UC San Diego Health

Integration of Emerging Treatment Strategies for Patients with Advanced Prostate Cancer

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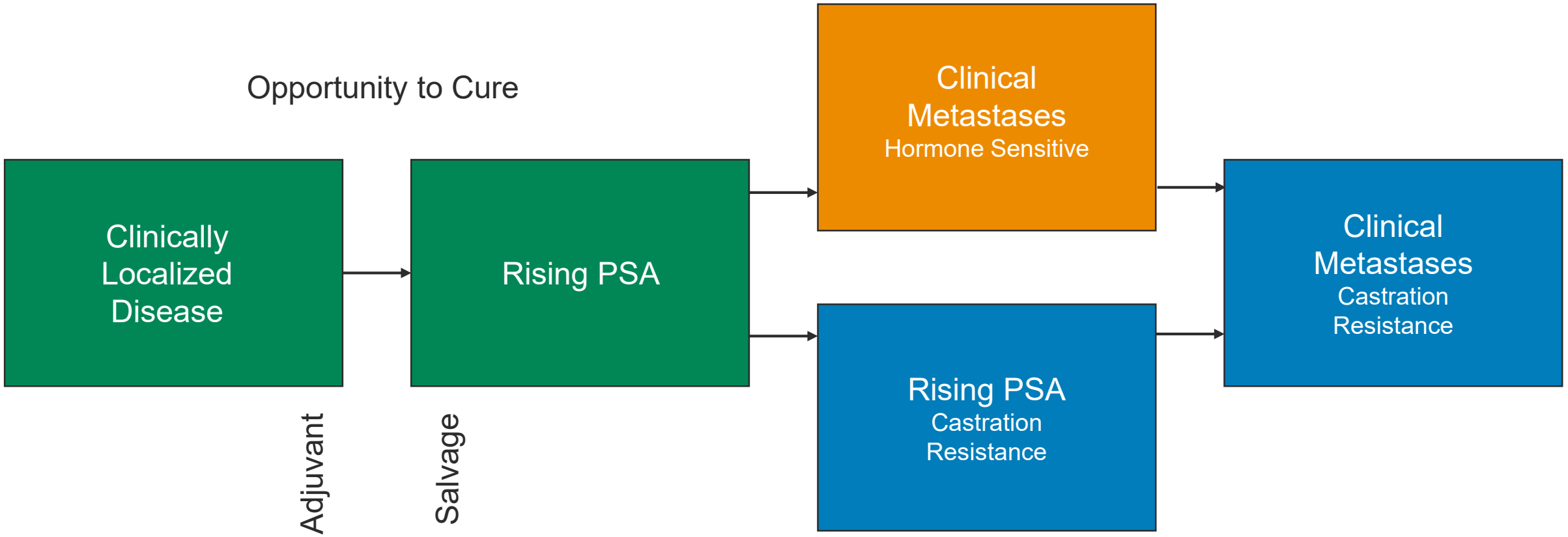
Disclosures

- Consultant: AstraZeneca, Aveo, Bayer, Bristol-Myers Squibb, Calithera, Caris, Dendreon, Esiai, Exelixis, Johnson & Johnson, Lilly, Merck, Myovant, Novartis, Pfizer, Sanofi, SeaGen, Sorrento Therapeutics, Telix, Tempus.
- Research Support: AstraZeneca, Bayer, BMS, Exelixis, Oncternal, Tempus.

Clinical States of Prostate Cancer



ADT is the Backbone of Therapy in mHSPC

Studies on Prostatic Cancer

I. The Effect of Castration, of Estrogen and of Androgen Injection on Serum Phosphatases in Metastatic Carcinoma of the Prostate*

Charles Huggins, M.D., and Clarence V. Hodges, M.D.

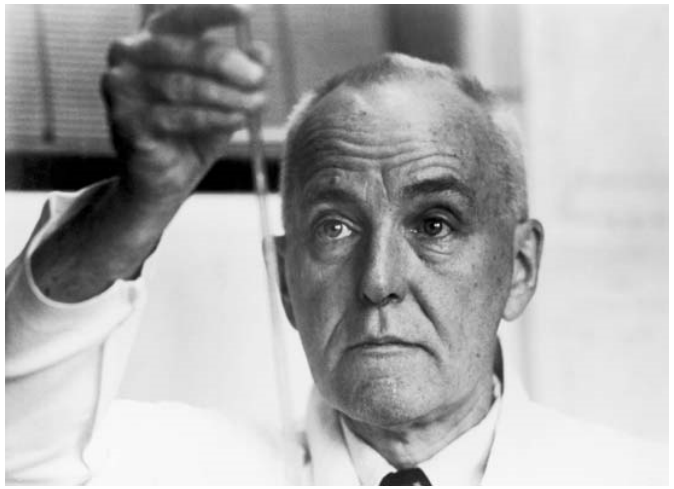
(From the Department of Surgery, the University of Chicago, Chicago, Illinois)

(Received for publication March 22, 1941)

Carcinoma of the prostate gland is peculiarly favorable for endocrine investigation since frequent serial observations of the activity of phosphatases in serum were found to provide objective indices of activity of the neoplasm when the enzymes were increased in amount above normal. In the present paper data are given for the values of serum phosphatases in car-

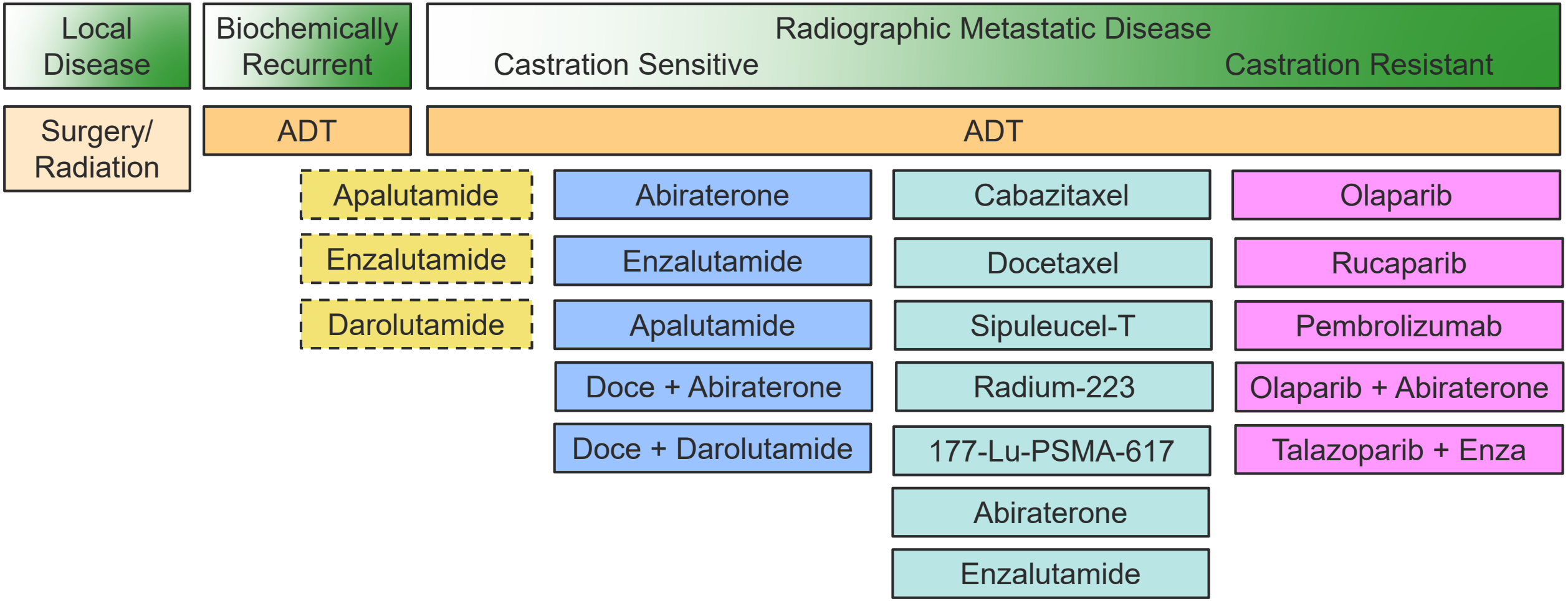
METHODS AND MATERIALS

The phosphatase activity of serum was determined by the method of King and Armstrong (10) using 0.005 M disodium monophenylphosphate as substrate. The buffers used were 0.05 M barbital-sodium at pH 9.3, and 0.1 M Sörensen's citrate-HCl or Walpole's



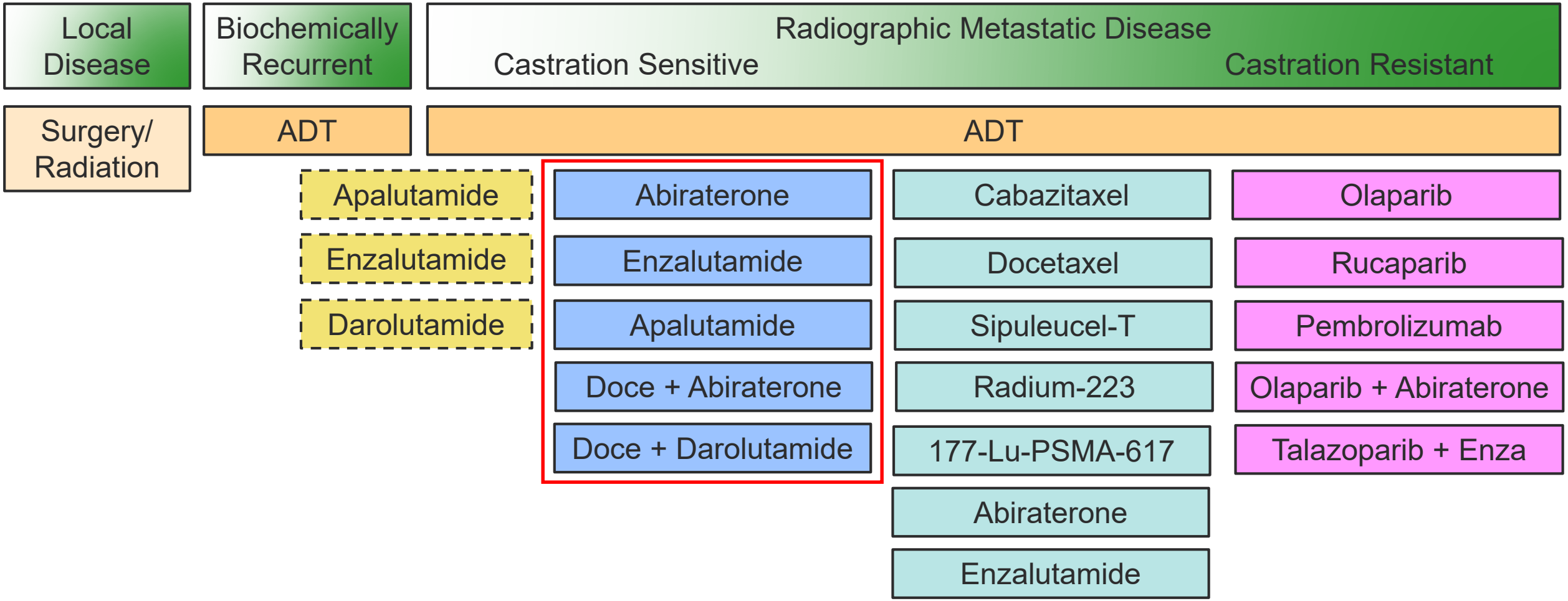
Huggins awarded the 1966
Nobel Prize for Physiology or Medicine

> 80 Years Later



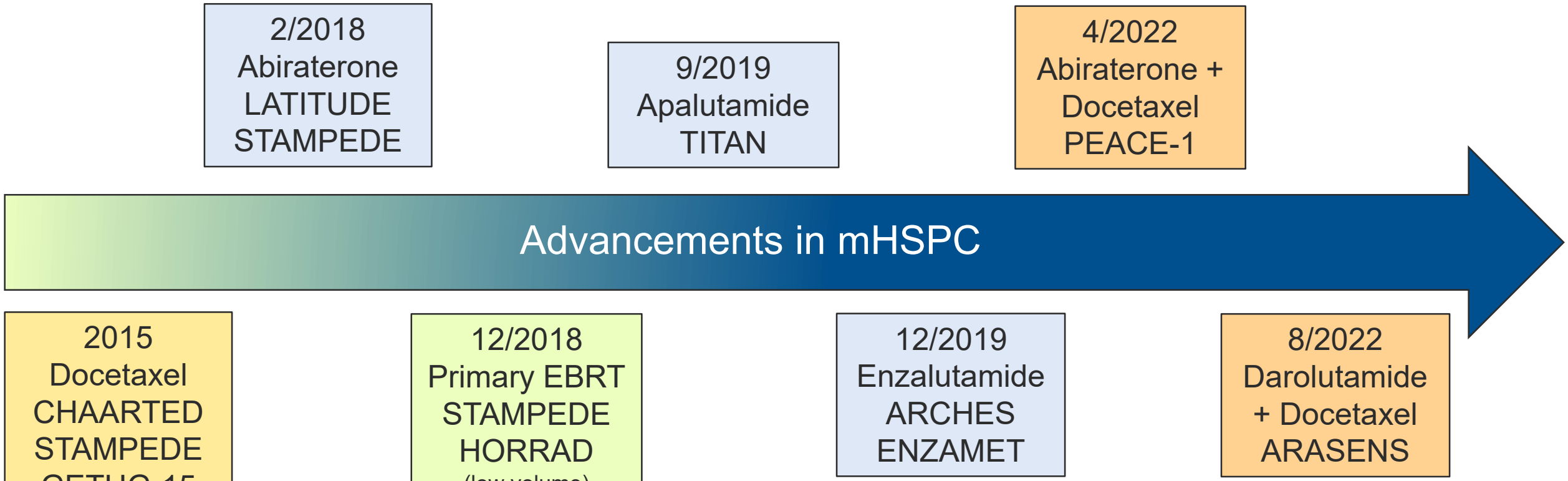
ADT is still the mainstay of therapy…but treatments have evolved for different disease states

> 80 Years Later



ADT is still the mainstay of therapy…but treatments have evolved for different disease states

Treatment Landscape for mHSPC



NCCN Guidelines – mHSPC

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2023
Prostate Cancer

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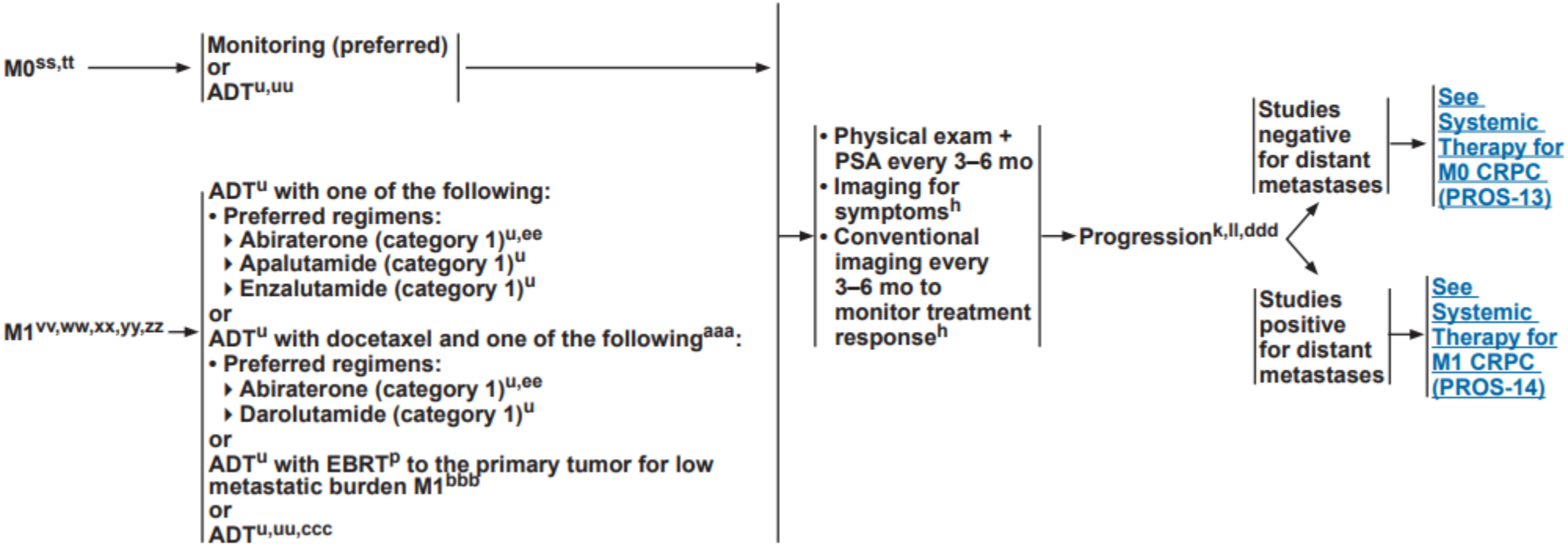
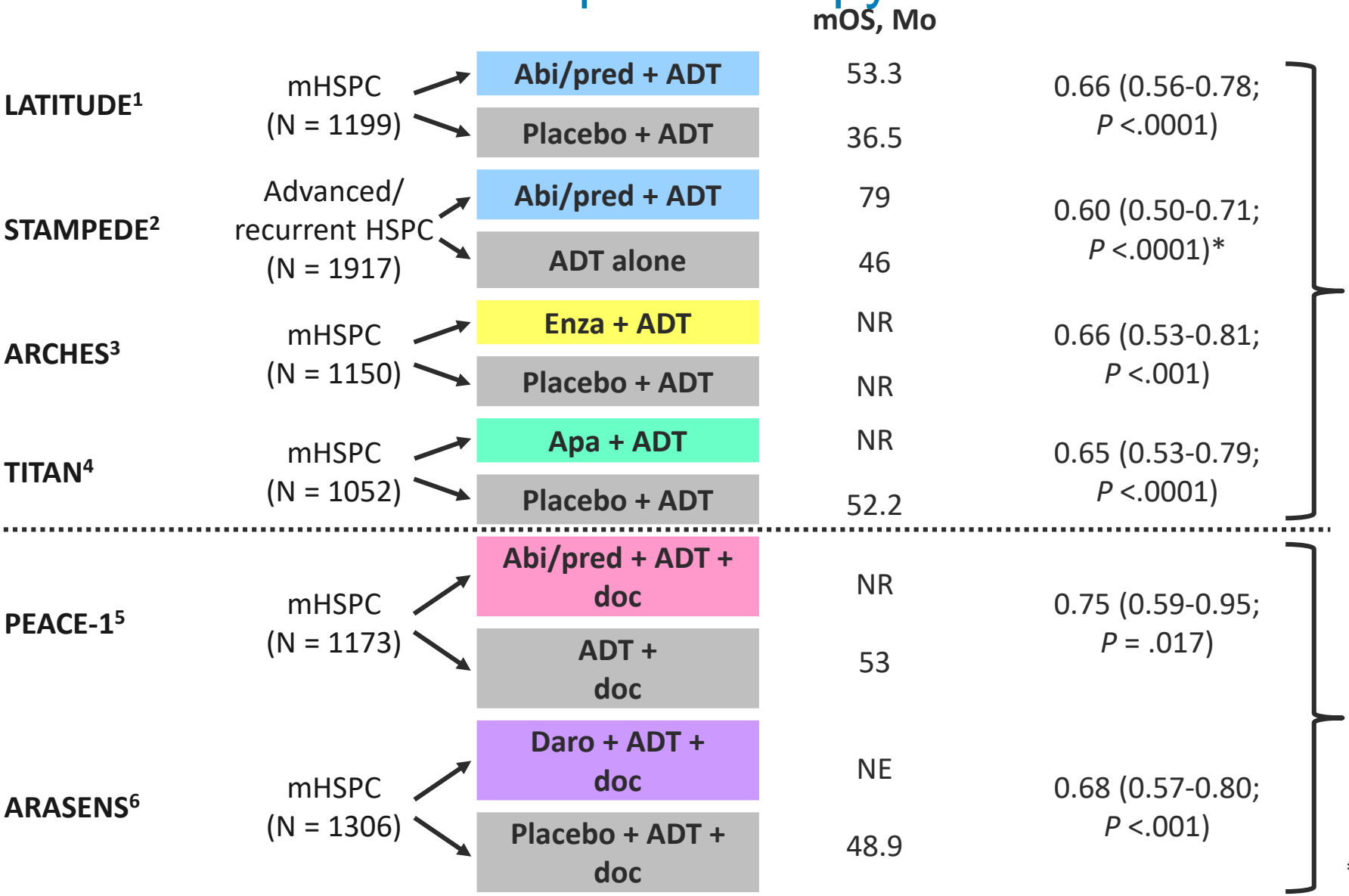
SYSTEMIC THERAPY FOR CASTRATION-SENSITIVE PROSTATE CANCER[rr]



OS With Doublet and Triplet Therapy in mHSPC



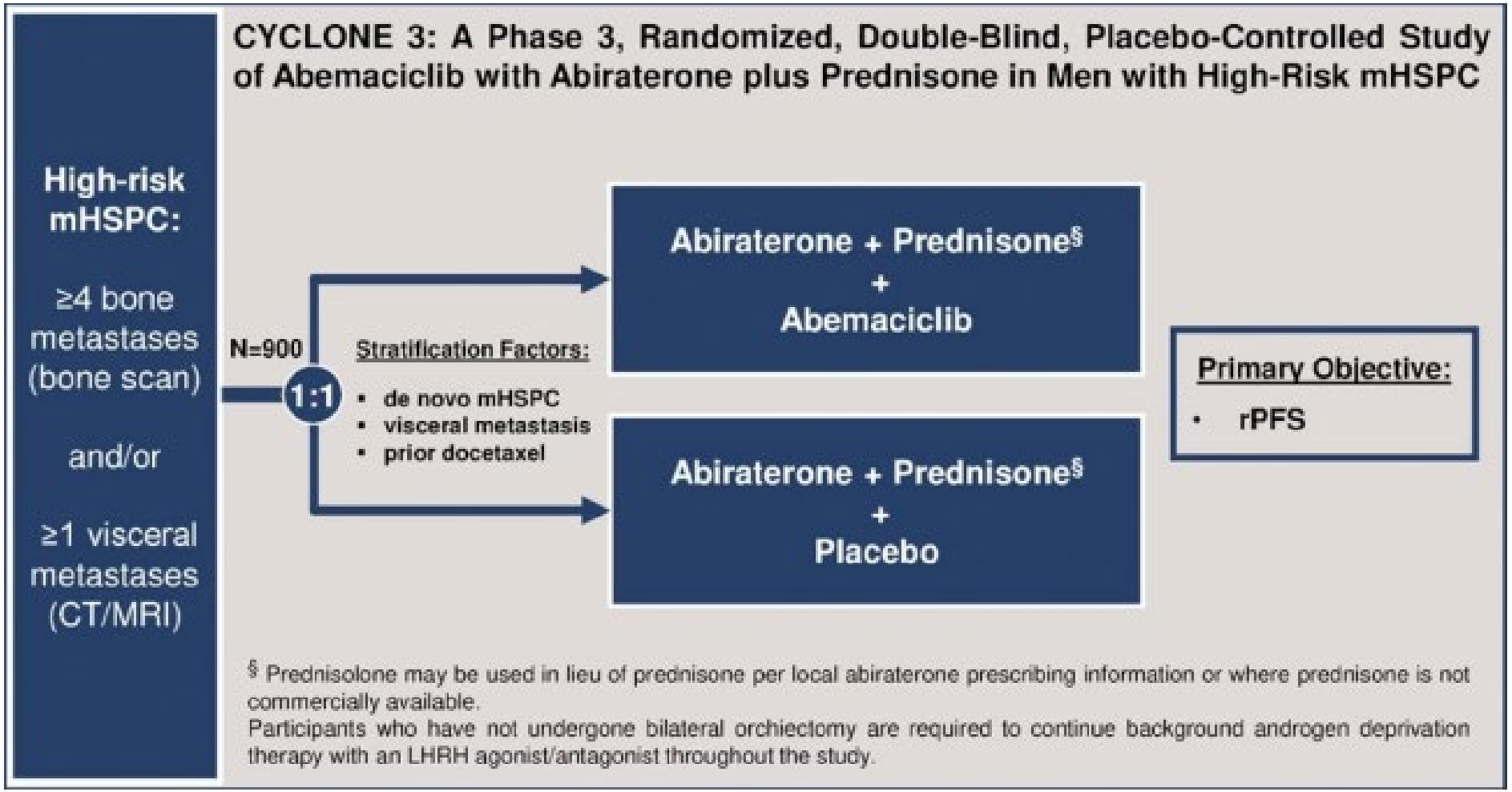
*In subgroup with metastatic disease.

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.

Trials on the Horizon in mHSPC

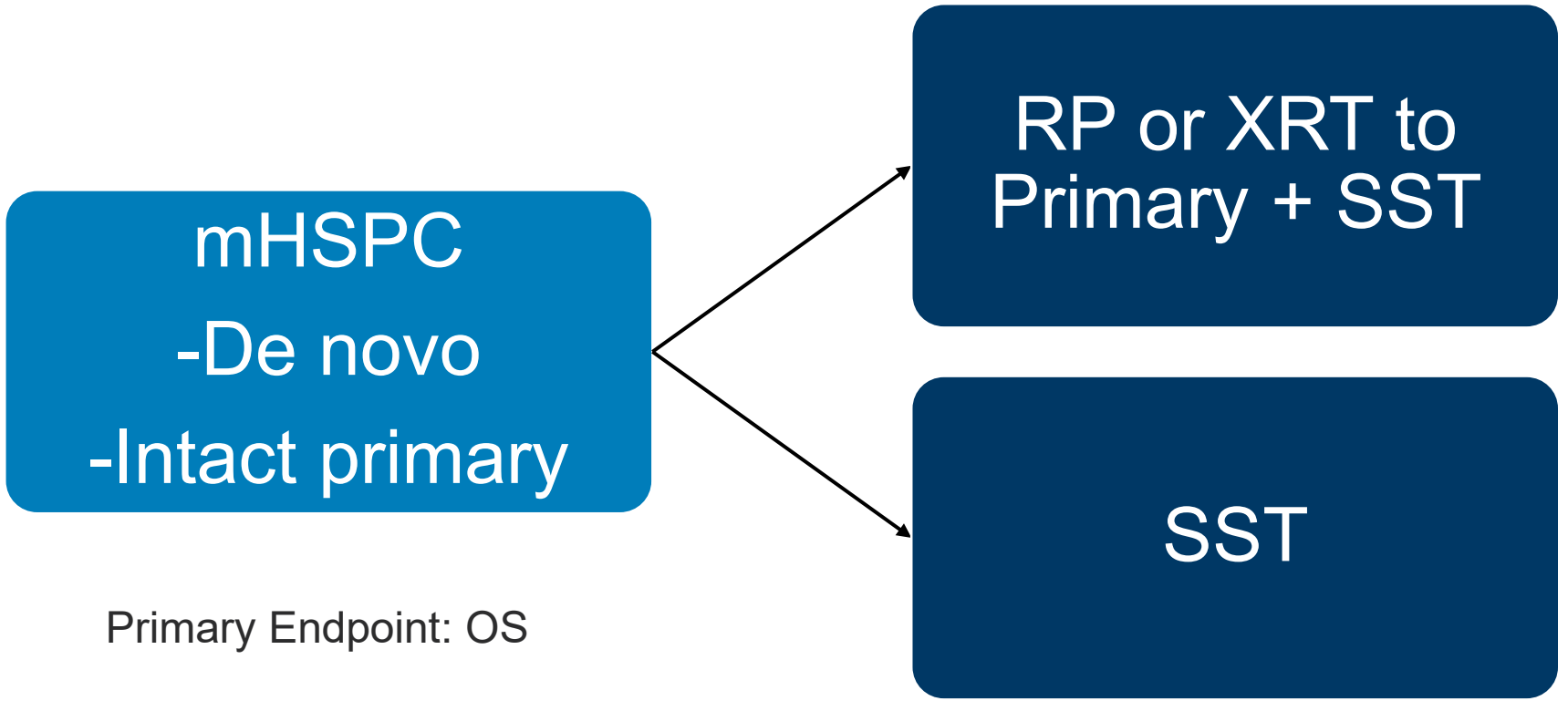
Study	Patients	Treatment Arm	Control Arm	Primary End
ARANOTE		Darolutamide + ADT	Placebo + ADT	03/2024
Keynote-991		Pembro + Enza + ADT	Placebo + Enza + ADT	01/2026
CAPItello-281	PTEN-	Capivasertib + Abi + ADT	Placebo + Abi + ADT	11/2024
PSMAddition		^{177}Lu-PSMA-617 + ARTA + ADT	ARTA + ADT	08/2024
AMPLITUDE	HRR+	Niraparib + Abi + ADT	Placebo + Abi + ADT	11/2024
TALAPRO-3	DDR+	Talazoparib + Enza + ADT	Placebo + Enza + ADT	12/2024
Cyclone 3	High-Risk	Abemaciclib + Abi + ADT	Placebo + Abi + ADT	10/2025

Cyclone 3 – mHSPC



McKay et al, ESMI, 2022

SWOG 1802– mHSPC

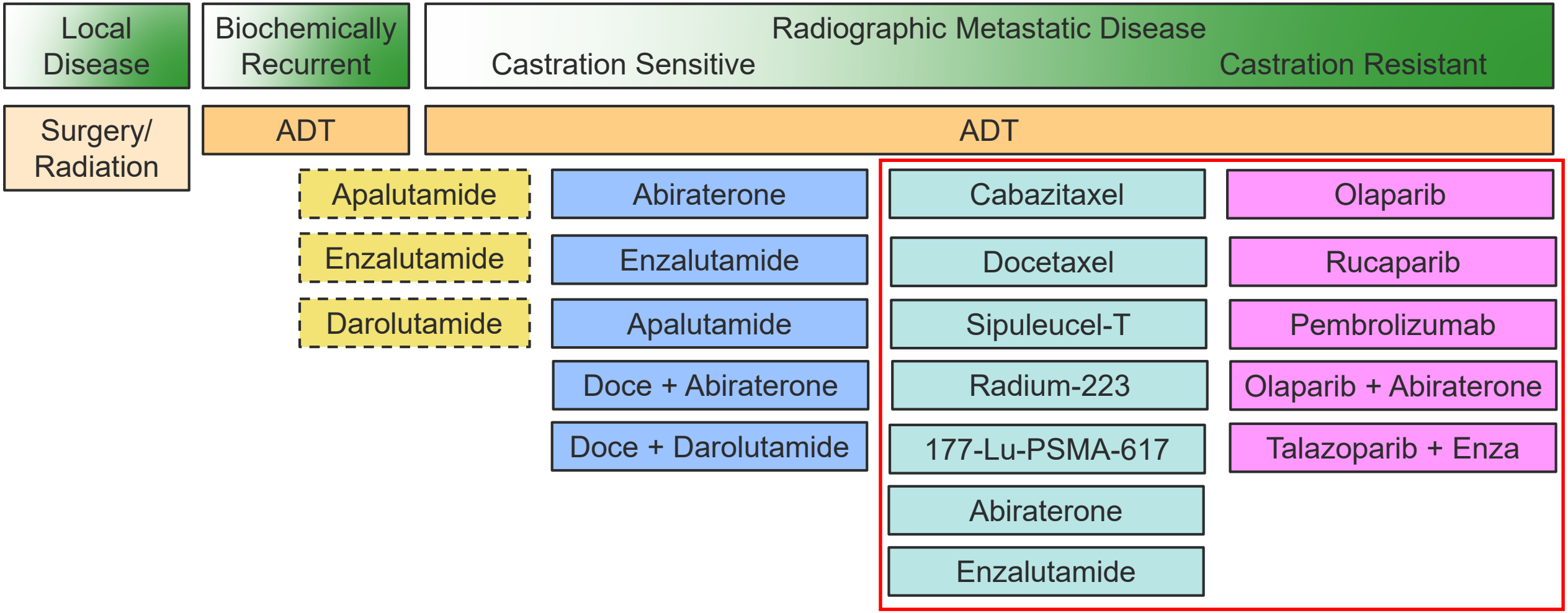


Primary Endpoint: OS

Treatment continues until radiographic progression (PCWG2) or toxicity or withdrawal

McKay et al, ESMI, 2022

> 80 Years Later



ADT is still the mainstay of therapy…but treatments have evolved for different disease states

NCCN Guidelines – mCRPC

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2023
Prostate Cancer

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SYSTEMIC THERAPY FOR M1 CRPC: ADENOCARCINOMA[iii,kkk,lll]

No prior docetaxel/no prior novel hormone therapy[mmm]

- Preferred regimens
  - Abiraterone[u,nnn] (category 1[ooo])
  - Docetaxel[fff,ppp] (category 1)
  - Enzalutamide[u] (category 1)
- Useful in certain circumstances
  - Olaparib/abiraterone[u,fff] for BRCA mutation (category 1)[nnn,qqq]
  - Radium-223[rrr] for symptomatic bone metastases (category 1)
  - Sipuleucel-T[fff,sss] (category 1)
  - Talazoparib/enzalutamide for HRRm[u,fff,yyy] (category 1)
- Other recommended regimens
  - Other secondary hormone therapy[u]

Prior novel hormone therapy/no prior docetaxel[mmm,ttt]

- Preferred regimens
  - Docetaxel (category 1)[fff]
- Useful in certain circumstances
  - Cabazitaxel/carboplatin[fff,jjj]
  - Olaparib for HRRm (category 1)[uuu]
  - Radium-223[rrr] for symptomatic bone metastases (category 1)
  - Rucaparib for BRCA mutation[vvv]
  - Sipuleucel-T[fff,sss]
  - Talazoparib/enzalutamide for HRRm[u,fff,yyy]
- Other recommended regimens
  - Abiraterone[u,nnn]
  - Abiraterone[u] + dexamethasone[nnn,www]
  - Enzalutamide[u]
  - Other secondary hormone therapy[u]

Prior docetaxel/no prior novel hormone therapy[mmm]

- Preferred regimens
  - Abiraterone[u,nnn] (category 1)
  - Cabazitaxel[fff]
  - Enzalutamide[u] (category 1)
- Useful in certain circumstances
  - Cabazitaxel/carboplatin[fff,jjj]
  - Mitoxantrone for palliation in symptomatic patients who cannot tolerate other therapies[fff]
  - Radium-223[rrr] for symptomatic bone metastases (category 1)
  - Sipuleucel-T[fff,sss]
  - Talazoparib/enzalutamide for HRRm[u,fff,yyy]
- Other recommended regimens
  - Other secondary hormone therapy[u]

Prior docetaxel and prior novel hormone therapy[mmm,ttt]

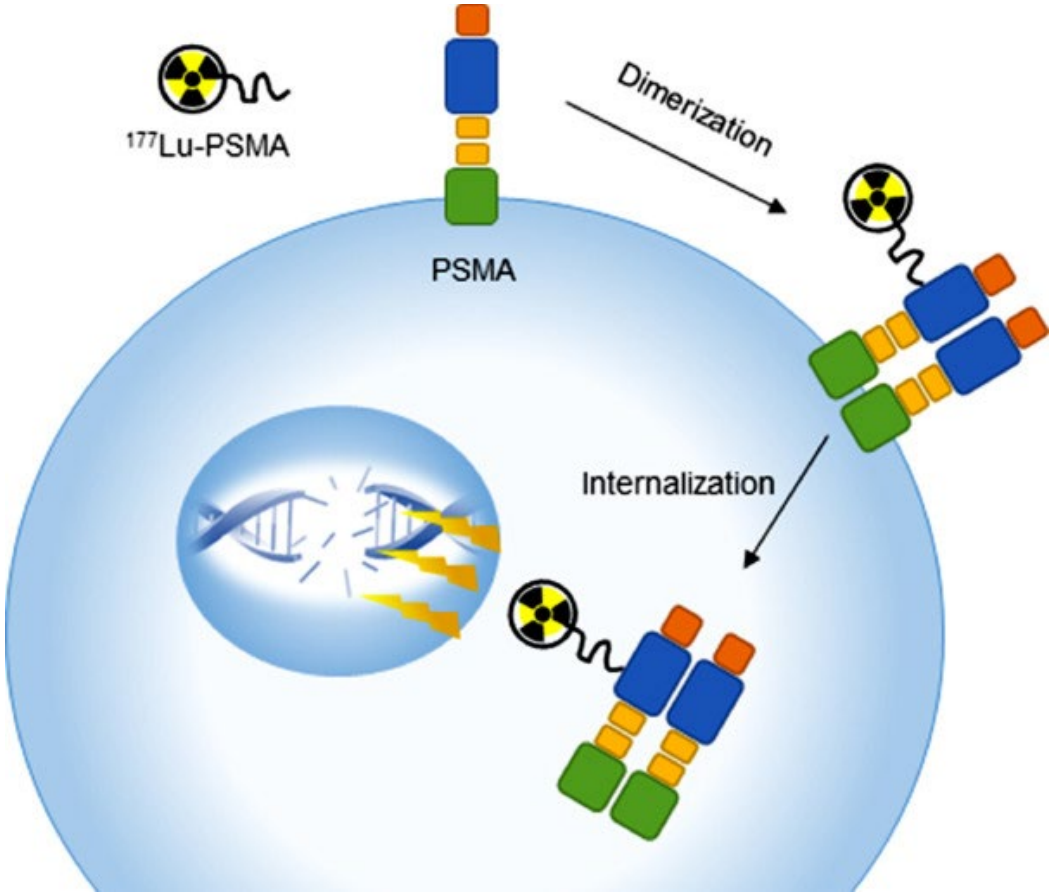
- Useful in certain circumstances
  - Lutetium Lu 177 vipivotide tetraxetan (Lu-177–PSMA-617) for PSMA-positive metastases (category 1)[xxx]

(The following systemic therapies are category 2B if visceral metastases are present)

- Preferred regimens
  - Cabazitaxel[fff] (category 1[ooo])
  - Docetaxel rechallenge[fff]
- Useful in certain circumstances
  - Cabazitaxel/carboplatin[fff,jjj]
  - Mitoxantrone for palliation in symptomatic patients who cannot tolerate other therapies[fff]
  - Olaparib for HRRm (category 1[ooo])[uuu]
  - Pembrolizumab for MSI-H, dMMR, or TMB ≥10 mut/Mb[fff]
  - Radium-223[rrr] for symptomatic bone metastases (category 1[ooo])
  - Rucaparib for BRCA mutation[vvv]
- Other recommended regimens
  - Abiraterone[u,nnn]
  - Enzalutamide[u]
  - Other secondary hormone therapy[u]

^{177}Lu-PSMA-617 (Lutetium Lu-177 Vipivotide Tetraxetan)

- ^{177}Lu-PSMA-617: β-emitting radioligand conjugated to PSMA-binding peptide
- PSMA (prostate-specific membrane antigen): cell surface receptor involved in folate uptake and cell migration, proliferation, survival
  - Overexpressed in ~80% of mCRPC
  - Also expressed in normal prostate, proximal renal tubules, small intestine, salivary glands
- FDA approved for PSMA+ mCRPC with prior AR pathway inhibition and taxane-based CT
  - Select using PET with approved companion radioactive diagnostic agent (gallium GA 68 gozetotide)
  - Administration: 7.4 GBq (200 mCi) IV Q6W for up to 6 doses or until PD/unacceptable toxicity



Jia. Pract Radiat Oncol. 2022;12:294. Deluce. Curr Oncol. 2022;29:5054. Emmett. J Med Radiat Sci. 2017;64:52. Lutetium Lu 177 vipivotide tetraxetan. Kalinauskaite. PLoS One. 2020;15:e0240892.

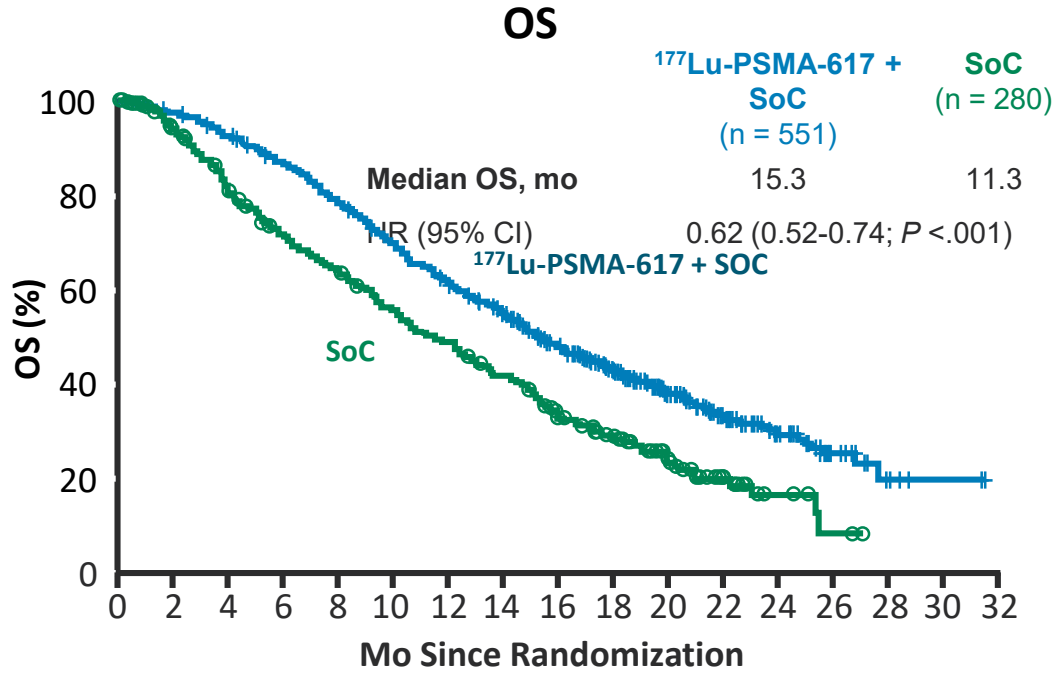
Phase III VISION – ^{177}Lu-PSMA-617 + SoC vs SoC Alone

Patients with PSMA+ mCRPC on PET/CT with ^{68}Ga-PSMA-11; ≥1 prior AR pathway inhibitor and prior ≥1 taxane; ECOG PS 0-2
(N = 831)

^{177}Lu-PSMA-617 7.4 GBq (200 mCi) Q6W x 4-6 cycles + Protocol-permitted SoC*
(n = 551)

Protocol-permitted SoC*
(n = 280)

*Excludes CT, immunotherapy, systemic radioisotopes, and investigational drugs.



- PSMA+ mCRPC defined as ≥1 PSMA+ metastatic lesion with ^{68}Ga uptake > liver *and* no PSMA- lesions in bone with soft tissue component ≥1 cm, lymph nodes ≥2.5 cm, or solid organ ≥1 cm
- Of 1003 patients who underwent scanning for VISION, 12.6% did not meet PSMA+ criteria

Sartor. NEJM. 2021;385:1091.

Availability of ^{177}Lu-PSMA-617

UC San Diego

UC SAN DIEGO **TODAY**

RESEARCH PEOPLE CAMPUS & COMMUNITY ARTS & CULTURE VOICES

Patient First in Region to Receive New Treatment for Advanced Prostate Cancer

Novel drug travels through body and uses targeted radiation to kill prostate cancer cells

Administering the treatment to UC San Diego Health patients requires a multi-disciplinary approach with teams in oncology, urology, radiation oncology, radiology, nuclear medicine, pharmacy, nursing and integrative medicine teams.

October 05, 2022 **By:**

Phase III PROfound – Olaparib vs Physician's Choice in Progressing mCRPC

Adult men with mCRPC with PD on prior abiraterone or enzalutamide; prior taxane permitted; alterations in ≥1 qualifying gene with a direct or indirect role in HRR (N = 387)

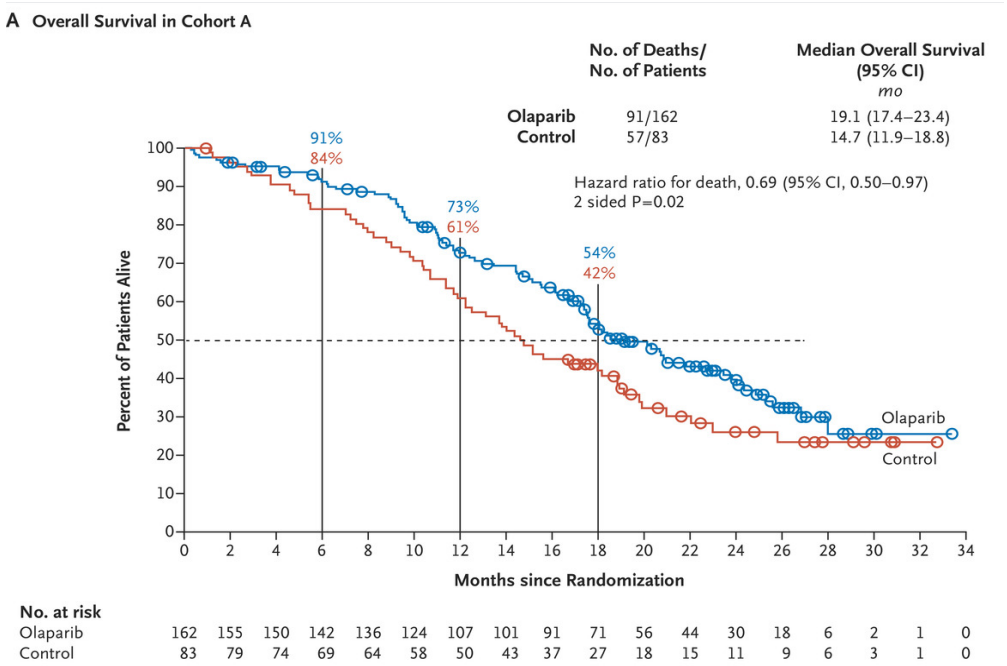
Cohort A
BRCA1, BRCA2, or *ATM*
(n = 245)

- **Olaparib** 300 mg BID (n = 162)
- **Physician's choice** (n = 83)

81% crossed over upon BICR progression

Cohort B
Other alterations
(n = 142)

- **Olaparib** 300 mg BID (n = 94)
- **Physician's choice** (n = 48)



In cohort A, olaparib significantly reduced:

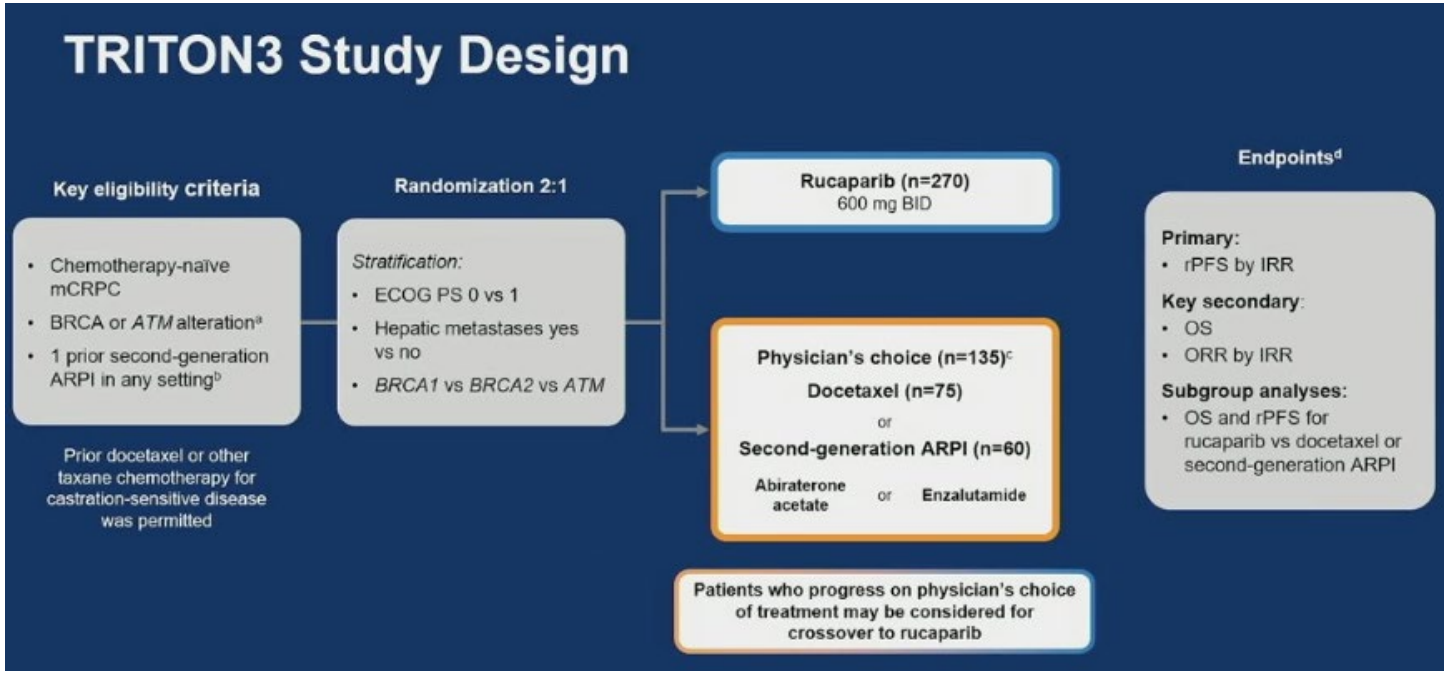
Risk of death by 31%

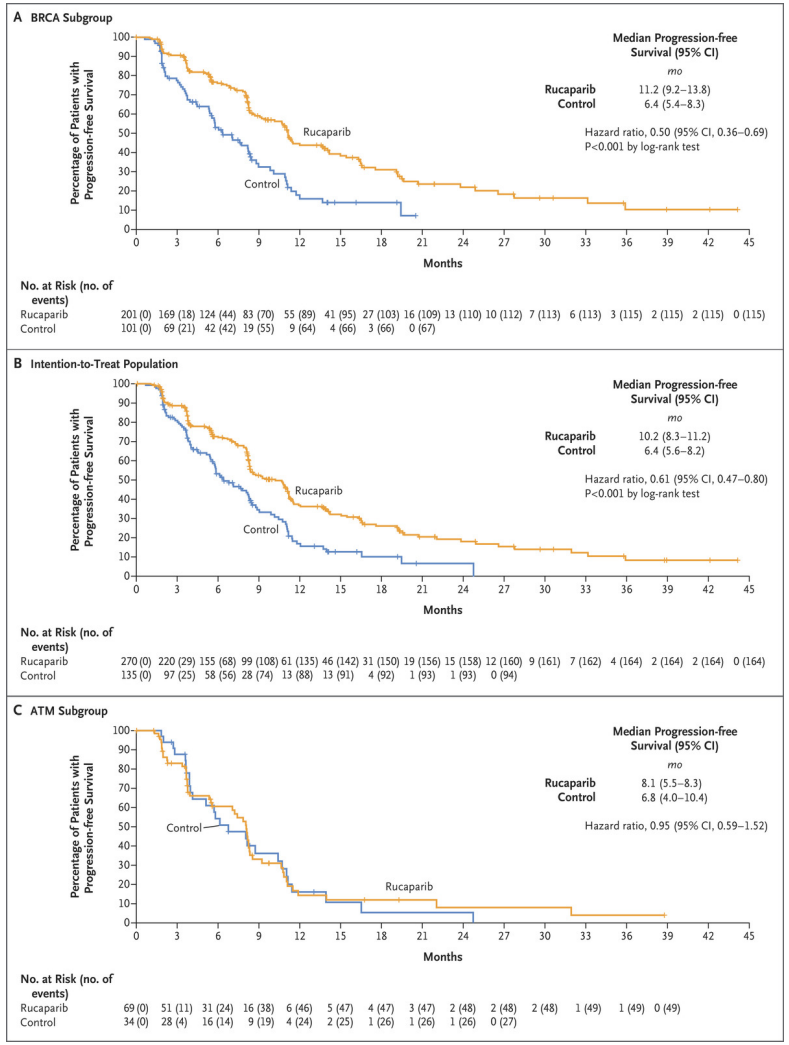
Risk of imaging-based progression or death by 66% (*P* <.001; primary endpoint)

No OS benefit in cohort B

de Bono. NEJM. 2020;382:2091. Hussain. NEJM. 2020;383:2345.

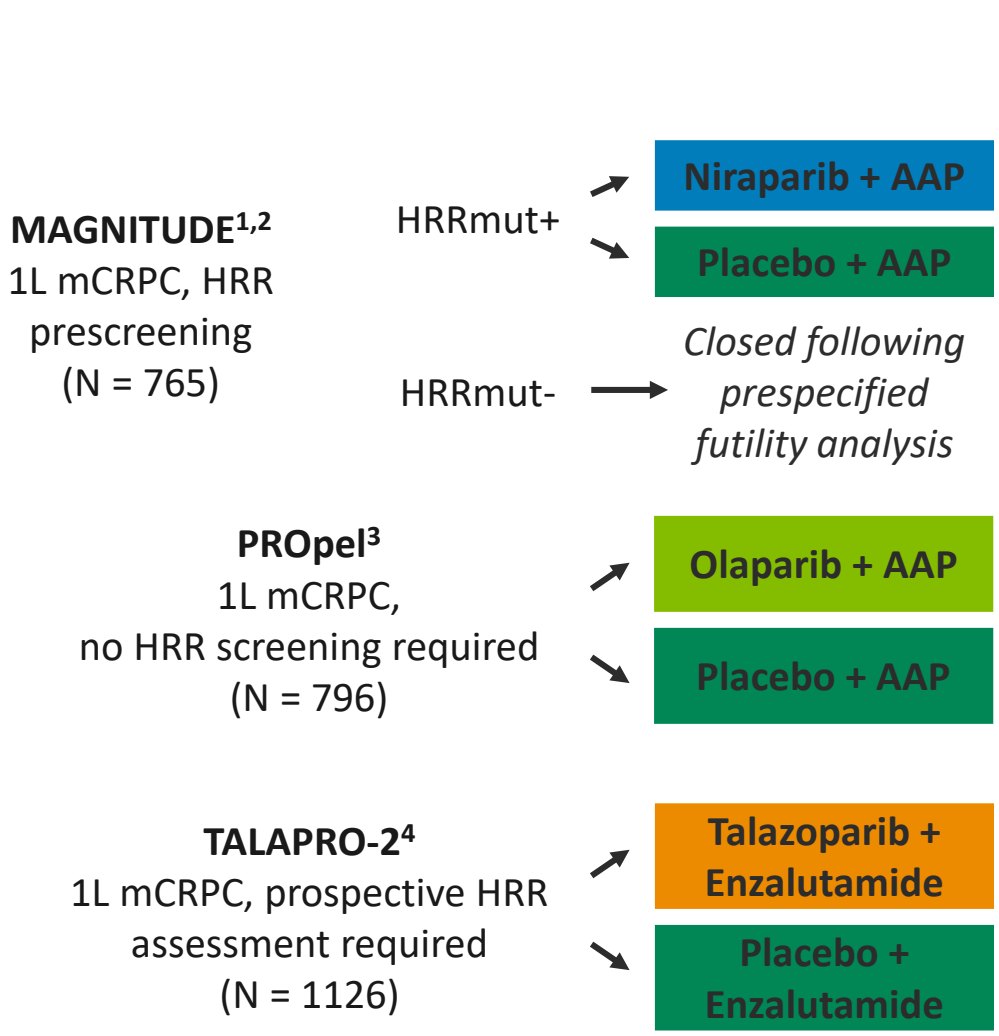
Phase III TRITON3 – Rucaparib vs Physician's Choice in mCRPC With *BRCA1/2* or *ATM* Mutations





Fizazi et al, NEJM, 2023

Phase III Trials of First-line PARP Inhibitor + AR Inhibitor in mCRPC – PFS



Median rPFS per BICR *in HRRmut+ Cohort*

16.5

13.7

HR (95% CI): 0.73; (0.56-0.96; *P* = .0217

FDA Approved 8/11/2023 in BRCA mutated mCRPC

Median ibPFS per Investigator

24.8

16.6

HR (95% CI): 0.66; (0.54-0.81; *P* <.001)

FDA Approved 5/31/2023 in BRCA mutated mCRPC

Median rPFS per BICR

NR

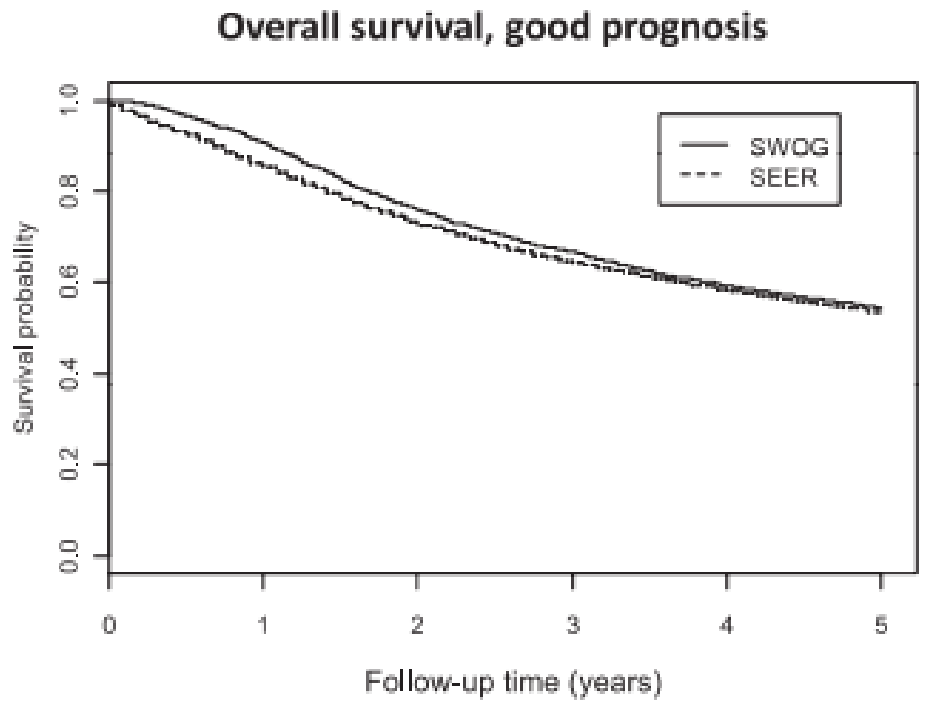
21.9

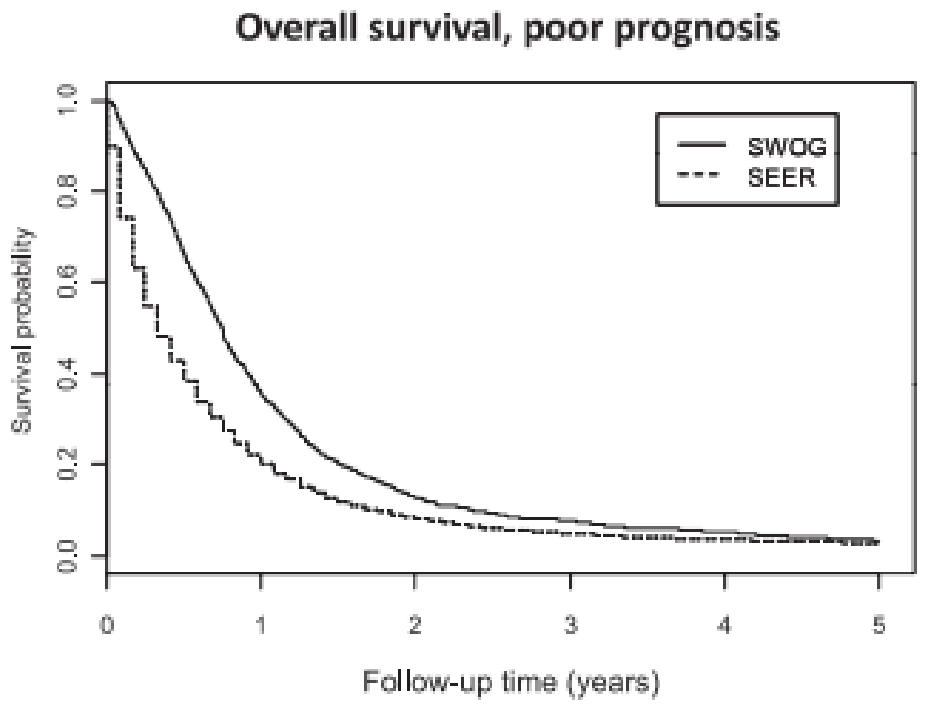
HR (95% CI): 0.63; (0.51-0.78; *P* <.001)

FDA Approved 6/20/2023 in HRR mutated mCRC

1. Efstathiou. ASCO GU 2023. Abstr 170. 2. Chi. ASCO GU 2022. Abstr 12. 3. Clarke. NEJM Evid. 2022;1. 4. Agarwal. ASCO GU 2023. Abstr LBA17.

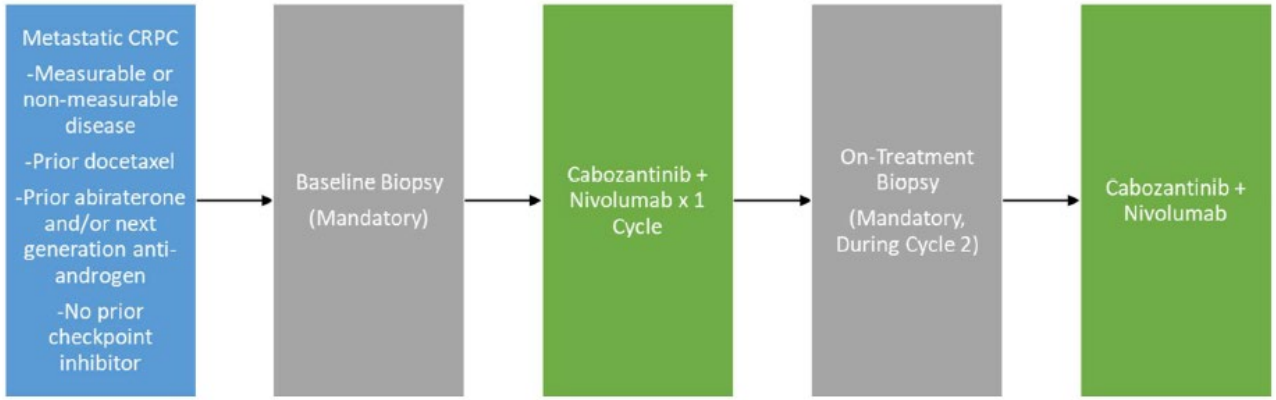
Survival Improved in Patients Treated on Clinical Trials





Unger et al, JNCI, 2014

Canopy Trial – mCRPC



EXELIXIS Inside Exelixis Treating Cancer Innovating R&D Creati

Press release

Investors & News / Press Releases /

Exelixis and Ipsen Announce Positive Results from Phase 3 CONTACT-02 Pivotal Trial Evaluating Cabozantinib in Combination with Atezolizumab in Metastatic Castration-Resistant Prostate Cancer

August 21, 2023 PDF Version

– Cabozantinib in combination with atezolizumab demonstrated a statistically significant reduction in the risk of disease progression or death compared with a second novel hormonal therapy in patients with metastatic castration-resistant prostate cancer –

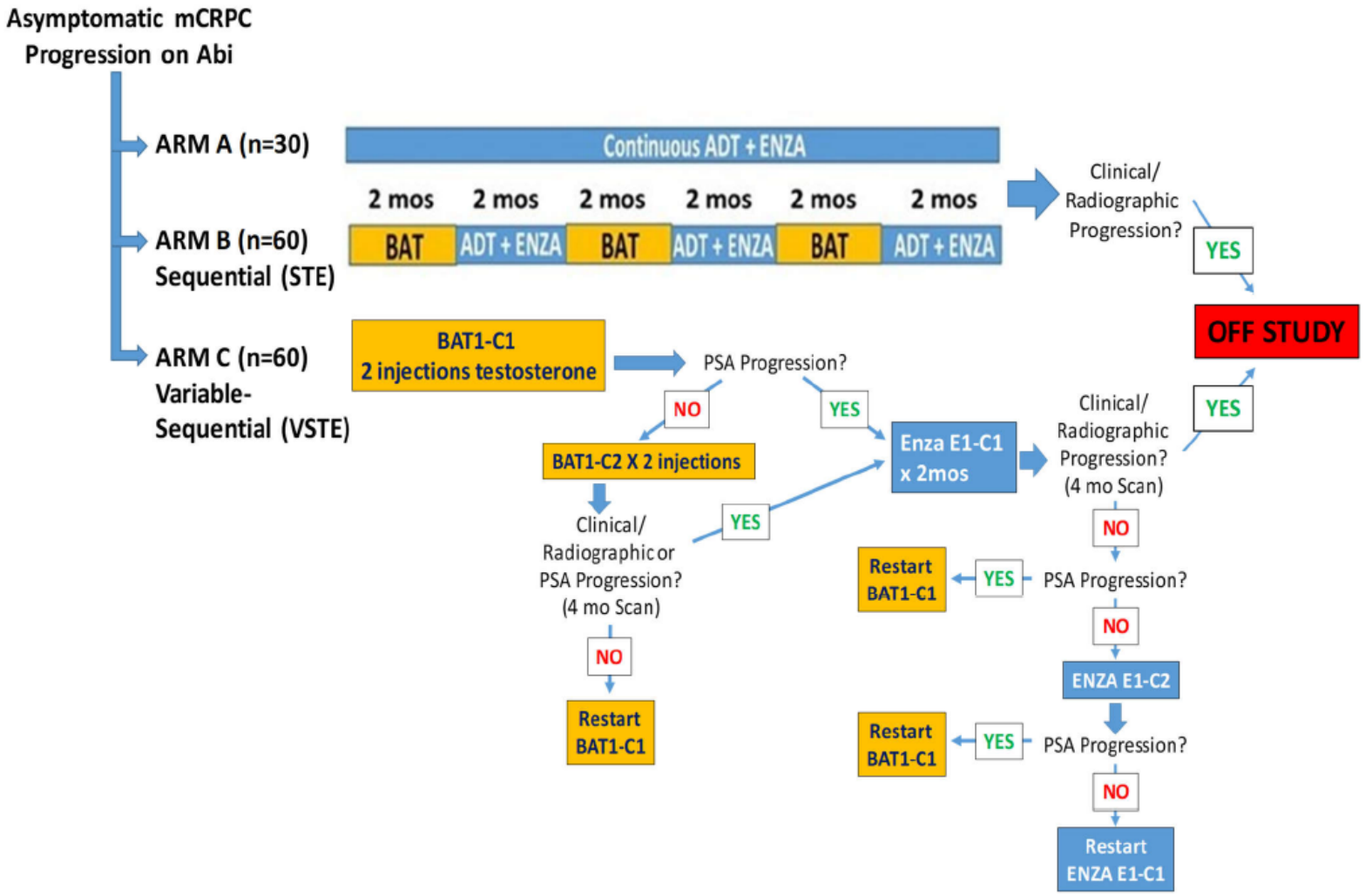
– A trend toward improvement in overall survival was observed at first interim analysis –

– Findings will be presented at an upcoming medical meeting and discussed with health authorities globally –

Cirmtuzumab + Docetaxel – mCRPC

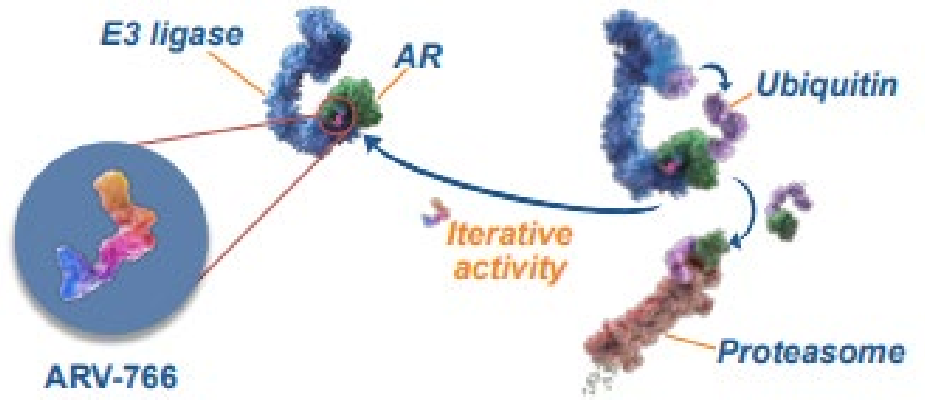
Cirmtuzumab – ROR1 Targeting Monoclonal Antibody

Step-Up Trial (Bipolar Androgen Therapy) – mCRPC



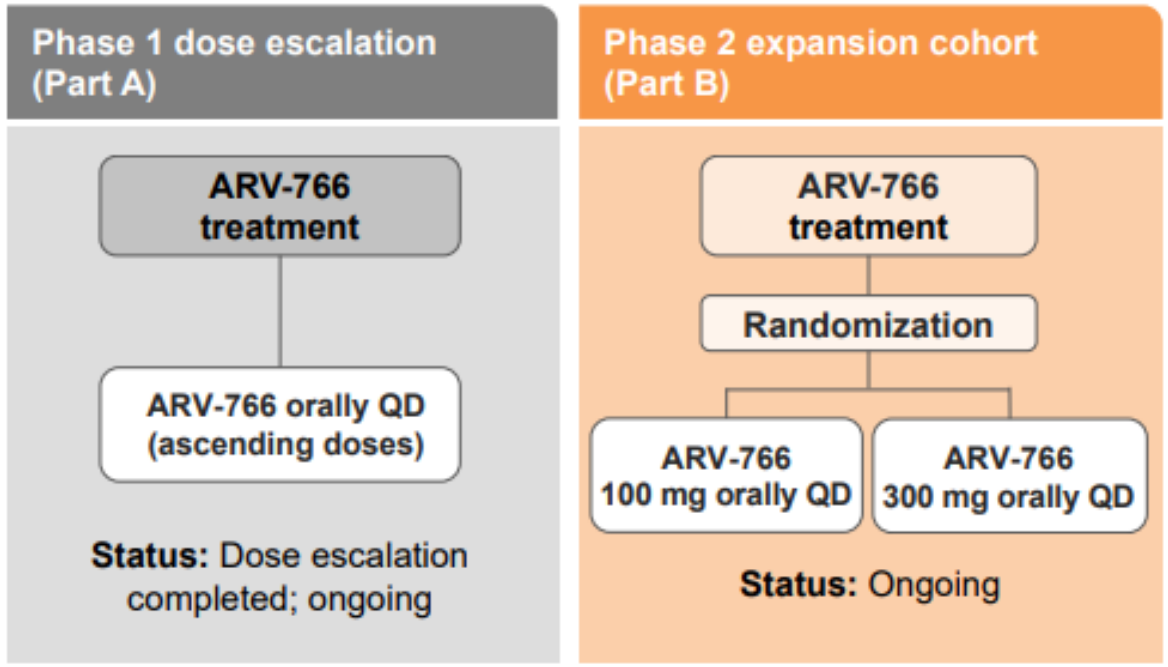
ARV-766 – mCRPC

Figure 1: Mechanism of action of ARV-766[a]



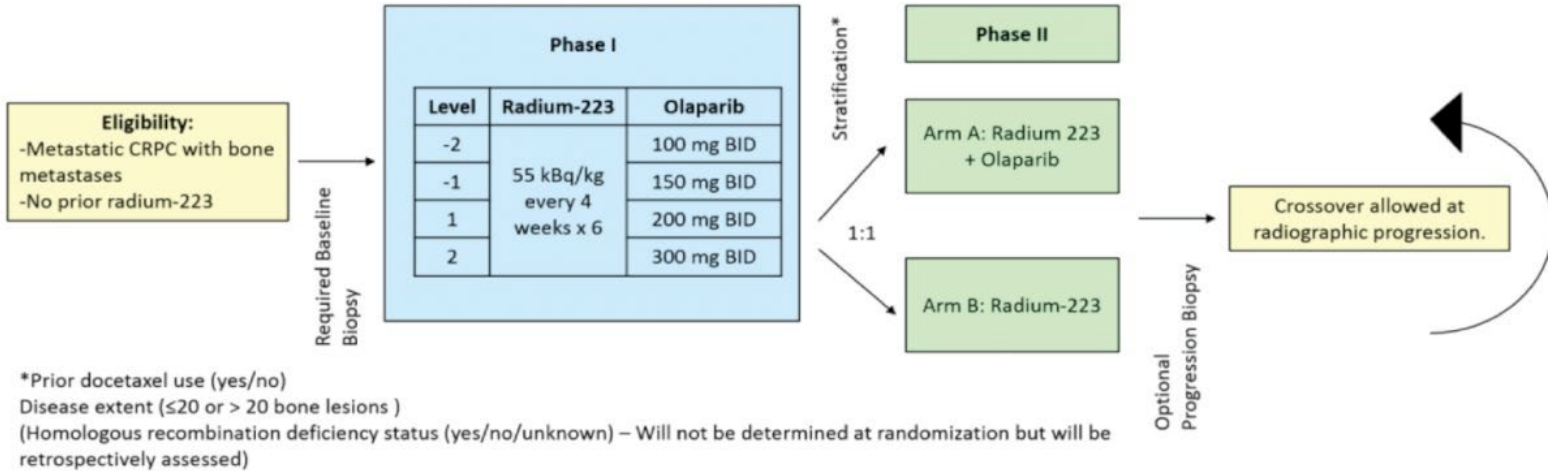
[a]General PROTAC protein degrader is shown
AR=androgen receptor; PROTAC=PROteolysis TArgeting Chimera

Figure 2: Trial schema



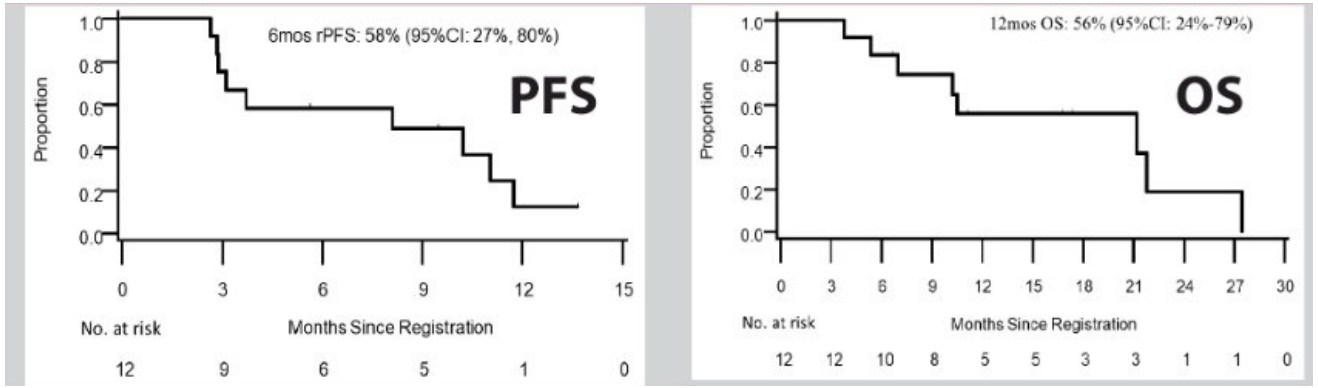
QD=once daily

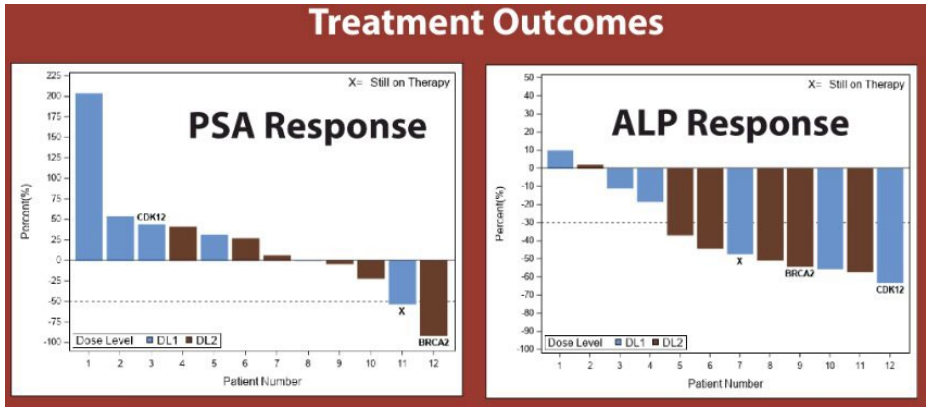
COMRADE Trial – mCRPC



*Prior docetaxel use (yes/no)
Disease extent (≤20 or > 20 bone lesions)
(Homologous recombination deficiency status (yes/no/unknown) – Will not be determined at randomization but will be retrospectively assessed)

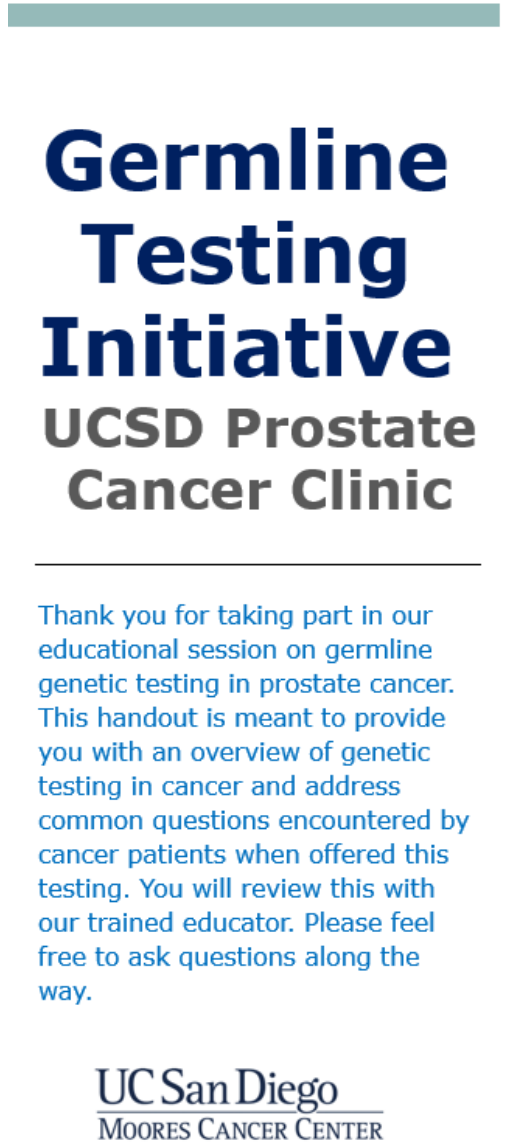
Phase 1 Study Outcomes



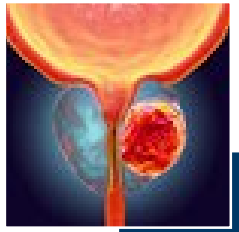


IMPRINT Trial – Germline Genetic Testing

- Educational intervention to improve patient understanding of germline genetic testing
- Integrated patient video and brochure
- Available in English and Spanish



Factors that Impact Treatment Decision



Disease Factors

- Volume/Risk of disease
- Recurrent/De Novo
- Sites of Metastasis
- Gleason score
- Genomic features

Clinical Factors

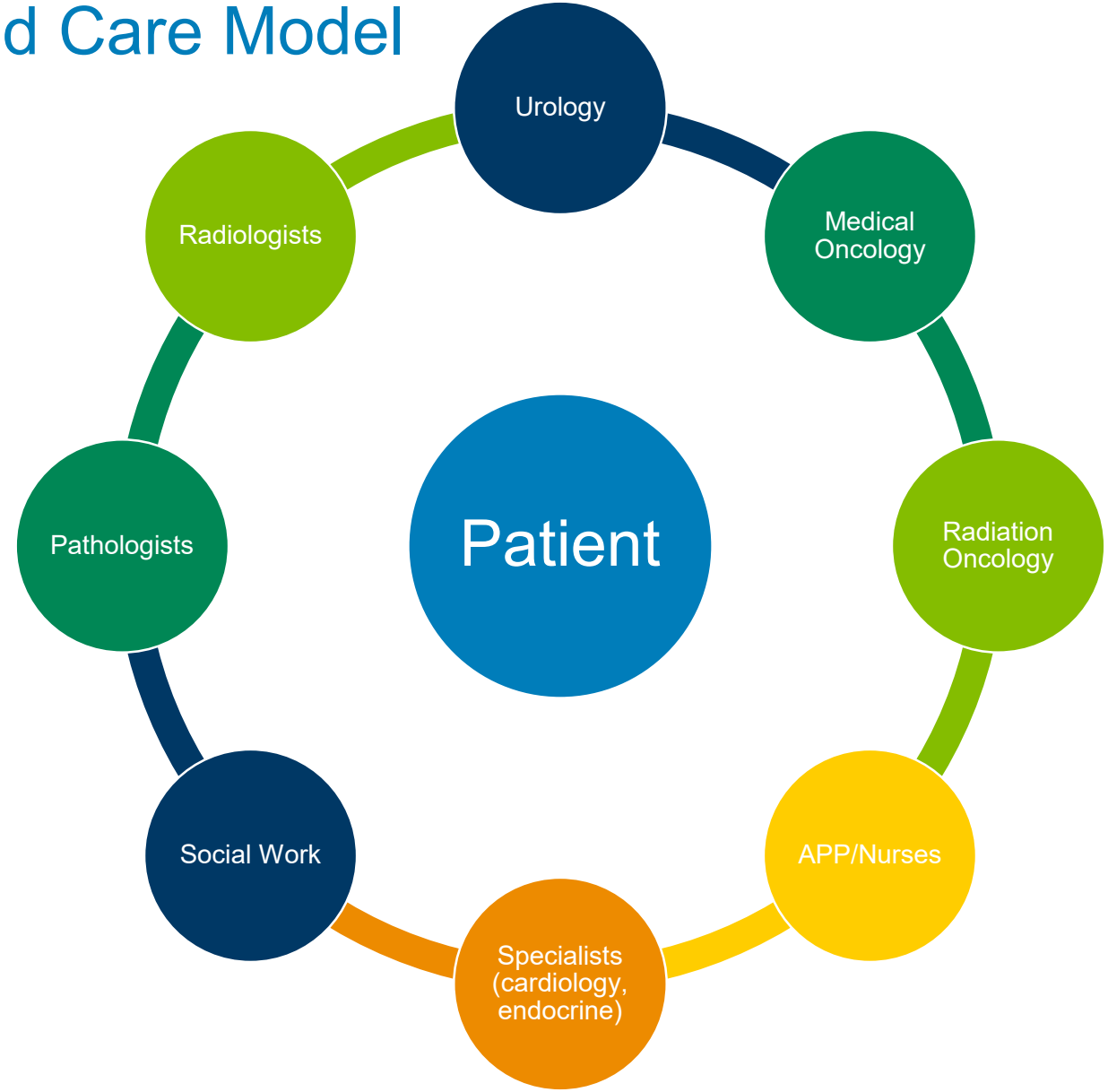
- Symptoms
- Performance status
- Comorbidities
- Concurrent Medications

Drug Factors

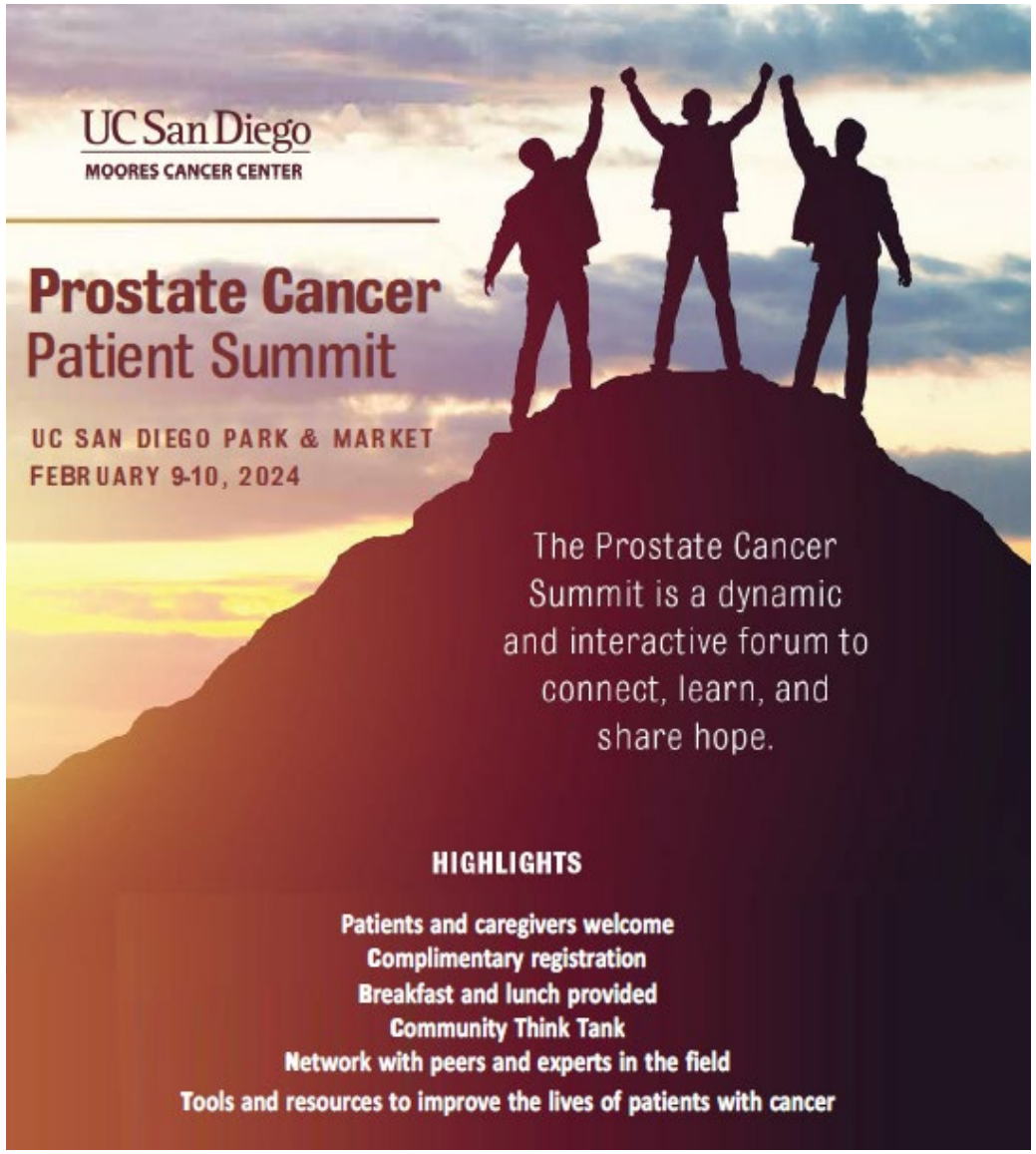
- Mechanism of action
- Mode of administration
- Cost

Multidisciplinary Clinic – Integrated Care Model

- Weekly multidisciplinary clinic (Friday PM)
- Joint consultation with medical oncology, urology, and radiation oncology
- Integrated platform for molecular tumor profiling
- Screening for clinical trial eligibility
- Personalized treatment strategy



Prostate Cancer Patient Summit



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E-mail: ocme@health.ucsd.edu

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Conclusions

- There have been significant advances in life prolonging therapies for patients with advanced prostate cancer
- The care of patients with advanced prostate cancer is highly multidisciplinary and integrated with urology, medical oncology, and radiation oncology
- Clinical trials