Kastrasyona Duyarlı Metastatik Prostat Kanserinde Doz Yoğun Tedavi

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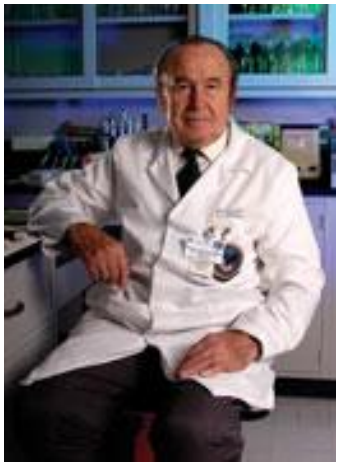
Ders Planı

- ❑ Giriş
- ❑ Tedavi kararında etkili faktörler
- ❑ Dosetaksel hangi hasta grubuna eklenmeli
- ❑ Diğer doz yoğun kombinasyonlar
- ❑ Genomik analize göre tedaviyi yoğunlaştırmak veya azaltmak
- ❑ Gelecek perspektif
- ❑ Sonuç

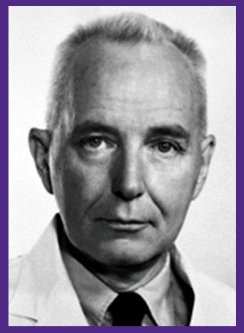
Kastrasyona Duyarlı Metastatik Prostat Kanseri ADT Tedavisi



- Charles Brenton Huggins(1901-1997)
- 1927'de Chicago Üniversitesinde Üroloji kliniğinde akademik kadro aldı
- Köpeklerde yaptığı deneylerle, prostat hücrelerinin büyümesinde testosteron hormonuna bağımlı olduğunu tespit etti
- Prostat kanseri olanlarda orişektomi ile tümörün küçüldüğünü belirledi.
- Bu çalışmalarıyla 1966 Nobel ödülü aldı
- Dr. Andrew V. Schally LHRH analoğu keşfi ile 1977 Nobel ödülü alıyor

Kastrasyona Duyarlı Metastatik Prostat Kanseri ADT Tedavisi

Historical Perspective: Androgens & Prostate Cancer



C. Huggins
1966 Nobel Prize

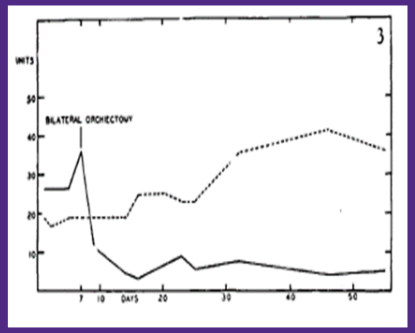
Studies on Prostatic Cancer

I. The Effect of Castration, of Estrogen and of Androgen Injection on Serum Phosphatases in Metastatic Carcinoma of the Prostate*

Charles Huggins, M.D., and Clarence V. Hodges, M.D.

(From the Department of Surgery, the University of Chicago, Chicago, Illinois)

(Received for publication March 22, 1941)



Cancer Res 1941;1:293-297

- **Seminal Observation**: PCa is an androgen driven/dependent disease & surgical or medical castration can induce significant regressions of PC.
  - *Role of acid phosphatase as a biomarker*
- >90% of patients initially respond to androgen deprivation therapy (ADT), however, most will progress to castration resistance with a median survival of about 4 years.

Tedavi Kararında Etkili Faktörler

Hastalıkla İlişkili Faktörler

1- Yüksek volüm/Düşük volüm

2- Denovo/metakron metastaz

3-Metastaz bölgesi

4-Gleason skoru

5-Primer tümörün genetik profil

Klinik Faktörler

1-Semptomatik olması

2-ECOG PS

3-Ek hastalıklar

4-Başka hastalıklar için aldığı tedaviler

5-Hastalık için daha önce aldığı tedaviler

Başlanacak tedavi ile ilgili faktörler

1-Uygulama şekli

2-Etki etme mekanizması

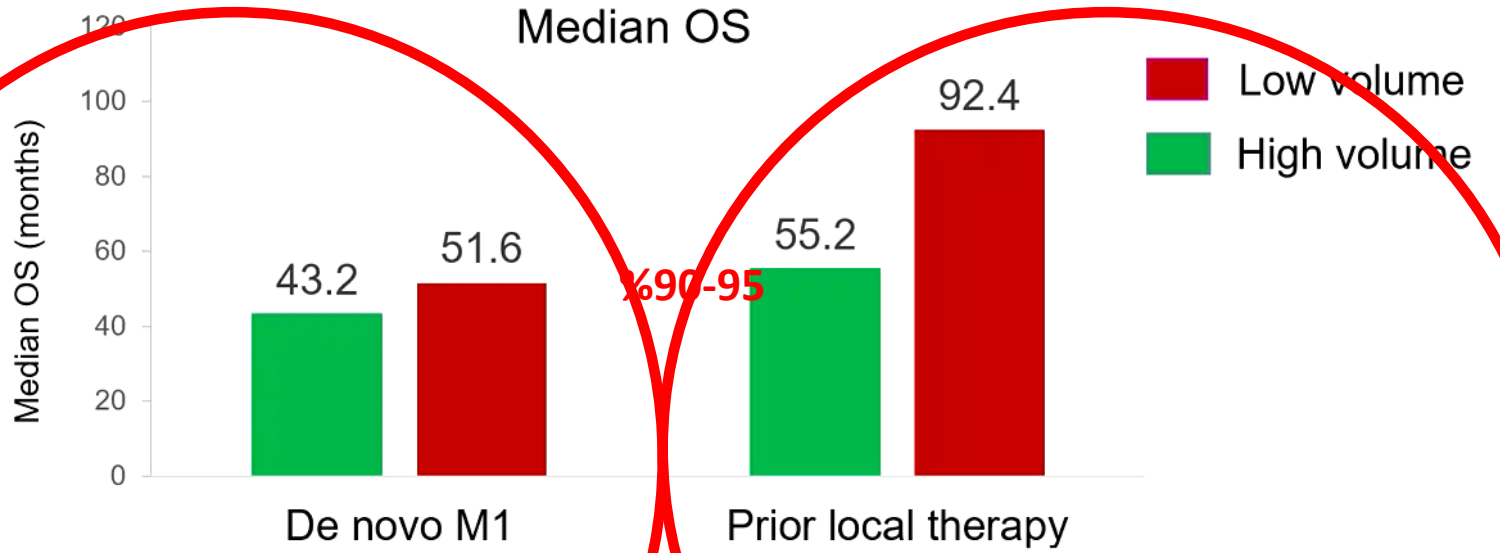
3- Yan etkileri

4-İlaç etkileşimi

5-Tedavi maliyeti

Tanı Anında Metastatik Hastalık Agresif Seyirli

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.

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%90-95

%5-10

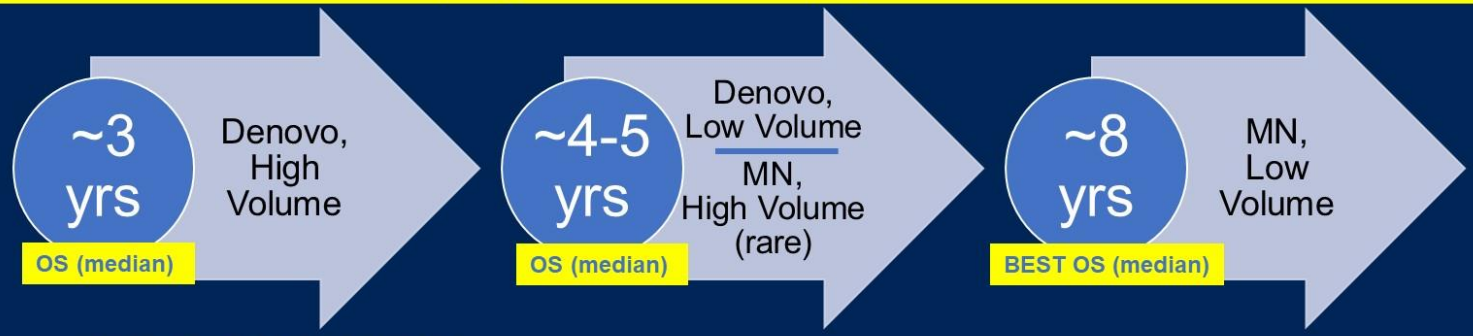
%90-95

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?

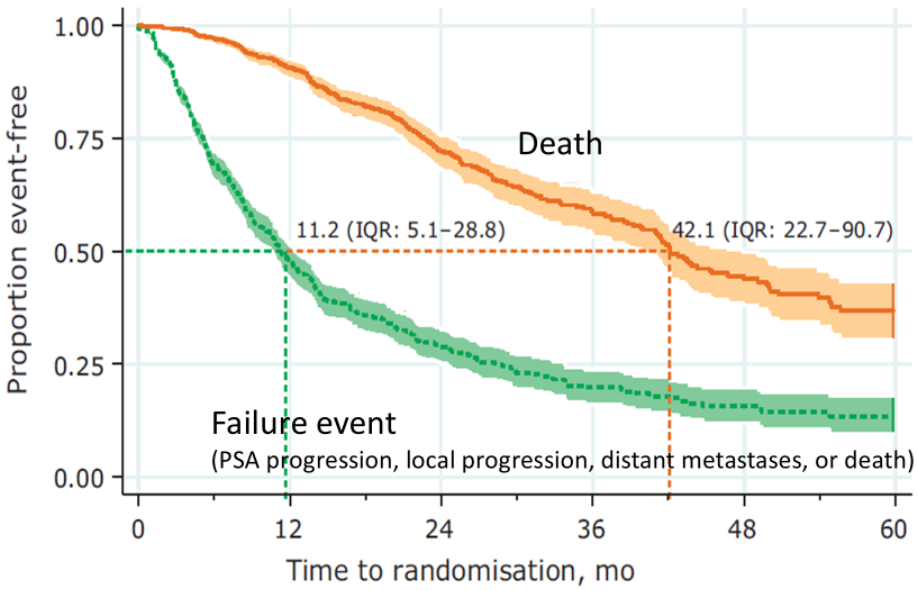


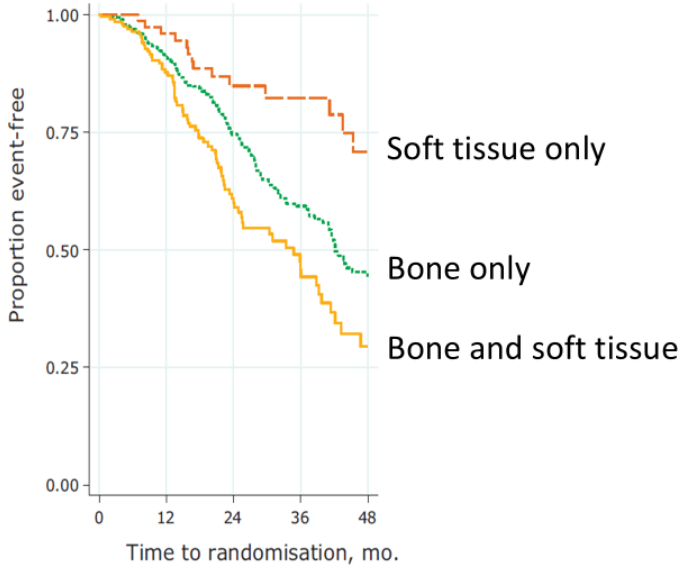
Denovo = new diagnosis/untreated
MN = metachronous diagnosis/previously treated

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

ADT alan hastalarda metastaz bölgesine göre sağkalım

Clinical Outcomes in Metastatic Prostate Cancer: STAMPEDE Experience with ADT





STAMPEDE Control Arm
- Metastatic disease
- Accrued 10/2005-1/2014
- N=917

James ND *et al* (2015) Eur Urol 67: 1028-1038

Yalnız ADT alanlarda 5-yıllık sağkalım %30-40. Non-regional lenf nodu iyi prognoz ile ilişkili

Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisinin Seyri

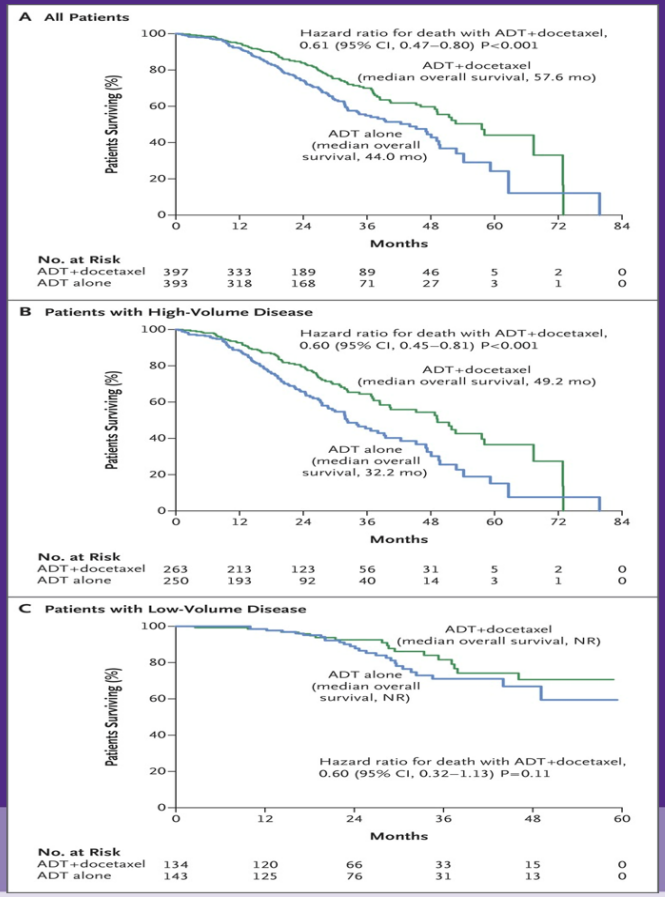
Sağkalımı artıran kanıt düzeyi yüksek çalışmalar

Studies	Intervention	Control	Comments
GETUG-AFU 15 CHAARTED STAMPEDE-C	Docetaxel + ADT	ADT	Benefit in high-volume subgroup
LATITUDE STAMPEDE-G	Abiraterone + ADT	ADT	Similar benefits by risk group
ARCHES ENZAMET	Enzalutamide + ADT	ADT	Similar benefits by risk group
TITAN	Apalutamide + ADT	ADT	Similar benefits by risk group
ARASENS	Darolutamide + ADT + docetaxel	ADT + docetaxel	Similar benefits for recurrent and de novo metastatic disease
PEACE-1	Abiraterone +ADT + docetaxel (+/- prostate radiation)	ADT + docetaxel (+/- prostate radiation)	Subgroup analysis

Gravis et al Lancet Oncol 2013; Sweeney et al NEJM 2015; James N et al Lancet 2015; Attard G et al Lancet Oncol 2023; Fizazi K et al NEJM 2017; James et al NEJM 2017; Armstrong et al JCO 2021; Davis et al NEJM 2019; Chi KN et al NEJM 2019; Smith MR et al NEJM 2022; Fizazi K et al Lancet 2022

Hastalık Volümü Dosetaksel Tedavi Etkinliği için Prediktif

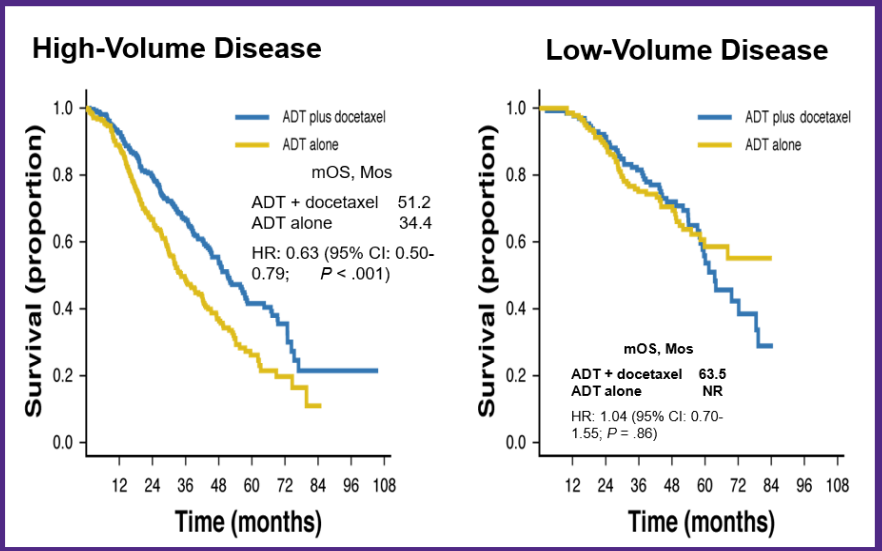
CHAARTED: ADT +/- Docetaxel in mHSPC



Sweeney CJ et al. NEJM 2015

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

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

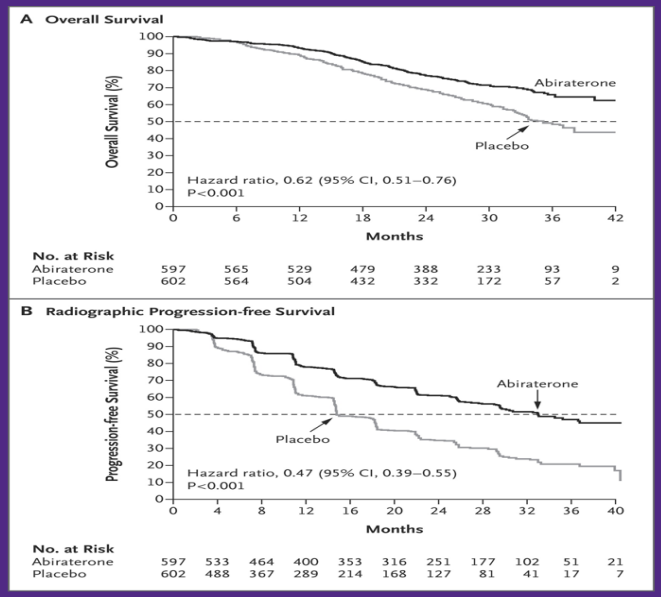


Kyriakopoulos CE, et al. J Clin Oncol. 2018

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

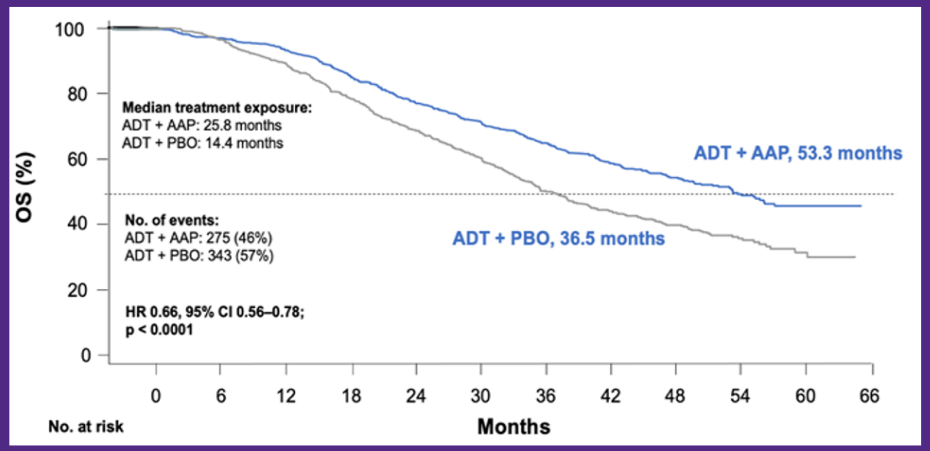
Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

LATITUDE: ADT + Abiraterone/Prednisone or Placebo in Newly Diagnosed High-Risk mHSPC



OS rate at 3 years:
ADT + AA + P: 66%
ADT + placebos: 49%

Fizazi et al. NEJM 2017



- Median follow-up of 51.8 months
- 34% reduction in risk of death
- Median OS was significantly longer for abiraterone + ADT vs placebo + ADT
  - 53.3 months vs 36.5 months
  - **HR = 0.66; $p < 0.0001$**

Fizazi K et al. Lancet Oncol 2019;20(5):686-700

En az 2≥ kötü risk grubuna sahip hastalar dahil edilmiş; Gleason skoru≥8, 3≥ fazla kemik metastazı, Viseral metastaz

Dışlama kriterleri; Daha önce cerrahi, Radyoterapi ,Kemoterapi

Metastatik hastalığa bağlı semptomu olanlarda RT ve Cerrahiye izin verilmiş

Yeni nesil androjen yolağı inhibitörleri riskten bağımsız etkili

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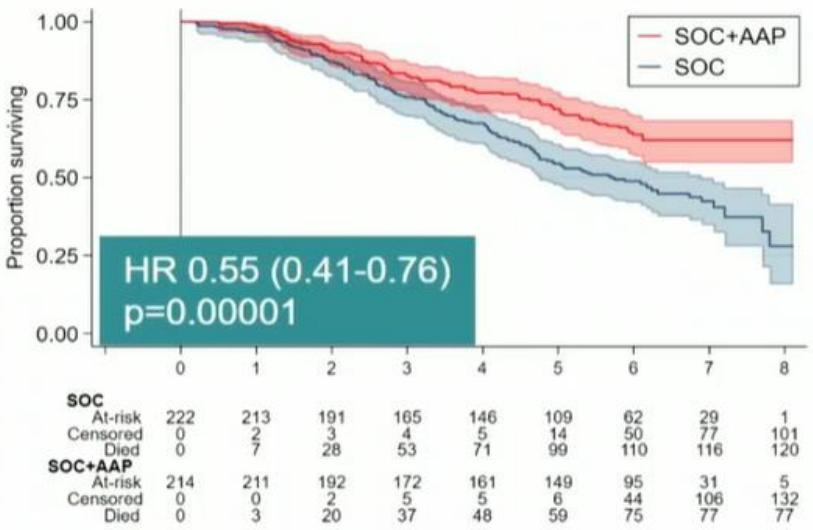
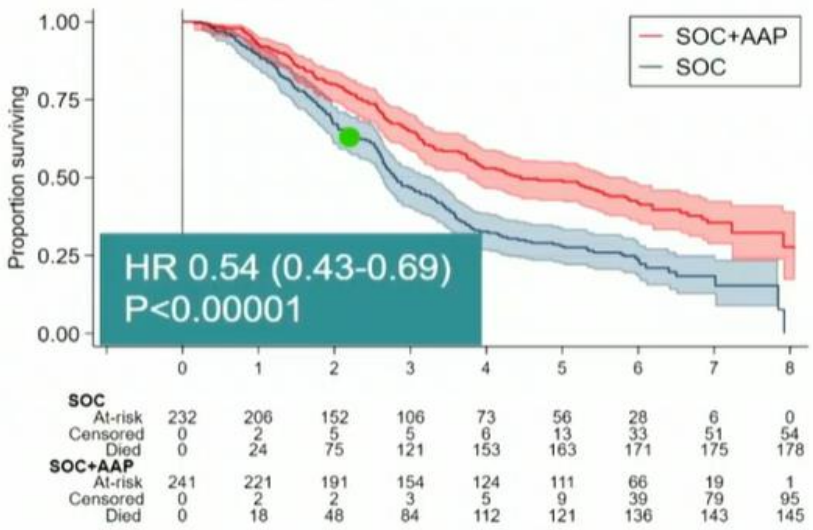
STAMPEDE: OS by risk group (LATITUDE)

Low risk



HR 0.66 (0.44-0.98)
p=0.041

High risk



HR 0.54 (0.41-0.70)
P<0.001

Yeni nesil androjen yolağı inhibitörleri tümör yükünden bağımsız etkili

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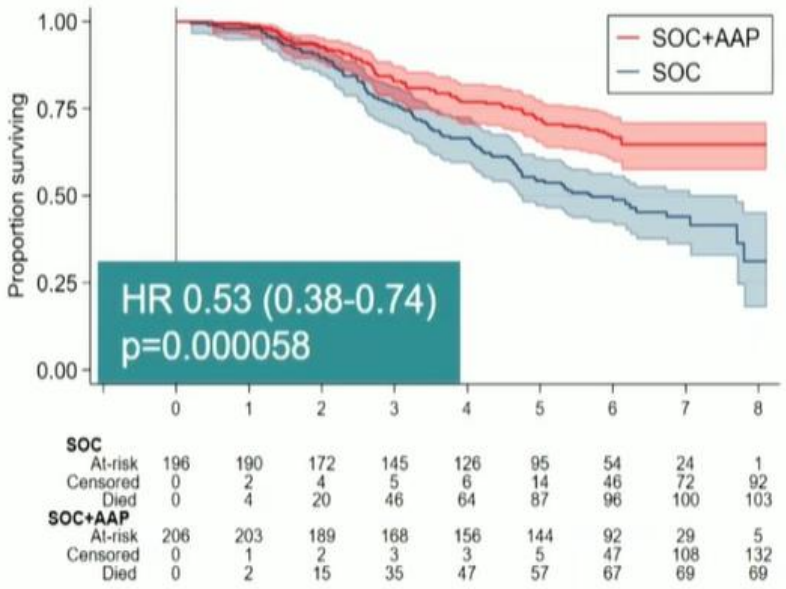
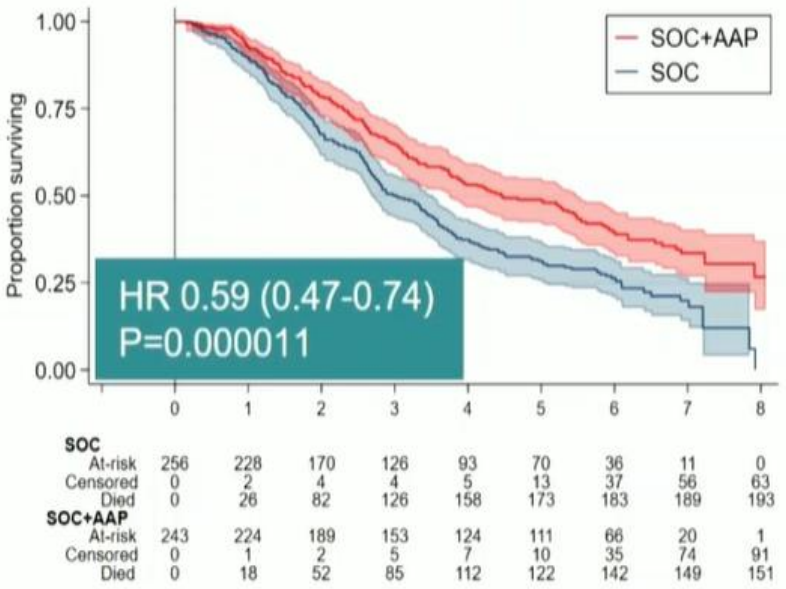
STAMPEDE: OS by disease burden (CHAARTED)

Low volume



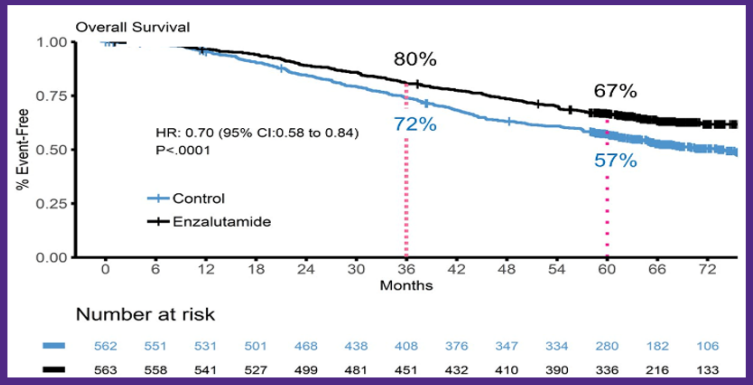
High volume



Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

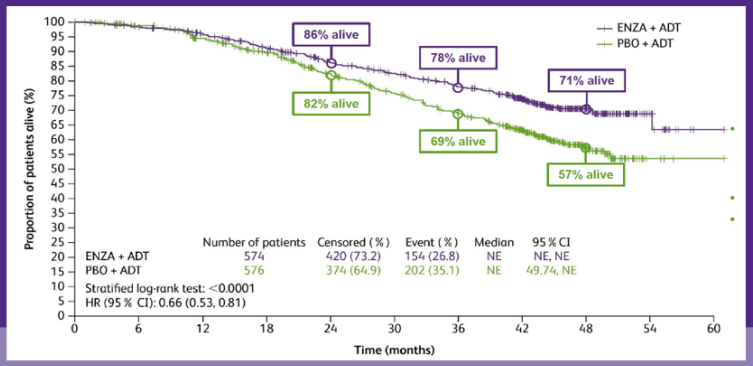
Final Overall Survival (OS) Analyses: Enzalutamide for Metastatic Hormone-Sensitive Prostate Cancer

ENZAMET[1]
Enzalutamide + testosterone suppression (TS)



- Median follow-up of 68.0 months
- 30% reduction in risk of death
- Median OS was significantly longer for enzalutamide + TS versus standard NSAA + TS
  - **Not reached vs 73.2 months**
  - **HR = 0.70; p < 0.0001**

ARCHES[2]
Enzalutamide + ADT

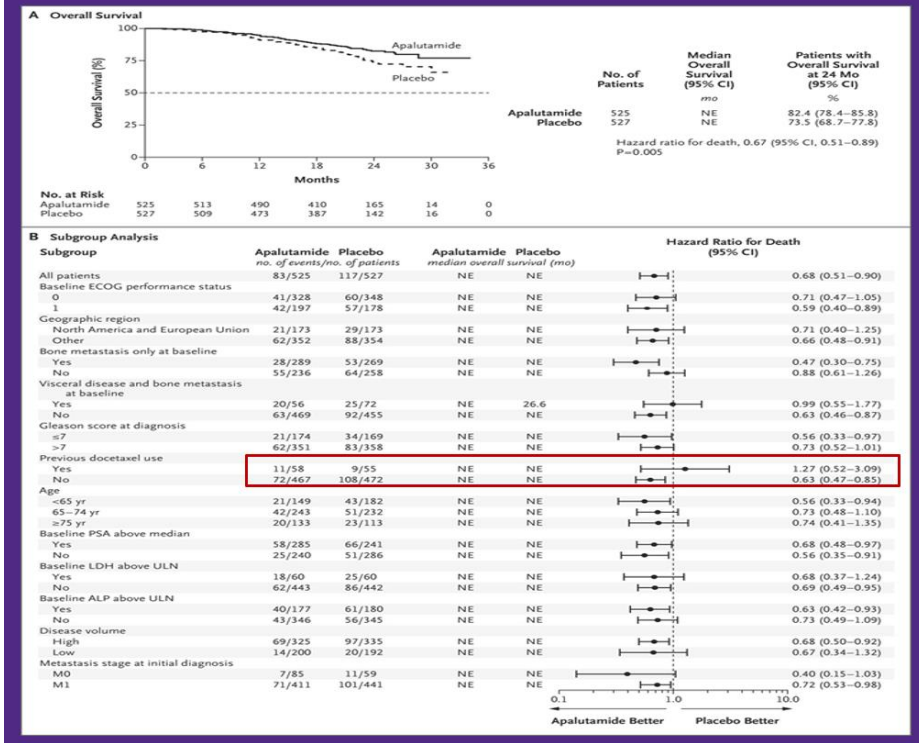


- Median follow-up of 44.6 months
- 34% reduction in risk of death
- Median OS was not reached for enzalutamide plus ADT, but was 47.7 months (95% CI, 43.3 to not evaluable) for placebo plus ADT.
  - **- HR = 0.66; p< 0.001**

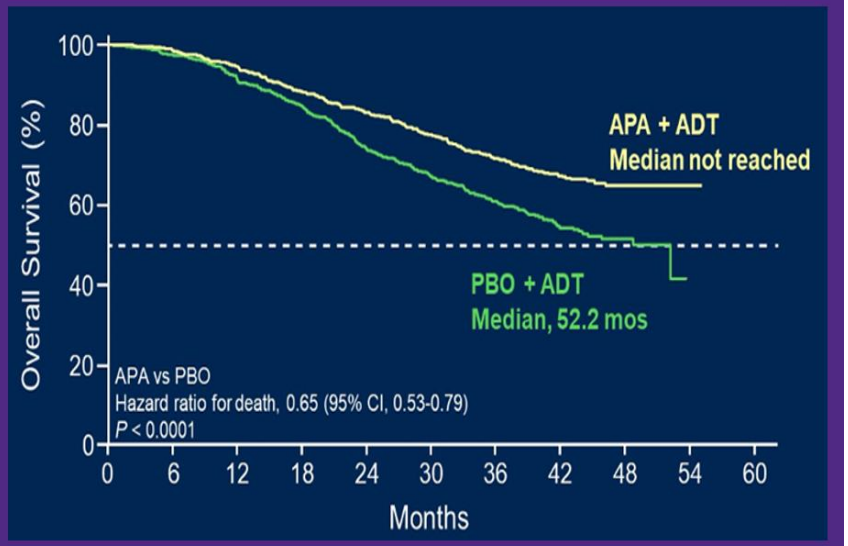
1. Davis ID et al. ASCO 2022;Abstract LBA5004; 2. Armstrong AJ et al. J Clin Oncol 2022;40(15):1616-22.

Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

Apalutamide for Metastatic, Castration-Sensitive Prostate Cancer



- **8% difference in OS at 2 years**
- **Reduced risk of death by 33%**

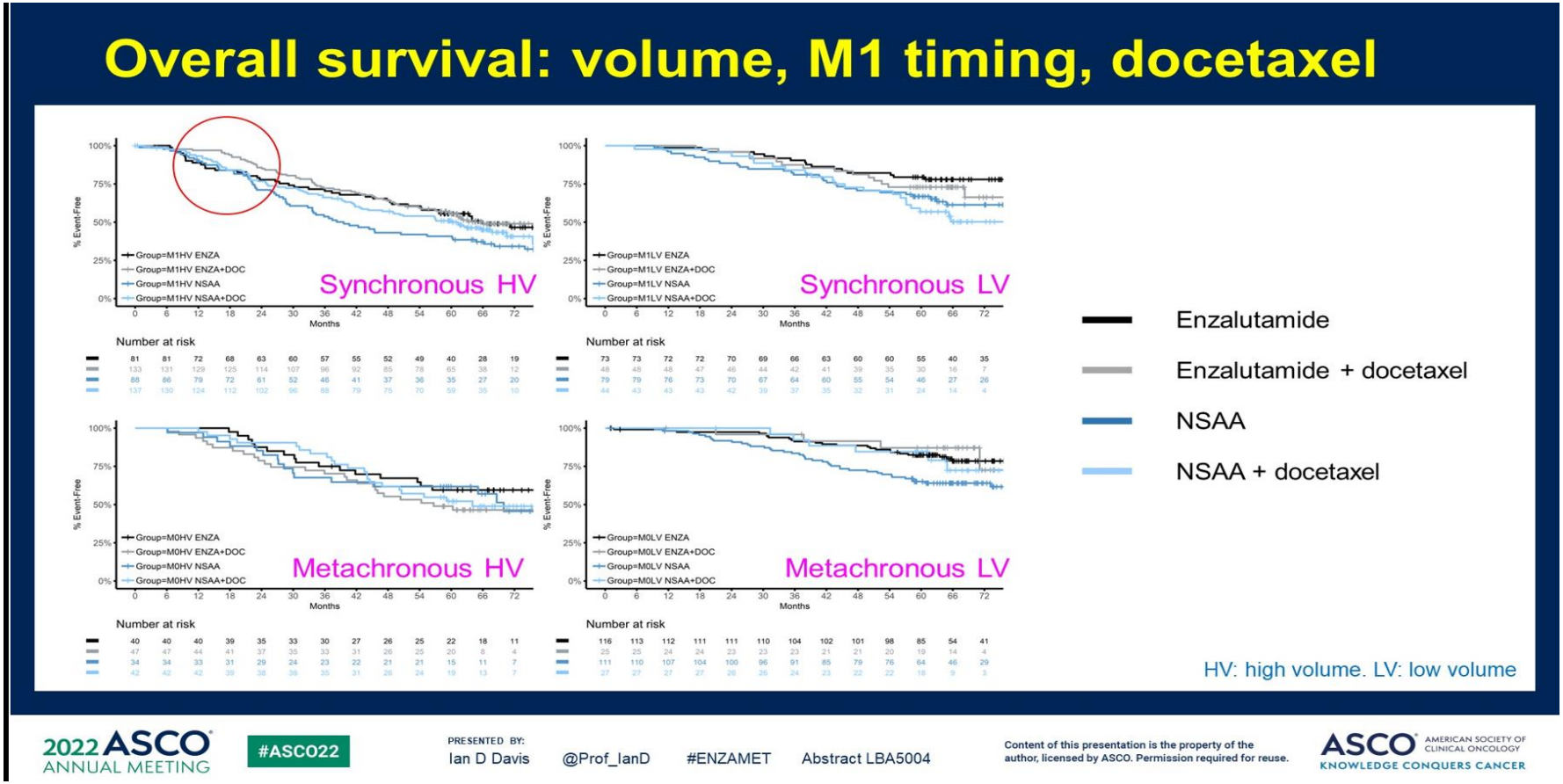


- Median follow-up of 44.0 months
  - 35% reduction in risk of death
- Median OS was significantly longer for apalutamide + ADT vs placebo + ADT:
  - Not reached vs 52.2 months
  - HR = 0.65; p < 0.0001

Chi KN et al.NEJM 2019

Chi KN et al. J Clin Oncol 2021

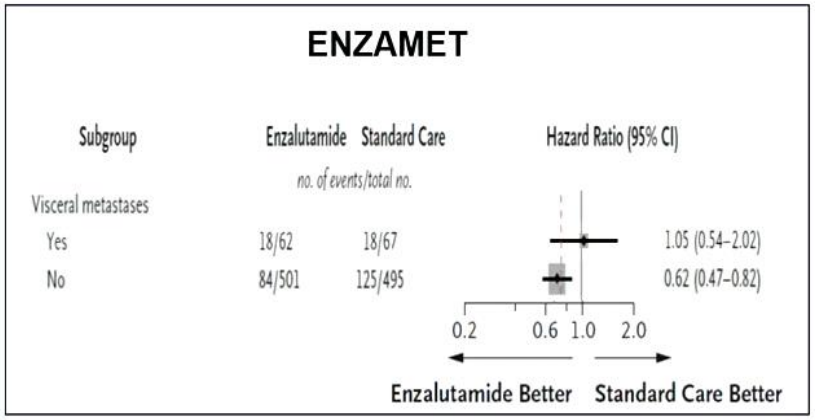
ENZAMET çalışması de novo yüksek volümde üçlü tedavi etkili

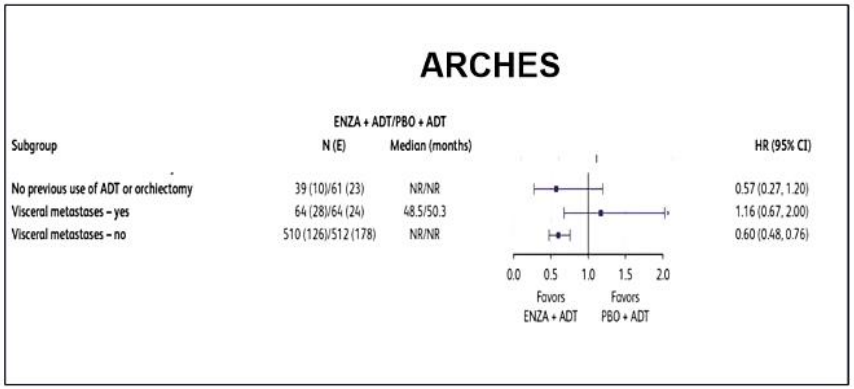


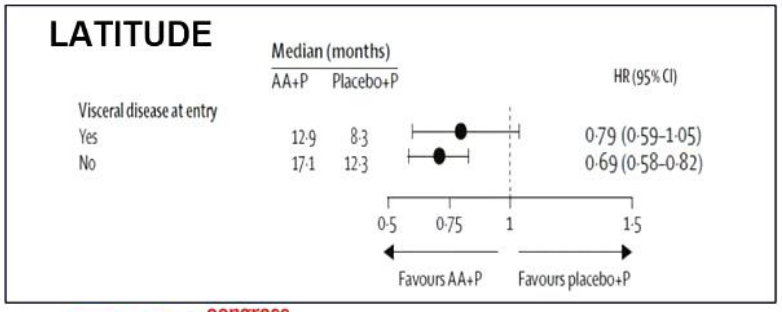
Yeni nesil androjen yolağı inhibitörleri viseral metastazda etkinliği düşük

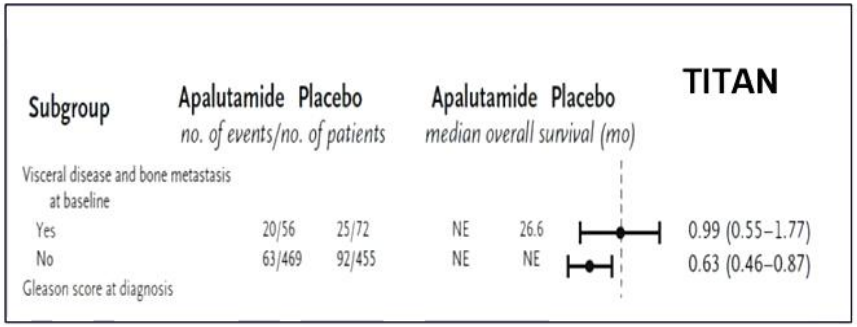
Does type of metastasis matter in mHNPC?

Results from new hormonal treatments in mHNPC according visceral mets









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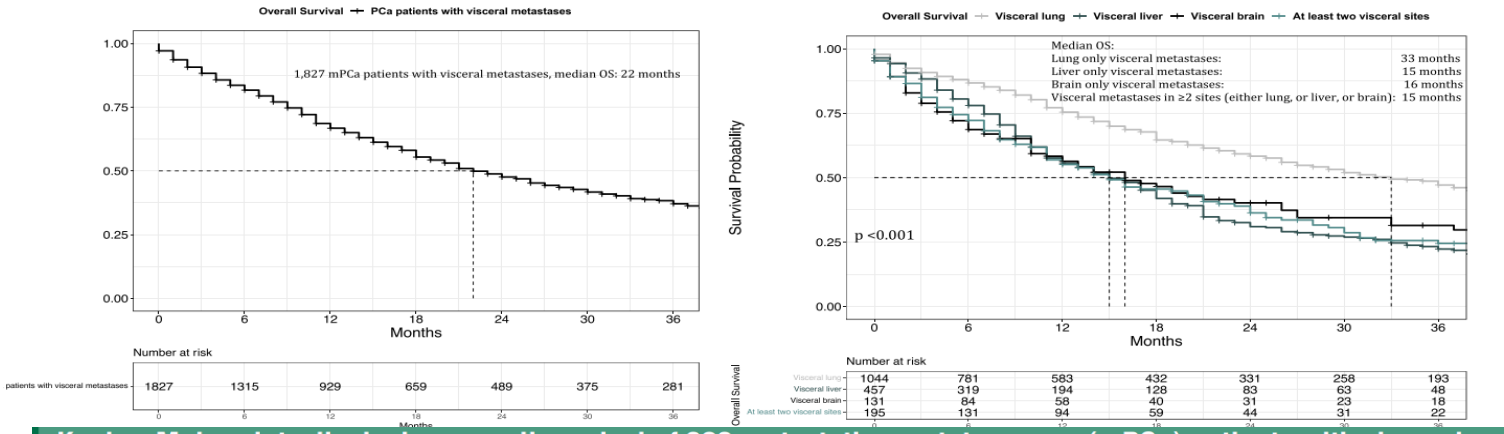
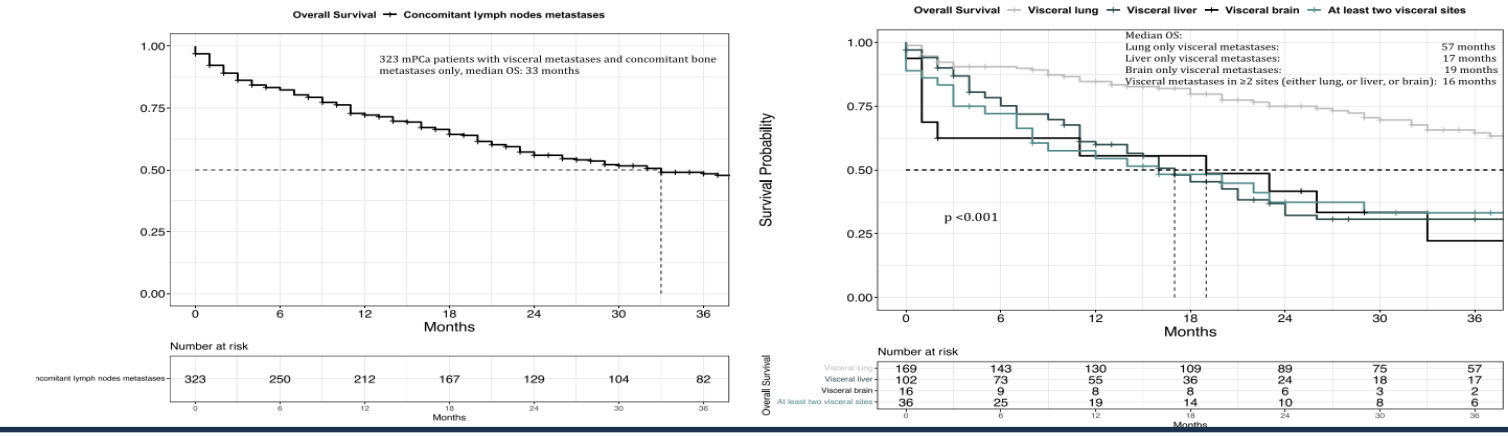
1. Davis I, et al. NEJM 2019;381:121-131 2. Armstrong A, et al. ESMO 2021 oral comm. abstract LBA25 3. Chi K, et al. NEJM 2019;381:13-24 4. Fizazi K, et al. Lancet Oncol. 2019 May;20(5):686-700.

Viseral metastaz tanımı

Kaplan-Meier plots displaying overall survival in 1827 metastatic prostate cancer (mPCa) patients with visceral metastases, regardless of presence of lymph node and/or bone metastases: (A) in the overall population; (B) according to location of visceral metastatic sites.



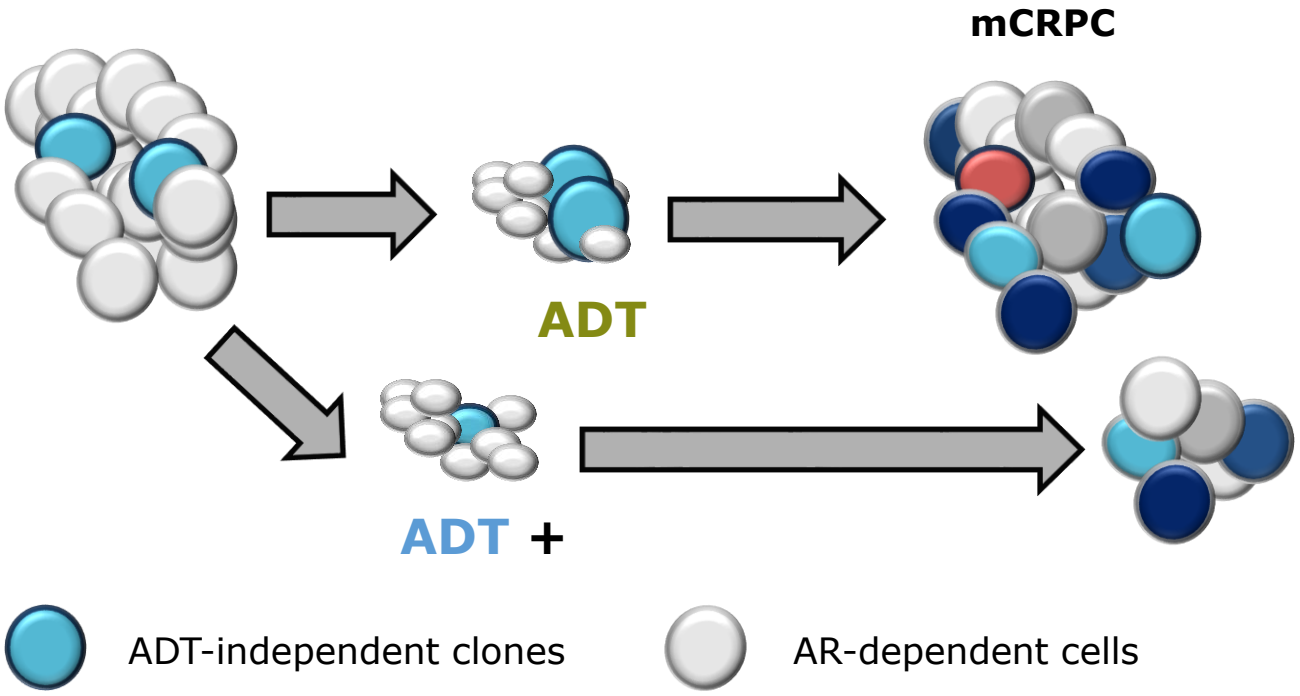
Kaplan-Meier plots displaying overall survival of 323 metastatic prostate cancer (mPCa) patients with visceral metastases with concomitant lymph node metastases only: (A) in the overall population; (B) according to location of visceral metastatic sites.



Akciğer+/-lenf met(kemik met olmadan) mOS; 57 ay, Karaciğer ve beyin met; 15 ve 19 ay

Tappero S, at al. Clinical Genitourinary Cancer 2023

Kastrasyona Duyarlı Metastatik Prostat Kanseri Daha Yoğun Tedavisi



Role of Effective Systemic Therapy

Tedaviyi yoğunlaştırma stratejileri

APPIs: enza/apa/darolutamide

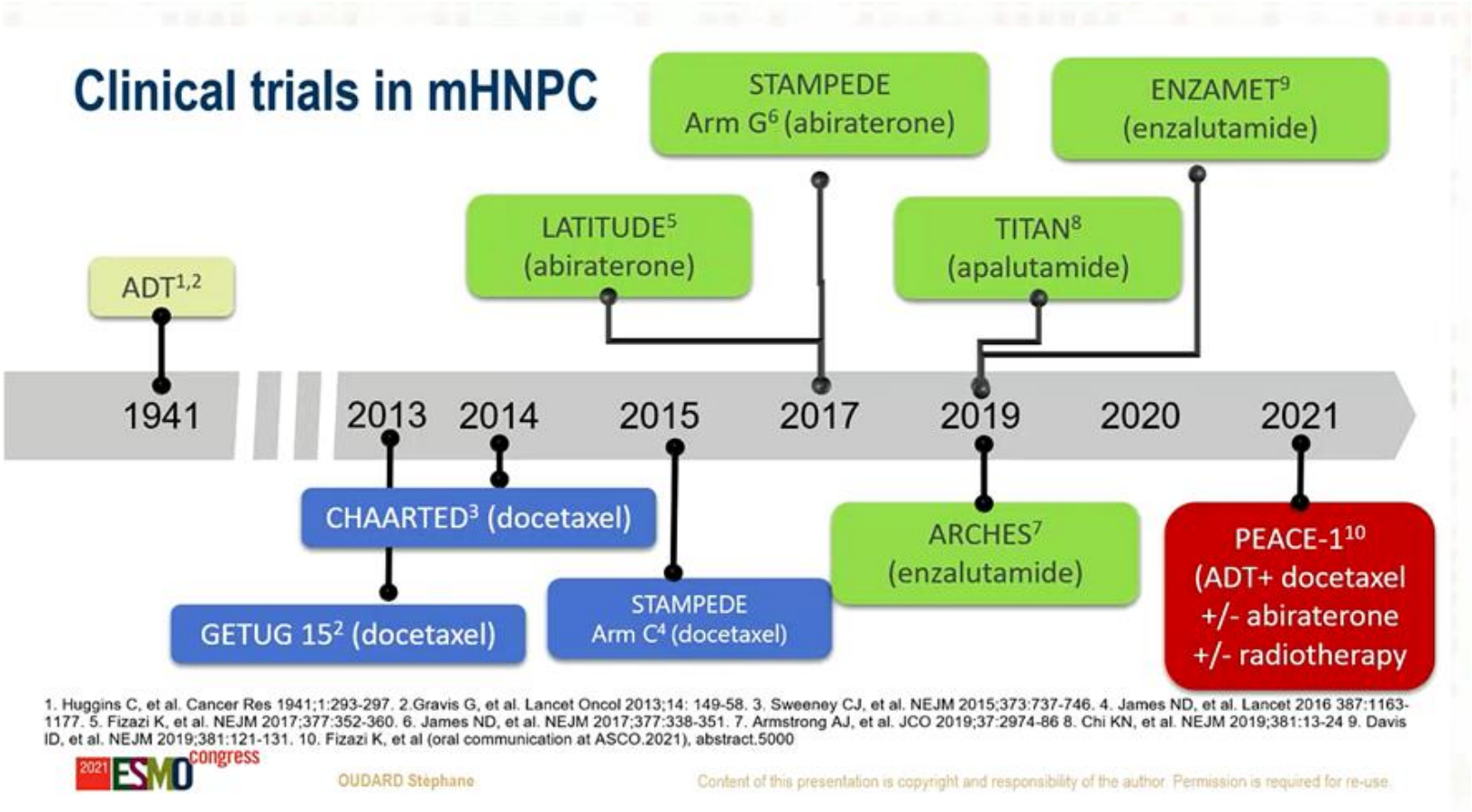
- ❑ARPİs +/- Docetaxel
  - ❑ Abiraterone
  - ❑ enza/apa/darolutamide
- ❑Radyoterapi prosatat
- ❑SBRT to metastatik lezyonlar

Klink pratiğe geçek stratejiler

- Biomarker Directed Therapy?
- Tedaviye ara verme?

- **PARP inhibitor?**
- **LuPSMA?**
- **AKT inhibitor?**

Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

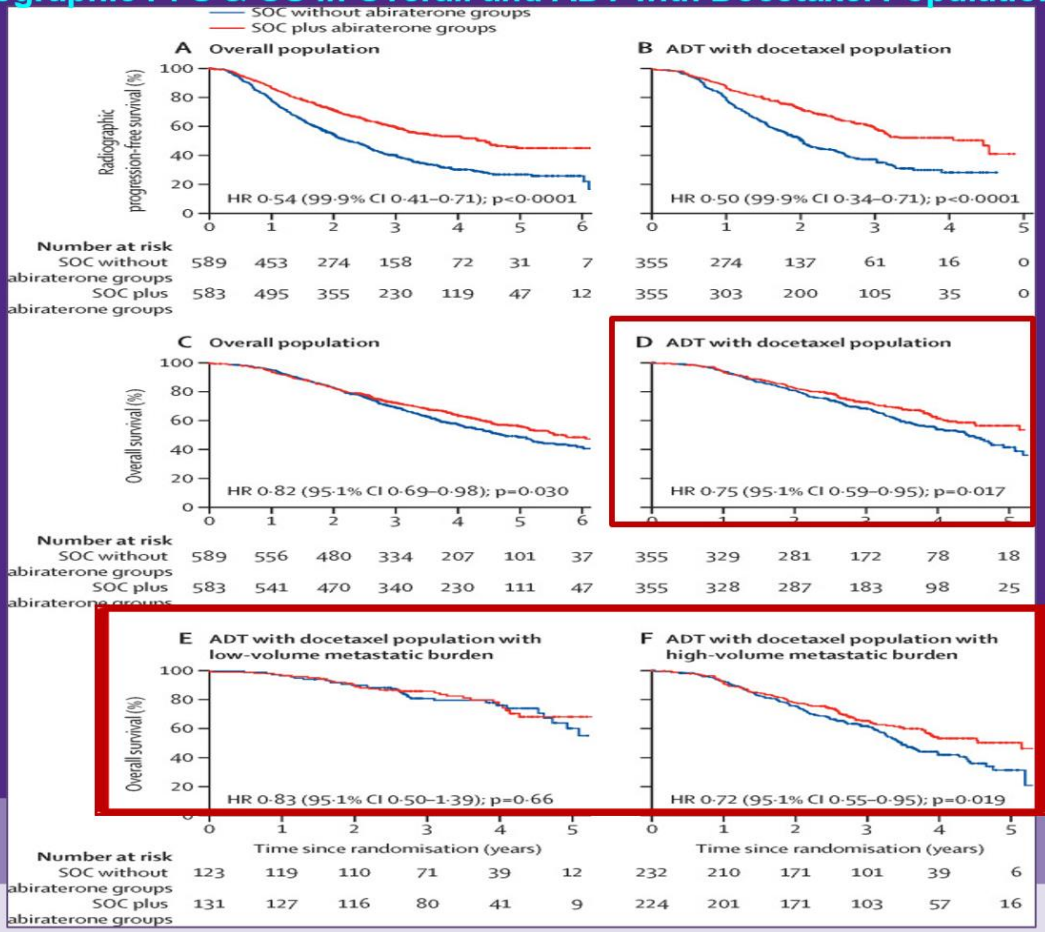


1. Huggins C, et al. Cancer Res 1941;1:293-297. 2.Gravis G, et al. Lancet Oncol 2013;14: 149-58. 3. Sweeney CJ, et al. NEJM 2015;373:737-746. 4. James ND, et al. Lancet 2016 387:1163-1177. 5. Fizazi K, et al. NEJM 2017;377:352-360. 6. James ND, et al. NEJM 2017;377:338-351. 7. Armstrong AJ, et al. JCO 2019;37:2974-86 8. Chi KN, et al. NEJM 2019;381:13-24 9. Davis ID, et al. NEJM 2019;381:121-131. 10. Fizazi K, et al (oral communication at ASCO.2021), abstract.5000

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 Tedavisi

PEACE-1: Adverse Events

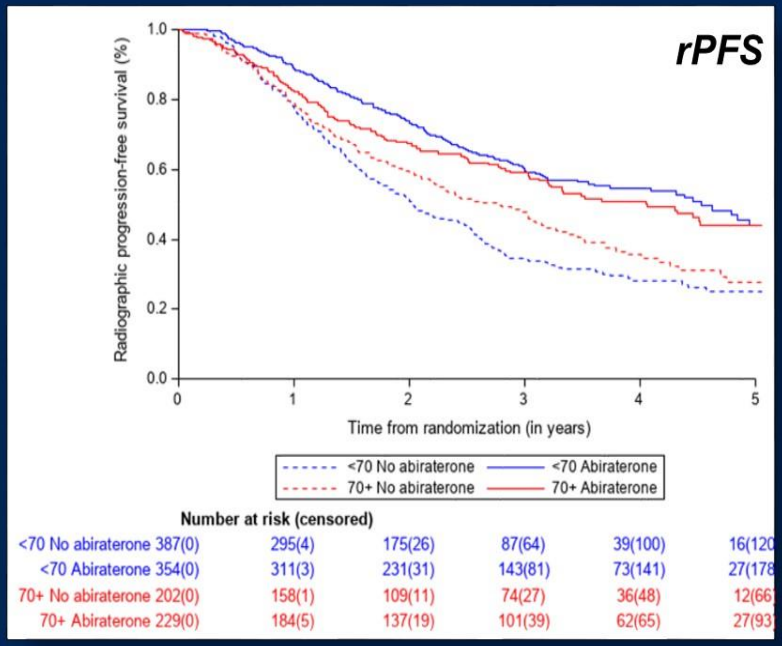
	ADT with Docetaxel		ADT without Docetaxel	
	SOC + Abi (+/- RT)	SOC (+/- RT)	SOC + Abi (+/- RT)	SOC (+/- RT)
Any AE	346 (100%)	349 (100%)	226 (100%)	233 (99%)
Severe (grade >3)	217 (63%)	181 (52%)	149 (66%)	97 (41%)
Fatal (grade 5)	7 (2%)	3 (1%)	8 (4%)	5 (2%)
Frequent severe AEs				
Hypertension	76 (22%)	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

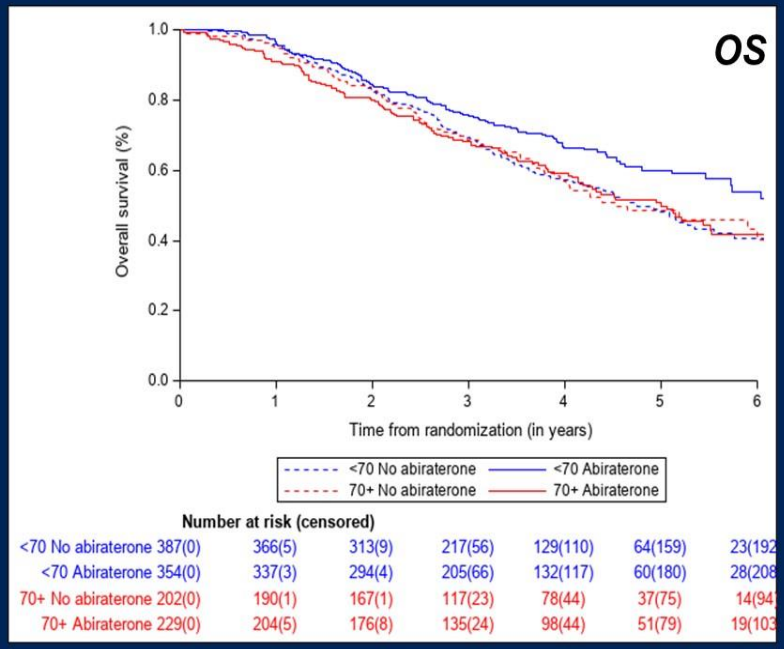
Fizazi et al, Lancet, 2022

Üçlü Kombinasyonda Yaş Sınırlaması

Results (*1*)

Overall population





Age ≥ 70: HR 0.65, 95%CI (0.42-1.01)
Age <70: HR 0.49, 95%CI (0.35-0.69)
p-value of the interaction test 0.08

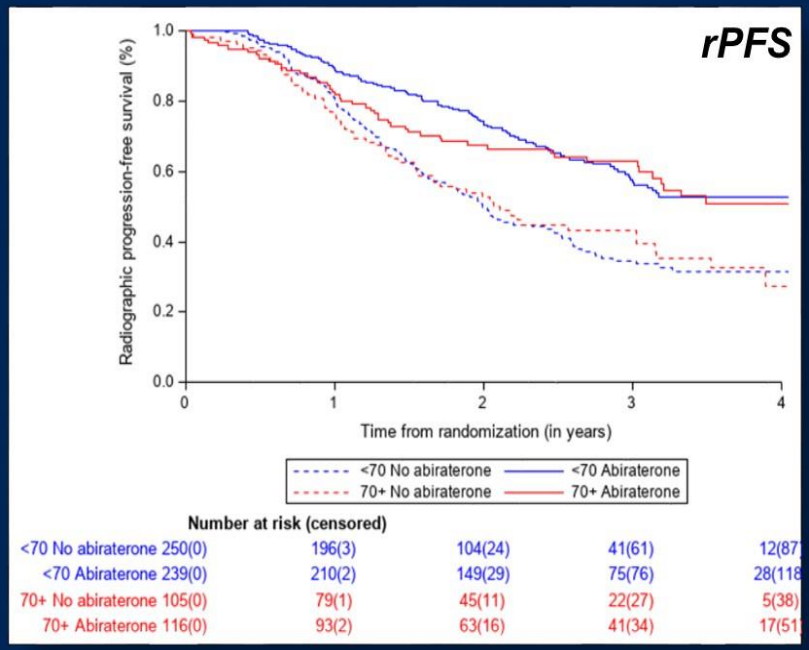
Age ≥ 70: HR 0.95, 95%CI (0.72-1.25)
Age <70: HR 0.73, 95%CI (0.58-0.92)
p-value of the interaction test 0.15

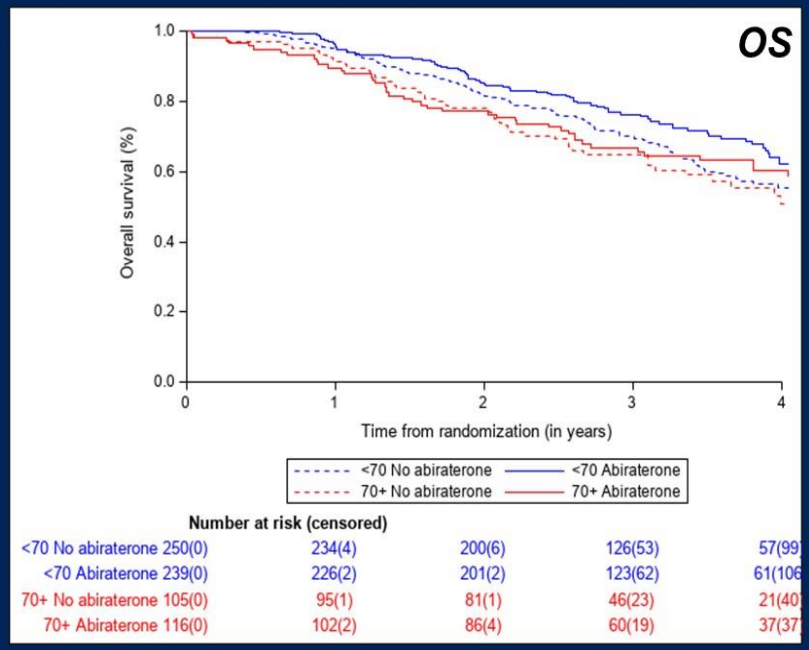
Benefit of AA+P on rPFS and OS may decrease with age

Üçlü Kombinasyonda Yaş Sınırlaması

Results (2)

Docetaxel population





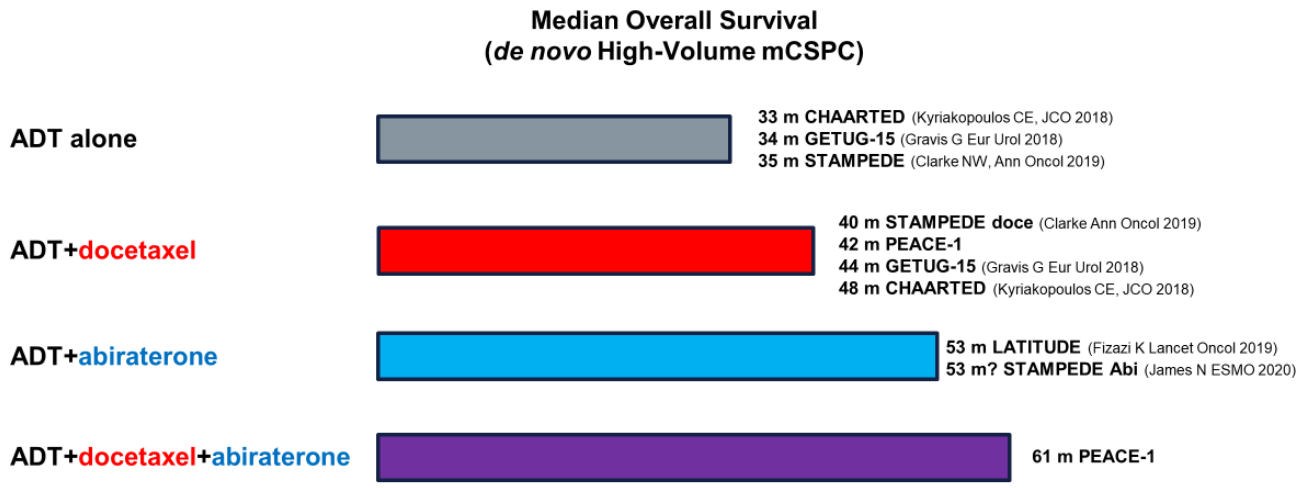
Age ≥ 70: HR 0.55, 95%CI (0.29-1.04)
Age < 70: HR 0.50, 95%CI (0.33-0.78)
p-value of the interaction test 0.67

Age ≥ 70: HR 0.80, 95%CI (0.53-1.2)
Age < 70: HR 0.71, 95%CI (0.52-0.95)
p-value of the interaction test 0.63

- **rPFS benefit of AA+P was comparable in older and younger patients**
- **OS benefit difficult to assess (insufficient number of older patients/events)**

Kastrasyona Duyarlı Metastatik Prostat Kanseri Üçlü Kombinasyon

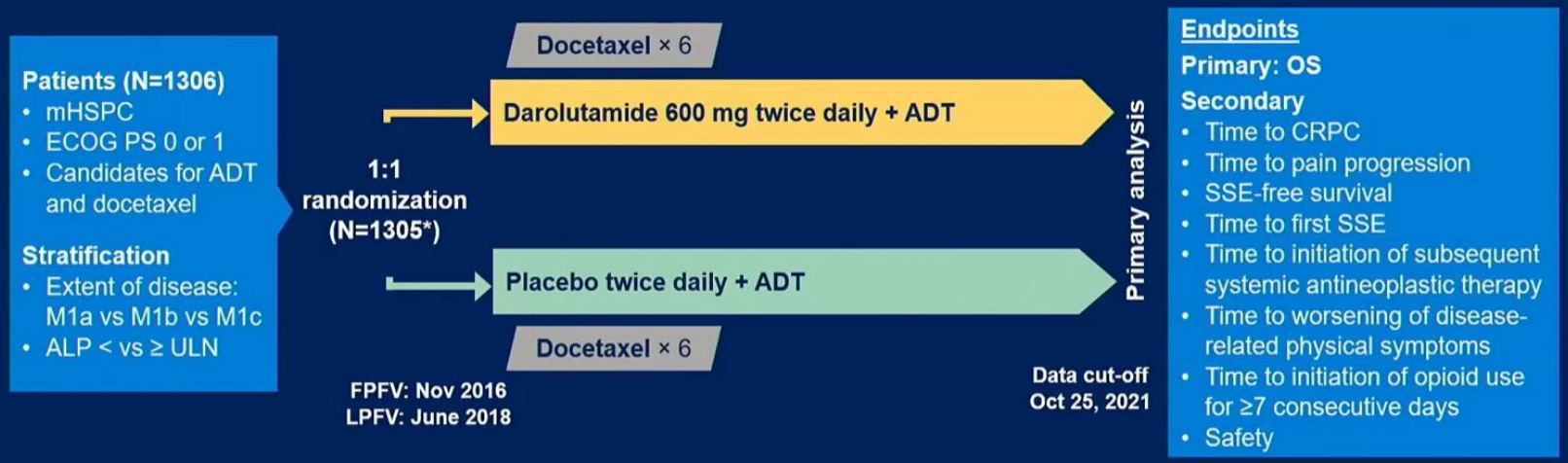
Triplet PEACE-1 OS results in the context of recent data



Kastrasyona Duyarlı Metastatik Prostat Kanseri Üçlü Kombinasyon

ARASENS Study Design

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



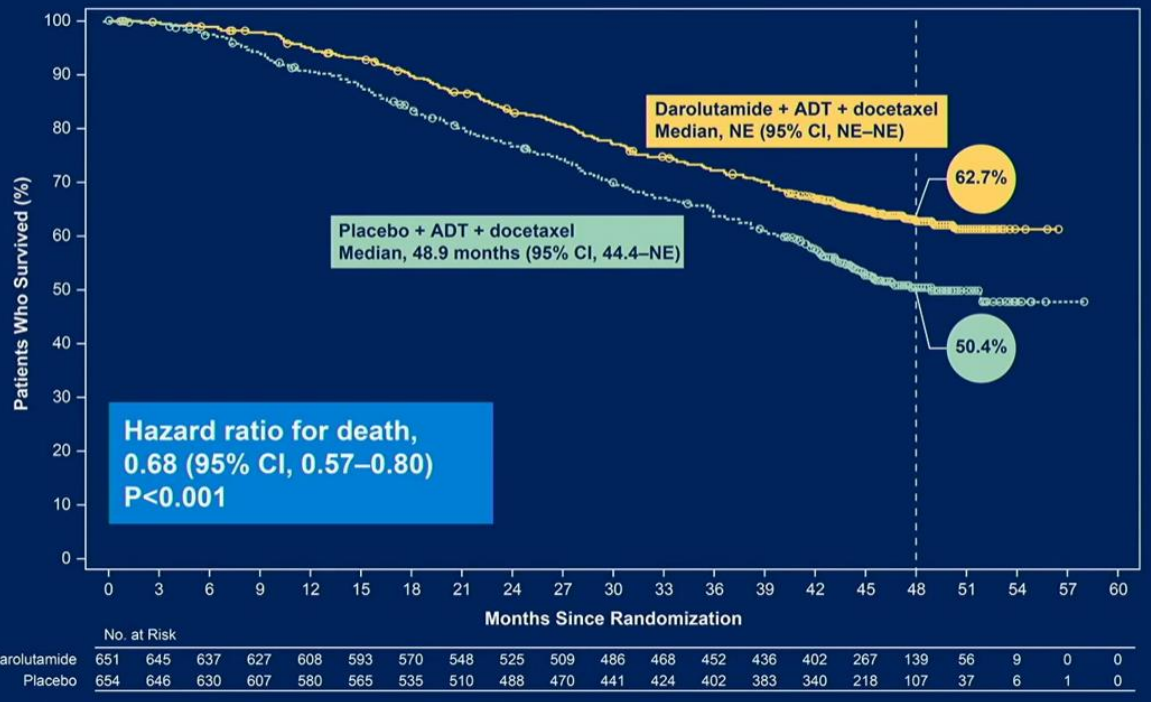
- The primary analysis was planned to occur after ~509 deaths
- Secondary efficacy endpoints were tested hierarchically

*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

ARASENS Primary Endpoint*: Overall Survival

Darolutamide significantly reduced the risk of death by 32.5%



No. at Risk

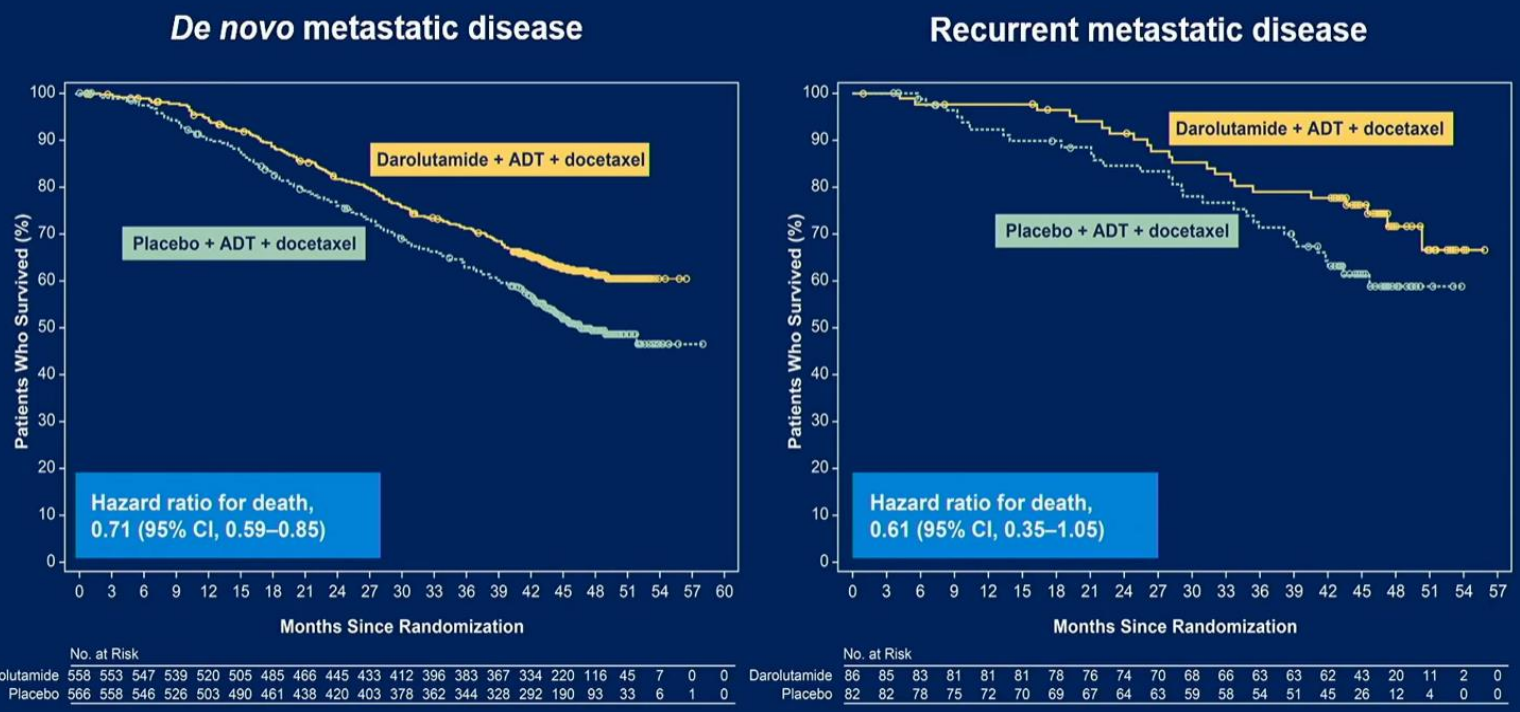
Darolutamide	651	645	637	627	608	593	570	548	525	509	486	468	452	436	402	267	139	56	9	0	0
Placebo	654	646	630	607	580	565	535	510	488	470	441	424	402	383	340	218	107	37	6	1	0

*Primary analysis occurred after 533 deaths (darolutamide, 229; placebo, 304). CI, confidence interval; NE, not estimable.

PRESENTED BY: Matthew R. Smith, MD, PhD

Kastrasyona Duyarlı Metastatik Prostat Kanseri Üçlü Kombinasyon

Overall Survival By Metastatic Stage at Initial Diagnosis



Kastrasyona Duyarlı Metastatik Prostat Kanseri
Üçlü Kombinasyon

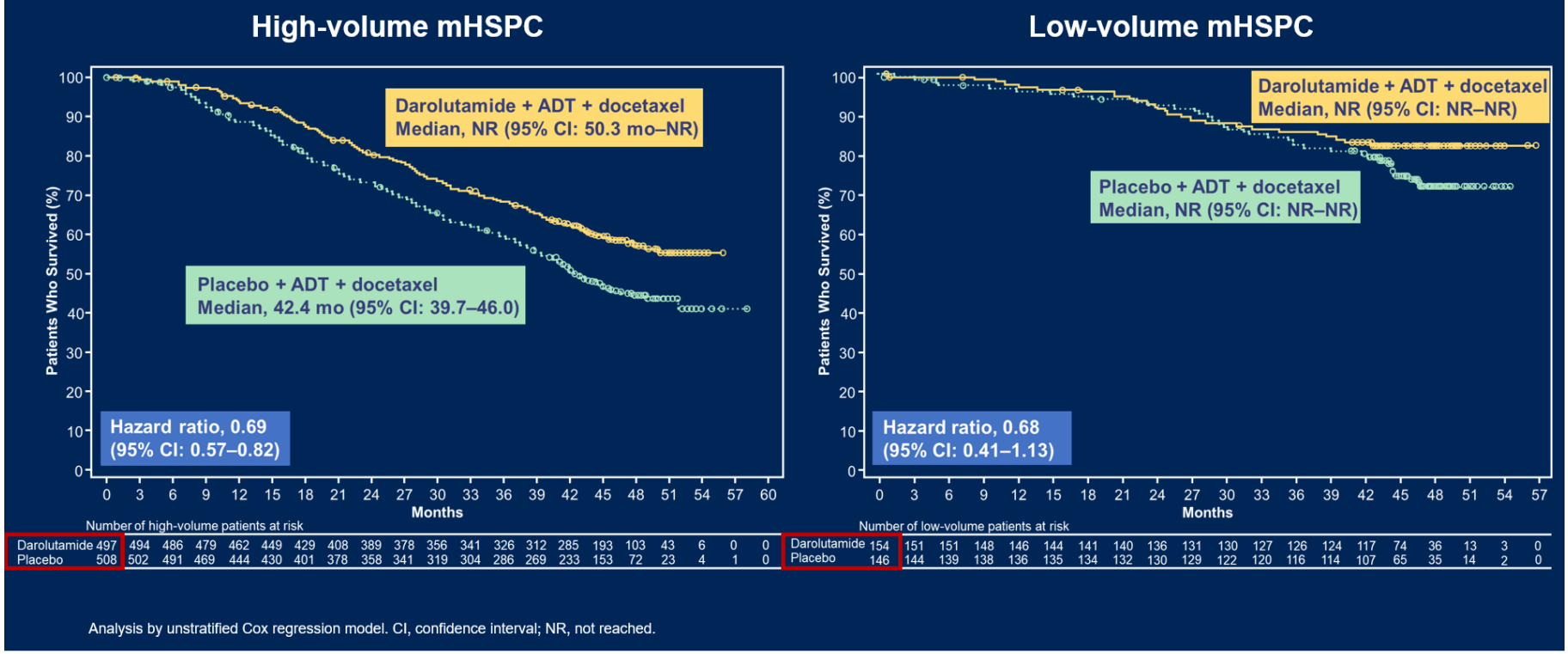
Adverse Events of Special Interest for AR Pathway Inhibitors

AEs associated with AR pathway inhibitor therapy	Darolutamide + ADT + docetaxel (n=652)		Placebo + ADT + docetaxel (n=650)	
	Patients, n (%)	EAIR/100 PY*	Patients, n (%)	EAIR/100 PY*
Fatigue	216 (33.1)	12.5	214 (32.9)	17.8
Bone fracture	49 (7.5)	2.8	33 (5.1)	2.7
Falls	43 (6.6)	2.5	30 (4.6)	2.5
Rash†	108 (16.6)	6.2	88 (13.5)	7.3
Diabetes mellitus and hyperglycemia‡	99 (15.2)	5.7	93 (14.3)	7.7
Weight decreased	22 (3.4)	1.3	35 (5.4)	2.9
Vasodilatation and flushing	133 (20.4)	7.7	141 (21.7)	11.7
Breast disorders/gynecomastia‡	21 (3.2)	1.2	10 (1.5)	0.8
Hypertension‡	89 (13.7)	5.1	60 (9.2)	5.0
Cardiac disorder‡	71 (10.9)	4.1	76 (11.7)	6.3
Cerebral ischemia	8 (1.2)	0.5	8 (1.2)	0.7
Mental impairment disorder‡	23 (3.5)	1.3	15 (2.3)	1.2
Depressed mood disorder‡	21 (3.2)	1.2	24 (3.7)	2.0
Seizure	4 (0.6)	0.2	1 (0.2)	0.1

*EAIR is the number of patients with a given AE divided by the total darolutamide/placebo treatment duration of all patients in years and expressed in 100 PY. †This category combines the following MedDRA terms: rash, maculopapular rash, drug eruption, pruritic rash, erythematous rash, macular rash, papular rash, follicular rash, pustular rash, and vesicular rash. ‡This category is a MedDRA High-Level Group Term. EAIR, exposure-adjusted incidence rate; PY, patient year.

Kastrasyona Duyarlı Metastatik Prostat Kanseri
Üçlü Kombinasyon

ARASENS VOLUME Subgroups: Overall Survival



Analysis by unstratified Cox regression model. CI, confidence interval; NR, not reached.

Kastrasyona Duyarlı Metastatik Prostat Kanseri Üçlü Kombinasyon

	ENZAMET (N=1125)	PEACE-1 (N=1173)	ARASENS (N=1306)
Agent | comparator	Enzalutamide | NSAA	2x2: SoC; abiraterone; RT; both. RT arms collapsed for analysis.	ADT + docetaxel + darolutamide / placebo
Docetaxel	45% (concurrent)	60% (concurrent)	100% (concurrent)
Primary endpoint: HR (CI)	OS: 0.70 (0.58-0.84)	rPFS: 0.50 (0.40-0.62) OS: 0.82 (0.69-0.98)	OS: 0.68 (0.57-0.80)
Relevant "triplet" outcome	Med OS: NR vs 73.2mo 3yr OS: 80% vs 72% 5yr OS: 67% vs 57%	Med rPFS: 4.5 vs 2.0yr Med OS: 5.7 vs 4.7yr	Improved OS Improved secondary endpoints Similar toxicity
Prior ADT	Up to 3mo	Up to 3mo	Up to 12 weeks
Anti-androgen with ADT	Both arms	No	Experimental arm only
Synchronous M1	67%	100%	86%
Visceral metastases	11%	11%	17%
Volume/burden of disease (high | low)	53% | 47%	57% | 43%	77% high volume, 70% high risk

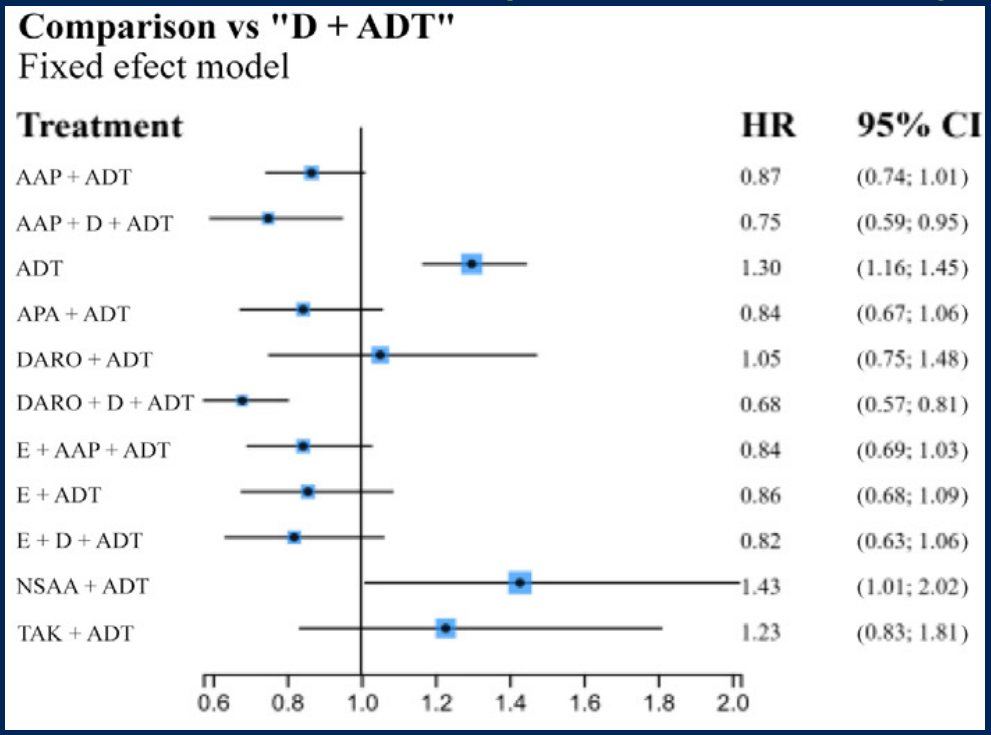
Kastrasyona Duyarlı Metastatik Prostat Kanseri
Üçlü Kombinasyon

Comparative Survival in Metastatic Hormone-sensitive Prostate Cancer by Volume of Disease and Timing of Metastasis: A Living Network Meta-analysis

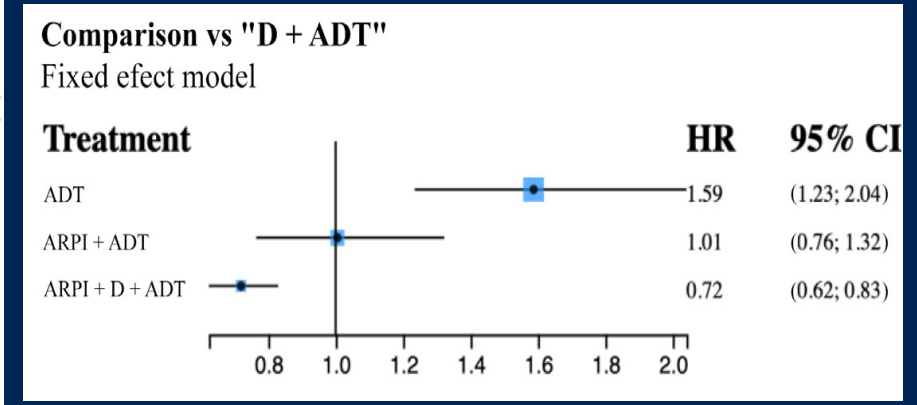
Eur Urol 2025

Irbaz Bin Riaz[a,,†], Syed Arsalan Ahmed Naqvi[a,†], Kunwer Sufyan Faisal[b], Huan He[c], Kaneez Zahra Rubab Khakwani[d], Daniel S. Childs[e], Jacob J. Orme[e], Praful Ravi[f], Parminder Singh[a], Syed A. Hussain[g], Kim Chi[h], Neeraj Agarwal[i], Axel S. Merseburger[j], Ian D. Davis[k,l], Andrew Armstrong[m], Maha H. Hussain[n], Matthew Smith[o], Gerhardt Attard[p], Bertrand Tombal[q], Karim Fizazi[r], Nick James[s], Aurelius Omlin[t], Silke Gillessen[u], Mohammad Hassan Murad[e], Eliezer M. Van Allen[f], Christopher J. Sweeney[v,‡], Alan Haruo Bryce[w,‡]*

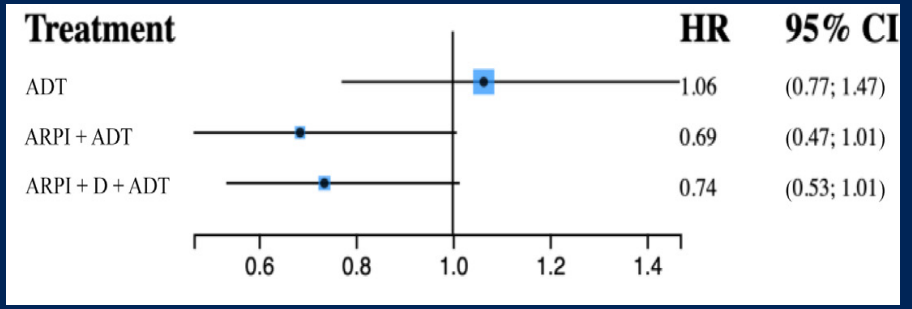
Overall Survival Overall Population All Trials All Drugs



Synchronous High Volume

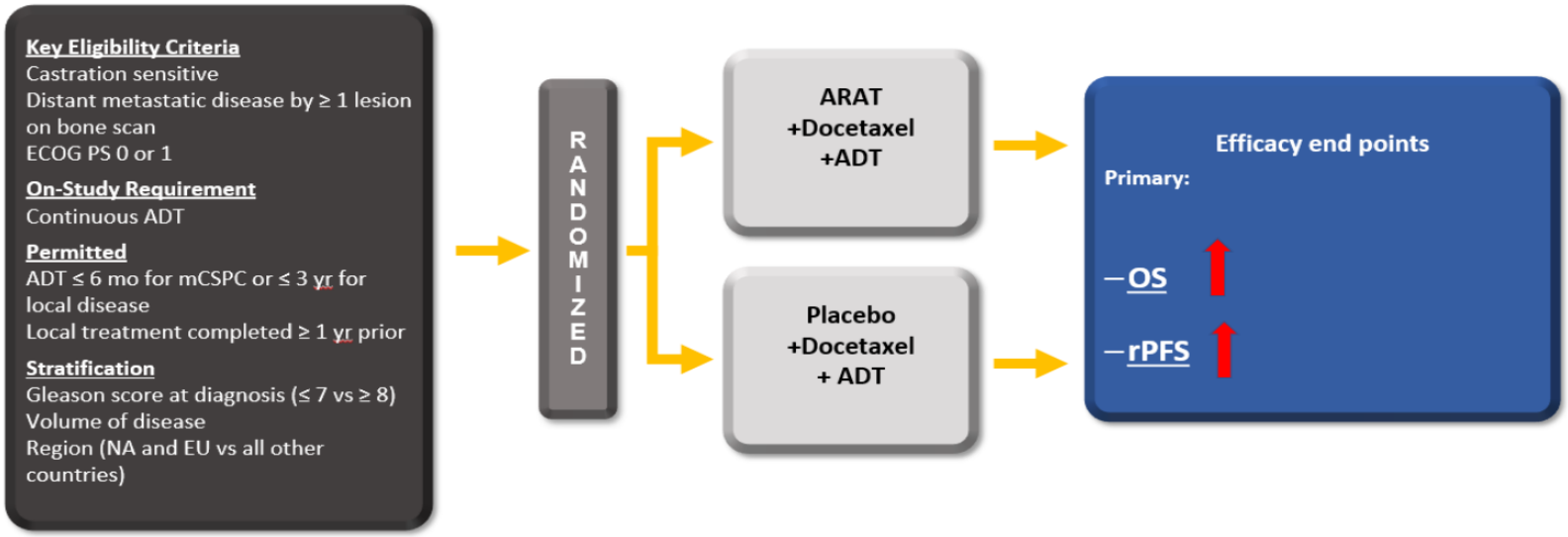


Synchronous Low Volume



Evre IV Kastrasyona Duyarlı Prostat Kanseri
Üçlü Kombinasyonlar

Phase III Trial: Triplets (ARAT+ Docetaxel + ADT) vs. Docetaxel + ADT

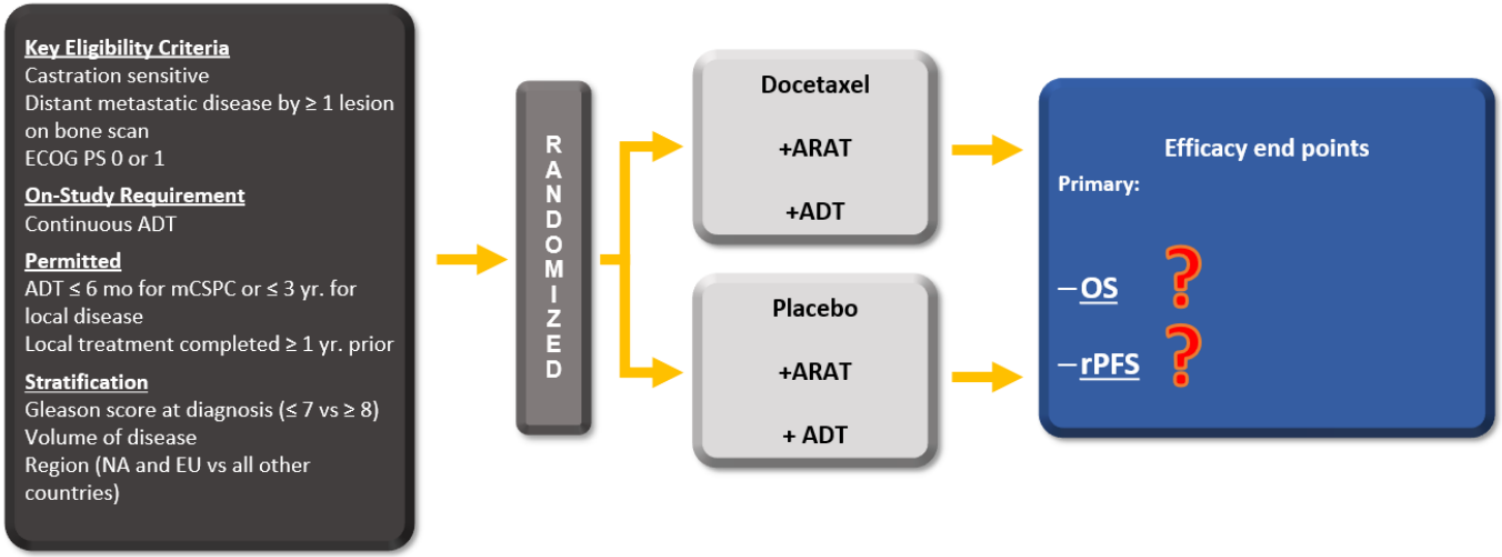


ECOG PS, Eastern Cooperative Oncology Group performance status; ART, Androgen receptor targeted therapy; NA, North America; PSA, prostate-specific antigen; OS, Overall survival; rPFS, radiographic progression-free survival.

Evre IV Kastrasyona Duyarlı Prostat Kanseri
Üçlü Kombinasyonlar

This trial has not been done yet:

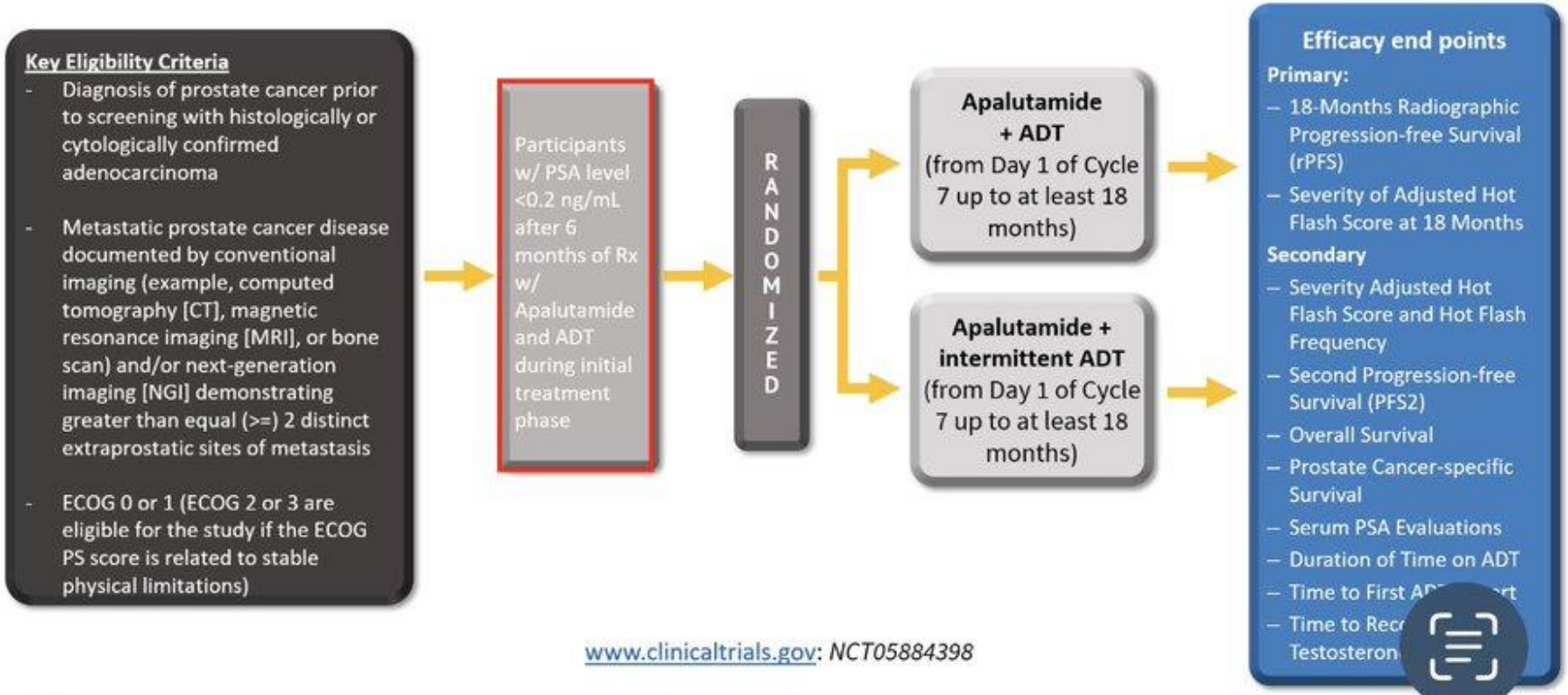
Triplet (Docetaxel + ARAT + ADT) versus ARAT + ADT



ECOG PS, Eastern Cooperative Oncology Group performance status; ART, Androgen receptor targeted therapy; NA, North America; PSA, prostate-specific antigen; OS, Overall survival; rPFS, radiographic progression-free survival.

Gelecek Perspektif

LIBERTAS Trial: Phase 3 Trial Design



www.clinicaltrials.gov: *NCT05884398*

Prostat kanserinde genomik profil

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

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

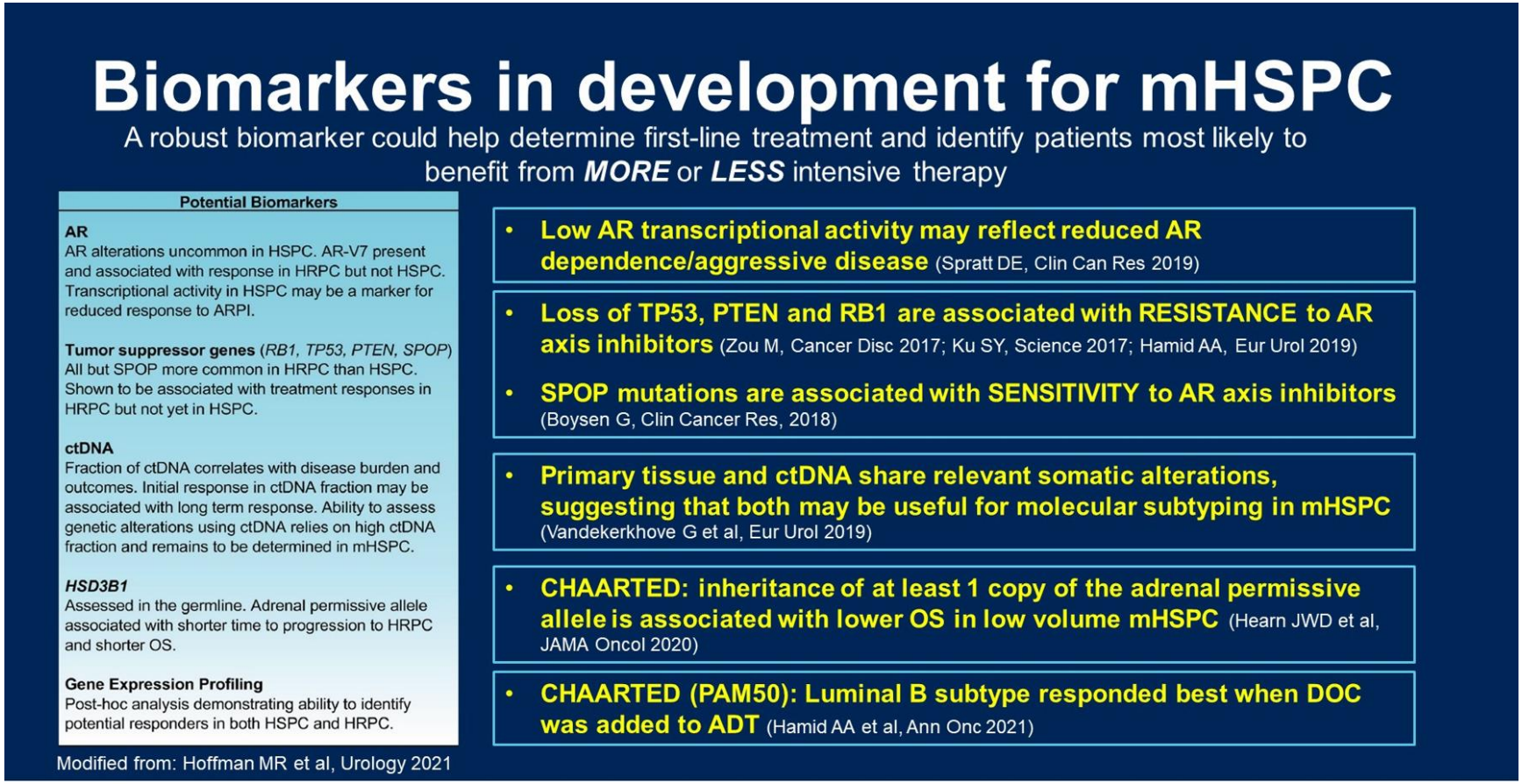
PSMA appears to be the most broadly applicable potential biomarker and actionable target in advanced PC[1–6]

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

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

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

Gelecek Perspektif



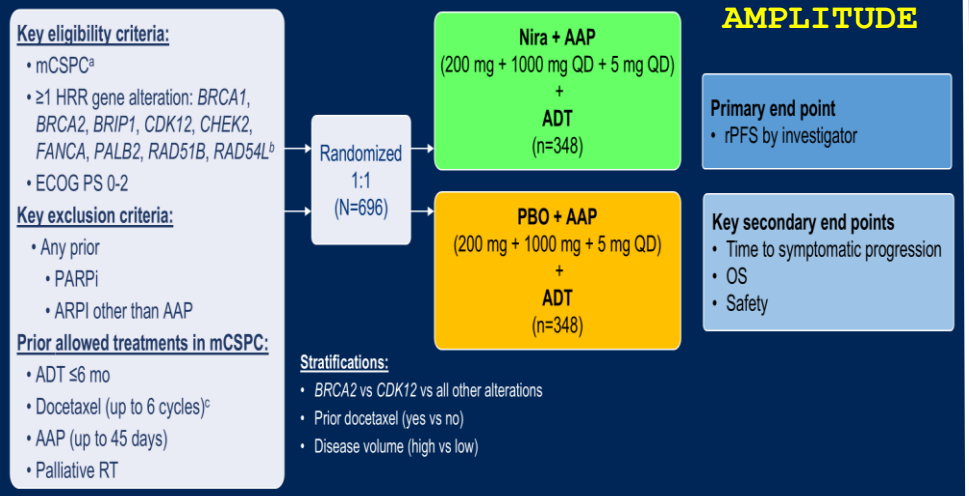
Gelecek Perspektif

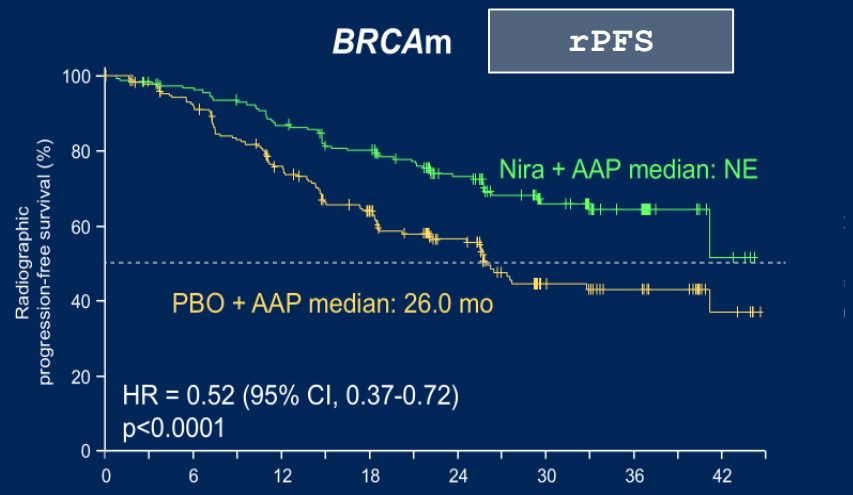
Biomarker	Details	Sensitivity	Trials in mHSPC (BM selected)
DNA repair	BRCA1, BRCA2, PALB2	PARPi	ProBIO
	HRRm	PARPi-ARPI	TALAPRO-3, EvoPAR-01, AMPLITUDE
	MMR-d/MSI-H	ICI	NCT04126070, NCT03879122
PI3K	PTEN	PI3Ki	CAPITELLO-281
	PIK3CA, AKT1	PI3Ki	
Cell-cycle	RB1 or RB1/TP53 doublet, high Ki67	Platinum (doublet)	
	Cyclin D1, intact RB1, CDK2NA, low Ki67	CDK4/6i	CYCLONE-3
TMPRSS2-ERG / ERG	ERG alter microtubule (dynamics)	Taxanes (triplet)	ProBIO
TSG	Compound mutation in TP53, PTEN, RB1	Taxanes (triplet)	-
SPOP	Role in AR regulation	ARPI	-
RNA	Decipher, GC Q4	Taxanes	STAMPEDE
	PAM50: Luminal B	Taxanes	STAMPEDE
ctDNA%	Low ctDNA%	ICI, PSMA-RLT	-
	High ctDNA%	Taxanes (triplet)	-

Diğer Doz Yoğun Seçenekler

Name/Sponsor	ARTA	3rd agent	Design (n)
AMPLITUDE	Abiraterone	Niraparib	Randomized, HRR+ (788)
TALAPRO-3	Enzalutamide	Talazoparib	Randomized HRR+ (550)
City of Hope PCF	Abiraterone	Talazoparib	Single arm, Unselected (70)
PSMAddition	Lu177-PSMA-617	Any ARTA	Randomized, PSMA PET + (1126)
KEYNOTE-991	Enzalutamide	Pembrolizumab	Randomized (1232)
NCT03951831	n/a (ADT + Doce)	Cemiplimab	Single arm (20)
MSKCC	Abi/Enza	Atezolizumab	SBRT, Single arm (44)
CABIOS	Abiraterone	Cabozantinib, Nivolumab	Single arm (22)
CASCARA (U Minn)	Abiraterone	Cabazi + Carbo	Single arm (60)
Capitello-281	Abiraterone	Capivasertib	Randomized, PTEN def (1000)
CYCLONE-3	Abiraterone	Abemaciclib	Randomized, unselected (900)

Kastrasyona Duyarlı Metastatik Prostat Kanseri
Üçlü Kombinasyon; PARP inhibitörü





%86 senkron

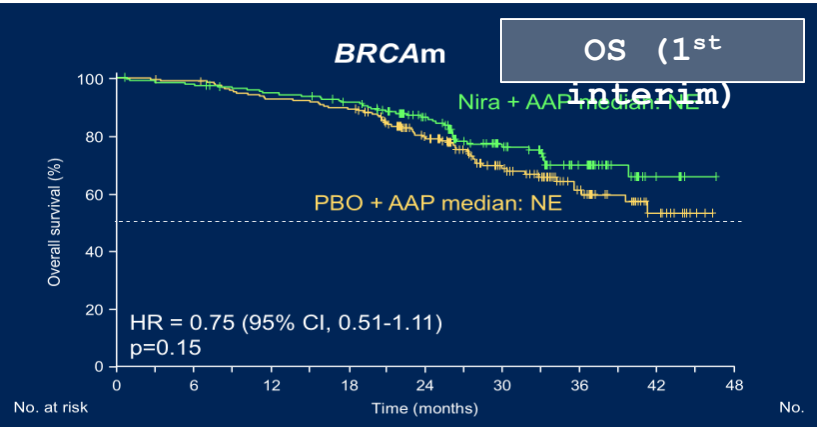
%77 yüksek hacimli

%55 BRCAm

%16 önceden dosetaksel tedavisi görmüş

Primer tümöre radyasyon uygulanmamış

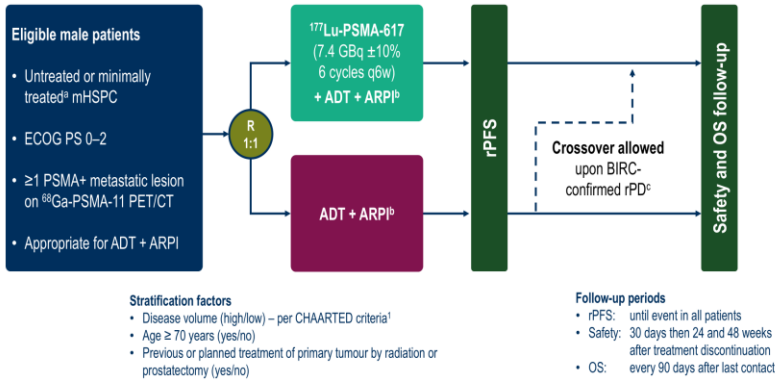
(BRCA dışı HRR'de fayda: "belirsiz")



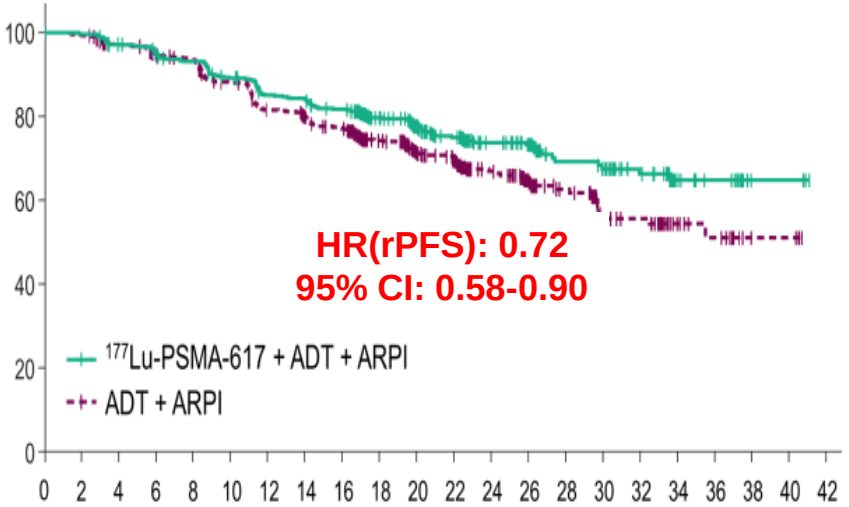
Attard G et al Nat Med 2025

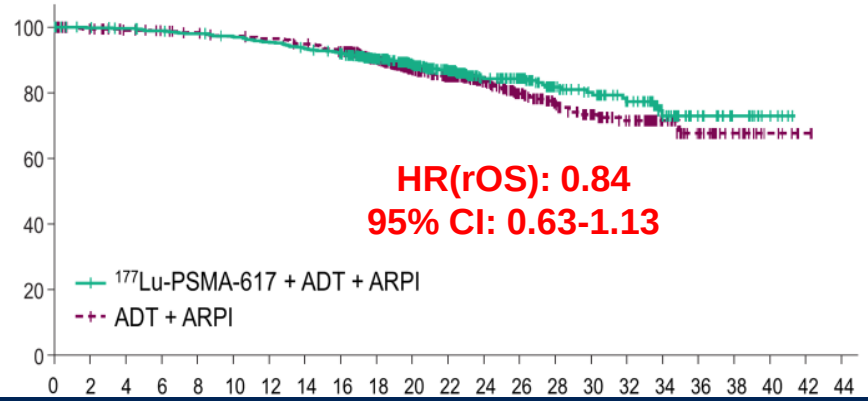
Kastrasyona Duyarlı Metastatik Prostat Kanseri
Üçlü Kombinasyon; Lutetium-177–PSMA-617

PSMAddition: randomized phase 3 trial of ^{177}Lu-PSMA-617 in mHSPC



[a] ≤45 days before consent | [b] Any ARPI with one switch allowed | [c] ADT/ARPI not mandatory after crossover
ADT, androgen deprivation therapy; BIRC, blinded independent review committee; ECOG PS, Eastern Cooperative Oncology Group performance status; OS, overall survival; PET/CT, positron-emission tomography/computed tomography; q6w, every 6 weeks; rPD, radiographic disease progression; rPFS, radiographic progression-free survival
1. Sweeney CT *et al. N Engl J Med* 2015;373:737–46





%52 senkron

%68 yüksek hacimli

%43 ≥ 70 yaşında

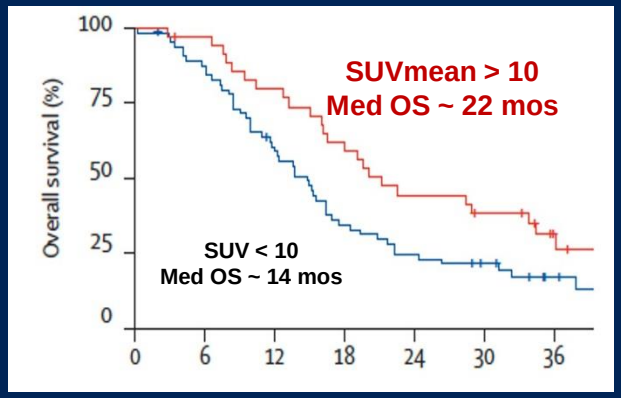
Önceden dosetaksel uygulanmamış

Primer bölgeye radyasyon uygulanmamış

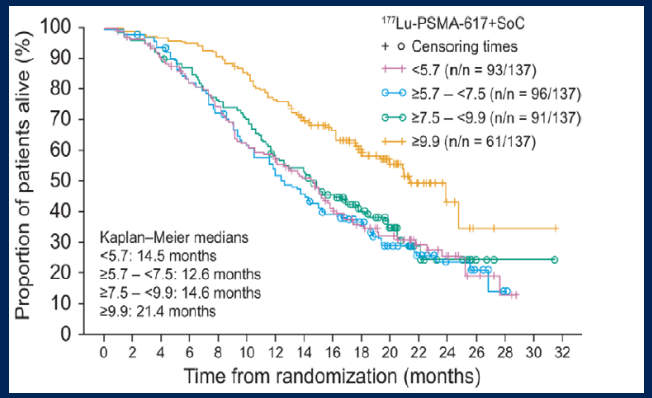
Tagawa S et al ESMO 2025

SUVmean'in, mCRPC'den (ARPI ve Docetaxel Sonrası) Fayda Görecek Hastaların Seçiminde Biyobelirteç Olarak Kullanılması

TheraP LuPSMA
Hofman et al Lancet Onc 2024



VISION LuPSMA
Kuo et al Radiology 2024



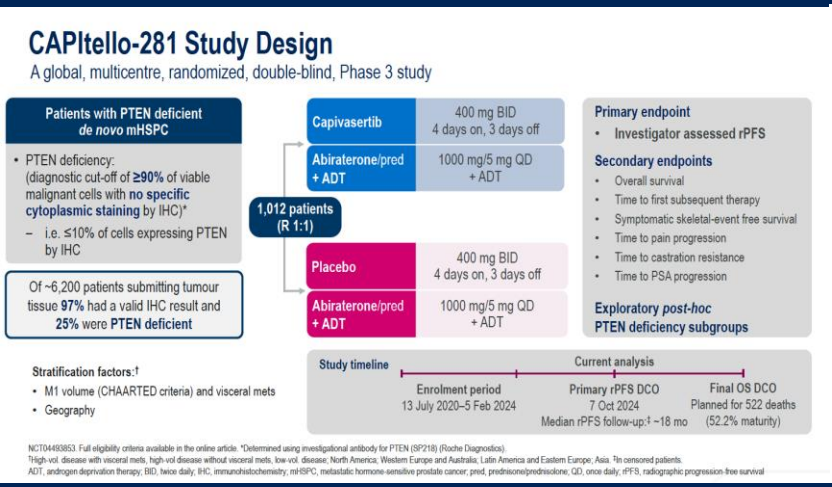
VISION Median OS
SUVmean > 10: ~ 21 months
[~ 30% of pts enrolled and OS w/out LuPSA 15 mos]

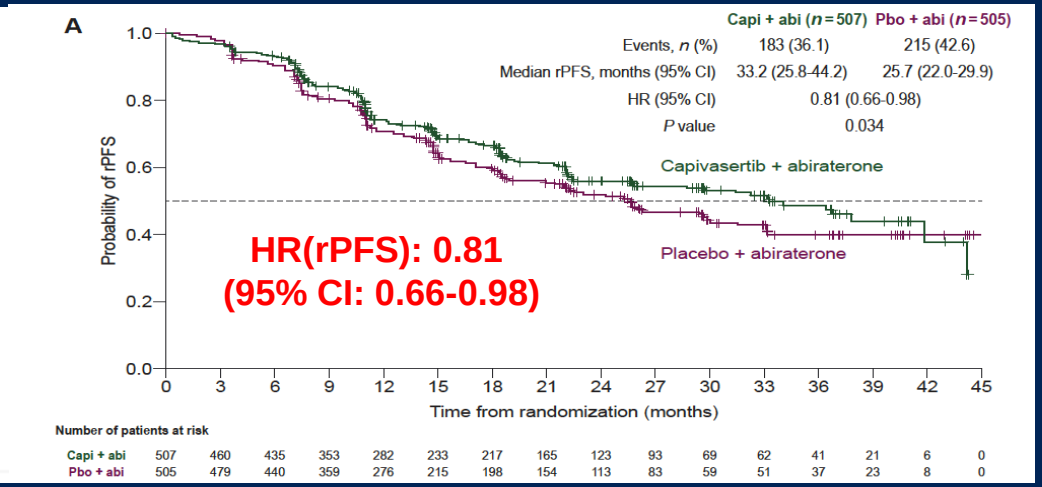
SUV < 10: ~ 14 months
[~ 70% of pts enrolled and OS w/out LuPSMA ~12 mos]

mHSPC'de LuPSMA kullanımına yönelik optimal biyobelirteci tanımlamak gerekiyor.

ARPI ile kombinasyon halinde ve PSMA PET aviditesi ortadan kalktığında kullanımın durdurulup durdurulamayacağı da önemli.

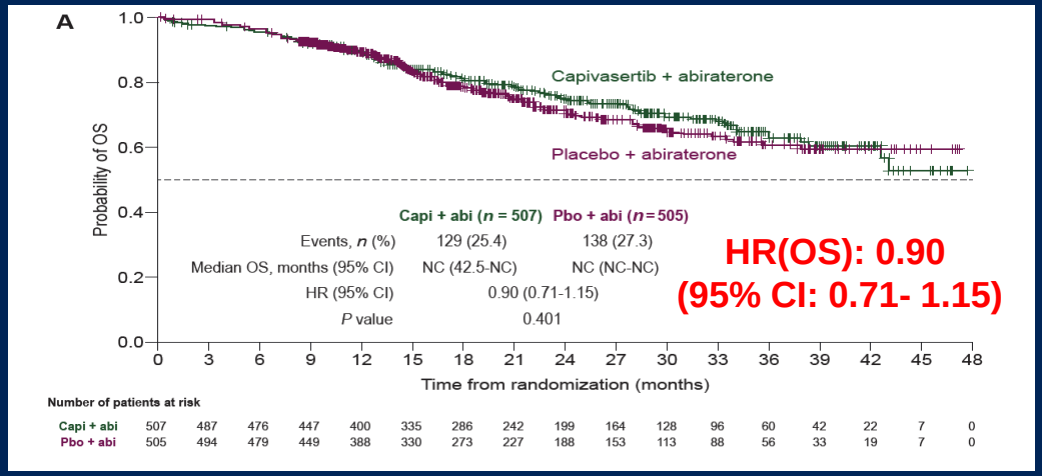
Kastrasyona Duyarlı Metastatik Prostat Kanseri
Üçlü Kombinasyon; AKT inhibitörü





6566 pts screened

- 1012 ≥ 90% IHC loss (25% of screened)
- 75% high volume
- 100% synchronous
- No prior prostate radiation
- No prior docetaxel



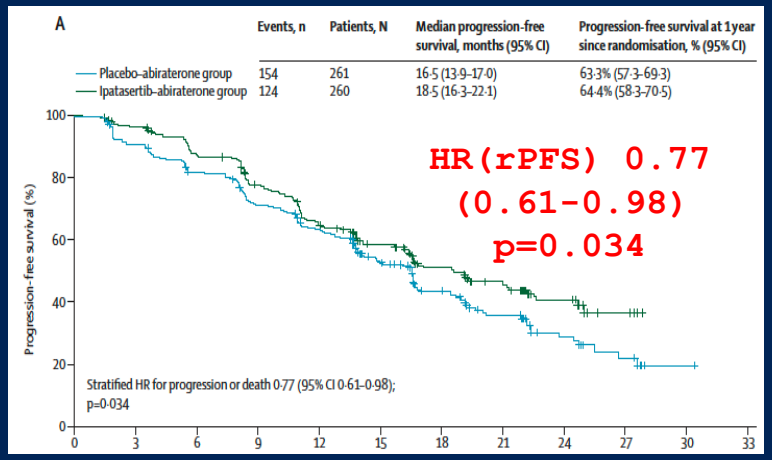
- 100% loss: N=303 [4.6%] HR(OS): 0.77 (0.51-1.14)
- Would NGS biomarker identify more pts who would benefit more?

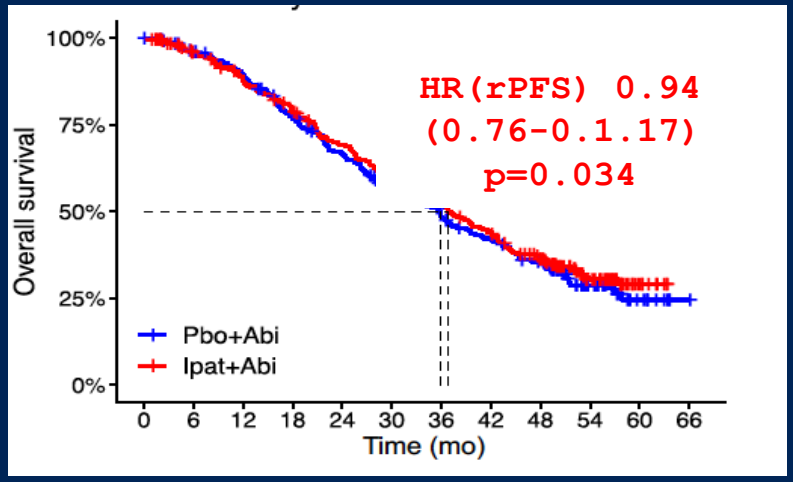
Fizazi et al. Ann Onc 2025

Christopher Sweeney, MBBS, DHS, FRACP (@chrissweens1 X and bsky)

PTEN IHC'nin mHSPC'de en uygun biyobelirteç olmayabileceğine işaret eden diğer veriler

IPATENTIAL 150: Abiraterone +/- Ipatasertib as 1L mCRPC treatment
PTEN deficient tumors *(IHC cut-off ≥50%)*

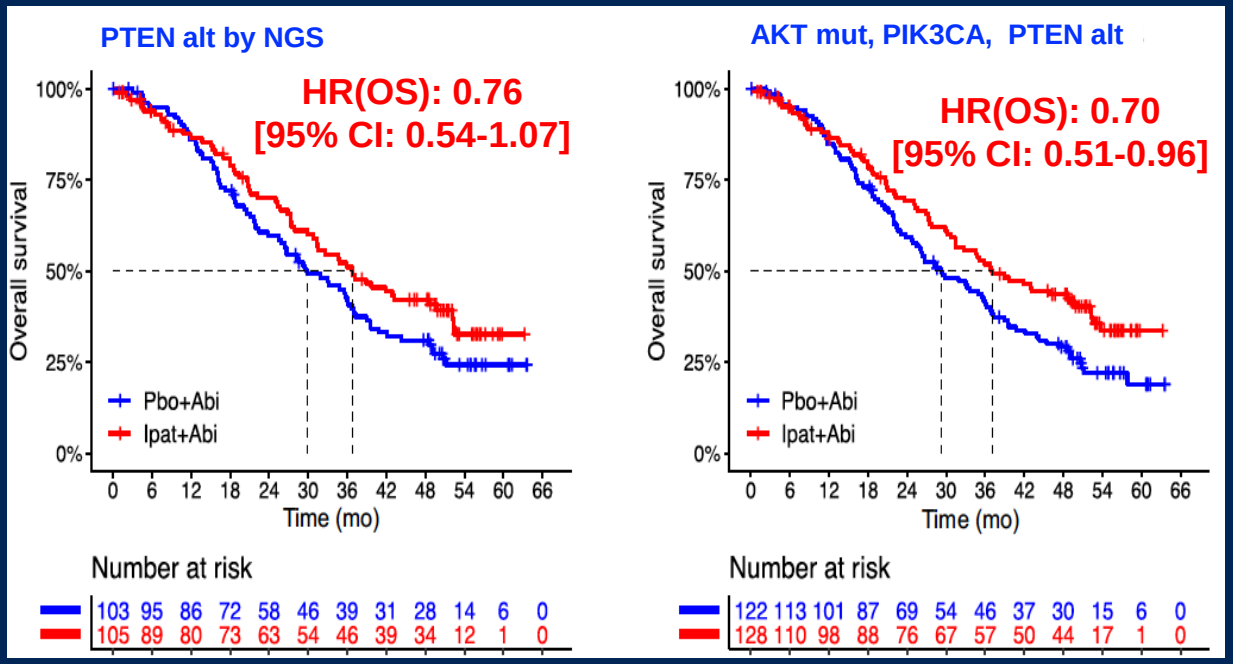




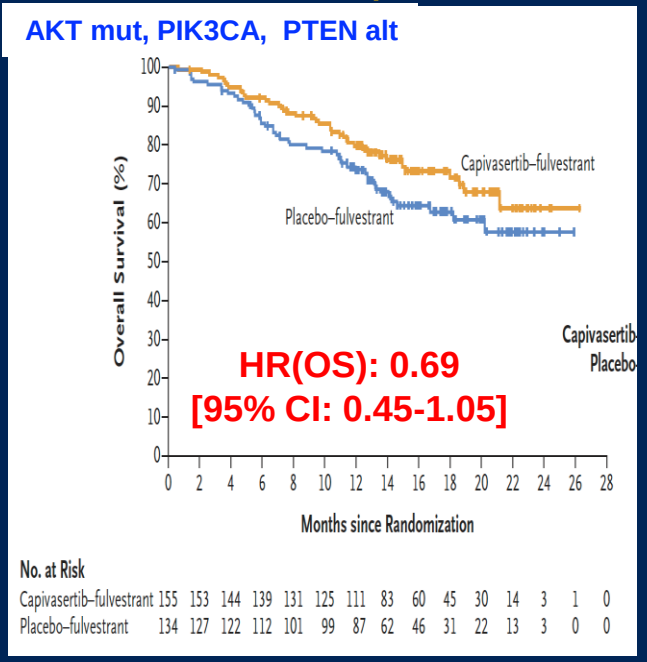
Sweeney et al, Lancet 2021, DeBono et al. : Eur Urol 2024

NGS ve AKT inhibisyonu tedavisi mCRPC ve ER+ Meme kanseri

First line mCRPC: Abi +/ - Ipatatersertib (IPATENTIAL 150)



ER + Breast Cancer with Fulvestrant +/- capiversitib



Turner et al NEJM 2023

NGS AKT sinyal yolu aktivasyonu: prognostik ve prediktif

DeBono J et al Ipatential Team: Eur Urol 2024

Kastrasyona Duyarlı Prostat Kanseri Tedavi sonrası PSA değeri Sağkalım İlişkisi

Overall Survival after Androgen Deprivation in New Metastatic Prostate Cancer

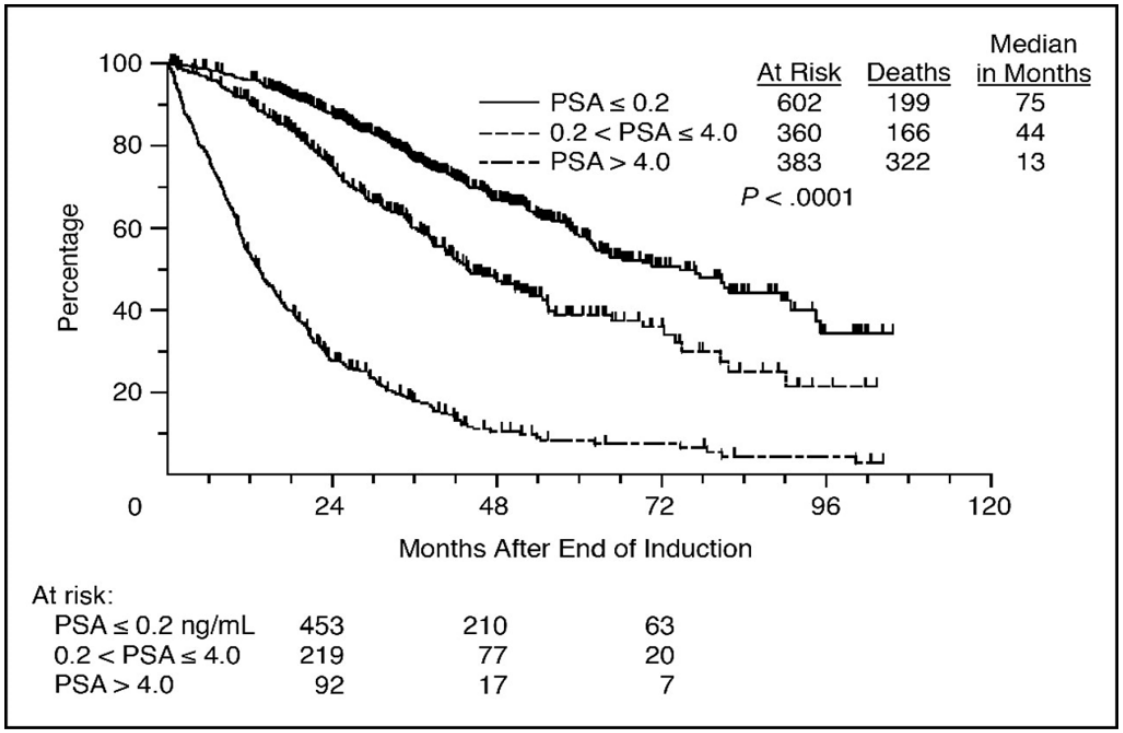
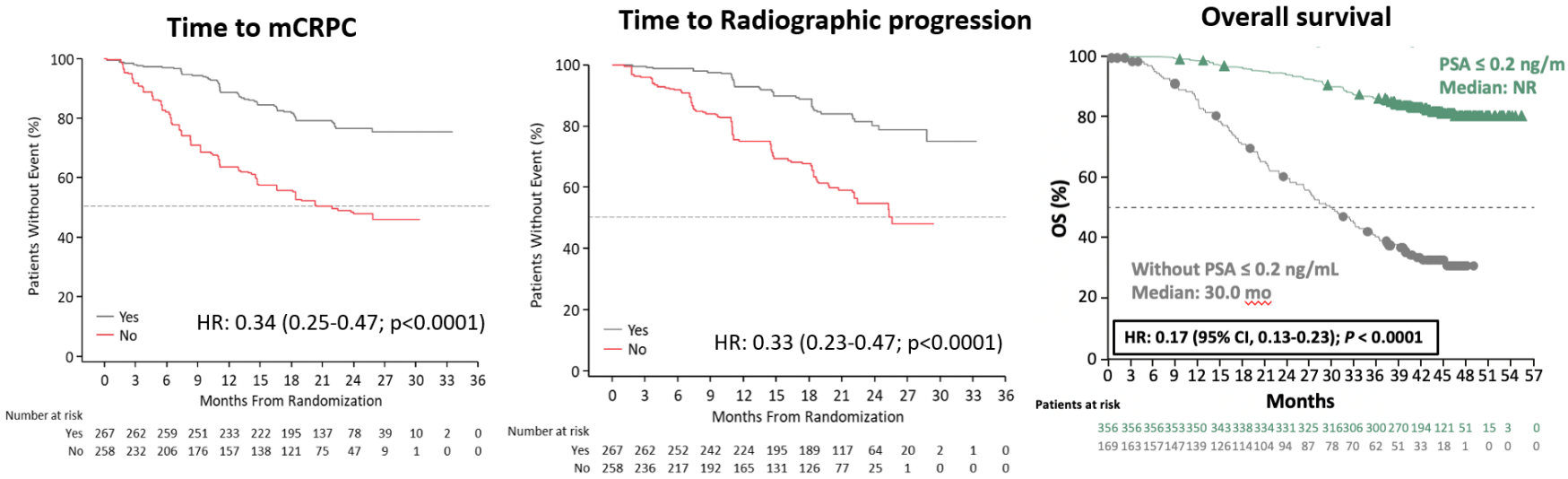


Fig 2. Overall survival by prostate-specific antigen (PSA, ng/mL) status at end of induction
Maha Hussain: Journal of Clinical Oncology 2006; 24 3984-3990.

Courtesy of Simon Chowdhury, MD, PhD

Kastrasyona Duyarlı Metastatik Prostat Kanseri Nadir PSA Uzun Sağkalımı Gösterir

Patients who achieved reduction of PSA ≤0.2 ng/mL by 3 months



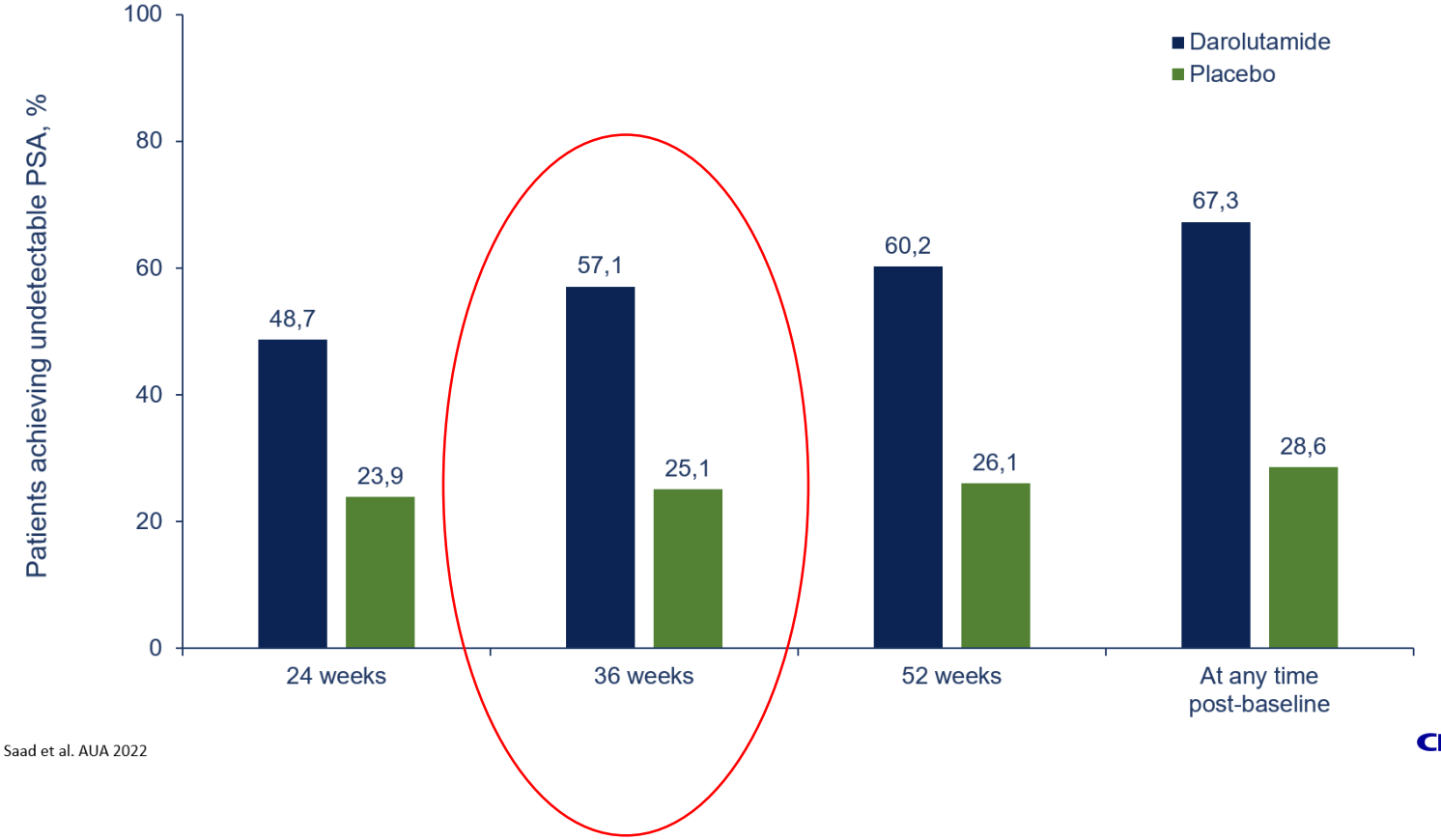
Data from the TITAN study: Chi K et al. N Engl J Med. 2019 Jul 4;381(1):13-24.

Chi KN, et al. Oral presentation at AUA Annual Meeting (Virtual), September 10-13, 2021

CHUM

Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

Objective: Undetectable (≤0.2) PSA Levels



Saad et al. AUA 2022

CHUM

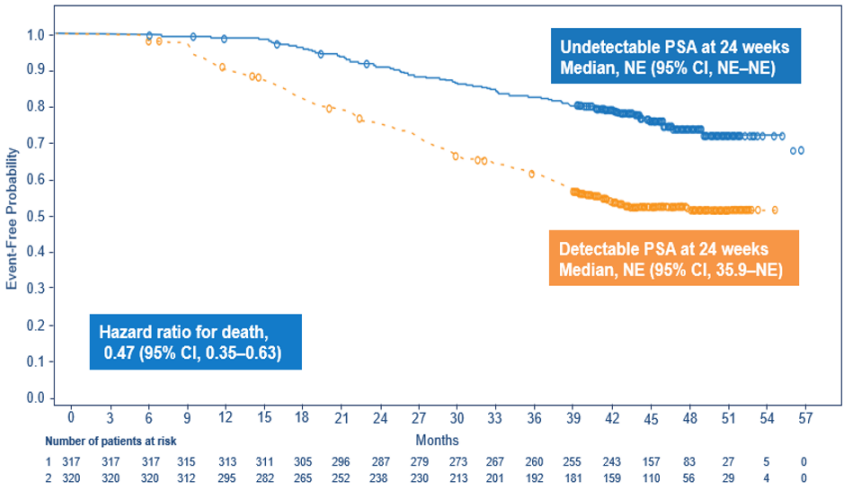
Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

Results: Overall Survival

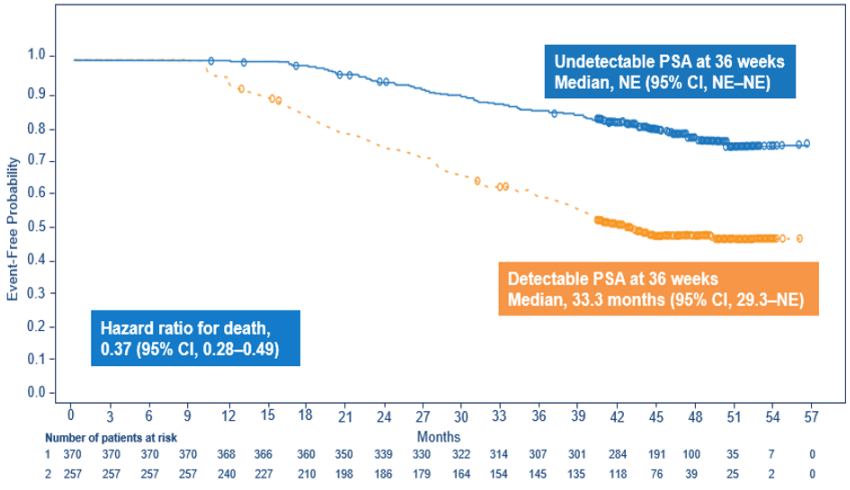
Undetectable PSA at 24 and 36 weeks was associated with a 53% and 63% reduction in the risk of death

Darolutamide + ADT + docetaxel

Undetectable vs detectable PSA at 24 weeks



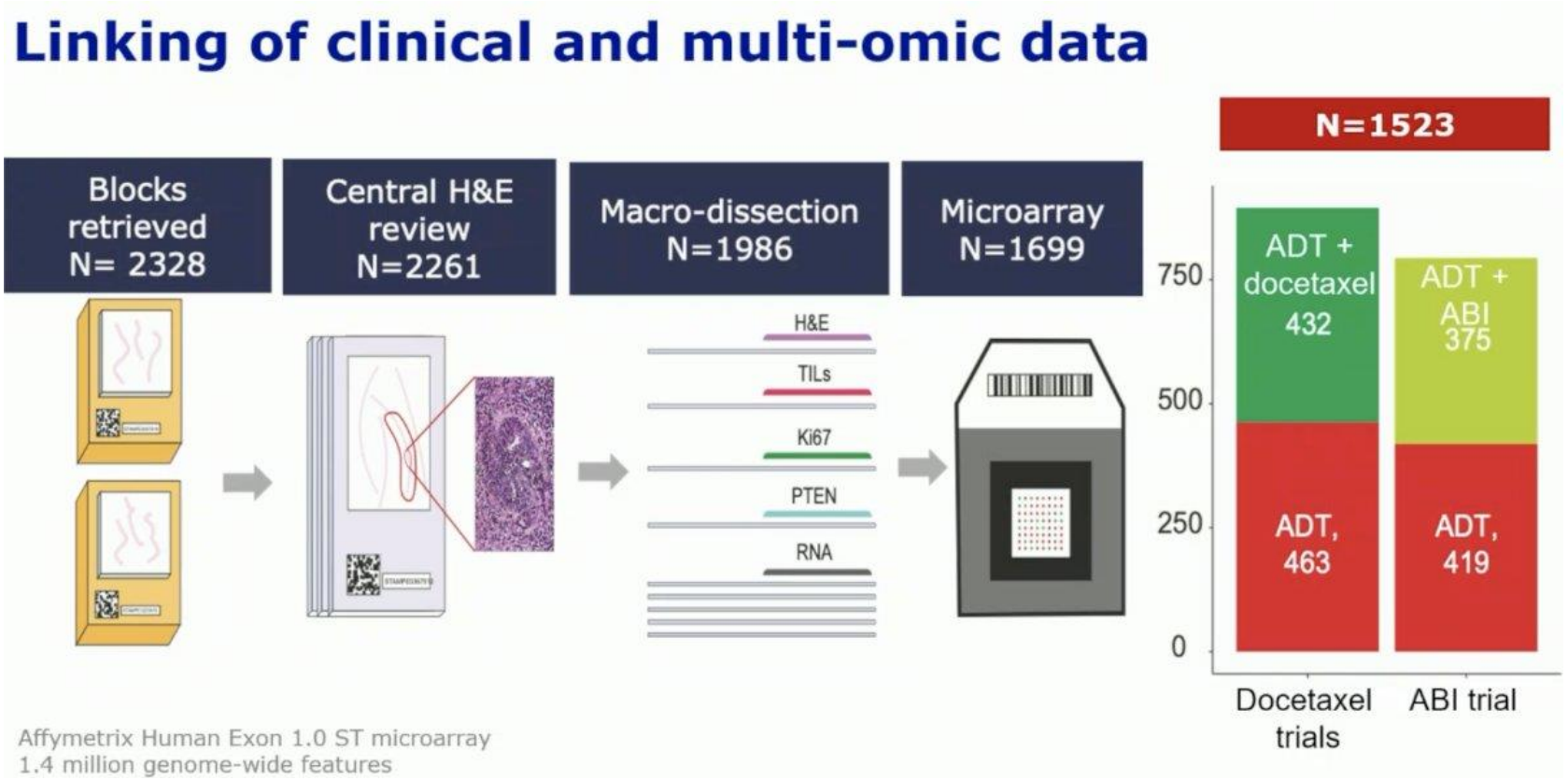
Undetectable vs detectable PSA at 36 weeks



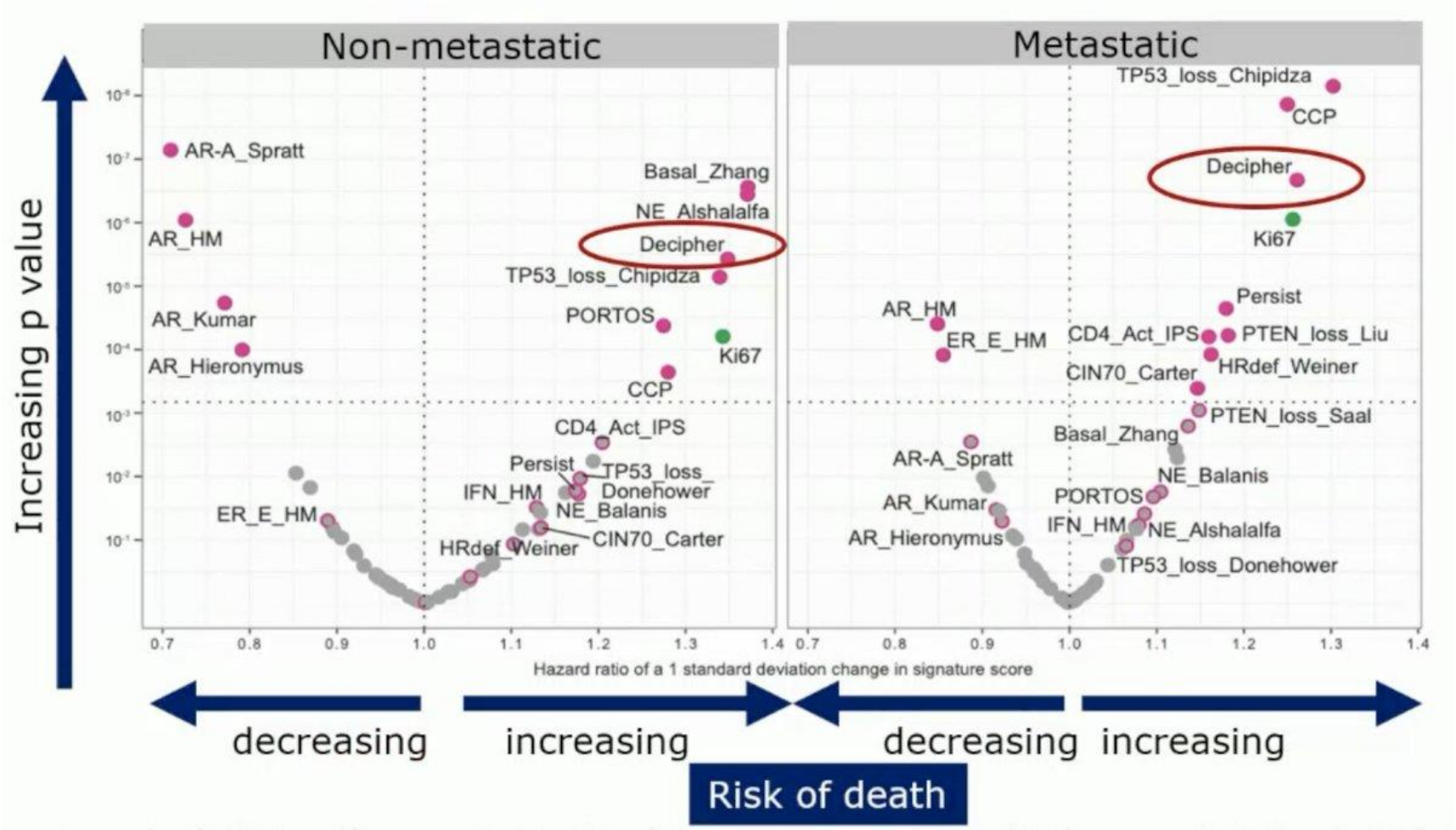
Saad et al. AUA 2022

CHUM

Gelecek Perspektif; klinik bulgulara gen ve genomik verilerin eklenmesi



Gelecek Perspektif; klinik bulgulara gen ve genomik verilerin eklenmesi



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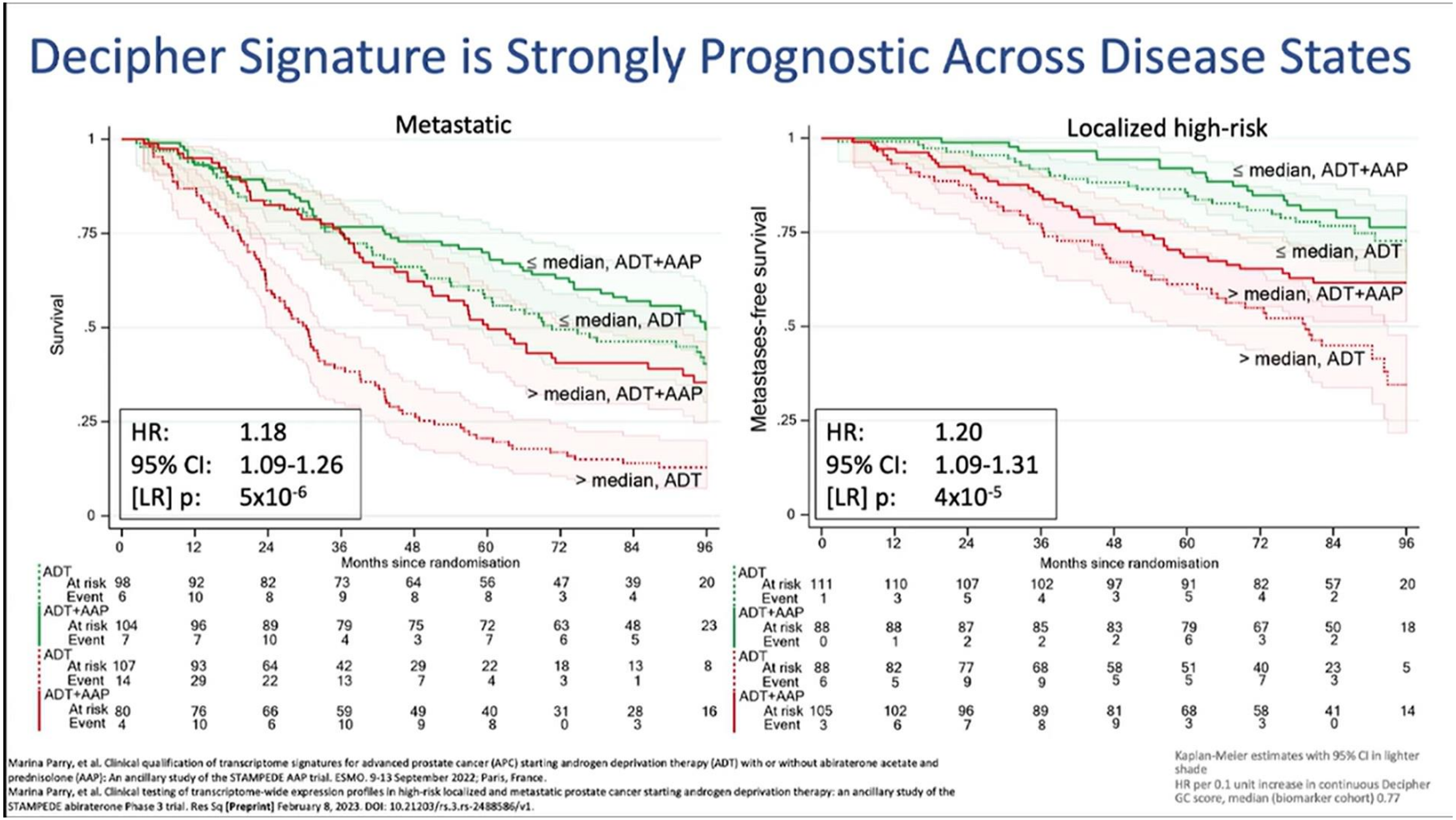
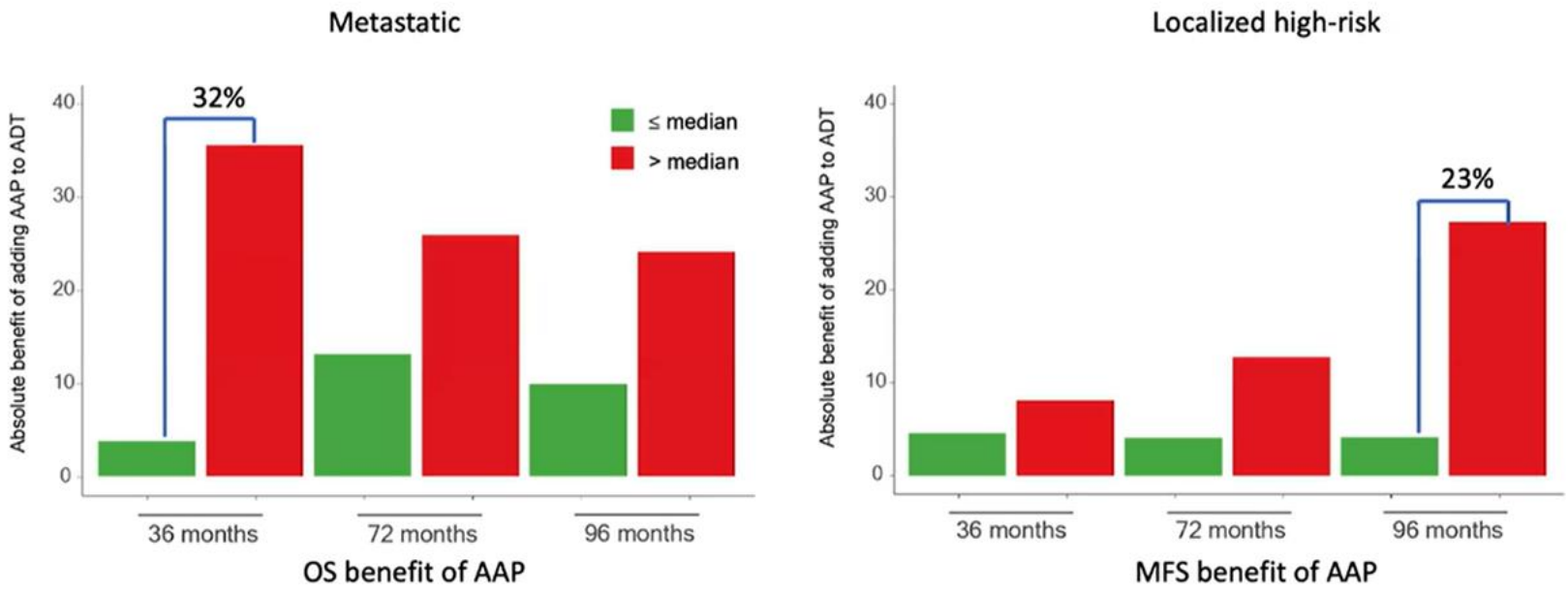


Marina Parry, et al. Clinical qualification of transcriptome signatures for advanced prostate cancer (APC) starting androgen deprivation therapy (ADT) with or without abiraterone acetate and prednisolone (AAP): An ancillary study of the STAMPEDE AAP trial. ESMO. 9-13 September 2022; Paris, France.
Marina Parry, et al. Clinical testing of transcriptome-wide expression profiles in high-risk localized and metastatic prostate cancer starting androgen deprivation therapy: an ancillary study of the STAMPEDE abiraterone Phase 3 trial. Res Sq **[Preprint]** February 8, 2023. DOI: 10.21203/rs.3.rs-2488586/v1.

Kaplan-Meier estimates with 95% CI in lighter shade
HR per 0.1 unit increase in continuous Decipher GC score, median (biomarker cohort) 0.77

Gelecek Perspektif; klinik bulgulara gen ve genomik verilerin eklenmesi

Absolute Benefit of Adding AAP to ADT Varies by Decipher Score



Event rate calculated using flexible parametric modelling adjusted for baseline characteristics

Marina Parry, et al. Clinical qualification of transcriptome signatures for advanced prostate cancer (APC) starting androgen deprivation therapy (ADT) with or without abiraterone acetate and prednisolone (AAP): An ancillary study of the STAMPEDE AAP trial. ESMO. 9-13 September 2022; Paris, France.
Marina Parry, et al. Clinical testing of transcriptome-wide expression profiles in high-risk localized and metastatic prostate cancer starting androgen deprivation therapy: an ancillary study of the STAMPEDE abiraterone Phase 3 trial. Res Sq [Preprint] February 8, 2023. DOI: 10.21203/rs.3.rs-2488586/v1.

Gelecek Perspektif; klinik bulgulara gen ve genomik verilerin eklenmesi

Decipher mRNA score for prediction of survival benefit from docetaxel at start of androgen deprivation therapy for advanced prostate cancer: an ancillary study of the STAMPEDE docetaxel trials

Emily Grist, Peter Dutey-Magni, Larissa Mendes, Marina A. Parry, Ashwin Sachdeva, James Proudfoot, Anis A. Hamid, Claire L. Amos, William R. Cross, Silke Gillessen, Daniel M. Berney, Matthew R. Sydes, Mahesh K.B. Parmar, Felix Y. Feng, Noel W. Clarke, Elai Davicioni, Christopher J. Sweeney, Nicholas D. James, Louise C. Brown, Gerhardt Attard on behalf of the STAMPEDE Investigators

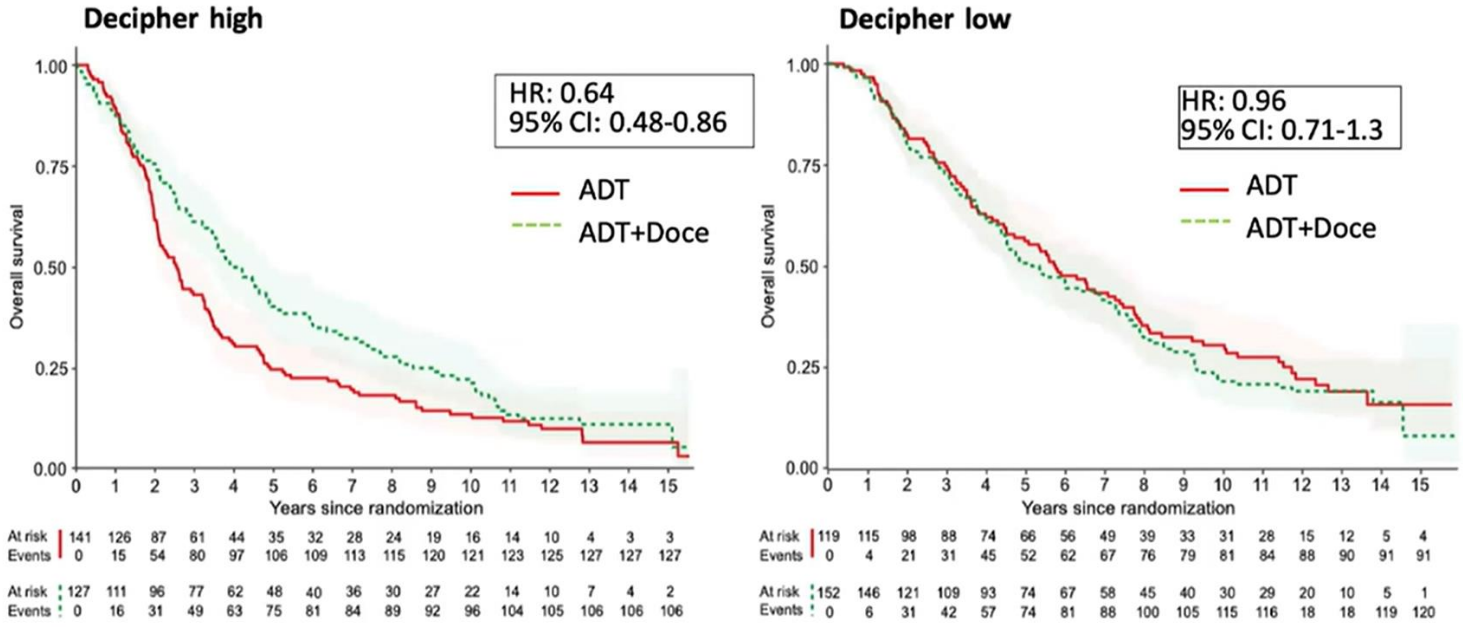
ClinicalTrials.gov number, NCT00268476 & Current Controlled Trials number, ISRCTN78818544 Trial conducted by Medical Research Council Trials Unit at University College London, U.K.

105 UK trial sites participated in this study

Emily Grist, et al. Decipher mRNA score for prediction of survival benefit from docetaxel at start of androgen deprivation therapy (ADT) for advanced prostate cancer (PC): An ancillary study of the STAMPEDE docetaxel trials. ESMO. 13-17 September 2024; Barcelona, Spain.

Gelecek Perspektif; klinik bulgulara gen ve genomik verilerin eklenmesi

Decipher Score Predicts Docetaxel Efficacy in Metastatic Prostate Cancer



High Decipher score identifies patients more likely to benefit from docetaxel

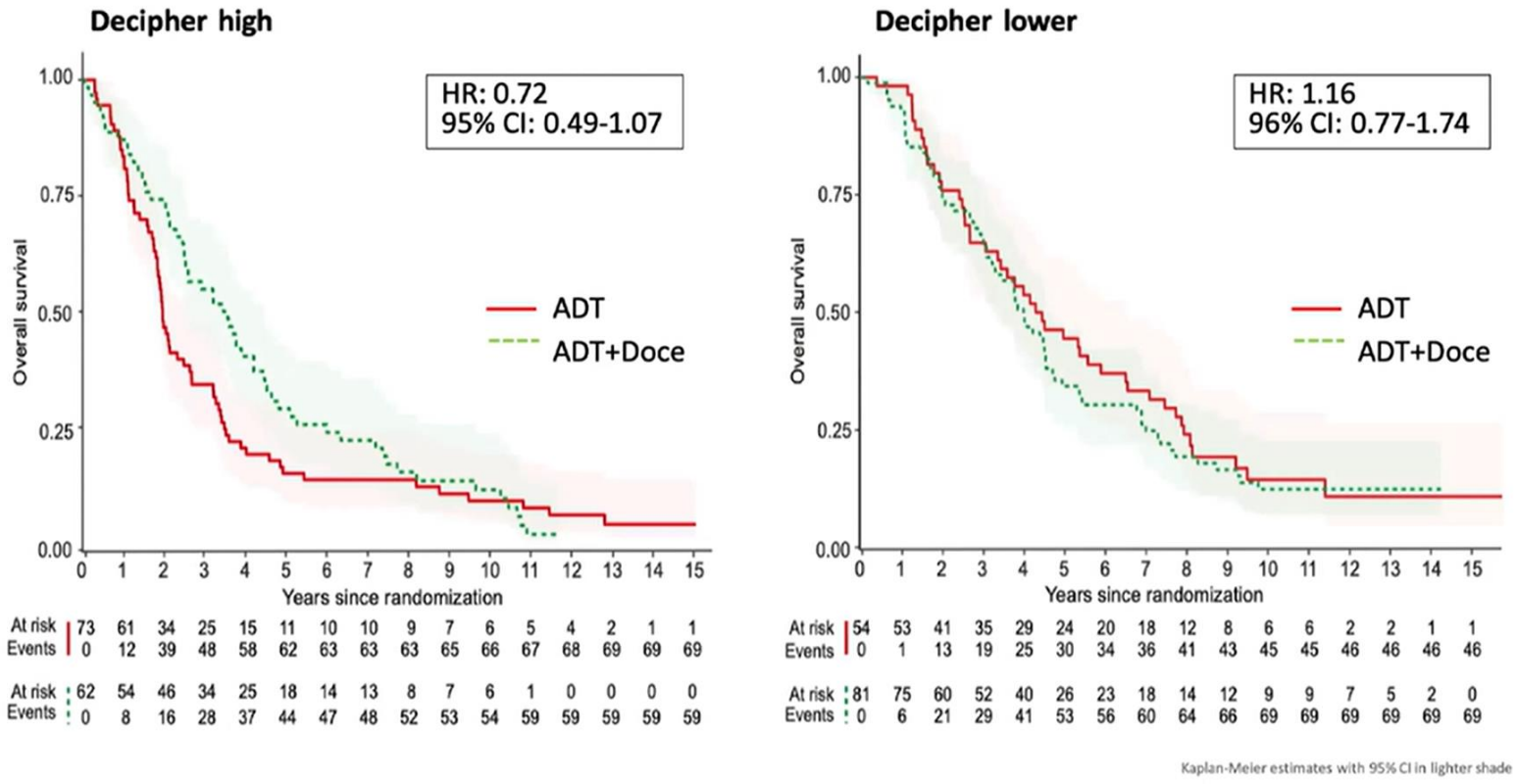
Biomarker-treatment interaction effect p value= 0.039*

No significant interaction effect demonstrated in non-metastatic disease
Kaplan-Meier estimates with 95% CI in lighter shade.
Decipher score dichotomized around median of metastatic cohort in combined docetaxel and abiraterone trials
Interaction test from multivariable model adjusted for Gleason score, disease burden, age, pre-ADT PSA, WHO PS, nodal stage, tumor stage, NSAID/aspirin use, and metastatic volume.

Emily Grist, et al. Decipher mRNA score for prediction of survival benefit from docetaxel at start of androgen deprivation therapy (ADT) for advanced prostate cancer (PC): An ancillary study of the STAMPEDE docetaxel trials. ESMO. 13-17 September 2024; Barcelona, Spain.

Gelecek Perspektif; klinik bulgulara gen ve genomik verilerin eklenmesi

Direction of Treatment Effect Consistent in High Volume



Kaplan-Meier estimates with 95% CI in lighter shade

Emily Grist, et al. Decipher mRNA score for prediction of survival benefit from docetaxel at start of androgen deprivation therapy (ADT) for advanced prostate cancer (PC): An ancillary study of the STAMPEDE docetaxel trials. ESMO. 13-17 September 2024; Barcelona, Spain.

Gelecek Perspektif; klinik bulgulara gen ve genomik verilerin eklenmesi

PEACE-1 phase 3 trial

- A paradigm shift in de novo mCSPC first line treatment

Key Eligibility Criteria
- *De novo* mCSPC
- Distant metastatic disease by ≥ 1 lesion on bone scan and/or CT scan
- ECOG PS 0 -2

On-Study Requirement
- Continuous ADT

Permitted
- ADT ≤ 3 months

Stratification
- ECOG PS (0 vs 1-2)
- Metastatic sites (LN vs bone vs visceral)
- Type of castration (orchidectomy vs LHRH agonist vs LHRH antagonist)
- Docetaxel (yes vs no)

Nov 2013 – Dec 2018

RANDOMISATION 1:1:1:1

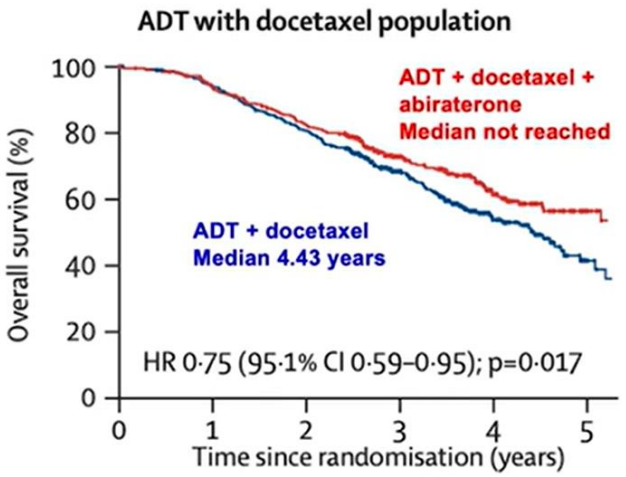
n = 1173

A SOC (n = 296)

B SOC+Abiraterone (n = 292)

C SOC+Radiotherapy (n = 293)

D SOC+Abiraterone+ Radiotherapy (n = 292)



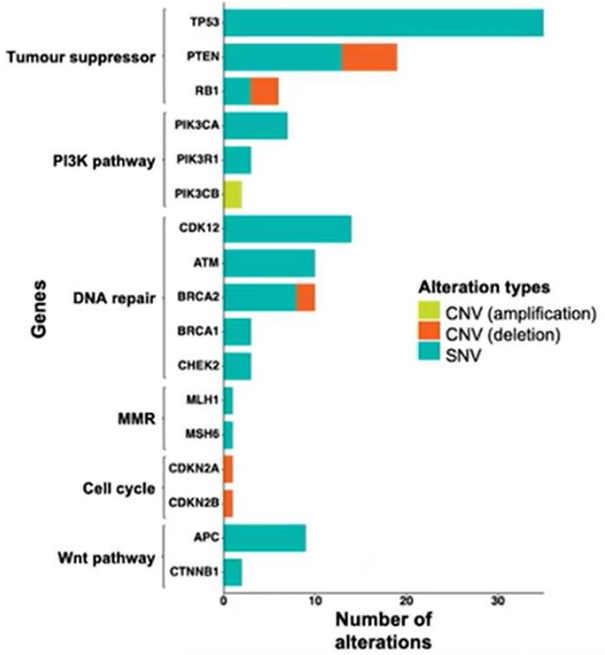
Hypothesis for ancillary study: aggressive/neuroendocrine-like variants could be detected at diagnosis and are associated with prognosis

References: Fizazi et al. The Lancet 2022

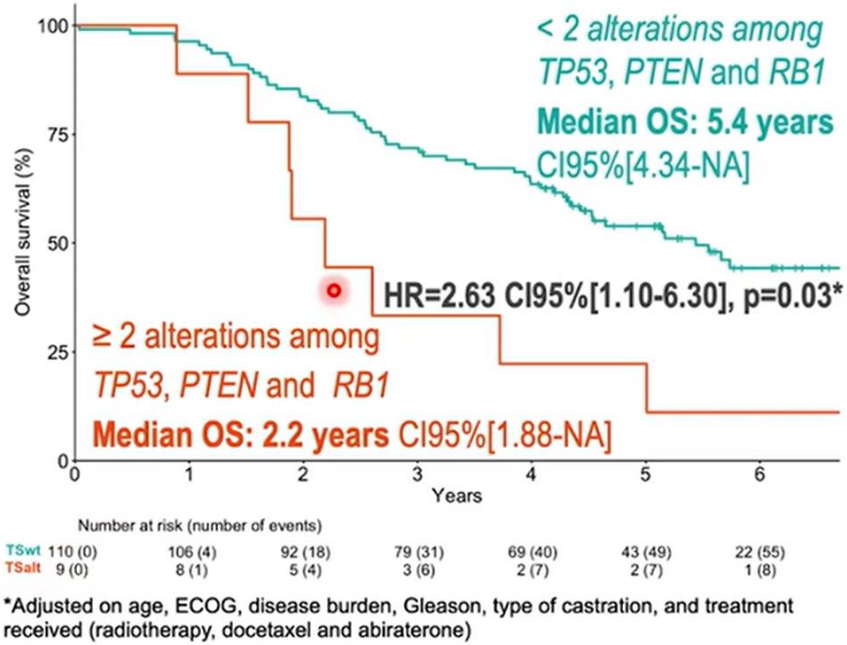
Gelecek Perspektif; klinik bulgulara gen ve genomik verilerin eklenmesi

Genomic analysis

- NGS contributive among 119 patients



- Multiple tumour suppressor gene alterations[1] are associated with worse prognosis:



*Adjusted on age, ECOG, disease burden, Gleason, type of castration, and treatment received (radiotherapy, docetaxel and abiraterone)

References: 1. AM Aparicio et al. Clinical Cancer Research 2016

Metastatik Kastrasyona Duyarlı Prostat Kanseri Tedavi

WORKUP AND TREATMENT OF LOW-VOLUME M1 (METACHRONOUS OR SYNCHRONOUS) OR SYNCHRONOUS OLIGOMETASTIC CSPC[c,h,tt,uu,vv,ww]

WORKUP FOR METASTASES[xx]

- Perform physical exam
- Perform imaging for staging[g]
- Perform and/or collect PSA and calculate PSADT
- Estimate life expectancy (Principles of Life Expectancy Estimation [PROS-A])
- Perform germline and somatic genetic testing[e] (if not previously done)
- Obtain family history[e]
- Assess quality-of-life measures[f]

Synchronous low-volume metastases or Synchronous oligometastatic disease

ADT[aa,zz] with one of the following:
- Preferred:
  - Abiraterone (category 1)[aa]
  - Apalutamide (category 1)[aa]
  - Enzalutamide (category 1)[aa]
- Other Recommended:
  - Darolutamide (category 2B)[aa]

or

ADT[aa,zz] with docetaxel and one of the following (low-volume disease only):
- Abiraterone (category 2B)[aa]
- Apalutamide (category 2B)[aa]
- Darolutamide (category 2B)[aa]
- Enzalutamide (category 2B)[aa]

or

ADT[aa,zz] with EBRT[t] to the primary tumor[aaa] alone or with one of the following:
- Abiraterone[aa]
- Apalutamide (category 2B)[aa]
- Docetaxel (category 2B)
- Enzalutamide (category 2B)[aa]

or

ADT[aa,zz] with:
- Useful in Certain Circumstances
  - Niraparib/abiraterone[bbb] (*BRCA2*m only) (category 2B)

Metachronous low-volume metastases

ADT[aa,zz] with one of the following:
- Preferred:
  - Abiraterone (category 1)[aa]
  - Apalutamide (category 1)[aa]
  - Enzalutamide (category 1)[aa]
- Other Recommended:
  - Darolutamide (category 2B)[aa]

or

ADT[aa,zz] with:
- Useful in Certain Circumstances
  - Niraparib/abiraterone[bbb] (*BRCA2*m only) (category 2B)

- Physical examination + PSA every 3–6 mo
- Imaging for symptoms[g]
- Periodic imaging to monitor treatment response

Progression[ff] on ADT ± androgen receptor pathway inhibitor (ARPI)

Workup and Treatment of M1 CRPC (PROS-17)

Metastatik Kastrasyona Duyarlı Prostat Kanseri Tedavi

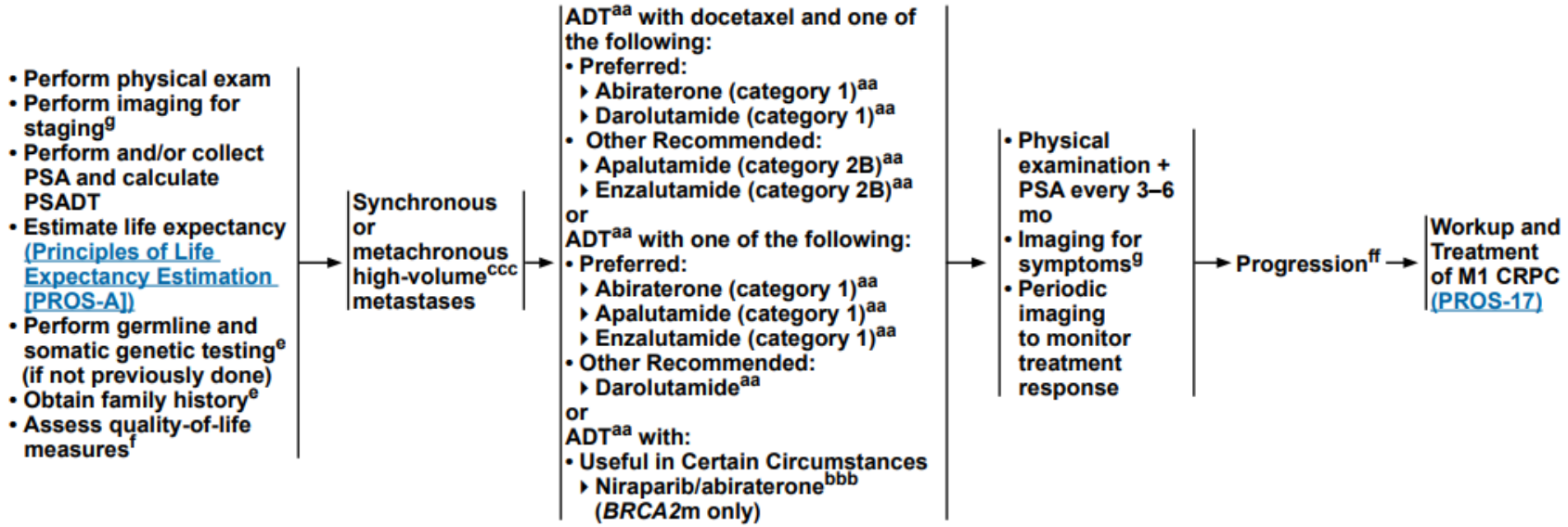
National Comprehensive Cancer Network®

NCCN Guidelines Version 5.2026
Prostate Cancer

NCCN Guidelines Index
Table of Contents
Discussion

WORKUP AND TREATMENT OF HIGH-VOLUME M1 CSPC[c,tt,uu,vv,ww,ccc]

WORKUP FOR METASTASES[xx]



Tedavi Kararında Etkili Faktörler

Hastalıkla İlişkili Faktörler

1- Yüksek volüm/Düşük volüm

2- Denovo/metakron metastaz

3-Metastaz bölgesi

4-Gleason skoru

5-Primer tümörün genetik profil

Klinik Faktörler

1-Semptomatik olması

2-ECOG PS

3-Ek hastalıklar

4-Başka hastalıklar için aldığı tedaviler

5-Hastalık için daha önce aldığı tedaviler

Başlanacak tedavi ile ilgili faktörler

1-Uygulama şekli

2-Etki etme mekanizması

3- Yan etkileri

4-İlaç etkileşimi

5-Tedavi maliyeti

Sonuç

- ADT+yeni nesil androjen yolağı inhibitörü/ ADT+yeni nesil androjen yolağı+dosetaksel karşılaştırması yok
- Üçlü tedavi

Viseral metastaz, de novo, yüksek volüm, genç, yaşam beklentisi uzun hastalarda ön planda düşünülebilir

- İkili kombinasyon

CHARTED kriterlerine göre düşük volüm, metakron metastaz, non-regioneal lenf nodu, akciğer metastazı olan hastalarda ikili kombinasyon düşünülebilir

- Yeni nesil androjen yolağı inhibitörü, hastanın ek hastalığı, ilaç etkileşimi ve yan etki profiline göre seçilmesi önerilir
- Lütesyum için daha uzun takip süresi ve OS datası
- PARP inhibitörleri için daha uzun takip ve OS datası
- Genomik profilleme tedavi seçiminde etkili olacak.
- Gelecek dönem PSA yanıtına göre tedavi yoğunluğunda azaltma ya da yoğunluğunu artırma bir seçenek olabilir