AUA 2026
Washington, DC
MAY 15-18

040IC - Contemporary Management of Advanced Prostate Cancer: Guidelines and Beyond

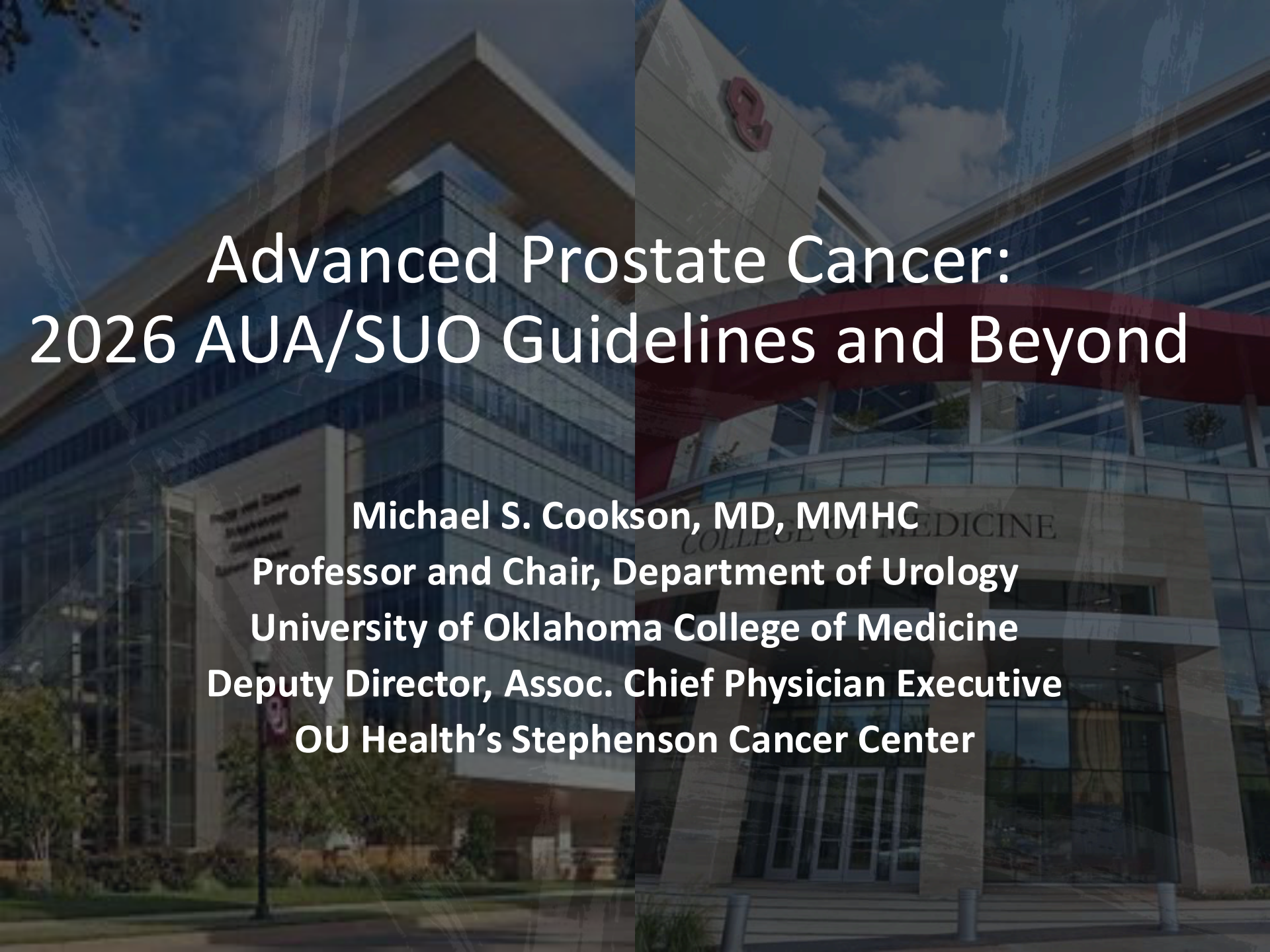
Sunday, May 17

Michael S. Cookson, MD

David F. Jarrard, MD

Adam S. Kibel, MD

Kristen R. Scarpato, MD



Advanced Prostate Cancer: 2026 AUA/SUO Guidelines and Beyond

Michael S. Cookson, MD, MMHC
Professor and Chair, Department of Urology
University of Oklahoma College of Medicine
Deputy Director, Assoc. Chief Physician Executive
OU Health's Stephenson Cancer Center

COURSE FACULTY

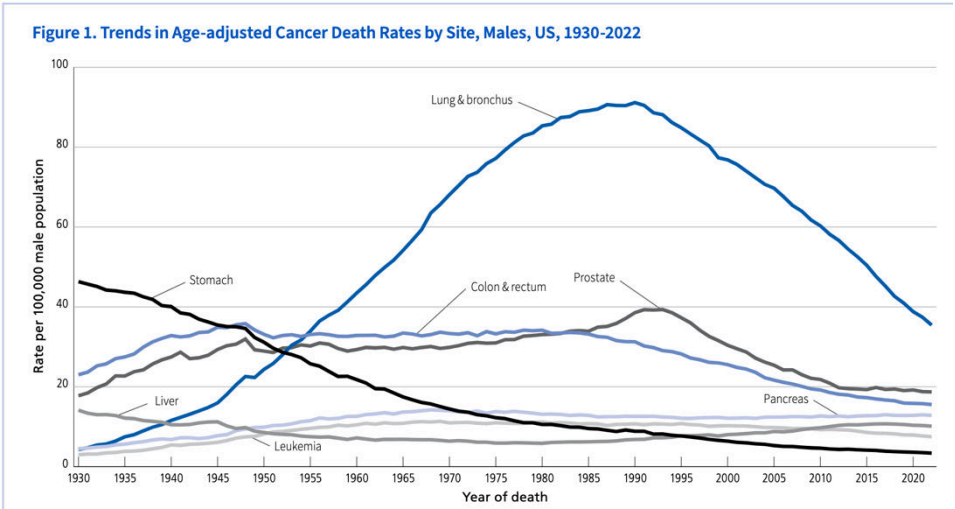
Adam Kibel, MD, MBA
Brigham and Women's Hospital and Dana-Farber/Brigham and Women's Cancer Center

David Jarrard, MD
University of Wisconsin

Kristen Scarpato, MD, MPH
Vanderbilt University

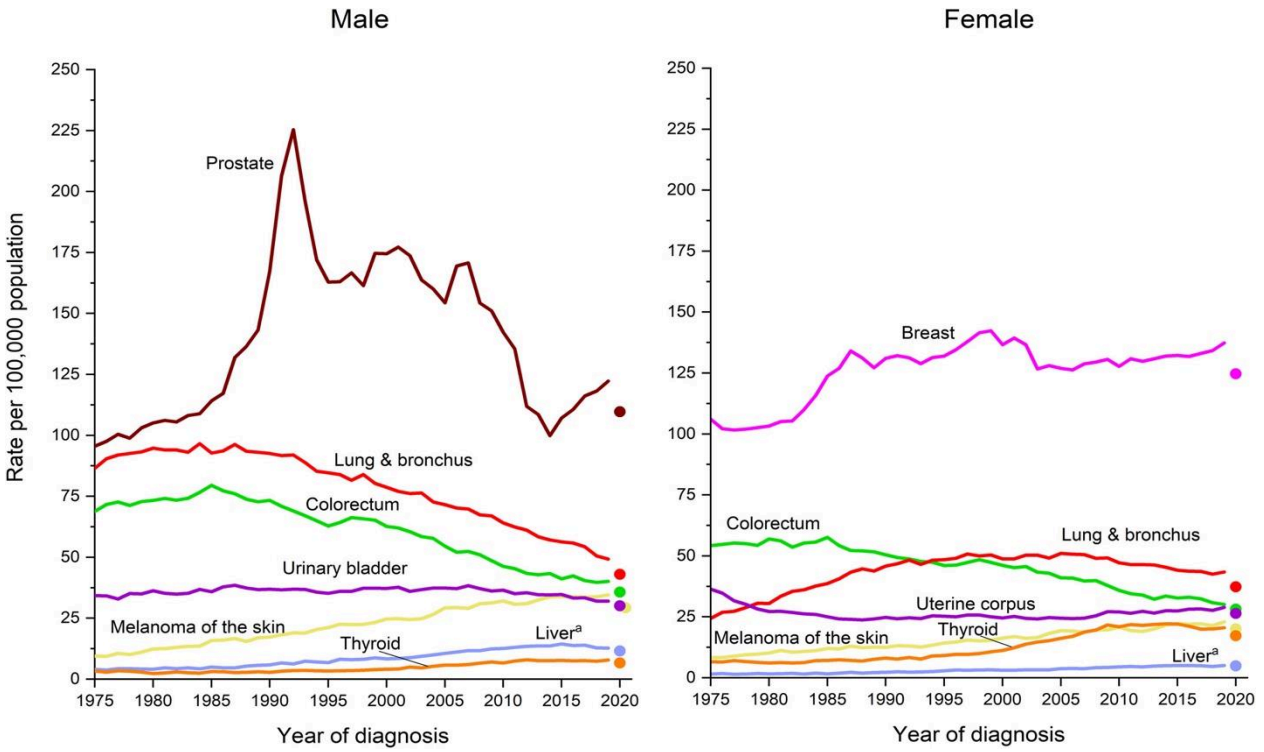
Prostate Cancer in the US: 2026

- 288,300 new cases (1 in 4 men)
  - #1 male cancer
  - 70% higher in Black men
- 34,700 deaths (1 in 44 men)
  - #2 Cancer Killer in Men
  - Slowing decline in mortality, from 3% to 4% annually 1994 through 2013 to 0.6% during 2013 through 2020, reflects the uptick in advanced-stage diagnoses



Cancer Facts & Figures 2026

Cancer Statistics, 2026



"**Since 2014, prostate cancer incidence rate has risen by 3% per year, mostly driven by 4%–5% per year increases for regional-stage and distant-stage diagnoses** that began as early as 2011… more than one half of men in the US living with metastatic prostate cancer were initially diagnosed with localized or regional stage disease."

CA A Cancer J Clinicians, 2026

Advanced Prostate Cancer: AUA/SUO Guideline

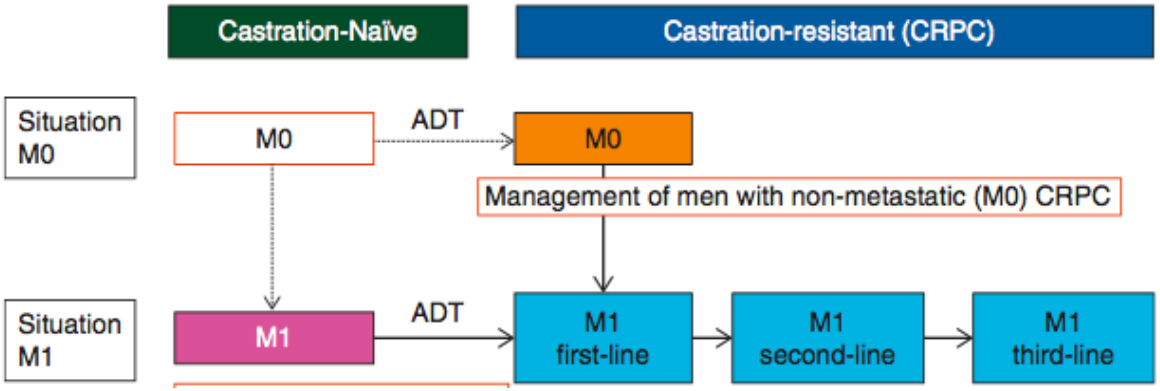
Published 2020, Amended 2023, 2026

Panel Members

William Lowrance, MD, MPH, MBA; Rodney Breau, MSc, MD; Roger Chou, MD; Brian F. Chapin, MD; Tony Crispino; Robert Dreicer, MD, MS, MACP; David F. Jarrard, MD; Adam S. Kibel, MD; Todd M. Morgan, MD; Alicia K. Morgans, MD, MPH; William K. Oh, MD; Matthew Resnick, MD, MPH, MMHC; Anthony Zietman, MD; Michael S. Cookson, MD, MMHC

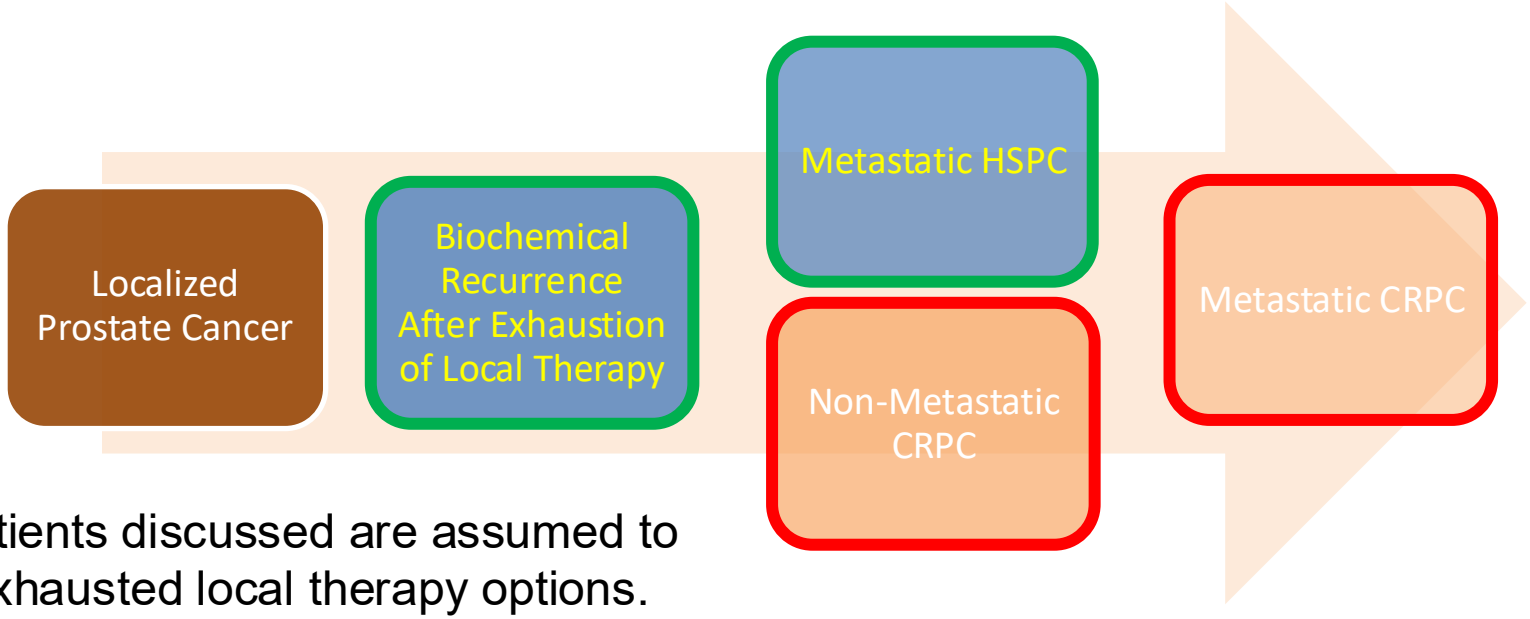
Amendment

William Lowrance, MD, MPH, MBA; Robert Dreicer, MD, MS, MACP; David F. Jarrard, MD; Kristen R. Scarpato, MD, MPH; David I. Buckley, MD, MPH; Jessica C. Griffin, MS; Michael S. Cookson, MD, MMHC



Lowrance W, Dreicer R, Jarrard DF, et al. Updates to advanced prostate cancer: AUA/SUO guideline (2023). J Urol. 2023;209(6):1082-1090.

ADVANCED PROSTATE CANCER PATIENT POPULATION



The patients discussed are assumed to have exhausted local therapy options.

Advanced Prostate Cancer: AUA/SUO Guideline

Prognosis

In patients with PSA recurrence after exhaustion of local therapy who are at higher risk for the development of metastases, clinicians should perform periodic staging evaluations consisting of imaging preferentially with PSMA PET and/or CT, MRI and technetium bone scan. (*Clinical Principle*)

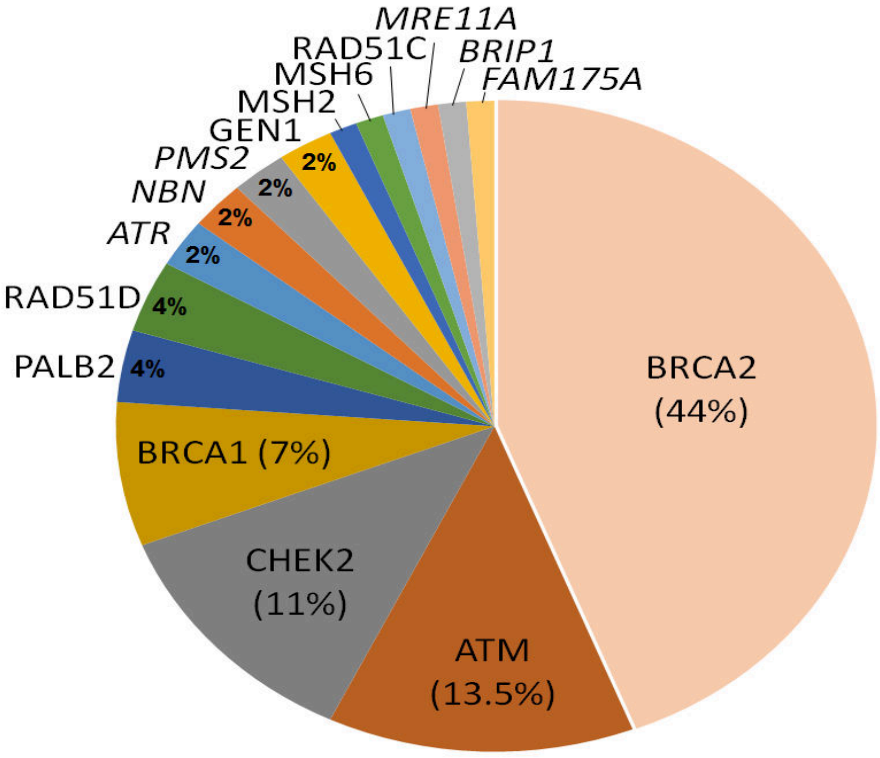
Advanced Prostate Cancer: AUA/SUO Guideline

Evaluation & Counseling

For all patients with advanced prostate cancer, clinicians should offer germline testing, if not already performed. For patients with metastatic disease, somatic tumor testing should also be offered. (*Clinical Principle*)

Germline Mutations in Metastatic PCa

- BRCA-2 best studied for potential screening and treatment
- PCa males with BRCA-2 have more aggressive disease
- More work is needed on the other PCa genes identified
- Germline mutations in 11.8% of metastatic vs. 4.6% localized disease
- Later studies indicate this may be up to 25% of mCRPC
- Clinicians should offer genetic counseling and germline testing



Pritchard, N Engl J Med. 2016 Aug 4;375(5):443-53; Cindamore A, Future Oncology VOL. 16, NO. 5 Online:9 Jan 2020

Advanced Prostate Cancer: AUA/SUO Guideline

Prognosis

Clinicians should utilize PSMA PET imaging preferentially in patients with PSA recurrence after exhaustion of local therapy due to its greater sensitivity, or in the setting of negative conventional imaging. (*Expert Opinion*)

Advanced Prostate Cancer: AUA/SUO Guideline

Prognosis

Clinicians should utilize PSMA PET imaging preferentially in patients with PSA recurrence after exhaustion of local therapy due to its greater sensitivity, or in the setting of negative conventional imaging. (*Expert Opinion*)

Advanced Prostate Cancer: AUA/SUO Guideline

Treatment

For patients with a rising PSA after exhaustion of local therapy and no demonstrated metastatic disease, clinicians should risk stratify as low- or high-risk. High-risk patients generally are defined as patients with PSADT </= 9 months.
(*Clinical Principle*)

Advanced Prostate Cancer: AUA/SUO Guideline

Treatment

ADT should not be routinely initiated for low-risk patients (PSADT > 9 months) with biochemical recurrence after exhaustion of local therapy. (Expert Opinion)

Advanced Prostate Cancer: AUA/SUO Guideline

Treatment

For patients with a rising PSA after exhaustion of local therapy with high-risk features, including PSADT </= 9 months, patients should be offered ADT with enzalutamide.

For patients with a rising PSA after exhaustion of local therapy with high-risk features and no metastatic disease in whom ADT +/- ARPI is initiated, intermittent therapy may be offered in lieu of continuous therapy in the setting of a favorable response.

Systemic Therapies after Exhaustion of Local Tx

EMBARK

High-risk BCR patients

- Failed local therapy, no metastatic disease
- PSAdt < 9 months
- PSA > 2 + nadir after RT
- PSA > 1 after surgery +/- XRT (w/wo ADT)

Randomized 1:1:1 to Leuprolide + Placebo, Leuprolide + Enzalutamide, or Enzalutamide

- Tx stopped at 9 months if PSA <0.2, restarted and continued once PSA >2 for surgery or >5 for XRT
- 1° Endpoint: MFS

N Engl J Med 2023;389:1453-1465 DOI: 10.1056/NEJMoa2303974

PRESTO

High-risk BCR patients

- Prior prostatectomy with adjuvant/salvage RT +/- ADT
- PSA > 0.5 with PSAdt < 9 months
- No evidence of metastases on conventional imaging (Axumin/PSMA PET lesions allowed)

Randomized 1:1:1 to 12 months of:

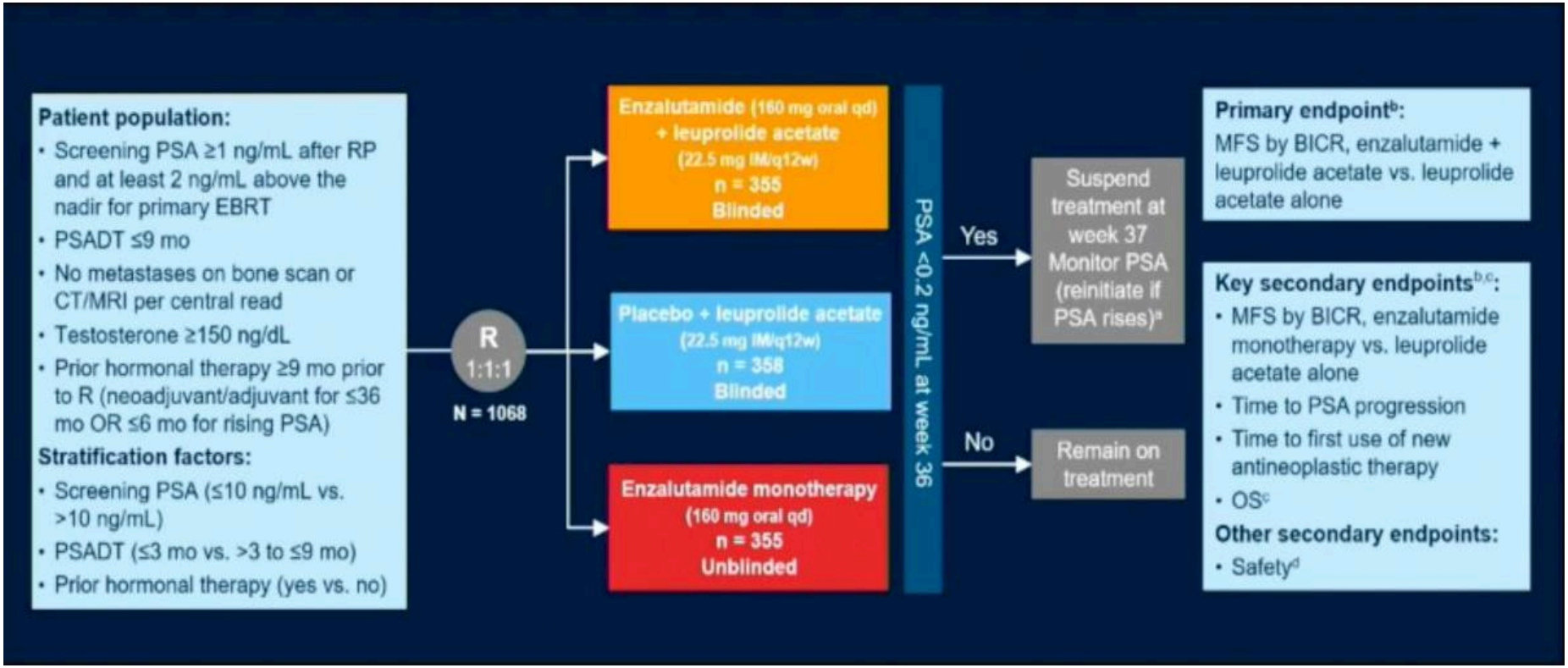
- ADT alone
- ADT + Apalutamide,
- ADT + Apalutamide + Abiraterone

1° endpoint: PSA progression-free survival

Journal of Clinical Oncology Volume 42, Number 10 https://doi.org/10.1200/JCO.23.01157

ORIGINAL ARTICLE FREE PREVIEW

Improved Outcomes with Enzalutamide in Biochemically Recurrent Prostate Cancer



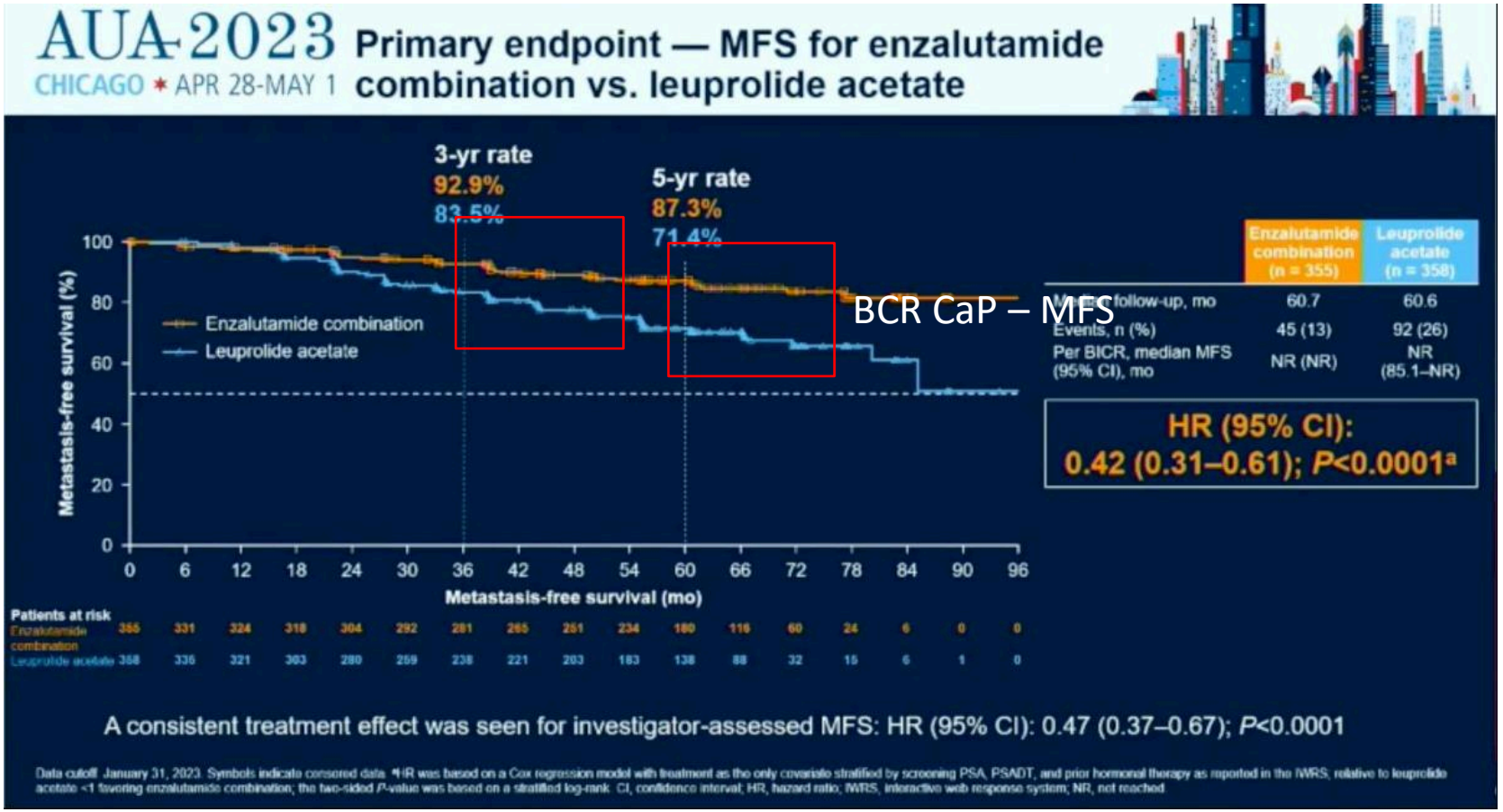
The NEW ENGLAND JOURNAL of MEDICINE

October 19, 2023

N Engl J Med 2023; 389:1453-1465

DOI: 10.1056/NEJMoa2303974

Improved Outcomes with Enzalutamide in Biochemically Recurrent Prostate Cancer



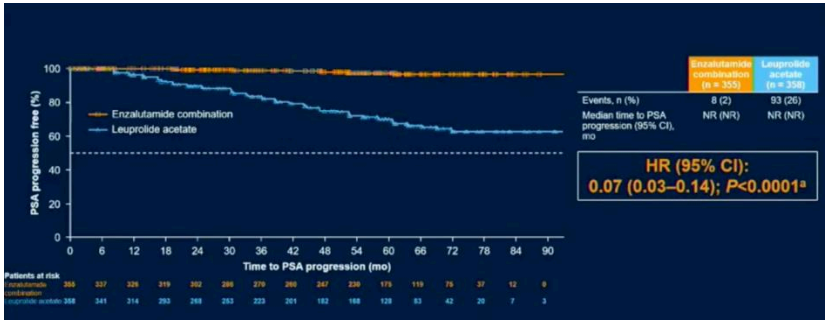
October 19, 2023
N Engl J Med 2023; 389:1453-1465
DOI: 10.1056/NEJMoa2303974

ORIGINAL ARTICLE FREE PREVIEW

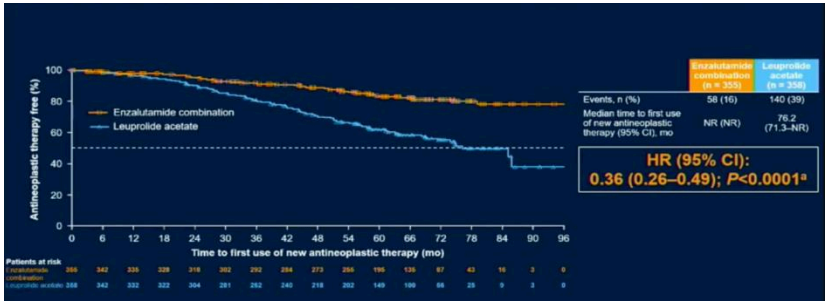
Improved Outcomes with Enzalutamide in Biochemically Recurrent Prostate Cancer

Benefits were seen for:

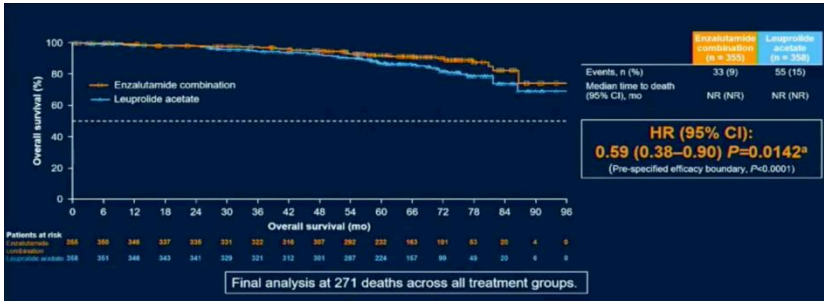
PSA progression



Time to first use of antineoplastic therapy



Overall survival



October 19, 2023

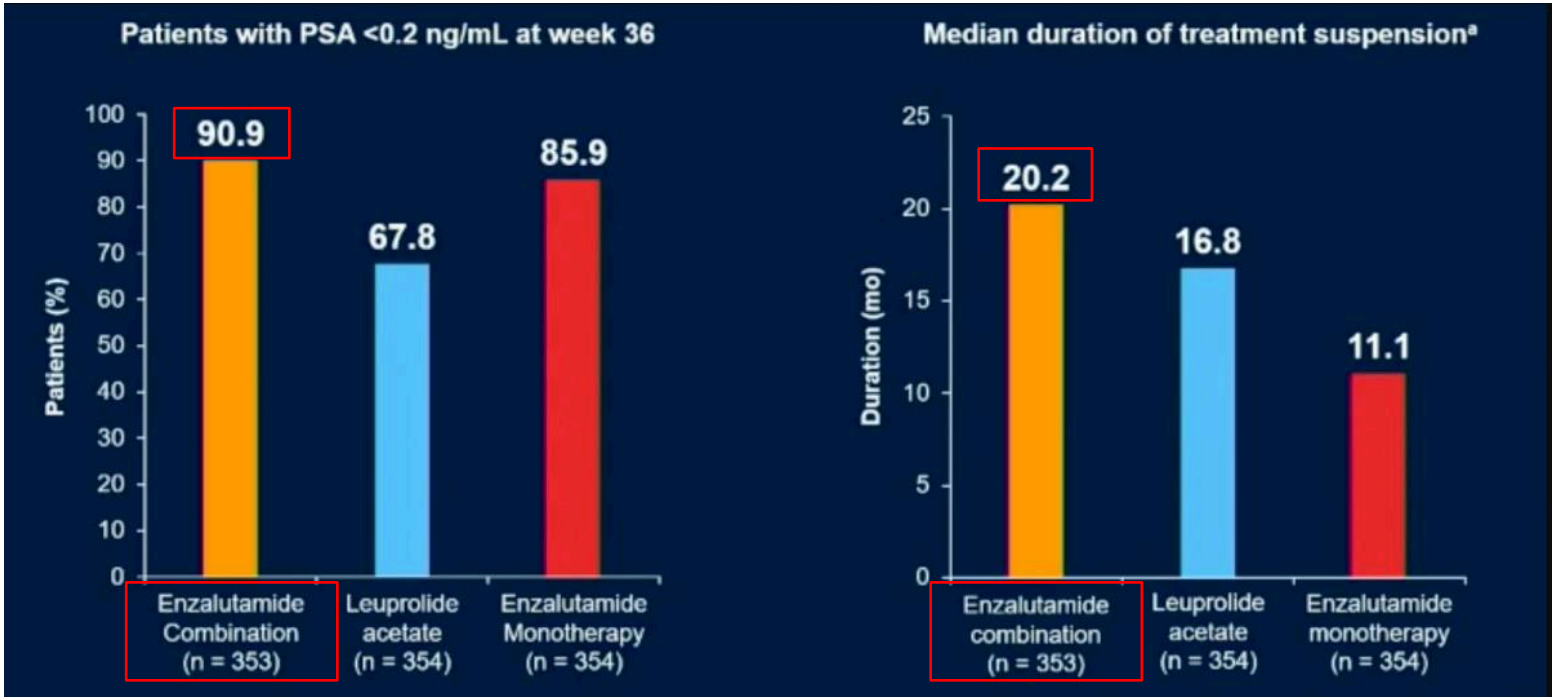
N Engl J Med 2023; 389:1453-1465

DOI: 10.1056/NEJMoa2303974

Improved Outcomes with Enzalutamide in Biochemically Recurrent Prostate Cancer

Assessment of PSA <0.2 at 36 weeks

Duration of treatment suspension

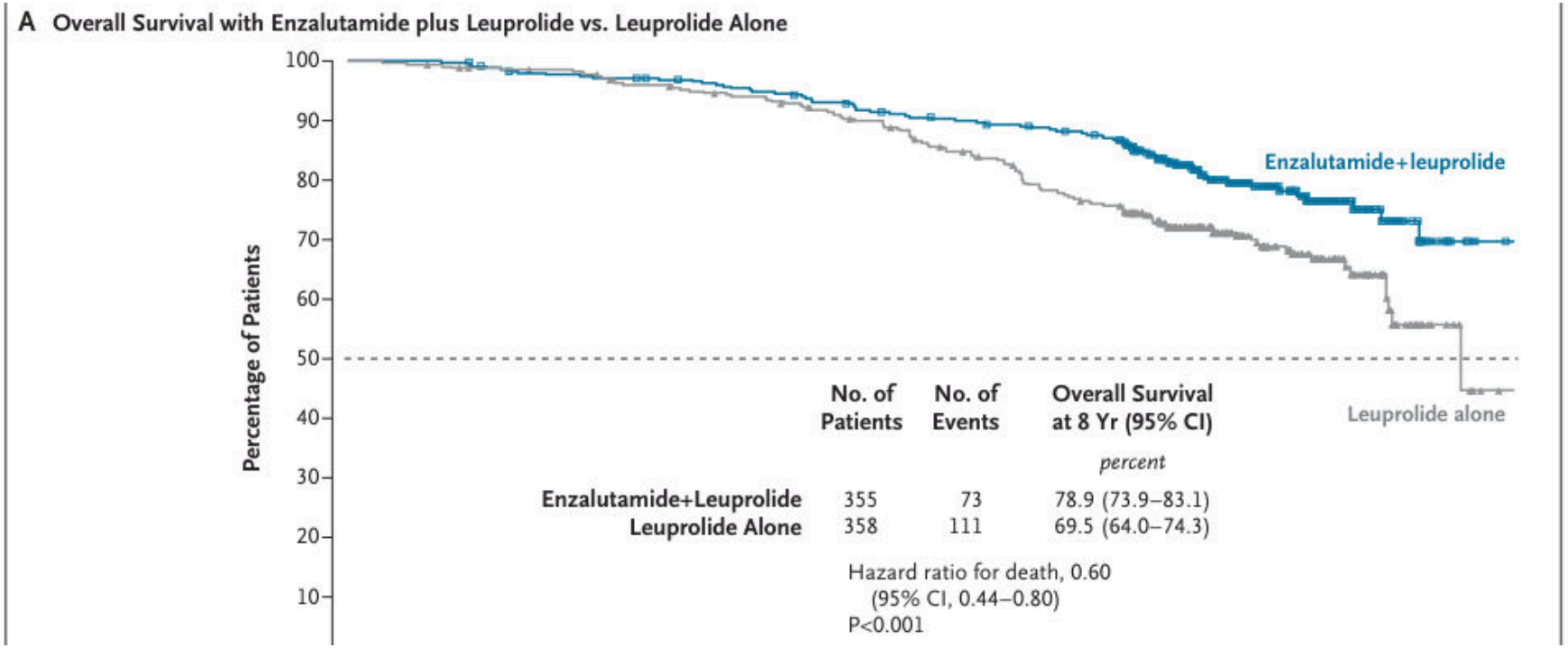


Both favor combination of enzalutamide and leuprolide acetate

October 19, 2023
N Engl J Med 2023; 389:1453-1465
DOI: 10.1056/NEJMoa2303974

Overall survival: enzalutamide + leuprolide vs leuprolide alone

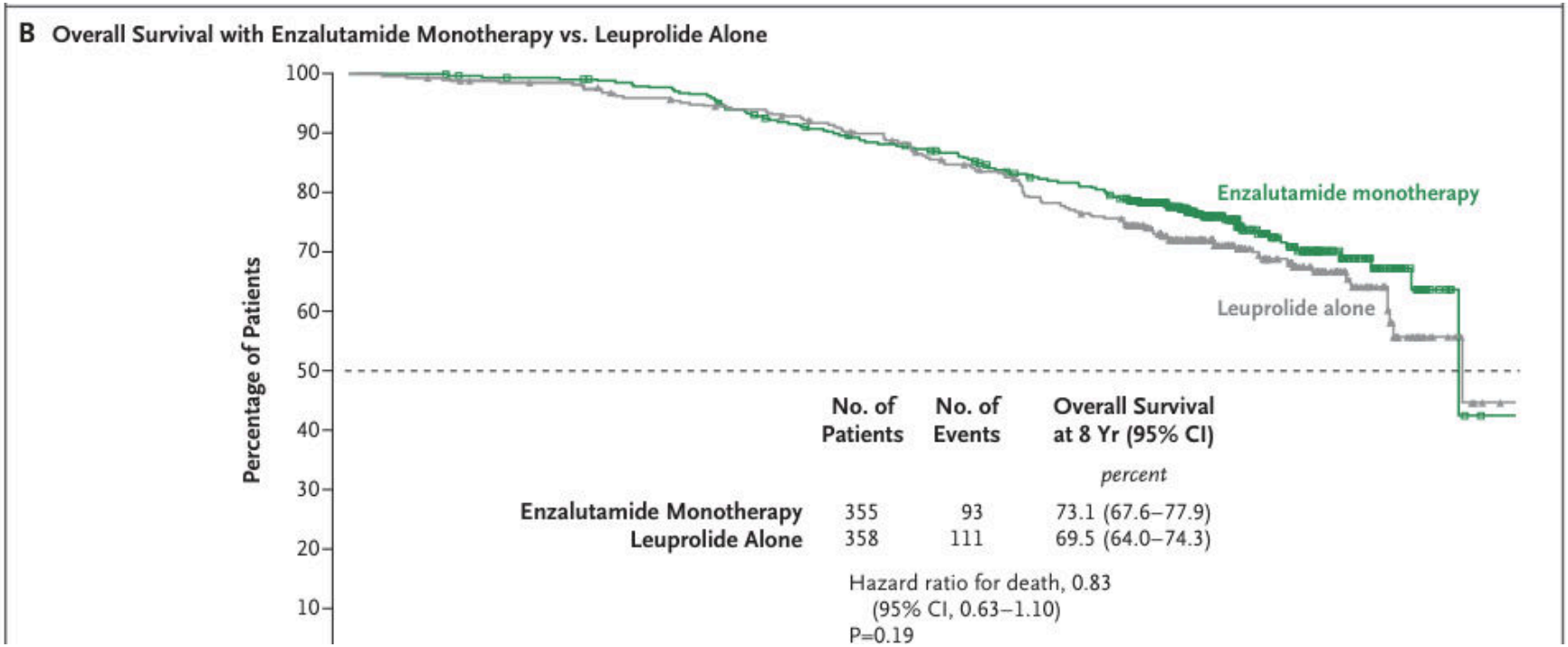
8-year OS: 78.9% vs 69.5% • HR 0.60 (95% CI, 0.44–0.80) • P<0.001



Freedland SJ, Shore ND, et al. N Engl J Med 2026;394:563–575.
DOI:10.1056/NEJMoa2510310. Fig. 1A.

Overall survival: enzalutamide monotherapy vs leuprolide alone

8-year OS: 73.1% vs 69.5% • HR 0.83 (95% CI, 0.63–1.10) • P=0.19



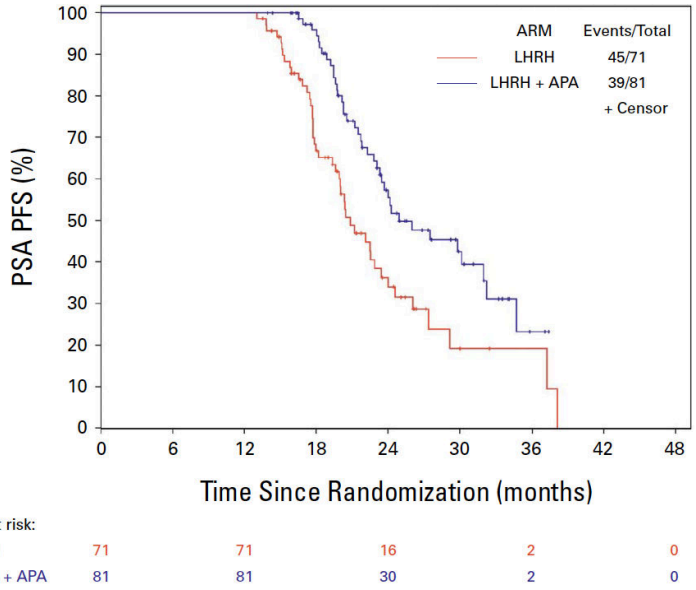
Freedland SJ, Shore ND, et al. N Engl J Med 2026;394:563–575. DOI:10.1056/NEJMoa2510310. Fig. 1B.

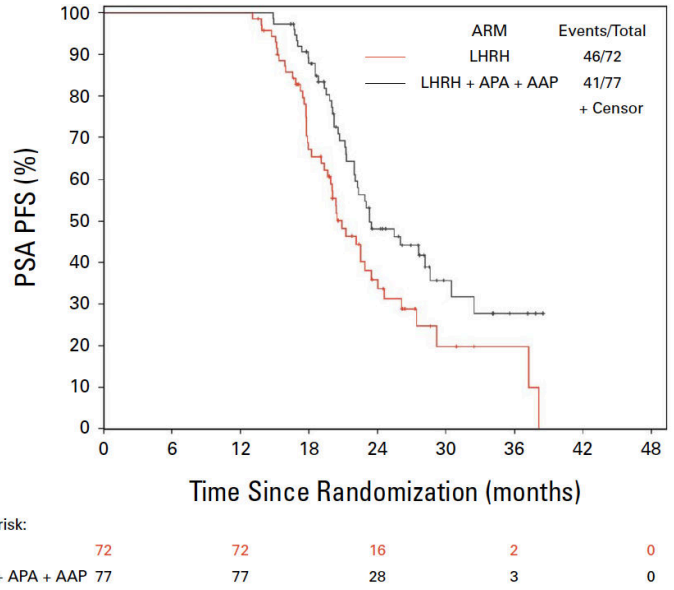
PRESTO: A Phase III, Open-Label Study of Intensification of Androgen Blockade in Patients With High-Risk Biochemically Relapsed Castration-Sensitive Prostate Cancer (AFT-19)

- High risk biochemically recurrent patients
  - Prior prostatectomy with adjuvant/salvage XRT +/- ADT
  - PSA >0.5 with PSAdt < 9 months
  - No evidence of metastases on conventional imaging (Axumin/PSMA PET lesions allowed)
- Randomized 1:1:1 to ADT, ADT + Apalutamide, ADT + Apalutamide + Abiraterone for 1 year
- Primary endpoint: PSA progression-free survival

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

- Both intensification arms significantly improved PSA-PFS compared to ADT alone





Journal of Clinical Oncology Volume 42, Number 10 https://doi.org/10.1200/JCO.23.01157

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

CONCLUSION Intensified AR blockade for a finite duration prolongs PSA-PFS with a manageable safety profile, without adversely affecting time to testosterone recovery. The addition of apalutamide to ADT should be considered in patients with high-risk BRPC.

Journal of Clinical Oncology Volume 42, Number 10 https://doi.org/10.1200/JCO.23.01157

Advanced Prostate Cancer: AUA/SUO Guideline

Metastatic Hormone-Sensitive Prostate Cancer

Prognosis

9. Clinicians should assess the extent of metastatic disease (lymph node, bone, and visceral metastases) in newly diagnosed mHSPC patients. *(Clinical Principle)*

10. In newly diagnosed mHSPC patients, clinicians should assess the extent of metastatic disease (low- versus high-volume). High-volume is defined as greater than or equal to four bone metastases with at least one metastasis outside of the spine/pelvis and/or the presence of visceral metastases. *(Moderate Recommendation: Evidence Level: Grade B)*

11. Clinicians should assess if a newly diagnosed mHSPC patient is experiencing symptoms from metastatic disease at the time of presentation to guide discussions of prognosis and further disease management. *(Moderate Recommendation; Evidence Level: Grade B)*

12. Clinicians should obtain a baseline PSA and serial PSAs at three- to six-month intervals after initiation of ADT in mHSPC patients and consider periodic conventional imaging. *(Clinical Principle)*

13. In patients with mHSPC, clinicians should offer germline testing, and consider somatic testing and genetic counseling. *(Clinical Principle)*

Advanced Prostate Cancer: AUA/SUO Guideline

Prognosis

In newly diagnosed mHSPC patients, clinicians should assess the extent of metastatic disease (lymph node, bone, and visceral metastases) and stratify based on low- versus high-volume. High-volume is defined as greater than or equal to four bone metastases with at least one metastasis outside of the spine/pelvis and/or the presence of visceral metastases based on conventional imaging . (*Moderate Recommendation: Evidence Level: Grade B*)

Disease Extent → Overall Survival

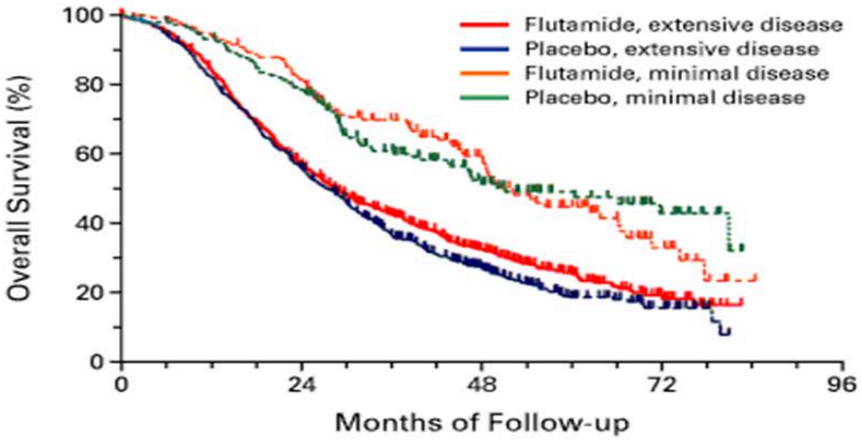
1. **First report on disease extent & OS**: Crawford, NEJM,1989

   Minimal: Spine, pelvis &/or Lymph nodes

   vs.

   Extensive: Ribs, long bones and/or visceral organs

2. **S8894 - Bilateral orchiectomy ± flutamide** Eisenberger et al. NEJM,1998



Minimal: 51 mo
Extensive: 27.5 mo

<u>Current definitions of high-volume:</u>

- **CHAARTED**: Visceral (lung or liver) and/or 4+ bone mets, at least one beyond pelvis and vertebral column
- **SWOG**: visceral and/or any appendicular skeletal involvement

Advanced Prostate Cancer: AUA/SUO Guideline

Prognosis

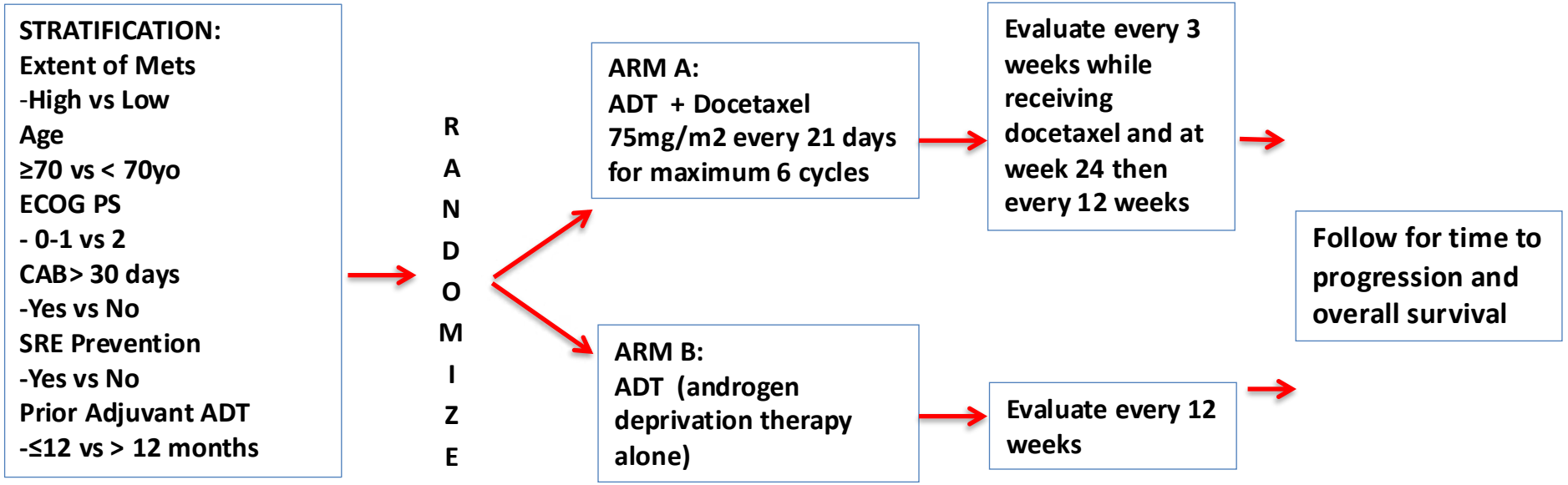
Clinicians should obtain a baseline PSA and serial PSAs at three- to six-month intervals after initiation of ADT in mHSPC patients and consider periodic imaging. (*Clinical Principle*)

Improving Survival: M1 HSPC "Treatment Intensification"

- Chemo-Hormonal Therapy
  - ADT + docetaxel
- More Potent Androgen Targeting
  - ADT + androgen axis therapy
    - Abiraterone
    - Apalutamide/darolutamide/enzaluatimide
- Triplet Therapy
  - ADT + docetaxel + abiraterone (or darolutamide)

Strategy: Chemo-Hormonal Therapy

E3805:CHAARTED: Randomized Trial



- **High volume: visceral metastases or 4 or more bone mets (at least 1 beyond pelvis and vertebral column)**
- **At inception, only patients with high volume disease were to be accrued**

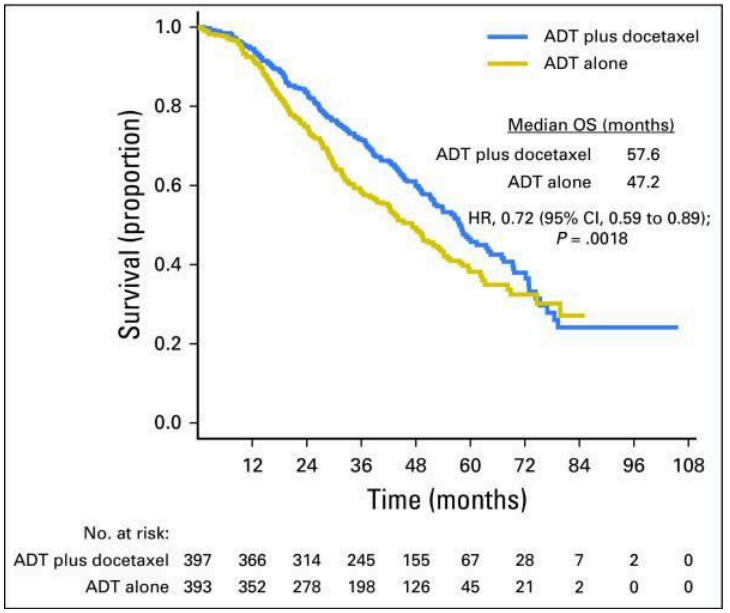
Sweeney C, et al NEJM 2015

Strategy: Chemo-Hormonal Therapy

E3805:CHAARTED: Randomized Trial

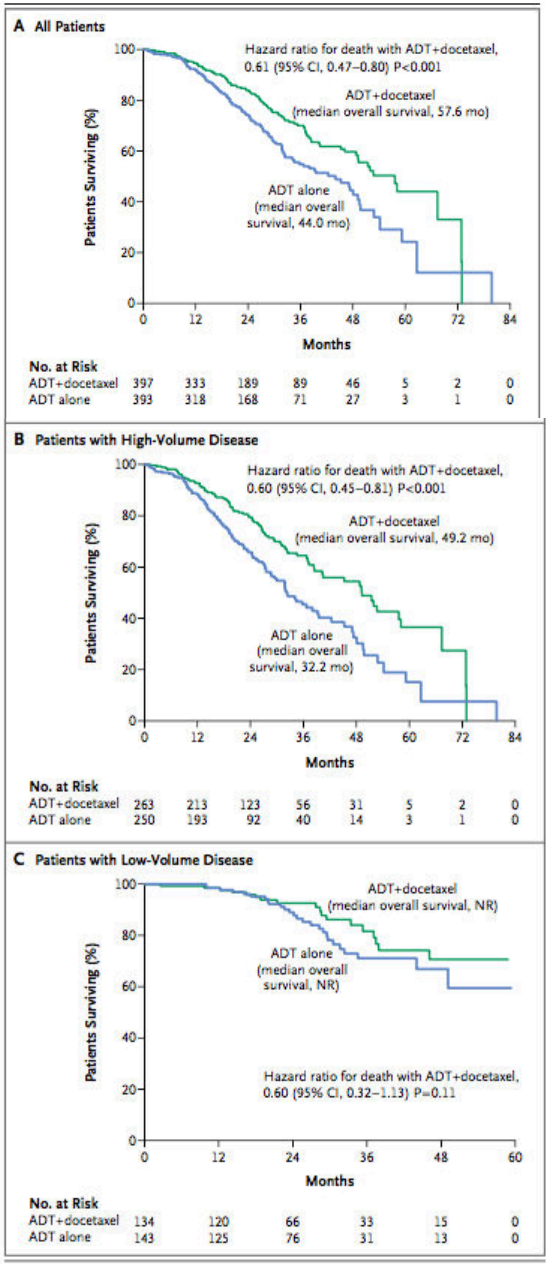
DOCETAXEL

Trial	Overall Survival	
CHAARTED n=790	57.6 months docetaxel + ADT 47.2 months ADT	HR= 0.72; 95%CI 0.59 to 0.89 P=0.0018



Kyriakopoulos CE et al: Chemohormonal therapy in metastatic hormone-sensitive prostate cancer: long-term survival analysis of the randomized pase III E3805 CHAARTED trial. J Clin Oncol 2018; 36:1080.

CHAARTED: Chemohormonal Rx



N=790
Median OS:
ADT + D: 57.6 months
ADT alone: 44.0 months
HR=0.61 (0.47-0.80)
p=0.0003

All Patients

N=514
Median OS:
ADT + D: 49.2 months
ADT alone: 32.2 months
HR=0.60 (0.45-0.81)
p=0.0006

High volume

N=276
Median OS:
ADT + D: Not reached
ADT alone: Not reached
HR=0.63 (0.34-1.17)
p=0.1398

Low volume

Sweeney CJ et al. NEJM 2015

Advanced Prostate Cancer: AUA/SUO Guideline

Treatment

In addition to ADT, clinicians should also offer androgen pathway-directed therapy with abiraterone acetate plus prednisone, apalutamide, enzalutamide, or darolutamide to the majority of patients with mHSPC. (*Strong Recommendation; Evidence Level: Grade A*)

ORIGINAL ARTICLE

Abiraterone plus Prednisone in Metastatic, Castration-Sensitive Prostate Cancer

Karim Fizazi, M.D., Ph.D., NamPhuong Tran, M.D., Luis Fein, M.D., Nobuaki Matsubara, M.D., Alfredo Rodriguez-Antolin, M.D., Ph.D., Boris Y. Alekseev, M.D., Mustafa Özgüroğlu, M.D., Dingwei Ye, M.D., Susan Feyerabend, M.D., Andrew Protheroe, M.D., Ph.D., Peter De Porre, M.D., Thian Kheoh, Ph.D., Youn C. Park, Ph.D., Mary B. Todd, D.O., and Kim N. Chi, M.D., for the LATITUDE Investigators*

N ENGL J MED 377;4 NEJM.ORG JULY 27, 2017

The NEW ENGLAND JOURNAL of MEDICINE

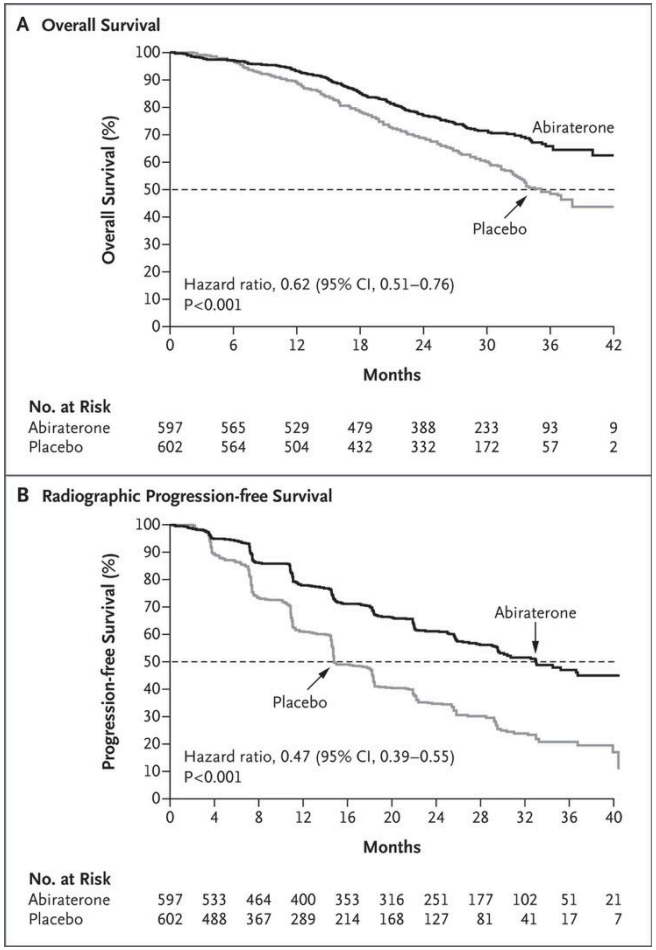
ORIGINAL ARTICLE

Abiraterone for Prostate Cancer Not Previously Treated with Hormone Therapy

N.D. James, J.S. de Bono, M.R. Spears, N.W. Clarke, M.D. Mason, D.P. Dearnaley, A.W.S. Ritchie, C.L. Amos, C. Gilson, R.J. Jones, D. Matheson, R. Millman, G. Attard, S. Chowdhury, W.R. Cross, S. Gillessen, C.C. Parker, J.M. Russell, D.R. Berthold, C. Brawley, F. Adab, S. Aung, A.J. Birtle, J. Bowen, S. Brock, P. Chakraborti, C. Ferguson, J. Gale, E. Gray, M. Hingorani, P.J. Hoskin, J.F. Lester, Z.I. Malik, F. McKinna, N. McPhail, J. Money-Kyrle, J. O'Sullivan, O. Parikh, A. Protheroe, A. Robinson, N.N. Srihari, C. Thomas, J. Wagstaff, J. Wylie, A. Zarkar, M.K.B. Parmar, and M.R. Sydes, for the STAMPEDE Investigators*

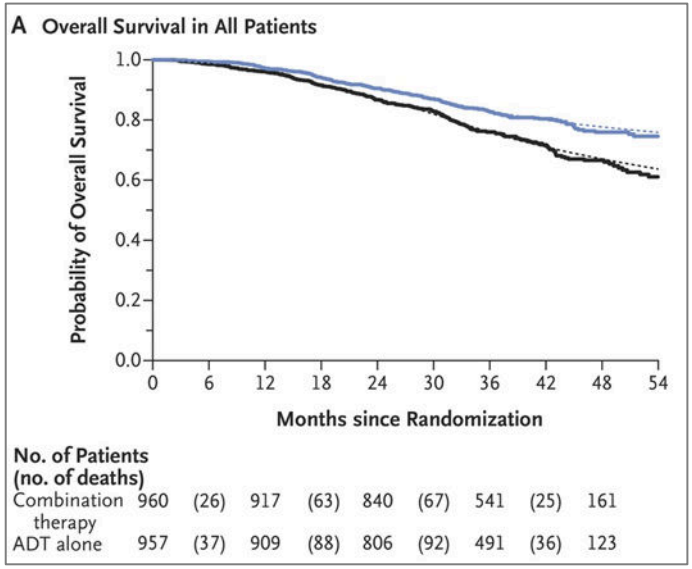
ABIRATERONE ACETATE

Trial	Primary Endpoints
LATITUDE n=1,199	Overall Survival • Not reached abiraterone + ADT • 34.7 months ADT + placebo Radiographic Progression-Free Survival • 33.0 months abiraterone + ADT • 14.8 months ADT + placebo



1. Fizazi K et al: Abiraterone plus prednisone in metastatic, castration-sensitive prostate cancer. N Engl J Med 2017; 377:352.

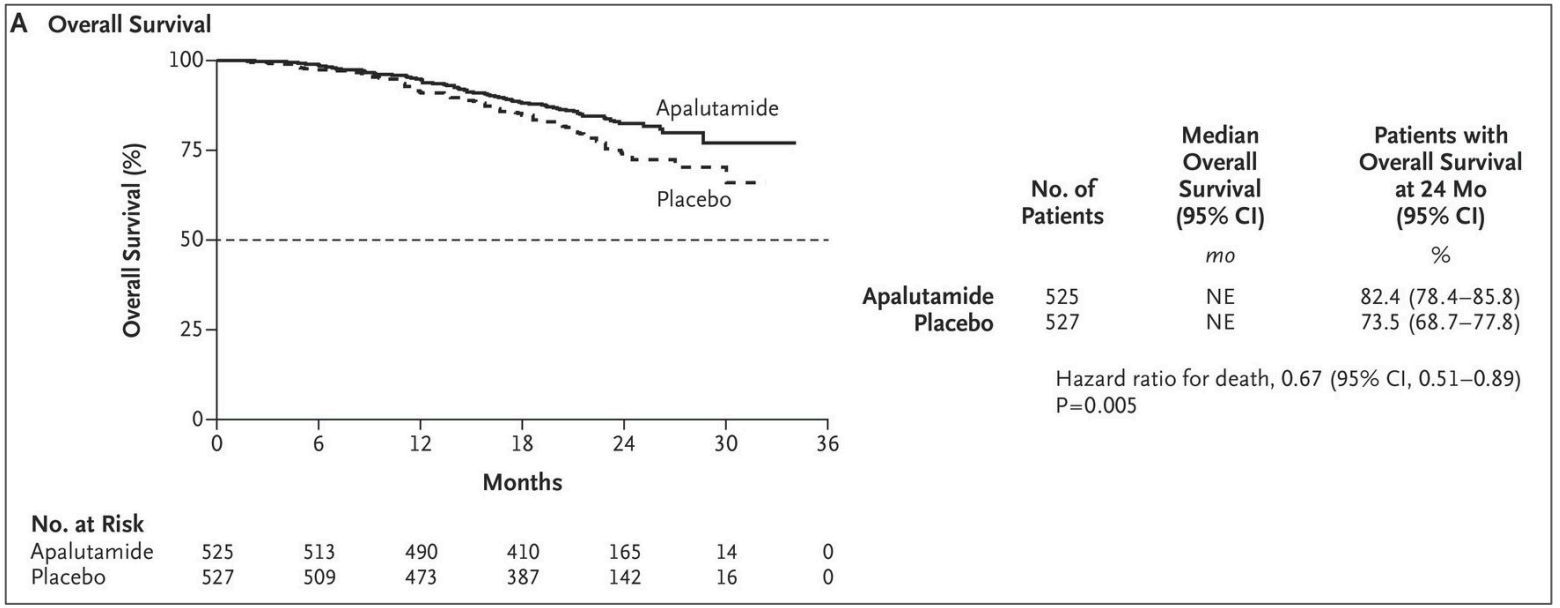
ABIRATERONE ACETATE



Trial	Primary Endpoint	
STAMPEDE n=1,917	Overall Survival 83% at 3 years abiraterone + ADT 76% at 3 years ADT	HR for death = 0.63; 95%CI 0.52 to 0.76 P<0.001

James ND et al: Abiraterone for prostate cancer not previously treated with hormone therapy. N Engl J Med 2017;377:338.

APALUTAMIDE– TITAN

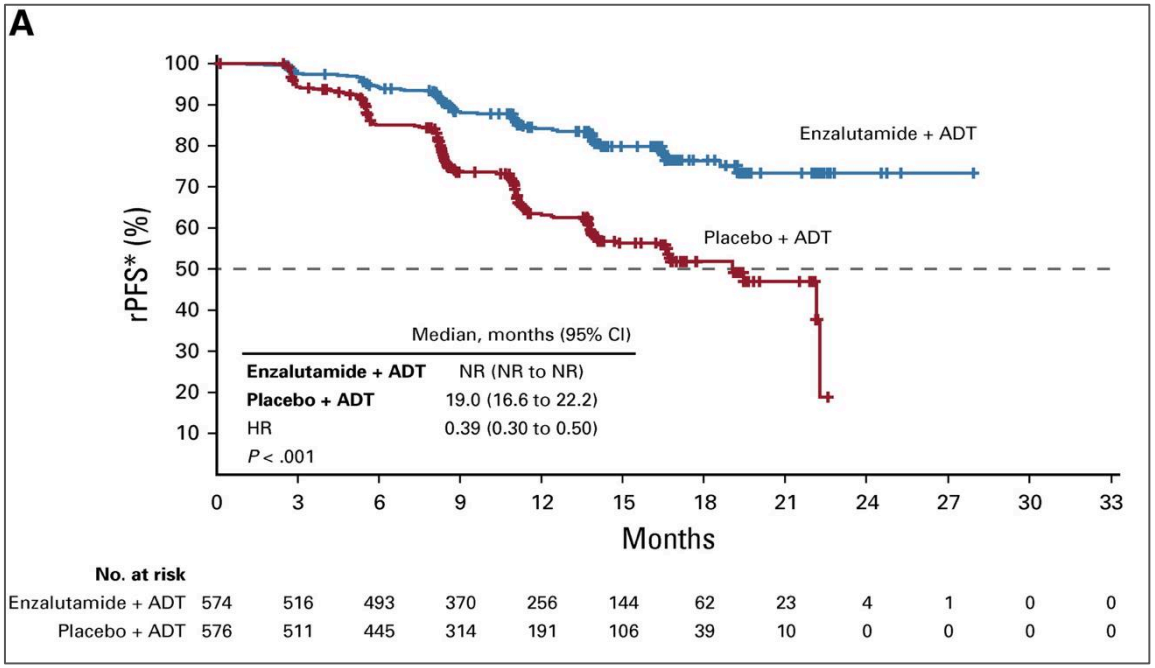


	No. of Patients	Median Overall Survival (95% CI)	Patients with Overall Survival at 24 Mo (95% CI)
		mo	%
Apalutamide	525	NE	82.4 (78.4–85.8)
Placebo	527	NE	73.5 (68.7–77.8)

Hazard ratio for death, 0.67 (95% CI, 0.51–0.89)
P=0.005

Chi KN et al: Apalutamide for metastatic, castration-sensitive prostate cancer. N Engl J Med 2019; 381: 13.

ENZALUTAMIDE - ARCHES

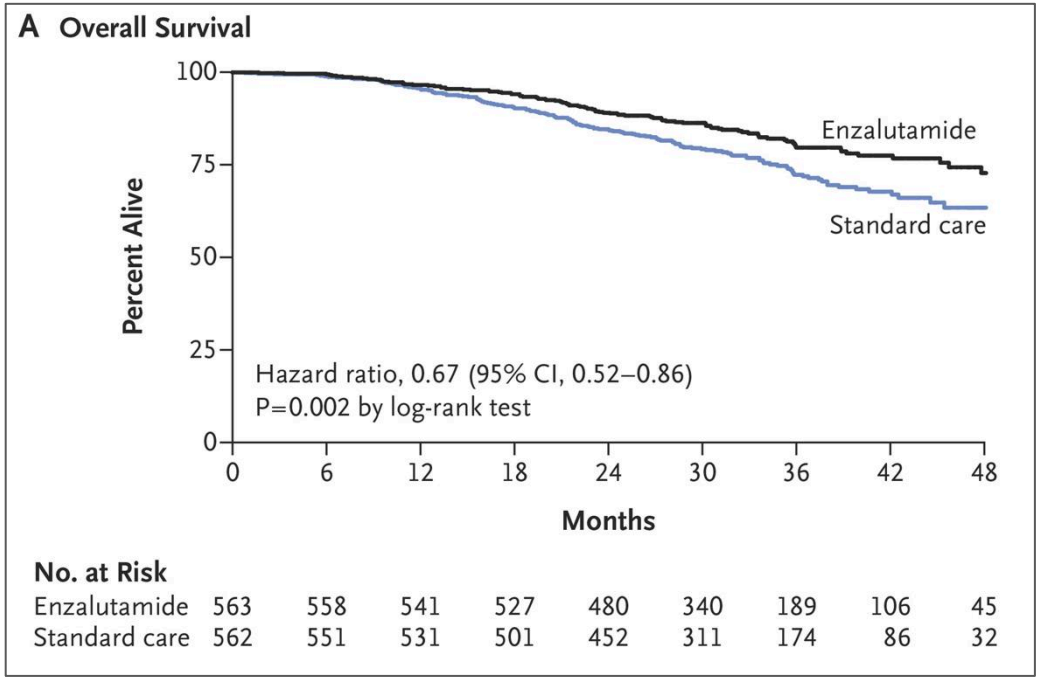


Trial	Primary Endpoints
ARCHES n=1,150	Radiographic Progression-Free Survival • Not reached enzalutamide + ADT • 19.0 months ADT + placebo

Armstrong AJ et al: ARCHES: a randomized, phase III study of androgen deprivation therapy with enzalutamide or placebo in men with metastatic hormone-sensitive prostate cancer. J Clin Oncol 2019; 37: 2974.

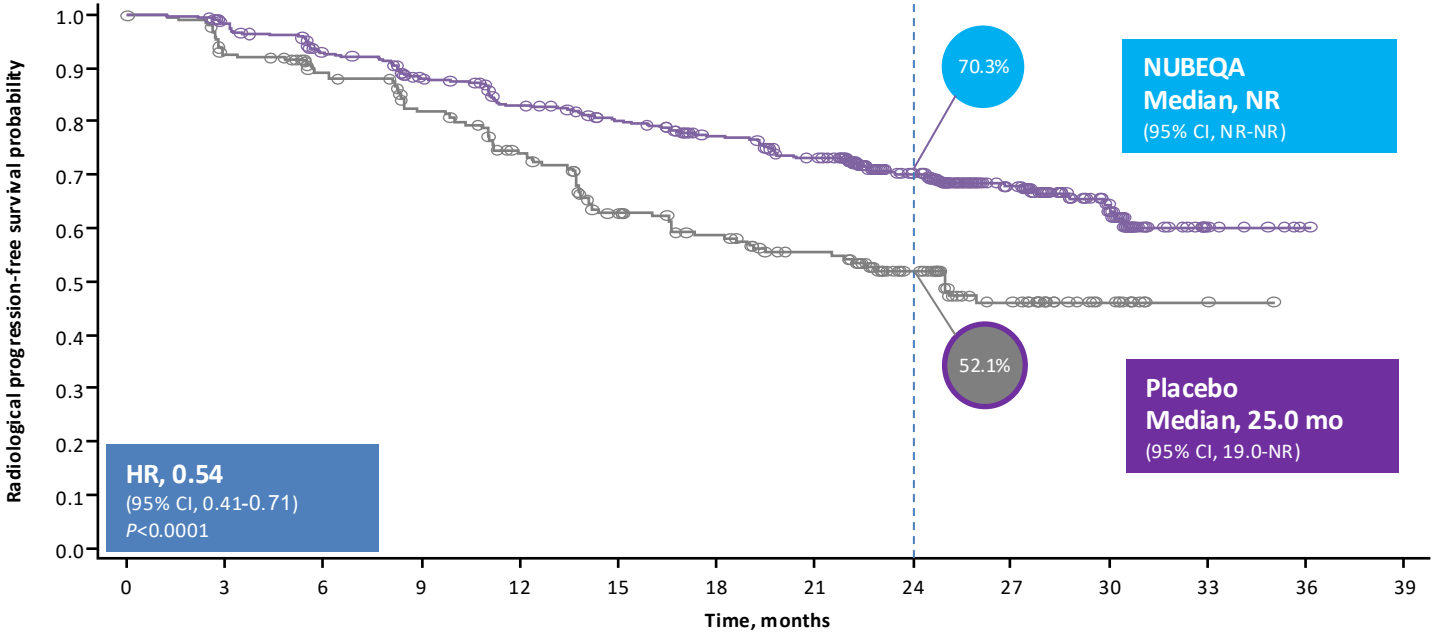
ENZALUTAMIDE - ENZAMET

Trial	Primary Endpoints
ENZAMET n=1,125	Overall Survival (at 34 months) • 102 deaths enzalutamide • 143 deaths standard care



Davis ID et al: Enzalutamide with standard first-line therapy in metastatic prostate cancer. N Engl J Med 2019; 381: 121.

DAROLUTAMIDE - ARANOTE



Saad F, et al. JCO, 2024 :42:4271-4281

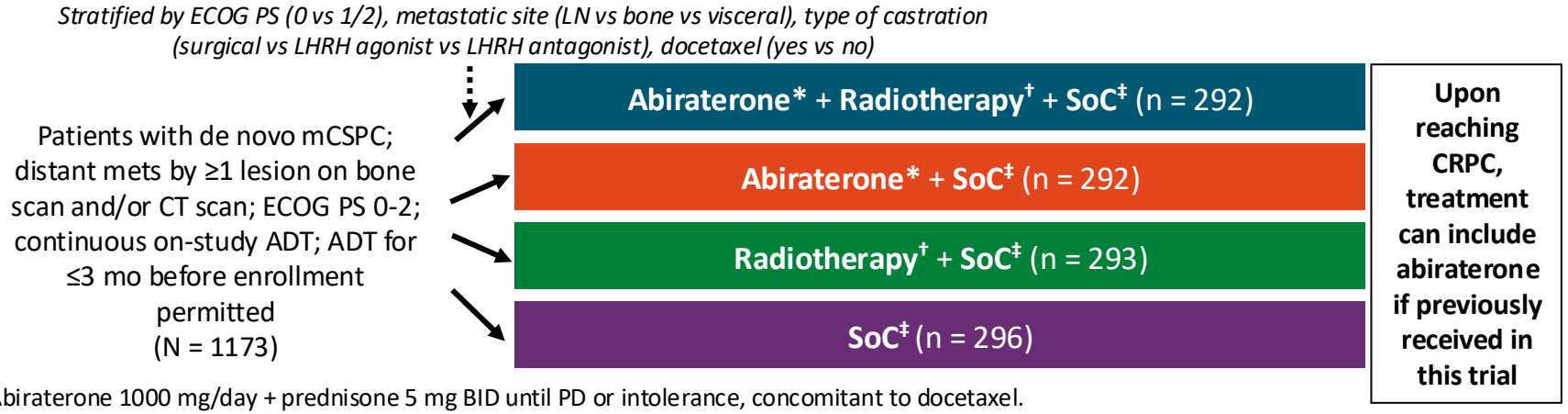
Advanced Prostate Cancer: AUA/SUO Guideline

Treatment

In selected mHSPC patients, clinicians should offer ADT in combination with docetaxel and either abiraterone acetate plus prednisone or darolutamide. (*Strong Recommendation; Evidence Level: [Abiraterone] Grade A/[Darolutamide] Grade B*)

PEACE-1: Study Design

- Multicenter, randomized, open-label phase III trial[1,2]



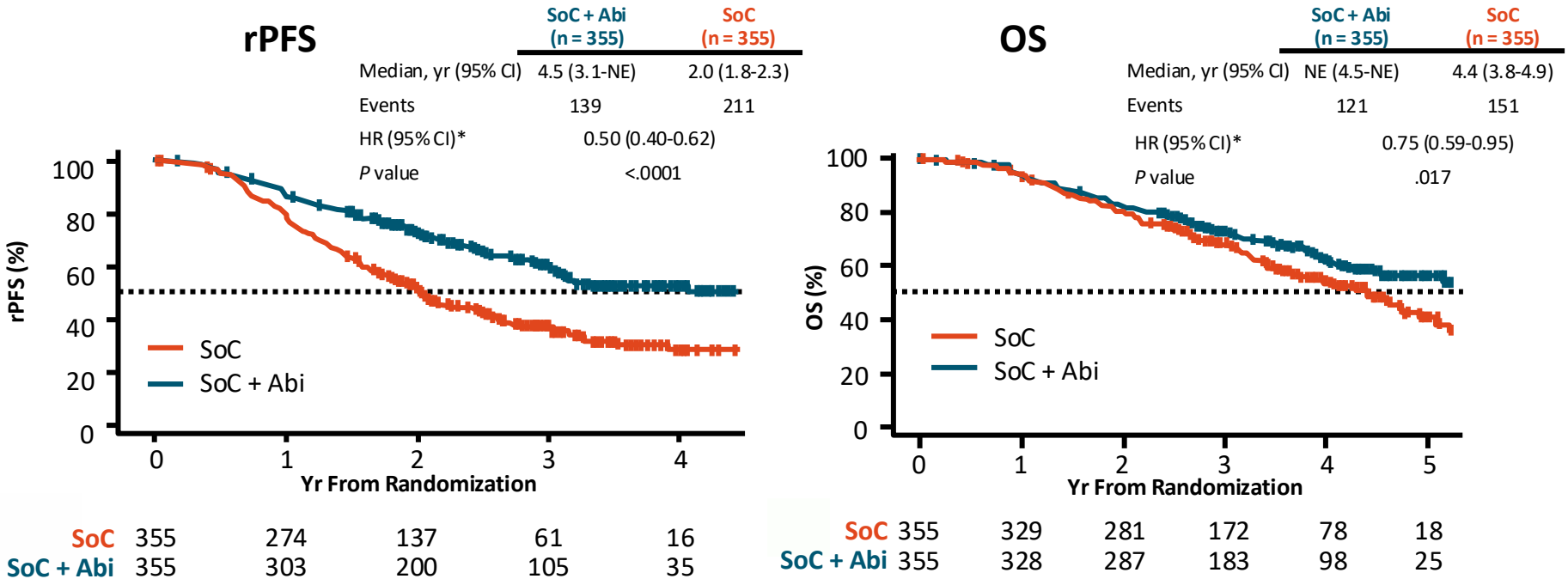
*Abiraterone 1000 mg/day + prednisone 5 mg BID until PD or intolerance, concomitant to docetaxel.
†74 Gy in 37 fractions after completion of docetaxel. ‡Continuous ADT ± docetaxel 75 mg/m^2 Q3W x 6 cycles.

- **Coprimary endpoints:** rPFS and OS with 2x2 factorial design and hierarchical testing[1]
- **Key secondary endpoints:** castration resistance-free survival, time to next SRE, PSA response rate, time to pain progression, QoL, safety[1]

1. Fizazi. ASCO 2021. Abstr 5000. 2. Fizazi. ESMO 2021. Abstr LBA5.

Fizazi K, Carles Galceran J, Foulon S, et al. A phase III trial with a 2x2 factorial design in men with de novo metastatic castration-sensitive prostate cancer: over-all survival with abiraterone acetate plus prednisone in PEACE-1. Ann Oncol 2021.

PEACE-1: rPFS and OS With Abiraterone in the Docetaxel (± Radiotherapy) Population

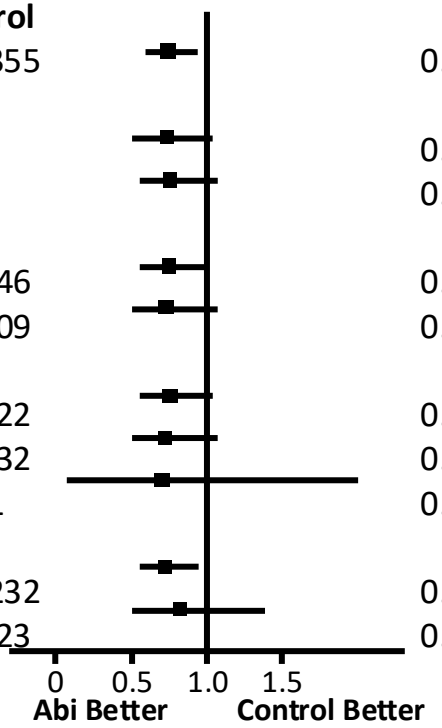


*Adjusted on stratification parameters (RXT, PS, type of castration, metastatic burden).

Fizazi K, Carles Galceran J, Foulon S, et al. A phase III trial with a 2x2 factorial design in men with de novo metastatic castration-sensitive prostate cancer: over-all survival with abiraterone acetate plus prednisone in PEACE-1. Ann Oncol 2021

PEACE-1: OS by Subgroup With Abiraterone in ADT + Docetaxel Population (± Radiotherapy)

Subgroup	N Events/N Pts		HR	*P* Value
	Abi	Control		
Overall	121/355	151/355	0.75 (0.59-0.95)	
Radiotherapy				.85
▪ No			0.73 (0.52-1.03)	
▪ Yes			0.76 (0.54-1.07)	
Performance status				.93
▪ 0	76/250	93/246	0.75 (0.56-1.02)	
▪ 1/2	45/105	58/109	0.74 (0.50-1.09)	
Type of castration				.98
▪ LHRH agonist	72/219	88/222	0.76 (0.56-1.04)	
▪ LHRH antagonist	47/134	62/132	0.73 (0.50-1.06)	
▪ Surgical castration	2/2	1/1	0.71 (0.06-7.91)	
Metastatic burden				.64
▪ High	92/224	120/232	0.72 (0.55-0.95)	
▪ Low	29/131	31/123	0.83 (0.50-1.38)	



Fizazi. ESMO 2021. Abstr LBA5.

Fizazi K, Carles Galceran J, Foulon S, et al. A phase III trial with a 2x2 factorial design in men with de novo metastatic castration-sensitive prostate cancer: over-all survival with abiraterone acetate plus prednisone in PEACE-1. Ann Oncol 2021

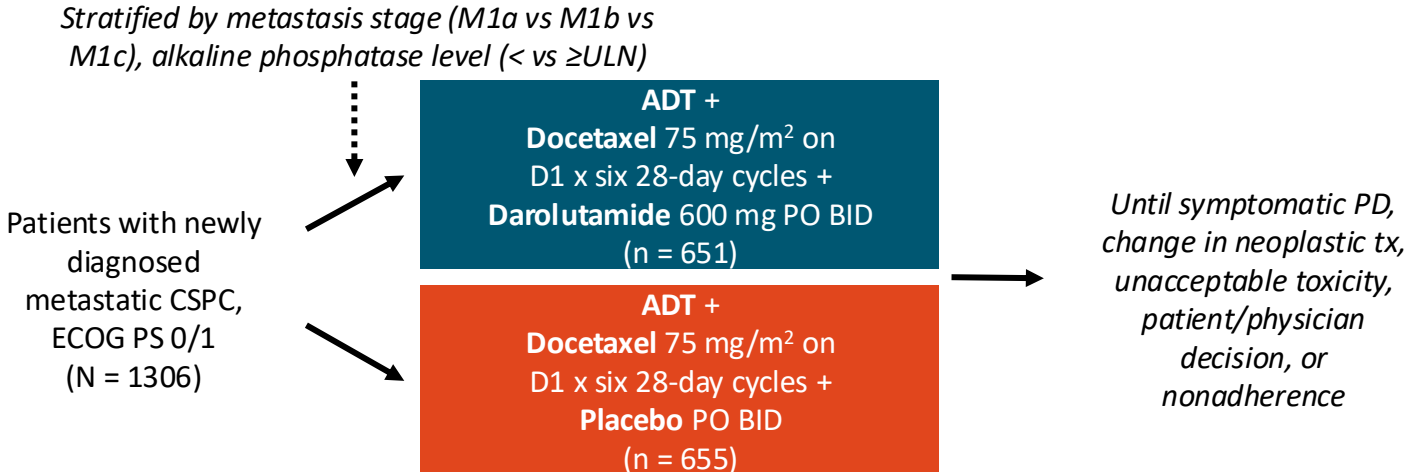
PEACE-1: Grade 3-5 AEs Reported in ADT + Docetaxel Population

Grade 3-5 AEs, n (%)	Abiraterone + SoC (± Radiotherapy) (n = 346)	SoC (± Radiotherapy) (n = 350)
Neutropenia	34 (10)	32 (9)
Febrile neutropenia	18 (5)	19 (5)
Liver	20 (6)	2 (1)
Hypertension	76 (22)	45 (13)
Hypokalemia	11 (3)	1 (0)
Cardiac	6 (2)	5 (1)
Fatigue	10 (3)	15 (4)
Gastrointestinal	14 (4)	18 (5)
Grade 5	7 (2)	3 (1)

Fizazi K, Carles Galceran J, Foulon S, et al. A phase III trial with a 2x2 factorial design in men with de novo metastatic castration-sensitive prostate cancer: over-all survival with abiraterone acetate plus prednisone in PEACE-1. Ann Oncol 2021

Phase III ARASENS Trial: Darolutamide in mCSPC

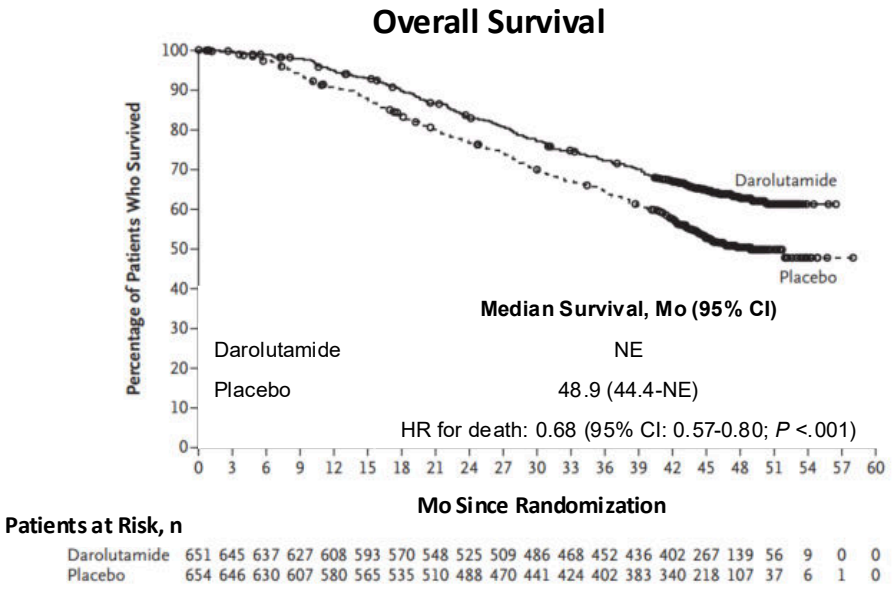
- International, randomized, double-blind, placebo-controlled trial in 286 sites in 23 countries



- **Primary endpoint:** OS
- **Secondary endpoints tested hierarchically in this order:** time to CRPC, time to pain progression, SSE-free survival, time to first SSE, time to initiation of subsequent anticancer therapy, time to worsening of physical symptoms, time to first opioid use, safety

.Smith, M. R. *et al.* Darolutamide and Survival in Metastatic, Hormone-Sensitive Prostate Cancer. *New Engl J Medicine* **386**, 1132–1142 (2022).

ARASENS: Primary Endpoint (Overall Survival), Safety



- Addition of darolutamide to ADT + docetaxel significantly lowered risk of death by 32.5% vs placebo

Safety Outcome, n (%)	ADT + Docetaxel + Darolutamide (n = 652)	ADT + Docetaxel + Placebo (n = 650)
Any AE	649 (99.5)	643 (98.9)
Serious AE	292 (44.8)	275 (42.3)
AE leading to permanent d/c of trial agent		
▪ Darolutamide or placebo	88 (13.5)	69 (10.6)
▪ Docetaxel	52 (8.0)	67 (10.3)

- Comparable rates between treatment arms of any-grade, grade 3-5, and serious AEs
- Most common grade 3/4 AEs in darolutamide arm included neutropenia (33.7%), febrile neutropenia (7.8%), hypertension (6.4%), and anemia (4.8%)
- Similar rates of death due to treatment-emergent AEs (darolutamide arm, 4.1%; placebo arm, 4.0%)

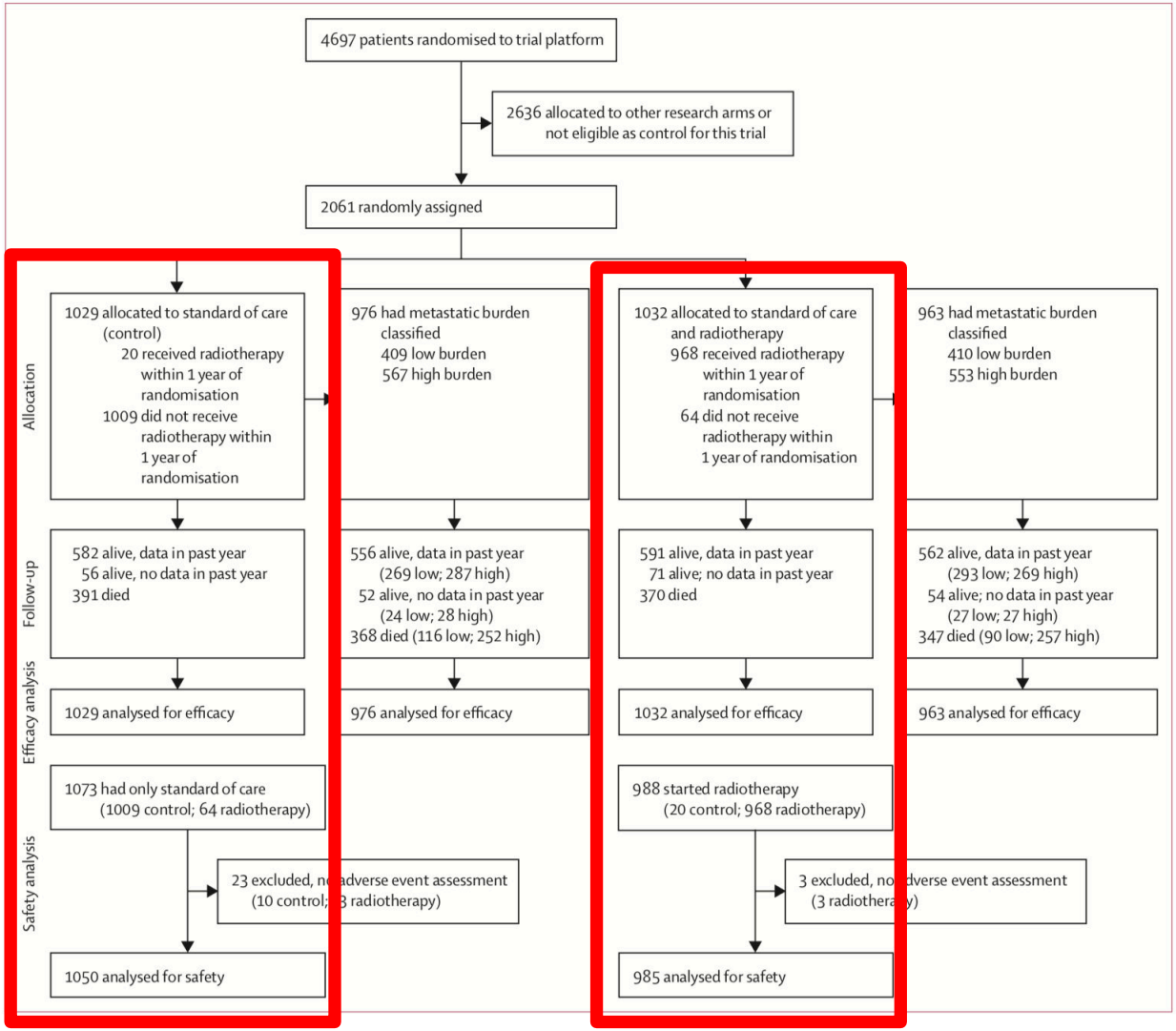
.Smith, M. R. *et al.* Darolutamide and Survival in Metastatic, Hormone-Sensitive Prostate Cancer. *New Engl J Medicine* **386**, 1132–1142 (2022).

Advanced Prostate Cancer: AUA/SUO Guideline

Treatment

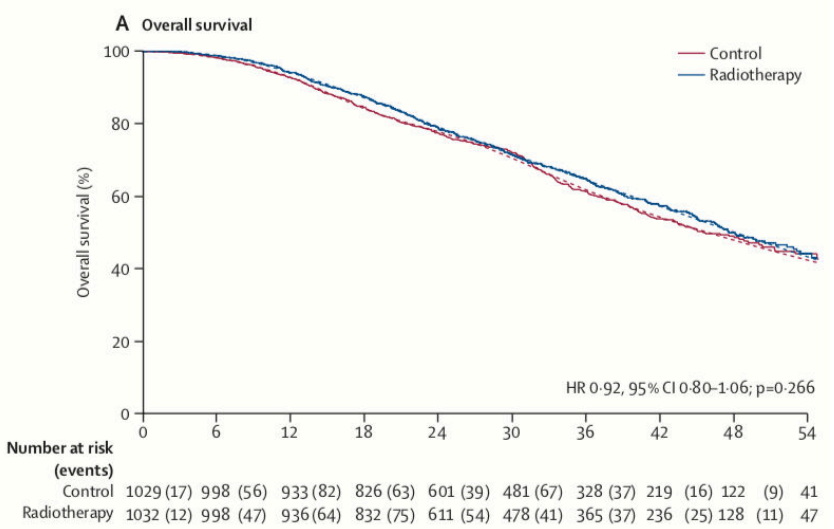
In selected mHSPC patients, clinicians may offer primary radiotherapy to the prostate in combination with ADT with or without androgen receptor pathway inhibitor. (*Conditional Recommendation; Evidence Level: Grade C*)

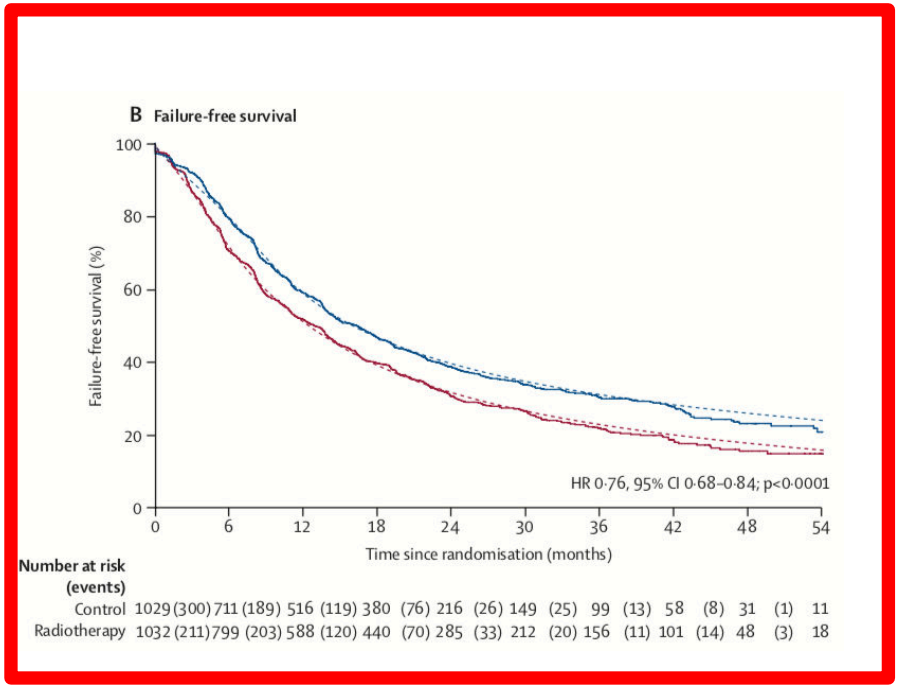
Stampede: ADT +/- RT



Parker C, et al: The Lancet 2018; 392: 2353

Overall Survival and Failure-Free Survival by Treatment (Median f/u 37 mos)



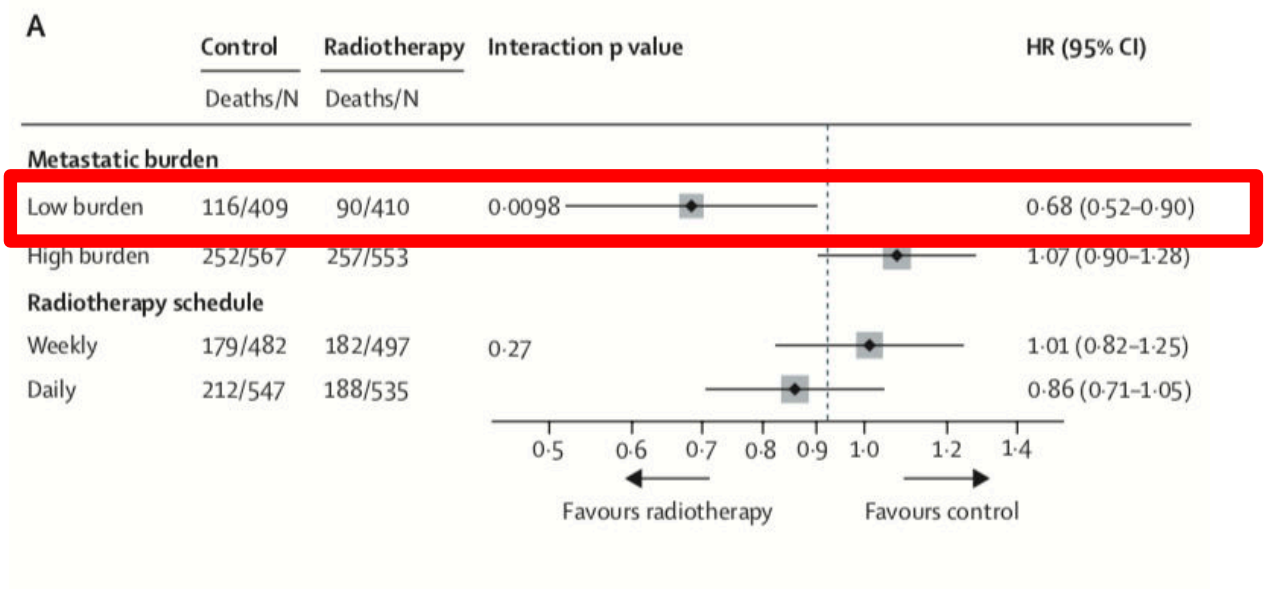


Radiotherapy improved failure-free survival (HR 0·76, 95% CI 0·68–0·84; p<0·0001) but not overall survival (0·92, 0·80–1·06; p=0·266) for unselected men with M1 HSPC

Parker C, et al: The Lancet 2018; 392: 2353

Pre-specified subgroup analysis (CHAARTED definition)

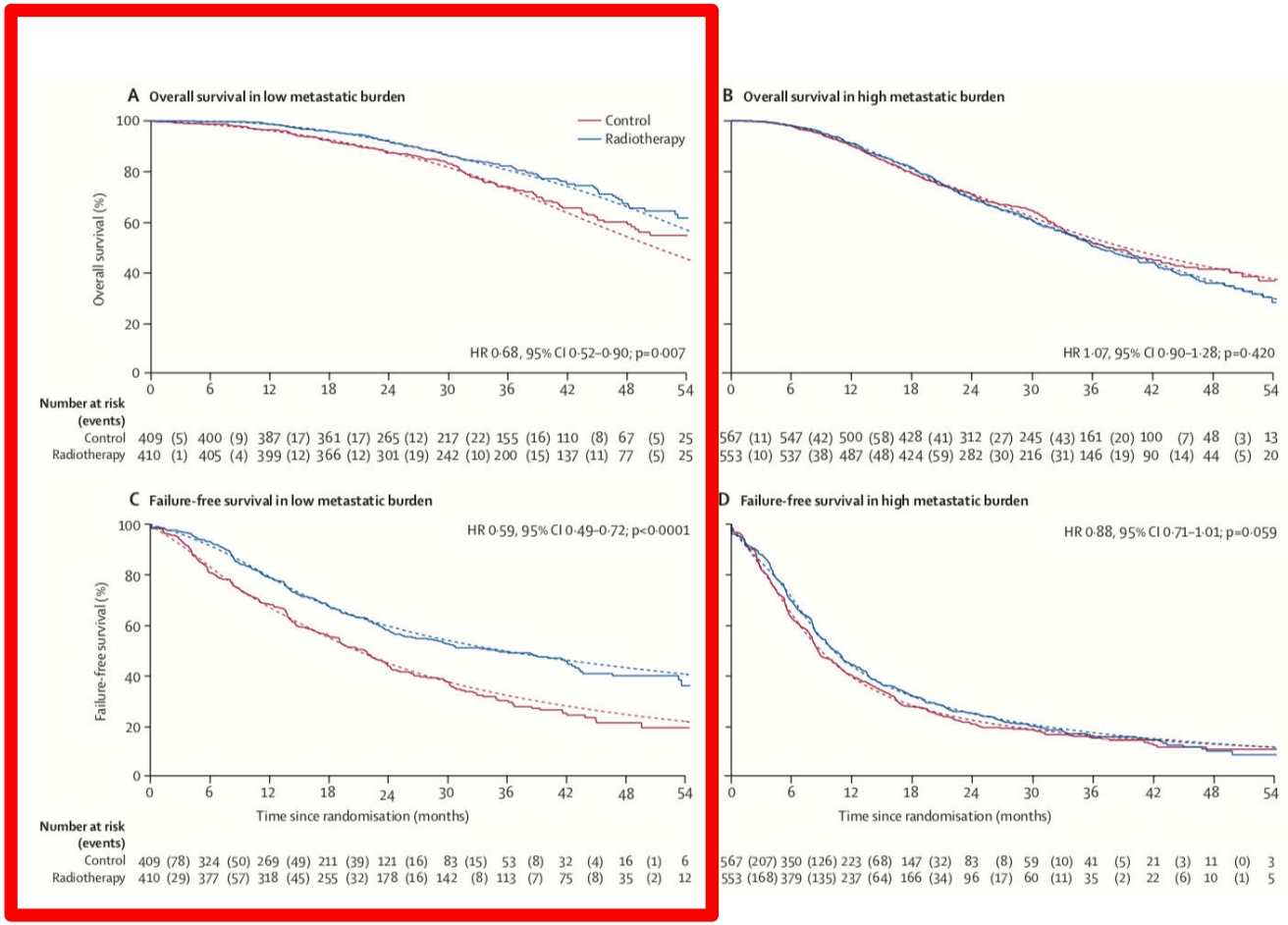
Low volume significant



Parker C, et al: The Lancet 2018; 392: 2353

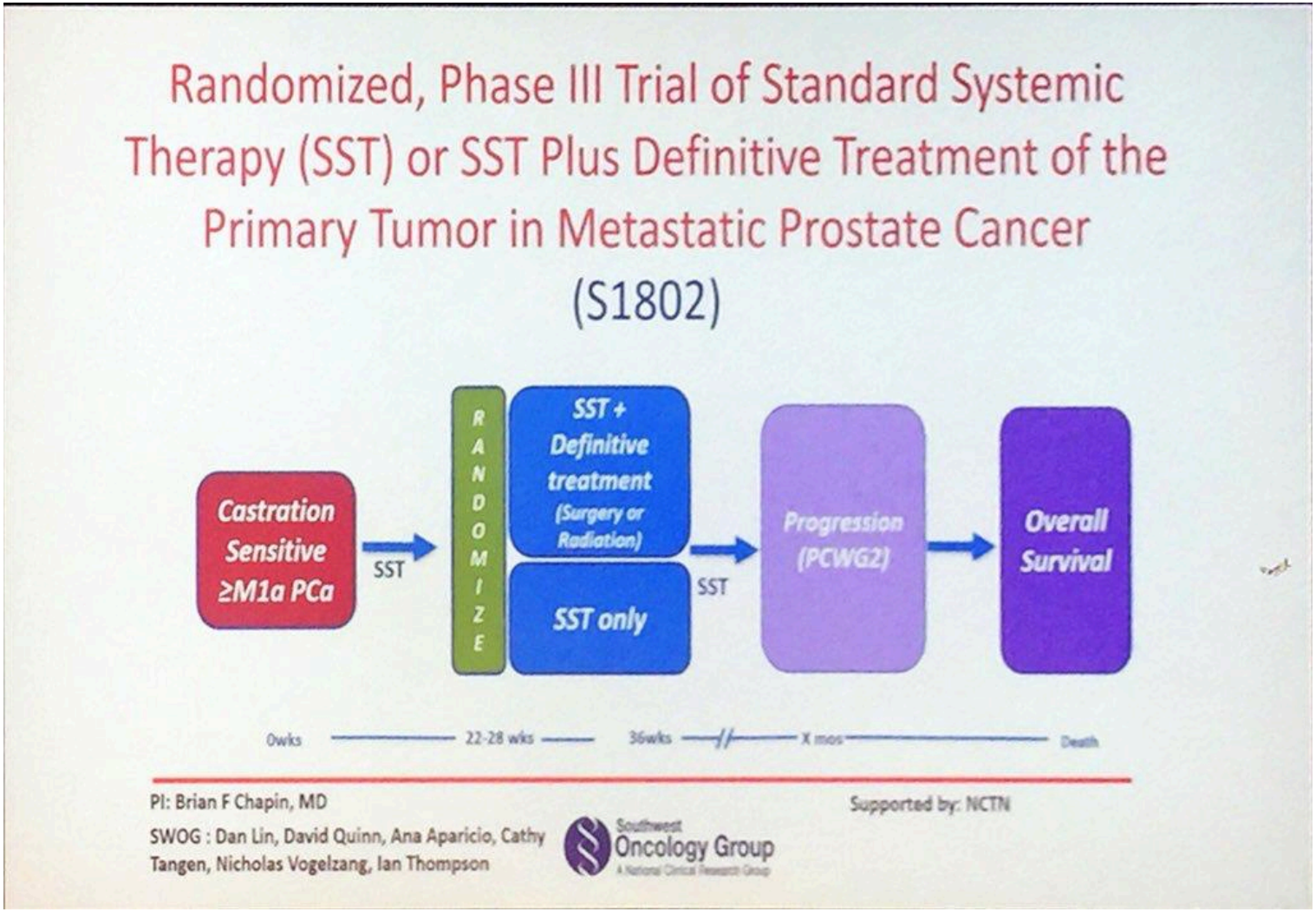
Low vs. High Volume
(CHAARTED definition)

Low volume significant for failure-free and overall survival with RT +ADT



Parker C, et al: The Lancet 2018; 392: 2353

SWOG 1802


Randomized, Phase III Trial of Standard Systemic Therapy (SST) or SST Plus Definitive Treatment of the Primary Tumor in Metastatic Prostate Cancer (S1802)
Castration Sensitive ≥M1a PCa
SST
RANDOMIZE
SST + Definitive treatment (Surgery or Radiation)
SST only
SST
Progression (PCWG2)
Overall Survival
0wks
22-28 wks
36wks
X mos
Death
PI: Brian F Chapin, MD
SWOG : Dan Lin, David Quinn, Ana Aparicio, Cathy Tangen, Nicholas Vogelzang, Ian Thompson
Southwest Oncology Group
A National Clinical Research Group
Supported by: NCTN

Advanced Prostate Cancer: AUA/SUO Guideline

Treatment

In mHSPC patients with BRCA mutations, clinicians may offer the combination of ADT, abiraterone, and a PARP inhibitor. *(Expert Opinion*

Level 1 Evidence for Improved OS in mHSPC

Clinical Trial(s)	Intervention	Control	Comments
STAMPEDE-H	Prostate radiation + ADT (± docetaxel)	ADT (± docetaxel)	Benefit in low-volume subgroup
GETUG-15 CHAARTED STAMPEDE-C	Docetaxel + ADT	ADT	Benefit in high-volume subgroup
LATITUDE STAMPEDE-G	Abiraterone + ADT	ADT	Similar benefits by risk group
ARCHES ENZAMET	Enzalutamide + ADT	ADT	Similar benefits by risk group
TITAN	Apalutamide + ADT	ADT	Similar benefits by risk group
ARANOTE	Darolutamide +ADT	ADT	\\ Similar benefits by risk group
ARASENS	Darolutamide + ADT + docetaxel	ADT + docetaxel	Similar OS benefit for recurrent and de novo metastatic disease
PEACE-1	Abiraterone + ADT + docetaxel (± prostate radiation)	ADT + docetaxel (± prostate radiation)	rPFS benefit for all; OS benefit in high-volume

1. Parker CC et al. *Lancet*. 2018;392:2353-2366. 2. Armstrong AJ et al. *J Clin Oncol*. 2022;40:1616-1622. 3. Davis ID et al. *N Engl J Med*. 2019;381:121-131.
4. James N et al. *Lancet*. 2016;387:1163-1177. 5. Sweeney CJ et al. *N Engl J Med*. 2015;373:737-746. 6. Chi KN et al. *N Engl J Med*. 2019;381:13-24.
7. Fizazi K et al. *N Engl J Med*. 2017;377:352-360. 8. James ND et al. *N Engl J Med*. 2017;377:338-351. 9. Smith MR et al. *N Engl J Med*. 2022;386:1132-1142.
10. Fizazi K et al. *Lancet*. 2022;399:1695-1707.

Take Home Messages: BCR & mHSPC

- High Risk BCR: Improved OS with ADT + Enza vs. ADT alone; Low Risk appropriate for Observation
- Doublet Therapy (ADT + ARPI): SOC with improved OS vs. ADT alone; benefit in both high and low volume mHSPC (ADT + abiraterone) or (ADT + enzalutamide/apalutamide/darolutamide)
- Triplet therapy (ADT+ Doce + ARPI): SOC with OS benefit for adding abiraterone or darolutamide to ADT + docetaxel: may be best in high volume pts
- Treatment of the primary prostate: Improved OS with RT to primary in low volume pts

AUA Advanced Prostate Cancer Guideline Overview 2026

Kristen R. Scarpato MD, MPH, FACS

Vanderbilt University Medical Center

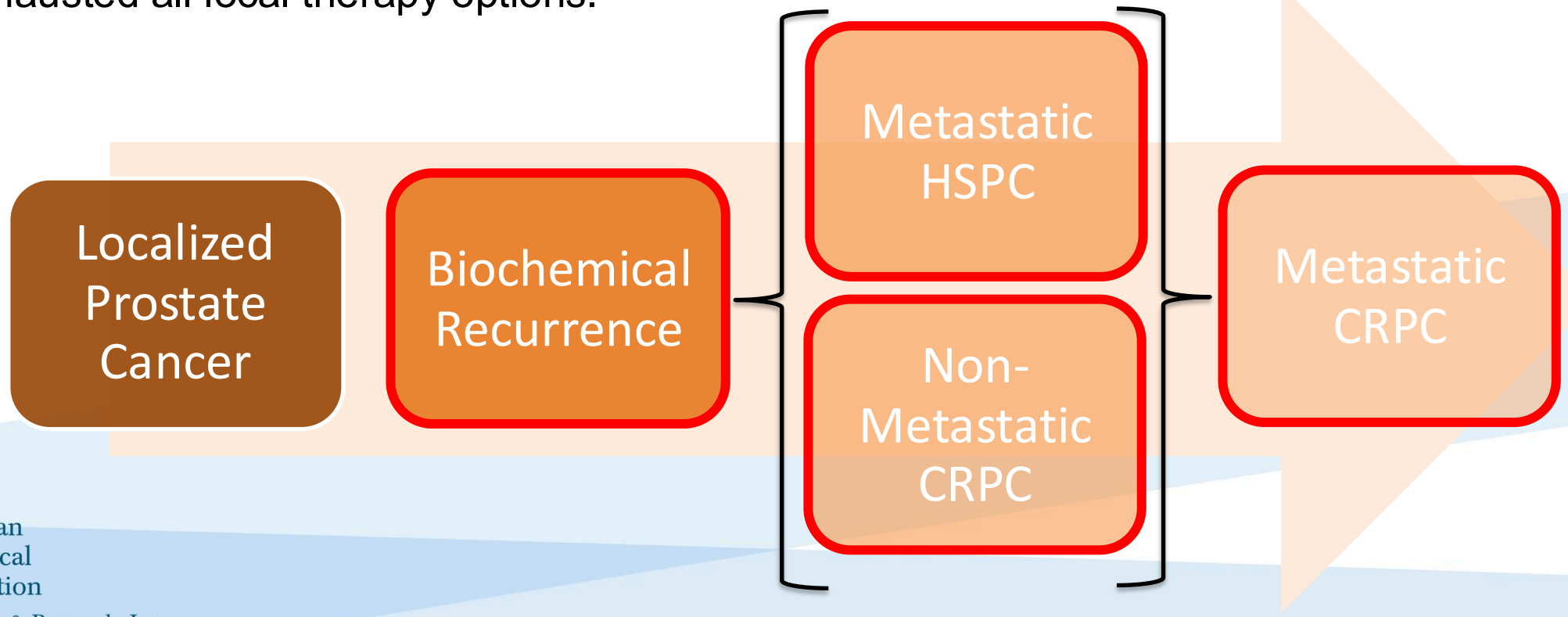
Nashville, TN

American Urological Association

Education & Research, Inc.

ADVANCED PROSTATE CANCER PATIENT POPULATION

The patients discussed are assumed to have exhausted all local therapy options.



KEY DEFINITIONS

Biochemical recurrence without metastatic disease	• a rise in PSA in prostate cancer patients after treatment with surgery or radiation (PSA of 0.2ng/mL and a confirmatory value of 0.2ng/mL or greater following radical prostatectomy and nadir + 2.0ng/mL following radiation); this may occur in patients who do not have symptoms
Hormone-sensitive prostate cancer	• prostate cancer that has either not yet been treated with ADT or is still responsive to ADT
Castration-resistant prostate cancer 	• disease progression despite ADT and a castrate level of testosterone (<50 ng/dL); progression may present as either a continuous rise in serum PSA levels (values identified at a minimum of 1 week intervals with a minimal value of 2.0ng/mL, with estimations of PSADT with at least 3 values measured ≥4 weeks apart), the progression of pre-existing or new radiographic disease, and/or clinical progression with symptoms
High-volume metastatic disease	• presence of visceral metastases and/or greater than or equal to four bone metastases with at least one outside of the vertebral column and pelvis
High-risk metastatic disease	• disease that has a poorer prognosis in the presence of two of the three following high-risk features: Gleason ≥8, ≥3 bone lesions, or measurable visceral metastases

MULTIDISCIPLINARY PATIENT CARE

As the therapeutic landscape evolves to include increasingly complex combinations of systemic therapies with or without local therapies, advances in imaging, and germline and somatic genetic testing, treating men with advanced prostate cancer is increasingly one that must embrace multidisciplinary management approaches.

Multidisciplinary Care Team	
Urologist	Pathologist
Medical Oncologist	Genetic Counselor
Radiation Oncologist	Palliative Care

Disease States of Advance Prostate Cancer

1. Biochemical Recurrence Without Metastatic Prostate Cancer
2. Metastatic Hormone Sensitive Prostate Cancer
3. Non-Metastatic Castration Resistant Prostate Cancer
4. Metastatic Castration Resistant Prostate Cancer

NON-METASTATIC CRPC

DISEASE STATE #3

American Urological Association
Education & Research, Inc.

NON-METASTATIC CRPC

Men with a rising PSA but no visible metastatic disease on conventional imaging despite medical or surgical castration represent a uniquely distinct disease state.

Assessment	Recommended Interval
Serial PSA	3-6 months
Conventional Imaging	6-12 months

NON-METASTATIC CRPC

Prognosis

19. In nmCRPC patients, clinicians should obtain serial PSA measurements at three- to six-month intervals and calculate a PSADT starting at the time of development of castration-resistance. (Clinical Principle)

20. Clinicians should assess nmCRPC patients for development of metastatic disease using conventional imaging or PSMA PET imaging at intervals of 6 to 12 months. (Expert Opinion)

NON-METASTATIC CRPC

Treatment

21. Clinicians should offer apalutamide, darolutamide, or enzalutamide with continued ADT to nmCRPC patients at high risk for developing metastatic disease (PSADT ≤10 months). (Strong Recommendation; Evidence Level Grade A)

22. Clinicians may recommend observation with continued ADT to nmCRPC patients, particularly those at lower risk (PSADT >10 months) for developing metastatic disease. (Clinical Principle)

23. Clinicians should not offer systemic chemotherapy or immunotherapy to nmCRPC patients outside the context of a clinical trial. (Clinical Principle)

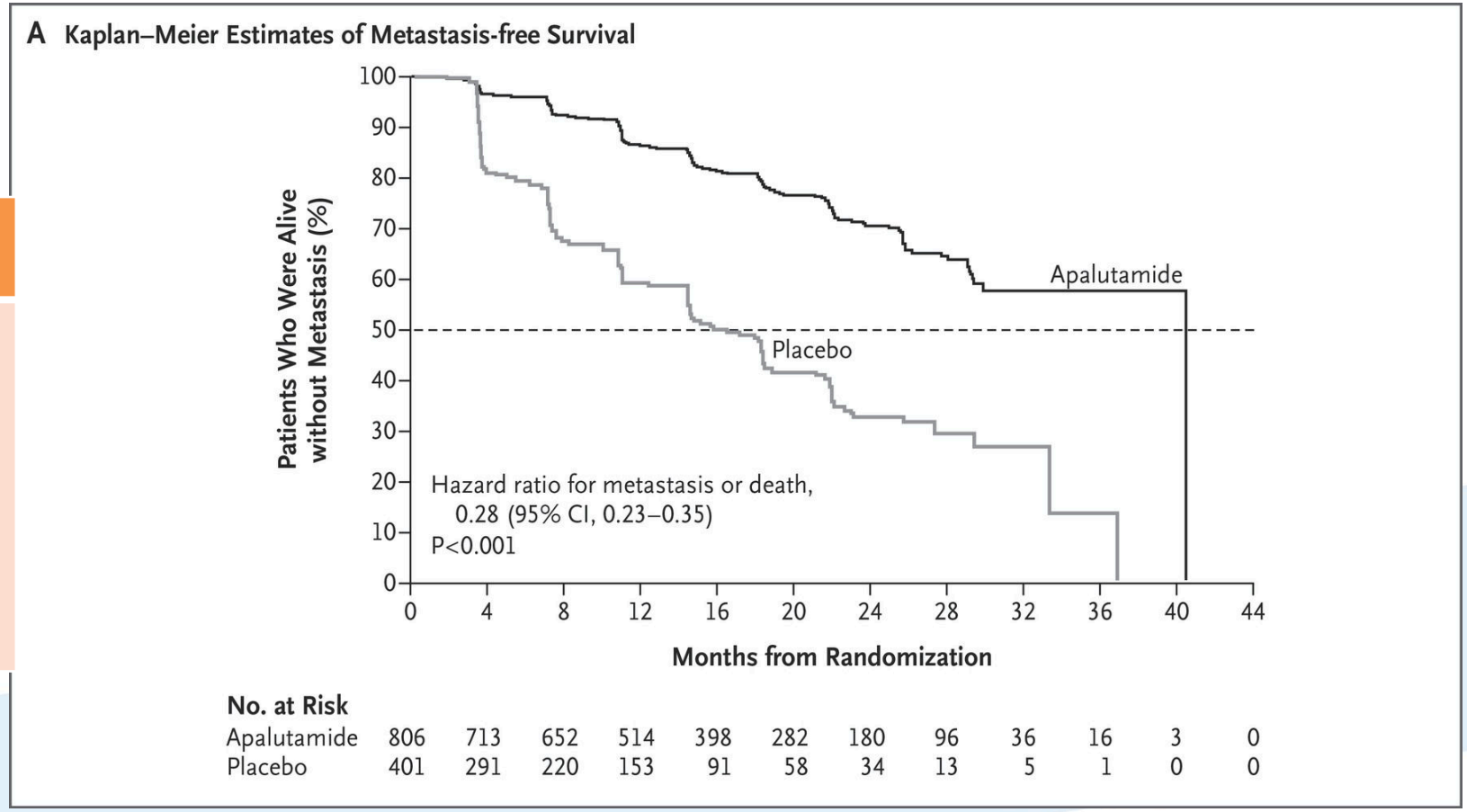
NON-METASTATIC CRPC

There are 3 FDA approved agents for the treatment of men with nmCRPC. These ARPIs successfully prolonged MFS when compared with ADT plus placebo in men with nmCRPC.

- Apalutamide
- Darolutamide
- Enzalutamide

NON-METASTATIC CRPC

Trial	MFS
SPARTAN n=1,207	40.5 months apalutamide 16.2 months placebo

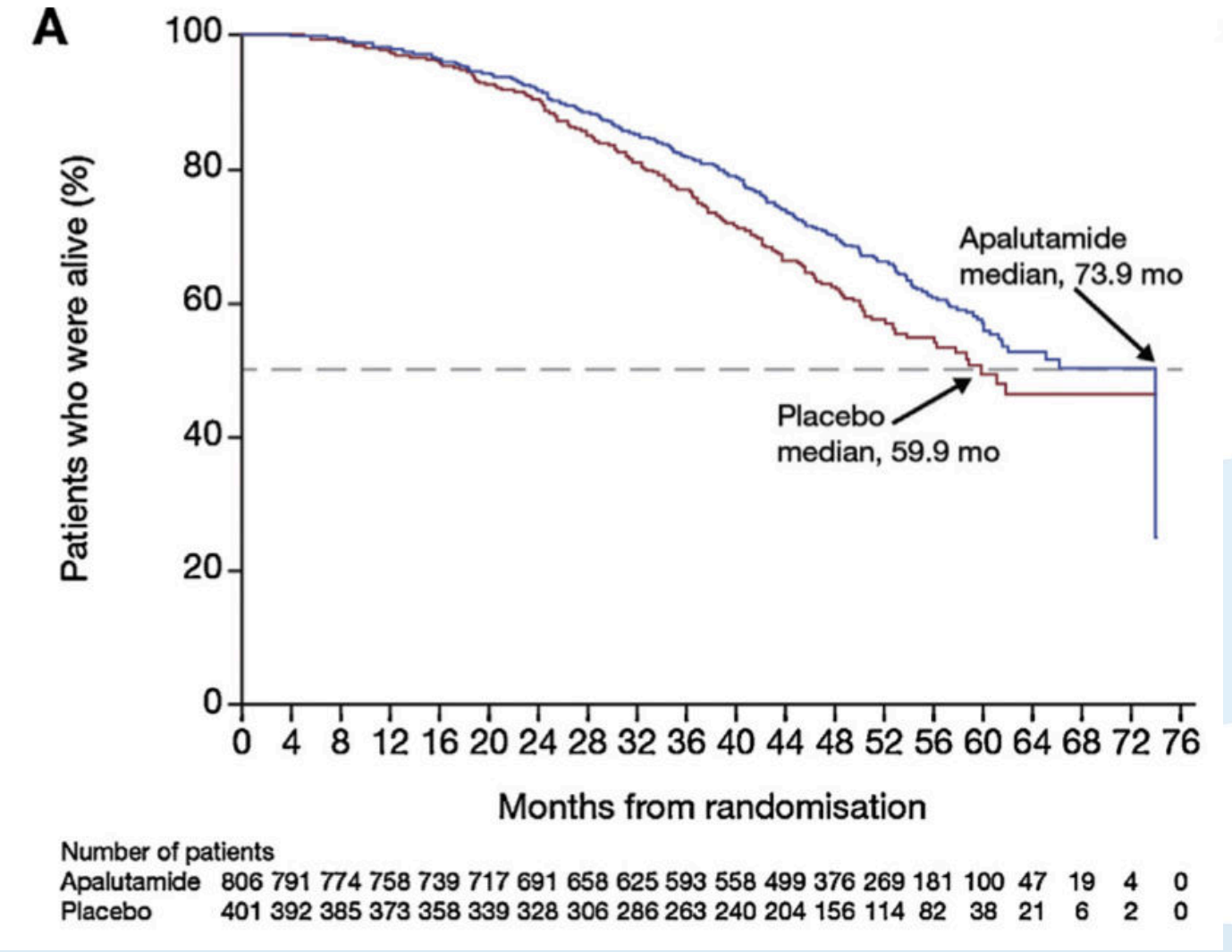


American Urological Association Education & Research, Inc.

Smith MR et al: Apalutamide treatment and metastasis-free survival in prostate cancer. N Engl J Med 2018; 378: 1408.

NON-METASTATIC CRPC

Trial	OS
SPARTAN n=1,207	73.9 months apalutamide 59.5 months placebo

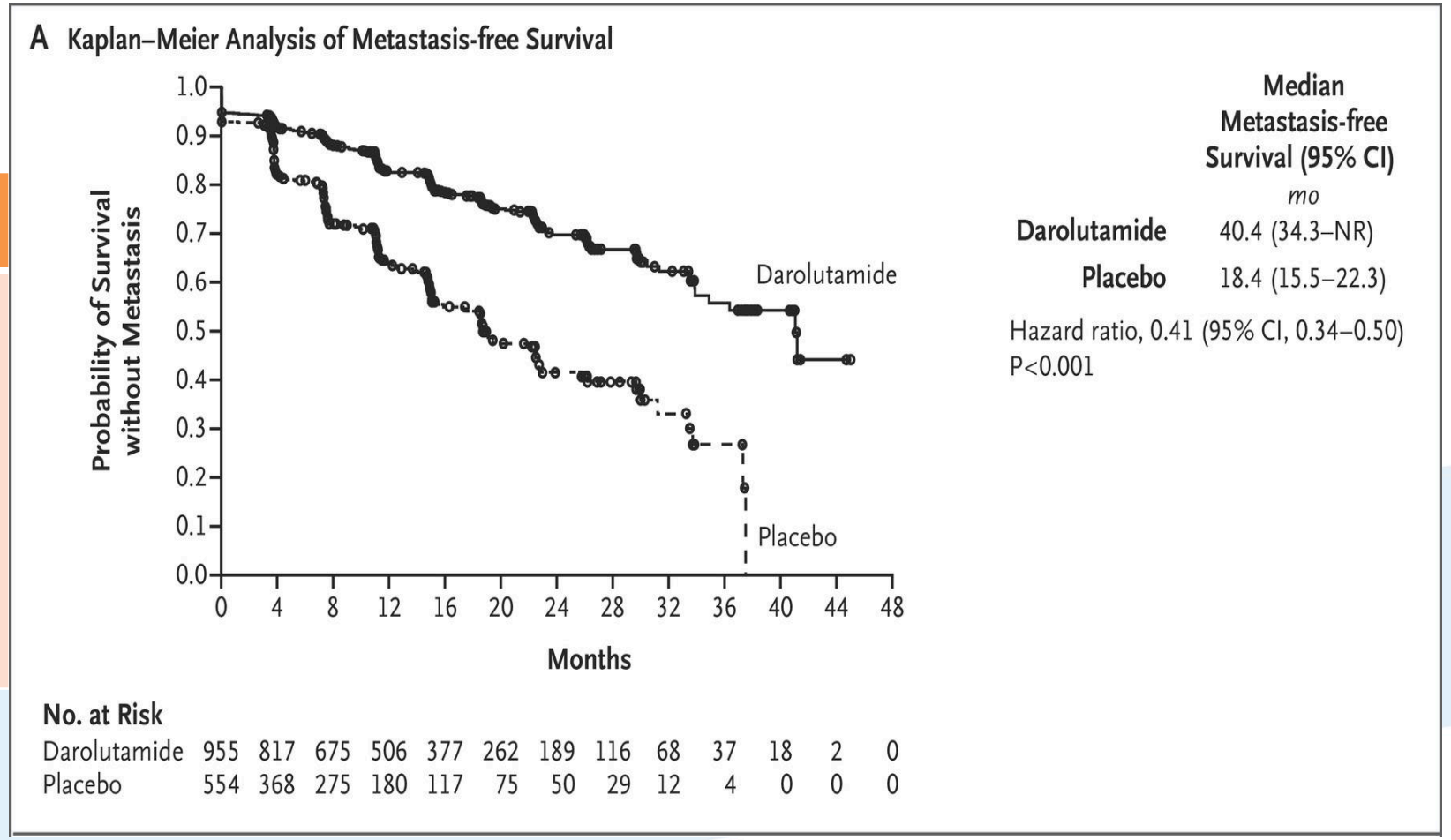


American Urological Association
Education & Research, Inc.

Smith MR et al: Apalutamide and overall survival in prostate cancer. Eur Urol 2020;79:150

NON-METASTATIC CRPC

Trial	MFS
ARAMIS n= 1,509	40.4 months darolutamide 18.4 months placebo

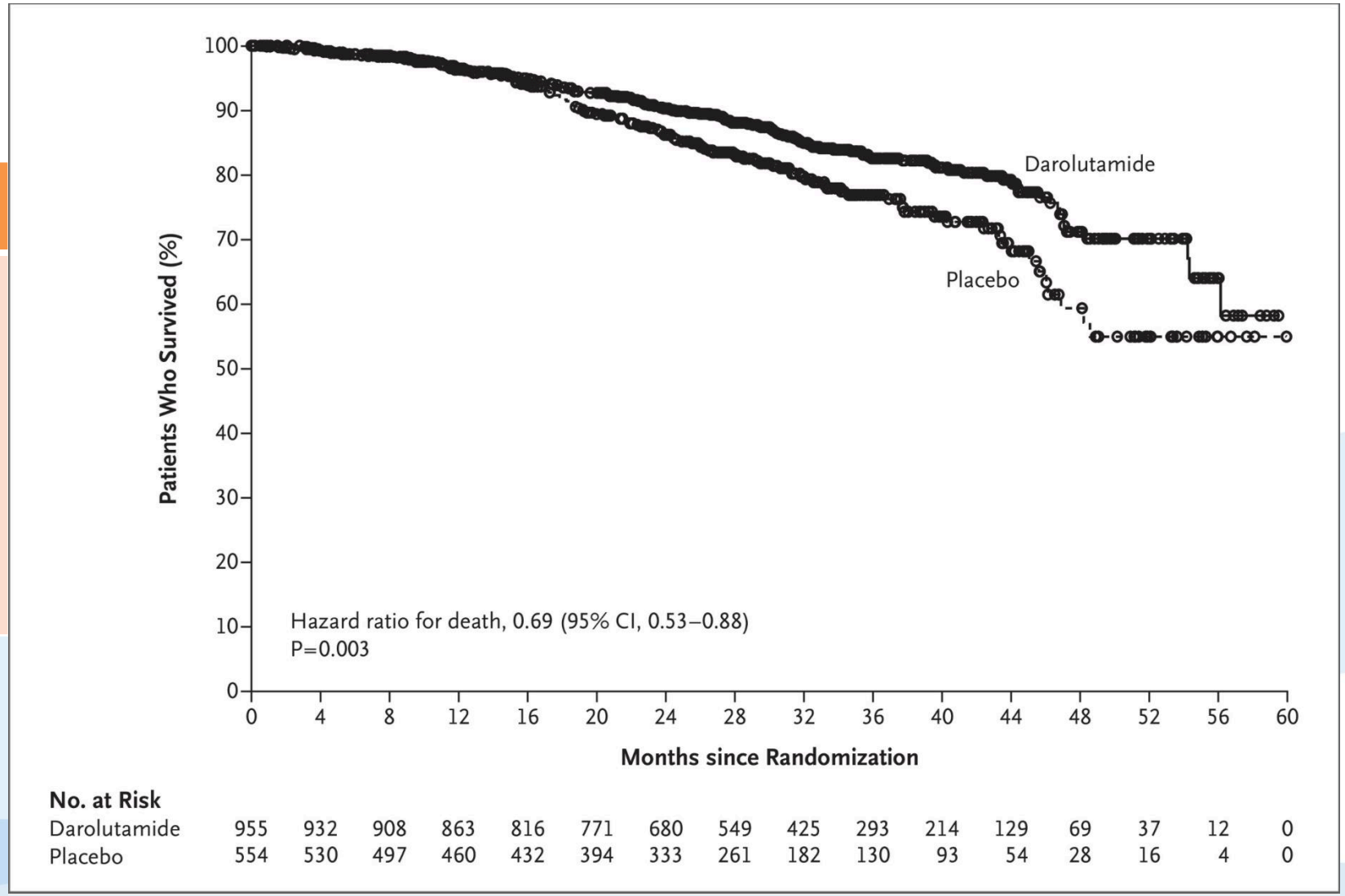


American Urological Association Education & Research, Inc.

Fizazi K et al: Darolutamide in nonmetastatic, castration-resistant prostate cancer. N Engl J Med 2019; 380:1235.

NON-METASTATIC CRPC

Trial	3-yr OS
ARAMIS n= 1,509	83% darolutamide 77% placebo

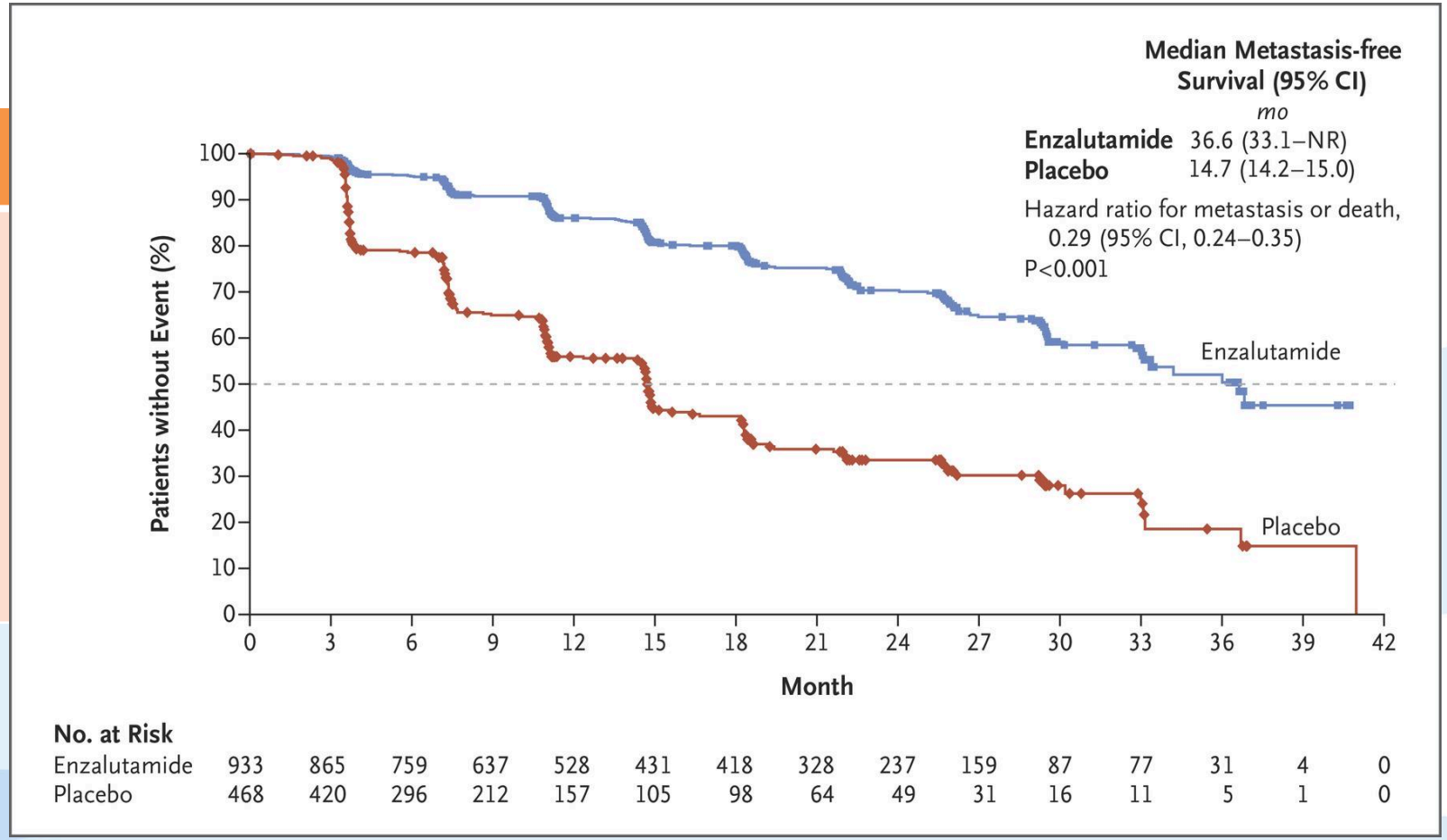


American Urological Association Education & Research, Inc.

Fizazi K et al: Darolutamide in nonmetastatic, castration-resistant prostate cancer. N Engl J Med 2020; 383:1040.

NON-METASTATIC CRPC

Trial	MFS
PROSPER n=1,401	36.6 months enzalutamide 14.7 months placebo

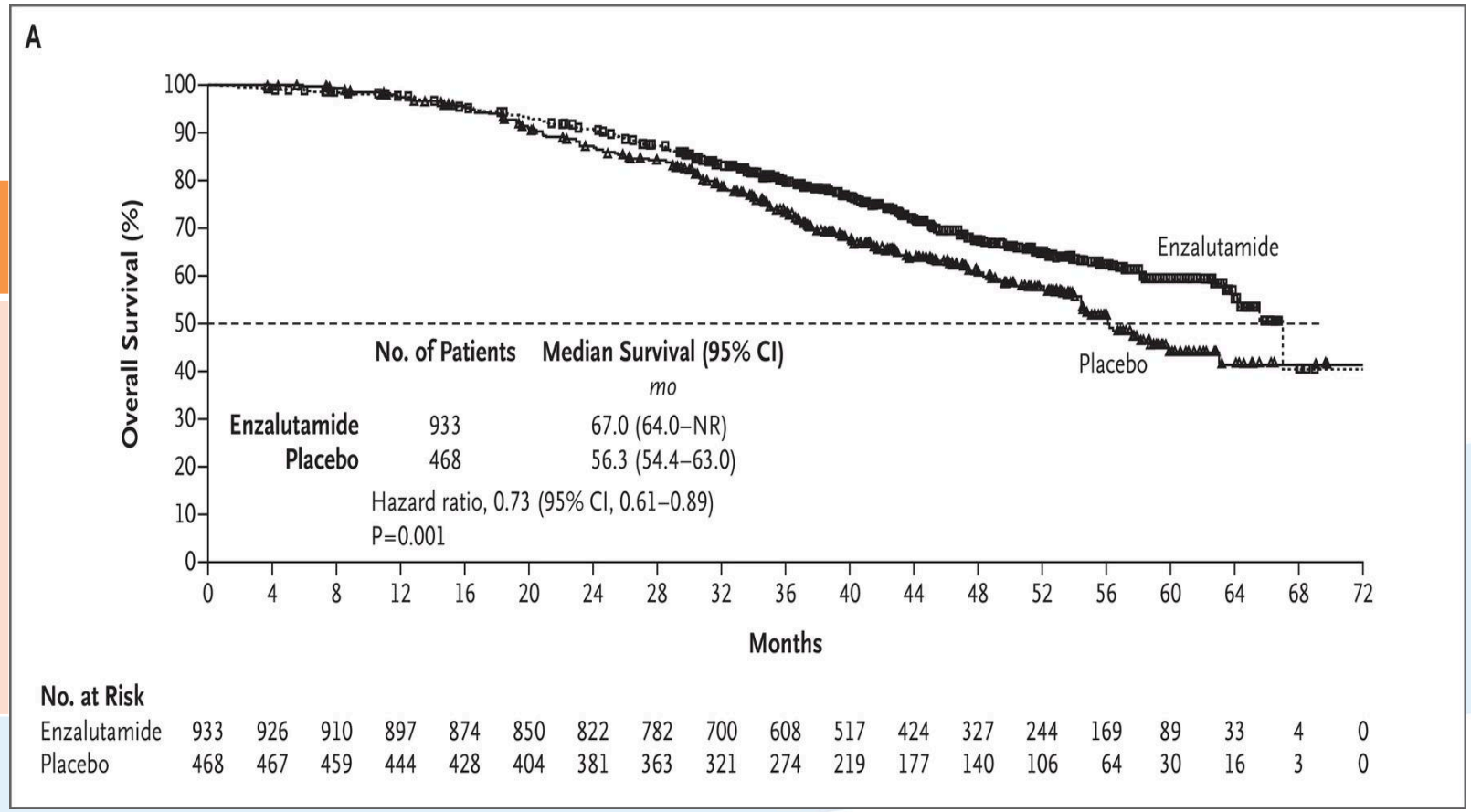


American Urological Association Education & Research, Inc.

Hussain M et al: Enzalutamide in men with nonmetastatic, castration-resistant prostate cancer. N Engl J Med 2018; 378: 2465.

NON-METASTATIC CRPC

Trial	OS
PROSPER n=1,401	67.0 months enzalutamide 56.3 months placebo



Sternberg CN et al: Enzalutamide and survival in nonmetastatic, castration-resistant prostate cancer. N Engl J Med 2020;382:2197

METASTATIC CRPC

DISEASE STATE #4

American Urological Association
Education & Research, Inc.

METASTATIC CRPC

Prognostic Assessment

Baseline labs

- PSA
- Testosterone
- LDH
- Hgb
- Alkaline phosphatase

Disease-related symptoms

Performance status

Conventional imaging

Germline/somatic tumor testing

METASTATIC CRPC: Performance Status

ECOG PERFORMANCE STATUS*	
Grade	**ECOG**
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

* As published in Am. J. Clin. Oncol.:

Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

METASTATIC CRPC

Prognosis

24. In mCRPC patients, clinicians should obtain baseline labs (e.g., PSA, testosterone, LDH, Hgb, alkaline phosphatase level) and review location of metastatic disease (lymph node, bone, visceral), disease-related symptoms, and performance status to inform discussions of prognosis and treatment decision-making. (*Clinical Principle*)

25. In mCRPC patients without PSA progression or new symptoms, clinicians should perform imaging at least annually. (Expert Opinion)

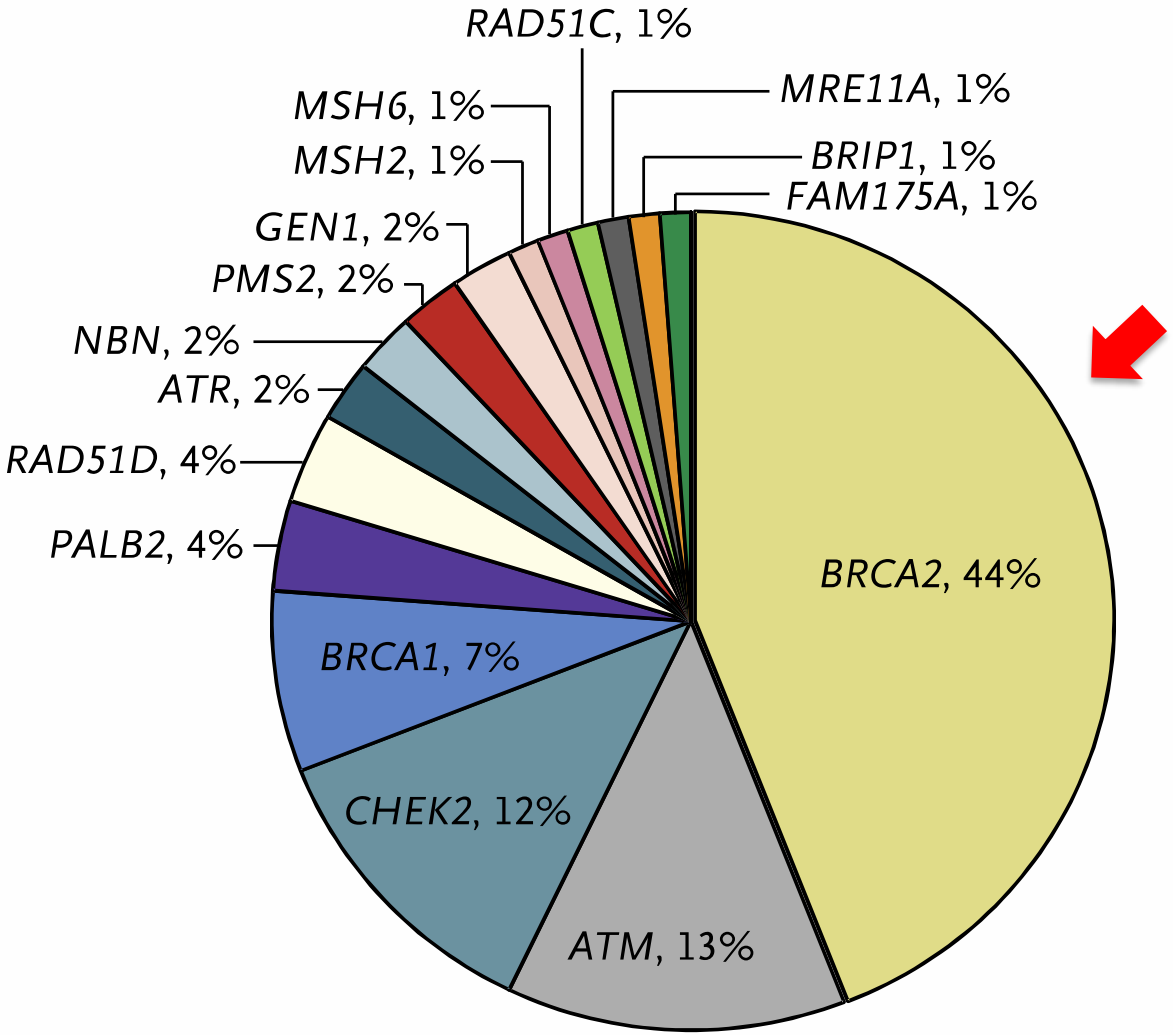
26. In mCRPC patients with disease progression (PSA or radiographic progression or new disease related symptoms) having previously received ~~docetaxel and~~ androgen pathway inhibitor, who are considering 177Lu-PSMA-617, clinicians should order PSMA PET imaging. (Expert Opinion)

UPDATE

GERMLINE TESTING

27. In patients with mCRPC, clinicians should offer germline (if not already performed) and somatic genetic testing to identify DNA repair deficiency, microsatellite instability (MSI) status, tumor mutational burden, and other potential mutations that may inform prognosis and familial cancer risk as well as direct potential targeted therapies. (Clinical Principle)

DNA Repair Gene Alterations are common in Metastatic Pca (Germline)



ORIGINAL ARTICLE

Inherited DNA-Repair Gene Mutations in Men with Metastatic Prostate Cancer

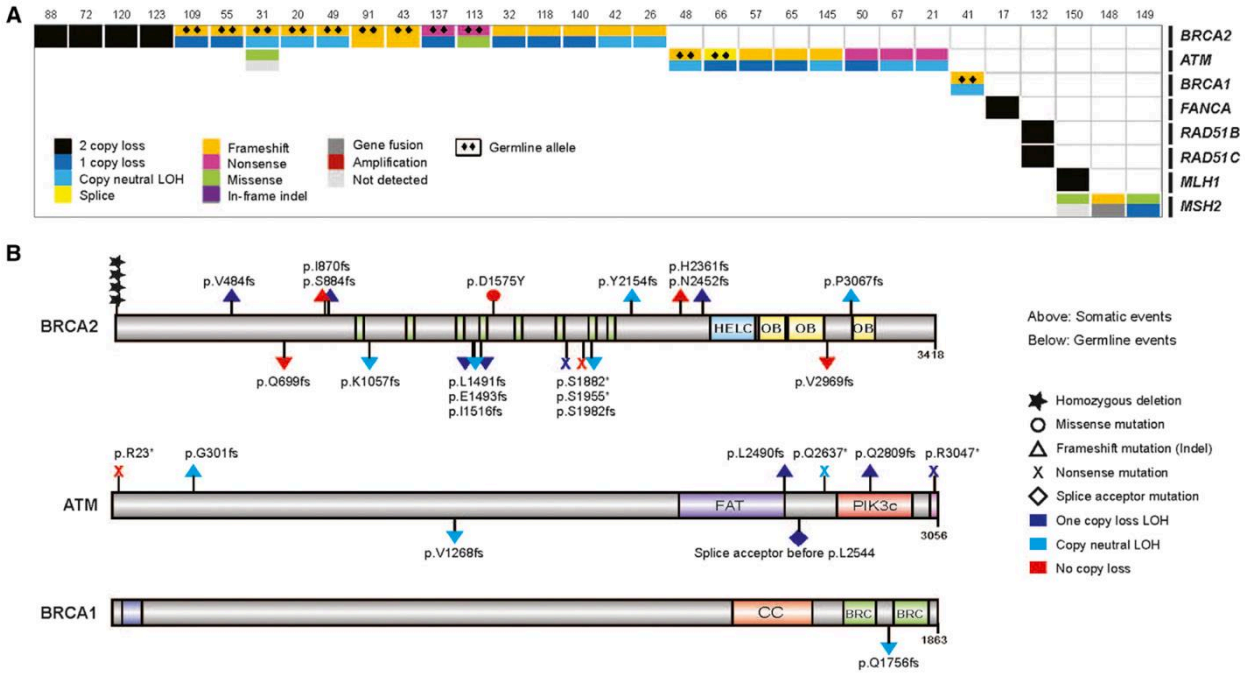
C.C. Pritchard, J. Mateo, M.F. Walsh, N. De Sarkar, W. Abida, H. Beltran, A. Garofalo, R. Gulati, S. Carreira, R. Eeles, O. Elemento, M.A. Rubin, D. Robinson, R. Lonigro, M. Hussain, A. Chinnaiyan, J. Vinson, J. Filipenko, L. Garraway, M.-E. Taplin, S. AlDubayan, G.C. Han, M. Beightol, C. Morrissey, B. Nghiem, H.H. Cheng, B. Montgomery, T. Walsh, S. Casadei, M. Berger, L. Zhang, A. Zehir, J. Vijai, H.I. Scher, C. Sawyers, N. Schultz, P.W. Kantoff, D. Solit, M. Robson, E.M. Van Allen, K. Offit, J. de Bono, and P.S. Nelson

- 692 men with metastatic PCA
- Sequenced their genome
- 84 germline DNA-repair gene mutations
- **82 men (11.8%)**
- Mutations were found in 16 genes

N Engl J Med. 2016;375(5):443-453.

DNA Repair Gene Alterations are common in Metastatic Pca (Somatic)

- Of mCRPCs, 23% harbor DNA repair alterations
- **The frequency of DNA repair alterations increases with disease progression (metastatic vs. local)**



Cell 2015;161:1215-1228

METASTATIC CRPC

Since the approval of docetaxel, multiple additional agents that show a survival benefit have been FDA-approved on the basis of RCTs. These agents have been tested in multiple "disease states" of mCRPC, both before and after docetaxel chemotherapy, to determine when patients might benefit from each treatment.

Continued ADT +

- Abiraterone
- Enzalutamide
- Docetaxel
- Sipuleucel-T
- Radium-223
- Lutetium
- Cabazitaxel
- Platinum-based chemotherapy
- PARP inhibitors
- Pembrolizumab

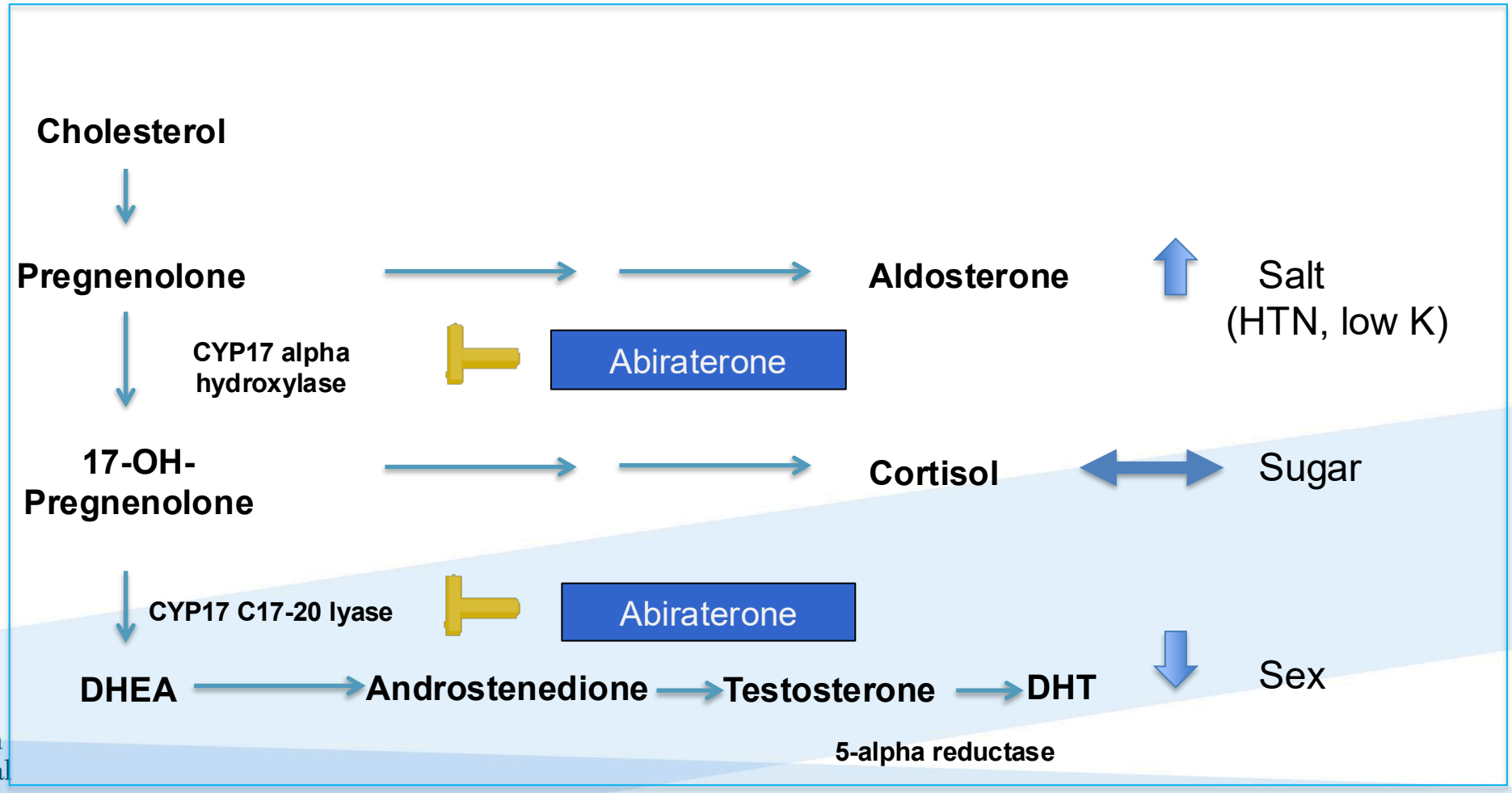
METASTATIC CRPC

Treatment

28. For most patients progressing to mCRPC who have not received prior androgen receptor pathway inhibitors, clinicians should offer continued ADT with abiraterone acetate plus prednisone or enzalutamide. (Strong Recommendation; Evidence Level: Grade A [abiraterone acetate plus prednisone and enzalutamide]

For patients who have received prior ARPI, continued ADT with docetaxel is an option. (Recommendation: Grade B)

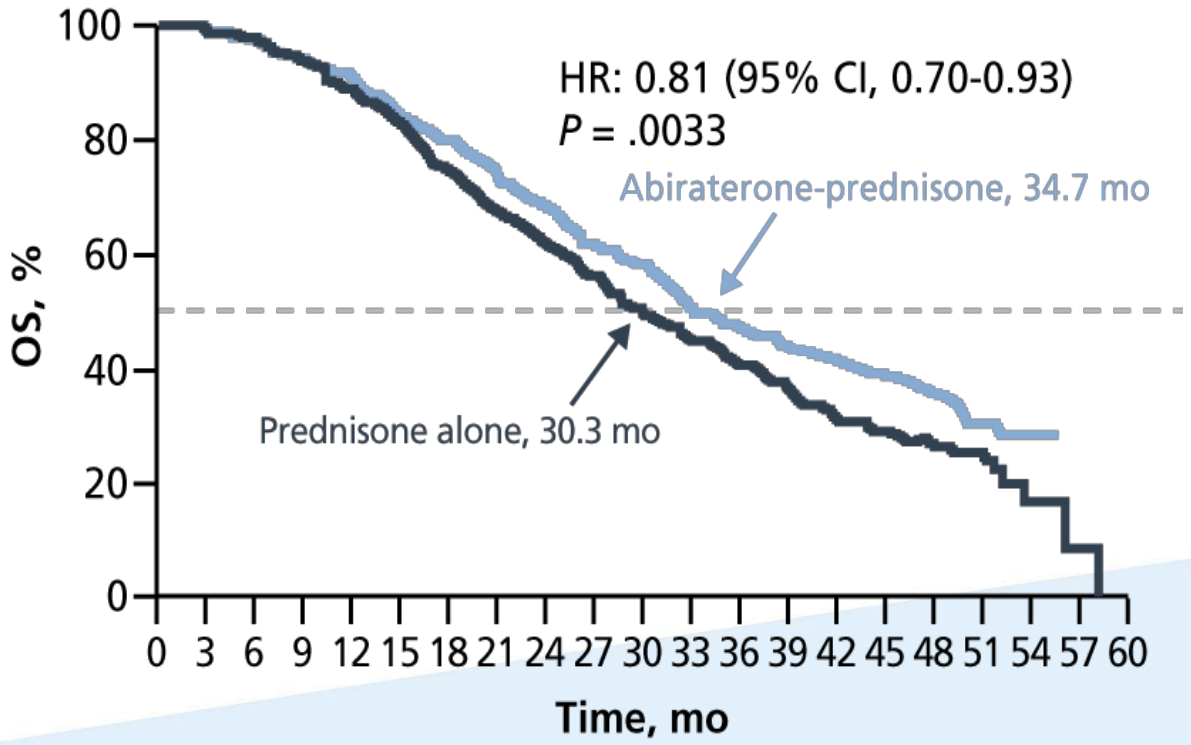
ABIRATERONE MECHANISM



De Bono JS et al. *N Engl J Med*. 2011
Ryan et al. 2012

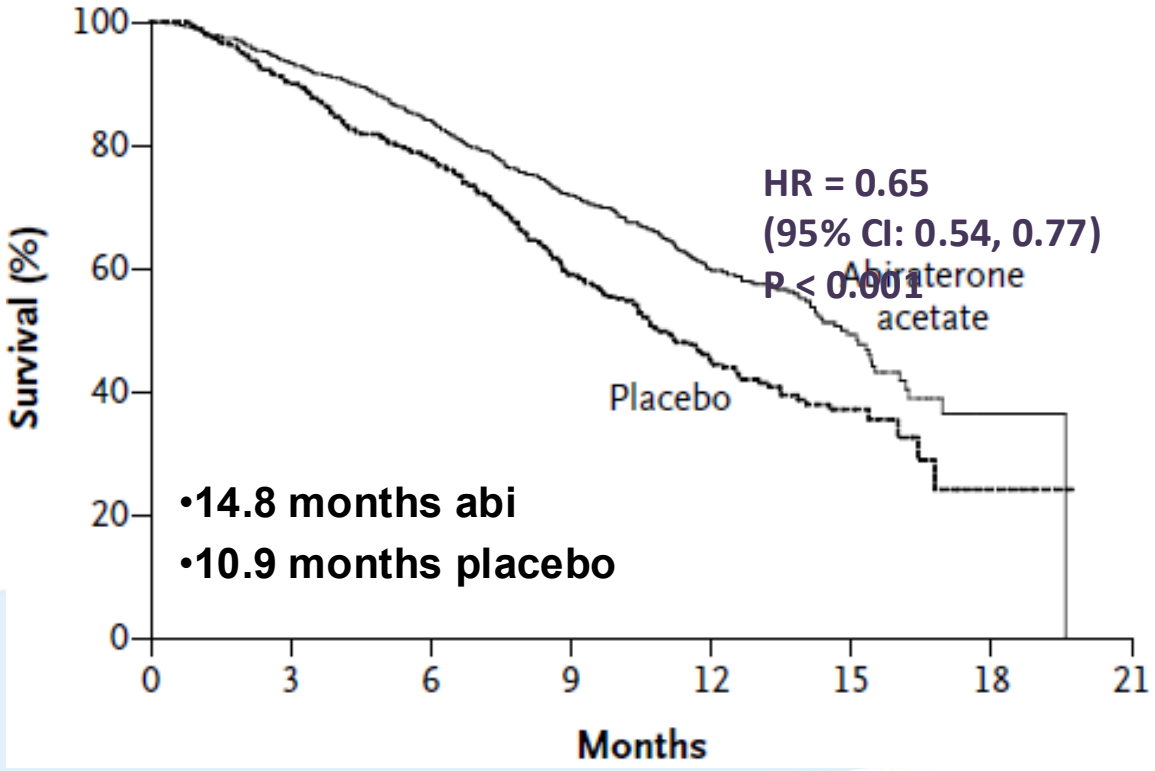
ABIRATERONE ACETATE: Pre & Post-Chemo

PRE CHEMO (COU-AA-302)



Ryan CJ et al Lancet Oncol 2015;16:152.

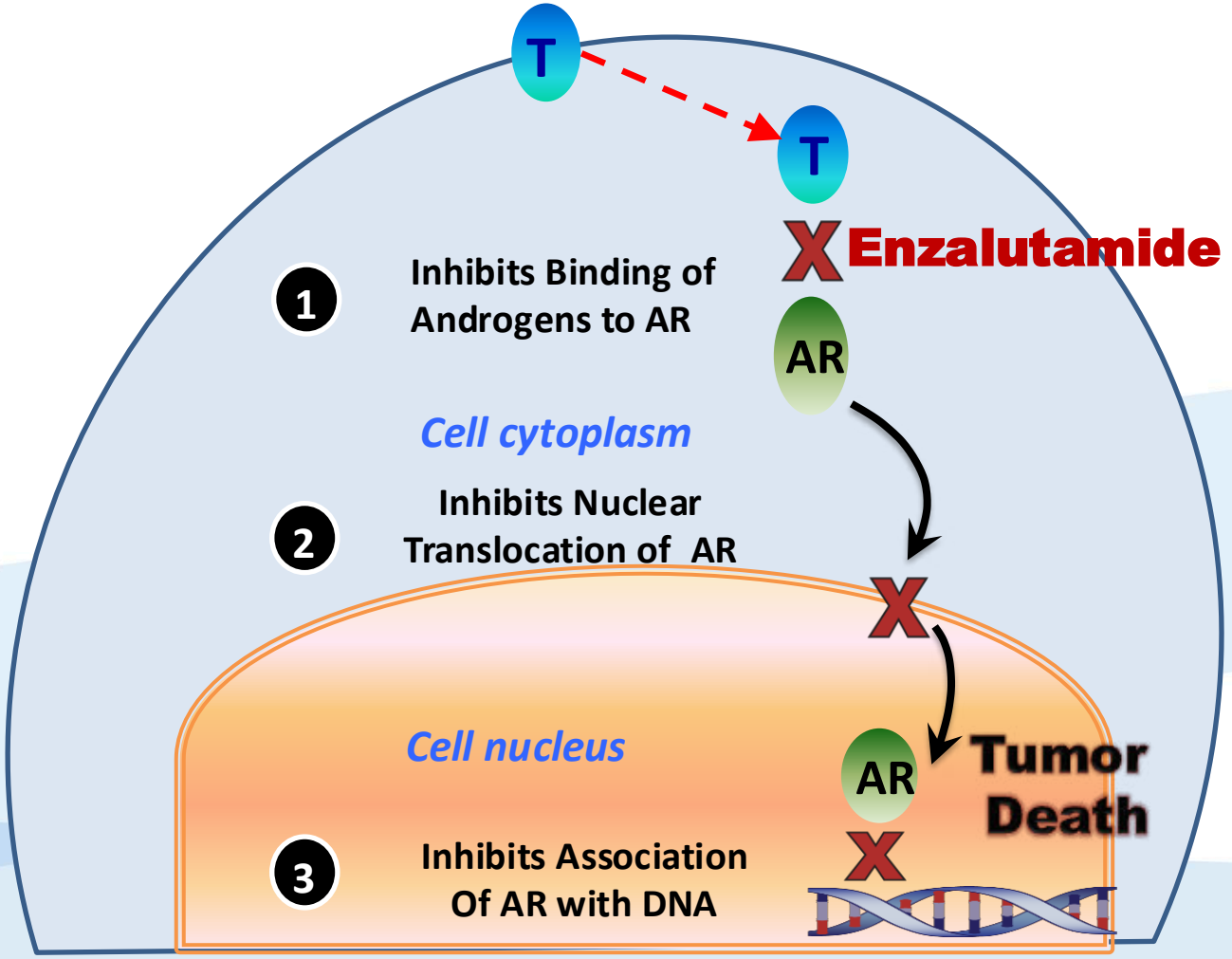
POST –CHEMO (COU-AA-301)



de Bono et al. NEJM 2011

ENZALUTAMIDE: AR Signaling Inhibitor

- Oral drug designed to target AR signaling
- Impacts multiple steps in AR signaling pathway.
- Apalutamide and Daralutamide have similar mechanism of action

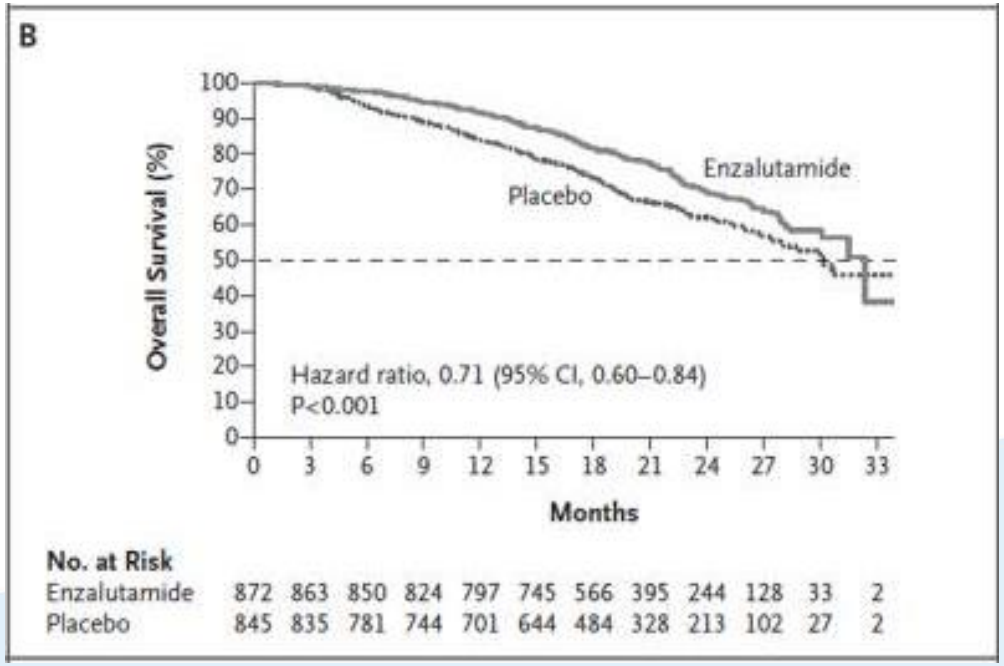


American Urological Association Education & Research, Inc.

Tran et al. Science 2009;324:787–90.

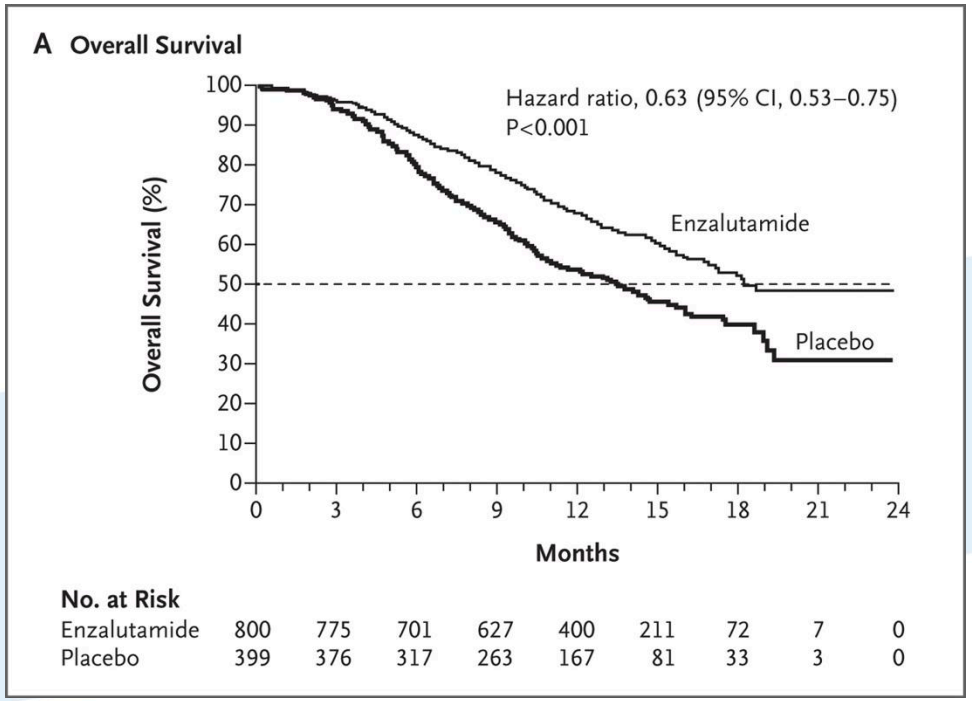
ENZALUTAMIDE: Pre & Post-Chemo

Trial	Overall Survival
PREVAIL n=1,717	32.4 months enzalutamide 30.2 months placebo



Beer TM et al: N Engl J Med. 2014;371:424.

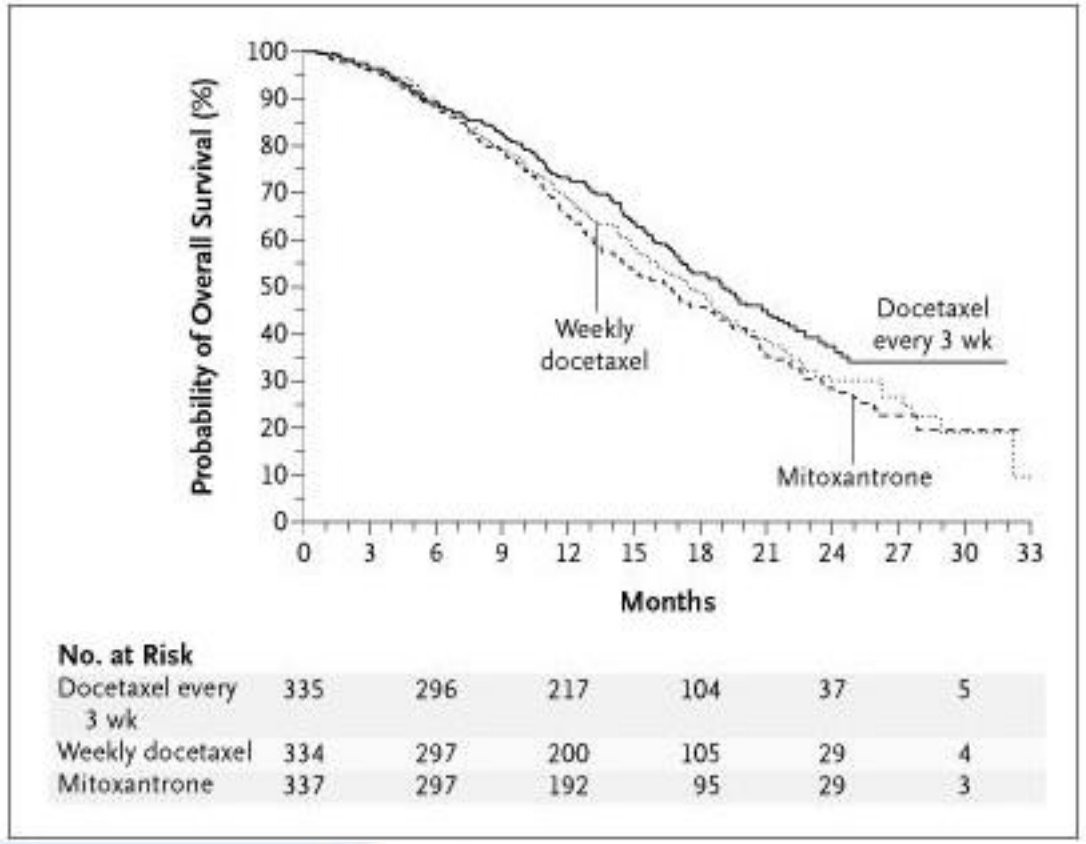
Trial	Overall Survival
AFFIRM n=1,199	18.4 months enza 13.6 months placebo



Scher HI et al: N Eng J Med 2012; 367: 1187.

DOCETAXEL: First-Line Chemotherapy

Trial	Overall Survival
TAX-327 n=1,006 First-line therapy	A: 18.9 months docetaxel (every 3 weeks) B: 17.4 months docetaxel (weekly) C: 16.5 months mitoxantrone
	A+C: HR=0.76; 95%CI 0.62 to 0.94 P=0.009 B+C: HR=0.91; 95%CI 0.75 to 1.11 P=0.36



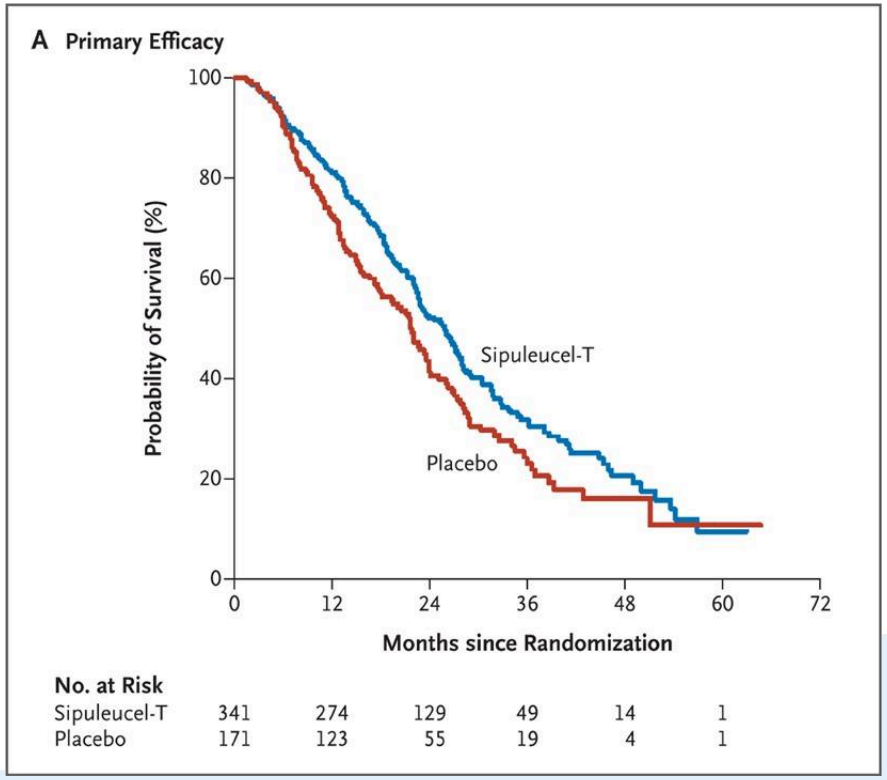
American Urological Association Education & Research, Inc.

Tannock IF et al: Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Eng J Med 2004; 351: 1502.

METASTATIC CRPC

29. In mCRPC patients who are asymptomatic or minimally symptomatic, clinicians may offer sipuleucel-T. (Conditional Recommendation; Evidence Level: Grade B)

SIPULEUCEL-T: Pre-Chemotherapy



Trial	Overall Survival
IMPACT n=512	25.8 months sipuleucel-T 21.7 months placebo
	HR= 0.78; 95%CI 0.61 to 0.98 P=0.03

American Urological Association Education & Research, Inc.

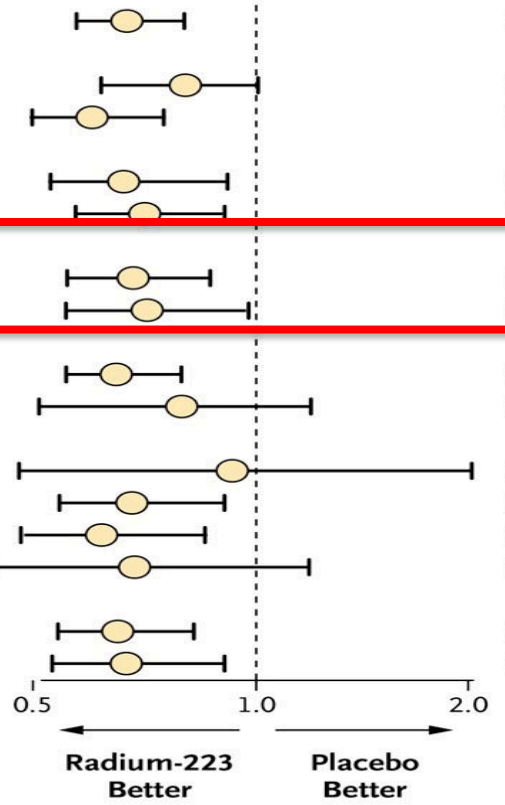
Kantoff PW et al: Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med 2010; 363: 411.

METASTATIC CRPC

30. Clinicians should offer radium-223 to patients with symptoms from bony metastases from mCRPC and without known visceral disease or lymphadenopathy >3cm. (Strong Recommendation; Evidence Level: Grade B)

RADIUM-223

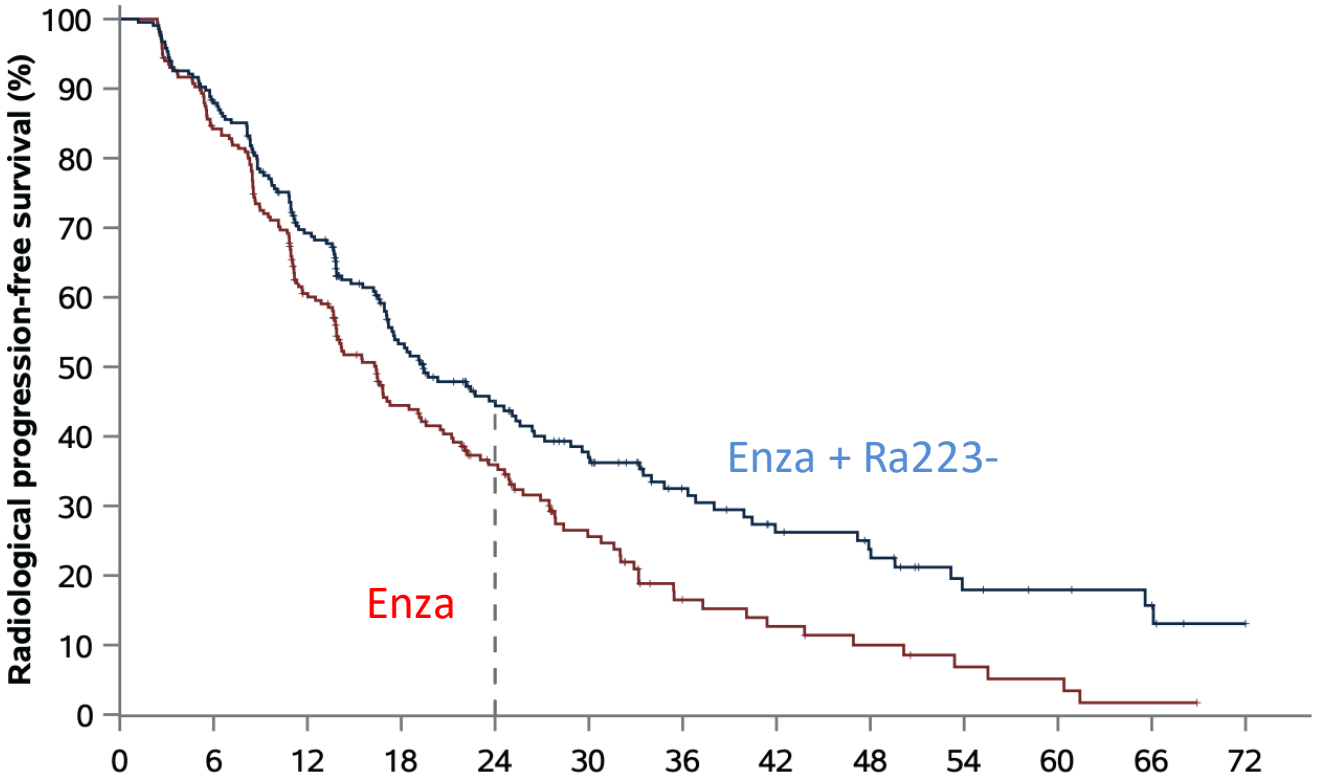
Subgroup	Radium-223	Placebo	Radium-223	Placebo	Hazard Ratio (95% CI)
	no. of patients		*median overall survival (mo)*		
All patients	614	307	14.9	11.3	0.70 (0.58–0.83)
Total ALP level at baseline					
<220 U/liter	348	169	17.0	15.8	0.82 (0.64–1.07)
≥220 U/liter	266	138	11.4	8.1	0.62 (0.49–0.79)
Current bisphosphonate use					
Yes	250	124	15.3	11.5	0.70 (0.52–0.93)
No	364	183	14.5	11.0	0.74 (0.59–0.92)
Previous docetaxel use					
Yes	352	174	14.4	11.3	0.71 (0.56–0.89)
No	262	133	16.1	11.5	0.74 (0.56–0.99)
Baseline ECOG performance-status score					
0 or 1	536	265	15.4	11.9	0.68 (0.56–0.82)
≥2	77	41	10.0	8.4	0.82 (0.50–1.35)
Extent of disease					
<6 metastases	100	38	27.0	NE	0.95 (0.46–1.95)
6–20 metastases	262	147	13.7	11.6	0.71 (0.54–0.92)
>20 metastases	195	91	12.5	9.1	0.64 (0.47–0.88)
Superscan	54	30	11.3	7.1	0.71 (0.40–1.27)
Opioid use					
Yes	345	168	13.9	10.4	0.68 (0.54–0.86)
No	269	139	16.4	12.8	0.70 (0.52–0.93)



American Urological Association Education & Research, Inc.

Parker C et al: Alpha emitter radium-223 and survival in metastatic prostate cancer. N Engl J Med 2013; 369: 213.

Enzalutamide plus radium-223 in metastatic castration-resistant prostate cancer: results of the EORTC 1333/PEACE-3 trial



Patients at risk

Enza-	224	180	122	77	52	28	13	10	7	4	3	1	0
Enza + Ra223-	222	188	138	91	64	48	32	23	19	11	9	7	3

No. cumulative events

Enza-	0	34	84	114	128	141	150	153	155	157	158	160	160
Enza + Ra223-	0	26	65	94	107	118	123	129	131	135	135	136	137

rPFS 19.4 mos vs 16.4 mos
HR 0.69, (95%CI 0.54-0.87)
P 0.0009

2yr rPFS 36% vs. 45%

Ann Oncol. 2025;36(9):1058-1067

METASTATIC CRPC

UPDATE

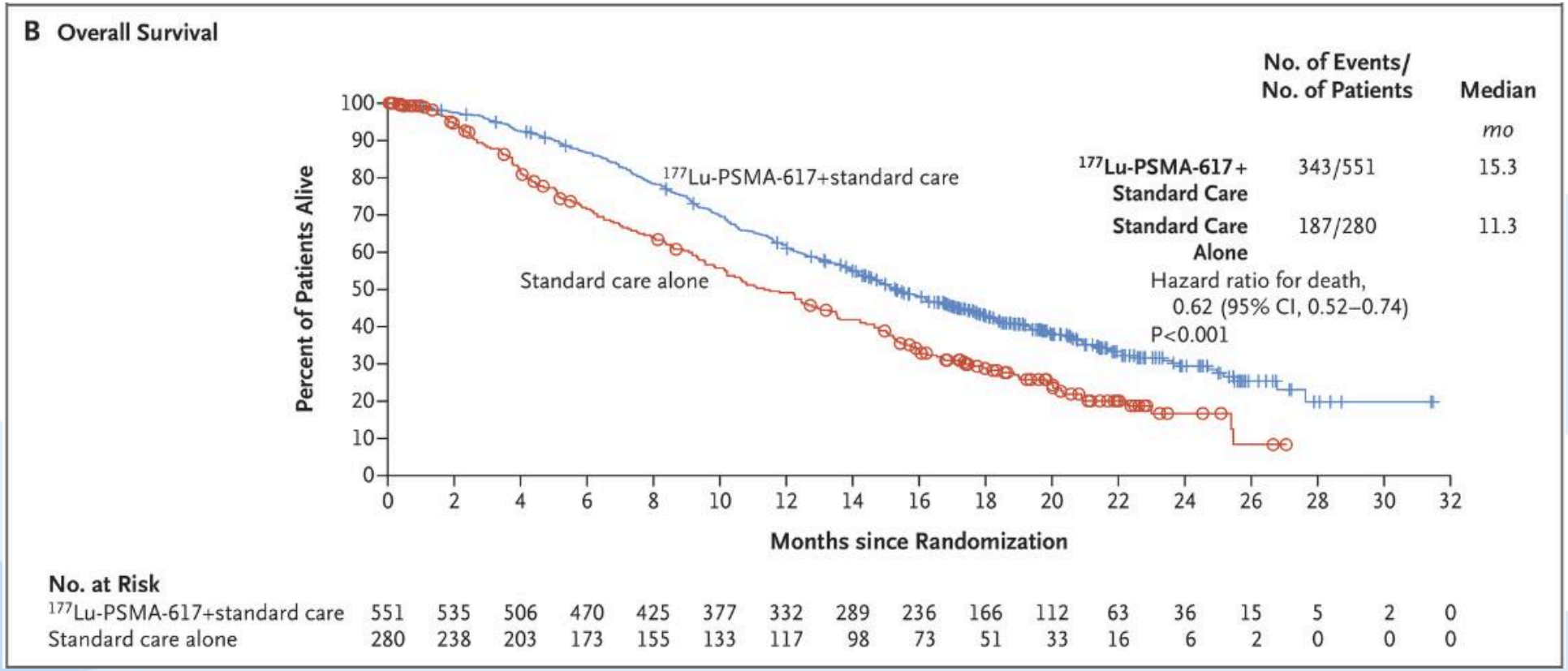
31. Clinicians ~~should~~ may offer 177Lu-PSMA-617 to patients with progressive mCRPC having previously received ~~docetaxel and~~ androgen pathway inhibitor with a positive PSMA PET imaging study. (Strong Recommendation; Evidence Level Grade: B)

VISION Trial

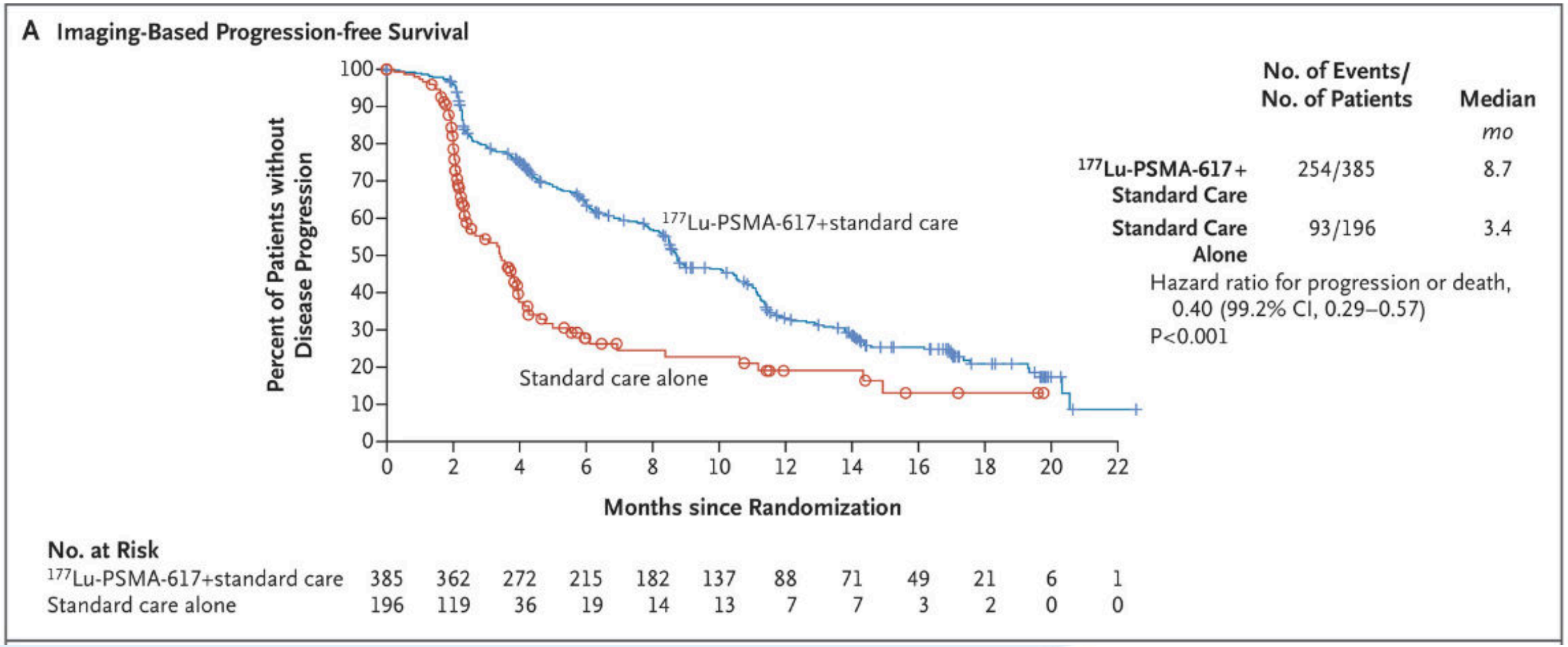
ORIGINAL ARTICLE

Lutetium-177–PSMA-617 for Metastatic Castration-Resistant Prostate Cancer

Oliver Sartor, M.D., Johann de Bono, M.B., Ch.B., Ph.D., Kim N. Chi, M.D., Karim Fizazi, M.D., Ph.D., Ken Herrmann, M.D., Kambiz Rahbar, M.D., Scott T. Tagawa, M.D., Luke T. Nordquist, M.D., Nitin Vaishampayan, M.D., Ghassan El-Haddad, M.D., Chandler H. Park, M.D., Tomasz M. Beer, M.D., et al., for the VISION Investigators*

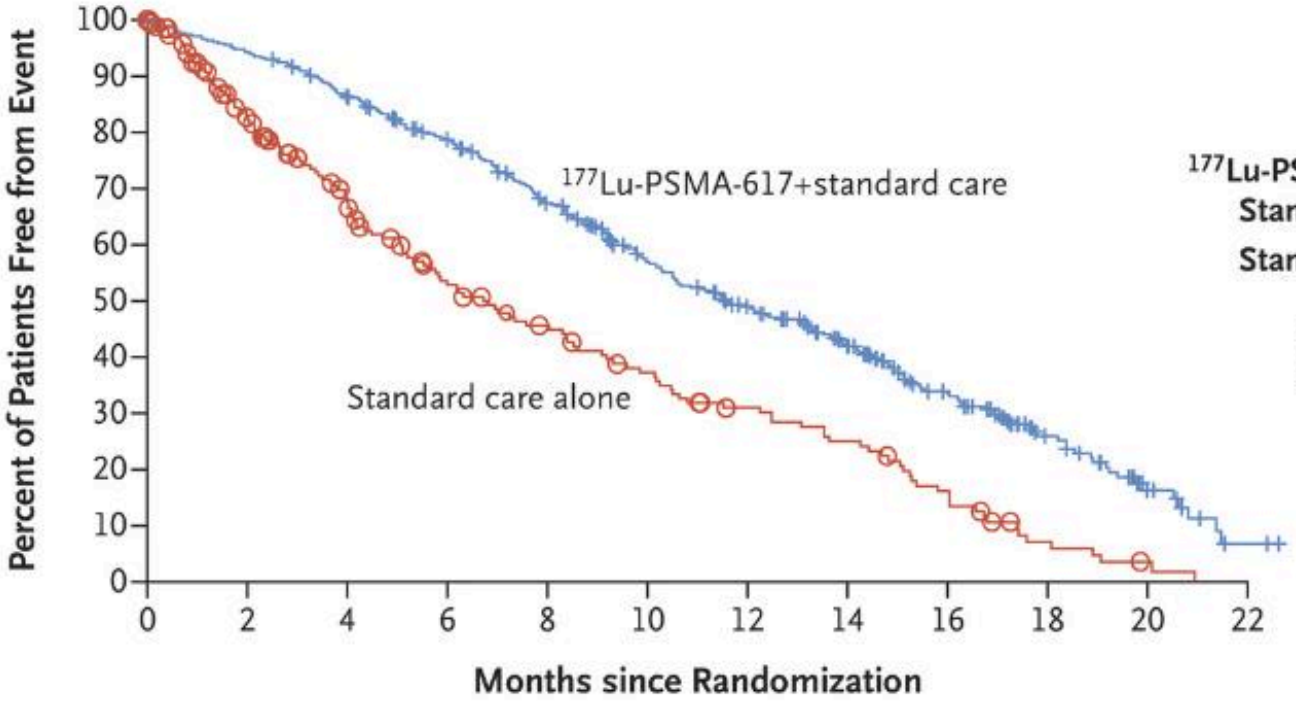


VISION Trial



VISION Trial

C Time to First Symptomatic Skeletal Event



	No. of Events/ No. of Patients	Median
		mo
^{177}Lu-PSMA-617+ Standard Care	256/385	11.5
Standard Care Alone	137/196	6.8

Hazard ratio, 0.50 (95% CI, 0.40–0.62)
P<0.001

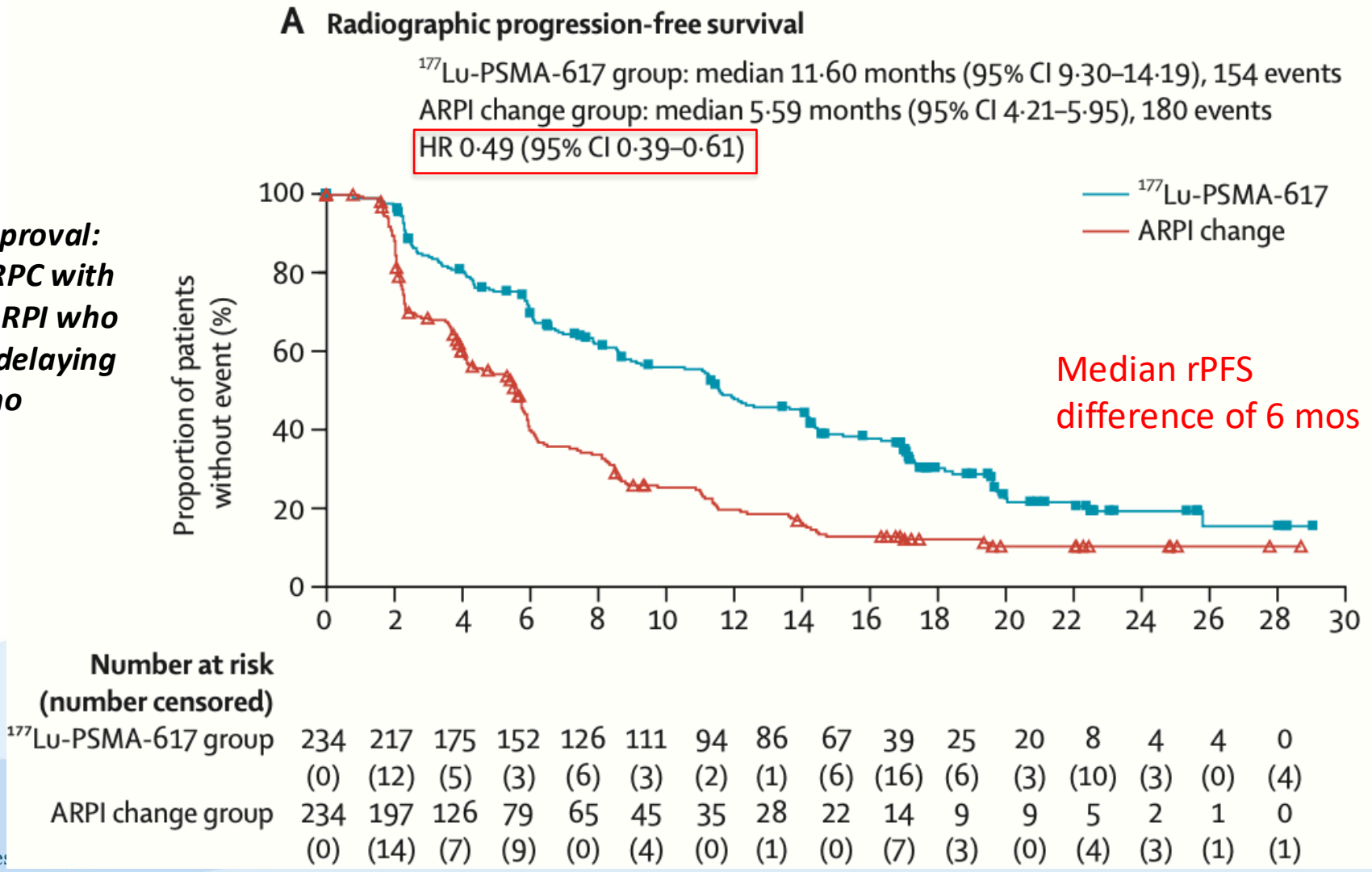
No. at Risk

^{177}Lu-PSMA-617+standard care	385	363	329	290	240	189	153	117	73	34	12	2
Standard care alone	196	141	104	75	61	48	36	29	15	6	2	0

^{177}Lu-PSMA-617 versus a change of androgen receptor pathway inhibitor therapy for taxane-naive patients with progressive metastatic castration-resistant prostate cancer (PSMAfore): a phase 3, randomised, controlled trial

Radiographic progression-free survival

Expanded FDA Approval: PSMA Positive mCRPC with progression after ARPI who are candidates for delaying taxane chemo



Median rPFS difference of 6 mos

American Urological Association
Education & Res

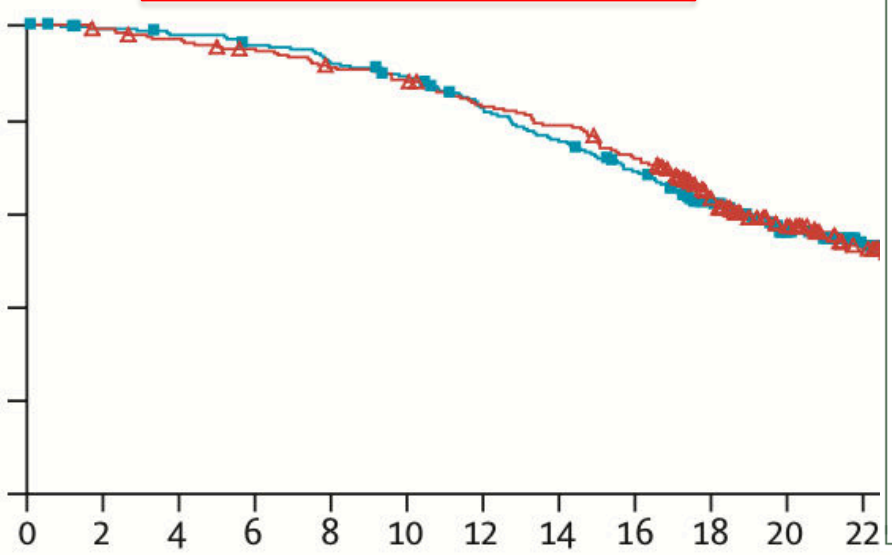
Lancet 2024; 404: 1227–39

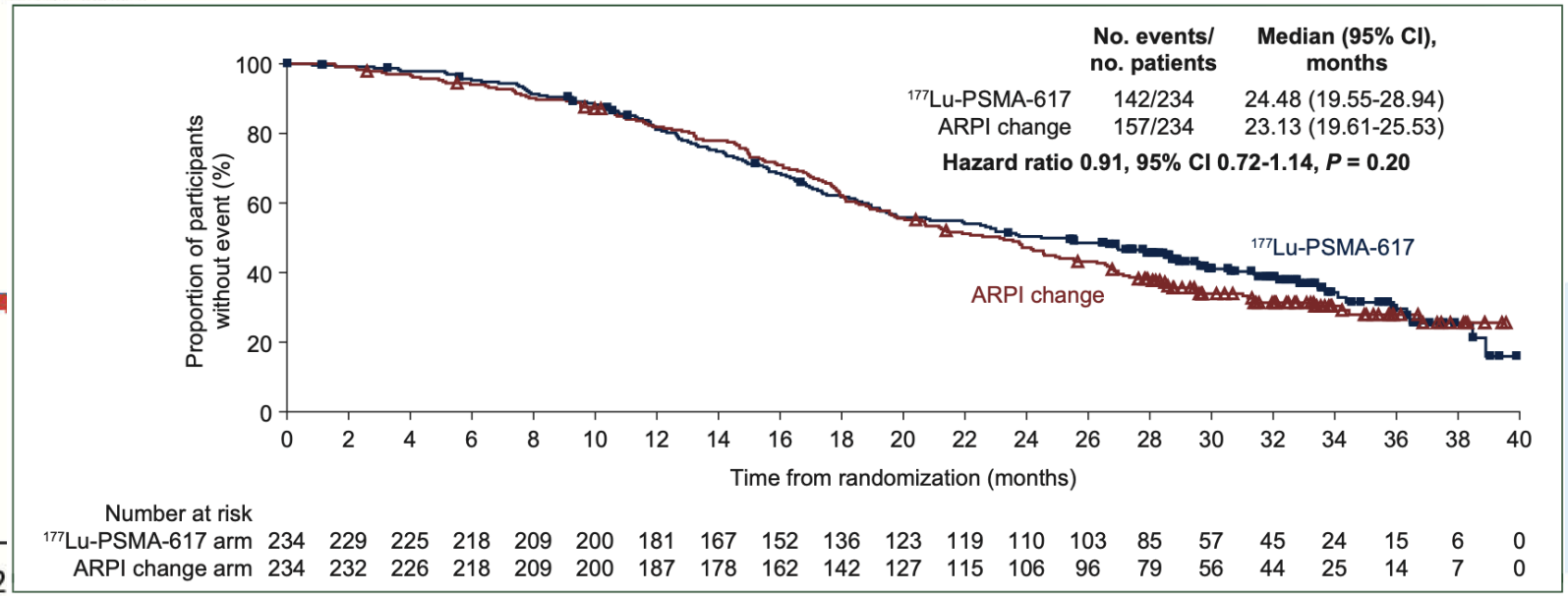
^{177}Lu-PSMA-617 versus a change of androgen receptor pathway inhibitor therapy for taxane-naive patients with progressive metastatic castration-resistant prostate cancer (PSMAfore): a phase 3, randomised, controlled trial

Overall Survival

B **Overall survival (intention-to-treat analysis)**

^{177}Lu-PSMA-617 group: median 23·66 months (95% CI 19·75–NE), 104 events
ARPI change group: 23·85 months (20·60–26·55), 112 events
HR 0·98 (95% CI 0·75–1·28), p=0·44





234 228 224 218 20
(0) (4) (1) (1) (0
234 231 225 217 208 200 187 178 161 126 95 71 40 20 7 1 0
(0) (1) (1) (2) (1) (1) (1) (0) (1) (17) (20) (17) (27) (16) (10) (6) (1)

Conclusions: OS analyses did not show a statistically significant difference between the ^{177}Lu-PSMA-617 and ARPI arms based on the ITT principle; results were likely confounded by the high rate of crossover. The safety profile of ^{177}Lu-PSMA-617 was favourable with no new safety signals identified.

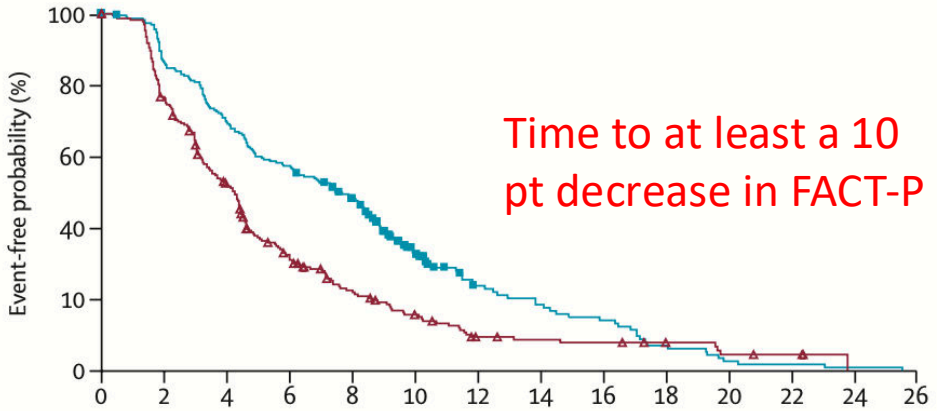
Ann Oncol. 2025;36(11):1319-1330.

Lancet 2024; 404: 1227–39

Health-related quality of life, pain, and symptomatic skeletal events with [^{177}Lu]Lu-PSMA-617 in patients with progressive metastatic castration-resistant prostate cancer (PSMAfore): an open-label, randomised, phase 3 trial

A

	Events/ patients	Median (95% CI), months	HR (95% CI)
[^{177}Lu]Lu-PSMA-617 group	187/234	7·46 (6·08–8·54)	0·61 (0·50–0·75)
ARPI change group	199/234	4·27 (3·45–4·50)	

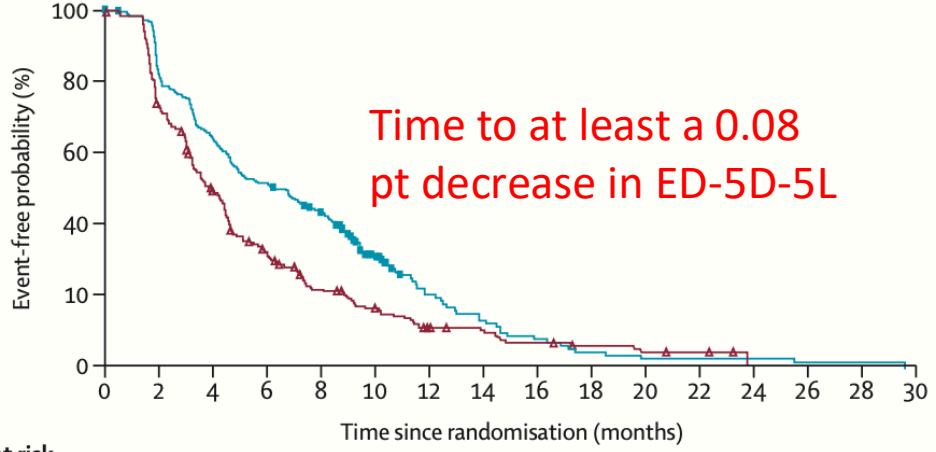


Time to at least a 10 pt decrease in FACT-P

Number at risk (censored)														
[^{177}Lu]Lu-PSMA-617 group	234 (0)	200 (4)	161 (0)	132 (0)	105 (6)	52 (24)	27 (13)	21 (0)	16 (0)	8 (0)	3 (0)	2 (0)	1 (0)	0 (0)
ARPI change group	234 (0)	177 (3)	116 (6)	66 (7)	41 (6)	26 (3)	13 (3)	11 (1)	10 (0)	7 (3)	4 (0)	3 (1)	0 (2)	0 (0)

B

	Events/ patients	Median (95% CI), months	HR (95% CI)
[^{177}Lu]Lu-PSMA-617 group	189/234	6·28 (4·70–7·89)	0·67 (0·54–0·82)
ARPI change group	206/234	3·88 (3·25–4·44)	



Time to at least a 0.08 pt decrease in ED-5D-5L

Number at risk (censored)																
[^{177}Lu]Lu-PSMA-617 group	234 (0)	189 (4)	147 (0)	118 (0)	93 (6)	45 (25)	22 (10)	14 (0)	8 (0)	4 (0)	2 (0)	2 (0)	2 (0)	1 (0)	1 (0)	0 (0)
ARPI change group	234 (0)	189 (3)	108 (6)	67 (3)	42 (4)	29 (3)	17 (2)	14 (2)	9 (0)	6 (2)	4 (0)	3 (1)	0 (2)	0 (0)	0 (0)	0 (0)

American Urological Association Education & Research, Inc.

Interpretation [^{177}Lu]Lu-PSMA-617 might delay worsening of patient-reported outcomes and prevent symptomatic skeletal events versus ARPI change in taxane-naive patients with PSMA-positive metastatic castration-resistant prostate cancer whose disease has progressed once on a previous ARPI.

Lancet Oncol 2025; 26: 948–59

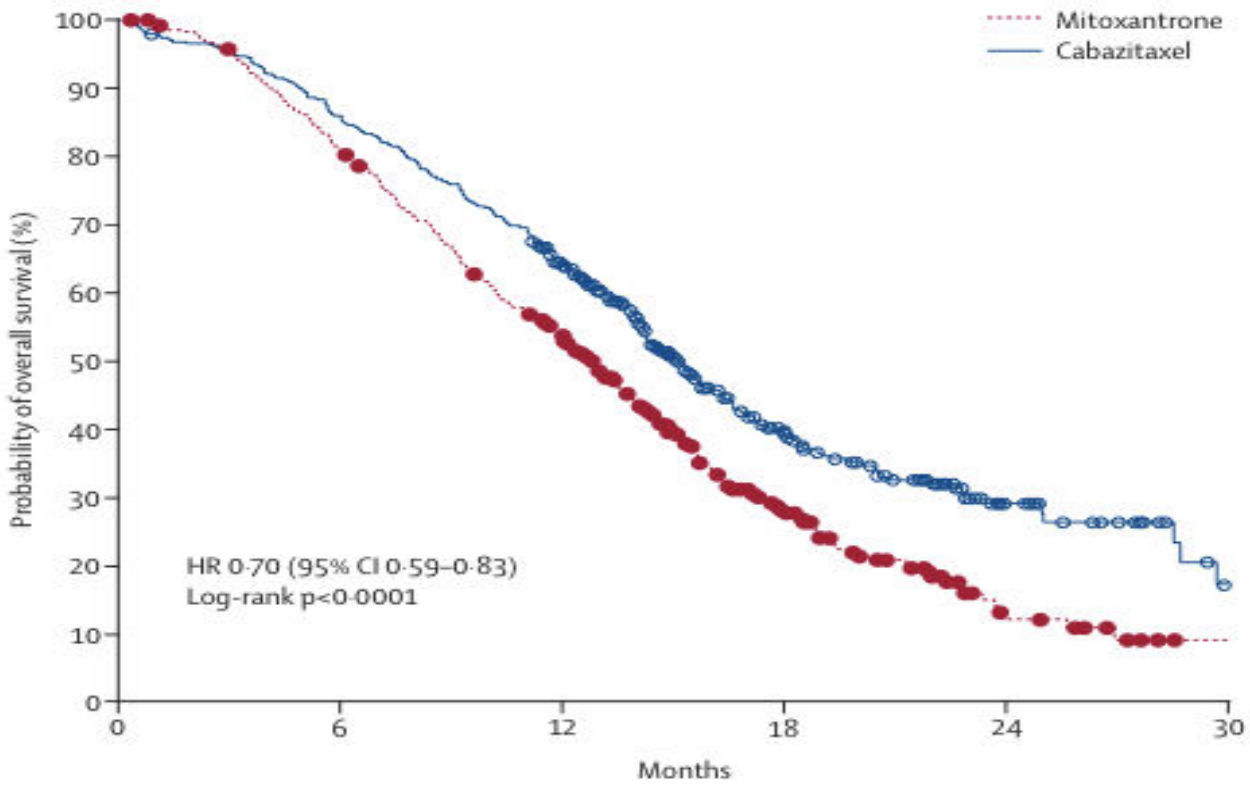
METASTATIC CRPC

32. In mCRPC patients who received prior docetaxel chemotherapy either in the mHSPC or mCRPC setting, clinicians may offer **cabazitaxel**. (Conditional Recommendation; Evidence Level: Grade B)

33. In mCRPC patients who received prior docetaxel chemotherapy and and androgen pathway inhibitory, clinicians should recommend **cabazitaxel** rather than an alternative androgen pathway directed therapy. (Strong Recommendation; Evidence Level: Grade B)

CABAZITAXEL: Second-Line Therapy

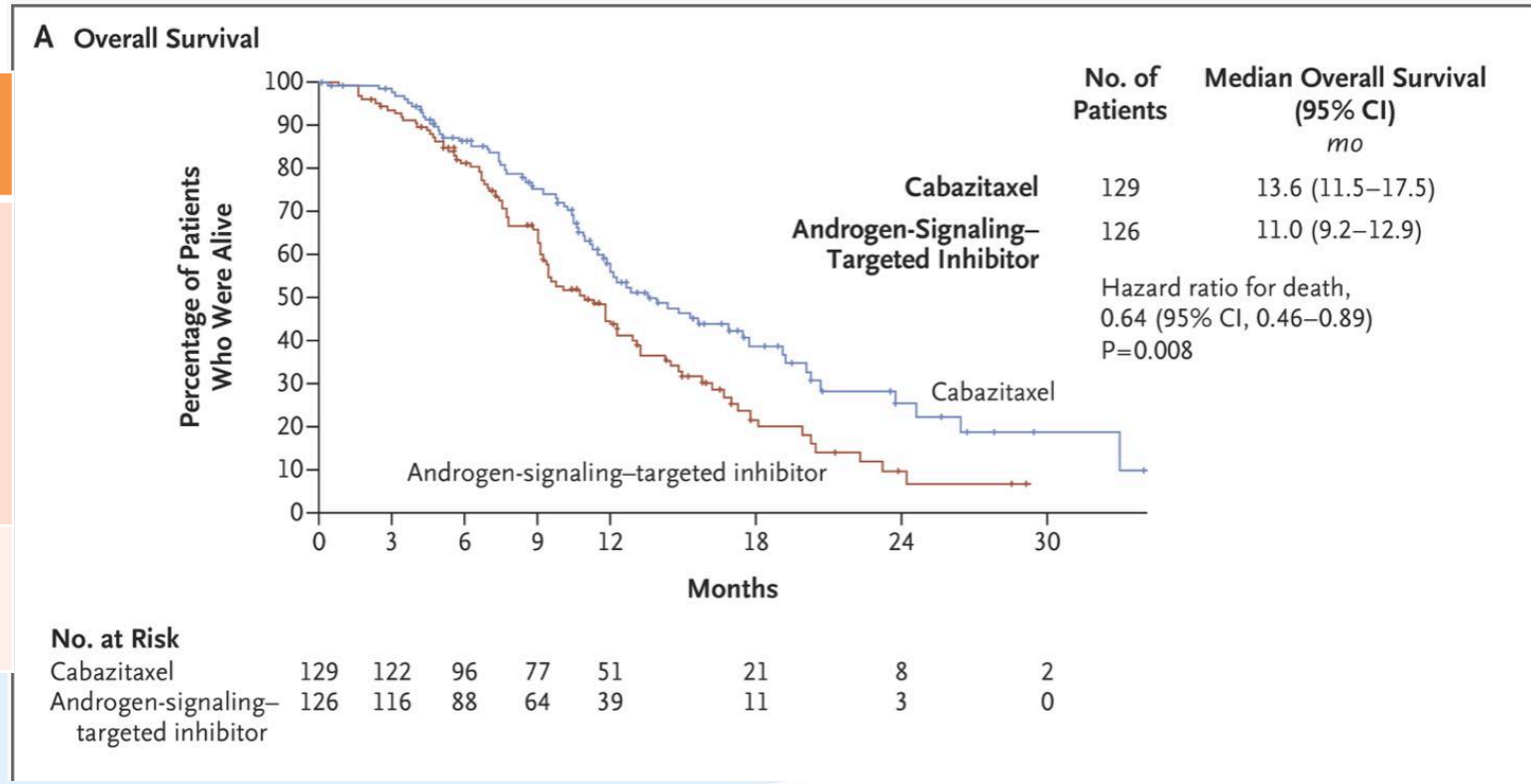
Trial	Overall Survival
TROPIC n=755 Second-line therapy	15.1 months cabazitaxel 12.7 months mitoxantrone
	HR=0.70; 95%CI 0.59 to 0.83 p<0.0001



de Bono JS et al: Lancet 2010; 376: 1147.

Cabazitaxel: Second-Line Therapy

Trial	Overall Survival
CARD n=755 Second-line therapy	13.6 months cabazitaxel 11.0 months ARPI switch
	HR=0.64; 95%CI 0.46 to 0.89 p<0.008



American Urological Association Education & Research, Inc.

De Wit R. N Engl J Med 2019;381:2506

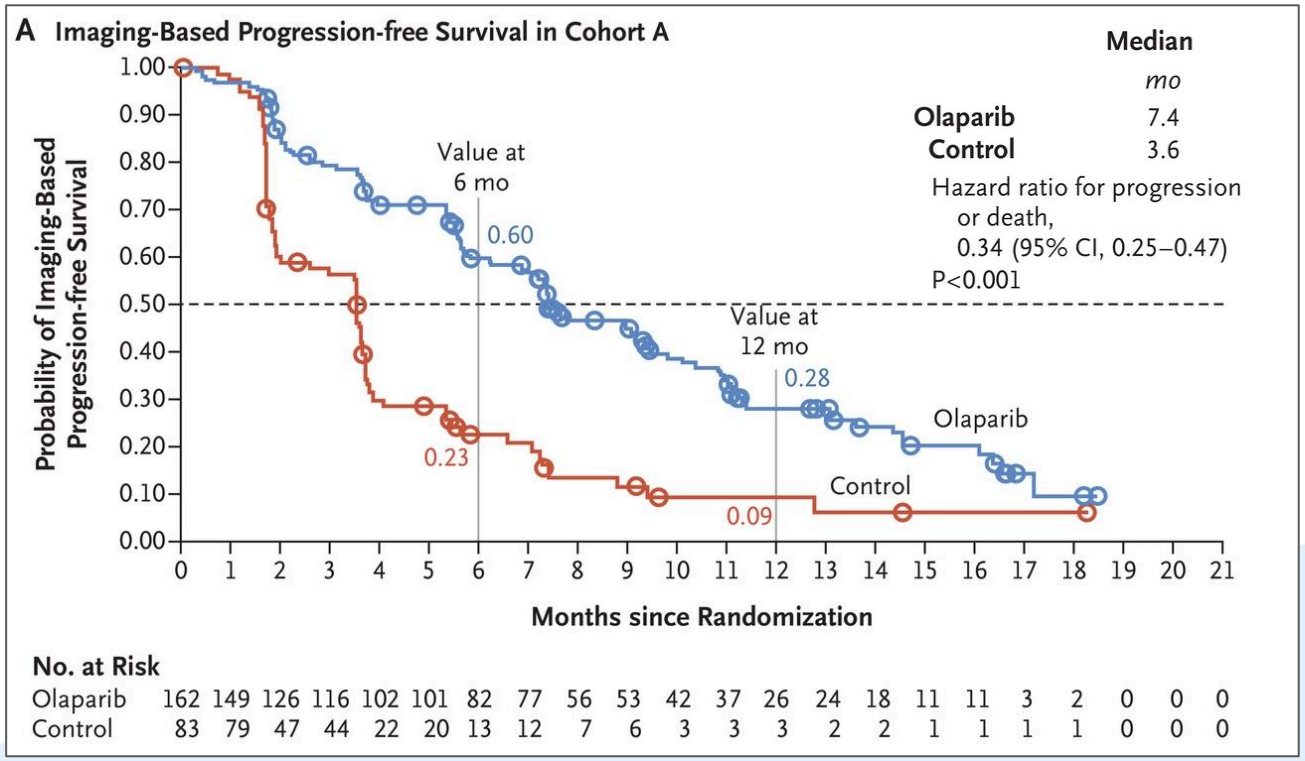
METASTATIC CRPC: Molecular testing

34. Clinicians should offer a **PARP inhibitor alone or in combination with an androgen receptor pathway inhibitor** to select patients with deleterious or somatic homologous recombination repair gene-mutated mCRPC. **Platinum based chemotherapy** may be offered as an alternative for patients who cannot use or obtain a PARP inhibitor. (Moderate Recommendation; Evidence Level: Grade C)

UPDATE

35. In patients with mismatch repair deficient or microsatellite instability high mCRPC, clinicians should offer **pembrolizumab**. (Moderate Recommendation; Evidence Level: Grade C)

METASTATIC CRPC:
Homologous Recombination Repair Mutation

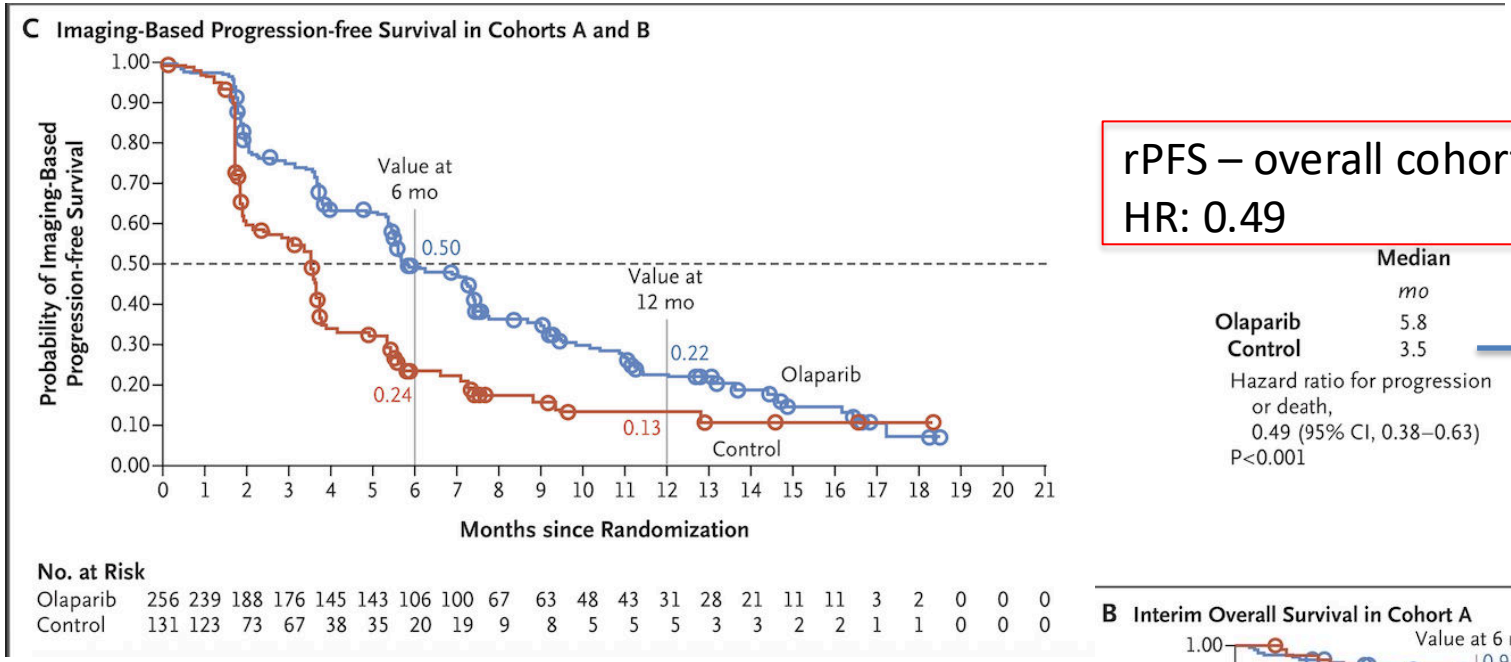


Trial	PFS (A)
PROfound n=387	7.4 months olaparib 3.6 months control

American Urological Association Education & Research, Inc.

de Bono et al: Olaparib for metastatic castration-resistant prostate cancer. N Engl J Med 2020. Epub ahead of print.

METASTATIC CRPC:
Homologous Recombination Repair Mutation

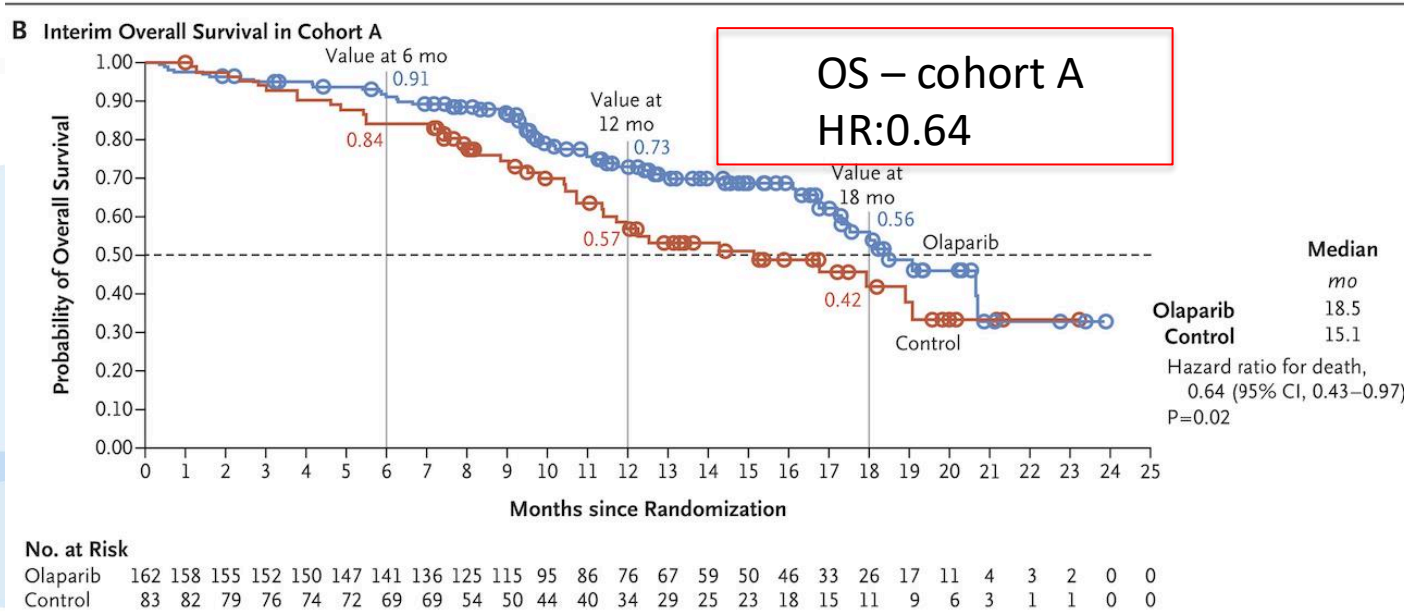


rPFS – overall cohort
HR: 0.49

	Median (mo)
Olaparib	5.8
Control	3.5

Hazard ratio for progression or death, 0.49 (95% CI, 0.38–0.63)
P<0.001

mPFS ~3.5 mos when switching ARPI



OS – cohort A
HR:0.64

	Median (mo)
Olaparib	18.5
Control	15.1

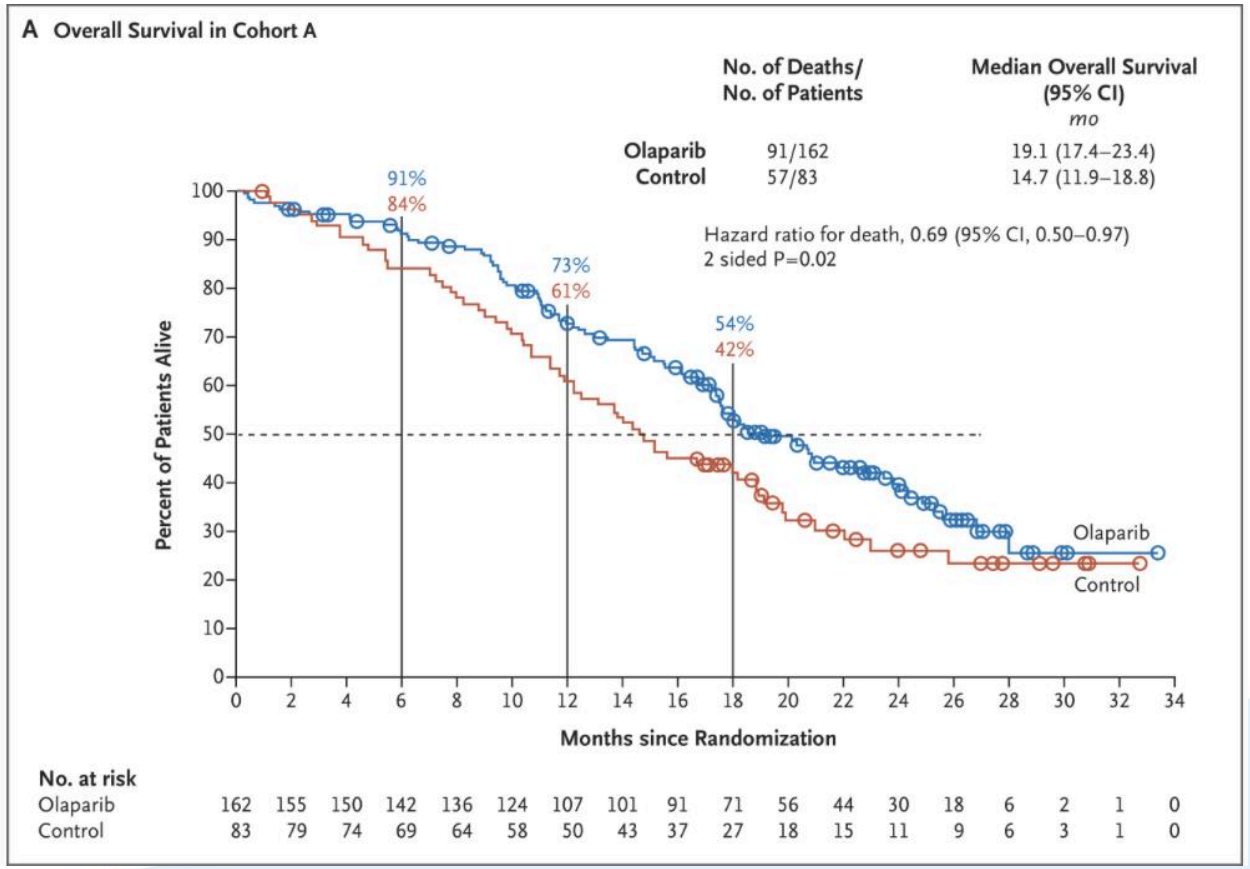
Hazard ratio for death, 0.64 (95% CI, 0.43–0.97)
P=0.02

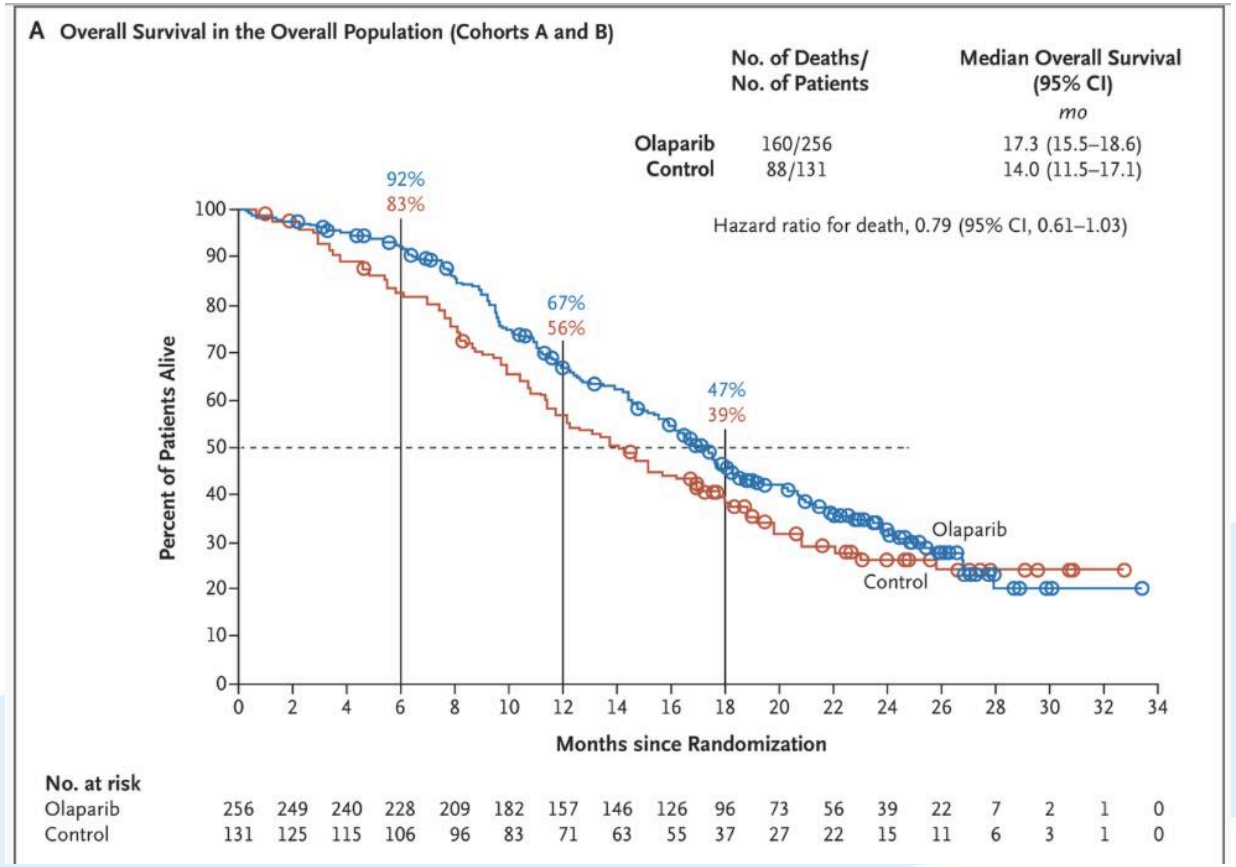
PROfound

N Engl J Med 2020 28;382(22):2091-2102

METASTATIC CRPC:
Homologous Recombination Repair Mutation

PROfound
FDA Approved May 2020





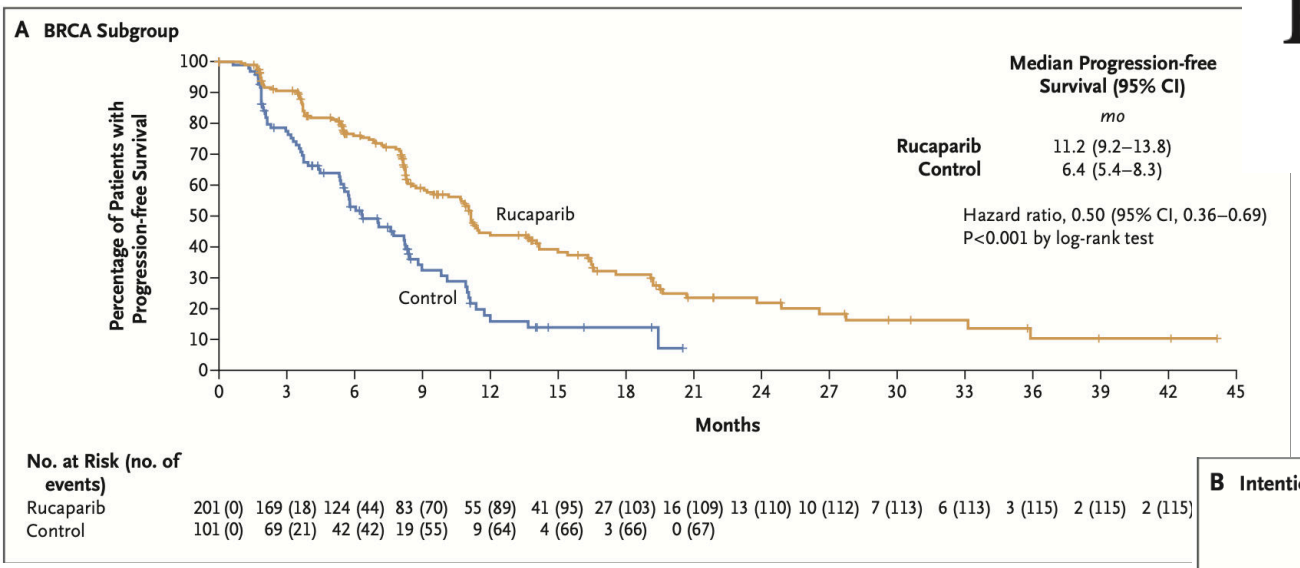
COHORT A
HR: 0.69
CI: 0.50-0.97

Overall Population
HR: 0.79
CI: 0.69 – 1.03

American Urological Association
Education & Research, Inc.

N Engl J Med 2020 Dec 10;383(24):2345-2357

METASTATIC CRPC:
Homologous Recombination Repair Mutation

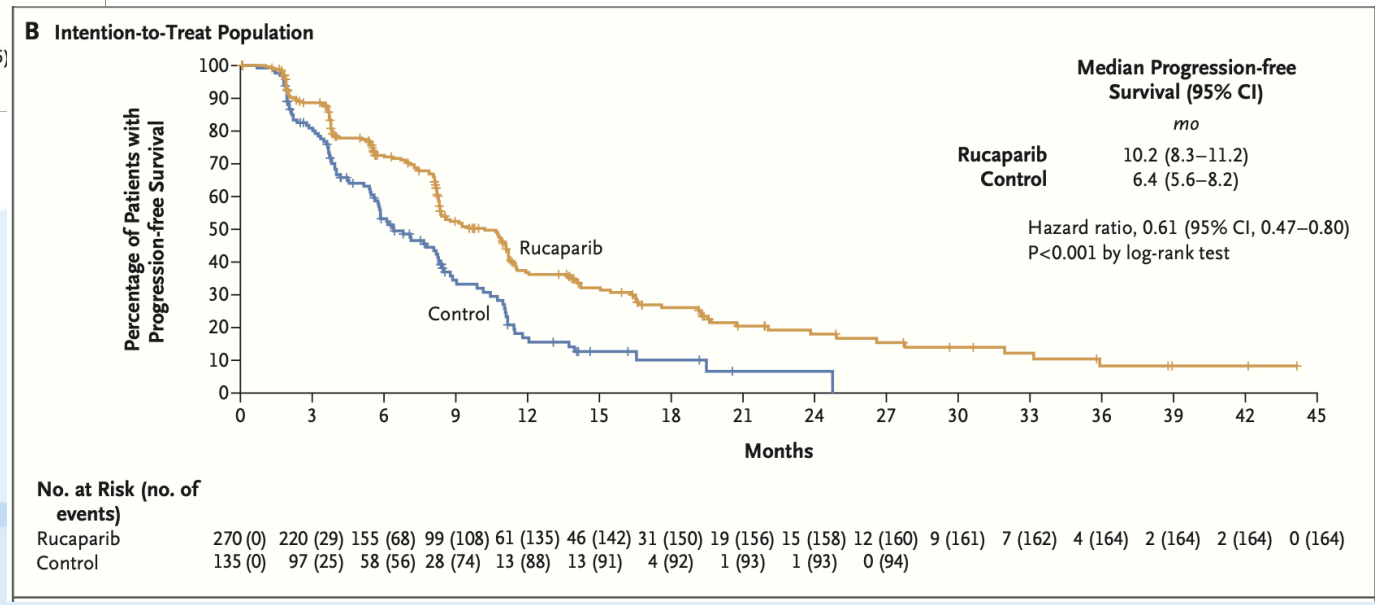


BRCA subgroup
HR 0.50 with rucaparib

Rucaparib or Physician's Choice in Metastatic Prostate Cancer

TRITON3

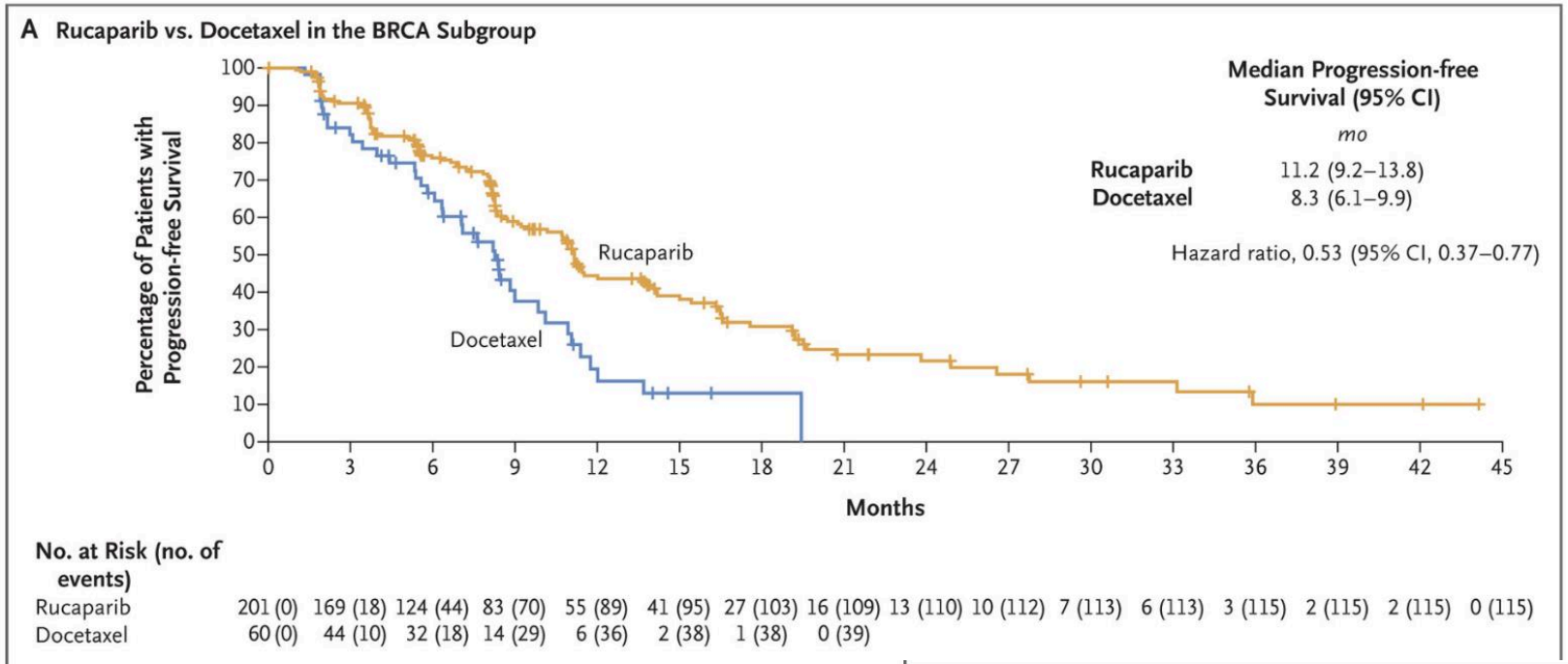
ITT Population
HR 0.61 with rucaparib



N Engl J Med 2023;388:719-32.

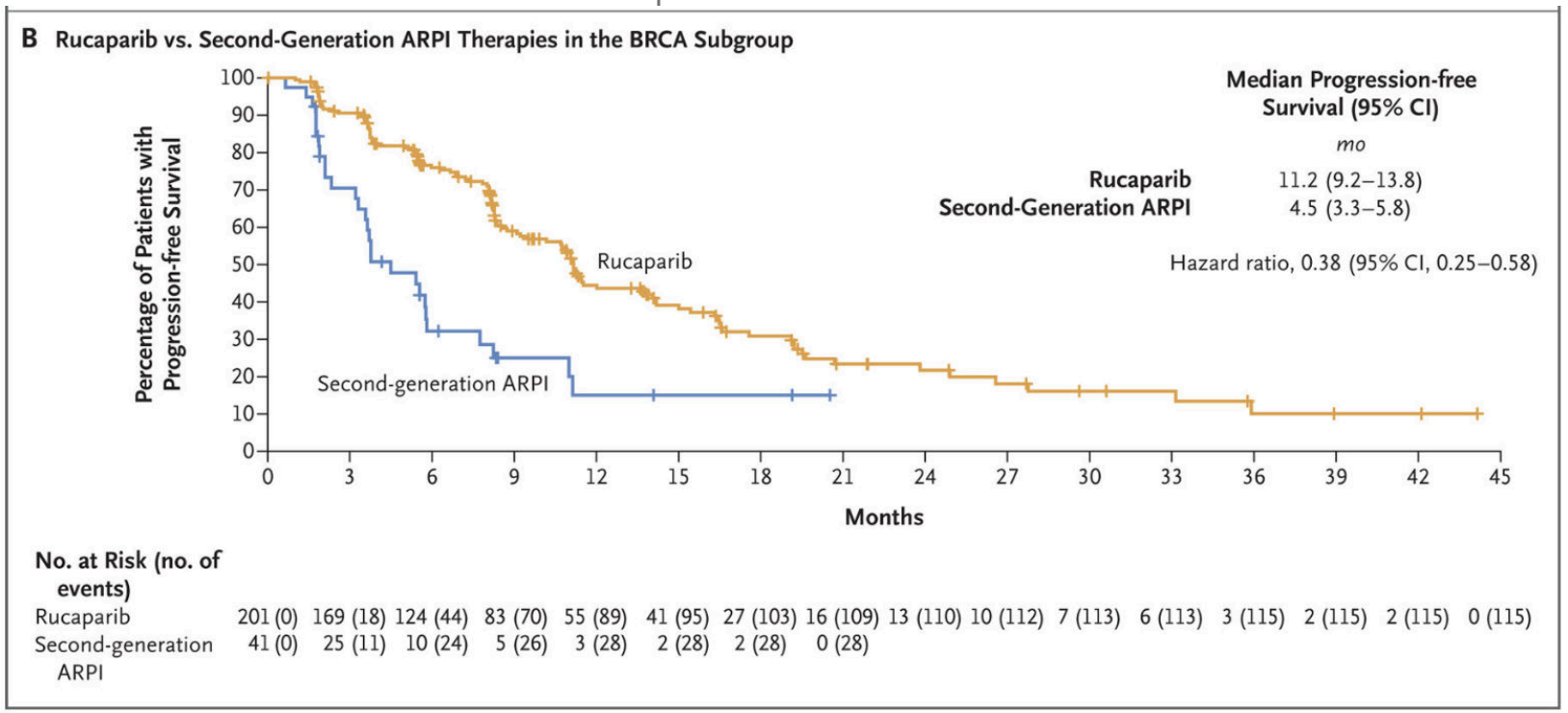
Rucaparib or Physician's Choice in Metastatic Prostate Cancer

TRITON3



rPFS: Rucaparib superior to docetaxel by ~ 3 months

rPFS: Rucaparib superior to 2nd ARPI by ~ 8 months



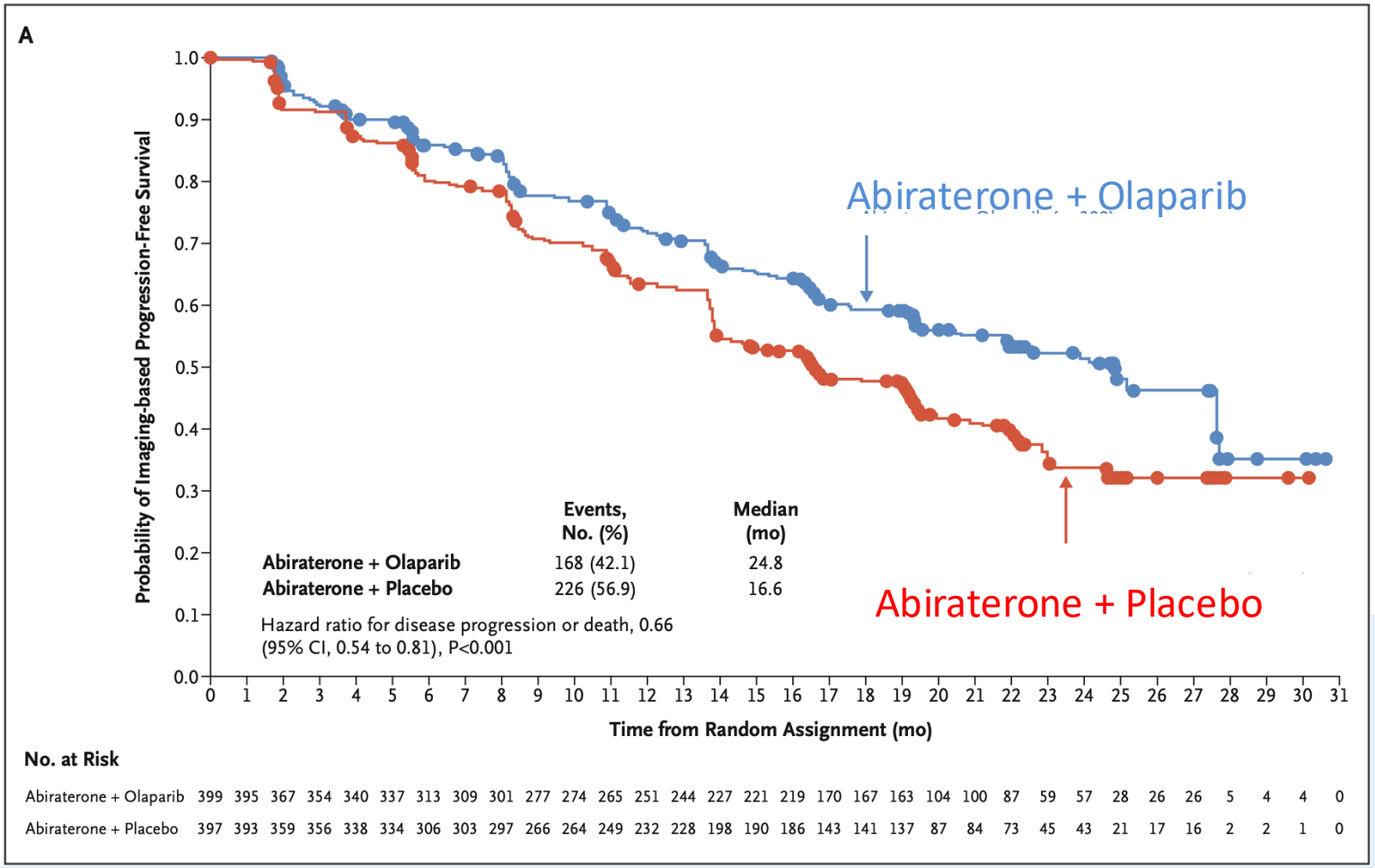
American Urological Association
Education & Research, Inc.

N Engl J Med.2023;388(8):719–732

PARP Inhibitors – Combination therapy

- Combination with androgen receptor pathway inhibitors
  - Olaparib + abiraterone (PROpel)
  - Niraparib + abiraterone (MAGNITUDE)
  - Talazoparib + enzalutamide (TALAPRO)

Abiraterone and Olaparib for Metastatic Castration-Resistant Prostate Cancer



Imaging-based PFS by investigator assessment
24.8 mos vs. 16.6 mos
HR 0.66

American Urological Association
Education & Research, Inc.

NEJM Evid 2022;1(9)

Olaparib plus abiraterone versus placebo plus abiraterone in metastatic castration-resistant prostate cancer (PROpel): final prespecified overall survival results of a randomised, double-blind, phase 3 trial

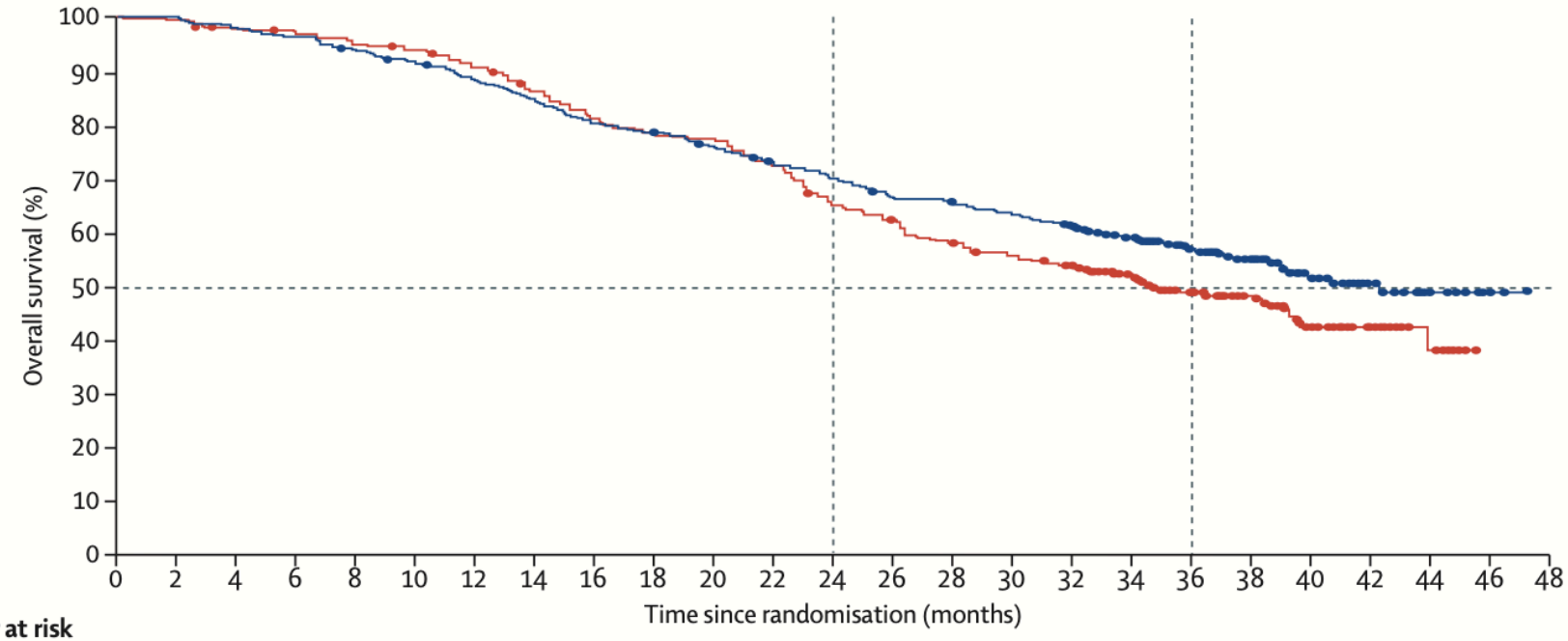
PROpel: Overall Survival

FDA approved May 2023 for BRCAm mCRPC

A

	Number of events/ number of patients	Median overall survival, months (95% CI)	2-year overall survival	3-year overall survival
Olaparib + abiraterone	176/399 (44%)	42·1 (38·4–NR)	70·2% (95% CI 65·4–74·4)	56·9% (95% CI 51·7–61·7)
Placebo + abiraterone	205/397 (52%)	34·7 (31·0–39·3)	65·5% (95% CI 60·5–70·0)	49·5% (95%CI 44·3–54·5)
Hazard ratio (95% CI)		0·81 (0·67–1·00); p=0·054*		

*2-sided boundary for significance 0·0377



Number at risk

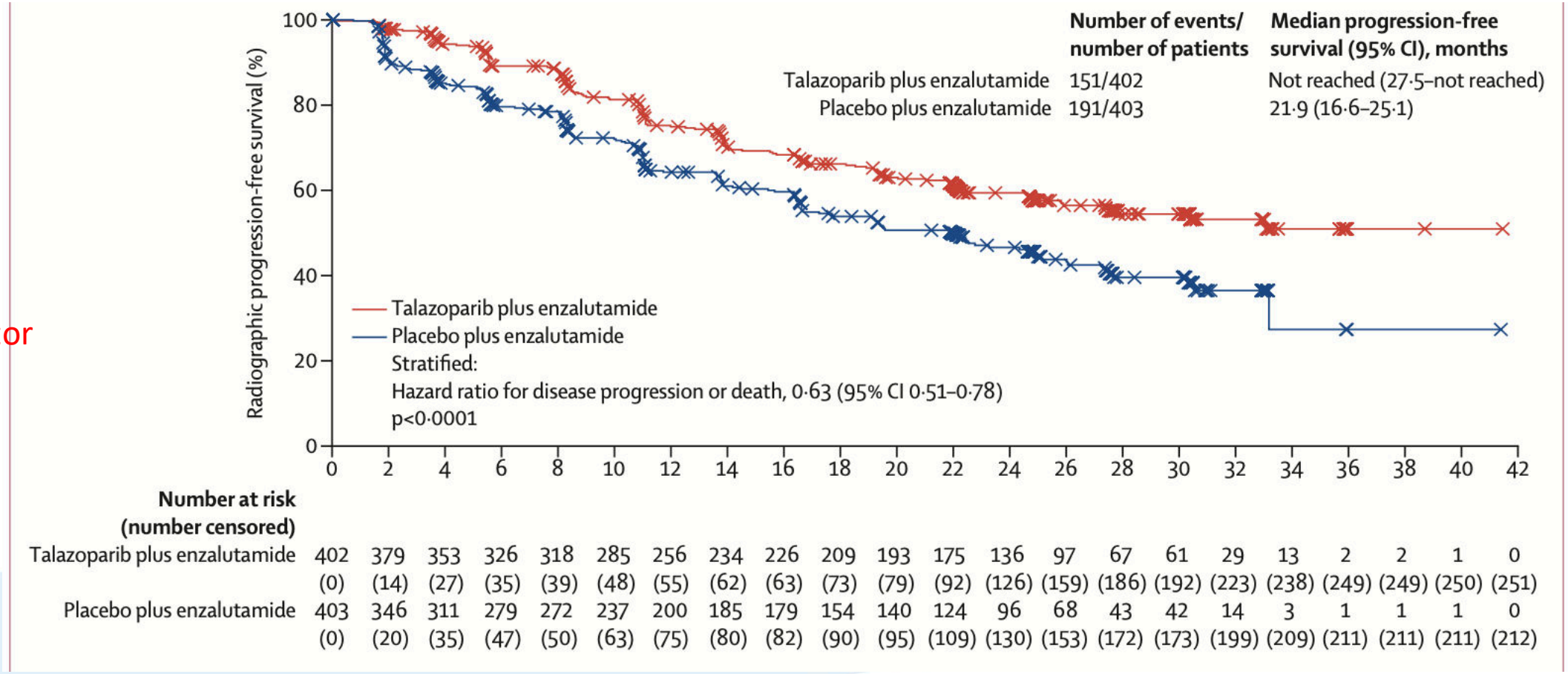
ITT population with mOS benefit of ~7 mos longer in the abiraterone + Olaparib arm → not statistically significantly different at final prespecified analysis

Lancet Oncol 2023;24: 1094–108

TALAPRO-2
Talazoparib + Enzalutamide

Radiographic Progression Free Survival

Blinded investigator assessment



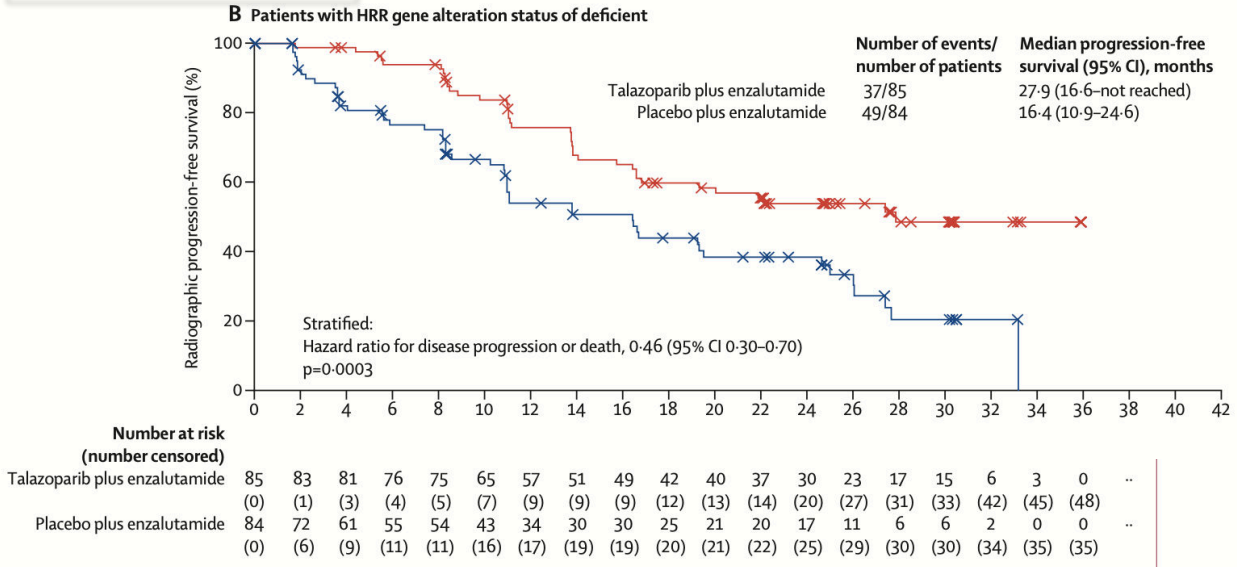
American Urological Association Education & Research, Inc.

Lancet 2023; 402: 291–303

TALAPRO-2

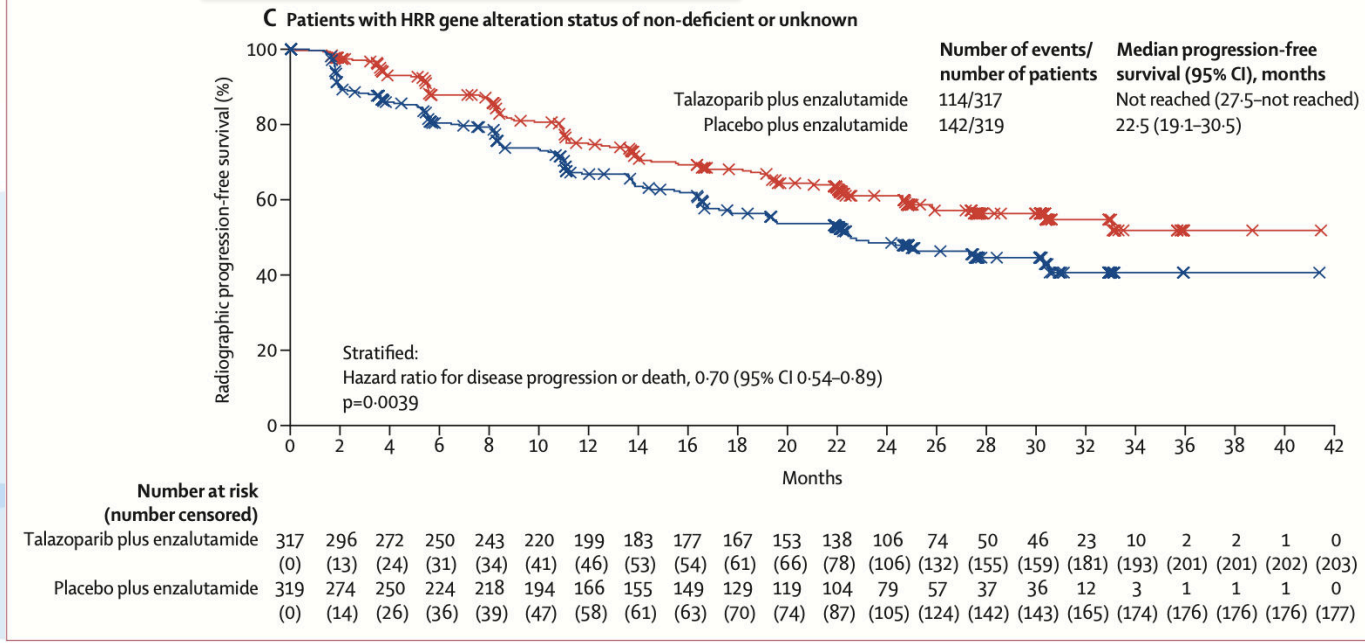
Talazoparib + Enzalutamide

HRR Deficient



rPFS by HRR Status

HRR Non-deficient or unk



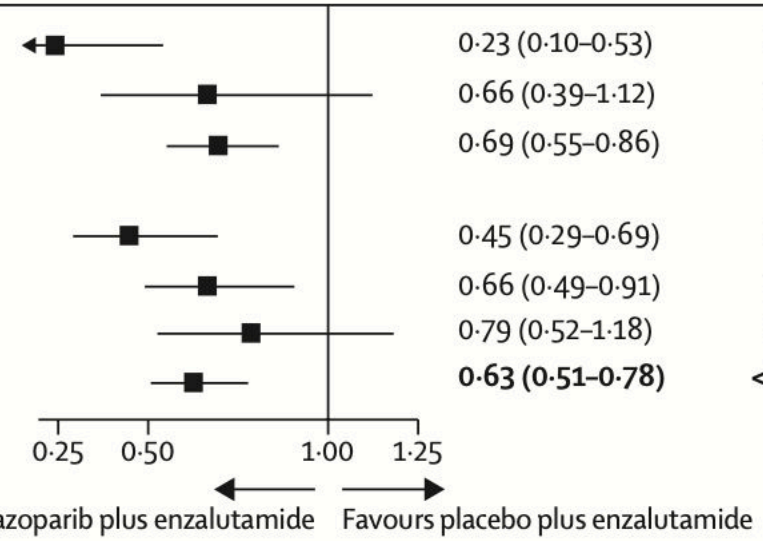
American Urological Association Education & Research, Inc.

Lancet 2023; 402: 291–303

TALAPRO-2
Talazoparib + Enzalutamide

B **By *BRCA1/2* status, HRR gene alteration status, and prospective tumour tissue testing**

BRCA1/2-altered, HRR-deficient	8/27	22/32	0·23 (0·10–0·53)	0·0002
Non-*BRCA1/2*-altered, HRR-deficient	29/58	27/52	0·66 (0·39–1·12)	0·12
Non-*BRCA1/2*-altered or unknown, intention-to-treat	143/375	169/371	0·69 (0·55–0·86)	0·0011
By prospective tumour tissue testing				
HRR-deficient	36/83	47/80	0·45 (0·29–0·69)	0·0002
HRR-non-deficient	70/198	96/214	0·66 (0·49–0·91)	0·0092
HRR-unknown	45/121	48/109	0·79 (0·52–1·18)	0·25
Overall	**151/402**	**191/403**	**0·63 (0·51–0·78)**	**<0·0001**

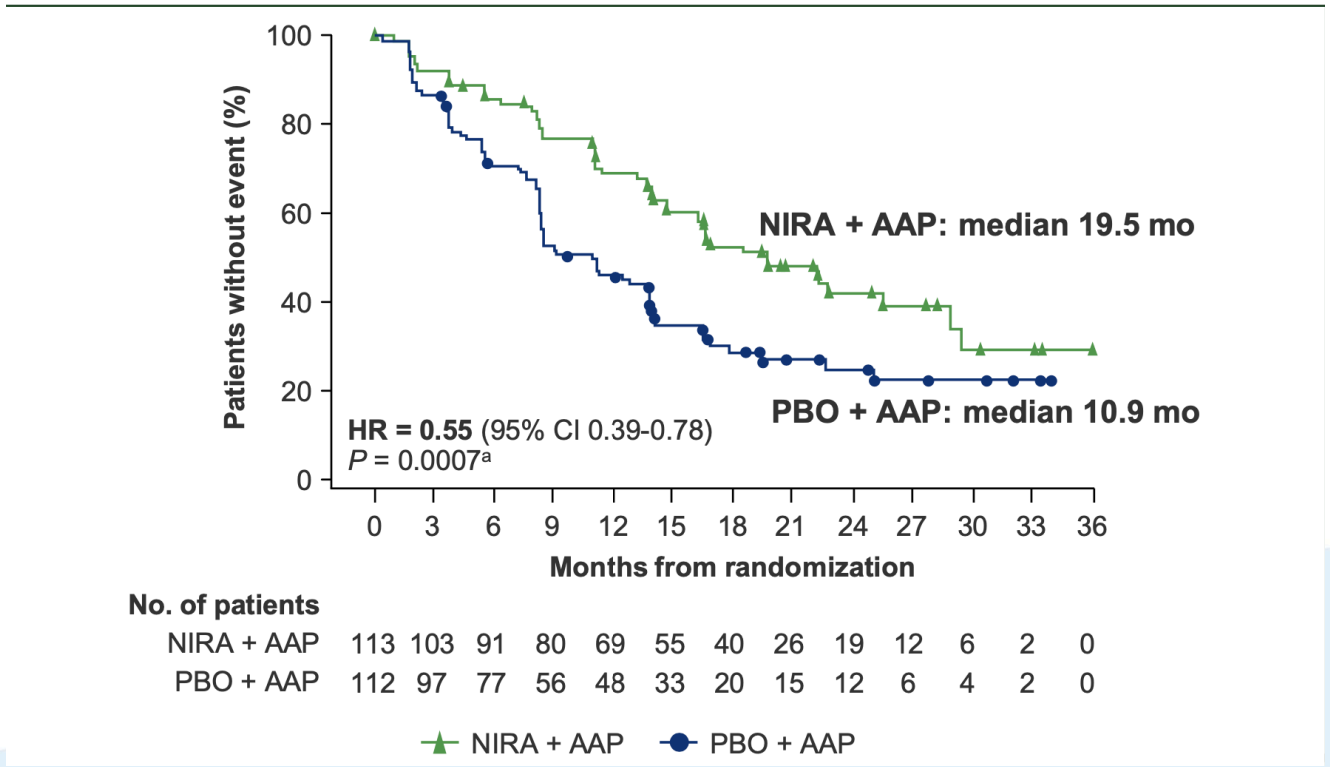


Subgroup analysis by genetics

FDA approved 6/2023 for HRRm mCRPC

Lancet 2023; 402: 291–303

Niraparib plus abiraterone acetate with prednisone in patients with metastatic castration-resistant prostate cancer and homologous recombination repair gene alterations: second interim analysis of the randomized phase III MAGNITUDE trial☆



rPFS by central review in the BRCA subgroup

- Improved rPFS with NIRA + AAP compared with PBO + AAP in BRCA+ mCRPC
  - 16.6 mos vs 10.9 mos (HR 0.53; 95%CI 0.36-0.79; p = 0.001)
- 45% reduction in risk of progression or death and extension of the median rPFS to >1.5 years compared with PBO + AAP
- **FDA-approved August 2023 for BRCAm-mCRPC**

American Urological Association
Education & Research, Inc.

Ann Oncol 2023:34:772

Take Home

- Rapidly evolving treatment landscape
- Germline and somatic testing – do it!
- Avoid 2nd AR-targeted therapy after failure of first – try different MOA
- PARP inhibitors for mCRPC with HRR mutations
  - Single agent post ARPI and/or chemo(Olaparib/rucaparib)
  - Combination IL (olaparib/abi, niraparib/abi, talazoparib/enza)
- Lutetium-PSMA-617 is an option after progression on ARPI

For additional information, please see the full guideline available on the AUA website

www.AUAnet.org

American Urological Association
Education & Research, Inc.

ACKNOWLEDGEMENTS

APC Amendment Panel

Robert Dreicer, MD, MS, MACP

Alice Yu, MD

Mutlay Sayan, MD

Kristen R. Scarpato, MD, MPH

Michael Cookson, MD, MMHC

Methodology

Kristin D'Anci

AUA Guidelines Staff

Lauren J Pak, MHS, MS

External Reviewers

Androgen Receptor Signaling Inhibitors, Chemotherapy and Treatment Intensification

David Jarrard MD,
Professor, Vice Chair Dept. Urology
John Livesey Chair in Urologic Oncology
Director UW Prostate Cancer SPORE, Carbone Cancer Center

Department of Urology
UNIVERSITY OF WISCONSIN
SCHOOL OF MEDICINE AND PUBLIC HEALTH

Carbone Cancer Center
UNIVERSITY OF WISCONSIN
SCHOOL OF MEDICINE AND PUBLIC HEALTH

Disclosures

- Gregor Diagnostics
- PUER Health
- NCCN Guidelines for Early Prostate Cancer Detection Committee

Advanced Prostate Cancer: AUA/SUO Guideline

www.auanet.org/guidelines-and-quality/guidelines/advanced-prostate-cancer

OUTLINE:

- Chemohormonal therapy in mHSPC
- Mechanisms, dosing and side effects of androgen receptor pathway inhibitor (ARSIs)
- Choosing between docetaxel, ARSIs and ‘triplet therapy’ in mHSPC
- Understand guideline approaches to oligometastatic disease

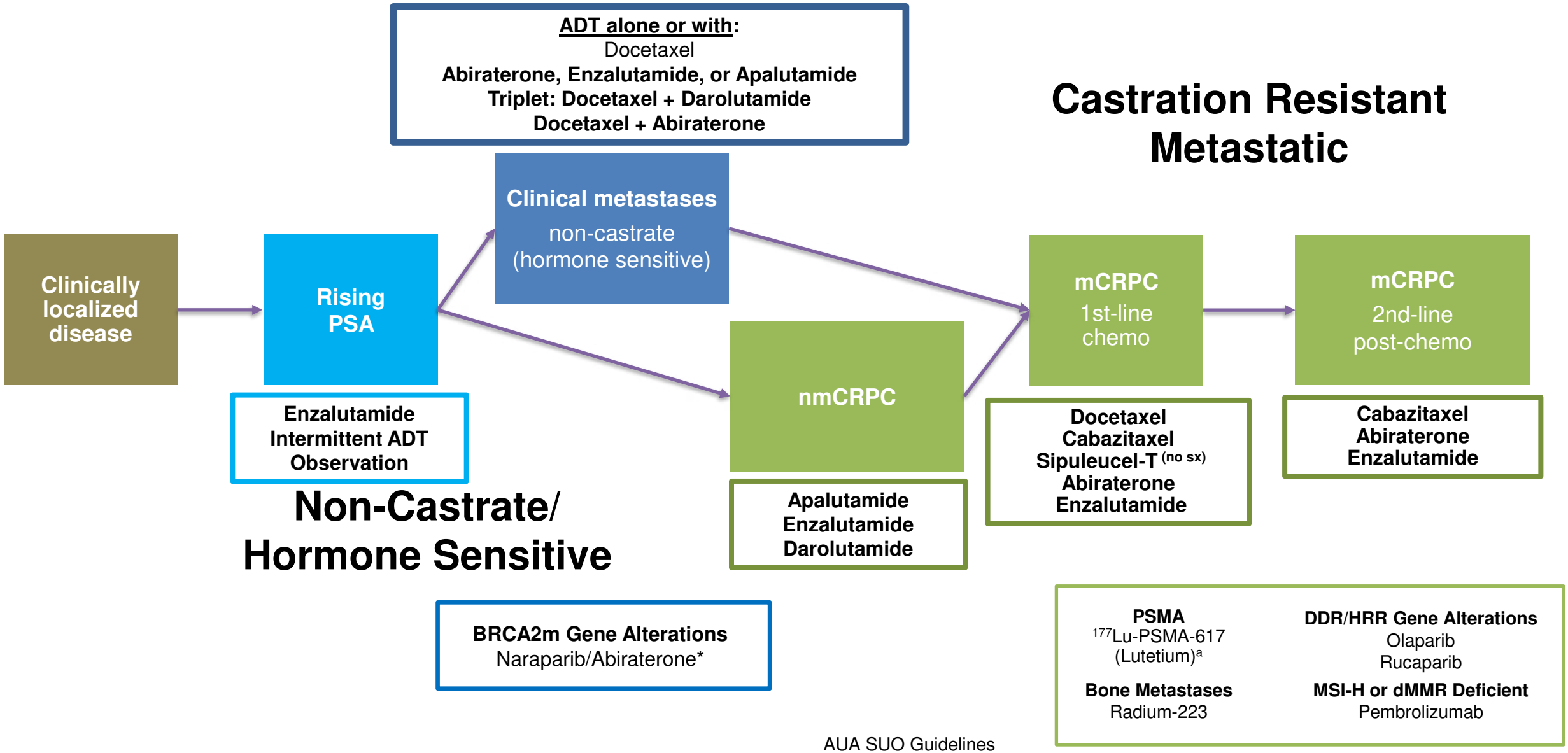
Case #1: 60yo with new diagnosis of metastatic HSPC - high volume

- Presents with bone pain and fatigue
- PSA 120 ng/ml
- GG5 prostate biopsy extensive
- Multiple pelvic bony metastases noted on imaging with enlarged pelvic and retroperitoneal lymph nodes.

Stage and Options?

F-18 DCFPyL PSMA PET

Current Prostate Cancer Therapeutic Landscape[1]



AUA SUO Guidelines

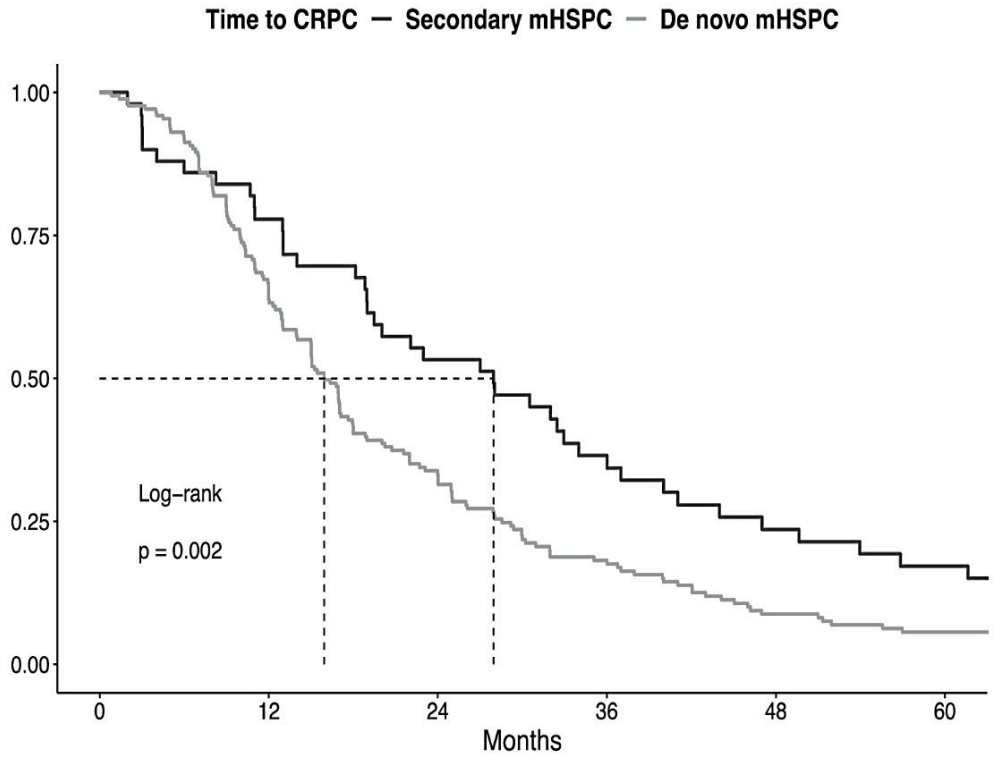
INITIAL EVALUATION METASTATIC HSPC

Prognosis: The presence and extent of metastatic disease plays a central role in determining which and if any therapy is beneficial.

- Radiographic assessment (imaging)
- Discussion of symptoms
- Baseline and serial PSA
- Genetic counseling and germline testing

Presentation and Pace of Disease

- State of metastatic disease
  - ***De novo* synchronous** (mets at presentation)
  - ***Recurrent/metachronous*** *(mets after prior localized)*
- Survival worse for *de novo* disease presentation
  - ~56mo vs 85mo
- **Greatest improvements in de-novo/high volume disease with treatment intensification**



Wenzel et al. Urol Oncol 2024

Genetics: METASTATIC HSPC

4. For all patients with advanced prostate cancer, clinicians should offer germline testing, if not already performed. For patients with metastatic disease, somatic tumor testing should also be offered. (Clinical Principle)

Genes Influencing Homologous Recombination Repair*		
BRCA1	BRCA2	ATM
BRIP1	BARD1	CDK12
CHEK1	CHEK2	FANCL
PALB2	PPP2R2A	RAD51B
RAD51C	RAD51D	RAD54L

*Note, this list is not exhaustive

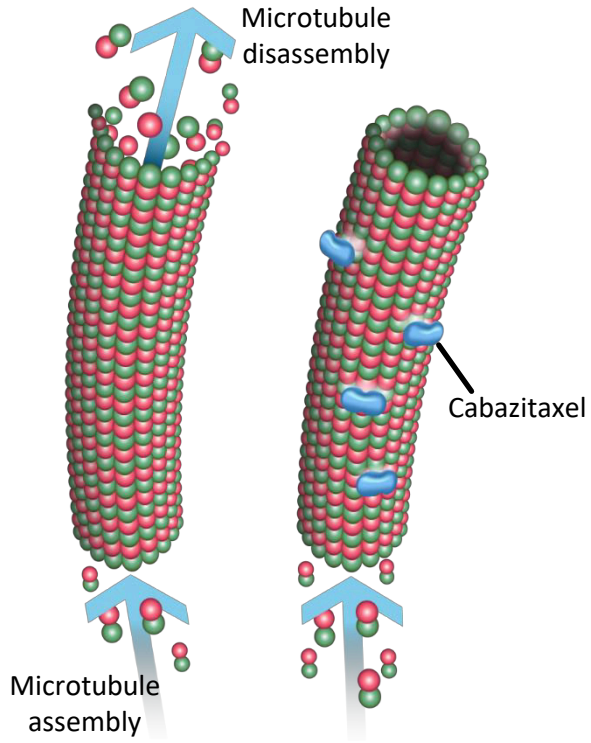
Case: 60yo with new diagnosis (de novo) of metastatic HSPC - high volume

- Options Include ADT plus:
  - Docetaxel
  - Abiraterone
  - Enzalutamide
  - Apalutamide
  - Docetaxel + Darolutamide (triplet)
  - Docetaxel + Abiraterone

F-18 DCFPyL PSMA PET

Docetaxel and Cabazitaxel Chemotherapy: Mechanism of Action

- Mechanism: Binds to tubulin and promotes microtubule assembly
  - Disrupts mitotic and interphase cellular functions
- Docetaxel first approved in mCRPC in 2004 (Tax327 trial)
  - 3mo improved survival!
- Cabazitaxel used in mCRPC after chemohormonal or docetaxel failure (Guidelines 31 and 32)

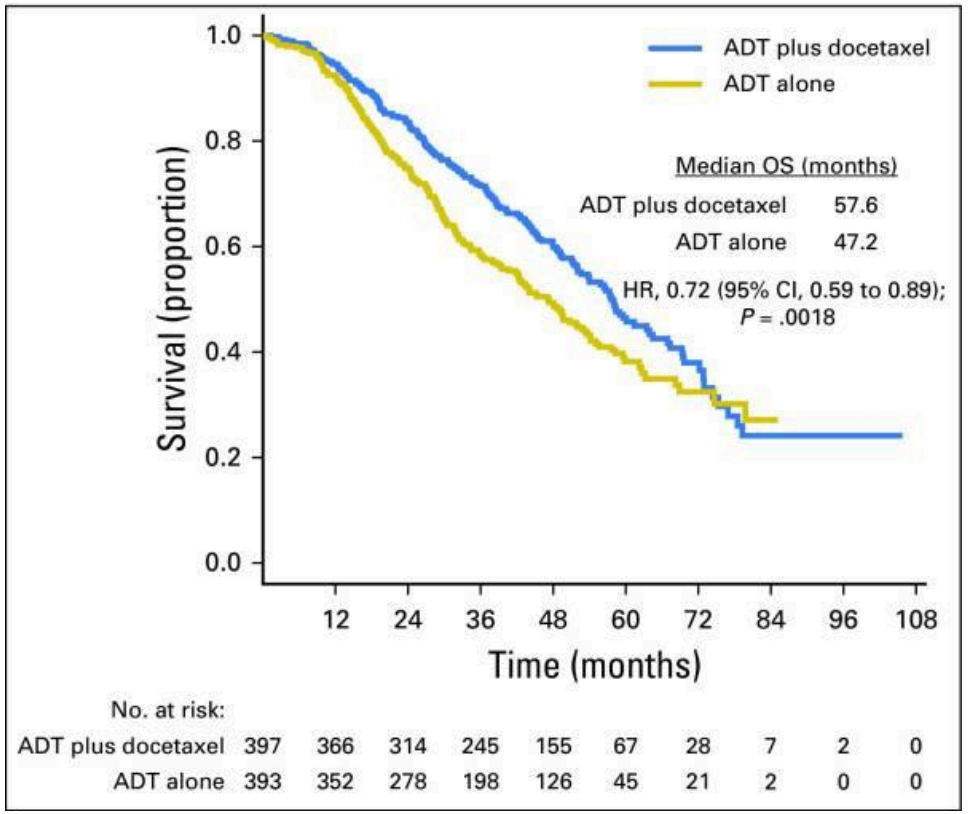


Cabazitaxel SPC, 2014.

DOCETAXEL and ADT for mHSPC

Trial	Overall Survival	
CHAARTED n=790	57.6 months docetaxel + ADT 47.2 months ADT	HR= 0.72; 95%CI 0.59 to 0.89 P=0.0018

- Volume of disease important:
  - High-volume disease OS 51.2 mo for chemohormonal therapy versus 34.4mo with ADT alone
  - Low-volume disease no OS benefit was observed
- Generally, first-line chemotherapy for mCRPC or used after oral inhibitors



Kyriakopoulos CE et al: Chemohormonal therapy in metastatic hormone-sensitive prostate cancer: long-term survival analysis of the randomized pase III E3805 CHAARTED trial. J Clin Oncol 2018; 36:1080.

Comorbidities of Concern with Docetaxel

- Performance status is critical – OK to treat ECOG PS 0-2
- CHF/volume overload
  - Severe fluid retention 6.5% even with dexamethasone
- Peripheral neuropathy
- Monitor LFTs
- Increased risk of arrhythmia in patients with h/o CAD or arrhythmia
- Brittle diabetic – concern with associated dexamethasone and prednisone

Determining Chemotherapy Fitness

Table 1 Predictors of Chemotherapy Toxicity, and Scoring Algorithm

Risk Factor	Score
Age: ≥ 72	2
Cancer type: gastrointestinal or genitourinary	2
Chemotherapy dosing: standard dose	2
Number of chemotherapy drugs: polychemotherapy	2
Hemoglobin: < 11 g/dL (male), < 10 g/dL (female)	3
Creatinine clearance (Jelliffe formula – ideal weight): < 34 mL/min	3
Hearing: described as fair or worse	2
Number of falls in last 6 months: 1 or more	3
Needs assistance with taking medications	1
Limited in walking one block	2
Decreased social activity because of physical or emotional health	1

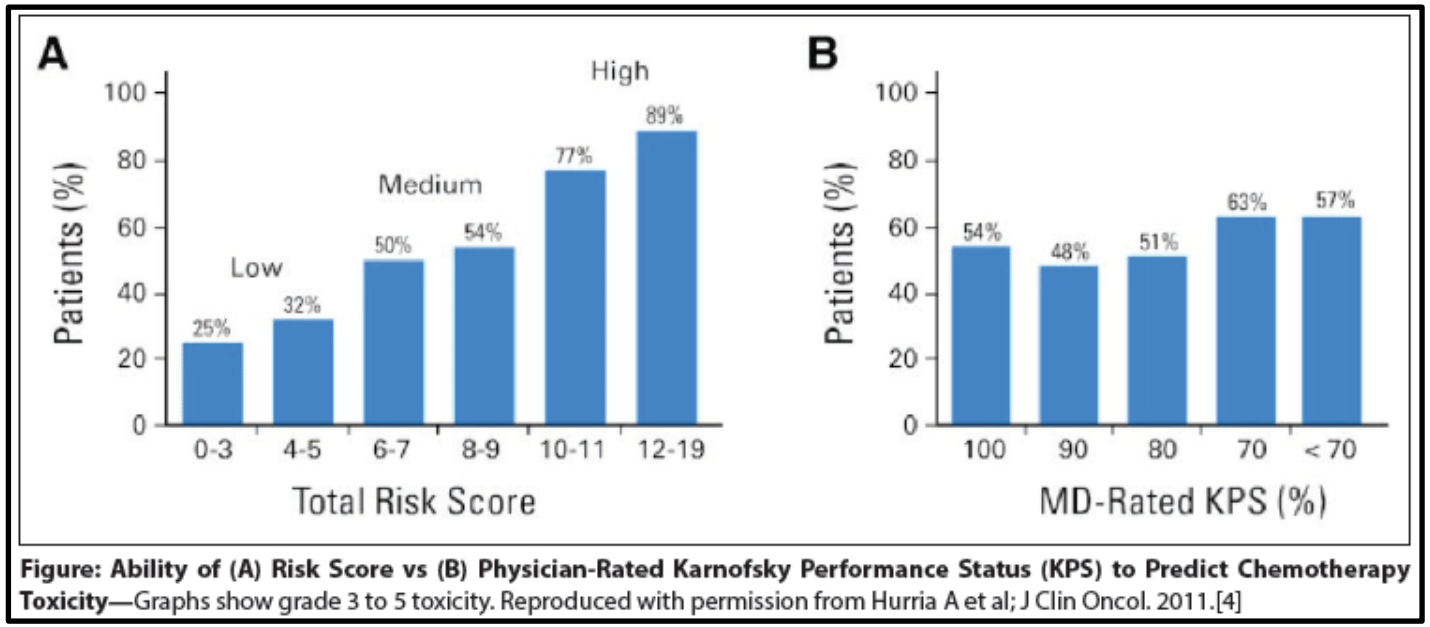


Figure: Ability of (A) Risk Score vs (B) Physician-Rated Karnofsky Performance Status (KPS) to Predict Chemotherapy Toxicity—Graphs show grade 3 to 5 toxicity. Reproduced with permission from Hurria A et al; J Clin Oncol. 2011.[4]

Hurria A e t al. J Clin Oncol. 2011;29:3457-65.

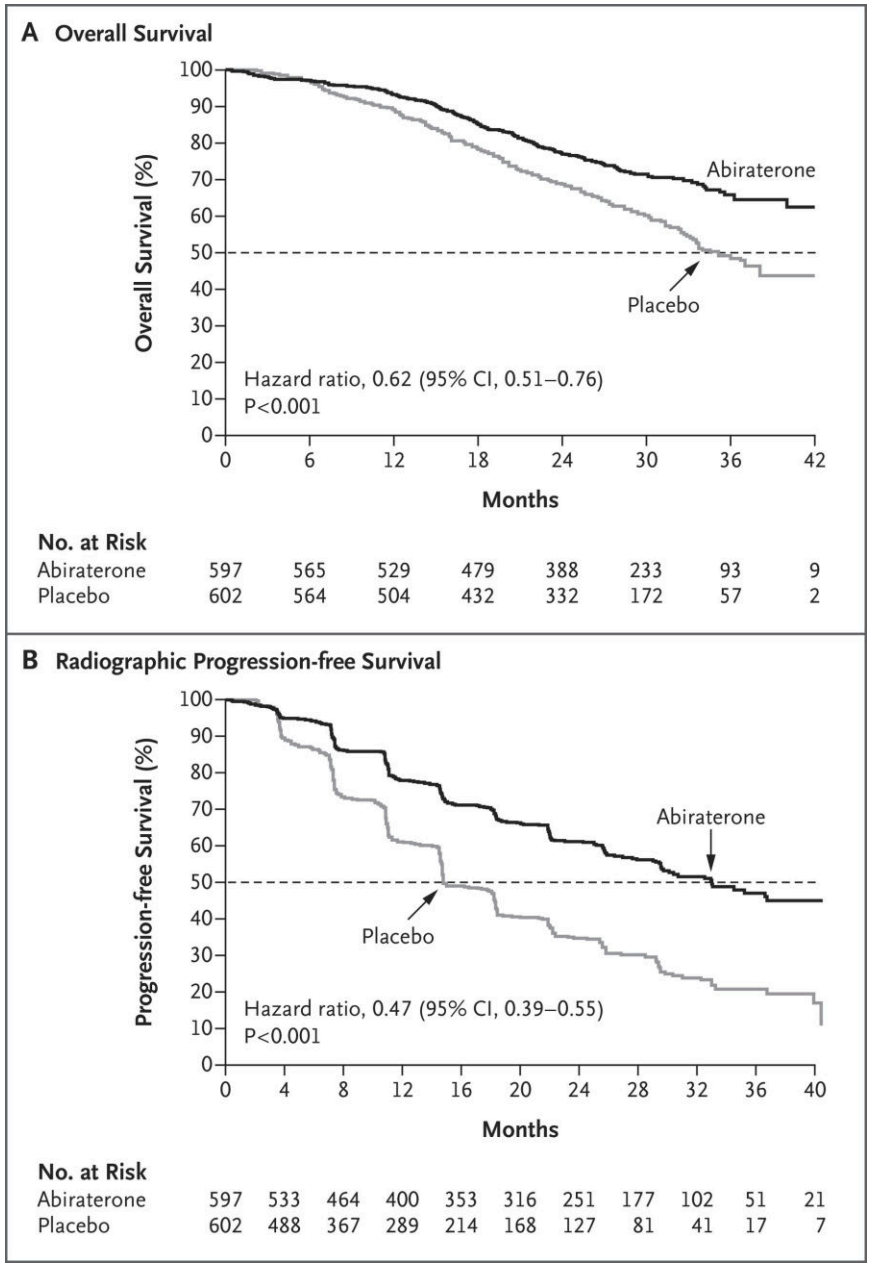
Results From Phase III Trials of ADT + Docetaxel or ARI

Trial	Regimens of Interest	n	Primary Endpoint(s)	Median OS	OS HR (95% CI)	*P* Value
CHAARTED[1]	ADT alone ADT + docetaxel	393 397	OS	47.2 mo 57.6 mo	0.72 (0.59-0.89)	<.0018
STAMPEDE[2]	ADT alone ADT + docetaxel	724 362	OS	57.1 mo 63.1 mo	0.81 (0.69-0.95)	.009
STAMPEDE[3]	ADT alone ADT + abiraterone	957 960	OS	NE NE	0.63 (0.52-0.76)	<.001
LATITUDE[4]	ADT alone ADT + abiraterone	602 597	OS and rPFS	34.7 mo NE	0.62 (0.51-0.76)	<.001
TITAN[5]	ADT alone ADT + apalutamide	527 525	OS and rPFS	52.2 mo NE	0.65 (0.53-0.79)	<.0001
ARCHES[6]	ADT alone ADT + enzalutamide	576 574	rPFS	NE NE	0.66 (0.53-0.81)	<.0001
ENZAMET[7]	ADT + NSAA ADT + enzalutamide	562 563	OS	NE NE	0.67 (0.52-0.86)	.002

1. Kyriakopoulos. JCO. 2018;36:1080. 2. Clarke. Ann Oncol. 2019;30:1992. 3. James. Lancet. 2016;387:1163.
4. Fizazi. NEJM. 2017;377:352. 5. Chi. JCO. 2021;39:2294. 6. Armstrong. ESMO 2021. Abstr LBA25. 7. Davis. NEJM. 2019;381:121.

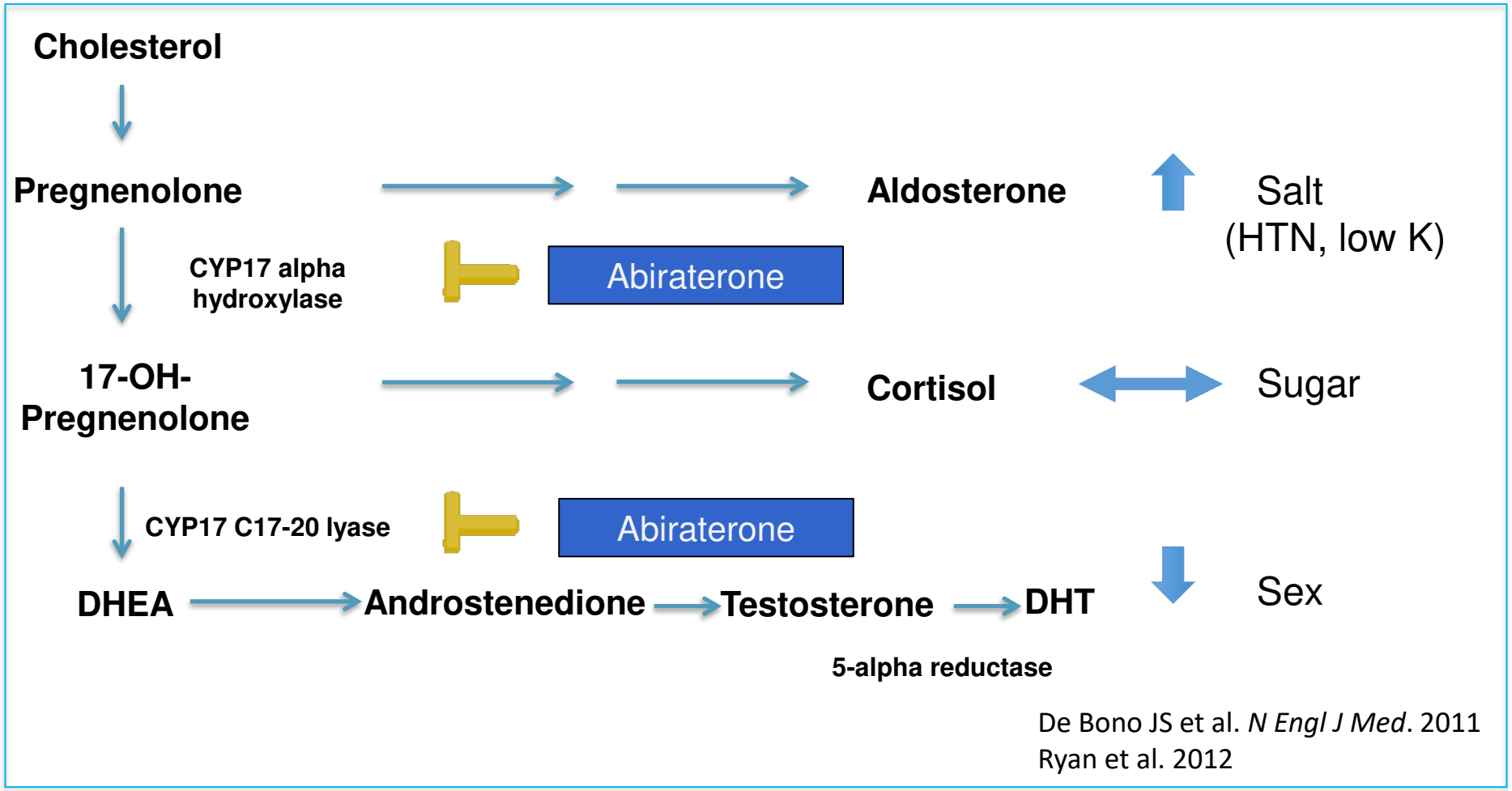
ABIRATERONE ACETATE ± ADT in mHSPC

Trial	Primary Endpoints
LATITUDE n=1,199	Overall Survival • Not reached abiraterone + ADT • 34.7 months ADT + placebo Radiographic Progression-Free Survival • 33.0 months abiraterone + ADT • 14.8 months ADT + placebo



1. Fizazi K et al: Abiraterone plus prednisone in metastatic, castration-sensitive prostate cancer. N Engl J Med 2017; 377:352.

ABIRATERONE MECHANISM EXPLAINS SIDE EFFECTS



De Bono JS et al. *N Engl J Med*. 2011
Ryan et al. 2012

Abiraterone Acetate

- Which patients?
  - FDA approved for men with mHSPC (with ADT)
  - mCRPC *before* and *after* chemotherapy.
- Side Effects
  - HTN, hypokalemia, edema: routine assessments
  - Steroid induced hyperglycemia
  - LFT elevation (ALT, AST or Bilirubin): Check q2 weeks initially then routinely
- Which patients are poor candidates?
  - Cannot tolerate systemic steroids, i.e. brittle DM, gastric ulcer, rapidly progressive disease, infection
  - Cardiac disease (heart failure, edema)
  - Hepatic dysfunction, active viral hepatitis, ETOH abuse

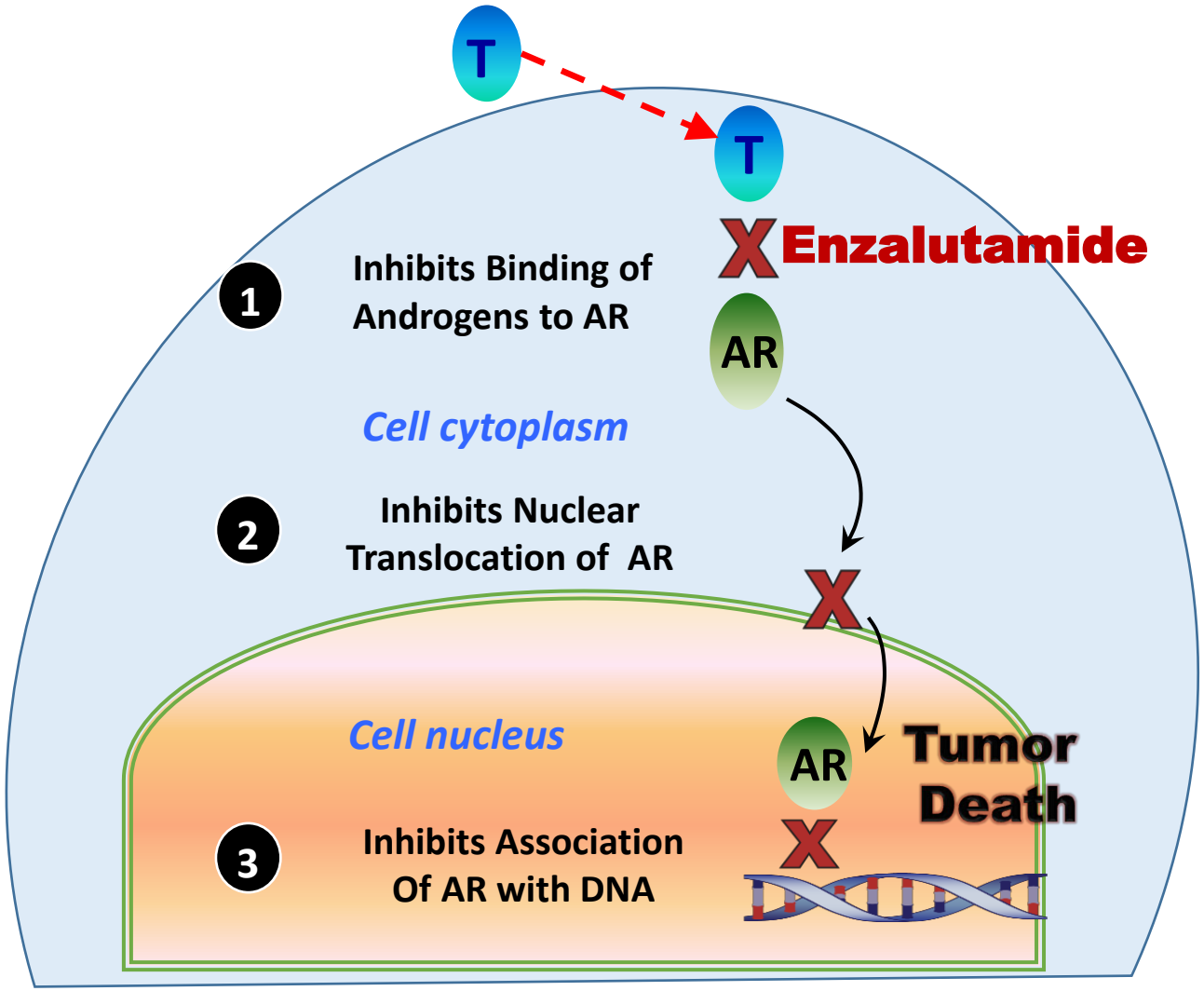
Results From Phase III Trials of ADT + Docetaxel or ANDROGEN RECEPTOR INHIBITOR (ARI)

Trial	Regimens of Interest	n	Primary Endpoint(s)	Median OS	OS HR (95% CI)	*P* Value
CHAARTED[1]	ADT alone ADT + docetaxel	393 397	OS	47.2 mo 57.6 mo	0.72 (0.59-0.89)	<.0018
STAMPEDE[2]	ADT alone ADT + docetaxel	724 362	OS	57.1 mo 63.1 mo	0.81 (0.69-0.95)	.009
STAMPEDE[3]	ADT alone ADT + abiraterone	957 960	OS	NE NE	0.63 (0.52-0.76)	<.001
LATITUDE[4]	ADT alone ADT + abiraterone	602 597	OS and rPFS	34.7 mo NE	0.62 (0.51-0.76)	<.001
TITAN[5]	ADT alone ADT + apalutamide	527 525	OS and rPFS	52.2 mo NE	0.65 (0.53-0.79)	<.0001
ARCHES[6]	ADT alone ADT + enzalutamide	576 574	rPFS	NE NE	0.66 (0.53-0.81)	<.0001
ENZAMET[7]	ADT + NSAA ADT + enzalutamide	562 563	OS	NE NE	0.67 (0.52-0.86)	.002

1. Kyriakopoulos. JCO. 2018;36:1080. 2. Clarke. Ann Oncol. 2019;30:1992. 3. James. Lancet. 2016;387:1163.
4. Fizazi. NEJM. 2017;377:352. 5. Chi. JCO. 2021;39:2294. 6. Armstrong. ESMO 2021. Abstr LBA25. 7. Davis. NEJM. 2019;381:121.

ENZALUTAMIDE: AR Signaling Inhibitor

- Oral drug rationally designed to target AR signaling
- Impacts multiple steps in AR signaling pathway.
- Apalutamide and Darolutamide have similar mechanism of action



Tran et al. Science 2009;324:787–90.

Enzalutamide and Androgen Receptor Signaling Inhibitors

- Which patients?
  - FDA approved for men with mHSPC
  - mCRPC *before* and *after* chemotherapy. *M0 CRPC*
- Side Effects
  - Profound fatigue (dose reduction), HTN, constipation/diarrhea, rare seizure, Posterior Reversible Encephalopathy Syndrome (PRES)
- Care when using other CYP inhibitors (statin: gemfibrozil)
- Which patients are poor candidates?
  - History of seizure, strokes, falls
  - Pts who already have significant fatigue
  - Advanced age (e.g. >70)

Which ASI Should Go First in Advanced Disease?

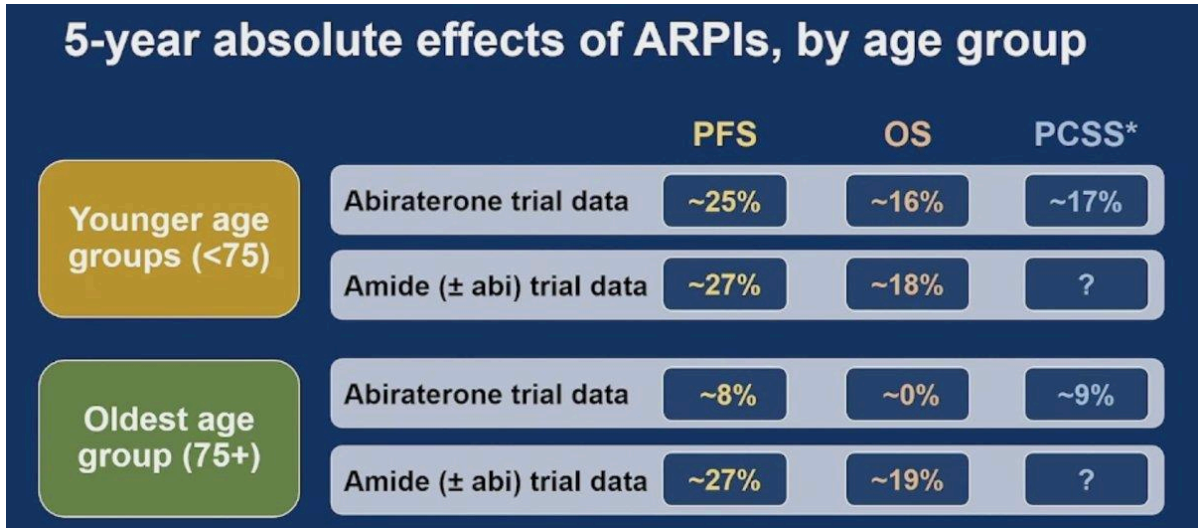
- Limited randomized data to guide in choosing first agent
  - Financial issues and clinical situation should dictate
- Avoid following ASI with another of similar mechanism
- Unique situations with rapid disease progression, significant symptoms and/or visceral disease consider:
  - Triplet therapy (ADT, Darolutamide, docetaxel)
  - Etoposide/cisplatin for neuroendocrine/small cell

STOPCAP: Meta-Analysis of ARSIs in mHSPC

- ‘Real world data’
- 7778 patients treated with ARSIs: ARSI + ADT improved survival compared to ADT
- No differences between ‘amides’ in responses (e.g. enzalutamide vs apalutamide)
- Note: Decreased overall survival with abiraterone in oldest age groups

Trial ID	Synchronous	High volume	Median age (IQR)	Docetaxel as part of SOC	cT4*
STAMPEDE (abi)	94%	56%*	67 (62-71)	0%	28%
LATITUDE (abi)	100%	94%	65 (60-70)	0%	27%
PEACE-1 (abi)	100%	57%	67 (60-72)	61%†	19%
ENZAMET (enz)	68%*	54%	69 (64-75)	45%†	14%
TITAN (apa)	86%*	63%	65 (60-70)	11%‡	19%
STAMPEDE (abi+enz)	93%	53%*	69 (63-74)	9%§	26%
SWOG 1216 (ort)	Unknown	Unknown	68 (62-74)	0%	Unknown

* Some data unavailable
† Stratified by planned use of docetaxel
§ Stratified by use of docetaxel
‡ Stratified by prior use of docetaxel



GU ASCO 2025, Fisher et al.

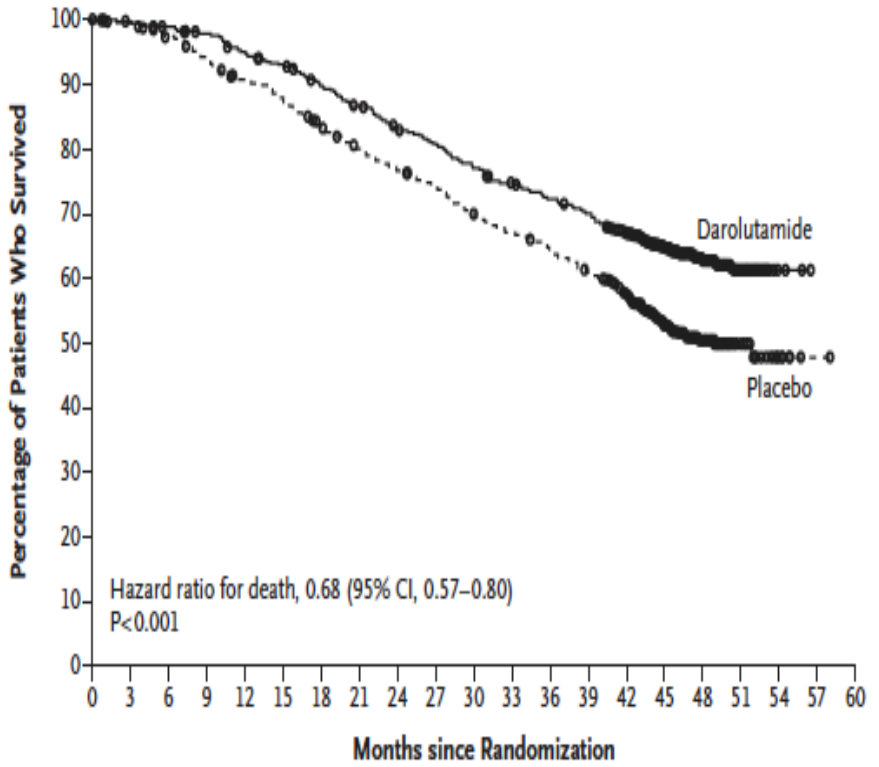
Case: 60yo with new diagnosis (de novo) of metastatic HSPC - high volume

- Options Include ADT plus:
  - Docetaxel
  - Abiraterone
  - Enzalutamide
  - Apalutamide
  - Docetaxel + Darolutamide (triplet)
  - Docetaxel + Abiraterone

F-18 DCFPyL PSMA PET

What About Triplet Therapy for mHSPC? ADT/Docetaxel ± Darolutamide (ARASENS)

- Improved median OS
  - 48.9 months vs NR
- Curves separate early at 9 months.
- Triplet therapy not meaningfully more toxic than ADT/Docetaxel
- Patients with aggressive features do very poorly on ADT alone

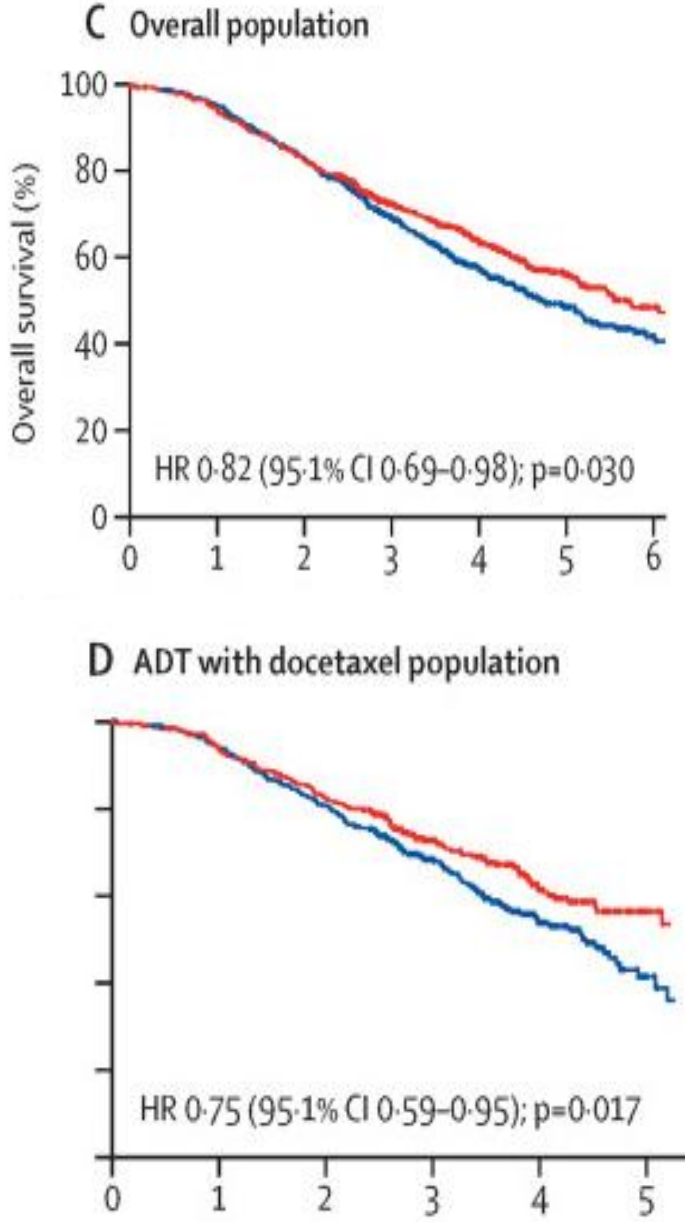


	Median Survival (95% CI)
	mo
Darolutamide	NE
Placebo	48.9 (44.4–NE)

Smith et al NEJM 2023.

‘Triplet’ Therapy for mHSPC

- **ARASENS trial** for men with metastatic HSPC improves overall survival
- **PEACE-1 Trial**
  - 2x2 factorial design ADT and docetaxel ± abiraterone
  - Abi improves overall survival (0·75, 95·1% CI 0·59–0·95; p=0·017).
  - Increased Gr ≥3 events with abi arm (63% vs 52%; p=0.02)
- **Conclusion: Adding androgen signaling inhibitor to docetaxel + ADT improves overall survival**
  - Overtreatment for some patients
  - Increased cost
  - Must be chemofit



PEACE Trial : Fizazi. Lancet 2022.

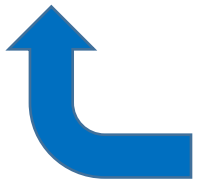
Choosing Between Docetaxel, an AR Pathway inhibitor or triplet therapy in mHSPC

- **ALL** patients should be offered treatment intensification
  - Triplet in *de novo* high volume disease or high volume
- Approach varies based on cost/SE/patient comorbidities
- Docetaxel: least expensive, done after 6 cycles, must be chemo-fit
- ARPI
  - Abiraterone: generic, requires K+/LFT/BP monitoring, long-term prednisone
  - Enzalutamide/Apalutamide/Daralutamide: expensive, less monitoring, long-term treatment, neurocognitive issues

CURRENT METASTATIC HSPC TREATMENT GUIDELINES

14. In addition to ADT, clinicians should offer androgen pathway directed therapy (abiraterone acetate plus prednisone, apalutamide, enzalutamide or darolutamide) to the majority of patients with mHSPC. (Strong Recommendation; Evidence Level: Grade A)

15. In selected mHSPC patients, clinicians should offer ADT in combination with docetaxel and either abiraterone acetate plus prednisone or darolutamide. (Strong Recommendation; Evidence Level: Grade A [Abiraterone]/Grade B [Darolutamide]



'Triplet Therapy'

ADT alone

ADT plus:

Abiraterone, Apalutamide, or Enzalutamide

Docetaxel

ADT plus:

Docetaxel + Darolutamide

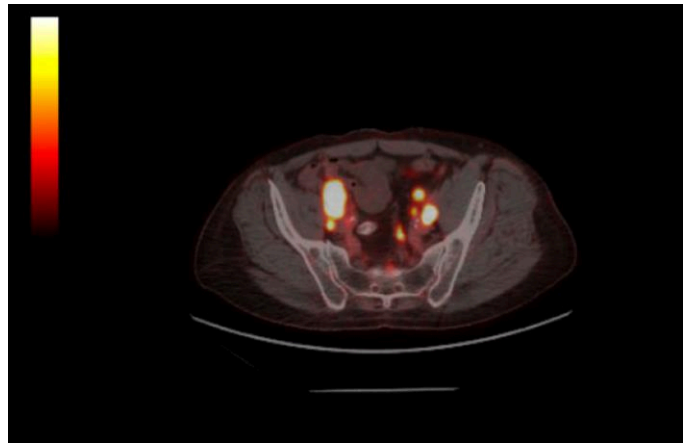
Docetaxel + Abiraterone

ADT plus EBRT to primary tumor (for low-volume disease)

NCCN. Clinical practice guidelines in oncology: prostate cancer. v2.2023.

Case #2: Healthy 53yo with pelvic adenopathy and bone metastasis

- Presents with urinary obstruction
- PSA 35 and GG5 tumor right (T2b)
- Large pelvic lymph nodes and a metastasis to humerous (N1 M1b)

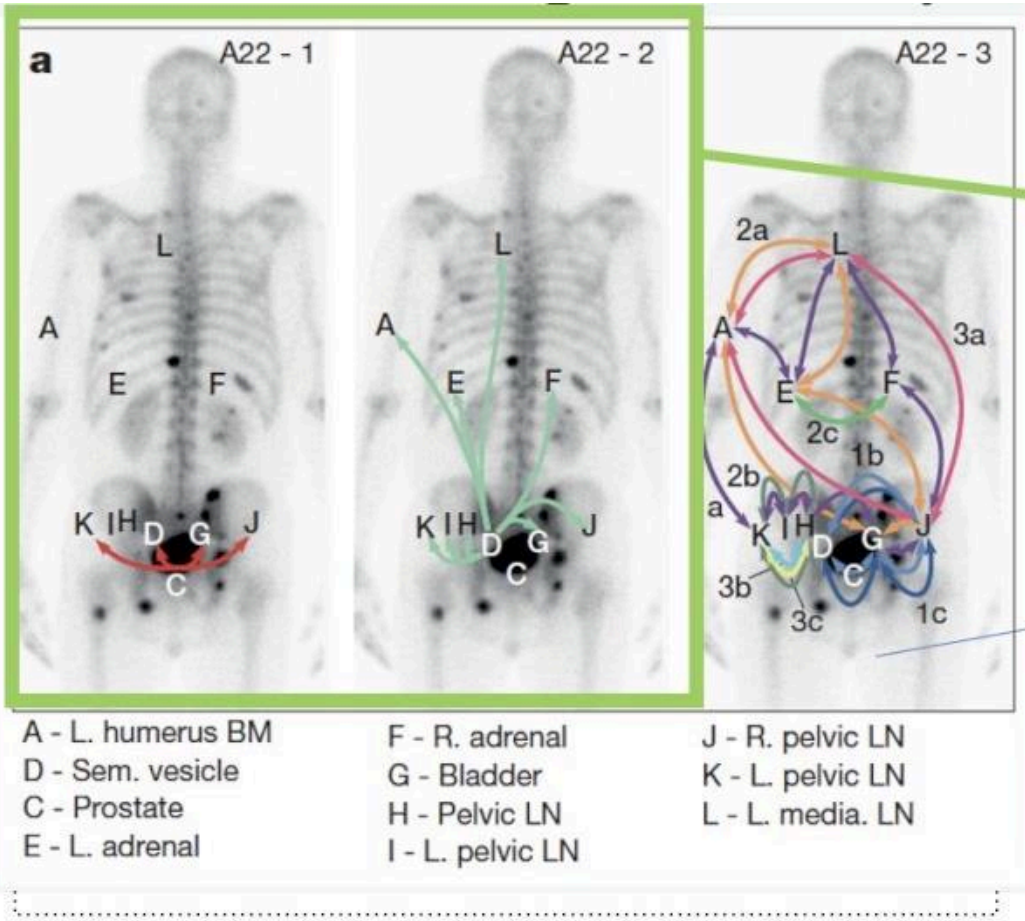


Oligometastatic Disease (Low volume)

- Intermediate state of cancer spread:
  - ***De novo* (synchronous)**
  - ***Oligorecurrent (after treatment)***

- Basic definition: related to the number of metastases you can reasonably treat
  - <5 metastatic sites

Early Oligometastatic Cancer is Genetically Distinct From Polymetastatic



1. **early/oligo:** most mets originate in the primary

2. **poly:** met-to-met

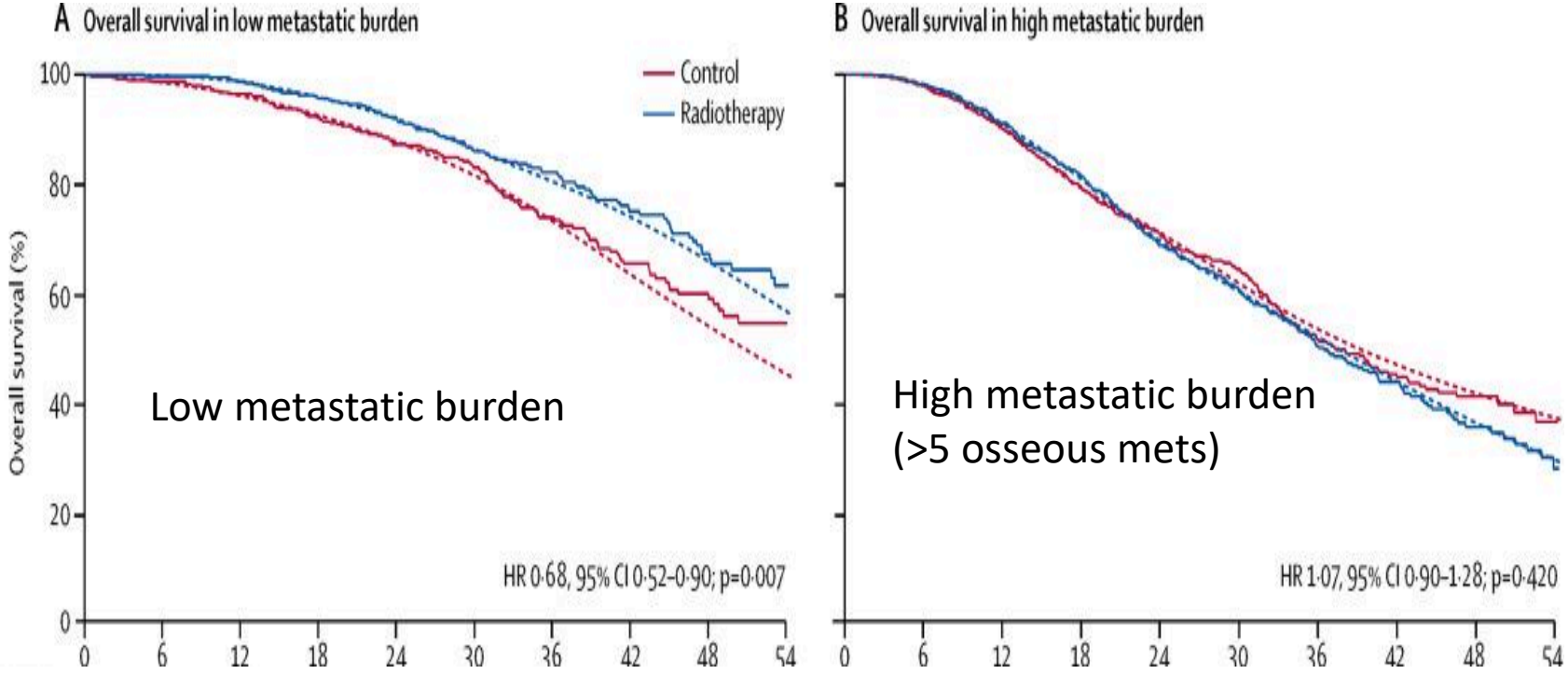
Nature. 2015;520(7547): 353-357.

What is the existing evidence for primary local therapy in low-volume mHSPC?

- STAMPEDE Arm H
- PEACE-1

METASTATIC HSPC: Role of Prostate Radiation (STAMPEDE Arm H)

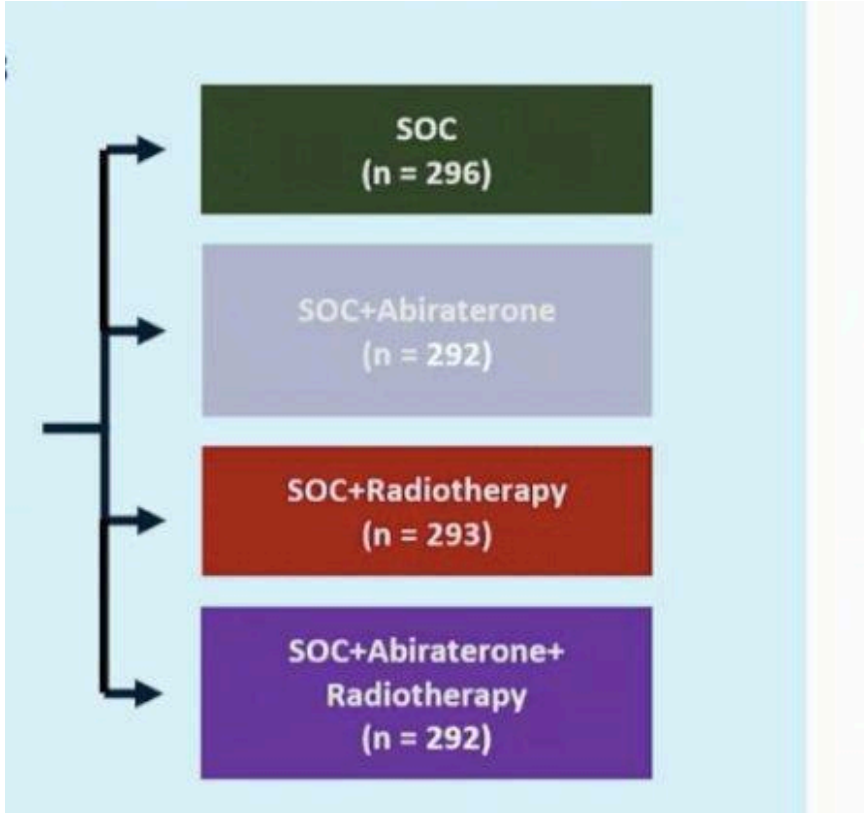
16. In selected mHSPC patients, clinicians may offer primary radiotherapy to the prostate in combination with ADT with or without an ARSI. (Conditional Recommendation; Evidence Level: Grade C)



Parker CCet al: Radiotherapy to the primary tumour for newly diagnosed, metastatic prostate cancer (STAMPEDE): a randomised controlled phase 3 trial. Lancet 2018; 392:2353.

Systemic treatment intensification with radiation in metastatic disease: PEACE-1

- 1173 patients with *de novo* mHSPC
- Improved radiographic-free survival when XRT added to abi ± docetaxel (7.5 vs 4.4 yr; HR 0.65, p=0.02)
- No OS benefit (yet) in low or high-volume disease with XRT ± abi (p=0.11)
- Reduction in serious GU events with XRT
- Conclusion: Be selective in offering treatment intensification



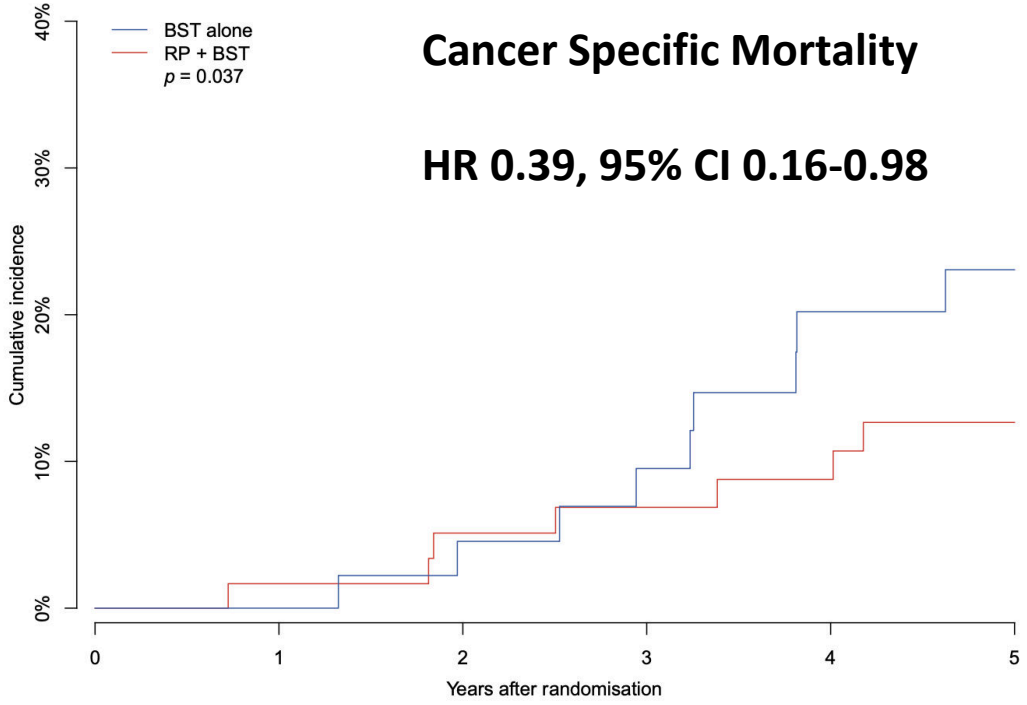
Bossi A, et al. Lancet. 2024

TRIALS ASSESS ROLE OF PROSTATE SURGERY OR RADIATION IN OLIGOMETASTATIC PC

	Trial	Design	Primary Outcome
SURGERY	**G-RAMPP**	**RP+ ADT vs. ADT alone**	**CSM improved**
	TRoMbone	**RP+ADT vs. ADT alone**	**Feasibility**
	SWOG 1802	**RP/RT + standard systemic therapy (SST) vs SST alone**	**OS**
RADIATION	**PEACE-1**	**RT + SOC + Abi vs SOC + Abi**	**rPFS improved OS ?**
	HORRAD	**RT + ADT vs. ADT alone**	**OS improved**
	STAMPEDE	**RT + standard of care (SOC) for newly diagnosed M1 vs SOC**	**OS improved**

Metastatic HSPC: Role of surgery with Best Systemic Therapy (RAMPP trial)

- 132 pt (1-5 bone mets) randomized 1:1
- CSM lower in the surgery group (13%) vs. systemic therapy-only group (23%;p=0.03)
- OS 81% RP+BST vs 74% BST (p=0.13)
- Study stopped early, not powered for OS
- RP is safe and effective in reducing cancer-specific death in low-volume metastatic disease



Cancer Specific Mortality

HR 0.39, 95% CI 0.16-0.98

Groefen, Eur Urology 2025

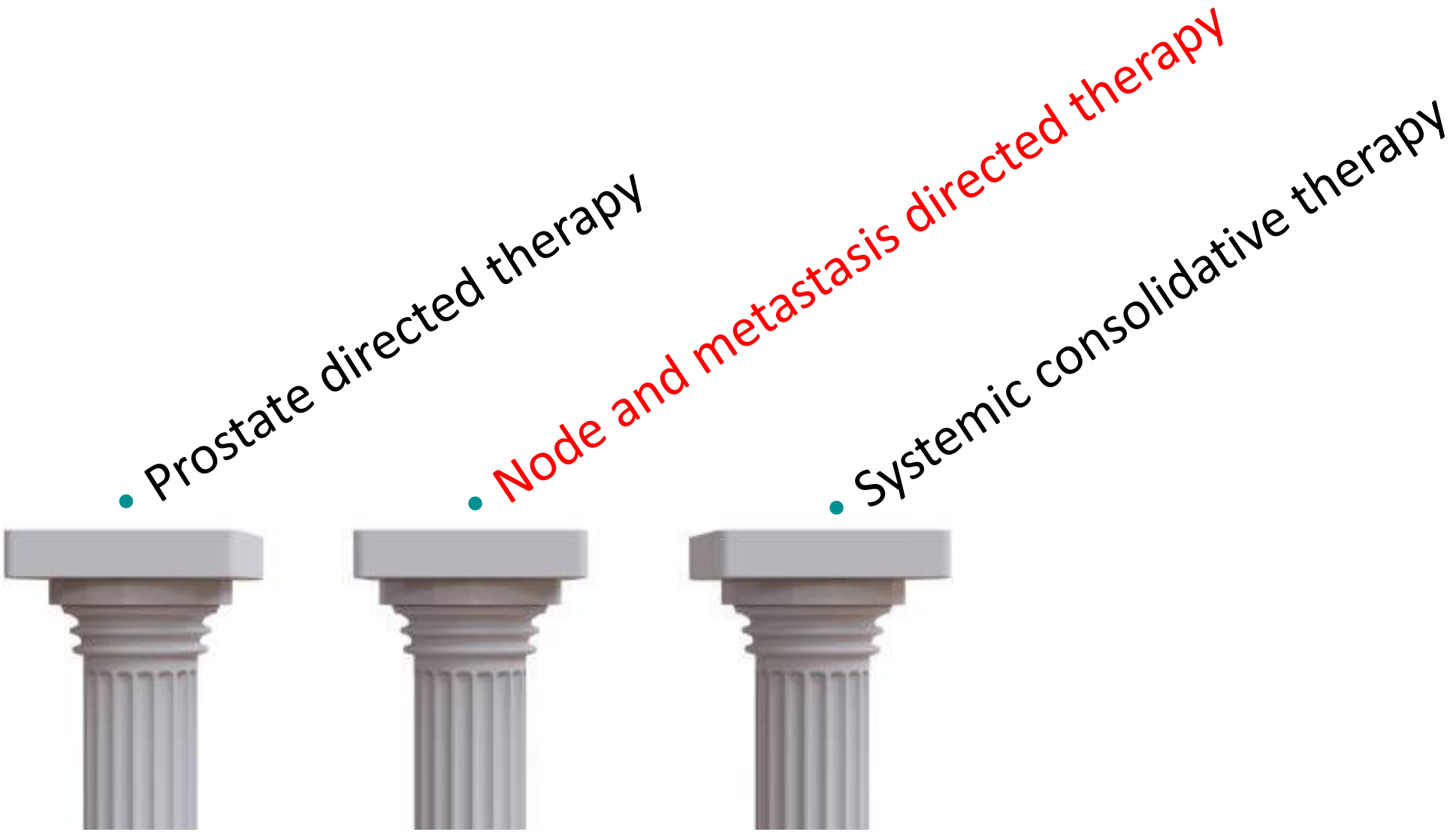
American Urological Association Education & Research, Inc.

Society of Urologic Oncology, Inc.

Case #2 Options: 52yo with N1 M1b

- Systemic therapy with ADT + ASI
- Systemic therapy with ADT (± ASI) and Prostate Radiation (consider metastasis directed therapy)
- Surgery? (± Neoadjuvant ASI) ± metastasis directed therapy

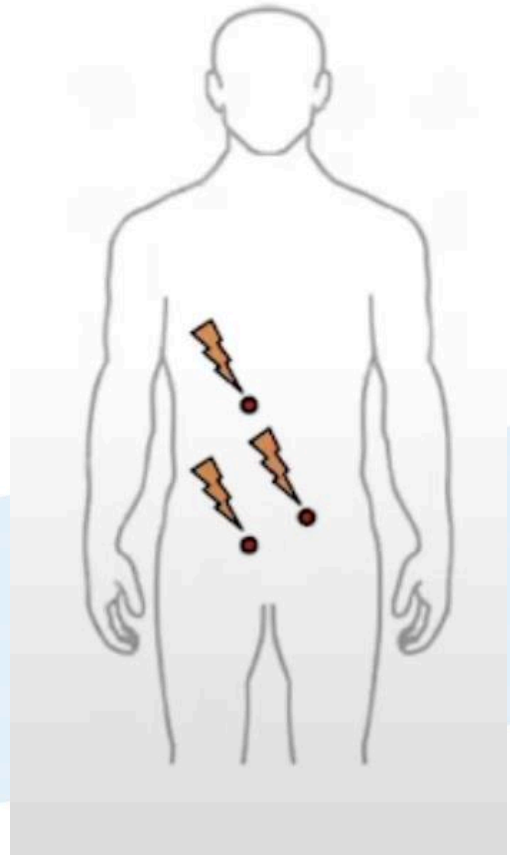
Oligometastatic Disease: 3 Treatment ‘pillars’



Stereotactic body radiation therapy (SBRT)

- Used in many cancer types for Metastasis Directed Therapy (MDT)
- Precise, image-guided, high-dose radiation in 5 or fewer treatments
- Settings for which MDT has utility with evidence:

Treatment Regimen	mCSPC		mCRPC	
	De novo Oligometastatic	Metachronous Oligorecurrent	Oligometastatic	Oligoprogressive
MDT	+/-	Preferred	Preferred	+/-



American Urological Association Education & Research, Inc.

SUO Society of Urologic Oncology, Inc.

Phase II: Metastasis directed therapy (MDT) in low volume mHSPC

- Two small trials to date in low volume oligometastatic patients (<3 sites) after local treatment – no survival benefit
- STOMP trial (n=62)
  - *PET choline* to identify lesions
  - Median ADT-free survival 21mo in AS vs 13mo in SBRT (HR=0.6; 80% CI, 0.40 to 0.90; P=0.11)
  - QOL comparable between arms
- ORIOLE trial (n=54)
  - *PSMA PET* imaging
  - Progression after 6 months which was lower adding SBRT than with surveillance (19% versus 61%, P=0.005).

Ost P, Reynders D, Decaestecker K et al. J Clin Oncol 2018
Phillips R, Shi WY, Deek M et al. JAMA Oncol 2020;

Addition of Metastasis-Directed Therapy to Intermittent ADT for Oligometastatic HSPC

POPULATION

87 Men

Adults with oligometastatic prostate cancer at ≤5 metastatic sites

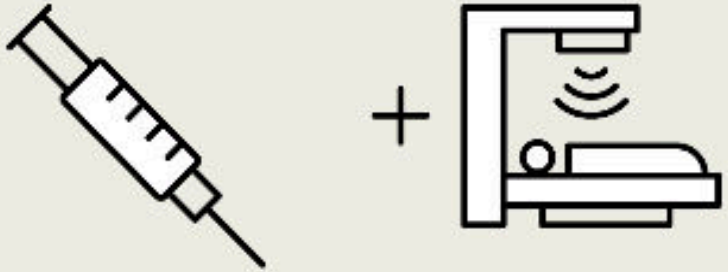
Median age, 67 y

SETTINGS / LOCATIONS

3 Tertiary care centers in US

INTERVENTION

87 Participants randomized



44 Hormone therapy alone
Intermittent hormone therapy

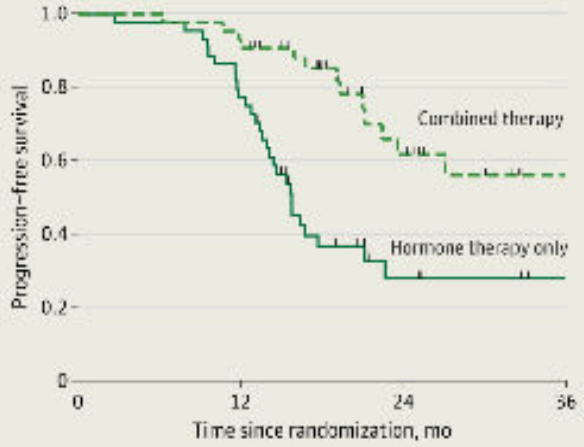
43 Combined therapy
Metastasis-directed therapy combined with intermittent hormone therapy

PRIMARY OUTCOME

Progression-free survival (PFS), defined as time from randomization to radiographic progression per RECIST 1.1 criteria, clinical progression, increasing prostate-specific antigen level, or death

FINDINGS

PFS was significantly improved with combined therapy compared with hormone therapy alone



Hazard ratio, 0.25 (95% CI, 0.12-0.55)
Median PFS: hormone therapy alone, 15.8 mo; combined therapy, median PFS not reached

Tang C, Sherry AD, Haymaker C, et al. Addition of metastasis-directed therapy to intermittent hormone therapy for oligometastatic prostate cancer: the EXTEND phase 2 randomized clinical trial. *JAMA Oncol*. Published online April 6, 2023. doi:10.1001/jamaoncol.2023.0161

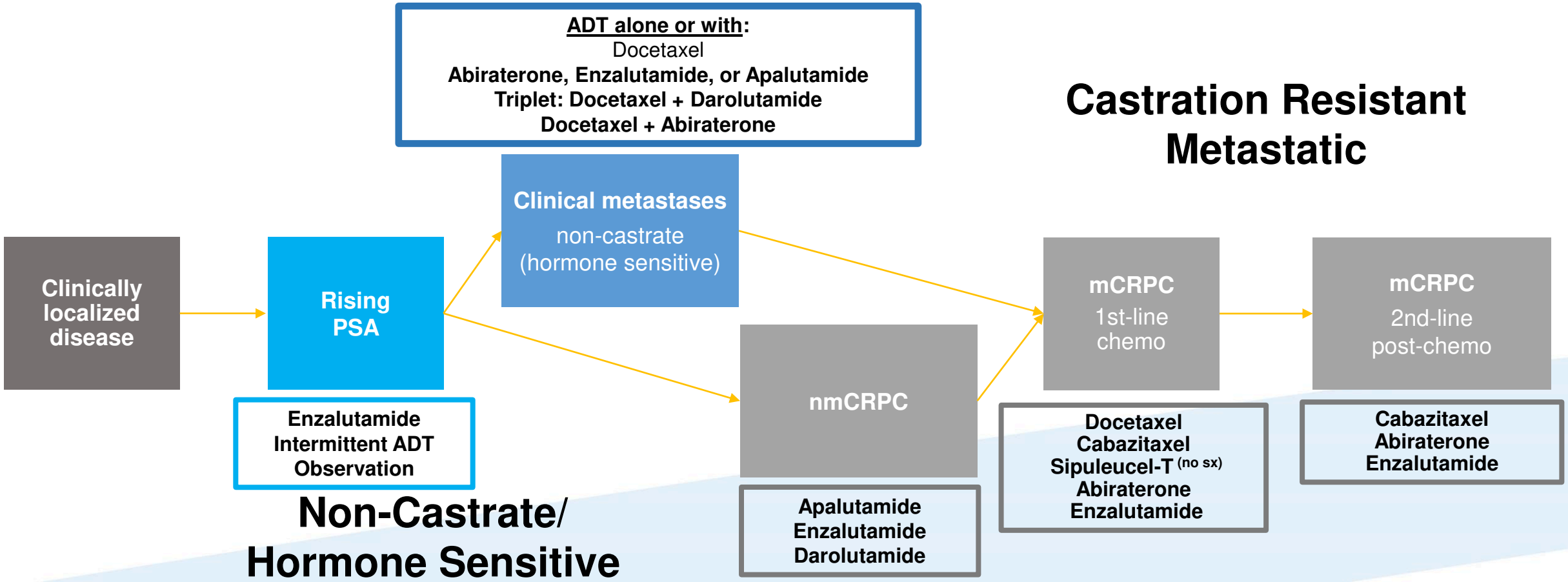
JAMA Oncol. 2023;9(6):825-834. doi:10.1001/jamaoncol.2023.0161

New Trials of Prostate and Metastasis-Directed Therapy

- **EXTEND trial**
  - RADIATION +MDT and INTERMITTENT ADT improved PFS (36mo vs 17mo)
- **METANOVA AND STAMPEDE TRIALS (in progress):**
  - PROSTATE RADIATION OR SURGERY ± MDRT in *de novo* oligometastatic PCa.

- **Note: Guidelines discuss MDT for selected situations but its use is still not guided by Phase III trial data**

Current Prostate Cancer Therapeutic Landscape[1]



American Urological Association Education & Research, Inc.

SUO Society of Urologic Oncology, Inc.

AUA SUO Guidelines

Take Home Messages: mHSPC

- Abiraterone is an androgen synthesis inhibitor (CYP17) (avoid brittle DM, liver diseases or gastric ulcers)
- Enzalutamide/Apalutamide/Daralutamide are direct androgen receptor inhibitors (care in *pts with seizure history, severe fatigue, or on coumadin)*
- Docetaxel is first-line chemotherapy for mCRPC generally used after oral inhibitors
- In patients *de novo* high-volume/high-risk PC, addition of abiraterone or daralutamide to docetaxel as "triplet therapy" is associated with OS benefit
- Radiation plus ADT (+ ARSI) improves survival in low-volume metastatic disease – does surgery?
  - Role of metastasis-directed therapy supported in oligomet disease
- Treatment sequencing will continue to evolve

Department of Urology
UNIVERSITY OF WISCONSIN
SCHOOL OF MEDICINE AND PUBLIC HEALTH