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

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Faculty

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Senior Director, Clinical Affairs
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MODERATOR
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Dr Gomella — Disclosures
Faculty

Advisory Committees	AstraZeneca Pharmaceuticals LP, Ferring Pharmaceuticals, Lantheus, Merck
Patents	Through Thomas Jefferson University

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Dr Yu — Disclosures
Faculty

Advisory Committees	AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Bristol Myers Squibb, Johnson & Johnson Pharmaceuticals, Lantheus, Loxo Oncology Inc, a wholly owned subsidiary of Eli Lilly & Company, Merck, Oncternal Therapeutics, Tolmar
Contracted Research	Bayer HealthCare Pharmaceuticals, Blue Earth Diagnostics, Dendreon Pharmaceuticals Inc, Lantheus, Merck, Oncternal Therapeutics, Seagen Inc, Tyra Biosciences Inc

Dr George — Disclosures
Moderator

Advisory Committees	Astellas, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Cardinal Health, Novartis, Pfizer Inc
Consulting Agreements	Astellas, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Bristol Myers Squibb, Exelixis Inc, Johnson & Johnson Pharmaceuticals, Merck, Novartis
Contracted Research	AstraZeneca Pharmaceuticals LP, Bristol Myers Squibb, Corvus Pharmaceuticals, Exelixis Inc, Merck, Novartis, Pfizer Inc
Data and Safety Monitoring Boards/ Committees	AstraZeneca Pharmaceuticals LP
Nonrelevant Financial Relationships	IDEOlogy Health, MJH Life Sciences, Targeted Oncology, UpToDate, UroToday

Dr Antonarakis — Disclosures
Consulting Faculty

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Prof Fizazi — Disclosures
Consulting Faculty

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Dr Rugo — Disclosures
Consulting Faculty

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Commercial Support

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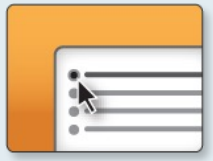
Clinicians in the Meeting Room

Networked iPads are available.

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



Answer Survey Questions: Complete the premeeting survey.

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

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

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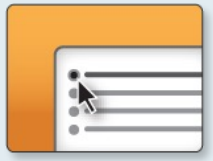
Clinicians Attending via Zoom

Review Program Slides: A link to the program slides will be posted in the chat room at the start of the program.



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

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

Get CME Credit: A CME credit link will be provided in the chat room at the conclusion of the program.

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About the Enduring Program

- The live meeting is being video and audio recorded.
- The proceedings from today will be edited and developed into an enduring web-based program. An email will be sent to all attendees when the activity is available.
- To learn more about our education programs, visit our website, **www.ResearchToPractice.com**

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Hope S Rugo, MD
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City of Hope Comprehensive Cancer Center
Professor Emeritus, UCSF
Duarte, California

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

Neil Love, MD
Research To Practice
Miami, Florida

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Meeting within a Meeting

Topics/Playlist

- PLAY mHSPC 2025
- PLAY PARPi in mHSPC
- PLAY AKTi as a model for targeted treatment in PC
  - Capivasertib in breast cancer
    - Available assays
    - Toxicities
- PLAY New agents and therapies

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Agenda

Module 1: Current Treatment Landscape for Metastatic Hormone-Sensitive Prostate Cancer (mHSPC) — Dr Gomella

Module 2: Clinical Implications of and Appropriate Strategies to Identify PTEN Deficiency in Prostate Cancer — Dr Yu

Module 3: Emerging Role of AKT Inhibition for mHSPC — Dr George

Agenda

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SIDNEY KIMMEL CANCER CENTER | NCI-DESIGNATED

Current Treatment Landscape for Metastatic Hormone-Sensitive Prostate Cancer (mHSPC)

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Senior Director Clinical Affairs, Sidney Kimmel Cancer Center
Enterprise VP for Urology, Jefferson Health
Thomas Jefferson University,
Philadelphia, PA

Current Treatment Landscape for mHSPC

- Current management paradigm for mHSPC
- Long-term outcomes with contemporary treatment strategies
- Factors guiding the selection of therapy for individual patients with mHSPC
- Trials using proven strategies effective in mCRPC into the mHSPC setting

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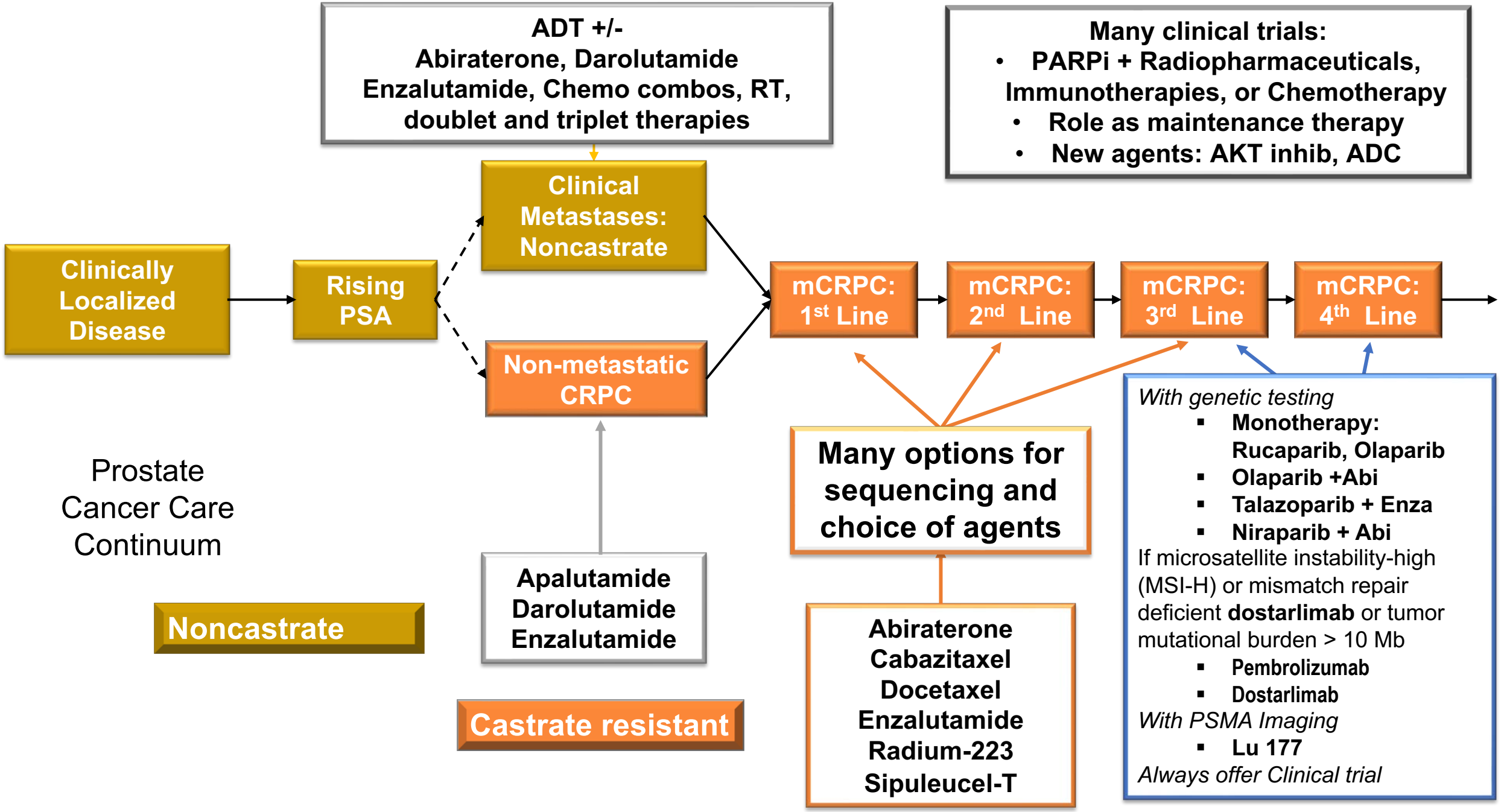

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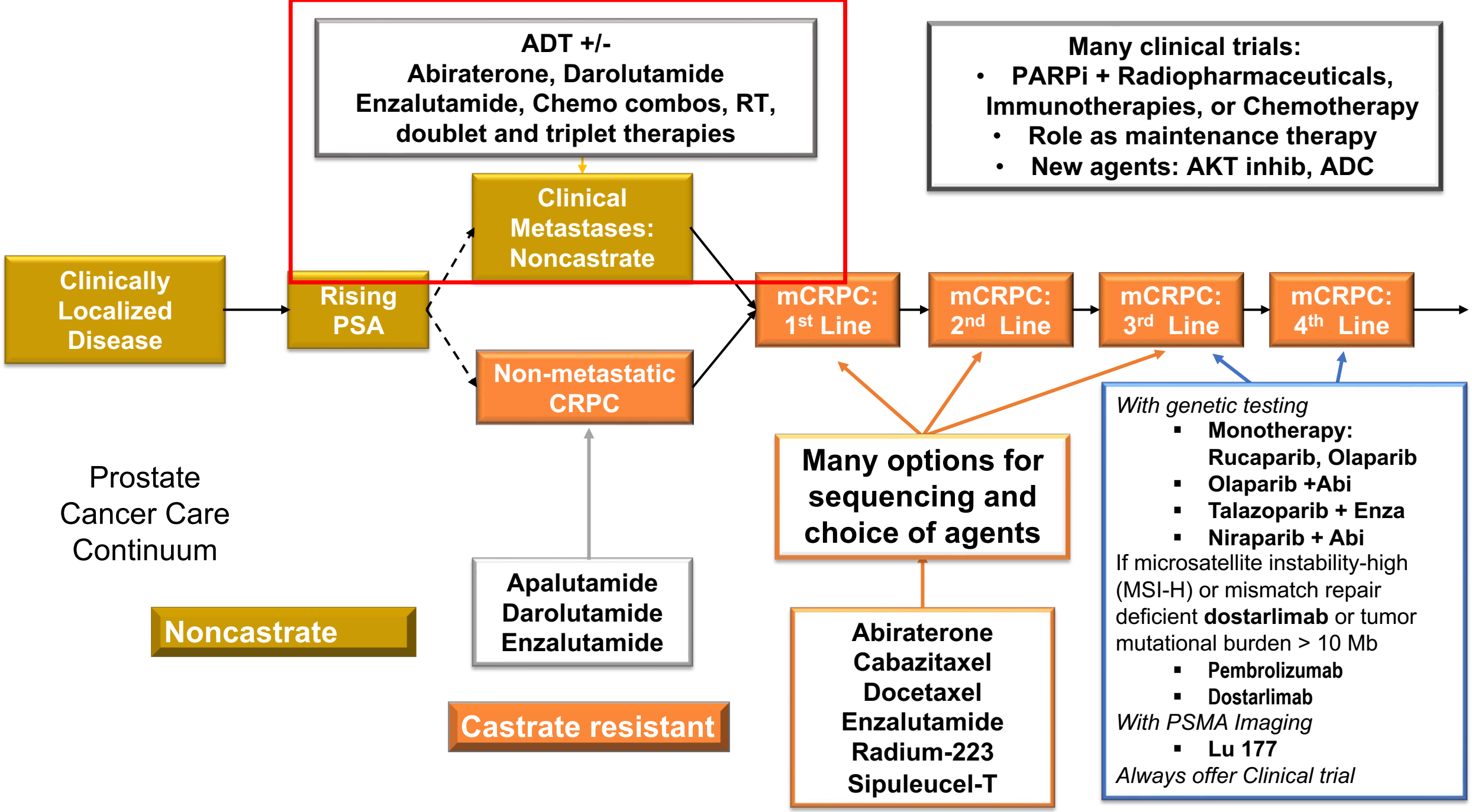

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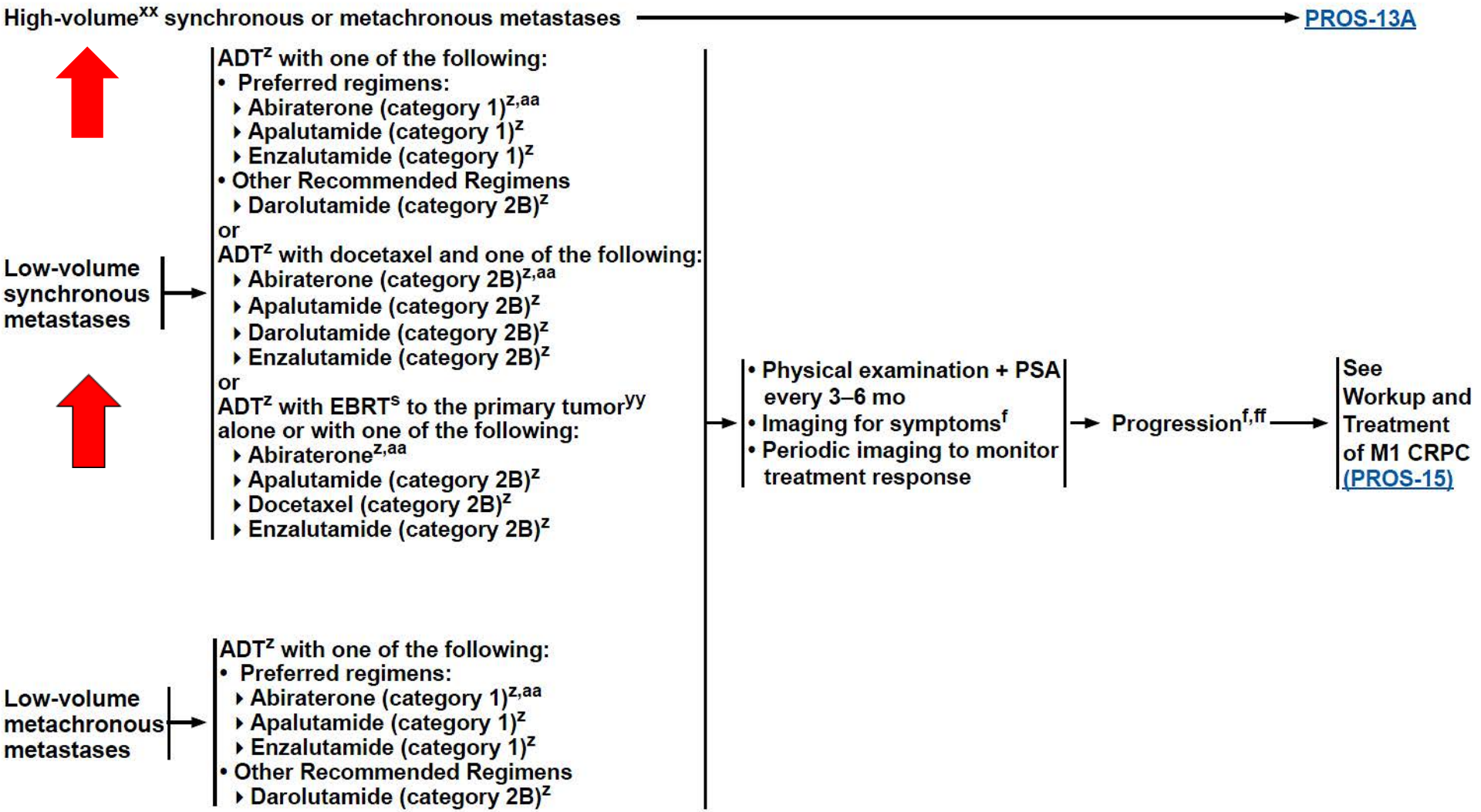
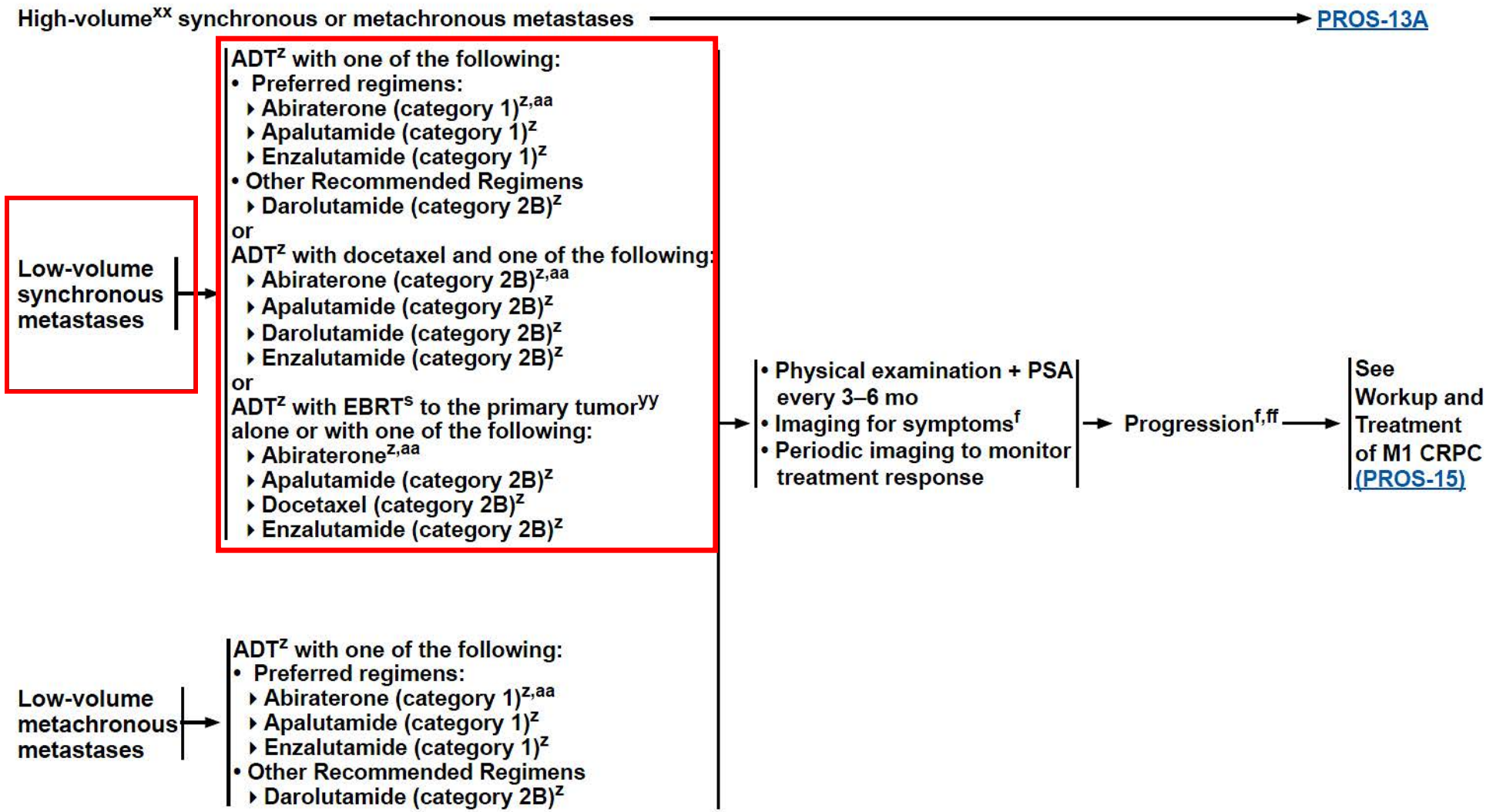
WORKUP AND TREATMENT OF M1 CSPC[c,rr,ss,tt,uu,vv]

WORKUP FOR METASTASES[ww]



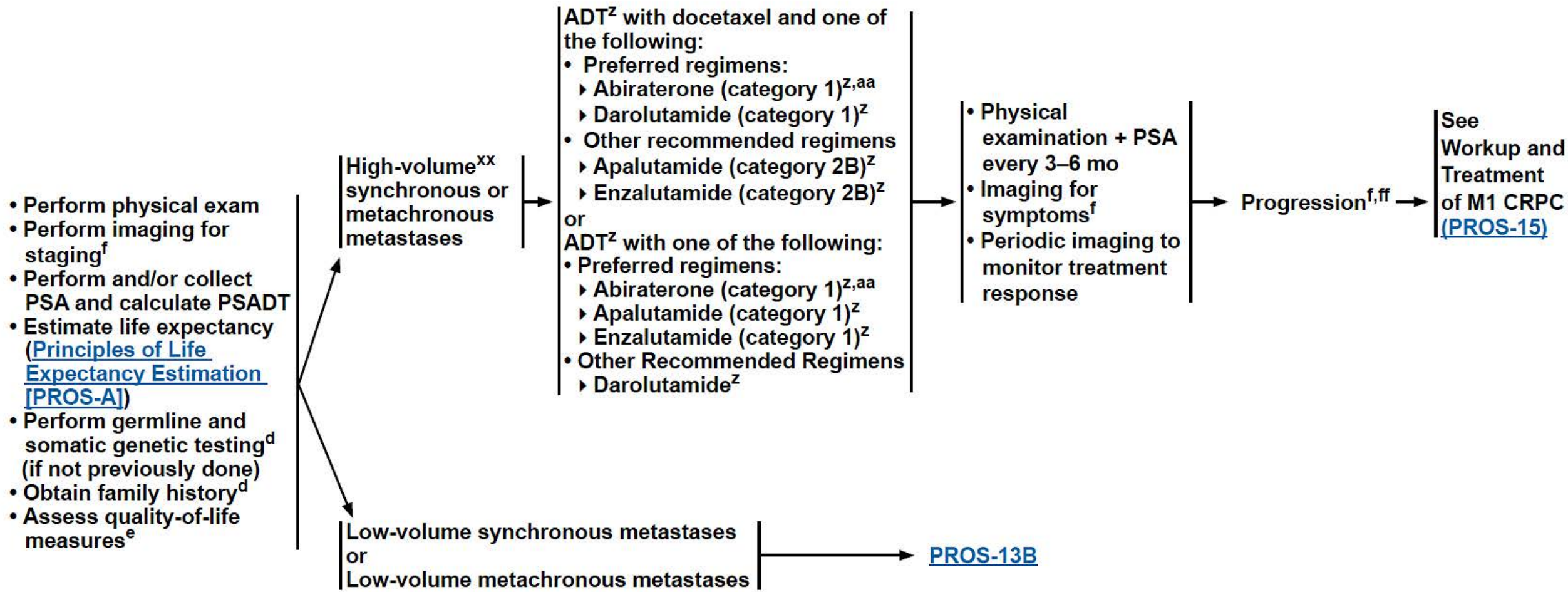
WORKUP AND TREATMENT OF M1 CSPC[c,rr,ss,tt,uu,vv]

WORKUP FOR METASTASES[ww]



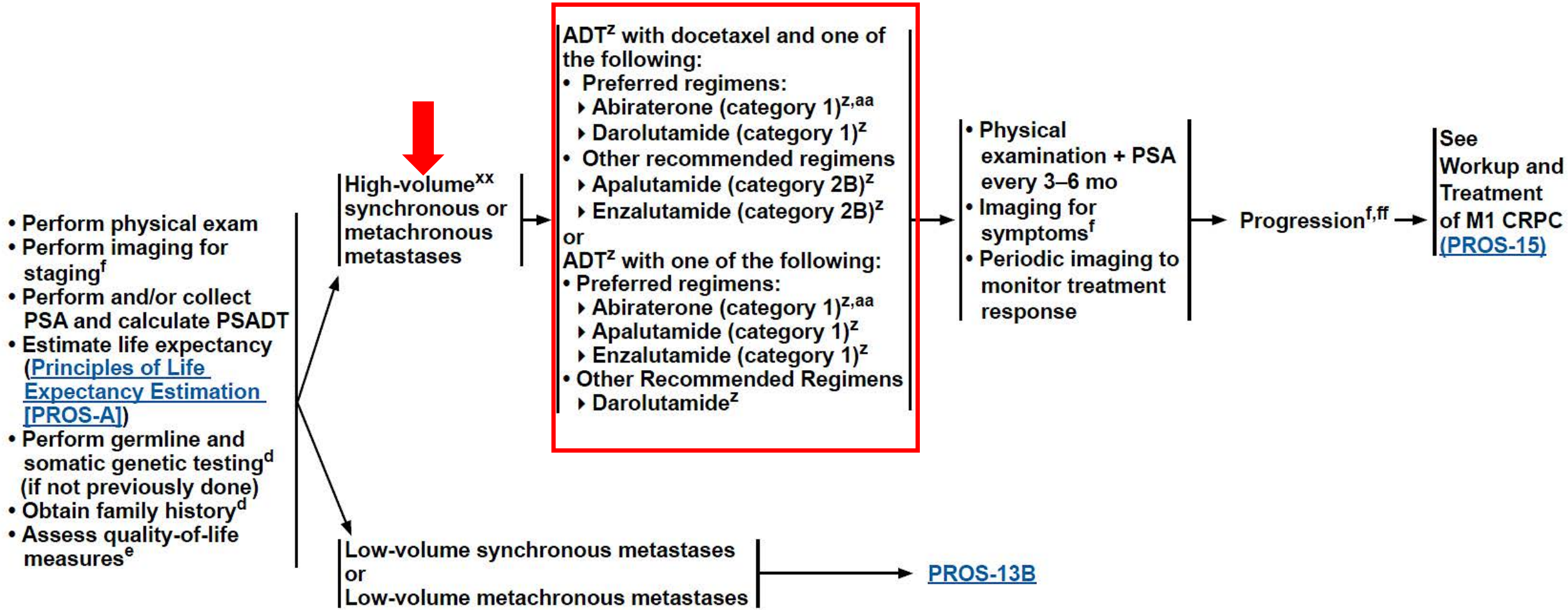
WORKUP AND TREATMENT OF M1 CSPC[c,rr,ss,tt,uu,vv]

WORKUP FOR METASTASES[ww]



WORKUP AND TREATMENT OF M1 CSPC[c,rr,ss,tt,uu,vv]

WORKUP FOR METASTASES[ww]



WORKUP AND TREATMENT OF M1 CSPC[c,rr,ss,tt,uu,vv]

WORKUP FOR METASTASES[ww]

High volume mHSPC regimens similar but no prostate RT

- PSA and calculate PSADT
- Estimate life expectancy (Principles of Life Expectancy Estimation [PROS-A])
- Perform germline and somatic genetic testing[d] (if not previously done)
- Obtain family history[d]
- Assess quality-of-life measures[e]

ADT[z] with docetaxel and one of the following:
- Preferred regimens:
  - Abiraterone (category 1)[z,aa]
  - Darolutamide (category 1)[z]
- Other recommended regimens
  - Apalutamide (category 2B)[z]
  - Enzalutamide (category 2B)[z]

or

ADT[z] with one of the following:
- Preferred regimens:
  - Abiraterone (category 1)[z,aa]
  - Apalutamide (category 1)[z]
  - Enzalutamide (category 1)[z]
- Other Recommended Regimens
  - Darolutamide[z]

- Physical examination + PSA every 3–6 mo
- Imaging for symptoms[f]
- Periodic imaging to monitor treatment response

→ Progression[f,ff] → See Workup and Treatment of M1 CRPC (PROS-15)

Low-volume synchronous metastases
or
Low-volume metachronous metastases

→ PROS-13B

Current Treatment Landscape for mHSPC

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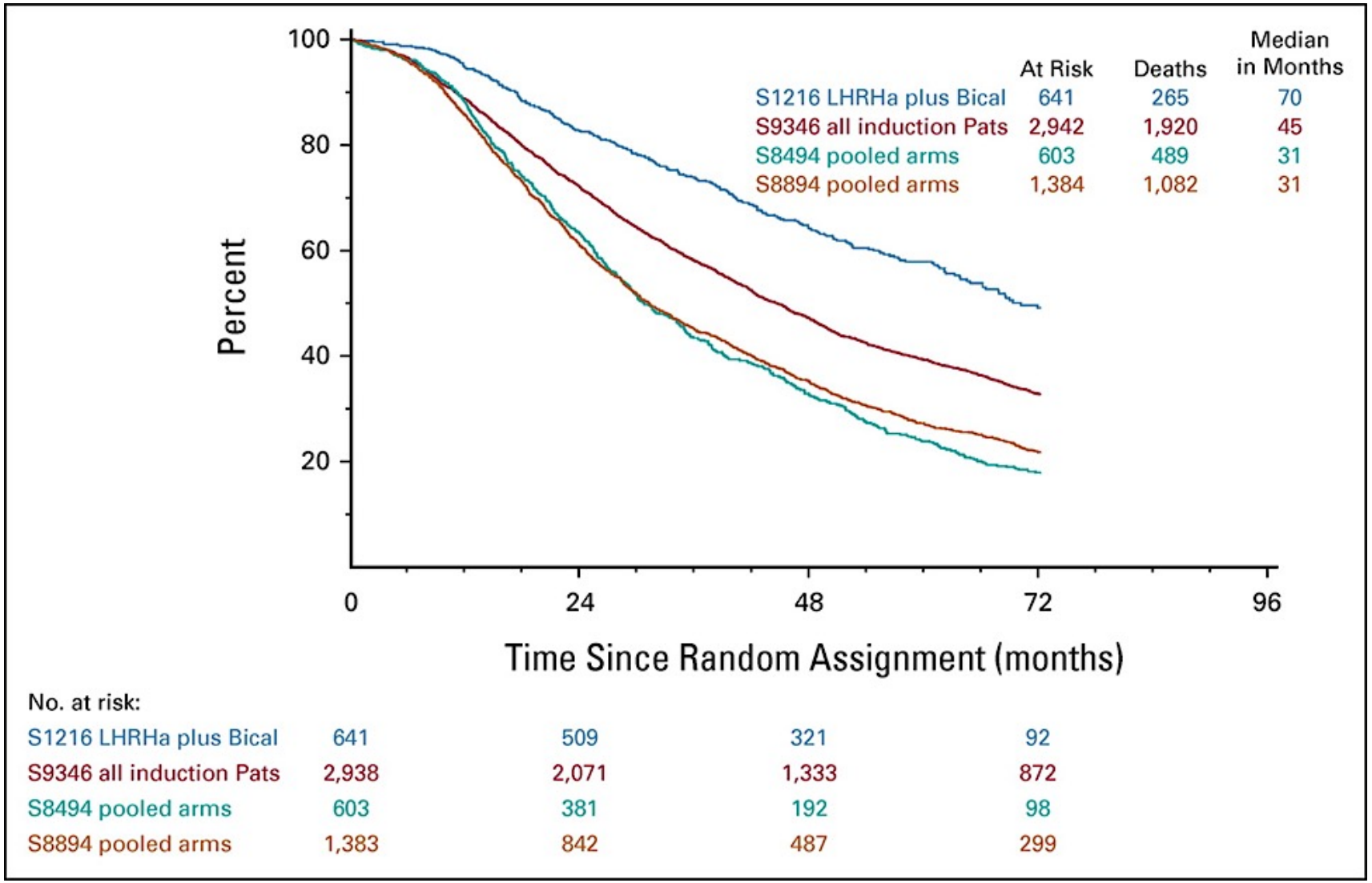
Metastatic Prostate Cancer Significant Survival Change Over Time



Historical data 2-2.5 years

Agarwal N et al. *J Clin Oncol.* 2022;40(28):3301-3309.

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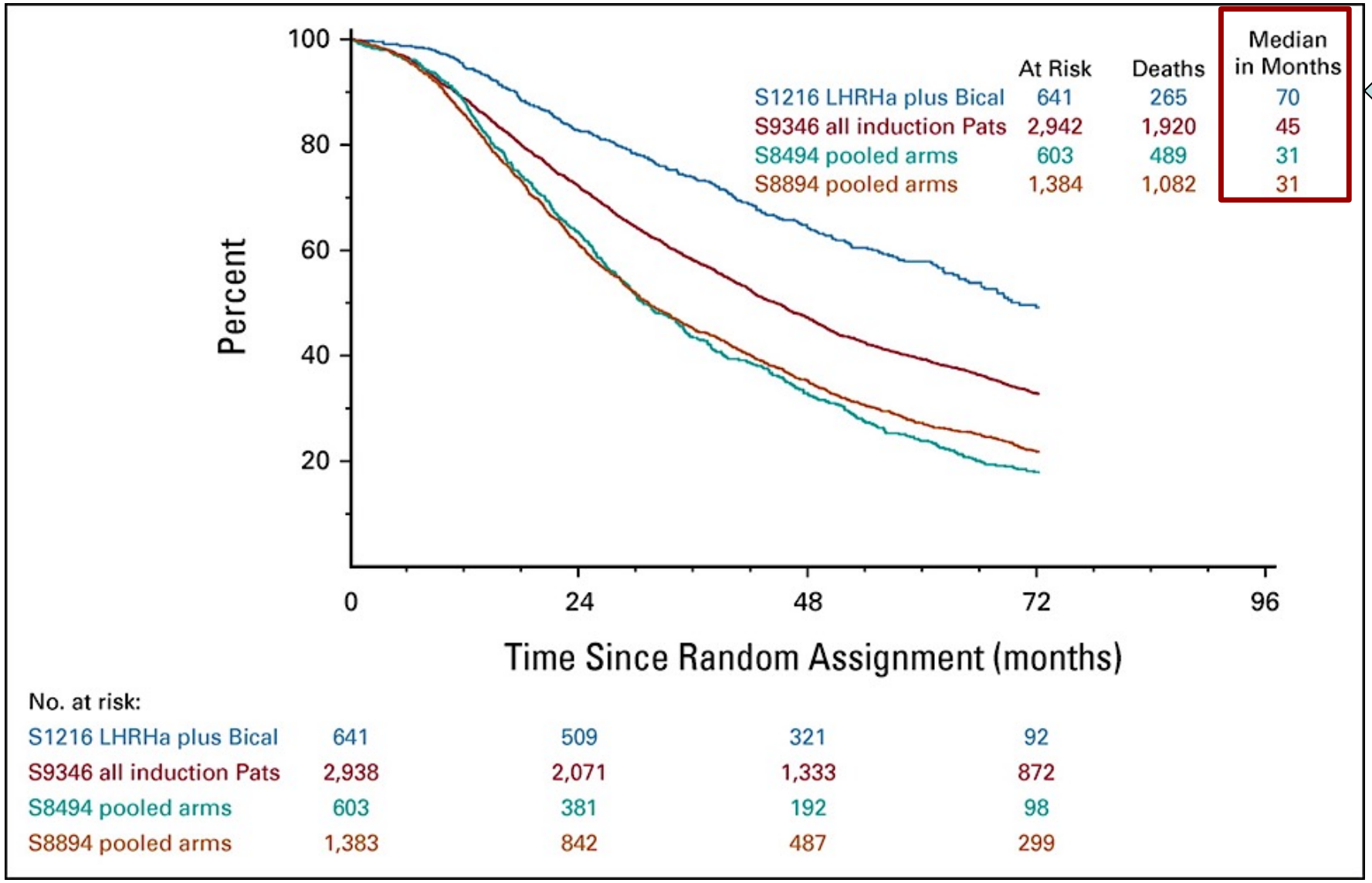

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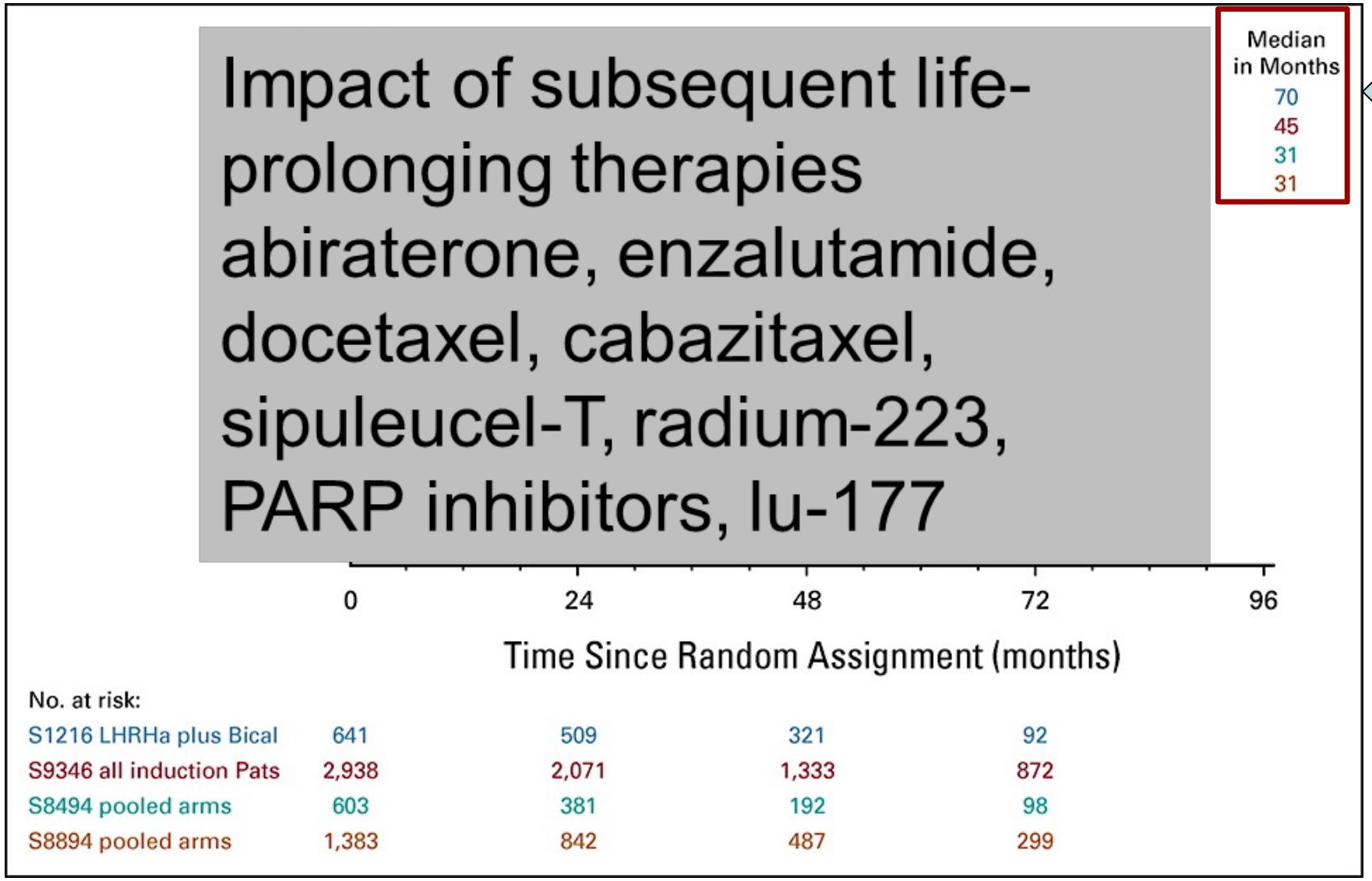


New data 5-6 years

Historical data 2-2.5 years

Agarwal N et al. *J Clin Oncol.* 2022;40(28):3301-3309.

Treatment Choices for Metastatic HSPC

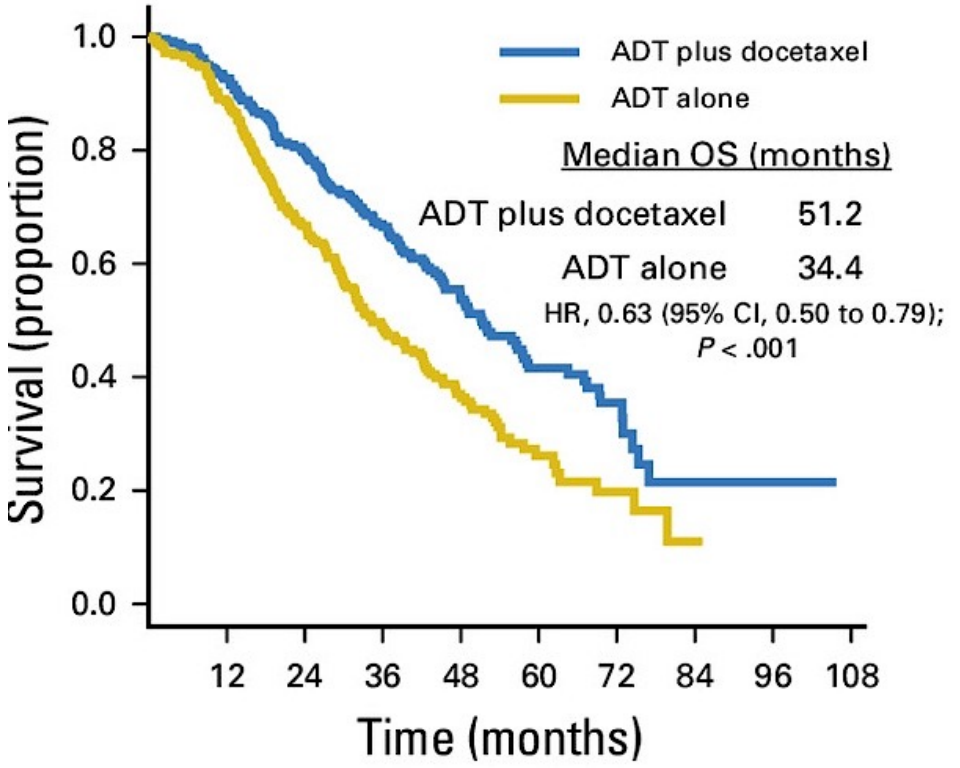
- Androgen-deprivation therapy (ADT) remains the foundation of managing mHSPC
- Intensifying therapy beyond ADT alone can further improve survival
  - **Doublet therapy:** AR-directed therapy (abiraterone/prednisone, apalutamide, enzalutamide) + ADT
  - **Triplet therapy:** Chemotherapy (docetaxel) + AR-directed therapy (abiraterone/prednisone, darolutamide) + ADT
  - **Radiation therapy** to the prostate for low-volume disease

NCCN. Clinical practice guidelines in oncology: prostate cancer. v.1.2023.

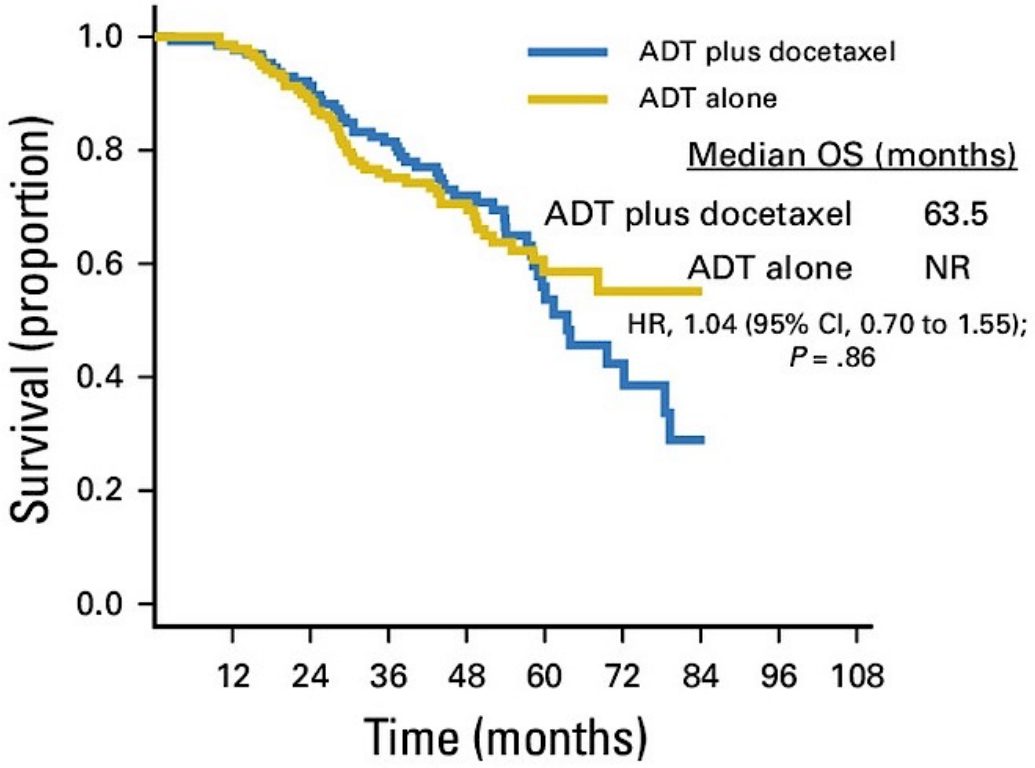
Phase III CHAARTED: High-Volume vs Low-Volume Disease

- Adding docetaxel to ADT showed greater benefit in high-volume disease and revealed the importance to **avoid overtreating low-volume disease**

High-Volume Disease

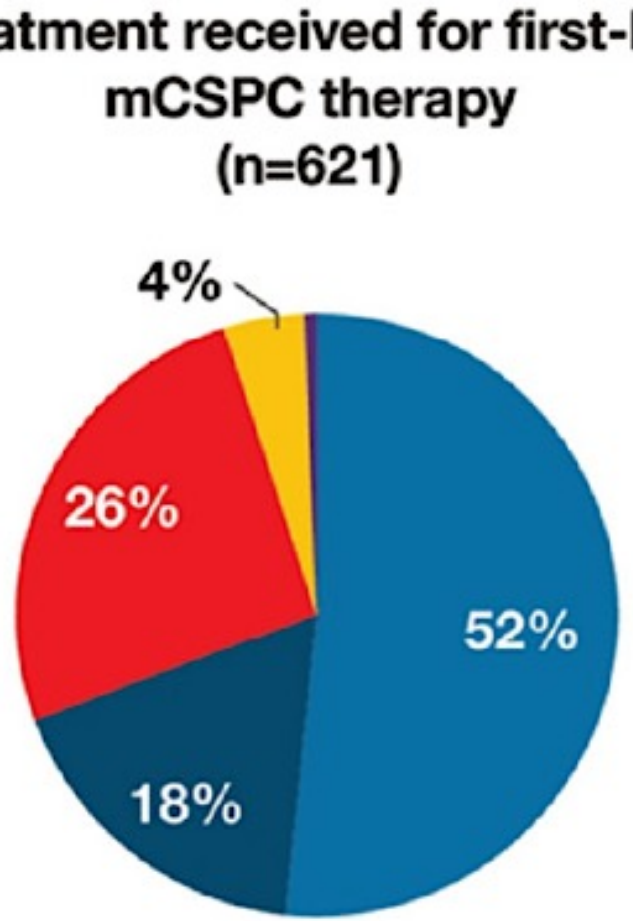


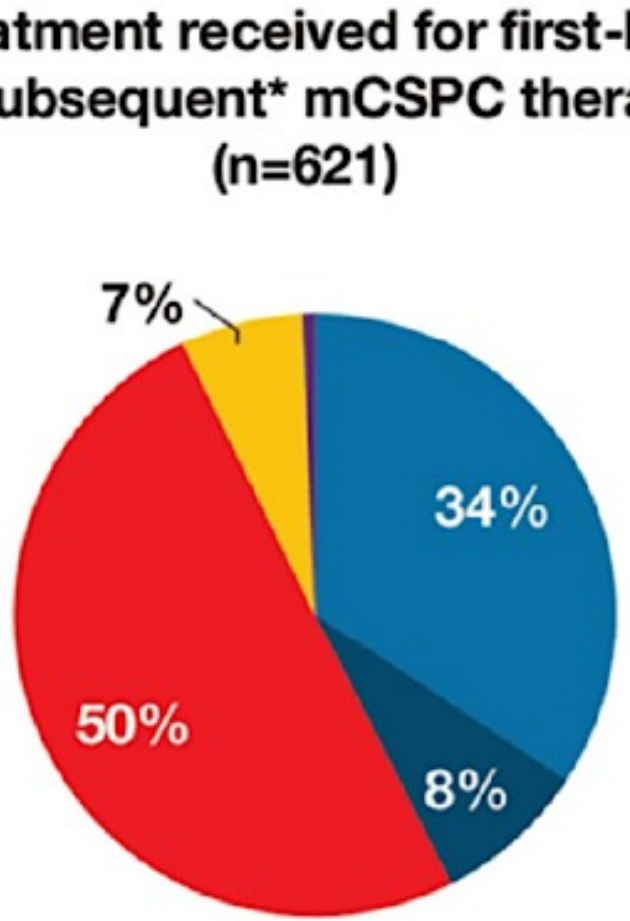
Low-Volume Disease



Kyriakopoulos. JCO. 2018;36:1080.

2013





2018

ADT alone ADT + NSAA ADT + NHT ADT + CHT ± NHT Other

Freedland SJ, Sandin R, Sah J, et al. T. Cancer Med. 2021;10(23):8570 8580
Freedland SJ et al. ASCO 2022;Abstract 5065

Current Treatment Landscape for mHSPC

- Current management paradigm for mHSPC
- Long-term outcomes with contemporary treatment strategies
- **Factors guiding the selection of therapy for individual patients with mHSPC**
- Trials using proven strategies effective in mCRPC into the mHSPC setting

Selecting Primary ADT

Initial Considerations: administration of therapy, safety, patient adherence, need for testosterone suppression, reversal in the event of toxicity

GnRH Agonists

- Longer history of use, more often used
- Only available as injection
- Often given Q3M (goserelin, leuprolide)
- First-generation antiandrogen may be required due to testosterone flare-up
- Slower testosterone recovery after stopping treatment

GnRH Antagonists

- Available as monthly injection (degarelix) or daily tablets (relugolix)
- Rapid suppression of testosterone
- Bicalutamide not required during treatment
- Relugolix may reduce cardiac risk
- Testosterone quickly recovered after stopping relugolix

American Cancer Society. Hormone therapy for prostate cancer. Revised August 9, 2022. Clinton. Expert Opin Pharmacother. 2017;18:825. Shore. NEJM. 2020;382:2187. Goserelin PI. Leuprolide acetate PI. Leuprolide mesylate PI. Degarelix PI. Relugolix PI.

mHSPC + ADT Treatment Selection

- Choice of agent depends on cost, safety profile, patient comorbidities

Abiraterone	Enzalutamide	Apalutamide	Darolutamide	Docetaxel
• Generic • K+/LFT/BP monitoring • Longterm HTN/prednisone concerns • Less fatigue • **Option to intensify to triplet therapy (PEACE-1)**	• Less monitoring • Neurocognitive concerns	• Less monitoring • Rash and neurocognitive concerns	• Less monitoring • **Option to intensify to triplet therapy (ARASENS)**	• Least expensive • Finished after 6 cycles • Risk for new or worsened neuropathy • Offer while fit for chemo • Can stop early if exceptional response or intolerant to chemo

- **Triplet therapy:** for fit patients with aggressive disease or with features suggesting less dependence on AR (high volume metastatic disease, low PSA given volume of disease, high grade or poorly differentiated)

Abiraterone PI. Shpilsky. Expert Opin Pharmacother. 2021;22:1227. Fizazi. Lancet. 2022;399:1695. Enzalutamide PI. Ryan. Prostate Cancer Prostatic Dis. 2020;23:207. Apalutamide PI. Schulte. Am Soc Clin Oncol Educ Book. 2020;40:1. Darolutamide PI. Smith. NEJM. 2022;386:1132. Docetaxel PI. Thomas. Cancers. 2022;14:8. NCCN Clinical Practice Guidelines in Oncology: Prostate Cancer. v.1.2023. Maluf. JCO Glob Oncol. 2021;7:559.

Managing Relevant AEs With Second-Generation AR Inhibitors

AEs Associated With All Approved AR Inhibitors

Hypertension	Falls/Fractures	Fatigue	Rash	Gastrointestinal
• Monitor BP, signs, and symptoms • Optimize antihypertensive medications • Treat risk factors	• Assess fall risk at each visit • "Get up and go" test • Counsel to remove rugs, use night lights, etc	• Take before bed • Encourage exercise and physical activity	• Emollients • Topical Corticosteroids	• Antiemetics for nausea • Antidiarrheals for diarrhea • Laxatives for constipation

AEs Associated With Specific AR Inhibitors

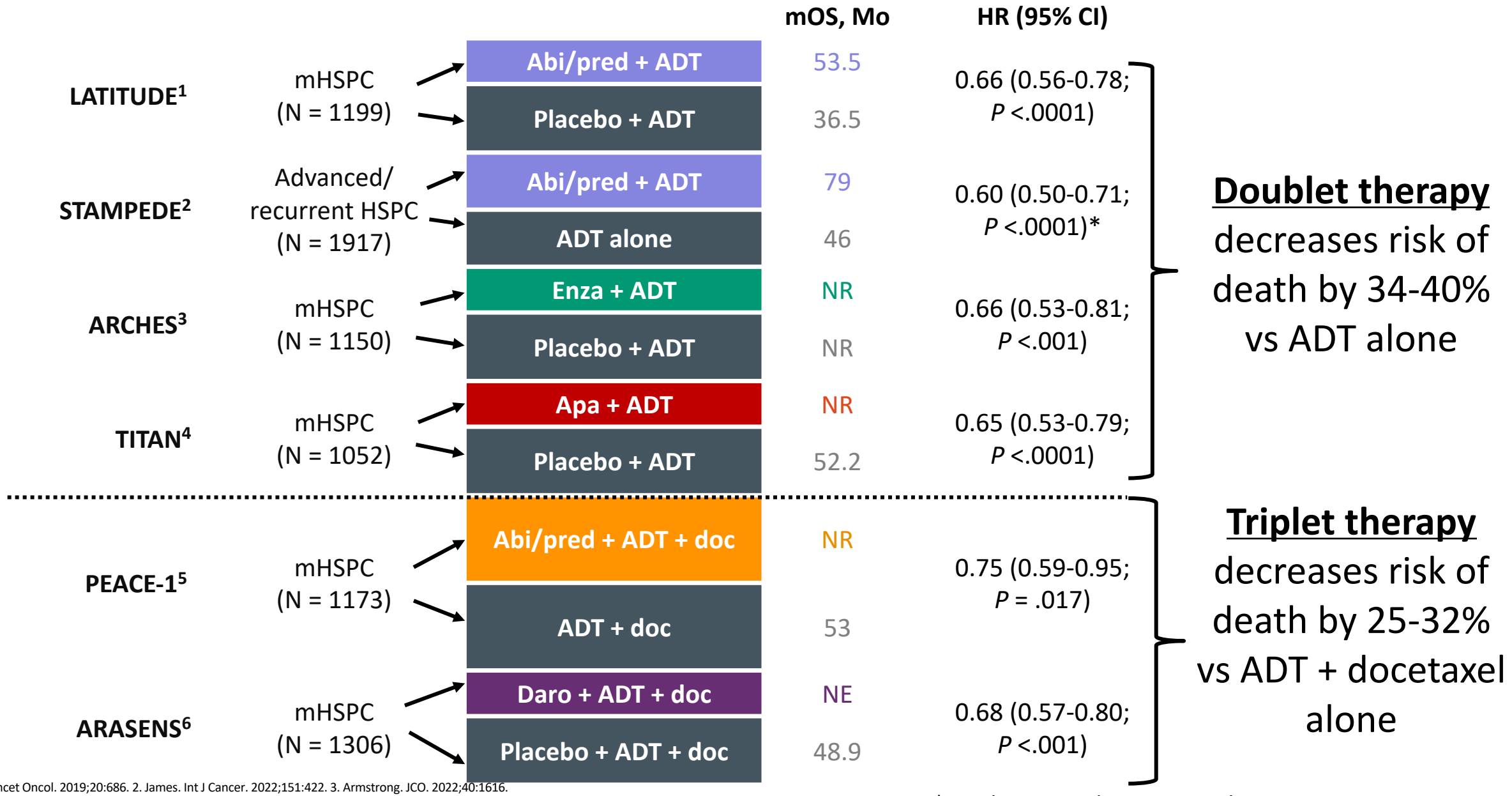
Seizures (Apalutamide, Enzalutamide, Darolutamide)	Headache* and Dizziness (Enzalutamide)	Cognitive Impairment (Apalutamide)	Hypothyroidism (Apalutamide)
• Counsel on potential loss of consciousness • Antiepileptic prophylaxis?	• Manage with OTC analgesics • Ask about other meds that can cause dizziness	• Ask abut cognition • Short cognitive tests	• Check TSH at baseline then every 4mo • Monitor T3, T4

- **High-grade/intolerable AEs:** Withhold, modify dose
- **If taking abiraterone/ prednisone:** Ensure adherent to prednisone

*Severe headache may be a symptom of PRES.

Abiraterone PI. Alkhudair. Saudi Pharm J. 2019;27:368. Apalutamide PI. Armstrong. JCO. 2022;40:1616. Auchus. Oncologist. 2014;19:1231. Chi. NEJM. 2019;381:13. Smith. NEJM. 2022;386:1132. Darolutamide PI. Enzalutamide PI.. Olivier. Int J Urol Nurs. 2021;15:47. van Dorst. Circ Res. 2021;128:1040. Rama. Clin J Oncol Nurs. 2015;19:723. Wefel. CNS Drugs. 2022;36:419. Wickham. J Adv Pract Oncol. 2017;8:149.

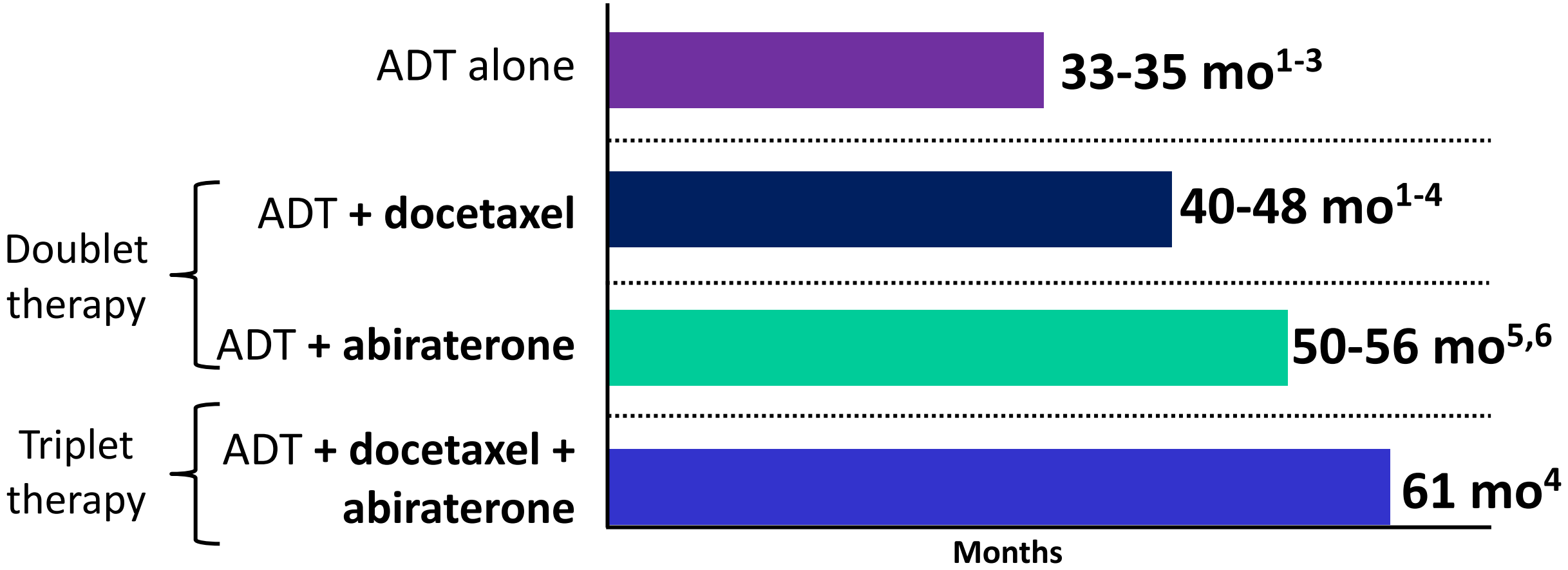
OS With Doublet and Triplet Therapy in mHSPC



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

*In subgroup with metastatic disease.

Median OS With Treatment Intensification in *De Novo* High-Volume mHSPC



*Cross-trial comparisons have significant limitations. Data are shown for discussion, not for direct comparison between trials.

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

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Ongoing Randomized Phase III Trials in mHSPC

Trial	Regimen	Population
CAPItello-281 (NCT04493853)	ADT + abiraterone ± capivasertib	De novo mHSPC, PTEN deficiency (planned N = 1000)
TALAPRO-3 (NCT04821622)	Enzalutamide ± talazoparib	mHSPC, DDR mutation (planned N = 550)
AMPLITUDE (NCT04497844)	Abiraterone/prednisone ± niraparib	mHSPC, HRR gene alteration (planned N = 788)
PSMAddition (NCT04720157)	AR-directed tx + ADT ± ^{177}Lu-PSMA-617	mHSPC, PSMA positive (planned N = 1126)
EvoPAR-Prostate01 (NCT06120491)	Saruparib + NHA	mHSPC, HRRm and Non-HRRm (planned N = 1800)

*NHA = Physician's choice of new hormonal agent

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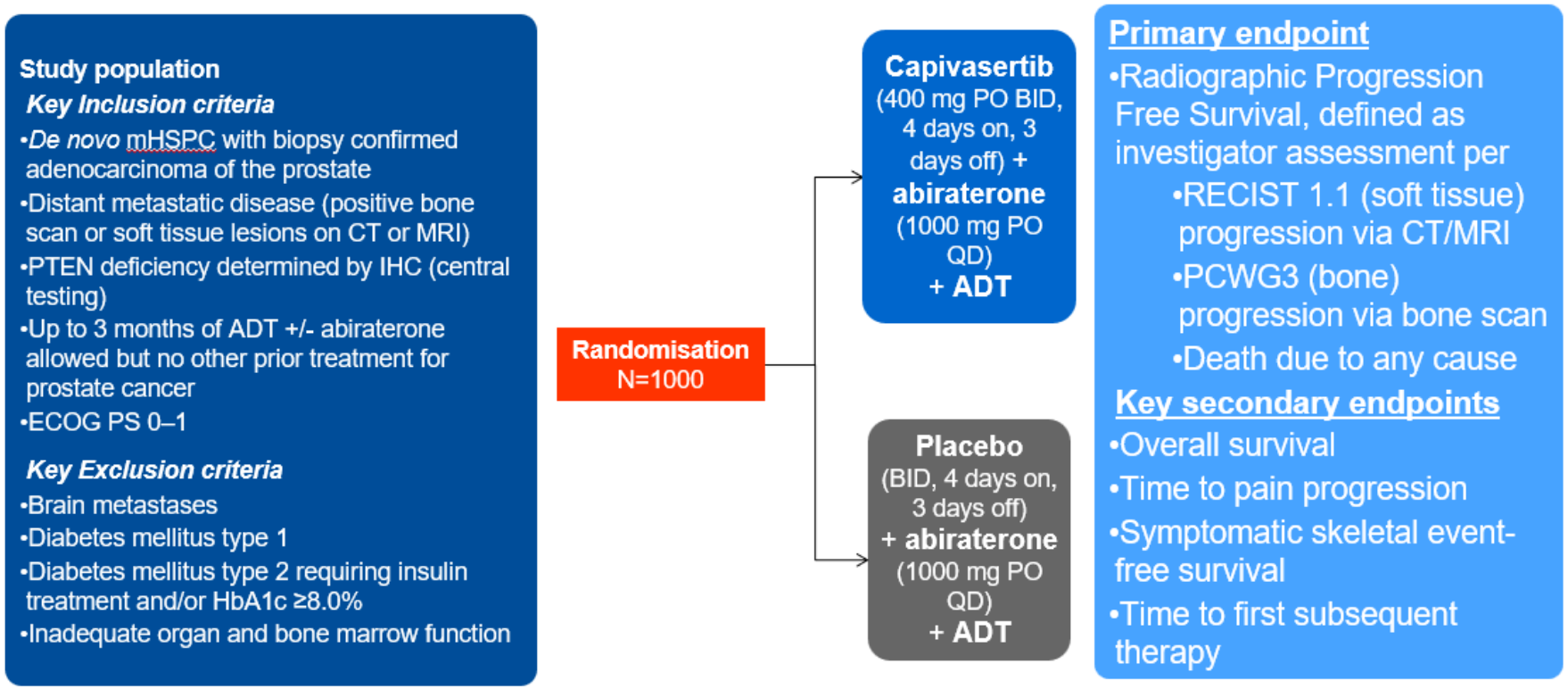
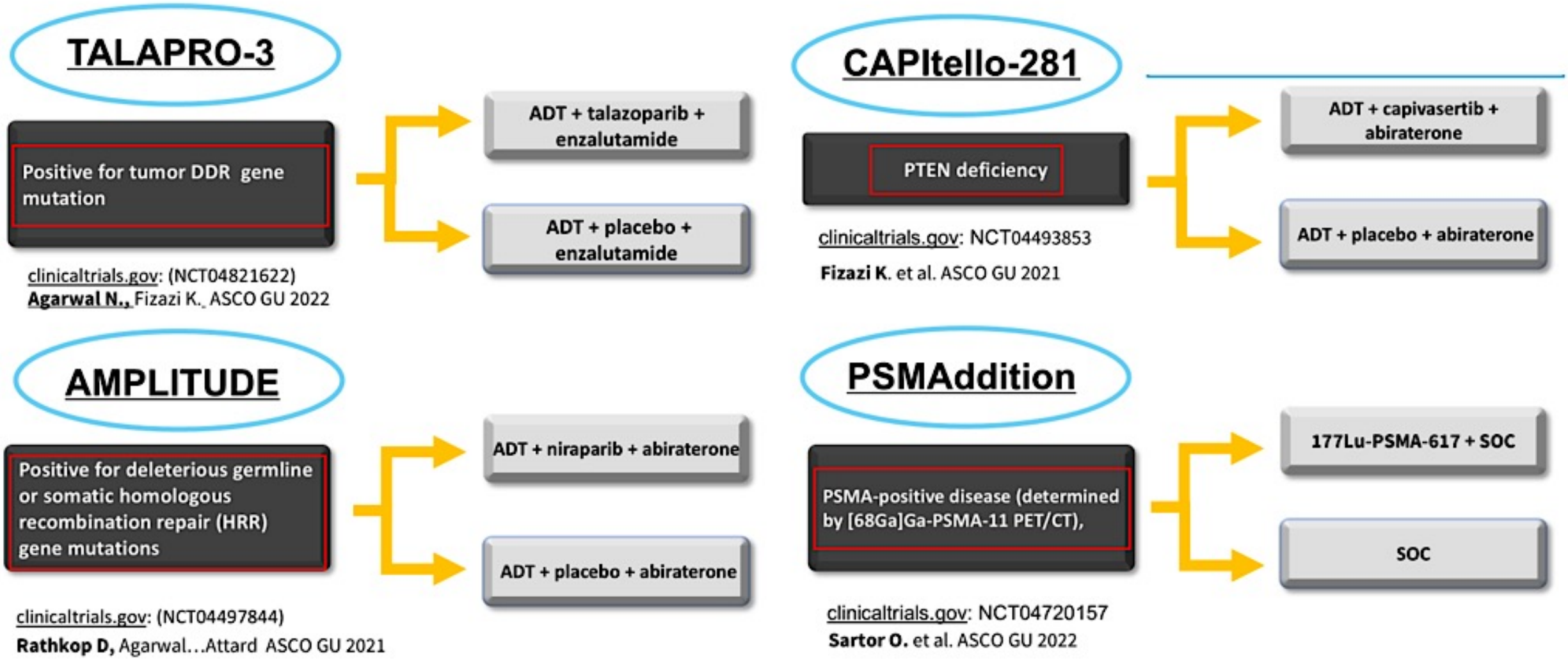
CAPItello-281
Capivasertib + Abiraterone + ADT in PTEN-Deficient mHSPC

- **Capivasertib: a PI3K/AKT signaling pathway inhibitor, prevents proliferation and tumor growth**
  - **A biomarker-driven therapy selection (PTEN deficiency)**
    - **Also an example treatment intensification**



ClinicalTrials.gov. https://clinicaltrials.gov/study/NCT04493853

mHSPC: Ongoing Biomarkers Based Phase 3 Trials



Courtesy Dr. Maha Hussein

Conclusions and Clinical Implications mHSPC

- Dose intensification with novel hormonal agents (NHA) and/or docetaxel, combined with ADT, is considered to be standard of care.
- Side effect profile of various agents, volume of disease, de novo vs metachronous cancer and concurrent medical conditions can be used to select treatment.
- Despite multiple positive clinical trials, the acceptance rate of dose intensification (doublet/triplet) remains low.
- Many new trials include biomarker assessment (PTEN, HRR, etc.).
- Trials are evaluating Lu-177 PSMA, PARP inhibition, novel agents in the metastatic hormone sensitive state.

Treatment options for mHSPC in the de novo and relapsed settings

Professor Karim Fizazi, MD, PhD (Villejuif, France)

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QUESTIONS FOR THE FACULTY

How would you most likely approach treatment for a 75-year-old man with:

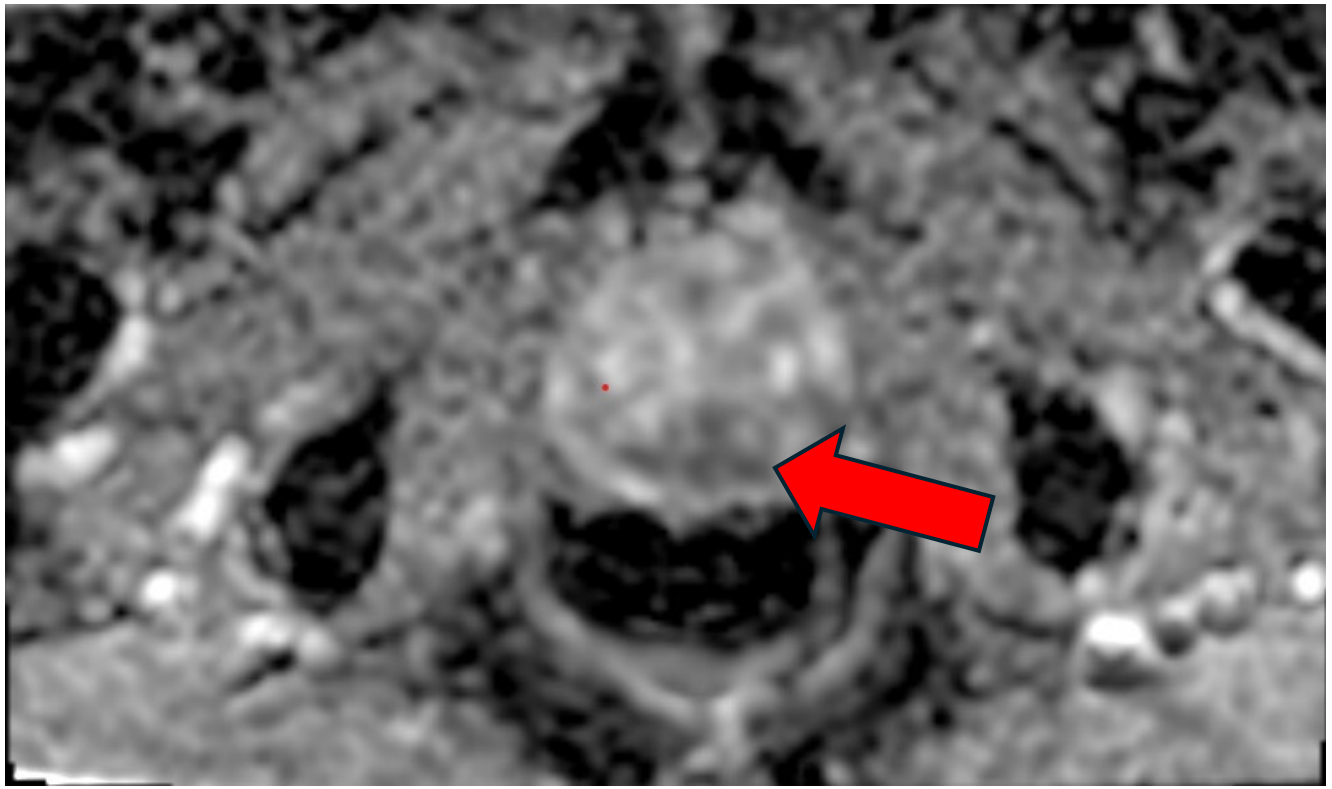
1. **De novo mHSPC with multiple asymptomatic bone-only metastases**
2. **A rapid PSA doubling time after local therapy with multiple asymptomatic bone-only metastases on PSMA PET but not on conventional imaging**
   - **ADT alone or ADT with abiraterone/prednisone or a "lutamide"? Which "lutamide"?**
   - **Docetaxel?**
   - **Intermittent endocrine therapy?**
   - **Enzalutamide monotherapy? Continuous or intermittent?**
   - **Role of evaluating PSA and intensifying or de-escalating therapy?**

Case Presentation: Dr Gomella

- 75 yo cardiologist.
- No major medical issues. No significant family Hx. DRE: no nodules.
- Not previously interested in PSA due to “poor” screening data.
- Worsening LUTS, started on tamsulosin by PCP.
- Minimal change in LUTS, started on finasteride 5/2024. PSA 8.7.
- No change in LUTS, referred to urology. PSA 11/2024 now 14.89.
- MRI prostate with PIRADS 4, >65cc with nodular BPH features.

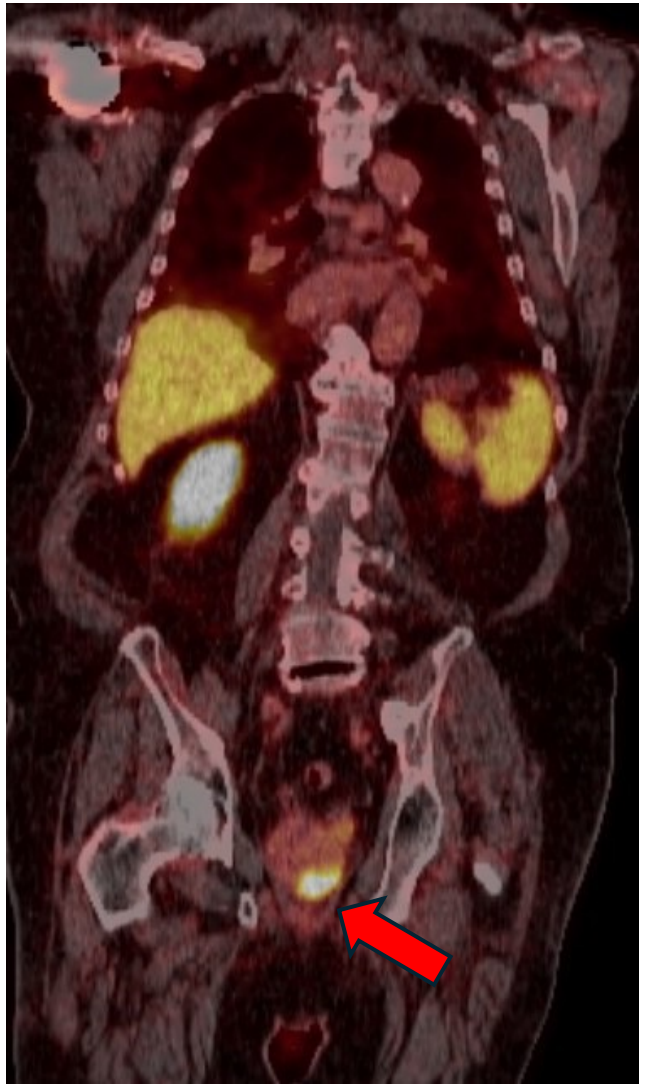
Case Presentation: Dr Gomella (cont'd) – Biopsy

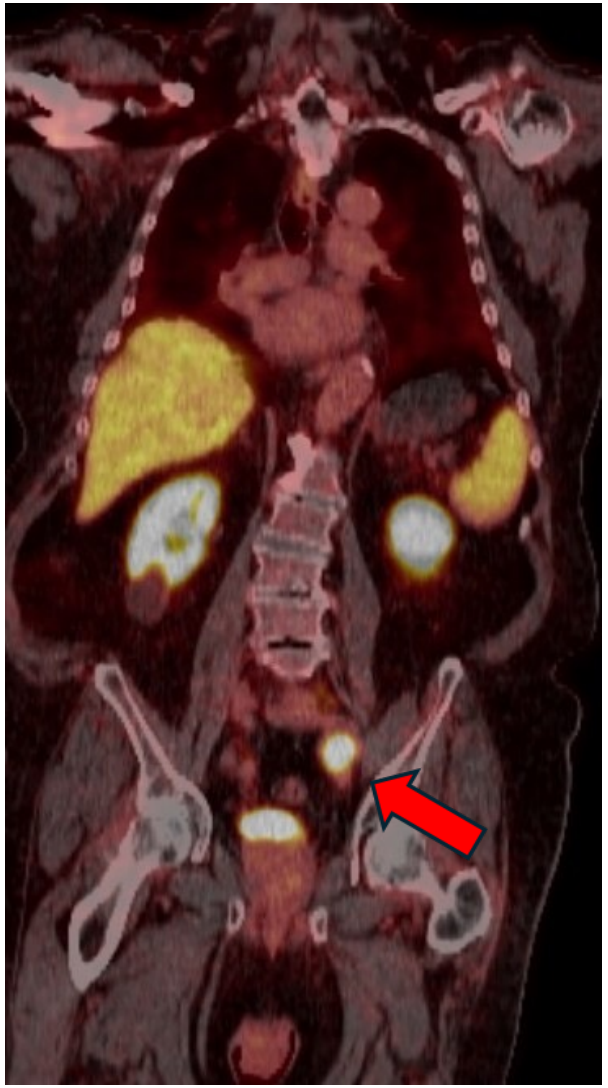
- Transperineal biopsy
- 7/12 cores GG 5
- 20-70% of core length



Case Presentation: Dr Gomella (cont'd) – Imaging and Markers

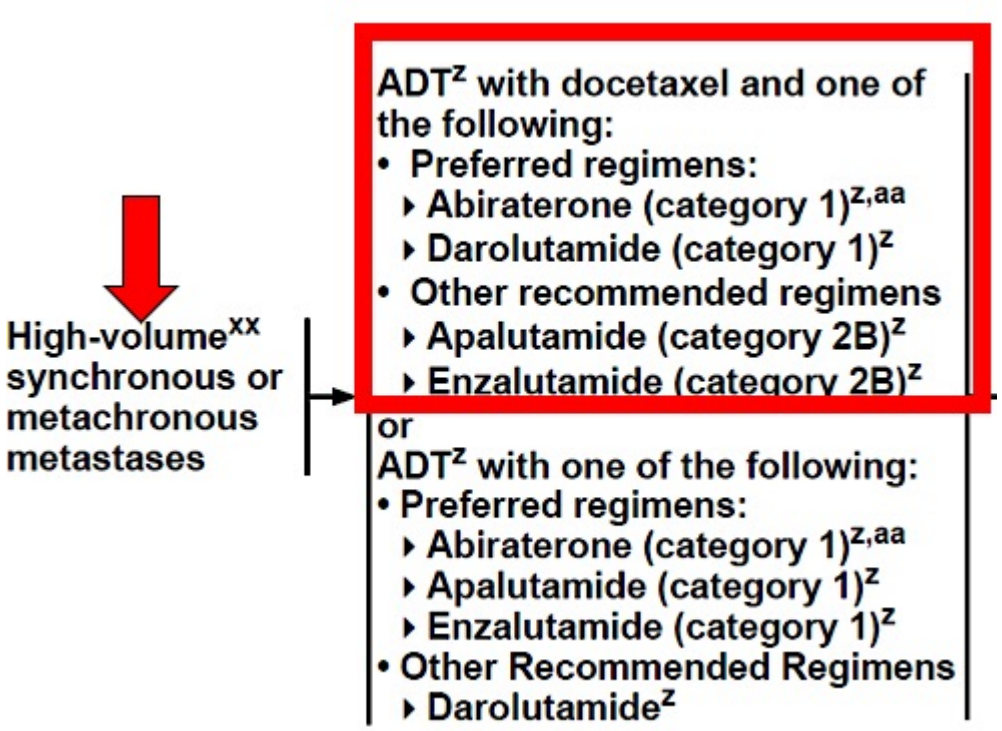
- PSMA Scan
  - Activity in the posterior mid/left central gland at the prostate apex
  - Left common iliac, many smaller retroperitoneal nodes
- Dx = high volume mHSPC
- Testosterone 385
- Negative germline testing





Case Presentation: Dr Gomella (cont'd) – Treatment Options

- Due to high volume, high Gleason grade group, primary consideration after clinical trial evaluation is triplet therapy



Potential integration of PARP inhibitors into the treatment of mHSPC

Professor Karim Fizazi, MD, PhD
(Villejuif, France)

Emmanuel S Antonarakis, MD
(Minneapolis, Minnesota)

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QUESTIONS FOR THE FACULTY

What outcomes from ongoing Phase III trials of PARP inhibitors in mHSPC would prompt you to employ them in that setting? What would you be looking for in terms of hazard ratios/advantages in PFS or OS?

If PARP inhibitors eventually reach the clinic for mHSPC, how would you select between this strategy and triplet therapy with an AR pathway inhibitor, docetaxel and ADT?

For how long would you likely administer the PARP inhibitor if these agents were available in mHSPC? How concerned are you about the risk of MDS/AML with prolonged use?

Case Presentation: Dr Gomella

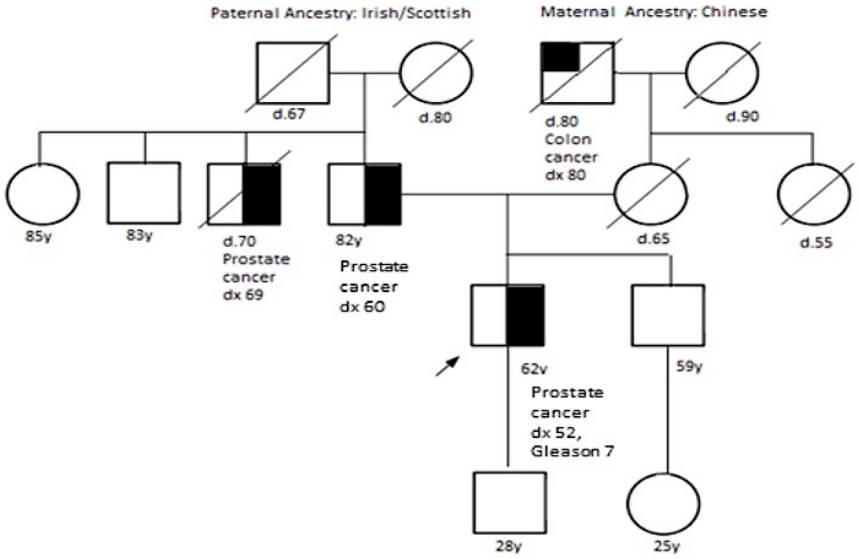
- March 2018: 59-year-old white male presents to PCP for routine, annual follow up appointment. Patient has no specific complaints.
- Saw program on TV about prostate cancer and asked about PSA test.
- He obtains his first PSA.
- PSA 38, repeated 41.

Case Presentation: Dr Gomella (cont'd)

- No MRI done
- Prostate biopsy: Gleason 3 + 4 = 6/10 cores
- CT chest/abd/pelvis: No soft tissue or visceral mets
- Bone scan: L3/L4 and right ischial lesions c/w metastatic prostate cancer
- PSMA testing not available in this area
- Urologist starts patient on ADT with leuprolide and refers to medical oncology for further management

Case Presentation: Dr Gomella (cont'd)

- Medical oncologist determines family history of hereditary prostate cancer and colon cancer.
- Germline sequencing: Pathogenic BRCA2 mutation.
- Somatic testing not done.



Case Presentation: Dr Gomella (cont'd)

The same screening advertisement for PSA screening also discussed the importance of clinical trial participation. The patient wants to be involved a clinical trial.

Trial	Regimen	Population
CAPItello-281 (NCT04493853)	ADT + abiraterone ± capivasertib	De novo mHSPC, PTEN deficiency (planned N = 1000)
TALAPRO-3 (NCT04821622)	Enzalutamide ± talazoparib	mHSPC, DDR mutation (planned N = 550)
AMPLITUDE (NCT04497844)	Abiraterone/prednisone ± niraparib	mHSPC, HRR gene alteration (planned N = 788)
PSMAddition (NCT04720157)	AR-directed tx + ADT ± ^{177}Lu-PSMA-617	mHSPC, PSMA positive (planned N = 1126)
EvoPAR-Prostate01 (NCT06120491)	Saruparib + NHA	mHSPC, HRRm and Non-HRRm (planned N = 1800)

Case Presentation: Dr Gomella (cont'd)

Some mHSPC clinical trial options for this patient based on his current clinical data.

Trial	Regimen	Population
CAPItello-281 (NCT04493853)	ADT + abiraterone ± capivasertib	De novo mHSPC, PTEN deficiency (planned N = 1000)
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Agenda

Module 1: Current Treatment Landscape for Metastatic Hormone-Sensitive Prostate Cancer (mHSPC) — Dr Gomella

Module 2: Clinical Implications of and Appropriate Strategies to Identify PTEN Deficiency in Prostate Cancer — Dr Yu

Module 3: Emerging Role of AKT Inhibition for mHSPC — Dr George

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CANCER CONSORTIUM

AUA - Emerging Role of AKT Inhibitors in Prostate Cancer Symposium

Neil Love – Research To Practice

Evan Y. Yu, M.D

Section Head, Medical Oncology, Clinical Research Division
Medical Director, Clinical Research Support
Fred Hutchinson Cancer Center
Professor of Medicine, Division of Hematology & Oncology
University of Washington, Seattle, WA

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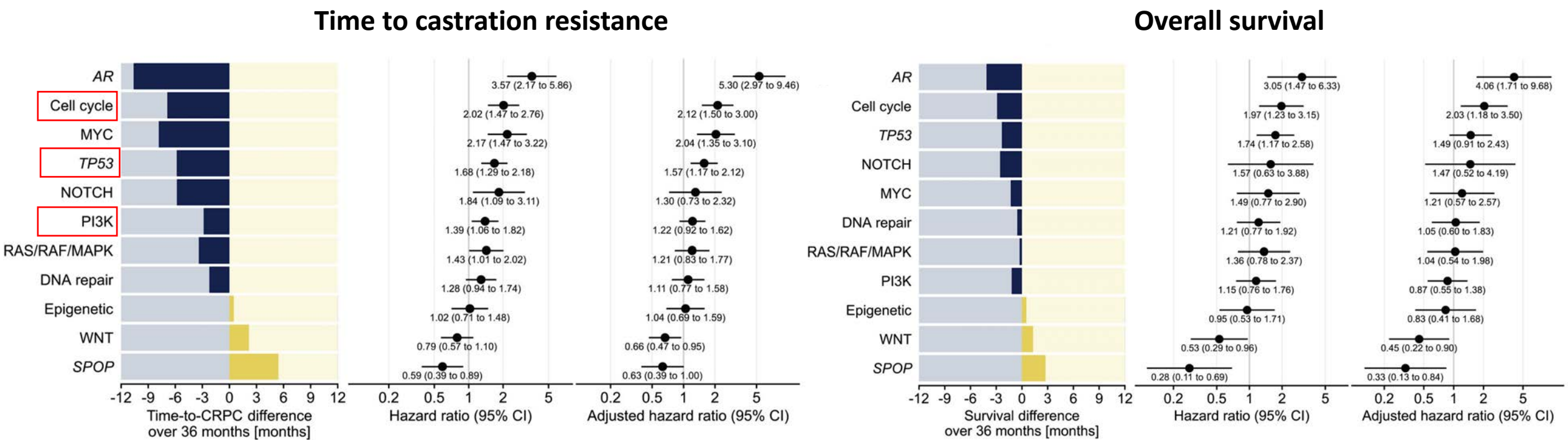
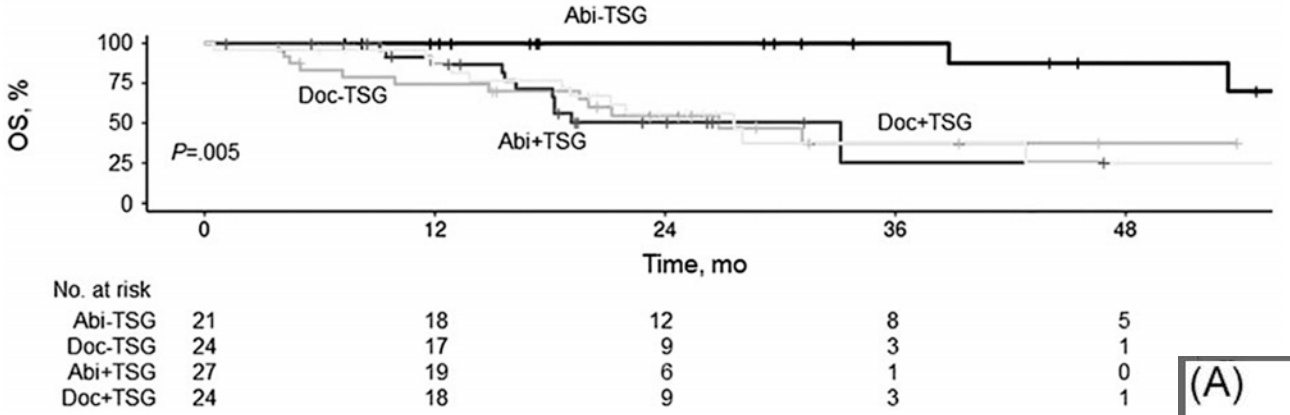
Outcomes Based on Tumor Suppressor Gene (TSG) Alterations in Metastatic Hormone-Sensitive Prostate Cancer

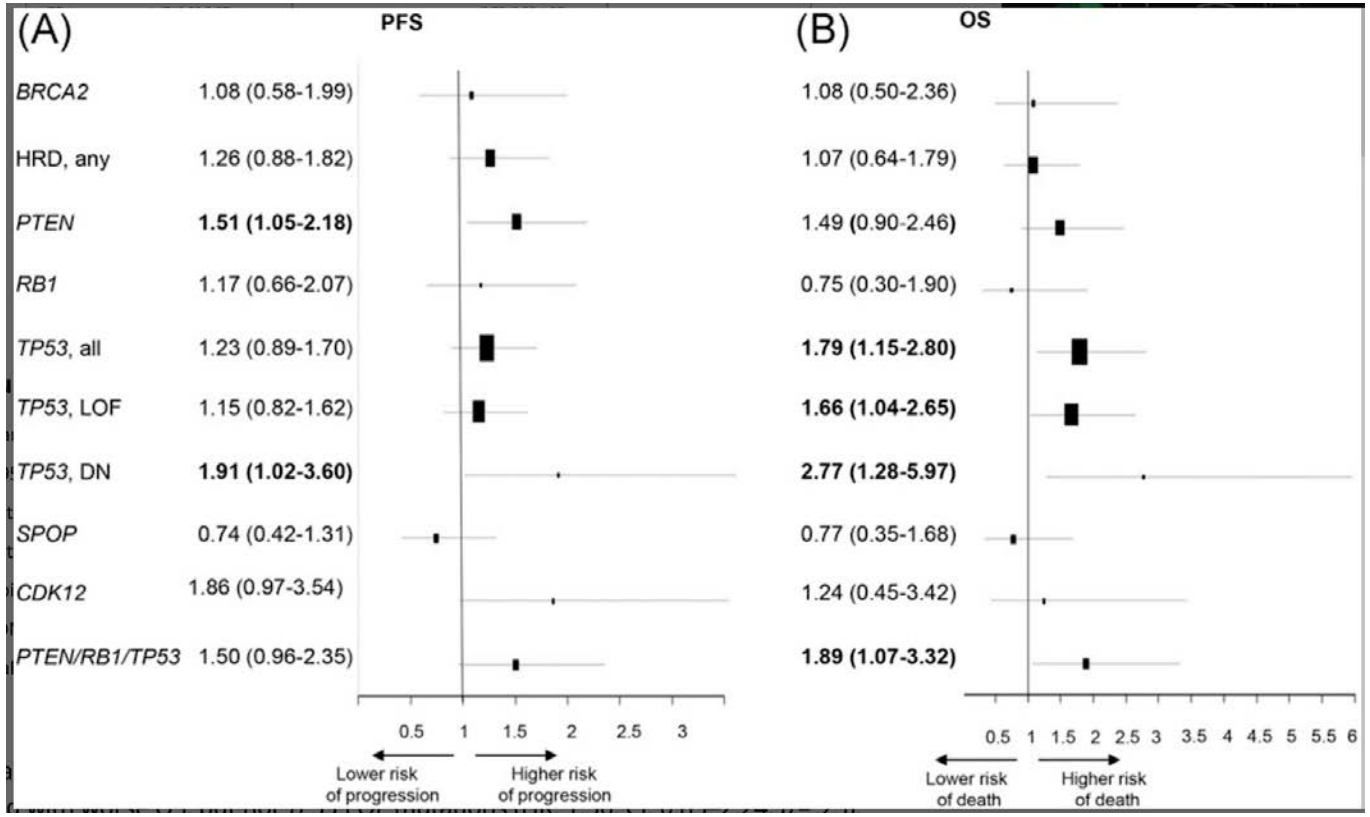


Stopsack et al. CCR 2020.

Outcomes Based on Tumor Suppressor Gene (TSG) Alterations in Metastatic Hormone-Sensitive Prostate Cancer (Continued)

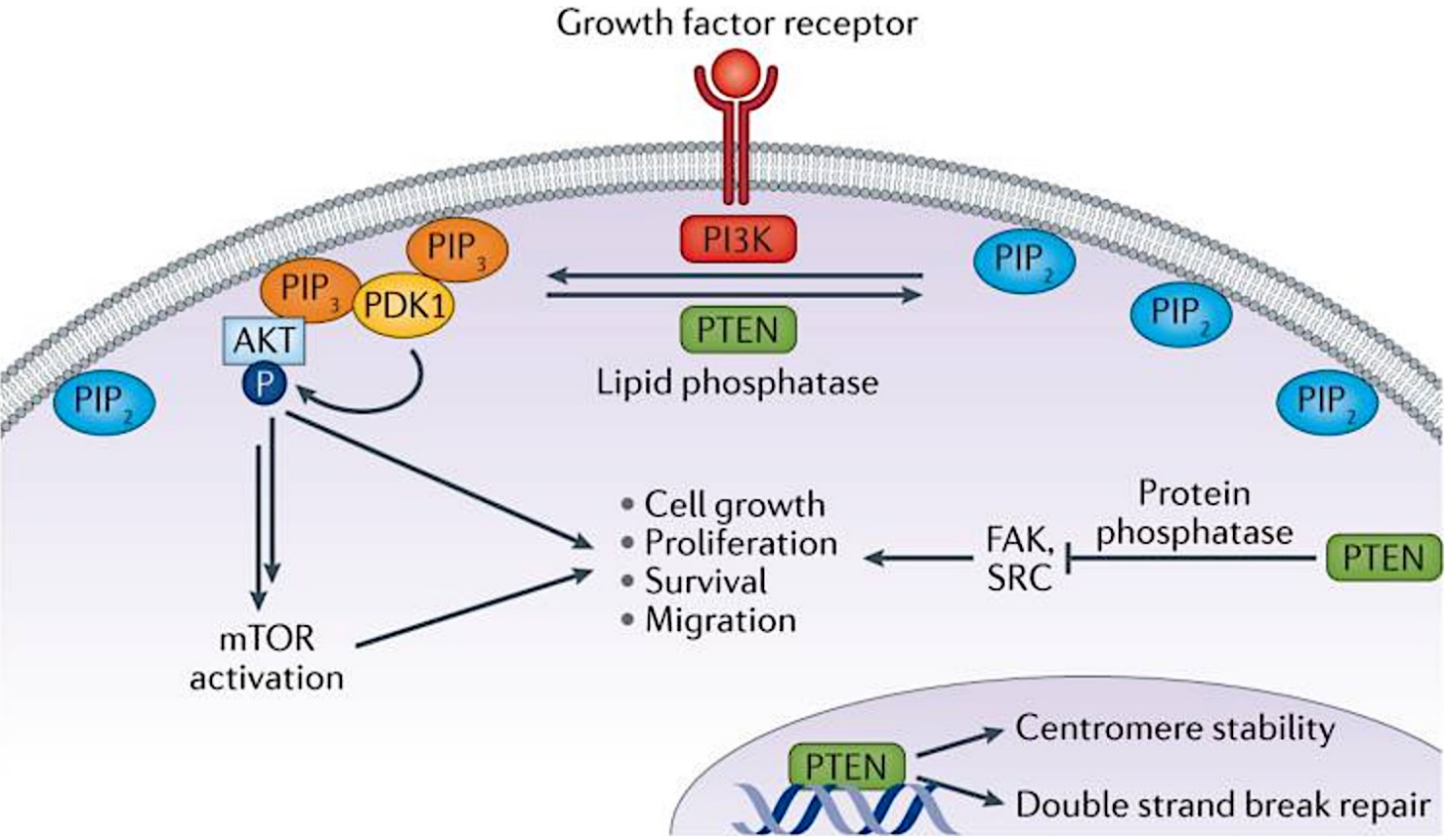


- **Radiographic PFS and OS Worse with TSG alteration**



Velez et al. 2020
Nizialek et al. Prostate 2020.

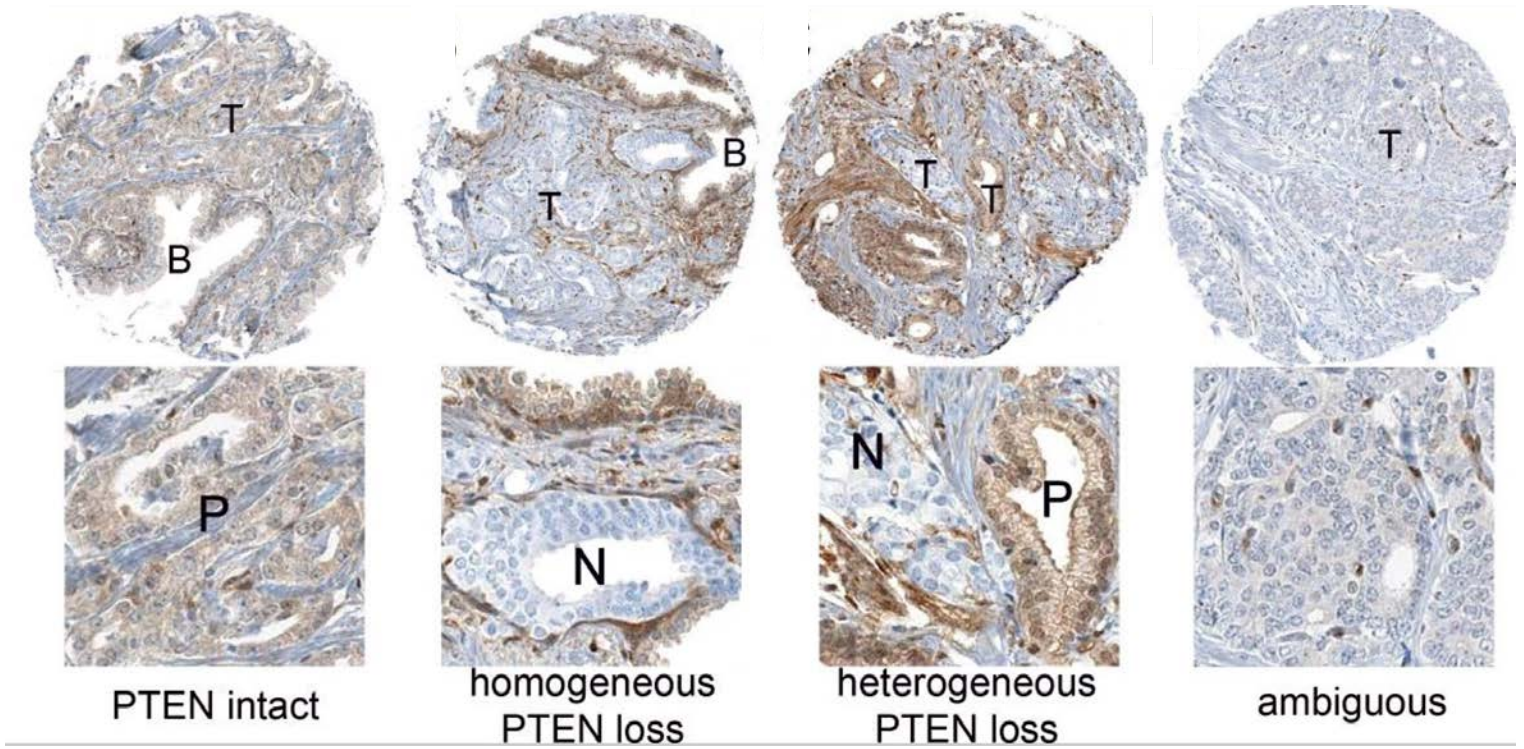
PTEN Deficiency in Prostate Tumor Formation and Progression



- Under normal conditions, PTEN antagonizes PI3K signaling by converting PIP3 back to PIP2.
- Functional loss of PTEN leads to accumulation of PIP3 which activates PI3K/AKT signaling promoting increased cell proliferation, survival and migration.
- PTEN loss has also been shown to cooperate with oncogenic mutations resulting in accelerated disease progression and therapeutic resistance.

Turnham DJ et al. *Cells* 2020; *9*(11), 2342.

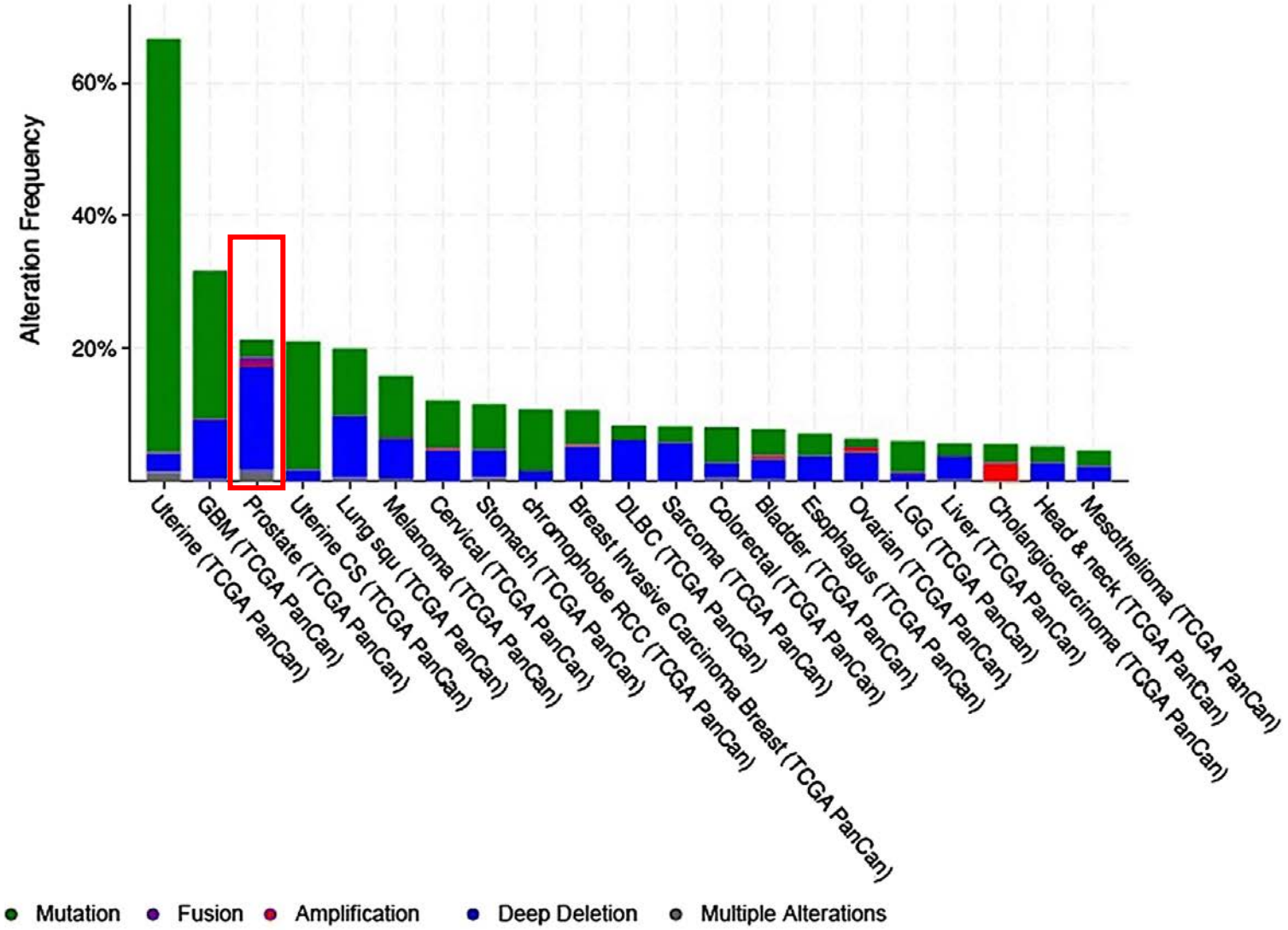
Methods to Assess PTEN Deficiency in Prostate Cancer



- IHC is the preferred testing method for PTEN deficiency/alterations in prostate cancer.
- IHC can detect PTEN protein levels compromised by mutations and other mechanisms undetectable by FISH/NGS.
- NGS is not recommended as it is less efficient and cost-effective than IHC and does not capture all forms of alterations that can lead to loss of protein expression.

Lotan TL, et al. Oncotarget. 2017; Jul 10;8(39):65566-65576.

Frequency of PTEN Deficiency in Patients with Prostate Cancer



Prevalence of *PTEN* mutations in different cancers. The graph is from cbioportal and has been restricted to pancancer studies

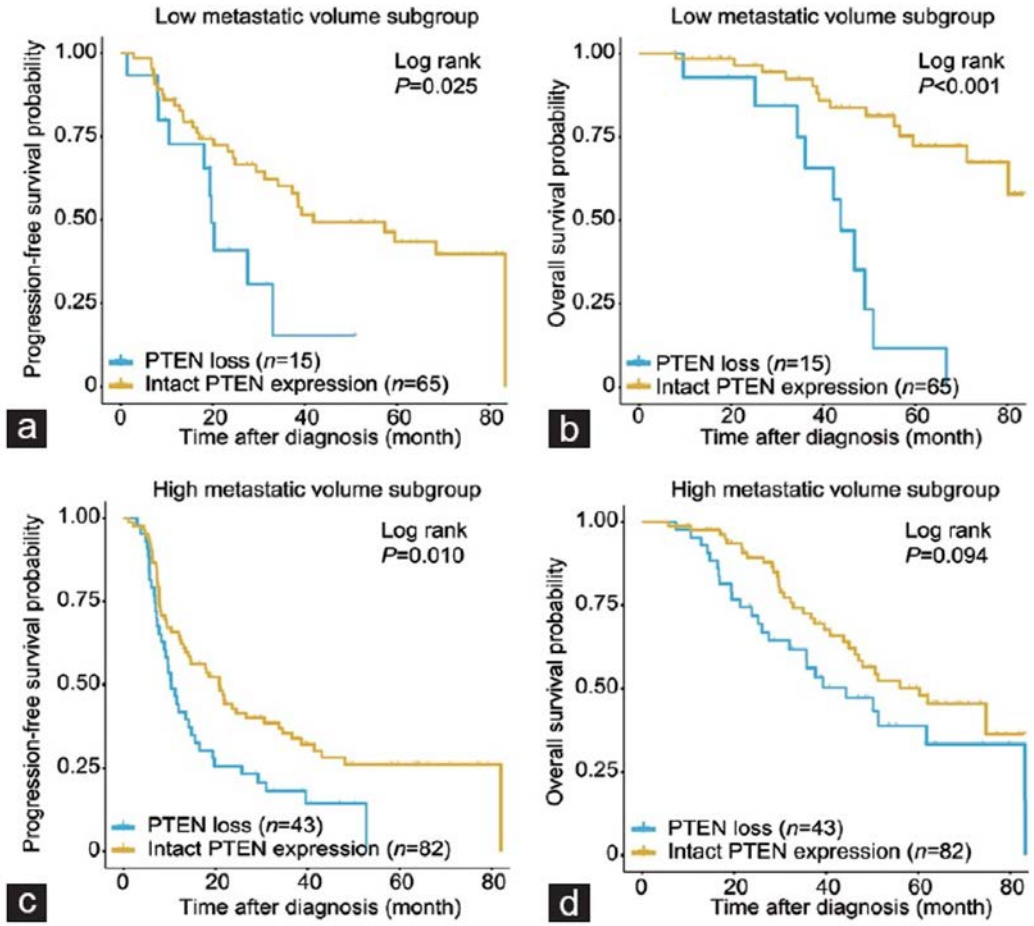
- PTEN is the most commonly lost tumor suppressor gene in primary prostate cancer, being observed in approximately 40-50% of cases by microsatellite analysis (higher by FISH)
  - 15-20% of surgically treated cases
  - ~40% in metastatic PC
- In CRPC, PTEN loss is more significant than in earlier stages, with approximately 30% of patients exhibiting deep and likely homozygous deletions, accompanied by additional mutations and gene fusions in another 10%.
- These genetic alterations contribute to the aggressive nature of CRPC and its resistance to conventional therapies.

Cetintas, V.B., Batada, N.N. *J Transl Med* **18**, 45 (2020). Esteban-Villarrubia, J et al. Immuno 2024; 4, 444–460.

Prognostic Value of PTEN in de novo Metastatic Prostate Cancer

Patient characteristic	PTEN expression		P
	Loss (total=58)	Intact (total=147)	
Age (year), median	68	68	0.699
Baseline PSA (ng ml^{-1}), *n* (%)			0.723
≤172	28 (48.3)	75 (51.0)	
>172	30 (51.7)	72 (49.0)	
Hemoglobin (g l^{-1}), *n* (%)			0.370
Normal (≥120)	45 (77.6)	122 (83.0)	
Decreased (<120)	13 (22.4)	25 (17.0)	
Albumin (g l^{-1}), *n* (%)			0.416
Normal (≥40)	44 (75.9)	119 (81.0)	
Decreased (<40)	14 (24.1)	28 (19.0)	
LDH (U l^{-1}), *n* (%)			0.010
Normal (≤250)	47 (81.0)	137 (93.2)	
Elevated (>250)	11 (19.0)	10 (6.8)	
ALP (U l^{-1}), *n* (%)			0.026
Normal (≤160)	32 (55.2)	105 (71.4)	
Elevated (>160)	26 (44.8)	42 (28.6)	
ECOG performance status, *n* (%)			0.202
<2	45 (77.6)	125 (85.0)	
≥2	13 (22.4)	22 (15.0)	
Gleason score, *n* (%)			0.289
<8	5 (8.6)	7 (4.8)	
≥8	53 (91.4)	140 (95.2)	
Metastatic volume, *n* (%)			0.017
Low	15 (25.9)	65 (44.2)	
High	43 (74.1)	82 (55.8)	

PSA: prostate-specific antigen; LDH: lactate dehydrogenase; ALP: alkaline phosphatase; ECOG: Eastern Cooperative Oncology Group; PTEN: phosphatase and tensin homolog on chromosome 10

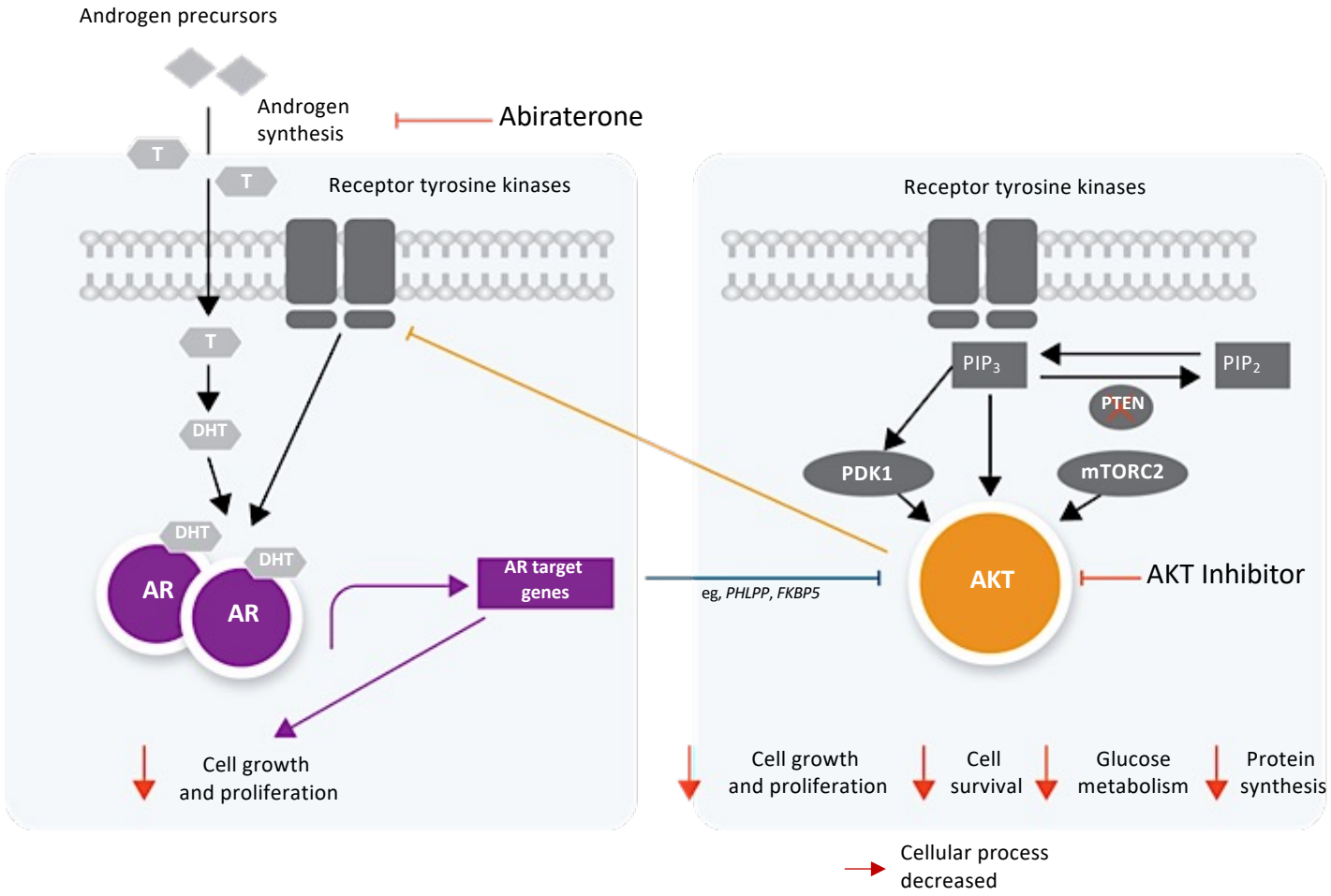


- PTEN loss was associated with higher metastatic volume; however, a correlation between PTEN loss and Gleason score, which was reported in localized prostate cancer, was not observed in this cohort.
- PTEN loss predicts poor prognosis for patients with CNPC independent of metastatic volume. PTEN expression evaluated by immunohistochemistry may be used for better risk stratification and subgroup analysis in clinical trials.

Zhang, Jun-Yu et al. Asian Journal of Andrology 24(1):p 50-55, Jan–Feb 2022.

Overview of PTEN-PI3K-AKT and Intersection with AR Pathway

Rationale for Dual Pathway Inhibition



Cross talk between P13K/AKT and AR pathways leads to reciprocal activation when one of the pathways is inhibited, providing an alternative mechanism for tumor growth and survival

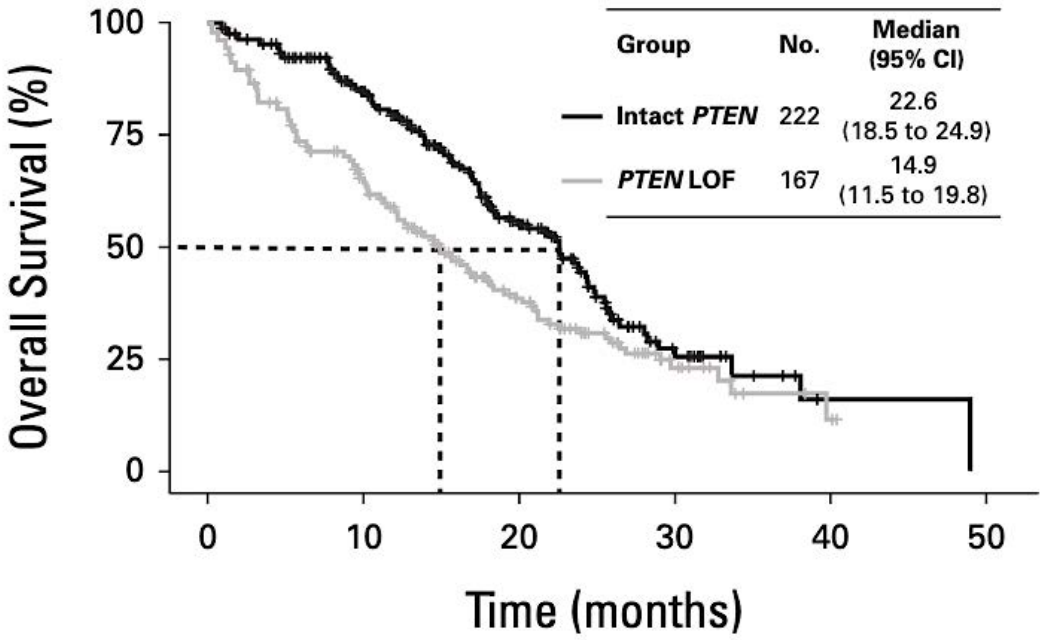
Dual targeting of both pathways may increase antitumor activity

Ipatasertib and Capivasertib are potent AKT Inhibitors

de Bono J et al *Ann Oncol*. 2020;31(suppl 4):s1142-s1215.

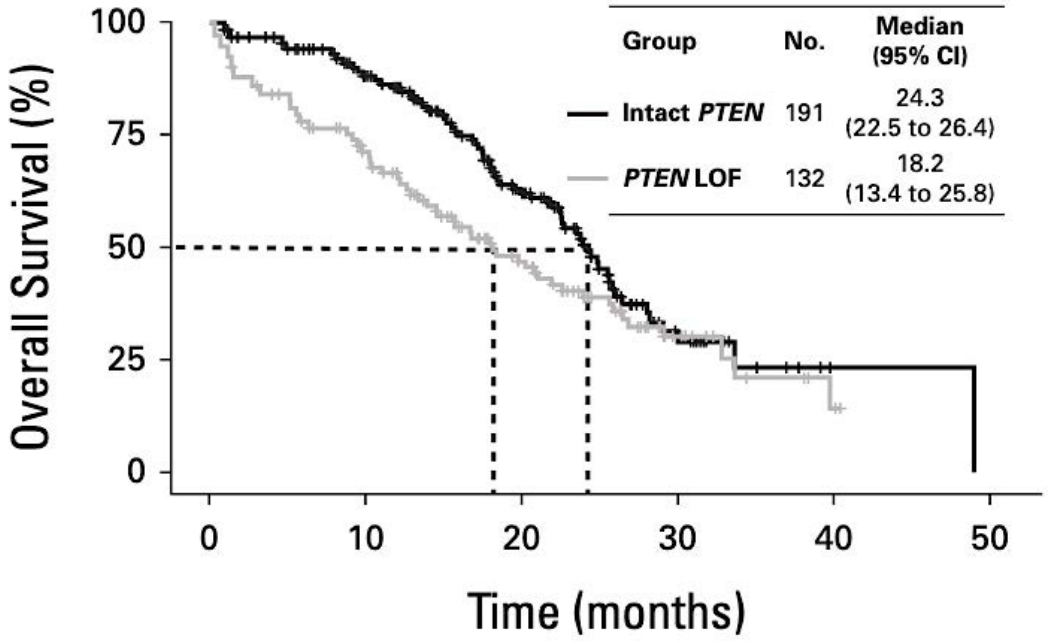
Real-World OS by PTEN Status in mCRPC

Intact PTEN vs PTEN Loss-of-Function



No. at risk:						
Intact *PTEN*	82	108	69	15	1	0
PTEN LOF	50	69	40	13	2	0

Intact PTEN vs PTEN Loss-of-Function Treated with NHT

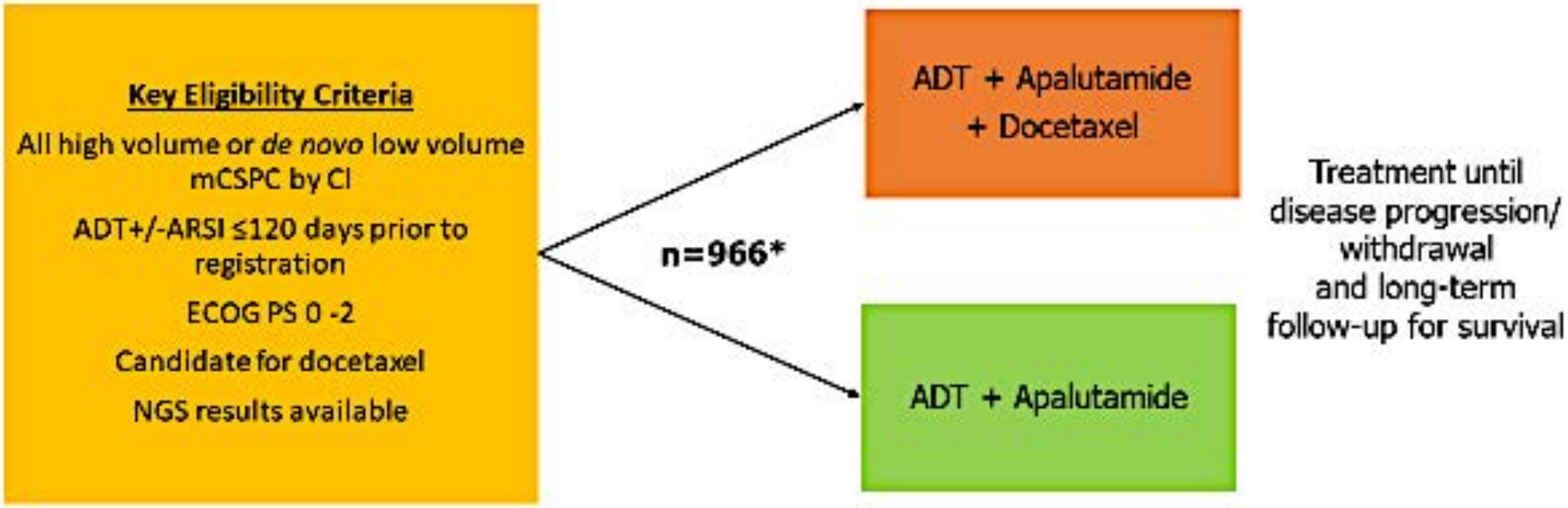


No. at risk:						
Intact *PTEN*	63	95	65	14	1	0
PTEN LOF	36	58	37	11	2	0

Gupta S et al. *JCO Precis Oncol*. 2024;8:e2300562.

Alliance Group ASPIRE Trial is Coming

Study Schema – Phase 3 "ASPIRE" Trial



Stratification
-**TSG alteration 0 vs 1 vs 2+**
-*De novo* high volume versus metachronous high volume versus *de novo* low volume
(modified CHAARTED)

TSG altered: any copy number loss or deleterious mutation in one or more (TP53, PTEN or RB1) on tissue testing from any CLIA based assay.
*updated sample size based on GUSC input

Primary Endpoint:
Overall Survival

mCSPC: metastatic castrate-sensitive prostate cancer; CI: conventional imaging (CT/MRI and bone scan); ADT: androgen deprivation therapy; ARSI: androgen receptor signaling inhibitor; ECOG PS: Eastern Cooperative Oncology Group performance status; TSG: Tumor suppressor gene; NGS: next generation sequencing.

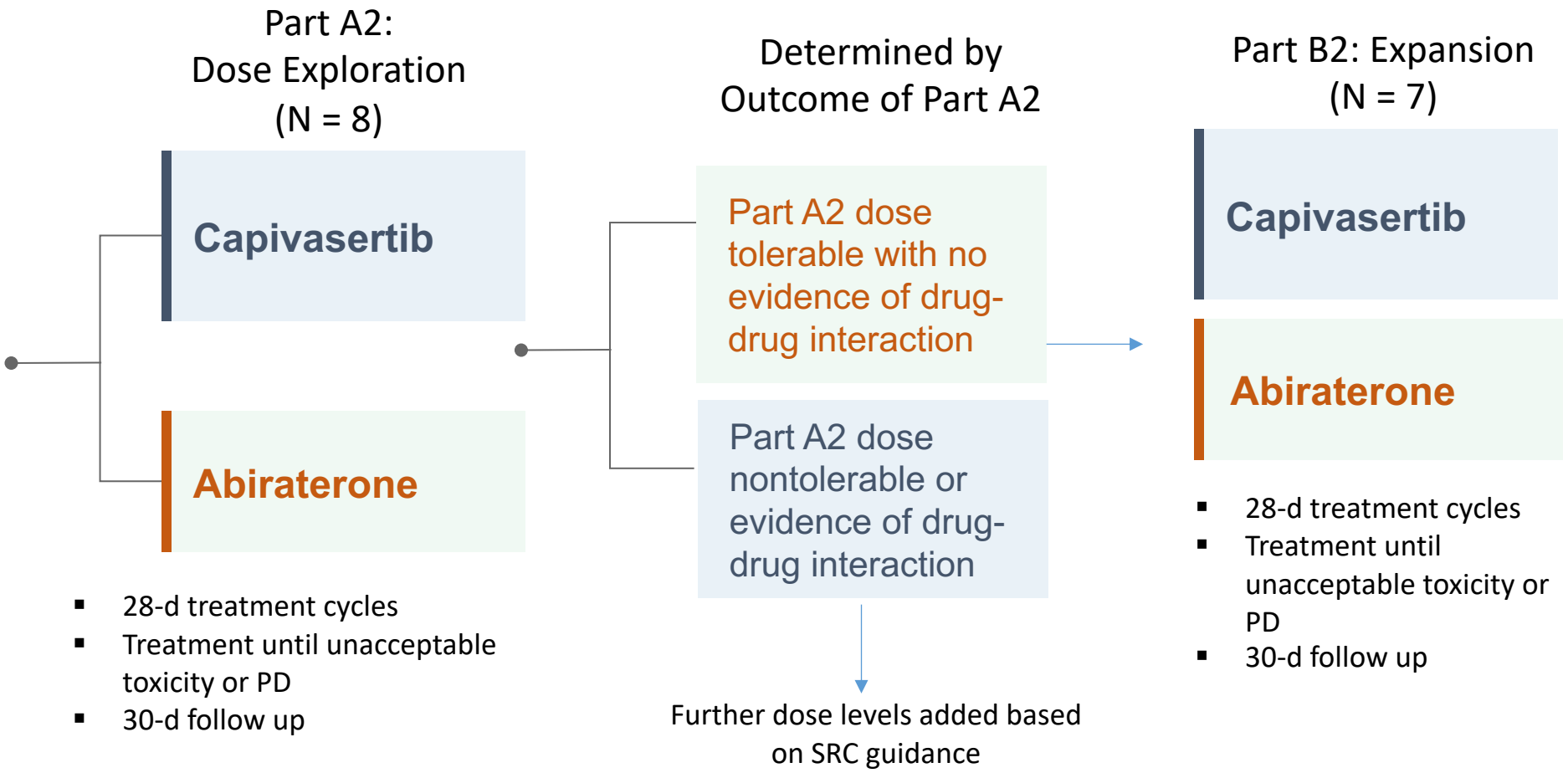
ECOG-ACRIN cancer research group
Alliance for Clinical Trials in Oncology

Phase 1 Trial of Capivasertib + Abiraterone in Metastatic Castration-Resistant Prostate Cancer (mCRPC)

Eligible patients:

- Patients with mCRPC who had ≥ 1 line of systemic therapy for mCRPC or for whom no alternative approved therapy is available
- WHO PS 0 to 2
- Cannot have had prior enzalutamide in last 8 wk

• Safety and Tolerability Phase 1 Study in Patients With mCRPC

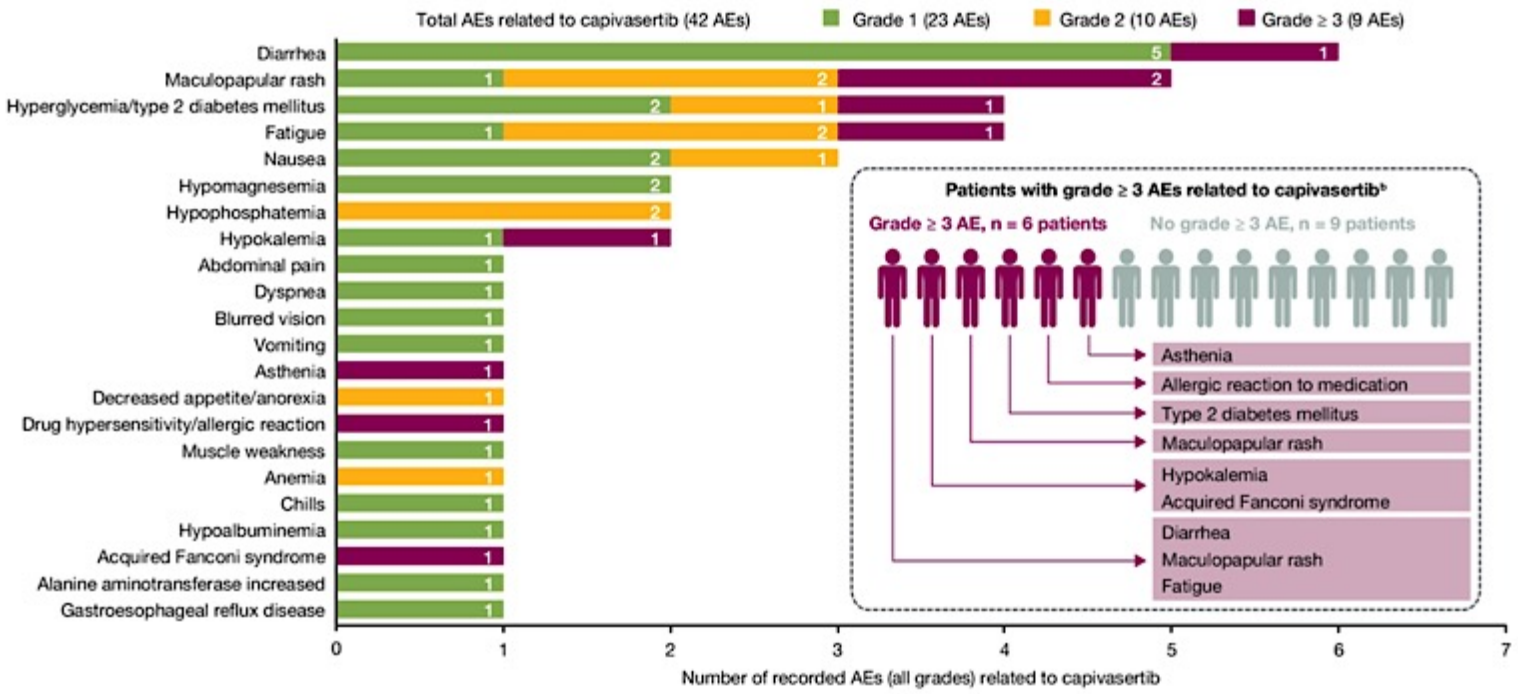


SRC, safety review committee.

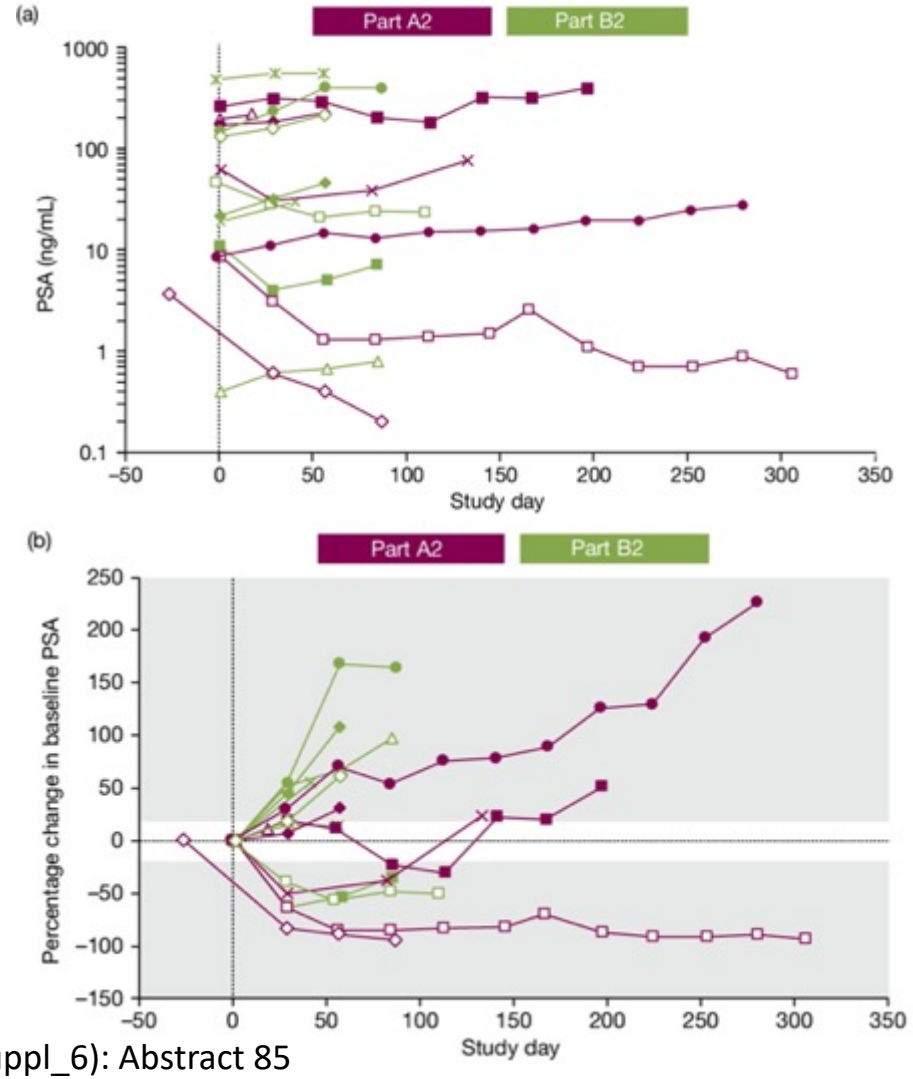
Shore N, et al. J Clin Oncol. 2021;39(suppl_6): Abstract 85; ClinicalTrials.gov. Accessed April 4, 2024. https://clinicaltrials.gov/ct2/show/NCT04087174

Phase 1 Capivasertib + Abiraterone Results

AEs of all grades related to capivasertib treatment



PSA levels (a) and percentage change in PSA levels from baseline (b) in patients with mCRPC treated with capivasertib and abiraterone



- [a]AEs were reported by the patients and the casual relationship between capivasertib and each AE was assessed by the investigator.
- [b]Six patients had a total of nine CTCAE grade ≥ 3 AEs. Seven patients had AEs recorded as grade 1 or 2, and 2 patients had no recorded AEs.
- CTCAE, Common Terminology Criteria for Adverse Events.

Shore N, et al. J Clin Oncol. 2021;39(suppl_6): Abstract 85

Capivasertib for mCRPC

ProCAID: Capivasertib and Docetaxel in mCRPC[1]

- Phase 2 trial with OS data
- Median OS: 25.3 mo for capivasertib + docetaxel vs 20.3 mo for placebo + docetaxel (HR 0.7 [95% CI: 0.47-1.05]; nominal *P* = .09)
- Overall survival benefit with capivasertib was maintained in a subset of patients previously treated with abiraterone and/or enzalutamide but not in abiraterone/enzalutamide-naive patients

CAPitello-280: Phase 3 Fully Accrued Study of Capivasertib + Docetaxel[2]

- A phase 3 study comparing efficacy and safety of capivasertib + docetaxel vs placebo + docetaxel in patients with mCRPC who have not previously received chemotherapy for mCRPC but whose disease has progressed on treatment with ARPI

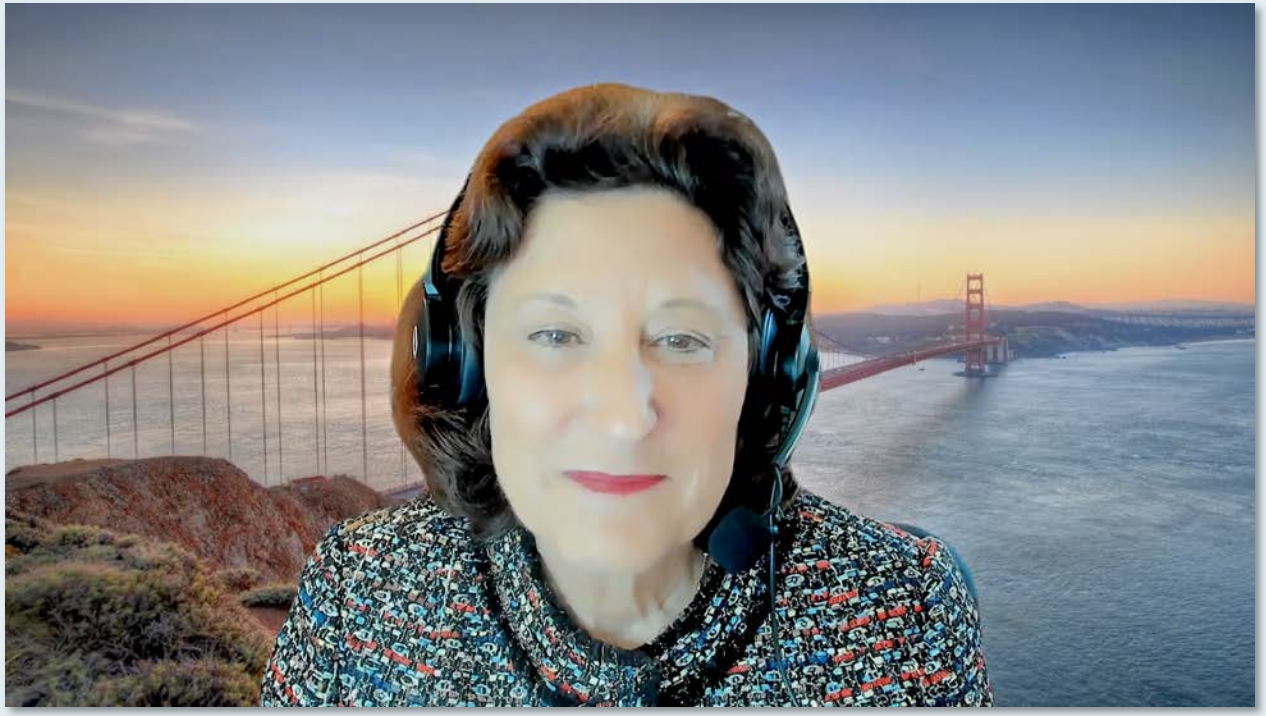
ARPI, androgen receptor pathway inhibitor.

1. Crabb S, et al. Eur Urology. 2022; 82:512-515; 2. Crabb S, et al. J Clin Oncol. 2023;41(suppl_6); TPS287.

Summary

- Current treatment for metastatic hormone sensitive prostate cancer includes doublet therapy with ADT + ARPI, at a minimum
- For patients fit for docetaxel with metastatic hormone sensitive prostate cancer, consideration should be given to add either darolutamide or abiraterone to ADT + docetaxel
  - Especially for those patients with de novo, high-volume prostate cancer
- PTEN, p53 and Rb are tumor suppressor genes that confer a poor prognosis
- It is unclear whether PTEN deficiency predisposes to better outcomes with docetaxel
- Early data looks promising for patients with PTEN deficiency and AKT inhibitors (e.g. capivasertib) and randomized phase 3 trial data for mHSPC is forthcoming
- Other classes of agents, like PSMA radioligand therapy and PARP inhibitors are also being tested in the metastatic hormone sensitive prostate cancer disease state

Use of circulating tumor DNA (ctDNA) testing to detect gene mutations in patients with prostate cancer



Hope S Rugo, MD (Duarte, California)

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QUESTIONS FOR THE FACULTY

What strategy would you use to detect PTEN deficiency if CAPItello-281 has sufficiently favorable outcomes?

How would you approach testing for PTEN deficiency in a patient with sclerotic bone metastases? Would you use archival tissue, or would you employ ctDNA testing or another method?

QUESTIONS FOR THE FACULTY

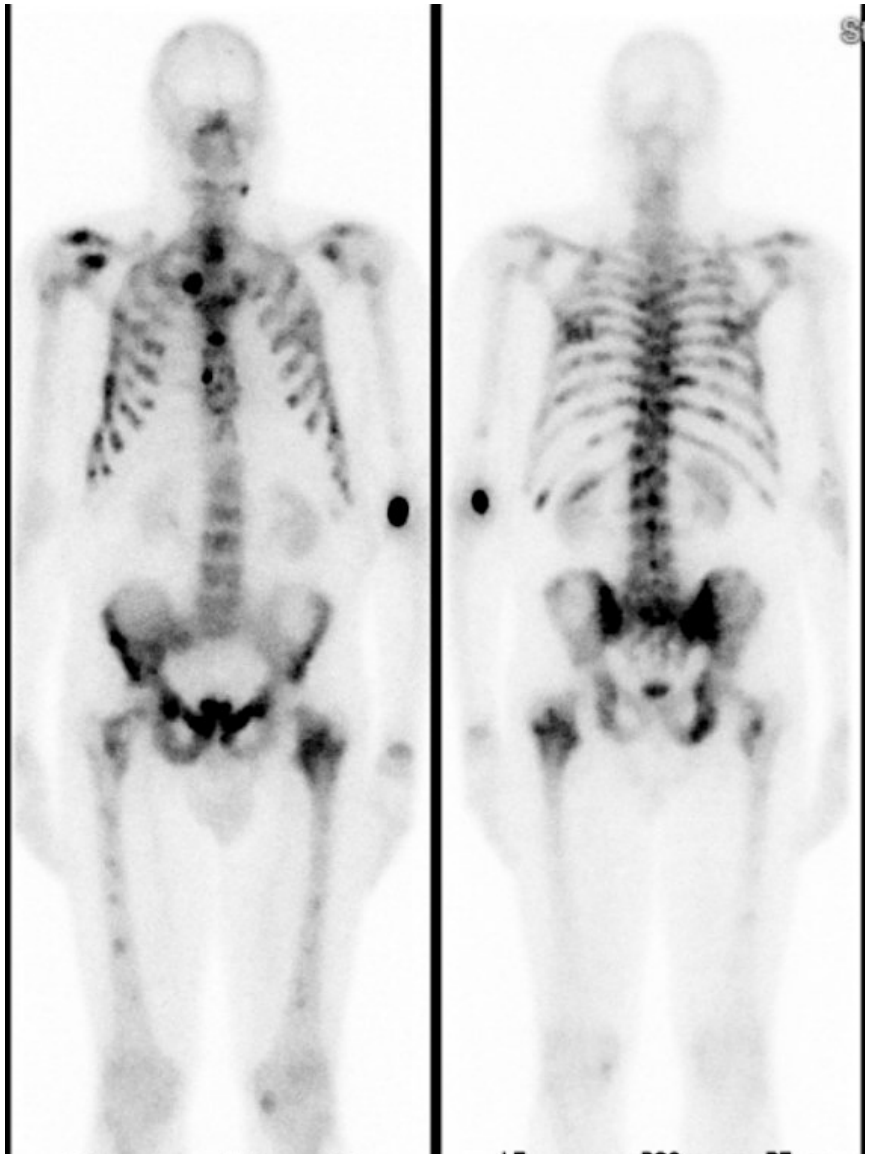
Given that CAPItello-281 has announced a PFS but not an OS benefit, do you think clinicians will want to use capivasertib/abiraterone/ADT? What hazard ratio would you need to see to enthusiastically employ capivasertib? When will these data be available?

Do recent findings suggesting that abiraterone may yield less benefit than enzalutamide or apalutamide in patients aged 75 years or older diminish your enthusiasm for capivasertib/abiraterone/ADT in older patients?

For a patient with mHSPC and PTEN deficiency for whom you would normally recommend a triplet regimen based on clinical characteristics, how would you select between an AR pathway inhibitor/docetaxel/ADT and capivasertib/abiraterone/ADT if capivasertib becomes available?

Case Presentation: Dr George

- 65 yo man who presented with bone pain in January 2025
- In November 2024 his PSA was 5.19 ng/ml. Prior PSA levels from 2017-2023 were all < 1.0 ng/ml
- 1/23/25 PSA 33.9 ng/ml
- 2/12/25 Prostate biopsies reveal multiple cores GG 4-5
- 3/6/25 Bone scan



Case Presentation: Dr George (cont'd)

- 3/12/25 Patient started on relugolix
- 3/26/25 Seen at Duke for management
- Guardant360® CDx sent revealing:

  RB1 (Tier 4: Benign or likely benign)

  A11Gfs*9VAF: 2.7%

  Contains abnormal data CDK6 (Tier 2: Potential significance)

  Amplification

  Contains abnormal data PIK3CA (Tier 2: Potential significance)

  Amplification
- 4/10/25 CT CAP – diffuse osseous metastases, no soft tissue/visceral metastases

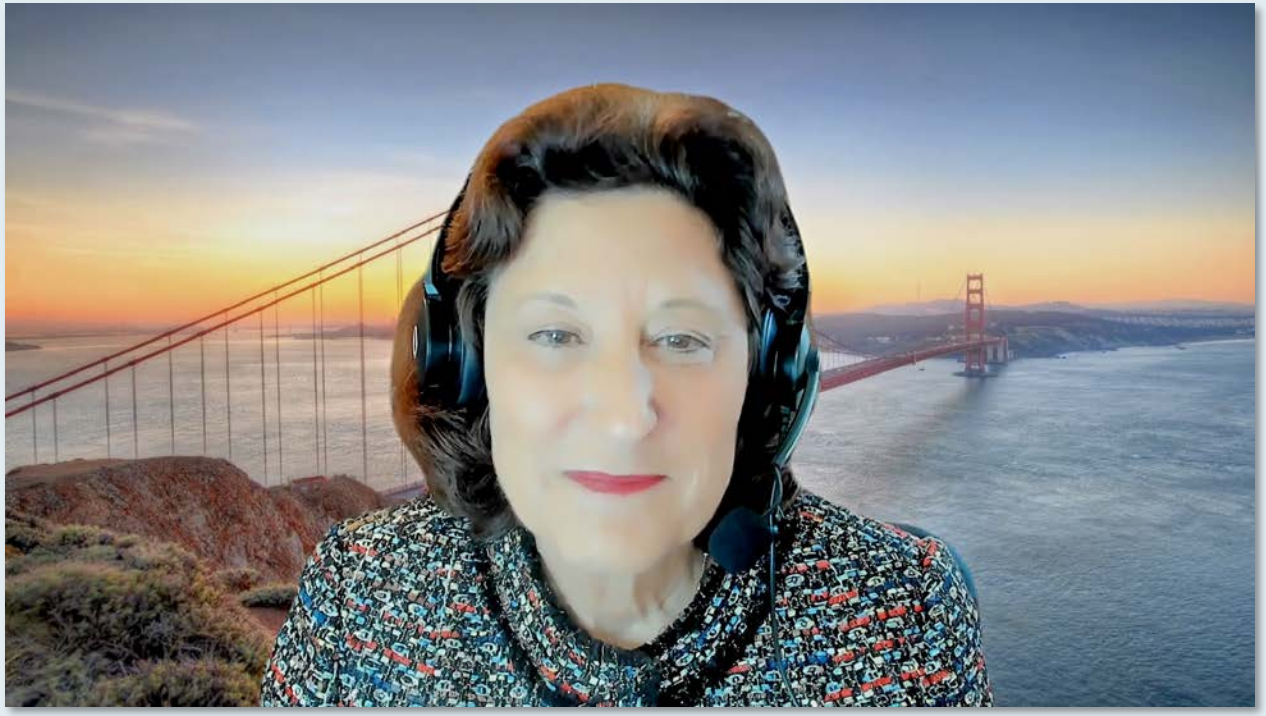
Case Presentation: Dr George (cont'd)

- What would you offer him?

- 3/26/25 Patient started on Darolutamide 600 mg BID
- 4/16/25 Patient receives C1 Docetaxel chemotherapy

- What if this patient were not a candidate for docetaxel chemotherapy? Would an AKT inhibitor make sense?

Capivasertib dosing schedule and common associated side effects



Hope S Rugo, MD (Duarte, California)

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QUESTIONS FOR THE FACULTY

How easy or difficult do you think it will be for the "typical" patient with mHSPC receiving abiraterone/prednisone/ADT to adhere to the capivasertib dosing schedule?

How frequently do patients receiving capivasertib develop rash and diarrhea? How much of a concern do you think rash and diarrhea would be for the "typical" patient with mHSPC receiving capivasertib in combination with abiraterone/prednisone/ADT?

How should antidiarrheal prophylaxis be approached for patients about to start treatment with capivasertib? How should rash and diarrhea be managed when they occur?

Case Presentation: Dr Yu

- A 60-year-old gentleman presents asymptomatically with an initial screening PSA found to be 21 ng/mL
- He has a h/o obesity, hypertension, and hyperlipidemia, but no known cardiac disease
- ECOG performance status is 0
- Labs are all WNL
- CT and bone scan imaging confirm 4 osteoblastic lesions in the thoracic and lumbar spine and 1 in the R acetabulum
- NGS reveals no alterations in *BRCA* or any other homologous recombination repair genes; however, the patient is labeled as having PTEN loss
  - This is confirmed on IHC with 90% of prostate tumor cells lacking PTEN immunostaining

Case Presentation: Dr Yu (cont'd) – Treatment Options

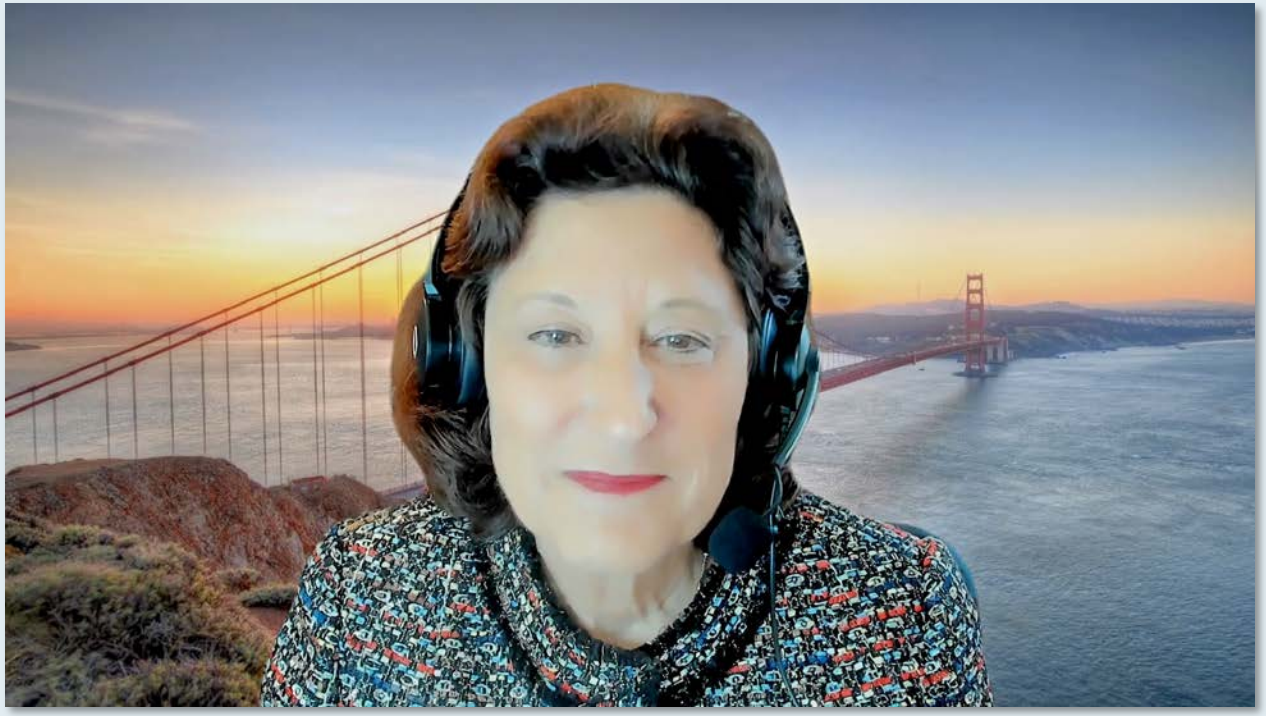
What treatment(s) should we consider for this patient?

1. ADT alone
2. ADT + abiraterone
3. ADT + abiraterone + capivasertib
4. ADT + docetaxel
5. ADT + darolutamide + docetaxel

Case Presentation: Dr Yu (cont'd) – Perspectives

- This patient has de novo, high volume disease (5 total bone metastases with 1 in the appendicular skeleton)
- He has multiple comorbidities that are not ideal for ADT, but none of which preclude him from any of the treatment intensification options
- Although ADT + abiraterone or ADT + docetaxel could be administered, he is a decent candidate for ADT + darolutamide + docetaxel
  - But do we need docetaxel?
- Given his PTEN deficiency, ADT + abiraterone + capivasertib is something to watch out for in the future

Managing hyperglycemia associated with PI3K inhibition



Hope S Rugo, MD (Duarte, California)

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QUESTIONS FOR THE FACULTY

Currently, to what extent is glucose control and diabetes management an issue for patients with metastatic prostate cancer?

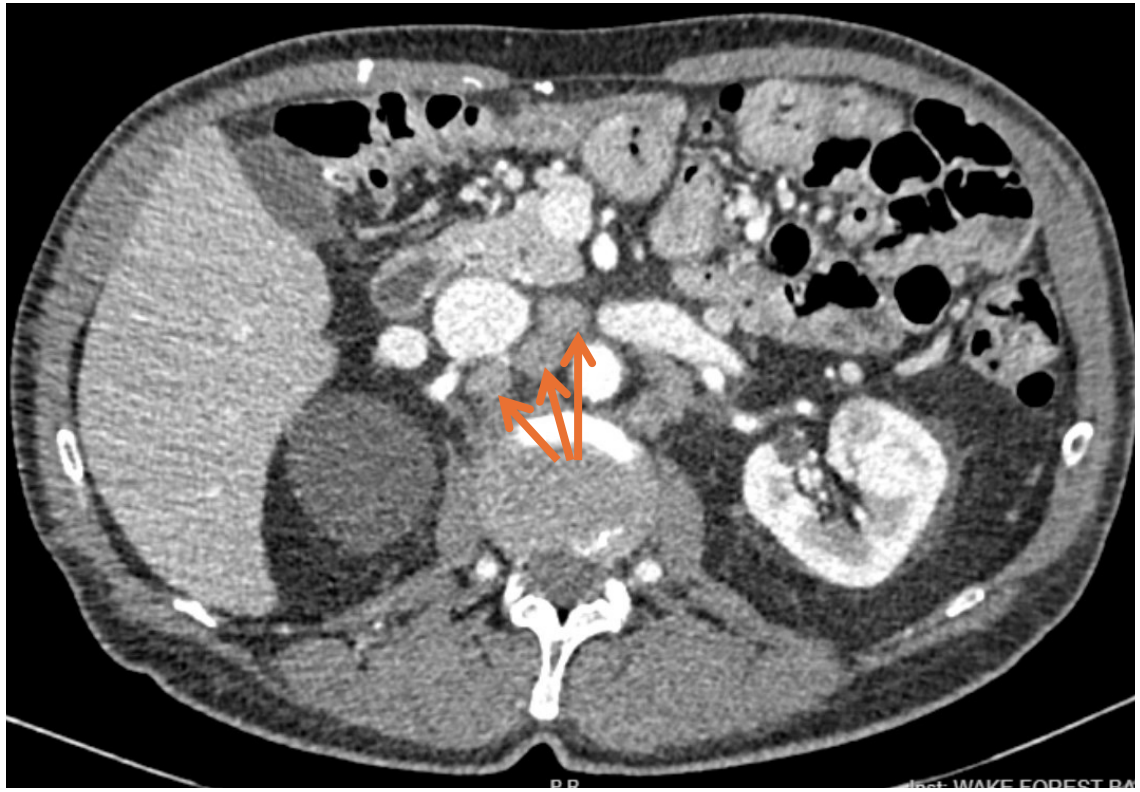
How frequently and at what severity is hyperglycemia noted in patients receiving capivasertib? How much of a concern do you think hyperglycemia would be for the "typical" patient with mHSPC receiving capivasertib in combination with abiraterone/prednisone/ADT?

Currently, do you employ continuous glucose monitoring for patients with metastatic prostate cancer and diabetes? What about GLP-1 agonists? What role might these strategies play if capivasertib were available?

How often should glucose levels be monitored in patients receiving capivasertib, and how should hyperglycemia be managed when it occurs?

Case Presentation: Dr George

- 80 year old man with a history of T2 DM, HTN, HLD, and Afib
- 2/11/25 – Presents to ED with abdominal pain. Abdominal CT reveals retroperitoneal adenopathy, multiple sclerotic bone lesions and enlarged prostate. PSA = 9.23



Case Presentation: Dr George (cont'd)

- 2/28/25 CT Chest – numerous L supraclavicular nodes, sclerotic ribs and thoracic spine lesions, PSA 9.41
- 3/6/25 FDG PET – positive uptake in supraclavicular and retroperitoneal nodes, spine, scapulae, iliac bones and sacrum
- 3/26/25 L supraclavicular node biopsy – Pathology c/w adenocarcinoma prostate origin (NKX3.1 positive)
- 4/2/25 Referred to Duke for consultation. PSA 15.3, Hgb 11.4, Alk Phos 140
- What other work up would you want?

Case Presentation: Dr George (cont'd)

Summary of Detected Somatic Alterations & Biomarkers with Associated Treatment Options

✓ Approved in indication ~ Approved in other indication ⊗ Lack of response

DETECTED ALTERATION(S) / BIOMARKER(S)	ASSOCIATED FDA-APPROVED THERAPIES	CLINICAL TRIALS (SEE PAGE 5)	% CFDNA OR COPY NUMBER
PTEN Y138C	~ Capivasertib	Yes	13.2%
PTEN Loss (Single Copy Deletion)	~ Capivasertib	Yes	DETECTED

Case Presentation: Dr George (cont'd)

- What therapy would you consider for this patient?

1. ADT alone
2. ADT + Androgen receptor pathway inhibitor
3. ADT + Androgen receptor pathway inhibitor + docetaxel
4. ADT + Androgen receptor pathway inhibitor + capivasertib

Agenda

Module 1: Current Treatment Landscape for Metastatic Hormone-Sensitive Prostate Cancer (mHSPC) — Dr Gomella

Module 2: Clinical Implications of and Appropriate Strategies to Identify PTEN Deficiency in Prostate Cancer — Dr Yu

Module 3: Emerging Role of AKT Inhibition for mHSPC — Dr George

RTP RESEARCH TO PRACTICE

Emerging Role of AKT Inhibition in Patients with mHSPC

Daniel J. George, MD
Eleanor Easley Distinguished Professor
Departments of Medicine, Surgery and Urology
Duke University School of Medicine
American Cancer Society IMPACT Research Professor
Co-lead, DCI Center for Prostate and Urologic Cancers
Duke Cancer Institute

Outline

- Role of PTEN/PI3K/Akt in Prostate Cancer
- Proof of concept: Akt + aromatase inhibitors for Advanced Breast Cancer
- IPATential150 trial evaluating ipatasertib and abiraterone in mCRPC
- Similarities and differences between ipatasertib and capivasertib
- Design and endpoints of CAPItello-281 in mHSPC
- Press release and implications for a positive result in the mHSPC landscape
- Phase III CAPItello-280 trial in mCRPC

AKT plays a central role in PTEN/PI3K/AKT pathway

The PI3K/AKT/PTEN pathway is **frequently hyperactivated** in several cancers, contributing to tumor growth, progression, and development of treatment resistance[1]

- The **PI3K/AKT/PTEN pathway** is one of the most commonly disrupted pathways in cancer cells[1]
- **AKT** plays a central role in the pathway and modulates a range of substrates involved in cell growth, proliferation, and metabolism[1]
  - AKT is a frequent driver of treatment resistance
- **Phosphatase and tensin homolog (PTEN)** is a protein that modulates PI3K/AKT signaling by preventing AKT activation[2,3]
  - PTEN deficiency activates AKT signaling resulting in: tumor growth/cell proliferation, worse outcomes and increased risk of recurrence

***PTEN prevalence*: Deficiency of PTEN protein function or gene inactivation occurs in ~25% of de novo mHSPC patients and is associated with poor outcomes[2-4]**

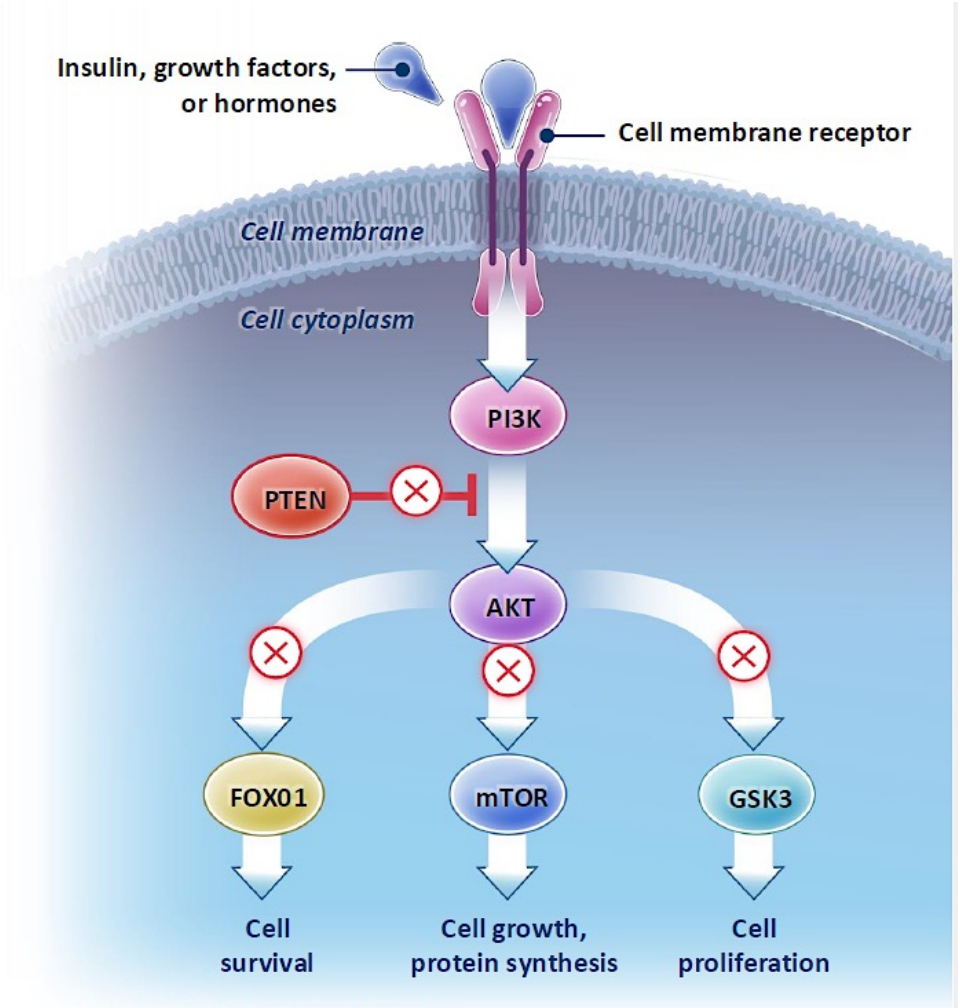


Image adapted from: Pompura, et al. 2018.

AKT, Ak strain transforming; **FOX01**, forkhead box protein 01; **GSK3**, glycogen synthase kinase 3; **mHSPC**, metastatic hormone-sensitive prostate cancer; **mTOR**, mammalian target of rapamycin; **PI3K**, phosphatidylinositol-3-kinase; **PTEN**, phosphatase and tensin homolog gene.

1. Brown JS, et al. *Pharmacol Ther*. 2017;172:101-115. 2. Marques RB, et al. *Eur Urol*. 2015;67:1177-1185. 3. Jamaspishvili T, et al. *Nat Rev Urol*. 2018;15:222-234. 4. Ferraldeschi R, et al. *Eur Urol*. 2015;67(4):795-802.

Interactive role of AR and AKT inhibition in prostate cancer

Targeting both **AR** and **PI3K/AKT/PTEN simultaneously** may help address multiple mechanisms of tumor growth and resistance

- AKT signaling activation through PTEN deficiency results in reduced benefit from AR pathway blockade
- AR signaling and the PI3K/AKT/PTEN pathway are **reciprocally cross-regulated**, so that inhibition of one leads to upregulation of the other[1]

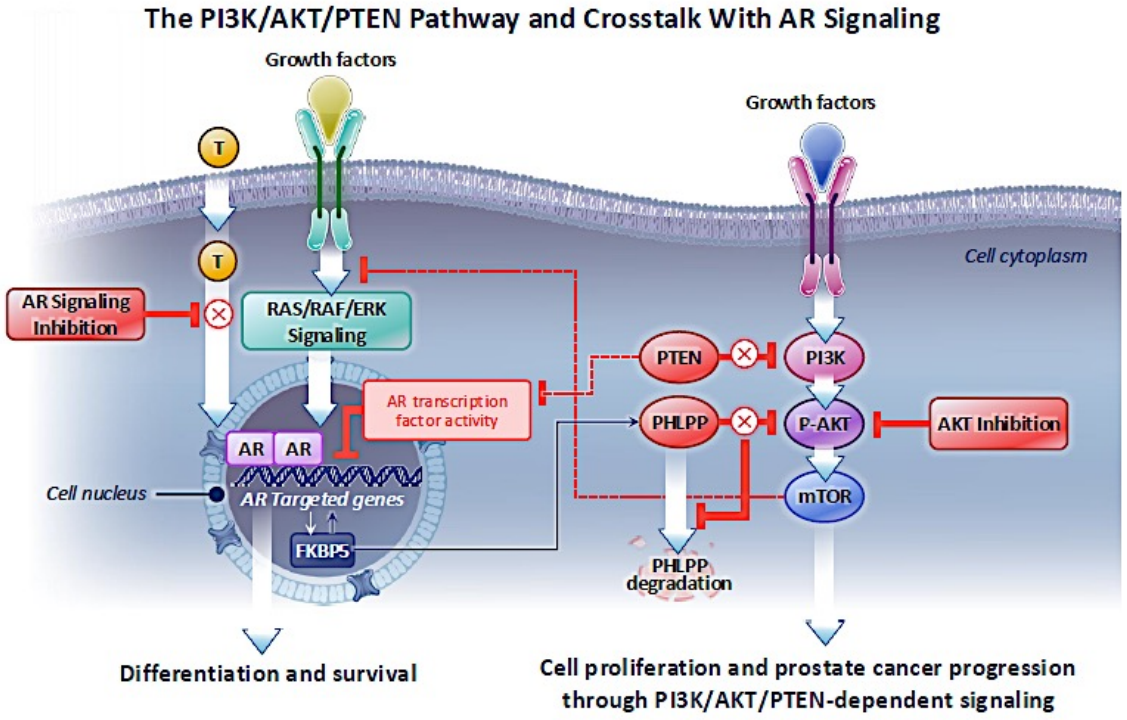


Image adapted from Fizazi, et al. 2021; modified from Mulholland, et al. 2011, and Carver, et al. 2011.[2-4]

AR, androgen receptor; **AKT**, Ak strain transforming; **ERK**, extracellular signal-regulated kinase; **FKBP5**, FK506 binding protein 5; **mTOR**, mammalian target of rapamycin; **P-AKT**, phosphorylated AKT; **PHLPP**, pleckstrin homology domain leucine-rich repeat protein phosphatase; **PI3K**, phosphatidylinositol-3-kinase; **PTEN**, phosphatase and tensin homolog gene; **T**, testosterone.

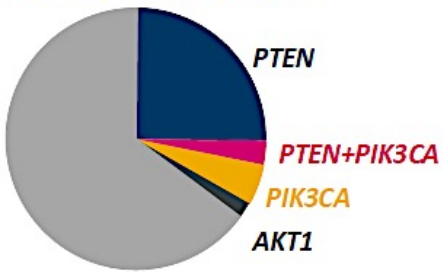
1. Gasmi A, et al. *J Clin Med*. 2022;11(1):160. doi:10.3390/jcm11010160. 2. Fizazi K, et al. Presented at ASCO-GU Virtual Congress 2021. 11–13 February. Abstract #TPS178. 3. Mulholland DJ, et al. *Cancer Cell*. 2011;19:792–804; 4. Carver BS, et al. *Cancer Cell*. 2011;19:575–586.

PTEN alterations more common in prostate than other cancers

Majority of *PTEN* alterations result in **"deficiency of protein,"**
and may be detected more accurately through IHC compared to NGS[1]

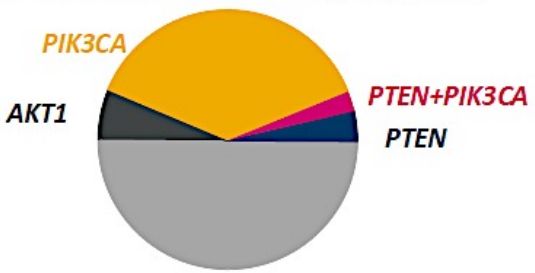
Spectrum of PI3K/AKT/PTEN Pathway Alterations in Prostate Cancer and Breast Cancer[6-8]

Metastatic Prostate Cancer



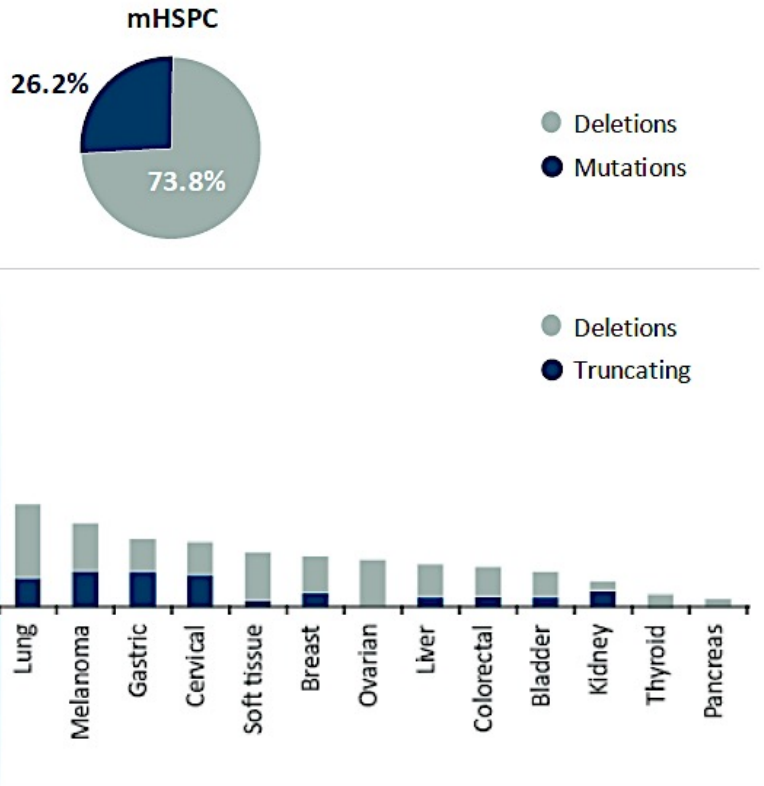
Robinson et al., Cell 2015; Sweeney et al., Lancet 2021, Abida et al., JCO 2017.

Metastatic Breast Cancer (ER+/HER2-)



based on tissue FMI data in CAPItello-291 (>500 samples)

***PTEN* gene deletions are common in prostate cancer[2-5]**

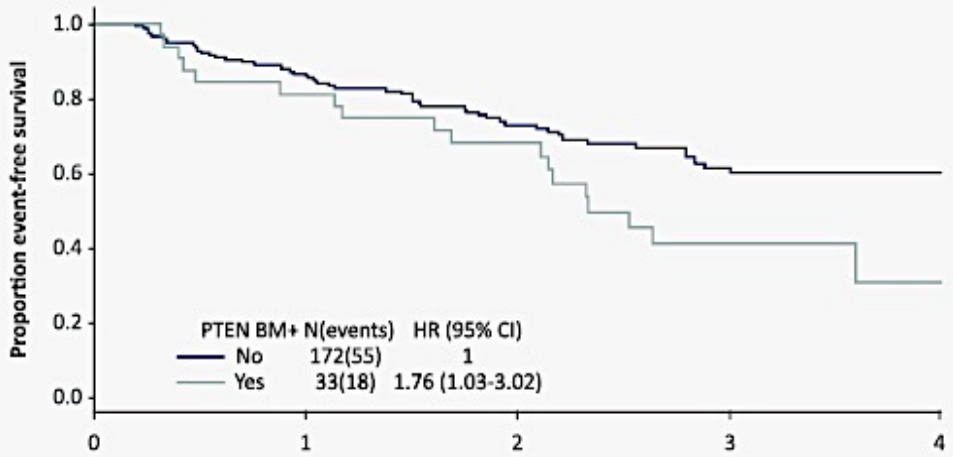


AKT, Ak strain transforming; **IHC**, immunohistochemistry; **PIK3CA**, phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha; **PI3K**, phosphatidylinositol-3-kinase; **PFS**, progression free survival; **PTEN**, phosphatase and tensin homolog gene.

1. de Bono J, et al. 2021. Presented at ASCO-GU Cancers Symposium 2021. Abstract #13. 2. Hamid AA, et al. *Eur Urol*. 2019;76(1):89-97. 3. Gilson C, et al. *J Clin Oncol Precis Oncol*. 2020;4:882-897. 4. Chalmers ZR, et al. *Prostate Cancer Prostatic Dis*. 2021;24(2):558-566. 5. Pulido R, et al. *Cold Spring Harb Perspect Med*. 2019;9(12):a036293. 6. Robinson D, et al. *Cell*. 2015;161:1215–1228. 7. Sweeney C, et al. *Lancet*. 2021; 398: 131–142. 8. Abida W, et al. *J Clin Oncol Precis Oncol*. 2017;2017:PO.17.00029. doi:10.1200/PO.17.00029.

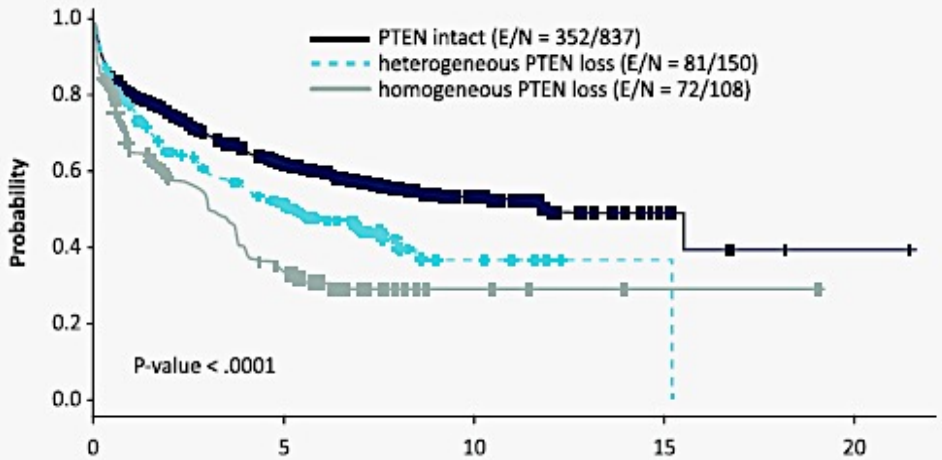
PTEN deficiency associated with worse prognosis

PFS in Patients With nmHSPC, BM+ Disease (N = 205)*[1]



Adapted from Hamid, et al. 2019.

Probability of RFS by PTEN Status[2]



Adapted from Lotan, et al. 2016.

BM+, bone-metastases positive; **HR**, hazard ratio; **mHSPC**, metastatic hormone-sensitive prostate cancer; **nmHSPC**, non-metastatic hormone-sensitive prostate cancer; **OS**, overall survival; **PFS**, progression free survival; **PTEN**, phosphatase and tensin homolog gene; **RFS**, recurrence-free survival; **TTP**, time to tumor progression.

*This curve comes from the supplementary appendix to the Hamid 2019 publication.

1. Hamid AA, et al. *Eur Urol*. 2019;76(1):89-97. 2. Lotan TL, et al. *Eur Urol Focus*. 2016;2(2):180–188. 3. Lotan TL, et al. *Oncotarget*. 2017;8(39):65566-65576. doi:10.18632/oncotarget.19217.
4. Antonarakis ES, et al. *Cancer*. 2012;118(24):6063-6071. 5. Nizialek E, et al. *Prostate*. 2021;81(9):572-579.

Capivasertib and fulvestrant for patients with aromatase inhibitor-resistant hormone receptor-positive/human epidermal growth factor receptor 2-negative advanced breast cancer: Results from the Phase III CAPItello-291 trial

Nicholas C Turner,[1] Mafalda Oliveira,[2] Sacha Howell,[3] Florence Dalenc,[4] Javier Cortes,[5] Henry Gomez,[6] Xichun Hu,[7] Komal Jhaveri,[8] Sibylle Loibl,[9] Serafin Morales Murillo,[10] Zbigniew Nowecki,[11] Meena Okera,[12] Yeon Hee Park,[13] Masakazu Toi,[14] Lyudmila Zhukova,[15] Chris Yan,[16] Gaia Schiavon,[16] Andrew Foxley,[16] and Hope S Rugo[17]

[1]Institute of Cancer Research, Royal Marsden Hospital, London, UK; [2]Medical Oncology Department, Vall d'Hebron University Hospital, Barcelona, Spain; [3]The Christie NHS Foundation Trust, Manchester, UK; [4]Institut Claudius Regaud, l'Institut Universitaire du Cancer de Toulouse Oncopole – IUCT Oncopole, Toulouse, France; [5]International Breast Cancer Center (IBCC), Barcelona, Spain; [6]Instituto Nacional de Enfermedades Neoplásicas (INEN), Departamento de Oncología Médica, Lima, Peru; [7]Shanghai Cancer Center, Fudan University, Shanghai, China; [8]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [9]GBG Forschungs GmbH, Neu-Isenburg, Germany; [10]Institut de Recerca Biomèdica, Barcelona, Spain; [11]The Maria Skłodowska Curie Memorial Cancer Center and Institute of Oncology, Warsaw, Poland; [12]ICON Cancer Centre, Adelaide, Australia; [13]Sungkyunkwan University School of Medicine, Samsung Medical Centre, Seoul, Republic of Korea; [14]Kyoto University Hospital, Kyoto, Japan; [15]Loginov Moscow Clinical Scientific Center, Moscow, Russia; [16]Oncology R&D, AstraZeneca, Cambridge, UK; [17]University of California San Francisco Helen Diller Family Comprehensive Cancer Center, San Francisco, CA, USA

CAPItello-291: Study overview

Phase III, randomized, double-blind, placebo-controlled study (NCT04305496)

Patients with HR+/HER2– ABC

- Men and pre-/post-menopausal women
- Recurrence or progression while on or <12 months from end of adjuvant AI, or progression while on prior AI for ABC
- ≤2 lines of prior endocrine therapy for ABC
- ≤1 line of chemotherapy for ABC
- Prior CDK4/6 inhibitors allowed (at least 51% required)
- No prior SERD, mTOR inhibitor, PI3K inhibitor, or AKT inhibitor
- HbA1c <8.0% (63.9 mmol/mol) and diabetes not requiring insulin allowed
- FFPE tumor sample from the primary/recurrent cancer available for retrospective central molecular testing

R1:1 (N=708)

Capivasertib	400 mg twice daily, 4 days on, 3 days off
Fulvestrant	500 mg: cycle 1, days 1 & 15; then every 4 weeks
Placebo	Twice daily, 4 days on, 3 days off
Fulvestrant	500 mg: cycle 1, days 1 & 15; then every 4 weeks

Stratification factors:
- Liver metastases (yes/no)
- Prior CDK4/6 inhibitor (yes/no)
- Region*

Dual primary endpoints

PFS by investigator assessment
- Overall
- AKT pathway-altered tumors (≥1 qualifying *PIK3CA*, *AKT1*, or *PTEN* alteration)

Key secondary endpoints

Overall survival
- Overall
- AKT pathway-altered tumors

Objective response rate
- Overall
- AKT pathway-altered tumors

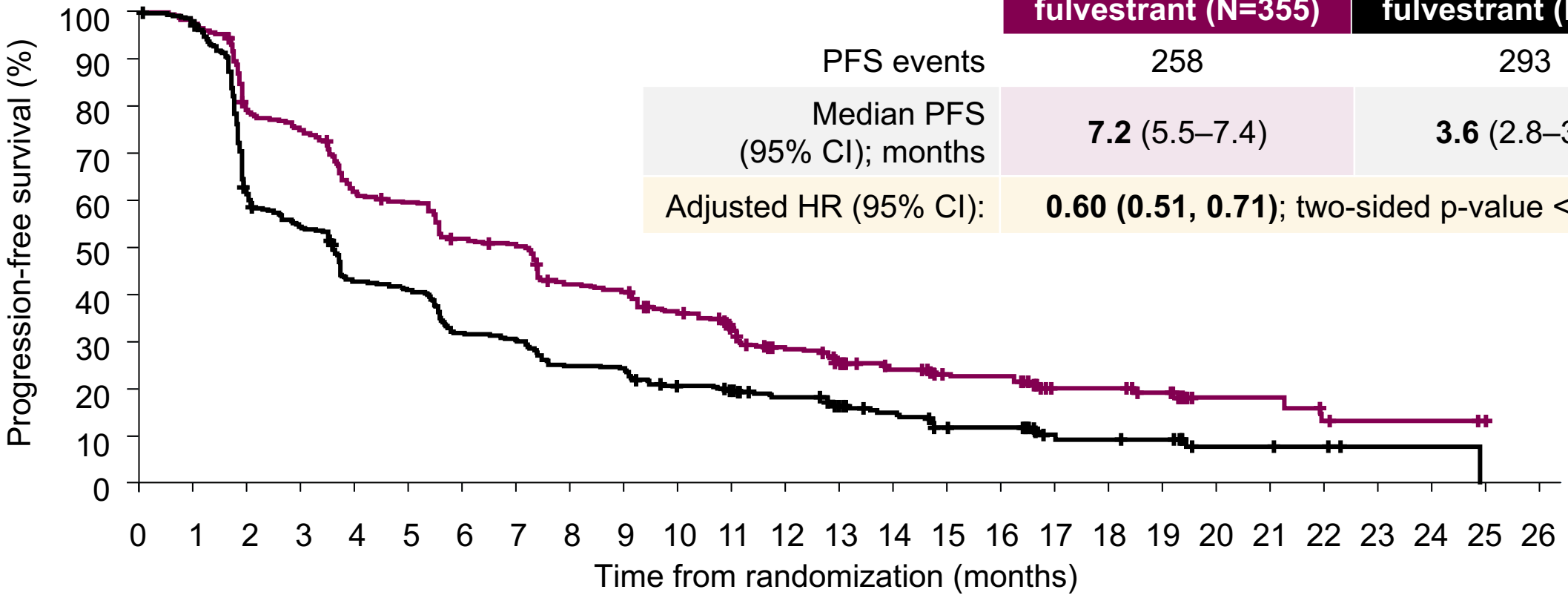
HER2– was defined as IHC 0 or 1+, or IHC 2+/ISH–. *Region 1: United States, Canada, Western Europe, Australia, and Israel, Region 2: Latin America, Eastern Europe and Russia vs Region 3: Asia.

ABC, advanced (locally advanced [inoperable] or metastatic) breast cancer.

Pre- or peri-menopausal women also received a luteinizing hormone-releasing hormone agonist for the duration of the study treatment

Dual-primary endpoint: Investigator-assessed PFS in the overall population

	Capivasertib + fulvestrant (N=355)	Placebo + fulvestrant (N=353)
PFS events	258	293
Median PFS (95% CI); months	**7.2** (5.5–7.4)	**3.6** (2.8–3.7)
Adjusted HR (95% CI):	**0.60 (0.51, 0.71)**; two-sided p-value <0.001	



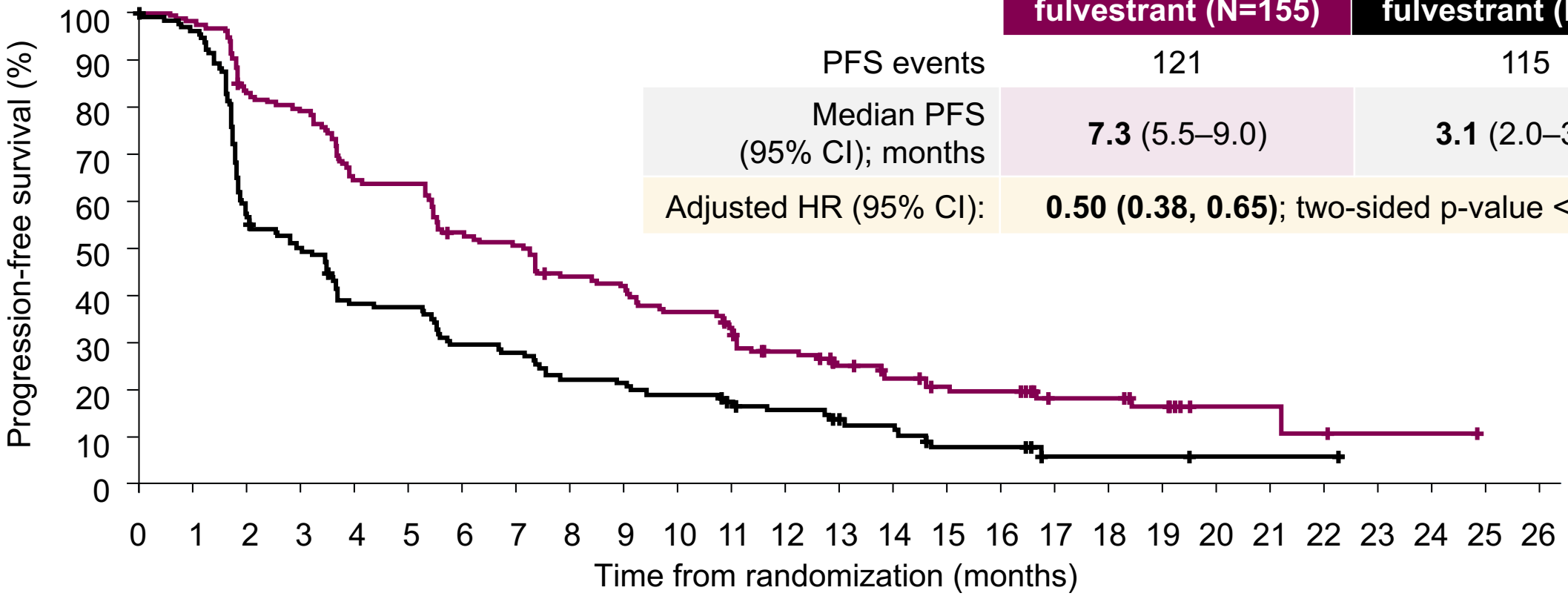
Number of patients at risk

Capivasertib + fulvestrant	355	330	266	252	207	199	172	166	138	133	115	98	78	64	55	44	43	25	25	21	8	8	5	2	2	1	0
Placebo + fulvestrant	353	329	207	182	142	136	106	100	83	81	66	59	51	41	33	24	23	12	11	10	4	4	3	1	1	0	0

+ indicates a censored observation. HR was estimated using the Cox proportional hazard model stratified by the presence of liver metastases, prior use of CDK4/6 inhibitor, and geographic region.

Dual-primary endpoint: Investigator-assessed PFS in the AKT pathway-altered population

	Capivasertib + fulvestrant (N=155)	Placebo + fulvestrant (N=134)
PFS events	121	115
Median PFS (95% CI); months	**7.3** (5.5–9.0)	**3.1** (2.0–3.7)
Adjusted HR (95% CI):	**0.50 (0.38, 0.65)**; two-sided p-value <0.001	



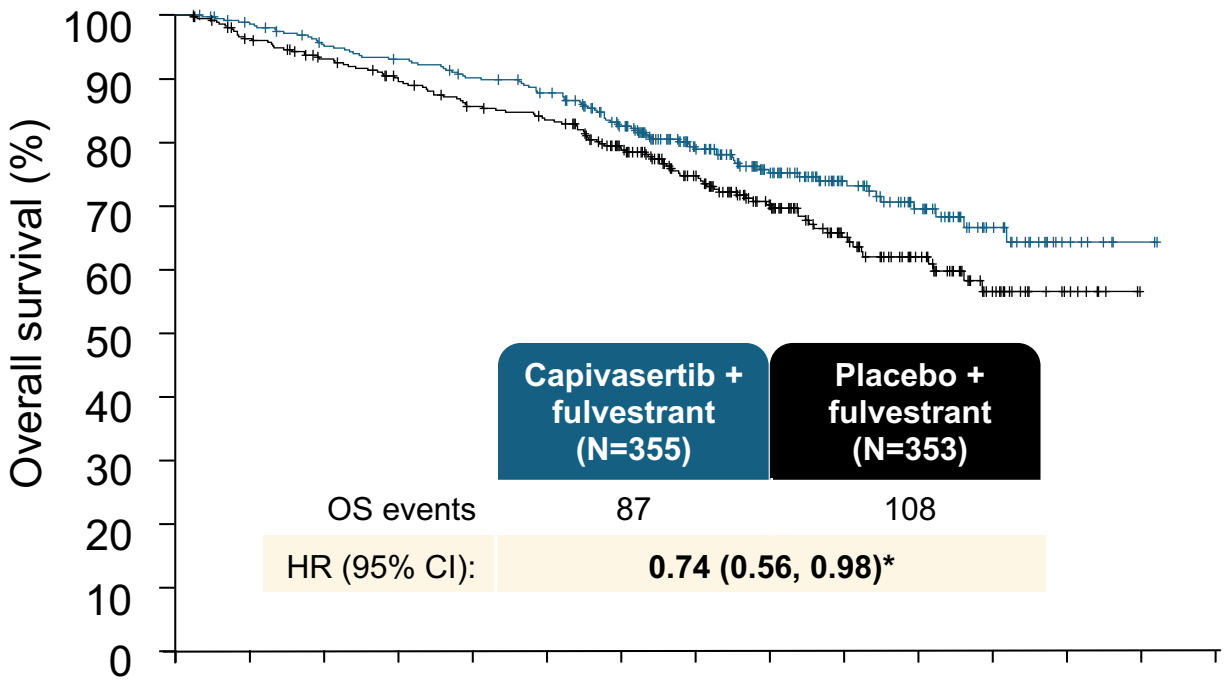
Number of patients at risk

Capivasertib + fulvestrant	155	150	127	121	99	97	80	76	65	62	54	49	38	31	26	22	21	12	12	9	3	3	2	1	1	0	0
Placebo + fulvestrant	134	124	77	64	48	47	37	35	28	27	24	20	17	14	11	6	6	2	2	2	1	1	1	0	0	0	0

+ indicates a censored observation. HR was estimated using the Cox proportional hazard model stratified by the presence of liver metastases and prior use of CDK4/6 inhibitor.

Overall survival at 28% maturity overall

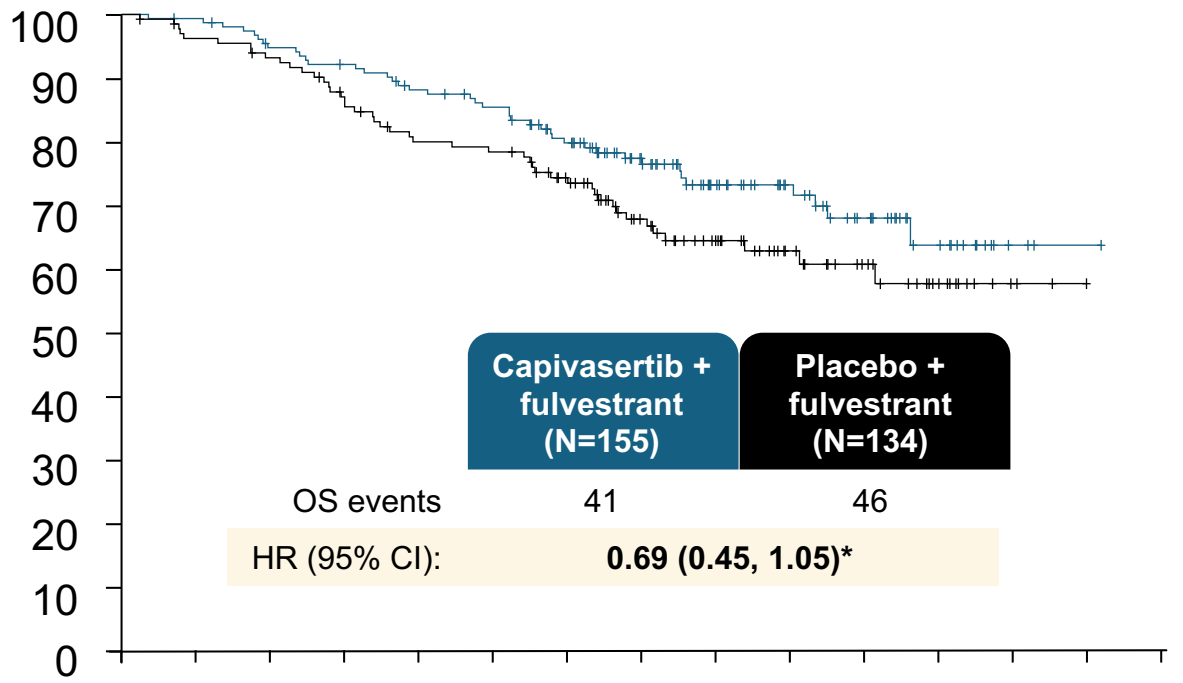
Overall population



Number of patients at risk

Capivasertib + fulvestrant	355	343	327	318	306	295	258	198	144	95	63	33	9	2	0
Placebo + fulvestrant	353	334	316	301	283	274	237	181	134	90	59	30	11	0	0

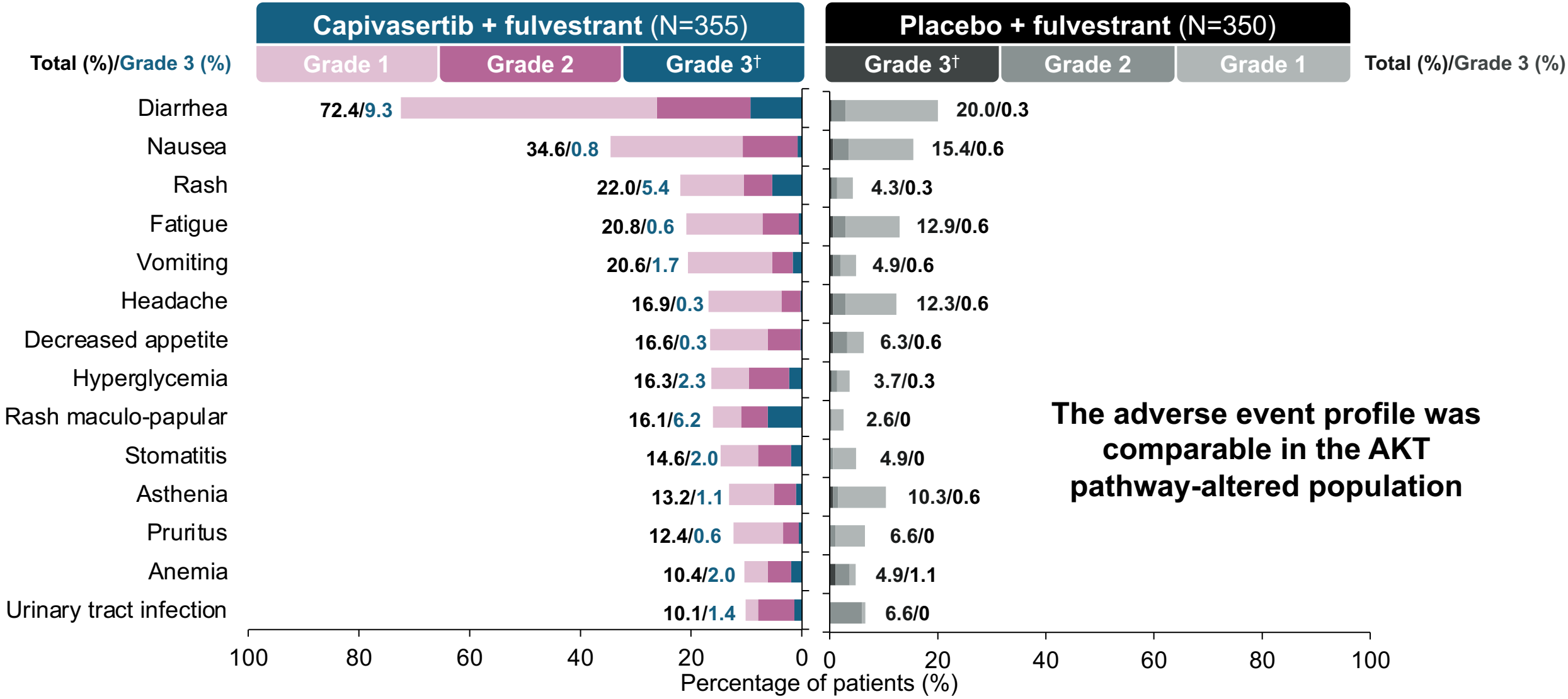
AKT pathway-altered population



Capivasertib + fulvestrant	155	153	144	139	131	125	111	83	60	45	30	14	3	1	0
Placebo + fulvestrant	134	127	122	112	101	99	87	62	46	31	22	13	3	0	0

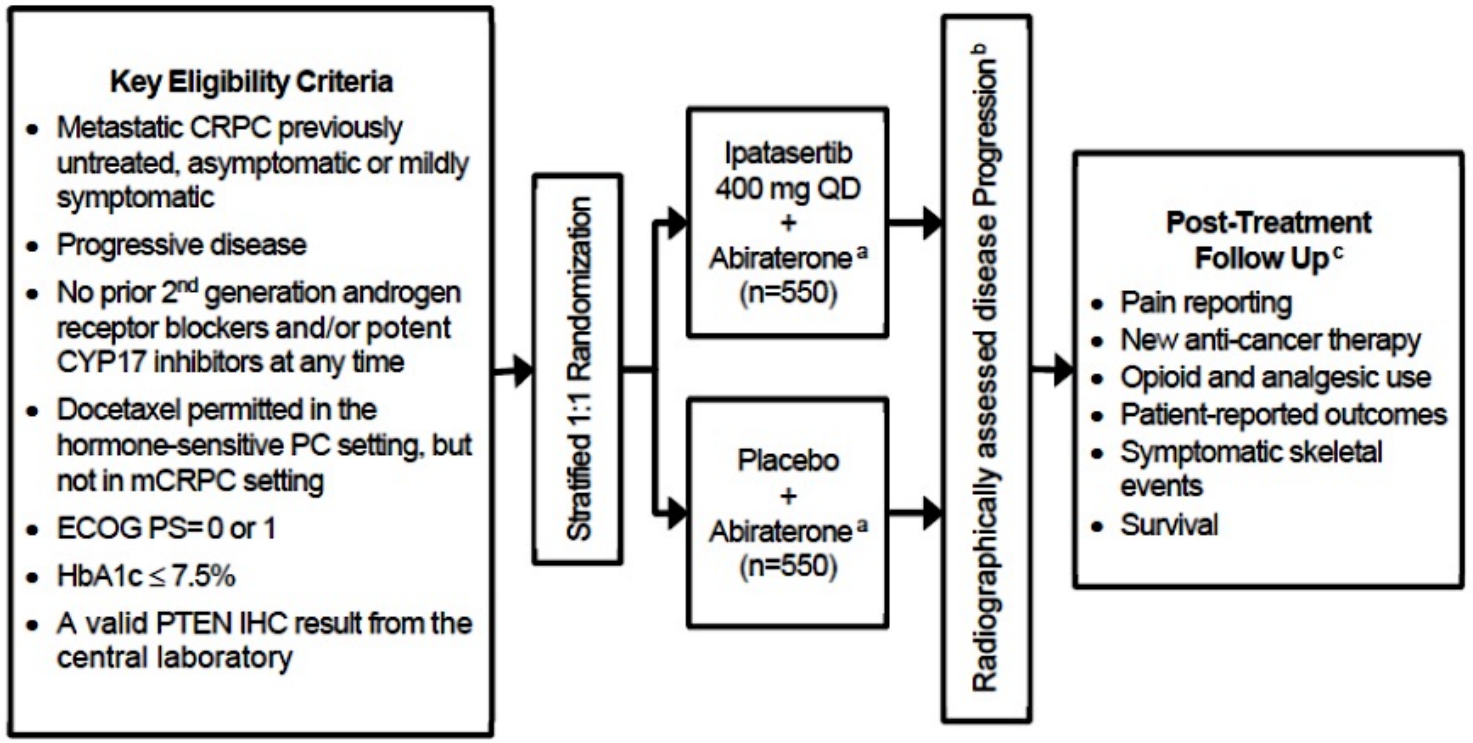
*0.01% alpha penalty assigned to OS analyses of no detriment. Formal analysis not prespecified. HR was estimated using the Cox proportional hazard model stratified by the presence of liver metastases (overall population only) and prior use of CDK4/6 inhibitor.

Adverse events (>10% of patients) – overall population



Adverse events of any grade related to rash (group term including rash, rash macular, maculo-papular rash, rash papular and rash pruritic) were reported in 38.0% of the patients in the capivasertib + fulvestrant arm (grade ≥3 in 12.1%) and in 7.1% of those in the placebo + fulvestrant group (grade ≥3 in 0.3%). †All events shown were Grade 3 except one case of Grade 4 hyperglycemia in the capivasertib + fulvestrant arm.

IPATential150: Phase III Study of Abiraterone + Ipatasertib/Placebo in mCRPC Patients: Study Schema



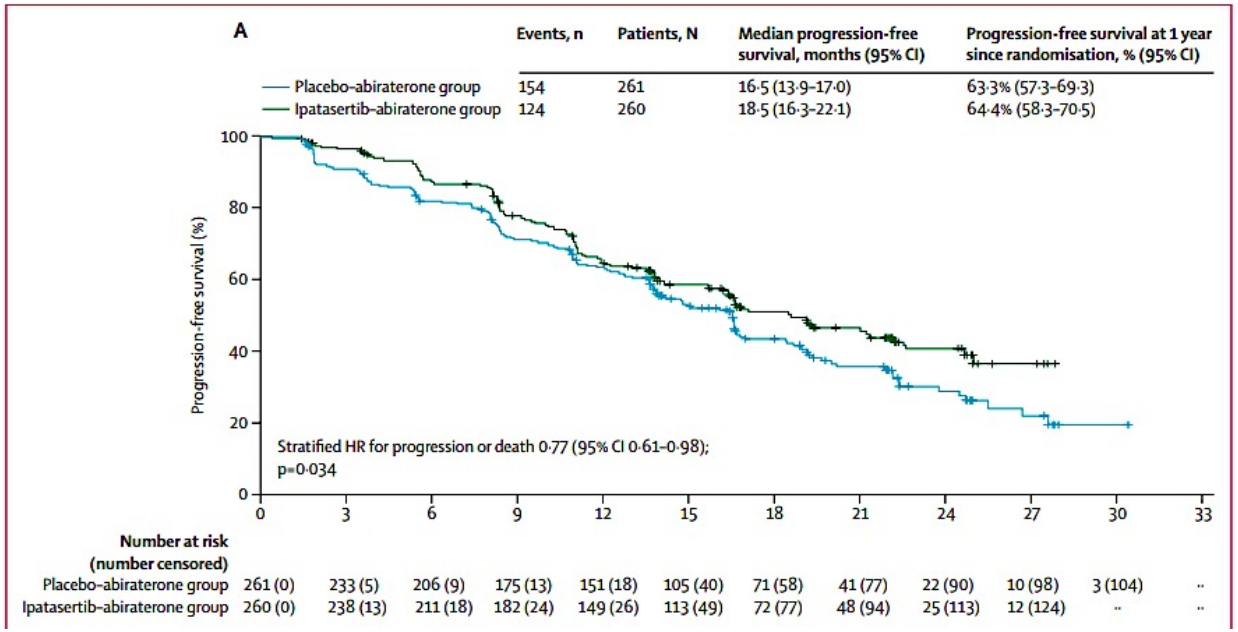
Stratification factors:

- Prior taxane-based therapy in hormone-sensitive PC setting (yes vs. no)
- Progression factor (PSA only vs. other)
- Presence of visceral metastasis (liver or lung) (yes vs. no)
- Tumor PTEN-diagnostic status by IHC assay (PTEN loss: yes vs. no)
- Geographic region (not a factor for stratified analysis)

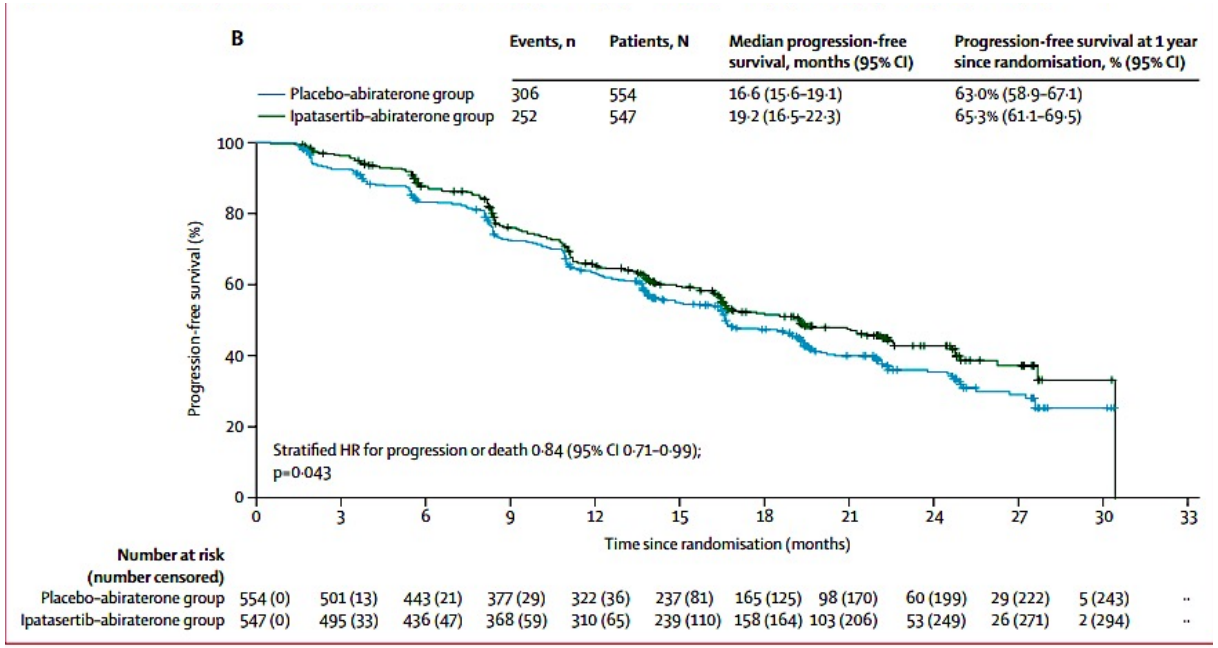
Clinicaltrials.gov. NCT03072238

IPATential150 primary endpoints: rPFS in PTEN loss and ITT populations

PTEN loss population



ITT population



Sweeney C, et al. Lancet. 2021 Jul 10;398(10295):131-142.

IPATential150: Adverse events and tolerability

Table S4. Incidence of Selected Adverse Events by Grouped Term.

	Placebo + Abiraterone (n=546)		Ipatasertib + Abiraterone (n=551)	
	All Grades	Grade 3-5	All Grades	Grade 3-5
Diarrhoea	123 (22·5)	4 (0·7)	440 (79·9)	57 (10·3)
Asthenia	154 (28·2)	6 (1·1)	211 (38·3)	22 (4·0)
Hyperglycaemia	100 (18·3)	7 (1·3)	264 (47·9)	78 (14·2)†
Rash	61 (11·2)	1 (0·2)	228 (41·4)	90 (16·3)
Transaminase increase	104 (19·0)	39 (7·1)	172 (31·2)	90 (16·3)
Nausea	55 (10·1)	2 (0·4)	155 (28·1)	4 (0·7)
Anaemia	68 (12·5)	9 (1·6)	114 (20·7)	17 (3·1)
Vomiting	48 (8·8)	2 (0·4)	94 (17·1)	5 (0·9)
Hyperlipidaemia	39 (7·1)	0	67 (12·2)	4 (0·7)
Peripheral neuropathy	48 (8·8)	4 (0·7)	37 (6·7)	2 (0·4)
Pneumonia	15 (2·7)	8 (1·5)	29 (5·3)	15 (2·7)‡
Oral mucositis	10 (1·8)	0	34 (6·2)	1 (0·2)
Thrombocytopenia	16 (2·9)	3 (0·5)	11 (2·0)	2 (0·4)
Neutropenia	6 (1·1)	1 (0·2)	9 (1·6)	2 (0·4)
Pneumonitis	7 (1·3)	2 (0·4)*	6 (1·1)	0
Erythema multiforme	1 (0·2)	0	6 (1·1)	5 (0·9)
Colitis	1 (0·2)	0	5 (0·9)	1 (0·2)

	Placebo–abiraterone group (n=546)	Ipatasertib–abiraterone group (n=551)
Adverse event of any grade	519 (95%)	548 (99%)
Grade 3 adverse event as highest grade	177 (32%)	316 (57%)
Grade 4 adverse event as highest grade	16 (3%)	46 (8%)
Grade 5 adverse event (death) as highest grade	20 (4%)	24 (4%)
Serious adverse event	124 (23%)	218 (40%)
Adverse event related to placebo or ipatasertib	308 (56%)	514 (93%)
Adverse event related to abiraterone	280 (51%)	411 (75%)
Adverse event leading to discontinuation of placebo or ipatasertib	28 (5%)	116 (21%)
Adverse event leading to dose reduction of placebo or ipatasertib	34 (6%)	220 (40%)
Adverse event leading to dose interruption of placebo or ipatasertib	125 (23%)	319 (58%)
Adverse event leading to discontinuation of abiraterone	22 (4%)	47 (9%)
Adverse event leading to dose reduction of abiraterone	27 (5%)	64 (12%)
Adverse event leading to dose interruption of abiraterone	101 (18%)	229 (42%)

Data are n (%).

Sweeney C, et al. Lancet. 2021 Jul 10;398(10295):131-142.

How do Ipatasertib and Capivasertib compare?

- Both are pan Akt-1,2,3 inhibitors with similar affinity and specificity
- Both are orally bioavailable
- However, Ipatasertib has a 45-hour half life and was dosed 400 mg daily continuously
- Capivasertib has a 12-hour half life and is dosed 400 mg BID 4 days on, 3 days off (halting cumulative toxicities each week)

Zhang J, et al. Clin Ther. 2025 Feb;47(2):128-134.

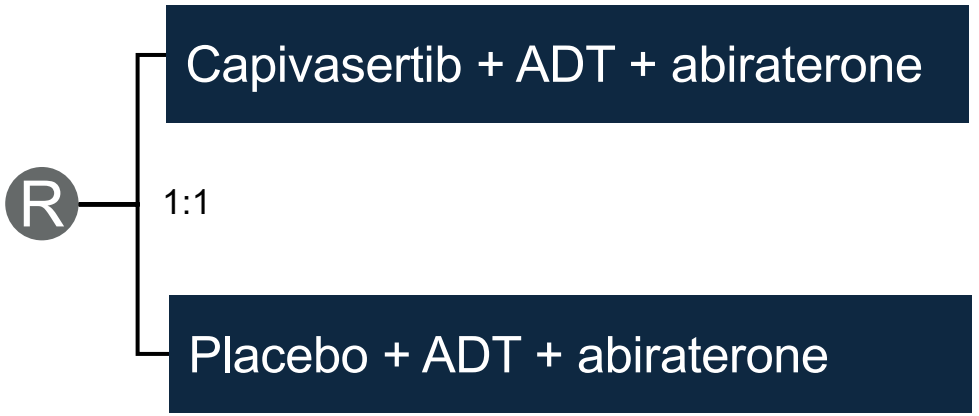
CAPItello-281: Biomarker select study in PTEN deficient de novo mHSPC

Treatments: Capivasertib 400mg bd (4 days on / 3 days off) or matching placebo. Abiraterone 1000mg daily (+ADT and steroids)

Key eligibility criteria

- De novo metastatic prostate cancer with histologically or cytologically confirmed adenocarcinoma of the prostate without neuroendocrine differentiation or small cell histology
- Distant metastatic disease documented by positive bone scan or metastatic lesions on computed tomography (CT) or magnetic resonance imaging (MRI) scan
- Consent to provide a FFPE tissue block for PTEN IHC prospective testing and other protocol-mandated assessments
- PTEN status by central testing (IHC) of tumour tissue
- No prior pharmacotherapy, radiation therapy, or surgery for metastatic prostate cancer: up to 3 months of ADT +/- abiraterone allowed)
- ECOG PS 0-1

N=1000



- Radiotherapy with therapeutic intent not permitted
- Treatment until disease progression, unacceptable toxicity, patient withdrawal
- Cross-over not permitted during the study

Study background	
32 countries inc China	
PTEN deficiency prevalence	~25% overall
FSI	July 2020
LSI	Dec2023

Primary endpoint

- rPFS (investigator assessed primary; BICR sensitivity)

Key secondary endpoints

- OS
- SSE-FS
- Time to first subsequent therapy
- Time to pain progression

Other secondary endpoints

- Time to PSA progression
- Time to castration resistance
- PFS2
- PRO measures (BPI-SF, FACT-P, BFI)

Stratification factors:

- Volume of disease and visceral mets (high volume with visceral mets/high volume without visceral mets/low volume disease)
- Region

Capivasertib Combination in PTEN-Deficient Metastatic Hormone-Sensitive Prostate Cancer Demonstrated Significant and Clinically Meaningful Improvement in Radiographic Progression-Free Survival in CAPItello-281 Phase III Trial

Press Release: November 25, 2024

"Positive high-level results from the CAPItello-281 Phase III trial showed that capivasertib in combination with abiraterone and androgen deprivation therapy (ADT) demonstrated a statistically significant and clinically meaningful improvement in the primary endpoint of radiographic progression-free survival (rPFS) versus abiraterone and ADT with placebo in patients with PTEN-deficient de novo metastatic hormone-sensitive prostate cancer (mHSPC).

Overall survival (OS) data were immature at the time of this analysis; however, the capivasertib combination showed an early trend towards an OS improvement versus abiraterone and ADT with placebo. The trial will continue as planned to further assess OS as a key secondary endpoint.

The safety profile of capivasertib in combination with abiraterone and ADT in CAPItello-281 was broadly consistent with the known profile of each medicine."

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https://www.astrazeneca.com/media-centre/press-releases/2024/truqap-improved-rpfs-in-advanced-prostate-cancer.html

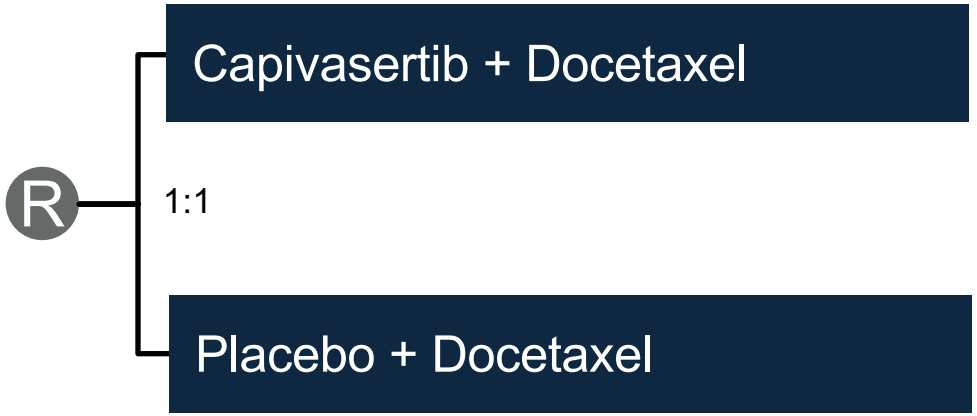
CAPItello-280: Non-biomarker select study in mCRPC

Treatments: Capivasertib 320mg bd (4 days on / 3 days off) or matching placebo. 3-weekly 75mg/m^2 docetaxel

Key eligibility criteria

- Metastatic castration resistant prostate cancer
- Received prior NHA for HSPC or mCRPC or non-metastatic CRPC
- Candidate for 1st exposure to docetaxel for mCRPC
- No prior treatment with AKTi, PI3Ki
- No prior chemo in the metastatic setting

N=1000



Primary endpoint
- OS
- rPFS

Key secondary endpoints
- OS by PTEN status
- rPFS by PTEN status
- Time to pain progression
- Time to skeletal events

Stratification factors

1. Received 2 or more lines of prior NHA with at least one in the CRPC setting (Y/N)
2. Visceral mets (Y/N)
3. Geographical region

Study background	
22 countries inc China	
FSI	March 2022
LSI	Aug 2024

Summary

- PTEN/PI3K/AKT activation is a common driver of poor prognosis in advanced prostate cancer
- Combination of AKT and AR inhibition in prostate cancer is a promising strategy
- Capivasertib is a pan-AKT inhibitor with acceptable side effect profile
- In advanced breast cancer capivasertib + fulvestrant has proven efficacy and tolerability
- CAPItello-281 is a Phase III trial comparing capivasertib + abiraterone vs abiraterone in mHSPC patients with loss of PTEN
- CAPItello-281 press release is promising…waiting for the public results

Perspectives on future treatment approaches for patients with prostate cancer

Emmanuel S Antonarakis, MD
(Minneapolis, Minnesota)

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QUESTIONS FOR THE FACULTY

What potential therapeutic targets are you most excited about in prostate cancer? In the coming years, do you think all patients with mHSPC will undergo NGS to inform initial therapy?

What do you see as the future for prostate cancer clinical research as it relates to:

- **Targeted therapies such as AKT inhibitors**
- **CAR T-cell therapy and bispecific antibodies (And how will these be tolerated by patients with prostate cancer?)**
- **Radiopharmaceuticals such as radium-223 and lutetium Lu 177 vipivotide tetraxetan**

Case Presentation: Dr Yu – A Likely Future Scenario

- A 62-year-old gentleman presents asymptomatically with an initial screening PSA found to be 15 ng/mL
- He has no previous medical history other than mild hyperlipidemia and some osteoarthritis
- ECOG performance status is 0
- Labs are all WNL
- PSMA PET/CT confirm 6 lesions in the spine and bilateral pelvic and retroperitoneal lymphadenopathy in the 1-2 cm range (SUV range 8-26)
- NGS reveals no alterations in *BRCA* or any other homologous recombination repair genes however, the patient is labeled as having PTEN loss

Case Presentation: Dr Yu (cont'd) – Treatment Options

What treatment(s) should we consider for this patient?

1. ADT alone
2. ADT + abiraterone
3. ADT + abiraterone + docetaxel
4. ADT + abiraterone + capivasertib
5. ADT + abiraterone + ^{177}Lu-PSMA-617

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

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Thank you for joining us!
Your feedback is very important to us.

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Online/Zoom attendees: The CME credit link is posted in the chat room.

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