Understanding the Current Paradigm and New Approaches in the Care of Patients with Cancer

A Complimentary NCPD Hybrid Symposium Series Held During the 50th Annual ONS Congress

Prostate Cancer

Thursday, April 10, 2025

12:15 PM – 1:45 PM

Faculty

Rahul Aggarwal, MD
Monica Averia, MSN, AOCNP, NP-C
Kathleen D Burns, RN, MSN, AGACNP-BC, OCN
William K Oh, MD

Moderator

Neil Love, MD

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Faculty

Monica Averia, MSN, AOCNP, NP-C
Oncology Nurse Practitioner
Clinical Instructor of Medicine
USC Norris Cancer Center
Los Angeles, California

Rahul Aggarwal, MD
Professor of Medicine and Thomas Perkins
Distinguished Professor of Cancer Research
Director, Genitourinary Medical Oncology
University of California, San Francisco
Department of Medicine
Division of Hematology/Oncology
Associate Director for Clinical Research
UCSF Helen Diller Family Comprehensive Cancer Center
San Francisco, California

Kathleen D Burns, RN, MSN, AGACNP-BC, OCN
Genitourinary Medical Oncology
City of Hope Comprehensive Cancer Center
Duarte, California

William K Oh, MD
Director of Precision Medicine
Yale Cancer Center
Professor of Medicine
Division of Medical Oncology
Yale School of Medicine
Medical Director, Service Line
Smilow Cancer Hospital at Greenwich Hospital
New Haven, Connecticut

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Dr Aggarwal — Disclosures

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Consulting Agreements	AbbVie Inc, AstraZeneca Pharmaceuticals LP, FibroGen Inc, Flare Therapeutics, Johnson & Johnson Pharmaceuticals, Merck, ORIC Pharmaceuticals, Pfizer Inc, Xencor
Contracted Research	Amgen Inc, AstraZeneca Pharmaceuticals LP, Johnson & Johnson Pharmaceuticals, Merck
Nonrelevant Financial Relationships	Prostate Cancer Clinical Trials Consortium

Ms Averia — Disclosures

No relevant conflicts of interest to disclose.

Ms Burns — Disclosures

Advisory Committees	Eisai Inc, Janssen Biotech Inc, Sumitomo Dainippon Pharma Oncology Inc
Speakers Bureaus	AstraZeneca Pharmaceuticals LP, Exelixis Inc, Pfizer Inc, Sumitomo Dainippon Pharma Oncology Inc

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Dr Oh — Disclosures

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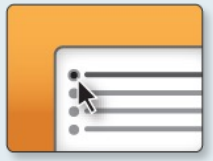
Clinicians in the Meeting Room

Networked iPads are available.

Review Program Slides: Tap the Program Slides button to review speaker presentations and other program content.



Answer Survey Questions: Complete the pre- and postmeeting surveys. Survey questions will be discussed throughout the meeting.

Ask a Question: Tap Ask a Question to submit a challenging case or question for discussion. We will aim to address as many questions as possible during the program.

For assistance, please raise your hand. Devices will be collected at the conclusion of the activity.

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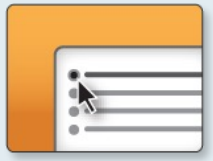
Clinicians Attending via Zoom

Review Program Slides: A link to the program slides will be posted in the chat room at the start of the program.



Answer Survey Questions: Complete the pre- and postmeeting surveys. Survey questions will be discussed throughout the meeting.

Ask a Question: Submit a challenging case or question for discussion using the Zoom chat room.

Get NCPD Credit: An NCPD credit link will be provided in the chat room at the conclusion of the program.

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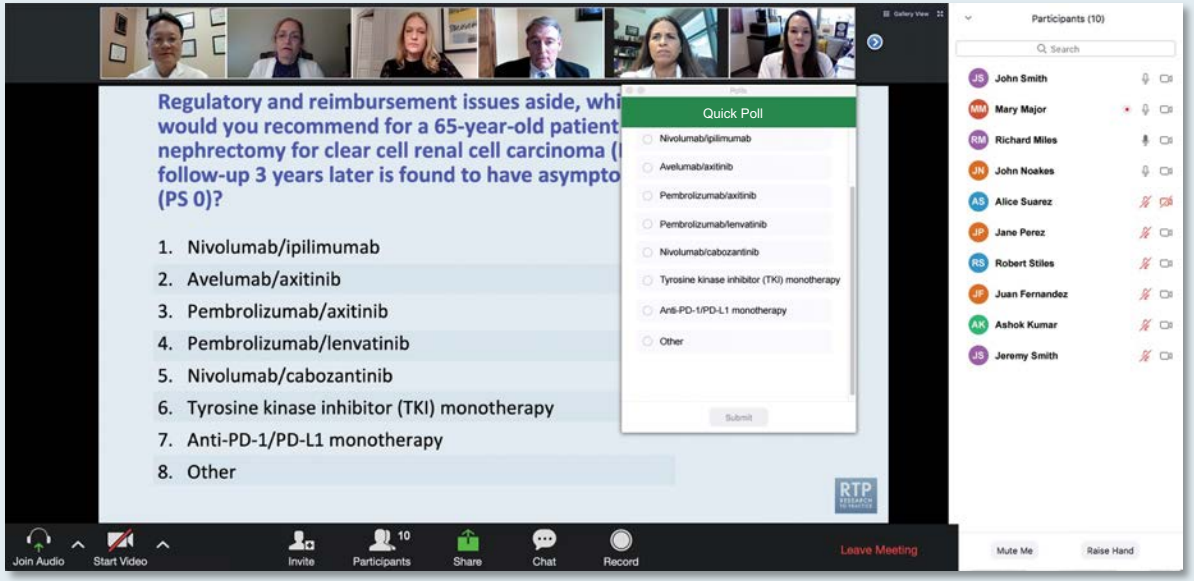
Clinicians, Please Complete the Pre- and Postmeeting Surveys



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About the Enduring Program

- The live meeting is being video and audio recorded.
- The proceedings from today will be edited and developed into an enduring web-based program. An email will be sent to all attendees when the activity is available.
- To learn more about our education programs, visit our website, **www.ResearchToPractice.com**

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ONCOLOGY NURSING UPDATE WITH DR NEIL LOVE

Bispecific Antibodies in Lymphoma Part 1 — An Interview with Ms Robin Klebig for Oncology Nurses

MS ROBIN KLEBIG
MAYO CLINIC

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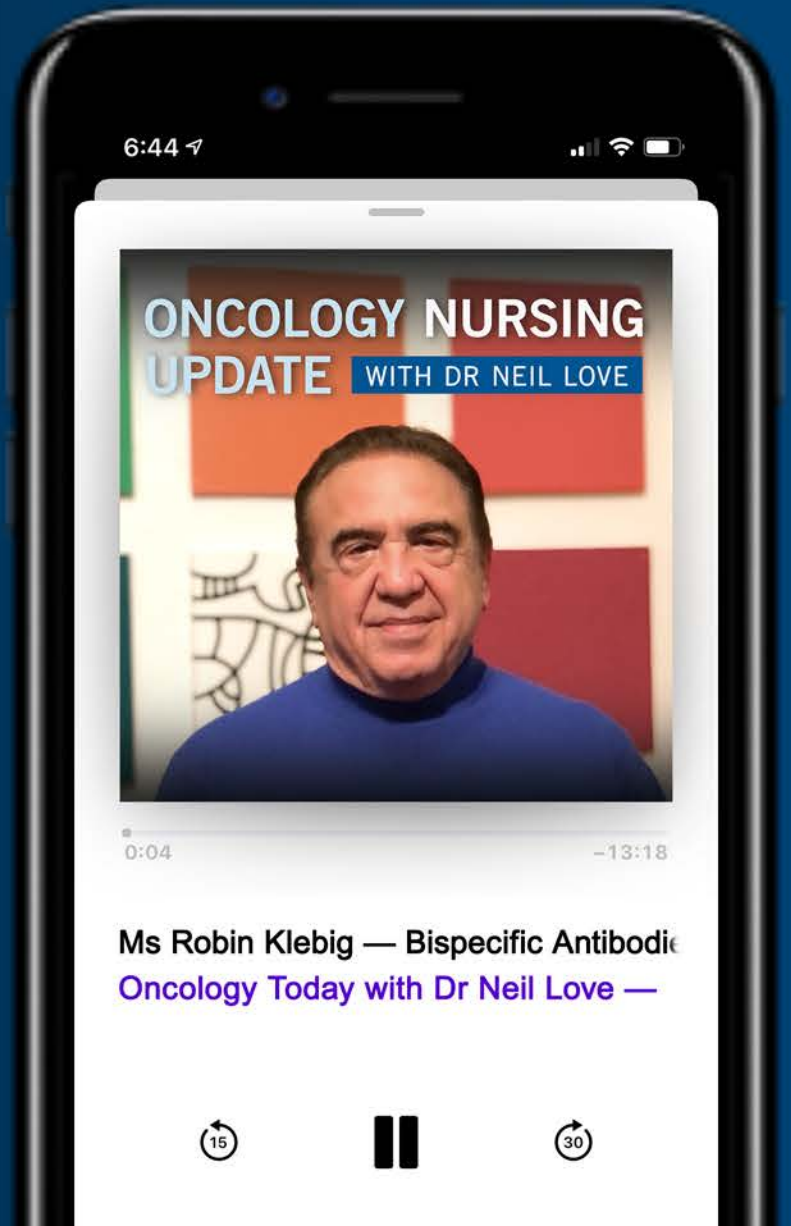
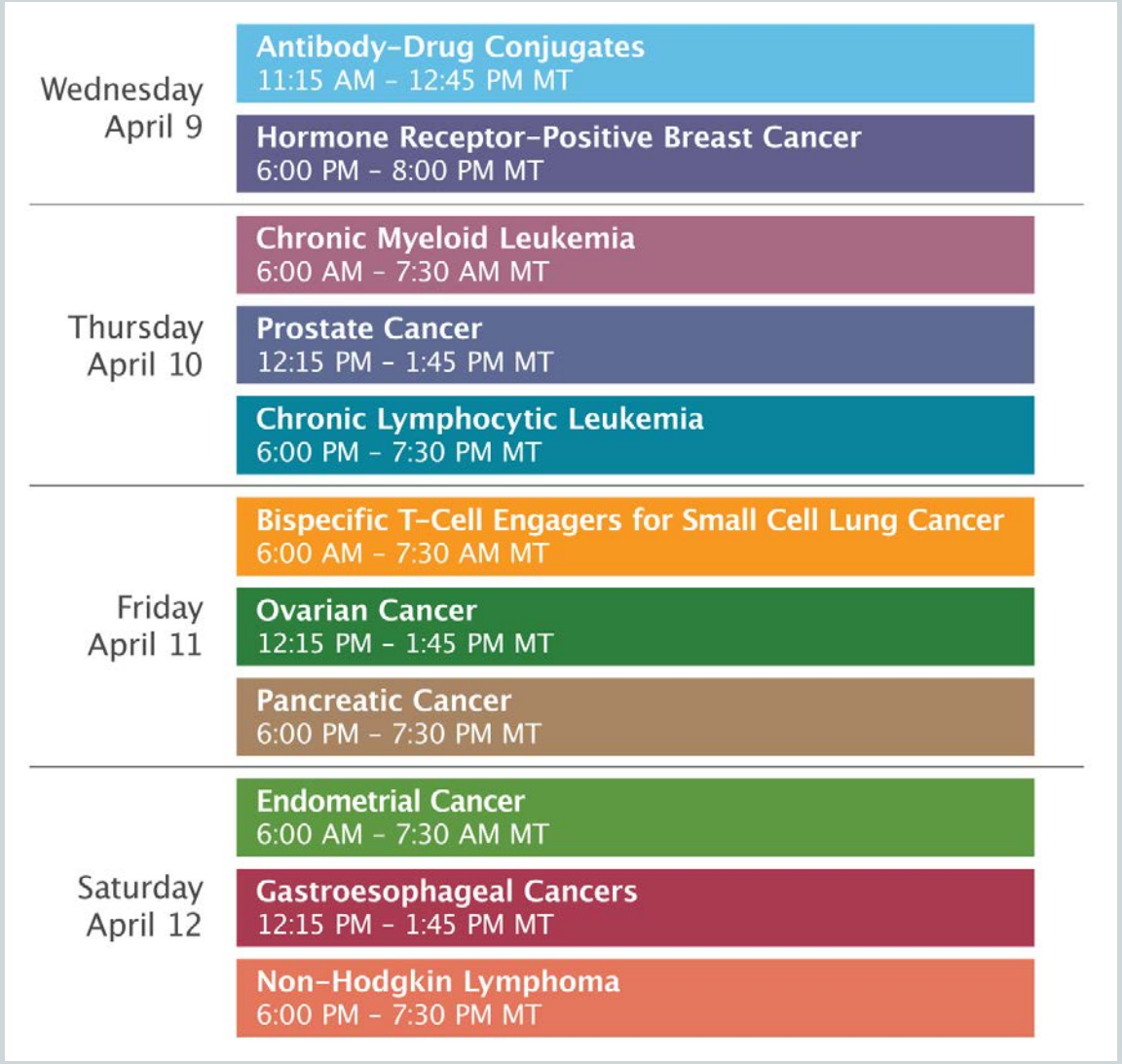


“Understanding the Current Paradigm and New Approaches”
Seventeenth Annual RTP-ONS NCPD Symposium Series



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Understanding the Current Paradigm and New Approaches
RTP Faculty at ONS 2025

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Agenda

Introduction: Overview of Prostate Cancer

Module 1: Recent Advances in the Treatment of Nonmetastatic Prostate Cancer

Module 2: Treatment Approaches for Metastatic Hormone-Sensitive Prostate Cancer

Module 3: Current Role of PARP Inhibitors in Metastatic Castration-Resistant Prostate Cancer (mCRPC)

Module 4: Current and Future Role of Radiopharmaceuticals in mCRPC

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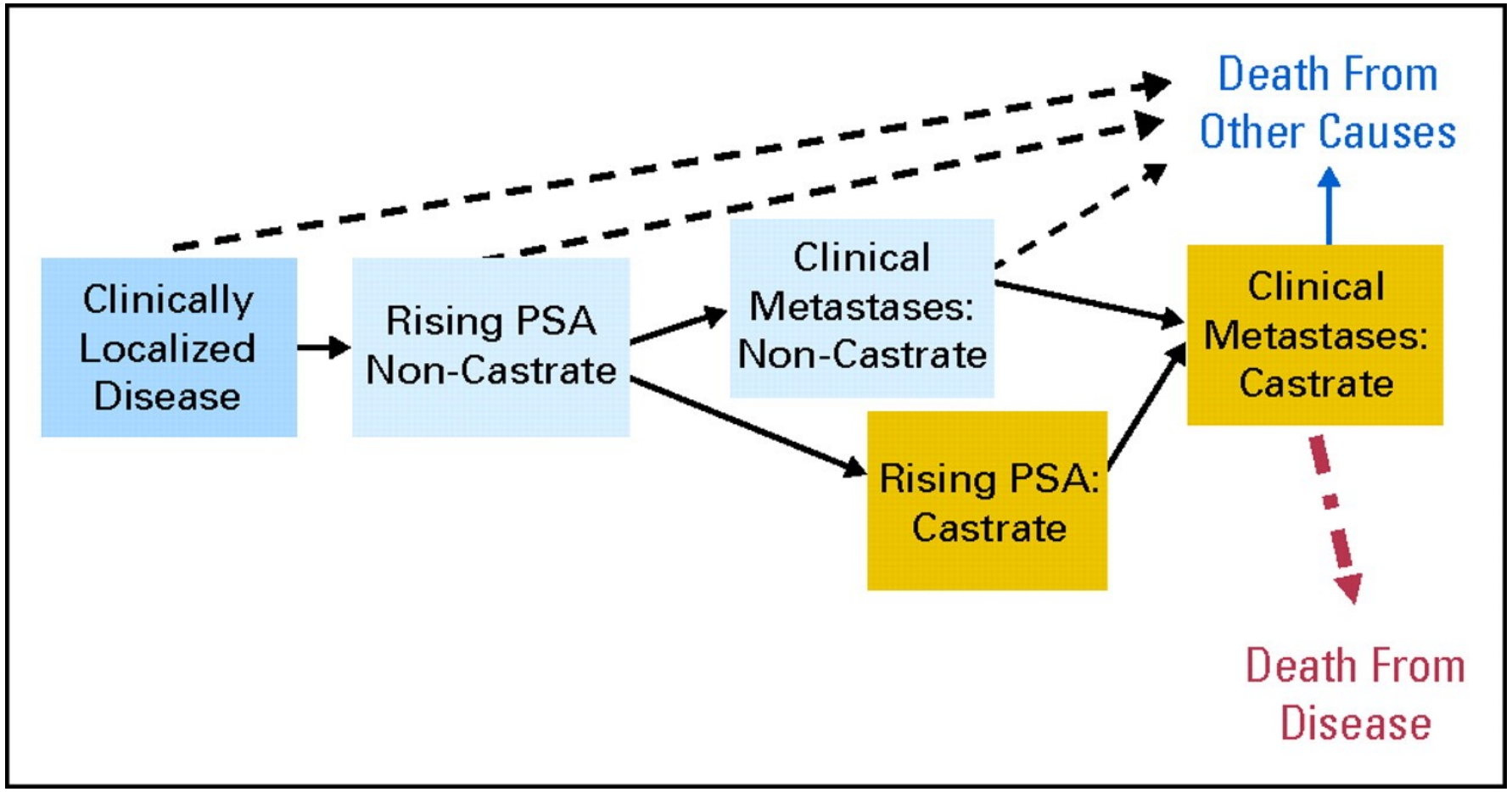
Clinical Disease States



Courtesy of Rahul Aggarwal, MD

Scher H, et al. J Clin Oncol 2008

Agenda

Introduction: Overview of Prostate Cancer

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Clinical Scenario

A patient with prostate cancer who has undergone prior local treatment now has a rising PSA and a rapid PSA doubling time but no evidence of metastatic disease and will be presented with the option of enzalutamide and androgen deprivation therapy or enzalutamide monotherapy

UCSF Helen Diller Family Comprehensive Cancer Center

Recent Advances in the Treatment of Nonmetastatic Prostate Cancer

Rahul Aggarwal, MD
Professor of Medicine
University of California San Francisco

A 67 year old male who presented to my clinic…

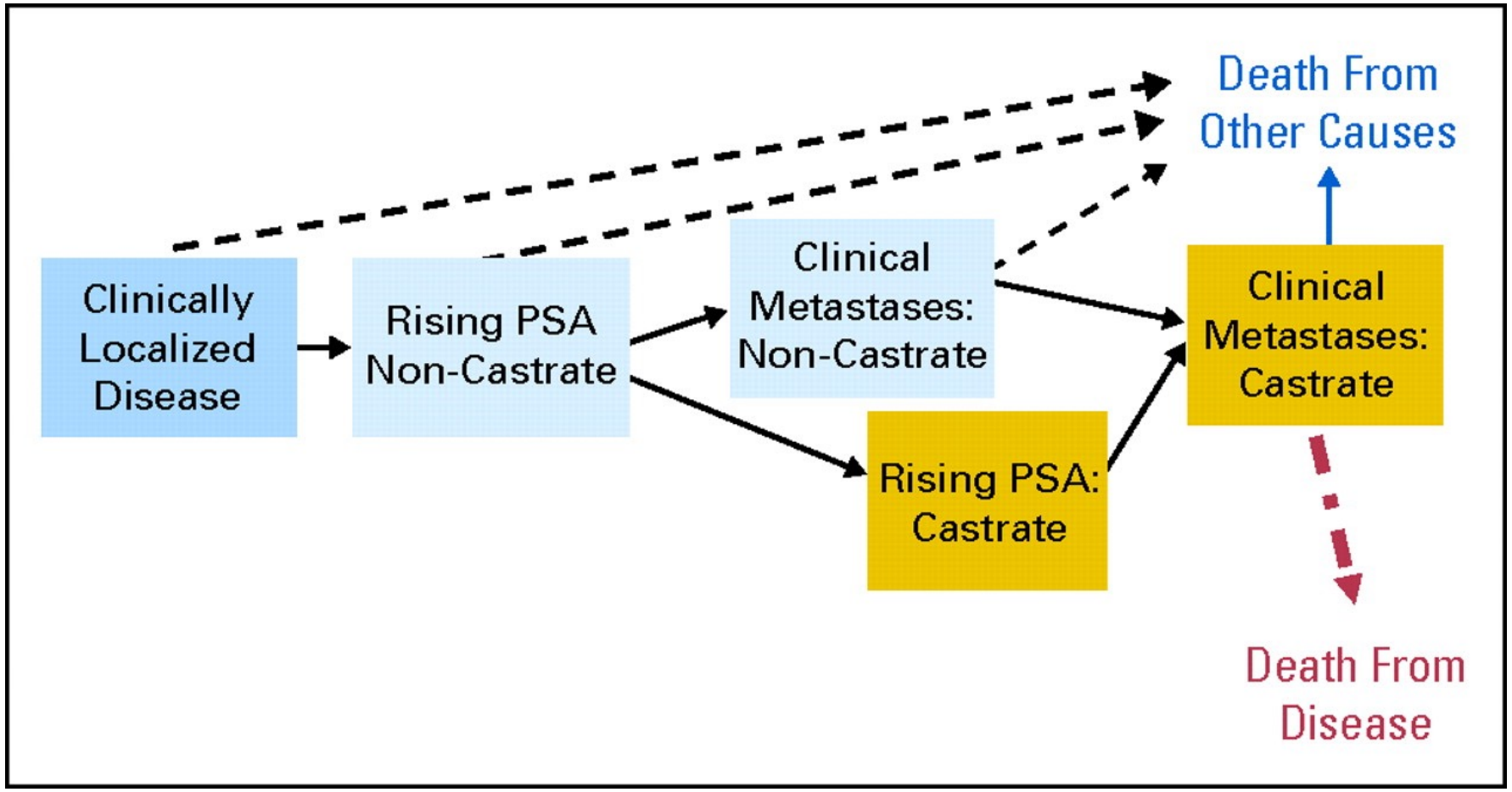
- Presented to PCP with obstructive urinary symptoms – dribbling, hesitancy, weak stream
- PSA was 24 ng/mL (no prior screening PSA measurements)
- TRUS biopsy with Gleason 4+4 prostate adenocarcinoma
- MRI of the prostate with PI-RADS 4 lesion in the right base with likely extraprostatic extension, normal appearing seminal vesicles (cT3a)
- PSMA PET without evidence of nodal or distant metastases

NCCN Risk Stratification and Staging

- Low risk (Gleason ≤ 6, PSA < 10, T1/T2, < 33% cores positive)
- Favorable intermediate risk (e.g. Gleason 3+4)
- Unfavorable intermediate risk (e.g. Gleason 4+3)
- High risk (any of Gleason ≥ 8, PSA > 20, T3/T4)
- Very high risk localized
- Node positive
- Metastatic (M1a, M1b, M1c)

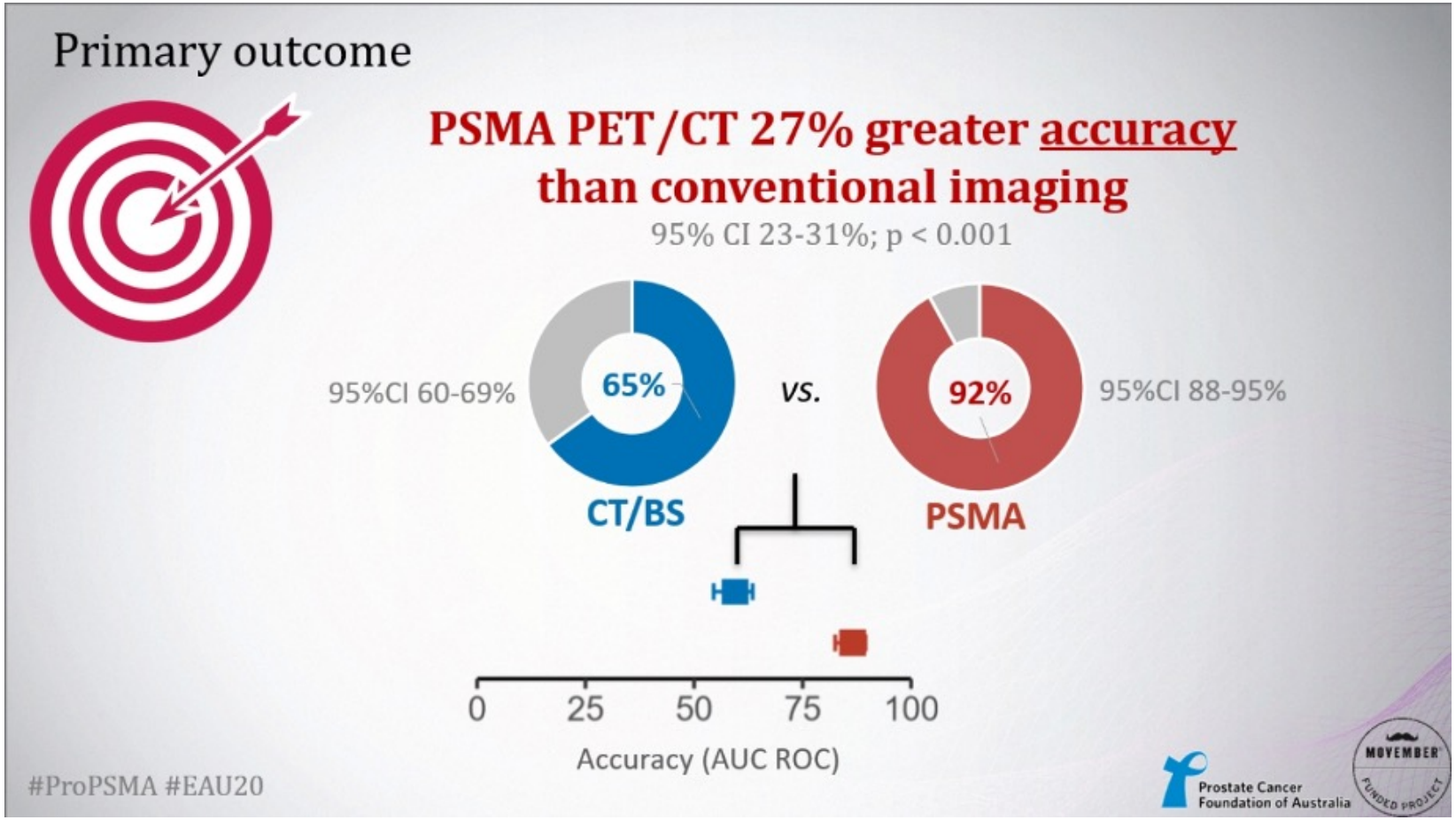
NCCN Guidelines version Jan 2025

Clinical Disease States



Scher H, et al. J Clin Oncol 2008

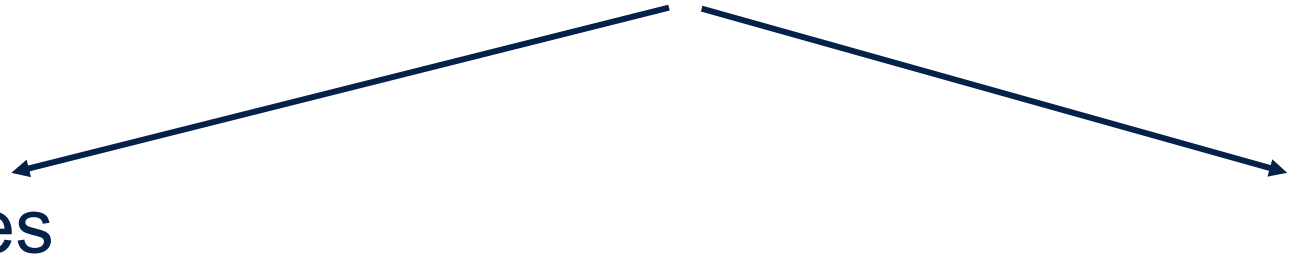
PSMA PET for Initial Staging of High Risk Prostate Cancer



Hofman M, et al. EAU 2020

Primary Therapy Options for Patients with Newly Diagnosed Localized Prostate Cancer

Is the patient appropriate for active surveillance?



Yes

Low or favorable intermediate risk:

- Gleason group 1 or 2
- PSA < 10
- Low risk by genomic classifier

No

- Radical Prostatectomy
- Radiation +/- ADT
- Focal Tx

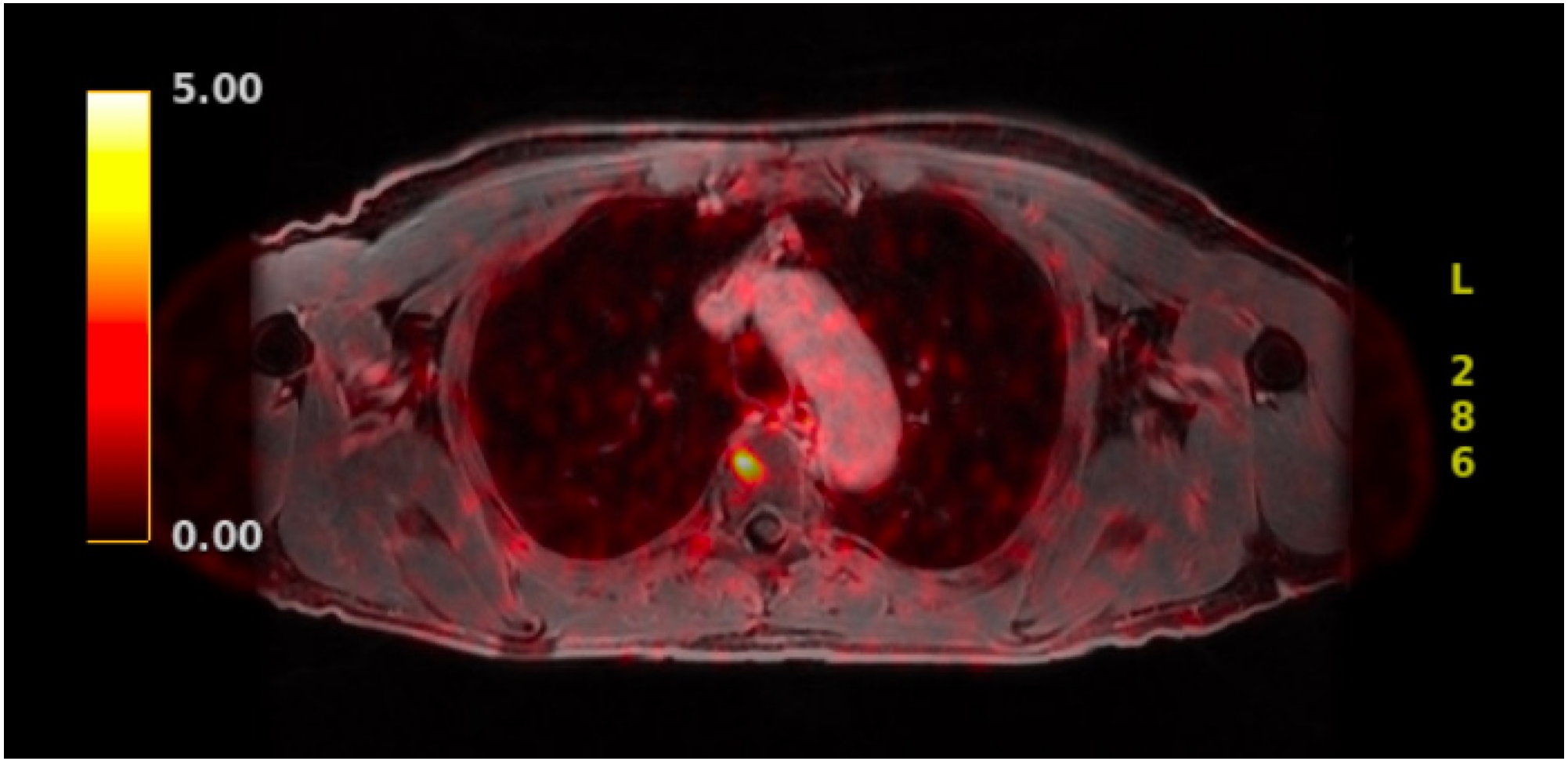
Back to our patient…

- Patient opted for radical prostatectomy + pelvic lymph node dissection
  - Pathology: Gleason 5+4 prostate adenocarcinoma, 0/13 nodes involved, + extracapsular extension, normal SV, negative margins (pT3aN0)
- PSA was undetectable at first check 8 weeks post-op
- 14 months later, PSA became detectable and rose from:
  - 0.03 → 0.12 → 0.56
  - PSA doubling time 2.4 months
- Repeat PSMA PET negative for local, regional, or distant recurrence
- Patient underwent salvage radiation to prostate bed + pelvis along with 6 months of androgen deprivation
  - Side effects: Urinary frequency/urgency, hot flashes, mild fatigue, erectile dysfunction, mild mood changes

Our patient's journey continued…

- PSA rapidly became undetectable with salvage radiation + 6 months of ADT
- Recovery of side effects was more variable
  - Persistent urinary frequency and urge incontinence
  - Intermittent hematuria → radiation cystitis on cystoscopy
- 2 years later…patient is now 71 years old, new co-morbidities of hypertension, CAD with stent placed 1 year prior
  - PSA started to rise again, up to 0.73 with PSA doubling time of 2.4 months
- PSMA PET with 3 new sites of metastasis (T5, L1, sternum)
- Patient underwent targeted radiation (SBRT) to the PET-avid sites of disease with a decline in PSA level

Our patient's journey continued…

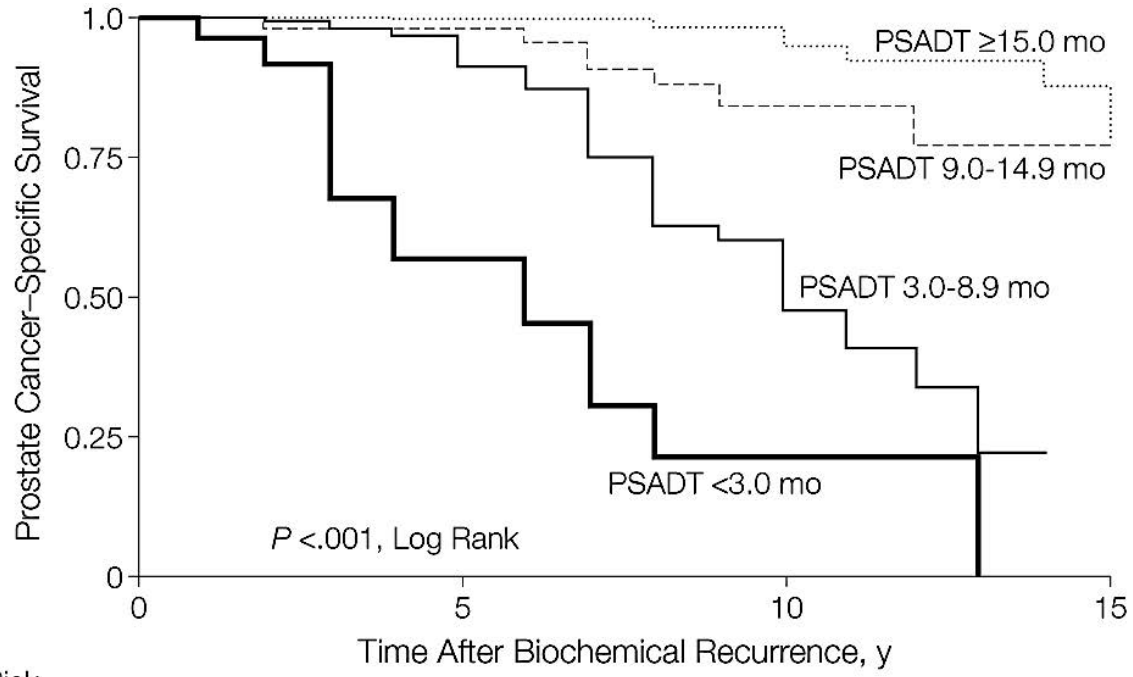


Back to our patient…

- PSA dropped to a nadir of 0.3 ng/mL with targeted radiation, with PSA response lasting for 11 months
- Subsequent rise as follows:
- 0.3 → 0.7 → 1.1, PSA doubling time of 3.1 months
- Repeat PSMA PET without new PET-avid foci amenable to targeted radiation
- What options to consider now?
  - Surveillance
  - ADT alone
  - ADT + oral androgen pathway inhibitor
  - Androgen pathway inhibitor alone

Chi K, et al. ASCO GU 2022

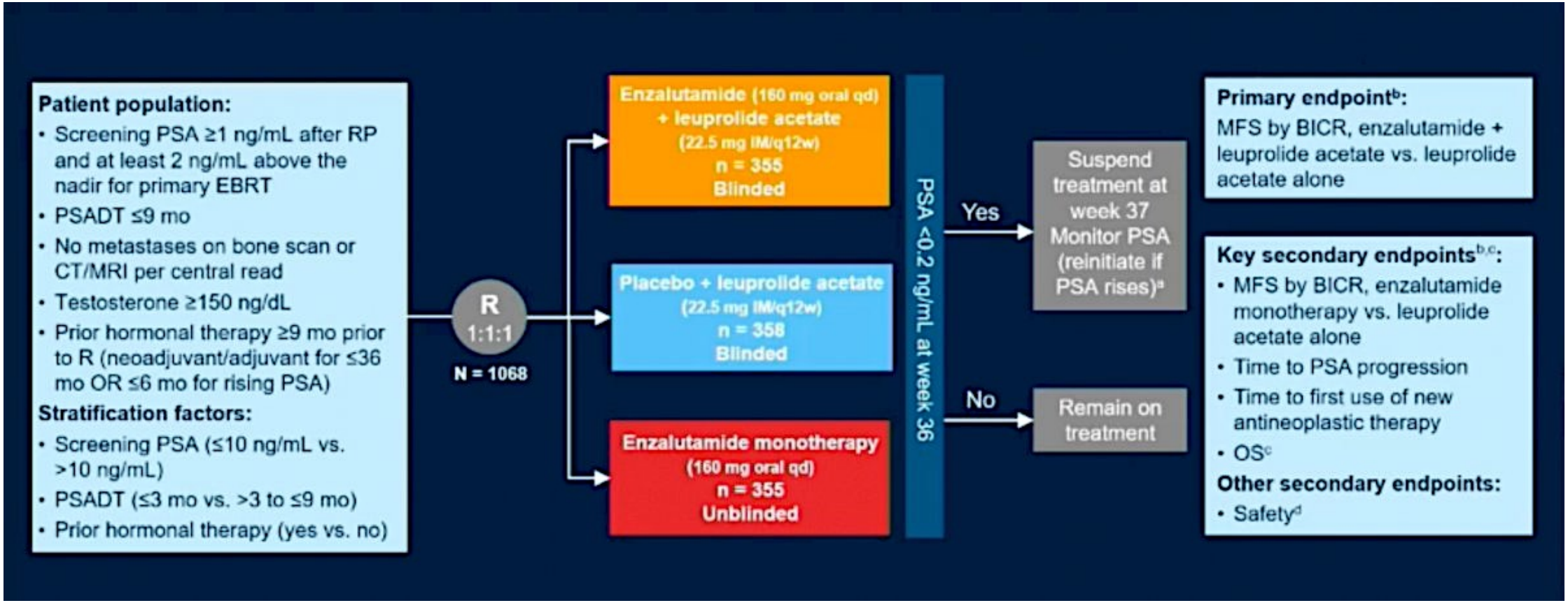
Patients with short PSA doubling time are at elevated risk of metastasis and prostate cancer related mortality



No. at Risk PSADT, mo				
<3.0	23	10	2	0
3.0-8.9	119	85	19	0
9.0-14.9	79	51	19	3
≤15	158	113	52	9

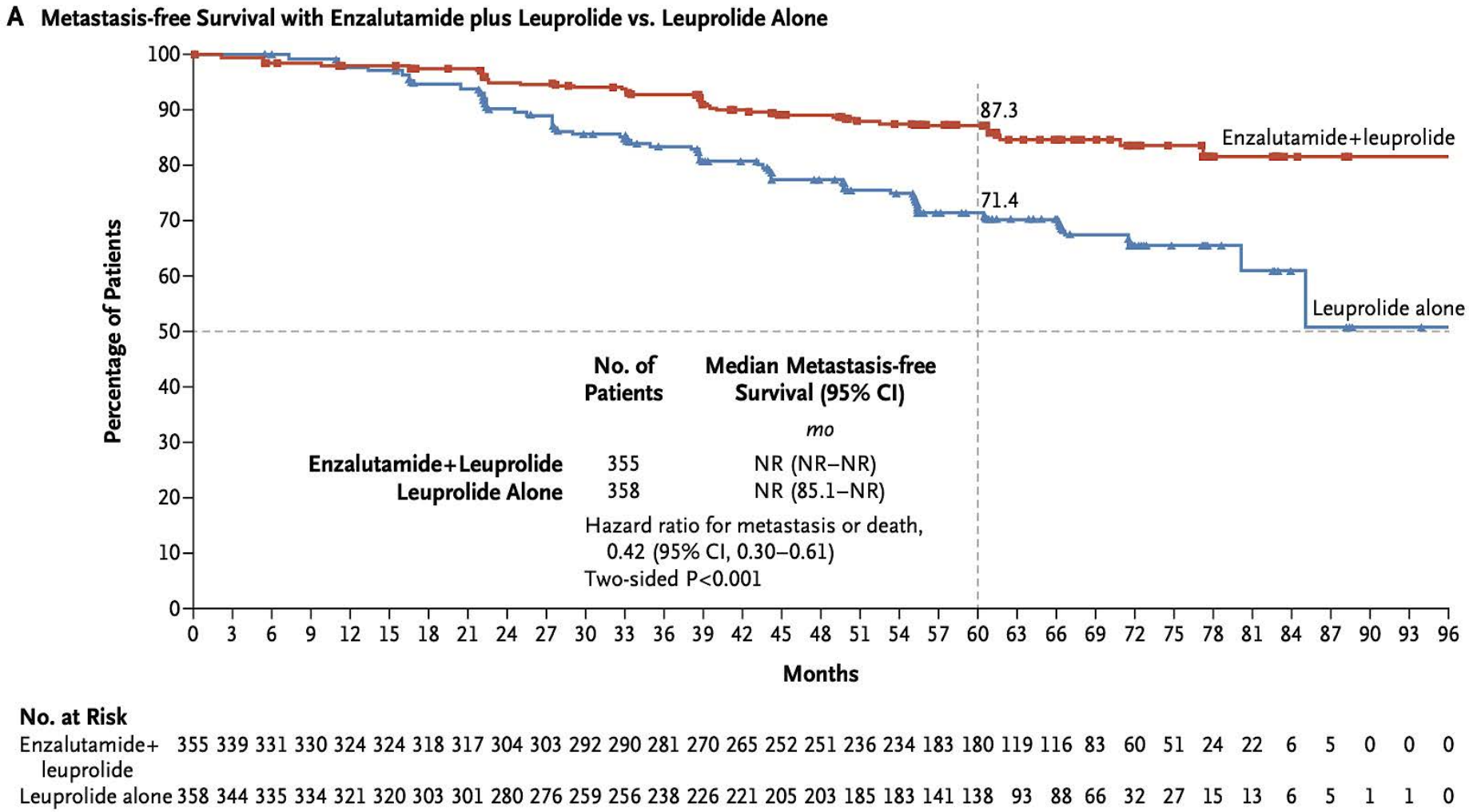
Freedland S, et al. JAMA 2005

EMBARK: Use of enzalutamide alone or in combination with ADT in biochemically relapsed prostate cancer



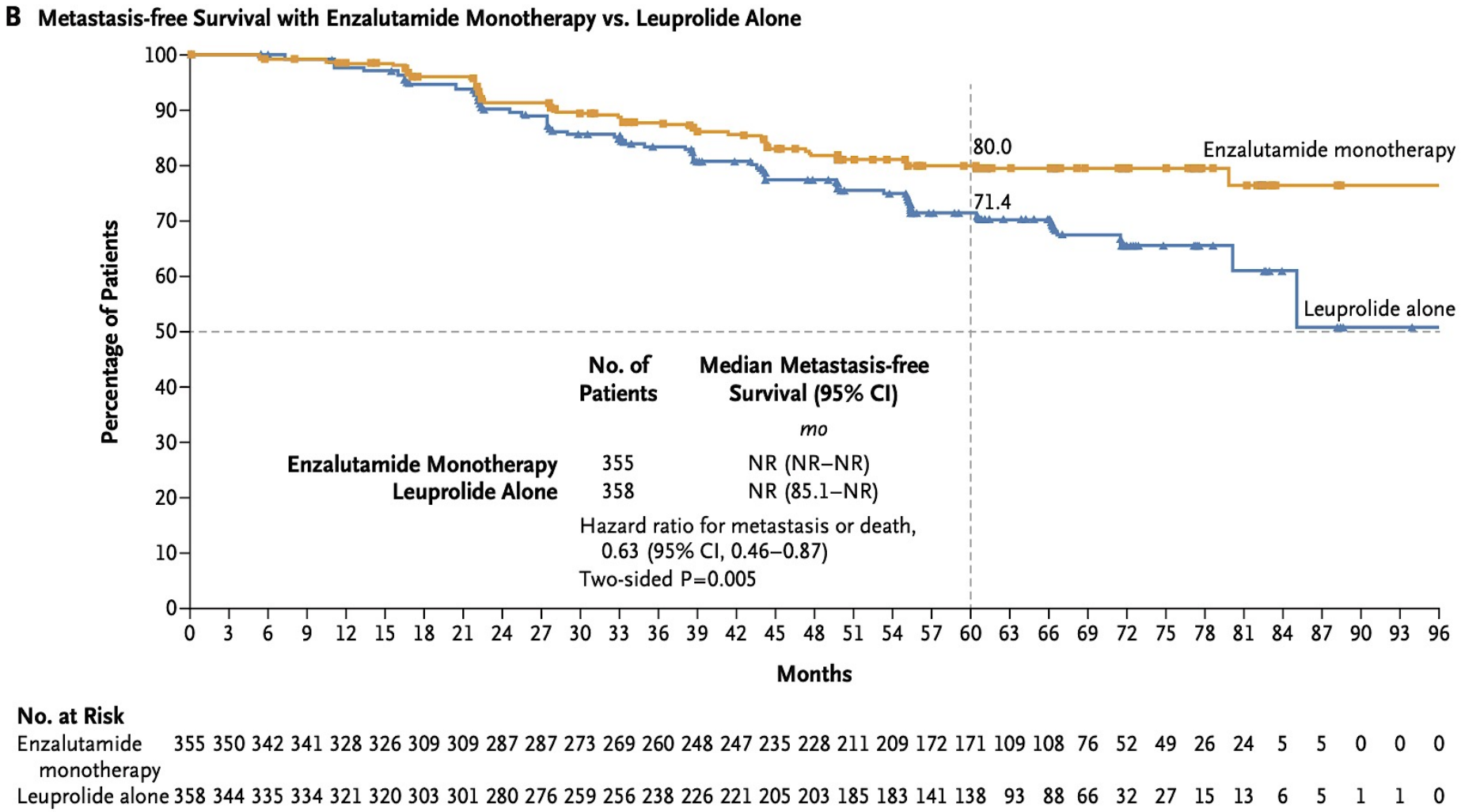
Freedland S, et al. New Engl J Med 2023

EMBARK: Enzalutamide plus Leuprolide – MFS



Freedland S, et al. New Engl J Med 2023

EMBARK: Enzalutamide Monotherapy – MFS



No. at Risk

Enzalutamide monotherapy	355	350	342	341	328	326	309	309	287	287	273	269	260	248	247	235	228	211	209	172	171	109	108	76	52	49	26	24	5	5	0	0	0
Leuprolide alone	358	344	335	334	321	320	303	301	280	276	259	256	238	226	221	205	203	185	183	141	138	93	88	66	32	27	15	13	6	5	1	1	0

Freedland S, et al. New Engl J Med 2023

EMBARK: Take home points

- ADT + enzalutamide improves metastasis-free and overall survival compared to ADT alone
- Enzalutamide monotherapy also improves outcomes but magnitude of benefit smaller than with enzalutamide + ADT
- Treatment break after 9 months of treatment in patients with optimal PSA response as part of intermittent treatment framework
- Choosing between ADT + enzalutamide versus enzalutamide alone:
  - Magnitude of benefit
  - Toxicity profile: higher gynecomastia/breast pain; lower rates of fatigue, hot flashes, sexual side effects
  - Anticipated off-treatment interval

Freedland S, et al. New Engl J Med 2023

Case conclusion

- Patient opted for ADT + enzalutamide
- Mild fatigue and hot flashes; no significant mood or cognitive side effects
- Undetectable PSA nadir after 9 months of treatment
- Currently on treatment break
- Testosterone has recovered to 256 ng/dL
- PSA remains less than 0.1 ng/mL

Roundtable Discussion

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Nursing Considerations for Patients Receiving ADT

Monica Averia, MSN, AOCNP, NP-C

What do you tell your patients about to start treatment with ADT about how it works and why they are receiving it?

- Androgen deprivation therapy (ADT) - cornerstone of prostate cancer therapy, but it has substantial side effects.

- Goal: reduce the levels of male hormones in the body to slow down or stop the growth of prostate cancer cells that rely on androgens for survival.

Side Effects of Androgen Deprivation Therapy (ADT)

Discuss potential side effects with patient and their significant other before starting therapy:

- Hot flashes
- Bone density loss
- Fatigue
- Depression/emotional lability
- Gynecomastia
- Erectile dysfunction
- Metabolic syndrome
- Cognitive changes

How do you monitor for and manage common ADT-associated toxicities?

- Hot flashes:
  - medications such as venlafaxine or gabapentin, acupuncture has a role of relieving symptoms
- Bone density loss:
  - DEXA scan monitoring, weight bearing exercises, Calcium + Vitamin D, Osteoclast inhibitors have shown a role in preventing skeletal related events (zoledronic acid or denosumab).
- Fatigue:
  - Encourage regular exercise, maintain activity level
- Depression/emotional lability:
  - Monitor and explore during clinic visits. May benefit from counseling, medications SSRI.

How do you monitor for and manage common ADT-associated toxicities?

- Gynecomastia:
  - surgical and single-dose radiation to targeted breast area
- Erectile dysfunction:
  - ED and decreased libido is common with pts on ADT. Review role of PDE inhibitors (Sildenafil and Tadalafil). Refer to urology to help manage side effects of ADT, mechanical therapy, offer referral for sexual health support.
- Metabolic syndrome:
  - Weight gain, insulin resistance, dyslipidemia can occur. Encourage exercise. Diet modification.
- Cognitive changes:
  - Dementia- multiple studies have reported this issue, with mixed/conflicting findings. This remains an active area of research. Refer to neuro for further work-up if needed

How do you monitor for and manage common ADT-associated toxicities?

Does this differ based on patient age/performance status and medical history?

- Individualized patient care. Consider treatment demand on patient:
    - Baseline performance status
    - Comorbidities
    - Identify potential barriers:
        - Financial- Copay, Access to patient assistance program
        - Compliance issues
        - Limitations: physical, mental, psychological, socioeconomic

Clinical examples/experiences from practice

- 75 y/o Asian male with cholangiocarcinoma + prostate adenocarcinoma.

Cholangiocarcinoma:

- 9/2023: presented to USC with cholangitis sp ERCP with biopsy: moderately differentiated adenocarcinoma
- 9/2023: Whipple resection: pT3N0M0 extrahepatic cholangiocarcinoma of the common bile duct. Margins were negative.
- 12/2023: Post op CT: showed no recurrence of cholangiocarcinoma.
- 02/2024 to 07/2024: Adjuvant capecitabine completed

Clinical examples/experiences from practice

Prostate cancer:

- 09/2023: PSA 31.10; Testosterone 511 (cholangio preop work-up)
- 10/18/23: Bx: GG 5 Gleason 4+5 Prostate Adenocarcinoma
- 11/2023: PSMA: metastases noted within the left pubic bone and the right acetabulum
- **12/15/23: ADT initiated**
- 1/3/24 to 1/16/24: SBRT to the prostate
- 04/2024: PSA 0.02; Testosterone <12
- 12/2024: CT (cholangio ca): showed mild increase in a para-aortic node to 1.4 cm.
- 12/2024: PSA 1.83; Testosterone <12
- 02/2025: PSMA: negative for definitive area of active prostate cancer
- 02/2025: PET/CT: new hypermetabolic mediastinal, left hilar, left retroperitoneal LAD concerning metastases
- 3/3/25: PSA 4.72; Testosterone <12
- 3/24/25: Paraaortic LN Bx: Metastatic prostatic carcinoma
- 4/2/25: Enzalutamide added to treatment. Continue ADT
    - Pt developed diabetes after Whipple procedure now on Metformin
- RTC 2 wks with labs: pending

Roundtable Discussion

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Clinical Scenario

A patient with de novo mHSPC receives ADT in combination with an androgen receptor pathway inhibitor, and the option of docetaxel is also discussed

Metastatic HSPC

William K. Oh, MD
Director, Precision Medicine
Yale Cancer Center and Smilow Cancer Hospital

Service Line Medical Director
Smilow Cancer Hospital at Greenwich Hospital

Chair, National Prostate Cancer Roundtable
American Cancer Society

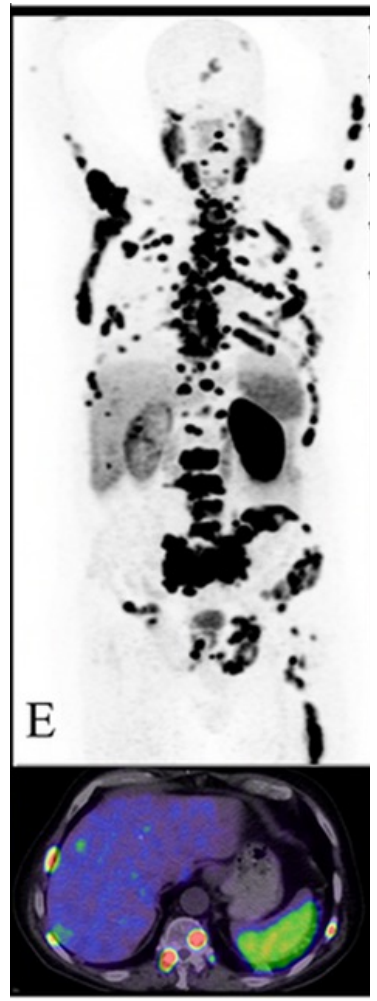
YaleNewHavenHealth
Smilow Cancer Hospital

Yale CANCER CENTER
A Comprehensive Cancer Center Designated by the National Cancer Institute

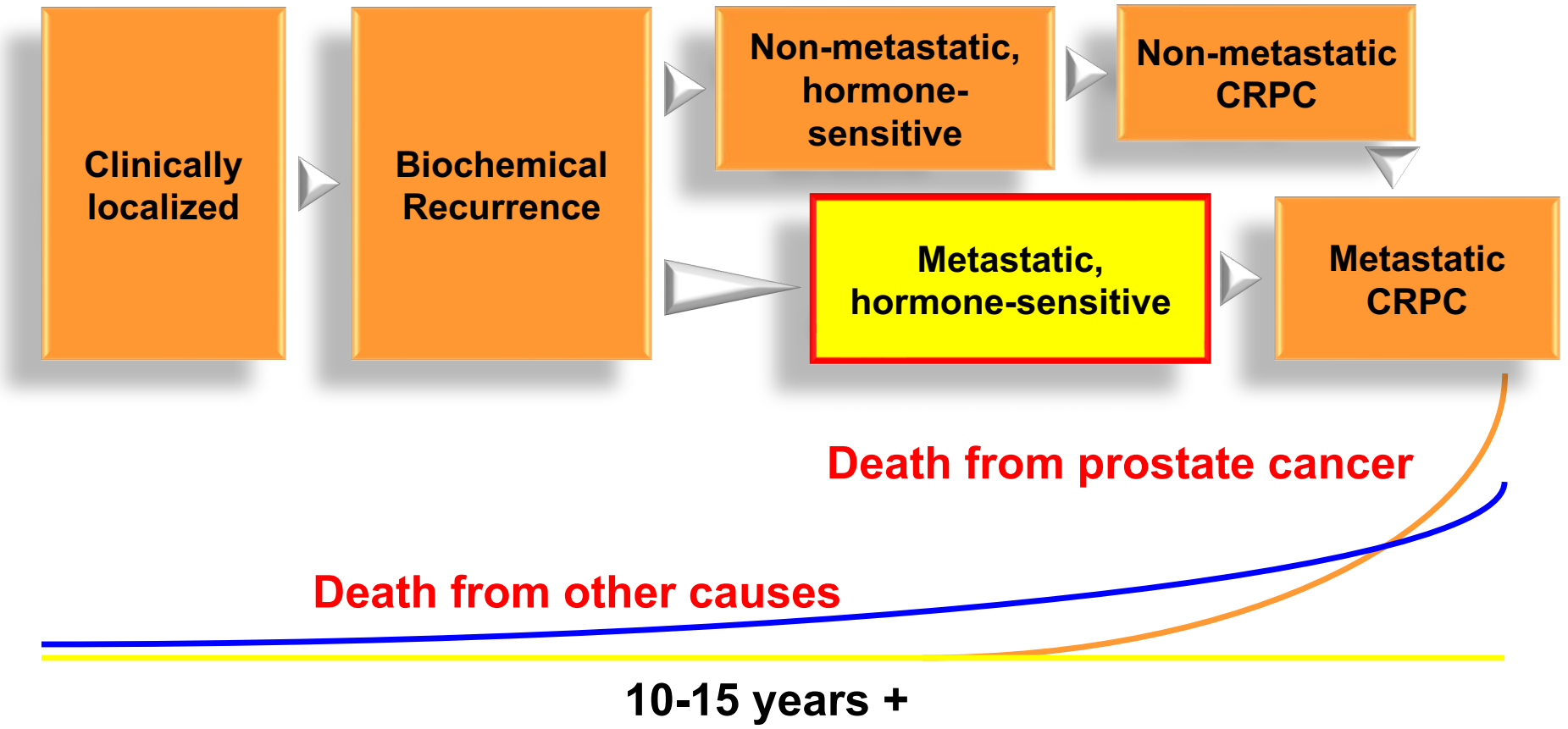
Case: A 60 year old Man with Liver Mets

A 60-year-old man presents with urinary retention, fatigue and poor appetite

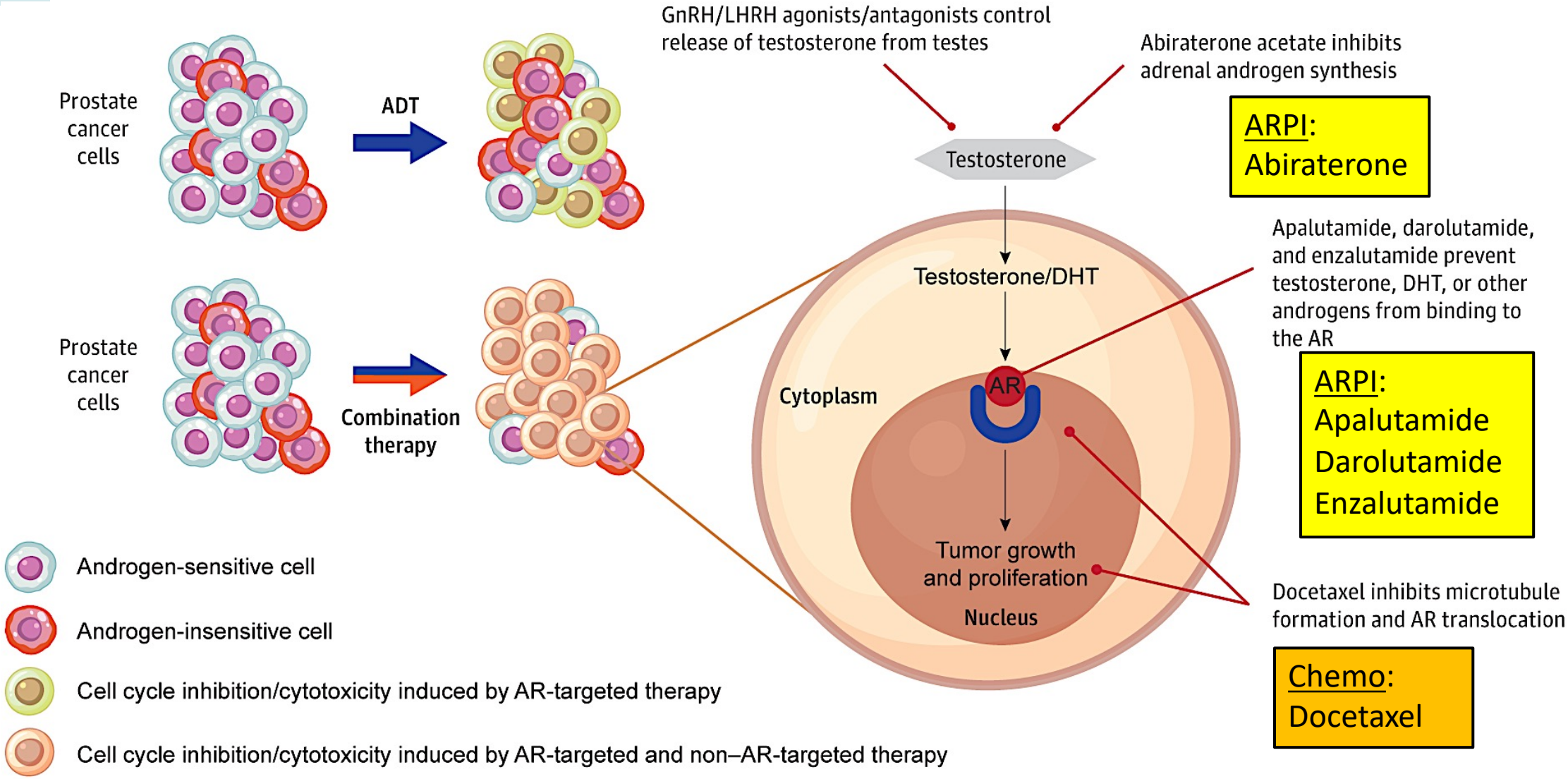
- Initial PSA 150 ng/mL (none prior)
- TRUS biopsy: adenocarcinoma of the prostate, Gleason score 8
- PSMA PET/CT shows multiple metastatic bone lesions in the pelvis, spine, ribs as well as diffuse liver lesions
- No family history of prostate or other cancers
- Germline and somatic genetic testing is negative
- PMH: HTN



Clinical States of Prostate Cancer



Combination Therapy Targets Tumor Heterogeneity in mHSPC



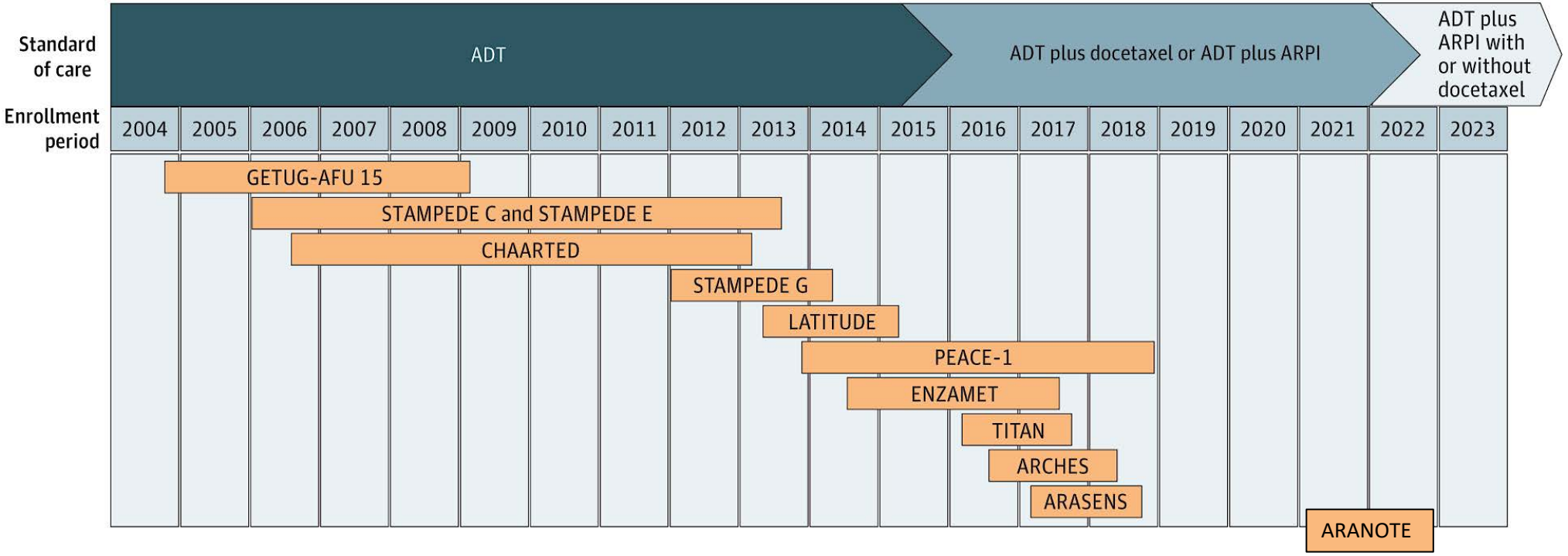
ARPI:
Abiraterone

ARPI:
Apalutamide
Darolutamide
Enzalutamide

Chemo:
Docetaxel

Hussain. JAMA Onc 10:807, 2024

11 Prospective RCTs Demonstrate Significant Survival Benefit for Combination Therapy in mHSPC



"Doublet" Therapies

[ADT] *vs* [ADT + ARPI]

HR for OS: 0.63-0.81

"Triplet" Therapies

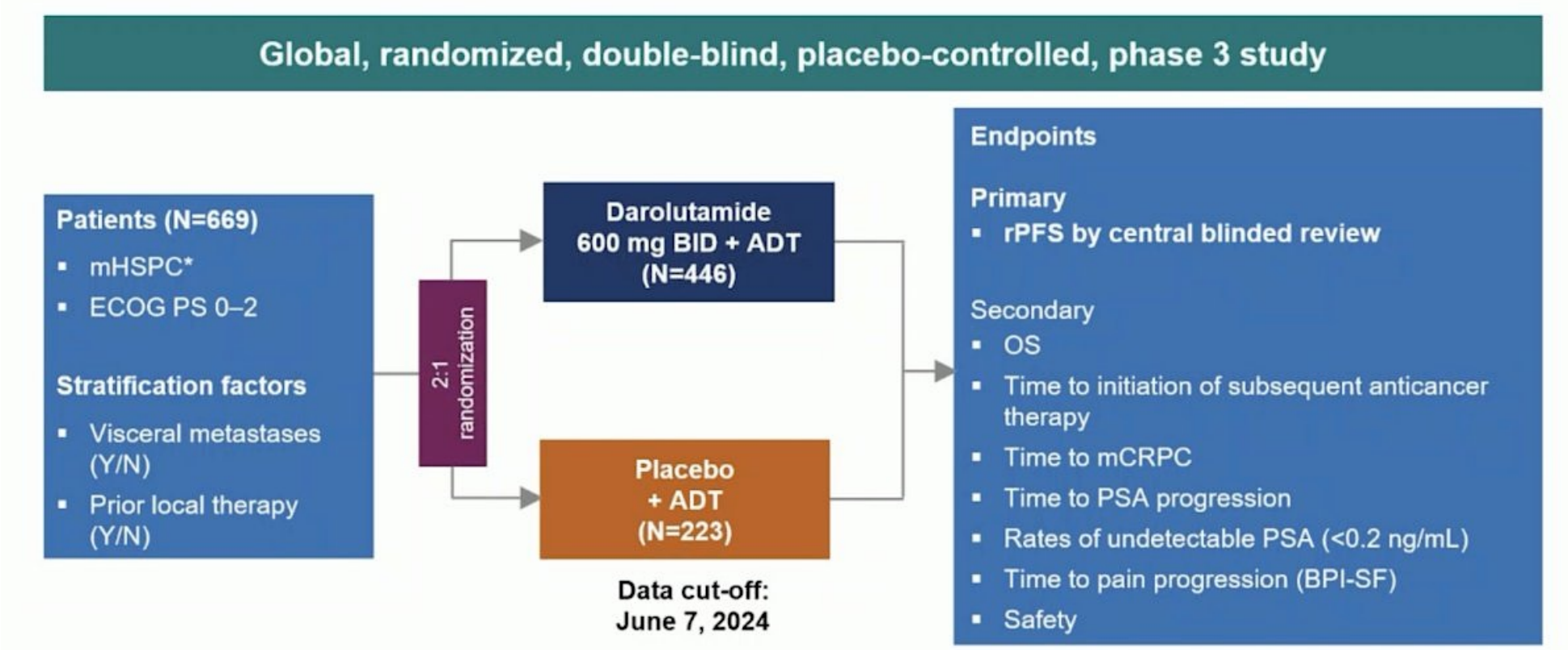
[ADT + Doce] *vs* [ADT + Doce + ARPI]

HR for OS: 0.68-0.75

Hussain. JAMA Onc 10:807, 2024

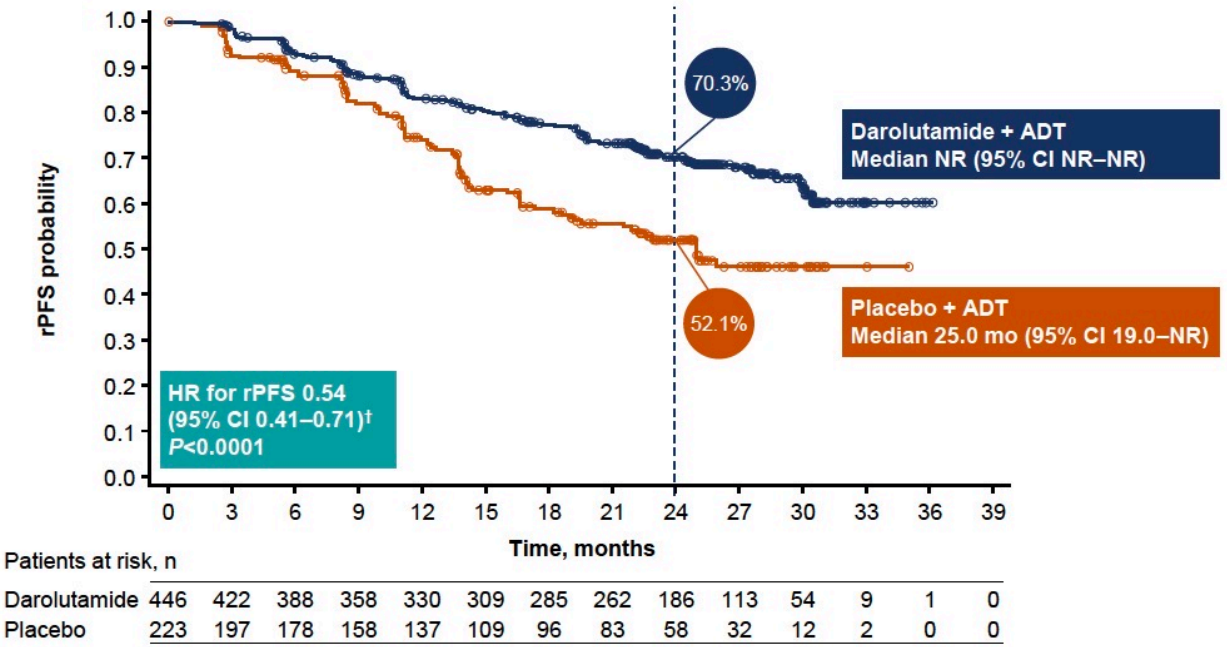
Darolutamide in Combination With Androgen-Deprivation Therapy in Patients With Metastatic Hormone-Sensitive Prostate Cancer From the Phase III ARANOTE Trial

Fred Saad, MD[1]; Egils Vjaters, MD[2]; Neal Shore, MD, FACS[3]; David Olmos, MD, PhD[4]; Nianzeng Xing, MD[5]; Andrea Juliana Pereira de Santana Gomes, MD[6]; Augusto Cesar de Andrade Mota, MD, PhD[7]; Pamela Salman, MD, PhD[8]; Mindaugas Jievaltas, MD, PhD[9]; Albertas Ulys, MD, PhD[10]; Maris Jakubovskis, MD[11]; Evgeny Kopyltsov, MD, PhD[12]; Weiqing Han, MD, PhD[13]; Liina Nevalaita, PhD[14]; Isabella Testa, MD[15]; Marie-Aude Le Berre, MSc[16]; Iris Kuss, MD[17]; and Kunhi Parambath Haresh, MD[18]



ARANOTE (Phase 3): Radiological PFS and PSA

Primary endpoint: Radiological PFS

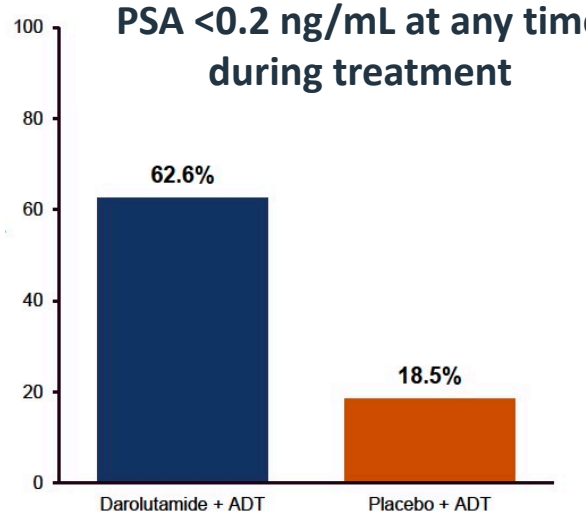


Patients at risk, n

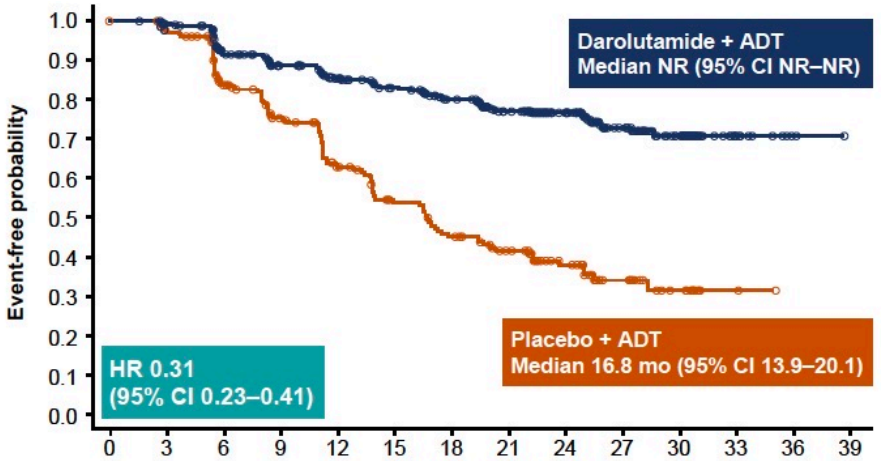
Darolutamide	446	422	388	358	330	309	285	262	186	113	54	9	1	0
Placebo	223	197	178	158	137	109	96	83	58	32	12	2	0	0

- Benefit of darolutamide was consistent across all subgroups

PSA <0.2 ng/mL at any time during treatment



Time to PSA progression



Patients at risk, n

Darolutamide	446	408	357	330	301	280	256	220	158	95	48	12	2	0
Placebo	223	195	158	130	102	81	67	54	36	20	9	2	0	0

ADT, androgen-deprivation therapy.

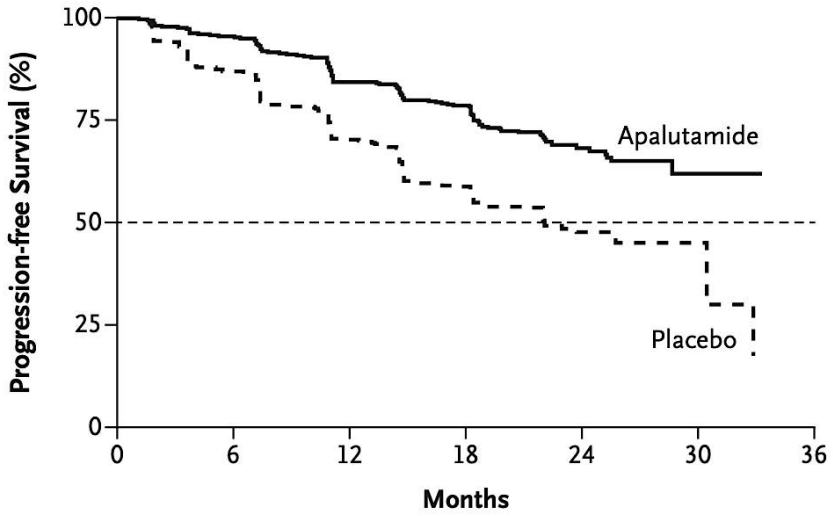
Saad F, et al. ESMO 2024. Abstract LBA68

ARPI + ADT: Radiological PFS Analyses

TITAN - apalutamide

	No. of Patients	Median Radiographic Progression–free Survival (95% CI) *mo*	Patients with Radiographic Progression–free Survival at 24 Mo (95% CI) %
Apalutamide	525	NE	68.2 (62.9–72.9)
Placebo	527	22.1 (18.5–32.9)	47.5 (42.1–52.8)

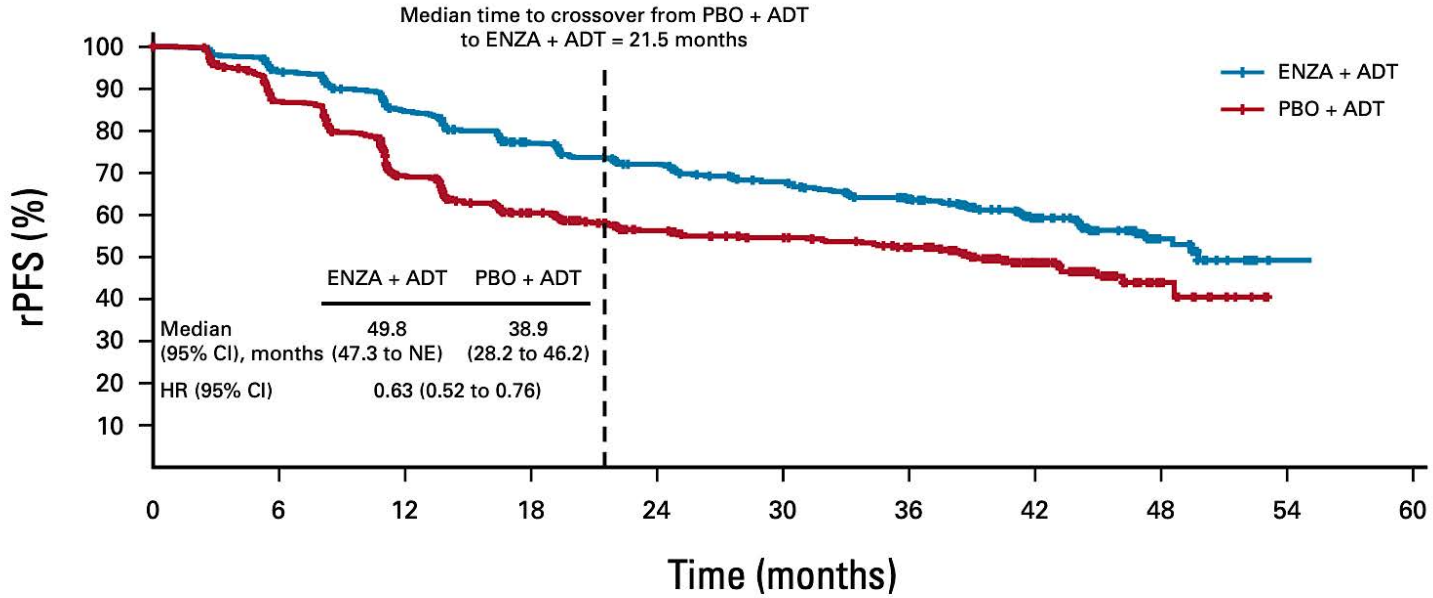
Hazard ratio for radiographic progression or death, 0.48 (95% CI, 0.39–0.60)
P<0.001



No. at Risk

Apalutamide	525	469	389	315	89	2	0
Placebo	527	437	325	229	57	3	0

ARCHES - enzalutamide

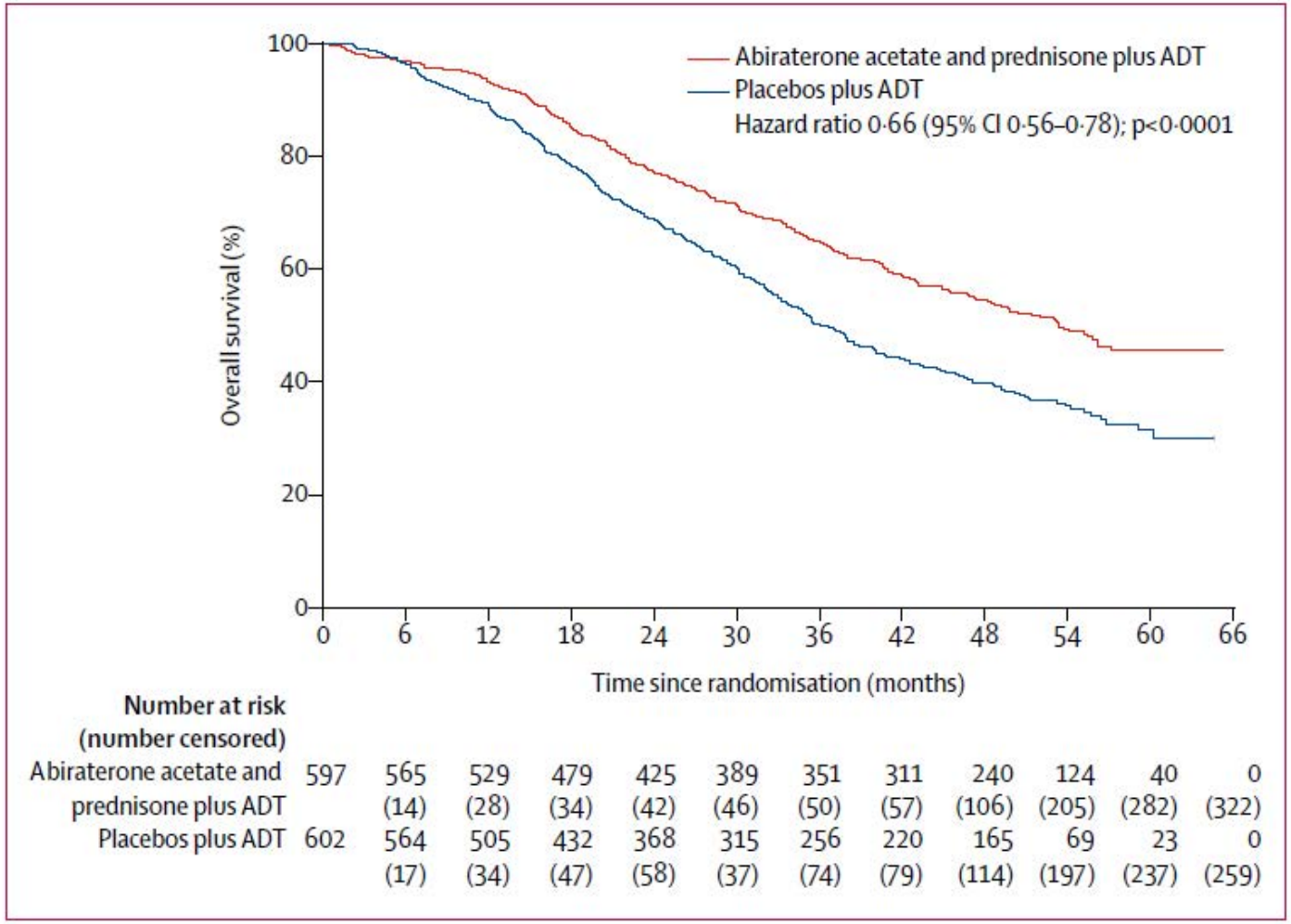


No. at risk:

ENZA + ADT	574	542	516	484	449	418	391	365	346	324	309	294	272	220	150	83	37	13	1	0	0
PBO + ADT	576	525	468	415	333	271	240	199	181	169	165	159	148	124	84	42	14	5	0	0	0

Armstrong AJ, et al. J Clin Oncol. 2022;40(15):1616-1622.
Chi KN et al. N Engl J Med. 2019;381(1):13-24.

Abiraterone acetate plus prednisone in patients with newly diagnosed high-risk metastatic castration-sensitive prostate cancer (LATITUDE): final overall survival analysis of a randomised, double-blind, phase 3 trial



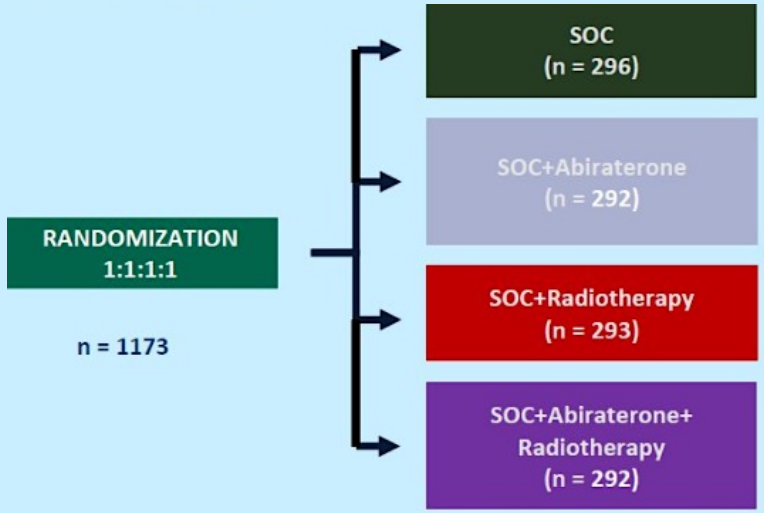
Number at risk (number censored)												
Abiraterone acetate and prednisone plus ADT	597	565 (14)	529 (28)	479 (34)	425 (42)	389 (46)	351 (50)	311 (57)	240 (106)	124 (205)	40 (282)	0 (322)
Placebos plus ADT	602	564 (17)	505 (34)	432 (47)	368 (58)	315 (37)	256 (74)	220 (79)	165 (114)	69 (197)	23 (237)	0 (259)

Figure 2: **Kaplan-Meier curve of overall survival in the intention-to-treat population**
ADT=androgen deprivation therapy.

Fizazi K et al. Lancet Oncol. 2019 May;20(5):686-700.

Phase 3 PEACE-1 Study (2x2): Abiraterone + ADT + Docetaxel ± RT for mHSPC

≥ 1 distant lesion on bone and/or CT scan), ECOG PS 0-2

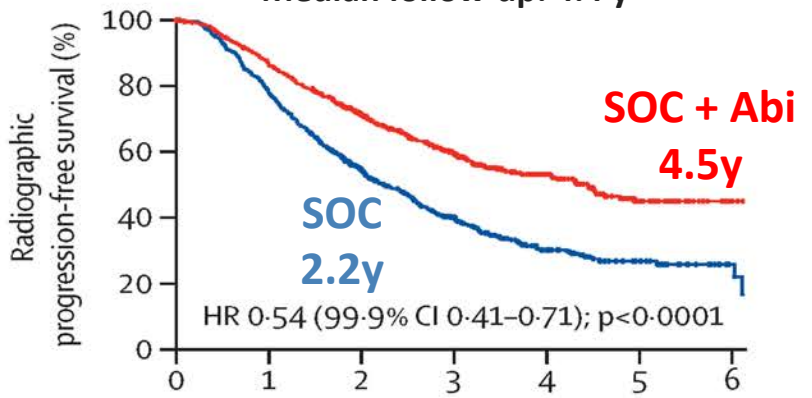


Grade 3-5 AEs (>5%, ABI vs control):
neutropenic fever (5% vs 5%), neutropenia (10% vs 9%), liver toxicity (6% vs 1%) and HTN (21% vs 13%)

Fizazi K, et al. *Lancet*. 2022 Apr 30;399(10336):1695-1707.

Coprimary Endpoints (Overall Population)

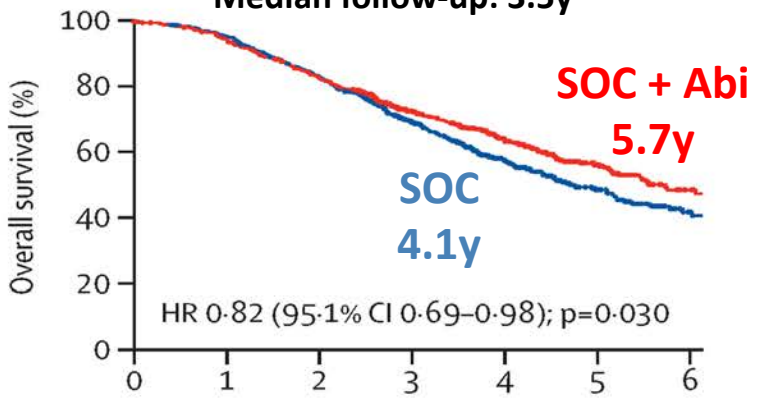
Median follow-up: 4.4 y



Number at risk							
SOC without abiraterone groups	589	453	274	158	72	31	7
SOC plus abiraterone groups	583	495	355	230	119	47	12

SOC without abiraterone groups
SOC plus abiraterone groups

Median follow-up: 3.5y



Number at risk							
SOC without abiraterone groups	589	556	480	334	207	101	37
SOC plus abiraterone groups	583	541	470	340	230	111	47

Phase 3 ARASENS Study of Darolutamide + ADT + Docetaxel for Advanced HSPC

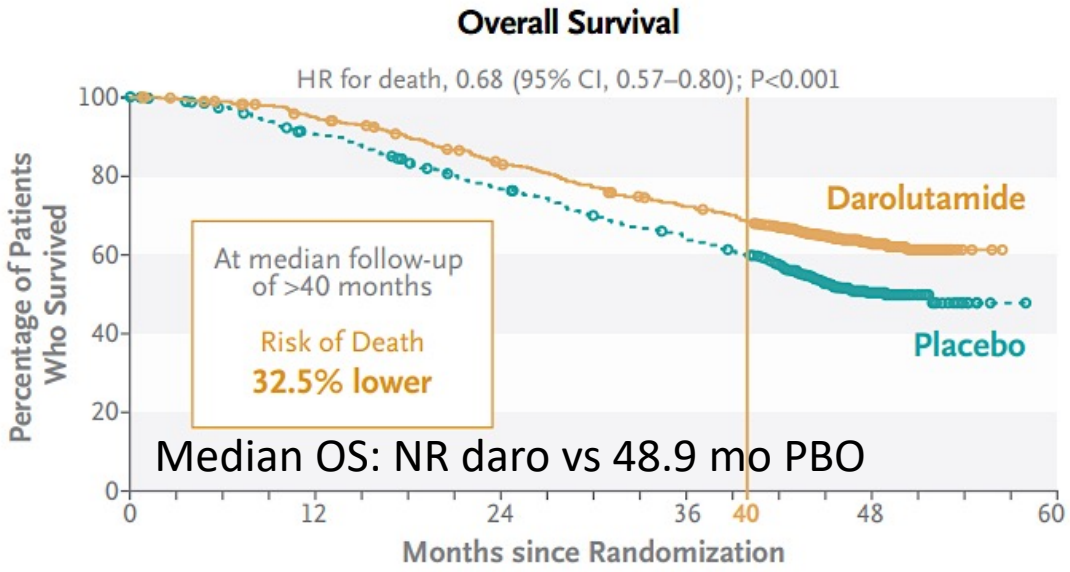
- mHSPC, ECOG PS 0-1, candidates for ADT and doecetaxel

Safety

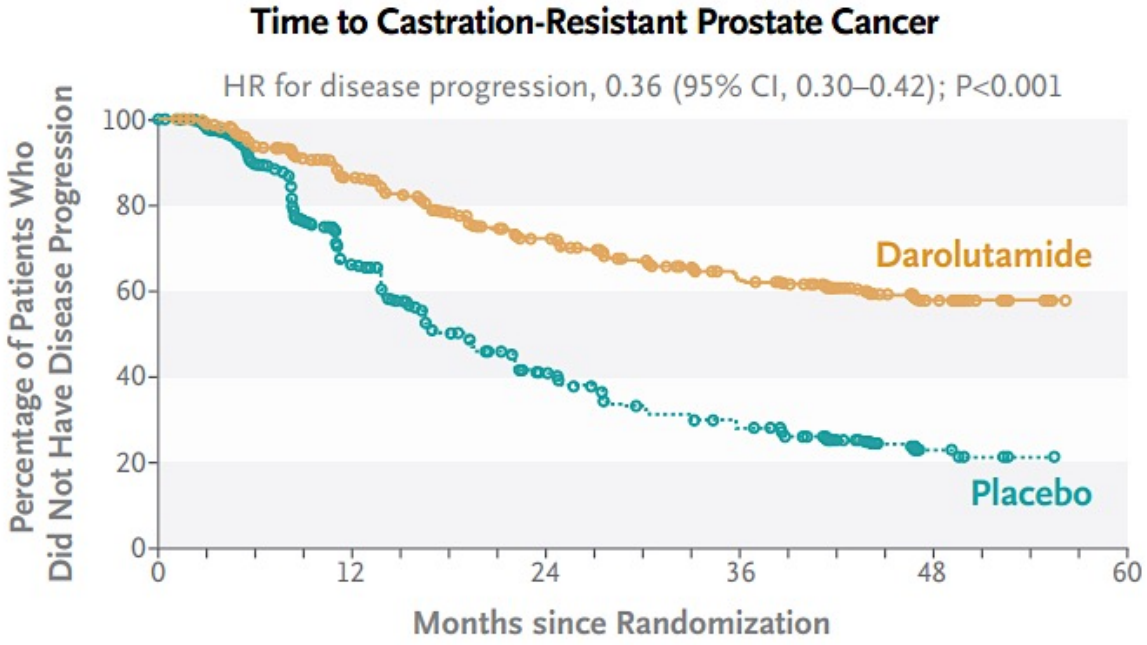
- AE incidence: similar in the 2 groups
- Incidences of most common AEs (≥ 10%) highest during overlapping docetaxel treatment period in both groups
- Grade 3/4 AEs: 66.1% (daro) vs 63.5% (pbo)
  - Neutropenia: 33.7% vs 34.2%
- Serious AEs: 45% vs 42%

N=1306

Primary Endpoint

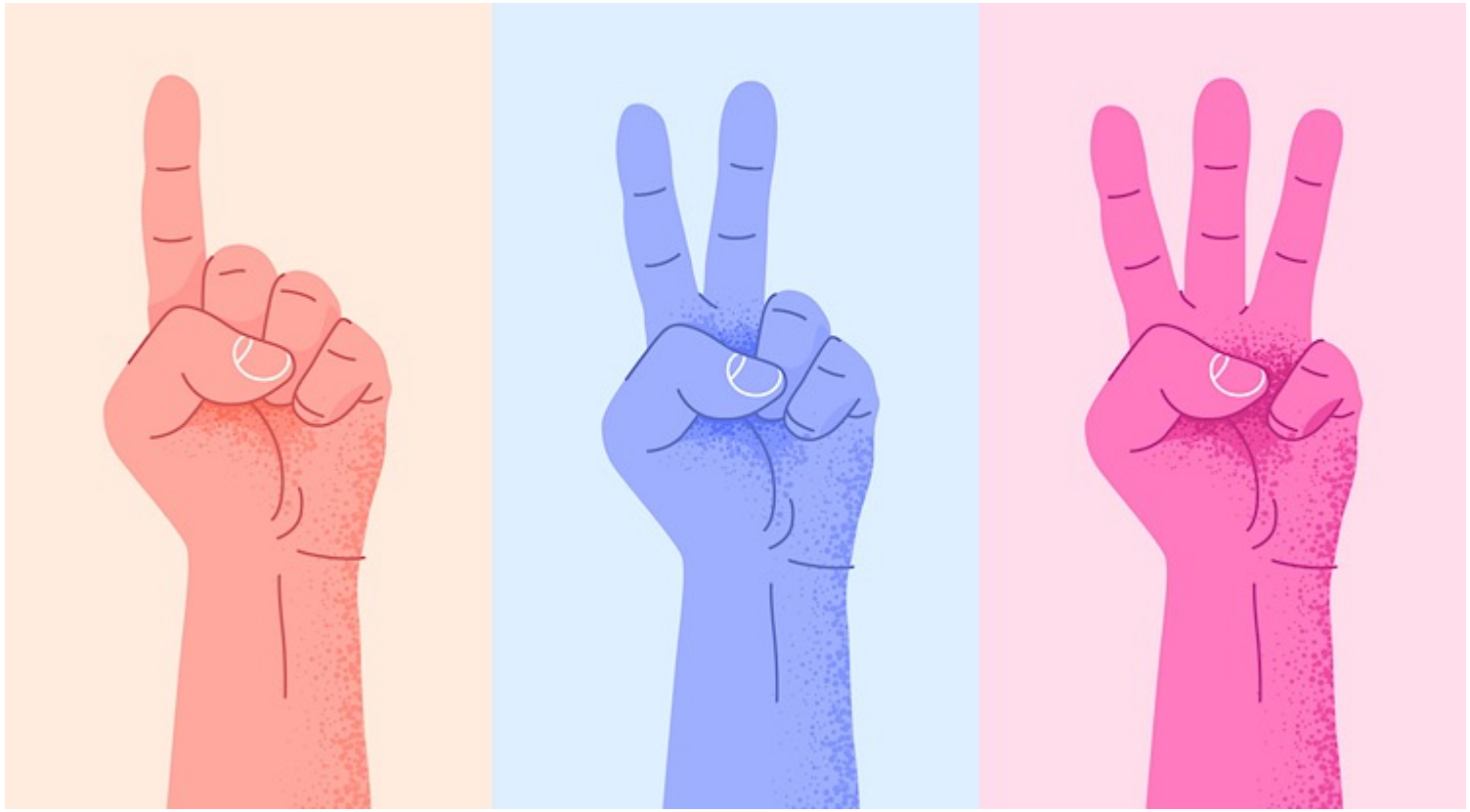


Median OS: NR daro vs 48.9 mo PBO



Smith MR, et al. *N Engl J Med.* 2022;386:1132-1142.

Metastatic Hormone Sensitive Prostate Cancer



~~ADT alone~~

ADT + ~~Docetaxel~~

ADT + ARPI

ADT + Docetaxel + Abiraterone

ADT + Docetaxel + Darolutamide

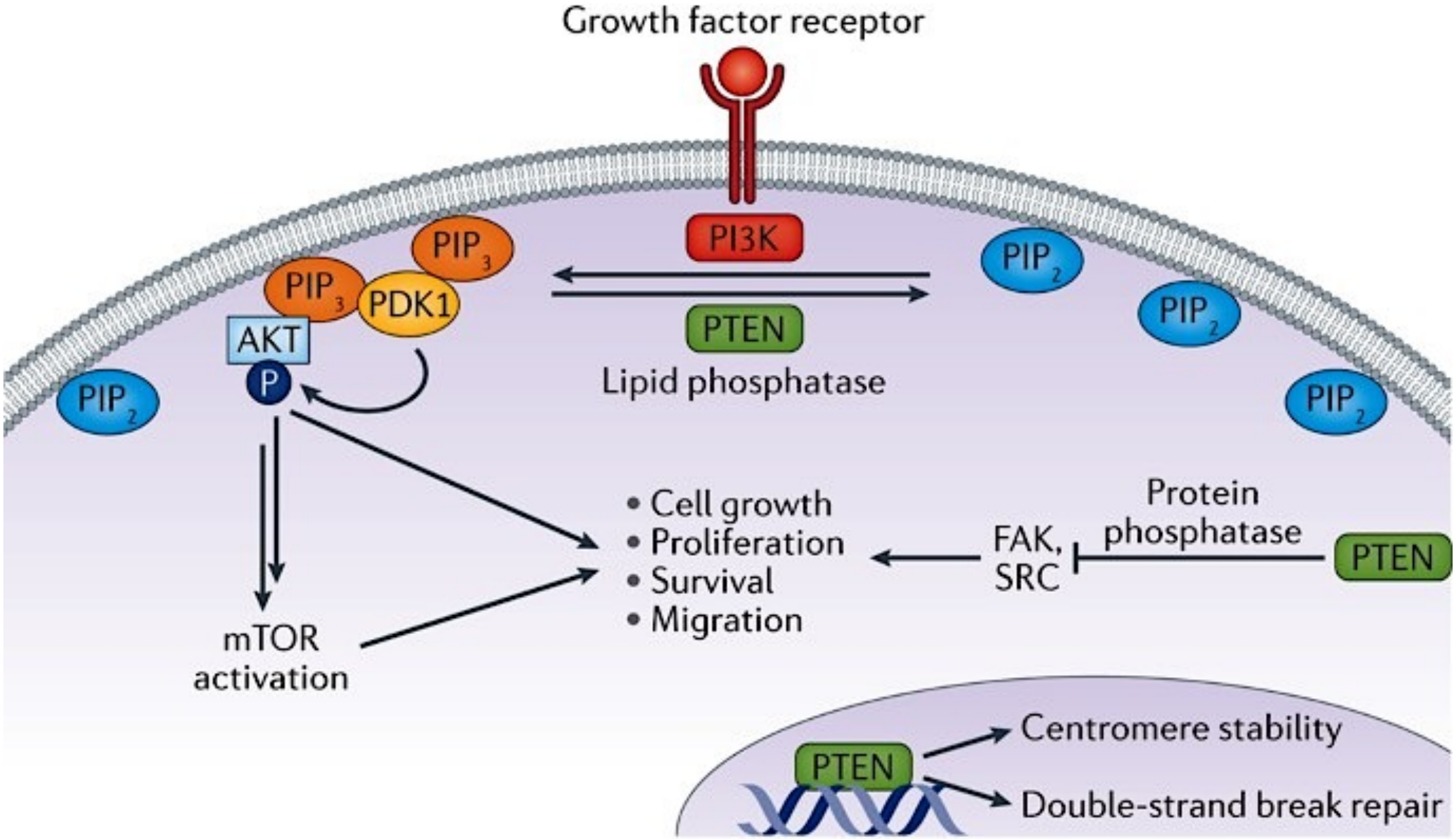
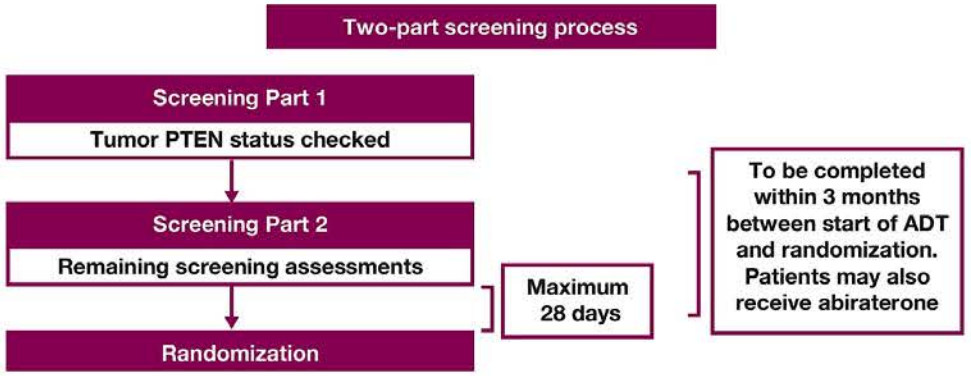
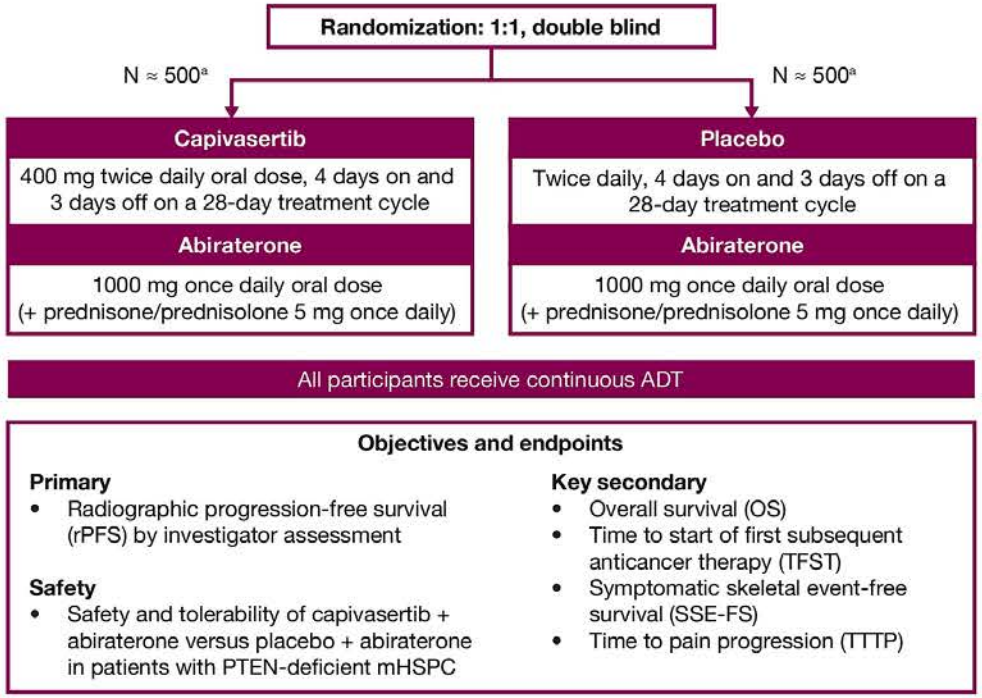

Growth factor receptor
PI3K
PTEN
Lipid phosphatase
PIP3
PIP3
PDK1
AKT
P
PIP2
PIP2
PIP2
PIP2
• Cell growth
• Proliferation
• Survival
• Migration
mTOR
activation
FAK,
SRC
Protein
phosphatase
PTEN
PTEN
Centromere stability
Double-strand break repair

Figure 3. Two-part screening process for CAPItello-281



ADT, androgen deprivation therapy; PTEN, phosphatase and tensin homolog

Figure 4. Trial design and outcome measures for CAPItello-281



[a]Estimated number to achieve appropriate statistical power
ADT, androgen deprivation therapy; mHSPC, metastatic hormone-sensitive prostate cancer; PTEN, phosphatase and tensin homolog

Capivasertib combination in PTEN-deficient metastatic hormone-sensitive prostate cancer demonstrated statistically significant and clinically meaningful improvement in radiographic progression-free survival in CAPItello-281 Phase III trial

PUBLISHED 25 November 2024

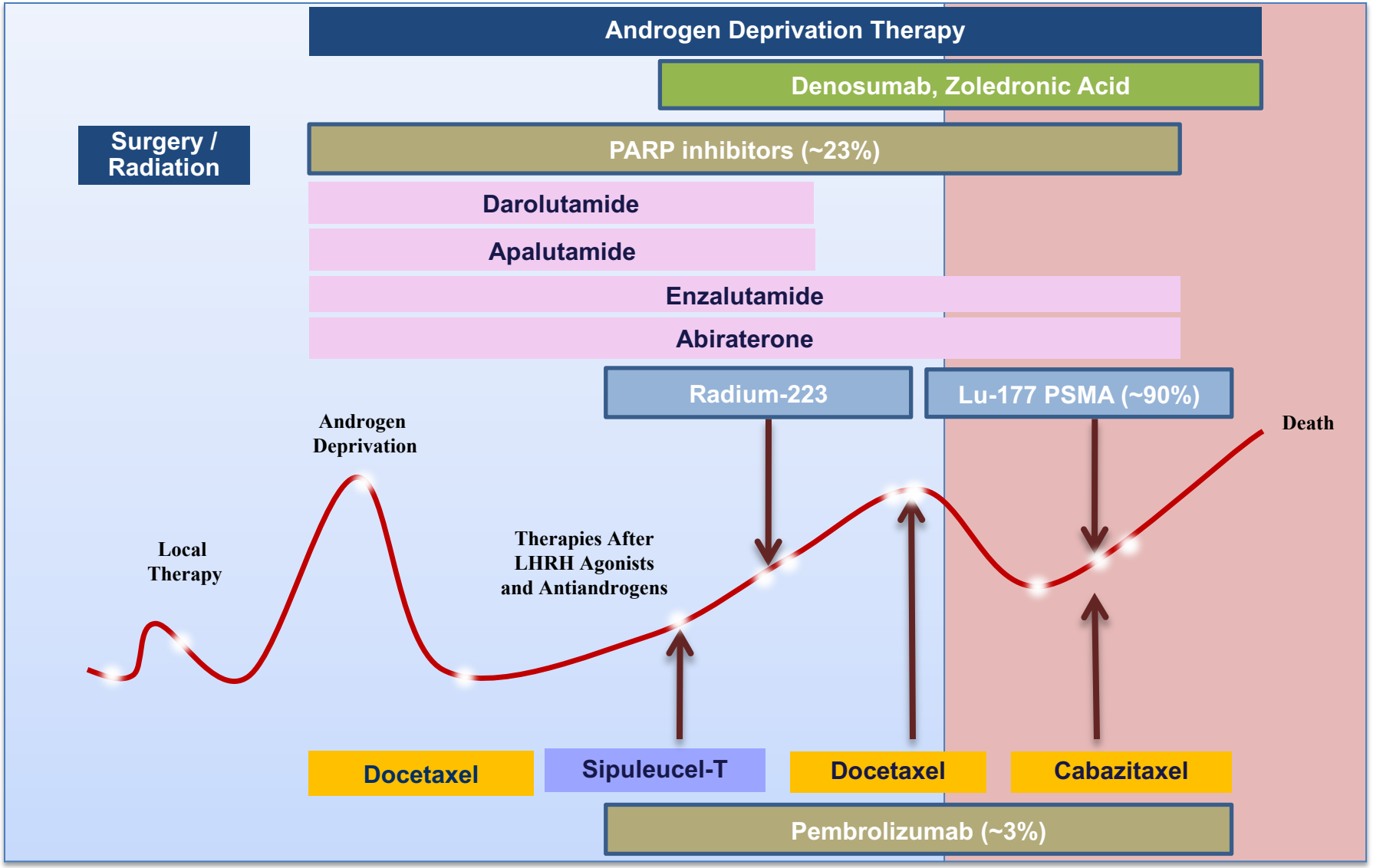
First and only AKT inhibitor combination to demonstrate benefit in this specific subtype of prostate cancer

Positive high-level results from the CAPItello-281 Phase III trial showed that capivasertib in combination with abiraterone and androgen deprivation therapy (ADT) demonstrated a statistically significant and clinically meaningful improvement in the primary endpoint of radiographic progression-free survival (rPFS) versus abiraterone and ADT with placebo in patients with PTEN-deficient *de novo* metastatic hormone-sensitive prostate cancer (mHSPC).

Overall survival (OS) data were immature at the time of this analysis; however, the capivasertib combination showed an early trend towards an OS improvement versus abiraterone and ADT with placebo. The trial will continue as planned to further assess OS as a key secondary endpoint.

Prostate cancer is the second most prevalent cancer in men and the fifth leading cause of male cancer death globally.[1] Only one-third of patients with metastatic prostate cancer survive five years after diagnosis.[2] Newly diagnosed mHSPC is an aggressive form of the disease associated with poor outcomes and survival.[3,4] Approximately 200,000 patients are diagnosed with mHSPC each year, and one in four have PTEN-deficient tumors.[5] Patients with a tumor biomarker of PTEN deficiency have a particularly poor prognosis.[6]

Treatment Landscape: 2025



Patient Case Continued

- Therapeutic options available were reviewed with the patient
- ADT was started immediately with leuprolide
- Darolutamide + docetaxel x 6 cycles was recommended given his young age and aggressive recurrence
- Chemotherapy was complicated by fatigue, but he actually gained weight as his tumor regressed
- His PSA responded, dropping to 0.4 after 6 months
- He continues on leuprolide and darolutamide
- PSA, labs and visits are conducted every 3 months

Roundtable Discussion

RTP
RESEARCH
TO PRACTICE

Kathleen Burns,
Nurse Practitioner
GU Medical
Oncology
City of Hope

Androgen Pathway Inhibitors

- Also called ARPI, ARSI, ARTA
- They intensify a single agent androgen deprivation therapy
- Patient education
  - Cost/insurance coverage/adherence
  - Like any other targeted agents, they have unique side effects
    - Enzalutamide – falls/fracture, fatigue, cognitive dysfunction, seizure
    - Abiraterone – liver toxicity, cardiac risk, potassium changes, needs prednisone
    - Darolutamide – bleeding, rash, hypertension, anemia
    - Apalutamide – rash, falls/fracture, hypothyroidism, decreased appetite

Preparing for ARPIs

- Baseline lipids
- Calcium and vitamin D
- Hypertension controlled
- Exercise – cardio and resistance training
- Nutrition counseling - reduce carbs

Case Study mHSPC

- **55 yr old man presented in 2/2024 – for a second opinion**

- **9/28/23** - PSA found to be elevated to 97.3 on routine labs and referred to urology for evaluation
- **11/9/23** - TRUS biopsy with GS 4+3 or 3+4 disease in all cores
- **12/23/23** - PSMA with high level radiotracer activity involving most of the prostate with relative sparing of left anterior transition zone demonstrating SUV max of 17.9, consistent with primary prostatic malignancy. Intermediate level radiotracer uptake noted in the nonenlarged prominent lymph nodes in the right pelvis, retroperitoneum, mediastinum, left axilla and bilateral lower cervical regions, concerning for metastasis. Indeterminate low intermediate level focal radiotracer activity in the bones involving right posterior rib, right iliac bone and left posterior seventh rib with mild sclerosis
- **1/3/24** - Started on leuprolide and bicalutamide
- **1/30/24** - Saw a medical oncologist who recommended the addition of docetaxel to his leuprolide and bicalutamide. He disagreed and came to City of Hope for another opinion

Case study:

- **mHSPC, de novo, low-volume**
- We tried to sign him onto clinical trial tala/abi/ADT but insurance denied
- We then recommended stopping the bicalutamide and starting doublet therapy with Leuprolide/abiraterone and he received radiation to the prostate
- PSMA PET 10/24 showed resolution of disease
- PSA has been undetectable indicating excellent response to treatment

---

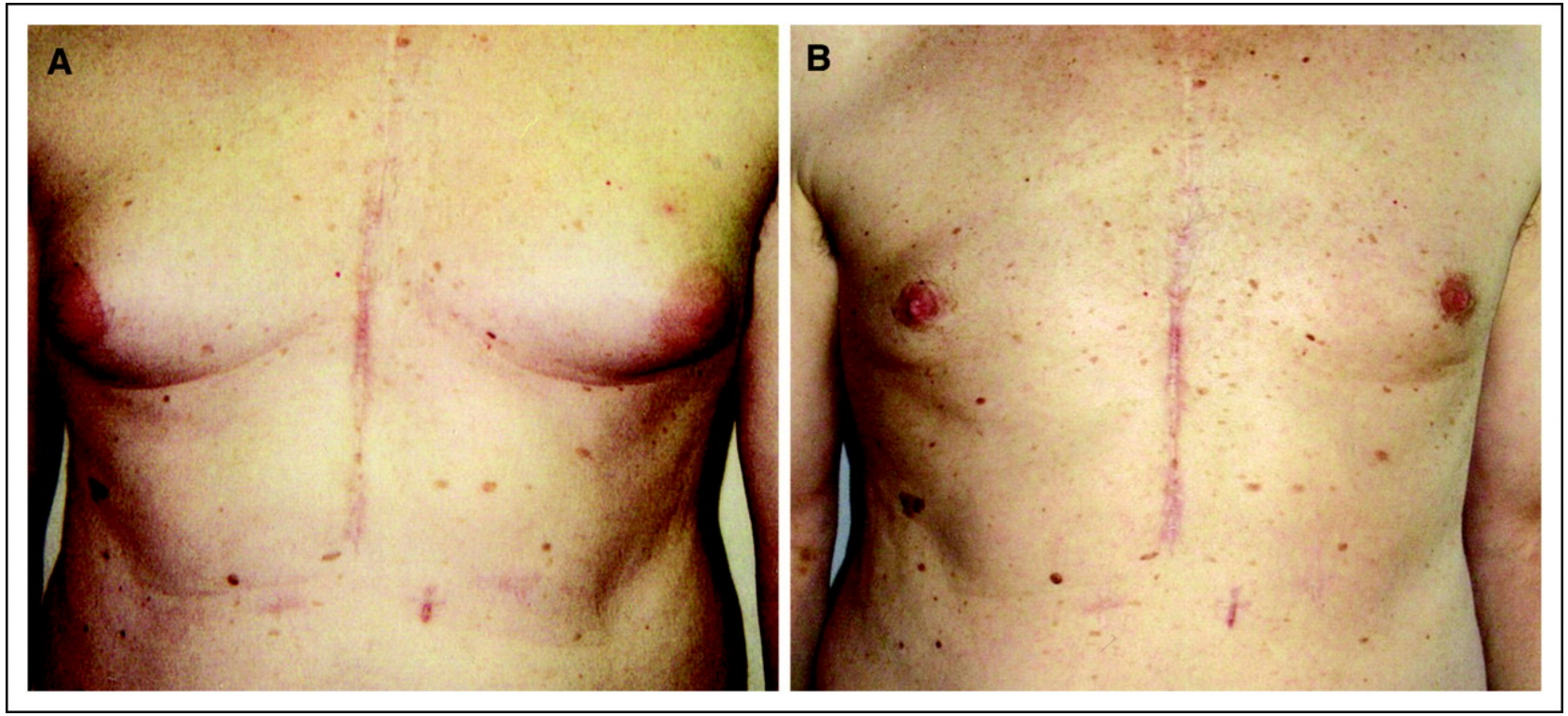
- **Patient single, self employed pop-up caterer without significant comorbidities**
- Developed hypocalcemia from denosumab (after dental screening)– calcium supplementation needed adjusting
- Developed transaminitis from the abi in the 2nd month – weekly labs, when resolved (4 weeks) restarted at ½ dose, never returned. Continues on therapy
- Health maintenance (no primary care): colonoscopy, repeat DEXA every 1-2 years while on ADT, exercise and heart health counseling, not sexually active but interested in reconnecting with ED education. Monitor insulin resistance/blood glucose/lipids. Social work and support group referral for minimal social support and potential financial issues with insurance coverage

Triplet therapy

- Darolutamide/ docetaxel/ ADT
- mHSPC – higher risk or more symptomatic from PC
- Prepare patients for changes in appearance
    - Hair loss
    - Potential refractory fluid retention
    - Steroid side effects – thinning or bruising skin/ weight gain

Enzalutamide monotherapy

- Gynecomastia
- Mastodynia



https://doi.org/10.1200/JCO.2005.03.8505

Roundtable Discussion

RTP
RESEARCH
TO PRACTICE

Agenda

Module 1: Recent Advances in the Treatment of Nonmetastatic Prostate Cancer

Module 2: Treatment Approaches for Metastatic Hormone-Sensitive Prostate Cancer

Module 3: Current Role of PARP Inhibitors in Metastatic Castration-Resistant Prostate Cancer (mCRPC)

Module 4: Current and Future Role of Radiopharmaceuticals in mCRPC

Clinical Scenario

A patient with mCRPC and a germline BRCA2 mutation is about to start treatment with a PARP inhibitor in combination with an AR pathway inhibitor

PARP inhibitors 2025

William K. Oh, MD
Director, Precision Medicine
Yale Cancer Center and Smilow Cancer Hospital

Service Line Medical Director
Smilow Cancer Hospital at Greenwich Hospital

Chair, National Prostate Cancer Roundtable
American Cancer Society

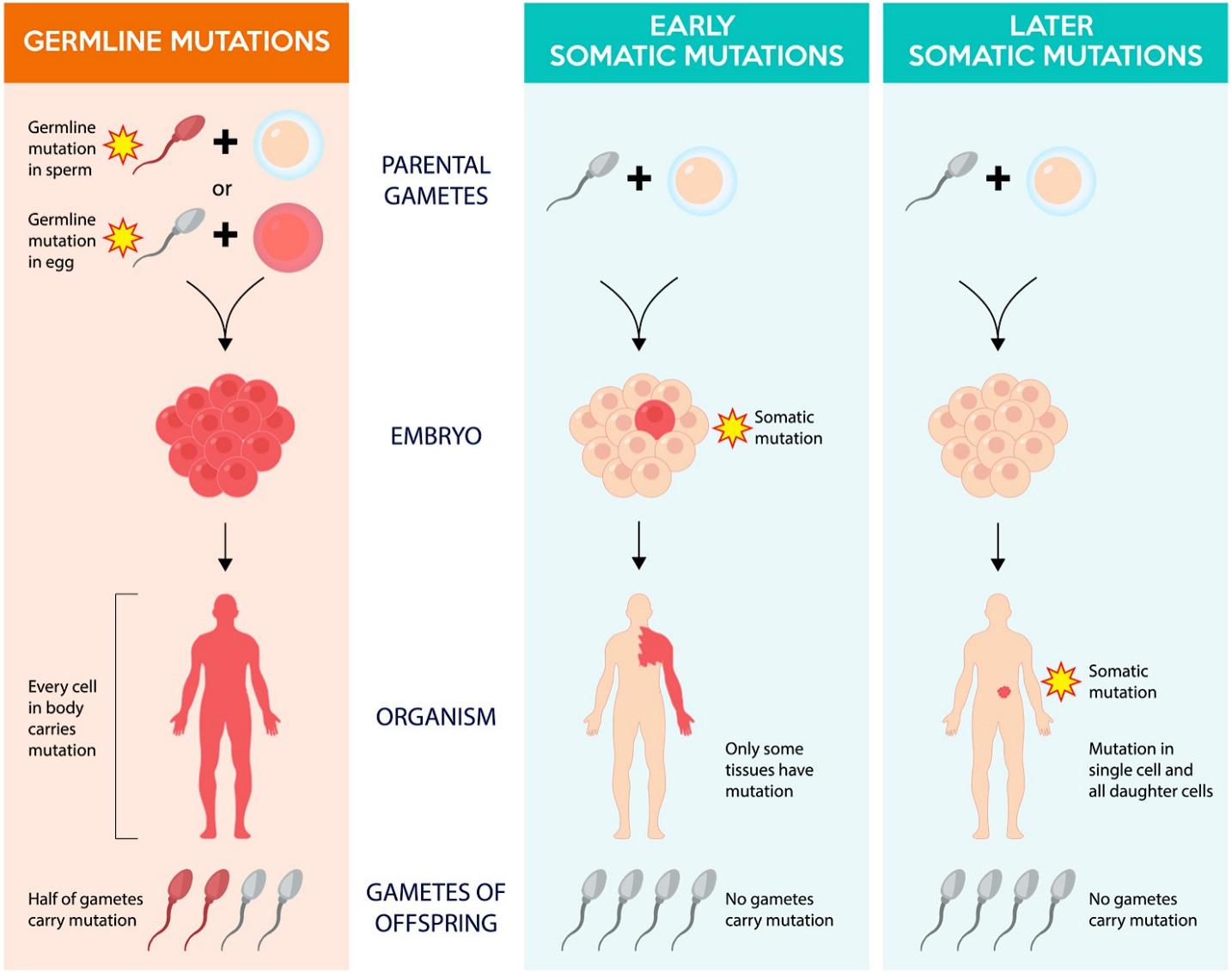
YaleNewHavenHealth
Smilow Cancer Hospital

Yale CANCER CENTER
A Comprehensive Cancer Center Designated by the National Cancer Institute

Patient Case: 74 yo M with Metastatic Prostate Cancer

- FH: mother with breast cancer at 37 yrs
- PSA 150, bone mets seen on bone scan
- Treated with leuprolide, abiraterone/prednisone
- PSA starts rising→docetaxel chemotherapy→progresses after 2 mo

Somatic & Germline Variants in Cancer Care

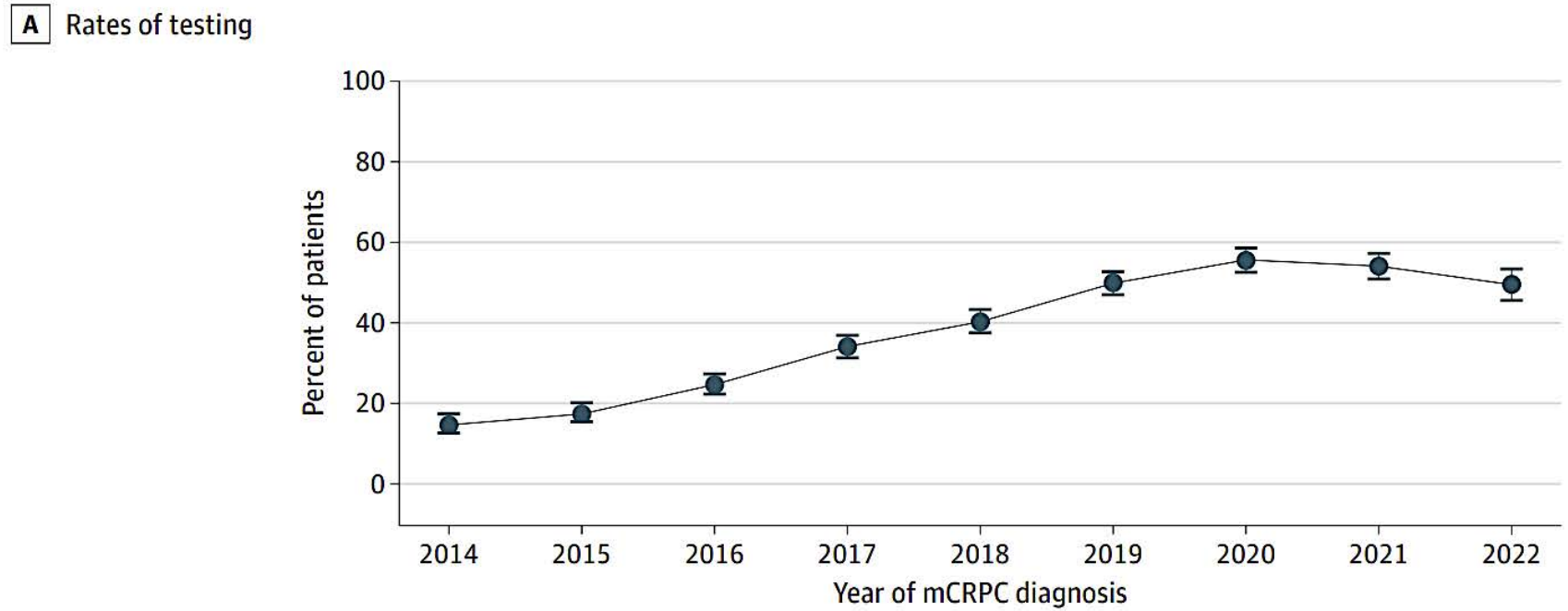


Germline testing is used to determine the lifetime risk for developing cancer in a patient as well as identify risk in family members

Somatic tumor profiling can assess prognosis, determine individualized therapy options, and provide information about clinical trials

~60% of mCRPC Patients Do Not Get Tested!

Figure 1. Homologous Recombination Repair Mutation Testing Rates and Timing of Testing Among Patients Diagnosed With Metastatic Castration-Resistant Prostate Cancer (mCRPC) Each Year



No. at risk									
Tested	130	185	283	426	454	612	596	525	327
Not tested	752	867	866	822	673	618	477	447	335
All	882	1052	1149	1248	1127	1230	1073	972	662

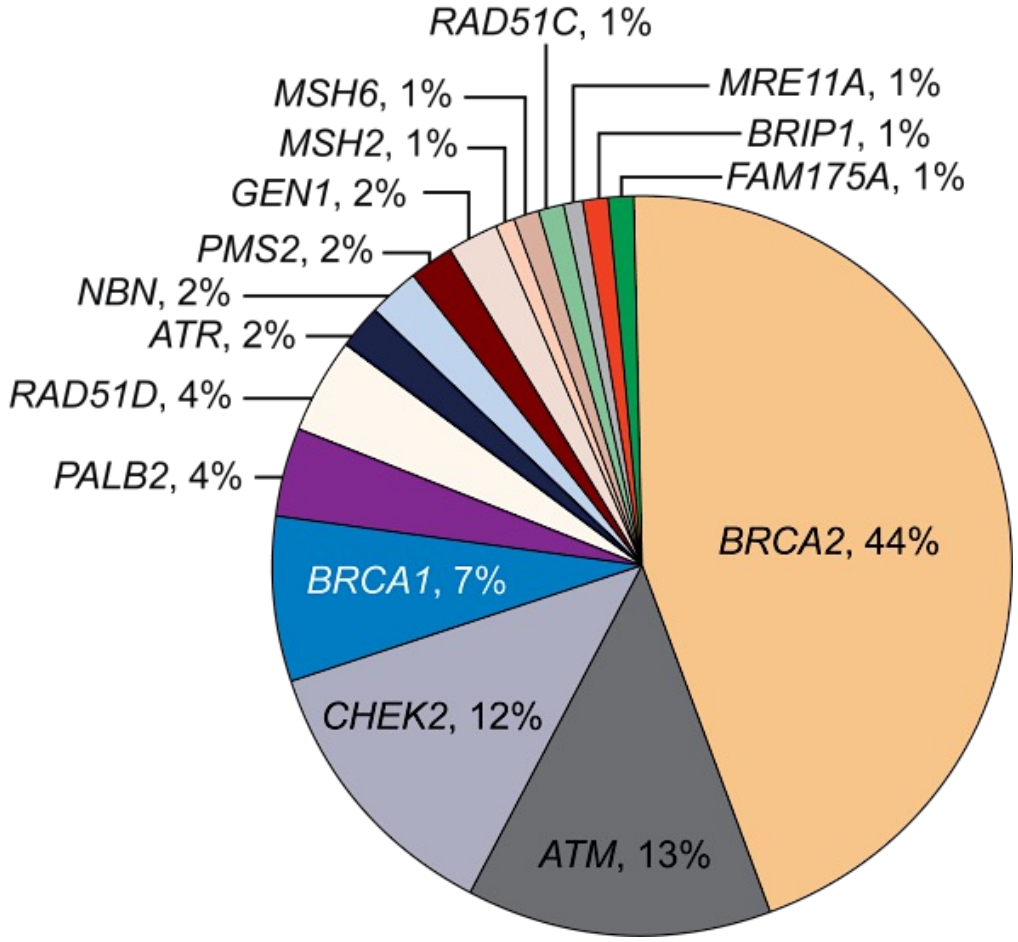
YaleNewHavenHealth
Smilow Cancer Hospital

Yale CANCER CENTER
A Comprehensive Cancer Center Designated by the National Cancer Institute

DNA Repair Gene Alterations Are Common in Metastatic Prostate Cancer[1,2]

- **23%** of mCRPCs harbor DNA damage repair (DDR) alterations
- The frequency of DDR mutations increases with disease progression

- **About half of these (~12%)** have germline alterations in DDR genes
- Age and family history do not affect mutation frequency



1. Robinson D et al. *Cell*. 2015;161:1215-1228. 2. Pritchard CC et al. *N Engl J Med*. 2016;375:443-453.

PARP Inhibitor Combination Strategies for M1 CRPC

Synergy: PARPi + Androgen Receptor Signaling

Induces “BRCAness”

- Induce a BRCA-loss like state that resembles HRR deficiency

Suppression of AR is associated with upregulated PARP activity

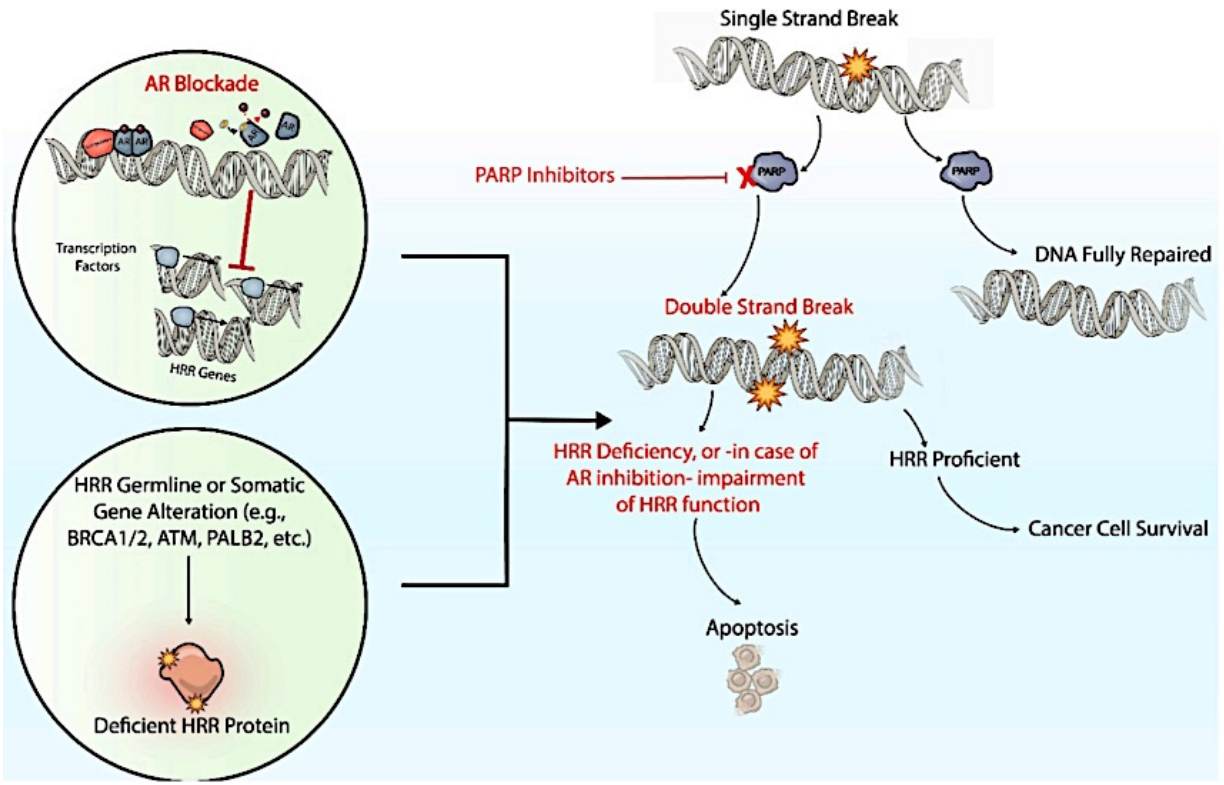
- AR inhibition might provide a sensitivity that can be exploited by PARPi

PARP augments AR activity

- PARP indirectly augments AR-driven gene expression programs by binding to transcriptional coactivators

PARPi may attenuate resistance to ARPIs

- Loss of Rb1 is associated with disease progression & ARPI resistance, & can be accompanied by codeletion of BRCA2



Agarwal N, et al. *Eur J Cancer* 2023;192:113249

YaleNewHavenHealth Smilow Cancer Hospital | Yale CANCER CENTER A Comprehensive Cancer Center Designated by the National Cancer Institute

PROpel: Study Design

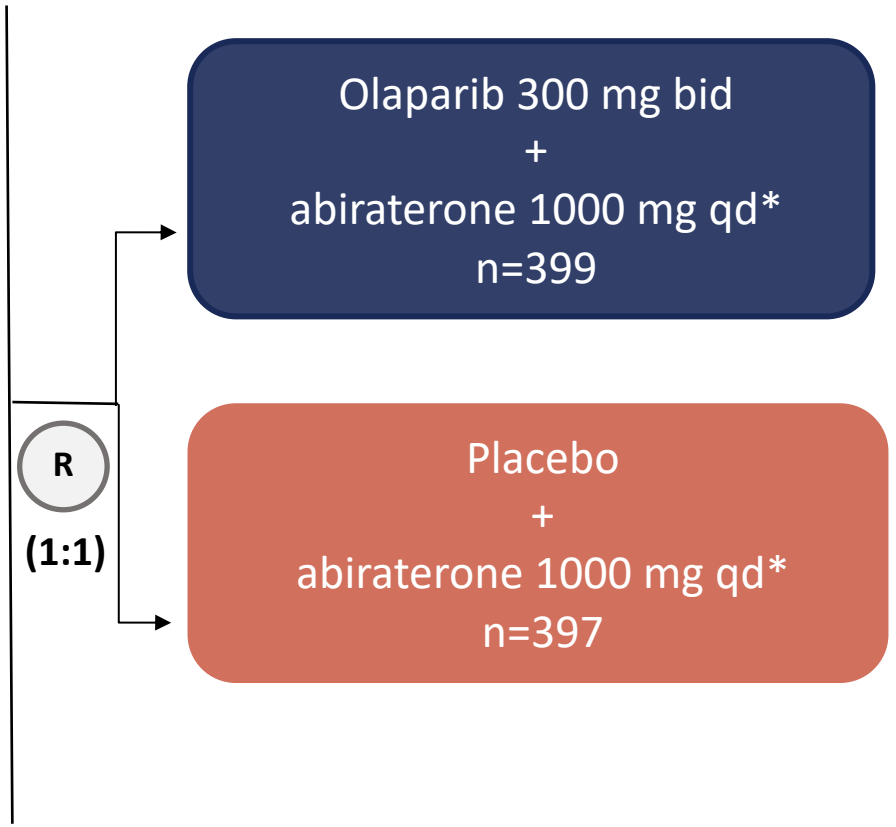
Phase 3, global, randomized, double-blind trial

Key Eligibility Criteria

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

Stratified by:

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



Primary Endpoint:

- **Radiographic progression or death (rPFS) by investigator assessment**

Key Secondary Endpoint:

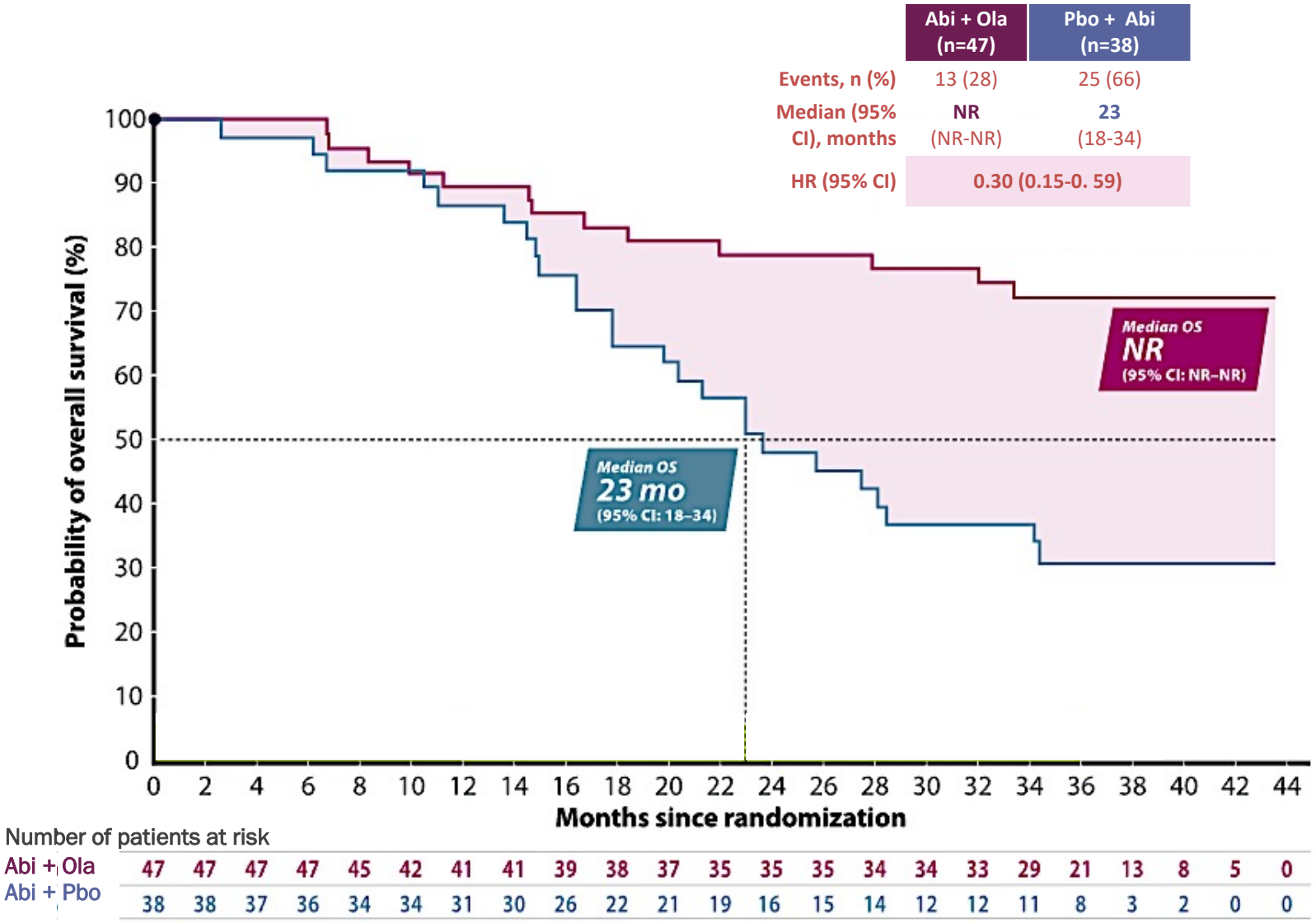
- Overall survival (alpha control)

Other Secondary Endpoints

- Time to first subsequent therapy or death (TFST)
- Time to second progression or death (PFS2)
- Objective response rate (ORR)
- HRRm† prevalence (retrospective testing)
- Health-related quality of life
- Safety and tolerability

Clarke NW. NEJM Evid 2022;1(9):EVIDoa2200043

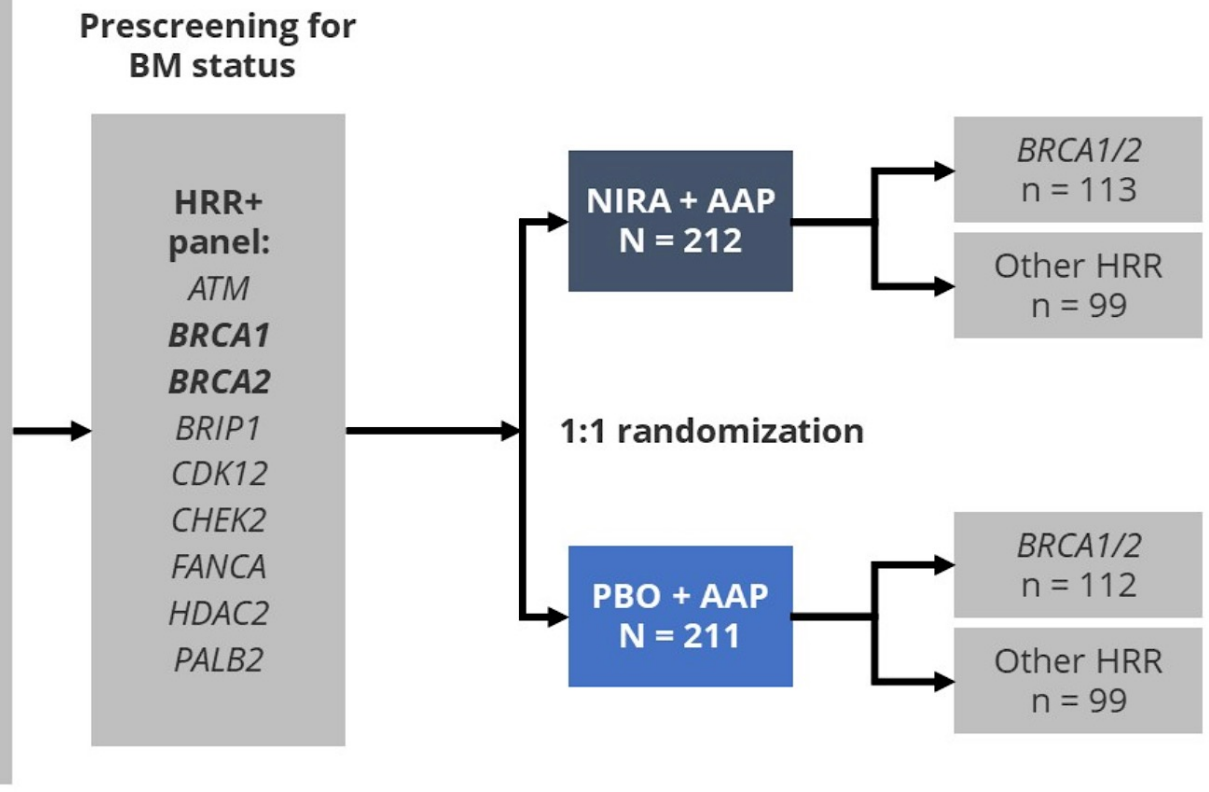
PROpel: Olaparib + Abiraterone for the 1L Treatment of Metastatic CRPC – OS in *BRCA*m



MAGNITUDE: Study Design

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

Stratifications
- Prior taxane-based chemotherapy for mCSPC
- Prior ARi for nmCRPC or mCSPC
- Prior AAP for L1 mCRPC
- HRR+ cohort only:
  - *BRCA1/2* vs other HRR gene alterations



IA2 assessments

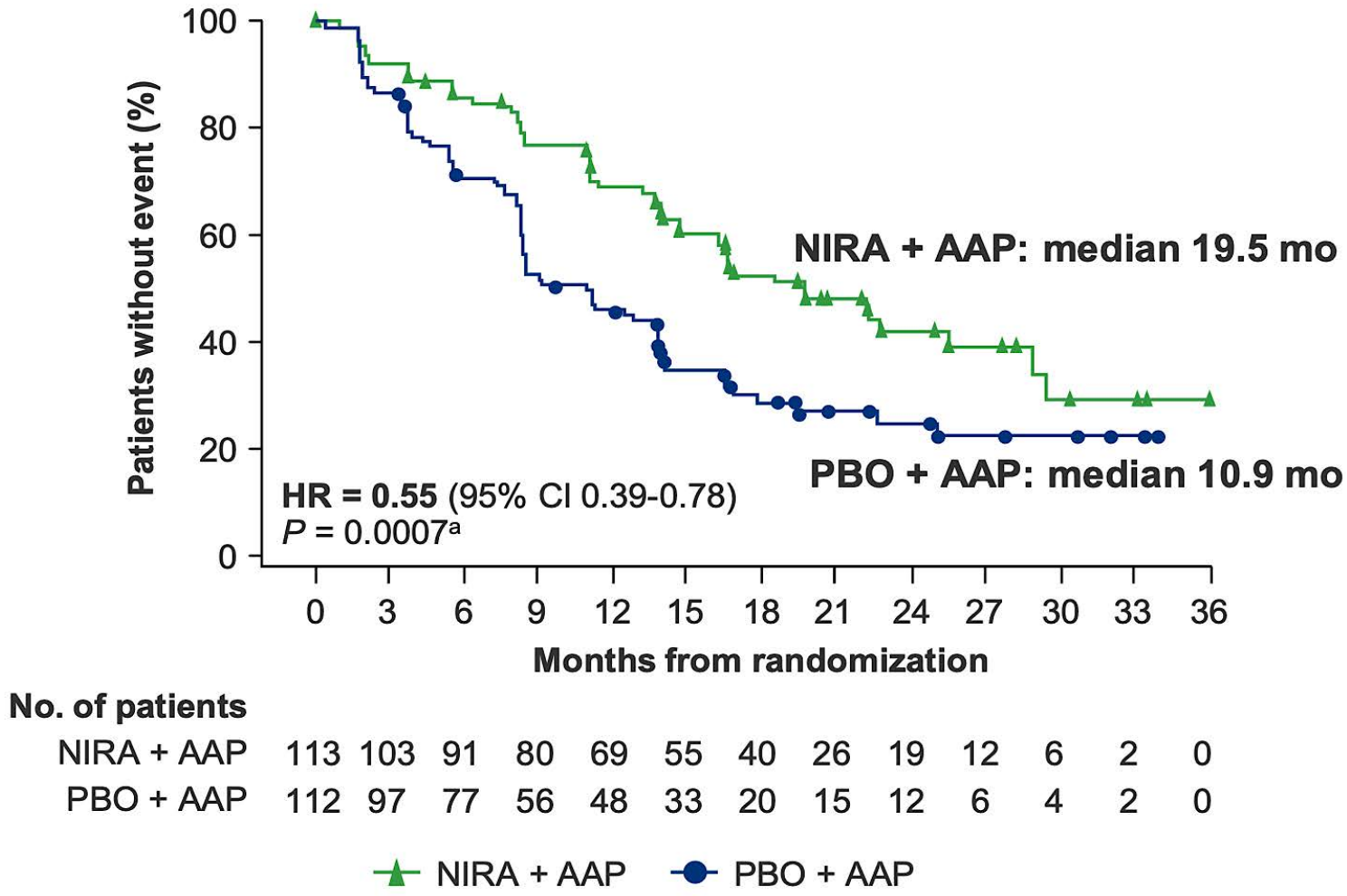
Primary endpoint[a]
- rPFS by central review

Secondary endpoints[b]
- TCC
- TSP
- OS

Other endpoints
- TTPP
- TTPI

Efstathiou et al. ASCO GU 2023;Abstract 170.

MAGNITUDE: rPFS in BRCA1/2 Subgroup



Efstathiou et al. ASCO GU 2023;Abstract 170.

TALAPRO-2: Study Design

Phase 3, randomized, double-blind, placebo-controlled trial

Key Eligibility Criteria

- **First-line mCRPC**
- **ECOG PS 0-1**

Stratified by:

- **Prior abiraterone or docetaxel in castration-sensitive setting: Y vs. N**
- **HRR gene alteration status: deficient vs. nondeficient vs. unknown**

N=805

R
1: 1

Talazoparib 0.5mg* + enzalutamide 160mg once daily
N=402

*0.35mg daily of moderate renal impairment

Placebo + enzalutamide 160mg once daily
N=403

Primary Endpoint:

- Radiographic progression-free survival (rPFS) by BICR

Key Secondary Endpoint:

- Overall survival (alpha protected)

Other Secondary Endpoints

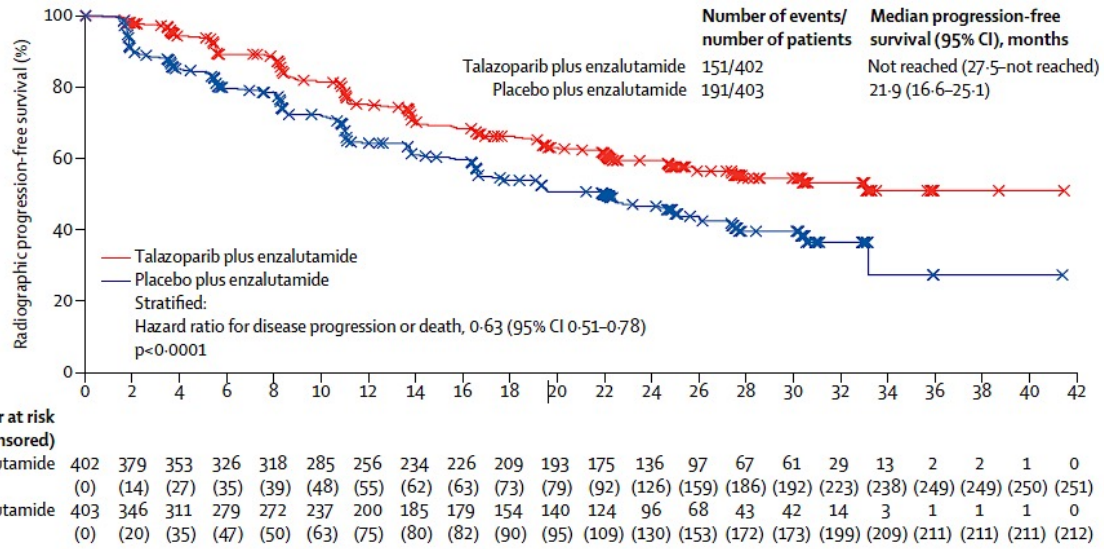
- Time to cytotoxic chemotherapy
- PFS2 by investigator assessment
- ORR
- Patient-reported outcomes
- Safety

ECOG, Eastern Cooperative Oncology Group; BICR: Blinded Independent Central Review; ORR: Objective Response Rate

Agarwal N et al. *Lancet* 2023;402(10398):291-303.

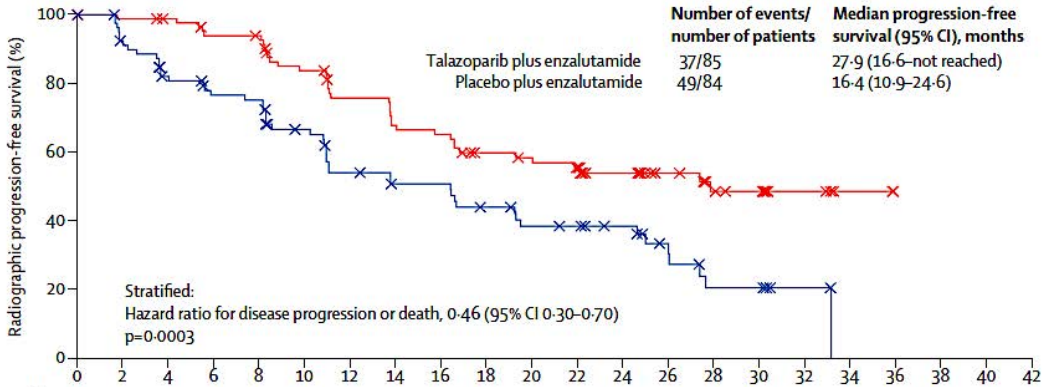
TALAPRO-2: rPFS by BICR

All Patients



Number at risk (number censored)																					
Talazoparib plus enzalutamide	402	379	353	326	318	285	256	234	226	209	193	175	136	97	67	61	29	13	2	2	1	0
	(0)	(14)	(27)	(35)	(39)	(48)	(55)	(62)	(63)	(73)	(79)	(92)	(126)	(159)	(186)	(192)	(223)	(238)	(249)	(249)	(250)	(251)
Placebo plus enzalutamide	403	346	311	279	272	237	200	185	179	154	140	124	96	68	43	42	14	3	1	1	1	0
	(0)	(20)	(35)	(47)	(50)	(63)	(75)	(80)	(82)	(90)	(95)	(109)	(130)	(153)	(172)	(173)	(199)	(209)	(211)	(211)	(211)	(212)

HRR - deficient



Number at risk (number censored)																					
Talazoparib plus enzalutamide	85	83	81	76	75	65	57	51	49	42	40	37	30	23	17	15	6	3	0	..	..	..
	(0)	(1)	(3)	(4)	(5)	(7)	(9)	(9)	(9)	(12)	(13)	(14)	(20)	(27)	(31)	(33)	(42)	(45)	(48)			
Placebo plus enzalutamide	84	72	61	55	54	43	34	30	30	25	21	20	17	11	6	6	2	0	0	..	..	..
	(0)	(6)	(9)	(11)	(11)	(16)	(17)	(19)	(19)	(20)	(21)	(22)	(25)	(29)	(30)	(30)	(34)	(35)	(35)			

Agarwal N et al. *Lancet* 2023;402(10398):291-303.

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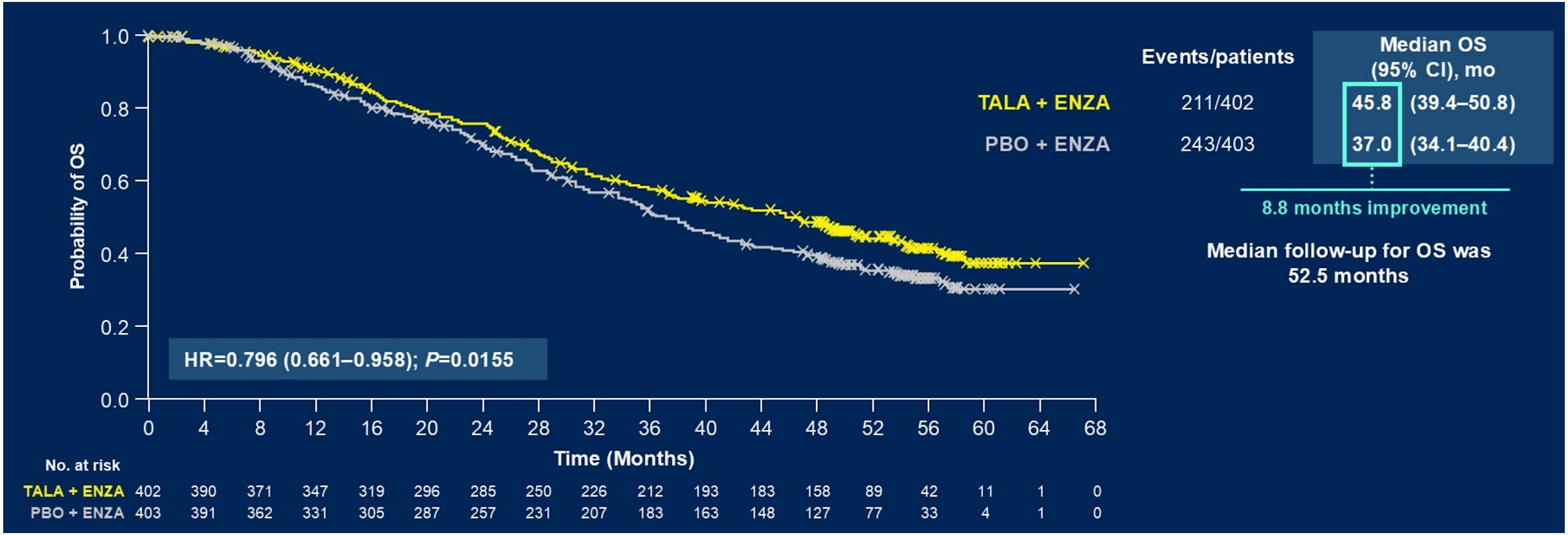
TALAPRO-2: OS Analysis



Agarwal et al. ASCO GU 2025;Abstract LBA18.

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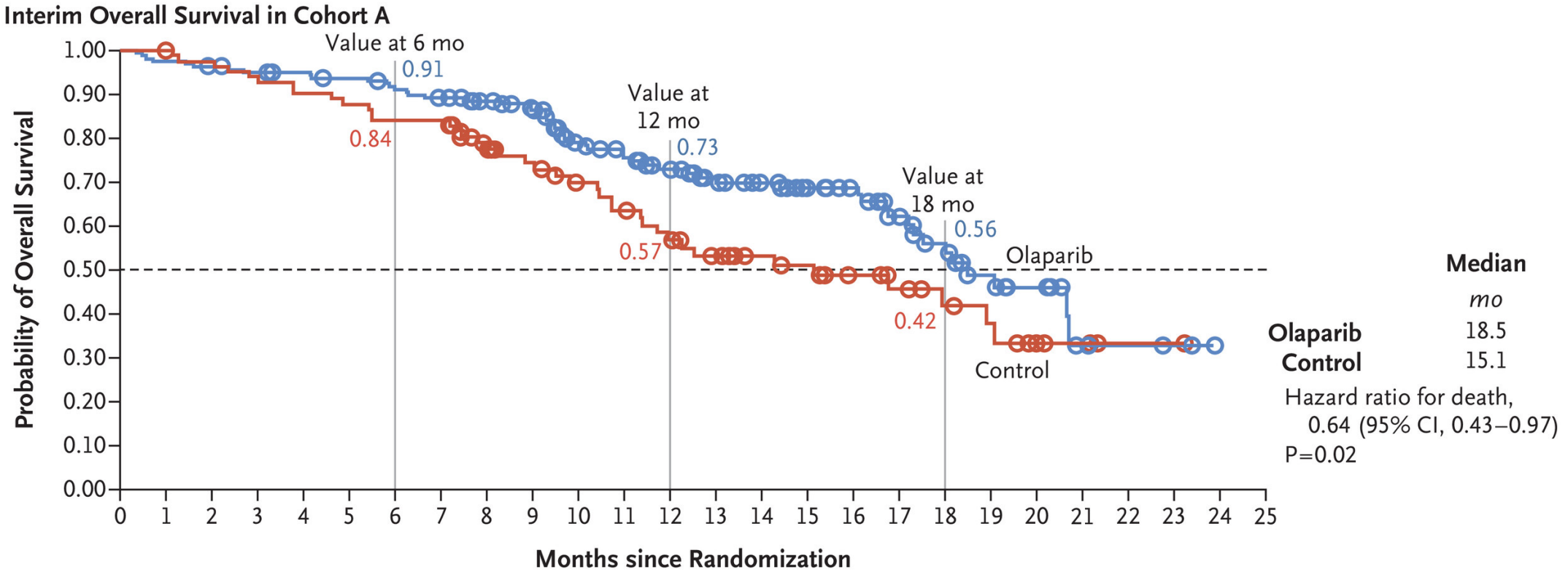
PARP Inhibitor Monotherapy Strategies in M1 CRPC

PROfound: OS in Cohort A (*BRCA1*, *BRCA2*, or ATM)



Mateo J, et al. *N Engl Med* 2020;382(22):2091-2102.

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PARPi Adverse Events

	Olaparib + AAP	Niraparib + AAP	Talazoparib + Enzalutamide	Olaparib	Rucaparib
	PROpel[1]	MAGNITUDE[2]	TALAPRO-2[3]	PROfound[4]	TRITON3[5]
Anemia					
Any Grade	198 (50)	105 (50)	262 (66)	119 (46)	126 (47)
Grade ≥3	64 (16)	64 (30)	165 (46)	55 (21)	64 (24)
Fatigue or Asthenia					
Any Grade	153 (39)	63 (30)	134 (34)	105 (41)	165 (61)
Grade ≥3	10 (3)	8 (4)	16 (4)	7 (3)	19 (7)
Nausea					
Any Grade	122 (31)	52 (25)	82 (21)	106 (41)	134 (50)
Grade ≥3	1 (<1)	1 (<1)	2 (<1)	7 (1)	7 (3)
PE	29 (7)	4 (2)	10 (3)	11 (4)	9 (3)
MDS / AML	MDS: 2 pts.	-	MDS: 1 pt AML: 1 pt	-	-

Represented as n,(%)

PE: Pulmonary ebmbolism; MDS: myelodysplastic syndrome; AML: acute myeloid leukemia

1. Saad F, et al. *Lancet Oncol*. 2023;24(10):1094-1108 2. Chi KN, et al. *Ann Oncol*. 2023;34(9):772-782. 3. Agarwal N et al. *Lancet* 2023;402(10398):291-303. 4. de Bono J, et al. *N Engl Med* 2020;382(22):2091-2102. 5. Fizazi K, et al. *N Engl J Med.* 2023;388(8):719-732.

Patient Case: 74 yo M with Metastatic Prostate Cancer

- FH: mother with breast cancer at 37 yrs
- PSA 150, bone mets seen on bone scan
- Treated with leuprolide, abiraterone/prednisone
- PSA starts rising→docetaxel chemotherapy→progresses after 2 mo
- Genomic testing on tumor shows BRCA2 mutation and he starts on Olaparib
- PSA declines by 90% and pain improves

Roundtable Discussion

RTP
RESEARCH
TO PRACTICE

Nursing Considerations for Patients Receiving PARP Inhibitors

Monica Averia, MSN, AOCNP, NP-C

Genetic counseling for patients with germline BRCA and other homologous recombination repair (HRR) abnormalities offers benefits for their children/grandchildren by:

- **Identifying At-Risk Family Members:**
  - Once a cancer-predisposing BRCA1 or BRCA2 germline variant is identified, testing at-risk relatives can identify those who also carry the familial variant.

- **Early Detection and Prevention:**
  - Allows for earlier and more targeted screening and preventive measures.

- **Personalized Treatment:**
  - Knowing about a BRCA mutation or other HRR abnormality can influence treatment decisions, as some therapies are more effective in individuals with these genetic changes.

Genetic counseling for patients with germline BRCA and other homologous recombination repair (HRR) abnormalities offers several benefits for their children/grandchildren:

- **Informed Decision-Making:**
  - Provides individuals with the knowledge and support they need to make informed decisions about their health and family planning.

- **Reducing Uncertainty:**
  - Help individuals and families understand the implications of genetic test results, potentially reducing anxiety and uncertainty.

- **Access to Resources and Support:**
  - Connect individuals and families with resources and support networks, including cancer support groups and other relevant organizations.

What do you tell your patients about to start treatment with a PARP inhibitor about how it works and why they are receiving it?

- PARP inhibitors target DNA repair mechanisms.
- A type of targeted therapy that interferes with a specific protein (PARP) that helps cancer cells repair DNA damage.
- By blocking PARP, PARP inhibitors can cause cancer cells to die, especially those with certain DNA repair defects.

What do you tell your patients about to start treatment with a PARP inhibitor about how it works and why they are receiving it?

- **Olaparib + Abiraterone + Prednisone:**
  - Approved for patients with mCRPC who have deleterious or suspected deleterious mutations in the BRCA1 or BRCA2 genes.
- **Rucaparib:**
  - Approved for patients with mCRPC with BRCA1/2 mutations, after progression on prior androgen receptor-targeting agents and taxane-based chemotherapy.
- **Niraparib + Abiraterone + Prednisone:**
  - Approved for patients with mCRPC who have deleterious or suspected deleterious mutations in the BRCA1 or BRCA2 genes.
- **Talazoparib + Enzalutamide:**
  - Approved for patients with mCRPC with homologous recombination repair (HRR) gene alterations.

Dosing and Side Effects

Olaparib + Abiraterone + Prednisone:

- Olaparib 300 mg po BID + Abiraterone 1000 mg po daily + Prednisone
- Fatigue
- GI: nausea, diarrhea, decreased appetite, abd pain
- Cough
- Anemia, Lymphopenia

Rare: Myelodysplastic syndrome, venous thrombolytic events, pneumonitis, embryo-fetal toxicity

Niraparib + Abiraterone + Prednisone:

- Niraparib 200 mg po daily + Abiraterone 1000 mg po daily + Prednisone
- Fatigue
- GI: nausea, vomiting, decreased appetite
- Anemia, Neutropenia, Thrombocytopenia

Rare: MDS, acute myeloid leukemia

Dosing and Side Effects

Talazoparib + Enzalutamide

- Talazoparib 0.5 mg po daily + Enzalutamide 160 mg po qd
- Fatigue
- GI: nausea, vomiting, diarrhea
- Anemia, Neutropenia, Thrombocytopenia

Rare: Myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML)

Rucaparib

- Rucaparib 600 mg po twice daily
- Fatigue
- GI: nausea, vomiting, diarrhea, constipation
- Anemia, thrombocytopenia
- Inc AST/ALT
- Rash

Rare: MDS, venous thrombolytic events, pneumonitis, embryo-fetal toxicity

How do you monitor and manage common toxicities associated with PARP inhibitors?

- **Fatigue:**
  - Exercise, massage, cognitive behavioral therapy
  - Evaluate for other potential causes: anemia, thyroid dysfunction, vitamin deficiencies

- **Nausea:**
  - Prophylactic antiemetics can be given about 30-60 minutes prior to each PARP inhibitor dose
  - Olaparib interacts with CYP3A4, patients should not take aprepitant
  - Recommend taking PARPI after meals to reduce risk of nausea

- **Vomiting:**
  - Identify food triggers, food diary.
  - Do not take a second dose of medication if they vomit after the first one.

How do you monitor and manage common toxicities associated with PARP inhibitors?

- **Diarrhea/constipation:** Loperamide and Laxatives, respectively.

- **Anemia, Thrombocytopenia, Neutropenia**

- Labs: initiation of treatment, q monthly CBC with differential

- Anemia:
  - Evaluate for other causes of anemia
  - Hold PARP inhibitor for grade ≥ 3 anemia
  - Transfuse prbc
  - Once Hgb returns to baseline and when symptoms resolve, restart PARP inhibitor at reduced dose

- Thrombocytopenia:
  - Transfusion for thrombocytopenia is rare, but consider for patient with Plt <10K

***Fatigue, GI symptoms, cytopenia: the 3 most common toxicities of PARP inhibitors**

How do you monitor and manage common toxicities associated with PARP inhibitors ?

- Treatment: until disease progression or unacceptable toxicity
- Manage PARP toxicities: with treatment hold, dose modification, supportive care
- Patient on PARP inhibitors: concomitant GnRH or s/p bilateral orchiectomy.
- Address side effects of ADT: sexual dysfunction, body changes, emotional lability, etc
- Less common effects: headache, insomnia, dizziness, cough, cutaneous reactions (rucaparib), HTN
- Assess therapeutic burden: Increased burden is associated with decreased QOL and well being.
- Identify potential barriers: Financial, compliance, etc

Clinical examples/experiences from practice

- 74 yr old male

- 9/10/21: PSA of 5.9

- 11/8/21: Prostatectomy: GG5 (4+5) Adenocarcinoma of the Prostate. pT3bN0

- 12/17/21: PSA 0.47

- 12/29/21: PET fluciclovine F 18: showed s/p radical prostatectomy with nonspecific radiotracer uptake in the prostatectomy bed (SUV max 5.4)

-Treatment: 6 months of ADT + RT: prostate fossa and pelvic LNs (2/16/22 - 4/5/22)

- 4/25/22: PSA <0.03; Testosterone <12

Clinical examples/experiences from practice

5/2022 to 11/2023: PSA <0.02; Testosterone <12

02/09/24: PSA 0.02; Testosterone <12

05/10/24: PSA: 0.07; Testosterone <12

8/14/24: PSA: 0.36; Testosterone <12

9/11/24: PET piflufolastat F 18: Increased uptake in the left proximal femur

9/11/24: PSA: 1.72; Testosterone <12

- New c/o left leg discomfort, with/without activity. No pain med required

Clinical examples/experiences from practice

-10/2024: Tumor profiling: ATM mutation

- 10/2024: Olaparib + Abiraterone + Prednisone

- 11/11/24: PSA 0.72 (from 1.72); Testosterone <12

- 12/6/24: PSA 0.17; Testosterone <12

- 12/13/24 to 12/30/24: SBRT to Left Femur

- 01/17/25: PSA <0.02; Testosterone <12

- 4/2/25: PSA <0.02; Testosterone <12. Pt asymptomatic. Tolerating Olaparib + Abi + Pred
- SE: G1: fatigue, nausea controlled with prn antiemetics 1-2 per wk
- Continue q mnth follow-up with labs, cont ADT, Ca + Vit D
- Daughter x 1: Genetic testing: No actionable mutations

Roundtable Discussion

RTP
RESEARCH
TO PRACTICE

Agenda

Module 1: Recent Advances in the Treatment of Nonmetastatic Prostate Cancer

Module 2: Treatment Approaches for Metastatic Hormone-Sensitive Prostate Cancer

Module 3: Current Role of PARP Inhibitors in Metastatic Castration-Resistant Prostate Cancer (mCRPC)

Module 4: Current and Future Role of Radiopharmaceuticals in mCRPC

Clinical Scenario

A patient receives darolutamide/docetaxel/ADT for mHSPC but is then found to have new bone-only metastases on PSMA PET and receives radium-223

UCSF Helen Diller Family Comprehensive Cancer Center

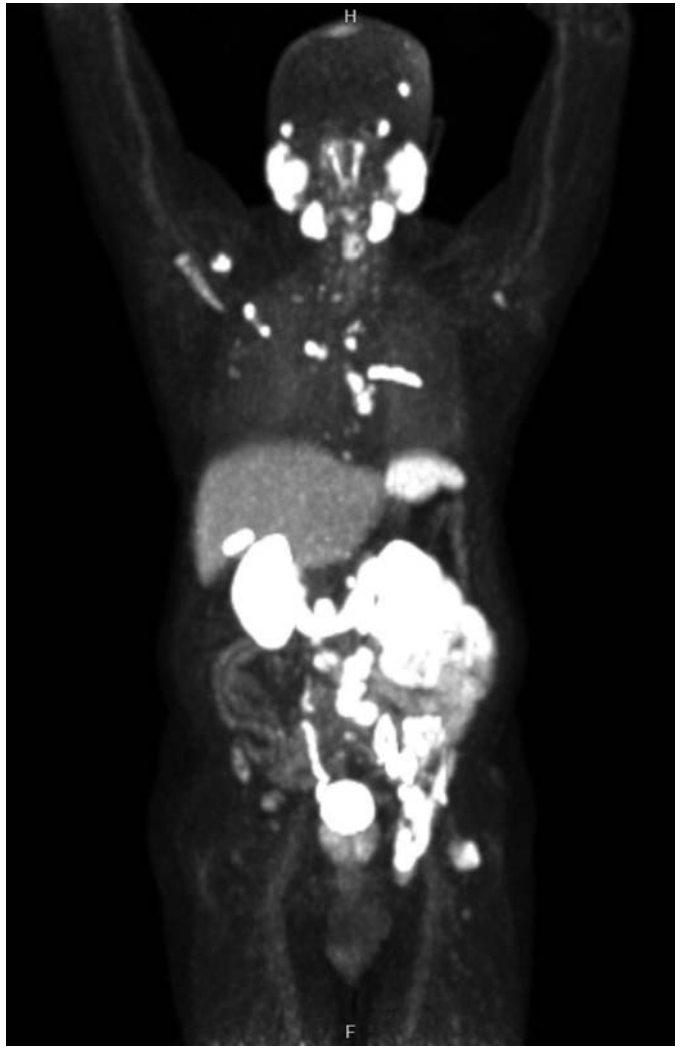
Current and Future Role of Radiopharmaceuticals in mCRPC

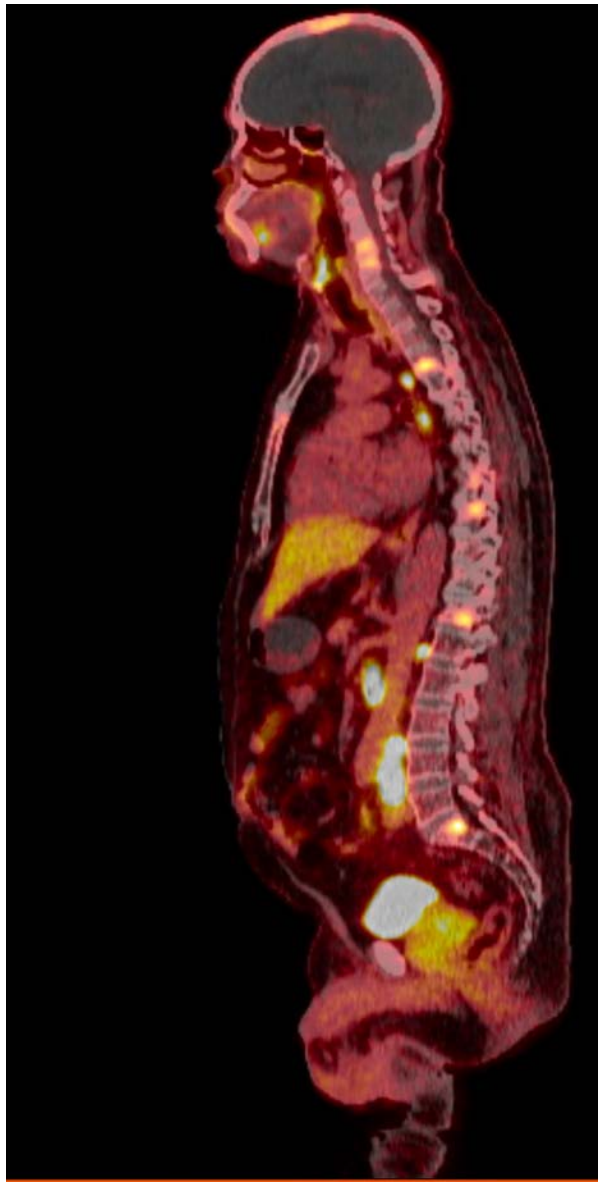
Rahul Aggarwal, MD
Professor of Medicine
University of California San Francisco

74 year old male who is a current patient of mine…

- Presented to PCP with back pain, obstructive urinary symptoms in 2020
- PSA was 124 ng/mL
- TRUS biopsy with Gleason 4+4 prostate adenocarcinoma
- Germline testing: negative for pathogenic mutations
- Somatic testing: *TMPRSS2-ERG fusion, PTEN deletion, TP53,* MSS, TMB 1 mutation/MB
- PSMA PET with multifocal osseous metastases + nodal metastases

Staging PSMA PET



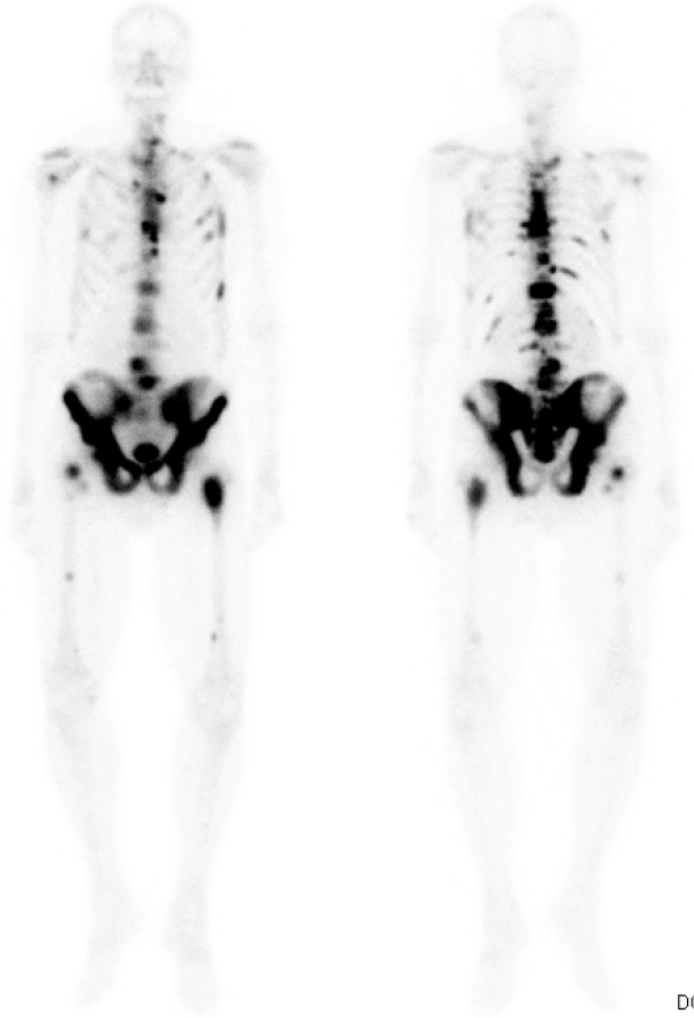


Case continued…

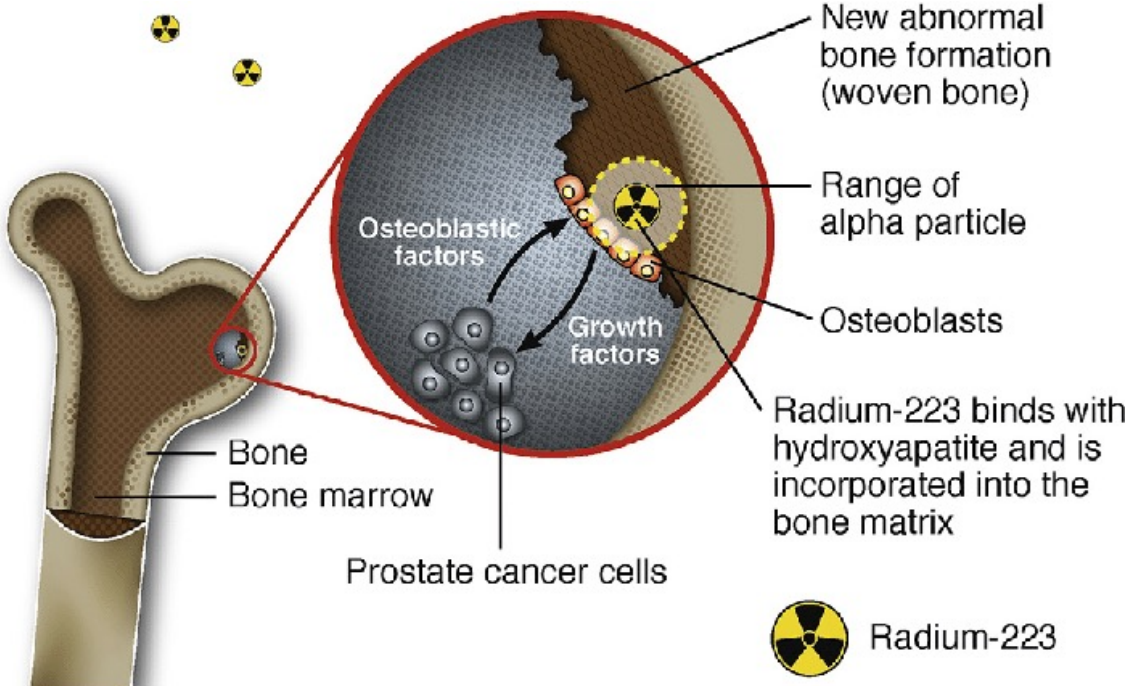
- Patient treated with ‘triplet therapy’ – ADT + darolutamide + docetaxel chemotherapy x 6 cycles
- Followed by continuation of ADT + darolutamide
- Nadir PSA was 0.02 ng/mL at 12 months following start of treatment
- Short time to castration resistance with subsequent rising PSA
  - 0.02 → 0.5 → 1.7 → 2.5 → 12.4
- Unable to obtain insurance authorization for PSMA PET
- Underwent conventional imaging (CT c/a/p + bone scan)

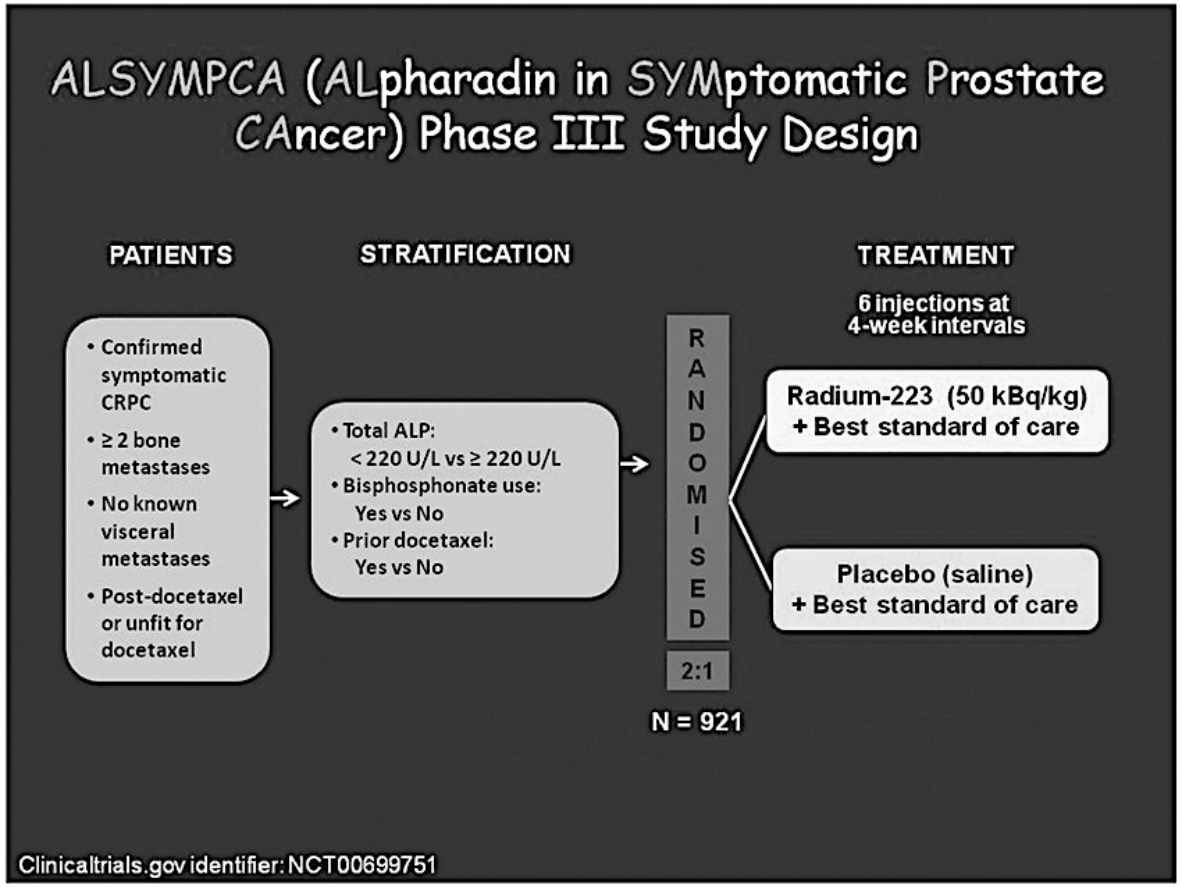
Conventional Imaging Results

- Bone scan with widespread osseous metastases
- CT c/a/p negative for enlarged nodes or visceral metastases
- Increasing bone pain noted in multifocal regions including lumbar spine and bilateral posterior iliac region
- Discussed options of docetaxel re-treatment, cabazitaxel +/- platinum, or radium-223



Radium-223 Improves Survival in Patients with Bone-Predominant Symptomatic mCRPC



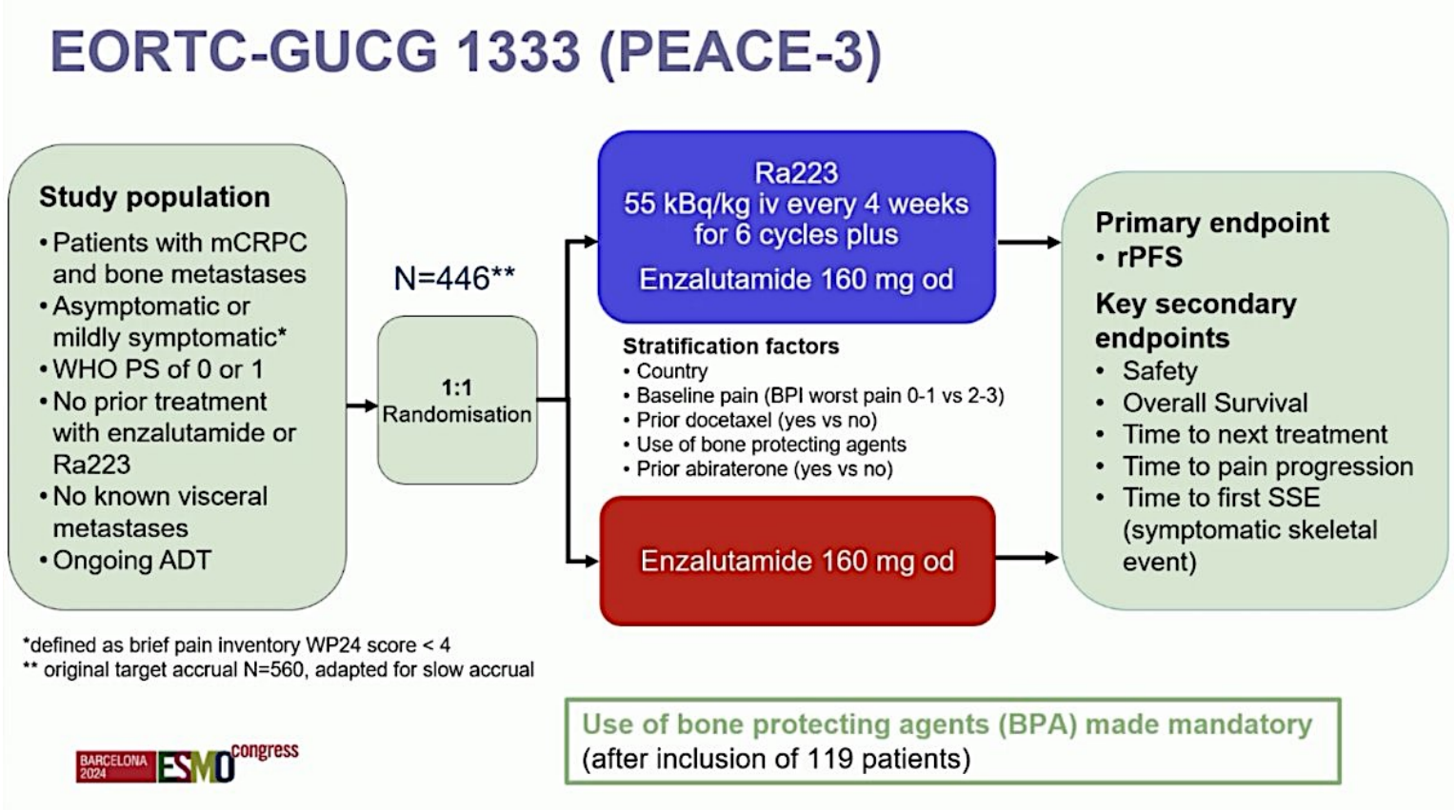


Parker C, et al. New Engl J Med 2013

Radium-223 + Enzalutamide is a First-Line mCRPC Treatment Option for Some Patients

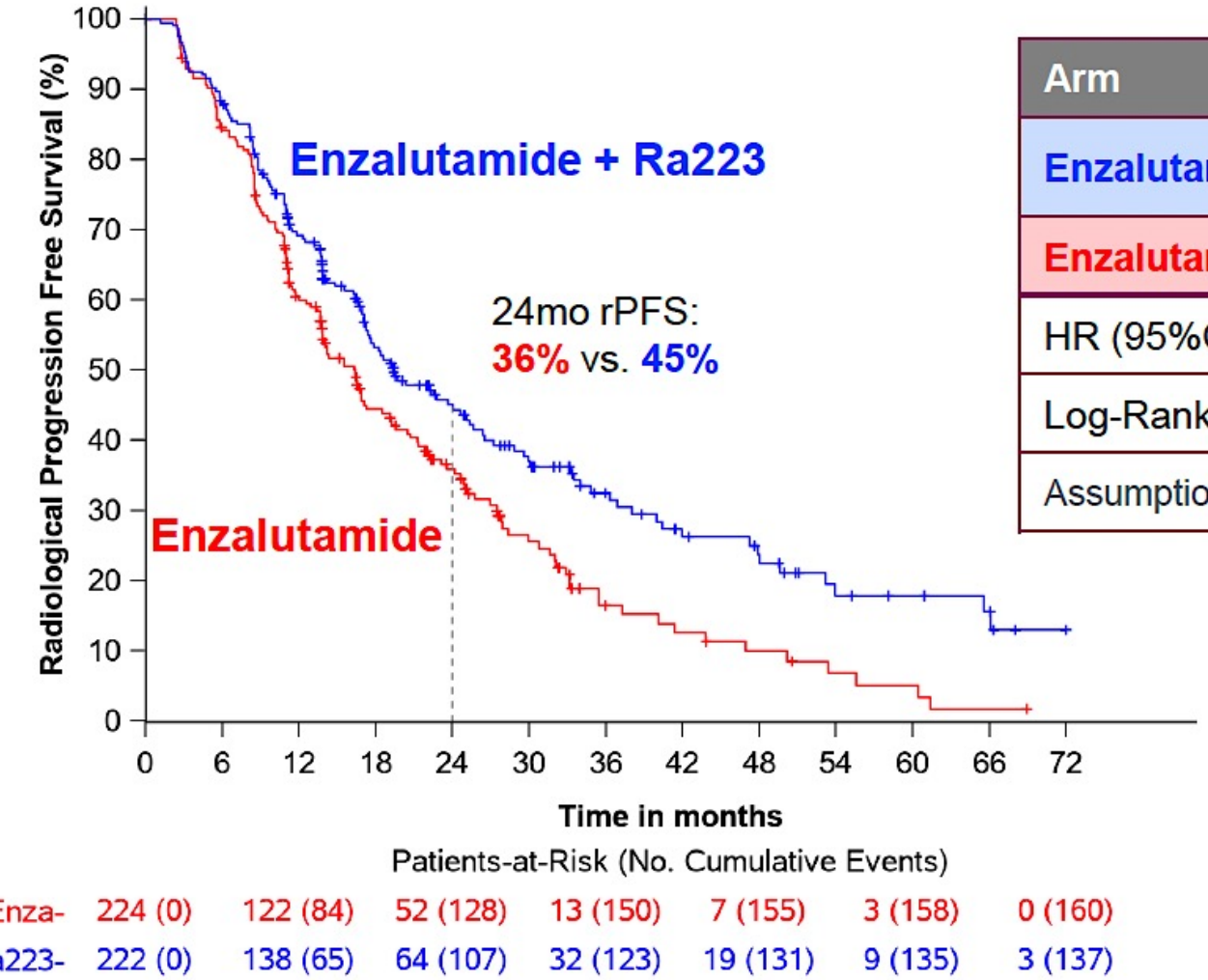
- Radium-223 + enzalutamide improves PFS
  - Unlike in ALSYMPCA, these were asymptomatic/minimally symptomatic patients
  - Potential improvement in OS but longer follow up needed

- Caveat: Majority of patients in this study had not received oral androgen pathway inhibitor



Gillessen S, et al. ESMO 2024

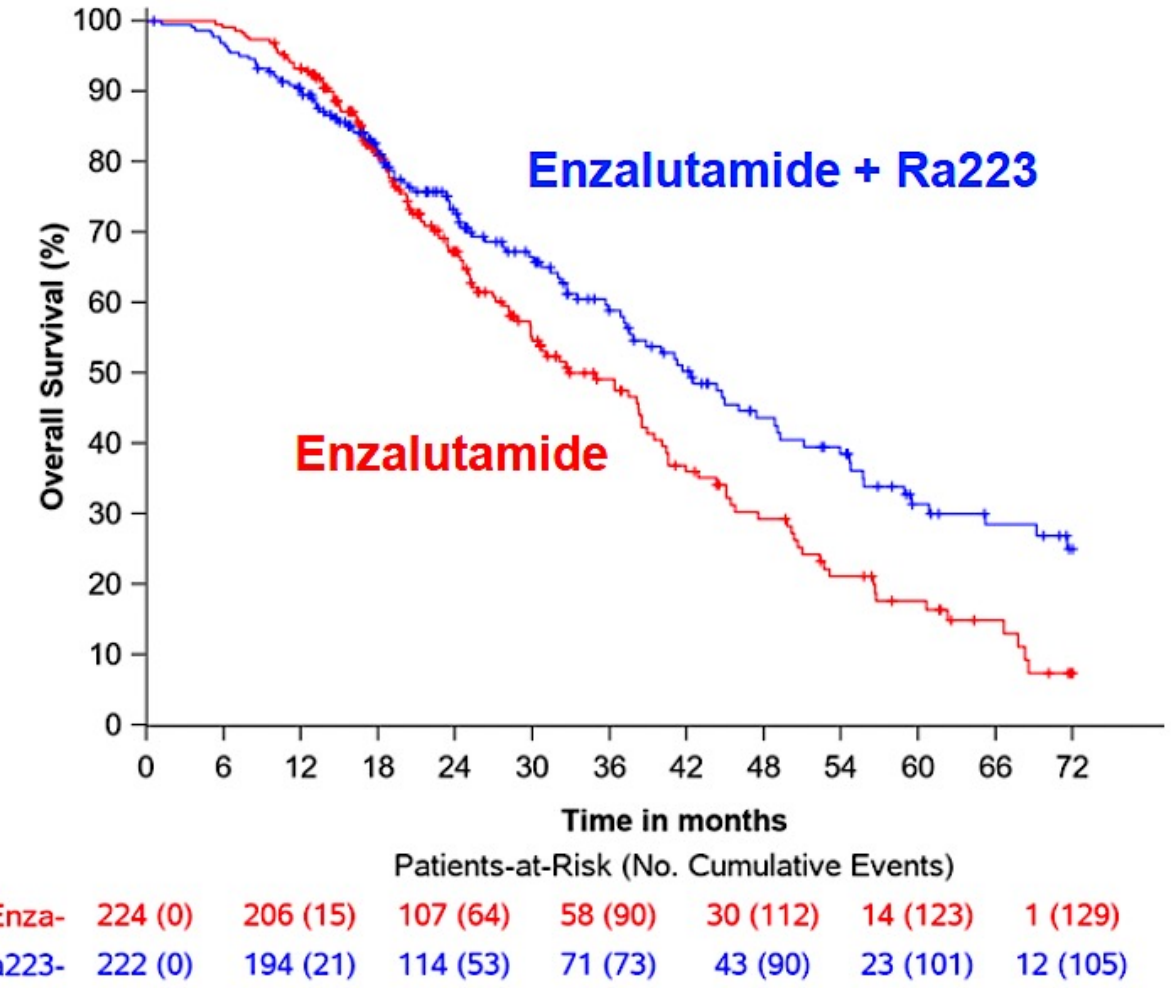
Radium-223 + Enzalutamide: rPFS Analysis



Arm	n/N	Median (95%CI)
Enzalutamide + Ra223	139/222	**19.4** (17.1-25.3) mo
Enzalutamide	160/224	**16.4** (13.8-19.2) mo
HR (95%CI)	**0.69** (0.54-0.87)	
Log-Rank p-value	**0.0009**	
Assumption of proportional hazard achieved		

Gillessen S, et al. ESMO 2024

Radium-223 + Enzalutamide: Interim OS



Arm	n/N	Median (95%CI)
Enzalutamide + Ra223	110/222	**42.3** (36.8-49.1) mo
Enzalutamide	129/224	**35.0** (28.8-38.9) mo
HR (95%CI)	**0.69** (0.52-0.90)	
Log-Rank p-value	**0.0031**	<0.0034

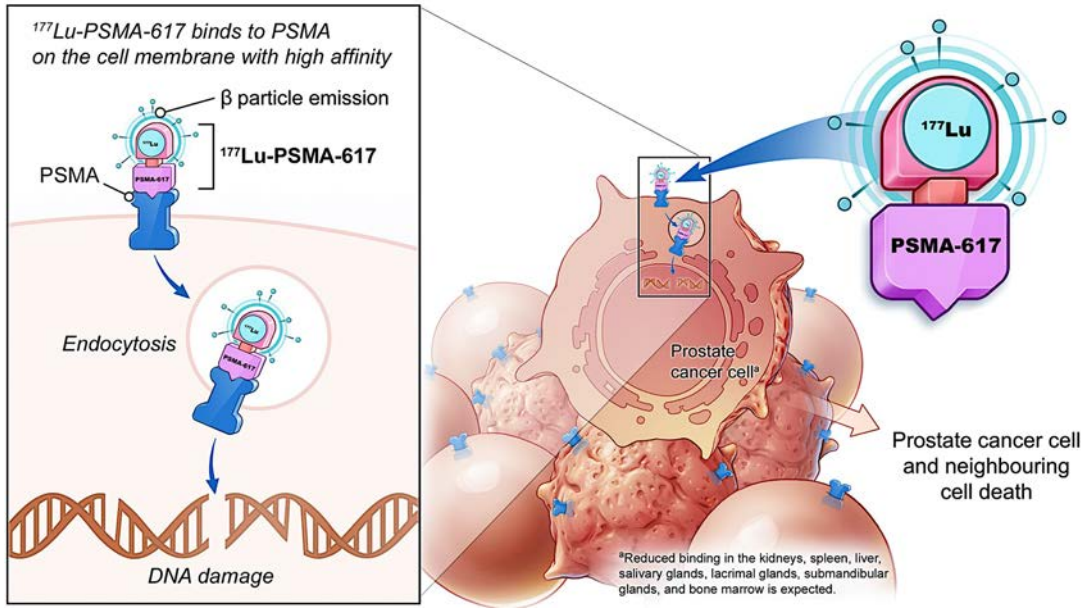
- Pre-set level of significance for interim analysis was ≤ 0.0034
- Due to non-proportional hazards plus lack of unequivocal significance for RMST (restricted mean survival time) sensitivity analysis, study will continue to final OS analysis

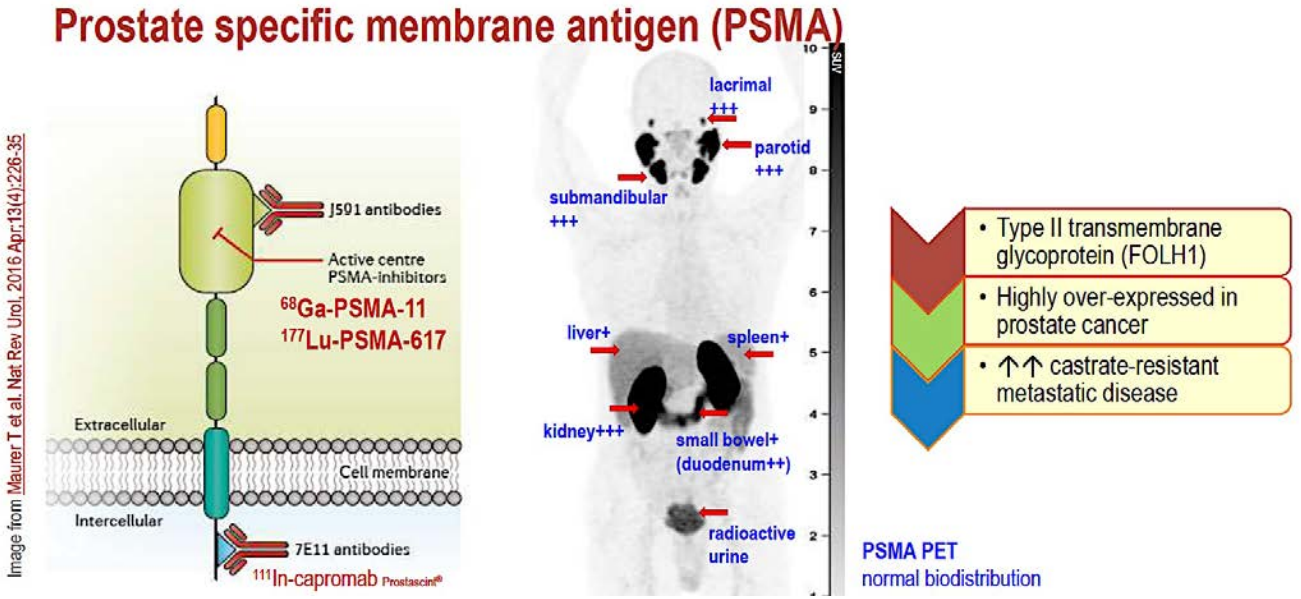
Gillessen S, et al. ESMO 2024

Back to our patient…

- Patient opted for radium-223 as next line of therapy
- Received first three cycles of treatment given IV every 4 weeks
- Improvement in bone pain and reduction in alkaline phosphatase
- Serum PSA continued to rise but slower pace
- Interim CT c/a/p after 3 cycles → no new soft tissue disease
- Completed 3 additional cycles of radium-223 (total of 6 doses)
- Toxicities: Mild flare in bone pain following dose #1, grade 1 anemia (Hgb from 12 to mid 10 range), intermittent mild fatigue and diarrhea
- Following cycle #6, patient asked me what should I do now?
  - Patient goals: Recently retired, wanted to travel and spend time with two grandchildren, wanted to avoid going back on chemotherapy if at all possible

PSMA-Directed Radioligand Therapy



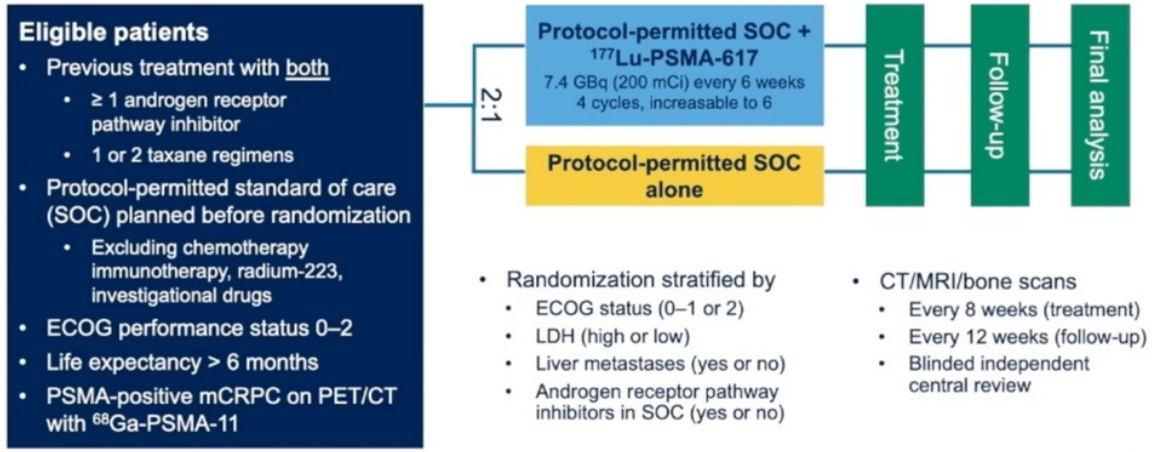


Selection criteria for Lu-PSMA treatment:

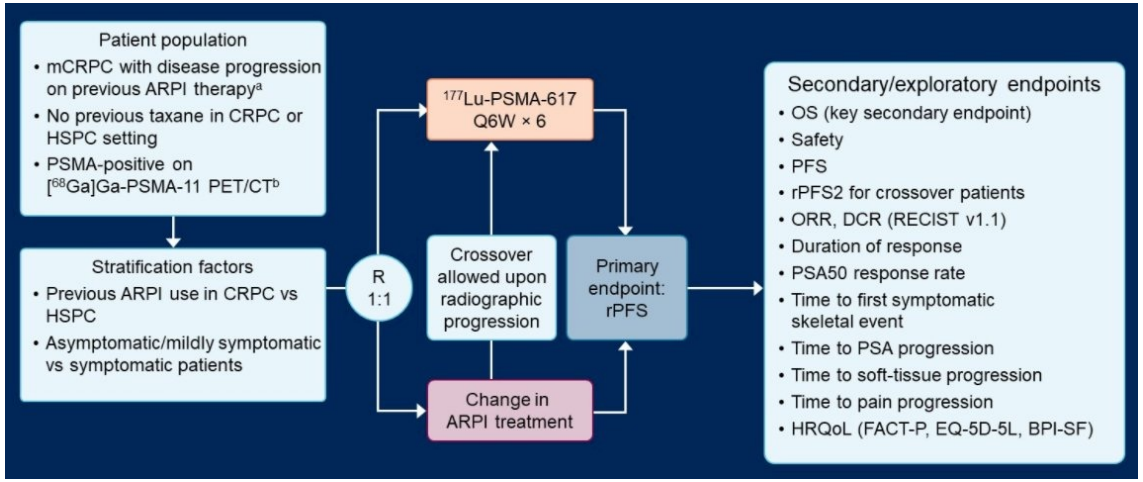
- At least one PSMA positive lesion on PET imaging (uptake above background liver)
- No soft tissue lesions that are PSMA PET negative
- Approximately 85% of mCRPC patients will qualify

VISION and PSMAfore Establish ^{177}Lu-PSMA-617 as a Standard of Care in mCRPC

VISION: Post-taxane, post-ARPI



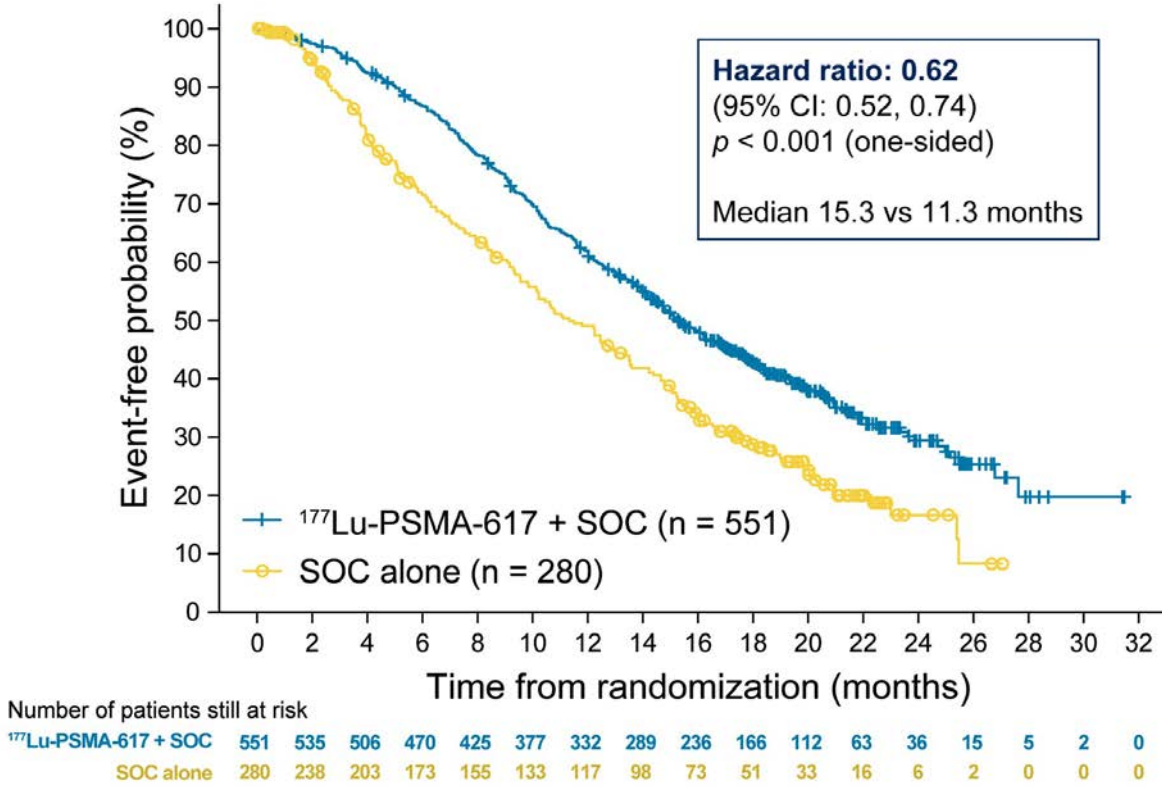
PSMAfore: Pre-taxane, post-ARPI



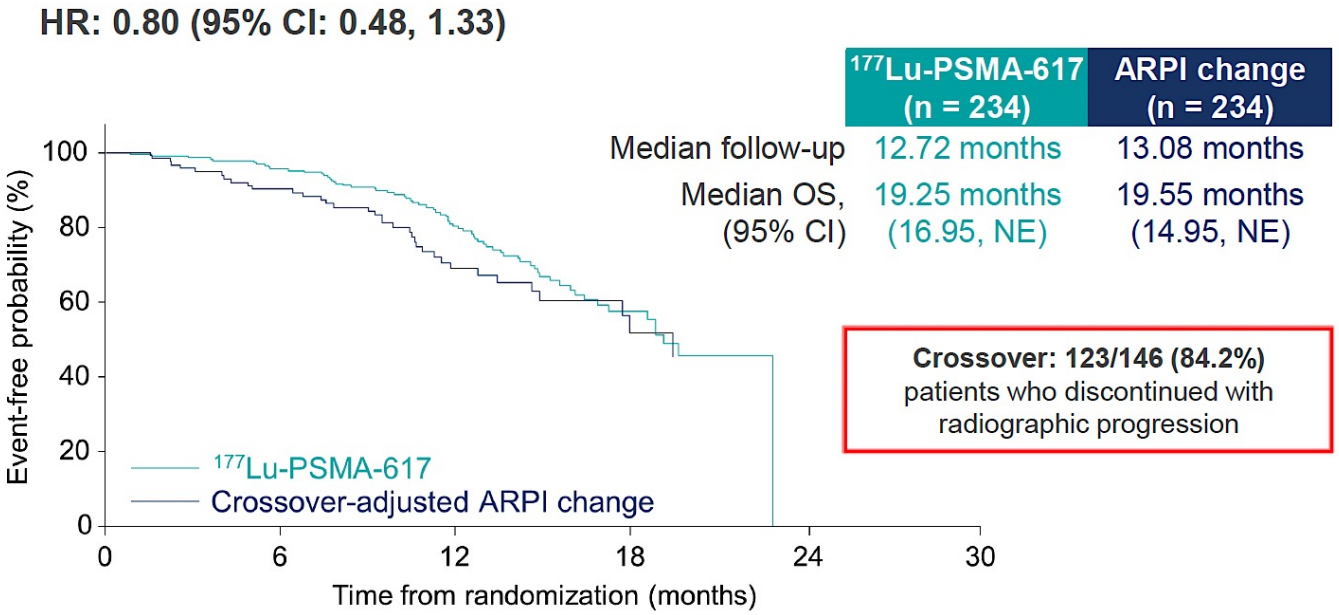
- Both trials met primary endpoint of PFS
- VISION demonstrated improvement in OS; PSMAfore – no difference in OS (follow up ongoing)
- FDA approval post-taxane (March 23rd, 2022) and pre-taxane (March 28th, 2025)

VISION and PSMAfore: OS Analyses

VISION: Post-taxane, post-ARPI



PSMAfore: Pre-taxane, post-ARPI



Morris et al. ASCO 2021;Abstract LBA4. Sartor et al. ESMO 2023;Abstract LBA13.

FDA Approves Lutetium Lu 177 Vipivotide Tetraxetan for Earlier Use Before Chemotherapy for PSMA-Positive Metastatic CRPC

Press Release: March 28, 2025

"The US Food and Drug Administration (FDA) approved lutetium Lu 177 vipivotide tetraxetan for patients with prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC) who have been treated with an androgen receptor pathway inhibitor (ARPI) therapy and are considered appropriate to delay chemotherapy.

The expanded indication… is based on results of the Phase III PSMAfore trial. In the study, lutetium Lu 177 vipivotide tetraxetan reduced the risk of radiographic progression or death by 59% (HR = 0.41; 95% CI: 0.29, 0.56; p <0.0001) compared to a change in ARPI in patients with PSMA-positive mCRPC after treatment with ARPI therapy. At an updated exploratory analysis, lutetium Lu 177 vipivotide tetraxetan more than doubled median radiographic progression-free survival (11.6 months vs. 5.6 months).

In PSMAfore, the final overall survival (OS) analysis numerically favored lutetium Lu 177 vipivotide tetraxetan, with a hazard ratio of 0.91 (95% CI: 0.72, 1.14), but was not statistically significant. The OS analysis was confounded by the high rate of patients who crossed over from the control arm to lutetium Lu 177 vipivotide tetraxetan (60.3%). When adjusted for crossover, the OS hazard ratio was 0.59 (95% CI: 0.38, 0.91)."

https://www.novartis.com/news/media-releases/fda-approves-novartis-radioligand-therapy-pluvicto-earlier-use-chemotherapy-psma-positive-metastatic-castration-resistant-prostate-cancer

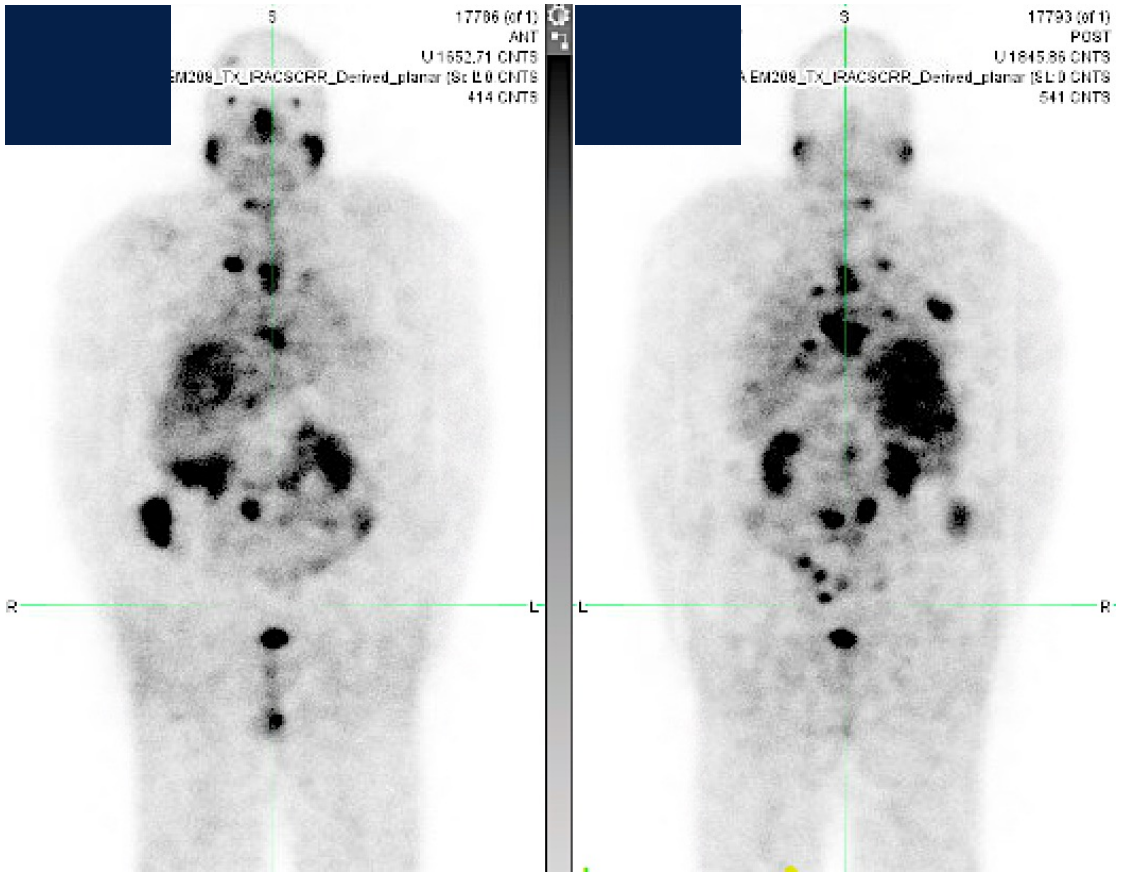
RTP RESEARCH TO PRACTICE

Our patient's journey continued…

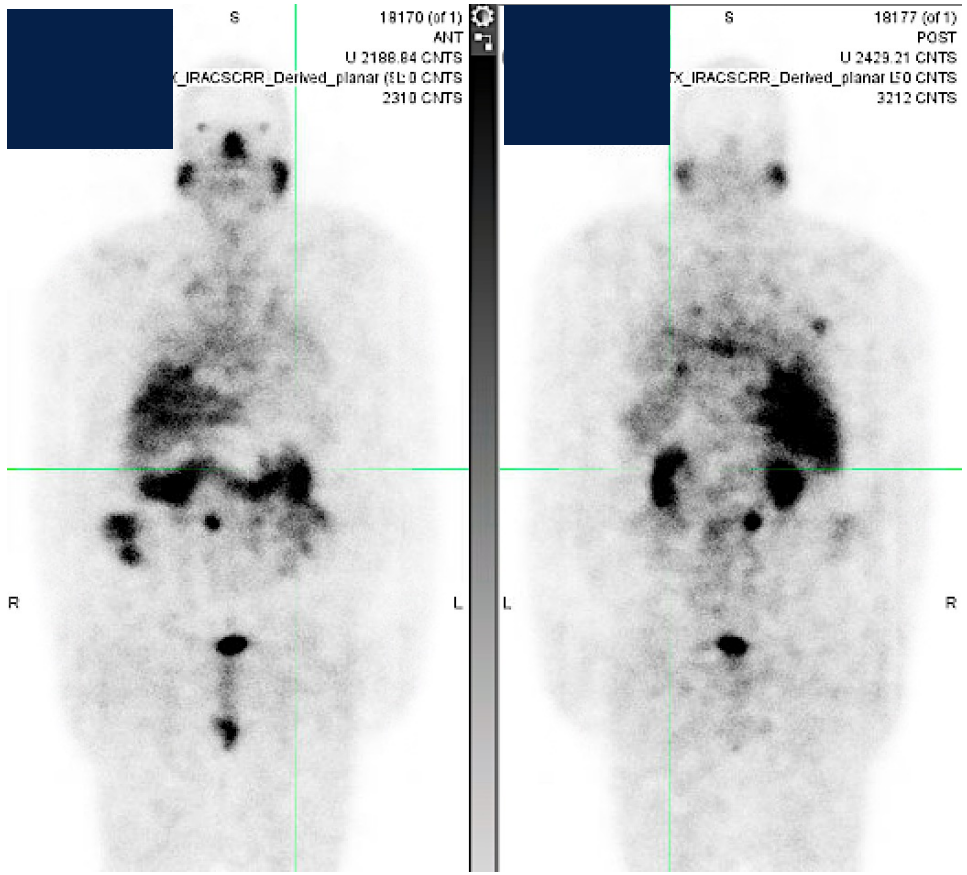
- Patient opted for treatment break following completion of radium-223
- Followed by PSA monthly and scans every 3 months
- Was able to travel with minimal symptoms
- Subsequent progression by PSA and scans
- PSMA PET obtained demonstrating multifocal nodal and osseous metastases
- Started 177Lu-PSMA-617 treatment with positive response by PSA and serial imaging
- Toxicities:
  - Chronic mild dry mouth, nausea for 3-4 days after each dose, low lymphocyte count, hemoglobin from 11 → mid 8 range

Serial SPECT Imaging

24 hours after dose #1 of Lu-PSMA-617



24 hours after dose #2 of Lu-PSMA-617



Back to our patient…

- PSA dropped to a nadir of 6.1 ng/mL following dose #6 of Lu-PSMA-617
- Remains on follow up
- Persistent mild dry mouth, not impacting eating/drinking/swallowing
- Persistent mild to moderate cytopenias
  - Hgb 8-9 range
  - Platelet count 60-75K
- Renal function intact
- Performance status good, bone pain minimal
- Currently on surveillance
- Future treatment options:
  - Cabazitaxel, ? re-treatment with Lu-PSMA-617, clinical trial

Chi K, et al. ASCO GU 2022

Emerging Directions for Radiopharmaceutical Treatments in Advanced Prostate Cancer

- Optimizing dosing schedule
  - Adaptive dosing with treatment breaks in those with good response
  - Dose escalation in those with high disease burden at baseline
- Earlier disease settings
  - Metastatic hormone sensitive
  - Biochemical relapse
  - Neoadjuvant prior to radical prostatectomy
- New radio-isotopes
  - Actinium-225, Lead-212, Terbium-161 → different energy, particle distance, decay patterns, half-lives
- Combinations: AR pathway inhibitors, PARP inhibitors, immunotherapy, etc.

Roundtable Discussion

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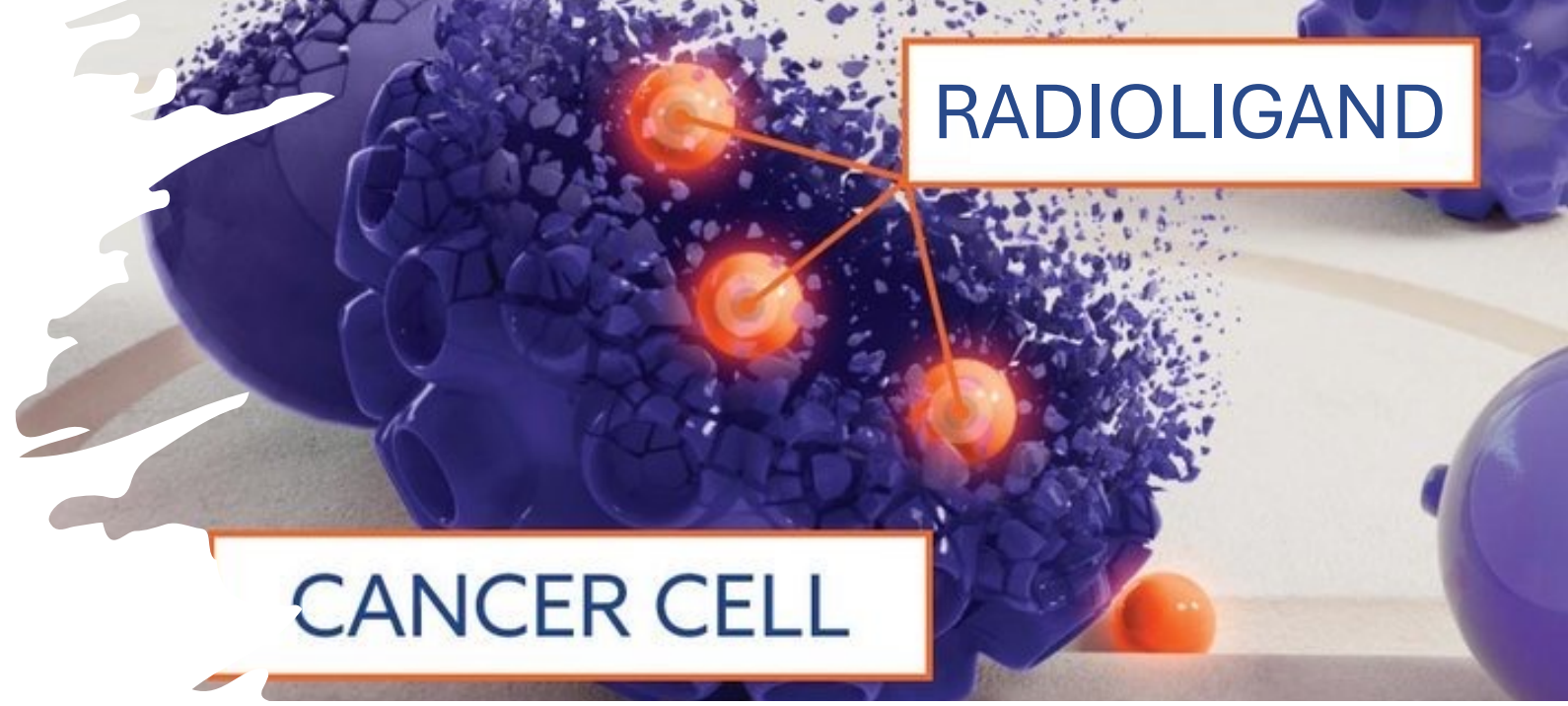
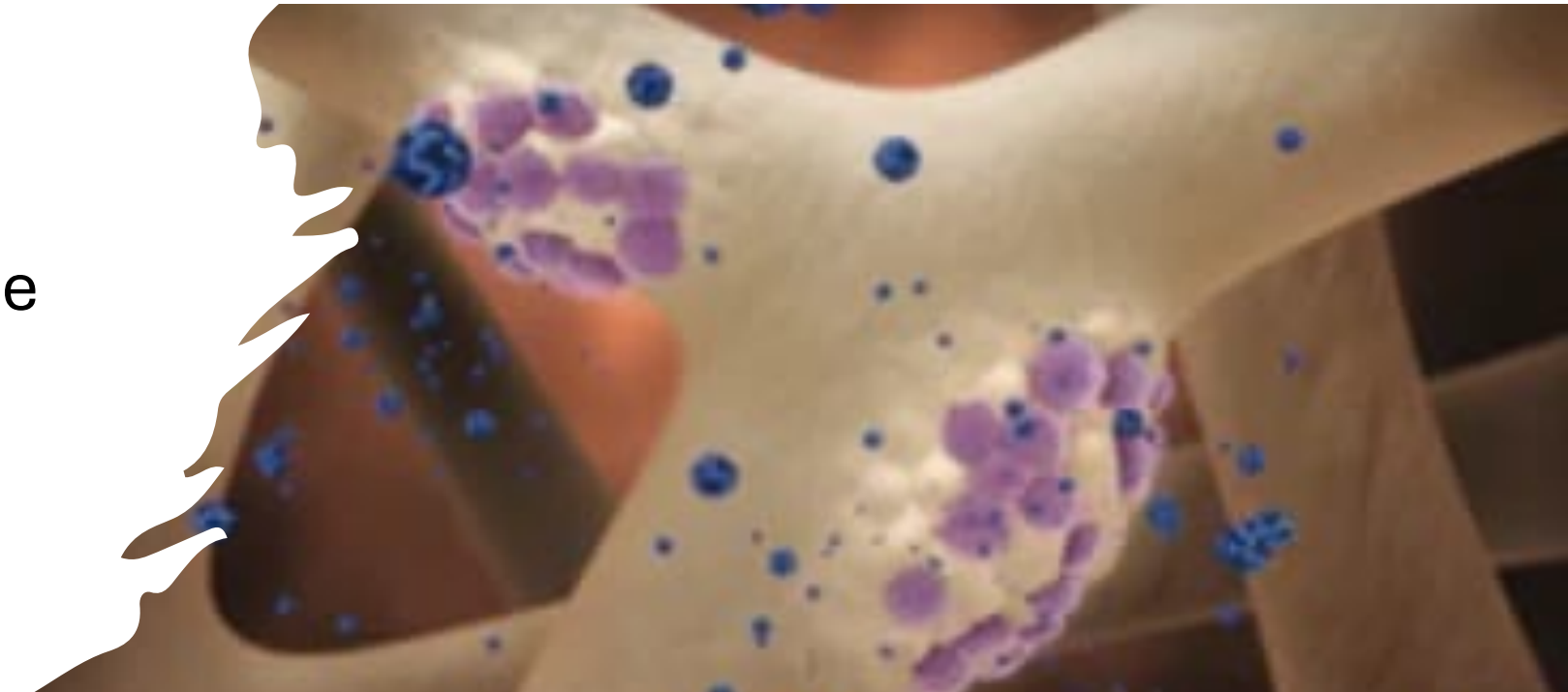
Kathleen Burns,
Nurse Practitioner
GU Medical
Oncology
City of Hope

Radio Ligand Therapy Theranostics



Lutetium Lu177 vipivotide tetraxetan

Radium-223



Radium-223

Indication: For the treatment of patients with castration-resistant prostate cancer, symptomatic bone metastases and no known visceral metastatic disease.

Side Effects (Alsympca trial)

- Bone marrow suppression
- Nausea/vomiting
- Diarrhea
- Peripheral edema

Patient Education

- No restrictions on personal contact
- Most of radioactivity is removed through the stool
- Until 1 week after dosing, radioactive body waste precautions
- Antiemetics and antidiarrheals available
- If adding enzalutamide (Peace-3), bone support

Radium case study

- 83 yr old male with mCRPC and diabetes mellitus with neuropathy.
- Dx as mHSPC high risk and took abiraterone/pred for 2 yrs.
- Radiographic progression, started sipuleucel-T.
- After completion, his bone scan showed 3 bone mets with his only pain in the right shoulder – EBRT which initially helped his pain.
- After developing more pain, his bone scan showed 1 more lesion.
- He started Radium-233/enza per Peace-3. He's completed 2 fractions with mild nausea not requiring medication.

Preparing patients for Lutetium-177

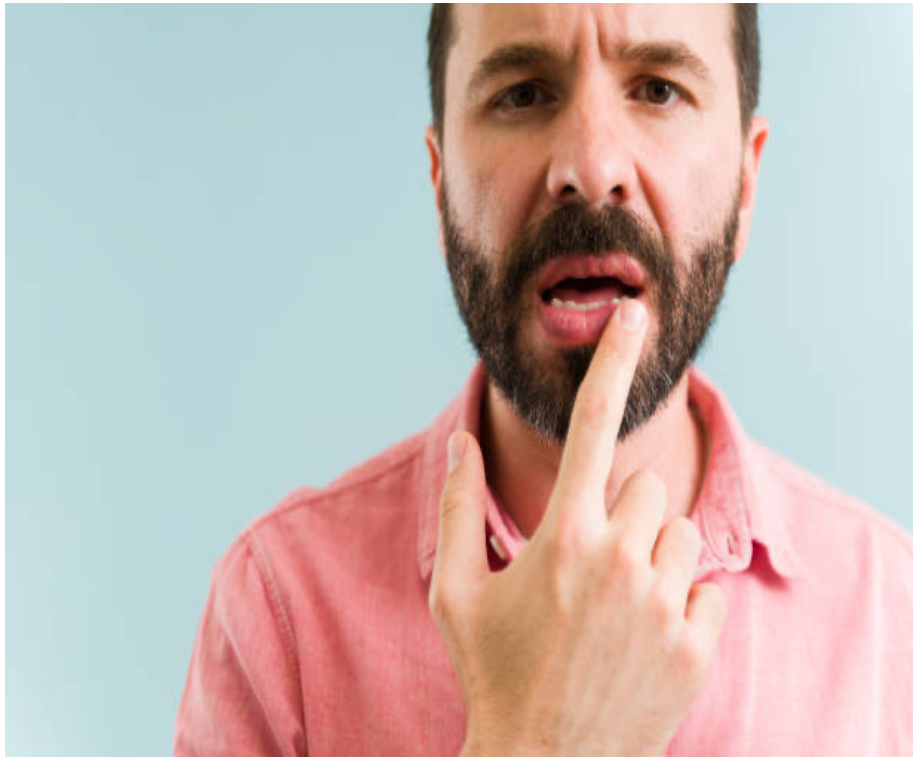
- Given in Radiation Oncology or Nuclear Medicine
- Family caregiver can play a big role – food/care while in isolation
- Radiation safety card – can they fly/travel?
- Specific instructions for radiation precautions
  - Time- distance –shielding
  - 3 day rule
  - Radioactive body fluids – urinary devices

Other considerations

- ~80% of men with PC express PSMA and qualify for treatment
- If the PSMA targets are resolved, treatment may be held
- Previously it was only indicated post chemo/ARPi
- New indication March 2025
- Post imaging – SPECT scans
- Urinary devices
- Family support – everyone needs to be educated – reporting symptoms

Managing Side Effects of Lu-177

- Nausea (36% VISION -32% PSMAfore)
- Kidney Injury (<10%)
- Marrow Suppression (28-64V/30-67%F)
- Dry Mouth (39V-61%F)
  - Prevention
  - Supportive Care
  - Dental Care- fluoride trays
  - We need more research
  - This becomes more critical as the therapy moves earlier in treatment



Calais J, Morris MJ, Kendi AT, Kalebasty AR, Tutrone R, Anderson MJ, Sartor O. Best Patient Care Practices for Administering PSMA-Targeted Radiopharmaceutical Therapy. J Nucl Med. 2024 Nov 1;65(11):1666-1671. doi: 10.2967/jnumed.124.268363. PMID: 39362764; PMCID: PMC11533911.

2 different Lutetium patients

- 64 yr old male with mHSPC started on triplet therapy
- Progressed and went onto sipT, talazoparib/enza, XRT X2
- Lutetium Lu 177 vipivotide tetraxetan 1/25 2 doses – psa from 20-87, pain increasing
- SPECT imaging – tells us how the drug is disseminating
- RLT conference and family mtg –pt wants to try one more then consider cabazitaxel or phase 1 clinical trial.
- The role of nursing is critical: educate, goc, supportive med

2 very different Lutetium patients…

- 61 yr old s/p triplet therapy
- Persistent PSMA+ bone mets
- Received 4 cycles with response to PSA and PET scan
- No dose limiting side effects
- He started to take vacations in between- felt great
- Transitioned to a clinical trial giving more than 6 cycles and has received 8 thus far

Collaboration for RLT management

- Multidisciplinary conferences can be really helpful
  - If you are familiar – reach out and teach
  - If you have questions – ask
  - Teaching others about what you contribute as nurses
    - Supportive care
    - Care coordination
    - Patient education
    - Symptom triage

Understanding the Current Paradigm and New Approaches in the Care of Patients with Cancer

A Complimentary NCPD Hybrid Symposium Series Held During the 50th Annual ONS Congress

Chronic Lymphocytic Leukemia

Thursday, April 10

6:00 PM – 7:30 PM

Faculty

Jacqueline Broadway-Duren, PhD, DNP, APRN, FNP-BC
Bita Fakhri, MD, MPH
Corinne Hoffman, MS, APRN-CNP, AOCNP
Jeff Sharman, MD

Moderator

Neil Love, MD

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Thank you for joining us! Please take a moment to complete the survey currently up on Zoom. Your feedback is very important to us. The survey will remain open up to 5 minutes after the meeting ends.

To Claim NCPD Credit

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Virtual attendees: The NCPD credit link is posted in the chat room.

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