

Kastrasyona Dirençli Metastatik Prostat Kanserinde Tedavi

Dr. Deniz Tural

**Bakırköy Dr. Sadi Konuk Eğitim ve Araştırma Hastanesi
Tıbbi Onkoloji**

Ders Planı

- ❑ Giriş
- ❑ DNA repair mutasyonu olan hastalarda seçenekler
- ❑ LU-177
- ❑ Kombinasyon tedavileri
- ❑ MSI ve diğer mutasyonlarda seçenekler
- ❑ Gelecek perspektif
- ❑ Sonuç

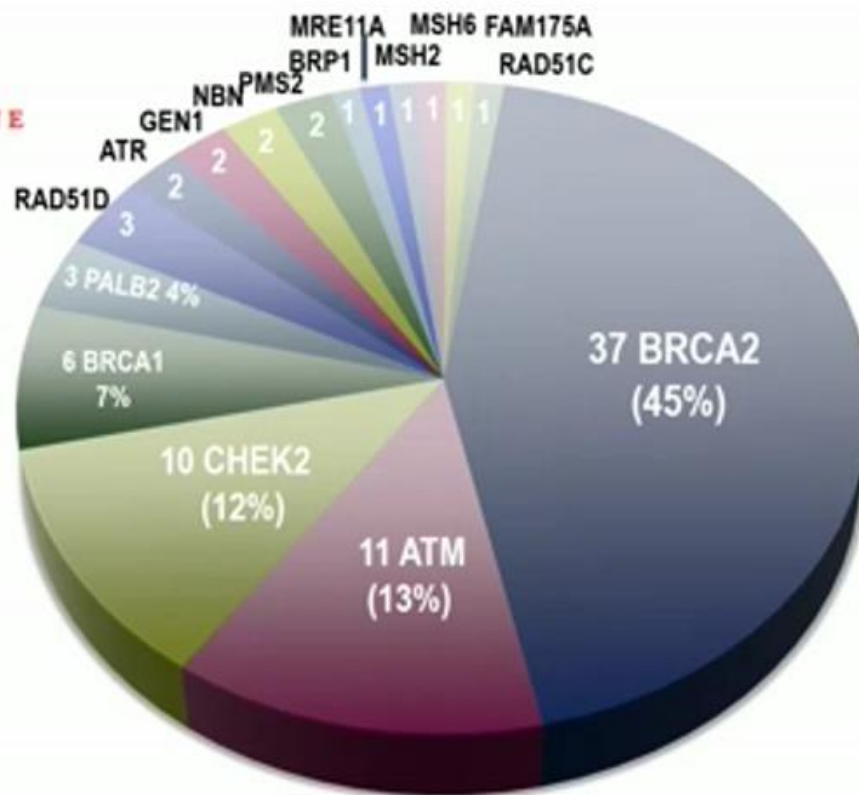
Prostat Kanseri Risk Faktörleri

GENETIC TESTING

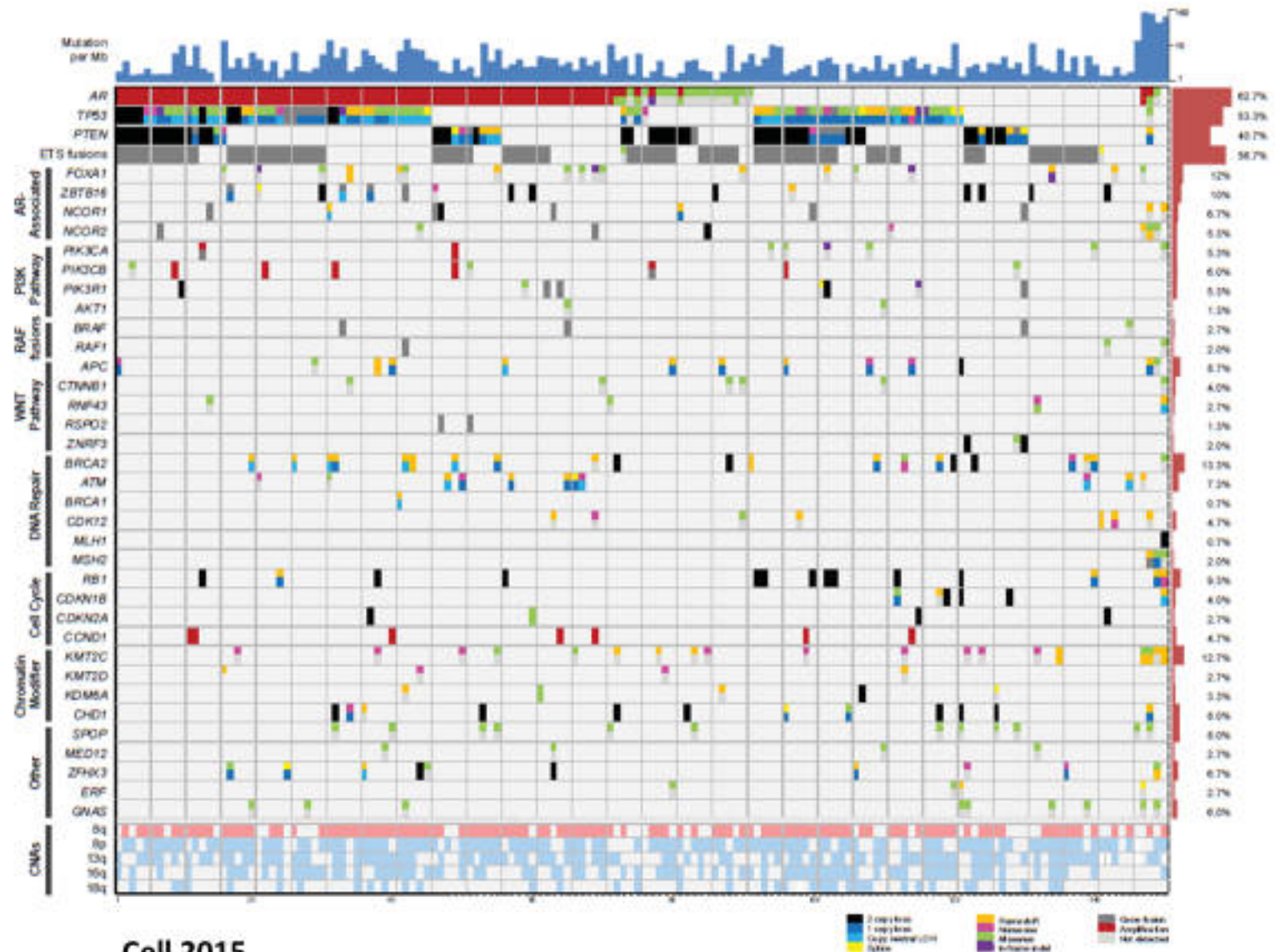
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The NEW ENGLAND JOURNAL of MEDICINE

Inherited DNA-Repair Gene Mutations
in Men with Metastatic Prostate Cancer



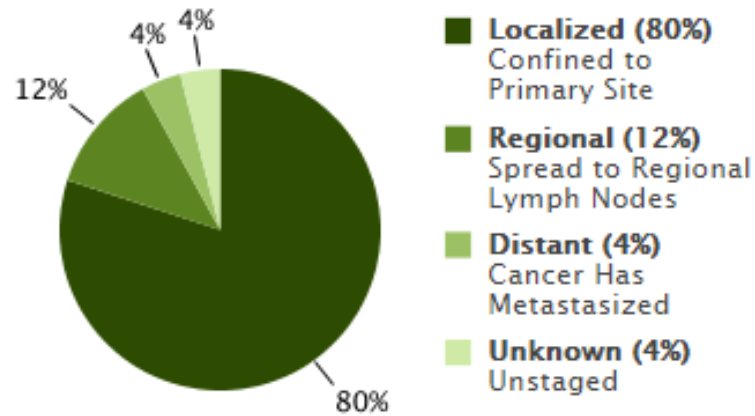
Prostat Kanseri Genomik Profil



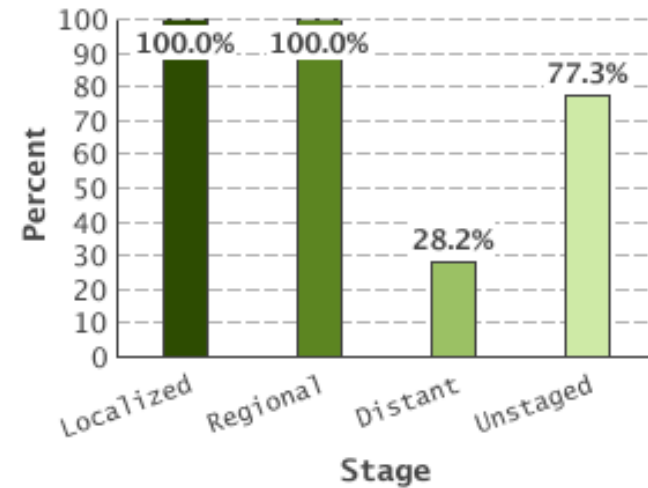
Prostat Kanseri İnsidans ve Mortalite

Percent of Cases & 5-Year Relative Survival by Stage at Diagnosis: Prostate Cancer

Percent of Cases by Stage

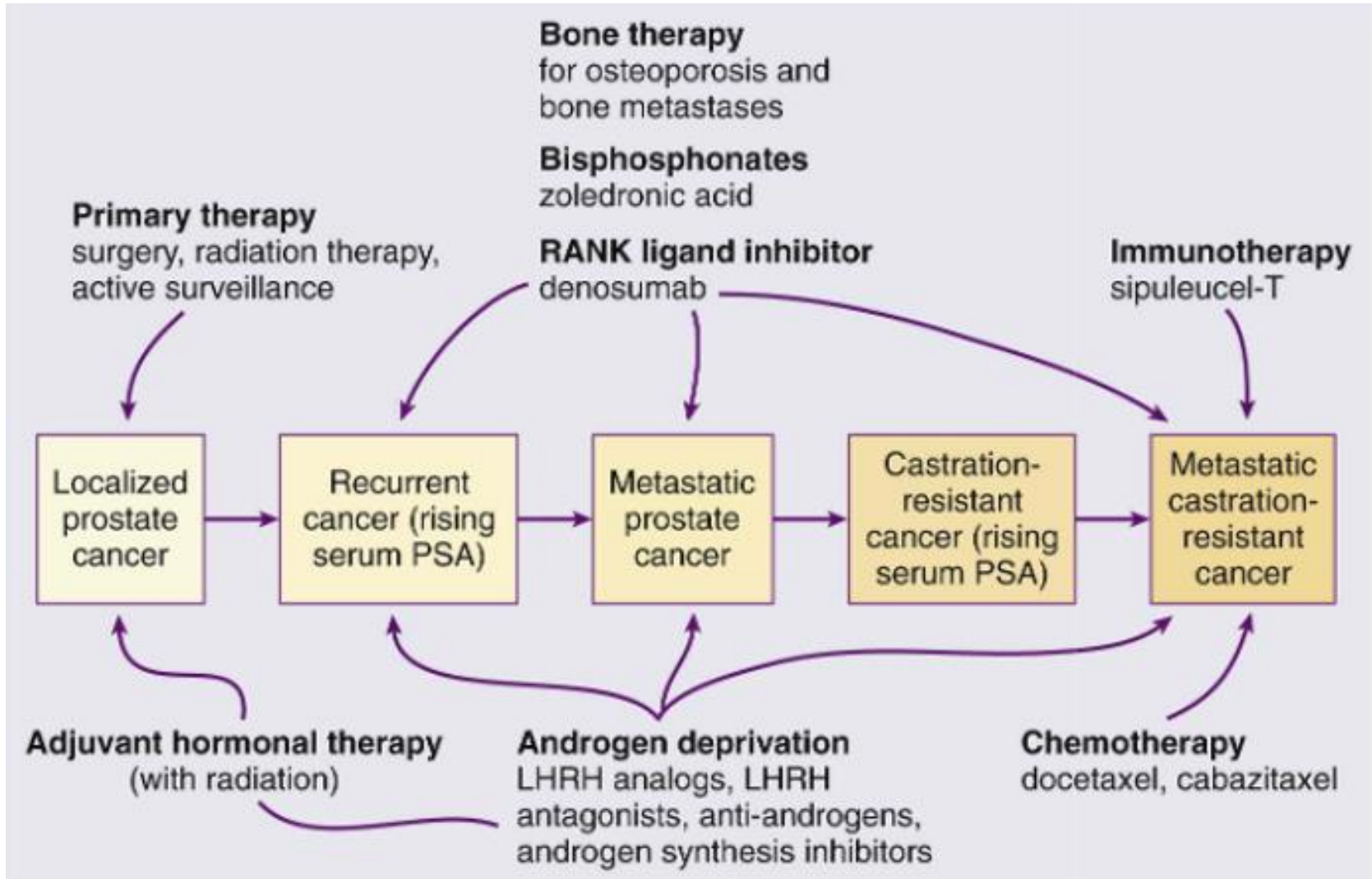


5-Year Relative Survival



SEER 18 2005-2011, All Races, Males by SEER Summary Stage 2000

Prostat Kanseri Tedavi Yaklaşımları



Kastrasyona Dirençli Metastatik Prostat kanseri



NCCN Guidelines Version 2.2021 Prostate Cancer

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SYSTEMIC THERAPY FOR M1 CRPC: ADENOCARCINOMA^{zz,ccc,ddd,eee}

No prior docetaxel/no prior novel hormone therapy^{fff} • Preferred regimens ▶ Abiraterone^{t,ggg} (category 1^{hhh}) ▶ Docetaxel^{aaa,iii} (category 1) ▶ Enzalutamide^t (category 1) • Useful in certain circumstances ▶ Sipuleucel-T^{aaa,jjj} (category 1) ▶ Radium-223^{kkk} for symptomatic bone metastases (category 1) • Other recommended regimens ▶ Other secondary hormone therapy^t	Prior novel hormone therapy/No prior docetaxel^{fff,iii} • Preferred regimens ▶ Docetaxel (category 1)^{aaa} ▶ Sipuleucel-T^{aaa,jjj} • Useful in certain circumstances ▶ Olaparib for HRRm (category 1)^{mmm} ▶ Cabazitaxel/carboplatin^{aaa,nnn} ▶ Pembrolizumab for MSI-H or dMMR^{aaa} ▶ Radium-223^{kkk} for symptomatic bone metastases (category 1) ▶ Rucaparib for BRCAm^{ooo} • Other recommended regimens ▶ Abiraterone^{t,ggg} ▶ Abiraterone + dexamethasone^{ggg,ppp} ▶ Enzalutamide^t ▶ Other secondary hormone therapy^t
Prior docetaxel/no prior novel hormone therapy^{fff} • Preferred regimens ▶ Abiraterone^{t,ggg} (category 1) ▶ Cabazitaxel^{aaa} ▶ Enzalutamide^t (category 1) • Useful in certain circumstances ▶ Mitoxantrone for palliation in symptomatic patients who cannot tolerate other therapies^{aaa} ▶ Cabazitaxel/carboplatin^{aaa,nnn} ▶ Pembrolizumab for MSI-H or dMMR^{aaa} ▶ Radium-223^{kkk} for symptomatic bone metastases (category 1) • Other recommended regimens ▶ Sipuleucel-T^{aaa,jjj} ▶ Other secondary hormone therapy^t	Prior docetaxel and prior novel hormone therapy^{fff,iii} (All systemic therapies are category 2B if visceral metastases are present) • Preferred regimens ▶ Cabazitaxel^{aaa} (category 1^{hhh}) ▶ Docetaxel rechallenge^{aaa,eee} • Useful in certain circumstances ▶ Olaparib for HRRm (category 1)^{hhh,mmm} ▶ Cabazitaxel/carboplatin^{aaa,nnn} ▶ Pembrolizumab for MSI-H or dMMR^{aaa} ▶ Mitoxantrone for palliation in symptomatic patients who cannot tolerate other therapies^{aaa} ▶ Radium-223^{kkk} for symptomatic bone metastases (category 1^{hhh}) ▶ Rucaparib for BRCAm^{ooo} • Other recommended regimens ▶ Abiraterone^{t,ggg} ▶ Enzalutamide^t ▶ Other secondary hormone therapy^t

Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

Treatment options in mCRPC

Study	Agents	N	Indication	HR	ΔOS (mo)
TAX-327 ¹	DOC/P vs mito/P	1,006	mCRPC, symptomatic or not	0.76	+2.9
COU-AA-302 ⁶	ABI/P vs P	1,088	mCRPC (pre-DOC), mild/no symptoms No visceral metastases	0.81	+4.4
COU-AA-301 ³	ABI/P vs P	1,195	mCRPC (post-DOC)	0.74	+4.6
PREVAIL ⁴	ENZ vs pbo	1,717	mCRPC (pre-DOC), mild/no symptoms	0.77	+4.0
AFFIRM ⁵	ENZ vs pbo (or P)	1,199	mCRPC (post-DOC)	0.63	+4.8
TROPIC ⁶	CABA/P vs mito/P	755	mCRPC (post-DOC)	0.70	+2.4
ALSYMPCA ⁷	Radium-223 vs pbo	921	mCRPC (post-DOC or unfit for DOC)	0.70	+3.6

ABI, abiraterone; CABA, cabazitaxel; DOC, docetaxel; ENZ, enzalutamide; HR, hazard ratio; mito, mitoxantrone; P, prednisone; pbo, placebo; OS, overall survival.

1. Tannock IF et al. *N Engl J Med* 2004; 351:1502-12. 2. Ryan CJ et al. *Lancet Oncol* 2015;16:152-60. 3. Rathkopf DE et al. *Eur Urol* 2014;66:815-25. 4. Beer TM et al. *Eur Urol* 2017;71:151-4. 5. Armstrong AJ et al. *Cancer* 2017;123:2303-11. 6. de Bono JS et al. *Lancet* 2010;376:1147-54. 7. Hoskin P et al. *Lancet Oncol* 2014;15:1397-406.

Kastrasyona Dirençli Metastatik Prostat kanseri

SYSTEMIC THERAPY FOR M1 CRPC: ADENOCARCINOMA^{iii, kkk, III}

No prior docetaxel/no prior novel hormone therapy^{mmm} • Preferred regimens › Abiraterone^{u, nnn, ooo} (category 1) › Docetaxel^{fff, ppp} (category 1) › Enzalutamide^u (category 1) • Useful in certain circumstances › Niraparib/abiraterone^{u, fff, zzz} for BRCA mutation (category 1) › Olaparib/abiraterone^{u, fff, nnn, qqq} for BRCA mutation (category 1) › Radium-223^{rrr} for symptomatic bone metastases (category 1) › Sipuleucel-T^{fff, sss} (category 1) › Talazoparib/enzalutamide for HRRm^{u, fff, yyy} (category 1) • Other recommended regimens › Other secondary hormone therapy^u	Prior novel hormone therapy/no prior docetaxel^{mmm, ttt} • Preferred regimens › Docetaxel (category 1)^{fff} • Useful in certain circumstances › Cabazitaxel/carboplatin^{fff, jjj} › Niraparib/abiraterone^{u, fff, zzz} for BRCA mutation (category 2B) › Olaparib for HRRm^{uuu} (category 1) › Radium-223^{rrr} for symptomatic bone metastases (category 1) › Rucaparib for BRCA mutation^{vvv} › Sipuleucel-T^{fff, sss} › Talazoparib/enzalutamide for HRRm^{u, fff, yyy} (category 2B) • Other recommended regimens › Abiraterone^{u, nnn} › Abiraterone^u + dexamethasone^{nnn, www} › Enzalutamide^u › Other secondary hormone therapy^u
Prior docetaxel/no prior novel hormone therapy^{mmm} • Preferred regimens › Abiraterone^{u, nnn} (category 1) › Cabazitaxel^{fff} › Enzalutamide^u (category 1) • Useful in certain circumstances › Cabazitaxel/carboplatin^{fff, jjj} › Mitoxantrone for palliation in symptomatic patients who cannot tolerate other therapies^{fff} › Niraparib/abiraterone^{u, fff, zzz} for BRCA mutation › Olaparib/abiraterone^{u, fff, nnn, qqq} for BRCA mutation › Radium-223^{rrr} for symptomatic bone metastases (category 1) › Sipuleucel-T^{fff, sss} › Talazoparib/enzalutamide for HRRm^{u, fff, yyy} • Other recommended regimens › Other secondary hormone therapy^u	Prior docetaxel and prior novel hormone therapy^{mmm, ttt} • Useful in certain circumstances › Lutetium Lu 177 vipivotide tetraxetan (Lu-177–PSMA-617) for PSMA-positive metastases^{xxx} (category 1) (The following systemic therapies are category 2B if visceral metastases are present) • Preferred regimens › Cabazitaxel^{fff, ooo} (category 1) › Docetaxel rechallenge^{fff} • Useful in certain circumstances › Cabazitaxel/carboplatin^{fff, jjj} › Mitoxantrone for palliation in symptomatic patients who cannot tolerate other therapies^{fff} › Olaparib for HRRm^{ooo, uuu} (category 1) › Pembrolizumab for MSI-H, dMMR, or TMB ≥10 mut/Mb^{fff} › Radium-223^{rrr} for symptomatic bone metastases^{ooo} (category 1) › Rucaparib for BRCA mutation^{vvv} • Other recommended regimens › Abiraterone^{u, nnn} › Enzalutamide^u › Other secondary hormone therapy^u

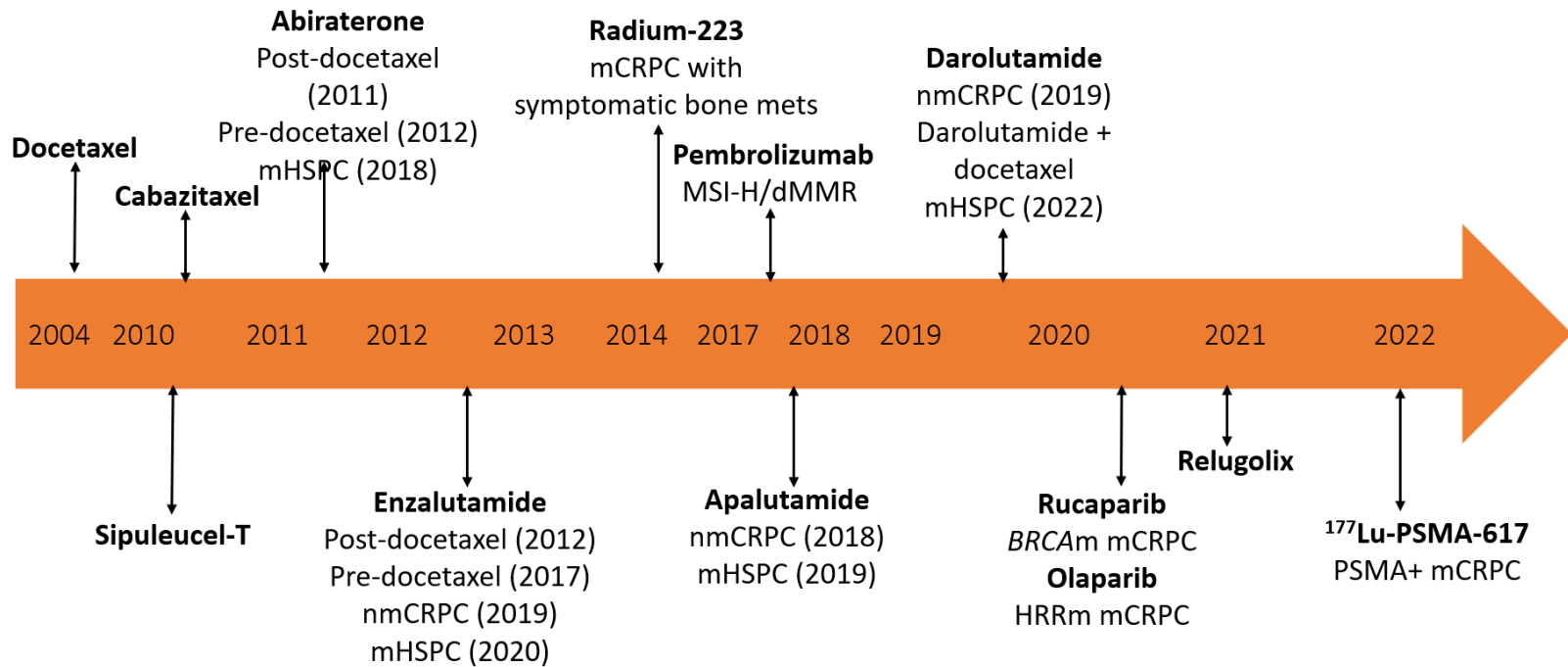
Kastrasyona Dirençli Metastatik Prostat kanseri

Prostate NCCN Guidelines v 1.2023

Germline Testing	Somatic Tumor Testing
Germline testing is <u>recommended</u> in patients with a personal history of prostate cancer who: • Have metastatic, regional (N+), very-high-risk localized, or high-risk localized prostate cancer • Have family history and/or ancestry with: • ≥1 first, second, or third degree relative with • Breast cancer at age ≤50 years • Colorectal or endometrial cancer at age ≤50 years • Male breast cancer at any age • Ovarian cancer at any age • Pancreatic cancer at any age • Metastatic, regional, very-high-risk, or high-risk prostate cancer at any age • ≥1 first degree relative with prostate cancer at age ≤60 years • ≥2 first, second, or third degree relatives with: • Breast cancer at any age • Prostate cancer at any age • ≥3 first or second degree relatives with: • Lynch syndrome-related cancers, especially if diagnosed at age <50 years • A known family history of a familial cancer risk mutation • Ashkenazi Jewish ancestry • Personal history of male breast cancer Germline testing <u>may be considered</u> in patients with a personal history of PCa who: • Have intermediate-risk prostate cancer with intraductal/criform histology • Have a personal history of pancreatic, colorectal, gastric, melanoma, upper tract urothelial, glioblastoma, biliary tract, or small intestinal cancer <i>Germline multigene testing that includes at least BRCA1, BRCA2, ATM, PALB2, CHEK2, HOXB13, MLH1, MSH2, MSH6, and PMS2 is recommended; additional genes may be appropriate based on clinical context</i>	Tumor testing for alterations in HRR DNA repair genes such as BRCA1, BRCA2, ATM, PALB2, FANCA, RAD51D, CHEK2, and CDK12 is recommended in patients with <u>metastatic</u> prostate cancer, and may be considered for patients with regional (N+) prostate cancer Tumor testing for MSI-H or dMMR is recommended in patients with mCRPC, and may be considered for patients with mCSPC TMB testing may be considered in patients with mCRPC

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Treatment Landscape of mCRPC continues to evolve



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Phase 3 trial of PARPi + AR signaling inhibitor
in 1st line mCRPC setting

PROpel: Abiraterone + Olaparib ¹

Published



MAGNITUDE: Abiraterone + Niraparib ²

Presented



TALAPRO-2: Enzalutamide + Talazoparib

Presented



CASPAR: Enzalutamide + Rucaparib

Enrolling



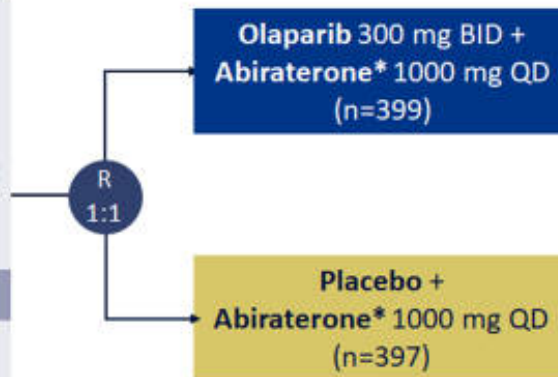
1- Clarke NW et al., NEJM Evidence. 2022 Aug 23;1(9):EVIDoa2200043.

2- Chi KN et al., JCO. 2022 Feb 20;40(6_suppl):12–12. Kim Chi, (2022 Genitourinary cancers symposium (ASCO GU). Abstract #12)

Kastrasyona Dirençli Metastatik Prostat kanseri

PROpel: Phase III Trial of Abiraterone +/- Olaparib

Patient population
▪ mCRPC ▪ Docetaxel for mCSPC allowed ▪ No prior abiraterone ▪ Other NHT allowed if stopped ≥12 months prior to enrollment ▪ Ongoing ADT ▪ ECOG PS 0–1
Stratification factors
▪ Site of distant metastases (bone only vs visceral vs other) ▪ Prior taxane for mCSPC



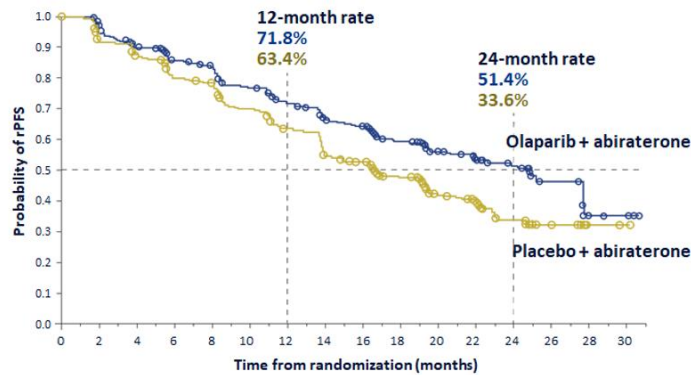
Primary endpoint
rPFS or death by investigator assessment
Key secondary endpoint
▪ OS
Additional endpoints
▪ TFST ▪ PFS2 ▪ ORR ▪ HRR mutation prevalence (tested retrospectively) ▪ HRQOL ▪ Safety and tolerability

*Plus prednisone or prednisolone 5 mg BID

Saad F et al. *ASCO GU* 2022; abstr 11; **NCT03732820**.

Kastrasyona Dirençli Metastatik Prostat kanseri

PROpel: Radiographic Progression-Free Survival



	Olaparib + abiraterone (n=399)	Placebo + abiraterone (n=397)
rPFS by investigator assessment		
Events, n (%)	168 (42.1)	226 (56.9)
Median rPFS, months	24.8	16.6
HR (95% CI)	0.66 (0.54–0.81); <i>P</i> <0.0001	
rPFS by blinded independent central review		
HR (95% CI)	0.61 (0.49–0.74); <i>P</i> <0.0001	

	Number of patients, n	Median rPFS, months	HR (95% CI)
All patients	796	24.8 16.6	0.66 (0.54–0.81)
Age at randomization			
<65	227	NR 16.4	0.51 (0.35–0.75)
≥65	569	22.0 16.7	0.78 (0.62–0.98)
ECOG performance status at baseline			
0	558	24.9 16.8	0.67 (0.52–0.85)
1	236	17.5 14.6	0.75 (0.53–1.06)
Site of distant metastases			
Bone only	434	27.6 22.2	0.73 (0.54–0.98)
Visceral	105	13.7 10.9	0.62 (0.39–0.99)
Other	257	20.5 13.7	0.62 (0.44–0.85)
Docetaxel treatment at mHSPC stage			
Yes	189	27.6 13.8	0.61 (0.40–0.92)
No	607	24.8 16.8	0.71 (0.56–0.89)
Baseline PSA			
Below median baseline PSA	396	25.2 22.0	0.75 (0.55–1.02)
Above or equal to median baseline PSA	397	18.5 13.8	0.63 (0.48–0.82)
HRRm status			
HRRm	226	NR 13.9	0.50 (0.34–0.73)
Non-HRRm	552	24.1 19.0	0.76 (0.60–0.97)

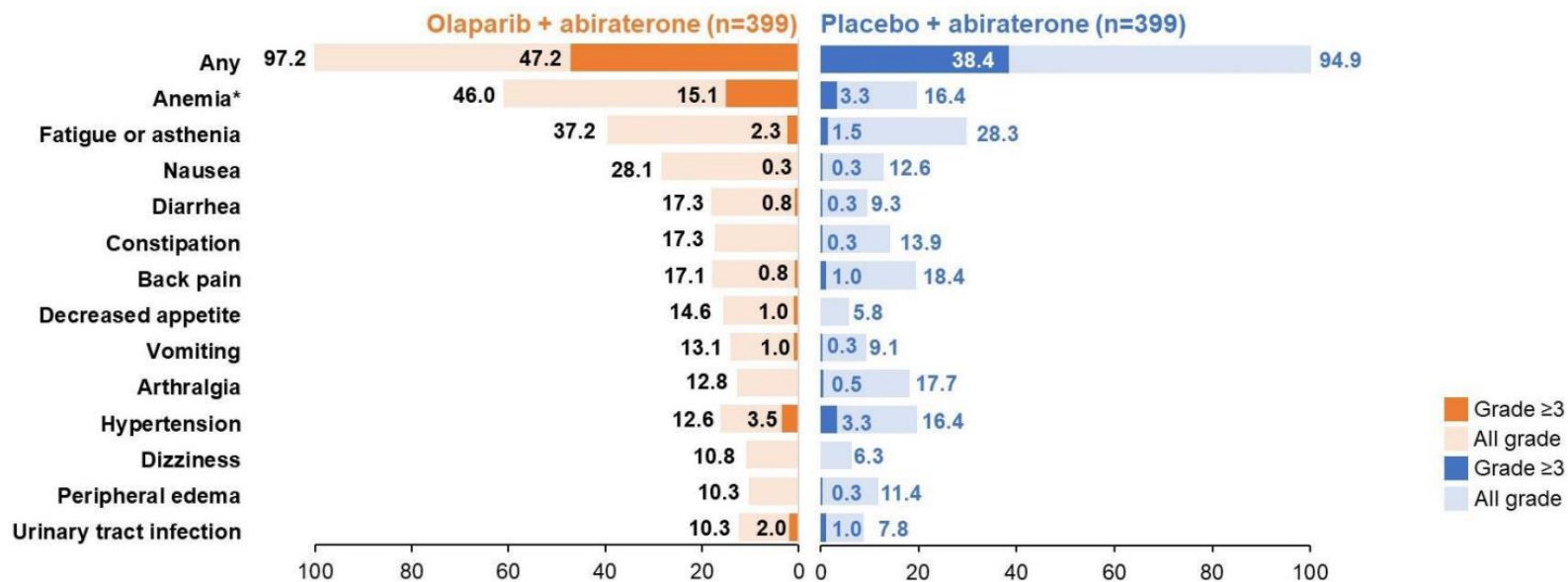
0.1 ← Olaparib + abiraterone better | 1 | → Placebo + abiraterone better 10

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

Kastrasyona Dirençli Metastatik Prostat kanseri

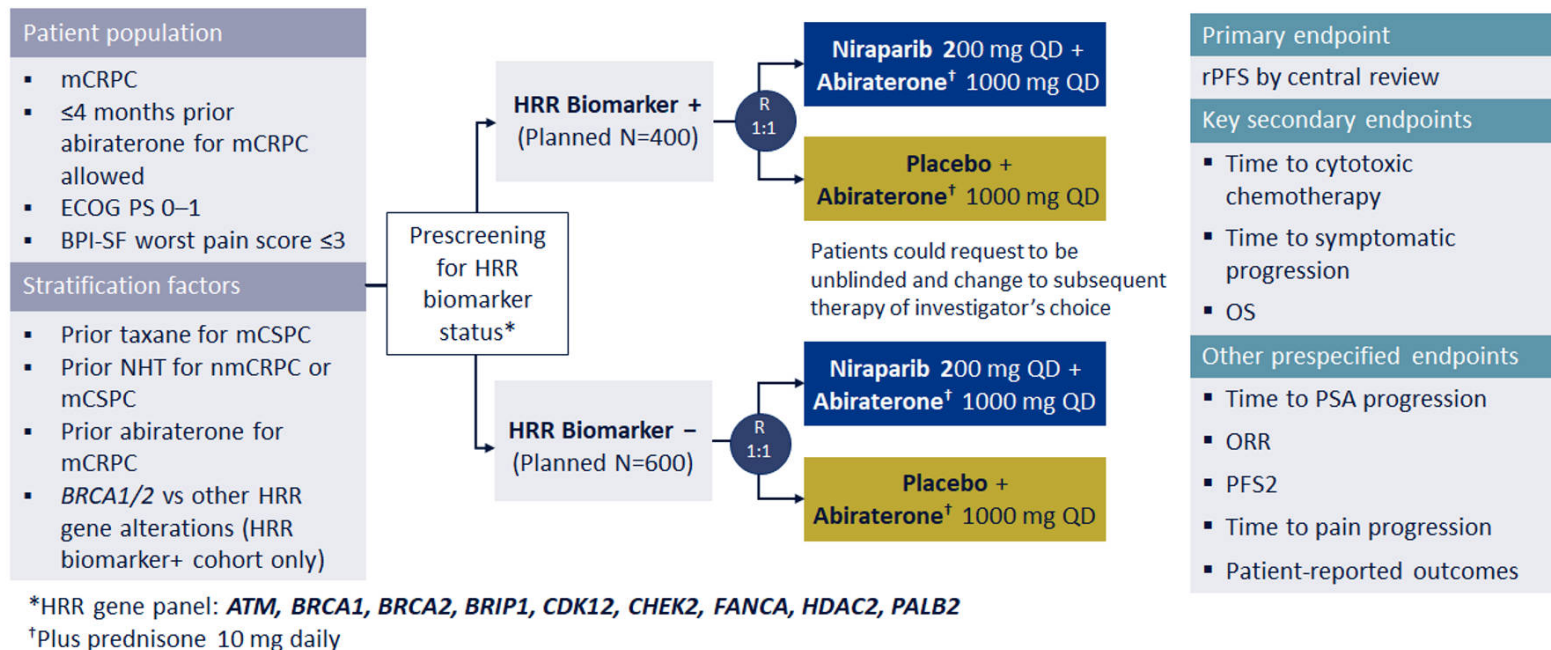
PROPEL

Overall safety profile



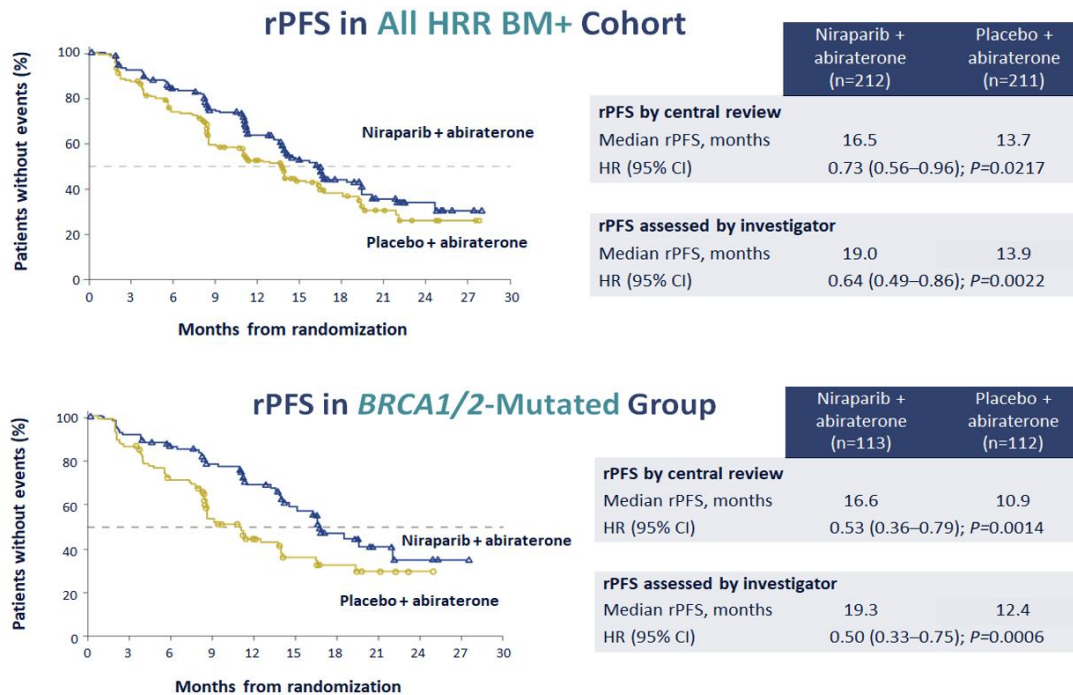
Kastrasyona Dirençli Metastatik Prostat kanseri

MAGNITUDE: Phase III Trial of Abi +/- Niraparib



Kastrasyona Dirençli Metastatik Prostat kanseri

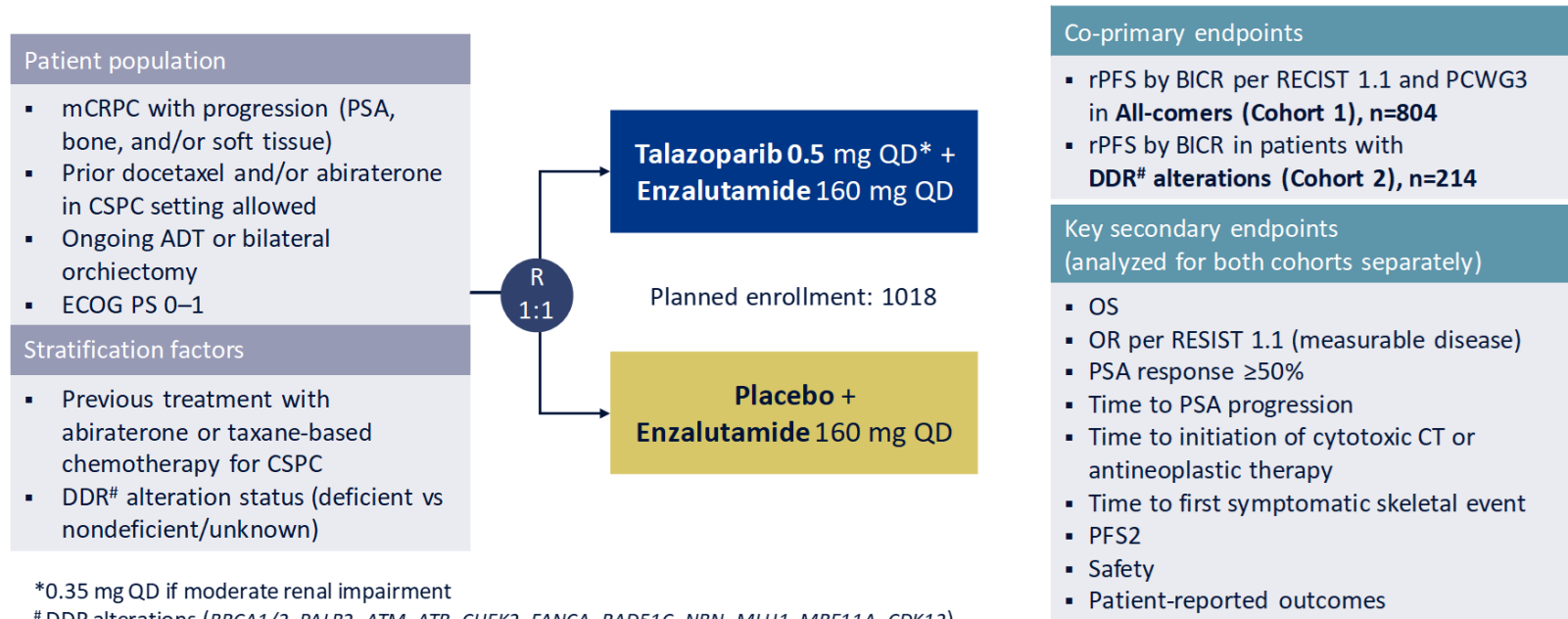
MAGNITUDE: Radiographic Progression-Free Survival



Chi KN et al. ASCO GU 2022; abstr 12.

Kastrasyona Dirençli Metastatik Prostat kanseri

TALAPRO-2: Phase III Trial of Enza +/- Talazoparib



Agarwal N et al. *Future Oncol.* 2022;18:425-436; **NCT03395197**.

Kastrasyona Dirençli Metastatik Prostat kanseri

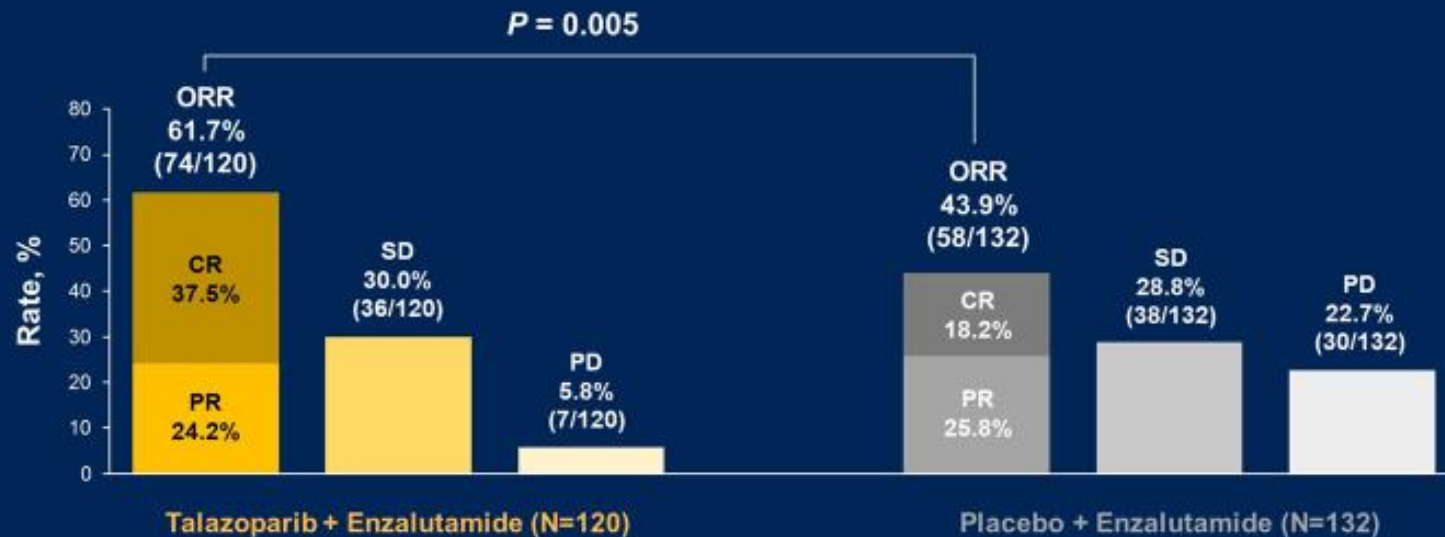
TALAPRO-2: Phase III Trial of Enza +/- Talazoparib

All-comers cohort	rPFS 21.9 mo → NR	HR 0.63 (0.51-0.78)	<i>P</i> <0.001
HRR <i>mutated</i>	rPFS 16.4 → 27.9 mo	HR 0.46 (0.30-0.70)	<i>P</i> <0.001
HRR <i>wild-type</i>	rPFS 16.6 → 25.8 mo	HR 0.66 (0.49-0.91)	<i>P</i> = 0.009

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TALAPRO-2: Objective Response by BICR

Higher rates of complete response (CR) suggest a cooperative effect of talazoparib plus enzalutamide treatment



PD=progressive disease; PR=partial response; SD=stable disease.

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TALAPRO-2: Most Common All-cause TEAEs

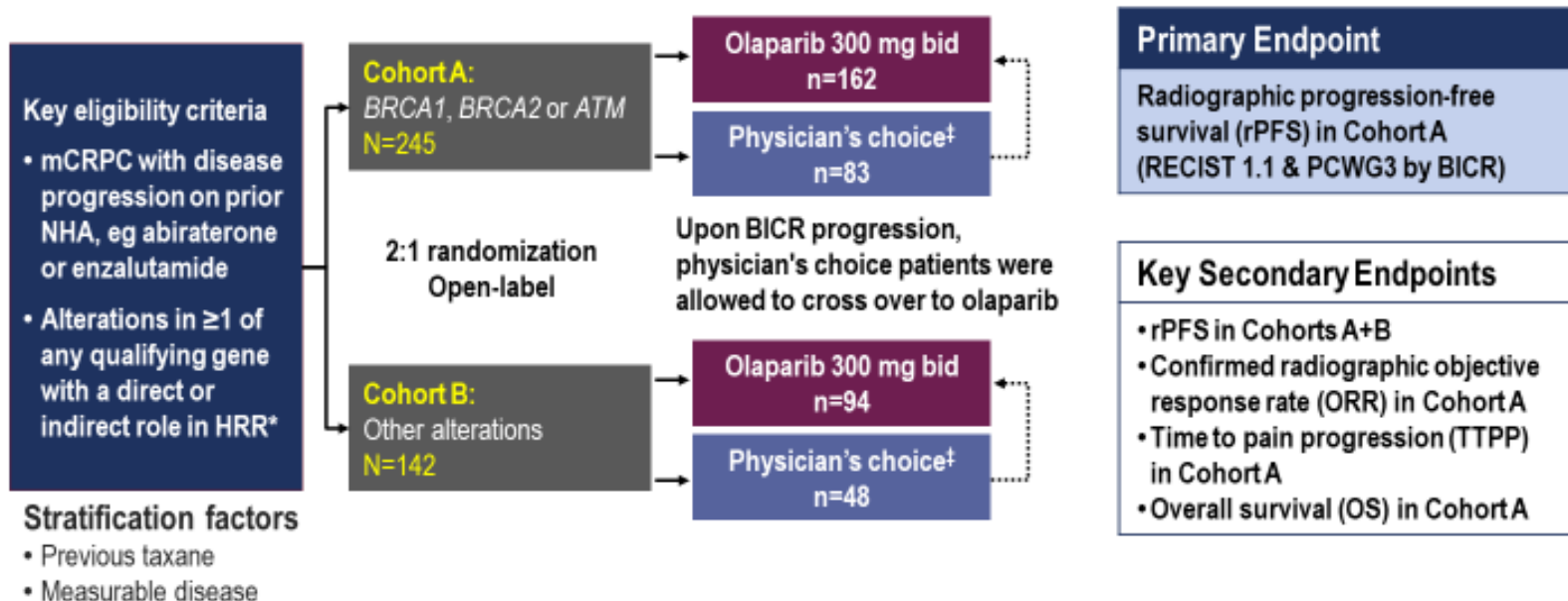


In the talazoparib arm:

- Most common TEAEs leading to a dose reduction of talazoparib were:
 - Anemia (43.2%)
 - Neutropenia (15.1%)
 - Thrombocytopenia (5.5%)
- 49.0% had grade 1–2 anemia at baseline
- Grade 3–4 anemia
 - Median time to onset was 3.3 months
 - Reported in 46.5% of men
- 8.3% discontinued talazoparib due to anemia
- The median relative dose intensity of talazoparib remained >80%

Kastrasyona Dirençli Prostat Kanseri

PROfound STUDY DESIGN

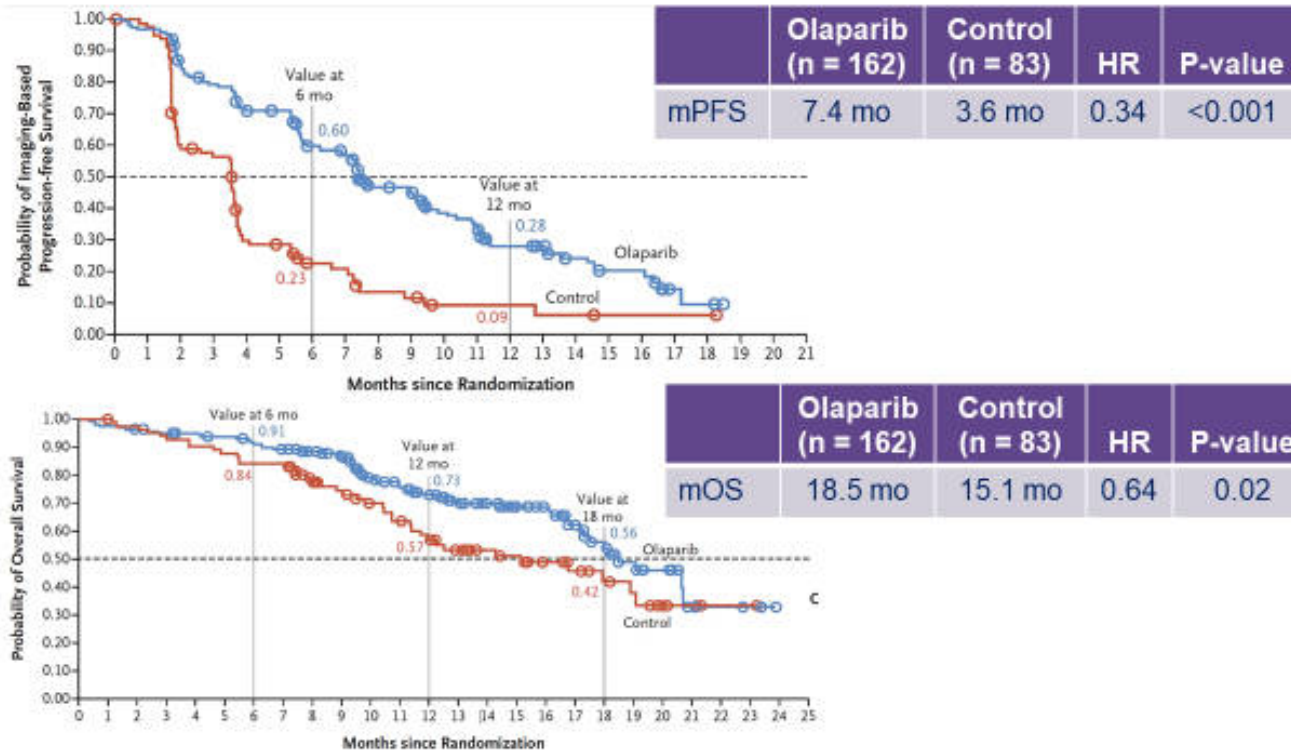


*An investigational Clinical Trial Assay, based on a next-generation sequencing test

Used to prospectively select patients harboring alterations in BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D and/ or RAD54L in their tumor tissue

Kastrasyona Dirençli Prostat Kanseri

PROfound: Imaging-Based PFS and OS in Cohort A



De Bono J et al. N Engl J Med 2020 May 28;382(22):2091-2101.

Olaparib Türkiye’de prostat kanseri tedavisinde ruhsatlı değildir.

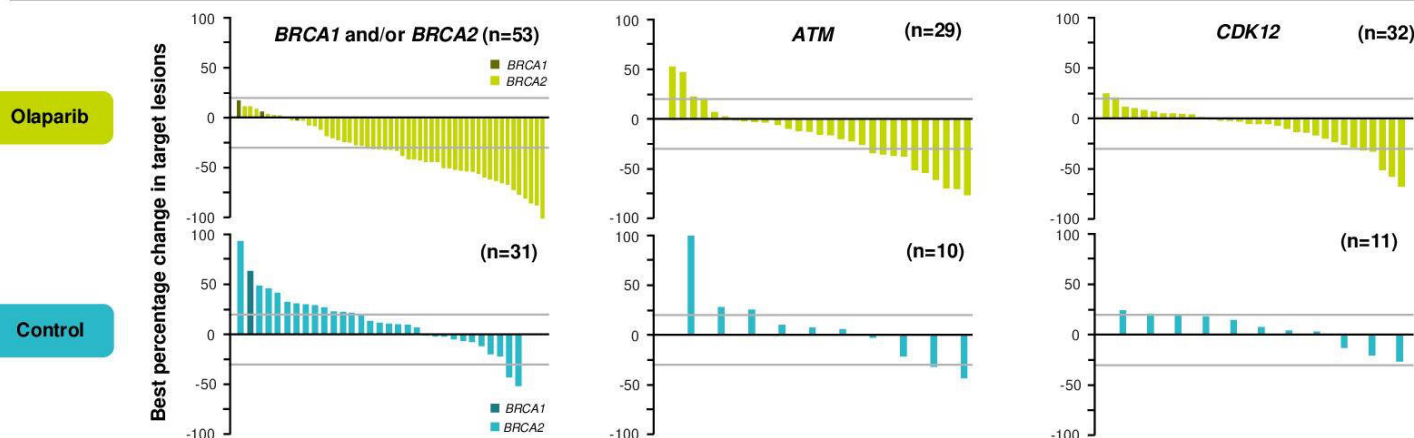
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Results



Activity of olaparib was observed for patients with alterations in *BRCA1* and/or *BRCA2*, *ATM*, and *CDK12*. Patients with tumors harboring a *BRCA1* and/or *BRCA2* alteration appeared to derive the greatest benefit

		Cohort A		Cohorts A+B		<i>BRCA1</i> and/or <i>BRCA2</i>		<i>ATM</i>		<i>CDK12</i>	
		Olaparib (N=162)	Control (N=83)	Olaparib (N=256)	Control (N=131)	Olaparib (N=102)	Control (N=58)	Olaparib (N=62)	Control (N=24)	Olaparib (N=61)	Control (N=28)
rPFS	Median, months	7.4	3.6	5.8	3.5	9.8	3.0	5.4	4.7	5.1	2.2
	HR (95% CI)	0.34 (0.25–0.47)		0.49 (0.38–0.63)		0.22 (0.15–0.32)		1.04 (0.61–1.87)		0.74 (0.44–1.31)	
OS	Median OS, months	19.1	14.7	17.3	14.0	20.1	14.4	18.0	15.6	14.1	11.5
	HR (95% CI)	0.69 (0.50–0.97)		0.79 (0.61–1.03)		0.63 (0.42–0.95)		0.93 (0.53–1.75)		0.97 (0.57–1.71)	
ORR	Evaluable patients, n	84	43	138	67	57	33	30	10	34	12
	ORR, %	33.3	2.3	21.7	4.5	43.9	0	10.0	10.0	5.9	0
PSA	Evaluable patients, n	153	77	243	123	94	54	61	22	58	27
	Confirmed response, %	43.1	7.8	30.0	9.8	61.7	0	13.1	22.7	5.2	3.7
CTC	Evaluable patients, n	52	22	78	32	29	17	25	3	14	5
	Conversion, %	55.8	22.7	52.6	21.9	69.0	23.5	40.0	33.3	50.0	40.0



Definitions for abbreviations, best percentage change in PSA and CTC for *BRCA1* and/or *BRCA2*, *ATM*, *CDK12* and remaining genes are included in the supplement

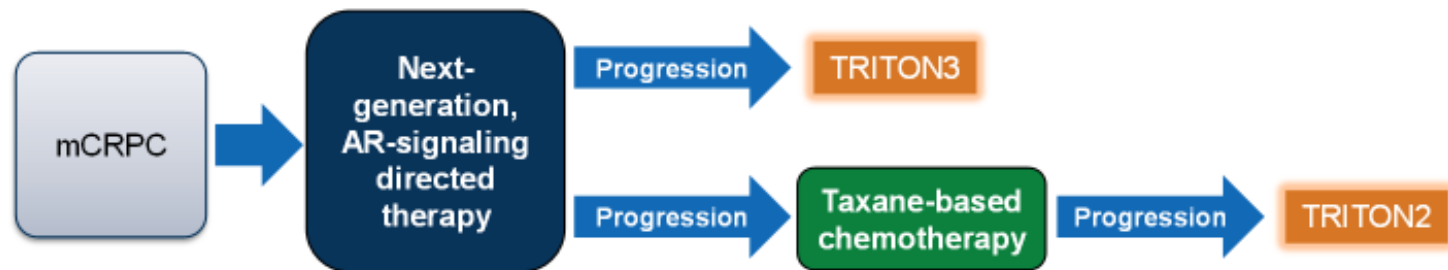


Cohort A, *BRCA1*, *BRCA2* and *ATM* alterations; Cohort A+B, all other HRR alterations; Control, physician's choice of enzalutamide or abiraterone; Evaluable patients: ORR, measurable disease at baseline; PSA, a valid baseline and post-baseline PSA measurement; CTC, CTC count ≥ 5 cells/7.5 mL at baseline

66% (n=86/131) of control patients in the overall population crossed over to olaparib treatment after their disease had progressed.² OS is not adjusted for crossover in this analysis

Kastrasyona Dirençli Metastatik Prostat kanseri

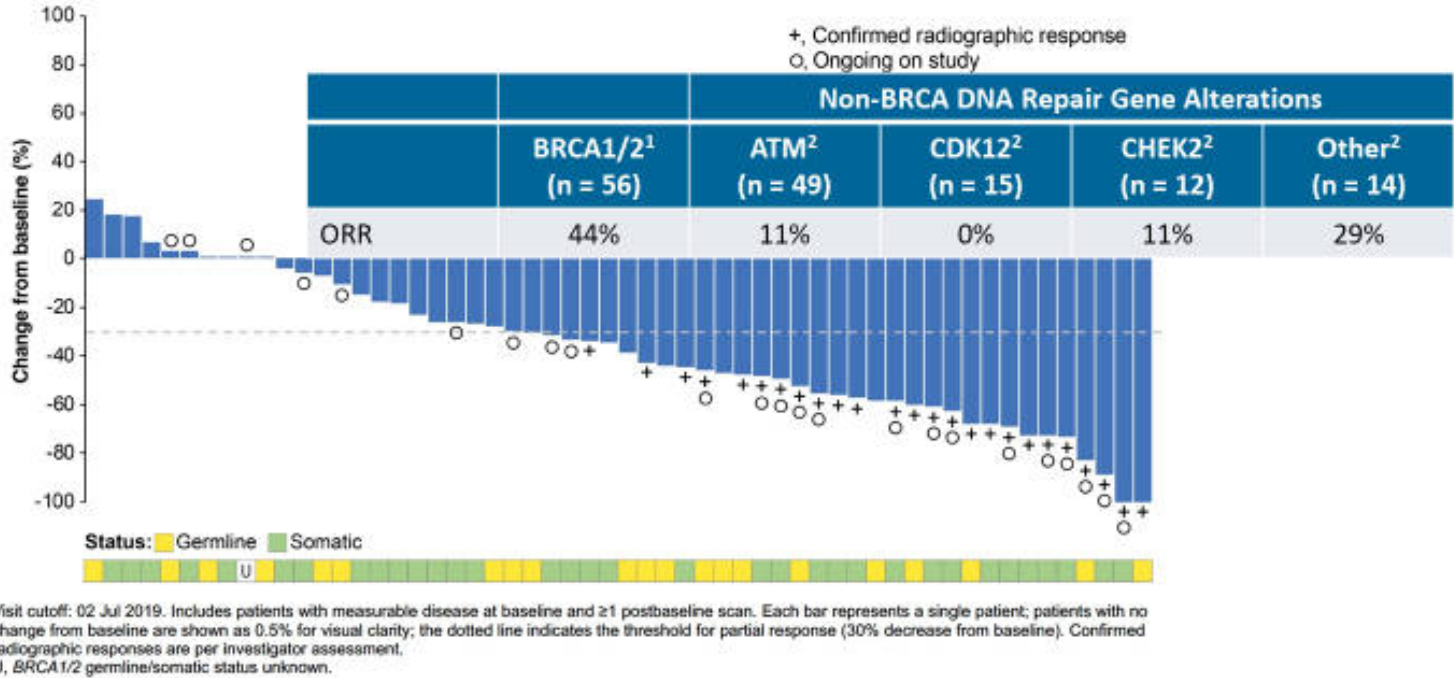
Rucaparib: TRITON2 and TRITON3 Studies



HRR-deficiency is defined by a deleterious alteration in *BRCA1*, *BRCA2*, *ATM*, or 12 other HRR genes (*BARD1*, *BRIP1*, *CDK12*, *CHEK2*, *FANCA*, *NBN*, *PALB2*, *RAD51*, *RAD51B*, *RAD51C*, *RAD51D*, *RAD54L*)

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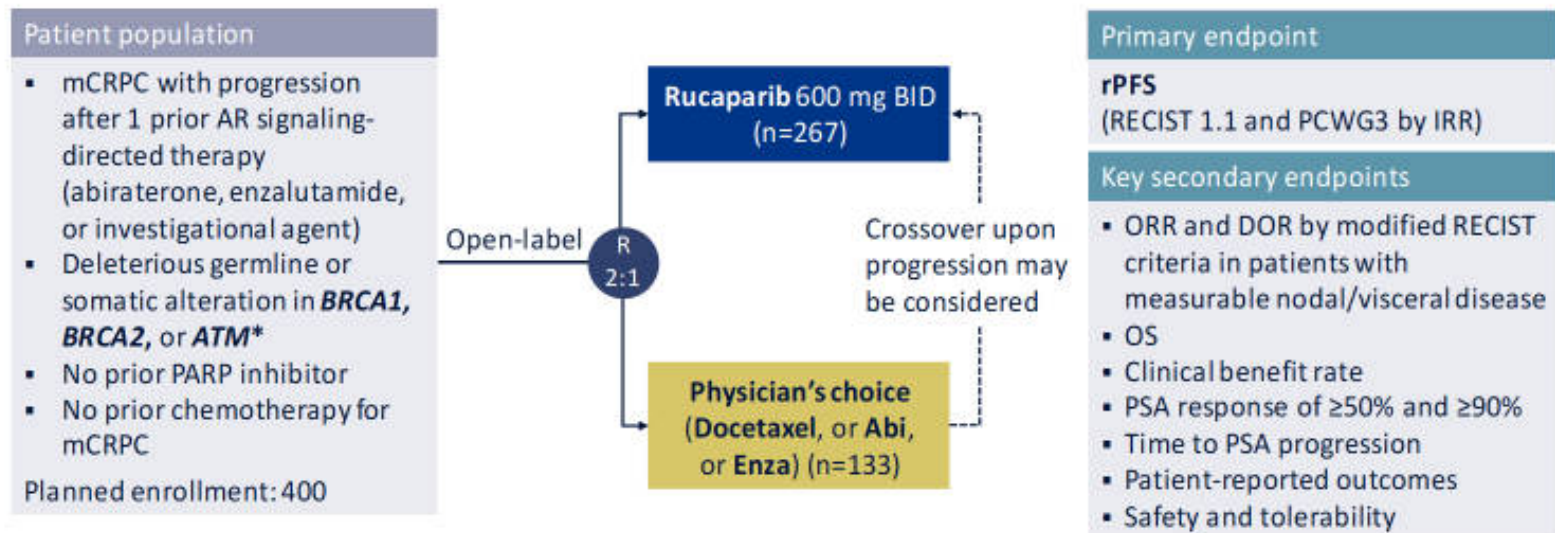
TRITON2: Best Change from Baseline in Sum of Target Lesions in Rucaparib-Treated Patients with a BRCA1/2 Alteration (N = 56)¹ and ORR in Patients with Non-BRCA DNA Damage Repair Gene Alterations (N = 78)²



¹Abida W et al. ESMO 2019; Abstract 846PD; ²Abida W et al. Clin Cancer Res 2020;26:2487-96.

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TRITON3: Randomized Phase III Trial



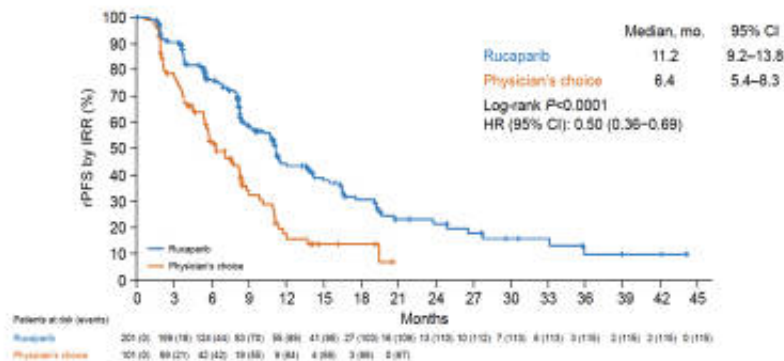
*Mutations identified in blood, archival tissue, or screening tumor tissue

Bryce A et al NEJM 2023; 388; 719-32. **NCT02975934**.

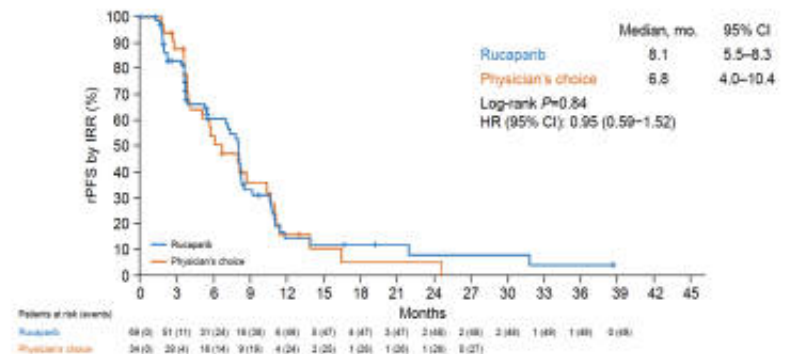
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TRITON3: rPFS in *BRCA1/2* and *ATM* Subgroups

***BRCA1/2* Subgroup**



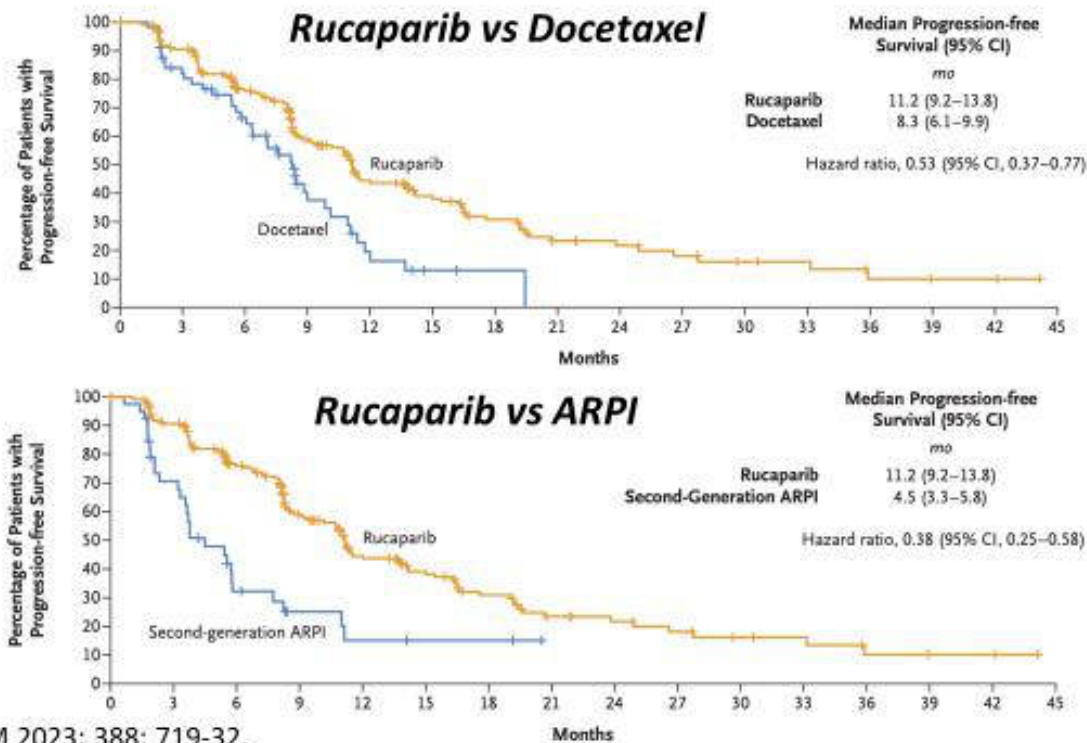
***ATM* Subgroup**



Bryce A et al NEJM 2023; 388; 719-32.

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TRITON3: rPFS by Control Treatment in *BRCA1/2* Subgroup



Bryce A et al NEJM 2023; 388; 719-32.

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Summary of PARPi *monotherapy* trials in mCRPC

Study and treatment	Prior therapy	HRR status criteria; Sample type	Primary endpoint	Results
TOPARP-A¹ Olaparib 400 mg BID (N=50)	1–2 taxane CT regimens; 98% had prior NHT	Deficiency not required; tumor	Composite response rate	33% overall; 88% (14 of 16) with DDR gene alterations
TOPARP-B² Olaparib 300 mg or 400 mg BID, randomized 1:1 (N=98)	1–2 taxane CT regimens; 88%–92% had prior NHT	Deleterious germline or somatic DDR gene alterations; tumor	Composite response rate	39.1% 300-mg cohort; 54.3% 400-mg cohort
TRITON2³ Rucaparib 600 mg BID (N=115)	1 taxane and 1–2 NHT	Deleterious germline or somatic <i>BRCA1/2</i> alteration; tumor or plasma	ORR by blinded independent radiology review	43.5% (27 of 62)
GALAHAD⁴ Niraparib 300 mg QD (N=289)	≥1 taxane and ≥1 NHT	Deleterious germline or somatic alteration in ≥1 of 8 prespecified DDR genes; tumor or plasma	ORR in patients with <i>BRCA</i> mutation and measurable disease	34.2% (26 of 76 measurable <i>BRCA</i> cohort) 10.6% (5 of 47 measurable non- <i>BRCA</i> cohort)
TALAPRO-1⁵ Talazoparib 1 mg QD (N=128)	1–2 CT regimens (≥1 taxane) and ≥1 NHT	Deleterious germline or somatic alterations in ≥1 of 11 prespecified DDR-HRR genes; tumor or plasma	ORR by blinded independent review	29.8% (31 of 104)

1. Mateo J et al. *N Engl J Med*. 2015;373:1697-708; 2. Mateo J et al. *Lancet Oncol*. 2020;21:162-174; 3. Abida W et al. *J Clin Oncol*. 2020;38:3763-3772; 4. Smith MR et al. *Lancet Oncol*. 2022;23:362-373; 5. de Bono JS et al. *Lancet Oncol*. 2021;22:1250-1264.

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Select Ongoing PARPi Combination Trials in Advanced PC

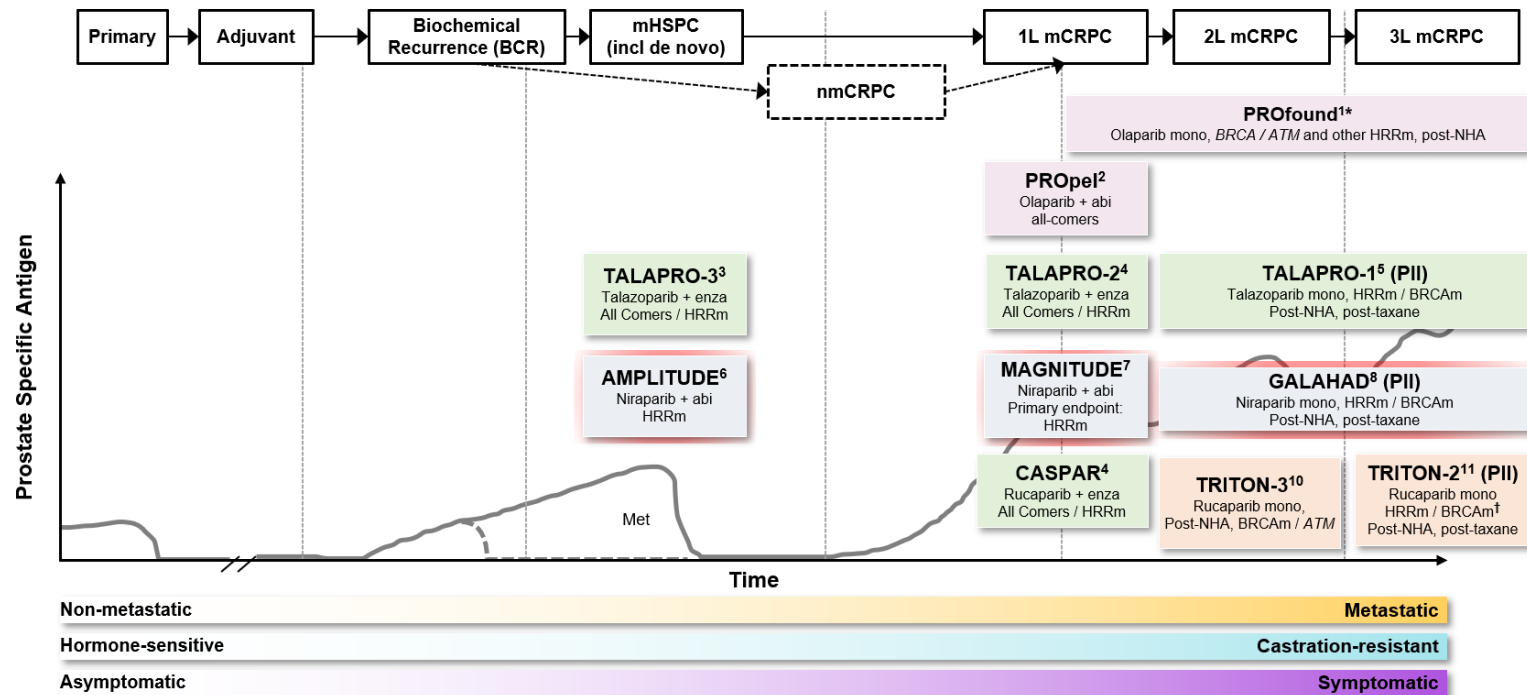
Study	Phase	Est. N	Patient Population	Study Arm(s)	Primary Endpoint(s)
COMRADE ^[1]	I/II	112	mCRPC with bone mets	Olaparib + radium-223 vs radium-223	MTD, rPFS
NCT02893917 ^[2]	II	90	mCRPC with progression on prior tx	Olaparib ± cediranib	rPFS
NCT03516812 ^[3]	II	30	Asymptomatic mCRPC with progression on ABI and/or ENZ	Olaparib + testosterone	PSA ↓
NCT03810105 ^[4]	II	32	Castration-sensitive PC with biochem recurrence, no mets, + DDR mut	Olaparib + durvalumab	Undetectable PSA
NCT03572478 ^[5]	Ib/IIa	60	mCRPC or metastatic/recurrent endometrial cancer	Phase Ib: rucaparib + nivolumab Phase IIa: rucaparib vs nivolumab vs rucaparib + nivolumab	DLT of combo
Javelin PARP Medley ^[6]	Ib/II	242	Locally advanced or metastatic CRPC and other solid tumors	Phase II: talazoparib + avelumab at MTD from phase Ib	Phase Ib: DLT Phase II: ORR
TALAPRO-2 ^[7]	III	872	DRD+ mCRPC	Talazoparib + AR-targeted therapy vs PBO + AR-targeted therapy	rPFS

All trials recruiting as of February 2019, except NCT03810105 is new.

1. NCT03317392. 2. NCT02893917. 3. NCT03516812. 4. NCT03810105. 5. NCT03572478. 6. NCT03330405. 7. NCT03395197.

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Ongoing trials investigating PARPi in advanced PC



Please see slide notes for references

*As a result of the data from PROfound, olaparib monotherapy was approved for treatment of mCRPC in patients with HRRm (FDA approval) or for patients with mutations in only *BRCA1/2* (EMA approval) after progression on a NHA^{12,13}

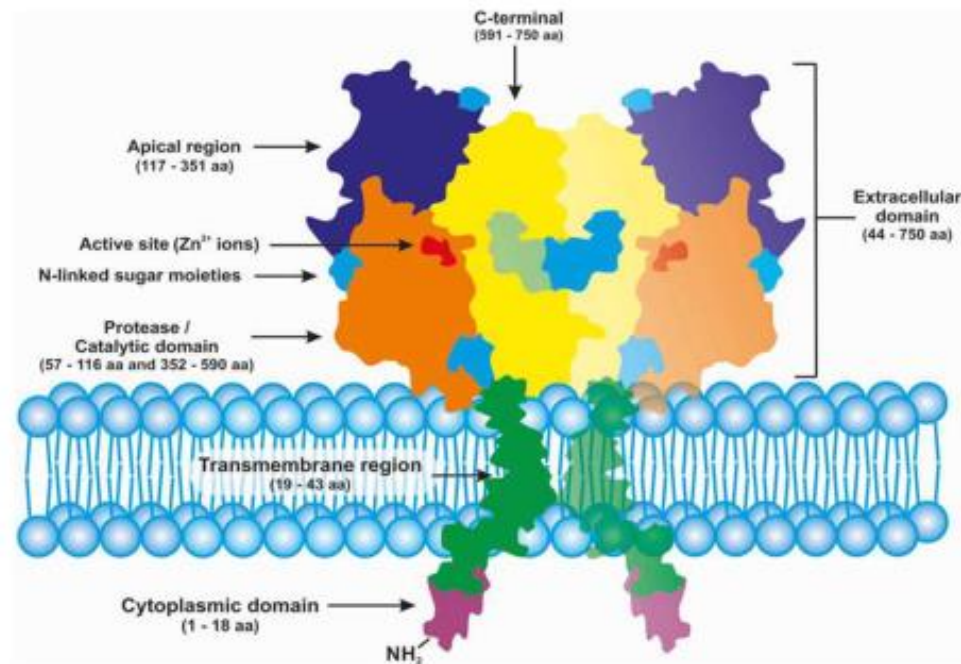
†As a result of the data from TRITON2, rucaparib monotherapy was approved by the FDA only for the treatment of mCRPC in patients with a *BRCA1/2*m who have disease progression after treatment with prior AR-directed therapy and prior taxane¹⁴

Abi=abiraterone; BCR=biochemical recurrence; enza=enzalutamide; FDA=US Food and Drug Administration; HRRm=homologous recombination repair mutation; mCRPC=metastatic castration-resistant prostate cancer; met=metastasis;

mono=monotherapy; mHSPC=metastatic hormone-sensitive prostate cancer; NHA=new hormonal agent; nmCRPC=non-metastatic castration-resistant prostate cancer; P2=Phase II; P3=Phase III.

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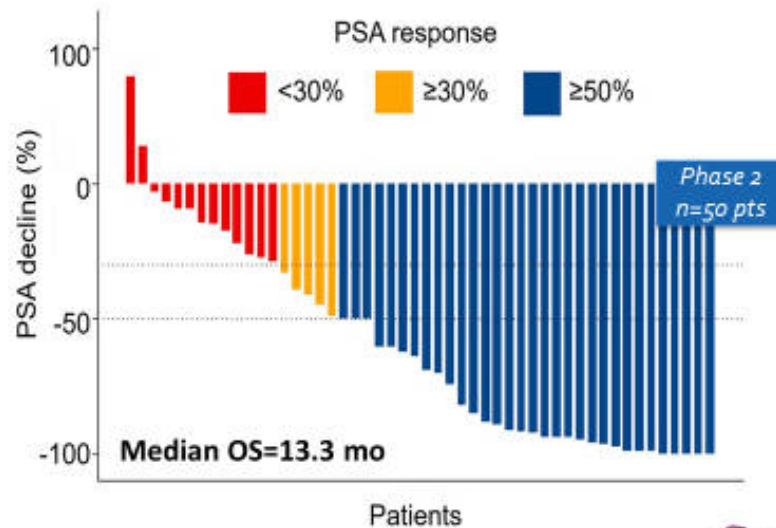
Targeting PSMA: Transmembrane Protein



Memorial Sloan Kettering
Cancer Center

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SML RNT in advanced prostate cancer PSMA-617 Lu¹⁷⁷(β): Phase 2 results



Heavily pre-treated patients

Highly selected [FDG-, PSMA+ PET]—30% rejected

Dose every 6 weeks x 4 (47% of subjects got 4 doses)

Toxicity= grade 1-2 dry mouth in 87%



Source: 1.) Hofman M et al. *Lancet Oncol.* 2018;19(6):825-833.; 2.) Violet J et al. *J Nucl Med.* 2020;61(6):857-865.



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Articles

[¹⁷⁷Lu]Lu-PSMA-617 versus cabazitaxel in patients with metastatic castration-resistant prostate cancer (TheraP): a randomised, open-label, phase 2 trial



Michael S Hofman, Louise Emmett, Shaheen Sandhu, Amir Iravani, Anthony M Joshua, Jeffrey C Goh, David A Pattison, Thean Hsiang Tan, Ian D Kirkwood, Siobhan Ng, Baslyn J Francis, Craig Gedy, Natalie K Rutherford, Andrew Weichardt, Andrew M Scott, Sze-Ting Lee, Edmond M Kwan, Arun A Azad, Shalke Ramdane, Andrew D Redfern, William Macdonald, Alex Gumsinki, Edward Hsiao, Wei Chua, Peter Lin, Alison Y Zhang, Margaret M McLennett, Martin R Stockler, John A Violet*, Scott G Williams, Andrew J Martin, Ian D Davis, for the TheraP Trial Investigators and the Australian and New Zealand Urogenital and Prostate Cancer Trials Group†

Summary

Background Lutetium-177 [¹⁷⁷Lu]Lu-PSMA-617 is a radiolabelled small molecule that delivers β radiation to cells expressing prostate-specific membrane antigen (PSMA), with activity and safety in patients with metastatic castration-resistant prostate cancer. We aimed to compare [¹⁷⁷Lu]Lu-PSMA-617 with cabazitaxel in patients with metastatic castration-resistant prostate cancer.

Methods We did this multicentre, unblinded, randomised phase 2 trial at 11 centres in Australia. We recruited men with metastatic castration-resistant prostate cancer for whom cabazitaxel was considered the next appropriate standard treatment. Participants were required to have adequate renal, haematological, and liver function, and an Eastern Cooperative Oncology Group performance status of 0–2. Previous treatment with androgen receptor-directed therapy was allowed. Men underwent gallium-68 [⁶⁸Ga]Ga-PSMA-11 and 2-fluorine-18 [¹⁸F]fluoro-2-deoxy-D-glucose (FDG) PET-CT scans. PET eligibility criteria for the trial were PSMA-positive disease, and no sites of metastatic disease with discordant FDG-positive and PSMA-negative findings. Men were randomly assigned (1:1) to [¹⁷⁷Lu]Lu-PSMA-617 (6–0.8–5 GBq intravenously every 6 weeks for up to six cycles) or cabazitaxel (20 mg/m² intravenously every 3 weeks for up to ten cycles). The primary endpoint was prostate-specific antigen (PSA) reduction defined by a reduction of at least 50% from baseline. This trial is registered with ClinicalTrials.gov, NCT03392428.

Findings Between Feb 6, 2018, and Sept 3, 2019, we screened 291 men, of whom 200 were eligible on PET imaging. Study treatment was received by 98 (99%) of 99 men randomly assigned to [¹⁷⁷Lu]Lu-PSMA-617 versus 85 (84%) of 101 randomly assigned to cabazitaxel. PSA responses were more frequent among men in the [¹⁷⁷Lu]Lu-PSMA-617 group than in the cabazitaxel group (65 vs 37 PSA responses; 66% vs 37% by intention to treat; difference 29% (95% CI 16–42; p<0.0001; and 66% vs 44% by treatment received; difference 23% [9–37]; p=0.0016). Grade 3–4 adverse events occurred in 32 (33%) of 98 men in the [¹⁷⁷Lu]Lu-PSMA-617 group versus 45 (53%) of 85 men in the cabazitaxel group. No deaths were attributed to [¹⁷⁷Lu]Lu-PSMA-617.

Interpretation [¹⁷⁷Lu]Lu-PSMA-617 compared with cabazitaxel in men with metastatic castration-resistant prostate cancer led to a higher PSA response and fewer grade 3 or 4 adverse events. [¹⁷⁷Lu]Lu-PSMA-617 is a new effective class of therapy and a potential alternative to cabazitaxel.

Funding Prostate Cancer Foundation of Australia, Endocyte (a Novartis company), Australian Nuclear Science and Technology Organization, Movember, The Distinguished Gentleman's Ride, It's a Bloke Thing, and CAN4CANCER.

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Introduction

Metastatic castration-resistant prostate cancer is incurable. Treatments that are proven to prolong overall survival include docetaxel,¹ androgen receptor-directed therapies such as abiraterone,² and enzalutamide.³ Cabazitaxel improves survival in men with metastatic castration-resistant prostate cancer⁴ progressing after previous treatment with docetaxel.

Radiolabelled small molecules that bind to prostate-specific membrane antigen (PSMA), such as lutetium-177 [¹⁷⁷Lu]Lu-PSMA-617, are promising treatments for

patients with advanced prostate cancer.⁵ [¹⁷⁷Lu]Lu-PSMA-617 delivers high doses of radiation to prostate cancer cells via β-particle emission with a 0.7 mm mean path length. This short range results in highly specific tumour targeting while limiting damage to normal tissues. Encouraging activity and safety has been reported in several non-randomised studies in men with metastatic castration-resistant prostate cancer that progressed after standard therapies.^{6–8} We reported a decrease in prostate-specific antigen (PSA) of 50% or more in 64% of men and a favourable toxicity profile in a

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See Online/Comment
[https://doi.org/10.1016/S0140-6736\(21\)00349-4](https://doi.org/10.1016/S0140-6736(21)00349-4)
*Deceased Oct 5, 2020
†A complete list of the TheraP Trial Collaborators is provided in the appendix (pp 3–4).
Prostate Cancer Therapeutics and Imaging Centre of Excellence, Molecular Imaging and Therapeutic Nuclear Medicine, Peter MacCallum Cancer Centre, Melbourne, VIC, Australia
(Prof M S Hofman MBBS, S Sandhu MBBS, A Iravani MD, A A Azad PhD, J A Violet PhD, Prof S G Williams MD); St Peter MacCallum Department of Oncology (Prof M S Hofman, S Sandhu, A A Azad, J A Violet, Prof S G Williams), and Department of Medicine (Prof A M Scott MD, S T Lee PhD), University of Melbourne, Melbourne, VIC, Australia; Department of Therapeutics and Nuclear Medicine (Prof L Emmett MD), and Department of Medical Oncology, Kinghorn Cancer Centre (Prof A M Joshua PhD), St Vincent's Hospital, Sydney, NSW, Australia; Faculty of Medicine, UNSW Sydney, Sydney, NSW, Australia (Prof L Emmett, Prof P Lin MBBS); Mallinckrodt Institute of Radiology, Washington University, St Louis, MO, USA (A Iravani); Department of Nuclear Medicine & Specialised PET Services (D A Pattison MBBS), and Medical Oncology (J C Goh MBBS), Royal Brisbane and Women's Hospital, Brisbane, QLD, Australia;

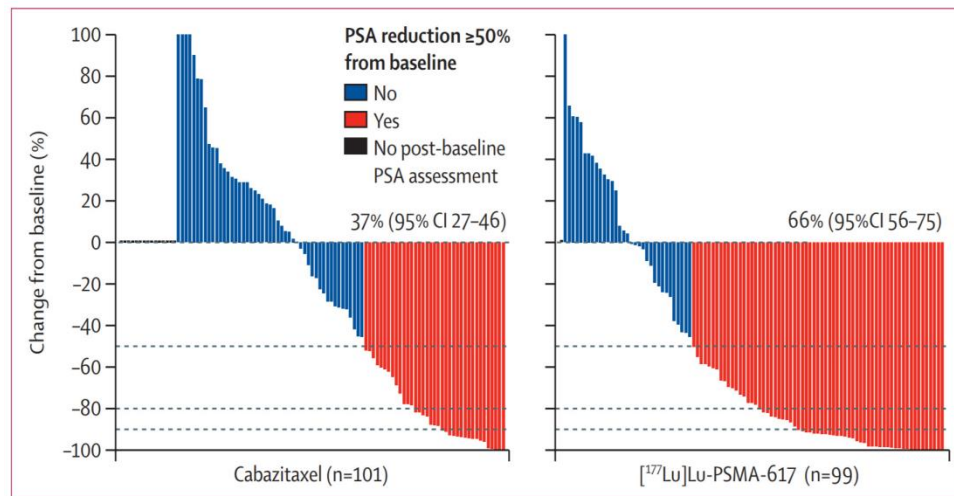


Figure 2: PSA response
PSA=prostate-specific antigen. ¹⁷⁷Lu=lutetium-177.

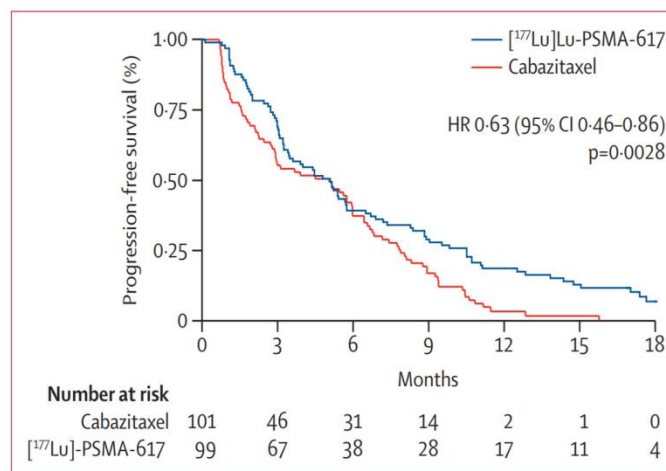


Figure 3: Radiographic or PSA progression-free survival

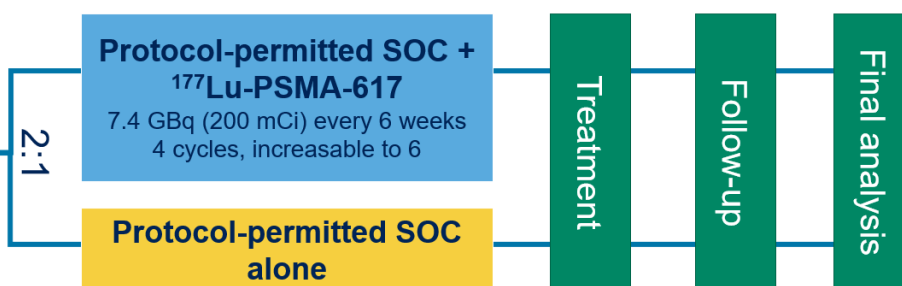
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Open-label study of protocol-permitted standard of care ± ^{177}Lu -PSMA-617 in adults with PSMA-positive mCRPC

Eligible patients

- Previous treatment with both
 - ≥ 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



- 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

Presented By: Michael J. Morris

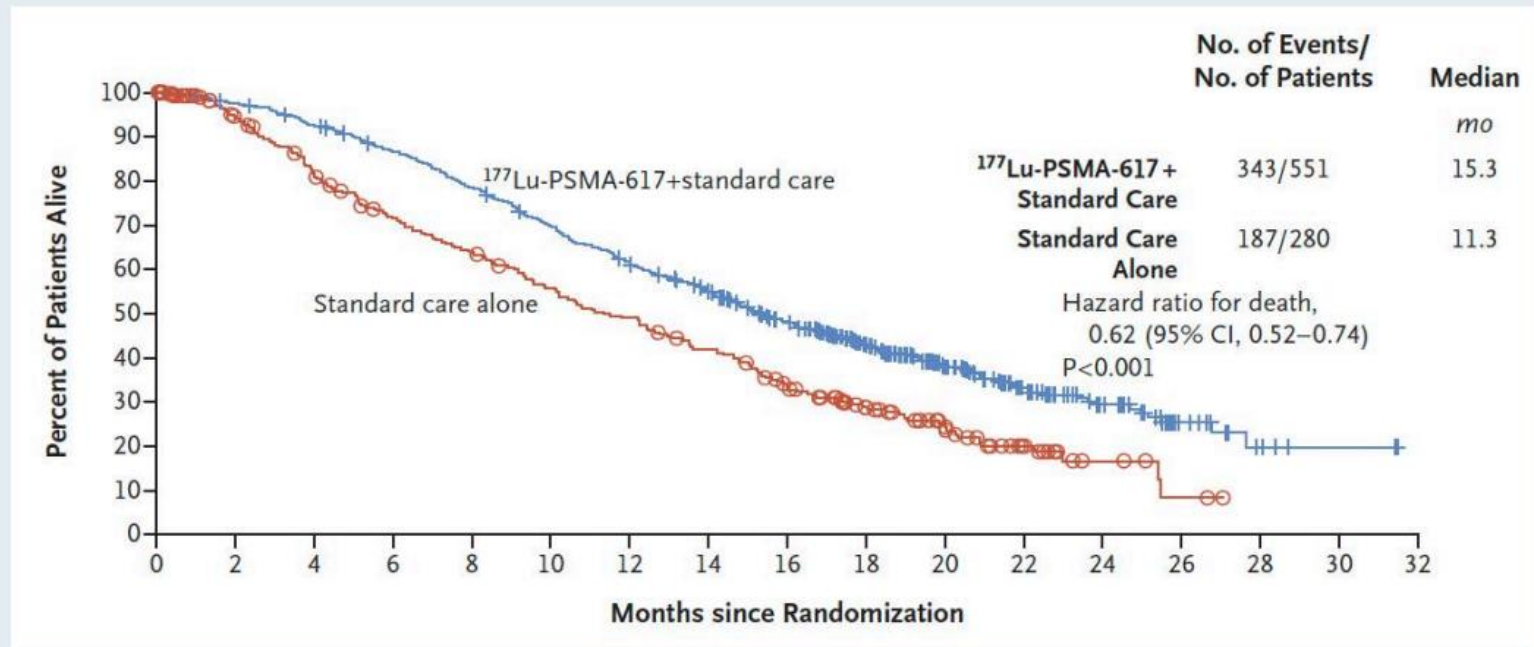
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VISION: Overall Survival



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Treatment-emergent adverse events grouped as topics of interest: no unexpected or concerning safety signals

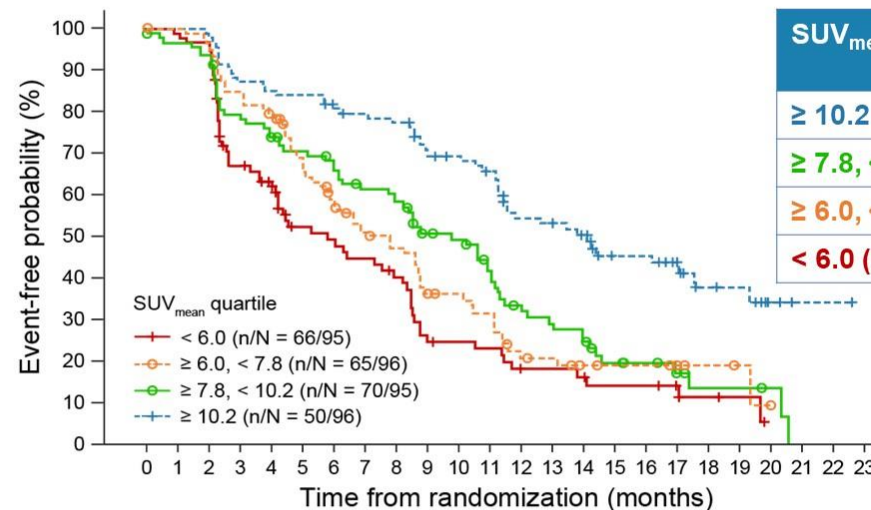
Patients, n (%)	All grades		Grade 3–5	
	¹⁷⁷ Lu-PSMA-617 + SOC (n = 529)	SOC alone (n = 205)	¹⁷⁷ Lu-PSMA-617 + SOC (n = 529)	SOC alone (n = 205)
Fatigue	260 (49.1)	60 (29.3)	37 (7.0)	5 (2.4)
Bone marrow suppression	251 (47.4)	36 (17.6)	124 (23.4)	14 (6.8)
Leukopenia	66 (12.5)	4 (2.0)	13 (2.5)	1 (0.5)
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)

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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
$\geq 7.8, < 10.2$	9.8
$\geq 6.0, < 7.8$	7.8
< 6.0 (lowest)	5.8

Number of patients still at risk

≥ 10.2	96	95	94	82	80	79	74	72	70	61	58	54	41	40	36	25	25	19	11	10	3	1	1	0
$\geq 7.8, < 10.2$	95	90	87	73	69	63	60	53	51	41	39	31	23	20	17	11	9	6	4	4	2	0	0	0
$\geq 6.0, < 7.8$	96	94	91	79	72	57	47	38	34	26	24	21	13	12	9	8	8	7	3	2	1	0	0	0
< 6.0	95	91	87	56	50	35	33	30	26	17	15	14	10	10	9	7	7	5	3	2	0	0	0	0

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

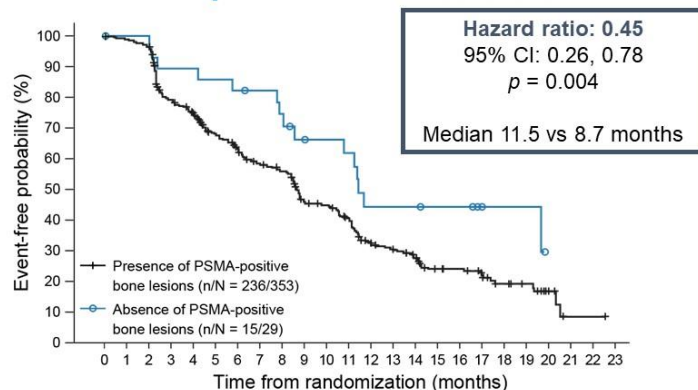
CI, confidence interval; HR, hazard ratio; PFS-FAS, progression-free survival-full analysis set; rPFS, radiographic progression-free survival; SUV, standardized uptake value

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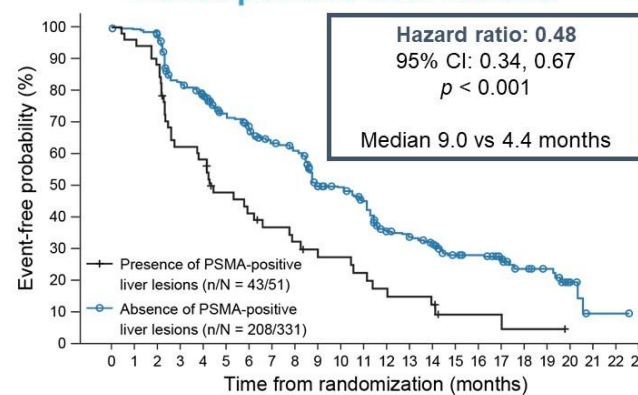
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rPFS by absence of PSMA-positive lesions (PFS-FAS)

PSMA-positive bone lesions



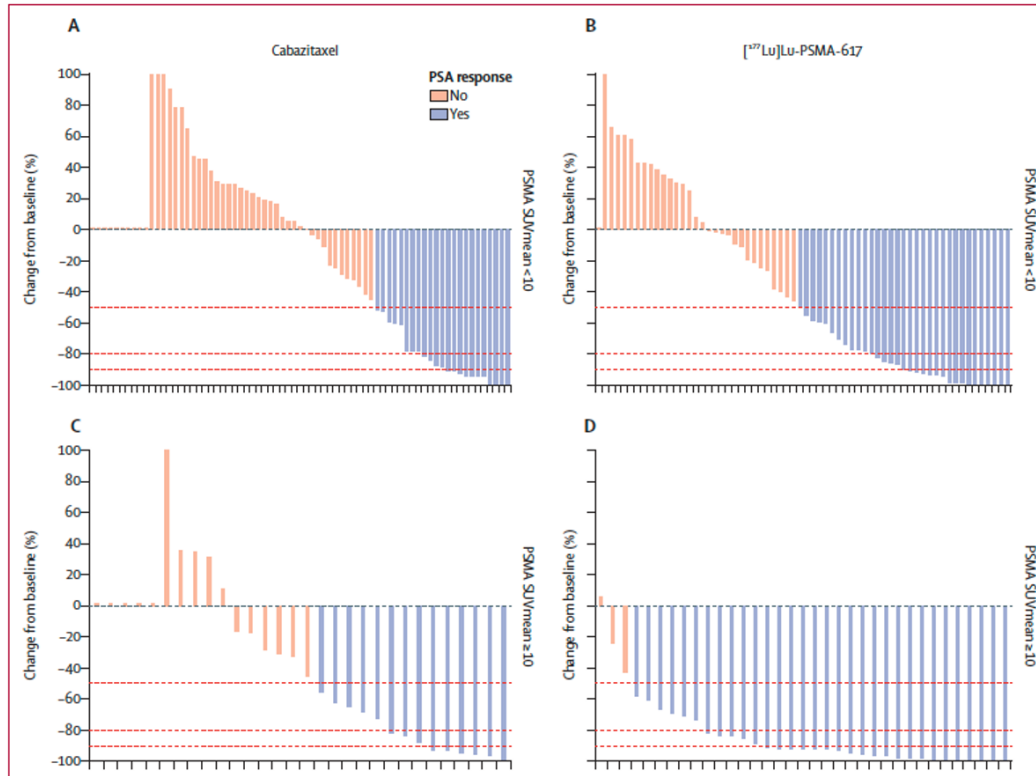
PSMA-positive liver lesions



Absence of PSMA+ lesions in bone or liver was associated with a decrease in the risk of an rPFS event compared with presence of ≥ 1 PSMA+ lesions in these organs

Comparison is between patients with ≥ 1 PSMA-positive bone (left panel) or liver (right panel) lesion and patients without any PSMA-positive (left panel) or liver (right panel) lesion
 CI, confidence interval; HR, hazard ratio; NS, not significant; PSMA, prostate-specific membrane antigen; rPFS, radiographic progression-free survival

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Buteau et al, Lancet Oncol 2022

Odds of PSA response to ¹⁷⁷Lu-PSMA-617 versus cabazitaxel significantly higher for SUVmean of 10 or higher compared with those with SUVmean of less than 10 (odds ratio [OR] 12.19 [95% CI 3.42, 58.76] vs 2.22 [1.11–4.51]).

SUVmean also correlates with outcomes in VISION (Kuo et al, ASCO 2022)

** Of note: Quantitative PET parameters used for SUVmean calculation require specialised software and are not yet routinely available in most clinics*

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FDG volume in TheraP prognostic

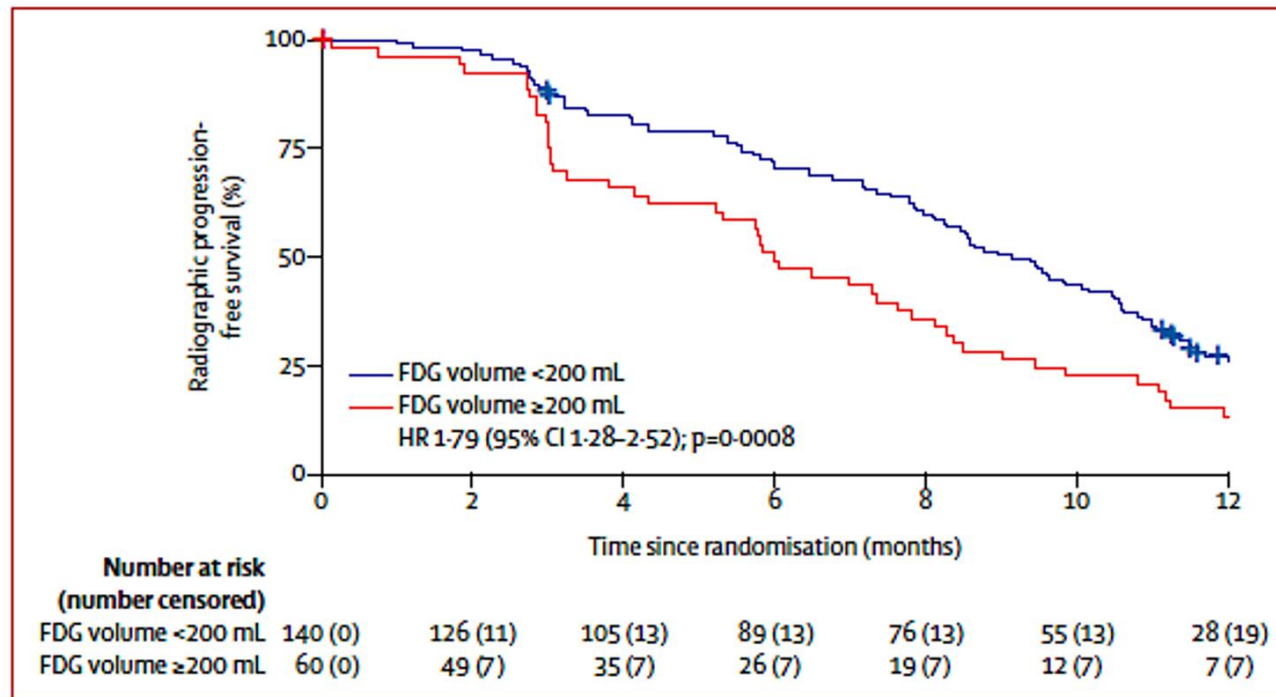


Figure 5: Radiographic progression-free survival according to FDG-PET MTV

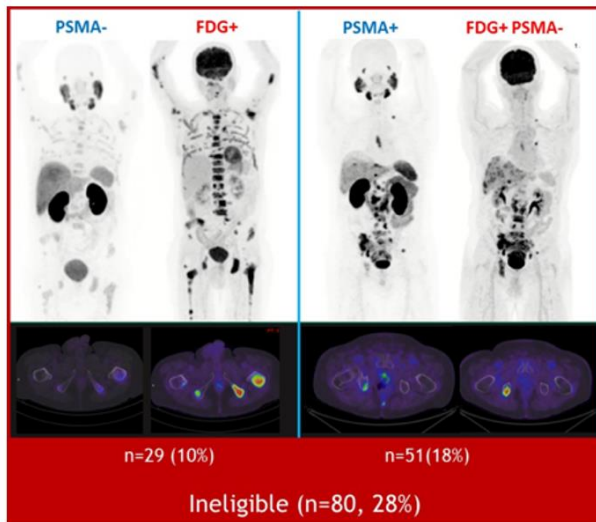
FDG-2-[18F]fluoro-2-deoxy-D-glucose. MTV-metabolic tumour volume.

Buteau et al, Lancet Oncol 2022

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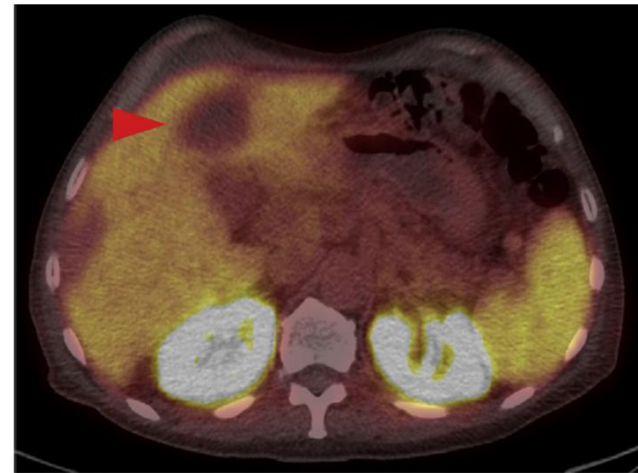
Loss of PSMA Expression in a Subset of CRPC

12.6% (VISION) + 28% (TheraP) were not eligible for Lu-PSMA due to PSMA-negative disease



Hofman et al. Lancet Oncol 2018, Thang et al, Eur Urol Oncol 2018

PSMA-low biopsies may reveal NEPC



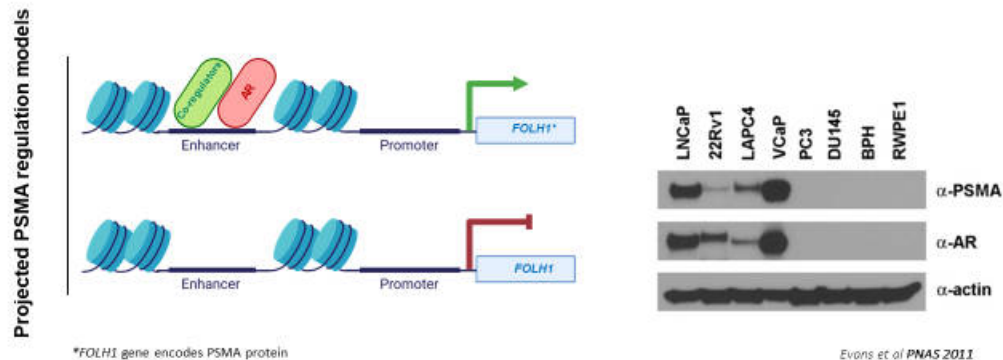
Tosoian et al, 2016

Bakht et al, Nat Cancer 2023

PSMA negative disease associated with poor prognosis (median OS 2.5 mo in TheraP)

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AR Regulation of PSMA

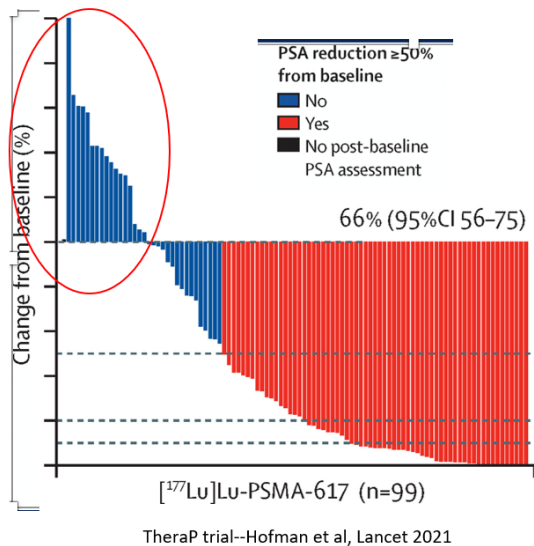


AR negative prostate cancer associates with loss of PSMA expression

But there are exceptions to this rule

Bakht et al, Nat Cancer 2023

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Patient selection for PSMA-directed therapy

- Expression of the target (PSMA)
- Other biomarkers of response (tumor features, drug features, drug mechanism)
- Mechanisms of resistance (guide next therapy)

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**Phase 3 trial of [^{177}Lu]Lu-PSMA-617
in taxane-naïve patients with
metastatic castration-resistant
prostate cancer (PSMAfore)**

Presenter: Oliver Sartor,*
Mayo Clinic, Rochester, MN, USA

Co-authors: D Castellano, K Herrmann, J de Bono,
ND Shore, KN Chi, M Crosby, JM Piulats, A Flechon,
XX Wei, H Mahammedi, G Roubaud, H Studentova,
S Ghebremariam, E Kpamegan, TN Kreisl,
N Delgosaie, K Lehnhoff, MJ Morris,* K Fizazi,*
on behalf of the PSMAfore investigators

*Contributed equally



Oliver Sartor

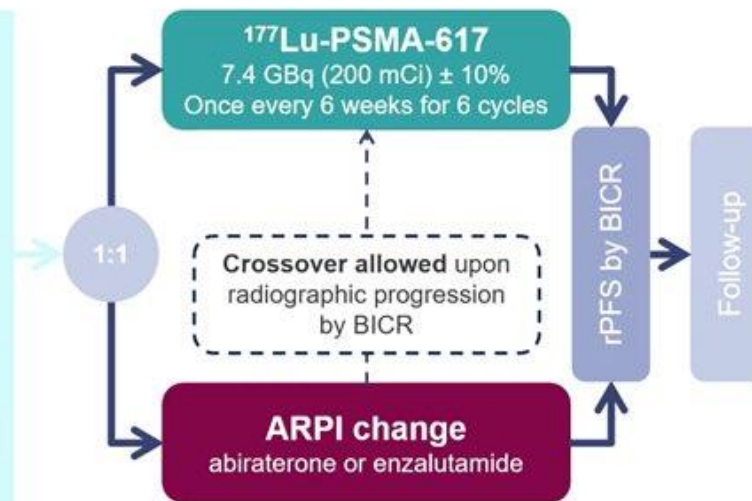
Phase III trial of [^{177}Lu]Lu-PSMA-617 in taxane-naïve patients with metastatic castration-resistant prostate cancer (PSMAfore)

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

Eligible adults

- Confirmed progressive mCRPC
- ≥ 1 PSMA-positive metastatic lesion on [^{68}Ga]Ga-PSMA-11 PET/CT and no exclusionary PSMA-negative lesions
- Progressed once on prior second-generation ARPI
 - Candidates for change in ARPI
- Taxane-naïve (except [neo]adjuvant > 12 months ago)
 - Not candidates for PARPi
- ECOG performance status 0–1



Stratification factors

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



Oliver Sartor

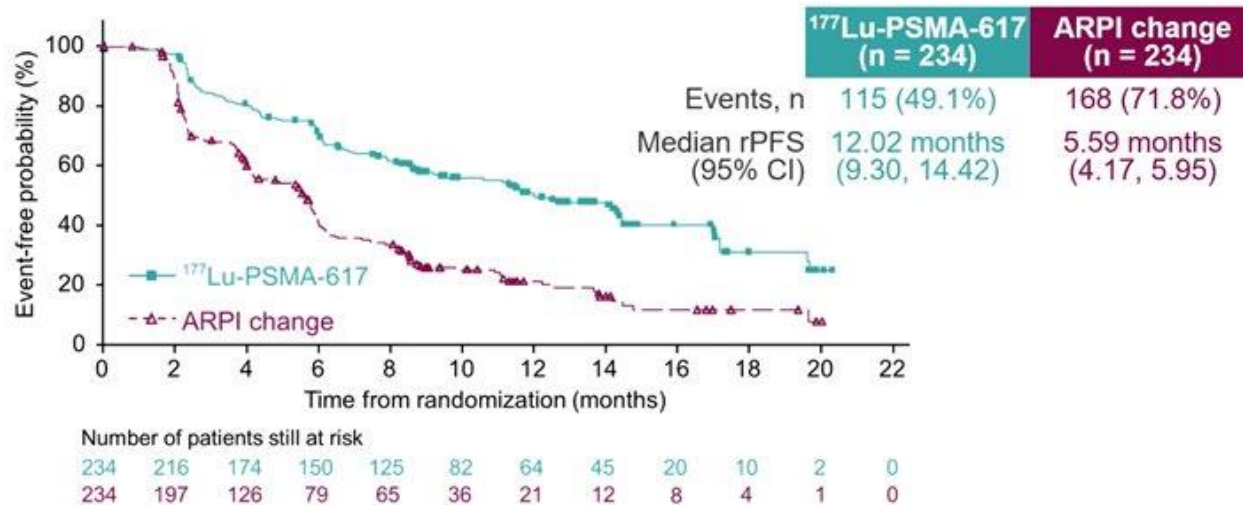
Phase III trial of [^{177}Lu]Lu-PSMA-617 in taxane-naïve patients with metastatic castration-resistant prostate cancer (PSMAfore)

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rPFS: primary endpoint was met

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

Updated HR: 0.43 (95% CI: 0.33, 0.54)



Oliver Sartor

Phase III trial of [¹⁷⁷Lu]Lu-PSMA-617 in taxane-naïve patients with metastatic castration-resistant prostate cancer (PSMAfore)

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PSMAfore: the primary rPFS endpoint was met with a favourable adverse event profile in taxane-naïve patients with mCRPC

- ^{177}Lu -PSMA-617 prolonged rPFS versus ARPI change
- Secondary and exploratory endpoints also favoured ^{177}Lu -PSMA-617
 - PSA response
 - Objective response rate
 - Time to symptomatic skeletal events
 - Time to worsening in HRQoL and pain
- Prespecified crossover-adjusted OS trended favourably
 - The 84.2% crossover rate may have confounded ITT analysis
 - OS data collection continues
- ^{177}Lu -PSMA-617 had a manageable safety profile and was well tolerated



Oliver Sartor

Phase III trial of [^{177}Lu]Lu-PSMA-617 in taxane-naïve patients with metastatic castration-resistant prostate cancer (PSMAfore)

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LuPSMA CRPC Data: Context in one Slide

Trial	Life-prolonging Control Arm	OS Benefit	Median OS with LuPSMA	PSMA-SUVmean ≥ 10 "Most benefit"
LuPSMA Post-docetaxel and post NHT				
VISION	No ~ hormone switch	Yes	~15 months	Yes
THERA-P	Yes - cabazitaxel	No	~ 19 months	Yes
LuPSMA Post-NHT but docetaxel naive				
PSMAfore	No - hormone switch	No (*84% x-over)	~19 months	Not reported (yet?)
Starting NHT Both Docetaxel and NHT naive				
Abiraterone Enzalutamide	No - Prednisone / Placebo	Yes	~32-34 months	Not available

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ENZA-p schema

Eligibility

mCRPC with PSA rising and >5ng/mL
No chemotherapy for mCRPC
≥2 high risk features for early enzalutamide failure
Positive ⁶⁸Ga PSMA PET/CT

Stratification

Study Site
Volume of disease (>20 vs ≤20)
Early docetaxel for hormone-sensitive disease
Prior treatment with abiraterone



Enzalutamide 160 mg

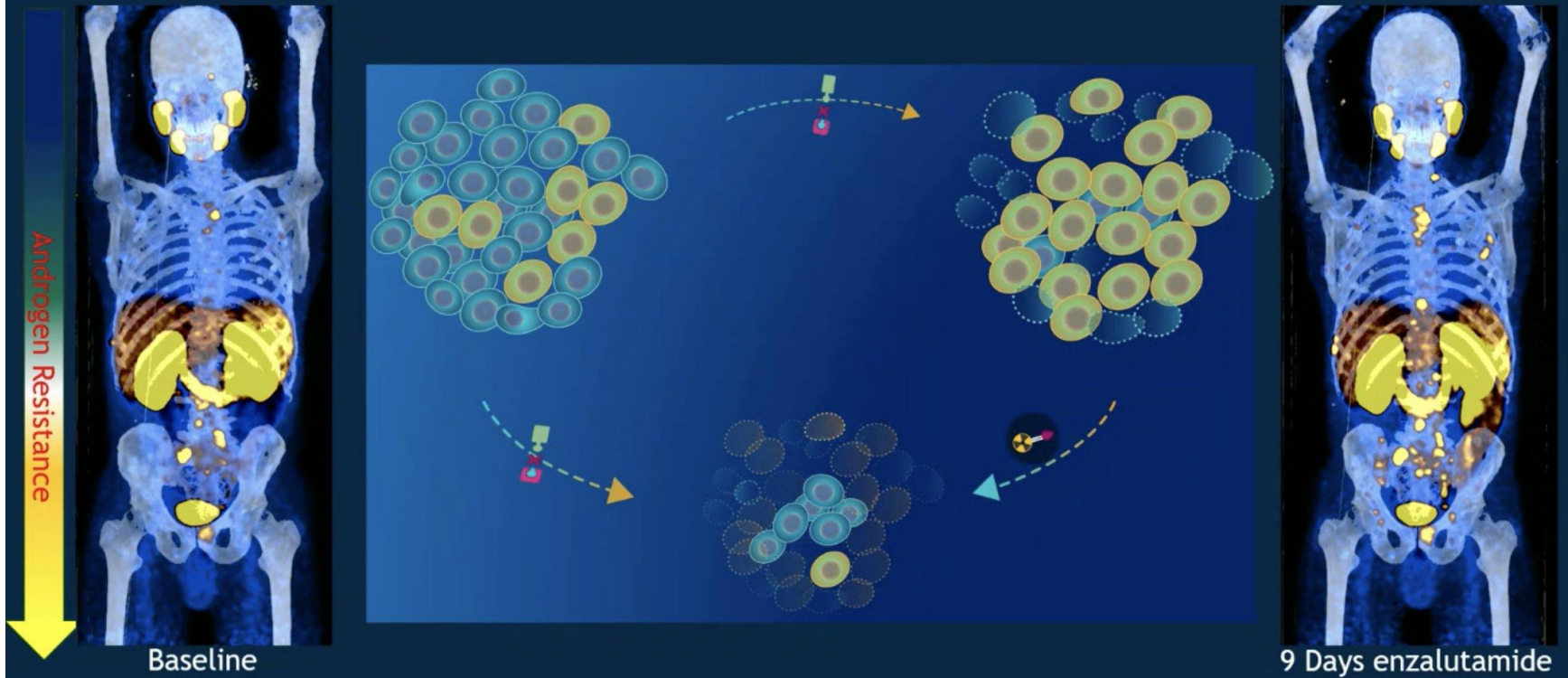
Enzalutamide 160 mg
+ Lu-PSMA 7.5 GBq
2-4 doses

Objectives

PSA-PFS (primary endpoint)
Radiographic PFS
PSA response rate
Pain response and PFS
Clinical PFS
HRQOL
Adverse events
Overall survival
Health economic analyses
Translational/correlative

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Clonal Adjustment

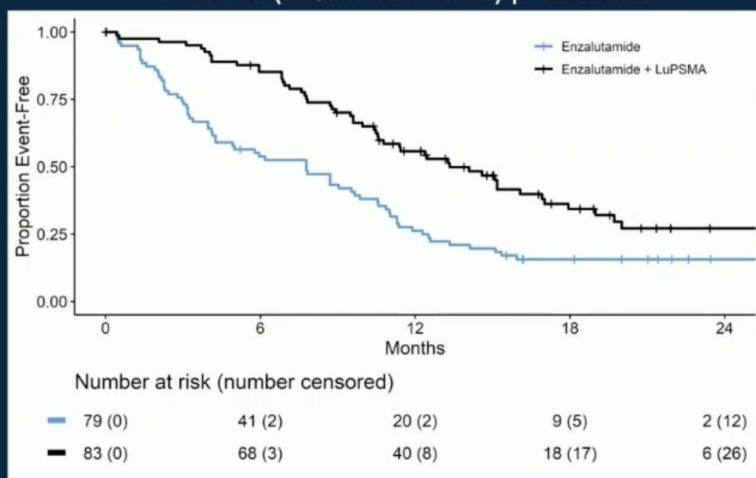


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Progression Free Survival

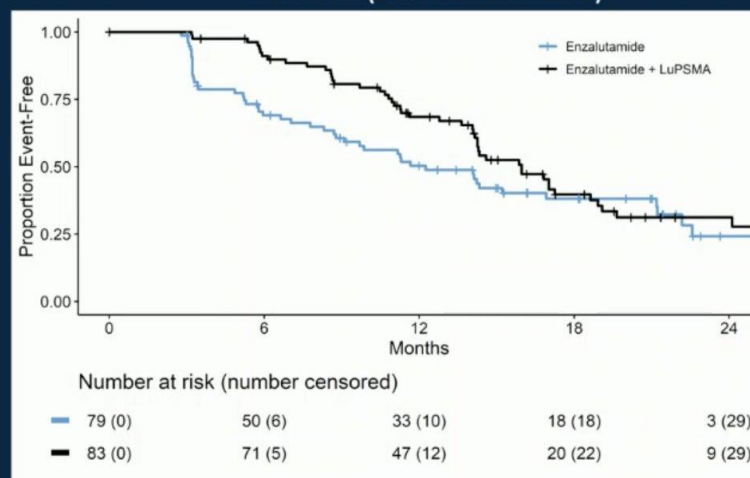
PSA-PFS

HR 0.43 (95%CI 0.29-0.63) p=0.00001



R-PFS

HR 0.67 (95% CI 0.44-1.01)



PSA-PFS	Participants	Events	Censored	Median Months
Enzalutamide	79	65	14	7.8
Enzalutamide + Lu-PSMA	83	52	31	13

Radiographic-PFS	Participants	Events	Censored	Median Months
Enzalutamide	79	47	35	12
Enzalutamide + Lu-PSMA	83	48	32	16

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Conclusions

- First randomised trial combining an ARSI with ^{177}Lu -PSMA-617
- Strong evidence of enhanced anticancer activity on primary endpoint PSA-PFS HR 0.43, median 13 vs 7.8 months ($p < 0.00001$)
- Active (life-prolonging) treatment for the control group
- First trial of adaptive-dosed Lu-PSMA based on interim PSMA PET
 - Potential to reduce toxicity by only administering if persistent PSMA-avid disease
 - 2-4 doses Lu-PSMA administered; further doses (2-6) may further improve PFS.
- Planned follow-up of progression free and overall survival July 2024

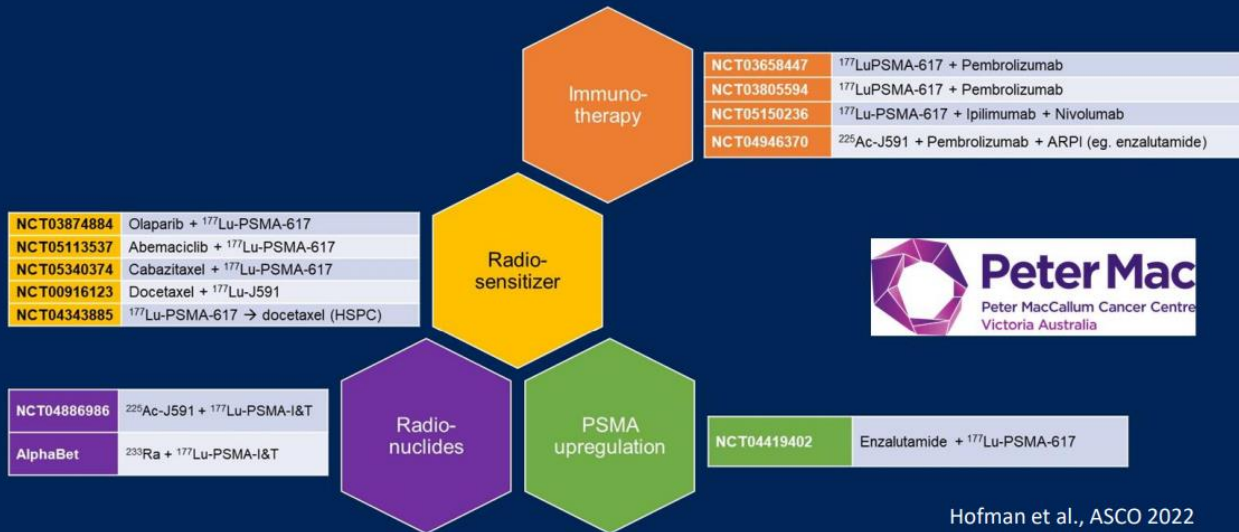
Evre IV Kastrasyona Dirençli Prostat Kanseri

PSMA ekspresyonu

EAU22 | AMSTERDAM
1-4 July 2022

Others

Current Lu-PSMA combination trials



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Other drugs that target PSMA

- Radionuclide therapies
 - ^{225}Ac -PSMA-617, ^{177}Lu -J591, ^{225}Ac -J591, ^{90}Y , others
- Bispecific T Cell Engager-- AMG160, BAY2010112, REGN5678
- CAR-T –CART-PSMA-TGF β RDN, P-PSMA-101
- PSMA-ADC
- Is there cross resistance between drugs?
- Optimal combination therapies?

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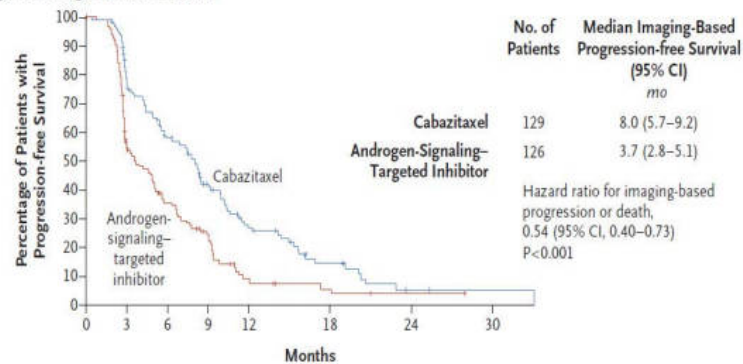
New and Emerging Therapies for mCRPC

- Targeting the AR – e.g., AR-degraders, ODM-208, BAT
 - AR is still key driver of mCRPC
- PSMA therapies – e.g., Ac-PSMA, T-cell engagers, CAR-T
 - PSMA may still be expressed in patients post-¹⁷⁷Lu-PSMA-617
- Other cell surface targets – e.g., TROP2, B7-H3, DLL3
 - Potential role for biomarkers selection/molecular imaging
- Targeting non-AR driven disease – e.g, NEPC
- Targeting other genomic alterations – e.g, PTEN (AKTi)
- Rationale combination strategies
 - mCRPC is a biologically heterogeneous disease

Kastrasyona Dirençli Metastatik Prostat kanseri

CARD: Imaging-Based PFS and OS with Cabazitaxel versus Abiraterone or Enzalutamide for mCRPC

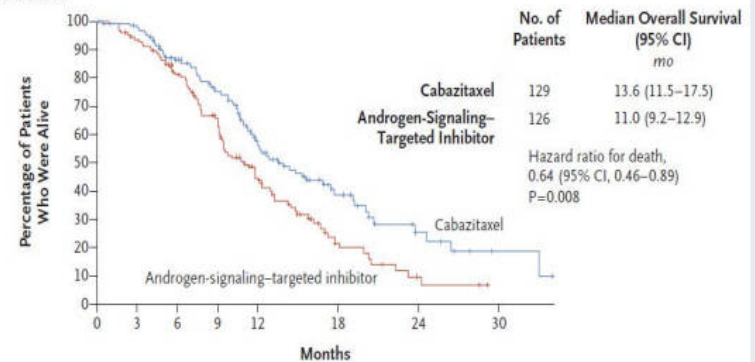
A Imaging-Based Progression-free Survival



No. at Risk

Cabazitaxel	129	91	64	41	23	9	2	1
Androgen-signaling-targeted inhibitor	126	61	36	22	7	3	1	0

A Overall Survival



No. at Risk

Cabazitaxel	129	122	96	77	51	21	8	2
Androgen-signaling-targeted inhibitor	126	116	88	64	39	11	3	0

Kastrasyona Dirençli Metastatik Prostat kanseri

CARD: Select Adverse Events

Table 2. Adverse Events (Safety Population).

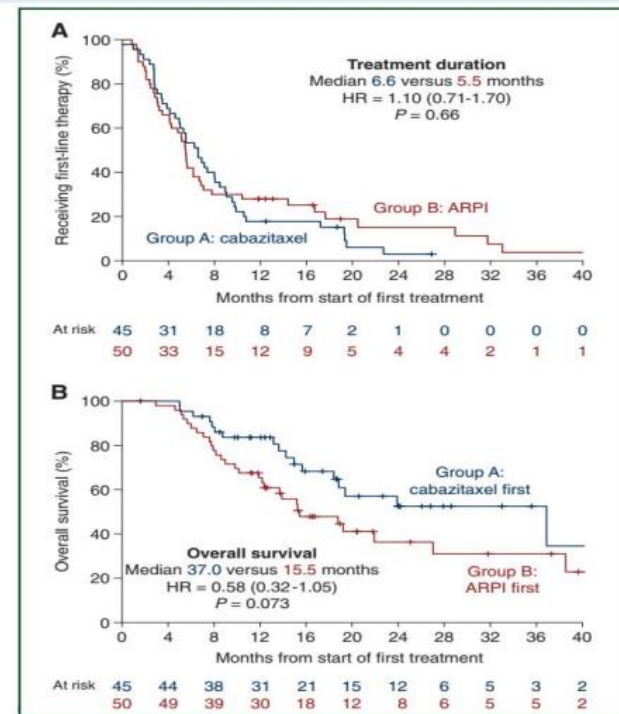
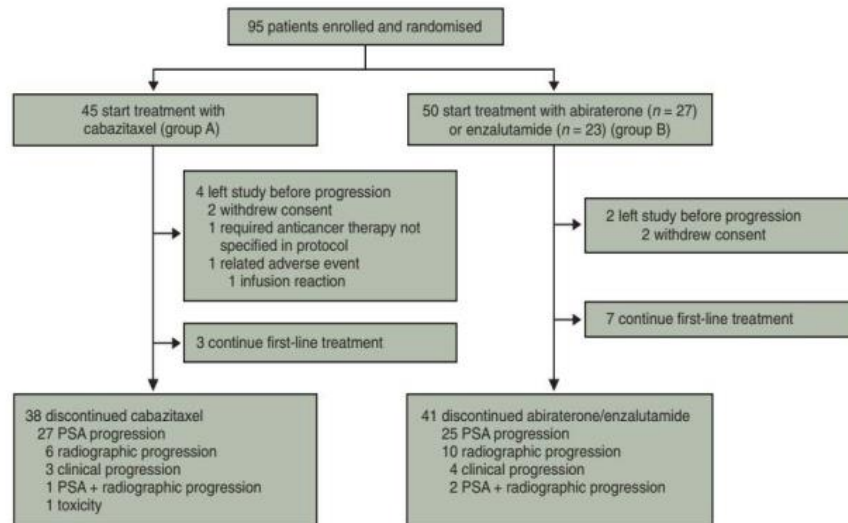
Event	Cabazitaxel (N = 126)		Androgen-Signaling-Targeted Inhibitor (N = 124)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Any adverse event — no. (%)	124 (98.4)	—	117 (94.4)	—
Any grade ≥3 adverse event — no. (%)	—	71 (56.3)	—	65 (52.4)
Any serious adverse event — no. (%)	49 (38.9)	—	48 (38.7)	—
Any adverse event leading to permanent discontinuation of treatment — no. (%)	25 (19.8)	—	11 (8.9)	—
Any adverse event leading to death — no. (%)*	7 (5.6)	—	14 (11.3)	—
Common adverse events — no. (%)†				
Asthenia or fatigue	67 (53.2)	5 (4.0)	45 (36.3)	3 (2.4)
Diarrhea	50 (39.7)	4 (3.2)	8 (6.5)	0
Infection	40 (31.7)	10 (7.9)	25 (20.2)	9 (7.3)
Musculoskeletal pain or discomfort‡	34 (27.0)	2 (1.6)	49 (39.5)	7 (5.6)
Nausea or vomiting	33 (26.2)	0	29 (23.4)	2 (1.6)
Peripheral neuropathy	25 (19.8)	4 (3.2)	4 (3.2)	0
Constipation	19 (15.1)	0	13 (10.5)	0
Hematuria	19 (15.1)	1 (0.8)	7 (5.6)	2 (1.6)
Laboratory abnormalities — no./total no. (%)‡‡				
Anemia	124/125 (99.2)	10/125 (8.0)	118/124 (95.2)	6/124 (4.8)
Leukopenia	93/125 (74.4)	40/125 (32.0)	39/124 (31.5)	2/124 (1.6)
Neutropenia	81/123 (65.9)	55/123 (44.7)	8/124 (6.5)	4/124 (3.2)
Thrombocytopenia	51/125 (40.8)	4/125 (3.2)	20/124 (16.1)	2/124 (1.6)
Aspartate aminotransferase increased	27/124 (21.8)	4/124 (3.2)	35/124 (28.2)	0/124
Alanine aminotransferase increased	24/124 (19.4)	1/124 (0.8)	11/124 (8.9)	0/124
Hypokalemia	15/125 (12.0)	1/125 (0.8)	19/124 (15.3)	1/124 (0.8)

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The Canadian Trial (Phase II OZM-054 Trial)

Poor prognosis:

liver mets,
CRPC <12 months,
or >3 of 6 (LDH, ECOG, visceral, albumin, ALP, <36 mo from Dx)



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Other Recently Reported Trials Investigating Cabazitaxel for mCRPC

CABASTY¹

Multicenter, randomized, open-label study
Enrollment: May 2017 to January 2021

mCRPC previously treated with docetaxel-containing regimen and ≥ 1 ARTA
Age ≥ 65 years
ECOG PS ≤ 2
G8 >14 (or ≤ 14 with reversible geriatric impairment)
N = 196 pts

Stratification factors:

- Geriatric assessment G8 (< 14 vs. ≥ 14)
- Age (< 70 vs. ≥ 70 years old)

R
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1:1

Cabazitaxel (25 mg/m² q3w)
+ prednisone (10 mg daily)
+ G-CSF
n = 97

31 centers (23 France, 8 Germany)

Cabazitaxel (16 mg/m² q2w)
+ prednisone (10 mg daily)
+ G-CSF
n = 99

Endpoints

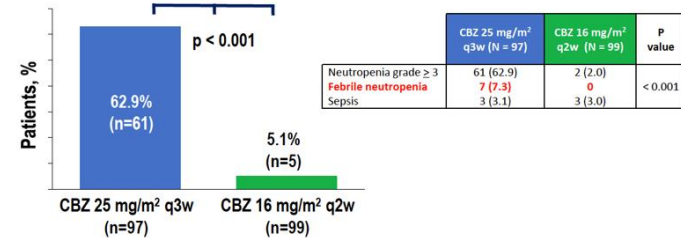
Primary: Incidence of grade ≥ 3 neutropenia (measured at nadir) and/or neutropenic complications

Secondary: OS, rPFS, PSA response, tumor response, time to symptomatic skeletal event, safety, HRQoL, biomarkers

Statistical hypothesis: Cabazitaxel 16 mg/m² q2w would have 20 % lesser grade ≥ 3 neutropenia and/or neutropenic complications than cabazitaxel 25 mg/m² q3w; around 90 patients per arm would be needed to achieve a power of 80%

PRIMARY ENDPOINT

Neutropenia grade ≥ 3 and/or neutropenic complications*



OSTRICH²

Inclusion criteria

- mCRPC
- ECOG PS 0-2
- Testosterone <50 ng/dL
- Adequate bone marrow and liver functions
- Prior docetaxel
- Previous ARTA was allowed
- Progressive disease
- Features of poor prognostic disease (≥ 1):
 - ❖ Liver metastasis
 - ❖ Castration resistant <12 m
 - ❖ Progressive <6 m after docetaxel

R

Cabazitaxel

Other life prolonging therapy

Abiraterone/P
OR enzalutamide

Other life prolonging therapy

12 weeks CBR

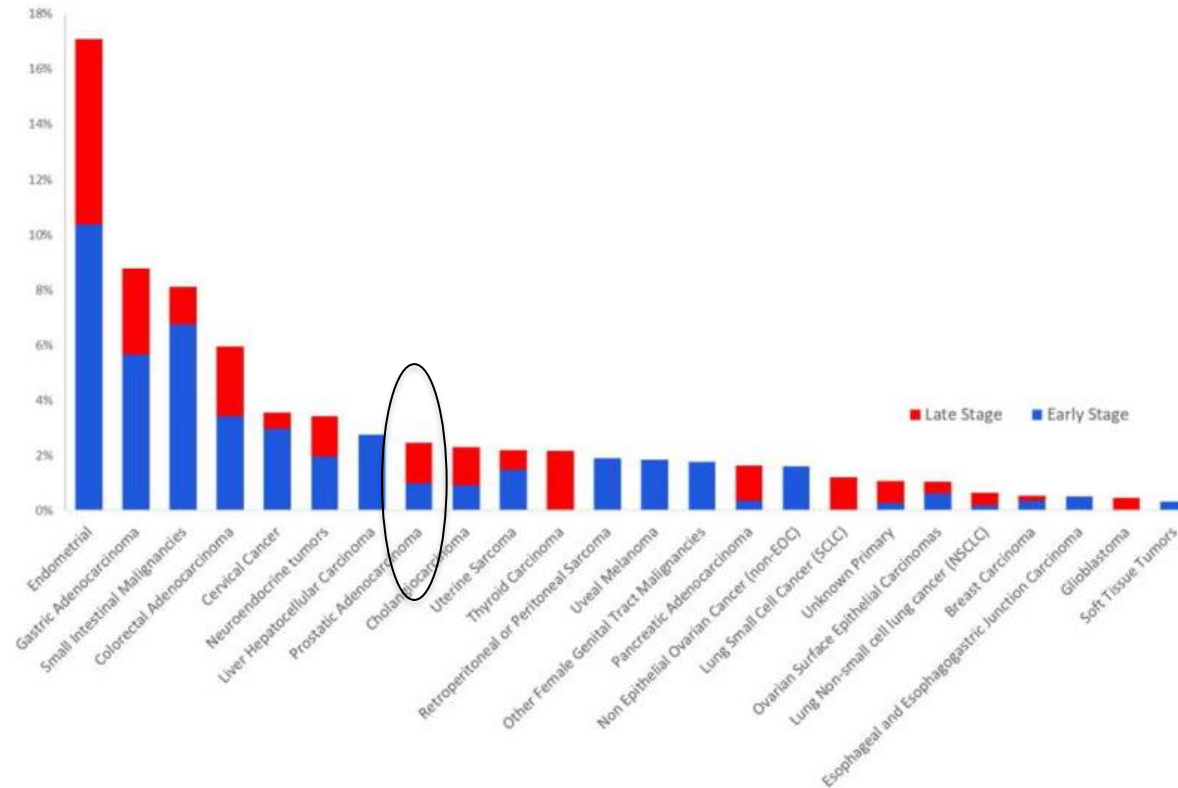
Follow-up for secondary endpoints

Conclusions

- No significant difference in CBR between CBZ and ARTA treated patients at 12 weeks
- Visceral metastases were more frequent in CBZ patients
- Radiological response and stable disease at 12 weeks was significantly higher in patients treated with CBZ than with ARTA
- Time to clinical progression was significantly prolonged in patients treated with ARTA
- Overall survival and rPFS was similar in both groups

¹ Oudard S et al. ESMO 2022; Abstract 1363MO; ² van der Zande K et al. ASCO 2021; Abstract 5059.

Mismatch Repair Deficiency



Le et al. Science 2017

Kastrasyona Dirençli Metastatik Prostat kanseri

16:00 - 17:20 Proffered Paper session - Genitourinary tumours, prostate

CHAIRS : KARIM FIZAZI, SHAHNEEN SANDHU



Interim Results From a Phase 1 Study of Xaluritamig (AMG 509), a STEAP1 x CD3 XmAb® 2+1 Immune Therapy, in Patients With Metastatic Castration-Resistant Prostate Cancer (mCRPC)

William K. Kelly, Daniel C. Danila, Chia-Chi Lin, Jae-Lyun Lee, Nobuaki Matsubara, Patrick J. Ward, Andrew J. Armstrong, David W. Pook, Miso Kim, Tanya Dorff, Stefanie Fischer, Yung-Chang Lin, Lisa Horvath, Christopher Sumey, Zhao Yang, Gabor Jurida, Jamie Connarn, Hweixian L. Penny, Julia Stieglmaier, Leonard Appleman



William Kelly

Interim results from a phase I study of AMG 509 (xaluritamig), a STEAP1 x CD3 XmAb 2+1 immune therapy, in patients with metastatic castration-resistant prostate cancer (mCRPC)



Granada Auditorium - Hall 3

MADRID SPAIN 20-24 OCTOBER 2023

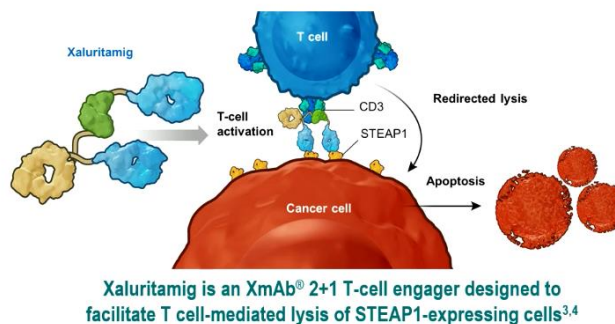
Kastrasyona Dirençli Metastatik Prostat kanseri

16:00 - 17:20 Proffered Paper session - Genitourinary tumours, prostate

CHAIRS : KARIM FIZAZI, SHAHNEEN SANDHU

Xaluritamig is a STEAP1-targeted T cell engager being evaluated for the treatment of prostate cancer

- Prostate cancer remains a leading cause of cancer deaths worldwide, and patients with mCRPC have a poor prognosis¹
- STEAP1 is a cell surface antigen highly expressed in prostate cancer and associated with poor survival^{2,3}
- In preclinical studies, xaluritamig showed broad anti-cancer effects in prostate cancer xenograft models³



William Kelly

Interim results from a phase I study of AMG 509 (xaluritamig), a STEAP1 x CD3 XmAb 2+1 immune therapy, in patients with metastatic castration-resistant prostate cancer (mCRPC)

XmAb® is a registered trademark of Xencor, Inc.
mAb, monoclonal antibody; mCRPC, metastatic castration-resistant prostate cancer; STEAP1, six transmembrane epithelial antigen of the prostate

1. Turco F, et al. *Res Rep Urol*. 2022;14:339-50.
2. Xu M, et al. *Cancers (Basel)*. 2022;14:4034.
3. Nolan-Stevaux O, et al. *Cancer Res*. 2020;80(16_Supplement):DDT02-03.
4. Li C, et al. *J Immunother Cancer*. 2020;8:718.

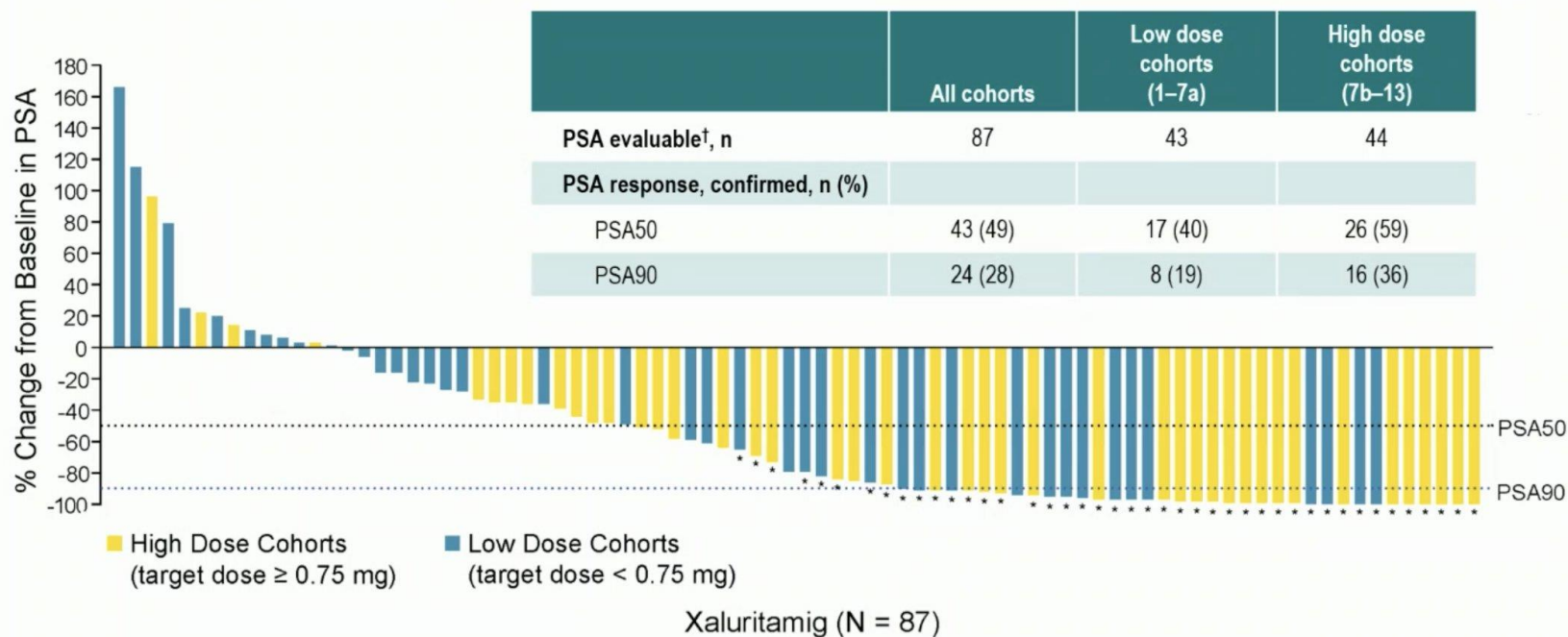


Granada Auditorium - Hall 3

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Kastrasyona Dirençli Metastatik Prostat kanseri

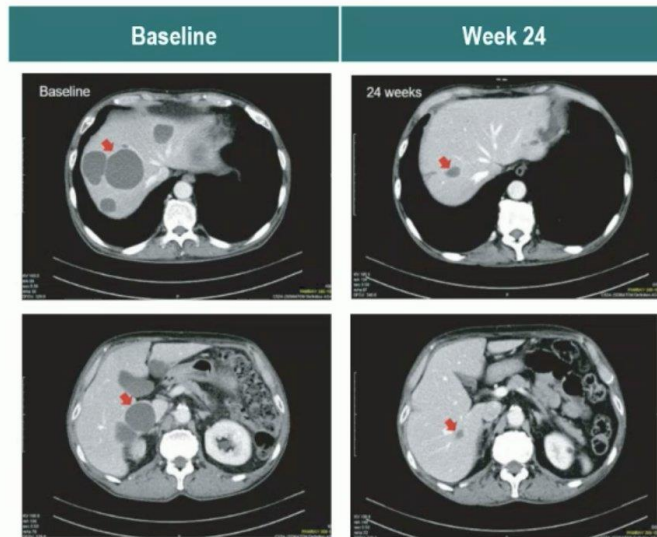
Confirmed PSA responses were observed across cohorts



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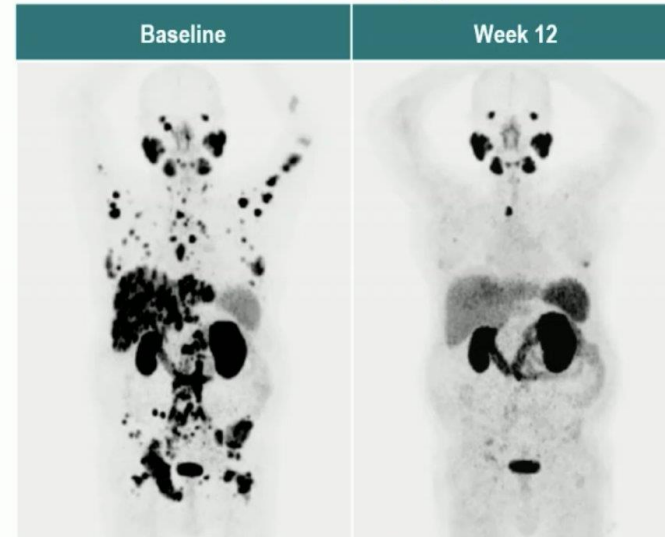
Anti-tumor activity has been observed against both soft tissue and bone disease

CT Scan



65-year-old heavily pre-treated patient with mCRPC. Patient was enrolled in cohort 11 and achieved a confirmed RECIST and PSA90 response.

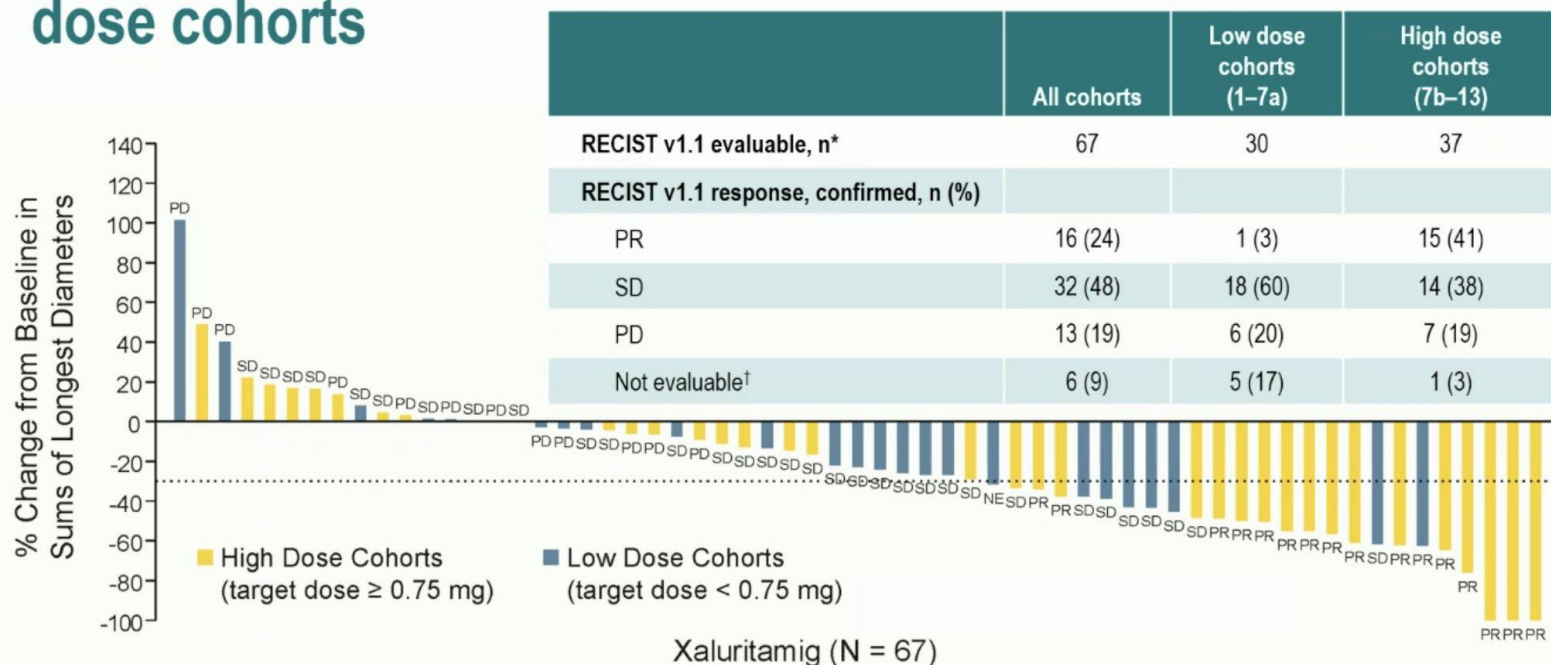
PSMA PET Imaging



56-year-old heavily pre-treated patient with mCRPC. Patient was enrolled in cohort 12 and achieved a confirmed PSA90 response (not RECIST evaluable).

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Confirmed RECIST responses occurred more often in high dose cohorts



Dashed line indicates 30% reduction in tumor sum of longest diameters from baseline. *Historically, ~40% of mCRPC patients have RECIST measurable disease^{1,2}. †BOR of NE includes 5 patients without post-baseline scans and 1 patient without sufficient follow up duration prior to post baseline assessment.

BOR, best overall response; NE, not evaluable; PD, progressive disease; PR, partial response; PSA, prostate specific antigen; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

1. Scher HI, et al. *Clin Cancer Res*. 2005;11(14):5223-5232. 2. Lorente D, et al. *Eur Urol Focus*. 2018;4(2):235-244.

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MSI-H and MRD

- 1346 patients with PC underwent paired tumor and germline sequencing
- 32 of 1033 (3.1%) had microsatellite instability–high or mismatch repair deficient disease
- 7/32 (21.9%) carried a germline mutation in a Lynch syndrome–associated gene.
- Five of 11 patients who received an anti–PD-1/PD-L1 agent had durable clinical benefit.

Sonuç

- ❑ BRCA mutasyonu olanlarda yeni nesil androjen reseptör yolağı inhibitörleri +PARP inhibitörleri
- ❑ Daha önce 1^o Taksan, 1^o yeni nesil androjen reseptör yolağı inhibitörleri alanlarda LU-177
- ❑ Kabazitaksel > switch yeni nesil androjen reseptör yolağı inhibitörlerinden daha etkili
- ❑ MSI ve TMB kastrasyona dirençli aşmada göz önüne alınmalı
- ❑ BITE tedavileri ve diğer kombinasyon tedavileri için umut var