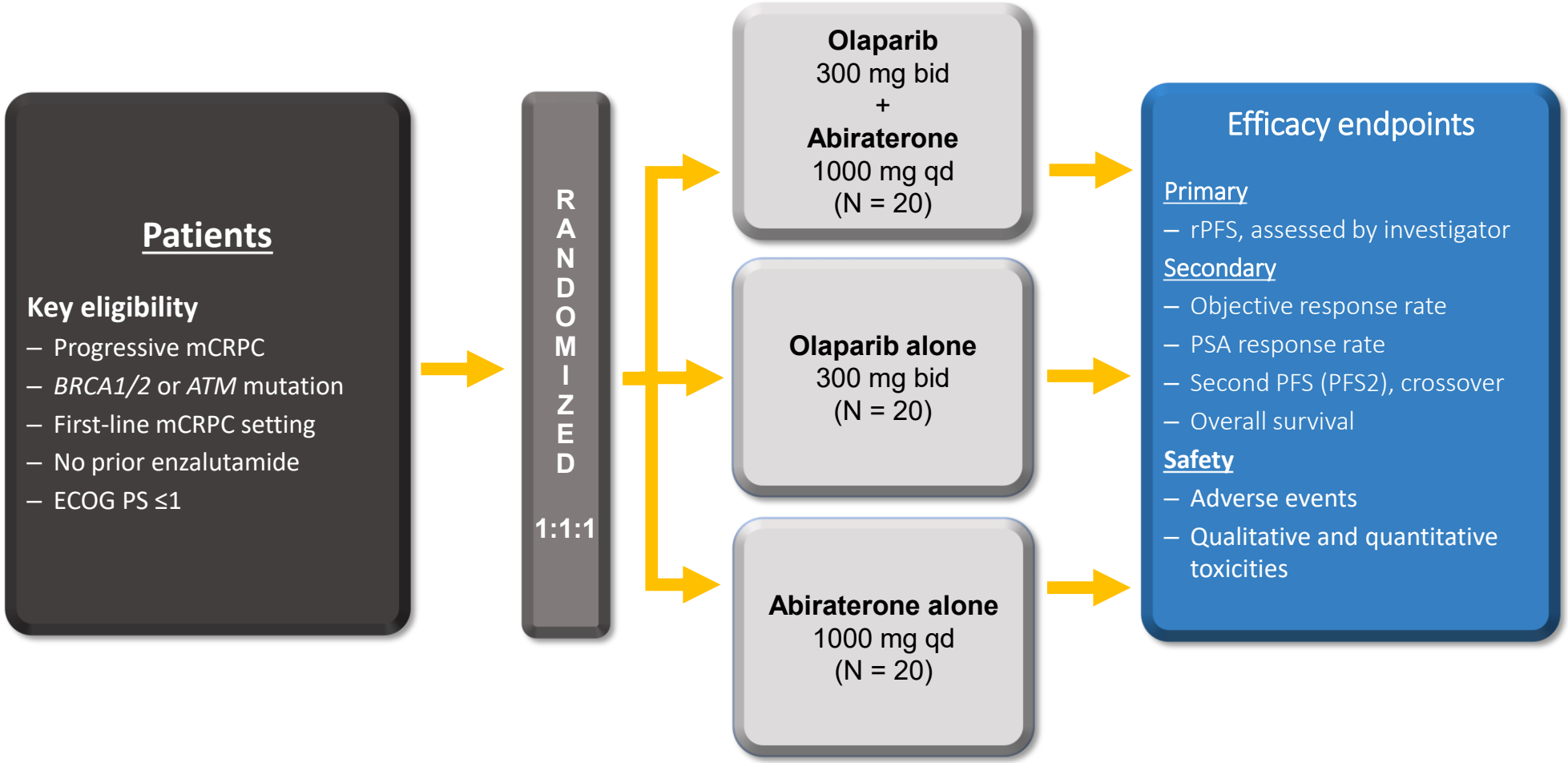
Courtesy of Emmanuel S Antonarakis, MD

Conclusions

- TALAPRO-2 was a randomized phase 3 trial of enza +/- talazop in both unselected and HRRm first-line mCRPC patients
- The primary PFS endpoint in unselected pts was met (HR 0.63, *P*<0.001) and was previously reported
- Here, we see that OS is also significantly improved with enza/ talazoparib in *unselected* first-line mCRPC pts
- Although this combo regimen is currently only FDA approved for HRR-altered mCRPC, expanded FDA approval will likely be sought

Courtesy of Emmanuel S Antonarakis, MD

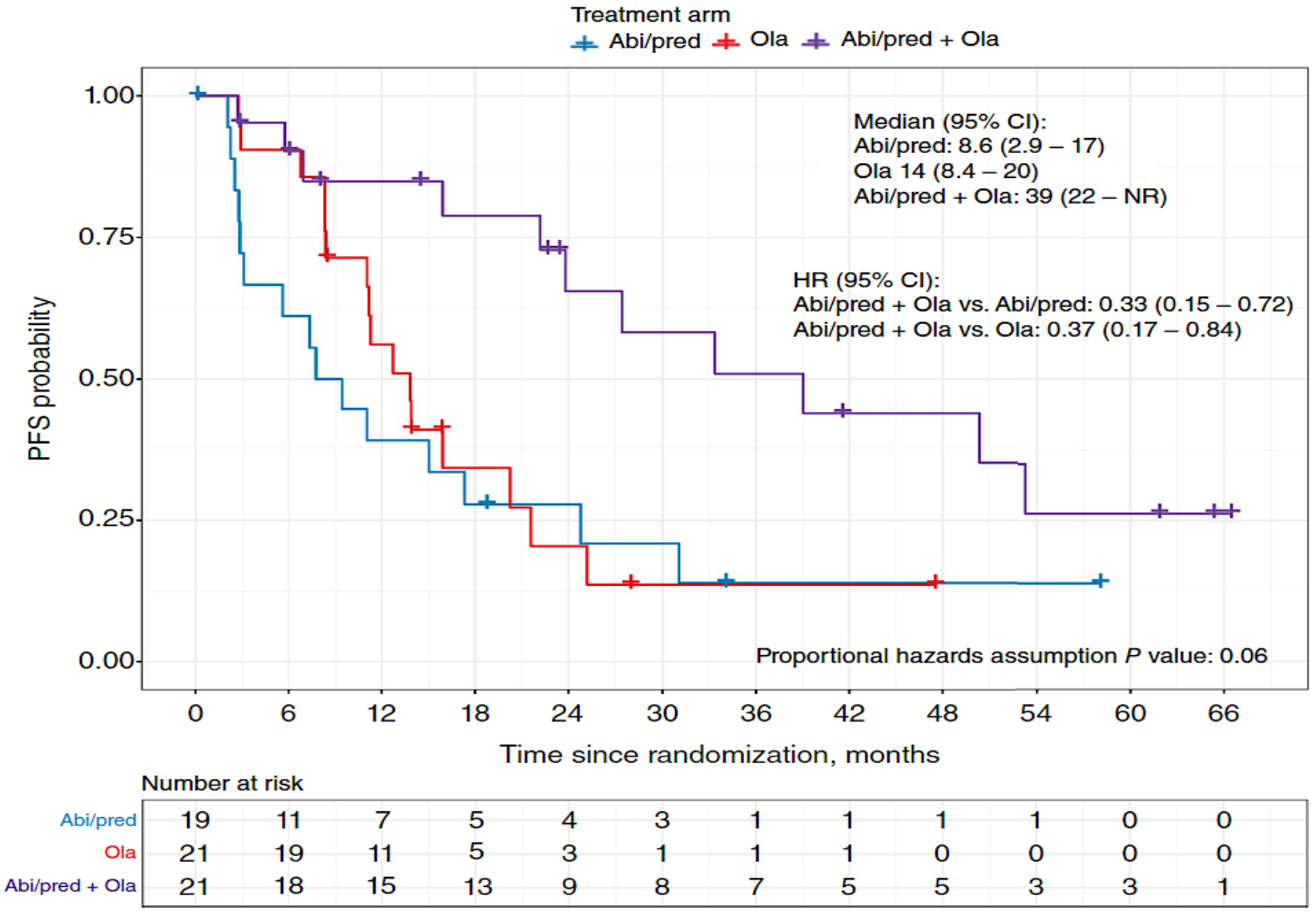
BRCAaway trial: Abi vs. Olap vs. Abi/Olap



Hussain M, et al. *Clin Cancer Res* 2024; 30: 4318-28. www.clinicaltrials.gov: **(NCT03012321)**

Courtesy of Emmanuel S Antonarakis, MD

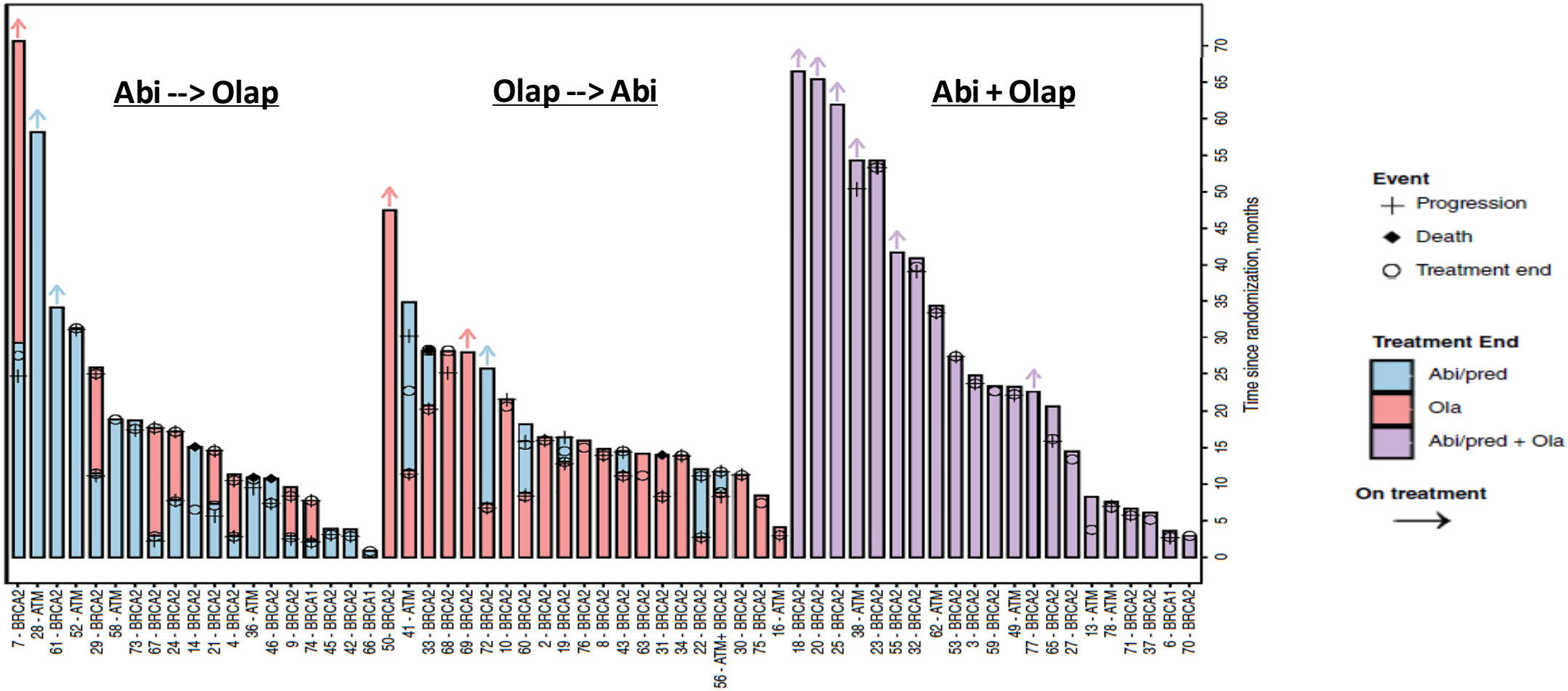
BRCAaway trial: Abi vs. Olap vs. Abi/Olap



Hussain M, et al. *Clin Cancer Res* 2024; 30: 4318-28.

Courtesy of Emmanuel S Antonarakis, MD

BRCAaway trial: Abi vs. Olap vs. Abi/Olap



Hussain M, et al. *Clin Cancer Res* 2024; 30: 4318-28.

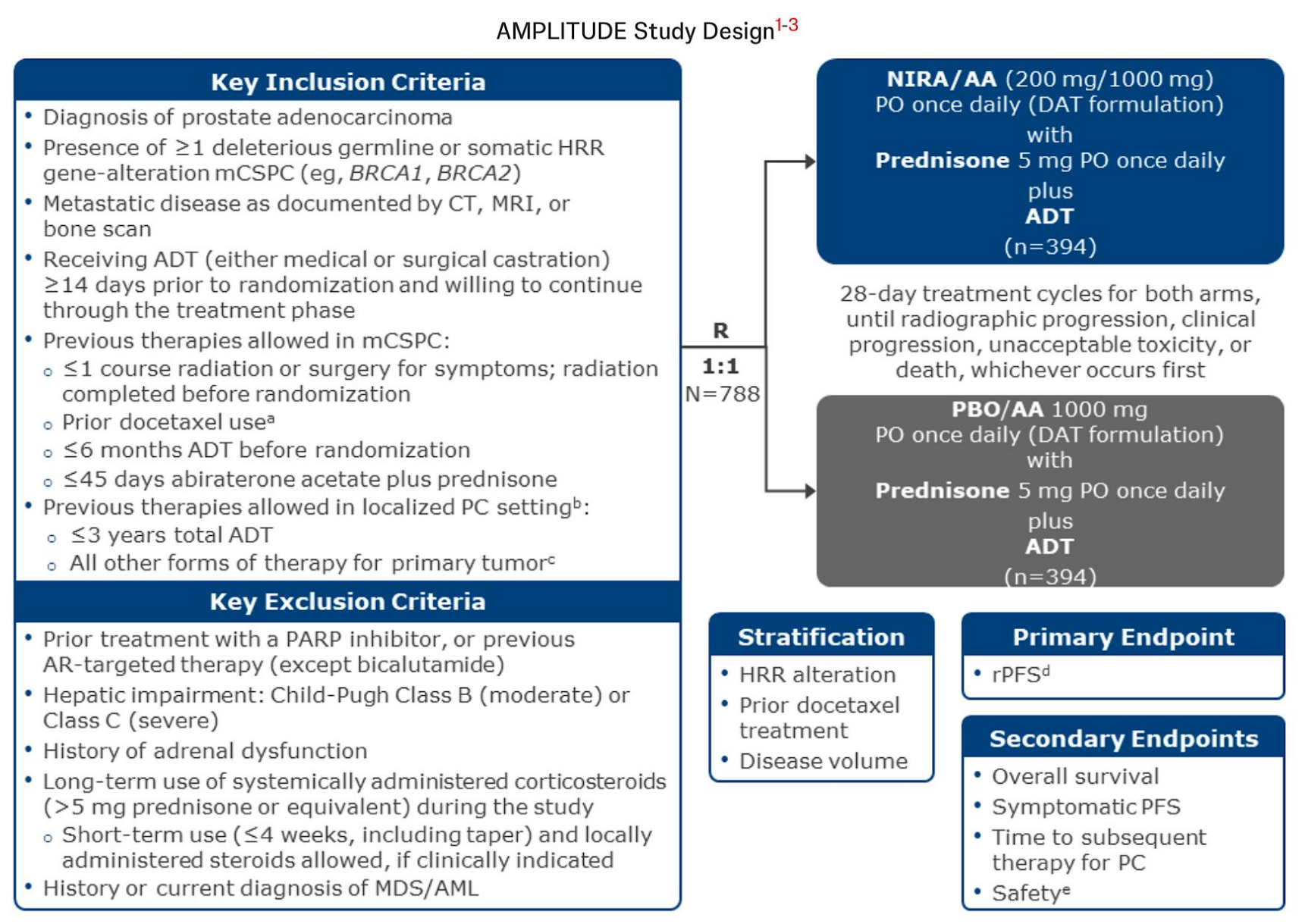
Courtesy of Emmanuel S Antonarakis, MD

Conclusions

- BRCAaway is the only PARPi/ARPI randomized trial with *two control* arms: Olaparib alone and Abiraterone alone
- The trial had a built-in crossover design for Arm A (abiraterone --> olaparib) and Arm B (olaparib --> abiraterone)
- Even accounting for crossover, the combo of olap/abi produced better PFS than sequential abi --> olap or olap --> abi
- Albeit a small trial, this is the best evidence that combination PARPi/ARPI therapy may be superior to sequential treatment

Courtesy of Emmanuel S Antonarakis, MD

AMPLITUDE: A Phase III Study of Niraparib/Abiraterone/ADT for mHSPC



mCSPC = metastatic castration-sensitive prostate cancer; rPFS = radiographic progression-free survival

Rathkopf DE et al. Genitourinary Cancers Symposium 2021;Abstract TPS176.

Saruparib: PARP1-selective inhibitor

Saruparib

- Saruparib (AZD5305), a first-in-class PARP1 inhibitor, was developed through rational design to be highly selective for PARP1, with increased potency and improved physicochemical properties versus other approved PARP inhibitors[12,13]
- In the PETRA study (NCT04644068), the favorable safety profile and low dose-reduction rate observed with saruparib monotherapy compared with approved PARP inhibitors suggests that patients may be able to remain on treatment longer at an optimal dose (60 mg QD), which may improve efficacy[12,*]
- The safety and efficacy of saruparib plus ARPIs for the treatment of mHSPC and mCRPC are being assessed in the phase I/IIa PETRANHA study (NCT05367440)[14]
  - Initial data indicated that saruparib (60 mg QD) can be safely combined with enzalutamide, abiraterone acetate plus prednisone(olone), or darolutamide
  - Low rates of hematologic and gastrointestinal toxicities, as well as low rates of dose reductions or discontinuations, were observed

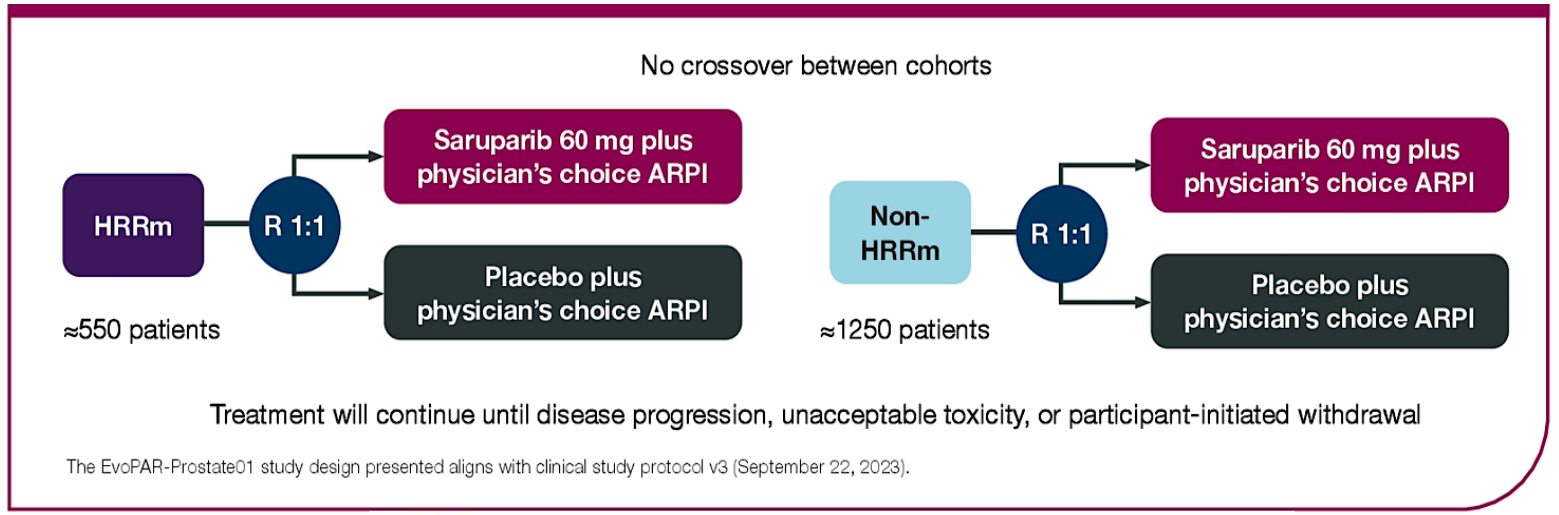
Azad A, et al. *ASCO GU Symposium* 2025; Abstract TPS279.

Courtesy of Emmanuel S Antonarakis, MD

EvoPAR-01 trial: ARPI +/- Saruparib in mHSPC

Key inclusion criteria

- Aged ≥18 years
- Histologically confirmed mHSPC (de novo or recurrent low- or high-volume disease)
- ECOG PS 0–1
- Prospectively defined HRRm status
  - HRRm cohort defined by the presence/absence of pathogenic/likely pathogenic mutations in ≥1 of the genes *BRCA1*, *BRCA2*, *ATM*, *CDK12*, *PALB2*, *RAD51B*, *RAD51C*, *RAD51D*, and *BARD1*, through prospective profiling of both tumor tissue and circulating tumor DNA
  - Participants in the non-HRRm cohort must have had a valid result of non-HRRm from prospective profiling of tumor tissue
- Must be receiving ADT plus a gonadotrophin-releasing hormone analog throughout the study or have undergone bilateral orchiectomy, and must be suitable for treatment with ARPIs
- Adequate organ and bone marrow function



Study endpoints

- Radiographic PFS, defined as the time from randomization to radiographic progression, as assessed by the investigator per RECIST 1.1 (soft tissue) and/or PCWG3 criteria (bone), or death due to any cause, in patients with:
  - BRCAm
  - HRRm
  - Non-HRRm
- OS, defined as the time from randomization until death from any cause
- Progression-free survival 2
- Symptomatic skeletal event-free survival
- Health-related quality of life
- Evaluation of somatic BRCAm and other HRRm status
- Pharmacokinetics
- Safety and tolerability
- Time to:
  - First subsequent therapy
  - First castration-resistant event
  - Pain progression
  - Deterioration in urinary symptoms
  - Deterioration in fatigue
  - Deterioration in physical function
  - PSA progression
- Exploratory analyses of additional safety and efficacy endpoints, as well as biomarkers (including PSMA PET), are planned

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

Azad A, et al. *ASCO GU Symposium* 2025; Abstract TPS279.

Courtesy of Emmanuel S Antonarakis, MD

Conclusions

- Saruparib is the first PARP1-selective inhibitor
- EvoPAR-01 is a Phase 3 randomized trial of ADT/ARPI +/- saruparib in mHSPC patients both with/without HRR muts
- Other PARPi trials in mHSPC: TALAPRO-3 (ADT/ARPI +/- Talazop), and AMPLITUDE (ADT/ARPI +/- Nirap)
- No indication currently for PARPi in mHSPC space, even for *BRCA1/2*-altered patients

Courtesy of Emmanuel S Antonarakis, MD

Year in Review: Management of Prostate Cancer

INTRODUCTION: Quality of Life

MODULE 1: PARP Inhibition (PARPi)

- Mutations that predict PARPi sensitivity
- Endocrine therapy and PARPi synergy
- Ongoing PARPi trials in metastatic hormone-sensitive prostate cancer

MODULE 2: M0 Disease

- PRESTO; EMBARK

MODULE 3: Metastatic Hormone-Sensitive Prostate Cancer

- De novo versus recurrent
- PTEN deficiency – CAPItello-281

MODULE 4: Radiopharmaceuticals

- Radium-223
- ^{177}Lu-PSMA-617; ^{177}Lu-PNT2002 – SPLASH

MODULE 5: Other Novel Investigational Approaches for Metastatic Castration-Resistant Prostate Cancer

- CYP11A1 inhibition – Opevesostat
- EZH2 inhibition – Mevrometostat

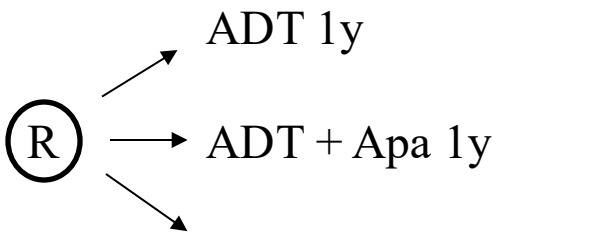
RTP Year in Review 2025

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

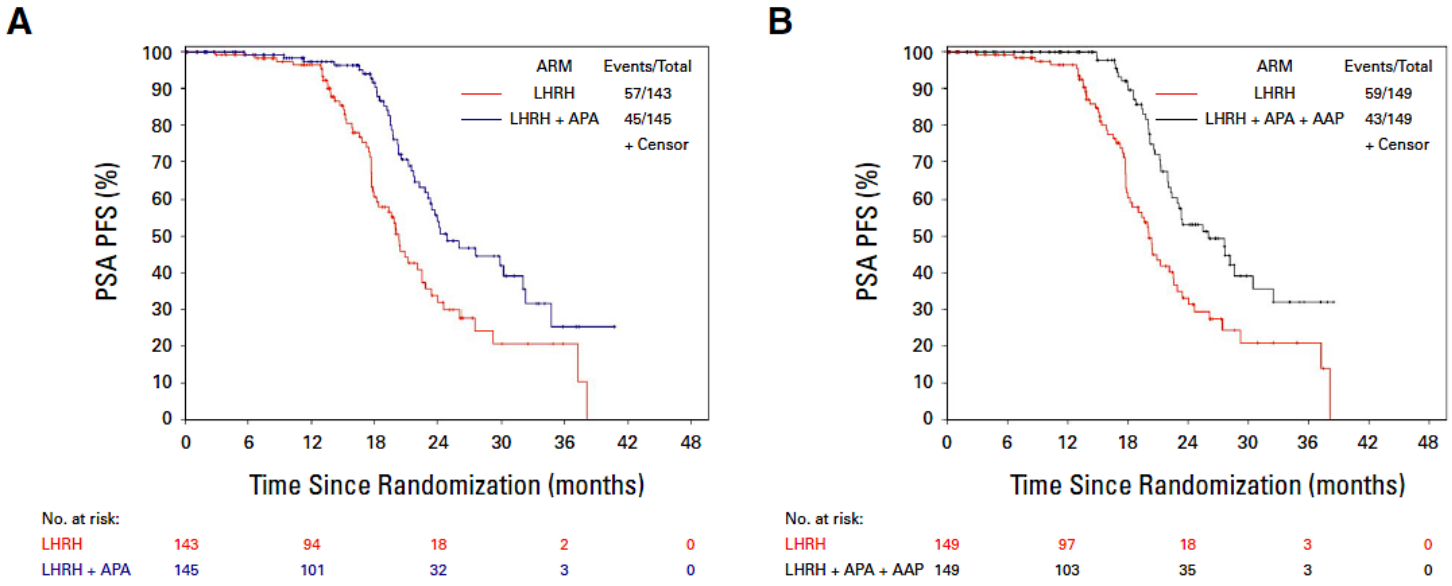
Rahul Aggarwal, MD[1]; Glenn Heller, PhD[2]; David W. Hillman, MS[3]; Han Xiao, MD[2]; Joel Picus, MD[4]; Mary-Ellen Taplin, MD[5]; Tanya Dorff, MD[6]; Leonard Appleman, MD[7]; Douglas Weckstein, MD[8]; Akash Patnaik, MD[9]; Alan Bryce, MD[10]; Daniel Shevrin, MD[11]; James Mohler, MD[12]; Daniel Anderson,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

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

BCR post RP
PSA DT<9m
n=503 pts



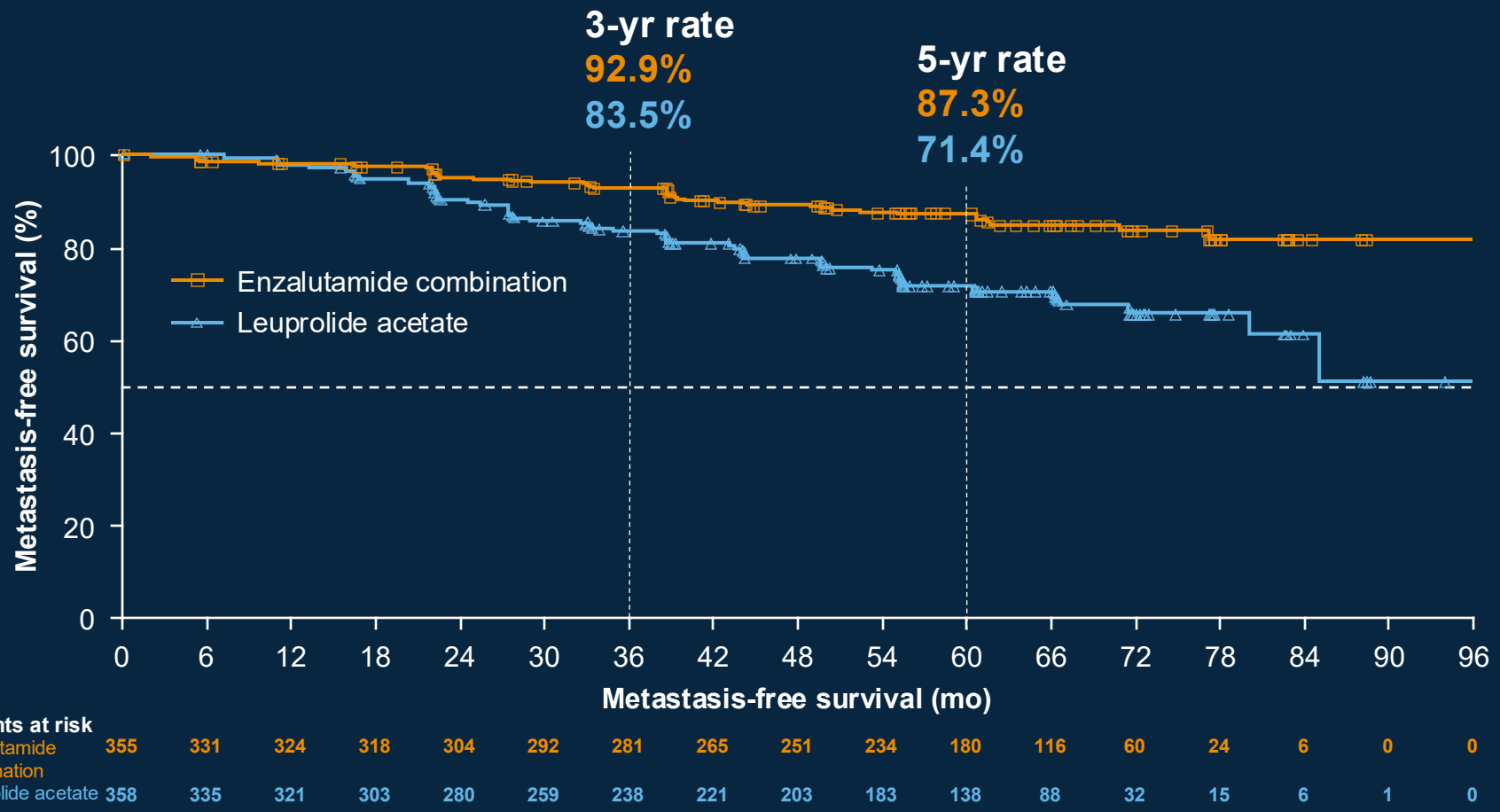
PSA-Progression free survival



Courtesy of Professor Karim Fizazi, MD, PhD

AUA 2023
CHICAGO ✶ APR 28-MAY 1

Biochemical failure: ADT+ Enzalutamide MFS (EMBARK)



	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]

A consistent treatment effect was seen for investigator-assessed MFS: HR (95% CI): 0.47 (0.37–0.67); *P*<0.0001

Data cutoff: January 31, 2023. Symbols indicate censored data. [a]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 was based on a stratified log-rank. CI, confidence interval; HR, hazard ratio; IWRS, interactive web response system; NR, not reached.

EUROPEAN UROLOGY xxx (xxxx) xxx–xxx

Courtesy of Professor Karim Fizazi, MD, PhD

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Brief Report

Effects of Enzalutamide on the Sexual Activity of Patients with Biochemically Recurrent Prostate Cancer: A Post Hoc Analysis of Patient-reported Outcomes in the EMBARK Study

Stephen J. Freedland[a,b], *John P. Mulhall*[c], *Martin Gleave*[d], *Ugo De Giorgi*[e], *Fred Saad*[f], *Antti Rannikko*[g], *Jasmina I. Ivanova*[h], *Anchen F. Nasr*[i], *Arlene L. Reisman*[h], *Arijit Ganguli*[i], *Pavol Kral*[j], *James Turnbull*[k], *Neal Shore*[l,*]

EUROPEAN UROLOGY xxx (xxxx) xxx–xxx

Courtesy of Professor Karim Fizazi, MD, PhD

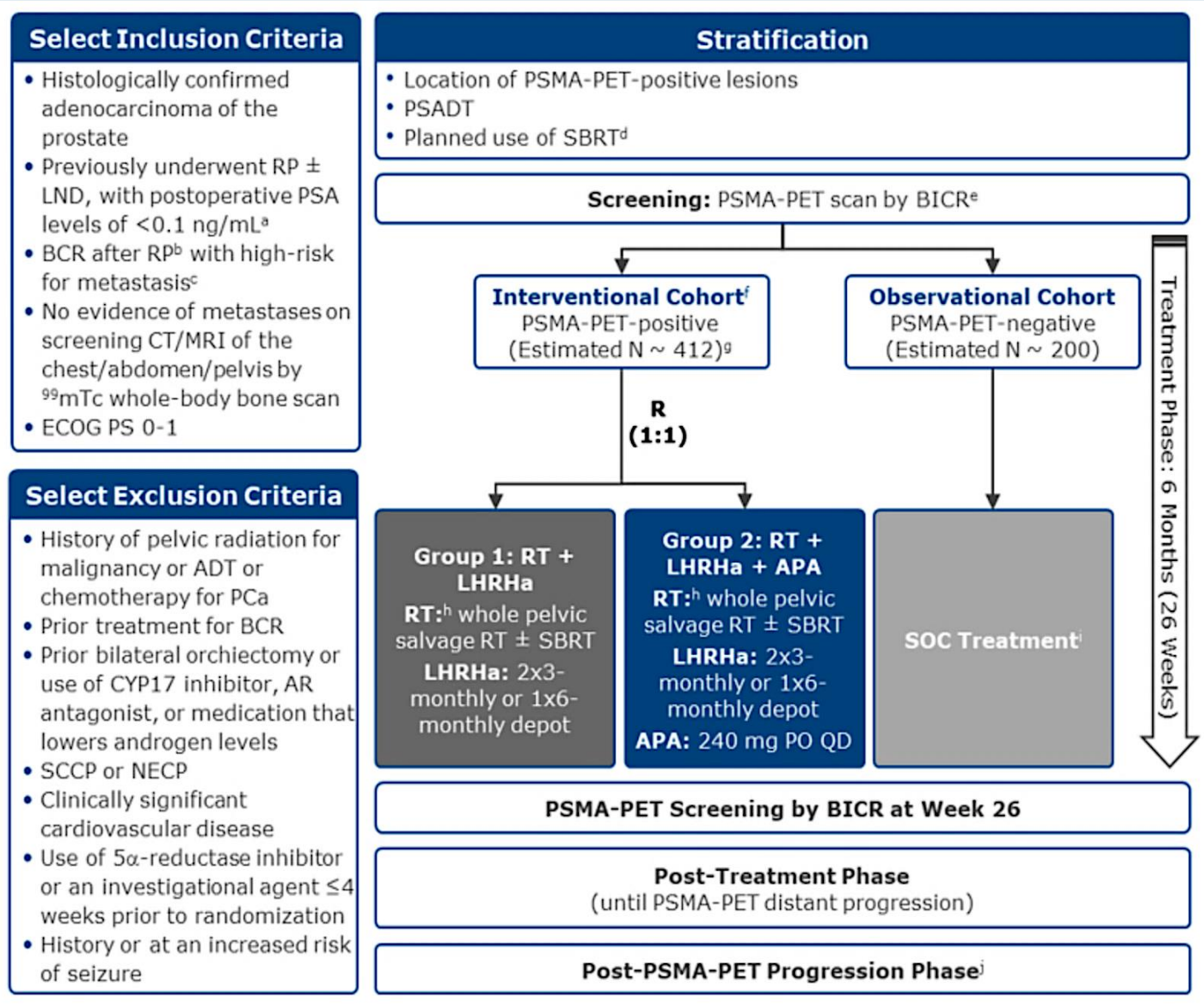
available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Brief Report

repeated measures analyses, respectively. In comparison to leuprolide alone, enzalutamide monotherapy delayed TTCD in interest in sex (8.5 vs 5.6 mo; hazard ratio [HR] 0.70, 95% confidence interval [CI] 0.57–0.87; $p < 0.001$), extent of SA (5.7 vs 3.0 mo; HR 0.69, 95% CI 0.54–0.90; $p = 0.004$), satisfaction with sex life (11.1 vs 5.4 mo; HR 0.61, 95% CI 0.45–0.84; $p = 0.001$), and erectile function (5.5 vs 2.9 mo; HR 0.67, 95% CI 0.50–0.88; $p = 0.003$). TTCD in SA-related HRQoL was similar with enzalutamide + leuprolide and leuprolide alone, except TTCD in erectile function was shorter by a statis-

PRIMORDIUM Trial: Addition of Apalutamide to RT and an LHRH Agonist for Patients at High Risk with PSMA-PET-Positive Prostate Cancer



RT = radiation therapy;
BCR = biochemical recurrence

Hadaschik B et al. ESMO 2021;Abstract 649TiP.

Darolutamide plus androgen-deprivation therapy in patients with high-risk biochemical recurrence of prostate cancer: A phase 3, randomized, double-blind, placebo-controlled study (ARASTEP)

TPS432

Alicia K. Morgans[1], Tamim Niazi[2], Neal D. Shore[3], Jürgen E. Gschwend[4], Ashley E. Ross[5], Thomas A. Hope[6], Alex Chehrazi-Raffle[7], Stephane Supiot[8], Philippe Barthélémy[9], Andreas Røder[10], Andrea Juliana Gomes[11], Bernardo Herrera Imbroda[12], Matthieu Gratton[13], Carmen Belen Congregado Ruiz[14], Heikki Joensuu[15], Marie-Aude Le Berre[16], Iris Kuss[17], Miryana Dimova-Dobreva[18], Karim Fizazi[19]

[1]Dana-Farber Cancer Institute, Boston, Massachusetts, USA; [2]Division of Radiation Oncology, Department of Oncology, McGill University, Montreal, Quebec, Canada; [3]Carolina Urologic Research Center and AUC Urology Specialists, Myrtle Beach, South Carolina, USA; [4]Universitätsklinikum rechts der Isar, Technical University Munich, Munich, Germany; [5]Northwestern Medicine, Chicago, Illinois, USA; [6]Radiology School of Medicine, University of California at San Francisco, San Francisco, California, USA; [7]Department of Medical Oncology and Therapeutics Research, City of Hope Comprehensive Cancer Center, Duarte, California, USA; [8]Institut de Cancérologie de l'Ouest, Saint-Herblain, France; [9]University Hospital Strasbourg, France; [10]Copenhagen Prostate Cancer Center, Copenhagen University Hospital – Rigshospitalet, Copenhagen, Denmark; [11]Liga Norte Riograndense Contra O Cancer, Natal, Brazil; [12]Virgen de la Victoria Hospital, Urology Unit, Malaga, Spain; [13]Hôpital Hôtel-Dieu de Lévis, Lévis, Québec, Canada; [14]Virgen del Rocio University Hospital, Seville, Spain; [15]Orion Corporation, Espoo, Finland; [16]Bayer Healthcare SAS, Lille, France; [17]Bayer AG, Berlin, Germany; [18]Bayer Consumer Care AG, Basel, Switzerland; [19]Institut Gustave Roussy, University of Paris-Saclay, Villejuif, France.

Key inclusion criteria

- Histologically or cytologically confirmed adenocarcinoma of the prostate with BCR after primary RP followed by ART or SRT, or RP in participants who are unfit for ART or SRT, or primary RT
- High-risk BCR defined as:
  - No metastasis on conventional imaging
  - PSADT <12 months
  - PSA ≥0.2 ng/mL after RP followed by ART or SRT (or RP alone in patients unfit for ART or SRT) OR
  - PSA ≥2 ng/mL above the nadir after primary RT only
- ≥1 PSMA PET/CT-positive lesions§
- Serum testosterone >150 ng/dL
- ECOG PS 0/1

R 1:1 (N=750)

24-month treatment period*

- **Darolutamide** 600 mg PO twice daily + ADT
- **Placebo** PO twice daily + ADT

Disease progression or end of treatment

Follow-up

- **Active**
- **Long-term†**

Stratification factors

- PSADT <6 months vs ≥6 to <12 months
- Intent to treat baseline PSMA PET/CT lesions with IGRT/surgery (Yes vs No)‡
- Distant metastasis (± locoregional lesions) vs locoregional lesions only

Endpoints

Primary:
- rPFS by PSMA PET/CT assessed by BICR

Secondary:
- MFS by conventional imaging by BICR
- Time to CRPC
- Time to initiation of first subsequent systemic antineoplastic therapy
- Time to locoregional progression by PSMA PET/CT
- Time to first SSE
- OS
- PSA <0.2 ng/mL at 12 months
- Time to deterioration in FACT-P total score
- Safety
- Time to symptomatic progression
- QoL

Courtesy of Professor Karim Fizazi, MD, PhD

Year in Review: Management of Prostate Cancer

INTRODUCTION: Quality of Life

MODULE 1: PARP Inhibition (PARPi)

- Mutations that predict PARPi sensitivity
- Endocrine therapy and PARPi synergy
- Ongoing PARPi trials in metastatic hormone-sensitive prostate cancer

MODULE 2: M0 Disease

- PRESTO; EMBARK

MODULE 3: Metastatic Hormone-Sensitive Prostate Cancer

- De novo versus recurrent
- PTEN deficiency – CAPItello-281

MODULE 4: Radiopharmaceuticals

- Radium-223
- ^{177}Lu-PSMA-617; ^{177}Lu-PNT2002 – SPLASH

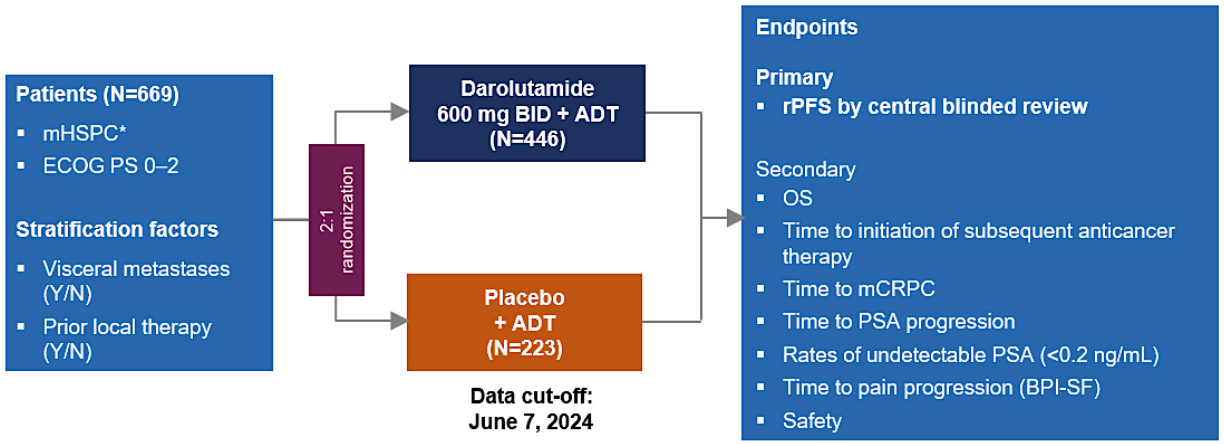
MODULE 5: Other Novel Investigational Approaches for Metastatic Castration-Resistant Prostate Cancer

- CYP11A1 inhibition – Opevesostat
- EZH2 inhibition – Mevrometostat

RTP Year in Review 2025

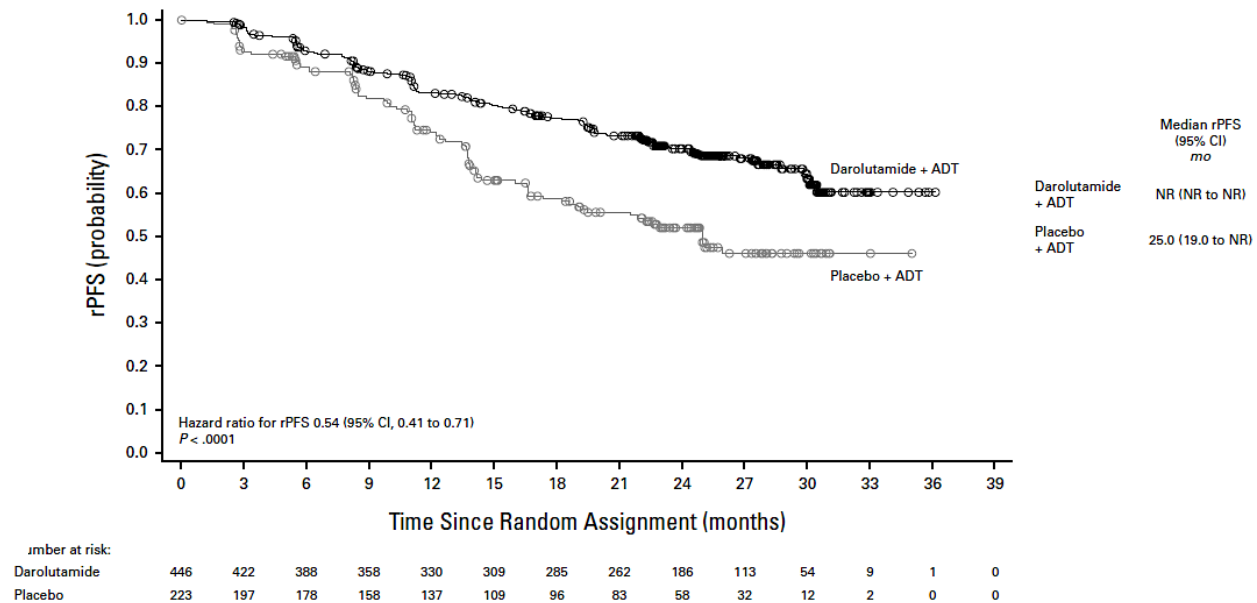
Darolutamide in Combination With Androgen-Deprivation Therapy in Patients With Metastatic Hormone-Sensitive Prostate Cancer From the Phase III ARANOTE Trial

Fred Saad, MD[1]; Egils Vjaters, MD[2]; Neal Shore, MD, FACS[3]; David Olmos, MD, PhD[4]; Nianzeng Xing, MD[5]; Andrea Juliana Pereira de Santana Gomes, MD[6]; Augusto Cesar de Andrade Mota, MD, PhD[7]; Pamela Salman, MD, PhD[8]; Mindaugas Jievaltas, MD, PhD[9]; Albertas Ulys, MD, PhD[10]; Maris Jakubovskis, MD[11]; Evgeny Kopyltsov, MD, PhD[12]; Weiqing Han, MD, PhD[13]; Liina Nevalaita, PhD[14]; Isabella Testa, MD[15]; Marie-Aude Le Berre, MSc[16]; Iris Kuss, MD[17]; and Kunhi Parambath Haresh, MD[18]



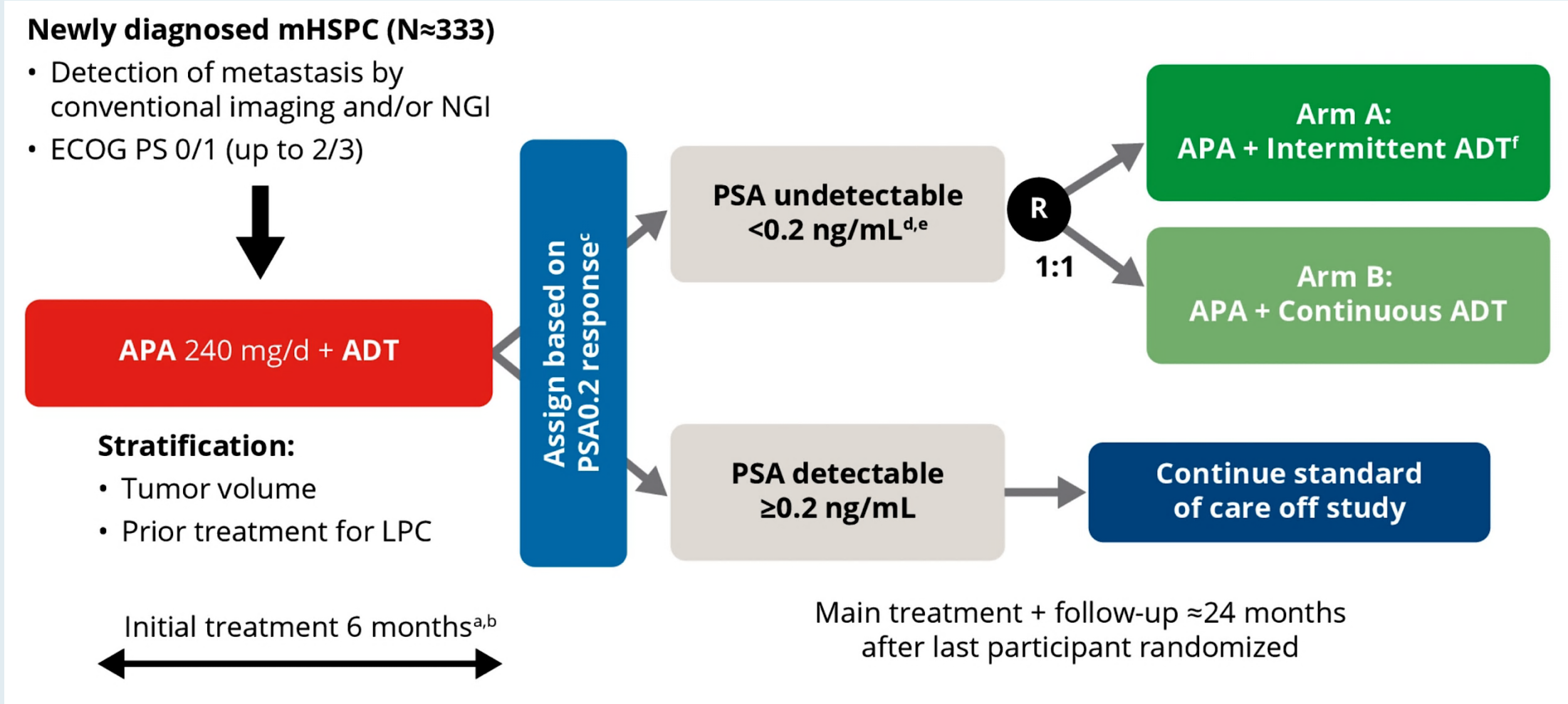
ClinicalTrials.gov: NCT04736199

*Metastatic disease confirmed by conventional imaging method as a positive ^{99m}Tc-phosphonate bone scan or soft tissue/visceral metastases on contrast-enhanced abdominal/pelvic/chest CT or MRI scan, assessed by central review.
BPI-SF, Brief Pain Inventory-Short Form.



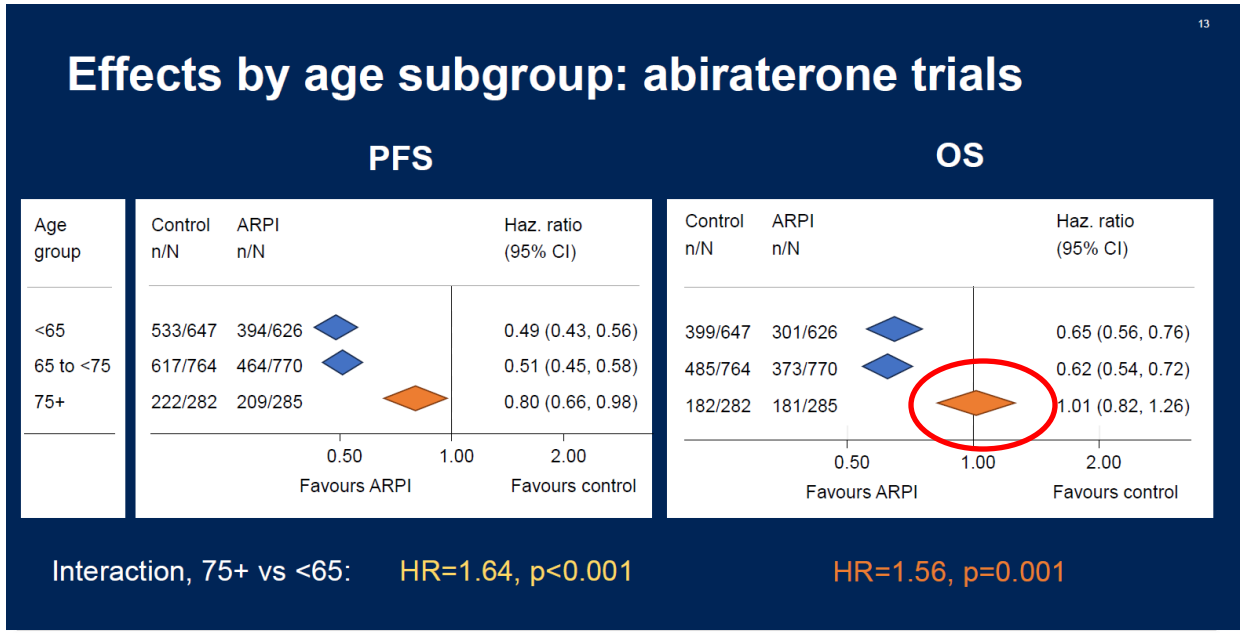
Courtesy of Professor Karim Fizazi, MD, PhD

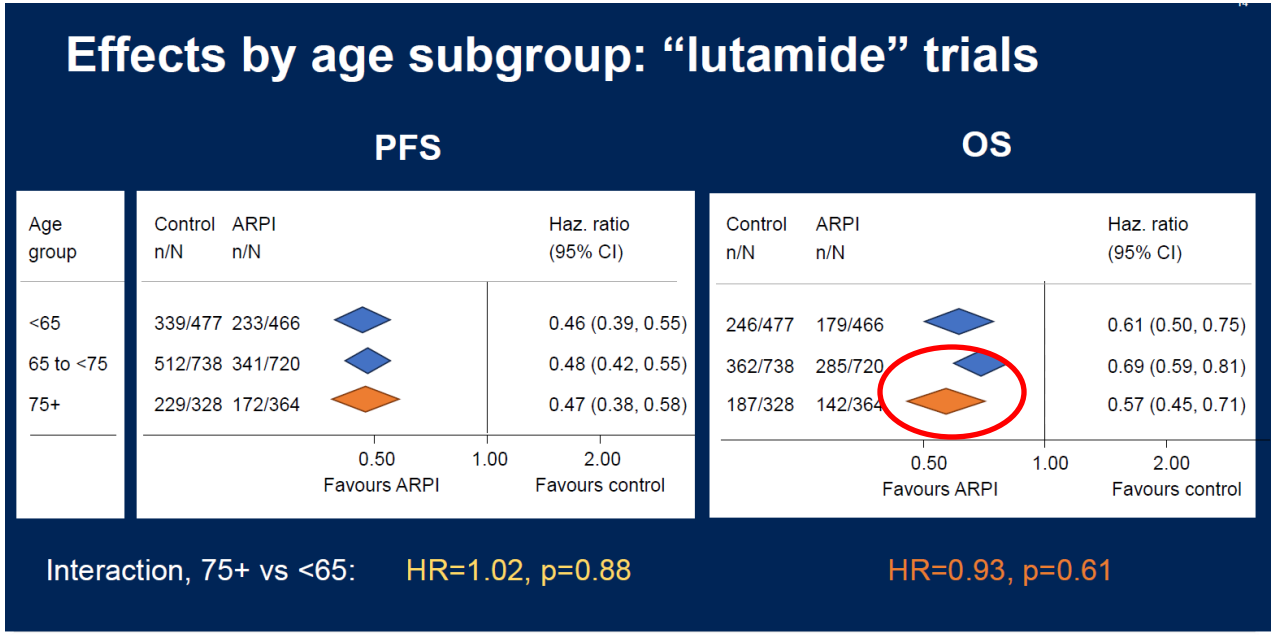
LIBERTAS: A Phase III Study of Apalutamide with Intermittent versus Continuous ADT for mHSPC



Azad A et al. Genitourinary Cancers Symposium 2024;Abstract TPS236.

« Lutamides » to be preferred over Abiraterone in older patients?





Courtesy of Professor Karim Fizazi, MD, PhD

EUROPEAN UROLOGY ONCOLOGY 7 (2024) 906–913

available at www.sciencedirect.com
journal homepage: euoncology.europeanurology.com

European Association of Urology

Testosterone Recovery for Relugolix Versus Leuprolide in Men with Advanced Prostate Cancer: Results from the Phase 3 HERO Study

Ronald Tutrone[a,*], *Fred Saad*[b], *Daniel J. George*[c], *Bertrand Tombal*[d], *James L. Bailen*[e], *Michael S. Cookson*[f], *Daniel R. Saltzstein*[g], *Sarah Hanson*[h], *Bruce Brown*[i], *Sophia Lu*[i], *Mark Fallick*[i], *Neal D. Shore*[j]

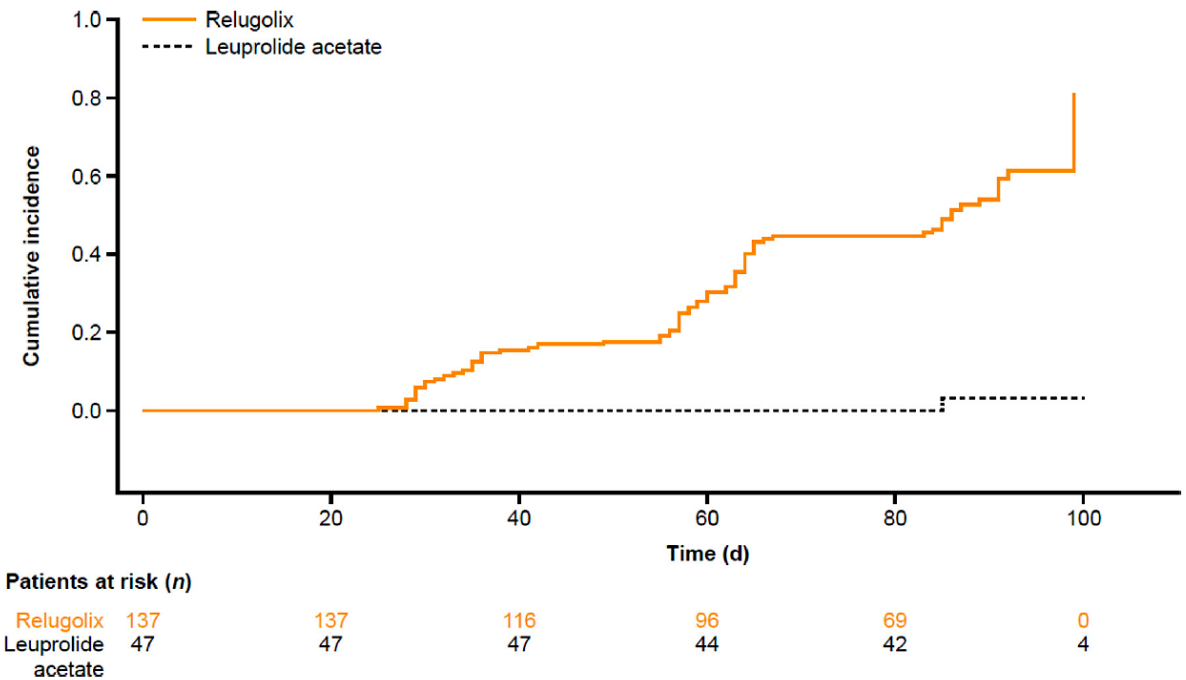


Fig. 1 – Cumulative incidence of time to testosterone recovery (>280 ng/dl; modified intent-to-treat population). The data cutoff date was December 10, 2019. Patient assessments were performed at 30-, 60-, and 90 d (±7 d) following treatment discontinuation. For the 90-d assessment, some patient assessments were delayed past 100 d. A total of 50 patients had their study visit at >90 d (relugolix, *n* = 45 [33%]; leuprolide acetate, *n* = 5 [11%]).

Courtesy of Professor Karim Fizazi, MD, PhD

THE JOURNAL of UROLOGY®
www.auajournals.org/journal/juro

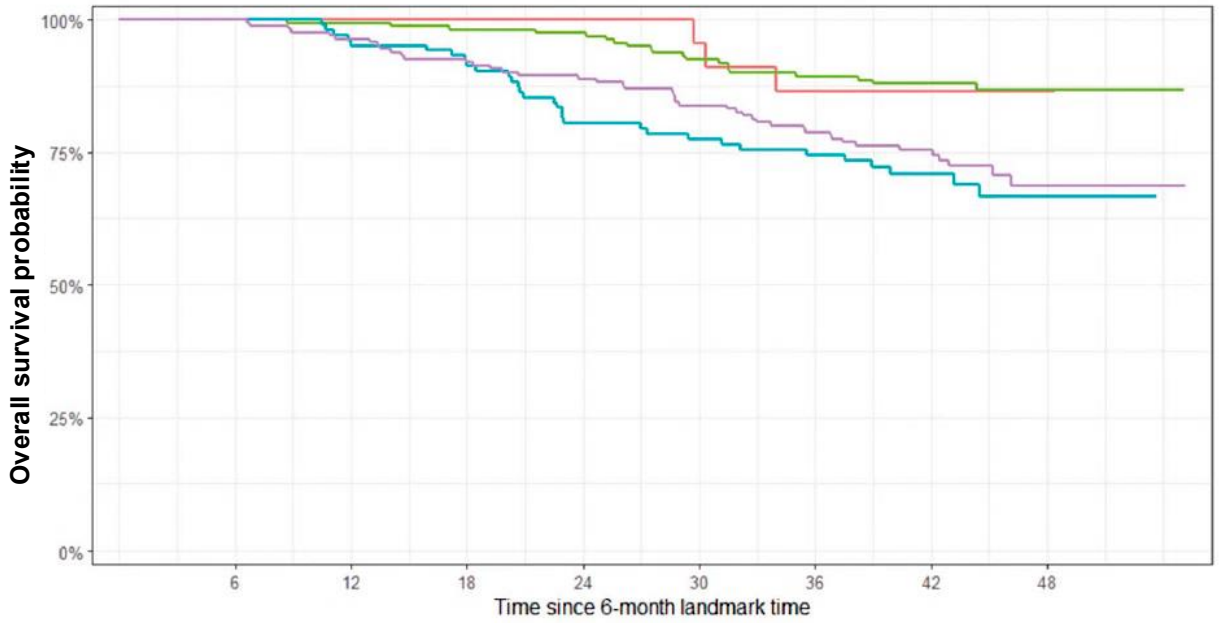
Original Research

Randomized Controlled Trials

JU Insight

Early Prostate-Specific Antigen Response by 6 Months Is Predictive of Treatment Effect in Metastatic Hormone Sensitive Prostate Cancer: An Exploratory Analysis of the TITAN Trial

Soumyajit Roy, Yilun Sun, Kim N. Chi, et al.



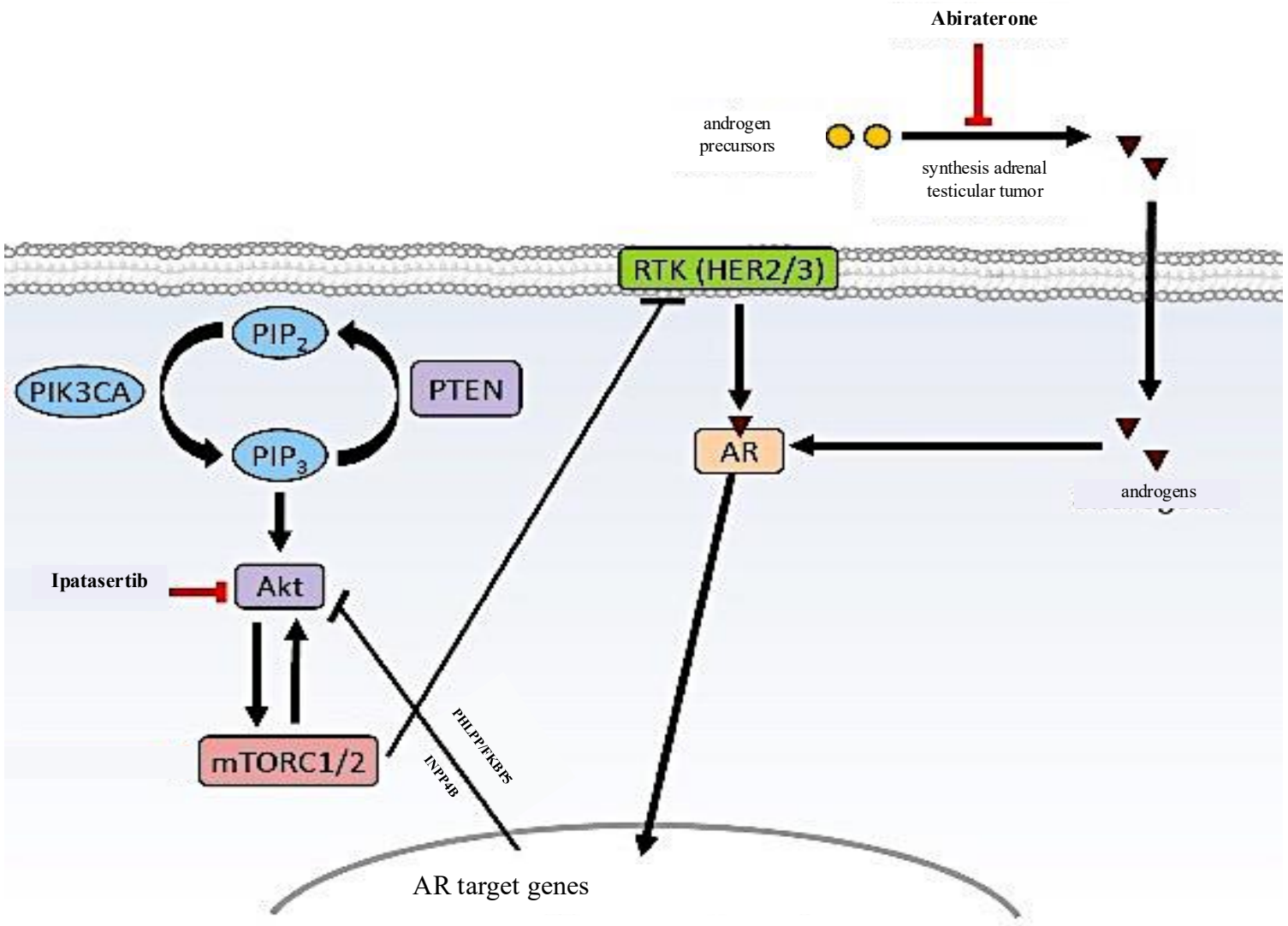
At Risk

<0.02, Placebo	22	22	22	22	21	18	6	2
<0.02, Apalutamide	159	157	155	154	146	140	99	34
0.02-0.2, Placebo	102	97	93	81	78	74	45	12
0.02-0.2, Apalutamide	162	156	146	141	133	124	78	17

Depth of PSA response	Treatment	Overall survival estimates at 4-years (95% CI)
<0.02 ng/mL	ADT alone	86% (73-100)
	ADT plus Apalutamide	87% (81-92)
0.02 to 0.2 ng/mL	ADT alone	67% (57-78)
	ADT plus Apalutamide	69% (61-78)

Courtesy of Professor Karim Fizazi, MD, PhD

Targeting both the Akt and the AR pathways



Courtesy of Professor Karim Fizazi, MD, PhD

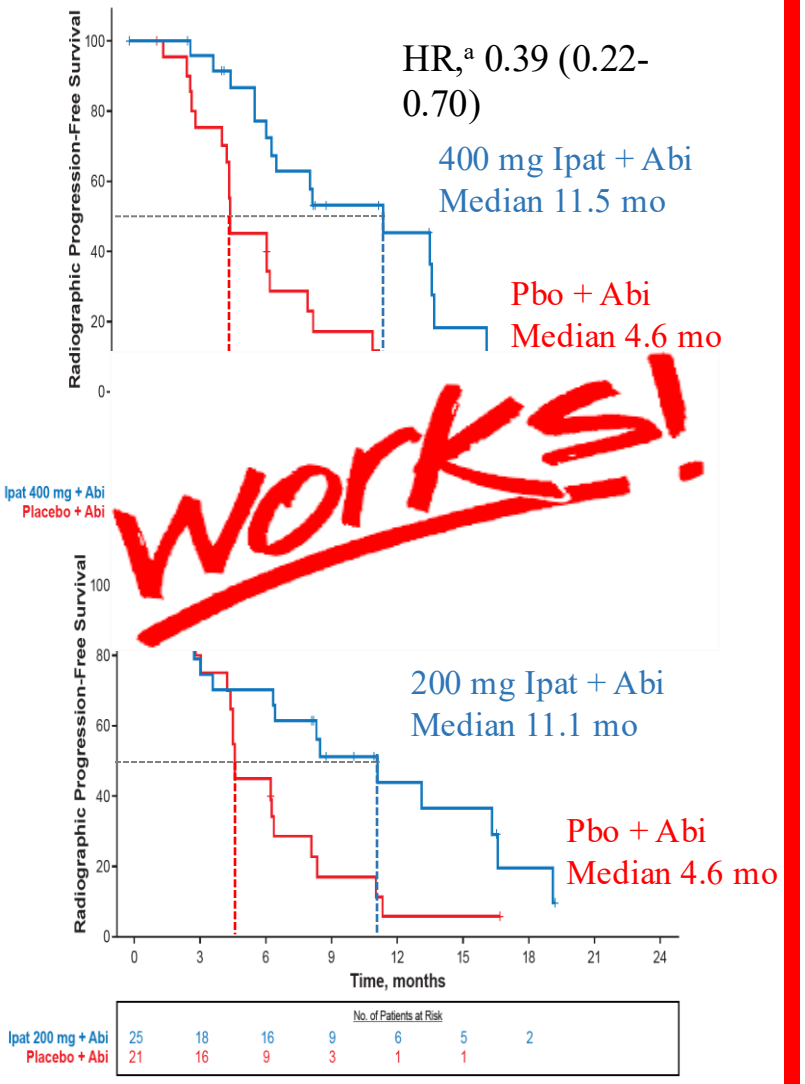
Abiraterone +/- Ipatasertib (Akt inhibitor): PFS

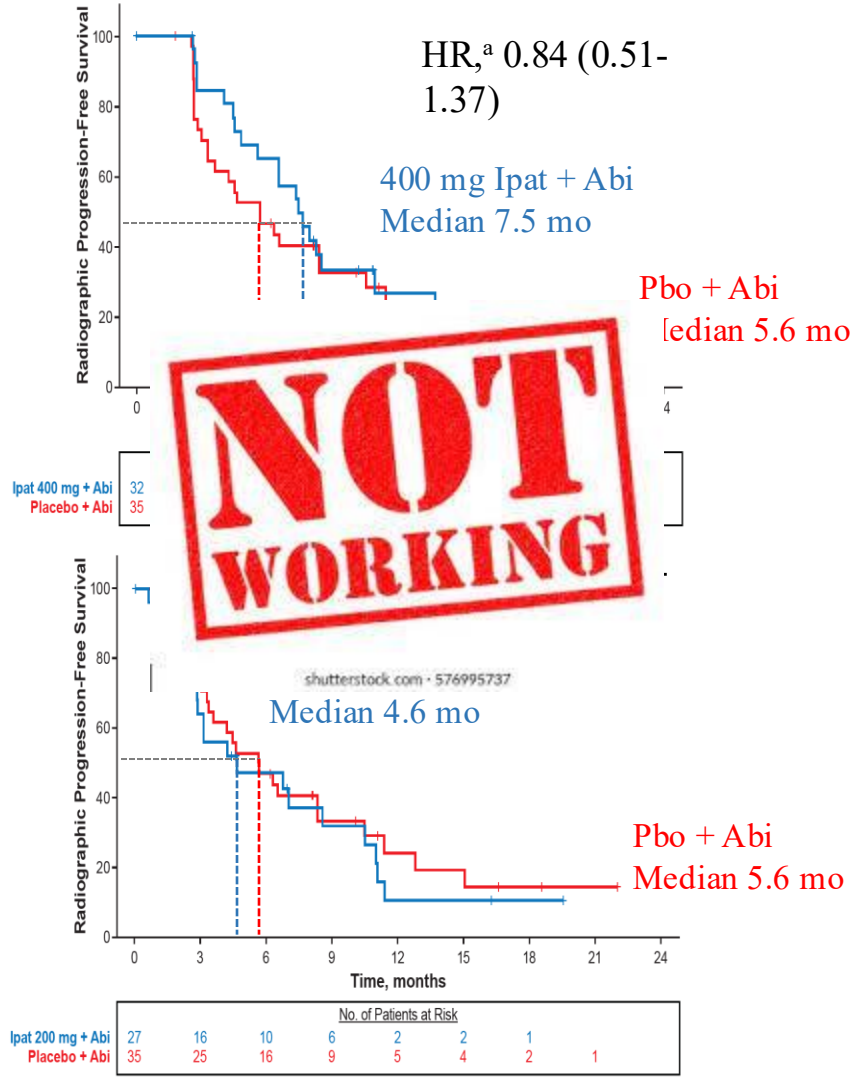
PTEN loss

PTEN non-loss

400 mg Ipatasertib

200 mg Ipatasertib





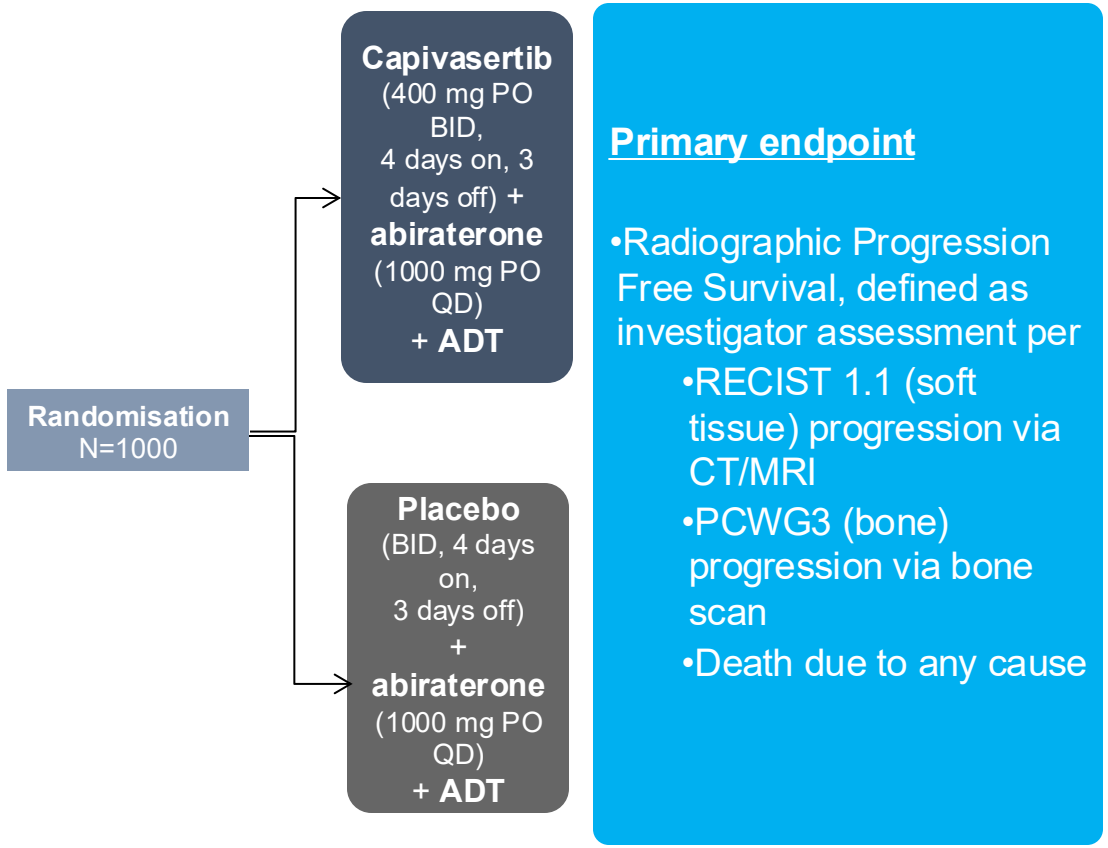
de Bono et al, Ipatasertib, ESMO 2016

Courtesy of Professor Karim Fizazi, MD, PhD

CAPItello-281: A Phase III study of capivasertib + abiraterone vs. placebo + abiraterone for patients with de novo mHSPC characterised by PTEN loss

Study population

- *De novo* metastatic prostate cancer
- PTEN deficiency determined by IHC (central testing)



Primary endpoint

- Radiographic Progression Free Survival, defined as investigator assessment per
  - RECIST 1.1 (soft tissue) progression via CT/MRI
  - PCWG3 (bone) progression via bone scan
  - Death due to any cause

Courtesy of Professor Karim Fizazi, MD, PhD

(NCT04493853)

CAPItello-281: A Phase III study of capivasertib + abiraterone vs. placebo + abiraterone for patients with de novo mHSPC characterised by PTEN loss

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

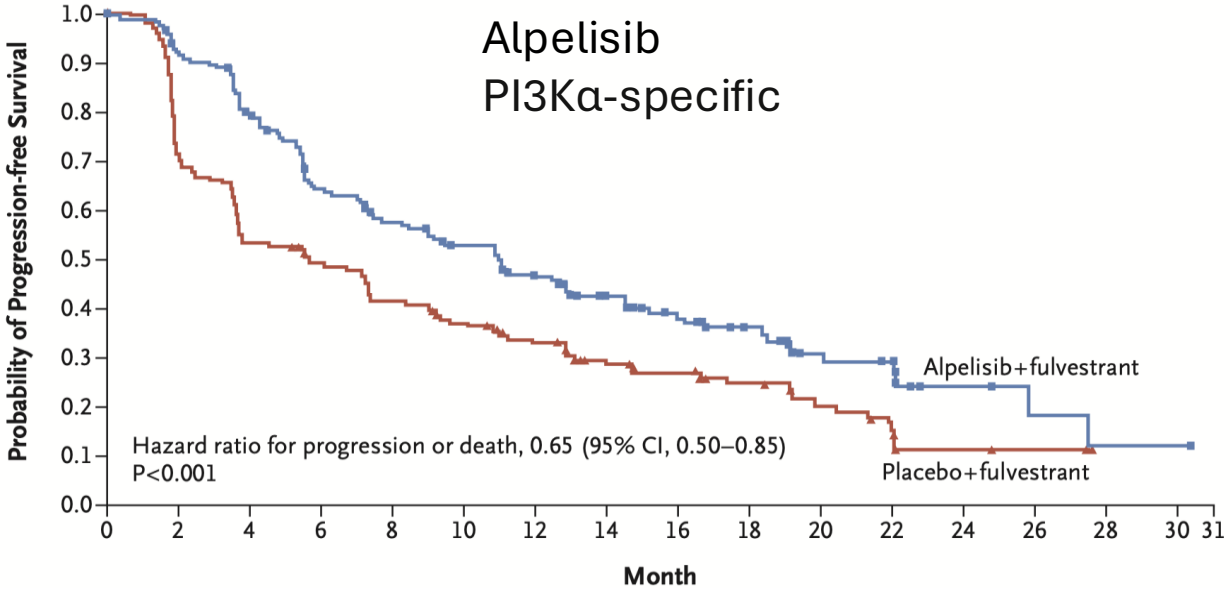
PUBLISHED 25 November 2024

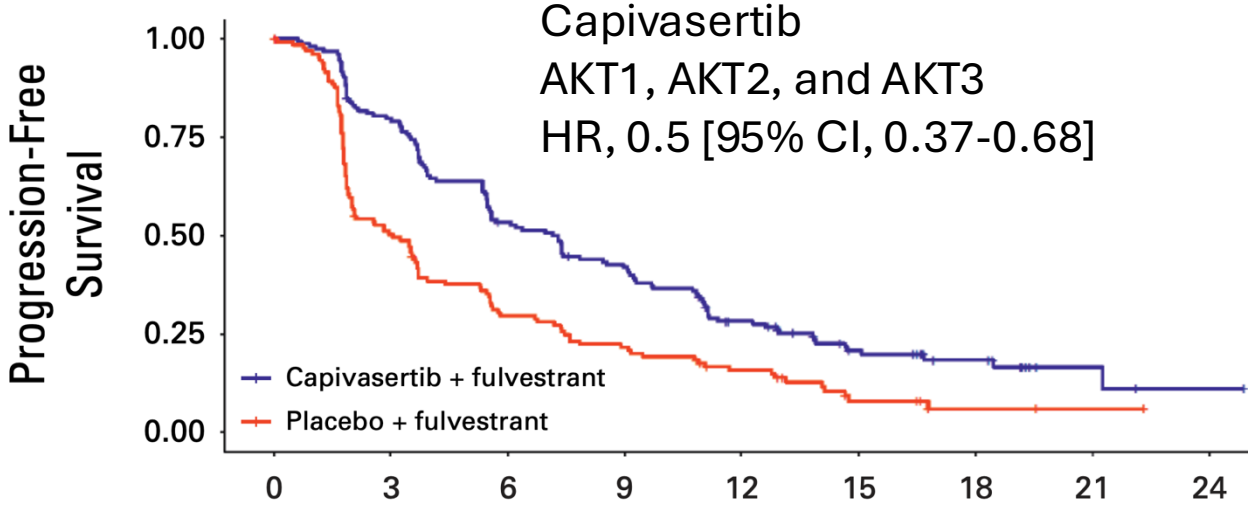
First and only AKT inhibitor combination to demonstrate benefit in this specific subtype of prostate cancer

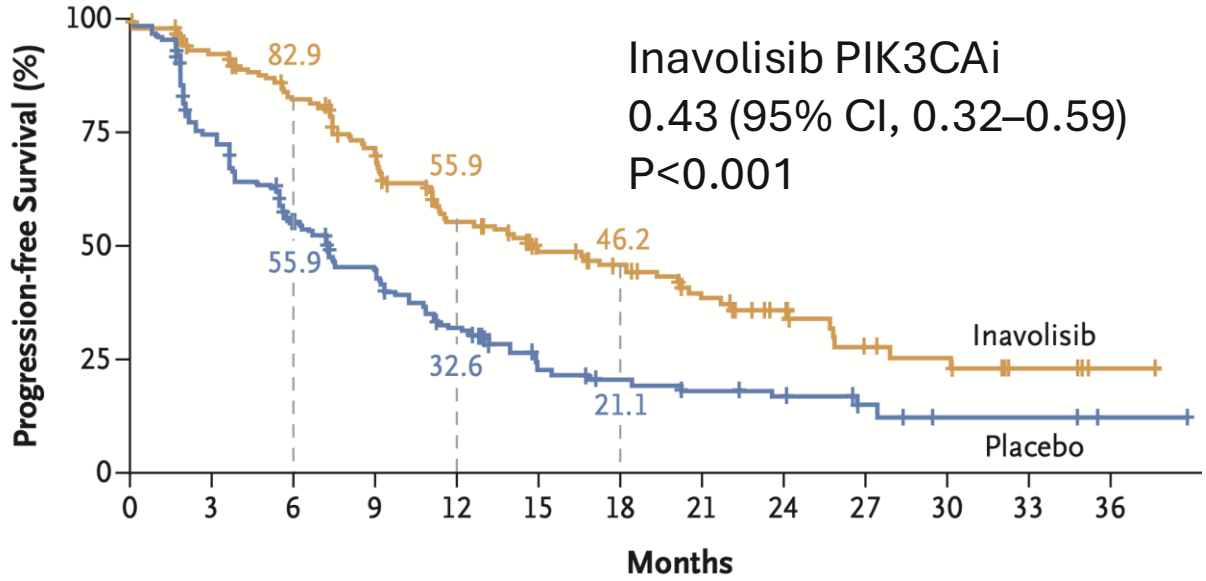
Courtesy of Professor Karim Fizazi, MD, PhD

(NCT04493853)

PIK3CA/PTEN/AKT Trials in Breast Cancer







<u>Toxicities:</u>

Neutropenia, hyperglycemia, stomatitis, diarrhea, rash

F Andre et al. NEJM 2019; M Oliveira et al. Lancet Oncology 2024; N Turner et al. NEJM 2024

Courtesy of Rebecca A Dent, MD, MSc

Year in Review: Management of Prostate Cancer

INTRODUCTION: Quality of Life

MODULE 1: PARP Inhibition (PARPi)

- Mutations that predict PARPi sensitivity
- Endocrine therapy and PARPi synergy
- Ongoing PARPi trials in metastatic hormone-sensitive prostate cancer

MODULE 2: M0 Disease

- PRESTO; EMBARK

MODULE 3: Metastatic Hormone-Sensitive Prostate Cancer

- De novo versus recurrent
- PTEN deficiency – CAPItello-281

MODULE 4: Radiopharmaceuticals

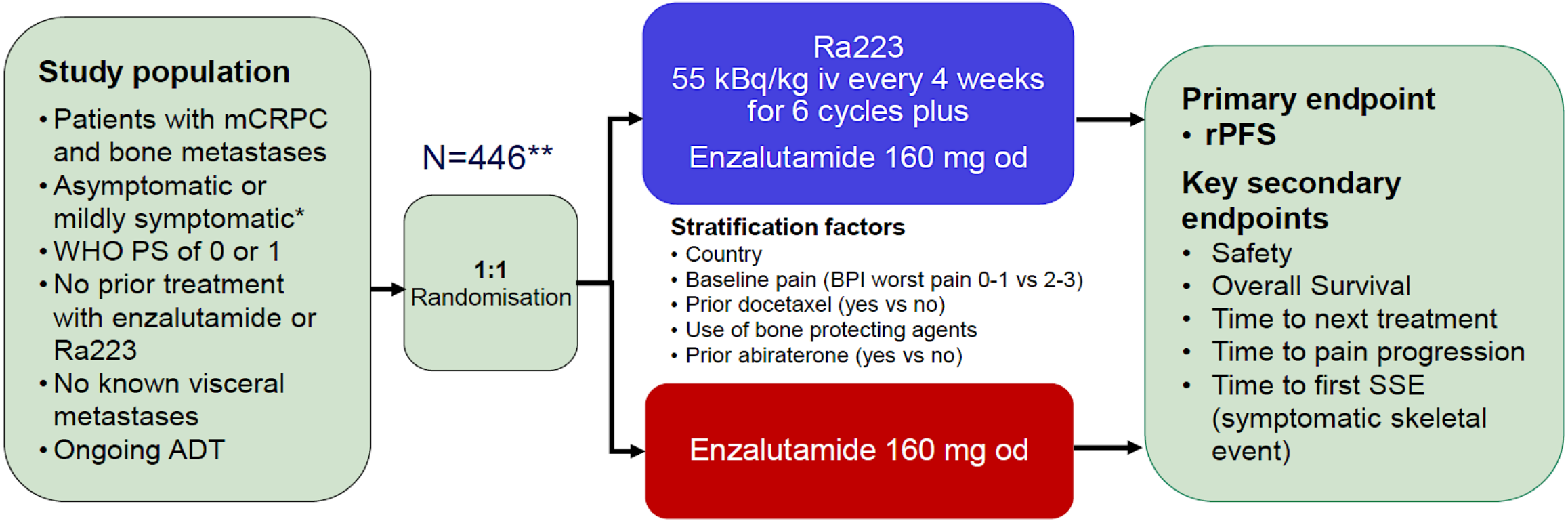
- Radium-223
- ^{177}Lu-PSMA-617; ^{177}Lu-PNT2002 – SPLASH

MODULE 5: Other Novel Investigational Approaches for Metastatic Castration-Resistant Prostate Cancer

- CYP11A1 inhibition – Opevesostat
- EZH2 inhibition – Mevrometostat

RTP Year in Review 2025

PEACE-3 trial: Enza +/- Radium^{223} in mCRPC



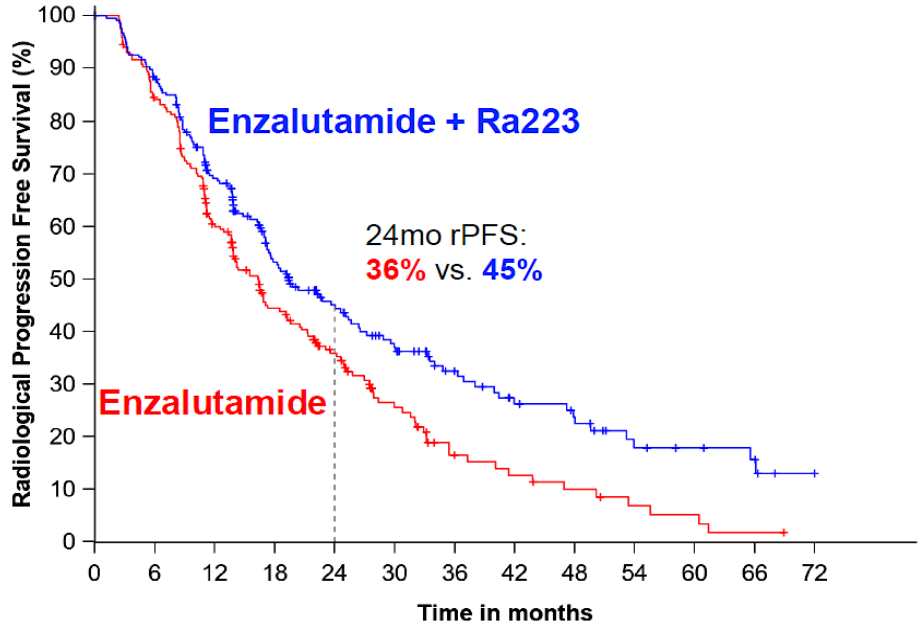
Use of bone protecting agents (BPA) made mandatory
(after inclusion of 119 patients)

Gillessen S, et al. *ESMO* 2024; Abstract LBA1.

Courtesy of Emmanuel S Antonarakis, MD

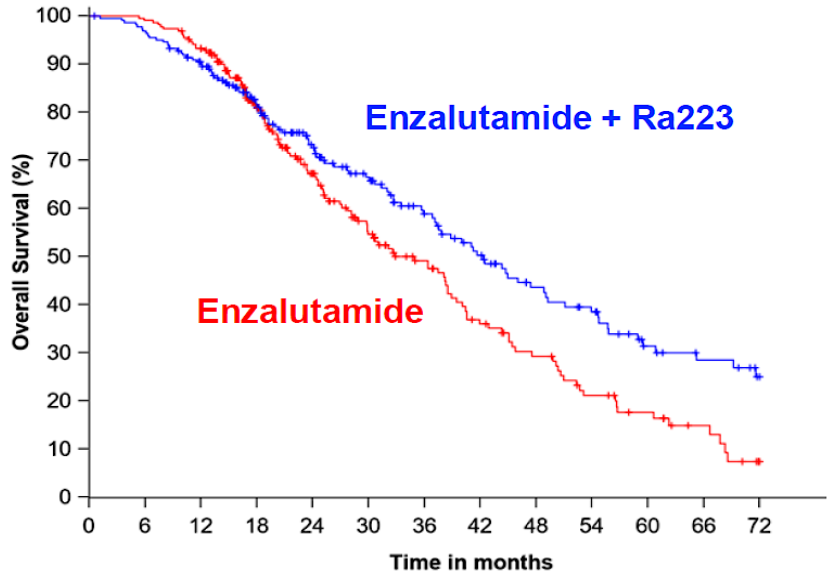
PEACE-3 trial: Enza +/- Radium^{223} in mCRPC

Primary endpoint: rPFS



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

Overall Survival at interim analysis



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

Gillessen S, et al. *ESMO* 2024; Abstract LBA1.

Courtesy of Emmanuel S Antonarakis, MD

PEACE-3 trial: Adverse Events

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

Gillessen S, et al. *ESMO* 2024; Abstract LBA1.

Courtesy of Emmanuel S Antonarakis, MD

Conclusions

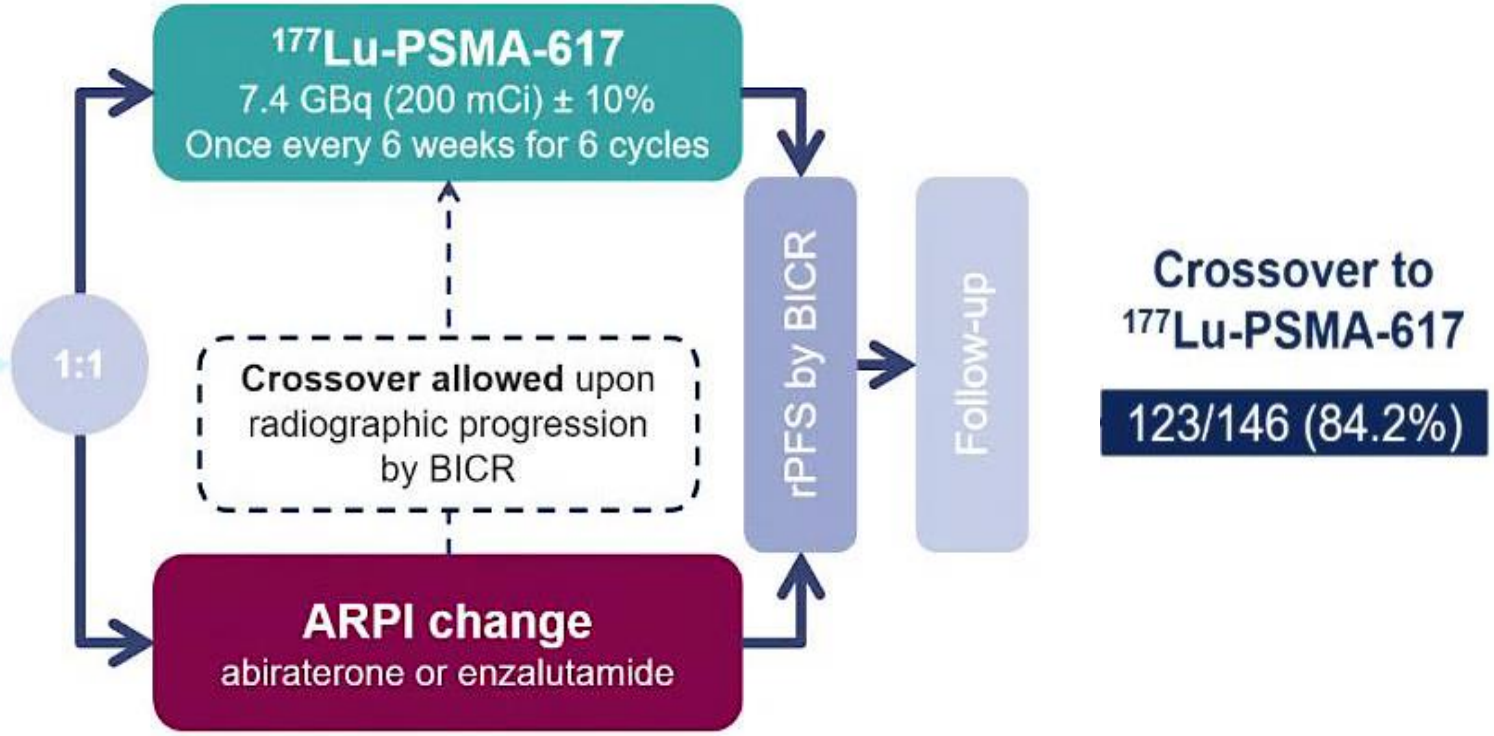
- PEACE-3 showed a statistically significant and clinically meaningful OS advantage with Enza/Rad^{223} vs. Enza alone
- Conversely, there is no demonstrable OS benefit with use of ^{177}Lu-PSMA therapies in the pre-docetaxel mCRPC space
- Safety of Enza/Rad^{223} seemed reasonable, with increased grade-3 fatigue, anemia, neutropenia, and weight loss
- Enza + Rad^{223} (+ bone protection) may be a new standard for first-line bone-dominant mCRPC without prior ARPI treatment

Courtesy of Emmanuel S Antonarakis, MD

PSMAfore: ^{177}Lu-PSMA-617 in pre-taxane mCRPC

Eligible adults

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



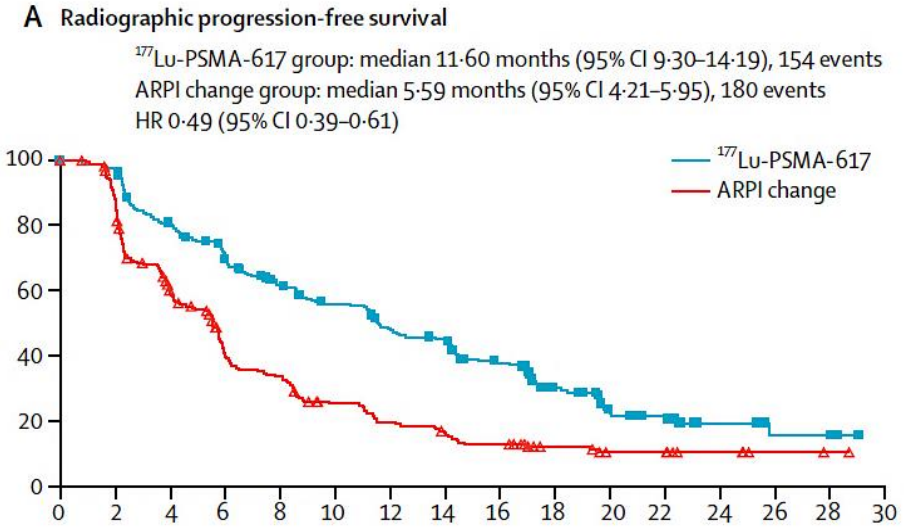
Stratification factors

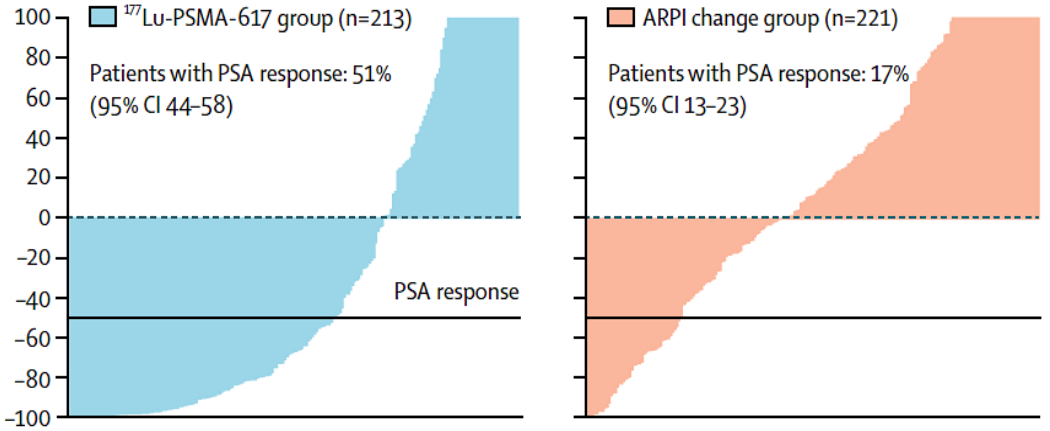
- Prior ARPI setting (castration-resistant vs hormone-sensitive)
- BPI-SF worst pain intensity score (0–3 vs > 3)

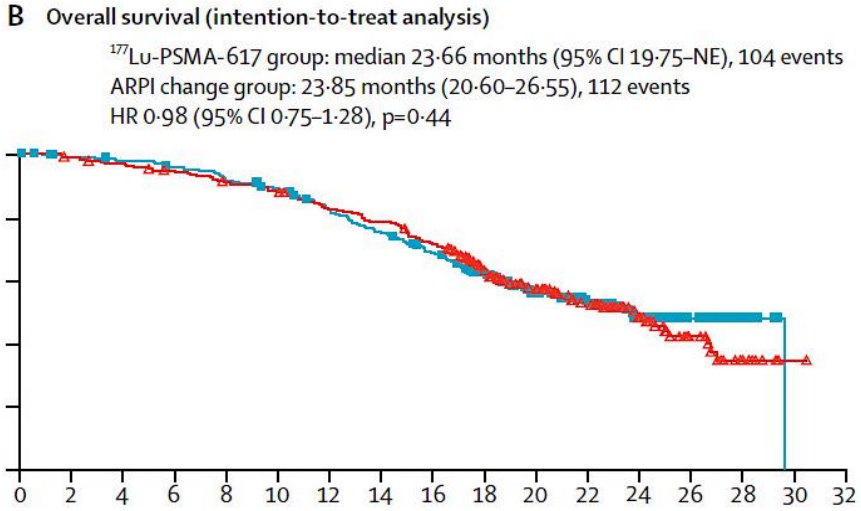
Morris MJ, et al. *Lancet* 2024; 404: 1227-39.

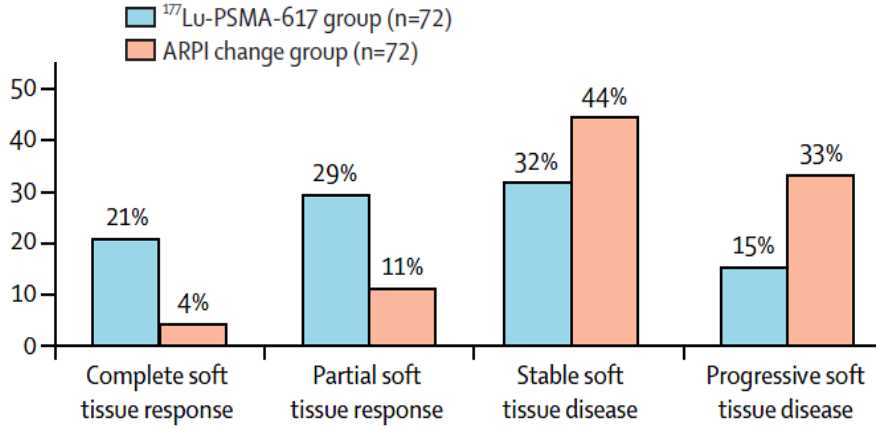
Courtesy of Emmanuel S Antonarakis, MD

PSMAfore: ^{177}Lu-PSMA-617 vs. ARPI switch









Morris MJ, et al. *Lancet* 2024; 404: 1227-39.

Courtesy of Emmanuel S Antonarakis, MD

PSMAfore: Adverse Events

	^{177}Lu-PSMA-617 group (n=227)		ARPI change group (n=232)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Any	224 (99%)	81 (36%)*	226 (97%)	112 (48%)*
Occurring in >10% of patients				
Dry mouth	131 (58%)†	2 (1%)	6 (3%)†	0
Asthenia	74 (33%)	2 (1%)	67 (29%)	8 (3%)
Nausea	72 (32%)	0	27 (12%)	1 (<1%)
Anaemia	61 (27%)	14 (6%)	44 (19%)	16 (7%)
Fatigue	53 (23%)	1 (<1%)	59 (25%)	4 (2%)
Constipation	50 (22%)	1 (<1%)	33 (14%)	0
Decreased appetite	49 (22%)	0	43 (19%)	1 (<1%)
Arthralgia	45 (20%)	0	54 (23%)	1 (<1%)
Diarrhoea	38 (17%)	0	21 (9%)	1 (<1%)
COVID-19	36 (16%)	1 (<1%)	27 (12%)	1 (<1%)
Back pain	31 (14%)	3 (1%)	46 (20%)	6 (3%)
Vomiting	26 (11%)	0	11 (5%)	0
Oedema peripheral	19 (8%)	0	28 (12%)	0
Pain in extremity	17 (7%)	1 (<1%)	25 (11%)	1 (<1%)
Weight loss	15 (7%)	1 (<1%)	32 (14%)	3 (1%)

Morris MJ, et al. *Lancet* 2024; 404: 1227-39.

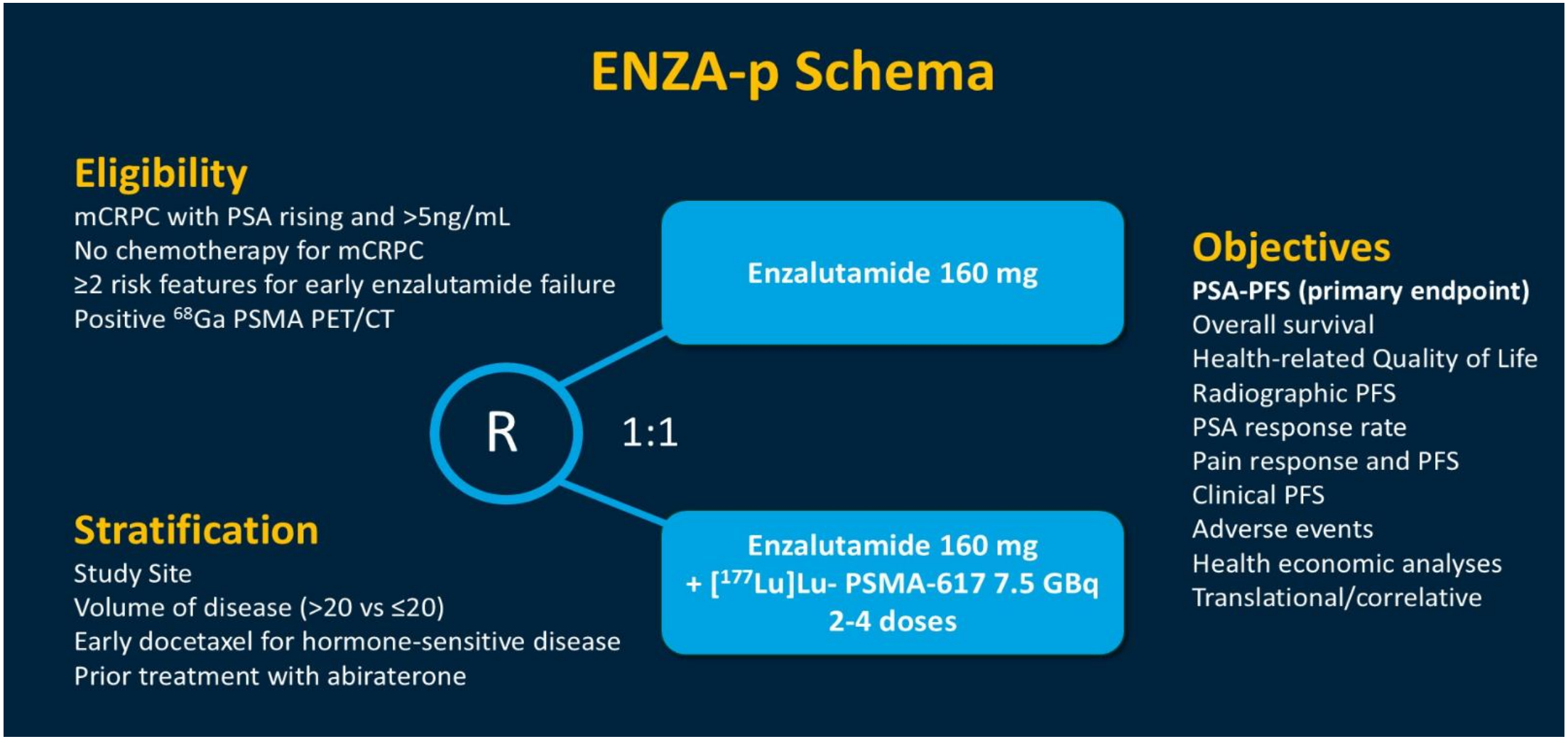
Courtesy of Emmanuel S Antonarakis, MD

Conclusions

- PSMAfore is the first randomized Phase 3 trial to assess ^{177}Lu-PSMA-617 in the pre-taxane mCRPC space
- In this setting, ^{177}Lu-PSMA-617 improved rPFS (but not OS) when compared to ARPI switch in patients with one prior ARPI
- The toxicity profile of ^{177}Lu-PSMA-617 is favorable, but includes dry mouth, nausea, diarrhea and anemia
- On 3/28/2025, based on this trial, the FDA expanded the indication for ^{177}Lu-PSMA-617 into the pre-taxane mCRPC setting

Courtesy of Emmanuel S Antonarakis, MD

Enza-P trial: Enza +/- ^{177}Lu-PSMA-617 in mCRPC

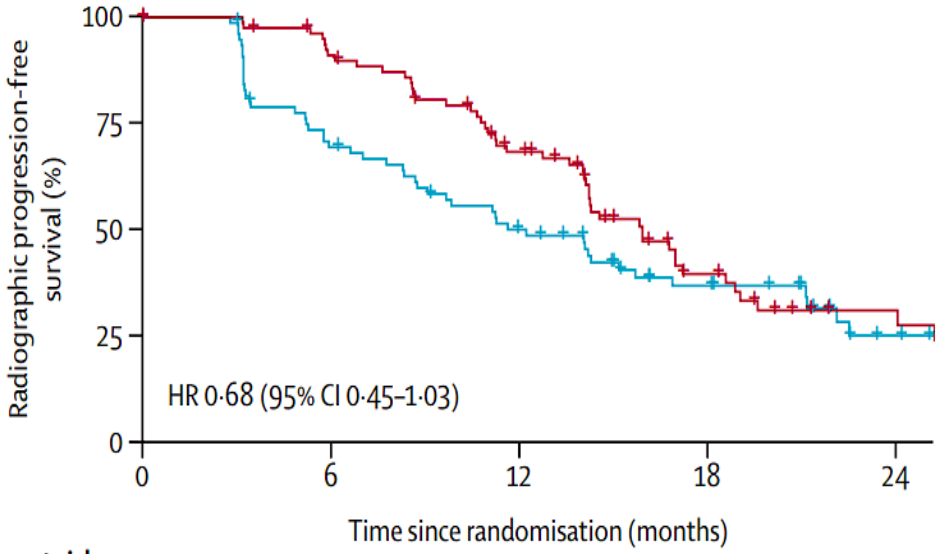


Emmett L, et al. *Lancet Oncol* 2025; 26: 291-9.

Courtesy of Emmanuel S Antonarakis, MD

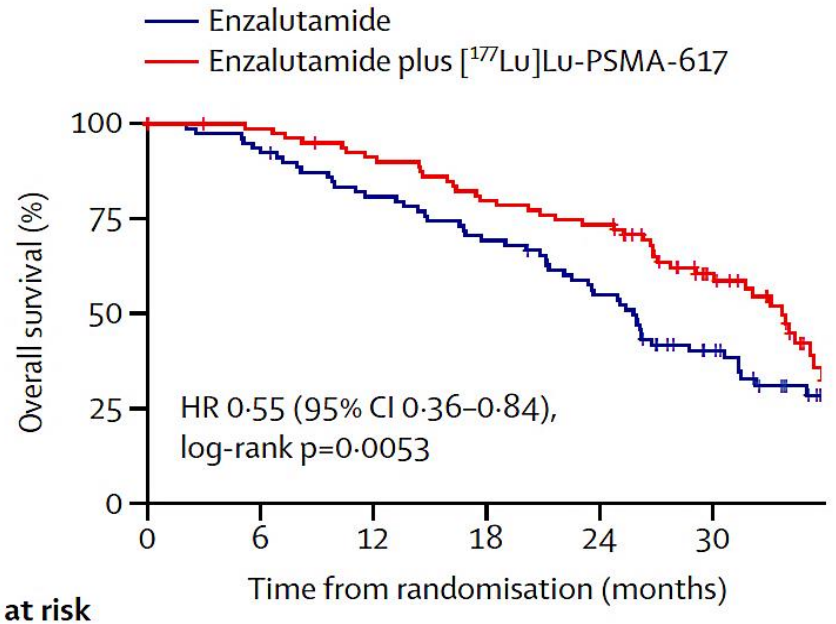
Enza-P trial: Enza +/- ^{177}Lu-PSMA-617 in mCRPC

rPFS



Number at risk (number censored)					
[^{177}Lu]Lu-PSMA-617	83 (0)	71 (5)	48 (11)	20 (22)	9 (29)
Enzalutamide	79 (0)	52 (4)	35 (7)	19 (15)	6 (24)

Survival



Number at risk (number censored)						
Enzalutamide group	79 (0)	74 (0)	63 (1)	54 (1)	42 (2)	24 (9)
Enzalutamide plus Lu-PSMA-617 group	83 (0)	79 (3)	72 (4)	63 (4)	58 (4)	33 (20)

Emmett L, et al. *Lancet Oncol* 2025; 26: 291-9.

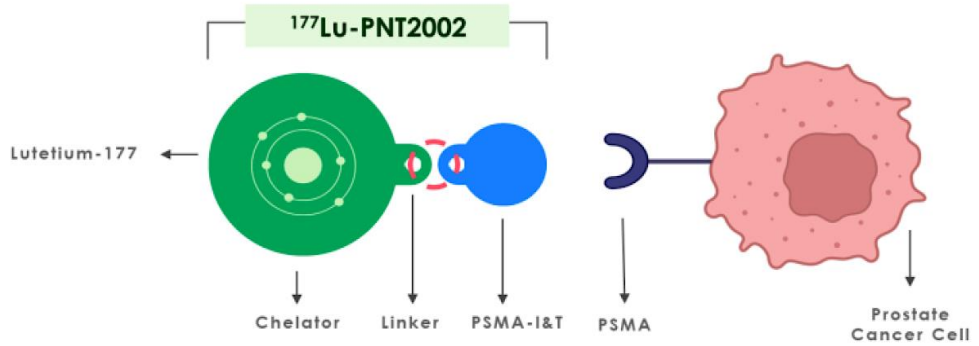
Courtesy of Emmanuel S Antonarakis, MD

Conclusions

- Enza-P is the first study to show an OS advantage using ^{177}Lu-PSMA-617 (w/ Enza) in the pre-taxane mCRPC setting
- Relative to Enza alone, ^{177}Lu-PSMA + Enza led to improved rPFS, improved deterioration-free survival, and improved pain/fatigue
- Adverse events were dry mouth/eyes, nausea, cytopenias
- The combination of Enza + ^{177}Lu-PSMA-617 is <u>not</u> currently FDA approved in the pre-taxane mCRPC setting
- Phase 3 trials of this combination are needed

Courtesy of Emmanuel S Antonarakis, MD

SPLASH: ^{177}Lu-PNT2002 vs. ARPI switch



Screening

Eligibility criteria

- Progressive mCRPC
- Progressed on previous treatment with one ARPI
- **PSMA-avid PET**
- ECOG performance status 0 to 1
- Taxane for CSPC allowed (>1 year prior to consent)

Randomization 2:1

^{177}Lu-PNT2002
6.8 GBq (±10%) every 8 weeks for up to 4 cycles

Alternate ARPI
enzalutamide or abiraterone

Stratification variables
- Prior taxane treatment for CSPC: Y/N
- Prior use of bisphosphonates: Y/N
- Metastatic status on prior ARPI: M0/M1
- Measurable disease at study entry: Y/N

Radiographic Progression

Crossover to ^{177}Lu-PNT2002
77/91 (84.6%)

^{177}Lu-PNT2002

Crossover

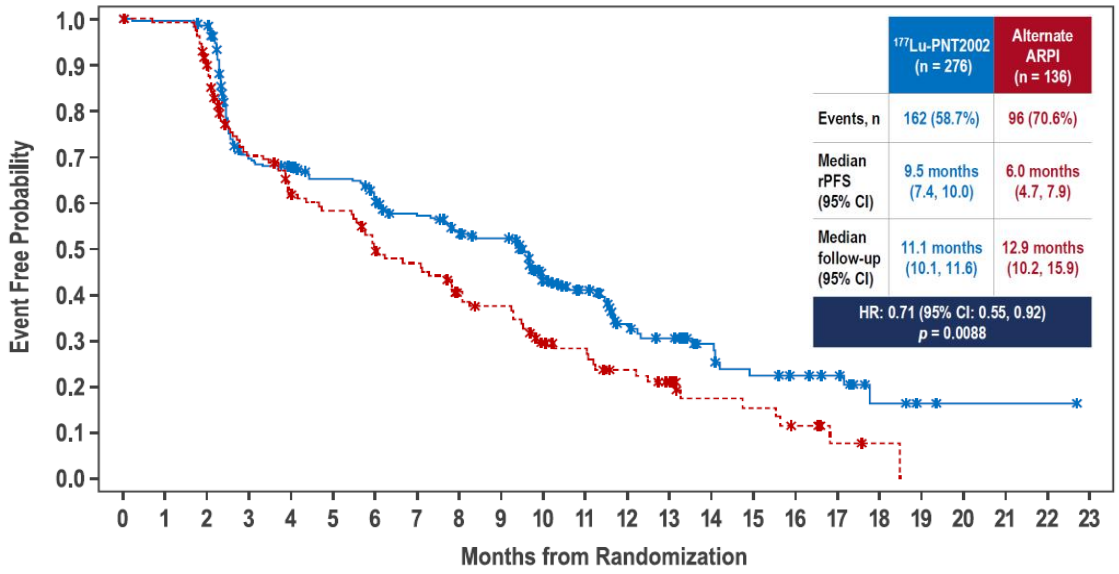
Endpoints
- rPFS
- OS
- ORR
- Time to skeletal event
- PSA50 response
- bPFS
- HRQoL
- Safety

Sartor O, et al. *ESMO 2024*; Abstract LBA65.

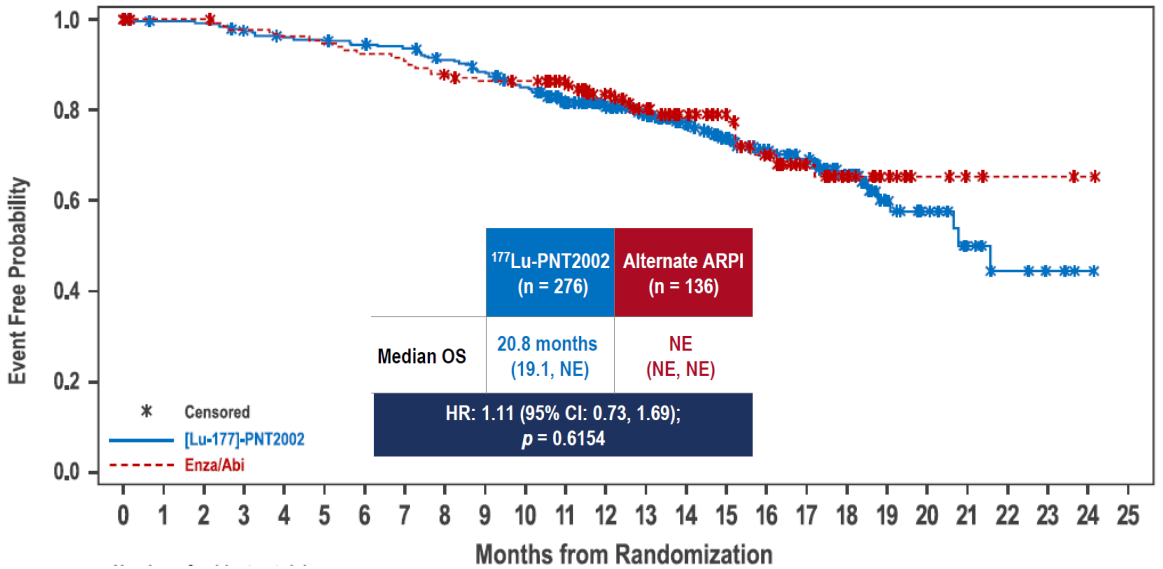
Courtesy of Emmanuel S Antonarakis, MD

SPLASH: ^{177}Lu-PSMA-PNT2002 vs. ARPI switch

Primary Endpoint - rPFS:



1st Interim OS: Intent-to-Treat Analysis



Sartor O, et al. *ESMO 2024*; Abstract LBA65.

Courtesy of Emmanuel S Antonarakis, MD

Head-to-head comparison: SPLASH vs. PSMAfore

Efficacy Endpoints	PSMAfore (N=468)		SPLASH (N=412)	
	Lu177 (n=234)	Control (n=234)	Lu177 (n=276)	Control (n=136)
rPFS, median	11.6 mo *	5.6 mo *	9.5 mo	6.0 mo
HR (95% CI)	HR 0.49 (0.39–0.61)		HR 0.71 (0.55–0.92)	
OS, median	23.7 mo *	23.8 mo *	20.8 mo	Non Estimable
HR (95% CI)	HR 0.98 (0.72–1.14)		HR 1.11 (0.73–1.69)	
PSA response	51%	17%	36%	15%
ORR	50%	15%	38%	12%

* In the PSMAfore trial:

- Primary data analysis of median rPFS: 9.3 mo in the Lu177 group vs. 5.6 mo in the control group (HR=0.41, 95% CI=0.2–0.56)
- Second interim analysis of median rPFS: 12.0 months in the Lu177 group vs. 5.6 months in the control group (HR=0.43, 95% CI=0.33–0.54)
- First interim analysis of median OS: 19.2 months in the Lu177 group vs 19.7 in the control group (HR=1.16, 95%=0.83–1.64)

Sartor O, et al. *ESMO 2024*; Abstract LBA65.
Morris MJ, et al. *Lancet* 2024; 404: 1227-39.

Courtesy of Emmanuel S Antonarakis, MD

Conclusions

- SPLASH (^{177}Lu-PNT2002) showed a more modest rPFS benefit vs. ARPI switch compared to PSMAfore (^{177}Lu-PSMA-617)
- In SPLASH: ^{177}Lu-PSMA was given at 6.8 GBq (184 mCi) x 4
- In PSMAfore: ^{177}Lu-PSMA was given at 7.4 GBq (184 mCi) x 6
- Dose intensity was higher in PSMAfore, leading to better PFS?
- Unclear if ^{177}Lu-PNT2002 will seek approval in 1st-L mCRPC
- ^{177}Lu-PNT2002 <u>not</u> currently FDA approved in any indication

Courtesy of Emmanuel S Antonarakis, MD

Year in Review: Management of Prostate Cancer

INTRODUCTION: Quality of Life

MODULE 1: PARP Inhibition (PARPi)

- Mutations that predict PARPi sensitivity
- Endocrine therapy and PARPi synergy
- Ongoing PARPi trials in metastatic hormone-sensitive prostate cancer

MODULE 2: M0 Disease

- PRESTO; EMBARK

MODULE 3: Metastatic Hormone-Sensitive Prostate Cancer

- De novo versus recurrent
- PTEN deficiency – CAPItello-281

MODULE 4: Radiopharmaceuticals

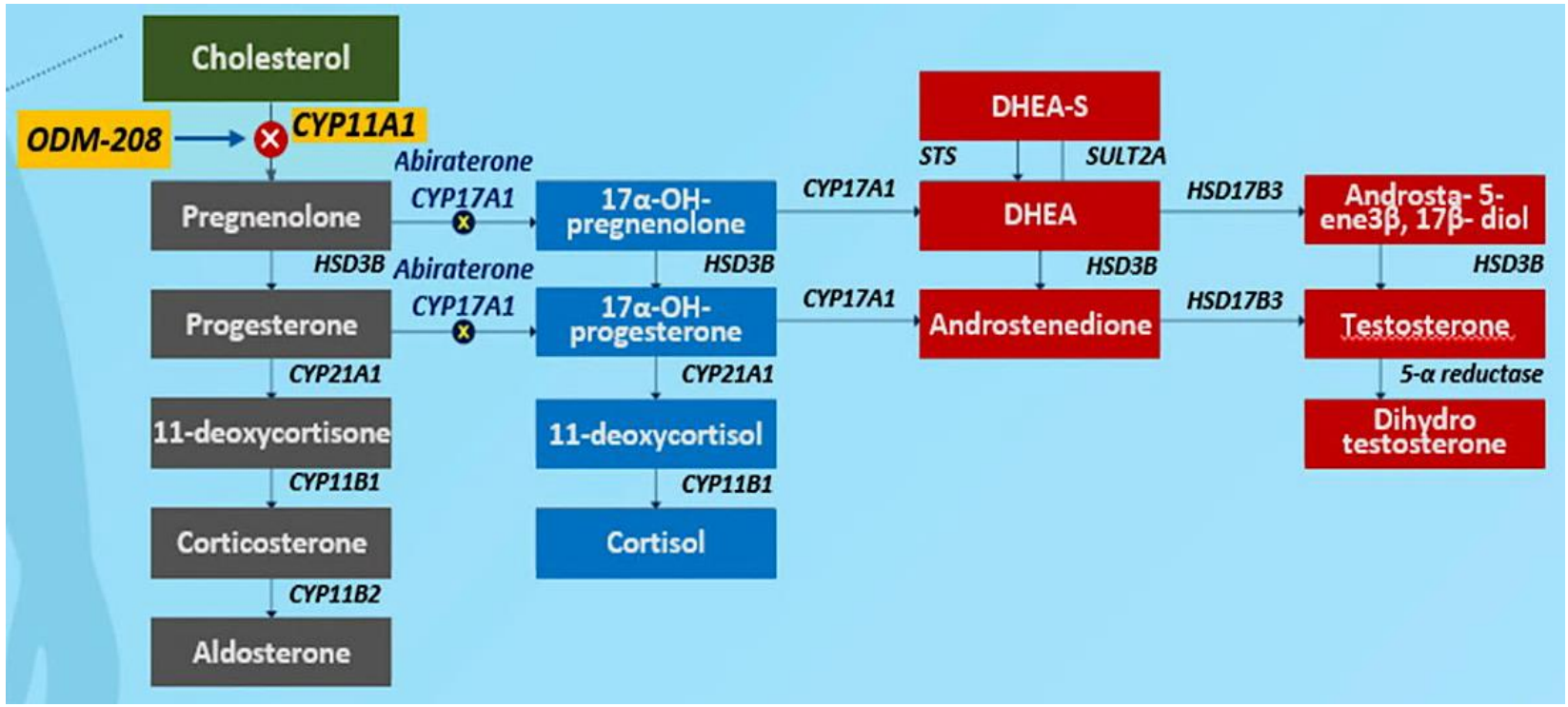
- Radium-223
- ^{177}Lu-PSMA-617; ^{177}Lu-PNT2002 – SPLASH

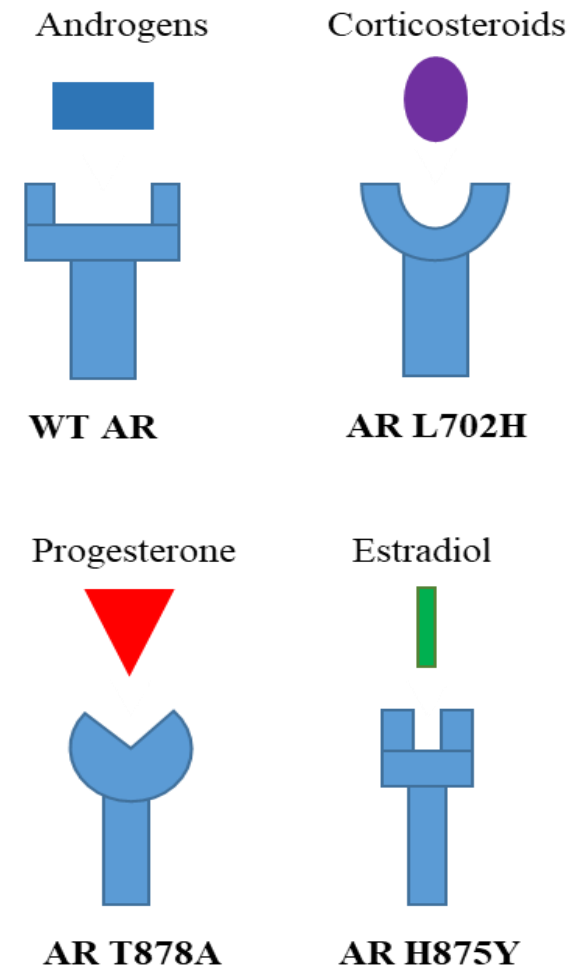
MODULE 5: Other Novel Investigational Approaches for Metastatic Castration-Resistant Prostate Cancer

- CYP11A1 inhibition – Opevesostat
- EZH2 inhibition – Mevrometostat

RTP Year in Review 2025

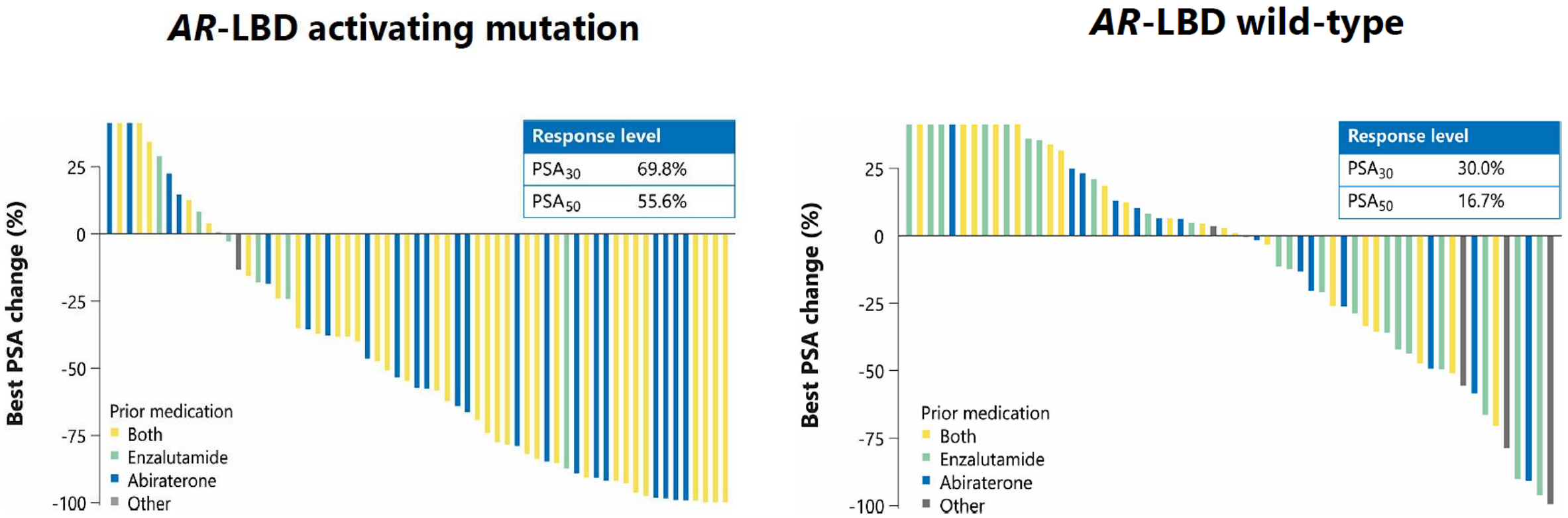
ODM-208 → MK-5684 → Opevesostat





Courtesy of Emmanuel S Antonarakis, MD

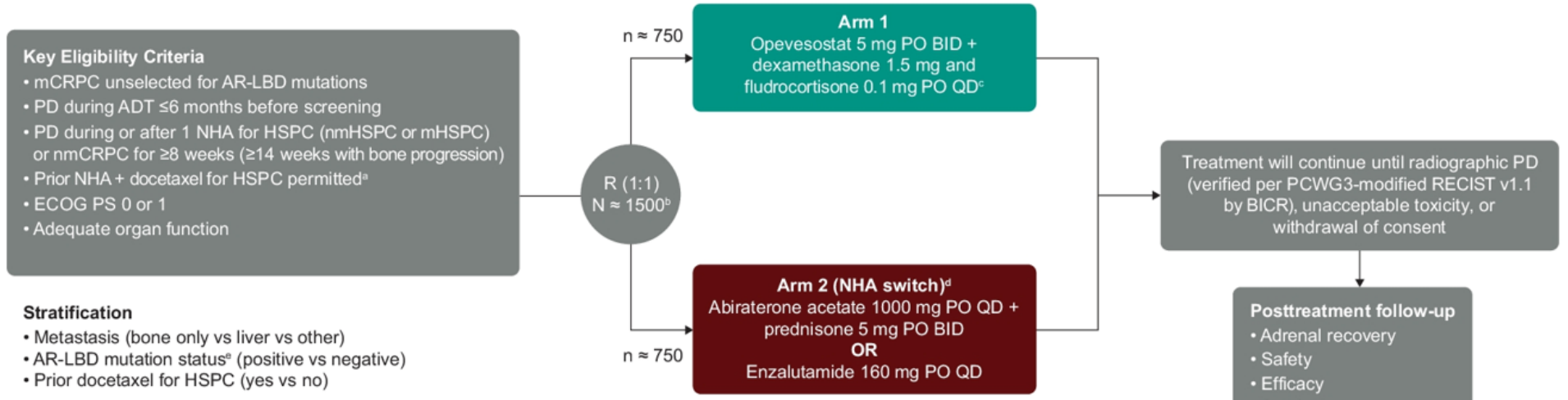
Opevesosostat: Phase 2 CYPIDES trial



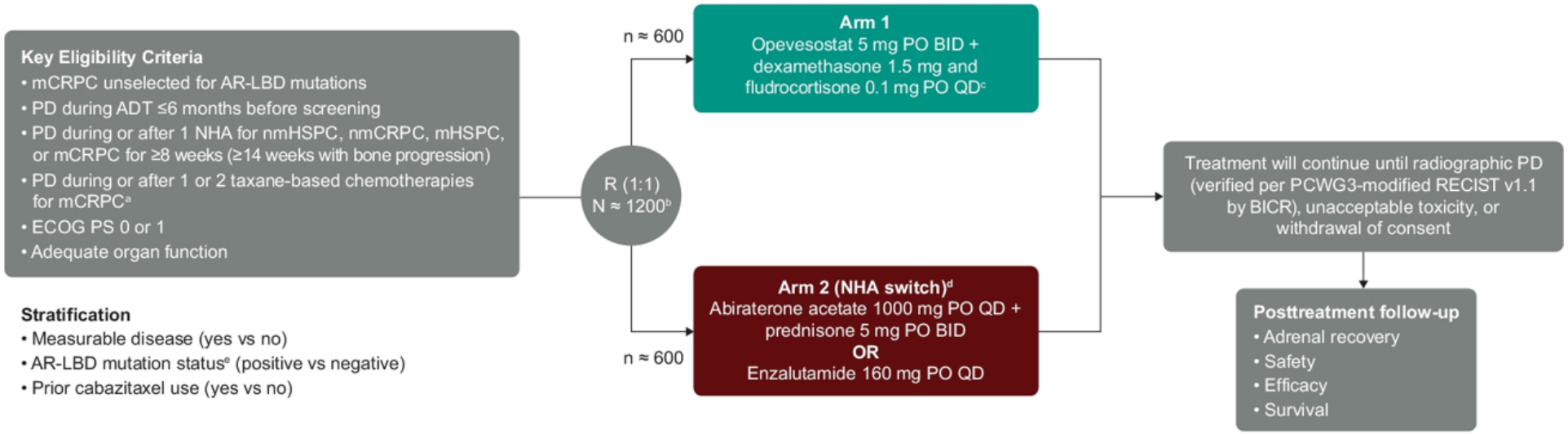
Fizazi K, et al. *NEJM Evid.* 2024;3:EVIDoa2300171; Fizazi K, et al. ASCO GU 2024; abstract 159.

Courtesy of Emmanuel S Antonarakis, MD

OMAHA-004 (Pre-chemo mCRPC)



OMAHA-003 (Post-chemo mCRPC)



Gratzke CJ, et al. *ASCO GU* 2025; Abstract TPS301; Yu EY, et al. *ASCO GU* 2025; Abstract TPS286.

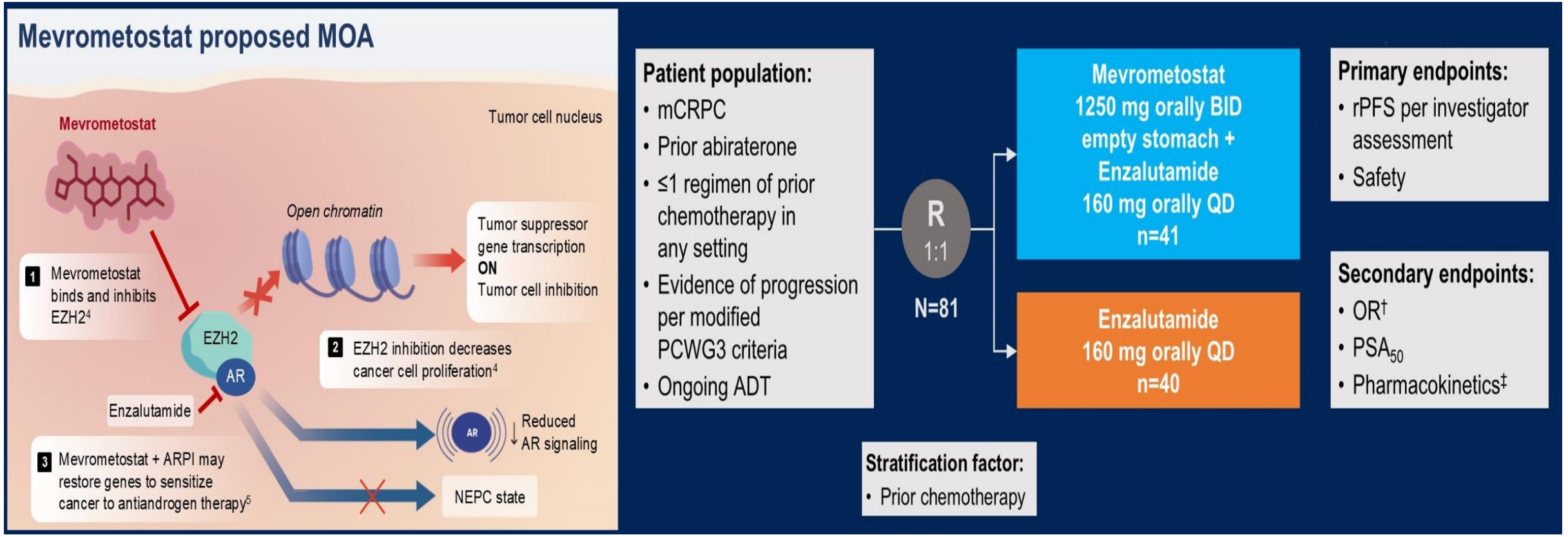
Courtesy of Emmanuel S Antonarakis, MD

Conclusions

- Opevesostat (MK-5684, formerly ODM-208) is an oral CYP11 inhibitor that suppresses production of all adrenal steroids
- Has shown clinical activity in mCRPC post-ARPI in phase 2
- Might show greater efficacy against *AR*-LBD+ mutations
- OMAHA-004 and OMAHA-003 are phase 3 randomized trials of opevesostat vs. ARPI switch in pre- and post-chemo mCRPC
- Opevesostat requires co-administration of glucocorticoid (dex) and mineralocorticoid (fludro) supplementation

Courtesy of Emmanuel S Antonarakis, MD

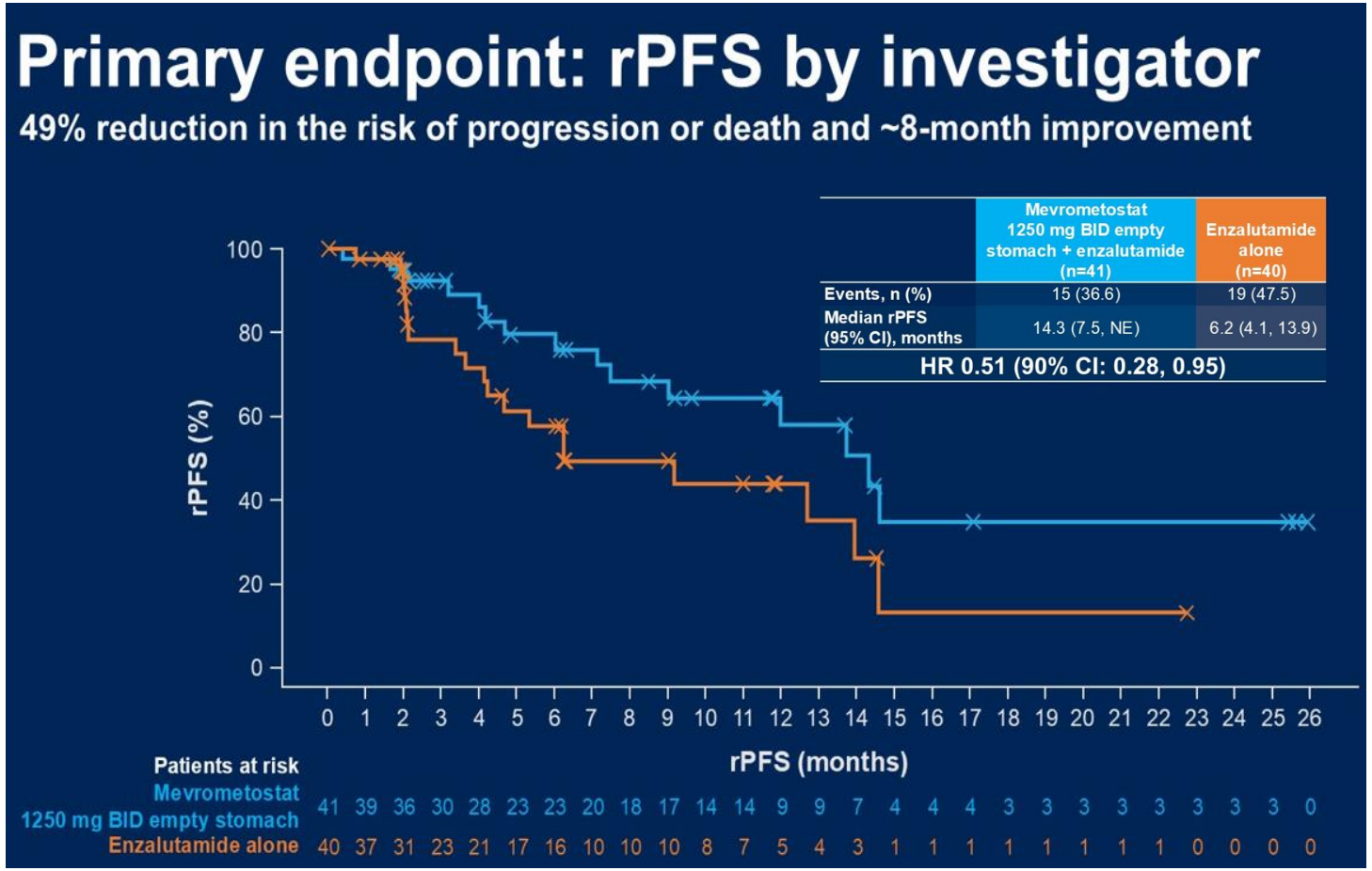
EZH2 Inhibitor: Mevrometostat

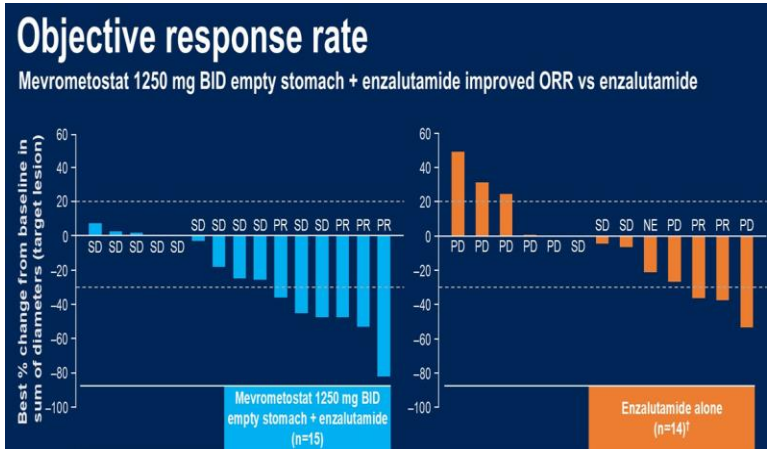


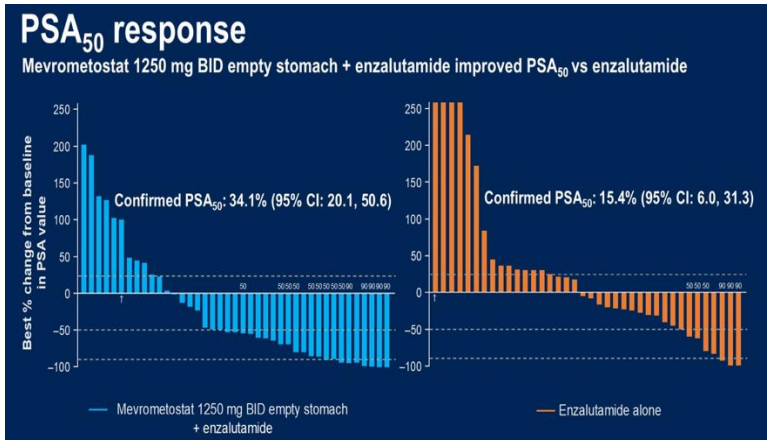
Schweizer MT , et al. *ASCO GU Symposium* 2025; Abstract LBA138.

Courtesy of Emmanuel S Antonarakis, MD

Post-Abiraterone mCRPC: Enza +/- Mevro







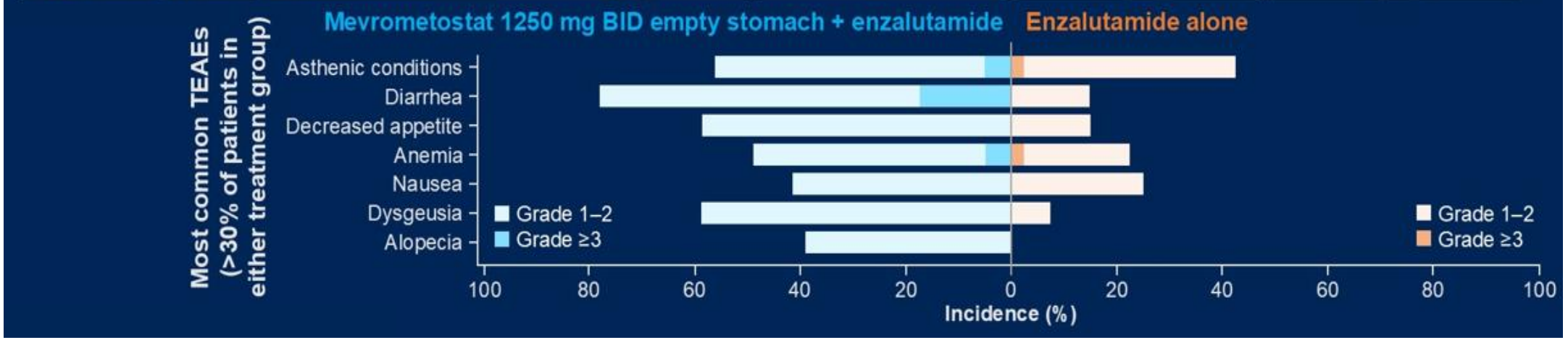
Schweizer MT , et al. *ASCO GU Symposium* 2025; Abstract LBA138.

Courtesy of Emmanuel S Antonarakis, MD

Adverse Events: Enza +/- Mevrometostat

Mevrometostat 1250 mg BID empty stomach + enzalutamide has a manageable safety profile

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



Schweizer MT , et al. *ASCO GU Symposium* 2025; Abstract LBA138.

Courtesy of Emmanuel S Antonarakis, MD

Conclusions

- Mevrometostat is an oral EZH2 inhibitor that enhances efficacy of enzalutamide in post-abiraterone mCRPC pts (rPFS, HR 0.51)
- Mevro 875 mg (with food) is the recommended Phase 3 dose
- Adverse events: diarrhea, nausea, dysgeusia, anemia, alopecia
- Phase 3 trials are in progress for mCRPC pts in the post-Abi space (MEVPRO-1) and the ARPI-naïve space (MEVPRO-2)

Courtesy of Emmanuel S Antonarakis, MD

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

Management of Non-Hodgkin Lymphoma

A CME/MOC-Accredited Live Webinar

Tuesday, April 22, 2025

5:00 PM – 6:00 PM ET

Faculty

Stephen M Ansell, MD, PhD

Brian T Hill, MD, PhD

Moderator

Neil Love, MD

RTP Year in Review 2025

Thank you for joining us!

Please take a moment to complete the survey currently up on Zoom. Your feedback is very important to us. The survey will remain open for 5 minutes after the meeting ends.

Information on how to obtain CME, ABIM MOC and ABS credit is provided in the Zoom chat room. Attendees will also receive an email in 1 to 3 business days with these instructions.

RTP Year in Review 2025