Kastrasyona Dirençli Metastatik Prostat Kanserinde Tedavi

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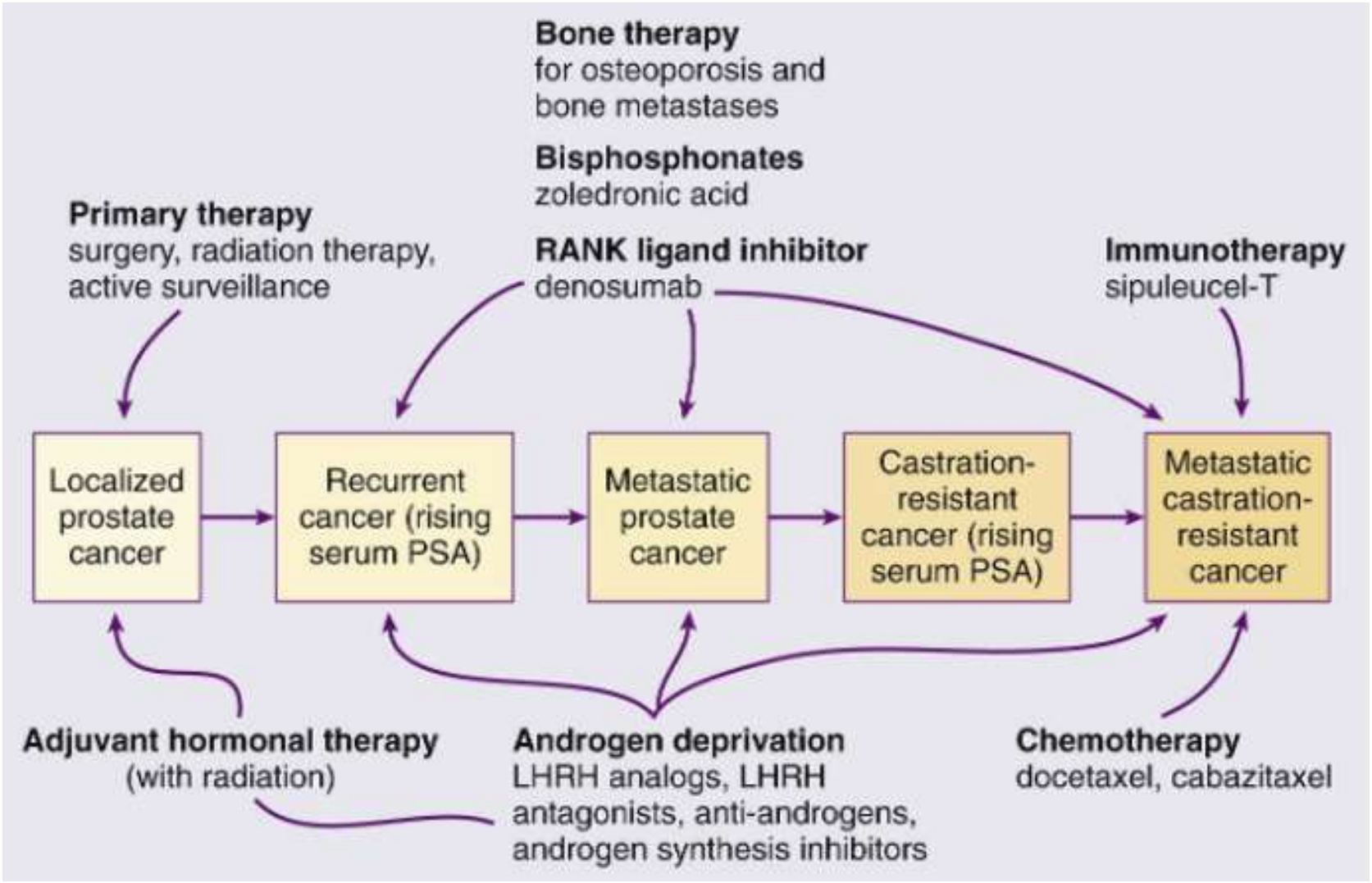
Tıbbi Onkoloji

Ders Planı

- Giriş
- DNA repair mutasyonu olan hastalarda seçenekler
- Lutesyum-177 ve kombinasyon tedavileri
- kabazitaksel ve Androjen Reseptör yolağı blokörleri ardışık kullanımı
- MSI ve diğer mutasyonlarda seçenekler
- Prostat ca nöroendokrin diferansiasyon seçenekleri
- Gelecek perspektif
- Sonuç

Prostat Kanseri Tedavi Yaklaşımları



Abeloff's Clinical Oncology, 10th edition

Prostat Kanseri Genomik Profil

TMB

AR

PI3K

RAF

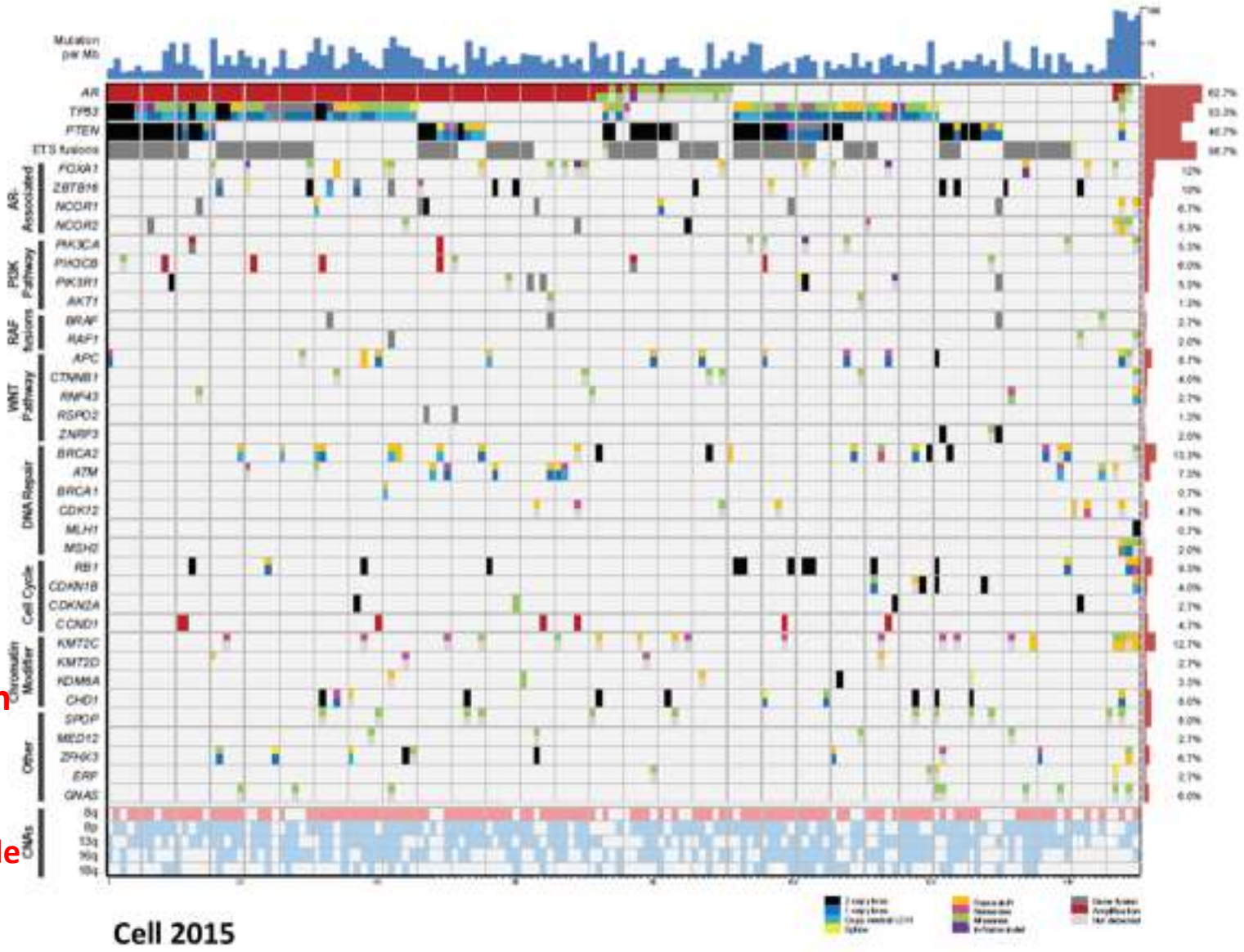
WNT

DNA repair

Cell cycle

chromatin modifier

Single nucleotide variant



Cell 2015

Prostat kanserinde genomik profil

Recent insights into the molecular landscape of advanced PC have identified the following potentially actionable targets:

Molecular alteration	Frequency of expression in advanced PC*
High levels of PSMA expression	**(>80%)[1–5]**
AR pathway mutations/alterations	(63%–71%)[6]
PTEN-PI3K-AKT pathway alterations	(49%)[6]
Cell cycle (CDK) pathway alterations	(21%)[6]
DNA repair pathway alterations	(19%–23%)[6]
WNT pathway alterations	(18%)[6]
MSI-H, dMMR	(~3–5%)[7,8]

PSMA appears to be the most broadly applicable potential biomarker and actionable target in advanced PC[1–6]

**Each figure represents 10% of patients with advanced PC.*

1. Hope TA, et al. J Nucl Med. 2017;58(12):1956–1961; 2. Hupe MC, et al. Front Oncol. 2018;8:623; 3. Pomykala KL, et al. J Nucl Med. 2020;61(3):405–411; 4. Minner S, et al. Prostate. 2011;71(3):281–288; 5. Bostwick DG, et al. Cancer. 1998;82(11):2256–2261; 6. Robinson D, et al. Cell. 2015;161(5):1215–1228; 7. Abida W, et al. JAMA Oncol. 2019; 5(4):471-478; 8. Lindh C, et al. APMIS. 2019; 127(8):554-560.

AKT, protein kinase B; AR, androgen receptor; CDK, cyclin-dependent kinase; PC, prostate cancer; PI3K, phosphoinositide 3-kinase; PSMA, prostate-specific membrane antigen; PTEN, phosphatase and tensin homolog; WNT, wingless int-1.

Kastrasyona Dirençli Metastatik Prostat kanseri

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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]	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 Dirençli 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

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SYSTEMIC THERAPY FOR M1 CRPC: ADENOCARCINOMA[nnn,ooo,ppp]

No prior docetaxel/no prior novel hormone therapy[qqq]	Progression on prior novel hormone therapy/no prior docetaxel[qqq]
• Preferred regimens ▸ Abiraterone[y,rrr] (category 1[sss]) ▸ Docetaxel[lll] (category 1) ▸ Enzalutamide[y] (category 1) • Useful in certain circumstances ▸ Niraparib/abiraterone[y,lll,ttt] for *BRCA* mutation (category 1) ▸ Olaparib/abiraterone[y,lll,rrr,uuu] for *BRCA* mutation (category 1) ▸ Pembrolizumab for MSI-high (MSI-H)/dMMR[lll] (category 2B) ▸ Radium-223[u,vvv] for symptomatic bone metastases (category 1) ▸ Sipuleucel-T[lll,www] (category 1) ▸ Talazoparib/enzalutamide for HRR mutation[y,lll,xxx] (category 1) • Other recommended regimens ▸ Other secondary hormone therapy[y]	• Preferred regimens ▸ Docetaxel (category 1)[lll] ▸ Olaparib for *BRCA* mutation[yyy] (category 1) ▸ Rucaparib for *BRCA* mutation[zzz] (category 1) • Useful in certain circumstances ▸ Cabazitaxel/carboplatin[lll,mmm] ▸ Niraparib/abiraterone[y,lll,ttt] for *BRCA* mutation (category 2B) ▸ Olaparib for HRR mutation other than *BRCA1/2*[yyy] ▸ Pembrolizumab for MSI-H/dMMR[lll] (category 2B) ▸ Radium-223[u,vvv] for symptomatic bone metastases (category 1) ▸ Sipuleucel-T[lll,www] ▸ Talazoparib/enzalutamide for HRR mutation[y,lll,xxx] (category 2B) • Other recommended regimens ▸ Other secondary hormone therapy[aaaa]
Progression on prior docetaxel/no prior novel hormone therapy[qqq]	**Progression on prior docetaxel and a novel hormone therapy[qqq]**
• Preferred regimens ▸ Abiraterone[y,rrr] (category 1) ▸ Cabazitaxel[lll] ▸ Enzalutamide[y] (category 1) • Useful in certain circumstances ▸ Cabazitaxel/carboplatin[lll,mmm] ▸ Mitoxantrone for palliation in symptomatic patients who cannot tolerate other therapies[lll] ▸ Niraparib/abiraterone[y,lll,ttt] for *BRCA* mutation ▸ Olaparib/abiraterone[y,lll,rrr,uuu] for *BRCA* mutation ▸ Pembrolizumab for MSI-H/dMMR[lll] (category 2B) ▸ Radium-223[u,vvv] for symptomatic bone metastases (category 1) ▸ Sipuleucel-T[lll,www] ▸ Talazoparib/enzalutamide for HRR mutation[y,lll,xxx] • Other recommended regimens ▸ Other secondary hormone therapy[y]	• Preferred regimens ▸ Cabazitaxel[lll] (category 1) ▸ Docetaxel rechallenge[lll] • Useful in certain circumstances ▸ Cabazitaxel/carboplatin[lll,mmm] ▸ Lutetium Lu 177 vipivotide tetraxetan (Lu-177–PSMA-617) for PSMA-positive metastases[bbbb] (category 1) ▸ Mitoxantrone for palliation in symptomatic patients who cannot tolerate other therapies[lll] ▸ Olaparib for HRR mutation[yyy] (category 1) ▸ Pembrolizumab for MSI-H, dMMR, or TMB ≥10 mut/Mb[lll] ▸ Radium-223[u,vvv] for symptomatic bone metastases (category 1) ▸ Rucaparib for *BRCA* mutation[zzz] • Other recommended regimens ▸ Other secondary hormone therapy[aaaa]

DNA repair ve Diğer Mutasyonları Ne Zaman Bakılmalı

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.

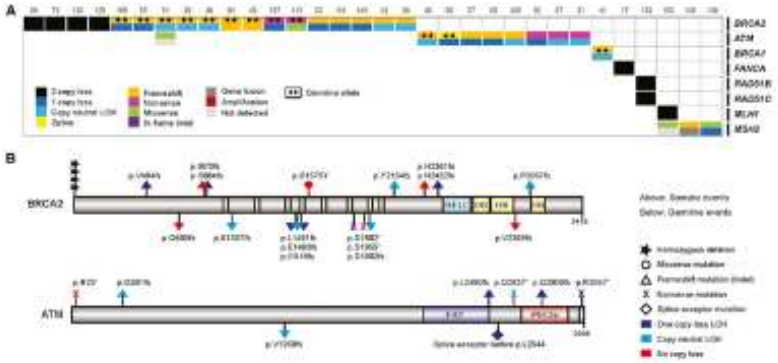
Germline ve somatik mutasyonlar metastatik aşamada istenmeli

Evre IV Prostat Kanserinde Mutasyonlar

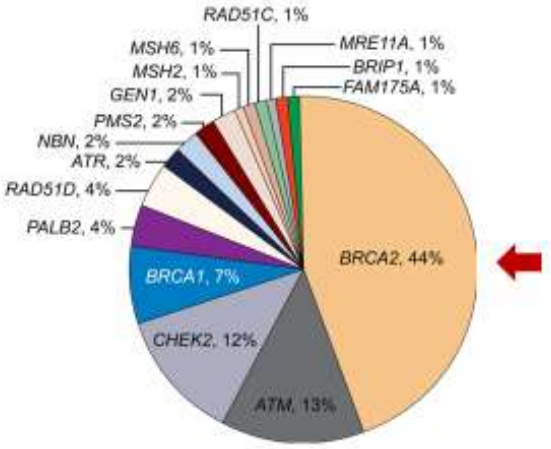
HRR Genes and Metastatic Prostate Cancer

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**



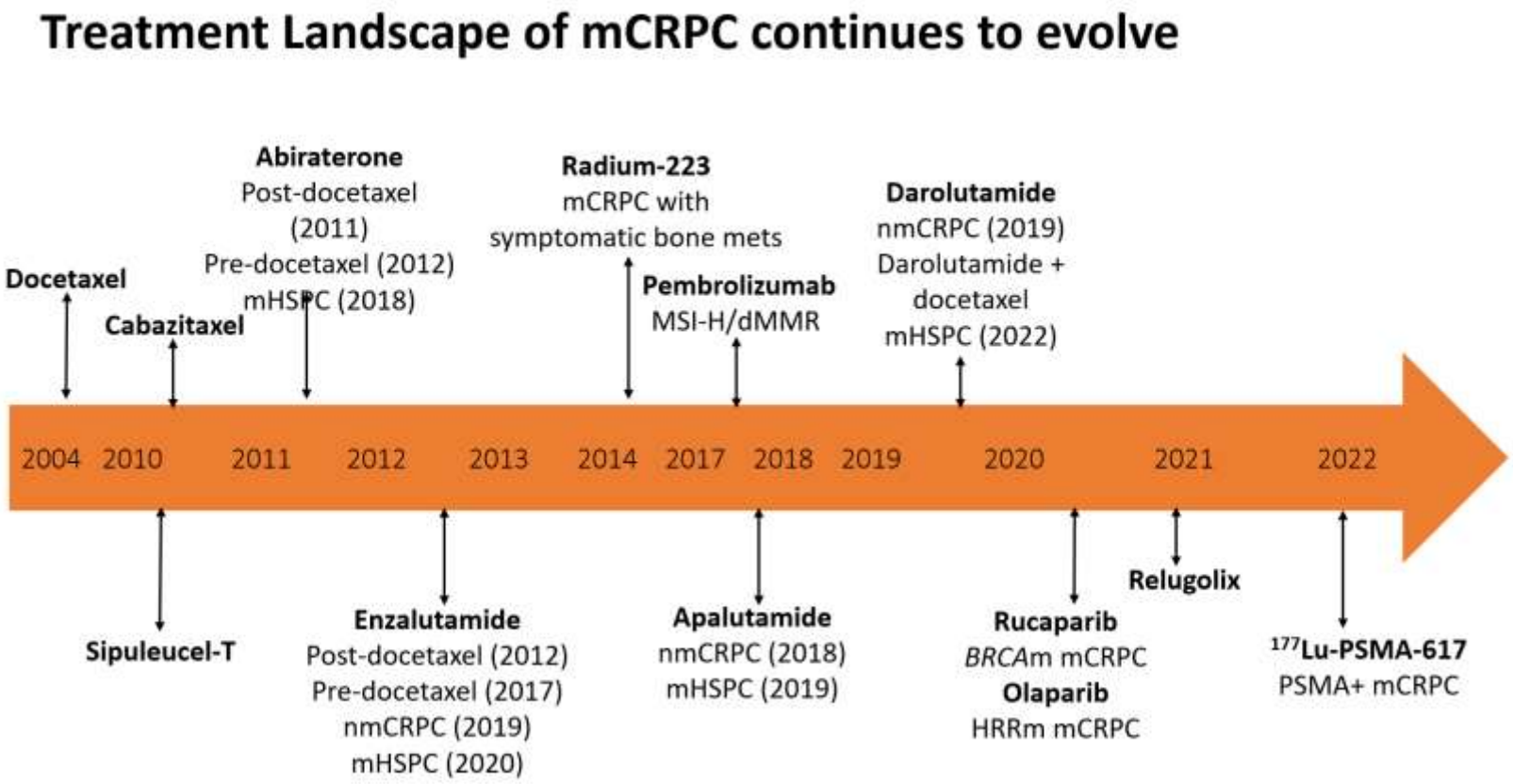
Germline



- **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



Kastrasyona Dirençli Metastatik Prostat kanseri
PARP inhibitörleri+Androjen Reseptör yolağı blokörleri

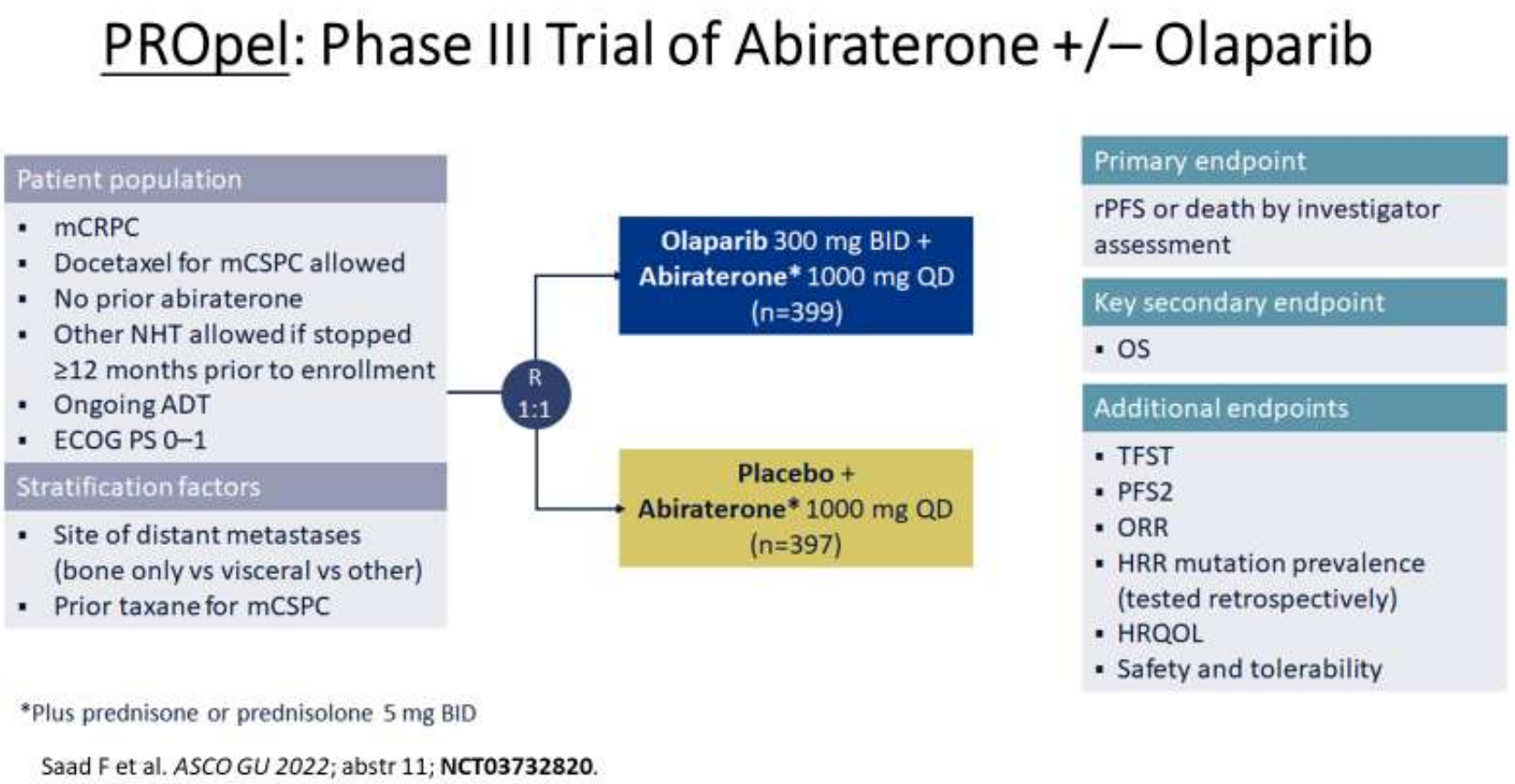
Phase 3 trial of PARPi + AR signaling inhibitor in 1st line mCRPC setting

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.

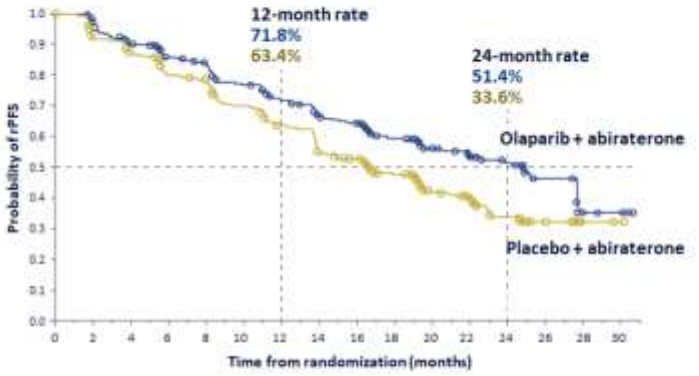
2- Chi KN et al., JCO. 2022 Feb 20;40(6_suppl):12–12. Kim Chi, (2022 Genitourinary cancers symposium (ASCO GU). Abstract #12)

Kastrasyona Dirençli Metastatik Prostat kanseri
PARP inhibitörleri+Androjen Reseptör yolağı blokörleri

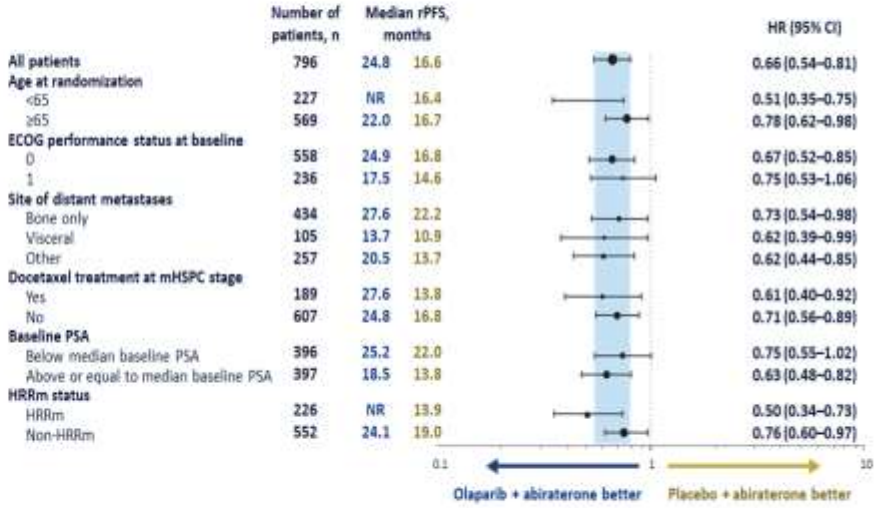


Kastrasyona Dirençli Metastatik Prostat kanseri
PARP inhibitörleri+Androjen Reseptör yolağı blokörleri

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	

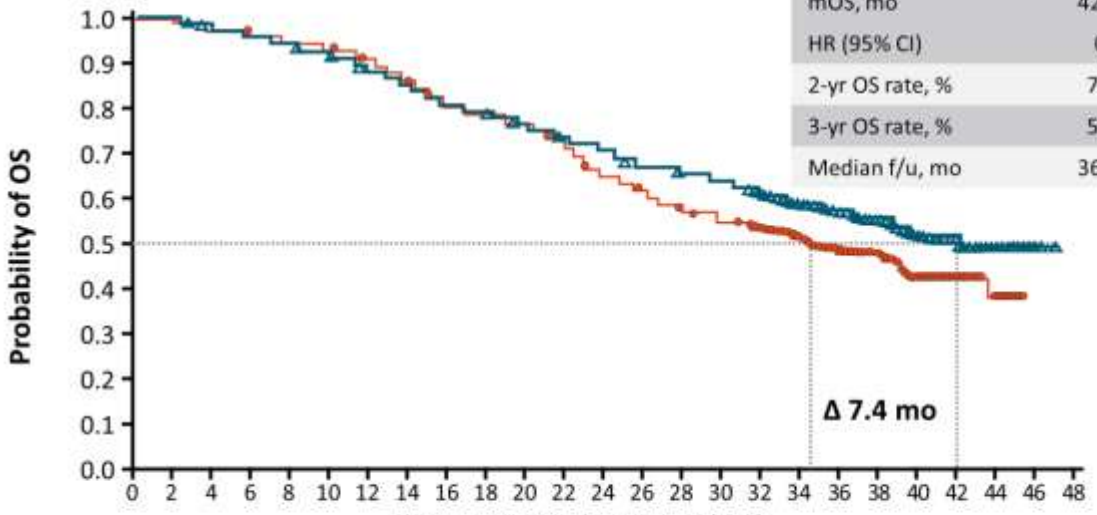


Clarke NW et al. *NEJM Evidence*; 2022.

Kastrasyona Dirençli Metastatik Prostat kanseri
PARP inhibitörleri+Androjen Reseptör yolağı blokörleri

PROpel: OS in ITT Population

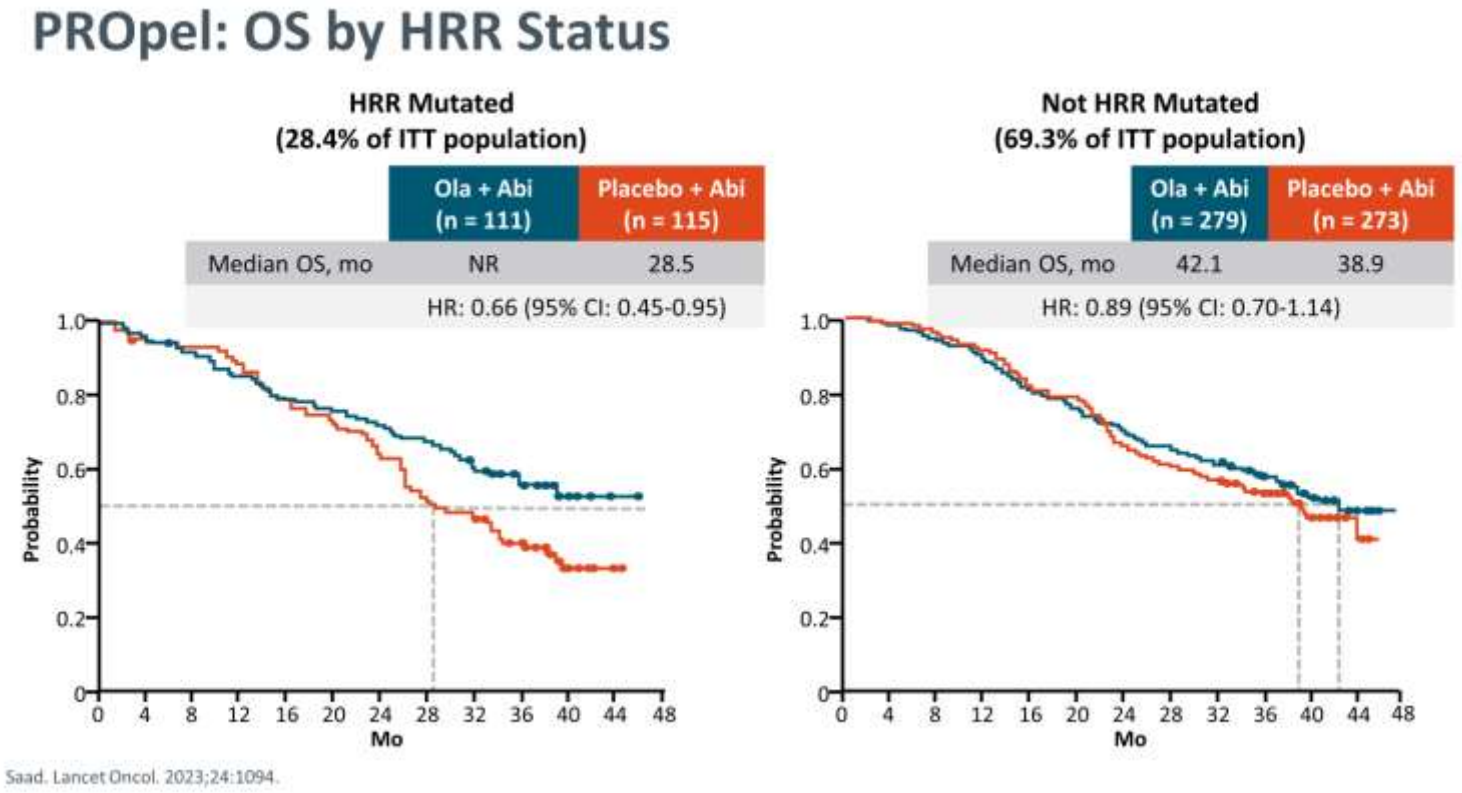
Outcome	Ola + Abi (n = 399)	Placebo + Abi (n = 397)
mOS, mo	42.1	34.7
HR (95% CI)	0.81 (0.67-1.00; *P* = .054)	
2-yr OS rate, %	70	67
3-yr OS rate, %	57	50
Median f/u, mo	36.6	36.5



Patients at Risk, n																								
Ola + Abi	399	399	391	385	374	364	349	334	318	312	298	283	273	258	253	246	226	192	135	96	63	29	10	2	0
Placebo + Abi	397	395	388	383	376	370	355	337	316	305	301	282	254	241	225	213	201	157	119	84	53	25	7	0	0

Clarke. ASCO GU 2023. Abstr LBA16. Saad. Lancet Oncol. 2023;24:1094.

Kastrasyona Dirençli Metastatik Prostat kanseri
PARP inhibitörleri+Androjen Reseptör yolağı blokörleri



Saad. Lancet Oncol. 2023;24:1094.

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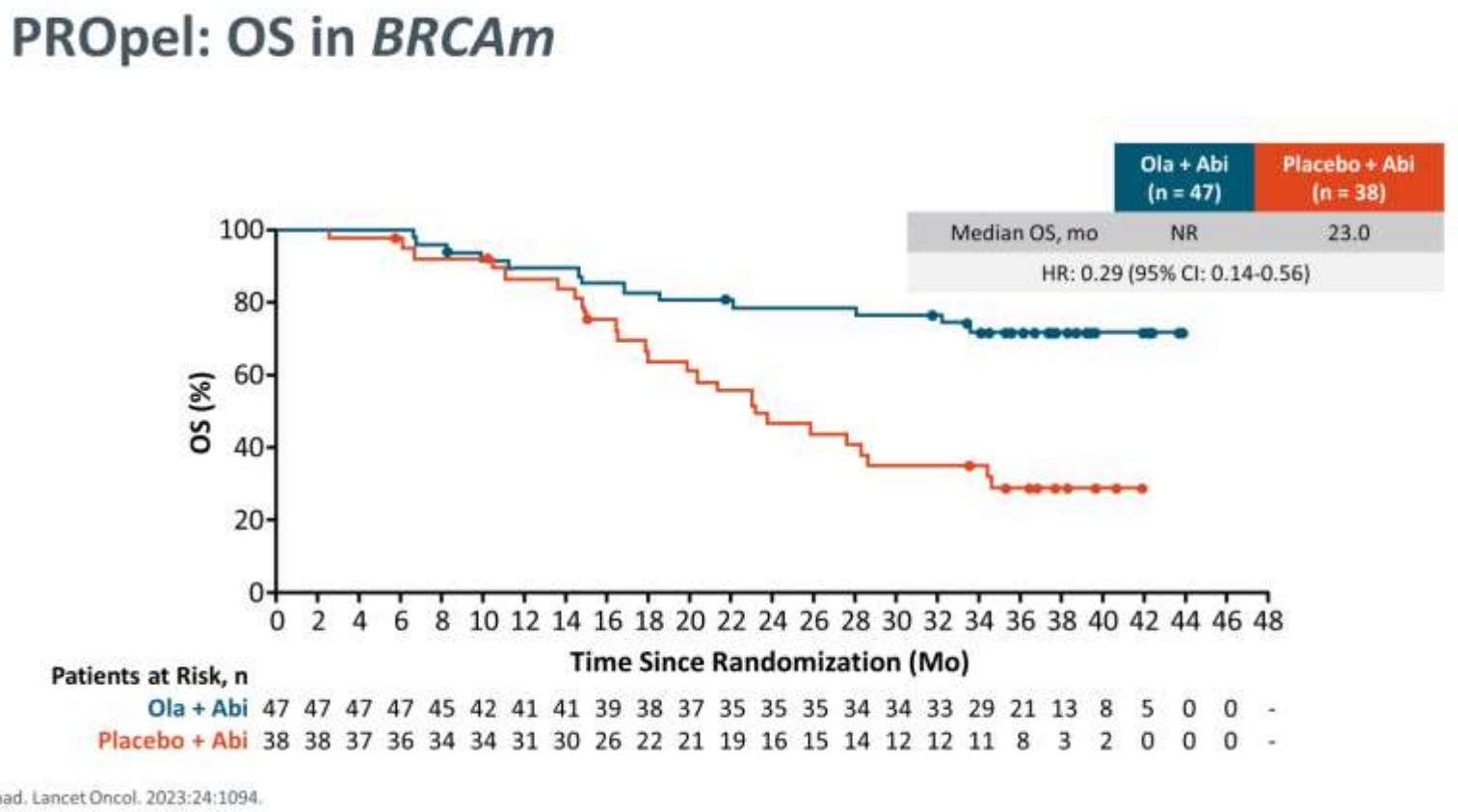
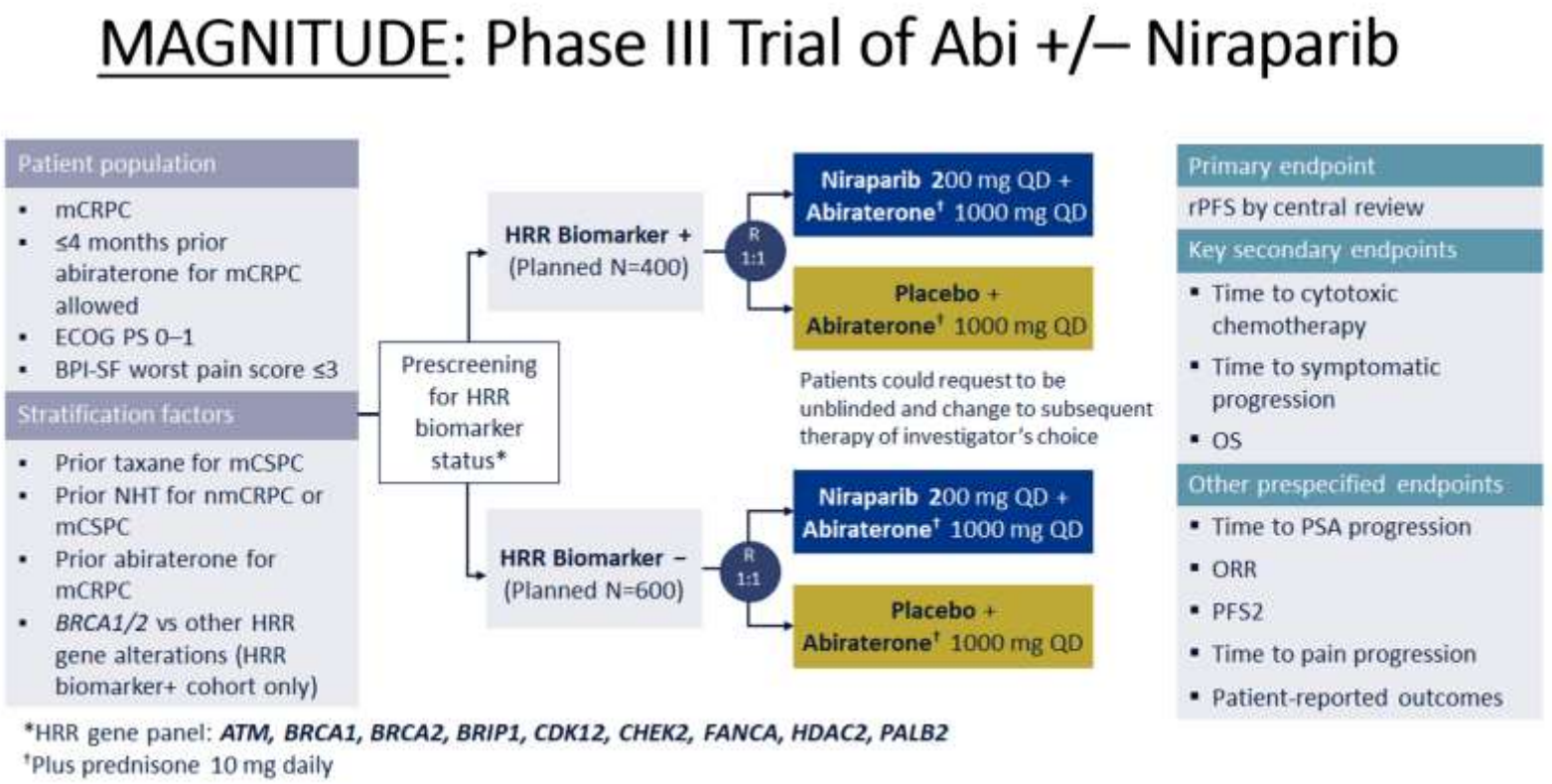
PARP inhibitörleri+Androjen Reseptör yolağı blokörleri



Saad. Lancet Oncol. 2023;24:1094.

Kastrasyona Dirençli Metastatik Prostat kanseri
PARP inhibitörleri+Androjen Reseptör yolağı blokörleri

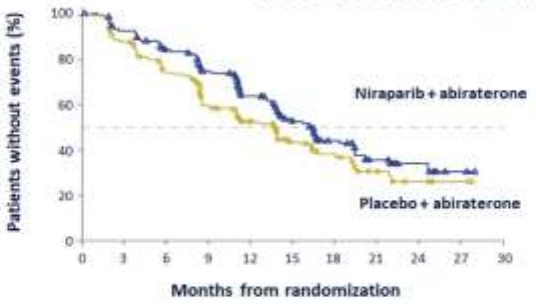


Chi KN et al. *ASCO GU 2022*; abstr 12; **NCT03748641**.

Kastrasyona Dirençli Metastatik Prostat kanseri
PARP inhibitörleri+Androjen Reseptör yolağı blokörleri

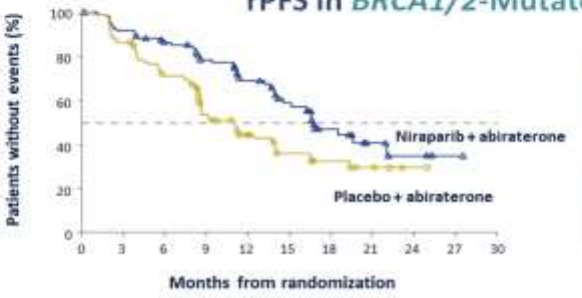
MAGNITUDE: Radiographic Progression-Free Survival

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	

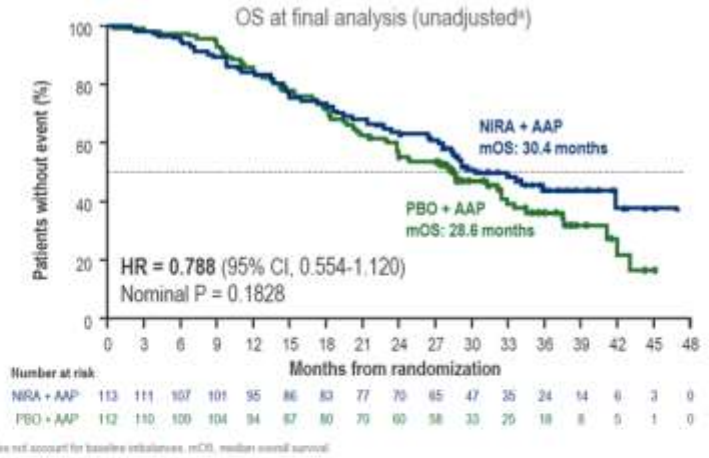
rPFS in *BRCA1/2*-Mutated Group



	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.

Kastrasyona Dirençli Metastatik Prostat kanseri
PARP inhibitörleri+Androjen Reseptör yolağı blokörleri

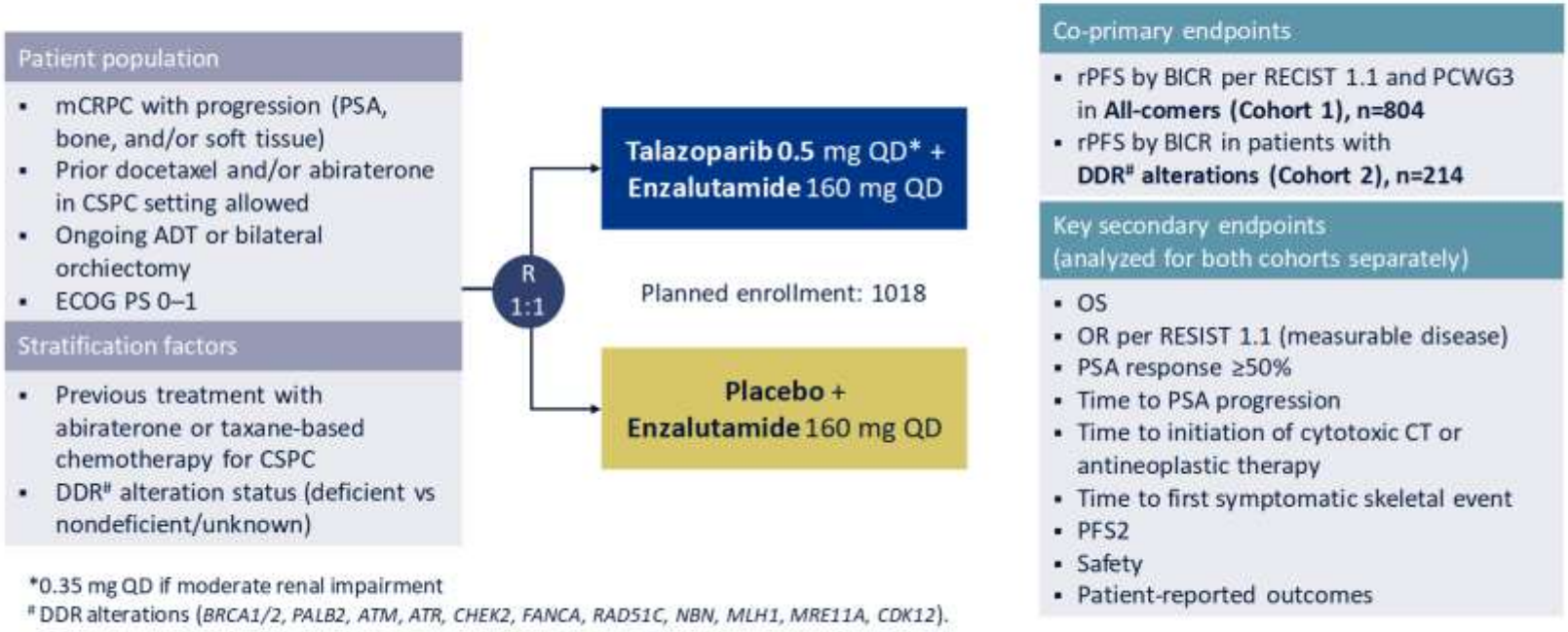


Chi et al ESMO 2023
LBA 85

TEAEs of special interest, n (%)	NIRA + AAP (N = 212)		PBO + AAP (N = 211)	
	All grade	Grade ≥ 3	All grade	Grade ≥ 3
Participants with ≥ 1 AESI	179 (84.4)	113 (53.3)	136 (64.5)	64 (30.3)
Anemia	111 (52.4)	65 (60.6)	48 (22.7)	18 (8.5)
Thrombocytopenia	51 (24.1)	18 (8.5)	20 (9.5)	5 (2.4)
Neutropenia	34 (16.0)	14 (6.6)	15 (7.1)	5 (2.4)
Pulmonary embolism	10 (4.7)	7 (3.3)	3 (1.4)	3 (1.4)
Acute myeloid leukemia	0	0	1 (0.5)	1 (0.9)

Kastrasyona Dirençli Metastatik Prostat kanseri
PARP inhibitörleri+Androjen Reseptör yolağı blokörleri

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

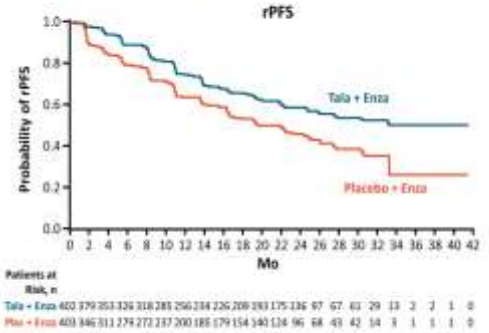


*0.35 mg QD if moderate renal impairment
DDR alterations (*BRCA1/2, PALB2, ATM, ATR, CHEK2, FANCA, RAD51C, NBN, MLH1, MRE11A, CDK12*).

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

Kastrasyona Dirençli Metastatik Prostat kanseri
PARP inhibitörleri+Androjen Reseptör yolağı blokörleri

TALAPRO-2: rPFS by BICR in Cohort 1 All Comers (Primary Endpoint)



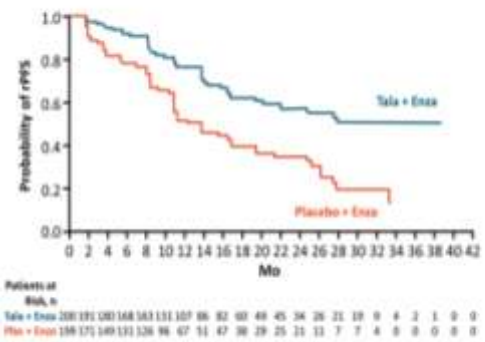
	Tala + Enza (n = 402)	Placebo + Enza (n = 403)
Events, n	151	191
Median rPFS, mo (95% CI)	NR (27.5-NR)	21.9 (16.6-25.1)
Median f/u, mo	24.9	24.6

HR: 0.63 (95% CI: 0.51-0.73; *P* <.001)

- Investigator-assessed rPFS HR: 0.64 (95% CI: 0.50-0.91; *P* <.001)

Agarwal. ASCO GU 2021. Abstr LBA17. Agarwal. Lancet. 2021;398:131.

TALAPRO-2: rPFS by BICR in HRR-Deficient Cohort 2



	Tala + Enza (n = 200)	Placebo + Enza (n = 199)
Events, n	66	104
Median rPFS, mo (95% CI)	NR (21.9-NR)	13.8 (11.0-16.7)
Median f/u, mo	17.5	16.8

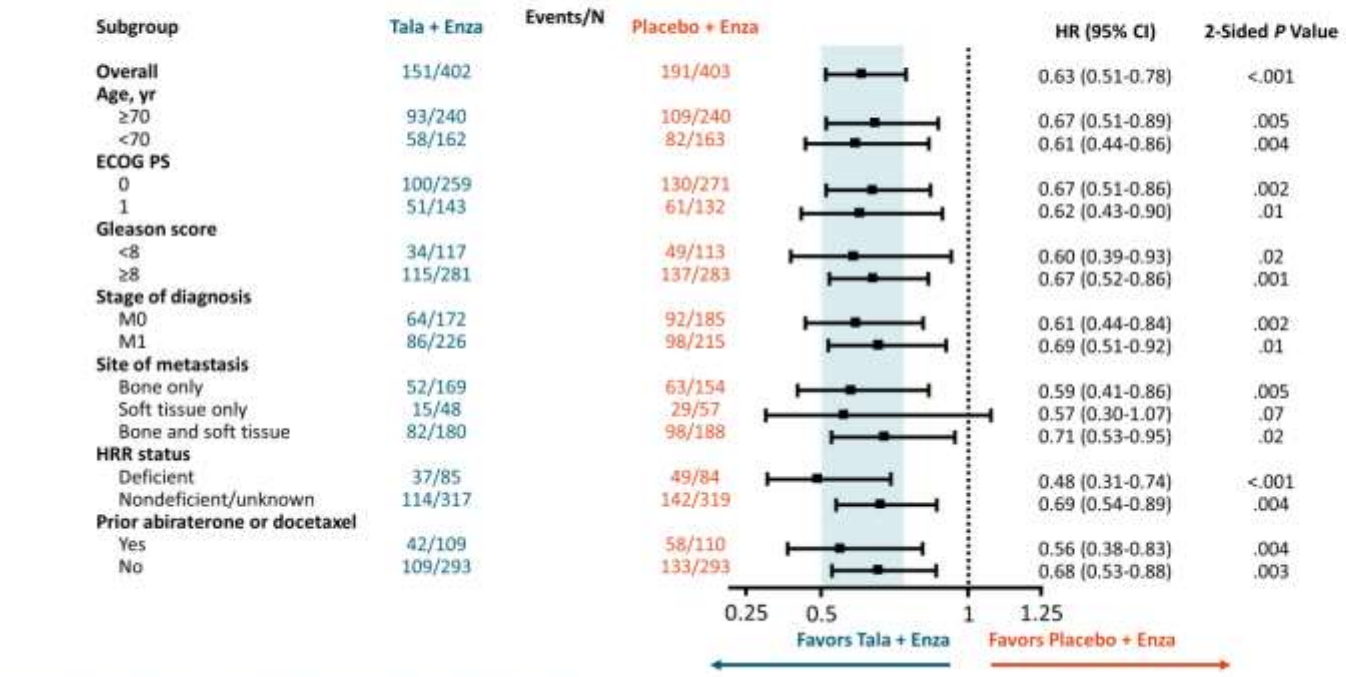
HR: 0.45 (95% CI: 0.33-0.61; *P* <.0001)

- Investigator-assessed rPFS HR: 0.48 (95% CI: 0.33-0.67; *P* <.0001)

Fizazi. ASCO 2021. Abstr 5004. Fizazi. Nat Med. 2021;27:e41.

Kastrasyona Dirençli Metastatik Prostat kanseri
PARP inhibitörleri+Androjen Reseptör yolağı blokörleri

TALAPRO-2: Subgroup Analysis of rPFS by BICR Cohort 1

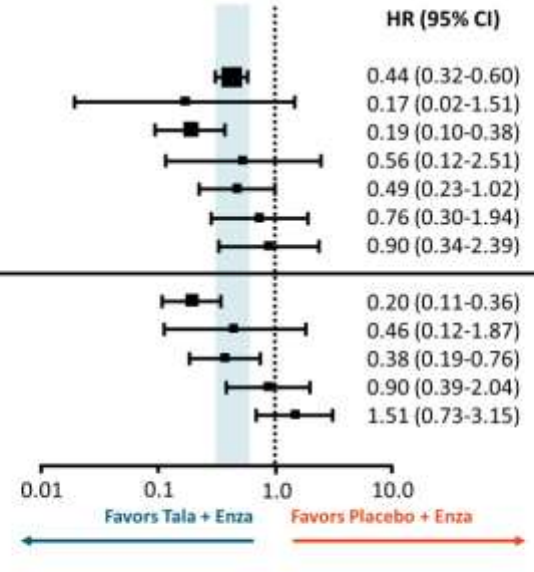


Agarwal. ASCO GU 2023. Abstr LBA17. Agarwal. Lancet. 2023;204:291.

Kastrasyona Dirençli Metastatik Prostat kanseri
PARP inhibitörleri+Androjen Reseptör yolağı blokörleri

TALAPRO-2: rPFS by BICR in Cohort 2 Selected Gene Subgroups

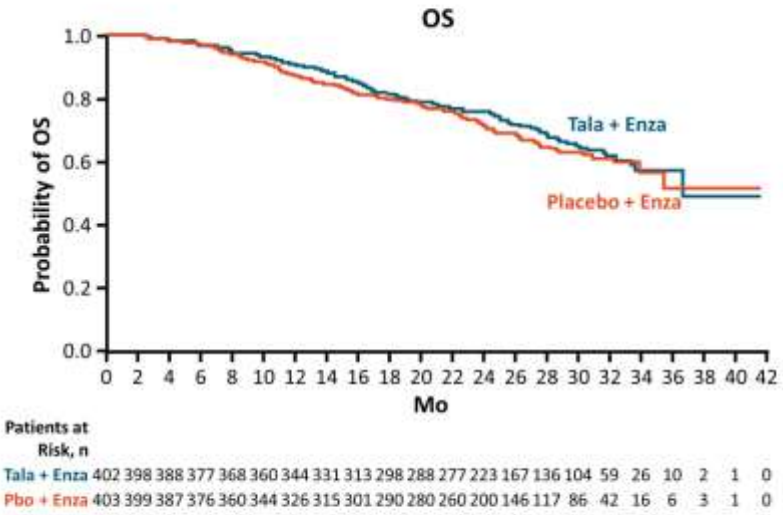
Subgroup	Events/N		Median, Mo	HR (95% CI)	2-Sided *P* Value
	Tala + Enza	Placebo + Enza			
All HRR deficient	65/198	104/197	NR/13.8	0.44 (0.32-0.60)	<.001
Only *BRCA1*	2/8	5/9	20.0/11.7	0.17 (0.02-1.51)	.074
Only *BRCA2*	11/55	40/60	NR/11.0	0.19 (0.10-0.38)	<.0001
Only *PALB2*	3/6	4/5	NR/8.6	0.56 (0.12-2.51)	.44
Only *CDK12*	12/28	18/30	21.9/13.8	0.49 (0.23-1.02)	.055
Only *ATM*	12/35	7/22	NR/27.7	0.76 (0.30-1.94)	.58
Only *CHEK2*	8/24	8/24	22.1/NR	0.90 (0.34-2.39)	.83
Hierarchy					
BRCA cluster	15/71	54/84	NR/11.0	0.20 (0.11-0.36)	<.0001
PALB2 cluster	3/7	6/8	NR/8.3	0.46 (0.12-1.87)	.27
CDK12 cluster	13/35	23/36	21.9/13.8	0.38 (0.19-0.76)	.0045
ATM cluster	16/43	9/29	27.9/27.7	0.90 (0.39-2.04)	.80
Other gene cluster	18/42	12/40	21.1/NR	1.51 (0.73-3.15)	.26



Fizazi. ASCO 2023. Abstr 5004. Fizazi. Nat Med. 2023;[Epub].

Kastrasyona Dirençli Metastatik Prostat kanseri
PARP inhibitörleri+Androjen Reseptör yolağı blokörleri

TALAPRO-2: Overall Survival in All-Comers Population



	Tala + Enza (n = 402)	Placebo + Enza (n = 403)
Events, n	123	123
Median OS, mo (95% CI)	36.4 (33.5-NR)	NR (33.7-NR)

HR: 0.89 (95% CI: 0.69-1.14; *P* = .35)

- OS data at 31% mature; additional follow-up needed

Agarwal. ASCO GU 2023. Abstr LBA17. Agarwal. Lancet. 2023;204:291.

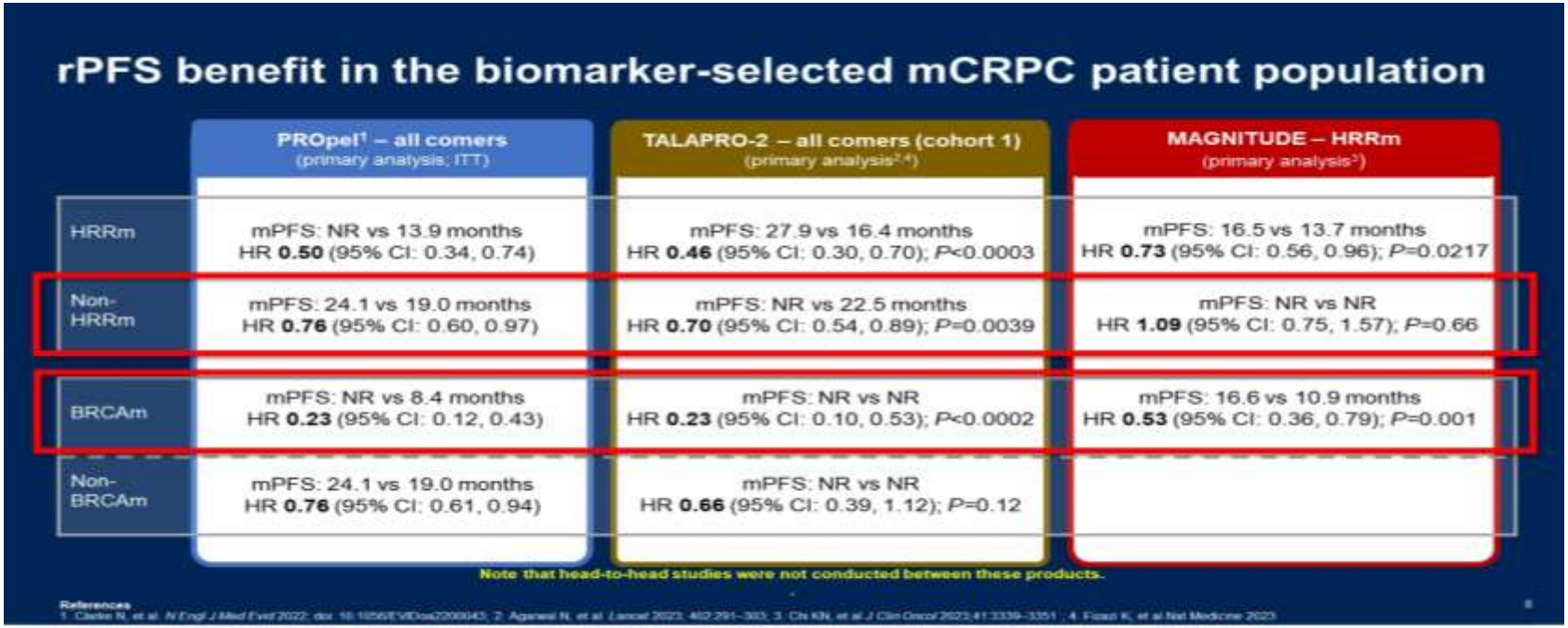
PARP inhibitörleri+Androjen Reseptör yolağı blokörleri Yan etkilerin karşılaştırılması

	PROPEL Olaparib + Abiraterone	MAGNITUDE Niraparib + Abiraterone	TALAPRO-2 Talazoparib + Enzaluatmide
Select G3-4 Toxicities % (all grades %)			
Anemia ---Transfusion Rate	16.3 (50) 18%	30.1 (50.0) 27.4%	46 (66) 39%
Fatigue	2.5 (39.0)	3.3 (29.7)	4 (34)
Nausea	0.3 (31.0)	0.5 (24.5)	<1 (21)
Hypertension	3.8 (15.0)	33 (15.6)	5 (14)
Pulmonary Embolism	7.3%	1.9%	2.5%
Outcomes			
PARP interruption	49%	49.1%	62.0%
PARP dose reduction	22.6%	20.3%	53.0%
PARP discontinuation	17.3%	15.1%	19.0%

- Toxicities are largely a class effect of PARPi's. Myelosuppression and GI toxicity are most prominent.
- AE's of special interest include MDS/AML and PE.

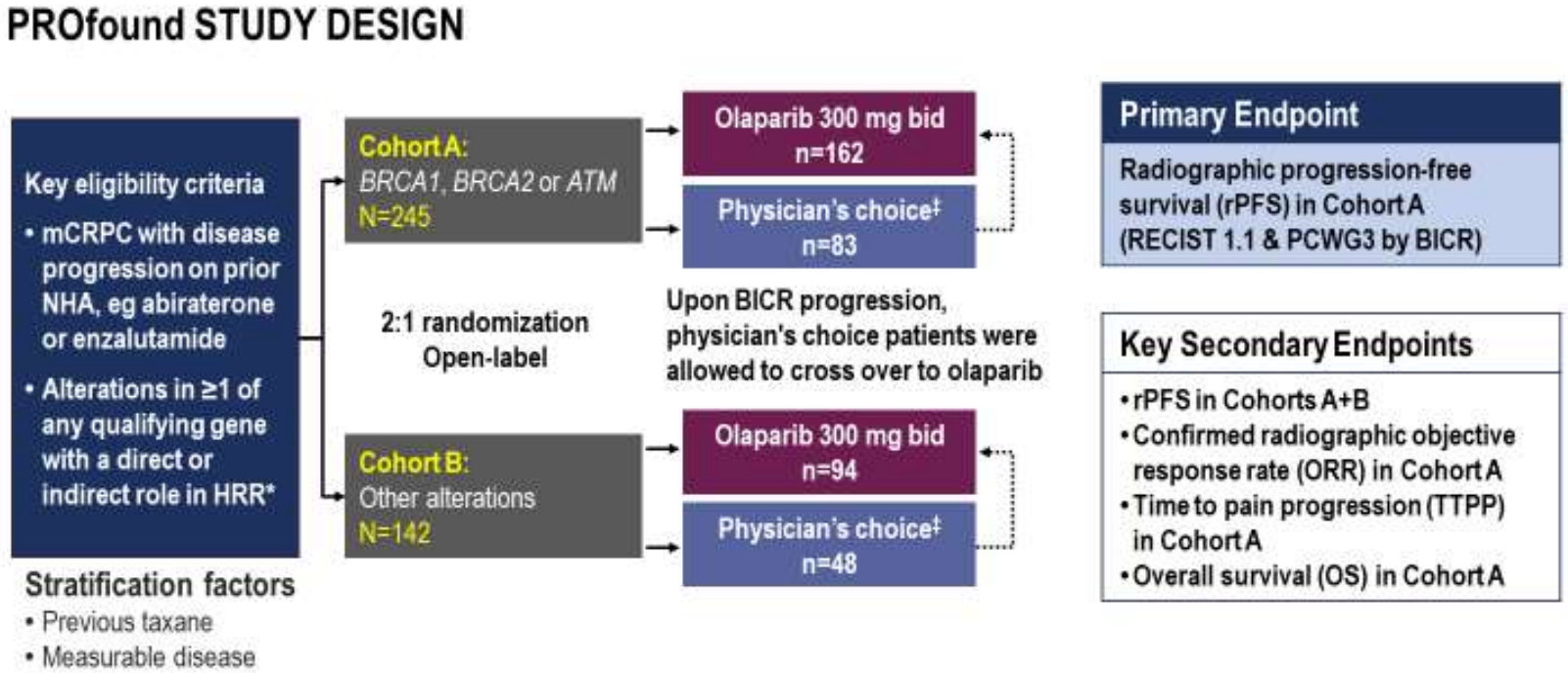
Clarke. NEJM Evid. 2022;1. Chi. J Clin Oncol. 2023; JCO2201649. Fizazi. Lancet. 2023;402

Kastrasyona Dirençli Metastatik Prostat kanseri
PARP inhibitörleri+Androjen Reseptör yolağı blokörleri



	EMA	FDA
Olaparib + AA	All patients	*BRCA1/2*
Talazoparib + Enza	All patients	HRR
Niraparib + AA	*BRCA1/2*	*BRCA1/2*

Kastrasyona Dirençli Metastatik Prostat kanseri PARP inhibitörleri



*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

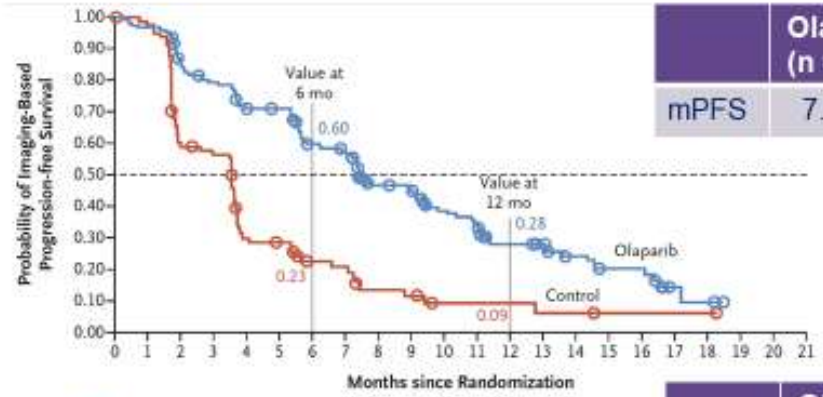
BARCELONA 2019 ESMO congress

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

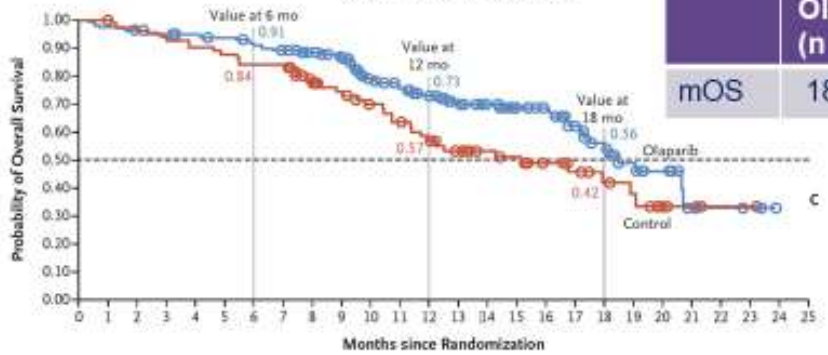
Hussain M et al. ESMO 2019;Abstract 5059.

Kastrasyona Dirençli Metastatik Prostat kanseri PARP inhibitörleri

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

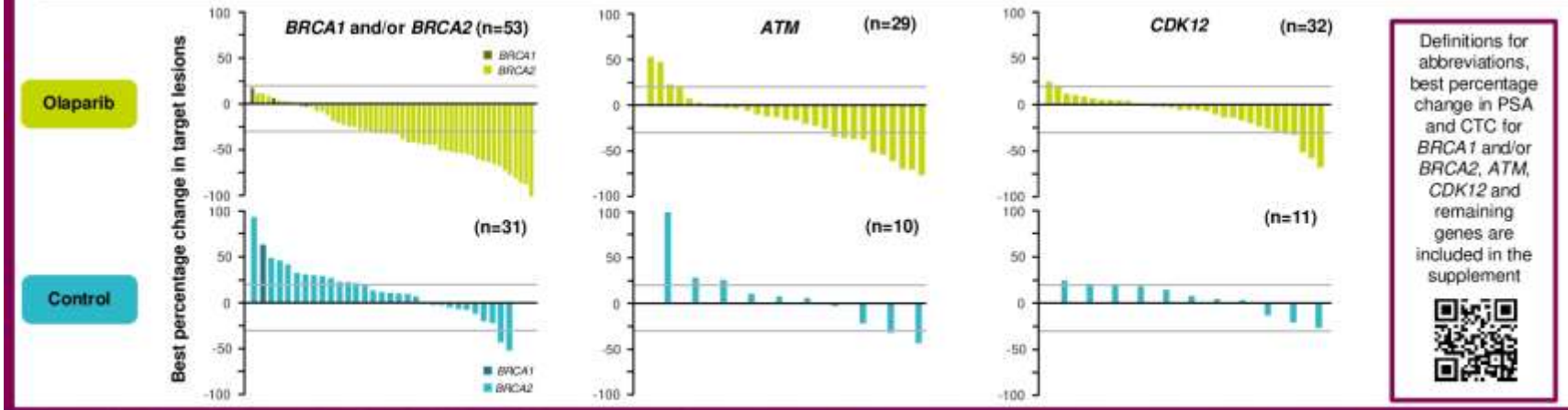
De Bono J et al. N Engl J Med 2020 May 28;382(22):2091-2101.

Kastrasyona Dirençli Metastatik Prostat kanseri PARP inhibitörleri

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



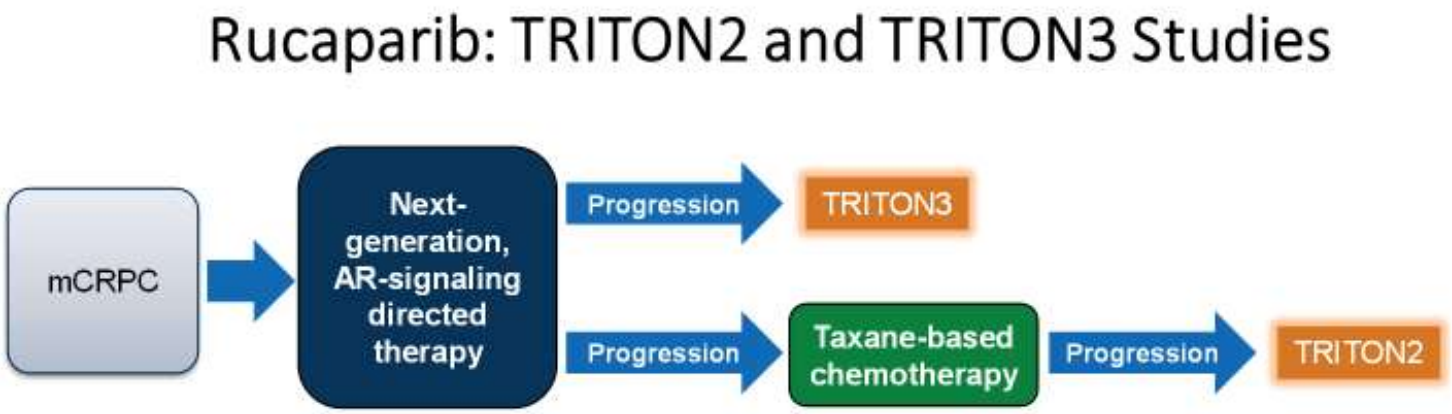
Definitions for abbreviations, best percentage change in PSA and CTC for *BRCA1* and/or *BRCA2*, *ATM*, *CDK12* and remaining genes are included in the supplement

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

Presented By Johann De Bono at 2021 Genitourinary Cancers Symposium

Kastrasyona Dirençli Metastatik Prostat kanseri PARP inhibitörleri

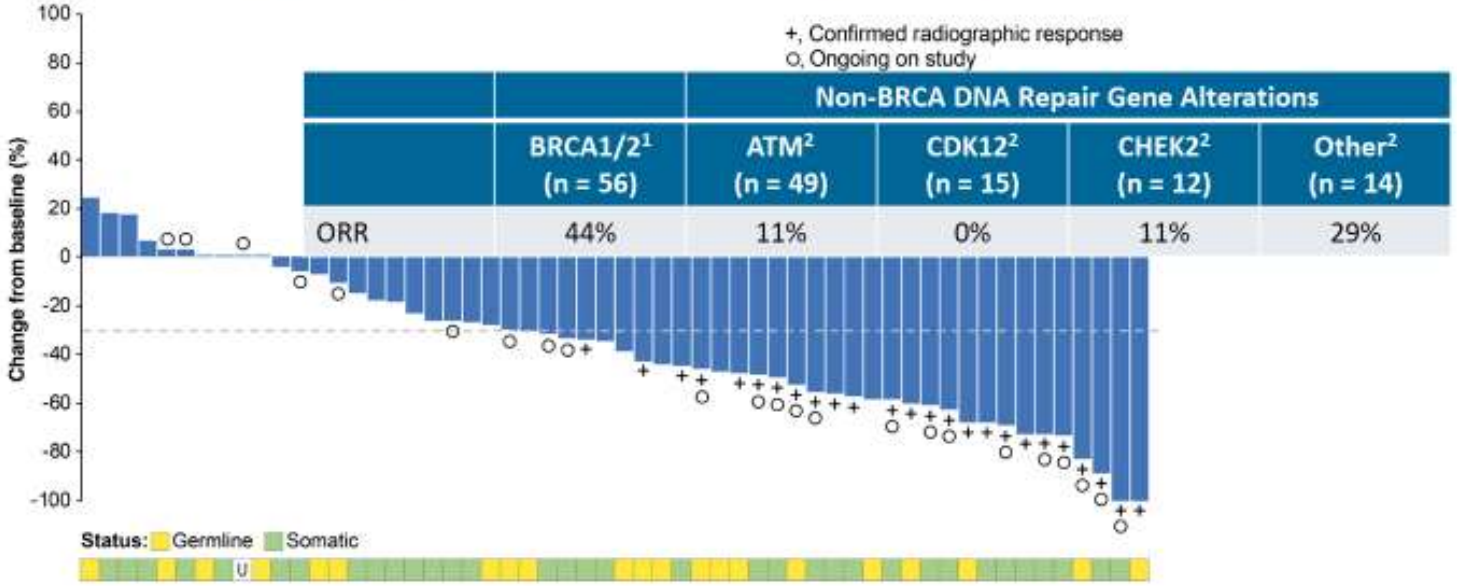


HRR-deficiency is defined by a deleterious alteration in *BRCA1*, *BRCA2*, *ATM*, or 12 other HRR genes (*BARD1*, *BRIP1*, *CDK12*, *CHEK2*, *FANCA*, *NBN*, *PALB2*, *RAD51*, *RAD51B*, *RAD51C*, *RAD51D*, *RAD54L*)

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

Kastrasyona Dirençli Metastatik Prostat kanseri PARP inhibitörleri

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]



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

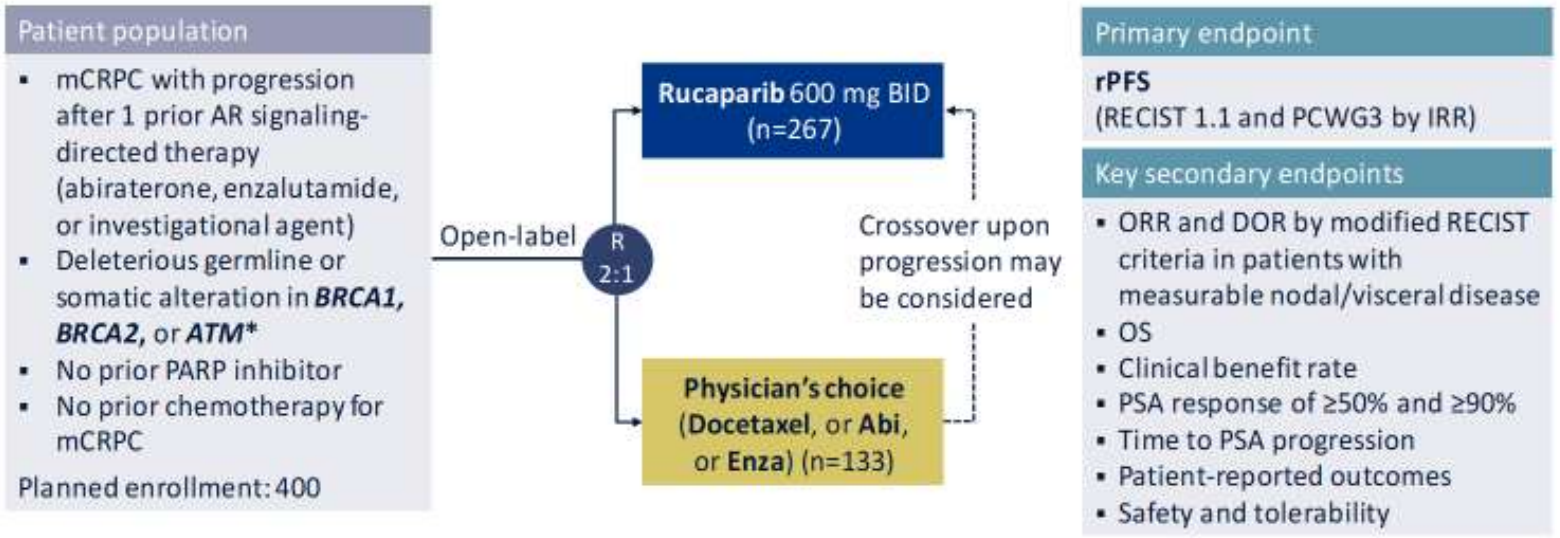
Visit cutoff: 02 Jul 2019. Includes patients with measurable disease at baseline and ≥1 postbaseline scan. Each bar represents a single patient; patients with no change from baseline are shown as 0.5% for visual clarity; the dotted line indicates the threshold for partial response (30% decrease from 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.

Kastrasyona Dirençli Metastatik Prostat kanseri PARP inhibitörleri

TRITON3: Randomized Phase III Trial



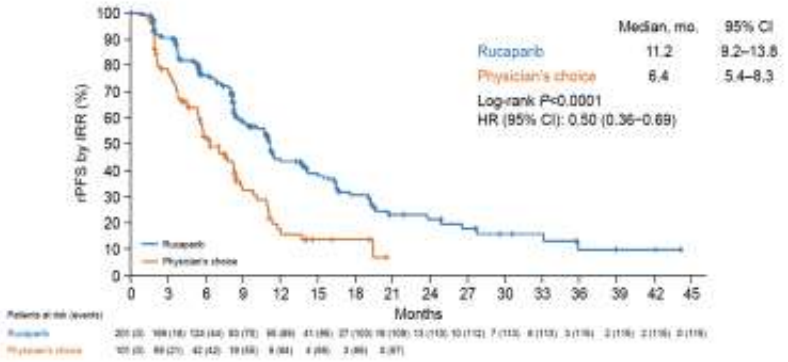
*Mutations identified in blood, archival tissue, or screening tumor tissue

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

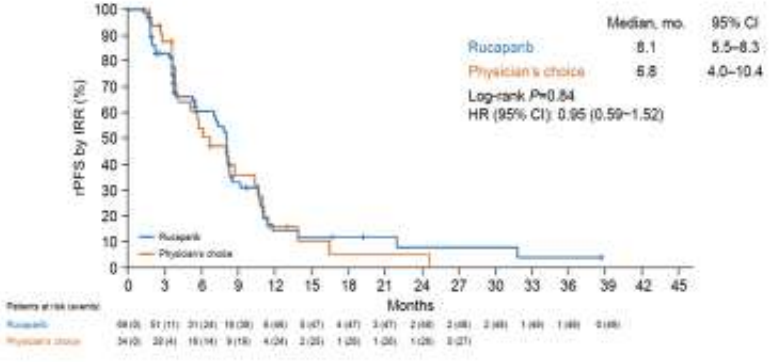
Kastrasyona Dirençli Metastatik Prostat kanseri PARP inhibitörleri

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

***BRCA1/2* Subgroup**



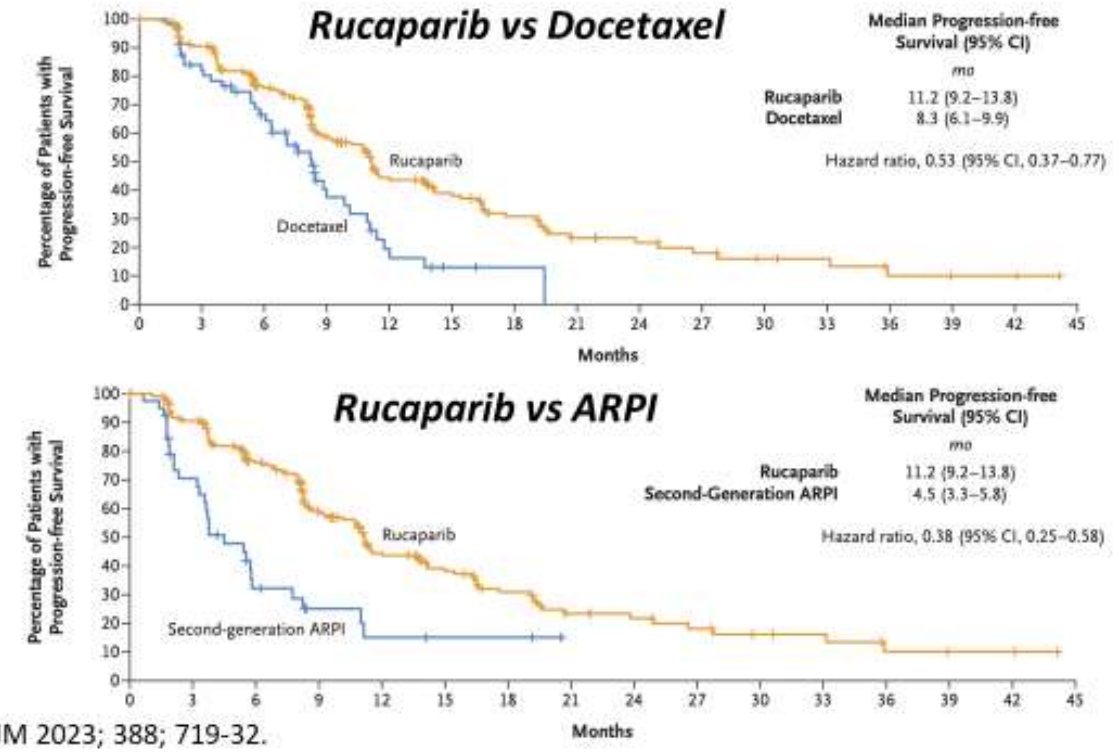
***ATM* Subgroup**



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

Kastrasyona Dirençli Metastatik Prostat kanseri PARP inhibitörleri

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



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

Kastrasyona Dirençli Metastatik Prostat kanseri Lutesyum 177 Tedavisi

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

Michael J 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 Bandaran, Andrew D Redfern, William Macdonald, Alex Gurney, Edward Hsiao, Wei Chua, Peter Lin, Alison Y Zhang, Margaret M McJannett, Marten 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) 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.

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

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

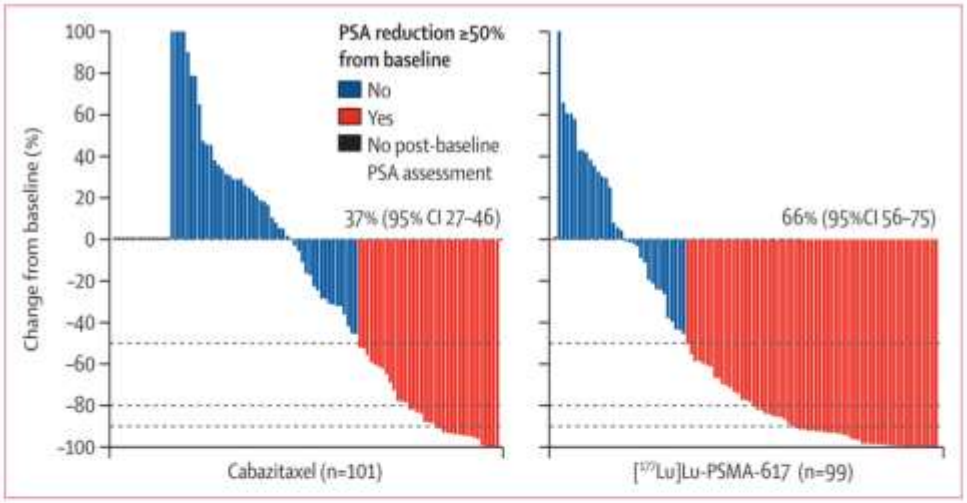


Figure 2: PSA response

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

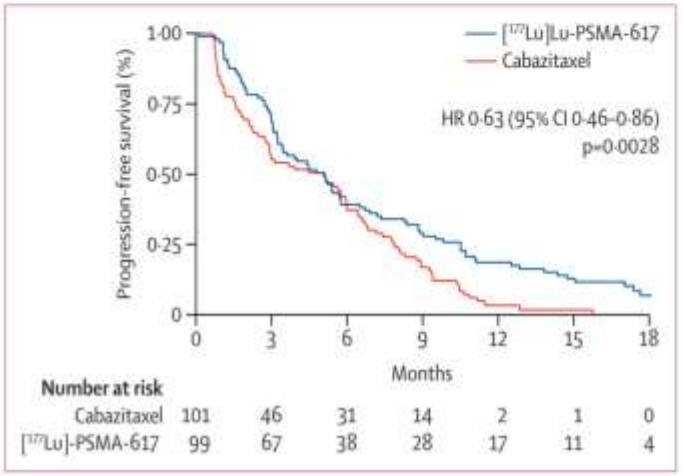
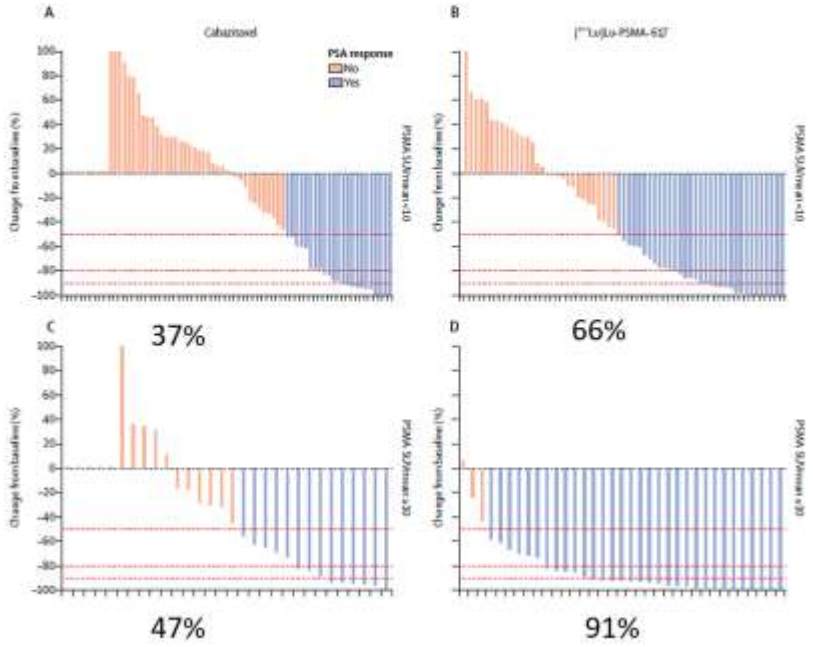


Figure 3: Radiographic or PSA progression-free survival

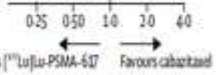
Kastrasyona Dirençli Metastatik Prostat kanseri Lutesyum 177 Tedavisi

PSMA-Lu177 vs Cabazitaxel: TheraP Trial



B Radiographic progression-free survival

	Cabazitaxel (n/N)	Cabazitaxel, median, months (95% CI)	[177Lu]Lu-PSMA-617 (n/N)	[177Lu]Lu-PSMA-617, median, months (95% CI)	HR (95% CI)
PSMA SUVmean <10	57/71	7·6 (6·4–8·6)	57/64	6·0 (4·3–9·5)	0·85 (0·59–1·24)
PSMA SUVmean ≥10	23/30	9·4 (8·1–11·2)	29/35	12·7 (11–NE)	0·46 (0·25–0·84)
Q1: PSMA SUVmean <6·9	23/28	8·1 (6·4–10·6)	19/21	5·6 (3·8–10·8)	1·21 (0·65–2·26)
Q2: PSMA SUVmean ≥6·9 to <8·5	15/20	5·7 (4·3–NE)	22/29	8·5 (5·6–11)	0·65 (0·34–1·26)
Q3: PSMA SUVmean ≥8·5 to <10·8	24/30	7·5 (6·8–9·5)	18/22	8·9 (6·13·8)	0·53 (0·28–1·00)
Q4: PSMA SUVmean ≥10·8	18/23	9·6 (8·1–12·4)	16/27	14·1 (8·3–NE)	0·52 (0·26–1·04)

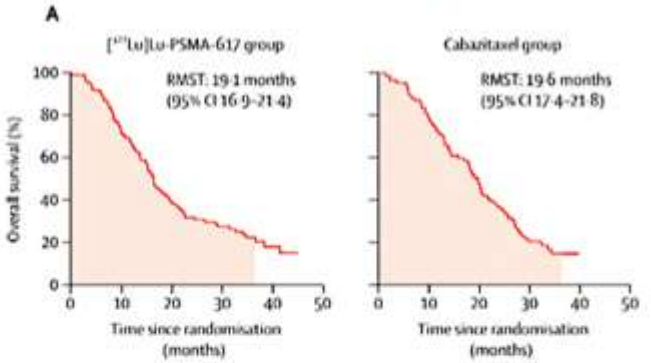


PSMA SUVmean<10: PSA50 32 vs 52% still favored PSMA-Lu177

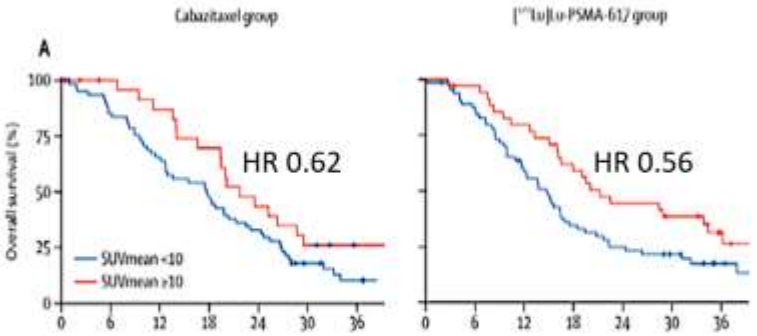
Hofman MS et al Lancet 2021
Burton JP et al Lancet Oncol 2022

Kastrasyona Dirençli Metastatik Prostat kanseri Lutesyum 177 Tedavisi

Lu177-PSMA-617 Updates: TheraP



Number at risk (number censored)							
Cabazitaxel group	101	75	60	45	30	14	6
	(0)	(17)	(17)	(17)	(17)	(20)	(25)
[177Lu]Lu-PSMA-617 group	99	88	63	41	30	23	11
	(0)	(2)	(3)	(3)	(3)	(6)	(14)



Conclusion: SUVmean≥10 is prognostic for survival with both cabazitaxel and Lu177-PSMA-617 therapy but not predictive (similar for FDG PET and adverse prognosis)

High SUV OS HR 0.96 vs 1.07 for low SUV mCRPC patients

P(interaction)=0.70 not significant

Hofman MS et al Lancet Oncol 2024

Kastrasyona Dirençli Metastatik Prostat kanseri Lutesyum 177 Tedavisi

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

2:1

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

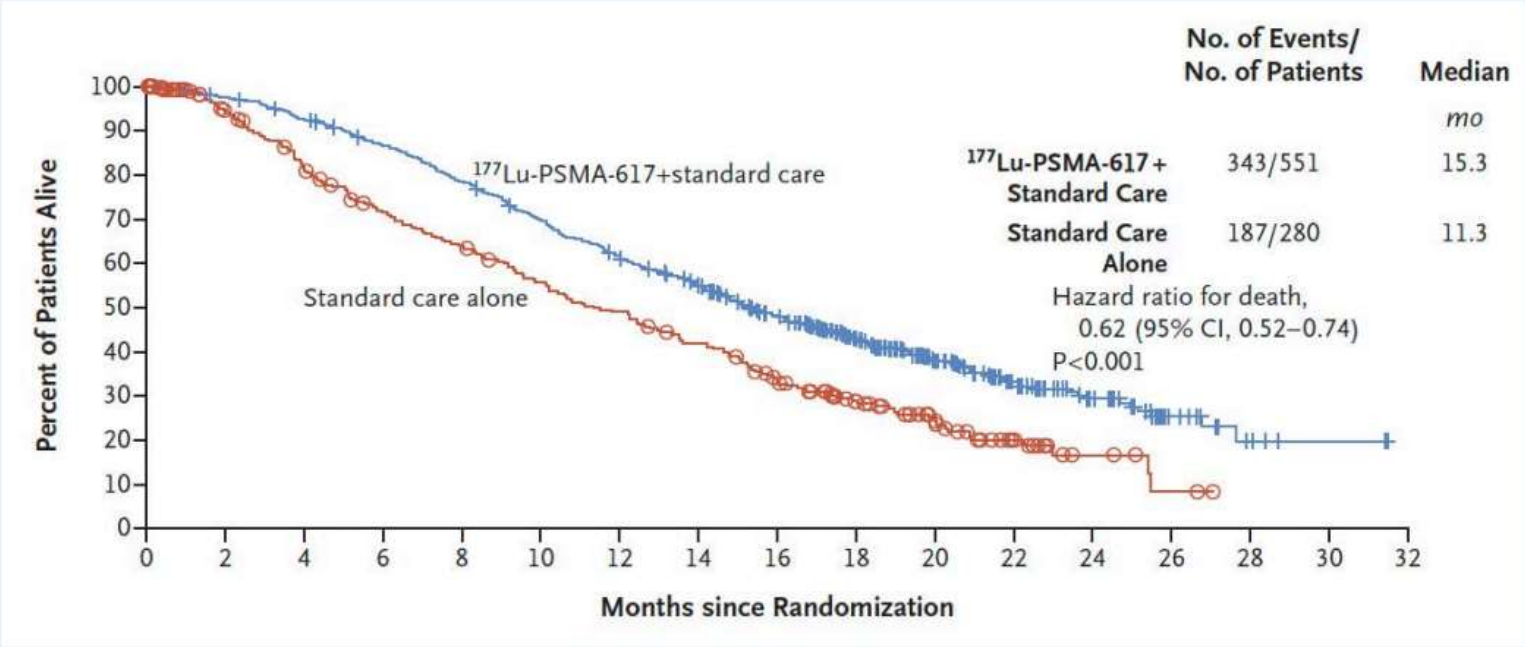
Protocol-permitted SOC alone

Treatment → Follow-up → Final analysis

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

Kastrasyona Dirençli Metastatik Prostat kanseri Lutesyum 177 Tedavisi

VISION: Overall Survival



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

Kastrasyona Dirençli Metastatik Prostat kanseri Lutesyum 177 Tedavisi

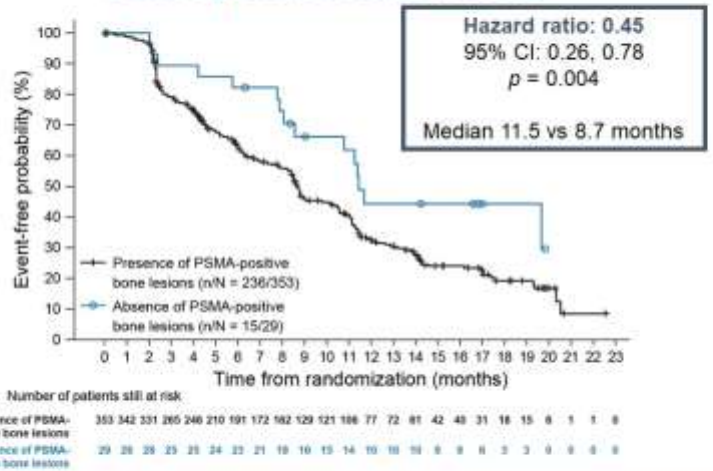
Treatment-emergent adverse events grouped as topics of interest: no unexpected or concerning safety signals

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)

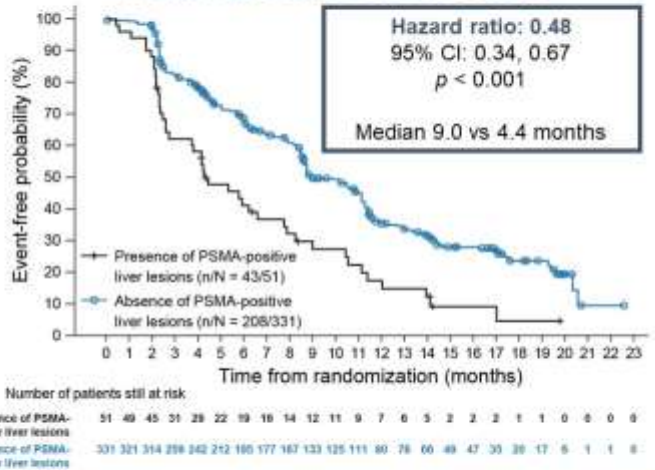
Kastrasyona Dirençli Metastatik Prostat kanseri

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

PSMA-positive bone lesions



PSMA-positive liver lesions



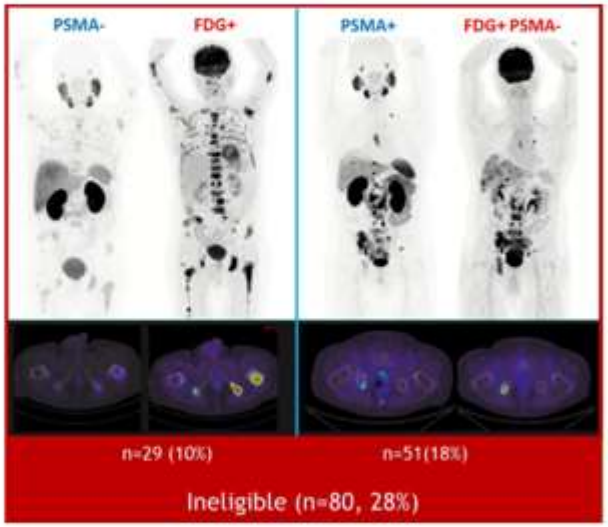
Absence of PSMA+ lesions in bone or liver was associated with a decrease in the risk of an rPFS event compared with presence of ≥ 1 PSMA+ lesions in these organs

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

Kastrasyona Dirençli Metastatik Prostat kanseri

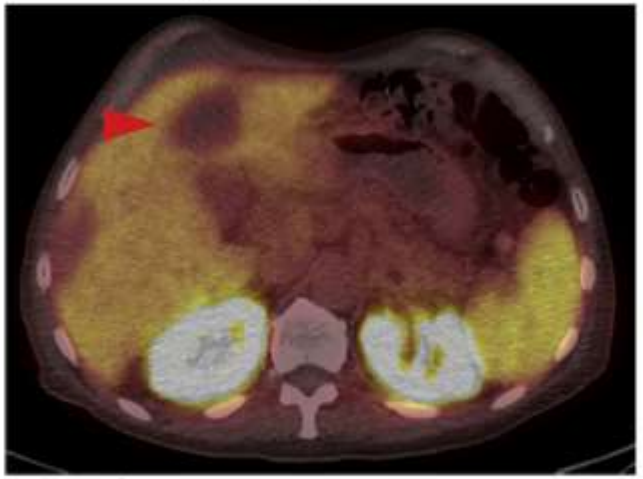
Loss of PSMA Expression in a Subset of CRPC

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
Lutesyum 177 Tedavisi-Dosetaksel öncesi

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)

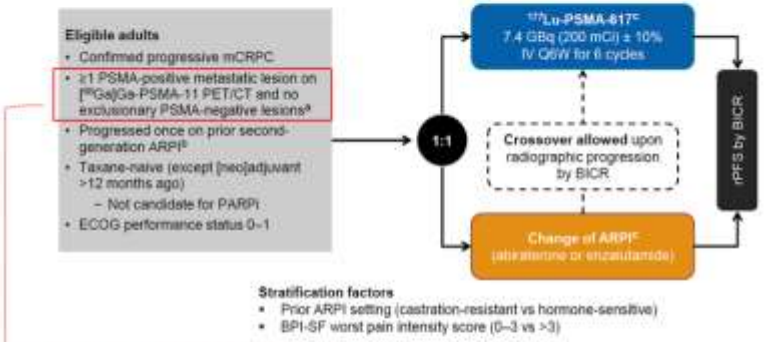
Kastrasyona Dirençli Metastatik Prostat kanseri Lutesyum 177 Tedavisi-Dosetaksel öncesi

PSMAfore: Ph 3 evaluating ^{177}Lu-PSMA-617 vs change in NHA in chemo-naïve, NHA-exposed mCRPC

Baseline characteristics were as expected for a chemo-naïve mCRPC patient population

PSMAfore: Study Design

An international, multicenter, randomized, open-label Phase III study



Note that 505/547 (92%) of patients meet ^{68}Ga-PSMA-11 screening criteria (see below)

PSMAfore: Baseline Patient and Disease Characteristics

	^{177}Lu-PSMA-617 N=234	Change of ARPI N=234
Age, median (range), years	71 (43–94)	72 (53–91)
White, n (%)	211 (90.2)	214 (91.5)
ECOG performance status, n (%)		
0	146 (62.4)	115 (49.1)
1	86 (36.8)	114 (48.7)
Gleason score 8–10, n (%)	136 (58.1)	107 (45.7)
PSA, median (range), µg/L	18.4 (0–1197)	14.9 (0–4224)
Hemoglobin, median (range), g/L	128.0 (88–155)	129.0 (88–156)
Alkaline phosphatase, median (range), IU/L	100.0 (38–1727)	103.5 (28–1319)
Site of disease, n (%)		
Liver	13 (5.6)	7 (3.0)
Lymph node	76 (32.5)	74 (31.6)
Bone	205 (87.6)	203 (86.8)
Prior ARPI, n (%)		
Abiraterone	119 (50.9)	130 (55.6)
Enzalutamide	94 (40.2)	84 (35.9)
Other	21 (9.0)	20 (8.5)

^{68}Ga PSMA +ve based on whether soft tissue or bone only disease: centrally determined visually based on a lesion showing greater intensity compared to background liver;

soft tissue disease (with or without bone disease), all of the following 5 requirements must be met for eligibility [68Ga]Ga-PSMA-11 PET positivity in:

1) ≥1 lesion (osseous or extraosseous) irrespective of size;
2) all lymph nodes that measure ≥25 mm in short axis;
3) all bone metastases with a soft tissue component ≥10 mm in the longest diameter (PSMA-negative bone metastases without a soft tissue component do not exclude pts);
4) all solid organ metastases ≥10 mm in the longest diameter;
5) all intraprostatic lesions regardless of size.

bone-only disease: ≥1 site of bone involvement must be [68Ga]Ga-PSMA-11 PET positive.

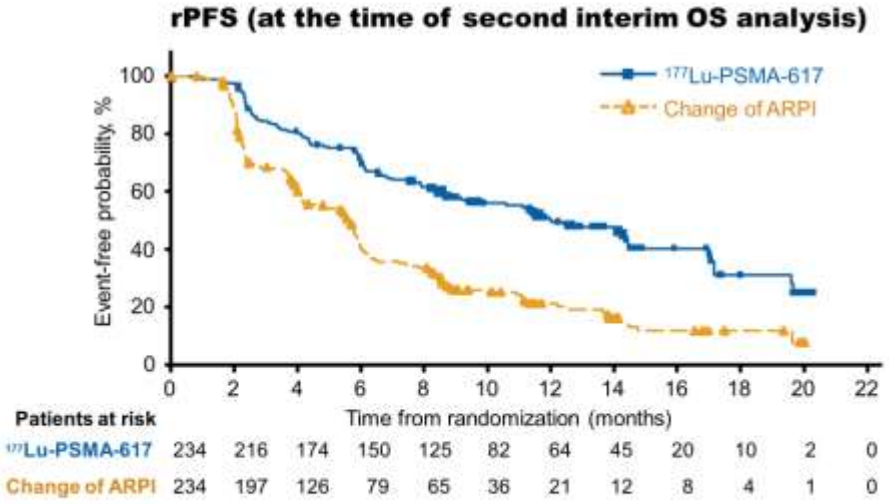
Sartor O, et al. Abstract presented at: ESMO Congress 2023; October 20-24, 2023; Madrid, Spain. Abstract LBA13

Kastrasyona Dirençli Metastatik Prostat kanseri Lutesyum 177 Tedavisi-Dosetaksel öncesi

PSMAfore study met primary endpoint of rPFS

Primary endpoint was met:

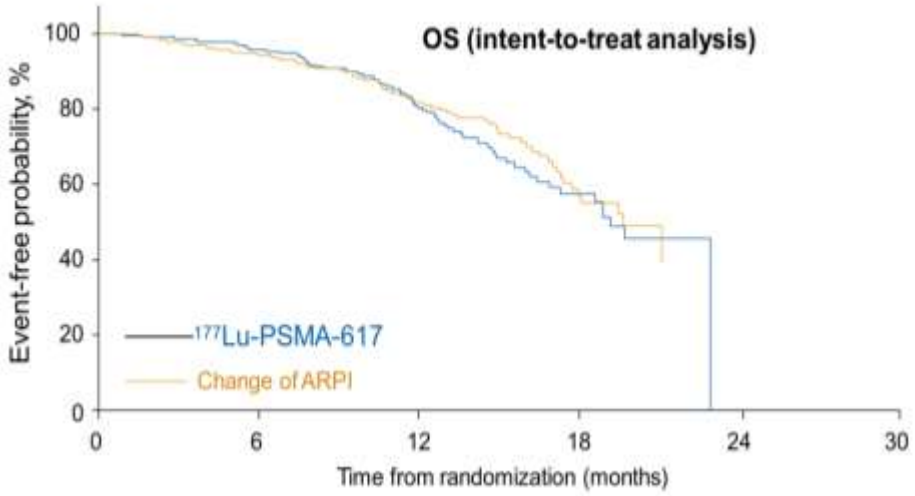
- **At the time of primary analysis** (DCO October 2, 2022): **HR was 0.41** (95% CI: 0.29, 0.56); *P* < .0001
- At the time of second interim OS analysis (DCO June 21, 2023): HR was 0.43 (95% CI: 0.33, 0.54)



	^{177}Lu-PSMA-617 (N=234)	Change of ARPI (N=234)
Events, n (%)	115 (49)	168 (72%)
Median rPFS , months (95% CI)	12.0 (9.30, 14.42)	5.6 (4.2, 5.9)
HR (95% CI)	**0.41** (0.29-0.56)	
P-value	< 0.0001	

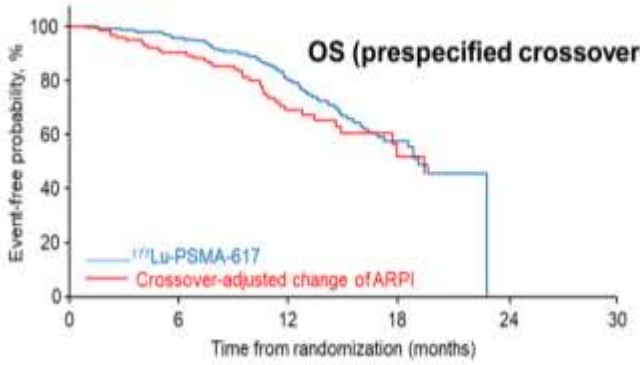
Sartor O, et al. Abstract presented at: ESMO Congress 2023; October 20-24, 2023; Madrid, Spain. Abstract LBA13

Kastrasyona Dirençli Metastatik Prostat kanseri
Lutesyum 177 Tedavisi-Dosetaksel Öncesi



ITT analysis

	^{177}Lu-PSMA-617 (N=234)	Change of ARPI (N=234)
Events, n (%)	69 (29)[a]	65 (28)
Median OS , months (95% CI)	**19.2** (16.9-NE)	**19.7** (17.8-NE)
HR (95% CI)	**1.16** (0.83-1.64)	
P-value	--	



Crossover: 123/146 (84%)
patients with radiographic progression crossed over

	^{177}Lu-PSMA-617 (N=234)	Change of ARPI (N=234)
Median OS , months (95% CI)	**19.2** (16.9-NE)	**19.5** (14.9-NE)
HR (95% CI)	**0.80** (0.48-1.33)	

[a]Three patients died before receiving ^{177}Lu-PSMA-617.

Sartor O, et al. Abstract presented at: ESMO Congress 2023; October 20-24, 2023; Madrid, Spain. Abstract LBA13

Kastrasyona Dirençli Metastatik Prostat kanseri Lutesyum-177 Tedavisi

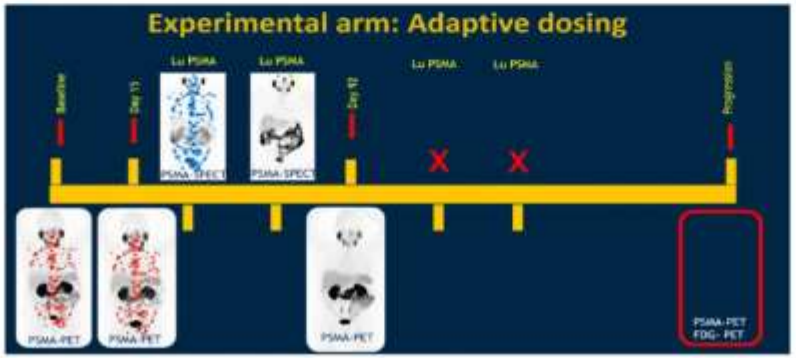
LuPSMA CRPC Data: Context in one Slide

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

Kastrasyona Dirençli Metastatik Prostat kanseri Lutesyum 177 Tedavisi + Androjen Reseptör yolağı blokörleri

Enza-p: Synergy with ARSI Therapy?

SUVmax>15 at one site, >10 at all sites PLUS 2 adverse prognostic factors



Emmett L et al ESMO 2023 LBA84

Patient population:
11-14% prior abiraterone
52-58% de novo M1
53-56% prior docetaxel for mHSPC

2-4 doses given adaptively based on PSMA PET response, with further dosing only for those with PSMA-avid persistent disease

Kastrasyona Dirençli Metastatik Prostat kanseri Lutesyum 177 Tedavisi + Androjen Reseptör yolağı blokörleri

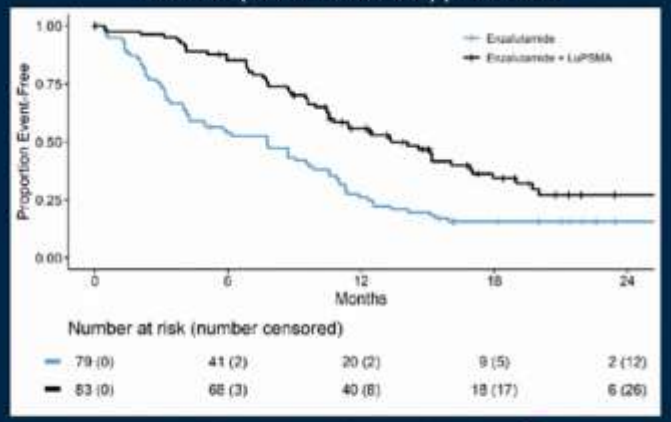
Enza-p Results

PSA50 93% (combo) vs 68% (enza alone)
Similar adverse event profile except slightly more dry mouth (40% vs 10%) and anemia (14% vs 3%)

Progression Free Survival

PSA-PFS

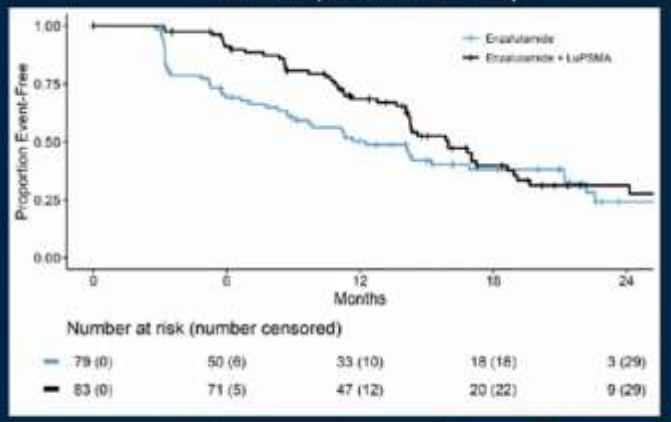
HR 0.43 (95%CI 0.29-0.63) p=0.00001



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

R-PFS

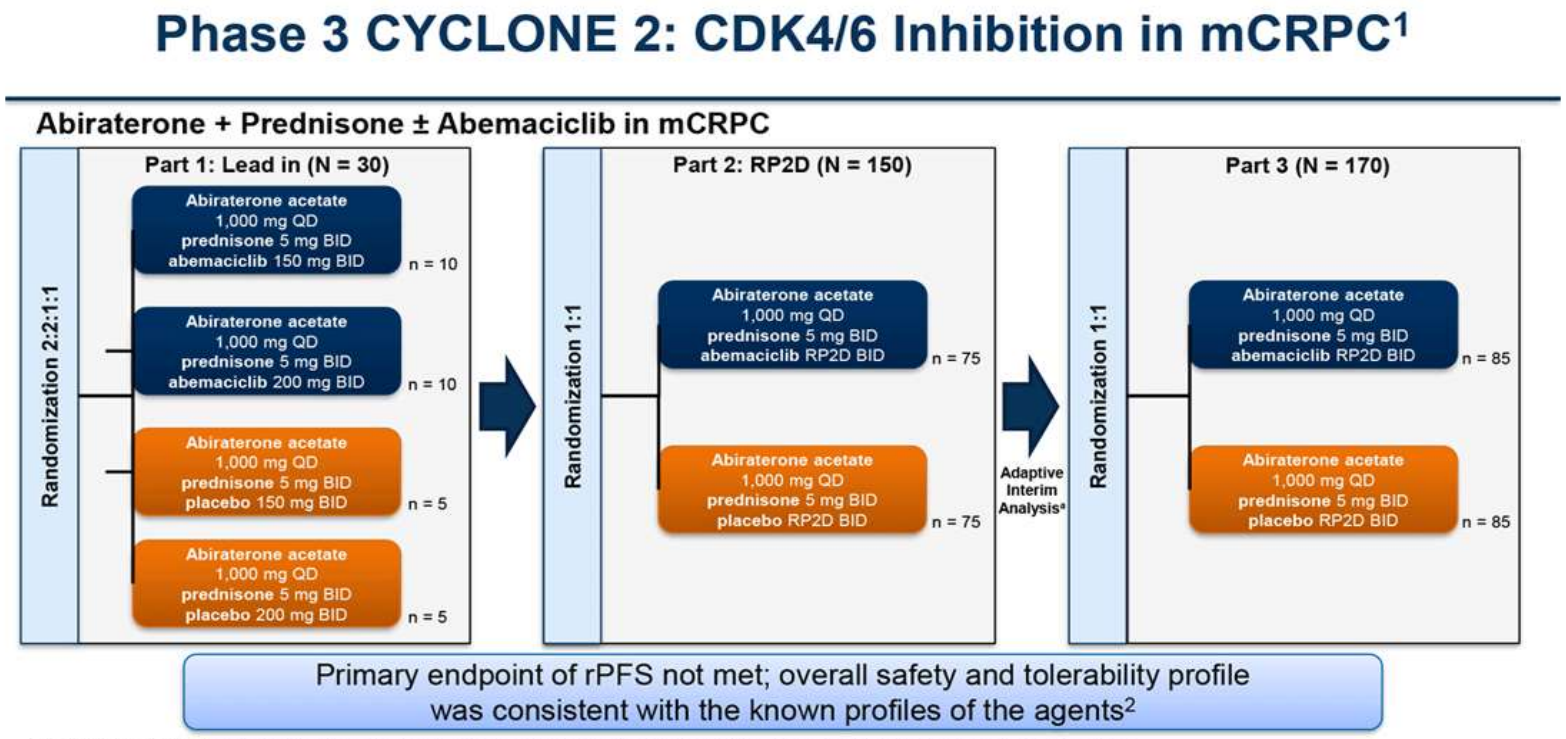
HR 0.67 (95% CI 0.44-1.01)



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

Emmett L et al ESMO 2023 LBA84

Kastrasyona Dirençli Metastatik Prostat kanseri CDK4/6 inhibitörleri + Androjen Reseptör yolağı blokörleri



[a] If prespecified adaptive expansion criteria are met at adaptive interim analysis, part 3 will open, and 170 additional patients will be randomized.

1. https://clinicaltrials.gov/study/NCT03706365. 2. . https://investor.lilly.com/news-releases/news-release-details/lilly-reports-strong-fourth-quarter-2023-financial-results-and.

PeerView.com

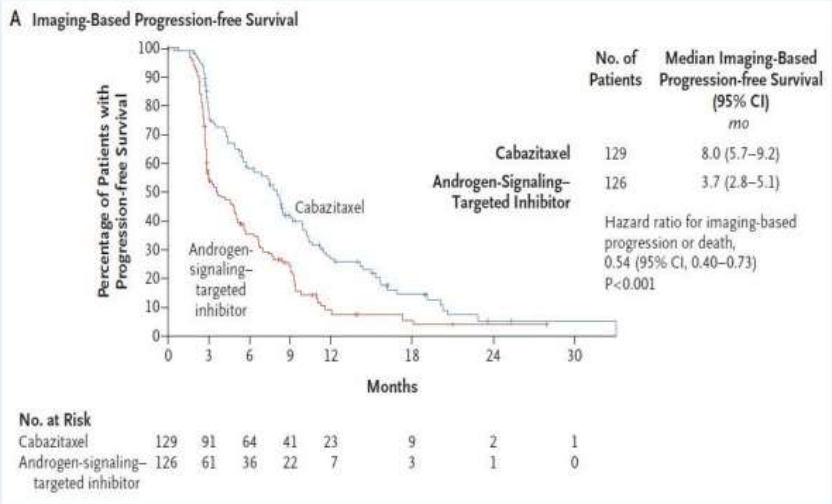
Kastrasyona Dirençli Metastatik Prostat kanseri CDK4/6 inhibitörleri + Androjen Reseptör yolağı blokörleri

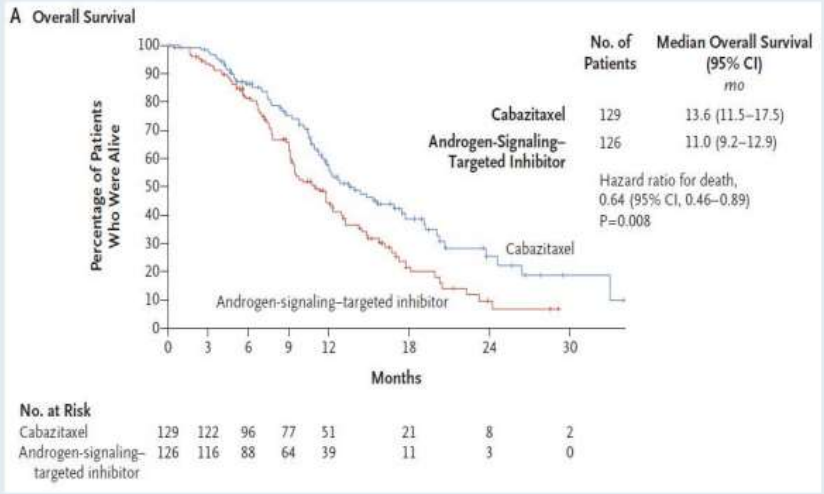
“Phase 3 CYCLONE-2 results [demonstrated that] abemaciclib added to abiraterone **did not meet the primary endpoint of improved radiographic progression-free** survival in men with metastatic castration-resistant prostate cancer (mCRPC); the overall safety and tolerability profile was consistent with the known profiles of the medicines.”

https://investor.lilly.com/news-releases/news-release-details/lilly-reports-strong-fourth-quarter-2023-financial-results-and

Kastrasyona Dirençli Metastatik Prostat kanseri Kabazitaksel Tedavisi

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 Kabazitaksel Tedavisi

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)

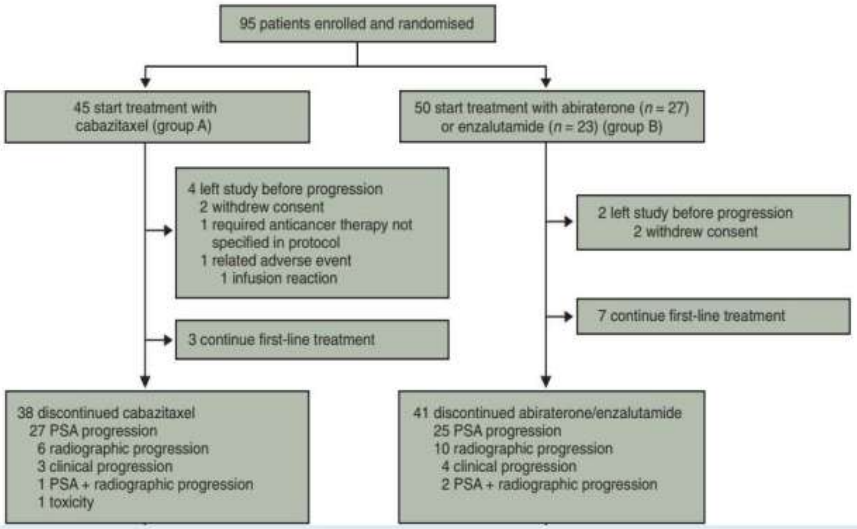
de Wit R et al. *NEJM* 2019;381:2506-18.

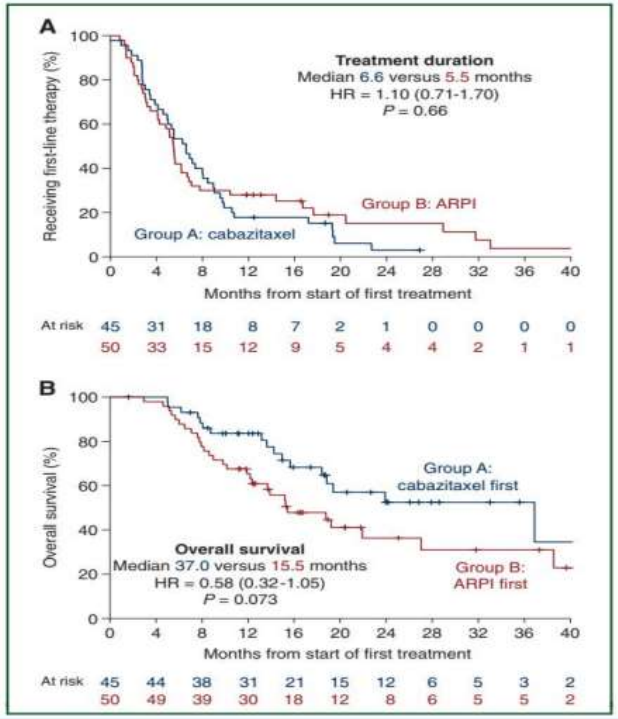
RTP RESEARCH TO PRACTICE

Kastrasyona Dirençli Metastatik Prostat kanseri Kabazitaksel Tedavisi

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)

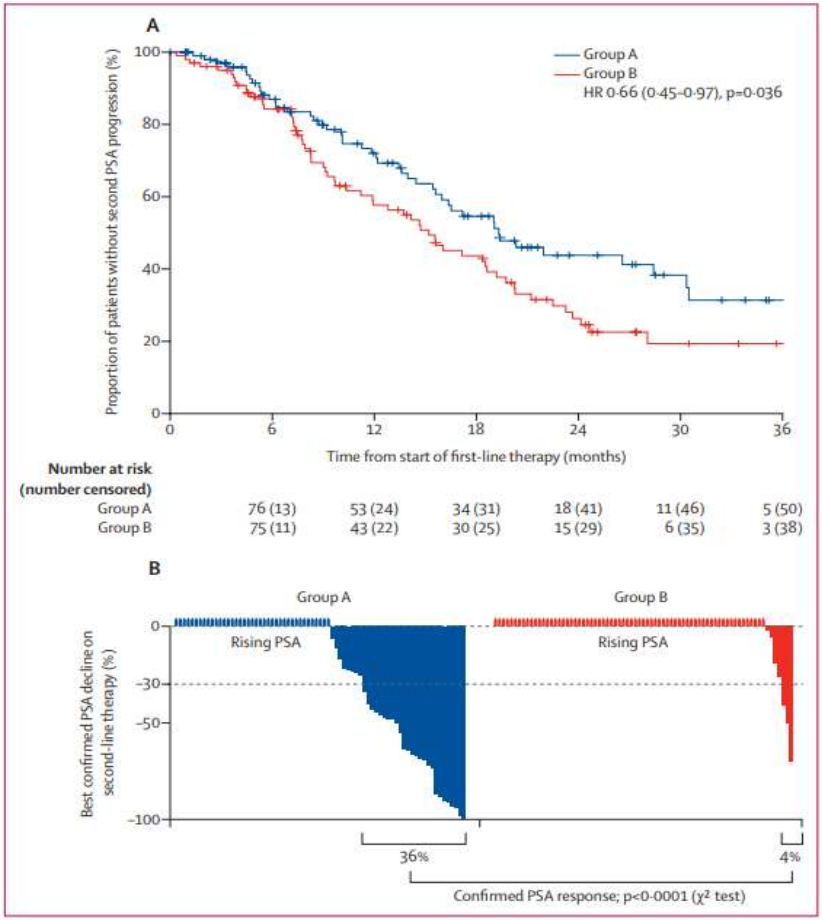




Annala M et al. *Ann Oncol* 2021;32:896-905.

RTP RESEARCH TO PRACTICE

Kastrasyona Dirençli Metastatik Prostat kanseri Ardışık Androjen Reseptör yolağı blokörleri



A-Abirateron progresyon sonrası ardışık Enzalutamid

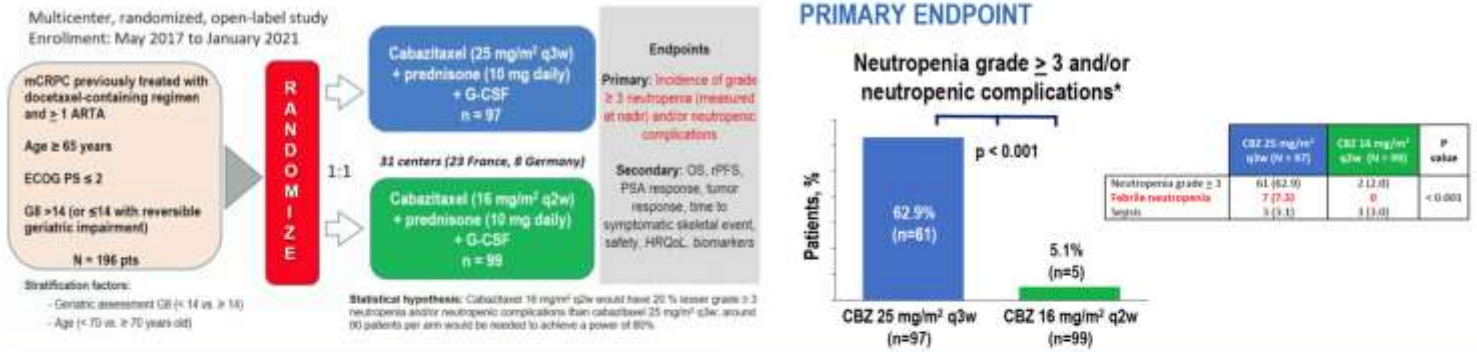
B-Enzalutamid progresyon sonrası ardışık Abirateron

Daniel J Khalaf, The Lancet Oncology 2019

Kastrasyona Dirençli Metastatik Prostat kanseri Kabazitaksel Tedavisi

Other Recently Reported Trials Investigating Cabazitaxel for mCRPC

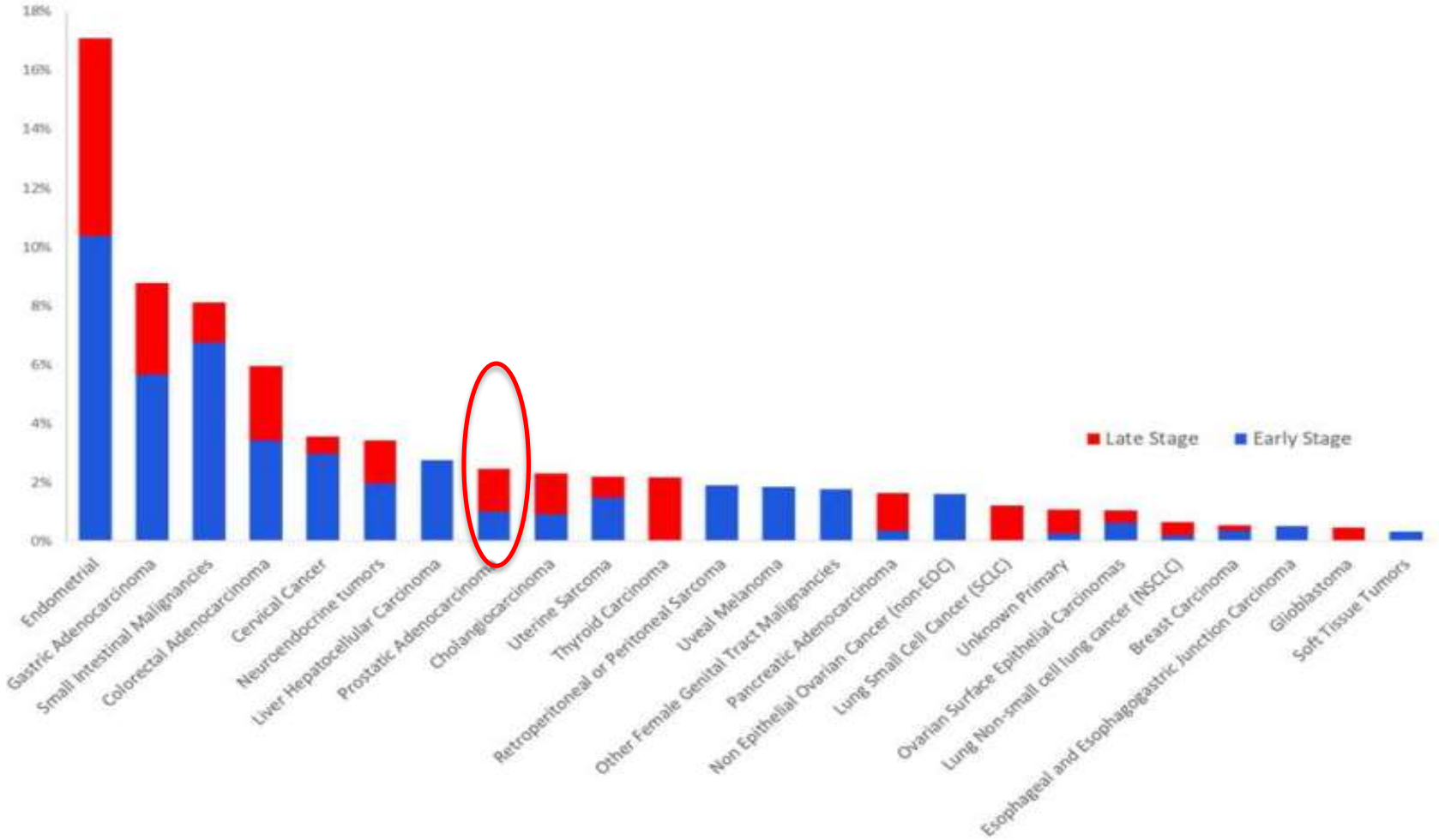
CABASTY[1]



OSTRICh[2]

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

Kastrasyona Dirençli Metastatik Prostat kanseri Mismatch Repair Deficiency



Le et al. Science 2017

Kastrasyona Dirençli Metastatik Prostat kanseri Mismatch Repair Deficiency

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.

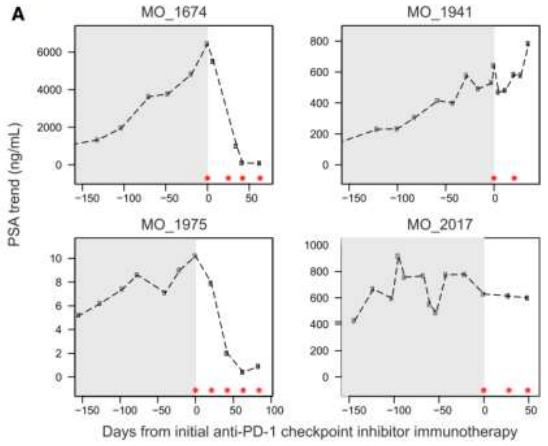
Abida et al, JAMA Onc 2018

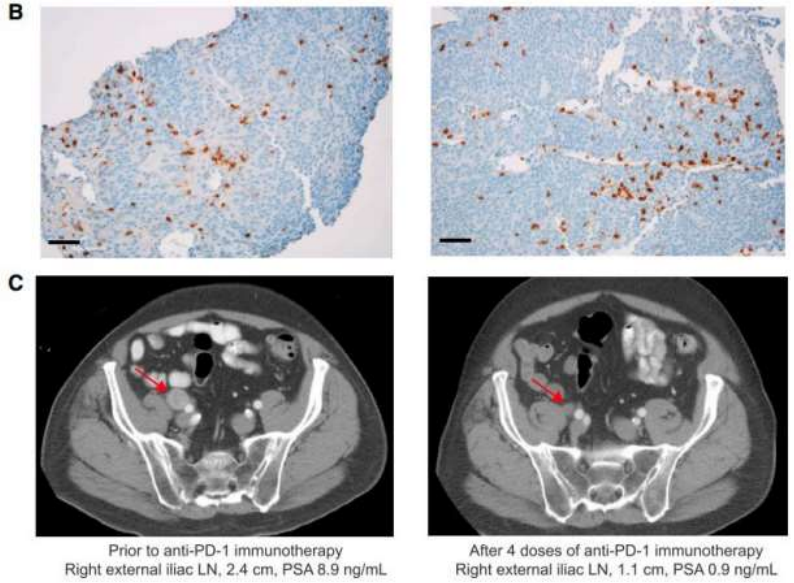
Evre IV Kastrasyona Dirençli Prostat Kanseri İmmüne Checkpoint İnhibitörleri

Pilot Clinical Study to Determine CDK12 Mutant Prostate Cancer Response to Checkpoint Inhibitor Immunotherapy

11 pts -5 tt anti PD1

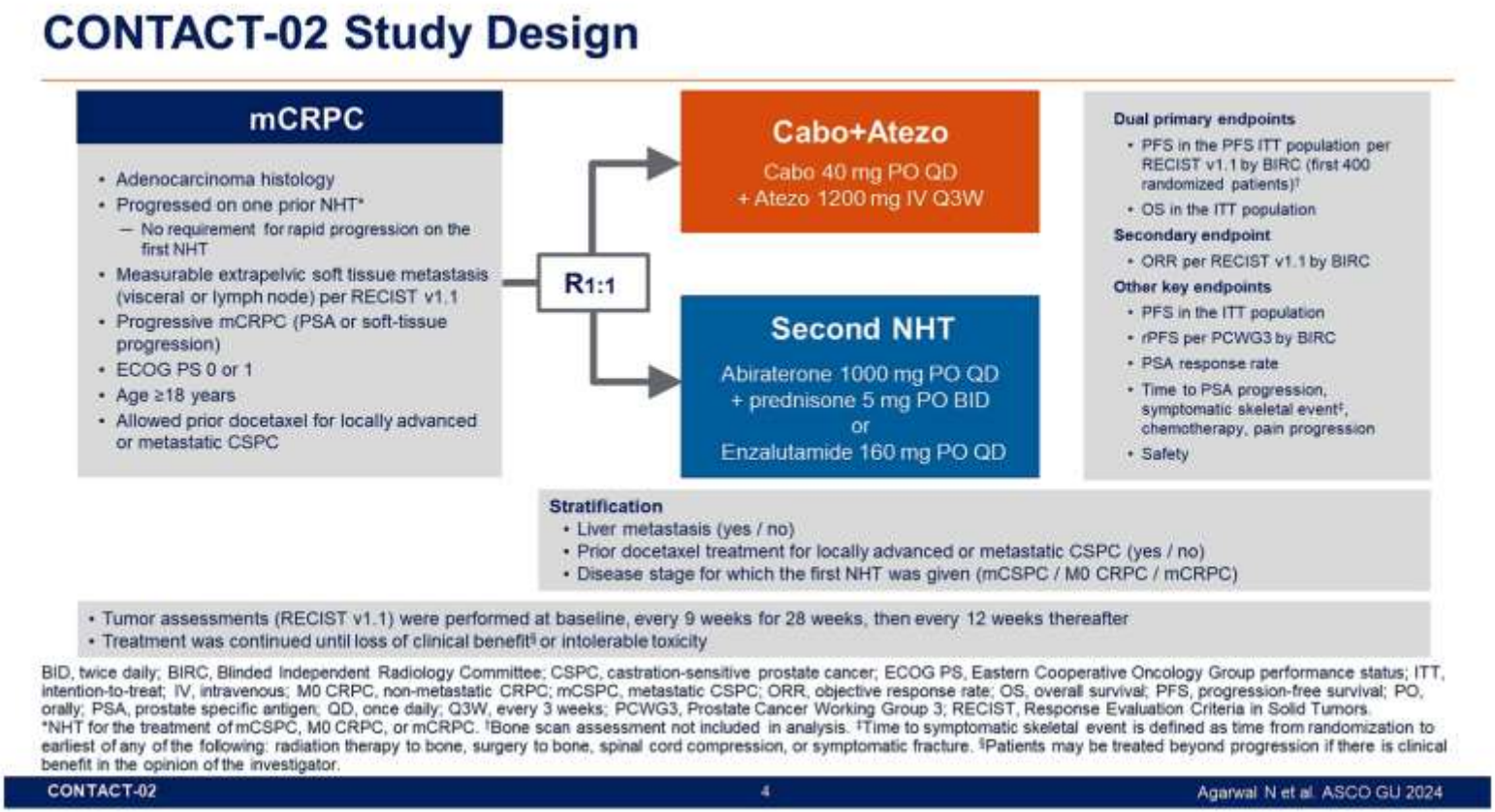
- 1 pt excluded
- 2 pts +++PSA decline





Wu et al., Cell 2028

Kastrasyona Dirençli Metastatik Prostat kanseri Cabozantinib ve Atezolizumab kombinasyonu

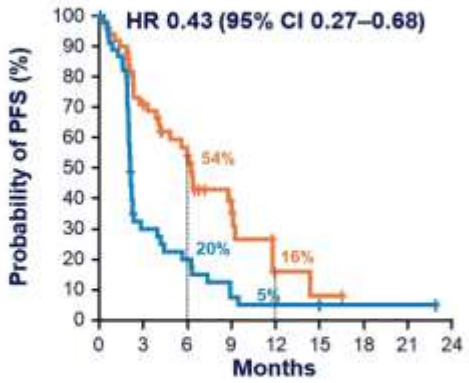


Kastrasyona Dirençli Metastatik Prostat kanseri Cabozantinib ve Atezolizumab kombinasyonu

PFS per BIRC in Prespecified Subgroups*

Liver Metastasis

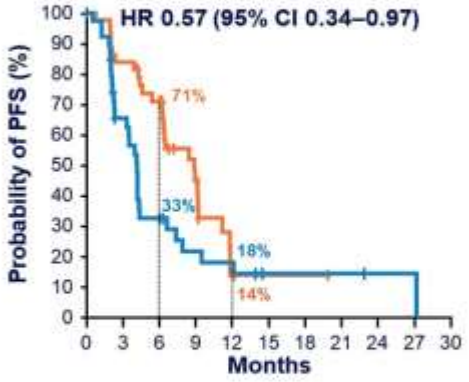
Reduction of risk† – 57%



	No. of Events	Median PFS mo (95% CI)
Cabo+Atezo (n=51)	32	6.2 (4.0–9.1)
Second NHT (n=48)	41	2.1 (2.0–2.3)

Prior Docetaxel

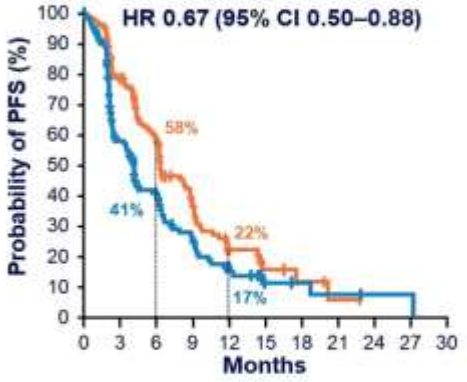
Reduction of risk† – 43%



	No. of Events	Median PFS mo (95% CI)
Cabo+Atezo (n=45)	27	8.8 (6.2–9.2)
Second NHT (n=44)	30	4.1 (2.3–4.3)

Bone Metastasis

Reduction of risk† – 33%



	No. of Events	Median PFS mo (95% CI)
Cabo+Atezo (n=162)	97	6.3 (6.0–8.8)
Second NHT (n=155)	104	4.1 (2.8–5.7)

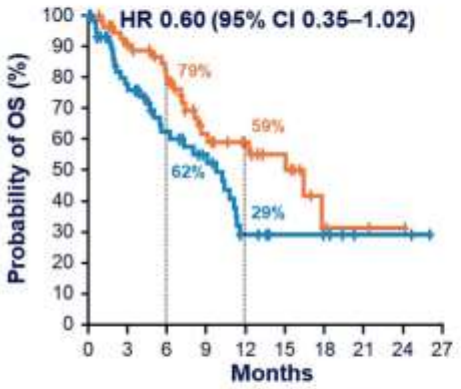
*PFS ITT population. †Reduction of risk of progression or death with Cabo+Atezo vs second NHT.

Kastrasyona Dirençli Metastatik Prostat kanseri Cabozantinib ve Atezolizumab kombinasyonu

Interim OS in Prespecified Subgroups*

Liver Metastasis

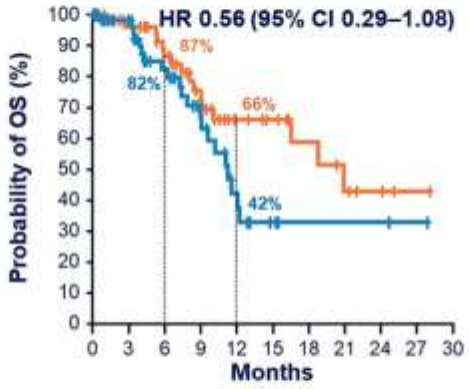
Reduction of risk of death – 40%



	No. of Events	Median OS mo (95% CI)
Cabo+Atezo (n=59)	23	16.4 (8.3–NE)
Second NHT (n=60)	31	9.8 (5.5–11.3)

Prior Docetaxel

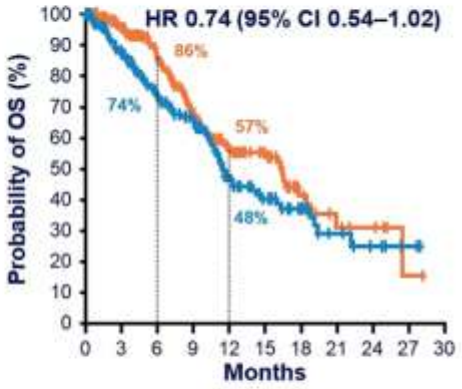
Reduction of risk of death – 44%



	No. of Events	Median OS mo (95% CI)
Cabo+Atezo (n=57)	16	20.9 (10.1–NE)
Second NHT (n=58)	21	11.3 (9.0–NE)

Bone Metastasis

Reduction of risk of death – 26%



	No. of Events	Median OS mo (95% CI)
Cabo+Atezo (n=206)	70	16.4 (11.4–18.8)
Second NHT (n=196)	84	11.4 (10.4–14.6)

NE, not evaluable. *ITT population.

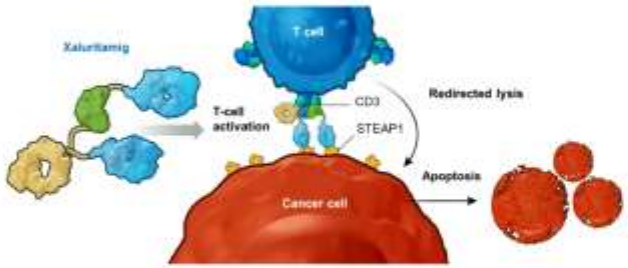
Kastrasyona Dirençli Metastatik Prostat kanseri Gelecek perspektif

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

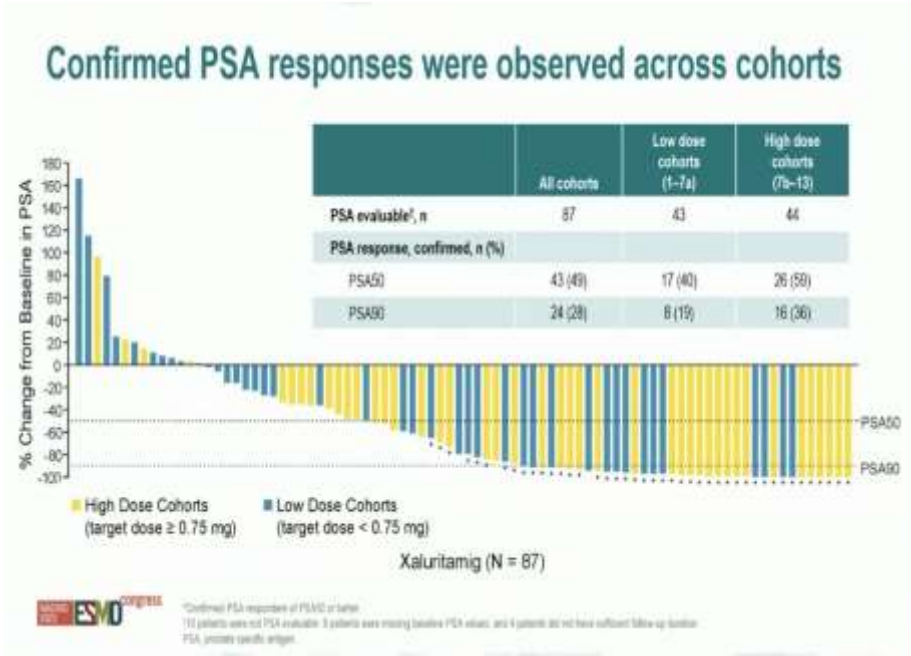
1. Tuzzo F, et al. Res Rep Urol. 2022;14:339-50.
2. Xu M, et al. Cancers (Basel). 2022;14:4334.
3. Nolen-Stevaux O, et al. Cancer Res. 2020;80(16 Supplement):DDT02-03.
4. Li C, et al. J Immunother Cancer. 2020;8:718.

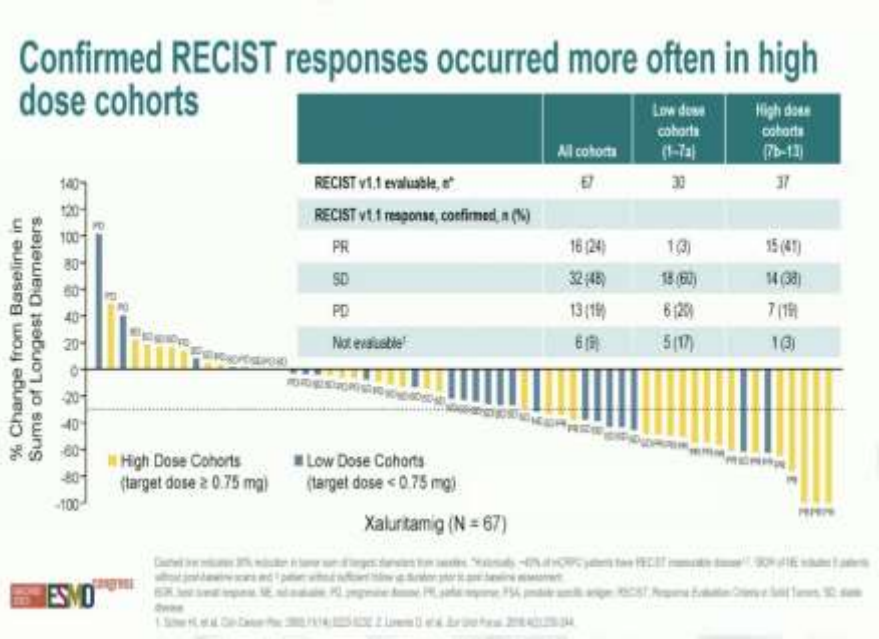
MADRID 2023 ESMO congress

Granada Auditorium - Hall 3

MADRID SPAIN 20-24 OCTOBER 2023

Kastrasyona Dirençli Metastatik Prostat kanseri Gelecek perspektif

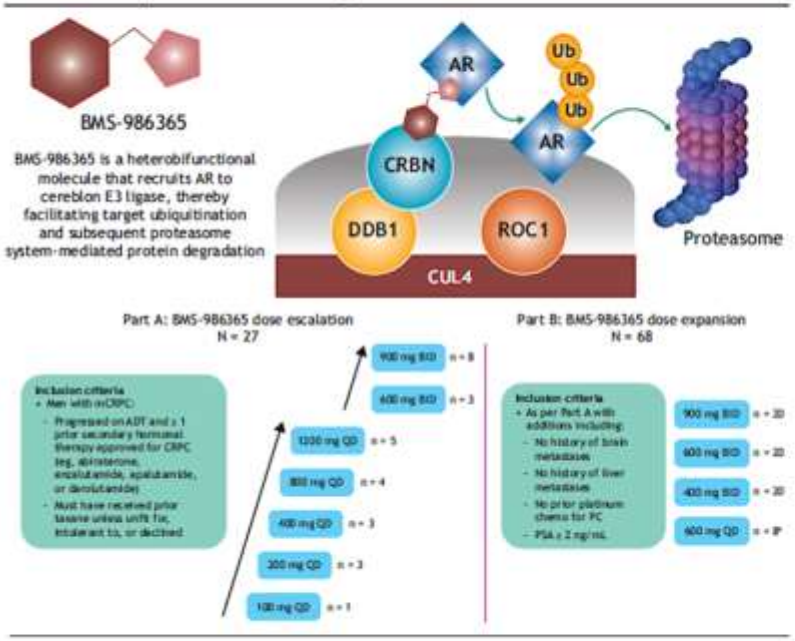




Kastrasyona Dirençli Metastatik Prostat kanseri Gelecek perspektif

First-in-human phase 1 study of BMS-986365 (CC-94676), an androgen receptor ligand-directed degrader, in men with mCRPC

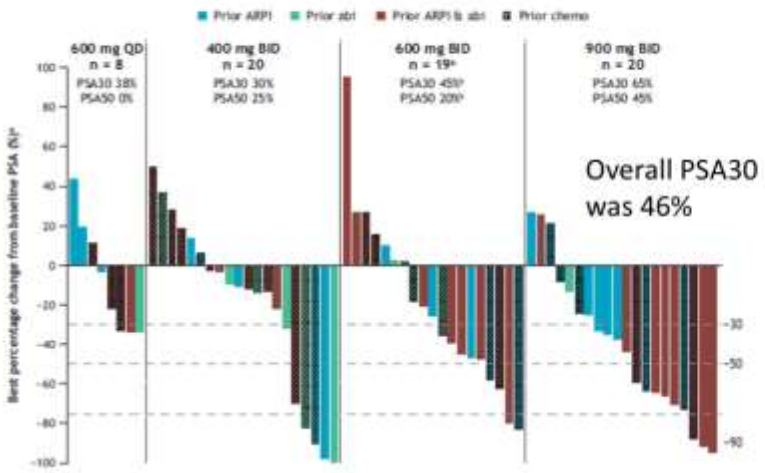
Rathkopf D...Armstrong AJ ASCO GU 2024 abstract 134



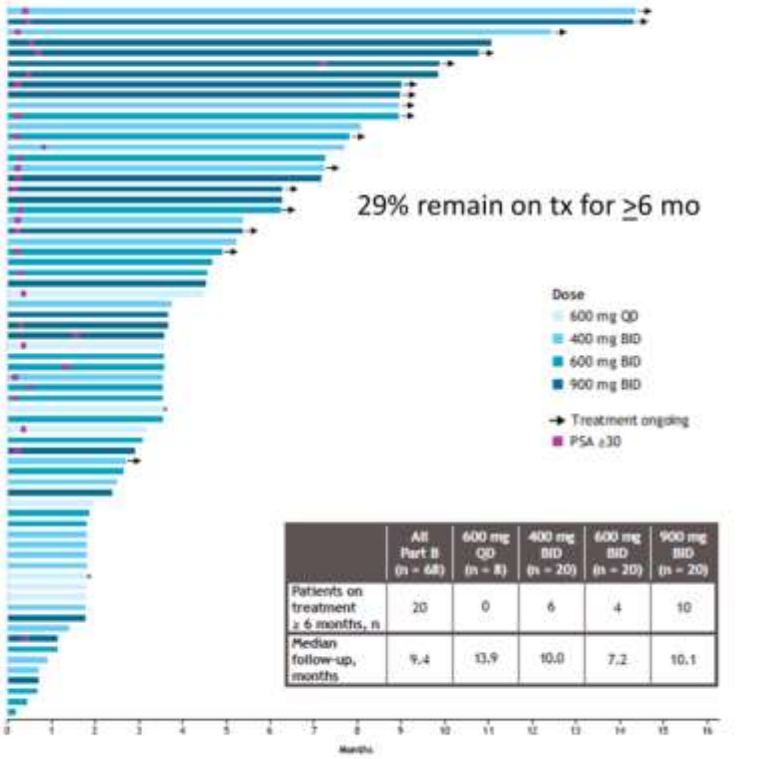
	Part A Dose escalation (n = 27)	Part B Dose expansion (n = 68)	All patients (N = 95)
Median age, years (range)	72 (49-83)	71 (50-87)	71 (49-87)
≥ 75 years, n (%)	7 (26)	24 (35)	31 (33)
Race, n (%)			
White	24 (89)	57 (84)	81 (85)
Black	2 (7)	3 (4)	5 (5)
Asian	1 (4)	3 (4)	4 (4)
Unknown	0	5 (7)	5 (5)
ECOG PS, n (%)			
0	10 (37)	36 (53)	46 (48)
1	17 (63)	32 (47)	49 (52)
Gleason score, n (%)			
≤ 6	2 (7)	3 (4)	5 (5)
7	5 (19)	17 (25)	22 (23)
8-10	18 (67)	40 (59)	58 (61)
Missing	2 (7)	8 (12)	10 (11)
Distant metastasis, n (%)			
Bone	24 (89)	56 (82)	80 (84)
Lymph node	15 (56)	36 (53)	51 (54)
Visceral liver	4 (15)	1 (1)[a]	5 (5)[a]
Visceral lung	4 (15)	7 (10)	11 (12)
Median serum PSA, µg/L (range)	96 (1-1699)	37 (3-1610)	51 (1-1699)
Median number of prior regimens (range)[b]	7.0 (3-10)	4.0 (2-12)	5.0 (2-12)
Prior therapies, n (%)			
Enzalutamide	25 (93)	51 (75)	76 (80)
Abiraterone	24 (89)	44 (65)	68 (72)
Both enzalutamide and abiraterone[c]	22 (81)	31 (46)	53 (56)
Chemotherapy	22 (81)	31 (46)	53 (56)
Docetaxel	21 (78)	31 (46)	52 (55)
Cabazitaxel	14 (52)	5 (7)	19 (20)

Kastrasyona Dirençli Metastatik Prostat kanseri Gelecek perspektif

Results



TEAE, n (%)	Part A Dose escalation (n = 27)		Part B Dose expansion (n = 68)		All patients (N = 95)	
	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4
Patients with ≥ 1 TEAE	26 (96)	8 (30)	65 (96)	24 (35)	91 (96)	32 (34)
QTc prolongation	7 (26)	2 (7)	32 (47)	6 (9)	39 (41)	8 (8)
Fatigue	7 (26)	0	24 (35)	3 (4)	31 (33)	3 (3)
Bradycardia*	5 (19)	0	23 (34)	0	28 (30)	0
Nausea	12 (44)	0	11 (16)	1 (1)	23 (24)	1 (1)
Anemia	6 (22)	3 (11)	12 (18)	5 (7)	18 (19)	8 (8)
Hypertension	2 (7)	0	14 (21)	5 (7)	16 (17)	5 (5)
Vomiting	7 (26)	0	7 (10)	1 (1)	14 (15)	1 (1)
Diarrhea	2 (7)	0	9 (13)	0	11 (12)	0
ALT increased	3 (11)	0	7 (10)	0	10 (11)	0
Back pain	1 (4)	0	9 (13)	1 (1)	10 (11)	1 (1)

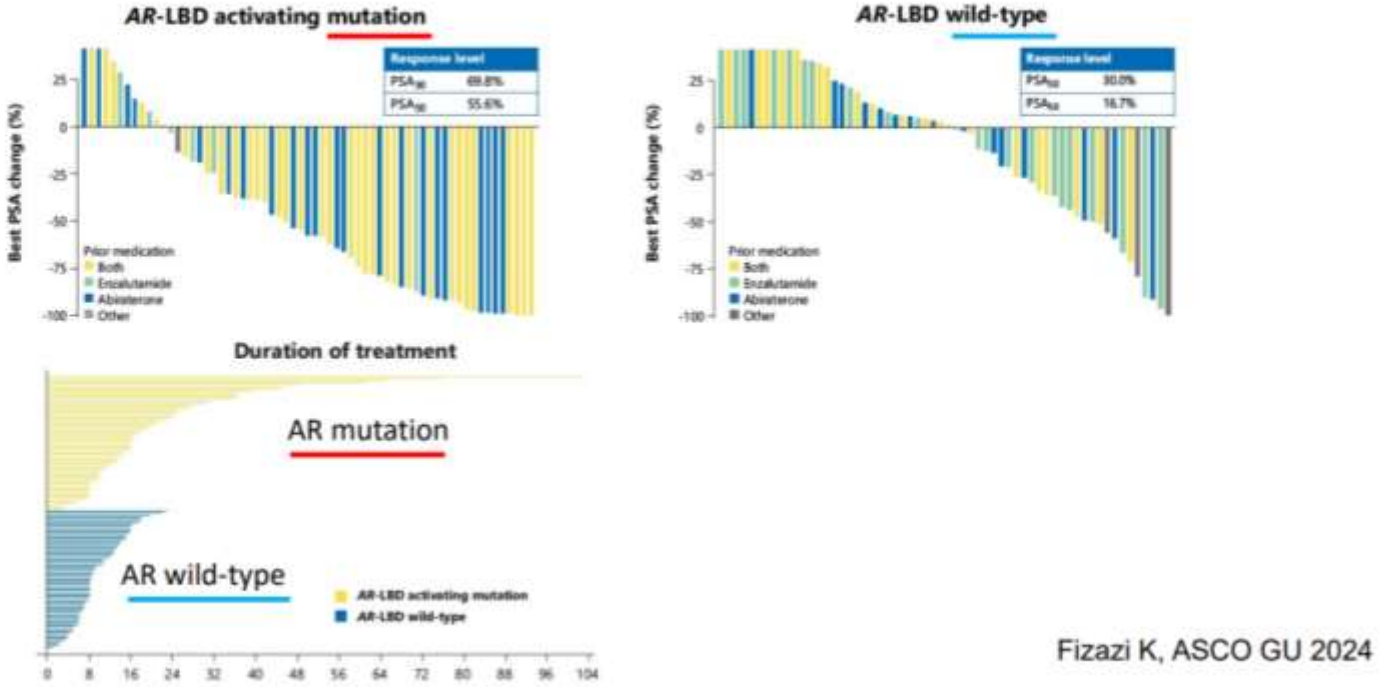


	All Part B (n = 68)	600 mg QD (n = 8)	400 mg BID (n = 20)	600 mg BID (n = 20)	900 mg BID (n = 20)
Patients on treatment ≥ 6 months, n	20	0	6	4	10
Median follow-up, months	9.4	13.9	10.0	7.2	10.1

Rathkopf D...Armstrong AJ ASCO GU 2024 abstract 134

Kastrasyona Dirençli Metastatik Prostat kanseri Gelecek perspektif

Confirmation of CYP11 inhibition activity in patients with AR-LBD mutations



Fizazi K, ASCO GU 2024

Kastrasyona Dirençli Metastatik Prostat kanseri Nöroendokrin diferansiasyon

Combination Carboplatin and Cabazitaxel

Cabazitaxel 20 mg/m² plus carboplatin AUC 4 mg/mL per min with growth factor support can be considered for fit patients with aggressive variant prostate cancer (visceral metastases, low PSA and bulky disease, high LDH, high CEA, lytic bone metastases, NEPC histology) or unfavorable genomics (defects in at least 2 of PTEN, *TP53*, and RB1). Corn PG, et al. Lancet Oncol 2019;20:1432-1443.

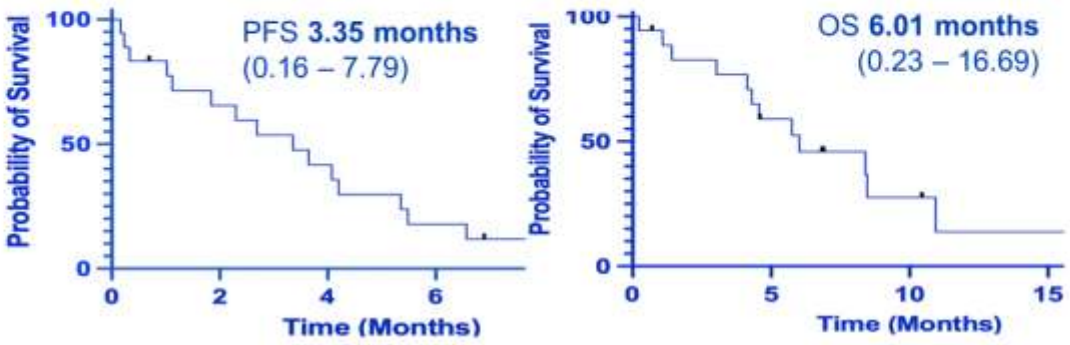
- Targeting more aggressive prostate cancers
  - Patients were randomly assigned (1:1) to intravenous cabazitaxel 25 mg/m2 with or without intravenous carboplatin AUC 4
  - At a median follow-up of 31·0 months, the combination improved the median PFS from 4.5 months to 7.3 months (95% CI 0·50–0·95, p=0·018)
  - All toxicities were worse with the combination
    - Myelosuppression
    - Fatigue, nausea, others

Corn et al Lancet Oncology 2019

Kastrasyona Dirençli Metastatik Prostat kanseri
Nöroendokrin diferansiasyon

Lurbinectedin in Small Cell NEPC

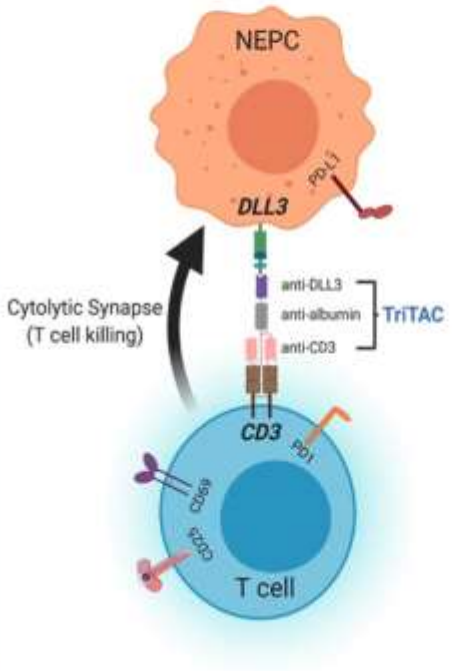
- Derived from the marine tunicate Ecteinascidia, inhibits oncogenic transcription and leads to dsDNA breaks
- Approved in SCLC based on a single arm phase 2 study of 105 patients, ORR 35%, PFS 3.5 mo, OS 9.3 mo
- Retrospective multicenter study presented at GU24 of 18 men with SCPC/NEPC treated with Lurbi: PR in 31%, SD in 25%, PD in 43%, PFS 3.35 mo, OS 6.01 mo



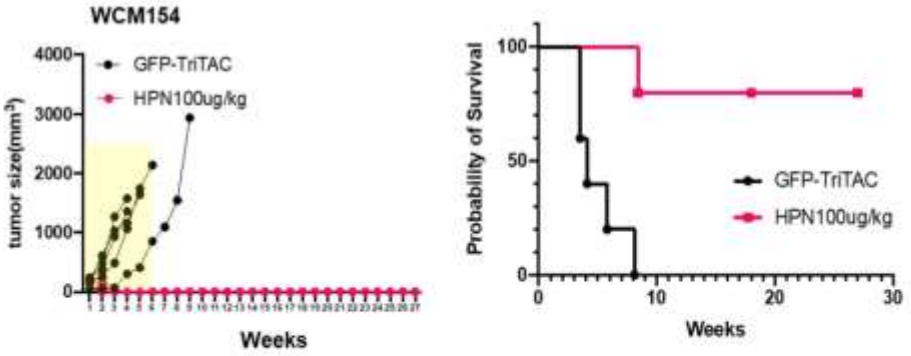
Trigo J et al Lancet 2020
Meyer H et al abstract 164 GU 2024

Kastrasyona Dirençli Metastatik Prostat kanseri Nöroendokrin diferansiasyon

HPN328 is a DLL3-targeting T Cell Engager with strong activity in DLL3+ cancer models

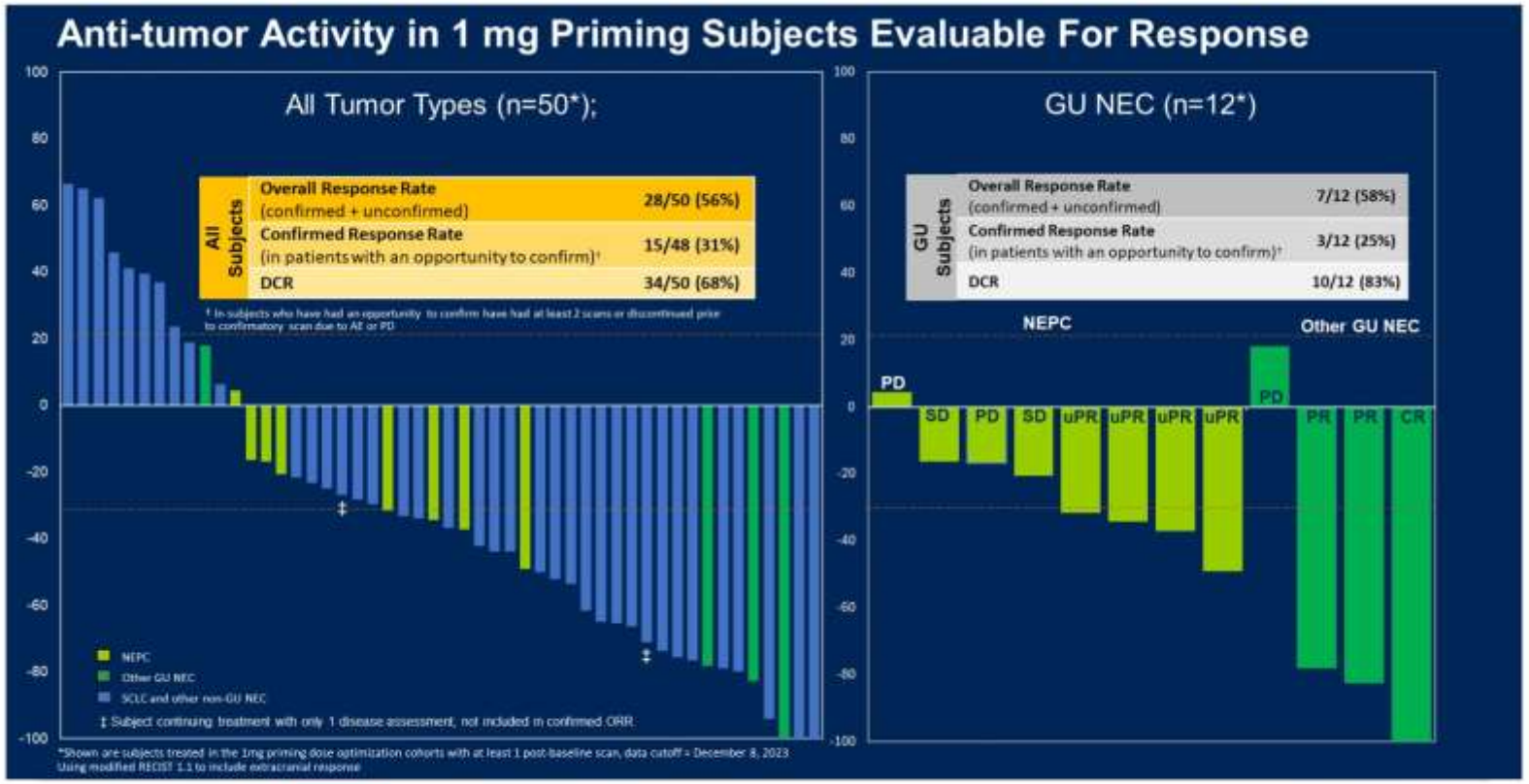


Anti-tumor activity *in vivo*: DLL3+ WCM154 Patient- Derived NEPC Xenografts



HPN328 and co-injection with human T cells resulted in tumor regression and prolonged survival of mice

Kastrasyona Dirençli Metastatik Prostat kanseri
Nöroendokrin diferansiasyon



Sonuç

- BRCA mutasyonu olanlarda yeni nesil androjen reseptör yolağı inhibitörleri +PARP inhibitörleri ve
- 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, androjen reseptör degrader vb tedaviler umut vaat ediyor
- Nöroendokrin diferansiasyon olanlarda, kabazitaksel+carboplatine