

Kastrasyona Dirençli Metastatik Prostat Kanserinde Tedavi

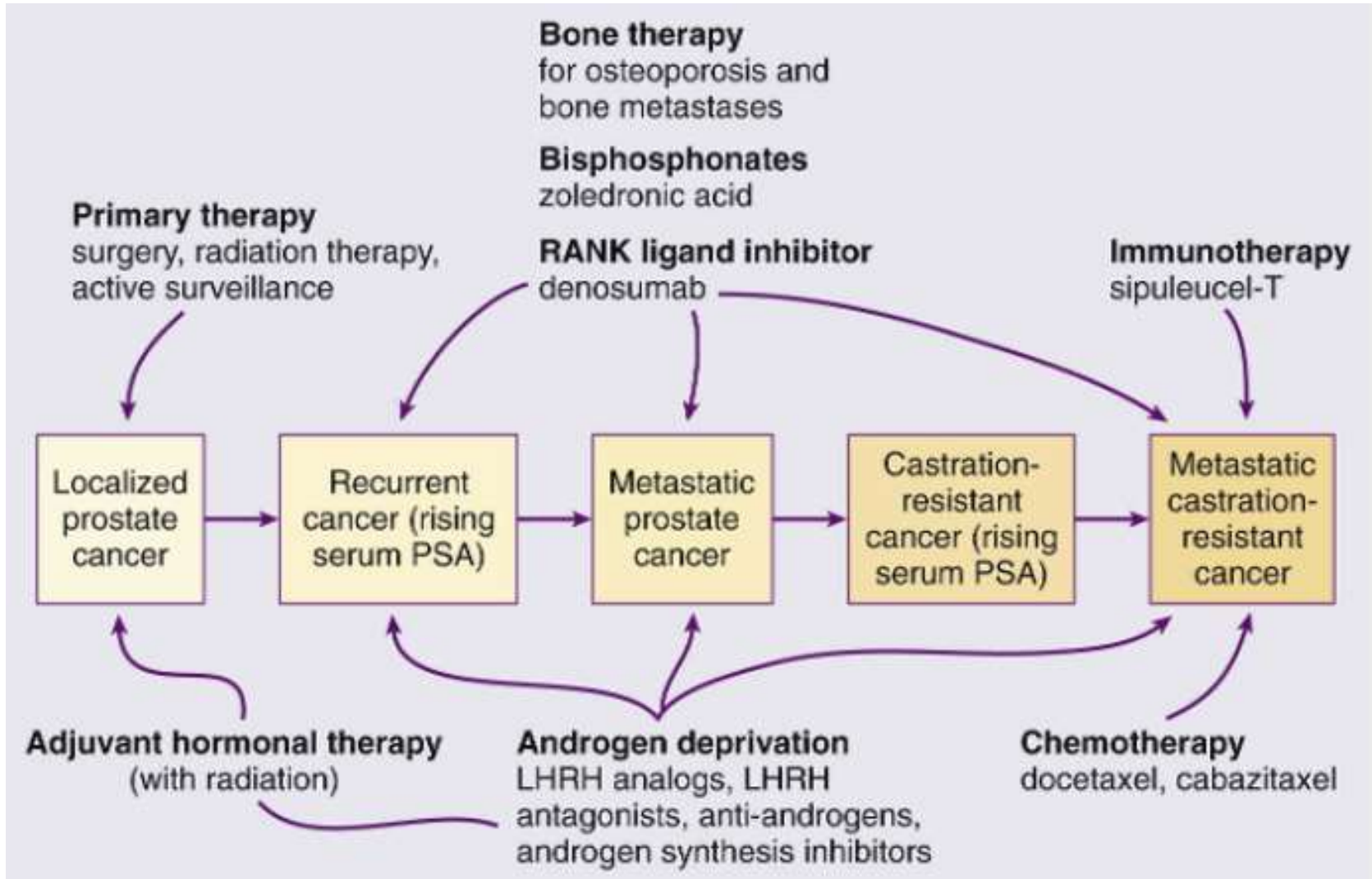
Dr. Deniz Tural

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

Ders Planı

- Giriş
- DNA repair mutasyonu olan hastalarda seçenekler
- Lutecium-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



Prostat Kanseri Genomik Profil

TMB

AR

PI3K

RAF

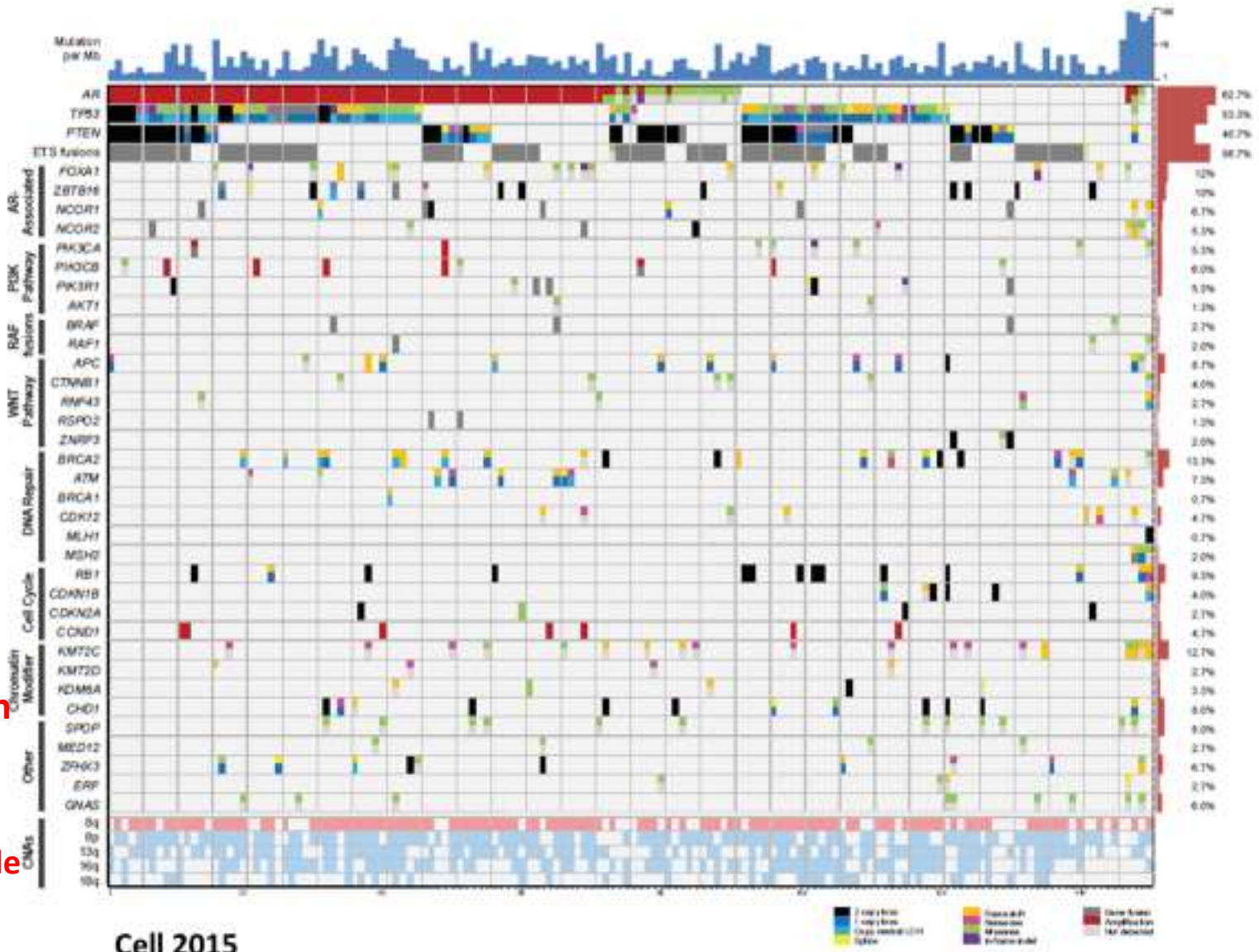
WNT

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 PC¹⁻⁶

*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}

<p>No prior docetaxel/no prior novel hormone therapy^{fff}</p> <ul style="list-style-type: none"> • Preferred regimens <ul style="list-style-type: none"> ▶ Abiraterone^{t,999} (category 1^{hhh}) ▶ Docetaxel^{aaa,iii} (category 1) ▶ Enzalutamide^t (category 1) • Useful in certain circumstances <ul style="list-style-type: none"> ▶ Sipuleucel-T^{aaa,jjj} (category 1) ▶ Radium-223^{kkk} for symptomatic bone metastases (category 1) • Other recommended regimens <ul style="list-style-type: none"> ▶ Other secondary hormone therapy^t 	<p>Prior novel hormone therapy/No prior docetaxel^{fff,iii}</p> <ul style="list-style-type: none"> • Preferred regimens <ul style="list-style-type: none"> ▶ Docetaxel (category 1)^{aaa} ▶ Sipuleucel-T^{aaa,jjj} • Useful in certain circumstances <ul style="list-style-type: none"> ▶ 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 <ul style="list-style-type: none"> ▶ Abiraterone^{t,999} ▶ Abiraterone + dexamethasone^{999.ppp} ▶ Enzalutamide^t ▶ Other secondary hormone therapy^t
<p>Prior docetaxel/no prior novel hormone therapy^{fff}</p> <ul style="list-style-type: none"> • Preferred regimens <ul style="list-style-type: none"> ▶ Abiraterone^{t, 999} (category 1) ▶ Cabazitaxel^{aaa} ▶ Enzalutamide^t (category 1) • Useful in certain circumstances <ul style="list-style-type: none"> ▶ 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 <ul style="list-style-type: none"> ▶ Sipuleucel-T^{aaa,jjj} ▶ Other secondary hormone therapy^t 	<p>Prior docetaxel and prior novel hormone therapy^{fff,iii} (All systemic therapies are category 2B if visceral metastases are present)</p> <ul style="list-style-type: none"> • Preferred regimens <ul style="list-style-type: none"> ▶ Cabazitaxel^{aaa} (category 1^{hhh}) ▶ Docetaxel rechallenge^{aaa,eee} • Useful in certain circumstances <ul style="list-style-type: none"> ▶ 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 <ul style="list-style-type: none"> ▶ Abiraterone^{t,999} ▶ 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}
<ul style="list-style-type: none"> • Preferred regimens <ul style="list-style-type: none"> ▶ Abiraterone^{y,rrr} (category 1^{sss}) ▶ Docetaxel^{lll} (category 1) ▶ Enzalutamide^y (category 1) • Useful in certain circumstances <ul style="list-style-type: none"> ▶ Niraparib/abiraterone^{y,ill,ttt} for <i>BRCA</i> mutation (category 1) ▶ Olaparib/abiraterone^{y,ill,rrr,uuu} for <i>BRCA</i> 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,ill,xxx} (category 1) • Other recommended regimens <ul style="list-style-type: none"> ▶ Other secondary hormone therapy^y 	<ul style="list-style-type: none"> • Preferred regimens <ul style="list-style-type: none"> ▶ Docetaxel (category 1)^{lll} ▶ Olaparib for <i>BRCA</i> mutation^{yyy} (category 1) ▶ Rucaparib for <i>BRCA</i> mutation^{zzz} (category 1) • Useful in certain circumstances <ul style="list-style-type: none"> ▶ Cabazitaxel/carboplatin^{lll,mmm} ▶ Niraparib/abiraterone^{y,ill,ttt} for <i>BRCA</i> mutation (category 2B) ▶ Olaparib for HRR mutation other than <i>BRCA1/2</i>^{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,ill,xxx} (category 2B) • Other recommended regimens <ul style="list-style-type: none"> ▶ 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}
<ul style="list-style-type: none"> • Preferred regimens <ul style="list-style-type: none"> ▶ Abiraterone^{y,rrr} (category 1) ▶ Cabazitaxel^{lll} ▶ Enzalutamide^y (category 1) • Useful in certain circumstances <ul style="list-style-type: none"> ▶ Cabazitaxel/carboplatin^{lll,mmm} ▶ Mitoxantrone for palliation in symptomatic patients who cannot tolerate other therapies^{lll} ▶ Niraparib/abiraterone^{y,ill,ttt} for <i>BRCA</i> mutation ▶ Olaparib/abiraterone^{y,ill,rrr,uuu} for <i>BRCA</i> 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,ill,xxx} • Other recommended regimens <ul style="list-style-type: none"> ▶ Other secondary hormone therapy^y 	<ul style="list-style-type: none"> • Preferred regimens <ul style="list-style-type: none"> ▶ Cabazitaxel^{lll} (category 1) ▶ Docetaxel rechallenge^{lll} • Useful in certain circumstances <ul style="list-style-type: none"> ▶ 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 <i>BRCA</i> mutation^{zzz} • Other recommended regimens <ul style="list-style-type: none"> ▶ Other secondary hormone therapy^{aaaa}

DNA repair ve Diğer Mutasyonları Ne Zaman Bakılmalı

Prostate NCCN Guidelines v 1.2023

Germline Testing	Somatic Tumor Testing
<p>Germline testing is recommended in patients with a personal history of prostate cancer who:</p> <ul style="list-style-type: none">• Have metastatic, regional (N+), very-high-risk localized, or high-risk localized prostate cancer• Have family history and/or ancestry with:<ul style="list-style-type: none">• ≥1 first, second, or third degree relative with<ul style="list-style-type: none">• 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:<ul style="list-style-type: none">• Breast cancer at any age• Prostate cancer at any age• ≥3 first or second degree relatives with:<ul style="list-style-type: none">• 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 <p>Germline testing may be considered in patients with a personal history of PCa who:</p> <ul style="list-style-type: none">• Have intermediate-risk prostate cancer with intraductal/cniform histology• Have a personal history of pancreatic, colorectal, gastric, melanoma, upper tract urothelial, glioblastoma, biliary tract, or small intestinal cancer <p><i>Germline multigene testing that includes at least BRCA1, BRCA2, ATM, PALB2, CHEK2, HOXB13, MLH1, MSH2, MSH6, and PMS2 is recommended; additional genes may be appropriate based on clinical context</i></p>	<p>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</p> <p>Tumor testing for MSI-H or dMMR is recommended in patients with mCRPC, and may be considered for patients with mCSPC</p> <p>TMB testing may be considered in patients with mCRPC</p>

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

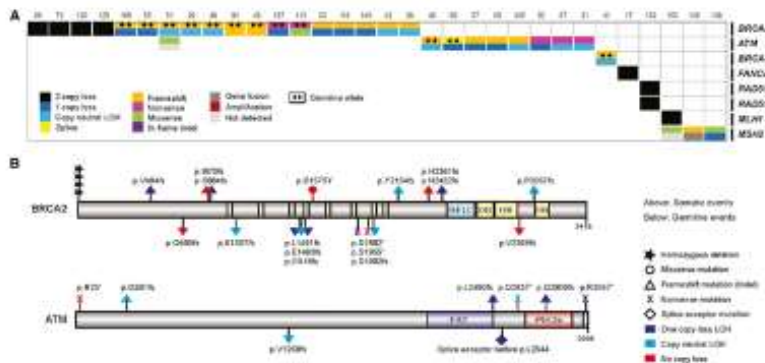
Germline ve somatik mutasyonlar metastatik aşamada istenmeli

Evre IV Prostat Kanserinde Mutasyonlar

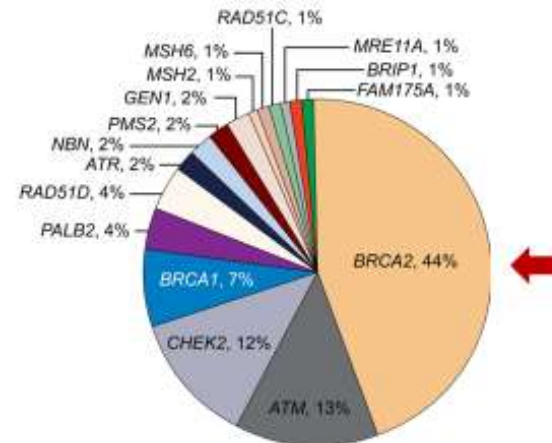
HRR Genes and Metastatic Prostate Cancer

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**



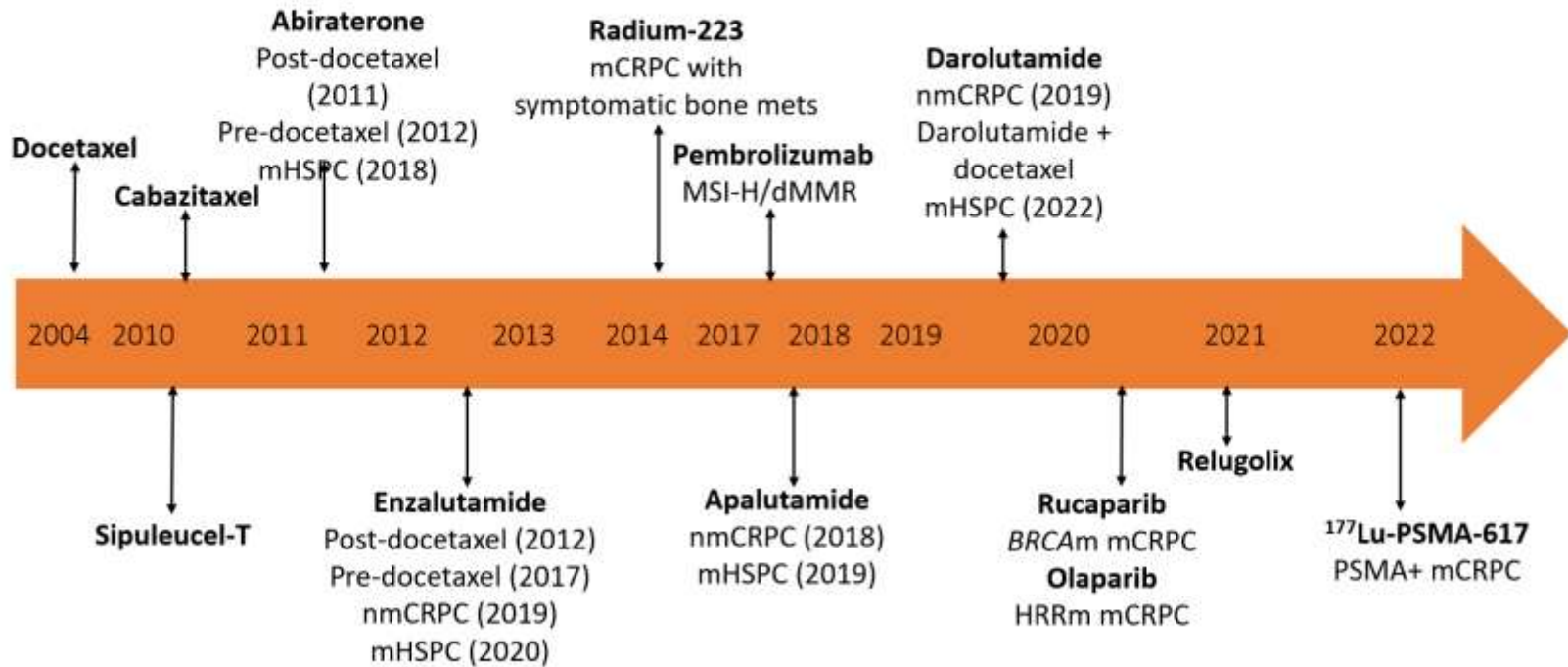
Germline



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

Kastrasyona Dirençli Metastatik Prostat kanseri

Treatment Landscape of mCRPC continues to evolve



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 + Olaparib¹

Published



MAGNITUDE: Abiraterone + Niraparib²

Presented



TALAPRO-2: Enzalutamide + Talazoparib

Presented



CASPAR: Enzalutamide + Rucaparib

Enrolling

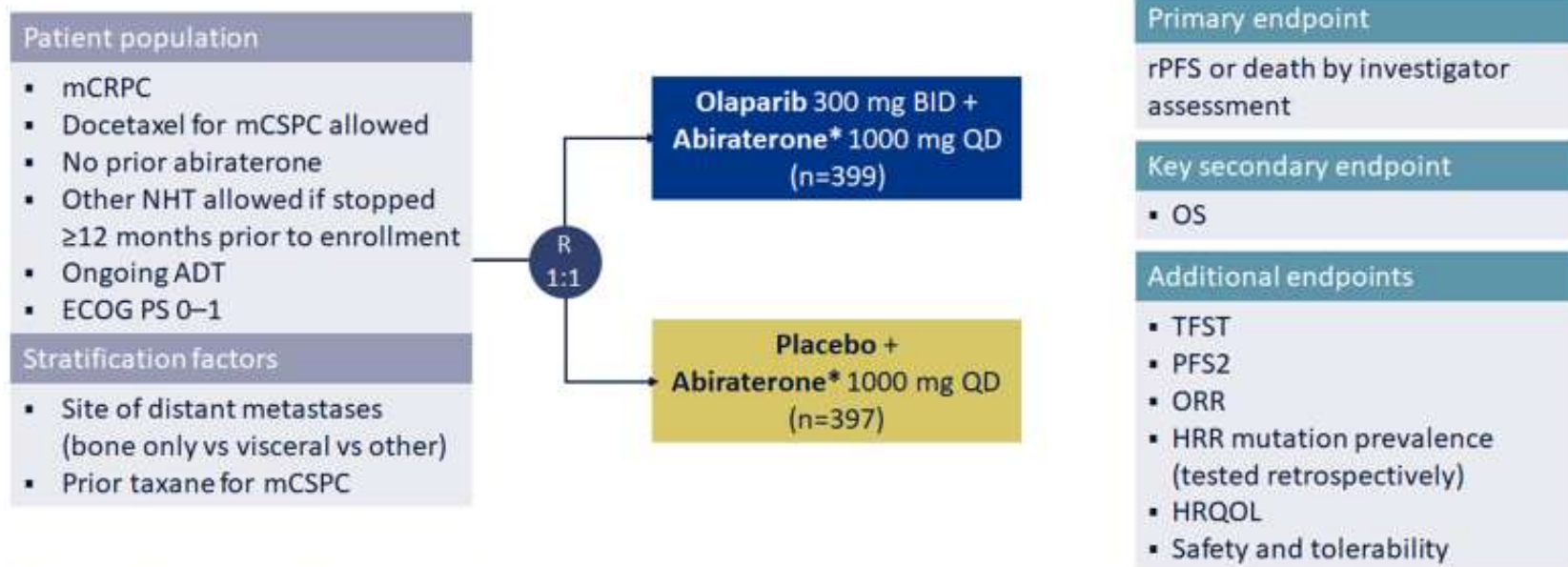


1- Clarke NW et al., NEJM Evidence. 2022 Aug 23;1(9):EVIDoa2200043.

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

PROpel: Phase III Trial of Abiraterone +/- Olaparib

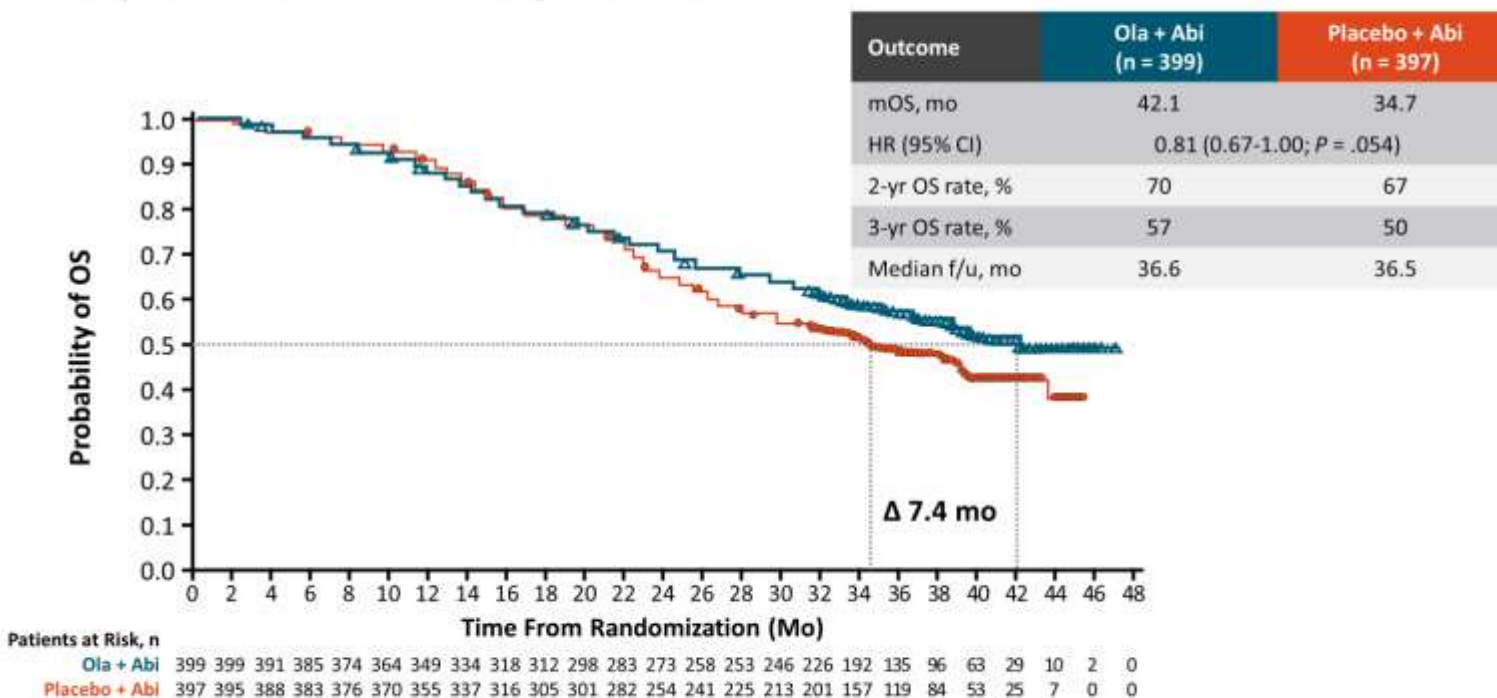


*Plus prednisone or prednisolone 5 mg BID

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

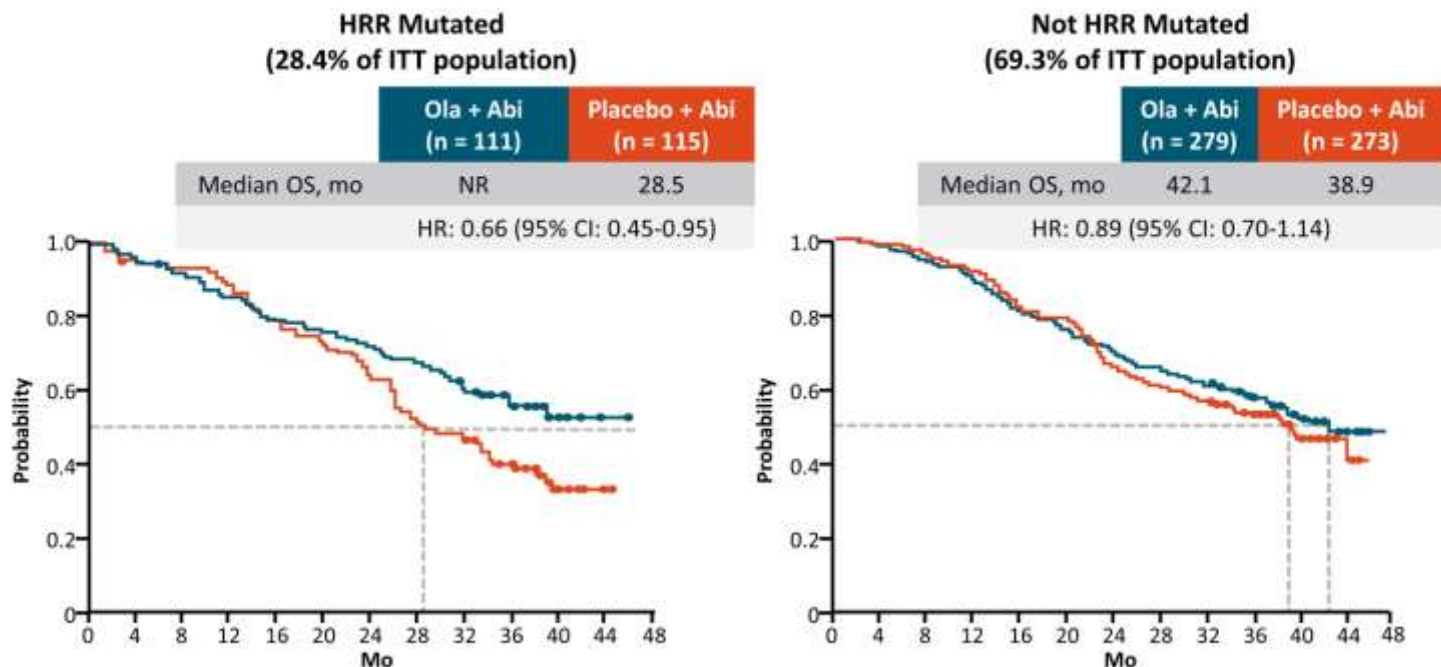
Kastrasyona Dirençli Metastatik Prostat kanseri PARP inhibitörleri+Androjen Reseptör yolağı blokörleri

PROpel: OS in ITT Population



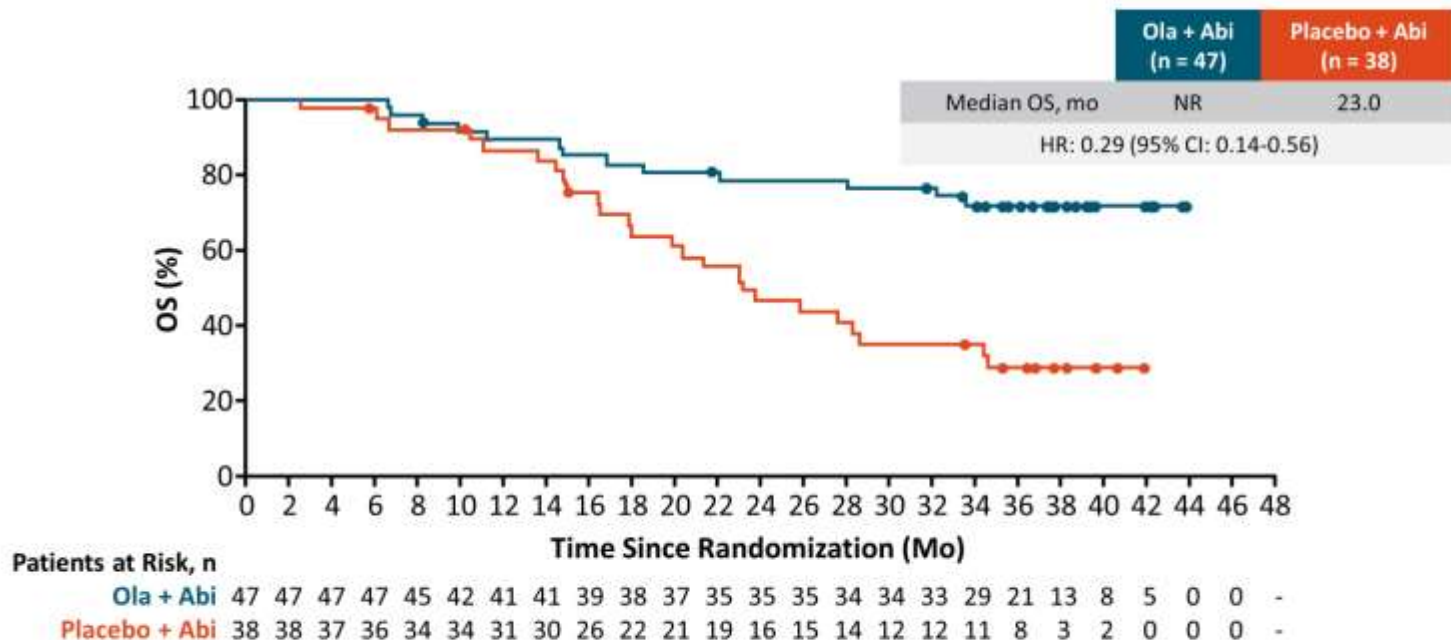
Kastrasyona Dirençli Metastatik Prostat kanseri PARP inhibitörleri+Androjen Reseptör yolağı blokörleri

PROpel: OS by HRR Status



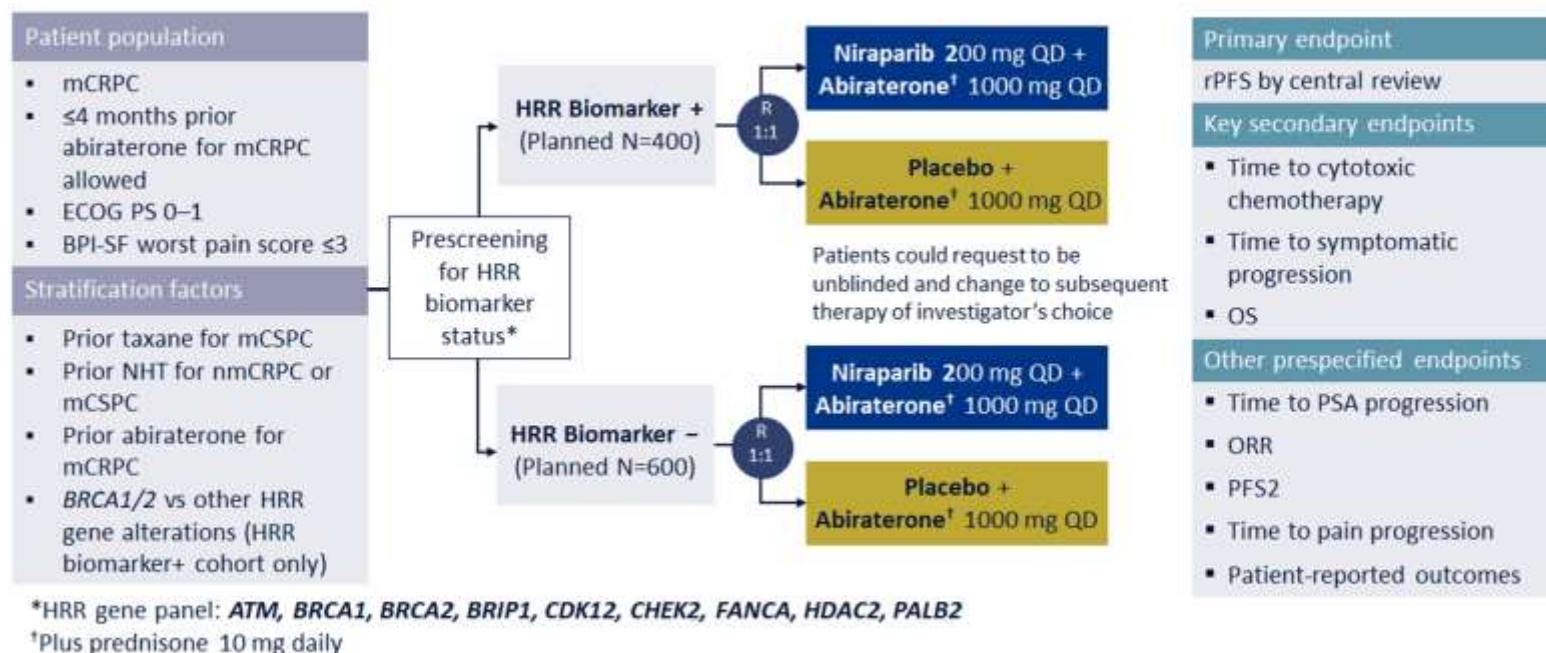
Kastrasyona Dirençli Metastatik Prostat kanseri PARP inhibitörleri+Androjen Reseptör yolağı blokörleri

PROpel: OS in *BRCAm*



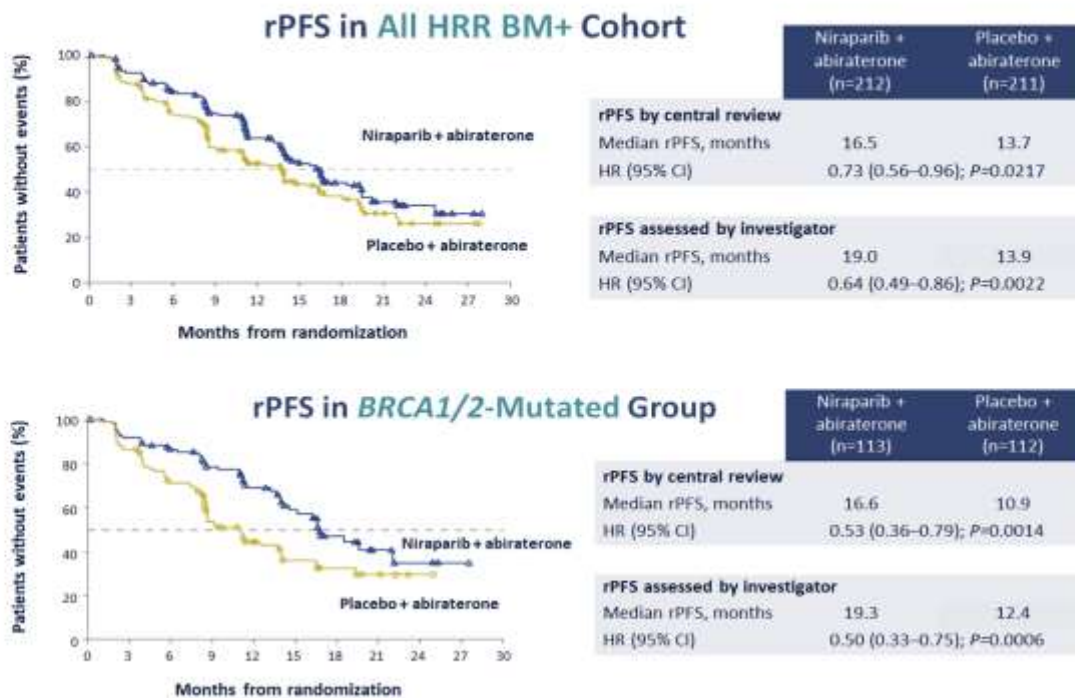
Kastrasyona Dirençli Metastatik Prostat kanseri PARP inhibitörleri+Androjen Reseptör yolağı blokörleri

MAGNITUDE: Phase III Trial of Abi +/- Niraparib

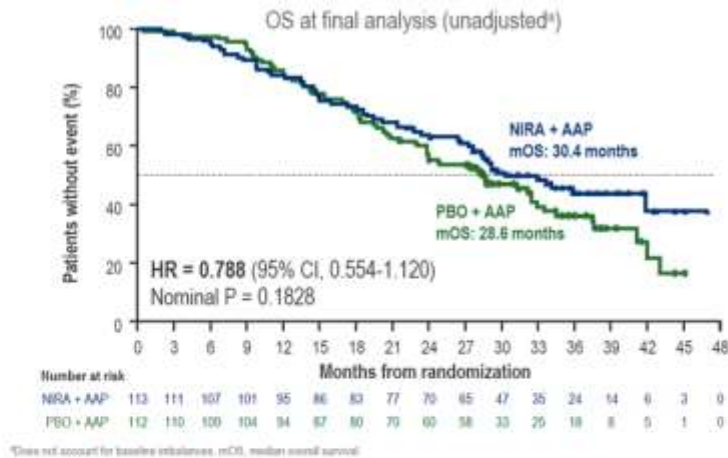


Kastrasyona Dirençli Metastatik Prostat kanseri PARP inhibitörleri+Androjen Reseptör yolağı blokörleri

MAGNITUDE: Radiographic Progression-Free Survival



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

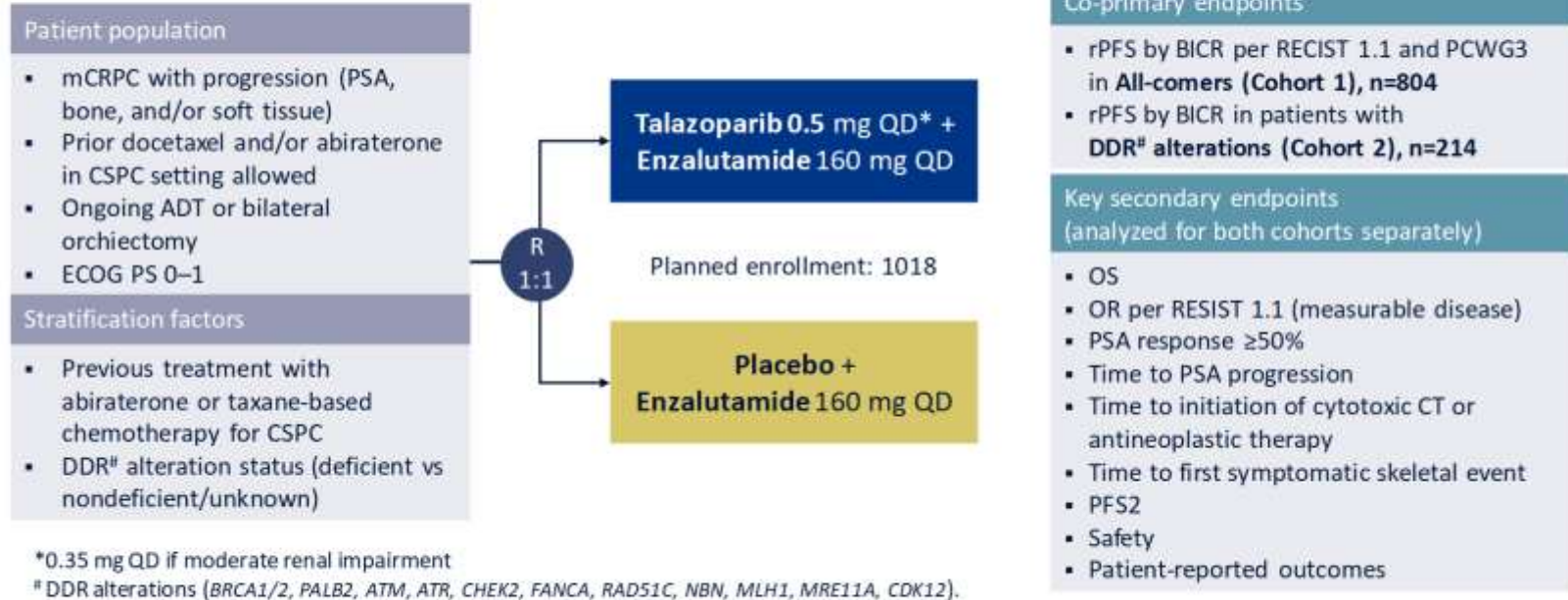


Chi et al ESMO 2023
LBA 85

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)

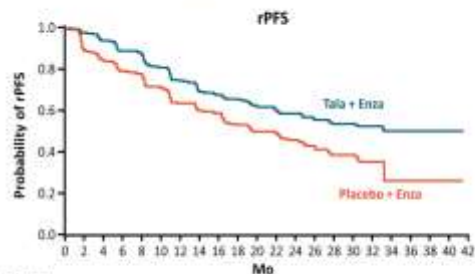
Kastrasyona Dirençli Metastatik Prostat kanseri PARP inhibitörleri+Androjen Reseptör yolağı blokörleri

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



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)		

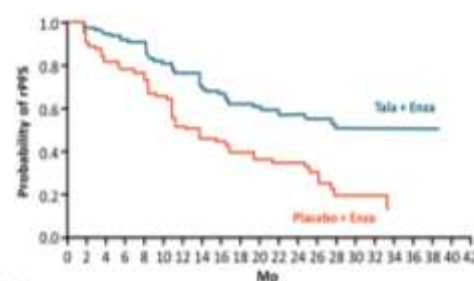
Patients at Risk, n

Mo	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42
Tala + Enza	403	379	353	326	318	285	256	234	226	209	183	175	136	67	67	43	29	13	2	1	0	0
Placebo + Enza	403	346	311	279	272	237	200	185	179	154	141	134	95	68	49	42	34	3	1	1	1	0

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

Agarwal. ASCO GU 2021. Abstr 509A.17. Agarwal. Lancet. 2021;394:281.

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	15.8
HR: 0.45 (95% CI: 0.33-0.61; P < .0001)		

Patients at Risk, n

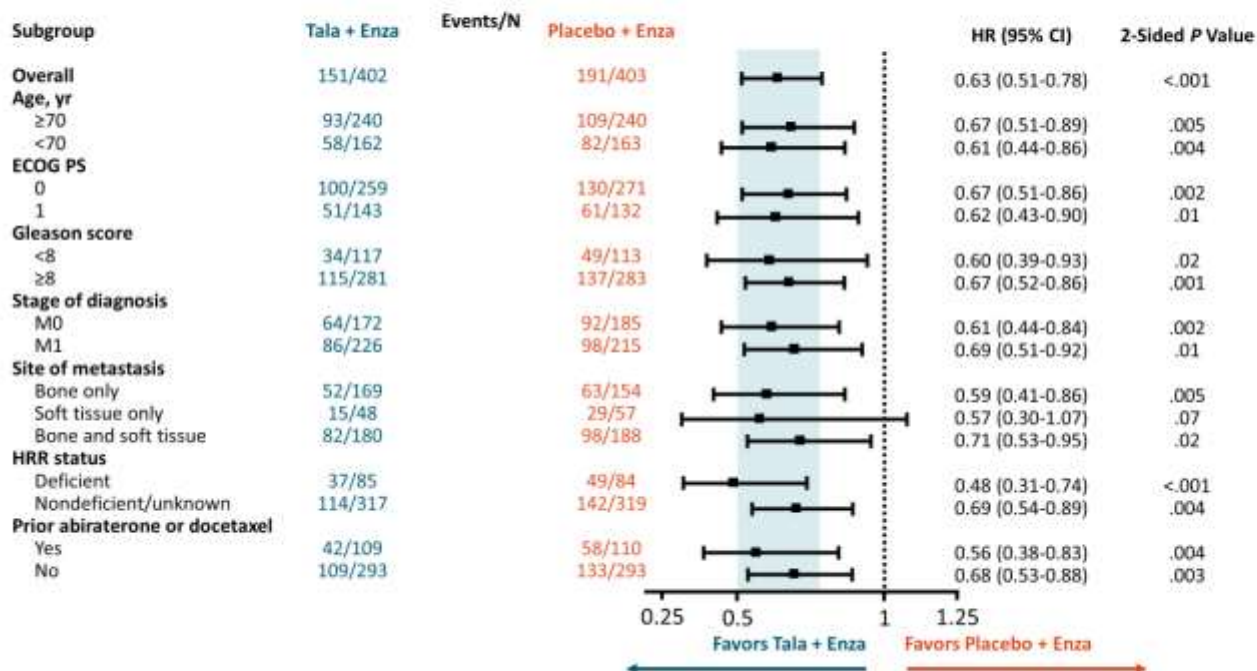
Mo	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42
Tala + Enza	200	191	180	168	163	151	107	86	62	48	45	34	26	21	19	9	4	1	0	0	0	0
Placebo + Enza	199	171	149	131	126	96	67	51	47	38	29	25	21	13	7	4	0	0	0	0	0	0

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

Agarwal. ASCO 2021. Abstr 509A.17. Agarwal. Lancet. 2021;394:281.

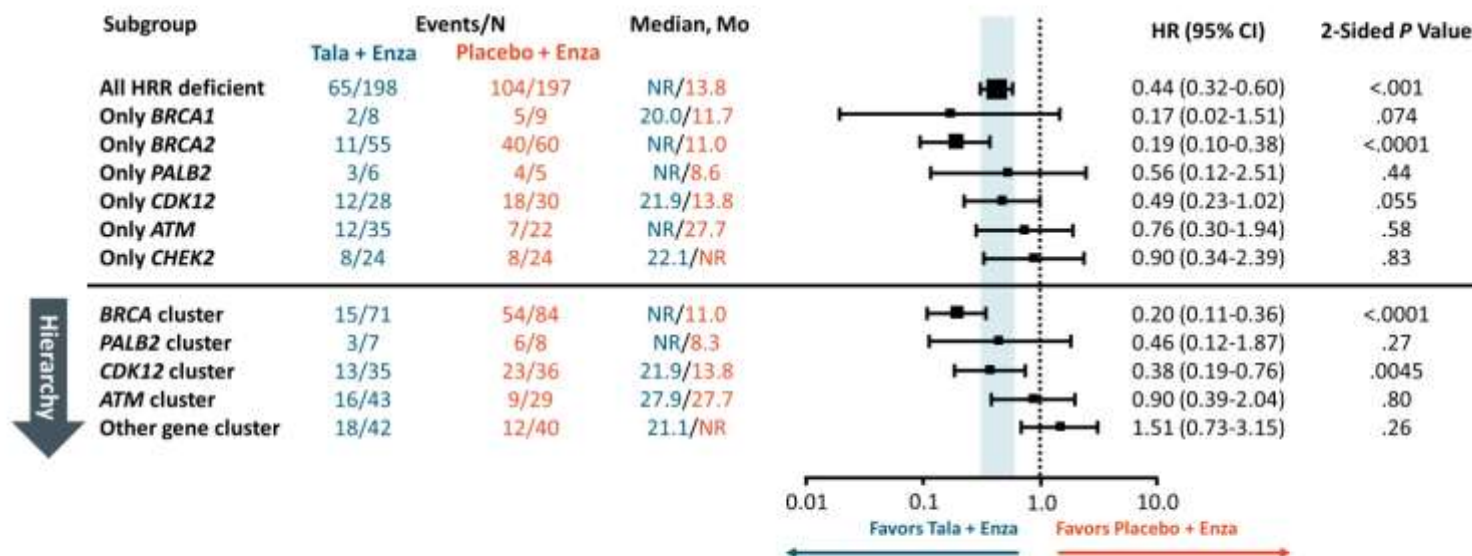
Kastrasyona Dirençli Metastatik Prostat kanseri PARP inhibitörleri+Androjen Reseptör yolağı blokörleri

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



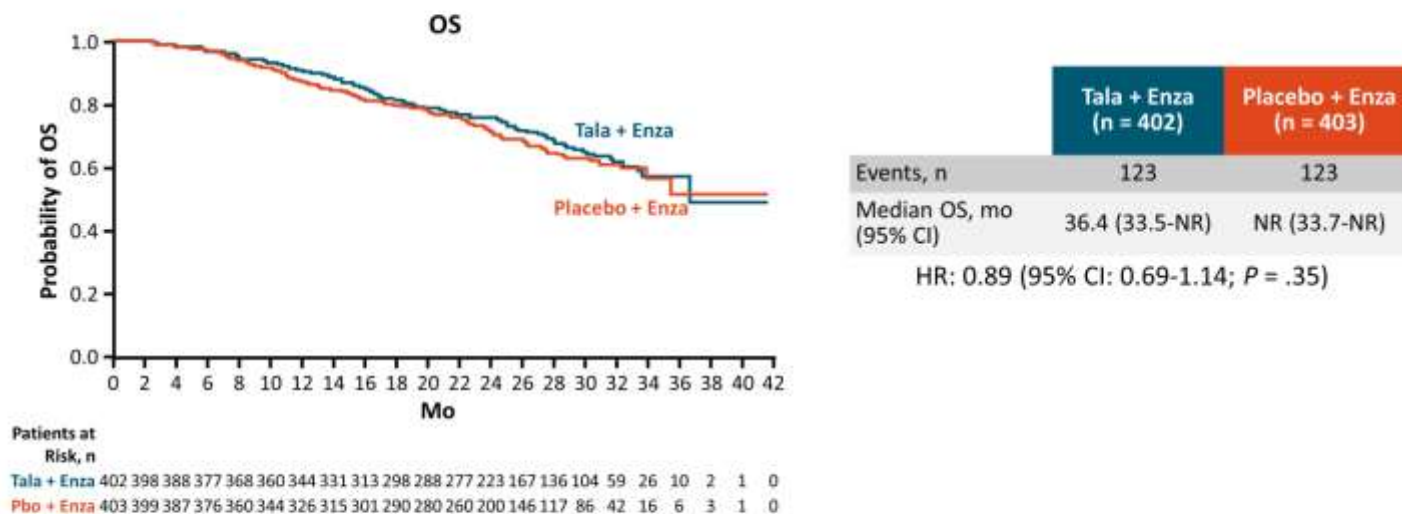
Kastrasyona Dirençli Metastatik Prostat kanseri PARP inhibitörleri+Androjen Reseptör yolağı blokörleri

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



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

TALAPRO-2: Overall Survival in All-Comers Population



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

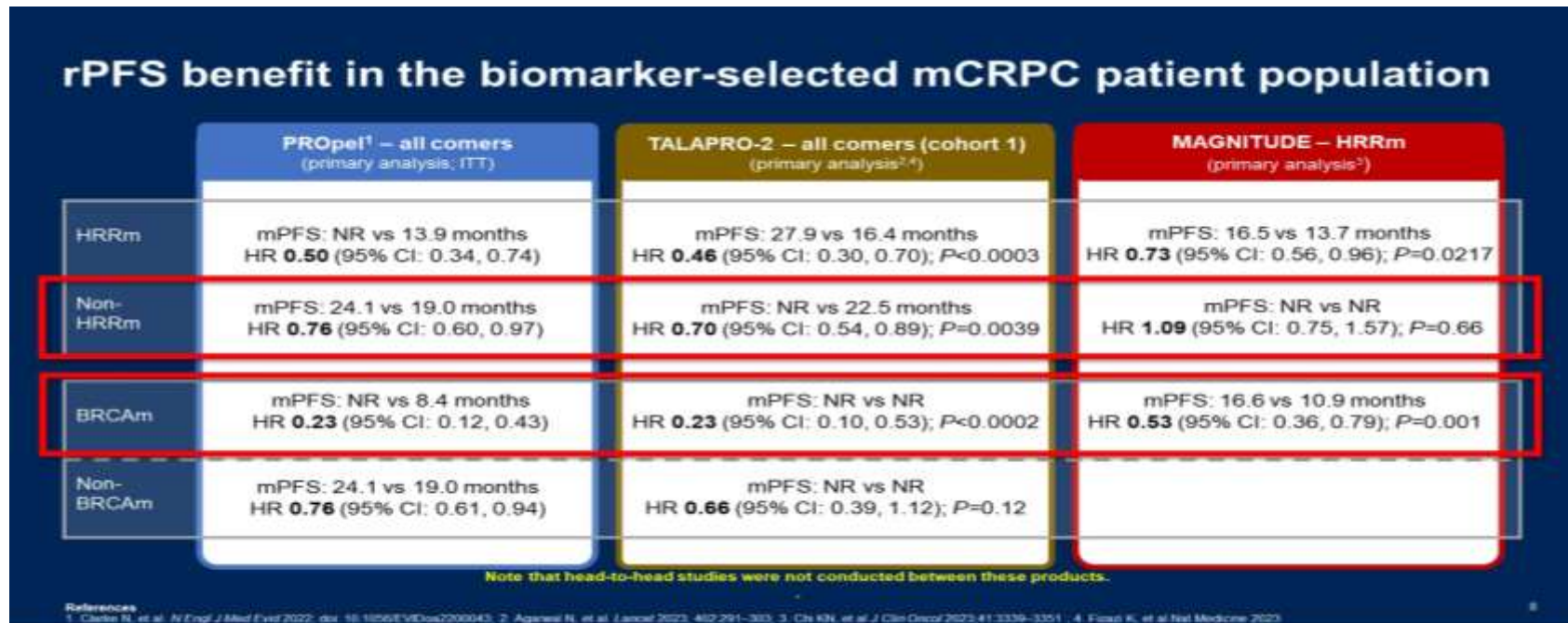
PARP inhibitörleri+Androjen Reseptör yolağı blokörleri

Yan etkilerin karşılaştırılması

	PROPEL Olaparib + Abiraterone	MAGNITUDE Niraparib + Abiraterone	TALAPRO-2 Talazoparib + Enzalutamide
Select G3-4 Toxicities % (all grades %)			
Anemia	16.3 (50)	30.1 (50.0)	46 (66)
---Transfusion Rate	18%	27.4%	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.

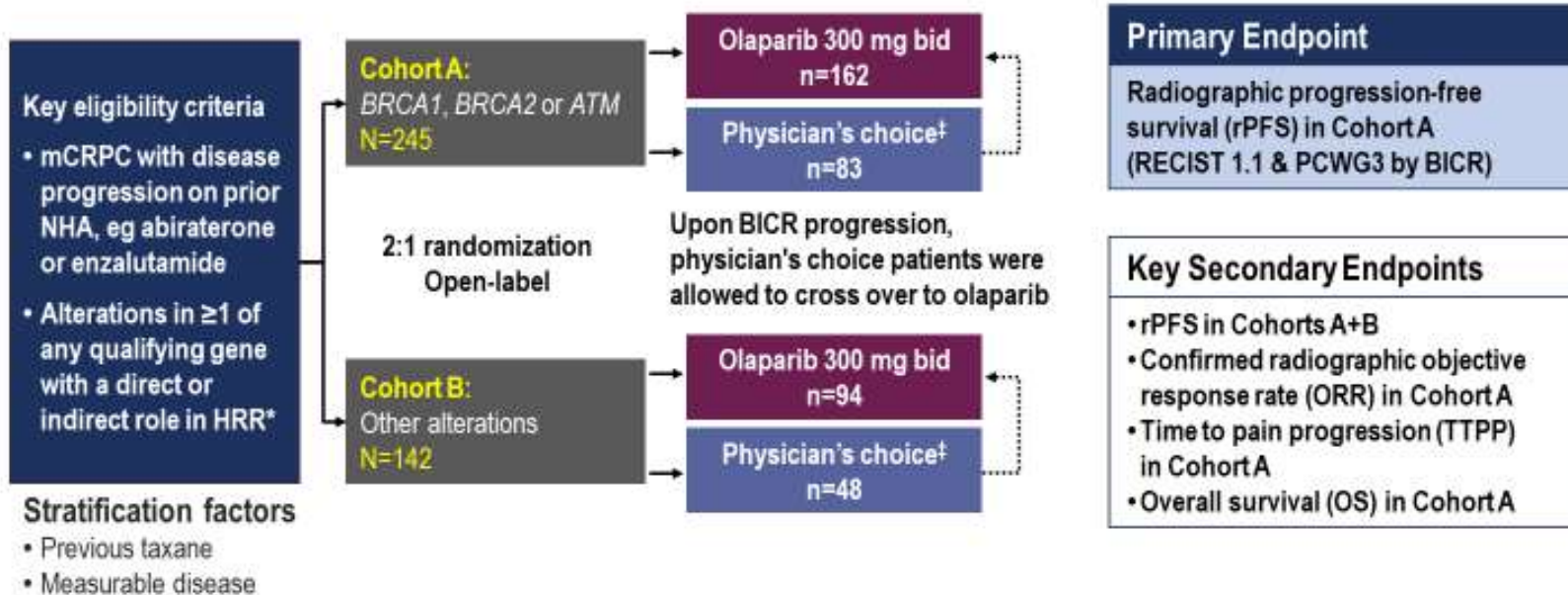
Kastrasyona Dirençli Metastatik Prostat kanseri PARP inhibitörleri+Androjen Reseptör yolağı blokörleri



	EMA	FDA
Olaparib + AA	All patients	<i>BRCA1/2</i>
Talazoparib + Enza	All patients	HRR
Niraparib + AA	<i>BRCA1/2</i>	<i>BRCA1/2</i>

Kastrasyona Dirençli Metastatik Prostat kanseri PARP inhibitörleri

PROfound STUDY DESIGN



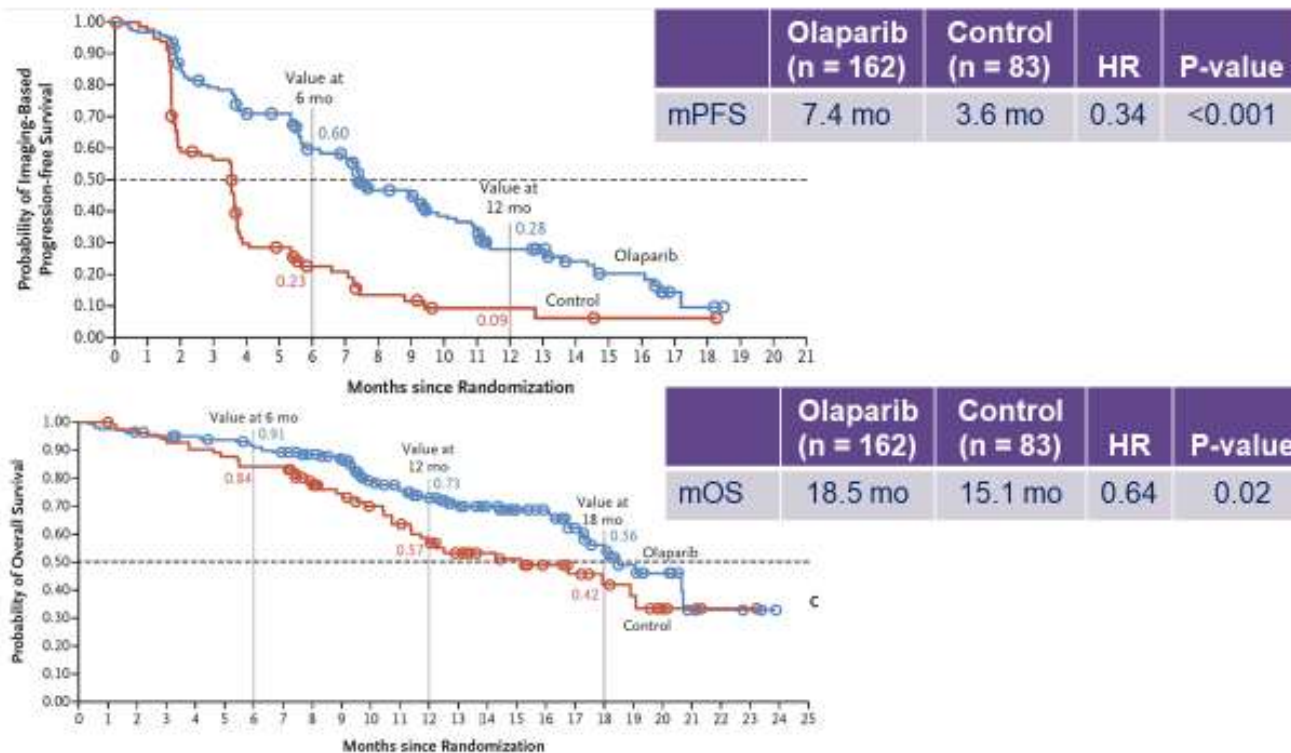
*An investigational Clinical Trial Assay, based on a next-generation sequencing test

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

Kastrasyona Dirençli Metastatik Prostat kanseri

PARP inhibitörleri

PROfound: Imaging-Based PFS and OS in Cohort A



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

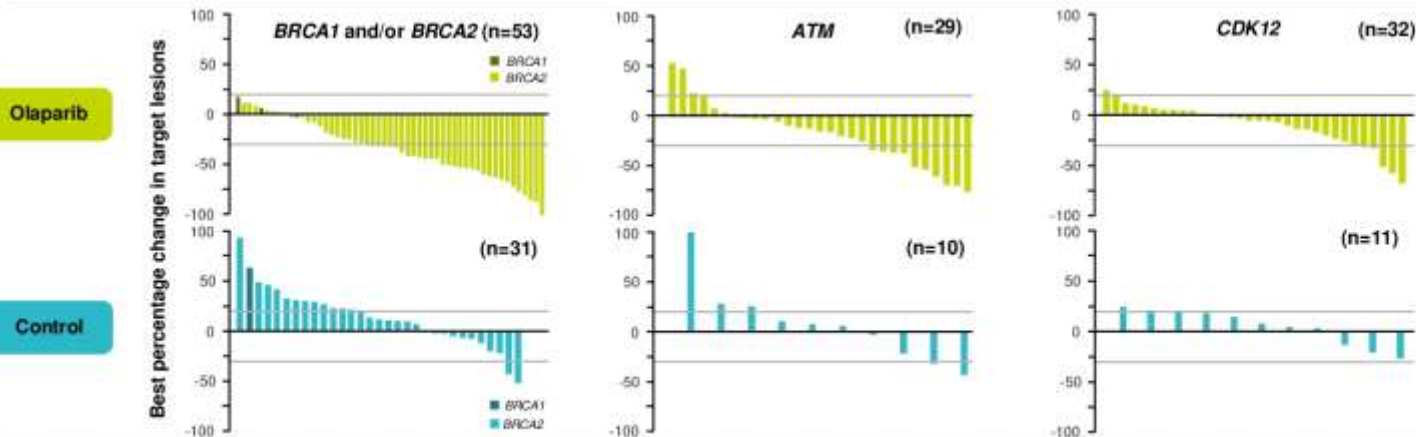
Kastrasyona Dirençli Metastatik Prostat kanseri PARP inhibitörleri

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		<i>BRCA1</i> and/or <i>BRCA2</i>		<i>ATM</i>		<i>CDK12</i>	
		Olaparib (N=162)	Control (N=83)	Olaparib (N=256)	Control (N=131)	Olaparib (N=102)	Control (N=56)	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



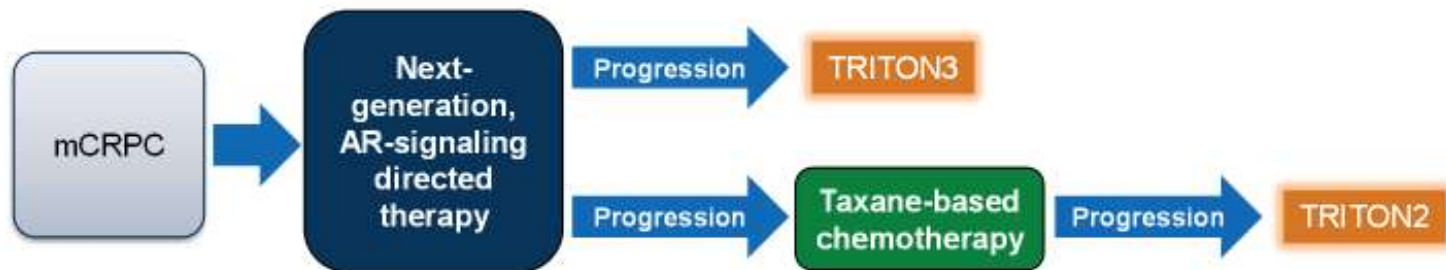
Definitions for abbreviations, best percentage change in PSA and CTC for *BRCA1* and/or *BRCA2*, *ATM*, *CDK12* and remaining genes are included in the supplement

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

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

Kastrasyona Dirençli Metastatik Prostat kanseri PARP inhibitörleri

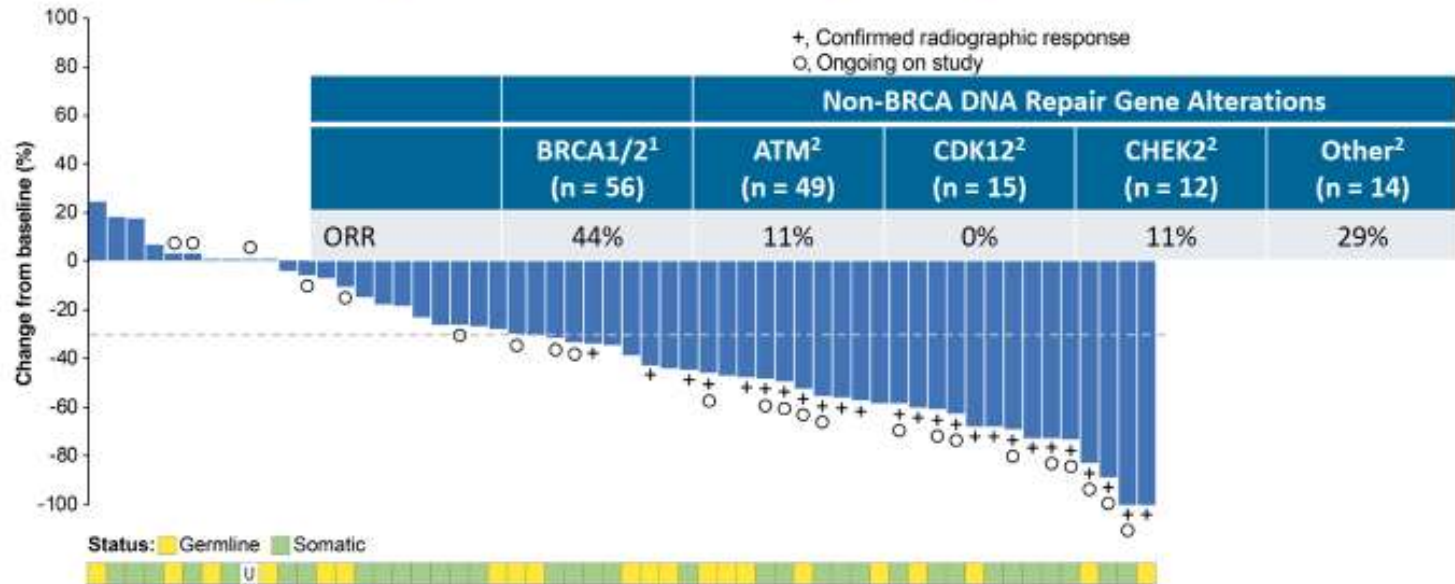
Rucaparib: TRITON2 and TRITON3 Studies



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

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



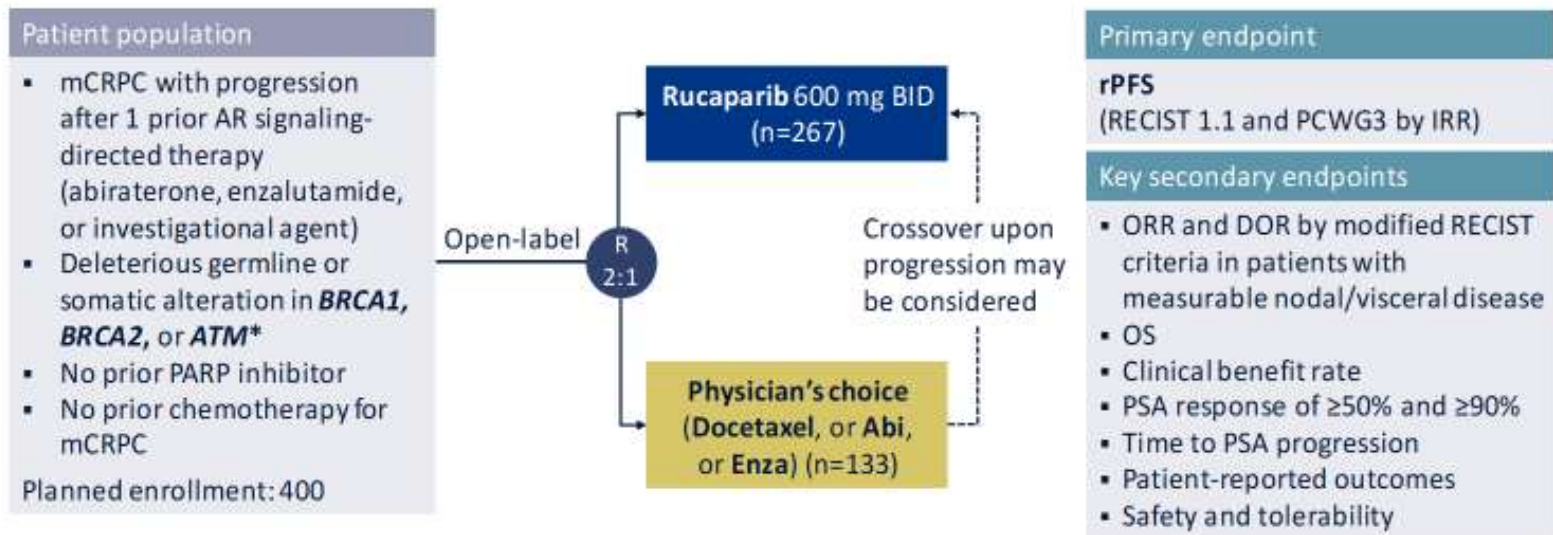
Visit cutoff: 02 Jul 2019. Includes patients with measurable disease at baseline and ≥1 postbaseline scan. Each bar represents a single patient; patients with no change from baseline are shown as 0.5% for visual clarity; the dotted line indicates the threshold for partial response (30% decrease from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

¹Abida W et al. ESMO 2019; Abstract 846PD; ²Abida 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

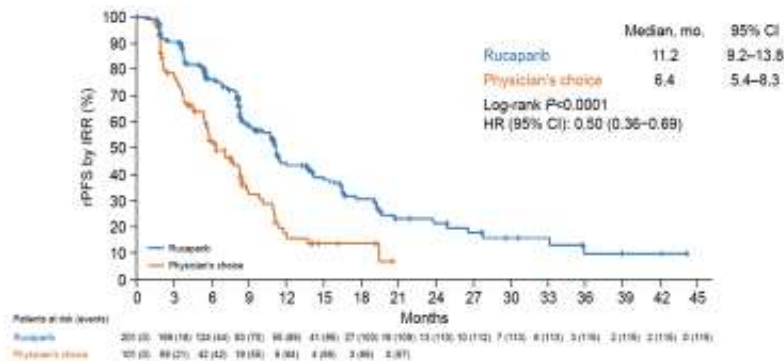
Bryce A et al NEJM 2023; 388; 719-32. **NCT02975934**.

Kastrasyona Dirençli Metastatik Prostat kanseri

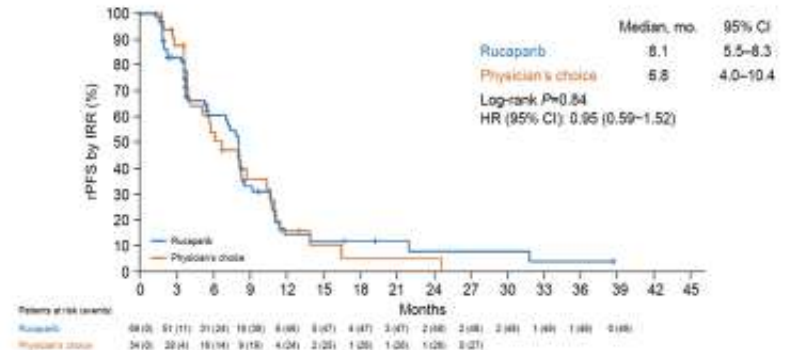
PARP inhibitörleri

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

***BRCA1/2* Subgroup**



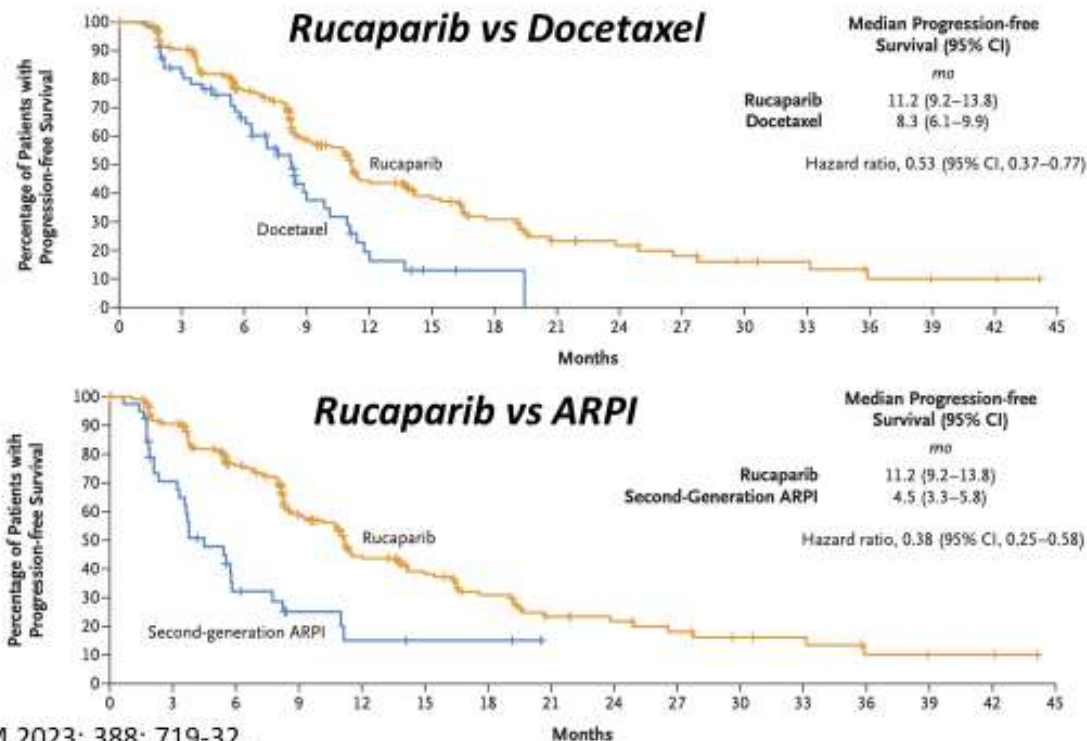
***ATM* Subgroup**



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

Kastrasyona Dirençli Metastatik Prostat kanseri PARP inhibitörleri

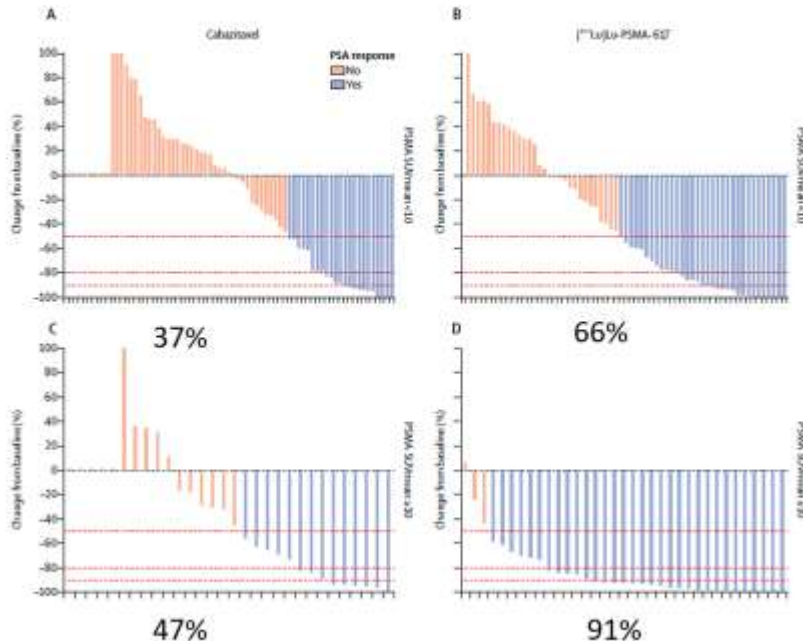
TRITON3: rPFS by Control Treatment in *BRCA1/2* Subgroup



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

Kastrasyona Dirençli Metastatik Prostat kanseri Lutesyum 177 Tedavisi

PSMA-Lu177 vs Cabazitaxel: TheraP Trial



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

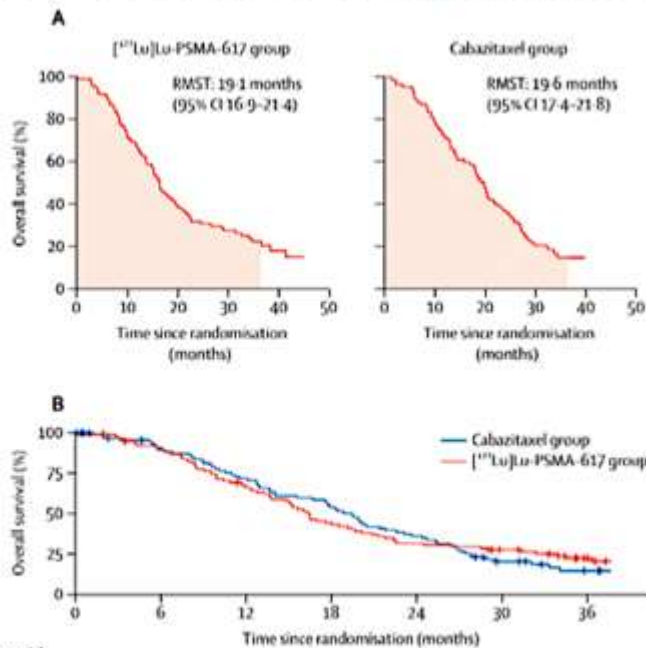
B Radiographic progression-free survival

	Cabazitaxel (n/N)	Cabazitaxel, median, months (95% CI)	[¹⁷⁷ Lu]Lu-PSMA-617 (n/N)	[¹⁷⁷ Lu]Lu-PSMA-617, median, months (95% CI)	HR (95% CI)
PSMA SUV/mean <10	57/71	7.6 (6.4-9.6)	57/64	6.0 (4.3-9.5)	0.85 (0.59-1.24)
PSMA SUV/mean ≥10	23/30	9.4 (8.0-11.2)	23/35	12.7 (11-NE)	0.46 (0.25-0.84)
Q1: PSMA SUV/mean <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 SUV/mean <6.9 to <8.5	15/20	5.7 (4.3-NE)	27/29	8.5 (5.6-11)	0.65 (0.34-1.26)
Q3: PSMA SUV/mean <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 SUV/mean ≥10.8	18/23	9.6 (8.3-12.4)	16/27	14.1 (8.3-NE)	0.52 (0.26-1.04)

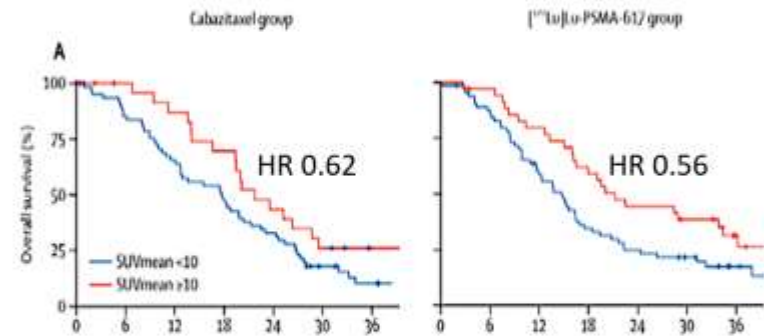
Hofman MS et al Lancet 2021
Burton JP et al Lancet Oncol 2022

Kastrasyona Dirençli Metastatik Prostat kanseri Lutesyum 177 Tedavisi

Lu177-PSMA-617 Updates: Therap



Number at risk (number censored)		0	6	12	18	24	30	36
Cabazitaxel group	101 (0)	75 (17)	60 (17)	45 (17)	30 (17)	14 (20)	6 (25)	
[¹⁷⁷ Lu]Lu-PSMA-617 group	99 (0)	88 (2)	63 (3)	41 (3)	30 (3)	23 (6)	11 (14)	



Conclusion: SUVmean \geq 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

Kastrasyona Dirençli Metastatik Prostat kanseri Lutesyum 177 Tedavisi

6

Open-label study of protocol-permitted standard of care ± ¹⁷⁷Lu-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 ⁶⁸Ga-PSMA-11



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

Presented By: Michael J. Morris

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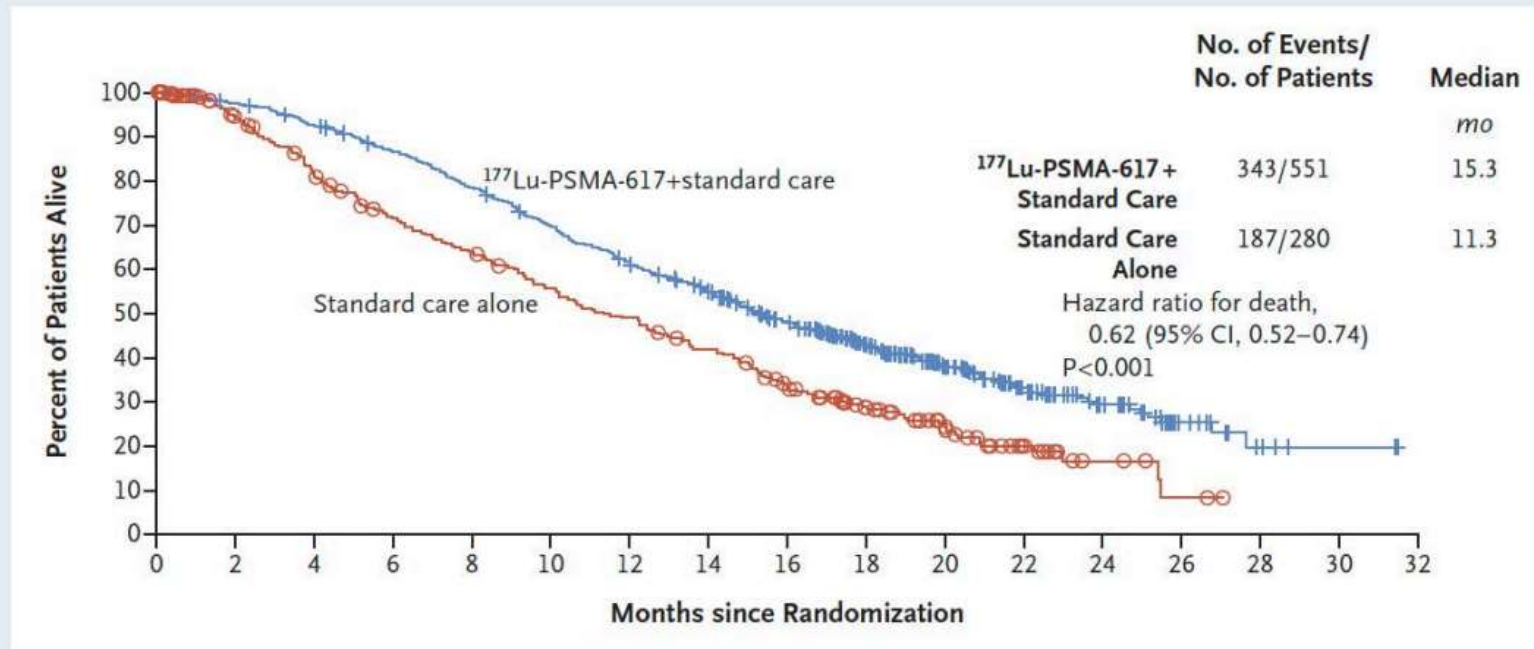
2021 ASCO
ANNUAL MEETING



Kastrasyona Dirençli Metastatik Prostat kanseri

Lutesyum 177 Tedavisi

VISION: Overall Survival



Kastrasyona Dirençli Metastatik Prostat kanseri

Lutesyum 177 Tedavisi

30

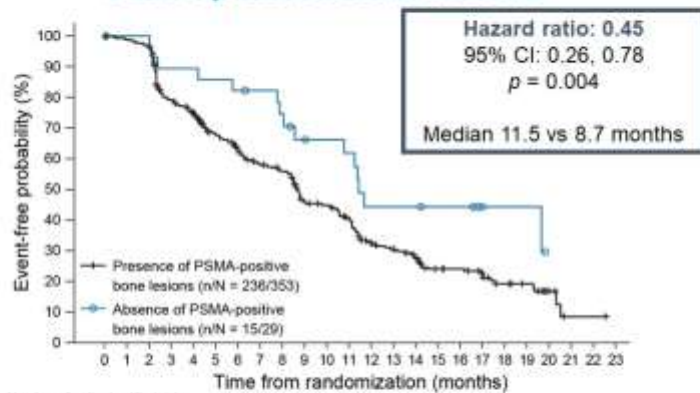
Treatment-emergent adverse events grouped as topics of interest: no unexpected or concerning safety signals

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

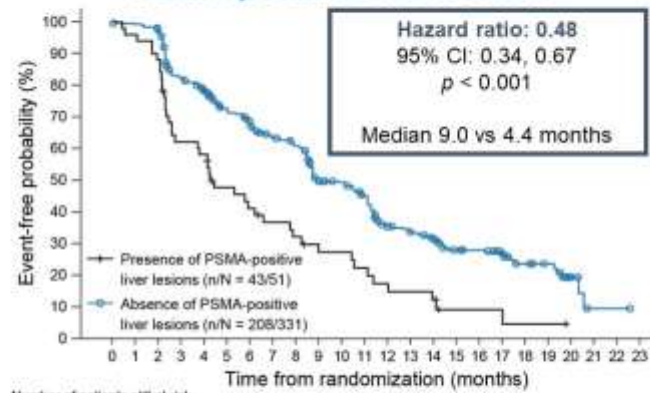
rPFS by absence of PSMA-positive lesions (PFS-FAS)

PSMA-positive bone lesions



Number of patients still at risk	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
Presence of PSMA-positive bone lesions	353	342	331	265	240	210	191	172	162	129	121	106	77	72	61	42	40	31	18	15	8	1	1	0
Absence of PSMA-positive bone lesions	29	28	28	25	24	23	21	19	16	15	14	10	10	10	6	6	8	5	3	3	0	0	0	0

PSMA-positive liver lesions



Number of patients still at risk	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
Presence of PSMA-positive liver lesions	51	49	45	31	28	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	298	242	212	185	177	167	133	125	111	80	76	60	49	47	35	30	17	6	1	1	0

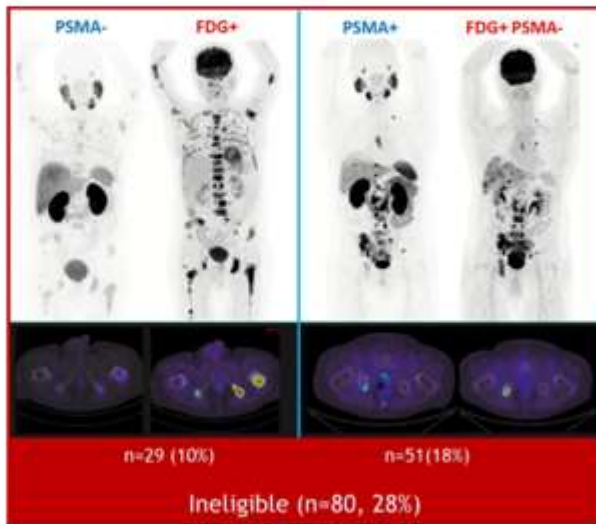
Absence of PSMA+ lesions in bone or liver was associated with a decrease in the risk of an rPFS event compared with presence of ≥ 1 PSMA+ lesions in these organs

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

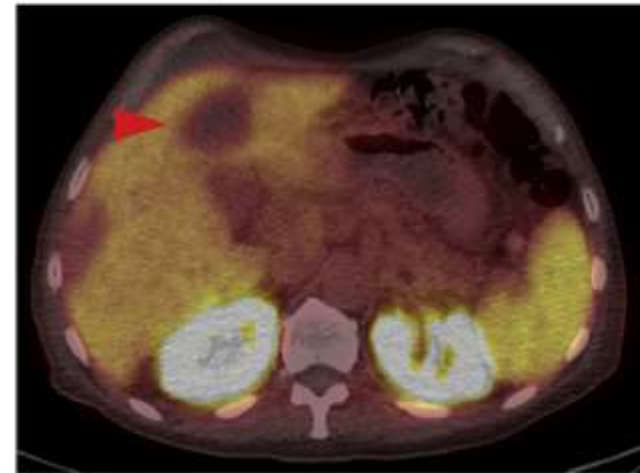
Loss of PSMA Expression in a Subset of CRPC

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-Dosetaksiel öncesi



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

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

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

*Contributed equally



Oliver Sartor

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



Madrid Auditorium - Hall 6

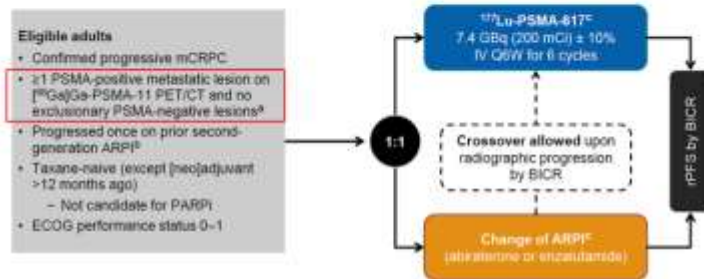
MADRID SPAIN 20-24 OCTOBER 2023

Kastrasyona Dirençli Metastatik Prostat kanseri Lutesyum 177 Tedavisi-Dosetaksi 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



Stratification factors

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

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 (88–185)	129.0 (86–198)
Alkaline phosphatase, median (range), U/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.

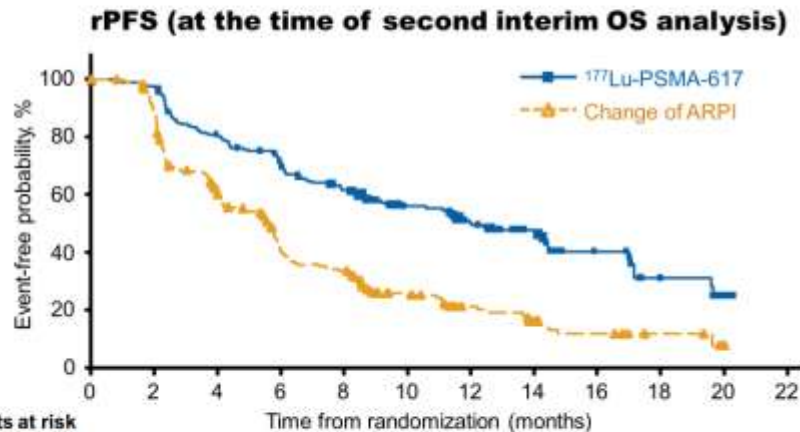
bone-only disease: ≥ 1 site of bone involvement must be [68Ga]Ga-PSMA-11 PET positive.

Kastrasyona Dirençli Metastatik Prostat kanseri Lutesyum 177 Tedavisi-Dosetaksiel öncesi

PSMAfore study met primary endpoint of rPFS

Primary endpoint was met:

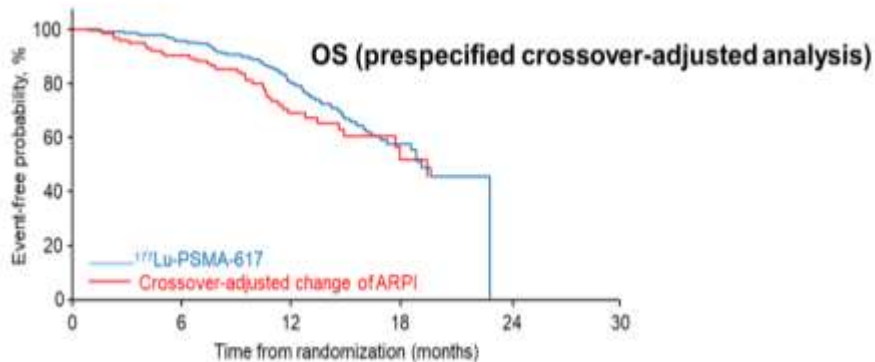
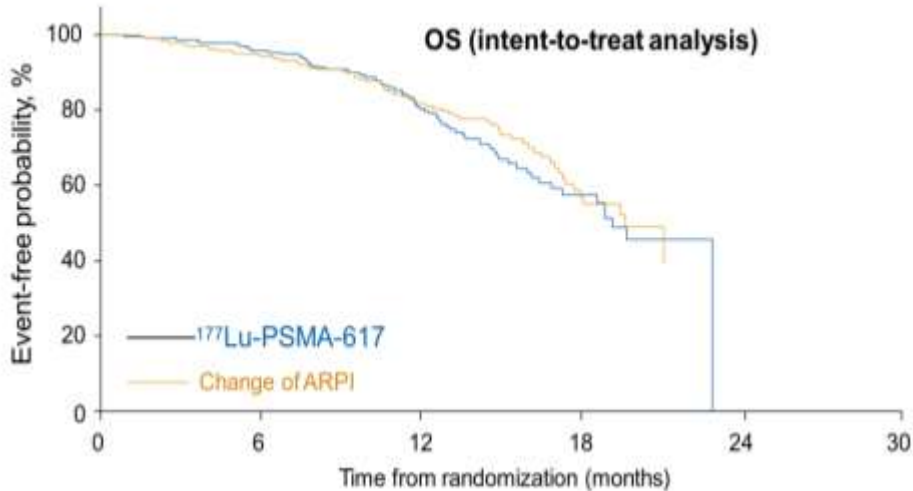
- At the time of primary analysis (DCO October 2, 2022): HR was 0.41 (95% CI: 0.29, 0.56); $P < .0001$
- At the time of second interim OS analysis (DCO June 21, 2023): HR was 0.43 (95% CI: 0.33, 0.54)



Patients at risk	0	2	4	6	8	10	12	14	16	18	20	22
¹⁷⁷ Lu-PSMA-617	234	216	174	150	125	82	64	45	20	10	2	0
Change of ARPI	234	197	126	79	65	36	21	12	8	4	1	0

	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	

Kastrasyona Dirençli Metastatik Prostat kanseri Lutesyum 177 Tedavisi-Dosetaksel Öncesi



*Three patients died before receiving $^{177}\text{Lu-PSMA-617}$.

ITT analysis

	$^{177}\text{Lu-PSMA-617}$ (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

	$^{177}\text{Lu-PSMA-617}$ (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)	

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?

ENZA-p schema

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

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

Risk Factors for Early Treatment Failure on Enzalutamide

- LDH ≥ULN
- ALP ≥ULN
- Albumin <35g/L
- De novo metastatic disease at diagnosis
- <3 Years since initial diagnosis
- >5 Bone metastases
- Visceral metastases
- PSA doubling time <84 days
- Pain requiring opiates >14 days
- Prior abiraterone

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

1:1

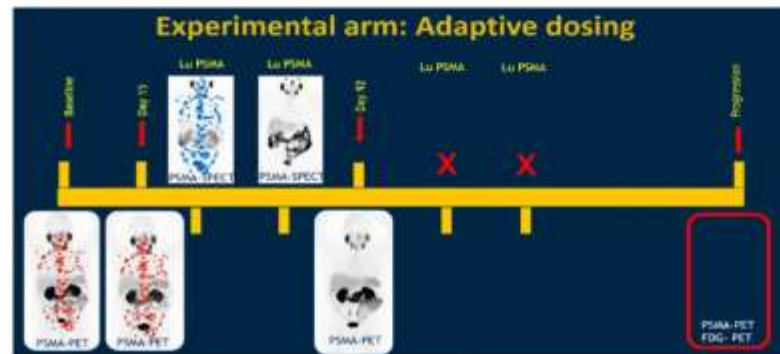
Enzalutamide 160 mg

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

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

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

Emmett L et al ESMO 2023 LBA84

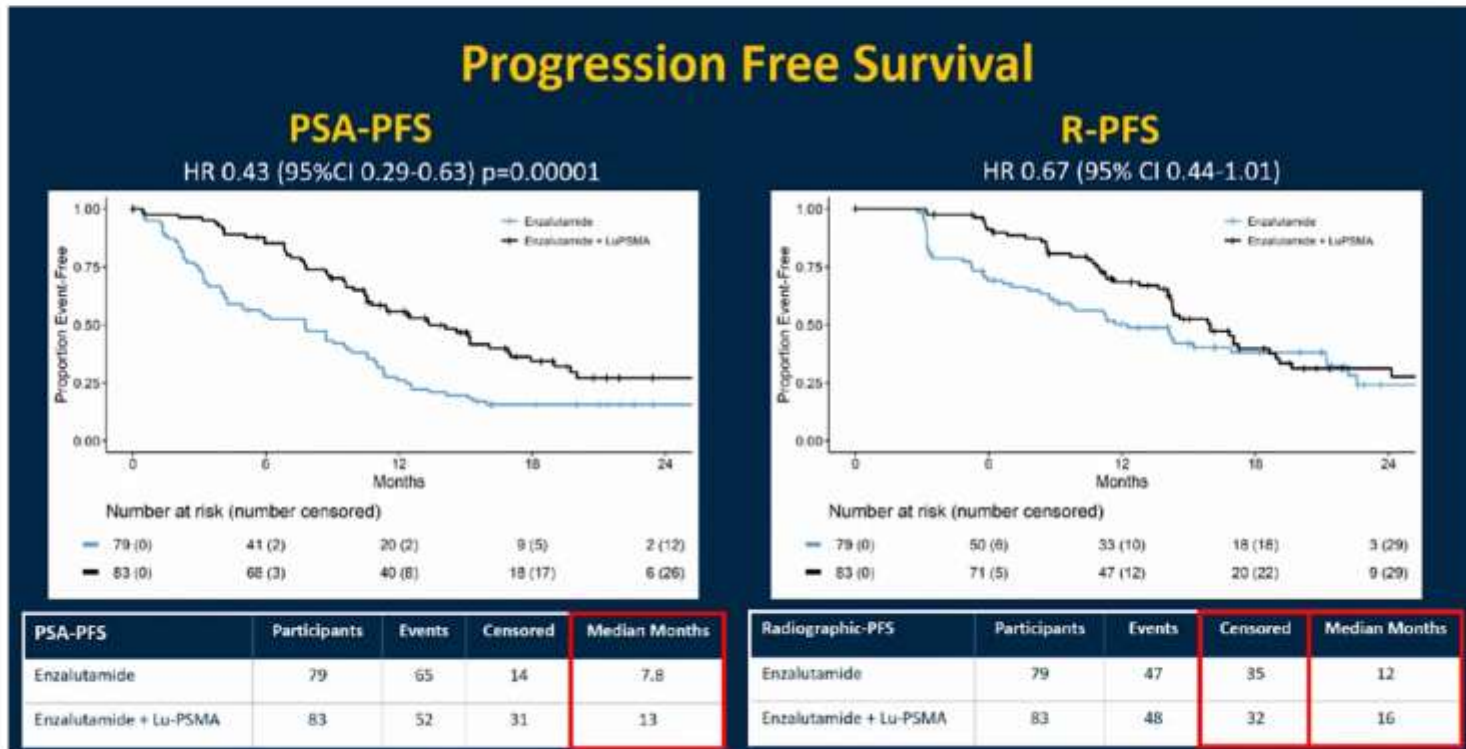


2-4 doses given adaptively based on PSMA PET response, with further dosing only for those with PSMA-avid persistent disease

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

Enza-p Results

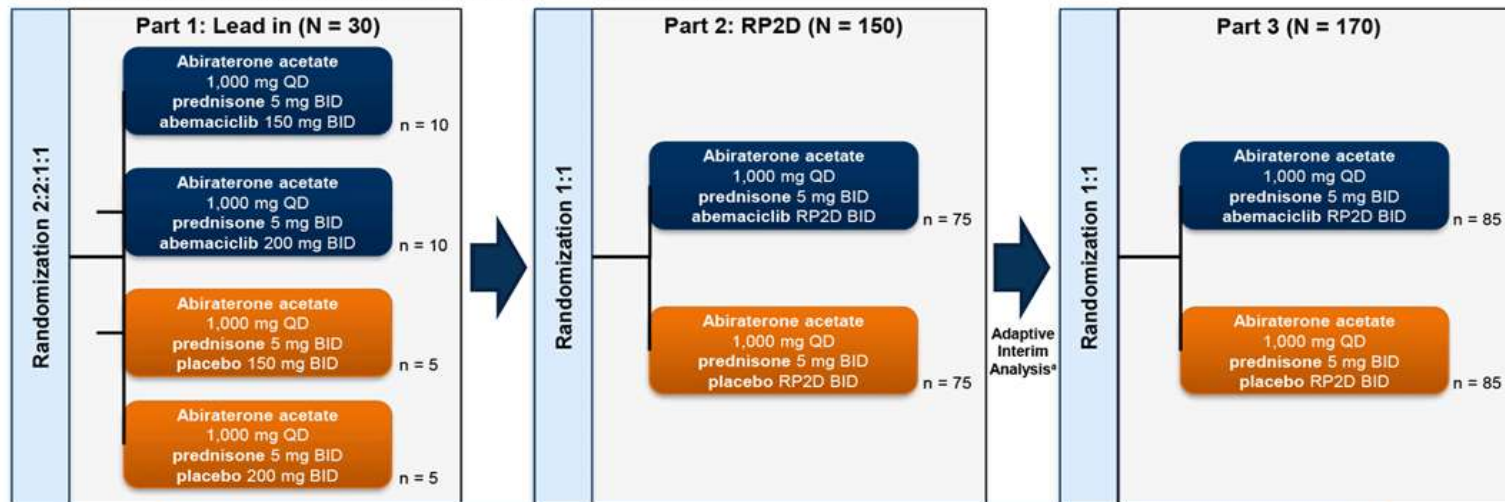
PSA50 93% (combo) vs 68% (enza alone)
 Similar adverse event profile except slightly more dry mouth (40% vs 10%) and anemia (14% vs 3%)



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

Phase 3 CYCLONE 2: CDK4/6 Inhibition in mCRPC¹

Abiraterone + Prednisone ± Abemaciclib in mCRPC



Primary endpoint of rPFS not met; overall safety and tolerability profile was consistent with the known profiles of the agents²

^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>.

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

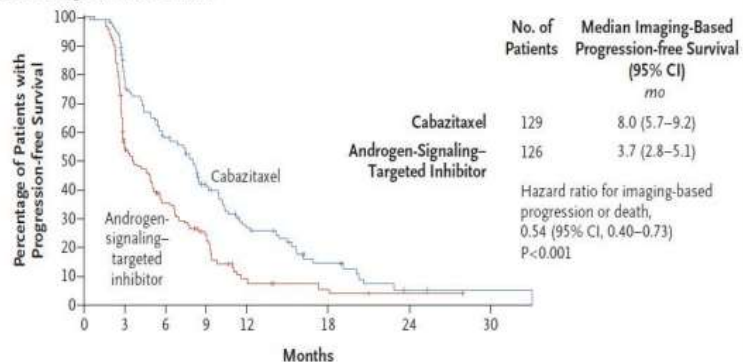
“Phase 3 CYCLONE-2 results [demonstrated that] abemaciclib added to abiraterone **did not meet the primary endpoint of improved radiographic progression-free** survival in men with metastatic castration-resistant prostate cancer (mCRPC); the overall safety and tolerability profile was consistent with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

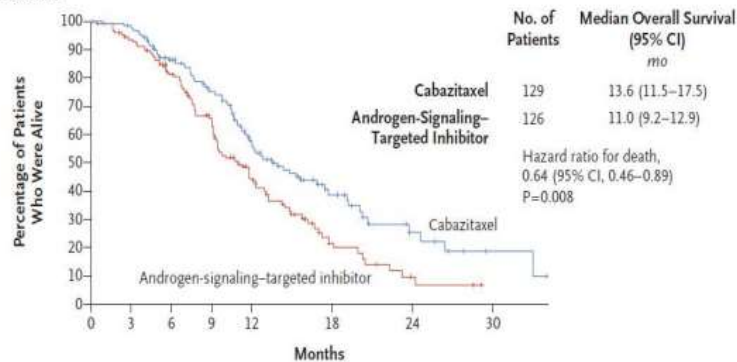
A Imaging-Based Progression-free Survival



No. at Risk

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

A Overall Survival



No. at Risk

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

Kastrasyona Dirençli Metastatik Prostat kanseri Kabazitaksel Tedavisi

CARD: Select Adverse Events

Table 2. Adverse Events (Safety Population).

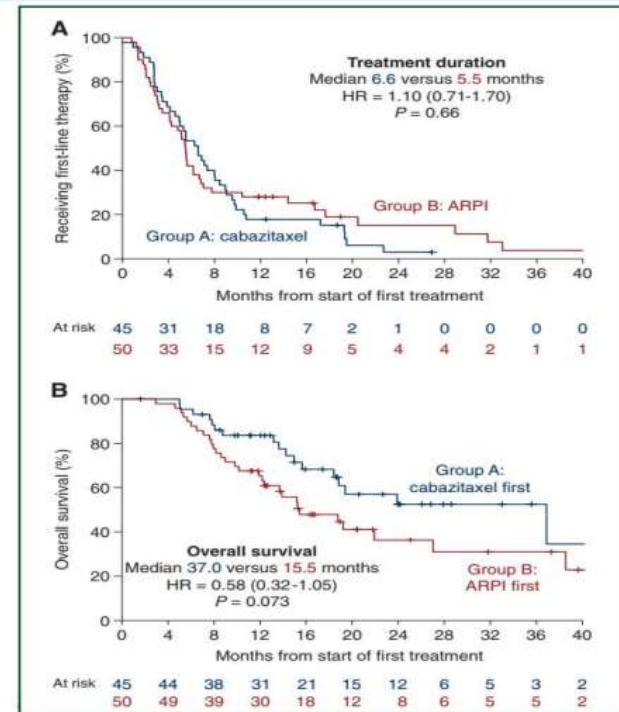
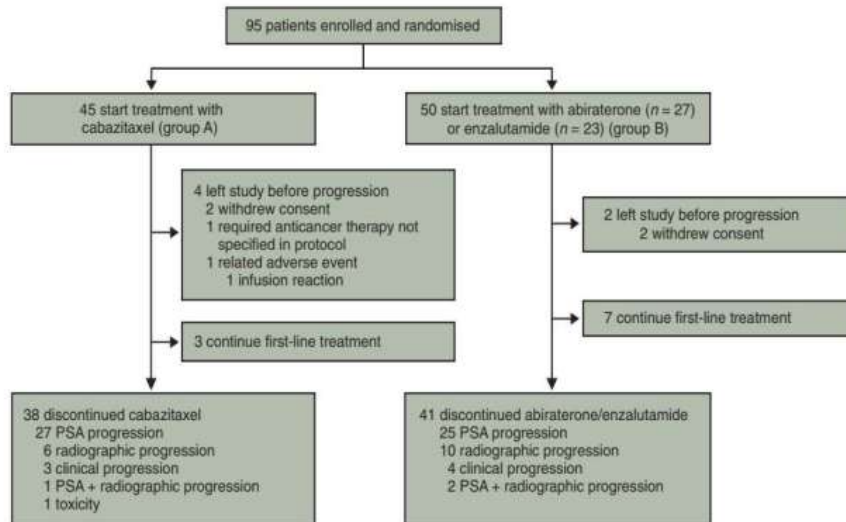
Event	Cabazitaxel (N = 126)		Androgen-Signaling-Targeted Inhibitor (N = 124)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Any adverse event — no. (%)	124 (98.4)	—	117 (94.4)	—
Any grade ≥3 adverse event — no. (%)	—	71 (56.3)	—	65 (52.4)
Any serious adverse event — no. (%)	49 (38.9)	—	48 (38.7)	—
Any adverse 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)

Kastrasyona Dirençli Metastatik Prostat kanseri Kabazitaksel Tedavisi

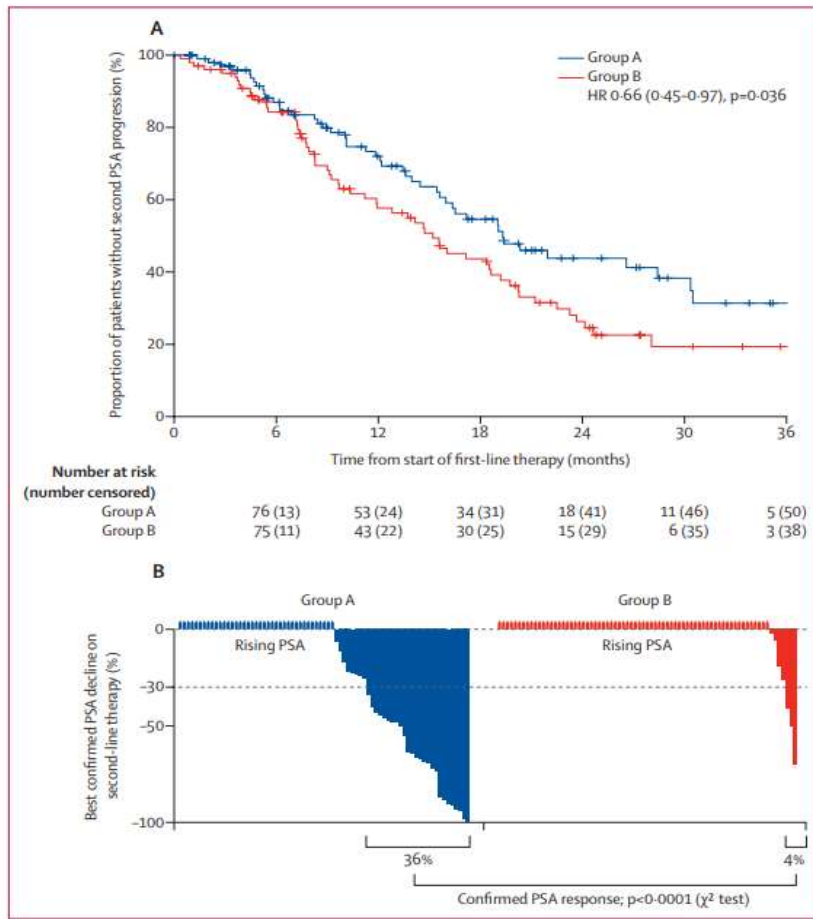
The Canadian Trial (Phase II OZM-054 Trial)

Poor prognosis:

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



Kastrasyona Dirençli Metastatik Prostat kanseri Ardışık Androjen Reseptör yolağı blokörleri



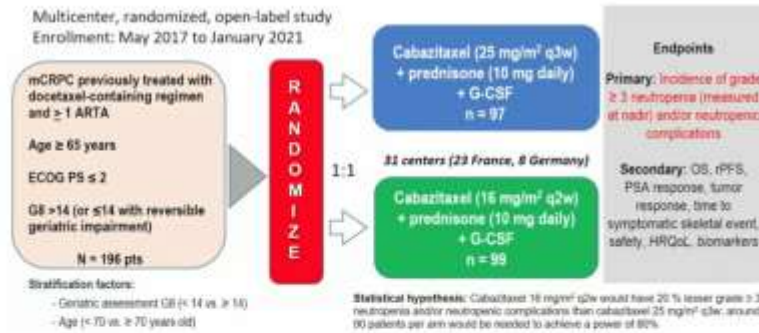
A-Abirateron progresyon sonrası ardışık Enzalutamid

B-Enzalutamid progresyon sonrası ardışık Abirateron

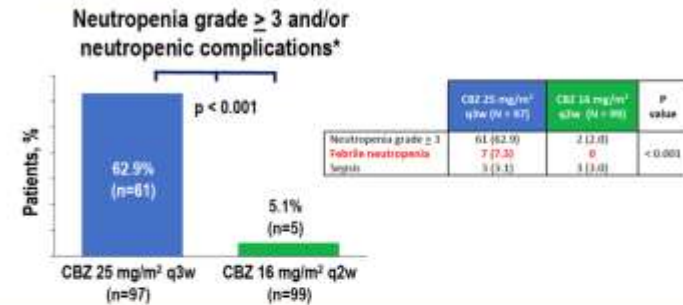
Kastrasyona Dirençli Metastatik Prostat kanseri Kabazitaksel Tedavisi

Other Recently Reported Trials Investigating Cabazitaxel for mCRPC

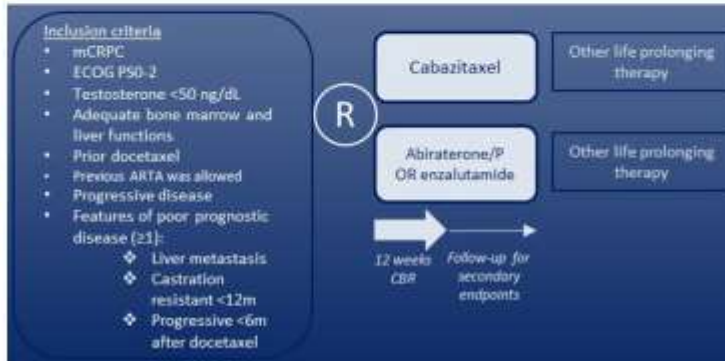
CABASTY¹



PRIMARY ENDPOINT



OSTRICH²

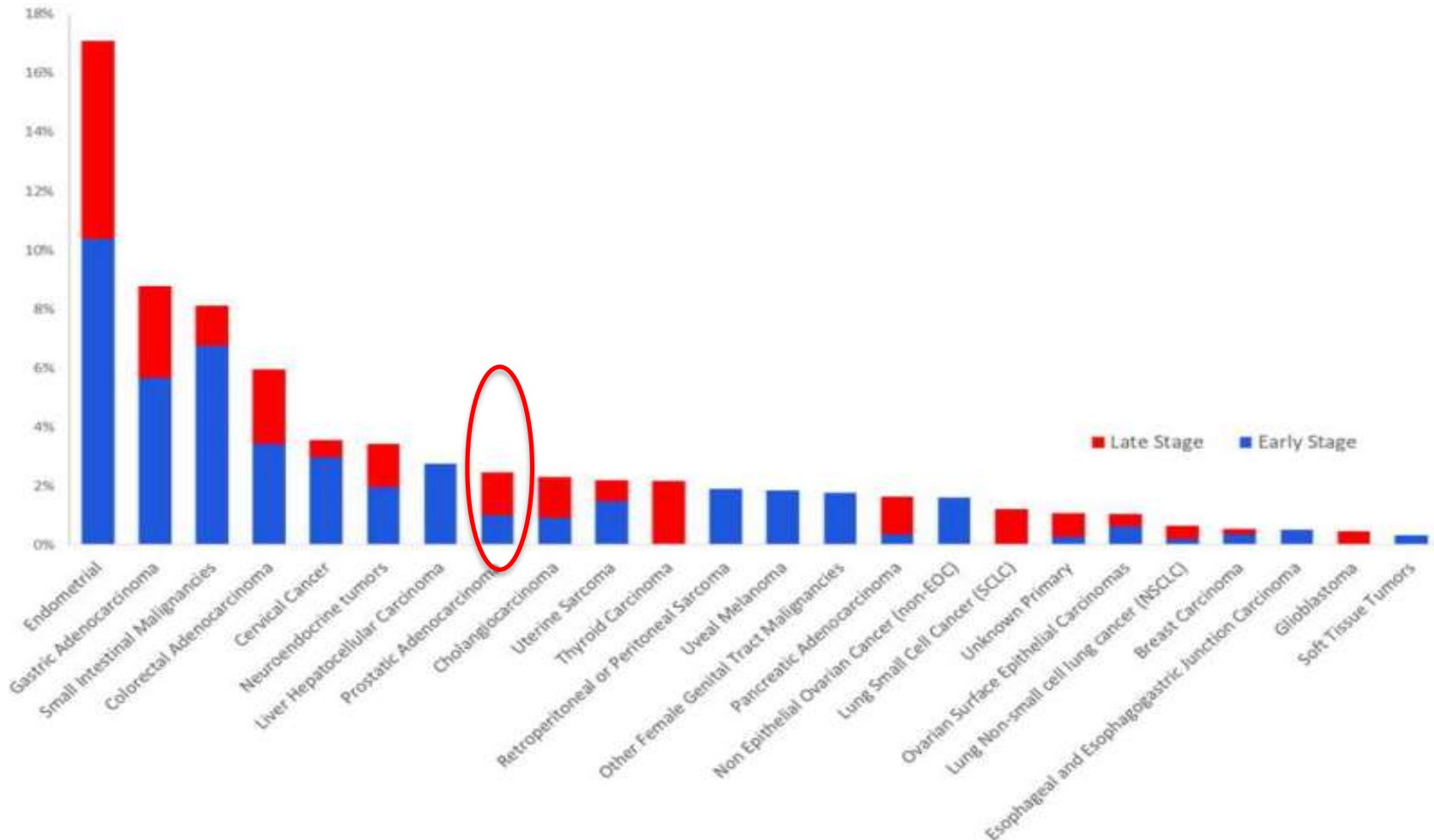


Conclusions

- 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.

Kastrasyona Dirençli Metastatik Prostat kanseri Mismatch Repair Deficiency



Kastrasyona Dirençli Metastatik Prostat kanseri

Mismatch Repair Deficiency

MSI-H and MRD

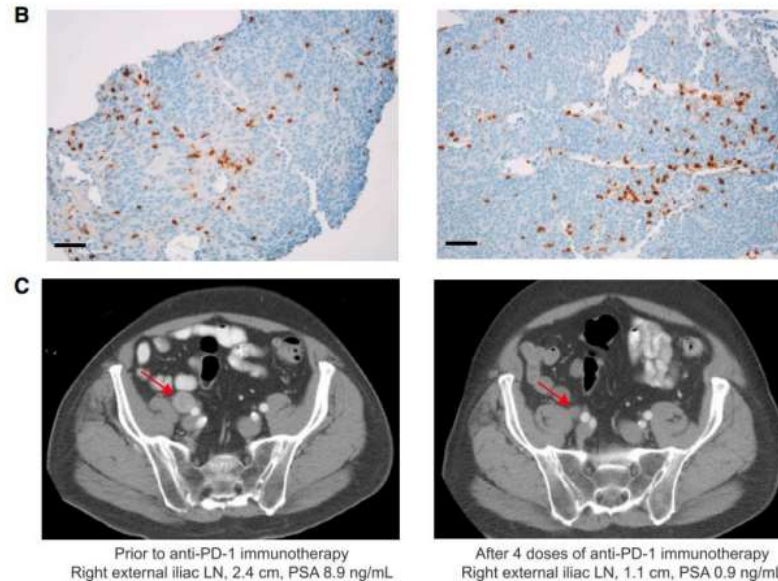
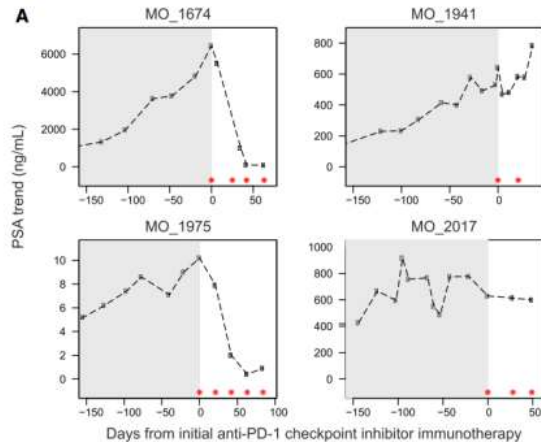
- 1346 patients with PC underwent paired tumor and germline sequencing
- 32 of 1033 (3.1%) had microsatellite instability–high or mismatch repair deficient disease
- 7/32 (21.9%) carried a germline mutation in a Lynch syndrome–associated gene.
- Five of 11 patients who received an anti–PD-1/PD-L1 agent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

Evre IV Kastrasyona Dirençli Prostat Kanseri İmmüne Checkpoint İnhibitörleri

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

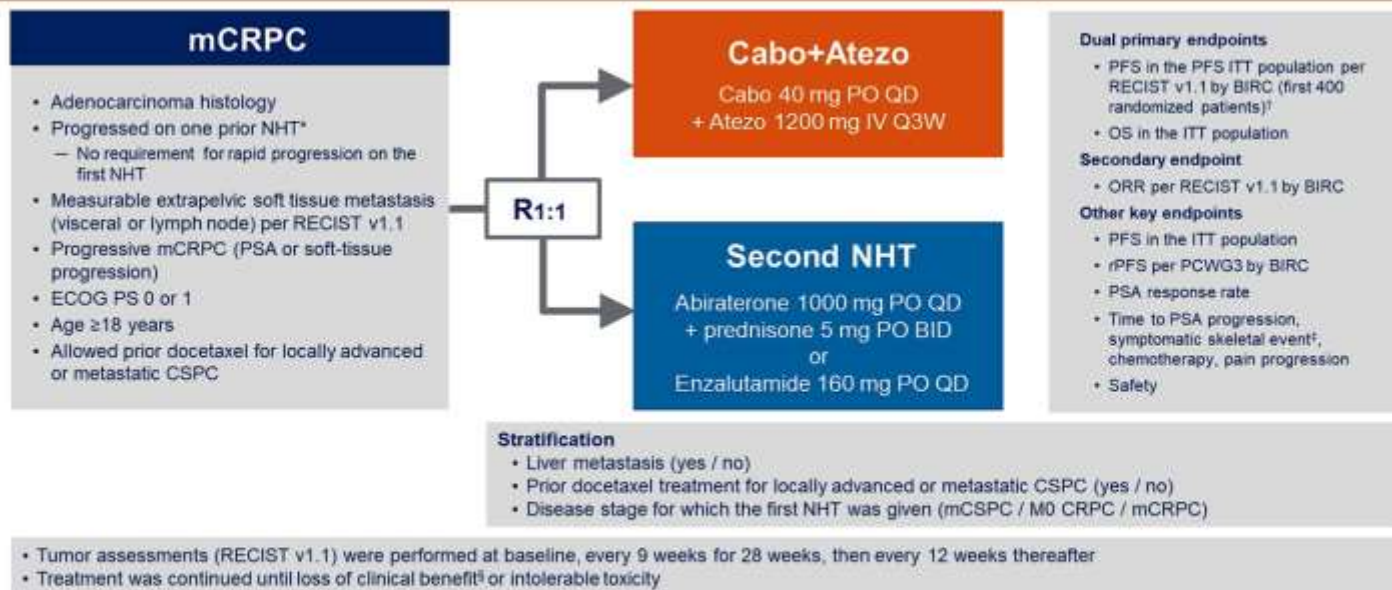
11 pts -5 tt anti PD1

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



Kastrasyona Dirençli Metastatik Prostat kanseri Cabozantinib ve Atezolizumab kombinasyonu

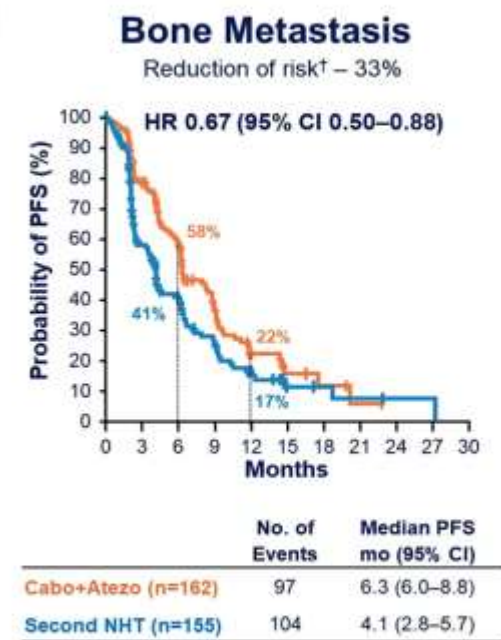
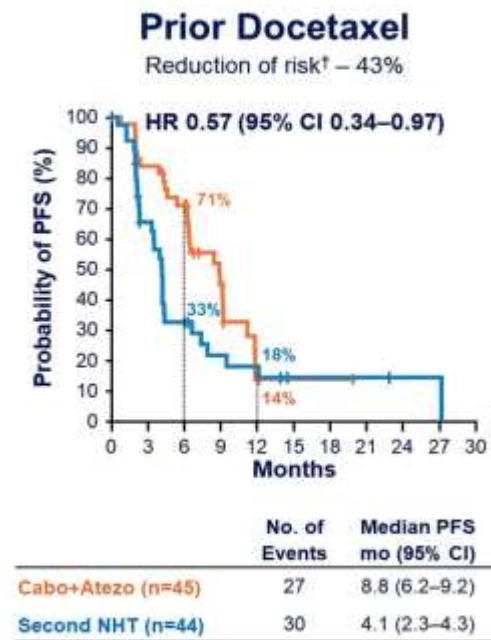
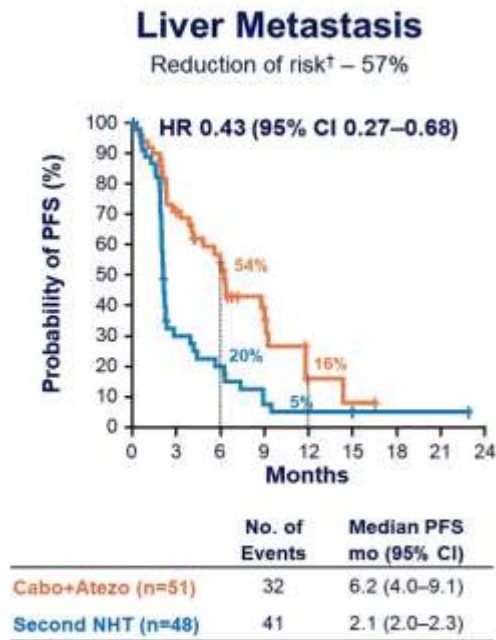
CONTACT-02 Study Design



BID, twice daily; BIRC, Blinded Independent Radiology Committee; CSPC, castration-sensitive prostate cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; ITT, intention-to-treat; IV, intravenous; M0 CRPC, non-metastatic CRPC; mCSPC, metastatic CSPC; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PO, orally; PSA, prostate specific antigen; QD, once daily; Q3W, every 3 weeks; PCWG3, Prostate Cancer Working Group 3; RECIST, Response Evaluation Criteria in Solid Tumors. *NHT for the treatment of mCSPC, M0 CRPC, or mCRPC. ¹Bone scan assessment not included in analysis. ²Time to symptomatic skeletal event is defined as time from randomization to earliest of any of the following: radiation therapy to bone, surgery to bone, spinal cord compression, or symptomatic fracture. ³Patients may be treated beyond progression if there is clinical benefit in the opinion of the investigator.

Kastrasyona Dirençli Metastatik Prostat kanseri Cabozantinib ve Atezolizumab kombinasyonu

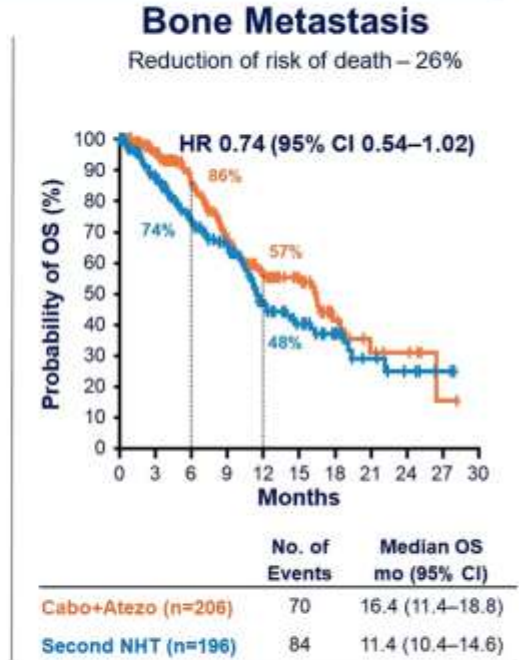
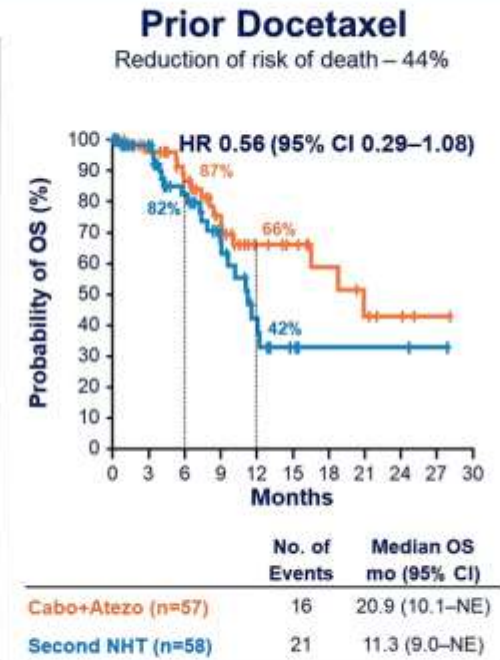
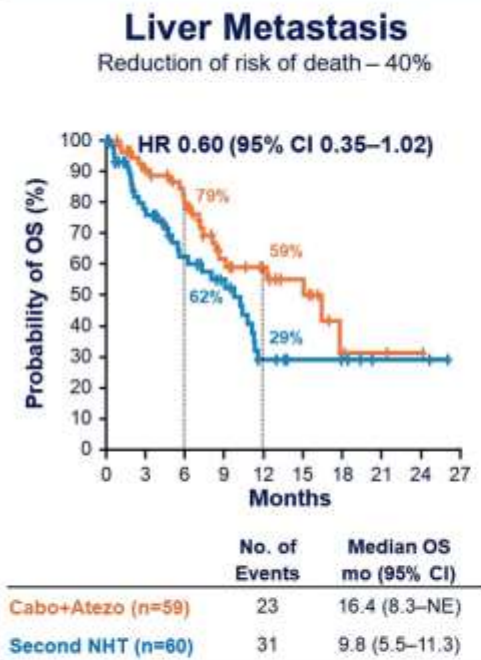
PFS per BIRC in Prespecified Subgroups*



*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*



NE, not evaluable. *ITT population.

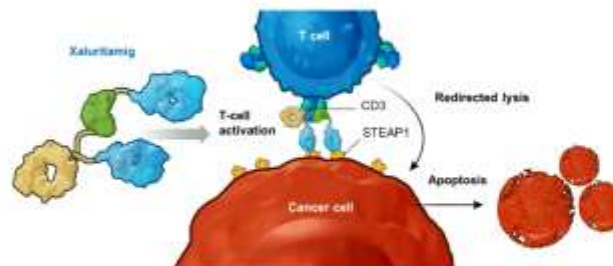
Kastrasyona Dirençli Metastatik Prostat kanseri Gelecek perspektif

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 prognosis¹
- STEAP1 is a cell surface antigen highly expressed in prostate cancer and associated with poor survival^{2,3}
- In preclinical studies, xaluritamig showed broad anti-cancer effects in prostate cancer xenograft models³



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. Toso F, et al. *Res Rep Urol* 2022;14:239-50.
2. Xu M, et al. *Cancers (Basel)* 2022;14:4534.
3. Miller-Sivasa O, et al. *Cancer Res* 2020;80(18, Supplement):DDT03-05.
4. U C, et al. *J Immunother Cancer* 2020;8:718.



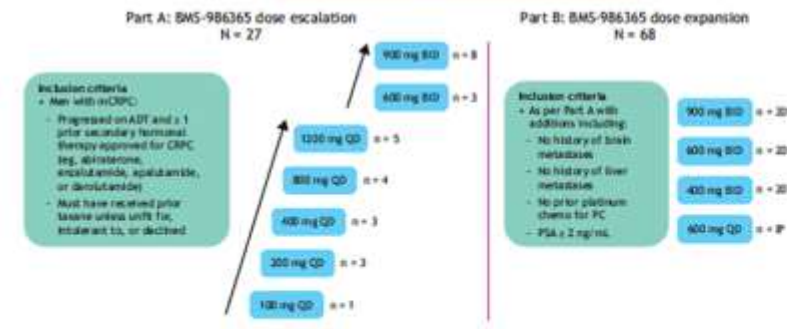
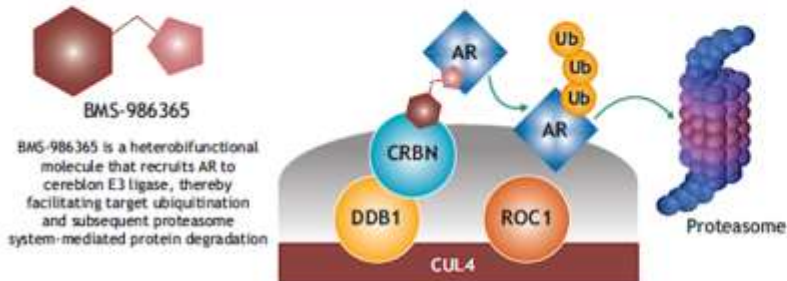
Granada Auditorium - Hall 3

MADRID SPAIN 20-24 OCTOBER 2023

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

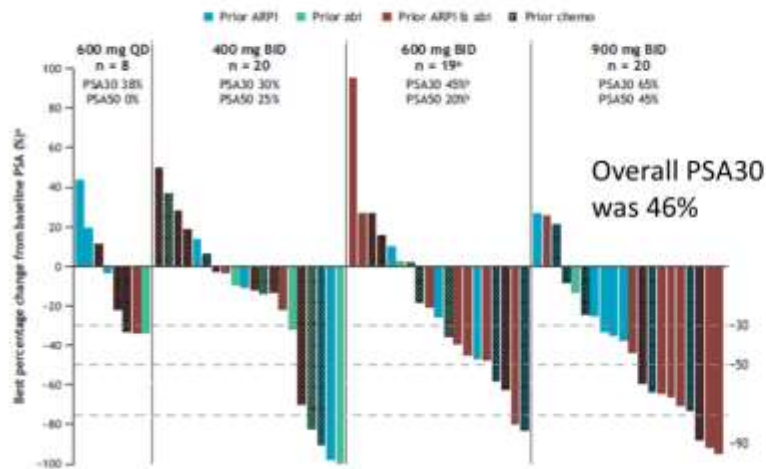
Rathkopf D...Armstrong AJ ASCO GU 2024 abstract 134



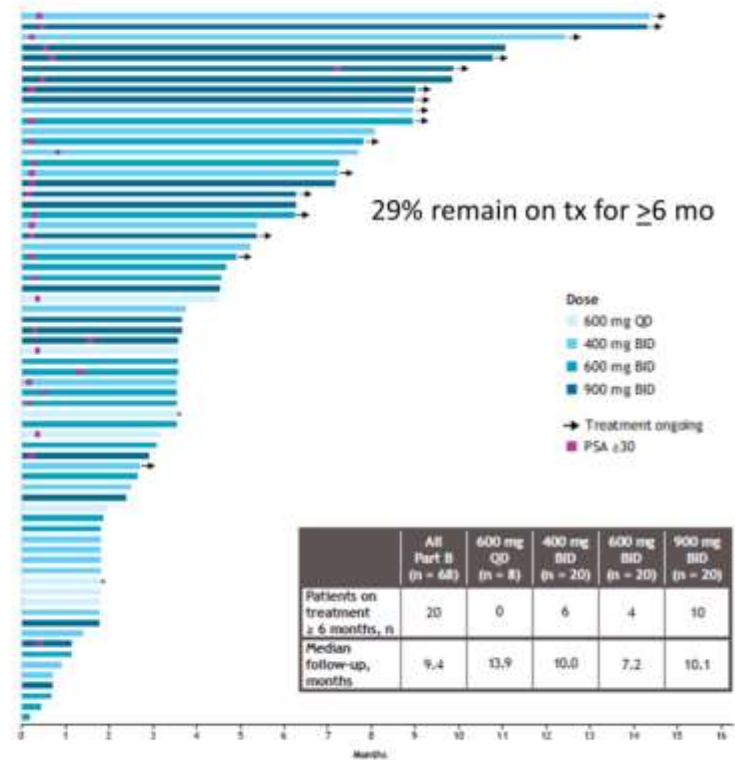
	Part A Dose escalation (n = 27)	Part B Dose expansion (n = 68)	All patients (N = 95)
Median age, years (range)	72 (49-83)	71 (50-87)	71 (49-87)
≥ 75 years, n (%)	7 (26)	24 (35)	31 (33)
Race, n (%)			
White	24 (89)	57 (84)	81 (85)
Black	2 (7)	3 (4)	5 (5)
Asian	1 (4)	3 (4)	4 (4)
Unknown	0	5 (7)	5 (5)
ECOG 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)*	5 (5)*
Visceral lung	4 (15)	7 (10)	11 (12)
Median serum PSA, $\mu\text{g/L}$ (range)	96 (1-1699)	37 (3-1610)	51 (1-1699)
Median number of prior regimens (range) [†]	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*	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



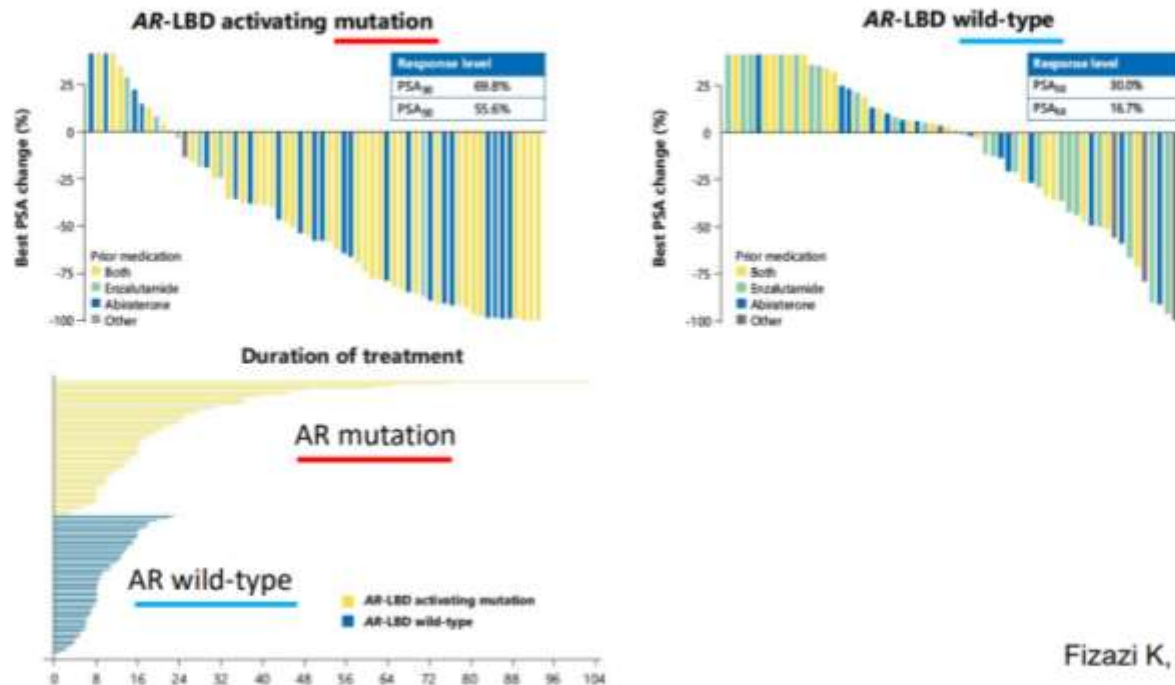
TEAE, n (%)	Part A Dose escalation (n = 27)		Part B Dose expansion (n = 48)		All patients (n = 75)	
	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4
Patients with ≥ 1 TEAE	26 (96)	8 (30)	65 (96)	24 (35)	91 (96)	32 (34)
QTc prolongation	7 (26)	2 (7)	32 (47)	6 (9)	39 (41)	8 (8)
Fatigue	7 (26)	0	24 (35)	5 (4)	31 (33)	3 (3)
Bradycardia ^b	5 (19)	0	23 (34)	0	28 (30)	0
Nausea	11 (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 = 48)	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

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.

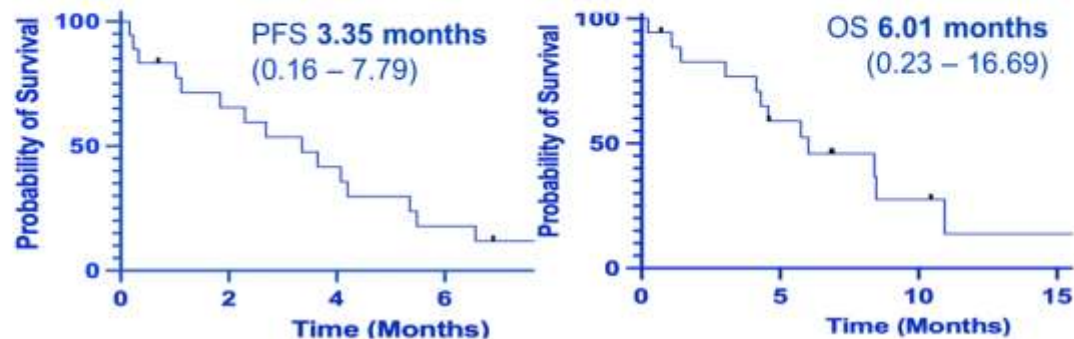


- Targeting more aggressive prostate cancers
 - Patients were randomly assigned (1:1) to intravenous cabazitaxel 25 mg/m² with or without intravenous carboplatin AUC 4
 - At a median follow-up of 31.0 months, the combination improved the median PFS from 4.5 months to 7.3 months (95% CI 0.50–0.95, p=0.018)
 - All toxicities were worse with the combination
 - Myelosuppression
 - Fatigue, nausea, others

Kastrasyona Dirençli Metastatik Prostat kanseri Nöroendokrin diferansiasyon

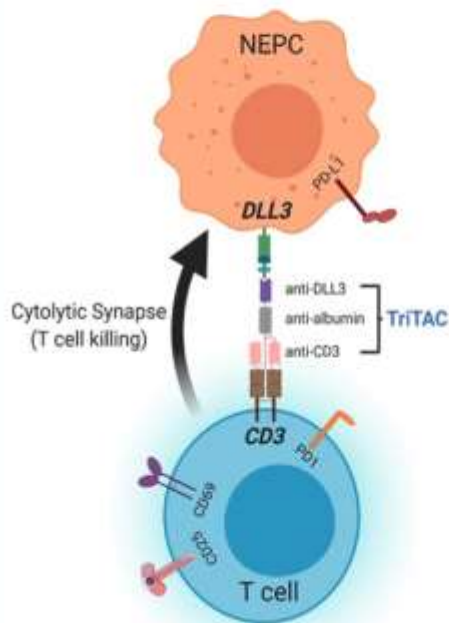
Lurbinectedin in Small Cell NEPC

- 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

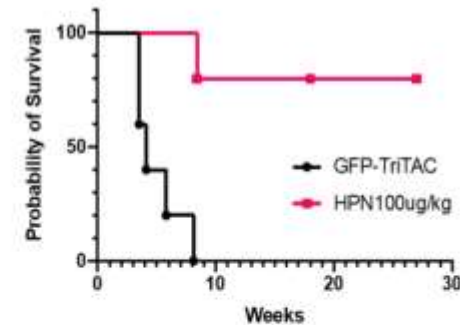
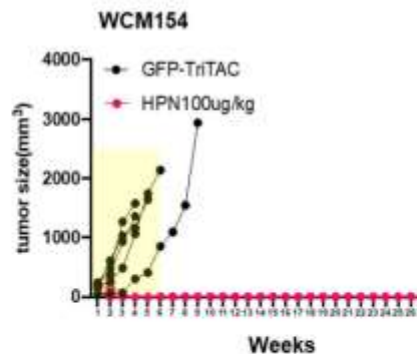


Kastrasyona Dirençli Metastatik Prostat kanseri Nöroendokrin diferansiasyon

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

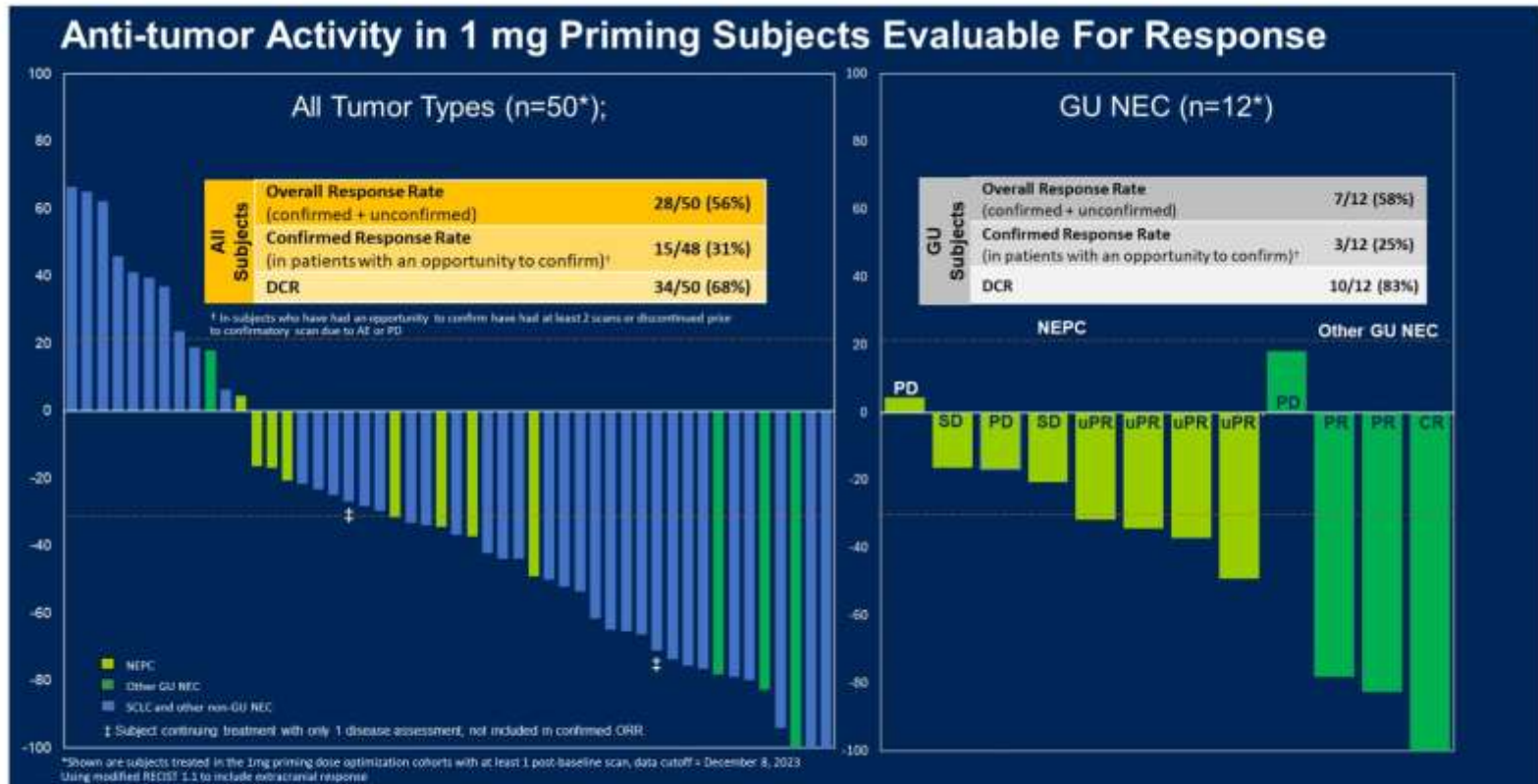


Anti-tumor activity *in vivo*: DLL3+ WCM154 Patient- Derived NEPC Xenografts



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