# **Starting Strong:** Frontline Options for Metastatic Castrate Sensitive Prostate Cancer

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# What We'll Cover

### Understanding your diagnosis

What “metastatic” and “hormone-sensitive” mean for you

### How your plan is chosen

Disease volume, timing, and biomarkers all play a role

### Combination therapies explained

Doublet and triplet treatment, in plain language

### Genetic testing & targeted options

Newer, precision treatments based on your tumor's biology

### Questions to ask your care team

A checklist to bring to your next appointment

# What Is mHSPC?

Your care team may use this term. Here's what each part means.

## Metastatic

The cancer has spread beyond the prostate such as bones or lymph nodes

## Hormone-Sensitive

The cancer still responds to treatments that lower testosterone

## Castration-Sensitive

Use of mCSPC interchangeably with mHSPC

**ANDROGEN PATHWAY MODULATION-SENSITIVE (APMS) OR ANDROGEN PATHWAY MODULATION-NAIIVE (APMN)**

# Clinical Factors Guiding Treatment Decisions

## Disease Volume

### Low Volume

Fewer than 4 bone lesions, none beyond the spine or pelvis, and no spread to organs

### High Volume

Spread to organs (like liver or lung), or 4+ bone spots with at least one beyond the spine/pelvis

## Timing of Diagnosis

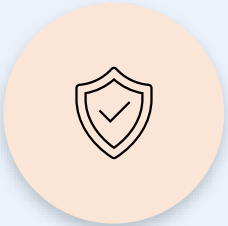
### De Novo (Synchronous)

Metastasis is found at the very first diagnosis of prostate cancer

### Recurrent (Metachronous)

Metastasis appears later, after earlier treatment for localized cancer

# Building Blocks of Treatment



## ADT

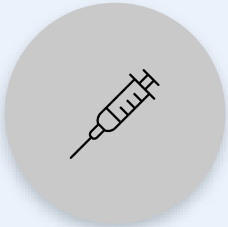
Androgen Deprivation Therapy with the goal of lowering testosterone

+

## + ARPI

Pills that block the androgen receptor pathway

+



## + Chemotherapy

Docetaxel, given by IV, added for higher-risk or higher-volume disease

**Doublet** = ADT + one additional medicine  **Triplet** = ADT + two additional medicines

# Treatment Intensification: Doublet Therapy

| ARPI | Trial(s) | N (Exp vs Ctrl) | Median Follow-Up | Median OS (Exp vs Ctrl) | OS HR (95% CI) |
|---|---|---|---|---|---|
| **Abiraterone** | **LATITUDE** (final) | 597 vs 602 | 51.8 months | 53.3 vs 36.5 months | 0.66 (0.56–0.78) |
| **Abiraterone** | **STAMPEDE** (final) | 502 vs 501 | 73.2 months | 66.0 vs 54.0 months | 0.60 (0.50–0.71) |
| **Enzalutamide** | **ARCHES** (5-yr update) | 574 vs 576 | 61.4 months | NR in both arms; 5-yr OS 66% vs 53% | 0.70 (0.58–0.85) |
| **Enzalutamide** | **ENZAMET** (8-yr update) | 563 vs 562 | 98 months | 95 vs 70 months; 8-yr OS 50% vs 40% | 0.73 (0.63–0.86) |
| **Apalutamide** | **TITAN** (final) | 525 vs 527 | 44.0 months | NR vs 52.2 months | 0.65 (0.53–0.79) |
| **Darolutamide** | **ARANOTE** (primary) | 446 vs 223 | 25.3 months | NR in both arms (OS immature) | 0.81 (0.59–1.12) |

Fizazi K et al. Lancet Oncol 2019;20(5):686-700. Attard G et al. Lancet Oncol. 2023;24(5):443-456. Zhang A et al. ASCO Annual Meeting; May 30–June 3, 2025; Chicago, IL. Abstract LBA5005. Armstrong A et al Eur Urol. 2026;89(5). Chi KN et al. J Clin Oncol. 2021 39:2294-2303. Saad F et al. J Clin Oncol. 2024;42(36):4271-4281.

# Doublet Therapy

ADT + ARPI are often used for lower-volume disease

UP TO

**34%**

lower risk of death, compared with ADT alone, in long-term trial follow-up

*LATITUDE trial (abiraterone), final follow-up*

### Abiraterone

Paired with a low-dose steroid

### Enzalutamide

Longest-studied ARPI option, 8-year data

### Apalutamide

Once-daily pill

### Darolutamide

Newest option in this class

# Treatment intensification: triplet therapy

| ARPI | Trial | N (Exp vs Ctrl) | Median Follow-Up | Median OS (Exp vs Ctrl) | OS HR (95% CI) |
|---|---|---|---|---|---|
| **Darolutamide** | **ARASENS** | 651 vs 655 | 43.7 months | NR vs 48.9 months | 0.68 (0.57–0.80) |
| **Abiraterone** | **PEACE-1** (docetaxel subgroup) | 355 vs 355 | 45.6 months | NR vs 52.8 months | 0.75 (0.59–0.95) |

Smith MR et al. *N Engl J Med.* 2022;386(12):1132-1142. Fizazi K et al. Lancet. 2022;399(10336):1695-1707.

# Triplet Therapy

ADT + ARPI + docetaxel are often used for higher-volume disease

UP TO

**32%**

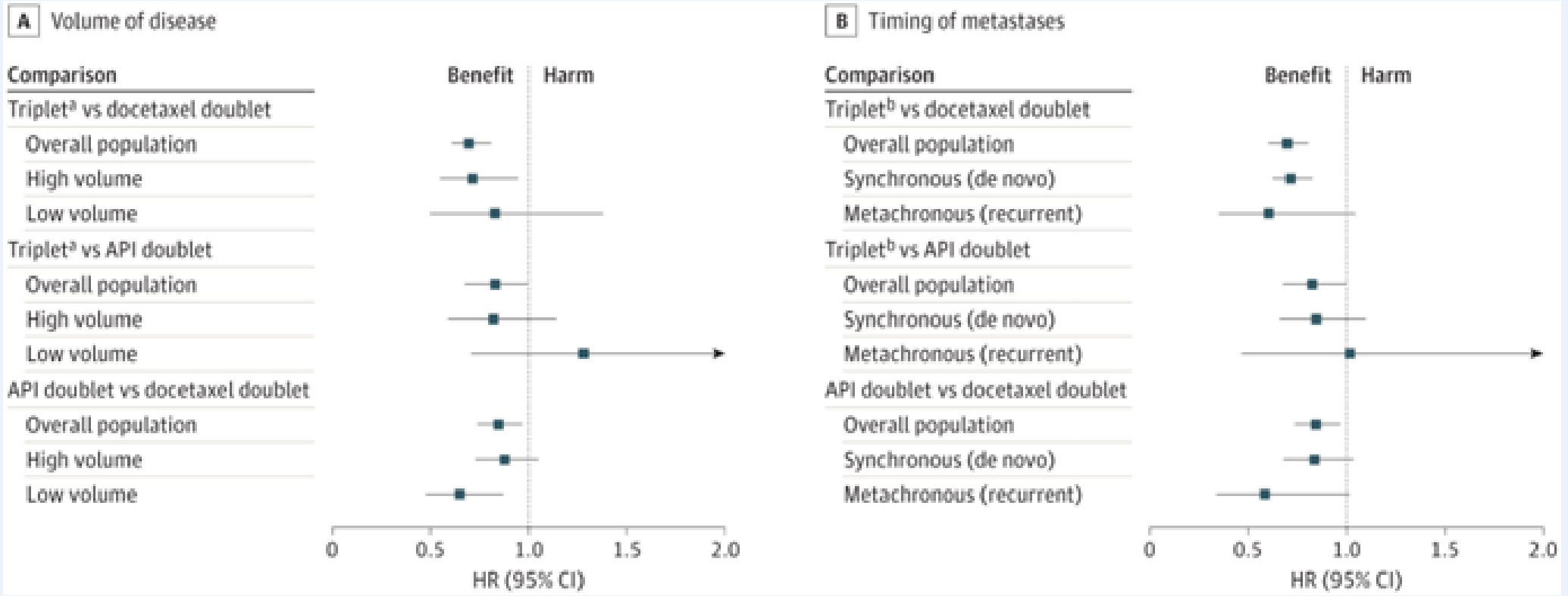
lower risk of death, compared with ADT + chemotherapy alone

*ARASENS trial (darolutamide + docetaxel)*

- ☑ Combines three approaches at once: hormone therapy, an ARPI pill, and chemotherapy (usually 6 cycles of docetaxel)
- ☑ Considered the standard approach for many patients with high-volume disease
- ☑ Most patients tolerate treatment well; your team will monitor for side effects and adjust as needed
- ☑ Two large trials (ARASENS and PEACE-1) both support this approach for eligible patients

# The Evidence at a Glance

Original forest plot: overall survival by disease volume and timing across the major mHSPC trials.




*HR < 1 favors the treatment shown; 95% CI crossing 1 indicates a statistically nonsignificant result.*

Riaz IB et al. JAMA Oncology. 2023;9(9):1252-1262.

# Living Network Meta-analysis: OS by subgroup

| Subgroup | % of Patients | Preferred Regimen | Key Finding |
|---|---|---|---|
| **Synchronous High-Volume (SHV)** | 57% | **Triplet** (ARPI + docetaxel + ADT) | Triplet superior to ARPI doublet (HR 0.71) AND docetaxel doublet (HR 0.72) |
| **Synchronous Low-Volume (SLV)** | 27% | **ARPI doublet** (ARPI + ADT) | No benefit of adding docetaxel to ARPI doublet (HR 1.08) |
| **Metachronous High-Volume (MHV)** | 6.5% | **ARPI doublet** (no significant differences) | Small N; wide CIs; no significant difference between triplet, ARPI doublet, or docetaxel doublet |
| **Metachronous Low-Volume (MLV)** | 8.5% | **ARPI doublet** (ARPI + ADT) | ARPI doublet superior to docetaxel doublet (HR 0.41); no benefit of triplet over ARPI doublet |

Riaz IB et al. European Urology. 2026;89(1):31-44. Riaz IB et al. JAMA Oncology. 2023;9(9):1252-1262.

# Genetic & Biomarker Testing

### Gene Mutations (BRCA2, HRR)

Inherited or tumor gene changes that open the door to PARP-inhibitor combinations

### PTEN Loss

A tumor marker that can guide use of newer targeted pills

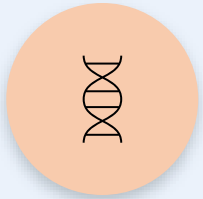
### PSMA PET Scan

A specialized scan that can identify candidates for targeted radioligand therapy

### Standard Imaging

CT, bone, and MRI scans that help confirm the extent of disease

# Newer Targeted Combinations



## Niraparib + Abiraterone

For BRCA2 mutations

FDA Approved

## Talazoparib + Enzalutamide

For HRR mutations

In Development

## $^{177}$Lu-PSMA-617

For PSMA-positive scans

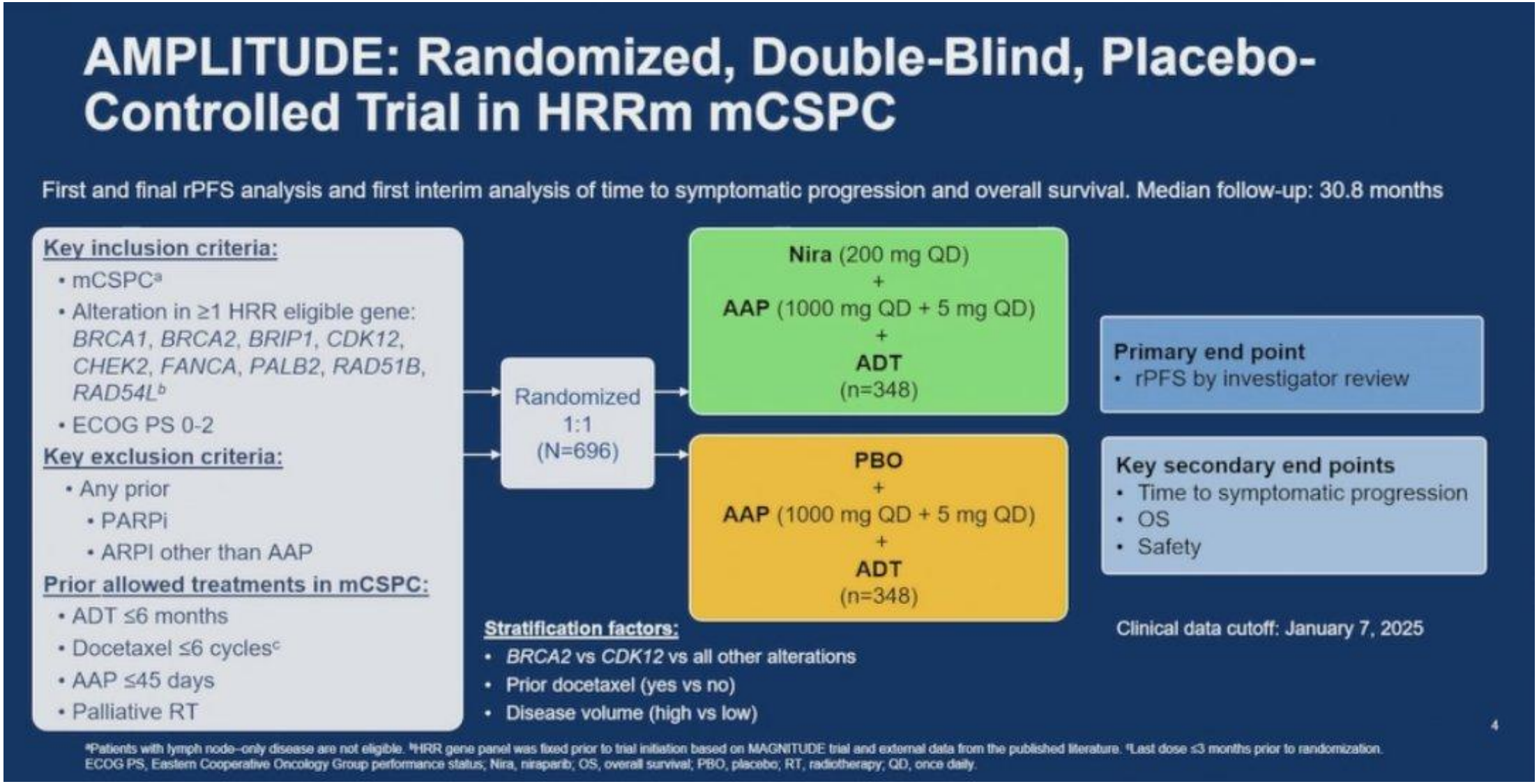
FDA Approved

## Capivasertib + Abiraterone

For PTEN loss

FDA Approved

# AMPLITUDE


AMPLITUDE: Randomized, Double-Blind, Placebo-Controlled Trial in HRRm mCSPC
First and final rPFS analysis and first interim analysis of time to symptomatic progression and overall survival. Median follow-up: 30.8 months
Key inclusion criteria:
• mCSPC[a]
• Alteration in ≥1 HRR eligible gene: BRCA1, BRCA2, BRIP1, CDK12, CHEK2, FANCA, PALB2, RAD51B, RAD54L[b]
• ECOG PS 0-2
Key exclusion criteria:
• Any prior
• PARPi
• ARPI other than AAP
Prior allowed treatments in mCSPC:
• ADT ≤6 months
• Docetaxel ≤6 cycles[c]
• AAP ≤45 days
• Palliative RT
Randomized 1:1 (N=696)
Nira (200 mg QD) + AAP (1000 mg QD + 5 mg QD) + ADT (n=348)
PBO + AAP (1000 mg QD + 5 mg QD) + ADT (n=348)
Primary end point
• rPFS by investigator review
Key secondary end points
• Time to symptomatic progression
• OS
• Safety
Clinical data cutoff: January 7, 2025
Stratification factors:
• BRCA2 vs CDK12 vs all other alterations
• Prior docetaxel (yes vs no)
• Disease volume (high vs low)
[a]Patients with lymph node–only disease are not eligible. [b]HRR gene panel was fixed prior to trial initiation based on MAGNITUDE trial and external data from the published literature. [c]Last dose ≤3 months prior to randomization.
ECOG PS, Eastern Cooperative Oncology Group performance status; Nira, niraparib; OS, overall survival; PBO, placebo; RT, radiotherapy; QD, once daily.

# FDA approval

U.S. FDA APPROVAL

**December 12, 2025**

REGIMEN

**Niraparib and abiraterone acetate with prednisone**

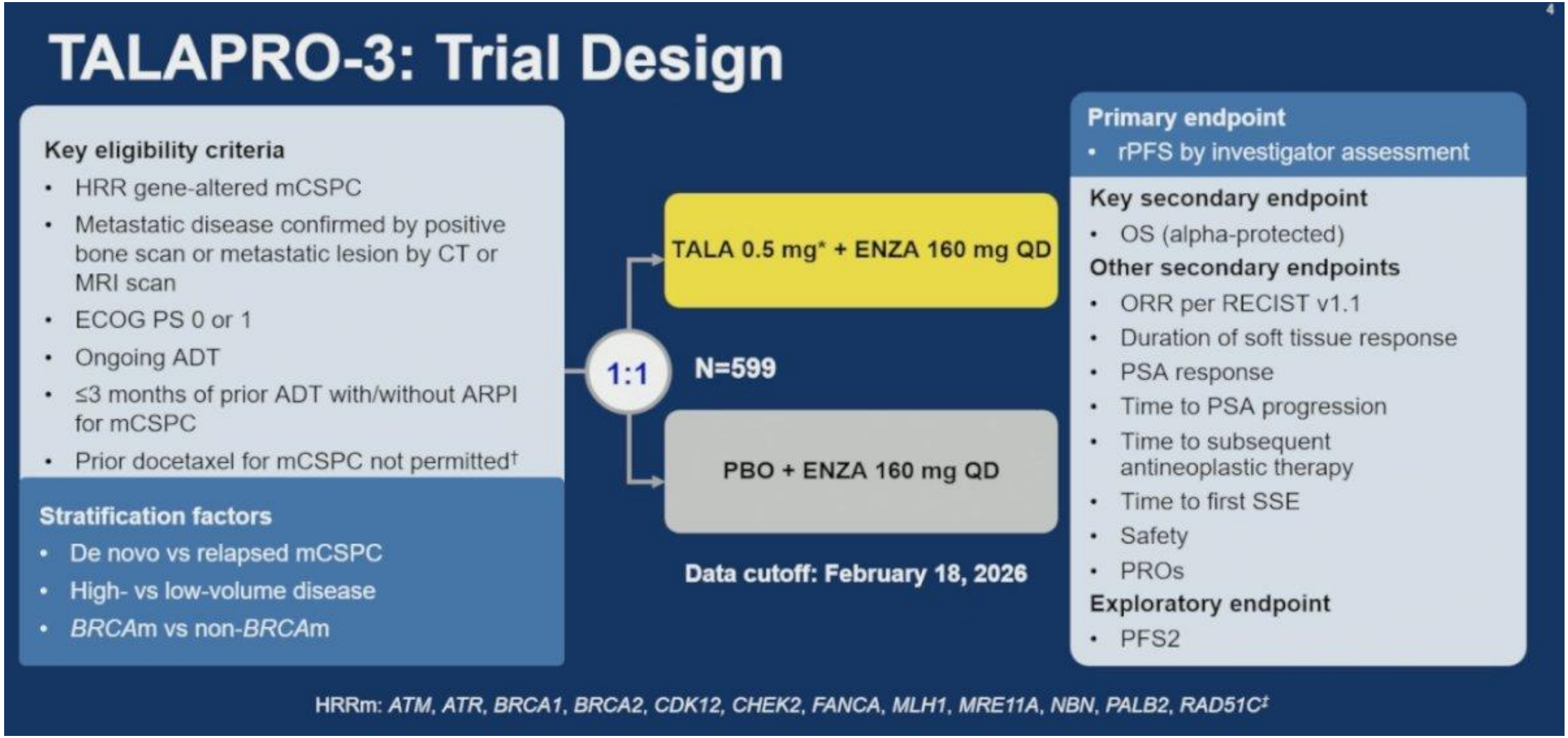
INDICATION

Adults with deleterious or suspected deleterious BRCA2-mutated (BRCA2m) metastatic castration-sensitive prostate cancer (mCSPC)

COMPANION DIAGNOSTIC

**As determined by an FDA-approved test**

# Talapro-3


TALAPRO-3: Trial Design
Key eligibility criteria
• HRR gene-altered mCSPC
• Metastatic disease confirmed by positive bone scan or metastatic lesion by CT or MRI scan
• ECOG PS 0 or 1
• Ongoing ADT
• ≤3 months of prior ADT with/without ARPI for mCSPC
• Prior docetaxel for mCSPC not permitted†
Stratification factors
• De novo vs relapsed mCSPC
• High- vs low-volume disease
• BRCAm vs non-BRCAm
1:1
N=599
TALA 0.5 mg* + ENZA 160 mg QD
PBO + ENZA 160 mg QD
Data cutoff: February 18, 2026
Primary endpoint
• rPFS by investigator assessment
Key secondary endpoint
• OS (alpha-protected)
Other secondary endpoints
• ORR per RECIST v1.1
• Duration of soft tissue response
• PSA response
• Time to PSA progression
• Time to subsequent antineoplastic therapy
• Time to first SSE
• Safety
• PROs
Exploratory endpoint
• PFS2
HRRm: ATM, ATR, BRCA1, BRCA2, CDK12, CHEK2, FANCA, MLH1, MRE11A, NBN, PALB2, RAD51C‡

# Topline results

TOPLINE RESULTS

**March 19, 2026**

STUDY

**Phase 3 TALAPRO-3 study**

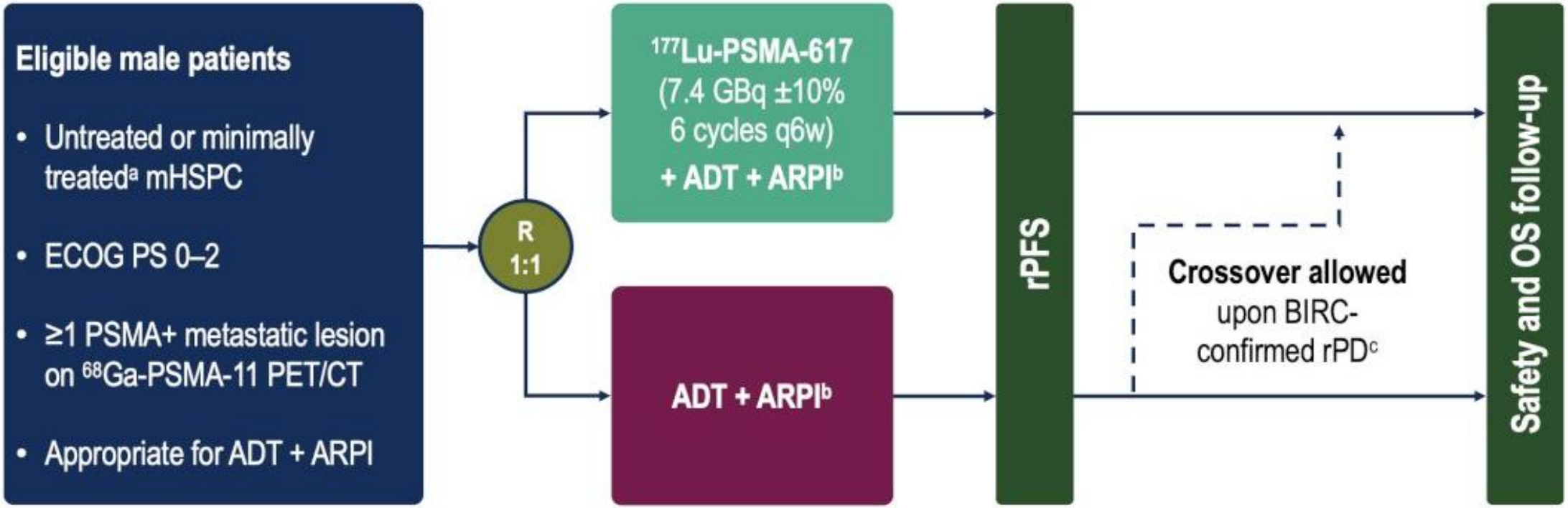
PRIMARY ENDPOINT

**Primary endpoint met a statistically significant and clinically meaningful reduction in risk of disease progression or death**

POPULATION

**HRR gene-mutated metastatic hormone sensitive prostate cancer**

# PSMAddition




**Stratification factors**

- Disease volume (high/low) – per CHAARTED criteria[1]
- Age ≥ 70 years (yes/no)
- Previous or planned treatment of primary tumour by radiation or prostatectomy (yes/no)

**Follow-up periods**

- rPFS: until event in all patients
- Safety: 30 days then 24 and 48 weeks after treatment discontinuation
- OS: every 90 days after last contact

# FDA approval

U.S. FDA APPROVAL

**July 31, 2026**

REGIMEN

**Pluvicto in combination with ARPI**

INDICATION

Adults with PSMA-positive mCSPC

COMPANION DIAGNOSTIC

**As determined by PSMA PET scan**

# CAPITELLO-281

**Patients with PTEN deficient *de novo* mHSPC**

- PTEN deficiency: (diagnostic cut-off of **≥90%** of viable malignant cells with **no specific cytoplasmic staining** by IHC)*
  - i.e. ≤10% of cells expressing PTEN by IHC

Of ~6,200 patients submitting tumour tissue **97%** had a valid IHC result and **25%** were **PTEN deficient**

**1,012 patients (R 1:1)**

| | |
|---|---|
| **Capivasertib** | 400 mg BID 4 days on, 3 days off |
| **Abiraterone**/pred + ADT | 1000 mg/5 mg QD + ADT |
| **Placebo** | 400 mg BID 4 days on, 3 days off |
| **Abiraterone**/pred + ADT | 1000 mg/5 mg QD + ADT |

**Primary endpoint**

- **Investigator assessed rPFS**

**Secondary endpoints**

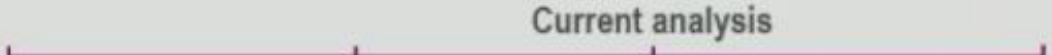
- Overall survival
- Time to first subsequent therapy
- Symptomatic skeletal-event free survival
- Time to pain progression
- Time to castration resistance
- Time to PSA progression

**Exploratory *post-hoc* PTEN deficiency subgroups**

**Stratification factors:†**

- M1 volume (CHAARTED criteria) and visceral mets
- Geography

**Study timeline**




**Enrolment period**
13 July 2020–5 Feb 2024

**Primary rPFS DCO**
7 Oct 2024
Median rPFS follow-up:‡ ~18 mo

**Final OS DCO**
Planned for 522 deaths
(52.2% maturity)

# FDA approval

U.S. FDA APPROVAL

**June 12, 2026**

REGIMEN

**Capivasertib and abiraterone**

INDICATION

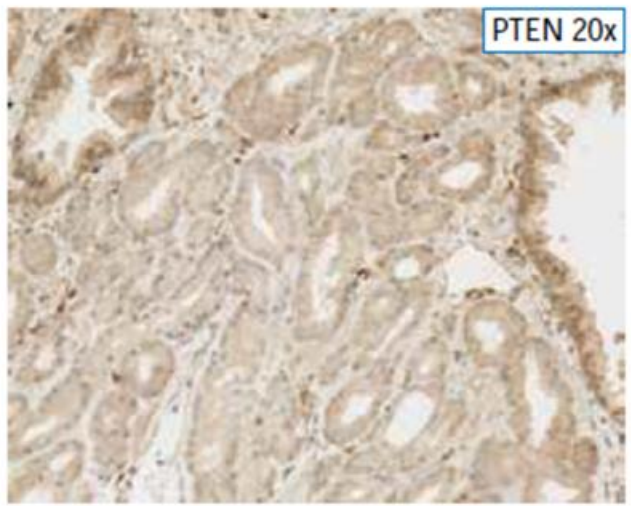
**mHSPC patients with PTEN-deficient disease**

COMPANION DIAGNOSTIC

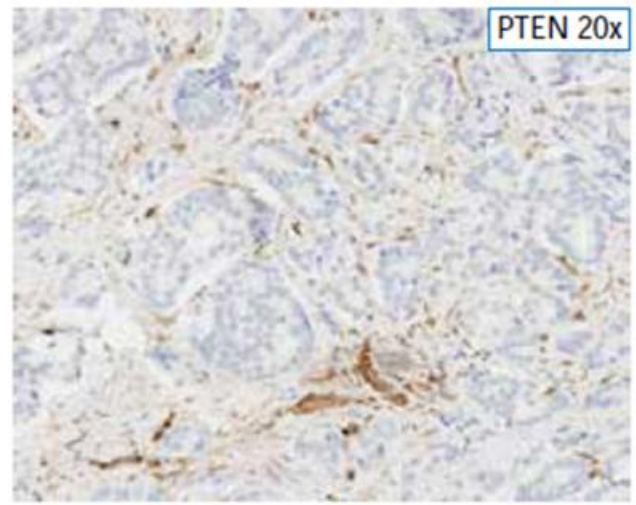
**PTEN deficient as detected by an FDA-authorized test**

# DETECTING PTEN DEFICIENCY IN CLINICAL PRACTICE: ROLE OF IMMUNOHISTOCHEMISTRY (IHC)

**PTEN-Proficient**
(>10% of viable malignant cells with any cytoplasmic staining)




**PTEN-Deficient**
(≥90% of viable malignant cells with no cytoplasmic staining)




VENTANA PTEN (SP218) RxDx Assay Interpretation Guide for Prostate Adenocarcinoma. © 2026 Ventana Medical Systems, Inc. and Roche Diagnostics International, Inc.

**IHC**

- Measures functional protein loss
- Captures all mechanisms of PTEN inactivation: deletion, mutation, methylation, post-translational modification
- Detects intratumoral heterogeneity by identifying focal PTEN loss
- Less expensive, faster turnaround

**NGS**

- Detects only sequence-level alterations
- Misses epigenetic silencing (methylation) and post-translational modification
- Bulk tissue sequencing averages out heterogenous loss
- Underestimates prevalence
- Requires adequate tissue

# Goals of Treatment

**DELAY**

Delay the cancer becoming resistant to hormone therapy

**DELAY**

Delay bone-related complications and skeletal events

**PRESERVE**

Preserve your quality of life and daily function

**PROLONG**

Prolong overall survival

# Your Treatment Path at a Glance

A simplified map of how disease features connect to treatment categories in 2026.

### Presentation with High Volume

ADT + ARPI + Docetaxel

### Presentation with Low Volume

ADT + ARPI

### BRCA2 Gene Mutation

ADT + niraparib + abiraterone

### HRR Gene Mutations (PENDING FDA)

ADT + talazoparib + enzalutamide

### PSMA PET–Positive Scan

ADT + $^{177}$Lu-PSMA-617

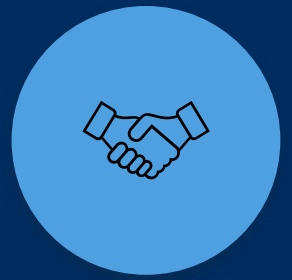
### PTEN Loss

ADT + abiraterone + capivasertib

# Questions to Ask Your Care Team

Bring this list to your next appointment.

- What is my disease volume and stage, and what does that mean for my options?
- Should I have genetic or biomarker testing, and what would it change about my plan?
- What are the expected benefits and possible side effects of each option?
- Am I a candidate for a clinical trial?
- How will treatment affect my daily life, work, and family?
- Who do I contact if I have side effects between visits?



# Thank You

Questions & Answers