

Kastrasyona Duyarlı Metastatik Prostat Kanserinde Doz Yoğun Tedavi

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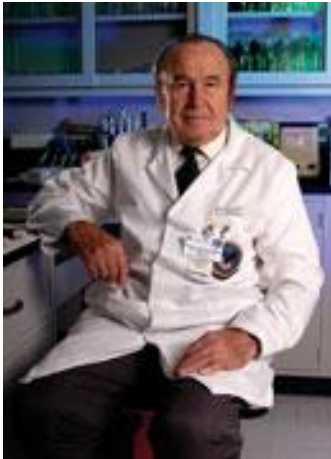
Ders Planı

- ❑ 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

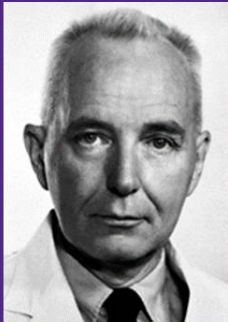


- Charles Brenton Huggins(1901-1997)
- 1927'de Chicago Üniversitesinde Üroloji kliniğinde akademik kadro aldı
- Köpeklerde yaptığı deneylerle, prostat hücrelerinin büyümesinde testosteron hormonuna bağımlı olduğunu tespit etti
- Prostat kanseri olanlarda orşektomi ile tümörün küçüldüğünü belirledi.
-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

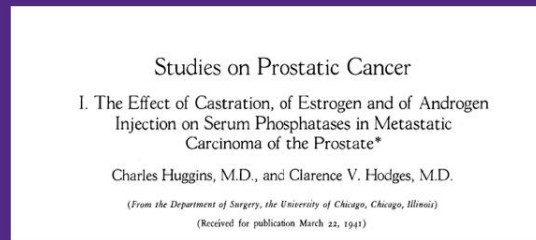


Kastrasyona Duyarlı Metastatik Prostat Kanseri ADT Tedavisi

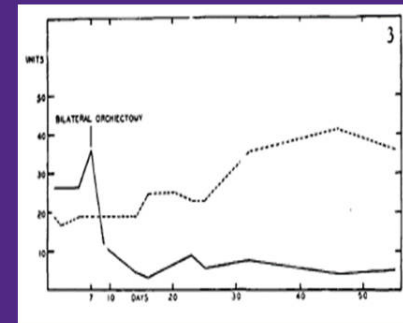
Historical Perspective: Androgens & Prostate Cancer



C. Huggins
1966 Nobel Prize



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

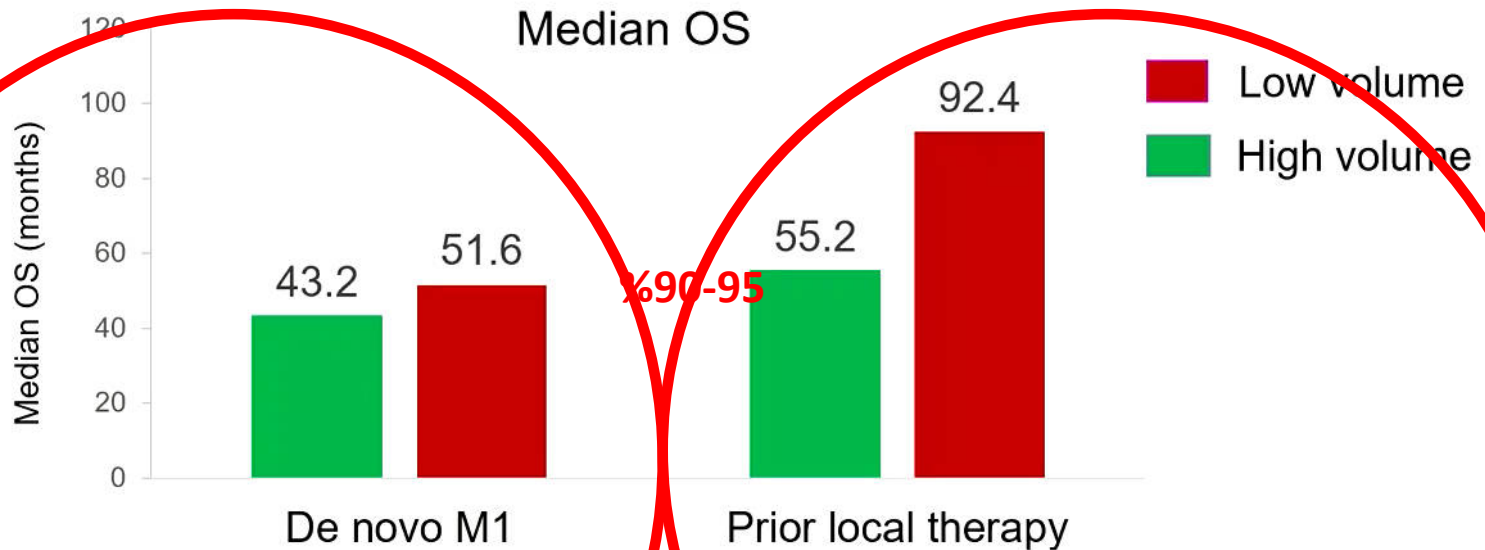
- 1-Semptomatik olması
- 2-ECOG PS
- 3-Ek hastalıklar
- 4-Başka hastalıklar için aldığı tedaviler
- 5-Hastalık için daha önce aldığı tedaviler

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.

2021 ESMO Congress

OUARD Stéphane

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%5-10

%90-95

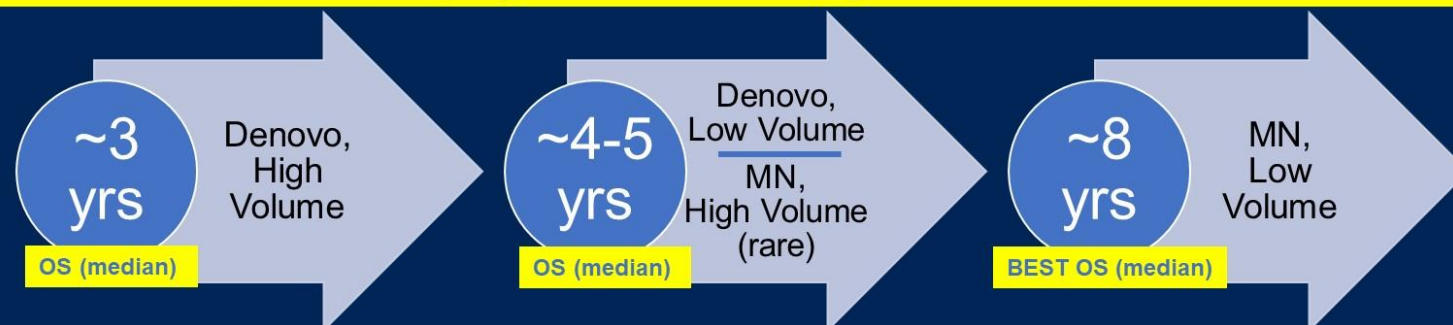
TANI ANINDA METASTATİK VE YÜKSEK VOLÜMLÜ HASTALIK AGRESİF SEYİRLİ

3

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?

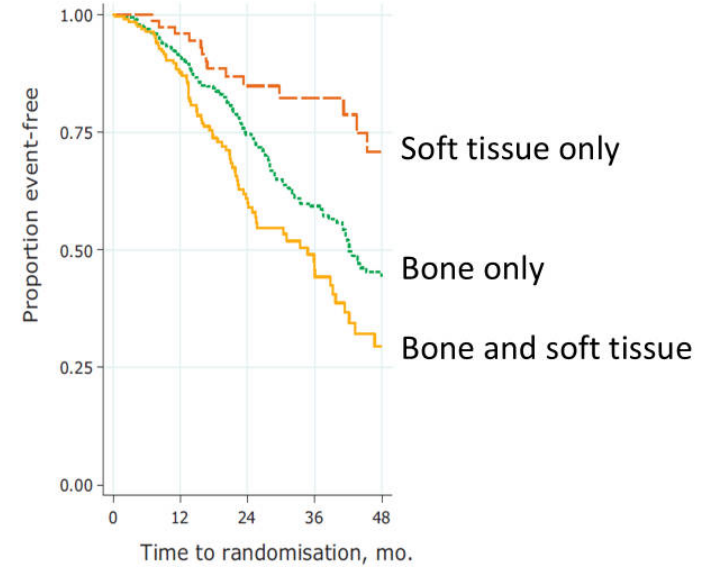
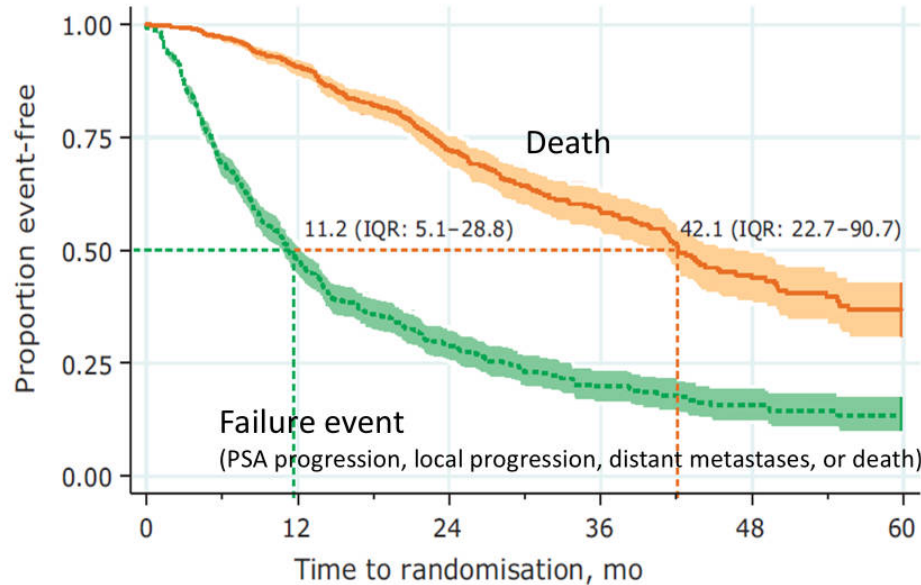


Denovo = new diagnosis/untreated
MN = metachronous diagnosis/previously treated

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



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

STAMPEDE Control Arm

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

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

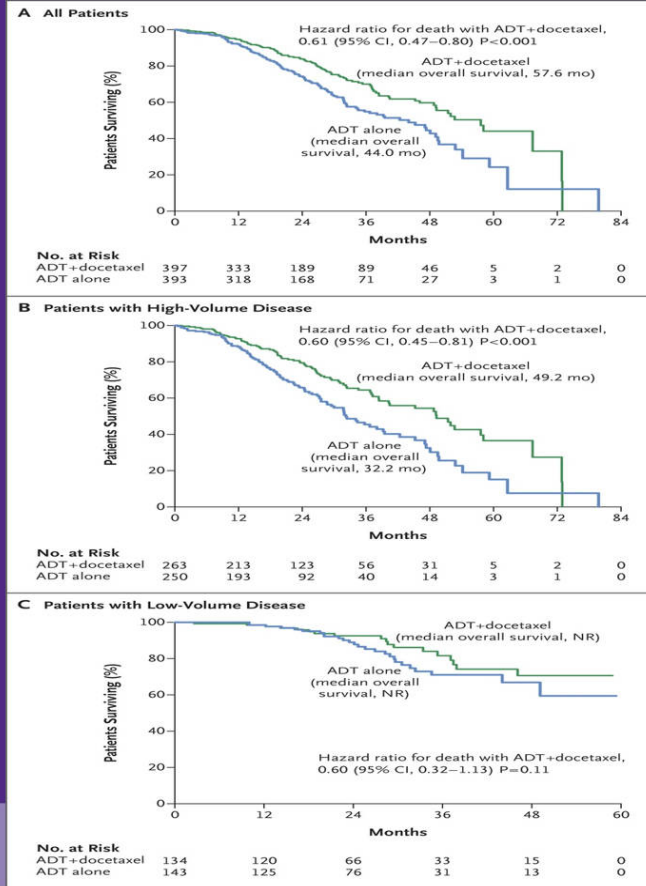
Gravis et al Lancet Oncol 2013; Sweeney et al NEJM 2015; James N et al Lancet 2015; Attard G et al Lancet Oncol 2023; Fizazi K et al NEJM 2017; James et al NEJM 2017; Armstrong et al JCO 2021; Davis et al NEJM 2019; Chi KN et al NEJM 2019; Smith MR et al NEJM 2022; Fizazi K et al Lancet 2022

Hastalık Volümü Dosetaksel Tedavi Etkinliği için Prediktif

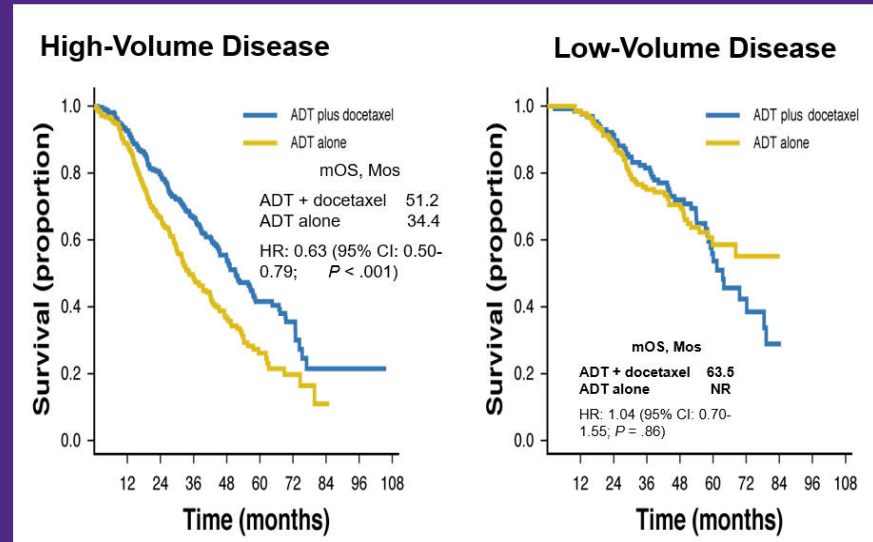
CHAARTED: ADT +/- Docetaxel in mHSPC

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

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



Sweeney CJ et al. NEJM 2015

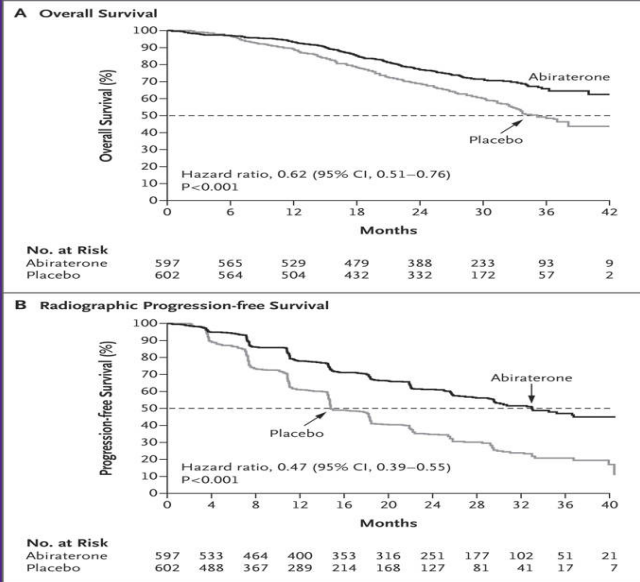


Kyriakopoulos CE, et al. J Clin Oncol. 2018

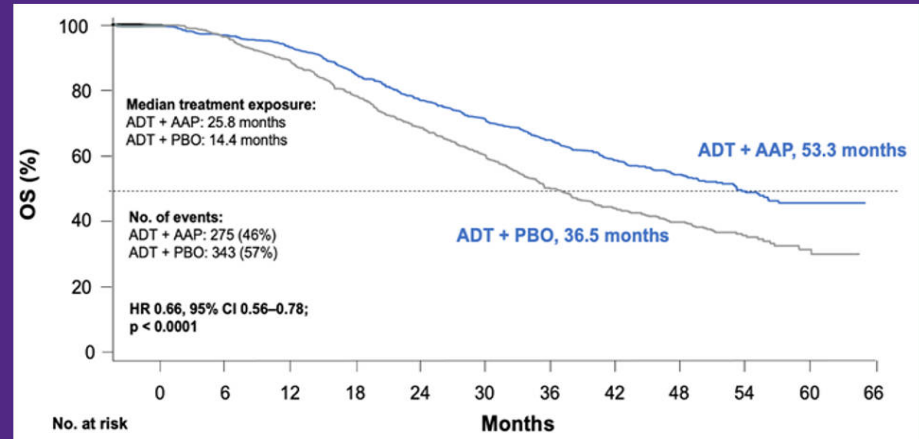
Yüksek volümlü hastalığı olanlar; viseral organ metastazı olan yada ≥ 4 kemik lezyonu olan ve en az ≥ 1 vertebra, pelvis dışı kemiklerde metastaz olmalı

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%



- 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 et al. NEJM 2017

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

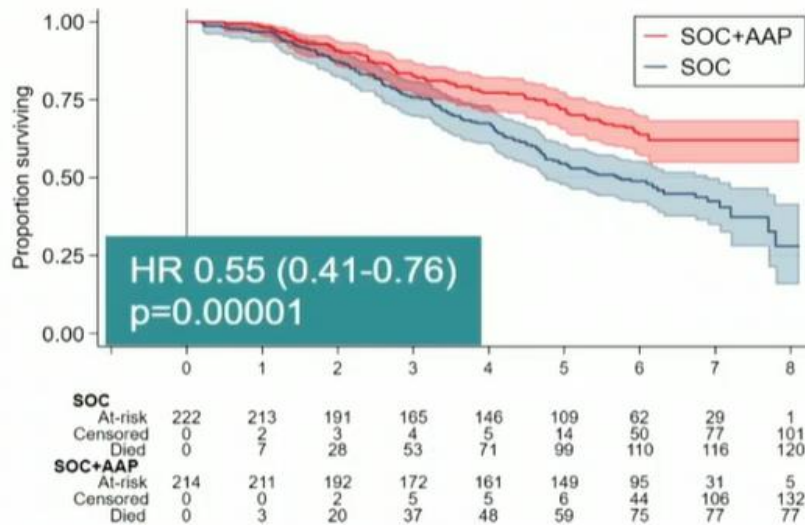
Metastatik hastalığa bağlı semptomu olanlarda RT ve Cerrahiye izin verilmiş

Yeni nesil androjen yolağı inhibitörleri riskten bağımsız etkili

VIRTUAL 2020 **ESMO** congress

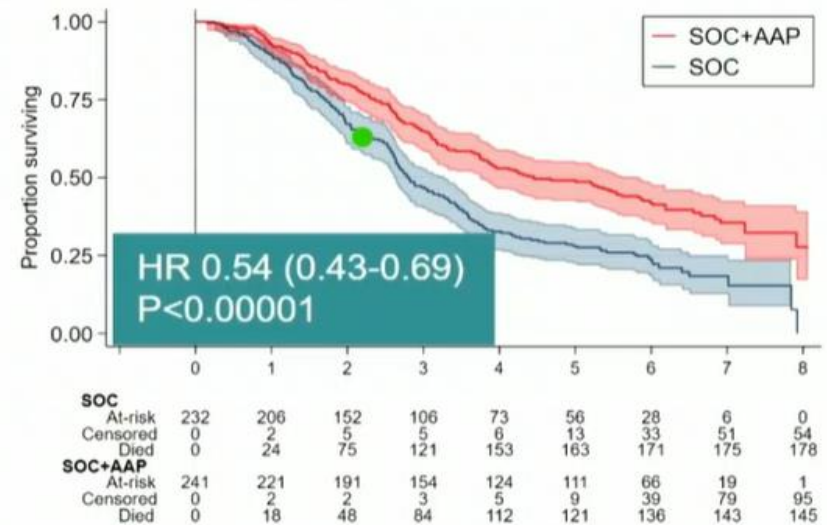
STAMPEDE: OS by risk group (LATITUDE)

Low risk



HR 0.66 (0.44-0.98)
p=0.041

High risk



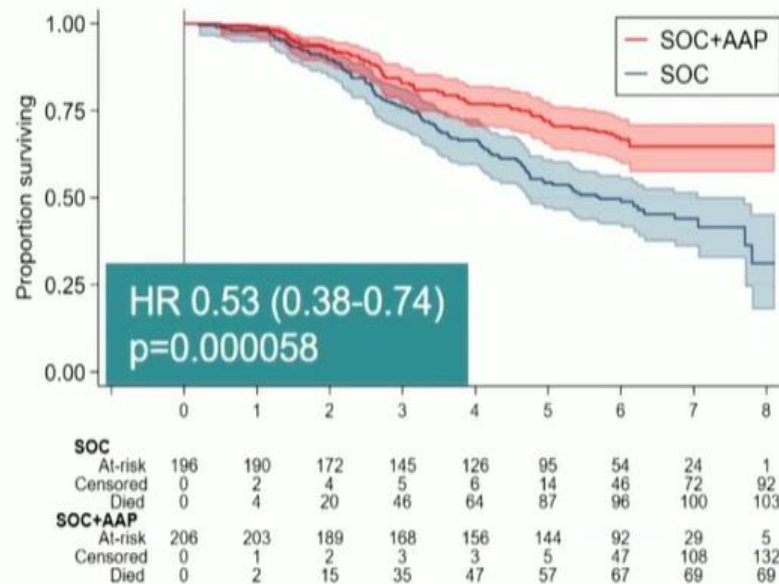
HR 0.54 (0.41-0.70)
P<0.001

Yeni nesil androjen yolağı inhibitörleri tümör yükünden bağımsız etkili

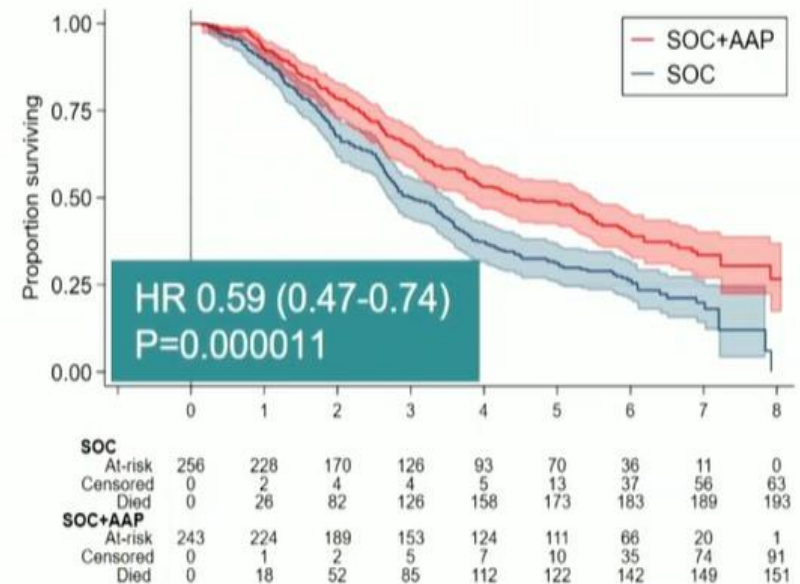


STAMPEDE: OS by disease burden (CHAARTED)

Low volume



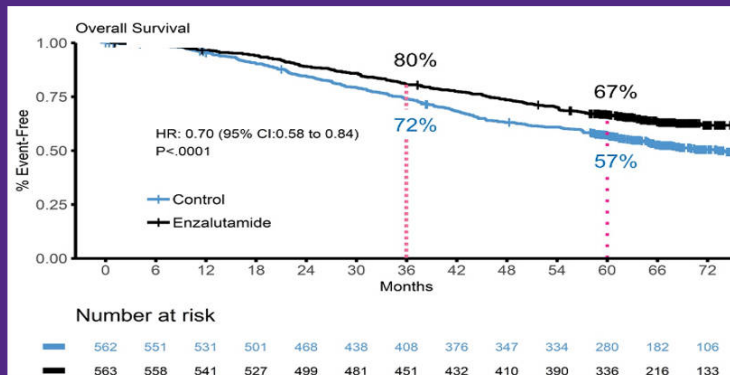
High volume



Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

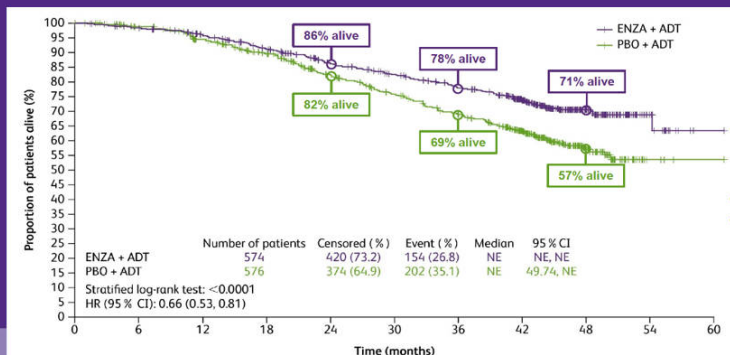
Final Overall Survival (OS) Analyses: Enzalutamide for Metastatic Hormone-Sensitive Prostate Cancer

ENZAMET¹
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

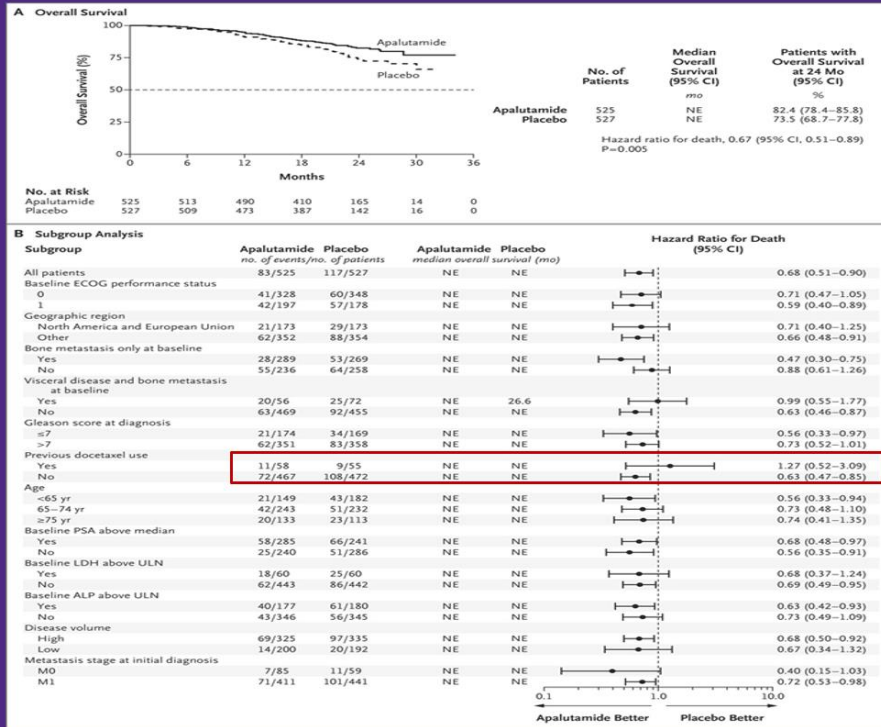
ARCHES²
Enzalutamide + ADT



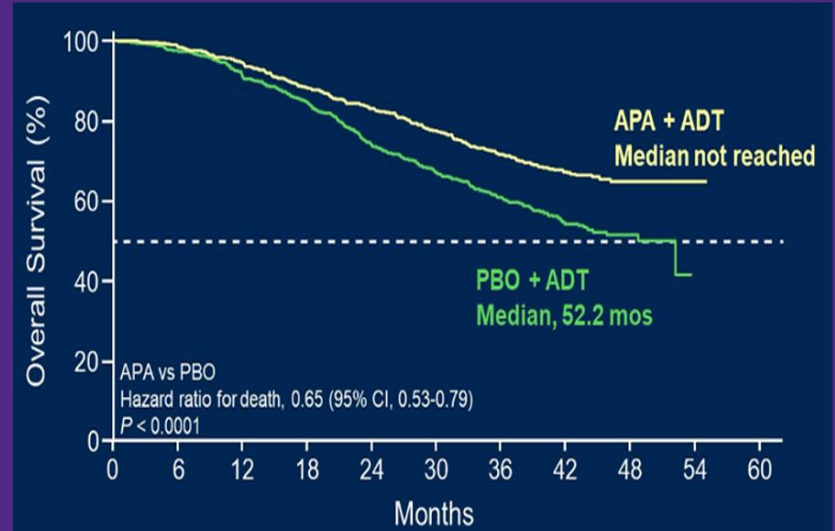
- Median follow-up of 44.6 months
- 34% reduction in risk of death
- Median OS was not reached for enzalutamide plus ADT, but was 47.7 months (95% CI, 43.3 to not evaluable) for placebo plus ADT.
 - HR = 0.66; p < 0.001

Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

Apalutamide for Metastatic, Castration-Sensitive Prostate Cancer



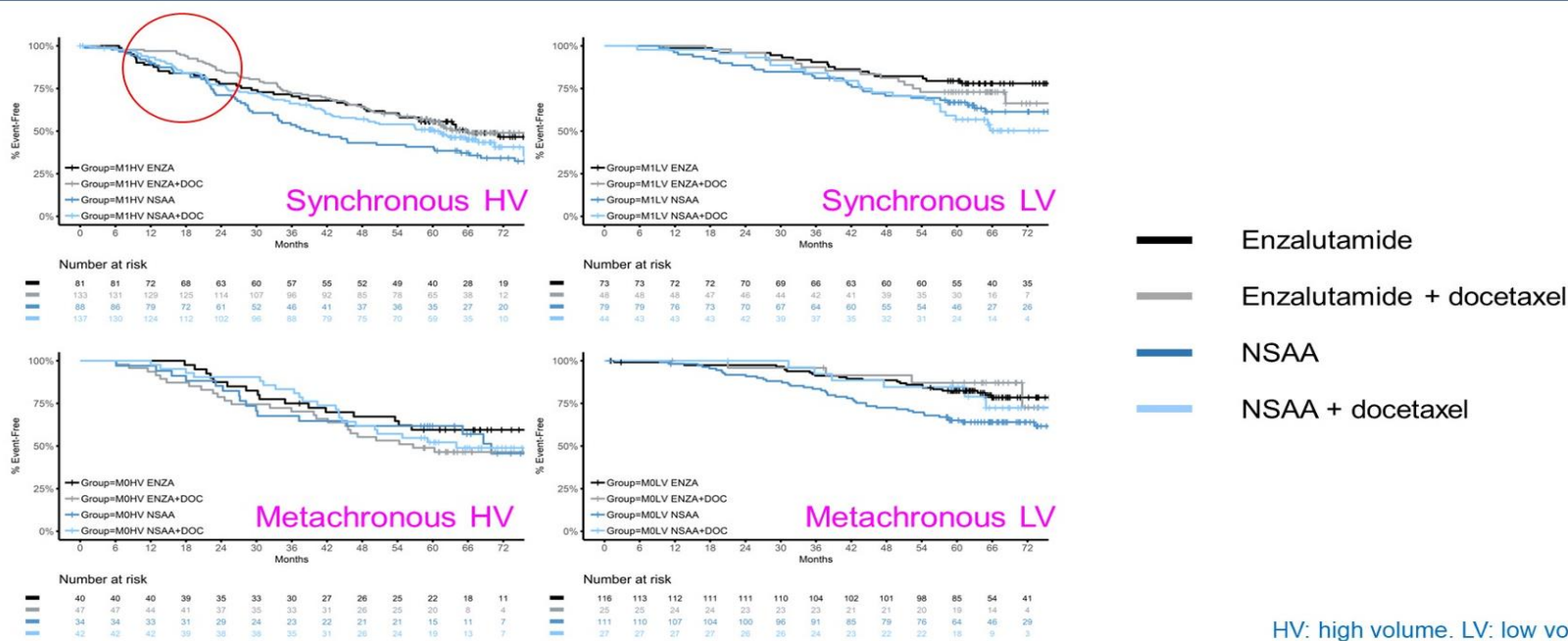
- 8% difference in OS at 2 years
- Reduced risk of death by 33%



- 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; $p < 0.0001$

ENZAMET çalışması de novo yüksek volümde üçlü tedavi etkili

Overall survival: volume, M1 timing, docetaxel

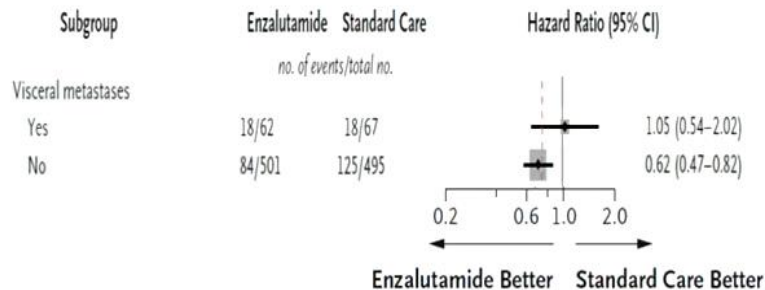


Yeni nesil androjen yolağı inhibitörleri viseral metastazda etkinliği düşük

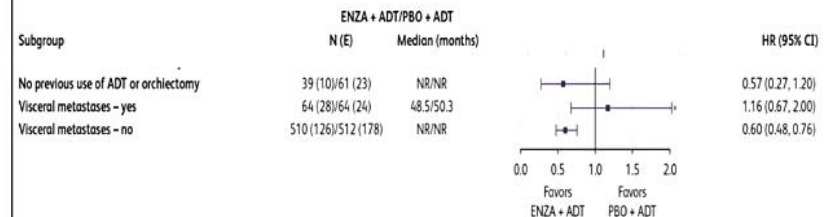
Does type of metastasis matter in mHNPC?

Results from new hormonal treatments in mHNPC according visceral mets

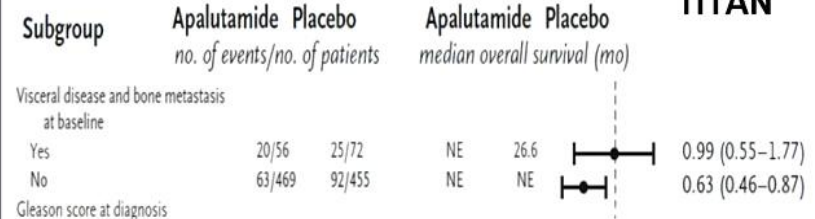
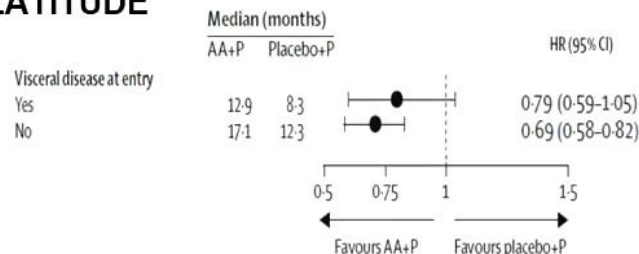
ENZAMET



ARCHES



LATITUDE



2021 ESMO congress

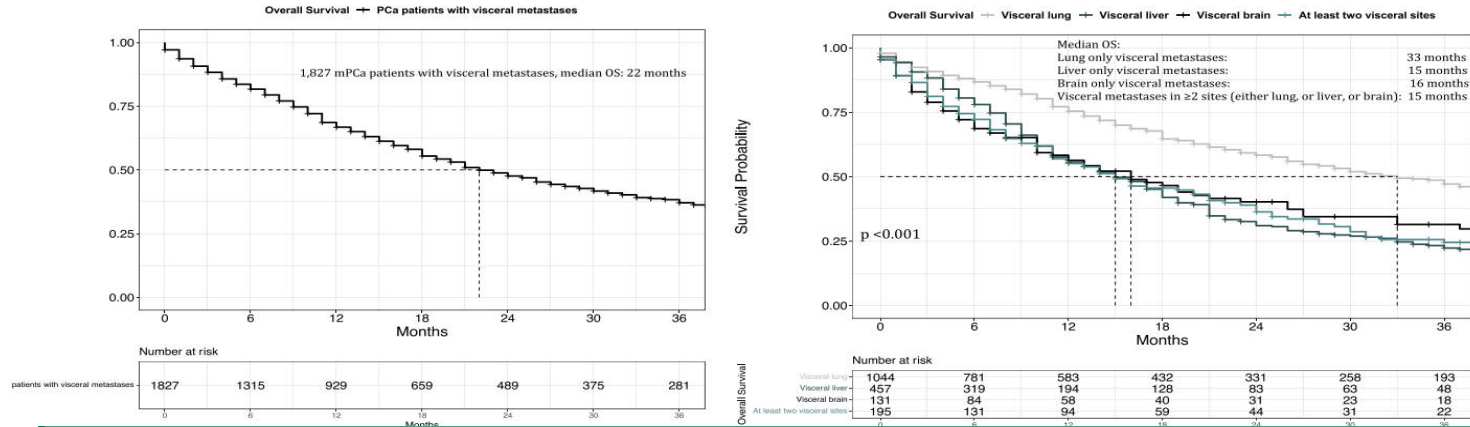
OUARD Stéphane

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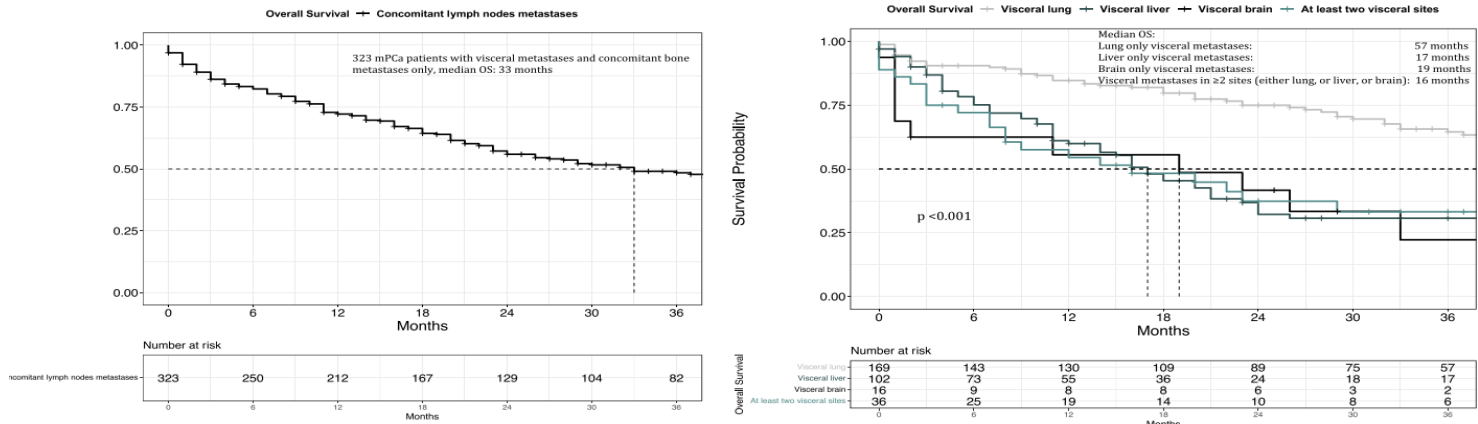
1. Davis I, et al. NEJM 2019;381:121-131 2. Armstrong A, et al. ESMO 2021 oral comm. abstract LBA25 3. Chi K, et al. NEJM 2019;381:13-24 4. Fizazi K, et al. Lancet Oncol. 2019 May;20(5):686-700.

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.

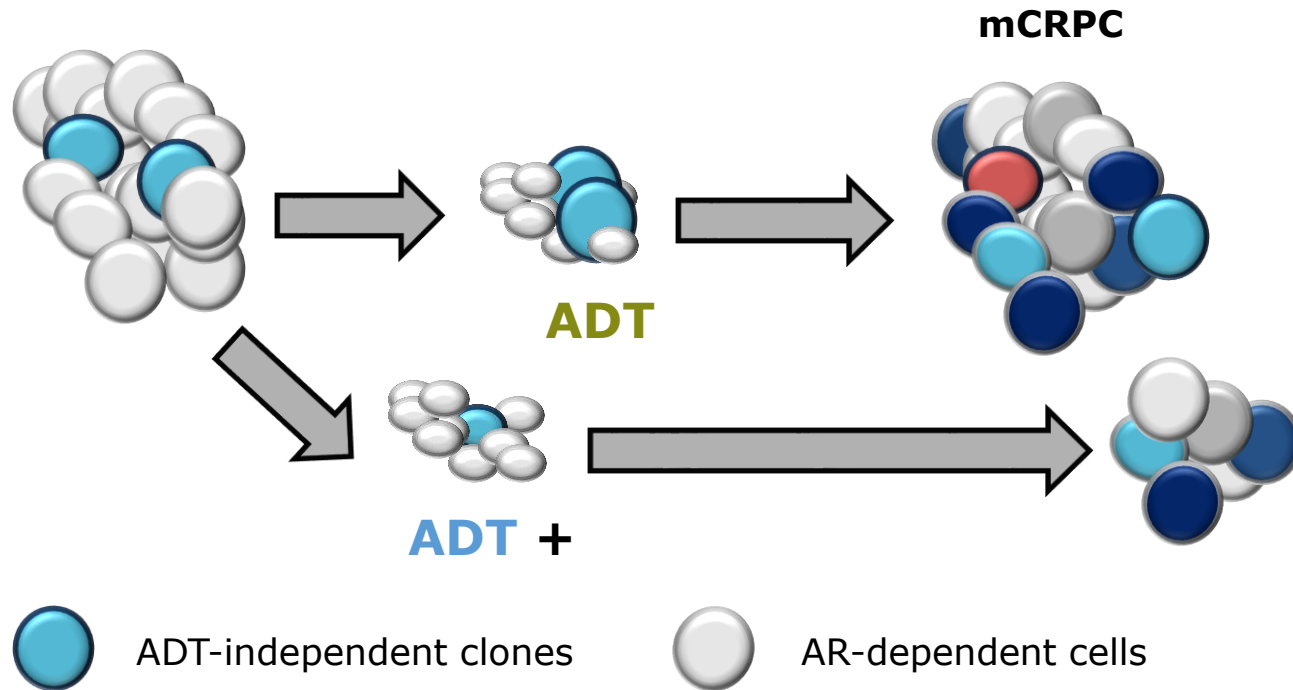


Kaplan-Meier plots displaying overall survival of 323 metastatic prostate cancer (mPCa) patients with visceral metastases with concomitant lymph node metastases only: (A) in the overall population; (B) according to location of visceral metastatic sites.



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

Kastrasyona Duyarlı Metastatik Prostat Kanseri Daha Yoğun Tedavisi



Role of Effective Systemic Therapy

Tedaviyi yoğunlaştırma stratejileri

APPIs: enza/apa/darolutamide

Klinik pratiğe geçek stratejiler

☐ ARPIs +/- Docetaxel

☐ Abiraterone

☐ enza/apa/darolutamide

☐ Radyoterapi prosatat

☐ SBRT to metastatik lezyonlar

• Biomarker Directed Therapy?

• Tedaviye ara verme?

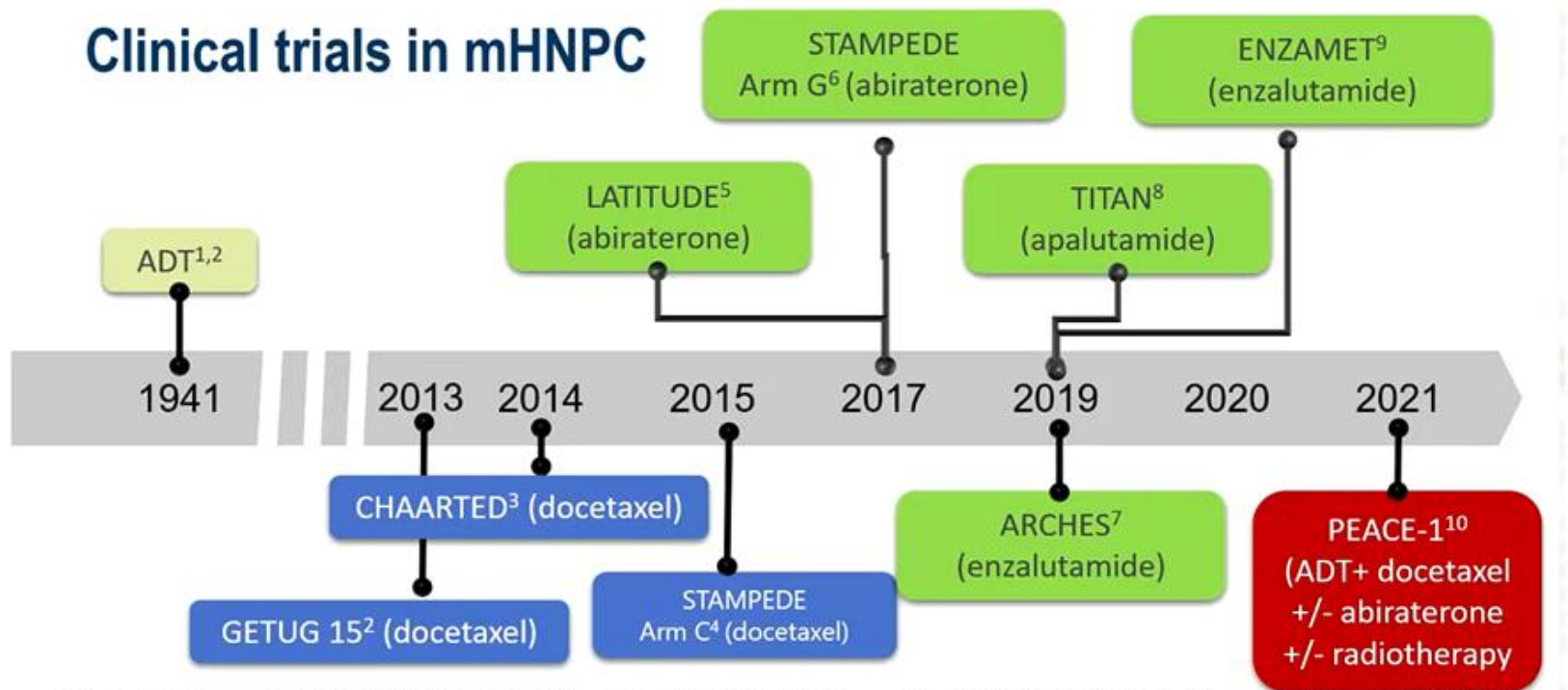
• **PARP inhibitor?**

• **LuPSMA?**

• **AKT inhibitor?**

Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

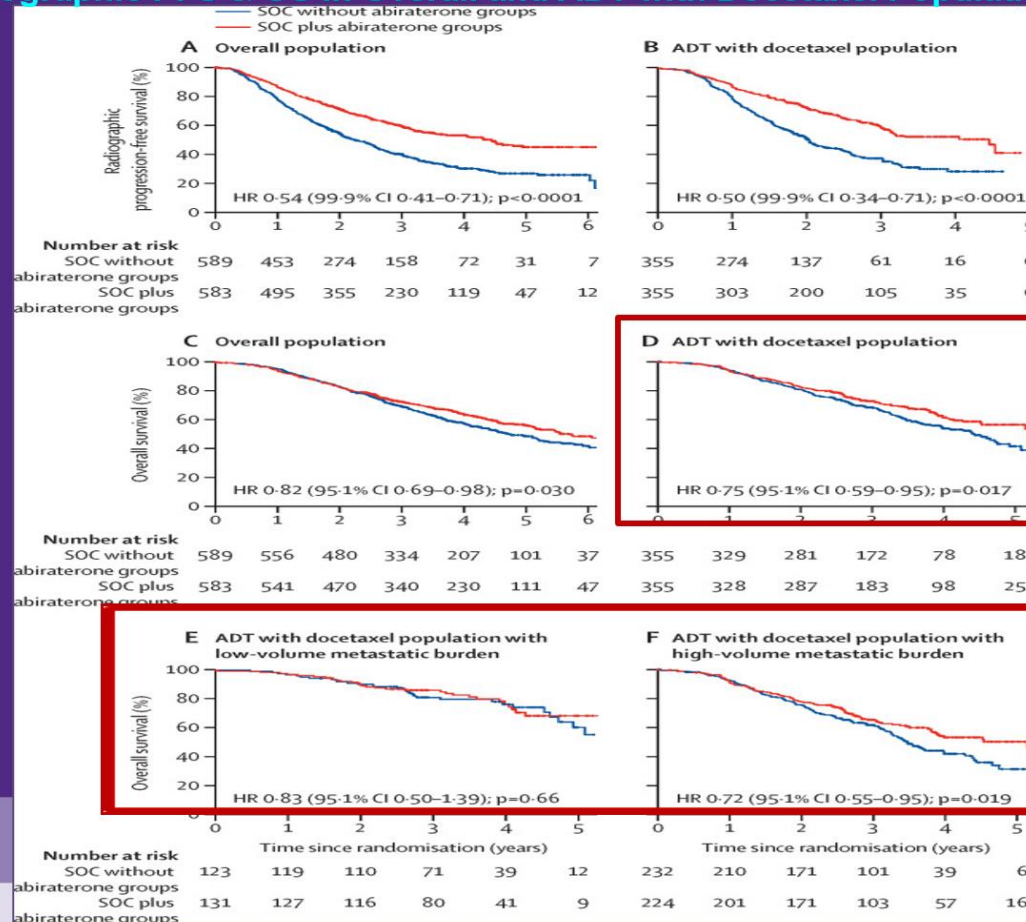
Clinical trials in mHNPc



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



Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

PEACE-1: Adverse Events

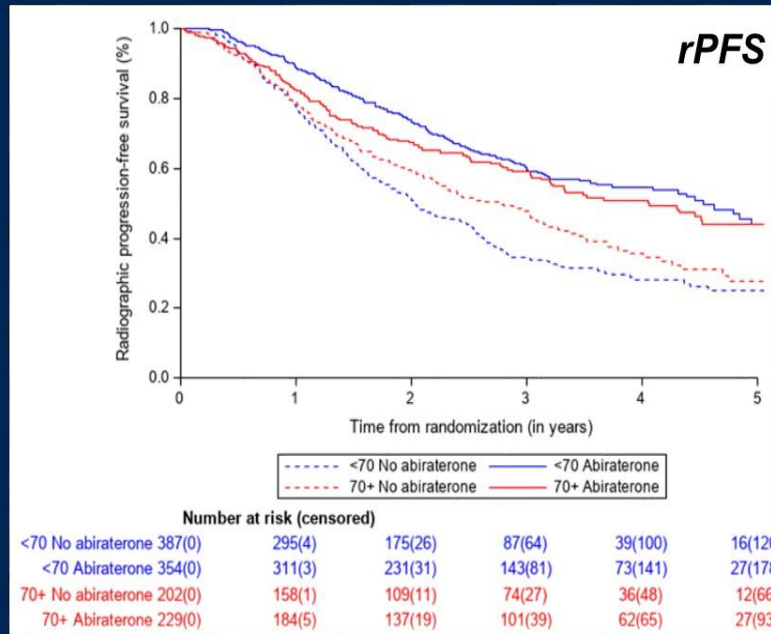
	ADT with Docetaxel		ADT without Docetaxel	
	SOC + Abi (+/- RT)	SOC (+/- RT)	SOC + Abi (+/- RT)	SOC (+/- RT)
Any AE	346 (100%)	349 (100%)	226 (100%)	233 (99%)
Severe (grade >3)	217 (63%)	181 (52%)	149 (66%)	97 (41%)
Fatal (grade 5)	7 (2%)	3 (1%)	8 (4%)	5 (2%)
Frequent severe AEs				
Hypertension	76 (22%)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

Üçlü Kombinasyonda Yaş Sınırlaması

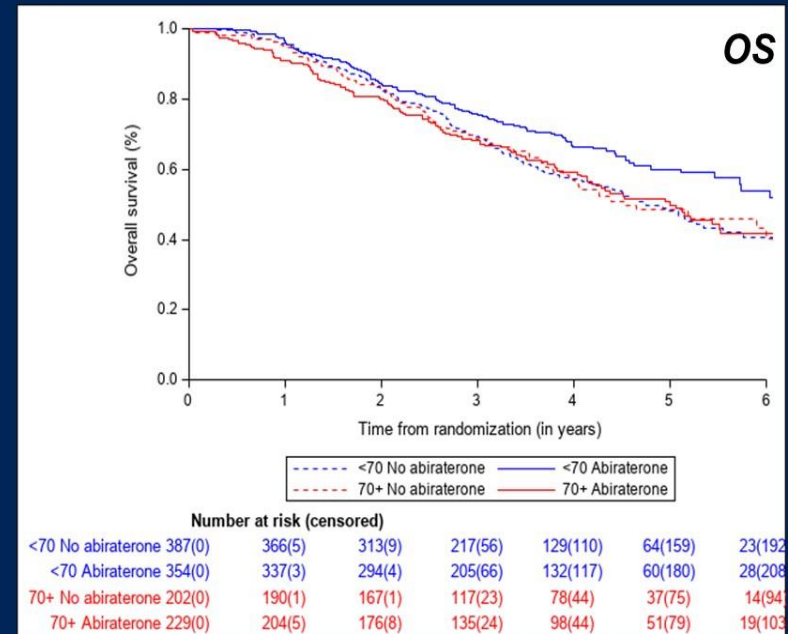
Results (1)

Overall population

6



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

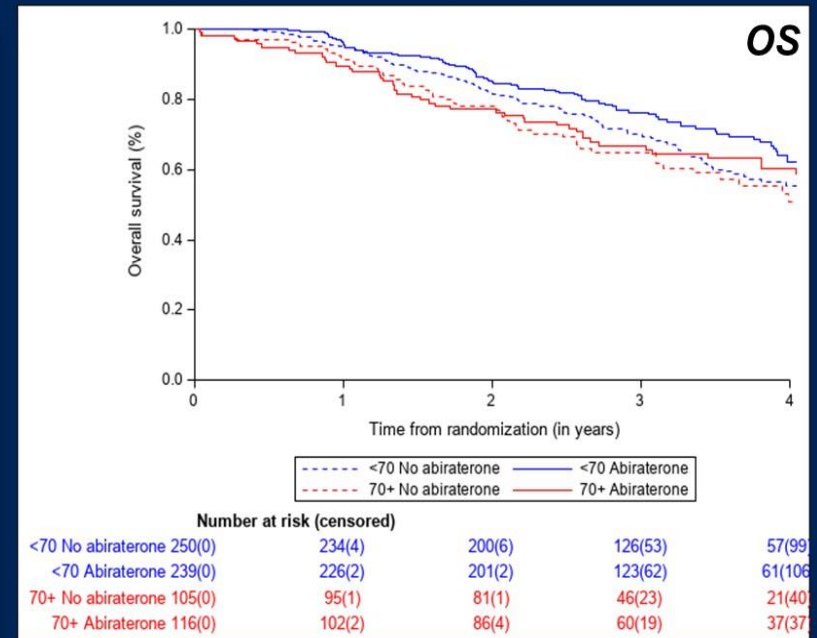
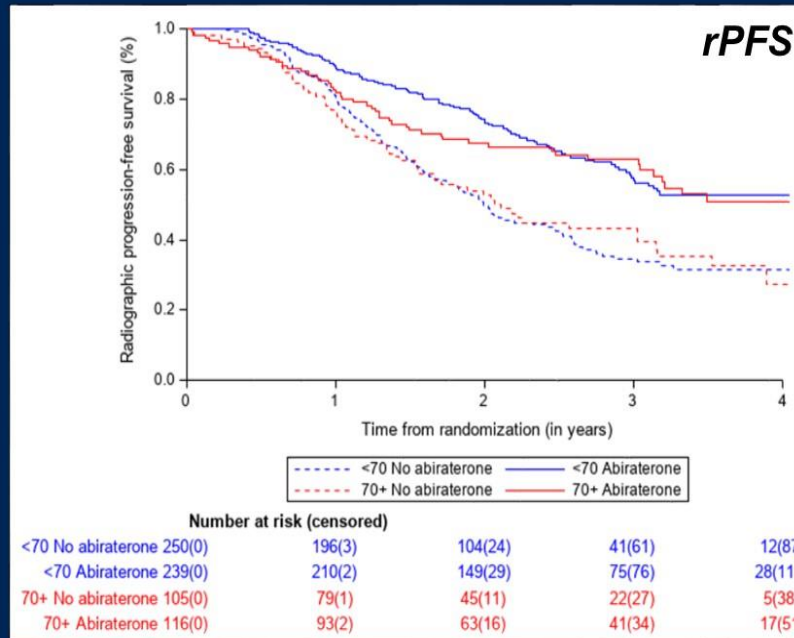
Benefit of AA+P on rPFS and OS may decrease with age

Üçlü Kombinasyonda Yaş Sınırlaması

Results (2)

Docetaxel population

7



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)

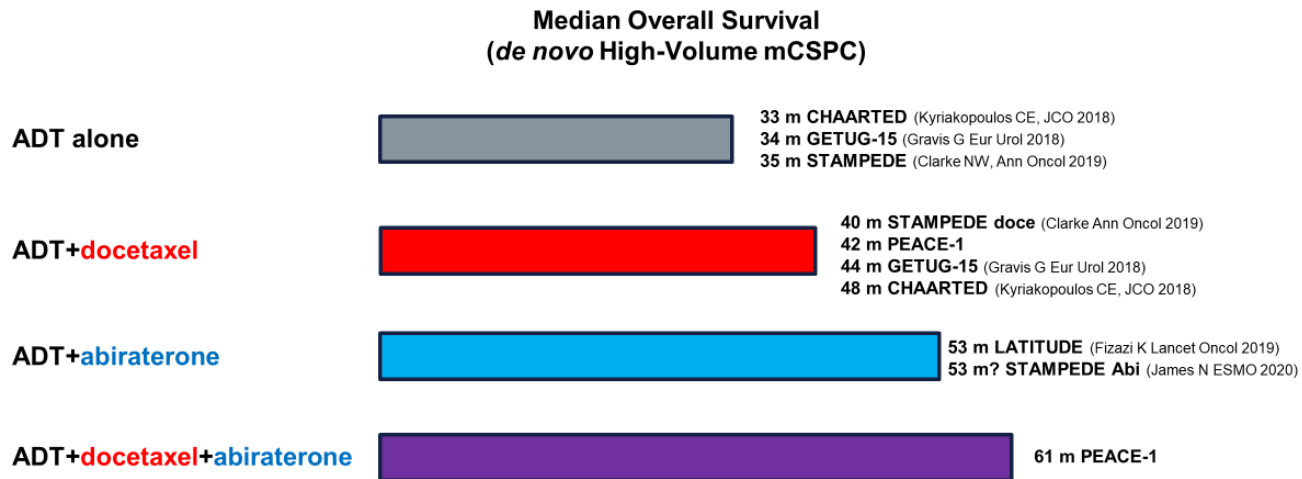
Age < 70 : HR 0.71, 95%CI (0.52-0.95)

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

3

ARASENS Study Design

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

Patients (N=1306)

- mHSPC
- ECOG PS 0 or 1
- Candidates for ADT and docetaxel

Stratification

- Extent of disease: M1a vs M1b vs M1c
- ALP < vs ≥ ULN

1:1
randomization
(N=1305*)

Docetaxel × 6

Darolutamide 600 mg twice daily + ADT

Placebo twice daily + ADT

Docetaxel × 6

FPFV: Nov 2016
LPFV: June 2018

Data cut-off
Oct 25, 2021

Primary analysis

Endpoints

Primary: OS

Secondary

- Time to CRPC
- Time to pain progression
- SSE-free survival
- Time to first SSE
- Time to initiation of subsequent systemic antineoplastic therapy
- Time to worsening of disease-related physical symptoms
- Time to initiation of opioid use for ≥7 consecutive days
- Safety

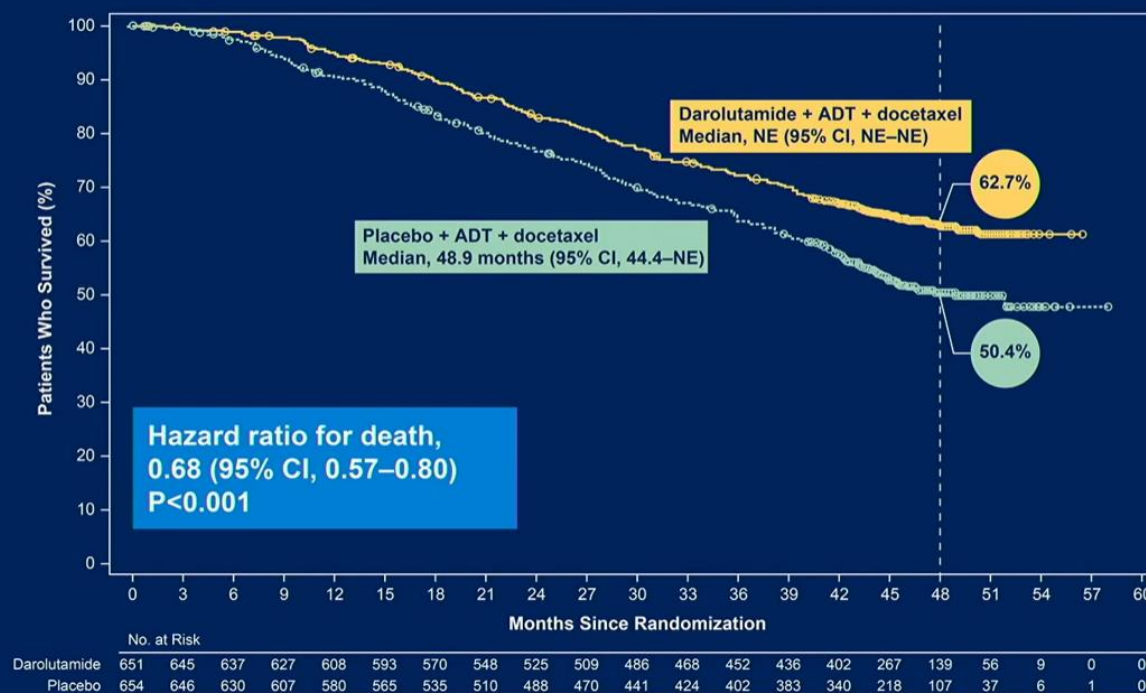
- The primary analysis was planned to occur after ~509 deaths
- Secondary efficacy endpoints were tested hierarchically

*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

5

ARASENS Primary Endpoint*: Overall Survival Darolutamide significantly reduced the risk of death by 32.5%



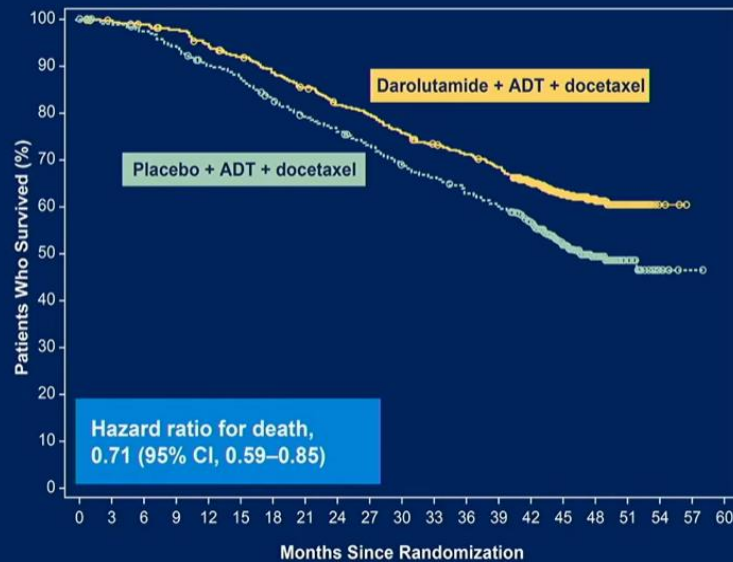
*Primary analysis occurred after 533 deaths (darolutamide, 229; placebo, 304). CI, confidence interval; NE, not estimable.

Kastrasyona Duyarlı Metastatik Prostat Kanseri Üçlü Kombinasyon

8

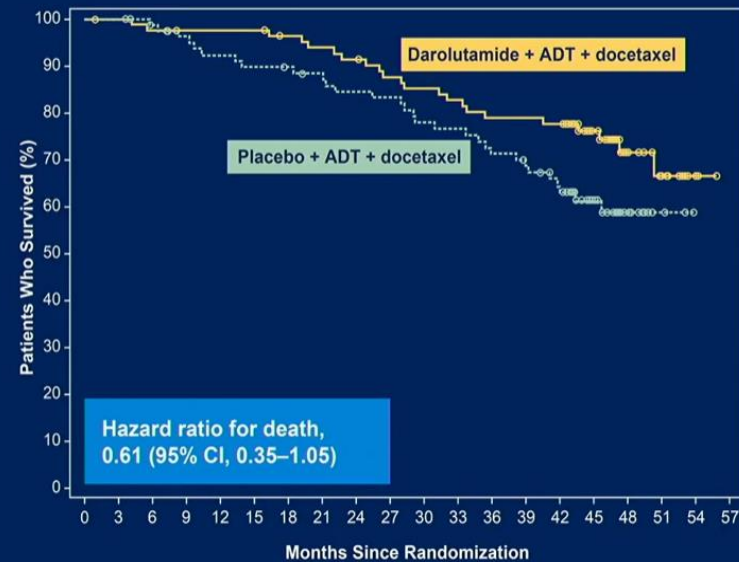
Overall Survival By Metastatic Stage at Initial Diagnosis

De novo metastatic disease



	No. at Risk																				
Darolutamide	558	553	547	539	520	505	485	466	445	433	412	396	383	367	334	220	116	45	7	0	0
Placebo	566	558	546	526	503	490	461	438	420	403	378	362	344	328	292	190	93	33	6	1	0

Recurrent metastatic disease



No. at Risk	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57
Darolutamide	86	85	83	81	81	81	78	76	74	70	68	66	63	63	62	43	20	11	2	0
Placebo	82	82	78	75	72	70	69	67	64	63	59	58	54	51	45	26	12	4	0	0

Kastrasyona Duyarlı Metastatik Prostat Kanseri Üçlü Kombinasyon

13

Adverse Events of Special Interest for AR Pathway Inhibitors

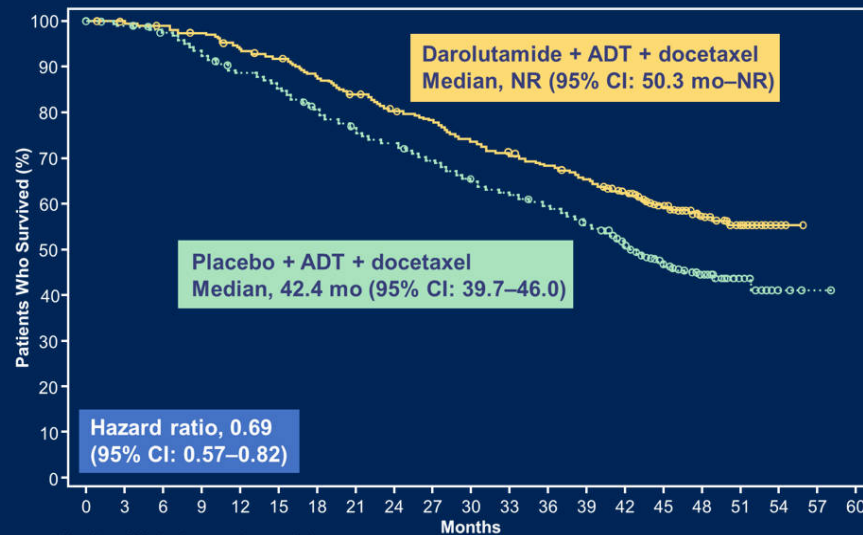
AEs associated with AR pathway inhibitor therapy	Darolutamide + ADT + docetaxel (n=652)		Placebo + ADT + docetaxel (n=650)	
	Patients, n (%)	EAIR/100 PY*	Patients, n (%)	EAIR/100 PY*
Fatigue	216 (33.1)	12.5	214 (32.9)	17.8
Bone fracture	49 (7.5)	2.8	33 (5.1)	2.7
Falls	43 (6.6)	2.5	30 (4.6)	2.5
Rash†	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

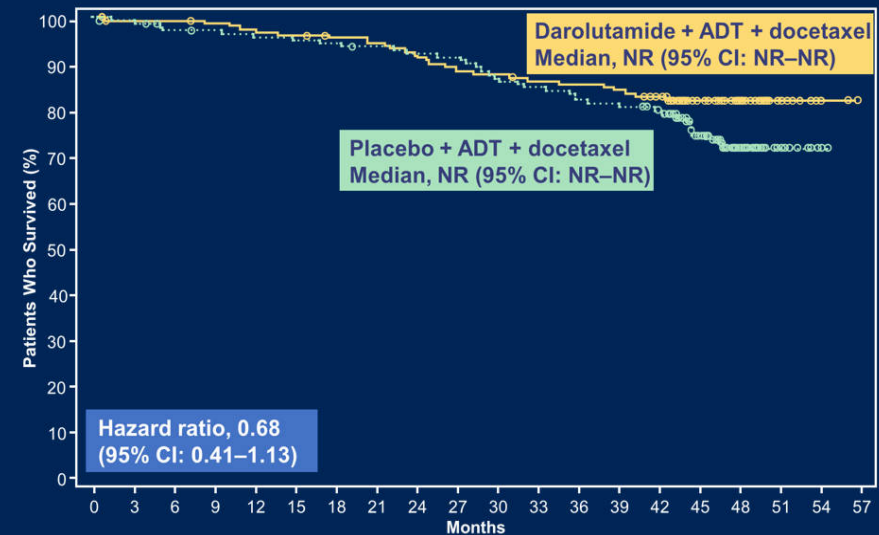
High-volume mHSPC



Number of high-volume patients at risk

Darolutamide	497	494	486	479	462	449	429	408	389	378	356	341	326	312	285	193	103	43	6	0	0
Placebo	508	502	491	469	444	430	401	378	358	341	319	304	286	269	233	153	72	23	4	1	0

Low-volume mHSPC



Number of low-volume patients at risk

Darolutamide	154	151	151	148	146	144	141	140	136	131	130	127	126	124	117	74	36	13	3	0
Placebo	146	144	139	138	136	135	134	132	130	129	122	120	116	114	107	65	35	14	2	0

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

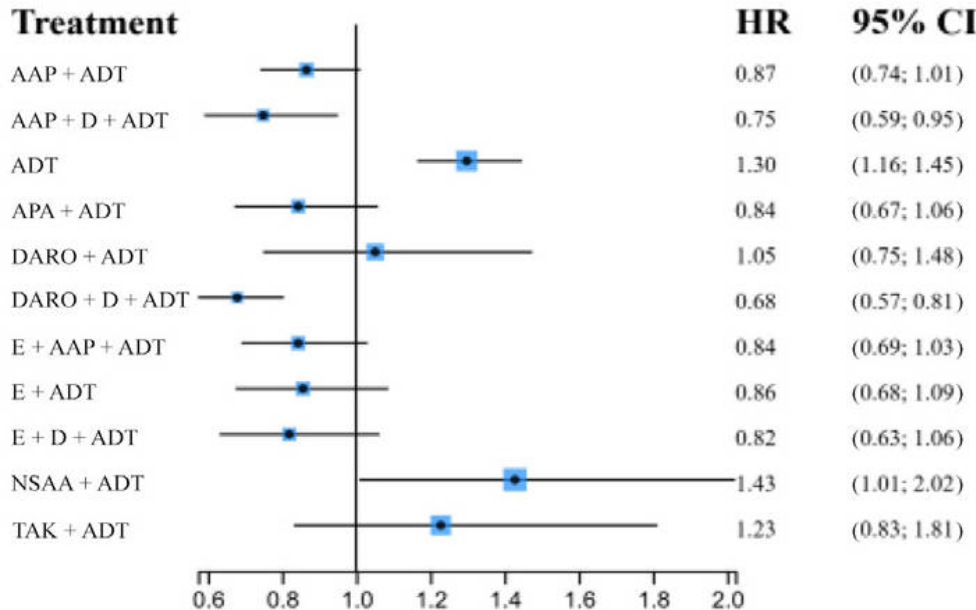
Eur Urol 2025

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 Agarwalⁱ, Axel S. Merseburger^j, Ian D. Davis^{k,l}, Andrew Armstrong^m, Maha H. Hussainⁿ, Matthew Smith^o, Gerhardt Attard^p, Bertrand Tombal^q, Karim Fizazi^r, Nick James^s, Aurelius Omlin^t, Silke Gillesen^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

Comparison vs "D + ADT"

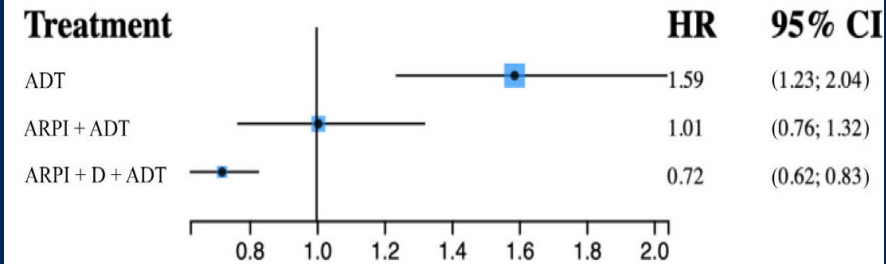
Fixed effect model



Synchronous High Volume

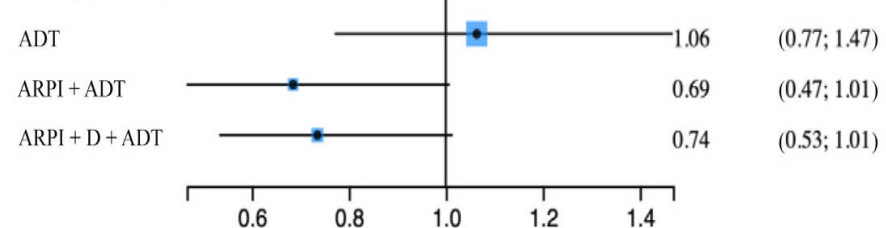
Comparison vs "D + ADT"

Fixed effect model



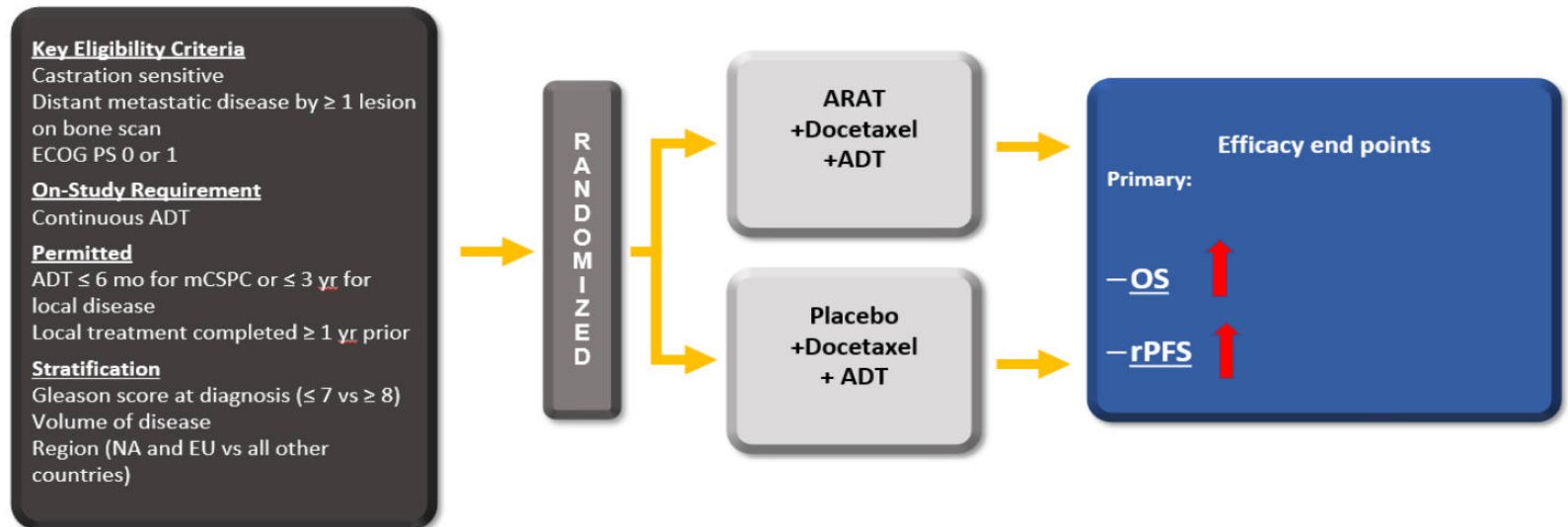
Synchronous Low Volume

Comparison vs "D + ADT"



Evre IV Kastrasyona Duyarlı Prostat Kanseri Üçlü Kombinasyonlar

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

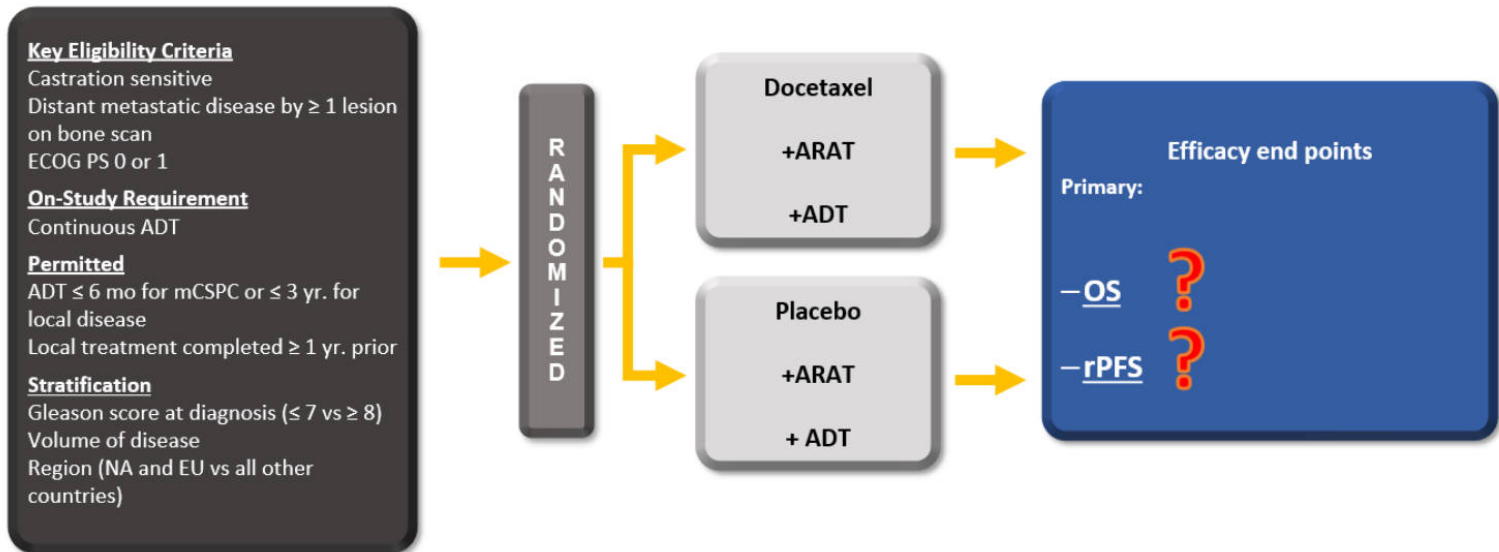


ECOG PS, Eastern Cooperative Oncology Group performance status; ART, Androgen receptor targeted therapy; NA, North America; PSA, prostate-specific antigen; OS, Overall survival; rPFS, radiographic progression-free survival.

Evre IV Kastrasyona Duyarlı Prostat Kanseri Üçlü Kombinasyonlar

This trial has not been done yet:

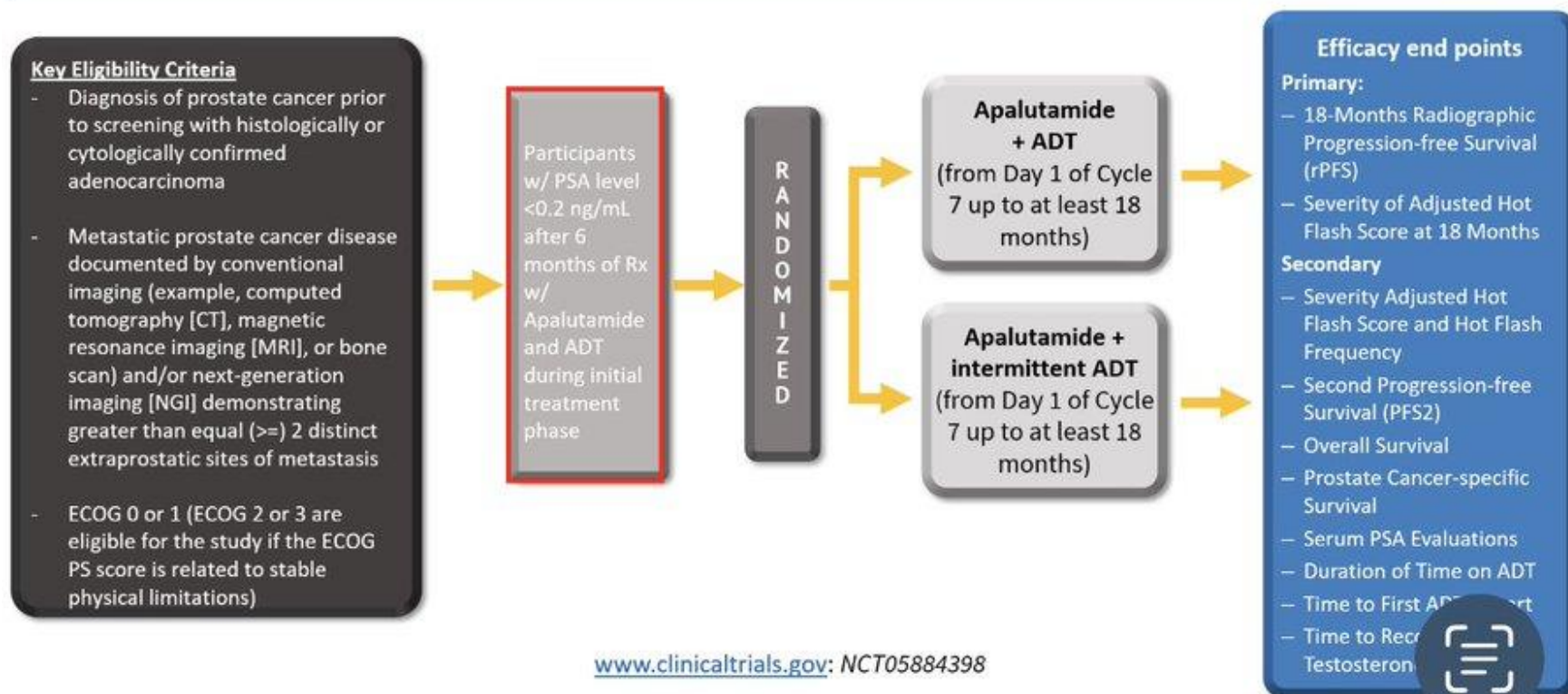
Triplet (Docetaxel + ARAT + ADT) versus ARAT + ADT



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



Prostat kanserinde genomik profil

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

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

PSMA appears to be the most broadly applicable potential biomarker and actionable target in advanced PC¹⁻⁶

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

1. Hope TA, et al. *J Nucl Med.* 2017;58(12):1956–1961; 2. Hupe MC, et al. *Front Oncol.* 2018;8:623; 3. Pomykala KL, et al. *J Nucl Med.* 2020;61(3):405–411; 4. Minner S, et al. *Prostate.* 2011;71(3):281–288; 5. Bostwick DG, et al. *Cancer.* 1998;82(11):2256–2261; 6. Robinson D, et al. *Cell.* 2015;161(5):1215–1228; 7. Abida W, et al. *JAMA Oncol.* 2019; 5(4):471–478; 8. Lindh C, et al. *APMIS.* 2019; 127(8):554–560.
 AKT, protein kinase B; AR, androgen receptor; CDK, cyclin-dependent kinase; PC, prostate cancer; PI3K, phosphoinositide 3-kinase;
 PSMA, prostate-specific membrane antigen; PTEN, phosphatase and tensin homolog; WNT, wingless int-1.

Gelecek Perspektif

Biomarkers in development for mHSPC

A robust biomarker could help determine first-line treatment and identify patients most likely to benefit from **MORE** or **LESS** intensive therapy

Potential Biomarkers

AR

AR alterations uncommon in HSPC. AR-V7 present and associated with response in HRPc but not HSPC. Transcriptional activity in HSPC may be a marker for reduced response to ARPI.

Tumor suppressor genes (*RB1*, *TP53*, *PTEN*, *SPOP*)

All but *SPOP* more common in HRPc than HSPC. Shown to be associated with treatment responses in HRPc but not yet in HSPC.

ctDNA

Fraction of ctDNA correlates with disease burden and outcomes. Initial response in ctDNA fraction may be associated with long term response. Ability to assess genetic alterations using ctDNA relies on high ctDNA fraction and remains to be determined in mHSPC.

HSD3B1

Assessed in the germline. Adrenal permissive allele associated with shorter time to progression to HRPc and shorter OS.

Gene Expression Profiling

Post-hoc analysis demonstrating ability to identify potential responders in both HSPC and HRPc.

- **Low AR transcriptional activity may reflect reduced AR dependence/aggressive disease** (Spratt DE, Clin Can Res 2019)
- **Loss of TP53, PTEN and RB1 are associated with RESISTANCE to AR axis inhibitors** (Zou M, Cancer Disc 2017; Ku SY, Science 2017; Hamid AA, Eur Urol 2019)
- **SPOP mutations are associated with SENSITIVITY to AR axis inhibitors** (Boysen G, Clin Cancer Res, 2018)
- **Primary tissue and ctDNA share relevant somatic alterations, suggesting that both may be useful for molecular subtyping in mHSPC** (Vandekerckhove G et al, Eur Urol 2019)
- **CHAARTED: inheritance of at least 1 copy of the adrenal permissive allele is associated with lower OS in low volume mHSPC** (Hearn JWD et al, JAMA Oncol 2020)
- **CHAARTED (PAM50): Luminal B subtype responded best when DOC was added to ADT** (Hamid AA et al, Ann Onc 2021)

Modified from: Hoffman MR et al, Urology 2021

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	3 rd 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)
PSMAAddition	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

Key eligibility criteria:

- mCSPC^a
- ≥1 HRR gene alteration: *BRCA1*, *BRCA2*, *BRIP1*, *CDK12*, *CHEK2*, *FANCA*, *PALB2*, *RAD51B*, *RAD54L*^b
- ECOG PS 0-2

Key exclusion criteria:

- Any prior
- PARPi
- ARPI other than AAP

Prior allowed treatments in mCSPC:

- ADT ≤6 mo
- Docetaxel (up to 6 cycles)^c
- AAP (up to 45 days)
- Palliative RT

Stratifications:

- *BRCA2* vs *CDK12* vs all other alterations
- Prior docetaxel (yes vs no)
- Disease volume (high vs low)

Randomized
1:1
(N=696)

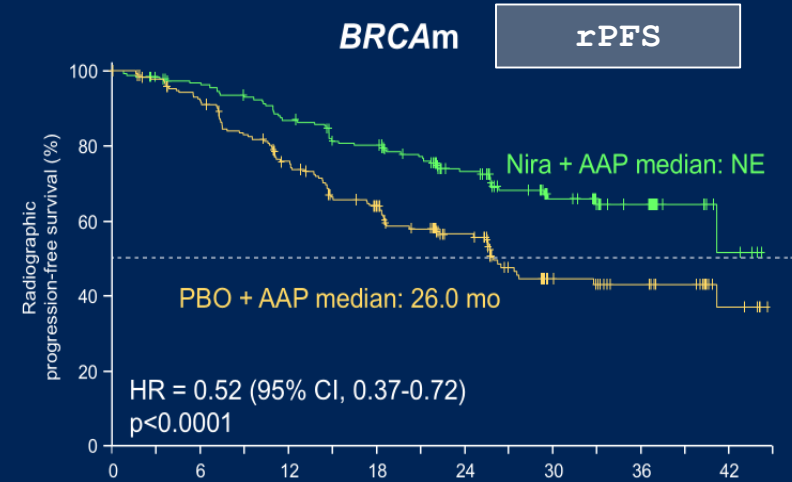
Nira + AAP
(200 mg + 1000 mg QD + 5 mg QD)
+
ADT
(n=348)

PBO + AAP
(200 mg + 1000 mg + 5 mg QD)
+
ADT
(n=348)

AMPLITUDE

Primary end point
• rPFS by investigator

Key secondary end points
• Time to symptomatic progression
• OS
• Safety



%86 senkron

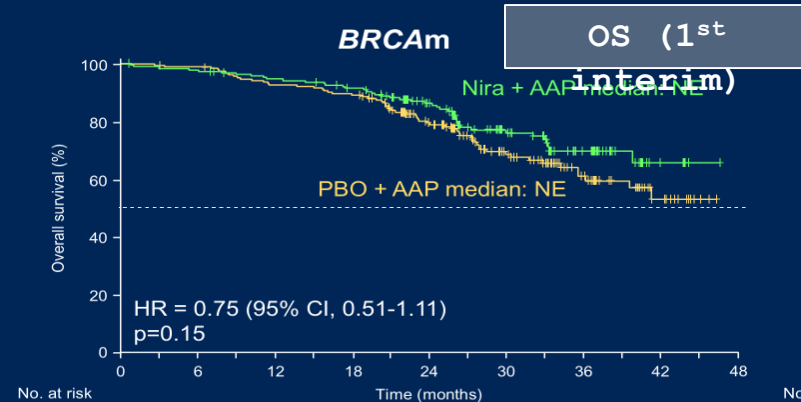
%77 yüksek hacimli

%55 BRCAm

%16 önceden dozetaksel tedavisi görmüş

Primer tümöre radyasyon uygulanmamış

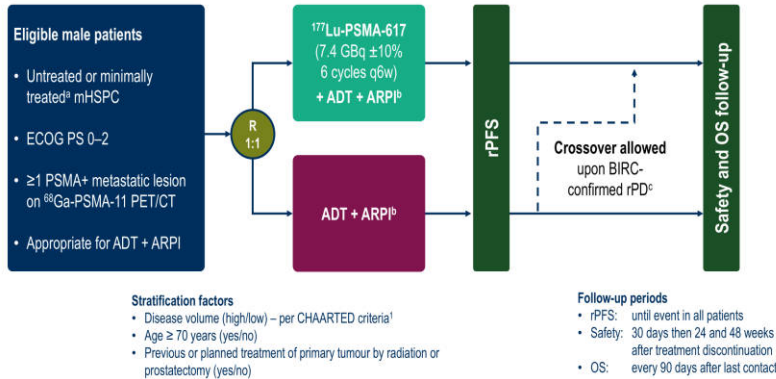
(BRCA dışı HRR'de fayda:



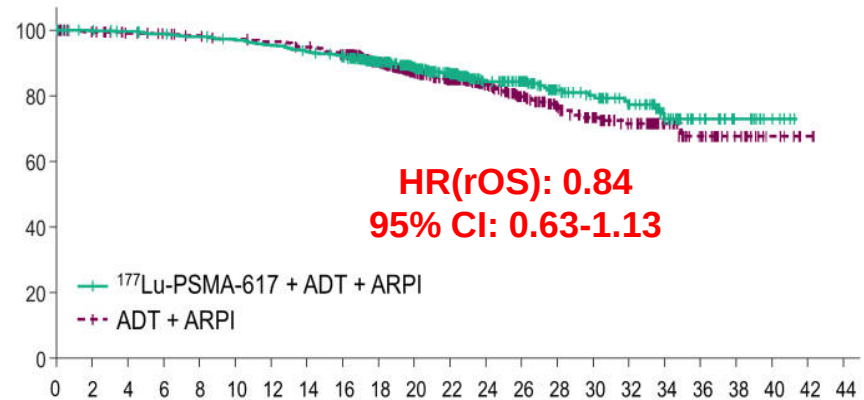
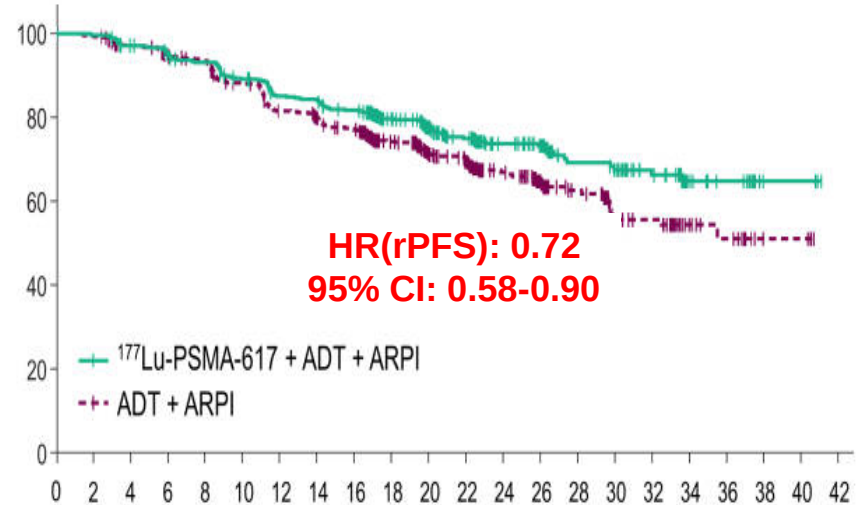
Attard G et al. Nat Med 2025

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

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



^a 545 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

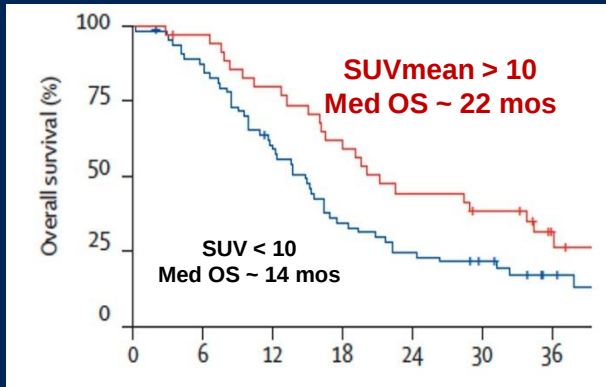


Tagawa S et al ESMO 2025

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

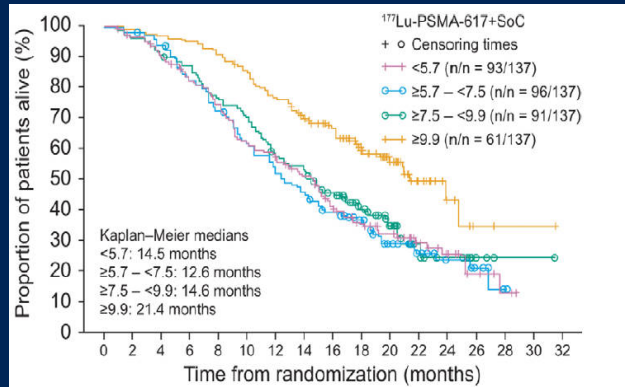
TheraP LuPSMA

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]

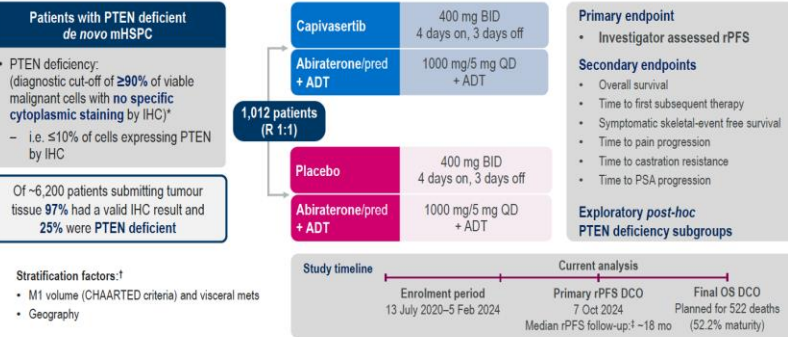
mHSPC'de LuPSMA kullanımına yönelik optimal biyobelirteci tanımlamak gerekiyor.

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

Kastrasyona Duyarlı Metastatik Prostat Kanseri Üçlü Kombinasyon; AKT inhibitörü

CAPitello-281 Study Design

A global, multicentre, randomized, double-blind, Phase 3 study

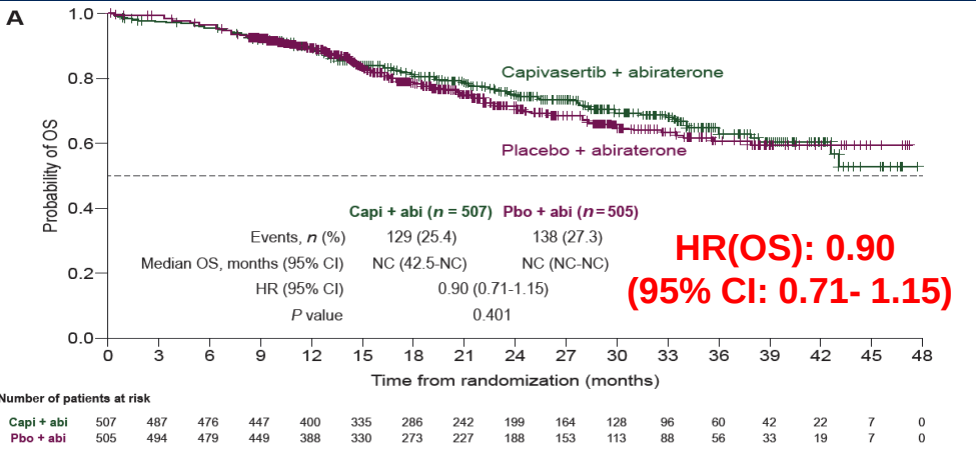
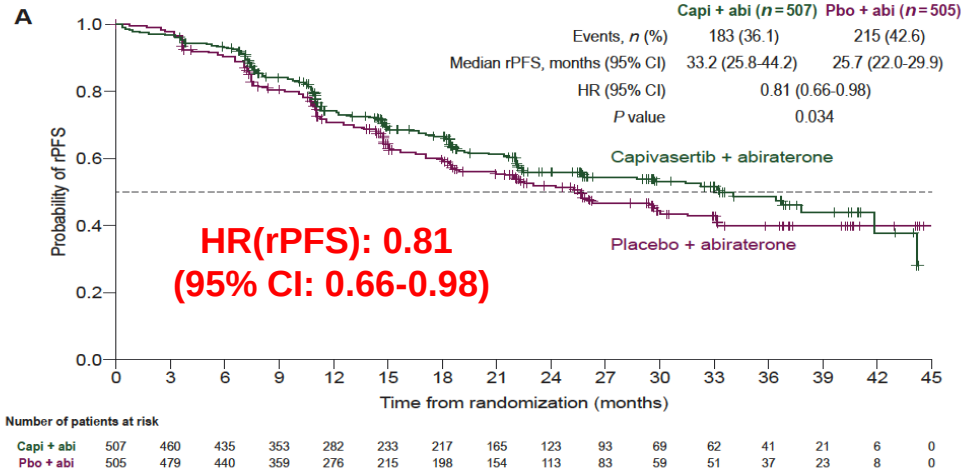


NCT04493853. Full eligibility criteria available in the online article. *Determined using investigational antibody for PTEN (SP218) (Roche Diagnostics). †High-vol. disease with visceral mets, high-vol disease without visceral mets, low-vol disease. North America, Western Europe and Australia, Latin America and Eastern Europe, Asia. ‡Inconsent patients. ADT, androgen deprivation therapy; BID, twice daily; IHC, immunohistochemistry; mHSPC, metastatic hormone-sensitive prostate cancer; pred, prednisone/prednisolone; QD, once daily; rPFS, radiographic progression-free survival.

6566 pts screened

- 1012 $\geq 90\%$ 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?

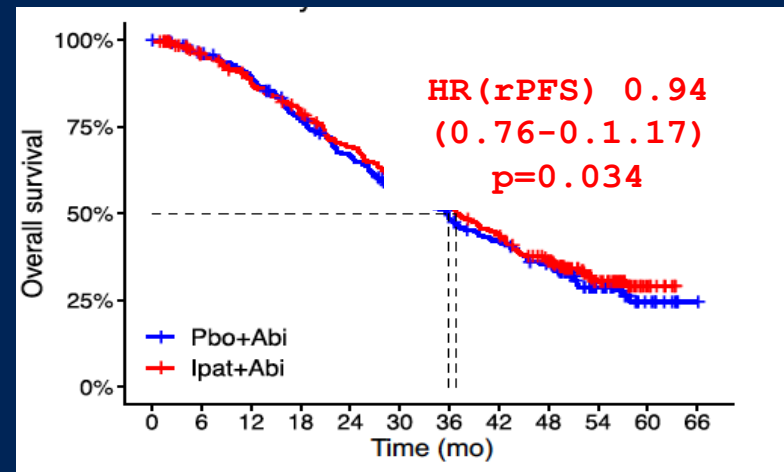
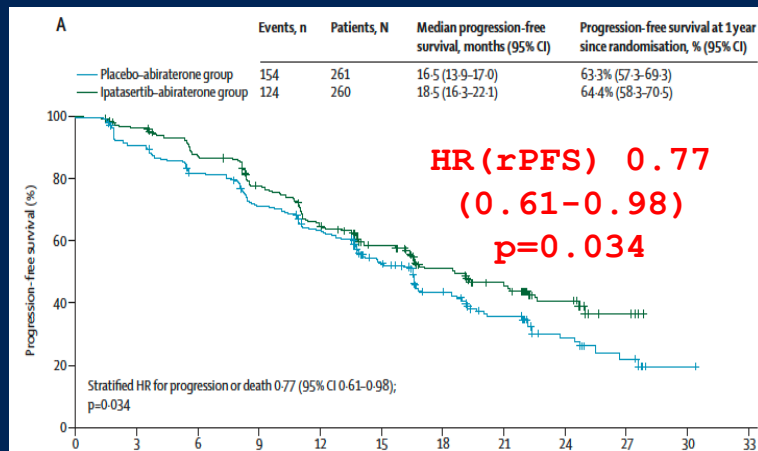


Fizazi et al. Ann Onc 2025

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

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

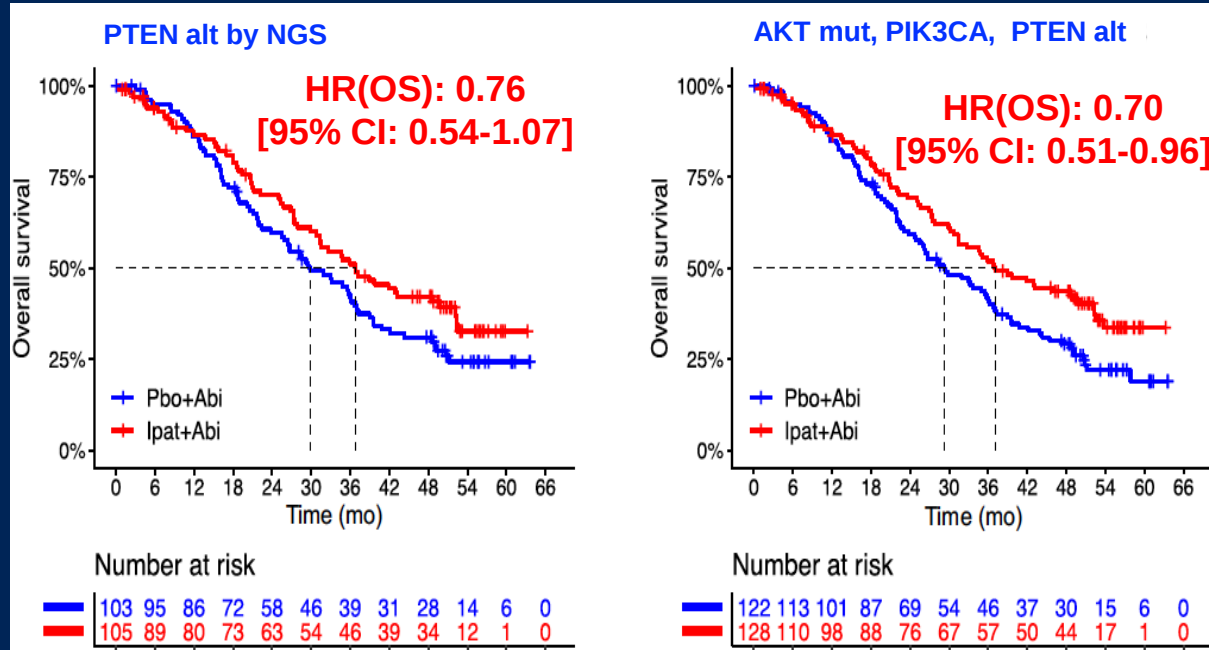
IPATENTIAL 150: Abiraterone +/- Ipatasertib as 1L mCRPC treatment PTEN deficient tumors (IHC cut-off $\geq 50\%$)



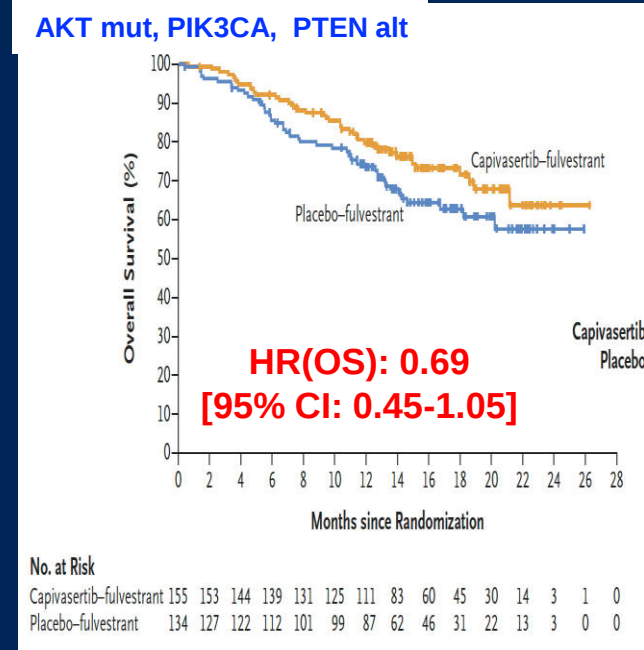
Sweeney et al, Lancet 2021, DeBono et al. : Eur Urol 2024

NGS ve AKT inhibisyonu tedavisi mCRPC ve ER+ Meme kanseri

First line mCRPC: Abi +/- Ipatatertertib (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

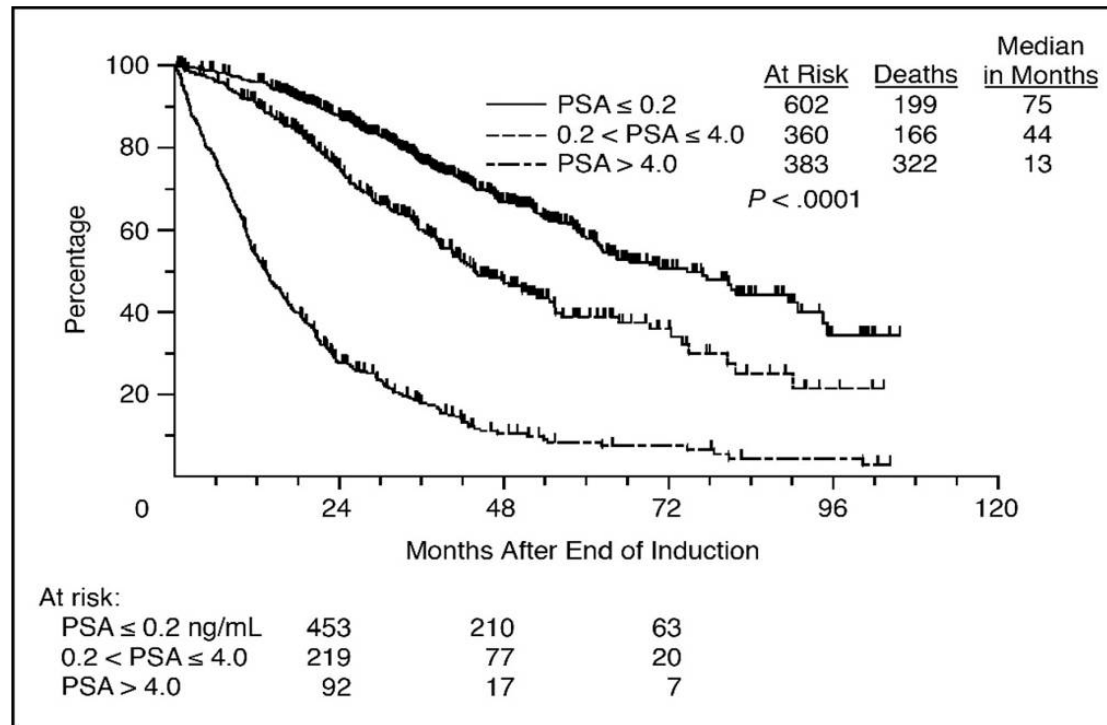
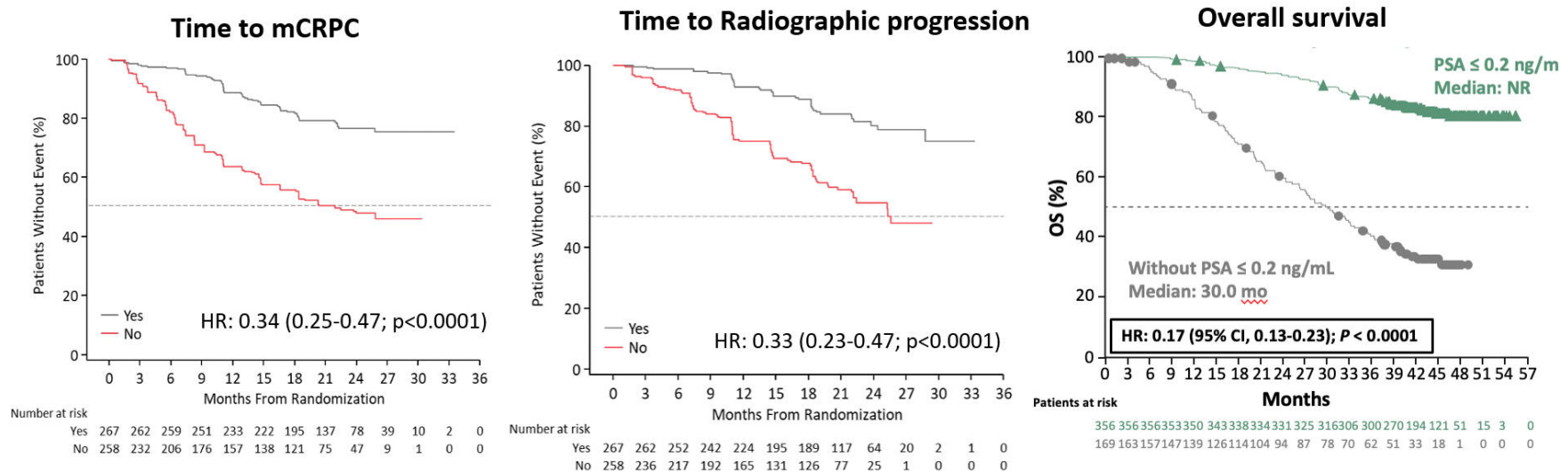


Fig 2. Overall survival by prostate-specific antigen (PSA, ng/mL) status at end of induction
Maha Hussain: Journal of Clinical Oncology 2006; 24 3984-3990.

Kastrasyona Duyarlı Metastatik Prostat Kanseri Nadir PSA Uzun Sağkalımı Gösterir

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



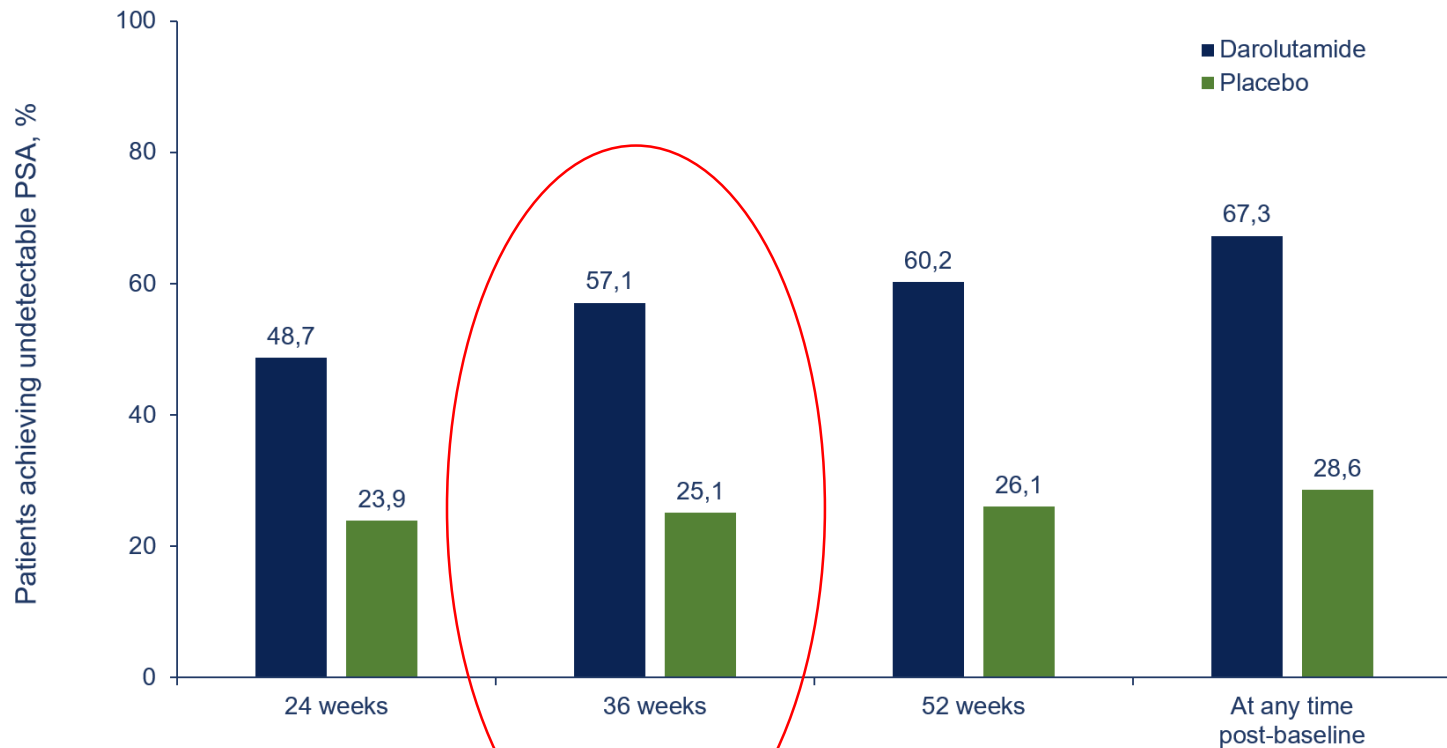
Data from the TITAN study: Chi K et al. *N Engl J Med.* 2019 Jul 4;381(1):13-24.

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



Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

Objective: Undetectable (≤ 0.2) PSA Levels



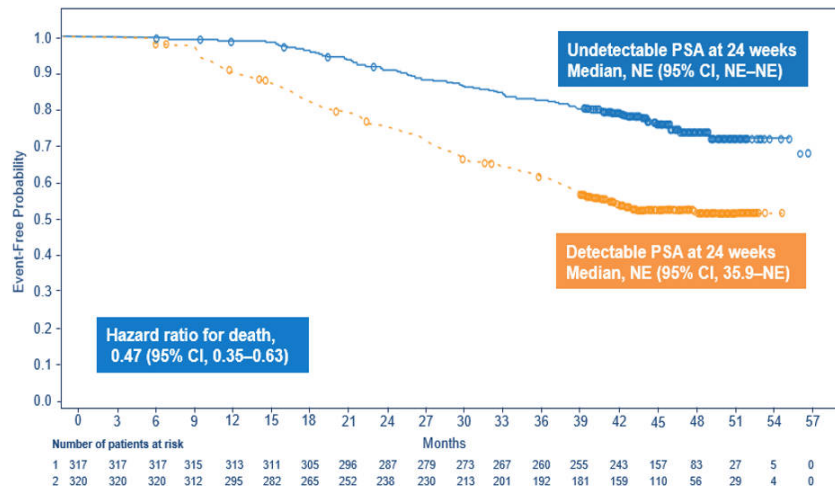
Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

Results: Overall Survival

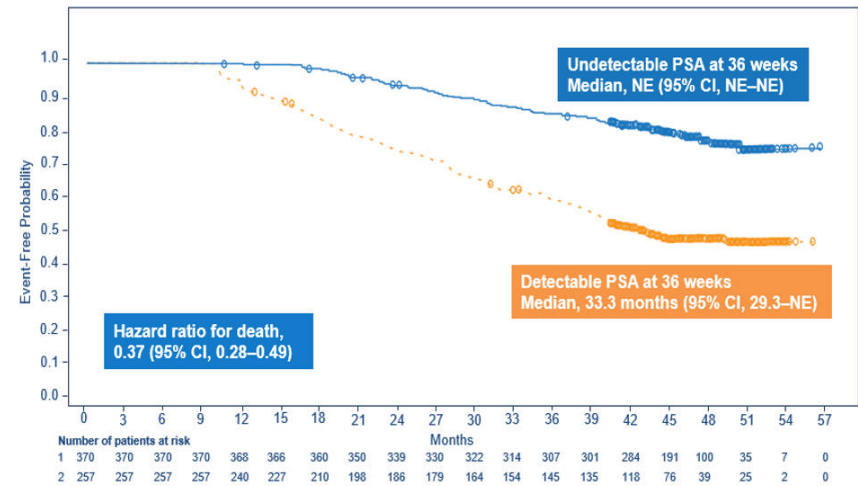
Undetectable PSA at 24 and 36 weeks was associated with a 53% and 63% reduction in the risk of death

Darolutamide + ADT + docetaxel

Undetectable vs detectable PSA at 24 weeks

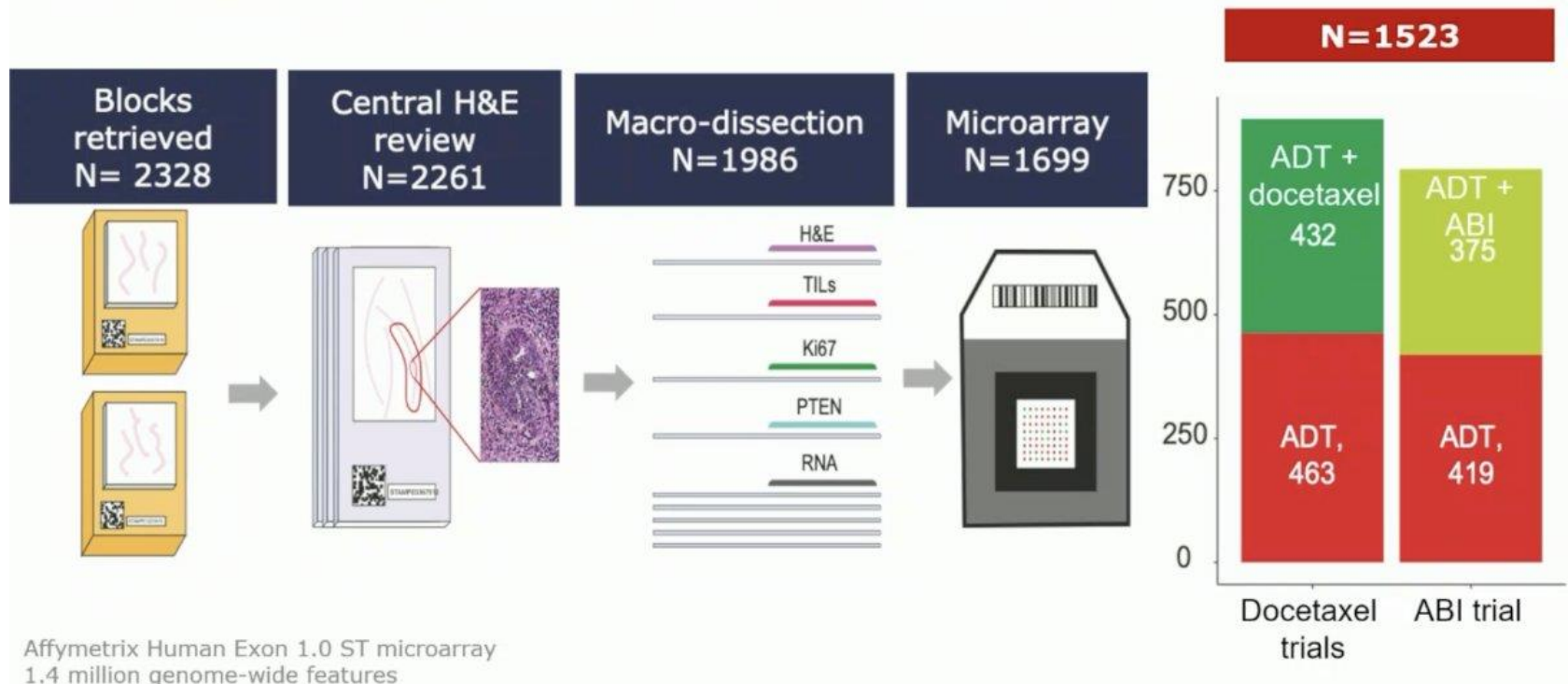


Undetectable vs detectable PSA at 36 weeks

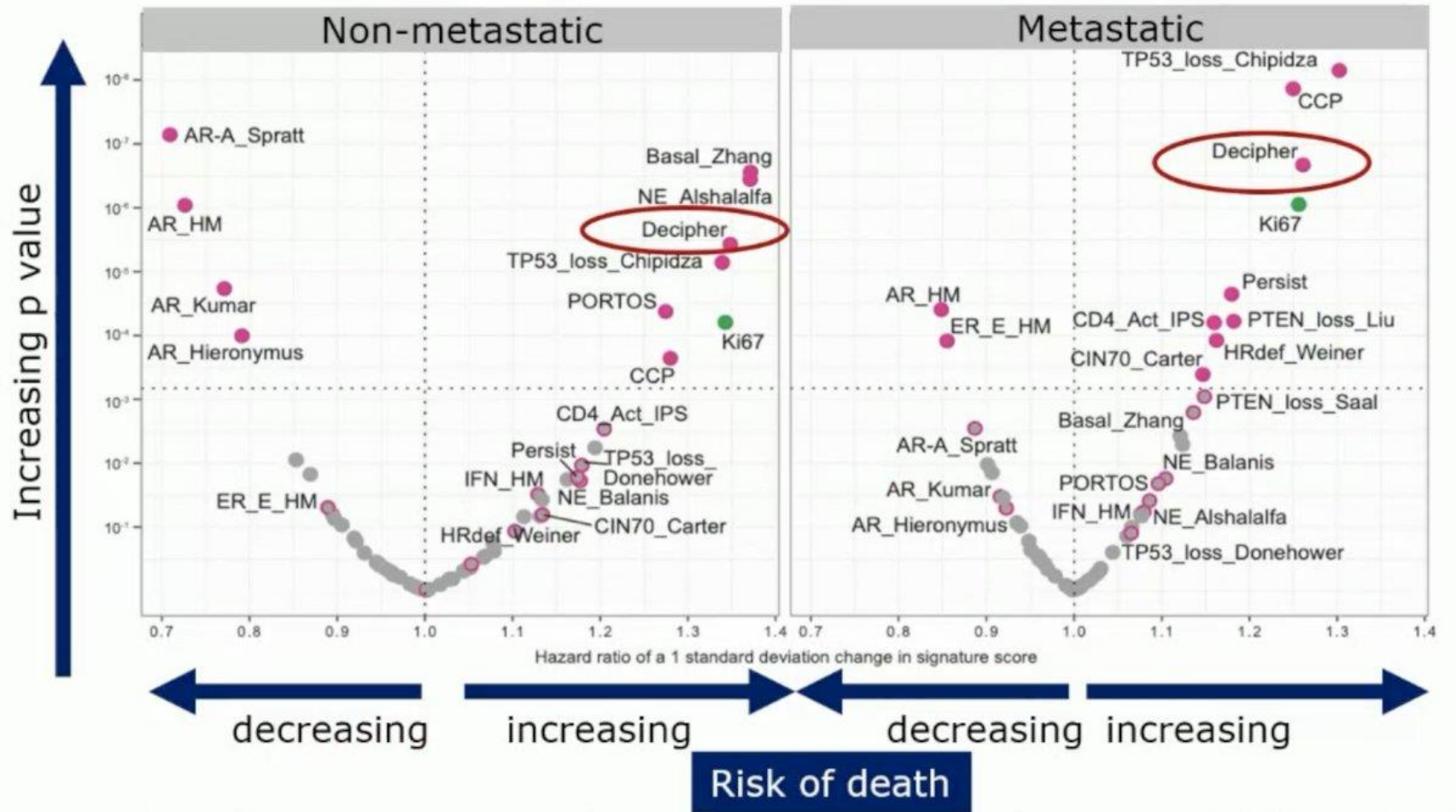


Gelecek Perspektif; klinik bulgulara gen ve genomik verilerin eklenmesi

Linking of clinical and multi-omic data

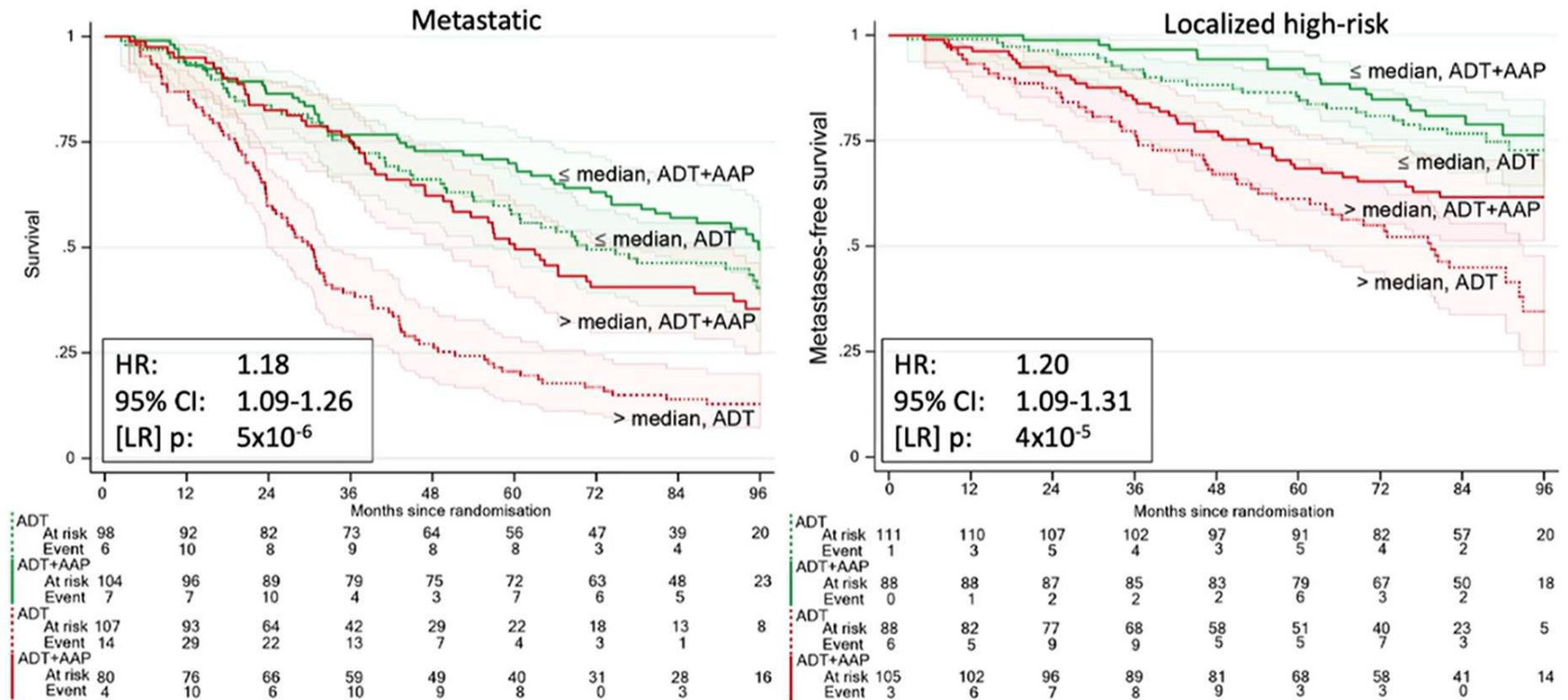


Gelecek Perspektif; klinik bulgulara gen ve genomik verilerin eklenmesi



Gelecek Perspektif; klinik bulgulara gen ve genomik verilerin eklenmesi

Decipher Signature is Strongly Prognostic Across Disease States

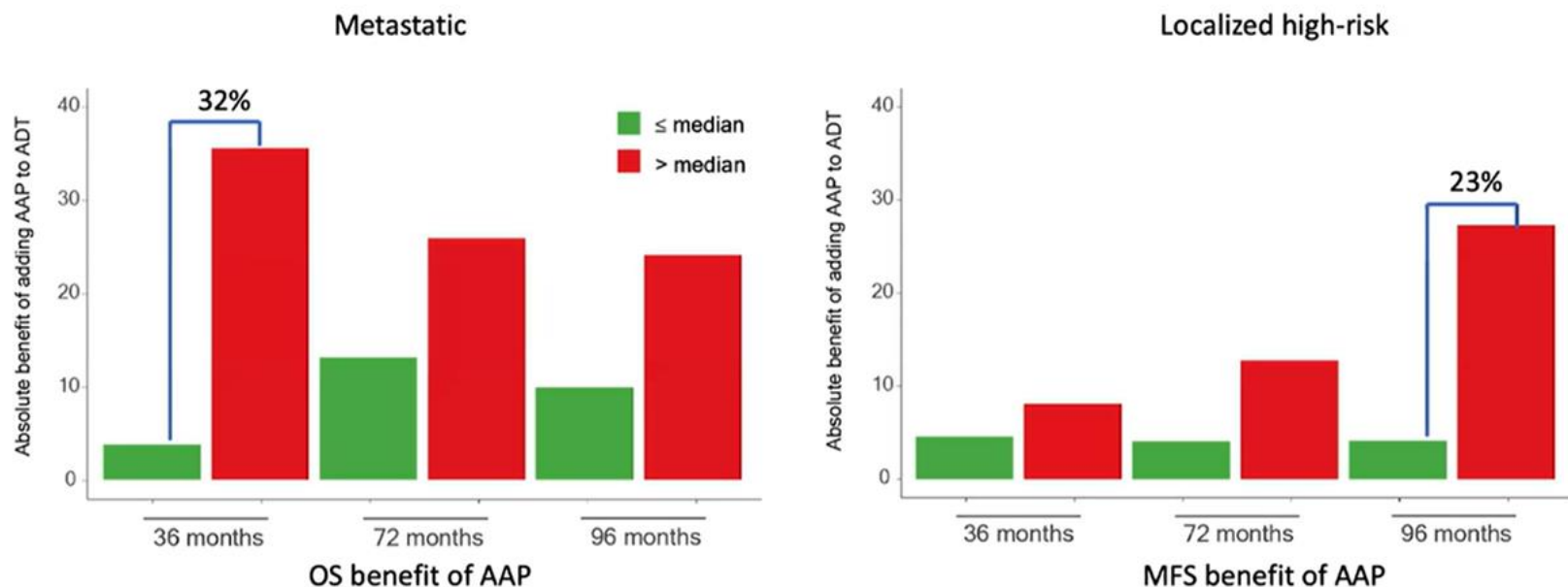


Marina Parry, et al. Clinical qualification of transcriptome signatures for advanced prostate cancer (APC) starting androgen deprivation therapy (ADT) with or without abiraterone acetate and prednisolone (AAP): An ancillary study of the STAMPEDE AAP trial. ESMO, 9-13 September 2022; Paris, France.
Marina 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

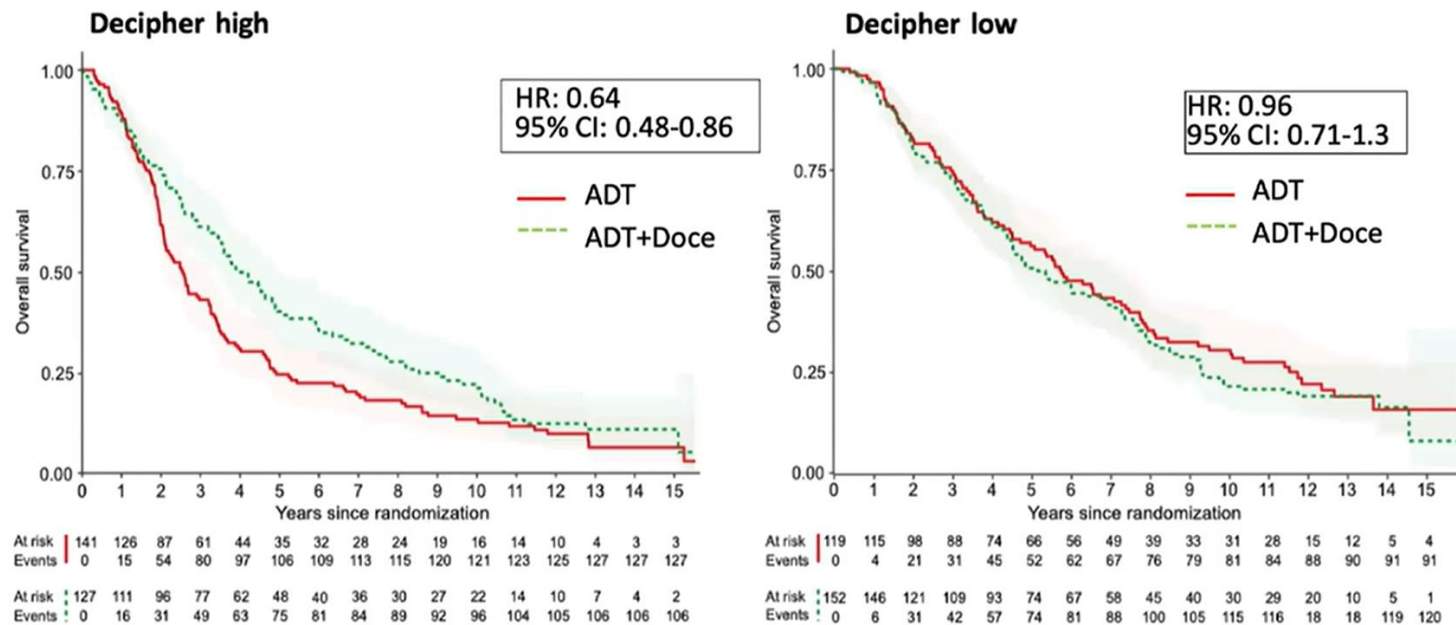
Emily Grist, Peter Dutey-Magni, Larissa Mendes, Marina A. Parry, Ashwin Sachdeva, James Proudfoot, Anis A. Hamid, Claire L. Amos, William R. Cross, Silke Gillesen, Daniel M. Berney, Matthew R. Sydes, Mahesh K.B. Parmar, Felix Y. Feng, Noel W. Clarke, Elai Davicioni, Christopher J. Sweeney, Nicholas D. 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

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

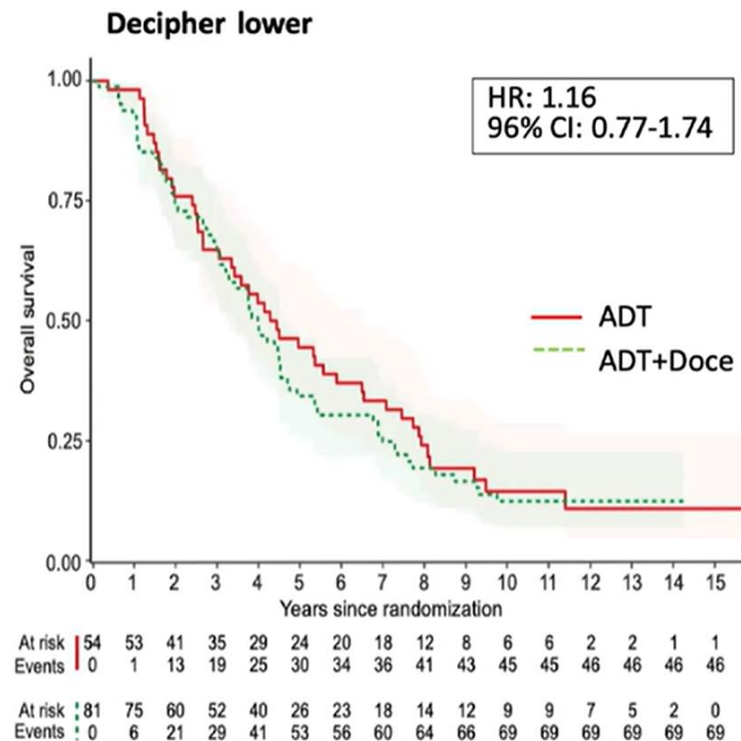
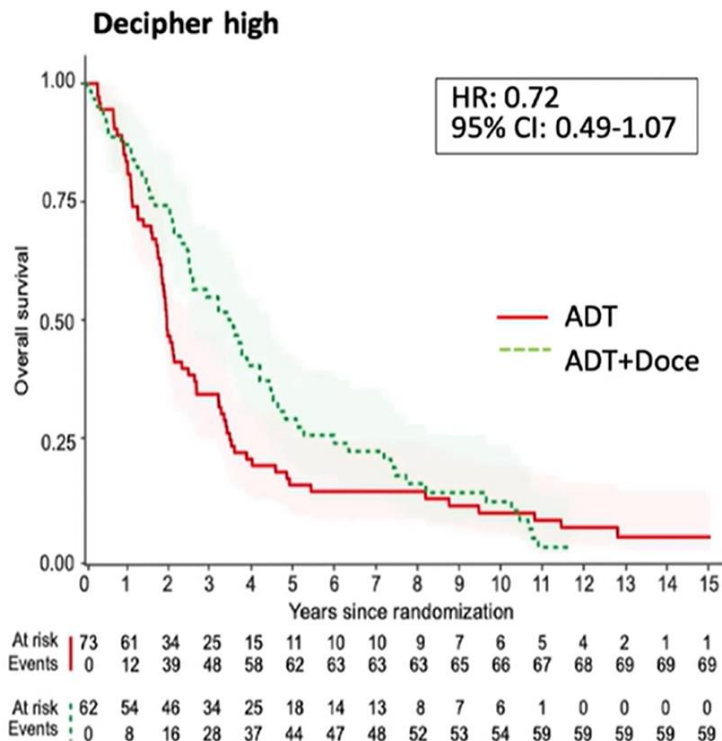
Biomarker-treatment interaction effect p value= 0.039*

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

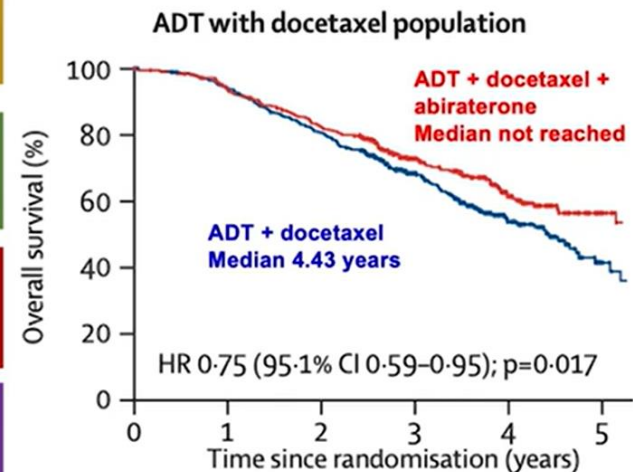
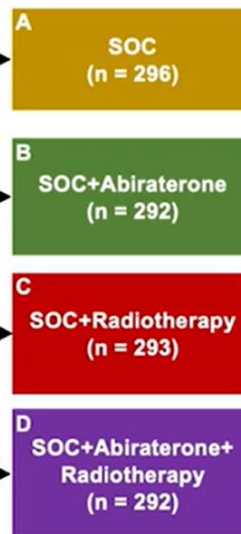
- ADT ≤ 3 months

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

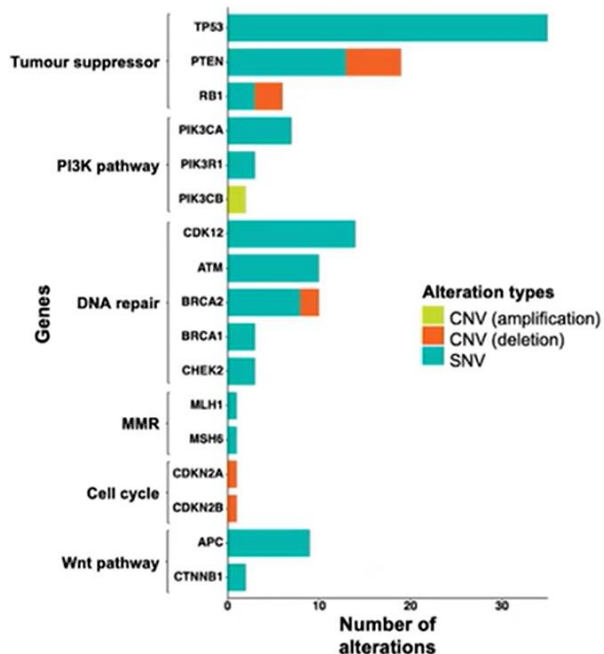


Hypothesis for ancillary study: aggressive/neuroendocrine-like variants could be detected at diagnosis and are associated with prognosis

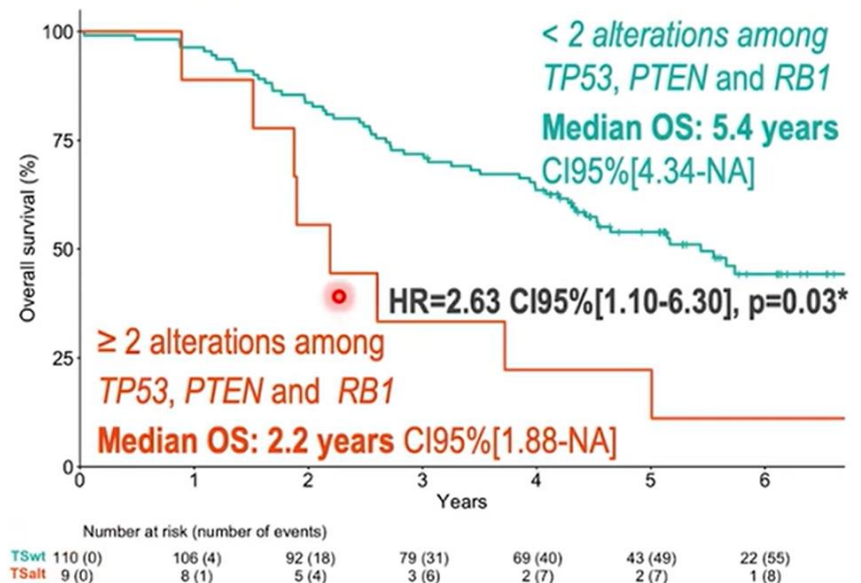
Gelecek Perspektif; klinik bulgulara gen ve genomik verilerin eklenmesi

Genomic analysis

- NGS contributive among 119 patients



- Multiple tumour suppressor gene alterations¹ are associated with worse prognosis:



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

Metastatik Kastrasyona Duyarlı Prostat Kanseri Tedavi



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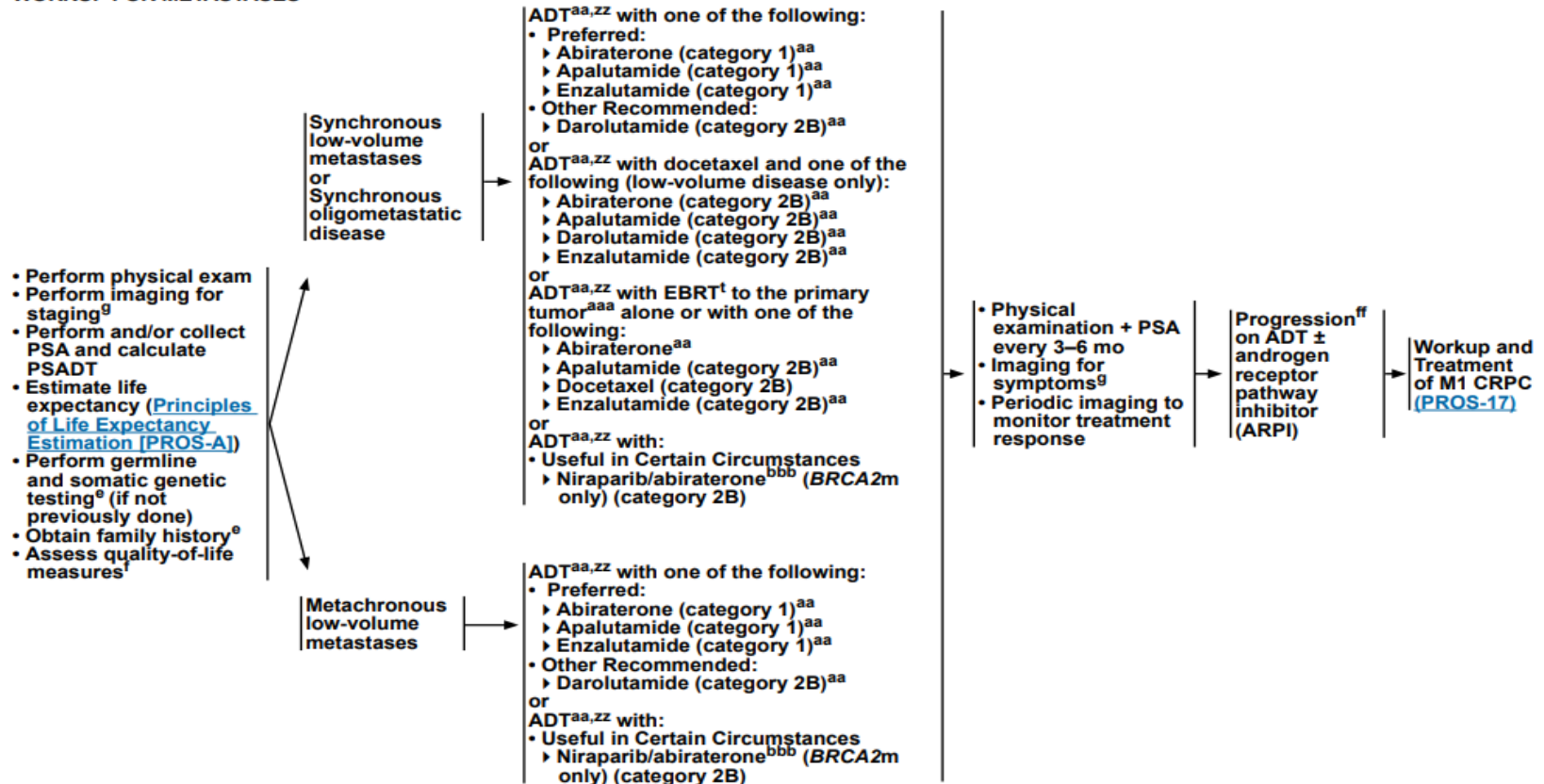
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WORKUP AND TREATMENT OF LOW-VOLUME M1 (METACHRONOUS OR SYNCHRONOUS) OR SYNCHRONOUS OLIGOMETASTATIC CSPC^{c,h,tt,uu,vv,ww}

WORKUP FOR METASTASES^{xx}



Metastatik Kastrasyona Duyarlı Prostat Kanseri Tedavi



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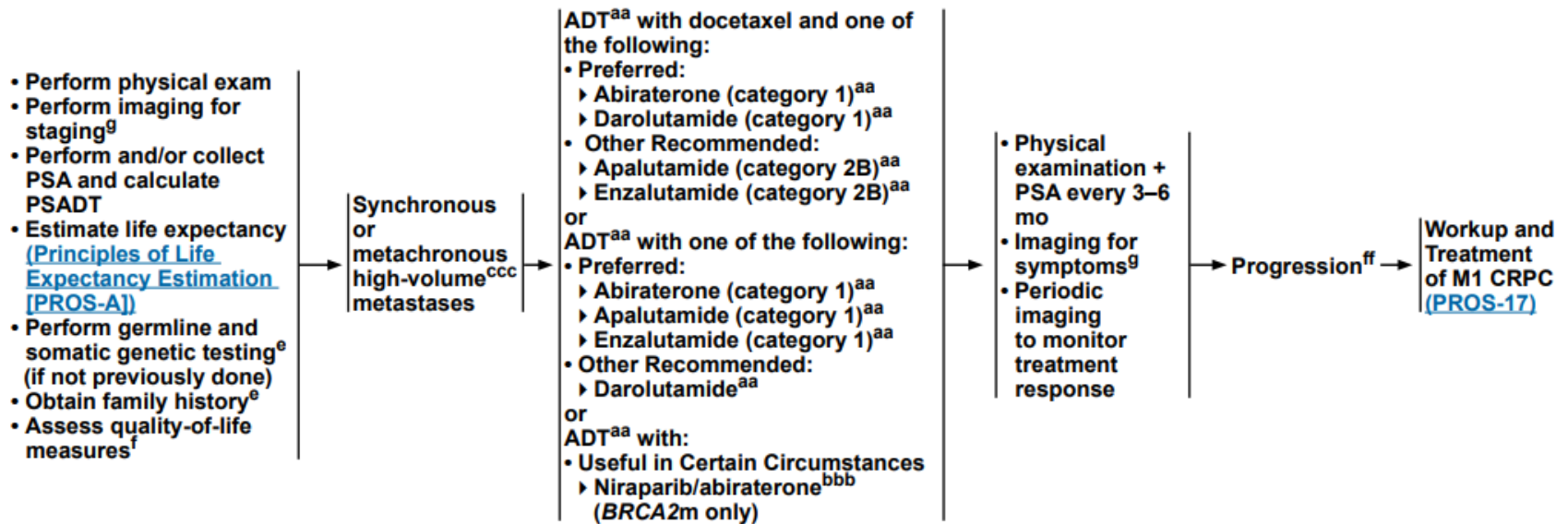
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WORKUP AND TREATMENT OF HIGH-VOLUME M1 CSPC^{c,tt,uu,vv,ww,ccc}

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 profillemeye tedavi seçiminde etkili olacak.

☐ Gelecek dönem PSA yanıtına göre tedavi yoğunluğunda azaltma ya da yoğunluğunu artırma bir seçenek olabilir