Novel Advances in Prostate Cancer

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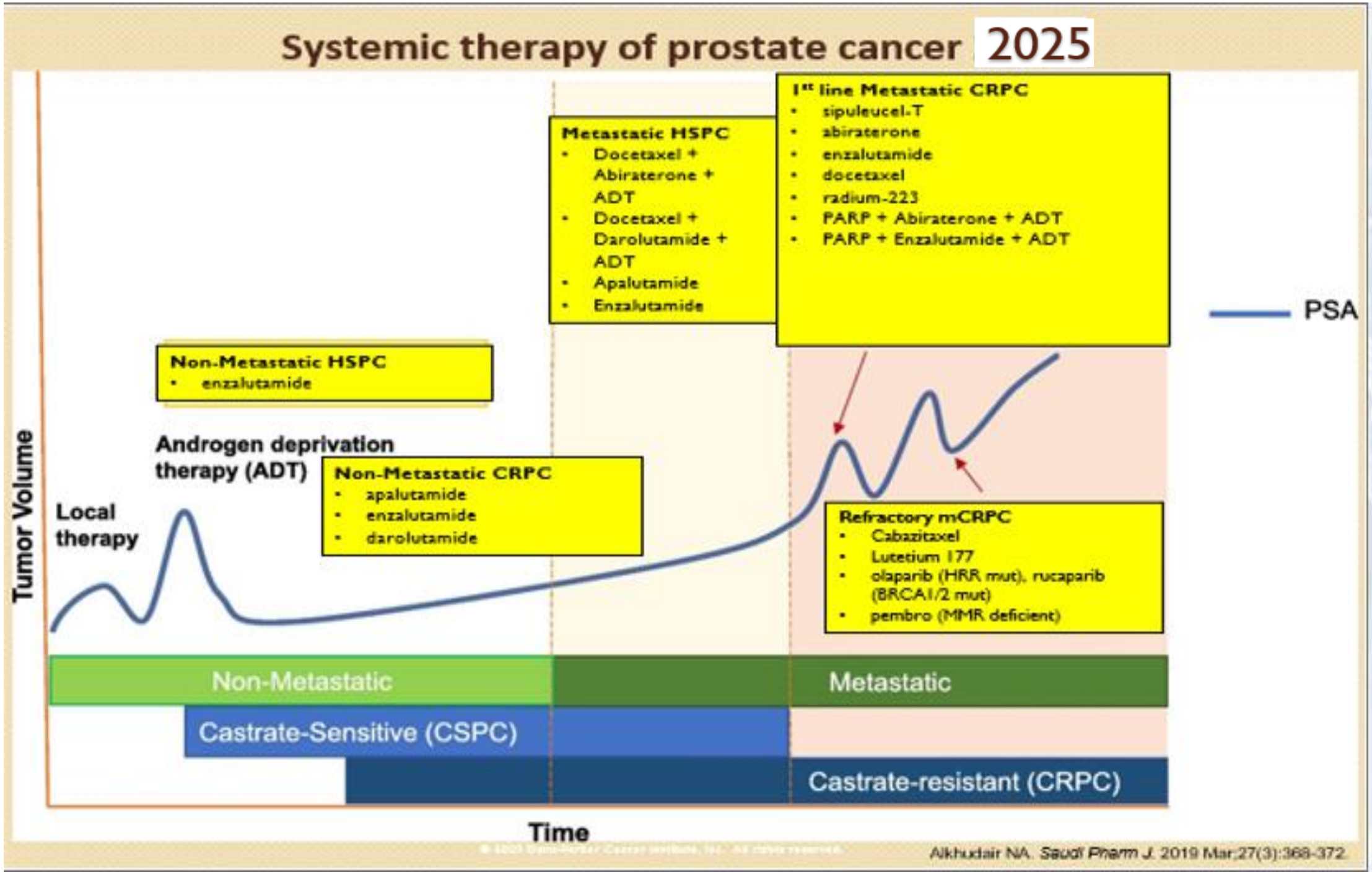
NORTON CANCER INSTITUTE


Systemic therapy of prostate cancer 2025
1st line Metastatic CRPC
• sipuleucel-T
• abiraterone
• enzalutamide
• docetaxel
• radium-223
• PARP + Abiraterone + ADT
• PARP + Enzalutamide + ADT
Metastatic HSPC
• Docetaxel + Abiraterone + ADT
• Docetaxel + Darolutamide + ADT
• Apalutamide
• Enzalutamide
PSA
Non-Metastatic HSPC
• enzalutamide
Androgen deprivation therapy (ADT)
Non-Metastatic CRPC
• apalutamide
• enzalutamide
• darolutamide
Local therapy
Refractory mCRPC
• Cabazitaxel
• Lutetium 177
• olaparib (HRR mut), rucaparib (BRCA1/2 mut)
• pembro (MMR deficient)
Tumor Volume
Non-Metastatic
Metastatic
Castrate-Sensitive (CSPC)
Castrate-resistant (CRPC)
Time
Alkhudair NA. Saudi Pharm J. 2019 Mar;27(3):368-372.

Todays Agenda

1. Doublet vs Triplet Therapy mHSPC (ESMO 2024)
2. PARP inhibitor for unselected patient population? (ASCO GU 2025)
3. Lutetium 177 update (ASCO 2024)
4. New Standard of Care in mCRPC? (ESMO 2024)

Prostate Cancer Classification

High Volume
- Visceral
- Greater than 3 bone lesions with 1 extra-axial

Newly-diagnosed
Any of:
- Metastatic
- Node-Positive
- ≥2 of: Stage T3/4, PSA≥40ng/ml, Gleason 8-10

Relapsing after previous RP or RT with ≥1 of:
- PSA ≥4ng/ml and rising with doubling time <6m
- PSA ≥20ng/ml
- Node-positive
- Metastatic

High Risk
Gleason 8-10
At least 3 bone lesion
Measurable visceral lesions

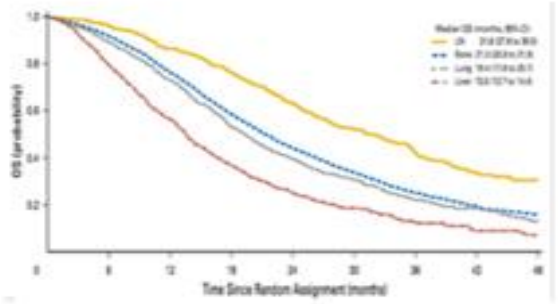
All patients
- Fit for all protocol treatment
- Fit for follow-up
- WHO performance status 0-2
- Written informed consent

Full criteria
www.stampedetrial.org

Synchronous
Patients diagnosed with a primary prostate cancer and metastases simultaneously

Metachronous
Patients diagnosed with nonmetastatic disease at initial diagnosis and develop metastases during follow up

Staging in prognostication



ADT Alone (using CHAARTED and GETUG)	Median OS
Relapsed Low Volume	~8 y
Relapsed High Volume	4.5
De Novo Low Volume	4.5
De Novo High Volume	3

Doublet vs Triplet Therapy for mHSPC?

The NEW ENGLAND JOURNAL of MEDICINE

Darolutamide and Survival in Metastatic, Hormone-Sensitive Prostate Cancer

Authors: Matthew R. Smith, M.D., Ph.D., Maha Hussain, M.D., Fred Saad, M.D., Karim Fizazi, M.D., Ph.D., Cora N. Sternberg, M.D., E. David Crawford, M.D., Evgeny Kopyltsov, M.D., Chandler H. Park, M.D., Boris Alekseev, M.D., Álvaro

Apalutamide for Metastatic, Castration-Sensitive Prostate Cancer

Authors: Kim N. Chi, M.D., Neeraj Agarwal, M.D., Anders Bjartell, M.D., Byung Ha Chung, M.D., Andrea J. Pereira de Santana Gomes, M.D., Robert Given, M.D., Álvaro Juárez Soto, M.D., Axel S. Merseburger, M.D., Mustafa Özgüroğlu,

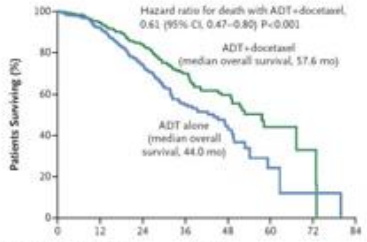
Abiraterone plus Prednisone in Metastatic, Castration-Sensitive Prostate Cancer

Authors: Karim Fizazi, M.D., Ph.D., NamPhuong Tran, M.D., Luis Fein, M.D., Nobuaki Matsubara, M.D., Alfredo Rodriguez-Antolin, M.D., Ph.D., Boris Y. Alekseev, M.D., Mustafa Özgüroğlu, M.D., Dingwei Ye, M.D., Susan Feyerabend,

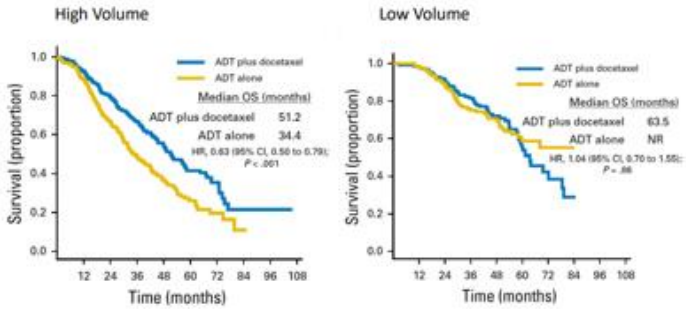
Enzalutamide with Standard First-Line Therapy in Metastatic Prostate Cancer

Authors: Ian D. Davis, M.B., B.S., Ph.D., Andrew J. Martin, Ph.D., Martin R. Stockler, M.B., B.S., Stephen Begbie, M.B., B.S., Kim N. Chi, M.D., Simon Chowdhury, M.B., B.S., Ph.D., Xanthi Coskinas, M.Med.Sc., Mark Frydenberg, M.B., B.S.,

Historical Data: CHAARTED Study

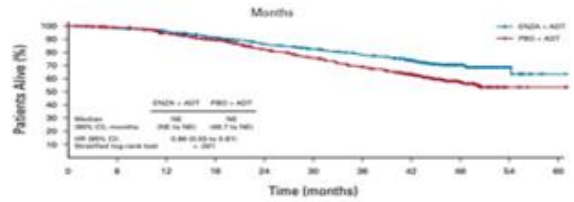


Sweeney et al (2015) *N Engl J Med 373*: 737-46

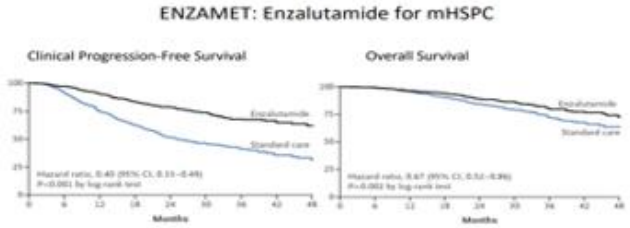


Kyriakopoulos et al (2018) *J Clin Oncol 36*: 1080-0187

ARCHES and ENZAMET

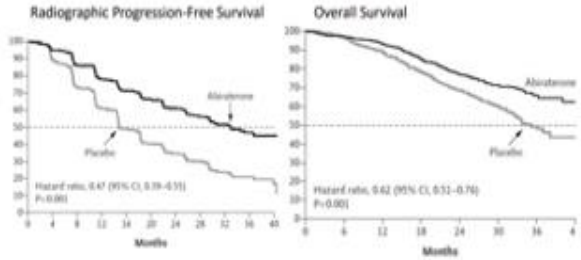


Armstrong et al (2019) *J Clin Oncol 37*: 2974-2986; Armstrong et al (2022) *J Clin Oncol* DOI: 10.1200/JC



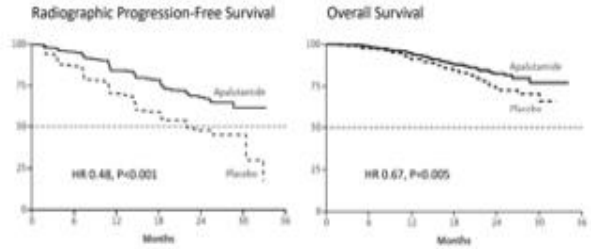
Davis et al (2019) *N Engl J Med 381*: 121-131

LATITUDE: Abiraterone Acetate for mHSPC



Fizazi et al (2017) *N Engl J Med 377*: 352-60

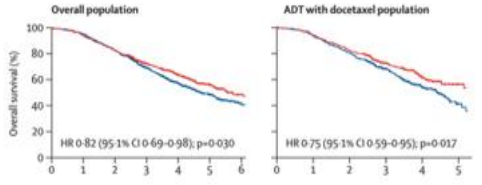
TITAN: Apalutamide for mHSPC



Chi et al (2019) *N Engl J Med 381*: 13-24

Triplet Therapy

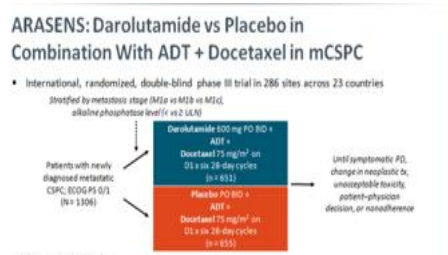
PEACE -1



Fizazi et al (2022) *Lancet* https://doi.org/10.1016/ S0140-6736(22)00367-1

ARASENS: Darolutamide vs Placebo in Combination With ADT + Docetaxel in mCSPC

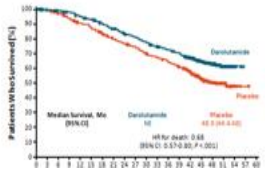
- International, randomized, double-blind phase III trial in 286 sites across 23 countries



- **Primary endpoint:** OS
- **Secondary endpoints tested hierarchically in this order:** time to CRPC, time to pain progression, SSE-free survival, time to first SSE, time to initiation of subsequent anticancer therapy, time to worsening of physical symptoms, time to first opioid use, safety

Overall Survival

ARASENS: OS (Primary Endpoint)



- Addition of darolutamide to ADT + docetaxel significantly reduced risk of death by 32.5% vs placebo (*P* <.001)
  - 75.6% of patients in placebo arm received subsequent life-prolonging systemic tx
- OS benefit observed across most subgroups
  - HR (95%) for those stratified

ESMO 2024 Update

BARCELONA 2024 ESMO congress

Efficacy and safety of darolutamide plus androgen-deprivation therapy in patients with metastatic hormone-sensitive prostate cancer from the phase 3 ARANOTE trial

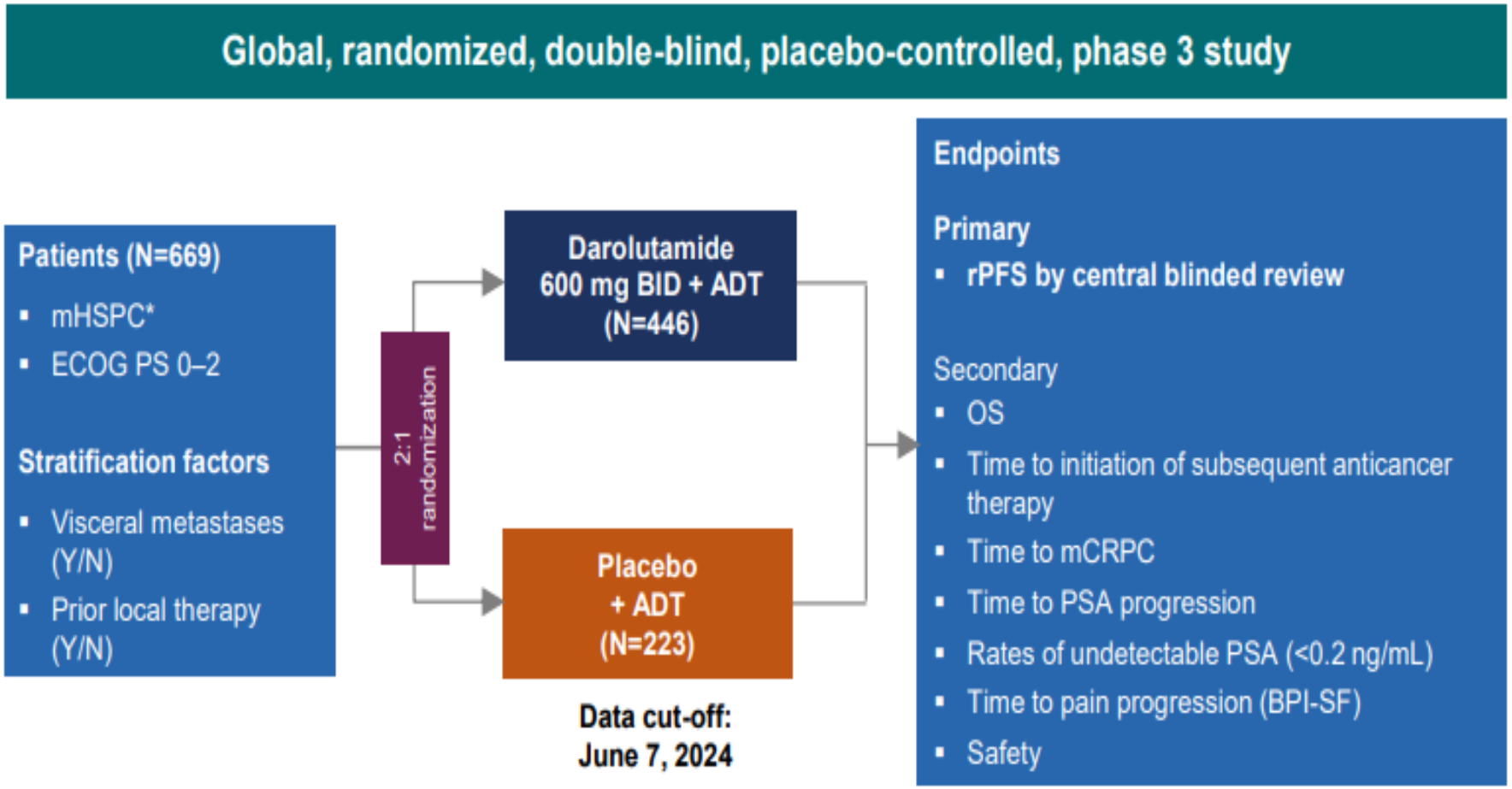
Fred Saad, CQ, MD, FRCS, FCAHS*

Centre Hospitalier de l'Université de Montréal, University of Montreal, Montreal, Quebec, Canada

*On behalf of Egils Vjaters, Neal Shore, David Olmos, Nianzeng Xing, Andrea Juliana P. de Santana Gomes, Augusto Cesar de Andrade Mota, Pamela Salman, Mindaugas Jievaltas, Albertas Ulys, Maris Jakubovskis, Evgeny Kopyltsov, Weiqing Han, Liina Nevalaita, Isabella Testa, Marie-Aude Le Berre, Iris Kuss, and Kunhi Parambath Haresh

Saad, ESMO 2024

ARANOTE Study Design



ClinicalTrials.gov: NCT04736199

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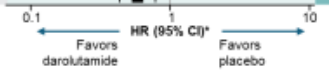
*Metastatic disease confirmed by conventional imaging method as a positive ^{99m}Tc-phosphonate bone scan or soft tissue/visceral metastases on contrast-enhanced abdominal/pelvic/chest CT or MRI scan, assessed by central review.
BPI-SF, Brief Pain Inventory-Short Form.

Saad, ESMO 2024

ARANOTE rPFS: Subgroup Analyses

Consistent benefit of darolutamide across all subgroups

rPFS		Darolutamide (n=446) Events/Patients, n/N	Darolutamide (n=446) Median, months	Placebo (n=223) Events/Patients, n/N	Placebo (n=223) Median, months	HR (95% CI)*
Overall population		128/446	NR	94/223	25.0	0.54 (0.41–0.71)
Age subgroups, years	<65	37/118	NR	32/65	14.2	0.44 (0.27–0.71)
	65–74	53/193	NR	35/96	NR	0.64 (0.41–0.98)
	75–84	29/117	NR	22/52	NR	0.48 (0.27–0.83)
	≥85	9/18	27.4	5/10	19.2	0.51 (0.16–1.66)
Baseline PSA values	< median	58/216	NR	44/111	26.0	0.55 (0.37–0.81)
	≥ median	67/220	NR	47/108	22.9	0.55 (0.38–0.80)
ECOG PS at baseline	0	61/235	NR	37/98	NR	0.55 (0.37–0.83)
	≥1	67/211	NR	57/125	22.6	0.56 (0.39–0.79)
Gleason score at initial diagnosis	Missing/not assessed	5/13	NR	4/10	13.8	
	<8	32/122	NR	30/67	22.9	0.46 (0.28–0.75)
	≥8	91/311	NR	60/146	25.1	0.58 (0.42–0.81)
Disease volume	High volume	113/315	30.2	75/157	19.2	0.60 (0.44–0.80)
	Low volume	15/131	NR	19/66	NR	0.30 (0.15–0.60)
Race	White	76/251	NR	55/125	22.2	0.52 (0.36–0.73)
	Asian	38/144	NR	24/65	25.0	0.59 (0.35–0.98)
	Black	10/41	NR	10/24	NR	0.51 (0.21–1.23)
	Other	4/10	NR	5/9	13.7	
Geographic region	Europe and RoW	56/186	NR	39/88	22.6	0.50 (0.33–0.75)
	Asia	37/141	NR	23/63	25.0	0.60 (0.35–1.01)
	Latin America	35/119	NR	32/72	25.1	0.56 (0.35–0.90)
Visceral metastases	Yes	21/53	NR	13/27	25.0	0.71 (0.35–1.41)
	No	107/393	NR	81/196	25.0	0.52 (0.39–0.69)
Prior local therapy	Yes	19/80	NR	18/40	19.5	0.34 (0.17–0.66)
	No	109/366	NR	76/183	25.0	0.59 (0.44–0.79)



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*HR and 95% CI were calculated from univariate analysis usir

TEAEs associated with ARPIs were generally similar between treatment groups

TEAEs	Darolutamide + ADT (n=445) Incidence, %	Darolutamide + ADT (n=445) EAIR/100 PY	Placebo + ADT (n=221) Incidence, %	Placebo + ADT (n=221) EAIR/100 PY
Fatigue	5.6	3.2	8.1	5.7
Mental impairment disorder	1.6	0.9	0.5	0.3
Hypertension	9.4	5.5	9.5	6.7
Cardiac arrhythmias	8.8	5.1	6.8	4.7
Coronary artery disorders	3.6	2.0	1.4	0.9
Heart failure	0.9	0.5	0.9	0.6
Falls, including accident	1.3	0.8	0.9	0.6
Bone fracture	4.0	2.3	2.3	1.5
Vasodilatation and flushing	9.2	5.6	7.2	5.0
Diabetes mellitus and hyperglycemia	9.0	5.3	9.5	6.7
Rash	4.3	2.4	3.6	2.4

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EAIR, exposure-adjusted incidence rate; PY, patient years.

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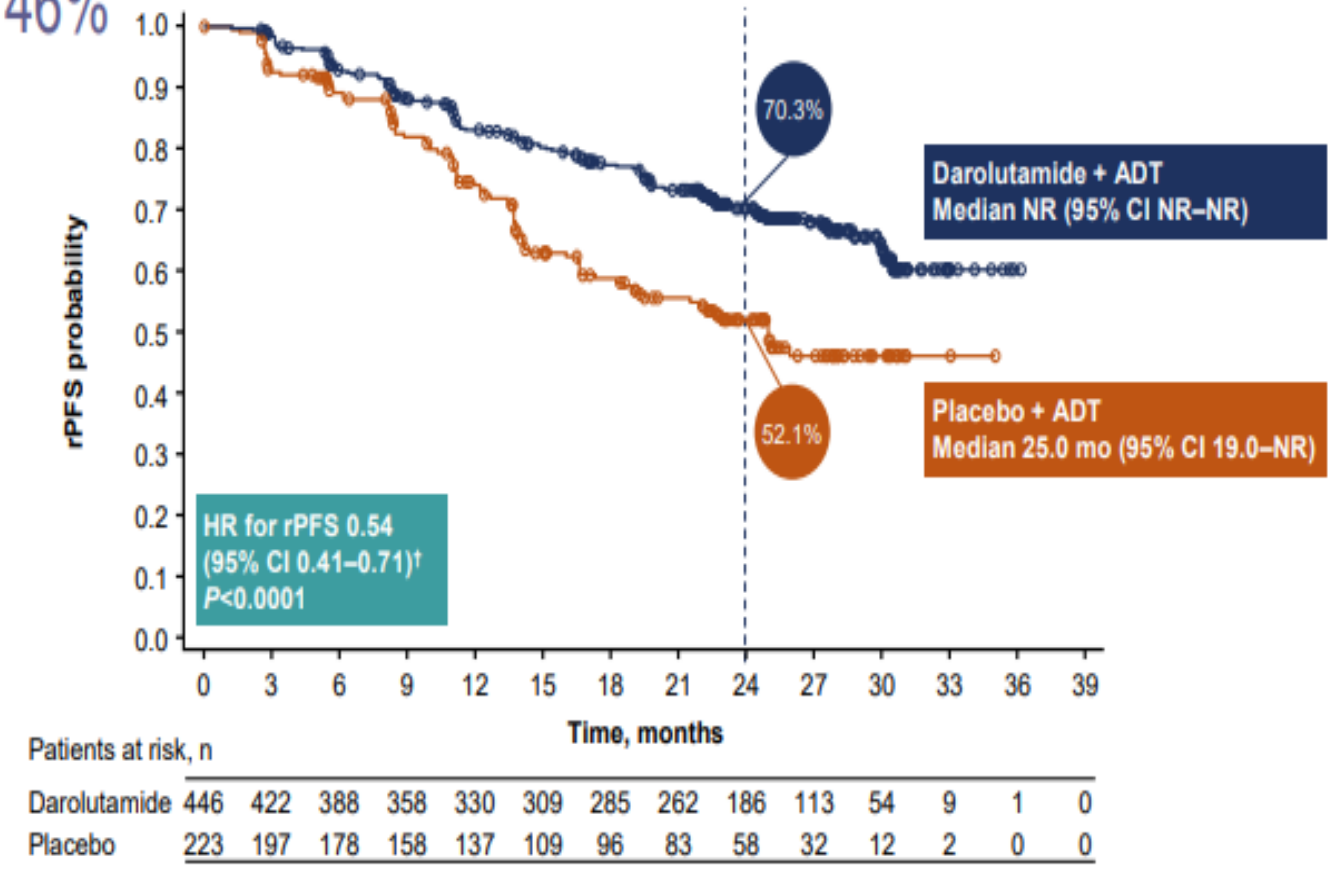
ARANOTE Primary Endpoint: rPFS*

Darolutamide significantly reduced the risk of radiological progression or death by 46%



Patients at risk, n

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

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Median follow-up: darolutamide group 25.3 months; placebo group 25.0 months

*Primary analysis occurred after 222 events (darolutamide 128; placebo 94).

†HR and 95% CI were calculated using the Cox model stratified on visceral metastases (Y/N) and prior therapy (Y/N).

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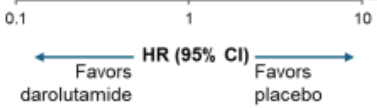
Darolutamide showed a benefit across all secondary endpoints

Endpoint	Darolutamide (n=446)		Placebo (n=223)		Stratified HR (95% CI)
	n (%)	Median, months	n (%)	Median, months	
OS*	103 (23.1)	NR	60 (26.9)	NR	0.81 (0.59–1.12)
Time to mCRPC	154 (34.5)	NR	143 (64.1)	13.8	0.40 (0.32–0.51)
Time to PSA progression	93 (20.9)	NR	108 (48.4)	16.8	0.31 (0.23–0.41)
Time to initiation of subsequent systemic therapy for prostate cancer	68 (15.2)	NR	74 (33.2)	NR	0.40 (0.29–0.56)
Time to pain progression	124 (27.8)	NR	79 (35.4)	29.9	0.72 (0.54–0.96)



*At the time of primary analysis, OS data are immature.

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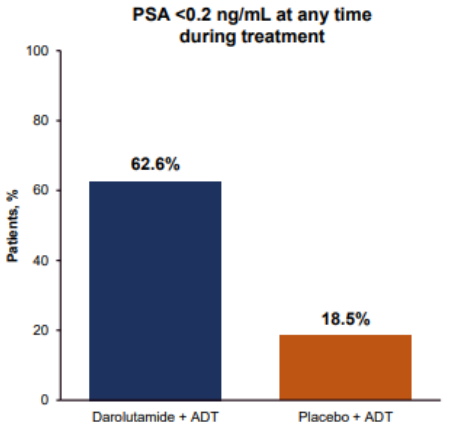
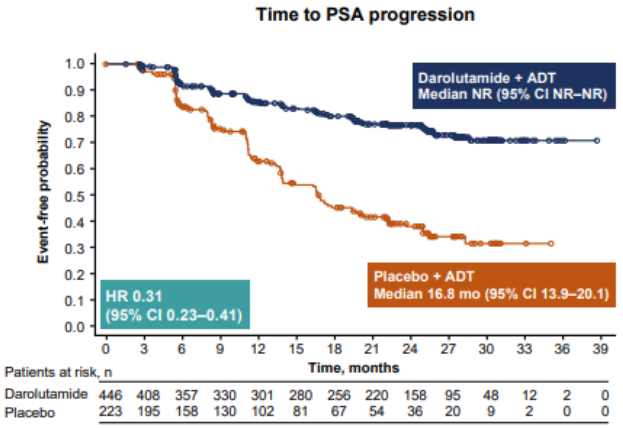
Darolutamide showed a higher rate of PSA <0.2 ng/mL and delayed time to PSA progression





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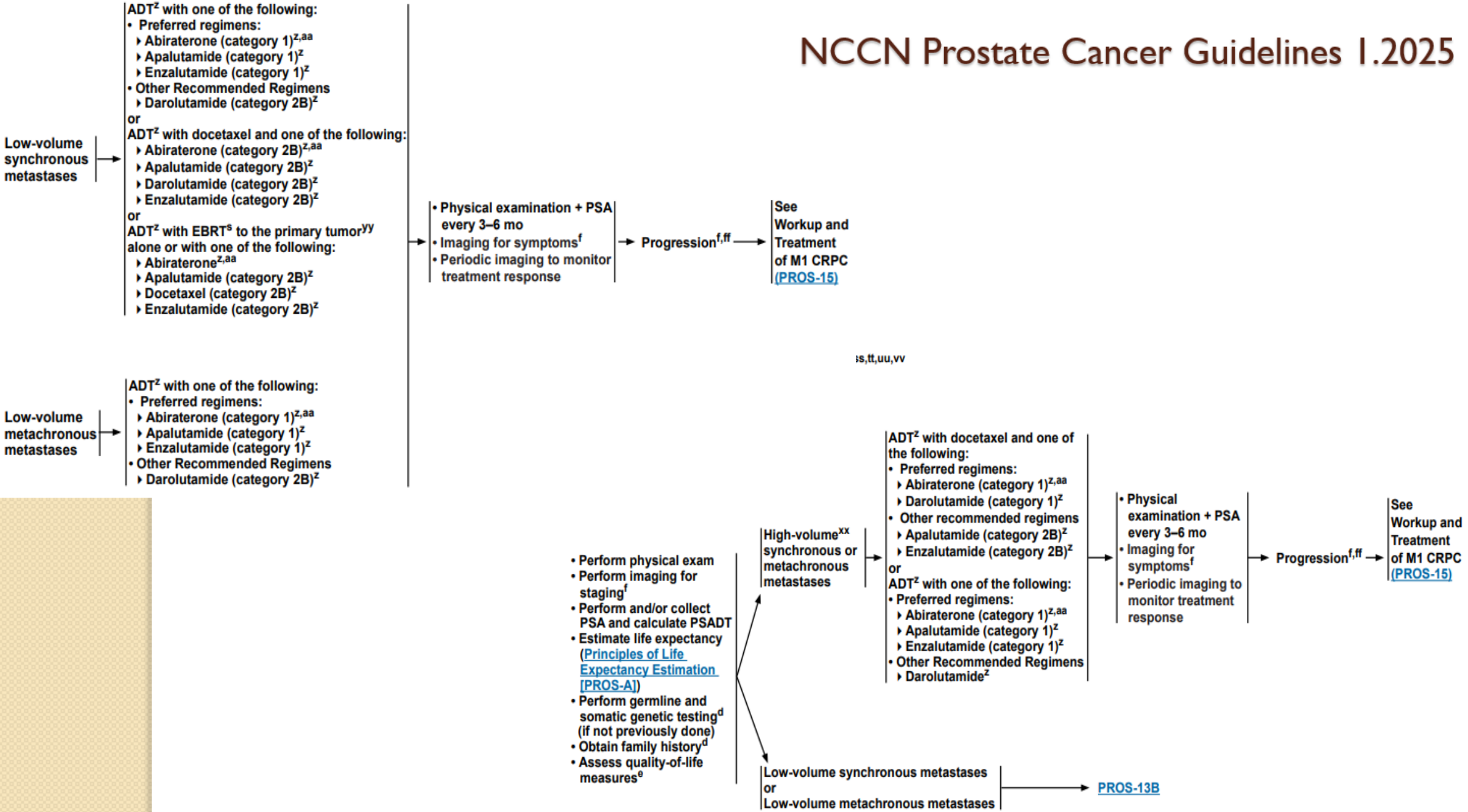
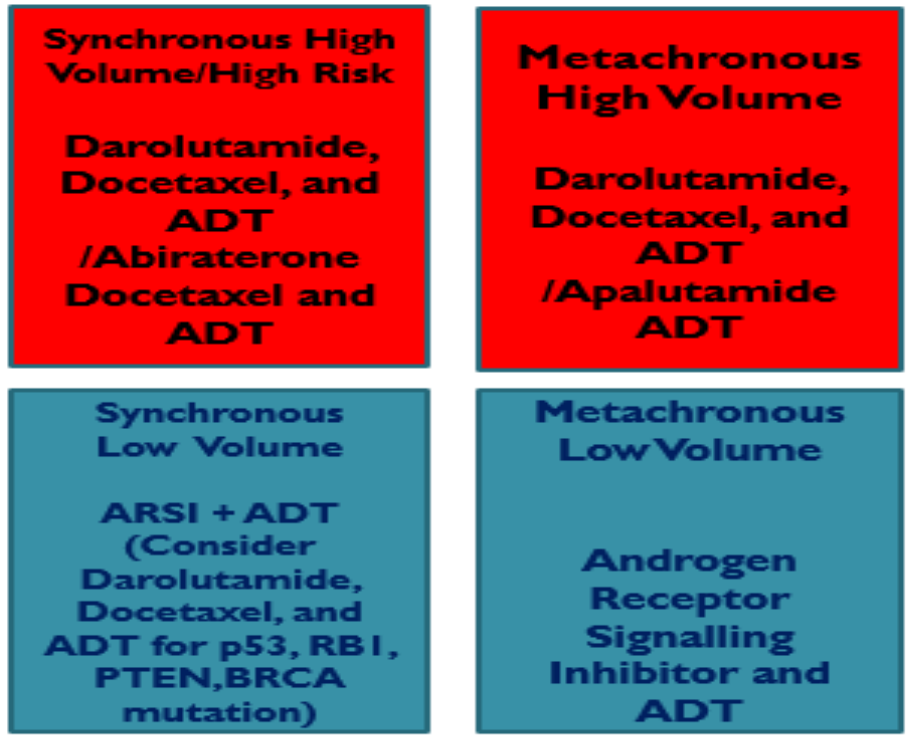
NCCN Prostate Cancer Guidelines 1.2025



What do I do in my practice?

- Doublet therapy
  - 1. Older patients (Will consider monotherapy Firmagon/Relugolix for over 80)
  - 2. Patients with metastatic lung disease
  - 3. Somatic mutations with SPOP mutation
  - 4. Don't forget about Abiraterone/ADT. Can add Taxotere later.

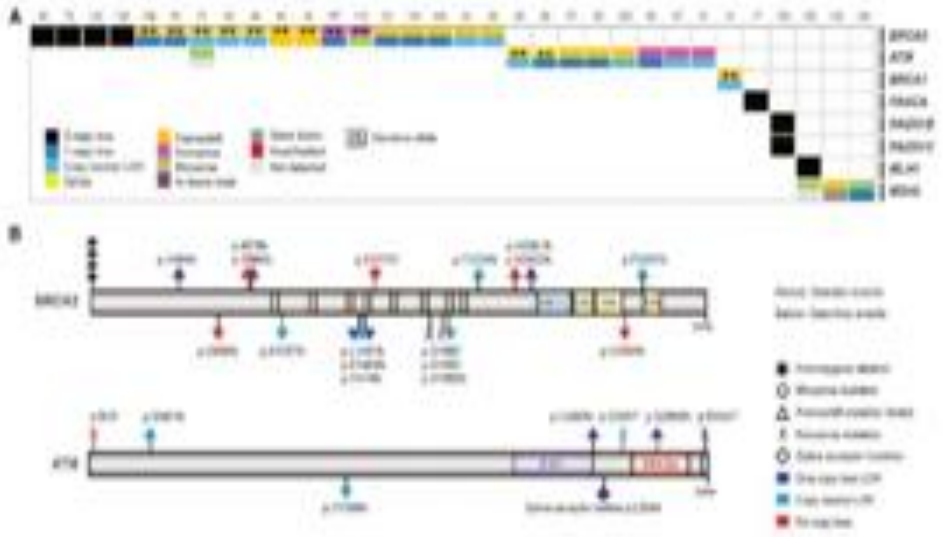
- Triplet therapy
  - 1. Younger patients with High risk and High Volume disease
  - 2. Patients with metastatic liver disease (liver biopsy to rule out small cell)
  - 3. Somatic mutations with p53, pTEN, RB1, and BRCA2 mutations.
  - 4. Germline BRCA2 mutations with High volume.



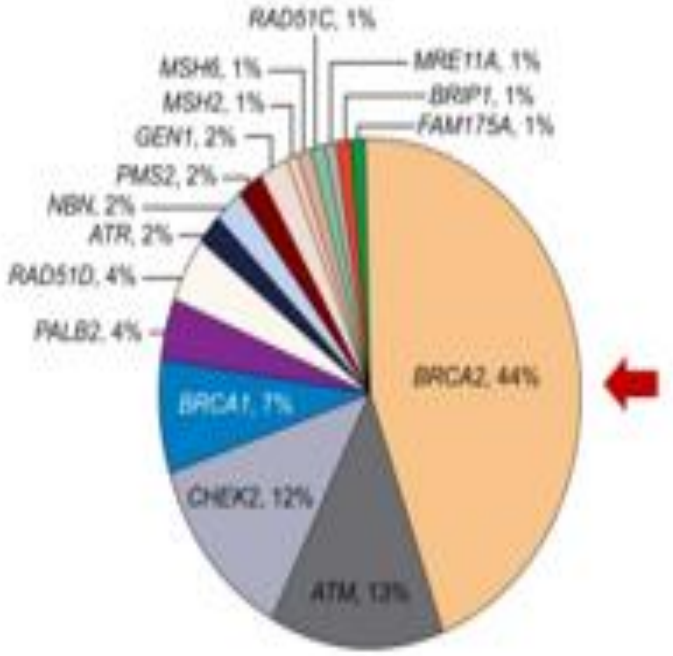
Combination vs Sequential PARP inhibitors

Somatic

- **23%** of metastatic castration-resistant prostate cancers harbor DNA repair alterations
- The frequency of DNA repair alterations **increases in metastatic disease vs. localized disease**

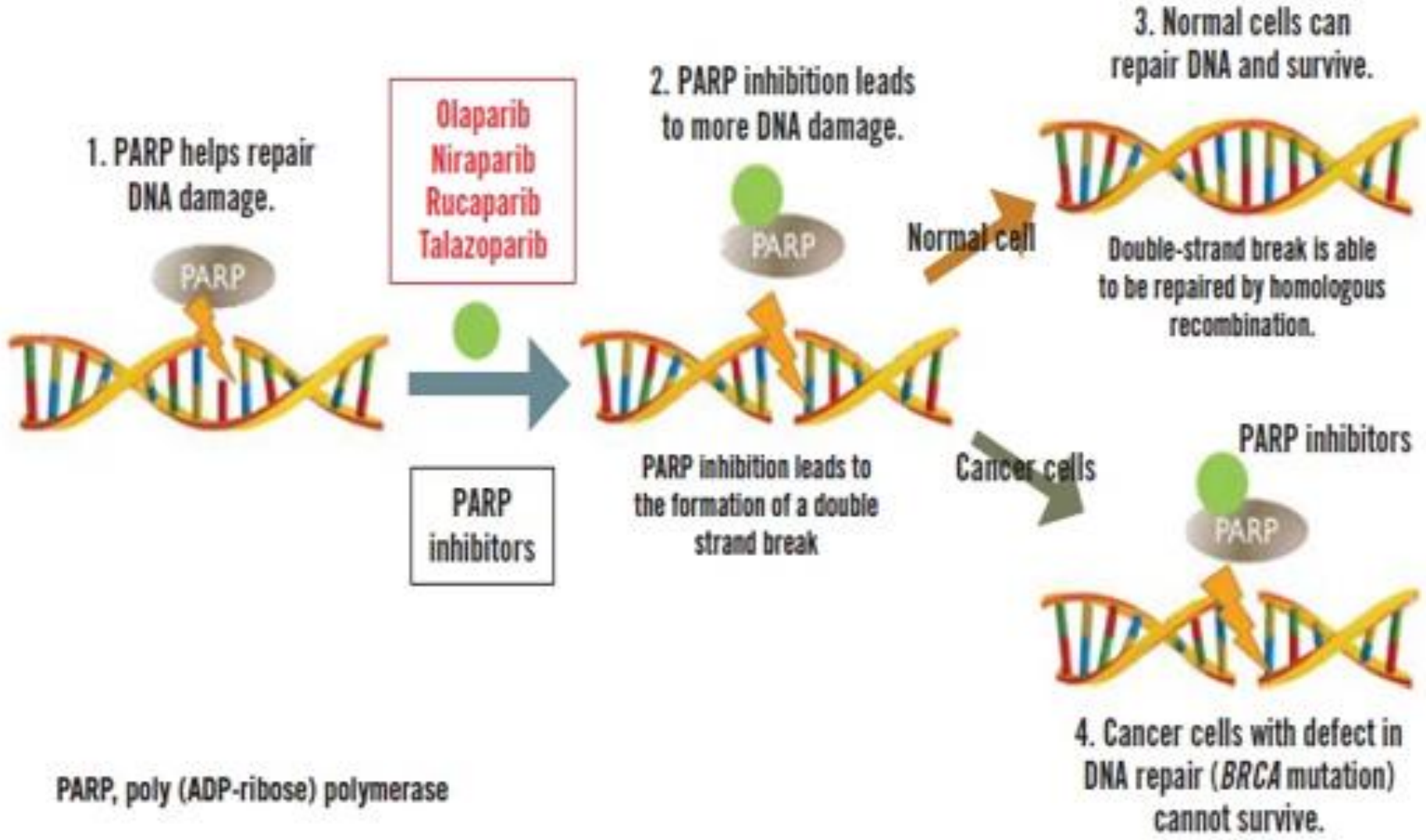


Germline



- **12%** of men with metastatic prostate cancer have a germline DNA repair defect

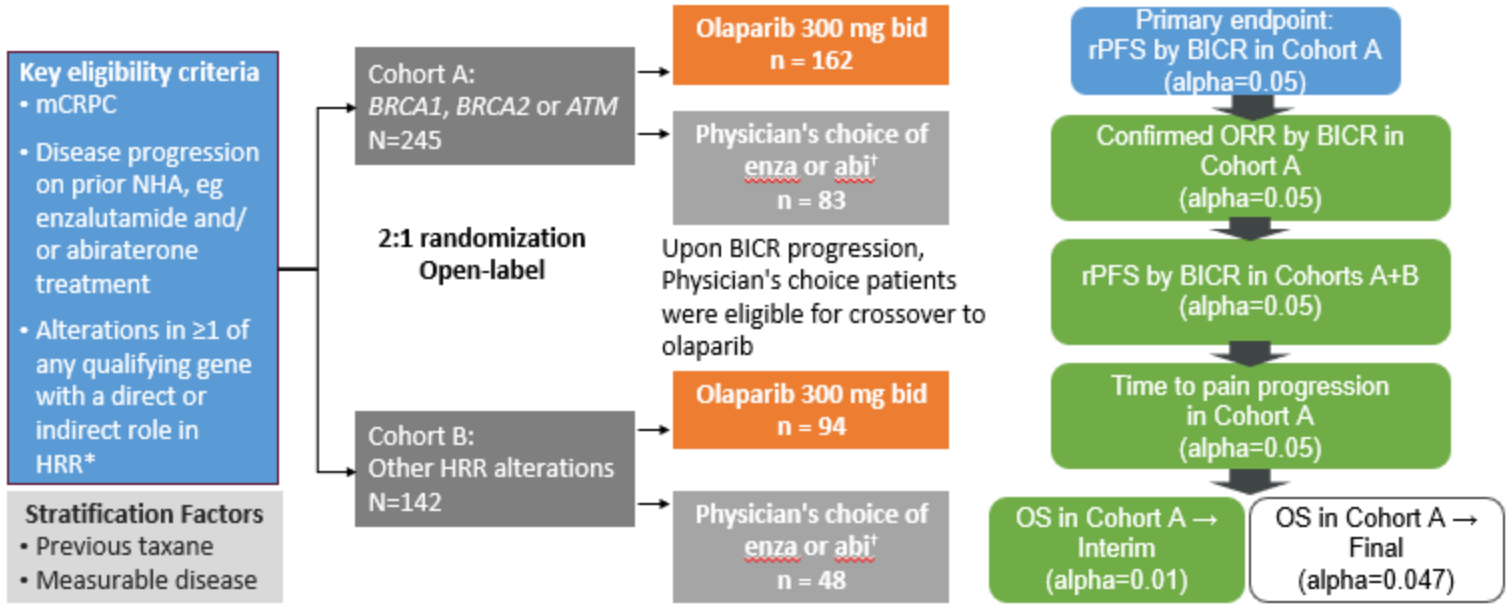
1. Robinson D, et al. Cell. 2015;161:1215-28. 2. Pritchard CC, et al. N Engl J Med. 2016;375:443-53.



PARP, poly (ADP-ribose) polymerase

Jacob et al. UCC December 2020,Volume 09, Issue 04

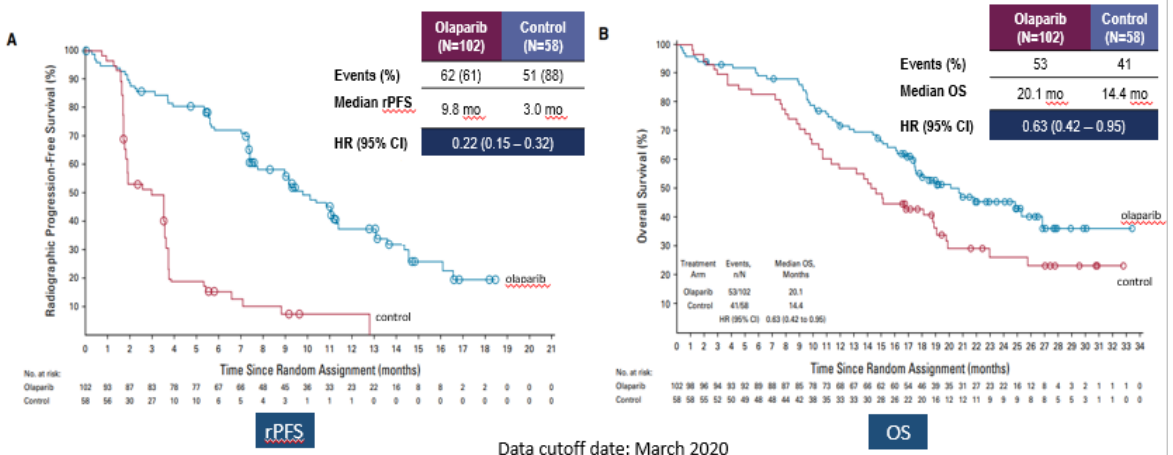
PROfound Trial: Phase 3 Trial Design



Statistical assumption for primary endpoint: Target hazard ratio = 0.53 (assumed 9.5 vs 5 months), 95% power, 2-sided 5% alpha (60% maturity, 143 events)

*BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANC, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D RAD54L; †Physician choice of either enzalutamide (160 mg qd) or abiraterone (1000 mg qd plus prednisone [5 mg bid]); BICR, blinded independent central review; bid, twice daily; ORR, objective response rate; OS, overall survival; rPFS, radiographic progression free survival.

Post-hoc Analysis of PROfound Trial: Olaparib Efficacy in Patients with *BRCA* Alterations



Data cutoff date: March 2020
Median follow-up 21.9 mo (olaparib group) and 21.0 mo (control group)

Mateo *et al.*, JCO, 2023

Androgen Receptor Pathway inhibitors w/ PARP inhibitors

ARPIs induce a phenotype resembling HRR deficiency

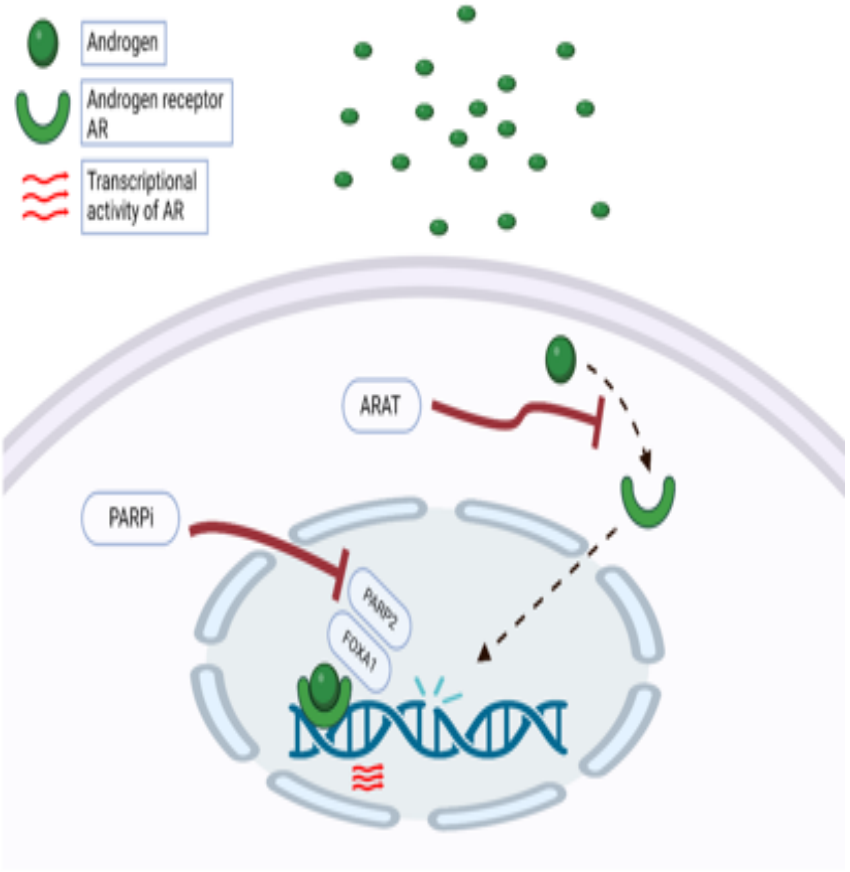
Suppressed AR function causes an upregulation of PARP

ARPIs prime tumor cells for PARP inhibition

PARP augments AR activity

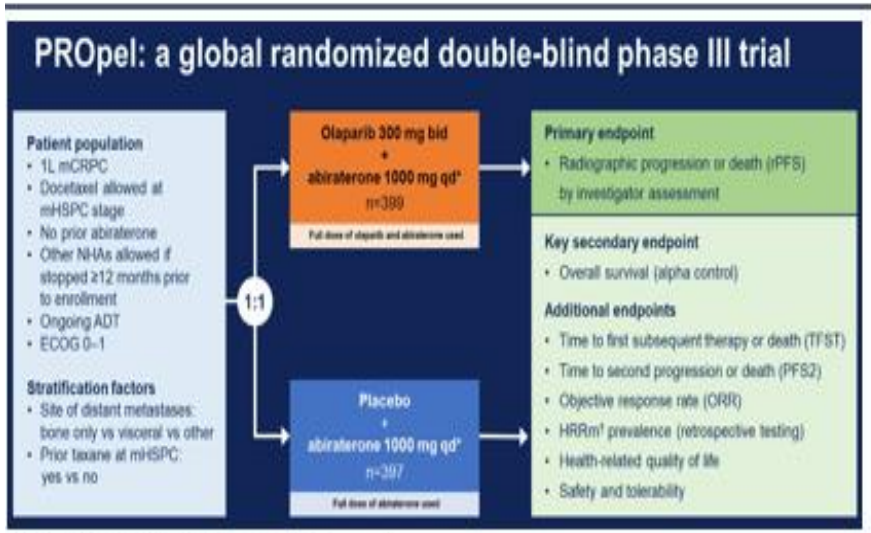
PARP inhibitors may attenuate resistance to ARPIs

PARP inhibitors extend the benefits of ARPIs

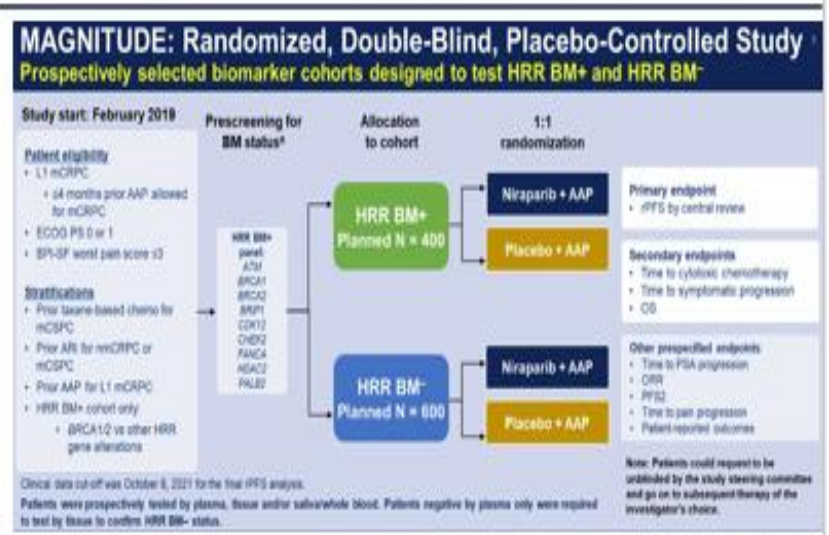


1. Adapted from Bin Gui et al. *PNAS* 2019 June, DOI https://doi.org/10.1073/pnas.1908547116
2. Agarwal N et al. *European Journal of Cancer* 2023.

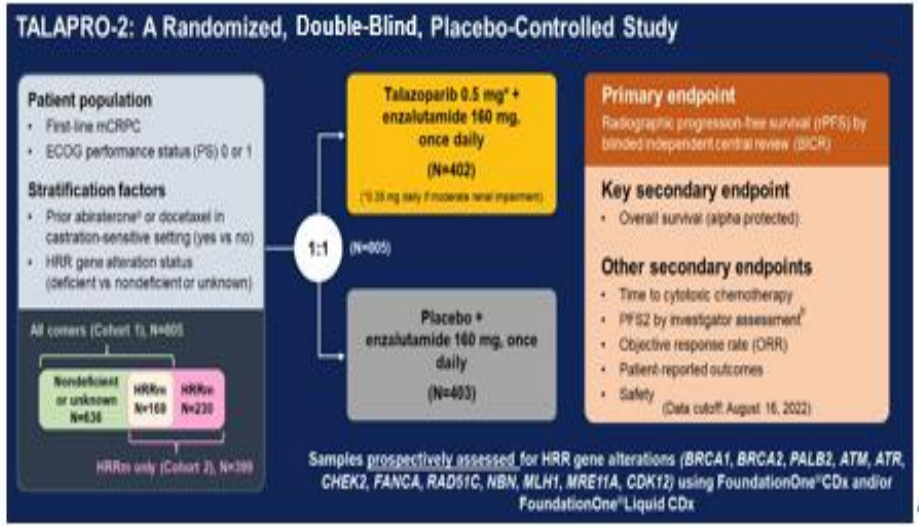
Phase 3 PARPi + ARPI Trials Design



Clarke, NW. *et al.* ***NEJM Evidence***, 2022



Chi, KN. *et al.* ***JCO***, 2022



Agarwal, N. *et al.* ***Lancet***, 2023

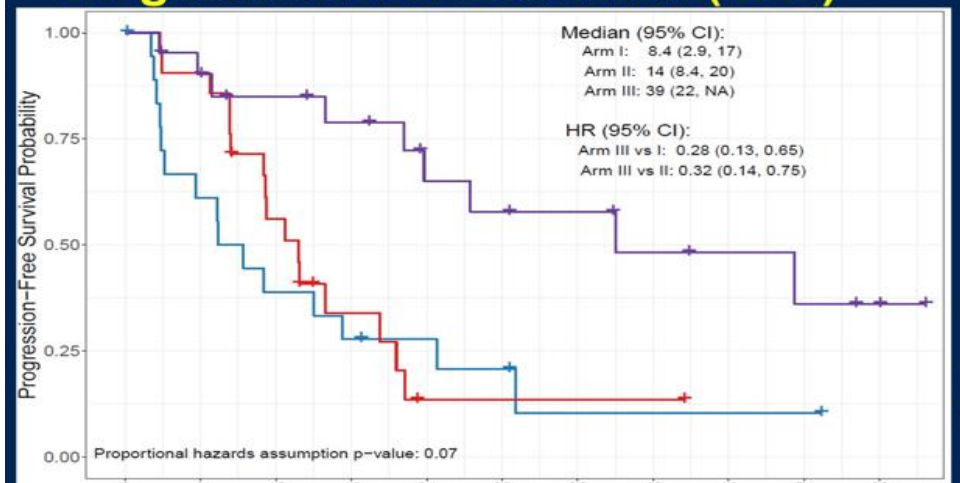
Phase 3 combination trials of PARP inhibitors with an ARPI

	PROpel (N = 796)	MAGNITUDE (N = 423)	TALAPRO-2 (Cohort 1: N = 805)	TALAPRO-2 (Cohort 2: N = 399)
Trial population mCRPC 1st line	Docetaxel / ARSI in mCSPC setting allowed (ARSI without progression and > 12 months ago)	Docetaxel / ARSI in mCSPC setting allowed ; Abiraterone in mCRPC allowed if given < 4 months	Docetaxel / Abiraterone in mCSPC setting allowed	
Design and randomization	1 : 1 randomization Abiraterone + olaparib (n = 399) vs abiraterone + placebo (n = 397)	Cohort 1: HRR cohort 1 : 1 randomization abiraterone + niraparib (n = 212) vs abiraterone + placebo (n = 211) Cohort 2: non-HRR cohort (closed prematurely because of futility)	All-comer population 1 : 1 randomization Enzalutamide + talazoparib (n = 402) vs enzalutamide + placebo (n = 403)	HRR cohort 1 : 1 randomization Enzalutamide + talazoparib (n = 200) vs enzalutamide + placebo (n = 199)
HRR analysis	Tissue or ctDNA / retrospective	100% tissue / prospective	100% tissue / prospective	99.5% tissue / prospective 0.5% ctDNA or unspecified tissue source / prospective
Primary endpoint	rPFS (investigator review)	rPFS (central review)	rPFS (central review)	rPFS (central review)
rPFS, HR (95% CI)				
All comers	HR 0.66 (0.54-0.81)	NR	HR 0.63 (0.51-0.78)	Not included
HRR -ve	HR 0.76 (0.6-0.97)	HR 1.09 (0.75-1.57)	HR 0.70 (0.54-0.89)	Not included
HRR +ve	**HR 0.50 (0.34-0.73)**	**HR 0.76 (0.60-0.97)**	**HR 0.46 (0.30-0.70)**	**HR 0.45 (0.33-0.61)**
BRCA+	**HR 0.23 (0.12-0.43)**	**HR 0.55 (0.39-0.78)**	**HR 0.23 (0.10-0.53)**	**HR 0.20 (0.11-0.36)**
ORR (all comers)	58% vs 48%	60% vs 28% (only HRR+ pts)	61.7% vs 43.9%	67% vs 40%
OS (all comers)	HR 0.81 (0.67-1)	HR 0.82 (0.60-1.10) (only for HRR+ pts)	Immature HR 0.89 (0.69-1.14)	Immature HR 0.69 (0.46-1.03)
FDA approval; EMA approval	**mCRPC with BRCA1/2 mutations; mCRPC when chemotherapy is not indicated**	**mCRPC with BRCA1/2 mutations**	**mCRPC with any HRR mutations; mCRPC when chemotherapy is not clinically indicated**	
Publication	Clarke N....Saad F. *NEJM Evidence*, 2022	Chi K....Sandhu S. *JCO*, 2023....Chi K Annals Oncol, 2023	Agarwal N....Fizazi K. *Lancet*, 2023	Fizazi K....Agarwal N. ***Nature Medicine***, 2023

1. Adapted from Bin Gui et al. *PNAS* 2019 June, DOI https://doi.org/10.1073/pnas.1908547116
2. Agarwal N et al. *European Journal of Cancer* 2023.

Combination vs Sequential PARP inhibitors?

Progression-Free Survival (PFS)



PFS: time from randomization until first progression or death.

Proportional hazards assumption was not met for Arm I versus II comparison.

Hussain, ASCO GU 2024

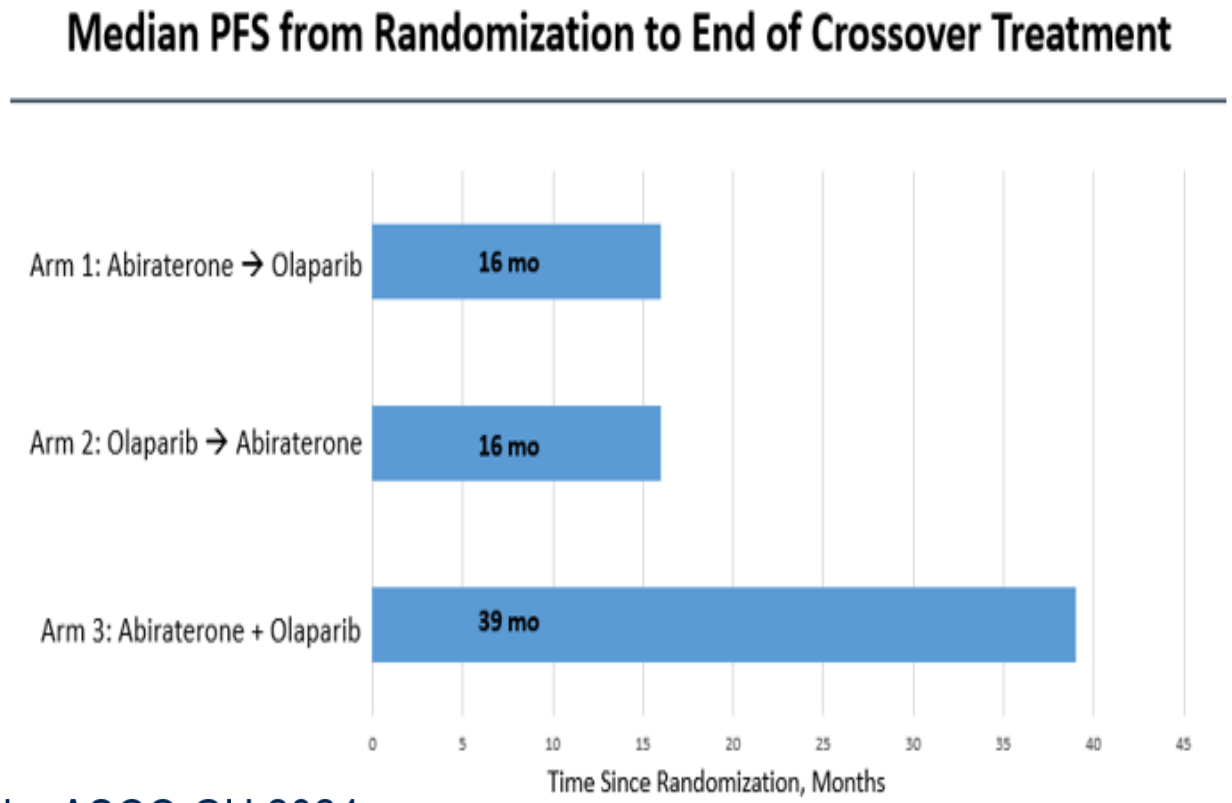
Efficacy Summary

- Arm I: abiraterone (1000 mg qd) + prednisone (5mg bid),
- Arm II: olaparib (300 mg bid)
- Arm III: olaparib + abiraterone/prednisone

	Arm I (n = 19)	Arm II (n = 21)	Arm III (n = 21)
Median PFS, months (95% CI)	**8.4 (2.9, 17)**	**14 (8.4, 20)**	**39 (22, NR)**
Objective RR, % (95% CI)	**22** (6.4, 48)	**14** (3, 36)	**33** (15, 57)
PSA RR, % (95% CI)	**61** (36, 83)	**67** (43, 85)	**95** (76, 100)
Undetectable PSA RR, % (95% CI)	**17** (3.6, 41)	**14** (3, 36)	**33** (15, 57)

NR, Not Reached

My Practice
Combination therapy preferred based on this practice changing study



Hussain, ASCO GU 2024

Presentation number LBA18

ASCO Genitourinary Cancers Symposium

Overall survival with talazoparib plus enzalutamide in unselected patients with metastatic castration-resistant prostate cancer in the Phase 3 TALAPRO-2 trial

Neeraj Agarwal,[1] Arun A. Azad,[2] Joan Carles,[3] Andre P. Fay,[4] Nobuaki Matsubara,[5] Cezary Szczylik,[6,7] Ugo De Giorgi,[8] Jae Young Joung,[9] Peter C. C. Fong,[10,11] Eric Voog,[12] Robert J. Jones,[13] Neal D. Shore,[14] Curtis Dunshee,[15] Stefanie Zschäbitz,[16] Jan Oldenburg,[17] Xun Lin,[18] Cynthia G. Healy,[19] Matko Kalac,[20] Dana Kennedy,[21] Karim Fizazi[22]

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ClinicalTrials.gov identifier: NCT03395197.
This study was sponsored by Pfizer Inc. Astellas Pharma Inc. provided enzalutamide.

TALAPRO-2: Trial Design

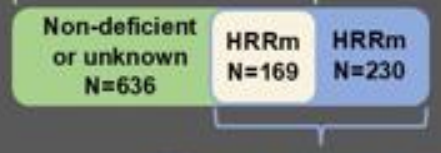
HRR-deficient cohort is being presented today in poster D15
Statistically significant and clinically meaningful improvement in OS

Patient population
- 1L mCRPC
- ECOG 0 or 1
- Ongoing androgen deprivation therapy

Stratification factors
- Prior abiraterone[a] or docetaxel for CSPC (yes vs no)
- HRR gene alteration status (deficient vs non-deficient or unknown)[b]

Sequential enrollment in two cohorts:

Unselected (Cohort 1), N=805



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Talazoparib + enzalutamide (N=402)

Unselected Cohort 1 (N=805)

Placebo + enzalutamide (N=403)

Primary endpoint
- rPFS by BICR

Key secondary endpoint
- OS (alpha protected)

Other secondary endpoints
- Time to cytotoxic chemotherapy
- PFS2
- ORR
- Patient-reported outcomes
- Safety

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

Analysis timeline: (unselected)

DCO1: Aug 16, 2022 rPFS (primary) → DCO2: March 28, 2023 OS (interim) → DCO3: Sept 3, 2024 OS (final) current

[a]Prior orteronel was received by two patients in each treatment arm in Cohort 1 and one patient in each treatment arm in Cohort 2. [b]Unselected cohort only.
BICR=blinded independent central review; CSPC=castration-sensitive prostate cancer; DCO=data cutoff; ORR=objective response rate; PFS2=time to second progression or death.

Baseline Characteristics[1]

		Talazoparib + Enzalutamide (N=402)	Placebo + Enzalutamide (N=403)
Age, median (range), years		71 (41–90)	71 (36–91)
Race, n (%)	White	243 (60.4)	255 (63.3)
	Black/African American	11 (2.7)	5 (1.2)
	Asian	127 (31.6)	120 (29.8)
	Native Hawaiian/Pacific Islander	2 (0.5)	1 (0.2)
	Not reported	19 (4.7)	21 (5.2)
	Multiracial	0	1 (0.2)
Ethnicity, n (%)	Hispanic/Latino/Spanish Origin	39 (9.7)	46 (11.4)
	Not Hispanic/Latino/Spanish Origin	341 (84.8)	327 (81.1)
	Not reported	22 (5.5)	30 (7.4)
PSA, median (range), ng/mL		18.2 (0.1–2796.0)	16.2 (0.1–2285.1)
Disease site, n (%)	Bone	349 (86.8)	342 (84.9)
	Lymph node	147 (36.6)	167 (41.4)
	Visceral (lung)	45 (11.2)	61 (15.1)
	Visceral (liver)	12 (3.0)	16 (4.0)
ECOG PS 0/1, n (%)		259 (64.4)/143 (35.6)	271 (67.2)/132 (32.8)
Prior abiraterone[a] or docetaxel, n (%)		109 (27.1)	110 (27.3)
	Abiraterone	21 (5.2)	25 (6.2)
	Docetaxel	86 (21.4)	93 (23.1)
HRR gene alteration status[b], n (%)	Deficient	85 (21.1)	84 (20.8)
	Non-deficient or unknown	317 (78.9)	319 (79.2)

[a]Two patients in each treatment arm received prior orteronel. [b]By randomization stratification.
Data cutoff: August 16, 2022. 1. Agarwal N, et al. *Lancet*. 2023;402:291-303.

Source of Tumor DNA for Assessment and Baseline HRR Gene Alterations

Tissue source for prospective HRR gene alteration testing, n (%)	Talazoparib + Enzalutamide (N=402)	Placebo + Enzalutamide (N=403)
Tumor tissue	**402 (100.0)**	**403 (100.0)**
Tumor tissue and blood (circulating tumor DNA)	**57 (14.2)**	**58 (14.4)**

BRCA1/2 gene alterations were detected in 7.3% of patients across both arms

HRR gene alterations by prospective tumor tissue testing, n (%)[1]	Talazoparib + Enzalutamide (N=402)	Placebo + Enzalutamide (N=403)
1 or more alterations in the corresponding gene	**85 (21.1)**	**82 (20.3)**
CDK12	**23 (5.7)**	**29 (7.2)**
BRCA2	**23 (5.7)**	**28 (6.9)**
ATM	**23 (5.7)**	**14 (3.5)**
CHEK2	**6 (1.5)**	**5 (1.2)**
BRCA1	**5 (1.2)**	**4 (1.0)**
Other (*ATR*, *FANCA*, *MLH1*, *MRE11A*, *NBN*, *PALB2*, *RAD51C*)	**14 (3.5)**	**13 (3.2)**

Data cutoff: August 16, 2022. 1. Agarwal N, et al. *Lancet*. 2023;402:291-303.

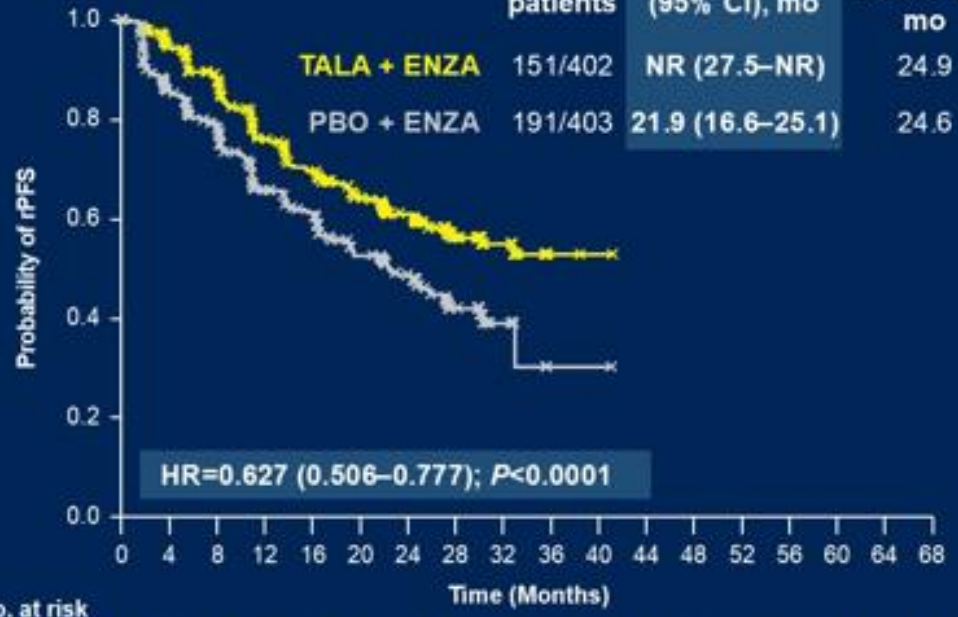
TALAPRO-2 Unselected

Primary Endpoint: rPFS by BICR

Statistically significant and clinically meaningful benefit maintained with ~2 years of additional follow-up

Primary analysis (DCO: Aug 16, 2022)[1]

	Events/ patients	Median rPFS (95% CI), mo	Median follow-up, mo
TALA + ENZA	151/402	NR (27.5–NR)	24.9
PBO + ENZA	191/403	21.9 (16.6–25.1)	24.6

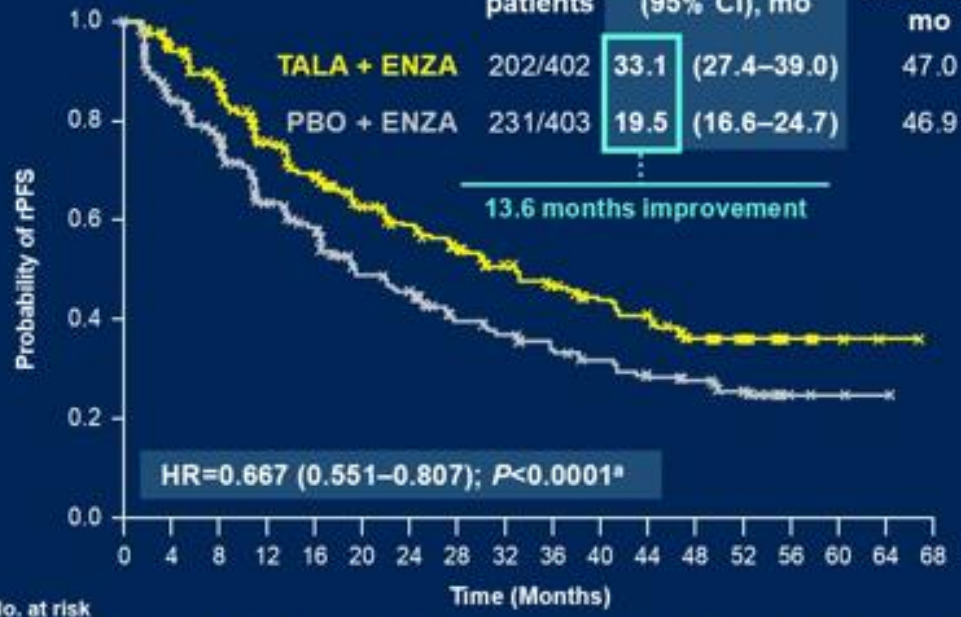


No. at risk

TALA + ENZA	402	353	318	256	226	193	136	67	29	2	1	0	0	0	0	0	0	0
PBO + ENZA	403	311	272	200	179	140	96	43	14	1	1	0	0	0	0	0	0	0

Update (DCO: Sept 3, 2024)

	Events/ patients	Median rPFS (95% CI), mo		Median follow-up, mo
TALA + ENZA	202/402	33.1	(27.4–39.0)	47.0
PBO + ENZA	231/403	19.5	(16.6–24.7)	46.9



No. at risk

TALA + ENZA	402	353	318	257	228	196	180	155	138	122	108	101	63	50	13	7	1	0
PBO + ENZA	403	312	273	201	180	138	128	100	92	81	72	66	44	35	5	2	1	0

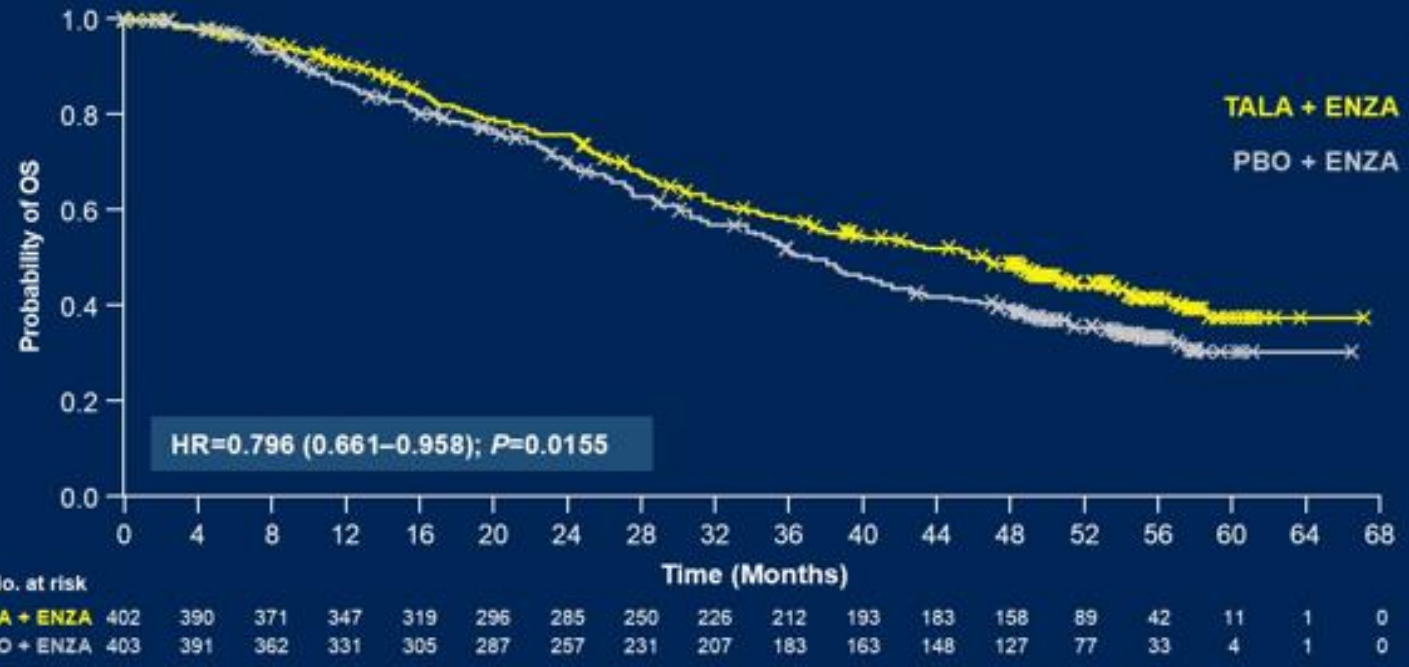
Stratified hazard ratios (HRs) and 2-sided *P* values are reported throughout this presentation unless otherwise stated.

aThe updated rPFS data are descriptive. DCO=data cutoff; ENZA=enzalutamide; NR=not reached; PBO=placebo; TALA=talazoparib. 1. Reproduced with permission from Agarwal N, et al. *Lancet*. 2023;402:291-303.

TALAPRO-2 Unselected

Overall Survival (Final Analysis)

20.4% reduction in risk of death, >8 months improvement in median OS



	Events/patients	Median OS (95% CI), mo
TALA + ENZA	211/402	45.8 (39.4–50.8)
PBO + ENZA	243/403	37.0 (34.1–40.4)

8.8 months improvement

Median follow-up for OS was 52.5 months

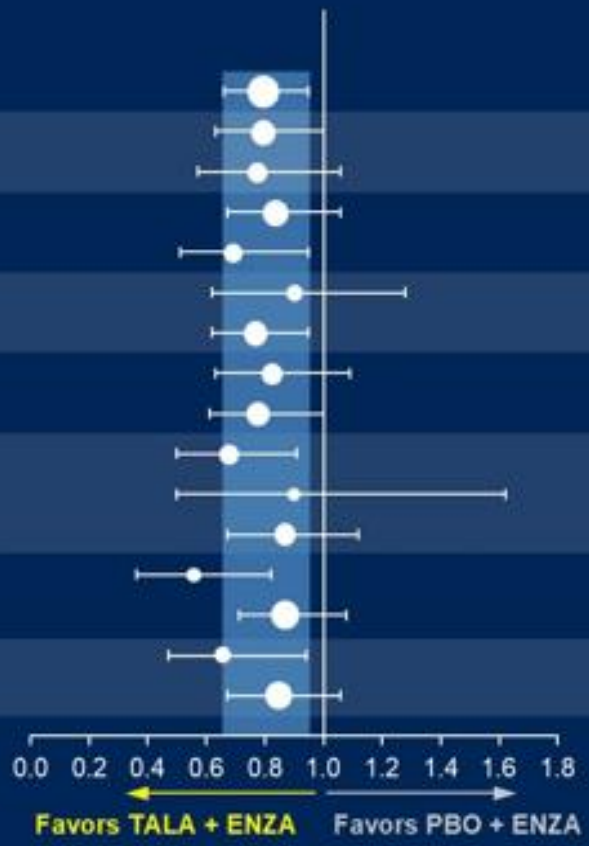
For statistical significance at the final overall survival analysis, the stratified log-rank 2-sided *P* value needed to be ≤0.022 based on a group sequential design with O'Brien-Fleming spending function.

Data cutoff: September 3, 2024.

TALAPRO-2 Unselected

Subgroup Analysis of Overall Survival

Subgroup		TALA + ENZA Events/patients	PBO + ENZA Events/patients	HR (95% CI)
Overall		211/402	243/403	0.796 (0.661–0.958)
Age, years	≥70	137/240	154/240	0.797 (0.633–1.004)
	<70	74/162	89/163	0.778 (0.571–1.059)
ECOG PS	0	134/259	156/271	0.842 (0.669–1.061)
	1	77/143	87/132	0.700 (0.514–0.952)
Gleason score	<8	56/117	60/113	0.895 (0.622–1.289)
	≥8	153/281	177/283	0.769 (0.619–0.955)
Stage at diagnosis	M0	91/172	111/185	0.828 (0.627–1.093)
	M1	118/226	129/215	0.781 (0.609–1.003)
Site of metastasis	Bone only	81/168	95/155	0.676 (0.502–0.910)
	Soft tissue only	19/48	25/57	0.900 (0.495–1.636)
	Bone and soft tissue	109/181	121/187	0.868 (0.670–1.125)
HRR status[a]	Deficient	40/85	56/84	0.542 (0.361–0.814)
	Non-deficient/unknown	171/317	187/319	0.874 (0.711–1.076)
Prior abiraterone[b] or docetaxel	Yes	55/109	74/110	0.663 (0.467–0.940)
	No	156/293	169/293	0.853 (0.686–1.060)



The HR for the overall ITT population was based on a Cox model stratified by the randomization stratification factors. For all subgroups, the HR was based on an unstratified Cox model with treatment as the only covariate. Data for the HRR-deficient cohort are presented at ASCO GU 2025 in poster D15.

[a]HRR gene alteration status (deficient vs non-deficient or unknown) by randomization stratification. [b]Includes two patients in each treatment arm who received prior orteronel.

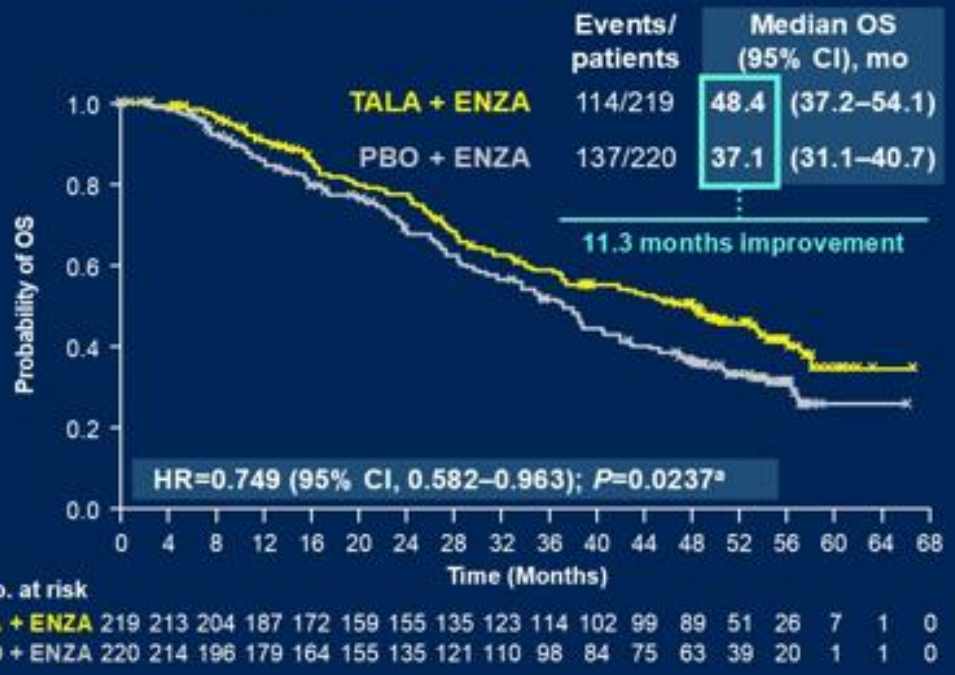
Data cutoff: September 3, 2024.

TALAPRO-2 Unselected

Overall Survival in Subgroups With No Alterations Detected by Both ctDNA and Tumor Tissue

Clinically meaningful reduction in risk of death in patients without *BRCA* or HRR alterations

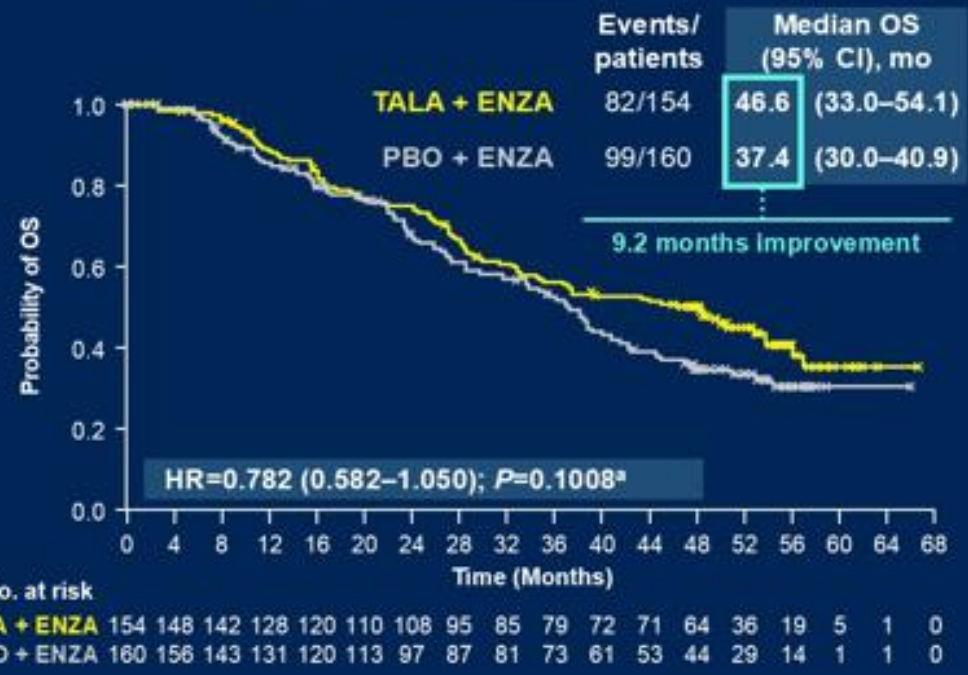
No *BRCA* alteration detected



No. at risk

TALA + ENZA	219	213	204	187	172	159	155	135	123	114	102	99	89	51	26	7	1	0
PBO + ENZA	220	214	196	179	164	155	135	121	110	98	84	75	63	39	20	1	1	0

No HRR alteration detected



No. at risk

TALA + ENZA	154	148	142	128	120	110	108	95	85	79	72	71	64	36	19	5	1	0
PBO + ENZA	160	156	143	131	120	113	97	87	81	73	61	53	44	29	14	1	1	0

Post hoc analysis employing all available test results of prescreening/screening samples including both prospective and retrospective analyses.
Data cutoff: September 3, 2024. aReported 2-sided *P* values are nominal and descriptive.

Agarwal GU 2025

Subsequent Antineoplastic Systemic Therapies

		Talazoparib + Enzalutamide (N=398)	Placebo + Enzalutamide (N=401)
Any subsequent antineoplastic therapy		**149 (37.4)**	**211 (52.6)**
Patients taking any of the following post-baseline antineoplastic therapies with demonstrated overall survival benefit			
Cytotoxic chemotherapy, n (%)	Docetaxel	**90 (22.6)**	**133 (33.2)**
	Cabazitaxel	**46 (11.6)**	**66 (16.5)**
	Carboplatin	**4 (1.0)**	**15 (3.7)**
	Paclitaxel	**1 (0.3)**	**2 (0.5)**
	Cisplatin	**1 (0.3)**	**6 (1.5)**
Androgen biosynthesis inhibitors, n (%)	Abiraterone	**44 (11.1)**	**68 (17.0)**
Radiopharmaceuticals, n (%)	Radium	**20 (5.0)**	**27 (6.7)**
	Lutetium-177	**15 (3.8)**	**16 (4.0)**
	Other[a]	**1 (0.3)**	**3 (0.7)**
Second-generation androgen receptor inhibitors, n (%)	Enzalutamide	**20 (5.0)**	**22 (5.5)**
	Apalutamide	**1 (0.3)**	**3 (0.7)**
	Darolutamide	**1 (0.3)**	**1 (0.2)**
	Rezvilutamide	**1 (0.3)**	**0**
Single-agent PARP inhibitor therapies, n (%)	Olaparib	**6 (1.5)**	**15 (3.7)**
Cellular immunotherapy, n (%)	Sipuleucel-T	**1 (0.3)**	**1 (0.2)**

Data cutoff: September 3, 2024. [a]**Includes PSMA-targeted radiopharmaceuticals, strontium, and therapeutic radiopharmaceuticals.**
PSMA=prostate-specific membrane antigen

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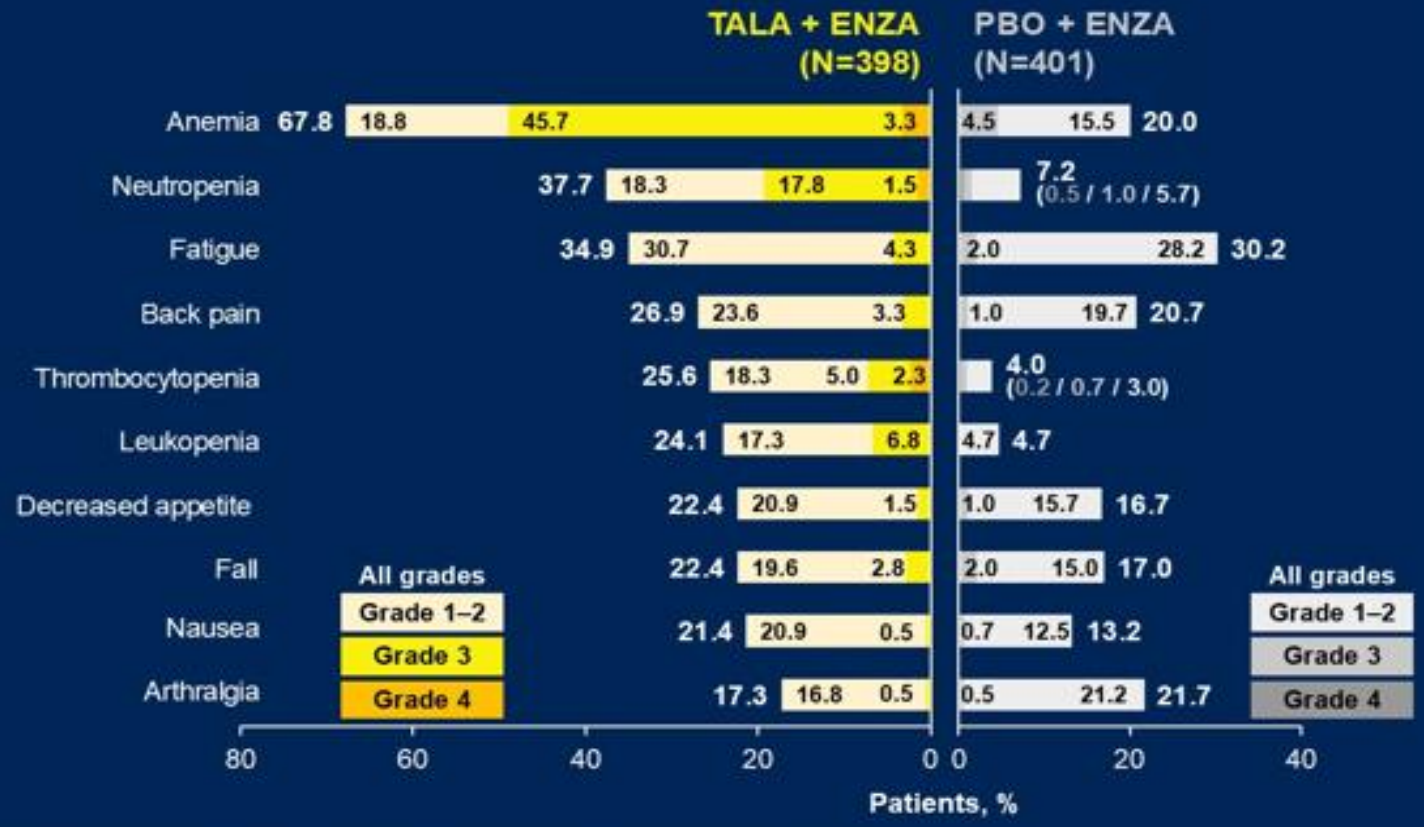
TALAPRO-2 Unselected

Most Common All-Cause TEAEs



In the talazoparib arm:

- 49.0% had grade 1–2 anemia at baseline
- Most common TEAEs leading to a dose reduction of talazoparib were:
  - Anemia (46.2%)
  - Neutropenia (16.3%)
  - Thrombocytopenia (6.2%)
- Grade 3–4 anemia
  - Reported in 49.0% of patients
  - Median time to onset was 3.3 months
  - 42.2% received an RBC transfusion (median of two transfusions)
- 8.5% discontinued talazoparib due to anemia
- Median duration of treatment with talazoparib was 19.7 months

Data cutoff: September 3, 2024. Figure includes TEAEs reported in ≥20% of patients in either arm.

Conclusions

- TALAPRO-2 is the first PARPi plus ARPI combination study to show a statistically significant and clinically meaningful improvement in OS vs standard-of-care ARPI in mCRPC – in patients unselected (Cohort 1) and selected for HRR gene alterations (Cohort 2 – poster D15)
  - Median OS in the talazoparib group was 45.8 months – **8.8 months longer** than active control
- Median OS with talazoparib plus enzalutamide was similar across the ITT, and HRR–non-deficient and HRR-deficient subgroup populations, ranging from 46 to 47 months
- Median rPFS in the talazoparib group was 33.1 months – **13.6 months longer** than active control
- No new safety signals were identified with extended follow-up

These data support talazoparib plus enzalutamide as a standard-of-care initial treatment option for mCRPC

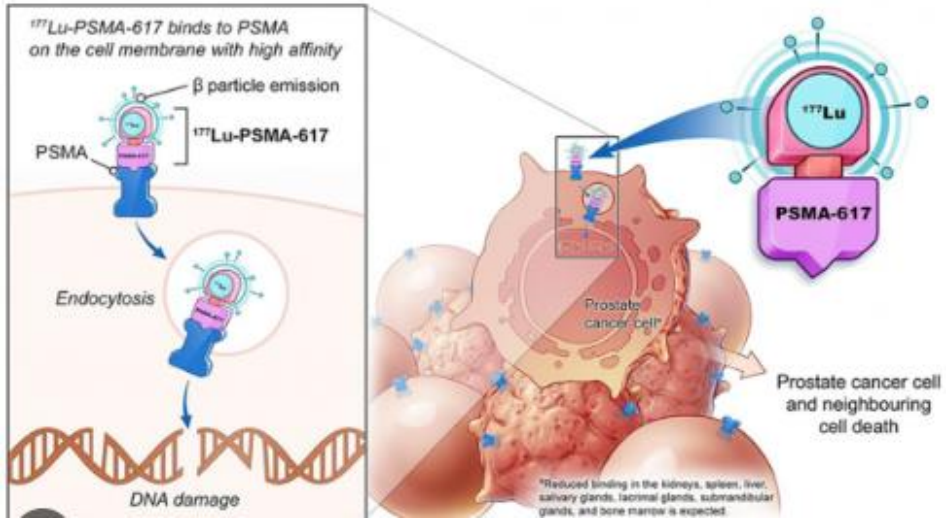
2024 Lutetium 177 Update

VISION Study

ORIGINAL ARTICLE

Lutetium-177–PSMA-617 for Metastatic Castration-Resistant Prostate Cancer

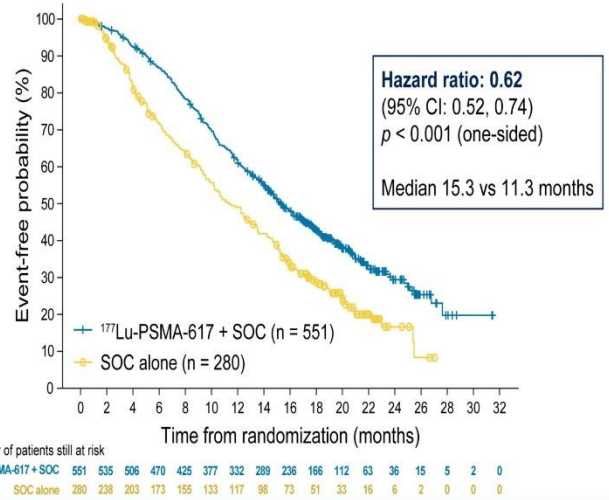
Oliver Sartor, M.D., Johann de Bono, M.B., Ch.B., Ph.D., Kim N. Chi, M.D., Karim Fizazi, M.D., Ph.D., Ken Herrmann, M.D., Kambiz Rahbar, M.D., Scott T. Tagawa, M.D., Luke T. Nordquist, M.D., Nitin Vaishampayan, M.D., Ghassan El-Haddad, M.D., Chandler H. Park, M.D., Tomasz M. Beer, M.D., et al., for the VISION Investigators*



Primary endpoints: ^{177}Lu-PSMA-617 prolonged OS

Primary analysis

All randomized patients (N = 831)



2024 ASCO ANNUAL MEETING

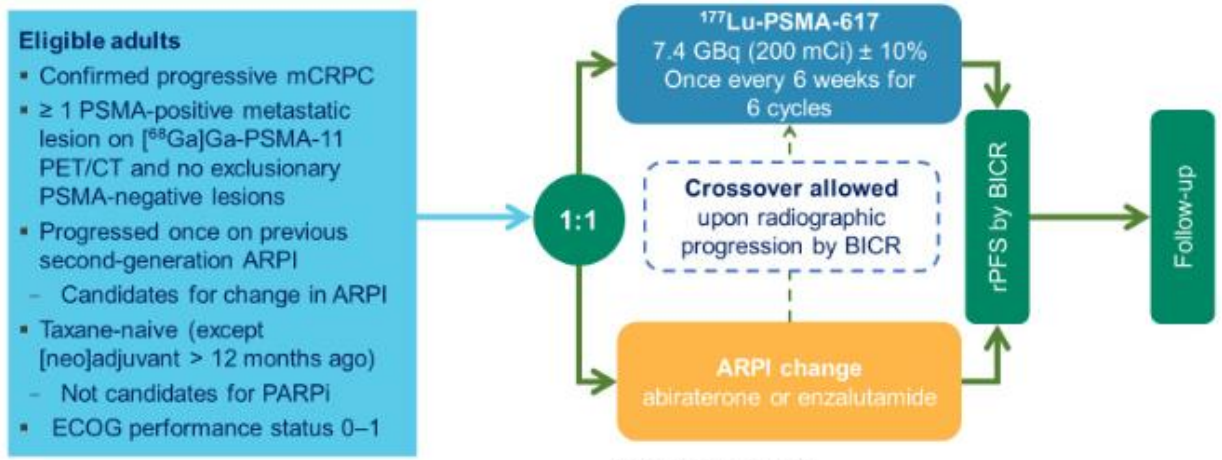
Health-related quality of life and pain in a phase 3 study of [^{177}Lu]Lu-PSMA-617 in taxane-naive patients with metastatic castration-resistant prostate cancer (PSMAfore)

Presenter: Karim Fizazi

Gustave Roussy Institute, Paris-Saclay University, Villejuif, France

Co-authors: MJ Morris, N Shore, K Chi, M Crosby, J de Bono, K Herrmann, G Roubaud, J Nagarajah, M Fleming, B Lewis, L Nordquist, D Castellano, N Carnahan, S Ghebremariam, M Hertelendi, O Sartor,
on behalf of the PSMAfore Investigators

PSMAfore: a phase 3, randomized, open-label study



Stratification factors
- Prior ARPI setting (castration-resistant vs hormone-sensitive)
- BPI-SF worst pain intensity score (0–3 vs > 3)

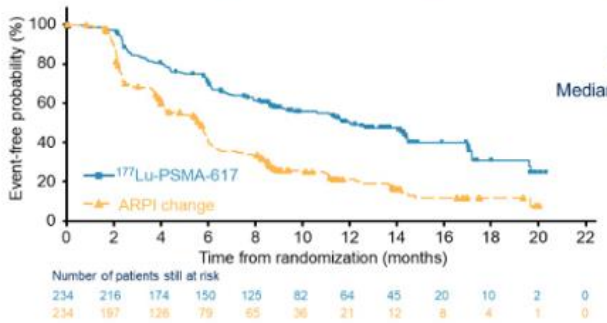
ARPI, androgen receptor pathway inhibitor; BICR, blinded independent central review; BPI-SF, brief pain inventory – short form; CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; mCRPC, metastatic castration-resistant prostate cancer; PARPi, Poly (ADP-ribose) polymerase (PARP) inhibitor; PET, positron emission tomography; PSMA, prostate-specific membrane antigen; rPFS, radiographic progression-free survival

Primary and second interim OS analysis

rPFS: the primary endpoint was met

Primary analysis[a] HR: 0.41 (95% CI: 0.29, 0.56); $p < 0.0001$

Second interim analysis[b] HR: 0.43 (95% CI: 0.33, 0.54)



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

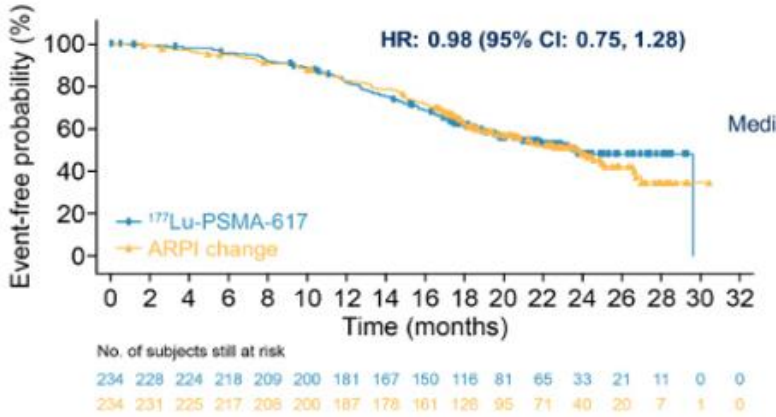
[a]Data cutoff October 2, 2022
[b]Data cutoff June 21, 2023
Previously presented at ESMO23
ARPI, androgen receptor pathway inhibitor; CI, confidence interval; HR, hazard ratio; PSMA, prostate-specific membrane antigen; rPFS, radiographic progression-free survival

Fizazi, ASCO 2024

OS: HR < 1 at third interim analysis with 73% information fraction

Intent-to-treat analysis

Third interim OS analysis



	177Lu-PSMA-617 (n = 234)	ARPI change (n = 234)
Events, n	104 (44.4%)	112 (47.9%)
Median, months (95% CI)	23.66 (19.75, NE)	23.85 (20.6, 26.55)

Crossover:
134/234 (57.3%) in ARPI change group
134/173 (77.5%) eligible patients

RPSFT crossover-adjusted OS analysis

- HR: 0.98 (95% CI: 0.76, 1.27)
- No difference versus the ITT analysis because RPSFT cannot adjust for crossover confounding in the context of overlapping ITT curves

ARPI, androgen receptor pathway inhibitor; CI, confidence interval; HR, hazard ratio; IF, information fraction; ITT, intent-to-treat ; NE, not evaluable; OS, overall survival; PSMA, prostate-specific membrane antigen; RPFST, rank-preserving structural failure time

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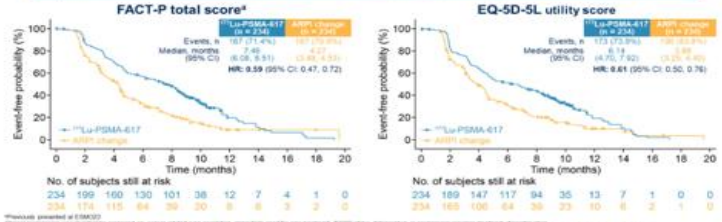
ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY KNOWLEDGE CONQUERS CANCER

Second interim OS analysis

Time to HRQoL worsening at second interim analysis

Prespecified analysis:
Composite time to worsening in FACT-P, EQ-5D-5L and BPI-SF including clinical progression and death



[a]Previously presented at ESMO20

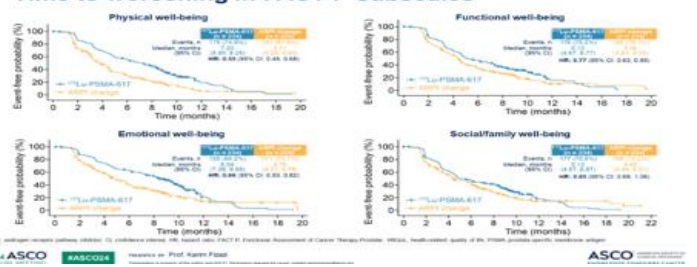
Clinical progression was investigator-assessed as: cancer-related pain escalation, immediate need for new treatment, ECOG status deterioration or progression requiring treatment discontinuation

ARPI, androgen receptor pathway inhibitor; BPI-SF, Brief Pain Inventory – Short Form; CI, confidence interval; EQ-5D-5L, EuroQol-5 Dimensions-5 Level; HR, hazard ratio; FACT-P, Functional Assessment of Cancer Therapy-Prostate; HRQoL, health-related quality of life; PSMA, prostate-specific membrane antigen

2024 ASCO ANNUAL MEETING #ASCO24 PRESENTED BY: Prof. Karim Fizazi

Second interim OS analysis

Time to worsening in FACT-P subscales



2024 ASCO ANNUAL MEETING #ASCO24 PRESENTED BY: Prof. Karim Fizazi

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Fizazi, ASCO 2024

BARCELONA 2024 ESMO congress

A randomized multicenter open-label phase III trial comparing enzalutamide vs a combination of Radium-223 and enzalutamide in asymptomatic or mildly symptomatic patients with bone metastatic mCRPC

Results of EORTC-GUCG 1333/PEACE-3, an EORTC/CTI/CUOG/LACOG/UNICANCER-GETUG cooperative study

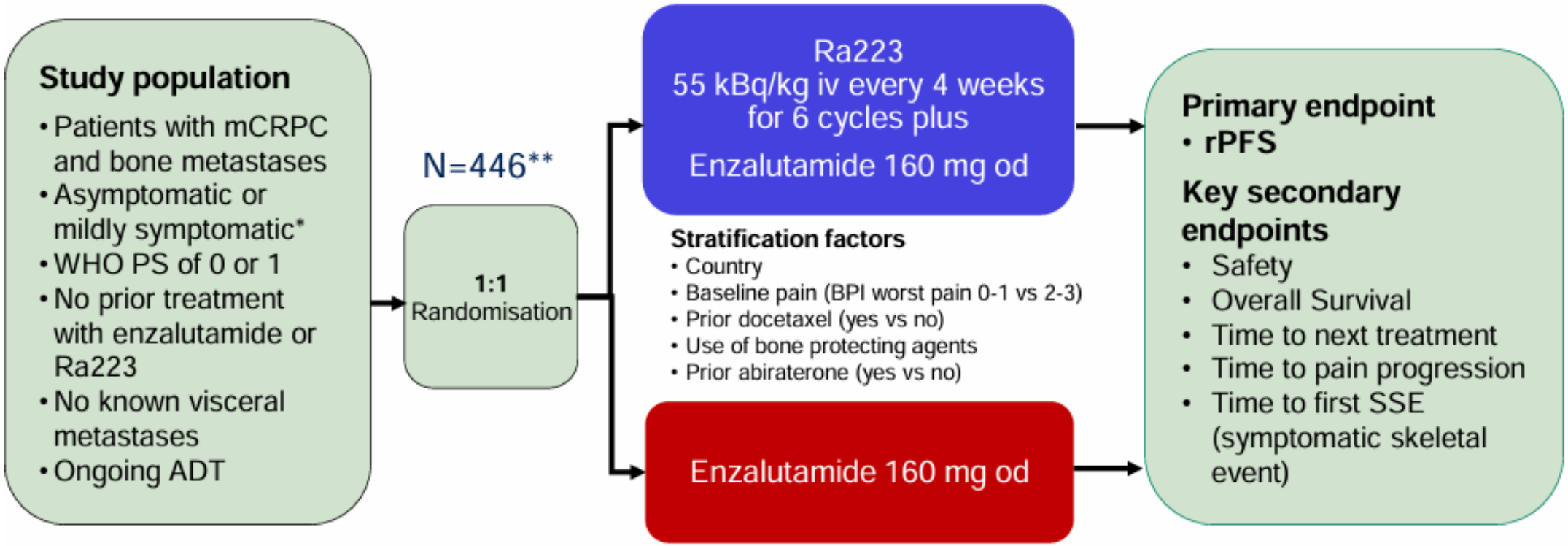
S. Gillessen
Oncology Institute of Southern Switzerland, EOC,
Bellinzona, Switzerland

On behalf of A. Choudhury, F. Saad , E. Gallardo Diaz, A. Soares, Y. Loriot, R. McDermott, A. Rodriguez-Vida, P. Isaacsson Velho, F. Nole, F. Cruz, T. Roumeguere, G. Daugaard, R. Yamamura, E. Bompas, P. Maroto, F. Gomez Veiga, I. Skoneczna, K. Martins da Trindade, F. Mavignier Carcano, F. Lecouvet, C.Coens, C. Poncet, B. Fournier, B. Tombal

PEACE Prostate Cancer Consortium Europe

EORTC European Organisation for Research and Treatment of Cancer

EORTC-GUCG 1333 (PEACE-3)



*defined as brief pain inventory WP24 score < 4
** original target accrual N=560, adapted for slow accrual

Use of bone protecting agents (BPA) made mandatory
(after inclusion of 119 patients)

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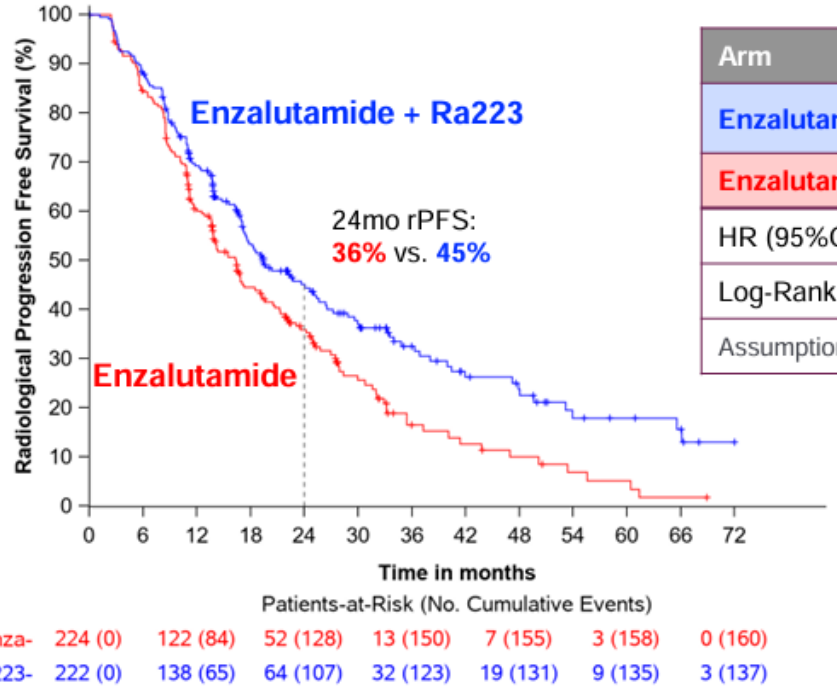
Primary endpoint: rPFS



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

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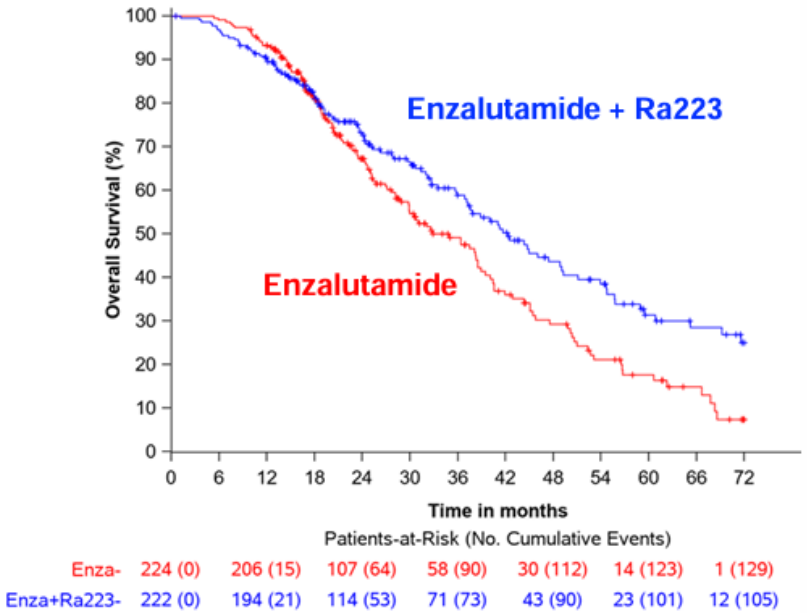
Overall Survival at interim analysis (80% of OS events)



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

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

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What I do in my practice for mCRPC after ESMO24 & ASCO GU25

- 1. After Taxane and ARP inhibitor. You have to choose between PARP inhibitor, Cabazitaxel (+/- Carboplatin) , and Lutetium 177. Get Germline and Somatic studies at metastatic disease)

- 2. If BRCA2/BRCA1 mutation. Preference is PARP inhibitor (+ ARPi if possible due to BRCAAWAY study) before Lutetium 177 and Cabazitaxel. For example if patient receives Abiraterone in hormone sensitive, would give Enzalutamide + Talazoparib). Consider PALB2, CDK 12, RAD51 (TALAPRO-2)

- 3. If PSMA PET scan shows mean SUV above 10 with many lesions, give Lutetium 177 before Cabizitaxel.

- 4. If patient progresses fast on ARP inhibitor (less than 12 months) and have mean SUV less than 10. Give Cabazitaxel. (PTEN, RB1, p53)

- 5. Get a 2nd liquid or tissue biopsy post Lutetium 177 when they progress. 15% of the time another somatic mutation develops .

- 6. Give Pembrolizumab for MSI High and TMB above 10. Have patients in my practice that developed BRCA2 somatic mutations and high TMB after "running" out of treatments. They are in stable condition now.

- 7. Consider clinical trials. Bispecific T cell engagers are very promising