

Metastatik prostat kanserinde yeni tedavi seçenekleri

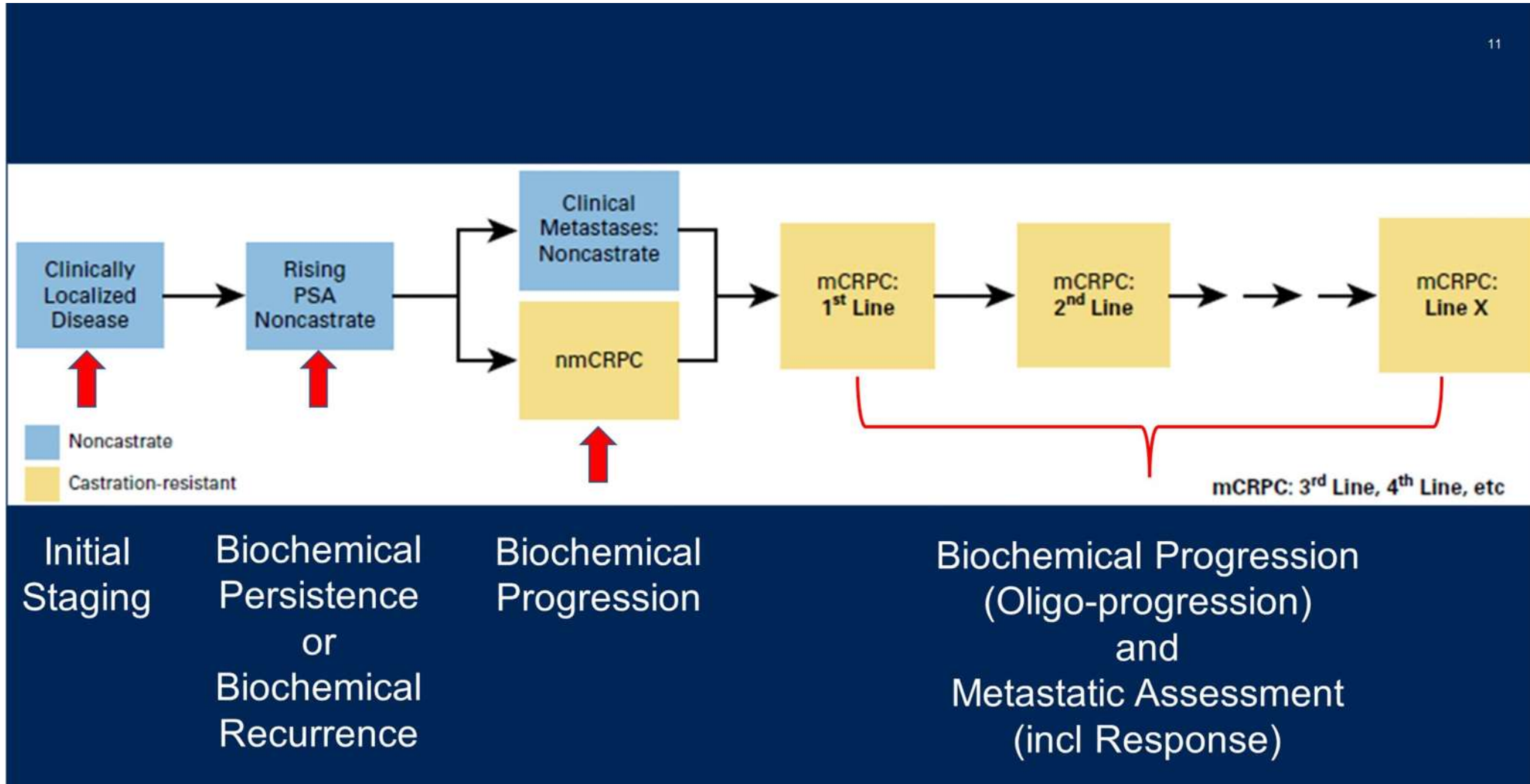
Dr. Deniz Tural
Bakırköy Dr. Sadi Konuk Eğitim ve Araştırma Hastanesi
Tıbbi Onkoloji

Ders programı

- ☐ **Prostat kanserinin seyri**
- ☐ **Lokalize yüksek riskli prostat kanseri tedavisinde yenilikler**
- ☐ **İzole PSA nüksü olan hastalarda yeni tedavi seçeneği**
- ☐ **Kastrasyona duyarlı metastatik prostat kanserinde yeni tedavi seçeneği**
- ☐ **Kastrasyona dirençli metastatik prostat kanserinde yeni tedavi seçeneği**
- ☐ **Gelecek perspektif**
- ☐ **Sonuç**

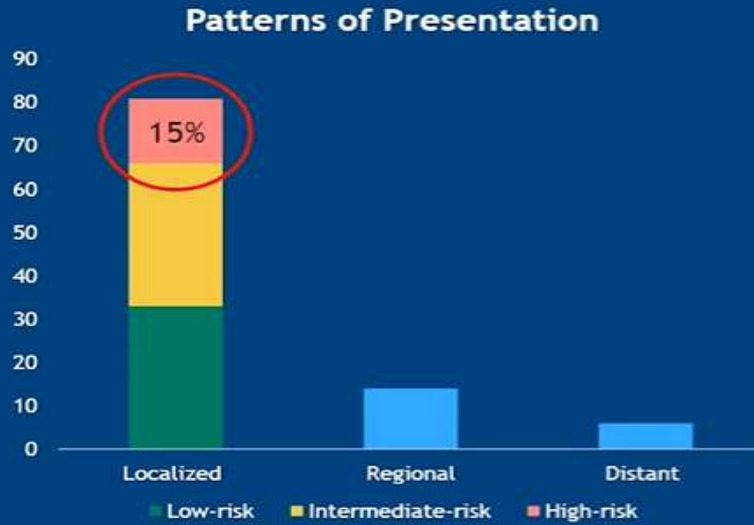
Prostat Kanserinde Klinik Seyir

11



Lokalize Yüksek Riskli Prostat Kanseri

Localized High-Risk Prostate Cancer



Increased Mortality in High-Risk Prostate Cancer

High-Risk Feature	15-Year PCSM
PSA > 20 ng/mL	22%
Gleason 8-10	34%
cT3	38%
High-risk Disease*	19%

PCSM=Prostate cancer specific mortality; PSA=Prostate specific antigen. *Defined by D'Amico criteria: PSA > 20 ng/mL, Gleason 8-10, or cT2c-T3.

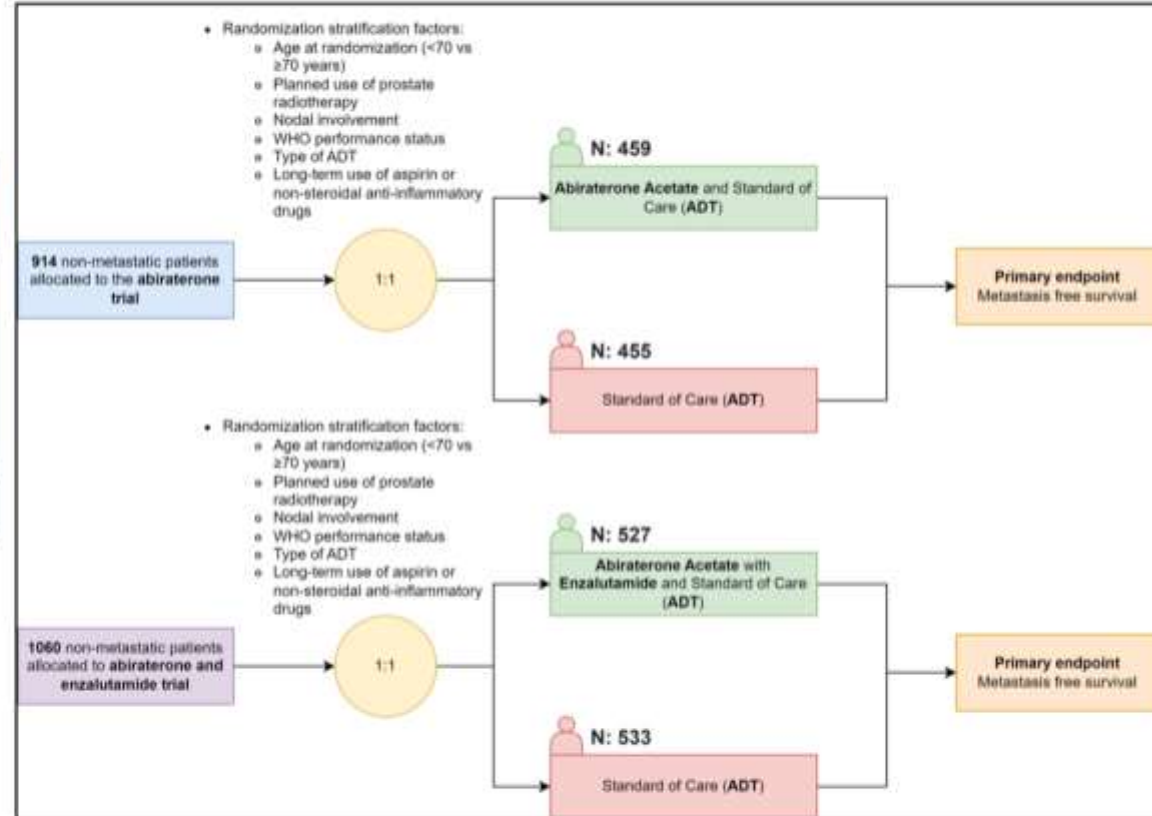
Cooperberg, JCO, 2010; Eggener, J Urol, 2011

- Patients with high-risk disease have an increased risk of biochemical recurrence (BCR), metastases, and death from prostate cancer
- 20% to 40% of patients with high-risk localized disease who undergo RP and/or RT develop BCR

Yüksek Riskli Lokalize Prostat Kanserinde Tedavi Seçeneği

PHASE III STAMPEDE TRIAL STUDY DESIGN

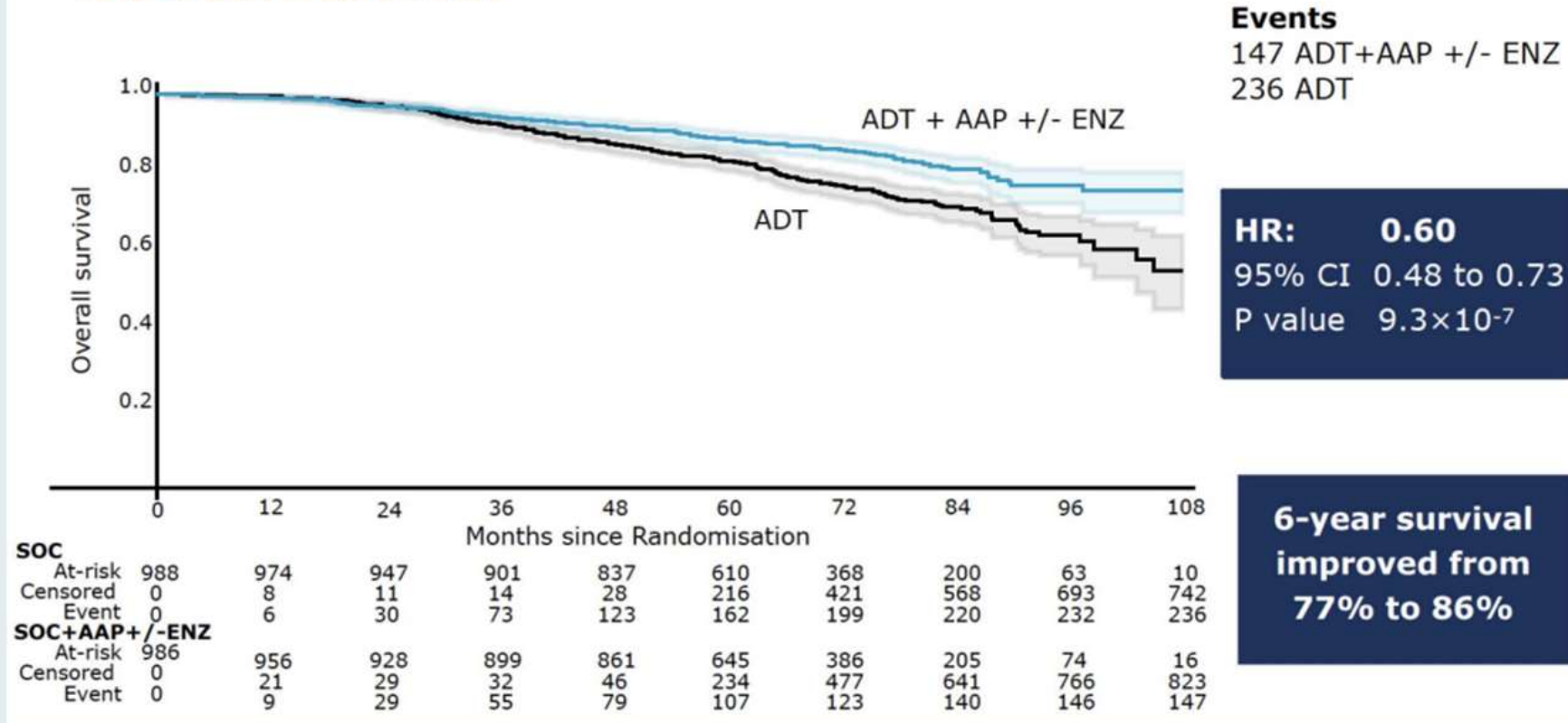
Inclusion criteria	Type of definitive therapy	High risk definition
High risk local, or locally advanced - histologically confirmed prostatic adenocarcinoma	Planned for radiation therapy	Either: a) at least two of the following: - T3 or T4 - GS 8-10 - PSA ≥ 40 ng/mL b) Relapsing with high-risk features (≤ 12 months of total ADT with an interval of ≥ 12 months without treatment and a PSA ≥ 4 ng/ml with a doubling time of < 6 months or a PSA ≥ 20 ng/ml)



Yüksek Riskli Prostat Kanserinde Tedavi Seçeneği

Overall Survival with the Addition of Abiraterone Acetate and Prednisolone with or without Enzalutamide to ADT for High-Risk M0 Prostate Cancer

Overall survival



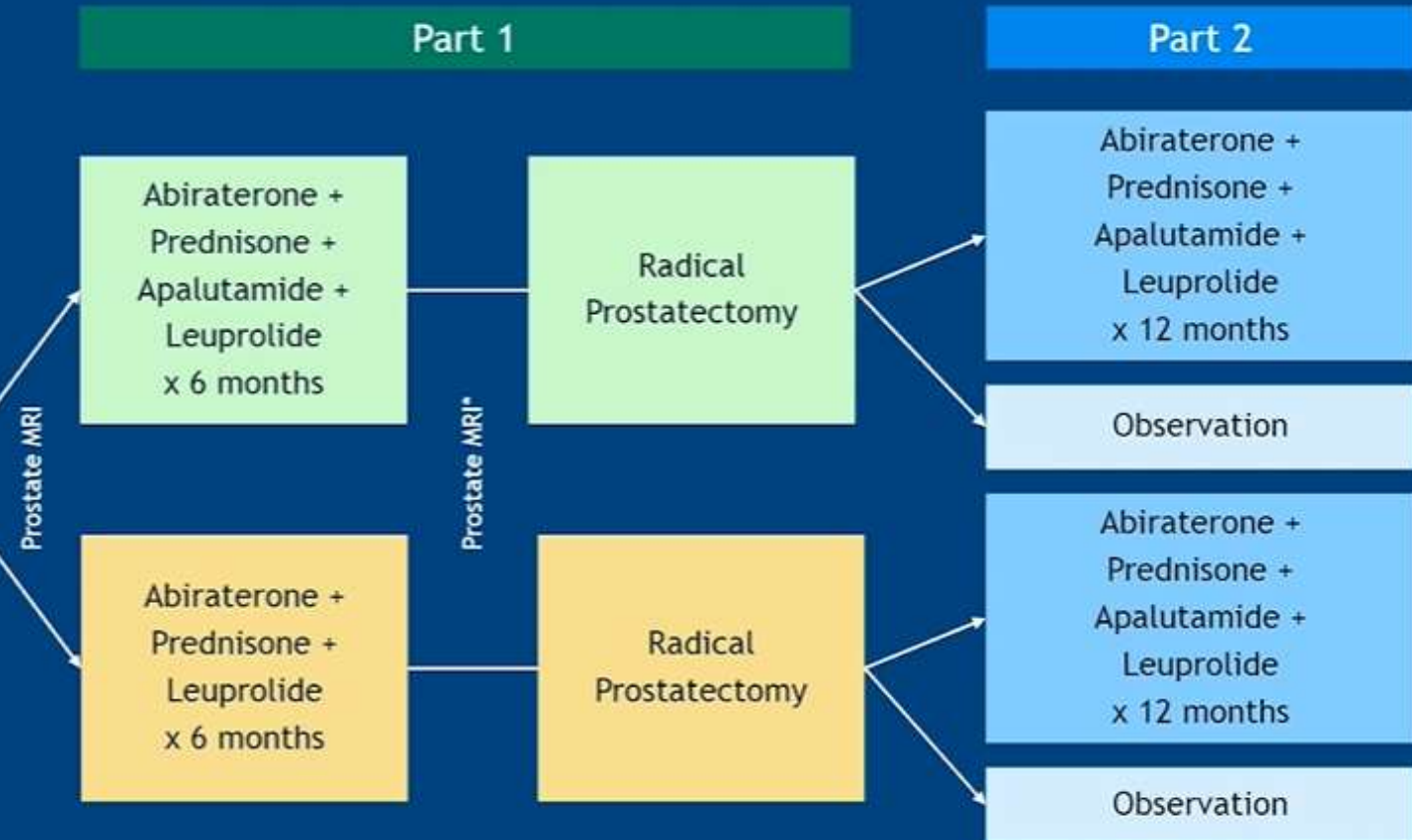
Neoadjuvan Yeni Nesil AR-yolağı İnhibötörleri

Trial Schema

Key Inclusion Criteria:

- Prostatic adenocarcinoma
- Gleason score $\geq 4+3=7$, PSA >20 ng/mL or T3 disease (by prostate MRI)
- Pelvic lymph nodes <20 mm
- 3 cores involved with cancer (minimum of 6 cores obtained) or >1 cm tumor or T3 disease on MRI
- ECOG Performance Status 0-1

N=120



Primary Part 1: Rate of pCR + MRD (≤ 5 mm tumor) by central review

Primary Part 2: 3-year Biochemical PFS

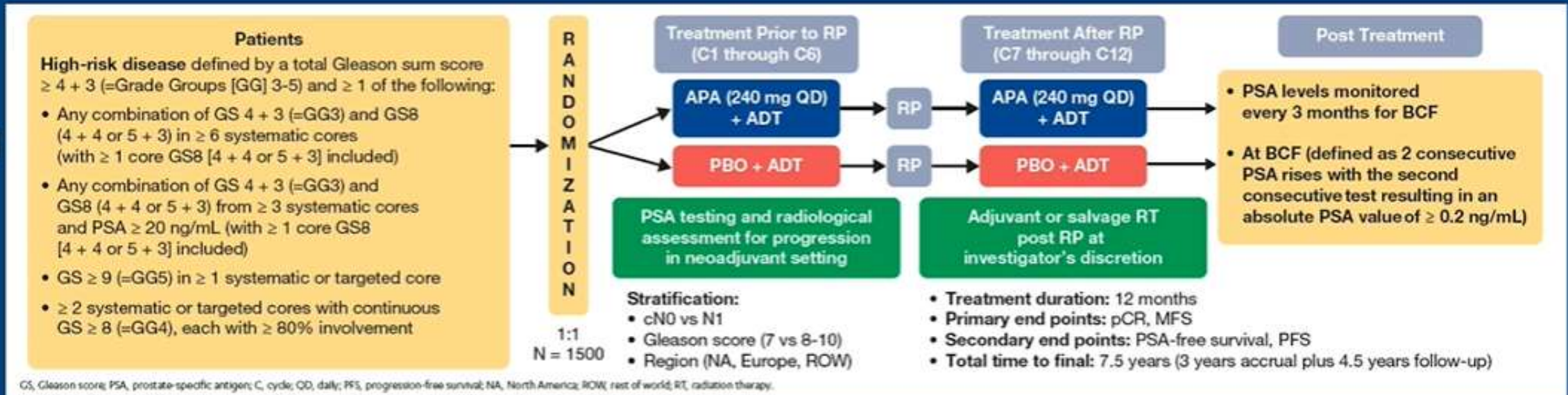
NCT02903368

PSA=Prostate specific antigen; MRI=Magnetic resonance imaging; ECOG=Eastern Cooperative Oncology Group; pCR=Pathologic complete response; MRD=Minimum residual disease; PFS=Progression-free survival. Part 1: Randomization will be stratified by risk factor: Intermediate (Gleason 4+3) vs. high risk (Gleason >7 , or PSA >20 , or T3 disease). Part 2: Randomization will be stratified by type of neoadjuvant therapy and pathological T-stage ($< pT3$ versus $\geq pT3$) at radical prostatectomy. Receipt of adjuvant radiation therapy is at the discretion of treating clinician. *Performed in a subset of patients.

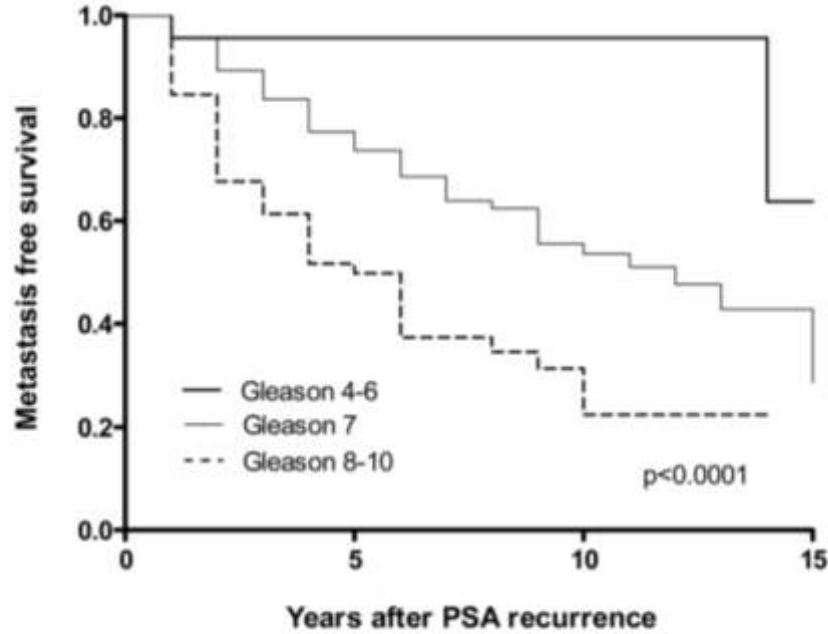
Devam Eden Çalışmalar

Proteus

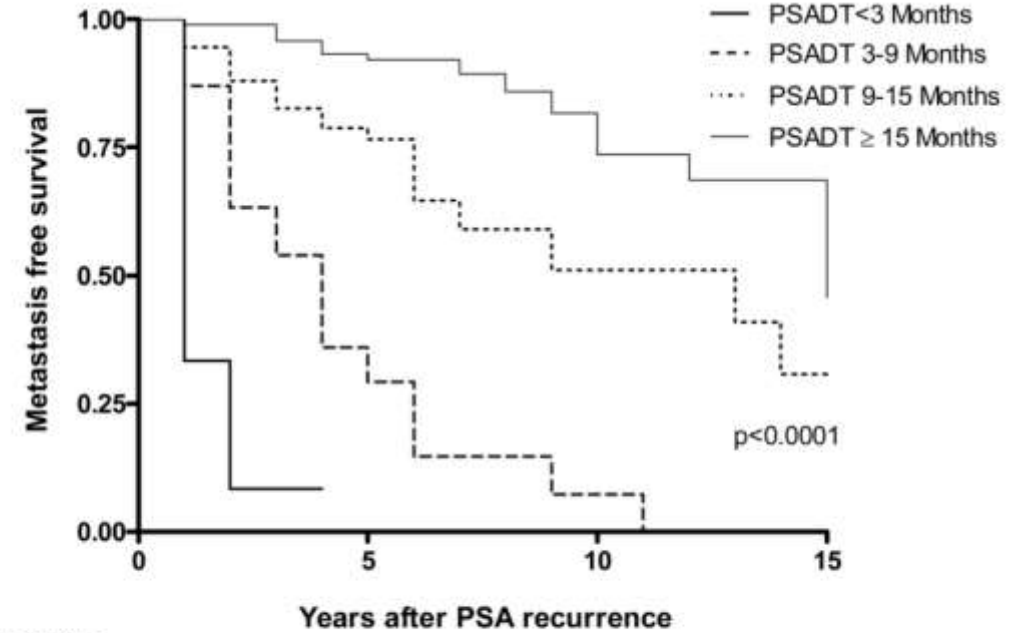
Randomized, Double-blind, Placebo-Controlled, Phase 3 Study of Apalutamide in Subjects with High-risk, Localized or Locally Advanced Prostate Cancer Who are Candidates for Radical Prostatectomy



Biyokimyasal Rekürens Metastaz riski



Number at risk		Years after PSA recurrence			
Gleason score 4-6	88	26	6	1	
Gleason score 7	239	85	29	3	
Gleason score 8-10	123	28	7	0	



Number at risk		Years after PSA recurrence			
PSADT < 3 Month	46	0	0	0	
PSADT 3-9 Month	106	16	2	0	
PSADT 9-15 Month	86	37	11	1	
PSADT ≥ 15 Month	212	86	30	3	

Cerrahi sonrası medyan 8 yıl takip süresinde, 450 biyokimyasal nüks gelişen ve herhangi bir salvage tedavi almayan hastanın 134'de metastaz görüldü (%29.8) .

Biyokimyasal Rekürens ve PSA Persistansı Doz Yoğun Tedavi

FORMULA 509 Schema

Patients With Recurrent Prostate Cancer After Prostatectomy

Stratify

1. PSA >0.5 vs. ≤0.5
2. pN1 vs. pN0

N=345

R
A
N
D
O
M
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Z
E

Salvage Radiation
with **6 mo GnRH Agonist and
bicalutamide**

Salvage Radiation
with **6 mo GnRH Agonist,
Abiraterone Acetate plus
Prednisone, and Apalutamide**

Primary outcome: Progression-free survival

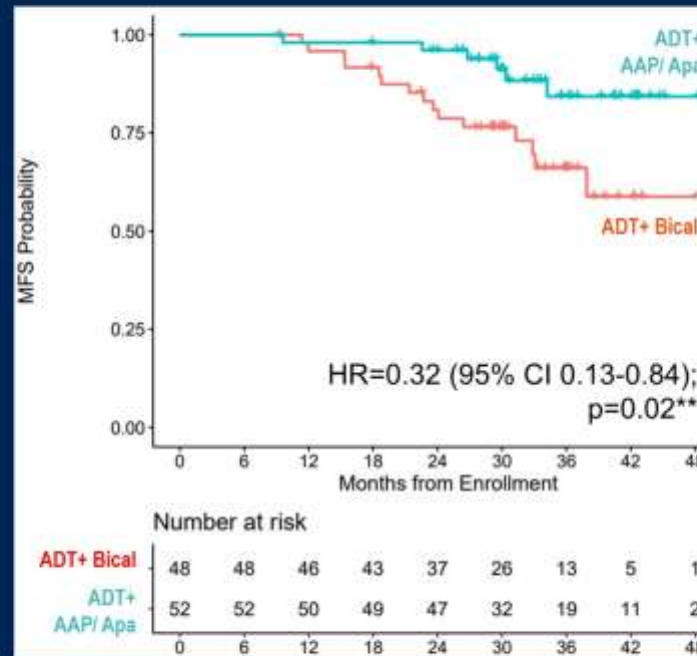
Secondary outcomes: Metastasis-free survival, Physician-reported toxicity,
Patient-reported toxicity



Biyokimyasal Rekürens ve PSA Persistansı

Doz Yoğun Tedavi

MFS Benefit Among PSA >0.5 (n=100)



3 year MFS
84.3% vs. 66.1%

Absolute improvement
18.2% at 3 years

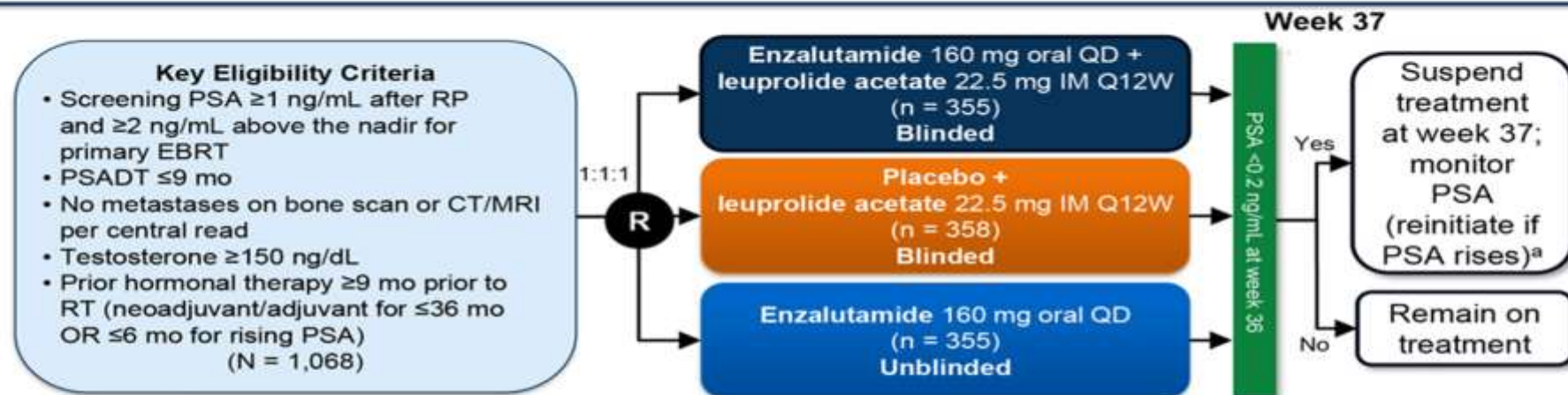
NNT = 5

**two-sided



İzole PSA nüksü olan hastalarda tedavi seçeneği

Phase 3 EMBARK: Enzalutamide Plus Leuprolide Acetate¹⁻⁶



- **Stratification factors:** screening PSA (≤ 10 ng/mL vs > 10 ng/mL), PSADT (≤ 3 mo vs > 3 to ≤ 9 mo), prior hormonal therapy (yes vs no)
- **Primary endpoint^b:** MFS by BICR (enzalutamide + leuprolide acetate vs leuprolide acetate)
- **Key secondary endpoints^{b,c}:** MFS by BICR (enzalutamide vs leuprolide acetate), time to PSA progression, time to first use of new antineoplastic therapy, OS^c
- **Other secondary endpoints:** safety,^d PRO

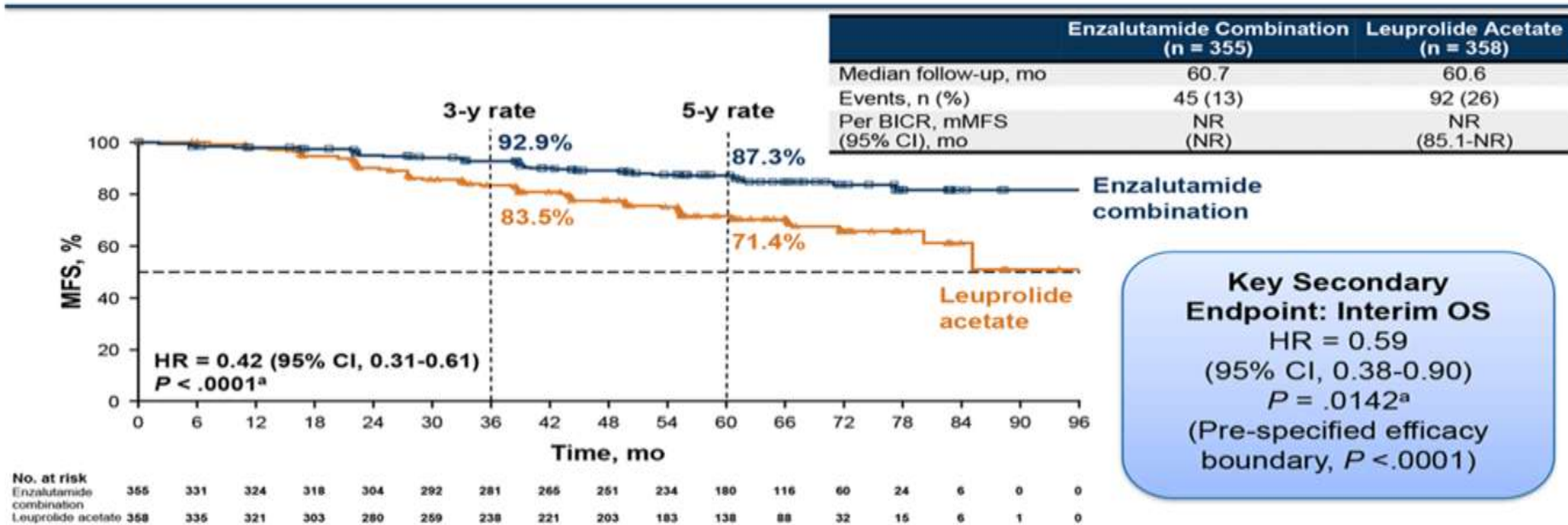
^a Study treatment was suspended once at week 37 if PSA was < 0.2 ng/mL and restarted when PSA was ≥ 5.0 ng/mL (without prior RP) and ≥ 2 ng/mL (prior RP). ^b ITT population. ^c Primary endpoint and key secondary endpoints for enzalutamide combination and enzalutamide monotherapy are alpha-protected. ^d P value to determine significance for OS of combination and monotherapy treatment comparisons was dependent on outcomes of primary endpoint and key secondary endpoints. ^e Safety population.

1. <https://clinicaltrials.gov/study/NCT02319837>. 2. Shore ND et al. AUA 2023. Abstract LBA02-09. 3. Freedland SJ et al. *N Engl J Med*. 2023;389:1453-1465. 4. Freedland SJ et al. *NEJM Evid*. 2023;2. 5. Shore ND et al. ASCO GU 2024. Abstract 15. 6. Shore ND et al. ASCO GU 2024. Abstract 156.

PeerView.com

İzole PSA nüksü olan hastalarda tedavi seçeneği

Phase 3 EMBARK: Met Primary Endpoint of MFS^{1,2}



Data cutoff: January 31, 2023. Symbols indicate censored data. ^aHR was based on a Cox regression model with treatment as the only covariate stratified by screening PSA, PSADT, and prior hormonal therapy as reported in the IWRS; relative to leuprolide acetate <1 favoring enzalutamide combination; the two-sided P value was based on a stratified log-rank.

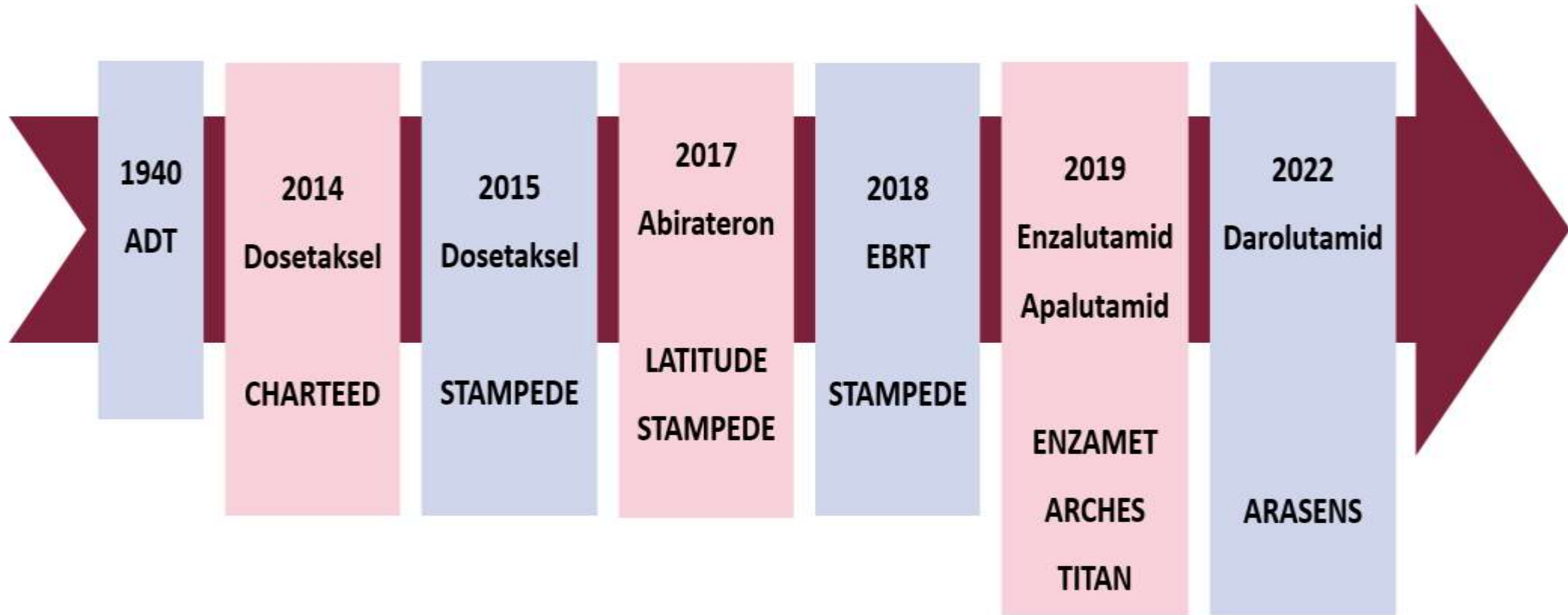
1. Shore ND et al. AUA 2023. Abstract LBA02-09. 2. Freedland SJ et al. *N Engl J Med*. 2023;389:1453-1465.

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İzole PSA nüksü olan hastalarda tedavi seçeneđi

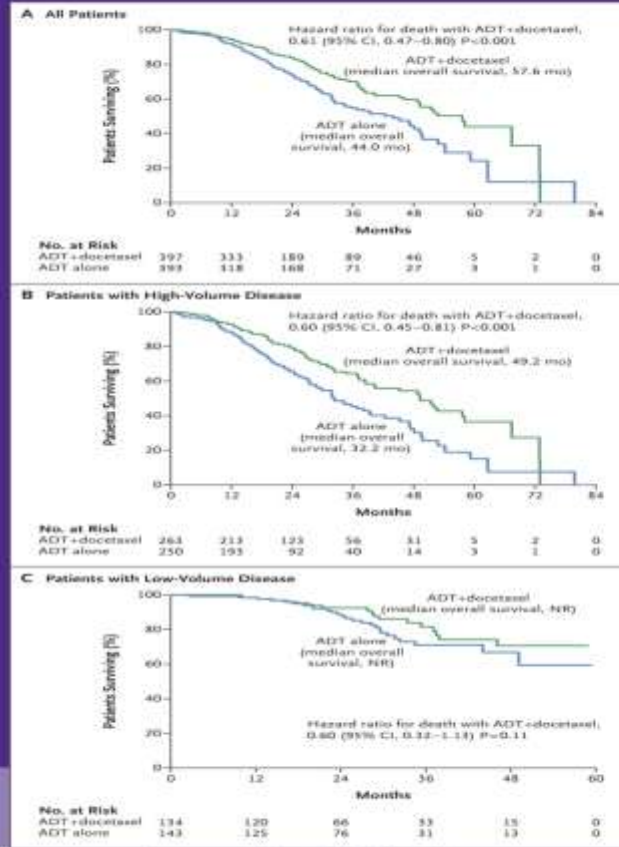


Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavi Tarihçesi



Hastalık Volümü Dosetaksel Tedavi Etkinliği için Prediktif

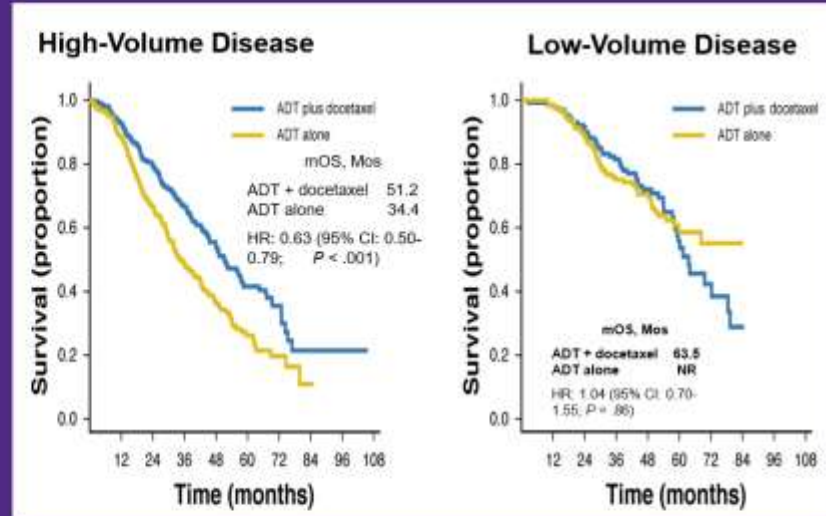
CHAARTED: ADT +/- Docetaxel in mHSPC



Sweeney CJ et al. NEJM 2015

(N = 790, Median follow-up 53.7m)

Long-Term Follow-up: High-Volume vs Low-Volume Disease

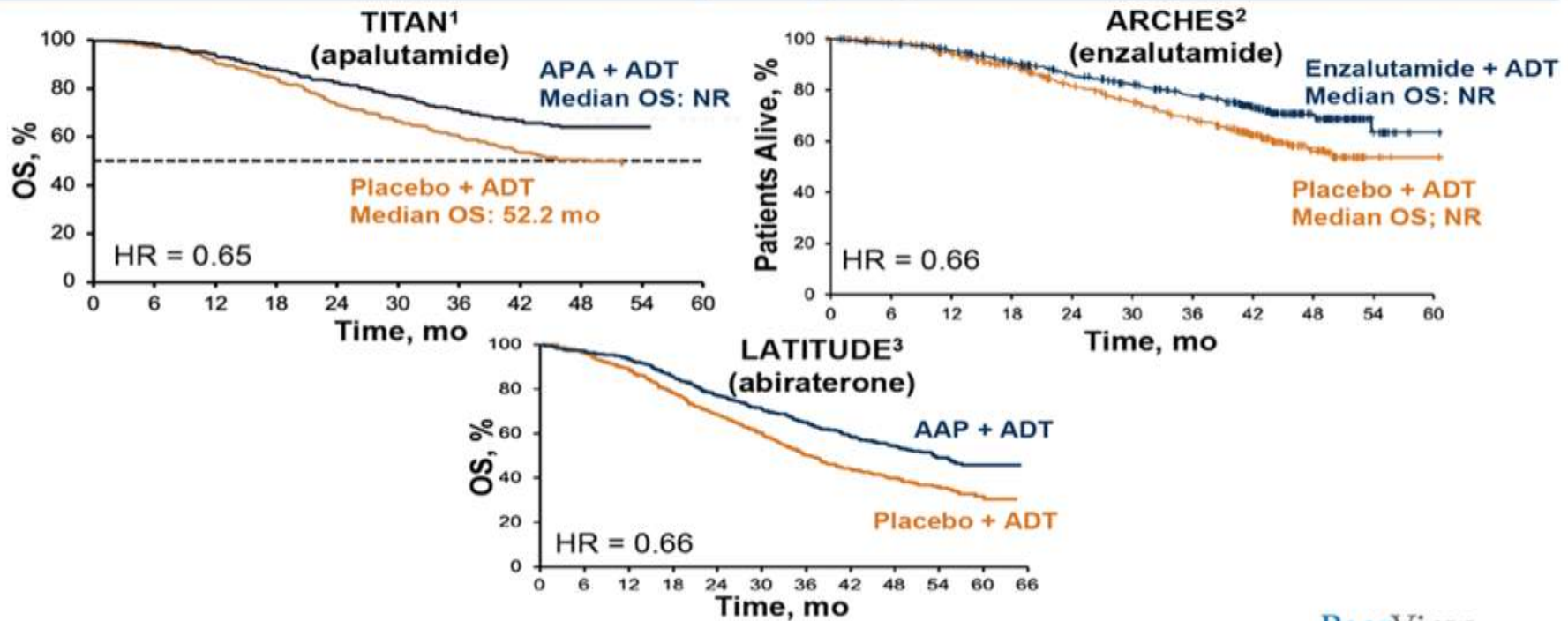


Kyriakopoulos CE, et al. J Clin Oncol. 2018

Yüksek volümlü hastalığı olanlar; visceral organ metastazı olan yada ≥ 4 kemik lezyonu olan ve en az ≥ 1 vertebra, pelvis dışı kemiklerde metastaz olmalı

Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

OS Benefit Confirmed With Other AR-Targeting Agents



1. Chi KN et al. *J Clin Oncol*. 2021;39:2294-2303. 2. Armstrong AJ et al. *J Clin Oncol*. 2022;41:1616-1622. 3. Fizazi K et al. *Lancet Oncol*. 2019;20:686-700.

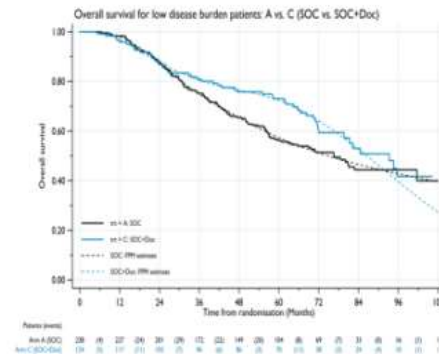
Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

VIRTUAL ESMO congress 2020

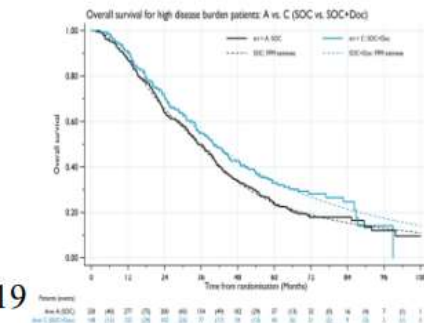
Should we count the metastases for decision making about systemic treatment? **No !!!**

Docetaxel

Low burden



High burden



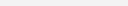
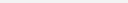
Clarke N, Ann Oncol 2019

Hormonal agents

STAMPEDE (Abi)

Low risk	59/220	41/208		0.657 (0.438-0.983)	0.041
High risk	136/232	94/241		0.536 (0.411-0.699)	<0.001

TITAN (Apa)

Disease volume						
High	109/325	173/335	NE	14.9		0.53 (0.41-0.67)
Low	25/200	58/192	NE	30.5		0.36 (0.22-0.57)

ENZAMET (Enza)

Volume of disease					
Low	22/272	46/265		0.43 (0.26-0.72)	
High	80/291	97/297		0.80 (0.59-1.07)	

Hoyle A, ESMO 2018; Chi K, NEJM 2019, Davis I, NEJM 2019

Yaşam Beklentisi ≥ 1 yıl olan tüm evre IV hastalara ADT+ Yeni nesil androjen yolağı inhibitörleri önerilir

Recommendations	Strength rating
Offer immediate systemic treatment with androgen deprivation therapy (ADT) to palliate symptoms and reduce the risk for potentially serious sequelae of advanced disease (spinal cord compression, pathological fractures, ureteral obstruction) to M1 symptomatic patients.	Strong
At the start of ADT offer luteinising hormone-releasing hormone (LHRH) antagonists or orchiectomy to patients with impending clinical complications like spinal cord compression or bladder outlet obstruction.	Strong
Offer early systemic treatment to M1 patients asymptomatic from their tumour.	Strong
Offer short-term administration of an older generation androgen receptor (AR) antagonist to M1 patients starting LHRH agonist to reduce the risk of the 'flare-up' phenomenon.	Weak
Do not offer AR antagonist monotherapy to patients with M1 disease.	Strong
Discuss combination therapy including ADT plus systemic therapy with all M1 patients.	Strong
Do not offer ADT monotherapy to patients whose first presentation is M1 disease if they have no contra-indications for combination therapy and have a sufficient life expectancy to benefit from combination therapy (≥ 1 year) and are willing to accept the increased risk of side effects.	Strong
Offer ADT combined with abiraterone acetate plus prednisone or apalutamide or enzalutamide to patients with M1 disease and who are fit for the regimen.	Strong
Offer docetaxel only in combination with ADT plus abiraterone or darolutamide to patients with M1 disease and who are fit for docetaxel.	Strong
Offer ADT combined with non-curative prostate radiotherapy (using doses up to the equivalent of 72 Gy in 2 Gy fractions) to patients whose first presentation is M1 disease and who have low volume of disease by CHAARTED criteria/M1a disease.	Strong
Do not offer ADT combined with any local treatment (RT/surgery) to patients with high-volume (CHAARTED criteria) M1 disease outside of clinical trials (except for symptom control).	Strong
Do not offer ADT combined with surgery to M1 patients outside of clinical trials.	Strong
Only offer metastasis-directed therapy to M1 patients within a clinical trial setting or well-designed prospective cohort study.	Strong

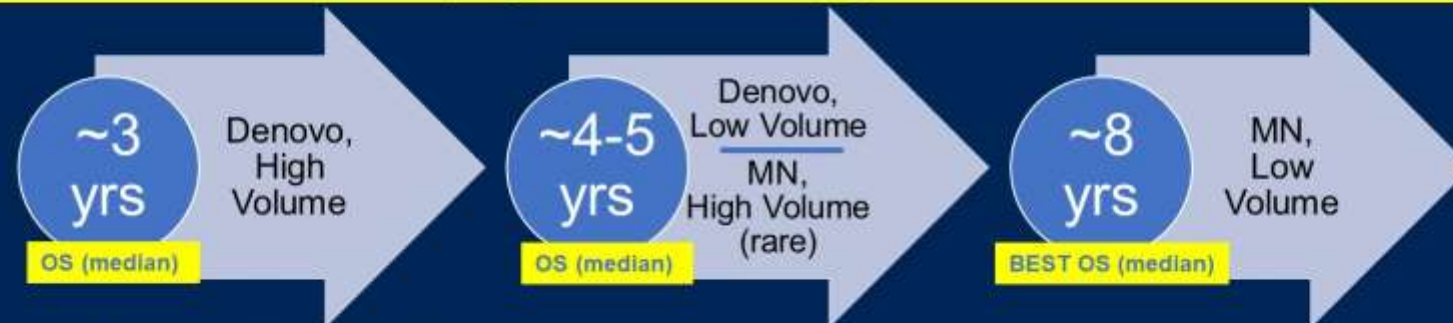
**All the following statements are based on metastatic disease defined by bone scintigraphy and CT scan/MRI.*

TANI ANINDA METASTATİK VE YÜKSEK VOLÜMLÜ HASTALIK AGRESİF SEYİRLİ

Metastatic HSPC Trials – Clinical Risk Groups

	CHAARTED N= 790	STAMPEDE, M1 N= 1086	LATITUDE N=1199	STAMPEDE, M1 N=999	ENZAMET N=1125	TITAN N=1052
ADT + *(NSAA)	DOC	DOC	ABI	ABI	ENZA*	APA
PRIMARY ENDPOINT, OS HR (95%, CI)	0.72 (0.59-0.89)	0.81 (0.69-0.95)	0.66 (0.56-0.78)	0.61 (0.49-0.75)	0.67 (0.52-0.86)	0.65 (0.53-0.79)

Can clinical prognostic factors help guide treatment selection?



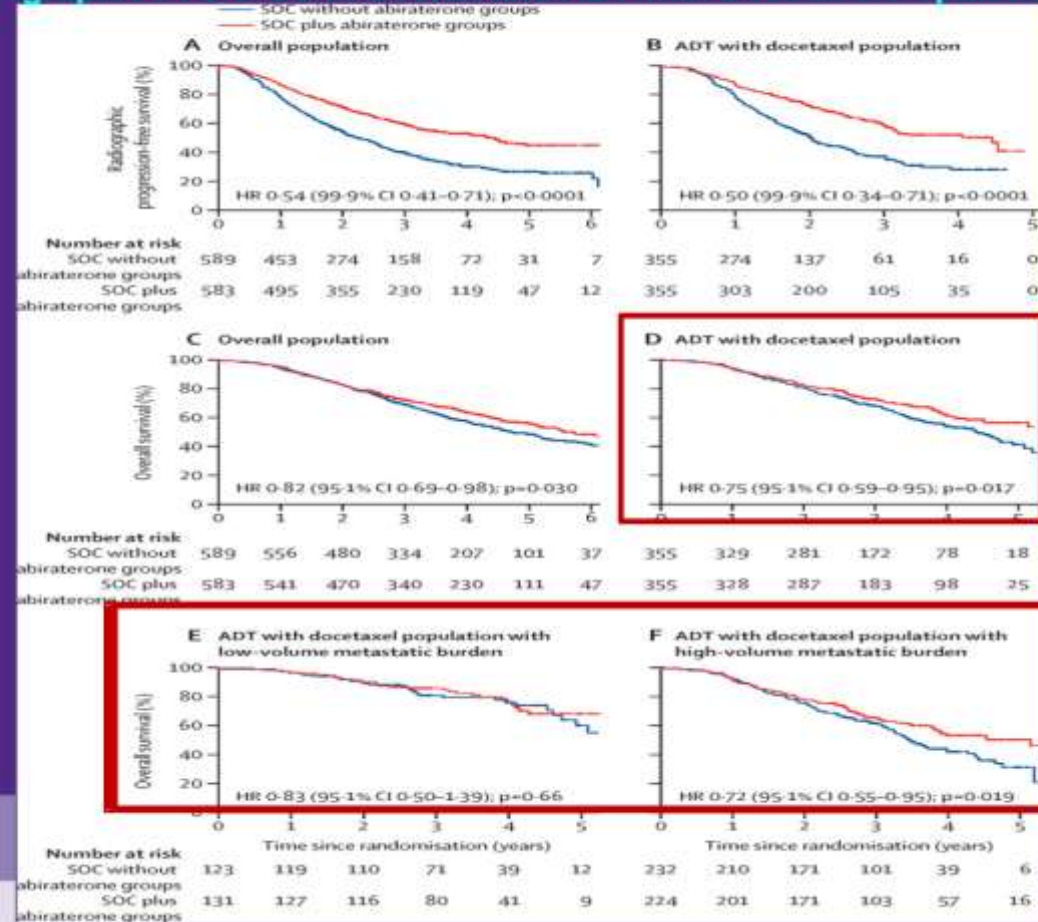
Denovo = new diagnosis/untreated
MN = metachronous diagnosis/previously treated

Modified from :Francini et al, Prostate, 2018; Gravis et al, Eur Urol, 2018

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Kastrasyona Duyarlı Metastatik Prostat Kanseri Üçlü Kombinasyon

Triplet #1: PEACE-1: ADT + Abiraterone/Prednisone in De Novo mHSPC Radiographic PFS & OS in Overall and ADT with Docetaxel Population



Fizazi et al:
Lancet 2022

Kastrasyona Duyarlı Metastatik Prostat Kanseri

Üçlü Kombinasyon

ARASENS Study Design

Global, randomized, double-blind, placebo-controlled phase III study (NCT02799602)

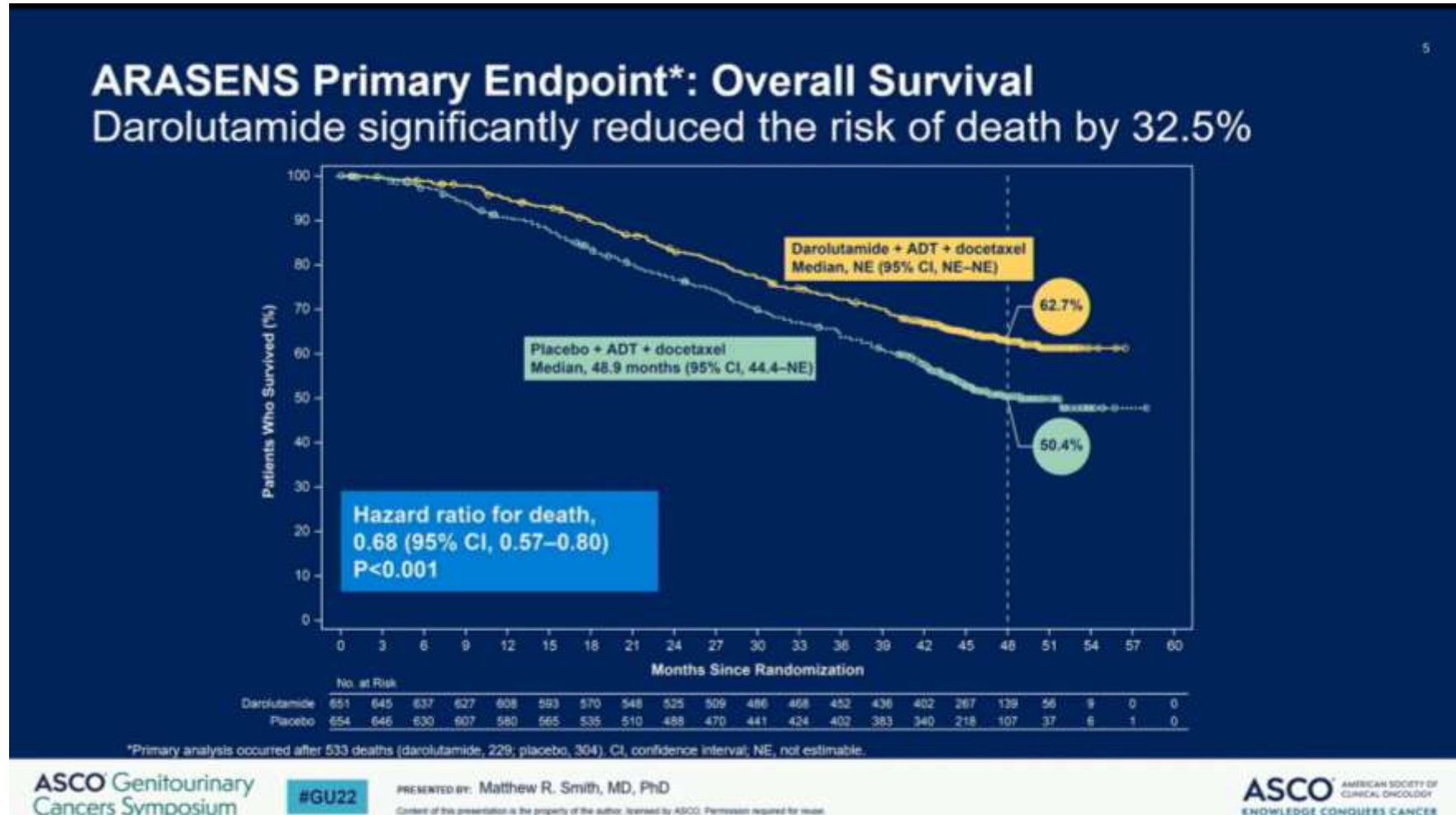


- The primary analysis was planned to occur after ~509 deaths
- Secondary efficacy endpoints were tested hierarchically

*One enrolled patient was excluded from all analysis sets because of Good Clinical Practice violations. ALP, alkaline phosphatase; CRPC, castration-resistant prostate cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; FPFV, first patient first visit; LPFV, last patient first visit; M1a, nonregional lymph node metastases only; M1b, bone metastases + lymph node metastases; M1c, visceral metastases + lymph node or bone metastases; Q3W, every 3 weeks; SSE, symptomatic skeletal event; ULN, upper limit of normal.

Kastrasyona Duyarlı Metastatik Prostat Kanseri

Üçlü Kombinasyon

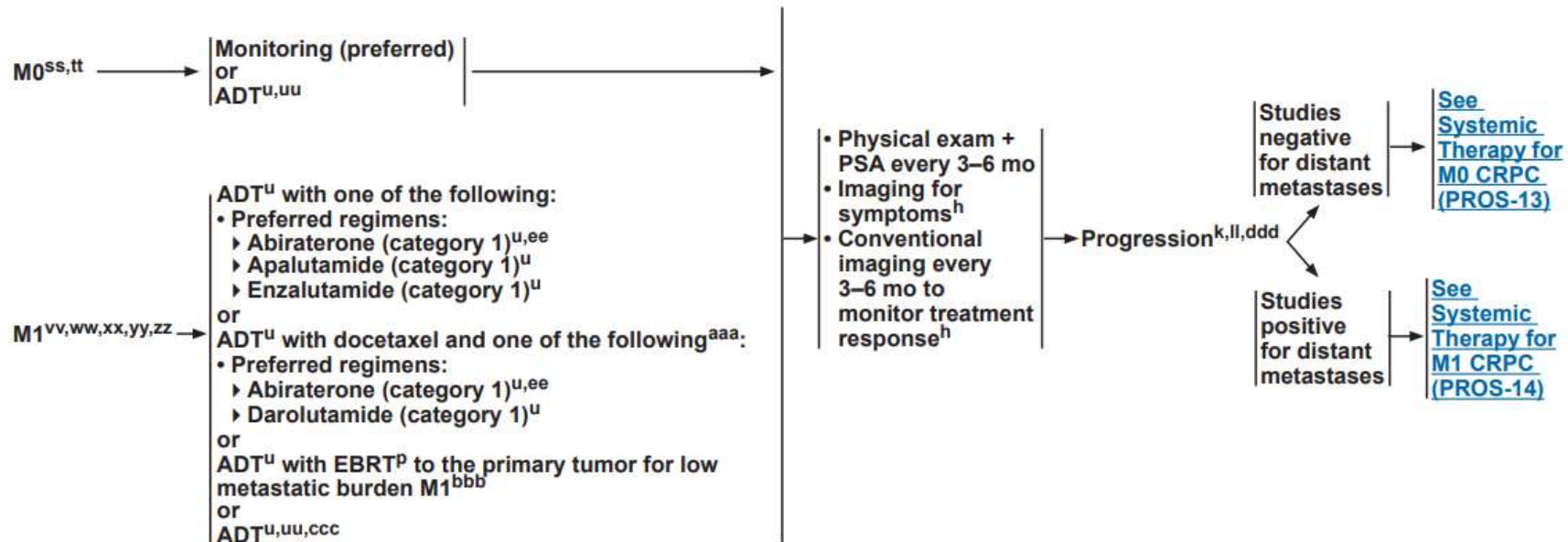


Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

PEACE-1: Adverse Events

	ADT with Docetaxel		ADT without Docetaxel	
	SOC + Abi (+/- RT)	SOC (+/- RT)	SOC + Abi (+/- RT)	SOC (+/- RT)
Any AE	346 (100%)	349 (100%)	226 (100%)	233 (99%)
Severe (grade >3)	217 (63%)	181 (52%)	149 (66%)	97 (41%)
Fatal (grade 5)	7 (2%)	3 (1%)	8 (4%)	5 (2%)
Frequent severe AEs				
Hypertension	76 (22%)	45 (13%)	66 (29%)	38 (16%)
Neutropenia	34 (10%)	32 (9%)	0	0
Hepatotoxicity	20 (6%)	2 (1%)	14 (6%)	3 (1%)
Febrile Neutropenia	18 (5%)	19 (5%)	2 (1%)	1 (<1%)
Fatigue	10 (3%)	15 (4%)	3 (1%)	0
Peripheral neuropathy	4 (1%)	6 (2%)	1 (<1%)	0

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Metastatik Kastrasyona Duyarlı Prostat Kanseri Tedavi



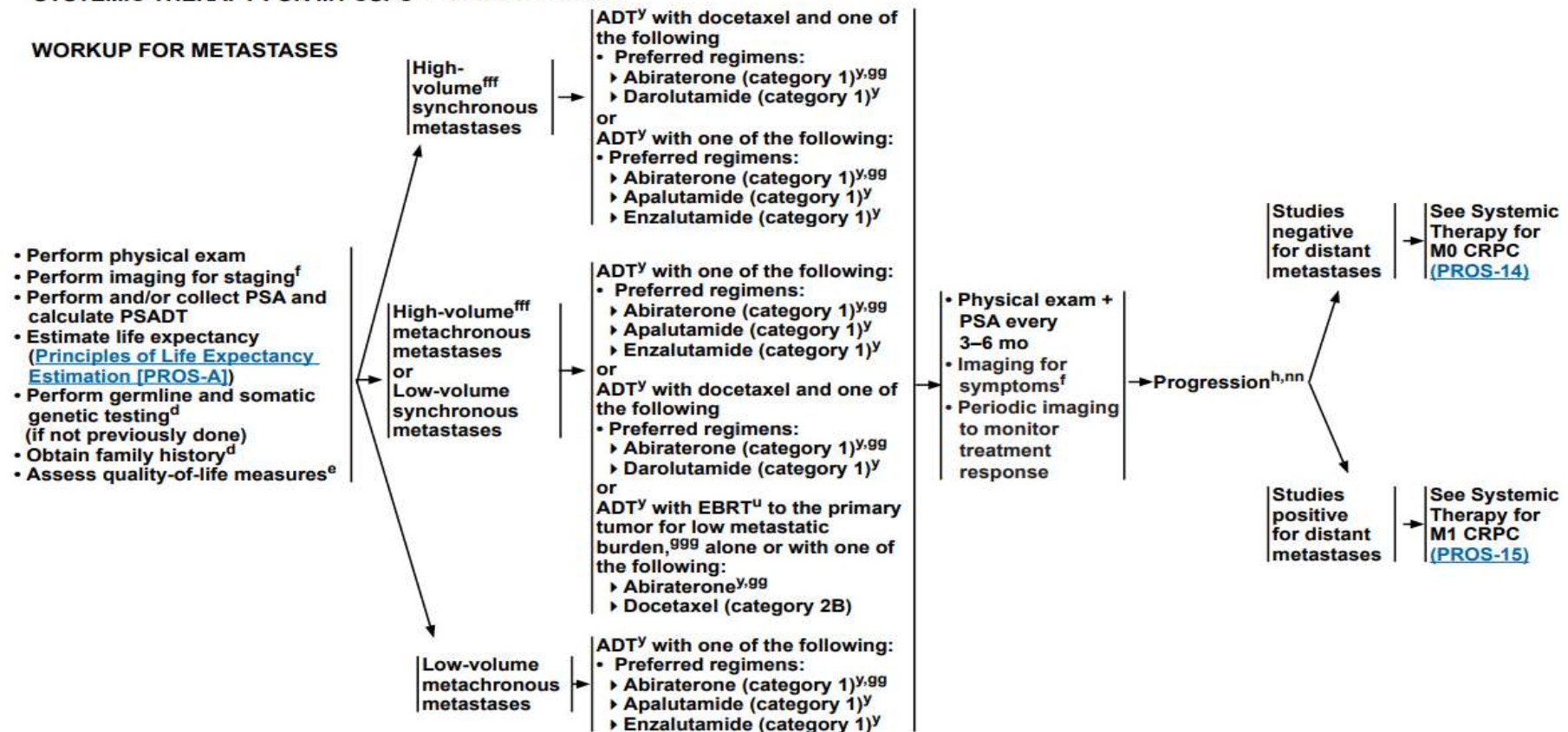
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SYSTEMIC THERAPY FOR M1 CSPC^{c,zz,aaa,bbb,ccc,ddd,eee}

WORKUP FOR METASTASES



Kastrasyona Dirençli Metastatik Prostat kanseri



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

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

Kastrasyona Dirençli Metastatik Prostat Kanseri Tedavisi

Treatment options in mCRPC

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

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

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

Kastrasyona Dirençli Metastatik Prostat kanseri



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SYSTEMIC THERAPY FOR M1 CRPC: ADENOCARCINOMA^{nnn,ooo,ppp}

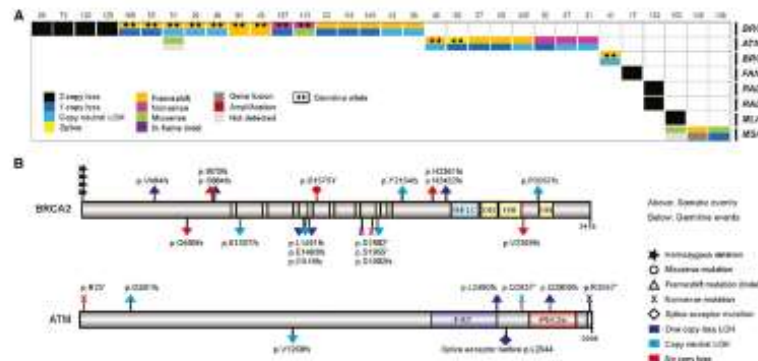
No prior docetaxel/no prior novel hormone therapy ^{qqq}	Progression on prior novel hormone therapy/no prior docetaxel ^{qqq}
- Preferred regimens - Abiraterone^{y,rrr} (category 1^{sss}) - Docetaxel^{lll} (category 1) - Enzalutamide^y (category 1) - Useful in certain circumstances - Niraparib/abiraterone^{y,lll,ttt}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

Evre IV Prostat Kanserinde Mutasyonlar

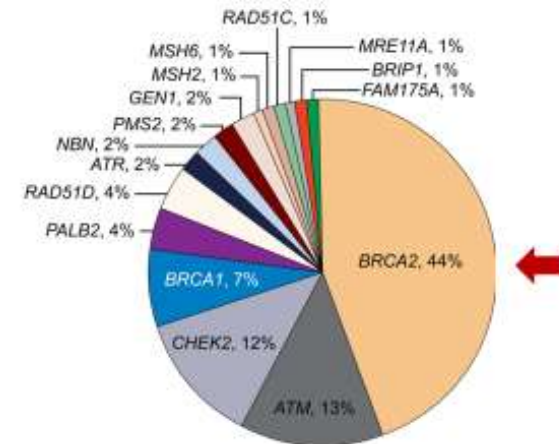
HRR Genes and Metastatic Prostate Cancer

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**



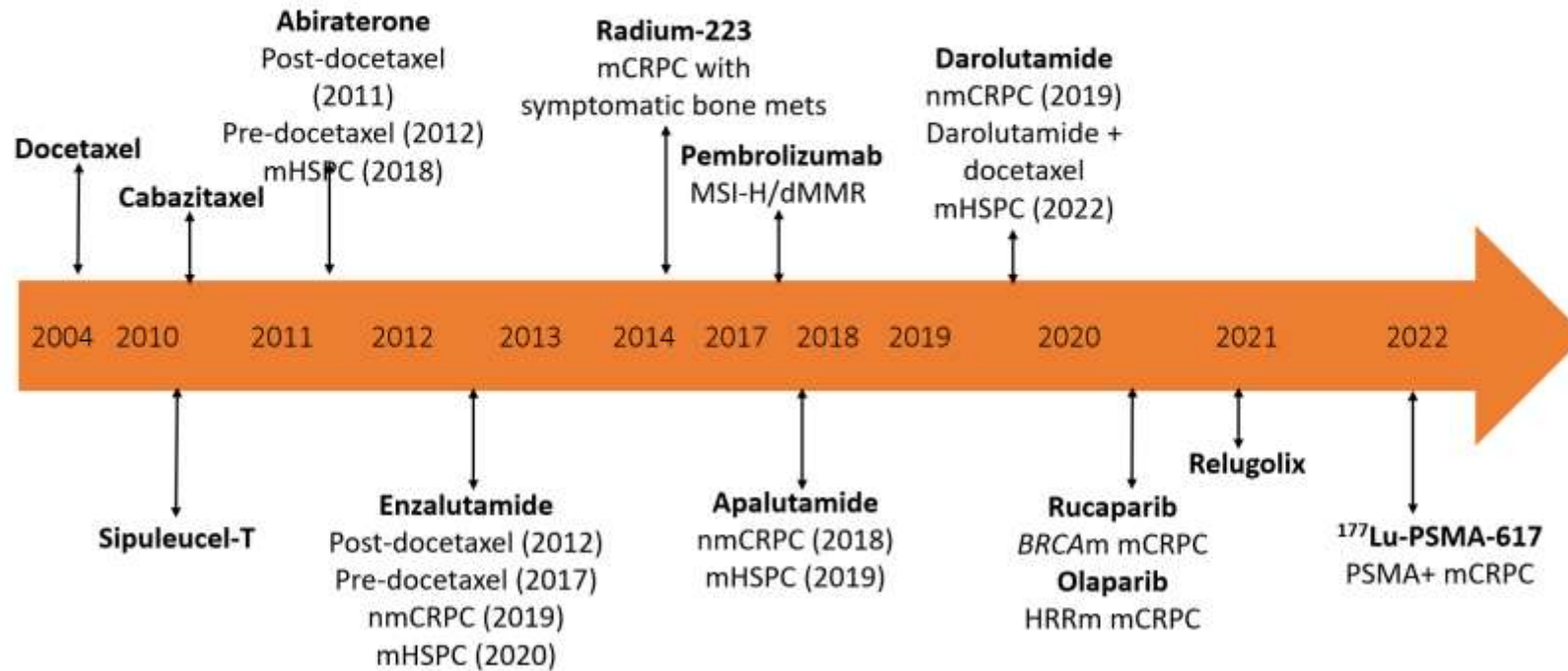
Germline



- **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 + Olaparib ¹

Published



MAGNITUDE: Abiraterone + Niraparib ²

Presented



TALAPRO-2: Enzalutamide + Talazoparib

Presented



CASPAR: Enzalutamide + Rucaparib

Enrolling



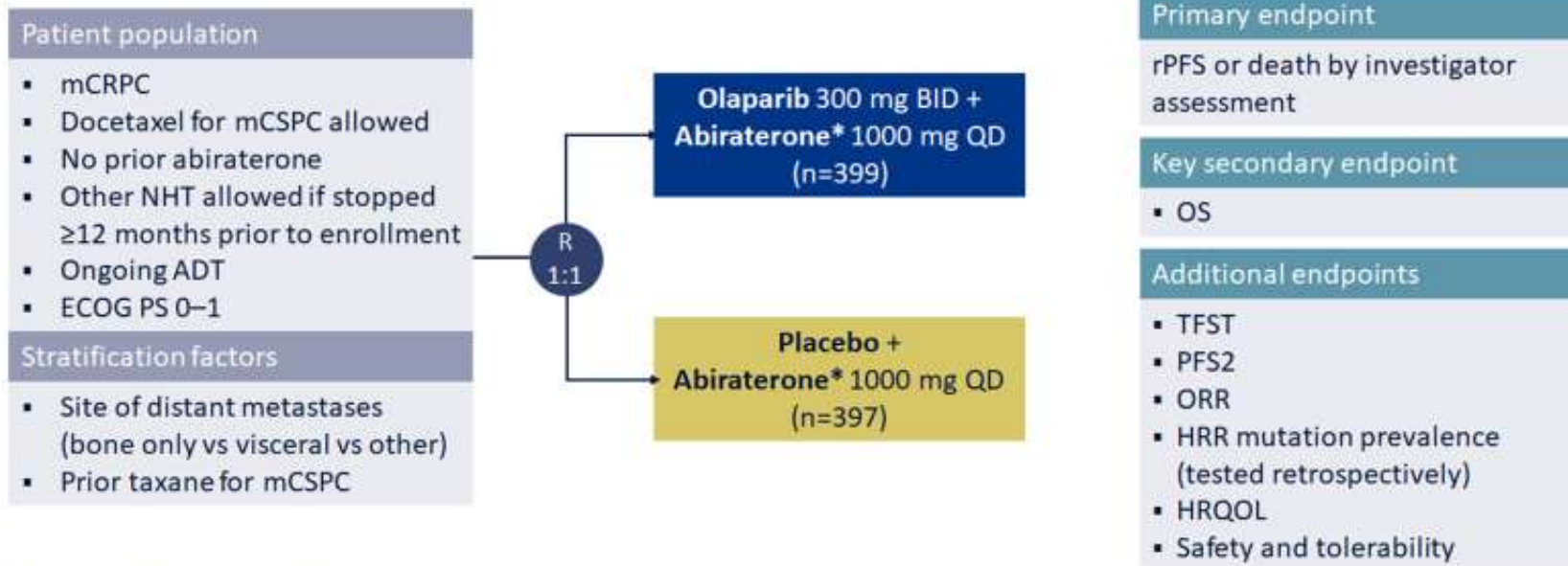
1- Clarke NW et al., NEJM Evidence. 2022 Aug 23;1(9):EVIDoa2200043.

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

Kastrasyona Dirençli Metastatik Prostat kanseri

PARP inhibitörleri+Androjen Reseptör yolağı blokörleri

PROpel: Phase III Trial of Abiraterone +/- Olaparib



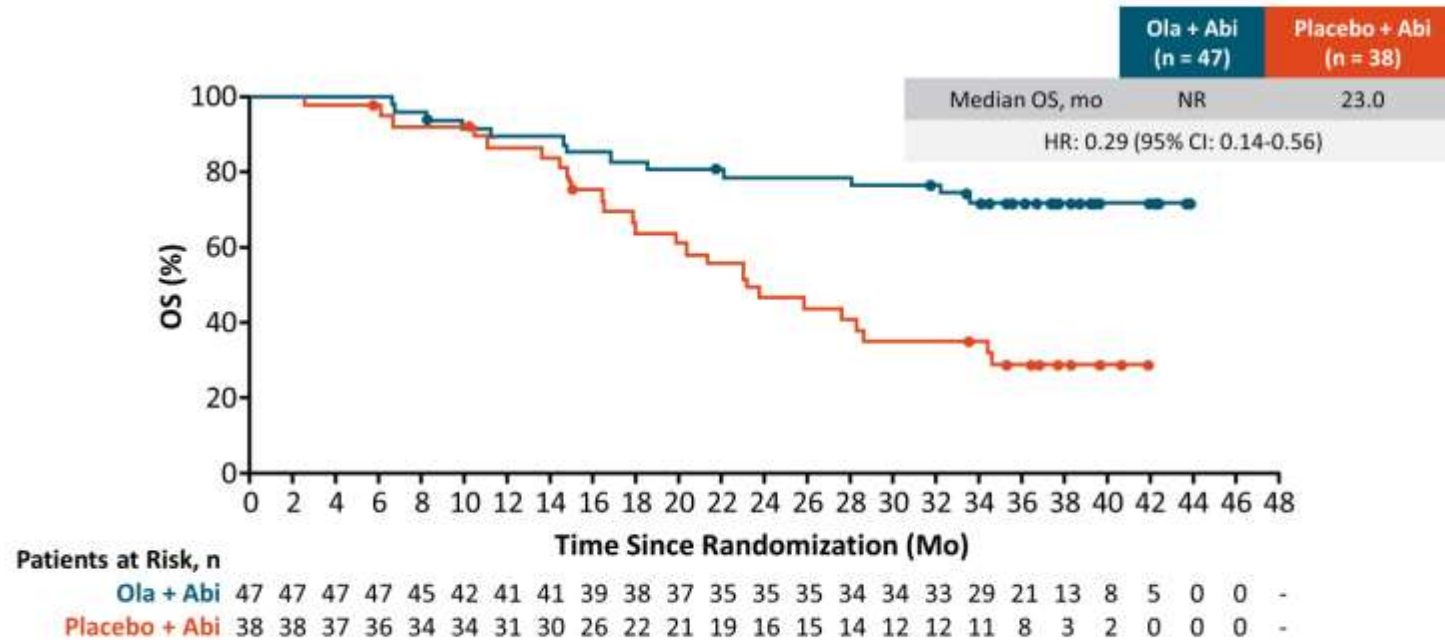
*Plus prednisone or prednisolone 5 mg BID

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

Kastrasyona Dirençli Metastatik Prostat kanseri

PARP inhibitörleri+Androjen Reseptör yolağı blokörleri

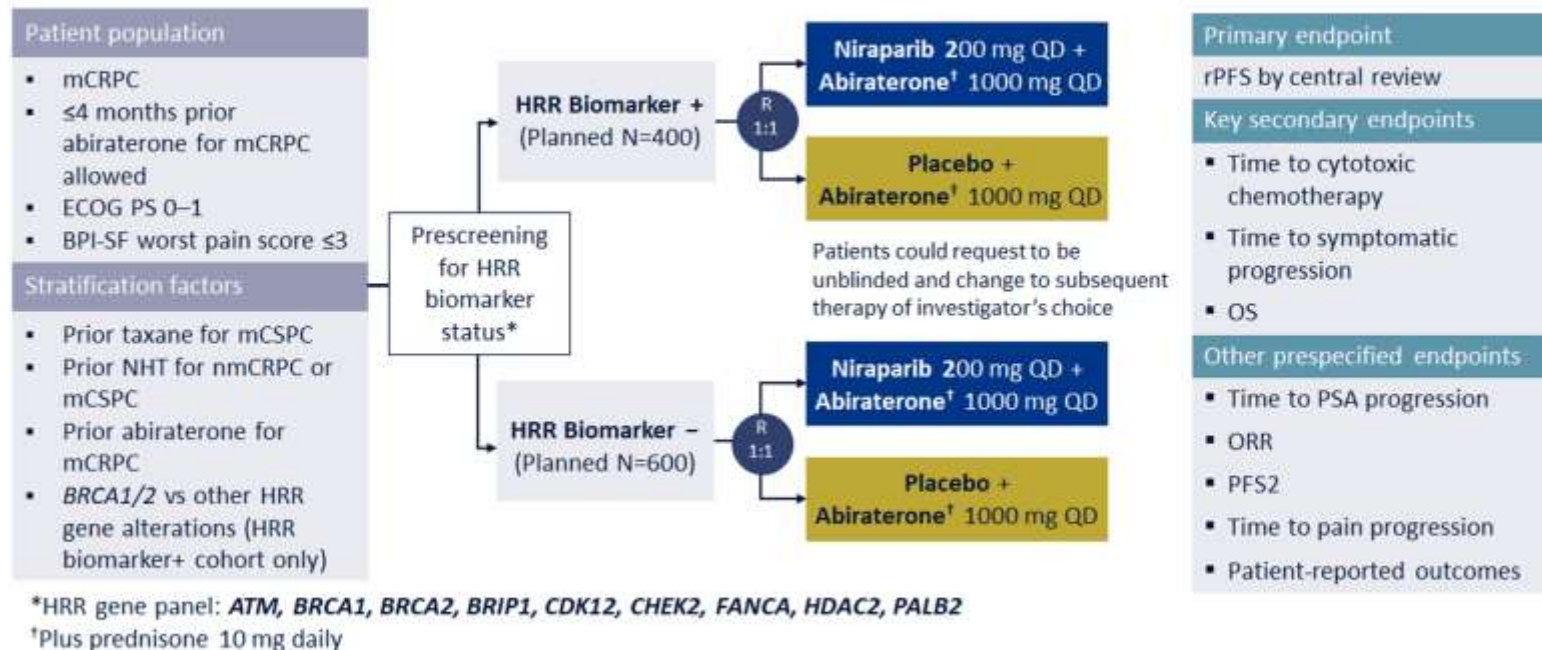
PROpel: OS in *BRCAm*



Kastrasyona Dirençli Metastatik Prostat kanseri

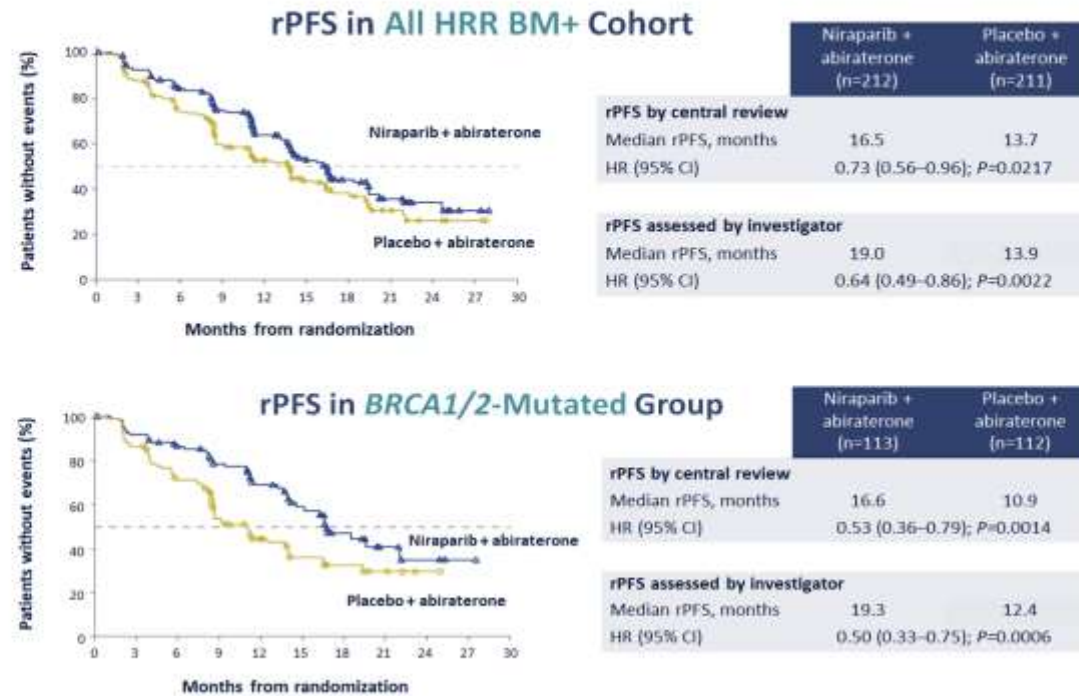
PARP inhibitörleri+Androjen Reseptör yolağı blokörleri

MAGNITUDE: Phase III Trial of Abi +/- Niraparib



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

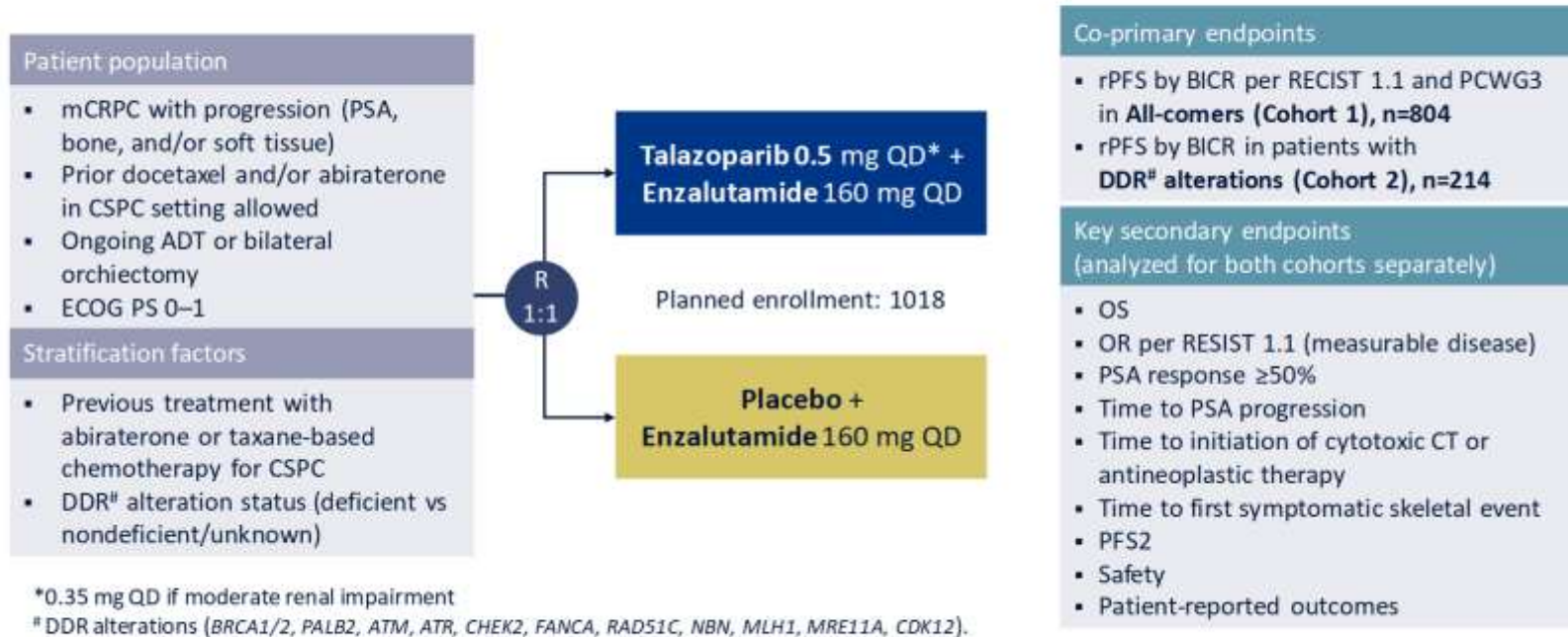
MAGNITUDE: Radiographic Progression-Free Survival



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

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

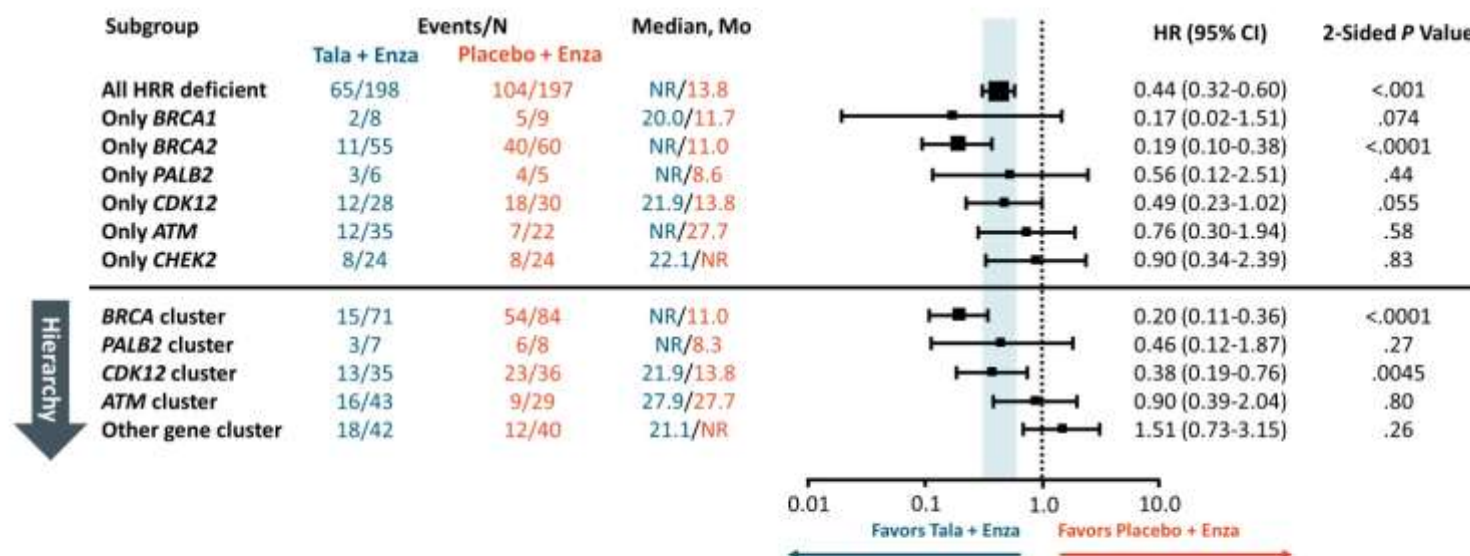
TALAPRO-2: Phase III Trial of Enza +/- Talazoparib



Kastrasyona Dirençli Metastatik Prostat kanseri

PARP inhibitörleri+Androjen Reseptör yolağı blokörleri

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



PARP inhibitörleri+Androjen Reseptör yolağı blokörleri

Yan etkilerin karşılaştırılması

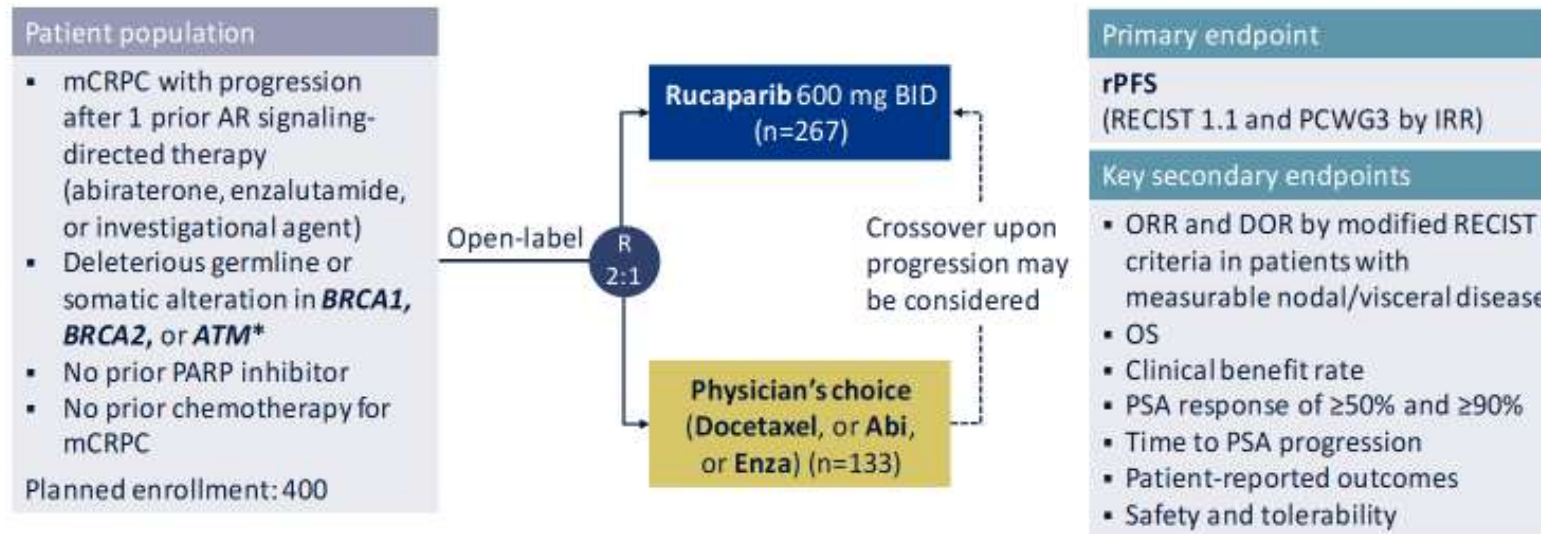
	PROPEL Olaparib + Abiraterone	MAGNITUDE Niraparib + Abiraterone	TALAPRO-2 Talazoparib + Enzalutamide
Select G3-4 Toxicities % (all grades %)			
Anemia	16.3 (50)	30.1 (50.0)	46 (66)
Transfusion Rate	18%	27.4%	39%
Fatigue	2.5 (39.0)	3.3 (29.7)	4 (34)
Nausea	0.3 (31.0)	0.5 (24.5)	<1 (21)
Hypertension	3.8 (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

TRITON3: Randomized Phase III Trial



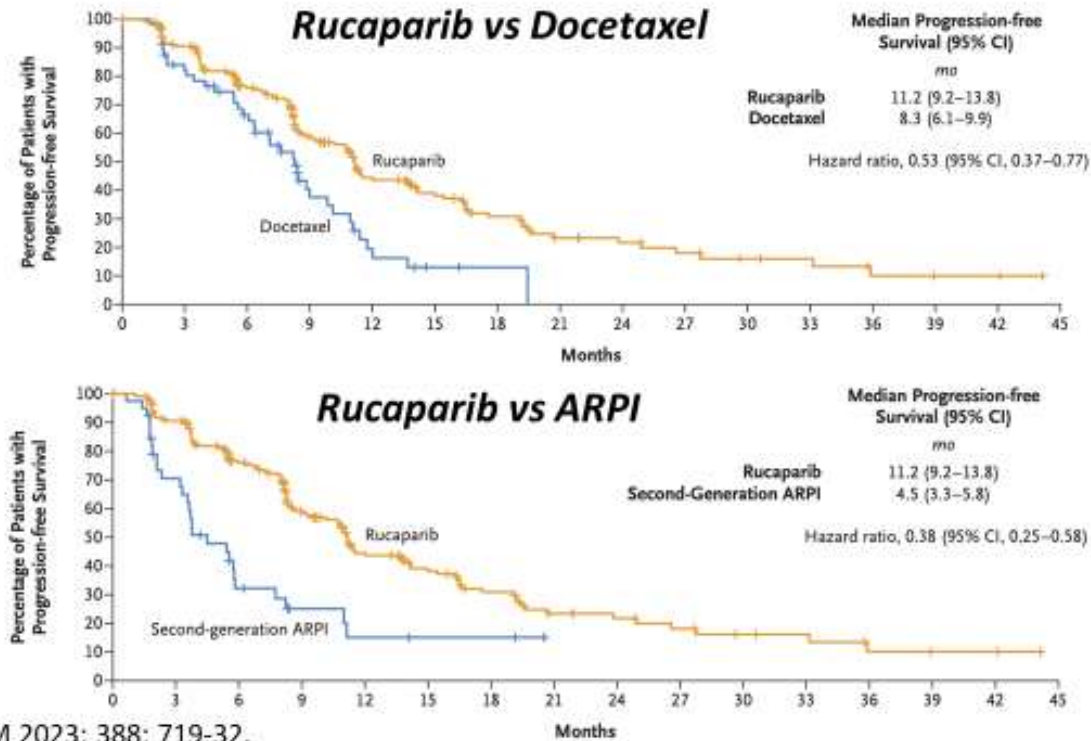
*Mutations identified in blood, archival tissue, or screening tumor tissue

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

Kastrasyona Dirençli Metastatik Prostat kanseri

PARP inhibitörleri

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



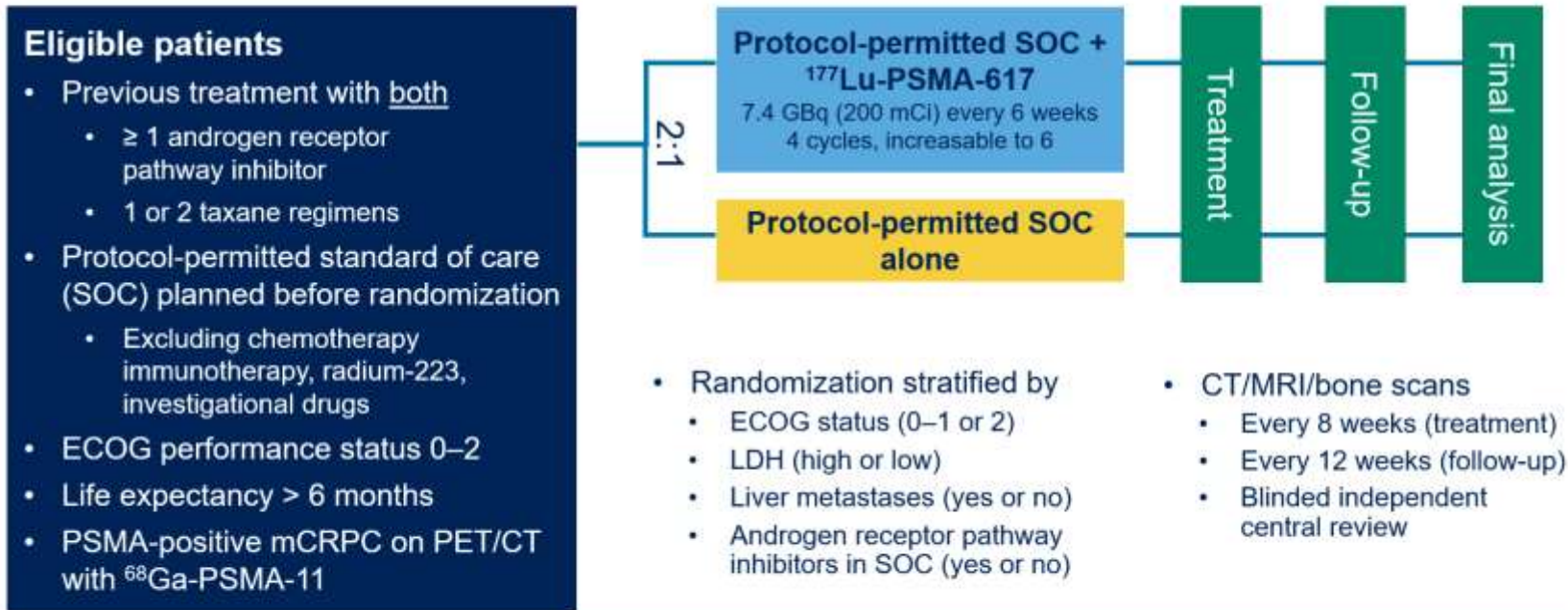
Bryce A et al NEJM 2023; 388; 719-32.

Kastrasyona Dirençli Metastatik Prostat kanseri

Lutesyum 177 Tedavisi

6

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



Presented By: Michael J. Morris



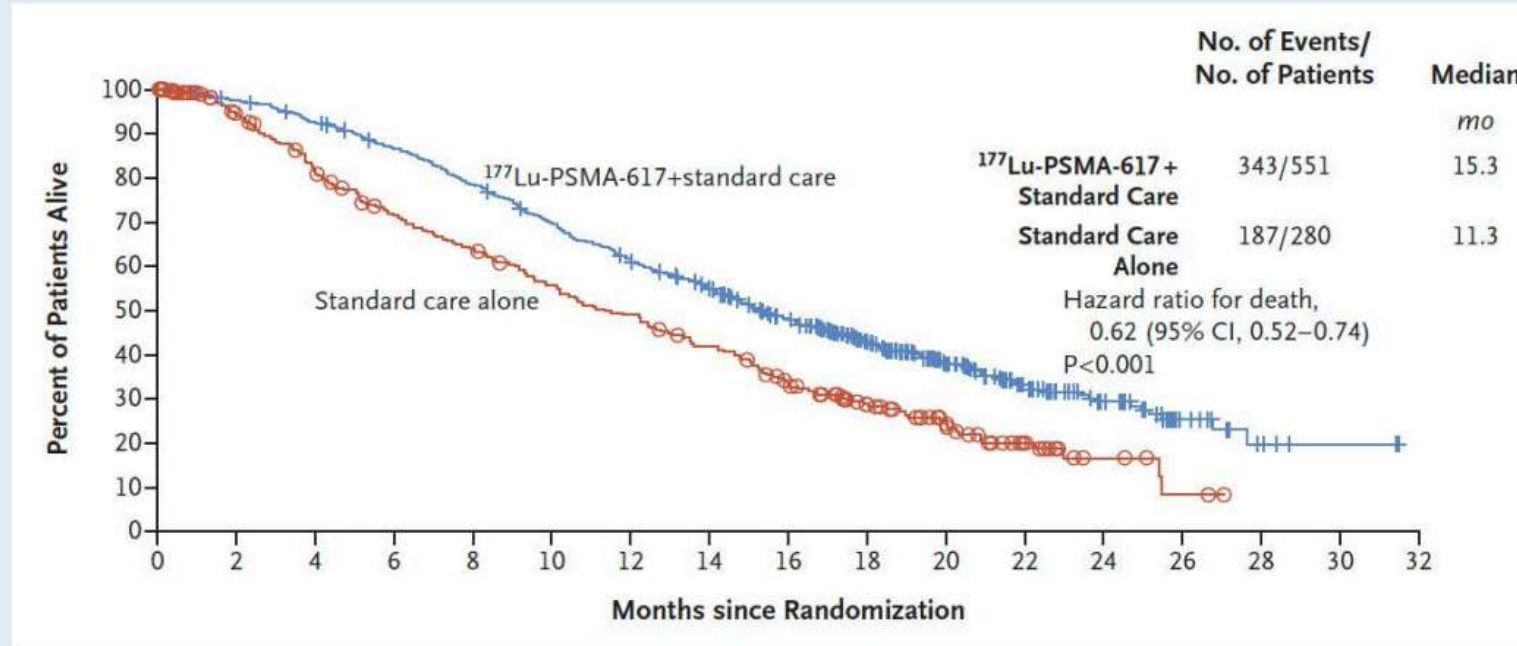
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2021 ASCO
ANNUAL MEETING

Kastrasyona Dirençli Metastatik Prostat kanseri

Lutesyum 177 Tedavisi

VISION: Overall Survival



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

Kastrasyona Dirençli Metastatik Prostat kanseri

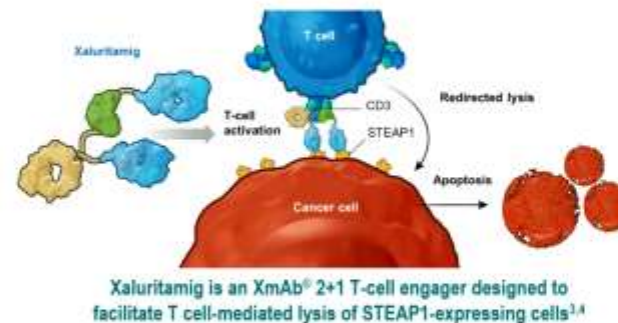
Gelecek perspektif

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



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. Tannir F, et al. *Rev Rep Urol*. 2022;14:239-50.
2. Xu M, et al. *Cancers (Basel)*. 2022;14:4534.
3. Miller-Stevens C, et al. *Cancer Res*. 2020;80(16, Supplement):DDT03-03.
4. Li C, et al. *J Immunother Cancer*. 2020;8:718.

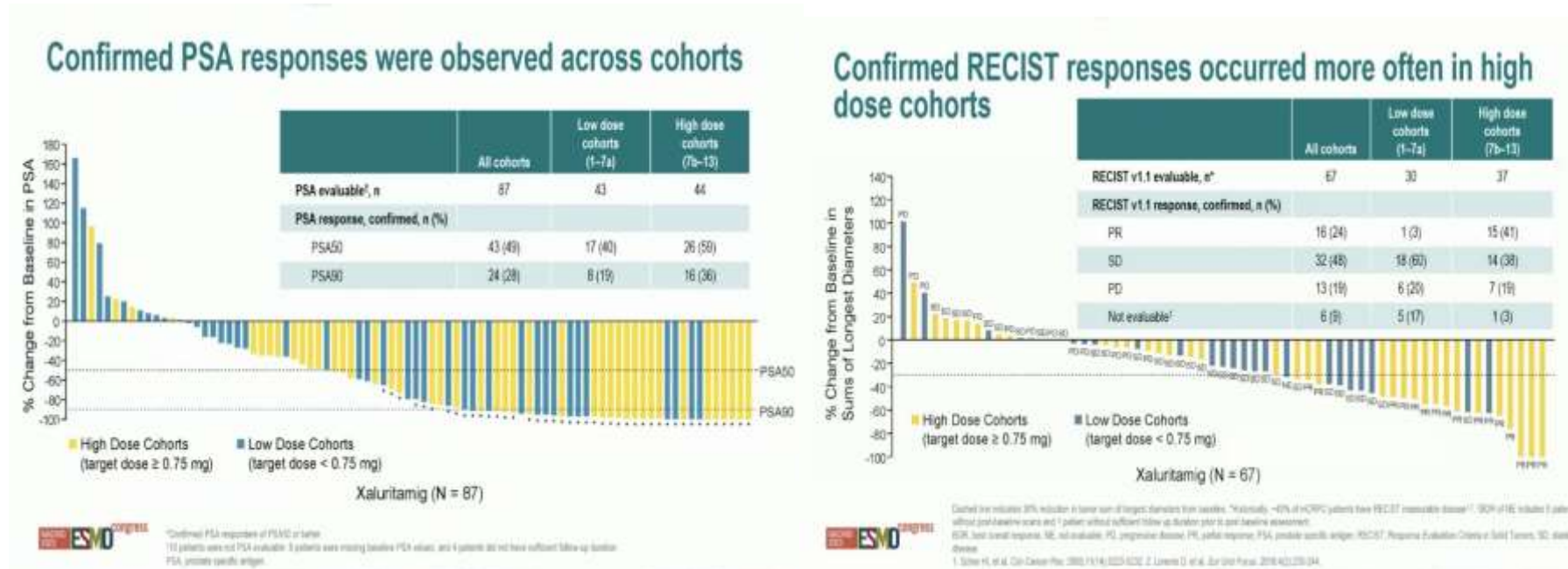


Granada Auditorium - Hall 3

MADRID SPAIN 20-24 OCTOBER 2023

Kastrasyona Dirençli Metastatik Prostat kanseri

Gelecek perspektif

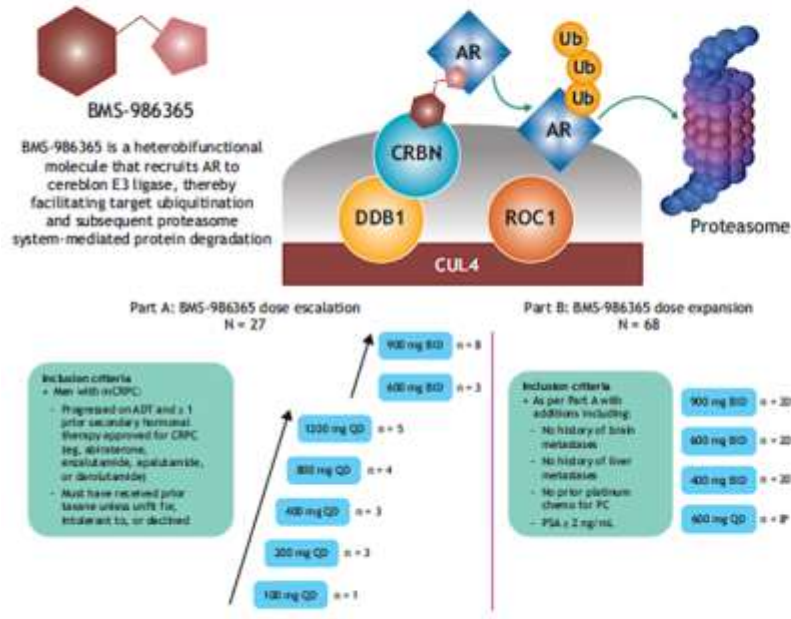


Kastrasyona Dirençli Metastatik Prostat kanseri

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

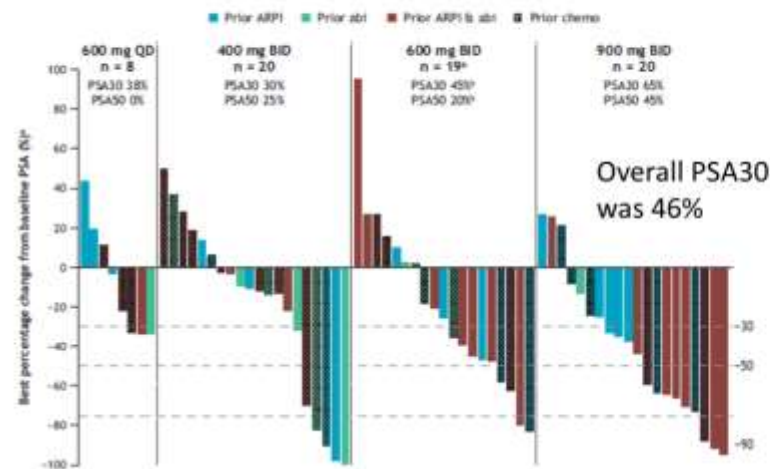


	Part A Dose escalation (n = 27)	Part B Dose expansion (n = 68)	All patients (N = 95)
Median age, years (range)	72 (49-83)	71 (50-87)	71 (49-87)
≥ 75 years, n (%)	7 (26)	24 (35)	31 (33)
Race, n (%)			
White	24 (89)	57 (84)	81 (85)
Black	2 (7)	3 (4)	5 (5)
Asian	1 (4)	3 (4)	4 (4)
Unknown	0	5 (7)	5 (5)
ECOG 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, μ 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)

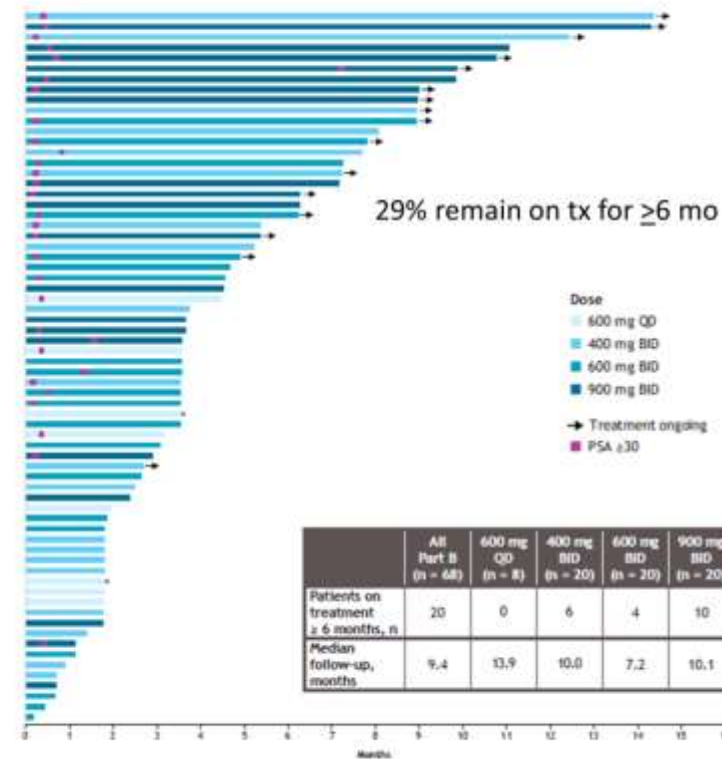
Kastrasyona Dirençli Metastatik Prostat kanseri

Gelecek perspektif

Results



TEAE, n (%)	Part A Dose escalation (n = 27)		Part B Dose expansion (n = 48)		All patients (n = 95)	
	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4
Patients with ≥ 1 TEAE	26 (96)	8 (30)	45 (94)	24 (50)	91 (96)	32 (34)
QTC prolongation	7 (26)	2 (7)	32 (67)	4 (9)	39 (41)	6 (6)
Fatigue	7 (26)	0	24 (50)	3 (6)	31 (33)	3 (3)
Bradycardia	5 (19)	0	23 (47)	0	28 (30)	0
Nausea	12 (44)	0	11 (23)	1 (2)	23 (24)	1 (1)
Anemia	4 (15)	3 (11)	12 (25)	5 (10)	16 (17)	8 (8)
Hypertension	2 (7)	0	14 (29)	5 (10)	16 (17)	5 (5)
Vomiting	7 (26)	0	7 (14)	1 (2)	14 (15)	1 (1)
Diarrhea	2 (7)	0	9 (19)	0	11 (12)	0
ALT increased	3 (11)	0	7 (14)	0	10 (11)	0
Back pain	1 (4)	0	9 (19)	1 (2)	10 (11)	1 (1)



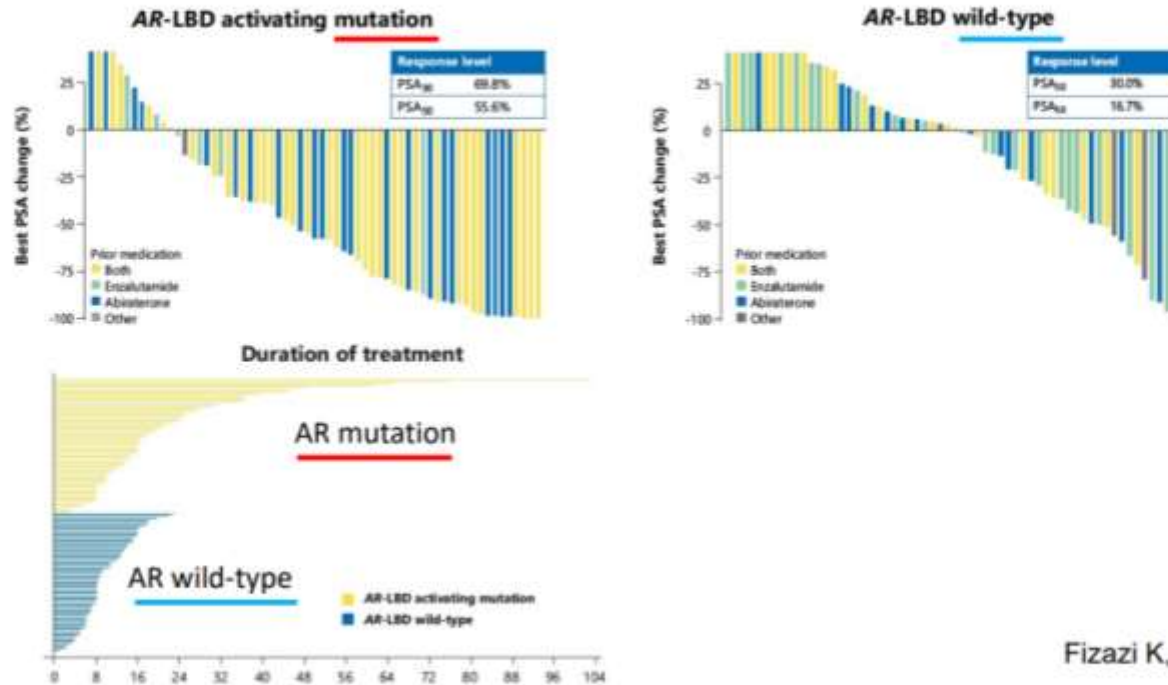
	All Part B (n = 48)	600 mg QD (n = 8)	400 mg BID (n = 20)	600 mg BID (n = 20)	900 mg BID (n = 20)
Patients on treatment ≥ 6 months, n	20	0	6	4	10
Median follow-up, months	9.4	13.9	10.0	7.2	10.1

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

Kastrasyona Dirençli Metastatik Prostat kanseri

Gelecek perspektif

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



Fizazi K, ASCO GU 2024

Sonuç

- ❑ Lokalize Yüksek Riskli Prostat Kanserinde, RT+ADT+Abiraterone 2 yıl seçeneği
- ❑ İzole PSA nüksü PSA double time $\leq$ 9 ay, Enzalutamid +ADT+/-RT
- ❑ Kastrasyona duyarlı metastatik prostat kanseri;
Üçlü tedavi(ADT+Doksetaksel+Abiraterone/Darolutamid) Viseral metastaz, denovo, yüksek volüm, genç, yaşam beklentisi uzun hastalarda ön planda düşünülebilir
- ❑ Kastrasyona dirençli metastatik prostat kanseri; BRCA mutasyonu olanlarda yeni nesil androjen reseptör yolağı inhibitörleri +PARP inhibitörleri.
Daha önce 1 $\geq$ Taksan, 1 $\geq$ yeni nesil androjen reseptör yolağı inhibitörleri alanlarda LU-177