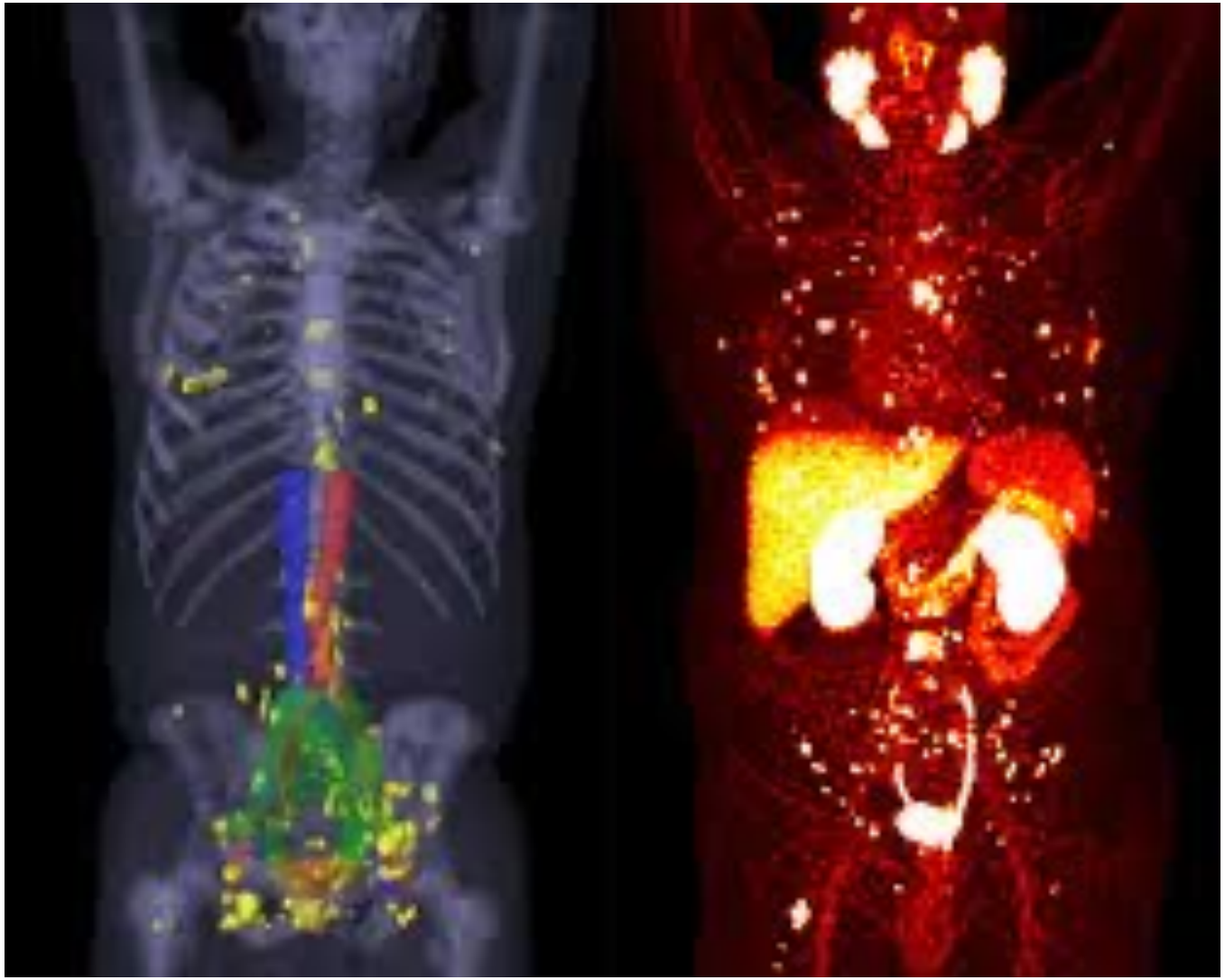
Prostate Cancer: Diagnostic & Therapeutic Updates



January 20, 2024

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Outline

Biochemical Recurrence

- Updates

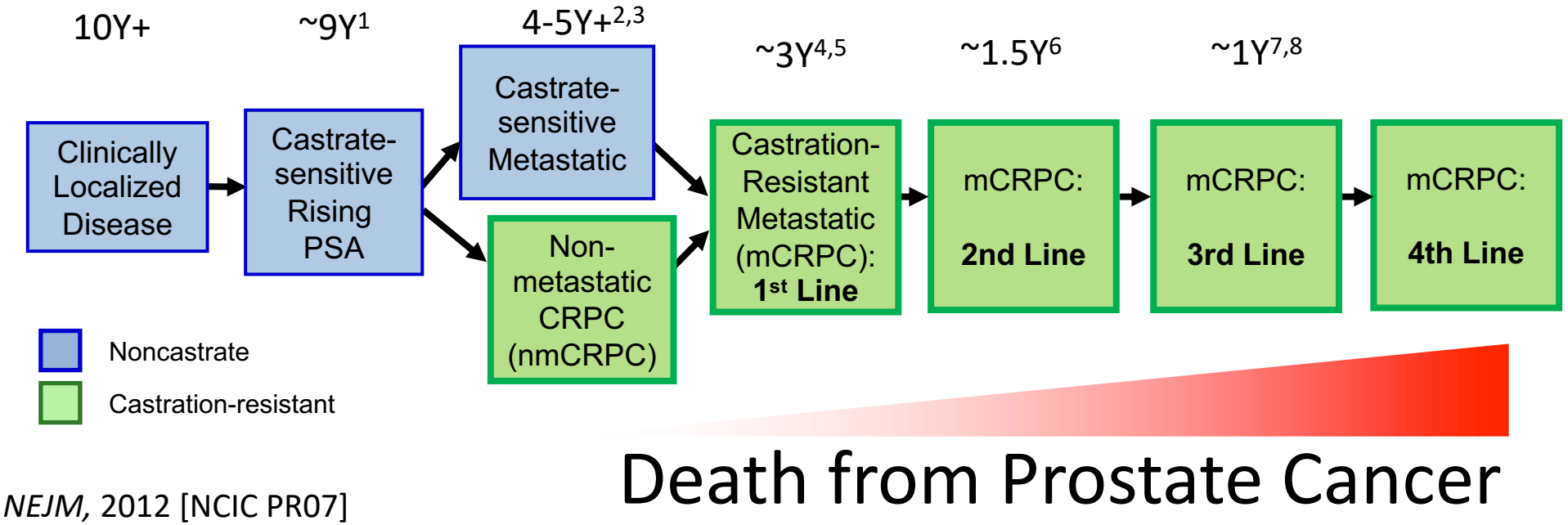
MCSPC

- Intensification

mCRPC

- The era of personalization, PARPi, PSMA & more

Clinical States



1. Crook et al, *NEJM,* 2012 [NCIC PR07]
2. Sweeney et al, *NEJM*, 2015 [CHAARTED]
3. Fizazi et al, *NEJM*, 2017 [LATITUDE]
4. Ryan et al, *Lanc Onc*, 2015 [COU-302]
5. Scher et al, *NEJM,* 2012 [AFFIRM]
6. deBono et al, *Lancet,* 2010 [TROPIC]
7. Smith et al, *JCO*, 2016 [COMET-I]
8. Mateo et al, *NEJM*, 2015 [TOPARP]

Modified from Scher, ASCO 2015

Slide adopted from Dr. Szmulewitz

Biochemically Recurrent PCa – EMBARK 11/16/23

ORIGINAL ARTICLE FREE PREVIEW

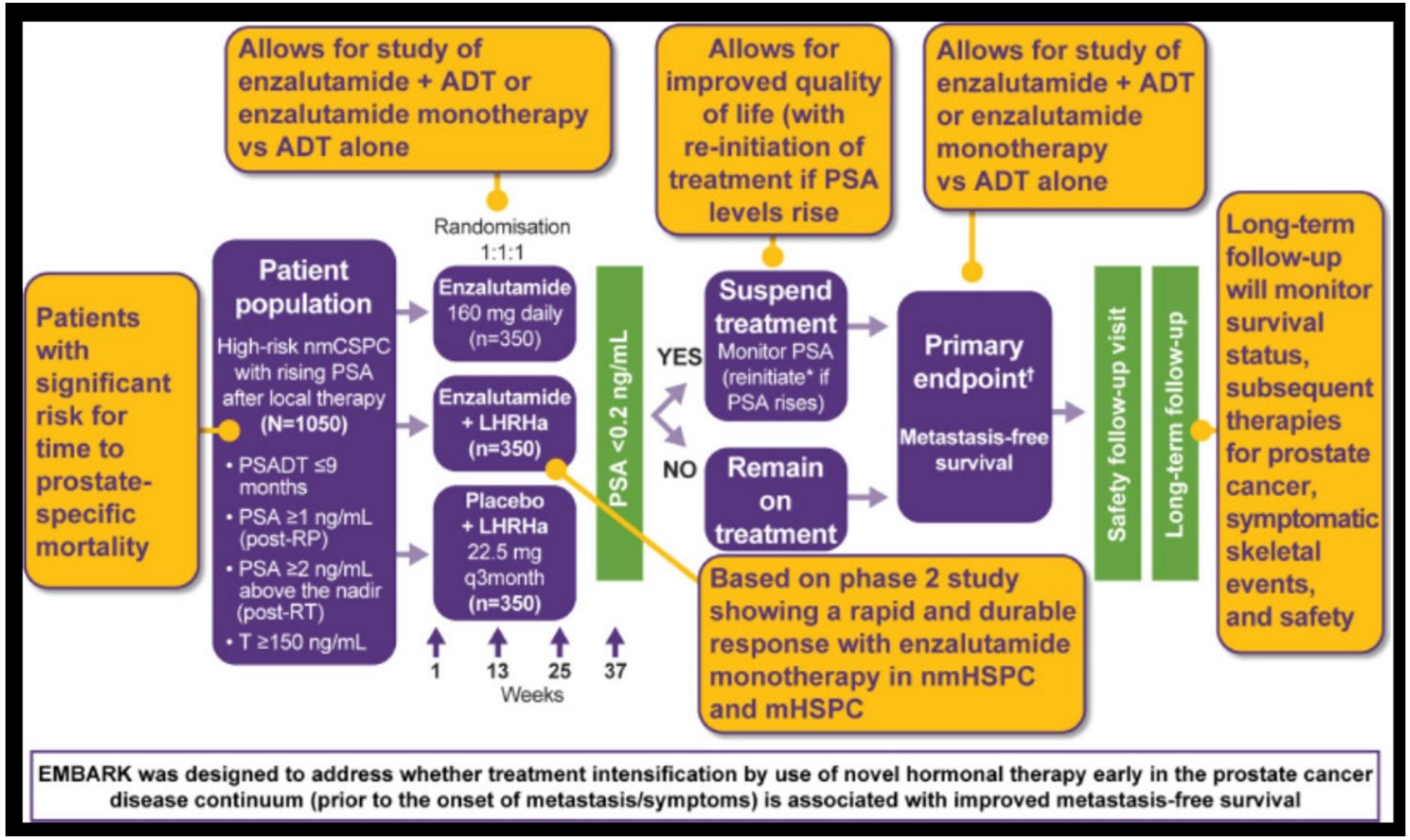
Improved Outcomes with Enzalutamide in Biochemically Recurrent Prostate Cancer

Stephen J. Freedland, M.D., Murilo de Almeida Luz, M.D., Ugo De Giorgi, M.D., Ph.D., Martin Gleave, M.D., Geoffrey T. Gotto, M.D., M.P.H., Christopher M. Pieczonka, M.D., Gabriel P. Haas, M.D., Choung-Soo Kim, M.D., Miguel Ramirez-Backhaus, M.D., Antti Rannikko, M.D., Ph.D., Jamal Tarazi, M.D., M.P.A., Swetha Sridharan, M.B., B.S., et al.

- **Phase 3**
- **High risk BCR (PSA DT <9 months)**
- **1:1:1 enza + ADT; enza alone, ADT alone**
- **Primary endpoint: MFS in combo vs. ADT alone**
- **Secondary endpoint: MFS in mono vs. ADT alone**

Slide adopted from Dr. Reizine

Biochemically Recurrent PCa - EMBARK



Freedland et al, NEJM, 2023

EMBARK

Key Findings and Conclusions

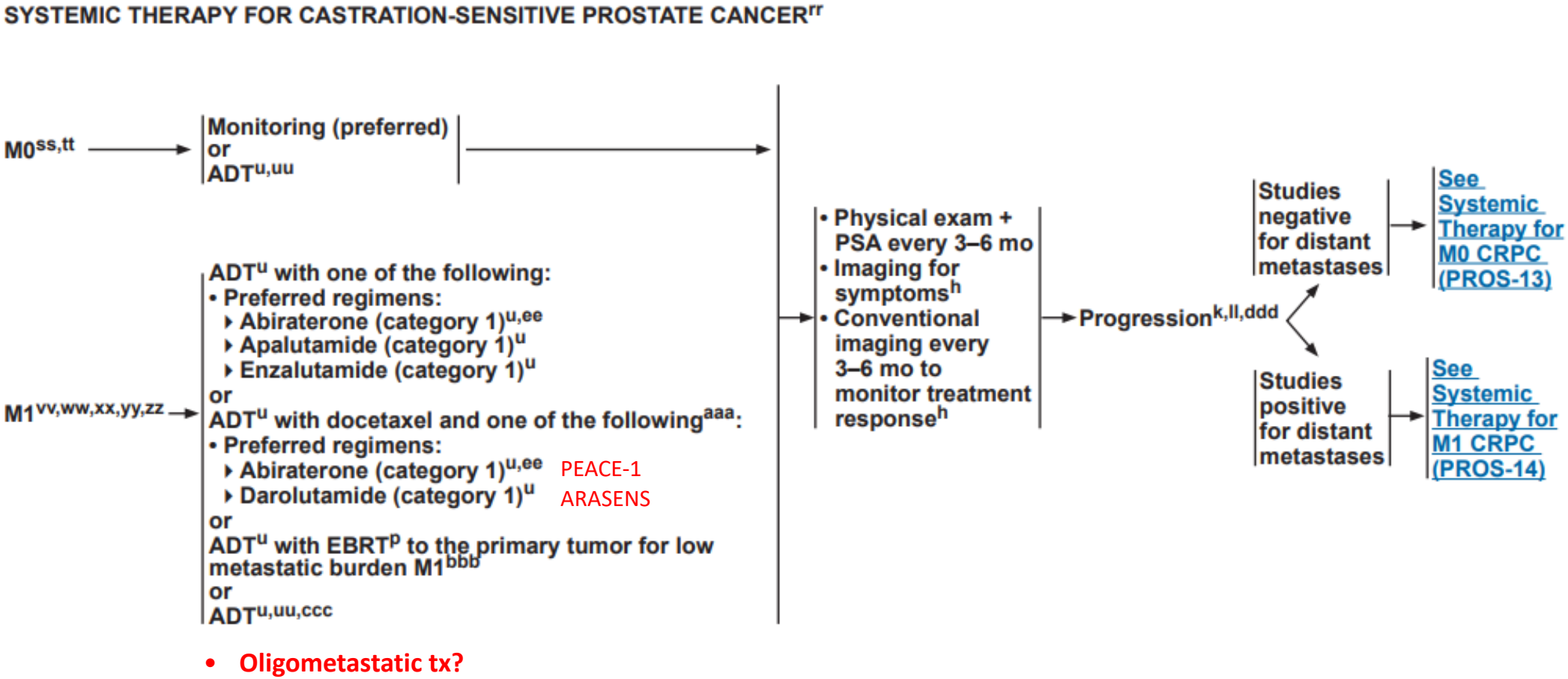
- In patients with high-risk BCR, enza monotherapy showed clinically meaningful delays in time to: distant metastasis (HR 0.61; 95% CI: 0.41, 0.92; *P*=0.017), symptomatic progression (HR 0.62; 95% CI: 0.49, 0.79; *P*<0.0001), and first symptomatic skeletal event (HR 0.42; 95% CI: 0.23, 0.79; *P*=0.006) versus leuprolide alone.
- After treatment suspension, the time to resumption of any hormonal therapy was shorter for enza monotherapy versus leuprolide alone (HR 1.66; 95% CI: 1.38, 1.98; *P*<0.0001).
- Time to first deterioration of Functional Assessment of Cancer Therapy-Prostate (FACT-P) total score was comparable in enza monotherapy and leuprolide alone cohorts (HR 1.17; 95% CI: 0.98, 1.39; *P*=0.09).
- Enza monotherapy represents a potential new treatment option for patients with high-risk BCR that improves outcomes relative to the current standard of care.

Freedland et al, NEJM, 2023

- Enzalutamide monotherapy group: better sexual function but high rate of gynecomastia
- In the PSMA PET era, how to utilize?
  - Most patients will have PSMA+ disease to treat…

Slide adopted from Dr. Reizine

mCSPC: Changing Landscape



PEACE-1

ARASENS

- **Oligometastatic tx?**

Criteria for “triplet”

- Benefit has been most convincingly shown in males with **high-risk/high-volume** metastatic disease:

1. Visceral metastases AND at least one bone lesion
2. OR at least four bone lesions with at least one outside the axial skeleton
3. OR Gleason score 8 disease
4. OR de novo metastatic disease
5. *Fit for chemotherapy, agreeable to port placement (institution dependent)

Local Tx in Metastatic Disease

- Consider prostate RT with systemic therapy for males with a **low burden of bone metastases**:
  - Four or fewer bone metastases, with none outside the vertebral bodies or pelvis)
  - No visceral metastases

- -> STAMPEDE subgroup: OS was improved with RT in the males with a low metastatic burden at diagnosis

3-year survival 81% versus 73%, HR for death 0.68, 95% CI 0.52-0.90 but not in those with a high metastatic burden (HR 1.07, 95% CI 0.90-1.28)

- -> PEACE-1 subgroup: Combining prostate RT to systemic treatment did not improve OS in men with de novo mCSPC and low metastatic burden

- -> SWOG 1802 trial (open at UIC) will help answer this:

Phase III Randomized Trial of Standard Systemic Therapy (SST) Versus Standard Systemic Therapy plus Definitive Treatment (Surgery or Radiation) of the Primary Tumor in Metastatic Prostate Cancer

Select mHSPC trials with triplets

Name	ARPI	Study Design	3rd agent	Biomarker
TALAPRO-3	Enzalutamide	Phase III	Talazoparib	HRR+
AMPLITUDE	Abiraterone	Phase III	Niraparib	HRR+
PSMAddition	Any ARPI	Phase III	Lu177-PSMA-617	PSMA PET+
CABIOS	Abiraterone	Phase Ib	Cabozantinib Nivolumab	
CASCARA	Abiraterone	Phase II	Cabazitaxel Carboplatin	
Capitello-281	Abiraterone	Phase III	Capivasertib	PTEN deficiency
CYCLONE-3	Abiraterone	Phase III	Abemaciclib	

Precision medicine in PCa – the future?

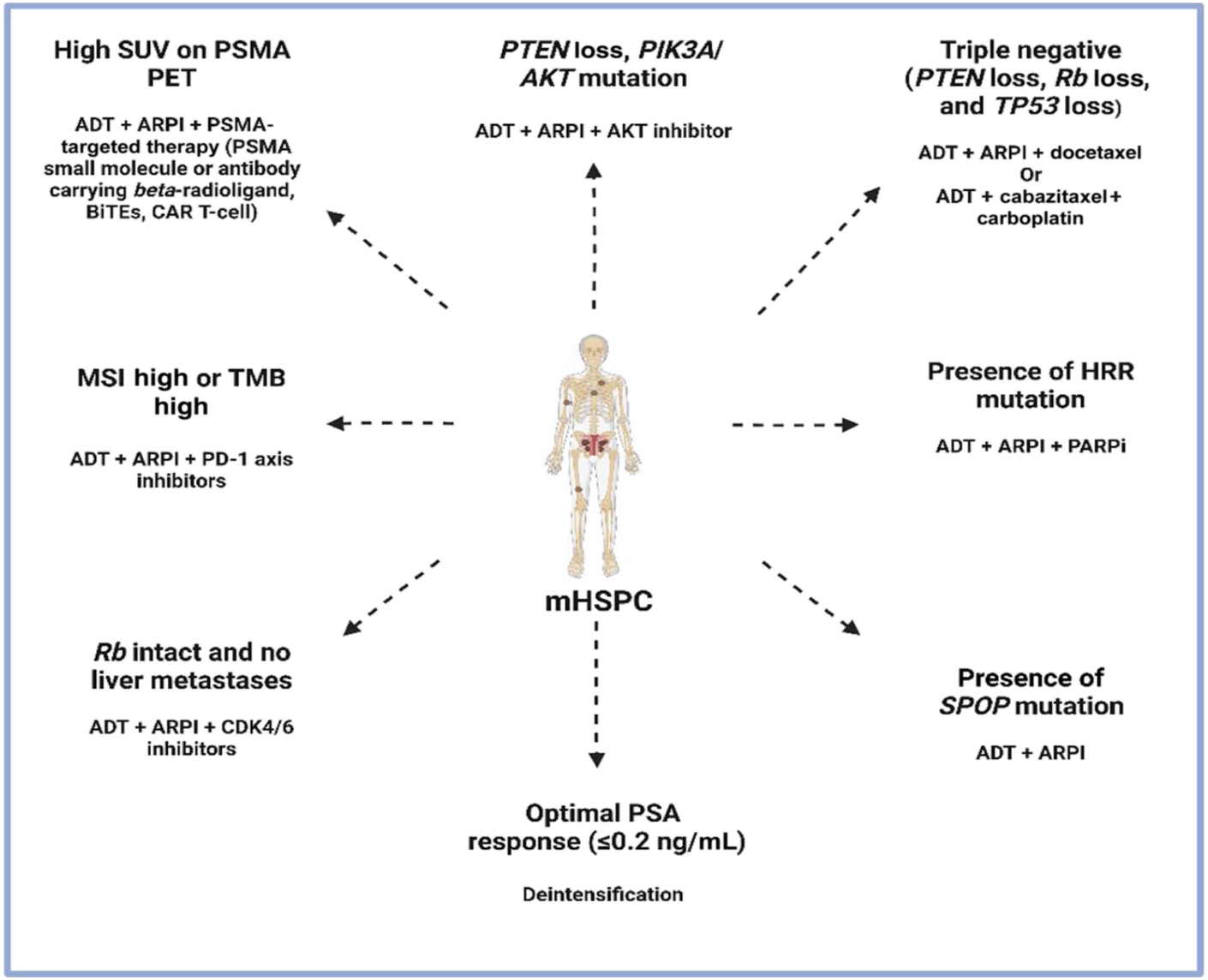


FIG 2. Potential precision therapy approaches in mHSPC. ADT, androgen deprivation therapy; ARPI, androgen receptor pathway inhibitor; BiTEs, bispecific T-cell engager; CAR T cell, chimeric antigen receptor T cell; CDK4/6, cyclin D Kinase 4/6; HRR, homologous recombination repair; mHSPC, metastatic hormone-sensitive prostate cancer; MSI, microsatellite instability; PARPi, poly (ADP-ribose) polymerase inhibitor; PD-1, programmed cell death protein 1; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen; TMB, tumor mutational burden.

Published in: Anis A. Hamid; Nicolas Sayegh; Bertrand Tombal; Maha Hussain; Christopher J. Sweeney; Julie N. Graff; Neeraj Agarwal; *American Society of Clinical Oncology Educational Book* 2023 43e390166.
DOI: 10.1200/EDBK_390166

mCSPC -> mCRPC: Changing Landscape

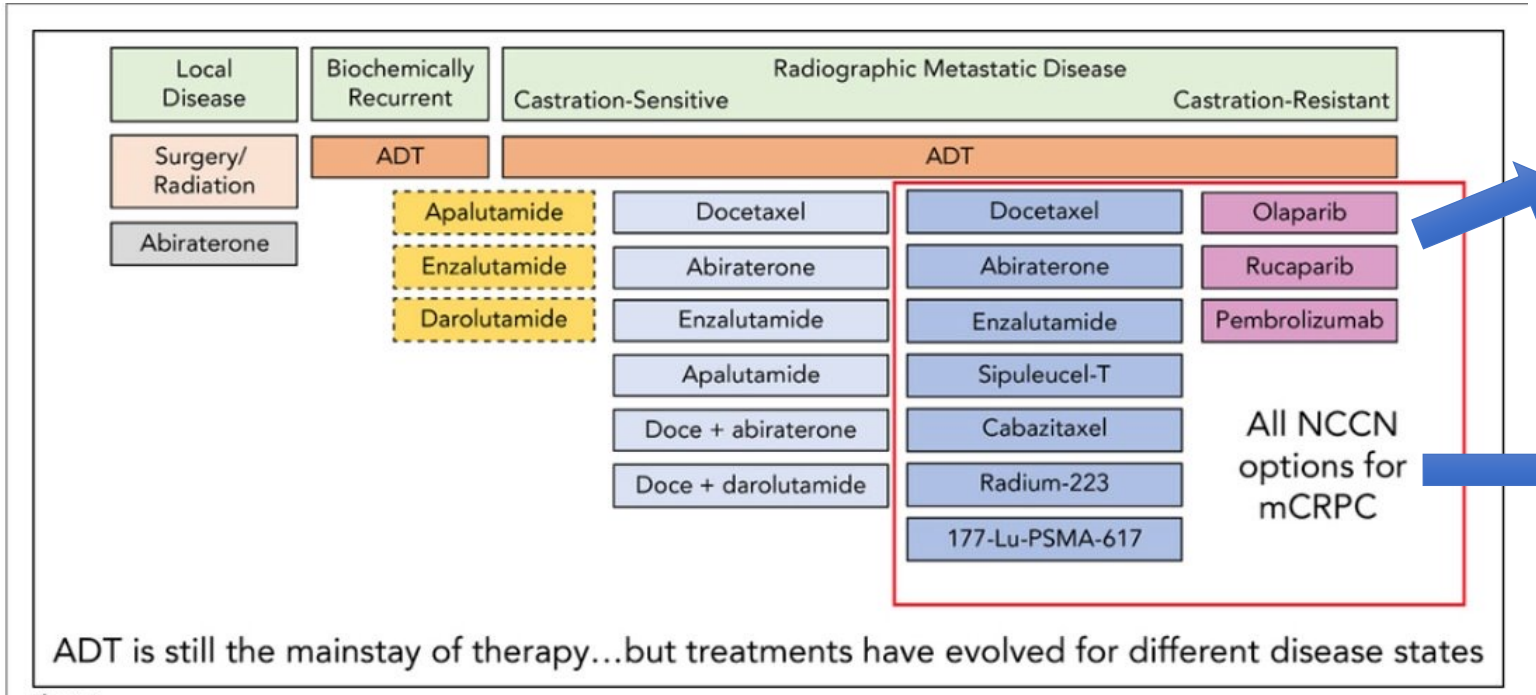


Figure 1.
Treatment landscape for advanced prostate cancer.

Abbreviations: ADT, androgen deprivation therapy; Doce, docetaxel; mCRPC, metastatic castration-resistant prostate cancer.

Data from NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Prostate Cancer, Version 1.2023. To view the most recent and complete version of these guidelines, visit www.nccn.org.

Citation: Journal of the National Comprehensive Cancer Network 21, 5.5; 10.6004/jnccn.2023.5004

May 2020	Rucaparib for 2L mCRPC w/ *BRCA1/2* muts TRITON-3
May 2020	Olaparib for 2L mCRPC w/ HRD PROfound
May 2023	Olaparib + abiraterone for 1L mCRPC w/ *BRCA1/2* only PROpel
June 2023	Talazoparib + Enzalutamide for 1L mCRPC w/ HRD+ cohort TALAPRO-2
August 2023	Niraparib + abiraterone for 1L mCRPC w/ *BRCA1/2* only MAGNITUDE

HRD mutations are prevalent in prostate cancer

- 6% germline in localized high risk
- 11.8% germline in metastatic
- 20% somatic in advanced disease

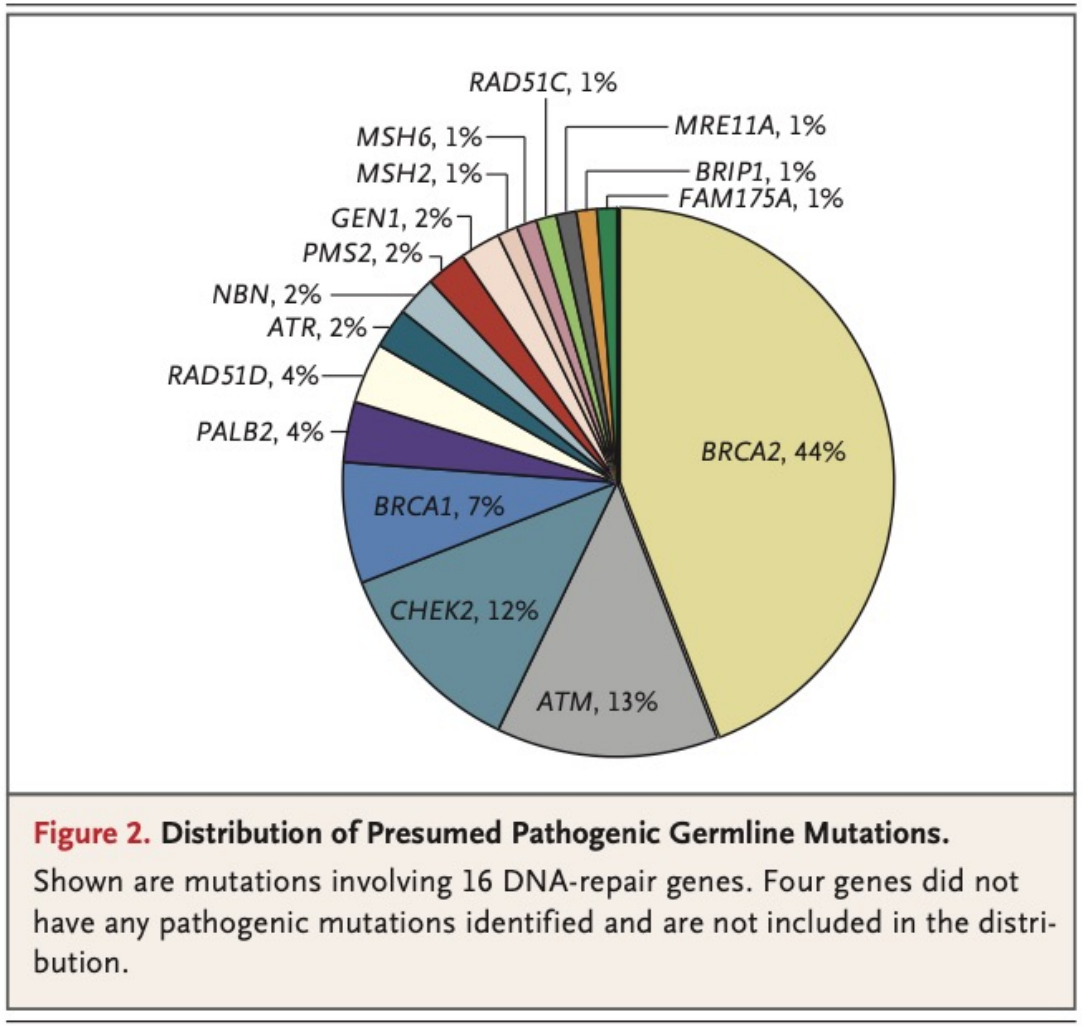


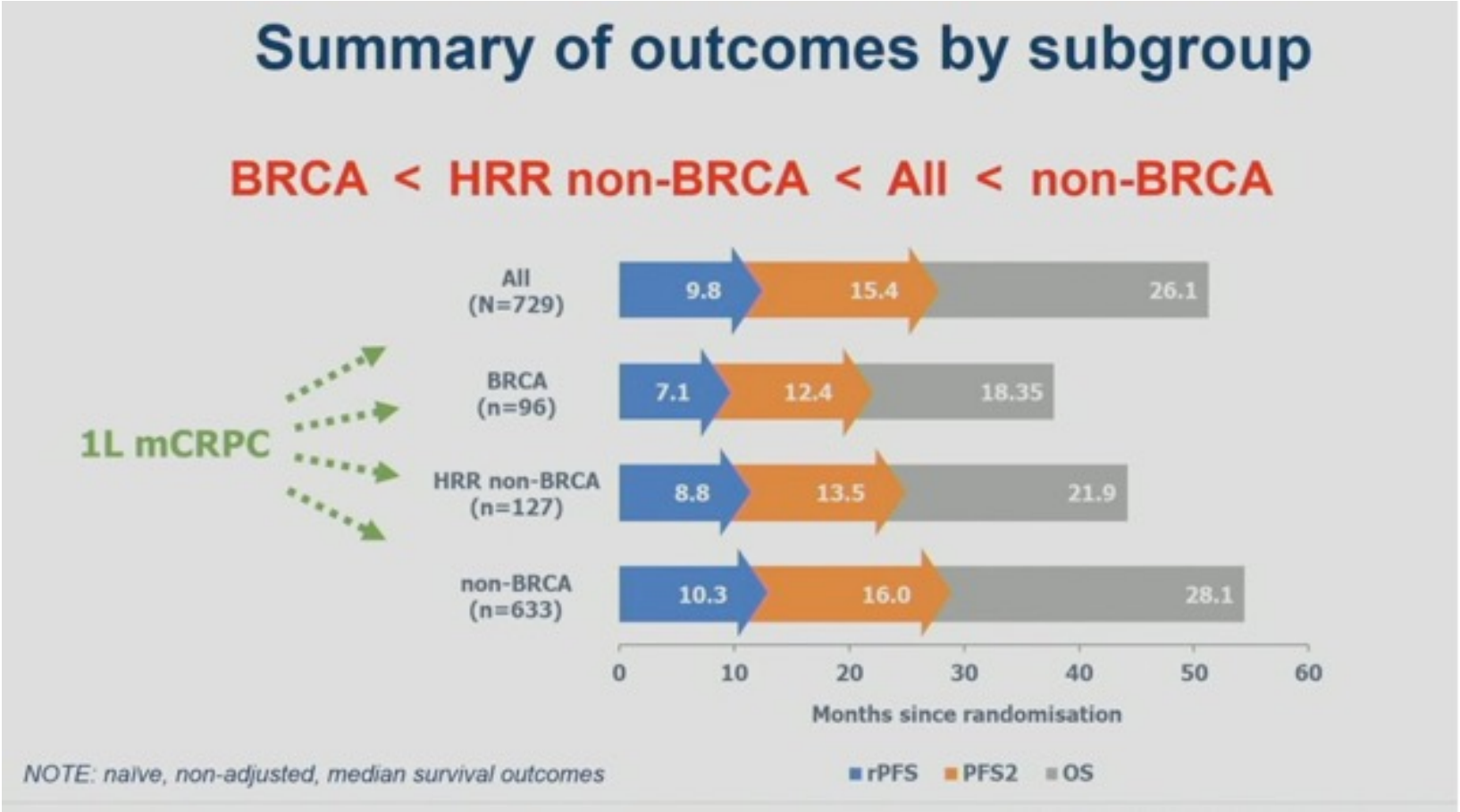
Figure 2. Distribution of Presumed Pathogenic Germline Mutations.

Shown are mutations involving 16 DNA-repair genes. Four genes did not have any pathogenic mutations identified and are not included in the distribution.

Pritchard et al NEJM 2016

BRCA1/2m+ in prostate cancer have worse outcomes

- *Tested for: ATM, BRCA1/2, BRIP1, CDK12, CHECK2, FANCA, HDAC2, PALB2, RAD51B*, and *RAD54L*
- *BRCA1/2* - 13.2%
  - Worse PFS, OS
- Irrespective of germline vs somatic; mono- vs bi-allelic



CAPTURE Olmos et al ASCO 2023

PARP inhibitors in Prostate cancer

- Poly (ADP-ribose) polymerase (PARP)
  - Involved in DNA damage response (DDR) pathways
    - Nucleotide excision repair, base excision repair, mismatch repair, homologous recombination (HR), etc
  - PARP Inhibition prevents cells from repairing damaged DNA
    - Accumulation of single-strand breaks
    - Entrapment of PARP-DNA complex
    - In cells harboring HR deficiencies: **Synthetic Lethality**

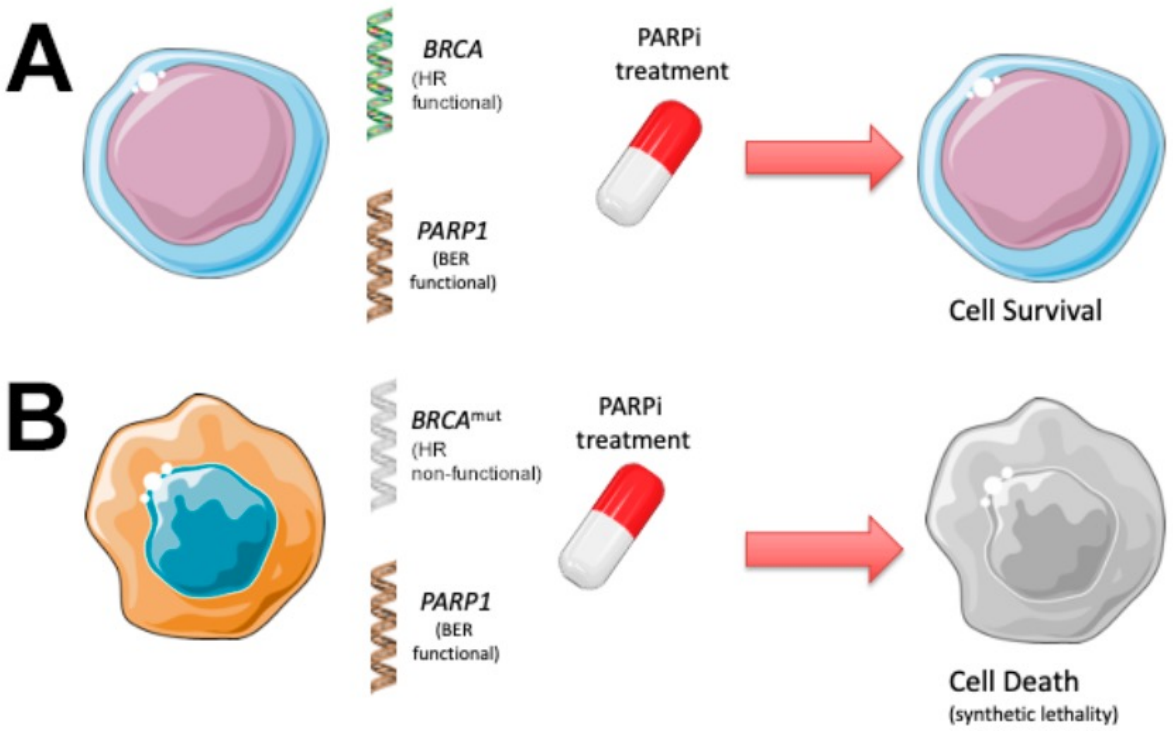


Figure 3. The principle of synthetic lethality—using PARP inhibitors (PARPi) to kill cancer cells with defects in DNA repair. (**A**) Normal cells without *BRCA* mutations have a functioning homologous recombination (HR) repair pathway and a functional base excision repair (BER) pathway. These cells remain alive when treated with PARPi. (**B**) Cancer cells with *BRCA* mutations have a non-functional HR pathway, but a functional BER pathway. When treated with PARPi, these cells are not able to repair DNA damage and subsequently undergo apoptosis.

Skelding et al, Cancers 2021

Guidelines support germline and somatic testing in most patients

National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2023
Prostate Cancer

NCCN Guidelines Index
Table of Contents
Discussion

PRINCIPLES OF GENETICS AND MOLECULAR/BIOMARKER ANALYSIS

Germline testing is recommended *in patients with a personal history of prostate cancer* in the following scenarios:

- **By prostate cancer stage or risk group (diagnosed at any age)**
  - **Metastatic, regional (node positive), very-high-risk localized, or high-risk localized prostate cancer**
- **By family history[a] and/or ancestry**
  - **≥1 first-, second-, or third-degree relative with:**
    - ◊ **breast cancer at age ≤50 y**
    - ◊ **colorectal or endometrial cancer at age ≤50 y**
    - ◊ **male (sex assigned at birth) breast cancer at any age**
    - ◊ **ovarian cancer at any age**
    - ◊ **exocrine pancreatic cancer at any age**
    - ◊ **metastatic, regional, very-high-risk, or high-risk prostate cancer at any age**
  - **≥1 first-degree relative (parent or sibling) with:**
    - ◊ **prostate cancer[b] at age ≤60 y**
  - **≥2 first-, second-, or third-degree relatives with:**
    - ◊ **breast cancer at any age**
    - ◊ **prostate cancer[b] at any age**
  - **≥3 first- or second-degree relatives with:**
    - ◊ **Lynch syndrome-related cancers, especially if diagnosed <50 y: colorectal, endometrial, gastric, ovarian, exocrine pancreas, upper tract urothelial, glioblastoma, biliary tract, and small intestinal cancer**
  - **A known family history of familial cancer risk mutation (pathogenic/likely pathogenic variants), especially in: *BRCA1, BRCA2, ATM, PALB2, CHEK2, MLH1, MSH2, MSH6, PMS2,* and *EPCAM***
  - **Ashkenazi Jewish ancestry**
- **Personal history of breast cancer**

Germline testing may be considered *in patients with a personal history of prostate cancer* in the following scenarios:

- **By prostate cancer tumor characteristics (diagnosed at any age)**
  - ◊ **intermediate-risk prostate cancer with intraductal/cribriform histology[c]**
- **By prostate cancer[b] AND a prior personal history of any of the following cancers:**
  - ◊ **exocrine pancreatic, colorectal, gastric, melanoma, upper tract urothelial, glioblastoma, biliary tract, and small intestinal**

[a] Close blood relatives include first-, second-, and third-degree relatives on the same side of the family. See Pedigree: First-, Second-, and Third-Degree Relatives of Proband (EVAL-B) in the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic.
[b] Family history of prostate cancer should not include relatives with clinically localized Grade Group 1 disease.
[c] Acinar prostate adenocarcinoma with invasive cribriform pattern, intraductal carcinoma of prostate, or ductal adenocarcinoma component have increased genomic instability, and germline testing may be considered.

Germline: almost all!

Somatic:
recommended in mCRPC
consider in mCSPC

JCO PO 2022

CANCER GENETICS

Germline Variant Spectrum Among African American Men Undergoing Prostate Cancer Germline Testing: Need for Equity in Genetic Testing

Veda N. Giri, MD[1,2]; Rebecca Hartman, MPH[3]; Mary Pritzlaff, MS, CGC[4]; Carrie Horton, MS, CGC[4]; and Scott W. Keith, PhD[3]

- 427 men tested using the 14-gene PCA panel: AA (n = 237, 56%) and White (n = 190, 44%)
- Pathogenic variant rate of 8.2%
  - AA men with lower rates then White (5.91% v 11.05%, P = .05).
- Difference in rates of variants of uncertain significance (VUSs) between AA and White men (25.32% v 16.32%; P = .02) and for carrying multiple VUSs (5.1% v 0.53%, P = .008).
- Germline evaluation in a cohort enriched for AA men highlights the **narrower spectrum of germline contribution to PCA** with **significantly higher rates of multiple VUSs in DNA repair genes**.

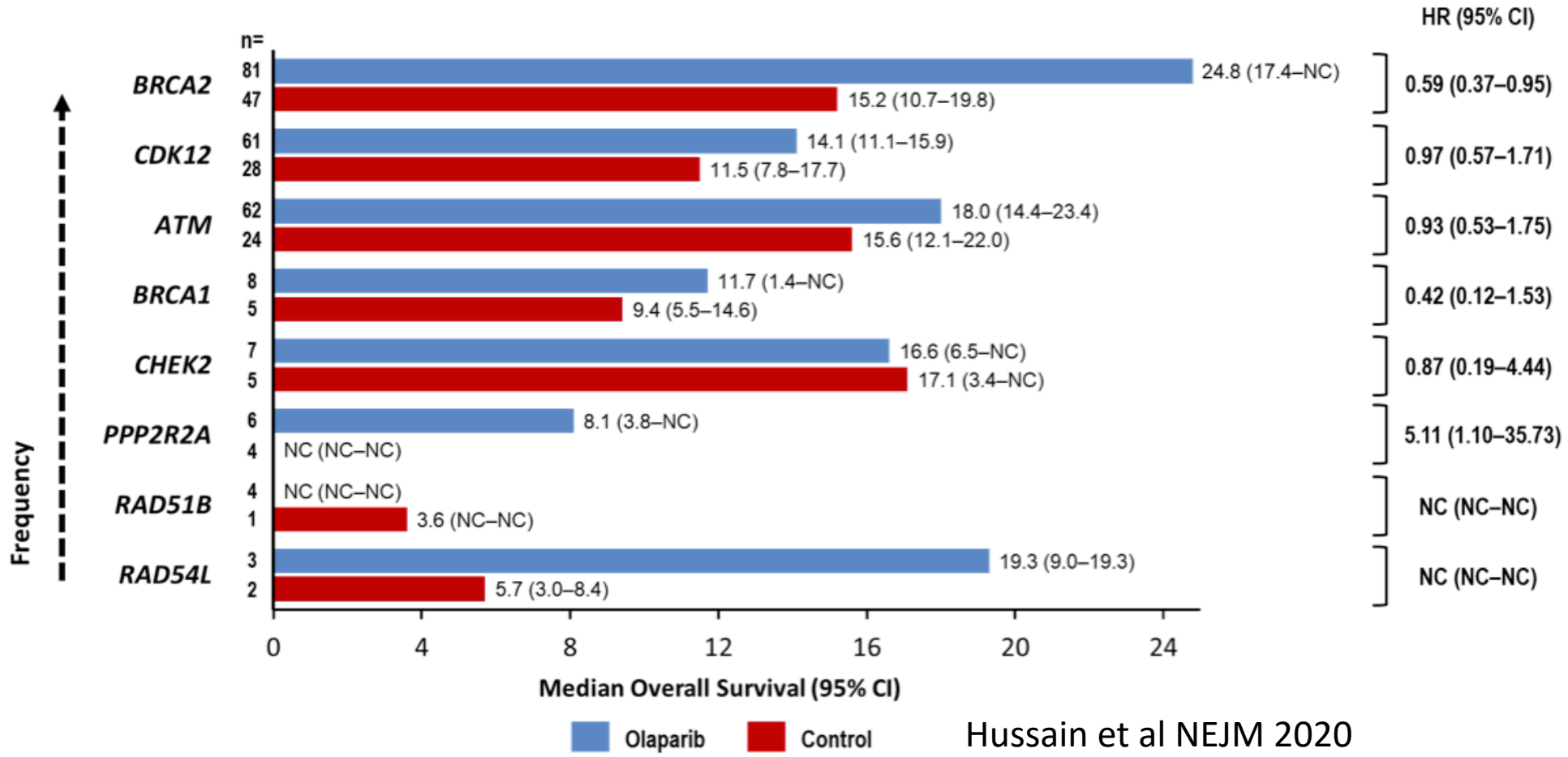
FDA approved PARPi Regimens in 1L mCRPC

	Olaparib	**Rucaparib**	**Olaparib + Abiraterone**	**Talazoparib + enzalutamide**	**Niraparib + Abiraterone**
Trial	PROfound NCT02987543	TRITON2 NCT02952534	Propel NCT03732820	Talapro-2 NCT03395197	MAGNITUDE NCT03748641
FDA approval	May 19, 2020	May 15, 2020	May 31, 2023	June 20, 2023	August 11, 2023
Biomarkers	**HRRm+** Cohort A: **BRCA1/2, ATM** Cohort B: **BARD1, BRIP1, CDK12, CHEK1/2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D, RAD54L**	**BRCA1/2m**	**BRCA1/2m** **(**n=85, 11% of ITT population)	**HRRm+** **ATM, ATR, BRCA1, BRCA2, CDK12, CHEK2, FANCA, MLH1, MRE11A, NBN, PALB2, RAD51C**	**BRCA1/2m**

N. Reizine, 2023

Not all mutations respond equally to PARPi

Fig. S6. Gene-by-Gene Analysis of Overall Survival in Patients with Alterations in a Single HRR Gene. Data at the End of Each Bar are Median Overall Survival in Months (95% CI).



Hussain et al NEJM 2020

Note that for secondary and exploratory outcomes, which were not alpha controlled, definitive treatment effects may not be inferred.

CI, confidence interval; HR, hazard ratio; HRR, homologous recombination repair; NC, not calculable; n, number of patients

PARPi Toxicities

Event	Olaparib (N=256)	
	All Grades	Grade ≥3
	number	
Adverse event		
Any	244 (95)	130 (51)
Anemia†	119 (46)	55 (21)
Nausea	106 (41)	3 (1)
Fatigue or asthenia	105 (41)	7 (3)
Decreased appetite	77 (30)	3 (1)
Diarrhea	54 (21)	2 (<1)
Vomiting	47 (18)	6 (2)
Constipation	45 (18)	0
Back pain	35 (14)	2 (<1)
Peripheral edema	32 (12)	0
Cough	28 (11)	0
Dyspnea	26 (10)	6 (2)
Arthralgia	24 (9)	1 (<1)
Urinary tract infection	18 (7)	4 (2)

- 45% dose interruption
- 22% dose reduce
- 18% d/c for AE
- 4% death from AE

de Bono et al NEJM 2020

Additional Treatment Nuances for PARPi

- Which genes benefit?
  - Not all respond equally role in non-HRR mutated?
  - How can we maximize/synergize?
- When and How to treat?
  - Local, CSPC, CRPC? More efficacy / increased synergy if used in earlier stages / pre androgen resistance?
  - Concurrent or sequential with ARPI?
- Mechanisms of Resistance
  - Restoration of HR capacity, diminished PARPi trapping, drug efflux, cell cycle control alterations, miRNA, etc…
- Better, more selective PARP? Other DDR strategies?

Select mCRPC PARPi trials

Drug Therapy	Study Name	Study Design	Trial Population	Homologous Recombination Repair Mutations	Primary Endpoint(s)
Olaparib + pembrolizumab vs. enza./AAP	**KEYLYNK-010**	Phase III, randomized	mCRPC	Unselected	overall survival, rPFS
Olaparib + durvalumab	**NCT03810105**	Phase II, single arm	Biochemically recurrent nmCRPC	Selected	# of patients with undetectable PSA
Olaparib + 177Lu-PSMA	**LuPARP**	Phase I, single arm	mCRPC	N/A	DLT, recommended phase II dose
Olaparib + Radium-223 vs. Radium 223	**COMRADE**	Phase I/II, randomized	mCRPC	N/A	rPFS, maximum tolerated dose
Niraparib + Radium-223	**NiraRad**	Phase Ib, single arm	mCRPC	Unselected	DLT
Olaparib + AZD6738 (ATR inhibitor)	**TRAP**	Phase II, nonrandomized	mCRPC	Selected	Rate of response, PSA response >50% decline

mCRPC: Changing Landscape with MANY options

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

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

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

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

- Preferred regimens
  - Docetaxel (category 1)[fff]
- Useful in certain circumstances
  - Cabazitaxel/carboplatin[fff,jjj]
  - Niraparib/abiraterone[u,fff,zzz] for BRCA mutation (category 2B)
  - Olaparib for HRRm[uuu] (category 1)
  - Radium-223[rrr] for symptomatic bone metastases (category 1)
  - Rucaparib for BRCA mutation[vvv]
  - Sipuleucel-T[fff,sss]
  - Talazoparib/enzalutamide for HRRm[u,fff,yyy] (category 2B)
- Other recommended regimens
  - Abiraterone[u,nnn]
  - Abiraterone[u] + dexamethasone[nnn,www]
  - Enzalutamide[u]
  - Other secondary hormone therapy[u]

Prior docetaxel/no prior novel hormone therapy[mmm]

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

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

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

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

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

See Footnotes for Systemic Therapy M1 CRPC (PROS-15A).

March 23, 2022:

FDA approval of **177Lu-PSMA-617** for **PSMA+ mCRPC** who have received **prior ARPI** and **taxane**

PSMA PET/CT

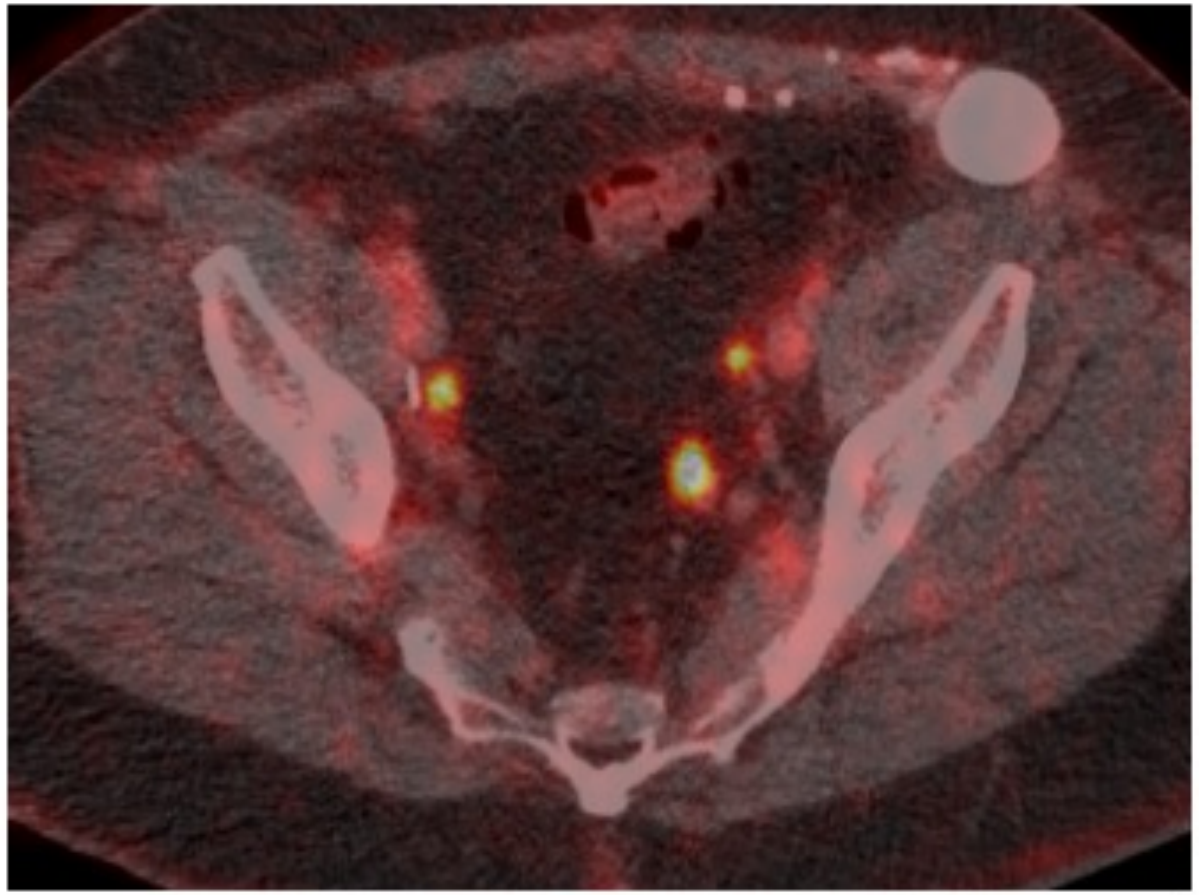
PSMA: cell membrane protein highly expressed on surface of PCa

Diagnostic radiotracers:

-Ga-68 PSMA-11

-F-18 piflufolast

Obtain scans in high, very high risk PCa, biochemical recurrence, mCRPC prior to PSMA-radioligand – replacing conventional imaging (bone scan + CT)



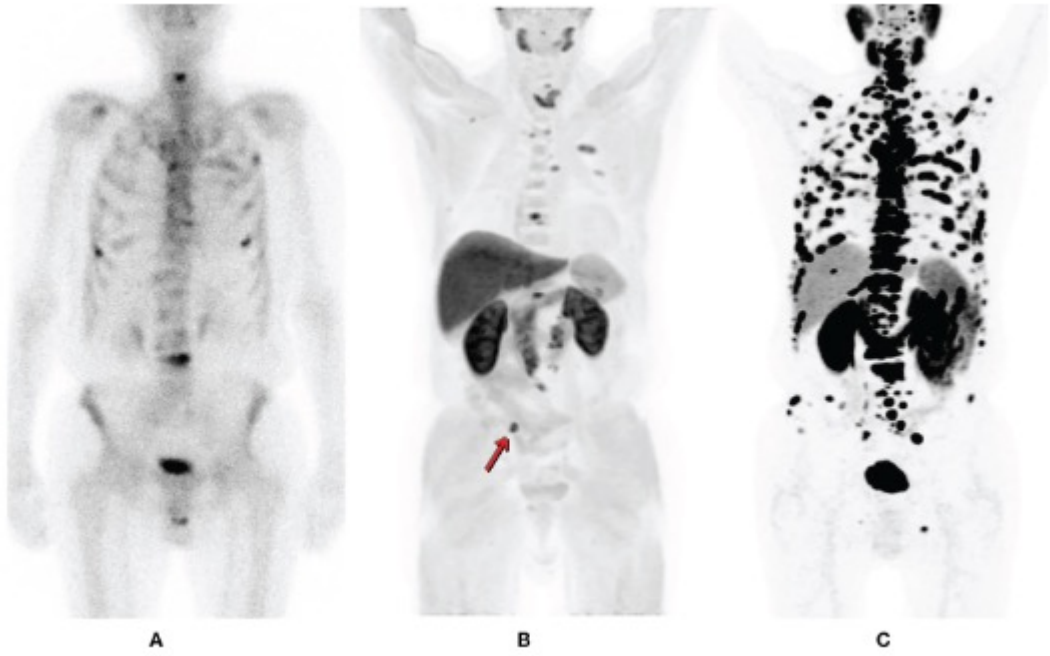
~15% of PCa lesions are PSMA-negative

Adapted from N. Reizine, 2023

https://cancerecology.com/psma-imaging

PSMA-Imaging Nuances

- Most recommended test for BCR/BCP
  - Detect pelvic and extra-pelvic disease
  - False positives can occur
  - Discuss findings if atypical
- Threshold of PSA 0.2 ng/mL
- Can affect outcomes of next steps



Adapted from Dr. Heather A Jacene, 2023

Frontiers in Oncology, 2022

177LuPSMA Radioligand

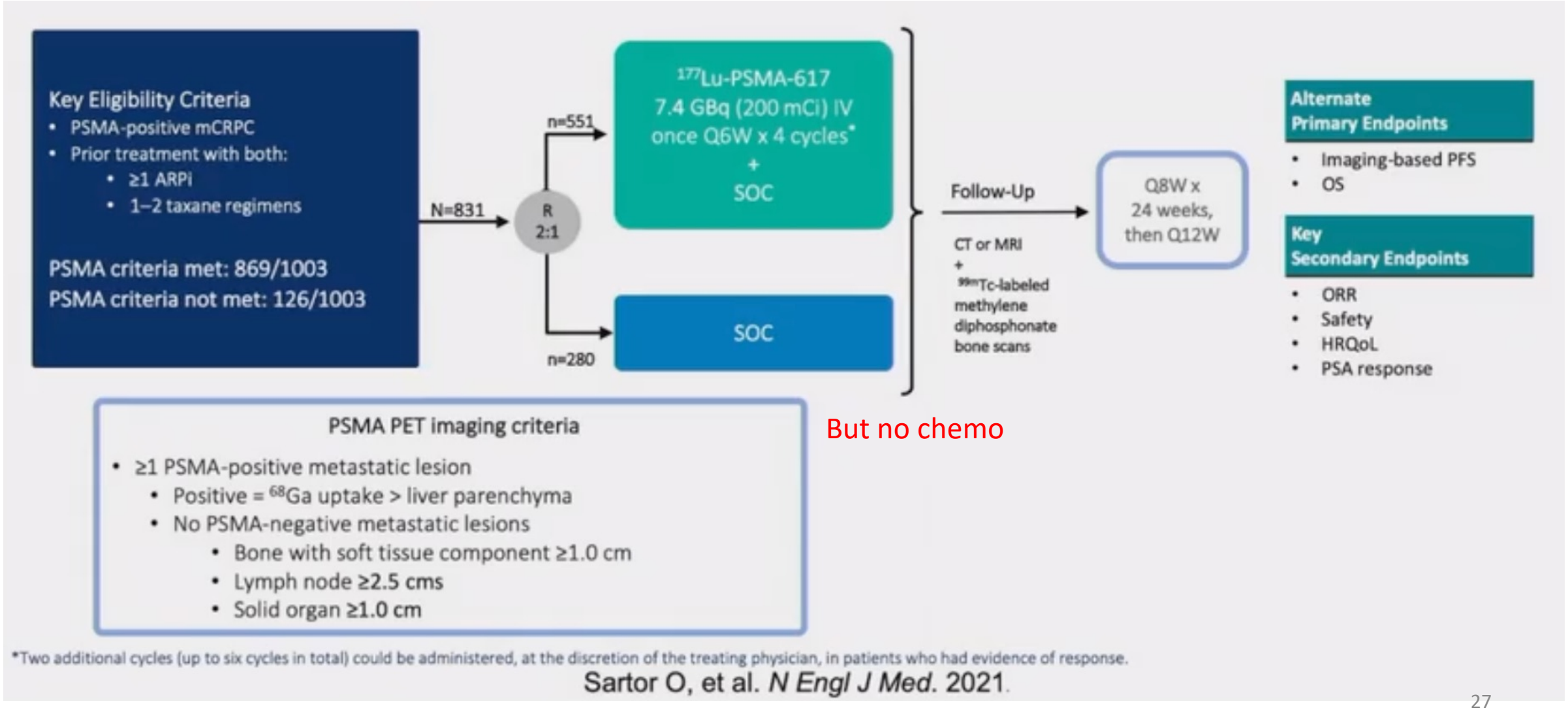
- Beta particle radiation taken up by PSMA-positive cells and surrounding tissues

- Internalization of radioligand results in accumulation of radioactivity in tumor tissue and irradiation

  - 6 injections (~20 minutes) q4-6 weeks
  - Hydration is important
  - AEs: salivary gland xerostomia, long-term renal toxicities

Adapted from N. Reizine, 2023

VISION: 177-Lu-PSMA-617 for Late Stage mCRPC

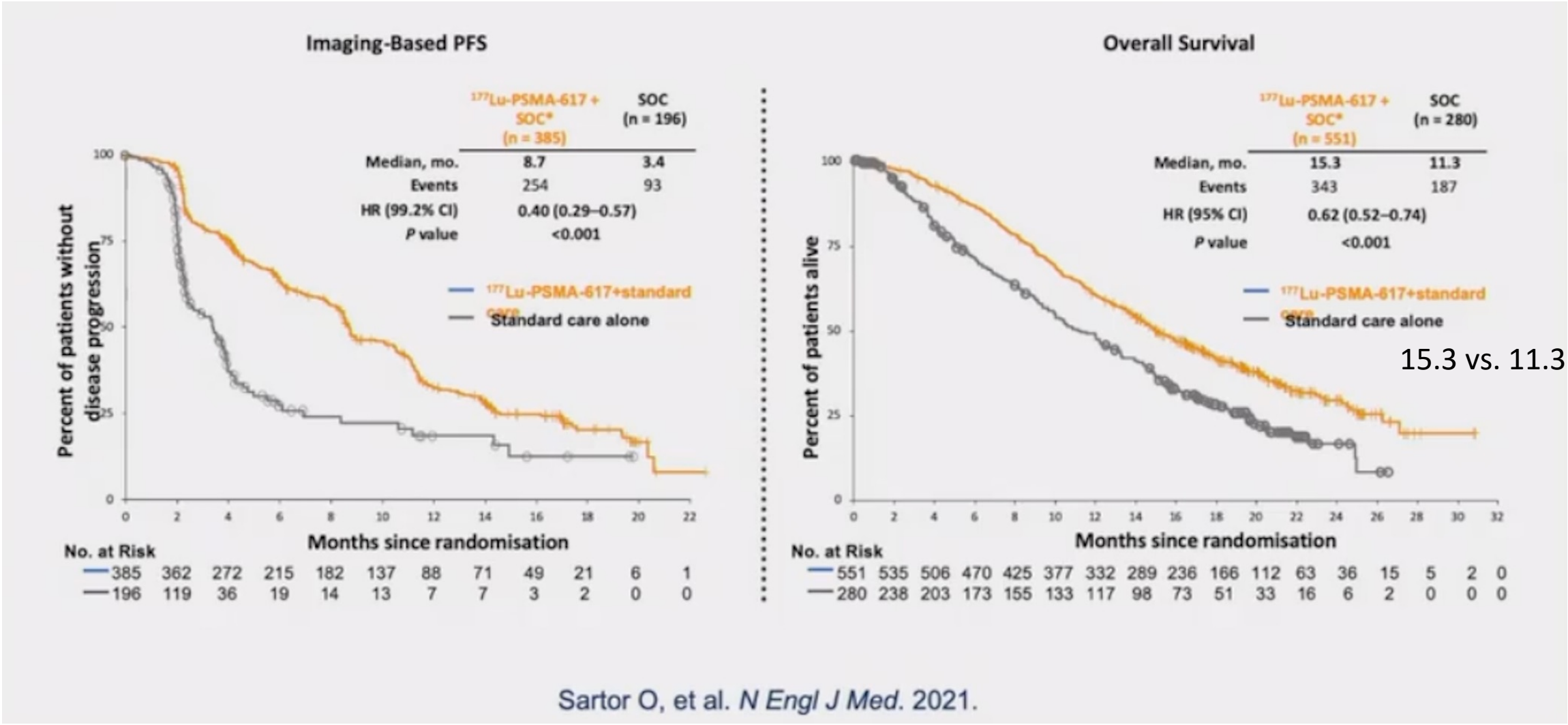


But no chemo

*Two additional cycles (up to six cycles in total) could be administered, at the discretion of the treating physician, in patients who had evidence of response.

Sartor O, et al. *N Engl J Med*. 2021.

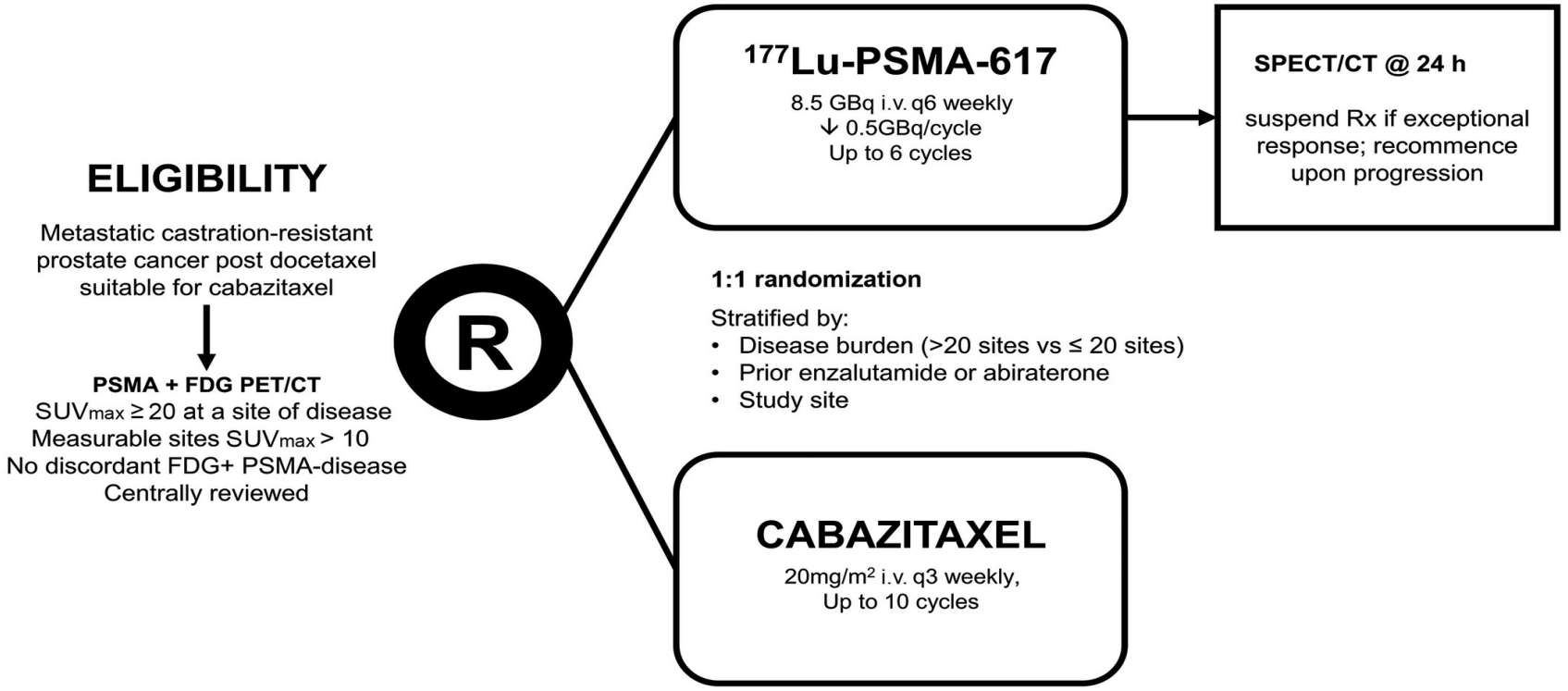
VISION: 177-Lu-PSMA-617 for Late Stage mCRPC



15.3 vs. 11.3m

Sartor O, et al. *N Engl J Med*. 2021.

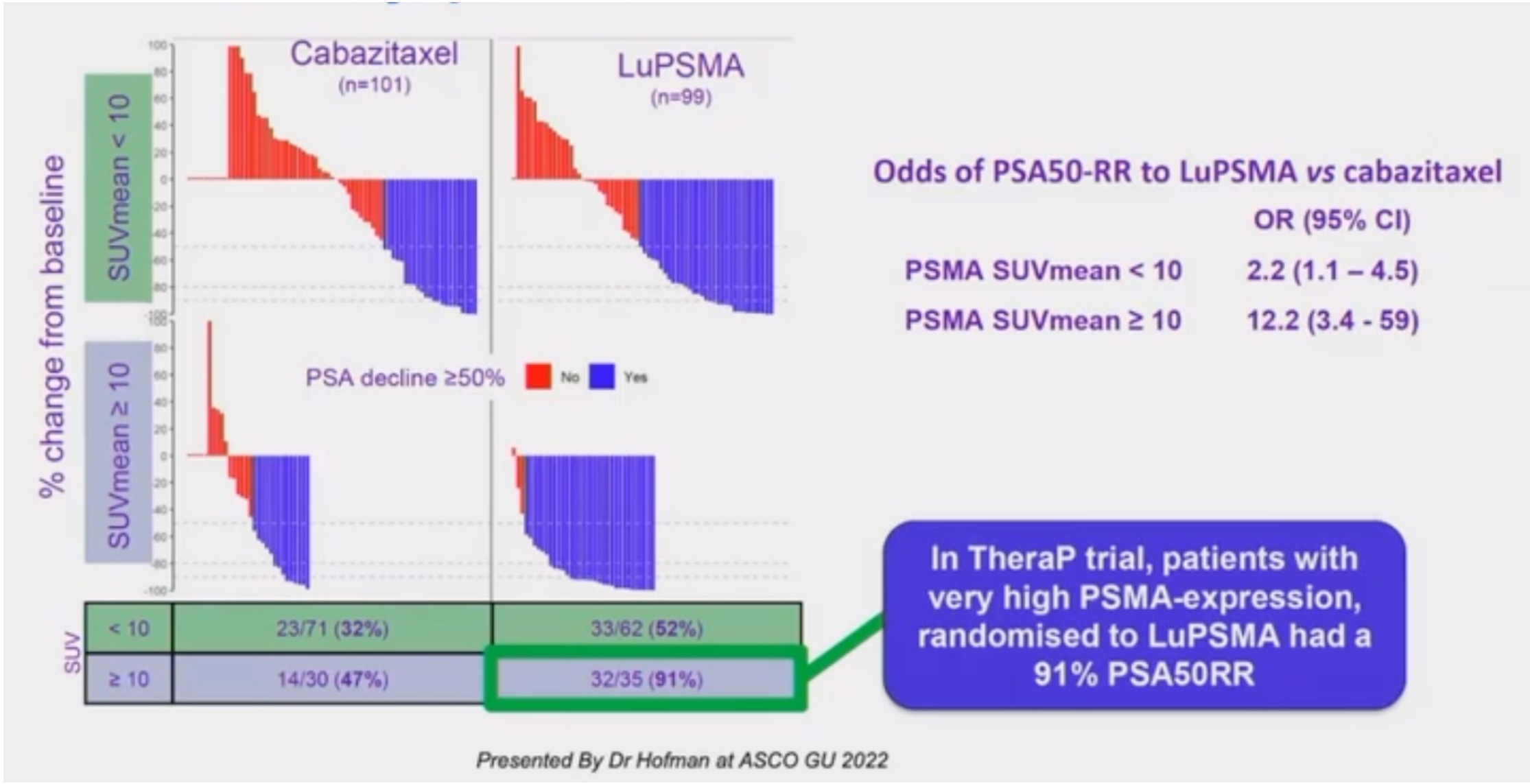
TheraP: randomized Ph2 in mCRPC



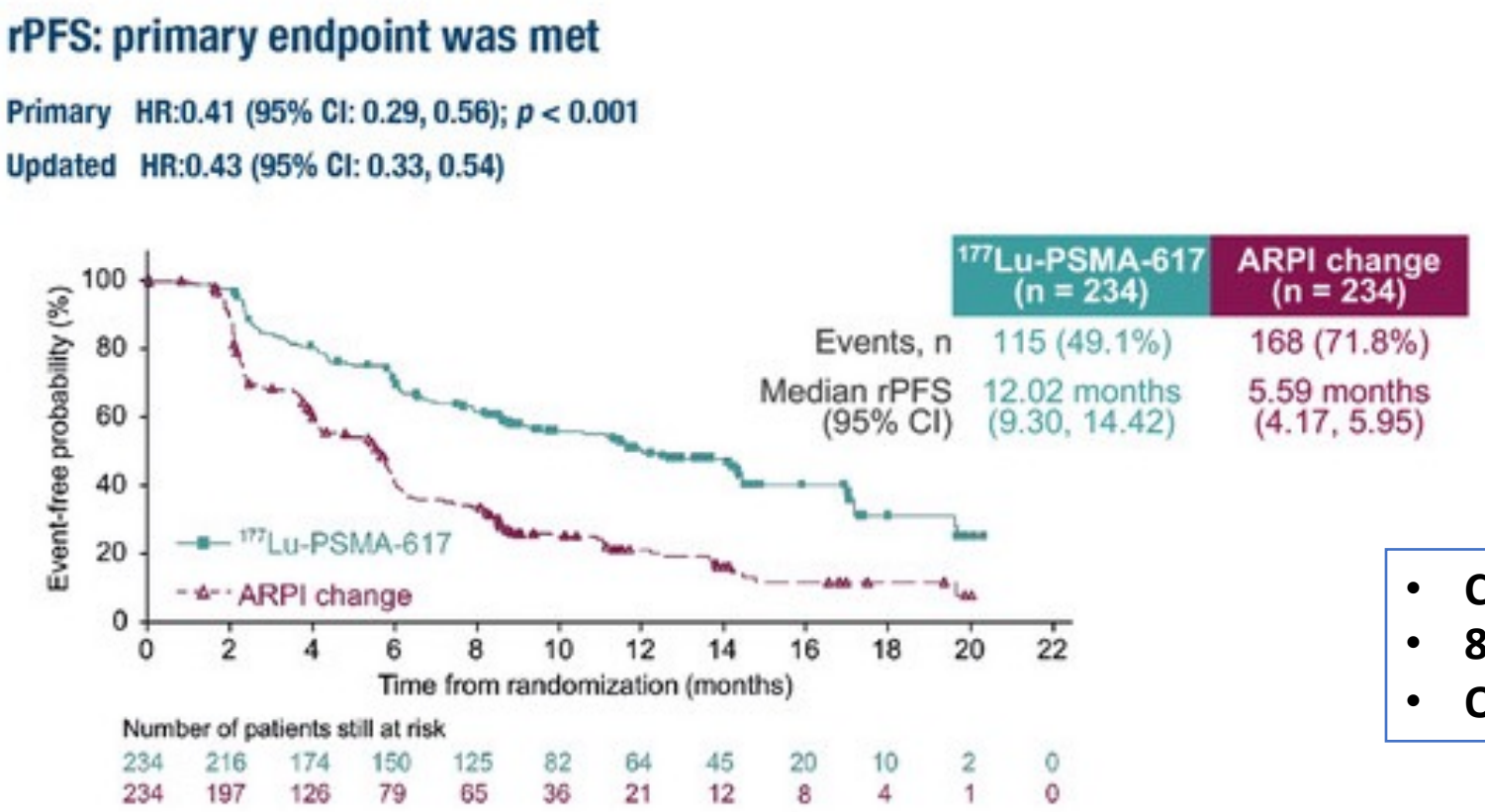
LuPSMA resulted in higher response rates (BCR, imaging), longer PFS, and reduced G3/4 toxicities compared to cabazitaxel

BJU International, Volume: 124, Issue: S1, Pages: 5-13, First published: 22 October 2019, DOI: (10.1111/bju.14876

TheraP: PSMA Intensity as a Predictive Biomarker



PSMA radioligand pre-chemo: PSMAfore



	177Lu-PSMA-617 (n = 234)	ARPI change (n = 234)
Events, n	115 (49.1%)	168 (71.8%)
Median rPFS (95% CI)	12.02 months (9.30, 14.42)	5.59 months (4.17, 5.95)

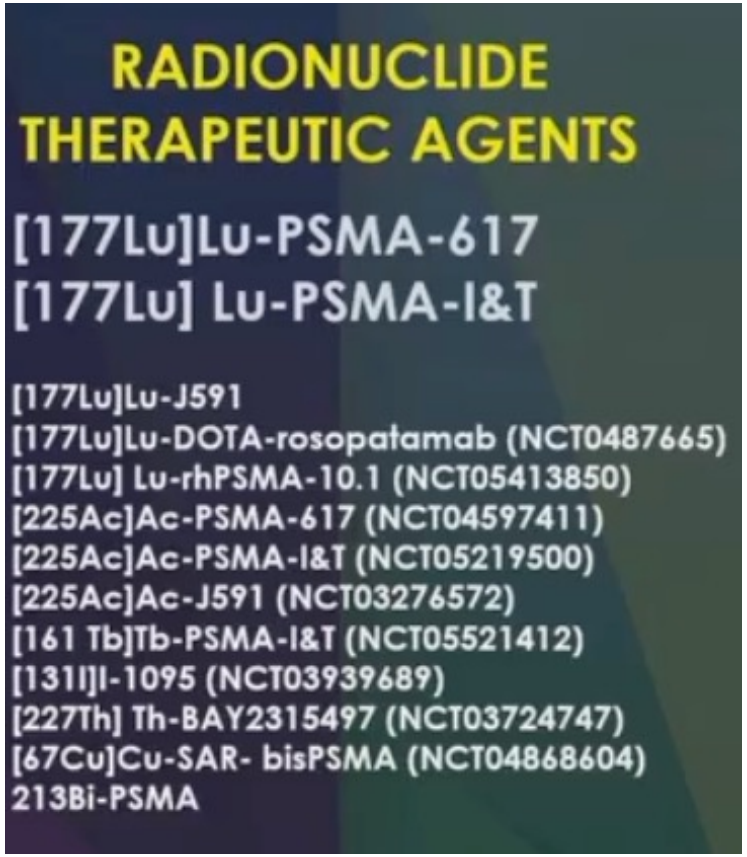
- **Control arm = ARPI change**
- **84% crossover**
- **OS data immature**

Figure. The PSMAfore trial met its primary endpoint, with a significant improvement in rPFS with 177Lu-PSMA-617 compared with ARPI change in mCRPC (ESMO Congress 2023, LBA13)

Sartor et al, 2023

Outstanding questions

- How to monitor response on therapy?
- What is the role of imaging in treatment selection?
  - And re-treatment?
- What is the optimal dose?
  - Adaptive strategies?
- How to sequence with other therapies?
- How to manage toxicities?
- How to prevent and overcome resistance?
  - 1/3 do not respond
- What is the role of other radioligands?
  - Alpha: higher energy transfer/more potent
- Equitable Access to Theranostics*
  - Availability, NM access, cost



Gopanath Gnanasegaran IUCS 2023

Adapted from N. Reizine, 2023

PSMA radioligand in earlier settings

Drug Therapy	Study Name	Study Design	Trial Population
LuPSMA before prostatectomy	Lutectomy	Phase I/II	High-risk localized or locoregional PCa
LuPSMA before SBRT vs. SBRT alone	LUNAR	Phase II	Oligorecurrent PCa
LuPSMA + EBRT	ProstACT TARGET	Phase II	Oligorecurrent PCa
LuPSMA + SABR vs. SABR alone	POPSTAR II	Phase II	Oligomestastatic PCa
LuPSMA + SOC vs. SOC alone	PSMAddition	Phase III	mHSPC
LuPSMA + Docetaxel vs Docetaxel alone	UpfrontPSMA	Phase II	mHSPC
LuPSMA vs. SOC	Bullseye	Phase II	Oligometastatic mHSPC

Tawagi and Reizine 2023

Improve efficacy in more homogenous population?

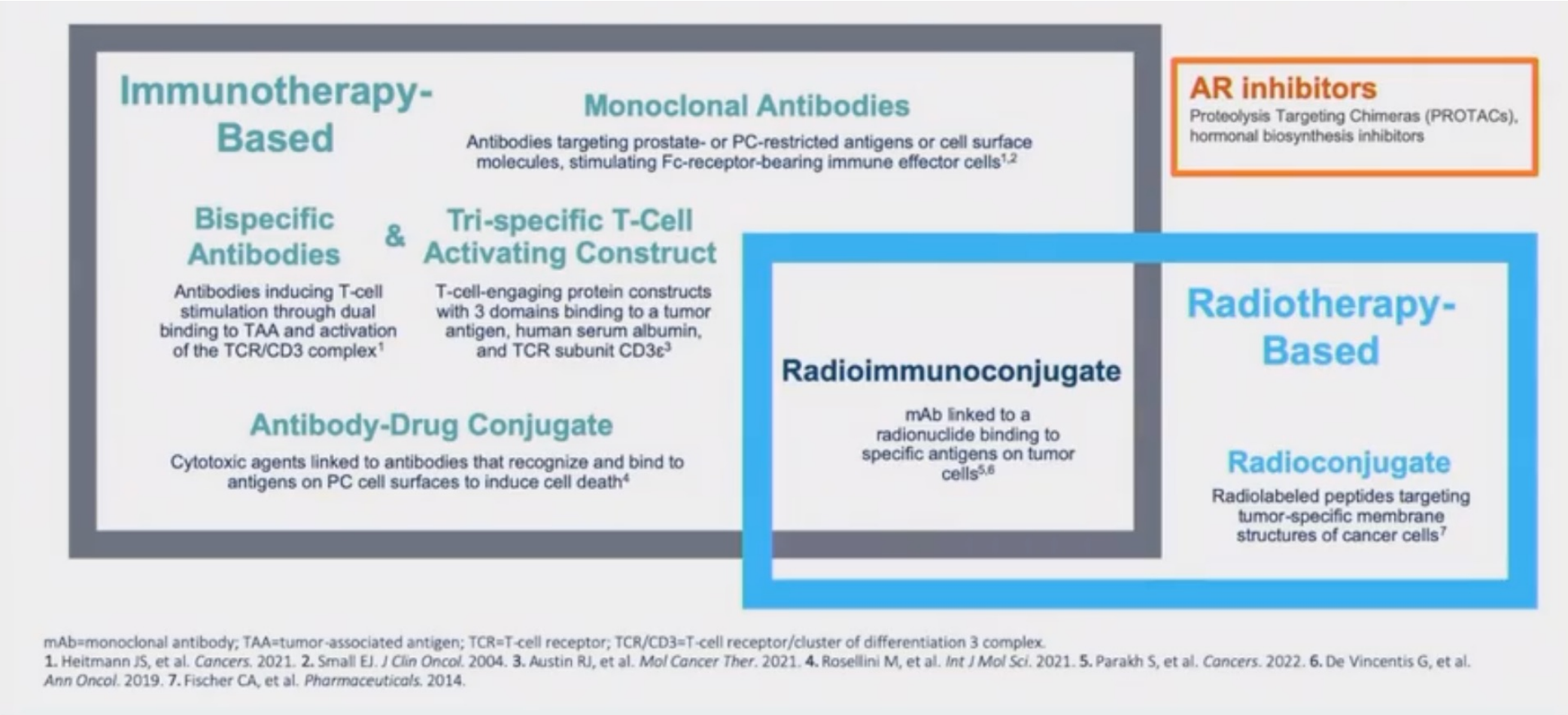
PSMA radioligand in combination regimens

Drug Therapy	Study Name	Study Design	Trial Population
Enzalutamide + LuPSMA vs Enzalutamide alone	ENZA-p	Phase II	mCRPC
LuPSMA after ARSI progression	SPLASH	Phase III	mCRPC
LuPSMA vs ARSI	ECLIPSE	Phase III	mCRPC
Abemaciclib before LuPSMA	UPLIFT	Phase I/II	mCRPC
LuPSMA vs LuPSMA with Ipilimumab + Nivolumab	EVOLUTION/ANZUP2001	Phase II	mCRPC
LuPSMA + Pembrolizumab	PRINCE	Phase I/II	mCRPC
LuPSMA + Cabazitaxel	LuCAB	Phase I/II	mCRPC
LuPSMA + Cabozantinib	CaboLu	Phase Ib	mCRPC
LuPSMA + Olaparib	LuPARP	Phase I	mCRPC

Tawagi and Reizine 2023

PSMA upregulation? Timing/significance of sequencing with other therapies?

Clinical Trials and Novel Therapies in PC



mAb=monoclonal antibody; TAA=tumor-associated antigen; TCR=T-cell receptor; TCR/CD3=T-cell receptor/cluster of differentiation 3 complex.

1. Heitmann JS, et al. *Cancers*. 2021. **2.** Small EJ. *J Clin Oncol*. 2004. **3.** Austin RJ, et al. *Mol Cancer Ther*. 2021. **4.** Rosellini M, et al. *Int J Mol Sci*. 2021. **5.** Parakh S, et al. *Cancers*. 2022. **6.** De Vincentis G, et al. *Ann Oncol*. 2019. **7.** Fischer CA, et al. *Pharmaceuticals*. 2014.

Presented by Elena Castro IUCS 2023

Thank You.

& special thanks to Dr. Natalie Reizine for her input with this presentation

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