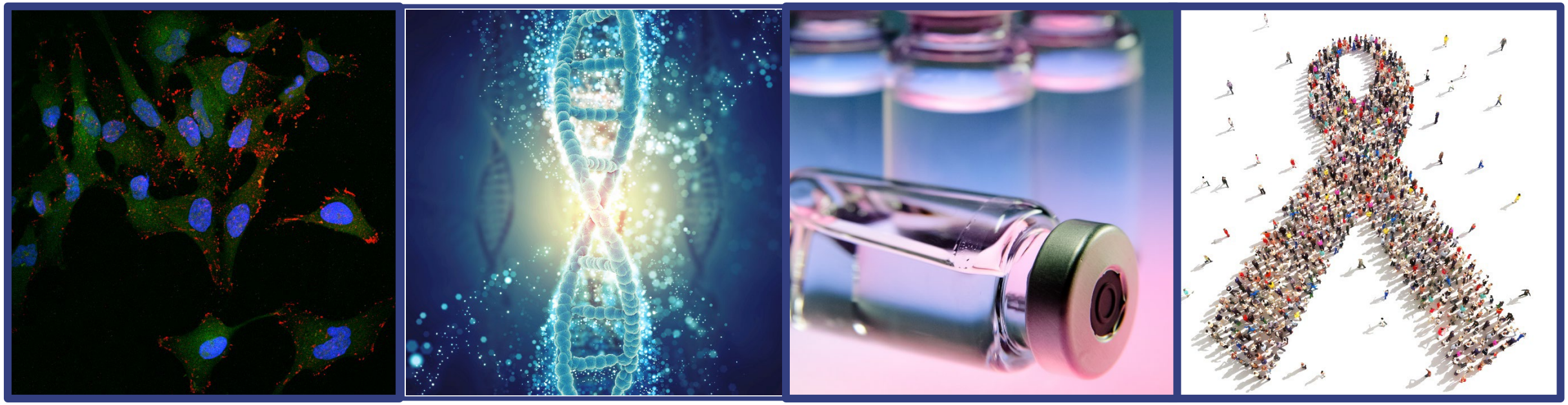

Biomarker-Based Treatment in Prostate Cancer

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Winship Cancer Institute of Emory University

DDHO, July 20th 2023

EMORY WINSHIP CANCER INSTITUTE

National Cancer Institute-Designated Comprehensive Cancer Center

Conflict of Interest

- Advisory board: Exelixis, Bayer, BMS, Eisai, Pfizer, AstraZeneca, Janssen, Calithera Biosciences, Genomic Health, Nektar, EMD Serono, SeaGen, and Sanofi

- Research: Xencor, Bayer, Bristol-Myers Squibb, Genentech/Roche, SeaGen, Incyte, Nektar, AstraZeneca, Tricon Pharmaceuticals, Genome & Company, AAA, Peloton Therapeutics, and Pfizer

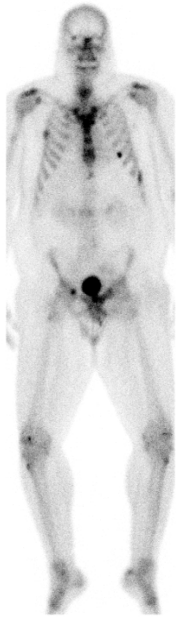
Outline

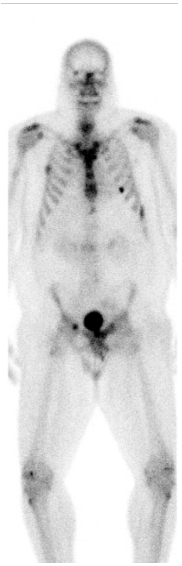
- General overview
- Role of genetic testing on patient management and therapy choice
  - Which testing? And what to order?
- Recent data for PARP combinations
- Lu-PSMA
- MSI-high, other targets
- Future direction

Therapeutic Options For Advanced Prostate Cancer 2023

CASTRATION SENSITIVE

CASTRATION RESISTANT





ANDROGEN DEPRIVATION

Orchiectomy / GnRH Agonist

GnRH Antagonist

Antiandrogens

Docetaxel

Enzalutamide

Apalutamide

Abiraterone+/- Docetaxel

Daralutamide+ Docetaxel

IMMUNOTHERAPY

Sipuleucel-T

SECONDARY HORMONAL TREATMENTS

Bicalutamide, flutamide, nilutamide

Ketoconazole

DES

Abiraterone

Enzalutamide

M0 CRPC AGENTS

Apalutamide

Enzalutamide

Daralutamide

Radiopharmaceuticals

Radium-223

Lu-177 PSMA

CHEMOTHERAPY

Docetaxel

Cabazitaxel

CRPC with DDR

Olaparib

Rucaparib

PARP combinations

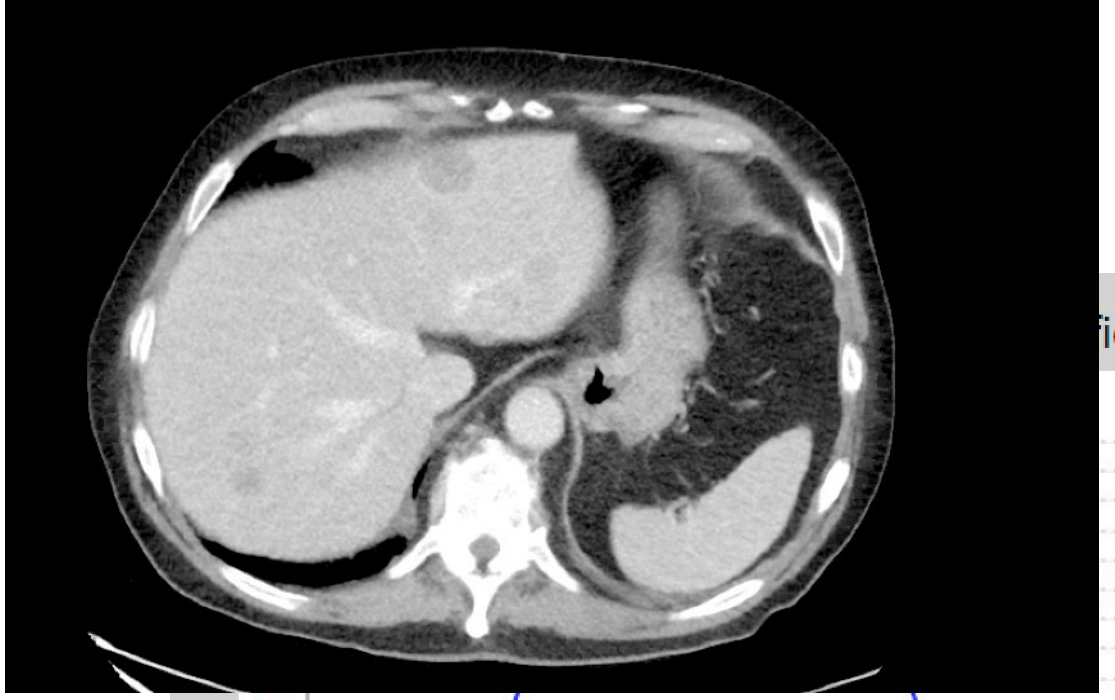
DES = diethylstilbestrol

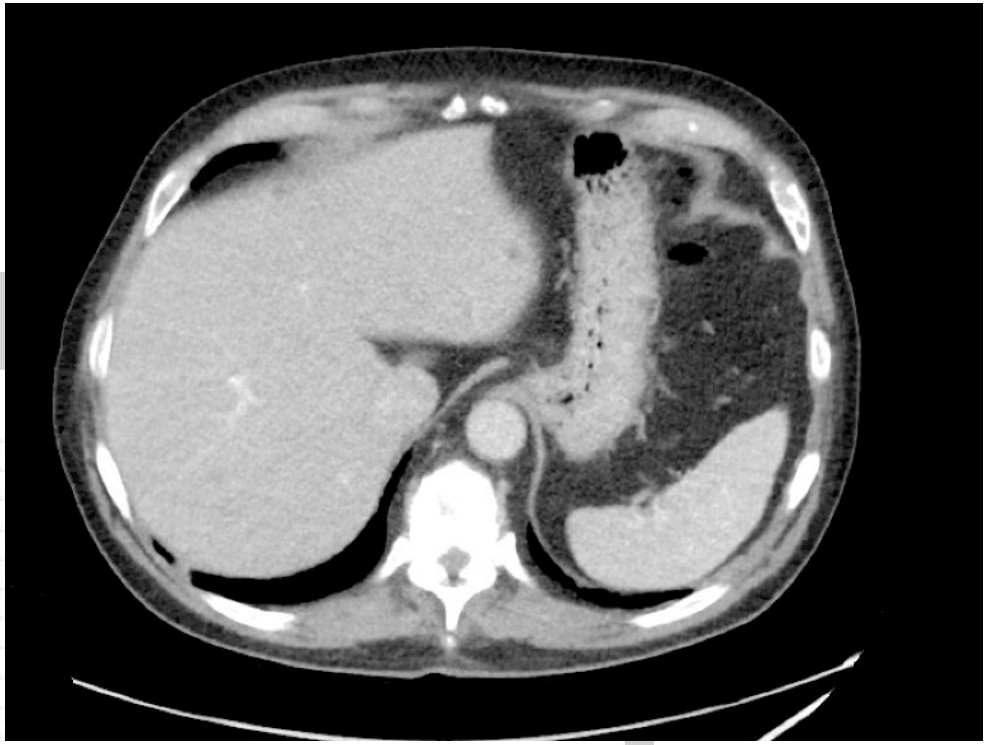
Case 1: NGS – Biomarker Positive

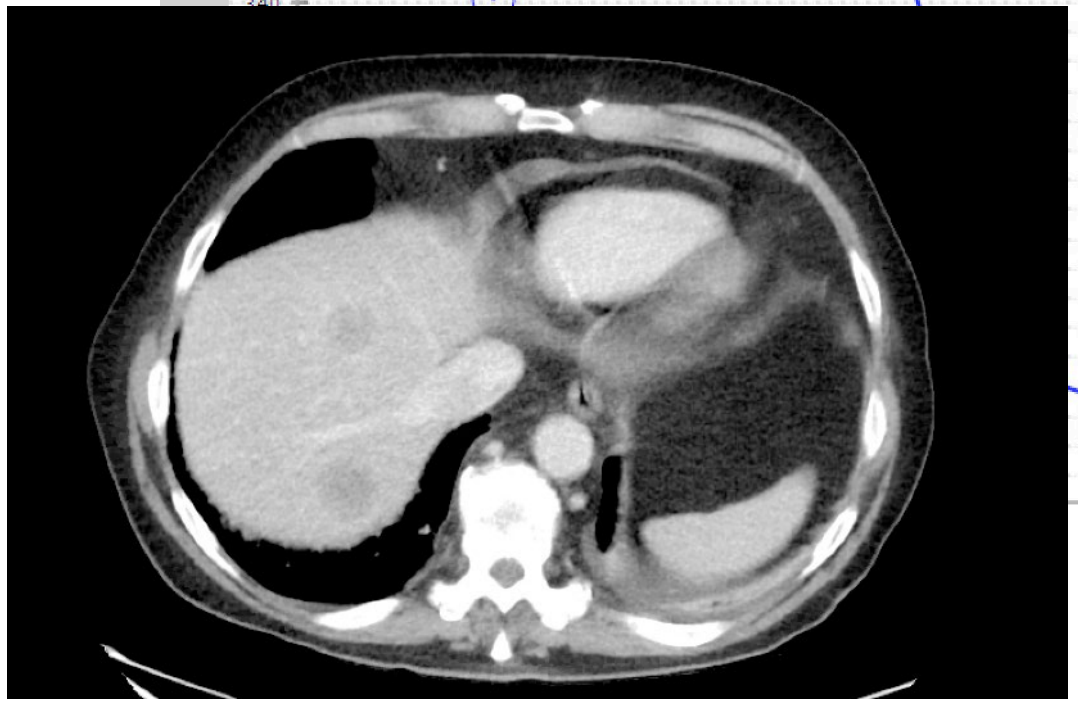
- 65 y/o male patient
- Good health with no major issues
- Diagnosed with prostate cancer, Gleason 4 + 5 = 9
- PSA >1300
- Staging work-up showed >20 bone metastases
- Initially treated with ADT plus abiraterone in castration-sensitive setting
- Recently became castration resistant

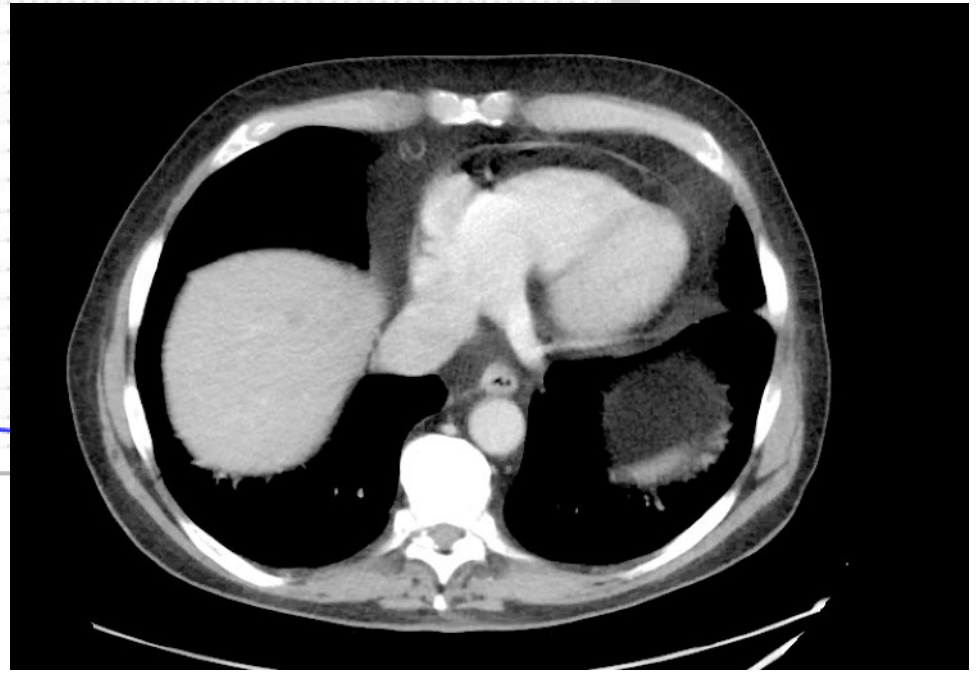
Case 1 (cont.): NGS – Biomarker Positive

- Obtained both germline and tissue-based somatic testing
- Patient is positive for somatic BRCA2
- Started olaparib 300mb BID

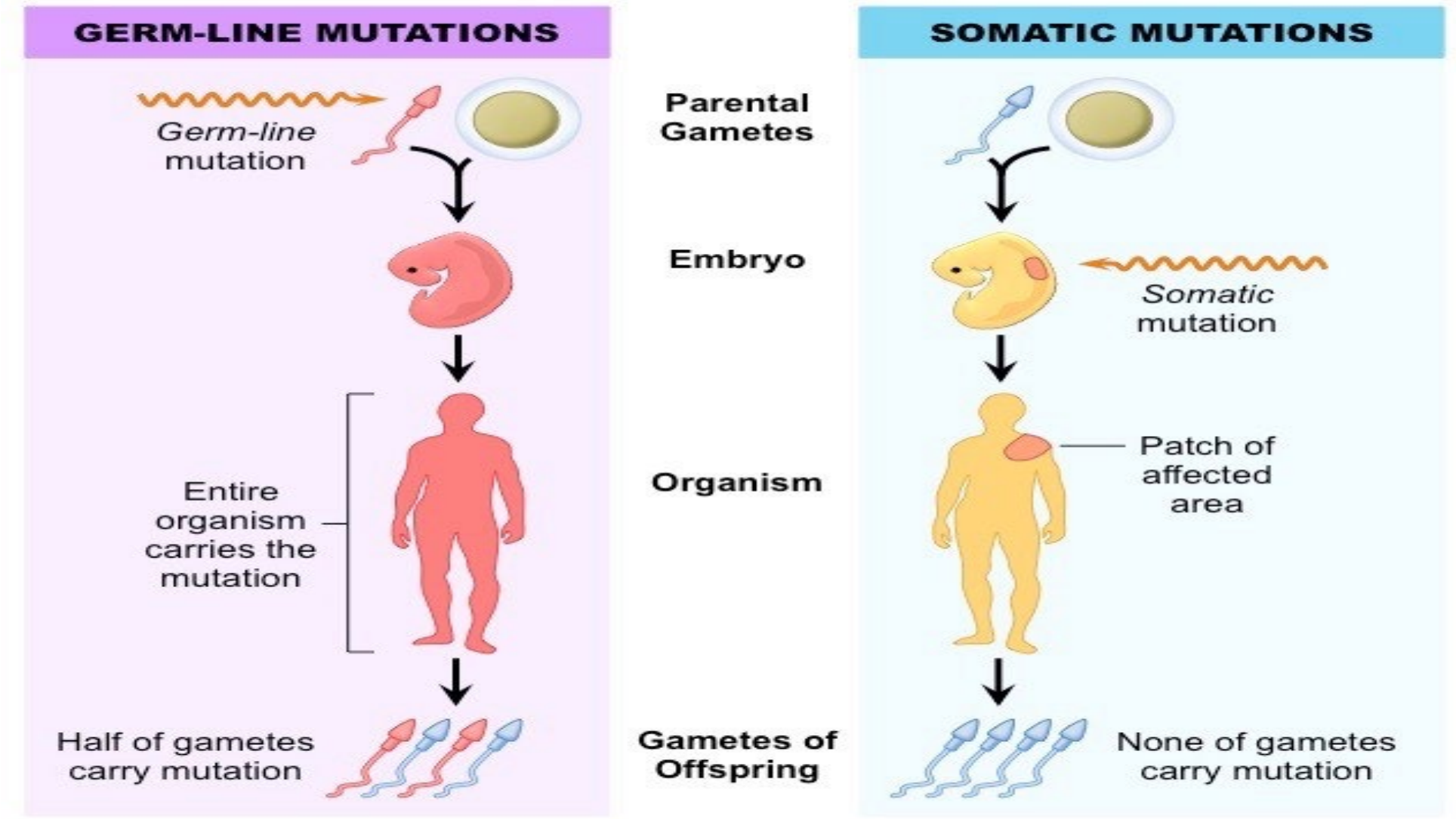






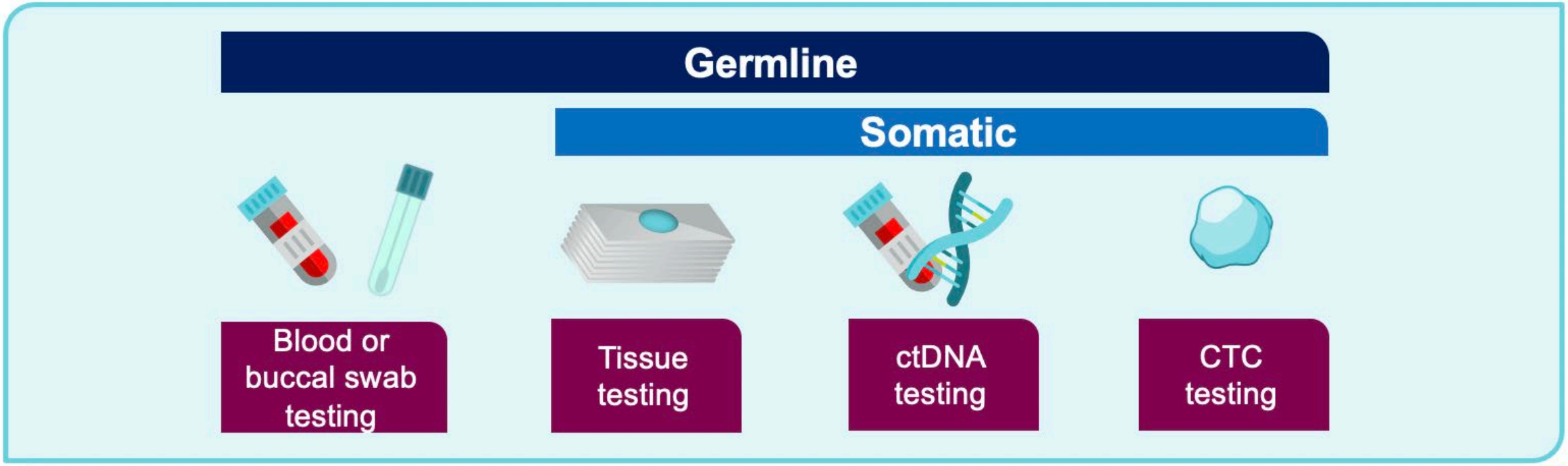


Germline vs Somatic Testing?



https://ib.bioninja.com.au/standard-level/topic-3-genetics/33-meiosis/somatic-vs-germline-mutatio.html

Approaches to Genetic Testing



- **Tumor molecular testing** can identify **both germline and somatic HRR mutations** (but cannot distinguish between them), while germline testing detects only germline HRR mutations
- **Germline mutations** offer information about **risk for associated cancers and family members**
- Performing both germline and tumor testing can identify the mutation status of a larger number of patients

Cheng H, et al. *Am Soc Clin Oncol Educ Book*. 2018;38:372-381; Haber DA, Velculescu VE. *Cancer Discov.* 2014;4:650-661; Raymond VM, et al. *J Natl Cancer Inst.* 2015;108(4):djv351; Catenacci DV, et al. *Int J Cancer*. 2015;136:1559-1567; Frey MK, Pothuri B. *Gynecol Oncol Res Pract*. 2017;4:4.

Testing Approaches: Strengths and Weaknesses

	Tumor testing	Germline testing	ctDNA testing
Advantages	• Most validated technique that allows **somatic and germline mutations** detection	• Easy to obtain **whole blood** or **buccal swab** samples to test for germline mutations • Can only detect **germline mutations**	• **Plasma ctDNA** is tested with easy-to-obtain **blood** samples • Can detect **germline mutations** • Plasma testing can also detect **somatic mutations** if there is an appreciable level of ctDNA
Disadvantages	• Requires invasive biopsies which may provide only limited tissue quantity and quality • Prostate cancer primarily spreads to bone; tissue samples from bone metastases are difficult to obtain and process • A biopsy may miss within-tumor genetic heterogeneity	• Unable to identify somatic mutations	• Tests not currently widely available • Highly sensitive tests are required • May miss patients who do not shed sufficient ctDNA

Capoluongo E, et al. *Oncotarget*. 2018;9:19463-19468; Cheng H, et al. *Am Soc Clin Oncol Educ Book*. 2018;38:372-381; Ossandon MR, et al. *J Natl Cancer Inst*. 2018;110:929-934; Kammesheidt A, et al. *Int J Mol Epidemiol Genet*. 2018;9(1):1-12.

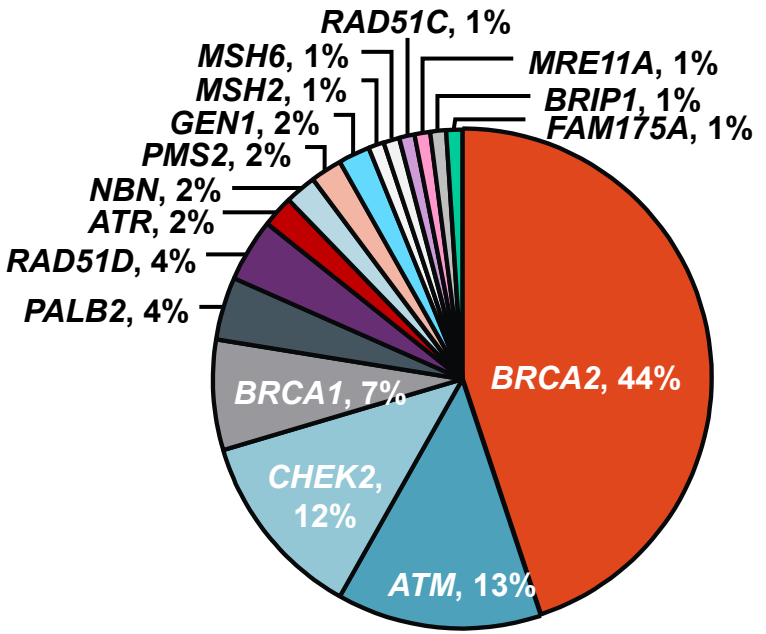
What I do?

- Definitely send both germline and somatic testing
- If newer tissue, use tissue-based testing
- If no recent tissue, or cannot do a biopsy (bone-only patients), or are not willing to do it, use liquid testing

DNA Repair Gene Alterations Are Common in Metastatic Prostate Cancer

- 23% of metastatic castration-resistant prostate cancers have DNA repair alterations1
- Frequency of DNA repair alterations increases with disease progression
- 11.8% of 692 men with metastatic prostate cancer had germline DNA repair defects2
- Not all men with germline mutations had a family history of cancer

Distribution of Presumed Pathogenic Germline Mutations[2]



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

PARPi FDA Approvals for Prostate Cancer

Rucaparib

On May 15, 2020, on the basis of data from the TRITON-2 study, the FDA granted accelerated approval to rucaparib for the treatment of patients with deleterious *BRCA1/2* (germline and/or somatic)-associated mCRPC who have been treated with an androgen receptor-directed therapy and a taxane-based chemotherapy

8/26/2020: FDA approved FoundationOne Liquid CDx as a companion diagnostic for rucaparib

Olaparib

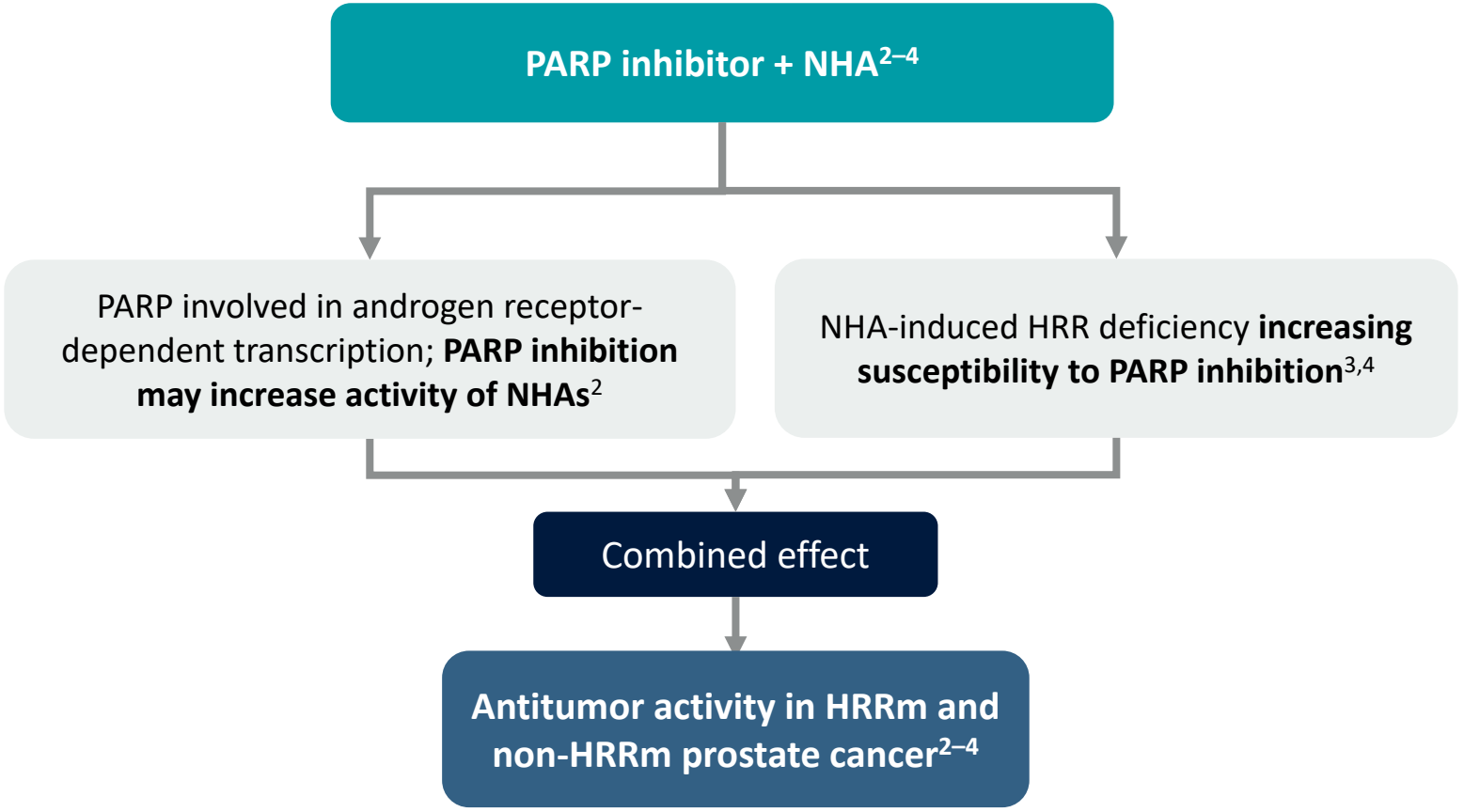
On May 19, 2020, on the basis of data from the PROfound study, the FDA approved olaparib for the treatment of patients with pathogenic germline or somatic HRR gene-mutated mCRPC who have progressed following prior treatment with enzalutamide or abiraterone

(*BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, RAD54L*)

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-rucaparib-brca-mutated-metastatic-castration-resistant-prostate
https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-olaparib-hrr-gene-mutated-metastatic-castration-resistant-prostate-cancer

Rationale for Combining PARP Inhibitors and NHAs[1]

Interaction between PARP signaling and AR signaling pathways may explain the combined effect of agents observed in preclinical models



AR, androgen receptor; HRR, homologous recombination repair; HRRm, homologous recombination repair gene mutation; NHA, novel hormonal agent; PARP, poly (ADP-ribose) polymerase.

Adapted from 1. Mateo J, et al. *N Engl J Med.* 2015;373:1697-1708; 2. Schiewer MJ, et al. *Cancer Discov.* 2012;2:1134-1149; 3. Polkinghorn WR, et al. *Cancer Discov.* 2013;3:1245-1153; 4. Asim M, et al. *Nat Commun.* 2017;8:374.

PARP Combinations: GU-ASCO 2022

PROPEL trial

Patient population
- 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

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

1:1

Olaparib 300 mg BID + Abiraterone 1000 mg QD*
n = 399
Full dose of olaparib and abiraterone used

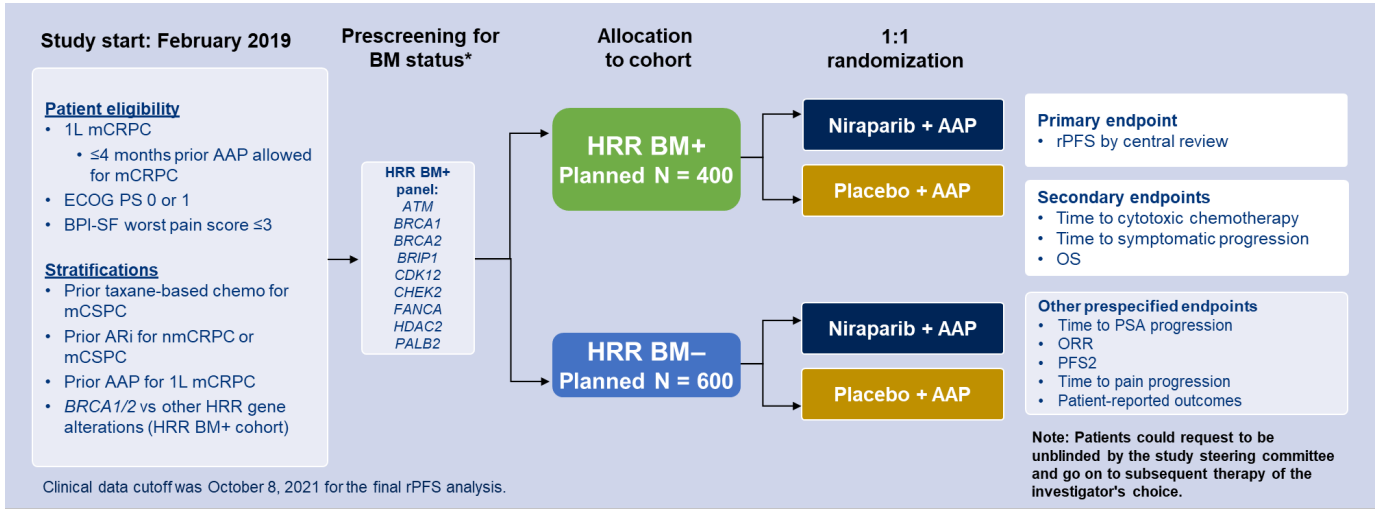
Placebo + Abiraterone 1000 mg QD*
n = 397
Full dose of abiraterone used

Primary endpoint
- Radiographic progression or death (rPFS) by investigator assessment

Key secondary endpoint
- Overall survival (alpha control)

Additional 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

MAGNITUDE trial



Saad et al, Genitourinary Cancer symposium, 2022
Chi et al, Genitourinary Cancer symposium, 2022

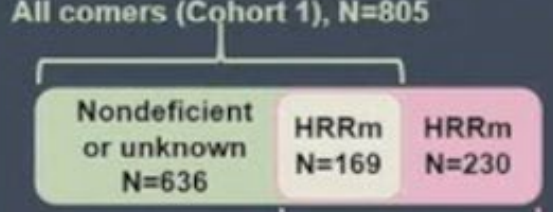
TALAPRO-2: A Randomized, Double-blind, Placebo-Controlled Study

Patient population

- First-line mCRPC
- ECOG performance status (PS) 0 or 1

Stratification factors

- Prior abiraterone[a] or docetaxel in castration-sensitive setting (yes vs no)
- HRR gene alteration status (deficient vs nondeficient or unknown)



1:1 (N=805)

Talazoparib 0.5 mg* + enzalutamide 160 mg, once daily

(N=402)

(*0.35 mg daily if moderate renal impairment)

Placebo + enzalutamide 160 mg, once daily

(N=403)

Primary endpoint

Radiographic progression-free survival (rPFS) by blinded independent central review (BICR)

Key secondary endpoint

- Overall survival (alpha protected)

Other secondary endpoints

- Time to cytotoxic chemotherapy
- PFS2 by investigator assessment[b]
- Objective response rate (ORR)
- Patient-reported outcomes
- Safety

(Data cutoff: August 16, 2022)

Samples prospectively assessed for HRR gene alterations *(BRCA1, BRCA2, PALB2, ATM, ATR, CHEK2, FANCA, RAD51C, NBN, MLH1, MRE11A, CDK12)* using FoundationOne®CDx and/or FoundationOne®Liquid CDx

We report results only from the all-comers cohort of men unselected for HRR gene alterations

To maintain the overall type I error at or below 1-sided 0.025, alpha for rPFS by BICR was split equally between the all-comers and forthcoming molecularly selected cohort (1-sided alpha of 0.0125 for each). If the rPFS showed statistically significant improvement, overall survival was tested in a hierarchical stepwise procedure to preserve the overall type I error.

[a]Two patients in each treatment arm received prior orteronel. [b]Time from randomization to the date of documented progression on the first subsequent antineoplastic therapy or death from any cause, whichever occurred first.

PRESENTED BY: Dr Neeraj Agarwal @neerajaiims

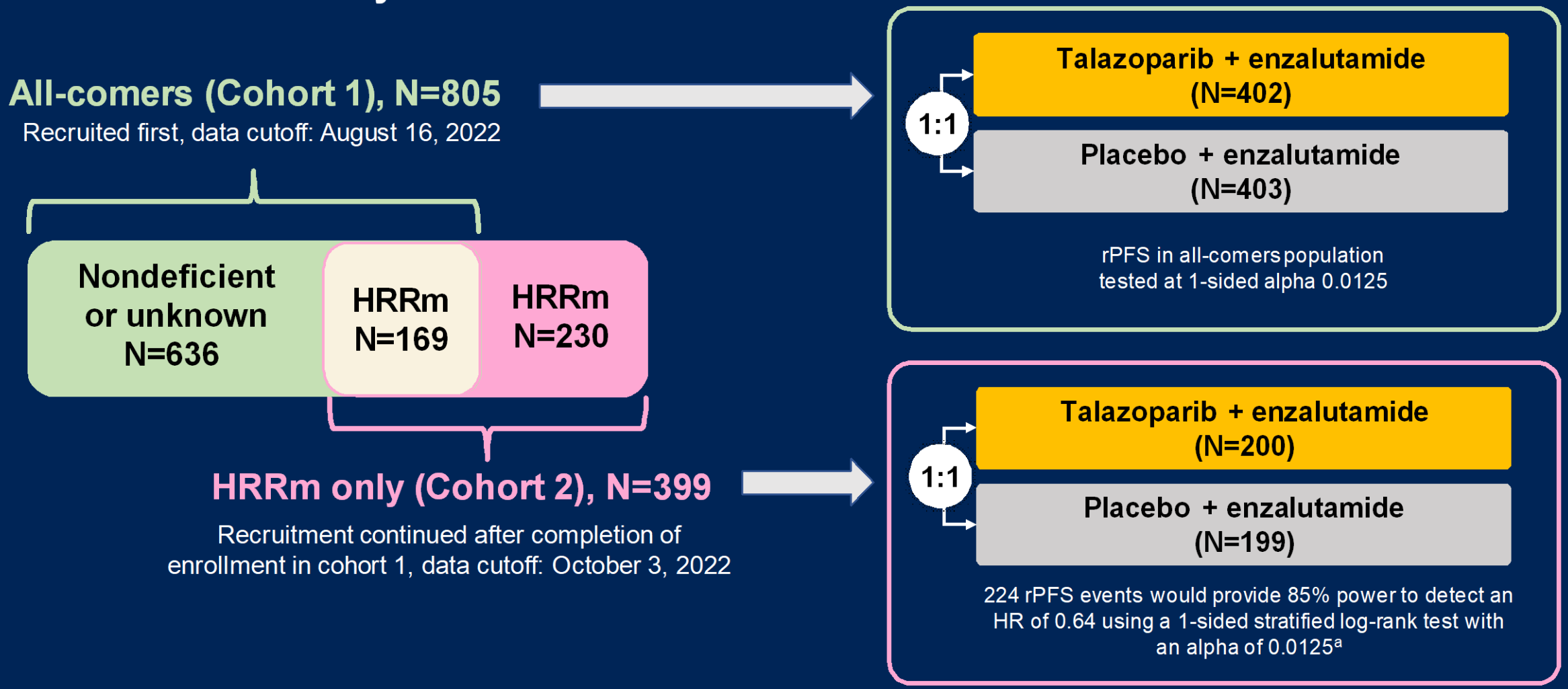
PARP Inhibitor-Based Combination Therapy

- PROpel analysis:
  - rPFS benefit in the overall population (24.8 vs 16.6 mo; HR: 0.66; P <.0001)
  - **Patients were not stratified by HRR status**

- MAGNITUDE analysis:
  - rPFS benefit in patients with HRR alterations (16.5 vs 13.7 mo; HR: 0.53; P = .0014)
  - **No benefit in HRRmut -ve cohort**

- TALAPRO-2 analysis:
  - rPFS benefit in the overall population (NR vs 21.9 mo; HR: 0.63; P = <.0001)

TALAPRO-2: Study Cohorts and Enrollment



[a]An interim analysis (IA) was planned with ~70% of the total required events. The HRRm cohort would be stopped for efficacy if the pre-specified efficacy boundary was crossed (P = 0.003). As the efficacy boundary was crossed at the IA rPFS, this became the final analysis. Survival and safety follow-up is continuing. All other endpoints are final.

TALAPRO-2 HRR-Deficient: Baseline Demographics and Disease Characteristics

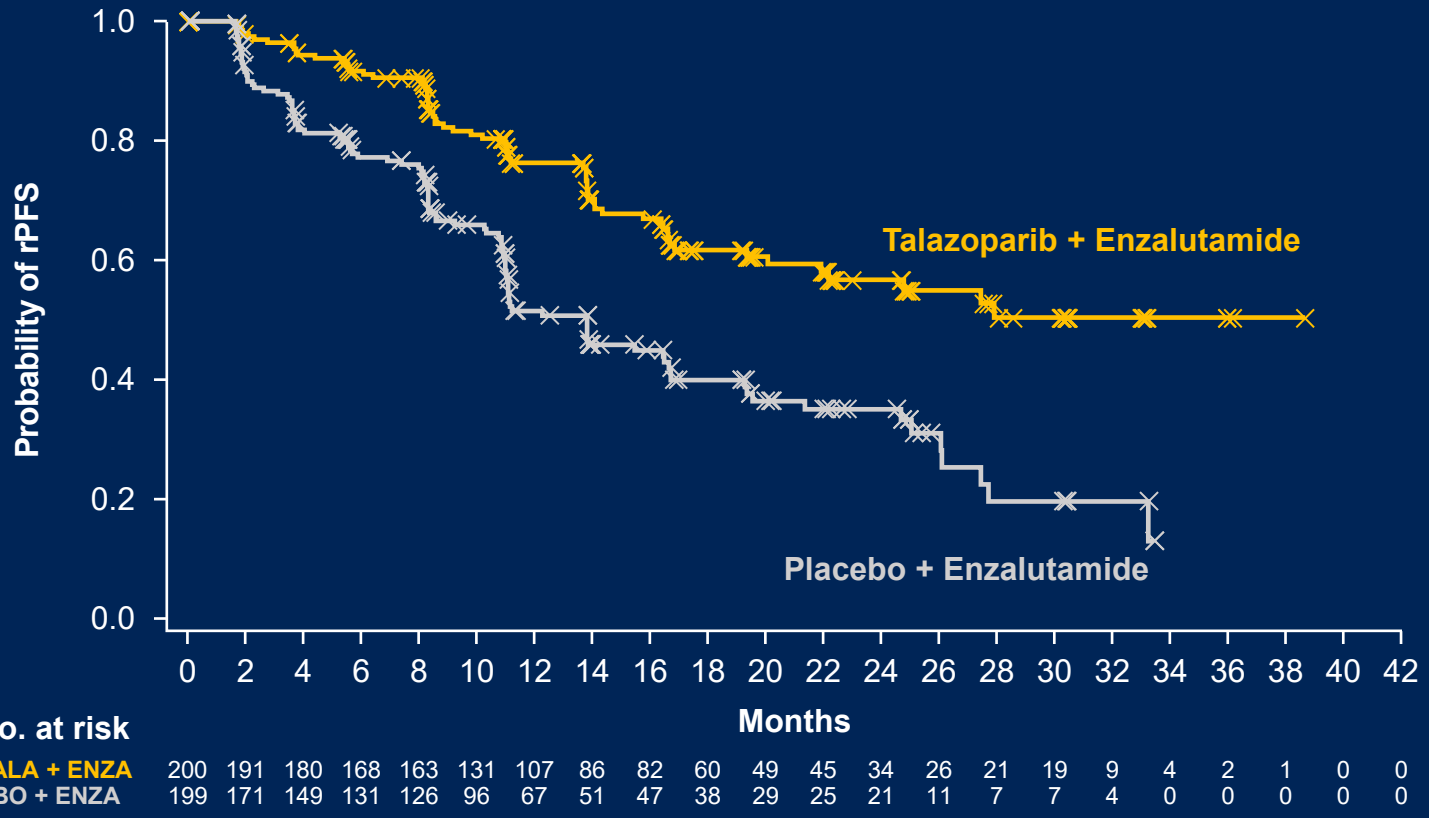
These were well-balanced between treatment arms

	Talazoparib + Enzalutamide (N=200)	Placebo + Enzalutamide (N=199)
Age, median (range), years	70 (41–90)	71 (44–90)
Prostate-specific antigen (PSA), median (range), ng/mL	19.6 (0.2–3412.0)	18.0 (0.0–1055.0)
Disease site, n (%)		
Bone	175 (87.5)	158 (79.4)
Lymph node	82 (41.0)	94 (47.2)
Visceral (lung/liver)	23 (11.5)/9 (4.5)	26 (13.1)/6 (3.0)
ECOG PS 0/1, n (%)	128 (64.0)/72 (36.0)	118 (59.3)/81 (40.7)
Prior abiraterone[a] or docetaxel, n (%)	75 (37.5)	74 (37.2)
Abiraterone	16 (8.0)	16 (8.0)
Docetaxel	57 (28.5)	60 (30.2)
Tissue source for prospective HRR gene alteration testing, n (%)		
Tumor tissue only	76 (38.0)	80 (40.2)
Tumor tissue and blood (circulating tumor DNA)	121 (60.5)	115 (57.8)
Blood (circulating tumor DNA) only	3 (1.5)	4 (2.0)

[a]One patient in each treatment arm received prior orteronel.

TALAPRO-2 HRR-Deficient Primary Endpoint: rPFS by BICR

Treatment with talazoparib plus enzalutamide resulted in a 55% reduced risk of progression or death



	TALA + ENZA (N=200)	PBO + ENZA (N=199)
Events, n	66	104
Median (95% CI), months	Not reached (NR) (21.9–NR)	13.8 (11.0–16.7)
HR (95% CI)	**0.45 (0.33–0.61); *P* < 0.0001**	

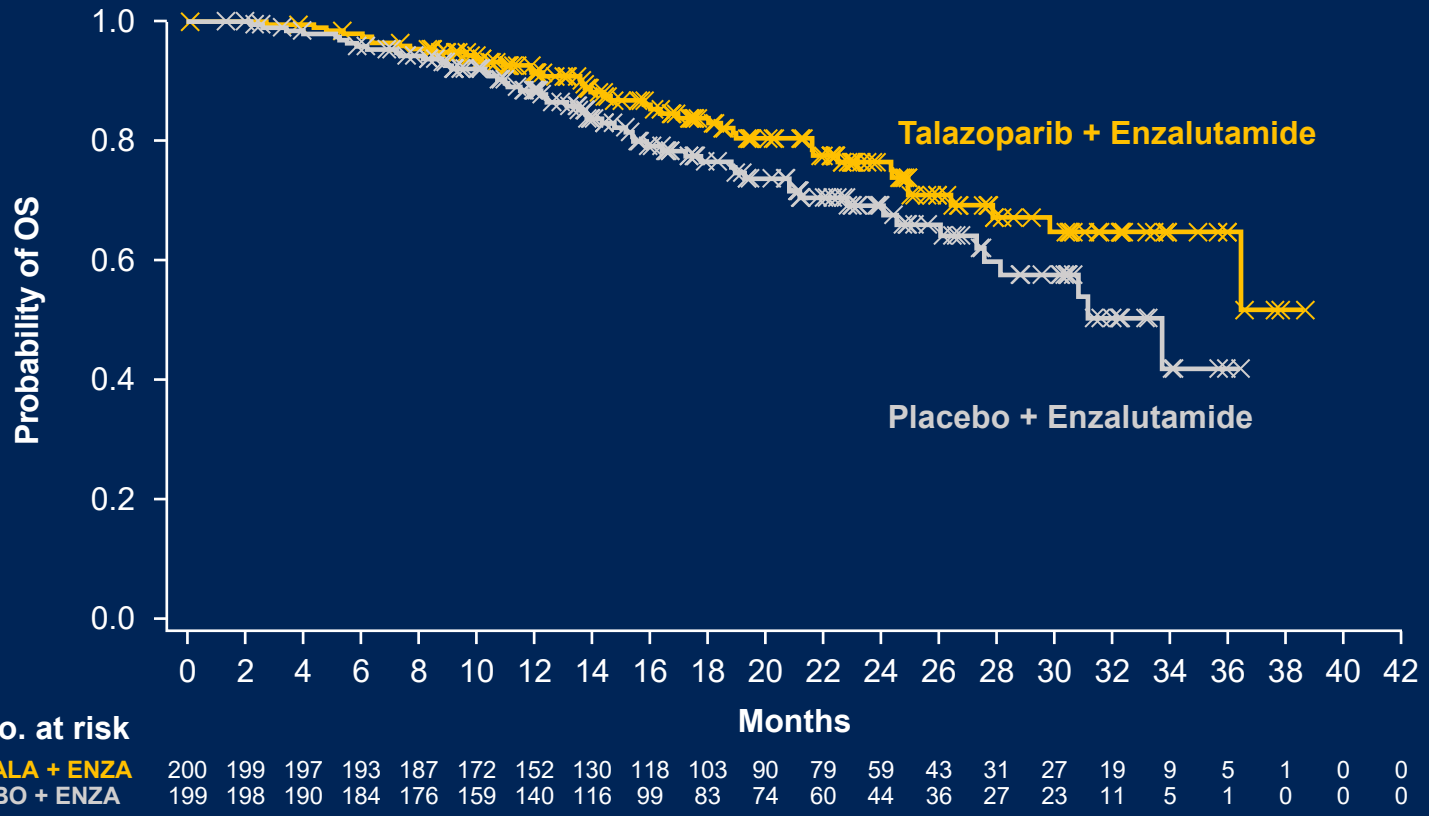
Median follow-up for rPFS was 17.5 and 16.8 months, respectively

A consistent treatment effect was seen for investigator-assessed rPFS: HR 0.48 (95% CI, 0.33–0.67); *P* < 0.0001

Stratified hazard ratios (HRs) and 2-sided *P* values are reported throughout this presentation unless otherwise stated.

TALAPRO-2 HRR-Deficient: Overall Survival (Interim Analysis)

Overall survival data are immature (24% maturity overall)



	TALA + ENZA (N=200)	PBO + ENZA (N=199)
Events, n	43	53
Median (95% CI), months	NR (36.4–NR)	33.7 (27.6–NR)
HR (95% CI)	HR 0.69 (95% CI, 0.46–1.03) *P* = 0.068	

***BRCA*m HR 0.61 (95% CI, 0.31–1.23; *P* = 0.16)**
non-*BRCA*m HR 0.71 (95% CI, 0.43–1.18; *P* = 0.18)

18 patients in the control arm and 3 patients in the talazoparib arm subsequently received olaparib

Conclusions/Take Home Points

- Based on TALAPRO-2:
  - Talazoparib plus enzalutamide resulted in a statistically significant improvement in rPFS for patients with HRR gene alterations.
  - OS data are immature, there was a favorable trend toward improved survival
- 3 large phase 3 trials reported regarding PARP+NHA combinations:
  - Positive rPFS in overall population (PROPEL and TALAPRO-2)
  - Benefit is higher in HRR+ patients
- mHSPC treatment changed which was not reflected in this trial
  - Progression after ADT+NHA for mHSPC, singe agent parp or combination?

ASCO® FDA Alerts

From the American Society of Clinical Oncology in cooperation with the Food and Drug Administration (FDA) and as a service to our members, ASCO will periodically distribute information about newly approved therapies for cancer patients. This helps FDA inform oncologists and professionals in oncology-related fields about recent approvals in a timely manner. Included in the email from the FDA will be a link to the product label, which will provide the relevant clinical information on the indication, contraindications, dosing, and safety. In sending this information, ASCO does not endorse any product or therapy and does not take any position on the safety or efficacy of the product or therapy described. The following is a message from the Director of the FDA ***Oncology Center of Excellence****, Dr. Richard Pazdur:*

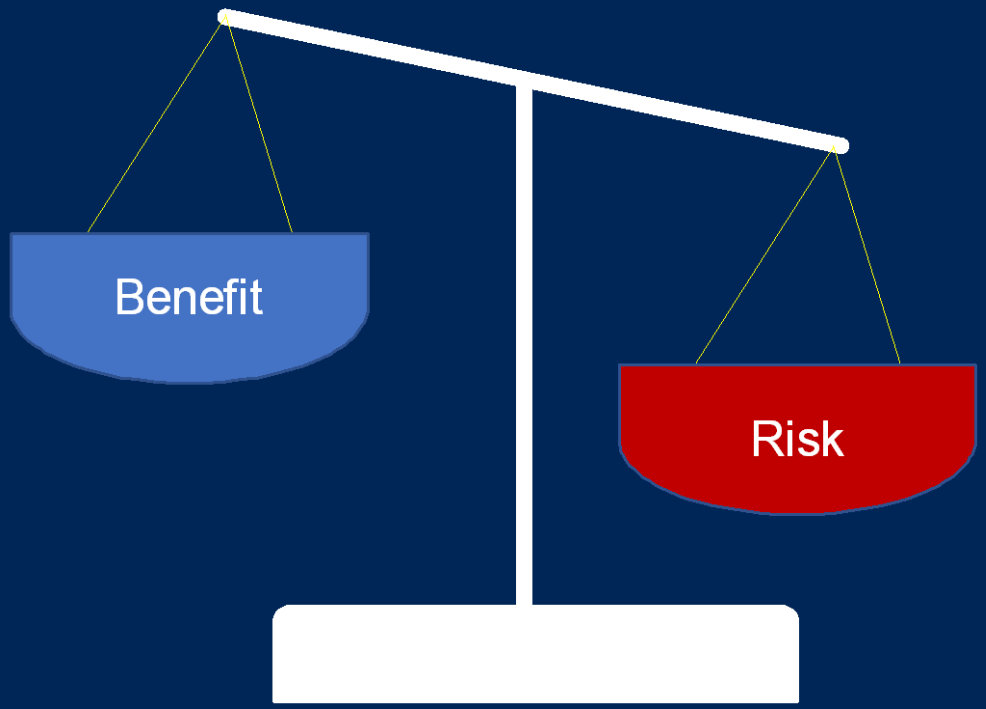
On May 31, 2023, the Food and Drug Administration approved olaparib with abiraterone and prednisone (or prednisolone) for adult patients with deleterious or suspected deleterious *BRCA*-mutated (*BRCA*m) metastatic castration-resistant prostate cancer (mCRPC), as determined by an FDA-approved companion diagnostic test.

FDA approves talazoparib with enzalutamide for HRR gene-mutated metastatic castration-resistant prostate cancer

On June 20, 2023, the Food and Drug Administration approved talazoparib with enzalutamide for homologous recombination repair (HRR) gene-mutated metastatic castration-resistant prostate cancer (mCRPC).

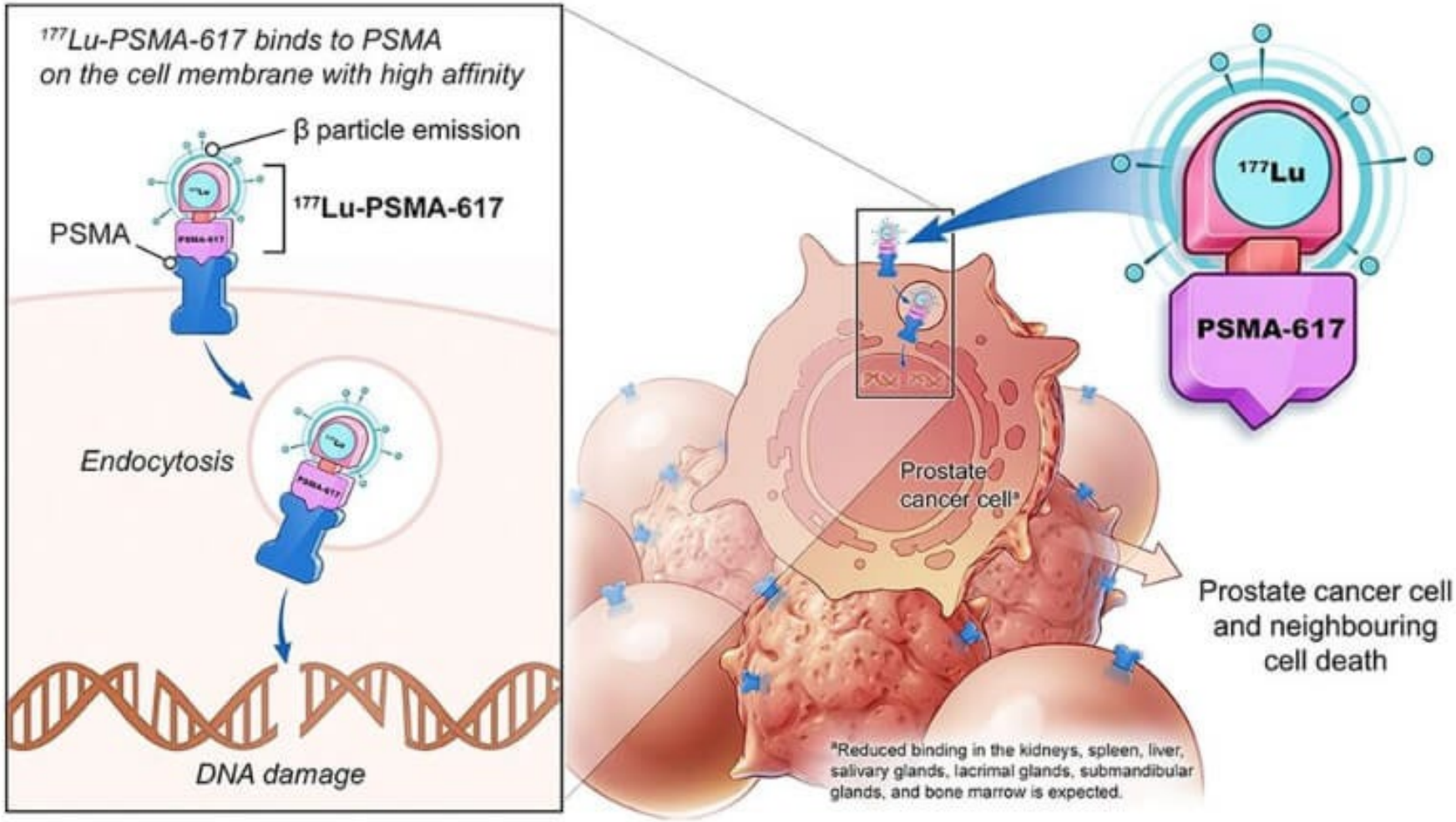
Balancing Outcomes for Selection of Therapy

Improved OS
Improved PFS
Improved response rate
Duration of response
Improved QOL



Toxicity
Risk of Grade 5 event
Primary progression
Worsening QOL
Financial toxicity

Radiopharmaceuticals: Lu-177 PSMA



VISION: Phase 3, Open-Label Study of Protocol-Permitted SOC ± ^{177}Lu-PSMA-617 for PSMA-Positive mCRPC

Eligible patients

- Previous treatment with <u>both</u>
  - ≥ 1 androgen receptor pathway inhibitor
  - 1 or 2 taxane regimens
- Protocol-permitted standard of care (SOC) planned before randomization
  - Excluding chemotherapy immunotherapy, radium-223, investigational drugs
- ECOG performance status 0–2
- Life expectancy > 6 months
- PSMA-positive mCRPC on PET/CT with ^{68}Ga-PSMA-11

2:1

Protocol-permitted SOC + ^{177}Lu-PSMA-617
7.4 GBq (200 mCi) every 6 weeks
4 cycles, increasable to 6

Protocol-permitted SOC alone

Treatment → Follow-up → Final analysis

- Randomization stratified by
  - ECOG status (0–1 or 2)
  - LDH (high or low)
  - Liver metastases (yes or no)
  - Androgen receptor pathway inhibitors in SOC (yes or no)
- CT/MRI/bone scans
  - Every 8 weeks (treatment)
  - Every 12 weeks (follow-up)
  - Blinded independent central review

SOC was investigator determined but excluded cytotoxic chemotherapy and radium-223

Protocol Definitions:

- **PSMA(+) lesions:** ^{68}Ga-PSMA-11 uptake > liver parenchyma in ≥ 1 metastatic lesions of any size in any organ system
- **PSMA(-) lesions:** PSMA uptake ≤ liver parenchyma in any LN w/ short axis of ≥ 2.5 cm, in any metastatic solid-organ lesions w/ short axis ≥ 1.0 cm, or in any metastatic bone lesion with a soft-tissue component of ≥ 1.0 cm in short axis. **<u>Pts w/ any PSMA(-) metastatic lesion meeting these criteria were ineligible</u>**.

Alternate primary endpoints

'Alternate' means the study would be positive if either or both primary endpoints were significant

Radiographic progression-free survival (rPFS) per PCWG3	• 84% power for HR of 0.67 at 364 events in 557 patients • Allocated one-sided α = 0.004 • Stratified log-rank test (plus Cox for HR)
Overall survival (OS)	• 90% power for HR of 0.7306 at 508 deaths in 814 patients • Allocated one-sided α = 0.021 (0.025 if rPFS positive) • Stratified log-rank test (plus Cox for HR)

Key secondary endpoints

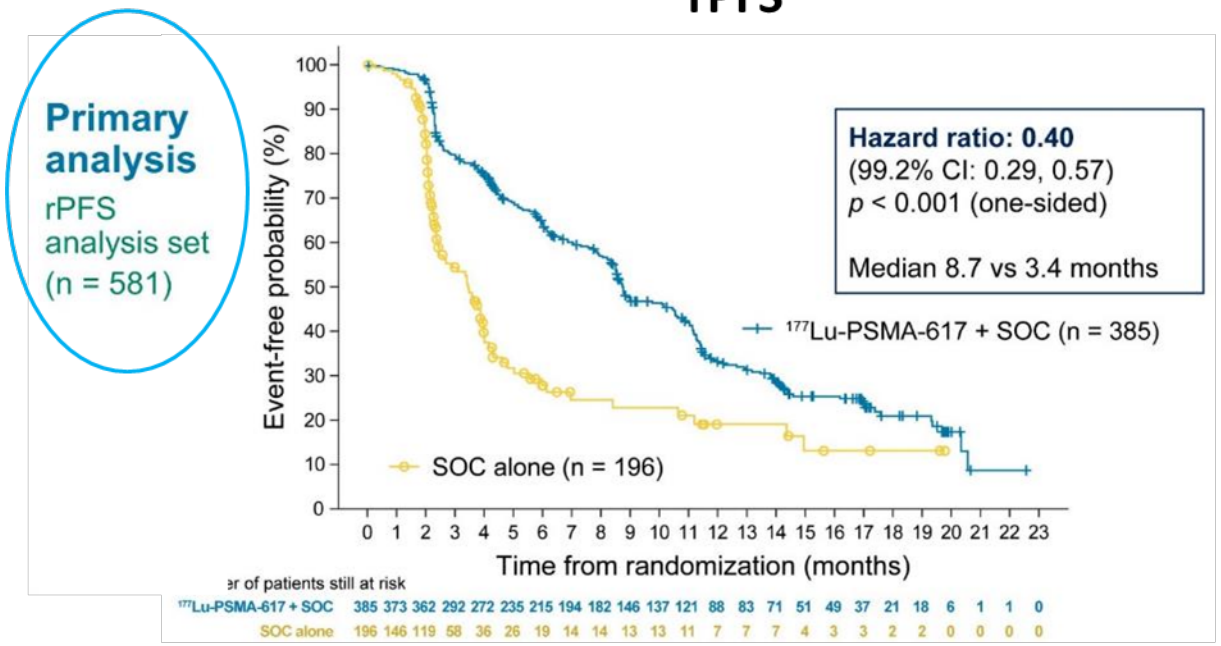
- Time to first symptomatic skeletal event (SSE)
- RECIST v1.1 overall response rate
- RECIST v1.1 disease control rate

NCT03511664

Sartor O, et al. *N Engl J Med*. Jun 23, 2021.
Morris M, et al. ASCO 2021. Abstract LBA4.

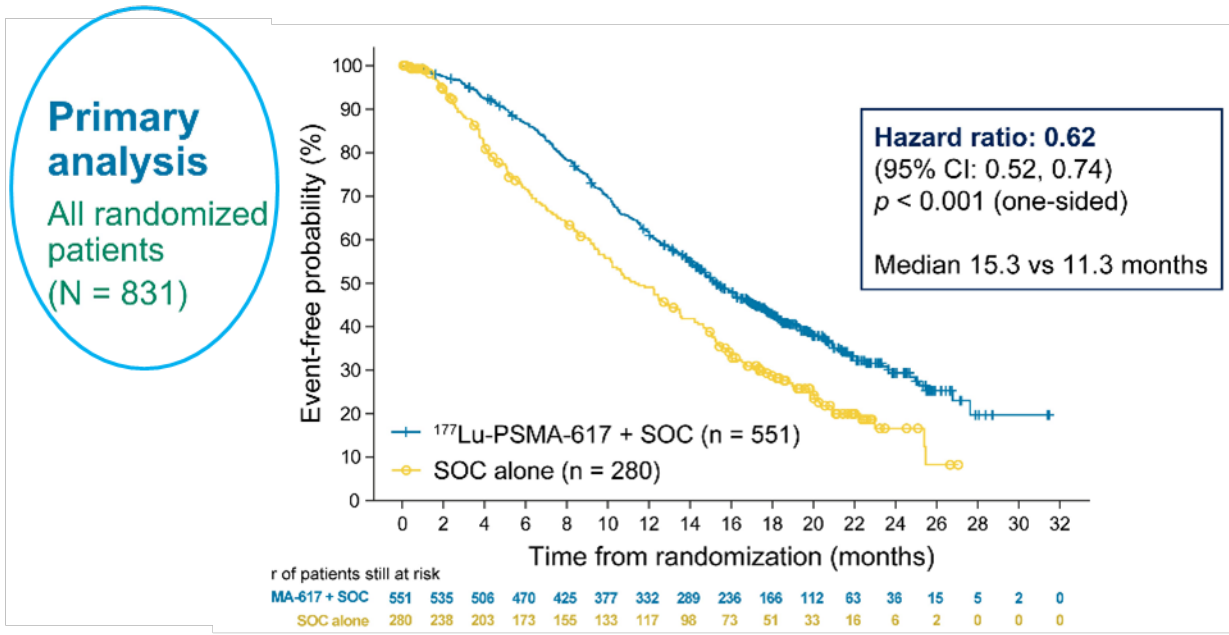
VISION: Co-Primary Endpoints

rPFS



- rPFS benefit observed across most prespecified subgroups

Overall Survival



- OS benefit was observed across most prespecified subgroups

All key secondary end points significantly favored 177Lu-PSMA-617

Median follow-up was 20.9 months

Sartor O, et al. *N Engl J Med*. Jun 23, 2021.

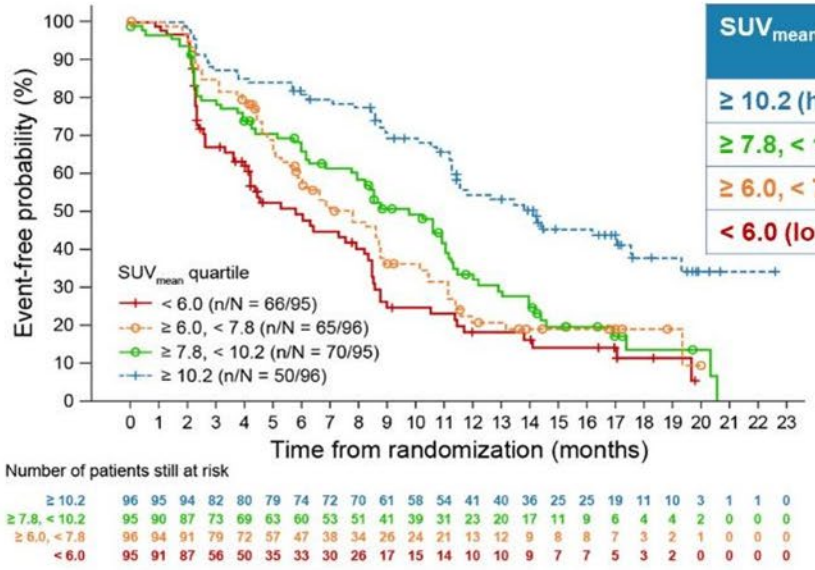
VISION: Efficacy by Whole-Body SUV_{mean}

Higher SUV_{mean} strongly associated with improved outcomes with 177Lu-PSMA-617

15

rPFS by whole-body SUV_{mean} quartiles (PFS-FAS)

- **Higher whole-body SUV_{mean} was associated with prolonged rPFS**



SUV_{mean} quartile	Median rPFS (months)
≥ 10.2 (highest)	14.1
≥ 7.8, < 10.2	9.8
≥ 6.0, < 7.8	7.8
< 6.0 (lowest)	5.8

SUV_{mean}	rPFS HR [95% CI], *p* value
Univariate analysis	**0.88** [0.84, 0.91], < 0.001
Multivariate analysis	**0.86** [0.82, 0.90], < 0.001

CI, confidence interval; HR, hazard ratio; PFS-FAS, progression-free survival-full analysis set; rPFS, radiographic progression-free survival; SUV, standardized uptake value

Median OS

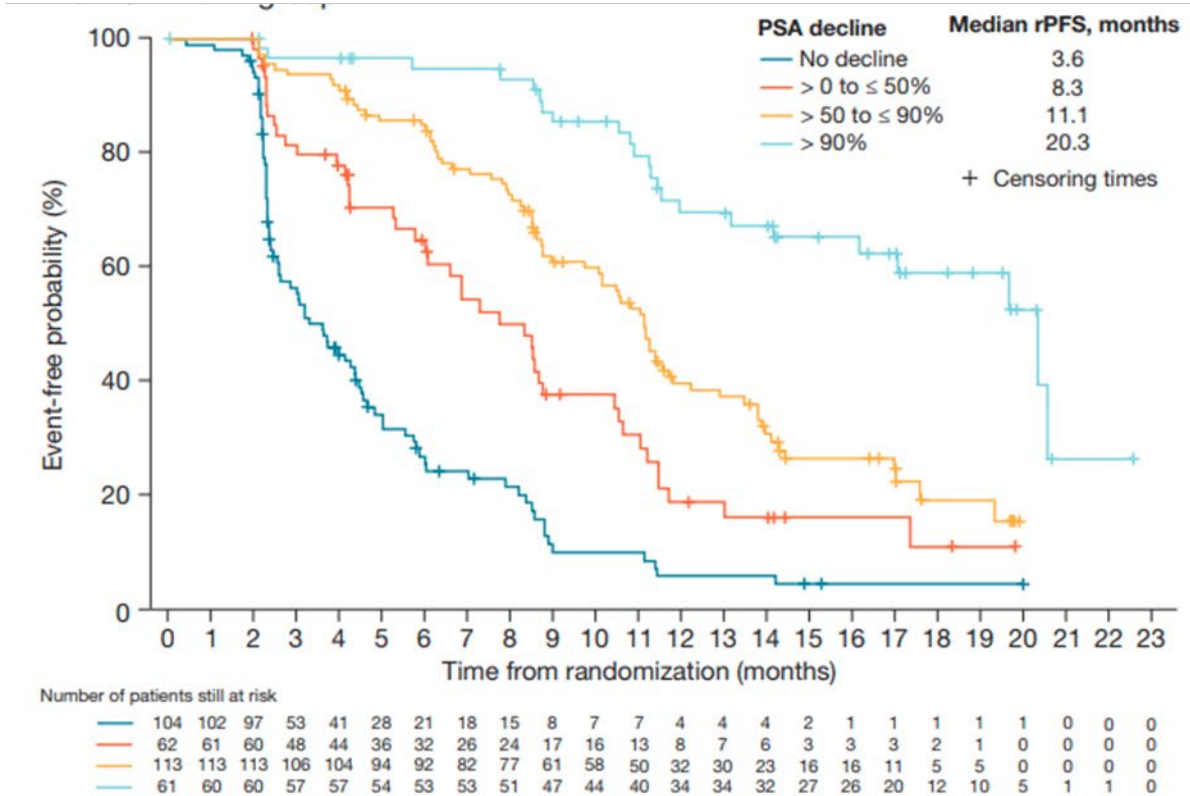
- Highest quartile (SUV_{mean} ≥ 9.9): 21.4 mo
- Lowest quartile (SUV_{mean} < 5.7): 14.5 mo

Absence of PSMA+ lesions in bone, liver, and lymph node, and lower PSMA+ tumor load, were indicators of good prognosis

Armstrong AJ et al. ASCO 2022. Abstract 5002.

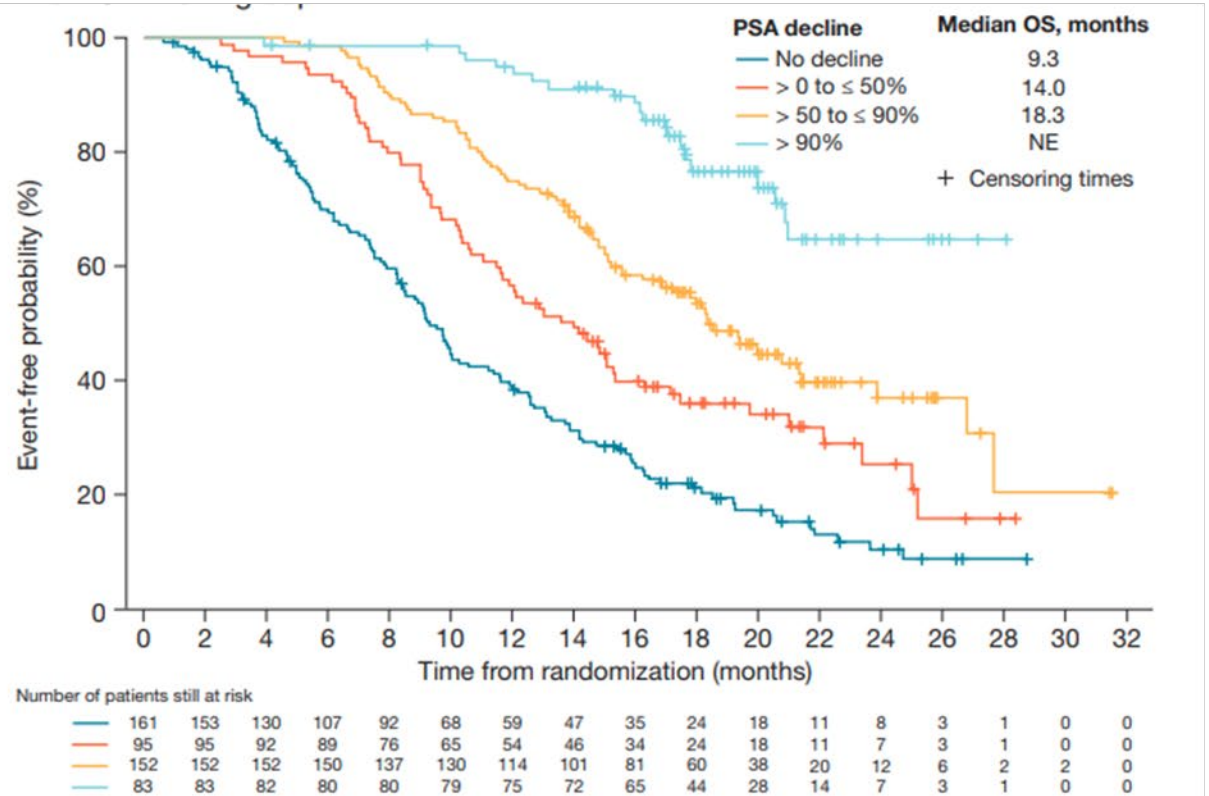
VISION Trial Post Hoc Analysis: Association Between PSA Decline and Clinical Outcomes

rPFS rate by PSA decline up to 12 weeks in the ^{177}Lu-PSMA-617 group (n = 385)



Analyses in patients randomized on or after 5 March 2019 (PFS-FAS).

OS rate by PSA decline up to 12 weeks in the ^{177}Lu-PSMA-617 group (n = 551)



Analyses in all randomized patients (FAS).

Armstrong et al. Abstract 1372P. ESMO 2022, Paris, France.

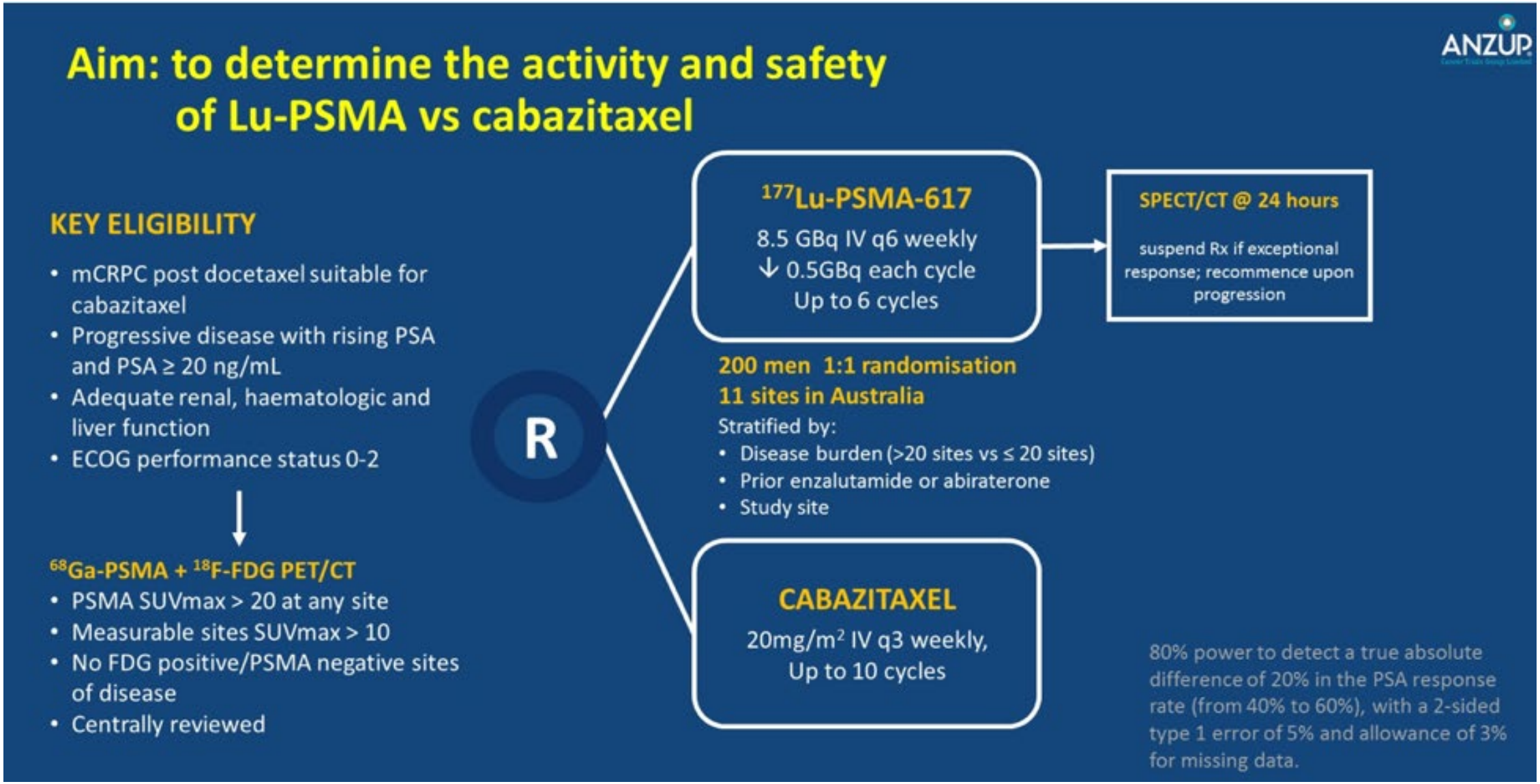
VISION: Treatment-Emergent Adverse Events

Patients, n (%)	All grades		Grade 3–5	
	^{177}Lu-PSMA-617 + SOC (n = 529)	SOC alone (n = 205)	^{177}Lu-PSMA-617 + SOC (n = 529)	SOC alone (n = 205)
Fatigue	260 (49.1)	60 (29.3)	37 (7.0)	5 (2.4)
Bone marrow suppression	251 (47.4)	36 (17.6)	124 (23.4)	14 (6.8)
Leukopenia	66 (12.5)	4 (2.0)	13 (2.5)	1 (0.5)
Lymphopenia	75 (14.2)	8 (3.9)	41 (7.8)	1 (0.5)
Anemia	168 (31.8)	27 (13.2)	68 (12.9)	10 (4.9)
Thrombocytopenia	91 (17.2)	9 (4.4)	42 (7.9)	2 (1.0)
Dry mouth	208 (39.3)	2 (1.0)	0 (0.0)	0 (0.0)
Nausea and vomiting	208 (39.3)	35 (17.1)	8 (1.5)	1 (0.5)
Renal effects	46 (8.7)	12 (5.9)	18 (3.4)	6 (2.9)
Second primary malignancies	11 (2.1)	2 (1.0)	4 (0.8)	1 (0.5)
Intracranial hemorrhage	7 (1.3)	3 (1.5)	5 (0.9)	2 (1.0)

Median duration of exposure to 177Lu-PSMA-617: 6.9 mo (range, 0.3-10.2); median cycles started: 5 cycles (range, 1-6); median cumulative dose: 37.5 GBq (range, 7.0-48.3).

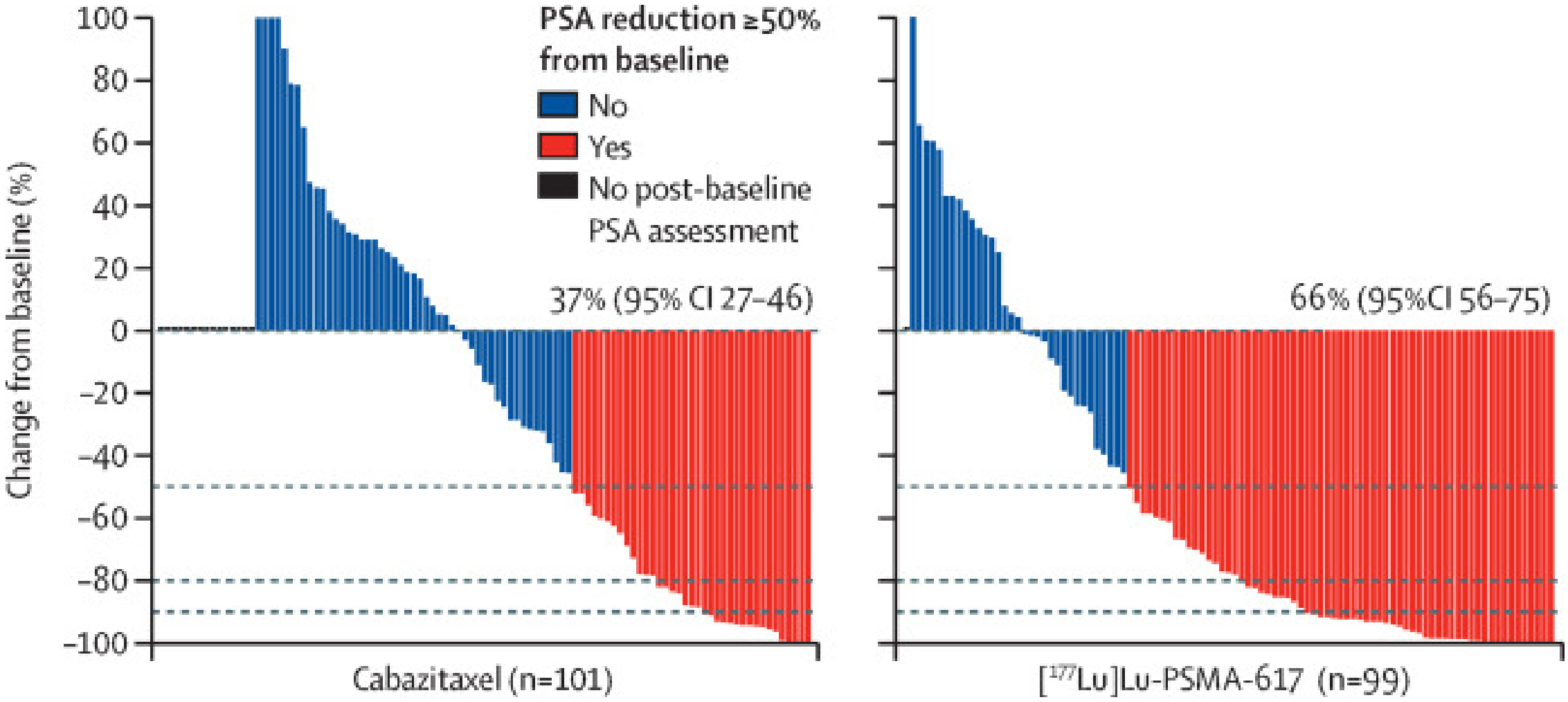
Sartor O, et al. *N Engl J Med*. Jun 23, 2021.
Morris M, et al. ASCO 2021. Abstract LBA4.

TheraP trial: Lu-177 PSMA vs cabazitaxel



Hofman et al. Lancet 2021

TheraP trial: Lu-177 PSMA vs cabazitaxel



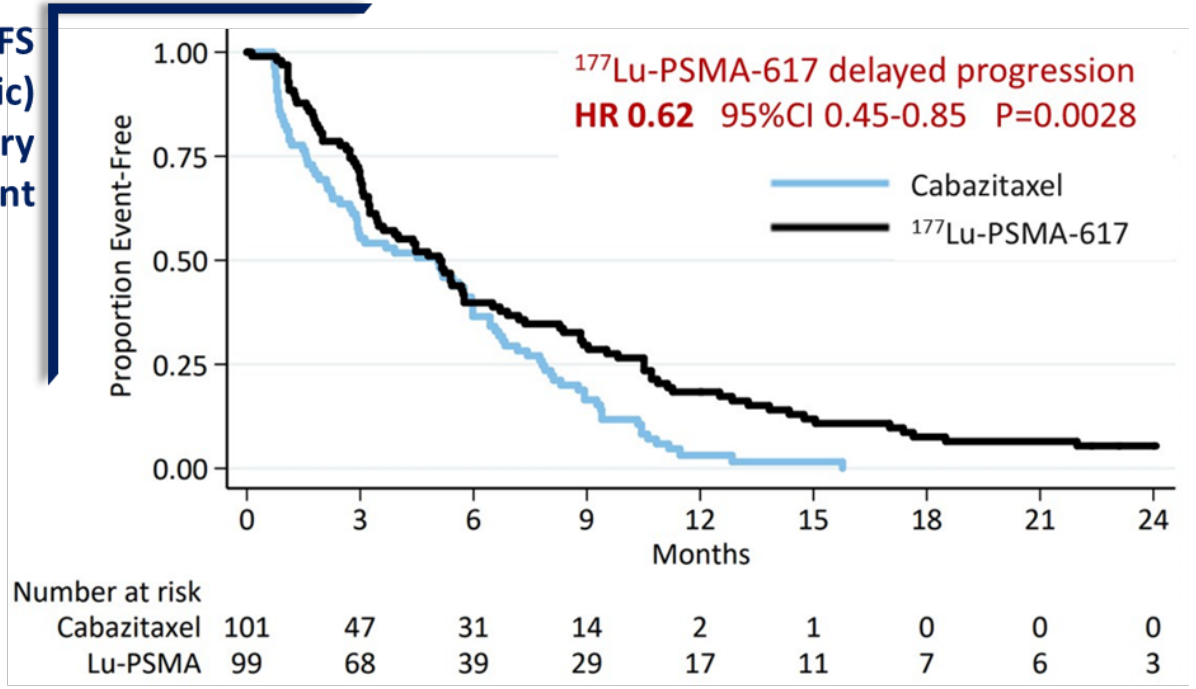
Hofman et al. Lancet 2021

Phase 2 TheraP Trial: Updated Results

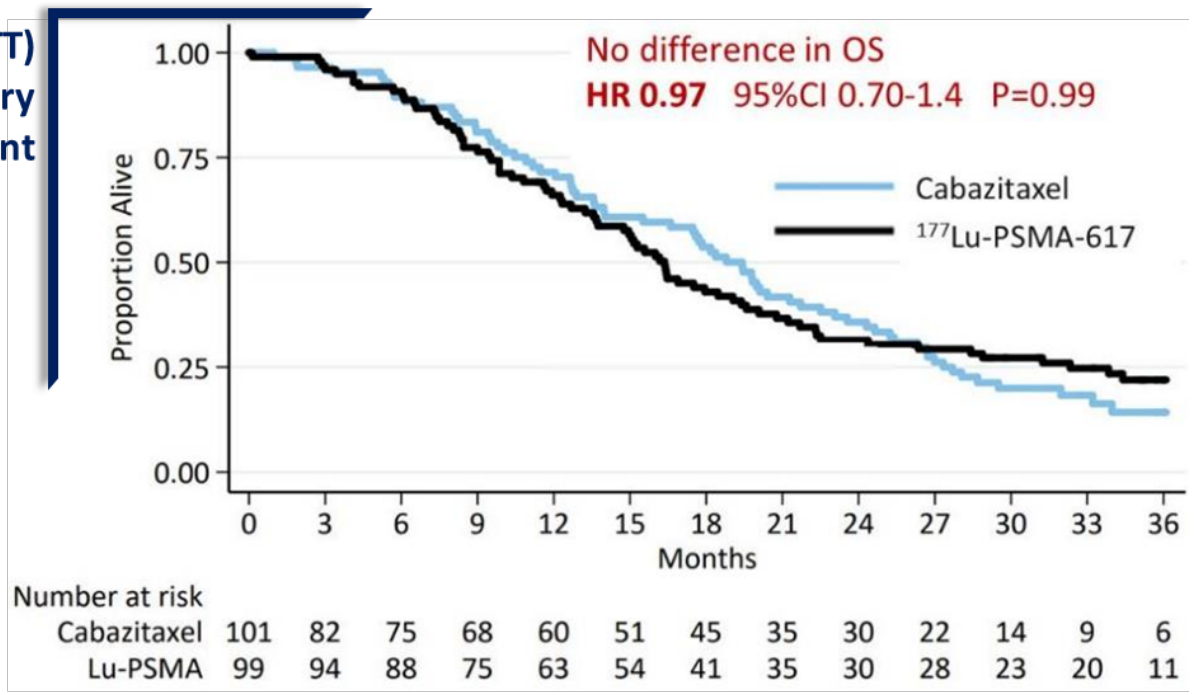
Primary Endpoint	LuPSMA	Cabazitaxel
PSA Reduction ≥ 50% From Baseline	66	37

Secondary Endpoints	LuPSMA	Cabazitaxel
ORR	49	24
AEs Gr 1-2 / 3-4	54 / 33	40 / 43

PFS (PSA + Radiographic) Secondary Endpoint



OS (ITT) Secondary Endpoint



Data cutoff for OS: 31 DEC 2021; median follow-up: 36 mo.

Hofman M, et al. ASCO 2022. Abstract 5000. Hofman M, et al. *Lancet*. 2021;397:797–804.

TheraP trial: Lu-177 PSMA vs cabazitaxel

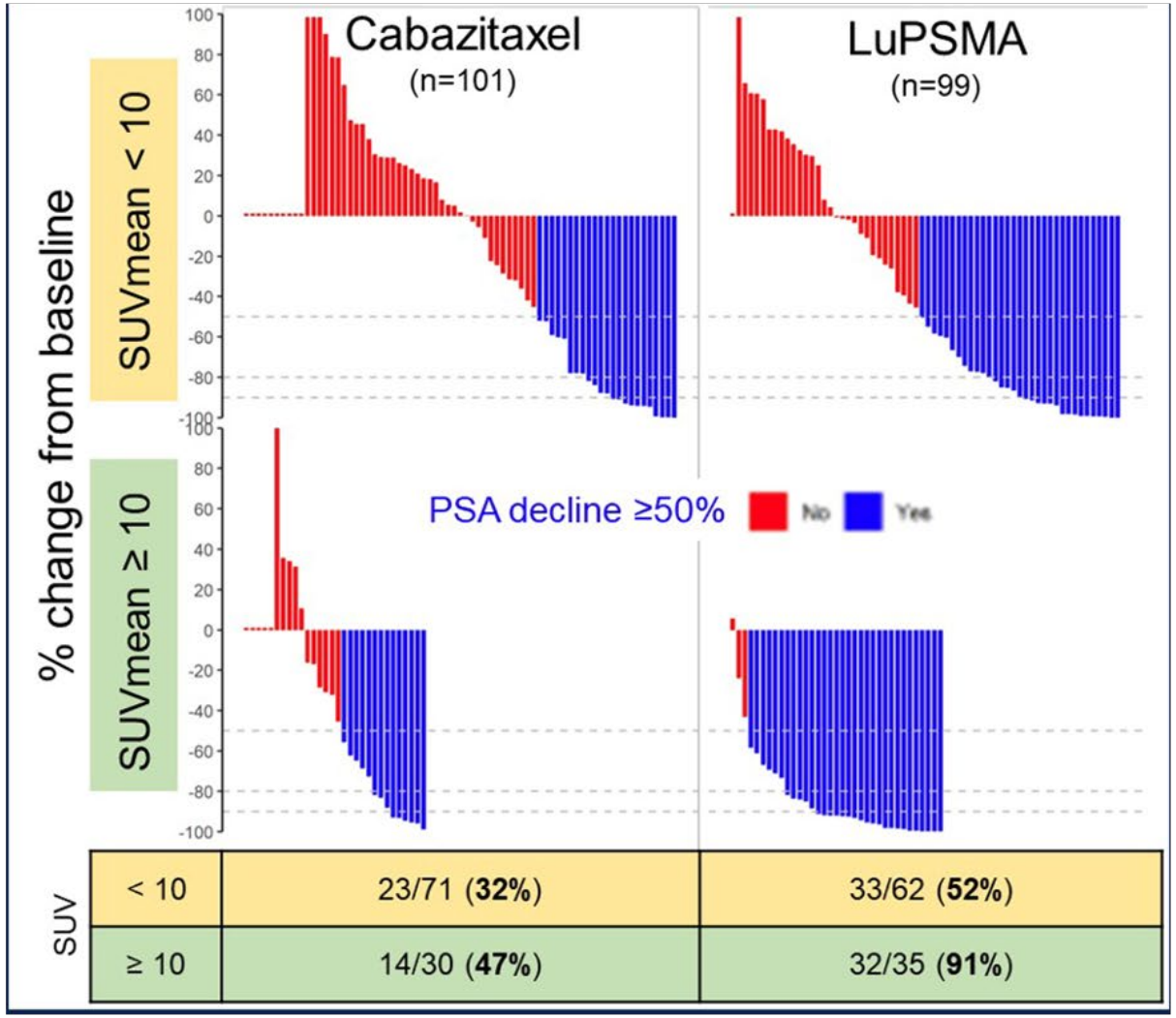
	[^{177}Lu]Lu-PSMA-617 (n=98)		Cabazitaxel (n=85)	
	Grade 1–2	Grade 3–4	Grade 1–2	Grade 3–4
Fatigue	69 (70%)	5 (5%)	61 (72%)	3 (4%)
Pain*	60 (61%)	11 (11%)	52 (61%)	4 (5%)
Dry mouth	59 (60%)	0	18 (21%)	0
Diarrhoea	18 (18%)	1 (1%)	44 (52%)	4 (5%)
Nausea	39 (40%)	1 (1%)	29 (34%)	0
Thrombocytopenia	18 (18%)	11 (11%)	4 (5%)	0
Dry eyes	29 (30%)	0	3 (4%)	0
Anaemia	19 (19%)	8 (8%)	11 (13%)	7 (8%)
Neuropathy†	10 (10%)	0	22 (26%)	1 (1%)
Dysgeusia	12 (12%)	0	23 (27%)	0
Haematuria	3 (3%)	1 (1%)	12 (14%)	5 (6%)
Neutropenia‡	7 (7%)	4 (4%)	4 (5%)	11 (13%)
Insomnia	9 (9%)	0	12 (14%)	1 (1%)
Vomiting	12 (12%)	1 (1%)	10 (12%)	2 (2%)
Dizziness	4 (4%)	0	11 (13%)	0
Leukopenia	10 (10%)	1 (1%)	5 (6%)	1 (1%)
Any adverse event	53 (54%)	32 (33%)	34 (40%)	45 (53%)

Data are n (%). Events that occurred in at least 10% of participants are shown. ^{177}Lu=Lutetium-177. PSMA=prostate-specific membrane antigen. *Including bone, buttock, chest wall, flank, neck, extremity, tumour pain, or pelvic pain. †Motor or sensory. ‡Febrile neutropenia.

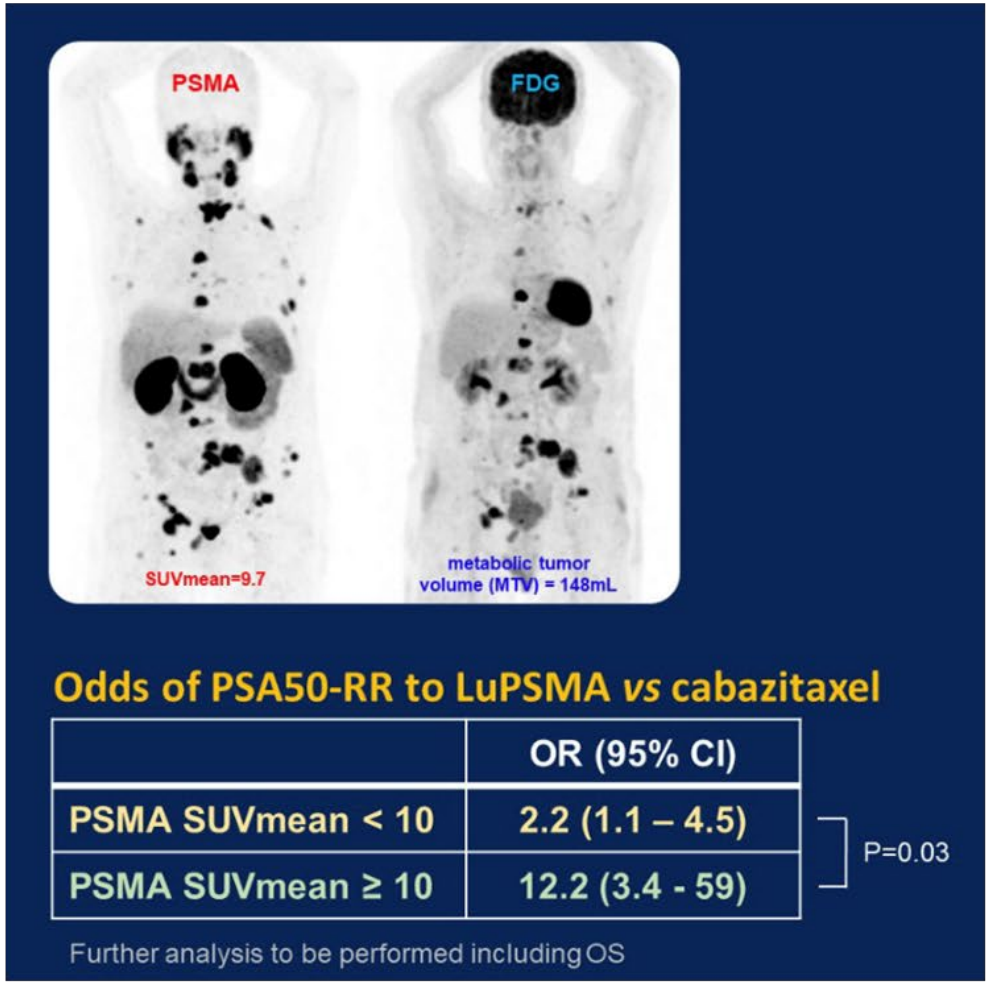
Table 2: **Adverse events**

Hofman et al. Lancet 2021

TheraP PSMA PET As Predictive of Response



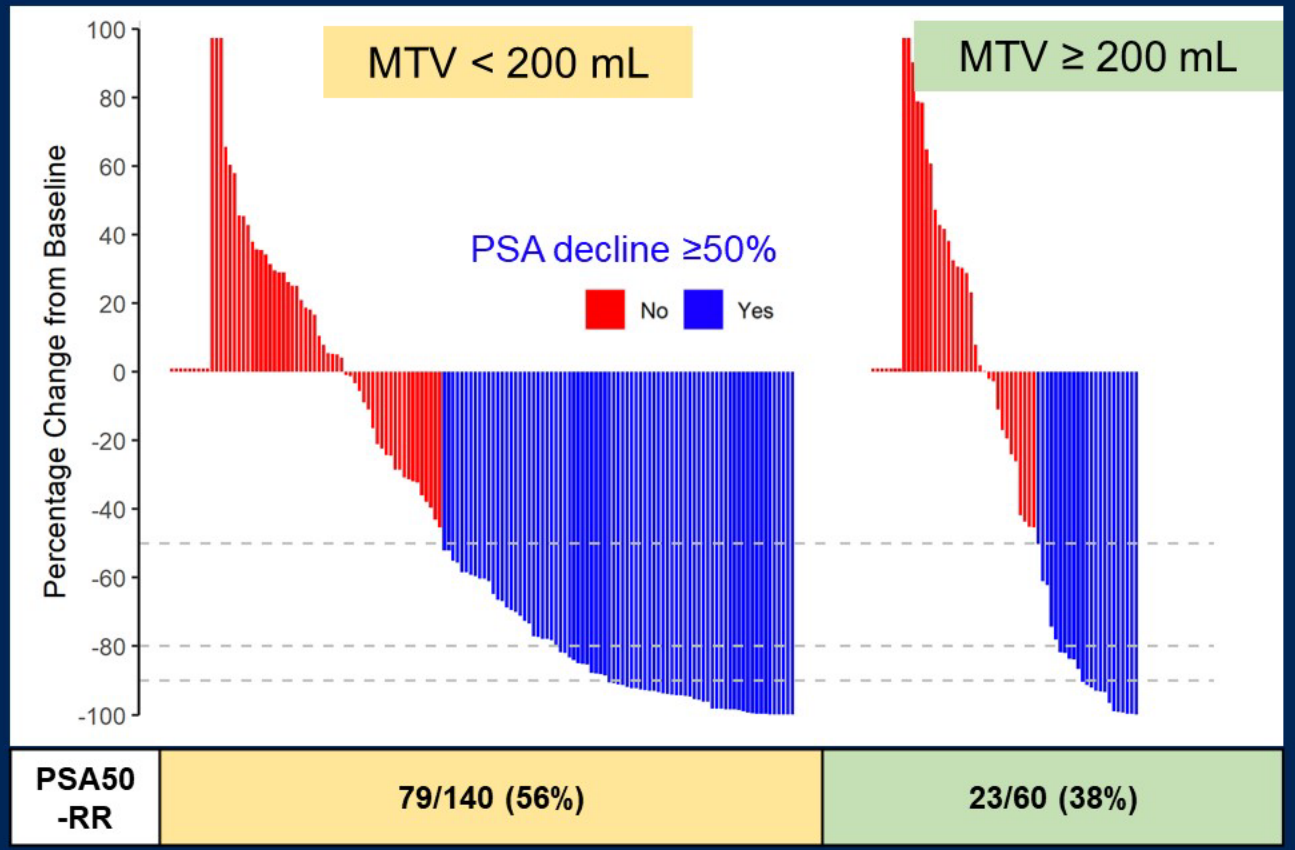
SUV	Cabazitaxel (n=101)	LuPSMA (n=99)
< 10	23/71 (**32%**)	33/62 (**52%**)
≥ 10	14/30 (**47%**)	32/35 (**91%**)



Buteau JP et al, GU ASCO 2022

Buteau JP et al, *Lancet Oncol*, 2022; 23(11): 1389-97.

FDG: prognostic biomarker (PSA50-RR)



PSA50-RR to LuPSMA *vs* cabazitaxel

MTV	Cabazitaxel	LuPSMA
< 200	31/71 (**44%**)	48/69 (**70%**)
≥ 200	6/30 (**20%**)	17/30 (**57%**)

Odds of PSA50-RR lower amongst men with high MTV
OR 0.44; P=0.01

Radiopharmaceuticals: Lu-177 PSMA

- Lu-PSMA is FDA approved as of March 2022 for patients with PSMA-positive mCRPC who received NHA and taxane-based chemo
- Few eligibility criteria:
  - Ga-68 PSMA scan (initially, later plan to expend PyL PSMA PET scan)
  - Any systemic anti-cancer therapy within 28 days
  - Radionuclide therapy (Strontium-89, Samarium-153, Rhenium-186, Rhenium-188, Radium-223, hemi-body irradiation) within 6 months
  - Unmanageable urinary tract obstruction or hydronephrosis
  - Progressive deterioration of organ function (GFR < 30 mL/min or creatinine > 2-fold upper limit of normal (ULN); liver enzymes > 5-fold ULN)
  - Myelosuppression: (a) Total white cell count less than 2.5 × 109 /L (b) Platelet count less than 75 × 109 /L
- This opens a new era with different combinations, such as IO, and also coming to the front line

Future clinical trials

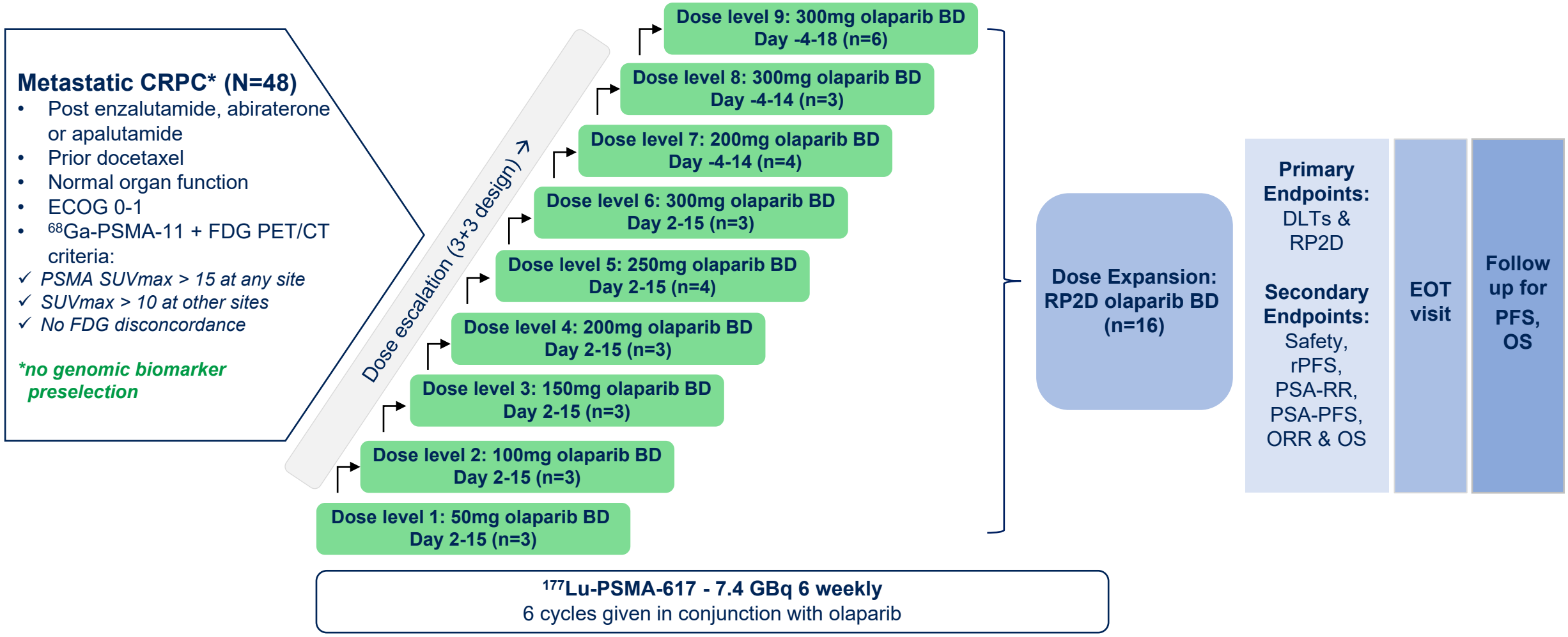
Table 1. Current active and recruiting phase III prostate cancer trials involving PSMA-RLT with lutetium-177. Search performed using clinicaltrials.gov on 15 October 2022 and updated on 21 January 2023.

Trial number (name)	Type of prostate cancer	Intervention	Total enrollment	Primary outcome measures
NCT0351164 (VISION)	mCRPC previously treated with ARPI and taxane chemotherapy	^{177}Lu-PSMA-617 with SoC *versus* SoC	831	rPFS and OS
NCT04876651 (PROSTACT)	mCRPC previously treated with ARPI	^{177}Lu-TLX591 with SoC *versus* SoC	387	rPFS
NCT04689828 (PSMAfore)	mCRPC previously treated with ARPI and without prior taxane therapy	^{177}Lu-PSMA-617 *versus* switch of ARPI	450	rPFS
NCT05204927 (ECLIPSE)	mCRPC previously treated with ARPI and without prior taxane therapy	^{177}Lu-PSMA-I&T *versus* abiraterone or enzalutamide	400	rPFS
NCT04647526 (SPLASH)	mCRPC previously treated with second-line ARPI	^{177}Lu-PSMA-I&T *versus* abiraterone or enzalutamide	415	rPFS
NCT04720157 (PSMAddition)	mHSPC	^{177}Lu-PSMA-617 with SoC *versus* SoC alone	1126	rPFS

ARPI, androgen receptor pathway inhibitor; mCRPC, metastatic castration-resistant prostate cancer; mHSPC, metastatic hormone-sensitive prostate cancer; OS, overall survival; PSMA-RLT, prostate-specific membrane antigen-radioligand therapy; rPFS, radiographic progression-free survival; SoC, standard of care.

Jang et al, Ther Adv Med Oncol . 2023

LuPARP: Phase 1 Trial Schema



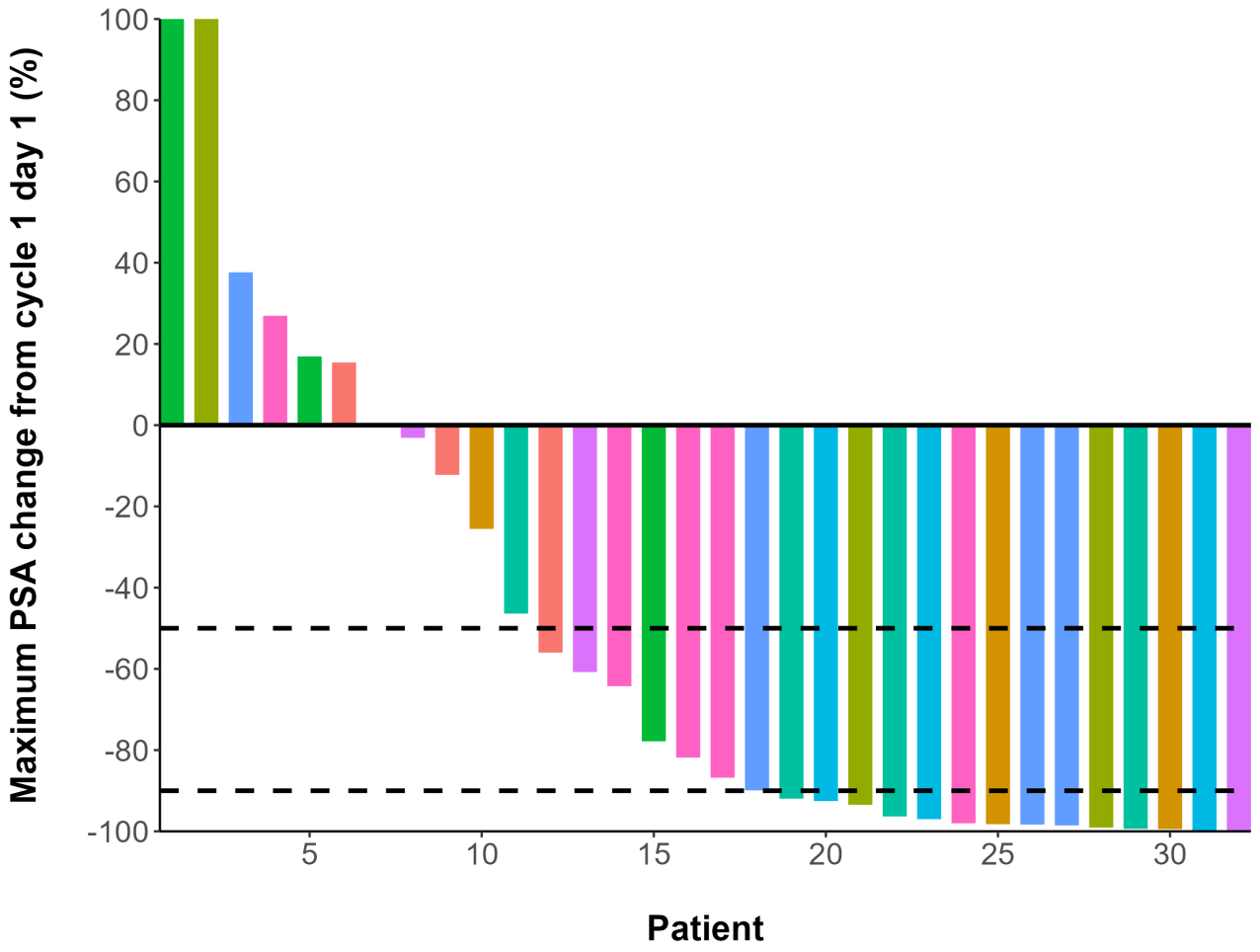
LuPARP results: Treatment Related AEs >5%

	N=3 Dose level 1 ^{177}Lu-PSMA & 50mg olaparib BD Day 2-15			N=3 Dose level 2 ^{177}Lu-PSMA & 100mg olaparib BD Day 2-15			N=3 Dose level 3 ^{177}Lu-PSMA & 150 olaparib BD Day 2-15			N=3 Dose level 4 ^{177}Lu-PSMA & 200mg olaparib BD Day 2-15			N=4 Dose level 5 ^{177}Lu-PSMA & 250mg olaparib BD Day 2-15			N=3 Dose level 6 ^{177}Lu-PSMA & 300 olaparib BD Day 2-15			N=4 Dose level 7 ^{177}Lu-PSMA & 200mg olaparib BD Day -4-14			N=3 Dose level 8 ^{177}Lu-PSMA & 300mg olaparib BD Day -4-14			N=6 Dose level 9 ^{177}Lu-PSMA & 300mg olaparib BD Day -4-18			Total (n=32)		
Adverse Event (AE) Grade (G)	***G1***	***G2***	***G3***	***G1***	***G2***	***G3***	***G1***	***G2***	***G3***	***G1***	***G2***	***G3***	***G1***	***G2***	***G3***	***G1***	***G2***	***G3***	***G1***	***G2***	***G3***	***G1***	***G2***	***G3***	***G1***	***G2***	***G3***	***G1***	***G2***	***G3***
Anemia	1	-	-	2	1	-	-	-	-	-	-	-	1	1	1	-	-	1	1	-	-	-	-	-	-	1	-	5	3	2
Neutropenia	-	-	-	1	-	-	-	-	-	-	-	-	-	-	1*	-	-	1	-	-	-	-	-	-	-	-	-	1	-	2
Thrombocytopenia	-	1	-	1	-	-	1	-	-	1	-	-	1	-	1	-	1	-	-	-	-	-	-	-	1	-	-	5	2	1
Nausea	1	2	-	3	-	-	1	1	-	2	-	-	1	1	-	1	1	-	2	1	-	-	-	-	2	-	-	13	6	-
Dry Mouth	3	-	-	3	-	-	3	-	-	2	-	-	3	1	-	2	1	-	1	1	-	2	-	-	3	-	-	22	3	-
Constipation	-	-	-	-	-	-	-	1	-	2	-	-	-	-	-	1	-	-	1	1	-	1	-	-	2	-	-	7	2	-
Vomiting	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	-	-	-	1	-	1	-	-	1	-	-	3	1	-
Gastroesophageal Reflux	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	1	-	-	-	-	-	-	-	1	-	-	2	1	-
Diarrhea	-	-	-	-	-	-	-	-	-	-	-	-	1	-	-	1	-	-	1	-	-	-	-	-	-	-	-	3	-	-
Weight Loss	-	-	-	-	-	-	-	-	-	-	-	-	-	1	-	1	-	-	-	-	-	-	-	-	-	-	-	1	1	-
Anorexia	1	-	-	2	-	-	1	-	-	-	-	-	-	-	-	1	-	-	-	-	-	-	-	-	1	-	-	6	-	-
Dry Eye	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	-	-	-	-	-	1	-	-	2	-	-
Fatigue	-	-	-	1	-	-	1	-	-	2	-	-	1	-	-	2	-	-	1	-	-	1	-	-	6	-	-	15	-	-

No DLTs were reported across the dose levels
One treatment related SAE – febrile neutropenia
No grade 4 AEs

*includes one grade 3 febrile neutropenia reported in dose level 5

LuPARP results: PSA Response

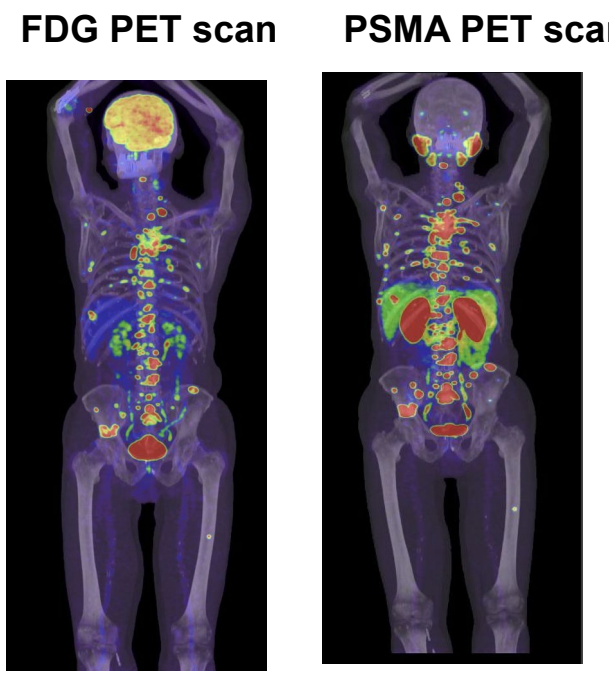


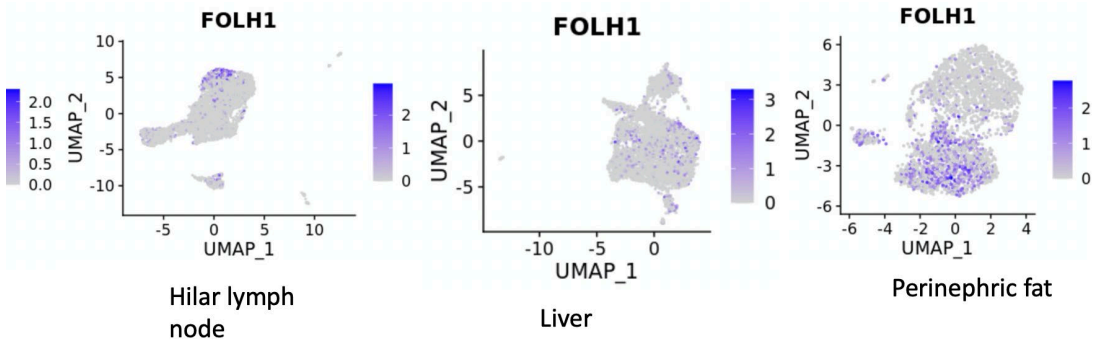
- Dose level 1: 50mg Day 2-15
- Dose level 2: 100mg Day 2-15
- Dose level 3: 150mg Day 2-15
- Dose level 4: 200mg Day 2-15
- Dose level 5: 250mg Day 2-15
- Dose level 6: 300mg Day 2-15
- Dose level 7: 200mg Day -4-14
- Dose level 8: 300mg Day -4-14
- Dose level 9: 300mg Day -4-18

PSA ≥ 50% response = 65% (21/32)
PSA ≥ 90% response = 47% (15/32)
ORR by RECIST 1.1 = 78% (7/9)

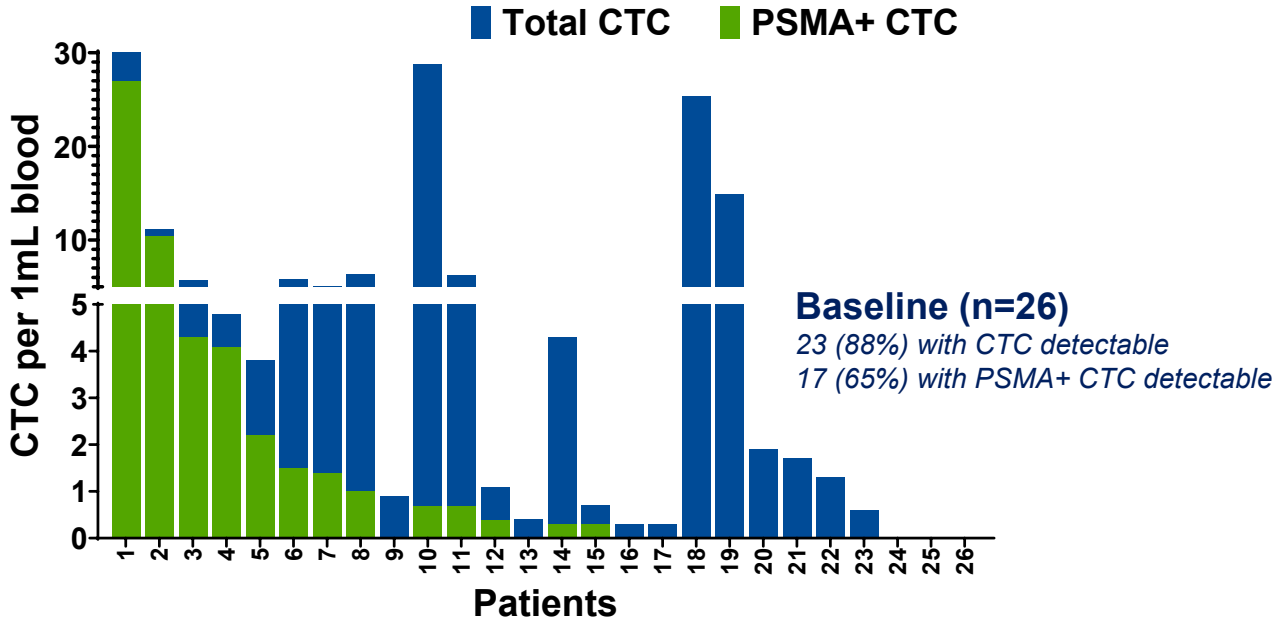
*Patients on dose levels 8 & 9 are early in treatment cycles

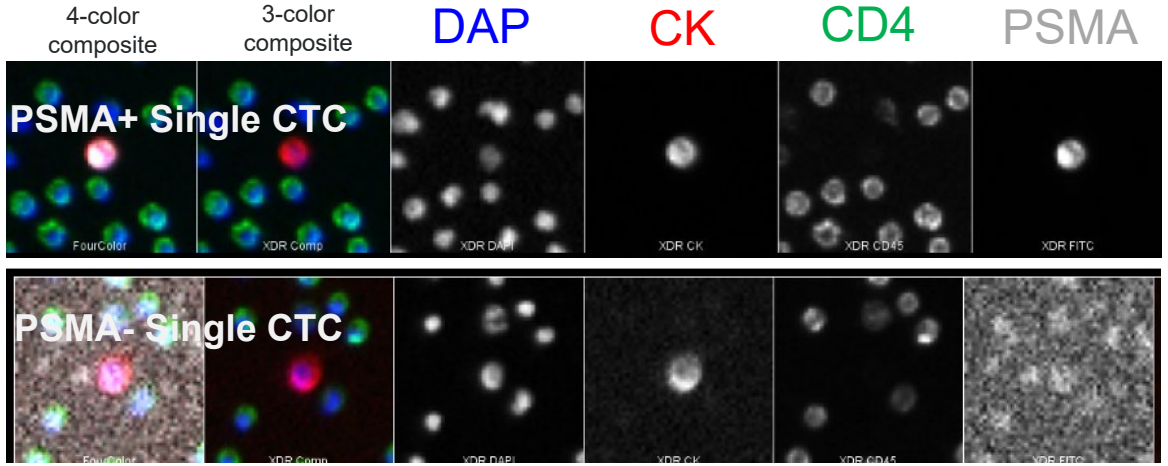
Heterogeneity in PSMA Expression





Single cell expression of PSMA across sites





Conclusions/Take Home Points

- Important early results of 177Lu-PSMA-617 in combination with olaparib:
  - PSA-RR of 65% (21/32)
  - No dose limiting toxicities
  - The RP2D is 7.4Gb of ^{177}Lu-PSMA-617 in conjunction with olaparib 300mg BD days -4 to18 of each 6 weekly cycle

- Need longer term follow-up and larger trial
  - Dose expansion is currently ongoing.

- Encouraging translational work presented to better understand the impact of this combination

Future clinical trials

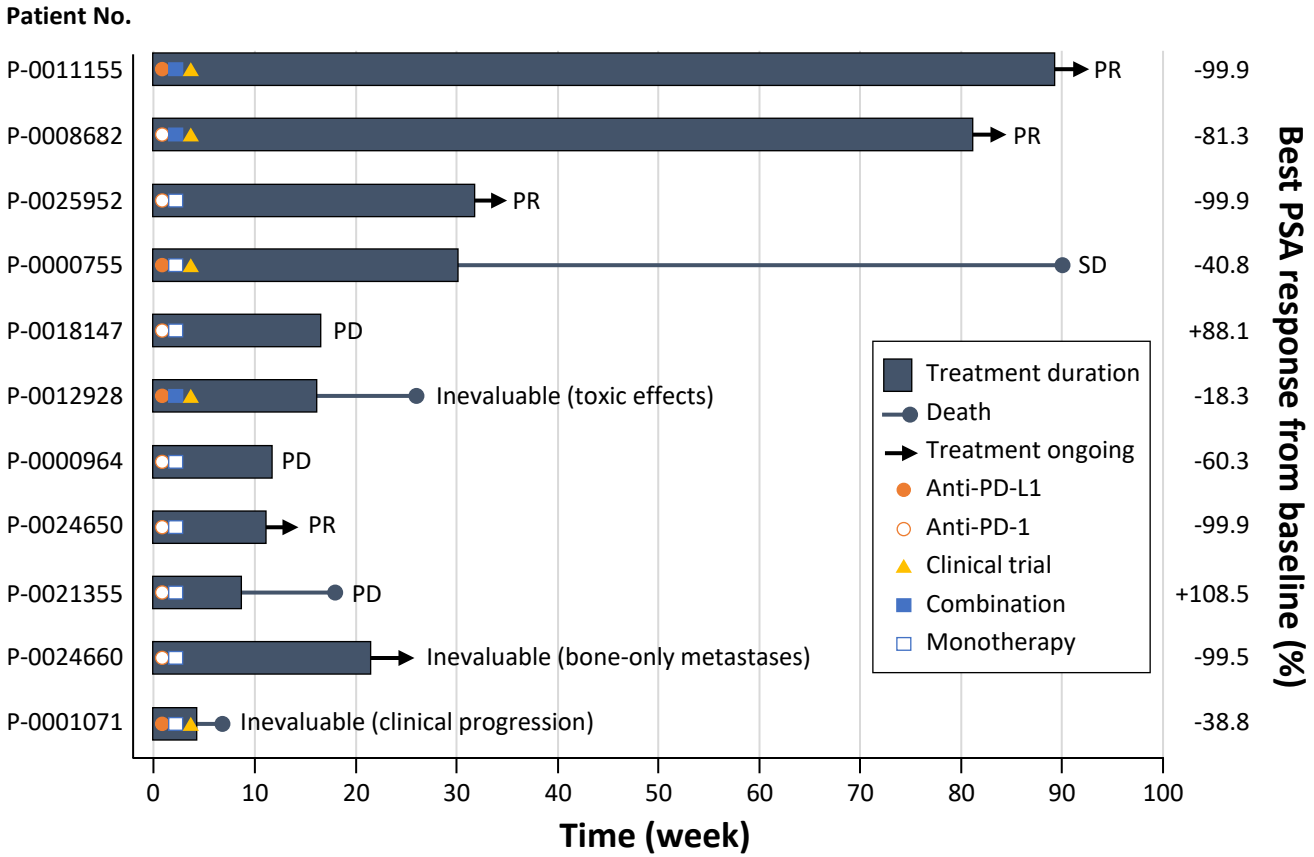
Trial number (name)	Notable characteristics	Intervention	Total enrollment	Primary outcome measures
^{177}Lu monotherapy				
NCT05079698	Hormone sensitive, oligometastatic	^{177}Lu-PSMA-617 with SBRT	6	DLTs
NCT04443062 (BULLSEYE)	Hormone sensitive, oligometastatic	^{177}Lu-PSMA-617 *versus* SoC	58	Disease progression
NCT05114746	mCRPC	^{177}Lu-PSMA-617 with SoC	28	DLTs and ORR
NCT05458544	mCRPC	^{177}Lu-Ludotadipep	26	DLTs and ORR
NCT05579184	mCRPC	^{177}Lu-Ludotadipep	30	PSA response rate
NCT04509557	mCRPC	^{177}Lu-Ludotadipep	30	DLTs
NCT05340374	mCRPC previously treated with docetaxel and ARPI	^{177}Lu-PSMA-617 with cabazitaxel	44	DLTs and MTD
NCT03454750	mCRPC	^{177}Lu-PSMA-617 with radiometabolic therapy	210	DCR, treatment-emergent adverse events
NCT03042468	mCRPC previously treated with ARPI	^{177}Lu-PSMA-617	50	DLTs and MTD
NCT03874884 (LuPARP)	mCRPC previously treated with ARPI	^{177}Lu-PSMA-617 with olaparib	52	DLTs and MTD
NCT04343885 (UpFrontPSMA)	mHSPC	^{177}Lu-PSMA-617 followed by docetaxel *versus* docetaxel	140	Undetectable PSA rate at 12 months
NCT05383079 (AlphaBet)	mCRPC previously treated with ARPI	^{177}Lu-PSMA-I&T with radium-223	36	DLTs, MTD, 50% PSA response rate
NCT04786847 (ProstACTSelect)	mCRPC previously treated with ARPI	^{177}Lu-DOTA-TLX591	50	Treatment-related adverse events
NCT05146973 (ProstACT TARGET)	Biochemically recurrent oligometastatic prostate cancer	^{177}Lu-DOTA-TLX591 with EBRT	50	PSA PFS
NCT03780075	mCRPC	^{177}Lu-EB-PSMA-617	50	PSA change, SUV change
NCT00859781	Biochemically relapsed prostate cancer after local therapy	^{177}Lu-J591 with ketoconazole	55	Proportion of subjects free of radiographically evident metastases
NCT03658447 (PRINCE)	mCRPC previously treated with ARPI	^{177}Lu-PSMA-617 with pembrolizumab	37	PSA response, treatment-related adverse events, tolerability
NCT04430192 (LuTectomy)	High-risk localized prostate cancer	^{177}Lu-PSMA-617	20	Radiation absorbed dose
NCT05547061	mCRPC	^{177}Lu-DGUL	73	ORR
NCT04663997	mCRPC previously treated with ARPI	^{177}Lu-PSMA-617 *versus* docetaxel	200	PFS
NCT05113537 (UPLIFT)	mCRPC previously treated with ARPI	Abemaciclib followed by ^{177}Lu-PSMA-617	30	DLTs and MTD
NCT05230251 (ROADSTER)	Localized prostate cancer with biochemical failure, previously treated with radiation therapy	^{177}Lu-PSMA-I&T with high-dose radiation *versus* high-dose radiation	12	Safety and efficacy
NCT03805594	mCRPC previously treated with ARPI	^{177}Lu-PSMA-617 with pembrolizumab	43	ORR
NCT05162573 (PROQURE-1)	N1M0	^{177}Lu-PSMA-617 with EBRT	18	MTD
NCT05413850	mCRPC	^{177}Lu-rhPSMA-10.1	150	DLTs, treatment-related adverse events, 50% PSA response rate
NCT05496959 (LUNAR)	Oligorecurrent	^{177}Lu-PSMA-I&T before SBRT	100	PSMA-PET/CT-based PFS
NCT03822871	mCRPC previously treated with ARPI	CTT1403	40	DLTs
NCT05150236 (EVOLUTION)	mCRPC previously treated with ARPI	^{177}Lu-PSMA-617 with nivolumab and ipilimumab *versus* ^{177}Lu-PSMA-617	110	PSA-PFS at 1 year
NCT04419402 (ENZA-p)	mCRPC	^{177}Lu-PSMA-617 with enzalutamide *versus* enzalutamide	160	PSA PFS
^{225}Ac monotherapy				
NCT03276572	mCRPC previously treated with ARPI	^{225}Ac-J591	32	DLTs and MTD
NCT04506567	mCRPC previously treated with ARPI	^{225}Ac-J591	105	DLTs and MTD
NCT04946370	mCRPC previously treated with ARPI	^{225}Ac-J591 with pembrolizumab	76	DLTs, optimal dose, response rates
NCT05219500 (TATCIST)	mCRPC previously treated with ARPI	^{225}Ac-PSMA-I&T	100	Efficacy and safety
NCT04597411 (AcTION)	Both prior exposure and naïve to ^{177}Lu acceptable	^{225}Ac-PSMA-517	60	MTD
Combination of ^{177}Lu and ^{225}Ac				
NCT04886986	mCRPC previously treated with ARPI	^{225}Ac-J591 with ^{177}Lu-PSMA-I&T	33	DLTs, MTD, 50% PSA response rate
^{161}Tb				
NCT05521412 (VIOLET)	mCRPC previously treated with ARPI	^{161}Tb-PSMA-I&T	36	DLTs, MTD, treatment-related adverse events
^{227}Th				
NCT03724747	mCRPC previously treated with ARPI	BAY2315497 with or without darolutamide	63	MTD

ARPI, androgen receptor pathway inhibitor; DCR, disease control rate; DLTs, dose-limiting toxicities; EBRT, external beam radiation therapy; mCRPC, metastatic castration-resistant prostate cancer; mHSPC, metastatic hormone-sensitive prostate cancer; MTD, maximum tolerated dose; ORR, objective response rate; PSA, prostate-specific antigen; PSMA-RLT, prostate-specific membrane antigen-radioligand therapy; SBRT, stereotactic body radiation therapy; SoC, standard of care.

Jang et al, Ther Adv Med Oncol . 2023

Pembrolizumab in MSI-high Prostate Cancer

- 32 (3.1%) of 1,033 of prostate cancer patients tested with germline + somatic DNA sequencing had MSI-high or mismatch-repair deficient status
- 6 of 11 treated with PD-1/PD-L1 antibody therapy had a PSA decline >50%
- 8 patients were evaluable for radiographic response
- Duration of therapy ranged from 4.6 to 89 weeks or longer



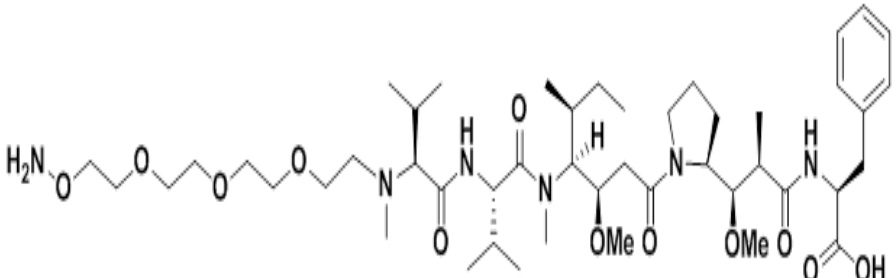
MSI, microsatellite instability; PD, progressing disease; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PR, partial response; PSA, prostate-specific antigen; SD, stable disease

Abida W, et al. JAMA Oncol. 2019;5:471-8

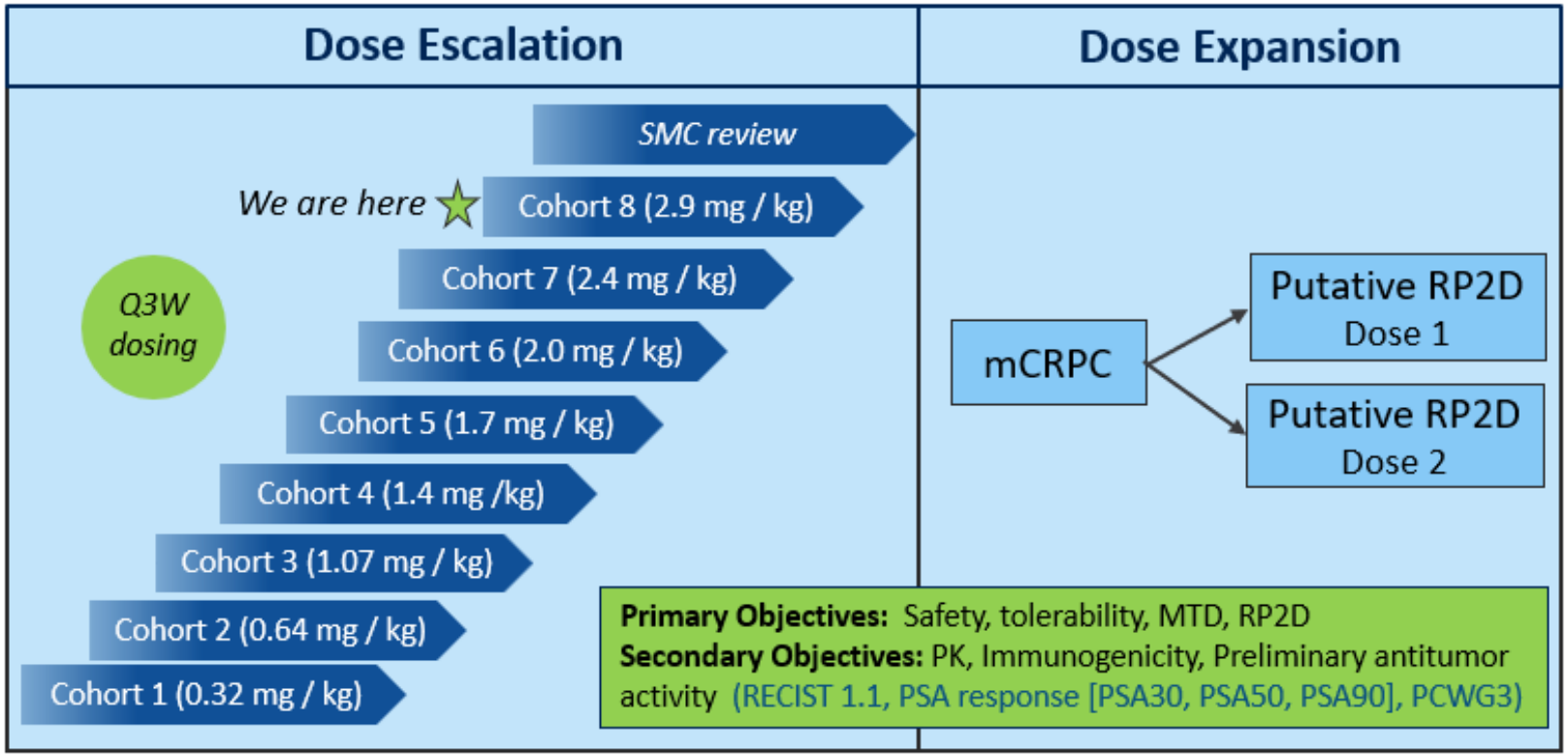
Other novel agents on pipeline

- **CDK 4/6:** Abemaciclib
- **BITE:** AMG 509 trial
- **PSMA- ADC:** ARX-517 trial
- **TROP2-ADC:** DS-1062a
- **Novel immunotherapy combinations**
  - For CRPC: Nivolumab + TLR, XL092 + Atezolizumab
- **CAR-T cell:**

ARX517, an anti-PSMA ADC targeting mCRPC



AS269 Drug-Linker



Conclusions

- Biomarker-based treatment selection is evolving in prostate cancer
- DNA repair gene alterations are seen in metastatic prostate cancer
  - Both germline and somatic testing are required
- PARP inhibitors have demonstrated efficacy in mCRPC
  - Olaparib and rucaparib are now FDA approved
  - Recently PARP+NHA combinations received FDA approval
- Lu-PSMA is available for patients with mCRPC
- Novel agents coming with different targets

Thank you….

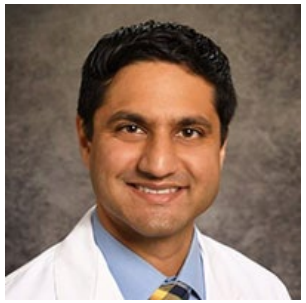
Medical Oncology





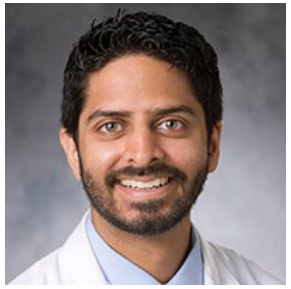


Urologic Oncology




Radiation Oncology

Nuclear Med

Immunology

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