



0401C - Contemporary Management of Advanced Prostate Cancer: Guidelines and Beyond

Sunday, May 17

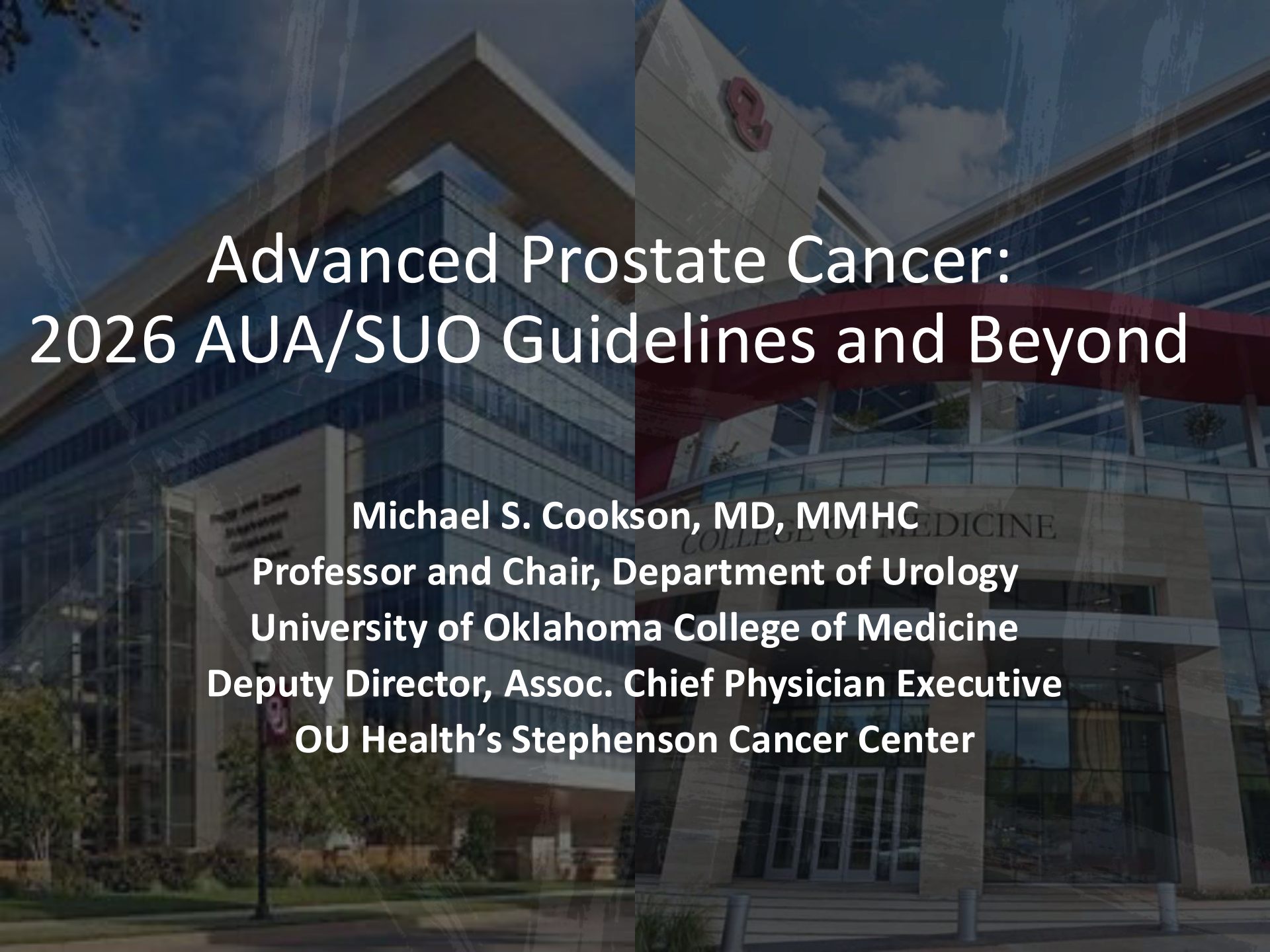
Michael S. Cookson, MD

David F. Jarrard, MD

Adam S. Kibel, MD

Kristen R. Scarpato, MD

ATTENTION: You are prohibited from using or uploading content you accessed through this activity into external applications, bots, software, or websites, including those using artificial intelligence technologies and infrastructure, including deep learning, machine learning and large language models and generative AI.



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

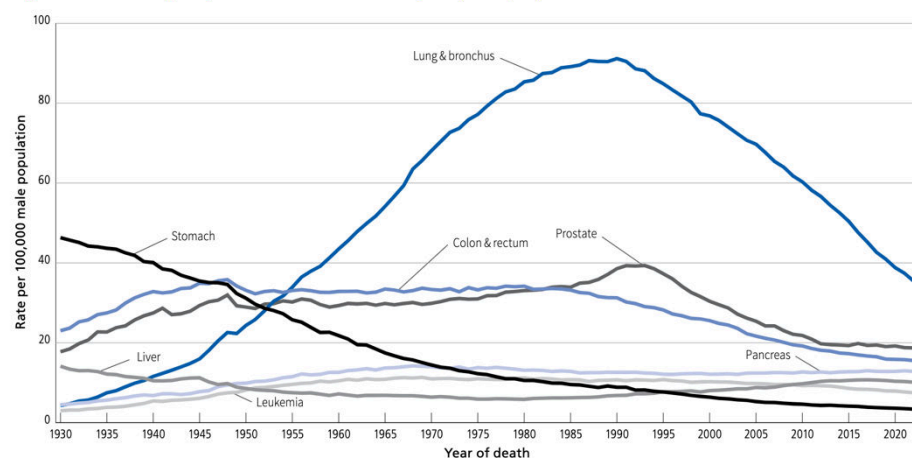


Kristen Scarpato, MD, MPH
Vanderbilt University

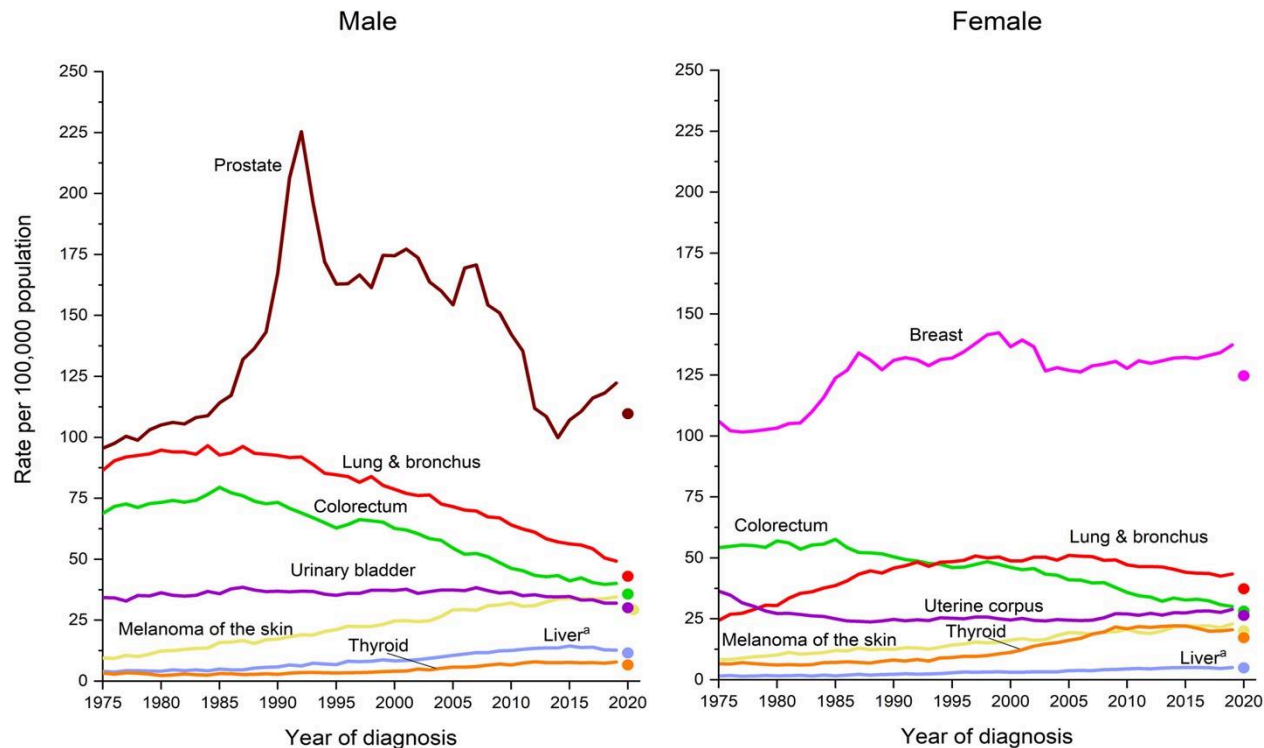
Prostate Cancer in the US: 2026

- 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

Figure 1. Trends in Age-adjusted Cancer Death Rates by Site, Males, US, 1930-2022



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.”

Advanced Prostate Cancer: AUA/SUO Guideline

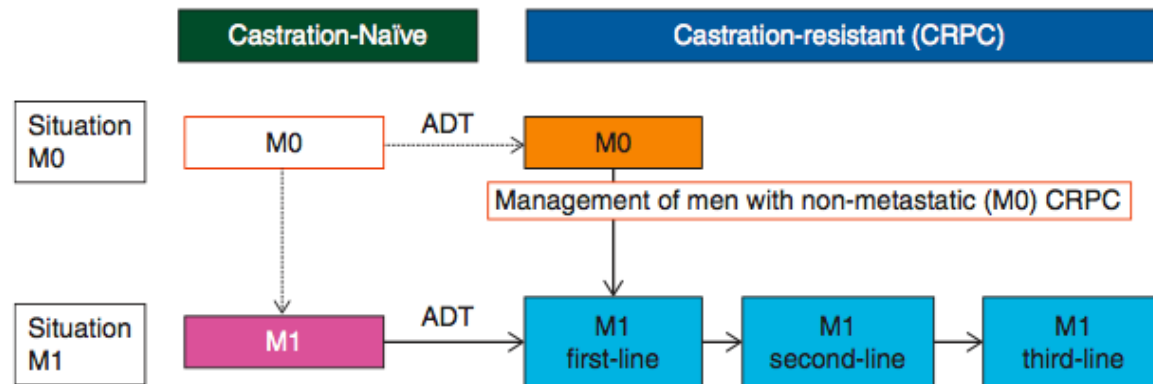
Published 2020, Amended 2023, 2026

Panel Members

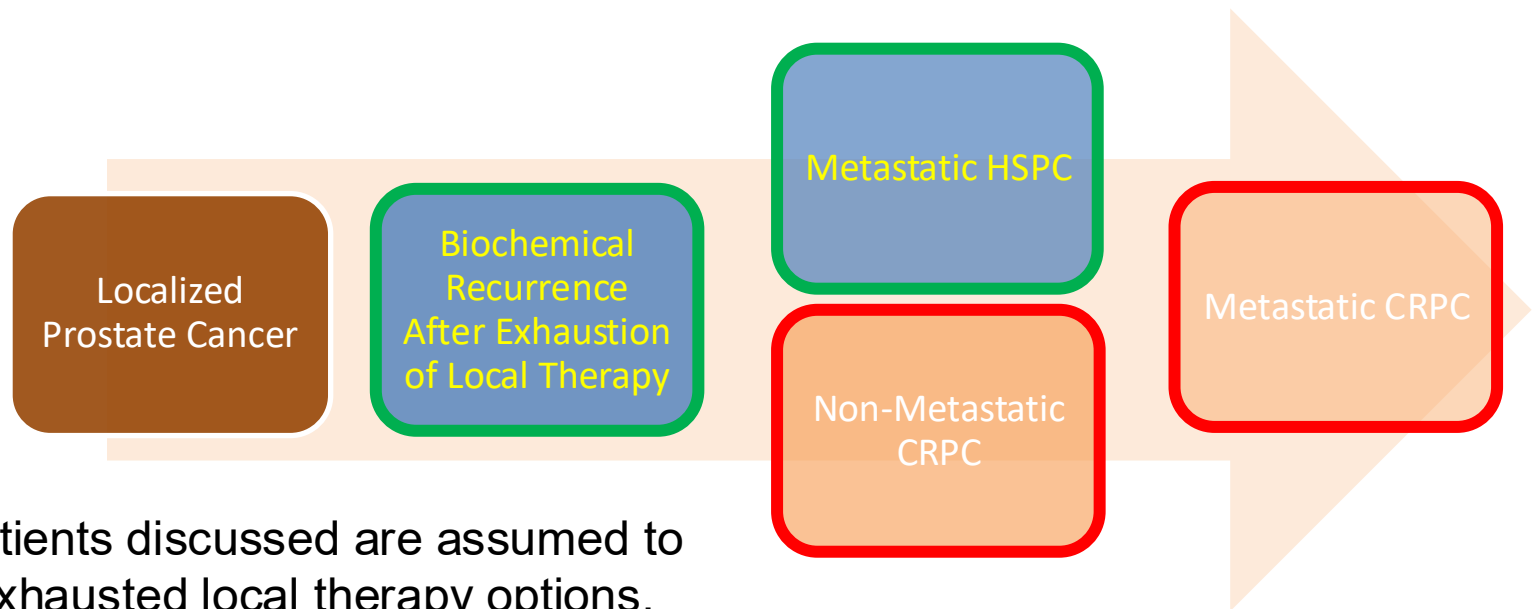
William Lowrance, MD, MPH, MBA; Rodney Breau, MSc, MD; Roger Chou, MD; Brian F. Chapin, MD; Tony Crispino; Robert Dreicer, MD, MS, MACP; David F. Jarrard, MD; Adam S. Kibel, MD; Todd M. Morgan, MD; Alicia K. Morgans, MD, MPH; William K. Oh, MD; Matthew Resnick, MD, MPH, MMHC; Anthony Zietman, MD; Michael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



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*)

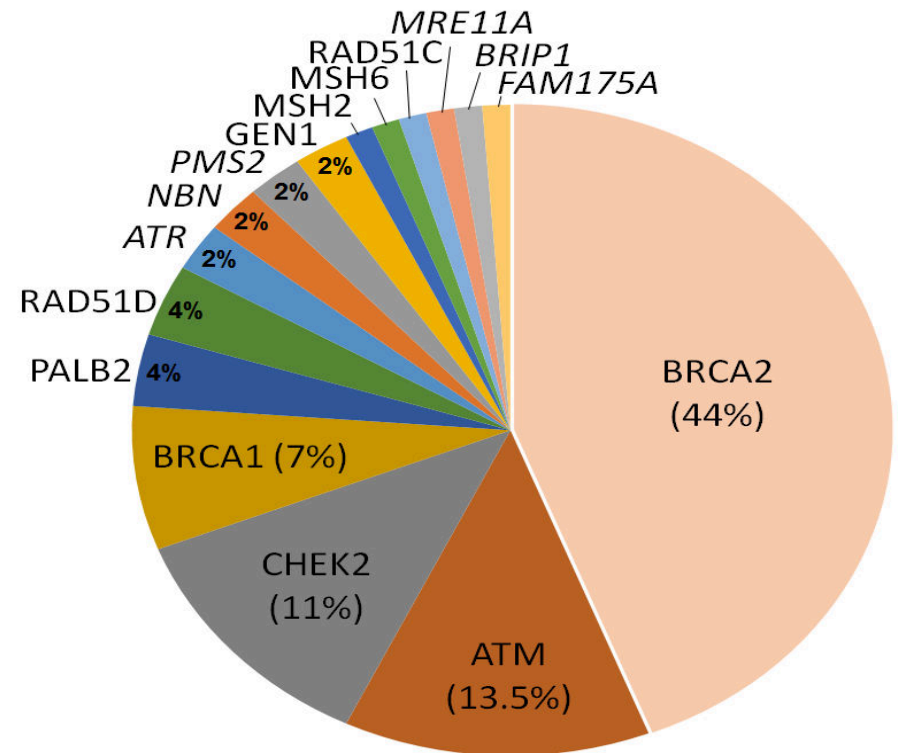
Advanced Prostate Cancer: AUA/SUO Guideline

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



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 $\leq$ 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 $\leq$ 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

EMBARC

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

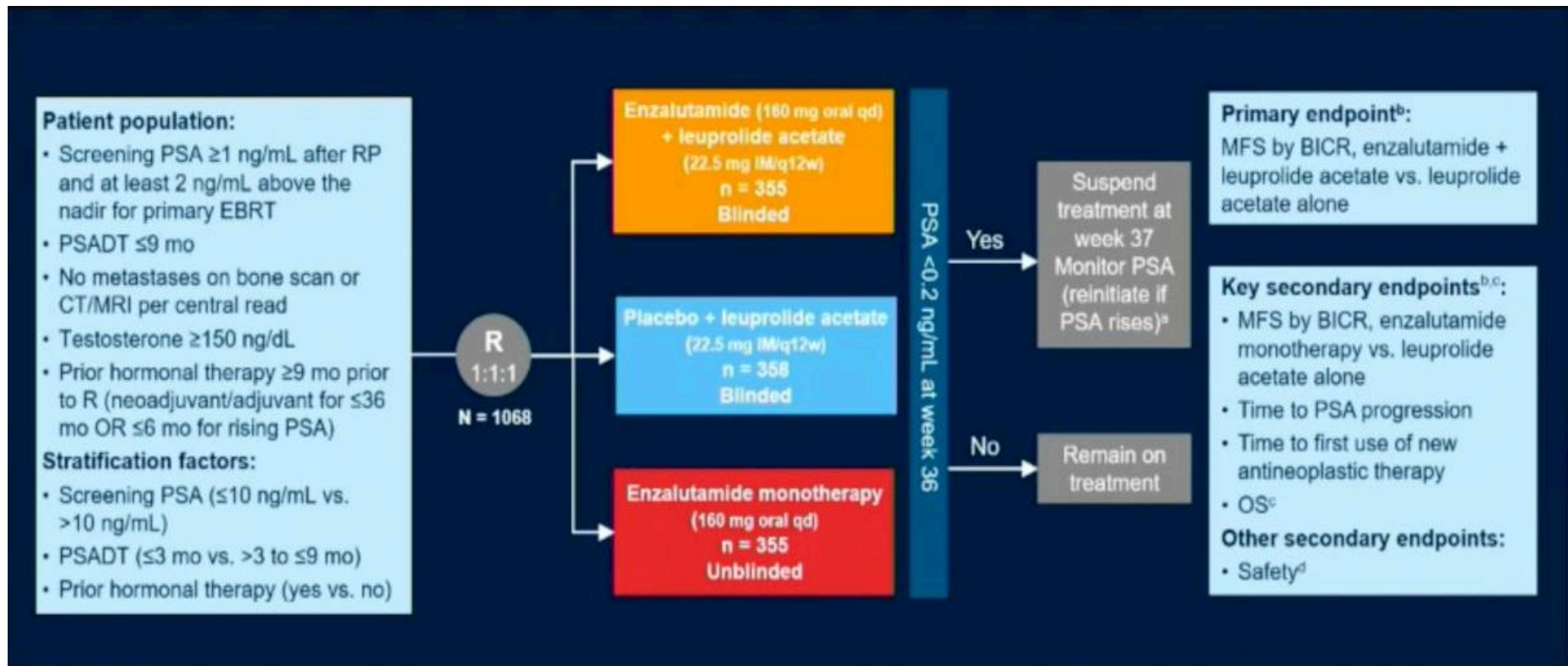
ADT + Apalutamide,

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>

Improved Outcomes with Enzalutamide in Biochemically Recurrent Prostate Cancer



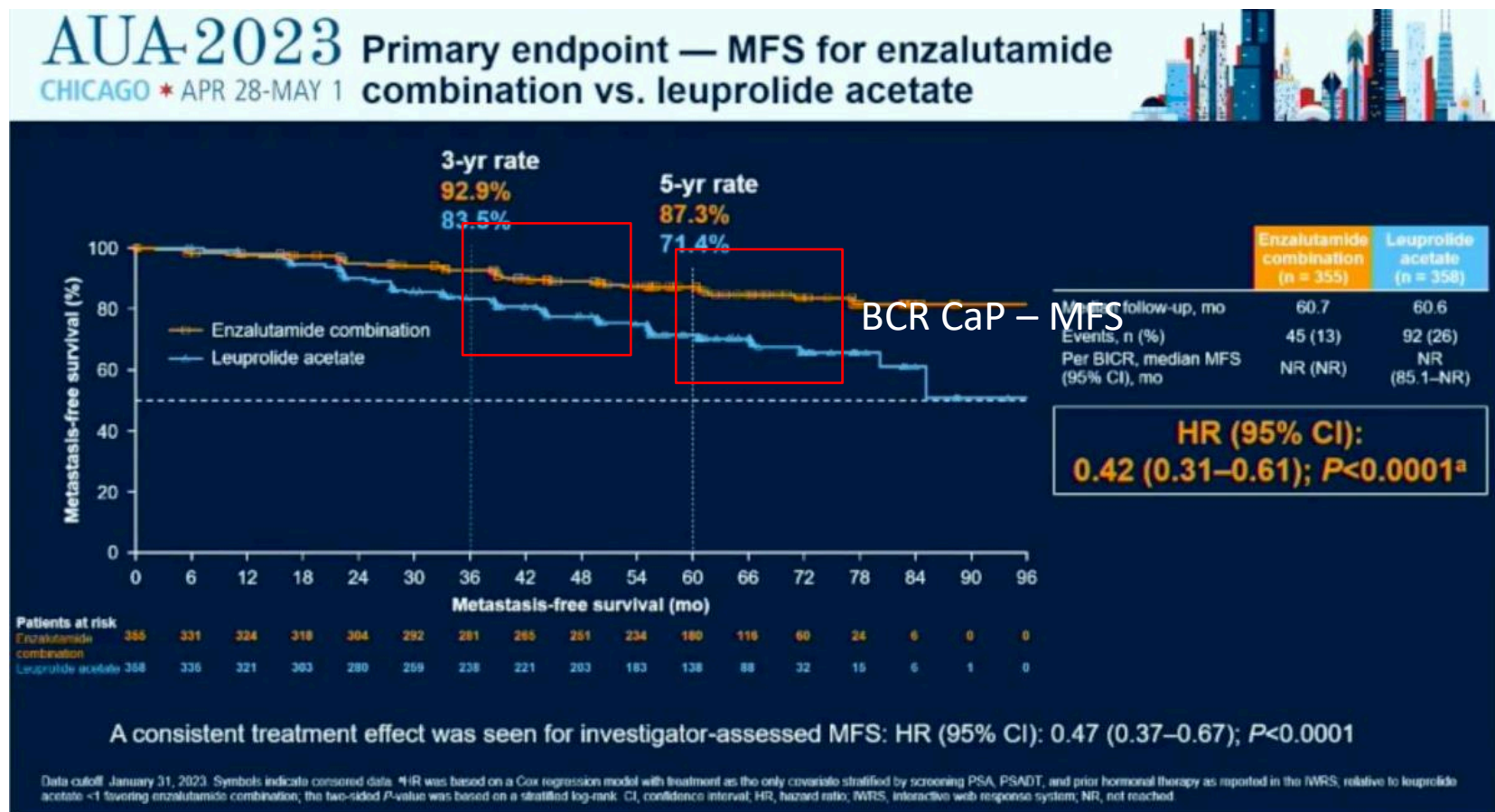
The NEW ENGLAND
JOURNAL of MEDICINE

October 19, 2023

N Engl J Med 2023; 389:1453-1465

DOI: 10.1056/NEJMoa2303974

Improved Outcomes with Enzalutamide in Biochemically Recurrent Prostate Cancer



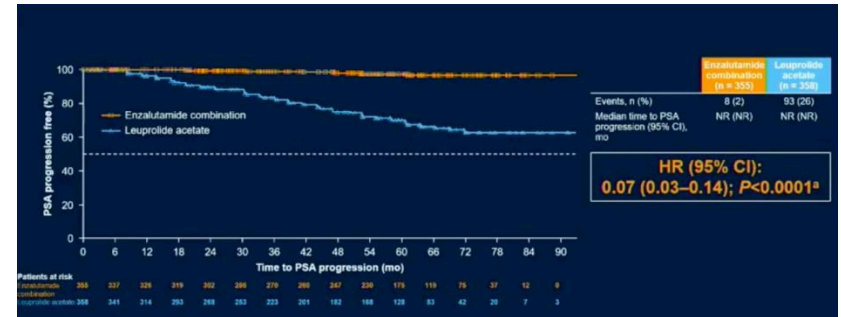
October 19, 2023

N Engl J Med 2023; 389:1453-1465

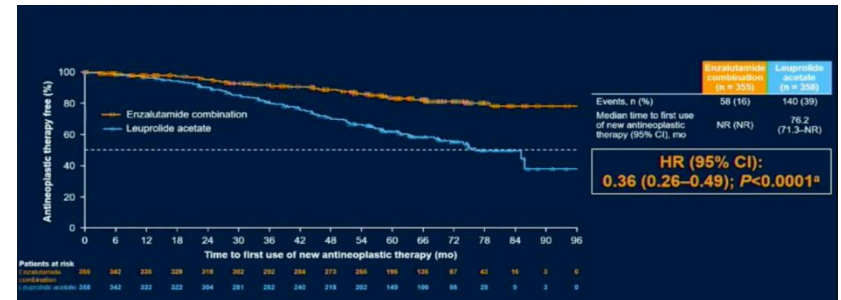
DOI: 10.1056/NEJMoa2303974

Improved Outcomes with Enzalutamide in Biochemically Recurrent Prostate Cancer

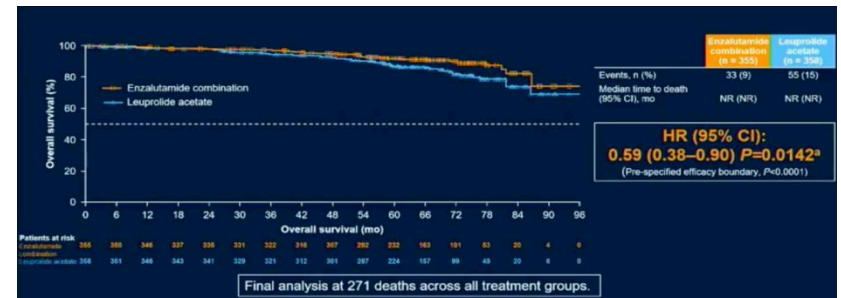
Benefits were seen for:
PSA progression



Time to first use of antineoplastic therapy



Overall survival



October 19, 2023

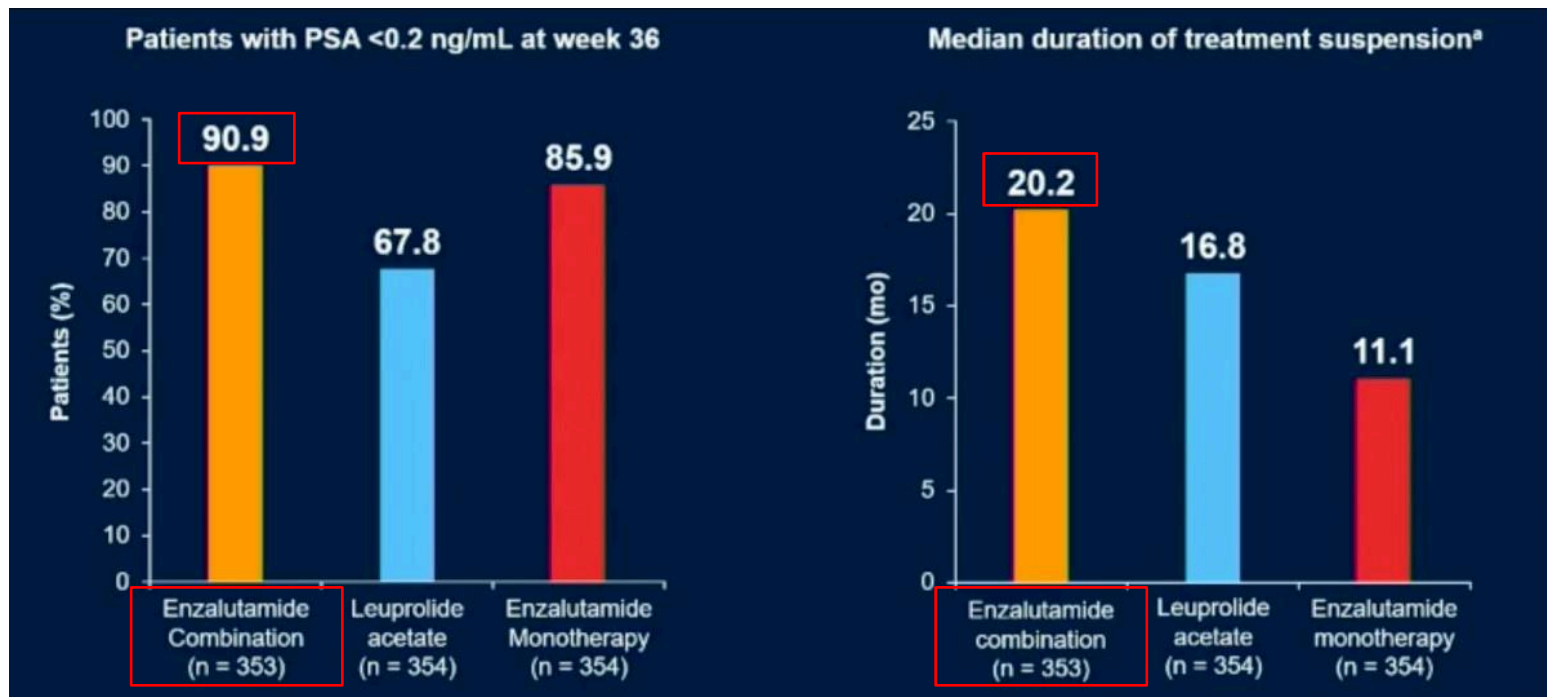
N Engl J Med 2023; 389:1453-1465

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

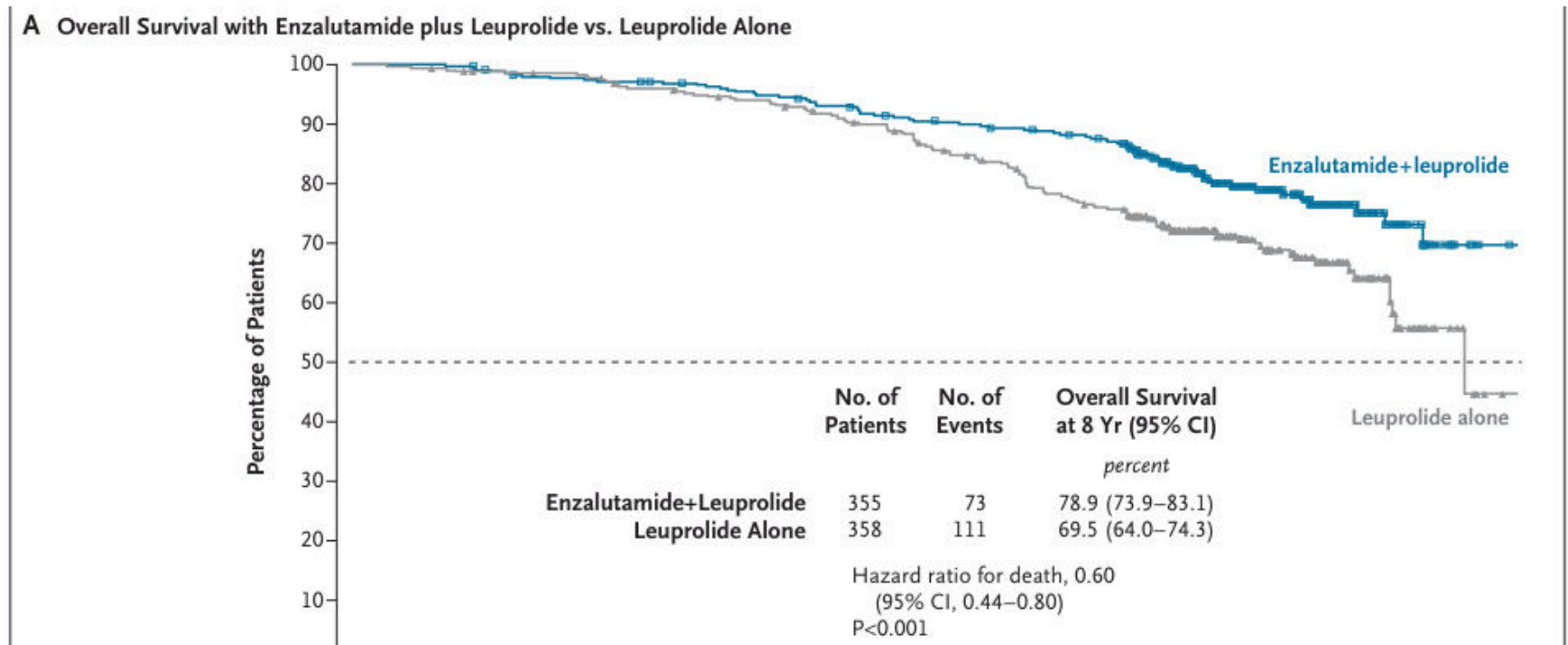
October 19, 2023

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) • $P < 0.001$

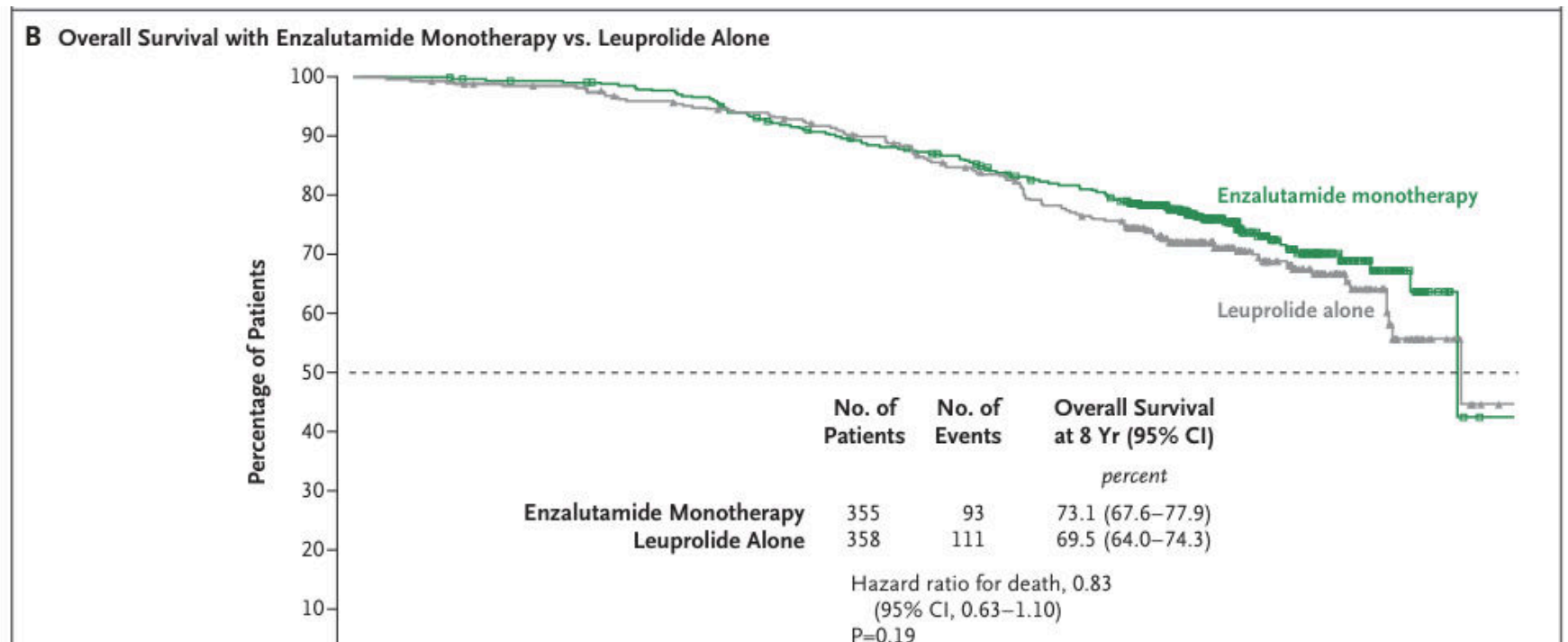


Freedland SJ, Shore ND, et al. N Engl J Med 2026;394:563–575.

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.



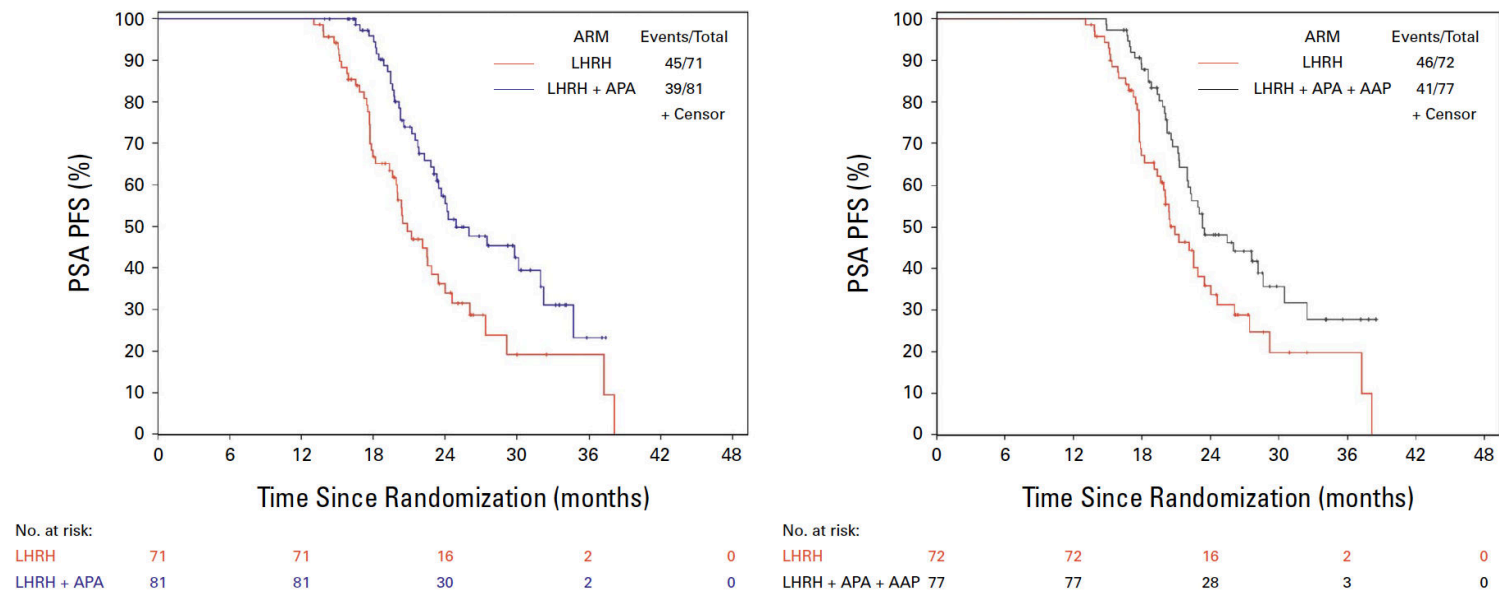
PRESTO: A Phase III, Open-Label Study of Intensification of Androgen Blockade in Patients With High-Risk Biochemically Relapsed Castration-Sensitive Prostate Cancer (AFT-19)

- High risk biochemically recurrent patients
 - Prior prostatectomy with adjuvant/salvage XRT +/- ADT
 - PSA >0.5 with PSA_{dt} < 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





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.

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

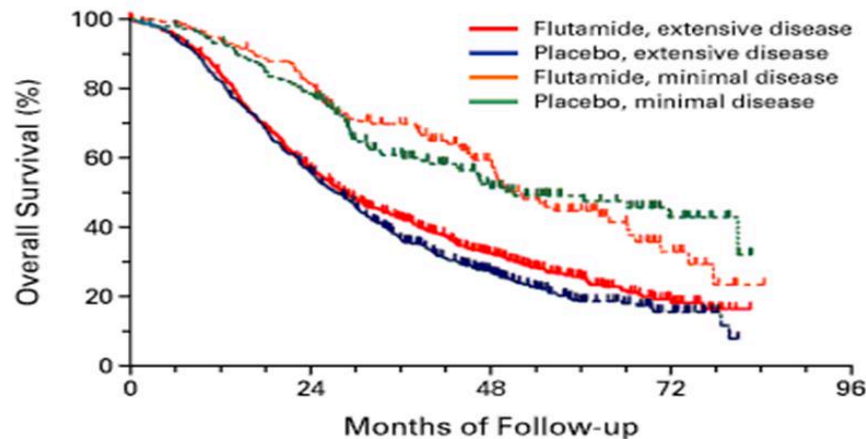
1. First report on disease extent & OS: Crawford, NEJM,1989

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

Current definitions of high-volume:

- **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*)

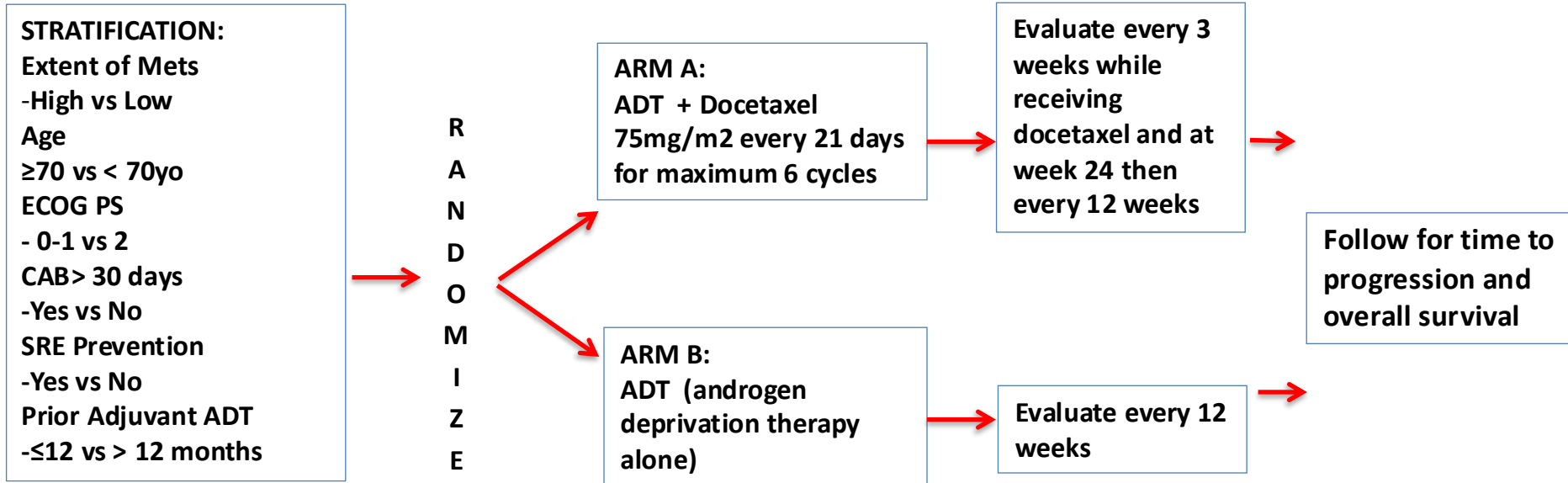
Improving Survival: M1 HSPC

“Treatment Intensification”

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

Strategy: Chemo-Hormonal Therapy

E3805:CHAARTED: Randomized Trial



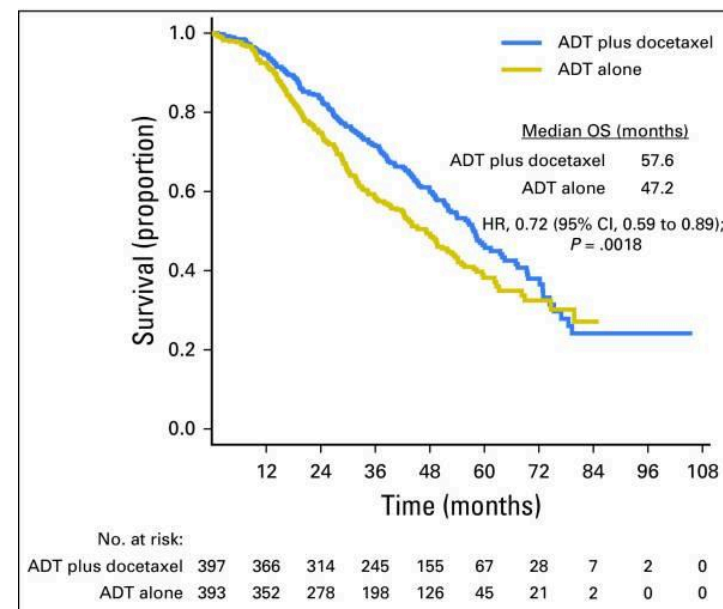
- **High volume: visceral metastases or 4 or more bone mets (at least 1 beyond pelvis and vertebral column)**
- **At inception, only patients with high volume disease were to be accrued**

Strategy: Chemo-Hormonal Therapy

E3805:CHAARTED: Randomized Trial

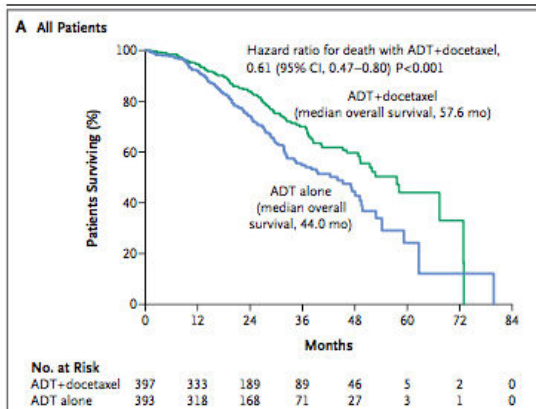
DOCETAXEL

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



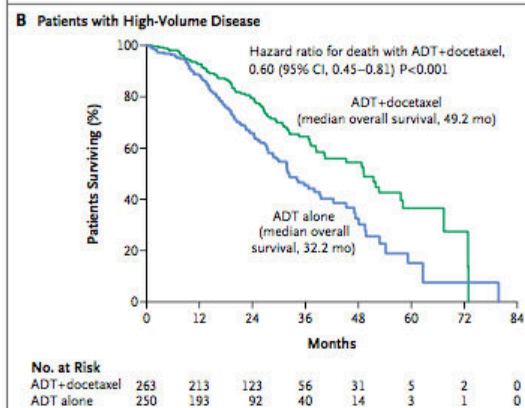
Kyriakopoulos CE et al: Chemohormonal therapy in metastatic hormone-sensitive prostate cancer: long-term survival analysis of the randomized phase III E3805 CHAARTED trial. J Clin Oncol 2018; 36:1080.

CHAARTED: Chemohormonal Rx



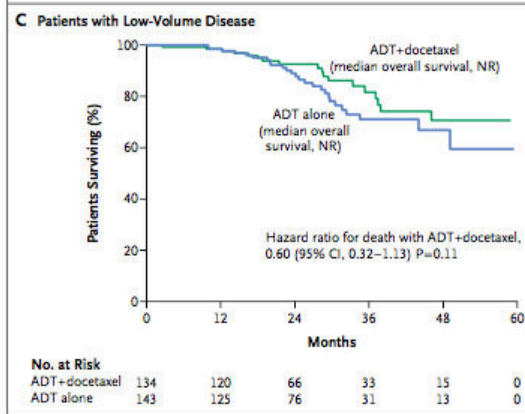
N=790
Median OS:
ADT + D: 57.6 months
ADT alone: 44.0 months
HR=0.61 (0.47-0.80)
p=0.0003

**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**

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

ORIGINAL ARTICLE

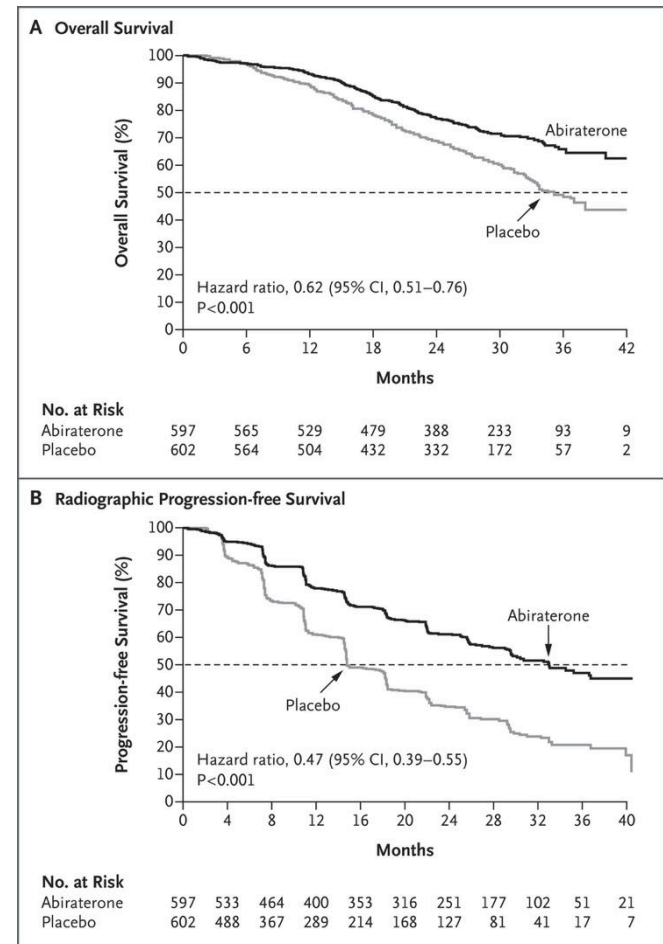
Abiraterone for Prostate Cancer Not Previously Treated with Hormone Therapy

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*

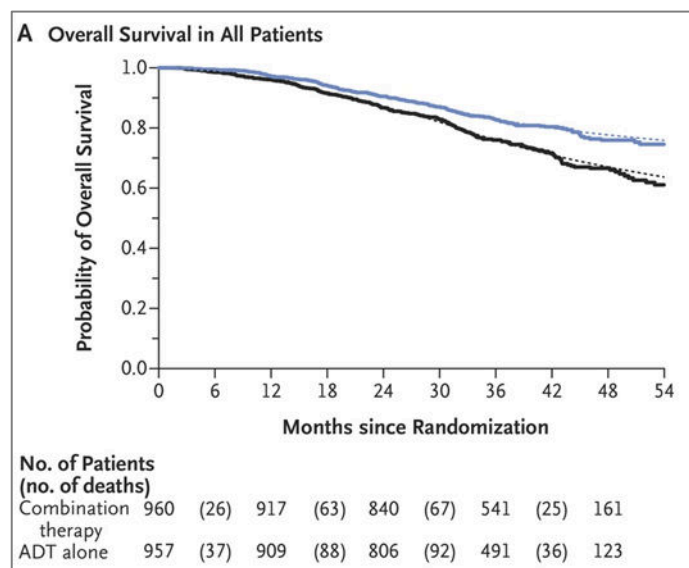
ABIRATERONE ACETATE

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



— Combination therapy by Kaplan–Meier estimates - - - - - Combination therapy by flexible parametric model
 — ADT alone by Kaplan–Meier estimates - - - - - ADT alone by flexible parametric model

Trial

Primary Endpoint

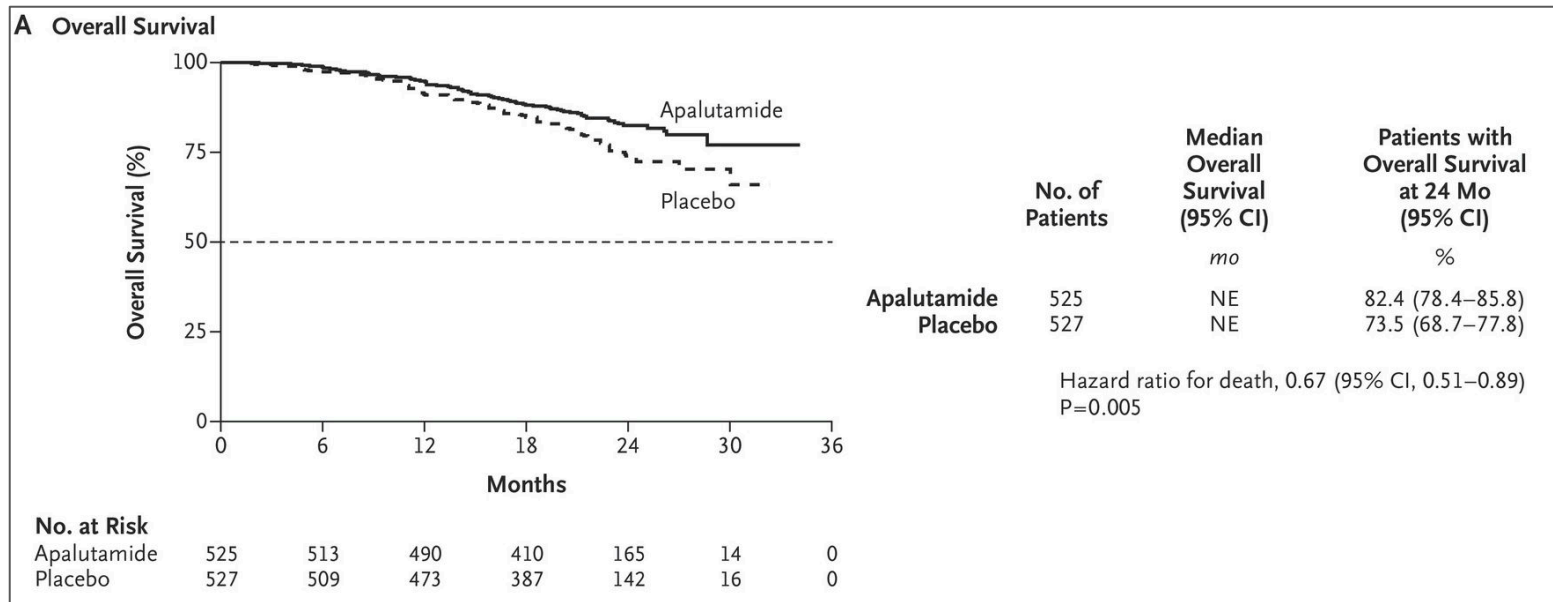
STAMPEDE
n=1,917

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

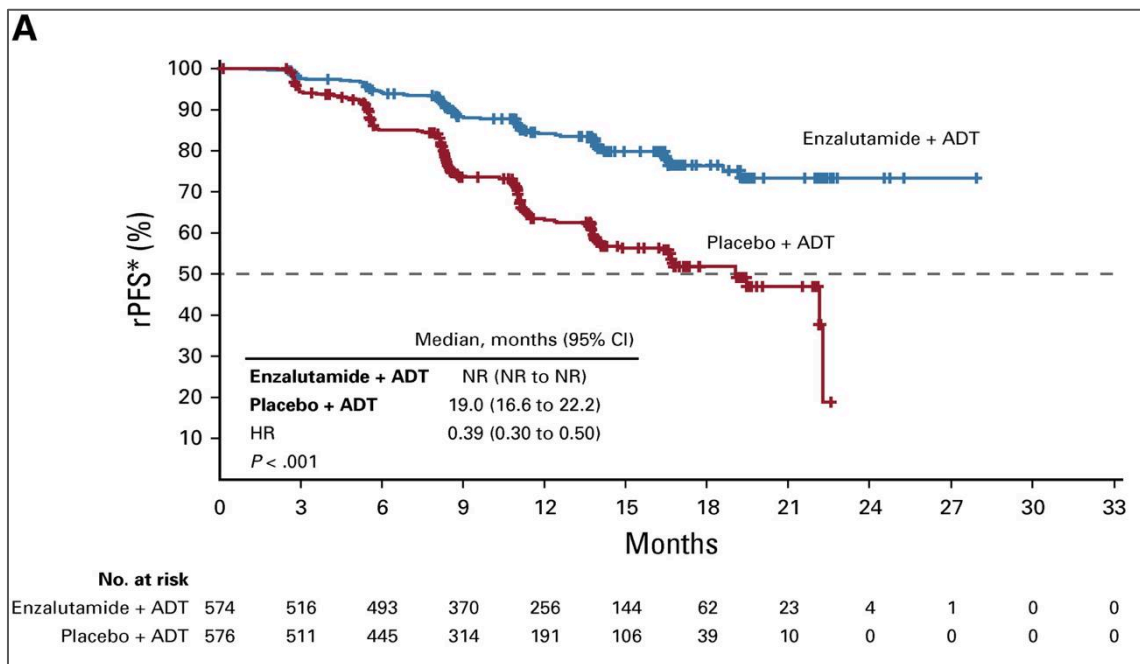
James ND et al: Abiraterone for prostate cancer not previously treated with hormone therapy. N Engl J Med 2017;377:338.

APALUTAMIDE– TITAN



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

ENZALUTAMIDE - ARCHES

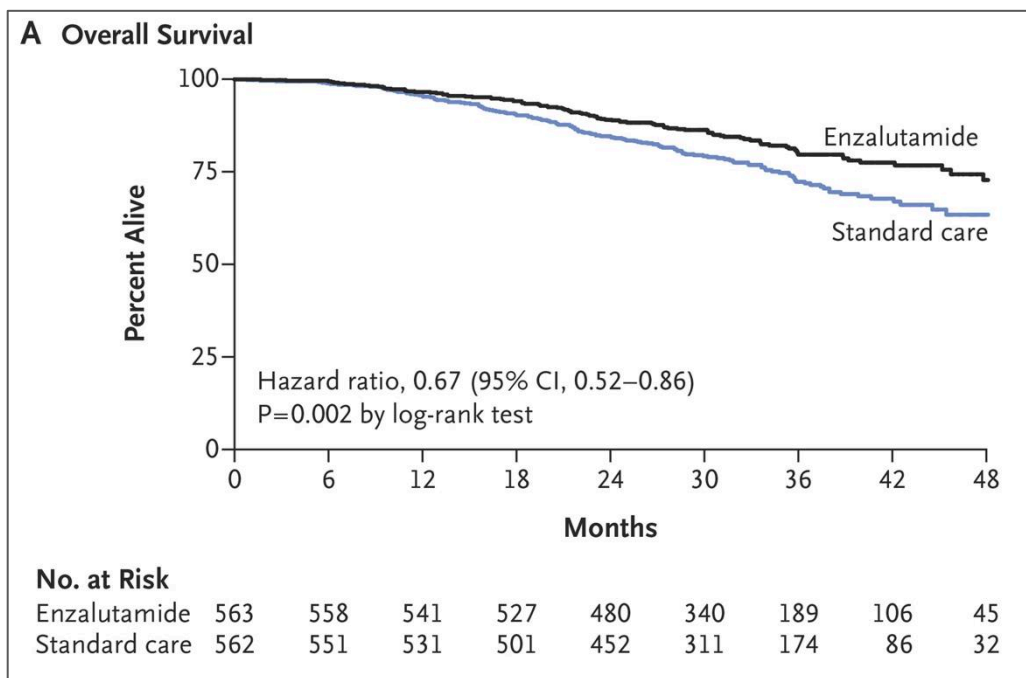


Trial	Primary Endpoints
ARCHES n=1,150	Radiographic Progression-Free Survival - Not reached enzalutamide + ADT 19.0 months ADT + placebo

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.

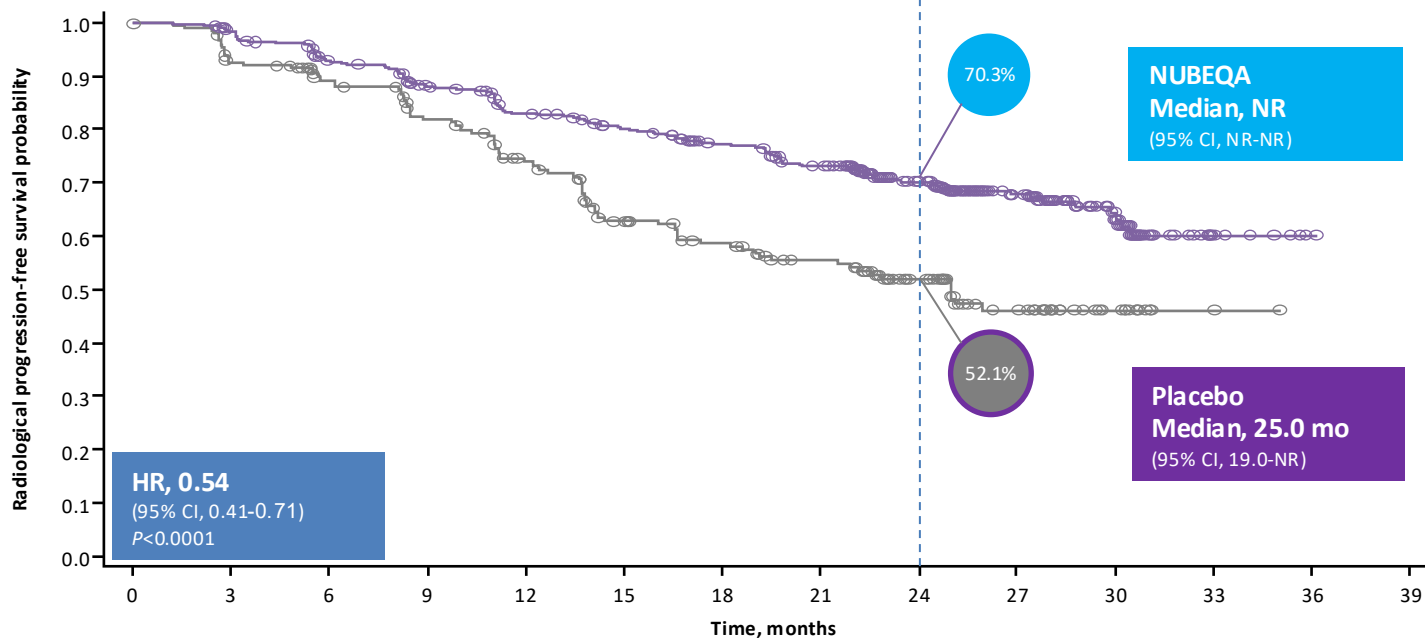
ENZALUTAMIDE - ENZAMET

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



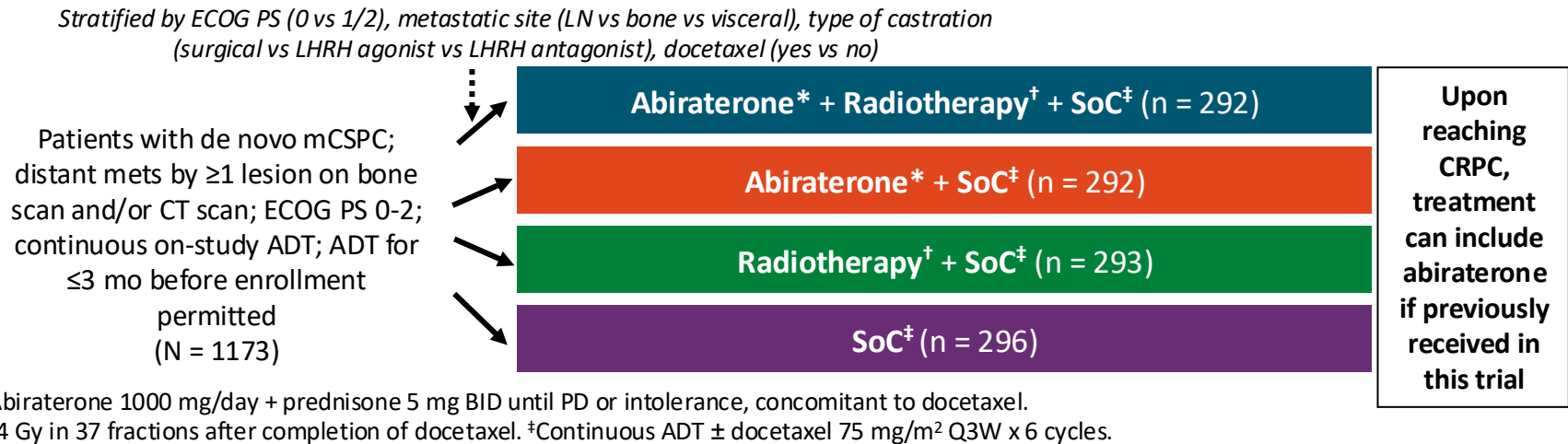
Advanced Prostate Cancer: AUA/SUO Guideline

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}

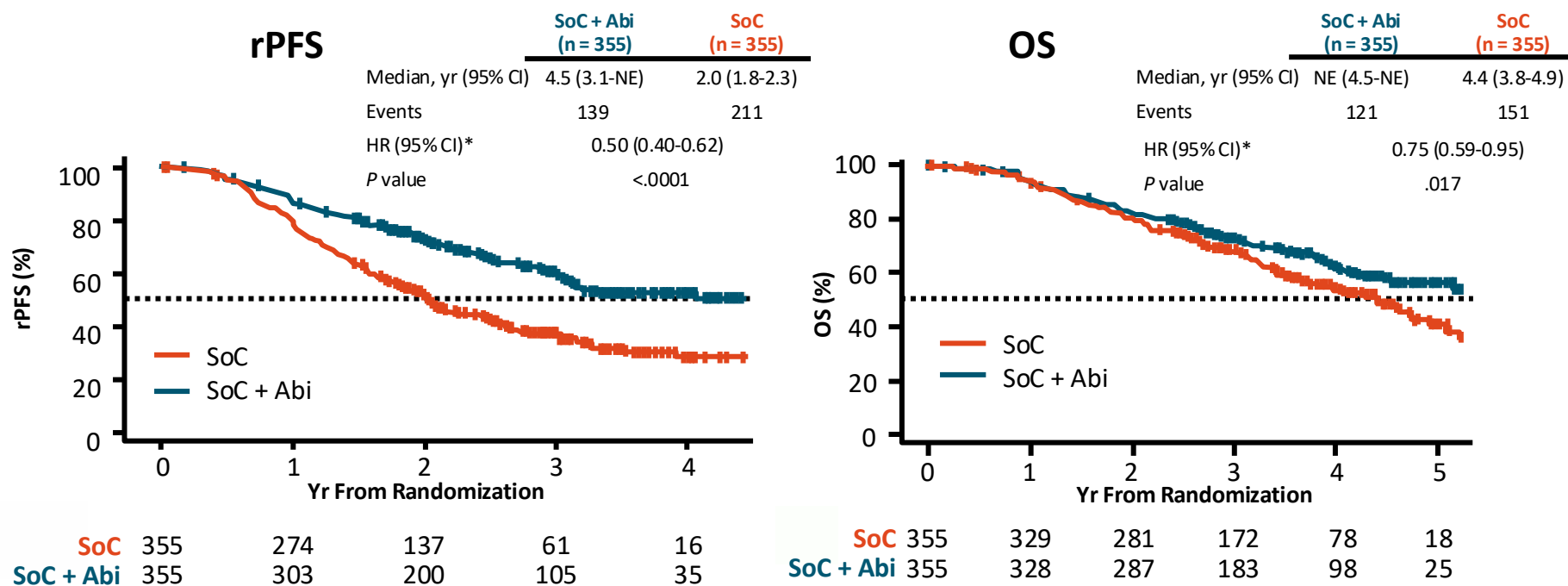


- **Coprimary endpoints:** rPFS and OS with 2x2 factorial design and hierarchical testing¹
- **Key secondary endpoints:** castration resistance-free survival, time to next SRE, PSA response rate, time to pain progression, QoL, safety¹

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

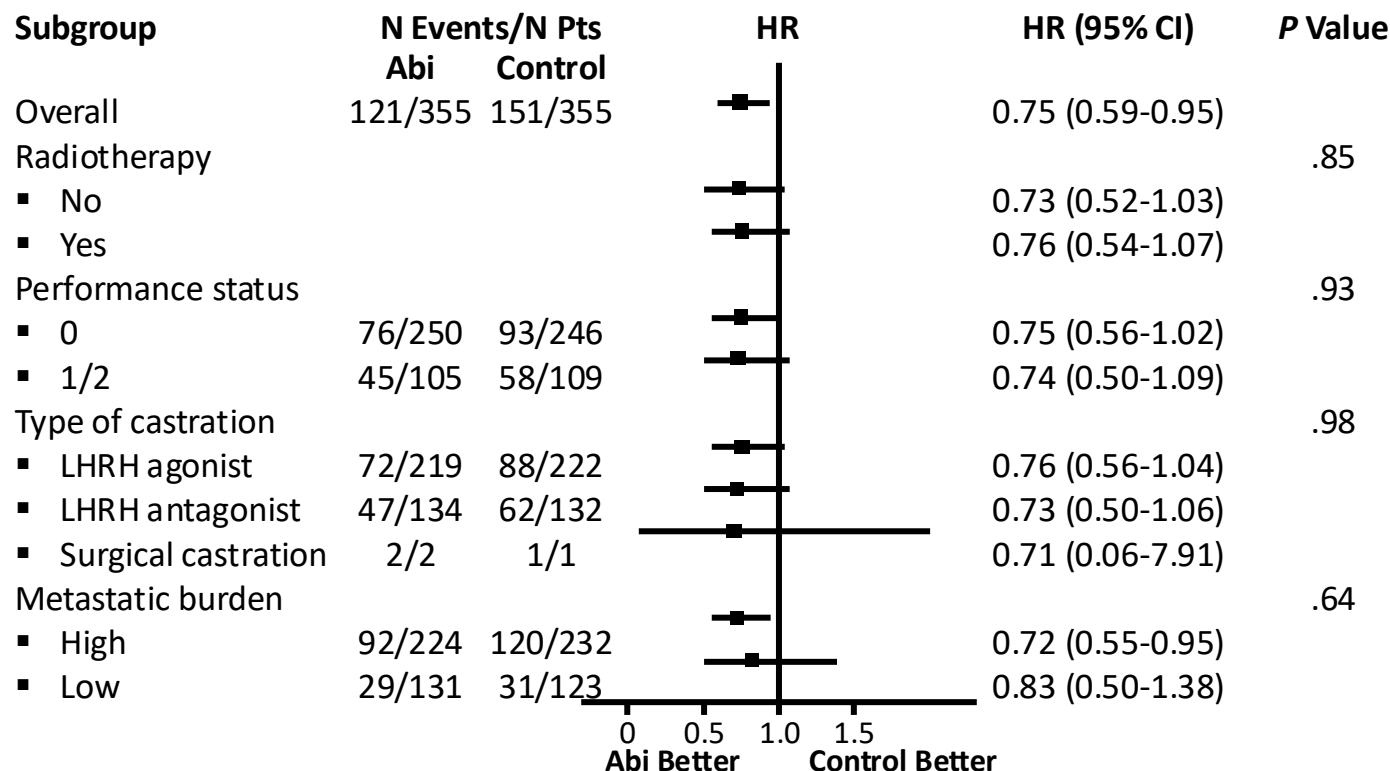
Fizazi K, Carles Galceran J, Foulon S, et al. A phase III trial with a 2x2 factorial design in men with de novo metastatic castration-sensitive prostate cancer: over-all survival with abiraterone acetate plus prednisone in PEACE-1. Ann Oncol 2021.

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



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

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



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

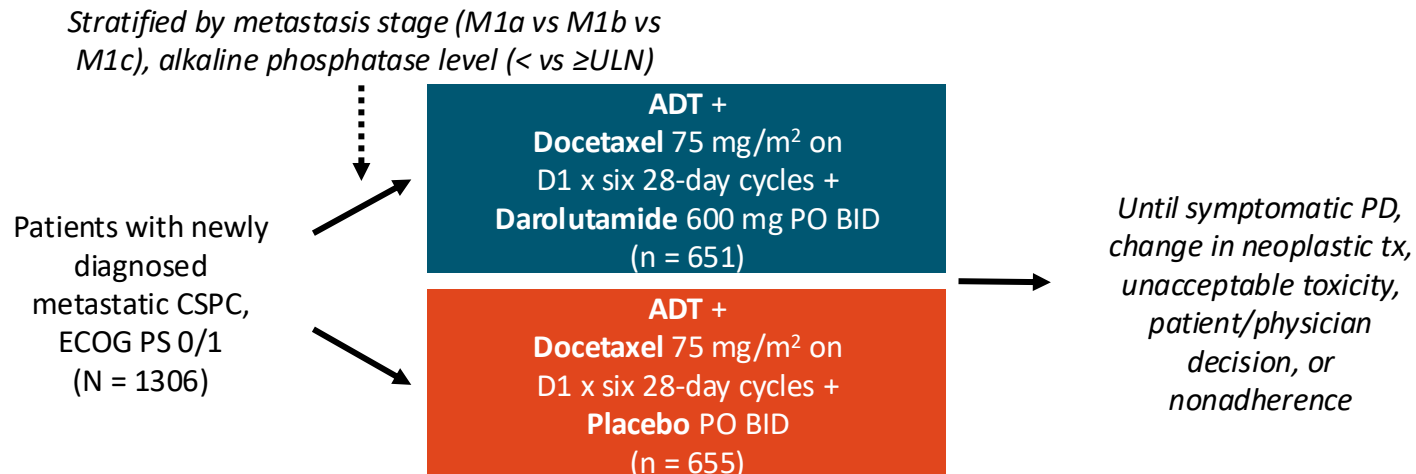
PEACE-1: Grade 3-5 AEs Reported in ADT + Docetaxel Population

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

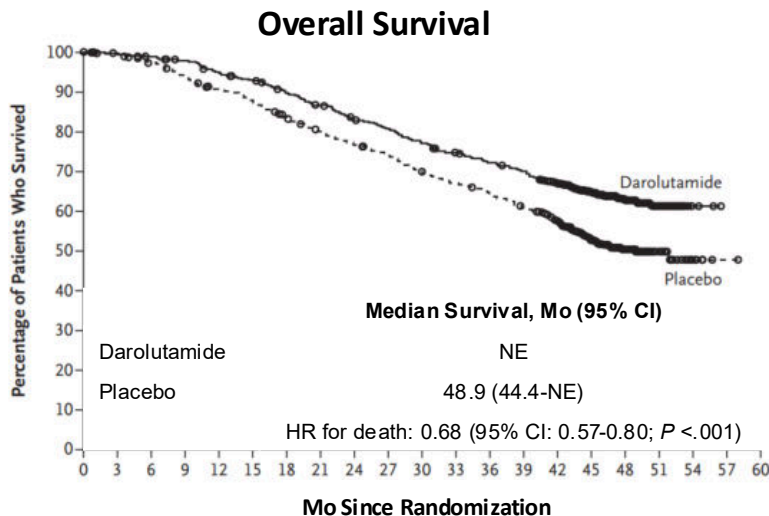
Phase III ARASENS Trial: Darolutamide in mCSPC

- 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

ARASENS: Primary Endpoint (Overall Survival), Safety



Patients at Risk, n

Darolutamide	651	645	637	627	608	593	570	548	525	509	486	468	452	436	402	267	139	56	9	0	0
Placebo	654	646	630	607	580	565	535	510	488	470	441	424	402	383	340	218	107	37	6	1	0

- 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)

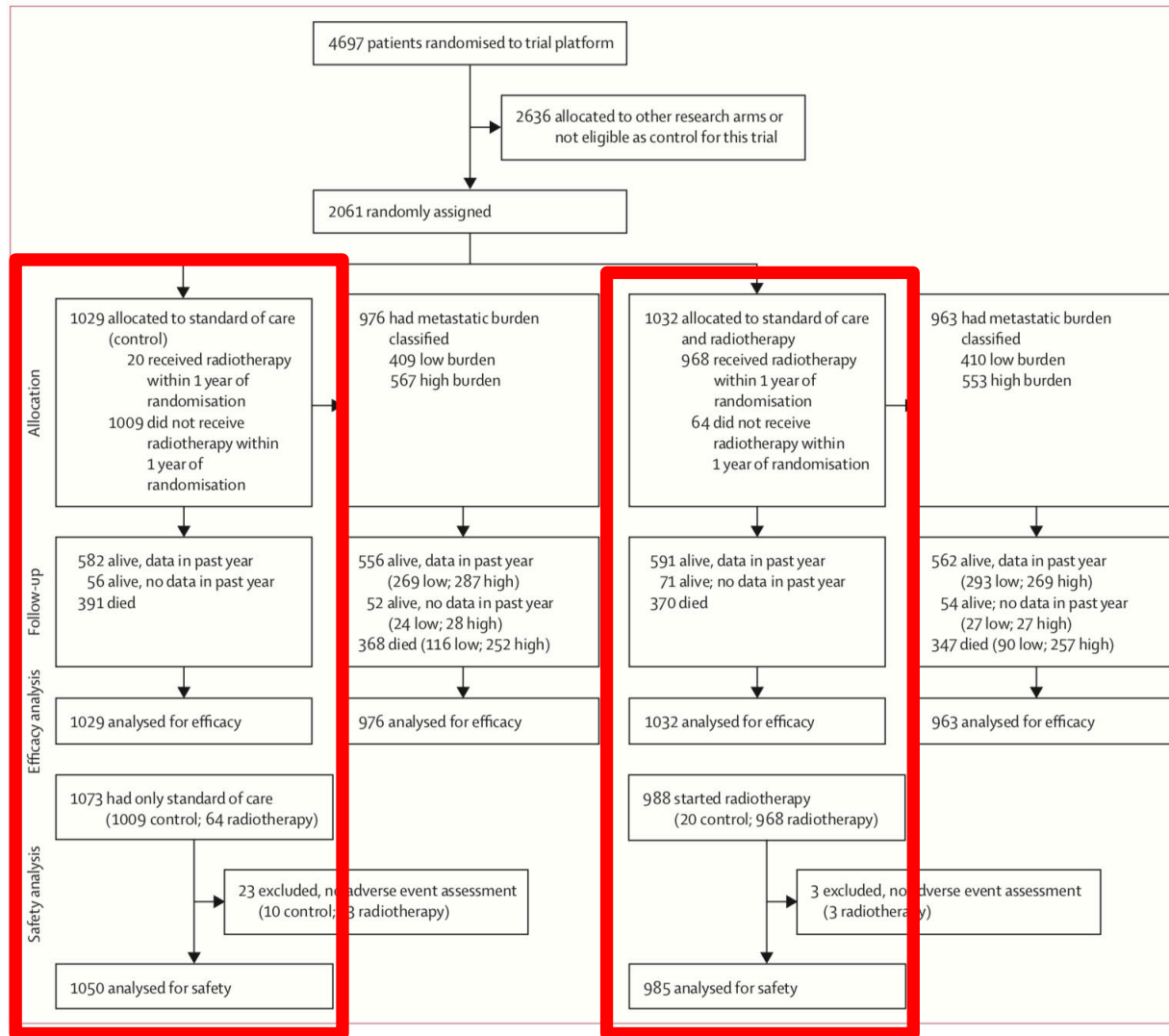
- Comparable rates between treatment arms of any-grade, grade 3-5, and serious AEs
- Most common grade 3/4 AEs in darolutamide arm included neutropenia (33.7%), febrile neutropenia (7.8%), hypertension (6.4%), and anemia (4.8%)
- Similar rates of death due to treatment-emergent AEs (darolutamide arm,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

Advanced Prostate Cancer: AUA/SUO Guideline

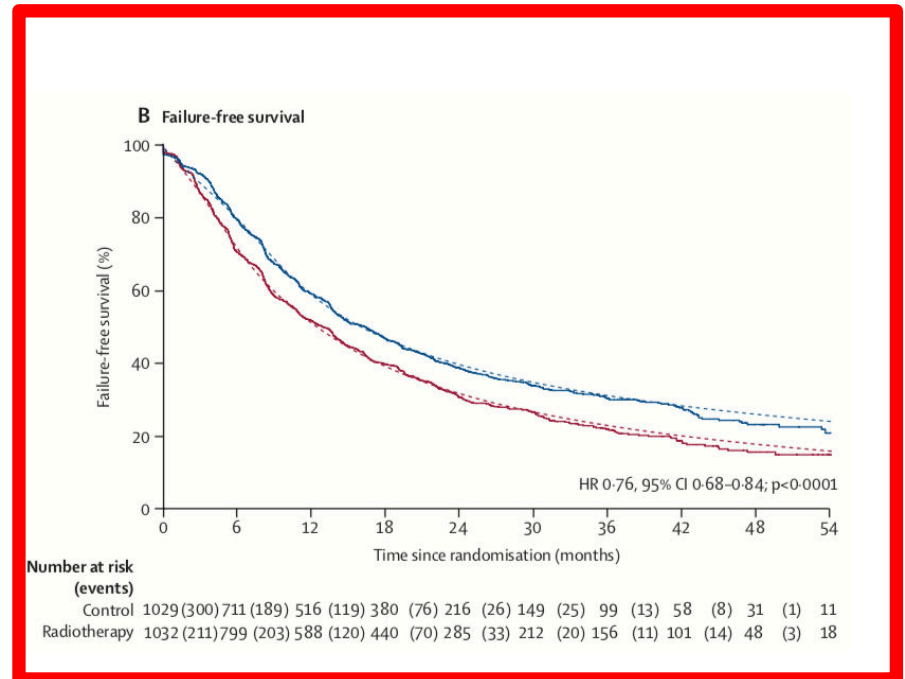
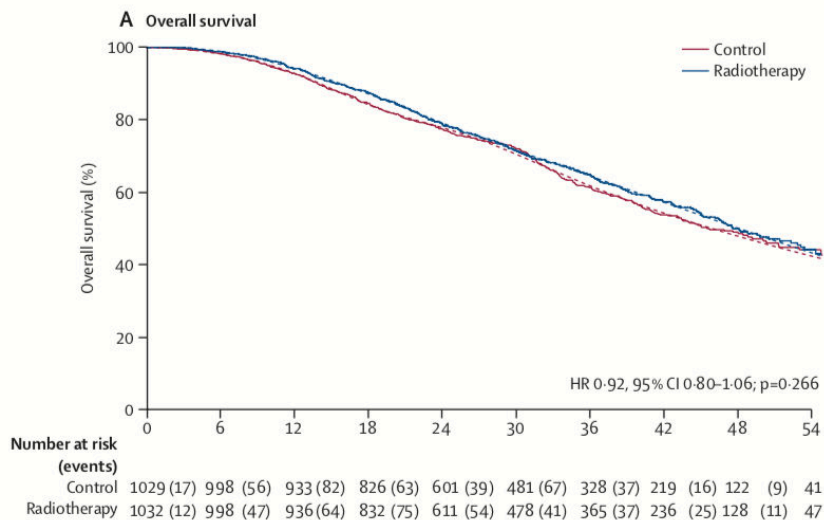
Treatment

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

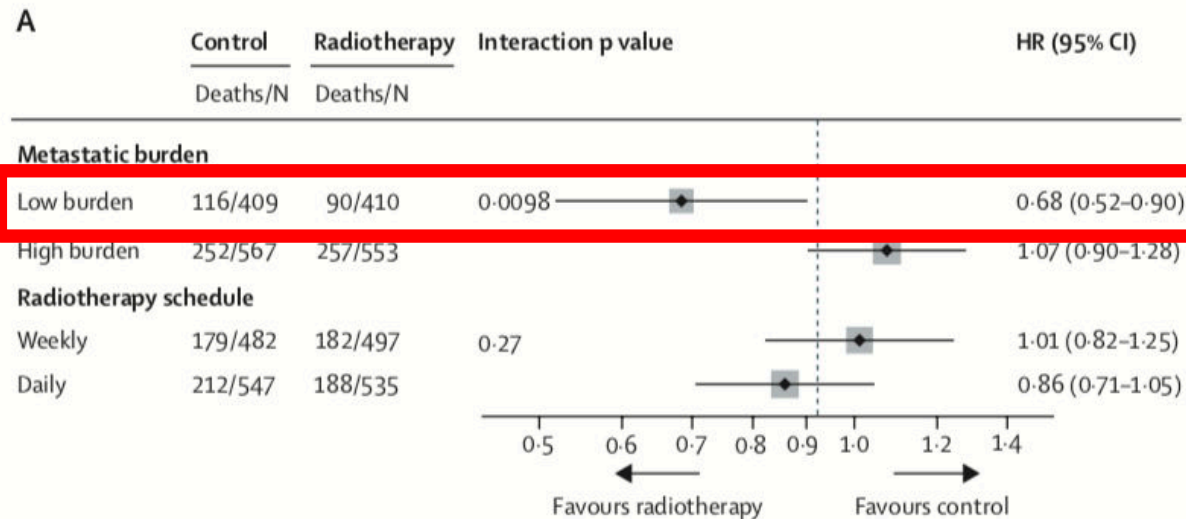


Overall Survival and Failure-Free Survival by Treatment (Median f/u 37 mos)



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

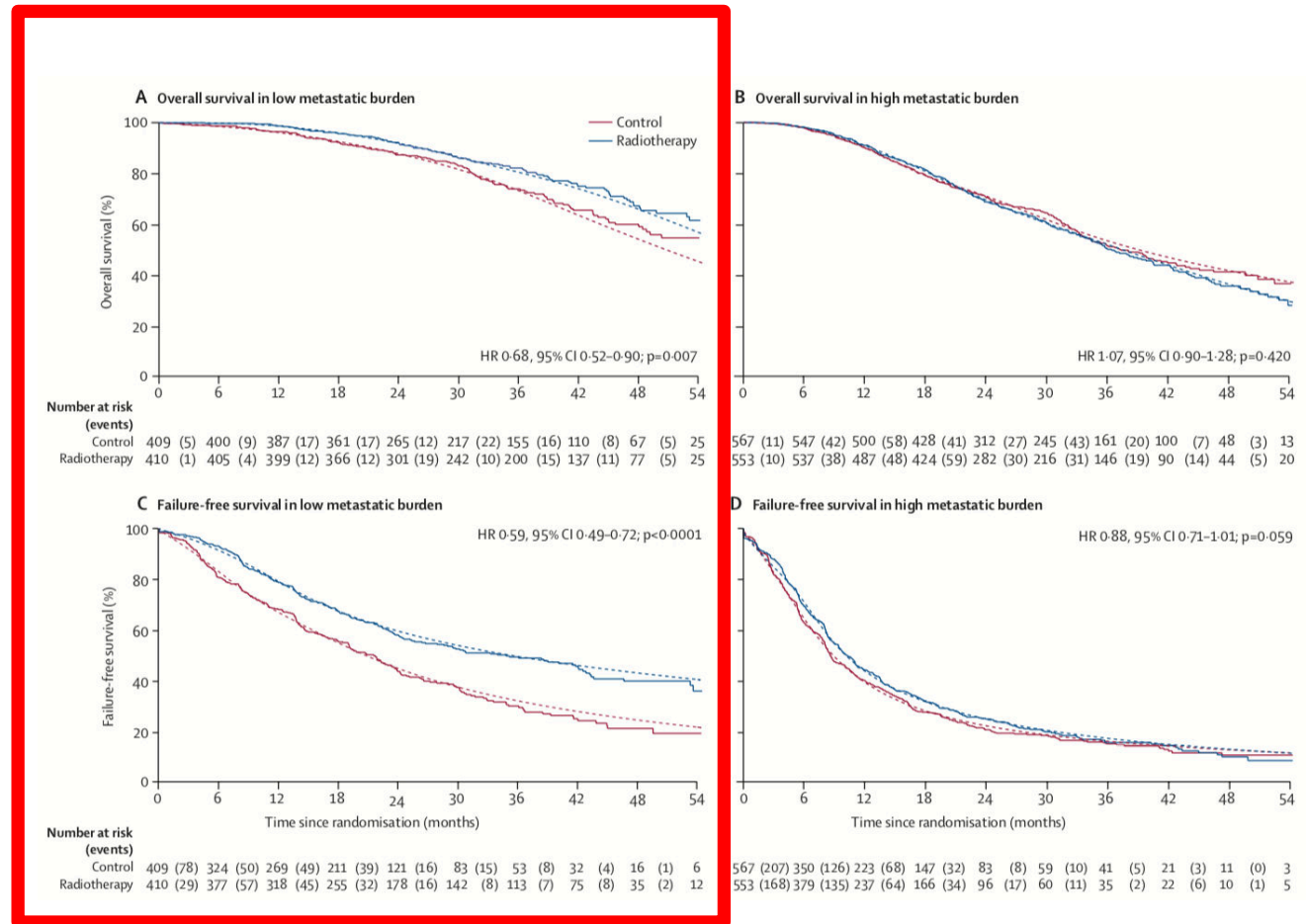
Pre-specified subgroup analysis (CHAARTED definition)



**Low volume
significant**

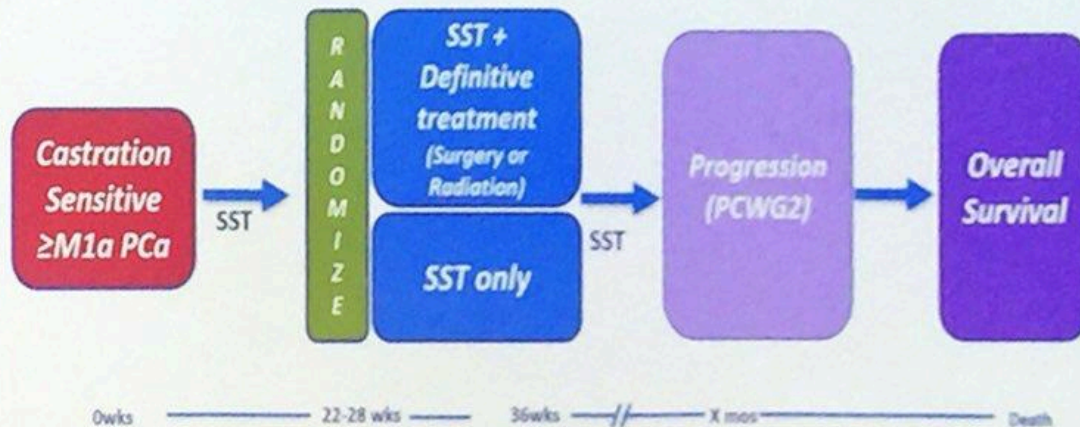
Low vs. High Volume (CHAARTED definition)

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



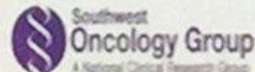
SWOG 1802

Randomized, Phase III Trial of Standard Systemic Therapy (SST) or SST Plus Definitive Treatment of the Primary Tumor in Metastatic Prostate Cancer (S1802)



PI: Brian F Chapin, MD

SWOG : Dan Lin, David Quinn, Ana Aparicio, Cathy Tangen, Nicholas Vogelzang, Ian Thompson



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

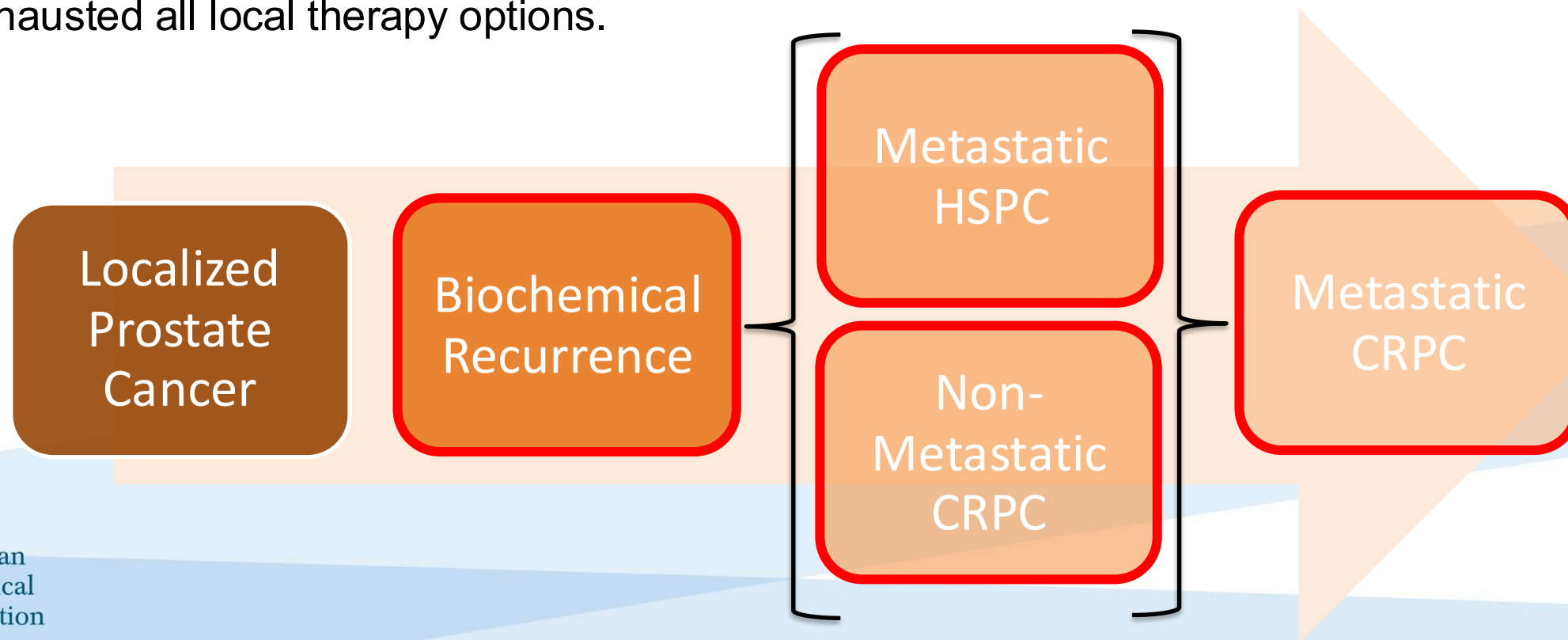


American
Urological
Association

Education & Research, Inc.

ADVANCED PROSTATE CANCER PATIENT POPULATION

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



American
Urological
Association

Education & Research, Inc.

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



American
Urological
Association

Education & Research, Inc.

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**



American
Urological
Association

Education & Research, Inc.

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)



American
Urological
Association

Education & Research, Inc.

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.

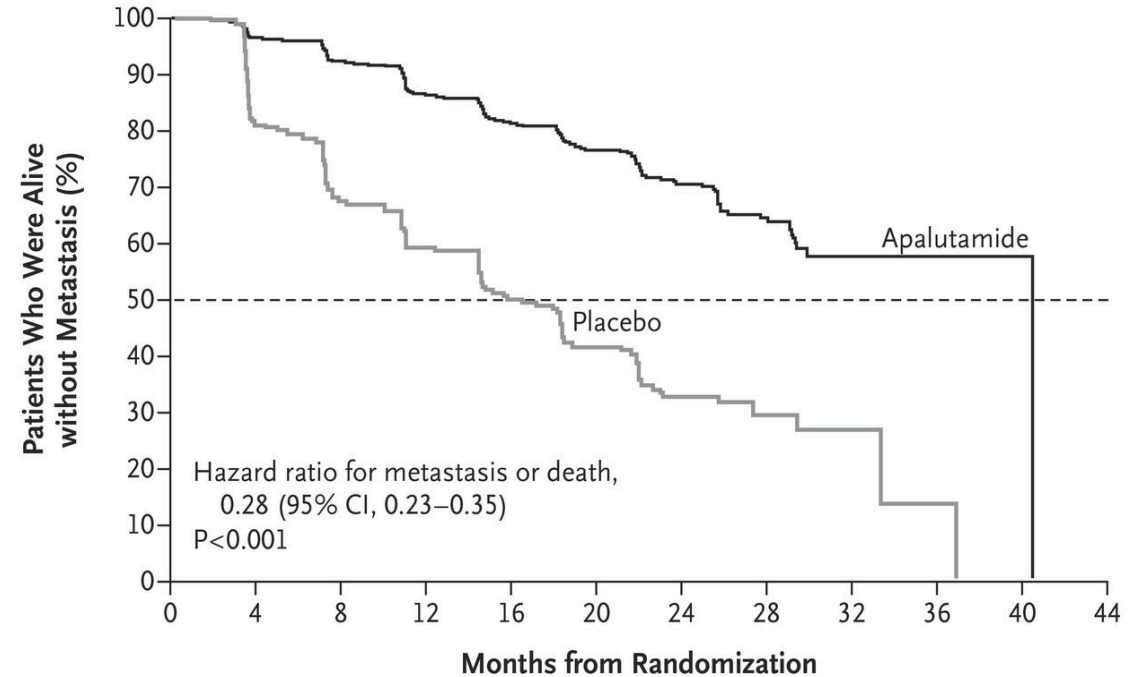
- Apalutamide
- Darolutamide
- Enzalutamide



NON-METASTATIC CRPC

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

A Kaplan–Meier Estimates of Metastasis-free Survival



No. at Risk

Apalutamide	806	713	652	514	398	282	180	96	36	16	3	0
Placebo	401	291	220	153	91	58	34	13	5	1	0	0



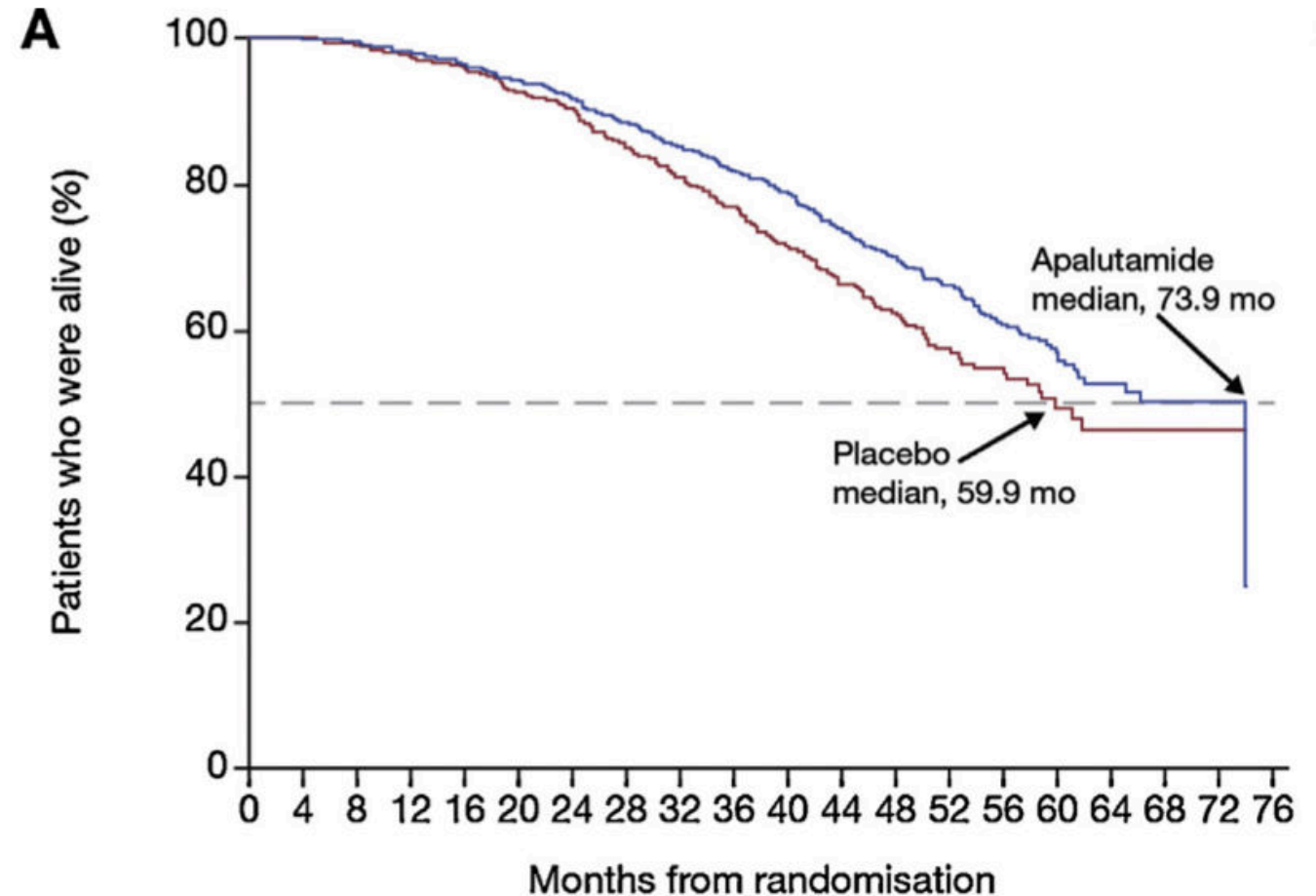
American
Urological
Association

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



Number of patients

Apalutamide	806	791	774	758	739	717	691	658	625	593	558	499	376	269	181	100	47	19	4	0
Placebo	401	392	385	373	358	339	328	306	286	263	240	204	156	114	82	38	21	6	2	0



American
Urological
Association

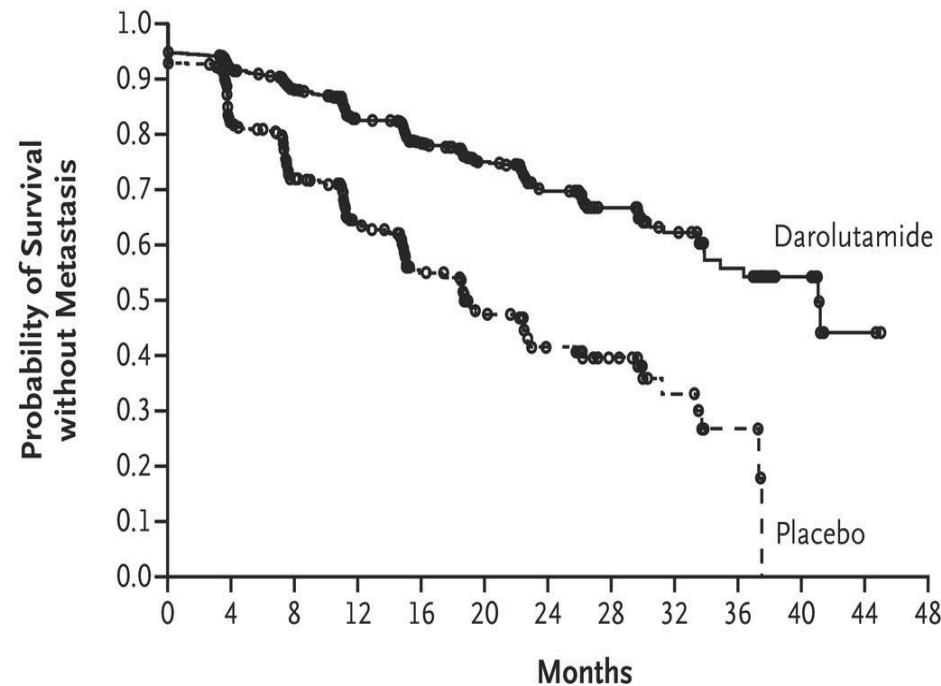
Education & Research, Inc.

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

A Kaplan–Meier Analysis of Metastasis-free Survival



	Median Metastasis-free Survival (95% CI) mo
Darolutamide	40.4 (34.3–NR)
Placebo	18.4 (15.5–22.3)
Hazard ratio, 0.41 (95% CI, 0.34–0.50) P<0.001	

No. at Risk

Darolutamide	955	817	675	506	377	262	189	116	68	37	18	2	0
Placebo	554	368	275	180	117	75	50	29	12	4	0	0	0



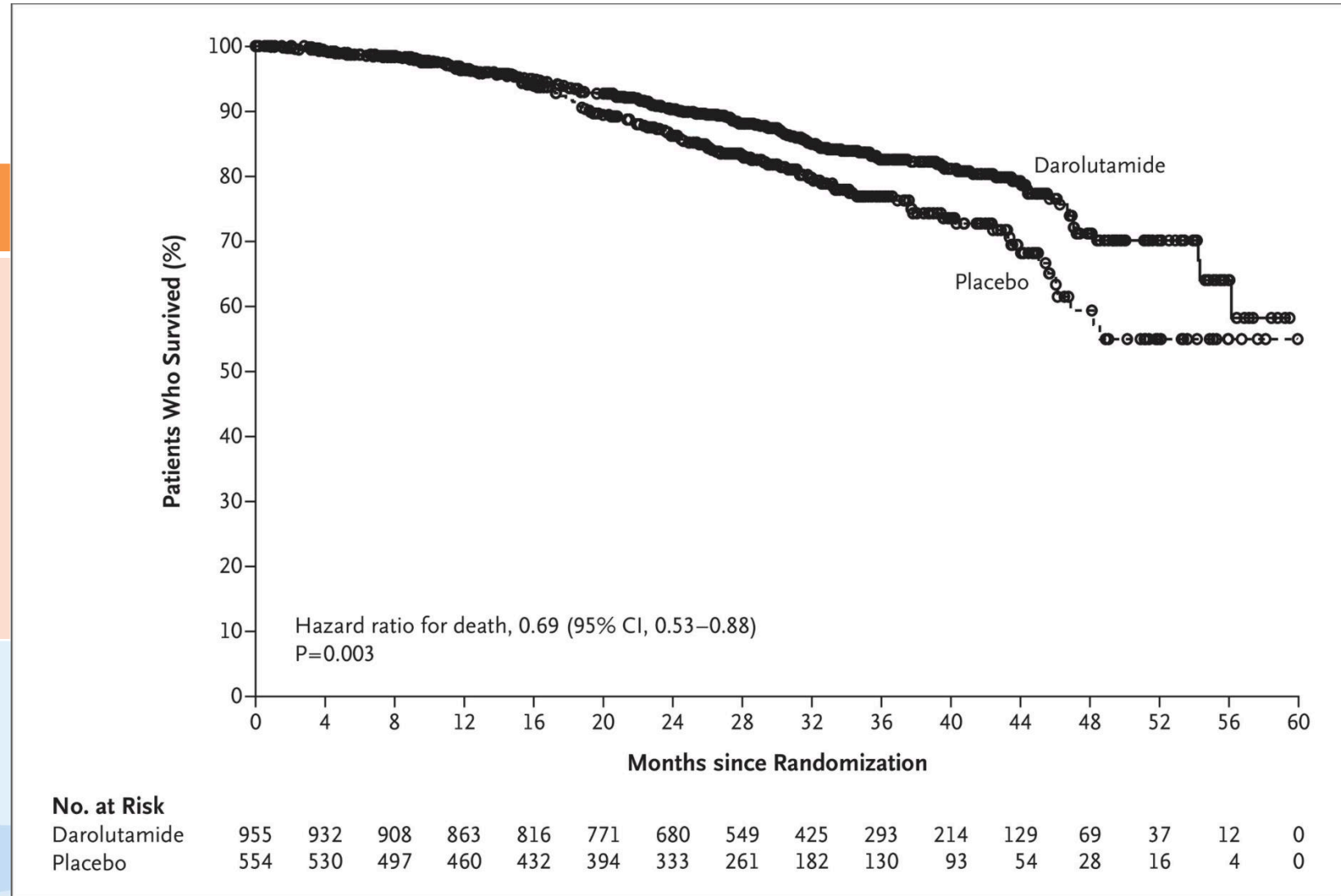
American
Urological
Association

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



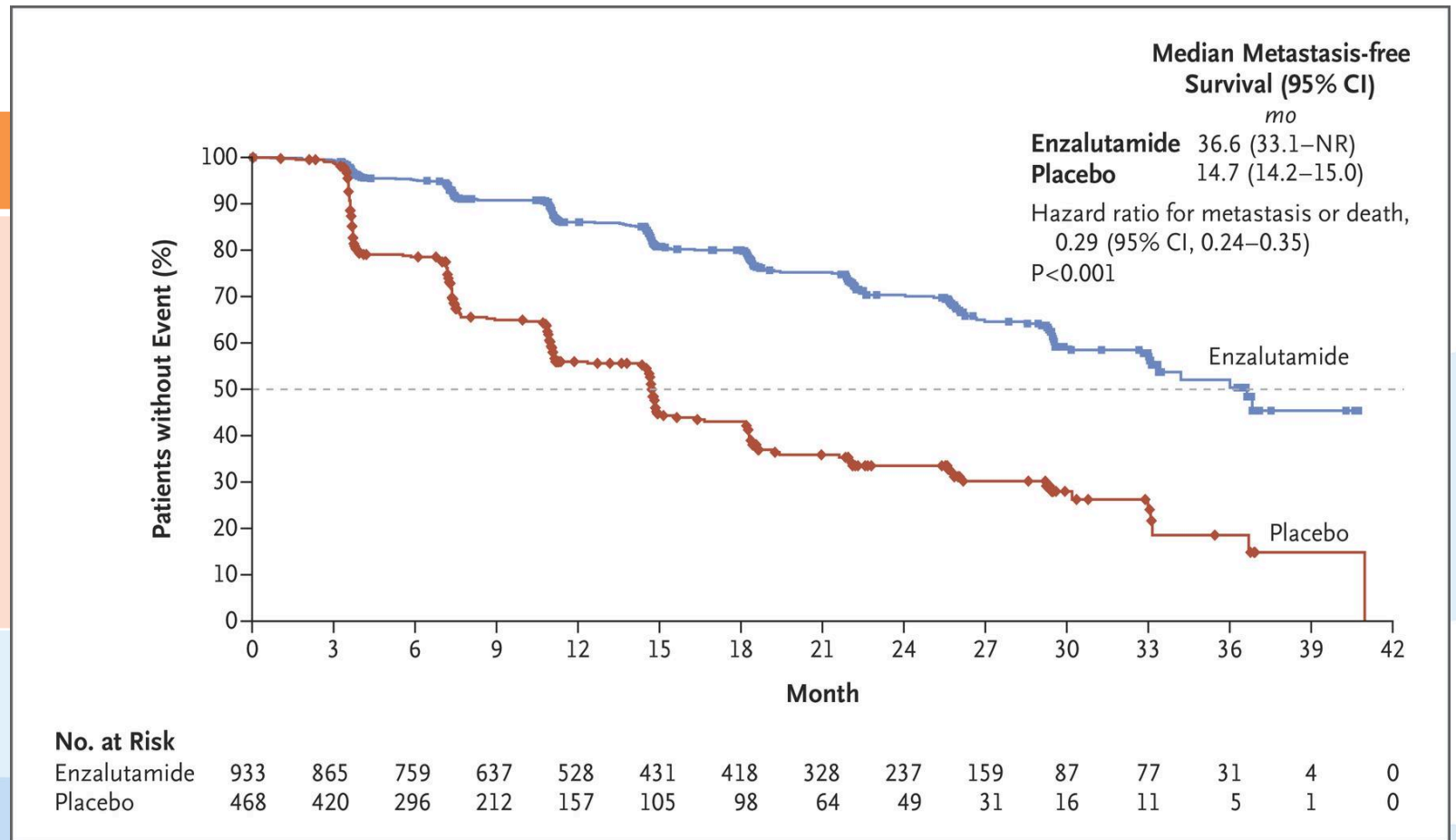
American
Urological
Association

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



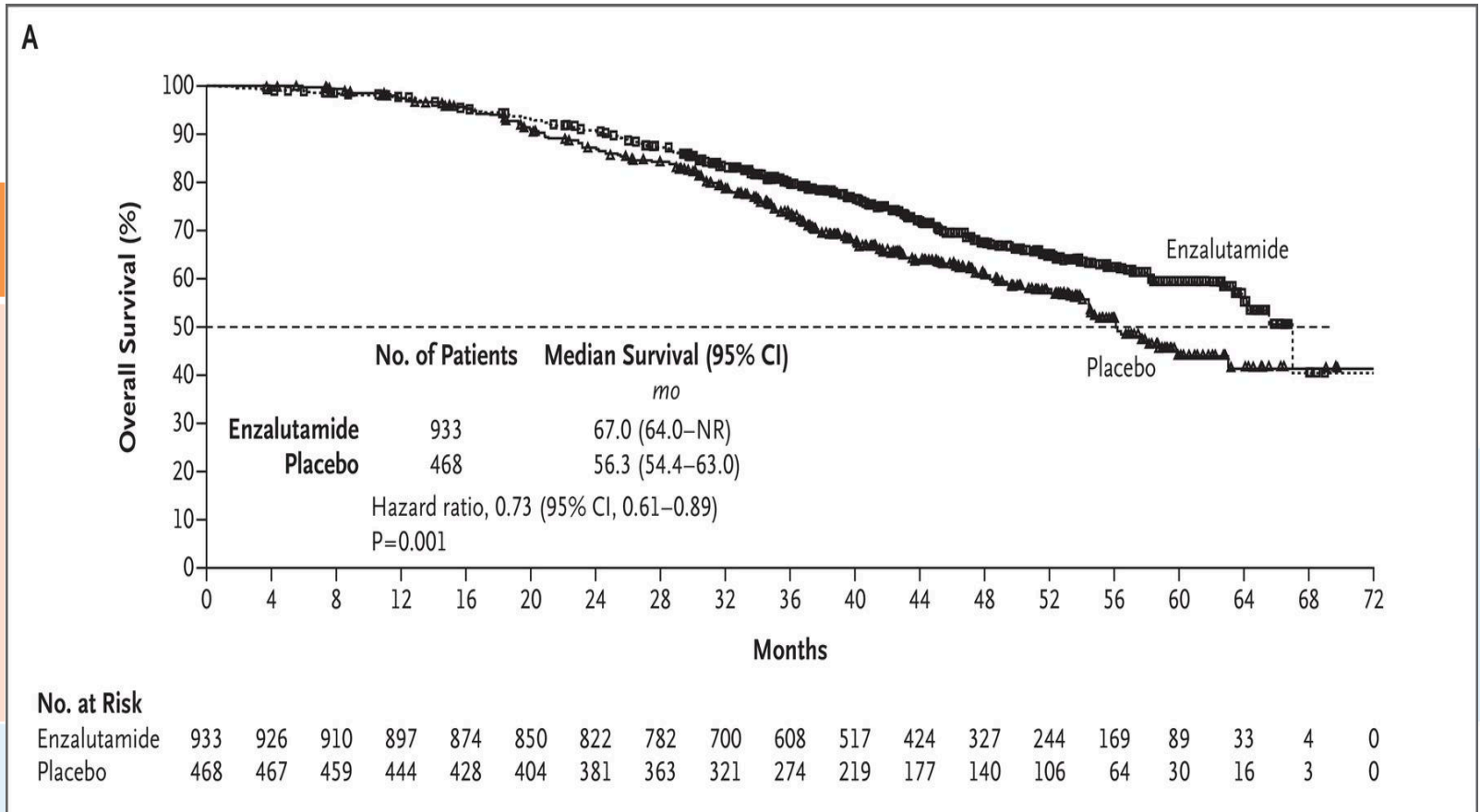
American
Urological
Association

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



American
Urological
Association

Education & Research, Inc. 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.



American
Urological
Association

Education & Research, Inc.

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



American
Urological
Association

Education & Research, Inc.

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)

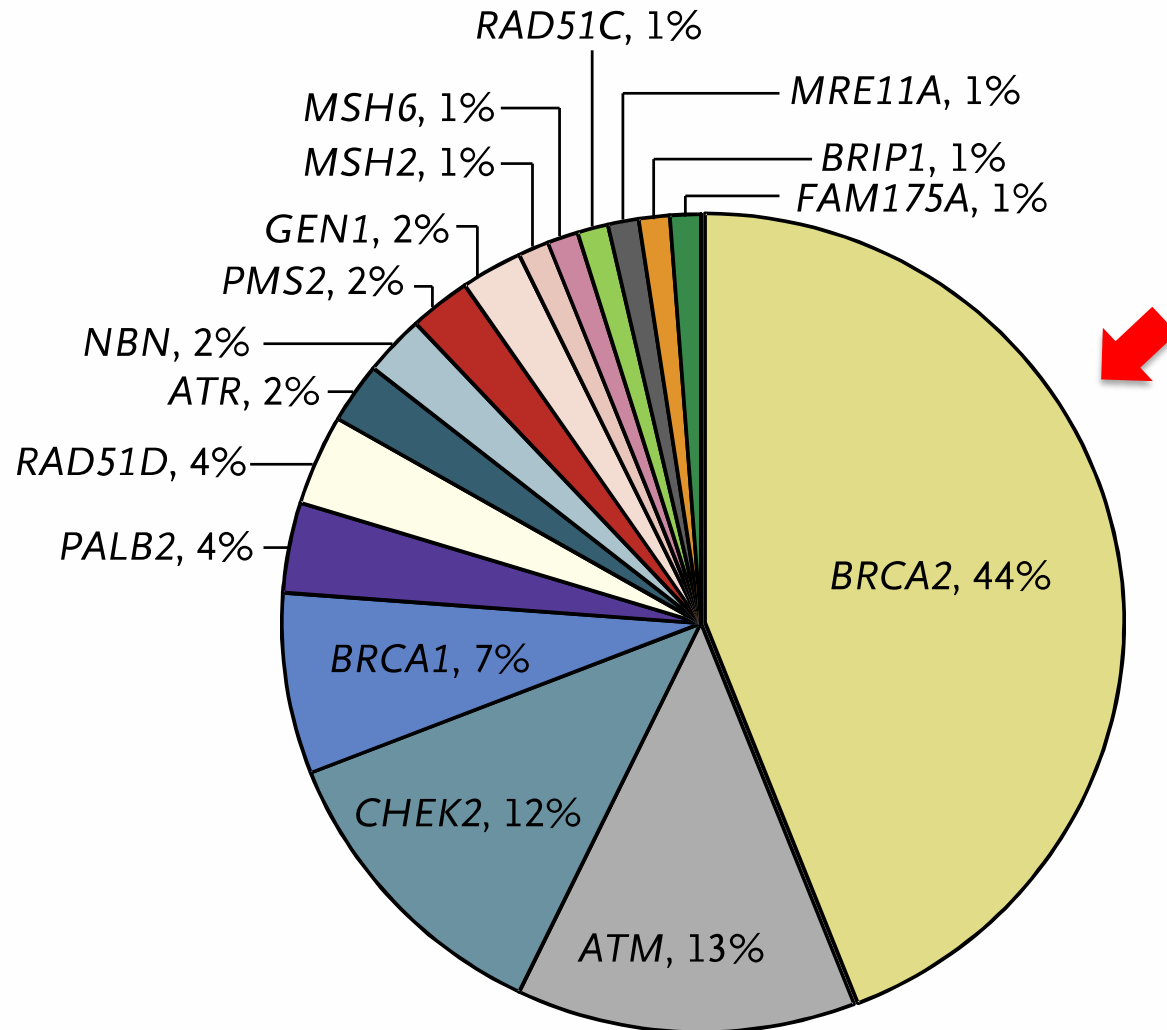


American
Urological
Association

Education & Research, Inc.

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

ORIGINAL ARTICLE



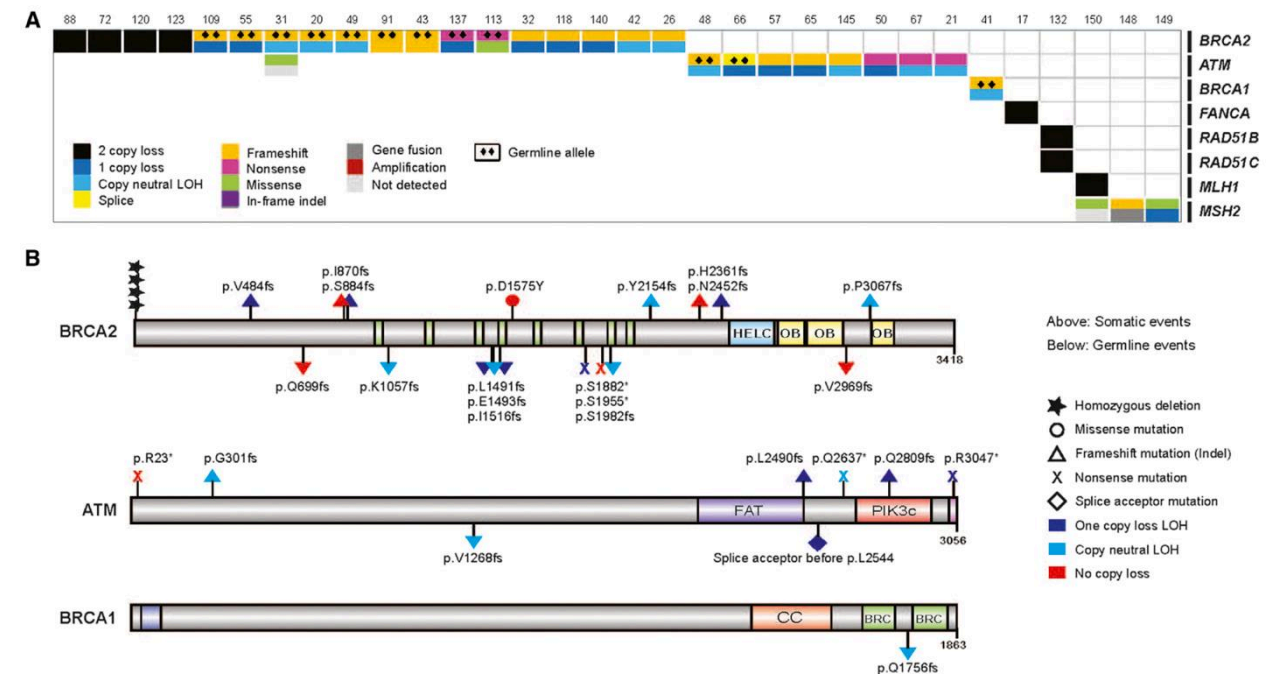
Inherited DNA-Repair Gene Mutations in Men with Metastatic Prostate Cancer

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

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)**



American
Urological
Association

Education & Research, Inc.

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



American
Urological
Association

Education & Research, Inc.

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])

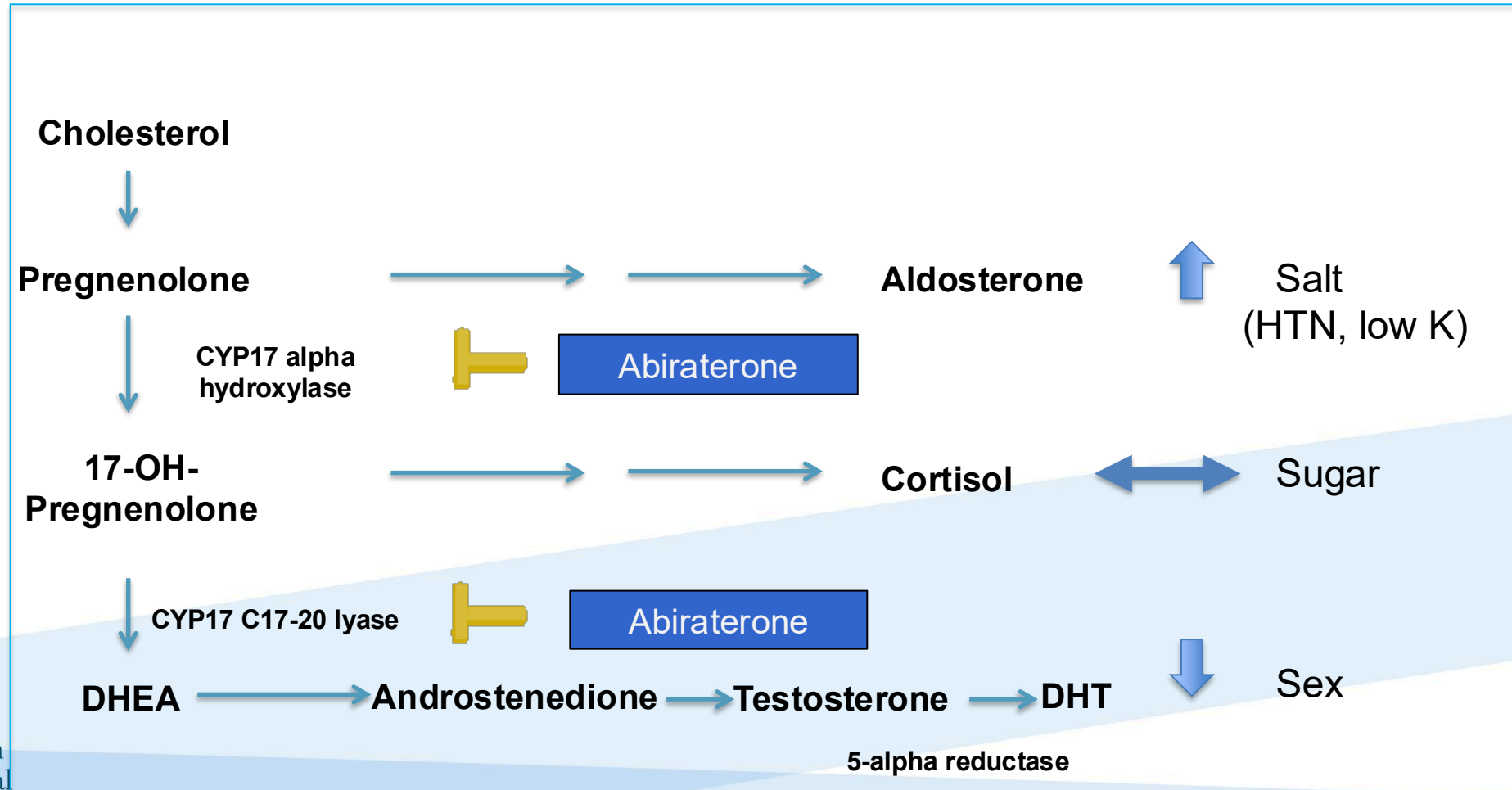
For patients who have received prior ARPI, continued ADT with docetaxel is an option. (Recommendation: Grade B)



American
Urological
Association

Education & Research, Inc.

ABIRATERONE MECHANISM



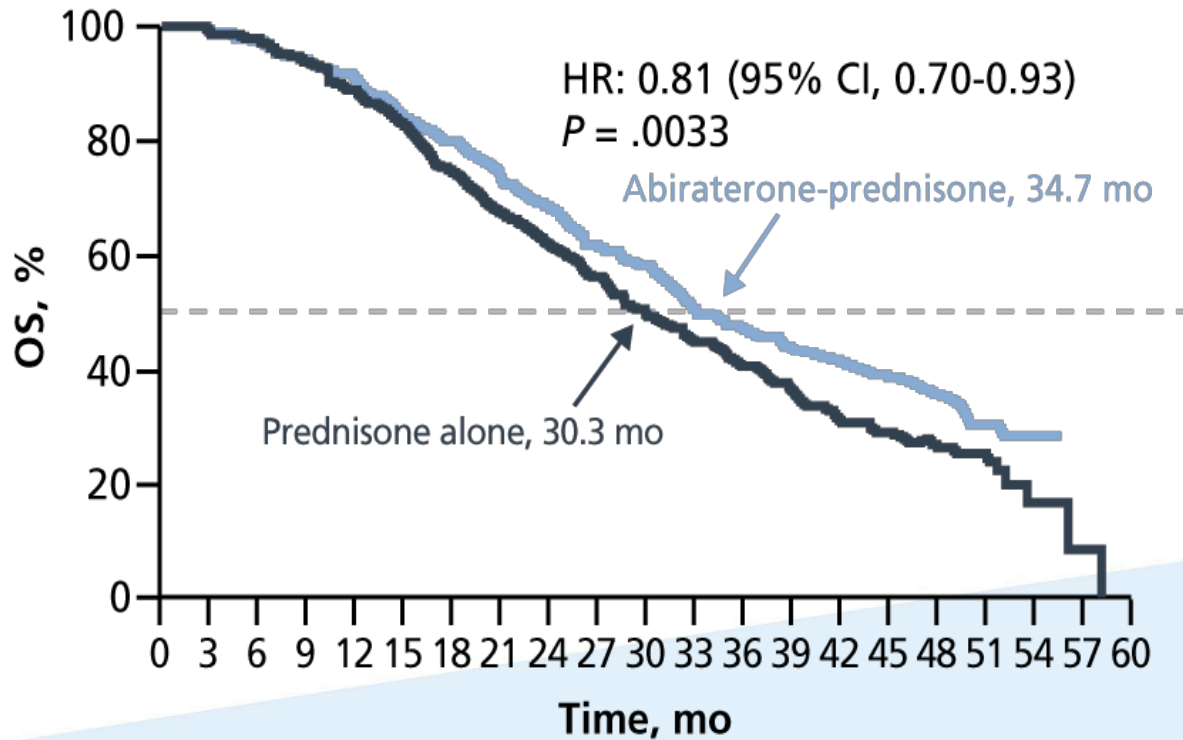
American
Urological
Association

Education & Research, Inc.

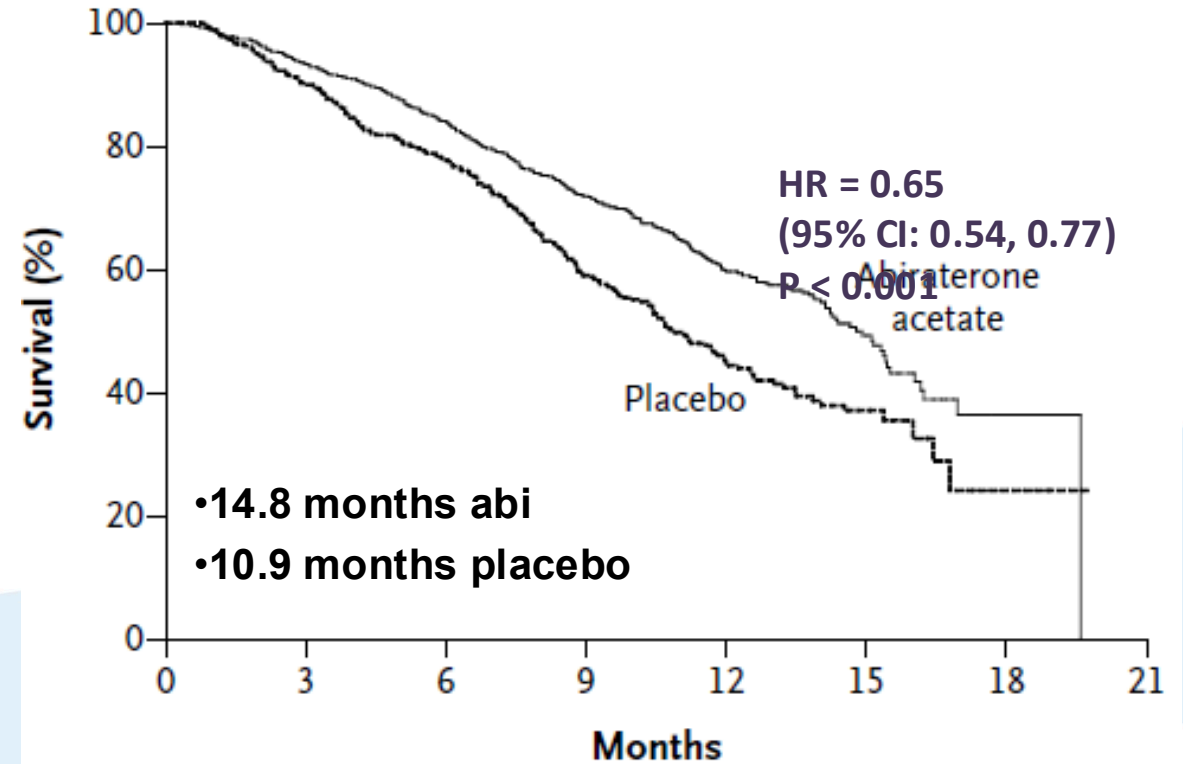
De Bono JS et al. *N Engl J Med*. 2011
Ryan et al. 2012

ABIRATERONE ACETATE: Pre & Post-Chemo

PRE CHEMO (COU-AA-302)



POST-CHемо (COU-AA-301)



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

de Bono et al. NEJM 2011

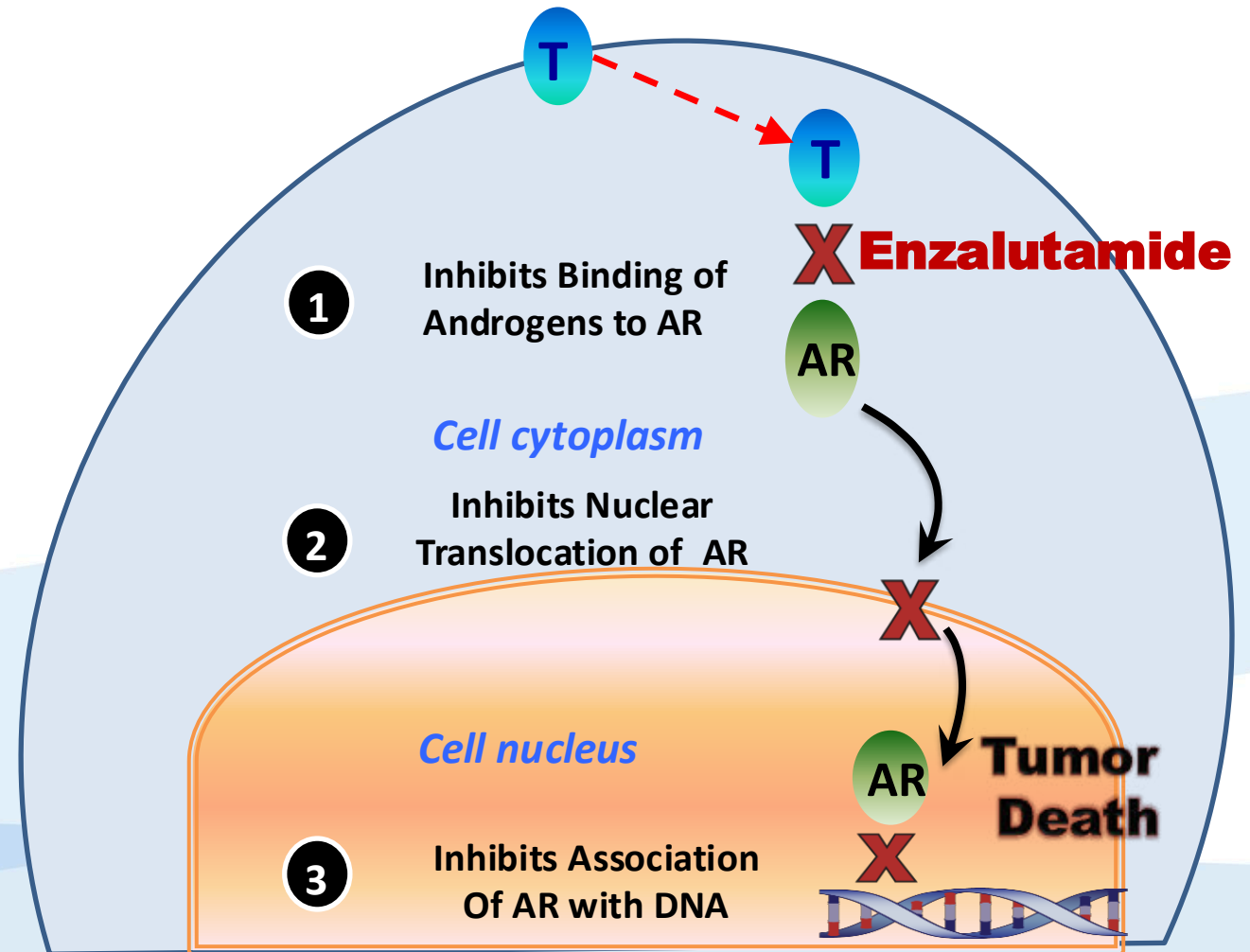


American
Urological
Association

Education & Research, Inc.

ENZALUTAMIDE: AR Signaling Inhibitor

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



American
Urological
Association

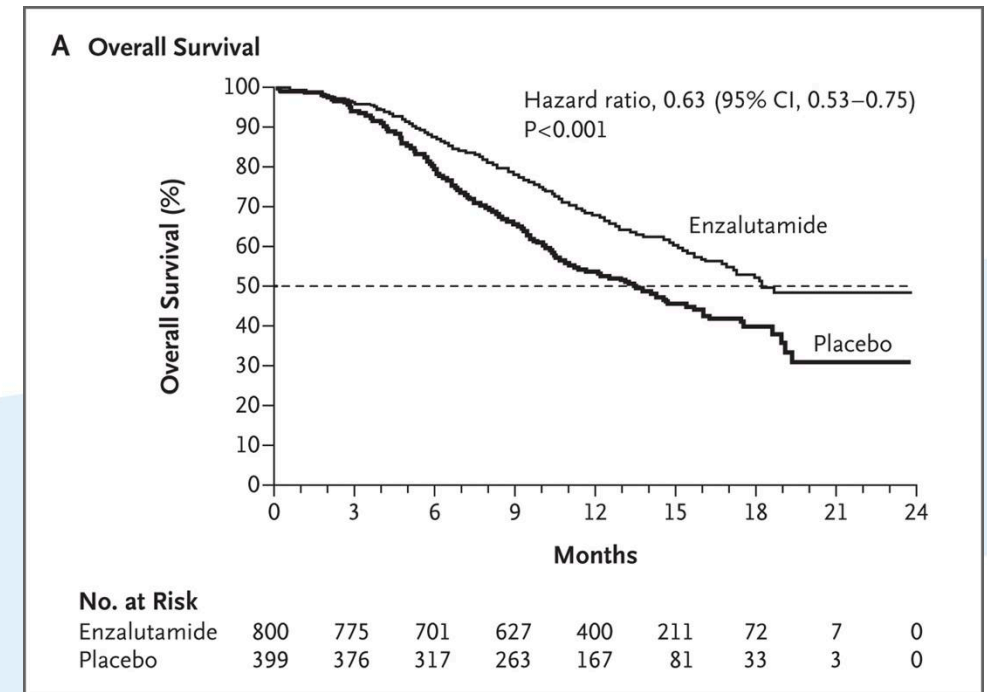
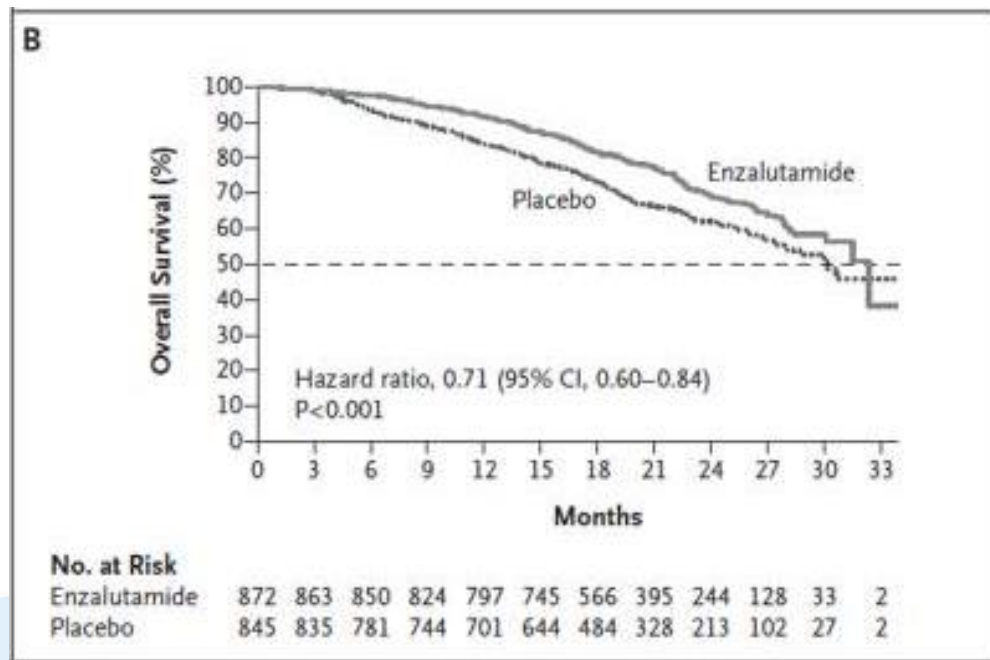
Education & Research, Inc.

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

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



American
Urological
Association

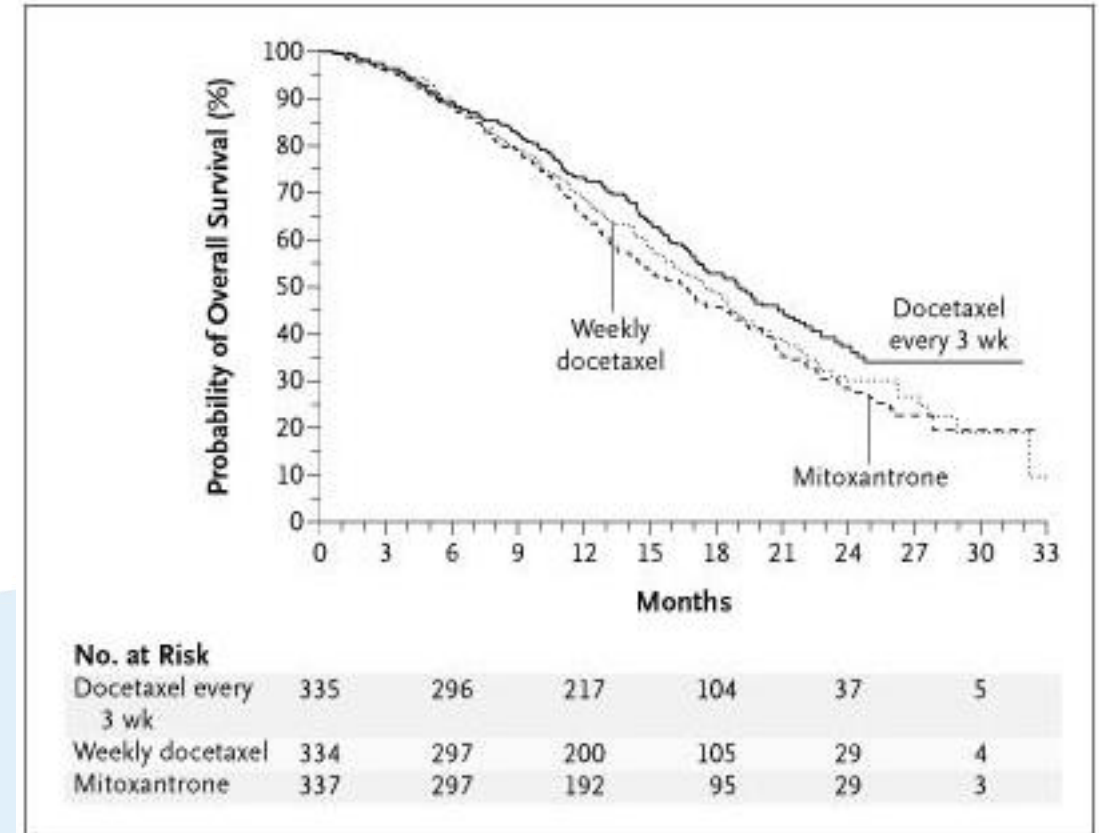
Education & Research, Inc.

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

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

DOCETAXEL: First-Line Chemotherapy

Trial	Overall Survival
TAX-327 n=1,006	A: 18.9 months docetaxel (every 3 weeks)
First-line therapy	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

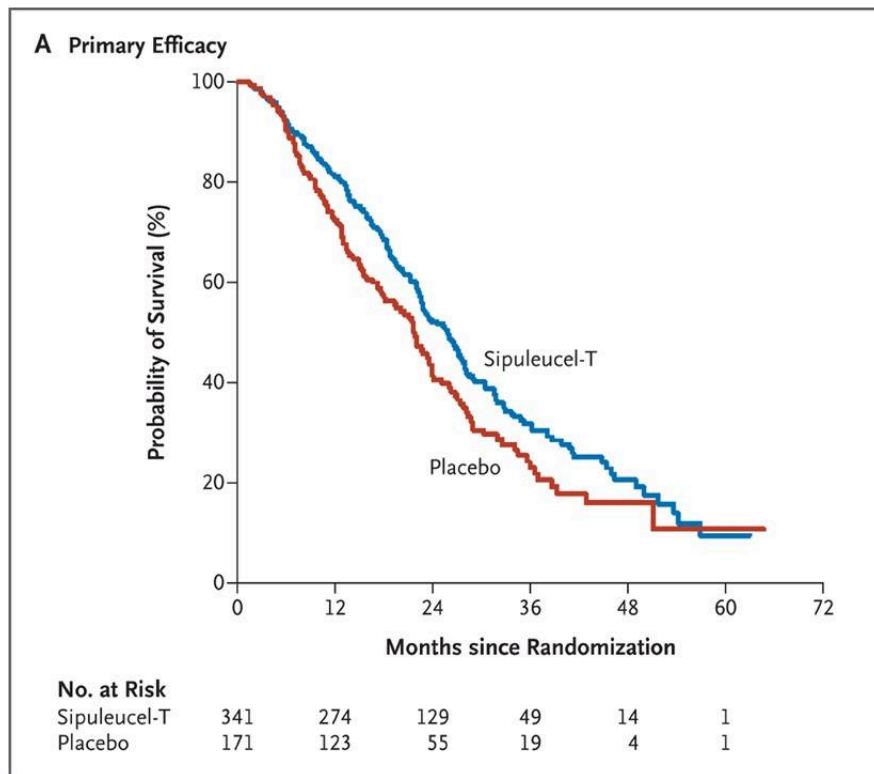
29. In mCRPC patients who are asymptomatic or minimally symptomatic, clinicians may offer sipuleucel-T. (Conditional Recommendation; Evidence Level: Grade B)



American
Urological
Association

Education & Research, Inc.

SIPULEUCEL-T: Pre-Chemotherapy



Trial

IMPACT
n=512

Overall Survival

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.

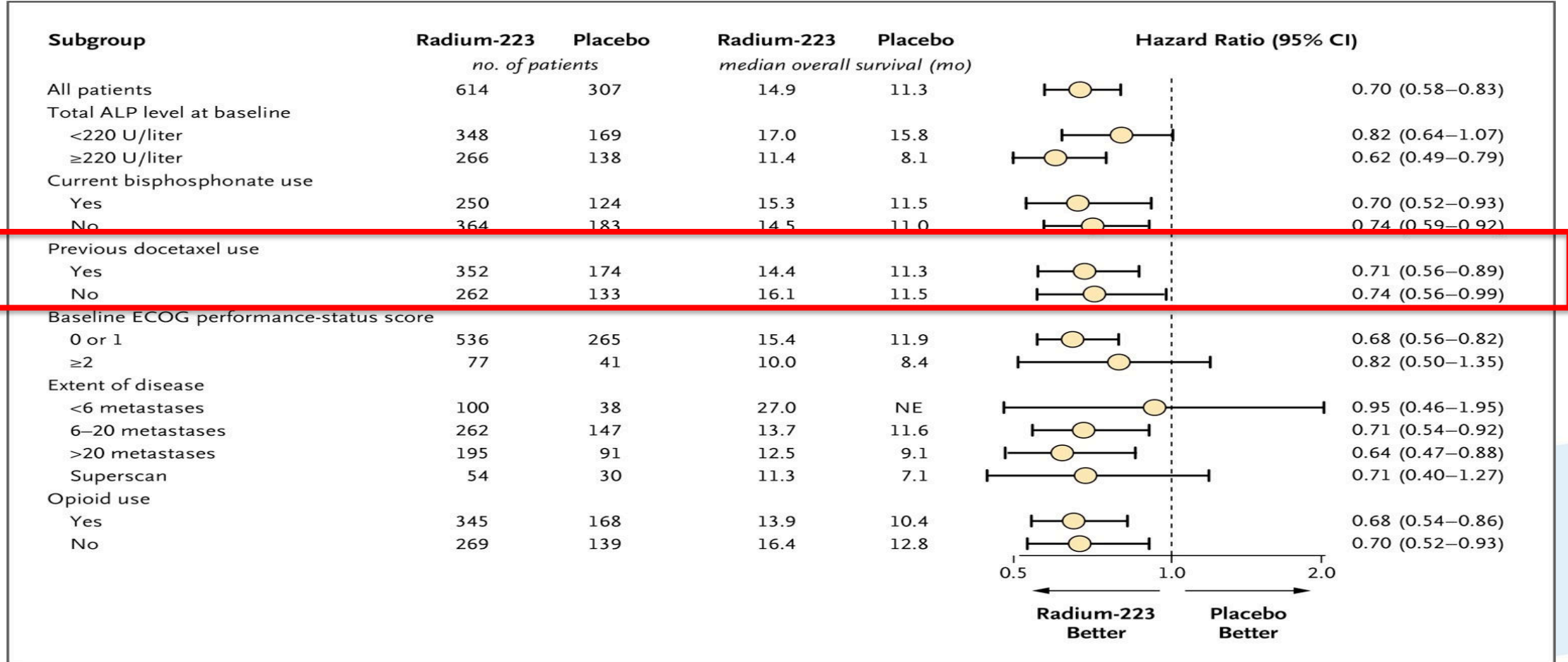
Kantoff PW et al: Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med 2010; 363: 411.

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

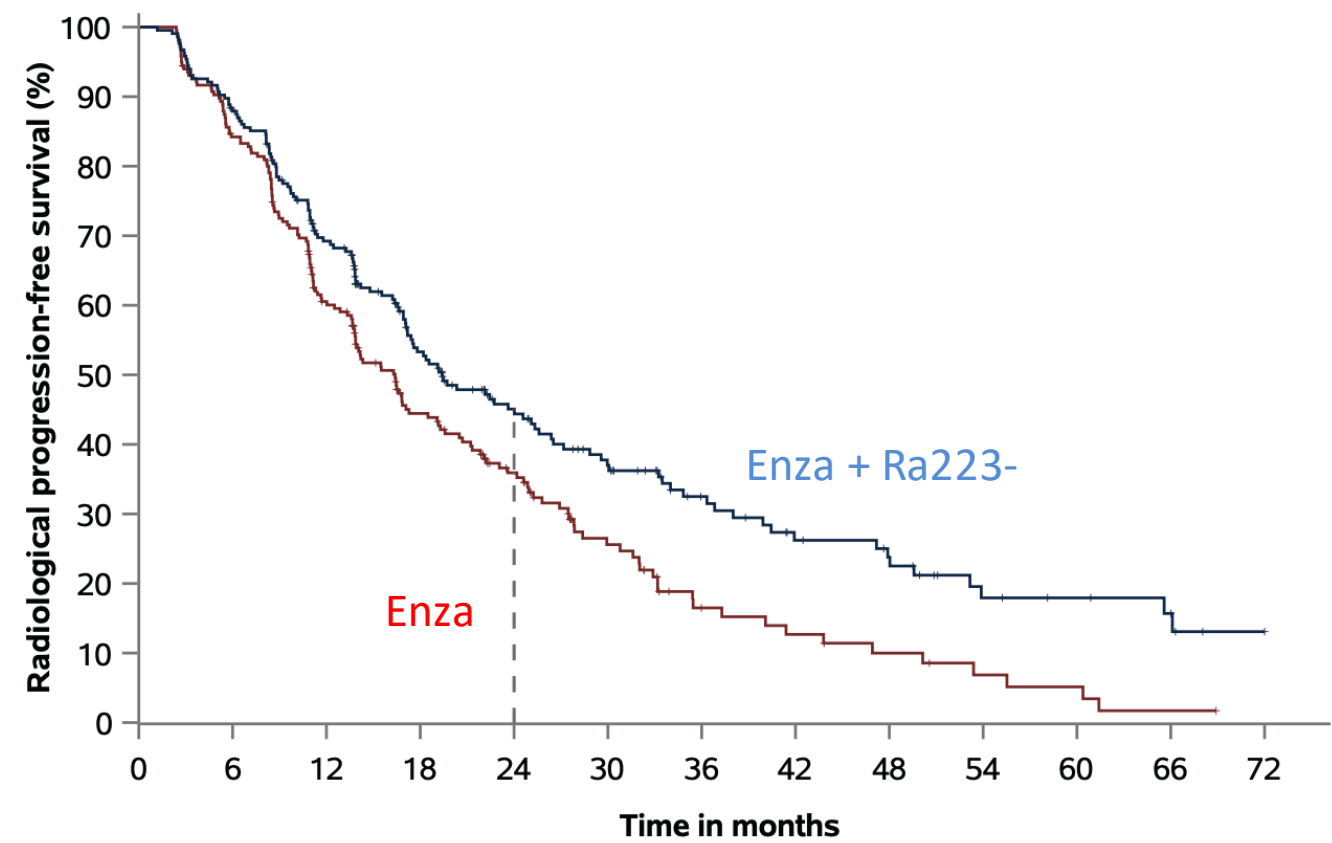


American
Urological
Association

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



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%

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



METASTATIC CRPC

may

31. Clinicians ~~should~~ offer ^{may} 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)



American
Urological
Association

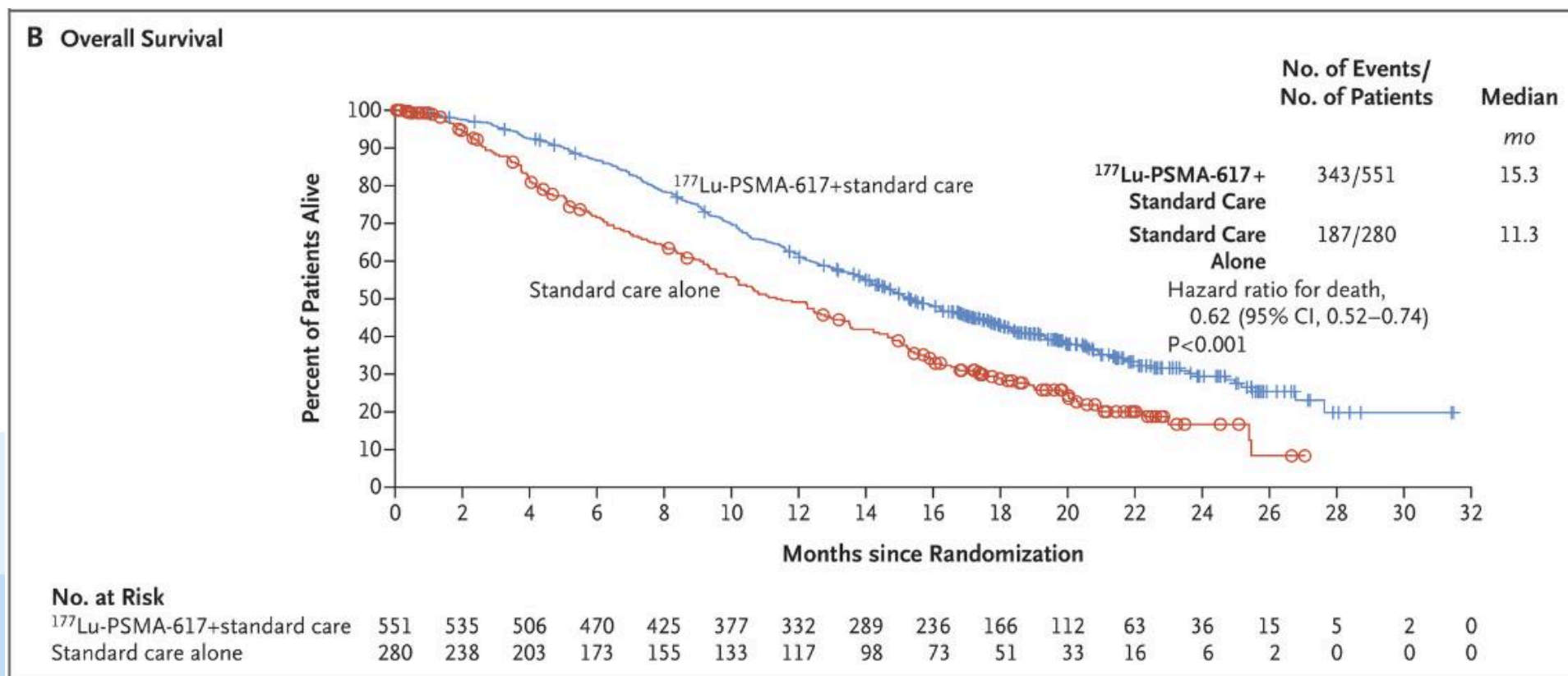
Education & Research, Inc.

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*

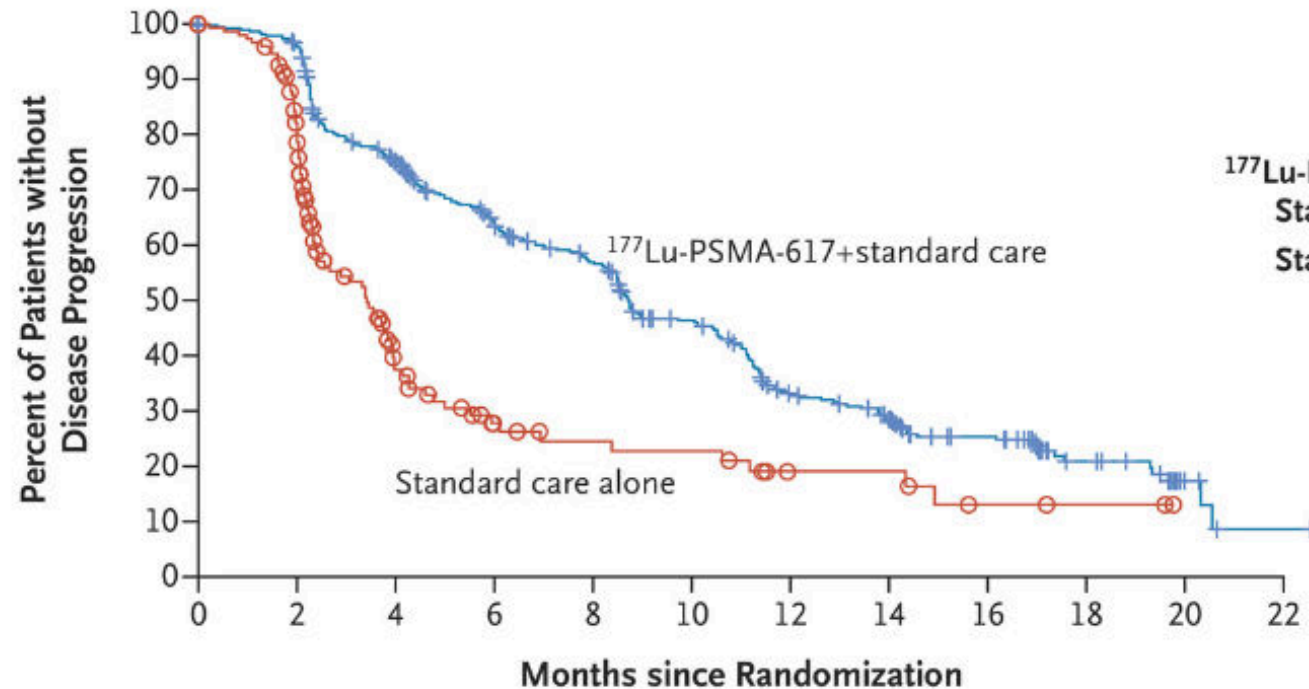


American
Urological
Association

Education & Research, Inc.

VISION Trial

A Imaging-Based Progression-free Survival



No. of Events/
No. of Patients

Median
mo

^{177}Lu -PSMA-617+
Standard Care
Standard Care
Alone

254/385

8.7

93/196

3.4

Hazard ratio for progression or death,
0.40 (99.2% CI, 0.29–0.57)
 $P < 0.001$

No. at Risk

^{177}Lu -PSMA-617+standard care	385	362	272	215	182	137	88	71	49	21	6	1
Standard care alone	196	119	36	19	14	13	7	7	3	2	0	0

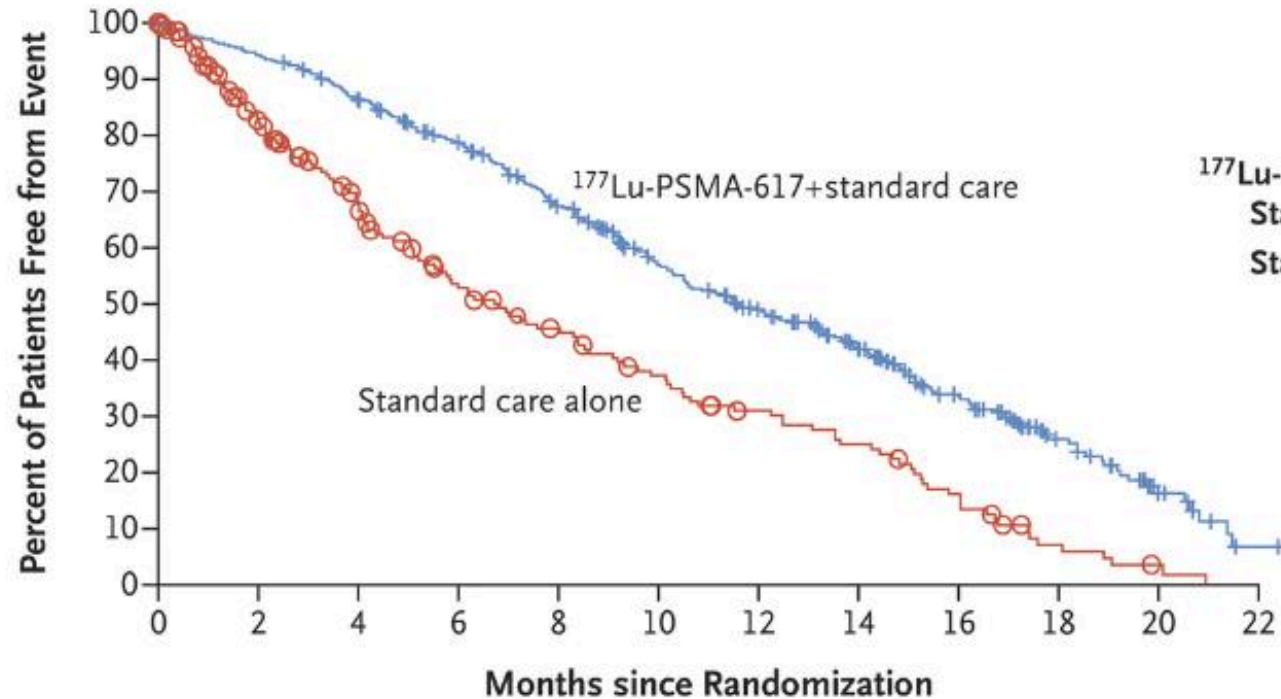


American
Urological
Association

Education & Research, Inc.

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



American
Urological
Association

Education & Research, Inc.

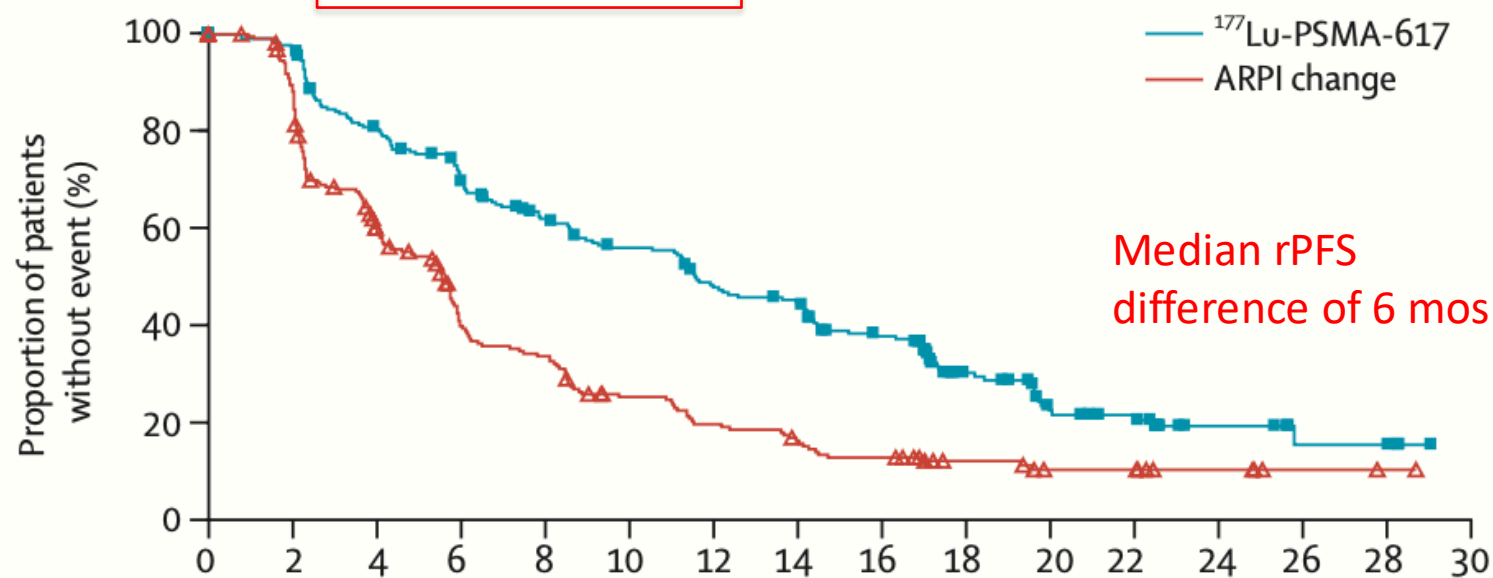
¹⁷⁷Lu-PSMA-617 versus a change of androgen receptor pathway inhibitor therapy for taxane-naïve patients with progressive metastatic castration-resistant prostate cancer (PSMAfore): a phase 3, randomised, controlled trial

Radiographic progression-free survival

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

A Radiographic progression-free survival

¹⁷⁷Lu-PSMA-617 group: median 11.60 months (95% CI 9.30–14.19), 154 events
 ARPI change group: median 5.59 months (95% CI 4.21–5.95), 180 events
 HR 0.49 (95% CI 0.39–0.61)



	Number at risk (number censored)															
¹⁷⁷ Lu-PSMA-617 group	234	217	175	152	126	111	94	86	67	39	25	20	8	4	4	0
	(0)	(12)	(5)	(3)	(6)	(3)	(2)	(1)	(6)	(16)	(6)	(3)	(10)	(3)	(0)	(4)
ARPI change group	234	197	126	79	65	45	35	28	22	14	9	9	5	2	1	0
	(0)	(14)	(7)	(9)	(0)	(4)	(0)	(1)	(0)	(7)	(3)	(0)	(4)	(3)	(1)	(1)

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

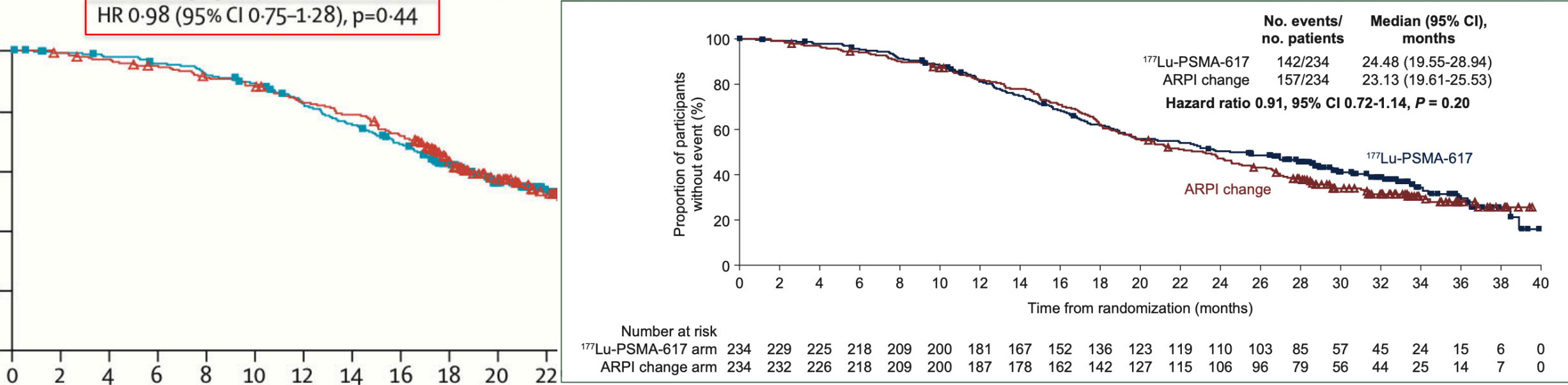
Overall Survival

B Overall survival (intention-to-treat analysis)

¹⁷⁷Lu-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



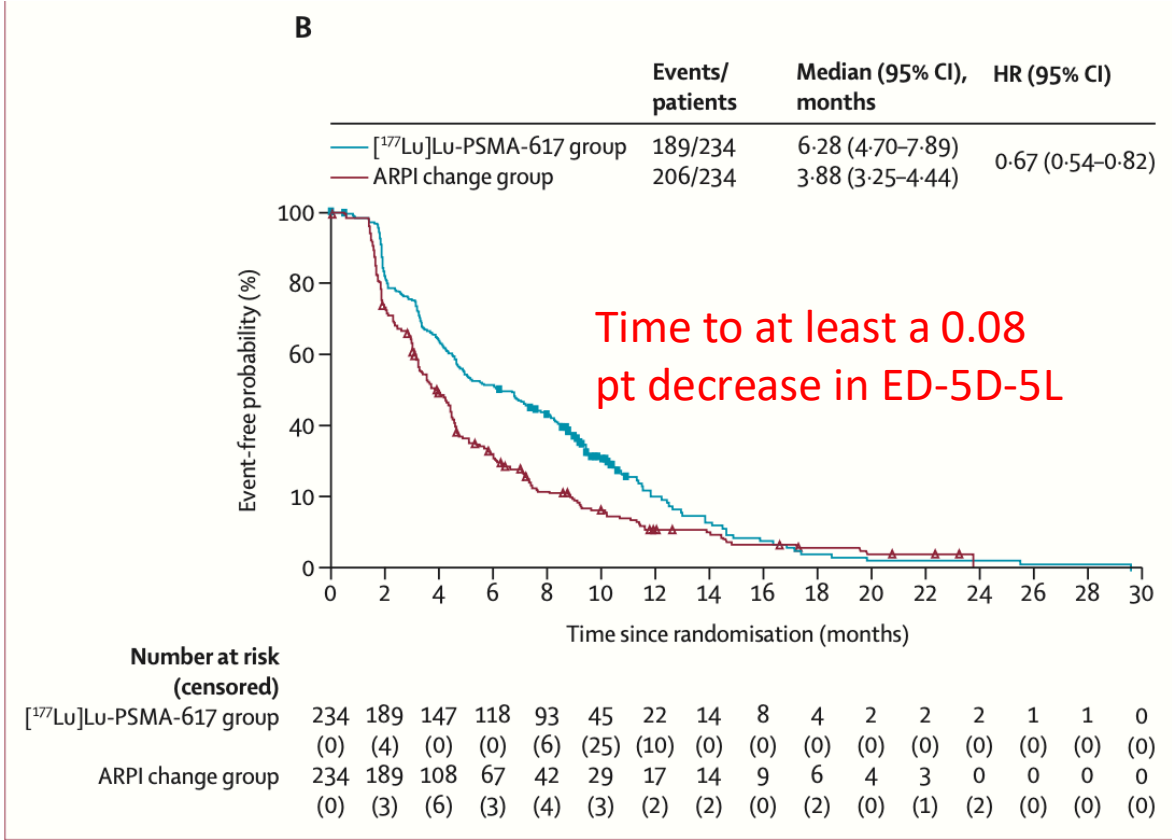
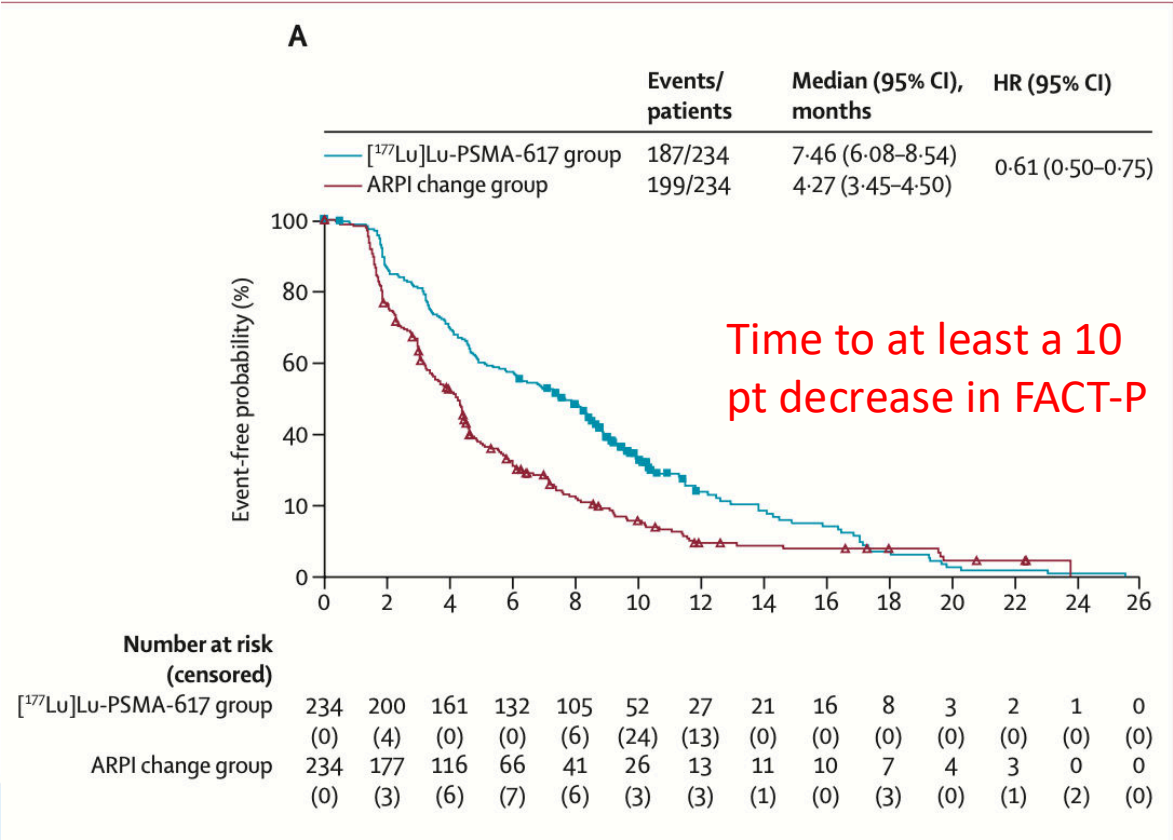
Conclusions: OS analyses did not show a statistically significant difference between the ¹⁷⁷Lu-PSMA-617 and ARPI arms based on the ITT principle; results were likely confounded by the high rate of crossover. The safety profile of ¹⁷⁷Lu-PSMA-617 was favourable with no new safety signals identified.

234	228	224	218	20	Based on the fit principle, results were likely correct											
(0)	(4)	(1)	(1)	(0)	PSMA-617 was favourable with no new safety signals											
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)

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

Lancet 2024; 404: 1227–39

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



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

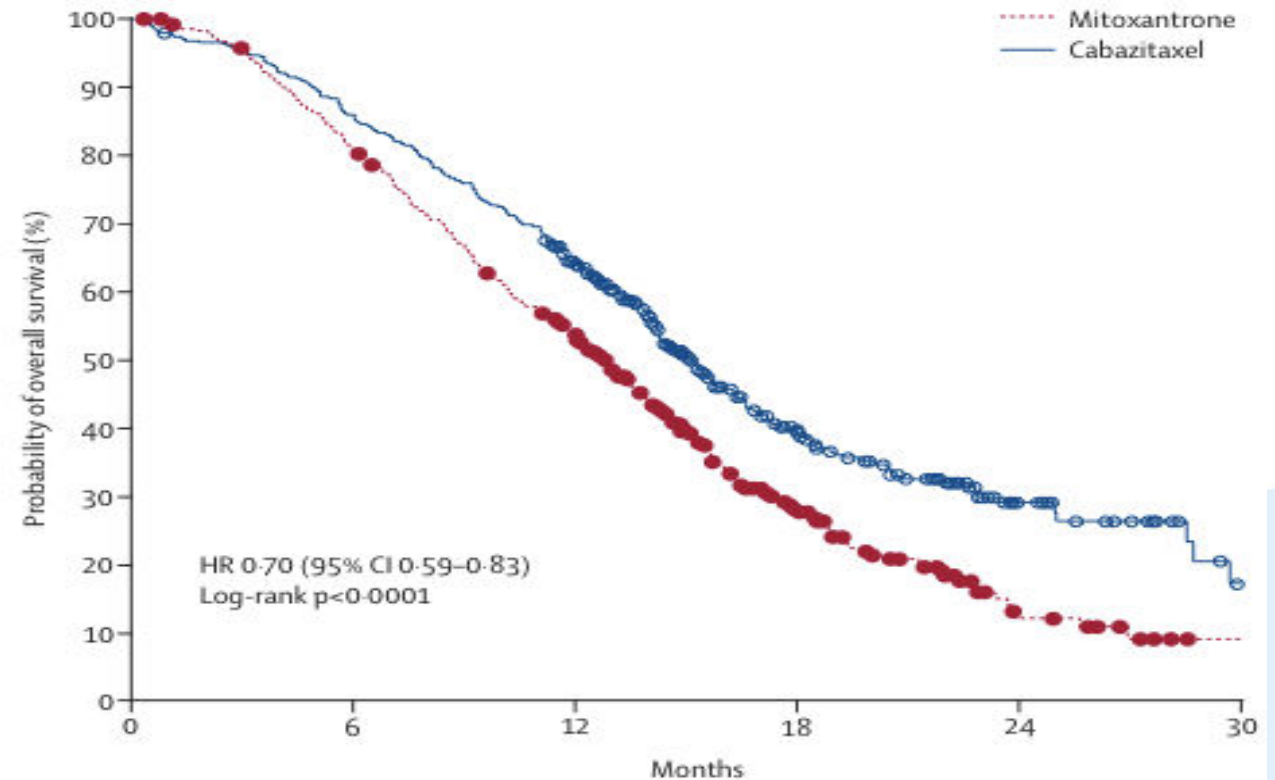
METASTATIC CRPC

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 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



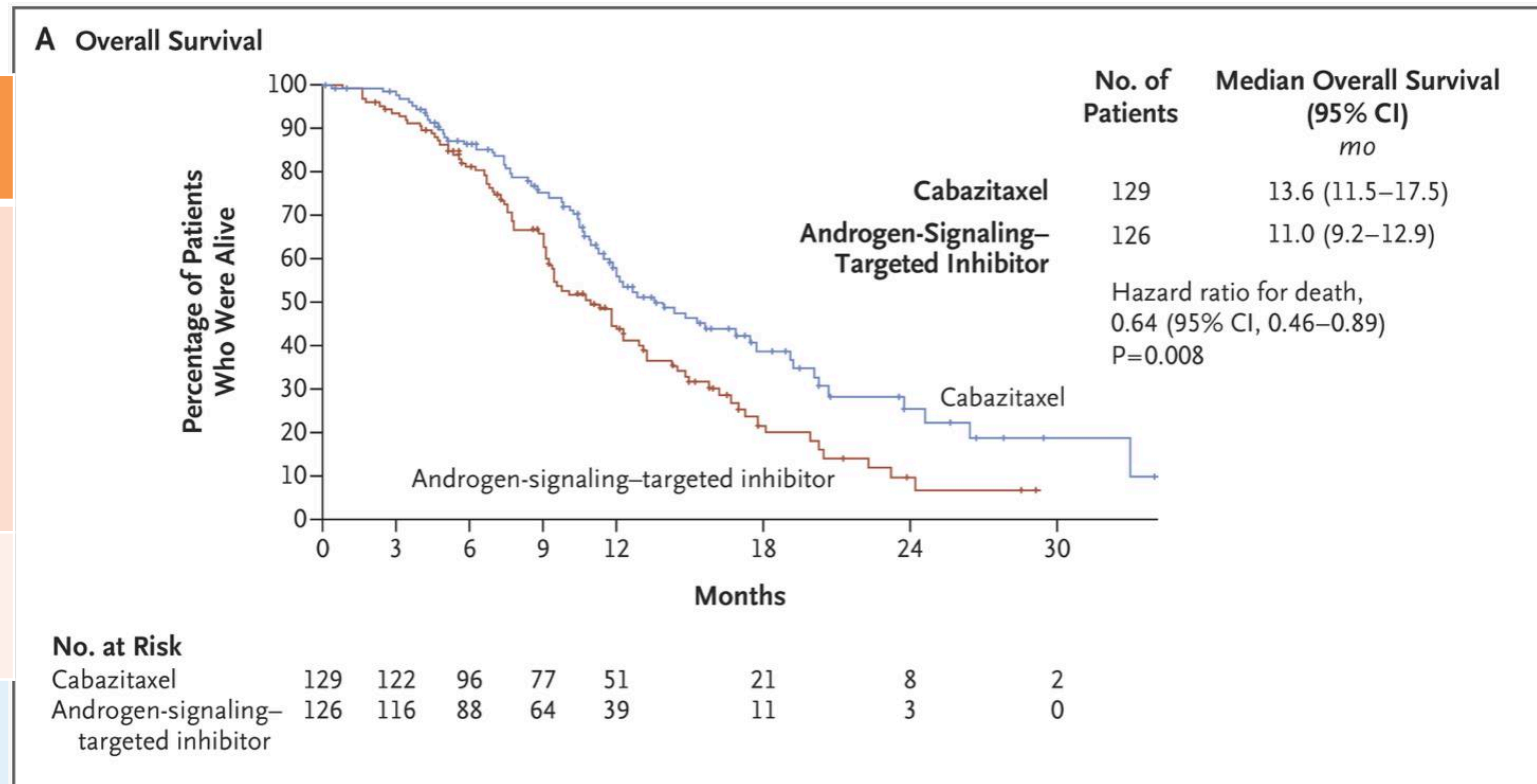
American
Urological
Association

Education & Research, Inc.

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

Cabazitaxel: Second-Line Therapy

Trial	Overall Survival
CARD n=755	13.6 months cabazitaxel 11.0 months ARPI switch
Second-line therapy	
	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

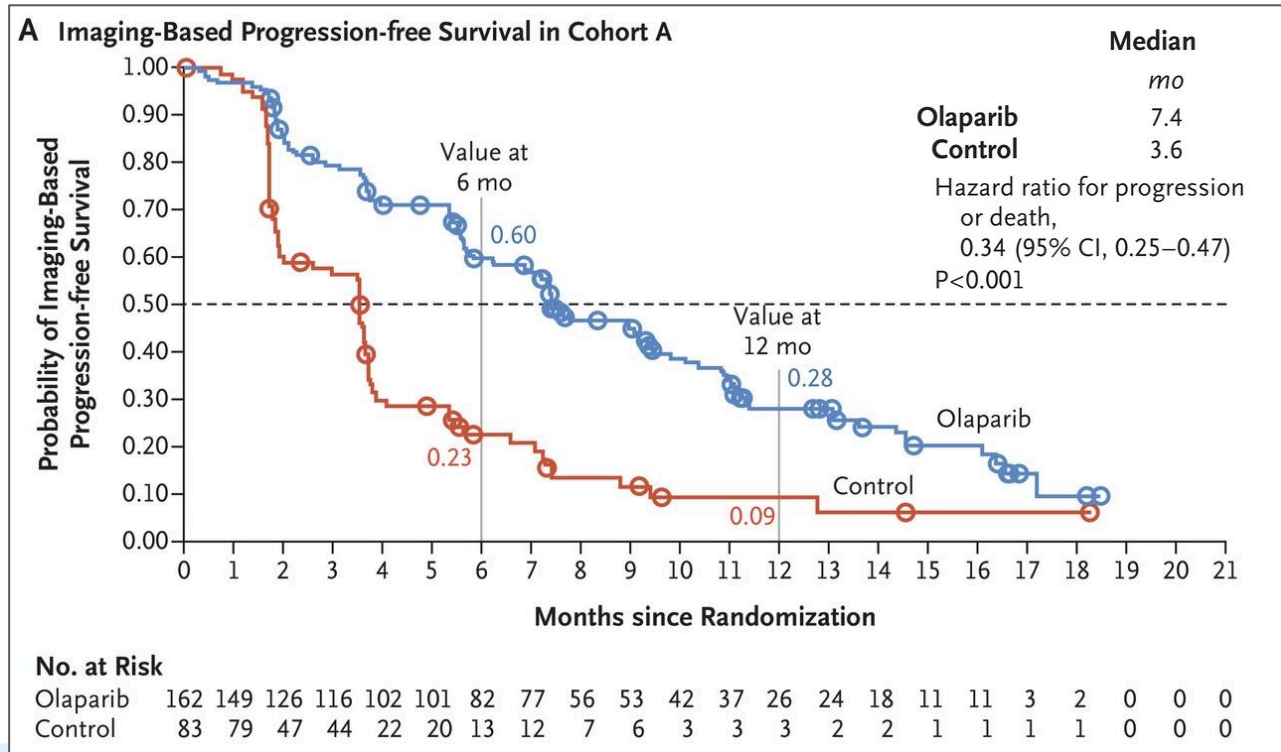
METASTATIC CRPC: Molecular testing

- UPDATE**
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)
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

PROfound
n=387

PFS (A)

7.4 months
olaparib
3.6 months
control



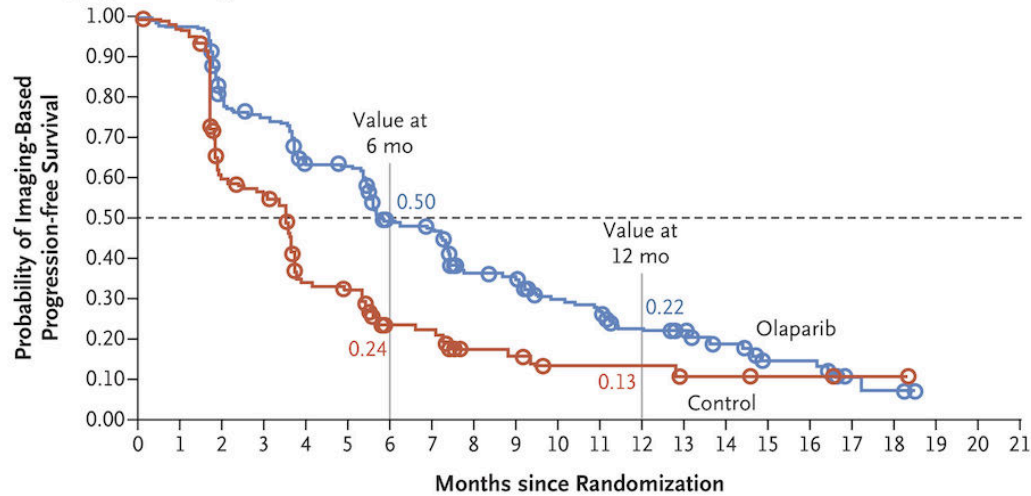
American
Urological
Association

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

C Imaging-Based Progression-free Survival in Cohorts A and B



No. at Risk

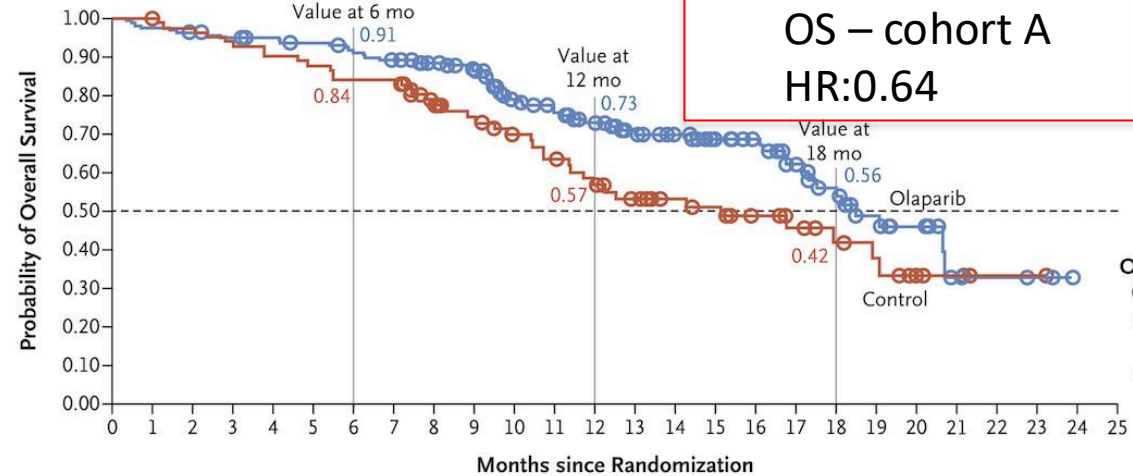
Olaparib	256	239	188	176	145	143	106	100	67	63	48	43	31	28	21	11	11	3	2	0	0	0
Control	131	123	73	67	38	35	20	19	9	8	5	5	5	3	3	2	2	1	1	0	0	0

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

B Interim Overall Survival in Cohort A



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

No. at Risk

Olaparib	162	158	155	152	150	147	141	136	125	115	95	86	76	67	59	50	46	33	26	17	11	4	3	2	0	0
Control	83	82	79	76	74	72	69	69	54	50	44	40	34	29	25	23	18	15	11	9	6	3	1	1	0	0

PROfound

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

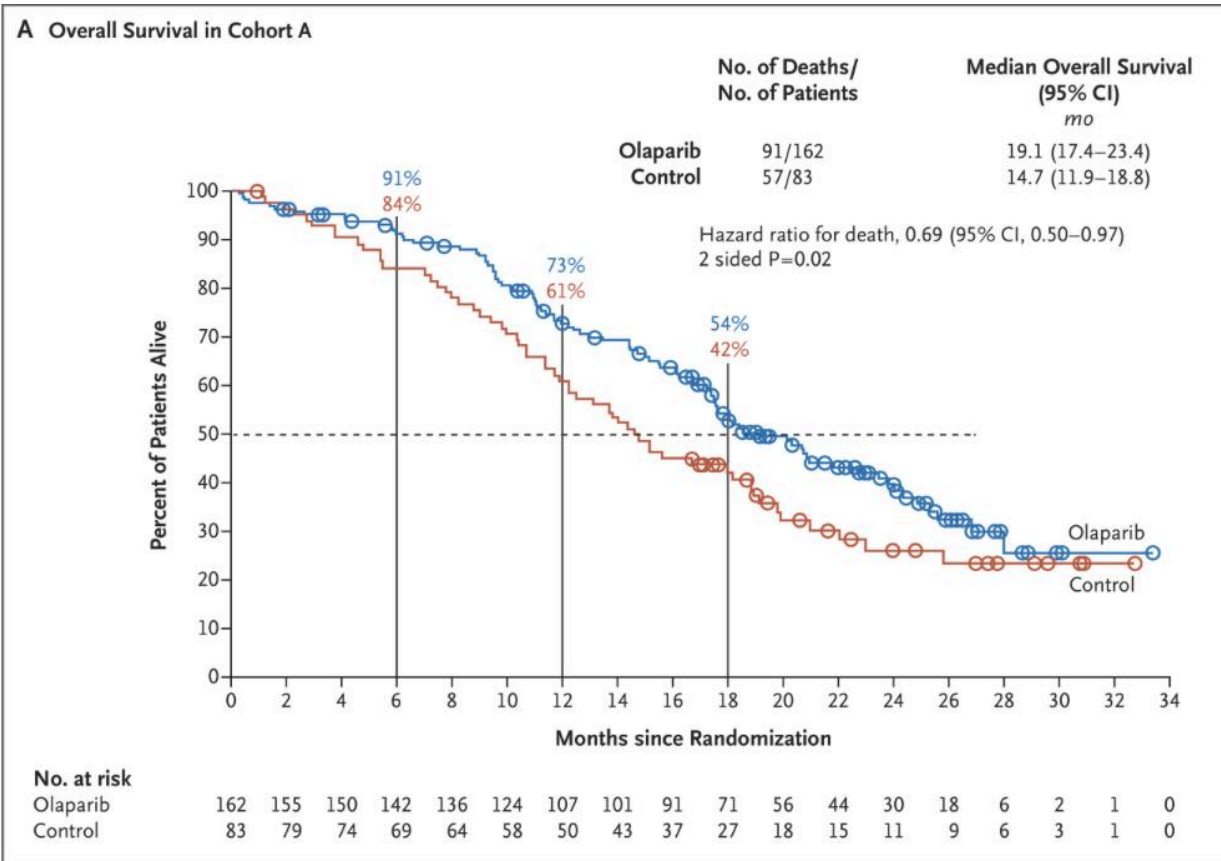


American
Urological
Association

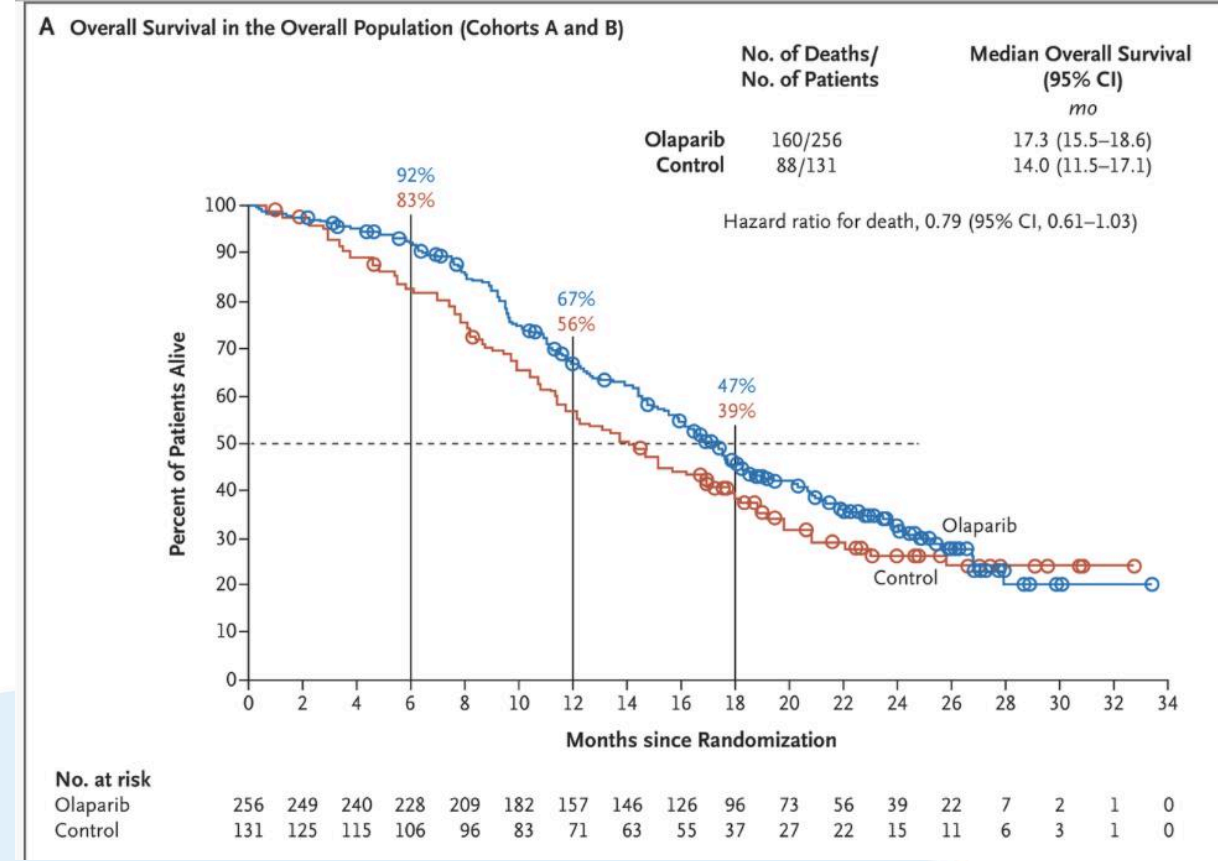
Education & Research, Inc.

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

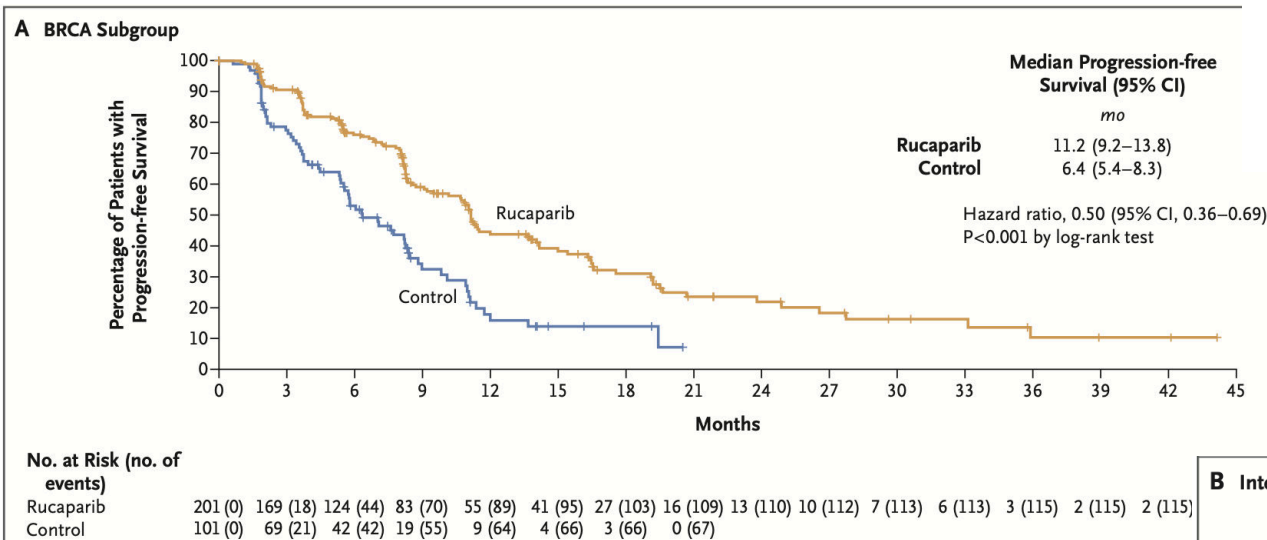
Education & Research, Inc.

METASTATIC CRPC: Homologous Recombination Repair Mutation

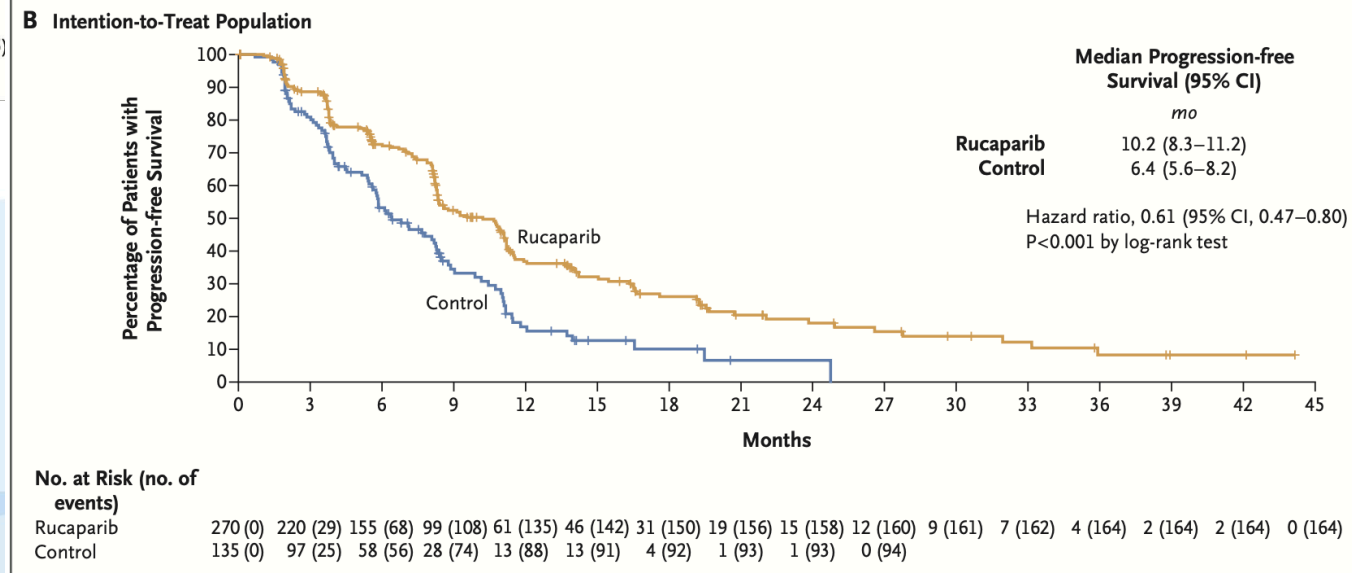
Rucaparib or Physician's Choice in Metastatic Prostate Cancer

TRITON3

ITT Population
HR 0.61 with rucaparib



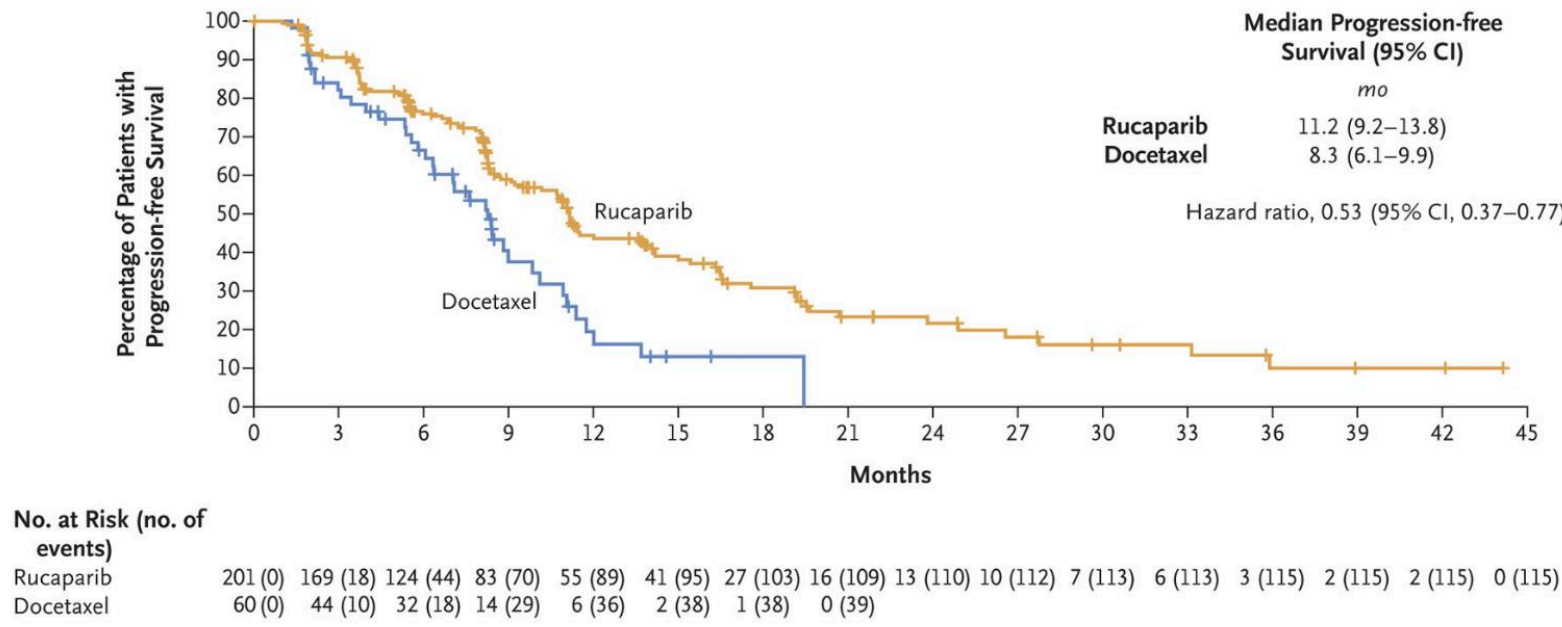
BRCA subgroup
HR 0.50 with rucaparib



American
Urological
Association

Education & Research, Inc.

A Rucaparib vs. Docetaxel in the BRCA Subgroup



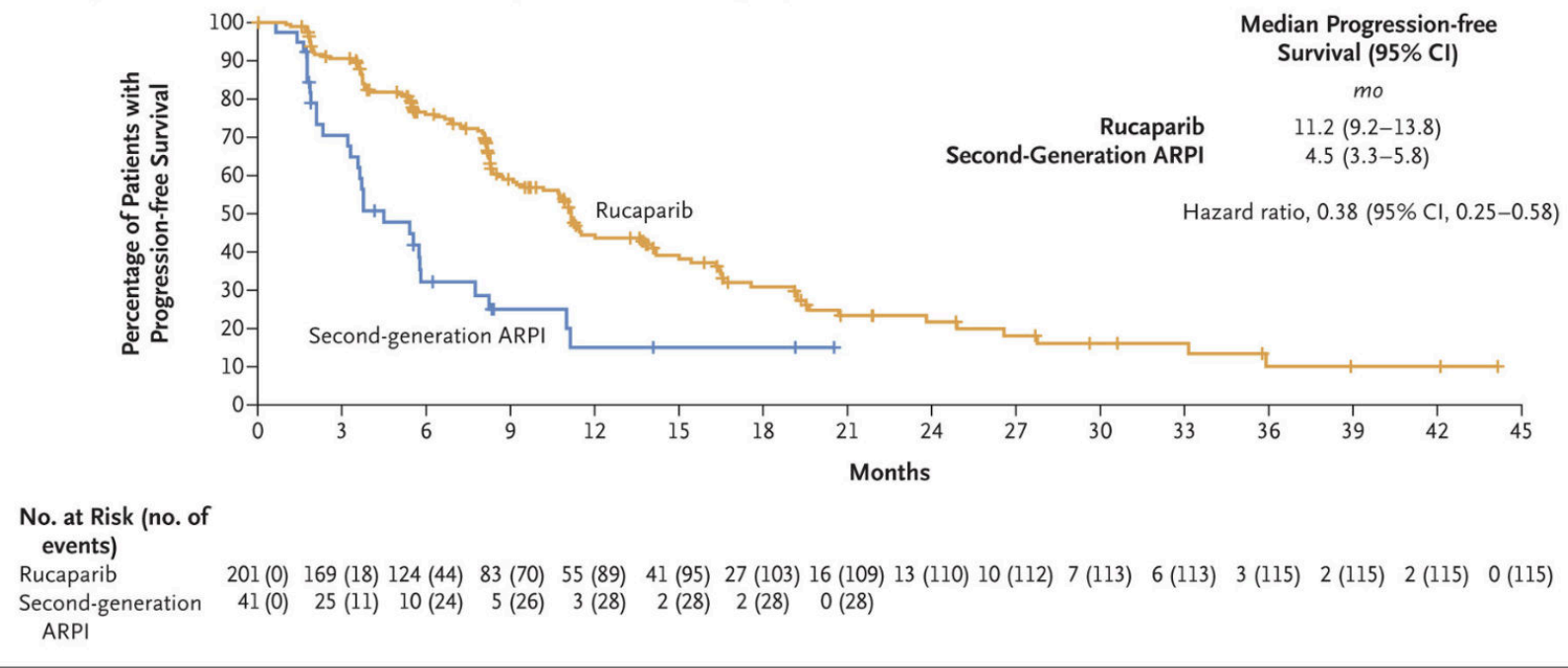
Rucaparib or Physician’s Choice in Metastatic Prostate Cancer

TRITON3

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

rPFS: Rucaparib superior to docetaxel by ~ 3 months

B Rucaparib vs. Second-Generation ARPI Therapies in the BRCA Subgroup



American Urological Association

Education & Research, Inc.

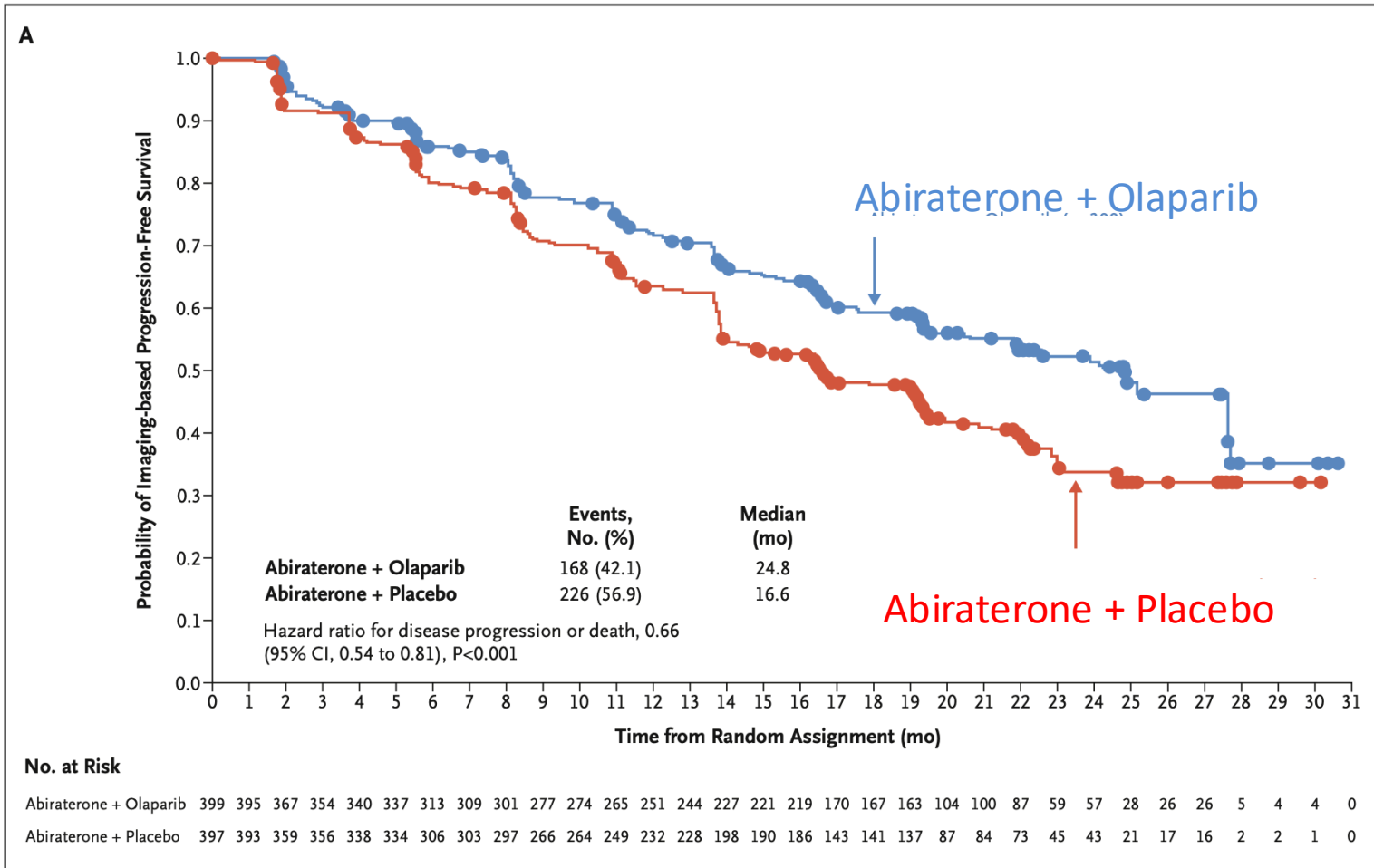
N Engl J Med.2023;388(8):719–732

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

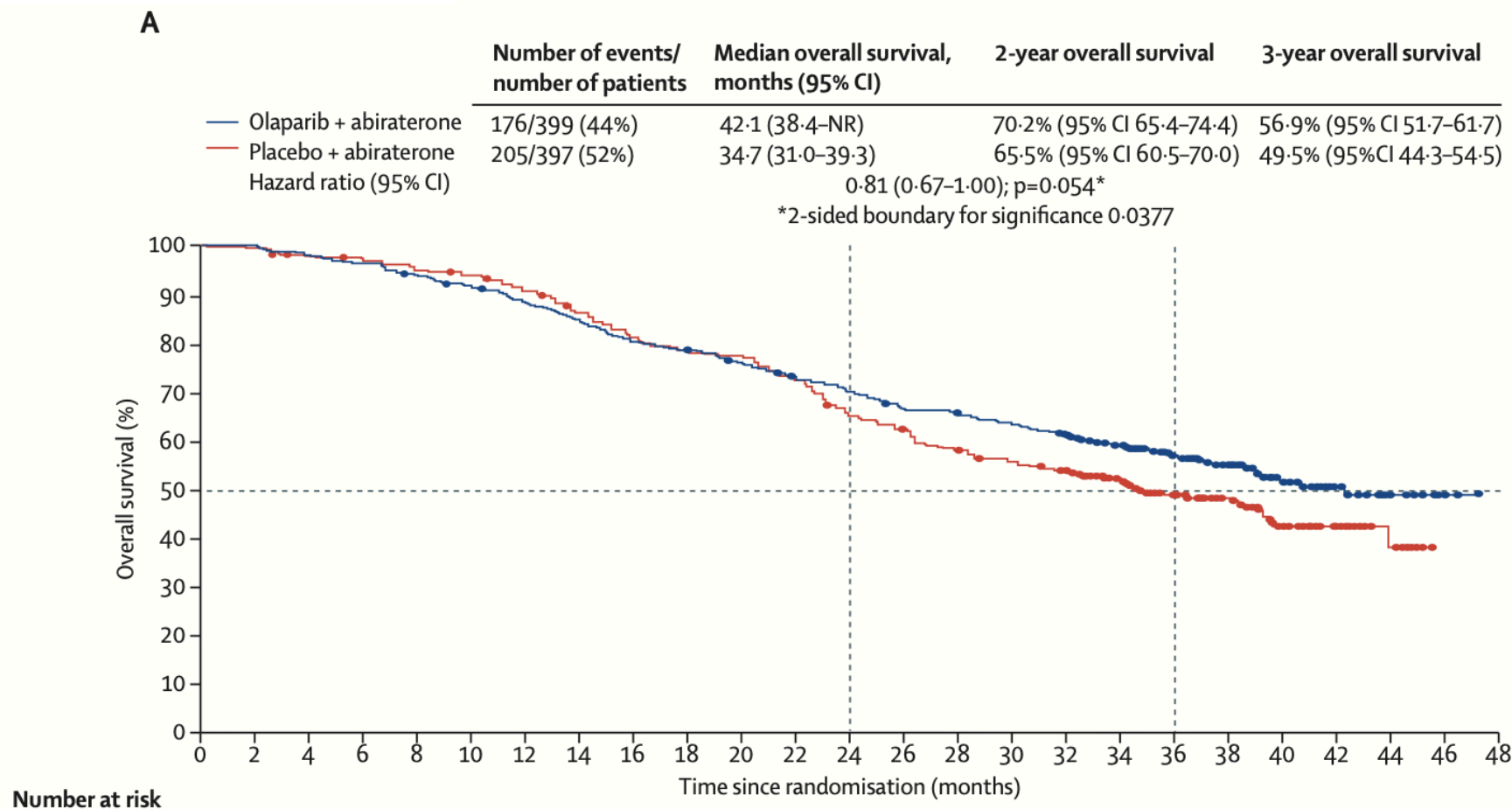
Education & Research, Inc.

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**



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



American
Urological
Association

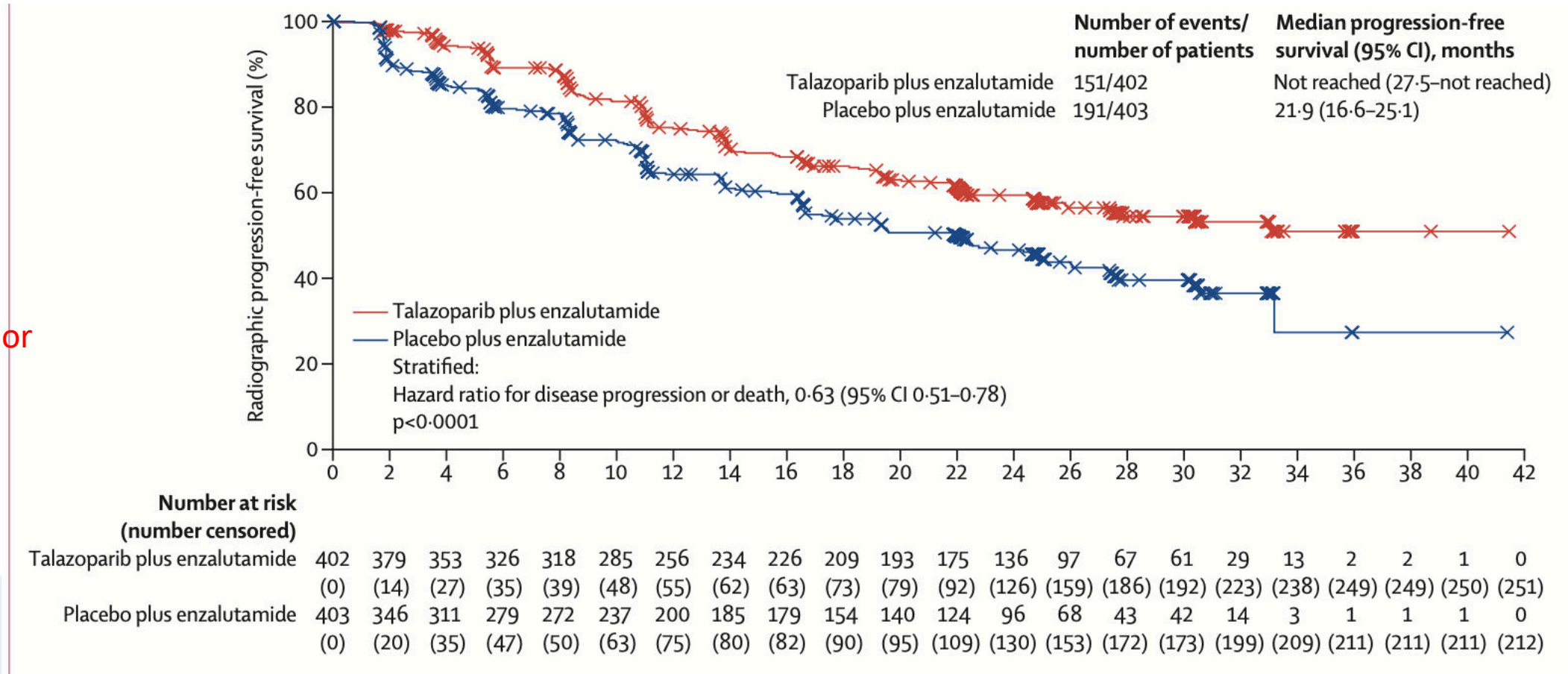
Education & Research, Inc.

TALAPRO-2

Talazoparib + Enzalutamide

Radiographic
Progression Free
Survival

Blinded investigator
assessment



American
Urological
Association

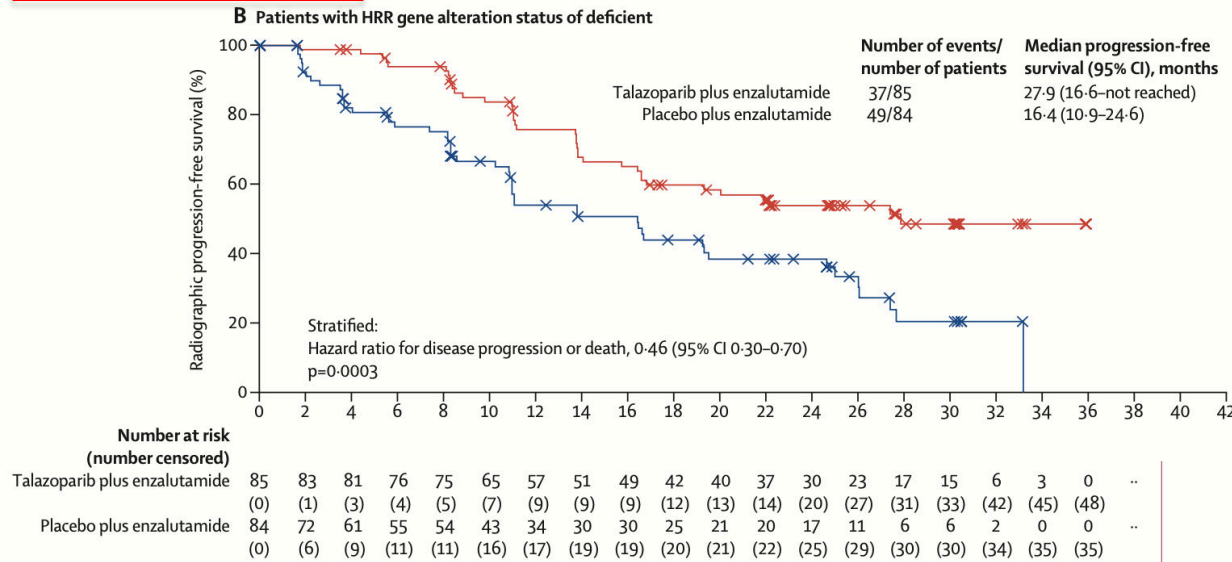
Education & Research, Inc.

Lancet 2023; 402: 291–303

TALAPRO-2

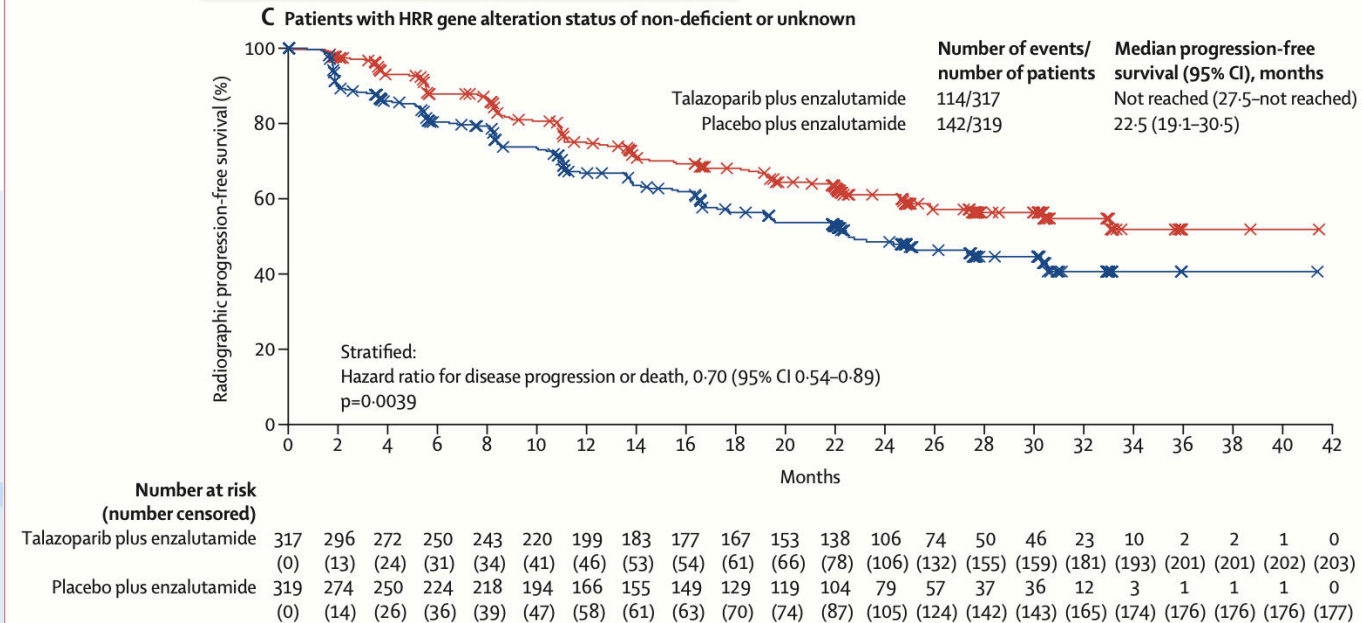
Talazoparib + Enzalutamide

HRR Deficient



rPFS by HRR Status

HRR Non-deficient or unk



American
Urological
Association

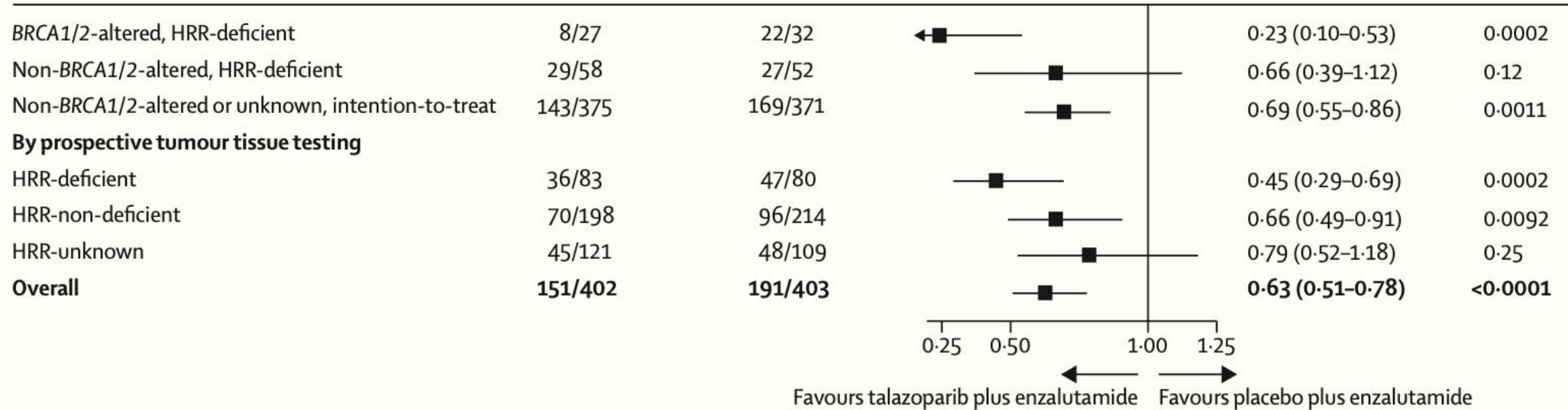
Education & Research, Inc.

Lancet 2023; 402: 291-303

TALAPRO-2

Talazoparib + Enzalutamide

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



Subgroup analysis by genetics



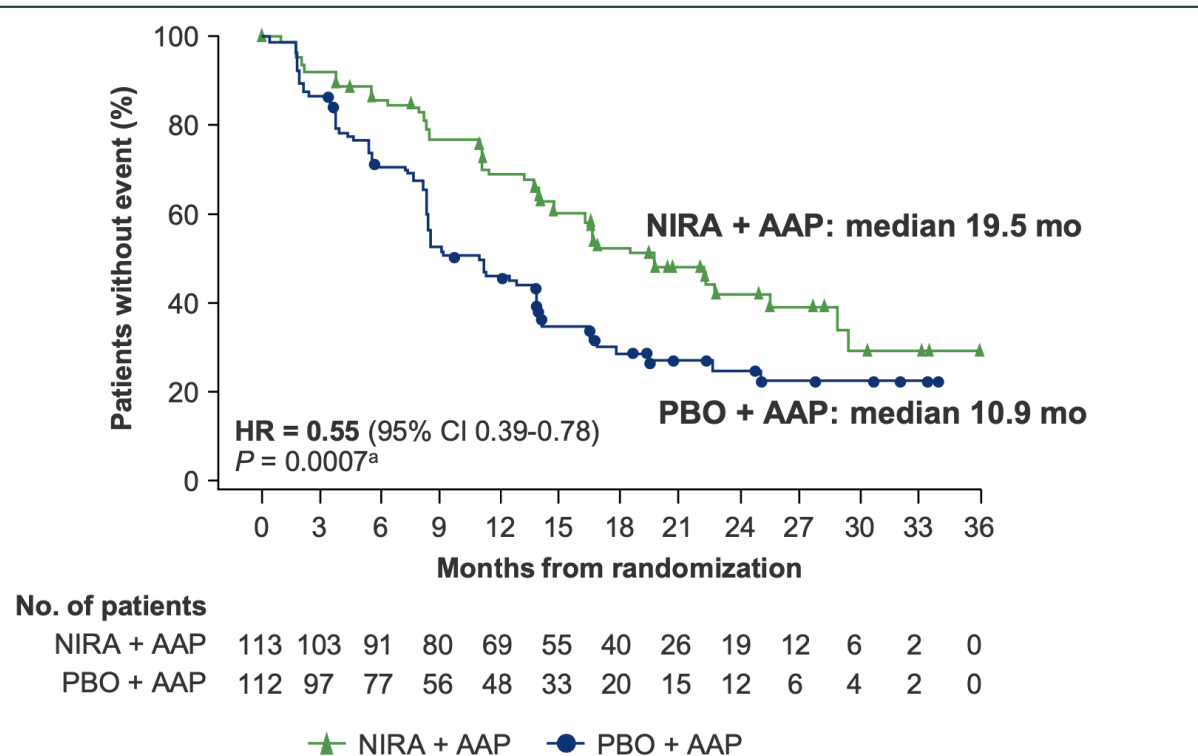
American
Urological
Association

Education & Research, Inc.

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★



- 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**

rPFS by central review in the BRCA subgroup



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



American
Urological
Association

Education & Research, Inc.



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

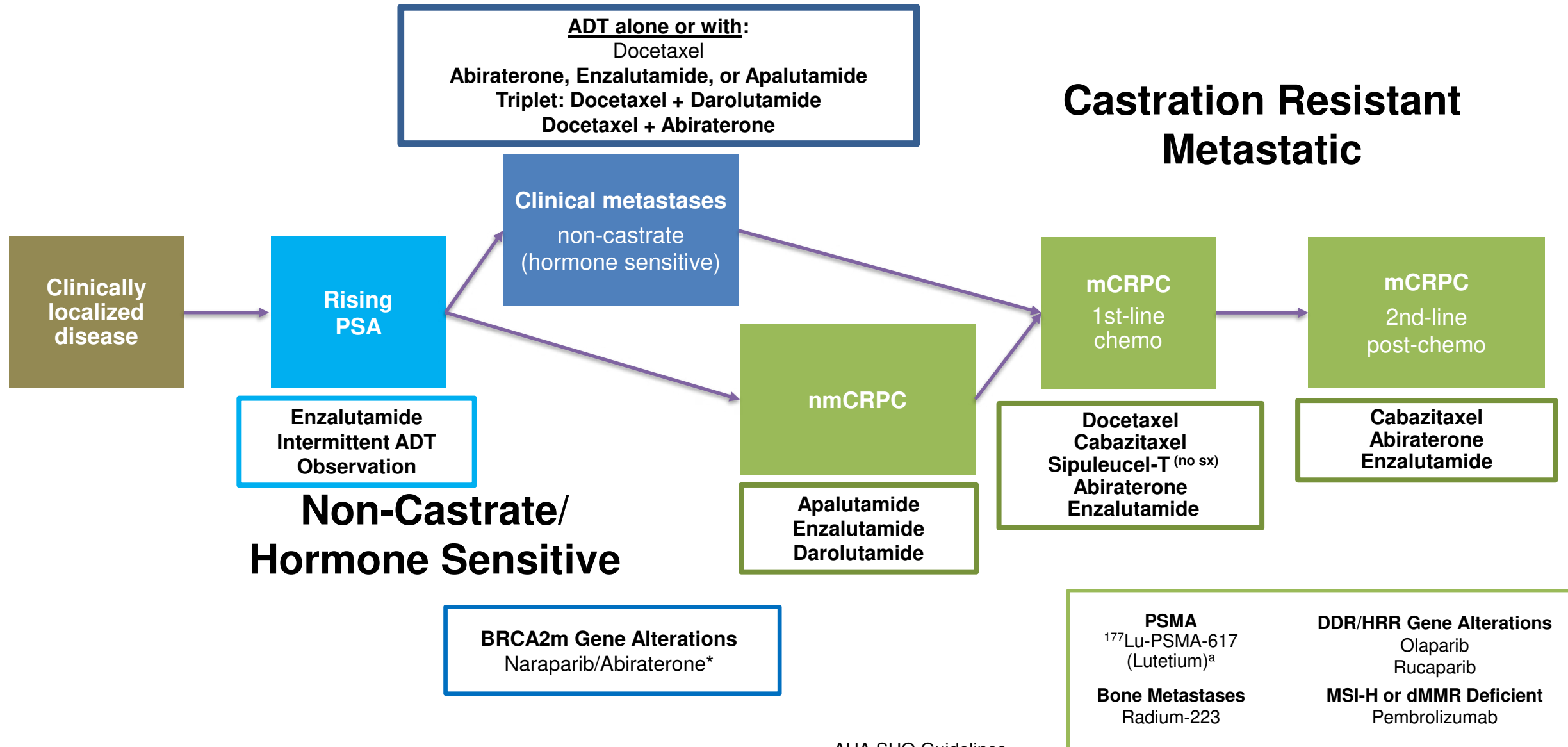
- Presents with bone pain and fatigue
- PSA 120 ng/ml
- GG5 prostate biopsy extensive
- Multiple pelvic bony metastases noted on imaging with enlarged pelvic and retroperitoneal lymph nodes.

Stage and Options?



F-18 DCFPyL PSMA PET

Current Prostate Cancer Therapeutic Landscape¹



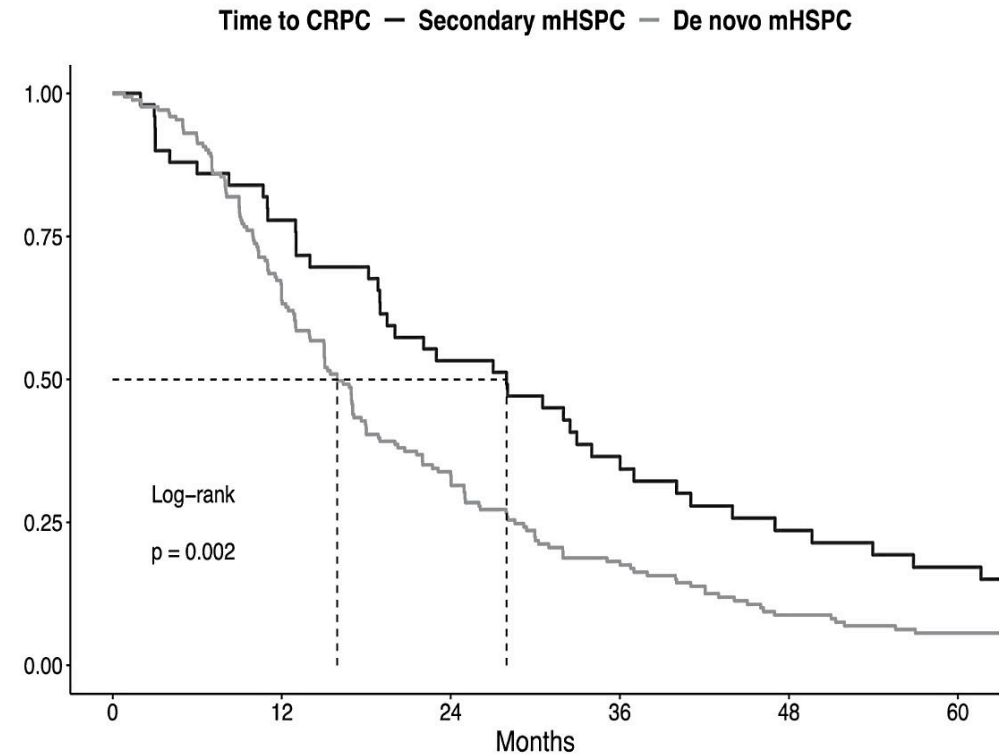
INITIAL EVALUATION METASTATIC HSPC

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**



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

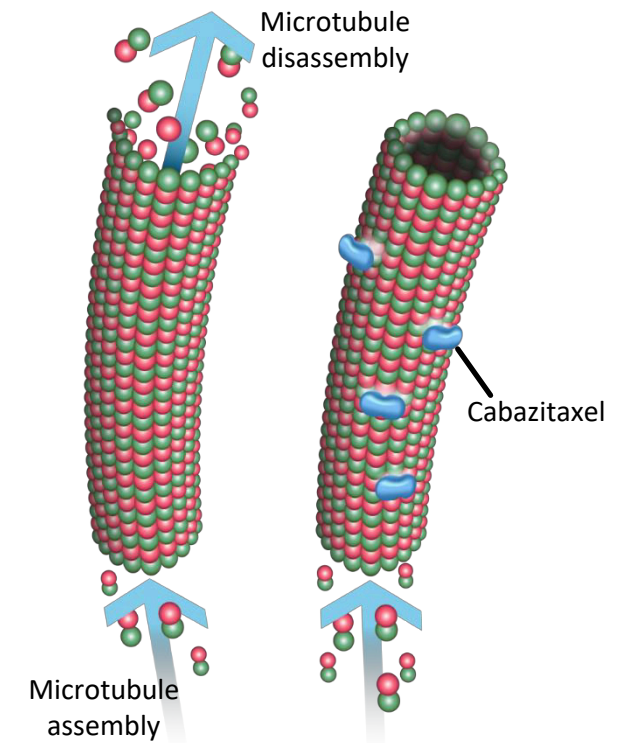


F-18 DCFPyL PSMA PET

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)

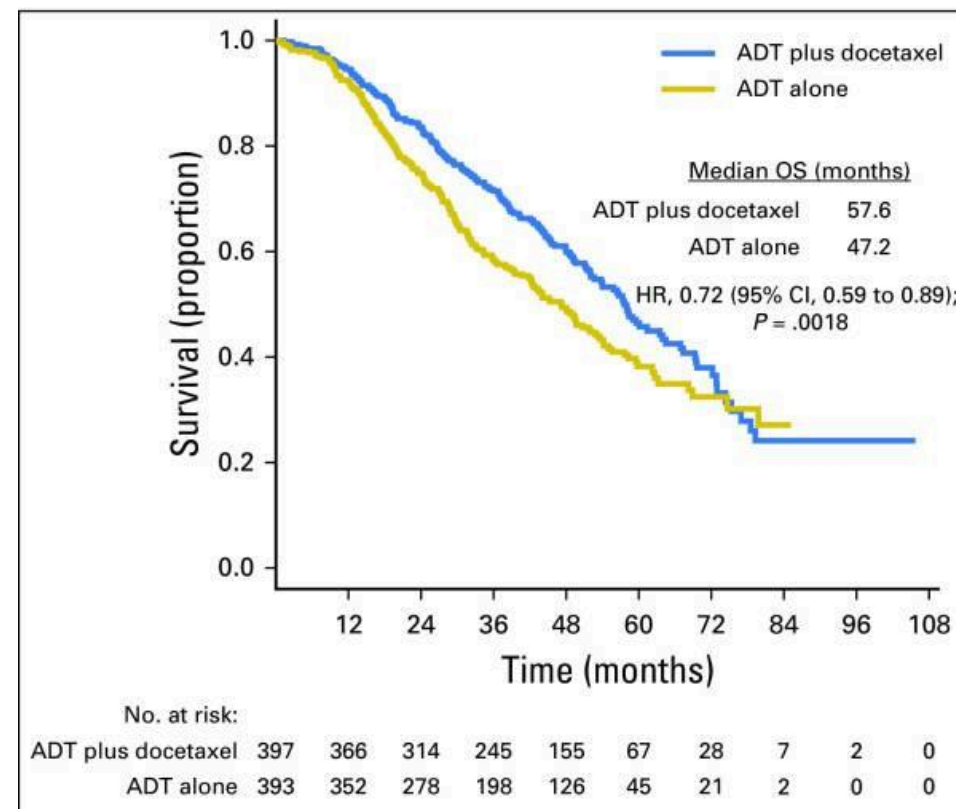


Cabazitaxel SPC, 2014.

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 phase III E3805 CHAARTED trial. J Clin Oncol 2018; 36:1080.

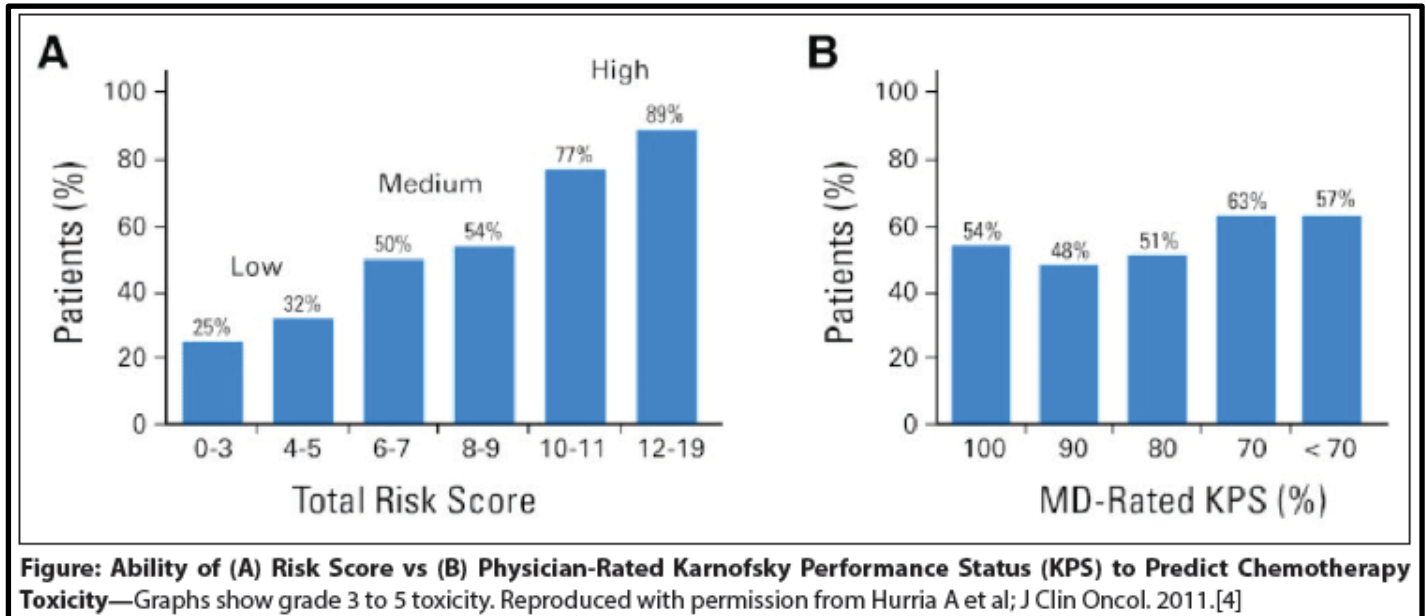
Comorbidities of Concern with Docetaxel

- 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



Results From Phase III Trials of ADT + Docetaxel or ARI

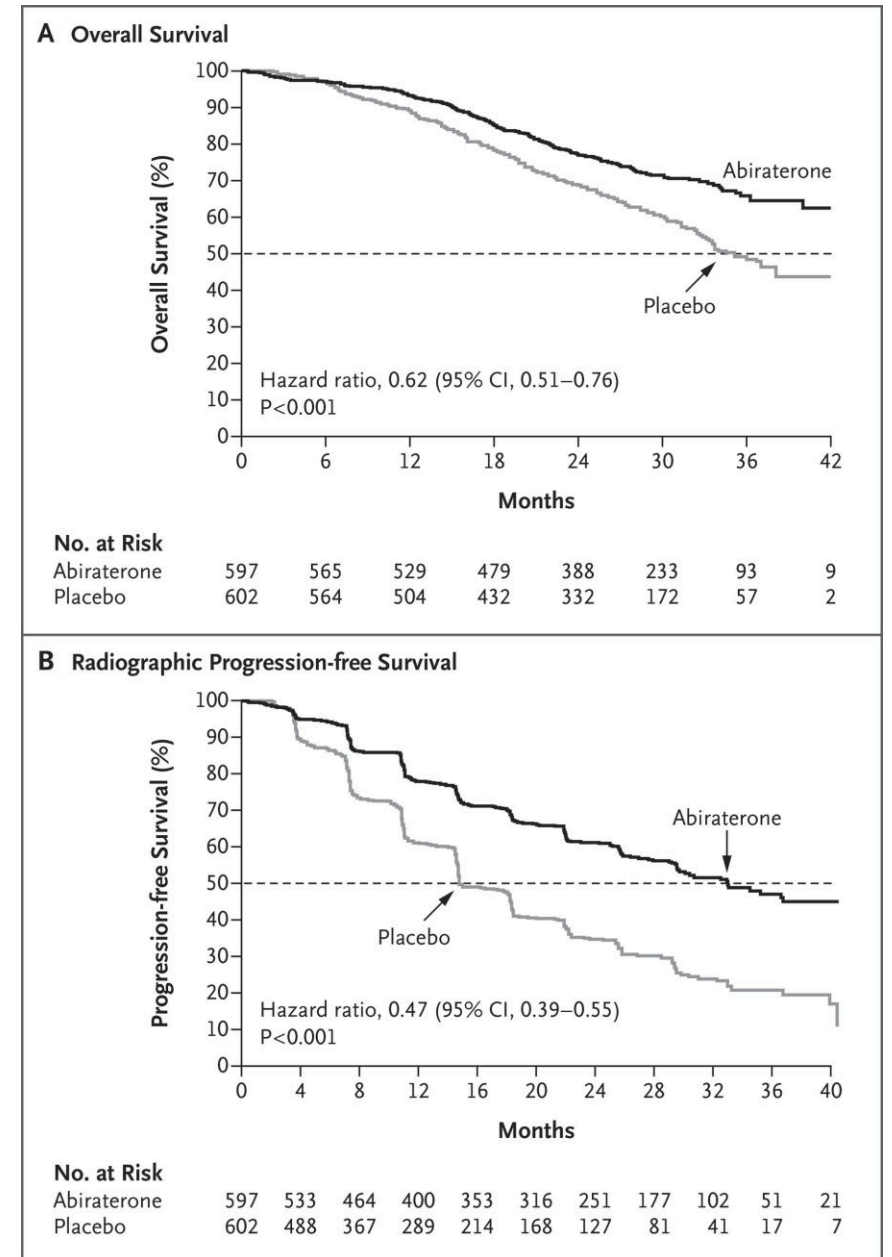
Trial	Regimens of Interest	n	Primary Endpoint(s)	Median OS	OS HR (95% CI)	<i>P</i> Value
CHAARTED ¹	ADT alone	393	OS	47.2 mo	0.72 (0.59-0.89)	<.0018
	ADT + docetaxel	397		57.6 mo		
STAMPEDE ²	ADT alone	724	OS	57.1 mo	0.81 (0.69-0.95)	.009
	ADT + docetaxel	362		63.1 mo		
STAMPEDE ³	ADT alone	957	OS	NE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

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.

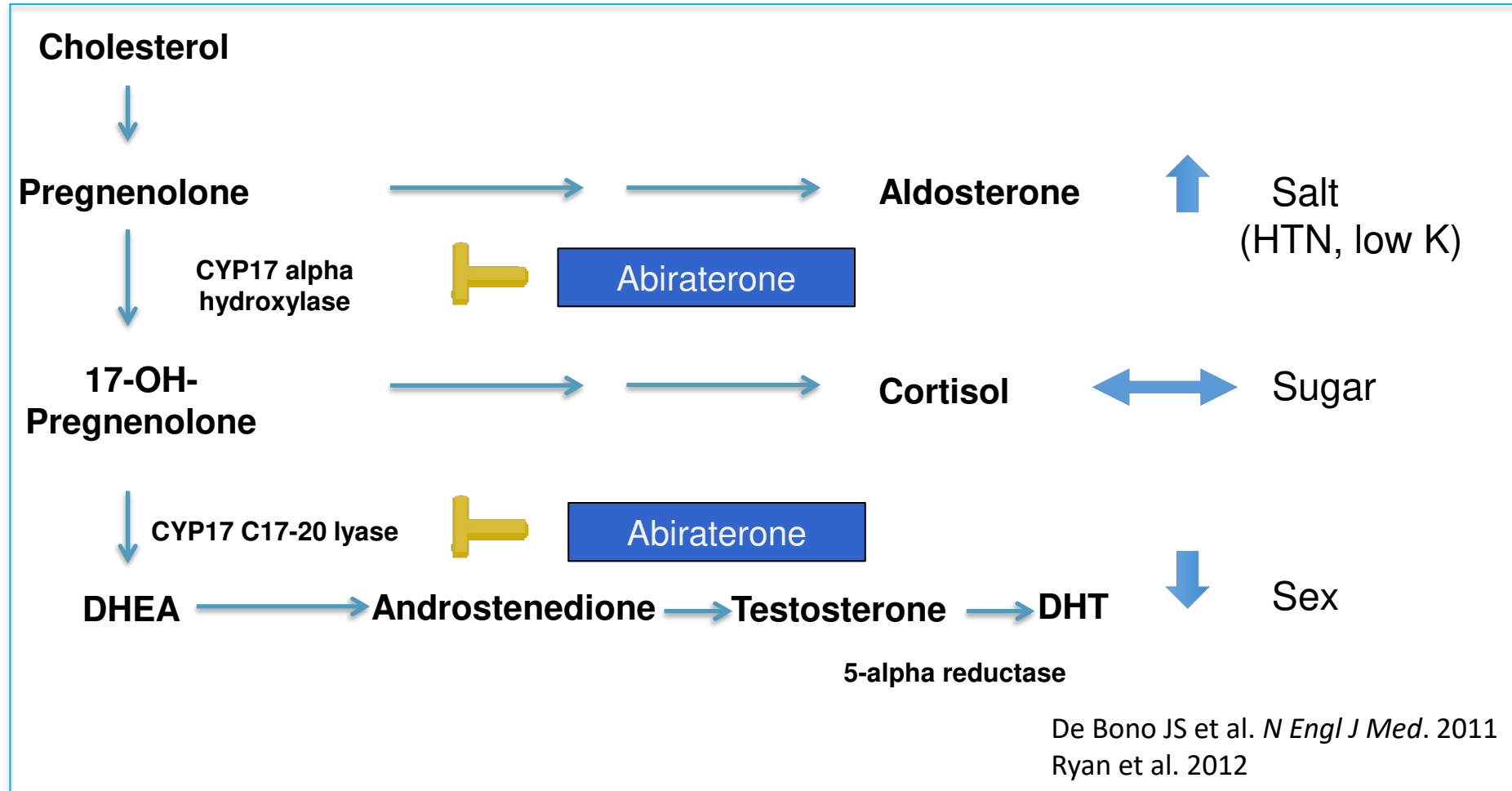
ABIRATERONE ACETATE ± ADT in mHSPC

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



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)

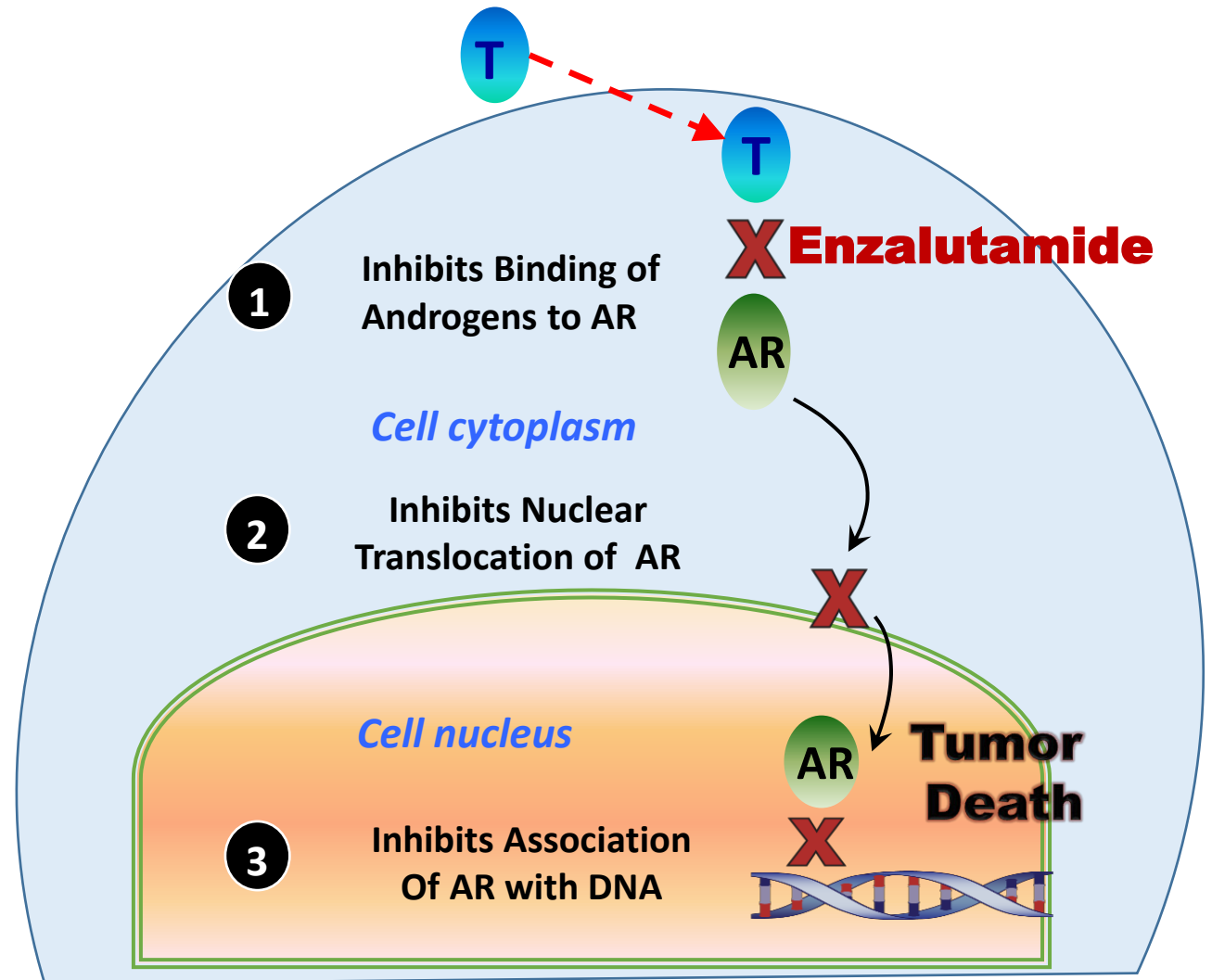
Trial	Regimens of Interest	n	Primary Endpoint(s)	Median OS	OS HR (95% CI)	P Value
CHAARTED ¹	ADT alone ADT + docetaxel	393 397	OS	47.2 mo 57.6 mo	0.72 (0.59-0.89)	<.0018
STAMPEDE ²	ADT alone ADT + docetaxel	724 362	OS	57.1 mo 63.1 mo	0.81 (0.69-0.95)	.009
STAMPEDE ³	ADT alone ADT + abiraterone	957 960	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



Enzalutamide and Androgen Receptor Signaling Inhibitors

- Which patients?
 - FDA approved for men with mHSPC
 - mCRPC *before* and *after* chemotherapy. *MO 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 use of docetaxel
† Stratified by planned use of docetaxel ‡ Stratified by prior use of docetaxel

5-year absolute effects of ARPIs, by age group				
		PFS	OS	PCSS*
Younger age groups (<75)	Abiraterone trial data	~25%	~16%	~17%
	Amide (± abi) trial data	~27%	~18%	?
Oldest age group (75+)	Abiraterone trial data	~8%	~0%	~9%
	Amide (± abi) trial data	~27%	~19%	?

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

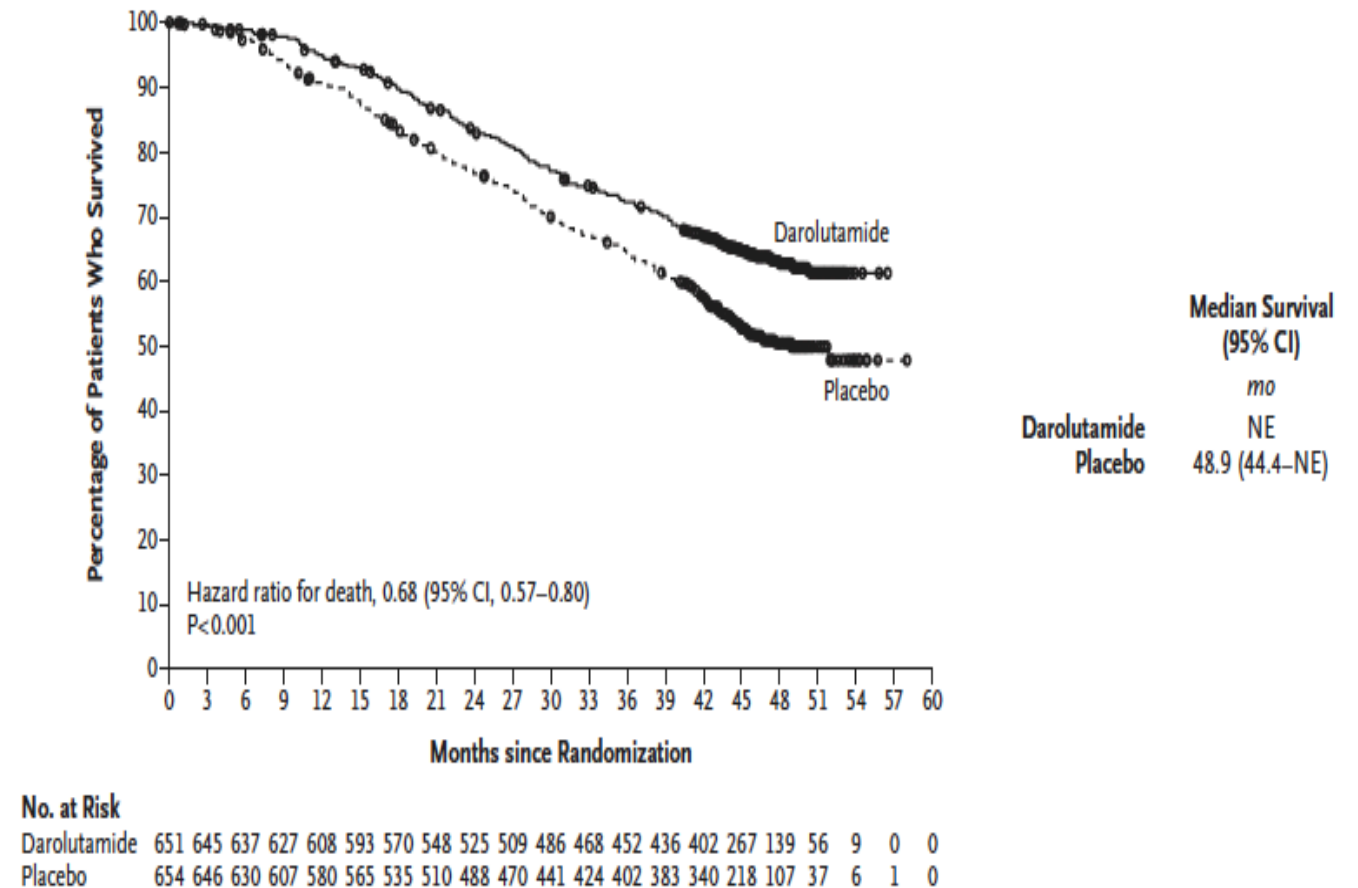


F-18 DCFPyL PSMA PET

What About Triplet Therapy for mHSPC?

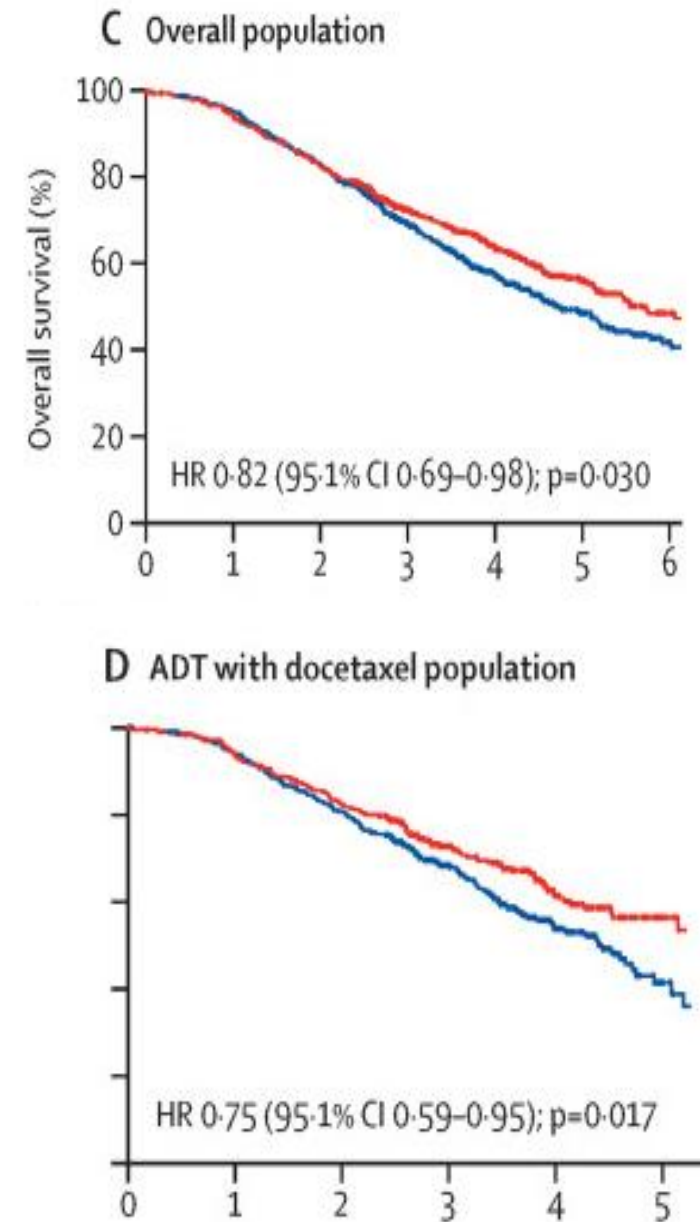
ADT/Docetaxel ± Darolutamide (ARASENS)

- 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



‘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



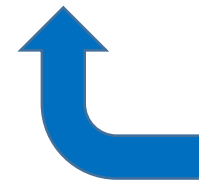
Choosing Between Docetaxel, an AR Pathway inhibitor or triplet therapy in mHSPC

- **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:

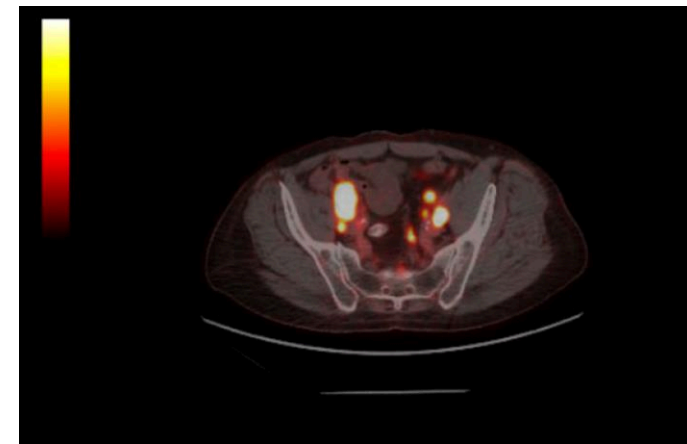
Docetaxel + Darolutamide

Docetaxel + Abiraterone

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

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

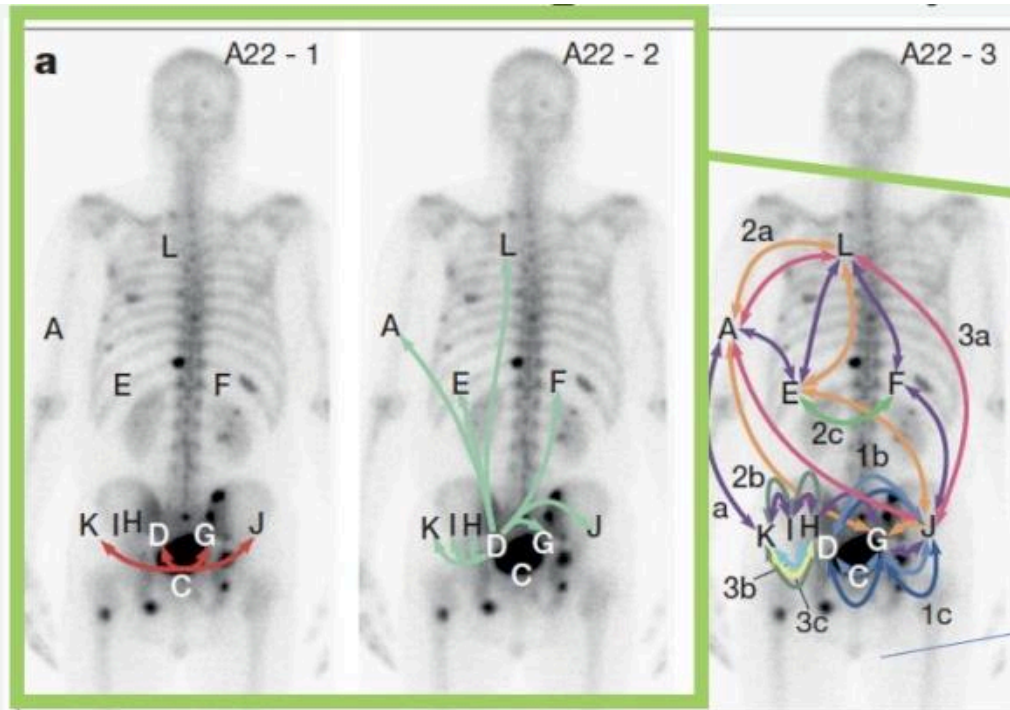
- Presents with urinary obstruction
- PSA 35 and GG5 tumor right (T2b)
- Large pelvic lymph nodes and a metastasis to humerus (N1 M1b)



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



A - L. humerus BM
D - Sem. vesicle
C - Prostate
E - L. adrenal

F - R. adrenal
G - Bladder
H - Pelvic LN
I - L. pelvic LN

J - R. pelvic LN
K - L. pelvic LN
L - L. media. LN

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

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

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

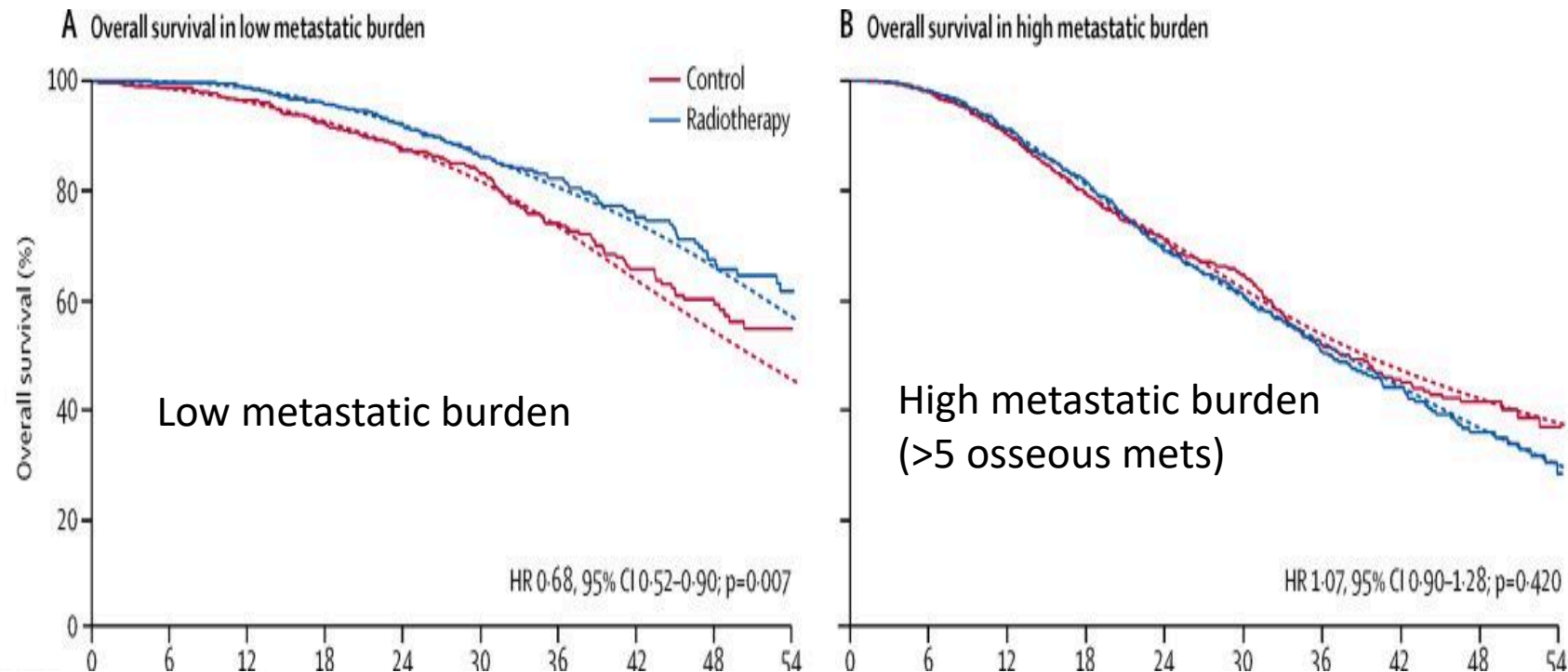
What is the existing evidence for primary local therapy in low-volume mHSPC?

- STAMPEDE Arm H
 - PEACE-1



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

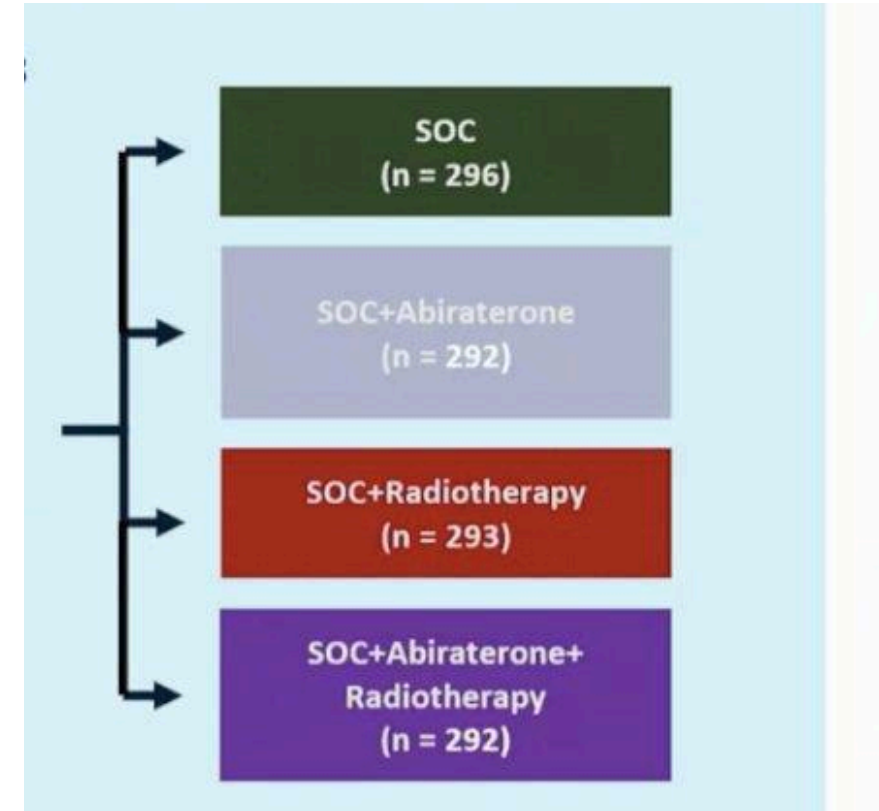
16. In selected mHSPC patients, clinicians may offer primary radiotherapy to the prostate in combination with ADT with or without an ARSI. (Conditional Recommendation; Evidence Level: Grade C)



Parker CC et 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 $\pm$ 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 $\pm$ abi ($p=0.11$)
- Reduction in serious GU events with XRT
- Conclusion: Be selective in offering treatment intensification

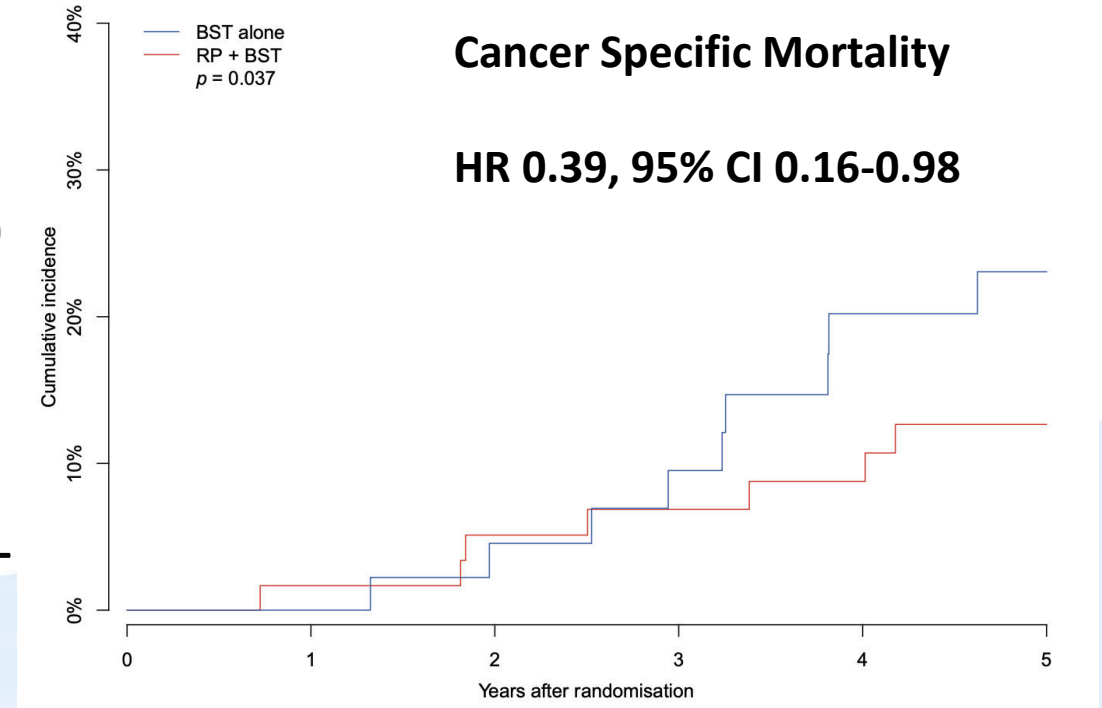


TRIALS ASSESS ROLE OF PROSTATE SURGERY OR RADIATION IN OLIGOMETASTATIC PC

	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



American
Urological
Association

Education & Research, Inc.



Society of Urologic Oncology, Inc.

Groefen, Eur Urology 2025

Case #2 Options: 52yo with N1 M1b

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



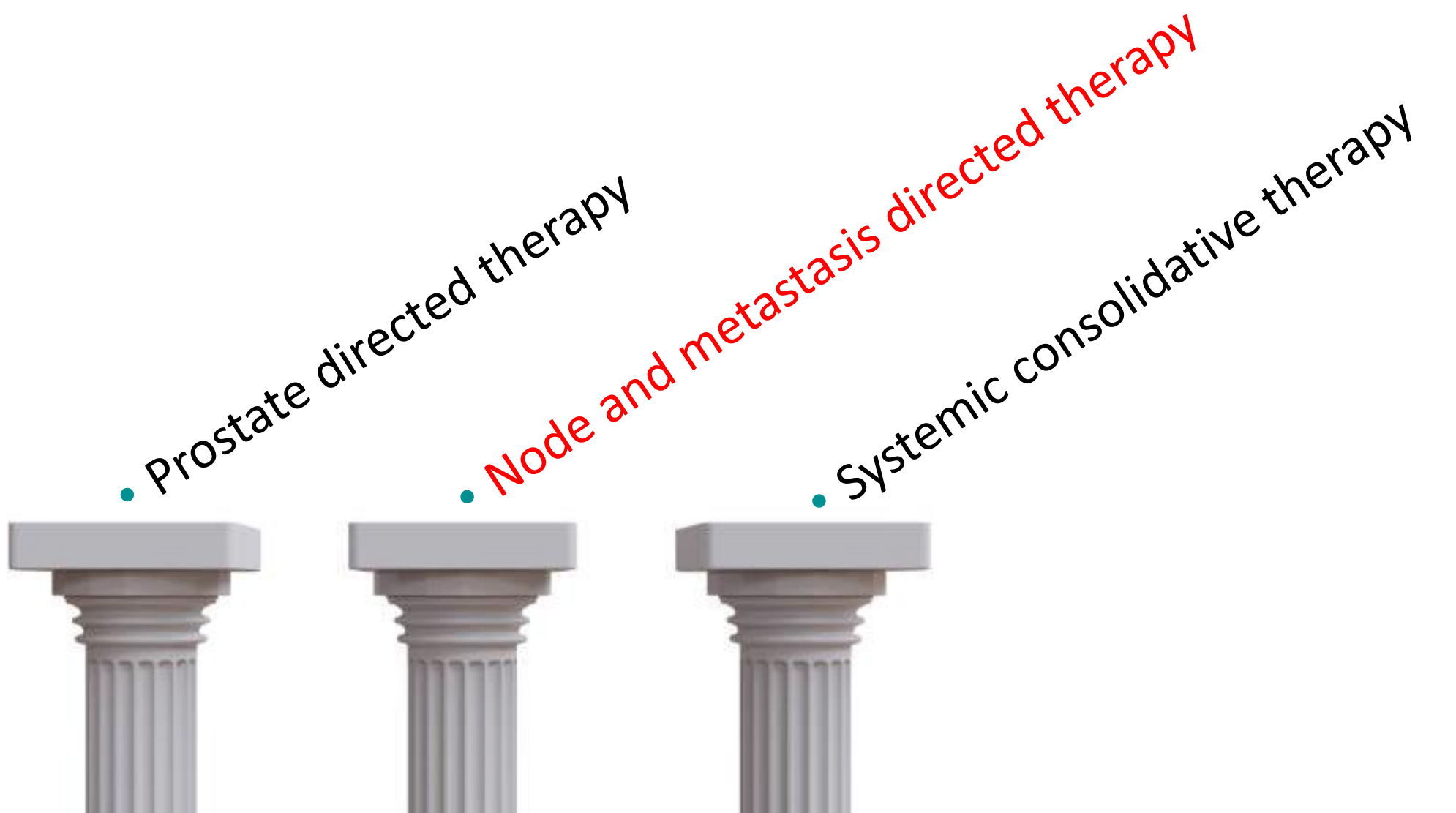
American
Urological
Association

Education & Research, Inc.



Society of Urologic Oncology, Inc.

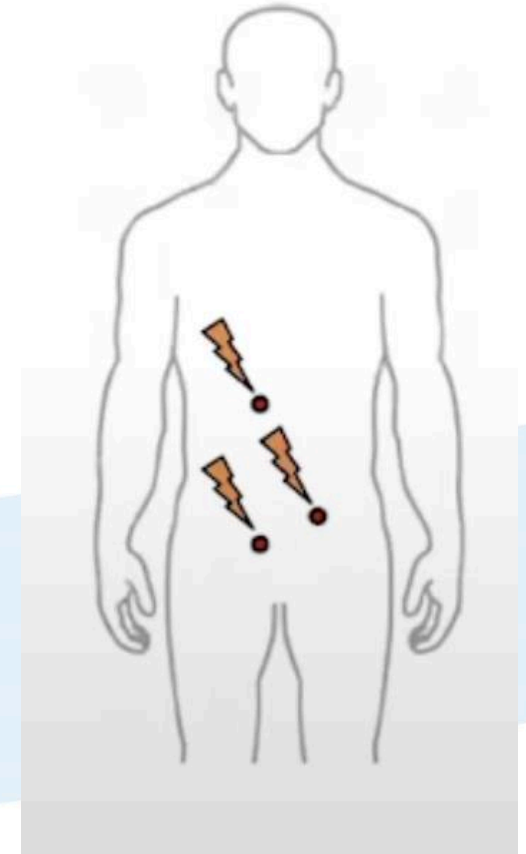
Oligometastatic Disease: 3 Treatment 'pillars'



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.



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).

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

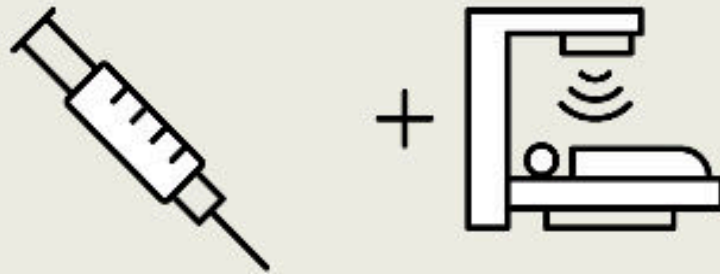
SETTINGS / LOCATIONS



3 Tertiary care centers in US

INTERVENTION

87 Participants randomized



44 Hormone therapy alone
Intermittent hormone therapy

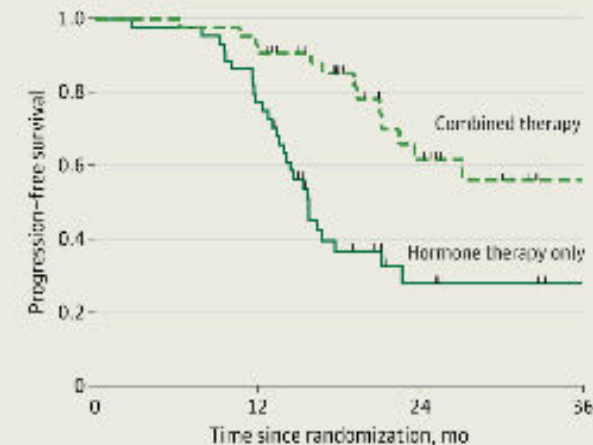
43 Combined therapy
Metastasis-directed therapy combined with intermittent hormone therapy

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

© AMA

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 $\pm$ 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**



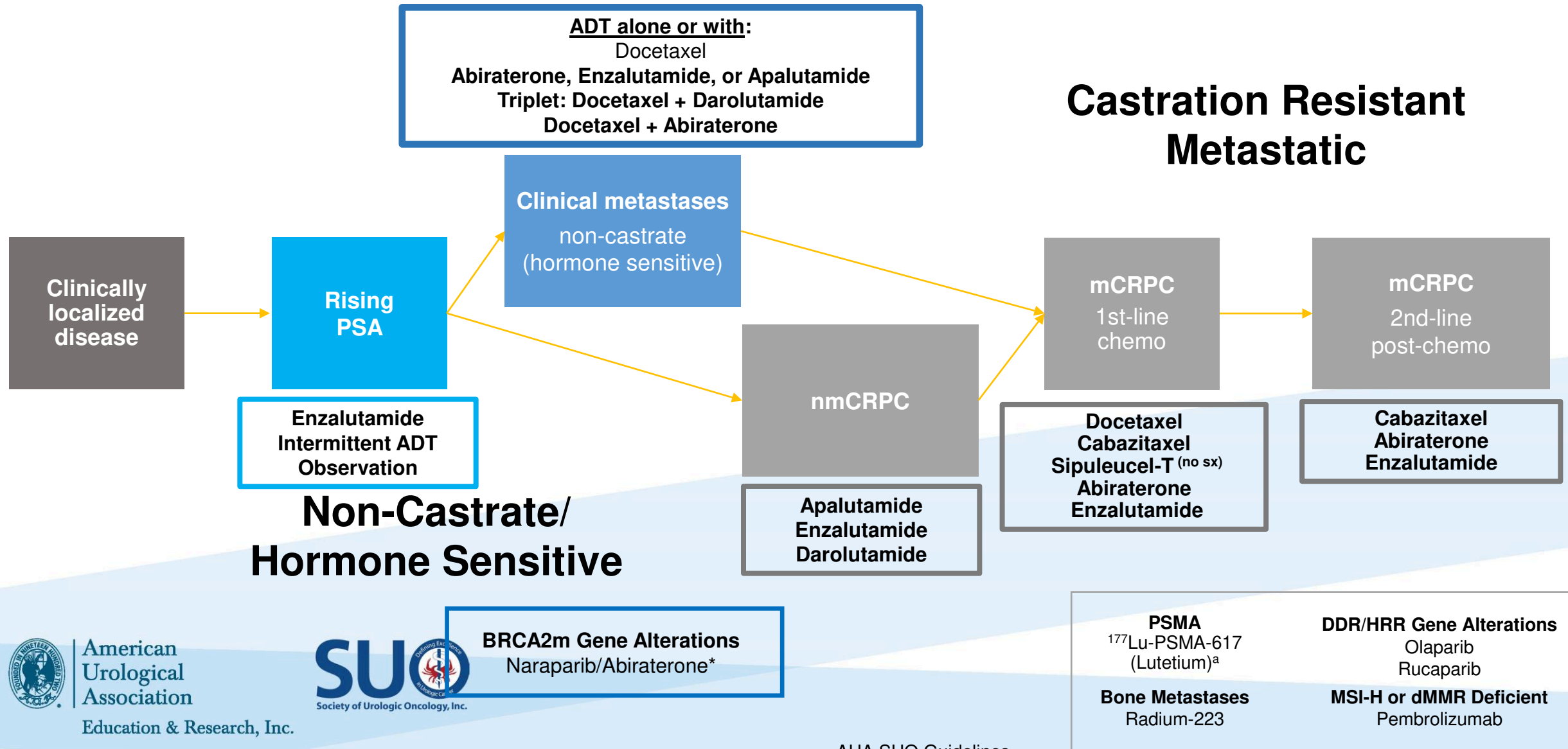
American
Urological
Association

Education & Research, Inc.



Society of Urologic Oncology, Inc.

Current Prostate Cancer Therapeutic Landscape¹



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



GRACIAS!
Alguna pregunta?



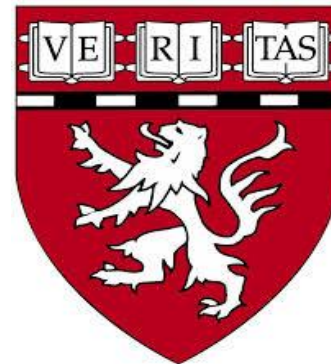
Department of Urology
UNIVERSITY OF WISCONSIN
SCHOOL OF MEDICINE AND PUBLIC HEALTH

BONE HEALTH AND RADIOPHARMACEUTICALS IN ADVANCED PROSTATE CANCER

Adam S. Kibel, MD

Elliott Carr Cutler Professor of Surgery
Harvard Medical School

Chair, Department of Urology
DiNovi Family Chair in Urology
Mass General Brigham



CLINICAL RELEVANCE OF BONE HEALTH IN CRPC

- The issue of bone loss
 - Elderly men have a decrease in bone mineral density
 - ADT is associated with loss of BMD
 - Increases risk of osteopenia, osteoporosis, fracture
 - Lose 2-4% of BMD in first year of ADT
 - Fracture risk with ADT increases 21-54%
- The issue of bone metastases
 - Bone = frequent site of PCa metastases

Smith MR et al, J Clin Oncol 2005

Shahinian VB et al, N Engl J Med 2005

Screening for Osteoporosis to Prevent Fractures

US Preventive Services Task Force Recommendation Statement

US Preventive Services Task Force

RECOMMENDATION The USPSTF recommends screening for osteoporosis to prevent osteoporotic fractures in women 65 years or older. (B recommendation) The USPSTF recommends screening for osteoporosis to prevent osteoporotic fractures in postmenopausal women younger than 65 years who are at increased risk for an osteoporotic fracture as estimated by clinical risk assessment. (B recommendation) The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening for osteoporosis to prevent osteoporotic fractures in men. (I statement)

JAMA 2025

THE ISSUE OF BONE LOSS

- Risk factors:
 - Age
 - Previous fracture
 - Parental history of hip fracture
 - Low body weight
 - Current cigarette smoking
 - Excessive alcohol consumption
- Risk factors of potential relevance to PCa patients:
 - GnRH suppression of gonadal function
 - Glucocorticoids
 - Radiation therapy
 - Other medications: Proton Pump Inhibitors, etc.

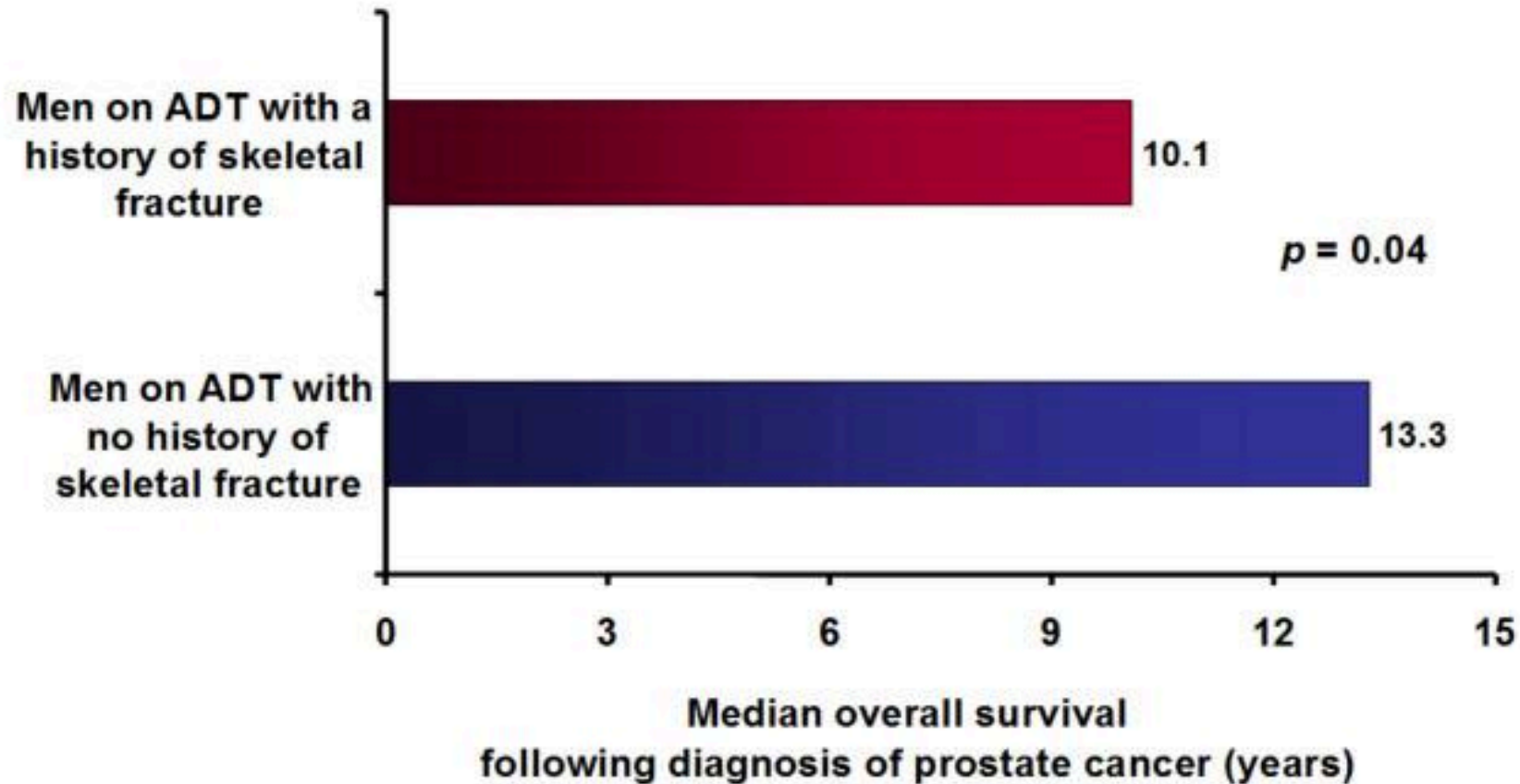
MULTIVARIABLE ANALYSIS OF FRACTURE RISK IN MEN WITH PCa ON ADT: DATA FROM SEER-MEDICARE

Table 3. Risk of Fracture Associated with Androgen-Deprivation Therapy.*

Variable	Any Fracture† RR (95% CI)	Fracture Resulting in Hospitalization† RR (95% CI)
Androgen-deprivation therapy		
None	1.00	1.00
Gonadotropin-releasing hormone agonist‡		
1–4 doses	1.07 (0.98–1.16)	0.98 (0.82–1.17)
5–8 doses	1.22 (1.11–1.35)	1.51 (1.26–1.80)
≥9 doses	1.45 (1.36–1.56)	1.66 (1.47–1.87)
Orchiectomy	1.54 (1.42–1.68)	1.70 (1.48–1.96)
Age (in 5-yr categories)	1.21 (1.19–1.24)	1.45 (1.40–1.50)

Shahinian VB et al, N Engl J Med 2005

OVERALL SURVIVAL AND FRACTURE IN MEN WITH PCa ON ADT



Oefelein MG et al, J Urol 2002

NCCN Guidelines

Table 1: Risk Assessment and Monitoring

Clinical Scenario	Recommendation
Baseline at ADT initiation	DEXA recommended for most patients. In select individuals at low probability of fracture based on FRAX risk assessment tool, DEXA can be omitted
On ADT	DEXA every 1–2 years, dependent on FRAX risk assessment tool
On antiresorptive therapy	DEXA at 1 year

Similar Recommendations:

1. American Urologic Association (AUA)
2. European Society for Radiotherapy and Oncology
3. European Association of Urology (EAU)
4. International Society of Geriatric Oncology

NCCN Prostate Cancer, 2025

FRAX

- Algorithm released by WHO
- On-line calculator for 10-year fracture risk based on clinical parameters (i.e. age, BMI, etc)
- Treatment recommended if:
 - 10-yr probability of hip fracture $\geq 3\%$, or
 - 10-year probability of major osteoporosis-related fracture $\geq 20\%$
 - <https://frax.shef.ac.uk/FRAX/>.

APPROACH TO BONE-LOSS RISK ASSESSMENT FOR MEN ON ADT

- Baseline tests:
 - Bone density scan (DEXA: dual-energy x-ray absorptiometry)
 - Osteopenia: T-score -1.0 to -2.5
 - Osteoporosis: T-score $\leq$ -2.5
 - Repeat Q 1-2 years
 - Blood tests
 - Calcium
 - Creatinine
 - 25-(OH) vitamin D
- Recommend: smoking cessation, ETOH moderation, weight-bearing exercise

VITAMIN D AND CALCIUM

- No specific dosage recommendations provided by AUA Guidelines
- The Bone Health and Osteoporosis Foundation guidelines:
 - Calcium 1000 mg daily -50-70 years of age
 - Calcium 1200 mg daily - > 70 years of age
 - Vitamin D3 800-1000 IU daily

WHAT ABOUT CALCIUM?

- Ca also important to prevent BMD loss
- Conflicting data on Ca - fatal prostate cancer
- Particularly important to supplement when treating with zoledronic acid or denosumab (risk of hypocalcemia)
- Better absorption with divided doses
- Calcium citrate absorbs better than Calcium carbonate

Cookson MS et al, J Urol 2013

ROLE FOR BONE-MODIFYING AGENTS IN NON-mCRPC PATIENTS ON ADT TO PREVENT BONE LOSS

- Concept = increase bone mineral density, decrease fracture risk
- Agents:
 - Zoledronic acid (5 mg IV annually)
 - Alendronate (70 mg PO weekly)
 - Denosumab (60 mg SQ q 6 months)
 - Only treatment demonstrated to decrease fracture risk

Smith MR et al, N Engl J Med 2009

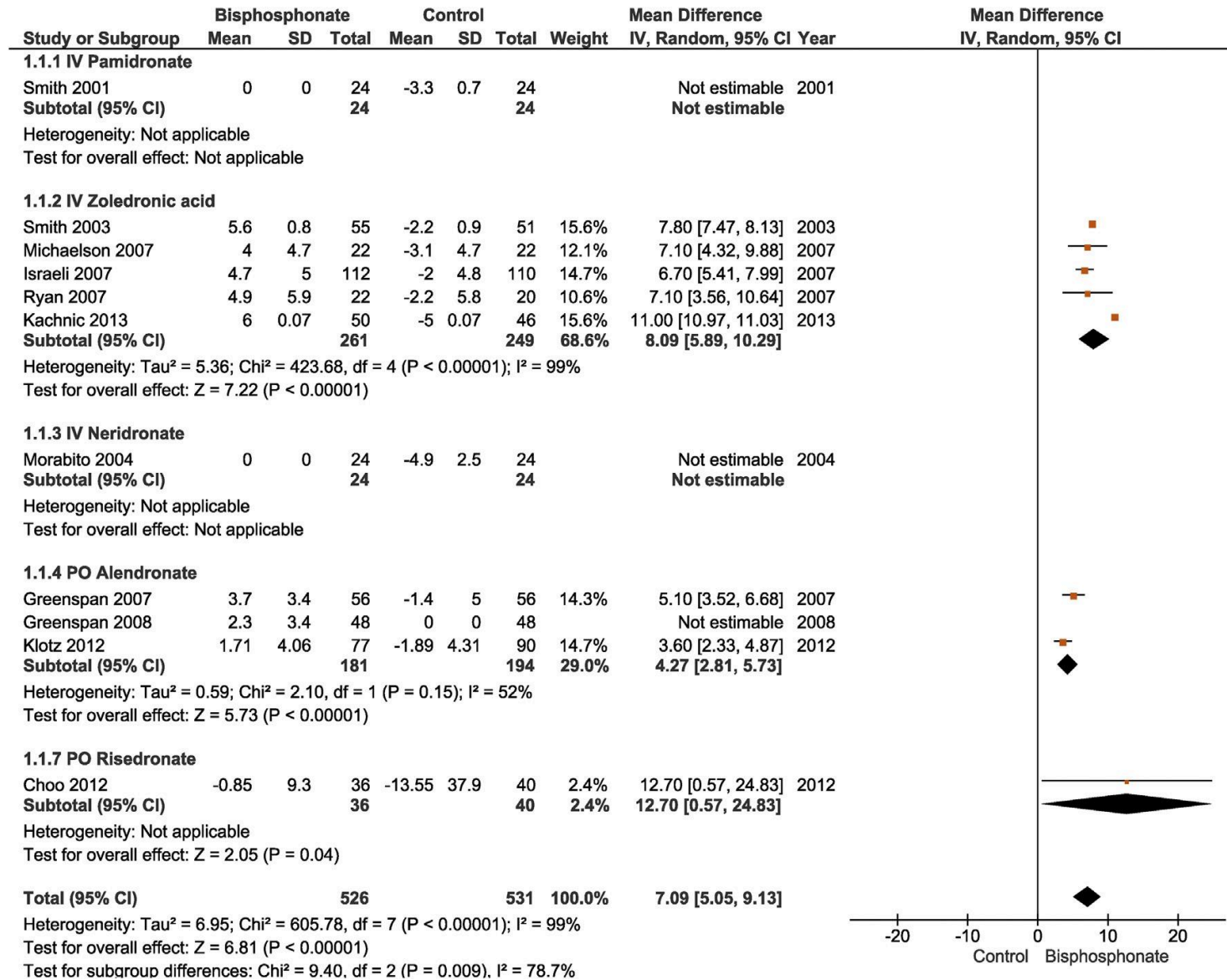
NCCN 2021 Prostate Cancer Guidelines

ZOLEDRONIC ACID

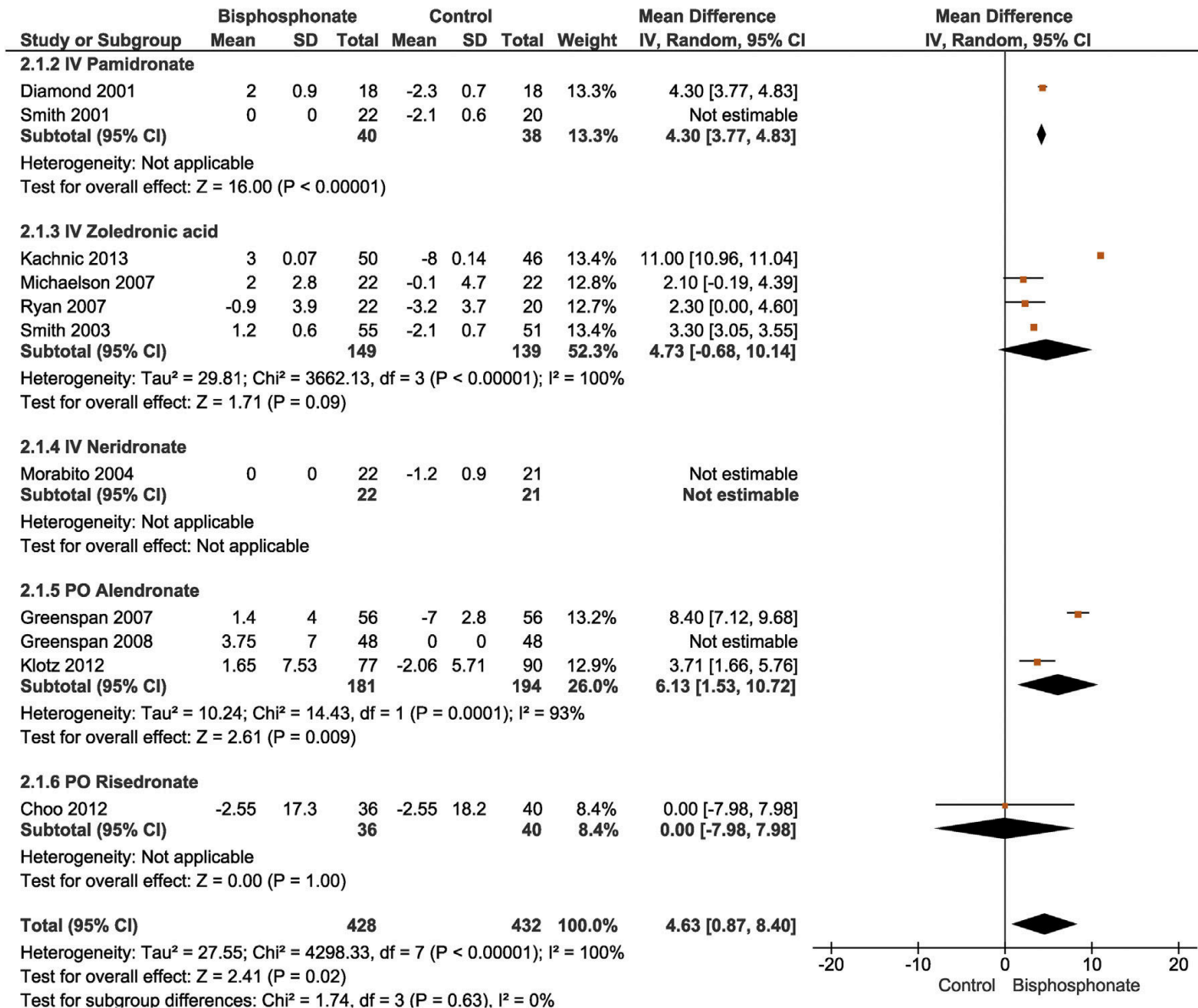
- Bisphosphonate
 - Inhibits bone resorption
- Given as IV infusion (4 mg q 4 wks)
- Zoledronic acid = only bisphosphonate to demonstrate benefit in mCRPC
 - Decrease SRE versus placebo
- Toxicity
 - Osteonecrosis of the jaw (dental exam first)
 - Hypocalcemia (Ca supplementation, monitor levels)
 - Nephrotoxicity (dose reduce if impaired renal fx)
 - Flu-like symptoms

Saad F et al, J Natl Cancer Inst 2004
Lowrance WT et al, J Urol 2021

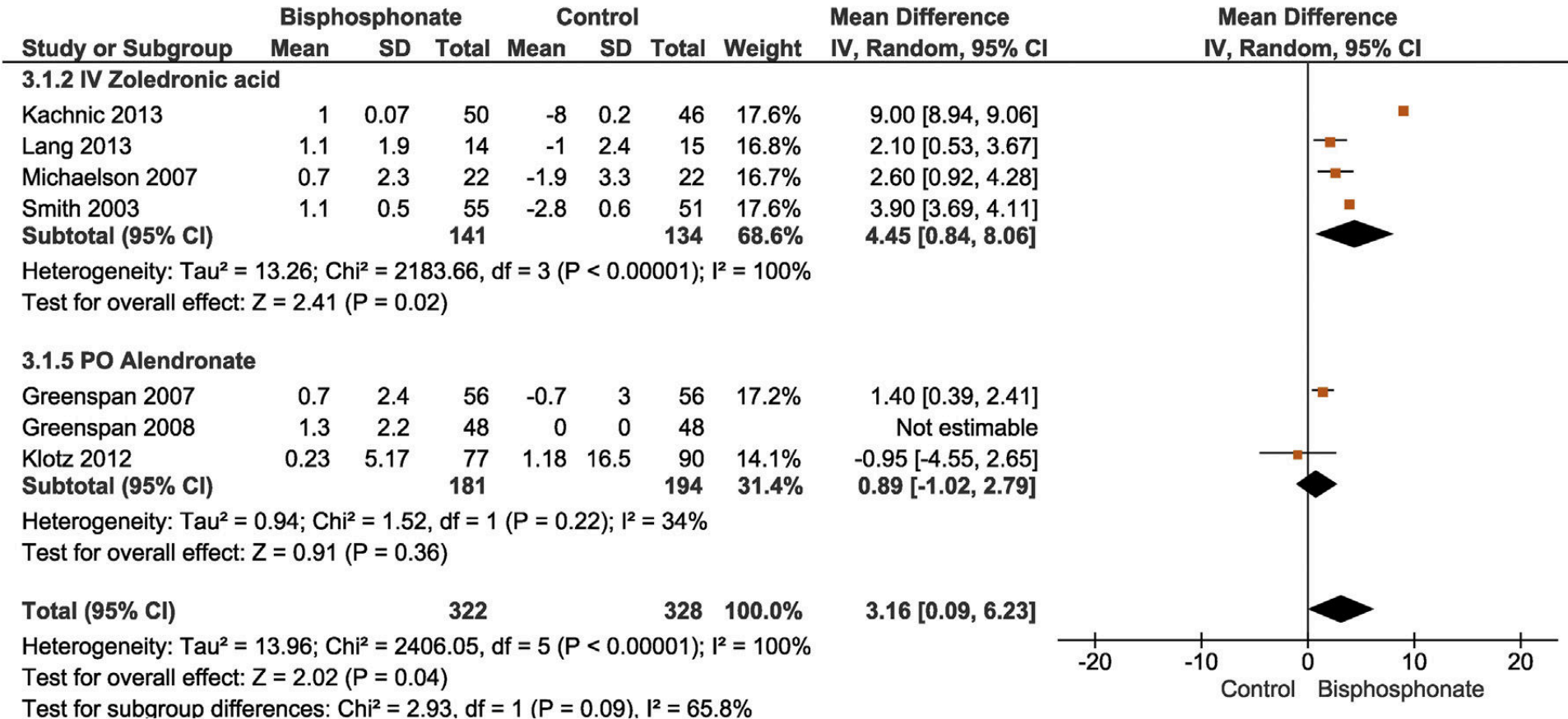
Lumbar BMD



Femoral Neck BMD



Hip BMD



ZOLEDRONIC ACID RENAL GUIDELINES FOR INITIATING THERAPY

- Calculate baseline creatinine clearance (CrCl) to determine starting dose
- For patients with CrCl >60 mL/min, administer 4 mg infused over no less than 15 minutes Q 3 to 4 weeks
- Ensure patients are adequately hydrated
- Slower infusion times have been shown to improve renal clearance and reduce the incidence of renal toxicity

Starting Dose Recommendations for Patients With Reduced Creatinine Clearance

Baseline Creatinine Clearance (mL/min)	Recommended Dose*
50-60	3.5 mg
40-49	3.3 mg
30-39	3.0 mg
<30	Not recommended

Calculate CrCl using the Cockcroft-Gault formula.

Zoledronic Acid Prescribing Information

DENOSUMAB

- Human monoclonal antibody – RANKL inhibitor
 - Receptor activator of nuclear factor κ B ligand
 - Inhibits osteoclast-mediated bone destruction
- Given as sub-q injection (120 mg Q 4 wks)
- Toxicity
 - Osteonecrosis of the jaw (dental exam first)
 - Hypocalcemia (Ca supplementation, monitor levels)

Lowrance WT et al, J Urol 2021
Cornford P et al, Eur Urol 2017

OSTEONECROSIS OF THE JAW (ONJ)



Clinical Features of Suspected ONJ

- Exposed bone in maxillofacial area that occurs in association with dental surgery or occurs spontaneously, with no evidence of healing*

Working Diagnosis of ONJ

- No evidence of healing after 6 weeks of appropriate evaluation and dental care
- No evidence of metastatic disease in the jaw or osteoradionecrosis

*Refer for appropriate dental evaluation and care as soon as possible

Weitzman R et al, Crit Rev Oncol Hematol 2007

RISK FACTORS FOR ONJ

- Cancer
- Radiation therapy
- Corticosteroids
- Poor dental hygiene
- Poor diet
- Dental work
- Trauma
- Ethanol or tobacco use
- Coagulopathy
- Chemotherapy
- Infection
- Bisphosphonates or denosumab therapy

MINIMIZING THE RISK OF ONJ

- Excellent oral hygiene is the best prophylaxis
- Limit alcohol and tobacco use
- Obtain a dental assessment prior to starting bone directed therapy
 - If possible, dental procedures (extensive) should be completed prior to starting IV bisphosphonate or denosumab
- Every 6 month dental visits are recommended
- Avoid extraction (increases risk of ONJ from ~1% up to 20%) and dental procedures once bone-targeted therapy is started
- Warn patients about ill-fitting dentures

IF ONJ DEVELOPS WHILE ON THERAPY...

- Weigh risk/benefit ratio, but usually hold bisphosphonate or denosumab until site has healed or stabilized
- Current treatment management of ONJ is empirical and management usually entails conservative approaches
 - Antibiotics
 - Oral rinses
 - Pain control
 - Limited debridement (only in hands of specialist in oral surgery)
- Cases refractory to conservative management may benefit from investigational therapies
 - Surgical treatment
 - Hyperbaric oxygen therapy

WIT Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: FOR a randomised, double-blind study

Karim Fizazi, Michael Carducci, Matthew Smith, Ronaldo Damião, Janet Brown, Lawrence Karsh, Piotr Milecki, Neal Shore, Michael Rader, Huei Wang, Qi Jiang, Sylvia Tadros, Roger Dansey, Carsten Goessl

- Phase 3 RCT in 1904 men with mCRPC

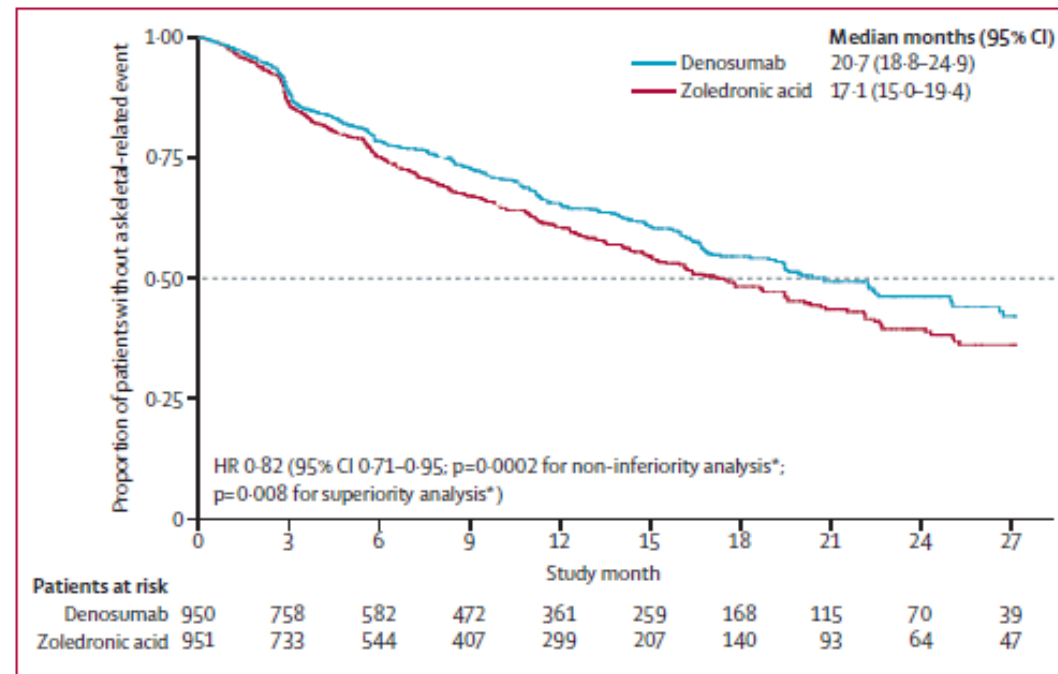


Figure 2: Kaplan-Meier estimates of time to first on-study skeletal-related event

Patients were assessed from baseline to the primary analysis cutoff date. HR=hazard ratio. *p values were adjusted for multiplicity.

- No difference in OS or time to dz progression

DENOSUMAB VERSUS ZOLEDRONIC ACID TRIAL RESULTS

- Hypocalcemia
 - Denosumab – 13%
 - Zoledronic acid – 6%
 - $p < 0.0001$
- Osteonecrosis of the jaw
 - Denosumab – 2%
 - Zoledronic acid – 1%
 - $p = 0.09$

Fizazi K et al, Lancet 2011

Special Note

- If giving denosumab and you stop (no treatment >9-12 months) **there is a rapid decline in BMD and return to original osteoporotic or high risk state.**
- Can “cap” the final dose with a dose of zoledronic acid, which does not leave the bone and can hold the BMD for longer.

Decrease Fractures and Mortality?

- 54,953 PCa in the SEER data base
- Started on ADT
 - DXA Screening Rates with one year
 - Fracture Rates
 - Bisphosphonate use
 - Survival

– Suarez-Almazor et al AMA Netw Open. 2022

Decrease Fractures and Mortality?

- 4362 men (7.9%) received DXA screening
- 9365 men (17.5%) developed fractures
- DXA screened men more likely put on bone modifying agents - (18.8% vs 1.8%; $P < 0.001$).
- DXA screening was associated with a 9.1% decrease in the risk of major fractures ($P=0.05$)
- 5-year OS was 78% in those without a fracture and 74% in those with a major fracture ($P<0.001$)

— Suarez-Almazor et al AMA Netw Open. 2022

Bone Health

Clinicians SHOULD

- Discuss the risk of osteoporosis associated with ADT and assess the risk of fragility fracture
- Recommend preventative treatment for fractures and skeletal-related events, including supplemental calcium, vitamin D, smoking cessation, and weight-bearing exercise, to patients on ADT
- Recommend preventative treatments with bisphosphonates or denosumab to patients at high fracture risk due to bone loss and recommend referral to physicians who have familiarity with the management of osteoporosis
- Prescribe a bone-protective agent (denosumab or zoledronic acid) for mCRPC patients with bony metastases to prevent skeletal-related events

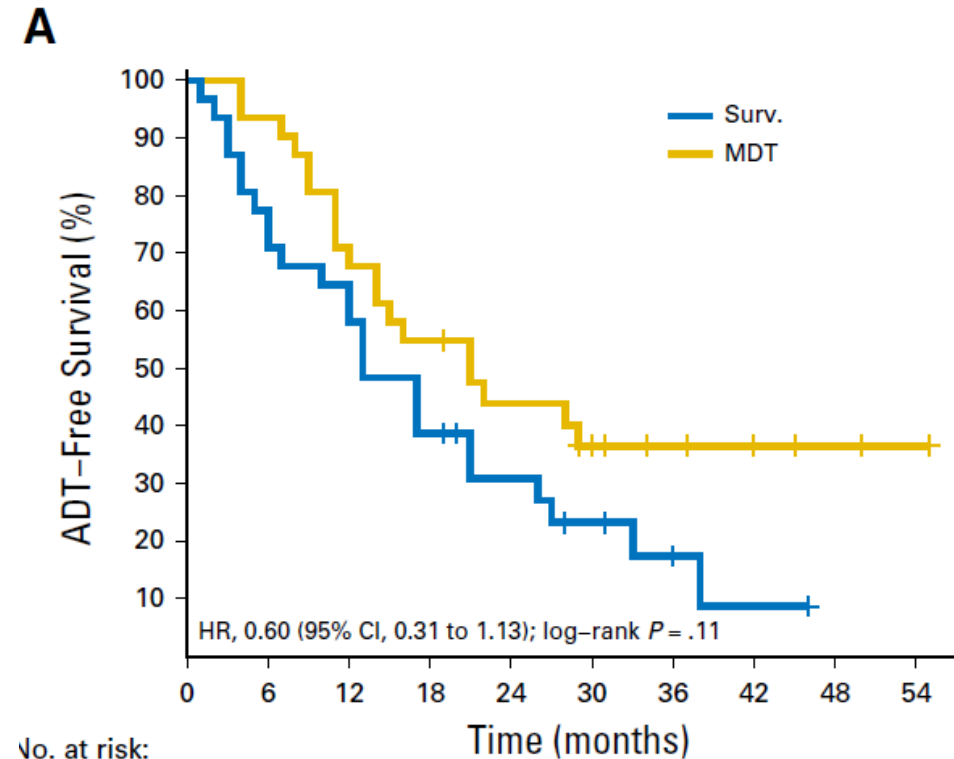
CONCLUSIONS

- Bone health issues = bone loss + metastases
- Patients on ADT should be encouraged calcium + Vitamin D supplementation
- Patients with bone mCRPC should be offered zoledronic acid or denosumab
- Beware hypocalcemia, osteonecrosis of jaw
- Patients on ADT should have baseline + ongoing assessment of risk of fracture
 - Consider bone-modifying agents pending FRAX

TARGETING THE BONE WITH RADIATION

SBRT - STOMP TRIAL

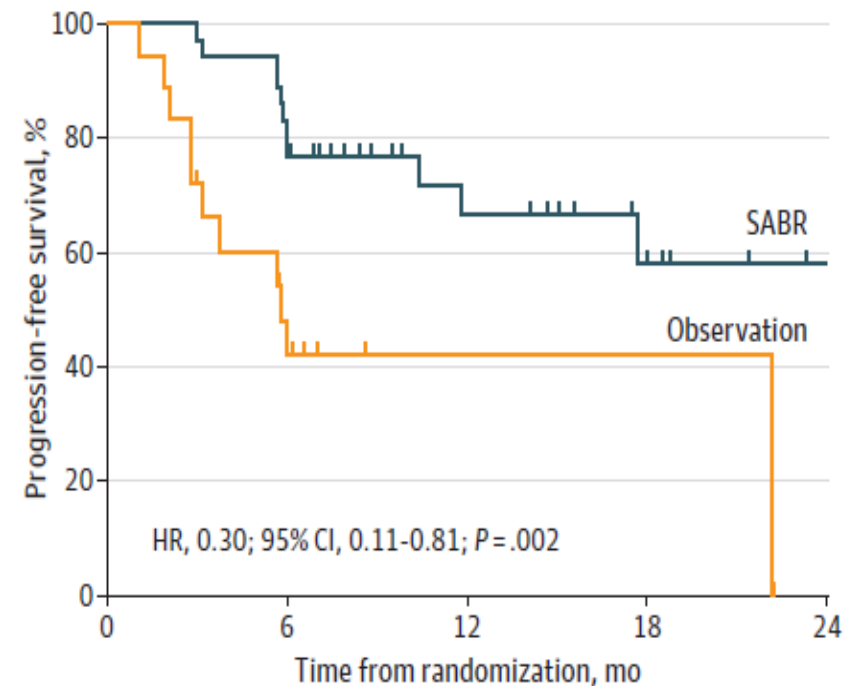
- 62 Patients with asymptomatic CRPC
- ≤ 3 extracranial mets on Choline PET
- Surveillance v. surgery or SBRT to all mets
- Endpoint was ADT free survival
- ADT indication –
 - symptomatic progression
 - progression to more than three metastases
 - local progression of baseline-detected metastases



ORIOLE TRIAL

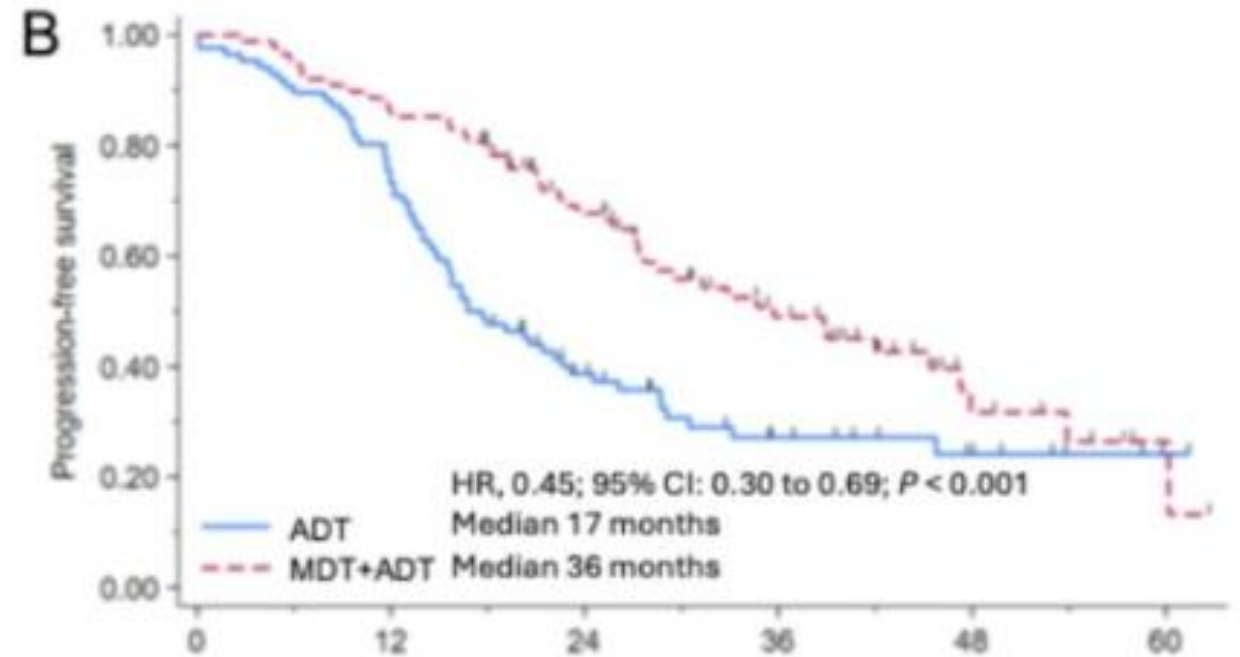
- 54 Patients with asymptomatic CSPC
- ≤ 3 Mets on Conv Image
- PSMA PET to assess if all lesions treated.
- Surveillance v. SBRT
- Progression Endpoint
 - PSA rise 2 ng/dL $\geq$ and 25% above nadir
 - radiologic progression
 - symptomatic progression
 - initiation of ADT for any reason
 - death.

A Composite PFS stratified by study arm



EXTEND TRIAL

- 87 Patients with asymptomatic CSPC
- ≤ 5 Mets on PET Image
ADT x 6 mo v.
SBRT + ADT x 6 mos
- Progression Endpoint
 - PSA rise 2 ng/dL $\geq$ and 25% above nadir
 - radiologic progression
 - symptomatic progression
 - death.

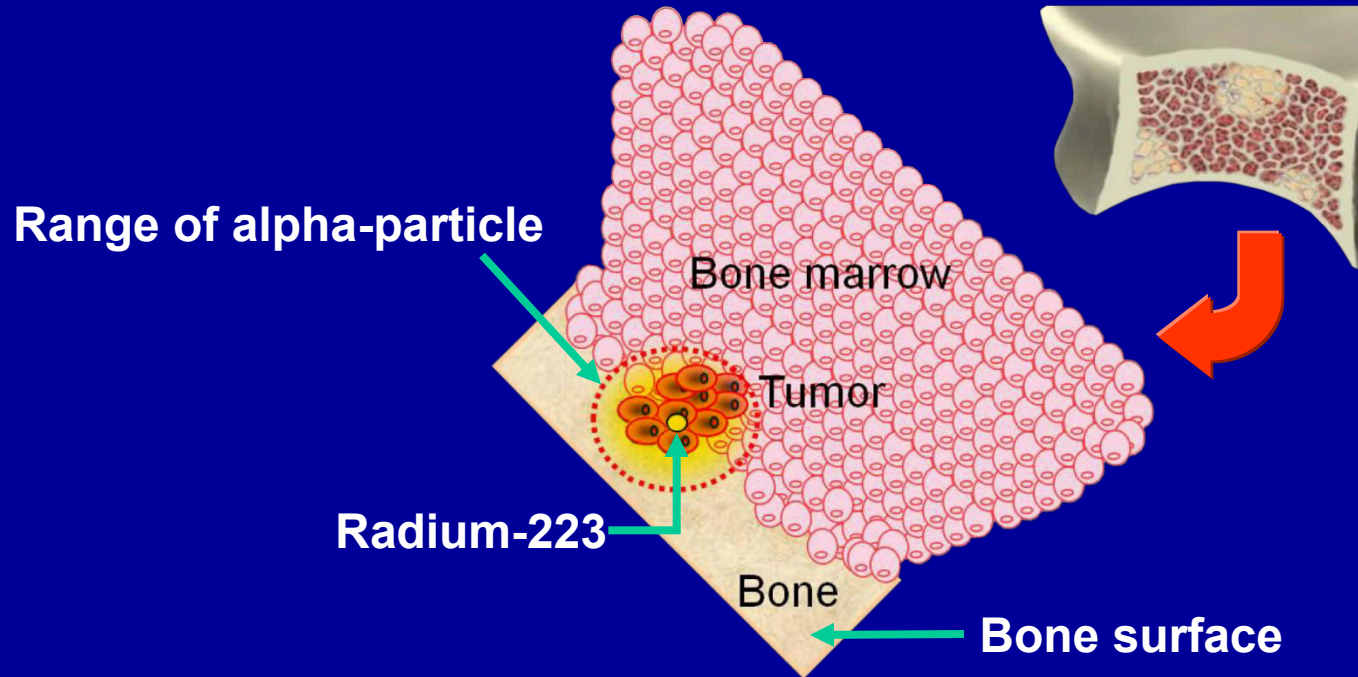


RADIOPHARMACEUTICALS IN ADVANCED PROSTATE CANCER

RADIUM-223

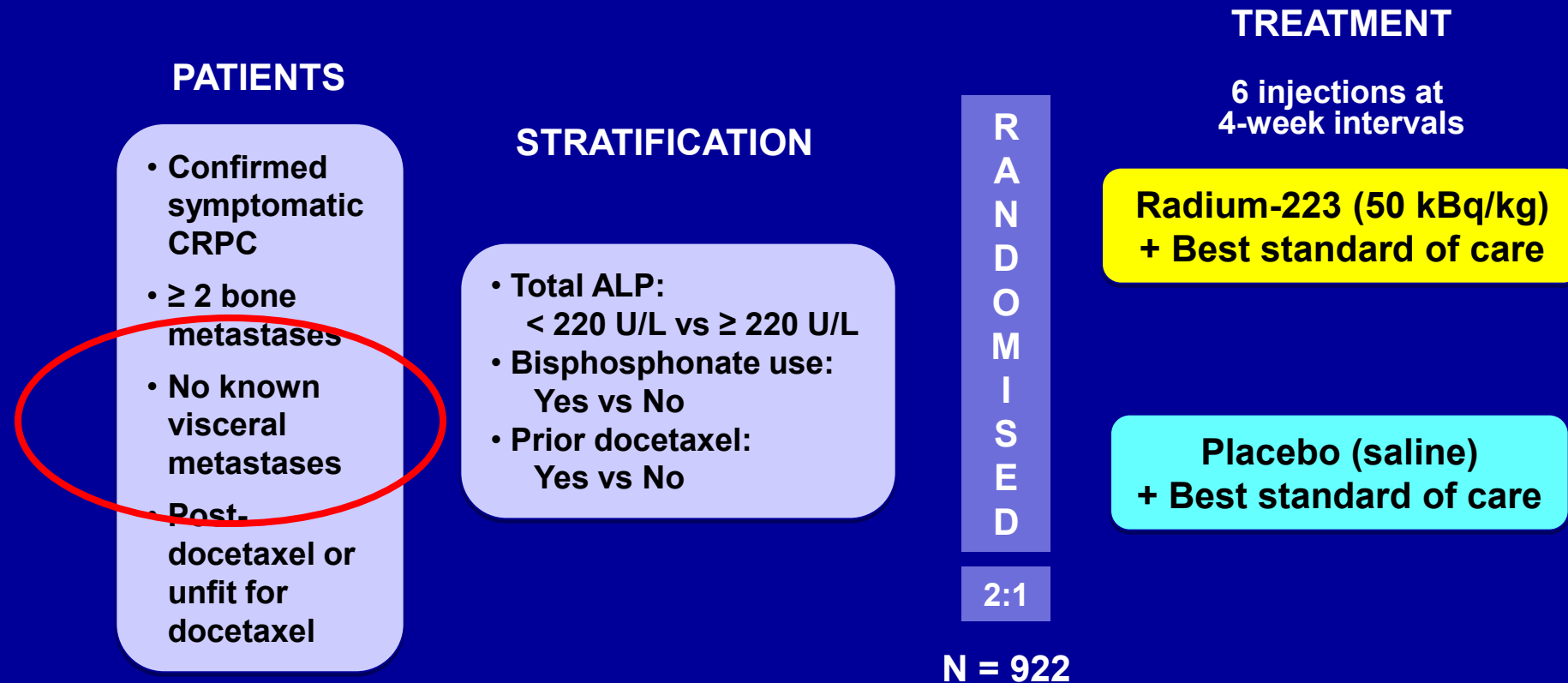
- Mimics calcium (chemically similar) → targets bone
 - Forms complexes with bone mineral hydroxyapatite at areas of increased bone turnover (i.e. metastases)
- α -emitting radiopharmaceutical
 - High energy, short wavelength
- Induces double-strand DNA breaks in cancer cells
- Short range of α -radiation
 - Minimal exposure to surrounding bone marrow and surrounding tissue (range = 100 micrometers (less than 10 cell diameters))
 - No contact restrictions during treatment

Radium-223 Targets Bone Metastases

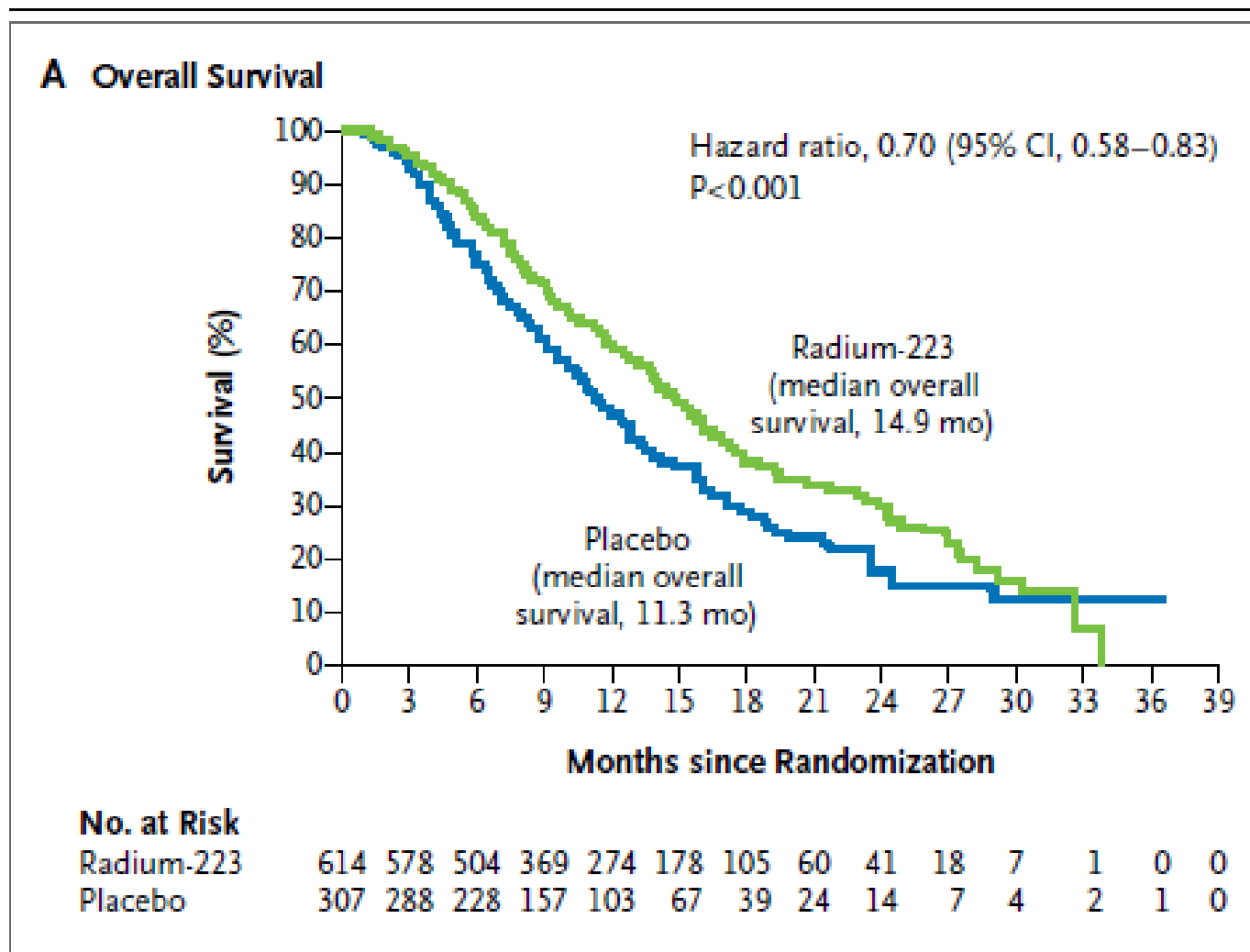


- Targets areas of high bone turn over
- Alpha-particles induce double-strand DNA breaks in adjacent tumor cells
- Short penetration of alpha emitters (2-10 cell diameters) = highly localised tumor cell killing and minimal damage to surrounding normal tissue

ALSYMPCA

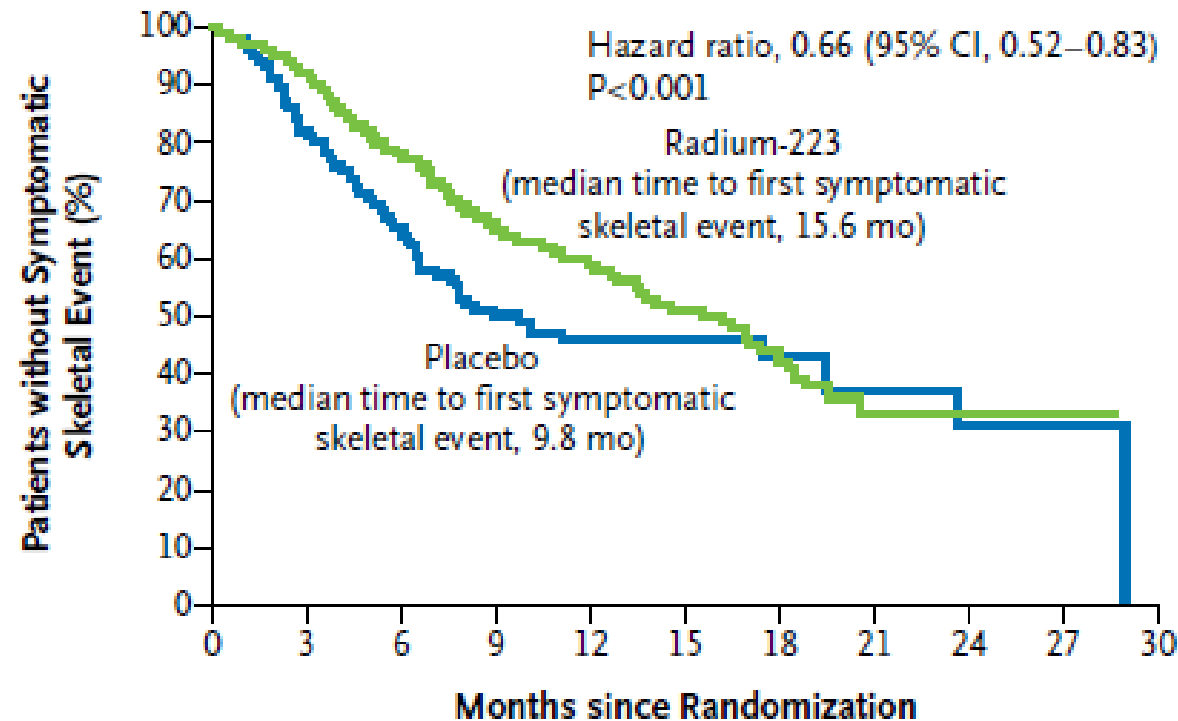


RADIUM-223 SIGNIFICANTLY PROLONGED OS



RADIUM-223 SIGNIFICANTLY PROLONGED TIME TO FIRST SYMPTOMATIC SRE

B Time to First Symptomatic Skeletal Event



No. at Risk

Radium-223	614	496	342	199	129	63	31	8	8	1	0
Placebo	307	211	117	56	36	20	9	7	4	1	0

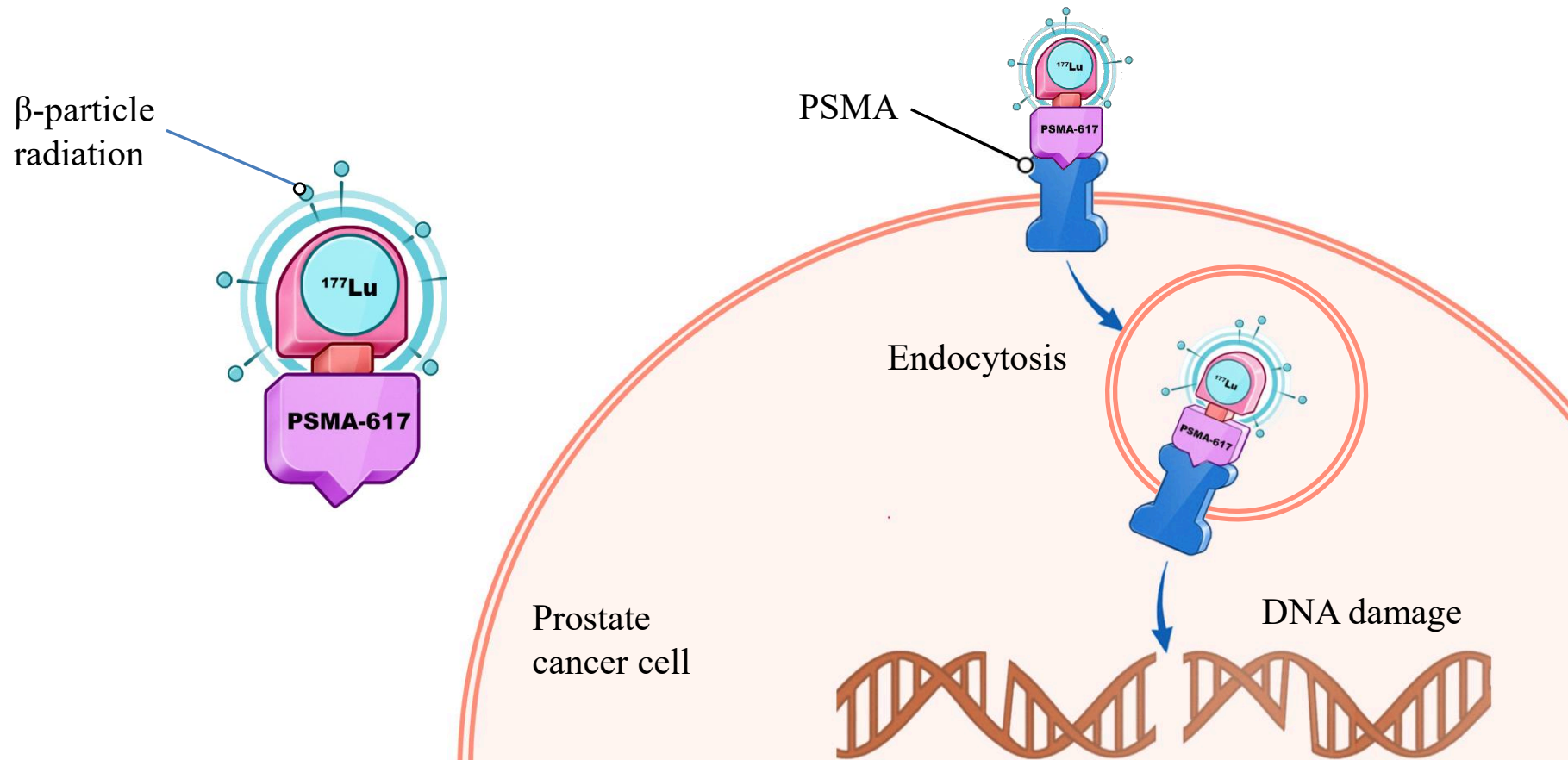
Ra-223 PLUS Abiraterone

- Phase 3 trial – 806
abiraterone plus Ra-223
versus
abiraterone alone patients
- All endpoints worse in combination
- Symptomatic skeletal event-free survival
 - 22.3 mos vs 26.0 mos, HR:1.12, p=0.26
- Overall Survival
 - 30.7 mos vs 33.3 mos HR 1.19, p=0.13
- Bone fragility (fractures)
 - 28.6% vs 11.4%

Smith M et al. Lancet Oncol 20:408-419, 2019.

Lutetium 177-PSMA 617

Targeted radioligand therapy for PSMA-positive mCRPC

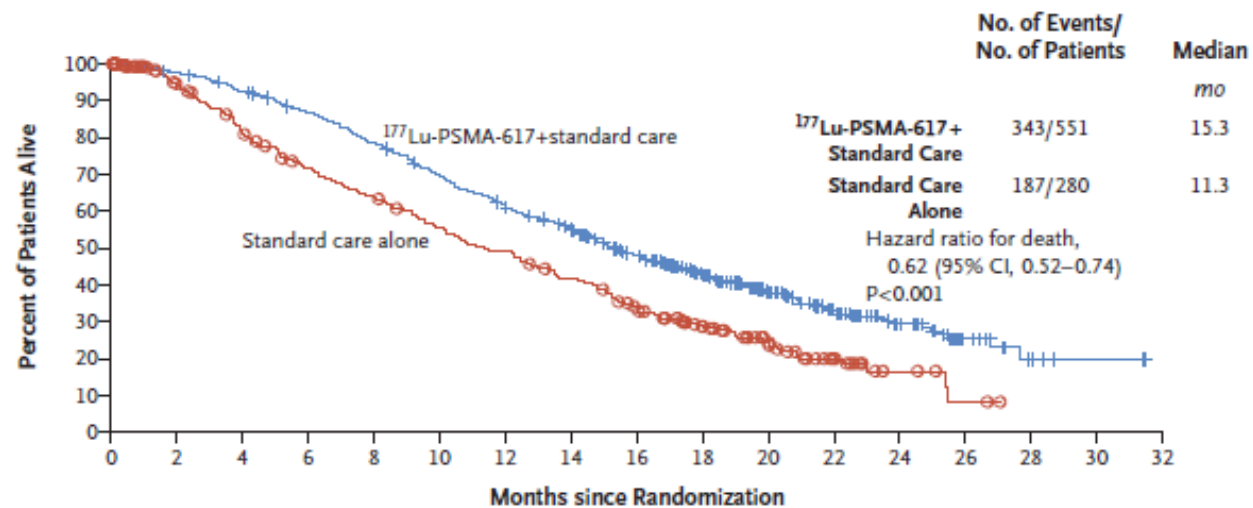


Vision Trial

- 1179 patients underwent ^{68}Ga -PSMA-11 PET/CT
- 831 patients with CRPC and Positive PSMA PET.
 - Patients with non PSMA + mets were ineligible
 - Bone, lymph node and visceral mets were eligible
- 551 - ^{177}Lu -PSMA plus standard of care
- 280 - standard of care
- Standard of Care decided before randomization.
 - No cytotoxic chemo, radium or immunotherapy
- 7.4 GBq 6 weeks x 4 cycles (up to 6 cycles)

Sartor NEJM, 2021

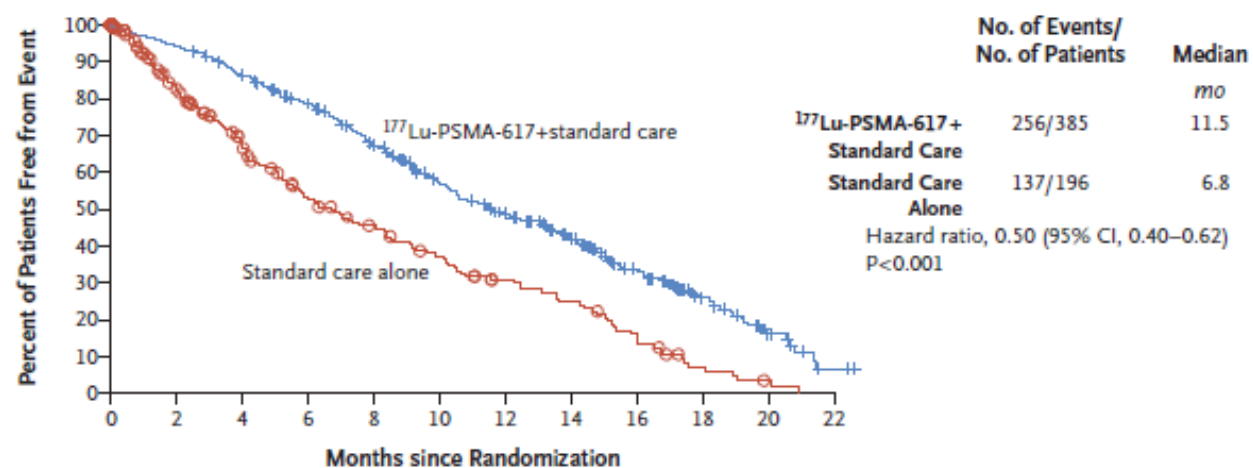
B Overall Survival



No. at Risk

¹⁷⁷ Lu-PSMA-617+standard care	551	535	506	470	425	377	332	289	236	166	112	63	36	15	5	2	0
Standard care alone	280	238	203	173	155	133	117	98	73	51	33	16	6	2	0	0	0

C Time to First Symptomatic Skeletal Event



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

Phase 2 TheraP:

^{177}Lu -PSMA-617 Versus Cabazitaxel

Key Eligibility Criteria

- Progressive PSMA + mCRPC
- Prior treatment with docetaxel for mCRPC
- No prior second-generation anti-hormonal agents

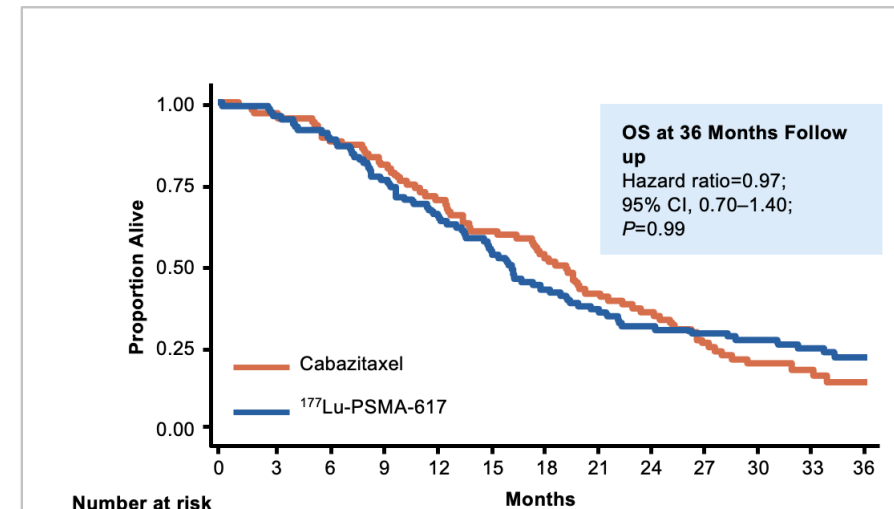
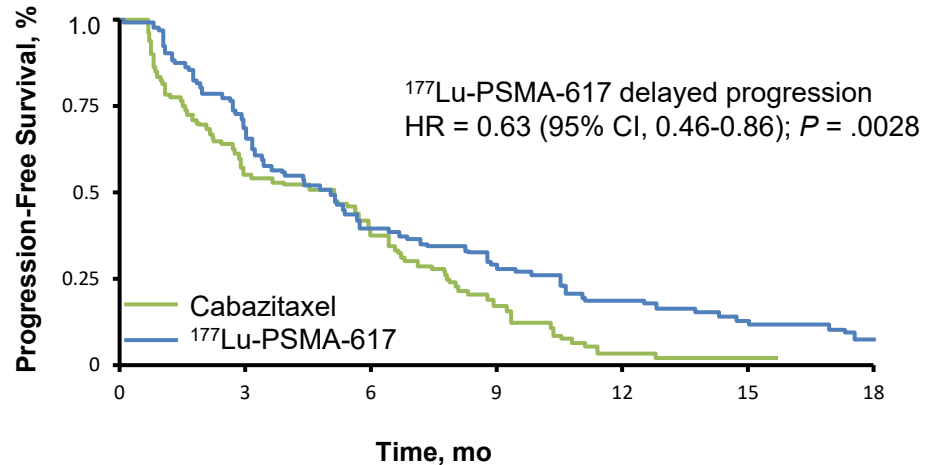
N = 200

R

^{177}Lu -PSMA-617 6-8 GBq IV Q6W
for maximum of 6 cycles

Cabazitaxel 20 mg/m² IV Q3W
for maximum of 10 cycles

- **Primary endpoint:** PSA $\geq$ 50% response rate (PSA50-RR)



Hoffman et al Lancet, 397:797-804, 2021

PSMAfore Trial

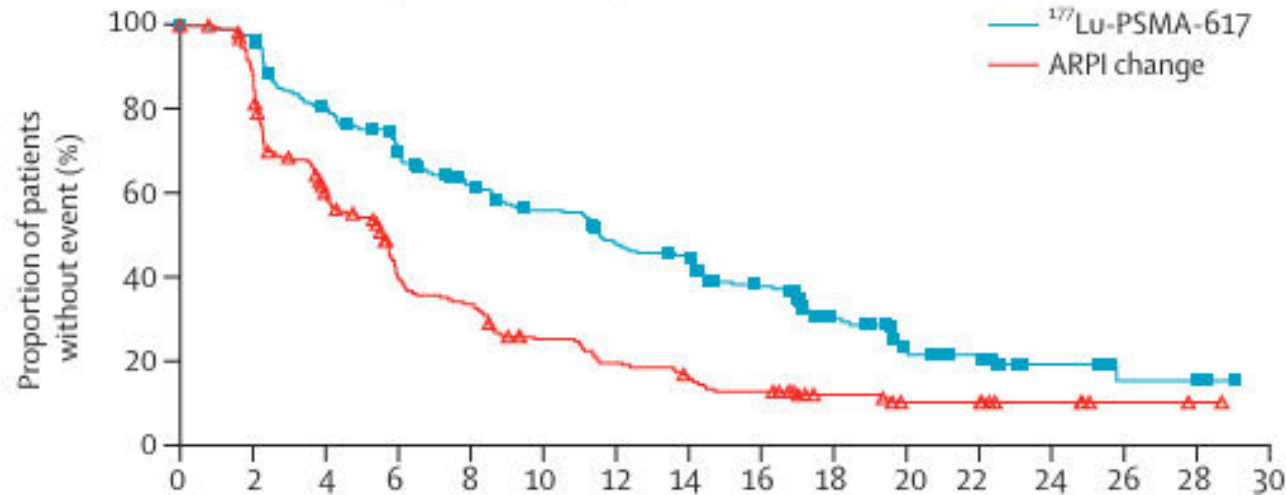
- 585 patients underwent ^{68}Ga -PSMA-11 PET/CT
- 468 patients with CRPC and Positive PSMA PET.
 - Patients with non PSMA avid mets were ineligible
 - Progressed on prior APRI
 - Not PARPi eligible
 - Taxane Naive
- APRI Change (Abby/Enza) v. ^{177}Lu -PSMA-617
- 280 - standard of care
- 7.4 GBq 6 weeks x 6 cycles
- Primary Endpoint Biochemical or RECIST progression

Morris et al, Lancet 404:1227-1239, 2024

rPFS: primary endpoint was met

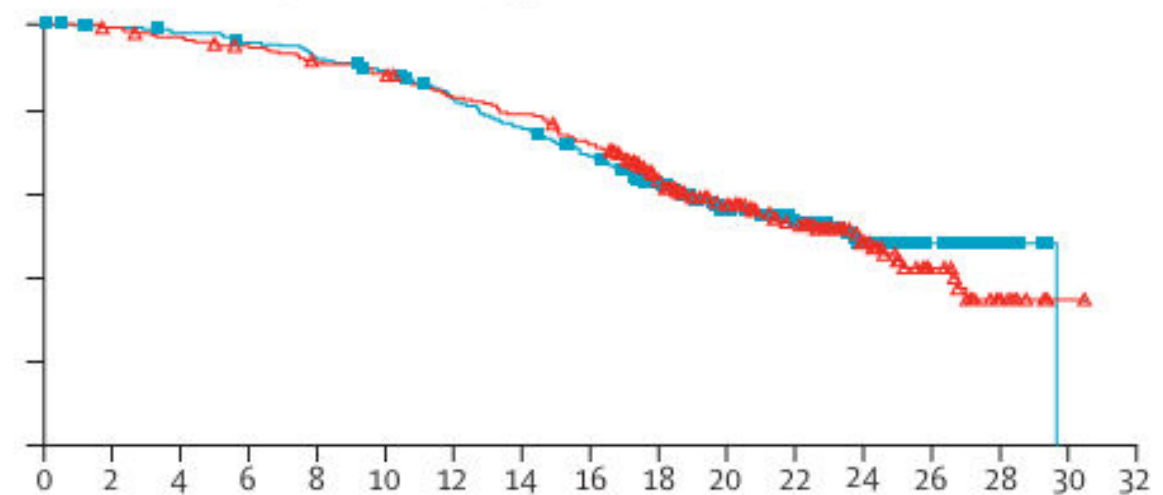
A Radiographic progression-free survival

^{177}Lu -PSMA-617 group: median 11.60 months (95% CI 9.30–14.19), 154 events
ARPI change group: median 5.59 months (95% CI 4.21–5.95), 180 events
HR 0.49 (95% CI 0.39–0.61)



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), $p=0.44$



Morris et al, Lancet 404:1227-1239, 2024

ENZA-p Trial

Eligibility

mCRPC with PSA rising and >5ng/mL
No chemotherapy for mCRPC
≥2 risk features for early enzalutamide failure
Positive ⁶⁸Ga PSMA PET/CT



1:1

Enzalutamide 160 mg

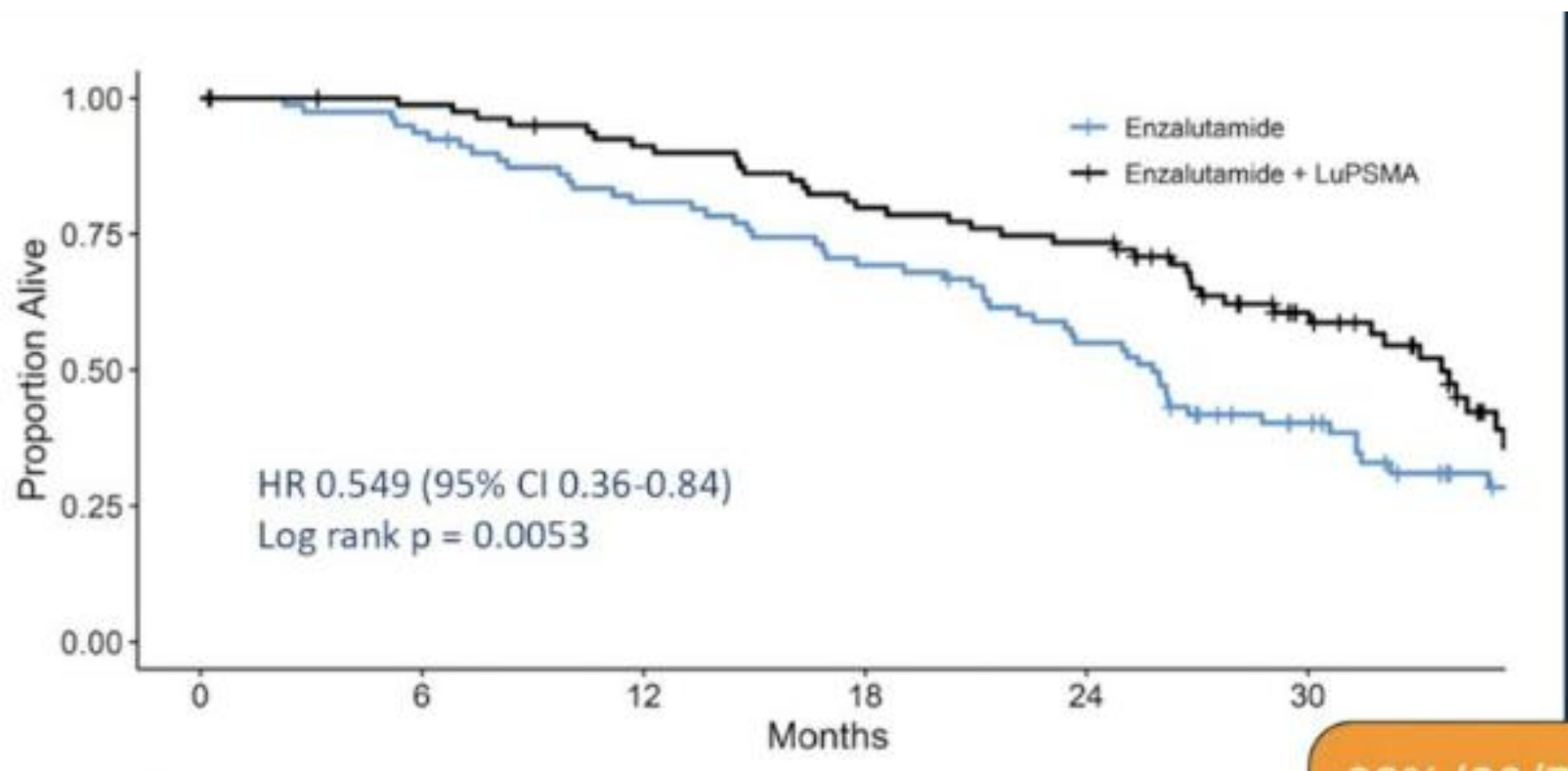
Enzalutamide 160 mg
+ [¹⁷⁷Lu]Lu- PSMA-617 7.5 GBq
2-4 doses

Stratification

Study Site
Volume of disease (>20 vs ≤20)
Early docetaxel for hormone-sensitive disease
Prior treatment with abiraterone

Emmett et al Lancet, GU ASCO 2025

ENZA-p Trial



Emmett et al Lancet, GU ASCO 2025

Bone Directed Therapy

- SBRT
 - ≤ 3 mets (non cranial)
 - Will increase time until ADT, symptoms etc
 - Combination with ADT likely new SOC
 - Does not improve survival
- Radium-223
 - Good performance status
 - Symptomatic bony metastases from mCRPC
 - No known visceral disease
 - LN < 3cm
 - Pre- or post- docetaxel chemotherapy
- ^{177}Lu -PSMA
 - Can be used in combination with novel ADT
 - Can be used for bone, LN and visceral mets
 - PET positive patients
 - Combination with novel ARi likely new SOC

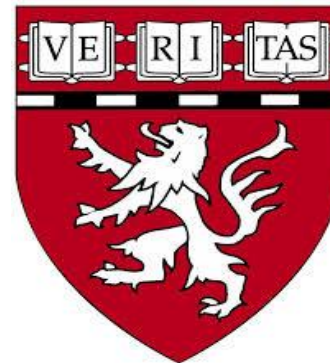
Thank you

Immunotherapy, Targeted Therapies and Future Approach's

Adam S. Kibel, MD

Elliott Carr Cutler Professor of Surgery
Harvard Medical School

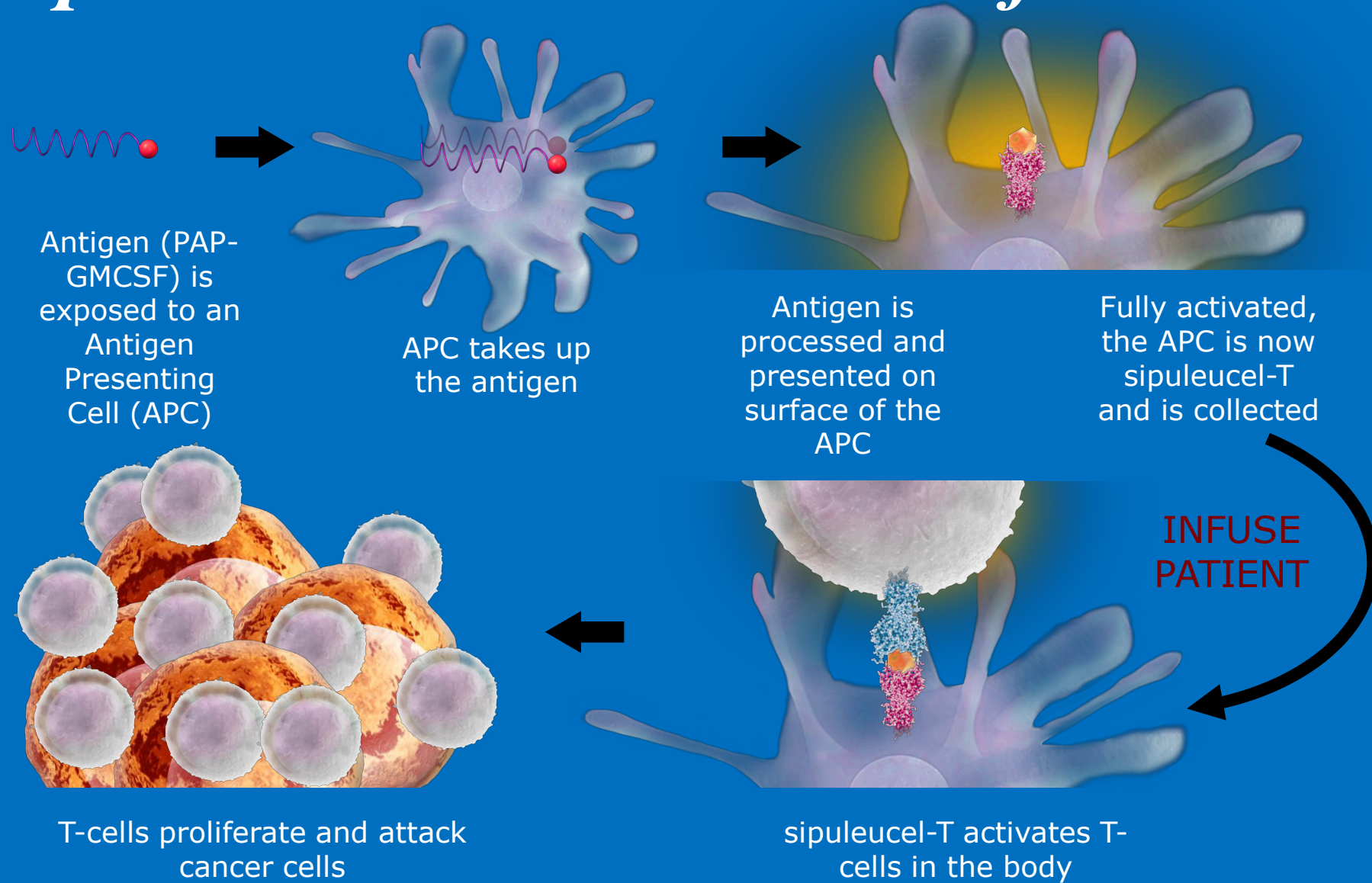
Chair, Department of Urology
DiNovi Family Chair in Urology
Mass General Brigham



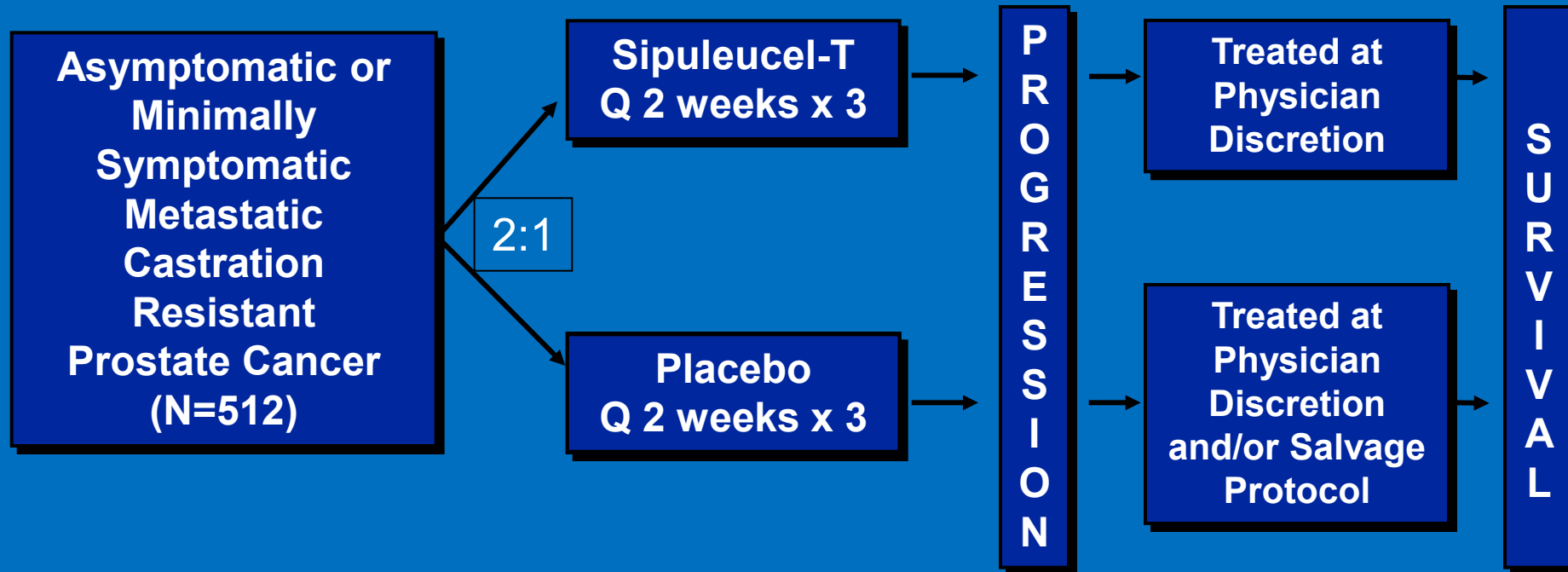
Overview

- Immunotherapy
- PARP Inhibition
- Future Approaches

Sipuleucel-T: Mechanism of Action

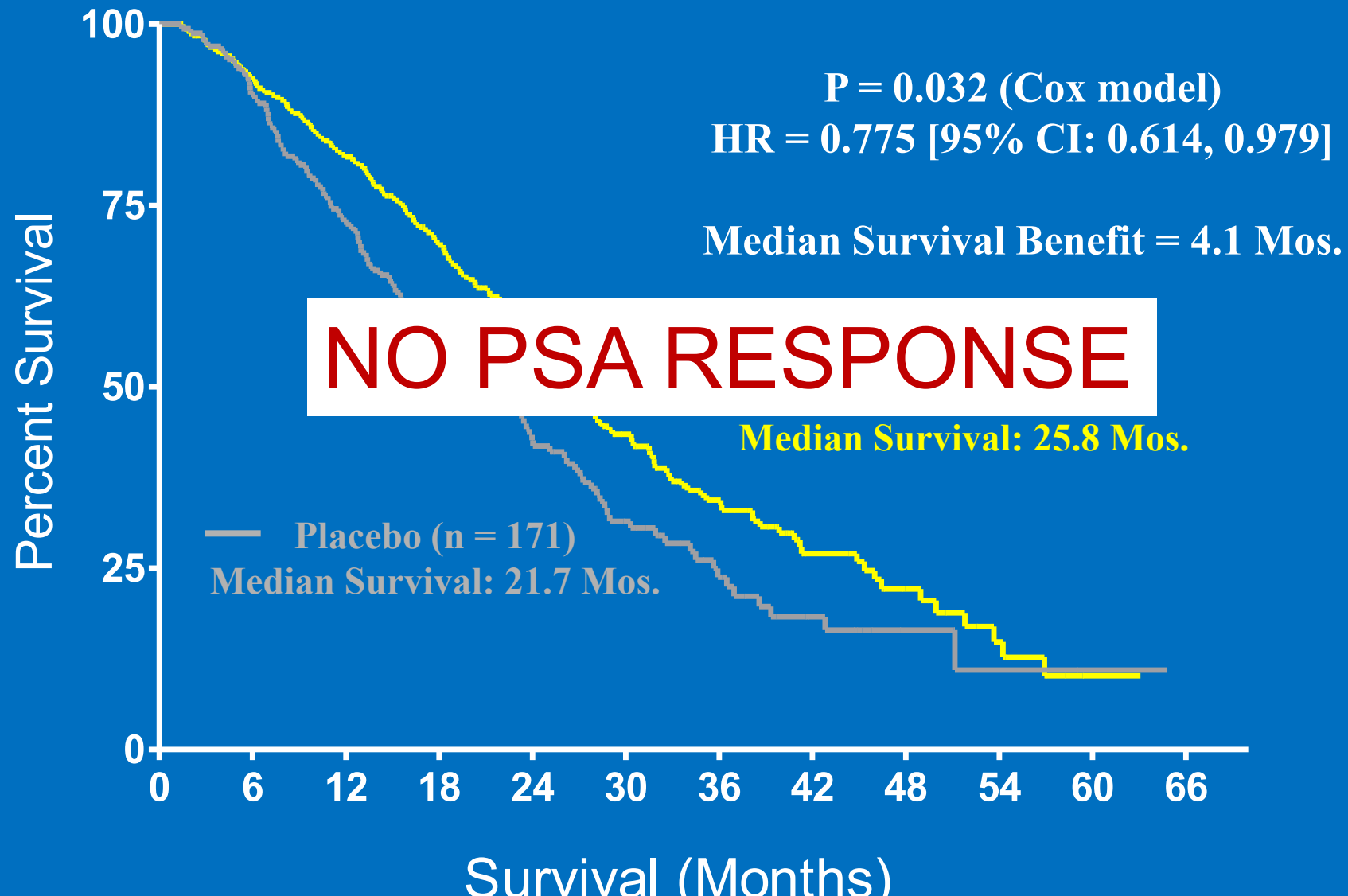


Phase 3 IMPACT Trial

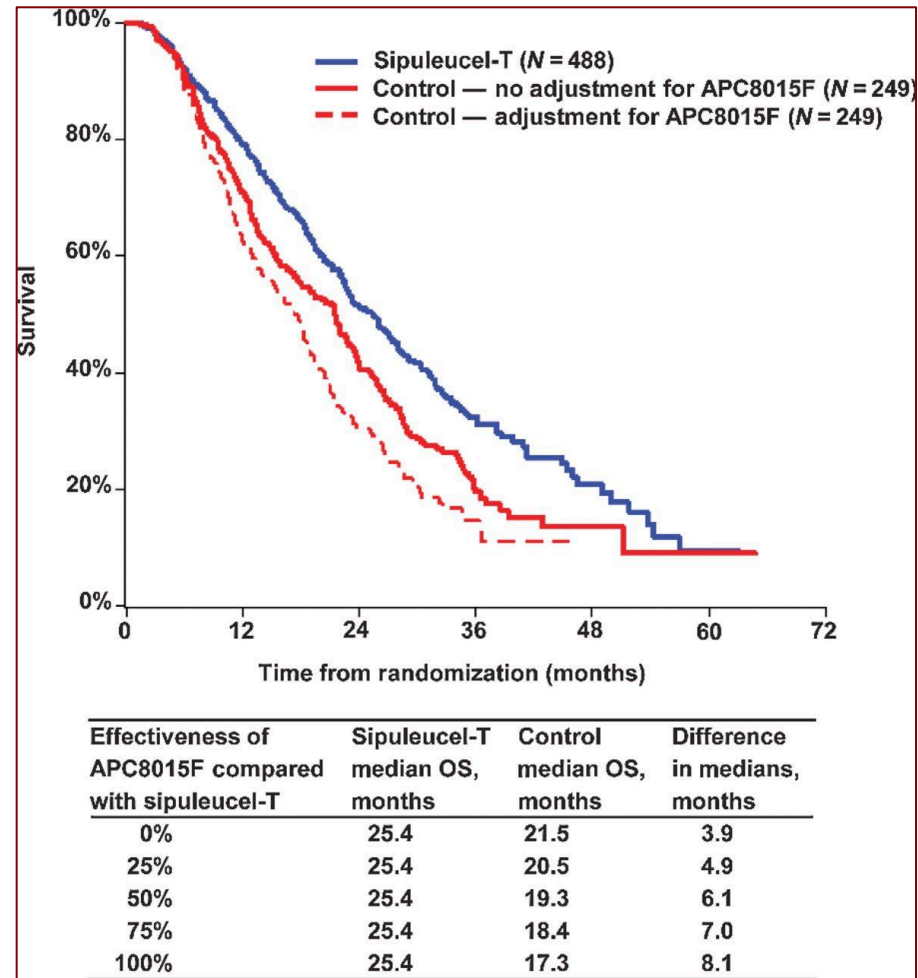


Primary Endpoint: Overall Survival
Secondary Endpoint: Objective Disease Progression

IMPACT Overall Survival: Primary Endpoint Intent-to-Treat Population



Sipuleucel-T: IMPACT Trial



George et al. Cancer Immunol Res. 3:1063, 2015

Adverse Events More Commonly Reported in Sipuleucel-T Group

Preferred Term	Sipuleucel-T N = 338 %	Placebo N = 168 %
Chills	9.8	3.6
Pyrexia	9.8	4.8
Headache	7.4	3.0
Influenza-Like Illness	5.3	0.6
Myalgia	5.0	2.4
Hypertension		
Hyperhidrosis		
Groin Pain		

Flu Like Symptoms

How Do You Treat the Flu

¹ Reported by $\geq 5\%$ of sipuleucel-T patients and having a ≥ 2 -fold difference from placebo.
The majority of the most common AEs were mild or moderate in severity.

METASTATIC CASTRATION RESISTANT PROSTATE CANCER

Prognosis

Clinicians SHOULD

- Obtain baseline labs and review location of metastatic disease, disease-related symptoms, and performance status
- Perform imaging at least annually in mCRPC patients without PSA progression or new symptoms
- Order PSMA PET imaging in mCRPC patients, who are considering ¹⁷⁷Lu-PSMA-617, with disease progression having previously received docetaxel and androgen pathway inhibitor
- Offer germline (if not already performed) and somatic genetic testing

Treatment

Clinicians SHOULD

- Offer continued ADT with abiraterone acetate plus prednisone, docetaxel, or enzalutamide in mCRPC patients who have not received prior androgen receptor pathway inhibitors
- Offer radium-223 to patients with symptoms from bony metastases from mCRPC and without known visceral disease or lymphadenopathy >3cm
- Offer ¹⁷⁷Lu-PSMA-617 to patients with progressive mCRPC having previously received docetaxel and androgen pathway inhibitor with a positive PSMA PET imaging study

Treatment (cont.)

Clinicians SHOULD (cont.)

- Recommend cabazitaxel rather than an alternative androgen pathway directed therapy in patients who received prior docetaxel and abiraterone acetate plus prednisone or enzalutamide
- Offer a PARP inhibitor to patients with deleterious or suspected deleterious germline or somatic HRR gene-mutated mCRPC following prior treatment with enzalutamide or abiraterone, and/or a taxane-based chemotherapy; platinum-based chemotherapy may be offered for patients who cannot use or obtain a PARP inhibitor
- Offer pembrolizumab to patients with mismatch repair deficient or microsatellite instability high mCRPC

Clinicians MAY

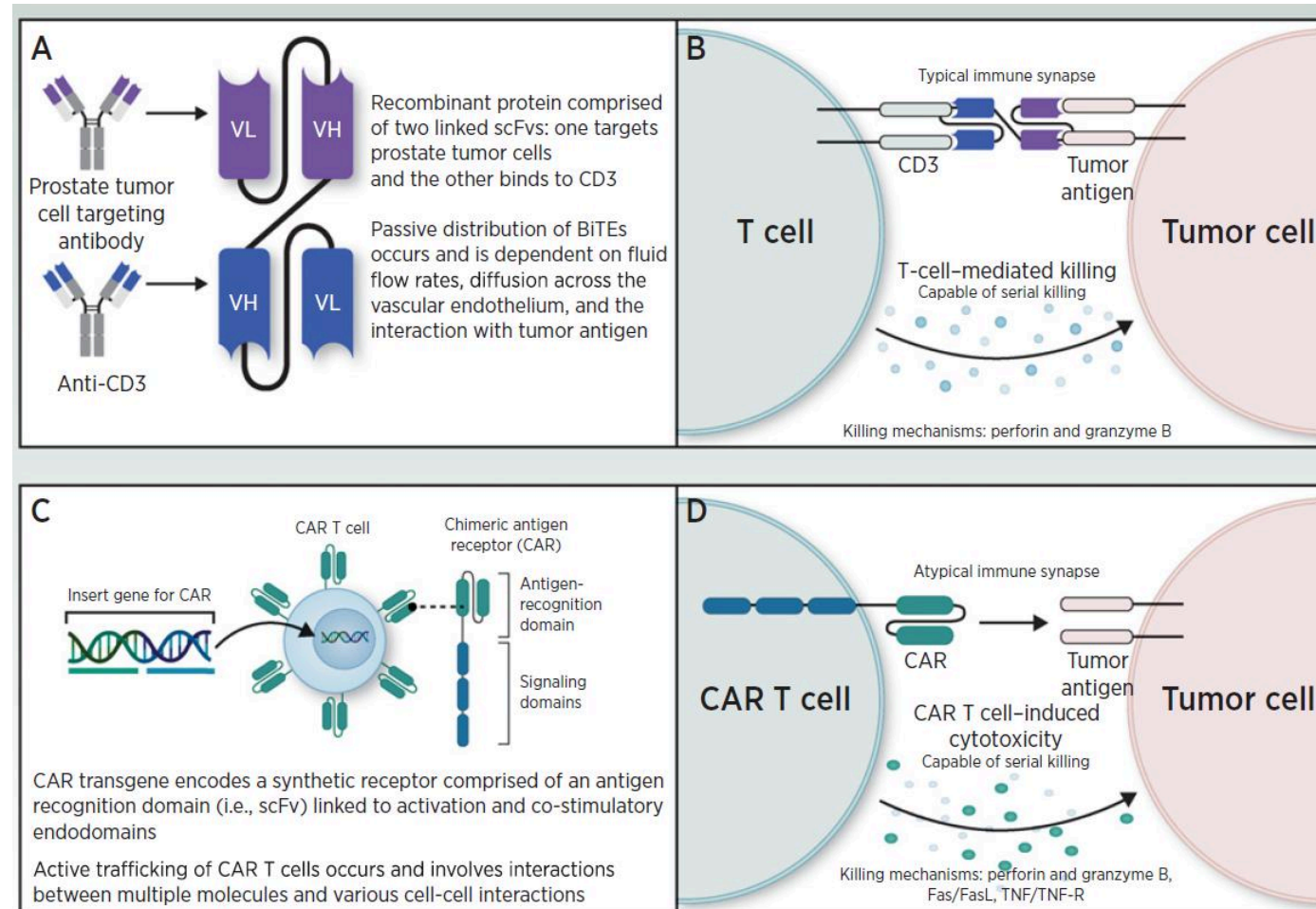
- Offer sipuleucel-T to asymptomatic/minimally symptomatic patients
- Offer cabazitaxel to patients who received prior docetaxel with or without prior abiraterone acetate plus prednisone or enzalutamide

Clinicians MAY

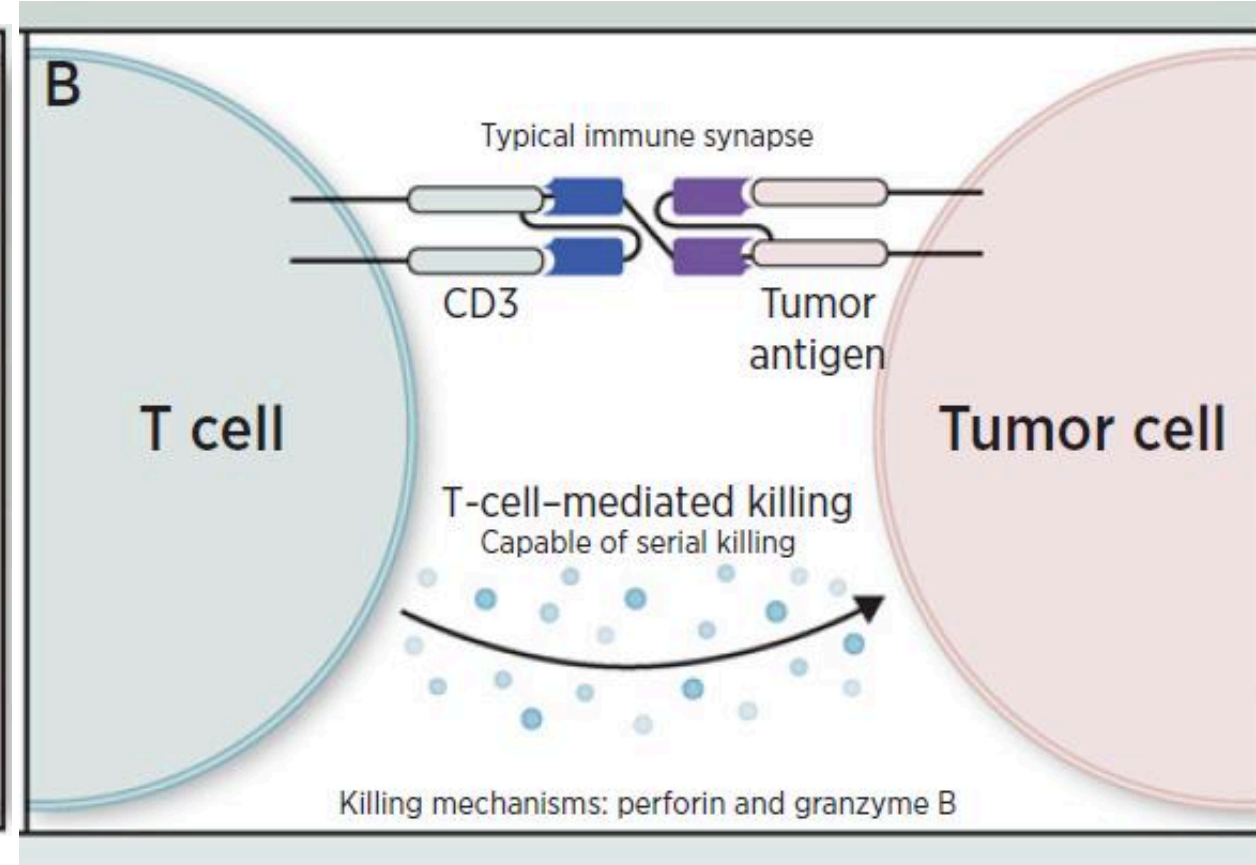
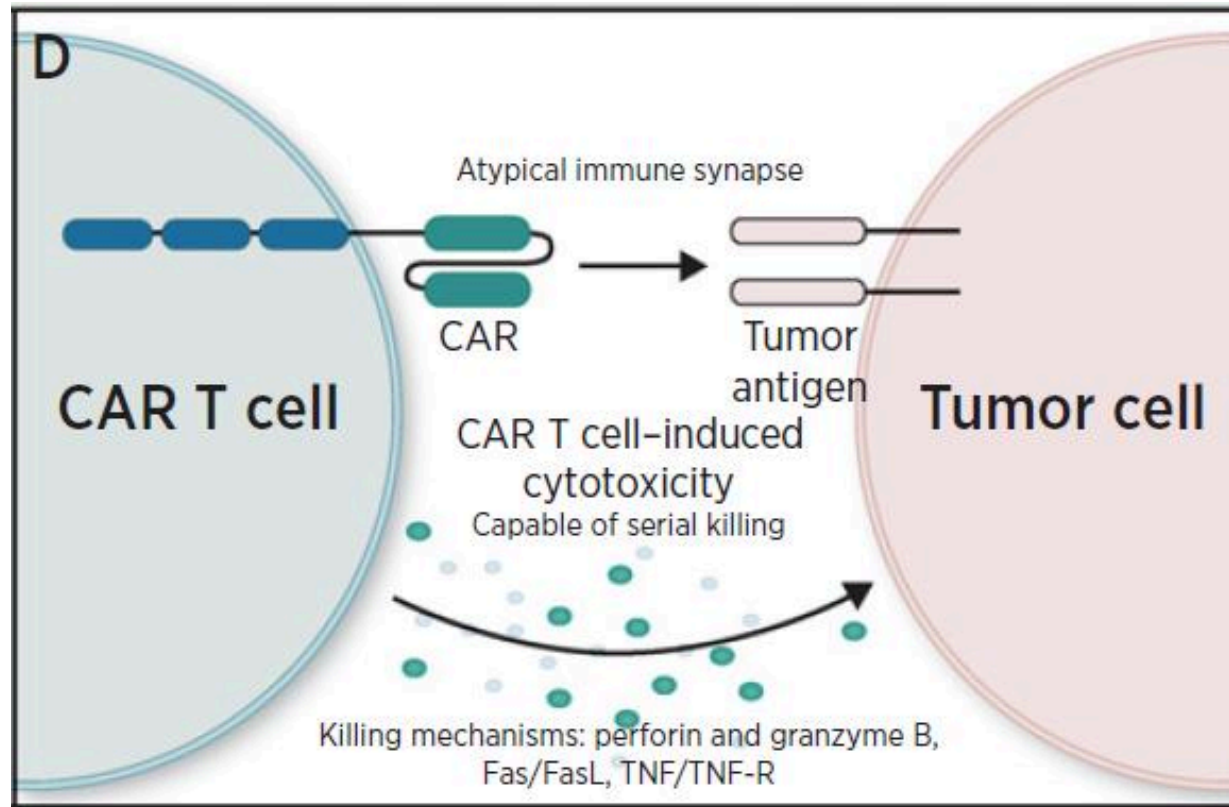
- Offer sipuleucel-T to asymptomatic/minimally symptomatic patients

CAR-T Cells (chimeric antigen receptor-modified T cells)

Bites (Bispecific T-cell Engagers)



Dorff et al, Clin Cancer Res, 28:576, 2022.



Dorff et al, Clin Cancer Res, 28:576, 2022.

CAR-T Cells (chimeric antigen receptor-modified T cells)

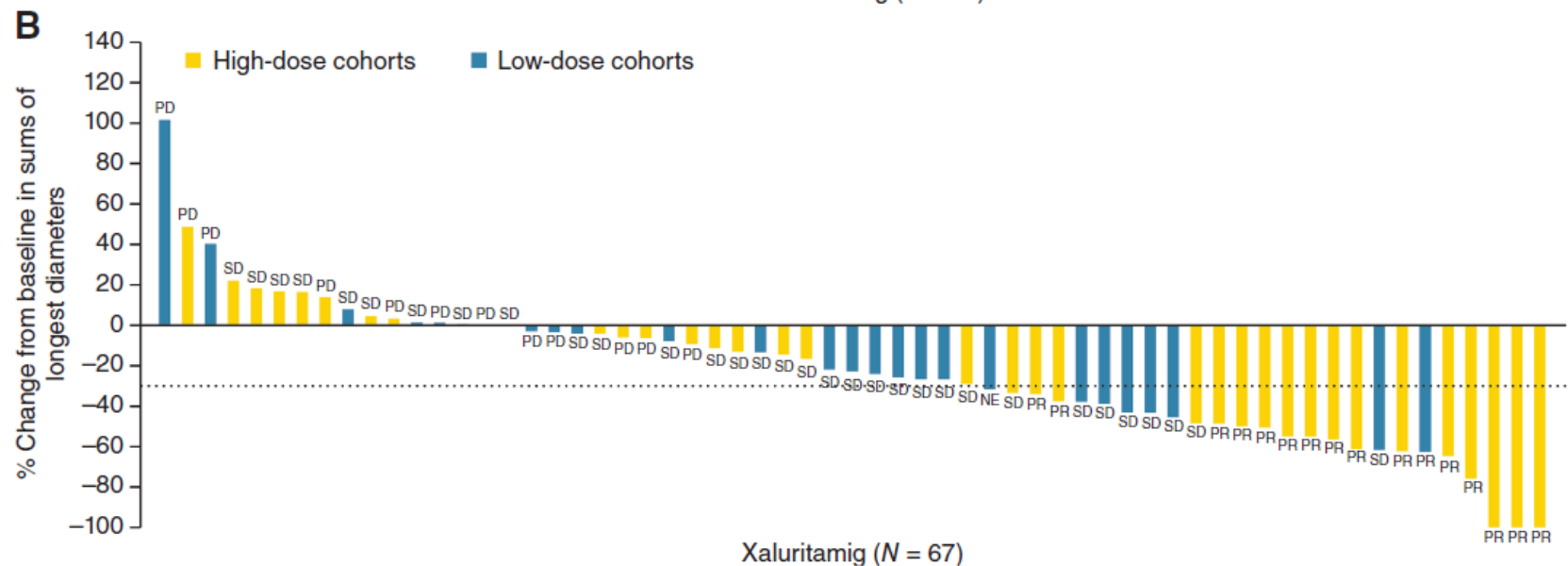
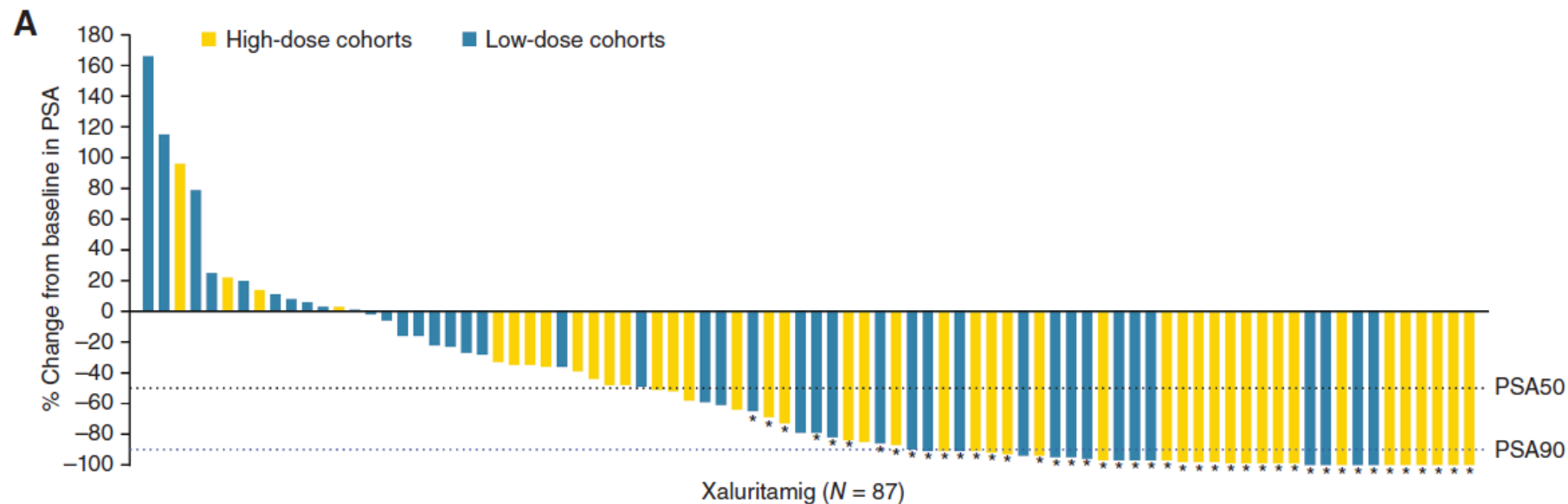
Bites (Bispecific Bispecific T-cell Engagers)

NCT#	Biological/drug name	Targets	Status	Phase
CAR-T				
NCT04227275	CART-PSMA-TGFβRDN	PSMA	Active	Phase I
NCT03873805	Autologous anti-PSCA-CAR-4-1BB/TCRzeta-CD19t-expressing T lymphocytes	PSCA	Recruiting	Phase I
NCT04053062	LIGHT-PSMA-CART	PSMA	Recruiting	Phase I
NCT01140373	Engineered autologous T cells	PSMA	Active	Phase I
NCT04249947	P-PSMA-101 CAR-T cells	PSMA	Recruiting	Phase I
NCT04107142	NKG2DL-targeting chimeric antigen receptor-grafted gamma delta T-cell	NKG2DL	Not yet recruiting	
NCT04633148	UniCAR02-T-pPSMA	PSMA	Recruiting	Phase I
NCT02744287	BPX-601	PSCA	Recruiting	Phase I
NCT04429451	4SCAR-PSMA T cells	PSMA	Recruiting	Phase I
BiTE				
NCT04104607	CC-1	PSMA x CD3	Recruiting	Phase I
NCT03406858	HER2 bi-armed activated T cells	HER2 x CD3	Recruiting	Phase II
NCT04702737	AMG 757	DLL3 x CD3	Not yet recruiting	Phase I
NCT03792841	AMG 160	PSMA x CD3	Recruiting	Phase I
NCT02262910	ES414	PSMA x CD3	Completed	Phase I
NCT00635596	MT110	EpCAM x CD3	Completed	Phase I
NCT03927573	GEM3PSCA	PSCA x CD3	Recruiting	Phase I
NCT01723475	BAY2010112	PSMA x CD3	Completed	Phase I
NCT04221542	AMG 509	STEAP-1 x CD3	Recruiting	Phase I
NCT04631601	AMG 160	PSMA x CD3	Not yet recruiting	Phase I
NCT04424641	GEN1044	5T4 x CD3	Recruiting	Phase I/II
NCT03517488	XmAb20717	PDL1 x CTLA4	Recruiting	Phase I
NCT03849469	XmAb22841	CTLA4 x LAG-3	Recruiting	Phase I

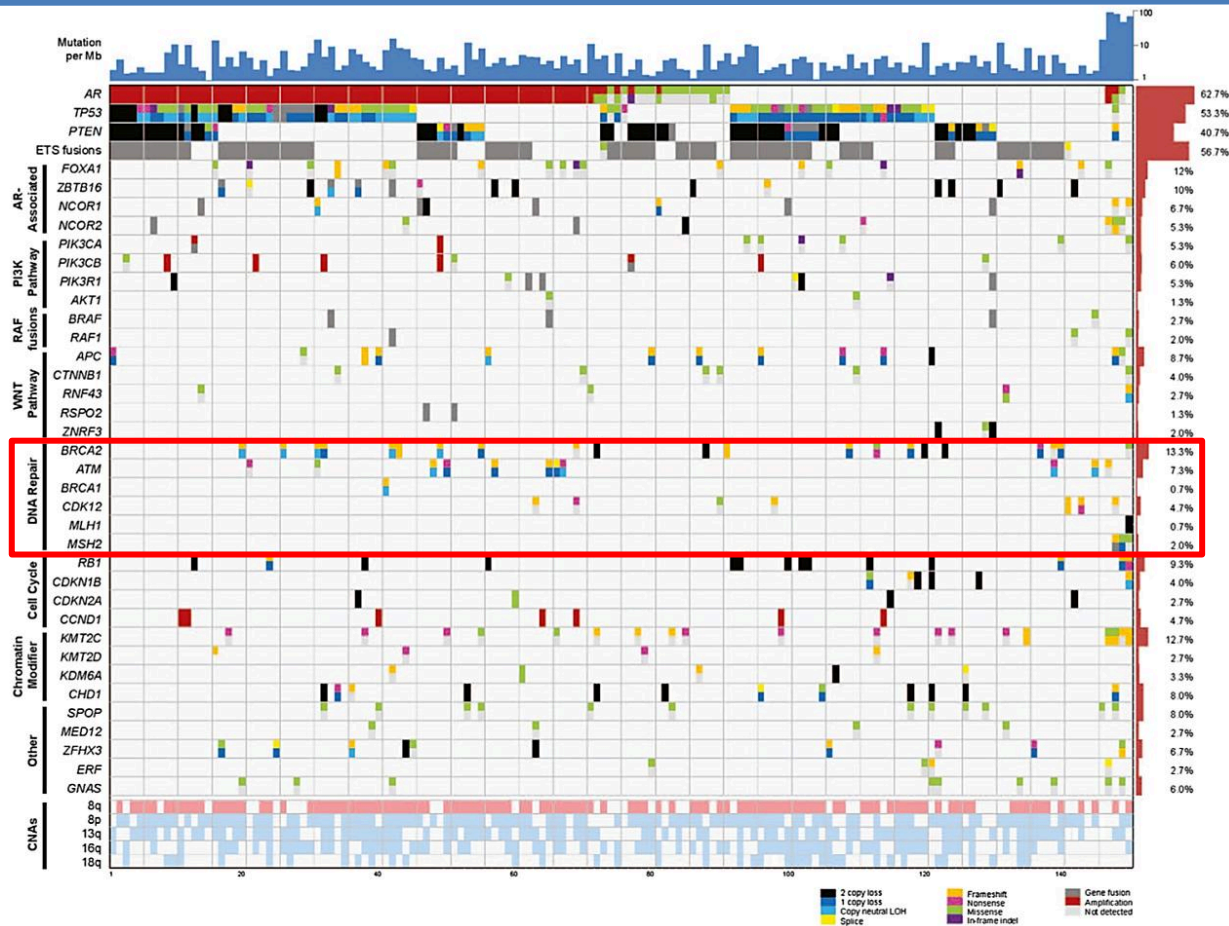
Bites (Bispecific Bispecific T-cell Engagers)

NCT04221542	AMG 509	STEAP-1 x CD3	Recruiting	Phase I
-------------	---------	---------------	------------	---------

AMG 509 (Xaluritamig), an Anti-STEAP1 Bite

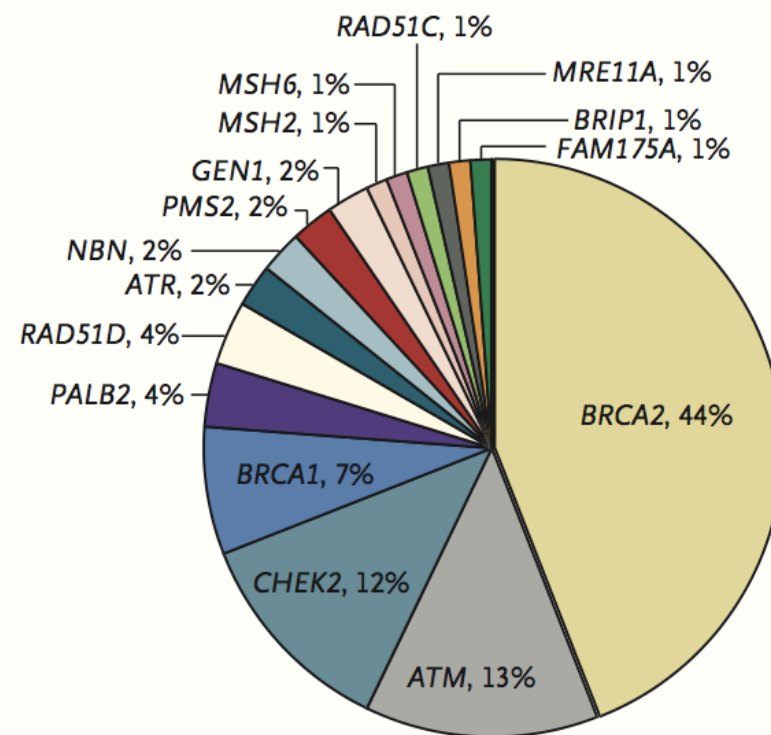


DNA Repair Gene Alterations are Common in Metastatic Prostate Cancer



- 23% of metastatic castration-resistant prostate cancers harbor DNA repair alterations
- The frequency of DNA repair alterations increases with disease progression

Robinson D et al. *Cell* 2015; 161:1215-28.

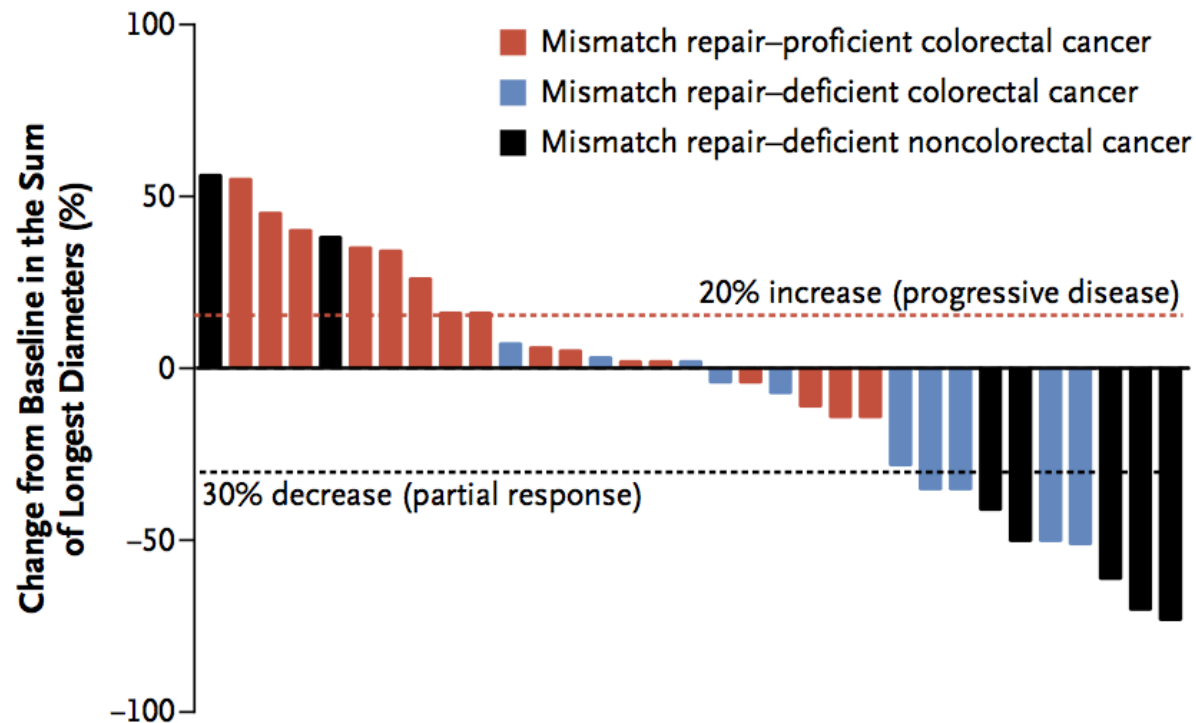


- 11.8% of men with metastatic prostate cancer have a germline alteration in 16 DNA damage repair genes
- Age and family history did not affect mutation frequency

Pritchard CC et al. *N Engl J Med*. July 6, 2016.

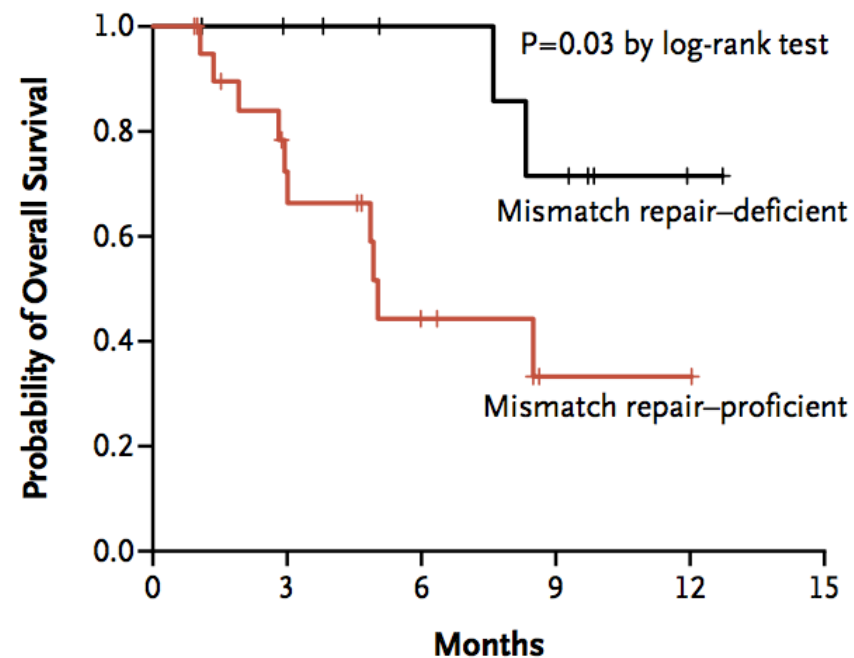
Pembrolizumab in MMR Deficient Cancers

B Radiographic Response



Le DT et al. *N Engl J Med.* 2015; 372:2509-2520.

B Overall Survival in Cohorts with Colorectal Cancer



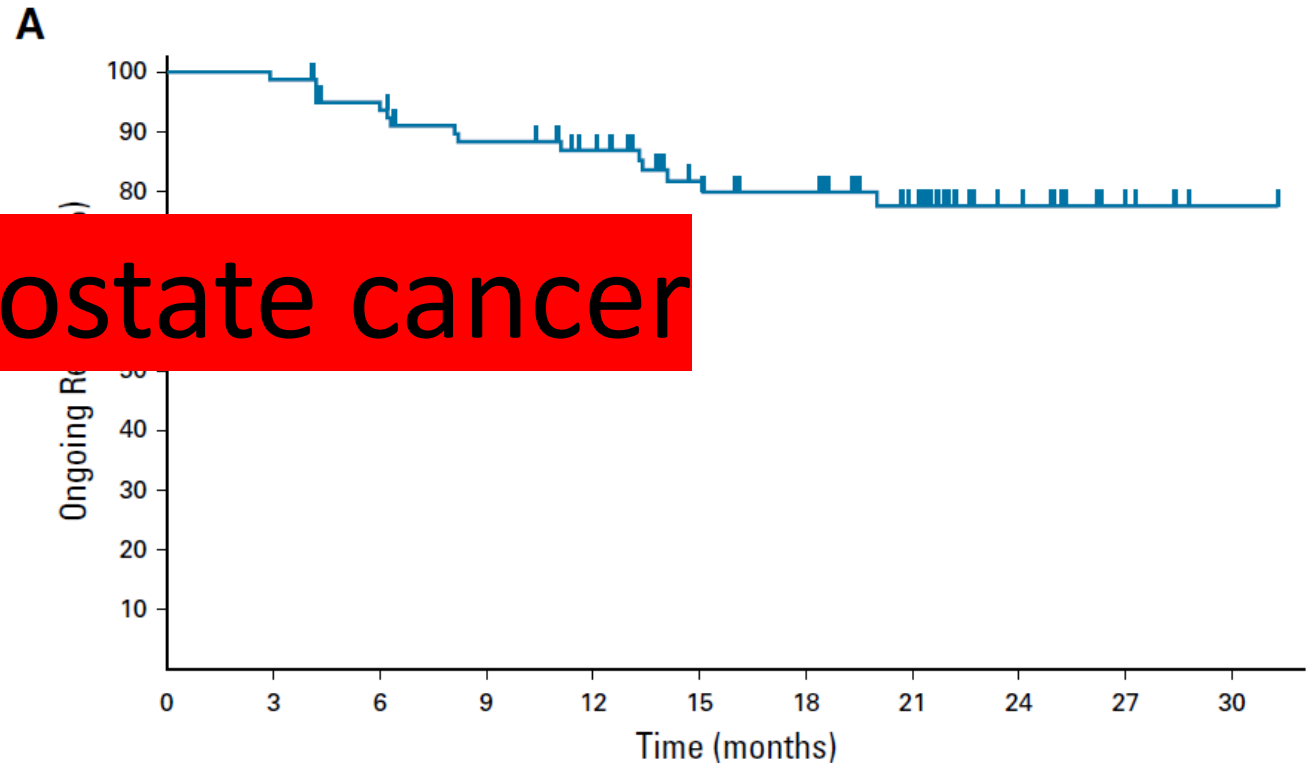
No. at Risk

Mismatch repair-deficient	11	9	7	5	1	0
Mismatch repair-proficient	21	12	5	1	1	0

Pembrolizumab in MMR Deficient Cancers

- Approved for patients with MSI-H or dMMR cancers
- Across the 5 clinical studies contributing data
- 149 patients were identified
 - 90 patients with Metastatic Colorectal cancer
 - 59 patients with other MSI-H/dMMR cancers (14 different cancer types).
 - Few prostate cancer patients
- Subsequent larger studies (Keynote 158)
 - 233 patients

6 had prostate cancer



Marcus et al Clin Cancer Res, 2019

Marabelle et al, JCO, 2020

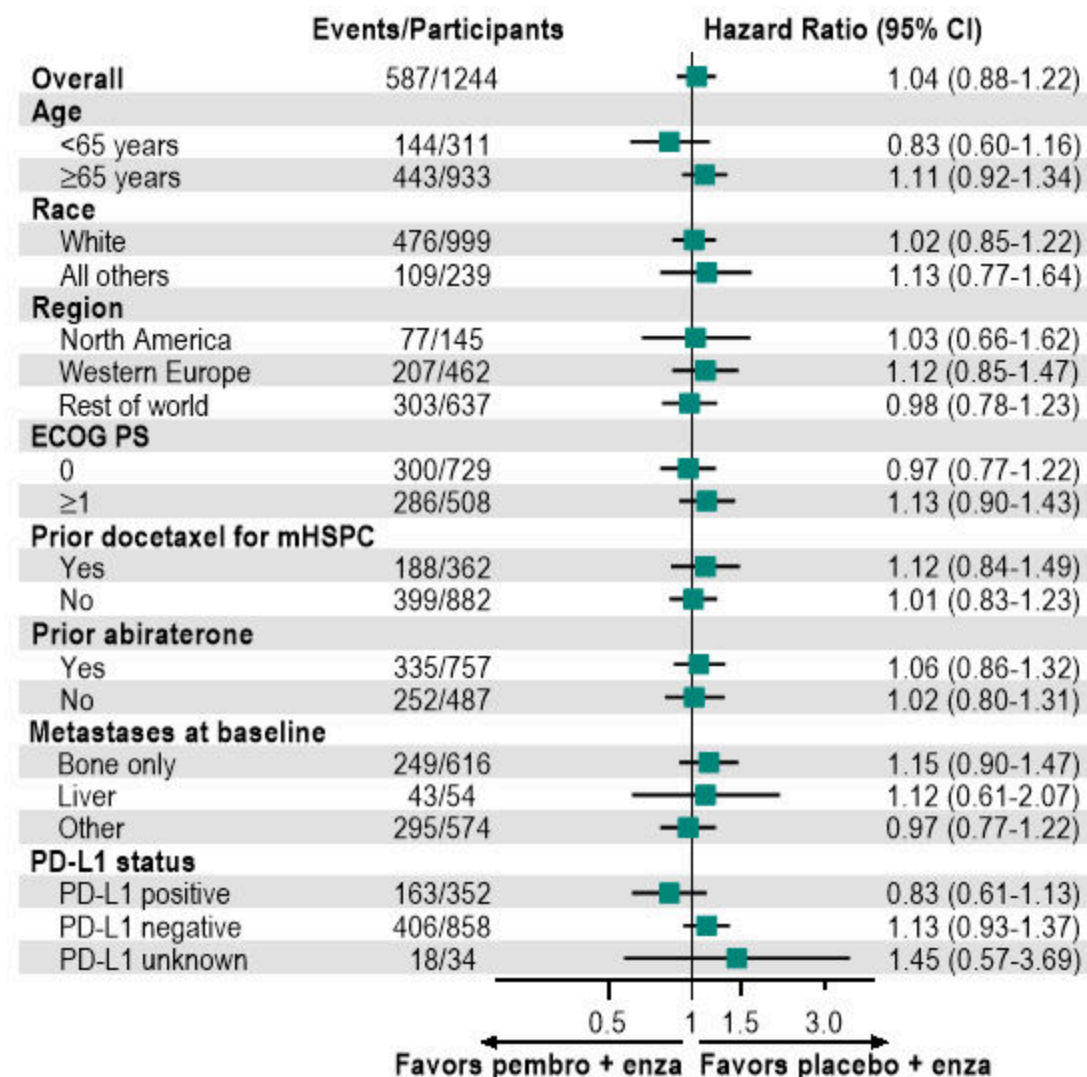
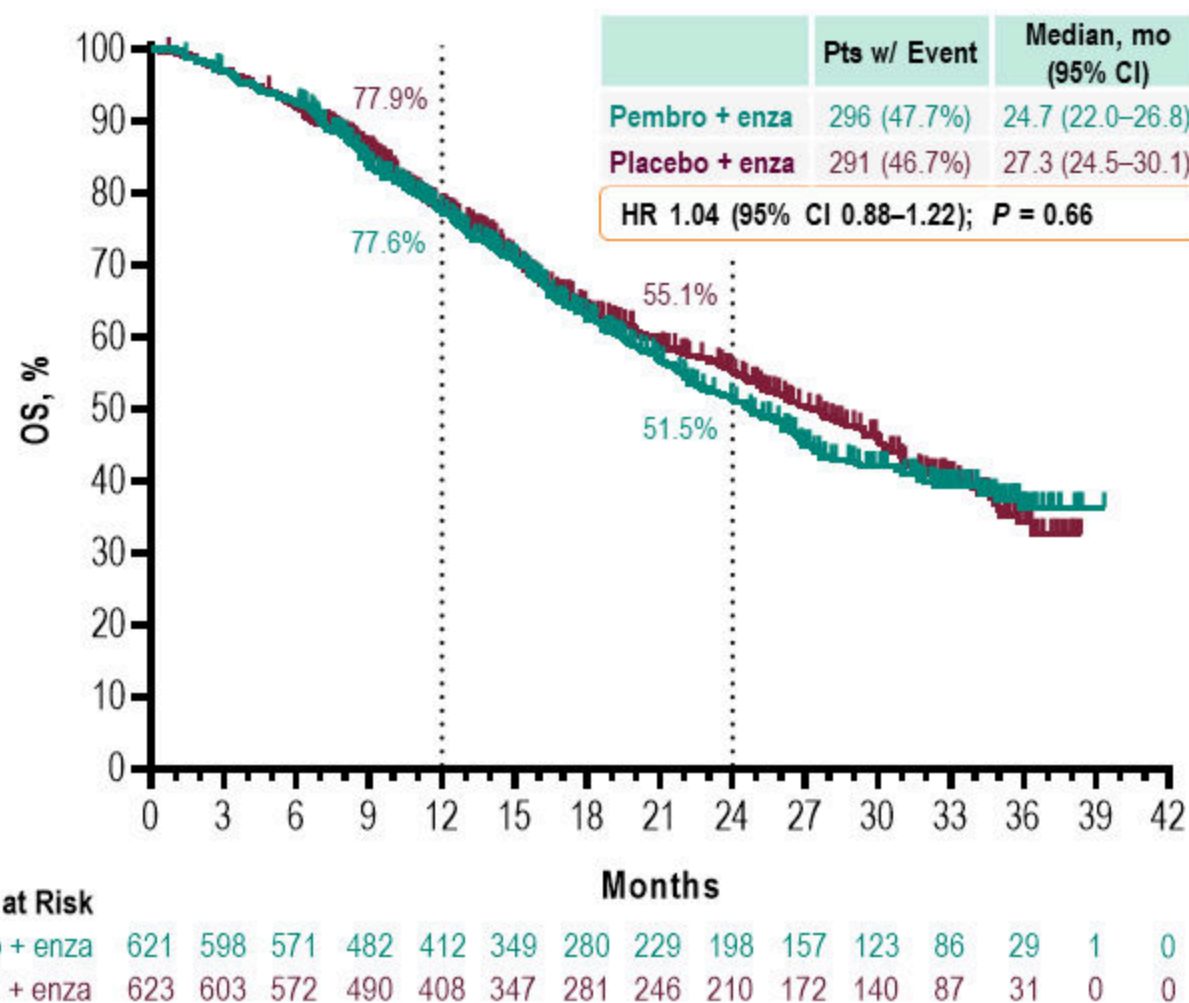
Expanded Use PDL1 Inhibition

- KEYNOTE 641 - Pembrolizumab plus Enza v. Enza – CRPC
- KEYNOTE 991 - Pembrolizumab plus Enza v. Enza – HSPC
- IMbassador 250 - Atezolizumab plus Enza – CRPC
- CONTACT-02 – Atezolizumab plus Cabozantinib v. ARi - CRPC

NEGATIVE

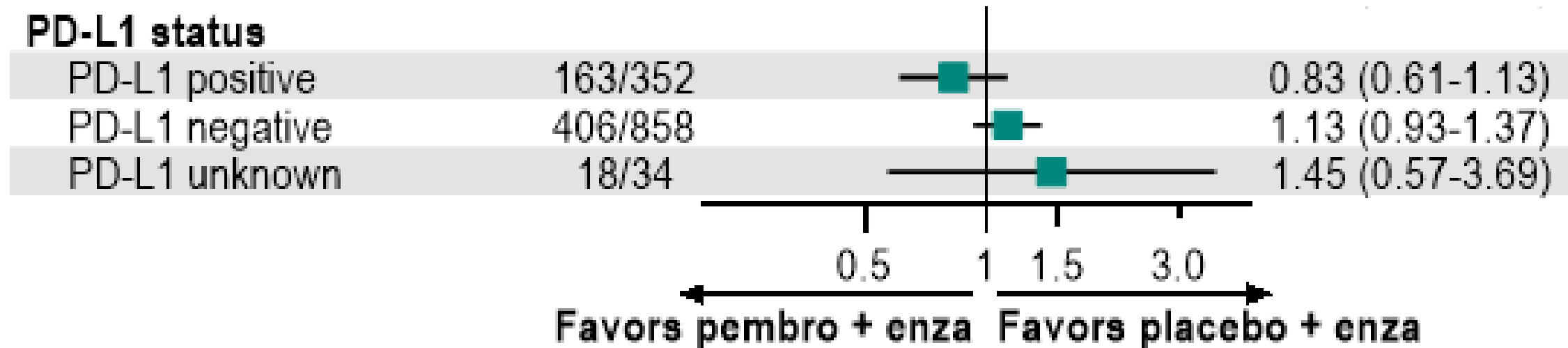
KEYNOTE – 641 - CRPC

Primary Endpoint: OS



KEYNOTE - 641

PD-L1 status

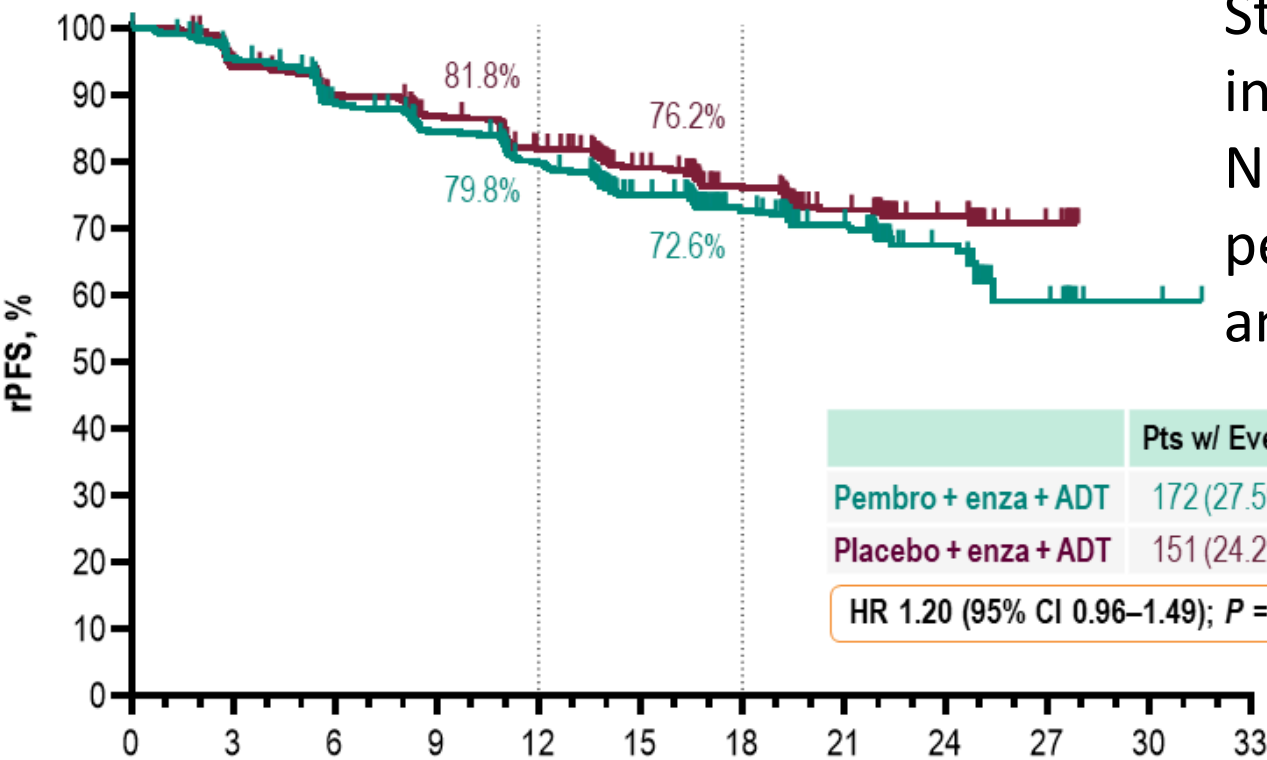


KEYNOTE – 991 - mHSPC

Gratzke KN991 ESMO 2023

Primary Endpoint: rPFS by BICR per PCWG-Modified RECIST 1.1

Stopped for futility at first interim analysis
No PFS benefit of adding pembrolizumab to enzalutamide and ADT in mHSPC



	Pts w/ Event	Median, mo (95% CI)
Pembro + enza + ADT	172 (27.5%)	NR (NR–NR)
Placebo + enza + ADT	151 (24.2%)	NR (NR–NR)

HR 1.20 (95% CI 0.96–1.49); P = 0.95

	No. at Risk												
	Months												
Pembro + enza + ADT	626	574	519	487	444	345	253	164	76	19	2	0	
Placebo + enza + ADT	625	578	542	514	475	380	277	166	79	18	0	0	

METASTATIC CASTRATION RESISTANT PROSTATE CANCER

Prognosis

Clinicians SHOULD

Obtain baseline labs and review location of metastatic disease, disease-related symptoms, and performance status

Assess the extent of metastatic disease using conventional imaging at least annually or at intervals determined by lack of response to therapy

Offer germline and somatic tumor genetic testing

Treatment

Clinicians SHOULD

Offer continued ADT with abiraterone acetate plus prednisone, docetaxel, or enzalutamide

Consider prior treatment in sequencing agents and recommend therapy with an alternative mechanism of action

Offer radium-223 to patients with symptoms from bony metastases from mCRPC and without known visceral disease or lymphadenopathy >3cm

Treatment (cont.)

Clinicians SHOULD (cont.)

Recommend cabazitaxel rather than an alternative androgen pathway directed therapy in patients who received prior docetaxel and abiraterone acetate plus prednisone or enzalutamide

Offer a PARP inhibitor to patients with deleterious or suspected deleterious germline or somatic HRR gene-mutated mCRPC following prior treatment with enzalutamide or abiraterone, and/or a taxane-based chemotherapy

Offer pembrolizumab to patients with mismatch repair deficient or microsatellite instability high CRPC

Clinicians MAY

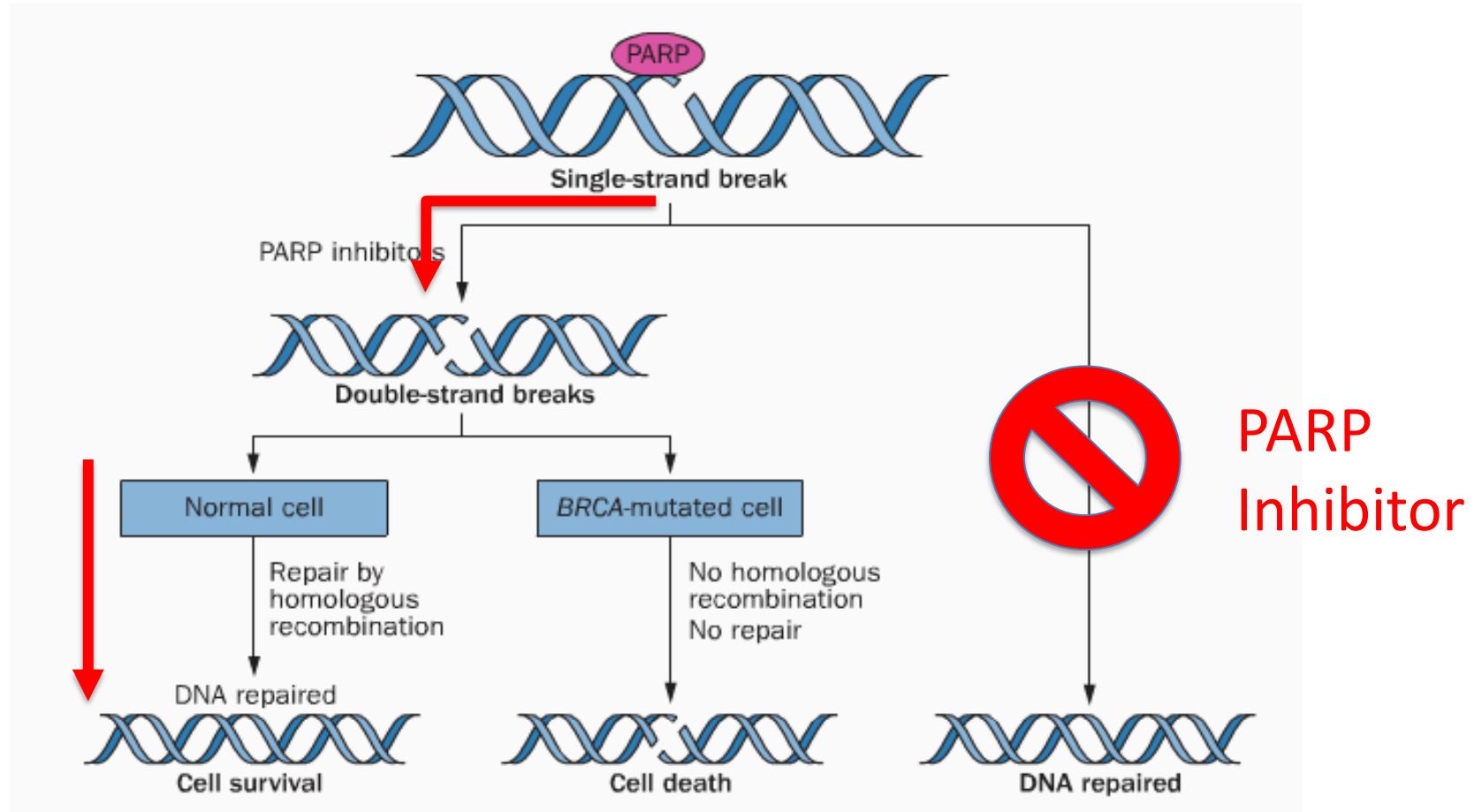
Offer sipuleucel-T to asymptomatic/minimally symptomatic patients

Offer cabazitaxel to patients who received prior docetaxel with or without prior abiraterone acetate plus prednisone or enzalutamide

Offer platinum-based chemotherapy to patients with deleterious or suspected deleterious germline or somatic HRR gene-mutated mCRPC following prior treatment with enzalutamide or abiraterone acetate, and/or a taxane-based chemotherapy who cannot use/obtain a PARP inhibitor

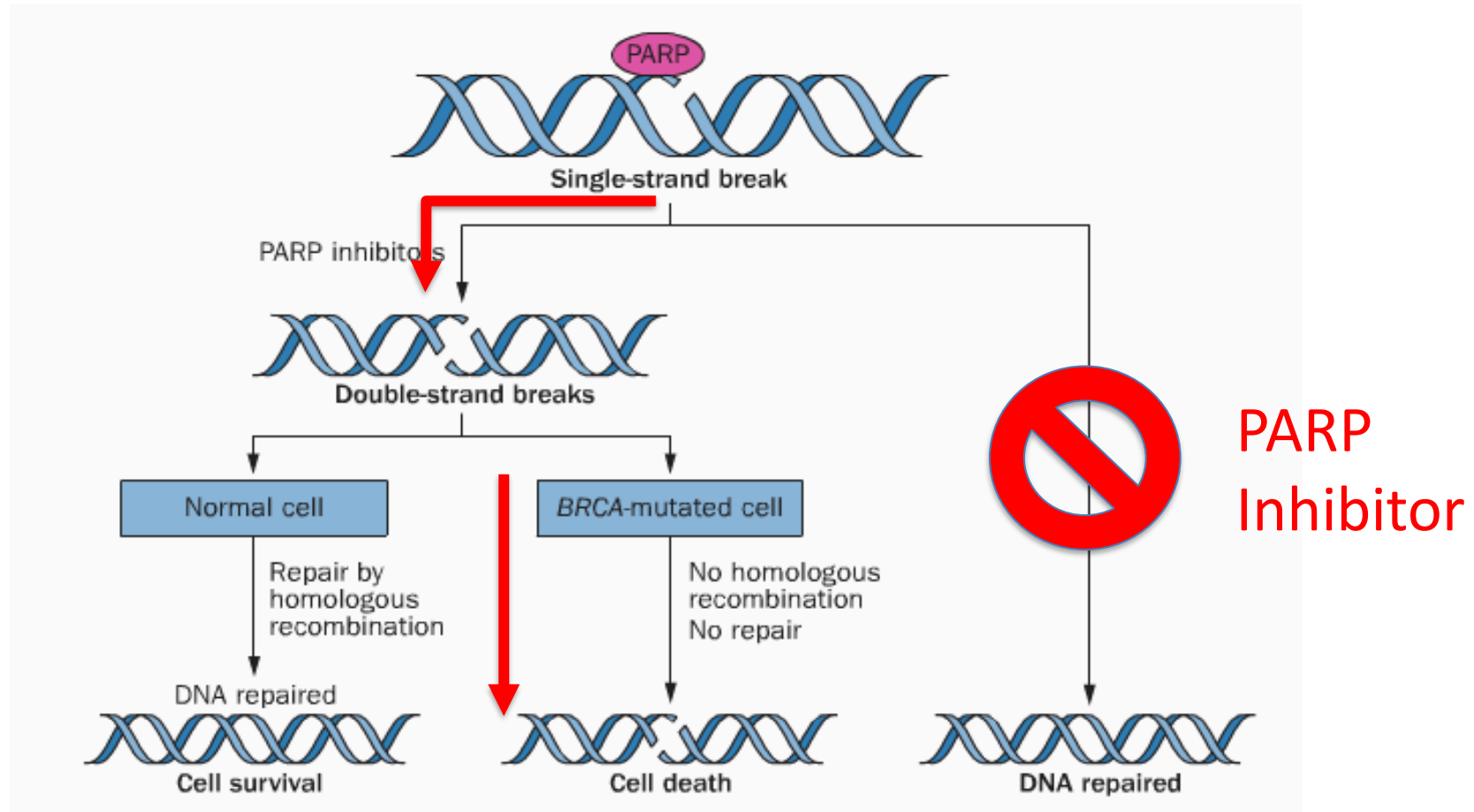
Offer pembrolizumab to patients with mismatch repair deficient or microsatellite instability high CRPC

Synthetic Lethality – Leverage DNA Repair



Nat. Rev. Clin. Oncol. 2015, **12**, 27–41

Synthetic Lethality – Leverage DNA Repair



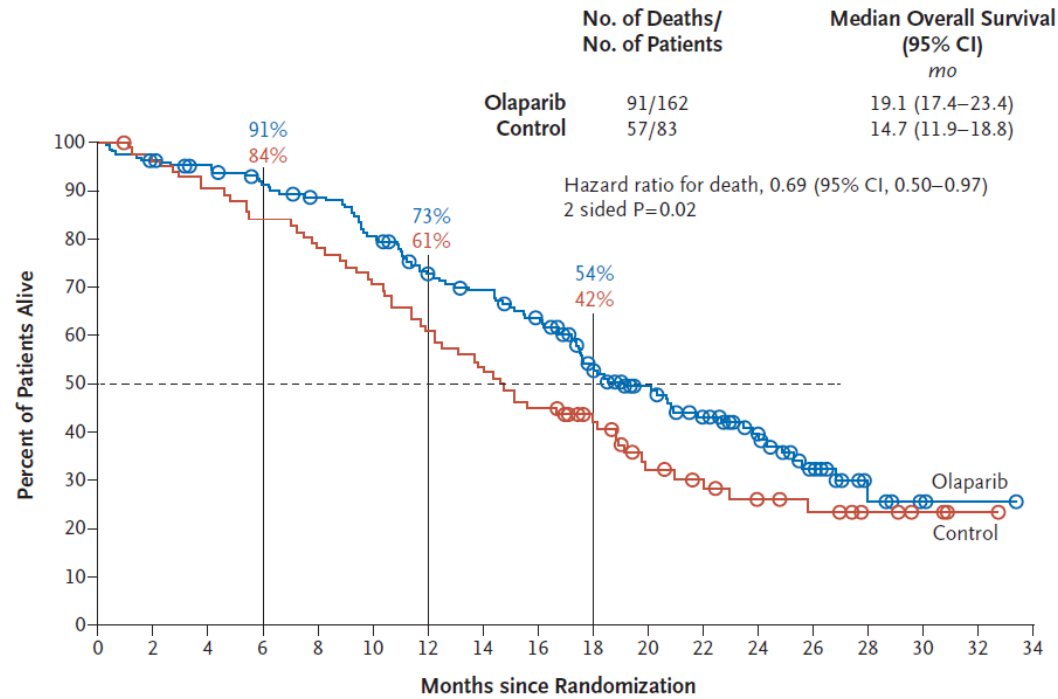
Nat. Rev. Clin. Oncol. 2015, **12**, 27–41

PROfound

- Phase 3 study evaluating OLAPARIB in mCRPC patients who progressed on prior enzalutamide or abiraterone
- Tumor sequenced for DNA repair defects
- Randomized 2:1
 - 387 patients, two cohorts:
 - A (256 pts)-1 alteration in BRCA1/2,ATM
 - -OS 19.1 vs 14.7 mos (sig)
 - B (131 pts)-1 alteration in 12 other HRR genes
 - -OS 14.1 vs 11.5 mos (not sig)
 - 86 patients in control group crossed over on progression
 - *FDA approval May 19, 2020*

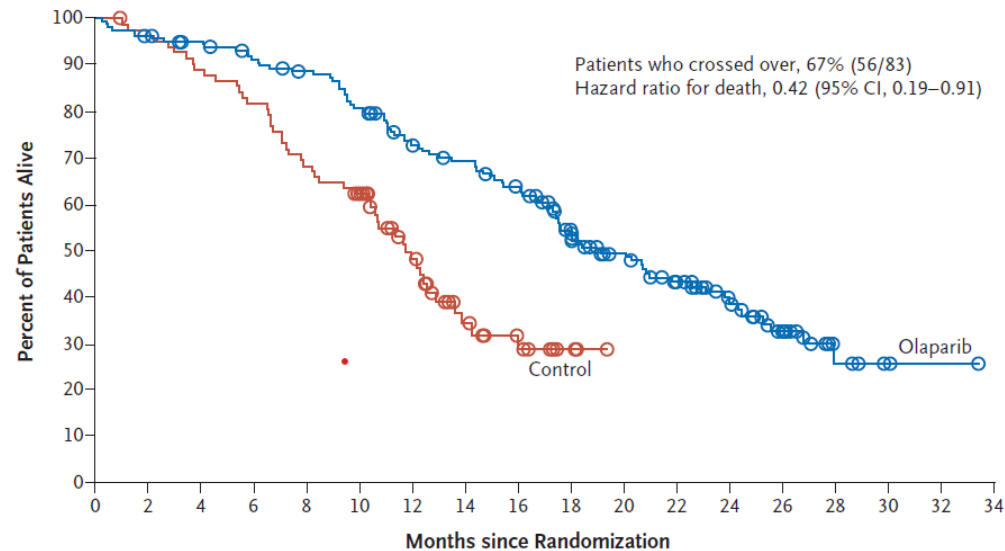
Hussain M et al. NEJM, 2020.

A Overall Survival in Cohort A



All Patients

B Crossover-Adjusted Analysis of Overall Survival in Cohort A



BRCA1/2, ATM

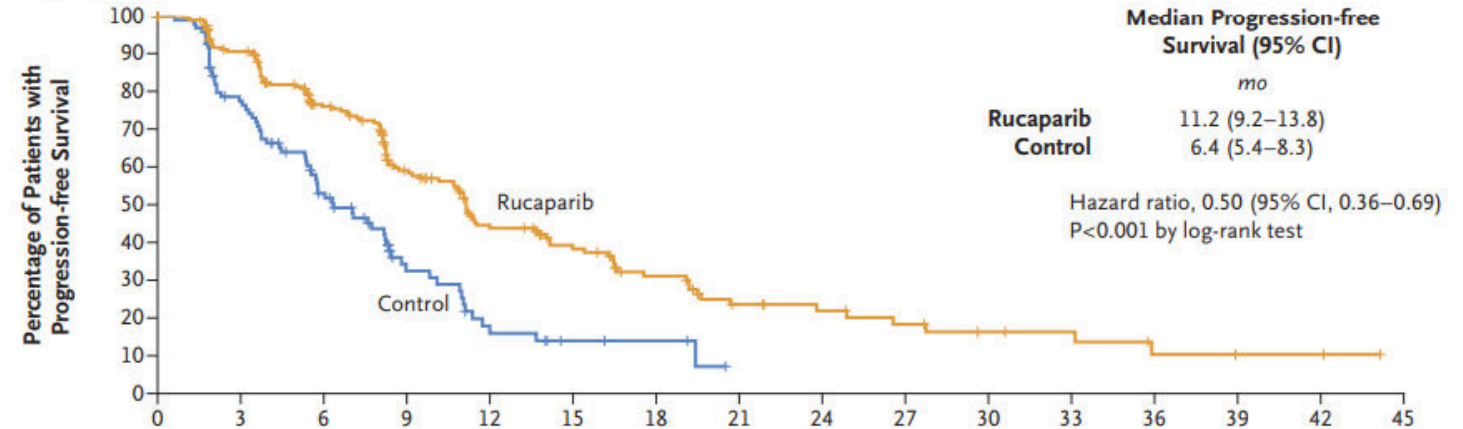
Hussain M et al. NEJM, 2020.

TRITON3- Phase 3

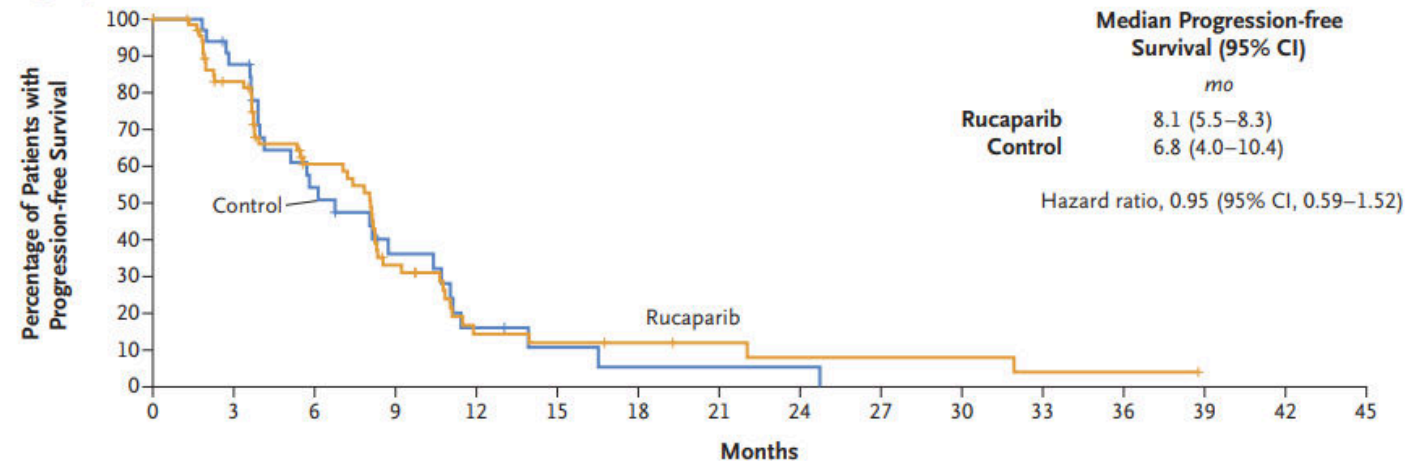
- Rucaparib in mCRPC patients who progressed on hormonal therapy and chemotherapy
- Germline or Tumor – BRCA1/2 or ATM
- 270 patients – Rucaparib
- 135 patients – Docetaxel or ARPi

Fizazi W et al. NEJM, 2023

A BRCA Subgroup



C ATM Subgroup



PARPi in Combination

MAGNITUDE:

CRPC - Abiraterone Versus Abiraterone Plus Niraparib

Key Eligibility Criteria

- L1 mCRPC
 - ≤4 months prior abiraterone allowed for mCRPC
- ECOG PS 0 or 1
- BPI-SF worst pain score ≤3

Stratification Factors

- Prior taxane-based chemo for mHSPC
- Prior ARi for nmCRPC
- Prior abiraterone for L1 mCRPC
- HRR BM+ cohort only
 - *BRCA1/2* vs other HRR gene alterations

Prescreening for Biomarker Status

HRR BM+ Panel
ATM
BRCA1
BRCA2
BRIP1
CDK12
CHEK2
FANCA
HDAC2
PALB2

Allocation to Cohort

HRR BM+
Planned n = 400

1:1
R

Niraparib + abiraterone

Placebo + abiraterone

HRR BM-
Planned n = 600

1:1
R

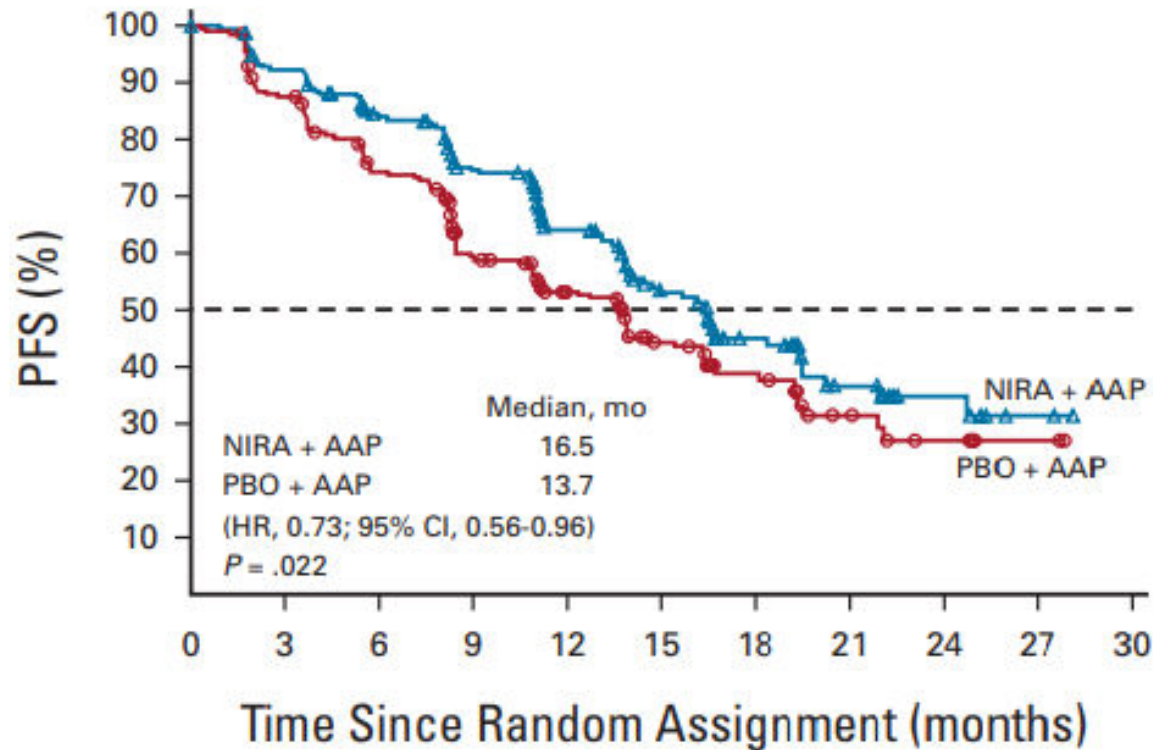
Niraparib + abiraterone

Placebo + abiraterone

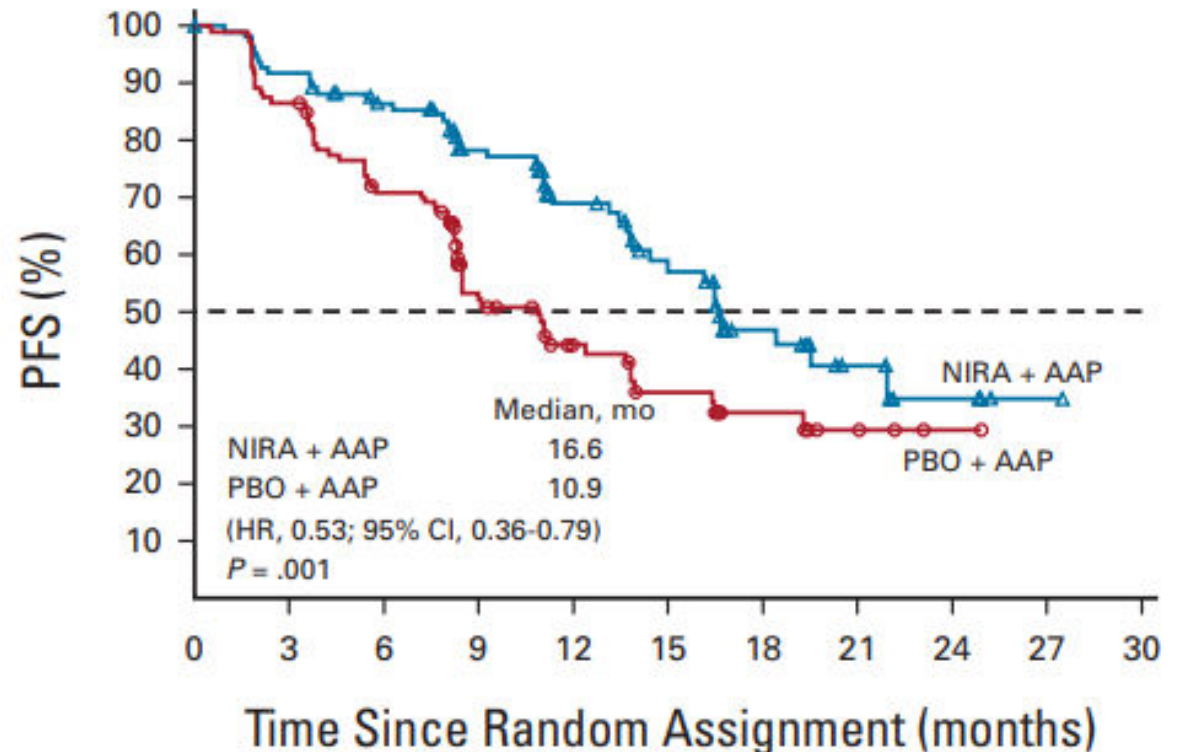
- **Primary endpoint**
 - rPFS by central review
- **Secondary endpoints**
 - Time to cytotoxicity chemotherapy
 - Time to symptomatic progression
 - OS

MAGNITUDE - Progression

rPFS in HRR+ cohort (central review)



rPFS in *BRCA1/2* subgroup (central review)



Chi KN, et al. *J Clin Oncol*. 2023;41:3339-3351

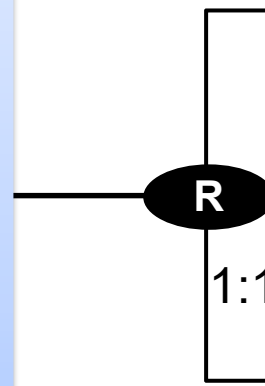
PROpel: Abiraterone Versus Abiraterone Plus Olaparib

Patient Population^a

- mCRPC
- Docetaxel allowed at mHSPC stage
- No prior abiraterone
- Other NHAs allowed if stopped ≥ 12 months prior to enrollment
- Ongoing ADT
- ECOG 0-1

Stratification Factors

- Site of distant metastases: bone only vs visceral vs other
- Prior taxane at mHSPC: yes vs no



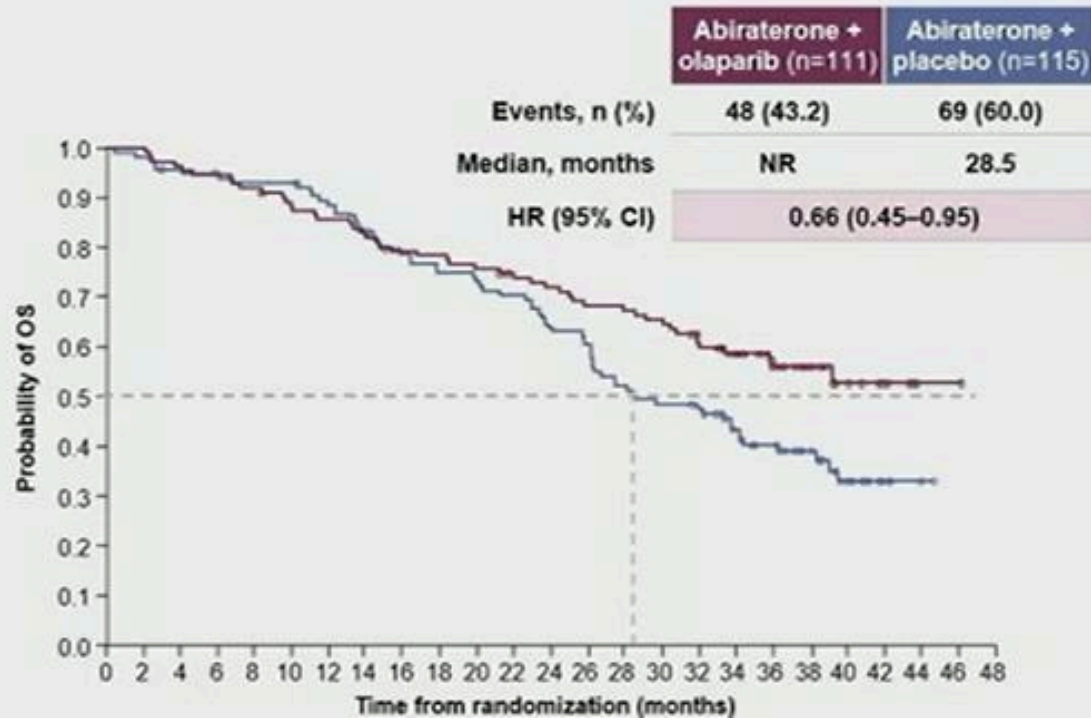
Olaparib 300 mg BID +
abiraterone 1,000 mg QD^b
n = 399

Placebo +
abiraterone 1,000 mg QD
n = 397

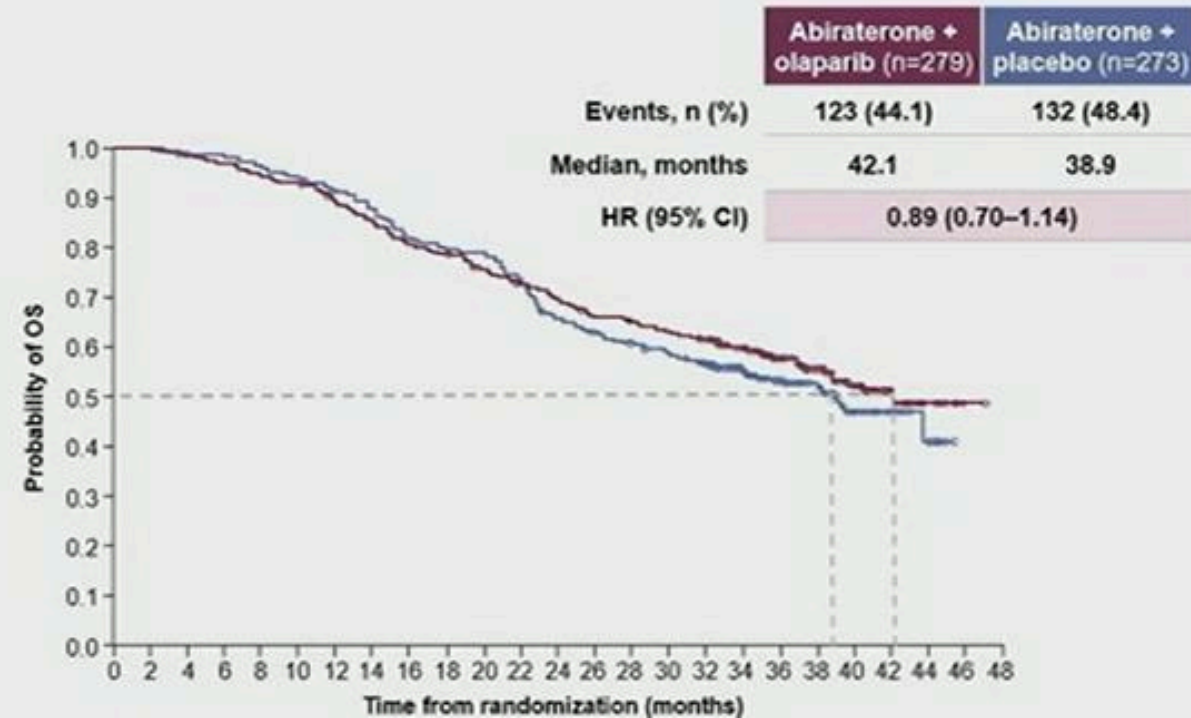
- **Primary endpoint:** rPFS
- **Secondary endpoint:** OS (alpha control)

PROpel: Abiraterone Versus Abiraterone Plus Olaparib

HRRm (28.4% of ITT population)

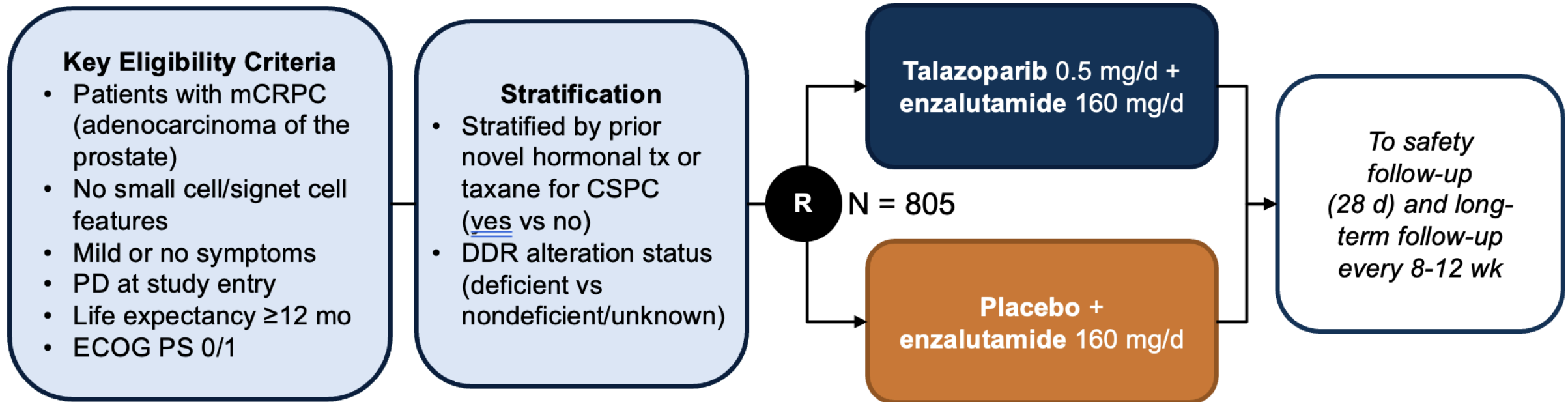


Non-HRRm (69.3% of ITT population)



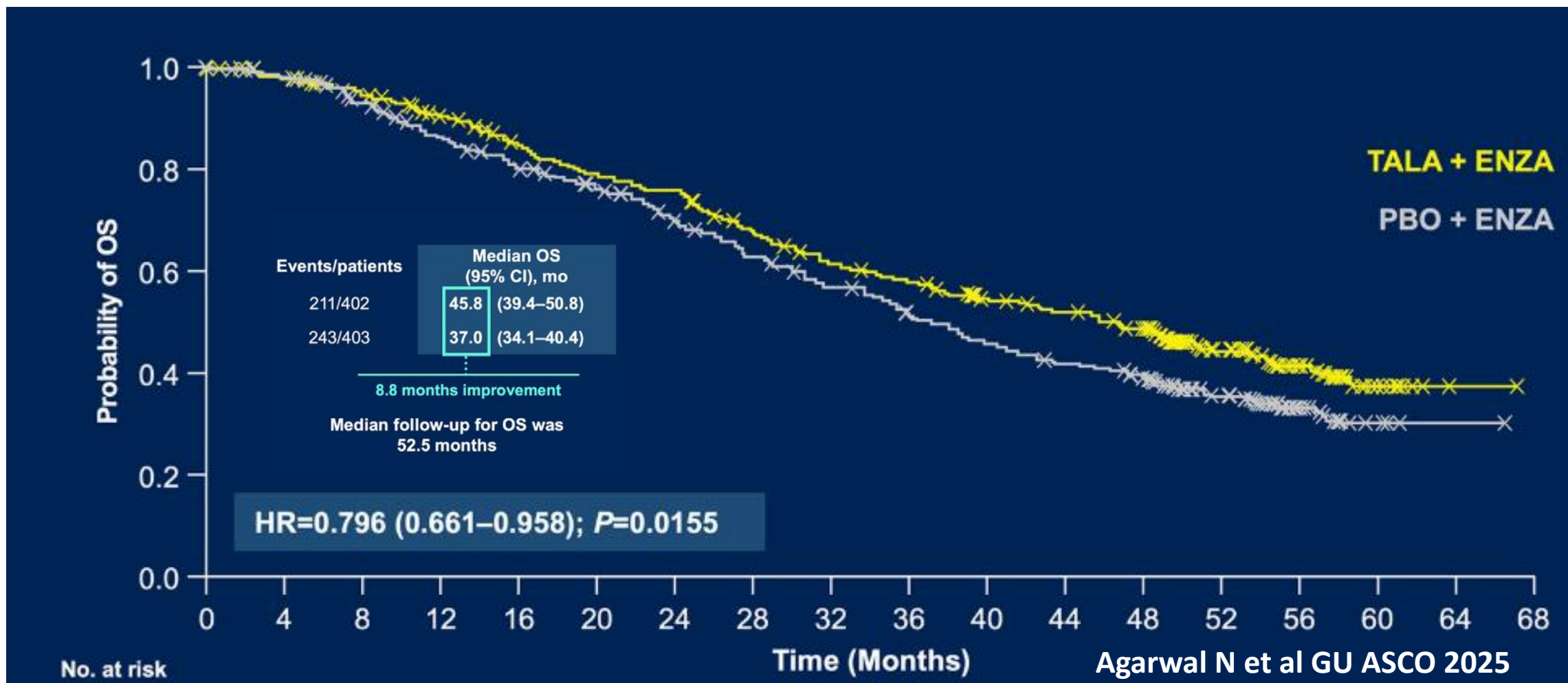
Saad F et al *Lancet Oncol* 2023;24:1094-1108

TALAPRO-2: First-line Talazoparib plus Enzalutamide in mCRPC



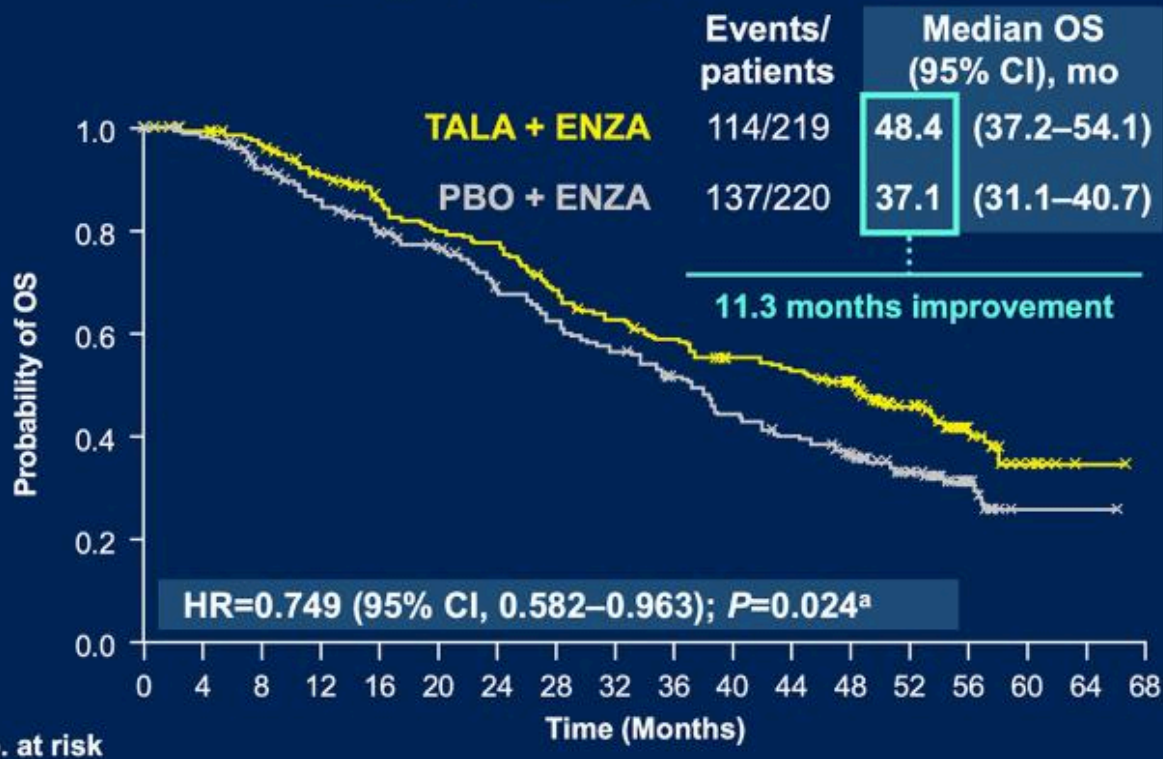
- **Primary endpoints:** rPFS per RECIST v1.1 for soft-tissue disease and per PCWG3 for bone disease in DDR-unselected and DDR-mutant populations
- **Key secondary endpoints:** OS, response, PSA, PFS2, TTNT, PK, HRQOL, safety

TALPRO-2 – PARP plus Enzalutamide

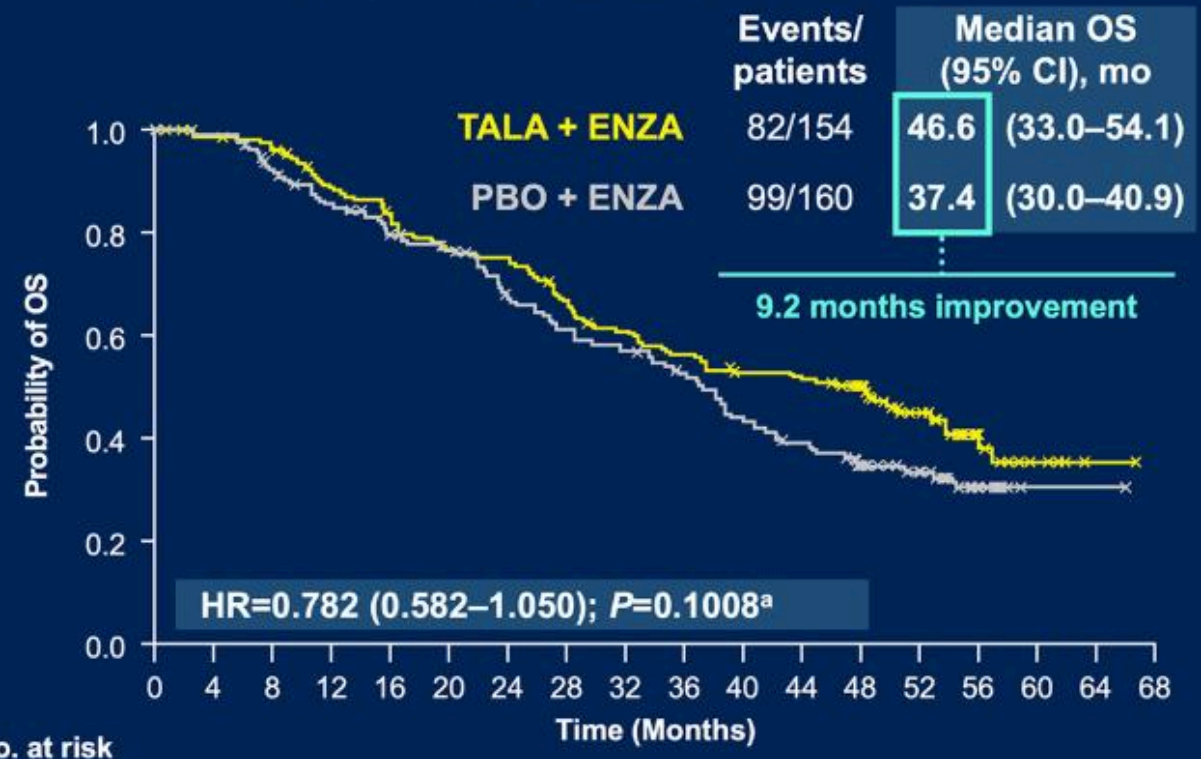


TALPRO-2 – PARP plus Enzalutamide

No *BRCA* alteration detected



No HRR alteration detected



Agarwal N et al GU ASCO 2025

PARP Inhibition

1. You need to sequence germline and tumor DNA on metastatic patients
2. HRR state matters for PARP monotherapy
 - BRCA1/2
 - Less clear for other HRR states
3. Drugs Matter – Not all are the same
4. Combination therapy will increasingly be used

METASTATIC CASTRATION RESISTANT PROSTATE CANCER

Prognosis

Clinicians SHOULD

Obtain baseline labs and review location of metastatic disease, disease-related symptoms, and performance status

Assess the extent of metastatic disease using conventional imaging at least annually or at intervals determined by lack of response to therapy

Offer germline and somatic tumor genetic testing

Treatment

Clinicians SHOULD

Offer continued ADT with abiraterone acetate plus prednisone, docetaxel, or enzalutamide

Consider prior treatment in sequencing agents and recommend therapy with an alternative mechanism of action

Offer radium-223 to patients with symptoms from bony metastases from mCRPC and without known visceral disease or lymphadenopathy >3cm

Treatment (cont.)

Clinicians SHOULD (cont.)

Recommend cabazitaxel rather than an alternative androgen pathway directed therapy in patients who received prior docetaxel and abiraterone acetate plus prednisone or enzalutamide

Offer a PARP inhibitor to patients with deleterious or suspected deleterious germline or somatic HRR gene-mutated mCRPC following prior treatment with enzalutamide or abiraterone, and/or a taxane-based chemotherapy

Offer pembrolizumab to patients with mismatch repair deficient or microsatellite instability high CRPC

Clinicians MAY

Offer sipuleucel-T to asymptomatic/minimally symptomatic patients

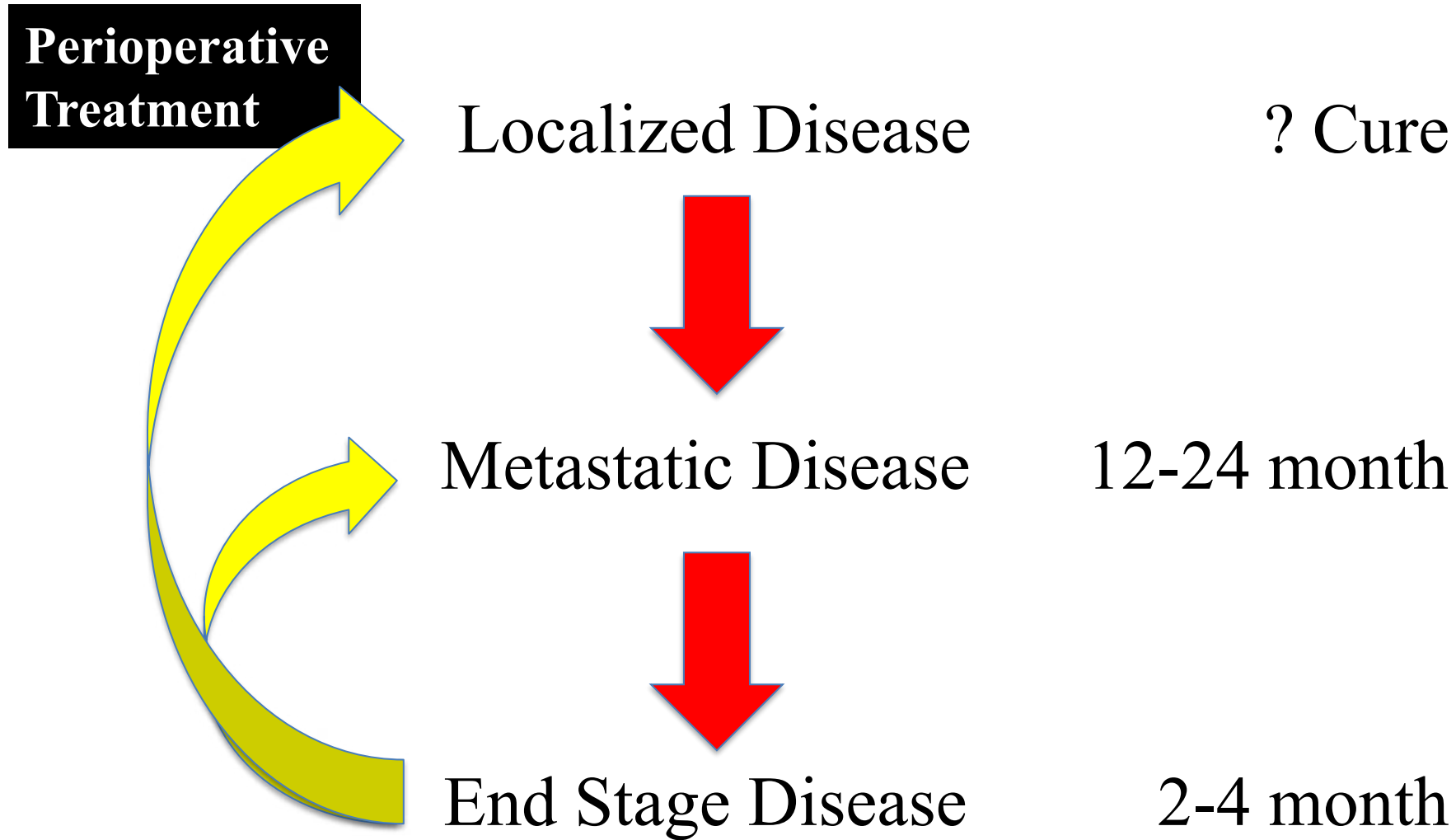
Offer cabazitaxel to patients who received prior docetaxel with or without prior abiraterone acetate plus prednisone or enzalutamide

Offer platinum-based chemotherapy to patients with deleterious or suspected deleterious germline or somatic HRR gene-mutated mCRPC following prior treatment with enzalutamide or abiraterone acetate, and/or a taxane-based chemotherapy who cannot use/obtain a PARP inhibitor

Offer a PARP inhibitor to patients with deleterious or suspected deleterious germline or somatic HRR gene-mutated mCRPC following prior treatment with enzalutamide or abiraterone, and/or a taxane-based chemotherapy

Integrate Systemic Treatment with Surgery

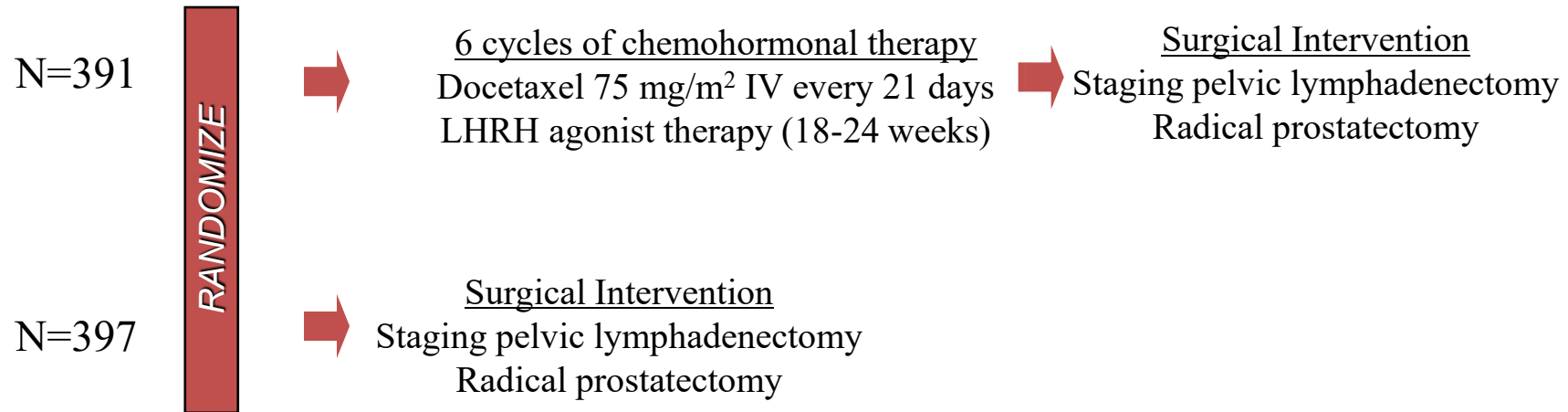
Integrate Systemic Treatment with Surgery



Systemic Therapy

	Response Metastatic	Survival Metastatic	Survival Neoajuvant
Breast	40-70%	17-24 mos	+
Colo-rectal	20-40%	12-21mos	+
Lung	17-32%	8-11 mos	+
Prostate	45-82%	15-19 mos	unknown

CALGB 90203 (Alliance): Neo-adjuvant chemohormonal therapy prior to RP in CLHRPC

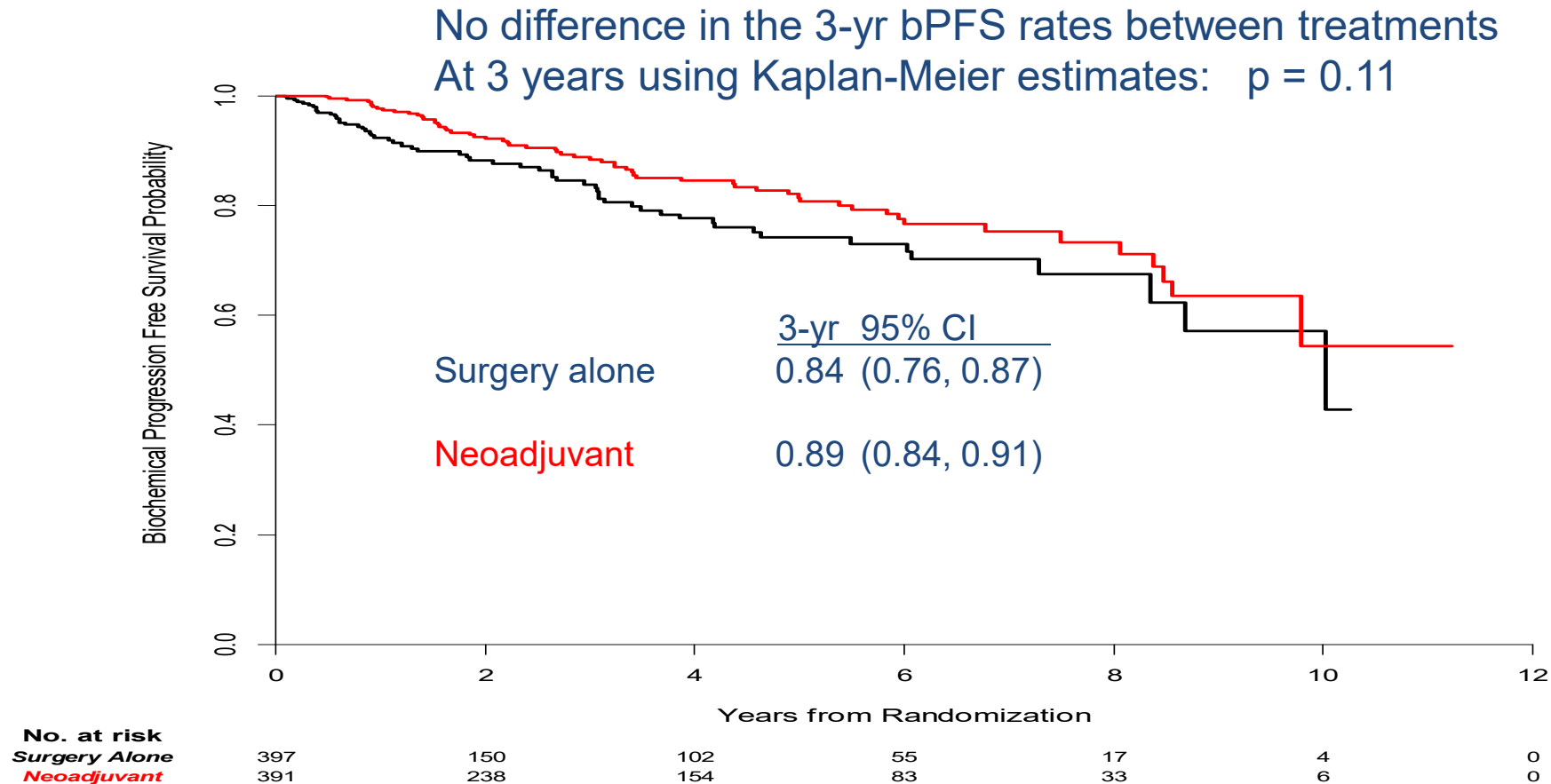


Stratification factors

- Nomogram predictions bPFS at 5-years or Gleason score 8-10
 - Pre-randomization ADT (up to 4 months permitted)

Adjuvant radiation therapy permitted within 6 months of RP

Biochemical Progression-Free Survival

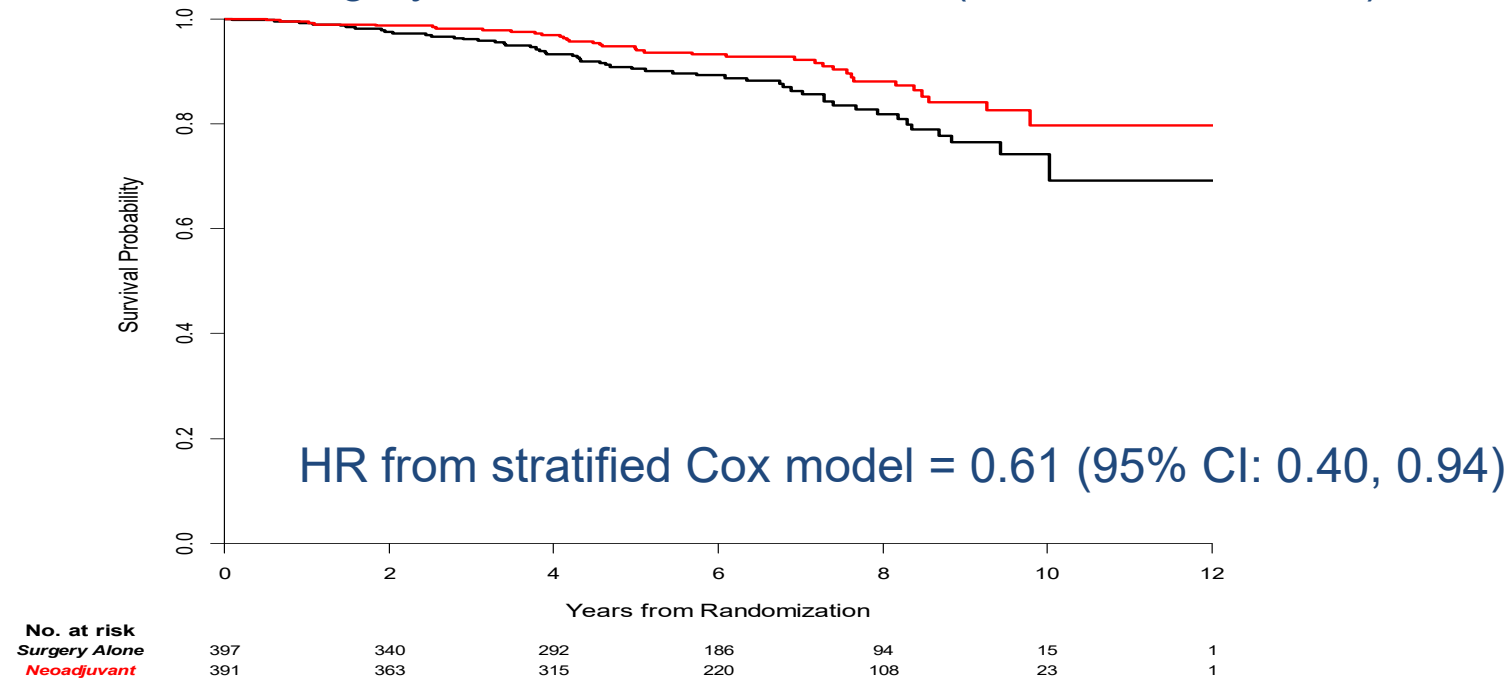


Eastham et al, JCO, 38:3042, 2020

Overall Survival

At 10 years, the survival probabilities were:

- **Neoadjuvant arm:** 0.80 (95% CI, 0.72, 0.88)
- **Surgery alone arm:** 0.74 (95% CI, 0.67, 0.83)

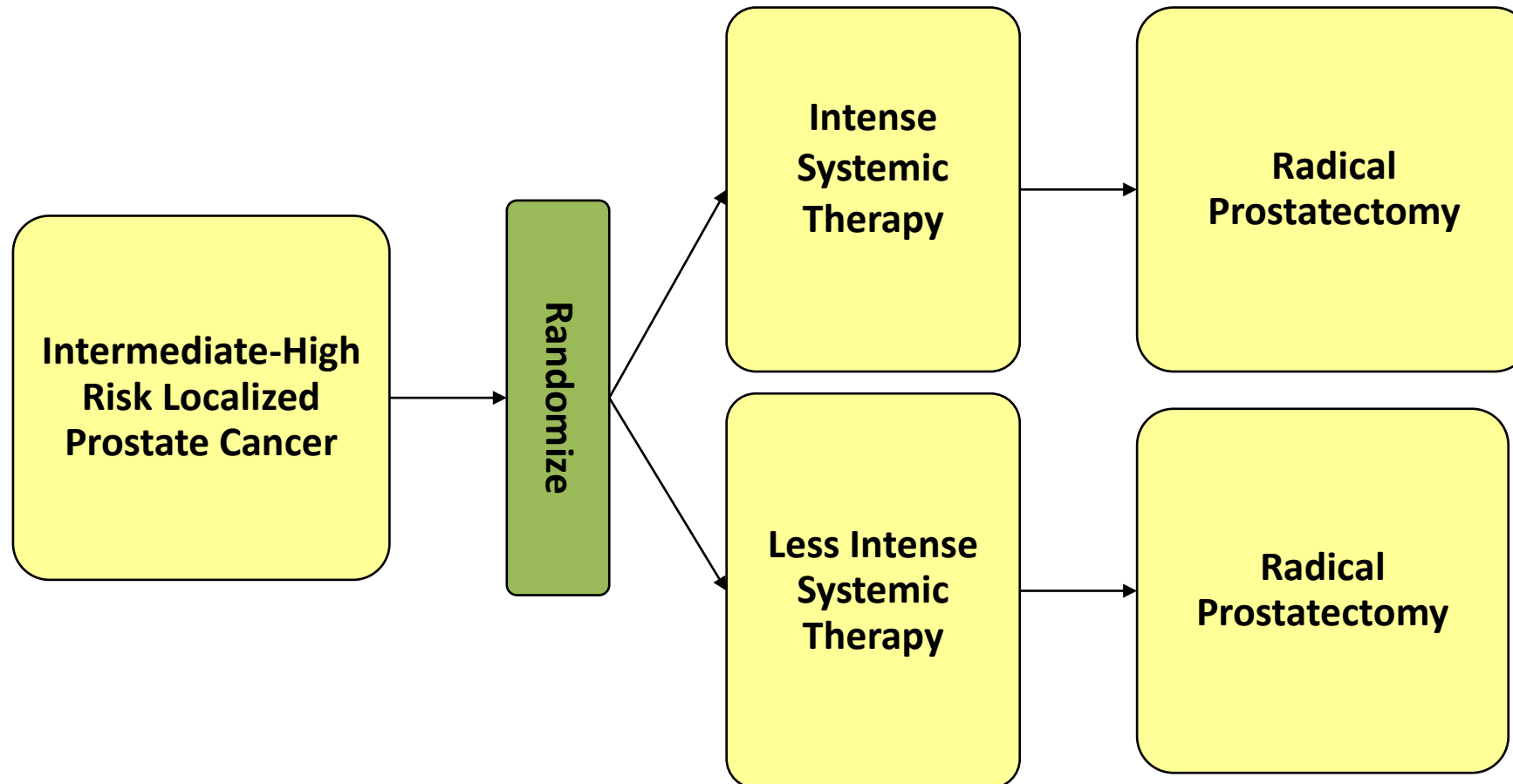


Eastham et al, JCO, 38:3042, 2020

Neoadjuvant Docetaxel

- Primary Endpoint – not statistically significant.
- Toxic Therapy
 - 26% had a grade 3 toxicity
 - 19% had a grade 4 toxicity

Multimodality Paradigm for ADT – 5 Trials



Multimodality Paradigm for ADT

Objectives: 1) To assess tissue response to biomarkers

Intratumoral hormones lower with more intense therapy

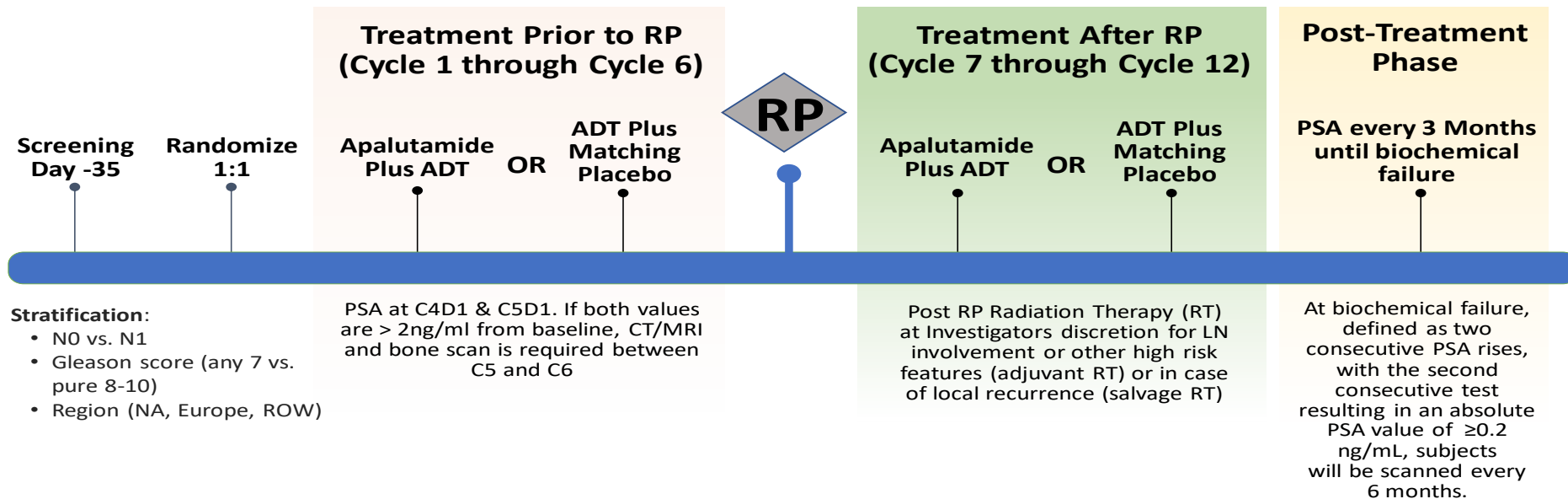
2) To assess the pCR & minimal residual disease rate

Less cancer in the Specimen with more intense therapy

3) Decrease Recurrence Rate

? Better with more intense therapy

Phase III - Study Schema



Endpoint: pCR
MFS

PI: Mary Ellen Taplin and Adam Kibel

Conclusions

- SipT was the only FDA approved immunotherapy
- CAR-T and BiTes are the future.
- Pembro for tumors with MMR defects ONLY
- PARPi for tumors with DNA repair defects (BRCA)
- Future is bright
 - New Targets
 - Earlier Treatment