mCRPC Treatment Sequencing and Future Directions

Alicia K. Morgans, MD, MPH, FASCO
Associate Professor of Medicine
Division of Oncology, Harvard Medical School
Director, Survivorship Program, Dana-Farber Cancer Institute

1

Disclosures

Consulting or Advisory Role: AstraZeneca, Astellas, AAA, Bayer, BMS, Clarity, Curium, Exact Science, Exelixis, Johnson and Johnson, Lantheus, Merck, Novartis, Pfizer, Sumitomo Pharma, Inc., Telix, Tolmar

Research Collaborations: Astellas, Bayer, Curium, Johnson and Johnson, Lantheus, Merck, Novartis, Pfizer, Sumitomo Pharma, Inc., Telix

2

General Principles in mCRPC

American Urological Association Education & Research, Inc.

SUO Society of Urologic Oncology, Inc.

3

General Principle: Clinical Factors Still Key

- **Prior treatments - Novel mechanism of action preferred**
- Is the cancer PSMA PET positive?
- Are there visceral metastases? Bone only metastases?
- How is the cancer progressing (symptomatic/aggressive, asymptomatic)?
- Is the patient a candidate for chemotherapy?
- Is there small cell/neuroendocrine differentiation?
- Are there targetable DRD mutations, MMR mutations, or is the tumor MSI high (did I do genetic testing to look for these?)?
- Which options are available in my practice location? What limitations may the patient have (support at home, number of bathrooms/ability to distance, etc.)?
- Clinical trials?

American Urological Association Education & Research, Inc.

SUO Society of Urologic Oncology, Inc.

4

National Comprehensive Cancer Network®

NCCN Guidelines Version 5.2026
Prostate Cancer

SYSTEMIC THERAPY FOR M1 CRPC: ADENOCARCINOMA[g,aa,jjj,kkk]

Pre-ARPI[aa,lll]	Post-ARPI[lll]/Pre-Docetaxel[aa]	Post-ARPI[lll]/Post-Docetaxel[aa]
Preferred: • Abiraterone (category 1) • Enzalutamide (category 1) **Other Recommended:** • Docetaxel[hhh] (category 1)	**Preferred:** • Docetaxel[hhh] (category 1) **Useful in Certain Circumstances:** • Molecular Biomarker-Directed Therapy ▸ *BRCA* mutation	**Preferred:** • Cabazitaxel[hhh] (category 1) • Docetaxel rechallenge[hhh] **Useful in Certain Circumstances:** • Molecular Biomarker-Directed Therapy
• Disease State-Specific Therapy ▸ Bone metastases ◊ Radium-223[ooo]/enzalutamide	◊ Lutetium Lu 177 vipivotide tetraxetan (Lu-177-PSMA-617)[qqq] ▸ Aggressive variant[iii] ◊ Cabazitaxel/Carboplatin[hhh]	◊ Lu-177-PSMA-617[qqq] (category 1) ▸ Aggressive variant[iii] ◊ Cabazitaxel/carboplatin[hhh] ▸ Palliation for symptomatic patients unable to tolerate other therapies ◊ Mitoxantrone[hhh]

To know where to go, we must know where we have been.

Additional Options Irrespective of Prior ARPI or Prior Docetaxel (Useful in Certain Circumstances)	
• Disease State-Specific Therapy ▸ Asymptomatic without visceral metastases ◊ Sipuleucel-T[hhh,ppp] ▸ Oligometastatic[h]/Oligoprogressive disease ◊ Metastasis-directed therapy[nnn] with metastatic castration-resistant prostate cancer (mCRPC) systemic therapy ▸ Symptomatic bone-predominant metastases ◊ Radium-223[ooo] (category 1)	• Molecular Biomarker-Directed Therapy ▸ MSI-High (MSI-H)/dMMR ◊ Pembrolizumab[hhh] (category 2B)

Spratt DE, et al. NCCN Prostate Cancer V5.2026.

5

National Comprehensive Cancer Network®

NCCN Guidelines Version 5.2026
Prostate Cancer

Prior ADT alone

Pre-ARPI[aa,lll]
Preferred: • Abiraterone (category 1) • Enzalutamide (category 1) **Other Recommended:** • Docetaxel[hhh] (category 1) **Useful in Certain Circumstances:** • Molecular Biomarker-Directed Therapy ▸ *BRCA* mutation ◊ Niraparib/abiraterone[mmm] (category 1) ◊ Olaparib/abiraterone[mmm] (category 1) ◊ Talazoparib/enzalutamide[mmm] (category 1) ▸ *HRRm* (other than BRCA1/2) ◊ Talazoparib/enzalutamide[mmm] (category 1) • Disease State-Specific Therapy ▸ Bone metastases ◊ Radium-223[ooo]/enzalutamide

Spratt DE, et al. NCCN Prostate Cancer V5.2026.

6

National Comprehensive Cancer Network®

NCCN Guidelines Version 5.2026
Prostate Cancer

Prior Doublet (ADT+ARPI)

Post-ARPI[III]/Pre-Docetaxel[aa]

Preferred:
- Docetaxel[hhh] (category 1)

Useful in Certain Circumstances:
- Molecular Biomarker-Directed Therapy
  - *BRCA* mutation
    - Olaparib[mmm] (category 1, preferred)
    - Rucaparib[mmm] (category 1, preferred)
    - Niraparib/abiraterone[mmm] (category 2B)
    - Talazoparib/enzalutamide[mmm] (category 2B)
  - *HRRm* (other than BRCA1/2)
    - Olaparib[mmm]
    - Talazoparib/enzalutamide[mmm] (category 2B)
- Disease State-Specific Therapy
  - PSMA-positive metastases
    - Lutetium Lu 177 vipivotide tetraxetan (Lu-177-PSMA-617)[qqq]
  - Aggressive variant[iii]
    - Cabazitaxel/Carboplatin[hhh]

Spratt DE, et al. NCCN Prostate Cancer V5.2026.

7

National Comprehensive Cancer Network®

NCCN Guidelines Version 5.2026
Prostate Cancer

Prior Triplet (ADT + ARPI + Docetaxel)

Post-ARPI[III]/Post-Docetaxel[aa]

Preferred:
- Cabazitaxel[hhh] (category 1)
- Docetaxel rechallenge[hhh]

Useful in Certain Circumstances:
- Molecular Biomarker-Directed Therapy
  - *BRCA* mutation
    - Olaparib[mmm] (category 1)
    - Rucaparib[mmm]
  - *HRRm* (other than *BRCA1/2*)
    - Olaparib[mmm]
  - Other FDA-approved agents for tissue agnostic indications[hhh]
- Disease State-Specific Therapy
  - PSMA-positive metastases
    - Lu-177-PSMA-617[qqq] (category 1)
  - Aggressive variant[iii]
    - Cabazitaxel/carboplatin[hhh]
  - Palliation for symptomatic patients unable to tolerate other therapies
    - Mitoxantrone[hhh]

Spratt DE, et al. NCCN Prostate Cancer V5.2026.

8

National Comprehensive Cancer Network®

NCCN Guidelines Version 5.2026
Prostate Cancer

Special Situations

Additional Options Irrespective of Prior ARPI or Prior Docetaxel (Useful in Certain Circumstances)	
• Disease State-Specific Therapy ▸ Asymptomatic without visceral metastases ◊ Sipuleucel-T[hhh,ppp] ▸ Oligometastatic[h]/Oligoprogressive disease ◊ Metastasis-directed therapy[nnn] with metastatic castration-resistant prostate cancer (mCRPC) systemic therapy ▸ Symptomatic bone-predominant metastases ◊ Radium-223[ooo] (category 1)	• Molecular Biomarker-Directed Therapy ▸ MSI-High (MSI-H)/dMMR ◊ Pembrolizumab[hhh] (category 2B)

Spratt DE, et al. NCCN Prostate Cancer V5.2026.

9

American Urological Association

American Urological Association (AUA)/
Society of Urologic Oncology (SUO)

APPROVED BY THE AUA BOARD OF DIRECTORS APRIL 2023

Authors' disclosure of potential conflicts of interest and author/staff contributions appear at the end of the article.

Reviewed and Updated 2023

ADVANCED PROSTATE CANCER: AUA/SUO GUIDELINE

(Published 2020; Amended 2023)

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

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

American Urological Association Education & Research, Inc.

SUO Society of Urologic Oncology, Inc.

METASTATIC CASTRATION RESISTANT PROSTATE CANCER

Prognosis

Clinicians SHOULD

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

Treatment

Clinicians SHOULD

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

Treatment (cont.)

Clinicians SHOULD (cont.)

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

Clinicians MAY

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

Lowrance W, et al. J Urol. 2023.

10

General Principle: Switch Mechanism of Action - Sequencing ARPIs is generally not effective

American Urological Association Education & Research, Inc.

SUO Society of Urologic Oncology, Inc.

11

PROfound: Olaparib vs ARPI switch for mCRPC

- Patients with mCRPC who had disease progression receiving a new hormonal agent (eg, enzalutamide or abiraterone)
- All men had a qualifying alteration in prespecified genes with a direct or indirect role in HRR

- Cohort A (n = 245) had ≥ 1 alteration in *BRCA1, BRCA2,* or *ATM*
- Cohort B (n = 142) had alterations in any of 12 other prespecified genes, prospectively and centrally determined from tumor tissue

R 2:1

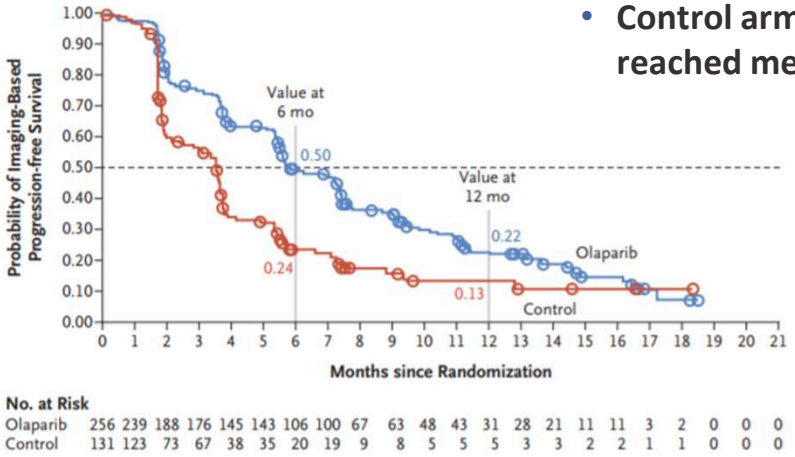
- Olaparib tablets (300 mg twice daily)
- Enzalutamide (160 mg once daily) + prednisone (5 mg twice daily)
- Abiraterone (1000 mg once daily) + prednisone (5 mg twice daily)

- **Primary Outcomes**: PFS in patients with at least 1 alteration
- **Secondary Outcomes**: PFS in the overall population, ORR, time to pain progression, OS, reduction of a least 50% in PSA, safety

de Bono J, et al. *N Engl J Med*. 2020;382:2091-2102.

12

PROfound: PFS Overall Population



- **Control arm (ARPI switch) reached median rPFS at first scan**

	Median *mo*
Olaparib	5.8
Control	3.5

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

de Bono J, et al. *N Engl J Med*. 2020;382:2091-2102.

13

CARD: Cabazitaxel vs ARPI switch for mCRPC

Cabazitaxel vs ARI switch in mCRPC patients progressing on docetaxel + ARI

Key Eligibility Criteria
- Patients with mCRPC who progressed ≤12 mo on prior alternative ARTA (before or after docetaxel)

1:1 **N = 255**

R

Cabazitaxel 25 mg/m² every 3 wk + prednisone + G-CSF (n = 129)

Abiraterone 1,000 mg once daily + prednisone *or* enzalutamide 160 mg once daily (n = 126)

Stratified by ECOG PS (0/1 vs 2), time to progression of prior alternative ARTA (≤ 6 mos vs > 6-12 mos), timing of prior AR-targeted therapy (before vs after docetaxel)

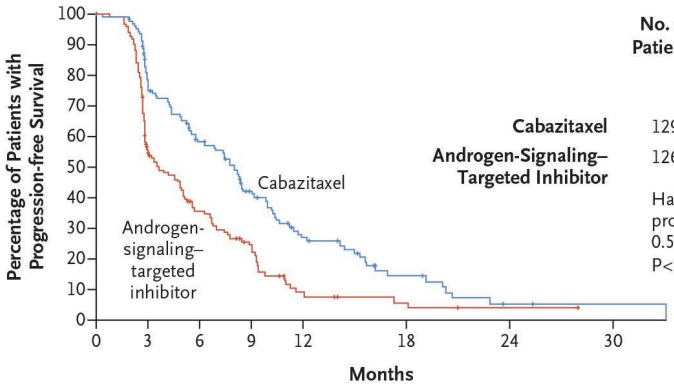
Primary Endpoint:
rPFS (ITT population)

Other endpoints:
OS, PFS, PSA response, tumor response, time to SSE, pain response, and safety

de Wit R et al. *N Engl J Med*. 2019;381:2506-2518

14

CARD - PFS



	No. of Patients	Median Imaging-Based Progression-free Survival (95% CI) *mo*
Cabazitaxel	129	8.0 (5.7–9.2)
Androgen-Signaling–Targeted Inhibitor	126	3.7 (2.8–5.1)

Hazard ratio for imaging-based progression or death, 0.54 (95% CI, 0.40–0.73)
P<0.001

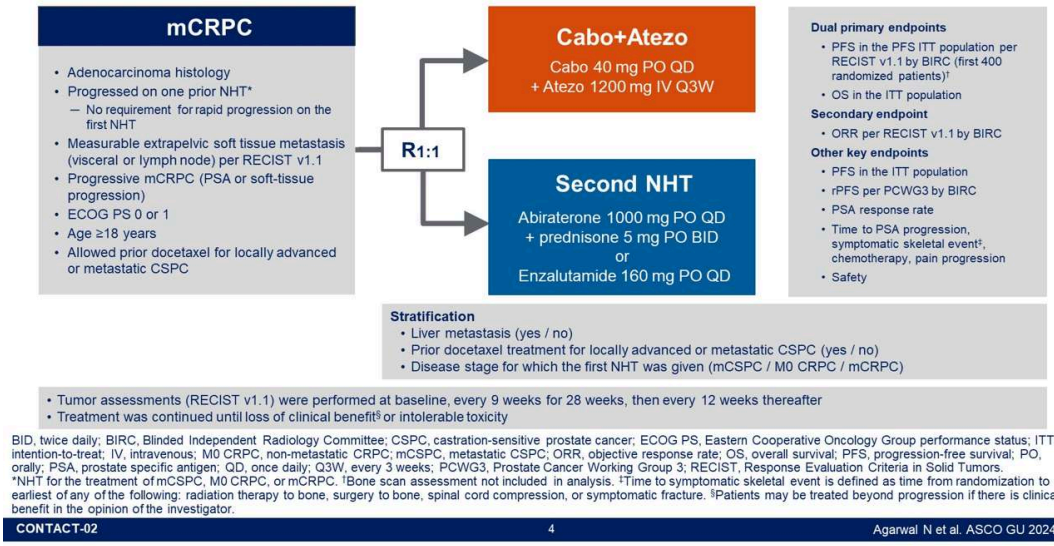
No. at Risk								
Cabazitaxel	129	91	64	41	23	9	2	1
Androgen-signaling–targeted inhibitor	126	61	36	22	7	3	1	0

de Wit R, et al. *N Engl J Med*. 2019;381:2506-2518.

- **Control arm (ARPI switch) reached median rPFS at first scan**

15

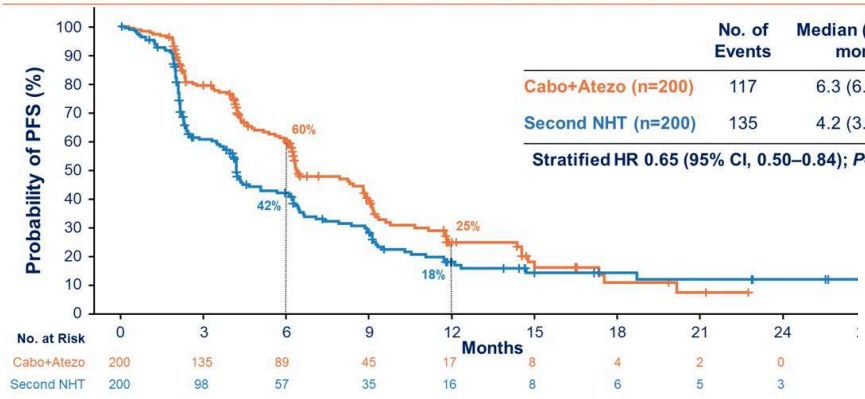
CONTACT-02: Cabozantinib + atezolizumab vs ARPI switch for mCRPC



16

PFS per BIRC* (PFS ITT Population†)

Cabo+Atezo Reduced the Risk of Progression or Death by 35% vs Second NHT



	No. of Events	Median (95% CI), months
Cabo+Atezo (n=200)	117	6.3 (6.2–8.8)
Second NHT (n=200)	135	4.2 (3.7–5.7)

Stratified HR 0.65 (95% CI, 0.50–0.84); *P*=0.0007†

- **Median PFS per BIRC (ITT): 6.3 vs 4.2 mo (HR 0.64 [95% CI, 0.50–0.81]; *P*=0.0002)**
- Median rPFS per PCWG3 in PFS ITT population: 6.3 vs 4.1 mo (HR, 0.62 [95% CI, 0.48–0.81])

CI, confidence interval; HR, hazard ratio. *PFS per RECIST v1.1 by BIRC or death. †Critical *P* value=0.002. ‡First 400 randomized patients.

CONTACT-02 8 Agarwal N et al. ASCO GU 2024

- **Control arm (ARPI switch) reached median rPFS just after first scan**

17

General Principle:
Genetic Testing is Standard of Care in mCRPC

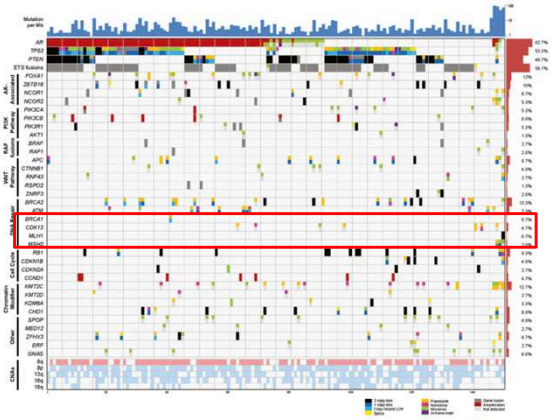
American Urological Association Education & Research, Inc.

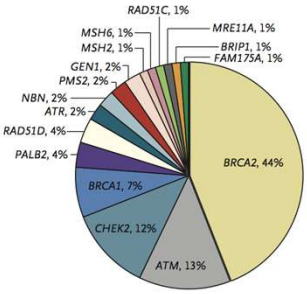
SUO Society of Urologic Oncology, Inc.

18

DNA Repair Gene Alterations Are Common in Metastatic Prostate Cancer

- Among patients with mCRPC, 23% harbor DNA repair alterations
- The frequency of DNA repair alterations increases **with disease progression**





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

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

19

American Urological Association

Advanced Prostate Cancer: AUA/ASTRO/SUO Guideline PART II

William T. Lowrance,* Rodney H. Breau, Roger Chou, Brian F. Chapin, Tony Crispino, Robert Dreicer, David F. Jarrard, Adam S. Kibel, Todd M. Morgan, Alicia K. Morgans, William K. Oh, Matthew J. Resnick, Anthony L. Zietman and Michael S. Cookson

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

General Principle:
Germline and somatic genetic testing should be offered to mCRPC patients

American Urological Association Education & Research, Inc.

SUO Society of Urologic Oncology, Inc.

Lowrance W, et al. J Urol. 2023.

20

Estimated Germline and Somatic Mutations in mPCa

	Somatic Mutation	Germline Mutation	Combined Rate
BRCA1	1%	1%	2%
BRCA2	5%	5.4%	10-11%
PALB2	4% *	0.4%	4.4%
ATM	2-3%	1.6%	3.5-4.5%
MSH2/6	4-5%	1.5%	5.5-6.5%

*** mCRPC rate**

Adapted from Pritchard C, APCCC Basel 2019, with estimates based on Robinson 2015, Pritchard 2016, Na 2017, Annala 2017, Giri 2018, Nava Rodriquez 2018, Nicolosi 2019, Cheng 2019, Lang, 2019.

21

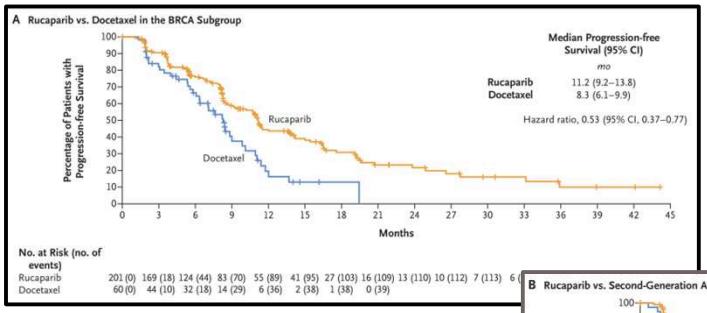
Considering PARPi in Sequencing

American Urological Association Education & Research, Inc.

SUO Society of Urologic Oncology, Inc.

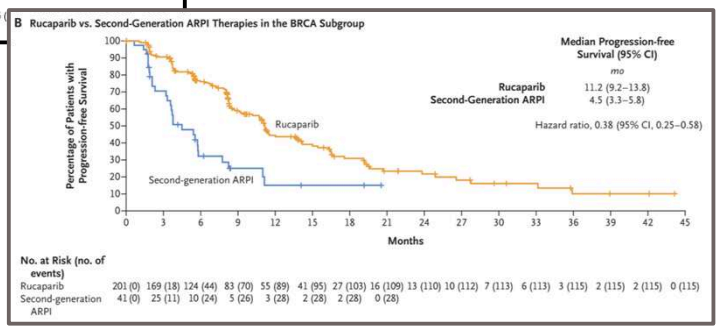
22

TRITON 3: Rucaparib vs Physician's Choice of Control
Earlier PARPi better for patients with BRCA1/2



Rucaparib superior to docetaxel by ~3 months for rPFS

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

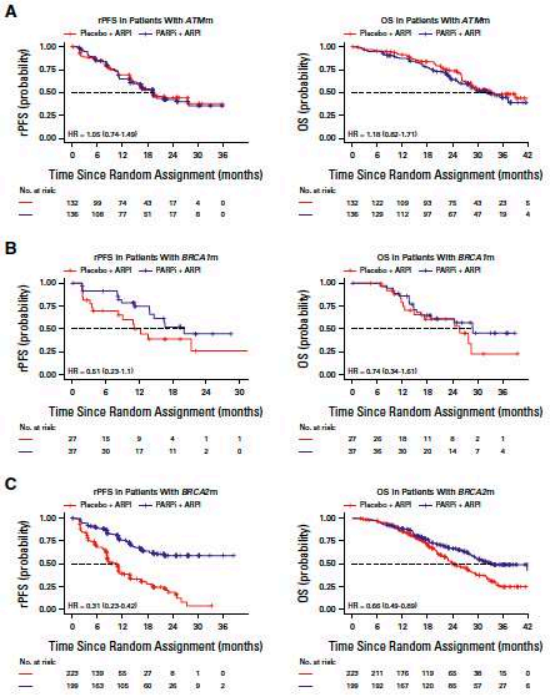


Fizazi K, et al. N Engl J Med. 2023.

23

PARPi + ARPi Efficacy Across Mutations

- Differential activity of these combinations across different genomic mutations
- Improved rPFS in BRCA 1 and BRCA 2
- Improved OS in BRCA2
- OS data still immature for BRCA1



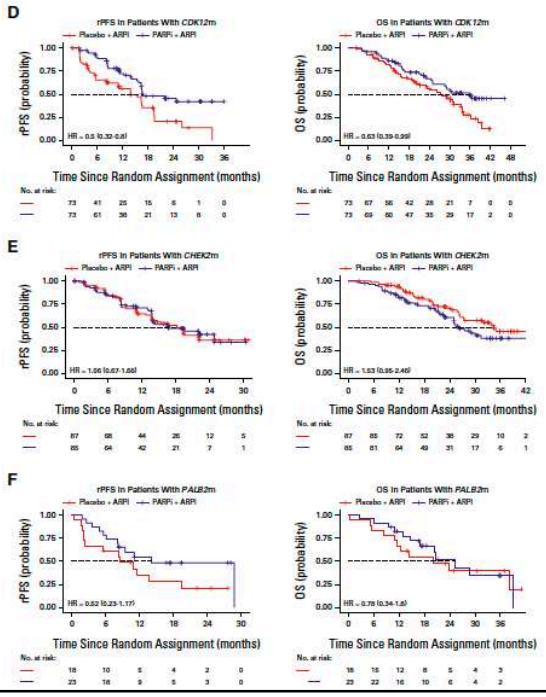
Fallah et al JCO 2024

24

PARPi + ARPi Efficacy Across Mutations

- PALB2 and CDK12 show improved rPFS with OS data immature.
- No benefit seen with ATM or CHEK2 mutant prostate cancer.
- Clonal hematopoeisis for ctDNA must be remembered

Fallah et al JCO 2024



25

MMR gene mutations (MLH2, MSH2, MSH6) may be best for prostate cancer to predict response to pembrolizumab (1-3% of mCRPC)

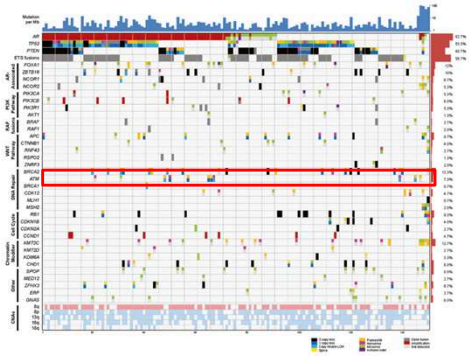
UW Rapid Autopsy

- 7/60 (11.7%) of advanced prostate cancers are hypermutated and all had mismatch repair gene mutations and MSI
- Hypermutation defined as >300 somatic protein altering mutations in metastatic tumors
- All mismatch repair alterations were in MSH2 or MSH6

Pritchard CC et al. Nat Commun. 2014; 5:4988.

SU2C mCRPC Biopsies

- 2.7% harbor MMR alterations in either MLH1 or MSH2, which are consistent with MSI



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

26

What about radioligand therapies?

American Urological Association Education & Research, Inc.

SUO Society of Urologic Oncology, Inc.

27

VISION: Phase 3 Study of ^{177}Lu-PSMA-617 in Patients with Progressive PSMA+ mCRPC

- International, prospective, open-label, multicenter, randomized phase 3 trial

N = 750

Key Eligibility Criteria

- Progressive mCRPC with a ^{68}Ga-PSMA-11 PET/CT positive scan (determined by central reader)
- Received at least 1 NAAD (enza or abi)
- Treated with at least 1 but no more than 2 previous taxane regimens
- ECOG PS 0-2

R 2:1

^{177}Lu-PSMA-617 7.4 GBq q6 wks x6 + best supportive/standard of care

Best supportive/standard of care

Stratification factors:

- Serum LDH (≤ 260 IU/L vs >260IU/L)
- Presence of liver mets (Y/N)
- ECOG PS (0-1 vs 2)
- Inclusion of NAAD in best supportive/best std of care at time of randomization (Y/N)

- Alternate Primary Endpoint: OS and rPFS
- Key Secondary Endpoints (with a control): RECIST response, time to first SSE
- Additional Secondary Endpoints: safety and tolerability, HRQoL, health economics, PFS, biochemical response

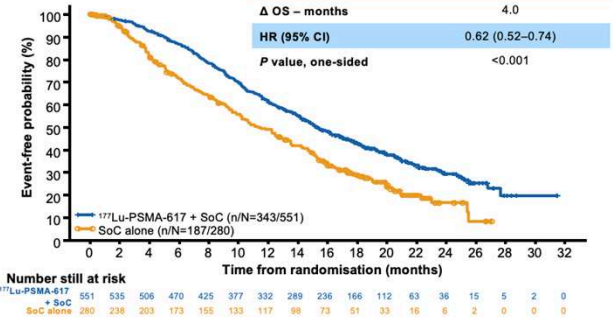
Sartor AO, et al. ASCO 2019. Abs TPS5099. ClinicalTrials.gov. NCT03511664

28

VISION: OS and rPFS Alternate Primary Endpoints

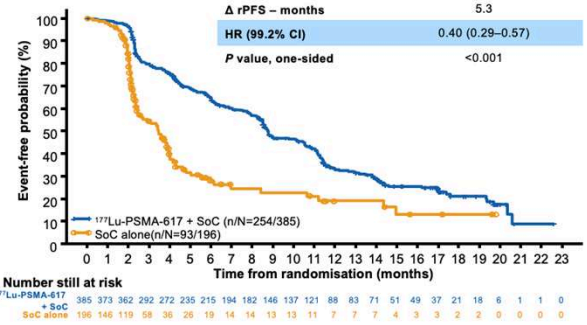
OS: 38% risk reduction for death
(OS analysis set)

	^{177}Lu-PSMA-617 + SoC (n=551)	SoC only (n=280)
Median OS – months	15.3	11.3
Δ OS – months	4.0	
HR (95% CI)	0.62 (0.52–0.74)	
P value, one-sided	<0.001	



rPFS: 60% risk reduction for progression/death
(rPFS analysis set)

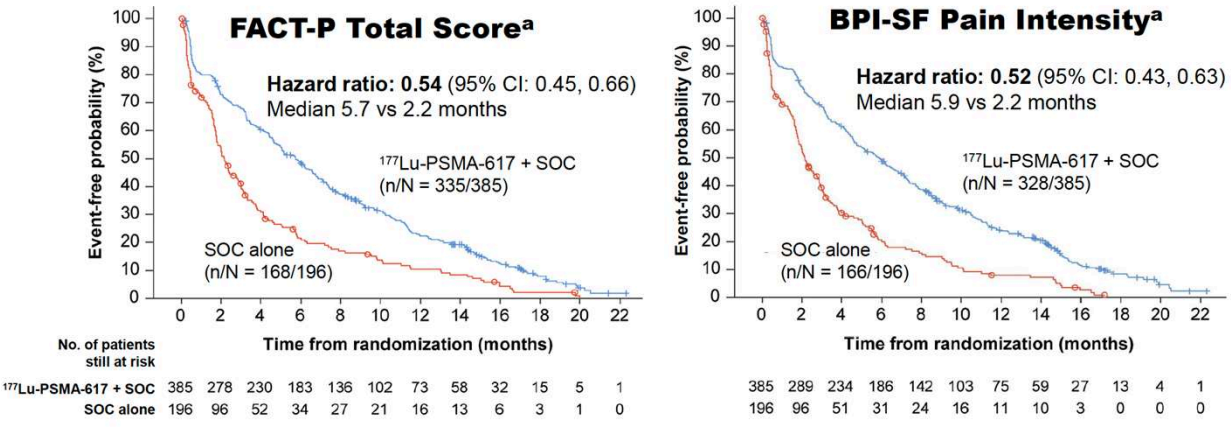
	^{177}Lu-PSMA-617 + SoC (n=385)	SoC only (n=196)
Median rPFS[a] – months	8.7	3.4
Δ rPFS – months	5.3	
HR (99.2% CI)	0.40 (0.29–0.57)	
P value, one-sided	<0.001	



Sartor AO, et al. New Engl J Med. 2021.

29

VISION secondary endpoint: FACT-P and BPI-SF Time to worsening

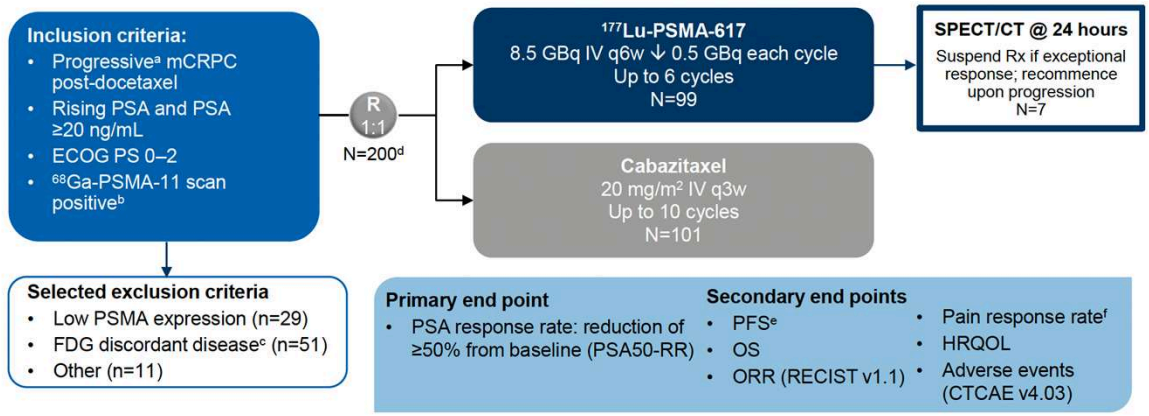


[a]Data are from patients randomized after implementation of enhanced study site education measures, who had baseline and ≥1 post-baseline assessments.

Sartor AO, et al. New Engl J Med. 2021.

30

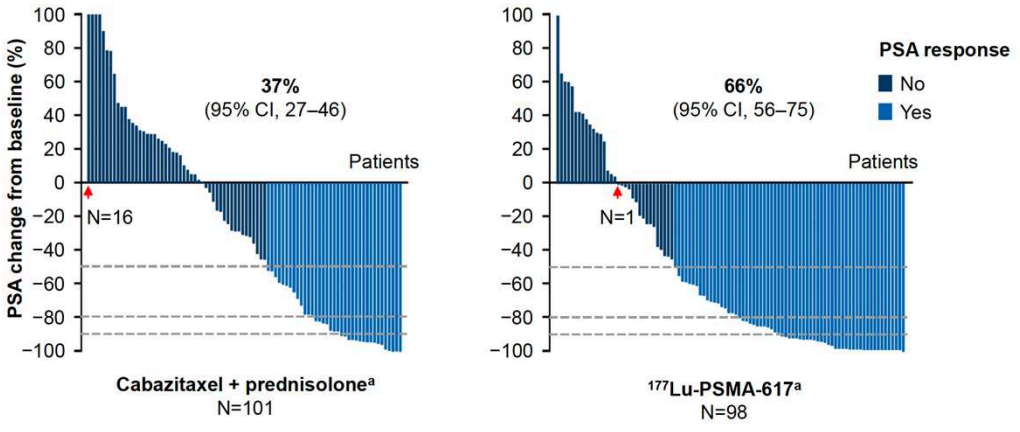
TheraP: ^{177}Lu PSMA-617 vs Cabazitaxel in mCRPC



Hofman M, et al. Lancet. 2021.

31

TheraP: Results – PSA ≥50% Response



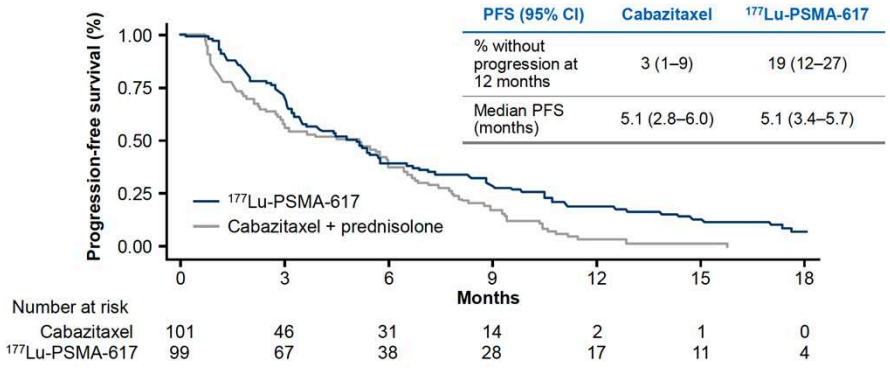
Absolute difference in PSA50-RR between groups: 29% (*P*<0.0001)

Education & Research, Inc.

Hofman M, et al. Lancet. 2021.

32

TheraP: Results – Progression-free survival
(PSA and radiologic)



PFS (95% CI)	Cabazitaxel	^{177}Lu-PSMA-617
% without progression at 12 months	3 (1–9)	19 (12–27)
Median PFS (months)	5.1 (2.8–6.0)	5.1 (3.4–5.7)

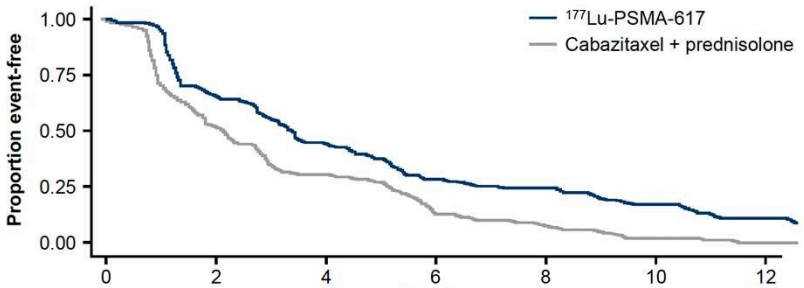
Number at risk							
Cabazitaxel	101	46	31	14	2	1	0
^{177}Lu-PSMA-617	99	67	38	28	17	11	4

^{177}Lu-PSMA-617 delayed progression compared with cabazitaxel (HR, 0.63; 95% CI, 0.46–0.86; *P*=0.0028)[b]

Hofman M, et al. Lancet. 2021.

33

TheraP: Results – Deterioration-free survival[a]



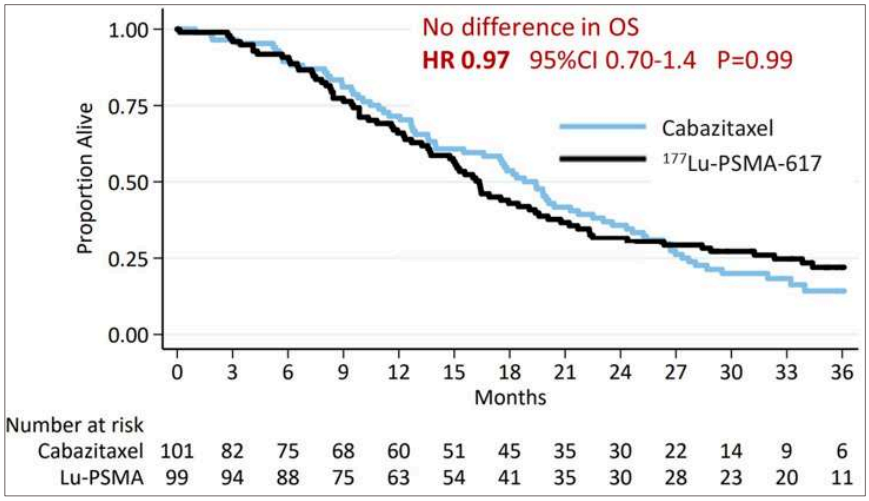
Number at risk							
Cabazitaxel	101	47	28	12	8	3	1
^{177}Lu-PSMA-617	99	66	45	29	25	18	12

At 6 months, a total of 29% (95% CI, 21–38) of ^{177}Lu-PSMA-617-treated patients and 13% (95% CI, 7–21) cabazitaxel-treated patients were event-free in terms of global health status (*P*=0.0002)

Hofman M, et al. Lancet. 2021.

34

Similar OS with ^{177}Lu-PSMA-617 vs cabazitaxel: 3-year follow-up of TheraP study

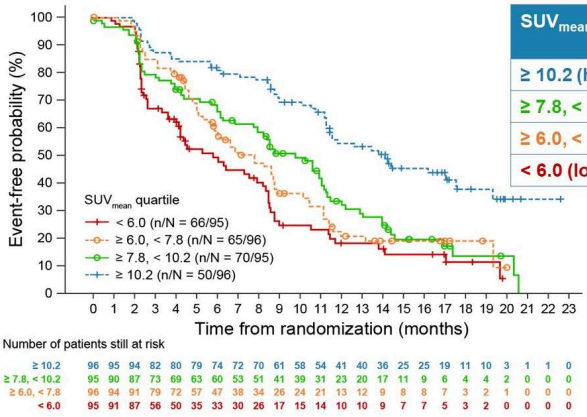


Hofman M, et al. ASCO 2022.

35

rPFS by Whole-Body SUV_{mean} Quartiles (PFS in VISION)

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



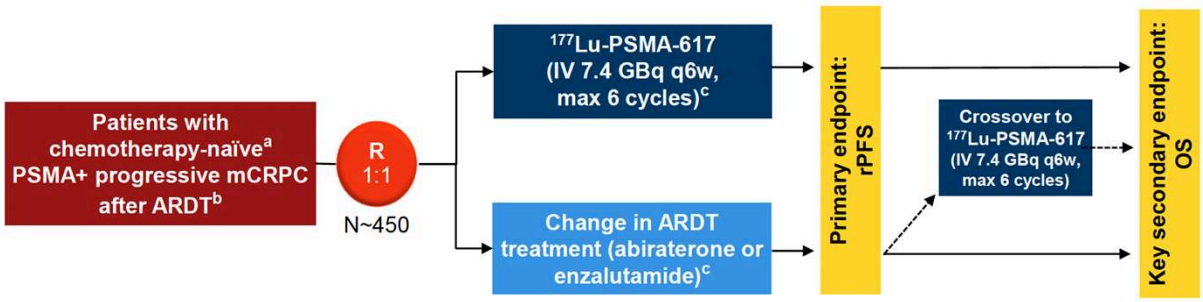
SUV_{mean} quartile	Median rPFS (months)
≥ 10.2 (highest)	14.1
≥ 7.8, < 10.2	9.8
≥ 6.0, < 7.8	7.8
< 6.0 (lowest)	5.8

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

Kuo P, et al. J Clin Oncol. 2022;40(16 suppl):5002.

36

PSMAfore Study Schema



Stratification factors
- Prior ARDT use in CRPC vs HSPC
- Presence of symptoms (asymptomatic/mildly symptomatic vs symptomatic)

Crossover
- Upon BICR-confirmed radiographic progression on ARDT, eligible patients meeting pre-defined criteria are permitted to crossover to receive ^{177}Lu-PSMA-617

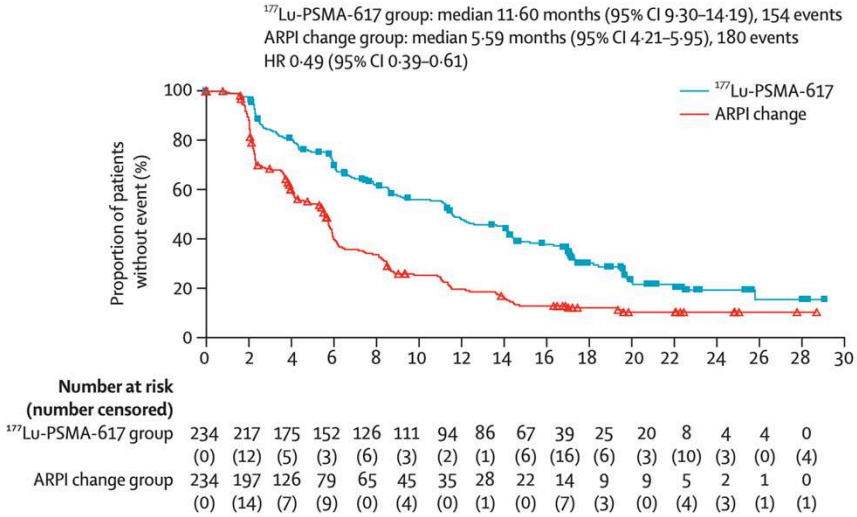
ClinicalTrials.gov Identifier: NCT04689828

37

PSMAfore: Updated rPFS Primary Endpoint

HR 0.49
(95% CI 0.39-0.61)

Median rPFS difference of 6 mo



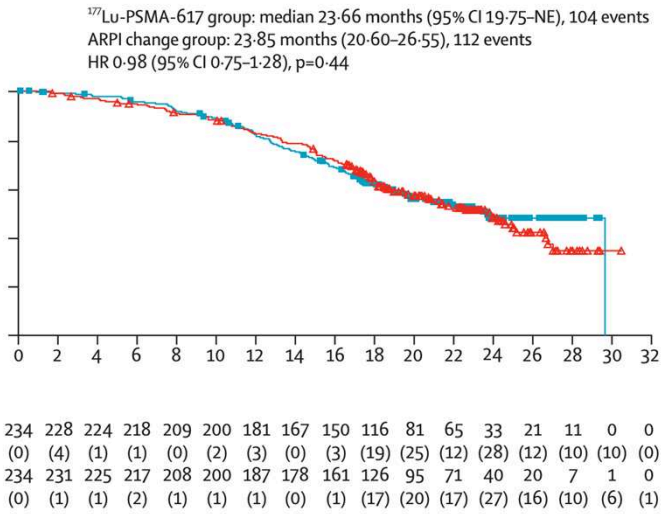
Number at risk (number censored)																
^{177}Lu-PSMA-617 group	234 (0)	217 (12)	175 (5)	152 (3)	126 (6)	111 (3)	94 (2)	86 (1)	67 (6)	39 (16)	25 (6)	20 (3)	8 (10)	4 (3)	4 (0)	0 (4)
ARPI change group	234 (0)	197 (14)	126 (7)	79 (9)	65 (0)	45 (4)	35 (0)	28 (1)	22 (0)	14 (7)	9 (3)	9 (0)	5 (4)	2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

Morris M, et al. Lancet, 2024.

38

Should we use 177-Lu PSMA-617 before chemotherapy? PSMAfore Overall Survival

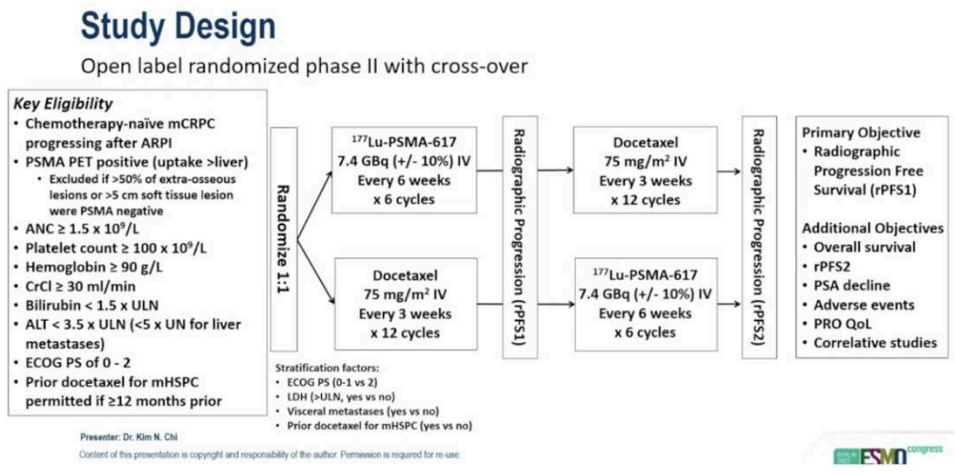
HR 0.98
(95% CI 0.75-1.28)
P=0.44



Morris M, et al. Lancet, 2024.

39

Should we use ^{177}Lu PSMA-617 before chemotherapy? PLUDO Study



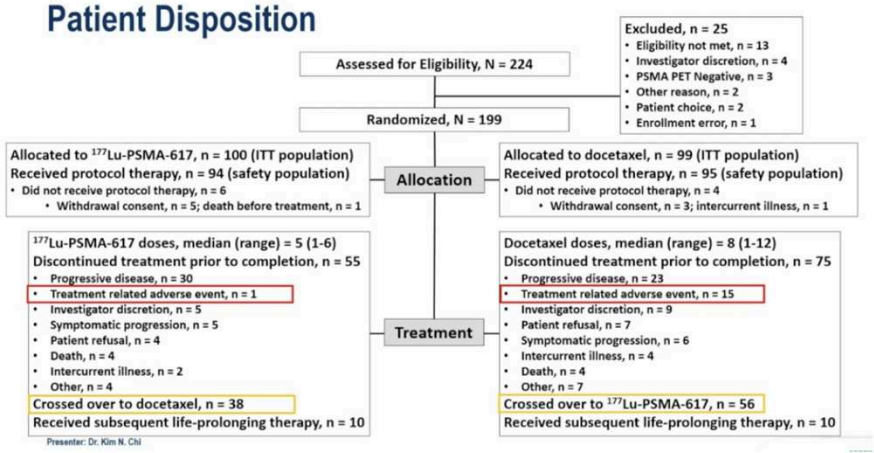
Chi K, et al. ESMO 2025.

40

Should we use ^{177}Lu PSMA-617 before chemotherapy? PLUDO Study

- **56 patients** treated with docetaxel **received subsequent ^{177}Lu PSMA-617**
- **38 patients** treated with ^{177}Lu PSMA-617 **received subsequent docetaxel**

Patient Disposition



Chi K, et al. ESMO 2025.

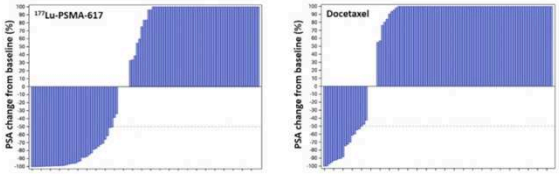
41

Should we use ^{177}Lu PSMA-617 before chemotherapy? PLUDO Study

Disease Response

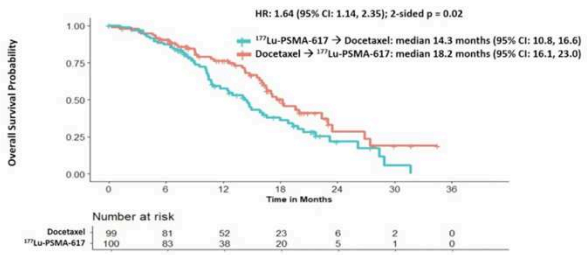
Response	^{177}LU-PSMA-617	Docetaxel	p-value
PSA decline ≥50%	36/100 (36%)	16/99 (16%)	0.0015
CR/PR*	8/49 (16%)	4/52 (8%)	0.23

*Patients with measurable disease



- **Response rates favored** ^{177}Lu PSMA-617

Overall Survival

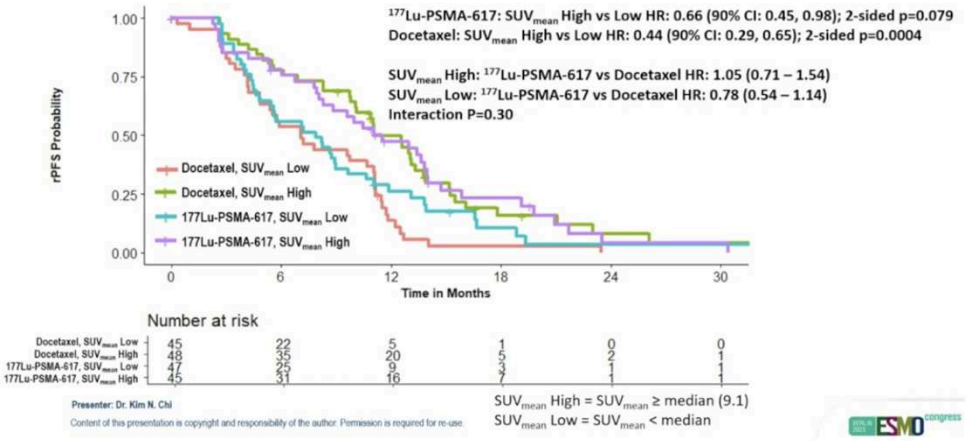


Chi K, et al. ESMO 2025.

42

Should we use ^{177}Lu PSMA-617 before chemotherapy? PLUDO Study

Median SUV_{mean} was Prognostic but not Predictive for rPFS

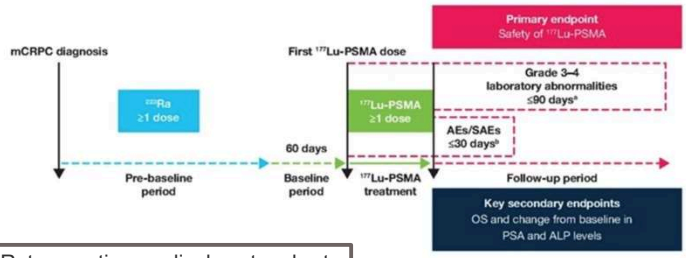


Chi K, et al. ESMO 2025.

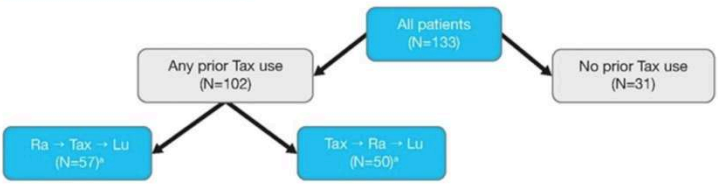
43

Can ^{177}Lu PSMA-617 be given after other radiopharmaceutical therapies?

RALU: Lutetium-177-PSMA Therapy in Patients with Prior Radium-223



- Retrospective medical center chart review of patients with radium-223 prior to ^{177}Lu-PSMA in German nuclear medical centers.
- 133 patients were included in this analysis.
- A majority received ^{177}Lu-PSMA after ARPI and taxane.



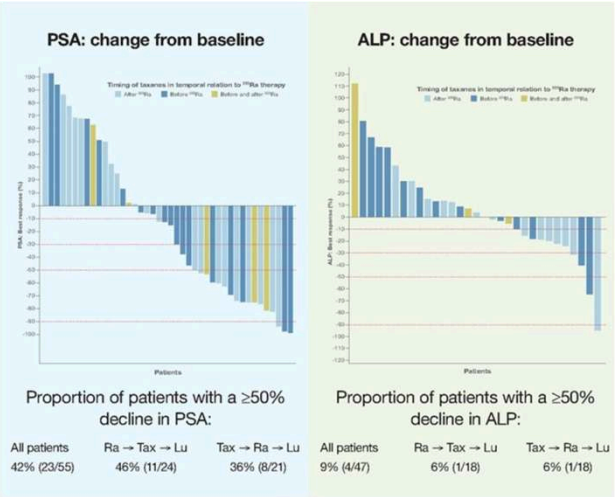
Kambiz R, et al. 2022 ESMO.

44

Can ^{177}Lu PSMA-617 be given after other radiopharmaceutical therapies?

RALU: Lutetium-177-PSMA Therapy in Patients with Prior Radium-223

- Median OS from the start of ^{177}Lu-PSMA treatment was 13 (95% CI 11–16) for the overall population, and **there were no concerning safety signals**
- Median OS from the start of ^{177}Lu-PSMA treatment was 12 (95% CI 9–15) for radium-223 followed by chemotherapy followed by ^{177}Lu-PSMA group
- Median OS from the start of ^{177}Lu-PSMA treatment was 14 (95% CI 9–17) months chemotherapy followed by radium-223 followed by ^{177}Lu-PSMA group

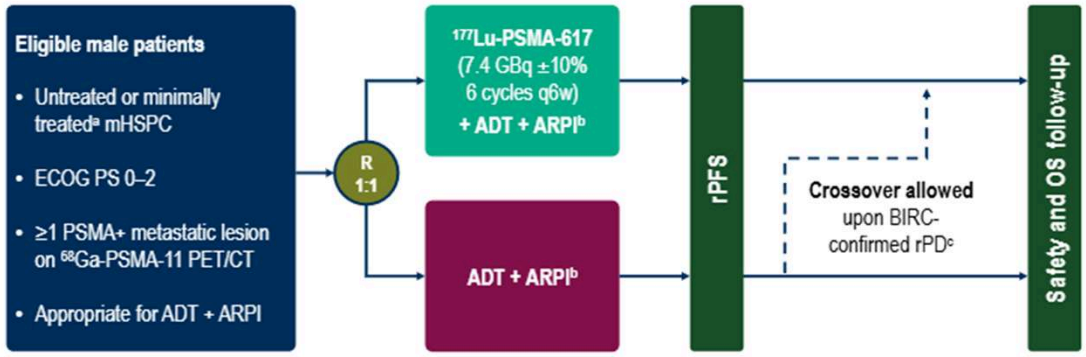


Kambiz R, et al. 2022 ESMO.

45

PSMAddition

^{177}Lu-PSMA-617 in mHSPC



Stratification factors
- Disease volume (high/low) – per CHAARTED criteria[1]
- Age ≥ 70 years (yes/no)
- Previous or planned treatment of primary tumour by radiation or prostatectomy (yes/no)

Follow-up periods
- rPFS: until event in all patients
- Safety: 30 days then 24 and 48 weeks after treatment discontinuation
- OS: every 90 days after last contact

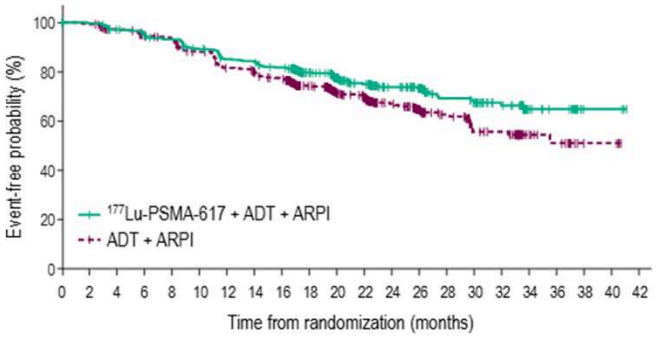
Tagawa ST, et al. ESMO Congress 2025; October 19, 2025; Berlin, Germany. LBA6

46

PSMAddition: rPFS ^{177}Lu-PSMA-617 + ARPI

- Median rPFS has not been reached in either arm yet
- Benefit consistent across subgroups

rPFS by BIRC



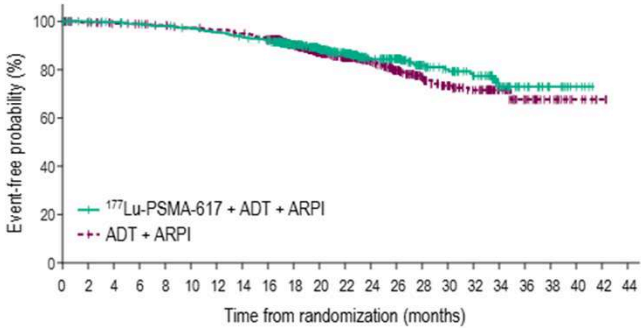
	^{177}Lu-PSMA-617 + ADT + ARPI (N = 572)	ADT + ARPI (N = 572)
Events – n (%) rPD Death without rPD	139 (24.3) 112 (19.6) 27 (4.7)	172 (30.1) 152 (26.6) 20 (3.5)
HR (95% CI)	0.72 (0.58, 0.90)	
p value	0.002[a]	
Median rPFS (95% CI) – months	NR (NE, NE)	NR (29.7, NE)

- Tagawa ST, et al. ESMO Congress 2025; October 19, 2025; Berlin, Germany. LBA6

47

PSMAddition: Overall Survival

Interim OS (prespecified intent-to-treat analysis – follow-up continues)



	^{177}Lu-PSMA-617 + ADT + ARPI (N = 572)	ADT + ARPI (N = 572)
Events – n (%)	85 (14.9)	99 (17.3)
Censored – n (%)	487 (85.1)	473 (82.7)
HR (95% CI)	0.84 (0.63, 1.13)	
p value	0.125[a]	
Median OS (95% CI) – months	NR (NE, NE)	NR (NE, NE)

- Tagawa ST, et al. ESMO Congress 2025; October 19, 2025; Berlin, Germany. LBA6

48

PSMAddition
Overall Incidence of AEs

Patients with on-treatment AE – n (%)[a]	^{177}Lu-PSMA-617 + ADT + ARPI (N = 564)		ADT + ARPI (N = 565)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Any	555 (98.4)	286 (50.7)	546 (96.6)	243 (43.0)
Related to any study treatment	504 (89.4)	128 (22.7)	394 (69.7)	69 (12.2)
^{177}Lu-PSMA-617-related	441 (78.2)	78 (13.8)	–	–
ADT and/or ARPI-related	418 (74.1)	81 (14.4)	394 (69.7)	69 (12.2)
Serious	180 (31.9)	150 (26.6)	162 (28.7)	129 (22.8)
Related to any study treatment	39 (6.9)	31 (5.5)	14 (2.5)	12 (2.1)
^{177}Lu-PSMA-617-related	17 (3.0)	13 (2.3)	–	–
ADT and/or ARPI-related	27 (4.8)	22 (3.9)	14 (2.5)	12 (2.1)
Leading to death	15 (2.7)	15 (2.7)	14 (2.5)	14 (2.5)
Treatment-related	0	0	0	0
Leading to discontinuation of any study treatment	91 (16.1)	46 (8.2)	51 (9.0)	23 (4.1)
Leading to ^{177}Lu-PSMA-617…				
Discontinuation	45 (8.0)	28 (5.0)	–	–
Dose reduction	22 (3.9)	13 (2.3)	–	–
Dose delay	68 (12.1)	27 (4.8)	–	–

- Tagawa ST, et al. ESMO Congress 2025; October 19, 2025; Berlin, Germany. LBA6

49

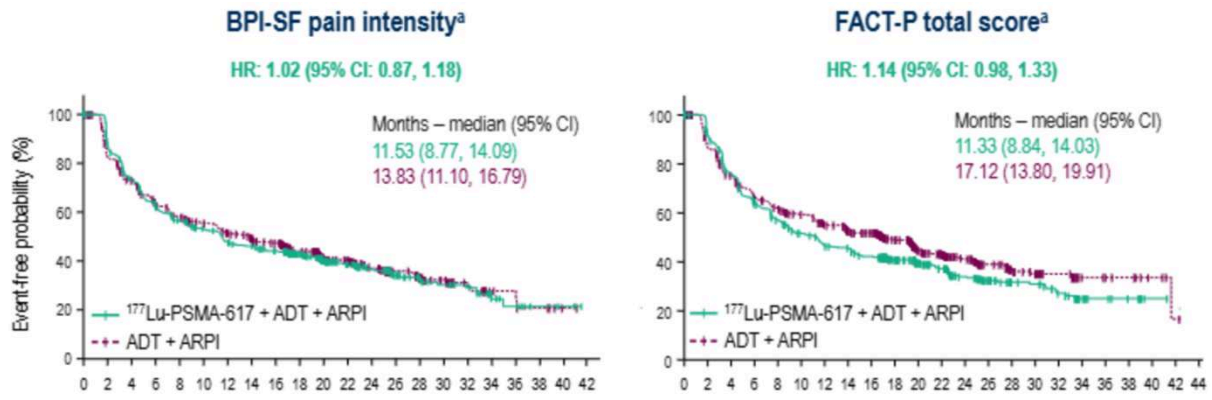
PSMAddition
Safety Findings Were Consistent With Known Profiles

AEs in ≥10% of patients in the ^{177}Lu-PSMA-617 arm – n (%)	^{177}Lu-PSMA-617 + ADT + ARPI (N = 564)		ADT + ARPI (N = 565)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Dry mouth[a]	258 (45.7)	0	21 (3.7)	0
Fatigue	196 (34.8)	6 (1.1)	158 (28.0)	6 (1.1)
Nausea	193 (34.2)	1 (0.2)	53 (9.4)	0
Hot flush	164 (29.1)	0	205 (36.3)	0
Anaemia	153 (27.1)	28 (5.0)	75 (13.3)	15 (2.7)
Arthralgia	111 (19.7)	5 (0.9)	130 (23.0)	9 (1.6)
Back pain	101 (17.9)	8 (1.4)	110 (19.5)	16 (2.8)
Constipation	101 (17.9)	0	91 (16.1)	0
Asthenia	92 (16.3)	2 (0.4)	73 (12.9)	5 (0.9)
Decreased appetite	81 (14.4)	5 (0.9)	37 (6.5)	1 (0.2)
Vomiting	78 (13.8)	4 (0.7)	21 (3.7)	0
COVID-19	76 (13.5)	5 (0.9)	60 (10.6)	2 (0.4)
Hypertension	76 (13.5)	34 (6.0)	95 (16.8)	35 (6.2)
Diarrhoea	69 (12.2)	1 (0.2)	56 (9.9)	0
Headache	69 (12.2)	0	51 (9.0)	2 (0.4)
Alanine aminotransferase increased	68 (12.1)	19 (3.4)	73 (12.9)	14 (2.5)
Dysgeusia	67 (11.9)	0	23 (4.1)	0
White blood cell count decreased	63 (11.2)	12 (2.1)	18 (3.2)	3 (0.5)
Aspartate aminotransferase increased	61 (10.8)	10 (1.8)	65 (11.5)	11 (1.9)
Lymphocyte count decreased	60 (10.6)	28 (5.0)	21 (3.7)	7 (1.2)

- Tagawa ST, et al. ESMO Congress 2025; October 19, 2025; Berlin, Germany. LBA6

50

PSMAddition: No Clinically Significant Difference in Time to Worsening in HRQoL and Pain



Tagawa ST, et al. ESMO Congress 2025; October 19, 2025; Berlin, Germany. LBA6

51

Confirming Histology in mCRPC

American Urological Association Education & Research, Inc.

SUO Society of Urologic Oncology, Inc.

52

Is this still an Adencoarcinoma? Situations to Consider a Metastatic Biopsy

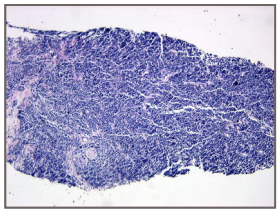
- Visceral lesions esp. liver metastasis
- Extremely bulky lymph nodes (>5cm)
- Low PSA in the setting of very high volume disease
- Predominantly lytic rather than blastic bone metastases

→Always biopsy a metastatic site for somatic testing

53

Neuroendocrine/Small Cell Prostate Cancer

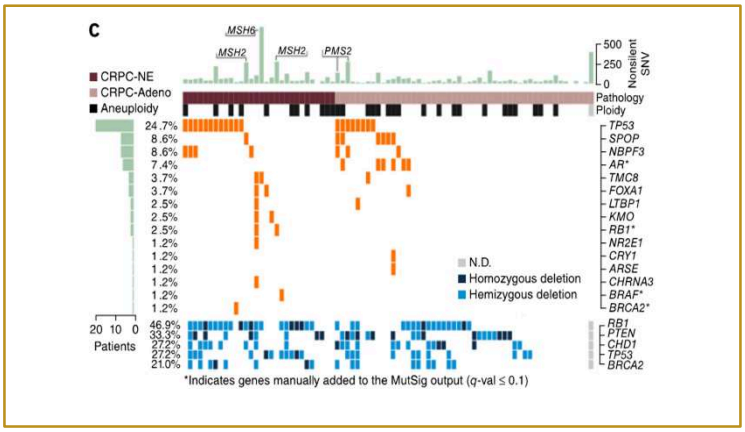
- De novo presentation rare (<1% new diagnoses)
- May arise as a mechanism of resistance to ADT
- Metastatic disease, including unusual sites of metastases
- Low or modestly rising PSA
- Paraneoplastic syndromes (uncommon)
- Elevated CEA or serum neuroendocrine markers (chromogranin, neuron specific enolase) can support the diagnosis
- Tissue IHC expresses chromogranin A and synaptophysin
- Treated like small cell lung cancer **(platinum-doublet chemotherapy, e.g. cisplatin or carboplatin with etoposide)**



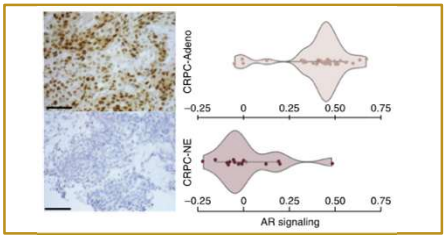
Slide adapted from Misha Beltran

54

Molecular Evaluation in CRPC



- Differential genomic and epigenomic signatures in histologically classified adenocarcinoma and NEPC
- AR signaling activity can be dramatically distinct across histologies



Beltran H et al. Nat Med 2016

55

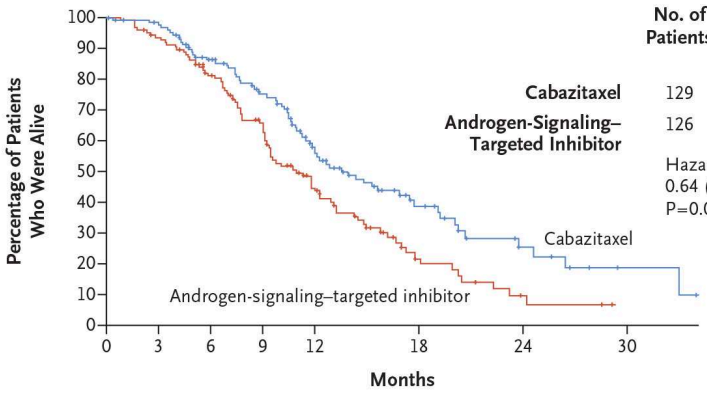
Remember: Chemotherapy works in mCRPC

American Urological Association Education & Research, Inc.

SUO Society of Urologic Oncology, Inc.

56

CARD - OS



	No. of Patients	Median Overall Survival (95% CI) *mo*
Cabazitaxel	129	13.6 (11.5–17.5)
Androgen-Signaling–Targeted Inhibitor	126	11.0 (9.2–12.9)

Hazard ratio for death, 0.64 (95% CI, 0.46–0.89)
P=0.008

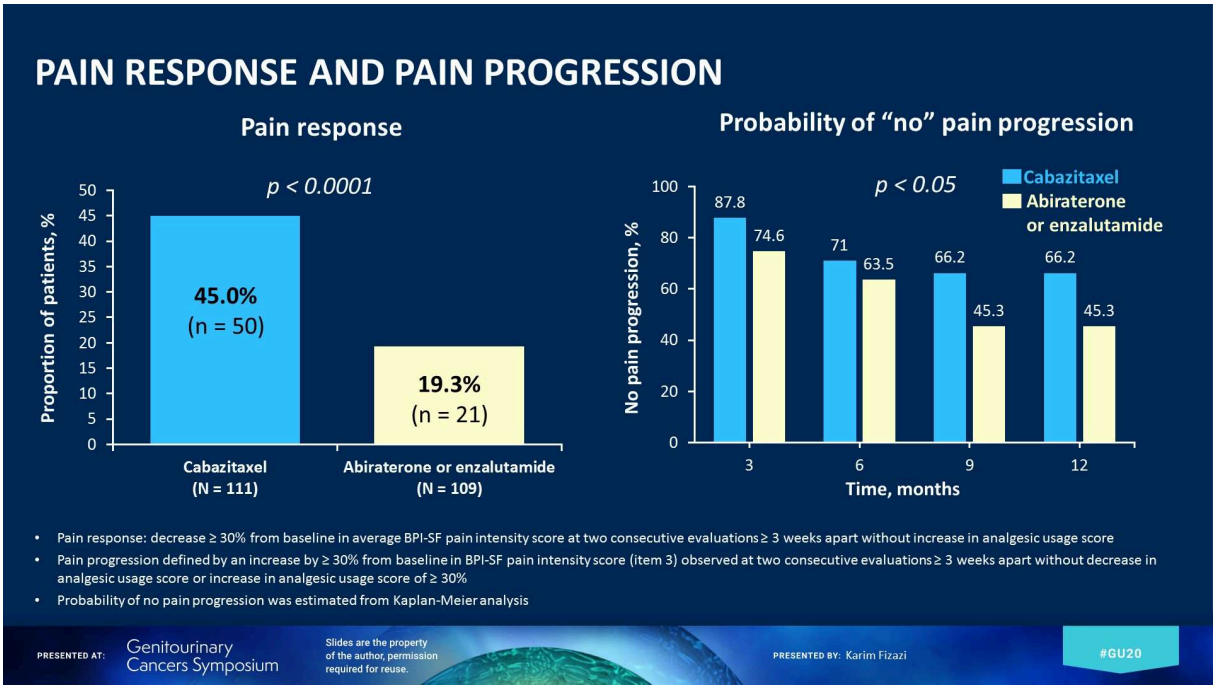
No. at Risk								
Cabazitaxel	129	122	96	77	51	21	8	2
Androgen-signaling–targeted inhibitor	126	116	88	64	39	11	3	0

- **Cabazitaxel is effective!**

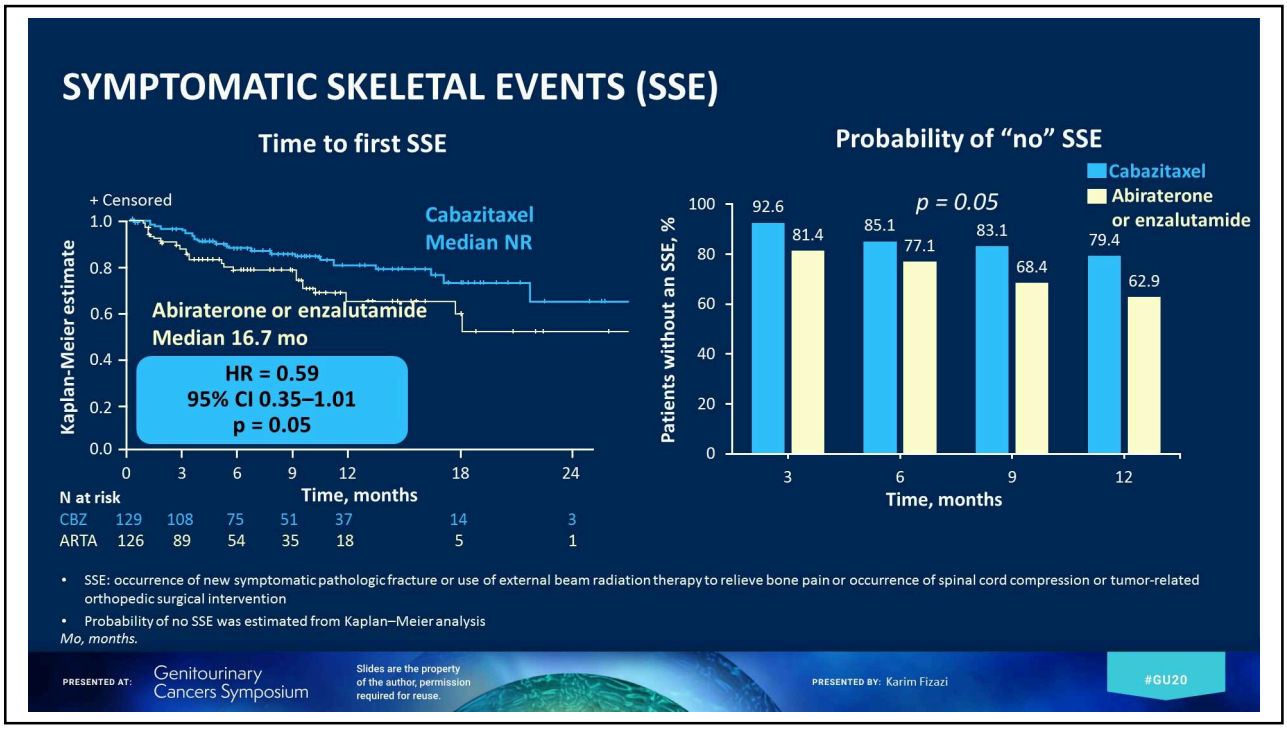
de Wit R, et al. *N Engl J Med*. 2019;381:2506-2518.

57

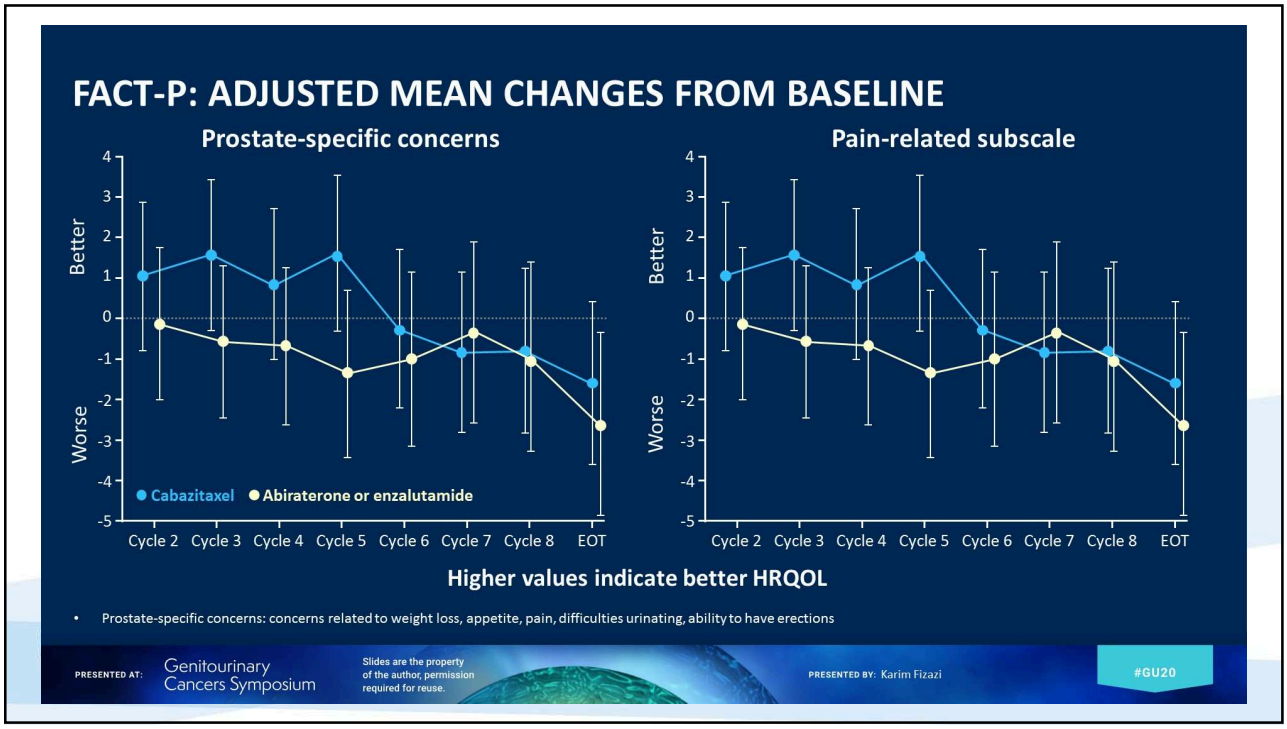
PAIN RESPONSE AND PAIN PROGRESSION



58



59



60

CARD - Safety

Patients, n (%)	Cabazitaxel (N = 126)	Abiraterone or enzalutamide (N = 124)
Any AE	124 (98.4)	117 (94.4)
Any grade ≥ 3 AE	71 (56.3)	65 (52.4)
Serious AE	49 (38.9)	48 (38.7)
AE leading to treatment discontinuation	25 (19.8)	11 (8.9)
AE leading to death*	7 (5.6)	14 (11.3)

*During treatment emergent AE period (from randomization to 30 days after last treatment administration).

American Urological Association Education & Research, Inc.

SUO Society of Urologic Oncology, Inc.

De Wit R, et al. 2019 ESMO. Abstract LBA13.
De Wit R, et al. *N Engl J Med*. 2019;381:2506-2518.

61

CARD - Safety

Patients, n (%)	Cabazitaxel (N = 126)	Abiraterone or enzalutamide (N = 124)
Any AE	124 (98.4)	117 (94.4)
Any grade ≥ 3 AE	71 (56.3)	65 (52.4)
Serious AE	49 (38.9)	48 (38.7)
AE leading to treatment discontinuation	25 (19.8)	11 (8.9)
AE leading to death*	7 (5.6)	14 (11.3)

*During treatment emergent AE period (from randomization to 30 days after last treatment administration).

American Urological Association Education & Research, Inc.

SUO Society of Urologic Oncology, Inc.

De Wit R, et al. 2019 ESMO. Abstract LBA13.
De Wit R, et al. *N Engl J Med*. 2019;381:2506-2518.

62

Key Summary Points

- There are 5 classes of FDA approved therapies that improve survival for men with metastatic castration-resistant prostate cancer (mCRPC)
  - Sequencing of abiraterone and enzalutamide has poor to no response rates for the second agent
  - ^{177}Lu PSMA 617 now FDA approved after ARPI both before and after docetaxel.
    - Requires PSMA PET for eligibility
  - Germline and somatic testing of patients with CRPC is required for PARPi eligibility
- Repeat biopsies if progression is unusual in distribution, PSA value, or if easily accessible.
  - If neuroendocrine cancer, platinum doublet chemotherapy is standard of care
- Cabazitaxel is an option after progression on docetaxel
- Future treatment strategies will likely incorporate PARP inhibitor combinations, Bi-specific antibodies, Antibody drug conjugates and PSMA-targeted theranostic combinations

American Urological Association Education & Research, Inc.

SUO Society of Urologic Oncology, Inc.

63