

Kanseri Kastrasyona Duyarlı Metastatik Prostat Kanserinde Yoęun Tedavi

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Tıbbi Onkoloji**

Ders Planı

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

Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

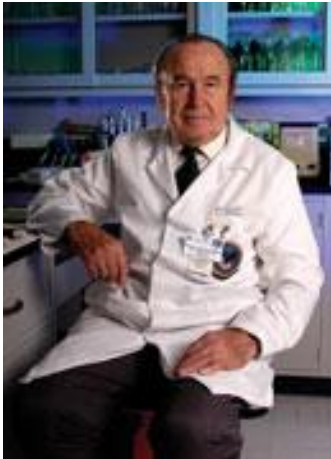
Androjen Baskılama Tedavisi(ADT)

- ☐ Cerrahi Kastrasyon(Bilateral orşektomi)
- ☐ Medikal Kastrasyon
 - ✓ LHRH analogları, LHRH antagonistler
 - ✓ Total androjen blokajı(Antiandrojenlerin eklenmesi)
- ☐ Uygulama seçenekleri
 - ✓ Continue androjen baskılanması
 - ✓ İntermittan androjen baskılanması

Kastrasyona Duyarlı Metastatik Prostat Kanseri ADT Tedavisi

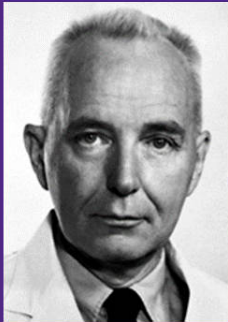


- Charles Brenton Huggins(1901-1997)
- 1927'de Chicago Üniversitesinde Üroloji kliniğinde akademik kadro aldı
- Köpeklerde yaptığı deneylerle, prostat hücrelerinin büyümesinde testosteron hormonuna bağımlı olduğunu tespit etti
- Prostat kanseri olanlarda orşektomi ile tümörün küçüldüğünü belirledi.
-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

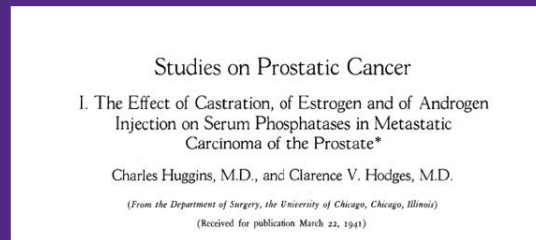


Kastrasyona Duyarlı Metastatik Prostat Kanseri ADT Tedavisi

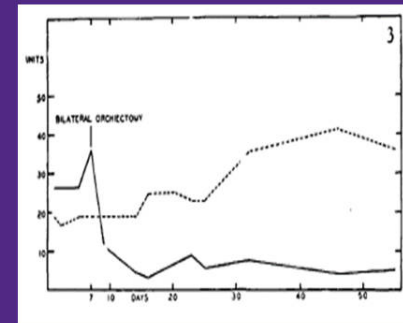
Historical Perspective: Androgens & Prostate Cancer



C. Huggins
1966 Nobel Prize

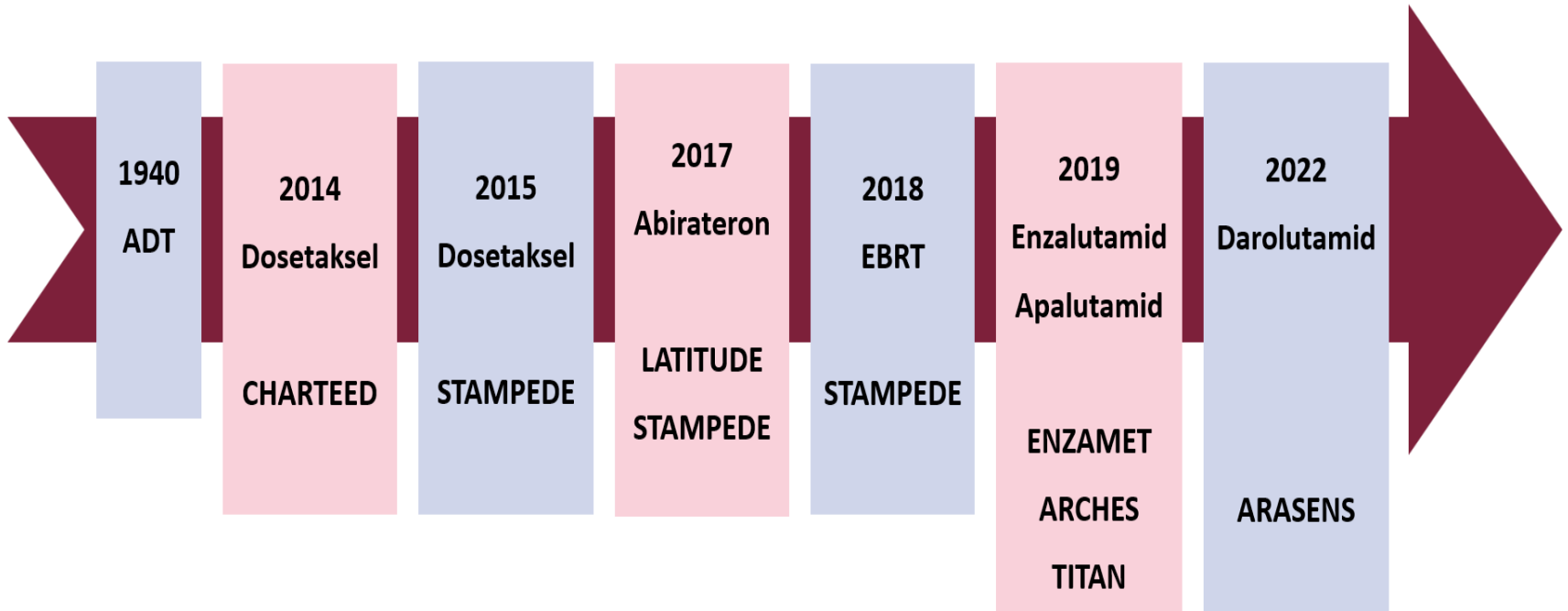


Cancer Res 1941;1:293-297



- **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.

Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavi Tarihçesi



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

Tedavi kararında etkili faktörler

Clinical Factors to Consider

Abiraterone



- ☐ Hypertension
- ☐ Edema
- ☐ Hypokalemia
- ☐ Liver dysfunction
- ☐ Concurrent prednisone

Docetaxel



- ☐ Performance status
- ☐ Fatigue
- ☐ Edema
- ☐ Peripheral neuropathy
- ☐ Cytopenias
- ☐ Hair loss

AR Antagonists



- ☐ Fatigue/Falls
- ☐ Rash
- ☐ Hypothyroidism
- ☐ Drug-Drug Interactions

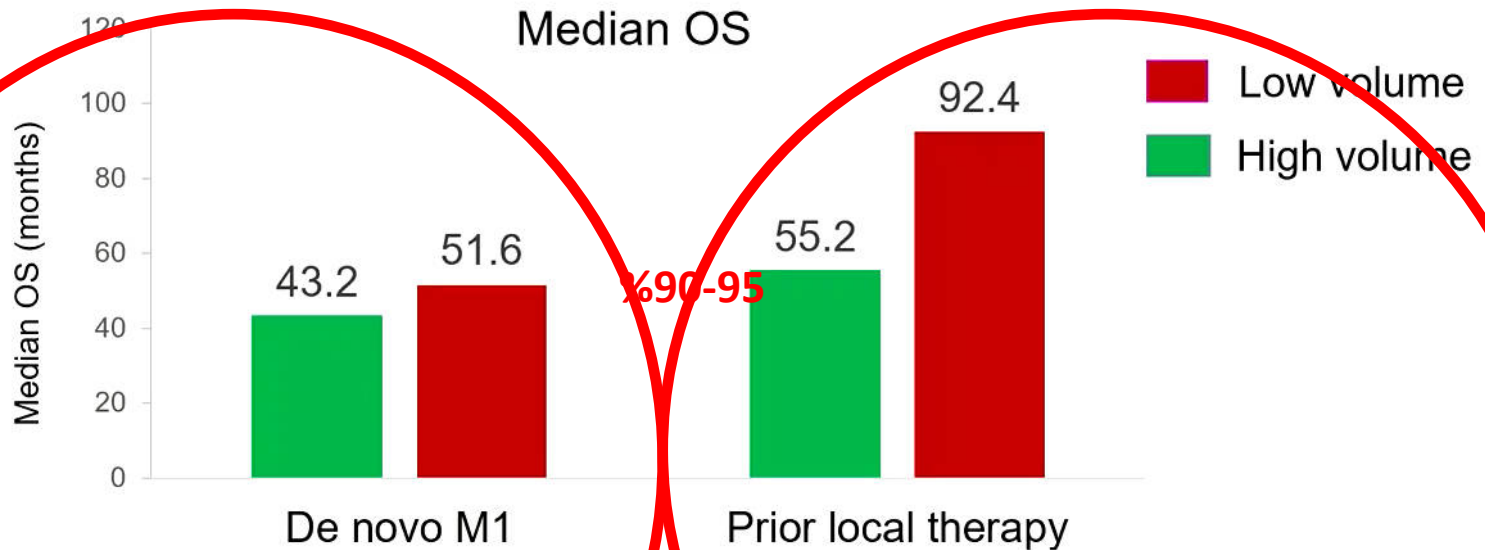
GNRH Antagonists



- ☐ Obstructive urination
- ☐ Cord compression
- ☐ Mitigate CV risk

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

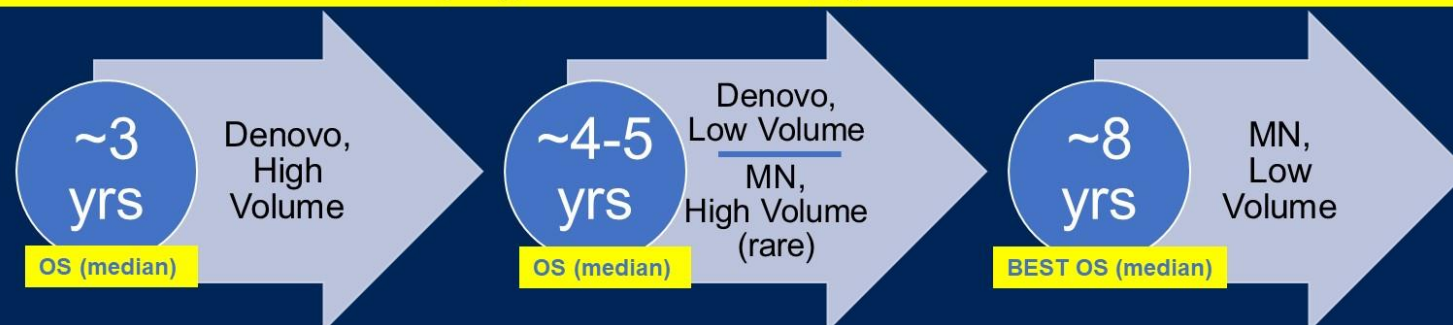
TANI ANINDA METASTATİK VE YÜKSEK VOLÜMLÜ HASTALIK AGRESİF SEYİRLİ

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?

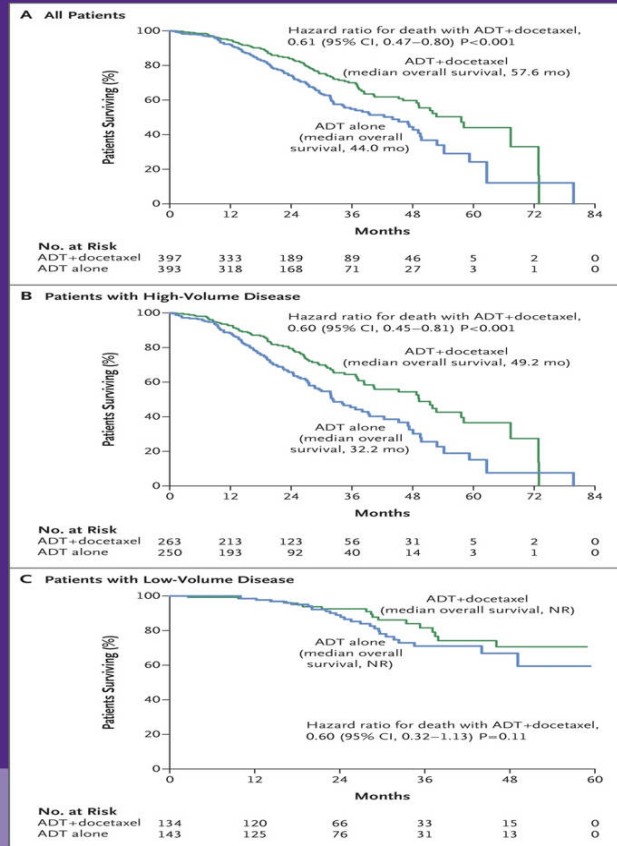


Denovo = new diagnosis/untreated
MN = metachronous diagnosis/previously treated

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

Hastalık Volümü Dosetaksel Tedavi Etkinliği için Prediktif

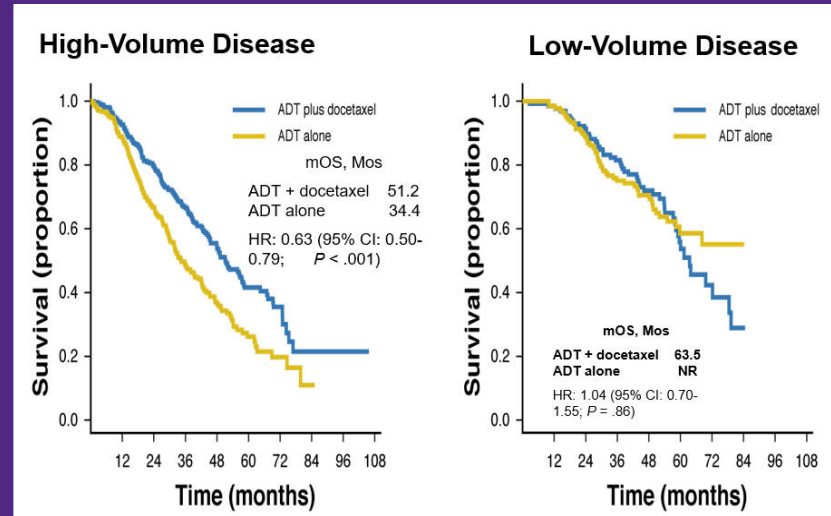
CHAARTED: ADT +/- Docetaxel in mHSPC



Sweeney CJ et al. NEJM 2015

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

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

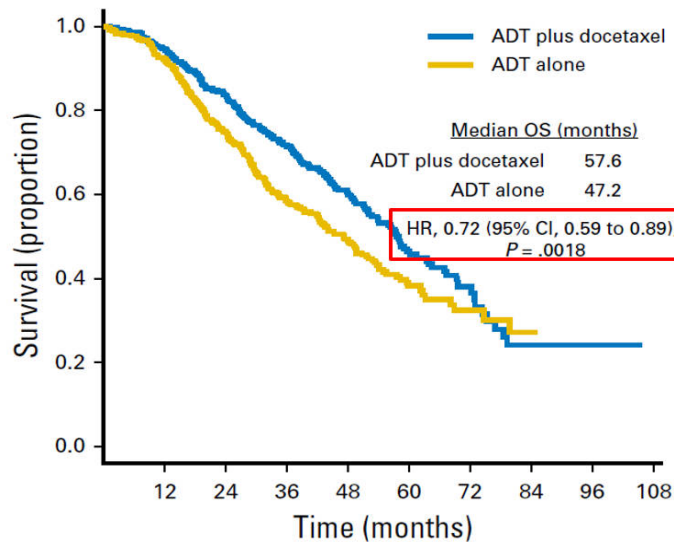


Kyriakopoulos CE, et al. J Clin Oncol. 2018

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

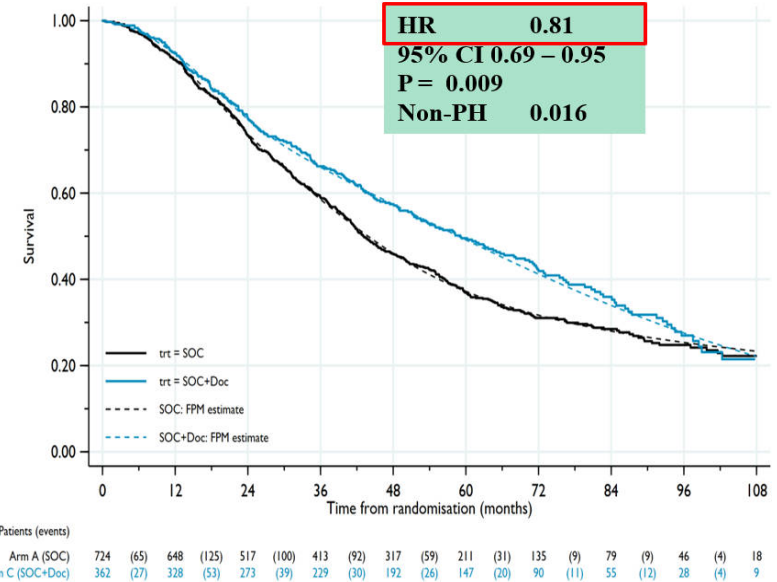
Hastalık Volümü Dosetaksel Tedavi Etkinliği için Prediktif

CHAARTED and STAMPEDE: Lower OS benefit of docetaxel in long-term analysis



No. at risk:										
ADT plus docetaxel	397	366	314	245	155	67	28	7	2	0
ADT alone	393	352	278	198	126	45	21	2	0	0

Kyriakopoulos CE, J Clin Oncol 2018

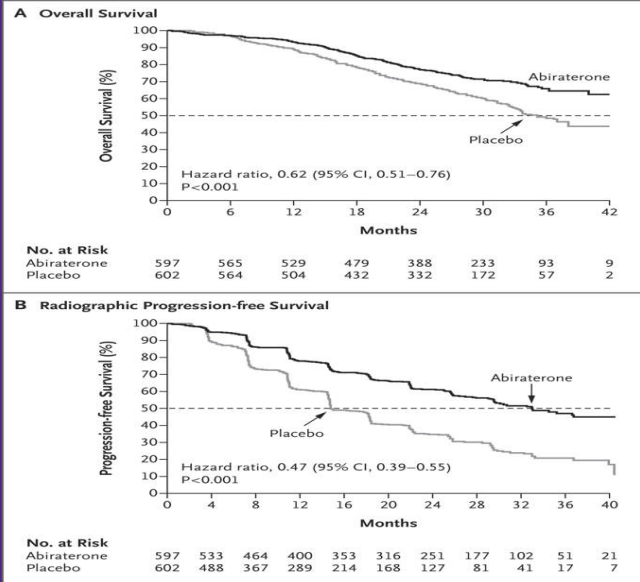


Clarke N, Ann Oncol. 2019

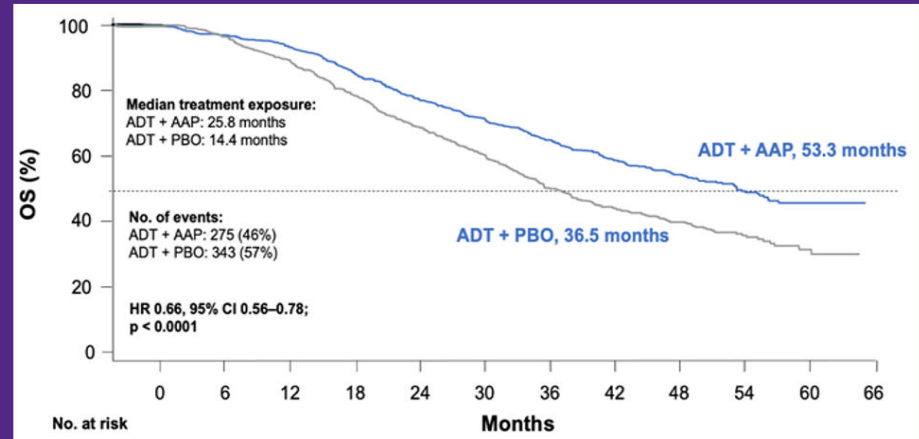
STAMPEDE Tüm hastalar denovo metastatik ve %41 high volüm, CHAARTED çalışmasında denovo metastaz oranı %72 ve %66 high volüm

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

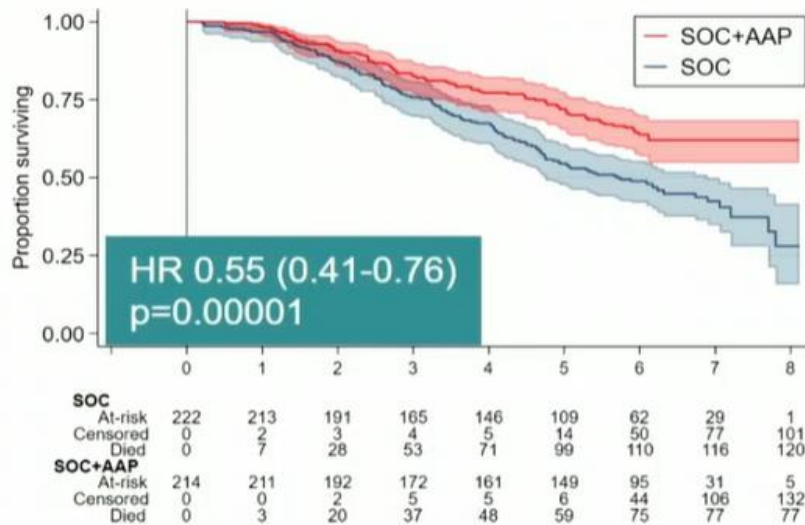
Metastatik hastalığa bağlı semptomu olanlarda RT ve Cerrahiye izin verilmiş

Yeni nesil androjen yolağı inhibitörleri riskten bağımsız etkili

VIRTUAL 2020 ESMO congress

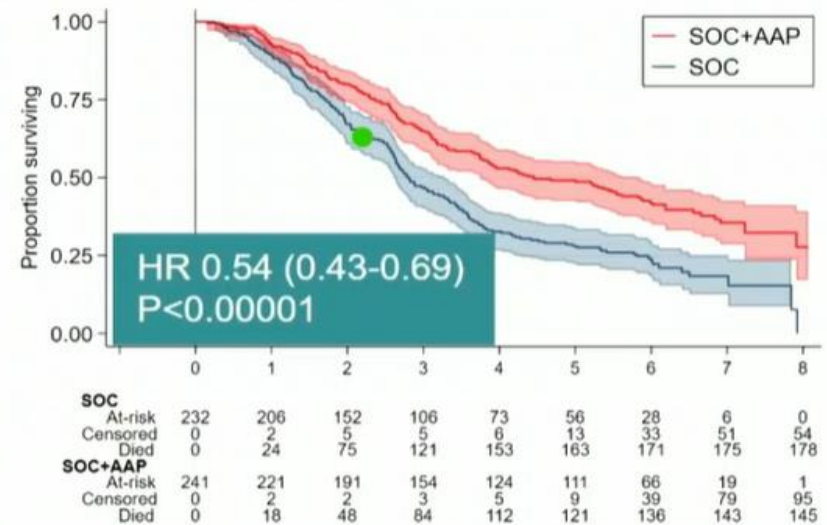
STAMPEDE: OS by risk group (LATITUDE)

Low risk



HR 0.66 (0.44-0.98)
p=0.041

High risk



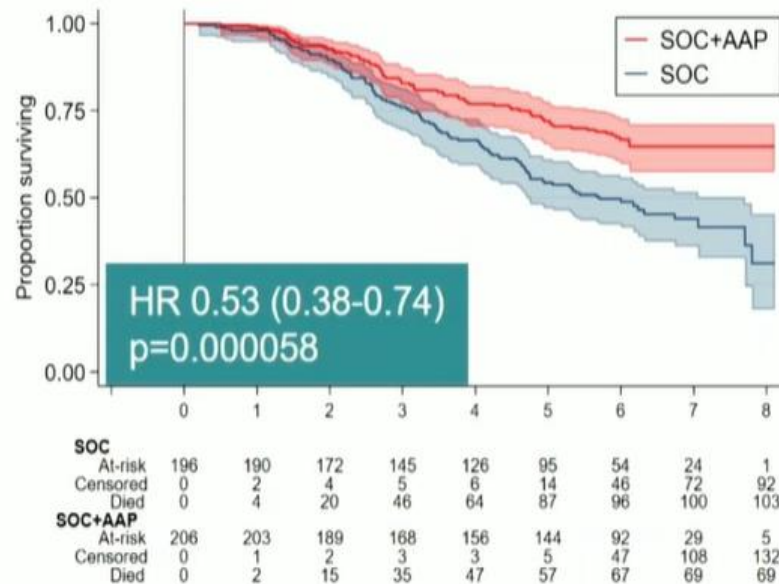
HR 0.54 (0.41-0.70)
P<0.001

Yeni nesil androjen yolağı inhibitörleri tümör yükünden bağımsız etkili

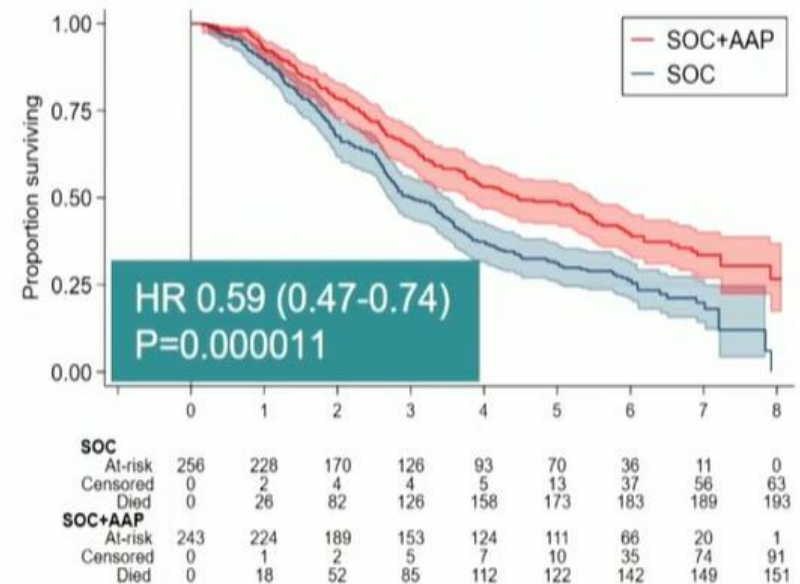


STAMPEDE: OS by disease burden (CHAARTED)

Low volume



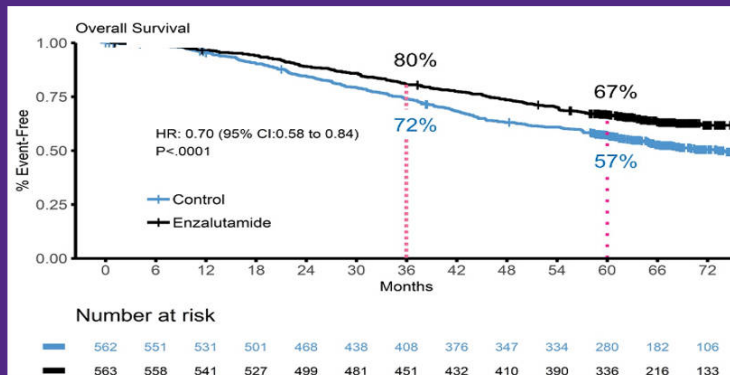
High volume



Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

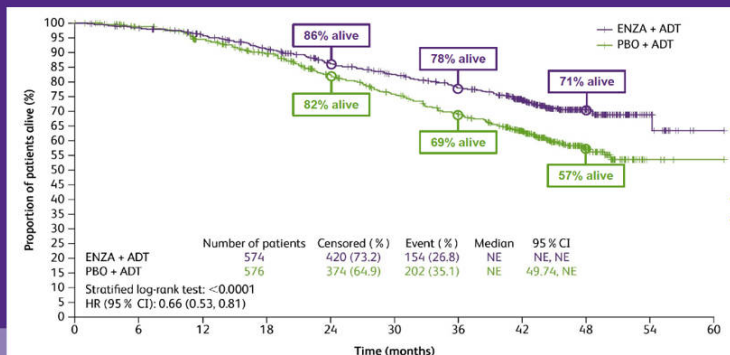
Final Overall Survival (OS) Analyses: Enzalutamide for Metastatic Hormone-Sensitive Prostate Cancer

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

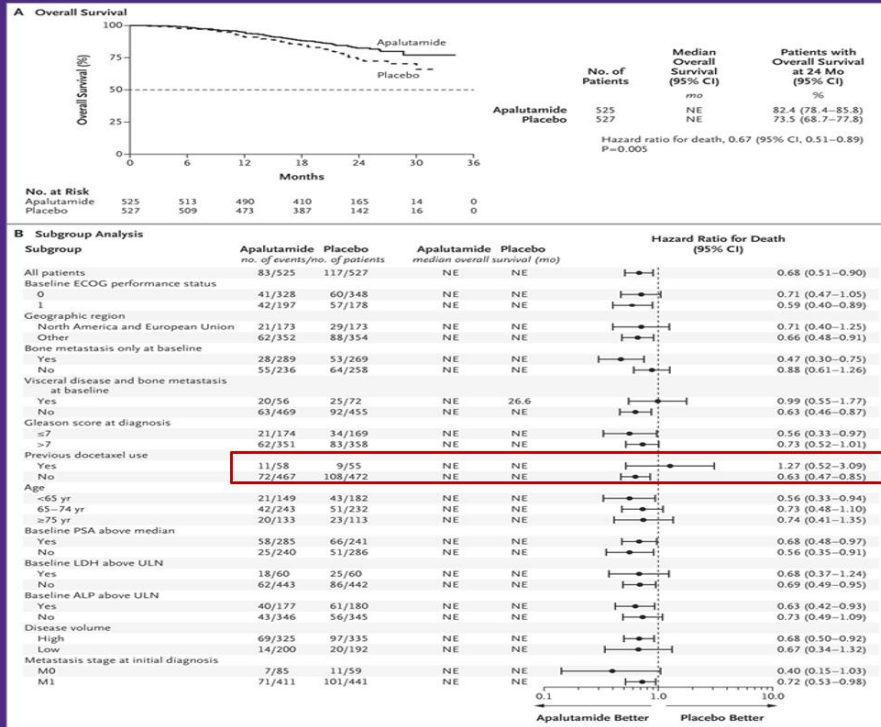
ARCHES²
Enzalutamide + ADT



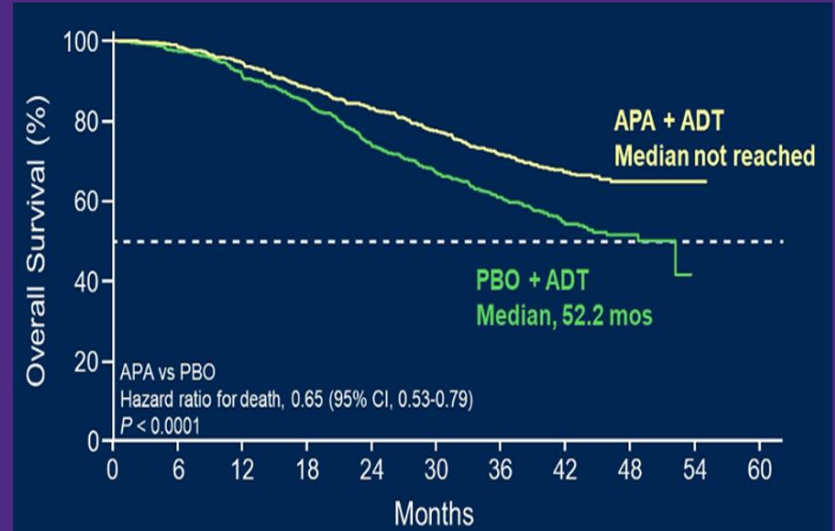
- Median follow-up of 44.6 months
- 34% reduction in risk of death
- Median OS was not reached for enzalutamide plus ADT, but was 47.7 months (95% CI, 43.3 to not evaluable) for placebo plus ADT.
 - HR = 0.66; p < 0.001

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

Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

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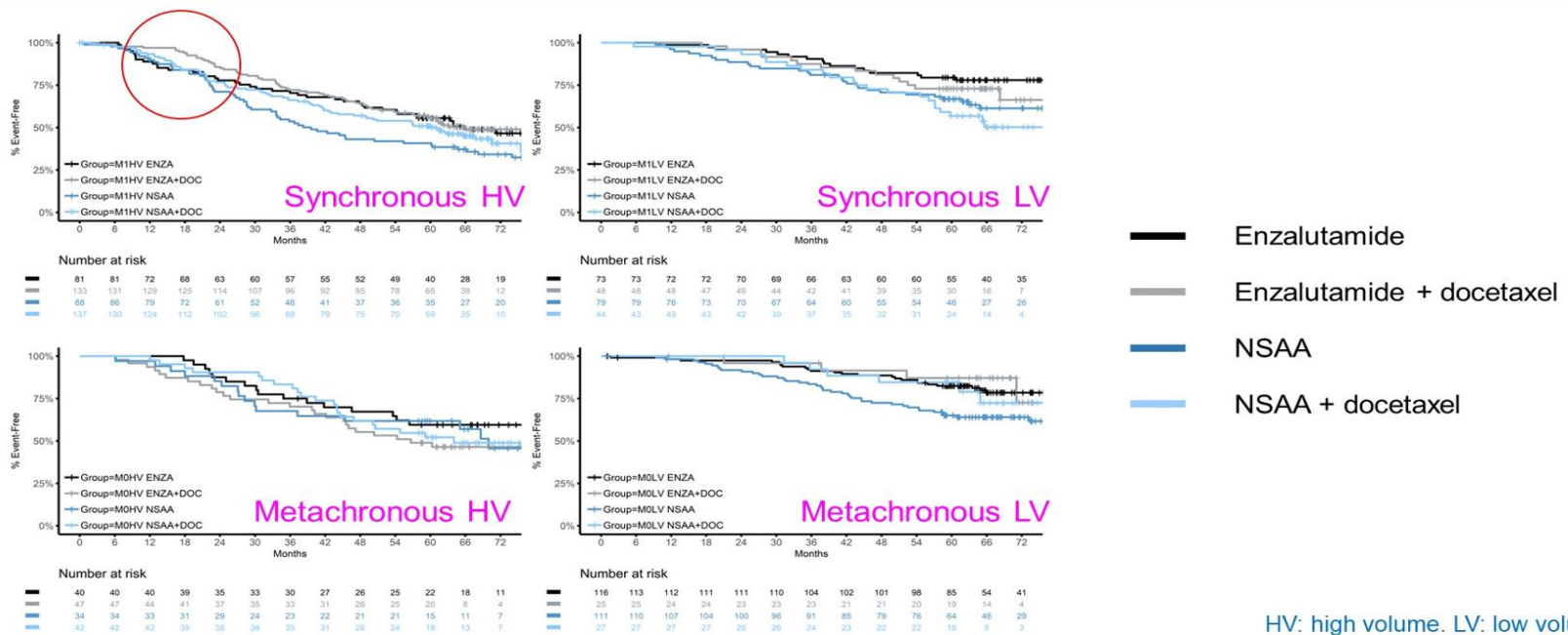
Metastatic HSPC Trials –Docetaxel Triplet

	ARCHES N=1150	ENZAMET N=1125	TITAN N=1052	PEACE-1 N=710*	ARASENS N=1306
ADT + *(+NSAA)	ENZA SOC = +/- DOC	ENZA* SOC = +/- DOC	APA SOC = +/- DOC	ABI SOC* = DOC (+/- RT)	DAROLUTAMIDE SOC = DOC
PRIMARY ENDPOINT, OS HR (95% CI)	Secondary endpoint: 0.66 (0.53-0.81)	0.67 (0.52-0.86)	0.65 (0.53-0.79)	0.75 (0.59-0.95)	0.675 (0.568 – 0.801)
DISEASE VOLUME					
HIGH (%) HR (95% CI)	63% 0.66 (0.52-0.83)	52% 0.80 (0.59-1.07)	63% 0.70 (0.56-0.88)	64% 0.72 (0.55-0.95)	NA
LOW (%) HR (95% CI)	37% 0.66 (0.43-1.03)	48% 0.43 (0.26-0.72)	37% 0.52 (0.35-0.79)	36% 0.83 (0.50-1.38) Data Immature	NA
DOC EXPOSURE (%) HR (95% CI)	18% Prior 0.74 (0.46-1.20)	45% Concurrent 0.90 (0.62-1.31) Interim analysis	11% Prior 1.12 (0.59-2.12)	100% Concurrent	100% Concurrent

Modified from: Armstrong AJ et al, JCO 2019; Armstrong AJ et al, ESMO 2021; Davis ID et al, NEJM 2019; Sweeney C et al, Eur Urol, 2021; Chi K et al, NEJM 2019; Chi K et al, JCO 2021; Fizazi K et al, ASCO 2021; Fizazi et al, ESMO 2021; Smith et al, GU ASCO 2022.

ENZAMET çalışması denovo yüksek volümde üçlü tedavi etkili

Overall survival: volume, M1 timing, docetaxel



Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

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Metastatic HSPC Trials – Disease Volume

	CHAARTED N=790	STAMPEDE, M1 N=1086	LATITUDE N=1199	STAMPEDE, M1 N=1002	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)
De novo, M1 (%)	73%	95%	100%	> 90%	72%	81%
HR (95% CI)	0.68 (0.54-0.85)		0.66 (0.56-0.78)		0.69 (0.52-0.91)	0.68 (0.55-0.85)
Metachronous (%)	27%	NA	-	NA	28%	19%
HR (95% CI)	0.97 (0.58-1.62)				0.56 (0.29-1.06)	0.39 (0.22-0.69)
Disease Volume						
HIGH (%)	65%	43%	100%	52%	52%	63%
HR (95% CI)	0.63 (0.50-0.79)	0.81 (0.64-1.02)	0.66 (0.56-0.78)	0.54 (0.41-0.70)	0.80 (0.59-1.07)	0.70 (0.56-0.88)
LOW (%)	35%	33%	-	48%	48%	37%
HR (95% CI)	1.04 (0.70-1.55)	0.76 (0.54-1.07)		0.66 (0.44-0.98)	0.43 (0.26-0.72)	0.52 (0.35-0.79)
		CHAARTED criteria, 23% unassessed		LATITUDE criteria, n=901	CHAARTED criteria	CHAARTED criteria

HIGH VOLUME: CHAARTED- visceral mets and/or ≥ 4 bone mets at least one outside the vert/pelvis; LATITUDE- 2 of 3: GS ≥8, ≥3 lesions on bone scan, and visceral mets

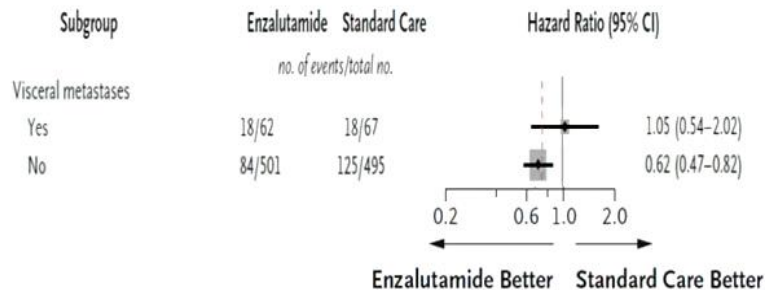
Modified from: Sweeney C et al, NEJM 2015; Kyriakopoulos C et al, JCO 2018; James ND et al, Lancet 2015; Clarke NW et al, Ann Oncol 2019; Fizazi K et al, NEJM 2017; Fizazi K et al, Lancet Onc 2019; James ND et al, NEJM 2017; Hoyle AP et al, Eur Urol 2019; Davis ID et al, NEJM 2019; Sweeney C et al, Eur Urol, 2021; Chi K et al, NEJM 2019; Chi K et al, JCO 2021.

Yeni nesil androjen yolağı inhibitörleri viseral metastazda etkinliği düşük

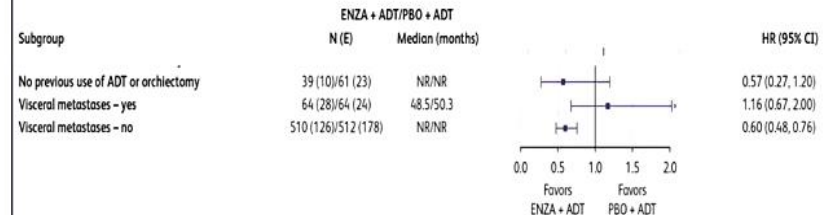
Does type of metastasis matter in mHNPC?

Results from new hormonal treatments in mHNPC according visceral mets

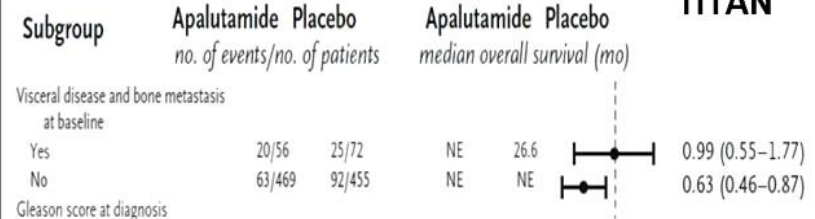
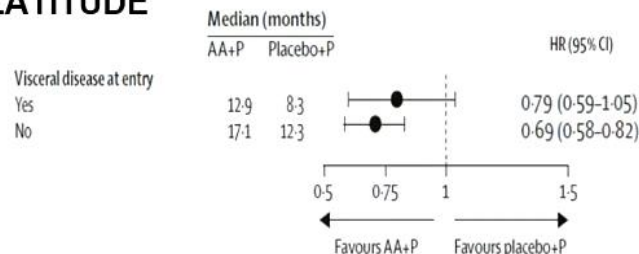
ENZAMET



ARCHES



LATITUDE



2021 ESMO congress

OUARD Stéphane

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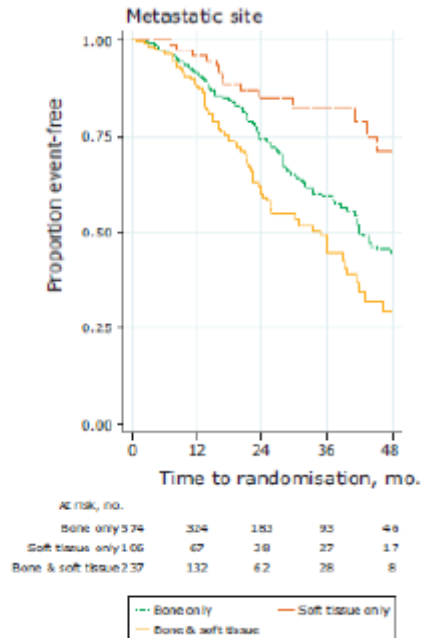
1. Davis I, et al. NEJM 2019;381:121-131 2. Armstrong A, et al. ESMO 2021 oral comm. abstract LBA25 3. Chi K, et al. NEJM 2019;381:13-24 4. Fizazi K, et al. Lancet Oncol. 2019 May;20(5):686-700.

Metastaz bölgesine göre hastalık seyri farklı

Survival with Newly Diagnosed Metastatic Prostate Cancer in the “Docetaxel Era”: Data from 917 Patients in the Control Arm of the STAMPEDE Trial (MRC PR08, CRUK/06/019)

Nicholas David James^{a,*}, Melissa R. Spears^b, Noel W. Clarke^c, David P. Deamaley^{d,e}, Johann S. De Bono^{d,e}, Joanna Gale^f, John Hetherington^g, Peter J. Hoskin^h, Robert J. Jonesⁱ, Robert Laing^j, Jason F. Lester^k, Duncan McLaren^l, Christopher C. Parker^{d,e}, Mahesh K.B. Parmar^b, Alastair W.S. Ritchie^b, J. Martin Russell^m, R  to T. Strebelⁿ, George N. Thalmann^o, Malcolm D. Mason^k, Matthew R. Sydes^b

EUROPEAN UROLOGY 67 (2015) 1028–1038



STAMPEDE  ALI MASI; 917 KONTROL KOLUNDE(ADT alan) BULUNAN M1 HASTALARIN SONU LARI

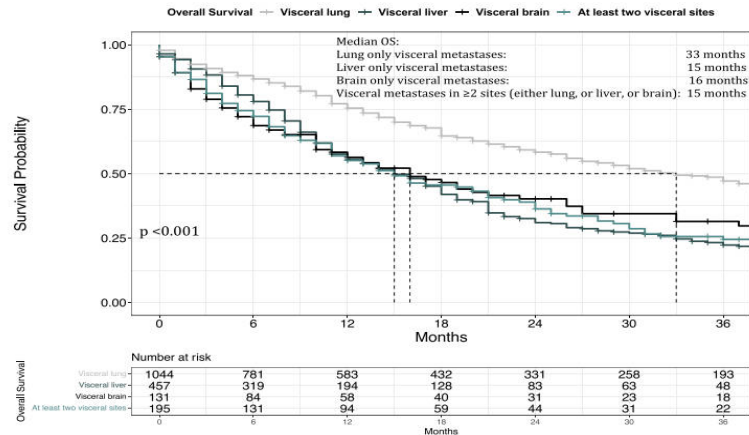
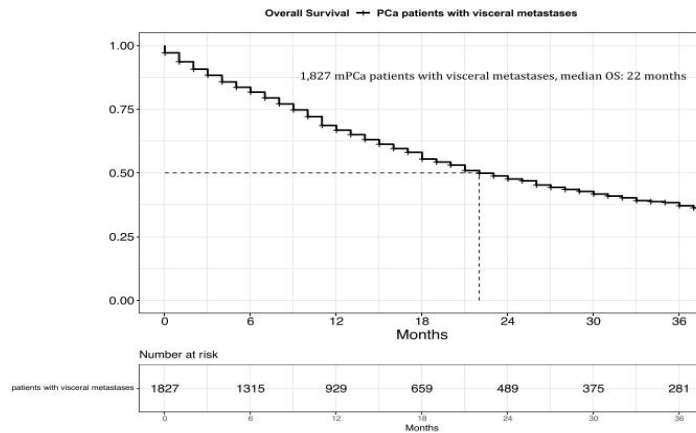
Hastaların %62 yalnız kemik ve %26 kemik+yumu  ka doku met.(lenf nodu metastazı)

2 Yıllık sa kalım; yumu  k doku met.%85
Kemik met.%75

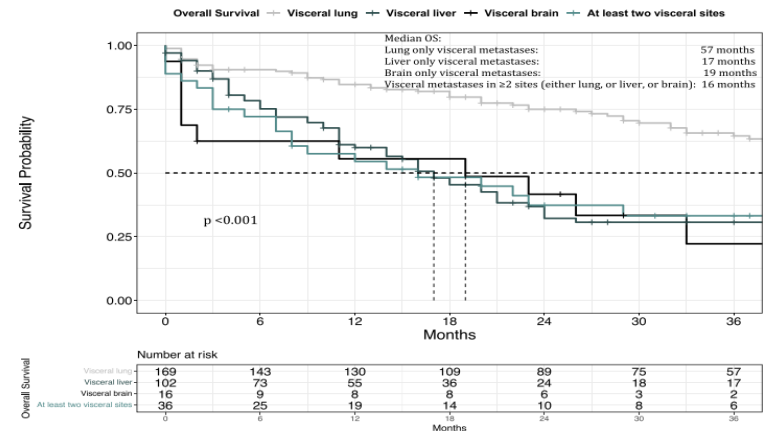
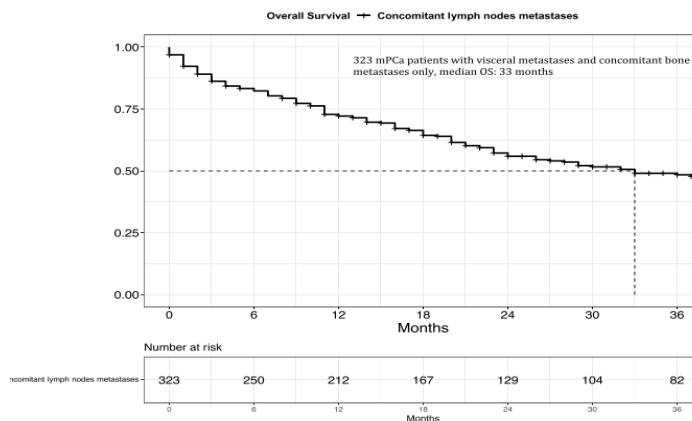
Yumu  k doku+kemik met.%60
2yıllık FFS; yumu  k dokuda %54, kemik met %28 , yumu  k doku+kemik met.%18

Karaciğer metastazı ve viseral metastaz olanlar tedavi yanıtları kötü

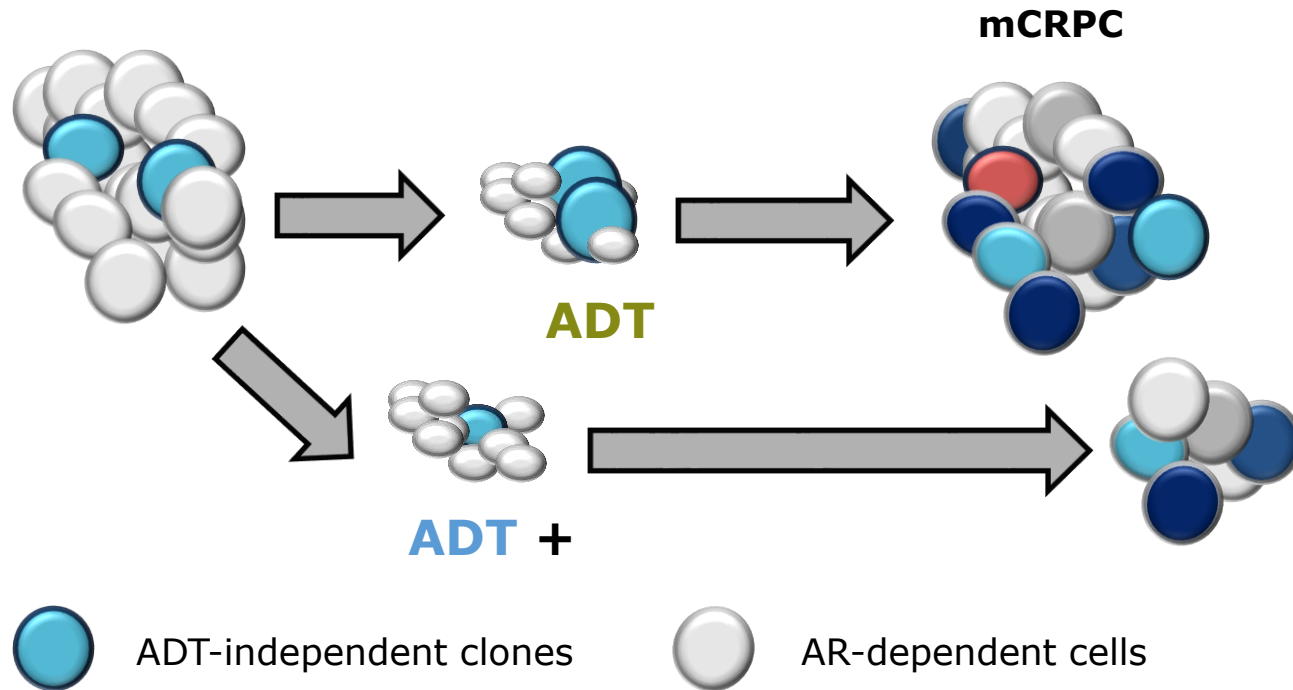
Kaplan-Meier plots displaying overall survival in 1827 metastatic prostate cancer (mPCa) patients with visceral metastases, regardless of presence of lymph node and/or bone metastases: (A) in the overall population; (B) according to location of visceral metastatic sites.



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.



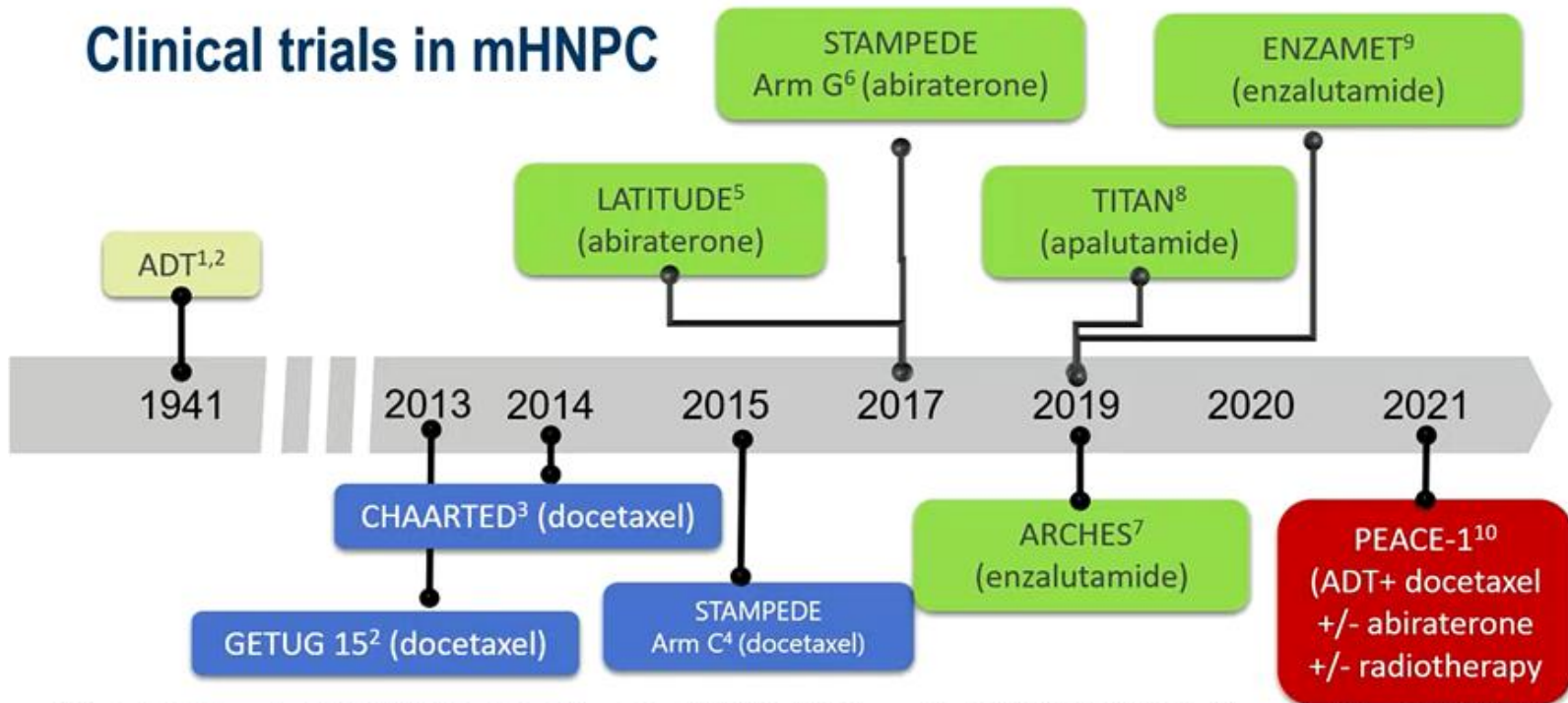
Kastrasyona Duyarlı Metastatik Prostat Kanseri Daha Yoğun Tedavisi



Role of Effective Systemic Therapy

Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

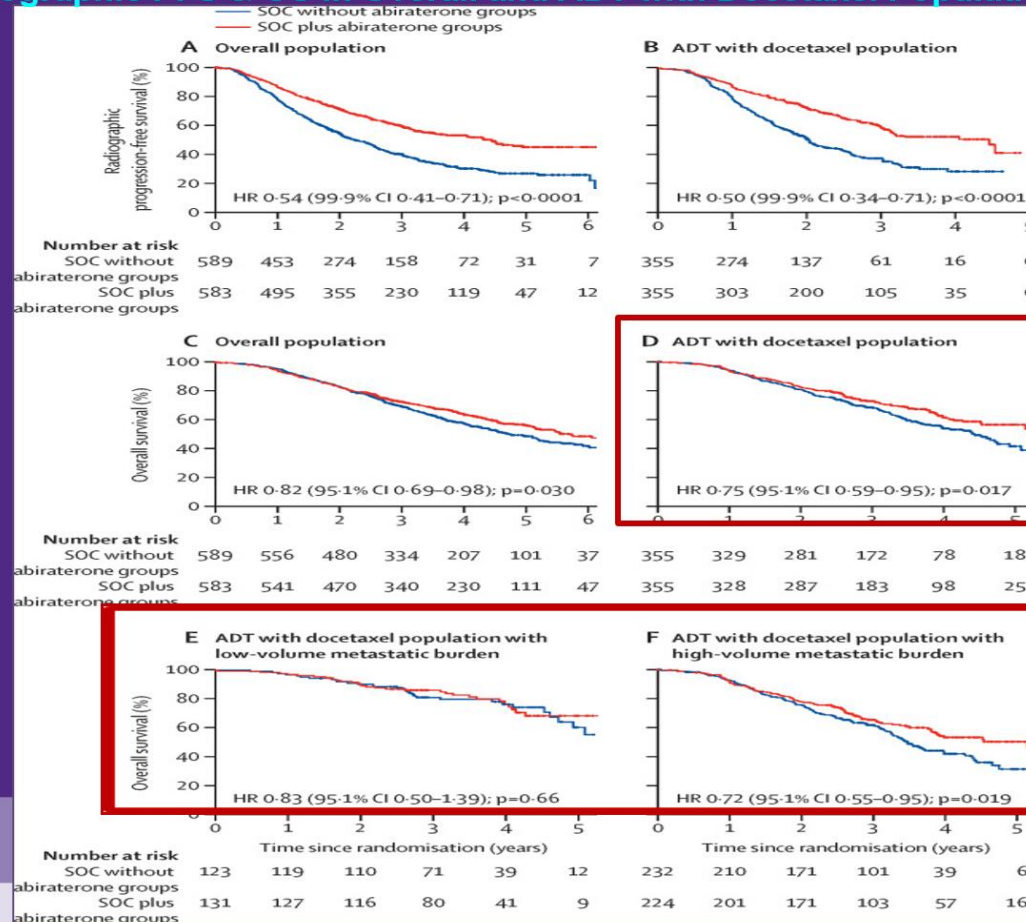
Clinical trials in mHNPc



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

Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

ASCO Genitourinary
Cancers Symposium



Efficacy and safety of abiraterone acetate plus prednisone and androgen deprivation therapy +/- docetaxel in older patients (≥ 70 years), with *de novo* metastatic castration sensitive prostate cancer, compared to younger patients (< 70 years), in the PEACE-1 trial Abst#20

Mourey L¹, Boyle H², Roubaud G³, McDermott R⁵, Supiot S⁶, Tombal B⁷, Flechon A², Berthold D⁸, Ronchin P⁹, Kacso G¹⁰, Berdah J-F¹¹, Calabro F¹², Gravis G¹³, Palumbo S¹⁴, Gil T¹⁵, Vie B¹⁶, Ribault H¹⁷, Fizazi K¹⁸, Foulon S¹⁸, Carles J¹⁹.

¹Institut Universitaire du Cancer-Oncopole, Toulouse, France; ²Centre Leon Bérard, Lyon, France; ³Institut Bergonié, Bordeaux, France; ⁵St. Vincent's University Hospital, Dublin, Ireland; ⁶Institut de Cancerologie de l'Ouest-Rene Gauducheau, Nantes, France; ⁷Cliniques Universitaires Saint-Luc, Brussels, Belgium; ⁸Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland; ⁹Centre Azuréen d'Oncologie, Mougins, France; ¹⁰Iuliu Hatieganu University Cluj Napoca, Romania; ¹¹Clinique Sainte Marguerite, Toulon, France; ¹²San Camillo and Forlanini Hospitals, Rome, Italy; ¹³Institut Paoli-Calmettes, Marseille, France; ¹⁴Pôle Hospitalier Jolimont, La Louvière, Belgium; ¹⁵Institut Jules Bordet, Brussels, Belgium; ¹⁶Centre Armorican Radiothérapie Imagerie Oncologie, Plerin, France; ¹⁷Unicancer, ¹⁸Institut Gustave Roussy, Villejuif, France; ¹⁹Vall d'Hebron University Hospital, Barcelona, Spain

ASCO Genitourinary
Cancers Symposium

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PRESENTED BY: LOIC MOUREY MD

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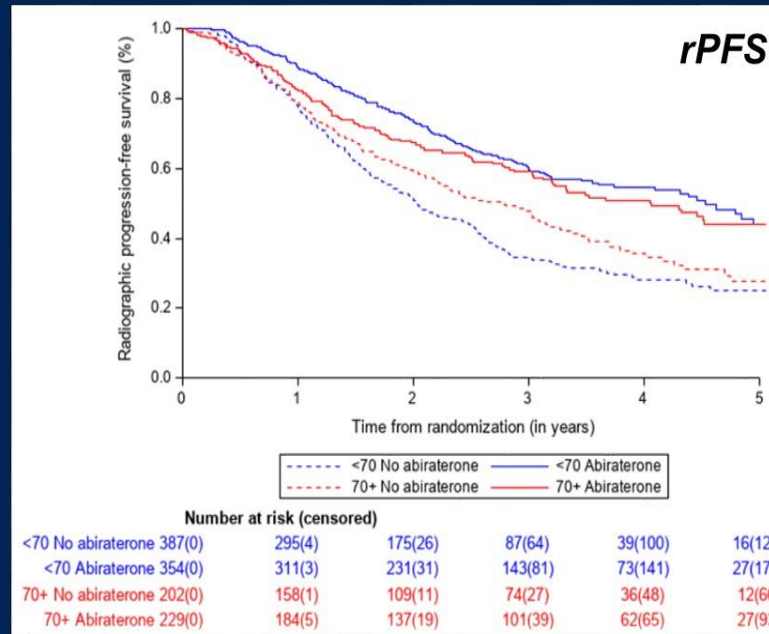
ASCO[®] AMERICAN SOCIETY OF
CLINICAL ONCOLOGY
KNOWLEDGE CONQUERS CANCER

Üçlü Kombinasyonda Yaş Sınırlaması

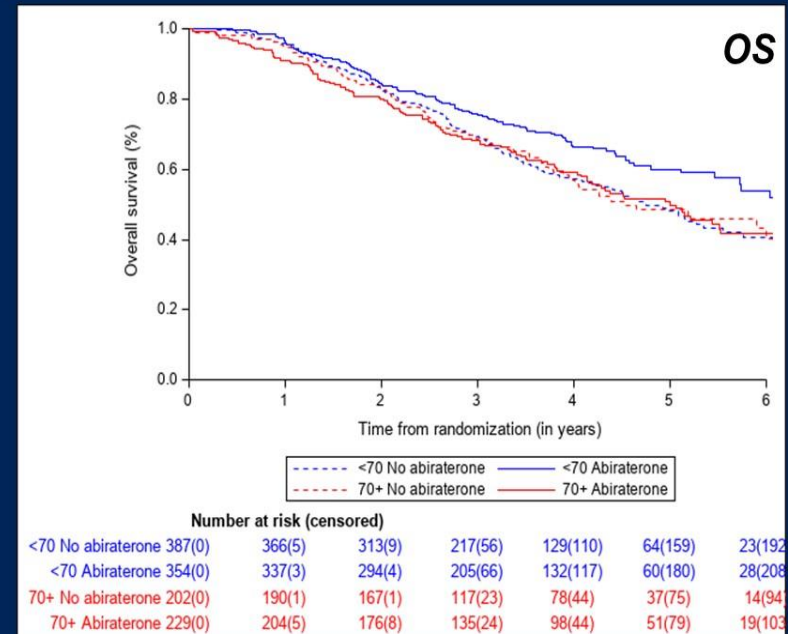
Results (1)

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

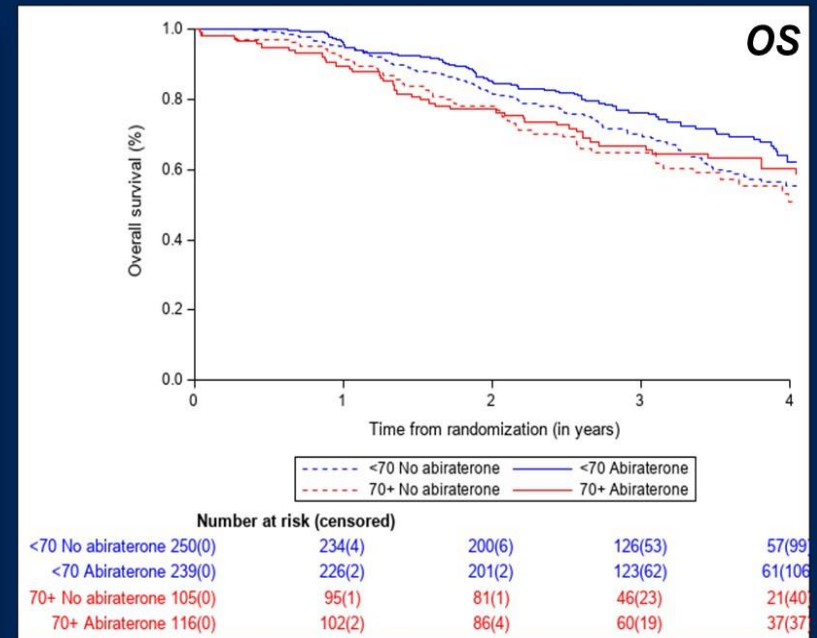
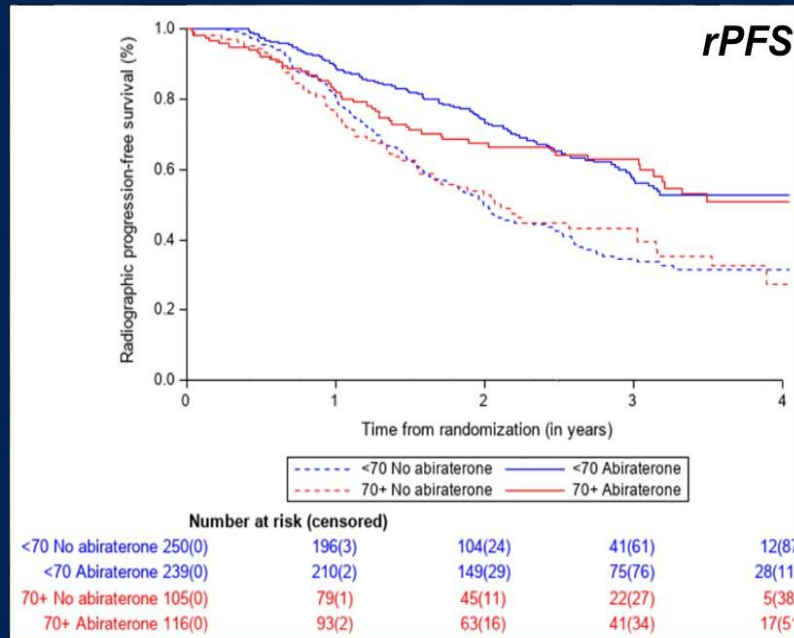
Benefit of AA+P on rPFS and OS may decrease with age

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

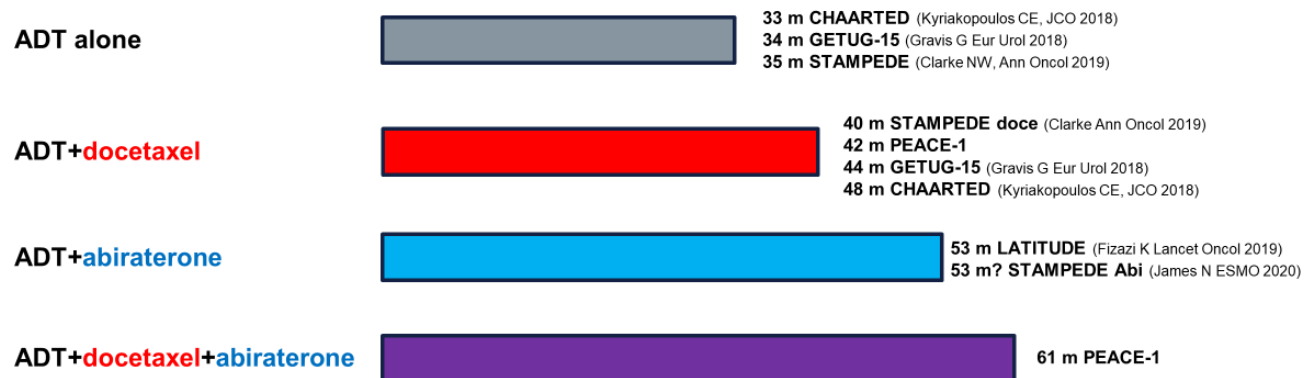
Age ≥ 70 : HR 0.80, 95%CI (0.53-1.2)
Age < 70 : HR 0.71, 95%CI (0.52-0.95)
 p-value of the interaction test 0.63

- 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 

Median Overall Survival (*de novo* High-Volume mCSPC)



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

4

Baseline Demographics and Disease Characteristics

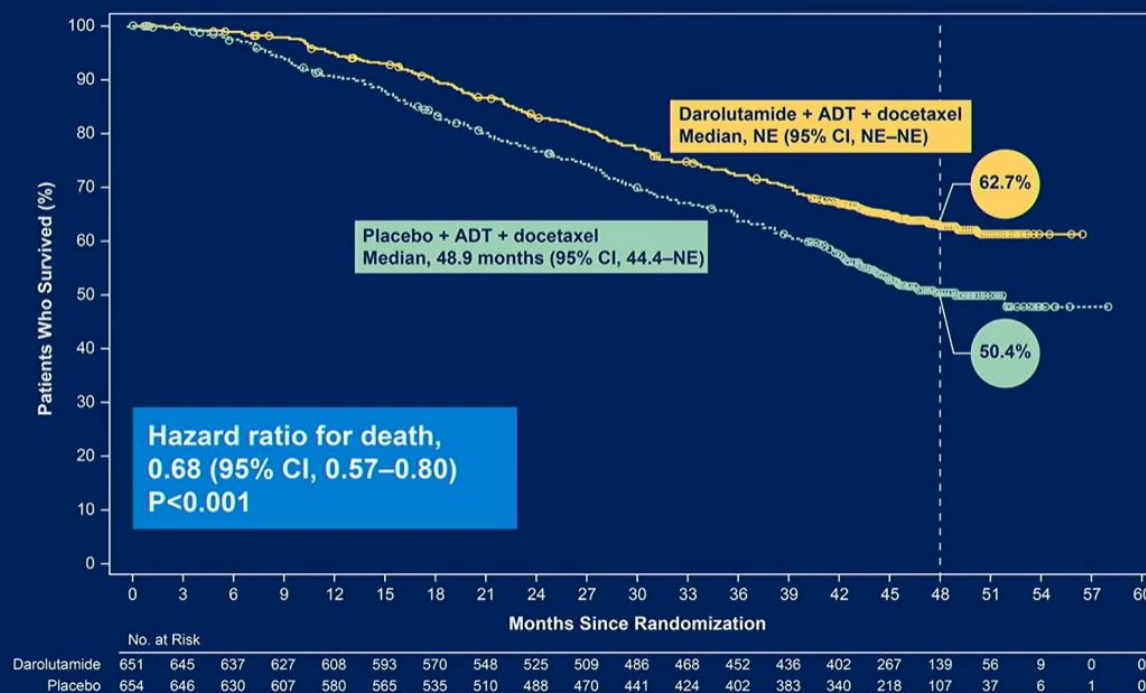
Patient demographics and disease characteristics		Darolutamide + ADT + docetaxel (n=651)	Placebo + ADT + docetaxel (n=654*)
Age, median (range), y		67 (41–89)	67 (42–86)
Region, n (%)	North American	125 (19.2)	119 (18.2)
	Asia Pacific	229 (35.2)	244 (37.3)
	Rest of World	297 (45.6)	291 (44.5)
EGOG performance status, n (%)	0/1	466 (71.6)/185 (28.4)	462 (70.6)/190 (29.1)
Gleason score ≥ 8 at initial diagnosis, n (%)		505 (77.6)	516 (78.9)
Metastatic stage at initial diagnosis, n (%)	M1	558 (85.7)	566 (86.5)
	M0	86 (13.2)	82 (12.5)
	Mx	7 (1.1)	6 (0.9)
Metastatic stage at screening, n (%)	M1a	23 (3.5)	16 (2.4)
	M1b	517 (79.4)	520 (79.5)
	M1c	111 (17.1)	118 (18.0)
Serum PSA, median (range), ng/mL [†]		30.3 (0.0–9219.0)	24.2 (0.0–11,947.0)
Serum ALP, median (range), U/L [†]		148 (40–4885)	140 (36–7680)
ALP stratification, n (%) [†]	$\geq$ ULN	361 (55.5)	363 (55.5)

*One patient randomized to placebo but who received darolutamide was included in the placebo group for the full analysis set. [†]Centrally assessed; samples were collected while patients were receiving ADT. PSA, prostate-specific antigen.

Kastrasyona Duyarlı Metastatik Prostat Kanseri Üçlü Kombinasyon

5

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



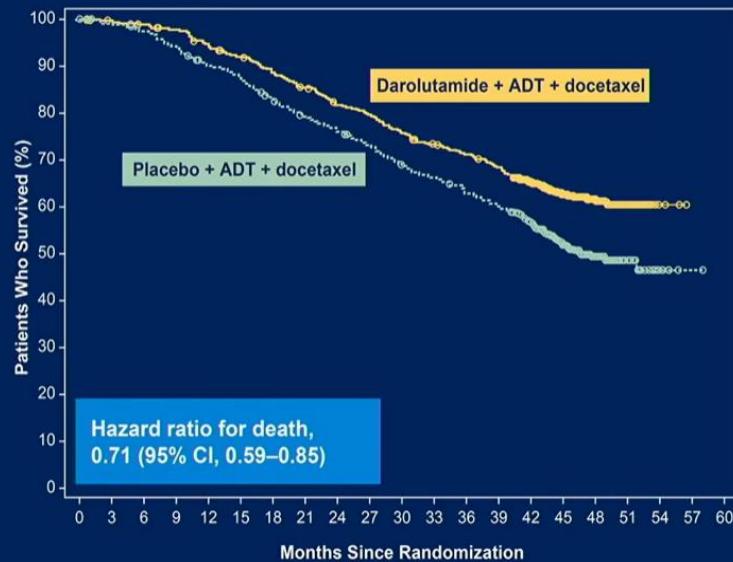
*Primary analysis occurred after 533 deaths (darolutamide, 229; placebo, 304). CI, confidence interval; NE, not estimable.

Kastrasyona Duyarlı Metastatik Prostat Kanseri Üçlü Kombinasyon

8

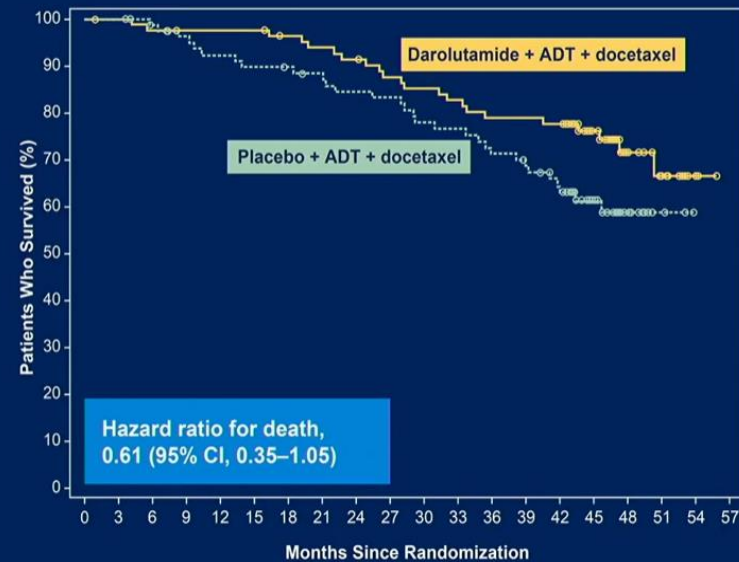
Overall Survival By Metastatic Stage at Initial Diagnosis

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

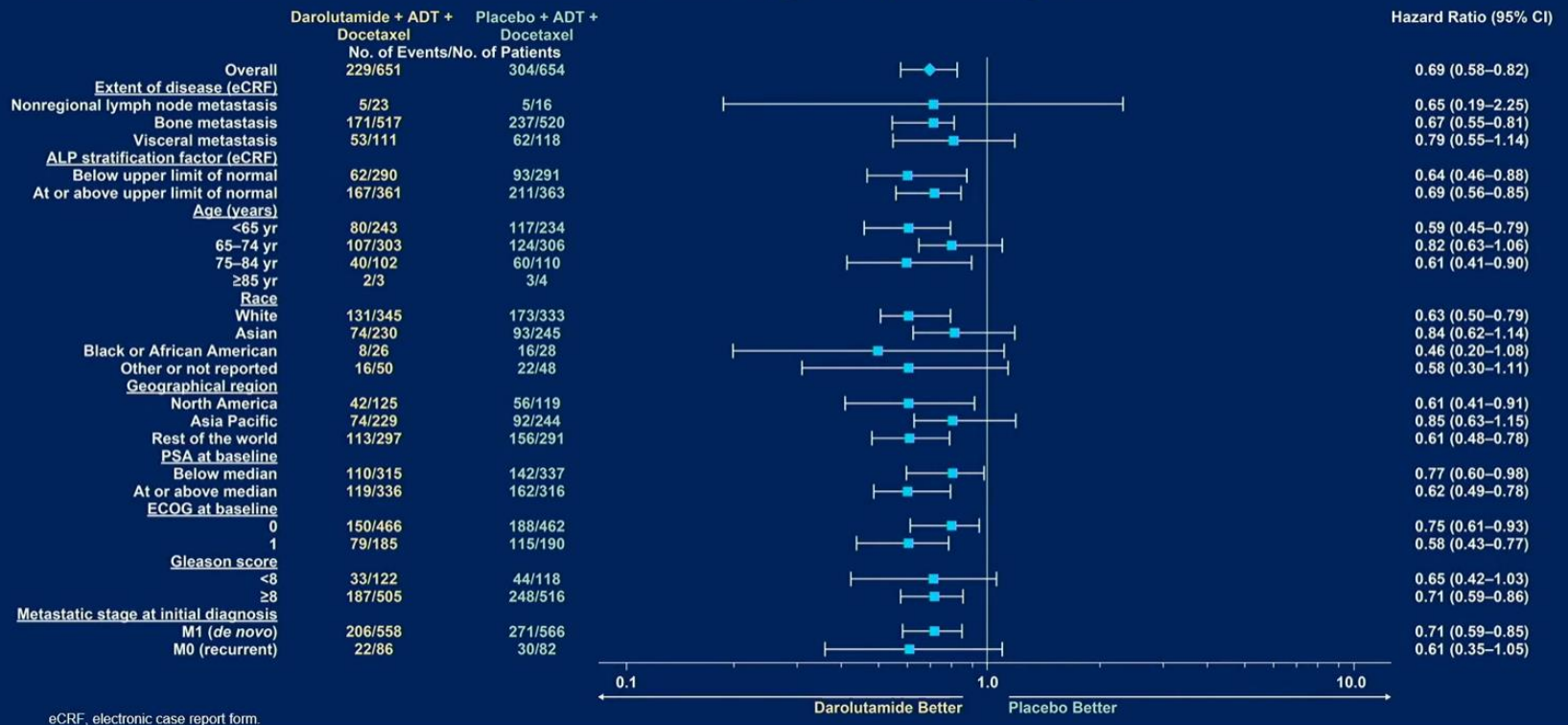


No. at Risk	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57
Darolutamide	86	85	83	81	81	81	78	76	74	70	68	66	63	63	62	43	20	11	2	0
Placebo	82	82	78	75	72	70	69	67	64	63	59	58	54	51	45	26	12	4	0	0

Kastrasyona Duyarlı Metastatik Prostat Kanseri Üçlü Kombinasyon

7

ARASENS Overall Survival: Subgroup Analyses



eCRF, electronic case report form.

Kastrasyona Duyarlı Metastatik Prostat Kanseri Üçlü Kombinasyon

13

Adverse Events of Special Interest for AR Pathway Inhibitors

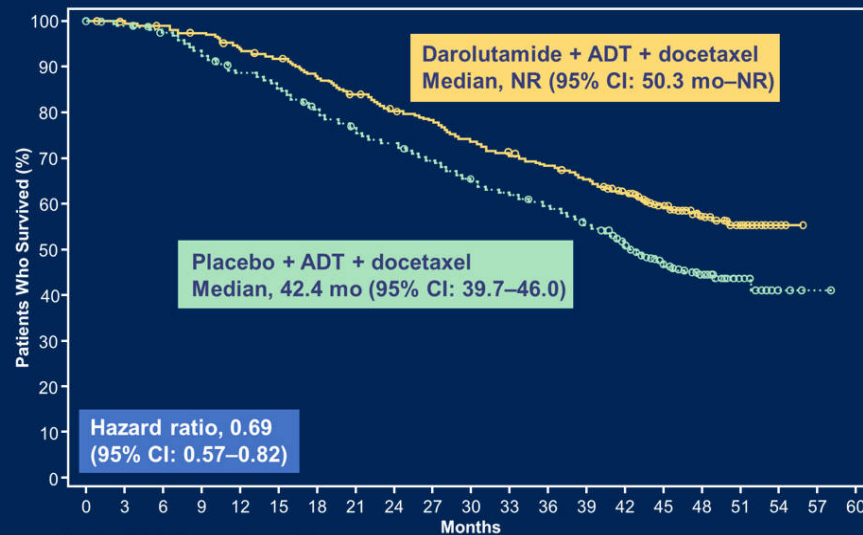
AEs associated with AR pathway inhibitor therapy	Darolutamide + ADT + docetaxel (n=652)		Placebo + ADT + docetaxel (n=650)	
	Patients, n (%)	EAIR/100 PY*	Patients, n (%)	EAIR/100 PY*
Fatigue	216 (33.1)	12.5	214 (32.9)	17.8
Bone fracture	49 (7.5)	2.8	33 (5.1)	2.7
Falls	43 (6.6)	2.5	30 (4.6)	2.5
Rash†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

ARASENS VOLUME Subgroups: Overall Survival

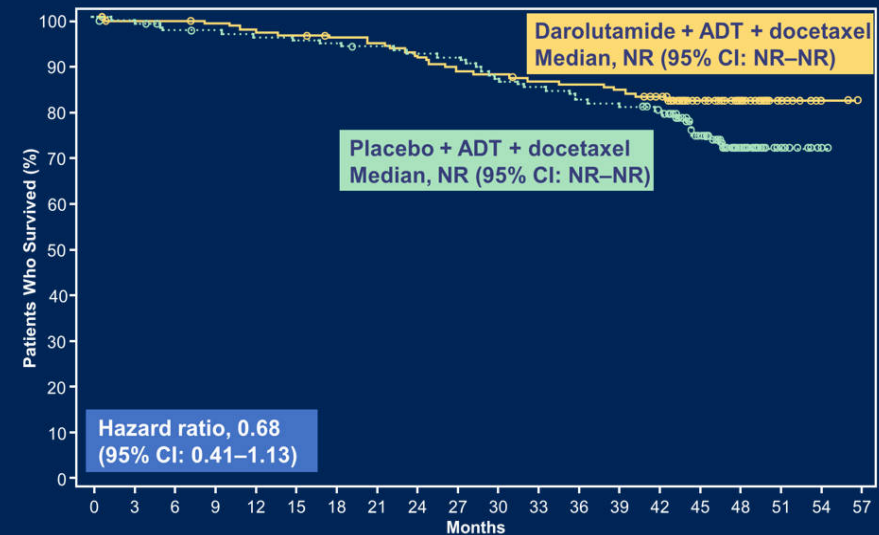
High-volume mHSPC



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

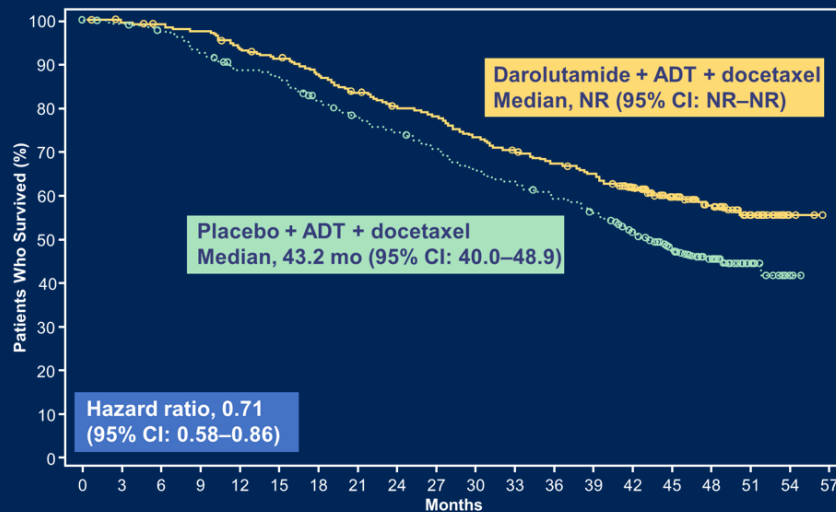
Darolutamide	154	151	151	148	146	144	141	140	136	131	130	127	126	124	117	74	36	13	3	0
Placebo	146	144	139	138	136	135	134	132	130	129	122	120	116	114	107	65	35	14	2	0

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

Kastrasyona Duyarlı Metastatik Prostat Kanseri Üçlü Kombinasyon

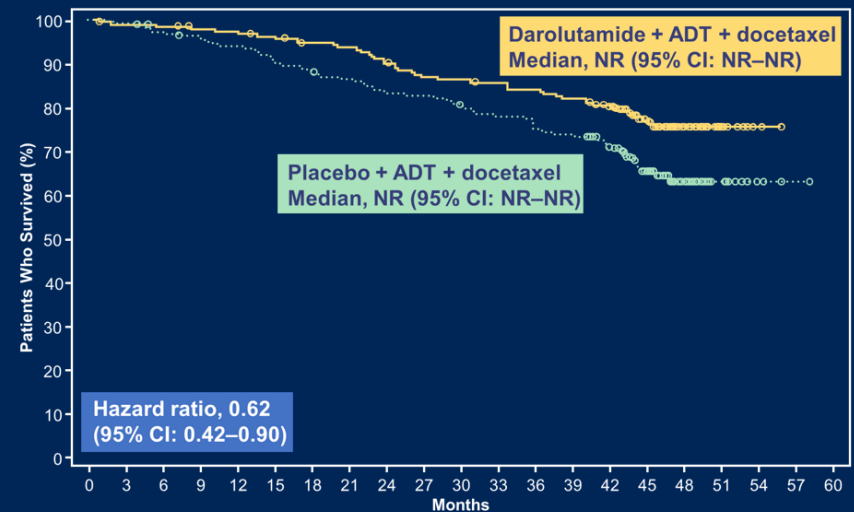
ARASENS RISK Subgroups: Overall Survival

High-risk mHSPC



	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57
Darolutamide	452	450	443	437	419	407	389	369	352	344	322	308	294	282	257	177	99	42	6	0
Placebo	460	453	443	423	400	392	367	346	330	313	290	277	261	245	215	148	72	24	3	0

Low-risk mHSPC



	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57	60
Darolutamide	199	195	194	190	189	186	181	179	173	165	164	160	158	154	145	90	40	14	3	0	0
Placebo	194	193	187	184	180	173	168	164	158	157	151	147	141	138	125	70	35	13	3	1	0

Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

	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

Viseral metastazı olanlarda dörtlü kombinasyon

Early results from CASCARA: A phase 2 study of cabazitaxel/carboplatin plus abiraterone in high-volume metastatic castrate-sensitive prostate cancer (mCSPC).

Background: Best treatment of mCSPC involves doublet therapy (ADT + novel hormonal agent) or triplet therapy (ADT + novel hormone + docetaxel); however, opportunity remains for further improvement. Studies show that homologous recombination repair (HRR) gene mutations are enriched in metastatic prostate cancer, and may portend resistance to docetaxel. CASCARA tested quadruplet therapy (ADT + cabazitaxel/carboplatin + abiraterone) in high-volume mCSPC, aiming to enhance PSA responses and decrease progression at 1 year. **Methods:** This phase 2 study enrolled 61 mCSPC patients with high-volume disease who received ADT plus cabazitaxel (20 mg/m² q21d x 6) and carboplatin (AUC=4 q21d x 6) followed by abiraterone (1000 mg, plus prednisone 5 mg). Primary endpoint was freedom from PSA/radiographic progression at 1 year. Other endpoints included PSA₅₀ response, freedom from PSA progression, and safety. Archival biopsies were retrospectively evaluated for HRR (*BRCA1/2*, *ATM*, *CHEK2*, *CDK12*, *BRIP1*, *RAD51B*) mutations at a CLIA-certified lab. A sample size of 61 was determined using a Simon two-stage design (stage 1: 32 men, stage 2: 29 men) with a null hypothesis of a 1-year PSA/radiographic progression-free rate of 0.80 against a one-sided alternative of 0.92. **Results:** From 11/2019 to 06/2022, 61 men enrolled at 7 sites. Median age was 64 (range, 45–76) years; 21% were African American. Median baseline PSA was 8.9 (range, 0.1–1021) ng/mL. 44% of men had ECOG=1. 91% had Gleason sum 8–10. Prevalence of DNA alterations (50 evaluable pts) was 18% for HRR mutations, 38% for *TP53* muts, 22% for *ERG* fusions, 10% for *SPOP* muts. Freedom from PSA/radiographic progression at 1 year was 77% (95% CI, 63–87%), and freedom from PSA progression at 1 year was 81% (95% CI, 67–90%). The PSA₅₀ rate response was 97%. PSA ≤0.2 ng/mL at month-7, a surrogate for survival in other mCSPC studies, was 61%; PSA ≤4 ng/mL at month-7 was 82%. Outcomes according to mutation status are shown. AEs included 7% grade (Gr)-3/4 myelosuppression, 8% Gr-3/4 infections, 10% Gr-3 GI disorders, and 3% Gr-3 fatigue. There were 4 treatment-related discontinuations. **Conclusions:** Quadruplet therapy with ADT + cabazitaxel/carboplatin + abiraterone was well tolerated. At 1 year, 77% of pts were progression-free. PSA ≤0.2 ng/mL at month-7 was 61%, exceeding the historical month-7 PSA ≤0.2 ng/mL rate of 45% in CHAARTED–docetaxel arm. Further exploration of this quadruplet strategy in randomized phase III studies is warranted. Clinical trial information: NCT03934840. Research Sponsor: Sanofi-Genzyme.

PSA≤0.2 oranı %61

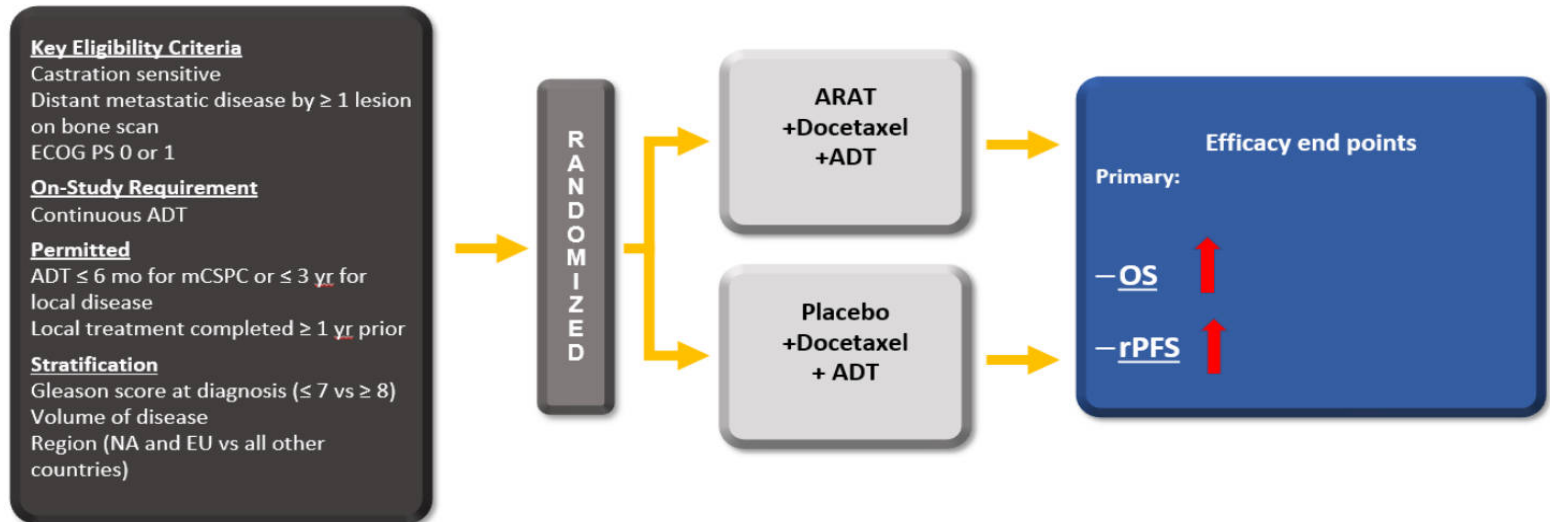
Viseral metastazı olanlarda dörtlü kombinasyon

	HRR status N (%)	TP53 status N (%)	ERG fusion N (%)	SPOP status N (%)
Freedom from PSA/radiographic progression at 1 yr	HRRm – 6 (67%) HRRwt – 34 (83%)	TP53m – 14 (77%) TP53wt – 26 (84%)	ERGm – 11 (100%) ERGwt – 29 (74%)	SPOPm – 5 (100%) SPOPwt – 35 (78%)
PSA ≤0.2 ng/mL at month 7	HRRm – 3 (38%) HRRwt – 27 (66%)	TP53m – 12 (67%) TP53wt – 18 (60%)	ERGm – 9 (82%) ERGwt – 21 (55%)	SPOPm – 4 (100%) SPOPwt – 26 (58%)

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Evre IV Kastrasyona Duyarlı Prostat Kanseri Üçlü Kombinasyonlar

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

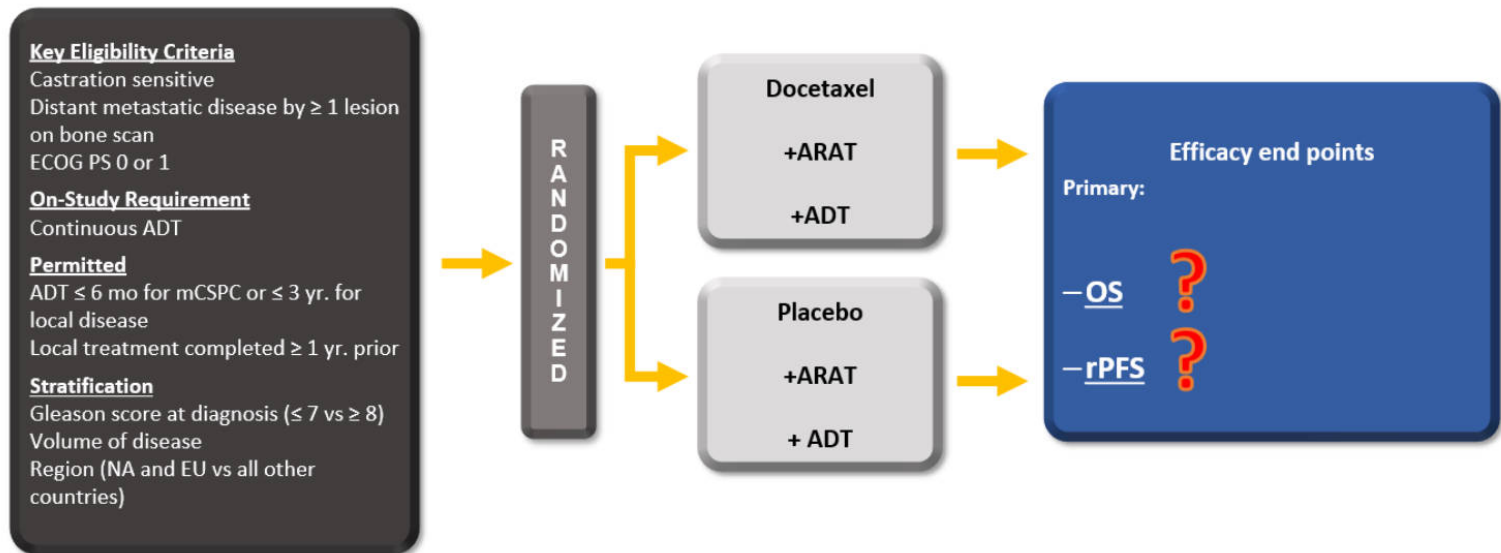


ECOG PS, Eastern Cooperative Oncology Group performance status; ART, Androgen receptor targeted therapy; NA, North America; PSA, prostate-specific antigen; OS, Overall survival; rPFS, radiographic progression-free survival.

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.

Tedavi sonrası ideal PSA değeri ne olmalı

Overall Survival after Androgen Deprivation in New Metastatic Prostate Cancer

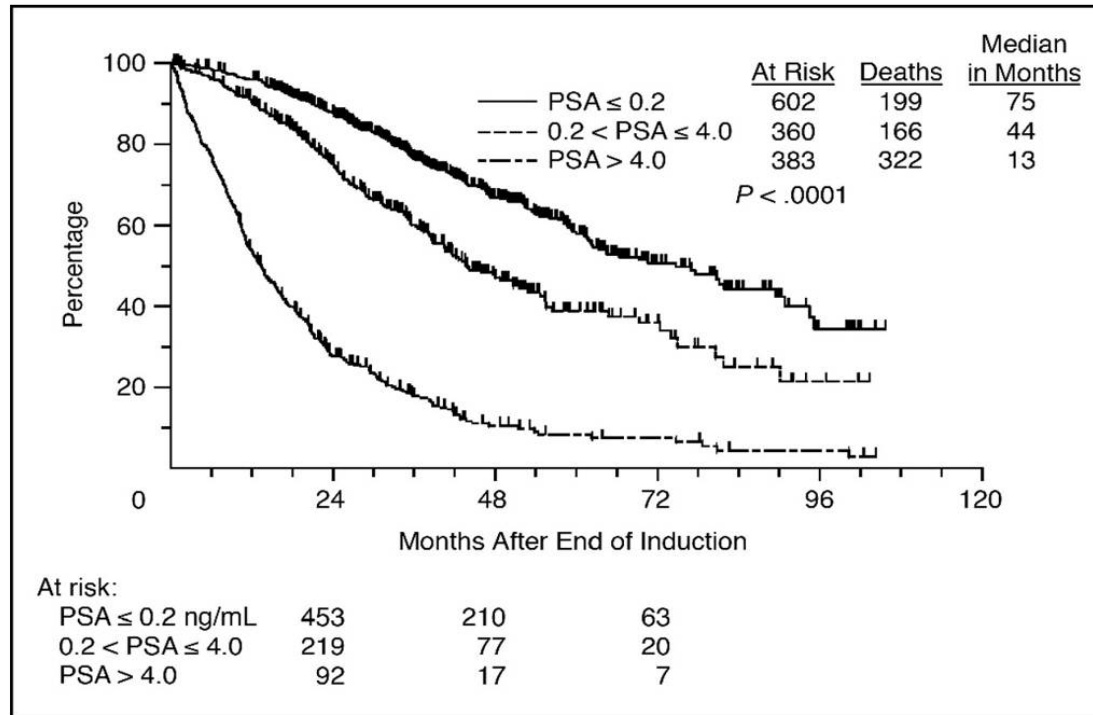
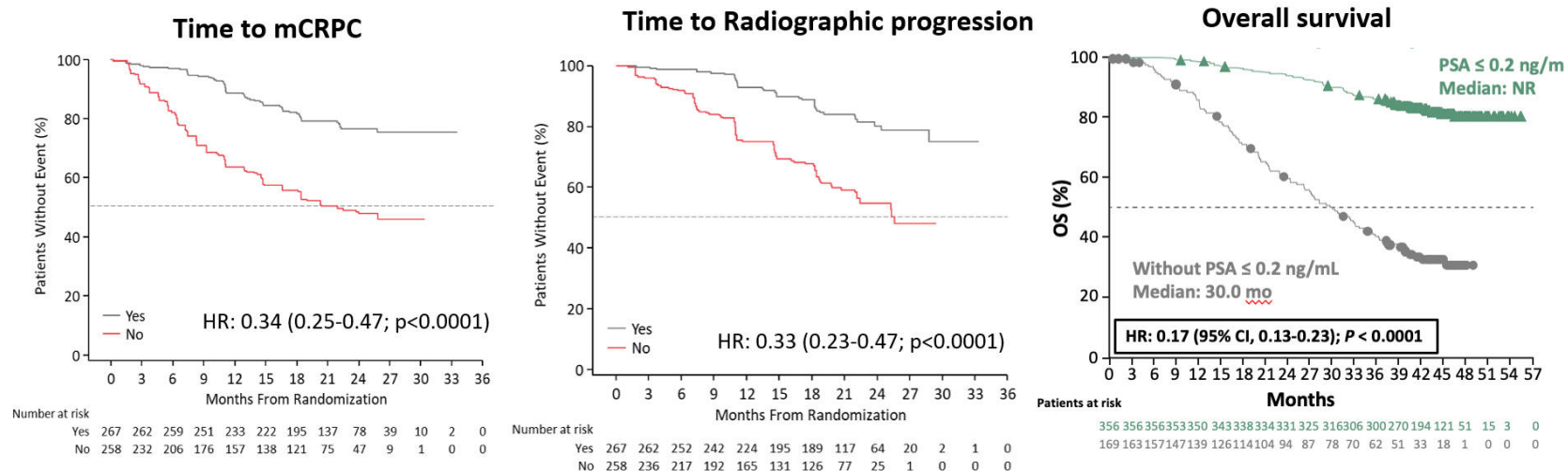


Fig 2. Overall survival by prostate-specific antigen (PSA, ng/mL) status at end of induction
Maha Hussain: Journal of Clinical Oncology 2006; 24 3984-3990.

Kastrasyona Duyarlı Metastatik Prostat Kanseri Nadir PSA Uzun Sağkalımı Gösterir

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

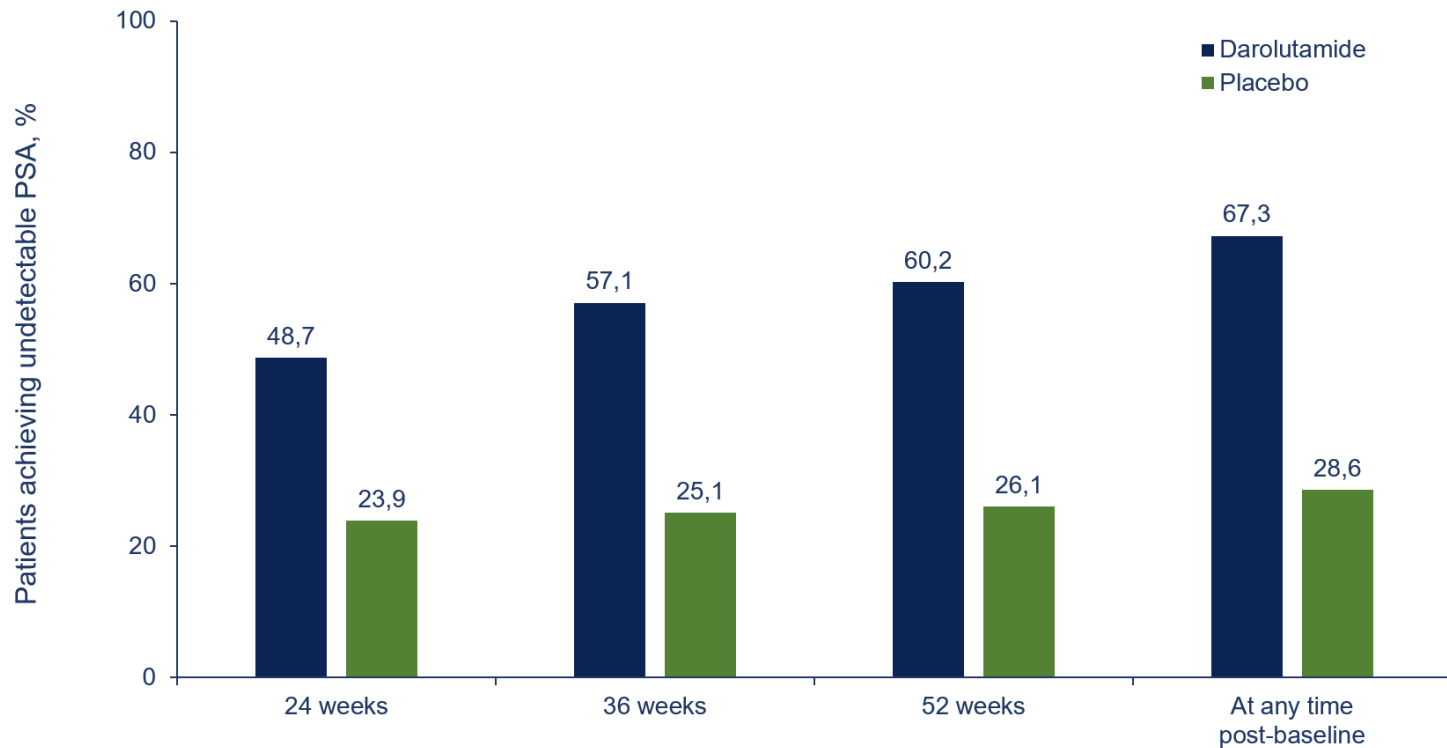


Data from the TITAN study: Chi K et al. *N Engl J Med*. 2019 Jul 4;381(1):13-24.

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



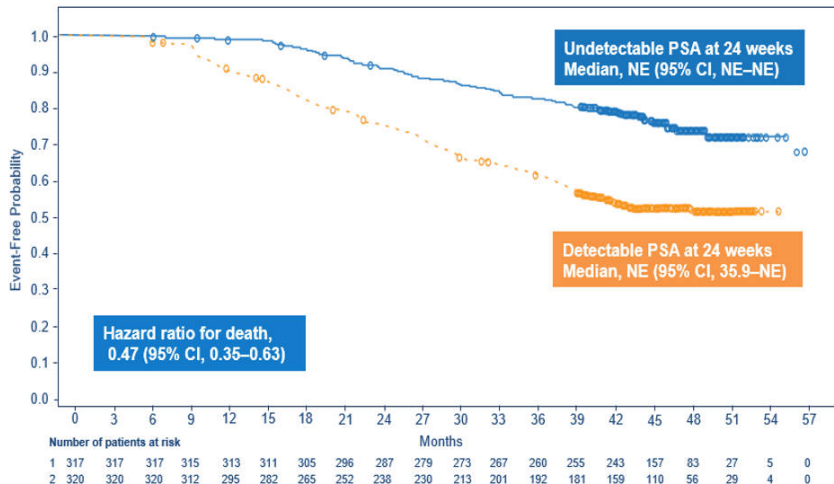
Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

Results: Overall Survival

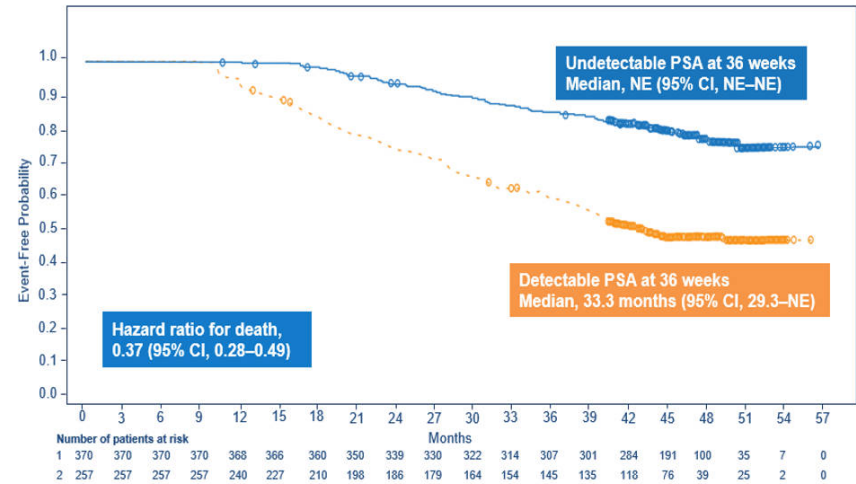
Undetectable PSA at 24 and 36 weeks was associated with a
53% and 63% reduction in the risk of death

Darolutamide + ADT + docetaxel

Undetectable vs detectable PSA at 24 weeks

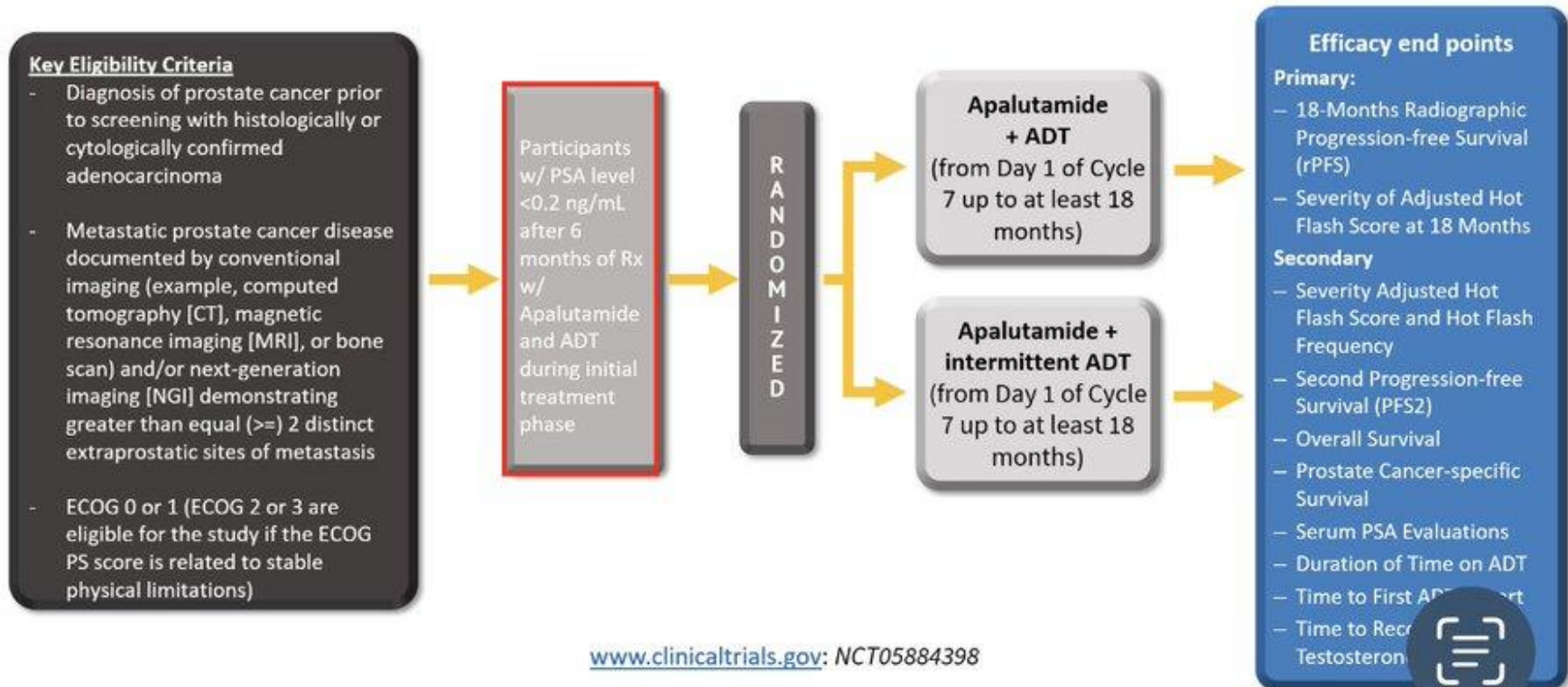


Undetectable vs detectable PSA at 36 weeks



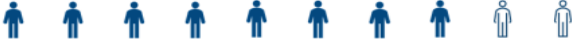
Gelecek Perspektif

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

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)

Metastatik Kastrasyona Duyarlı Prostat Kanseri Tedavi

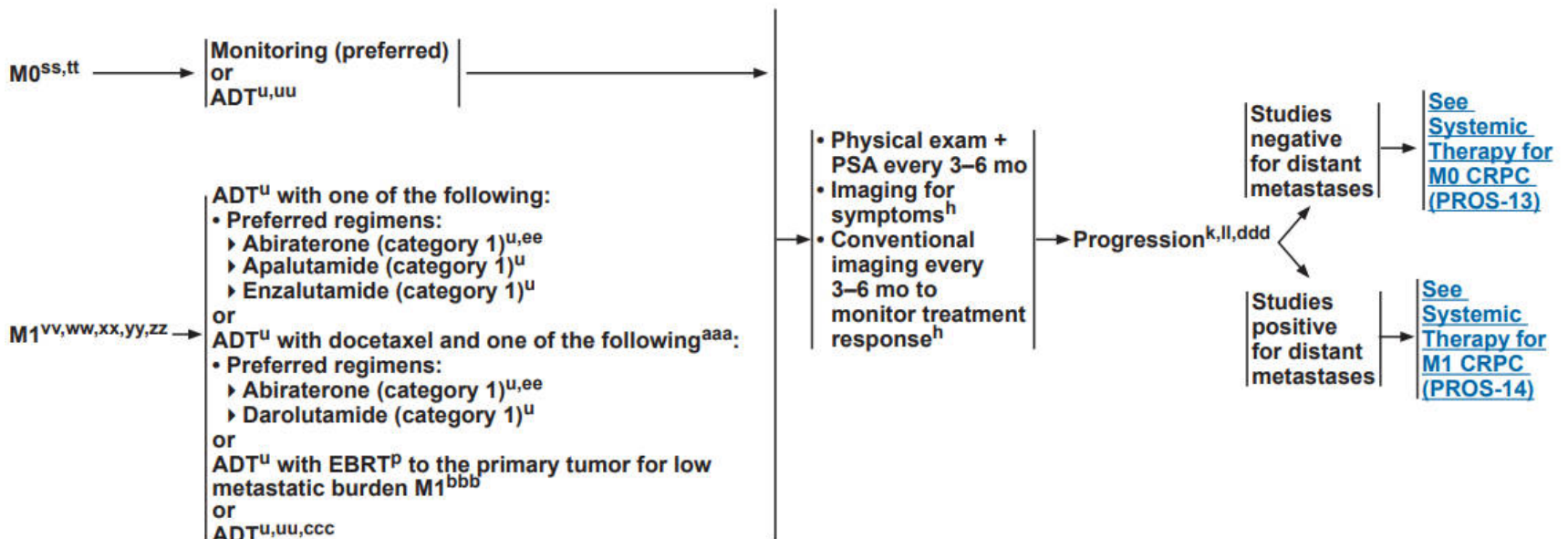


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NCCN Guidelines Version 4.2023 Prostate Cancer

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SYSTEMIC THERAPY FOR CASTRATION-SENSITIVE PROSTATE CANCER^{rr}



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, denovo, yüksek volüm, genç, yaşam beklentisi uzun hastalarda ön planda düşünülebilir

Karaciğer metastazı gibi kötü seyirli hastalarda dörtlü kombinasyon? Daha çok veriye ihtiyaç var

❑ 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

❑ Genomik profileme tedavi seçiminde etkili olacak.

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