Oncology
Learning Network

Treatment Advances for Advanced Prostate Cancer: Guideline Updates and Newer Therapies

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HMP Education

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Faculty Disclosures

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Program Information

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Learning Objectives

- Evaluate diagnostic and prognostic biomarkers and emerging applications for next-generation imaging in staging and treatment selection
- Assess key clinical efficacy and safety data associated with current and emerging anti-androgen therapies and PARP inhibitors in advanced PC
- Integrate evidence-based, guideline-directed treatment strategies, including managing AEs, associated with anti-androgen agents and PARP inhibitors into clinical practice

PARP = poly-adenosine diphosphate (ADP) ribose polymerase; PC = prostate cancer; AE = adverse event.

Screening and Risk Factors—Trying to Avoid Advanced Prostate Cancer!

Prostate Cancer in 2024

- 299,010 cases and over 35,250 deaths/year (2024) in the USA
- More common in Black men, men with a family history, and men over age 50
- Screening for the disease with PSA is **still debated**
- Early-stage is treated mainly with surgery, radiation, and active surveillance (also cryotherapy and HIFU)
- Late-stage disease is mainly treated with hormones, chemotherapy, and **many new novel therapies**

PSA = prostate-specific antigen; HIFU = high-intensity focused ultrasound.

American Cancer Society. Last updated January19, 2024. Accessed November 7, 2024. https://www.cancer.org/cancer/types/prostate-cancer/about/key-statistics.html.

1990-2010: The First 20 Years of Prostate Cancer Screening

- Prior to the introduction of PSA into clinical practice (prior to 1990)
  - 20% of PC patients presented with metastasis (1989)
- After PSA-based PC screening
  - Only 3% of new cases presented with metastasis (1998)

Screening was widely accepted.

Sun L, et al. *Urol Oncol*. 2001;6(5):203-209.

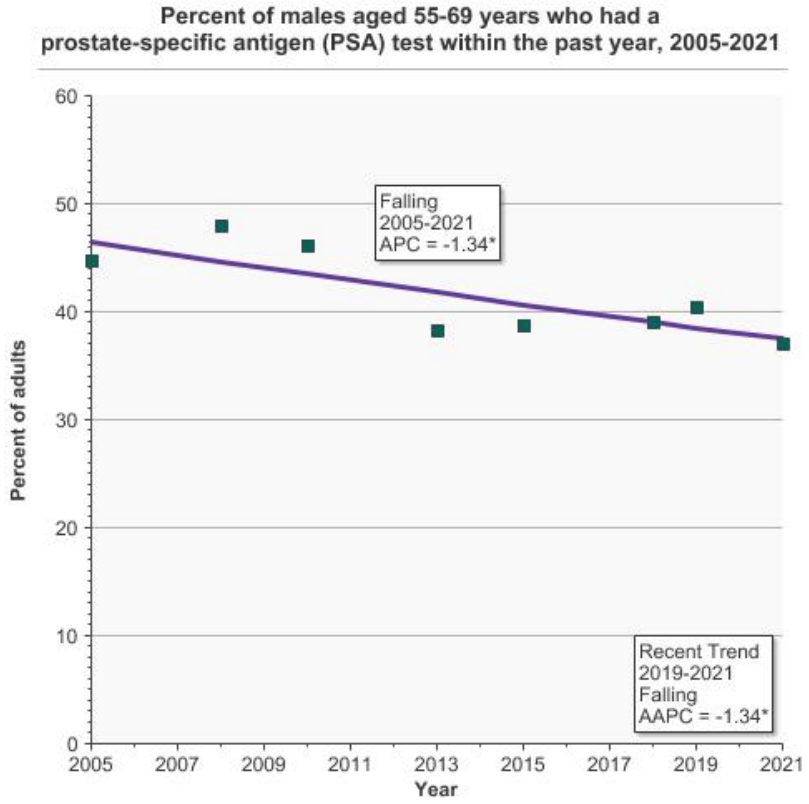
2011: United States Preventive Services Task Force (USPSTF) Gives "D" Rating for PSA Screening

2011-2018: the anti-screening era

Moyer VA. *Ann Intern Med*. 2012;157(2):120-134. Szabo L. *USA Today*. May 22, 2012.

2011-2018: PC Screening Decline

By 2017, 50% of US primary care physicians did not offer PC screening, even less so in healthy men 70 years and older.



- There is no Healthy People 2020 Target for PSA test rates; therefore, the desired direction is labeled as indeterminate
- Data are age-adjusted to the 2000 US standard population using age groups: 55-59, 60-69; weighted regression lines are calculated using the Joinpoint Trend Analysis Software, Version 4.9 April 2022, National Cancer Institute
- The AAPC is a weighted average of the APC estimates that occur over the specified year range

***Statistically significant.**
APC = annual percent change; AAPC = average annual percent change.
National Cancer Institute. Last updated March 2024. Accessed November 7. 2024. https://progressreport.cancer.gov/detection/prostate_cancer.

2023 AUA/SUO Best Practice Statement for PSA Screening

- Clinicians should engage in **shared decision-making (SDM)** with people for whom prostate cancer screening would be appropriate and proceed based on a person's values and preferences (Clinical Principle)
- When screening for prostate cancer, clinicians should use **PSA as the first screening** test (Strong Recommendation; Evidence Level: Grade A)
- For people with a newly elevated PSA, clinicians should **repeat the PSA** prior to a secondary biomarker, imaging, or biopsy (Expert Opinion)
- Clinicians may begin prostate cancer screening and offer a **baseline PSA test to people between ages 45 to 50 years** (Conditional Recommendation; Evidence Level: Grade B)

AUA = American Urological Association; SUO = Society of Urologic Oncology.

American Urological Association. Accessed November 7, 2024. https://www.auanet.org/guidelines-and-quality/guidelines/early-detection-of-prostate-cancer-guidelines.

2023 AUA/SUO Best Practice Statement for PSA Screening

- Clinicians should offer prostate cancer screening beginning at age 40 to 45 for people at increased risk of developing prostate cancer based on the following factors: **Black ancestry, germline mutations, strong family history of prostate cancer** (Strong Recommendation; Evidence Level: Grade B)
- Clinicians should offer regular **prostate cancer screening every 2 to 4 years to people aged 50 to 69 years** (Strong Recommendation; Evidence Level: Grade A)
- Clinicians may personalize the re-screening interval, or decide to **discontinue screening,** based on patient preference, age, PSA, prostate cancer risk, life expectancy, and general health following SDM (Conditional Recommendation; Evidence Level: Grade B)
- Clinicians may use **digital rectal exam (DRE)** alongside PSA to establish risk of clinically significant prostate cancer (Conditional Recommendation; Evidence Level: Grade C)

American Urological Association. Accessed November 7, 2024. https://www.auanet.org/guidelines-and-quality/guidelines/early-detection-of-prostate-cancer-guidelines.

2024 NCCN Prostate Cancer Screening Guidelines

- The **National Comprehensive Cancer Network (NCCN)** Guidelines for Prostate Cancer Early Detection recognize the current mixed evidence and controversies for screening
- **Start screening at age 45 with repeat testing for an initial PSA >1 ng/mL every 1 to 2 years and at every 2 to 4 years for an initial PSA <1 ng/mL**
- Recommend against PSA screening for patients with less than a 10-year life expectancy
- Recognize specific high-risk patient populations
  - Specifically, Black men and patients with a first-degree relative with prostate cancer and/or germline BRCA 1/2 mutations should consider beginning PSA screening at 40 years old
    - Men with metastatic castration-resistant prostate cancer and a family history of breast cancer should be screened for BRCA mutations

National Comprehensive Cancer Network. Accessed November 7, 2024. https://www.nccn.org/professionals/physician_gls/pdf/prostate_detection.pdf.

PSA Derivatives: Improving the Performance of PSA

PROBLEM: About up to 2/3 of men who undergo a prostate biopsy because they have PSA level of 4.0 to 10.0 ng/mL do NOT have cancer.

Solutions	What is it?
PSA density	Ratio of PSA to prostate size
Age-specific PSA	Different normal by age
PSA velocity	Changes in PSA over time
Free PSA	Free to total PSA ratio: “Free is Good”= lower free PSA=more cancer

Reference.

“Practical” PSA Early Detection Guidelines

- Baseline “risk assessment” PSA at age 40-45
  - Low risk: PSA ≤1.0 ng/mL → testing q 3-5 years
  - Intermediate risk: 1.1-2.4 ng/mL → consider annual testing
  - Higher risk: ≥2.5 ng/mL → consider prostate biopsy/MRI
  - In men with low PSA (≤1.0 ng/mL) → annual testing is not needed
- Every other year testing between ages 55-69
- Discourage testing in most men age 70-75+ especially when they still have low PSA (<3.0 ng/mL) at age 70

q = every; MRI = magnetic resonance imaging.

Carter HB, et al. *J Urol*. 2013;190:419-426.

Secondary Novel Screening Tests

- Blood markers: PHI, 4Kscore®
- Urine markers: ExoDx™ Prostate Intelliscore (EPI), AMACR, MPS2
- Prostate MRI

PHI = prostate health index; AMACR = alpha-methylacyl-CoA racemase; MPS2 = MyProstateScore 2.0.

Prostate Health Index (PHI)

How PHI is calculated:

$$\text{Prostate Health Index (PHI)} = \frac{\text{p2PSA}}{\text{Free PSA}} \times \sqrt{\text{PSA}}$$

- Serum total prostate-specific antigen (tPSA) and percent free from prostate-specific antigen (%fPSA) struggle to balance specificity and sensitivity in prostate cancer detection
- Validate for use in “gray zone” PSA range (4 to 10 ng/mL)
  - FDA approved in 2012
- In detecting >6 ng/mL, PHI increased predictive value and specificity compared to tPSA or %fPSA alone

FDA = US Food and Drug Administration.

Jansen FH, et al. *Eur Urol*. 2010;57(6):921-927.

EPI Urine Prostate Test

- Measures 3 genes associated with prostate cancer within exosomes in urine
- Independent of PSA and SOC; no digital rectal exam required
- Received traditional Medicare coverage in December 2019
- Included in the NCCN Guidelines since 2019 for early detection of cancer
- Included in the AUA Guidelines since May 2023
- >100,000 patients and >2000 urologists
- Cut point prospectively validated in two studies (JAMA Oncology and European Urology) in 1022 men

SOC = standard of care.

McKiernan J, et al. *JAMA Oncol.* 2016;2(7):882-889. McKiernan J, et al. *Eur Urol*. 2018;74(6):731-738. Centers for Medicare and Medicaid Services. Accessed November 7, 2024. https://www.cms.gov/medicare-coverage-database/view/lcd.aspx?lcdid=37733&ver=22&keyword=exodx&keywordType=starts&areaId=all&docType=NCA,CAL,NCD,MEDCAC,TA,MCD,6,3,5,1,F,P&contractOption=all&sortBy=relevance&bc=1.

EPI Urine Prostate Test

- May be utilized for men ≥50 years old with PSA of 2 to 10 ng/mL being considered for prostate biopsy
- Assesses a patient's risk for high-grade prostate cancer (Gleason score ≥7)
- Urine collection available with an at-home collection kit as well as in-office
- NO DRE required
- NO vigorous prostate massage

Reference.

EPI Urine Prostate Test

- The test score ranges from 0 to 100 and is separate from standard of care factors to help assess a man's risk for high-grade prostate cancer
- Used when men are being considered for an initial prostate biopsy or repeat biopsy due to a prior negative biopsy
- **Negative predictive value (NPV) of 91.3% for any Gleason ≥7 (3+4 and higher)**
- NPV of 97% for Gleason ≥ 7 (4+3)

Reference.

Prostate mpMRI

- In 2024, now widely accepted and techniques have improved greatly (multiparametric)
- PI-RADS® system
  - 0: no biopsy
  - 1: no biopsy
  - 2: no biopsy
  - 3: follow-up or biopsy
  - 4: biopsy, 50% risk
  - 5: biopsy, 70-90% risk

mpMRI = multiparametric MRI; PI-RADS = prostate imaging reporting and data system.

American College of Radiology. Last updated October 25, 2024. Accessed November 7, 2024. https://www.acr.org/-/media/ACR/Files/RADS/PI-RADS/PIRADS-V2-1.pdf.

Combining Biomarkers and MRI

- Study objective: evaluate biomarkers (EPI, PHI, etc.) with mpMRI in the detection of high-grade prostate cancer (HGPC: >GG2)
- Hypothesize that biomarkers can be used to avoid prostate biopsy in some men

Clinical Utility of 4Kscore®, ExosomeDx™ and Magnetic Resonance Imaging for the Early Detection of High Grade Prostate Cancer

Claire M de la Calle [1], Vittorio Fasulo [1 2], Janet E Cowan [1], Peter E Lonergan [1], Martina Maggi [1 3], Adam J Gadzinski [1], Reuben Au Yeung [1], Alberto Saita [2], Matthew R Cooperberg [1 4], Katsuto Shinohara [1], Peter R Carroll [1], Hao G Nguyen [1]

HGPCA = high-grade prostate cancer; GG = grade group.
de la Calle CM, et al. *J Urol.* 2021;205(2):452-460.

Screening for Genetic Alterations in Advanced Disease

- While screening for the presence of prostate cancer is critically important, screening for hereditary and acquired genetic alterations is also important
- We are now in the molecular-targeted treatment era!
- Prevalence study data

PREVALENCE (NCT03871816): Global Genetic Landscape of Advanced Prostate Cancer

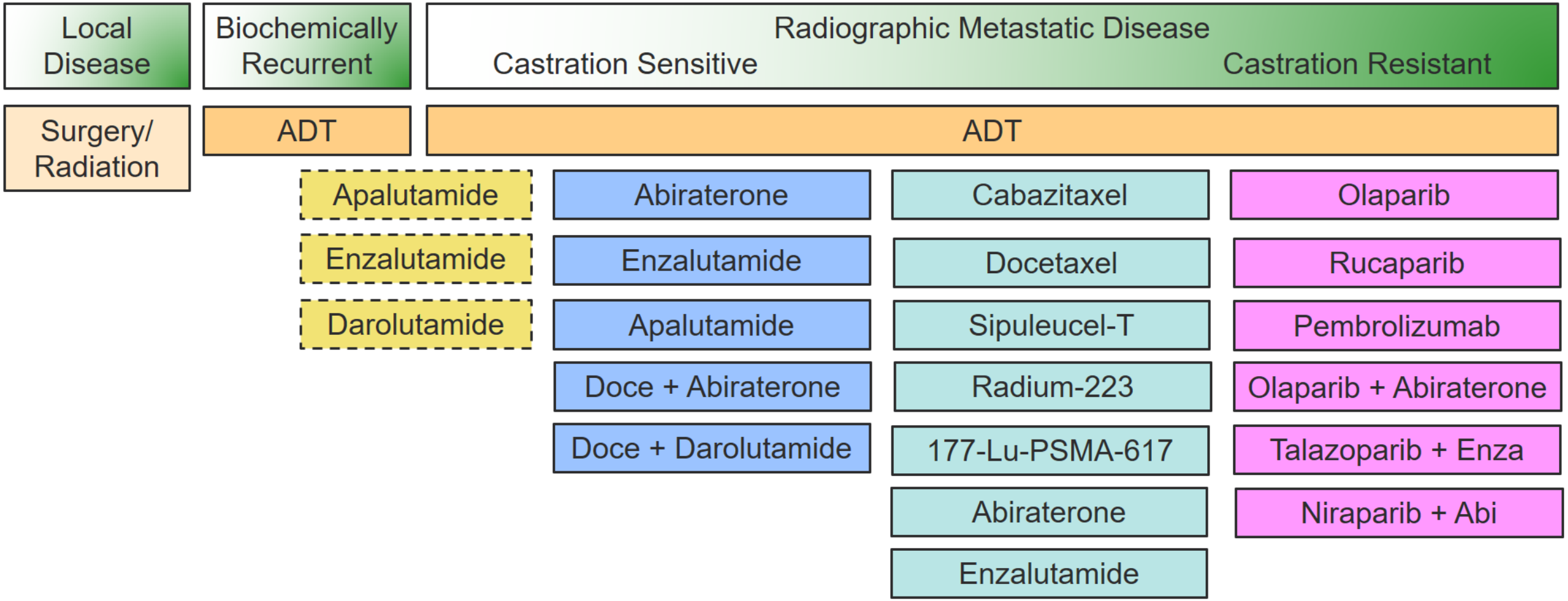
- N=14,598 patients enrolled April 2019-October 2022
- 14% had HRR gene mutation
- BRCA: 38%; ATM: 20.7%; CHEK2: 15.7%; CDK12:12%
- By testing method: tumor tissue:22%; ctDNA:11.5%; germline:7%
- Europe: 15.8%; NA:13%; Asia:14.4%; Australia:13%; SA:13.2%
- The frequency was similar for M1 HS PC and CRPC
- Test failure: tumor tissue: 24.1%; germline: 3.2%; ctDNA: 2.4%

HRR = homologous recombination repair; CRPC = castration-resistant prostate cancer; ctDNA = circulating tumor DNA.

Sandhu SK, et al. *Ann Oncol*. 2023;34(2):S993.

Treatment Strategies—Advanced Disease

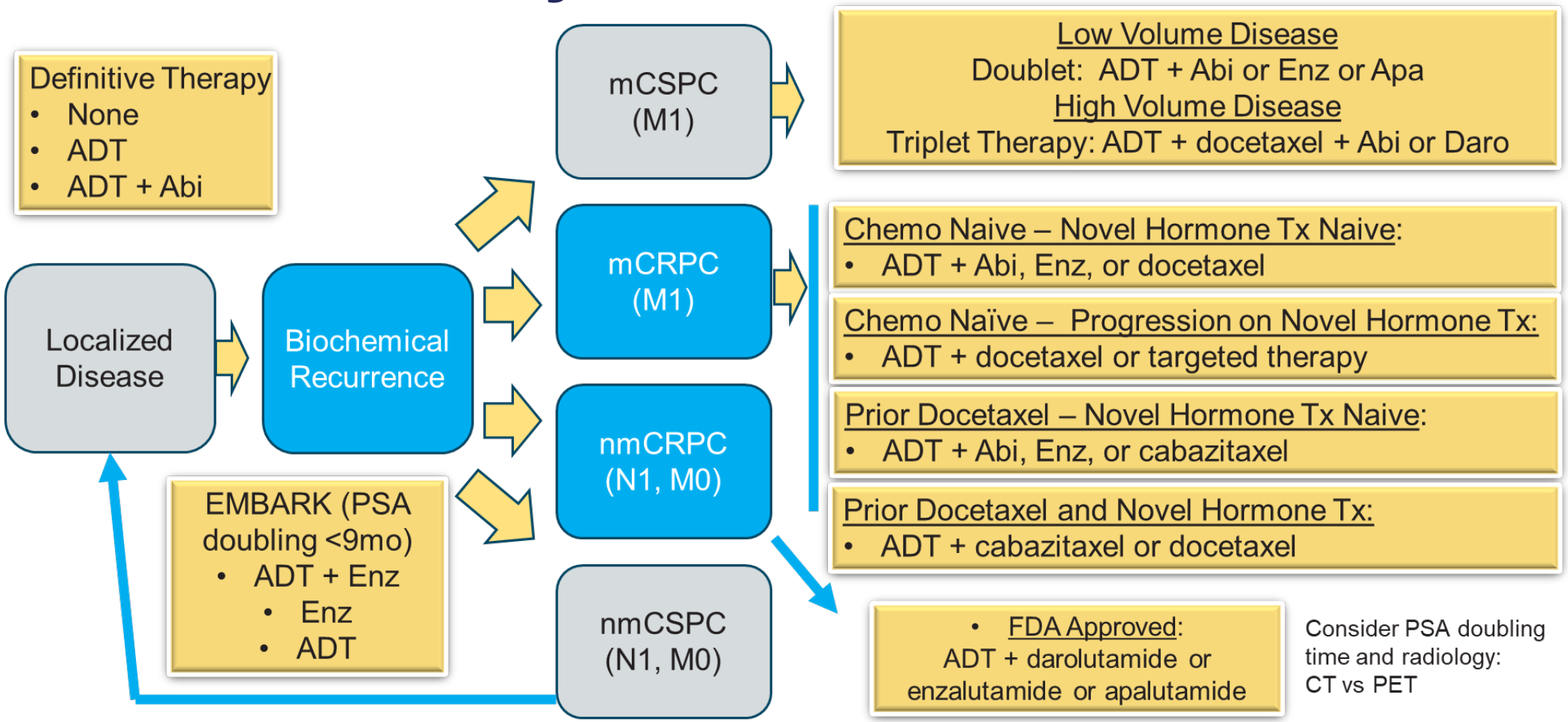
Treatment Options across Prostate Cancer Disease States



ADT = androgen deprivation therapy.

Ajmera A, et al. *J Natl Compr Canc Netw*. 2023;21(5.5):548-551.

Prostate Cancer Populations and Systemic Treatments



mCSPC = metastatic castration-sensitive prostate cancer; mCRPC = metastatic CRPC; nm = non-metastatic; Tx = treatment; PET = positron emission tomography.

National Comprehensive Cancer Network. Accessed November 7, 2024. https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf.

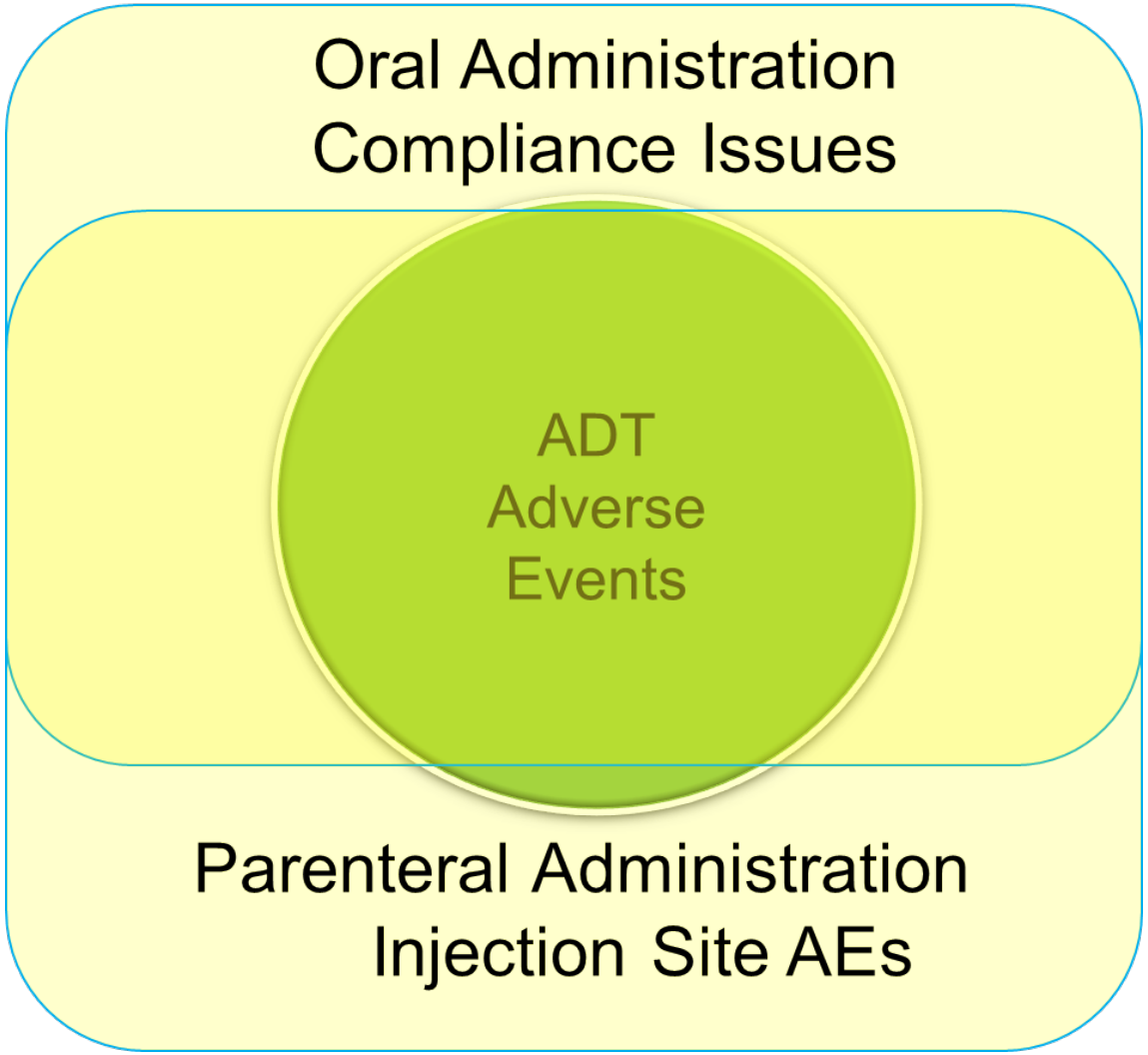
Adverse Events with ADT

	PRONOUNCE TRIAL Degarelix (n = 275) vs Leuprolide (n = 269)	HERO TRIAL Relugolix (n = 622) vs Leuprolide (n = 308)
Severe/serious AEs	21.5% vs 20.4%	12.2% vs 15.3%
Fatigue	18.2% vs 12.6%	21.5% vs 18.5%
Hot flushes	38.9% vs 44.6%	54.3% vs 51.6%
MACE	5.5% vs 4.1%	2.9% vs 6.2%
Injection site reactions	60.4% vs 26.8%	N/A

MACE = major adverse cardiovascular event.

Lopes R, et al. *Circulation.* 2021;144(16):1295-1307. Shore ND, et al. *N Engl J Med.* 2020;382(23):2187-2196. NIH. Accessed November 7, 2024. https://clinicaltrials.gov/study/NCT02663908; NCT03085095.

Individualized Choice for Chemical ADT



Chemical suppression of LH/FSH to prevent testicular production of testosterone

- LHRH agonist (parenteral)
  - Goserelin
  - Leuprolide
  - Triptorelin
- LHRH antagonist (parenteral)
  - Degarelix
- LHRH antagonist (oral)
  - Relugolix

LH = luteinizing hormone; FSH = follicle-stimulating hormone; LHRH = luteinizing hormone-releasing hormone.
Reference.

nmCRPC Approved Treatments

Medication	Outcomes		Trial
Enzalutamide vs Placebo n=933 vs n=468	MFS 36.6 mo vs 14.7 mo OS 67 mo vs 56.3 mo	HR 0.29 HR 0.73	PROSPER
Apalutamide vs Placebo n=806 vs n=401	MFS 40.5 mo vs 16.2 mo OS 73.9 mo vs 59.9 mo	HR 0.28 HR 0.78	SPARTAN
Darolutamide vs Placebo n=955 vs n=554	MFS 40.4 mo vs 18.4 mo Prostate cancer-related mortality at 30 mo 6% vs 8.2 mo	HR 0.41 HR 0.67	ARAMIS

MFS = metastasis-free survival; OS = overall survival; HR = hazard ratio.

Shore N, et al. Presented at: American Society of Clinical Oncology Genitourinary Cancers Symposium; January 25-27, 2024; San Francisco, California. FDA. Accessed November 7, 2024. https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/203415lbl.pdf; 2018/210951s000lbl.pdf; 2019/212099Orig1s000lbl.pdf. NIH. Accessed November 7, 2024. https://clinicaltrials.gov/study/NCT02003924; NCT01946204; NCT02200614.

nmCRPC

- How has PSMA PET scanning impacted this population?
- If you had a CT-negative, PSMA PET-positive case, how would you treat the patient?

PSMA = prostate-specific membrane antigen; CT = computed tomography.

mCSPC Approved Treatments

- Outcomes can be improved by adding a second agent to ADT
  - FDA-approved drugs: docetaxel, abiraterone, enzalutamide, apalutamide

Medication	Outcomes		Trial
ADT ± Docetaxel N=790	OS 57.6 mo vs 44 mo	HR 0.61	CHAARTED
ADT ± Abiraterone N=1003	OS 60.6 mo vs 50.4 mo	HR 0.62	STAMPEDE
ADT ± Enazalutamide N=1150	4-year OS 71% vs 57%	HR 0.66	ARCHES
ADT ± Apalutamide N=1052	4-year OS 65.1% vs 51.8%	HR 0.65	TITAN

Sweeney CJ, et al. *N Engl J Med.* 2015;373(8):737-746. Attard G, et al. *Lancet Oncol.* 2023;24(5):443-456. Armstrong AJ, et al. *J Clin Oncol.* 2022;40(15):1616-1622. Chi KN, et al. *J Clin Oncol*. 2021;39(20):2294-2303. NIH. Accessed November 7, 2024. https://clinicaltrials.gov/study/NCT00309985; NCT00268476; NCT02677896; NCT02489318.

mCSPC Math

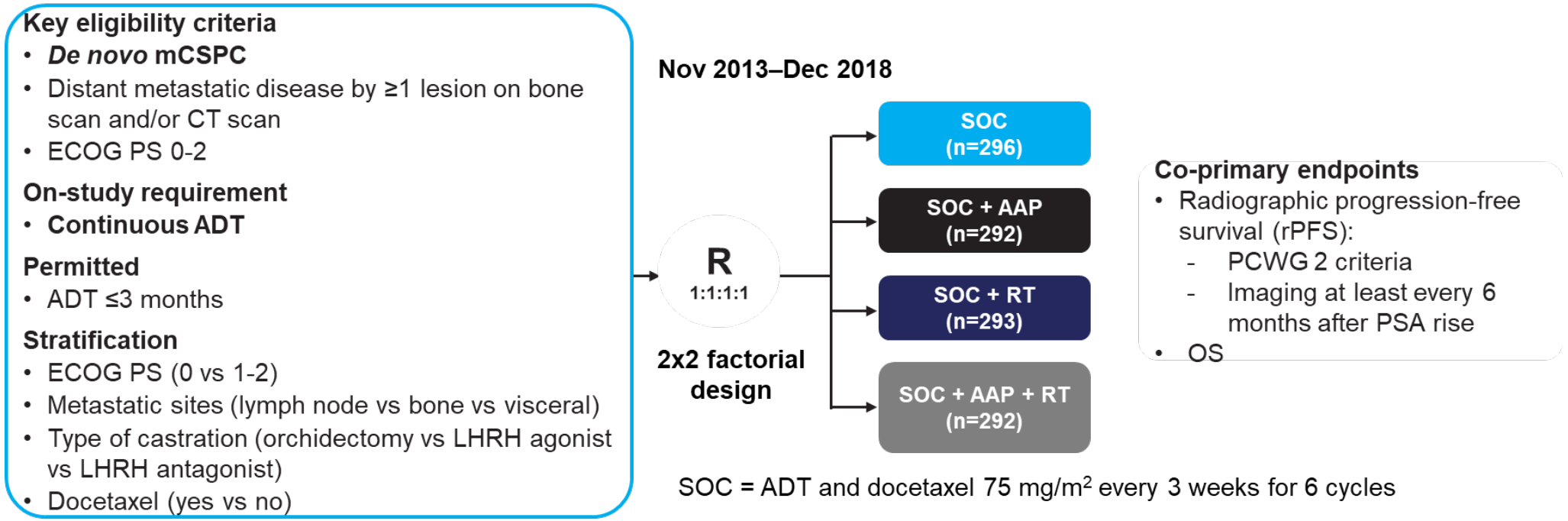
Number of agents: 2>1, but is 3>2?

Can triplet therapy further improve outcomes in mHSPC?

mHSCP = metastatic hormone-sensitive prostate cancer.

PEACE-1: Background and Study Design

- ADT was SOC for men **with mCSPC** for many years
- Since 2015, **combining ADT with either docetaxel, novel hormonal therapies, or RT** to the primary tumor (for those with low-burden metastases) was shown to improve OS and **is now a new SOC**
- **PEACE-1** evaluates whether combining these new treatments on top of ADT leads to improved outcomes



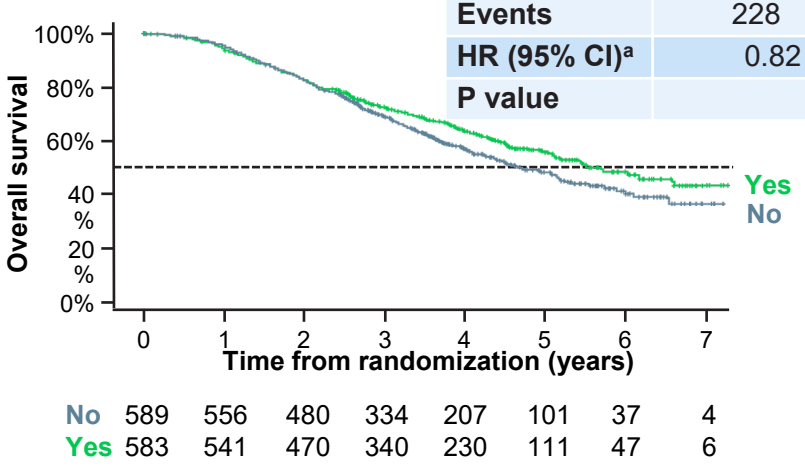
AAP = abiraterone and prednisone; ECOG PS = Eastern Cooperative Oncology Group performance status; R = randomize; PCWG 2 = Prostate Cancer Working Group 2; RT = radiotherapy.

Fizazi K, et al. Presented at: European Society for Medical Oncology Congress; September 19, 2021; Lugano, Switzerland. Abstract LBA5_PR. NIH. Accessed November 7, 2024. https://clinicaltrials.gov/study/NCT01957436.

PEACE-1: Results

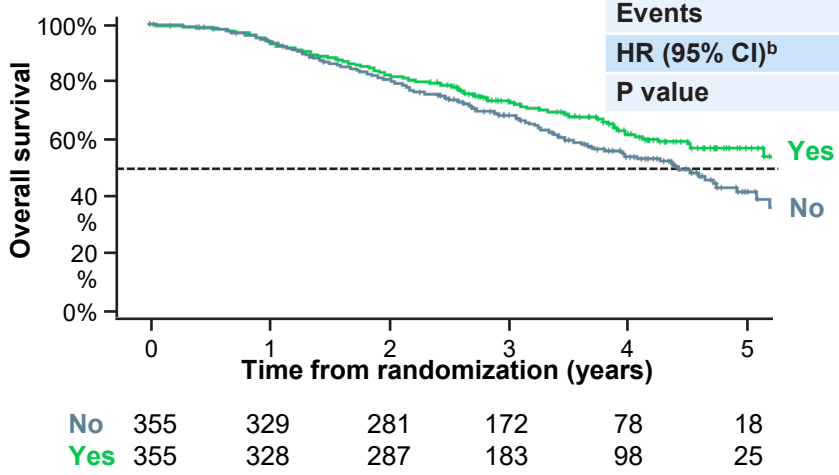
OS in the overall population

	SOC + AAP (n=583)	SOC (n=589)
Median, yr (95% CI)	**5.7** (5.1-NE)	**4.7** (4.3-5.3)
Events	228	268
HR (95% CI)[a]	0.82 (0.69-0.98)	
P value	0.030	



OS with AAP in the ADT + docetaxel (+/- RXT) population

	SOC + AAP (n=355)	SOC (n=355)
Median, yr (95% CI)	NE (4.5-NE)	4.4 (3.8-4.9)
Events	121	151
HR (95% CI)[b]	0.75 (0.59-0.95)	
P value	0.017	



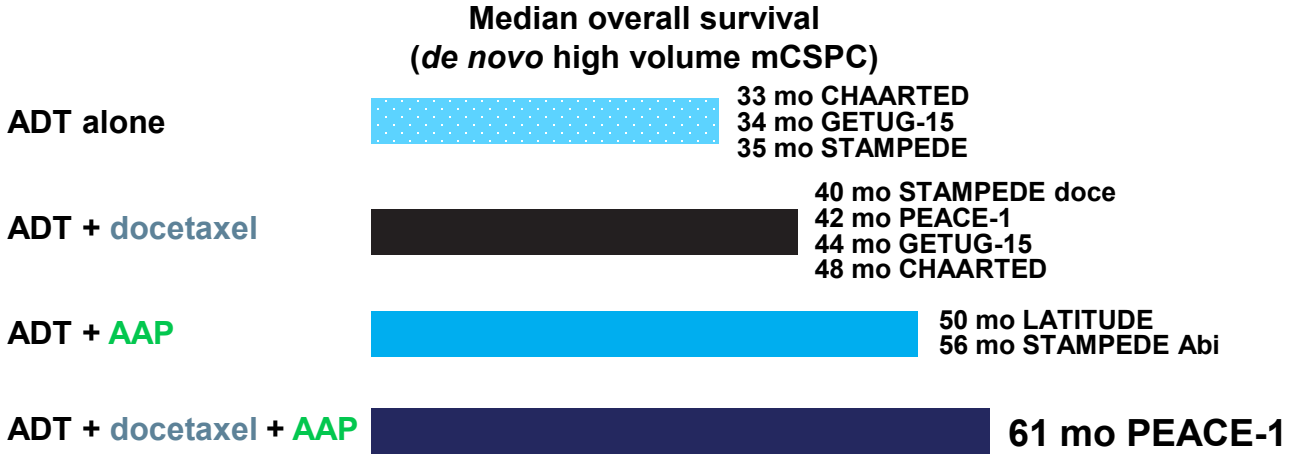
- **OS effect seen across subgroups**, including those with **high-volume disease** (HR 0.72, 95% CI 0.55-0.95) and **low-volume disease** (HR 0.83, 95% CI 0.50-1.38; data immature)
- Combination of **AAP + ADT + docetaxel was well-tolerated**
  - No difference in rates of grade 3 to 5 neutropenia or febrile neutropenia
  - Grade 3 to 5 liver toxicity (6% vs 1%) and hypertension (22% vs 13%) with SOC + AAP compared to SOC alone

[a]Adjusted on stratification parameters (RXT, PS, type of castration, metastatic burden, doxetaxel); [b]Adjusted on stratification parameters (RXT, PS, type of castration, metastatic burden)
NE = not estimable; RXT = radiotherapy to primary tumor.
Fizazi K, et al. Presented at: European Society for Medical Oncology Congress; September 19, 2021; Lugano, Switzerland. Abstract LBA5_PR.

PEACE-1: Summary

- **Adding AAP to ADT plus docetaxel improves both rPFS and OS** in men with mCSPC, even when 84% of mCRPC men from the control arm receive an androgen signalling inhibitor
- Toxicity was as expected—**no safety concerns** from combination treatment

PEACE-1 OS results in the context of recent data



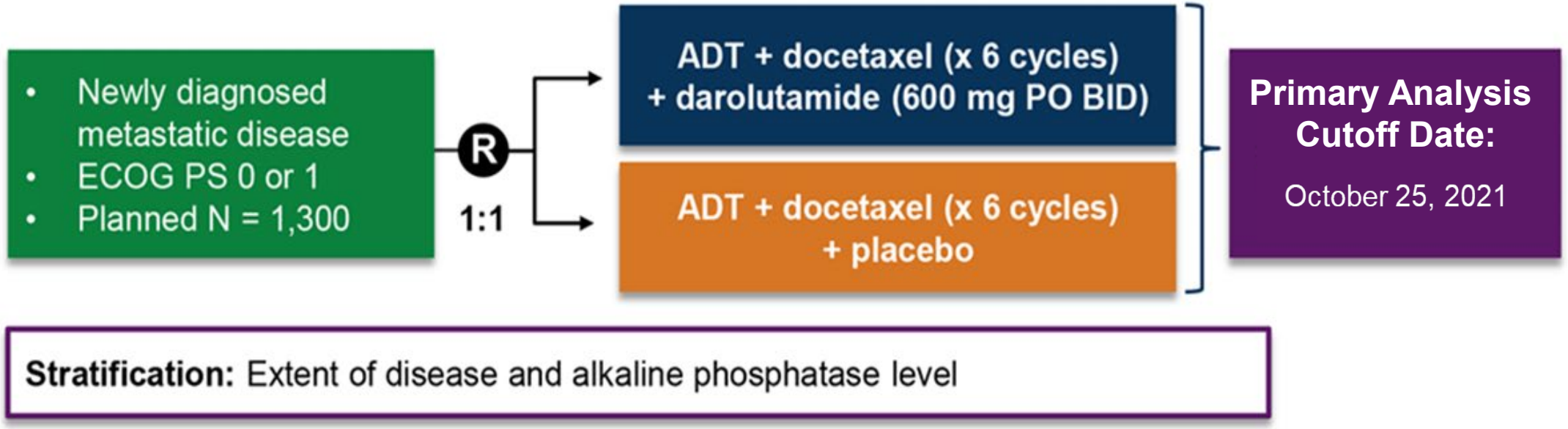
Clinical Perspective

- Benefit of a median **lifetime gain of more than 1.5 years** for mCSPC men with high-volume disease
  (5.1 vs 3.5 years)

Fizazi K, et al. Presented at: European Society for Medical Oncology Congress; September 19, 2021; Lugano, Switzerland. Abstract LBA5_PR. Kyriakopoulos CE, et al. *J Clin Oncol.* 2018;36(11):1080-1087. Gravis G, et al. *Eur Urol*. 2018;73(6):847-855. Clarke NW, et al. *Ann Oncol*. 2019;30(12):1992-2003. James N, et al. Presented at: European Society for Medical Oncology Congress; September 21, 2020; Virtual. Abstract 6110. Fizazi K, et al. *Lancet Oncol*. 2019;20(5):686-700.

ARASENS: Ongoing Phase 3 Trial in mCSPC

International trial conducted at >300 sites in 23 countries



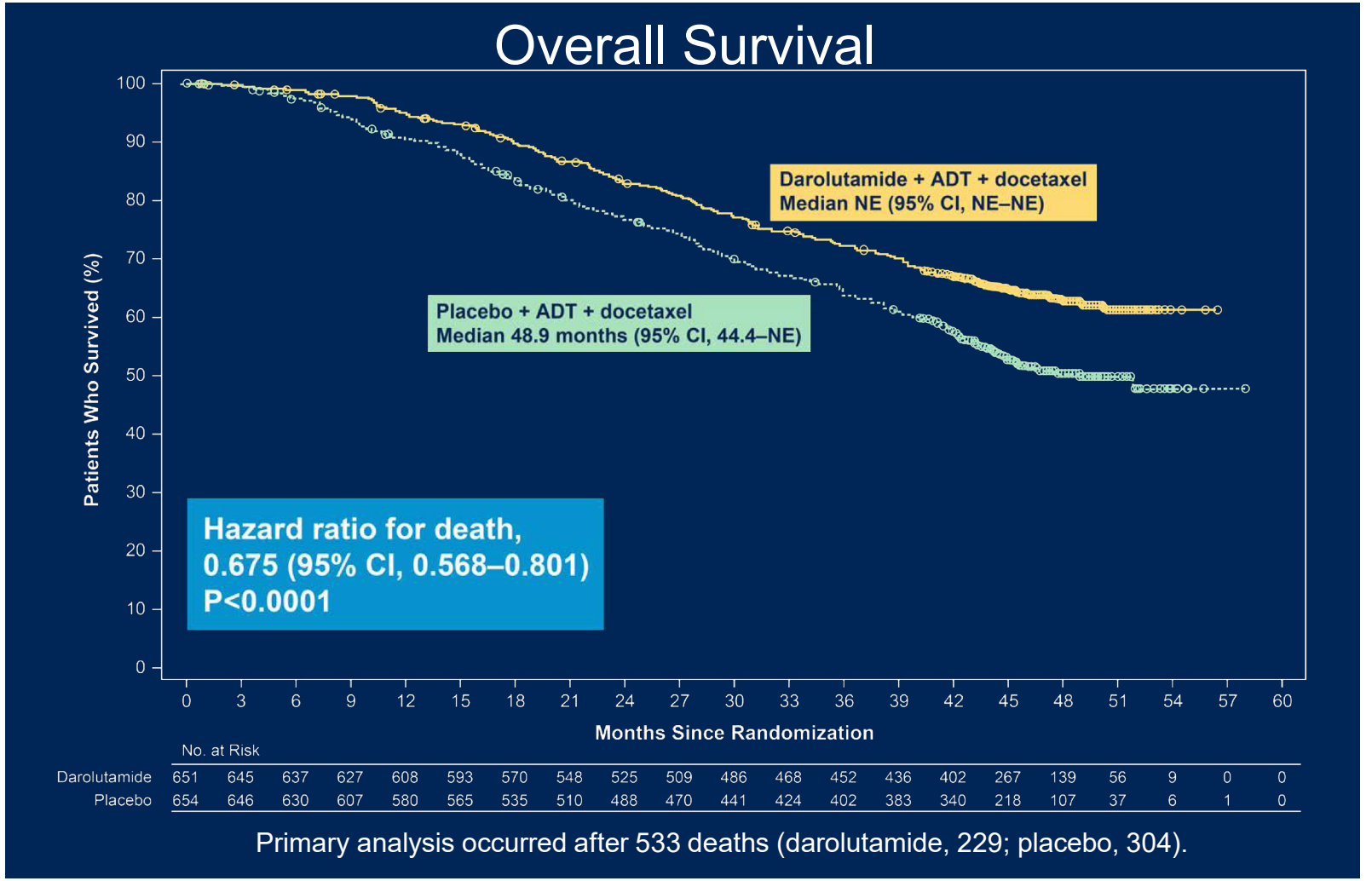
Stratification: Extent of disease and alkaline phosphatase level

- **Primary endpoint:** OS
- **Secondary endpoints:** Time to mCRPC, time to initiation of subsequent anticancer therapy, time to SSE-free survival, time to first SSE, time to first opioid use, time to pain progression, and time to worsening of physical symptoms

SSE = symptomatic skeletal event.

NIH. Accessed November 7, 2024. https://clinicaltrials.gov/study/NCT02799602.

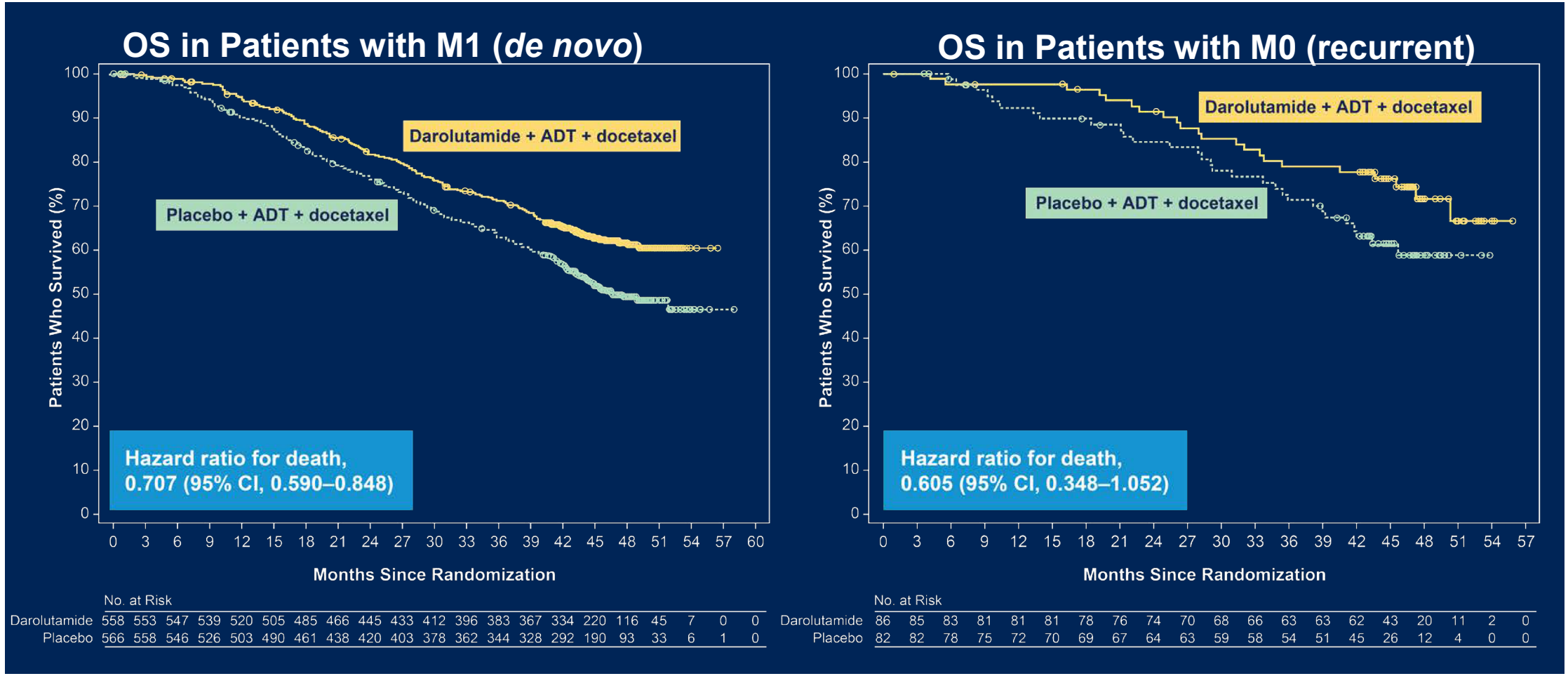
ARASENS: ADT + Docetaxel ± Darolutamide Primary Endpoint



Primary analysis occurred after 533 deaths (darolutamide, 229; placebo, 304).

Smith MR, et al. Presented at: American Society of Clinical Oncology Genitourinary Cancers Symposium; June 3-7, 2022; Chicago, Illinois.

ARASENS: ADT + Docetaxel ± Darolutamide
OS by Metastatic Stage at Initial Diagnosis



Smith MR, et al. Presented at: American Society of Clinical Oncology Genitourinary Cancers Symposium; June 3-7, 2022; Chicago, Illinois.

Metastatic Hormone-Sensitive Prostate Cancer Conclusions

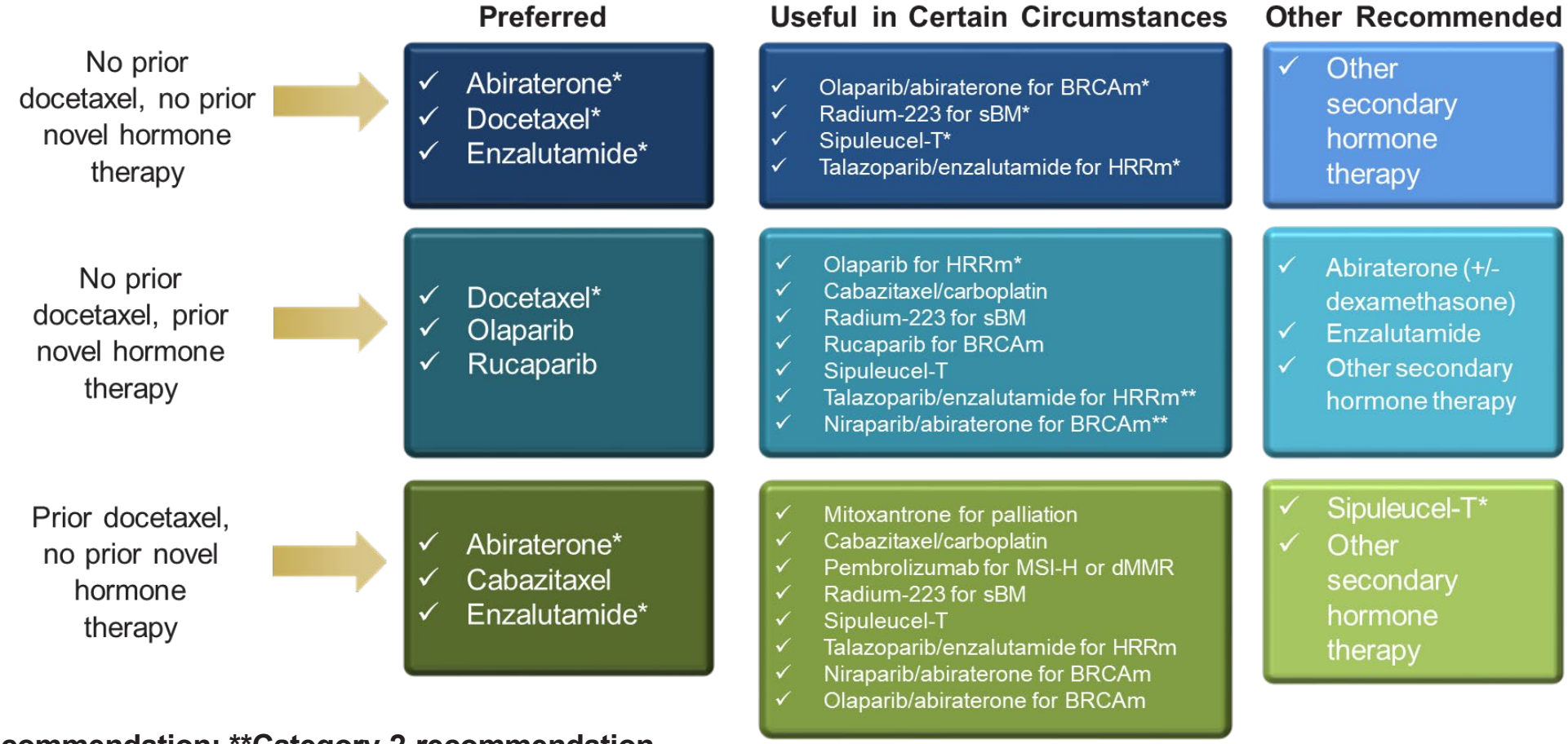
- **ADT monotherapy is no longer the standard of care**
- Treatment intensification strategies are stratified by high or low volume
  - Docetaxel (high)
  - Abiraterone/prednisone (high or low)
  - Apalutamide (high or low)
  - Enzalutamide (high or low)
- Docetaxel + darolutamide/abiratrone (ARASENS/PEACE-1)
- PARPi and emerging novel agents may be beneficial
- Consider radiation therapy to prostate in low-volume disease
- Germline genetic testing is recommended for all patients with metastatic and high-risk localized prostate cancer

PARPi = PARP inhibitor.

mHSPC Regimen Selection

- If you had a 65-year-old man with newly diagnosed prostate cancer with a bone metastasis, do you have a “go-to regimen”
- Follow-up question—Assuming you use both a two-drug and three-drug regimen, how do you differentiate which one to use?

NCCN Treatment Guidelines: Systemic Therapy for mCRPC



***Category 1 recommendation; **Category 2 recommendation.**
BRCAm = BRCA mutation; HRRm = HRR mutation; sBM = symptomatic bone metastases.
NCCN. NCCN Guidelines Version 4.2023: Prostate Cancer. https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf. Accessed 9/8/2023.

Novel Hormone Therapies for mCRPC

Medication	Outcomes	Trial
Abiraterone vs Placebo n=546 vs n=542	OS 34.7 mo vs 30.3 mo *P*<.0001	COU-AA-302
Enzalutamide vs Placebo n=872 vs n=845	OS 35.3 mo vs 32.3 mo *P*<.0001	PREVAIL
Enzalutamide vs Placebo n=800 vs n=399	Prior docetaxel OS 18.4 mo vs 13.6 mo *P*<.001	AFFIRM
Abiraterone vs Placebo n=797 vs n=398	Prior docetaxel OS 15.8 mo vs 11.2 mo *P*<.0001	COU-AA-301
Cabazitaxel vs Enz or Abi n=129 vs n=126	Prior Docetaxel AND Abi or Enz OS 15.8 mo vs 11.2 mo *P*<.0001	CARD

Shore N, et al. Presented at: American Society of Clinical Oncology Genitourinary Cancers Symposium; January 25-27, 2024; San Francisco, California. FDA. Accessed November 7, 2024. https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/203415lbl.pdf; 2011/202379lbl.pdf; 2010/201023lbl.pdf. NIH. Accessed November 7, 2024. https://clinicaltrials.gov/study/NCT00887198; NCT01212991; NCT05373316; NCT02485691.

Biomarker-Driven Therapy in mCRPC

PARP Inhibitors

Olaparib

FDA Indication

- Germline/somatic HRR gene-mutated mCRPC
- BRCA-mutated mCRPC

Rucaparib

FDA Indication

- Germline/somatic deleterious BRCA 1/2 mutation-associated mCRPC

Niraparib

FDA Indication

- In combination w/ AAP for patients with deleterious/ suspected deleterious *BRCA*-mutated mCRPC

Talazoparib

FDA Indication

- In combination with ARSI enzalutamide for patients with *HRR* gene-mutated mCRPC

ARPI = androgen receptor pathway inhibitor; ARSI = androgen receptor signaling inhibitor.

FDA. Accessed November 7, 2024. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/208558s028lbl.pdf; 2022/209115s013lbl.pdf; 2023/211651s010lbl.pdf; 2023/216793s000lbl.pdf.

Efficacy for PARP Inhibitors in mCRPC

Medication	Outcomes	Trial
Olaparib vs MD Choice n=256 vs n=131	rPFS 7.4 mo vs 3.6 mo (BRCA 1/2 or ATM mut) rPFS 4.8 mo vs 3.3 mo (HRR other)	PROFOUND
Rucaparib vs MD Choice n=201 vs n=101 (BRCA 1/2)	PFS 11.2 mo vs 6.4 mo *P*<.001	TRITON3
Niraparib ± Abiraterone n=113 vs n=112	rPFS 16.6 mo vs 10.9 mo *P*=.0014 (BRCA 1/2 mut group)	MAGNITUDE (Cohort 1)
Enzalutamide ± Talazoparib n=200 vs n=199 (HRR mut)	rPFS NE (21.9, NE) vs 13.8 (11, 16.7) HR 0.45 *P*<.0001	TALAPRO-2 (1st line)

Fizazi K, et al. *N Engl J Med.* 2023;388(8):719-732. FDA. Accessed November 7, 2024. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/208558s000lbl.pdf; 2023/216793s000lbl.pdf; 2023/211651s010lbl.pdf. NIH. Accessed November 7, 2024. https://clinicaltrials.gov/study/NCT06217900; NCT02975934; NCT03748641; NCT03395197.

Case Study

Patient is a 66-year-old man with recurrent prostate cancer

- Diagnosed with very high-risk localized prostate cancer 6 years ago and underwent radical prostatectomy + ADT (orchiectomy)
- Four months ago, he had a rising PSA; a follow-up PET PSMA scan was done and documented several bone lesions (mildly symptomatic—low-volume disease)
- He was started on enzalutamide for the recurrence and a liquid biopsy was ordered (NGS), which found a BRCA2 mutation

Discussion: Would you change his current treatment plan?

NGS = next-generation sequencing.

Case Study

If his treatment plan was changed to include a PARP inhibitor, which one would you choose and why?

Dose Modifications and Toxicity with PARPi + ARSI

Dose Modifications or Toxicities, %	Olaparib + Abiraterone (n=398)	Talazoparib + Enzalutamide (n=398)	Niraparib + Abiraterone (n=212)
Dose interruption PARPi	49	62	49
Dose reduction PARPi	23	53	20
Discontinuation PARPi	17	19	15
Pulmonary embolism/DVT	7/3	2.5/1.5	1.9/NR
MDS/AML	<1	<1	0
RBC transfusion rate	18	39	27

DVT = deep vein thrombosis; MDS = myelodysplastic syndrome; AML = acute myeloid leukemia; RBC = red blood cell; NR = not reported.
Clarke NW, et al. *NEJM Evid*. 2022;1(9):EVIDoa2200043. Saad F, et al. *Lancet Oncol*. 2023;24(10):1094-1108. Agarwal N, et al. *Lancet*. 2023;402(10398):291-303. Fizazi K, et al. Presented at: American Society of Clinical Oncology Annual Meeting; June 2-6, 2023; Chicago, Illinois. Abstract 5004. Azad A, et al. Presented at: American Society of Clinical Oncology Annual Meeting; June 2-6, 2023; Chicago, Illinois. Abstract 5053. Chi KN, et al. *J Clin Oncol*. 2023;41(18):3339-3351. Chi KN, et al. *Ann Oncol*. 2023;34(9):772-782.

Managing Key AEs and Safety Considerations with PARP Inhibitors and ARSI Combinations

- **Cytopenias**
  - Monitor using monthly CBC with differential
  - If occur, dose hold until recovery; discontinue if not resolved after 28 days
- **Fatigue:** exercise, massage, CBT; rule out anemia or other causes
- **GI:** prophylactic antiemetics, loperamide as needed for diarrhea
- **Hypertension:** Routine BP monitoring, exercise, DASH diet, antihypertensives as needed
- **Rare but serious AE:** Pulmonary embolism/DVT or MDS/AML
  - Activity, no role for prophylactic anticoagulation
  - MDS is a particular concern for younger patients treated for longer time periods
- **Manage AEs with dose holds and dose reductions**
- **Permanently discontinue for recurrent/ high-grade AEs**

CBC = complete blood count; CBT = cognitive behavioral therapy; GI = gastrointestinal; BP = blood pressure; DASH = Dietary Approaches to Stop Hypertension.

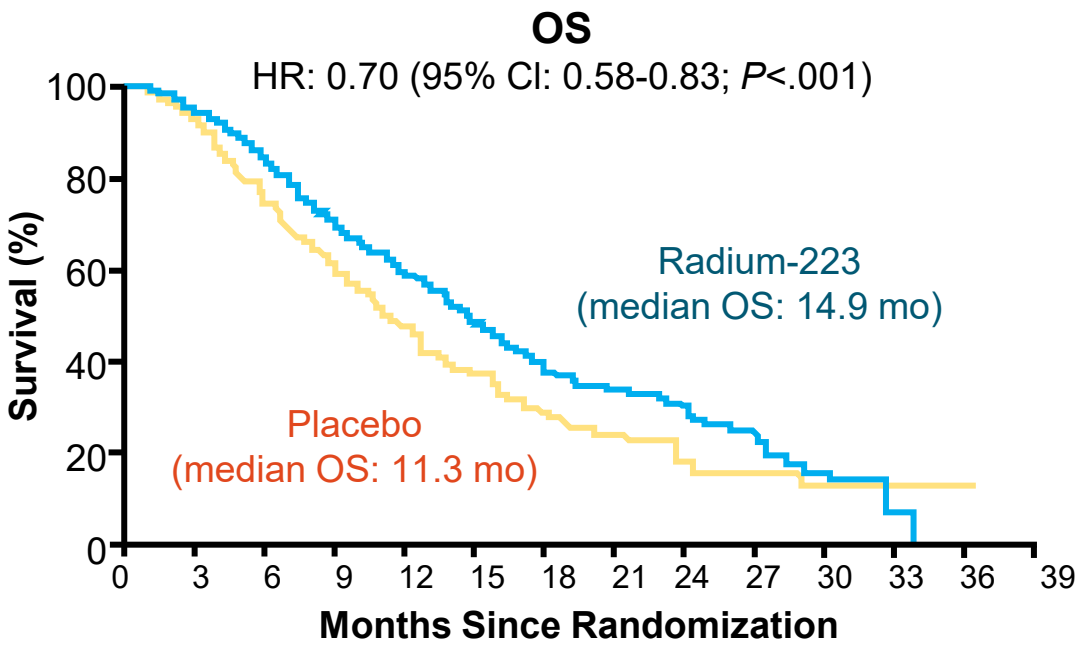
FDA. Accessed November 8, 2024. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/216793s000lbl.pdf; 2017/208558s000lbl.pdf; 2024/211651s012lbl.pdf.

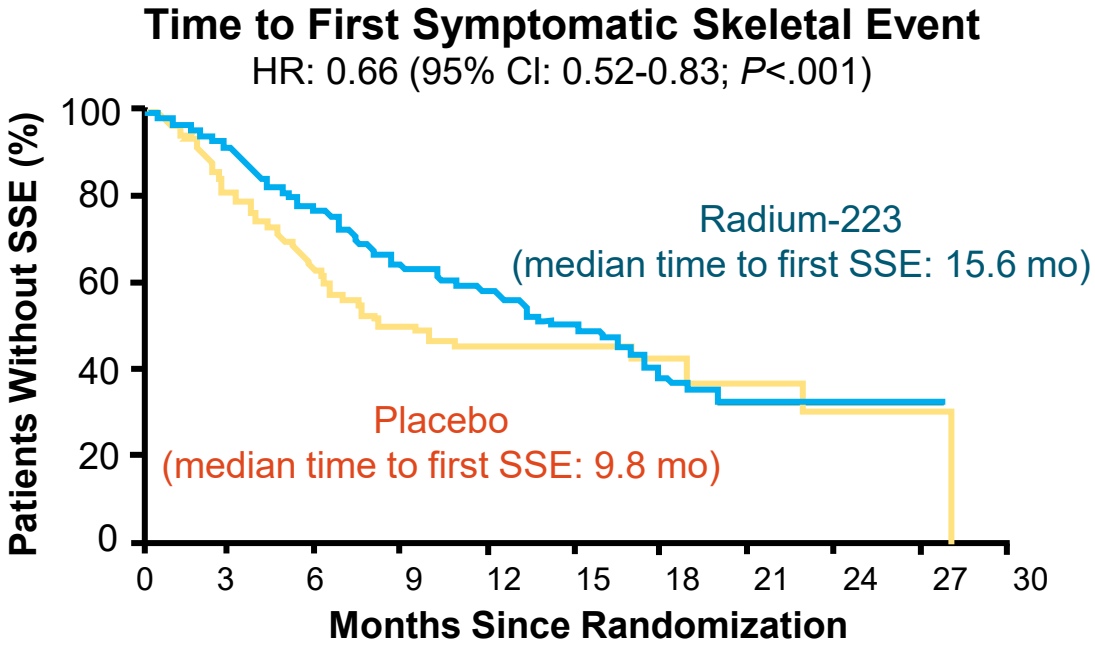
Case Study

At what point would you consider radium-223?

Radiopharmaceuticals: Radium-223

ALSYMPCA: Symptomatic mCRPC With Bone Metastases





- FDA approved for CRPC with symptomatic bone mets and no known visceral mets
- Unlike β-emitting radioisotopes, radium-223, an α-emitting isotope, delivers less radiation to bone marrow → fewer myelosuppressive AEs
- Most common AEs: bone pain, nausea, anemia (no between-group differences)

GI = gastrointestinal; BP = blood pressure.

NIH. Accessed November 8, 2024. https://clinicaltrials.gov/study/NCT00699751. Parker C, et al. *N Engl J Med.* 2013;369(3):213-223. FDA. Accessed November 8, 2024. https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/203971lbl.pdf. Goyal J, et al. *Cancer Lett.* 2012;323(2):135-146.

Key Learning Points

- There have been significant advances in life-prolonging therapies for patients with advanced prostate cancer with hormone therapy, chemotherapy, targeted therapy, and radioligand therapy
- Choice of agent in mCRPC dependent on multiple factors including prior therapy, AE profile, biomarker status, and imaging status
- All patients with mPC should receive germline plus somatic DNA testing and genetic counseling, regardless of family history
  - Most clinically important: actionable *BRCA1/2* mutations, especially in 50-year-old men with mCRPC and a family history of breast cancer
- Based on results from the MAGNITUDE study, niraparib and abiraterone acetate administered with prednisone was approved for deleterious BRCA+ mCRPC
- The most appropriate strategy for managing recurrent/high-grade AEs associated with PARP inhibitors and ARSI combinations is permanent discontinuation
- Shared decision-making with engagement of patient, caregiver, and multidisciplinary team is important in developing treatment plan for patient

Thank you