Metastatik prostat kanserinde yeni tedavi seçenekleri

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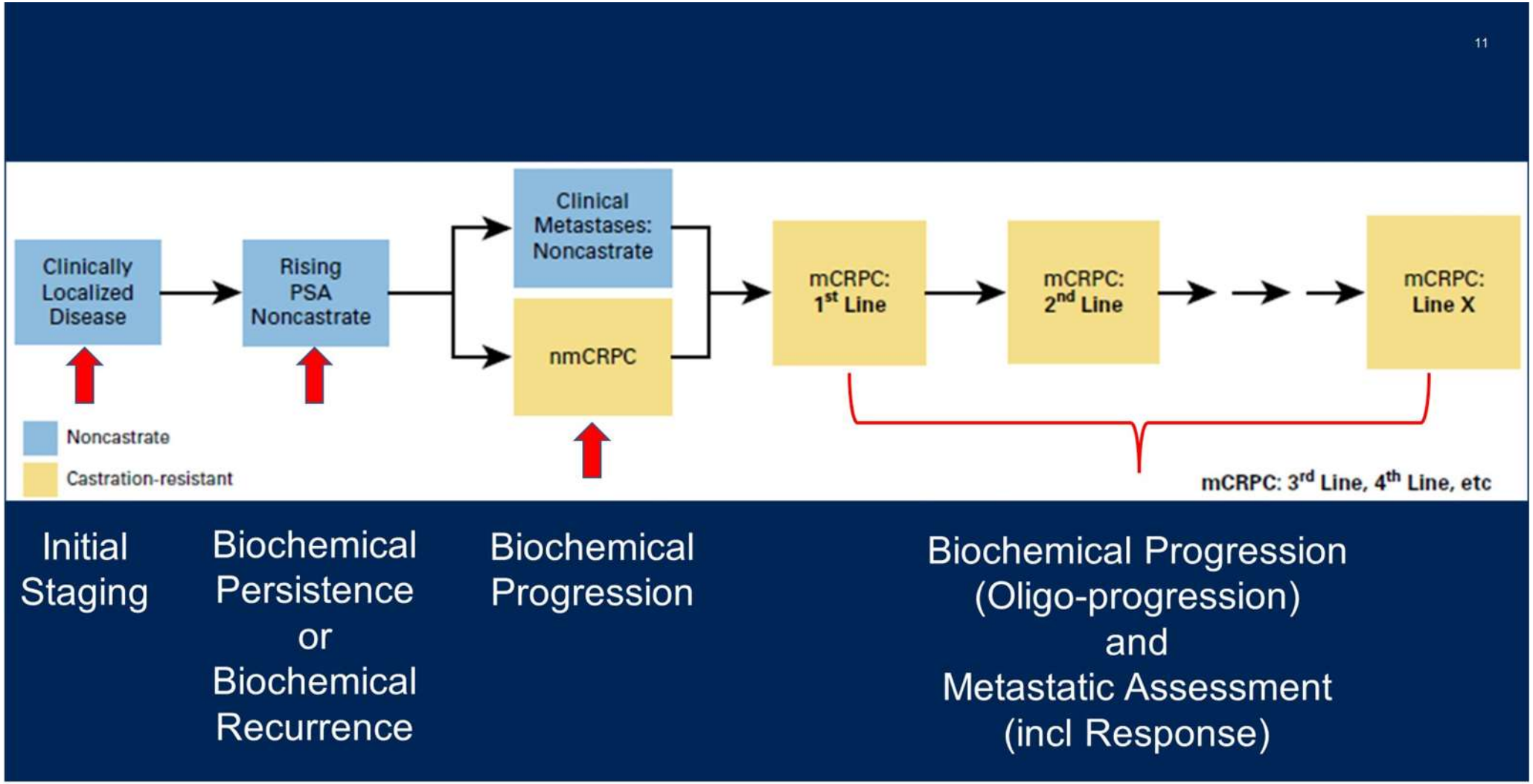
Tıbbi Onkoloji

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

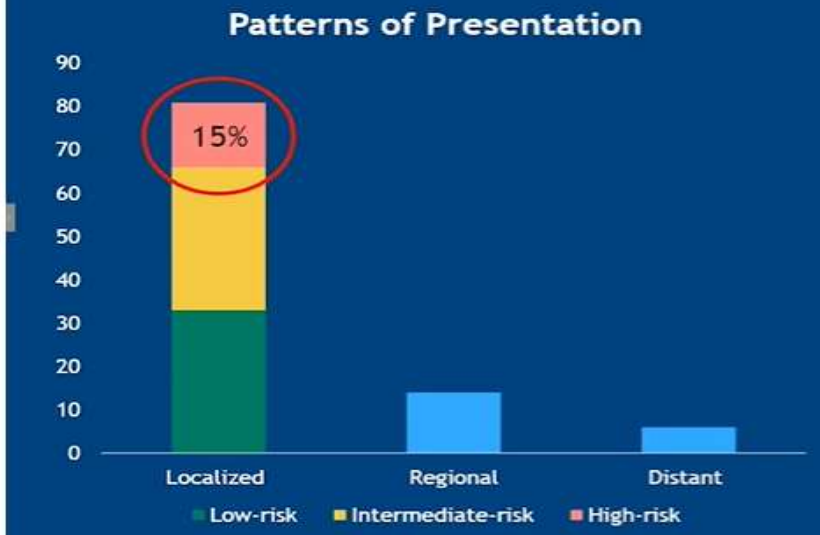
Prostat Kanserinde Klinik Seyir



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

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.

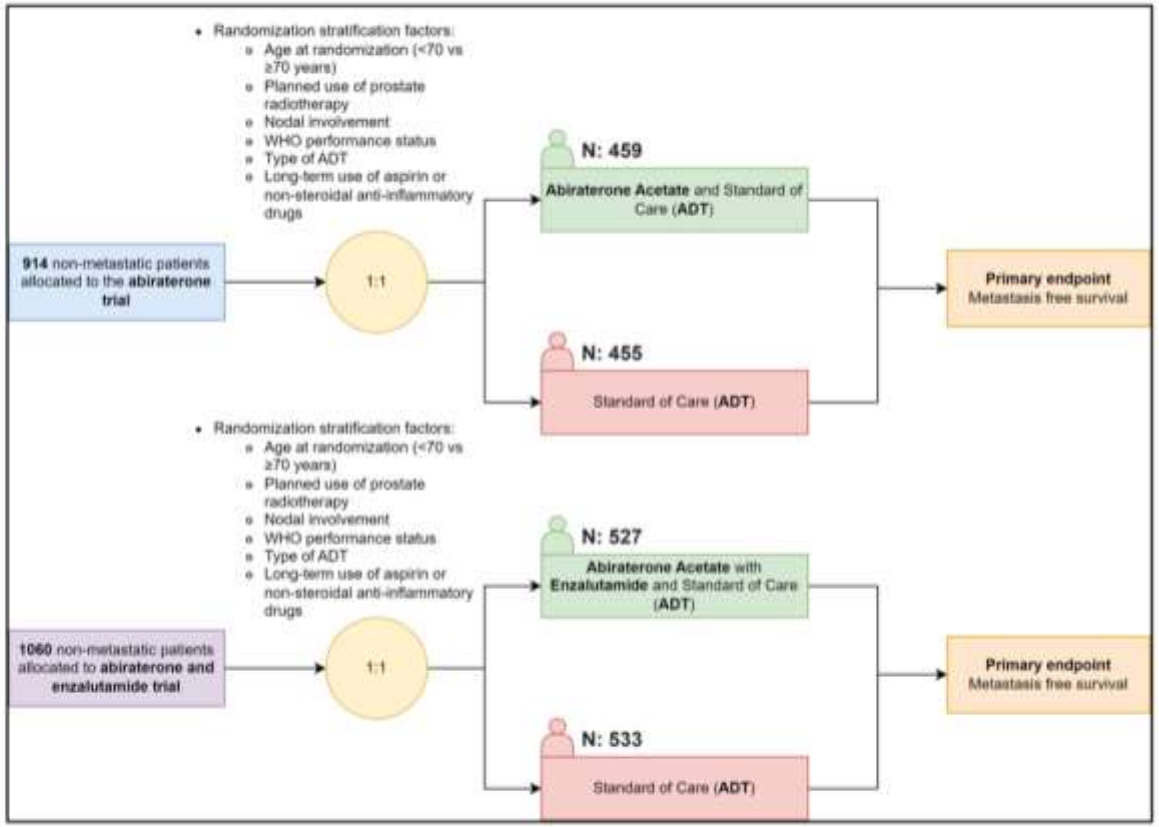
Cooperberg, JCO, 2010; Eggener, J Urol, 2011

- 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 ≥ 4ng/ml with a doubling time of <6 months or a PSA ≥20ng/ml)

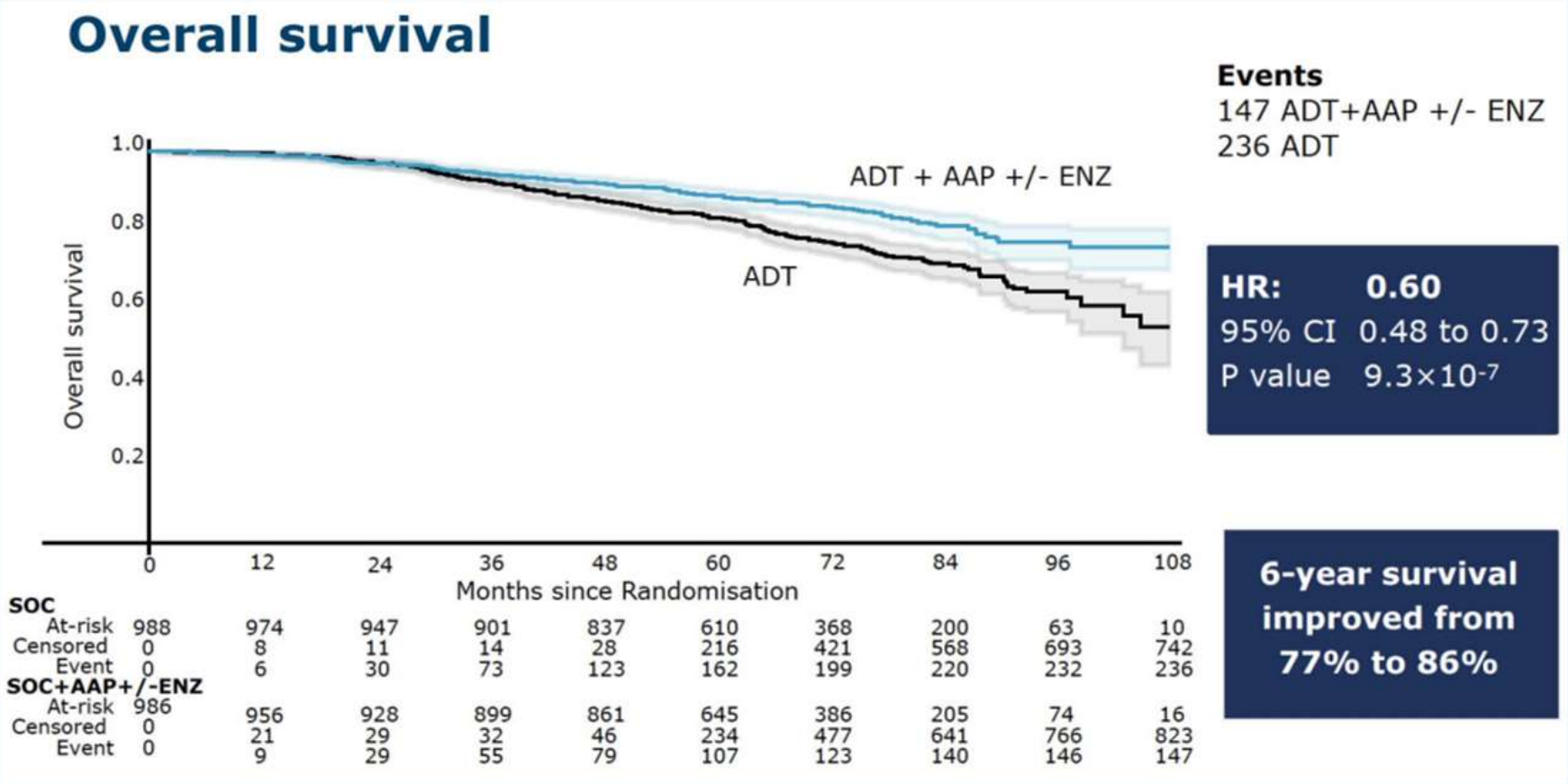


Attard G et al, Lancet 2022

Courtesy of Alan H Bryce, MD

Yüksek Riskli Prostat Kanserinde Tedavi Seçeneği

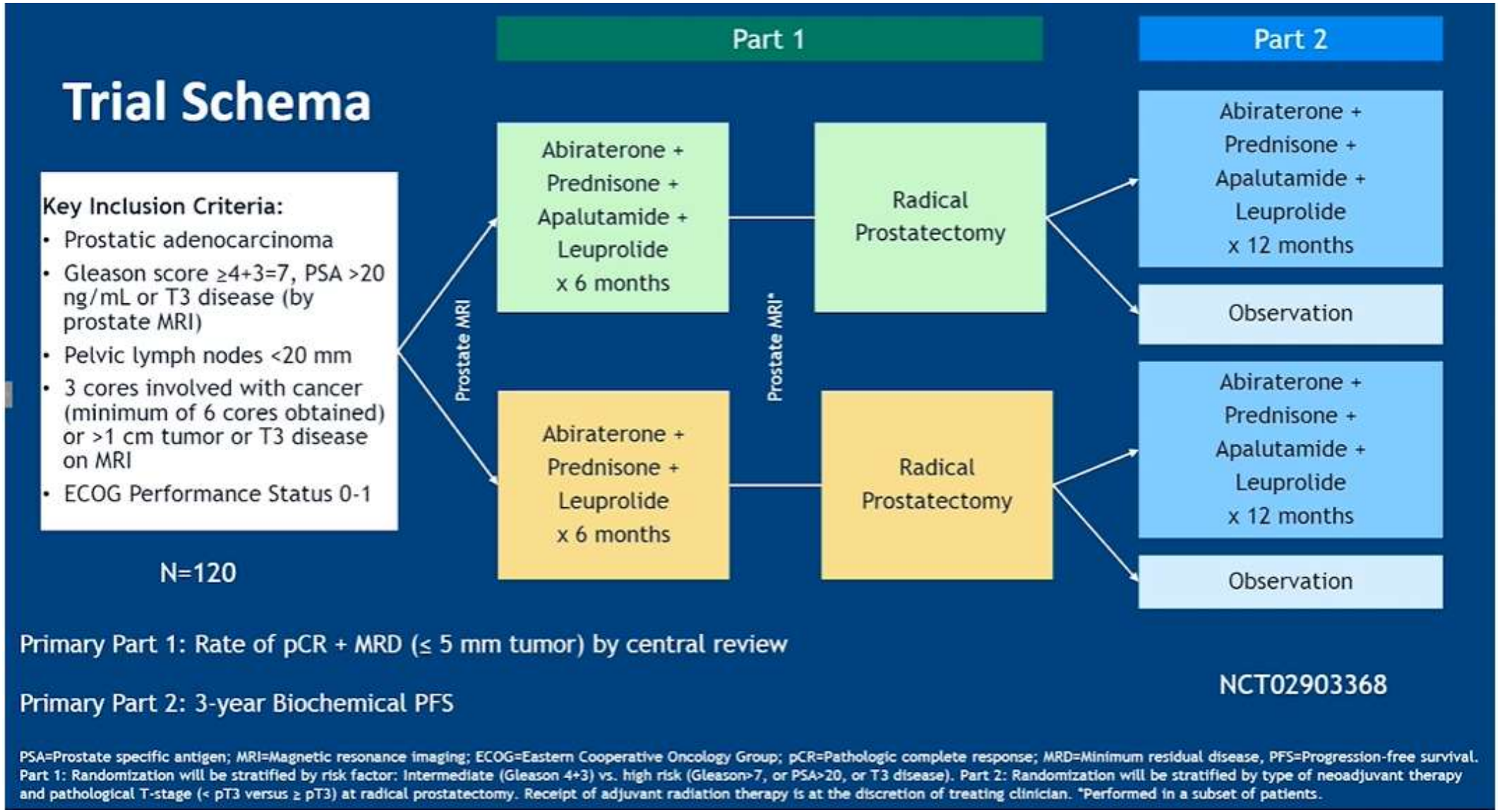
Overall Survival with the Addition of Abiraterone Acetate and Prednisolone with or without Enzalutamide to ADT for High-Risk M0 Prostate Cancer



Attard G et al. ESMO 2021;Abstract LBA4_PR.

RTP RESEARCH TO PRACTICE

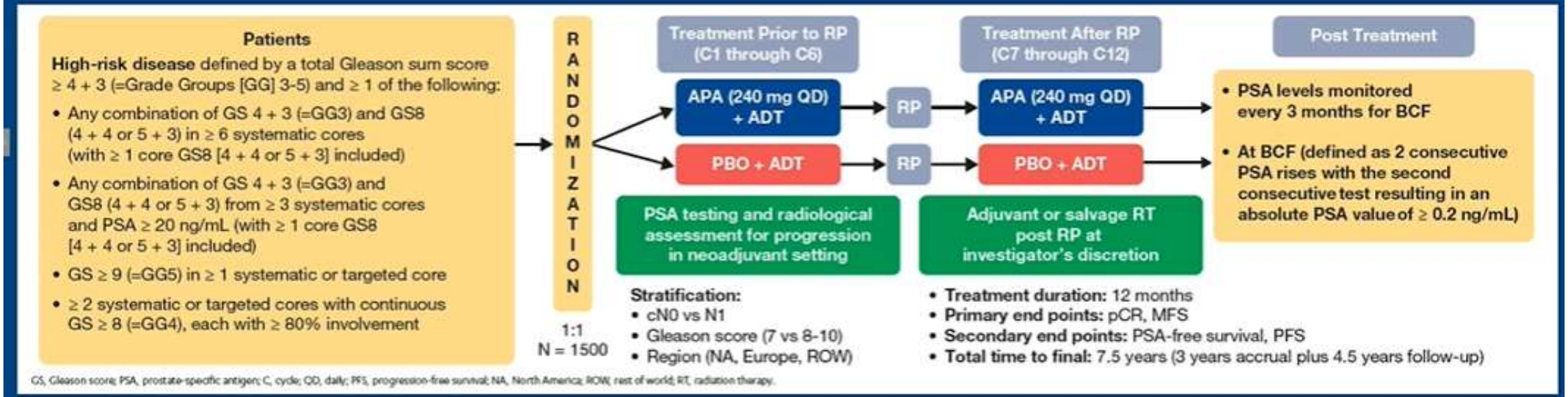
Neoadjuvan Yeni Nesil AR-yolağı İnhibötörleri



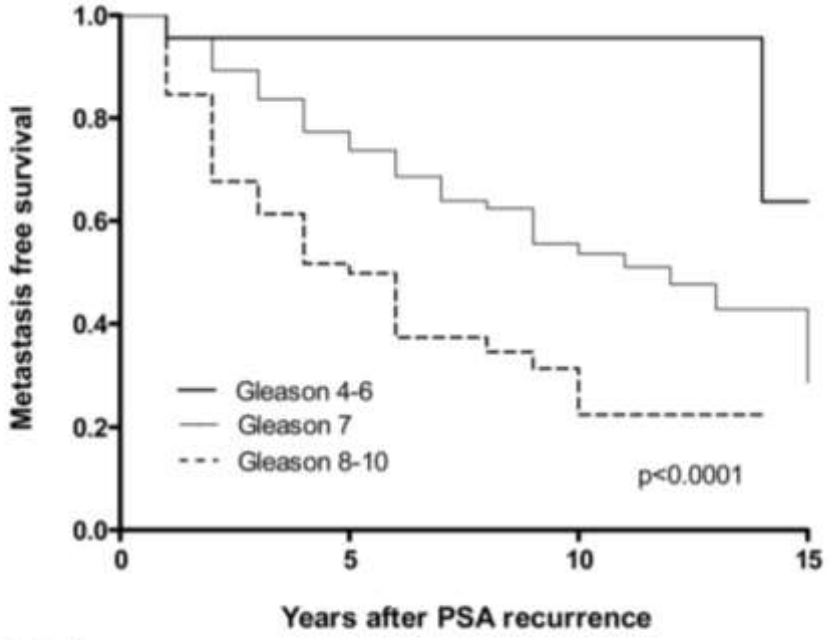
Devam Eden Çalışmalar

Proteus

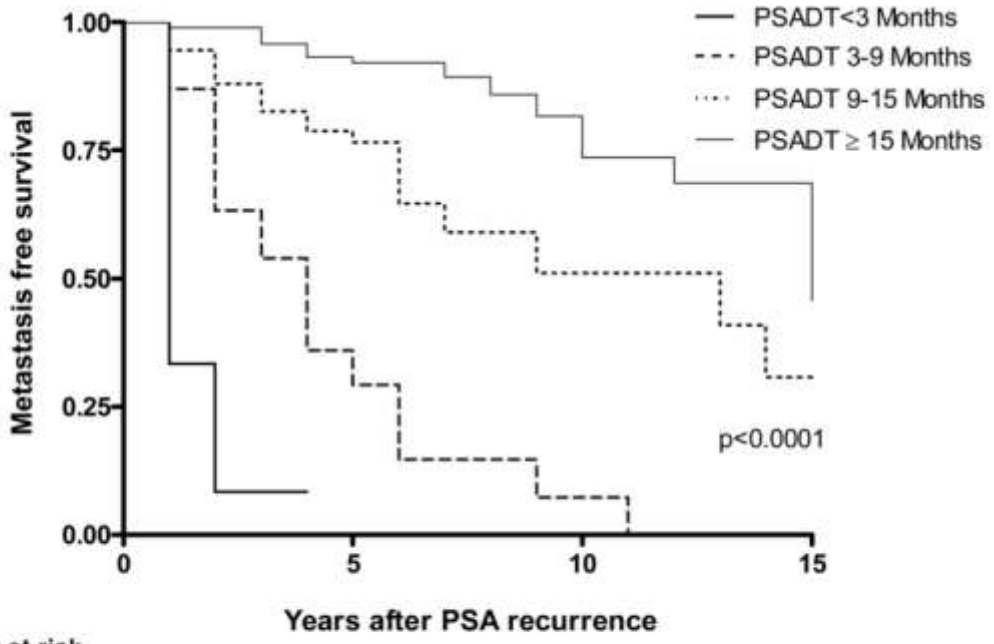
Randomized, Double-blind, Placebo-Controlled, Phase 3 Study of Apalutamide in Subjects with High-risk, Localized or Locally Advanced Prostate Cancer Who are Candidates for Radical Prostatectomy



Biyokimyasal Rekürens Metastaz riski



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

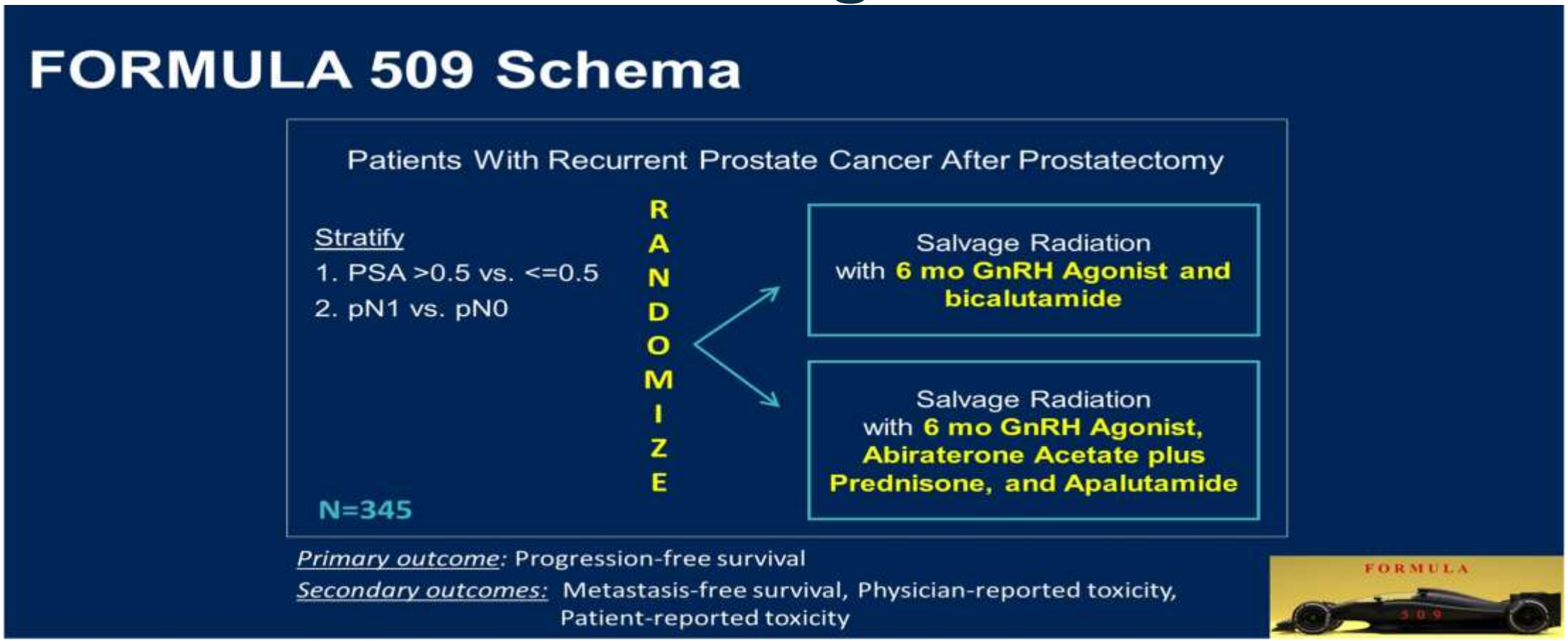


Number at risk				
PSADT < 3 Month	46	0	0	0
PSADT 3-9 Month	106	16	2	0
PSADT 9-15 Month	86	37	11	1
PSADT ≥ 15 Month	212	86	30	3

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

Emmanuel S. Antonarakis, BJU Int. 2012

Biyokimyasal Rekürens ve PSA Persistansı
Doz Yoğun Tedavi



Biyokimyasal Rekürens ve PSA Persistansı

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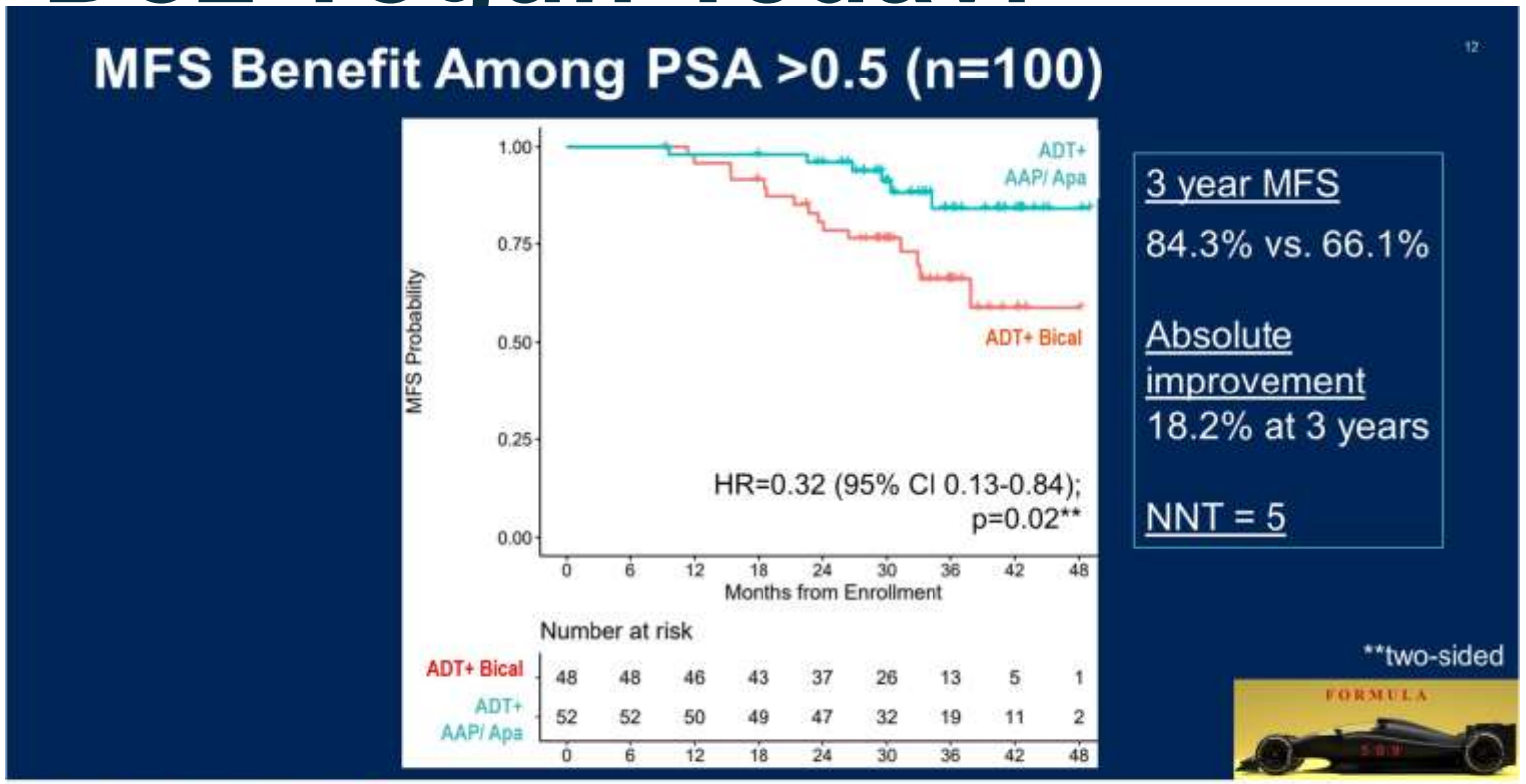
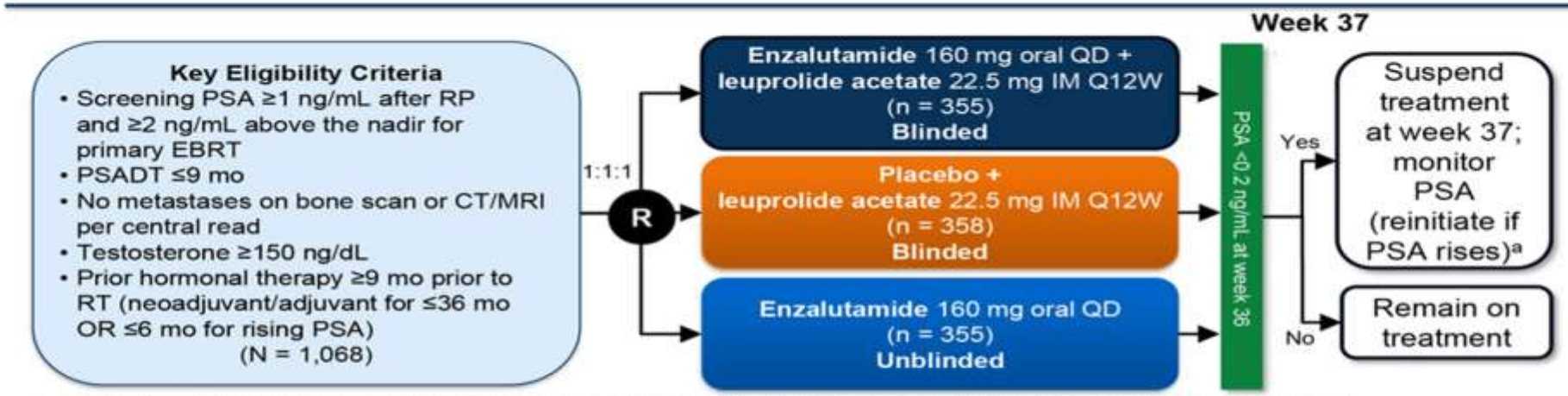


İzole PSA nüksü olan hastalarda tedavi seçeneği

Phase 3 EMBARK: Enzalutamide Plus Leuprolide Acetate[1-6]



- **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. *P* value to determine significance for OS of combination and monotherapy treatment comparisons was dependent on outcomes of primary endpoint and key secondary endpoints. [d] Safety population.

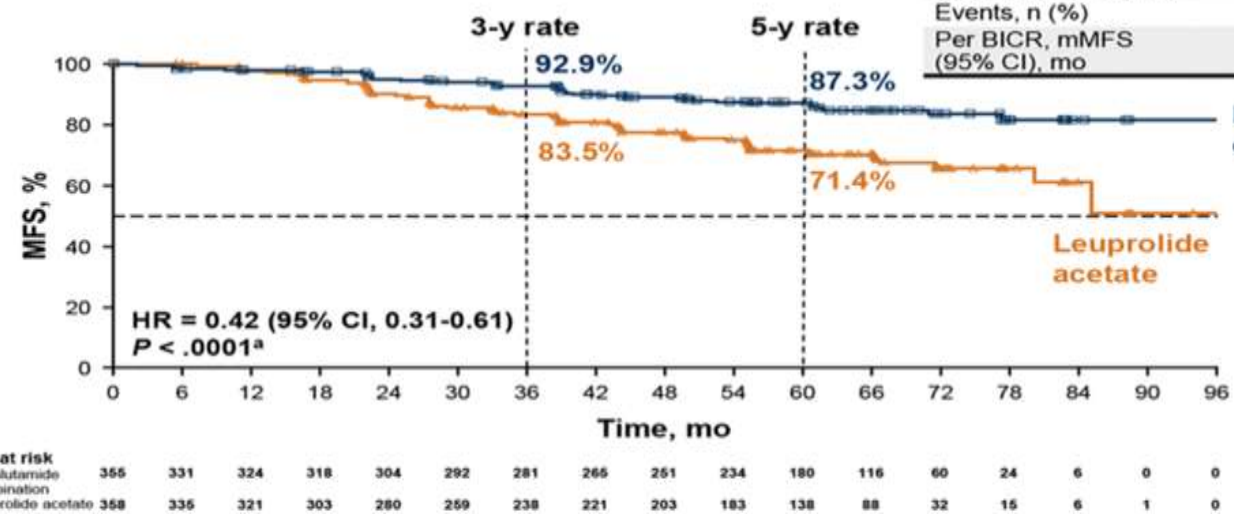
1. https://clinicaltrials.gov/study/NCT02319837. 2. Shore ND et al. AUA 2023. Abstract LBA02-09. 3. Freedland SJ et al. *N Engl J Med.* 2023;389:1453-1465. 4. Freedland SJ et al. *NEJM Evid.* 2023;2. 5. Shore ND et al. ASCO GU 2024. Abstract 15. 6. Shore ND et al. ASCO GU 2024. Abstract 156.

PeerView.com

İzole PSA nüksü olan hastalarda tedavi seçeneği

Phase 3 EMBARK: Met Primary Endpoint of MFS[1,2]

	Enzalutamide Combination (n = 355)	Leuprolide Acetate (n = 358)
Median follow-up, mo	60.7	60.6
Events, n (%)	45 (13)	92 (26)
Per BICR, mMFS (95% CI), mo	NR (NR)	NR (85.1-NR)



Key Secondary Endpoint: Interim OS
HR = 0.59
(95% CI, 0.38-0.90)
P = .0142[a]
(Pre-specified efficacy boundary, *P* <.0001)

Data cutoff: January 31, 2023. Symbols indicate censored data. [a]HR 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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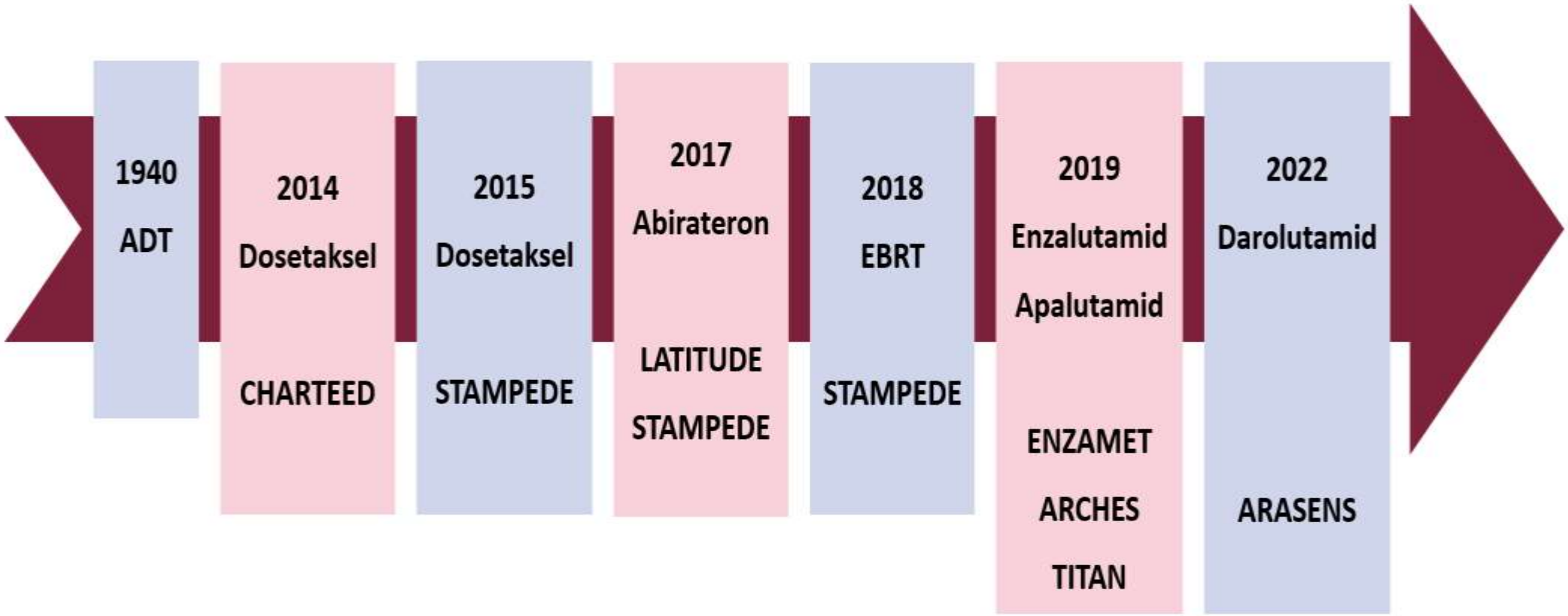
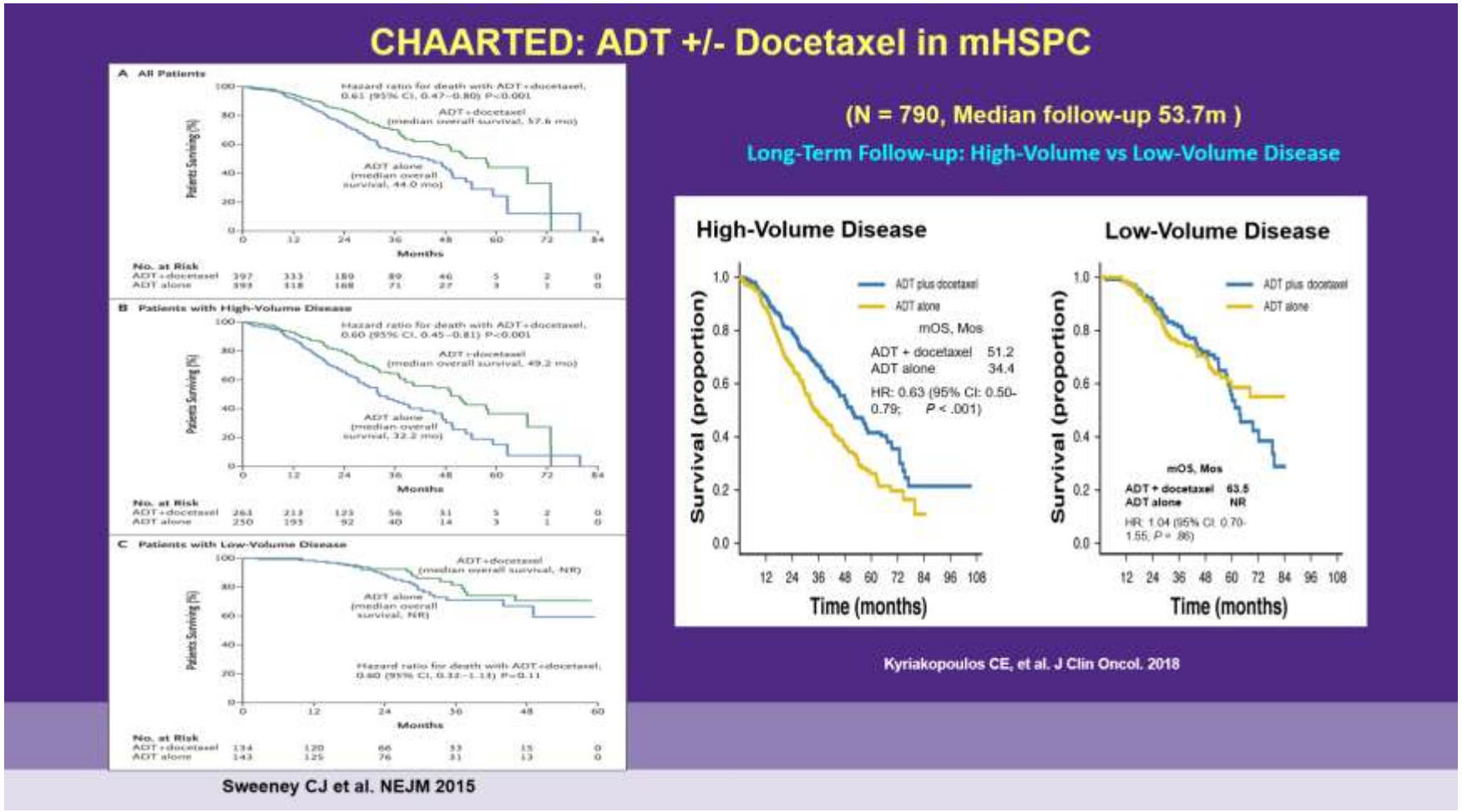
İzole PSA nüksü olan hastalarda tedavi seçeneği

Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavi Tarihçesi

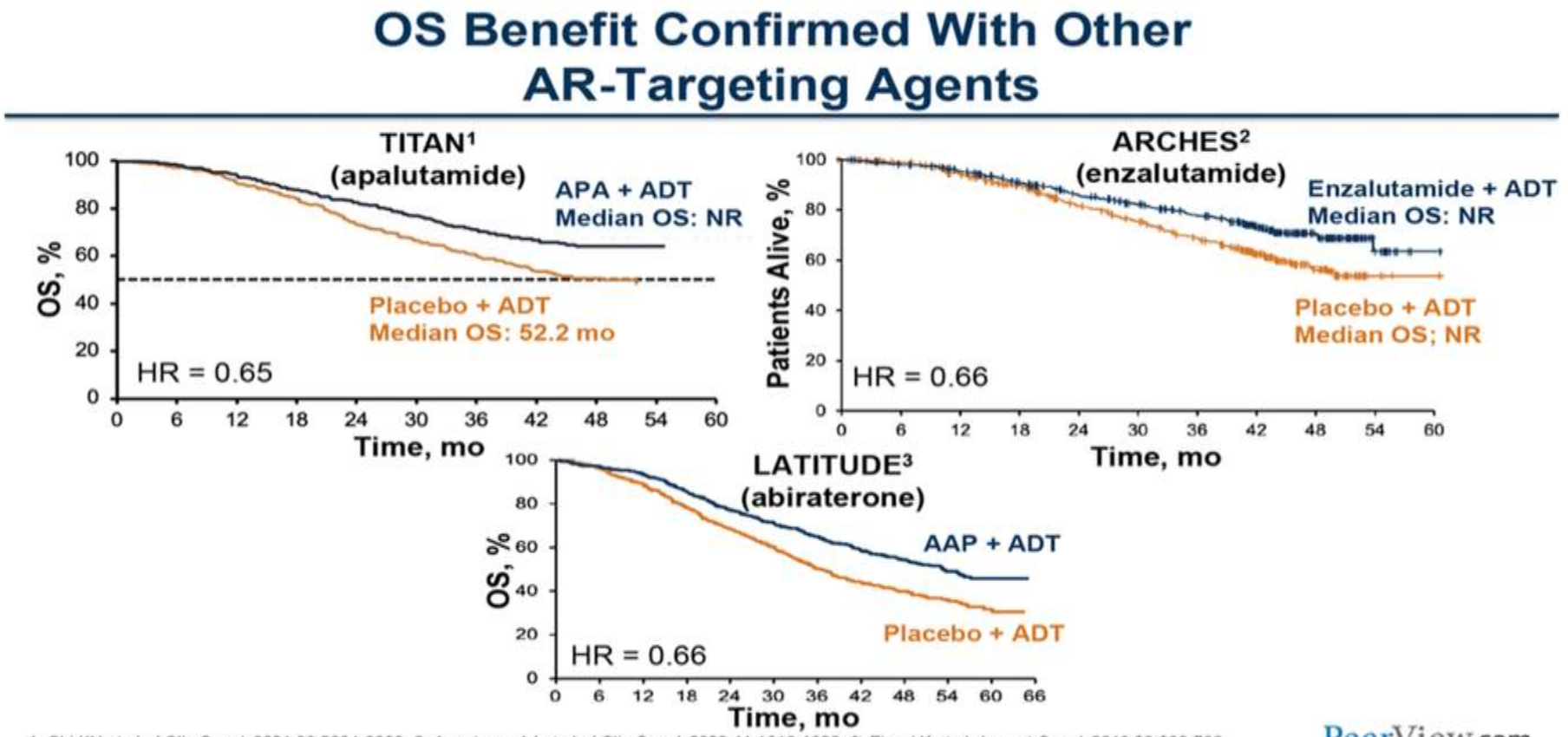


Hastalık Volümü Dosetaksel Tedavi Etkinliği için Prediktif



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

Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi



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.

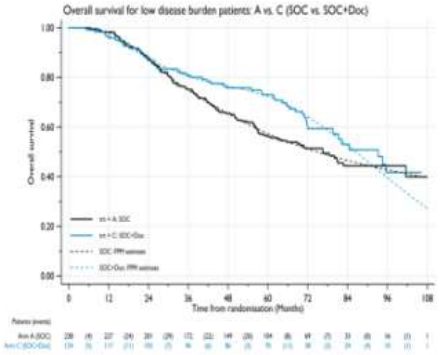
Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

VIRTUAL 2020 ESMO congress

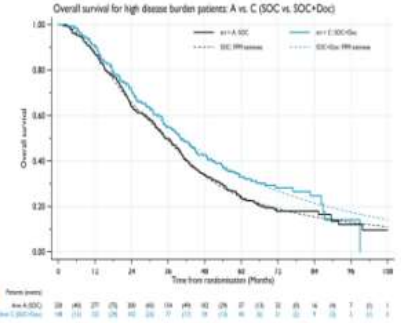
Should we count the metastases for decision making about systemic treatment? No !!!

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.*

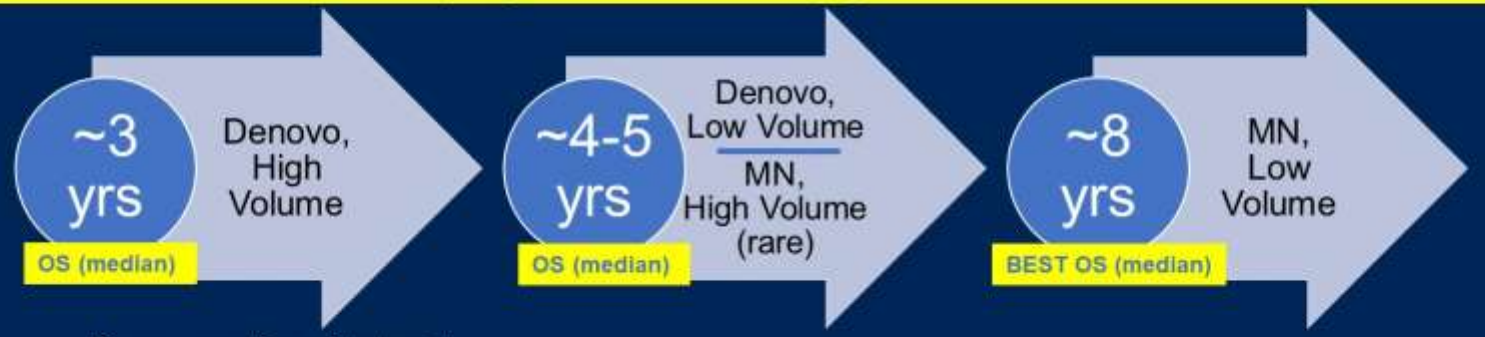
European Association of Urology kılavuzu 2023

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)

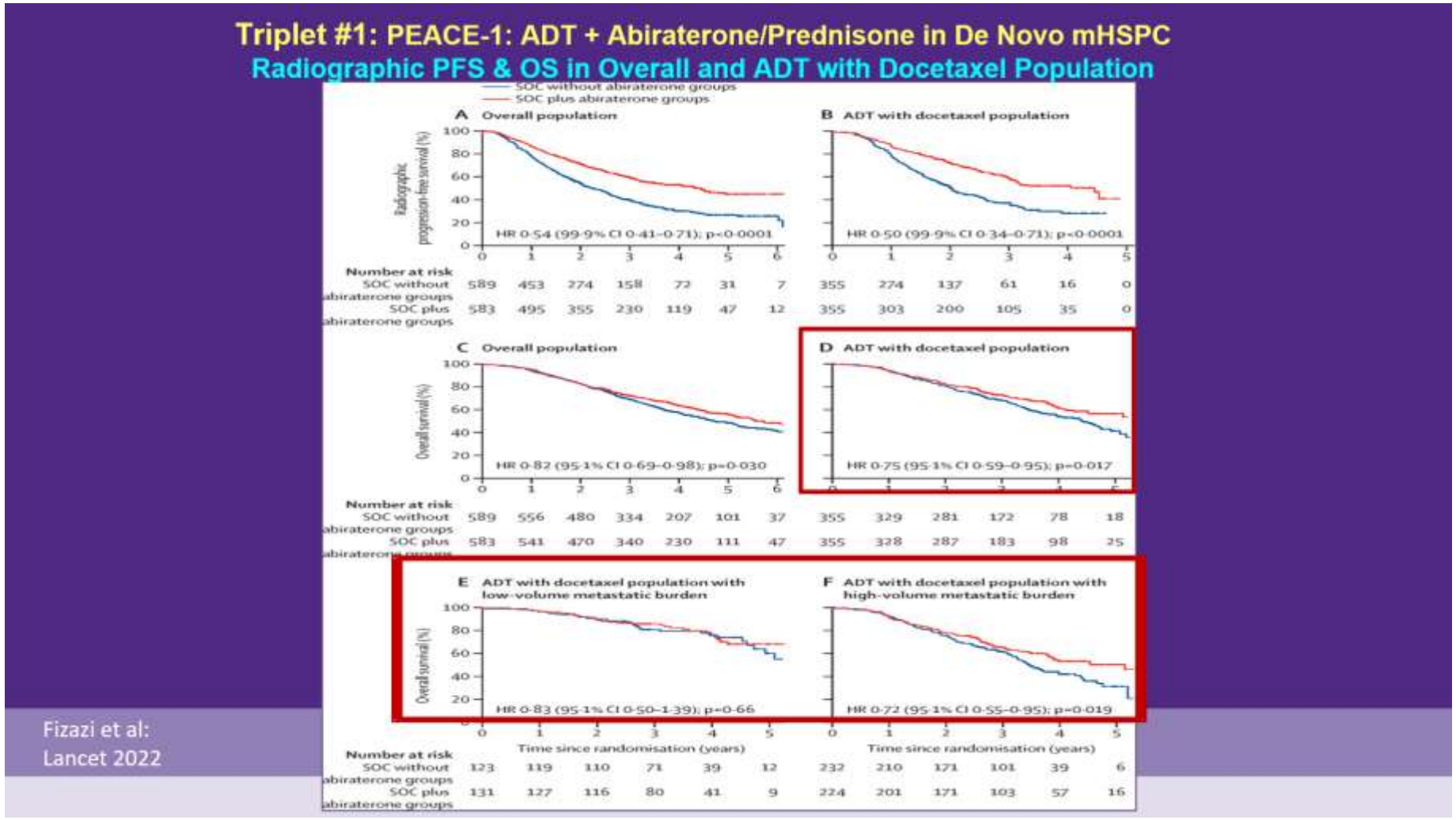
Can clinical prognostic factors help guide treatment selection?



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

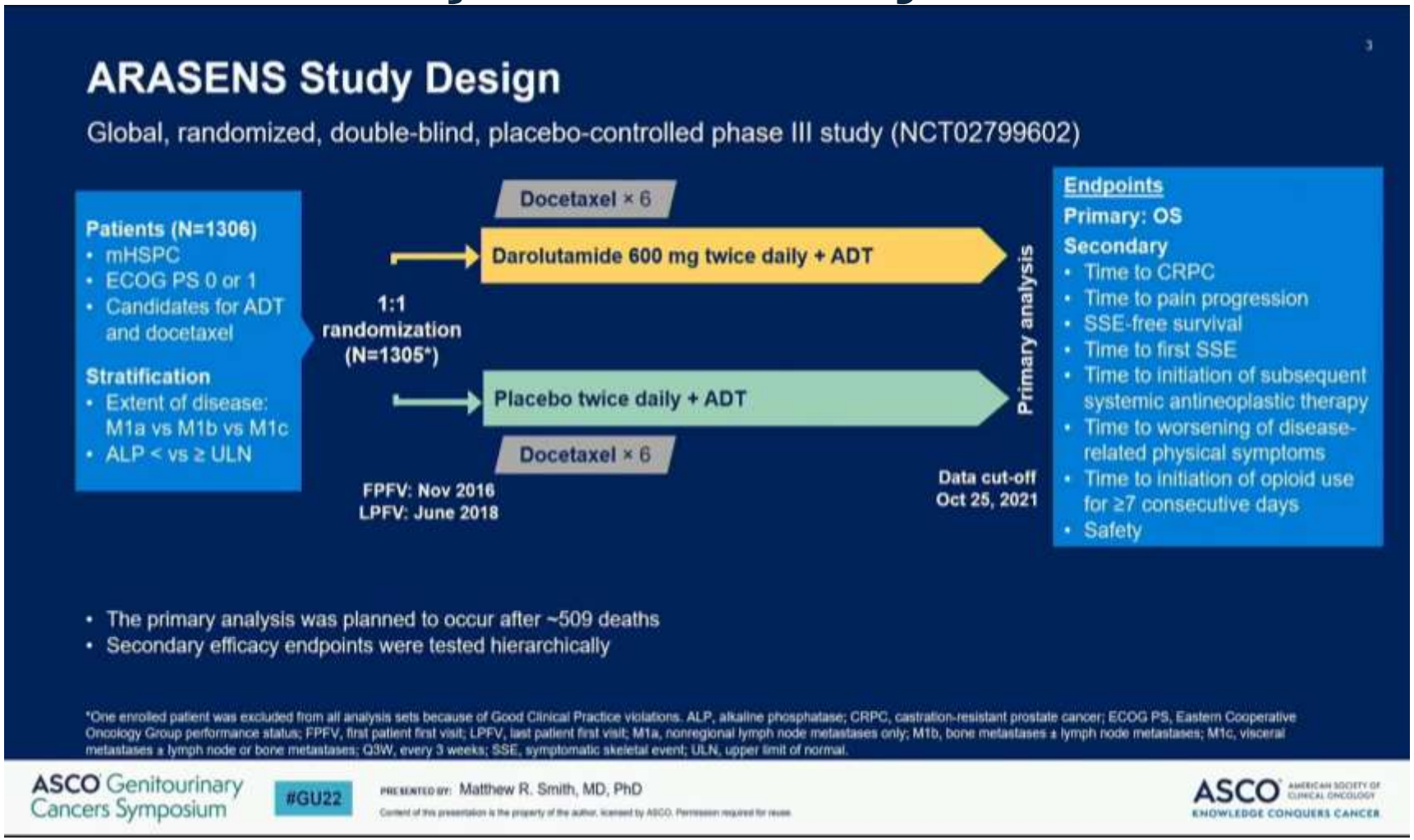
Modified from :Francini et al, Prostate, 2018; Gravis et al, Eur Urol, 2018

Kastrasyona Duyarlı Metastatik Prostat Kanseri Üçlü Kombinasyon

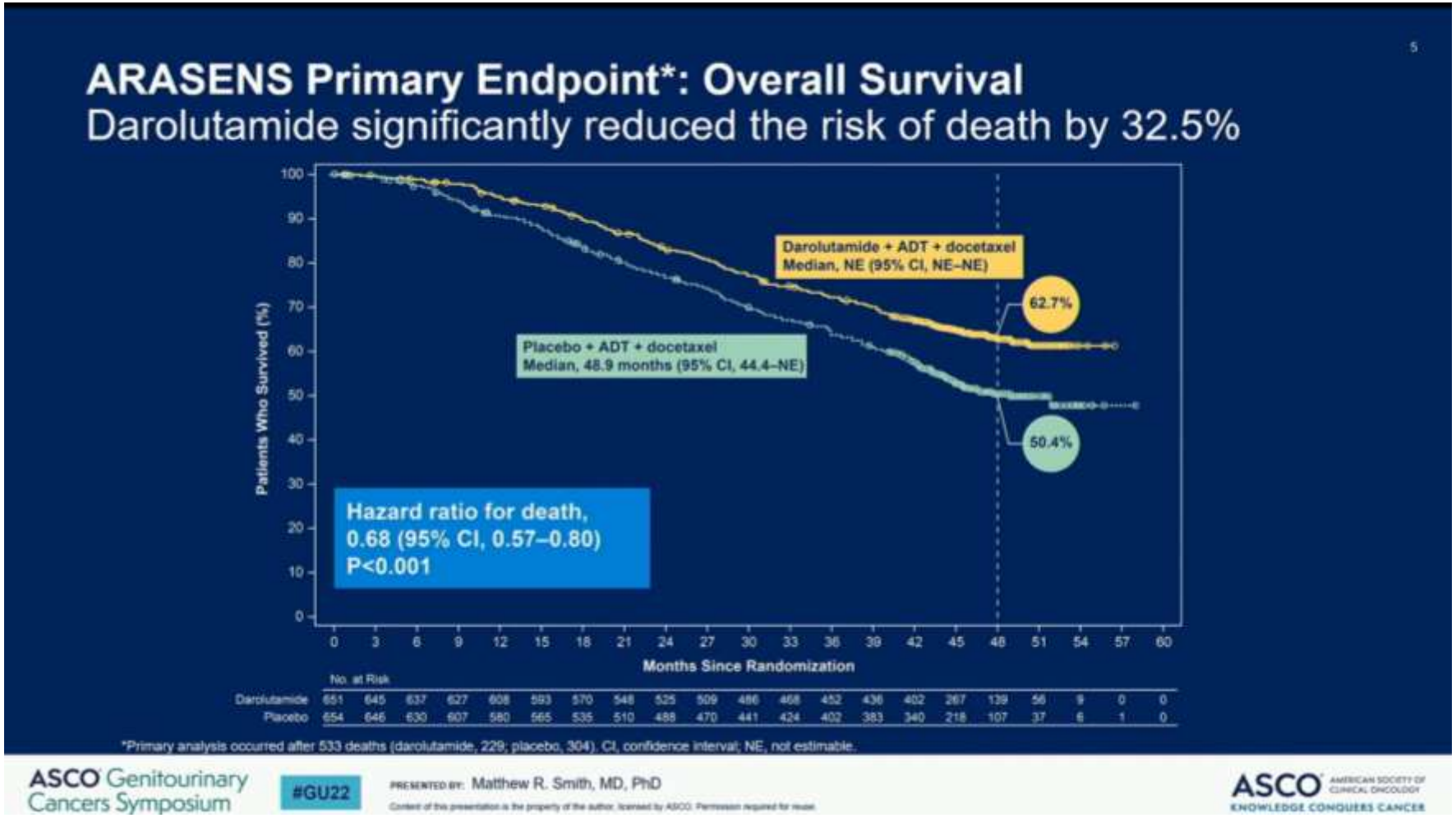


Fizazi et al:
Lancet 2022

Kastrasyona Duyarlı Metastatik Prostat Kanseri
Üçlü Kombinasyon



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

Fizazi et al, Lancet, 2022

Metastatik Kastrasyona Duyarlı Prostat Kanseri Tedavi

National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2023
Prostate Cancer

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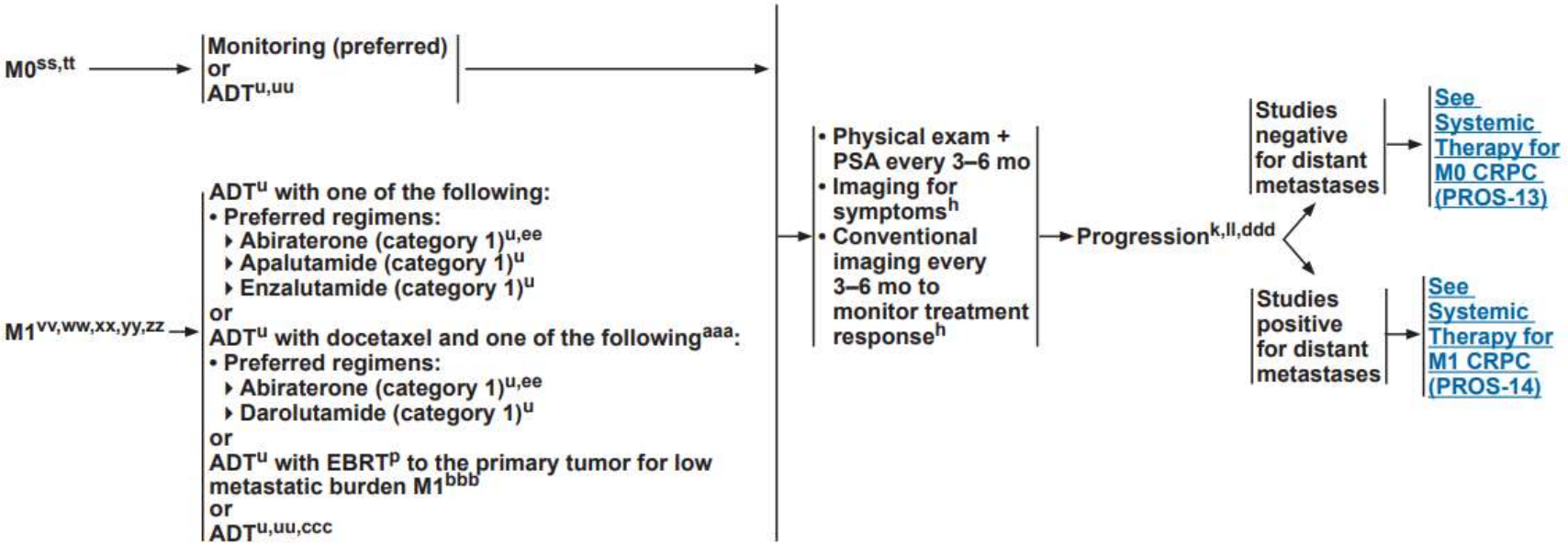
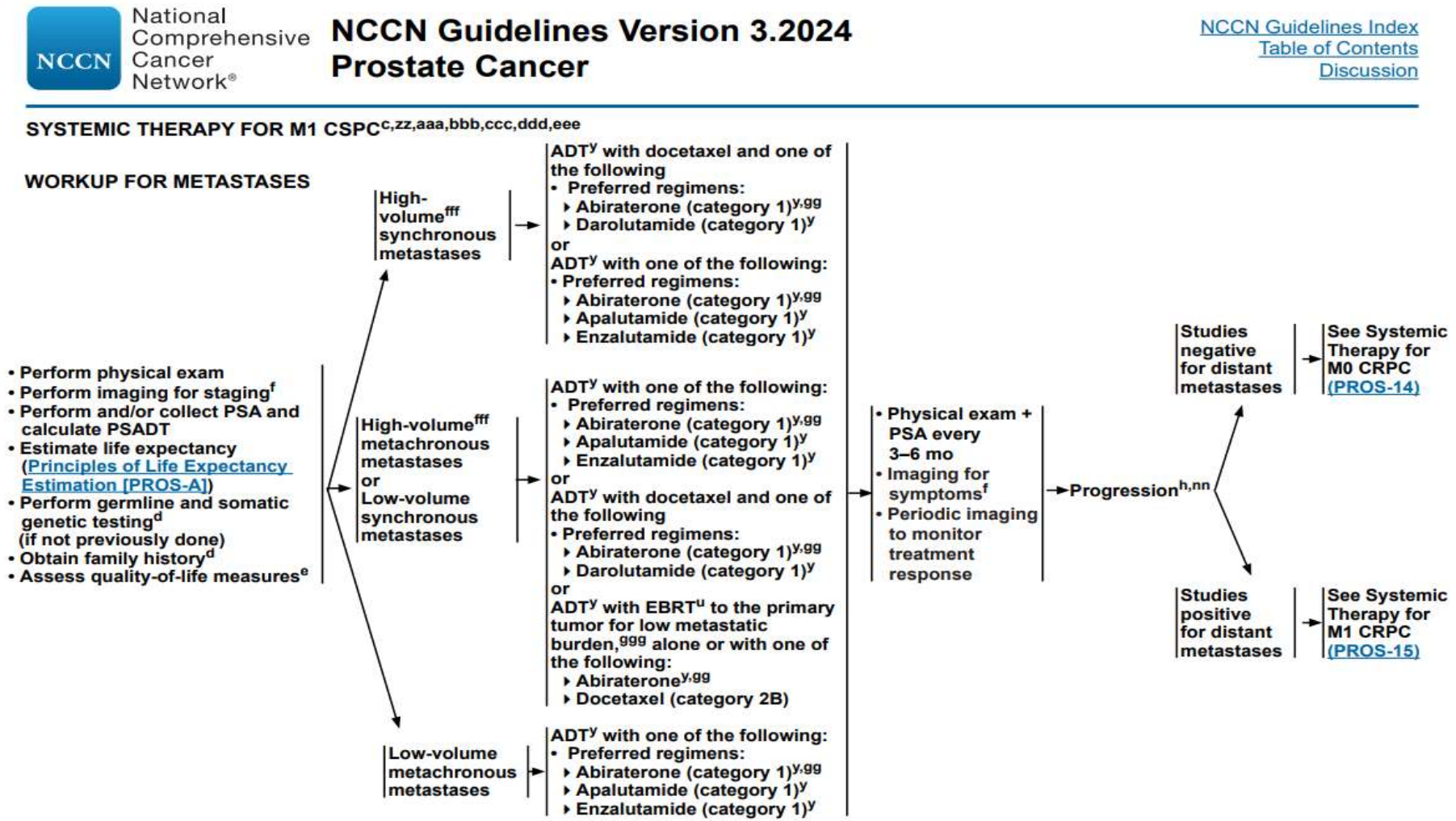
SYSTEMIC THERAPY FOR CASTRATION-SENSITIVE PROSTATE CANCER[rr]



Metastatik Kastrasyona Duyarlı Prostat Kanseri Tedavi



Kastrasyona Dirençli Metastatik Prostat kanseri

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2021
Prostate Cancer

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

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

Kastrasyona Dirençli Metastatik Prostat Kanseri Tedavisi

Treatment options in mCRPC

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

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

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

Kastrasyona Dirençli Metastatik Prostat kanseri

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2024
Prostate Cancer

NCCN Guidelines Index
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Discussion

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

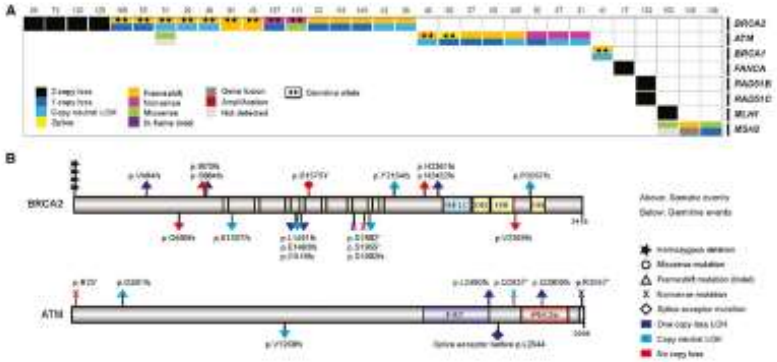
No prior docetaxel/no prior novel hormone therapy[qqq]	Progression on prior novel hormone therapy/no prior docetaxel[qqq]
• Preferred regimens ▸ Abiraterone[y,rrr] (category 1[sss]) ▸ Docetaxel[lll] (category 1) ▸ Enzalutamide[y] (category 1) • Useful in certain circumstances ▸ Niraparib/abiraterone[y,lll,ttt]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

Evre IV Prostat Kanserinde Mutasyonlar

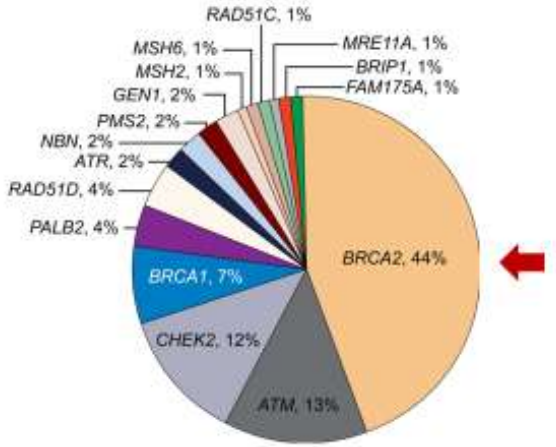
HRR Genes and Metastatic Prostate Cancer

Somatic

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



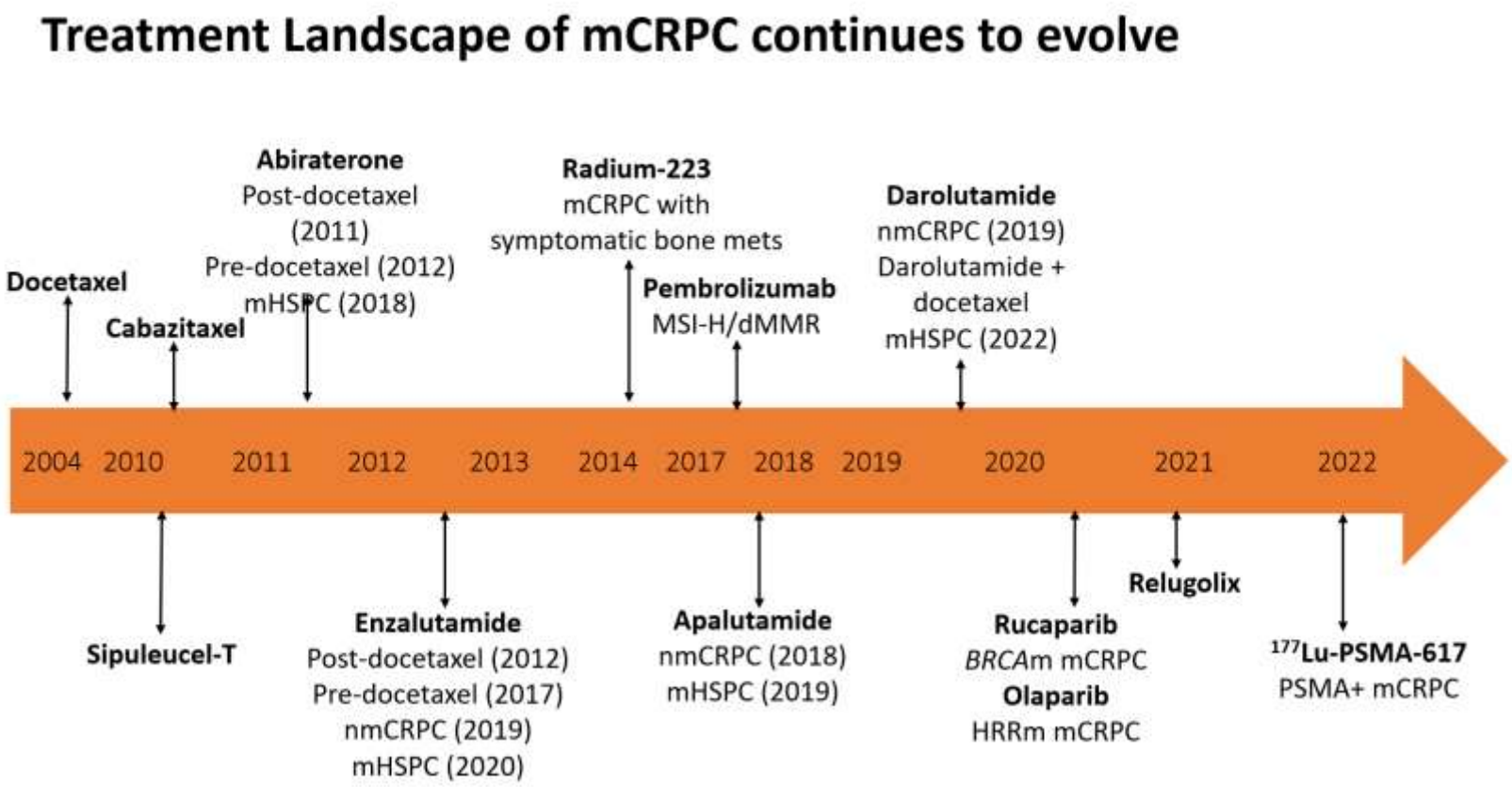
Germline



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

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

Kastrasyona Dirençli Metastatik Prostat kanseri



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

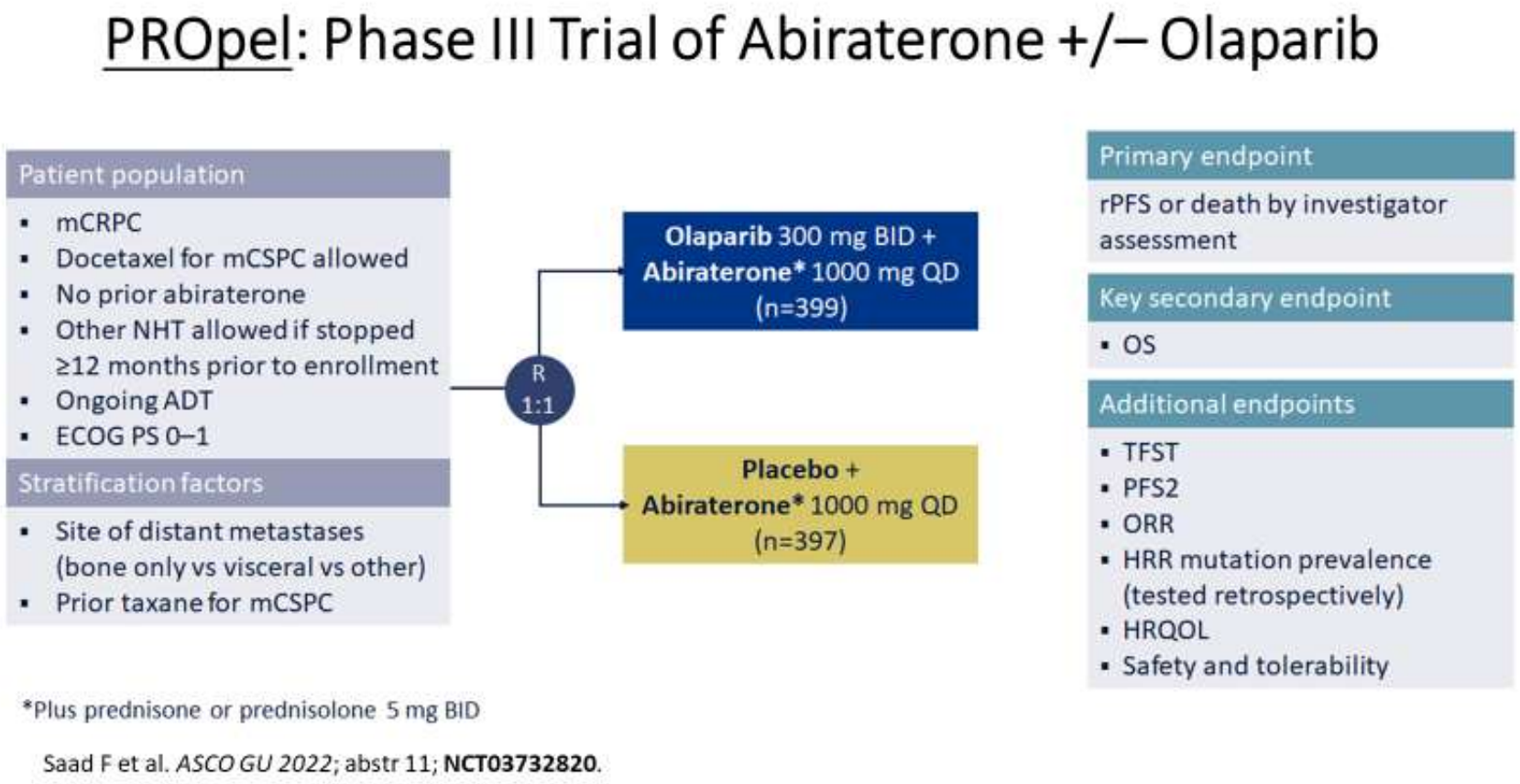
Phase 3 trial of PARPi + AR signaling inhibitor in 1st line mCRPC setting

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

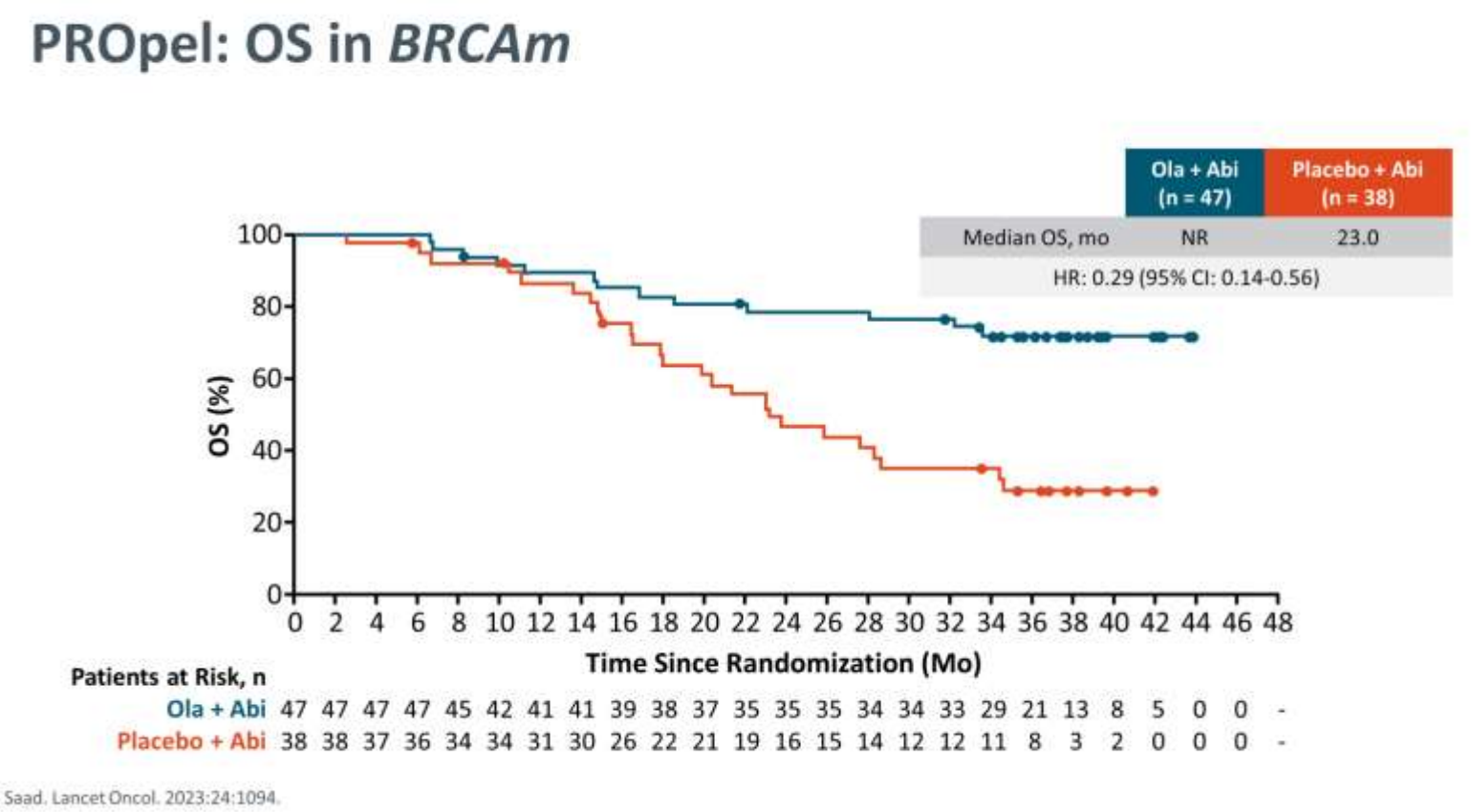
1- Clarke NW et al., NEJM Evidence. 2022 Aug 23;1(9):EVIDoa2200043.

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

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



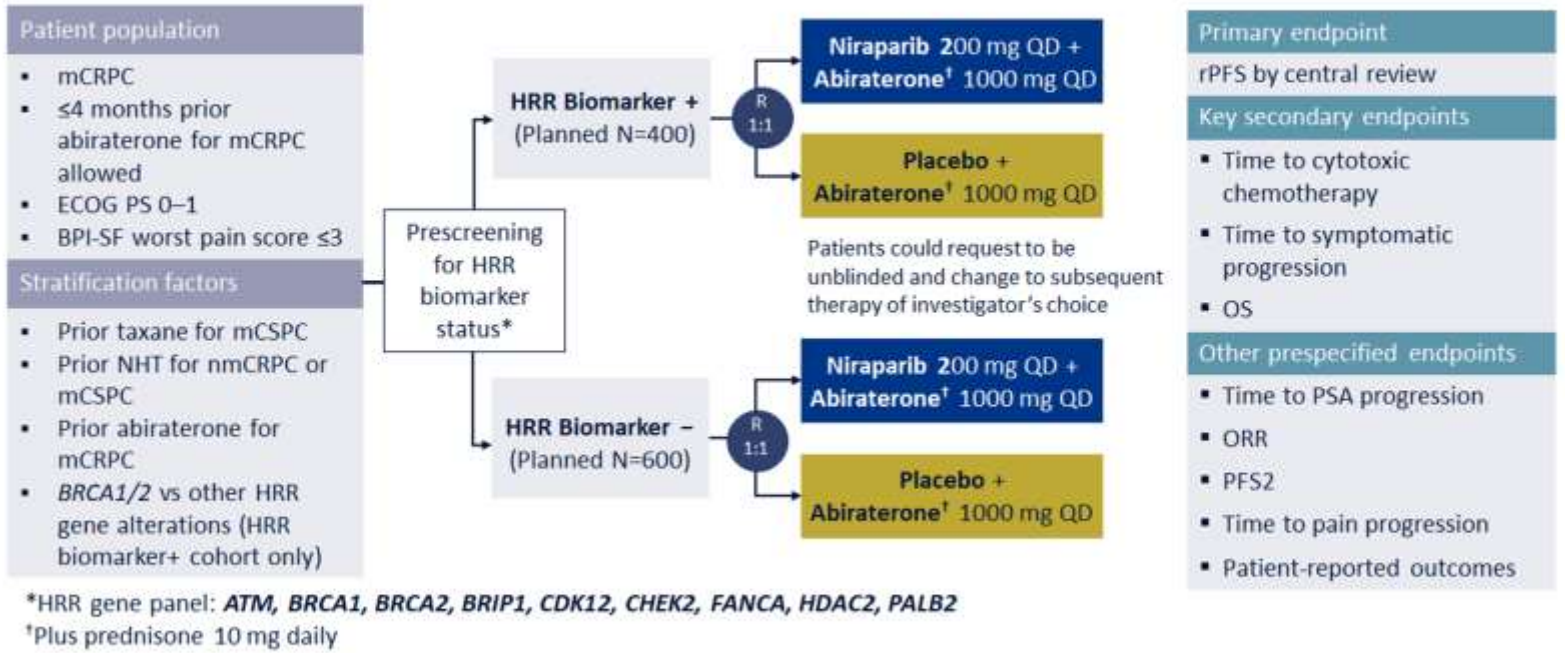
Kastrasyona Dirençli Metastatik Prostat kanseri
PARP inhibitörleri+Androjen Reseptör yolağı blokörleri



Saad. Lancet Oncol. 2023:24:1094.

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

MAGNITUDE: Phase III Trial of Abi +/– Niraparib



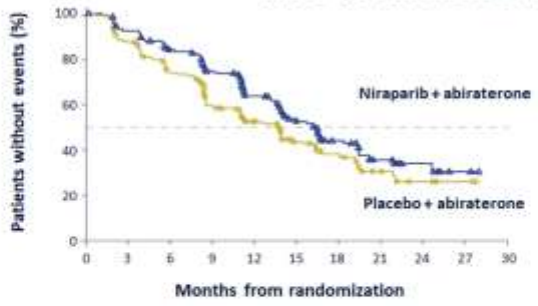
*HRR gene panel: ***ATM, BRCA1, BRCA2, BRIP1, CDK12, CHEK2, FANCA, HDAC2, PALB2***
†Plus prednisone 10 mg daily

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

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

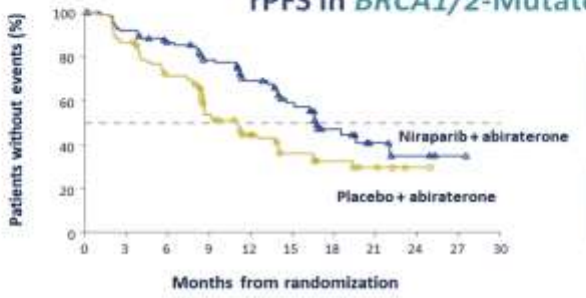
MAGNITUDE: Radiographic Progression-Free Survival

rPFS in All HRR BM+ Cohort



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

rPFS in *BRCA1/2*-Mutated Group

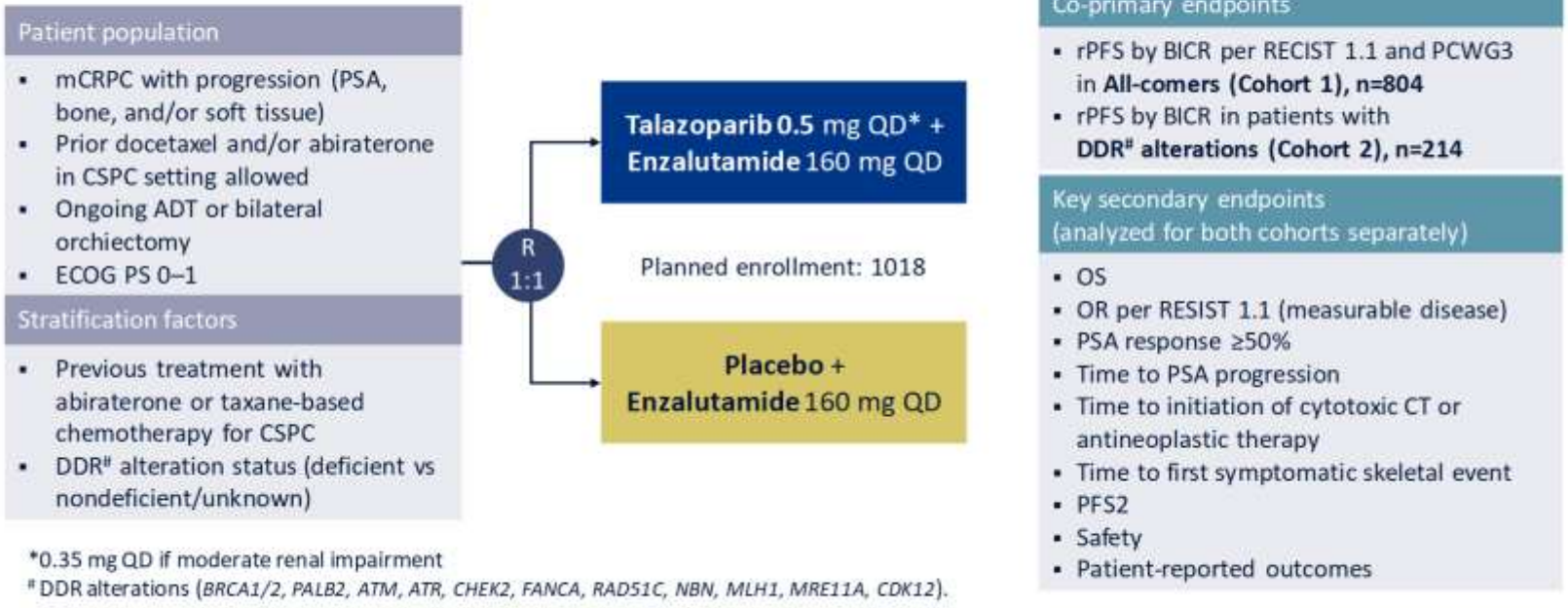


	Niraparib + abiraterone (n=113)	Placebo + abiraterone (n=112)
rPFS by central review		
Median rPFS, months	16.6	10.9
HR (95% CI)	0.53 (0.36–0.79); *P*=0.0014	
rPFS assessed by investigator		
Median rPFS, months	19.3	12.4
HR (95% CI)	0.50 (0.33–0.75); *P*=0.0006	

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

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

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



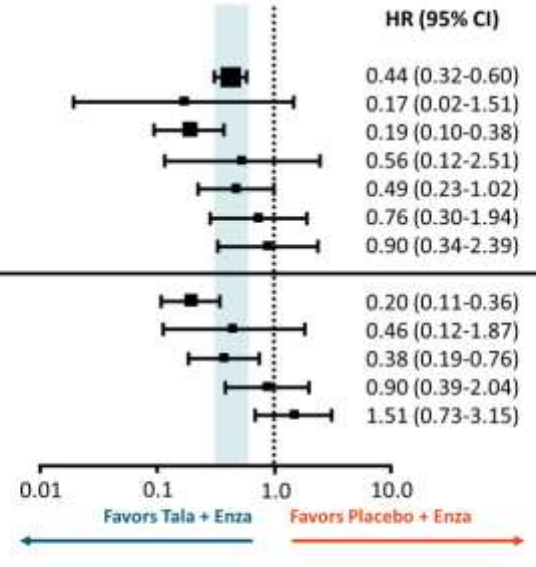
Agarwal N et al. *Future Oncol.* 2022;18:425-436; **NCT03395197**.

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

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

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

Hierarchy



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

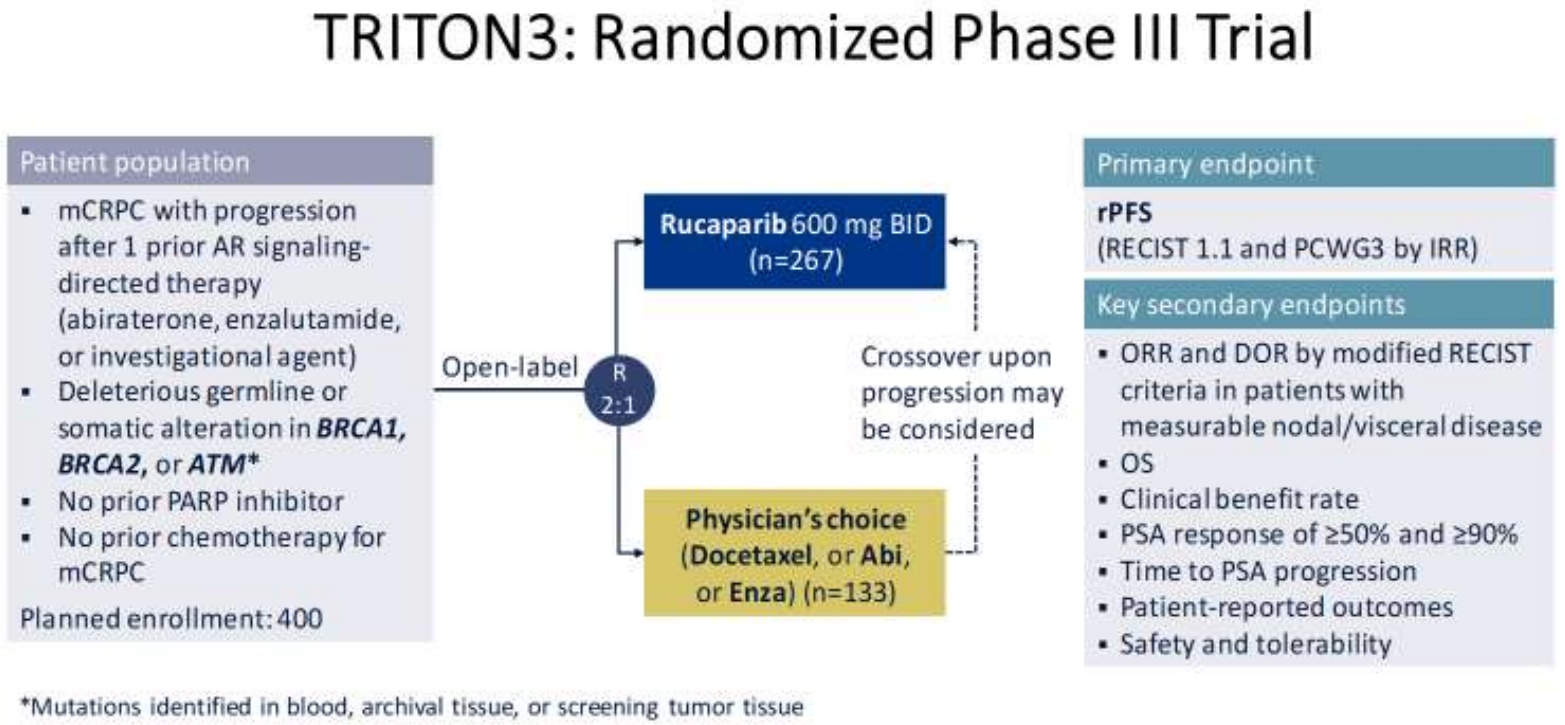
PARP inhibitörleri+Androjen Reseptör yolağı blokörleri
Yan etkilerin karşılaştırılması

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

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

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

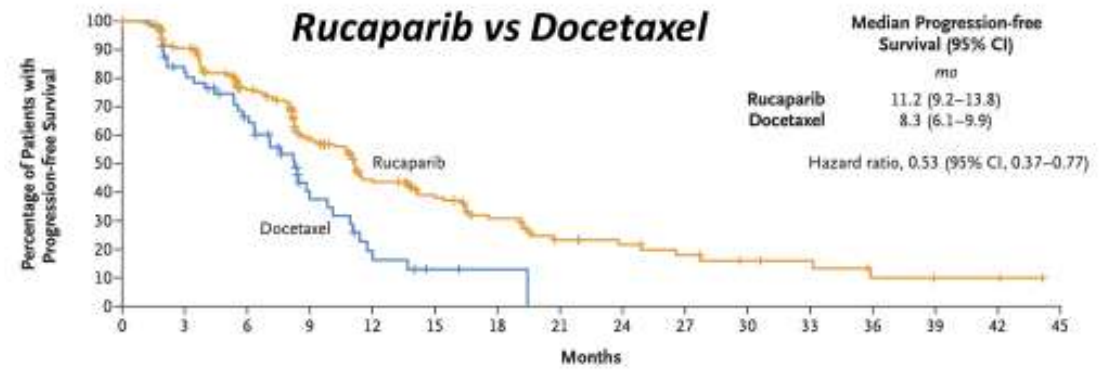
Kastrasyona Dirençli Metastatik Prostat kanseri
PARP inhibitörleri

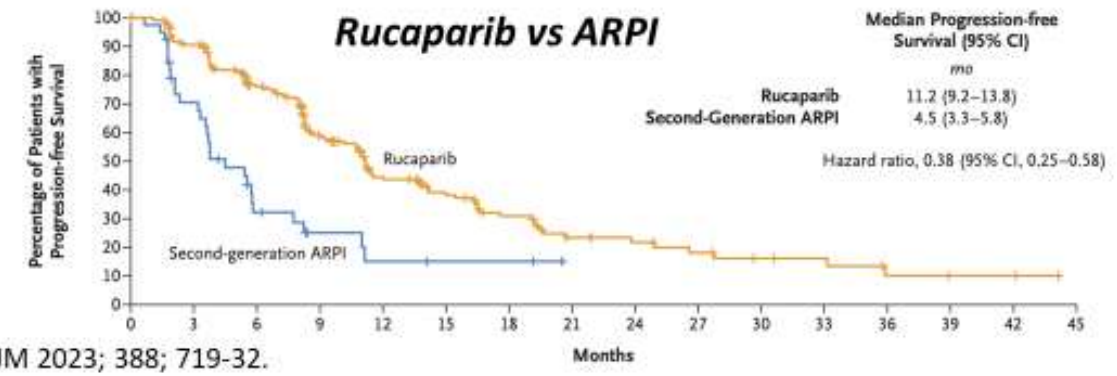


Bryce A et al NEJM 2023; 388; 719-32. **NCT02975934**.

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

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

Eligible patients

- Previous treatment with <u>both</u>
  - ≥ 1 androgen receptor pathway inhibitor
  - 1 or 2 taxane regimens
- Protocol-permitted standard of care (SOC) planned before randomization
  - Excluding chemotherapy immunotherapy, radium-223, investigational drugs
- ECOG performance status 0–2
- Life expectancy > 6 months
- PSMA-positive mCRPC on PET/CT with ^{68}Ga-PSMA-11

2:1

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

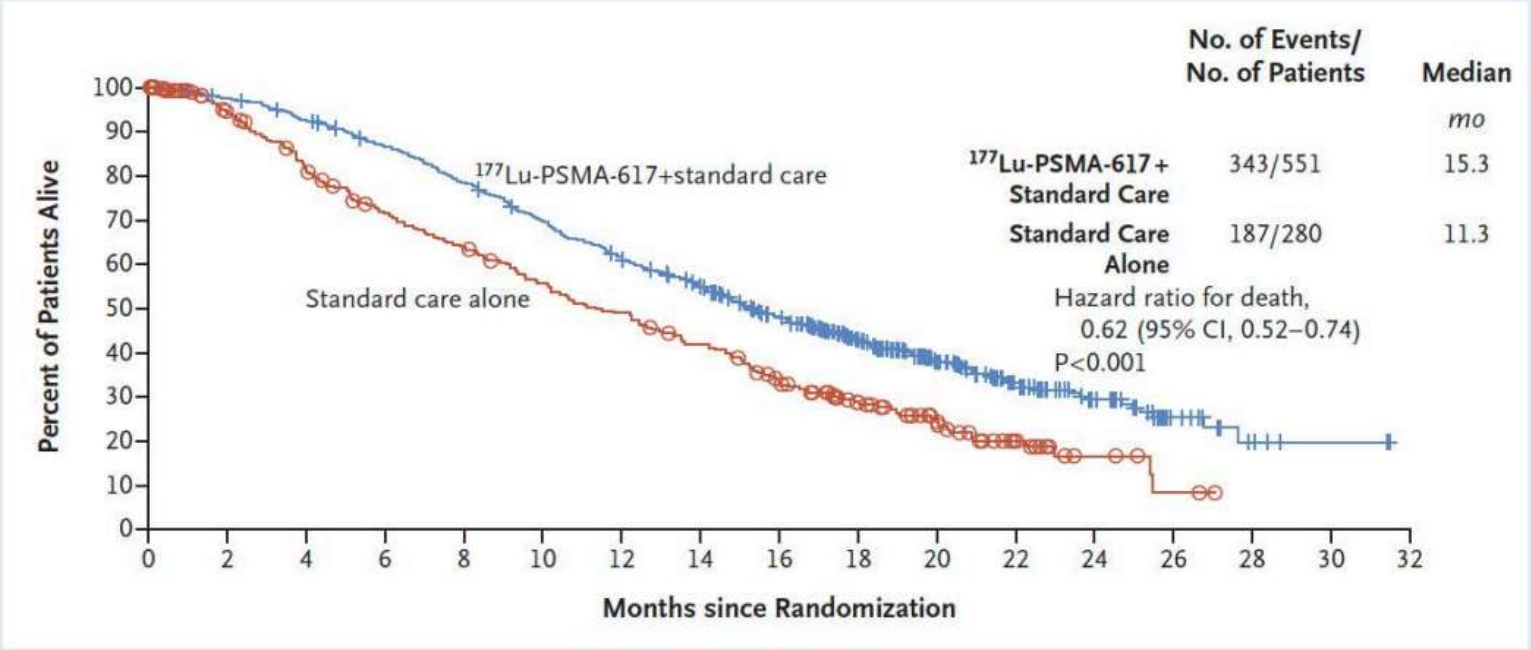
Protocol-permitted SOC alone

Treatment → Follow-up → Final analysis

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

Kastrasyona Dirençli Metastatik Prostat kanseri Lutesyum 177 Tedavisi

VISION: Overall Survival



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

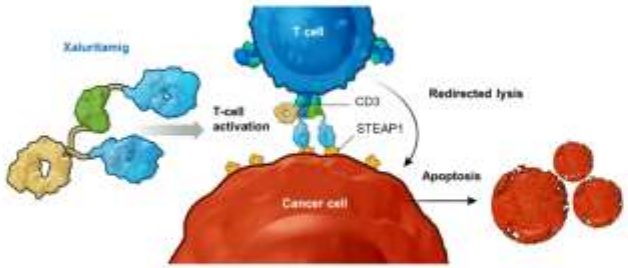
Kastrasyona Dirençli Metastatik Prostat kanseri
Gelecek perspektif

16:00 - 17:20 Proffered Paper session - Genitourinary tumours, prostate

CHAIRS : KARIM FIZAZI, SHAHNEEN SANDHU

Xaluritamig is a STEAP1-targeted T cell engager being evaluated for the treatment of prostate cancer

- Prostate cancer remains a leading cause of cancer deaths worldwide, and patients with mCRPC have a poor prognosis[1]
- STEAP1 is a cell surface antigen highly expressed in prostate cancer and associated with poor survival[2,3]
- In preclinical studies, xaluritamig showed broad anti-cancer effects in prostate cancer xenograft models[3]



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

William Kelly

Interim results from a phase I study of AMG 509 (xaluritamig), a STEAP1 x CD3 XmAb 2+1 immune therapy, in patients with metastatic castration-resistant prostate cancer (mCRPC)

XmAb® is a registered trademark of Xencor, Inc.
mAb, monoclonal antibody; mCRPC, metastatic castration-resistant prostate cancer; STEAP1, six transmembrane epithelial antigen of the prostate

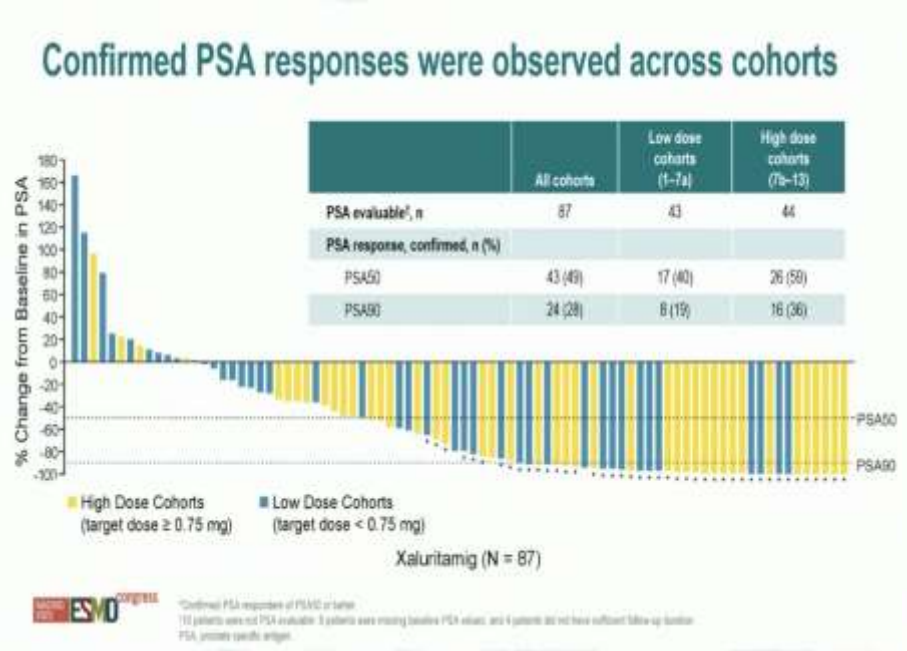
1. Turos F, et al. Res Rep Urol. 2022;14:339-50.
2. Xu M, et al. Cancers (Basel). 2022;14:4334.
3. Nolan-Stevaux O, et al. Cancer Res. 2020;80(16_Supplement):CT032-03.
4. Li C, et al. J Immunother Cancer. 2020;8:718.

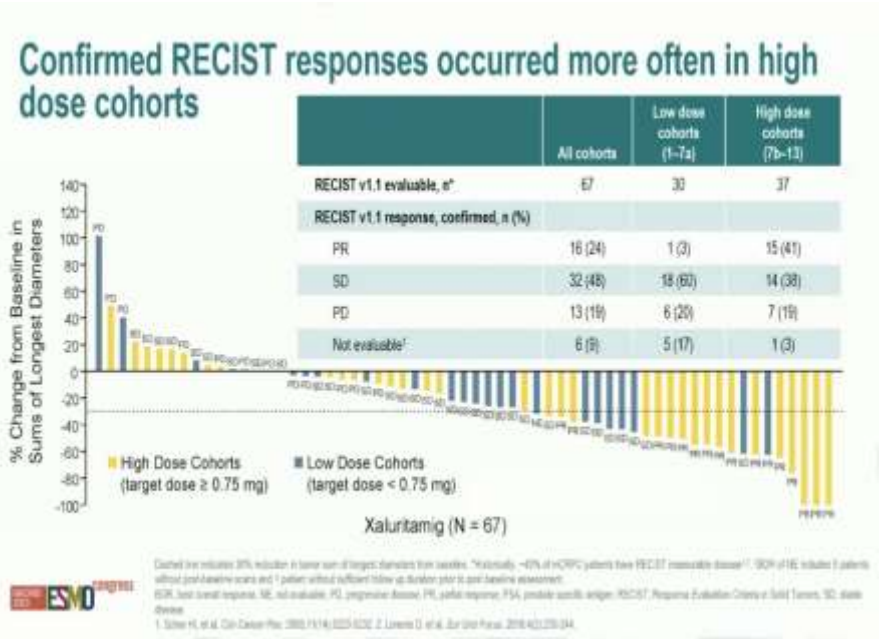
MADRID 2023 ESMO congress

Granada Auditorium - Hall 3

MADRID SPAIN 20-24 OCTOBER 2023

Kastrasyona Dirençli Metastatik Prostat kanseri
Gelecek perspektif

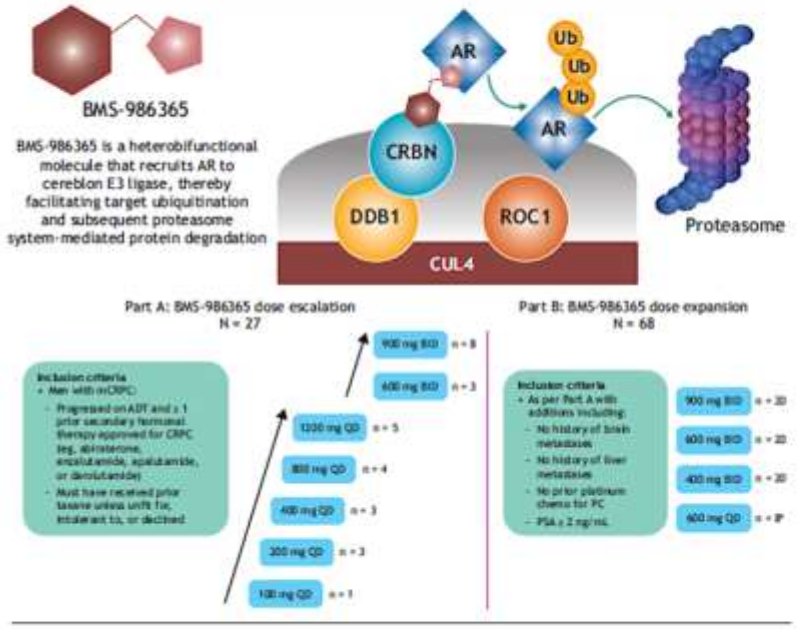




Kastrasyona Dirençli Metastatik Prostat kanseri
Gelecek perspektif

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

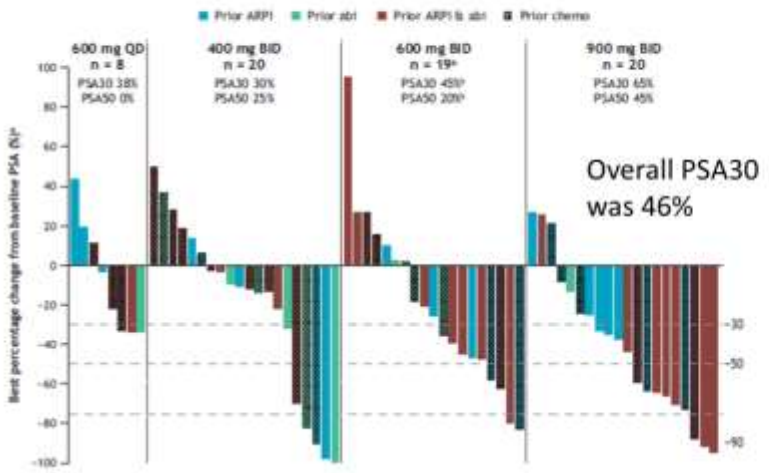
Rathkopf D...Armstrong AJ ASCO GU 2024 abstract 134



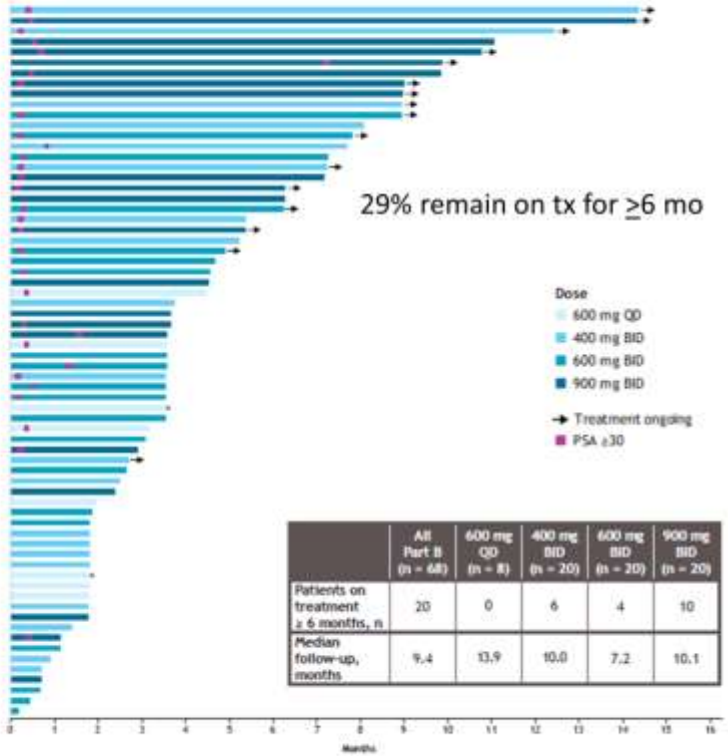
	Part A Dose escalation (n = 27)	Part B Dose expansion (n = 68)	All patients (N = 95)
Median age, years (range)	72 (49-83)	71 (50-87)	71 (49-87)
≥ 75 years, n (%)	7 (26)	24 (35)	31 (33)
Race, n (%)			
White	24 (89)	57 (84)	81 (85)
Black	2 (7)	3 (4)	5 (5)
Asian	1 (4)	3 (4)	4 (4)
Unknown	0	5 (7)	5 (5)
ECOG PS, n (%)			
0	10 (37)	36 (53)	46 (48)
1	17 (63)	32 (47)	49 (52)
Gleason score, n (%)			
≤ 6	2 (7)	3 (4)	5 (5)
7	5 (19)	17 (25)	22 (23)
8-10	18 (67)	40 (59)	58 (61)
Missing	2 (7)	8 (12)	10 (11)
Distant metastasis, n (%)			
Bone	24 (89)	56 (82)	80 (84)
Lymph node	15 (56)	36 (53)	51 (54)
Visceral liver	4 (15)	1 (1)*	5 (5)*
Visceral lung	4 (15)	7 (10)	11 (12)
Median serum PSA, µg/L (range)	96 (1-1699)	37 (3-1610)	51 (1-1699)
Median number of prior regimens (range)†	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 = 68)		All patients (N = 95)	
	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4
Patients with ≥ 1 TEAE	26 (96)	8 (30)	65 (96)	24 (35)	91 (96)	32 (34)
QTc prolongation	7 (26)	2 (7)	32 (47)	6 (9)	39 (41)	8 (8)
Fatigue	7 (26)	0	24 (35)	3 (4)	31 (33)	3 (3)
Bradycardia*	5 (19)	0	23 (34)	0	28 (30)	0
Nausea	12 (44)	0	11 (16)	1 (1)	23 (24)	1 (1)
Anemia	6 (22)	3 (11)	12 (18)	5 (7)	18 (19)	8 (8)
Hypertension	2 (7)	0	14 (21)	5 (7)	16 (17)	5 (5)
Vomiting	7 (26)	0	7 (10)	1 (1)	14 (15)	1 (1)
Diarrhea	2 (7)	0	9 (13)	0	11 (12)	0
ALT increased	3 (11)	0	7 (10)	0	10 (11)	0
Back pain	1 (4)	0	9 (13)	1 (1)	10 (11)	1 (1)



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

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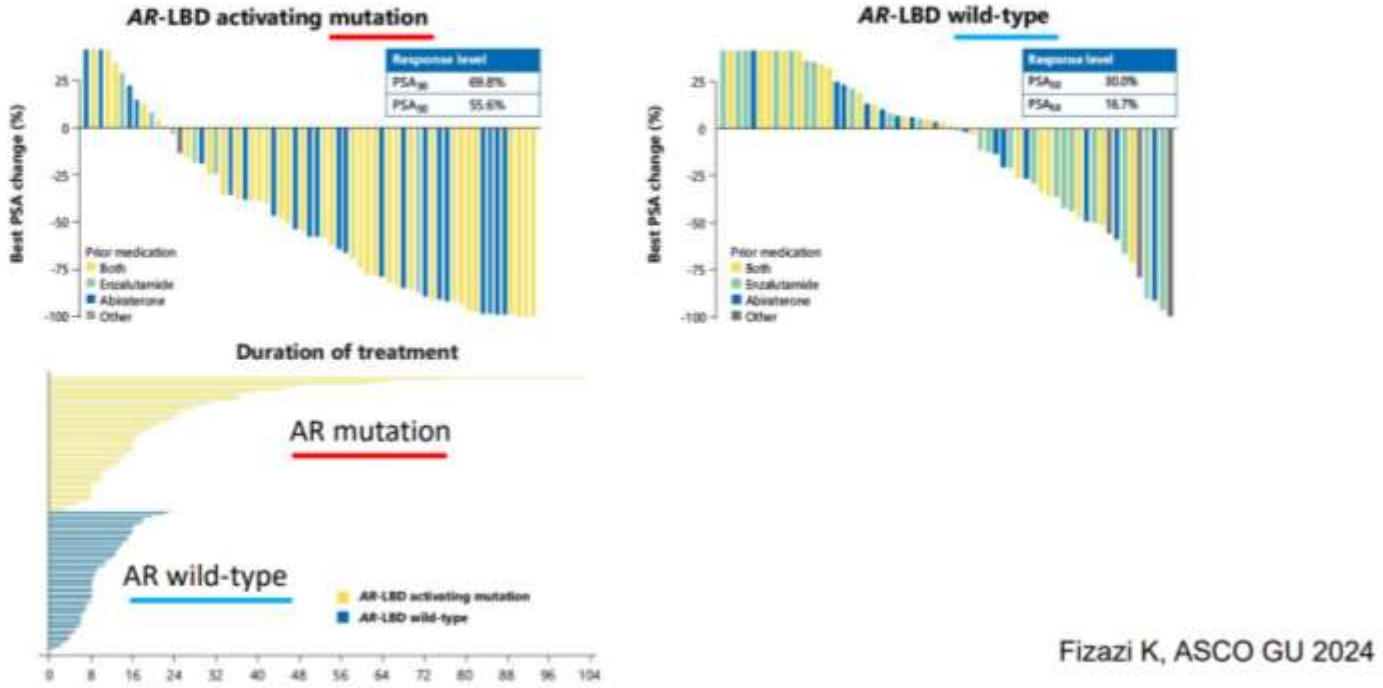
Kastrasyona Dirençli Metastatik Prostat kanseri
Gelecek perspektif

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≤ 9 ay, Enzalutamid +ADT+/-RT

- Kastrasyona duyarlı metastatik prostat kanseri;

  Üçlü tedavi(ADT+Dosetaksel+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≥ Taksan, 1≥yeni nesil androjen reseptör yolağı inhibitörleri alanlarda LU-177