Kastrasyona Dirençli Metastatik Prostat Kanserinde Vaka Eşliğinde Tedavi

Dr. Deniz Tural
Bakırköy Dr. Sadi Konuk Eğitim ve Araştırma Hastanesi
Tıbbi Onkoloji

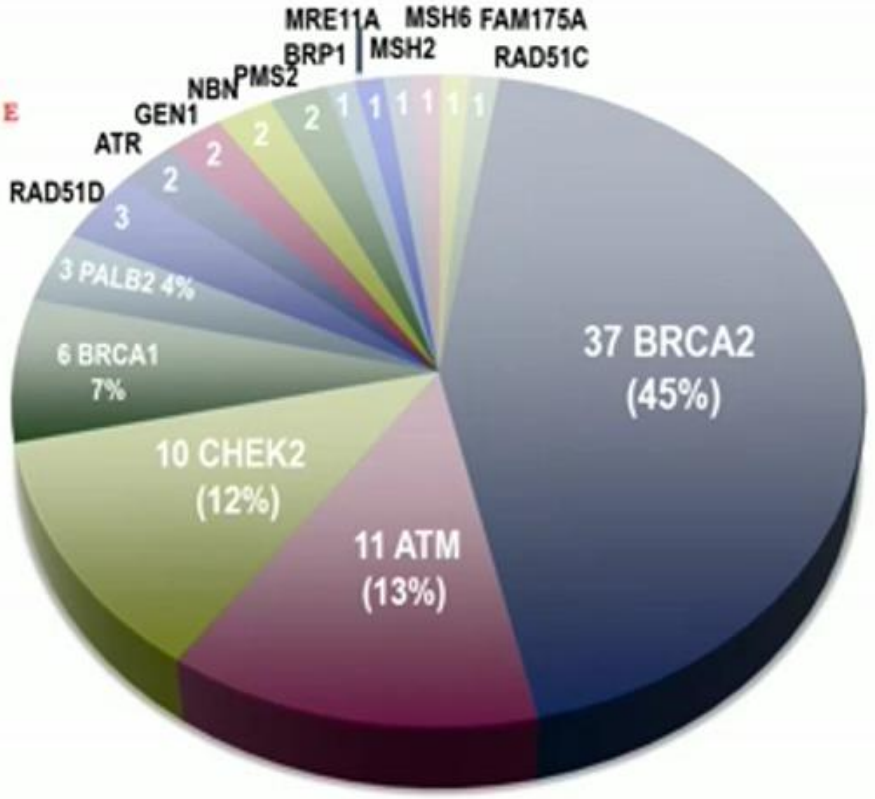
Prostat Kanseri Risk Faktörleri

GENETIC TESTING

Our new and shiny…

The NEW ENGLAND JOURNAL of MEDICINE

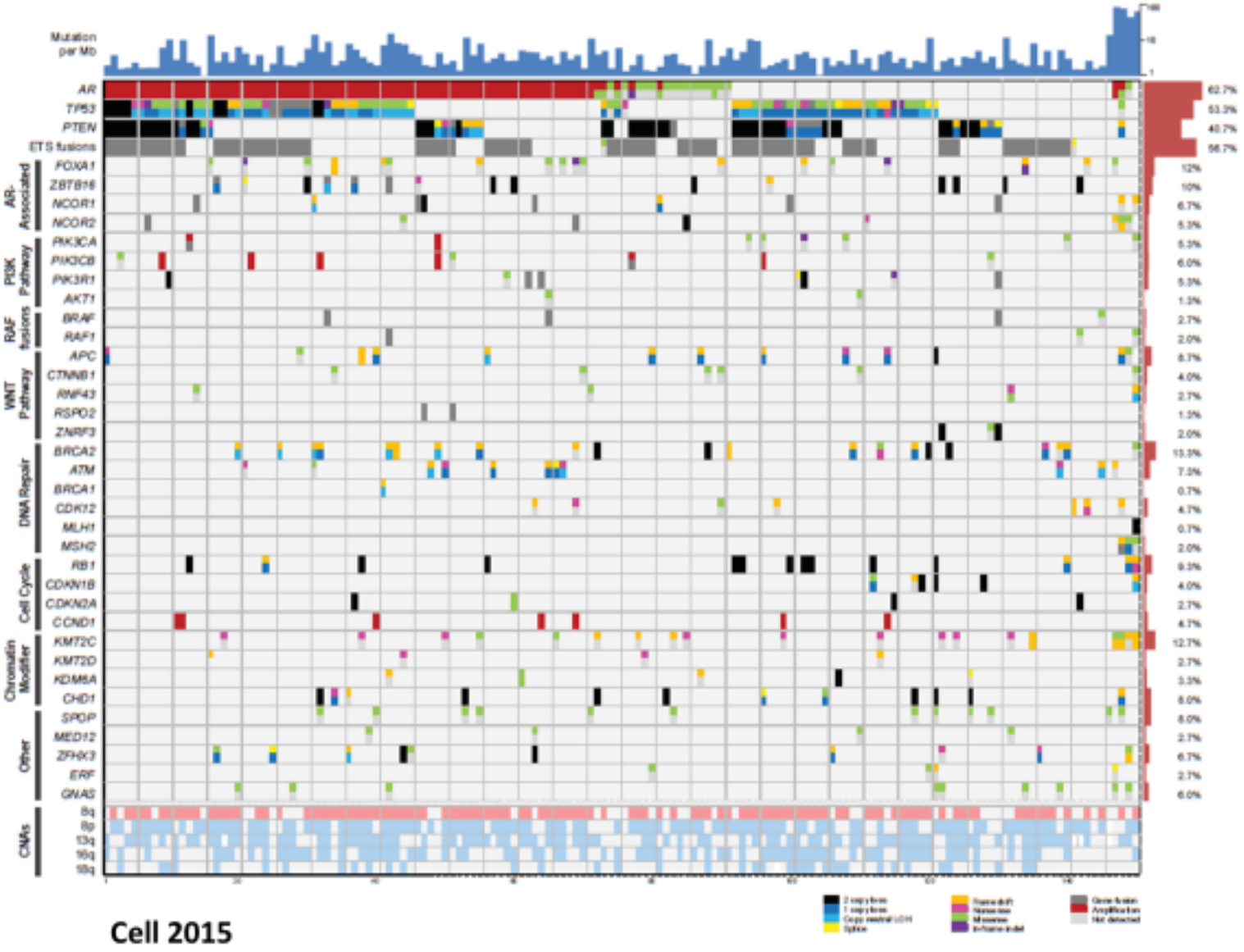
Inherited DNA-Repair Gene Mutations in Men with Metastatic Prostate Cancer



692 patients with metastatic PrCa Tested

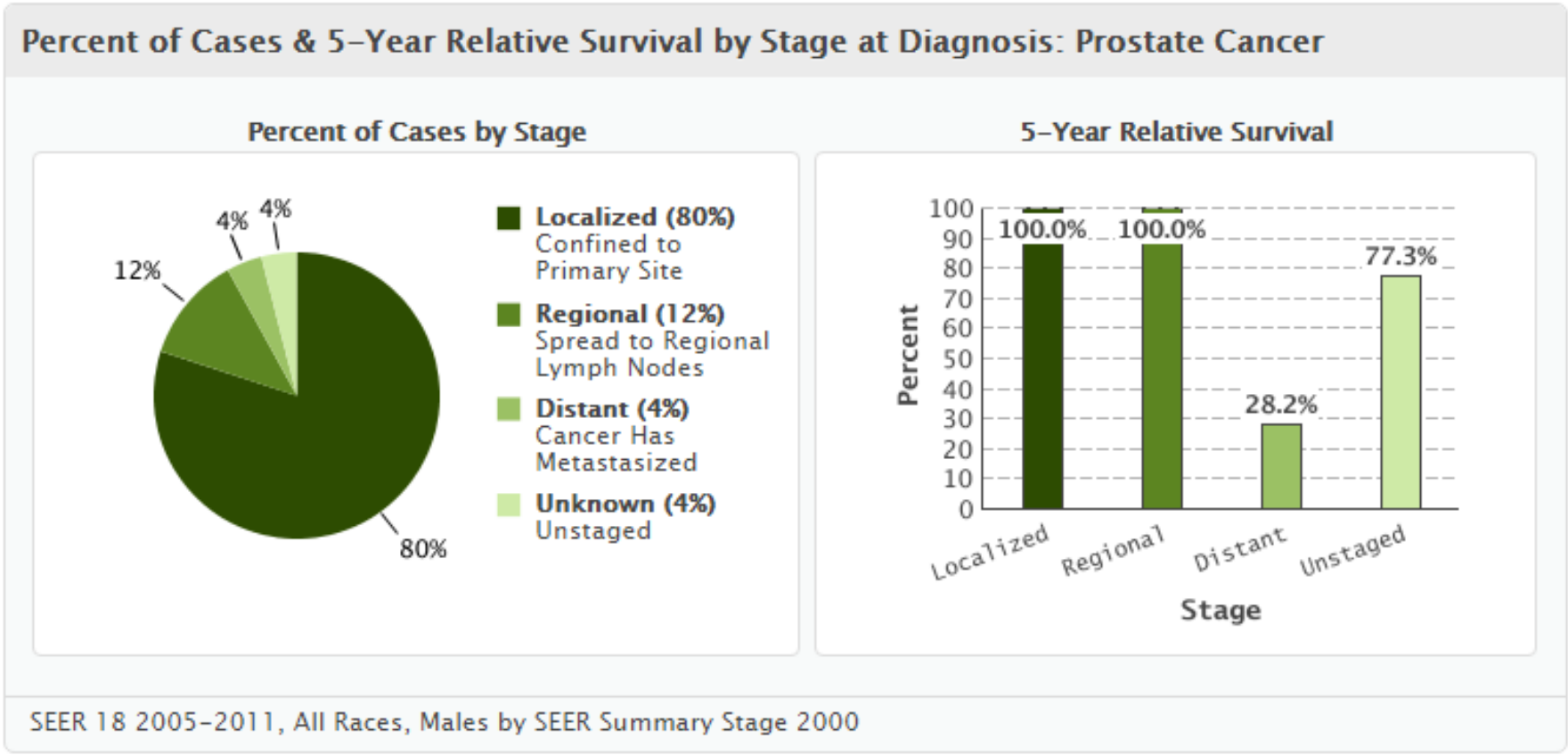
Pritchard, NEJM, 2016

Prostat Kanseri Genomik Profil

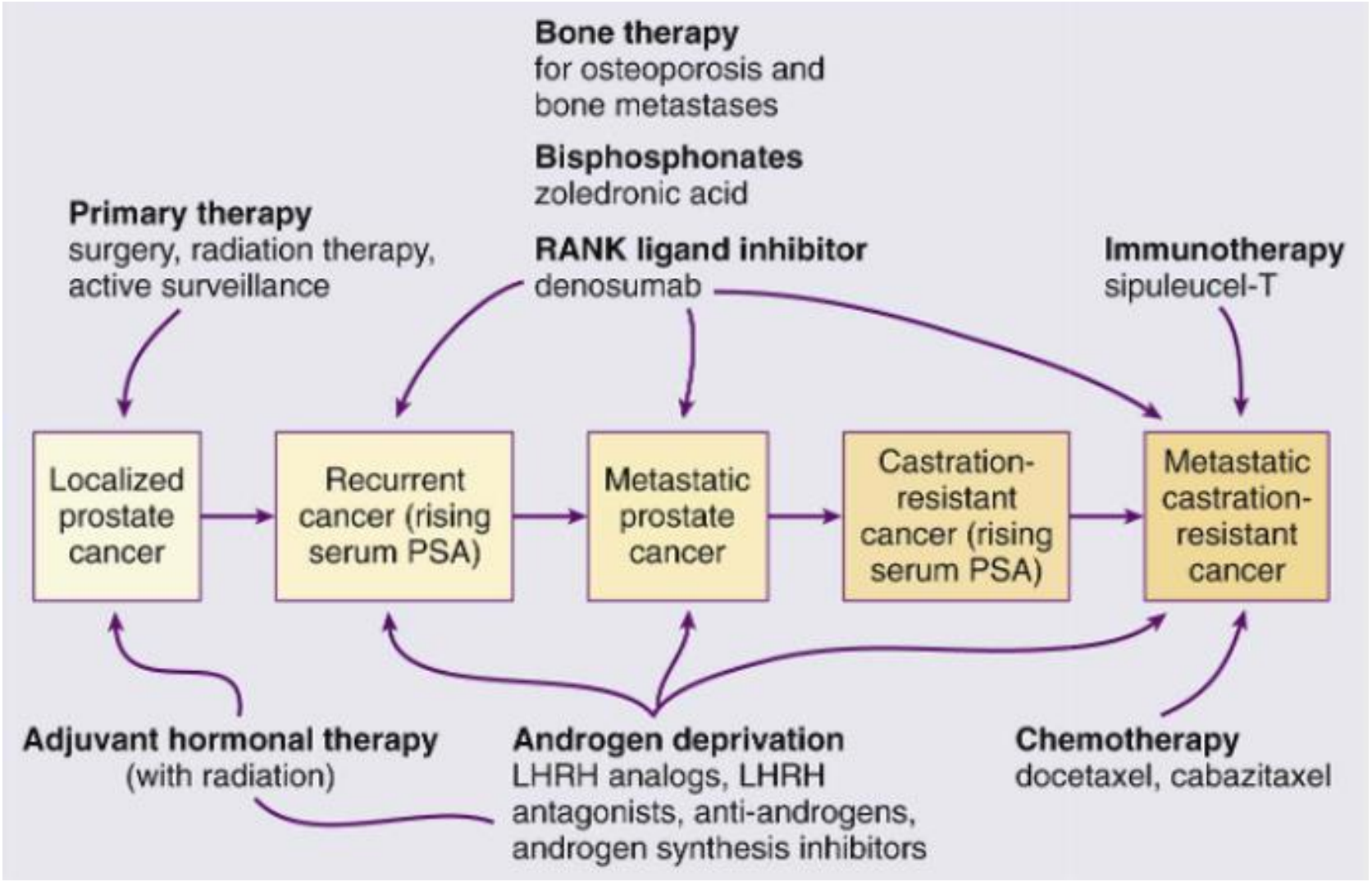


Cell 2015

Prostat Kanseri İnsidans ve Mortalite



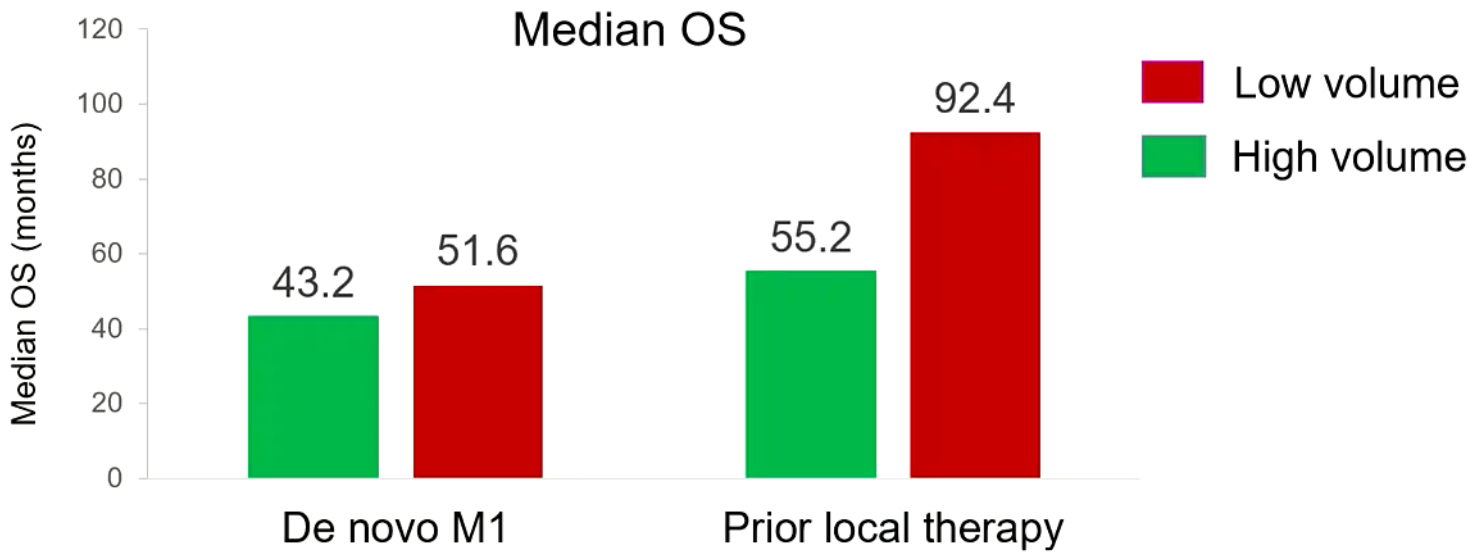
Prostat Kanseri Tedavi Yaklaşımları



Abeloff's Clinical Oncology, 10th edition

Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

De Novo mHNPC is associated with a worse prognosis



Retrospective analysis of 436 consecutive patients with M1 HSPC treated with ADT between 1990 and 2013 at the Dana-Farber Institute

Francini E, et al. The Prostate 2018;78:889-95.

Vaka Sunumu

- 73 yaşında
- Tip2 DM , glifor 1000 mg 2x1
- İdrar yaparken zorlanma ile başvuruyor
- PSA değeri(09/2014): 69 ng/ml saptanıyor
- Prostat biyopsisi(10/2014) yapılıyor
- Pelvik MR: cT3aN0

Prostat Biyopsi(10/2014)

Tetkik Adı	Rapor Bilgileri	Kabul Tarihi	Panik	D
Histokimyasal Boyamalar	2008 / P - 2307	19/02/2008		Y
Kolon, Biyopsi	2008 / P - 8732	13/06/2008		Y
Patoloji	2014 / P - 39646	21/10/2014		Y
Histokimyasal Boyamalar	2015 / P - 18150	30/04/2015		Y
Patoloji Tetkik	2020 / B - 6868	12/03/2020		Y

Tanı : ADENOKARSİNOMA ;
PROSTAT (4,7,10,14,16,17,18,19,20 kayıtlı doku örnekleri), TRU - CUT BİYOPSİ

sol bazis : 1 mm çapta tümör
sol dorsolateral : 3 mm çapta tümör
sol apeks : 1 mm çapta tümör
sağ bazis : 3 mm çapta tümör
sağ farlateral : 6 mm çapta tümör
sağ nodül : 8 mm çapta tümör
sağ nodül : 5 mm çapta tümör
sağ bazis : 3 mm çapta tümör
sağ apeks : 4 mm çapta tümör

BENİGN PROSTAT DOKULARI ;
PROSTAT (1,2,3,5,6,8,9,11,12,13,15 kayıtlı doku örnekleri), TRU - CUT BİYOPSİ

NotSERİ KESİTLERLE İNCELENEN DOKU ÖRNEKLERİNDE GLEASON SKOR : 8 (4+4)

Dokuz kadranda prostat adeno kanseri, gleason 4+4:8

Hasta için ideal evreleme nasıl olmalıdır

- 1-BT/MR ve TVS
- 2-PSMA-PET-CT
- 3-BT/MR ve TVS ya da PSMA PET-CT
- 4-Evreleme gerekmez

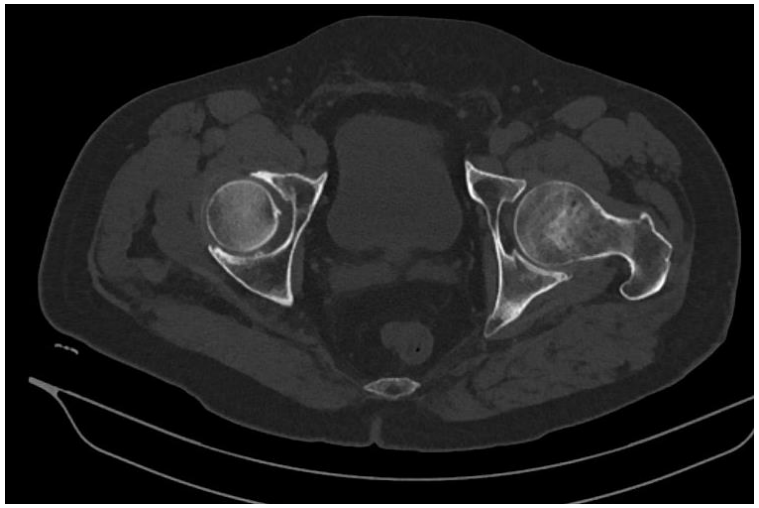
İdeal Evreleme Nasıl Yapılmalı

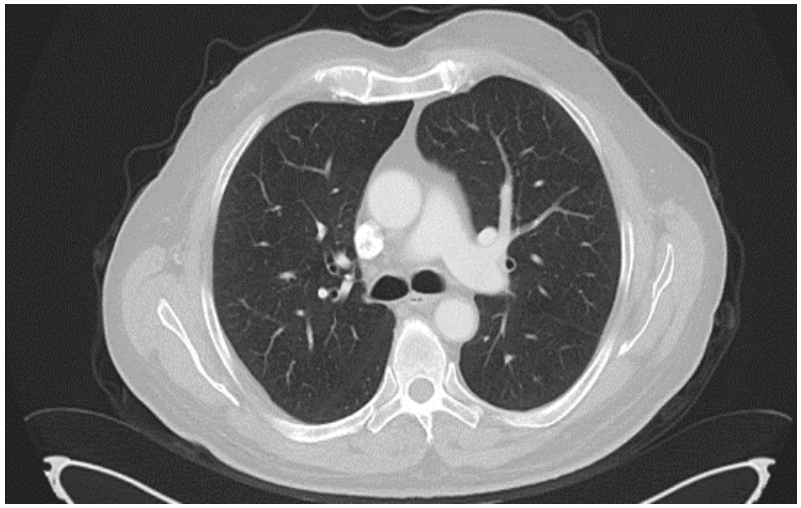
	Intermediate Risk T2b and GS7 and/or PSA 10-20	High Risk (or greater) ≥T2c or GS 9-10 or PSA>20	Biochemical Relapse / Progression
NCCN (ver 1.2023)	PSMA PET (unfavorable)	PSMA PET	PSMA PET
ESMO PAN-ASIAN ESMO	CT/MRI + Bone Scan or PSMA PET	CT/MRI + Bone Scan or PSMA PET	PSMA PET
EUA	CT/MRI + Bone Scan	PSMA PET or whole body MRI	PSMA PET

Unfavorable = ≥2 intermediate risk factors (cT2b-cT2c, GG 1 or 2, PSA 10-20) or GG3 or ≥ 50% biopsy cores positive

PRESENTED BY: David M. Nanus, M.D., Professor of Medicine and Urology, Weill Cornell Medicine

10/2014 Toraks-Batın BT





Viseral ve non-regional Lenf metastazı yok

10/2014 TVS

>> TÜM VÜCUT KEMIK SINTIGRAFISI : TÜM VÜCUT KEMİK SİNTİGRAFİSİ RAPORU
TEKNİK:
Tc-99m MDP'nin IV yoldan verildikten 4 saat sonra anterior ve posterior tüm vücut ve gerektiği takdirde SPECT ve bölgesel görüntüler alındı.
BULGULAR:
T8. vertebrada korpusunda ve orta servikal vertebraların (net lokalize edilememekle birlikte muhtemel C3) sol lateralinde osteoblastik artmış aktivite tutulumu izlenmektedir.
İskelet sisteminin diğer kısımlarında aktivite dağılımı normal sınırlardadır.
YORUM
- T8. vertebrada korpusunda ve orta servikal vertebraların (muhtemel C3) sol lateralinde osteoblastik aktivite tutulumu (Metastaz Dejeneratif değişiklikler MR ile değerlendirilmesi önerilir)
Uzm. Dr. Eylem BAŞTUĞ

De novo Oligometastatik(2kemik lezyonu) Kastrasyona Duyarlı Prostat Adeno CA

10/2014 Tedavi

- Prostat adeno ca, gleason 4+4: 8
- cT3aN0M1b(2 kemik lezyonu, de novo, kastrasyona duyarlı oligo metastaz
- Viseral metastazı yok
- CHARTED kriterlerine göre düşük volüm hastalığı

Bu Hasta İçin İdeal Tedavi Seçeneği

- 1-ADT
- 2-ADT+6 Kür Dosetaksel
- 3-ADT+Abireteron
- 4-ADT+Enzulutamid
- 5-ADT+LU-177
- 6-ADT+Abireteron/Darolutamide+Dosetaksel

Bifosfanat ya da RANK inh.?

- 1-Evet
- 2-Hayır

05.06.2015 Yanıt Değerlendirmesi

- Hastaya leuprolide asetat 22.5 mg
- Hastanın total PSA değeri : 0.23 ng/ml
- Total testosteron: 0.08 ng/ml
- TVS/BT yanıt değerlendirmesi: yeni lezyon yok

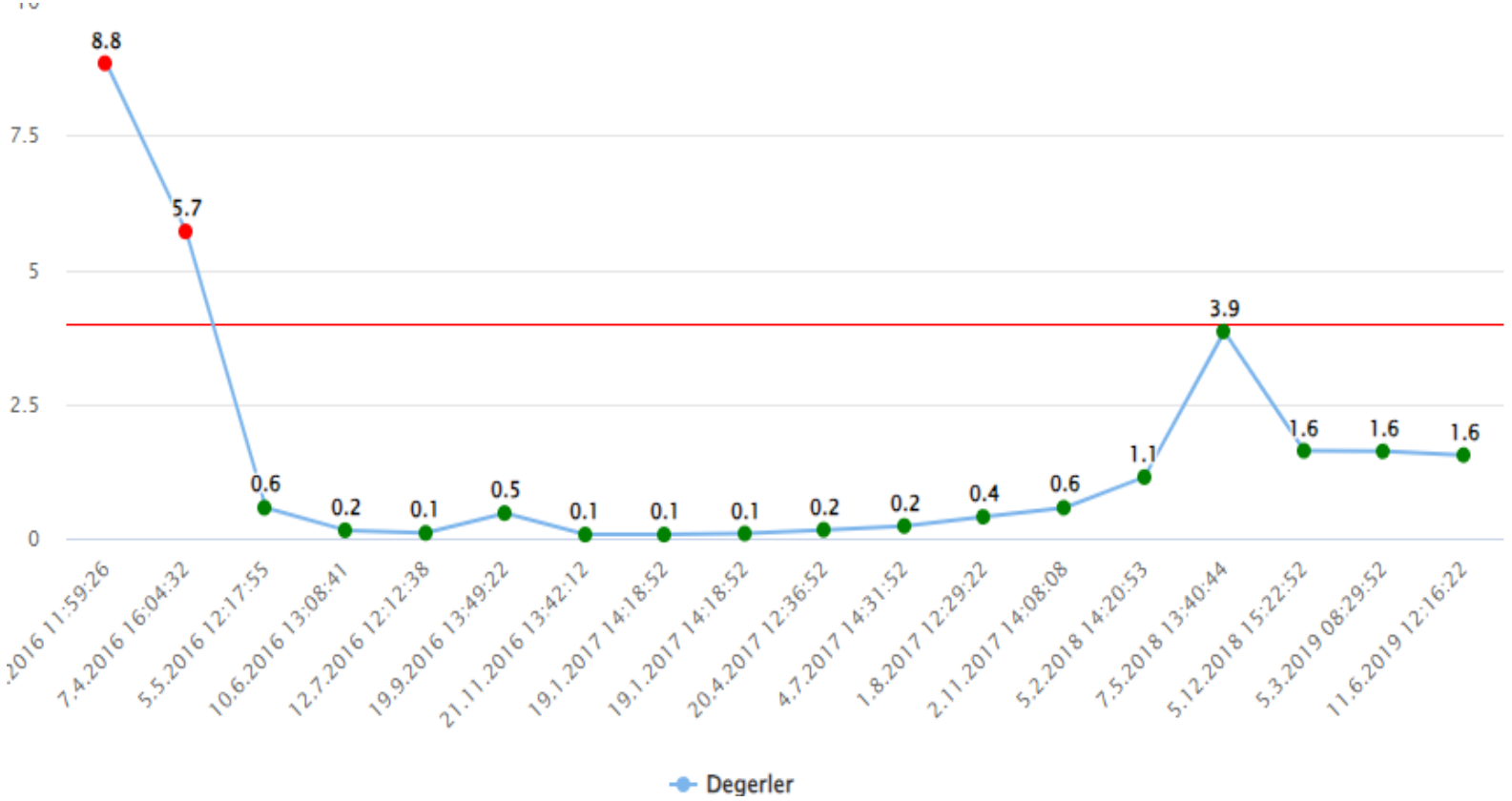
Tedavi Sonrası İdeal PSA değeri Ne Olmalı

- 1-PSA< 0.2 ng/ml
- 2-PSA<4 ng/ml
- 3-PSA> 4 ng/ml
- 4-PSA değeri önemsiz

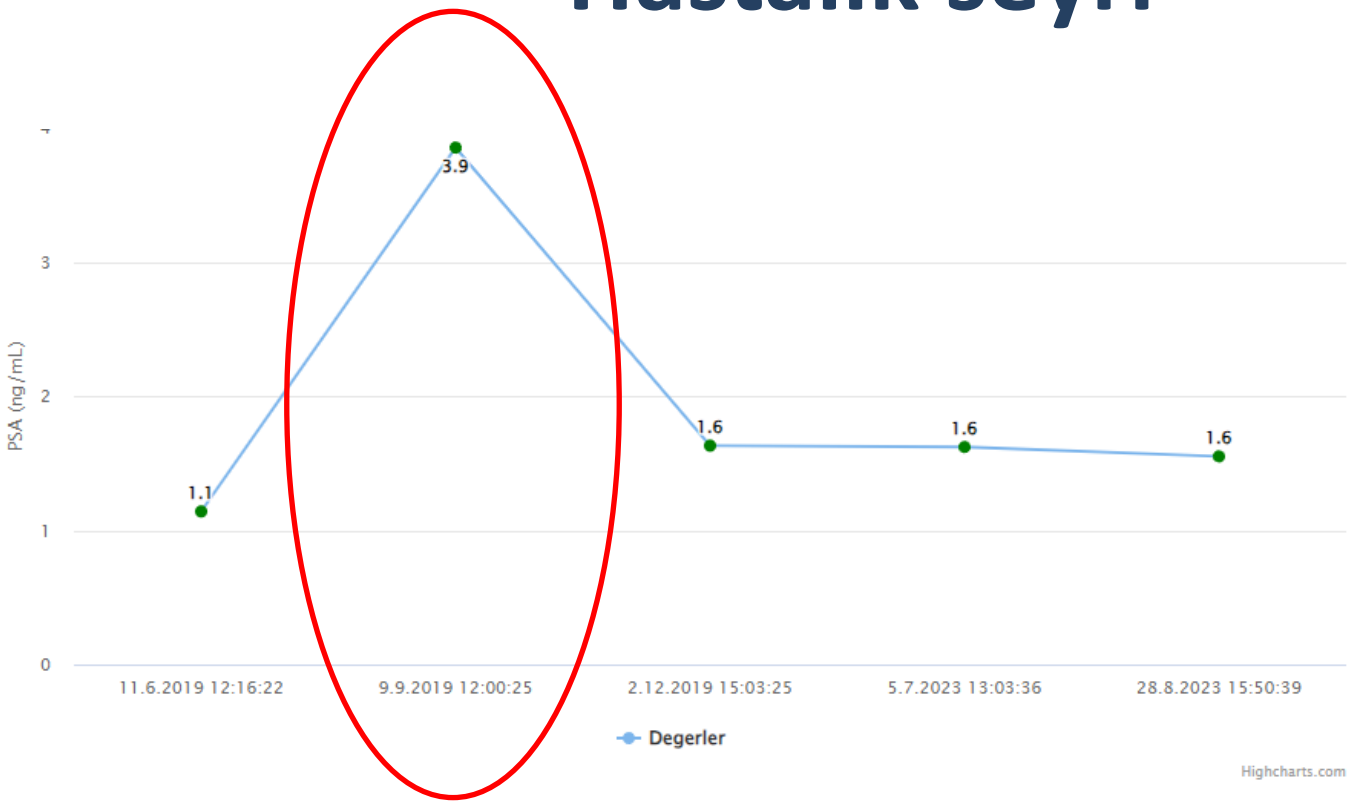
Tedaviye Devam

- Primer prostat ve pelvise EBRT
- T8, C3 lezyonlara SBRT
- Leuprolide asetat 22.5 mg/3 ayda bir devam

Hastalık seyri



Hastalık seyri



08/2019 Biyokimya-Hemogram

	Parametre Adı	Sonuc	Birim	Normal Değerler		Önceki Sonuc
↑	Glukoz	174	mg/dL	74	106	164 / 162.
	Üre	29	mg/dL	16.6	48.5	22 / 23.
	Kreatinin	0.73	mg/dL	0.7	1.2	0.72 / 0.76.
	eGFR	91.38	mL/min/1.7			91.9 / 89.88.
CKD-EPI formülü kullanilarak hesaplanmistir.						
	AST	22	U/L	0	40	25 / 25.
	ALT	16	IU/L	0	41	17 / 18.
	GGT	28	U/L	5	36	20 / 20.
	ALP	101	U/L	40	120	98 / 101.
↑	LDH	223	U/L	135	214	205 / 189.
	Total Protein	7.7	g/dL	6.4	8.3	7.2 / 7.4.
	Albumin	4.78	g/dL	3.5	5.2	4.71 / 4.84.
↑	Direkt Bilirubin	0.22	mg/dL	0	0.2	0.16 / 0.16.
	Total Bilirubin	0.67	mg/dL	0	1.2	0.39 / 0.38.
	İndirekt Bilirubin	0.45	mg/dL	0	1.2	0.23 / 0.22.
	Kalsiyum	9.7	mg/dL	8.6	10.2	9.9 / 10.
	Sodyum	145	mmol/L	136	145	134 / 136.
	Potasyum	4.08	mmol/L	3.5	5.1	4.68 / 4.57.
↓	Total Testosteron	0.18	ng/mL	1.32	8.92	0.21 / 0.17.

	Parametre Adı	Sonuc	Birim	Normal Değerler		Önceki Sonuc
	WBC	7.65	10e3/uL	3.7	10.1	5.42 / 6.88.
	RBC	4.71	10e6/uL	4.06	5.58	4.82 / 4.75.
	HGB	13.87	g/dL	12.9	15.9	13.7 / 14.5.
	HCT	41.54	%	39	49	42.1 / 42.6.
	PLT	204	10e3/uL	155	366	205 / 278.
	MCV	88.26	fL	81.1	96	87.3 / 89.7.
	MCH	29.47	pg	27.0	31.2	28.5 / 30.5.
	MCHC	33.39	g/dL	31.8	35.4	32.6 / 34.
	RDW	12.52	%	11.5	14.5	11 / 11.9.
	NEU#	4.62		1.63	6.96	3.15 / 4.35.
	LYM#	2.27		1.09	2.99	1.41 / 1.9.
	EO#	0.06		0.03	0.44	0.07 / 0.03.
	MON#	0.65		0.24	0.79	0.75 / 0.54.
	BASO#	0.05		0	0.8	0.04 / 0.07.
	NEU%	60.44	%	50.0	70.0	58.1 / 63.2.
	LYM%	29.65	%	18.0	48.3	26.1 / 27.6.
	EO%	0.78	%	0.6	7.3	1.28 / 0.43.
	MONO%	8.45	%	4.4	12.7	13.9 / 7.78.
	BASO%	0.68	%	0	1.7	0.69 / 1.02.
	MPV	7.97	fL	6.9	16	9.42 / 6.39.
	PCT	0.16	%	0.0	9.99	0.19 / 0.18.
↑	PDW	21.26	fL	9.30	14.30	22.8 / 16.7.

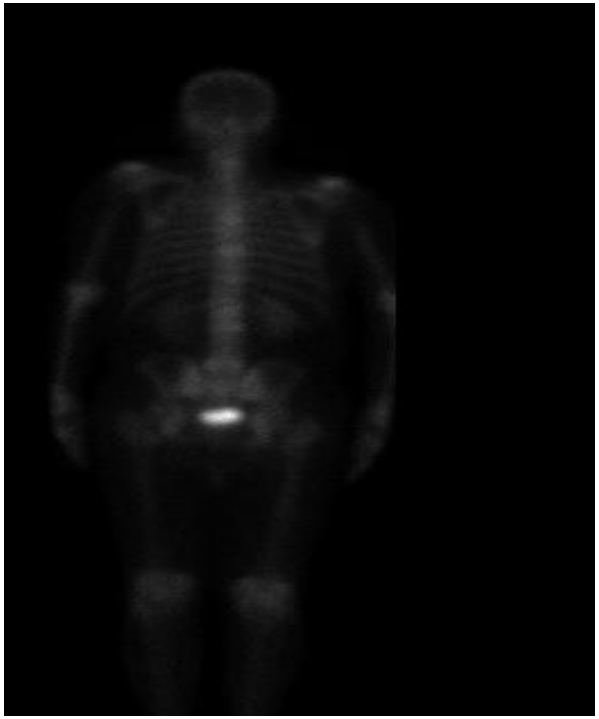
Metastatik Prostat Kanserinde Genel Değerlendirme

7.2.6 *Guidelines for follow-up during hormonal treatment*

Recommendations	Strength rating
The follow-up strategy must be individualised based on stage of disease, prior symptoms, prognostic factors and the treatment given.	Strong
In patients with stage M0 disease, schedule follow-up at least every 6 months. As a minimum requirement, include a disease-specific history, serum prostate-specific antigen (PSA) determination, as well as liver and renal function in the diagnostic work-up.	Strong
In M1 patients, schedule follow-up at least every 3–6 months.	Strong
In patients on long-term androgen deprivation therapy (ADT), measure initial bone mineral density to assess fracture risk.	Strong
During follow-up of patients receiving ADT, check PSA and testosterone levels and monitor patients for symptoms associated with metabolic syndrome as a side effect of ADT.	Strong
As a minimum requirement, include a disease-specific history, haemoglobin, serum creatinine, alkaline phosphatase, lipid profiles and HbA1c level measurements.	Strong
Counsel patients (especially with M1b status) about the clinical signs suggestive of spinal cord compression.	Strong
When disease progression is suspected, restaging is needed and the subsequent follow-up adapted/individualised.	Strong
In patients with suspected progression, assess the testosterone level. By definition, castration-resistant PCa requires a testosterone level < 50 ng/dL (< 1.7 nmol/L).	Strong

EUA guidelines, 2023

04.09.2019 Yeniden Evreleme



>> TÜM VÜCUT KEMIK SINTIGRAFISI : TÜM VÜCUT KEMİK SİNTİGRAFİSİ

Hastanın yaşı ve kilosuna uygun dozda 99mTc MDP' nin intravenöz olarak enjeksiyonundan 3 saat sonra anterior ve posterior pozisyonda tüm vücut taraması, planar ek görüntüleme ve spect çalışması yapılmıştır.

Sol I. kosta anteriorda, C5. vertebrada, T5.,6.,8.,10. vertebralarda ve L1.,2. ve L5. vertebralarda artmış aktivite tutulumu izlenmiştir. Spect çalışmasında tutulumların;

- T5.,6.,8. vertebralarda korpusta, T10. ve L1. vertebralarda sağ korpus-faset bileşkesinde L2. vertebra korpusta ve sağ faset eklemde olduğu, L5. vertebrada bilateral faset eklemlerde olduğu izlenmektedir.

Ayrıca her iki omuz ekleminde ve diz ekleminde osteodejeneratif/osteoartritik değişikler ile uyumlu olabilecek heterojen aktivite tutulumları izlenmektedir.

Vücudun diğer kemiklerinde aktivite tutulumu simetrik homojen ve beklenen düzeyde izlenmektedir.

23.05.2018 tarihli kemik sintigrafisi ile karşılaştırıldığında bulgular benzer olarak değerlendirilmiştir.

vertebra ve kostalarda yeni lezyonlar

Testosteron düzeyi ne zaman bakalım

- 1-Her ay
- 2-Üç ayda bir
- 3-Altı ayda bir
- 4-PSA yükseldiğinde
- 5-Radyolojik progresyon olduğunda
- 6-PSA ya da radyolojik progresyon olduğunda

09/2019 tedavi seçeneği

- Kastrasyona dirençli prostat ca
- Yeni kemik lezyonları
- PSA progresyonu
- Tedavi seçeneği

Tedavi Seçeneğiniz Ne Olur

- ❑ 1-Dosetaksel tedavisine geçerim
- ❑ 2-Yalnız ADT ile devam ederim
- ❑ 3-Tedavisiz izlerim
- ❑ 4-Abireteron eklerim
- ❑ 5-Enzulutamid eklerim
- ❑ 6-LU-177 tedavisi
- ❑ 7-BRCA ve diğer DNA repair genlere bakıp PARP inh.

Kastrasyona Dirençli Metastatik Prostat kanseri

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2021
Prostate Cancer

NCCN Guidelines Index
Table of Contents
Discussion

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

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

Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

Treatment options in mCRPC

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

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

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

CHUM

Kastrasyona Dirençli Metastatik Prostat kanseri

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

No prior docetaxel/no prior novel hormone therapy[mmm]	Prior novel hormone therapy/no prior docetaxel[mmm,ttt]
• Preferred regimens ▸ Abiraterone[u,nnn,ooo] (category 1) ▸ Docetaxel[fff,ppp] (category 1) ▸ Enzalutamide[u] (category 1) • Useful in certain circumstances ▸ Niraparib/abiraterone[u,fff,zzz] for BRCA mutation (category 1) ▸ Olaparib/abiraterone[u,fff,nnn,qqq] for BRCA mutation (category 1) ▸ Radium-223[rrr] for symptomatic bone metastases (category 1) ▸ Sipuleucel-T[fff,sss] (category 1) ▸ Talazoparib/enzalutamide for HRRm[u,fff,yyy] (category 1) • Other recommended regimens ▸ Other secondary hormone therapy[u]	• Preferred regimens ▸ Docetaxel (category 1)[fff] • Useful in certain circumstances ▸ Cabazitaxel/carboplatin[fff,jjj] ▸ Niraparib/abiraterone[u,fff,zzz] for BRCA mutation (category 2B) ▸ Olaparib for HRRm[uuu] (category 1) ▸ Radium-223[rrr] for symptomatic bone metastases (category 1) ▸ Rucaparib for BRCA mutation[vvv] ▸ Sipuleucel-T[fff,sss] ▸ Talazoparib/enzalutamide for HRRm[u,fff,yyy] (category 2B) • Other recommended regimens ▸ Abiraterone[u,nnn] ▸ Abiraterone[u] + dexamethasone[nnn,www] ▸ Enzalutamide[u] ▸ Other secondary hormone therapy[u]
Prior docetaxel/no prior novel hormone therapy[mmm]	**Prior docetaxel and prior novel hormone therapy**[mmm,ttt]
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Tedavi Öncesi Hangi Testler İstenmeli

- 1-Germline BRCA
- 2-Somatik BRCA
- 3-MSI ve TMB
- 4-Germline DNA repair genler
- 5-Somatik DNA repair genler
- 6-Hepsi
- 7-Hiçbiri

Kastrasyona Dirençli Metastatik Prostat kanseri

Prostate NCCN Guidelines v 1.2023

Germline Testing	Somatic Tumor Testing

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

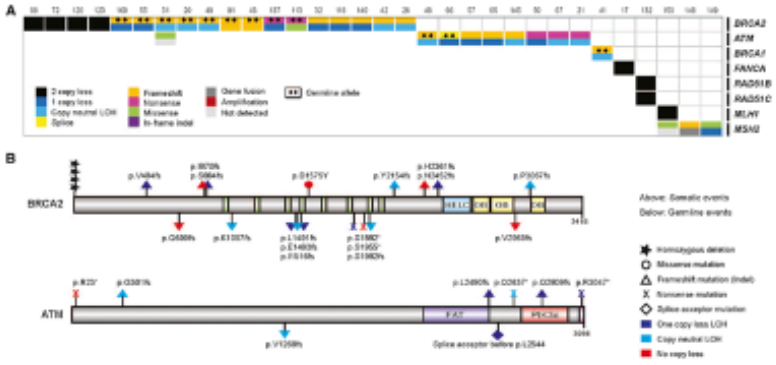
NCCN Practice Guidelines: Prostate Cancer. Version 1.2023. https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf.

Evre IV Prostat Kanserinde Mutasyonlar

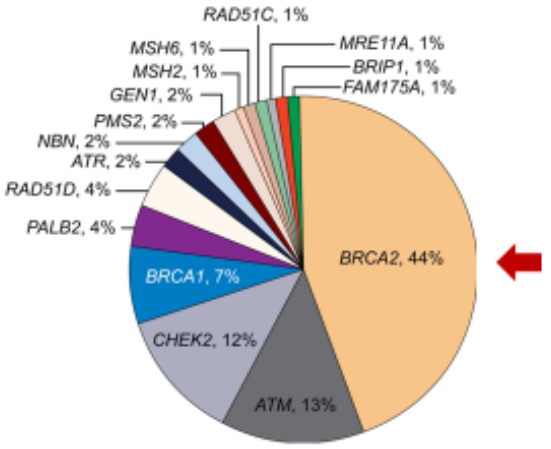
HRR Genes and Metastatic Prostate Cancer

Somatic

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



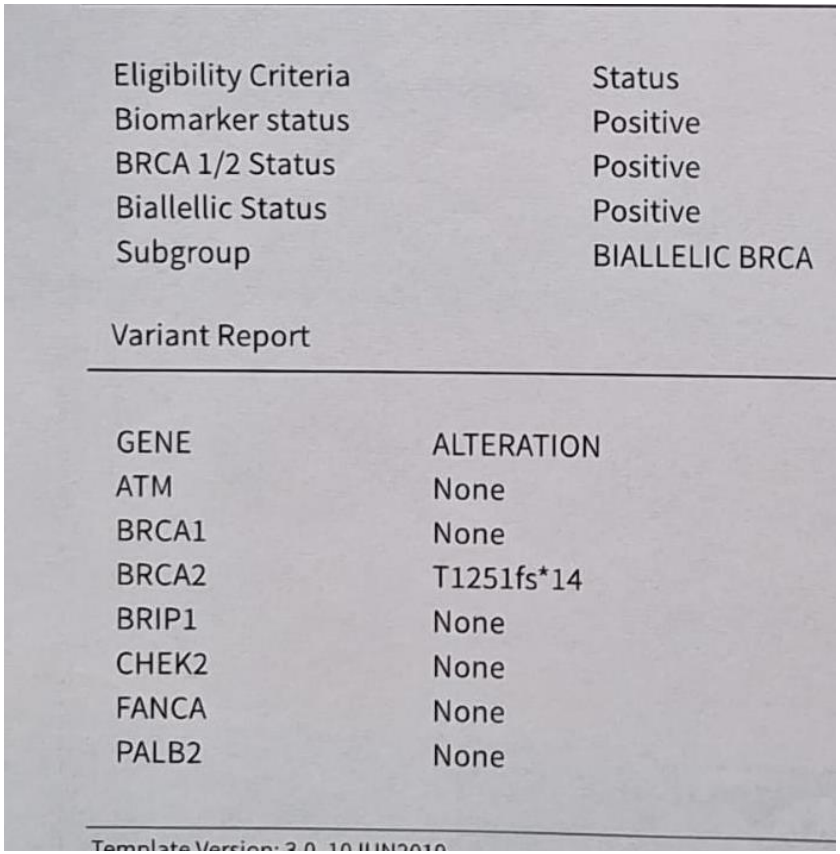
Germline



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

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

Hastanın Genetik inceleme Sonucu

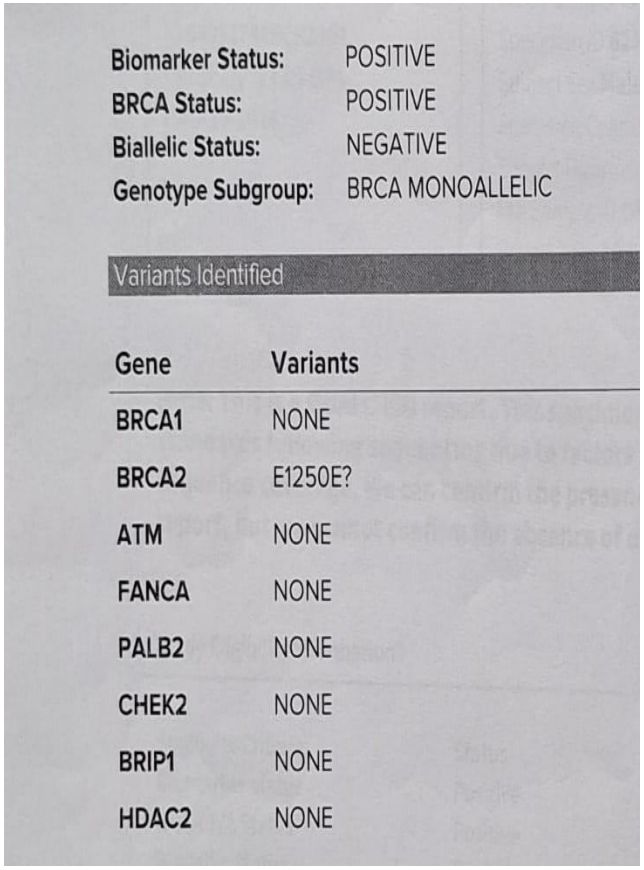


Eligibility Criteria	Status
Biomarker status	Positive
BRCA 1/2 Status	Positive
Biallellic Status	Positive
Subgroup	BIALLELIC BRCA

Variant Report

GENE	ALTERATION
ATM	None
BRCA1	None
BRCA2	T1251fs*14
BRIP1	None
CHEK2	None
FANCA	None
PALB2	None

Template Version: 3.0 10 JUN2019



Biomarker Status:	POSITIVE
BRCA Status:	POSITIVE
Biallelic Status:	NEGATIVE
Genotype Subgroup:	BRCA MONOALLELIC

Variants Identified

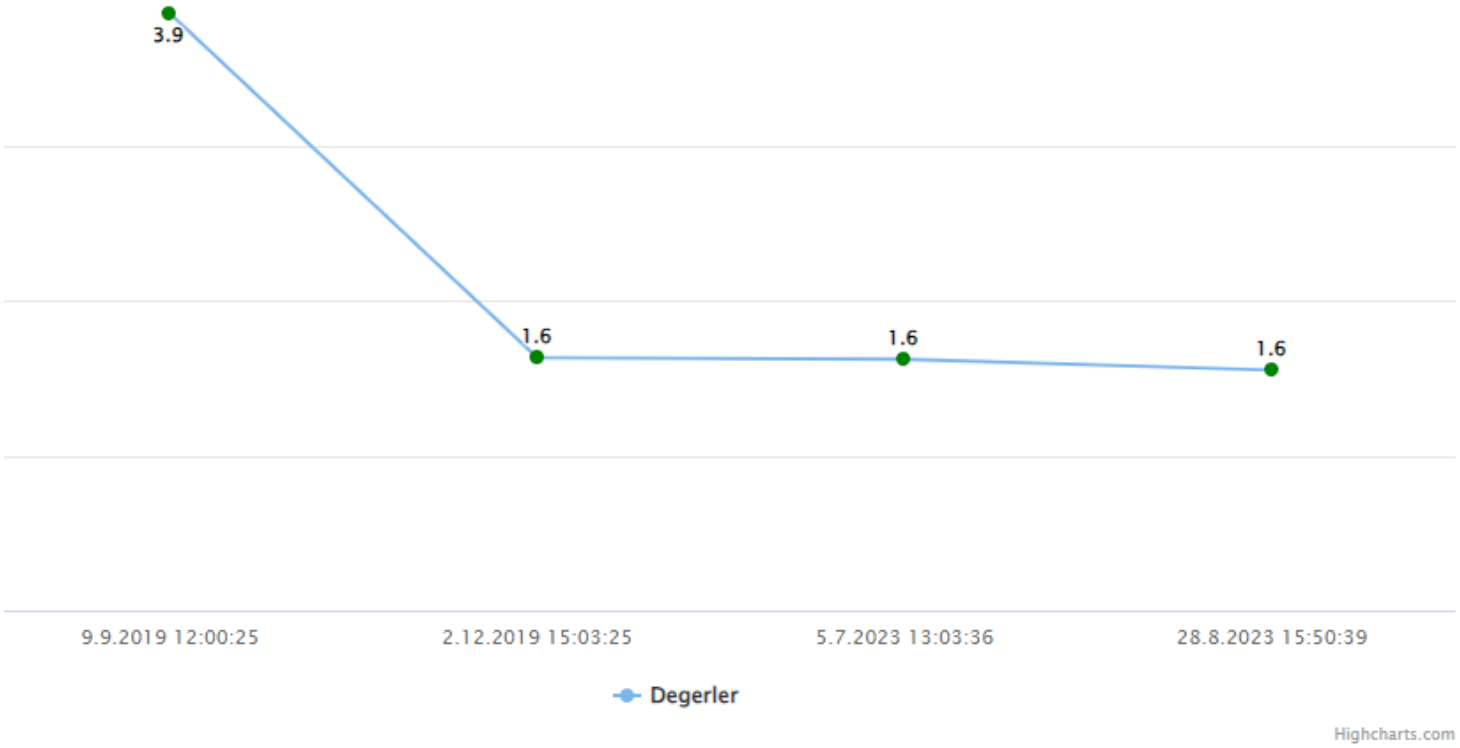
Gene	Variants
BRCA1	NONE
BRCA2	E1250E?
ATM	NONE
FANCA	NONE
PALB2	NONE
CHEK2	NONE
BRIP1	NONE
HDAC2	NONE

Biallelik BRCA2 mutasyonu pozitif

09/2019 Yeni Tedavi Başlandı

- Abireterone 1000 mg/gün
- Niraparib 200 mg/gün
- Deltacortril 2x5 mg/gün
- Leuprolide asetat 22.5 22.5 mg sc/3 ay
- Zoledronik asit 4 mg iv/3 ay

PSA yanıtı


3.9
1.6
1.6
1.6
9.9.2019 12:00:25
2.12.2019 15:03:25
5.7.2023 13:03:36
28.8.2023 15:50:39
Degerler
Highcharts.com

08/2023 Radyolojik Yanıt Değerlendirmesi

- TVS : yeni lezyon yok, Th 5-8 , L1, L2, L5, sol 9 kosta sklerotik stabil lezyonlar

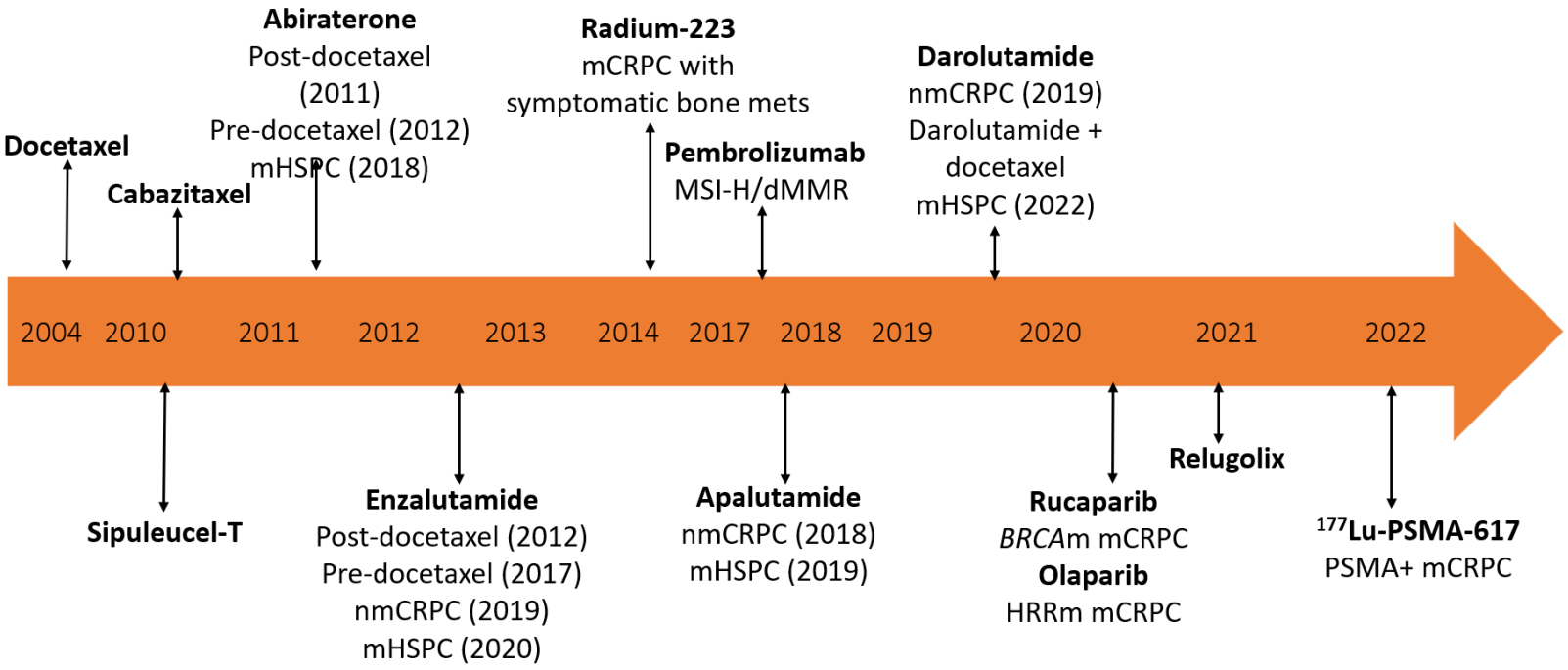
- Toraks-Batın BT: Viseral lezyon yok

Bu Hasta İçin RT

- ❑ 1-Primer Prostat lojuna RT
- ❑ 2-Metastaz bölgelerine RT
- ❑ 3-Metastaz ve primer prostat bölgesine RT
- ❑ 4-Yalnız ağrı palyasyonu için
- ❑ 5-Yük taşıyan kemik metastazlarına
- ❑ 6-Hiçbiri

Kastrasyona Dirençli Metastatik Prostat kanseri

Treatment Landscape of mCRPC continues to evolve



Kastrasyona Dirençli Metastatik Prostat kanseri

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

PROpel: Abiraterone + Olaparib [1]	Published
MAGNITUDE: Abiraterone + Niraparib [2]	Presented
TALAPRO-2: Enzalutamide + Talazoparib	Presented
CASPAR: Enzalutamide + Rucaparib	Enrolling

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

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

Kastrasyona Dirençli Metastatik Prostat kanseri

PROpel: Phase III Trial of Abiraterone +/– Olaparib

Patient population

- mCRPC
- Docetaxel for mCSPC allowed
- No prior abiraterone
- Other NHT allowed if stopped ≥12 months prior to enrollment
- Ongoing ADT
- ECOG PS 0–1

Stratification factors

- Site of distant metastases (bone only vs visceral vs other)
- Prior taxane for mCSPC

R 1:1

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

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

Primary endpoint

rPFS or death by investigator assessment

Key secondary endpoint

- OS

Additional endpoints

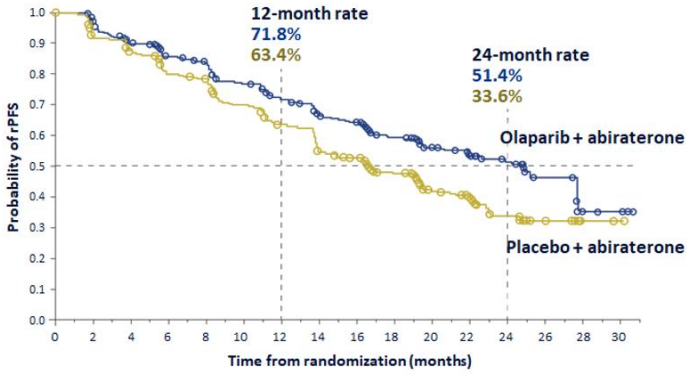
- TFST
- PFS2
- ORR
- HRR mutation prevalence (tested retrospectively)
- HRQOL
- Safety and tolerability

*Plus prednisone or prednisolone 5 mg BID

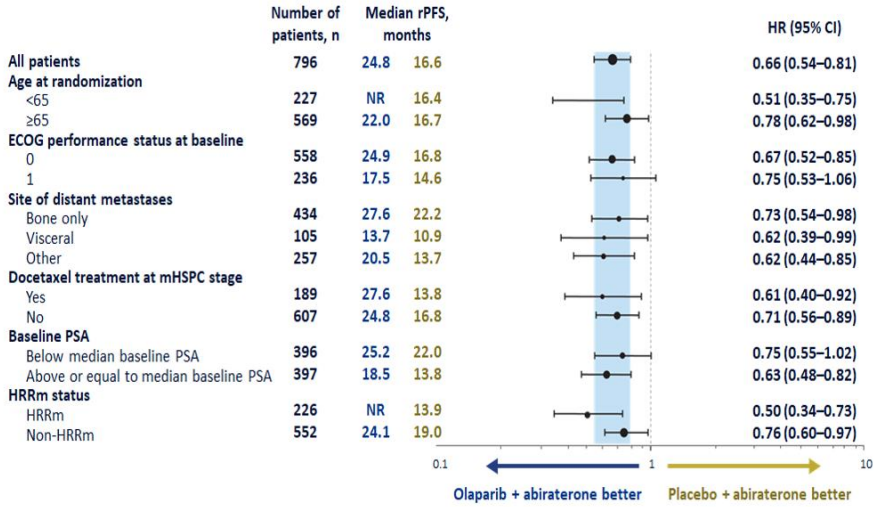
Saad F et al. *ASCO GU 2022*; abstr 11; **NCT03732820**.

Kastrasyona Dirençli Metastatik Prostat kanseri

PROpel: Radiographic Progression-Free Survival



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

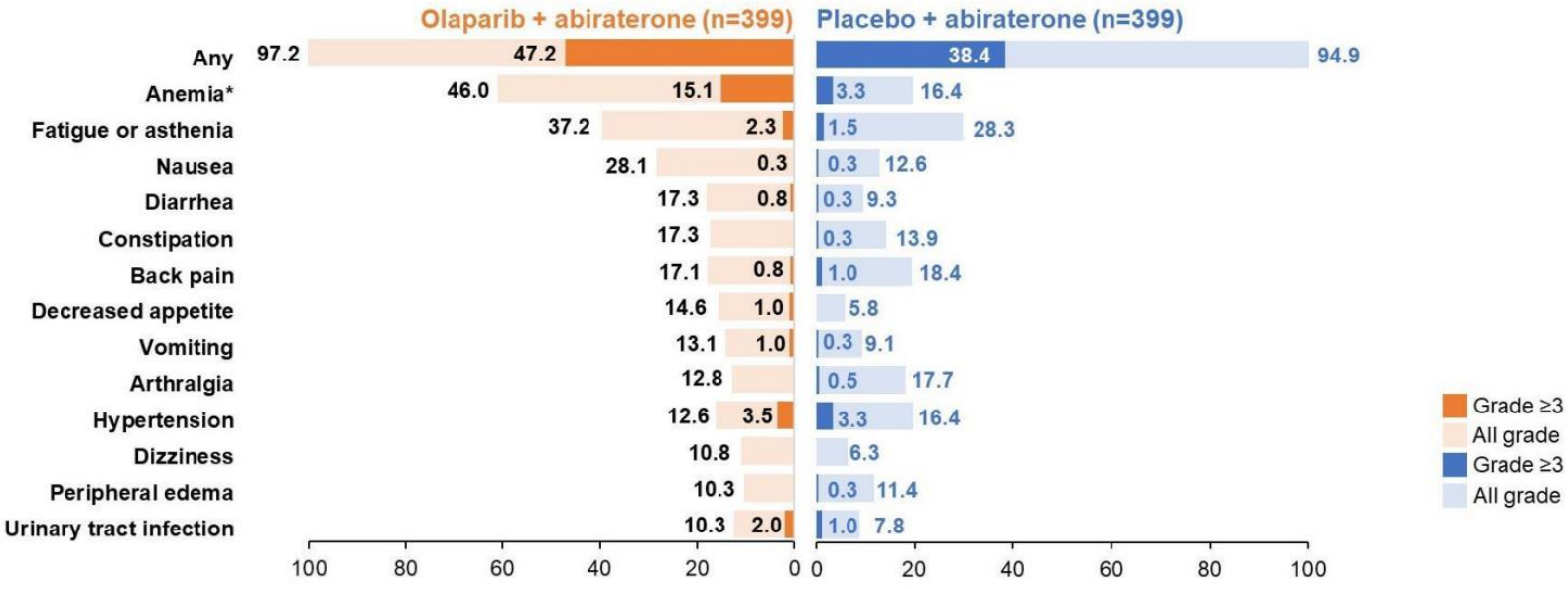


Clarke NW et al. *NEJM Evidence*; 2022.

Kastrasyona Dirençli Metastatik Prostat kanseri

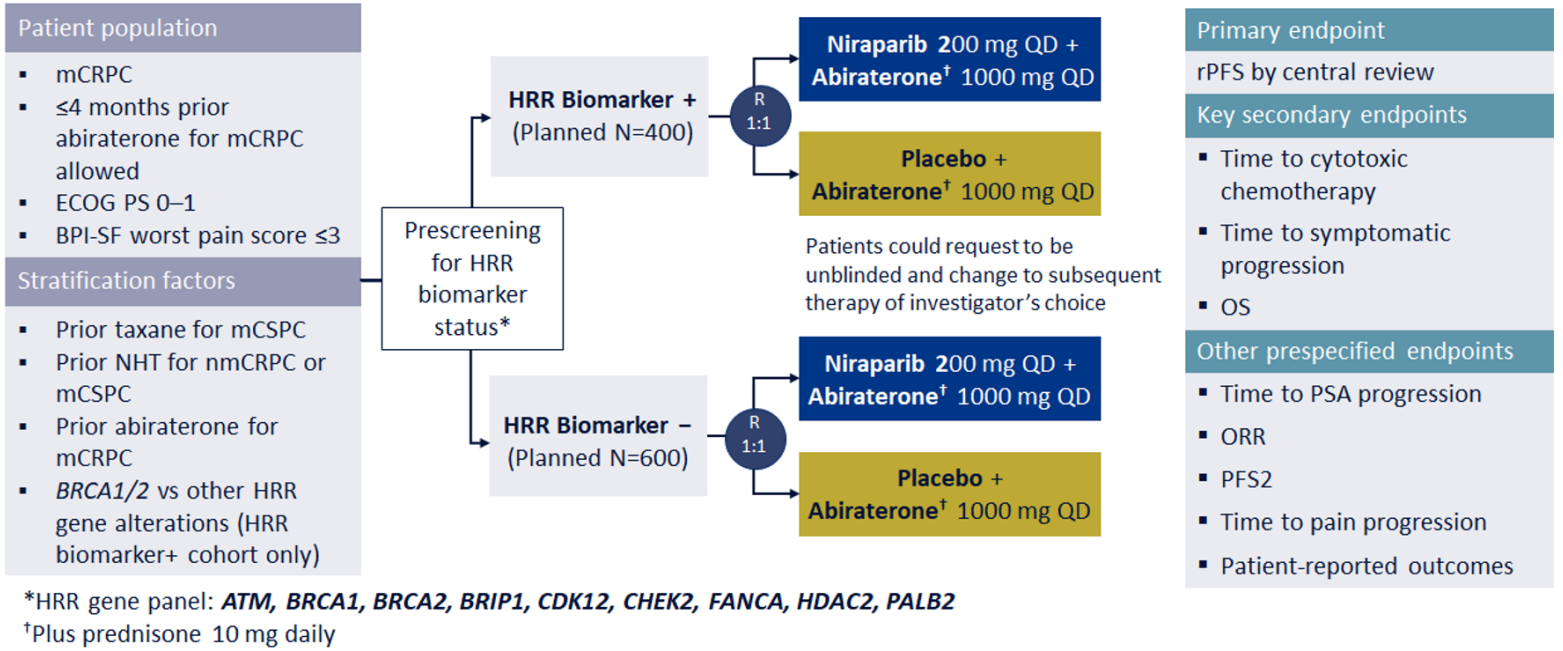
PROPEL

Overall safety profile



Kastrasyona Dirençli Metastatik Prostat kanseri

MAGNITUDE: Phase III Trial of Abi +/– Niraparib



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

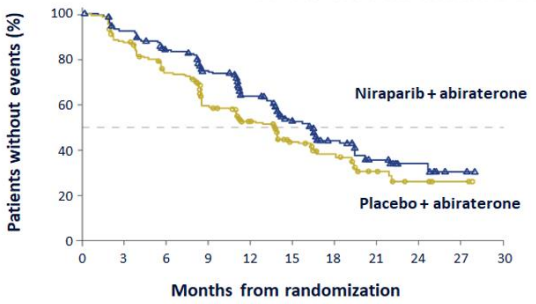
†Plus prednisone 10 mg daily

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

Kastrasyona Dirençli Metastatik Prostat kanseri

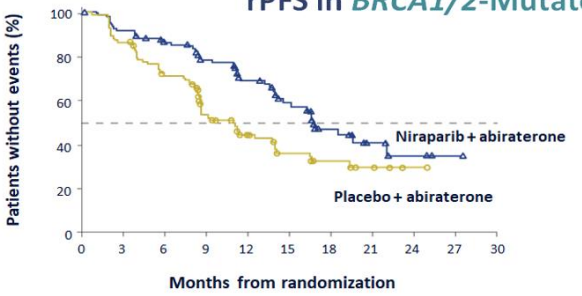
MAGNITUDE: Radiographic Progression-Free Survival

rPFS in All HRR BM+ Cohort



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

rPFS in *BRCA1/2*-Mutated Group

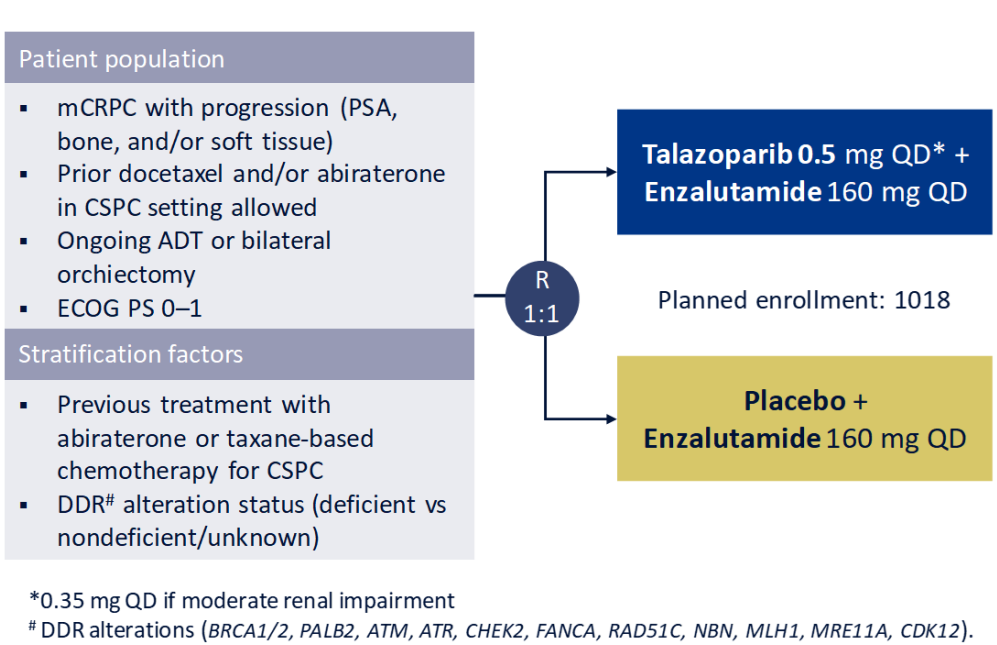


	Niraparib + abiraterone (n=113)	Placebo + abiraterone (n=112)
rPFS by central review		
Median rPFS, months	16.6	10.9
HR (95% CI)	0.53 (0.36–0.79); *P*=0.0014	
rPFS assessed by investigator		
Median rPFS, months	19.3	12.4
HR (95% CI)	0.50 (0.33–0.75); *P*=0.0006	

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

Kastrasyona Dirençli Metastatik Prostat kanseri

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



Co-primary endpoints

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

Key secondary endpoints
(analyzed for both cohorts separately)

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

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

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

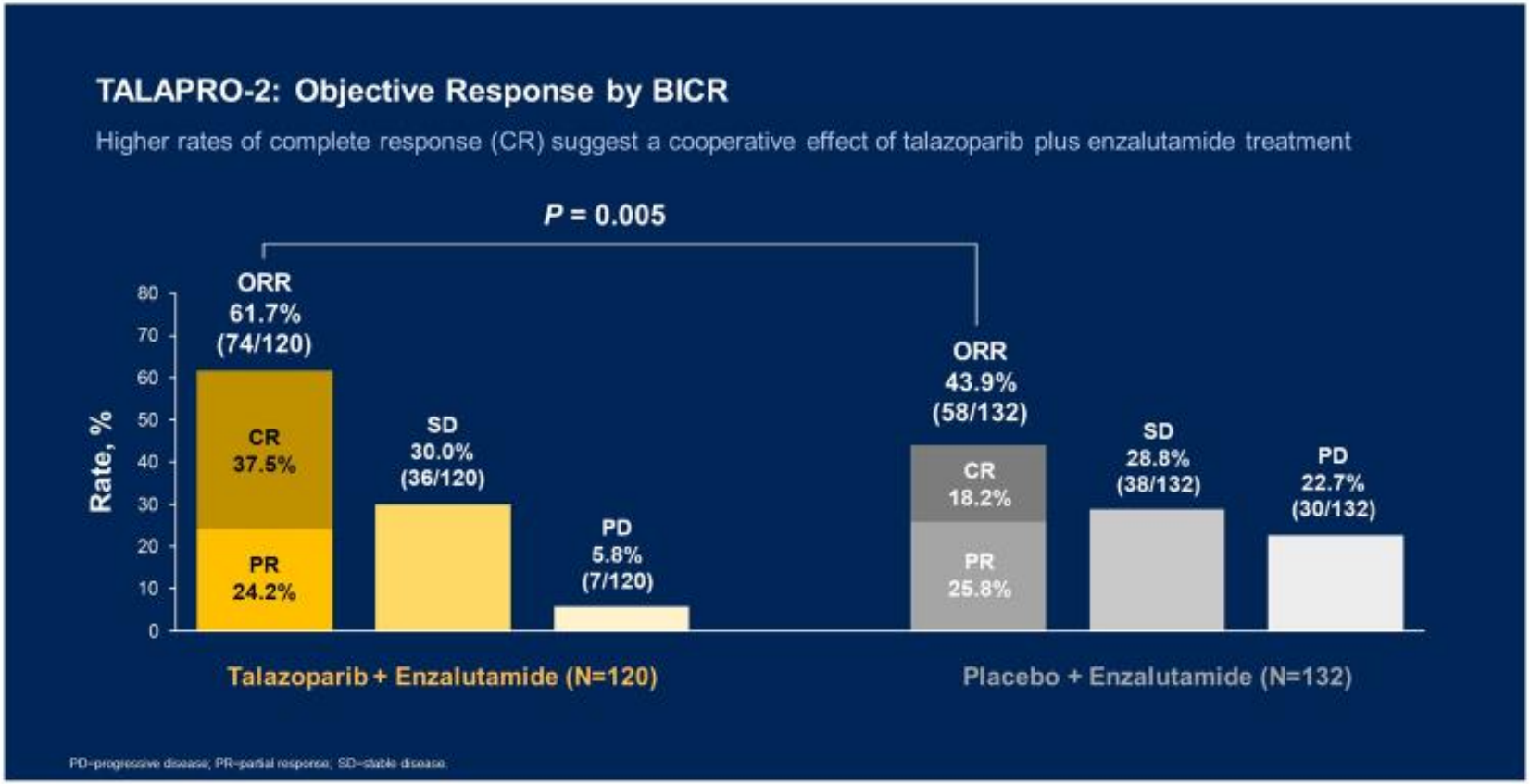
Kastrasyona Dirençli Metastatik Prostat kanseri

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

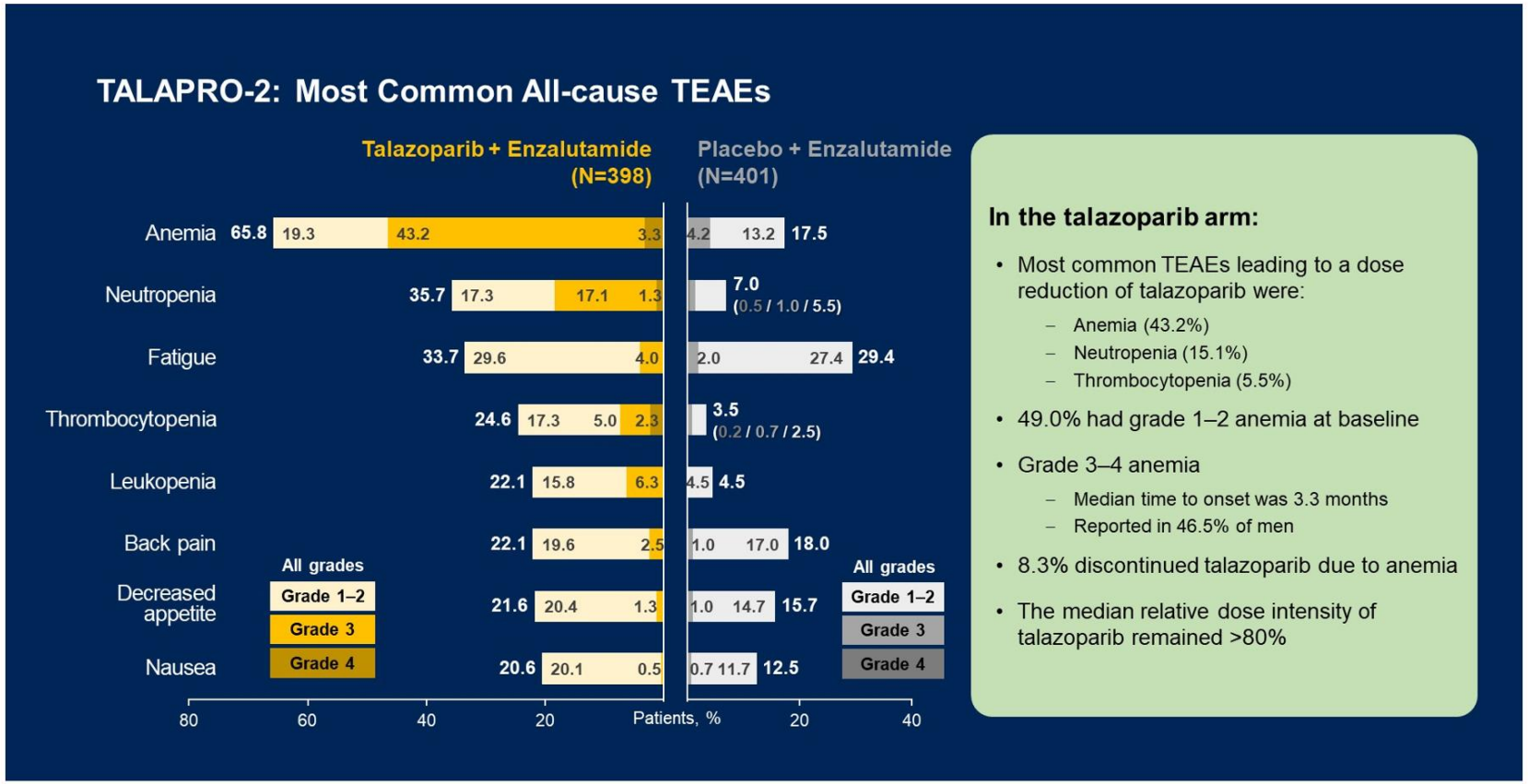
All-comers cohort	rPFS 21.9 mo → NR	HR 0.63 (0.51-0.78)	*P* <0.001
HRR *mutated*	rPFS 16.4 → 27.9 mo	HR 0.46 (0.30-0.70)	*P* <0.001
HRR *wild-type*	rPFS 16.6 → 25.8 mo	HR 0.66 (0.49-0.91)	*P* = 0.009

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

Kastrasyona Dirençli Metastatik Prostat kanseri



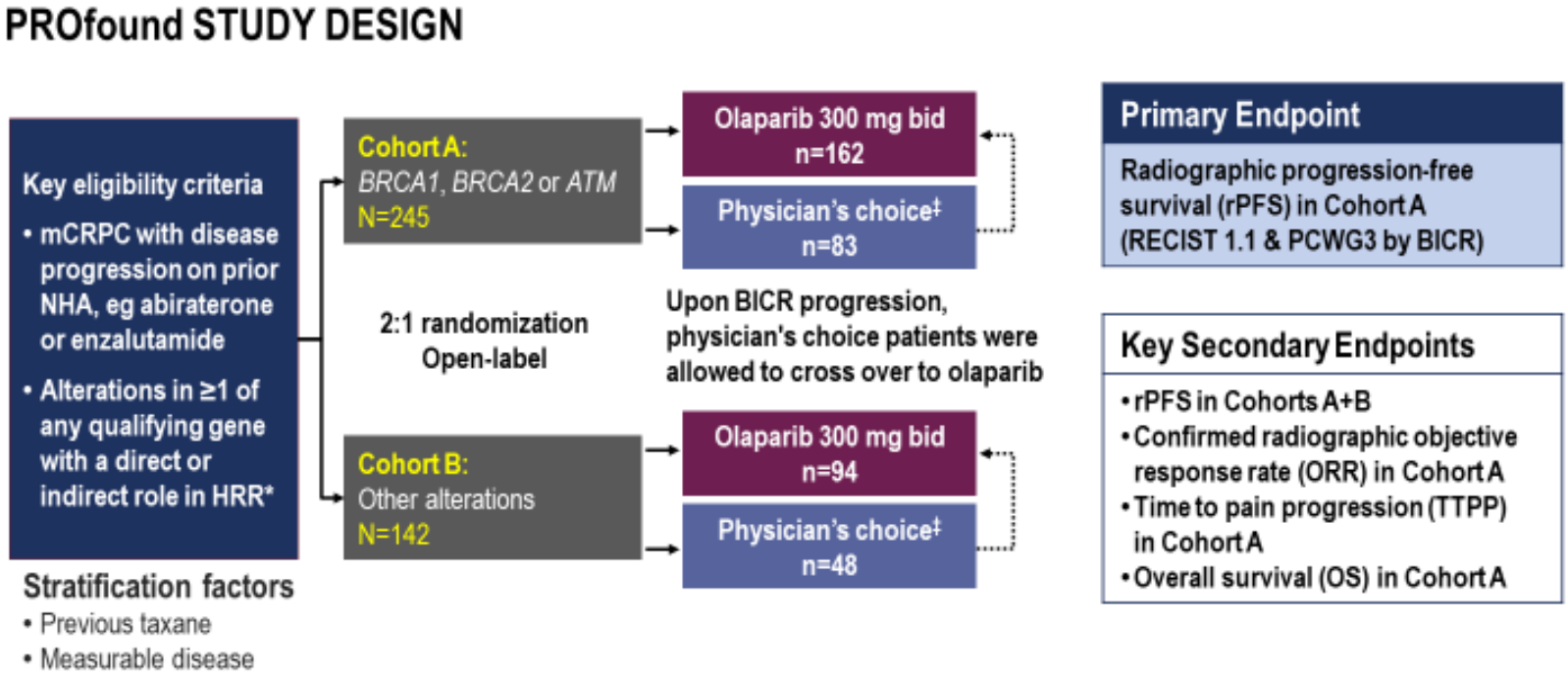
Kastrasyona Dirençli Metastatik Prostat kanseri



In the talazoparib arm:

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

Kastrasyona Dirençli Prostat Kanseri



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

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

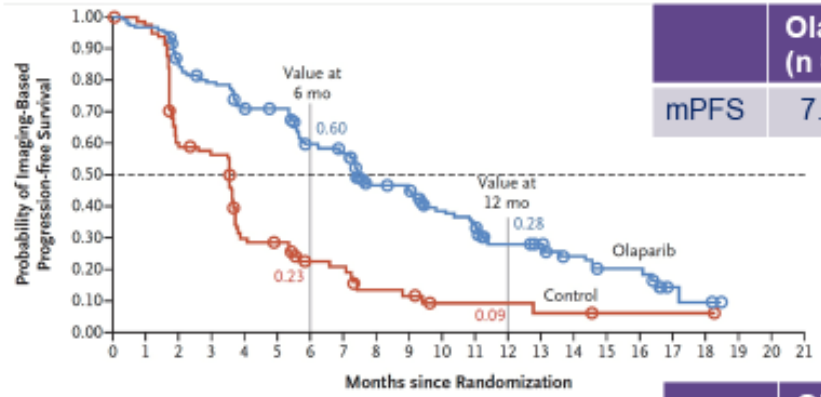
BARCELONA 2019 ESMO congress

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

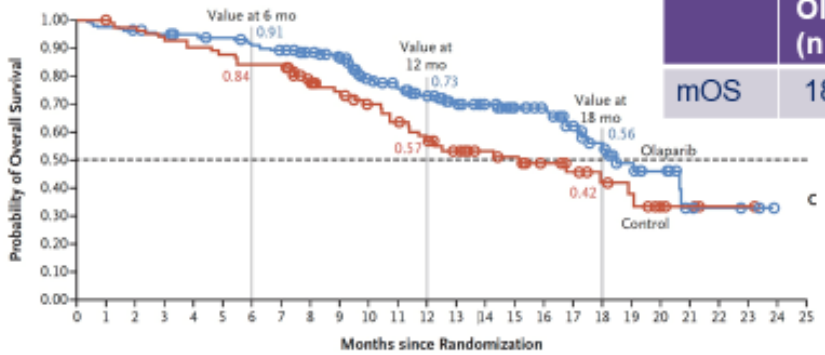
Hussain M et al. ESMO 2019;Abstract 5059.

Kastrasyona Dirençli Prostat Kanseri

PROfound: Imaging-Based PFS and OS in Cohort A



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



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

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

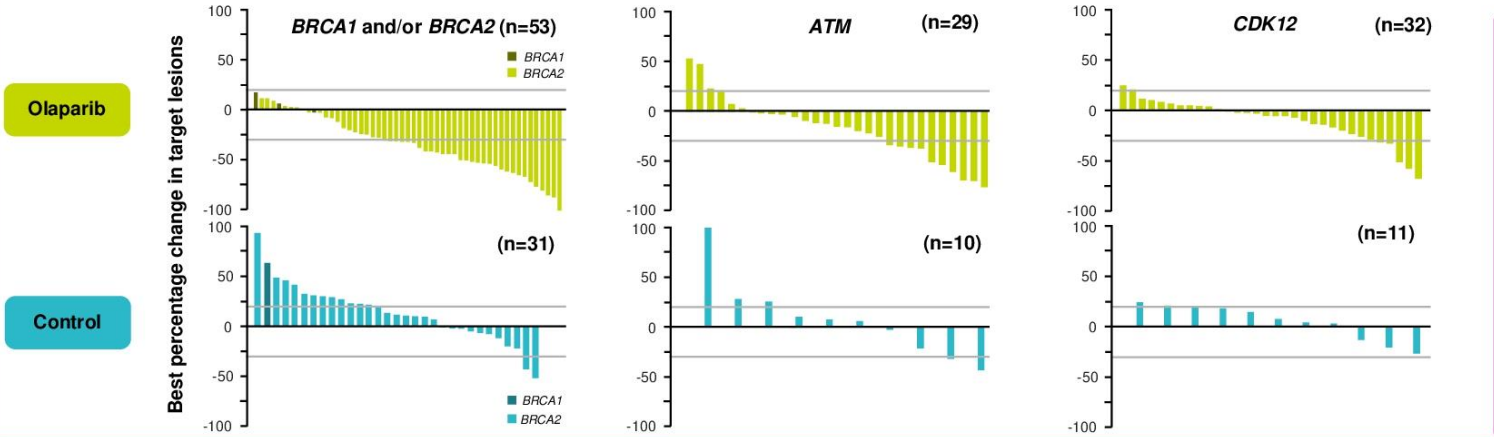
Olaparib Türkiye'de prostat kanseri tedavisinde ruhsatlı değildir.

Kastrasyona Dirençli Prostat Kanseri

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



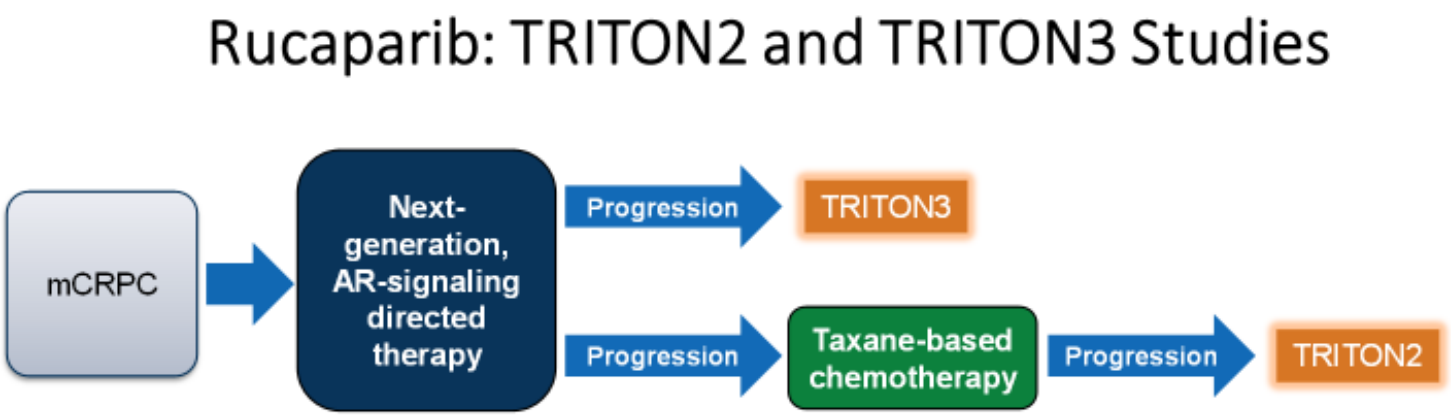
Definitions for abbreviations, best percentage change in PSA and CTC for *BRCA1* and/or *BRCA2*, *ATM*, *CDK12* and remaining genes are included in the supplement

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

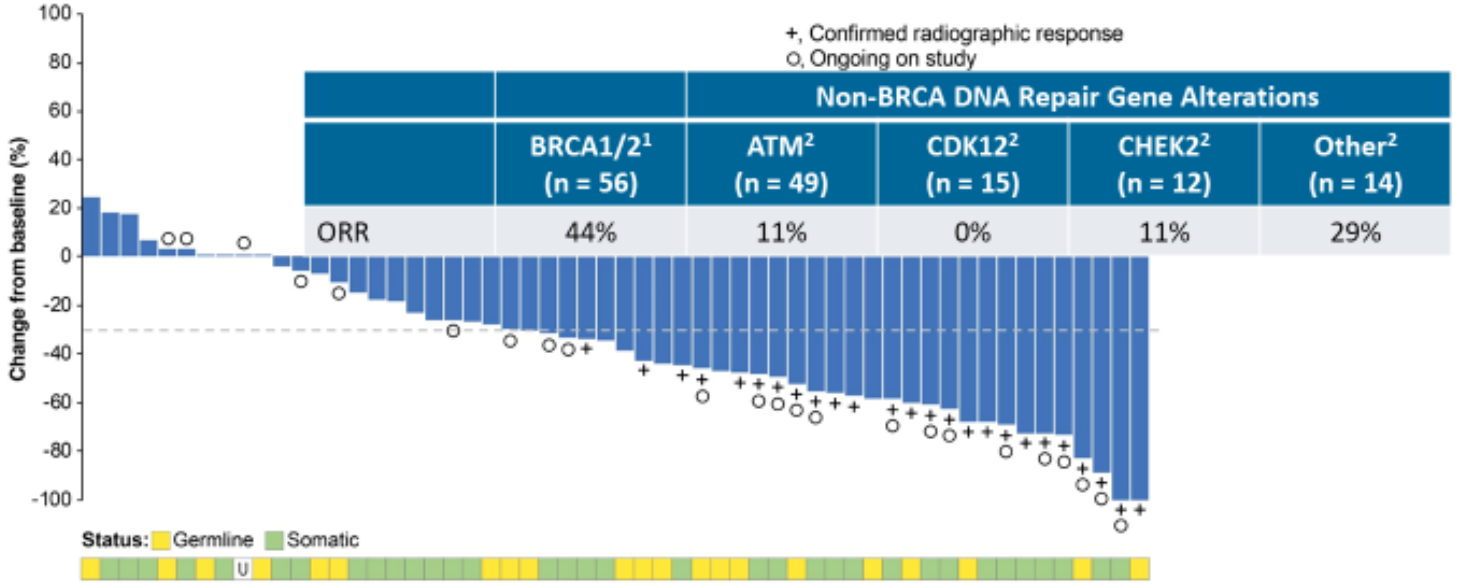


HRR-deficiency is defined by a deleterious alteration in *BRCA1*, *BRCA2*, *ATM*, or 12 other HRR genes (*BARD1*, *BRIP1*, *CDK12*, *CHEK2*, *FANCA*, *NBN*, *PALB2*, *RAD51*, *RAD51B*, *RAD51C*, *RAD51D*, *RAD54L*)

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

Kastrasyona Dirençli Prostat Kanseri

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



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

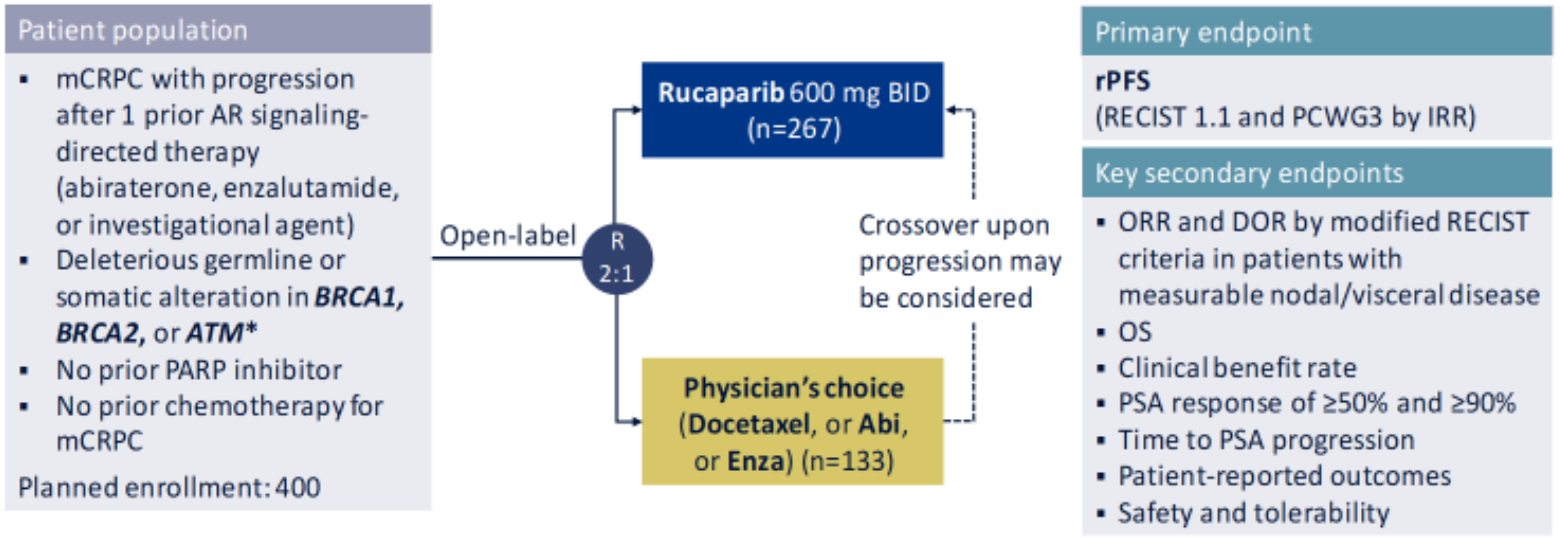
Visit cutoff: 02 Jul 2019. Includes patients with measurable disease at baseline and ≥1 postbaseline scan. Each bar represents a single patient; patients with no change from baseline are shown as 0.5% for visual clarity; the dotted line indicates the threshold for partial response (30% decrease from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

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

Rukaparib Türkiye'de prostat kanseri tedavisinde ruhsatlı değildir.

Kastrasyona Dirençli Metastatik Prostat kanseri

TRITON3: Randomized Phase III Trial



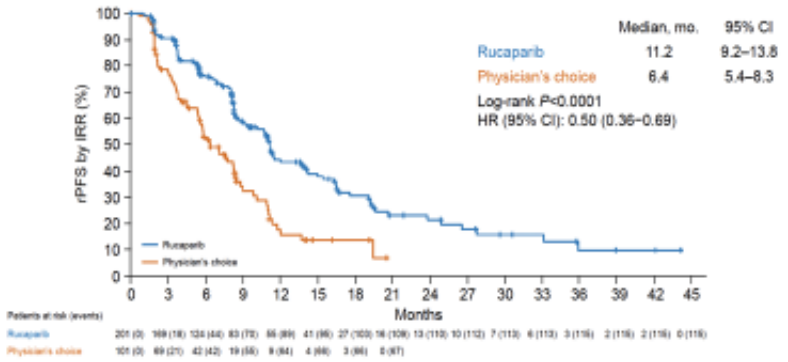
*Mutations identified in blood, archival tissue, or screening tumor tissue

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

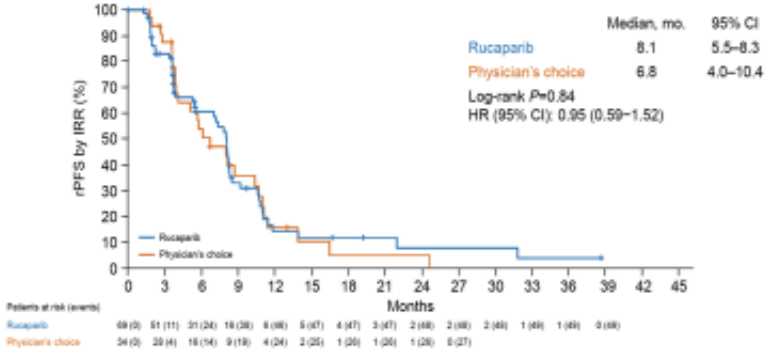
Kastrasyona Dirençli Metastatik Prostat kanseri

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

***BRCA1/2* Subgroup**



***ATM* Subgroup**



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

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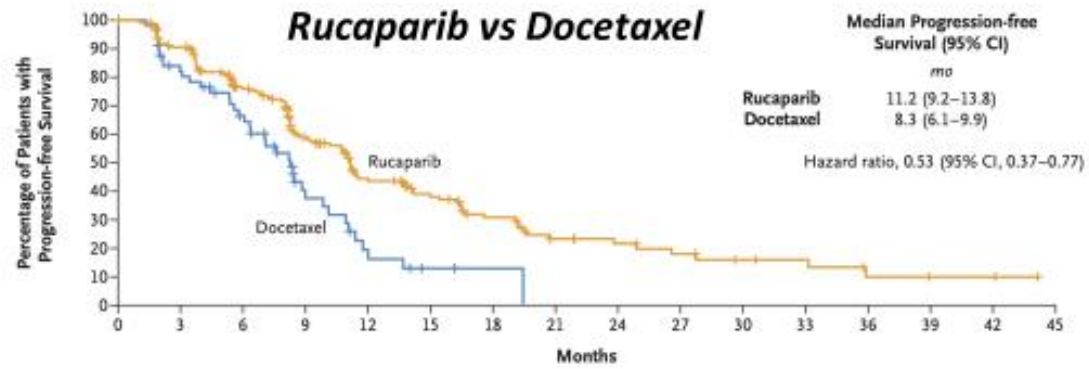
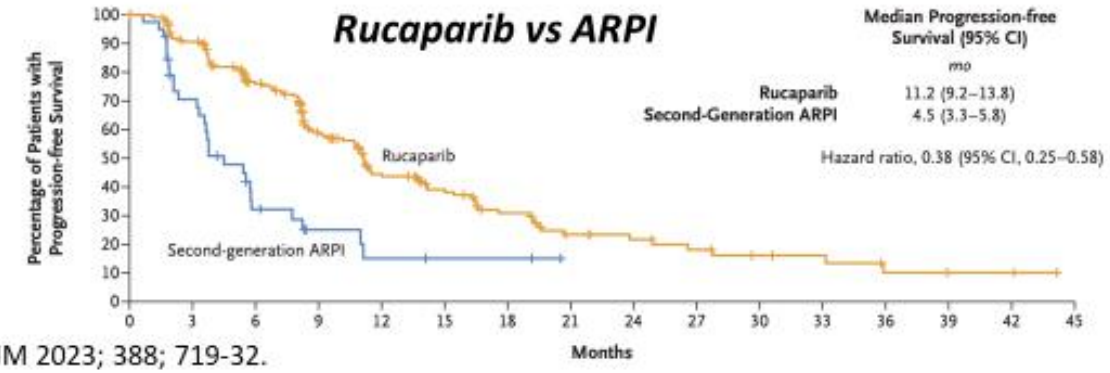
TRITON3: rPFS by Control Treatment in *BRCA1/2* Subgroup





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

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Summary of PARPi *monotherapy* trials in mCRPC

Study and treatment	Prior therapy	HRR status criteria; Sample type	Primary endpoint	Results
TOPARP-A[1] **Olaparib** 400 mg BID (N=50)	1–2 taxane CT regimens; 98% had prior NHT	Deficiency not required; tumor	Composite response rate	**33%** overall; 88% (14 of 16) with DDR gene alterations
TOPARP-B[2] **Olaparib** 300 mg or 400 mg BID, randomized 1:1 (N=98)	1–2 taxane CT regimens; 88%–92% had prior NHT	Deleterious germline or somatic DDR gene alterations; tumor	Composite response rate	**39.1%** 300-mg cohort; **54.3%** 400-mg cohort
TRITON2[3] **Rucaparib** 600 mg BID (N=115)	1 taxane and 1–2 NHT	Deleterious germline or somatic *BRCA1/2* alteration; tumor or plasma	ORR by blinded independent radiology review	**43.5%** (27 of 62)
GALAHAD[4] **Niraparib** 300 mg QD (N=289)	≥1 taxane and ≥1 NHT	Deleterious germline or somatic alteration in ≥1 of 8 prespecified DDR genes; tumor or plasma	ORR in patients with *BRCA* mutation and measurable disease	**34.2%** (26 of 76 measurable *BRCA* cohort) 10.6% (5 of 47 measurable non-*BRCA* cohort)
TALAPRO-1[5] **Talazoparib** 1 mg QD (N=128)	1–2 CT regimens (≥1 taxane) and ≥1 NHT	Deleterious germline or somatic alterations in ≥1 of 11 prespecified DDR-HRR genes; tumor or plasma	ORR by blinded independent review	**29.8%** (31 of 104)

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

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Select Ongoing PARPi Combination Trials in Advanced PC

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

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

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

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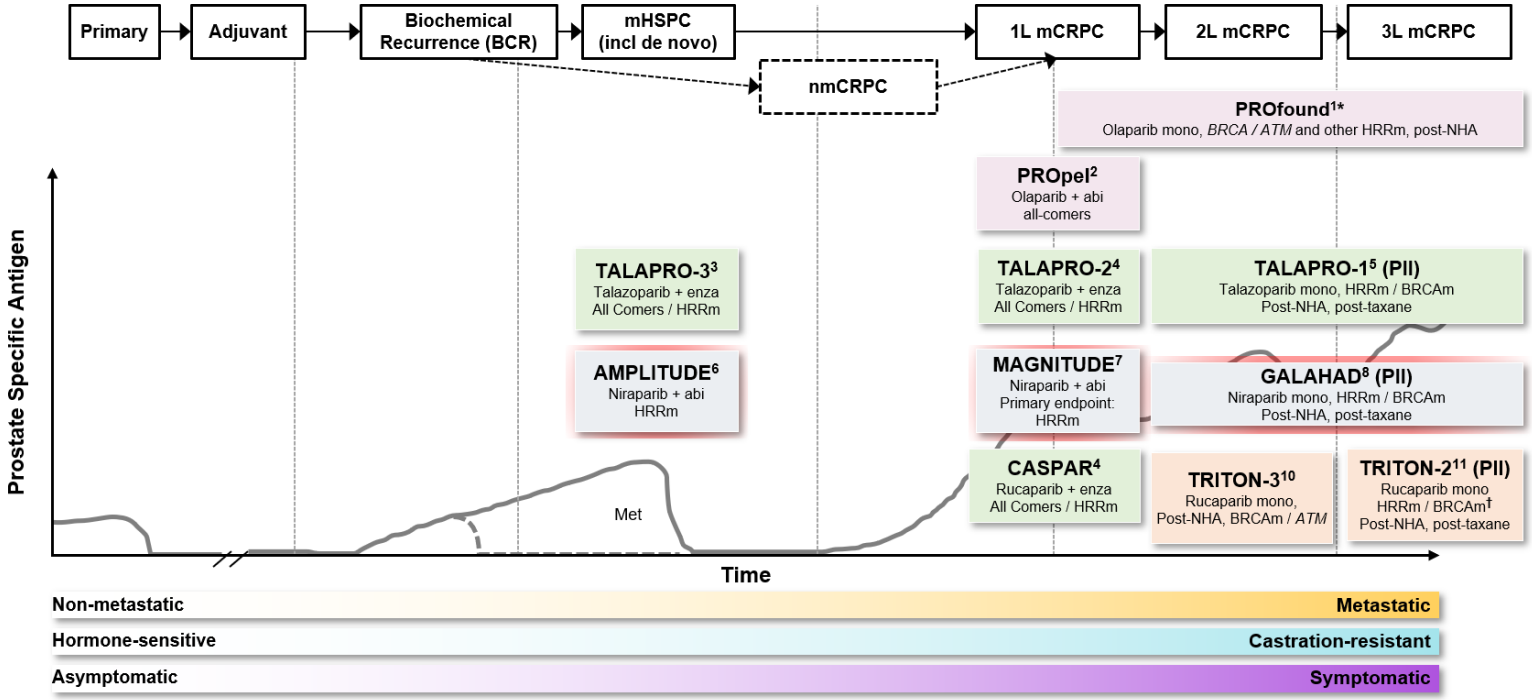
Ongoing trials investigating PARPi in advanced PC



Please see slide notes for references

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

†As a result of the data from TRITON2, rucaparib monotherapy was approved by the FDA only for the treatment of mCRPC in patients with a *BRCA1/2*m who have disease progression after treatment with prior AR-directed therapy and prior taxane[14]

Abi=abiraterone; BCR=biochemical recurrence; enza=enzalutamide; FDA=US Food and Drug Administration; HRRm=homologous recombination repair mutation; mCRPC=metastatic castration-resistant prostate cancer; met=metastasis; mono=monotherapy; mHSPC=metastatic hormone-sensitive prostate cancer; NHA=new hormonal agent; nmCRPC=non-metastatic castration-resistant prostate cancer; P2=Phase II; P3=Phase III.

CHUM

Kastrasyona Dirençli Metastatik Prostat kanseri

Side effects of PARPi *monotherapy*

Adverse event (any grade), n (%)	Olaparib TOPARP-A[1] (n=50)	Rucaparib TRITON2[2] (n=115)	Niraparib GALAHAD[3] (n=289)	Talazoparib TALAPRO-1[4] (n=127)
Anemia	38 (76)	50 (44)	156 (54)	62 (49)
Anorexia	14 (28)	32 (28)	93 (32)	36 (28)
Arthralgia	15 (30)	NR	44 (15)	10 (8)
AST/ALT increased	NR	38 (33)	37 (13)	15 (12)
Asthenia/fatigue	29 (58)	71 (62)	154 (53)	55 (43)
Back pain	11 (22)	NR	64 (22)	17 (13)
Constipation	7 (14)	31 (27)	101 (35)	23 (18)
Diarrhea	8 (16)	23 (20)	49 (17)	21 (17)
Dyspnea	14 (28)	15 (13)	39 (13)	17 (13)
Nausea	18 (36)	60 (52)	169 (58)	42 (33)
Rash	NR	33 (29)	1 (<1)	NR
Thrombocytopenia	5 (10)	29 (25)	99 (34)	24 (19)
Vomiting	10 (20)	25 (22)	111 (38)	17 (13)
AEs affecting ≥50 of patients in any study are highlighted				

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

08/2023 kontrol değerleri

	Parametre Adı	Sonuc	Birim	Normal Değerler		Önceki Sonuc
↓	WBC	2.88	10e3/uL	3.7	10.1	2.45 / 3.42.
↓	RBC	3.26	10e6/uL	4.06	5.58	3.31 / 3.65.
↓	HGB	9.5	g/dL	12.9	15.9	9.8 / 10.8.
↓	HCT	28.2	%	39	49	28.7 / 31.8.
↓	PLT	27	10e3/uL	155	366	30 / 39.
	MCV	86.5	fL	81.1	96	86.7 / 87.1.
	MCH	29.2	pg	27.0	31.2	29.5 / 29.6.
	MCHC	33.7	g/dL	31.8	35.4	34 / 34.
	RDW	13.3	%	11.5	14.5	13.3 / 13.3.
↓	NEU#	1.31		1.63	6.96	1.02 / 1.92.
	LYM#	1.23		1.09	2.99	1.16 / 1.16.
↓	EO#	0		0.03	0.44	0.01 / 0.
	MON#	0.34		0.24	0.79	0.26 / 0.34.
	BASO#	0		0	0.8	0 / 0.
↓	NEU%	45.4	%	50.0	70.0	41.5 / 56.1.
	LYM%	42.8	%	18.0	48.3	47.3 / 33.7.
↓	EO%	0.1	%	0.6	7.3	0.4 / 0.1.
	MONO%	11.6	%	4.4	12.7	10.7 / 10.
	BASO%	0.1	%	0	1.7	0.1 / 0.1.
	MPV	9.3	fL	6.9	16	8.7 / 9.3.
	PCT	0.03	%	0.0	9.99	0.03 / 0.04.
↑	PDW	16.5	fL	9.30	14.30	16.1 / 16.3.

	Parametre Adı	Sonuc	Birim	Normal Değerler		Önceki Sonuc
↑	Glukoz	157.8	mg/dL	82	115	112.5 / 126.1.
↑	Üre	59.2	mg/dL	17	43	44 / 40.3.
↓	Ürik Asit	2.2	mg/dL	3.4	7	2 / 1.9.
↓	Kreatinin	0.64	mg/dL	0.7	1.2	0.61 / 0.54.
	eGFR	92	mL/min/1.73m2	> 60		94 / 99.
CKD-EPI formülü kullanilarak hesaplanmistir.						
	AST	10.7	U/L	0	37	12.1 / 11.6.
	ALT	12.4	IU/L	0	41	11.6 / 14.6.
	GGT	22	U/L	0	60	18 / 22.
	ALP	80	U/L	40	129	87 / 87.
↑	LDH	247	U/L	135	225	305 / 294.
↓	Total Protein	56.1	g/L	64	83	53.8 / 54.9.
↓	Albumin	37.5	g/L	39	49	33.7 / 34.2.
	Direkt Bilirubin	0.21	mg/dL	0	0.3	0.21 / 0.23.
	Total Bilirubin	0.49	mg/dL	< 1.2		0.47 / 0.44.
	İndirekt Bilirubin	0.28	mg/dL	0.1	1	0.26 / 0.21.
	Kalsiyum	8.98	mg/dL	8.8	10.2	9.13 / 8.5.
	Sodyum	138	mmol/L	136	146	137 / 140.
	Potasyum	4.52	mmol/L	3.5	5.1	4.72 / 4.33.
	CRP	3	mg/L	0	5	5.5 / 10.

Lab ve Grup Açıklamaları

Hangi Tanıyı düşünürsünüz

- ❑1-MDS
- ❑2-AML
- ❑3-Abireterone bağlı kemik iliği toksisitesi
- ❑4-Niraparib ilişkili toksite
- ❑5-Diğer nedenler

Kastrasyona Dirençli Metastatik Prostat kanseri

MAGNITUDE

Safety data: HRR BM+

Treatment-emergent adverse events occurring at >20% in the NIRA arm or otherwise of clinical interest, n (%)		NIRA + AAP, n = 212		PBO + AAP, n = 211	
		All grades	Grade ≥3	All grades	Grade ≥3
Hematologic	Anemia	98 (46.2)	63 (29.7)	43 (20.4)	16 (7.6)
	Thrombocytopenia	45 (21.2)	14 (6.6)	18 (8.5)	5 (2.4)
	Neutropenia	29 (13.7)	14 (6.6)	12 (5.7)	3 (1.4)
	Acute myeloid leukemia/ Myelodysplastic syndrome	0	0	1 (0.5)	1 (0.5)
Cardiovascular	Hypertension	67 (31.6)	33 (15.6)	47 (22.3)	30 (14.2)
	Arrhythmia	27 (12.7)	6 (2.8)[a]	12 (5.7)	3 (1.4)
	Cardiac failure	4 (1.9)	3 (1.4)[a]	4 (1.9)	1 (0.5)
	Ischemic heart disease	4 (1.9)	4 (1.9)	8 (3.8)	6 (2.8)[b]
General disorders	Fatigue	56 (26.4)	7 (3.3)	35 (16.6)	9 (4.3)
Gastrointestinal	Constipation	65 (30.7)	–	29 (13.7)	–
	Nausea	50 (23.6)	1 (0.5)	29 (13.7)	0
Hepatotoxicity		25 (11.8)	4 (1.9)	26 (12.3)	10 (4.7)
Cerebrovascular disorders		6 (2.8)	2 (0.9)	2 (0.9)	1 (0.5)[a]

CHUM