Kastrasyona Dirençli Metastatik Prostat Kanserinde Tedavi

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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

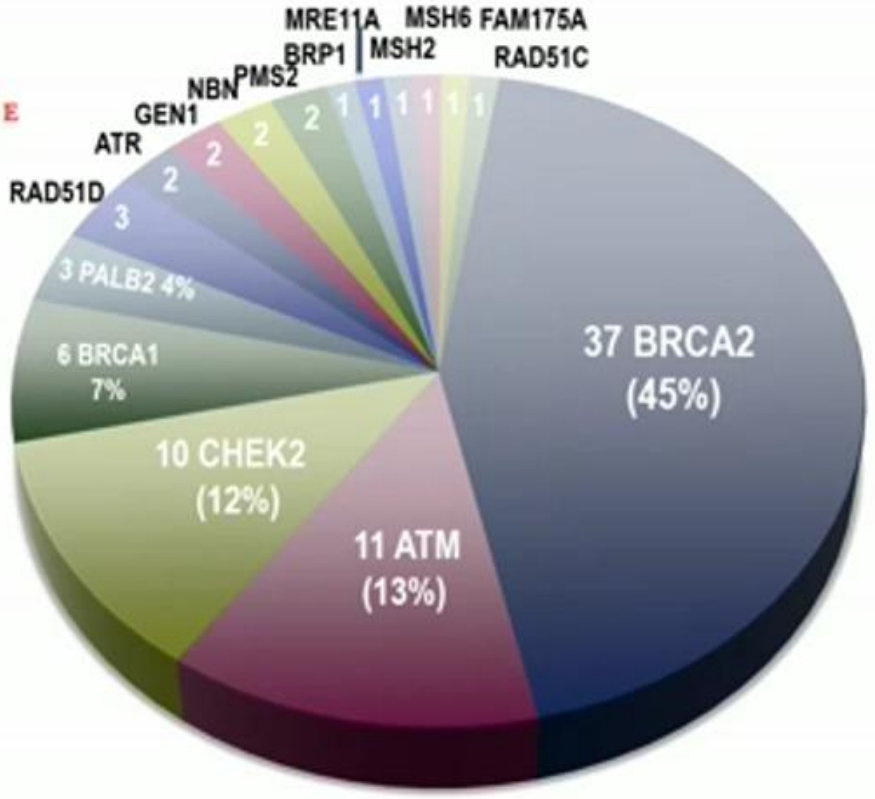
Prostat Kanseri Risk Faktörleri

GENETIC TESTING

Our new and shiny…

The NEW ENGLAND JOURNAL of MEDICINE

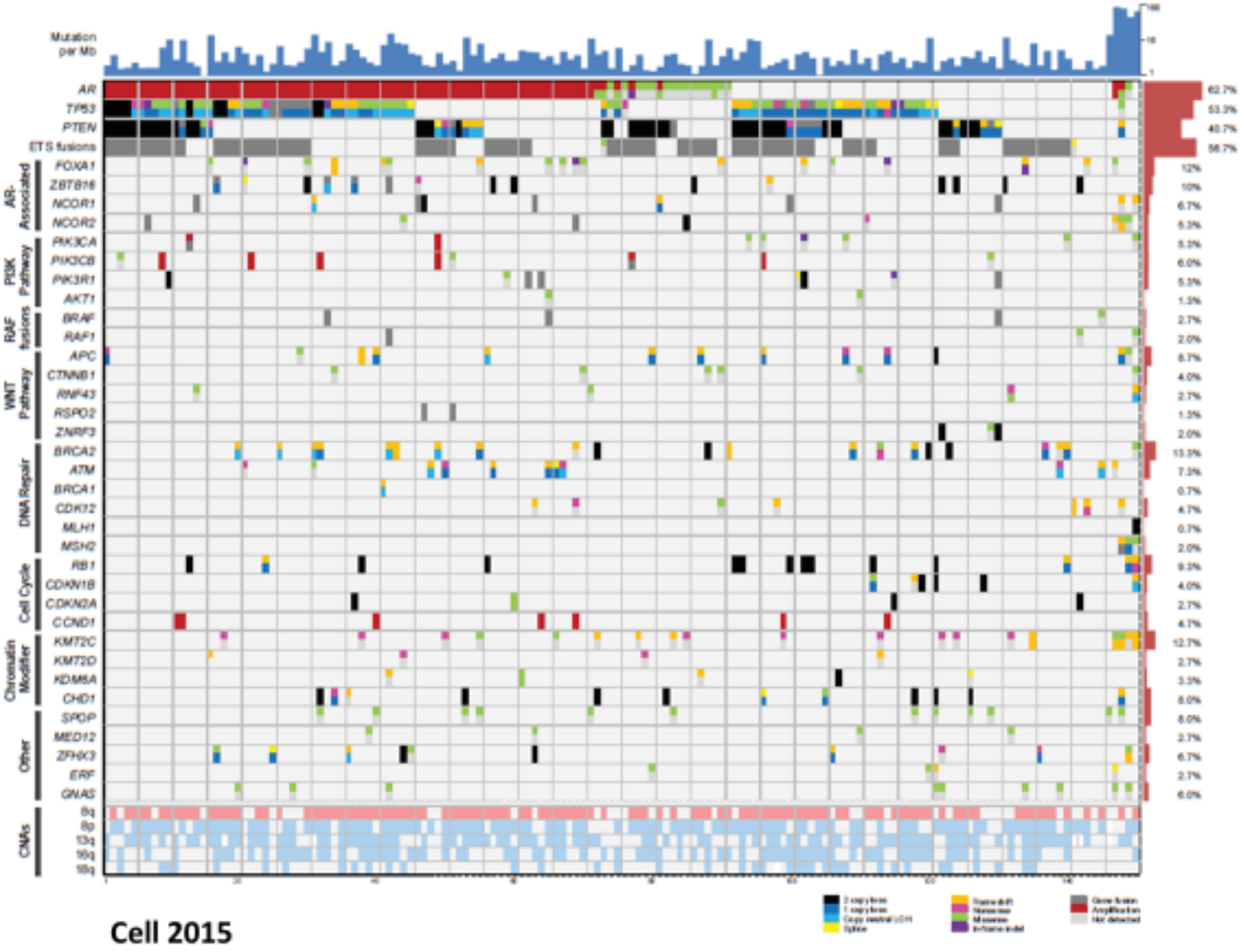
Inherited DNA-Repair Gene Mutations in Men with Metastatic Prostate Cancer



692 patients with metastatic PrCa Tested

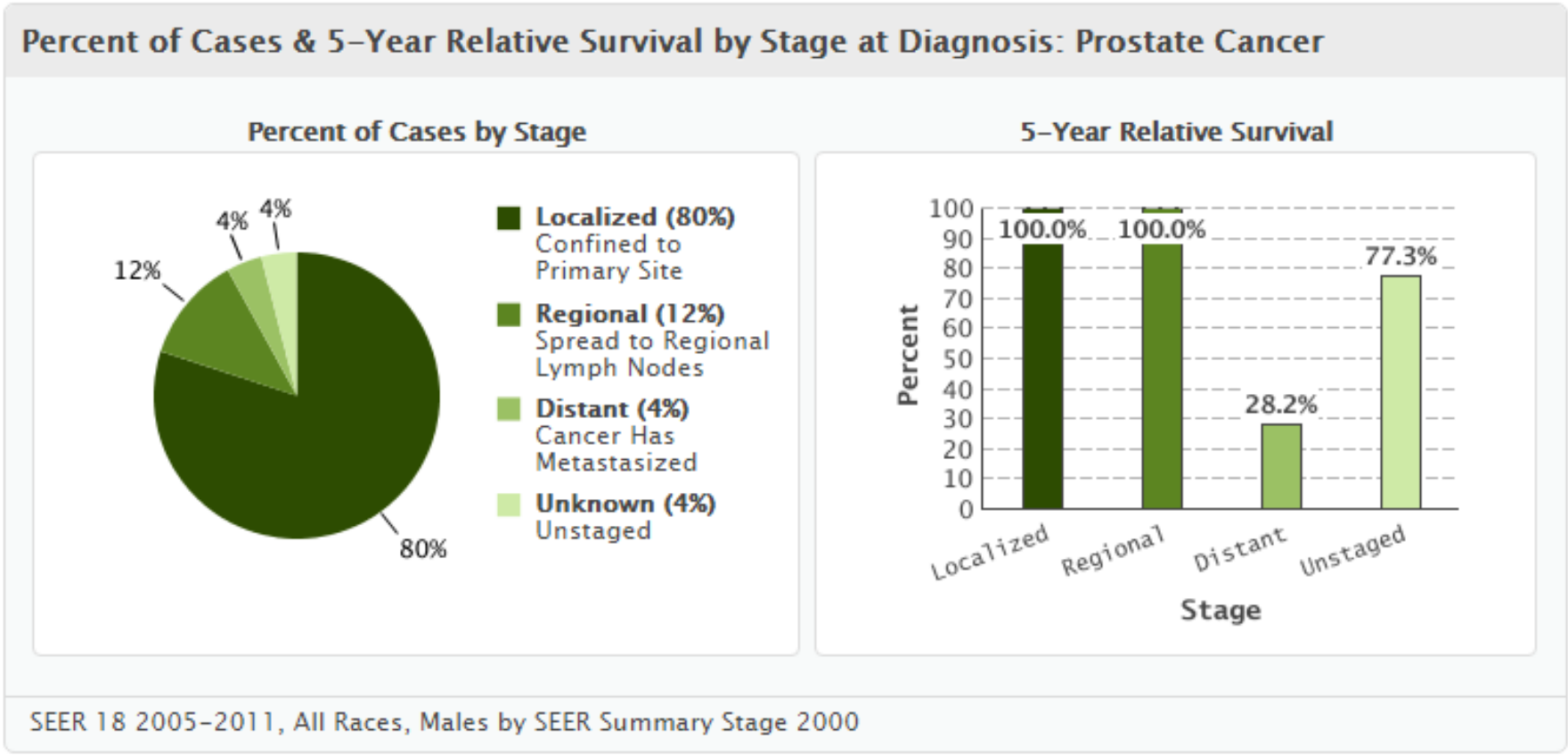
Pritchard, NEJM, 2016

Prostat Kanseri Genomik Profil

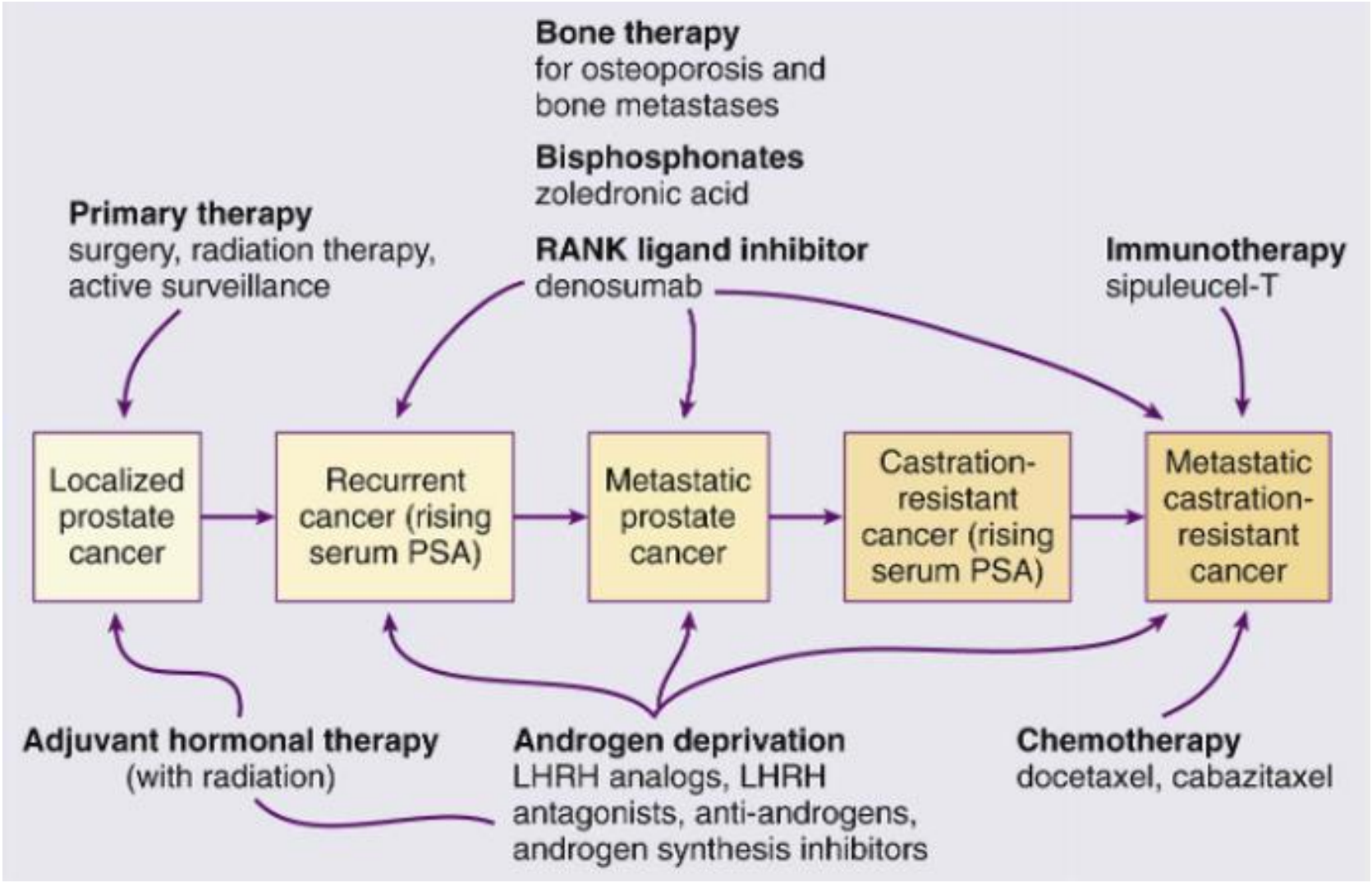


Cell 2015

Prostat Kanseri İnsidans ve Mortalite



Prostat Kanseri Tedavi Yaklaşımları



Abeloff's Clinical Oncology, 10th edition

Kastrasyona Dirençli Metastatik Prostat kanseri

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2021
Prostate Cancer

NCCN Guidelines Index
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SYSTEMIC THERAPY FOR M1 CRPC: ADENOCARCINOMA[zz,ccc,ddd,eee]

No prior docetaxel/no prior novel hormone therapy[fff]	Prior novel hormone therapy/No prior docetaxel[fff,lll]
• 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]	• 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,lll] (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.

CHUM

Kastrasyona Dirençli Metastatik Prostat kanseri

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

No prior docetaxel/no prior novel hormone therapy[mmm]	Prior novel hormone therapy/no prior docetaxel[mmm,ttt]
• 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]	• 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]	**Prior docetaxel and prior novel hormone therapy**[mmm,ttt]
• 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]	• 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 recommended 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 may be considered in patients with a personal history of PCa who:
• Have intermediate-risk prostate cancer with intraductal/cribriform histology
• Have a personal history of pancreatic, colorectal, gastric, melanoma, upper tract urothelial, glioblastoma, biliary tract, or small intestinal cancer
 	
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
	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 metastatic 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

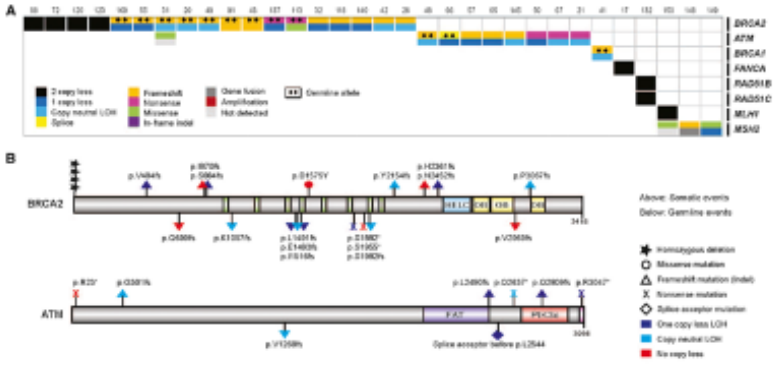
NCCN Practice Guidelines: Prostate Cancer. Version 1.2023. https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf.

Evre IV Prostat Kanserinde Mutasyonlar

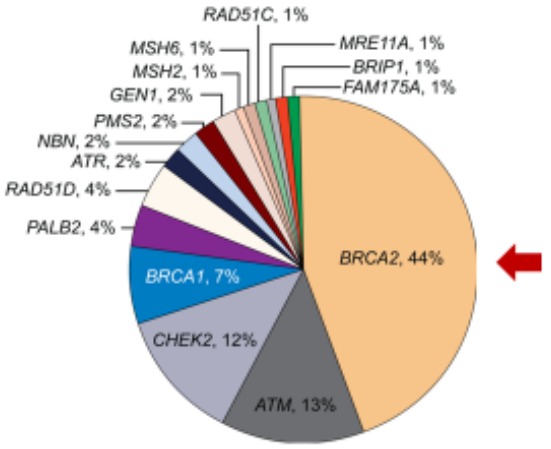
HRR Genes and Metastatic Prostate Cancer

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

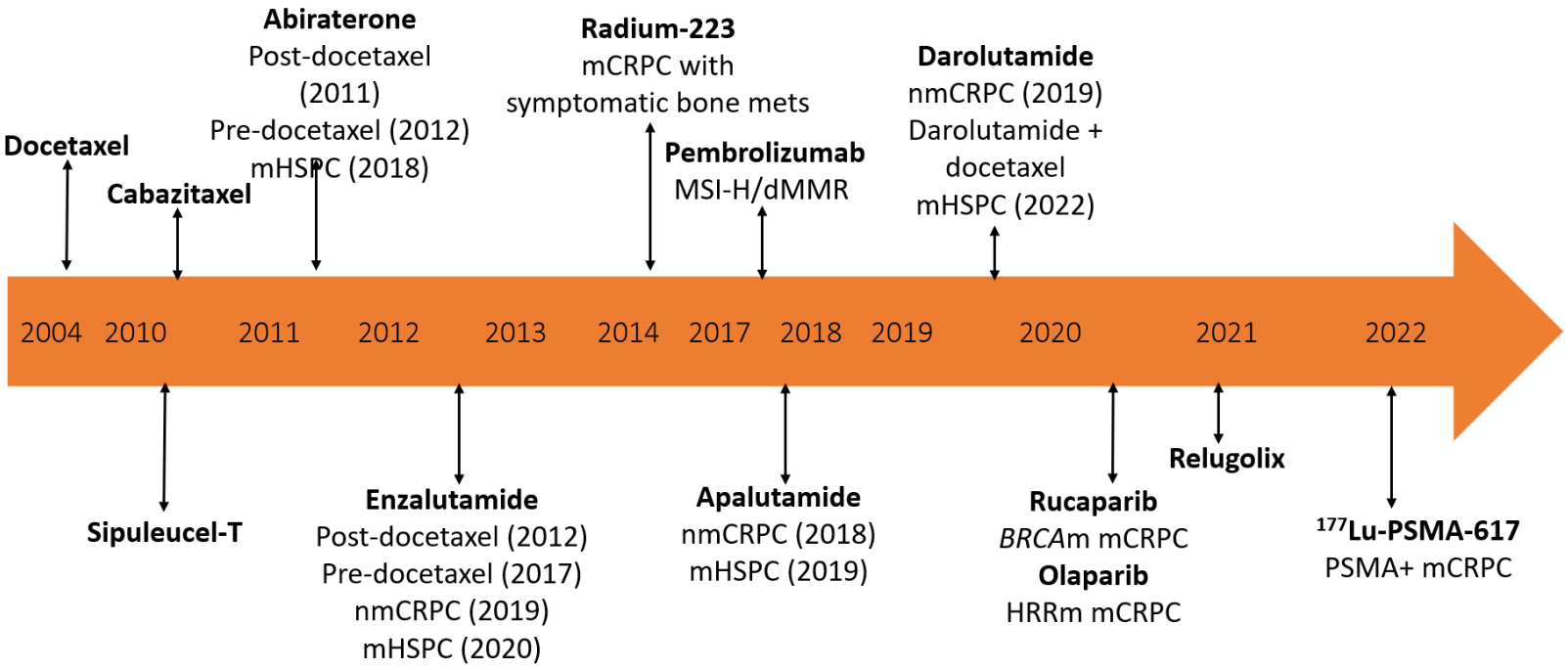


- **12%** of men with metastatic prostate cancer have a germline DNA repair defect

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

Kastrasyona Dirençli Metastatik Prostat kanseri

Treatment Landscape of mCRPC continues to evolve



Kastrasyona Dirençli Metastatik Prostat kanseri

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

R 1:1

Olaparib 300 mg BID + **Abiraterone*** 1000 mg QD (n=399)

Placebo + **Abiraterone*** 1000 mg QD (n=397)

Primary endpoint

rPFS or death by investigator assessment

Key secondary endpoint

- OS

Additional endpoints

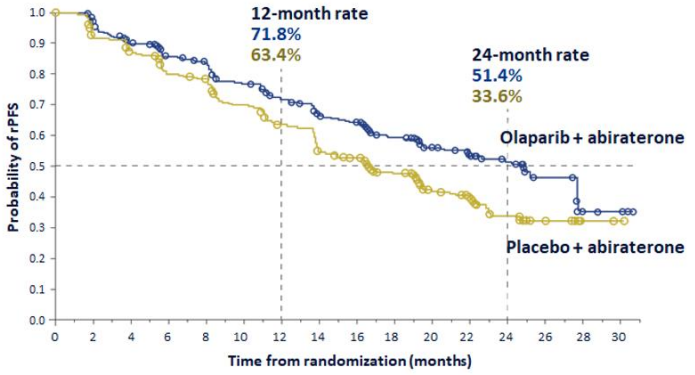
- TFST
- PFS2
- ORR
- HRR mutation prevalence (tested retrospectively)
- HRQOL
- Safety and tolerability

*Plus prednisone or prednisolone 5 mg BID

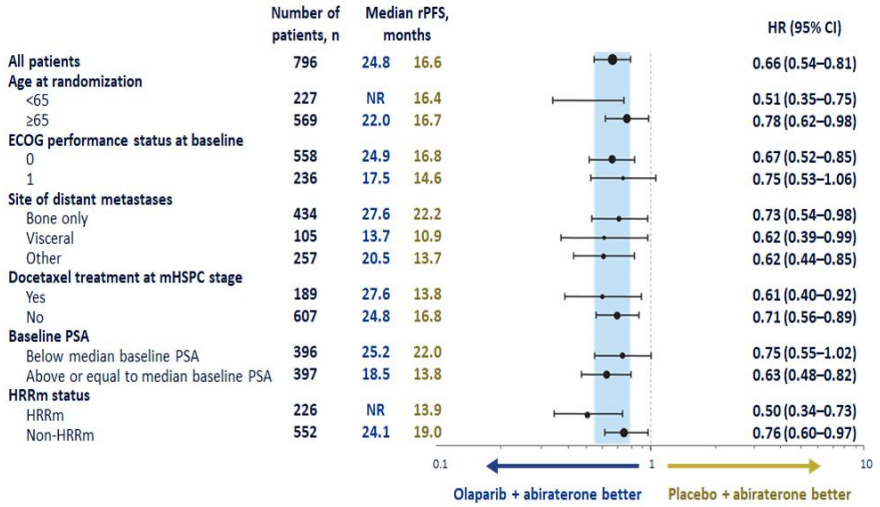
Saad F et al. *ASCO GU 2022*; abstr 11; **NCT03732820**.

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); *P*<0.0001	
rPFS by blinded independent central review		
HR (95% CI)	0.61 (0.49–0.74); *P*<0.0001	

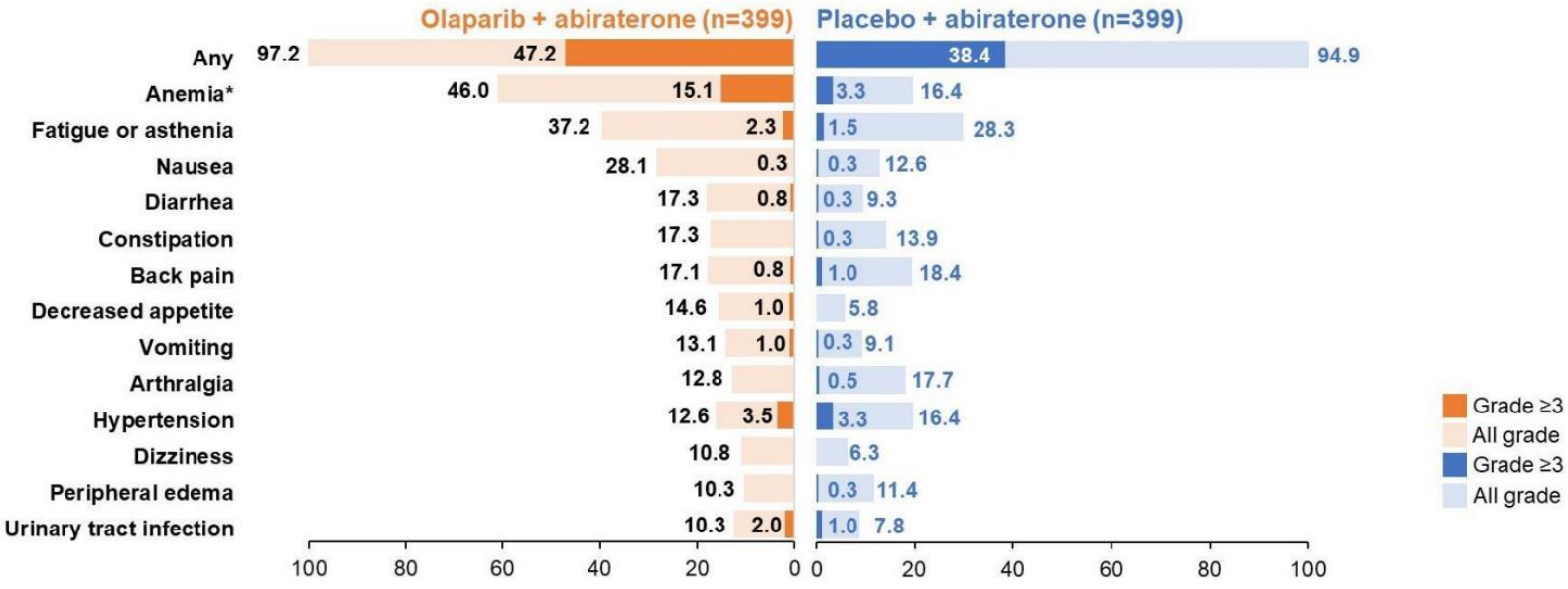


Clarke NW et al. *NEJM Evidence*; 2022.

Kastrasyona Dirençli Metastatik Prostat kanseri

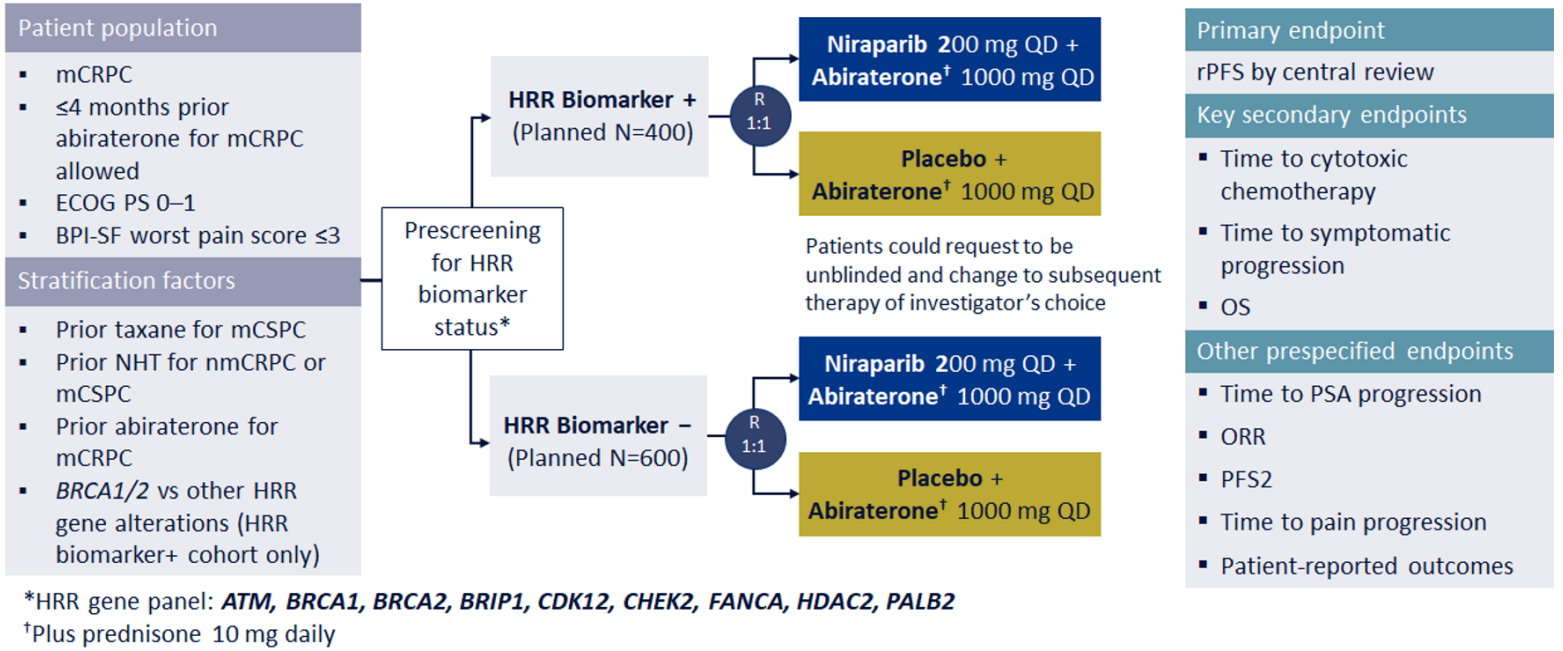
PROPEL

Overall safety profile



Kastrasyona Dirençli Metastatik Prostat kanseri

MAGNITUDE: Phase III Trial of Abi +/– Niraparib



*HRR gene panel: ***ATM, BRCA1, BRCA2, BRIP1, CDK12, CHEK2, FANCA, HDAC2, PALB2***

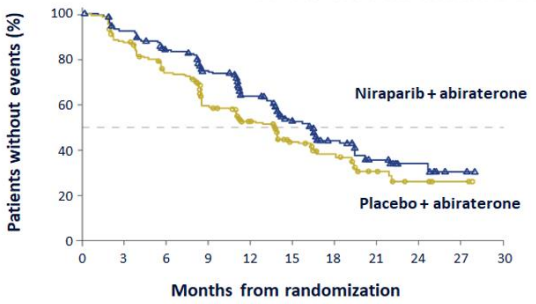
†Plus prednisone 10 mg daily

Chi KN et al. *ASCO GU 2022*; abstr 12; **NCT03748641**.

Kastrasyona Dirençli Metastatik Prostat kanseri

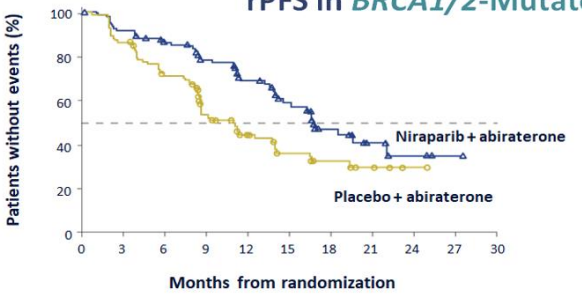
MAGNITUDE: Radiographic Progression-Free Survival

rPFS in All HRR BM+ Cohort



	Niraparib + abiraterone (n=212)	Placebo + abiraterone (n=211)
rPFS by central review		
Median rPFS, months	16.5	13.7
HR (95% CI)	0.73 (0.56–0.96); *P*=0.0217	
rPFS assessed by investigator		
Median rPFS, months	19.0	13.9
HR (95% CI)	0.64 (0.49–0.86); *P*=0.0022	

rPFS in *BRCA1/2*-Mutated Group



	Niraparib + abiraterone (n=113)	Placebo + abiraterone (n=112)
rPFS by central review		
Median rPFS, months	16.6	10.9
HR (95% CI)	0.53 (0.36–0.79); *P*=0.0014	
rPFS assessed by investigator		
Median rPFS, months	19.3	12.4
HR (95% CI)	0.50 (0.33–0.75); *P*=0.0006	

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

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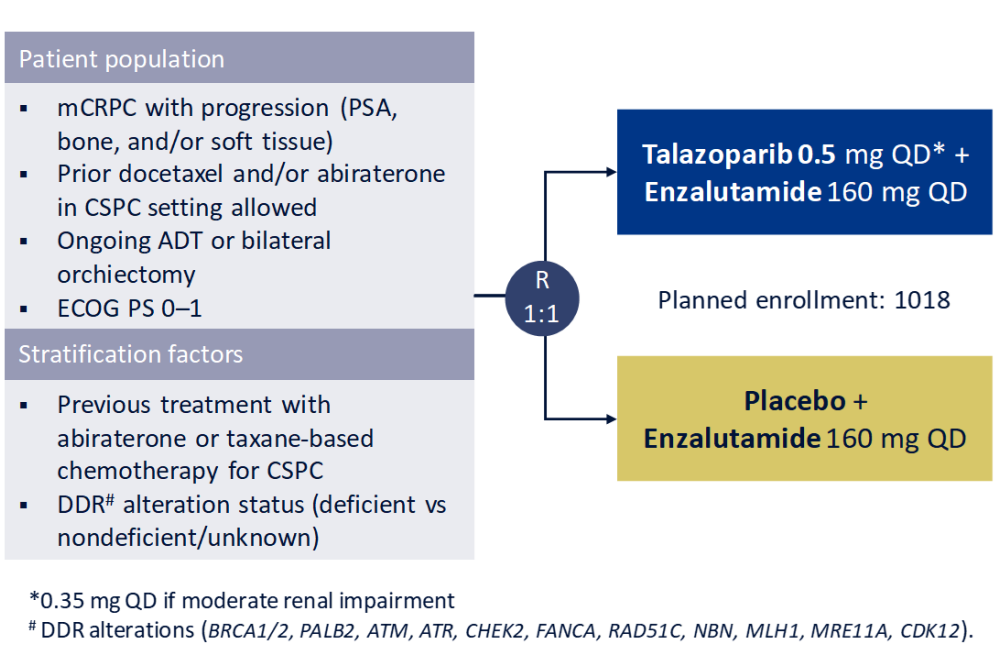
TALAPRO-2: Phase III Trial of Enza +/– Talazoparib



Co-primary endpoints

- rPFS by BICR per RECIST 1.1 and PCWG3 in **All-comers (Cohort 1), n=804**
- rPFS by BICR in patients with **DDR# alterations (Cohort 2), n=214**

Key secondary endpoints
(analyzed for both cohorts separately)

- OS
- OR per RESIST 1.1 (measurable disease)
- PSA response ≥50%
- Time to PSA progression
- Time to initiation of cytotoxic CT or antineoplastic therapy
- Time to first symptomatic skeletal event
- PFS2
- Safety
- Patient-reported outcomes

*0.35 mg QD if moderate renal impairment
DDR alterations (*BRCA1/2, PALB2, ATM, ATR, CHEK2, FANCA, RAD51C, NBN, MLH1, MRE11A, CDK12*).

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

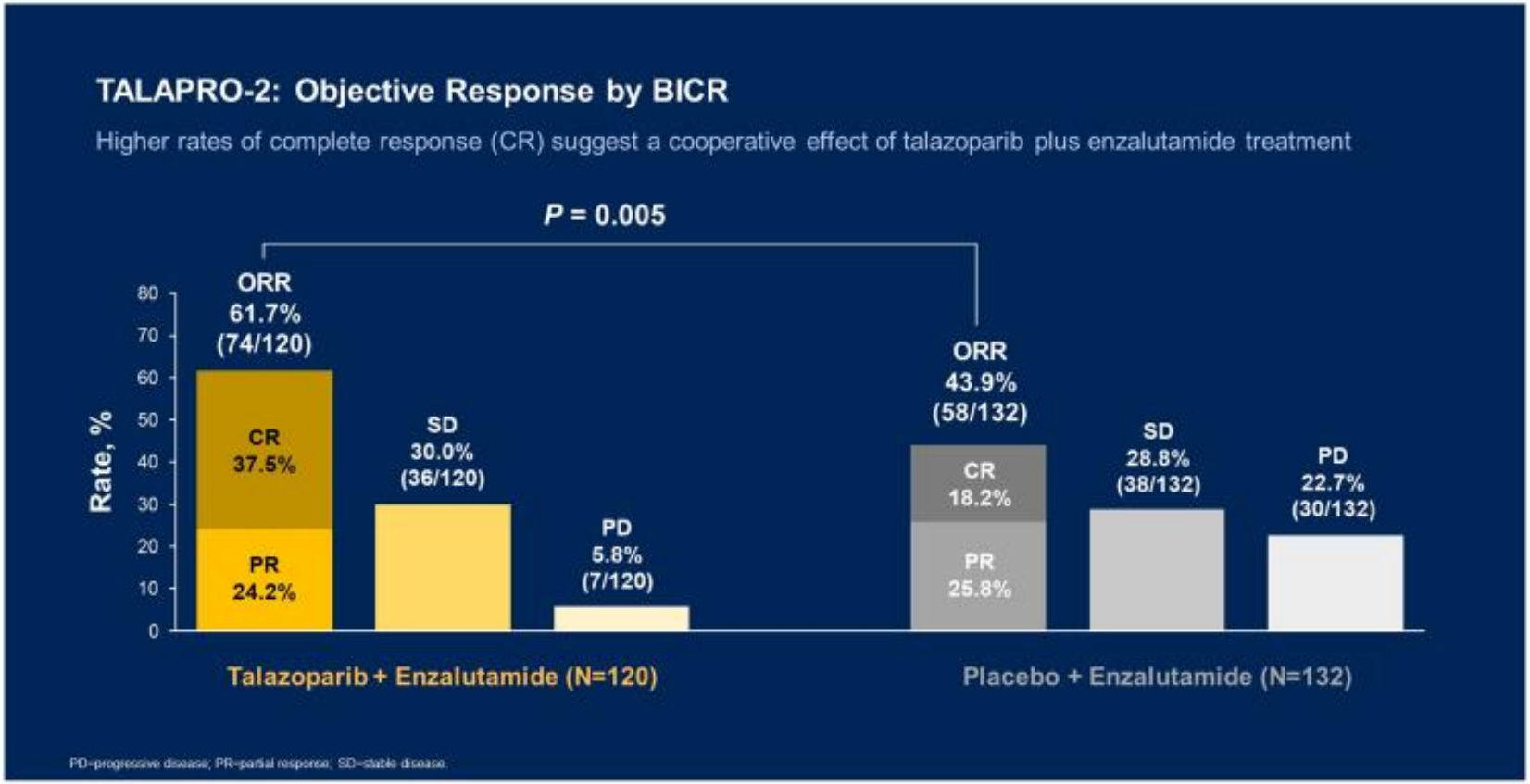
Kastrasyona Dirençli Metastatik Prostat kanseri

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

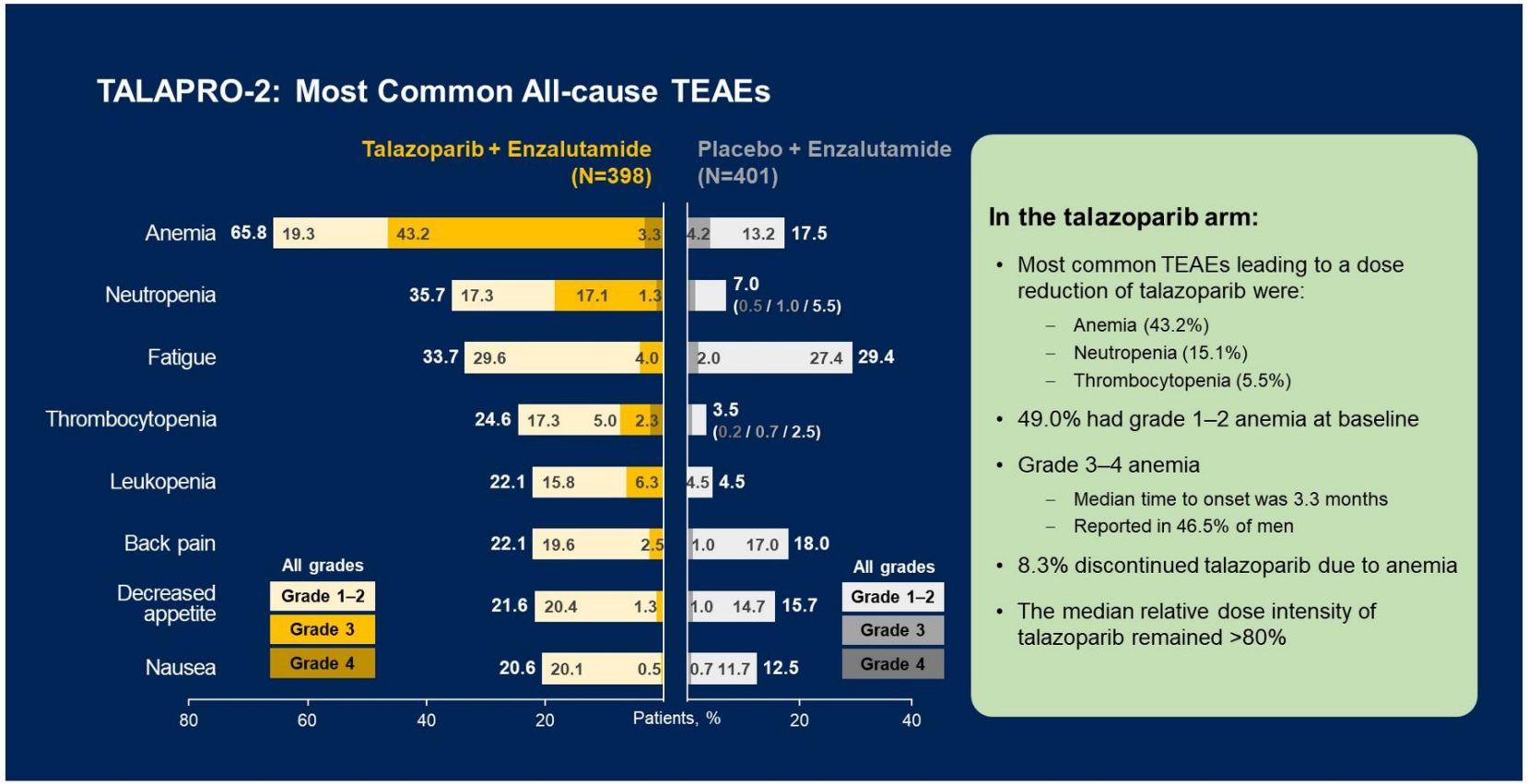
All-comers cohort	rPFS 21.9 mo → NR	HR 0.63 (0.51-0.78)	*P* <0.001
HRR *mutated*	rPFS 16.4 → 27.9 mo	HR 0.46 (0.30-0.70)	*P* <0.001
HRR *wild-type*	rPFS 16.6 → 25.8 mo	HR 0.66 (0.49-0.91)	*P* = 0.009

Agarwal N et al. *ASCO GU 2023*; abstr LBA17.

Kastrasyona Dirençli Metastatik Prostat kanseri



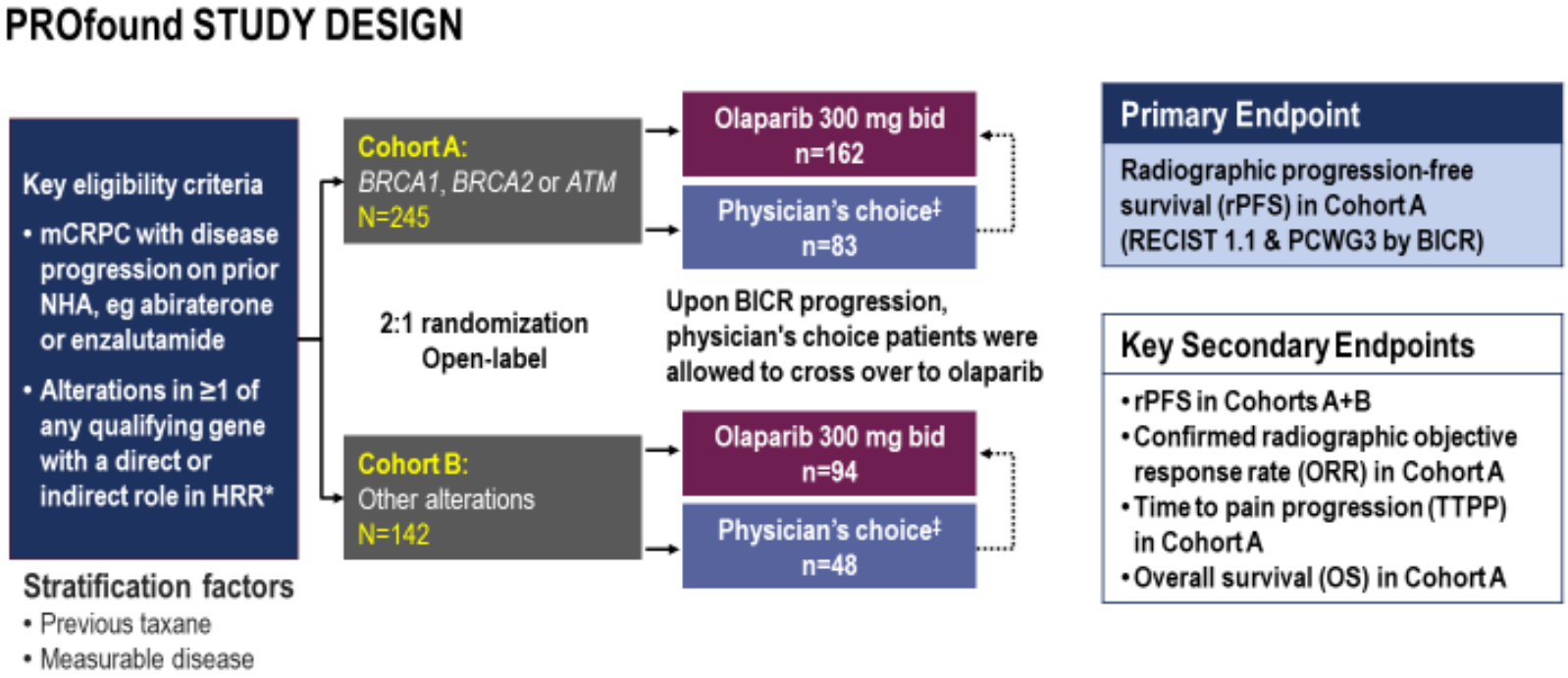
Kastrasyona Dirençli Metastatik Prostat kanseri



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



*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

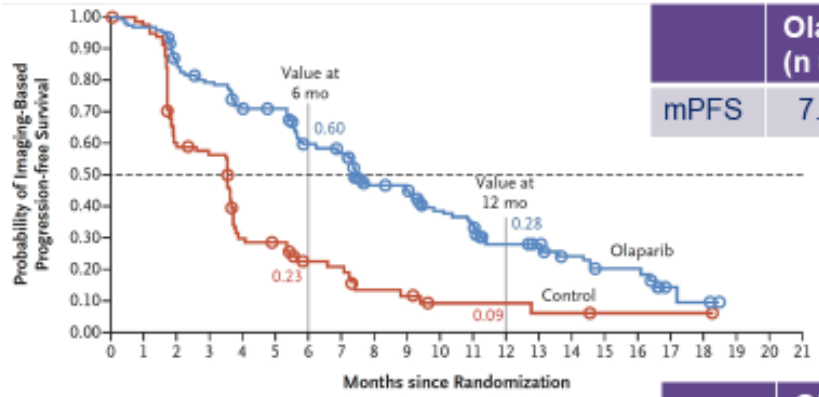
BARCELONA 2019 ESMO congress

‡Physician's choice of either enzalutamide (160 mg qd) or abiraterone (1000 mg qd + prednisone [5 mg bid])
BICR, blinded independent central review

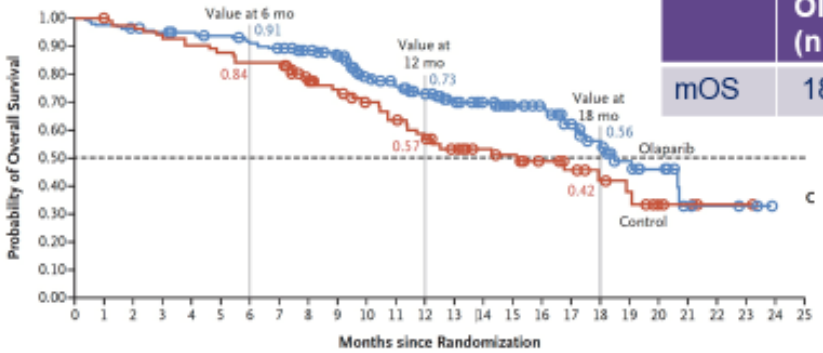
Hussain M et al. ESMO 2019;Abstract 5059.

Kastrasyona Dirençli Prostat Kanseri

PROfound: Imaging-Based PFS and OS in Cohort A



	Olaparib (n = 162)	Control (n = 83)	HR	P-value
mPFS	7.4 mo	3.6 mo	0.34	<0.001



	Olaparib (n = 162)	Control (n = 83)	HR	P-value
mOS	18.5 mo	15.1 mo	0.64	0.02

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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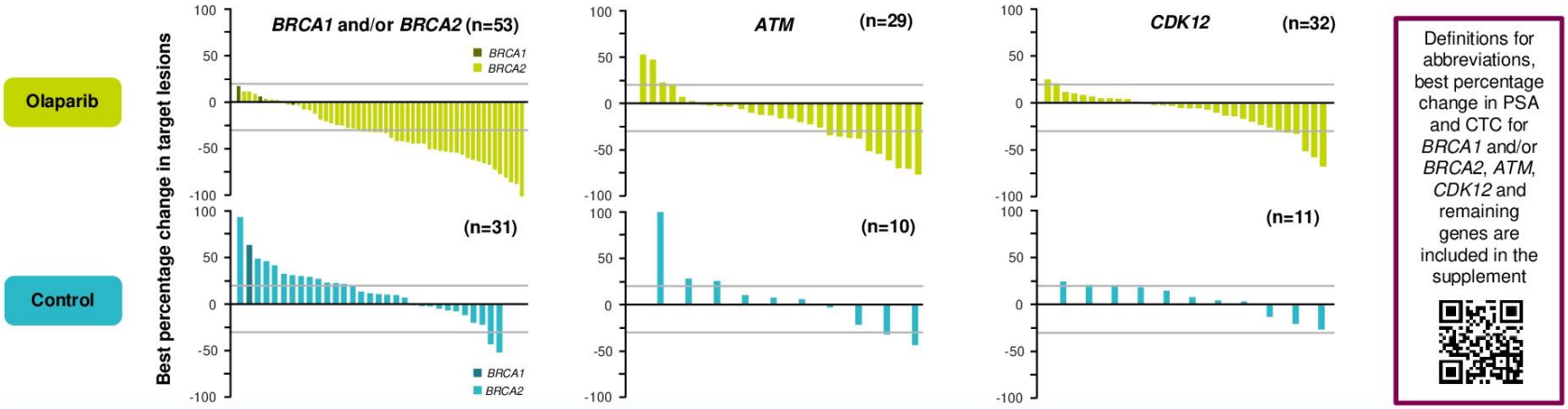
Results

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		*BRCA1* and/or *BRCA2*		*ATM*		*CDK12*	
		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



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

Presented By Johann De Bono at 2021 Genitourinary Cancers Symposium

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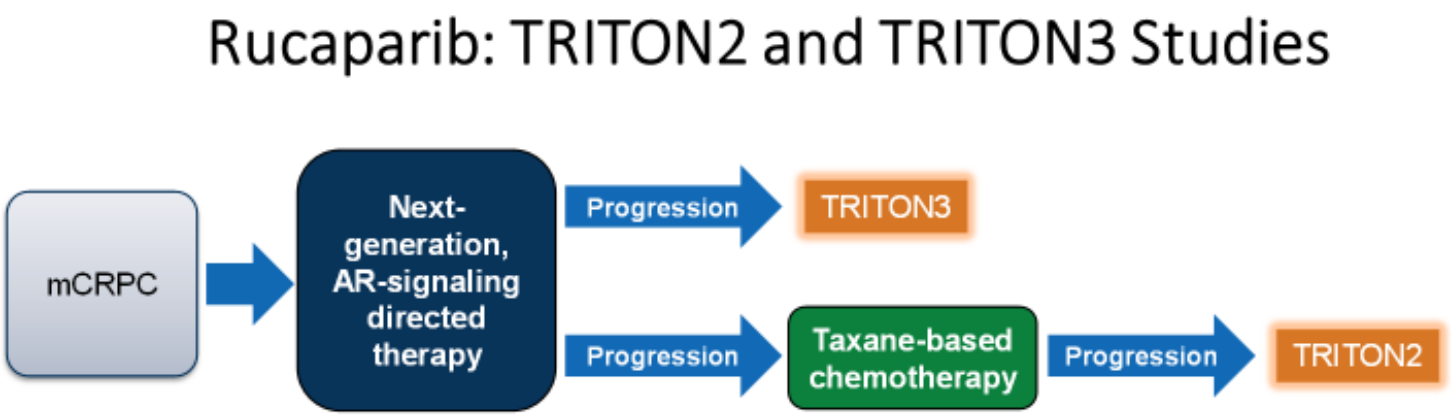
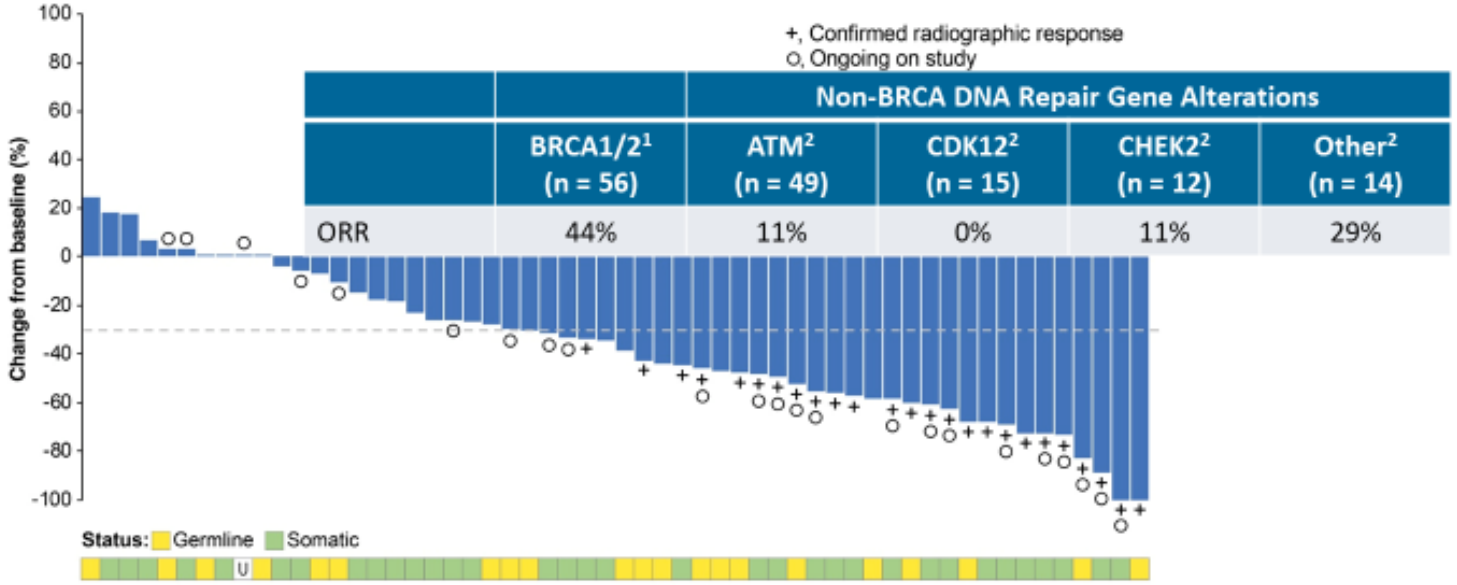


HRR-deficiency is defined by a deleterious alteration in *BRCA1*, *BRCA2*, *ATM*, or 12 other HRR genes (*BARD1*, *BRIP1*, *CDK12*, *CHEK2*, *FANCA*, *NBN*, *PALB2*, *RAD51*, *RAD51B*, *RAD51C*, *RAD51D*, *RAD54L*)

1. Abida W et al. *Annals Onc*. 2018:29(Suppl 8):viii271-viii302.

Kastrasyona Dirençli Prostat Kanseri

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]



	BRCA1/2[1] (n = 56)	Non-BRCA DNA Repair Gene Alterations: ATM[2] (n = 49)	CDK12[2] (n = 15)	CHEK2[2] (n = 12)	Other[2] (n = 14)
ORR	44%	11%	0%	11%	29%

Visit cutoff: 02 Jul 2019. Includes patients with measurable disease at baseline and ≥1 postbaseline scan. Each bar represents a single patient; patients with no change from baseline are shown as 0.5% for visual clarity; the dotted line indicates the threshold for partial response (30% decrease from baseline). Confirmed radiographic responses are per investigator assessment.
U, *BRCA1/2* germline/somatic status unknown.

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

Rukaparib Türkiye'de prostat kanseri tedavisinde ruhsatlı değildir.

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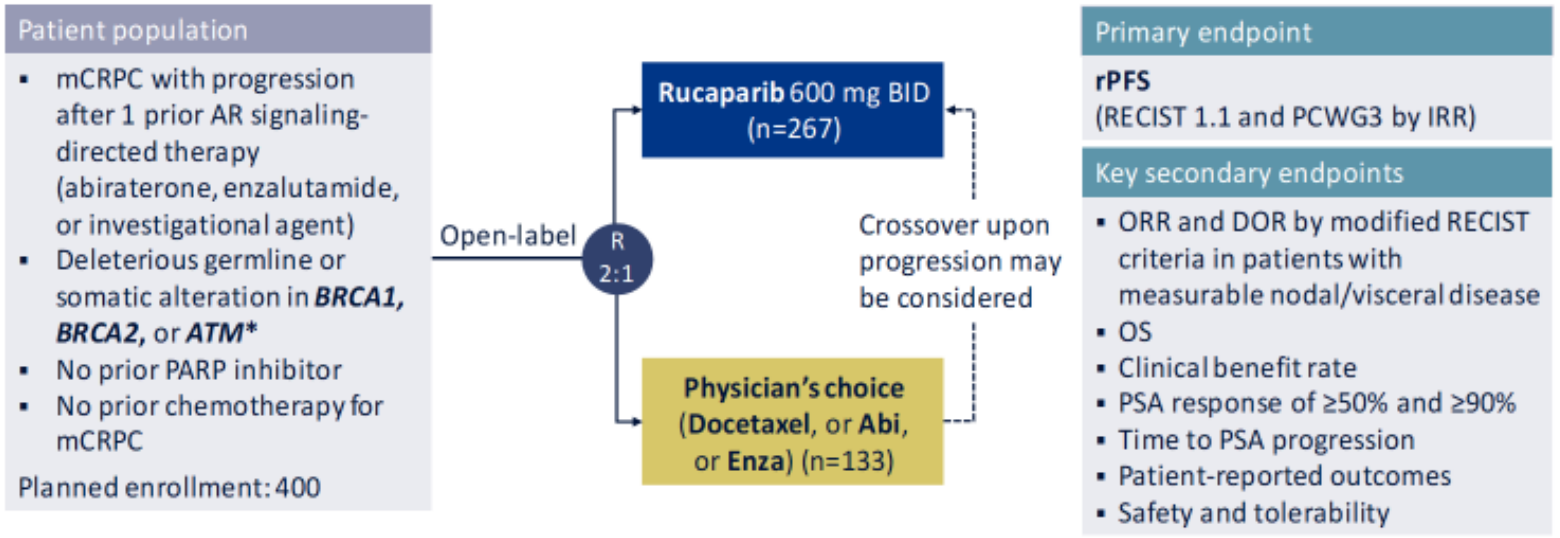
TRITON3: Randomized Phase III Trial



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

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

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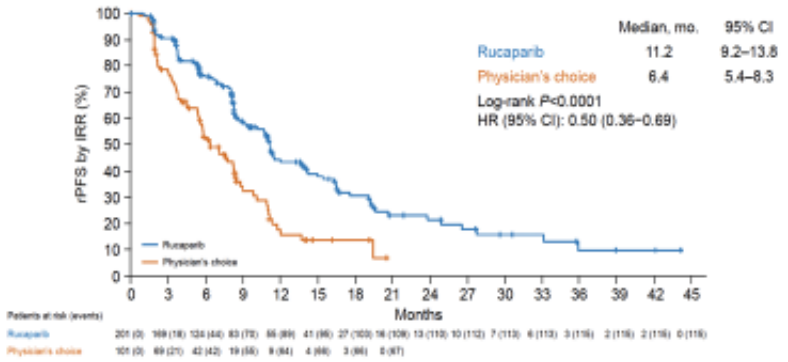
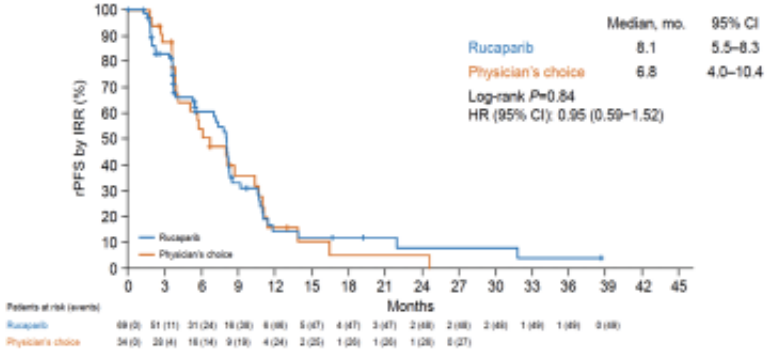
TRITON3: rPFS in *BRCA1/2* and *ATM* Subgroups

***BRCA1/2* Subgroup**



***ATM* Subgroup**



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

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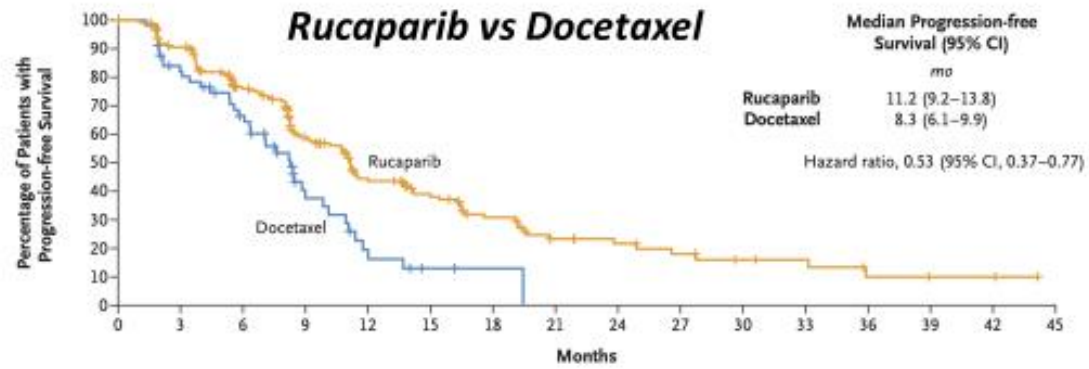
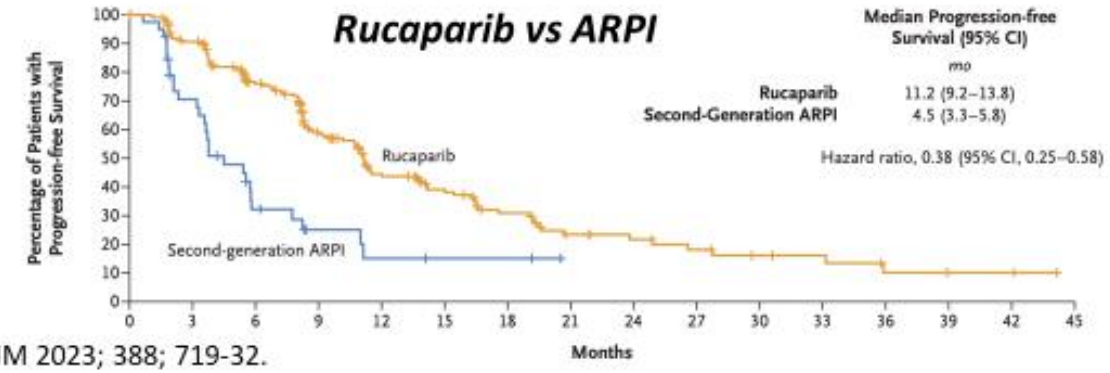
TRITON3: rPFS by Control Treatment in *BRCA1/2* Subgroup





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-A[1] **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-B[2] **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
TRITON2[3] **Rucaparib** 600 mg BID (N=115)	1 taxane and 1–2 NHT	Deleterious germline or somatic *BRCA1/2* alteration; tumor or plasma	ORR by blinded independent radiology review	**43.5%** (27 of 62)
GALAHAD[4] **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 *BRCA* mutation and measurable disease	**34.2%** (26 of 76 measurable *BRCA* cohort) 10.6% (5 of 47 measurable non-*BRCA* cohort)
TALAPRO-1[5] **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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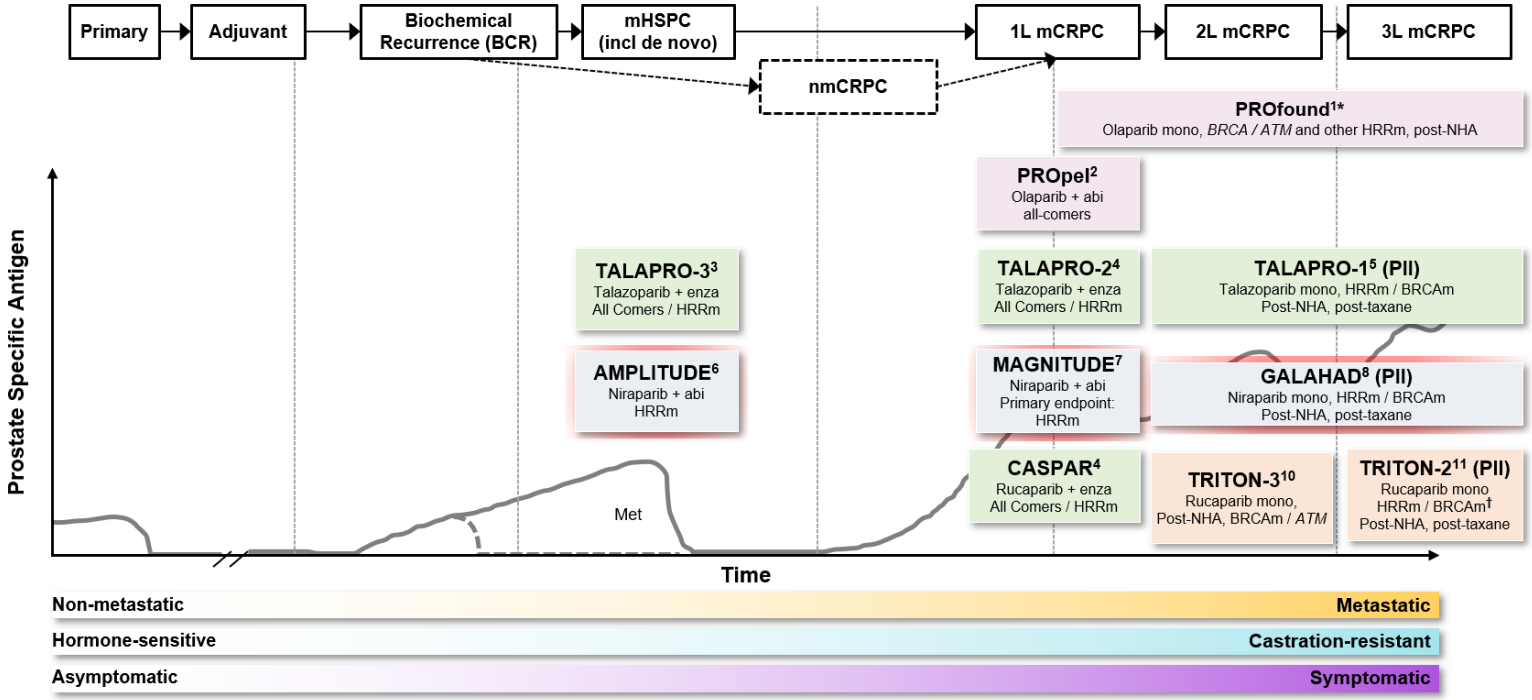
Ongoing trials investigating PARPi in advanced PC



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 taxane[14]

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.

CHUM

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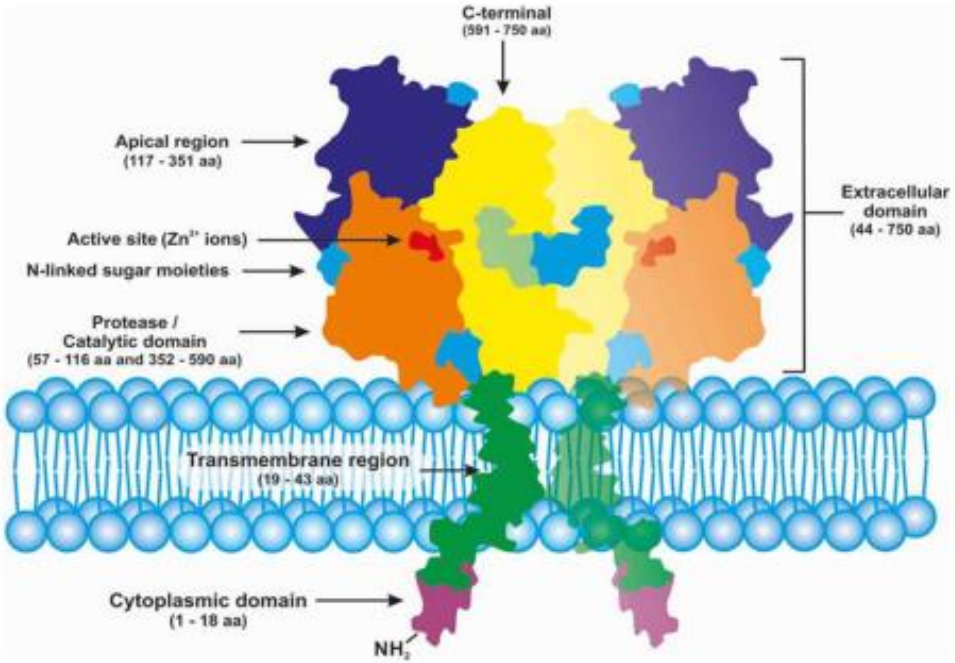
Targeting PSMA: Transmembrane Protein

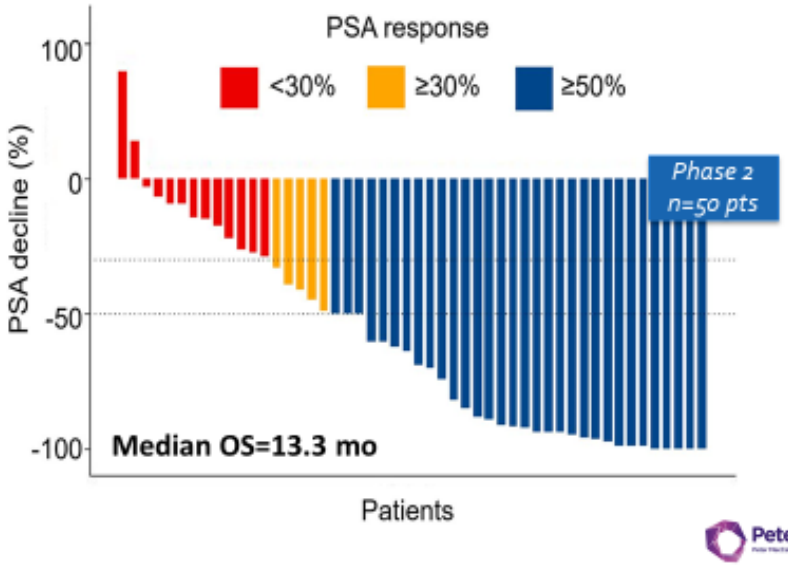


Memorial Sloan Kettering Cancer Center

Evans JC et al. Br J Pharmacol. 2016;173(21):3041-3079.

Kastrasyona Dirençli Metastatik Prostat kanseri

SML RNT in advanced prostate cancer
PSMA-617 Lu^{177}(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.

Memorial Sloan Kettering Cancer Center

Kastrasyona Dirençli Metastatik Prostat kanseri

[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, Shahneen Sandhu, Amir Iravani, Anthony M Joshua, Jeffrey C Goh, David A Pattison, Thean Hsiang Tan, Ian D Kirkwood, Siobhan Ng, Roslyn J Francis, Craig Gedye, Natalie K Rutherford, Andrew Weickhardt, Andrew M Scott, Sze-Ting Lee, Edmond M Kwan, Arun A Azad, Shakher Ramdave, Andrew D Redfern, William Macdonald, Alex Guminski, Edward Hsiao, Wei Chua, Peter Lin, Alison Y Zhang, Margaret M McJannett, 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-flourine-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) response 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.

Published Online February 11, 2021 https://doi.org/10.1016/S0140-6736(21)00237-3

See Online/Comment 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 Theranostics 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); Sir 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 Theranostics 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;

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 cancer[4,5] 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.[6] [177Lu]Lu-PSMA-617 delivers high doses of radiation to prostate cancer cells via β-particulate 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.[7–10] We reported a decrease in prostate-specific antigen (PSA) of 50% or more in 64% of men and a favourable toxicity profile in a

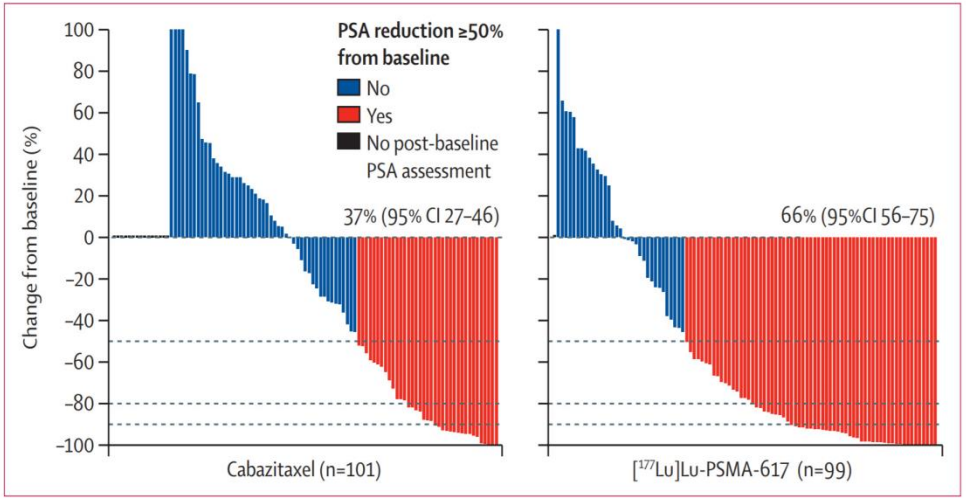


Figure 2: **PSA response**

PSA=prostate-specific antigen. 177Lu=lutetium-177.

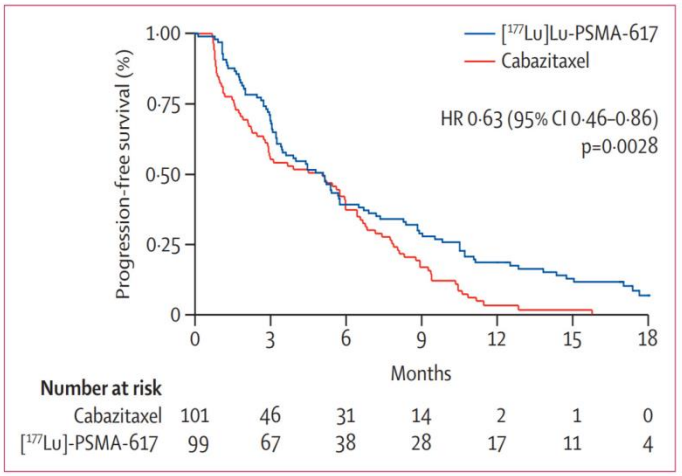


Figure 3: **Radiographic or PSA progression-free survival**

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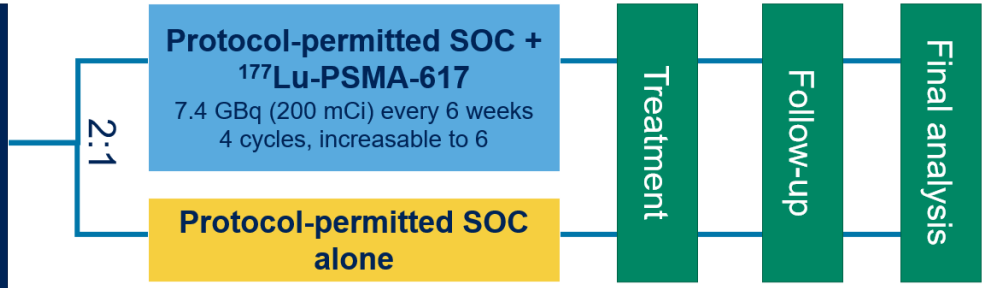
Open-label study of protocol-permitted standard of care ± ^{177}Lu-PSMA-617 in adults with PSMA-positive mCRPC

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

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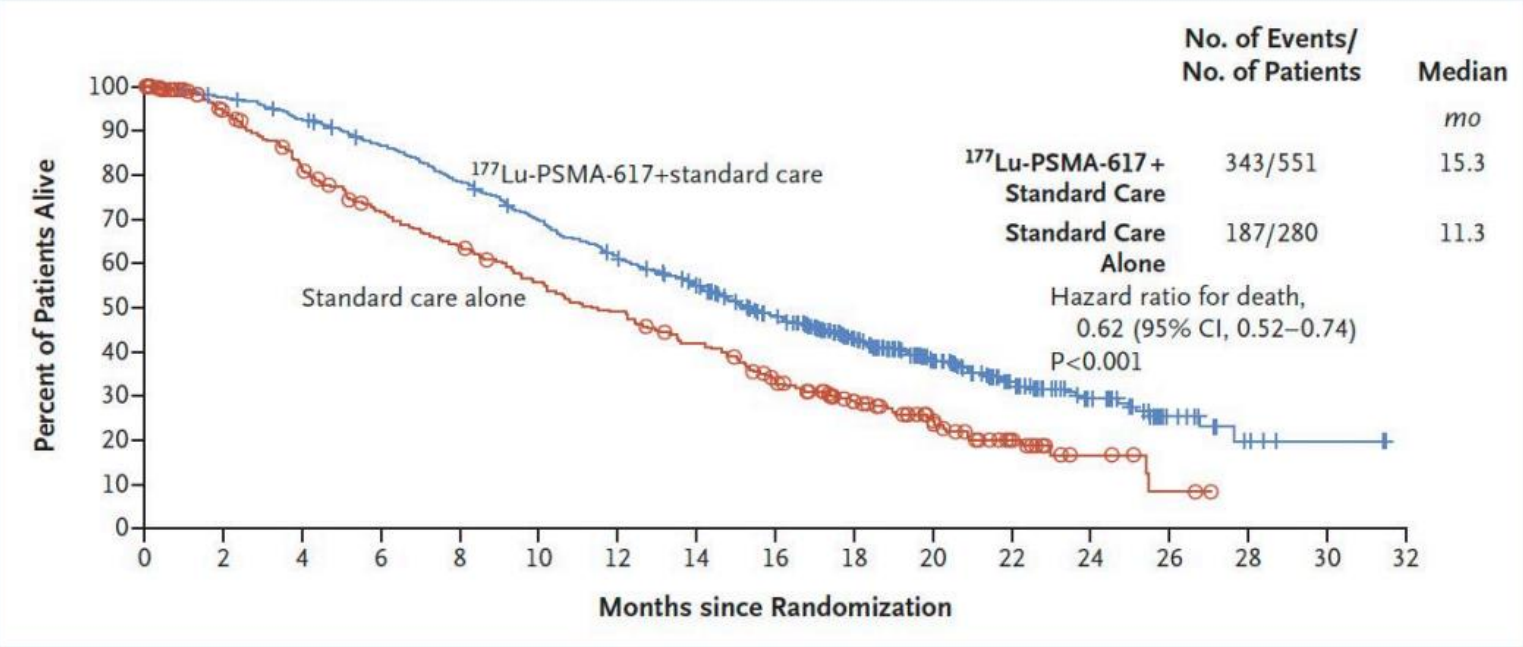
VISION: Overall Survival



Sartor O et al. *N Engl J Med* 2021;385:1091-103.

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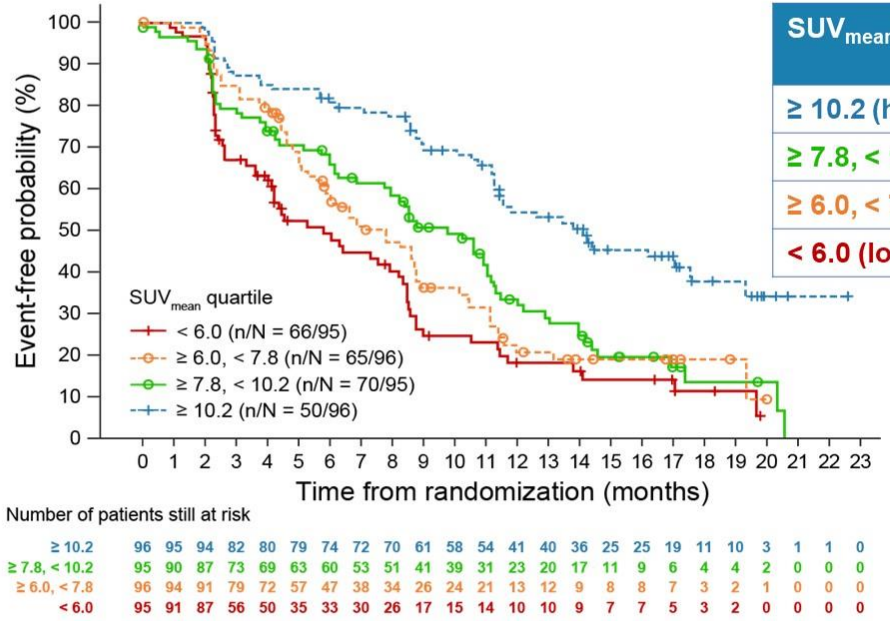
rPFS by whole-body SUV_{mean} quartiles (PFS-FAS)

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



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

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

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

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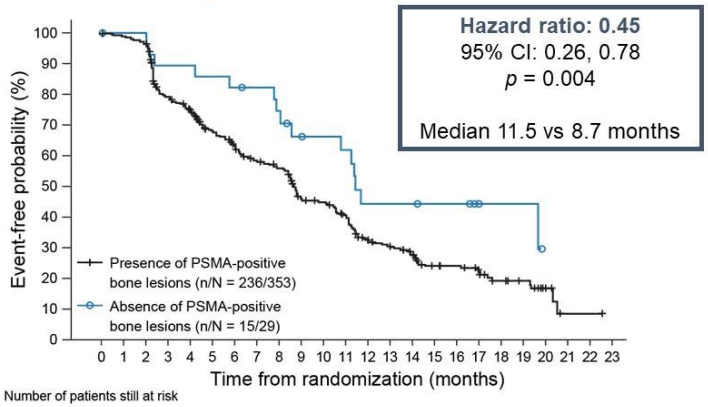
rPFS by absence of PSMA-positive lesions (PFS-FAS)

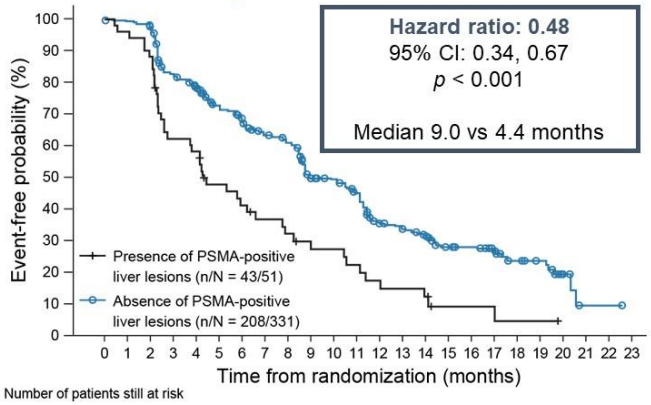
PSMA-positive bone lesions



Number of patients still at risk

Presence of PSMA-positive bone lesions	353	342	331	265	246	210	191	172	162	129	121	106	77	72	61	42	40	31	18	15	6	1	1	0
Absence of PSMA-positive bone lesions	29	28	28	25	25	24	23	21	19	16	15	14	10	10	10	9	9	6	3	3	0	0	0	0

PSMA-positive liver lesions



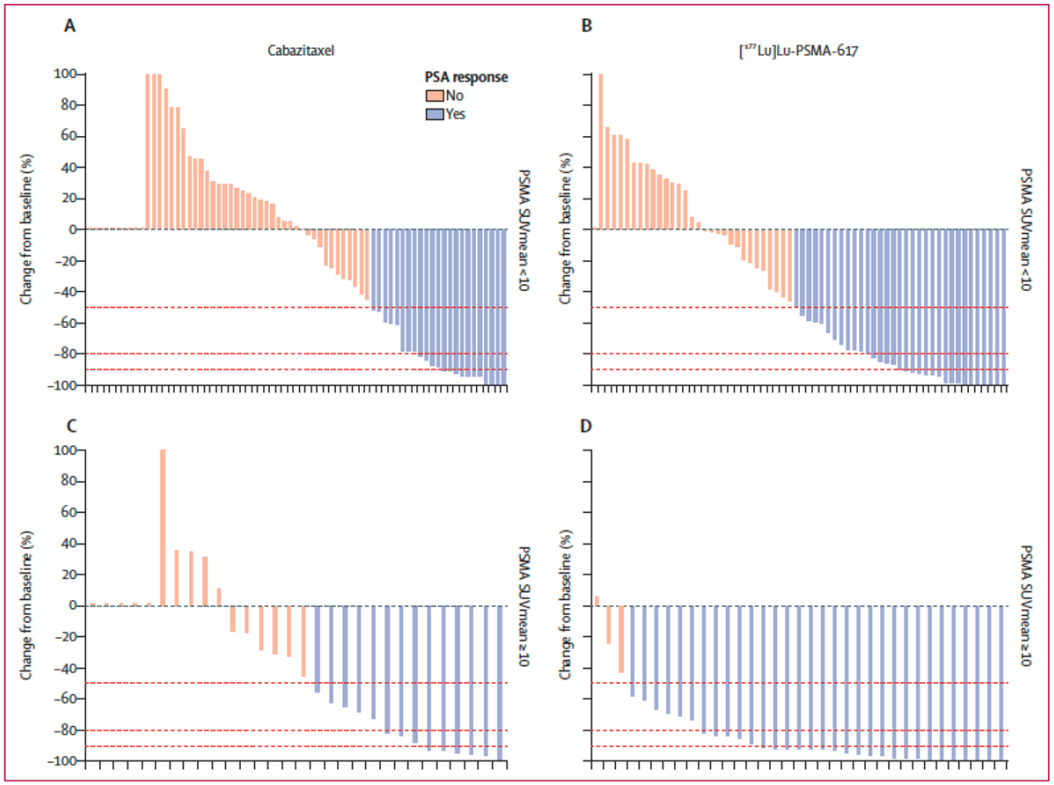
Number of patients still at risk

Presence of PSMA-positive liver lesions	51	49	45	31	29	22	19	16	14	12	11	9	7	6	5	2	2	2	1	1	0	0	0	0
Absence of PSMA-positive liver lesions	331	321	314	259	242	212	195	177	167	133	125	111	80	76	66	49	47	35	20	17	6	1	1	0

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

Kastrasyona Dirençli Metastatik Prostat kanseri



Buteau et al, Lancet Oncol 2022

Odds of PSA response to ^{177}Lu-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*

Kastrasyona Dirençli Metastatik Prostat kanseri

FDG volume in TheraP prognostic

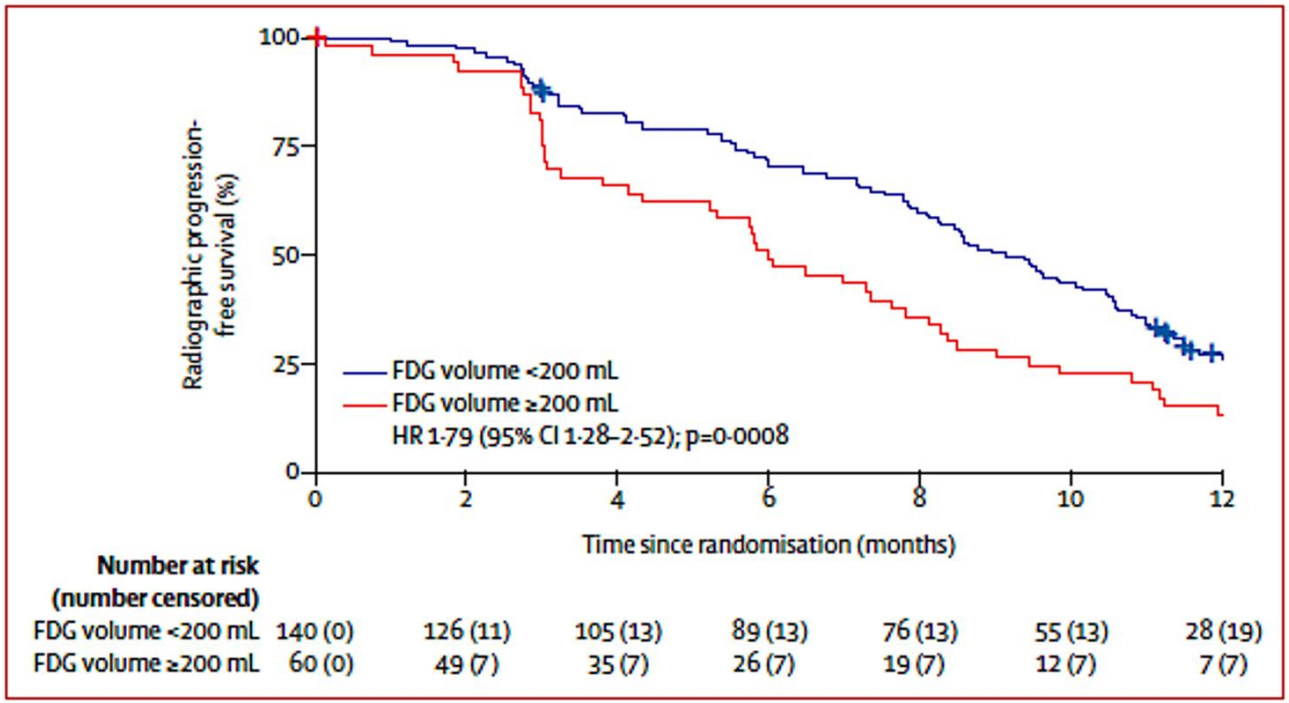


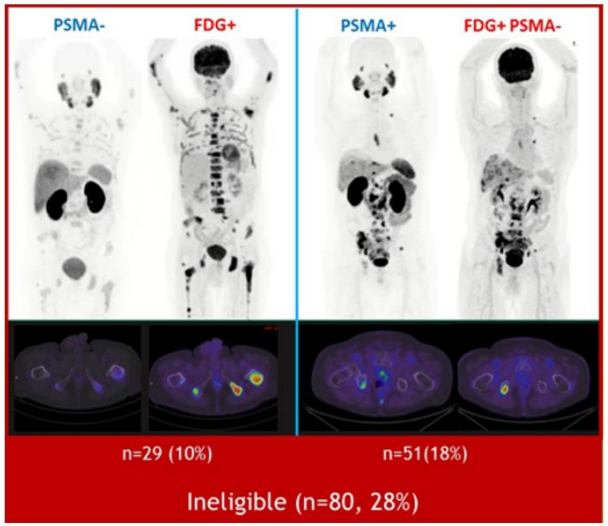
Figure 5: **Radiographic progression-free survival according to FDG-PET MTV**
FDG=2-[18F]fluoro-2-deoxy-D-glucose. MTV=metabolic tumour volume.

Buteau et al, Lancet Oncol 2022

Kastrasyona Dirençli Metastatik Prostat kanseri

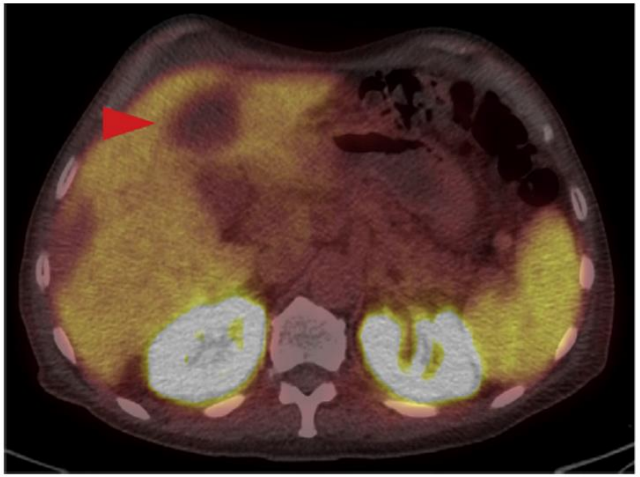
Loss of PSMA Expression in a Subset of CRPC

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

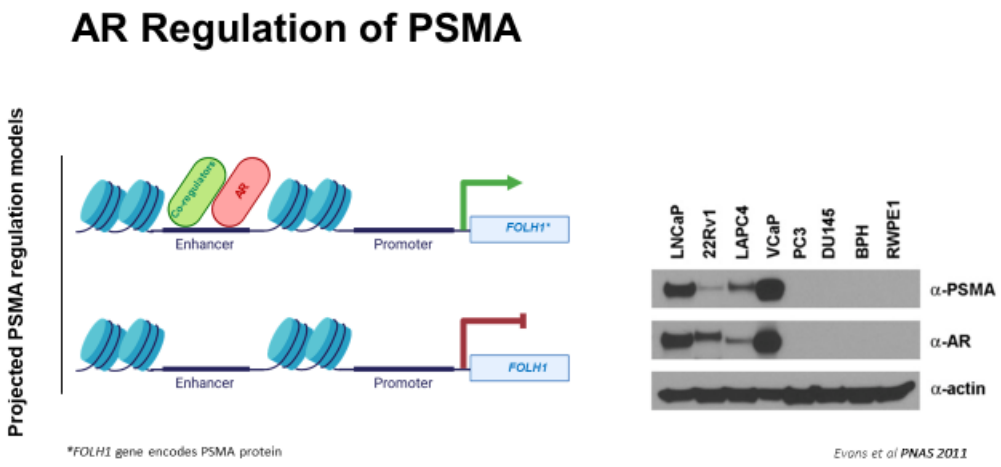


Tosoian et al, 2016

Bakht et al, Nat Cancer 2023

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

Kastrasyona Dirençli Metastatik Prostat kanseri



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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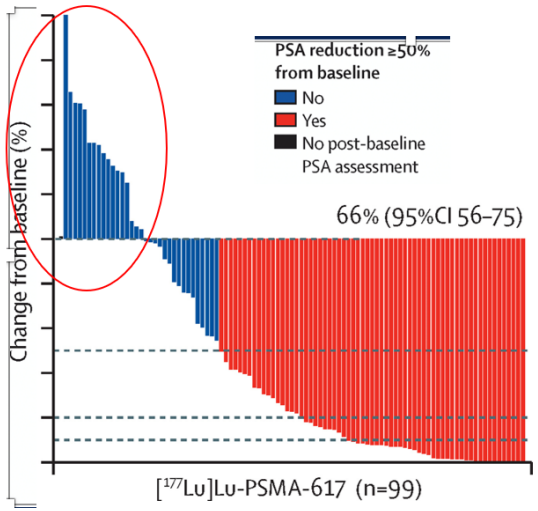


TheraP trial--Hofman et al, Lancet 2021

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)

Kastrasyona Dirençli Metastatik Prostat kanseri

MADRID 2023 ESMO congress

Phase 3 trial of [^{177}Lu]Lu-PSMA-617 in taxane-naive 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 Delgoshaie, K Lehnhoff, MJ Morris,* K Fizazi,*
on behalf of the PSMAfore investigators
*Contributed equally

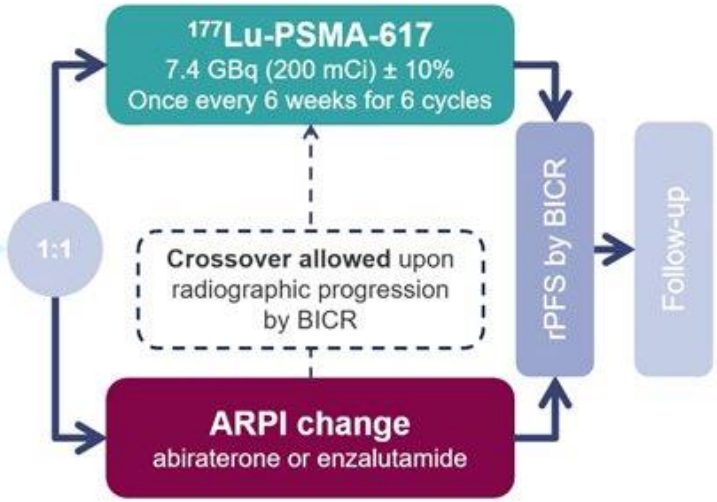
Oliver Sartor
Phase III trial of [177Lu]Lu-PSMA-617 in taxane-naive patients with metastatic castration-resistant prostate cancer (PSMAfore)

Kastrasyona Dirençli Metastatik Prostat kanseri

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-naive (except [neo]adjuvant > 12 months ago)
  - Not candidates for PARPi
- ECOG performance status 0–1



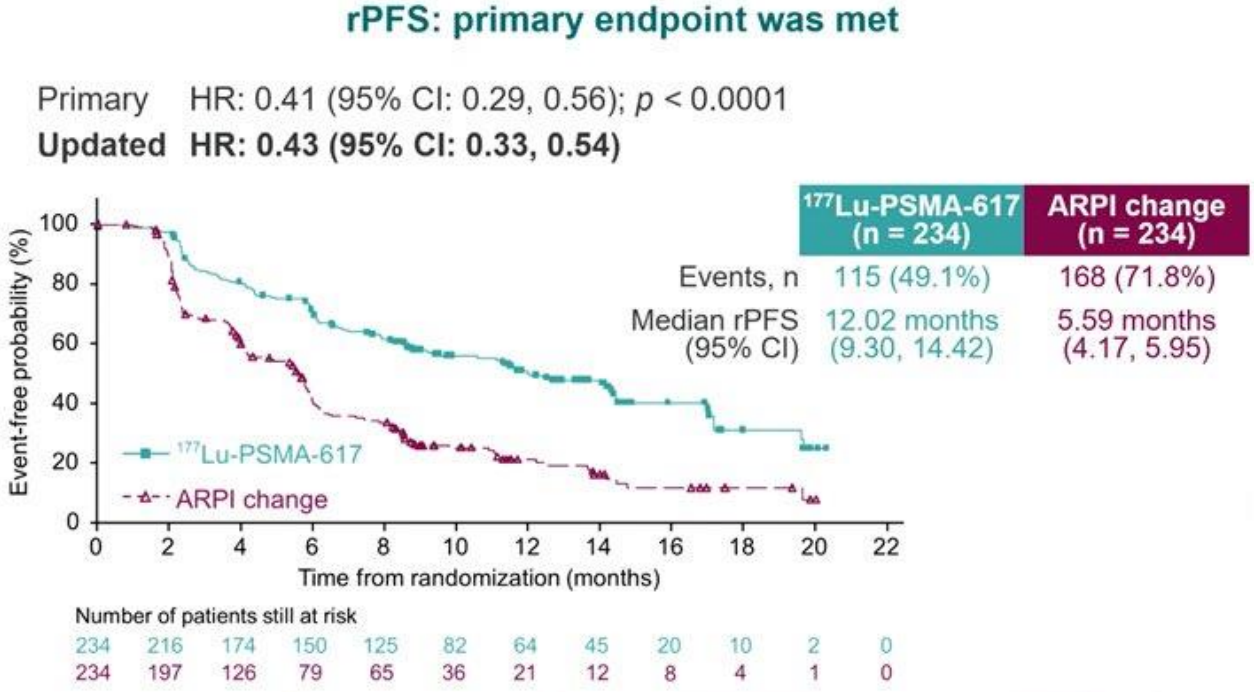
Stratification factors

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

Oliver Sartor

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

Kastrasyona Dirençli Metastatik Prostat kanseri



Oliver Sartor

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

Kastrasyona Dirençli Metastatik Prostat kanseri

PSMAfore: the primary rPFS endpoint was met with a favourable adverse event profile in taxane-naive 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 [177Lu]Lu-PSMA-617 in taxane-naive patients with metastatic castration-resistant prostate cancer (PSMAfore)

Kastrasyona Dirençli Metastatik Prostat kanseri

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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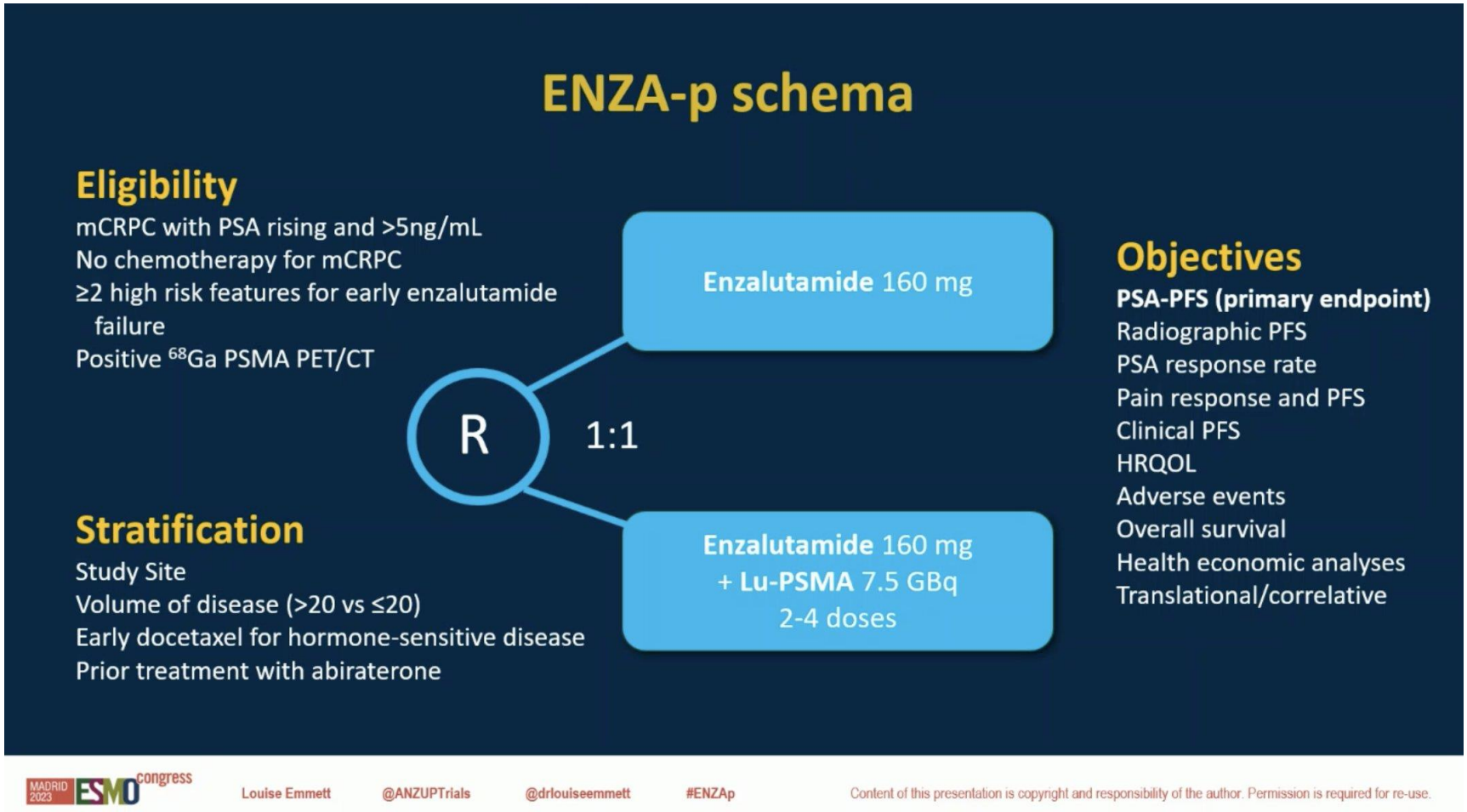
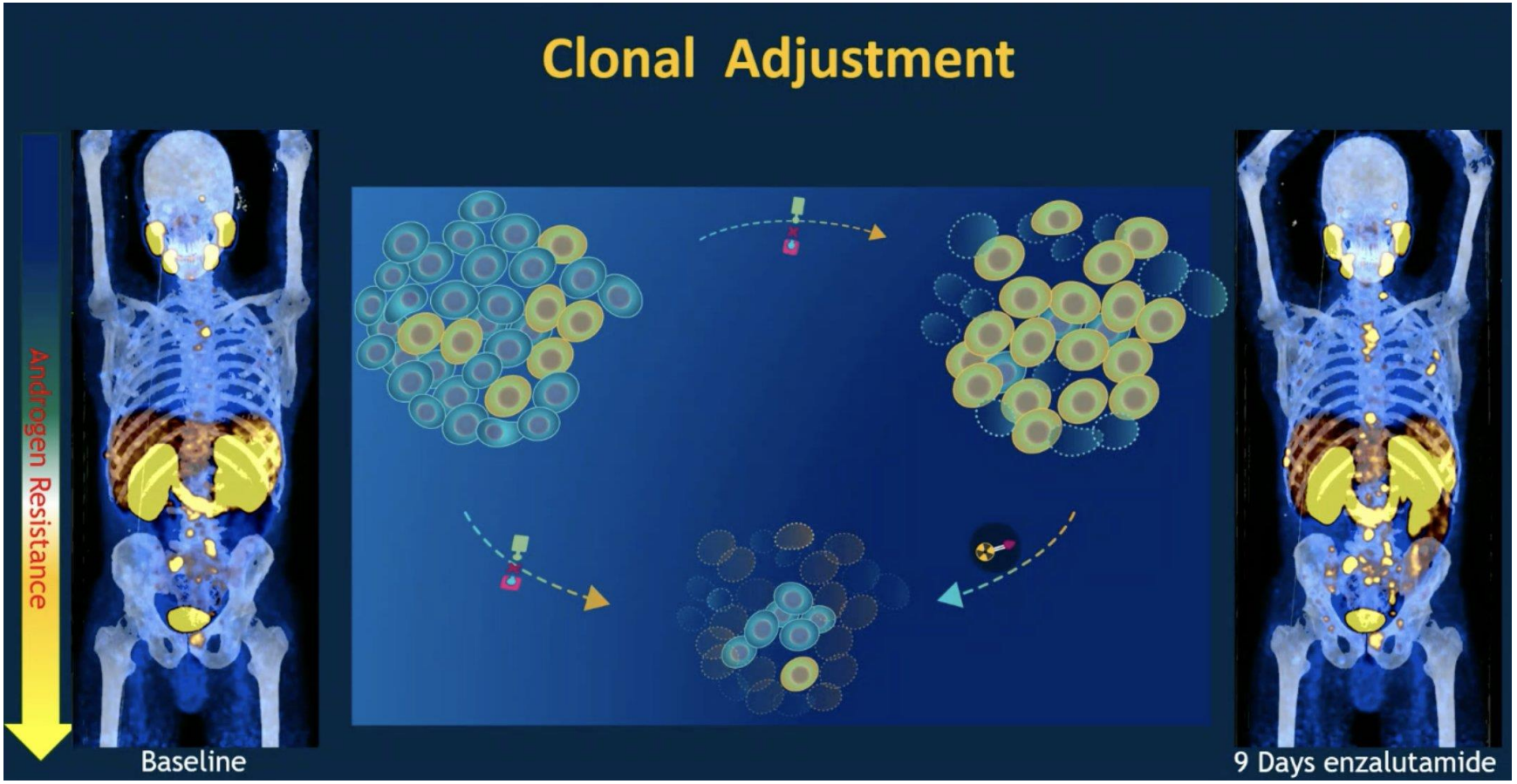


Kastrasyona Dirençli Metastatik Prostat kanseri

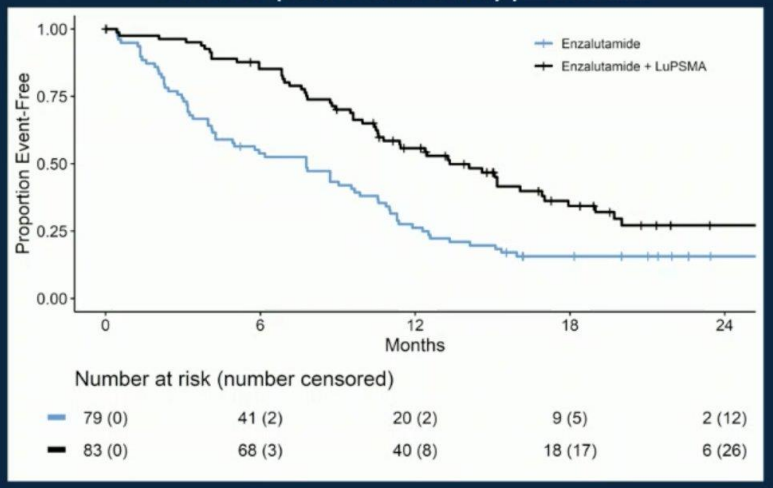


Kastrasyona Dirençli Metastatik Prostat kanseri

Progression Free Survival

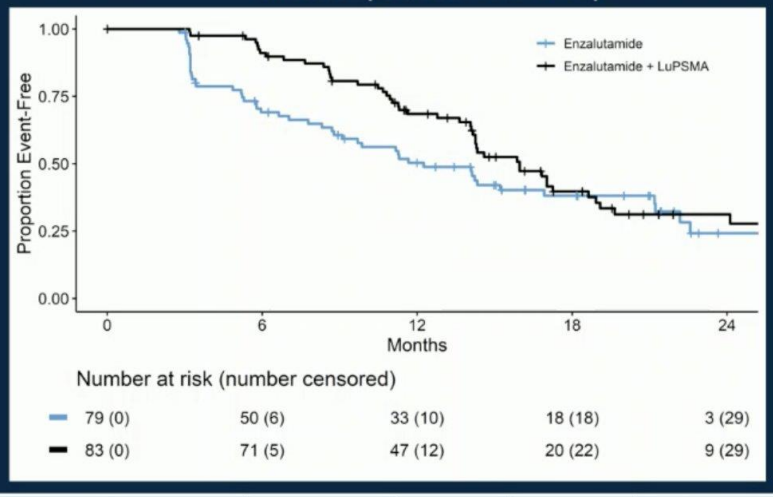
PSA-PFS

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

Kastrasyona Dirençli Metastatik Prostat kanseri

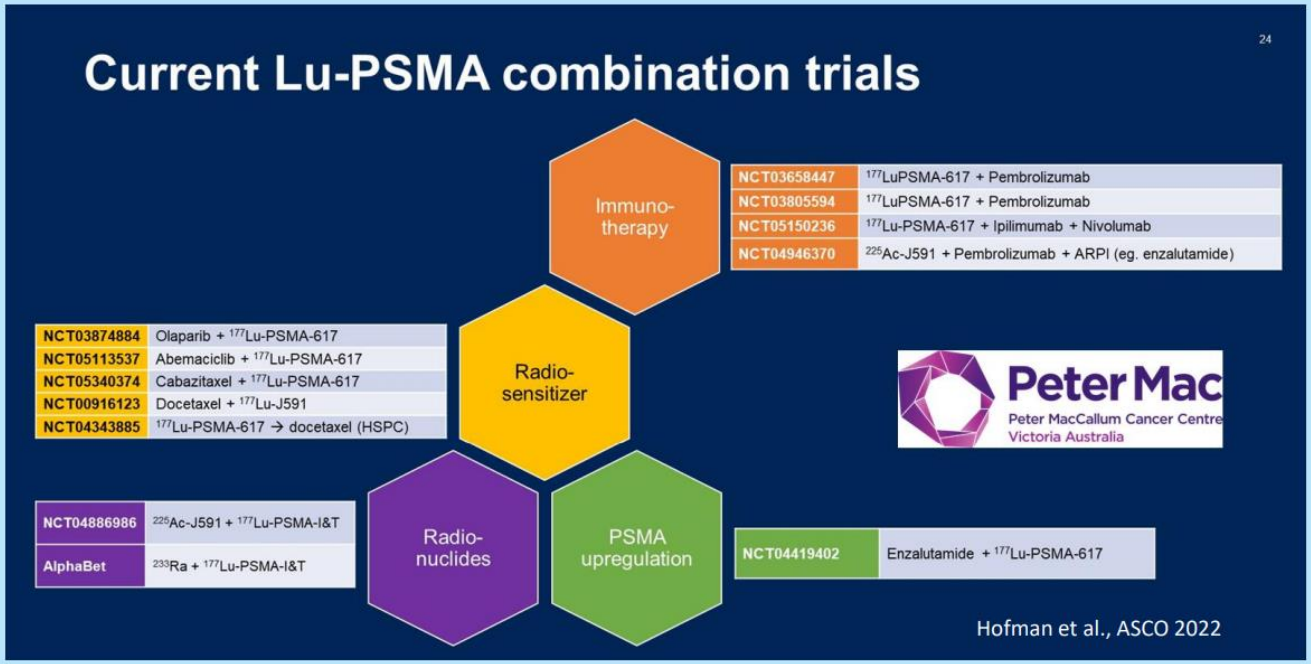
Conclusions

- 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



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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-TGFβRDN, P-PSMA-101
- PSMA-ADC
- **Is there cross resistance between drugs?**
- **Optimal combination therapies?**

Kastrasyona Dirençli Metastatik Prostat kanseri

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-^{177}Lu-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

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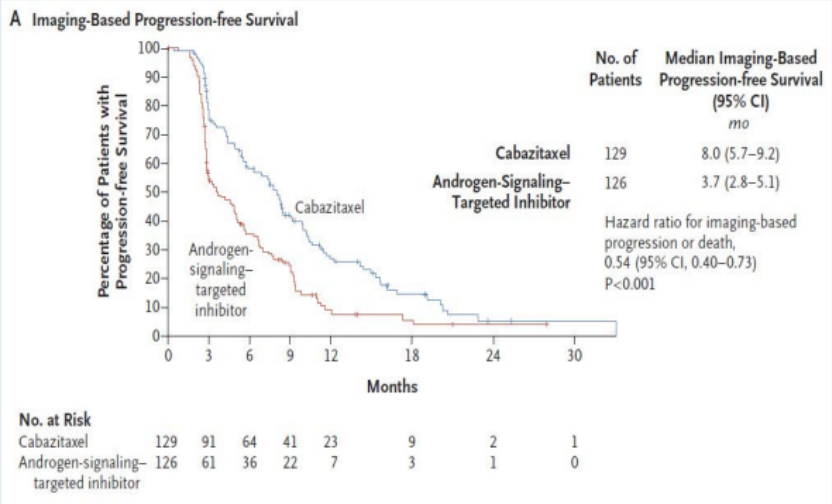
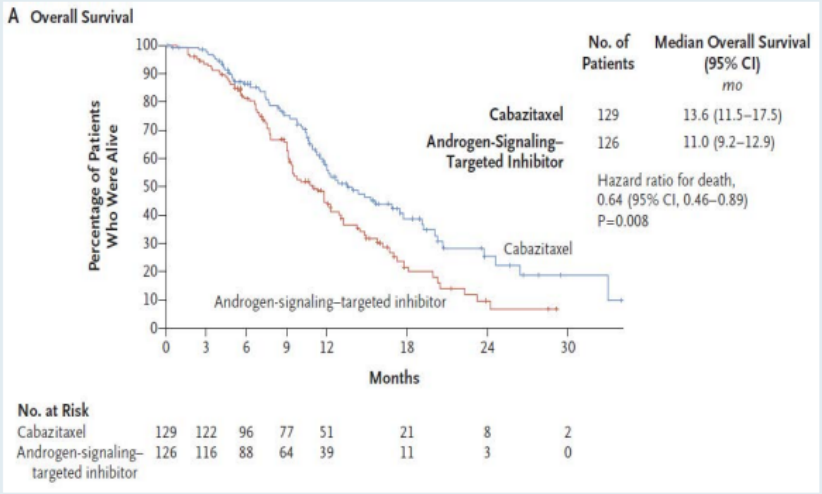
CARD: Imaging-Based PFS and OS with Cabazitaxel versus Abiraterone or Enzalutamide for mCRPC





de Wit R. et al. *NEJM* 2019;381:2506-18.

RTP RESEARCH TO PRACTICE

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)

de Wit R et al. *NEJM* 2019;381:2506-18.

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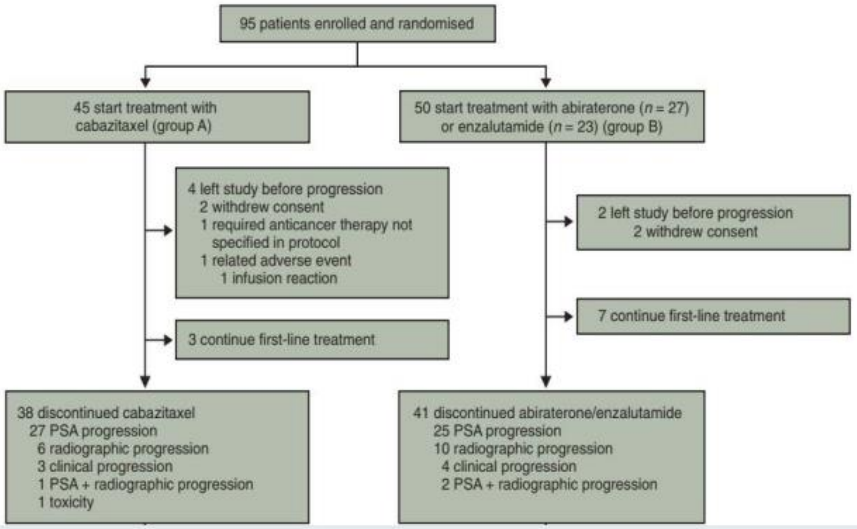
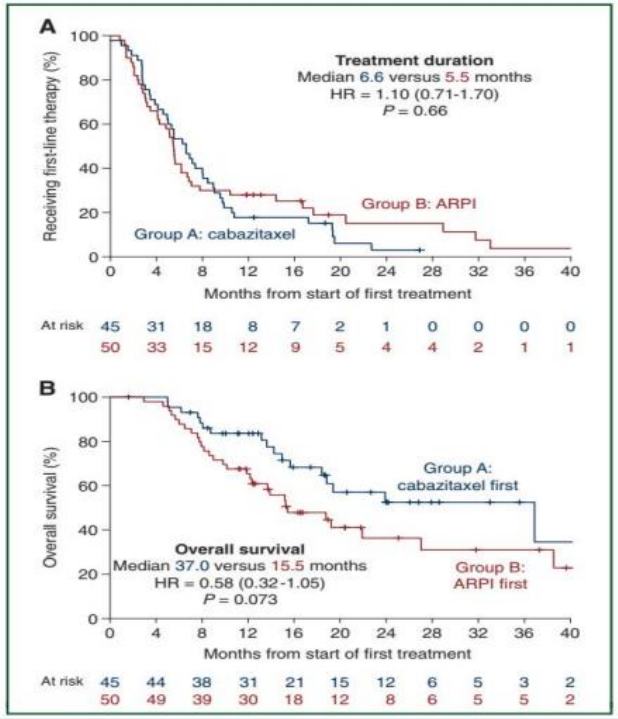
The Canadian Trial (Phase II OZM-054 Trial)

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





Annala M et al. *Ann Oncol* 2021;32:896-905.

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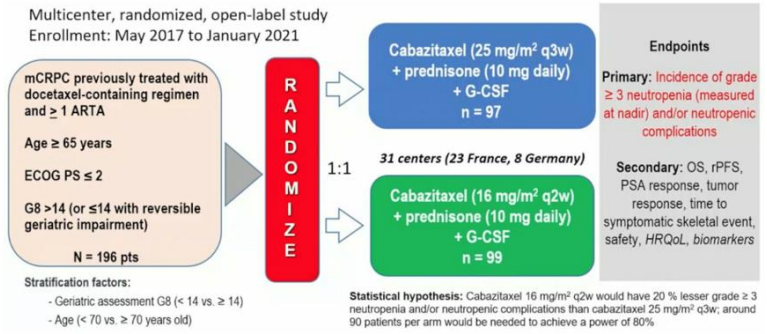
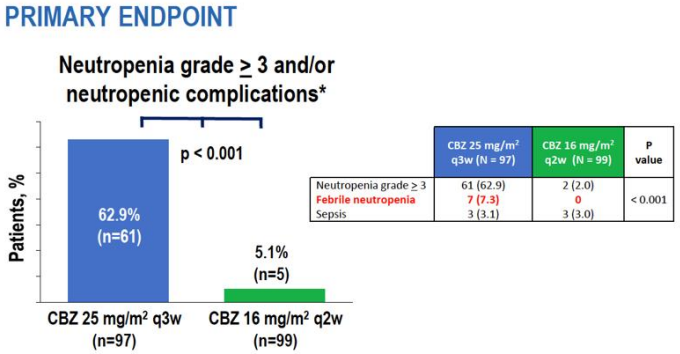
Other Recently Reported Trials Investigating Cabazitaxel for mCRPC

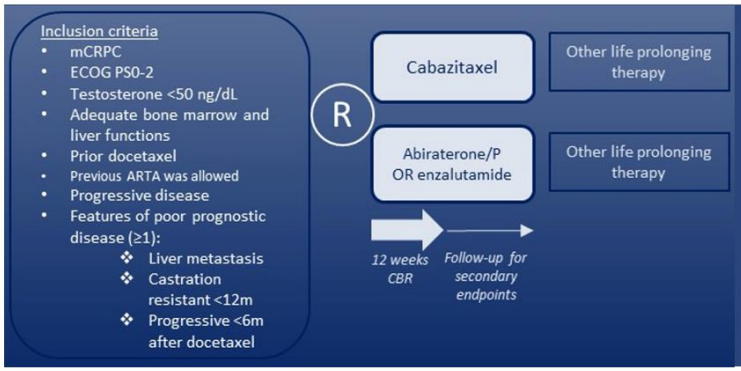
CABASTY[1]





	CBZ 25 mg/m² q3w (N = 97)	CBZ 16 mg/m² q2w (N = 99)	P value
Neutropenia grade ≥ 3	61 (62.9)	2 (2.0)	
Febrile neutropenia	7 (7.3)	0	< 0.001
Sepsis	3 (3.1)	3 (3.0)	

OSTRICh[2]

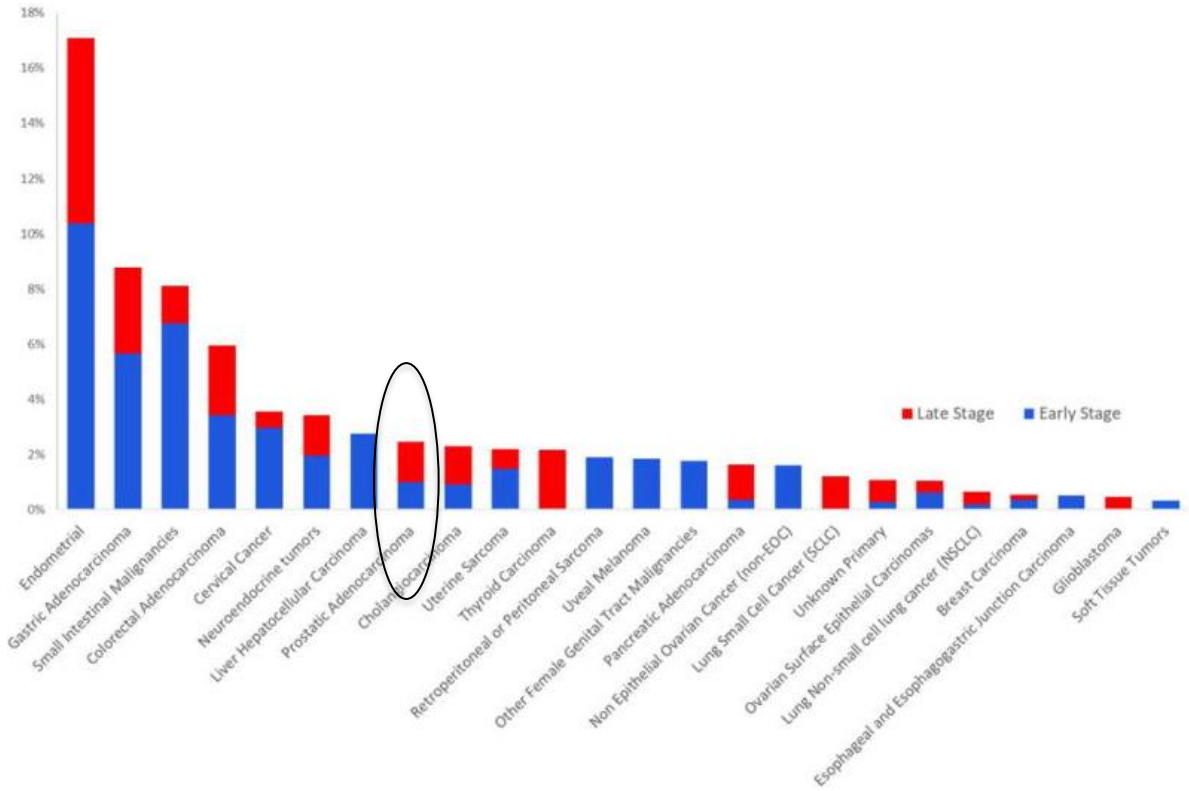


Conclusions

- 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

MADRID 2023 ESMO congress

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)

MADRID 2023 ESMO congress

Granada Auditorium - Hall 3

MADRID SPAIN **20-24 OCTOBER 2023**

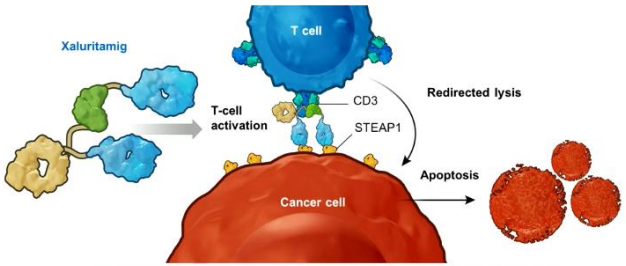
Kastrasyona Dirençli Metastatik Prostat kanseri

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 prognosis[1]
- 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 models[3]



Xaluritamig is an XmAb® 2+1 T-cell engager designed to facilitate T cell-mediated lysis of STEAP1-expressing cells[3,4]

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.

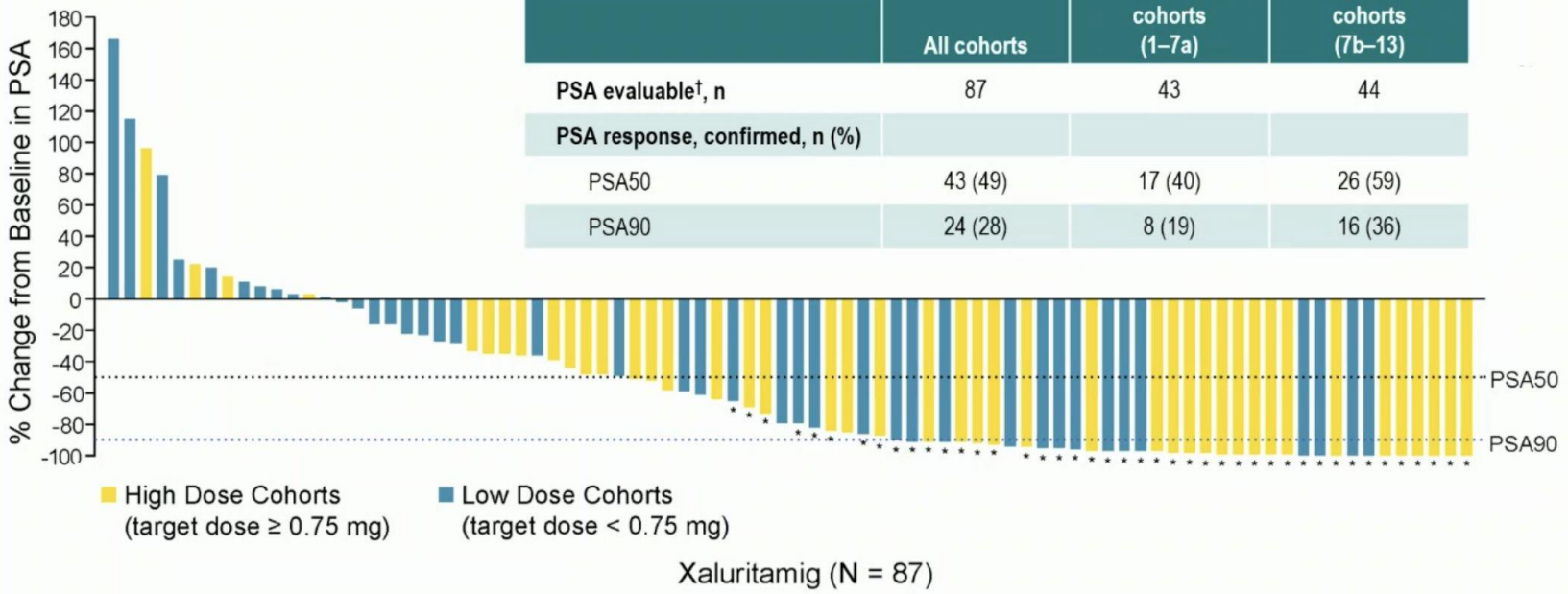
mAb, monoclonal antibody; mCRPC, metastatic castration-resistant prostate cancer; STEAP1, six transmembrane epithelial antigen of the prostate

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.

Kastrasyona Dirençli Metastatik Prostat kanseri

Confirmed PSA responses were observed across cohorts

	All cohorts	Low dose cohorts (1–7a)	High dose cohorts (7b–13)
PSA evaluable†, n	87	43	44
PSA response, confirmed, n (%)			
PSA50	43 (49)	17 (40)	26 (59)
PSA90	24 (28)	8 (19)	16 (36)



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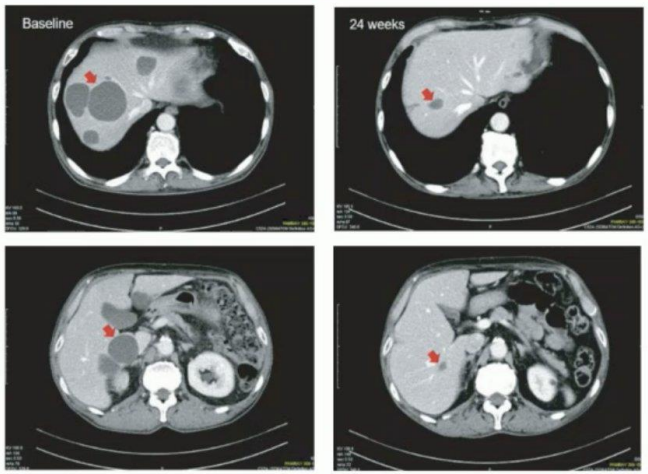
*Confirmed PSA responders of PSA50 or better.
†10 patients were not PSA evaluable: 6 patients were missing baseline PSA values, and 4 patients did not have sufficient follow-up duration.
PSA, prostate specific antigen.

Kastrasyona Dirençli Metastatik Prostat kanseri

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

CT Scan

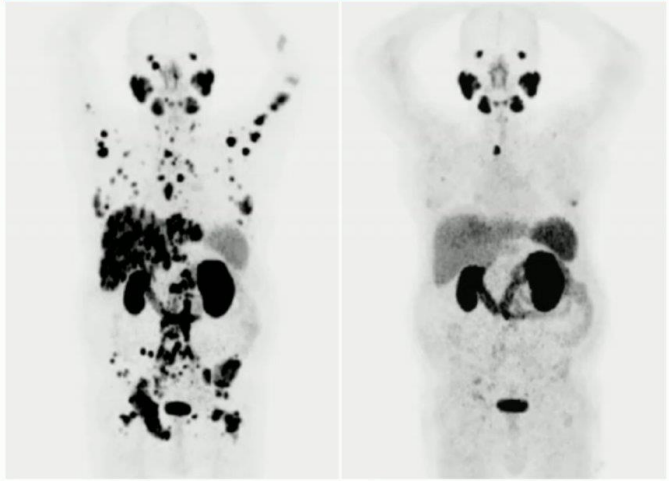
Baseline	Week 24



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

Baseline	Week 12



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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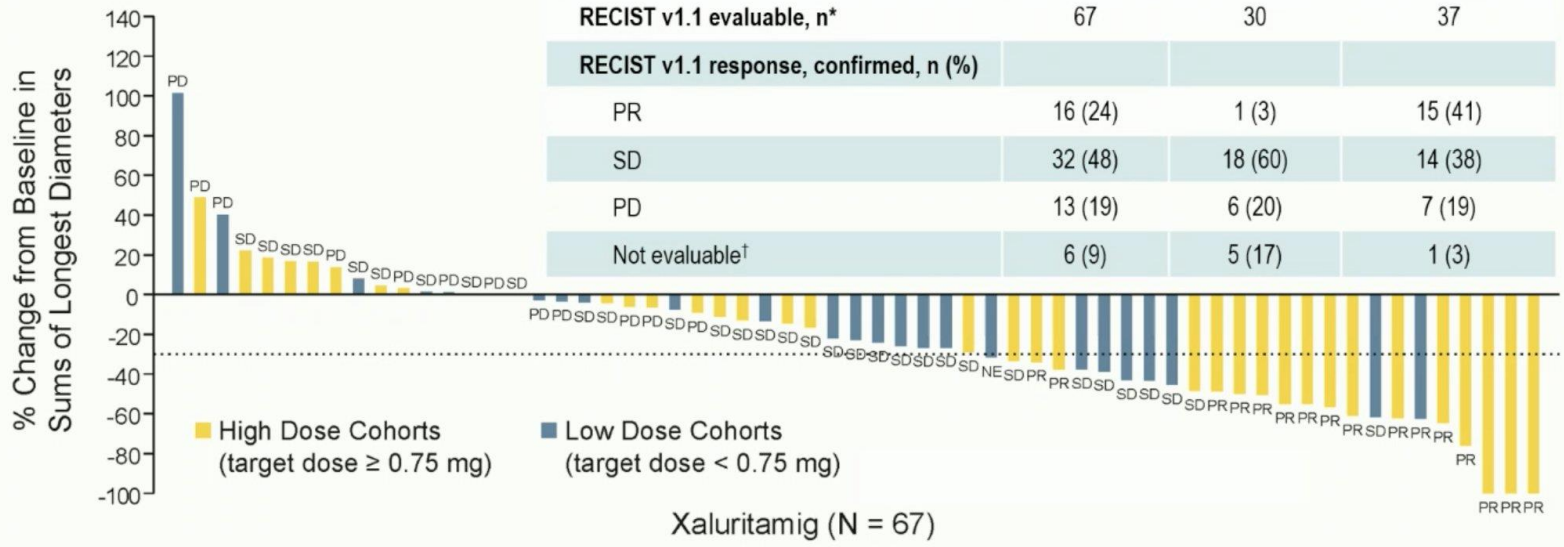
CT, computerized tomography; mCRPC, metastatic castration-resistant prostate cancer; PSA, prostate specific antigen; PSMA PET, prostate-specific membrane antigen positron emission tomography scan; RECIST, Response Evaluation Criteria in Solid Tumors.

Kastrasyona Dirençli Metastatik Prostat kanseri

Confirmed RECIST responses occurred more often in high dose cohorts

	All cohorts	Low dose cohorts (1–7a)	High dose cohorts (7b–13)
RECIST v1.1 evaluable, n*	67	30	37
RECIST v1.1 response, confirmed, n (%)			
PR	16 (24)	1 (3)	15 (41)
SD	32 (48)	18 (60)	14 (38)
PD	13 (19)	6 (20)	7 (19)
Not evaluable†	6 (9)	5 (17)	1 (3)



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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.

Kastrasyona Dirençli Metastatik Prostat kanseri

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.

Abida et al, JAMA Onc 2018

Sonuç

- BRCA mutasyonu olanlarda yeni nesil androjen reseptör yolağı inhibitörleri +PARP inhibitörleri
- Daha önce 1≥ Taksan, 1≥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