

Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

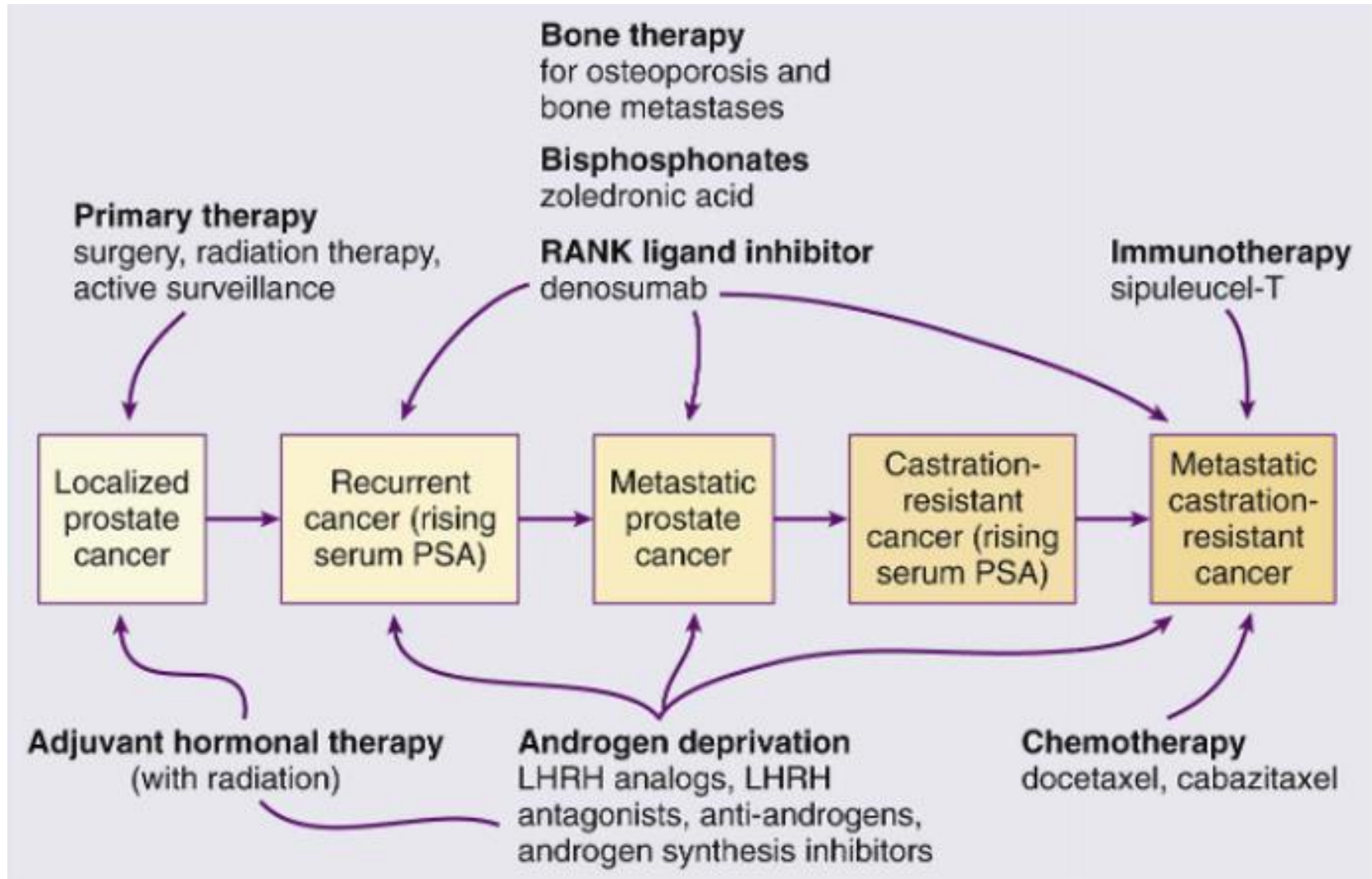
Dr. Deniz Tural

Bakırköy Dr. Sadi Konuk Eğitim ve Araştırma Hastanesi
Tıbbi Onkoloji

Ders Planı

- ❑ Giriş
- ❑ ADT
- ❑ Tedavi kararında etkili faktörler
- ❑ ADT+yeni nesil androjen yolağı inhibitörleri
- ❑ Dosetaksel hangi hasta grubuna eklenmeli
- ❑ Gelecek perspektif
- ❑ Sonuç

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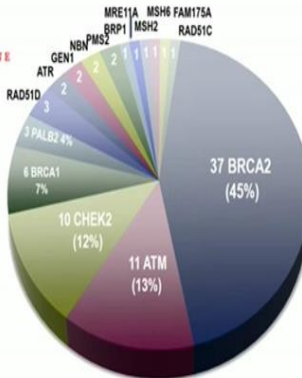
Prostat kanserin biyolojisi

GENETIC TESTING

Our new and shiny...

The NEW ENGLAND JOURNAL of MEDICINE

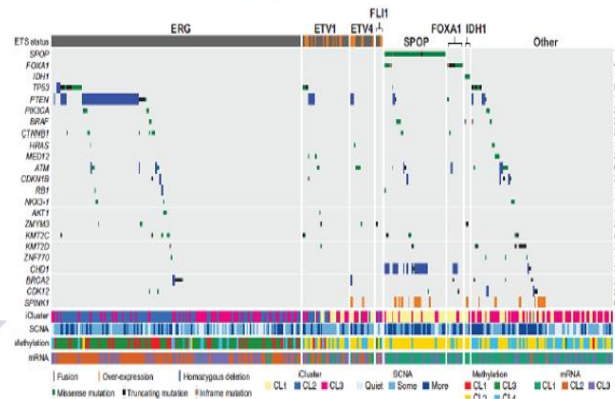
Inherited DNA-Repair Gene Mutations
in Men with Metastatic Prostate Cancer



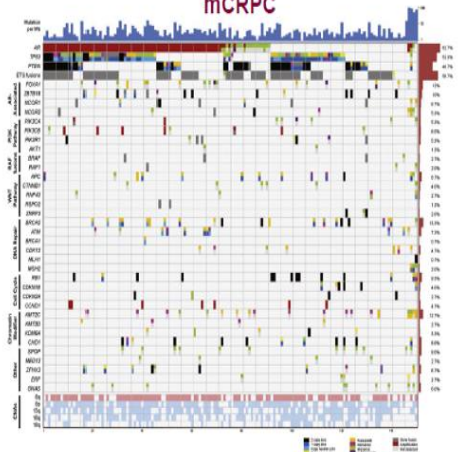
692 patients with metastatic PrCa Tested

Pritchard, NEJM, 2016

Localized PC

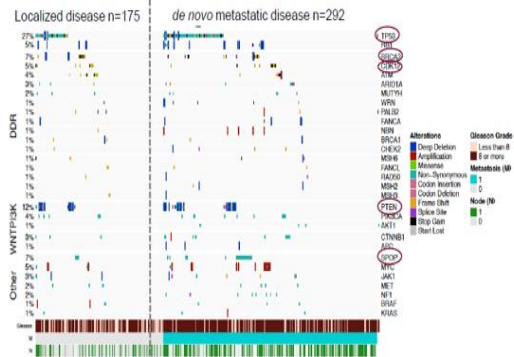


mCRPC



Actionable alterations in most mCRPC patients

mHSPC: de-novo metastatic vs metastatic recurrence



No significant differences in the prevalence of genomic alterations between localized disease that progress to mCRPC and de novo metastatic prostate cancer

TCG, Cell, 2015; Robinson et al, Cell, 2015

AR pathway: 70%
PI3K-AKT-mTOR: 40-60%
DDR: 25%
Cell cycle regulators RB1/CDK: 25%
Others



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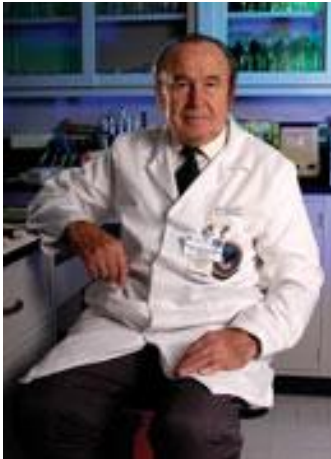
Androjen Baskılama Tedavisi(ADT)

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

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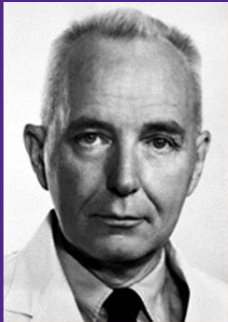


- Charles Brenton Huggins(1901-1997)
- 1927’de Chicago Üniversitesinde Üroloji kliniğinde akademik kadro aldı
- Köpeklerde yaptığı deneylerle, prostat hücrelerinin büyümesinde testosteron hormonuna bağımlı olduğunu tespit etti
- Prostat kanseri olanlarda orşektomi ile tümörün küçüldüğünü belirledi.
-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



Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

Historical Perspective: Androgens & Prostate Cancer

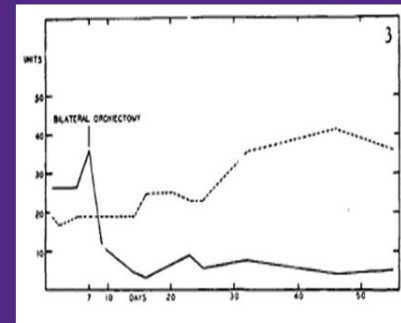


C. Huggins
1966 Nobel Prize

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

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

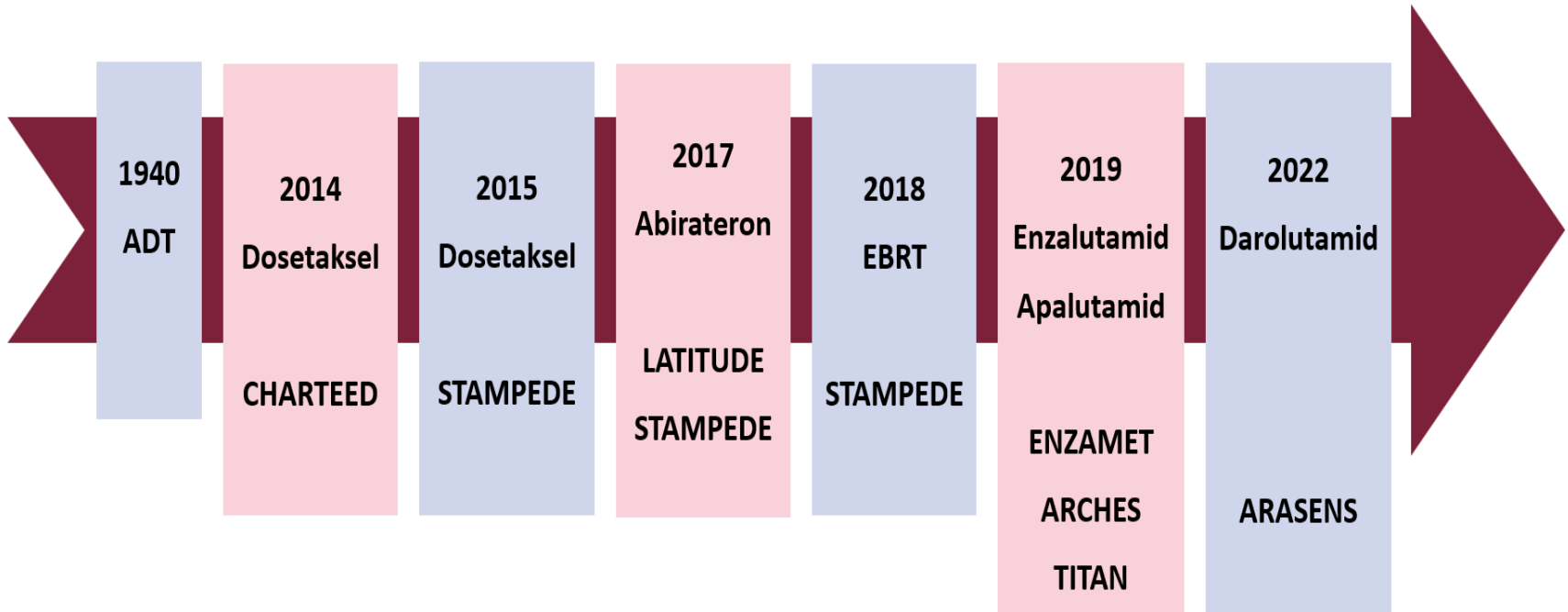
(From the Department of Surgery, the University of Chicago, Chicago, Illinois)
(Received for publication March 22, 1941)



Cancer Res 1941;1:293-297

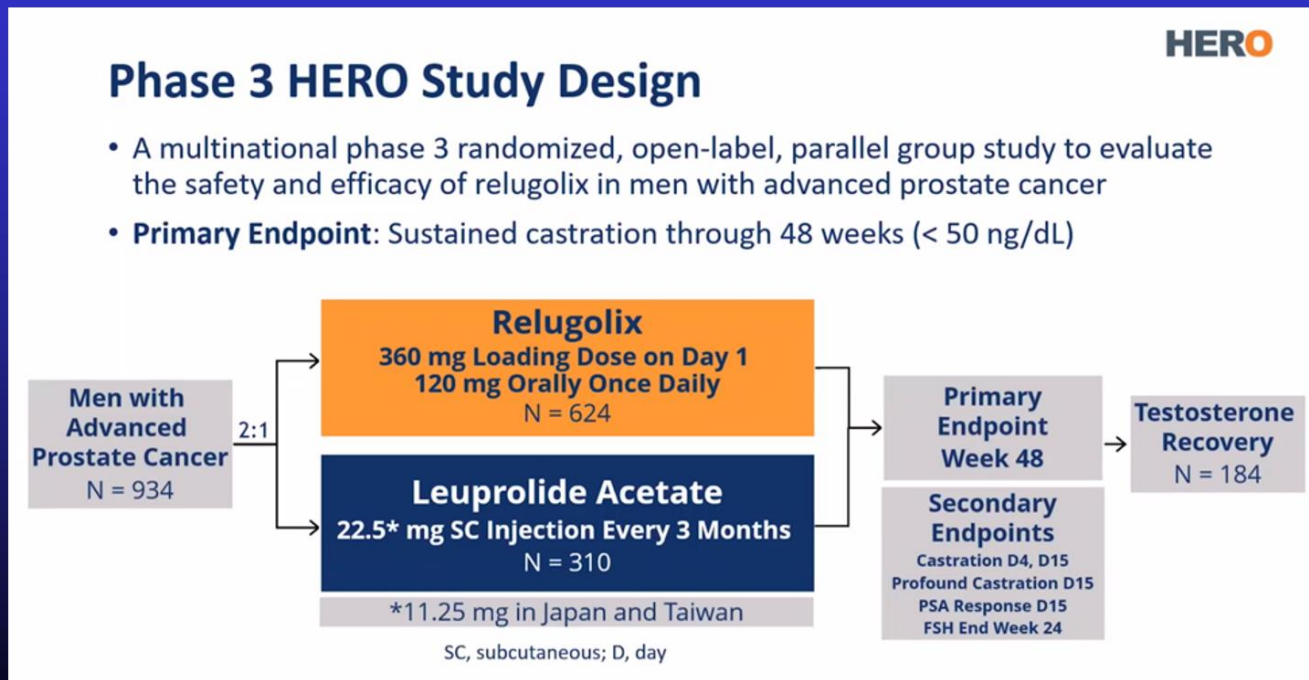
- **Seminal Observation:** PCa is an androgen driven/dependent disease & surgical or medical castration can induce significant regressions of PC.
 - *Role of acid phosphatase as a biomarker*
- >90% of patients initially respond to androgen deprivation therapy (ADT), however, most will progress to castration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

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Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

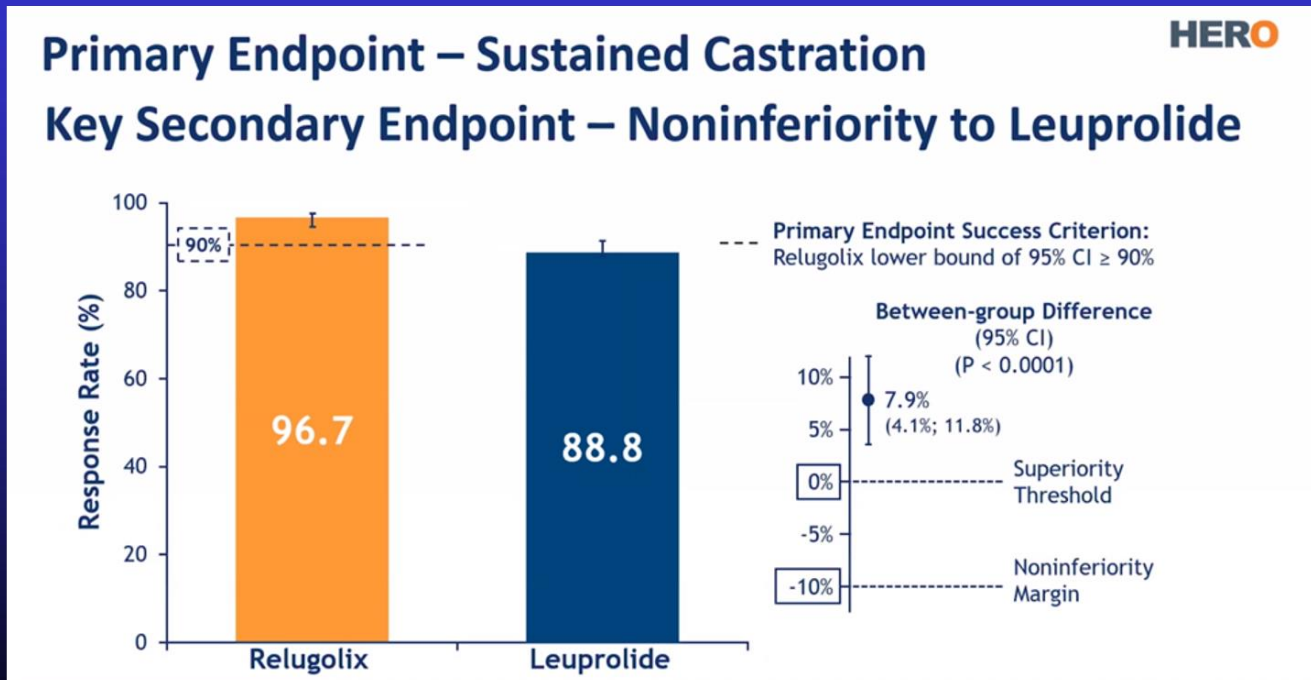
Phase 3 HERO Trial: Relugolix vs. Leuprolide



Shore, et al. NEJM, 2020

Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

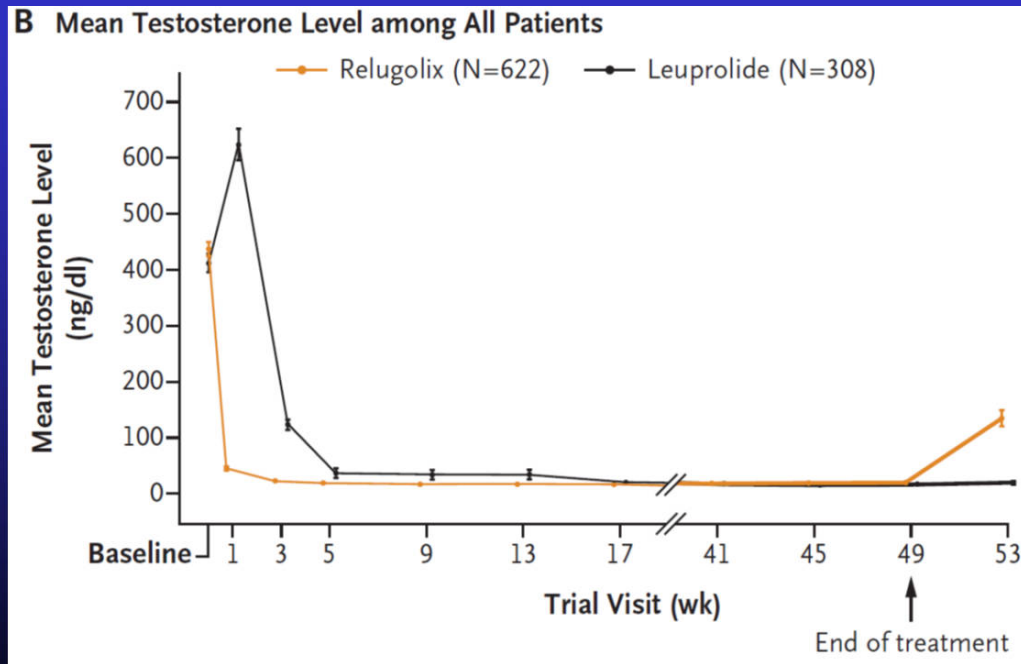
Phase 3 HERO Trial: Relugolix vs. Leuprolide



Shore, et al. NEJM, 2020

Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

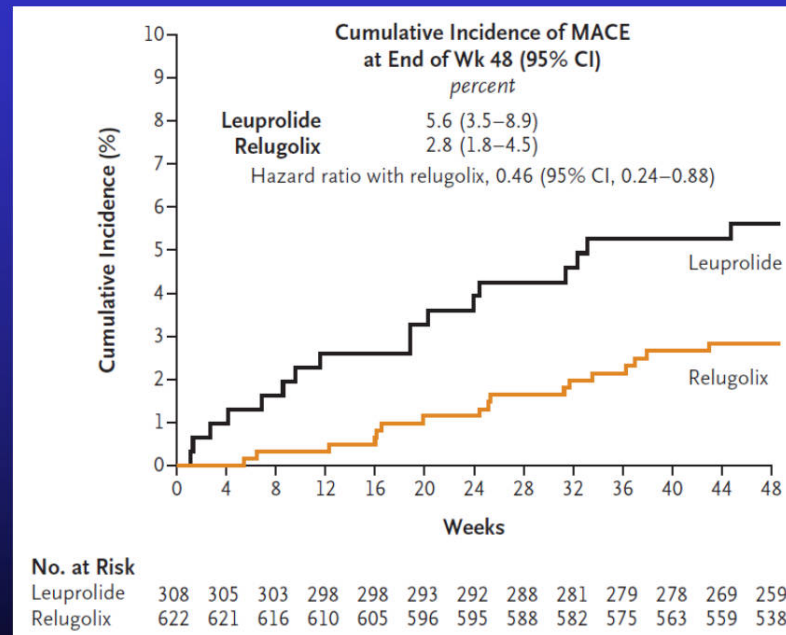
Phase 3 HERO Trial: Relugolix vs. Leuprolide



Shore, et al. NEJM, 2020

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Phase 3 HERO Trial: Relugolix vs. Leuprolide



Shore, et al. NEJM, 2020

Tedavi Kararında Etkili Faktörler

Hastalıkla İlişkili Faktörler

- 1- Yüksek volüm/Düşük volüm
- 2- De nova/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

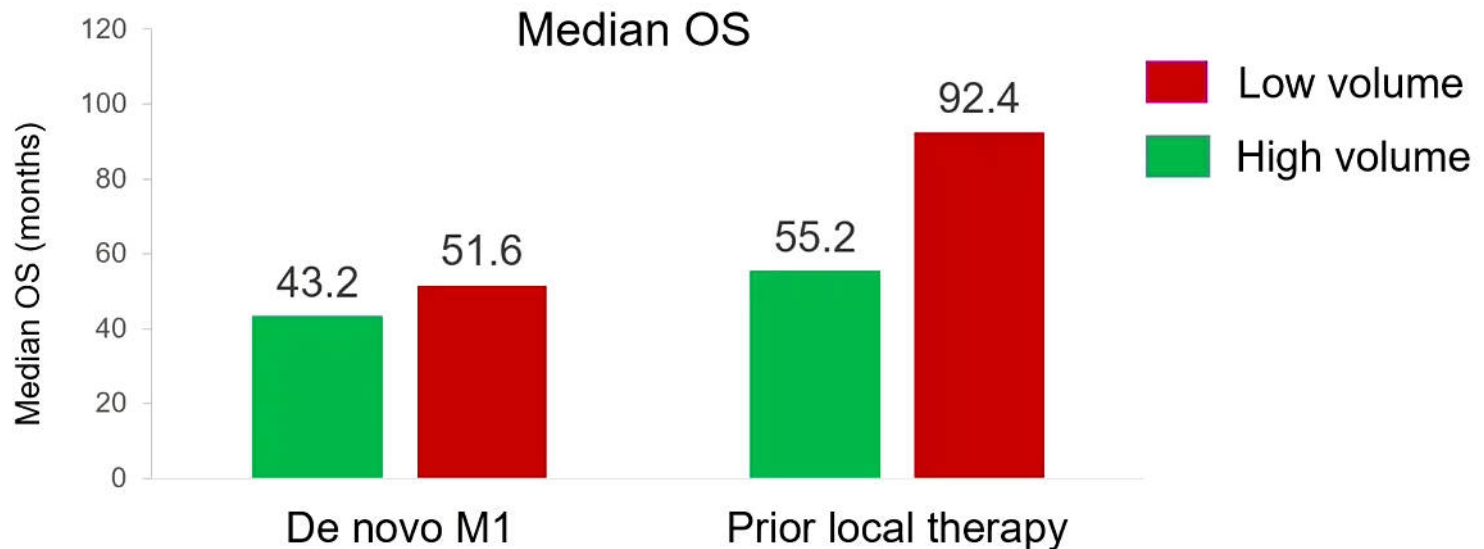
GNRH Antagonists



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

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De Novo mHNPC is associated with a worse prognosis



Retrospective analysis of 436 consecutive patients with M1 HSPC treated with ADT between 1990 and 2013 at the Dana-Farber Institute

Francini E, et al. The Prostate 2018;78:889-95.

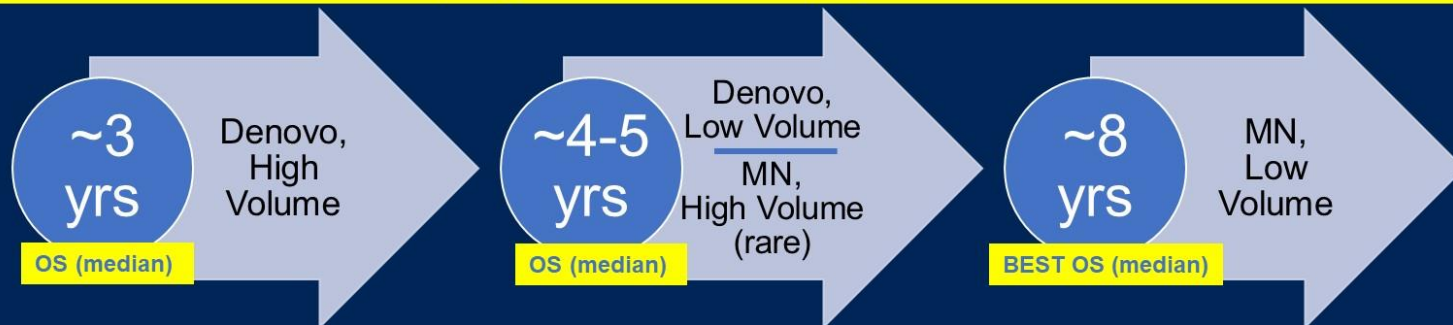
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3

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

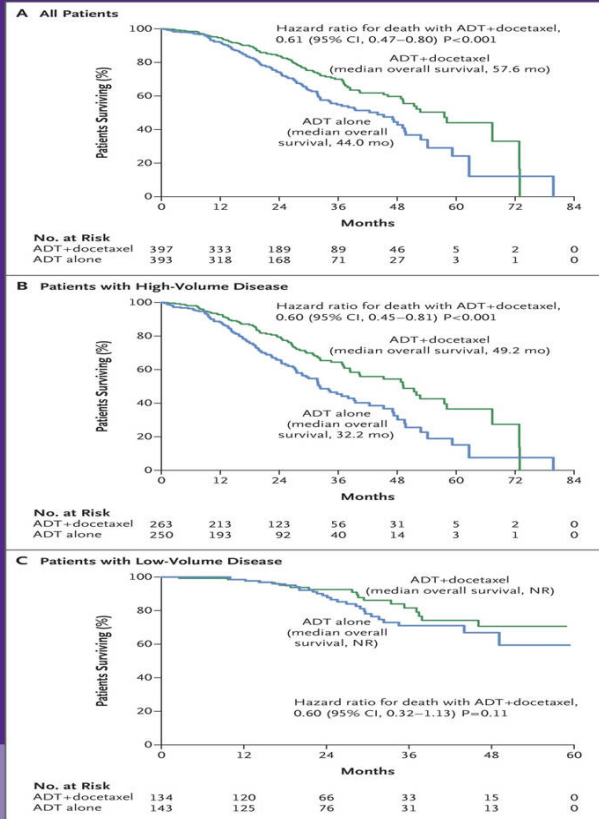
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Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

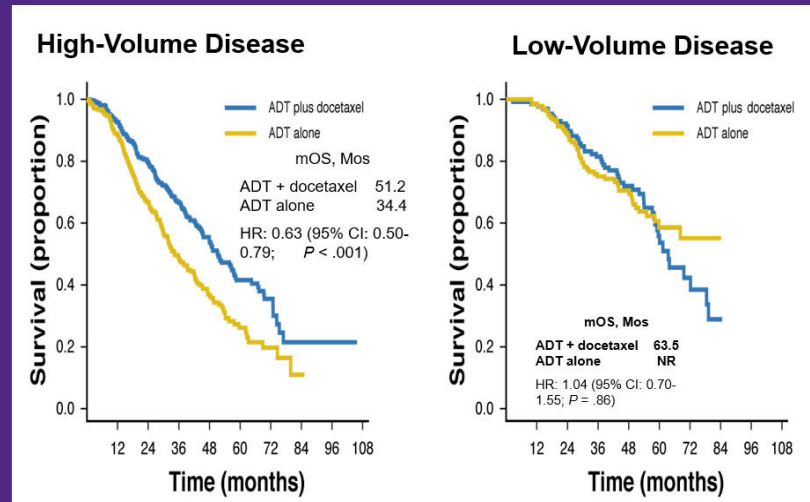
CHAARTED: ADT +/- Docetaxel in mHSPC

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

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



Sweeney CJ et al. NEJM 2015

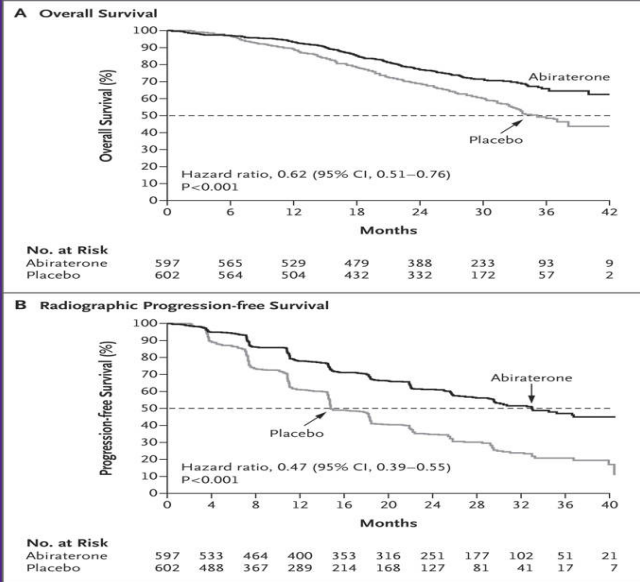


Kyriakopoulos CE, et al. J Clin Oncol. 2018

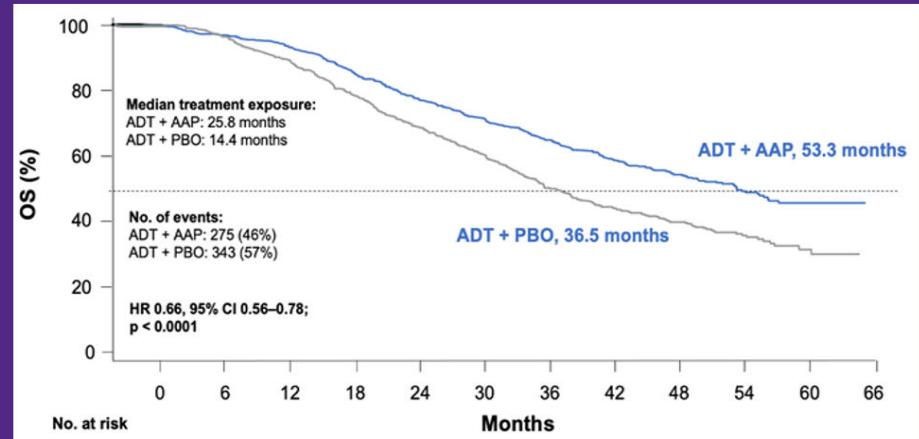
Yüksek volümlü hastalığı olanlar; viseral organ metastazı olan yada ≥ 4 kemik lezyonu olan ve en az ≥ 1 vertebra, pelvis dışı kemiklerde metastaz olmalı

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

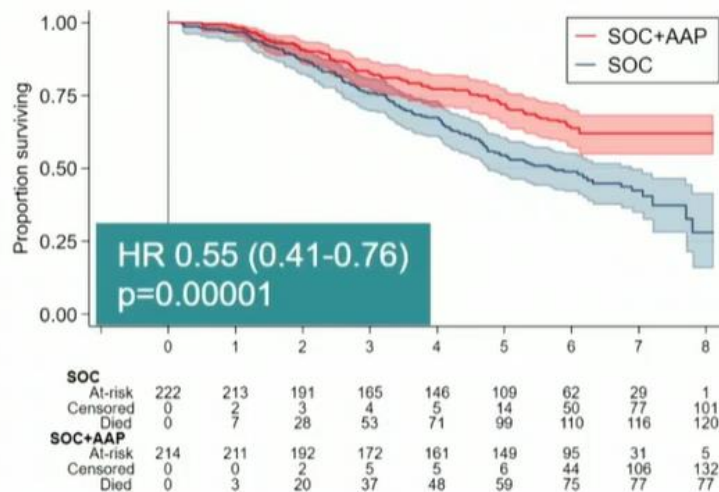
Metastatik hastalığa bağlı semptomu olanlarda RT ve Cerrahiye izin verilmiş

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VIRTUAL ESMO congress 2020

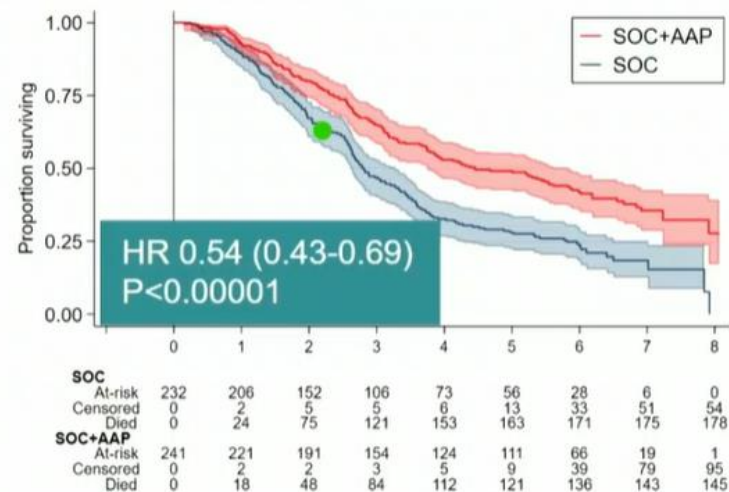
STAMPEDE: OS by risk group (LATITUDE)

Low risk



HR 0.66 (0.44-0.98)
p=0.041

High risk



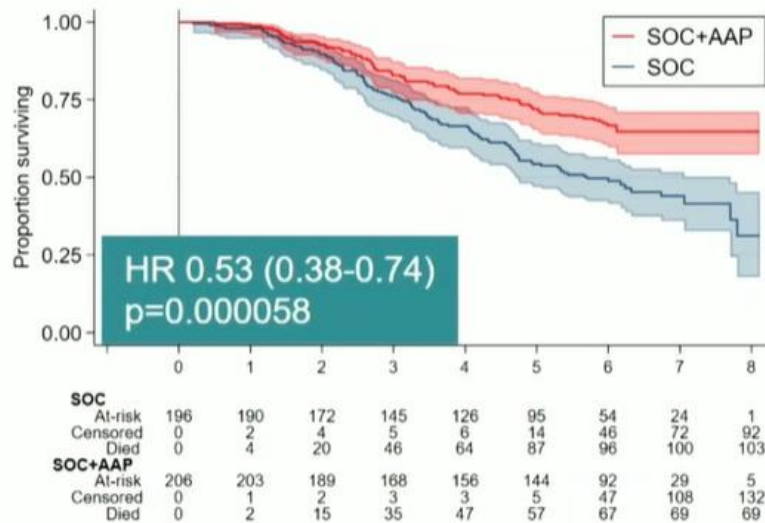
HR 0.54 (0.41-0.70)
P<0.001

Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

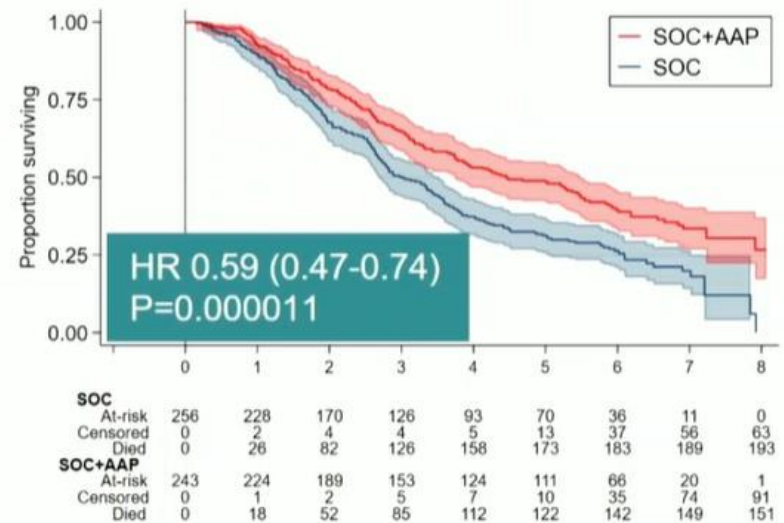
VIRTUAL 2020 ESMO congress

STAMPEDE: OS by disease burden (CHAARTED)

Low volume



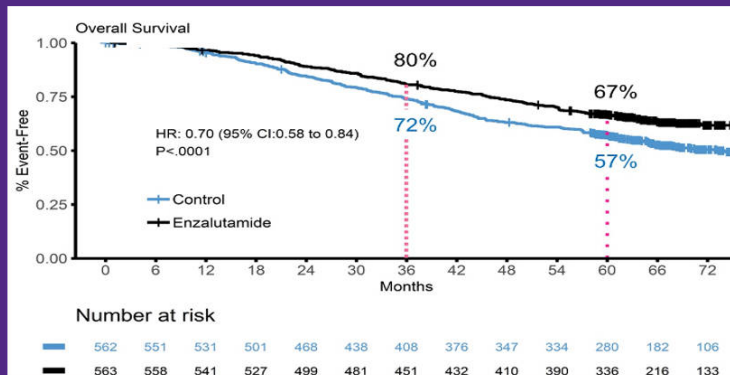
High volume



Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

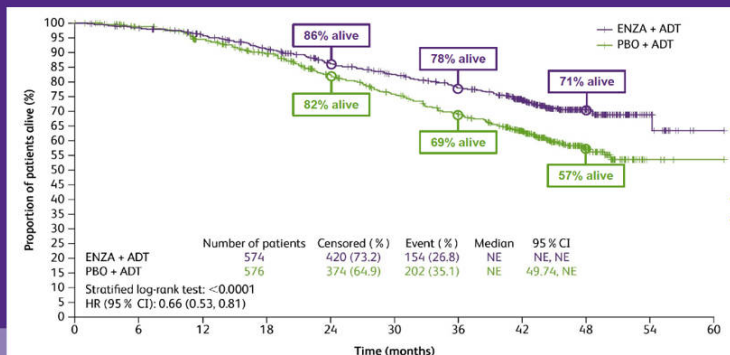
Final Overall Survival (OS) Analyses: Enzalutamide for Metastatic Hormone-Sensitive Prostate Cancer

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

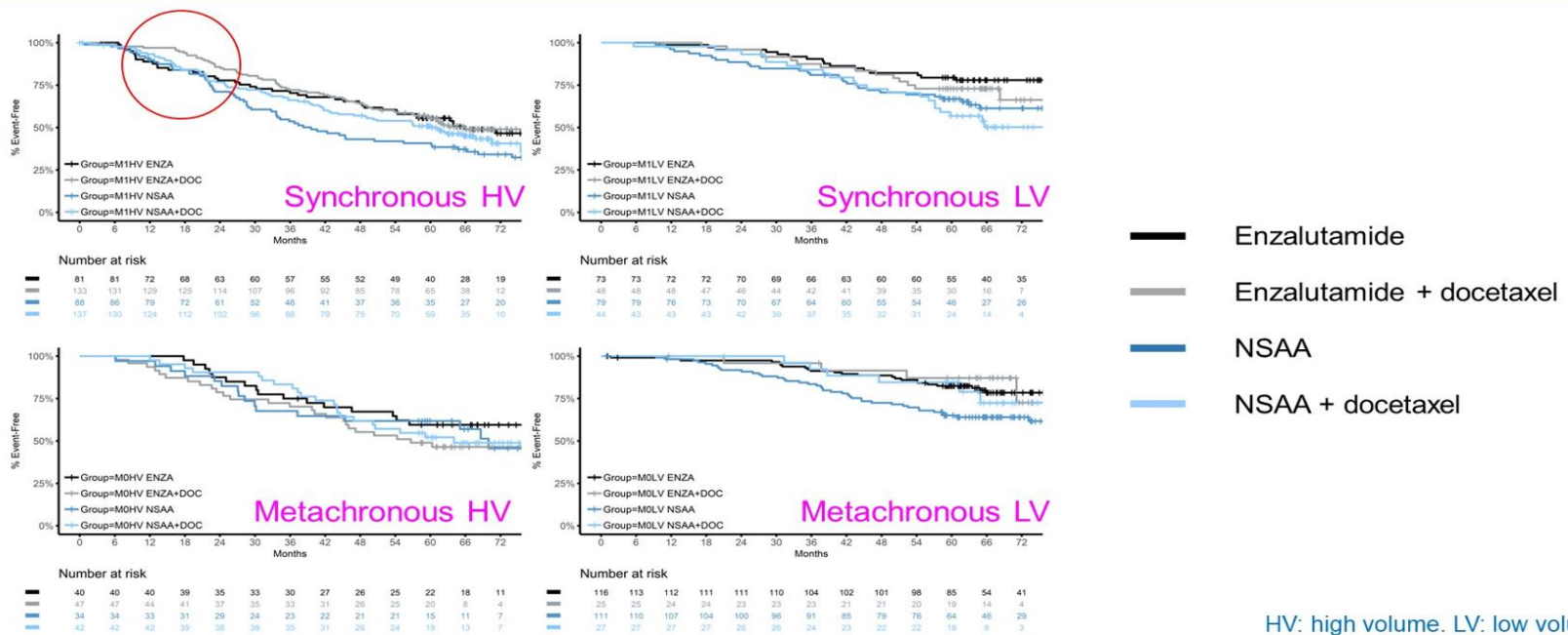
ARCHES²
Enzalutamide + ADT



- 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

Overall survival: volume, M1 timing, docetaxel



HV: high volume. LV: low volume

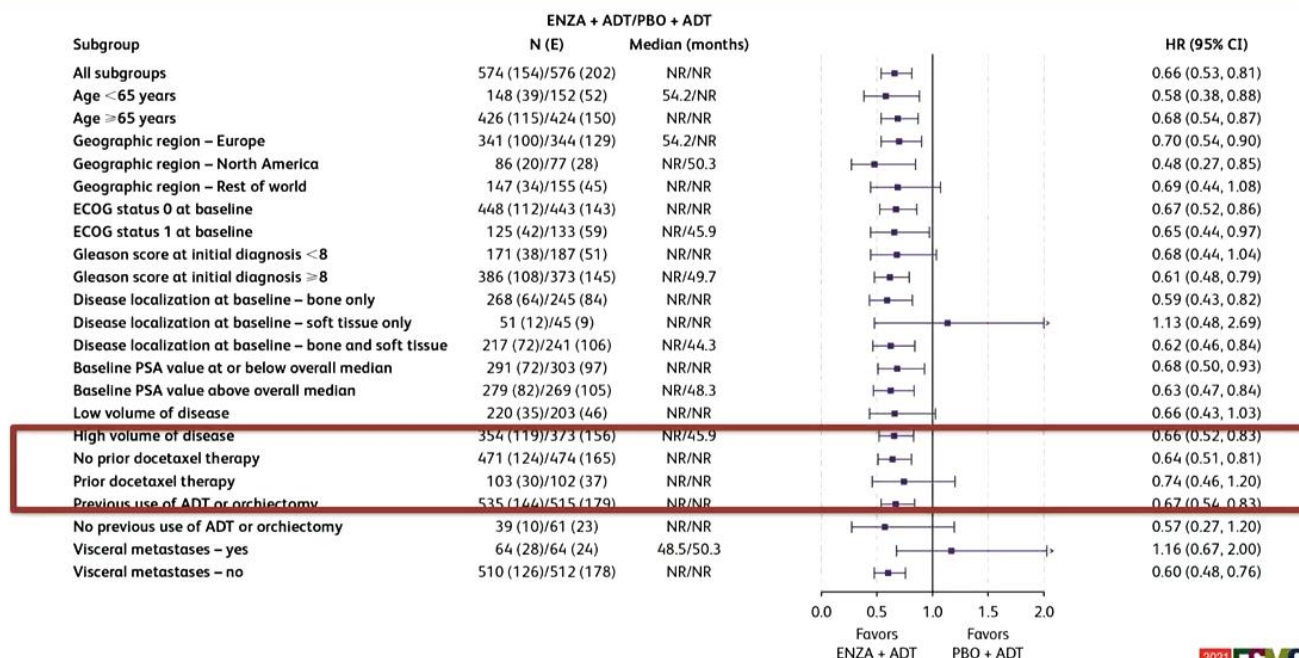
Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

	Enzalutamide		NSAA		HR (95% CI)
	Deaths/Total	5y OS %	Deaths/Total	5y OS %	
All participants	208/563	67	268/562	57	0.70 (0.58 to 0.84)
Concurrent docetaxel					
No	100/310	72	145/312	58	0.60 (0.47 to 0.78)
Yes	108/253	61	123/250	56	0.82 (0.63 to 1.06)
Volume of Disease (Vol)					
Low	59/262	80	97/261	66	0.54 (0.39 to 0.74)
High	149/301	55	171/301	49	0.79 (0.63 to 0.98)

Vol by docetaxel					
Low Vol, docetaxel no	41/189	81	70/190	66	0.51 (0.35 to 0.75)
Low Vol, docetaxel yes	18/73	78	27/71	67	0.61 (0.33 to 1.10)
High Vol, docetaxel no	59/121	57	75/122	47	0.69 (0.49 to 0.97)
High Vol, docetaxel yes	90/180	54	96/179	51	0.87 (0.66 to 1.17)
M1 at diagnosis					
All M1, docetaxel yes	79/181	60	96/181	52	0.73 (0.55 to 0.99)
Low Vol, docetaxel yes	14/48	73	21/44	57	0.57 (0.29 to 1.12)
High Vol, docetaxel yes	65/133	55	75/137	51	0.79 (0.57 to 1.10)

Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

ARCHES : Subgroup analysis. Prior Docetaxel Inconclusive on Benefit



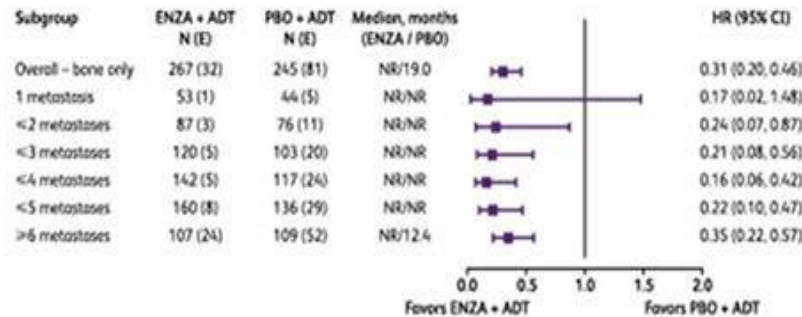
ADT=androgen deprivation therapy; CI=confidence interval; E=number of events; ECOG=Eastern Cooperative Oncology Group; ENZA=enzalutamide; HR=hazard ratio; N=number of patients; NR=not reached; PBO=placebo; PSA=prostate-specific antigen.
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Armstrong et al ESMO 2021

Discussant Eleni Efsthathiou MD PhD

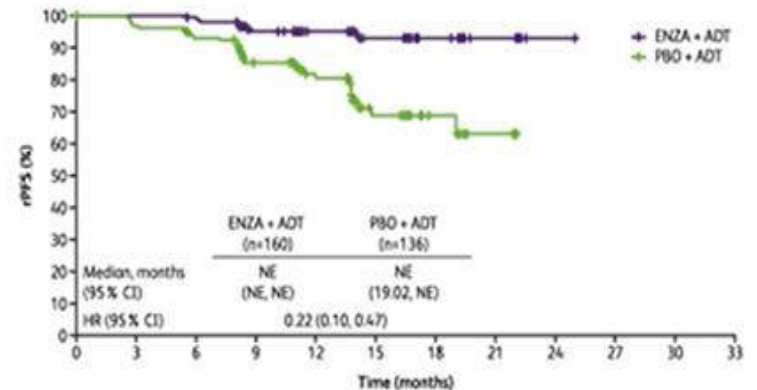
Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

Figure 1. Forest Plot of rPFS* for Oligometastatic and Polymetastatic Disease



FFS was defined as the time from randomization to first objective evidence of radiographic progression per RECIST version 1.1, as assessed by independent central review, or death from any cause within 24 weeks of treatment discontinuation, whichever occurred first.

Figure 2. Kaplan-Meier Curve of rPFS in Oligometastatic Patients With ≤ 5 Metastases



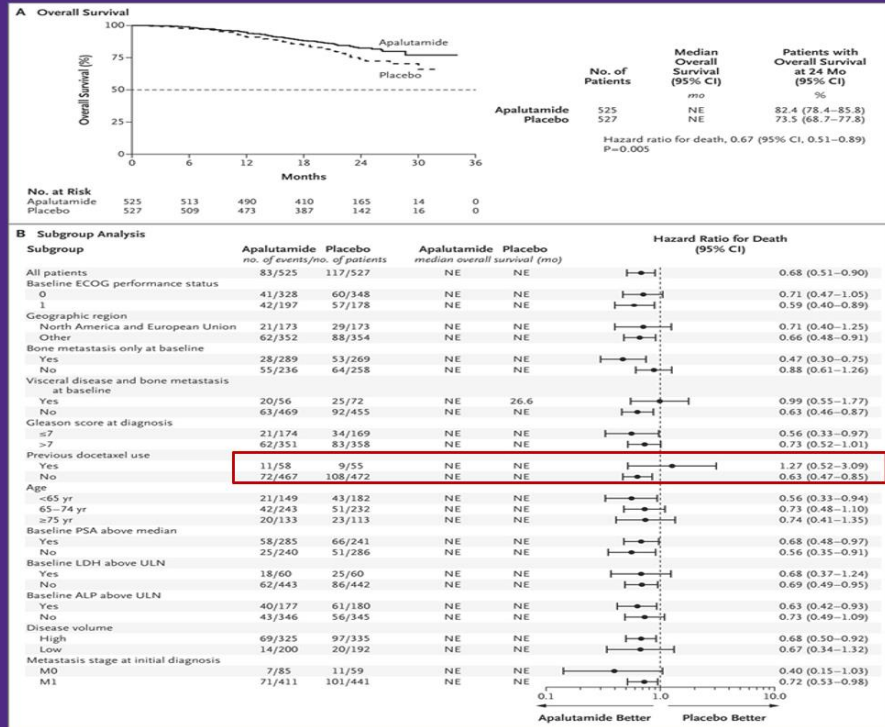
No. at risk	160	150	148	112	75	42	15	6	1	0	0	0
ENZA + ADT												
PSO + ADT	136	126	119	87	58	28	12	3	0	0	0	0

ADT=androgen deprivation therapy; CI=confidence interval; ENZA=enzalutamide; HR=hazard ratio; NE=not evaluable; NR=not reached; PBO=placebo; rPFS, radiographic progression-free survival.

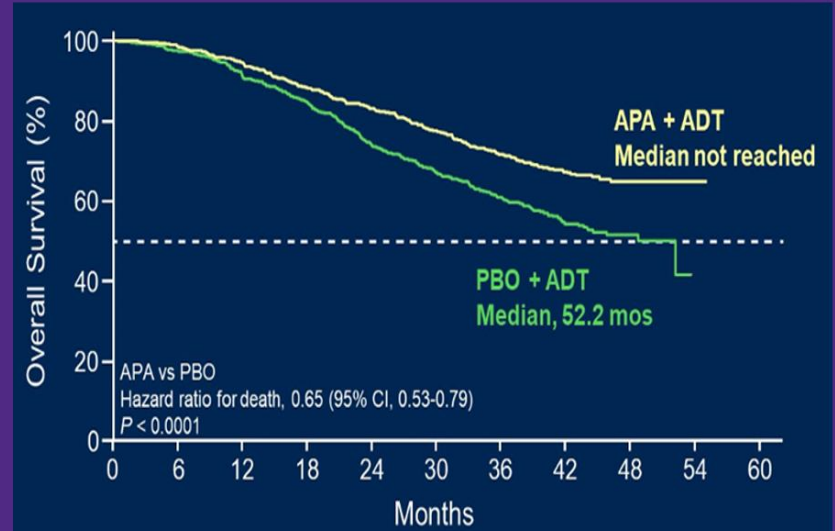
ARCHES post-hoc analiz; enzalutamid oligometastik hastalıkta etkinliği

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

> Eur J Cancer. 2023 Aug 11;193:113290. doi: 10.1016/j.ejca.2023.113290. Online ahead of print.

Apalutamide plus androgen deprivation therapy in clinical subgroups of patients with metastatic castration-sensitive prostate cancer: A subgroup analysis of the randomised clinical TITAN study

Axel S Merseburger ¹, Neeraj Agarwal ², Amitabha Bhaumik ³, Florence Lefresne ⁴, Laurence I Karsh ⁵, Andrea J Pereira de Santana Gomes ⁶, Álvaro Juárez Soto ⁷, Robert W Given ⁸, Sabine D Brookman-May ⁹, Suneel D Mundle ¹⁰, Sharon A McCarthy ¹¹, Hirotugu Uemura ¹², Simon Chowdhury ¹³, Kim N Chi ¹⁴, Anders Bjartell ¹⁵

Affiliations + expand

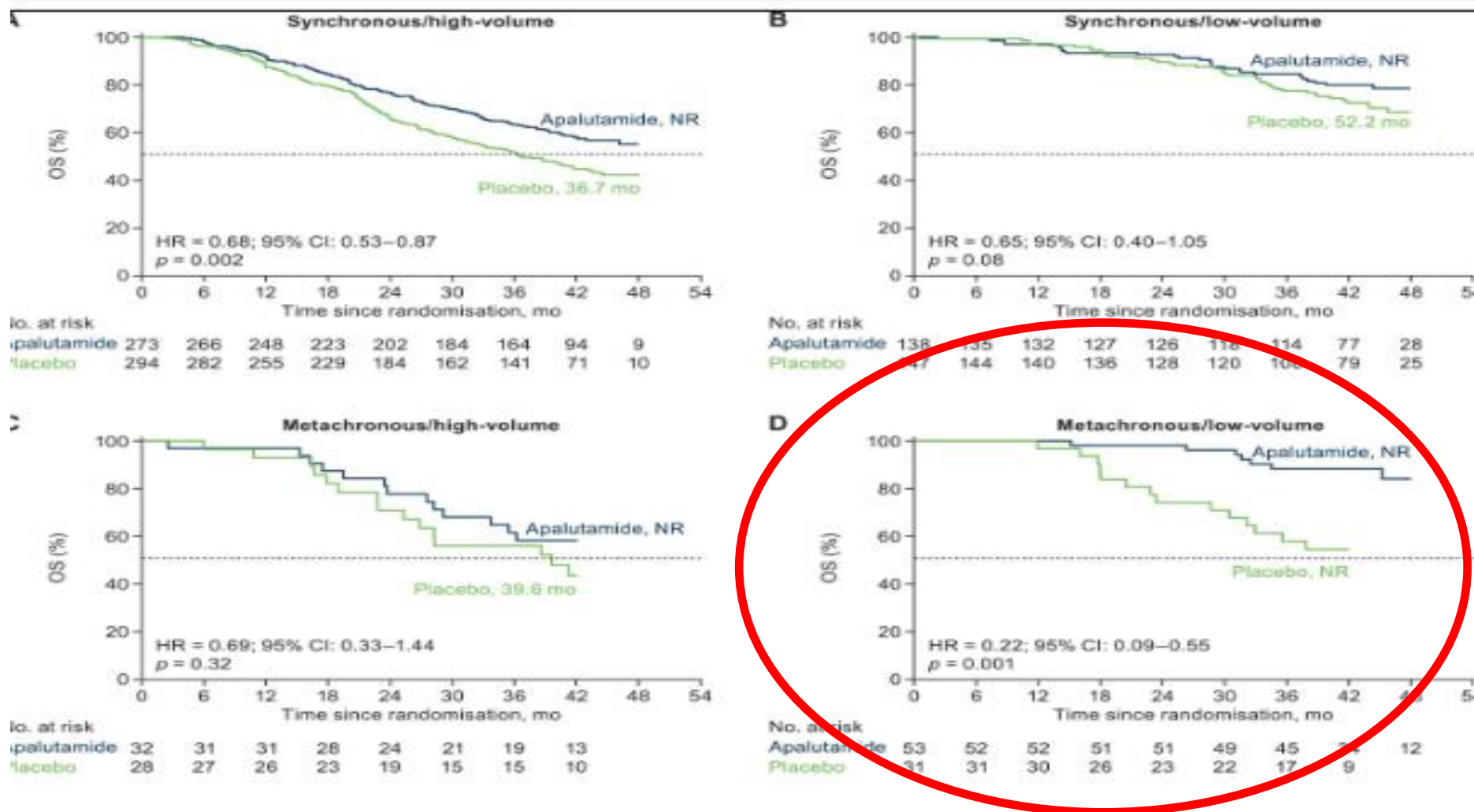
PMID: 37708629 DOI: 10.1016/j.ejca.2023.113290

[Free article](#)

Abstract

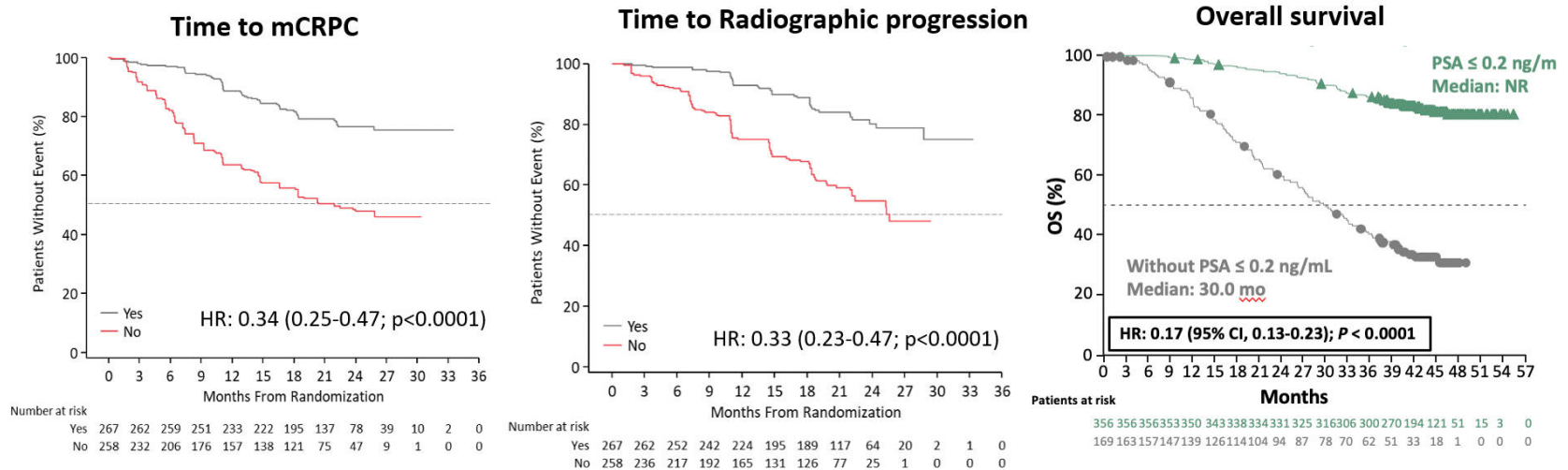
Background: Whether disease burden in patients with metastatic castration-sensitive prostate cancer (mCSPC) predicts treatment outcomes is unknown. We assessed apalutamide treatment effect in TITAN patients with mCSPC by disease volume, metastasis number and timing of metastasis presentation.

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Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

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.

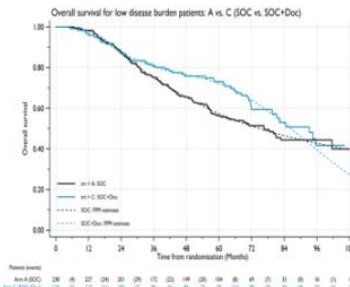
Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi



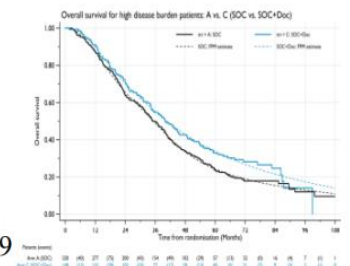
Should we count the metastases for decision making about systemic treatment? **No !!!**

Docetaxel

Low burden



High burden



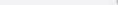
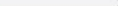
Clarke N, Ann Oncol 2019

Hormonal agents

STAMPEDE (Abi)

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

TITAN (Apa)

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

ENZAMET (Enza)

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

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

Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

**High level summary of all HR(OS) and 95% CI
TS + / - potent ARi mHSPC data: Consistent!**

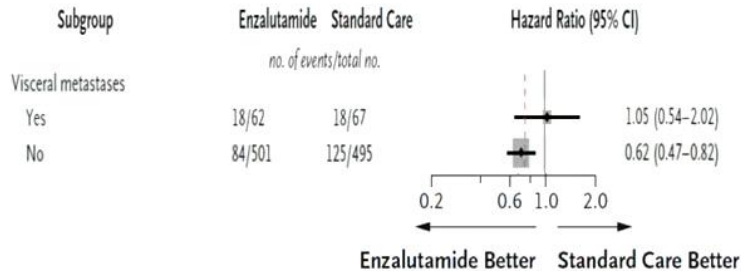
M1 HSPC	All M1	High Volume/risk	Low Volume/risk	Metachronous (mostly low volume)
LATITUDE-Abi (All <i>de novo</i>)	0.66 0.58-0.178	0.62 (0.52-0.74)	0.72 (0.47-1.10)	N/A
STAMPEDE-Abi (All <i>de novo</i>)	0.60 (0.49-0.71)	0.54 (0.43-0.69)	0.55 (0.41-0.76)	N/A
ENZAMET-Enza (45% conc doc)	0.67 (0.52-0.86)	0.53 (0.42-1.09)	0.39 (0.21-0.71)	0.72 (0.47-1.09)
TITAN-Apa (10% prior doc)	0.68 0.51-0.90	0.68 (0.50-0.92)	0.67 (0.34-1.32)	0.4 (0.15-1.03)

Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

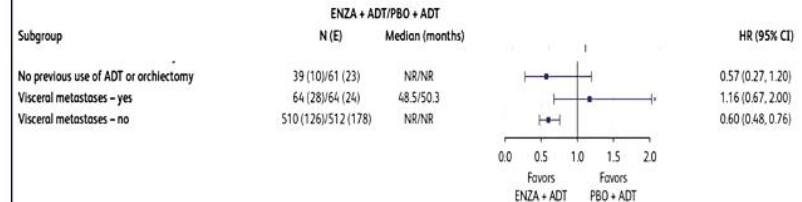
Does type of metastasis matter in mHNPc?

Results from new hormonal treatments in mHNPc according visceral mets

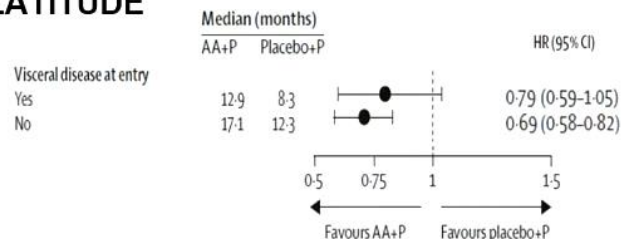
ENZAMET



ARCHES



LATITUDE



Subgroup

Apalutamide Placebo
no. of events/no. of patients

Apalutamide Placebo
median overall survival (mo)

TITAN

Visceral disease and bone metastasis
at baseline

Yes
No
Gleason score at diagnosis

20/56
63/469

25/72
92/455

NE
NE

26.6
NE

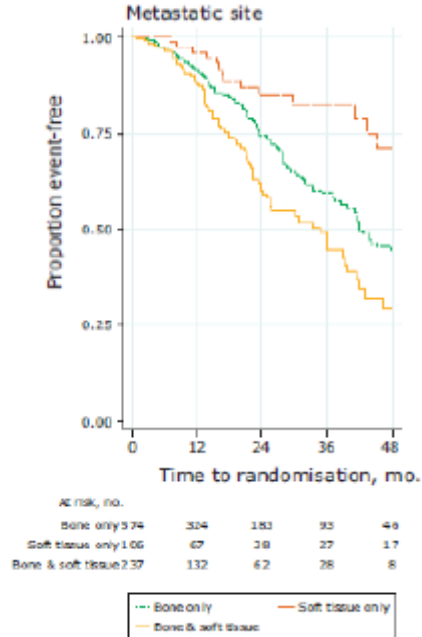
0.99 (0.55–1.77)
0.63 (0.46–0.87)

Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

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

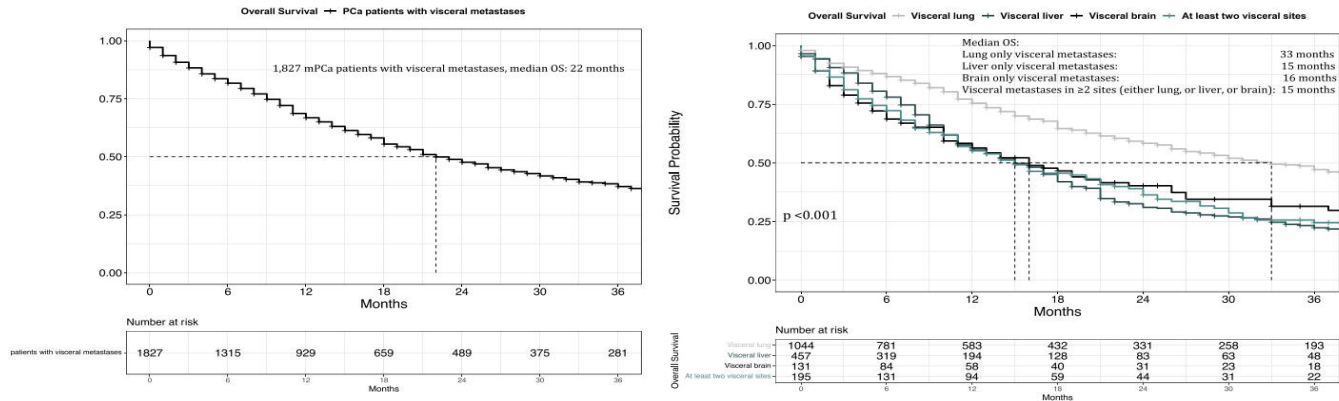
Hastaların %62 yalnız kemik ve %26 kemik+yumu  ka doku met.(lenf nodu metastazı)

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

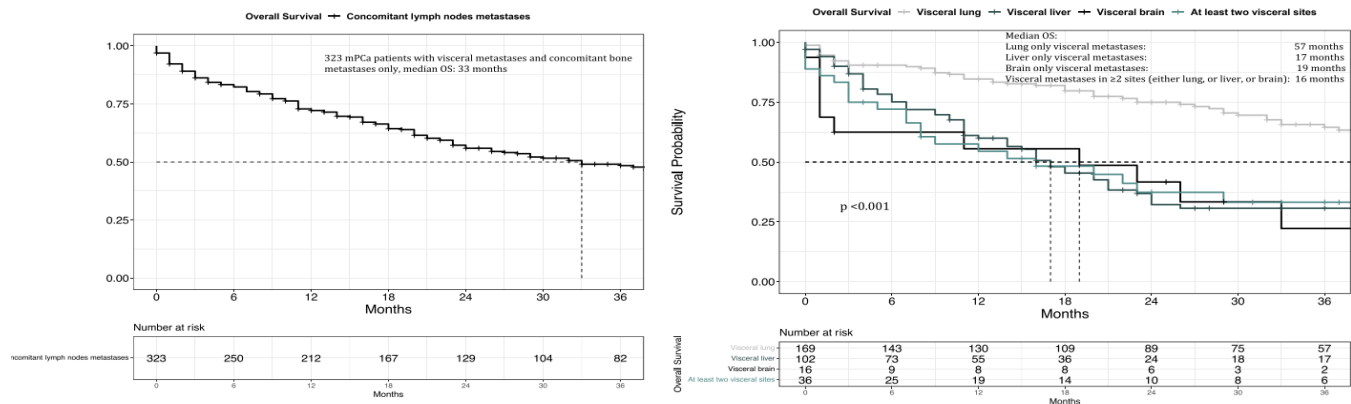
Yumu  k doku+kemik met.%60
2yıllık FFS; yumu  k dokuda %54, kemik met %28 , yumu  k doku+kemik met.%18

Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

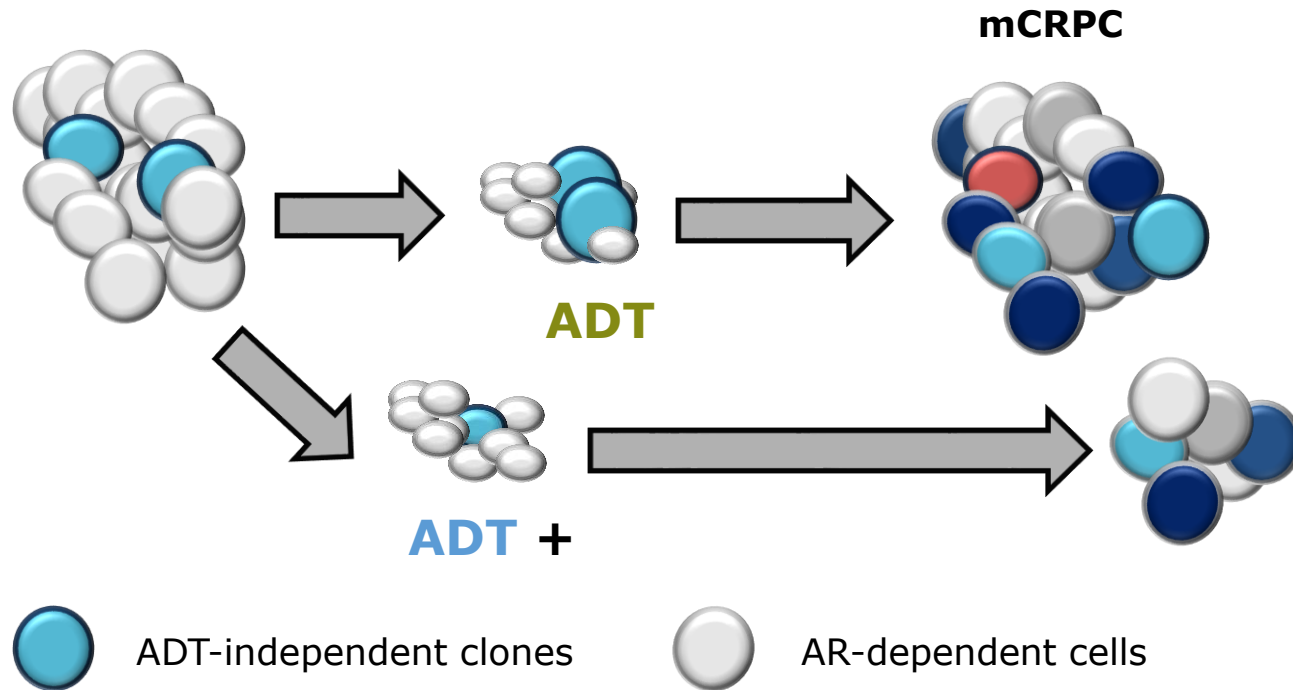
Kaplan-Meier plots displaying overall survival in 1827 metastatic prostate cancer (mPCa) patients with visceral metastases, regardless of presence of lymph node and/or bone metastases: (A) in the overall population; (B) according to location of visceral metastatic sites.



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.



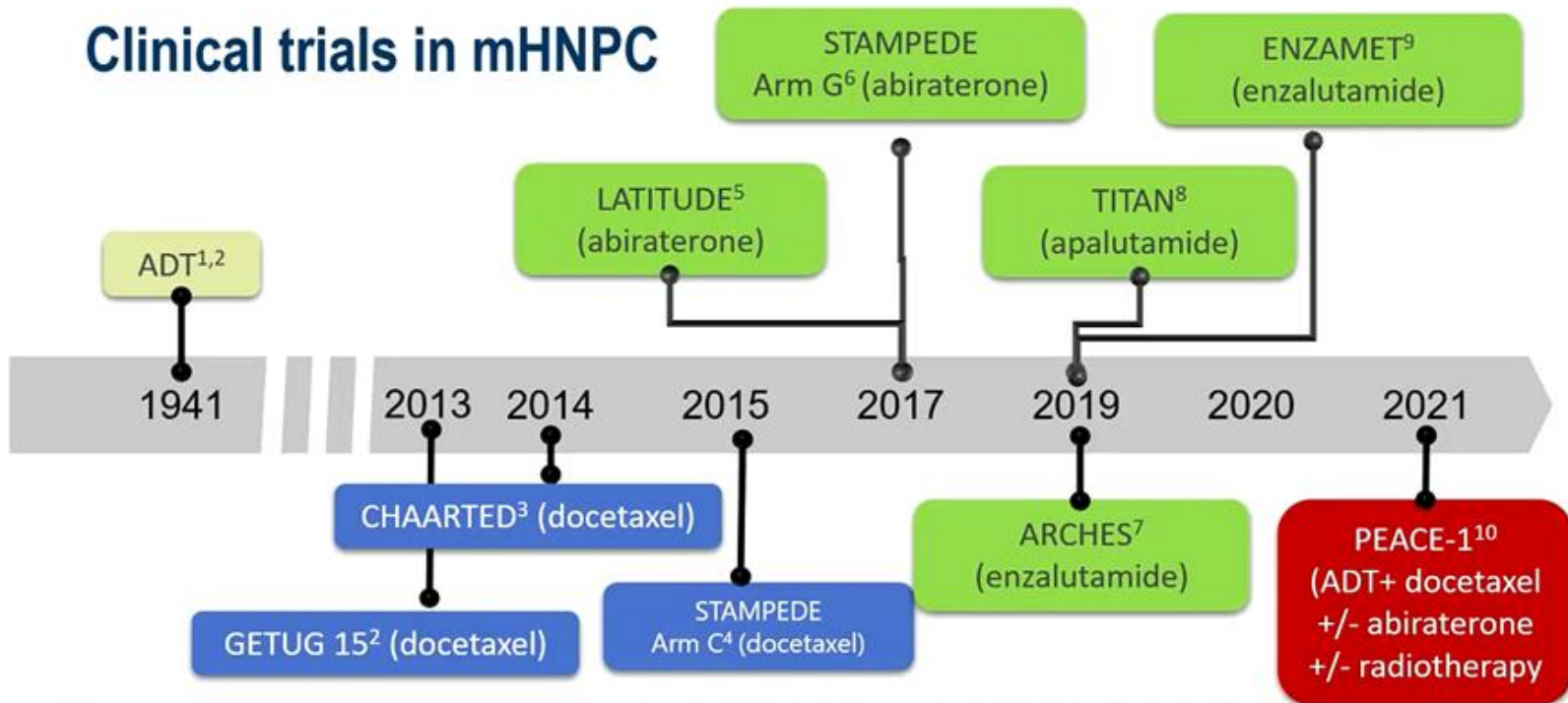
Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi



Role of Effective Systemic Therapy

Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

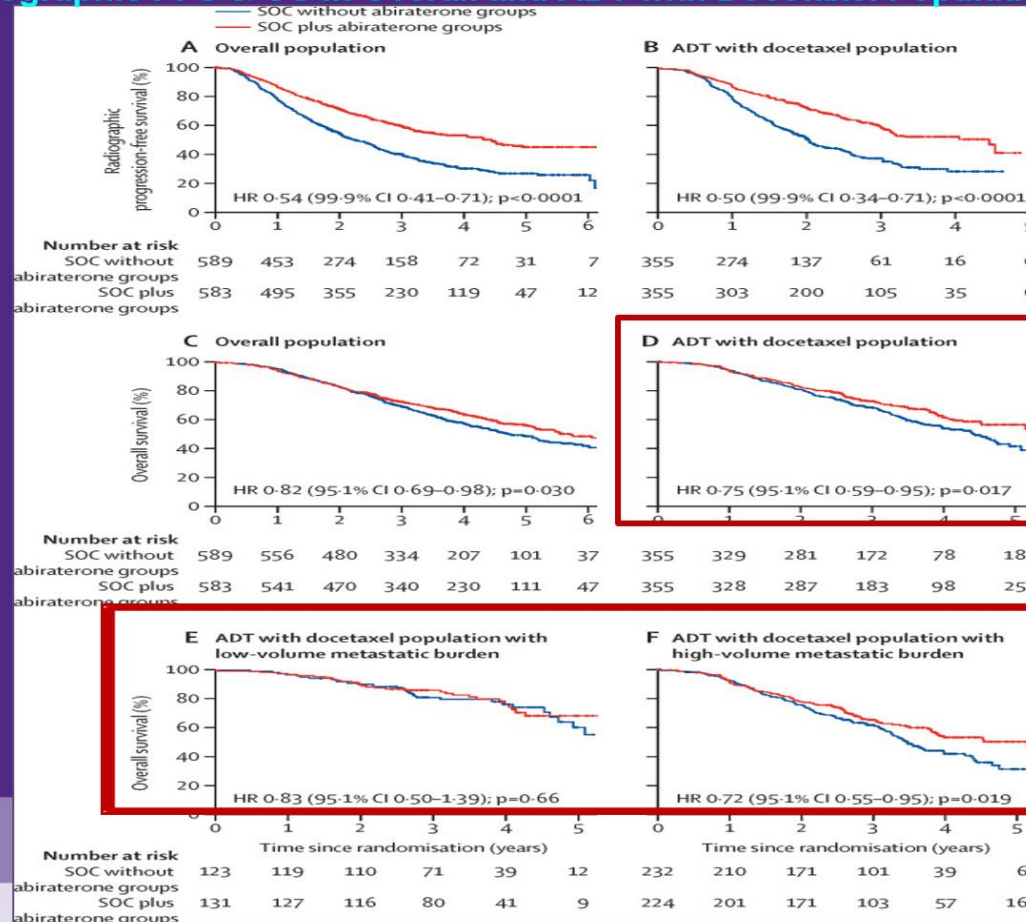
Clinical trials in mHNPc



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 Tedavisi

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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#GU23

PRESENTED BY: LOIC MOUREY MD

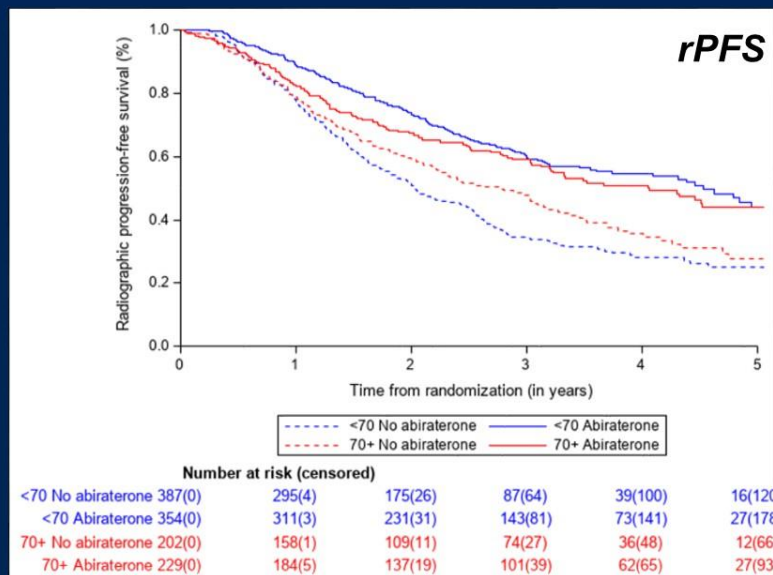
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CLINICAL ONCOLOGY
KNOWLEDGE CONQUERS CANCER

Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

Results (1)

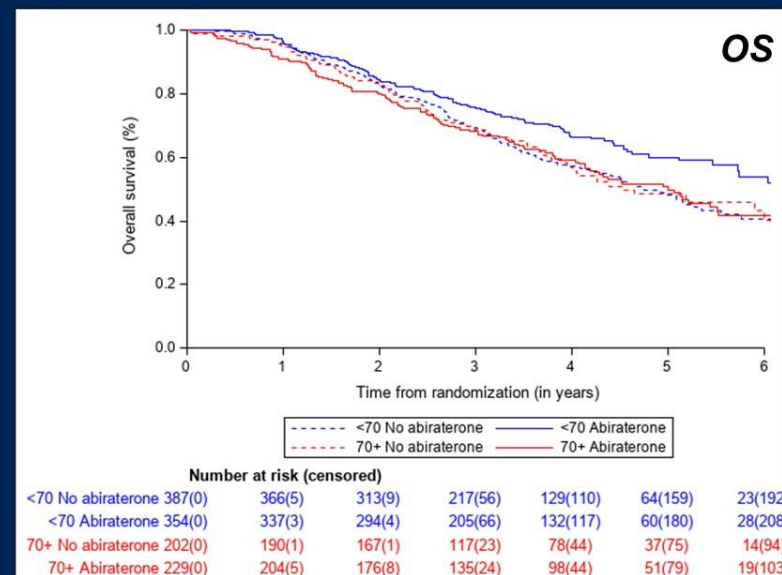
Overall population



Age ≥ 70: HR 0.65, 95%CI (0.42-1.01)

Age <70: HR 0.49, 95%CI (0.35-0.69)

p-value of the interaction test 0.08



Age ≥ 70: HR 0.95, 95%CI (0.72-1.25)

Age <70: HR 0.73, 95%CI (0.58-0.92)

p-value of the interaction test 0.15

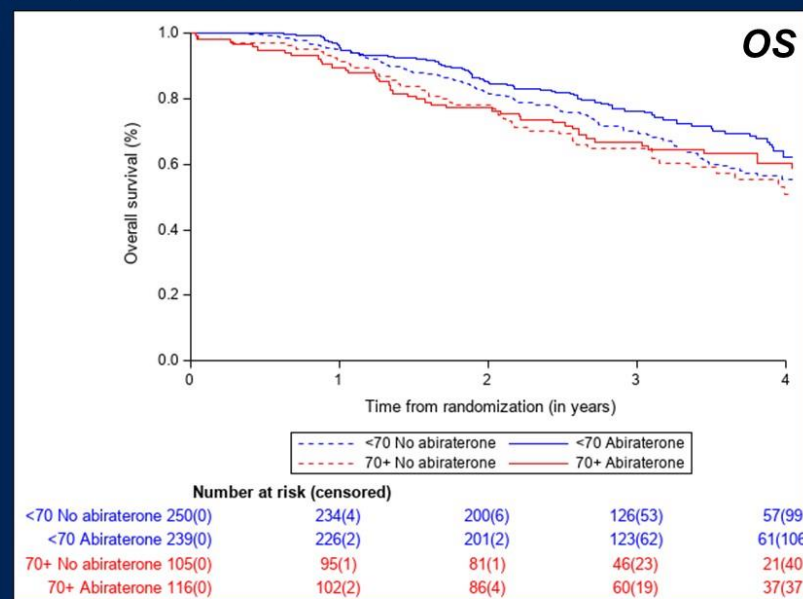
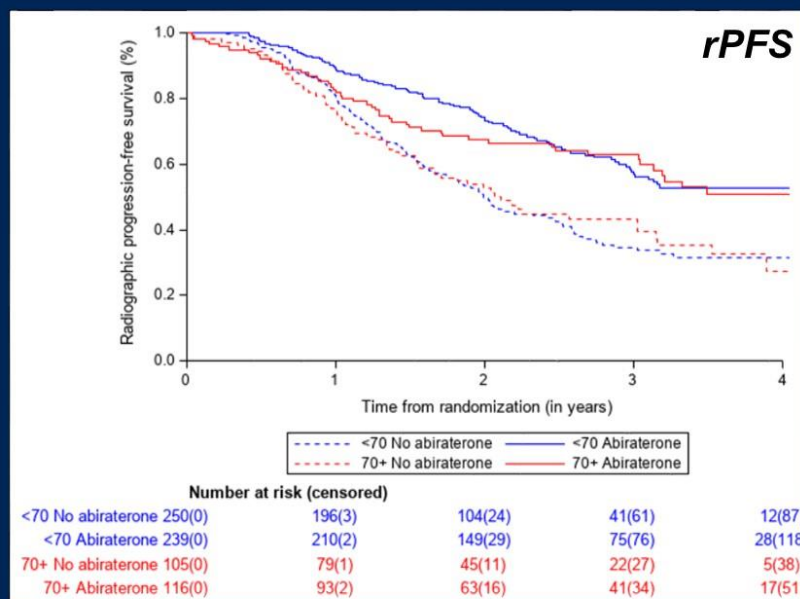
Benefit of AA+P on rPFS and OS may decrease with age

Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

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)

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Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

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

Primary analysis

Data cut-off
Oct 25, 2021

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 Tedavisi

4

Baseline Demographics and Disease Characteristics

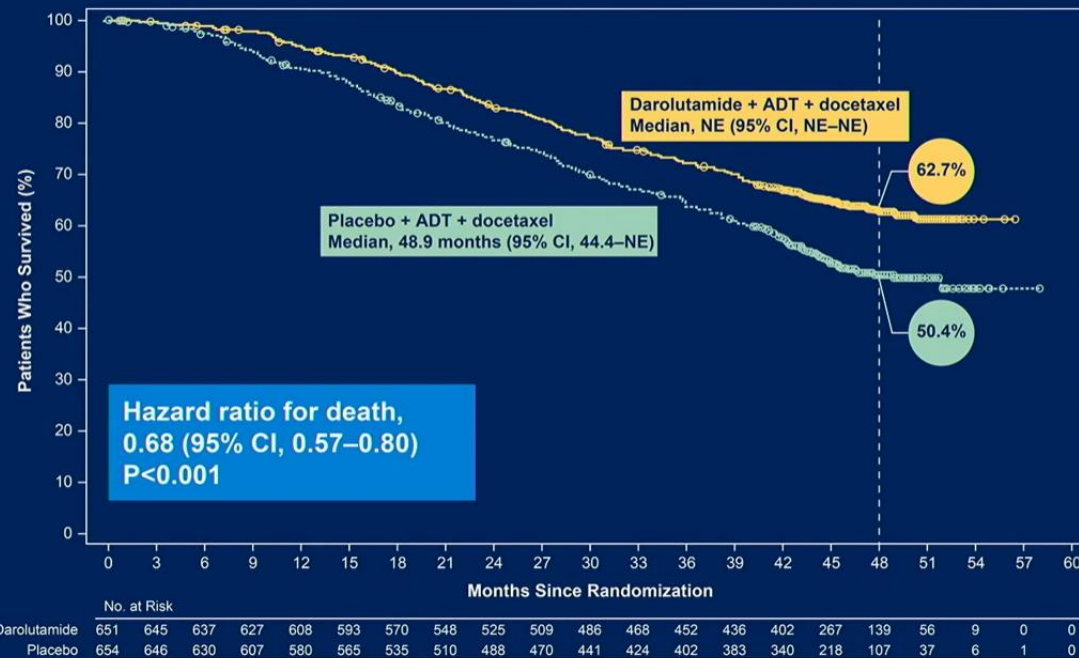
Patient demographics and disease characteristics		Darolutamide + ADT + docetaxel (n=651)	Placebo + ADT + docetaxel (n=654*)
Age, median (range), y		67 (41–89)	67 (42–86)
Region, n (%)	North American	125 (19.2)	119 (18.2)
	Asia Pacific	229 (35.2)	244 (37.3)
	Rest of World	297 (45.6)	291 (44.5)
EGOG performance 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 Tedavisi

5

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



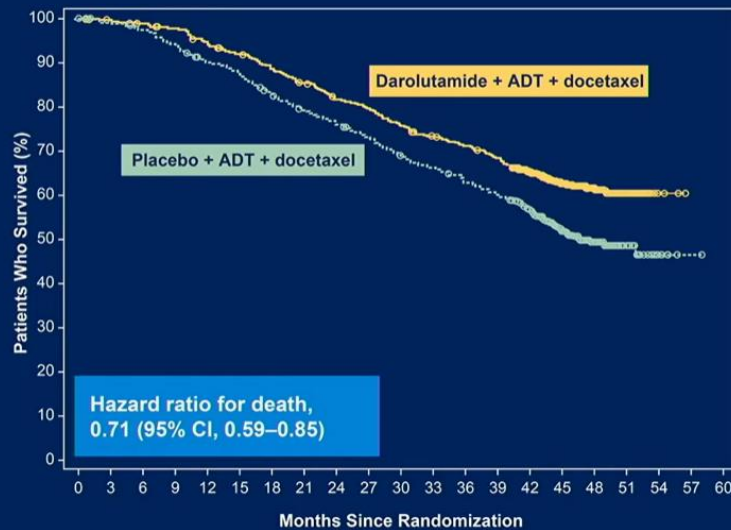
*Primary analysis occurred after 533 deaths (darolutamide, 229; placebo, 304). CI, confidence interval; NE, not estimable.

Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

8

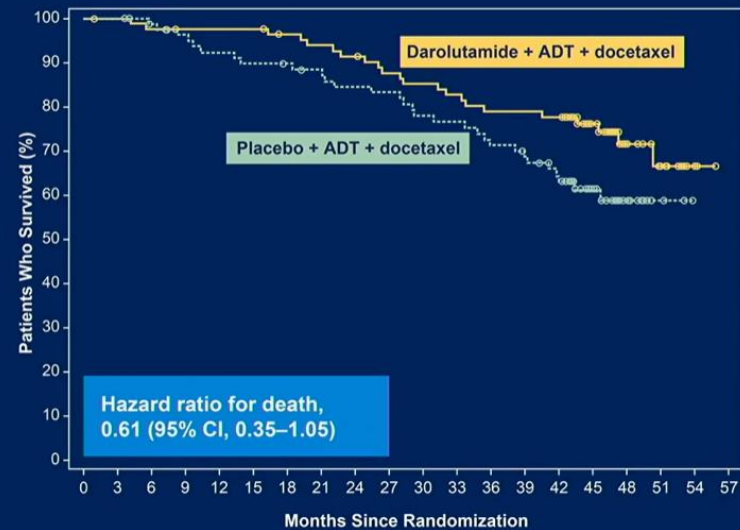
Overall Survival By Metastatic Stage at Initial Diagnosis

De novo metastatic disease



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

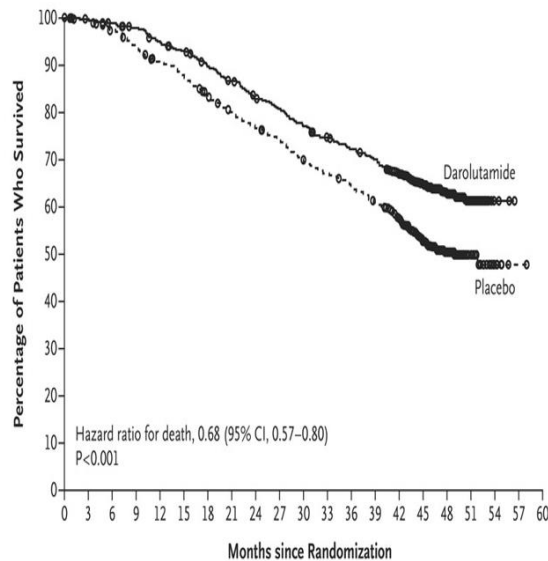
Recurrent metastatic disease



	No. at Risk															
Darolutamide	86	85	83	81	81	81	78	76	74	70	68	66	63	63	62	43
Placebo	82	82	78	75	72	70	69	67	64	63	59	58	54	51	45	26

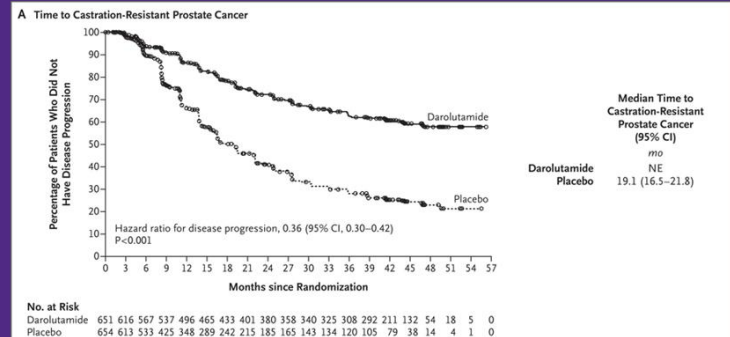
Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

Triplet #2: ARASENS: ADT + Docetaxel + Darolutamide vs Placebo Overall Survival



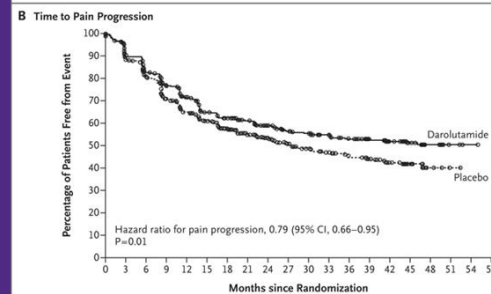
Median Survival
(95% CI)
mo
Darolutamide NE
Placebo 48.9 (44.4-NE)

No. at Risk	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57	60
Darolutamide	651	645	637	627	608	593	570	548	525	509	486	468	452	436	402	267	139	56	9	0	0
Placebo	654	646	630	607	580	565	535	510	488	470	441	424	402	383	340	218	107	37	6	1	0



Median Time to
Castration-Resistant
Prostate Cancer
(95% CI)
mo
Darolutamide NE
Placebo 19.1 (16.5-21.8)

No. at Risk	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57
Darolutamide	651	616	567	537	496	465	433	401	380	358	340	325	308	292	211	132	54	18	5	0
Placebo	654	613	533	423	348	289	242	215	185	165	143	134	120	105	79	38	14	4	1	0



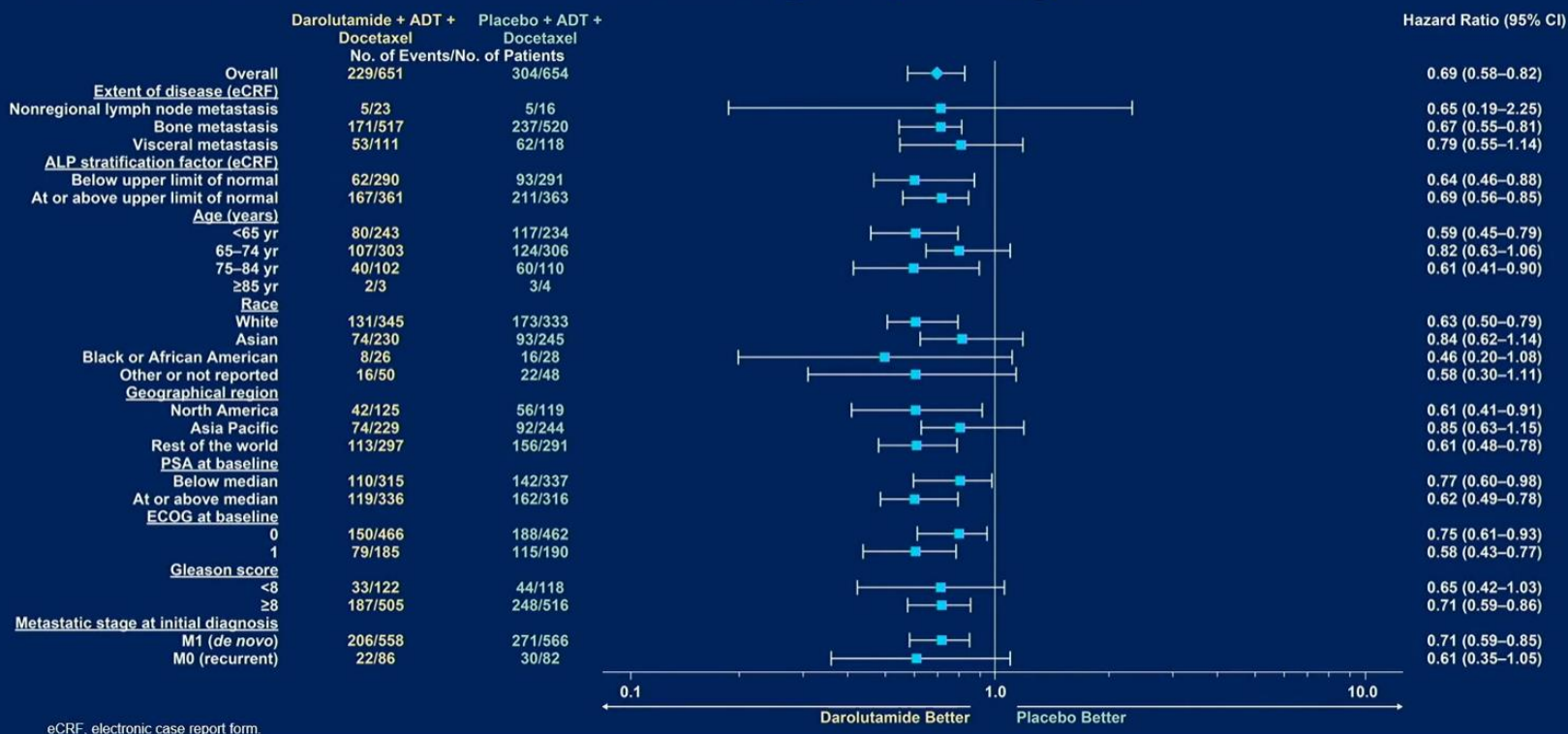
Median Time to
Pain Progression
(95% CI)
mo
Darolutamide NE (30.5-NE)
Placebo 27.5 (22.0-36.1)

No. at Risk	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57
Darolutamide	651	447	401	363	327	284	265	249	228	211	202	189	175	159	106	67	31	6	1	0
Placebo	654	442	395	332	288	255	221	188	160	134	119	107	93	86	62	35	8	1	0	0

Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

7

ARASENS Overall Survival: Subgroup Analyses



eCRF, electronic case report form.

Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

13

Adverse Events of Special Interest for AR Pathway Inhibitors

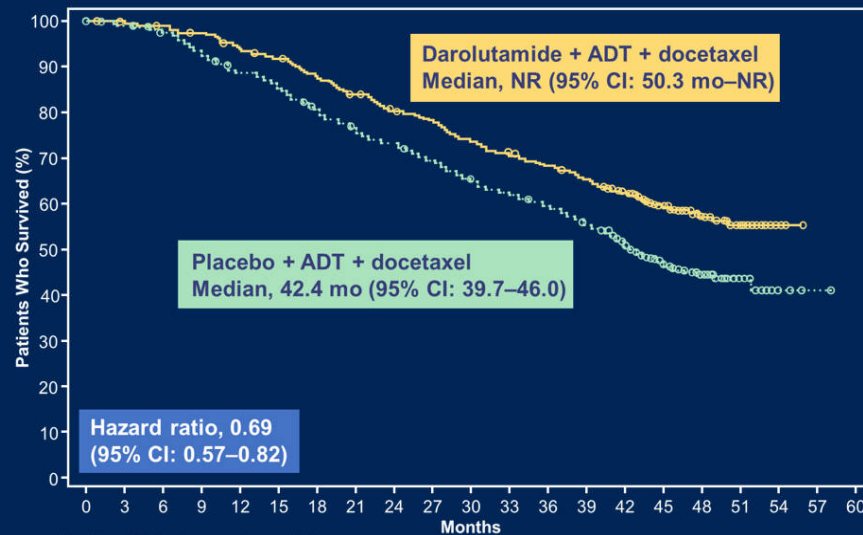
AEs associated with AR pathway inhibitor therapy	Darolutamide + ADT + docetaxel (n=652)		Placebo + ADT + docetaxel (n=650)	
	Patients, n (%)	EAIR/100 PY*	Patients, n (%)	EAIR/100 PY*
Fatigue	216 (33.1)	12.5	214 (32.9)	17.8
Bone fracture	49 (7.5)	2.8	33 (5.1)	2.7
Falls	43 (6.6)	2.5	30 (4.6)	2.5
Rash†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

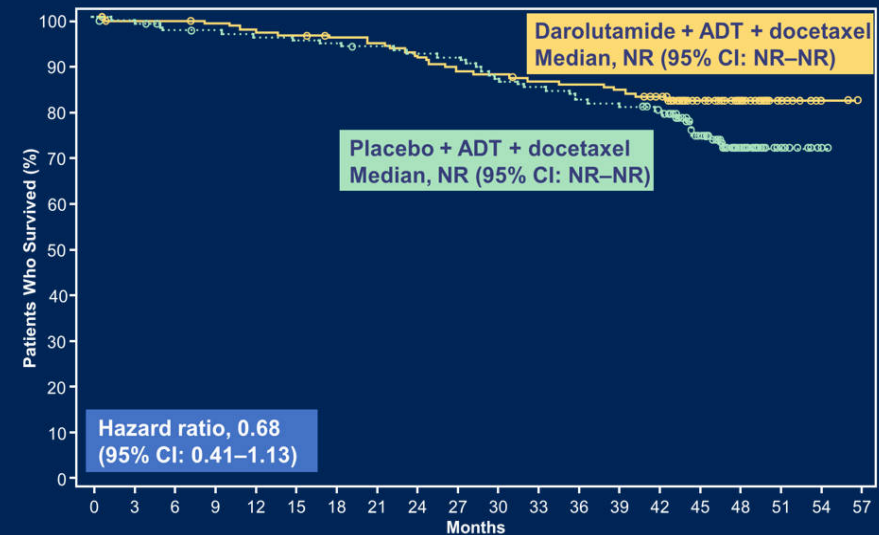
High-volume mHSPC



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

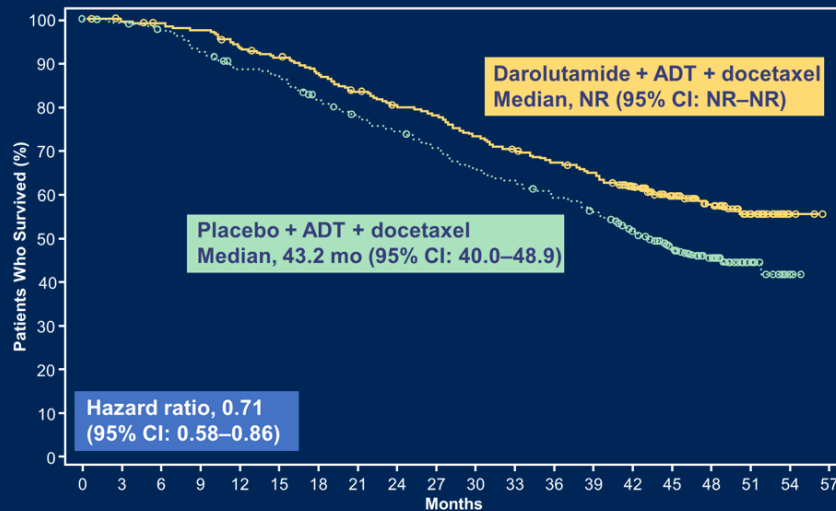
Darolutamide	154	151	151	148	146	144	141	140	136	131	130	127	126	124	117	74	36	13	3	0
Placebo	146	144	139	138	136	135	134	132	130	129	122	120	116	114	107	65	35	14	2	0

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

Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

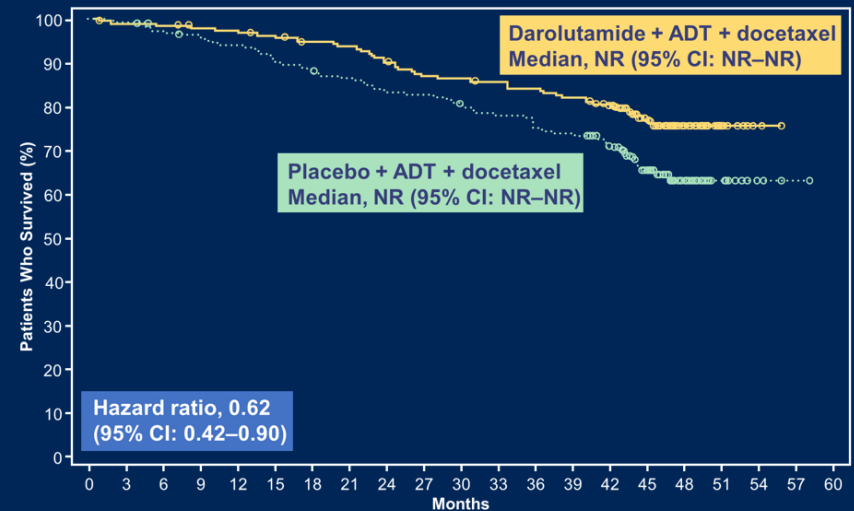
ARASENS RISK Subgroups: Overall Survival

High-risk mHSPC



	Number of high-risk patients at risk																			
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



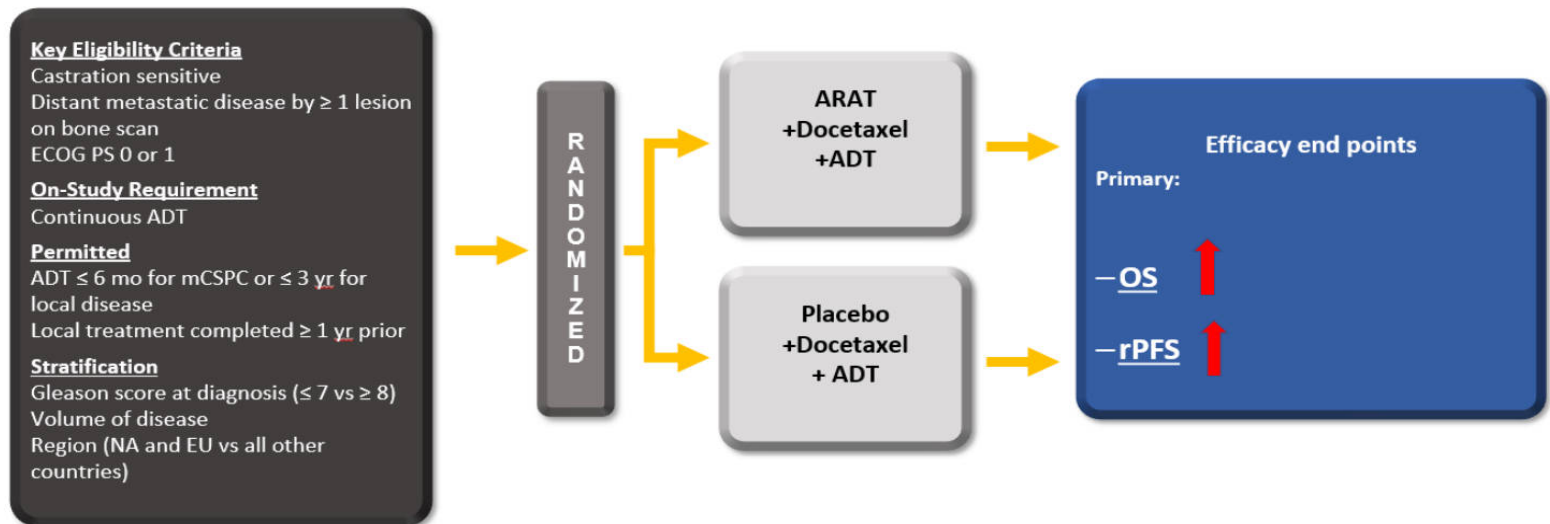
	Number of low-risk patients at risk																			
Darolutamide	199	195	194	190	189	186	181	179	173	165	164	160	158	154	145	90	40	14	3	0
Placebo	194	193	187	184	180	173	168	164	158	157	151	147	141	138	125	70	35	13	3	0

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

Evre IV Kastrasyona Duyarlı Prostat Kanseri Üçlü Kombinasyonlar

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

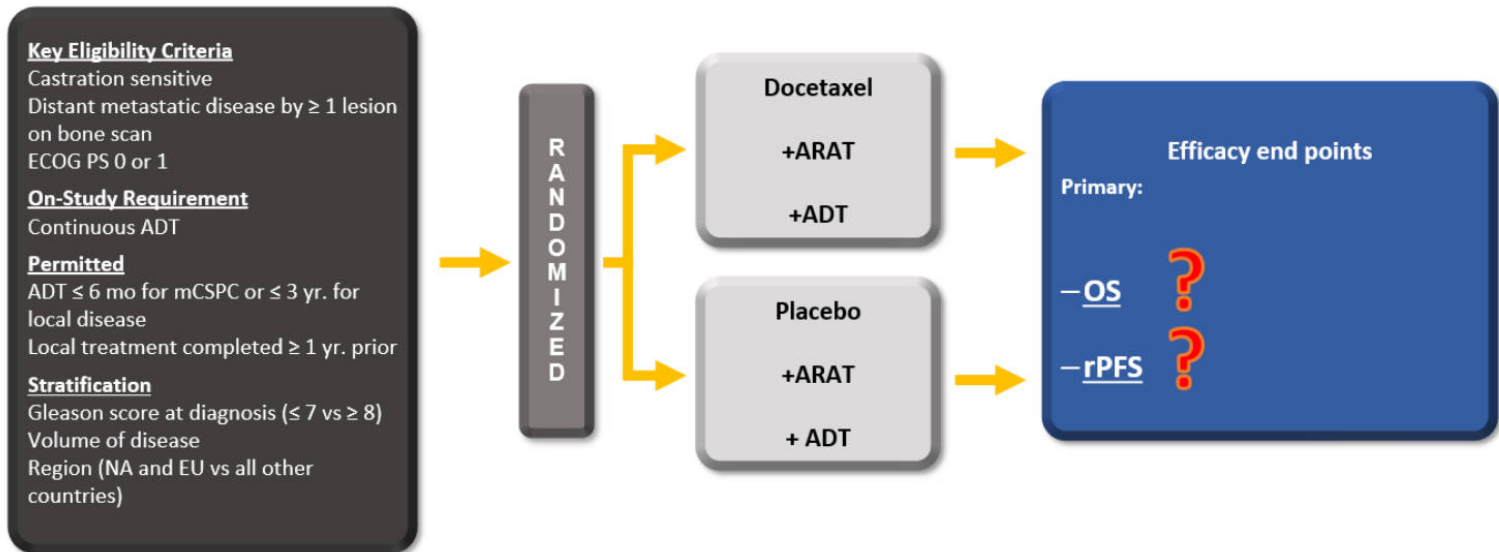


ECOG PS, Eastern Cooperative Oncology Group performance status; ART, Androgen receptor targeted therapy; NA, North America; PSA, prostate-specific antigen; OS, Overall survival; rPFS, radiographic progression-free survival.

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

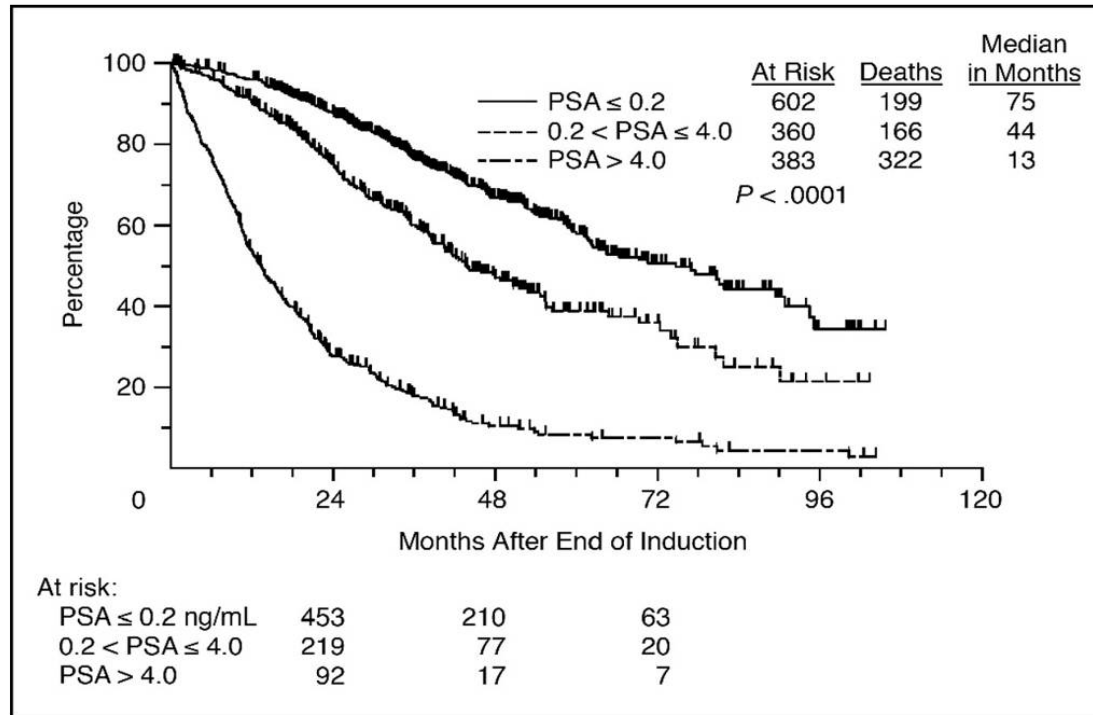
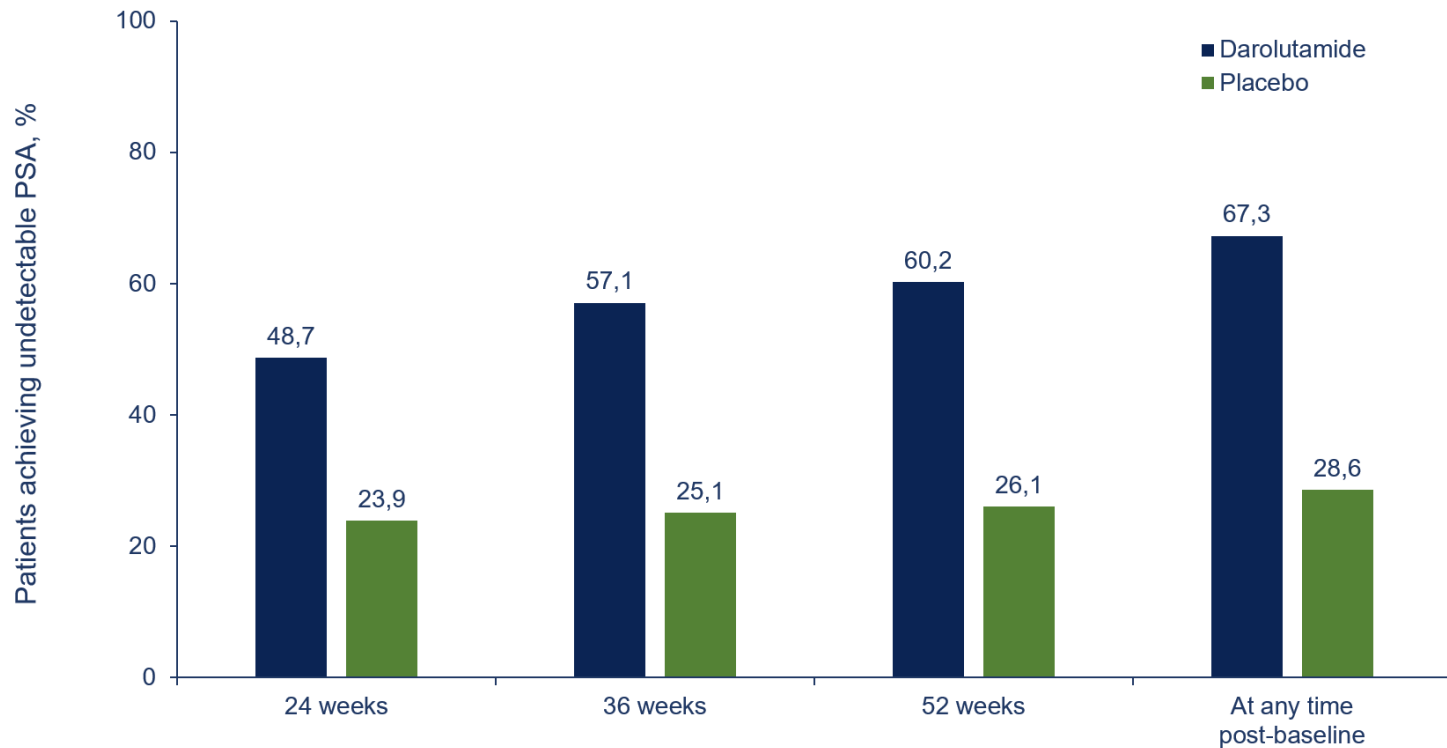


Fig 2. Overall survival by prostate-specific antigen (PSA, ng/mL) status at end of induction
Maha Hussain: Journal of Clinical Oncology 2006; 24 3984-3990.

Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

Objective: Undetectable (≤ 0.2) PSA Levels



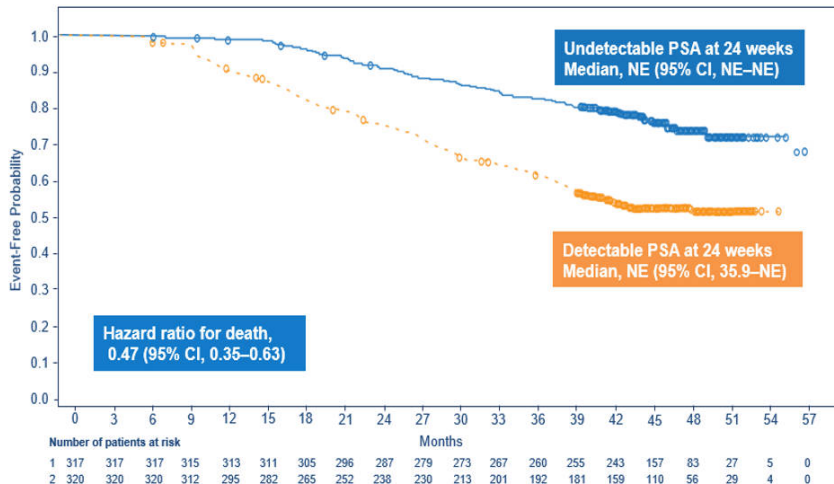
Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

Results: Overall Survival

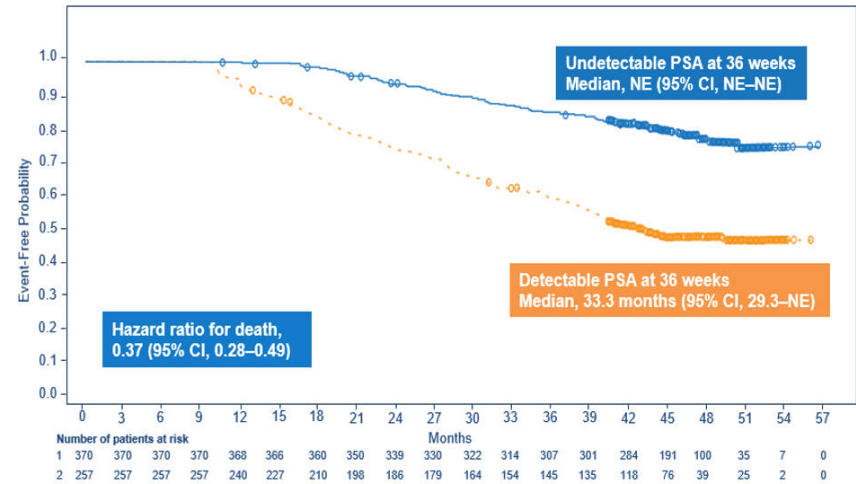
Undetectable PSA at 24 and 36 weeks was associated with a
53% and 63% reduction in the risk of death

Darolutamide + ADT + docetaxel

Undetectable vs detectable PSA at 24 weeks

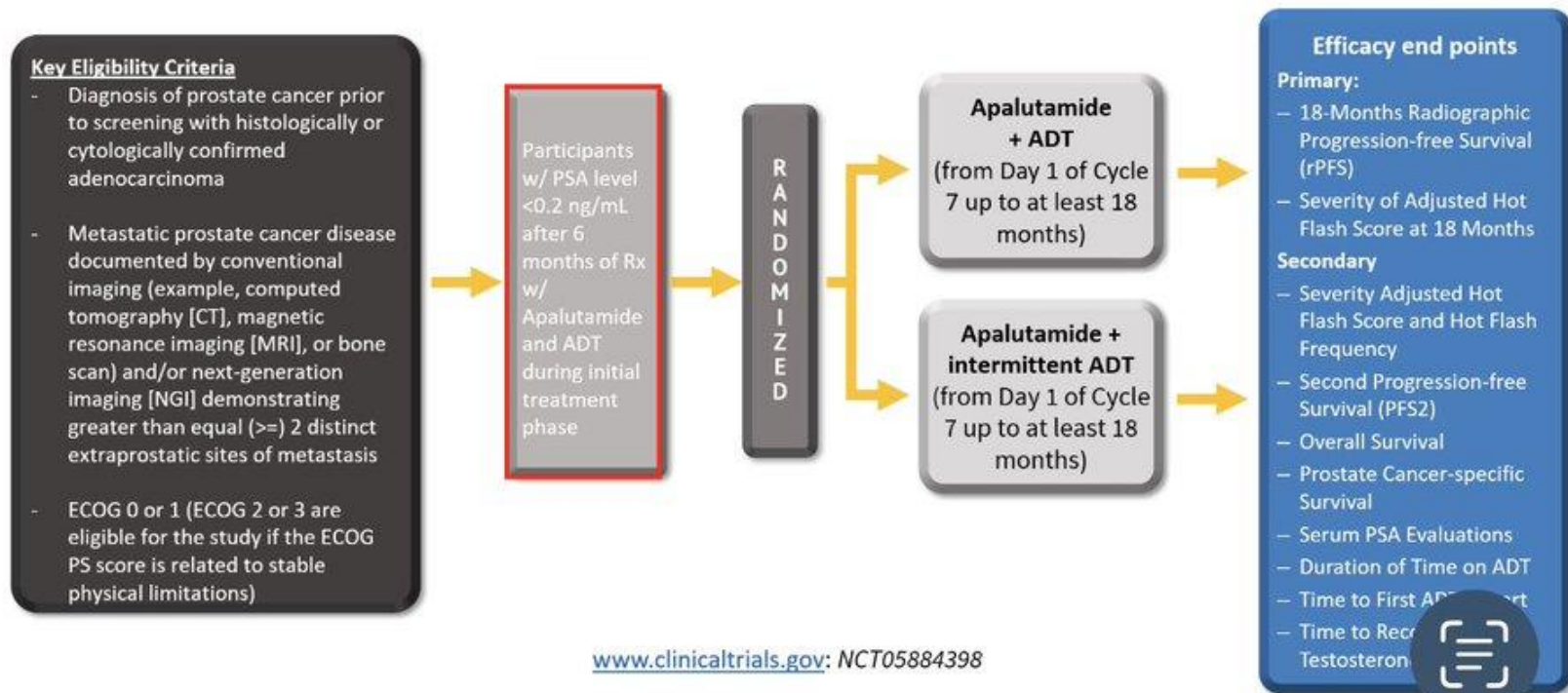


Undetectable vs detectable PSA at 36 weeks



Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

LIBERTAS Trial: Phase 3 Trial Design



Metastatik Kastrasyona Duyarlı Prostat Kanseri Tedavi

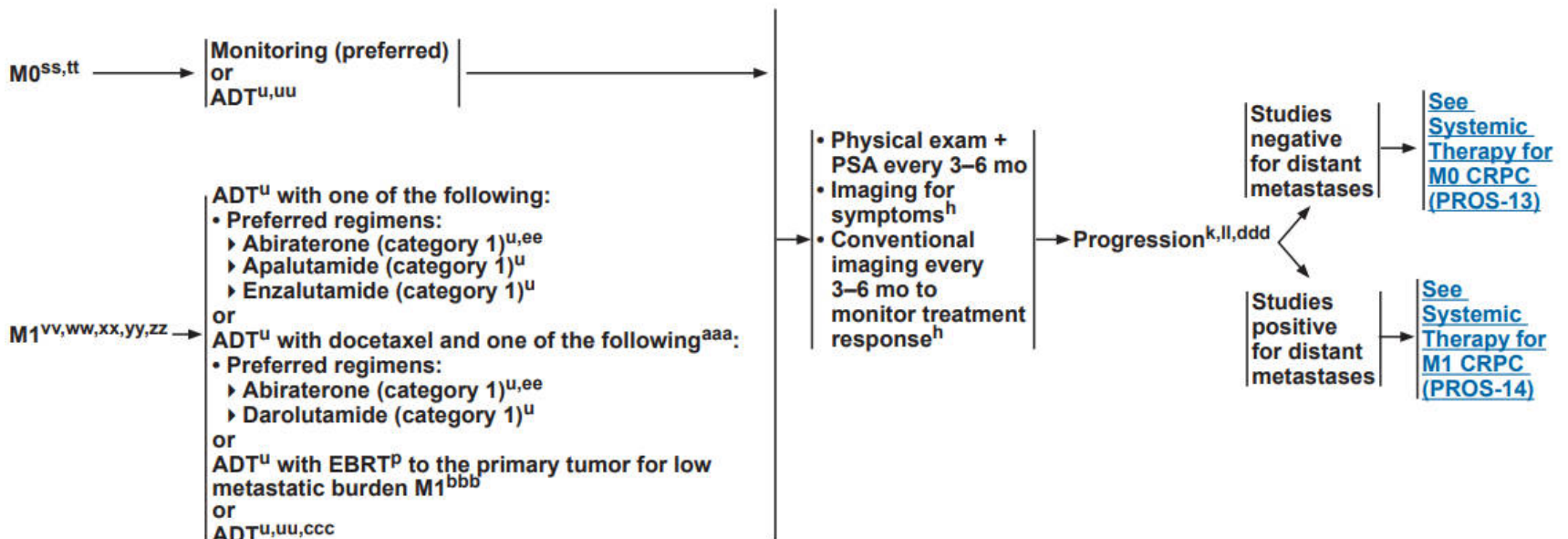


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SYSTEMIC THERAPY FOR CASTRATION-SENSITIVE PROSTATE CANCER^{rr}



Tedavi Kararında Etkili Faktörler

Hastalıkla İlişkili Faktörler

- 1- Yüksek volüm/Düşük volüm
- 2- De nova/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+dozetaksel karşılaştırması yok

❑ Üçlü tedavi

Viseral metastaz, de nova, 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

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