Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

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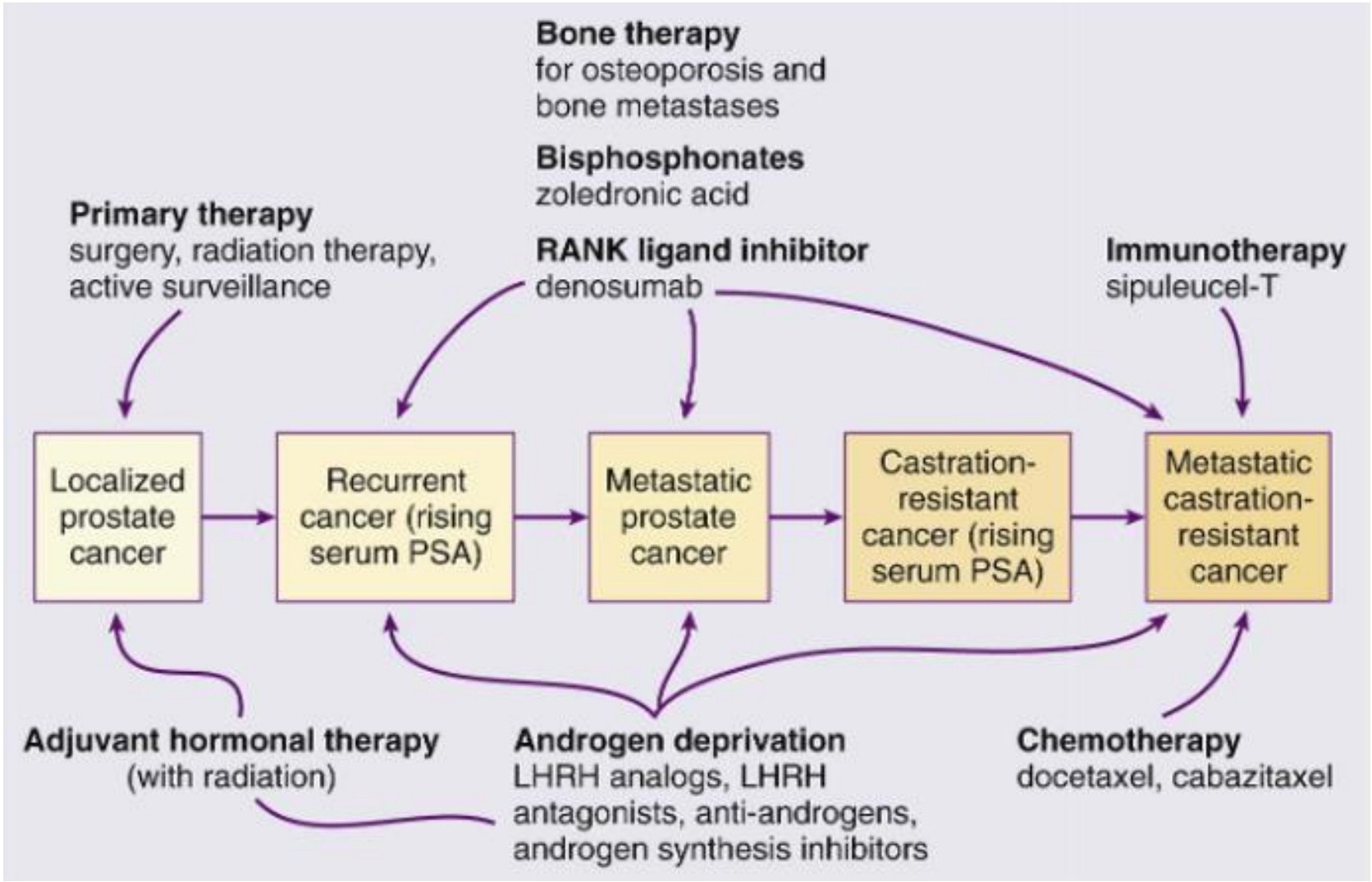
Bakırköy Dr. Sadi Konuk Eğitim ve Araştırma Hastanesi
Tıbbi Onkoloji

Ders Planı

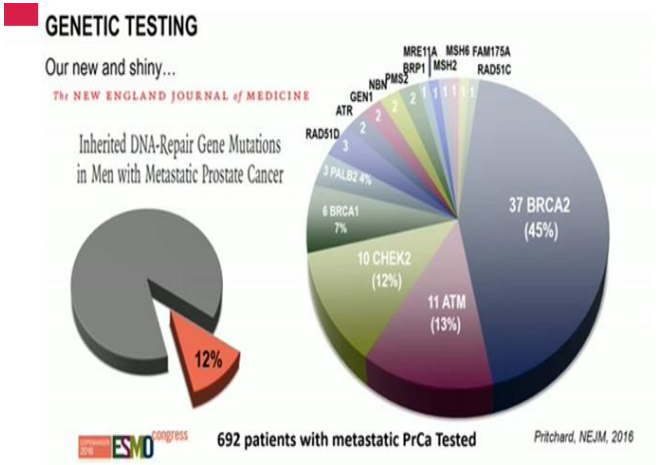
- ❑ Giriş
- ❑ ADT
- ❑ Tedavi kararında etkili faktörler
- ❑ ADT+yeni nesil androjen yolağı inhibitörleri
- ❑ Dosetaksel hangi hasta grubuna eklenmeli
- ❑ Gelecek perspektif
- ❑ Sonuç

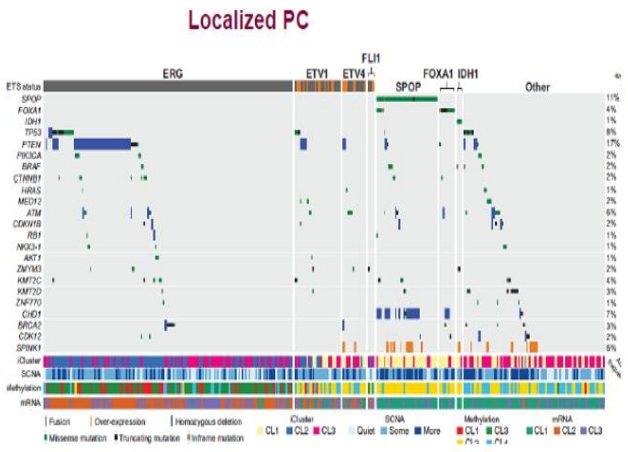
Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

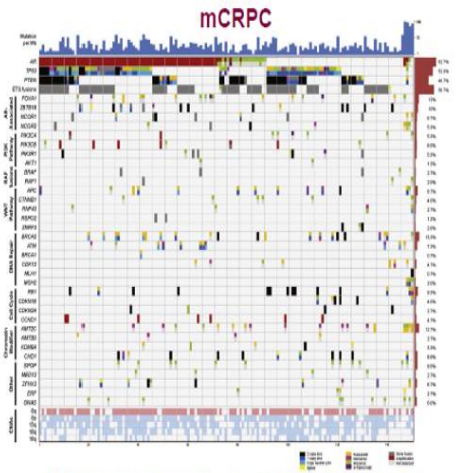


Şekil; Abeloff's Clinical Oncology, 10th edition

Prostat kanserin biyolojisi



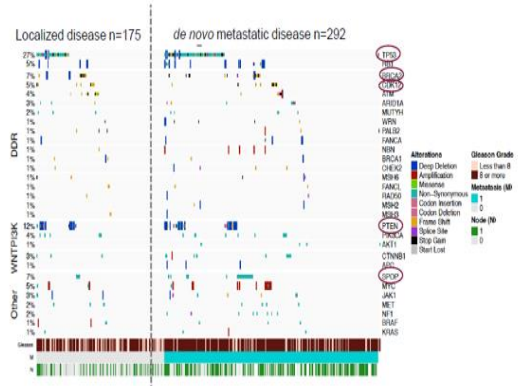




Actionable alterations in most mCRPC patients

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

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

Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

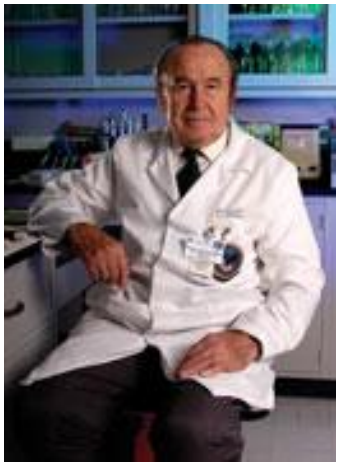
Androjen Baskılama Tedavisi(ADT)

- ❑ Cerrahi Kastrasyon(Bilateral orişektomi)

- ❑ Medikal Kastrasyon
  - ✓ LHRH analogları, LHRH antagonistler
  - ✓ Total androjen blokajı(Antiandrojenlerin eklenmesi)

- ❑ Uygulama seçenekleri
  - ✓ Continue androjen baskılanması
  - ✓ İntermittan androjen baskılanması

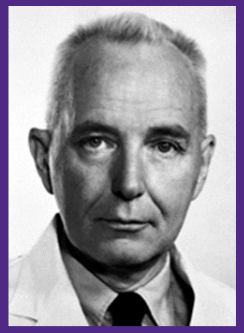
Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi



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

Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

Historical Perspective: Androgens & Prostate Cancer



C. Huggins
1966 Nobel Prize

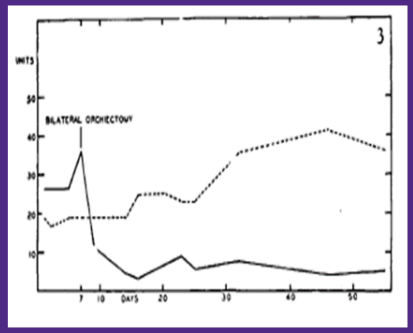
Studies on Prostatic Cancer

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)

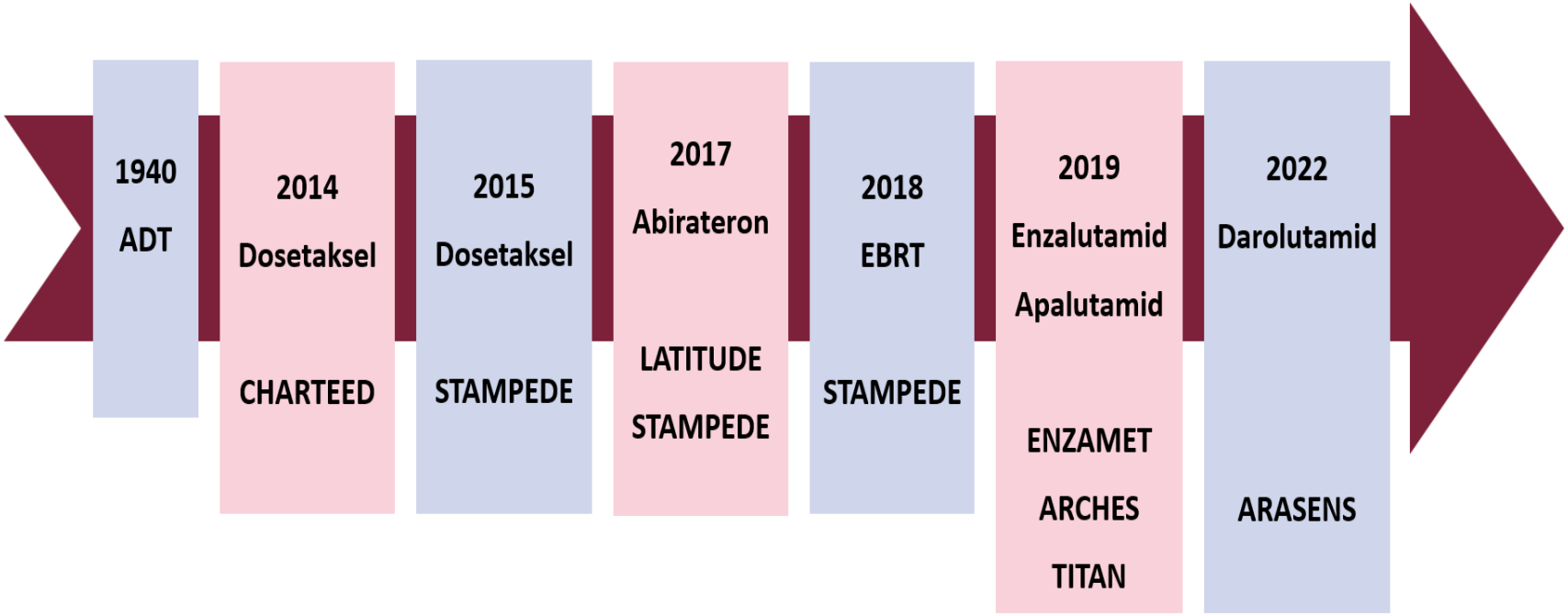
(Received for publication March 22, 1941)



Cancer Res 1941;1:293-297

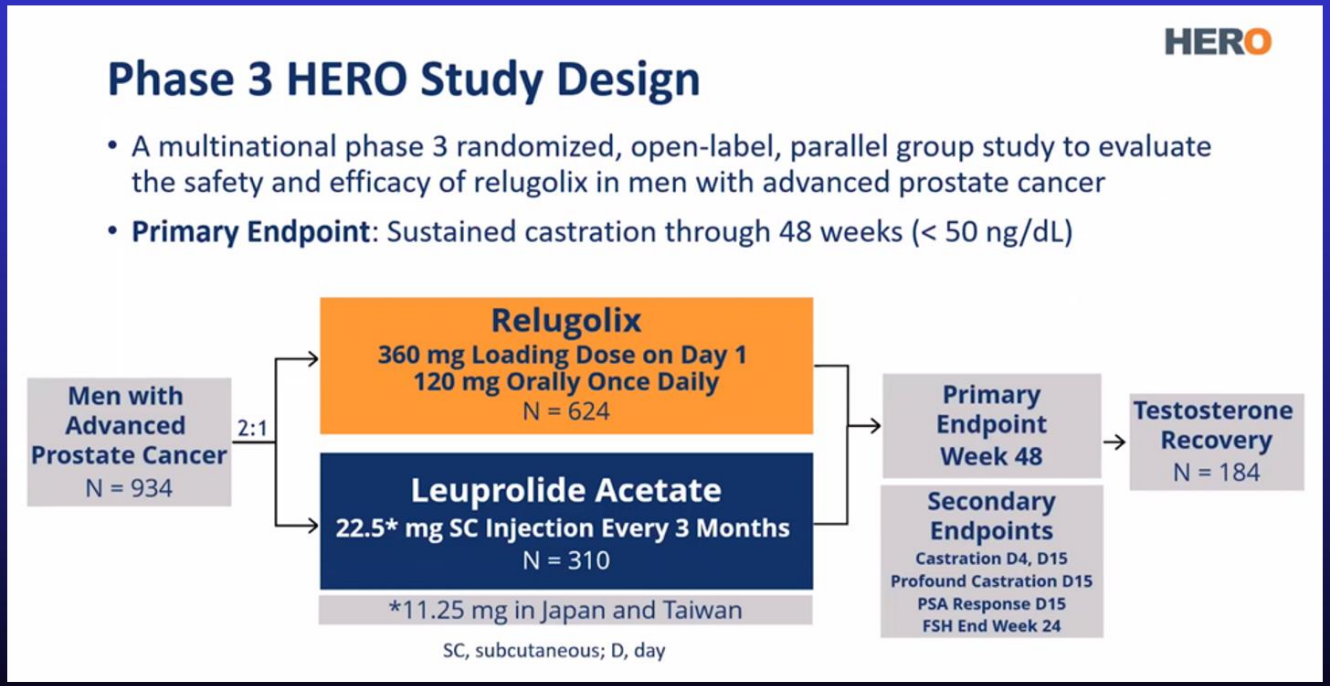
- **Seminal Observation**: PCa is an androgen driven/dependent disease & surgical or medical castration can induce significant regressions of PC.
  - *Role of acid phosphatase as a biomarker*
- >90% of patients initially respond to androgen deprivation therapy (ADT), however, most will progress to castration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

Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi



Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

Phase 3 HERO Trial: Relugolix vs. Leuprolide



Shore, et al. NEJM, 2020

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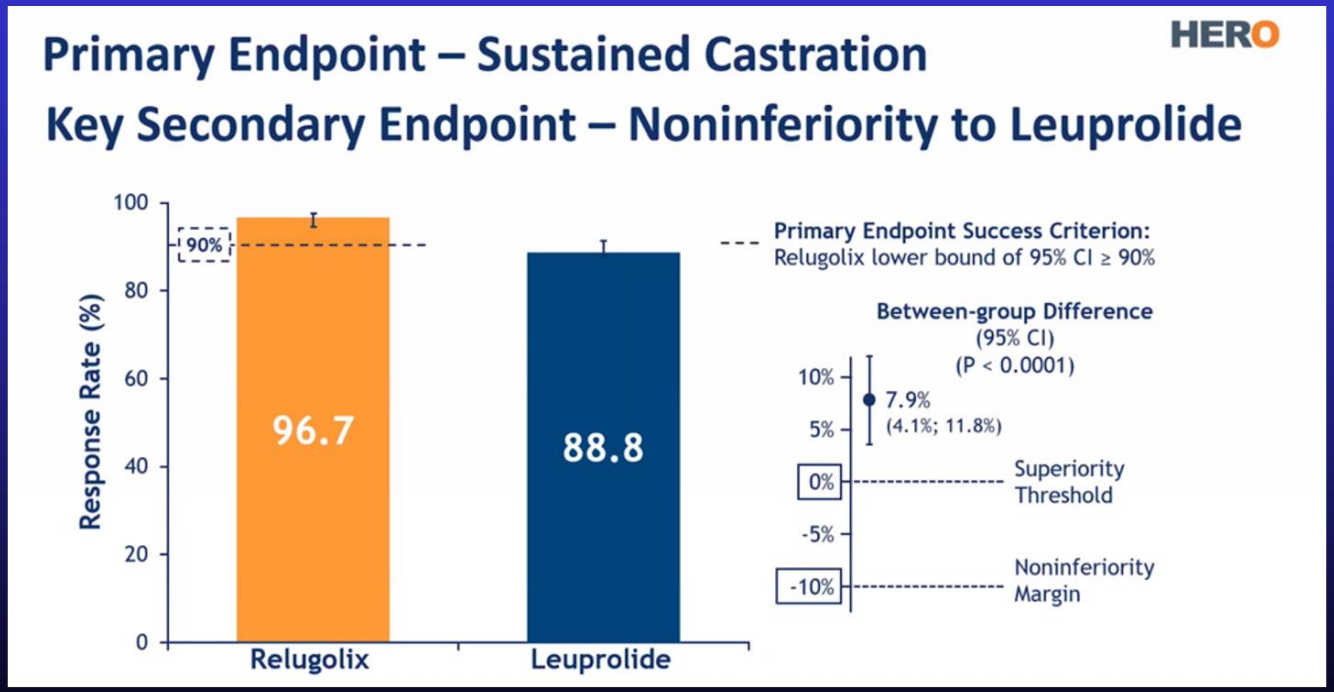

Shore, et al. NEJM, 2020

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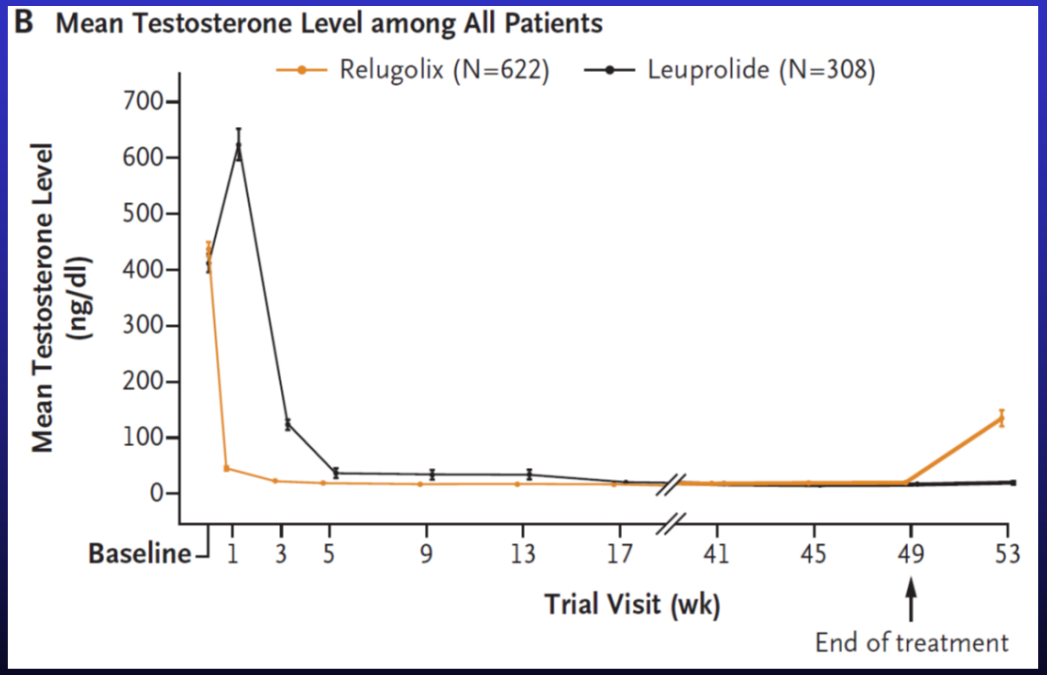

Shore, et al. NEJM, 2020

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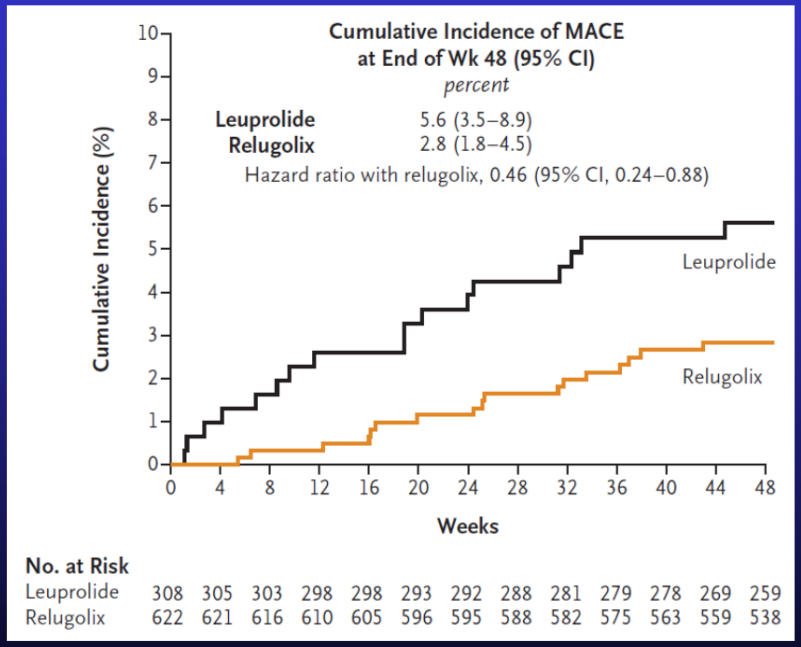


Shore, et al. NEJM, 2020

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

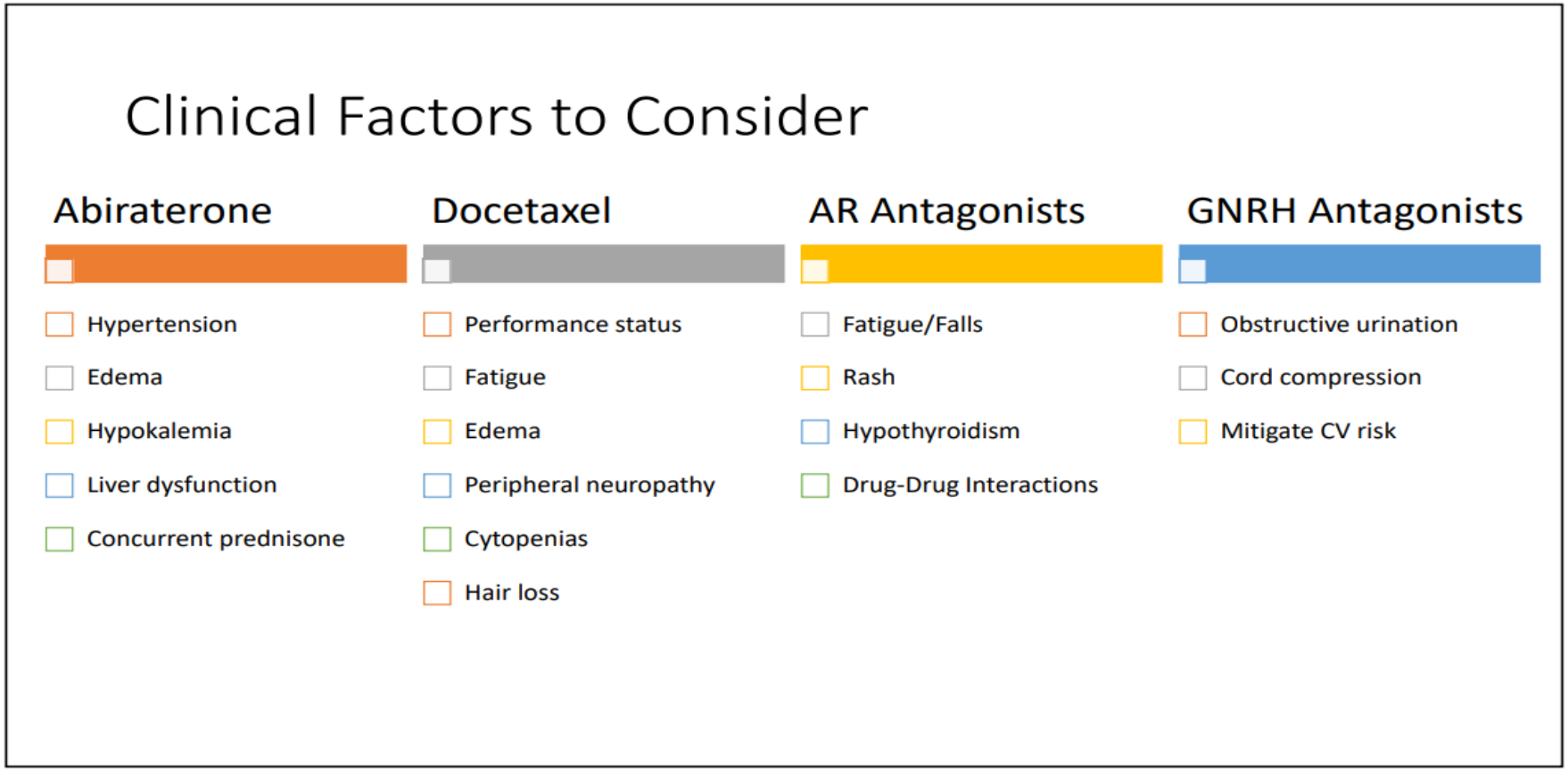
2-Etki etme mekanizması

3- Yan etkileri

4-İlaç etkileşimi

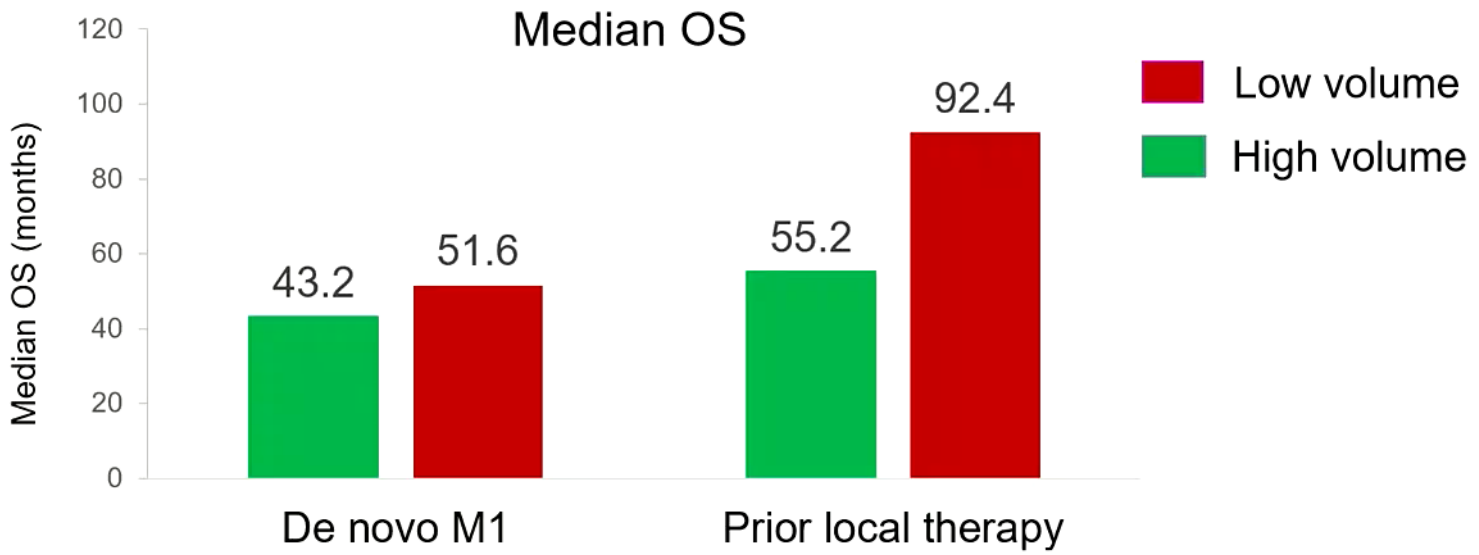
5-Tedavi maliyeti

Tedavi kararında etkili faktörler



Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

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

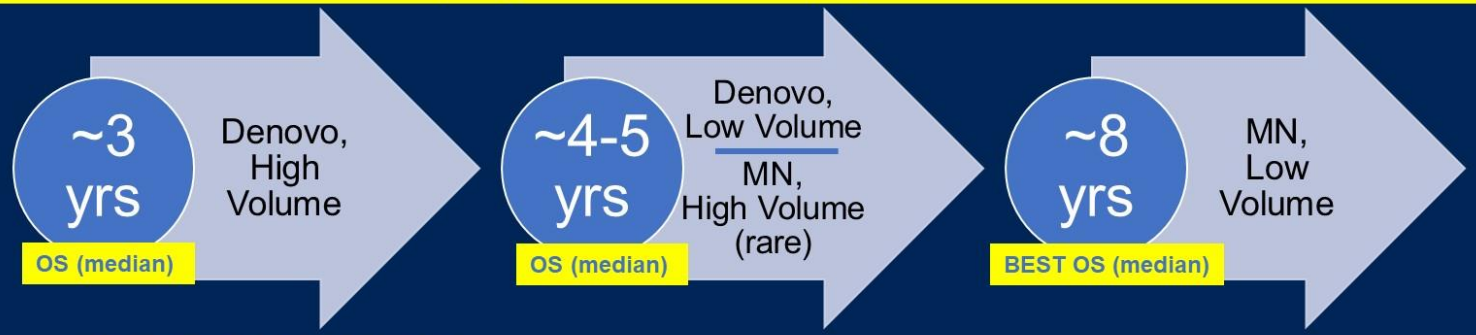
Francini E, et al. The Prostate 2018;78:889-95.

Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

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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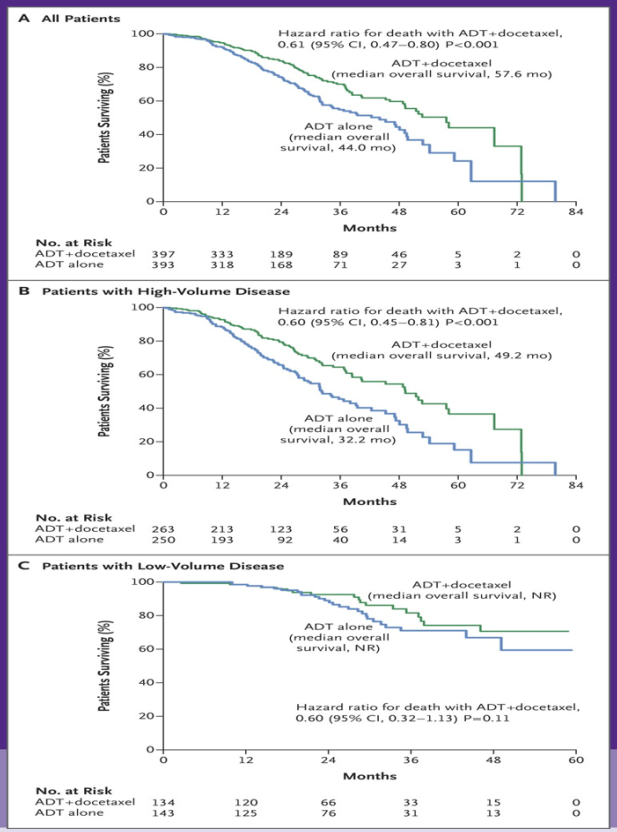
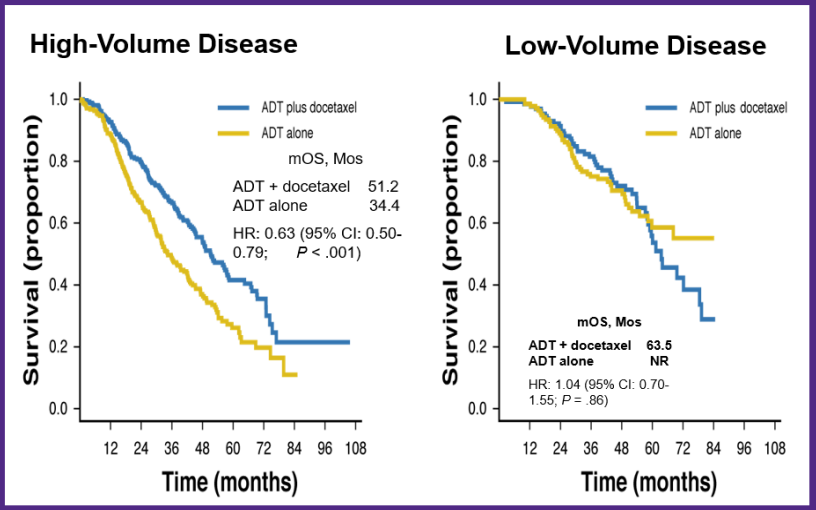
CHAARTED: ADT +/- Docetaxel in mHSPC



Sweeney CJ et al. NEJM 2015

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

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

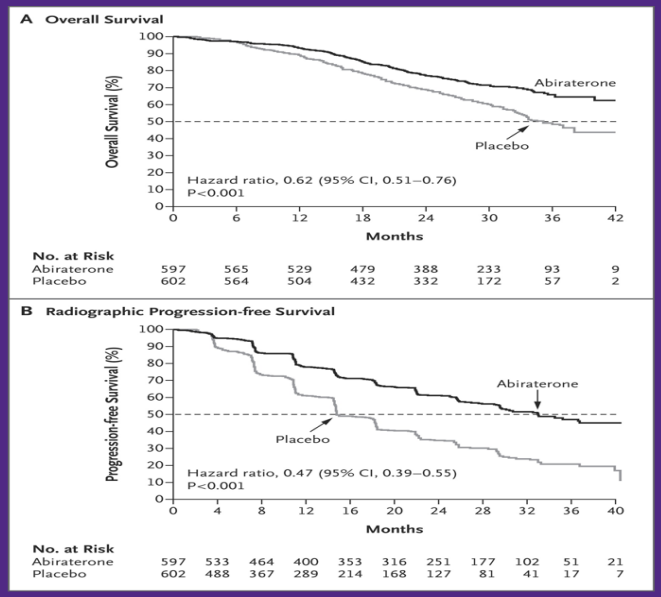


Kyriakopoulos CE, et al. J Clin Oncol. 2018

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

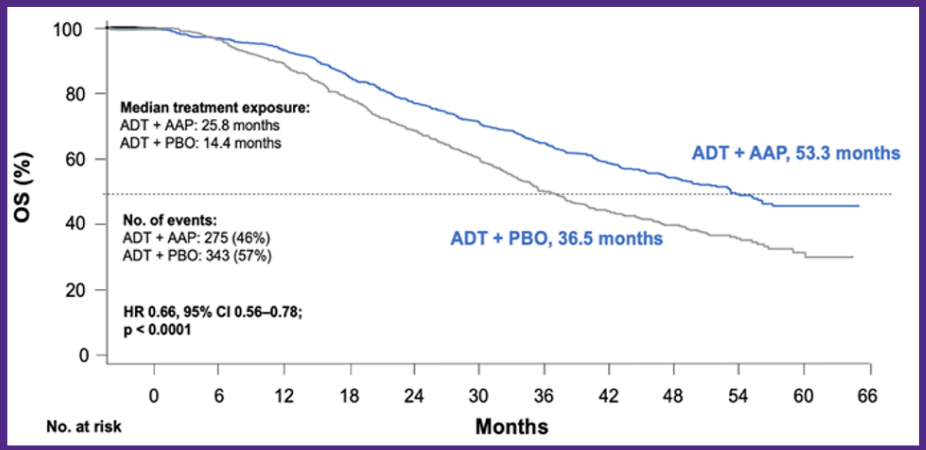
Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

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



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

Fizazi et al. NEJM 2017



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

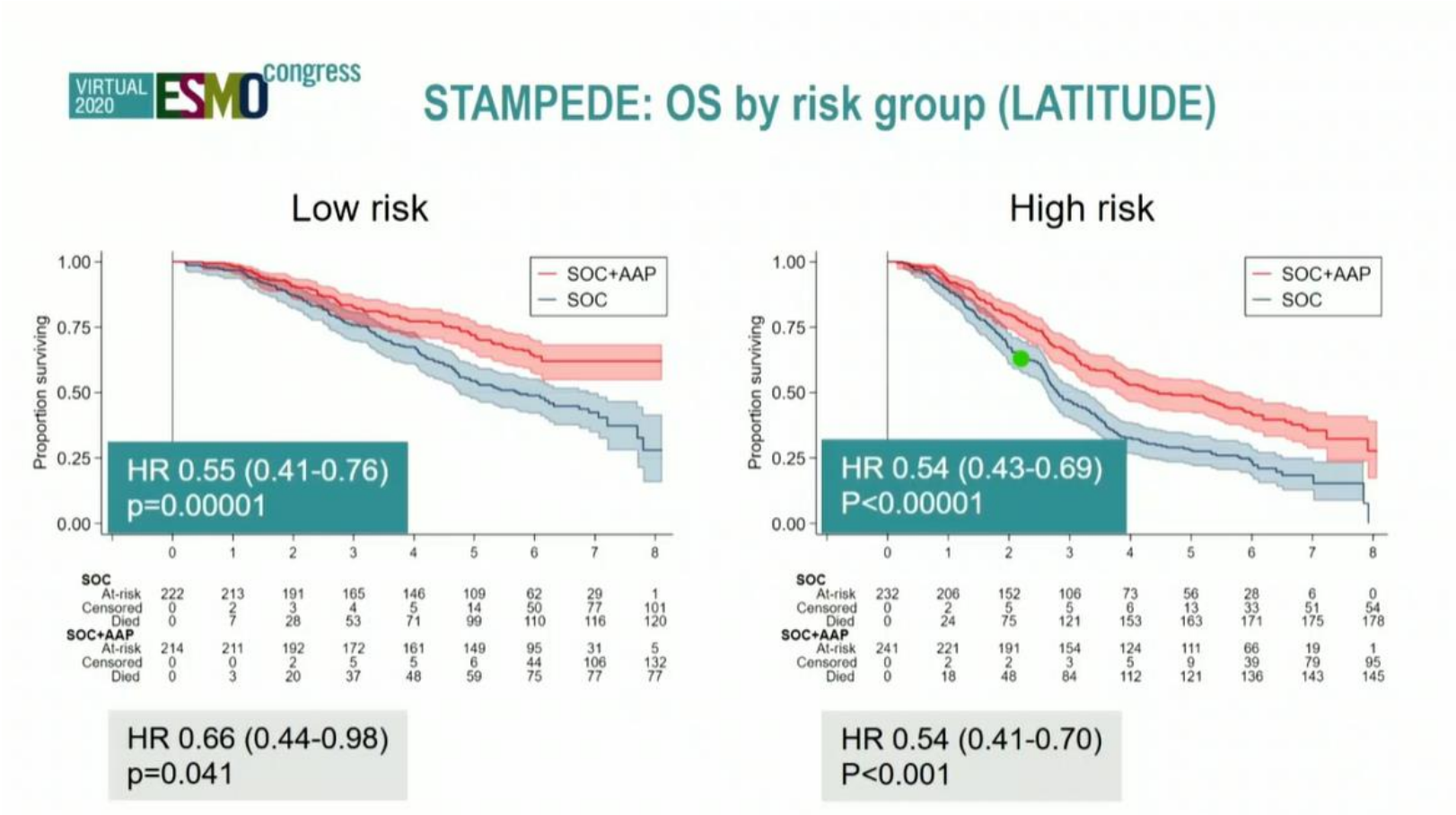
Fizazi K et al. Lancet Oncol 2019;20(5):686-700

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

Dışlama kriterleri; Daha önce cerrahi, Radyoterapi ,Kemoterapi

Metastatik hastalığa bağlı semptomu olanlarda RT ve Cerrahiye izin verilmiş

Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi



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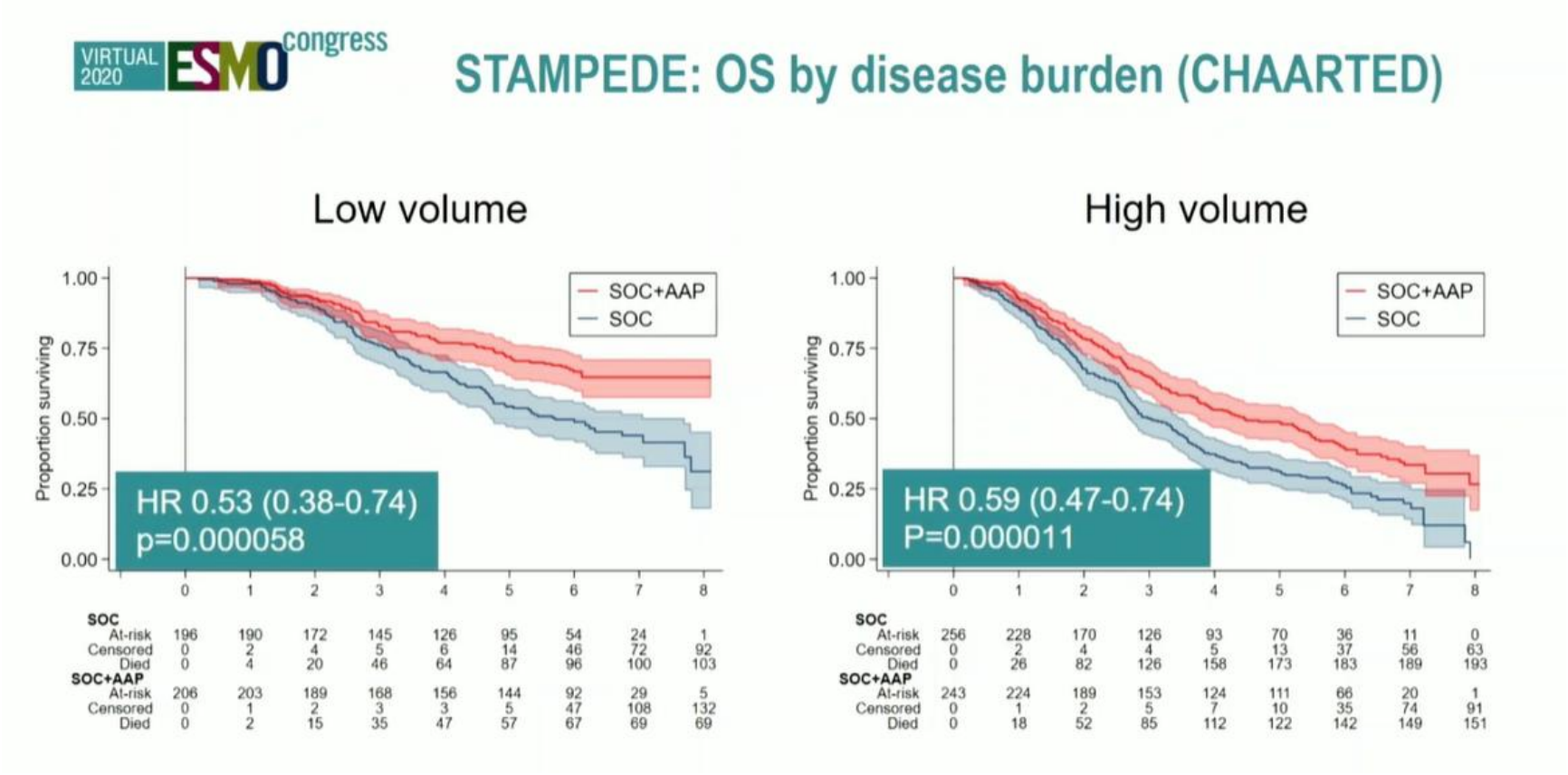
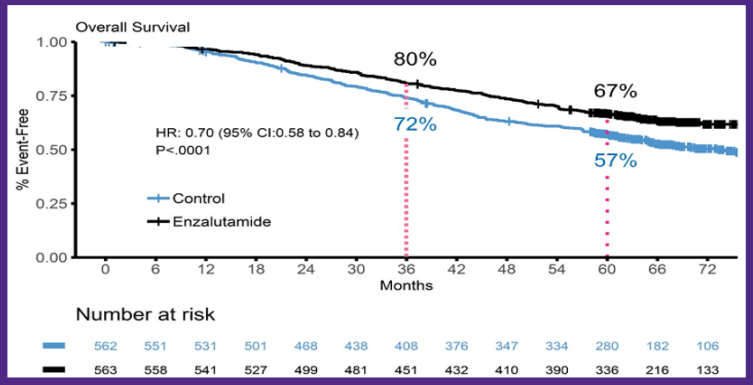


Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

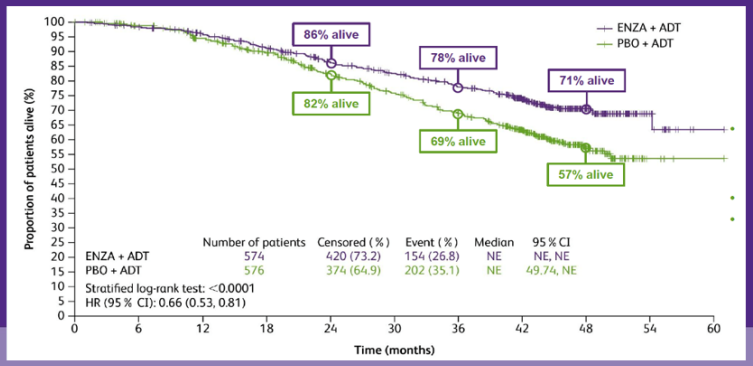
Final Overall Survival (OS) Analyses: Enzalutamide for Metastatic Hormone-Sensitive Prostate Cancer

ENZAMET[1]
Enzalutamide + testosterone suppression (TS)



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

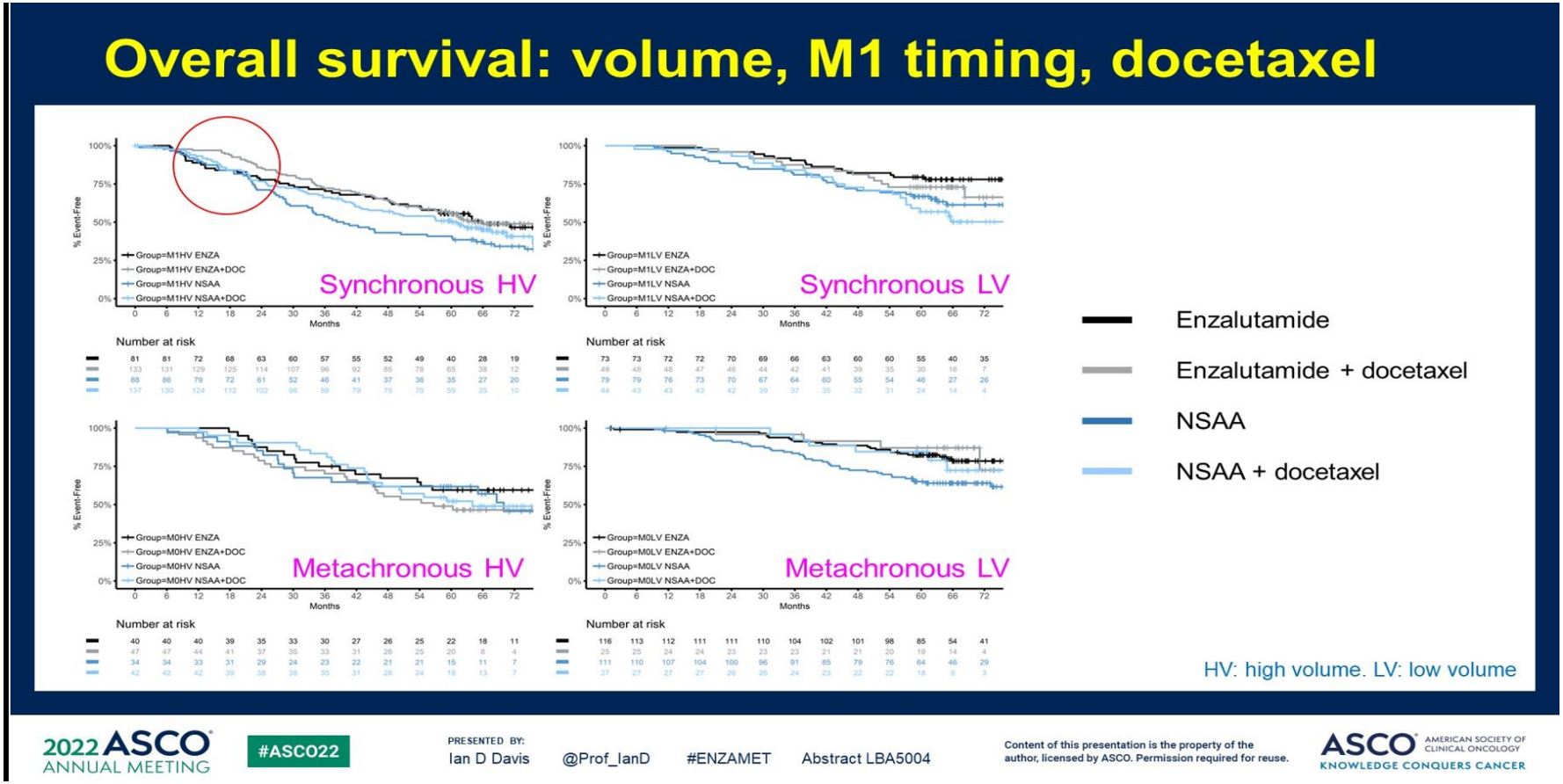
ARCHES[2]
Enzalutamide + ADT



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

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

Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi



Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

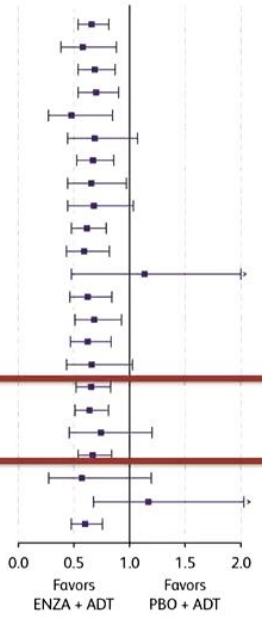
	Enzalutamide		NSAA		
	Deaths/Total	5y OS %	Deaths/Total	5y OS %	HR (95% CI)
All participants	208/563	67	268/562	57	0.70 (0.58 to 0.84)
Concurrent docetaxel					
No	100/310	72	145/312	58	0.60 (0.47 to 0.78)
Yes	108/253	61	123/250	56	0.82 (0.63 to 1.06)
Volume of Disease (Vol)					
Low	59/262	80	97/261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

Davis et al., J Clin Oncol 40, 2022 (suppl 17; abstr LBA5004) ASCO 2022

Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

ARCHES : Subgroup analysis. Prior Docetaxel Inconclusive on Benefit

Subgroup	ENZA + ADT/PBO + ADT N (E)	Median (months)	HR (95% CI)
All subgroups	574 (154)/576 (202)	NR/NR	0.66 (0.53, 0.81)
Age <65 years	148 (39)/152 (52)	54.2/NR	0.58 (0.38, 0.88)
Age ≥65 years	426 (115)/424 (150)	NR/NR	0.68 (0.54, 0.87)
Geographic region – Europe	341 (100)/344 (129)	54.2/NR	0.70 (0.54, 0.90)
Geographic region – North America	86 (20)/77 (28)	NR/50.3	0.48 (0.27, 0.85)
Geographic region – Rest of world	147 (34)/155 (45)	NR/NR	0.69 (0.44, 1.08)
ECOG status 0 at baseline	448 (112)/443 (143)	NR/NR	0.67 (0.52, 0.86)
ECOG status 1 at baseline	125 (42)/133 (59)	NR/45.9	0.65 (0.44, 0.97)
Gleason score at initial diagnosis <8	171 (38)/187 (51)	NR/NR	0.68 (0.44, 1.04)
Gleason score at initial diagnosis ≥8	386 (108)/373 (145)	NR/49.7	0.61 (0.48, 0.79)
Disease localization at baseline – bone only	268 (64)/245 (84)	NR/NR	0.59 (0.43, 0.82)
Disease localization at baseline – soft tissue only	51 (12)/45 (9)	NR/NR	1.13 (0.48, 2.69)
Disease localization at baseline – bone and soft tissue	217 (72)/241 (106)	NR/44.3	0.62 (0.46, 0.84)
Baseline PSA value at or below overall median	291 (72)/303 (97)	NR/NR	0.68 (0.50, 0.93)
Baseline PSA value above overall median	279 (82)/269 (105)	NR/48.3	0.63 (0.47, 0.84)
Low volume of disease	220 (35)/203 (46)	NR/NR	0.66 (0.43, 1.03)
High volume of disease	354 (119)/373 (156)	NR/45.9	0.66 (0.52, 0.83)
No prior docetaxel therapy	471 (124)/474 (165)	NR/NR	0.64 (0.51, 0.81)
Prior docetaxel therapy	103 (30)/102 (37)	NR/NR	0.74 (0.46, 1.20)
Previous use of ADT or orchiectomy	535 (144)/515 (179)	NR/NR	0.67 (0.54, 0.83)
No previous use of ADT or orchiectomy	39 (10)/61 (23)	NR/NR	0.57 (0.27, 1.20)
Visceral metastases – yes	64 (28)/64 (24)	48.5/50.3	1.16 (0.67, 2.00)
Visceral metastases – no	510 (126)/512 (178)	NR/NR	0.60 (0.48, 0.76)



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.

Armstrong et al ESMO 2021

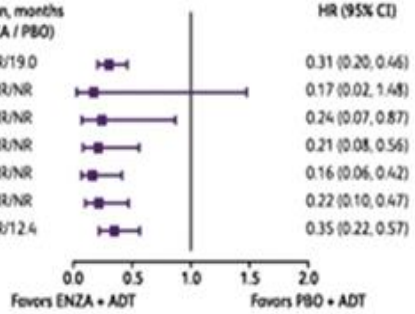
2021 ESMO congress

Discussant Eleni Efstathiou MD PhD

Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

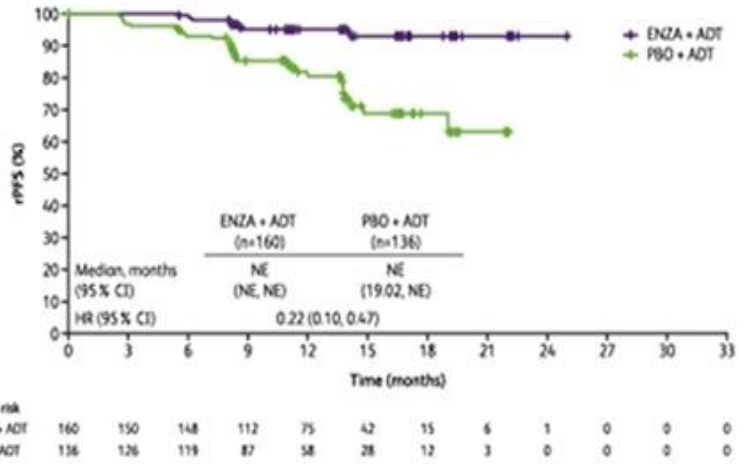
Figure 1. Forest Plot of rPFS[a] for Oligometastatic and Polymetastatic Disease

Subgroup	ENZA + ADT N (E)	PBO + ADT N (E)	Median, months (ENZA / PBO)	HR (95% CI)
Overall – bone only	267 (32)	245 (81)	NR/19.0	0.31 (0.20, 0.46)
1 metastasis	53 (1)	44 (5)	NR/NR	0.17 (0.02, 1.48)
≤2 metastases	87 (3)	76 (11)	NR/NR	0.24 (0.07, 0.87)
≤3 metastases	120 (5)	103 (20)	NR/NR	0.21 (0.08, 0.56)
≤4 metastases	142 (5)	117 (24)	NR/NR	0.16 (0.06, 0.42)
≤5 metastases	160 (8)	136 (29)	NR/NR	0.22 (0.10, 0.47)
≥6 metastases	107 (24)	109 (52)	NR/12.4	0.35 (0.22, 0.57)



[a]rPFS 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.
ADT=androgen deprivation therapy; CI=confidence interval; ENZA=enzalutamide; E=number of events; HR=hazard ratio; N=number of patients; NR=not reached; PBO=placebo; RECIST=Response Evaluation Criteria in Solid Tumors; rPFS=radiographic progression-free survival.

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



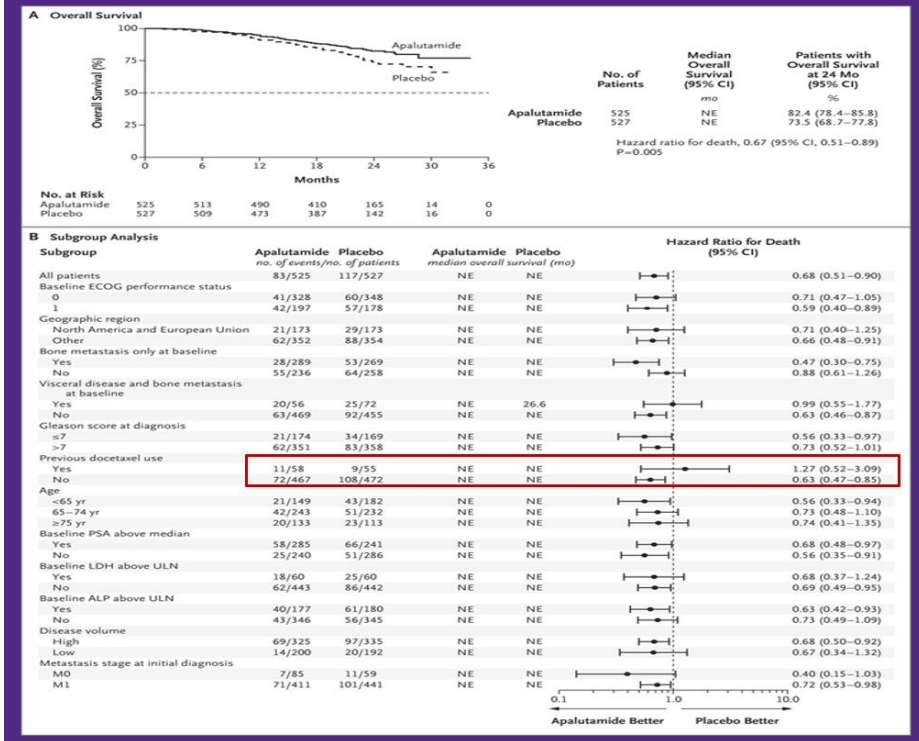
ADT=androgen deprivation therapy; CI=confidence interval; ENZA=enzalutamide; HR=hazard ratio; NE=not evaluable; NR=not reached; PBO=placebo; rPFS, radiographic progression-free survival.

ARCHES post-hoc analiz; enzalutamid oligometastik hastalıkta etkinliği

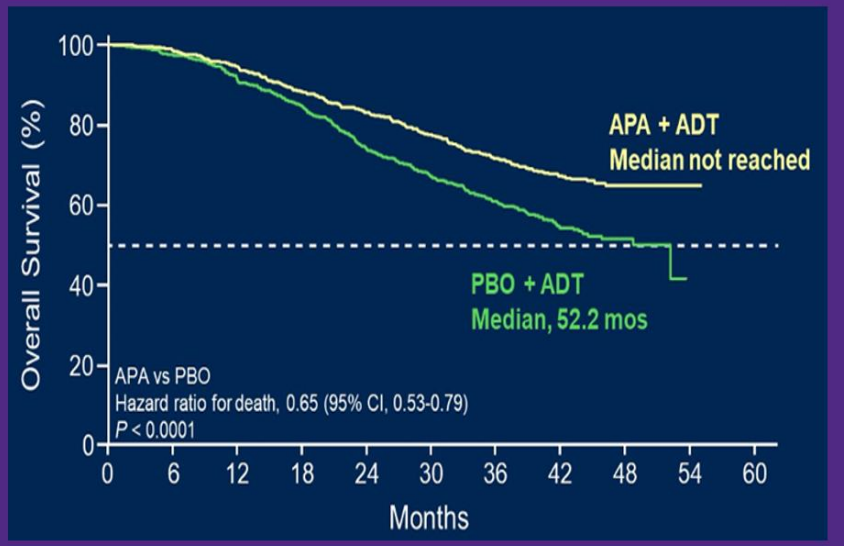
Eur Urol. 2023 May 11;S0302-2838(23)02723-9. doi: 10.1016/j.eururo.2023.04.002.

Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

Apalutamide for Metastatic, Castration-Sensitive Prostate Cancer



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



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

Chi KN et al.NEJM 2019

Chi KN et al. J Clin Oncol 2021

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], Hirotsugu Uemura [12], Simon Chowdhury [13], Kim N Chi [14], Anders Bjartell [15]

Affiliations + expand

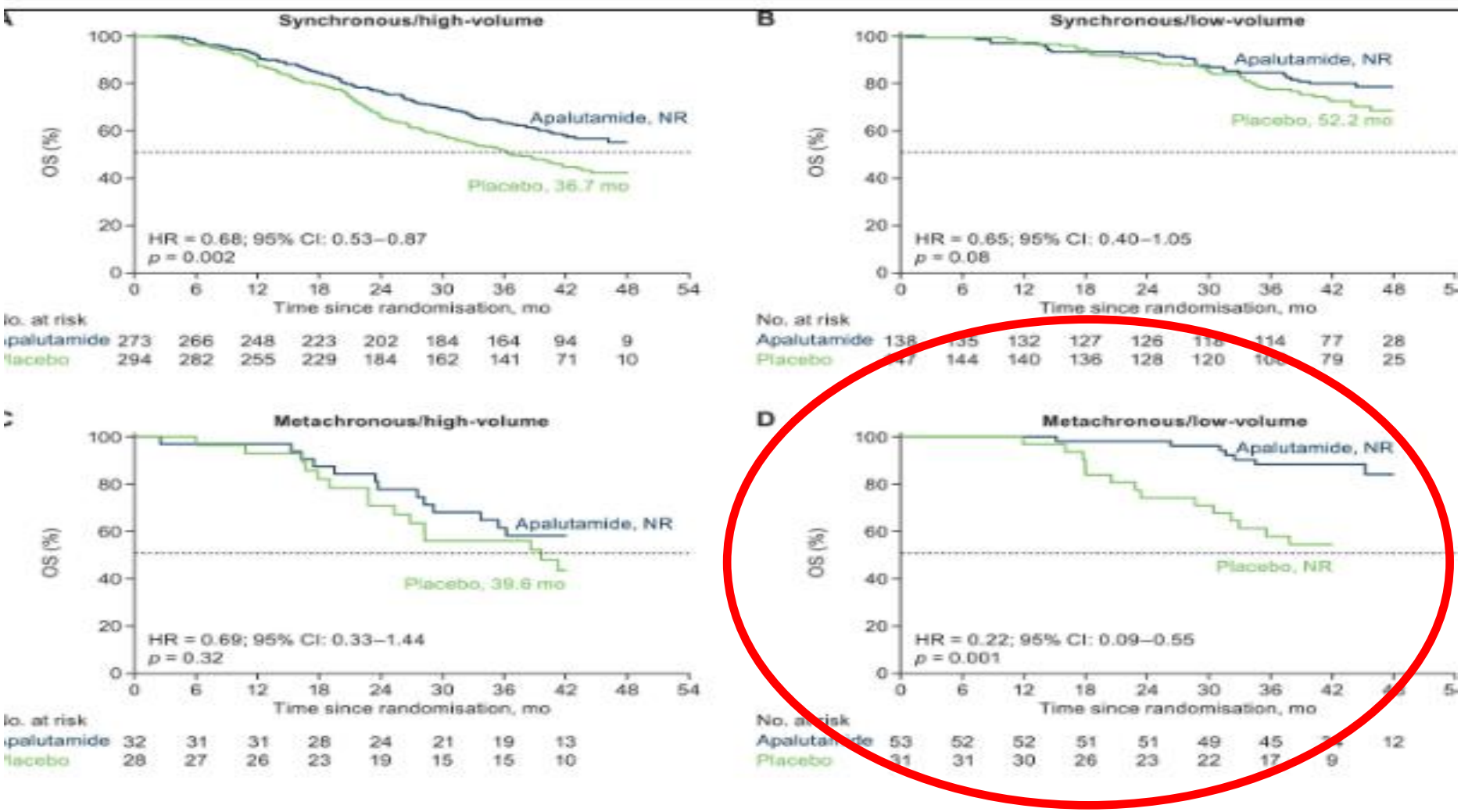
PMID: 37708629 DOI: 10.1016/j.ejca.2023.113290

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.

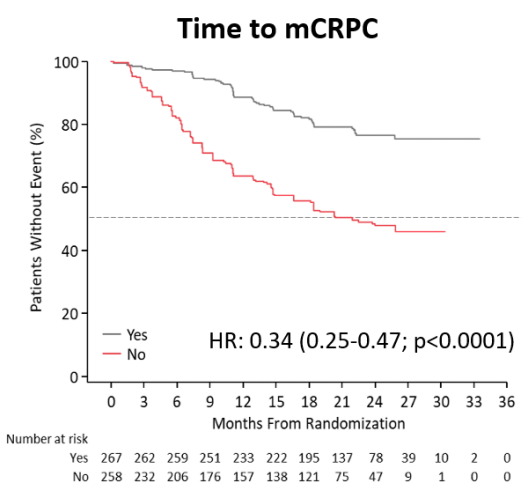
Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

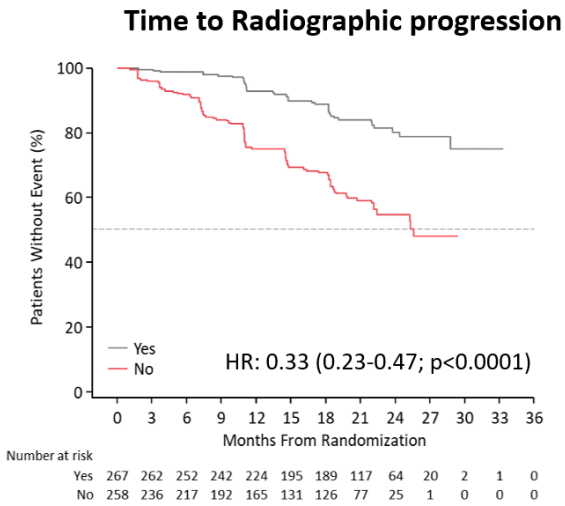


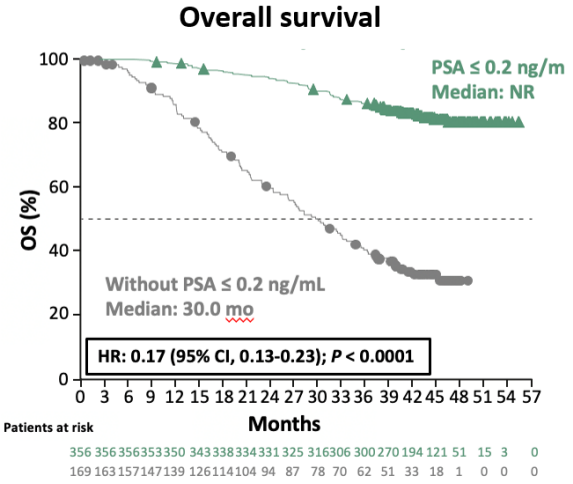
Merseburger A at al, European Journal of Cancer 2023

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

CHUM

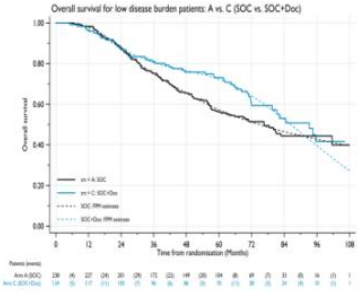
Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

VIRTUAL 2020 ESMO congress

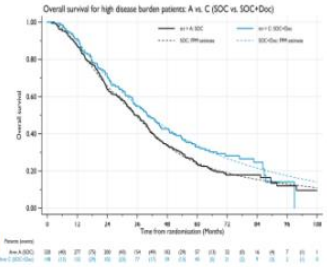
Should we count the metastases for decision making about systemic treatment? No !!!

Docetaxel | **Hormonal agents**

Low burden



High burden



Clarke N, Ann Oncol 2019

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 *de novo*)	0.66 0.58-0.178	0.62 (0.52-0.74)	0.72 (0.47-1.10)	N/A
STAMPEDE-Abi (All *de novo*)	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)

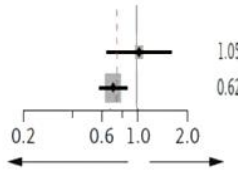
Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

Does type of metastasis matter in mHNPC?

Results from new hormonal treatments in mHNPC according visceral mets

ENZAMET

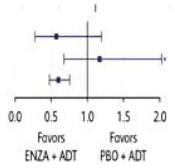
Subgroup	Enzalutamide (no. of events/total no.)	Standard Care (no. of events/total no.)	Hazard Ratio (95% CI)
Visceral metastases			
Yes	18/62	18/67	1.05 (0.54–2.02)
No	84/501	125/495	0.62 (0.47–0.82)



Enzalutamide Better Standard Care Better

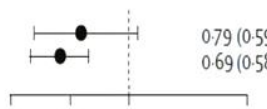
ARCHES

Subgroup	ENZA + ADT/PBO + ADT N (E)	Median (months)	HR (95% CI)
No previous use of ADT or orchiectomy	39 (10)/61 (23)	NR/NR	0.57 (0.27, 1.20)
Visceral metastases – yes	64 (28)/64 (24)	48.5/50.3	1.16 (0.67, 2.00)
Visceral metastases – no	510 (126)/512 (178)	NR/NR	0.60 (0.48, 0.76)



LATITUDE

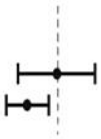
	Median (months) AA+P	Placeback+P	HR (95% CI)
Visceral disease at entry			
Yes	12·9	8·3	0·79 (0·59–1·05)
No	17·1	12·3	0·69 (0·58–0·82)



Favours AA+P Favours placebo+P

TITAN

Subgroup	Apalutamide (no. of events/no. of patients)	Placebo (no. of events/no. of patients)	Apalutamide (median overall survival (mo))	Placebo (median overall survival (mo))	
Visceral disease and bone metastasis at baseline					
Yes	20/56	25/72	NE	26.6	0.99 (0.55–1.77)
No	63/469	92/455	NE	NE	0.63 (0.46–0.87)
Gleason score at diagnosis					



2021 ESMO congress

OUDARD Stéphane

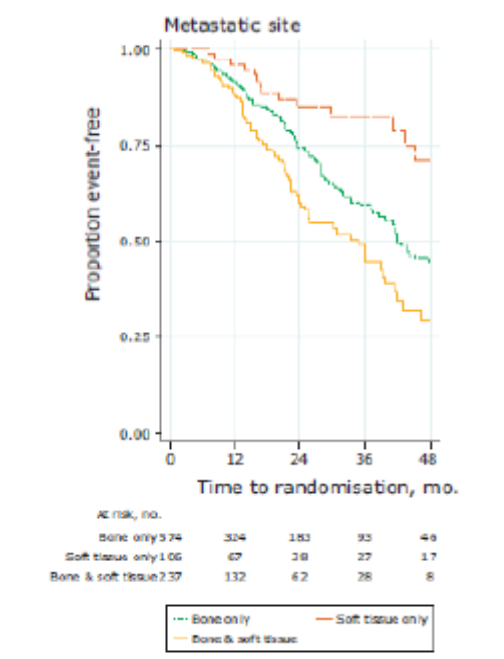
1. Davis I, et al. NEJM 2019;381:121-131 2. Armstrong A, et al. ESMO 2021 oral comm. abstract LBA25 3. Chi K, et al. NEJM 2019;381:13-24 4. Fizazi K, et al. Lancet Oncol. 2019 May;20(5):686-700.

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. Dearnaley[d,e], Johann S. De Bono[d,e], Joanna Gale[f], John Hetherington[g], Peter J. Hoskin[h], Robert J. Jones[i], 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], Räto T. Strebel[n], George N. Thalmann[o], Malcolm D. Mason[k], Matthew R. Sydes[b]*

EUROPEAN UROLOGY 67 (2015) 1028–1038



STAMPEDE ÇALIŞMASI; 917 KONTROL KOLUNDE(ADT alan) BULUNAN M1 HASTALARIN SONUÇLARI

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

2 Yıllık sağkalım; yumuşak doku met.%85

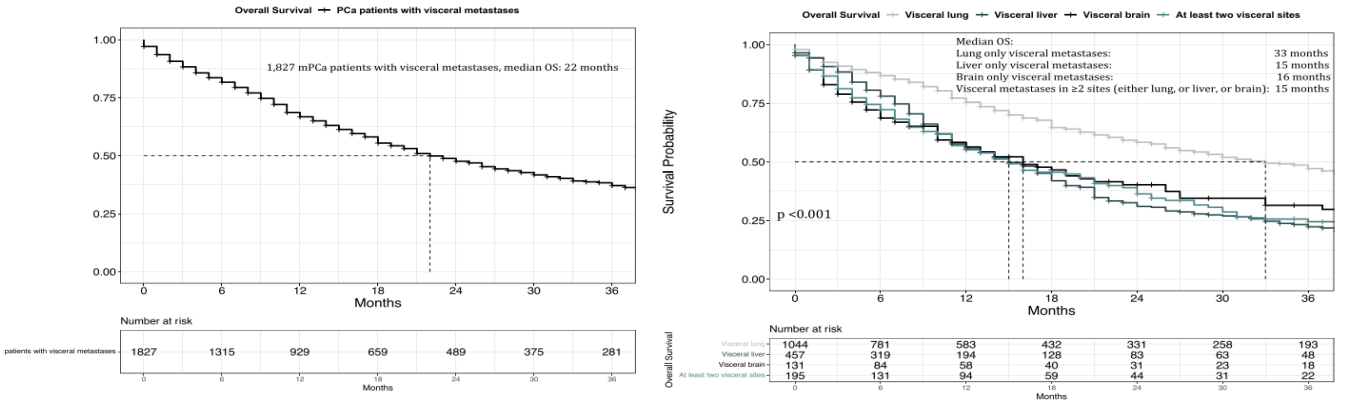
Kemik met.%75

Yumuşak doku+kemik met.%60

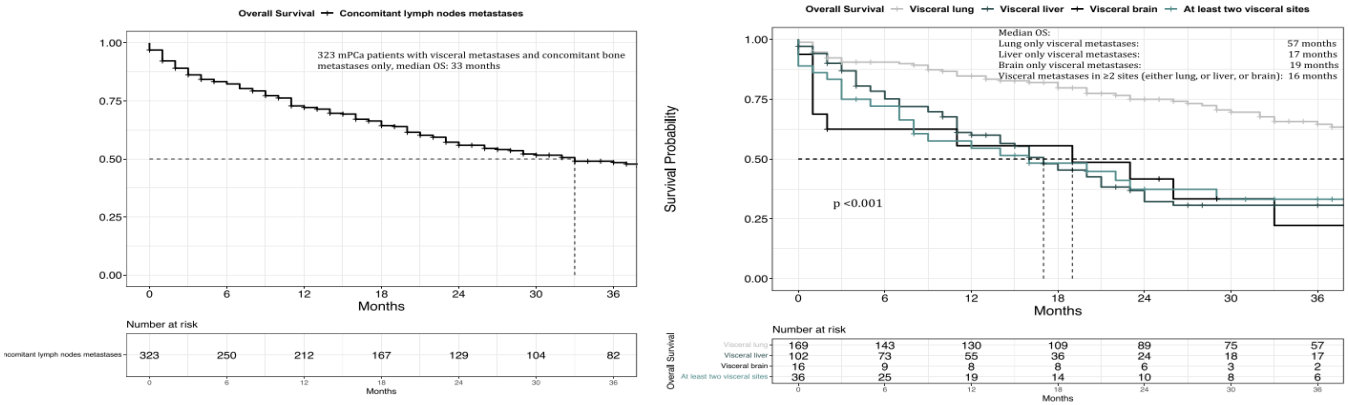
2yılık FFS; yumuşak dokuda %54, kemik met %28 , yumuşak doku+kemik met.%18

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.

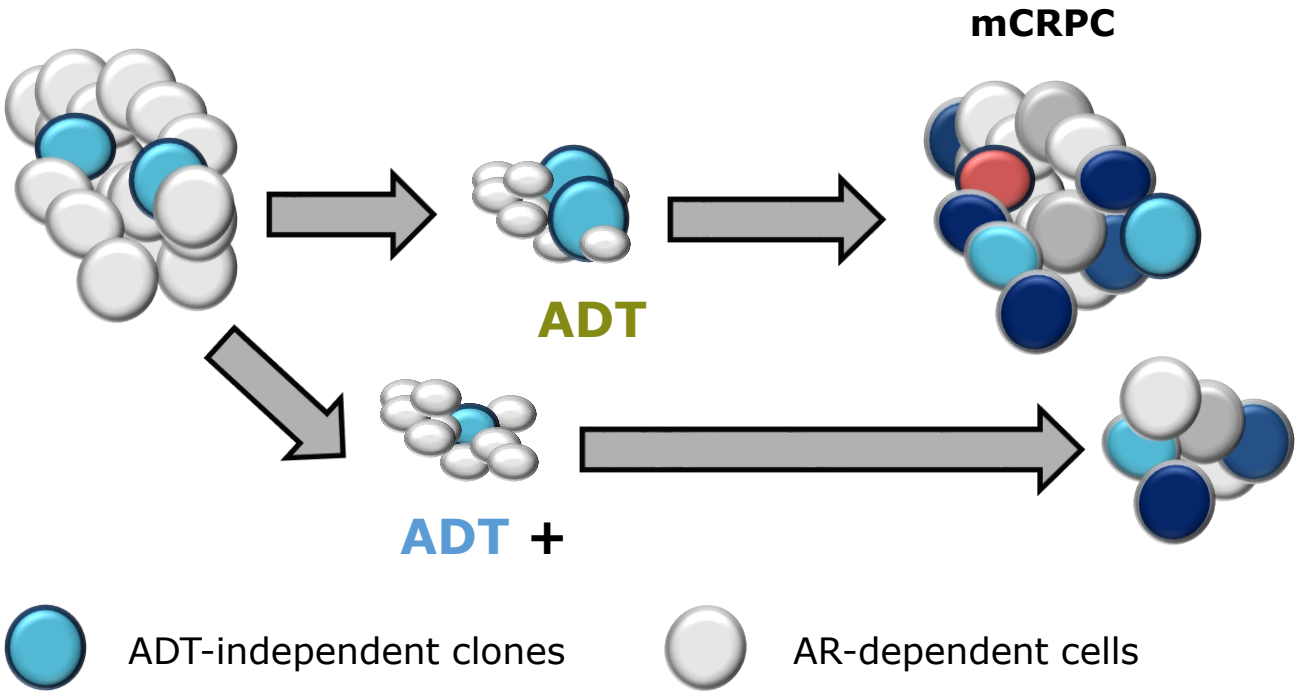


Kaplan-Meier plots displaying overall survival of 323 metastatic prostate cancer (mPCa) patients with visceral metastases with concomitant lymph node metastases only: (A) in the overall population; (B) according to location of visceral metastatic sites.



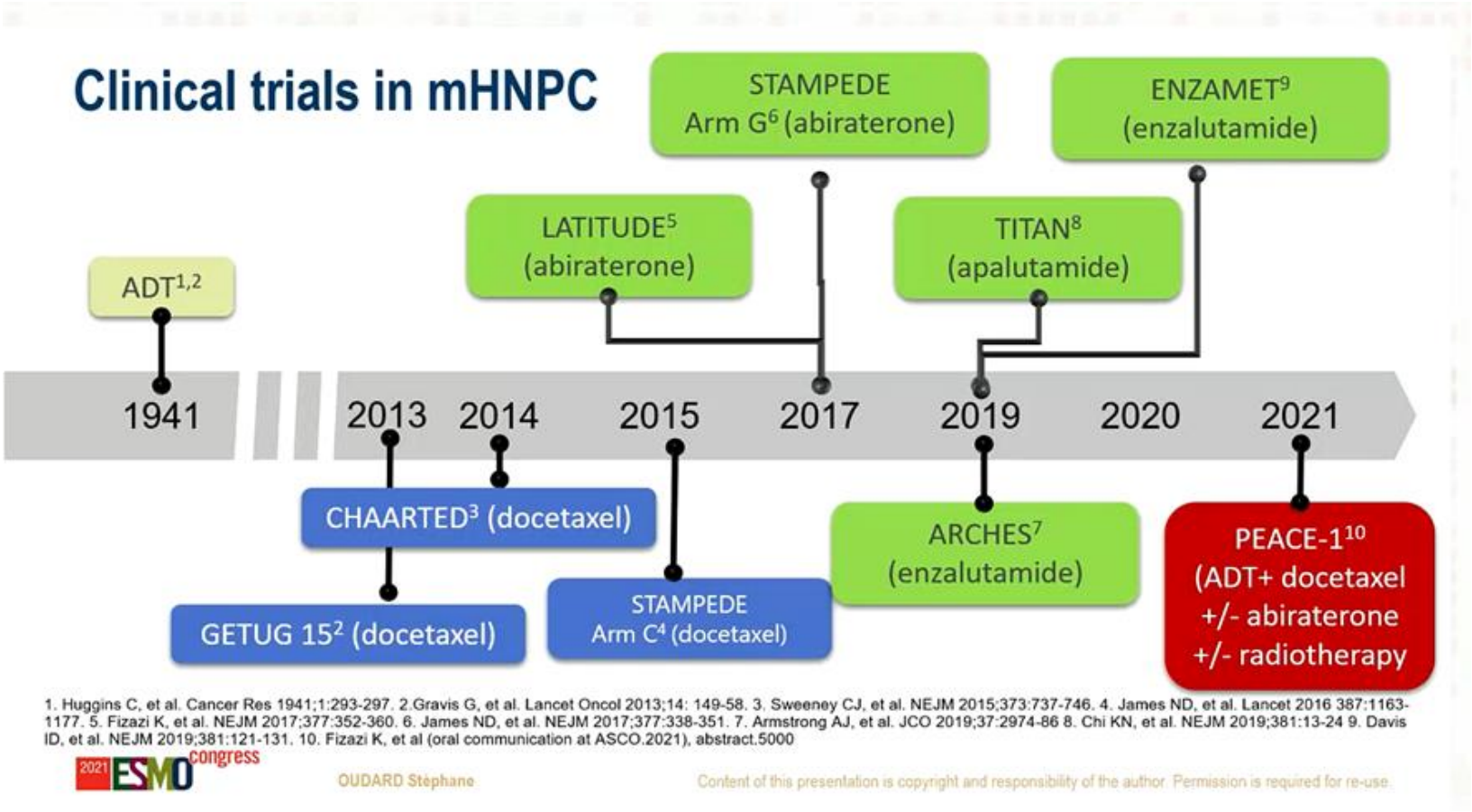
Tappero S, at al. Clinical Genitourinary Cancer 2023

Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi



Role of Effective Systemic Therapy

Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

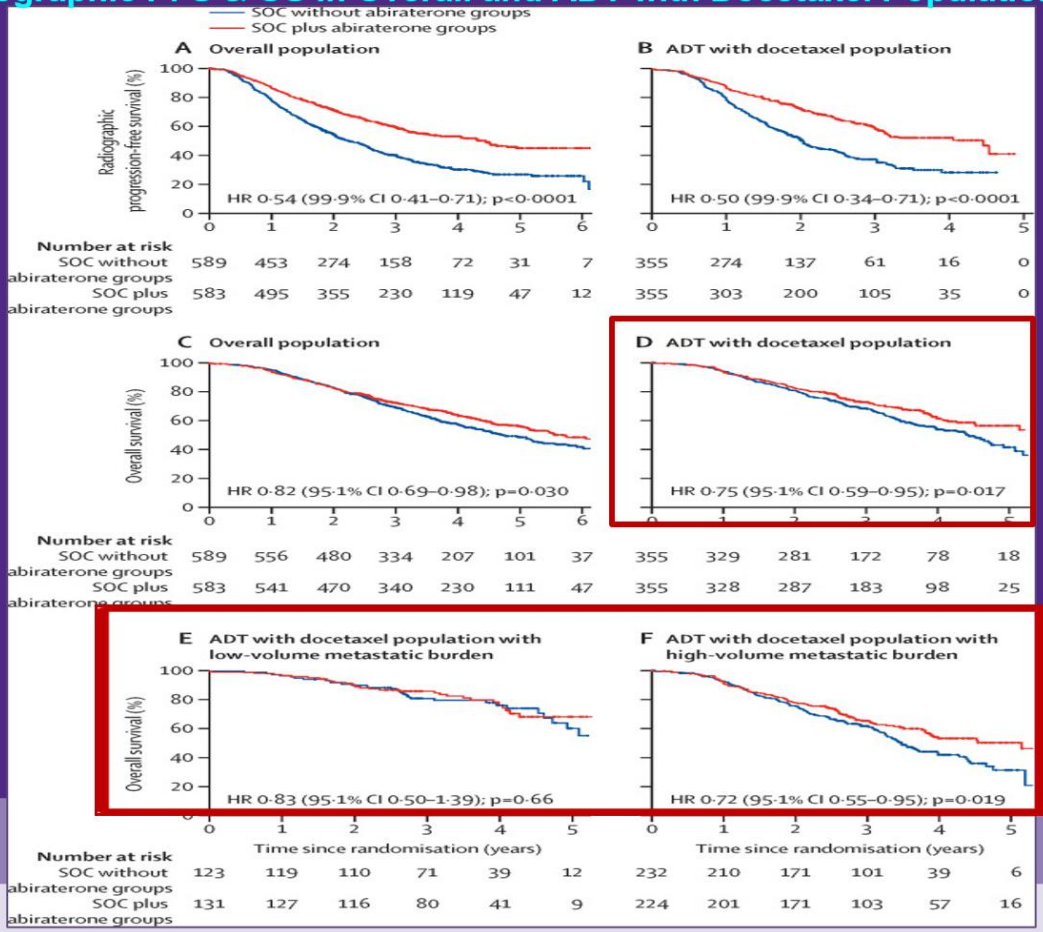


1. Huggins C, et al. Cancer Res 1941;1:293-297. 2.Gravis G, et al. Lancet Oncol 2013;14: 149-58. 3. Sweeney CJ, et al. NEJM 2015;373:737-746. 4. James ND, et al. Lancet 2016 387:1163-1177. 5. Fizazi K, et al. NEJM 2017;377:352-360. 6. James ND, et al. NEJM 2017;377:338-351. 7. Armstrong AJ, et al. JCO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

Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

Triplet #1: PEACE-1: ADT + Abiraterone/Prednisone in De Novo mHSPC

Radiographic PFS & OS in Overall and ADT with Docetaxel Population



Fizazi et al:
Lancet 2022

Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

PEACE-1: Adverse Events

	ADT with Docetaxel		ADT without Docetaxel	
	SOC + Abi (+/- RT)	SOC (+/- RT)	SOC + Abi (+/- RT)	SOC (+/- RT)
Any AE	346 (100%)	349 (100%)	226 (100%)	233 (99%)
Severe (grade >3)	217 (63%)	181 (52%)	149 (66%)	97 (41%)
Fatal (grade 5)	7 (2%)	3 (1%)	8 (4%)	5 (2%)
Frequent severe AEs				
Hypertension	76 (22%)	45 (13%)	66 (29%)	38 (16%)
Neutropenia	34 (10%)	32 (9%)	0	0
Hepatotoxicity	20 (6%)	2 (1%)	14 (6%)	3 (1%)
Febrile Neutropenia	18 (5%)	19 (5%)	2 (1%)	1 (<1%)
Fatigue	10 (3%)	15 (4%)	3 (1%)	0
Peripheral neuropathy	4 (1%)	6 (2%)	1 (<1%)	0

Fizazi et al, Lancet, 2022

Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

ASCO Genitourinary Cancers Symposium

PEACE ProstatE cAncer Consortium in Europe

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

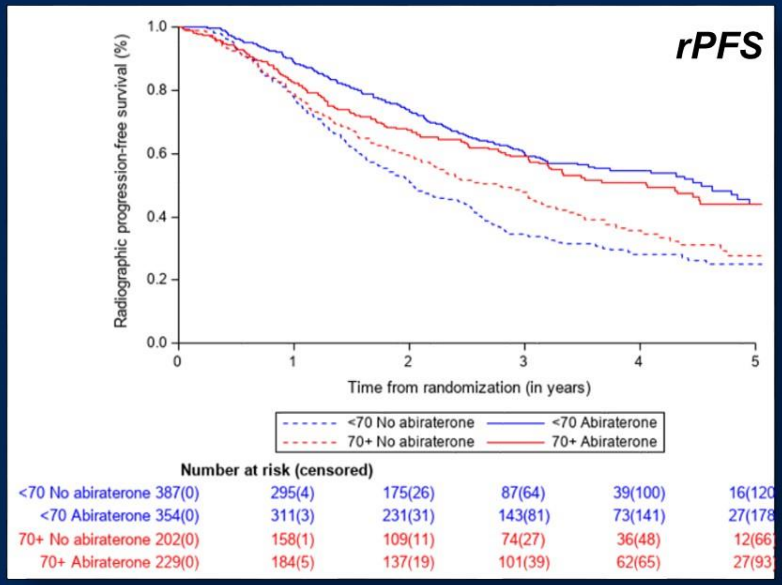
Mourey L[1], Boyle H[2], Roubaud G[3], McDermott R[5], Supiot S[6], Tombal B[7], Flechon A[2], Berthold D[8], Ronchin P[9], Kacso G[10], Berdah J-F[11], Calabro F[12], Gravis G[13], Palumbo S[14], Gil T[15], Vie B[16], Ribault H[17], Fizazi K[18], Foulon S[18], Carles J[19].

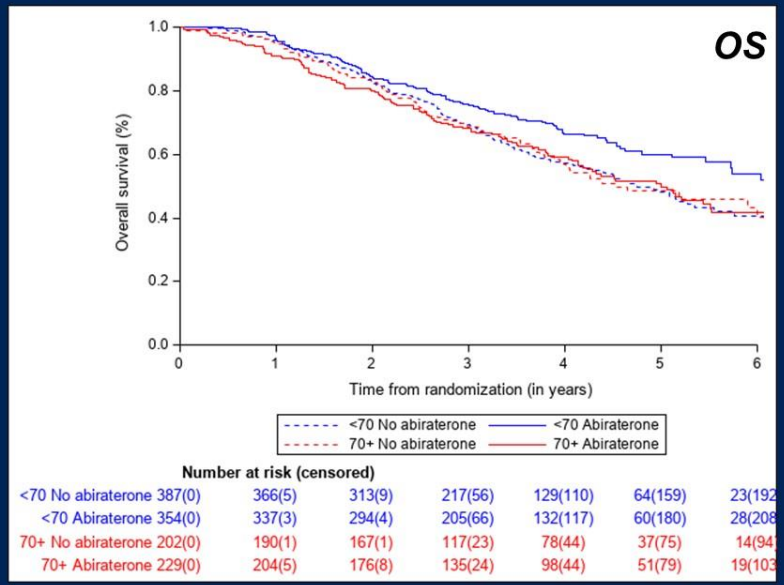
[1]Institut Universitaire du Cancer-Oncopole, Toulouse, France; [2]Centre Leon Bérard, Lyon, France; [3]Institut Bergonié, Bordeaux, France; [5]St. Vincent's University Hospital, Dublin, Ireland; [6]Institut de Cancerologie de l'Ouest-Rene Gauducheau, Nantes, France; [7]Cliniques Universitaires Saint-Luc,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

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

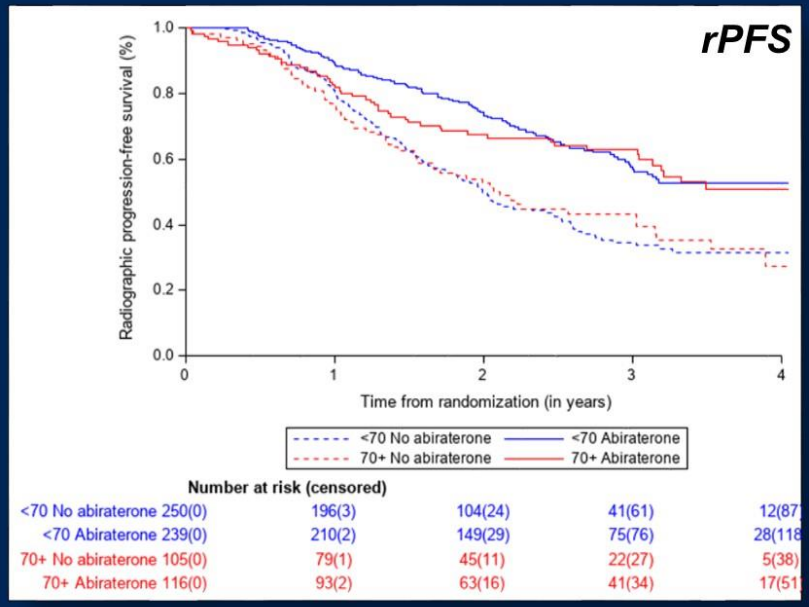
Age ≥ 70: HR 0.95, 95%CI (0.72-1.25)
Age <70: HR 0.73, 95%CI (0.58-0.92)
p-value of the interaction test 0.15

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

Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

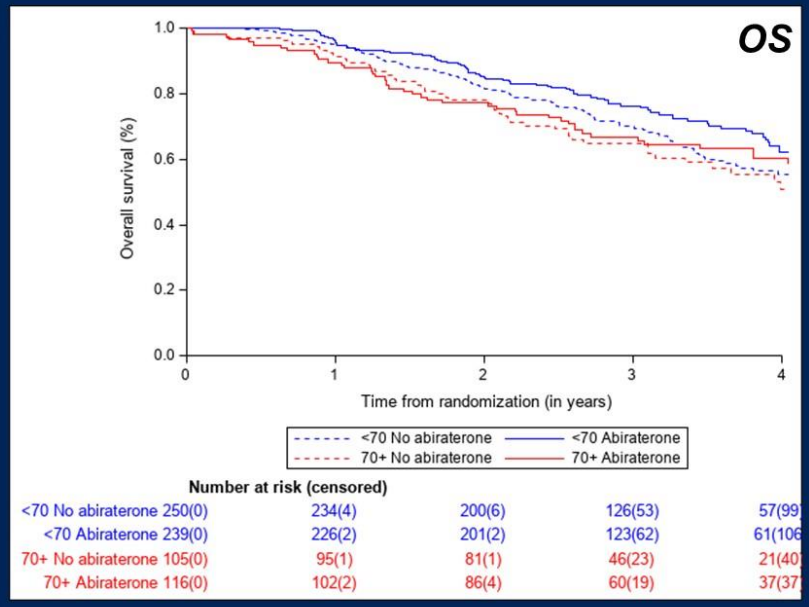
Results *(2)*

Docetaxel population



Number at risk (censored)

<70 No abiraterone 250(0)	196(3)	104(24)	41(61)	12(87)
<70 Abiraterone 239(0)	210(2)	149(29)	75(76)	28(118)
70+ No abiraterone 105(0)	79(1)	45(11)	22(27)	5(38)
70+ Abiraterone 116(0)	93(2)	63(16)	41(34)	17(51)



Number at risk (censored)

<70 No abiraterone 250(0)	234(4)	200(6)	126(53)	57(99)
<70 Abiraterone 239(0)	226(2)	201(2)	123(62)	61(106)
70+ No abiraterone 105(0)	95(1)	81(1)	46(23)	21(40)
70+ Abiraterone 116(0)	102(2)	86(4)	60(19)	37(37)

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 Tedavisi

ARASENS Study Design

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

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

*One enrolled patient was excluded from all analysis sets because of Good Clinical Practice violations. ALP, alkaline phosphatase; CRPC, castration-resistant prostate cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; FPFV, first patient first visit; LPFV, last patient first visit; M1a, nonregional lymph node metastases only; M1b, bone metastases ± lymph node metastases; M1c, visceral metastases ± lymph node or bone metastases; Q3W, every 3 weeks; SSE, symptomatic skeletal event; ULN, upper limit of normal.

Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

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 (%)†	≥ULN	361 (55.5)	363 (55.5)

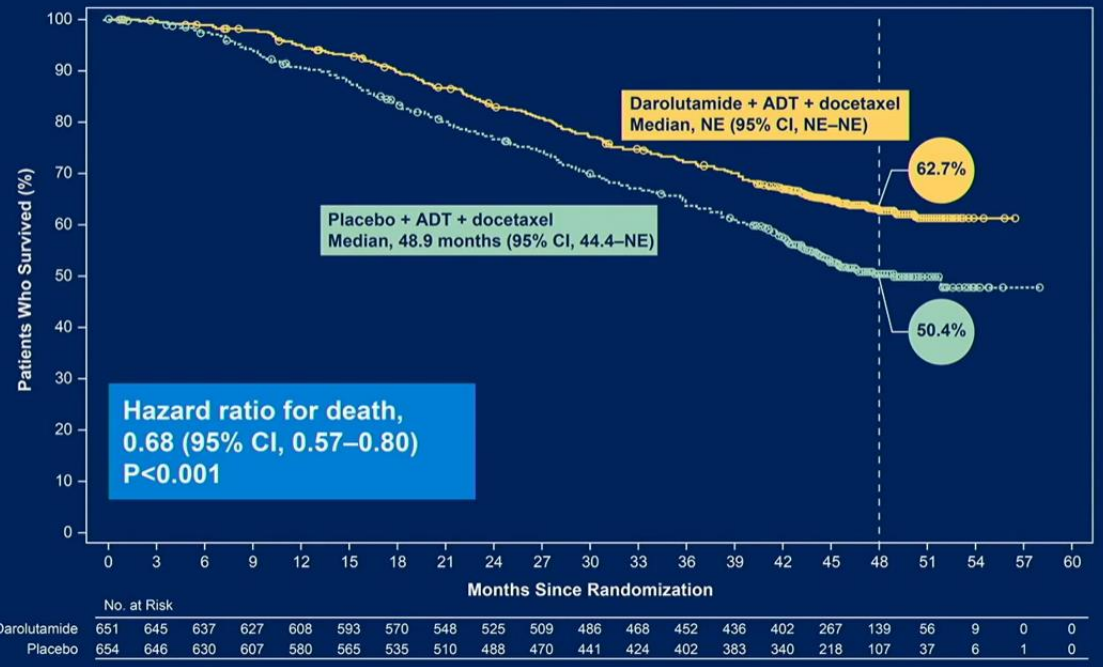
*One patient randomized to placebo but who received darolutamide was included in the placebo group for the full analysis set. †Centrally assessed; samples were collected while patients were receiving ADT.
PSA, prostate-specific antigen.

PRESENTED BY: Matthew R. Smith, MD, PhD

Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

ARASENS Primary Endpoint*: Overall Survival

Darolutamide significantly reduced the risk of death by 32.5%



No. at Risk

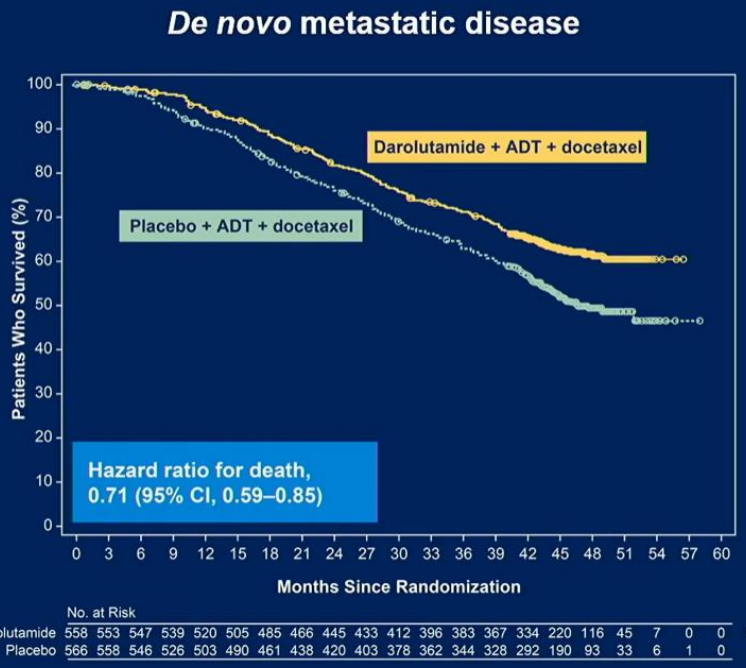
Darolutamide	651	645	637	627	608	593	570	548	525	509	486	468	452	436	402	267	139	56	9	0	0
Placebo	654	646	630	607	580	565	535	510	488	470	441	424	402	383	340	218	107	37	6	1	0

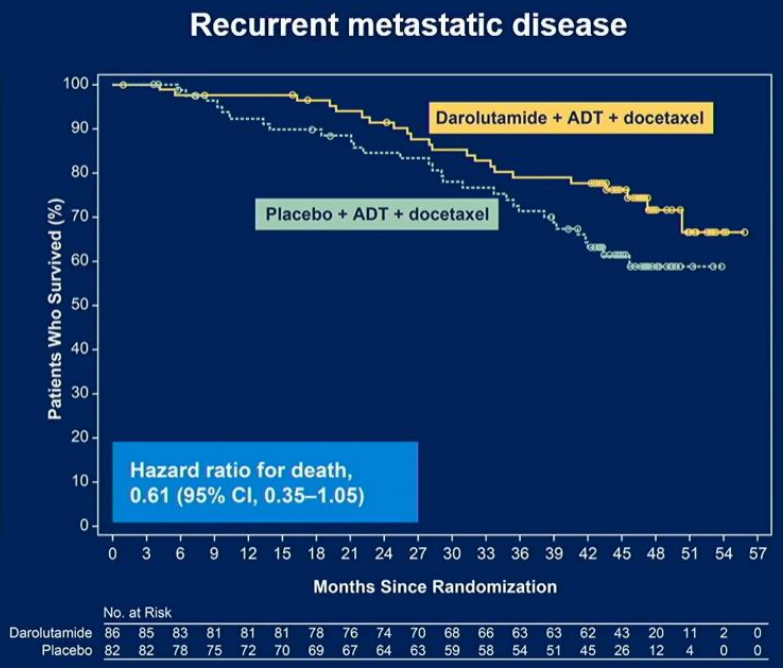
*Primary analysis occurred after 533 deaths (darolutamide, 229; placebo, 304). CI, confidence interval; NE, not estimable.

PRESENTED BY: Matthew R. Smith, MD, PhD

Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

Overall Survival By Metastatic Stage at Initial Diagnosis

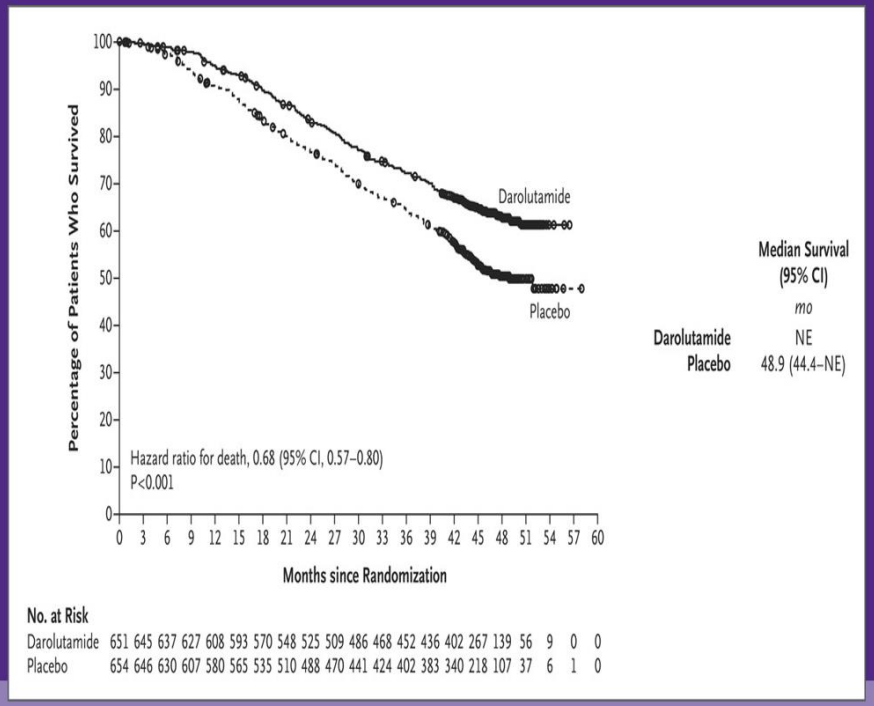


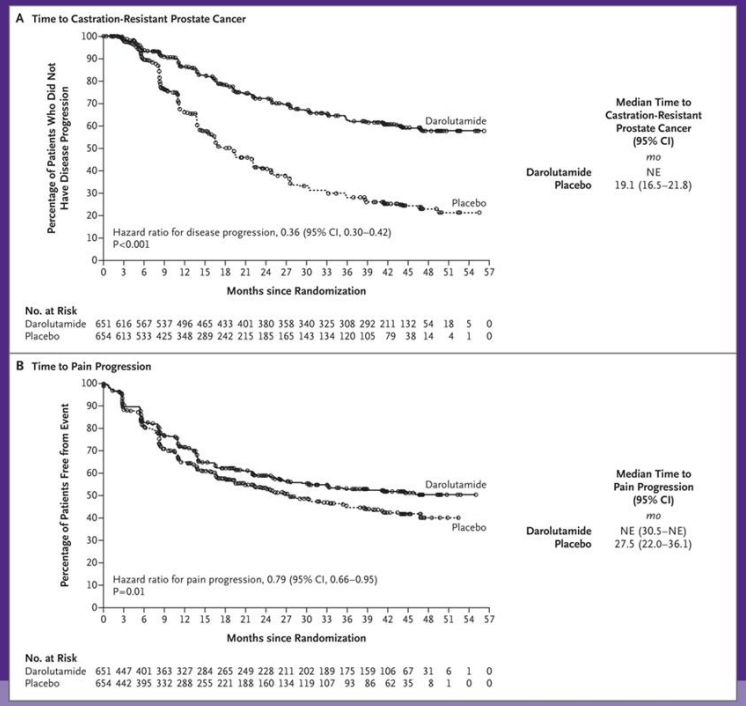


Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

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

Overall Survival





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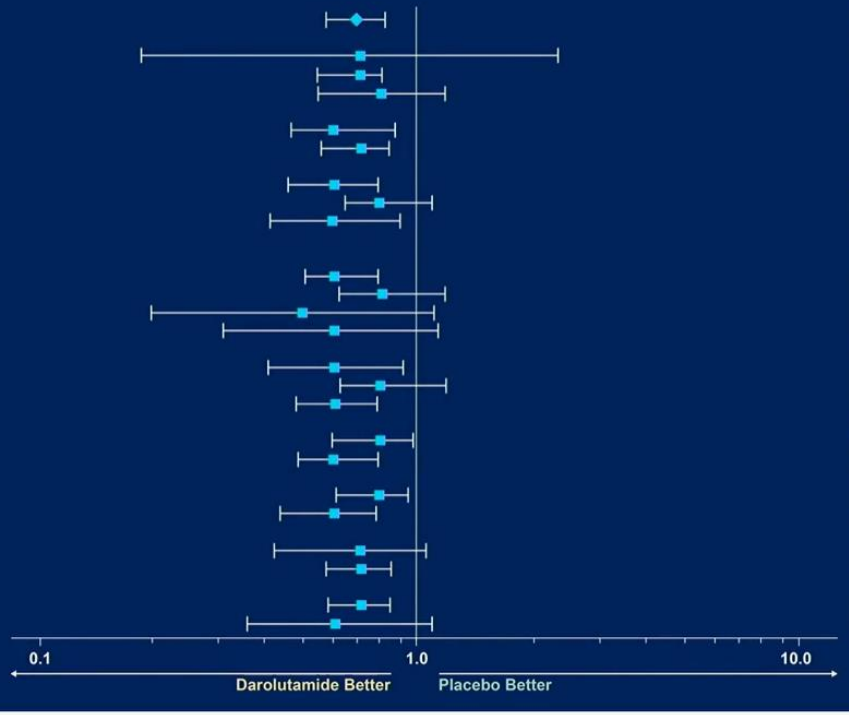
Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

ARASENS Overall Survival: Subgroup Analyses

	Darolutamide + ADT + Docetaxel	Placebo + ADT + Docetaxel	Hazard Ratio (95% CI)
	No. of Events/No. of Patients		
Overall	229/651	304/654	0.69 (0.58–0.82)
Extent of disease (eCRF)			
Nonregional lymph node metastasis	5/23	5/16	0.65 (0.19–2.25)
Bone metastasis	171/517	237/520	0.67 (0.55–0.81)
Visceral metastasis	53/111	62/118	0.79 (0.55–1.14)
ALP stratification factor (eCRF)			
Below upper limit of normal	62/290	93/291	0.64 (0.46–0.88)
At or above upper limit of normal	167/361	211/363	0.69 (0.56–0.85)
Age (years)			
<65 yr	80/243	117/234	0.59 (0.45–0.79)
65–74 yr	107/303	124/306	0.82 (0.63–1.06)
75–84 yr	40/102	60/110	0.61 (0.41–0.90)
≥85 yr	2/3	3/4	
Race			
White	131/345	173/333	0.63 (0.50–0.79)
Asian	74/230	93/245	0.84 (0.62–1.14)
Black or African American	8/26	16/28	0.46 (0.20–1.08)
Other or not reported	16/50	22/48	0.58 (0.30–1.11)
Geographical region			
North America	42/125	56/119	0.61 (0.41–0.91)
Asia Pacific	74/229	92/244	0.85 (0.63–1.15)
Rest of the world	113/297	156/291	0.61 (0.48–0.78)
PSA at baseline			
Below median	110/315	142/337	0.77 (0.60–0.98)
At or above median	119/336	162/316	0.62 (0.49–0.78)
ECOG at baseline			
0	150/466	188/462	0.75 (0.61–0.93)
1	79/185	115/190	0.58 (0.43–0.77)
Gleason score			
<8	33/122	44/118	0.65 (0.42–1.03)
≥8	187/505	248/516	0.71 (0.59–0.86)
Metastatic stage at initial diagnosis			
M1 (*de novo*)	206/558	271/566	0.71 (0.59–0.85)
M0 (recurrent)	22/86	30/82	0.61 (0.35–1.05)



eCRF, electronic case report form.

Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

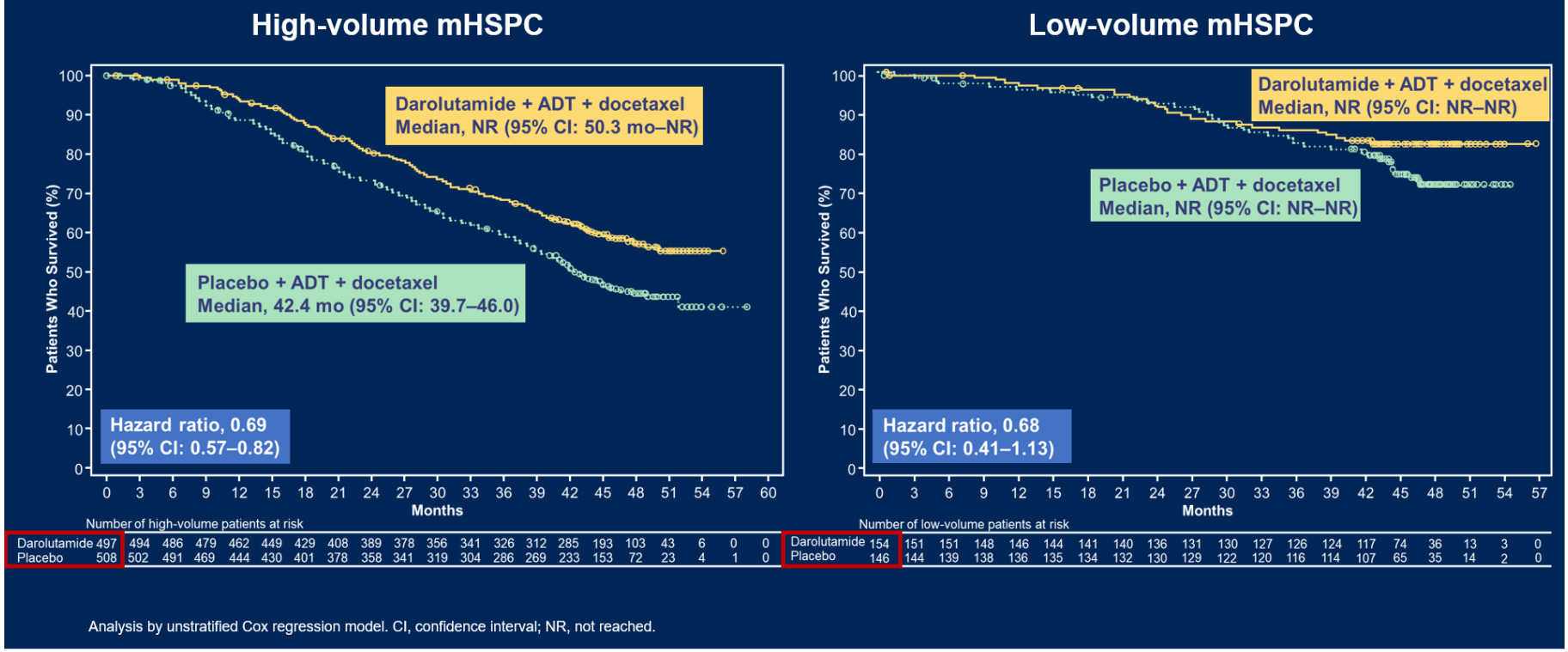
Adverse Events of Special Interest for AR Pathway Inhibitors

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.

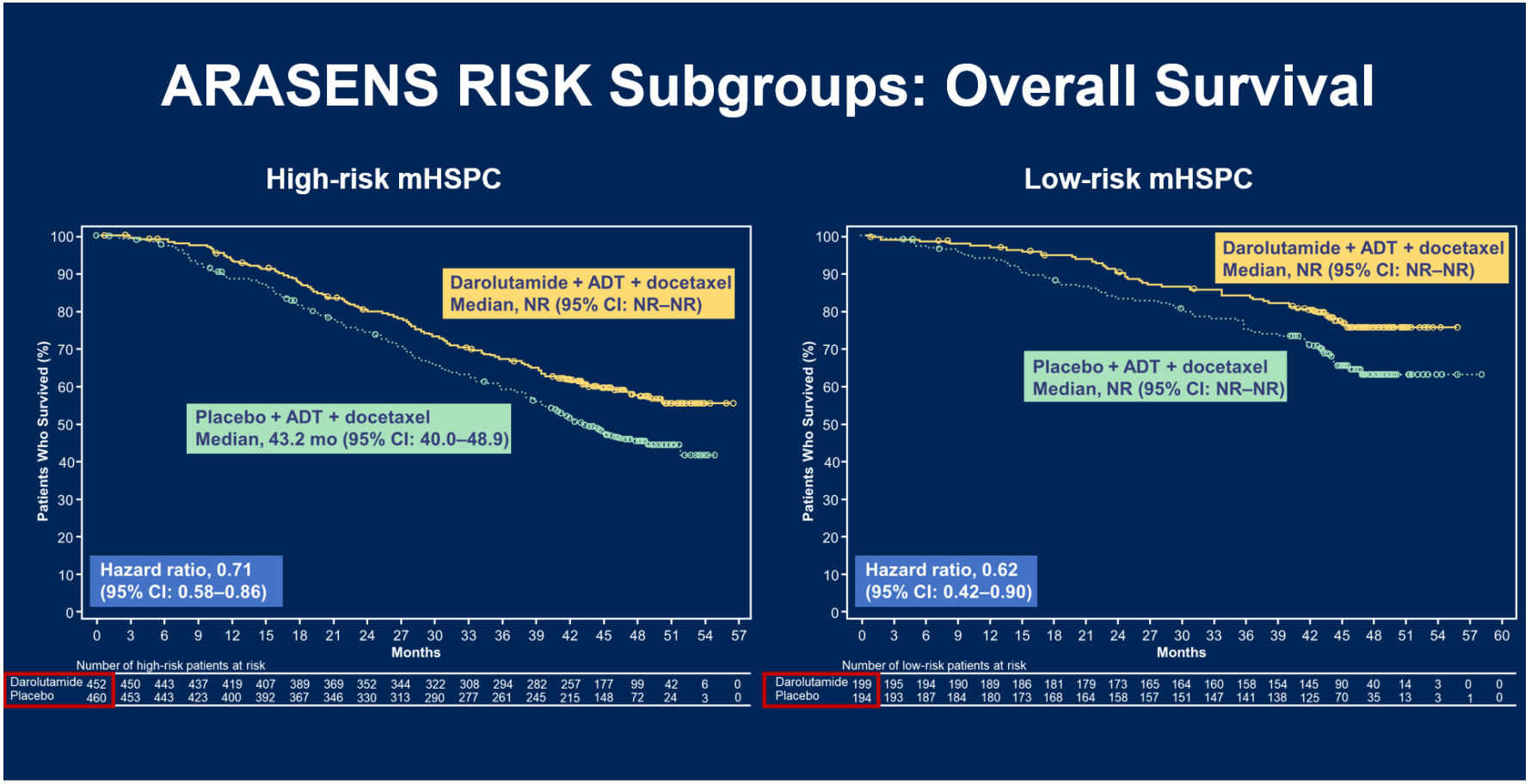
Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

ARASENS VOLUME Subgroups: Overall Survival



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

Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

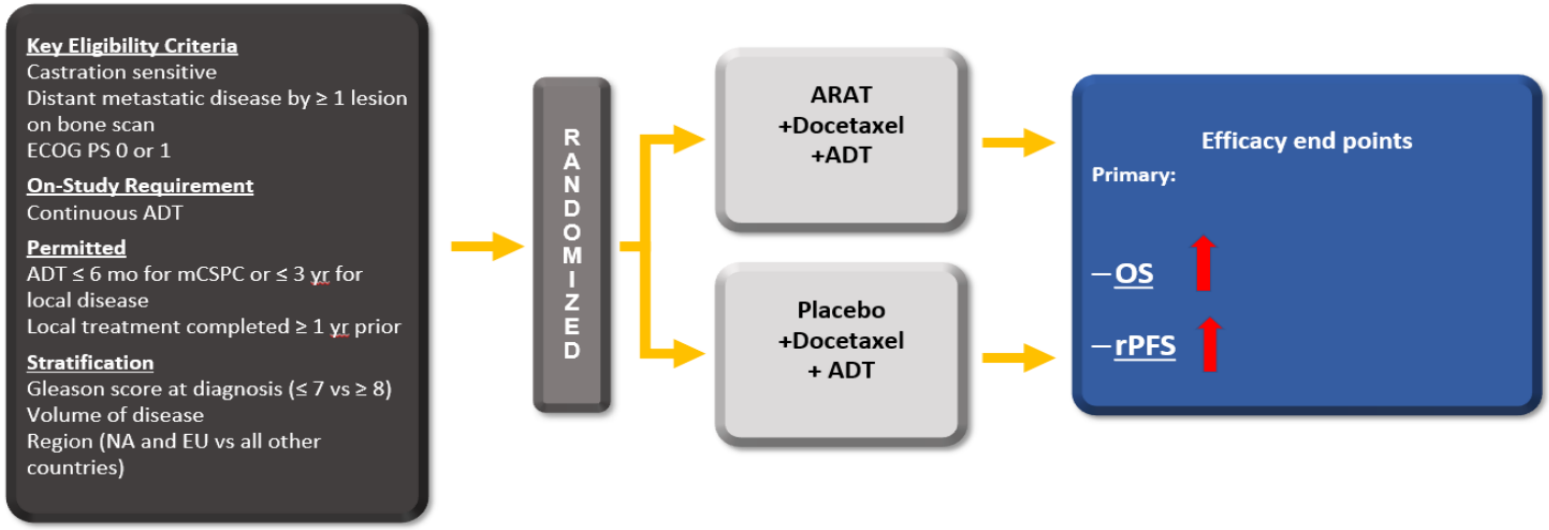


Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

	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

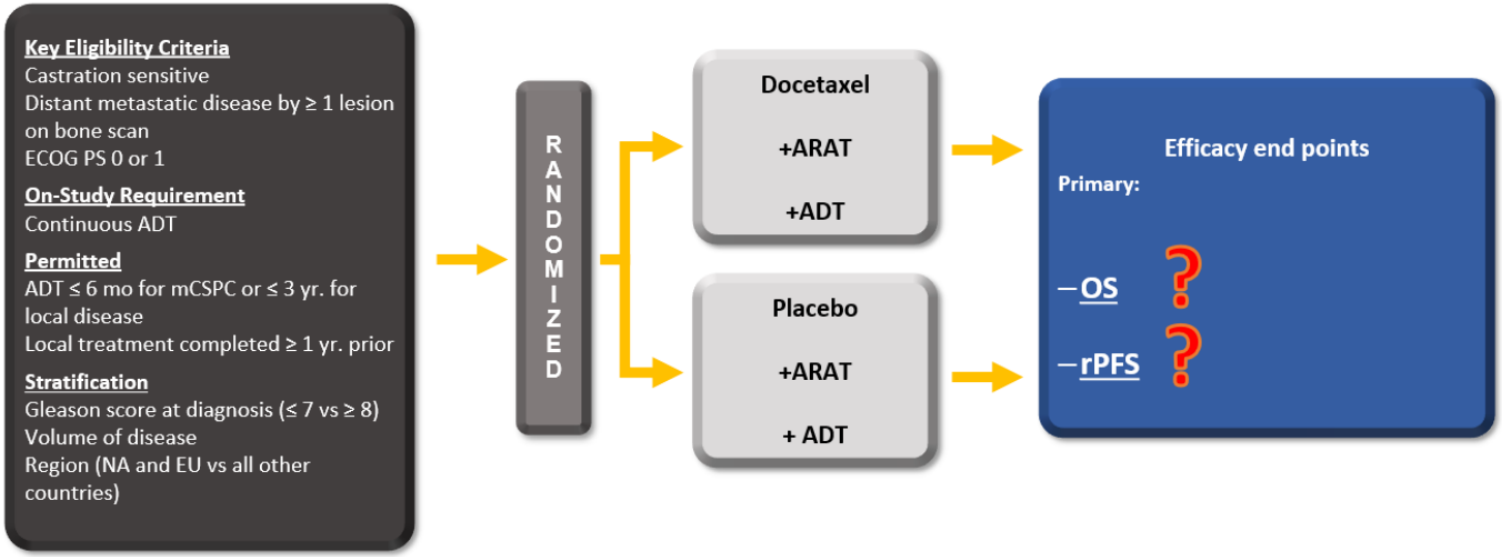


ECOG PS, Eastern Cooperative Oncology Group performance status; ART, Androgen receptor targeted therapy; NA, North America; PSA, prostate-specific antigen; OS, Overall survival; rPFS, radiographic progression-free survival.

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

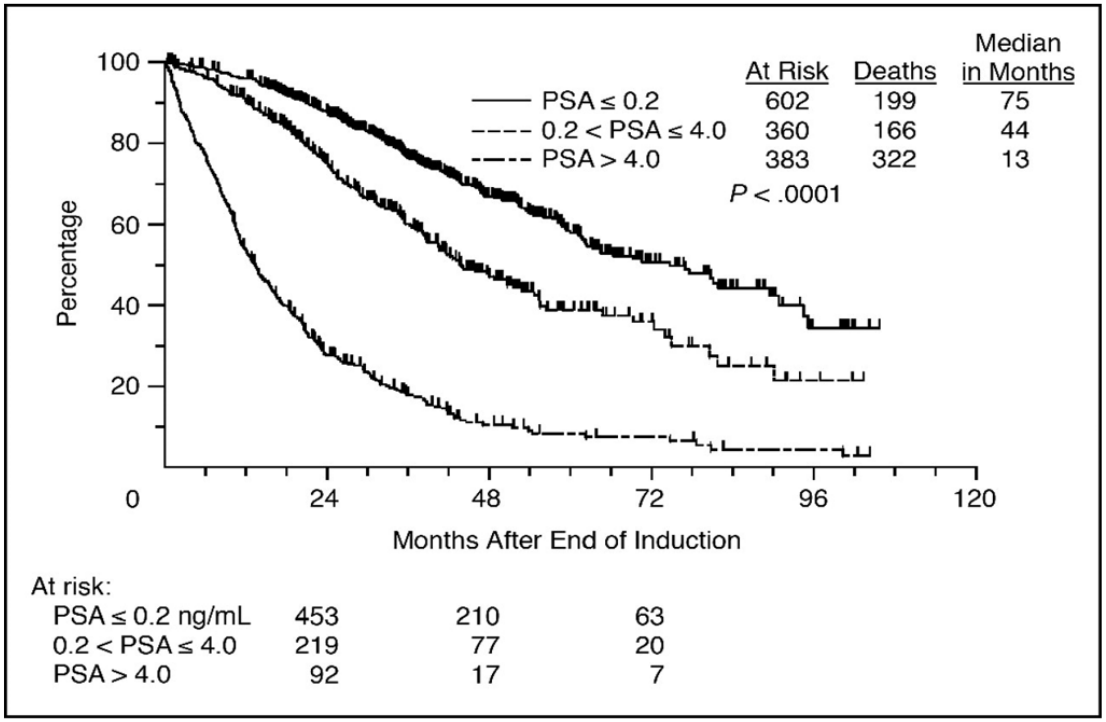
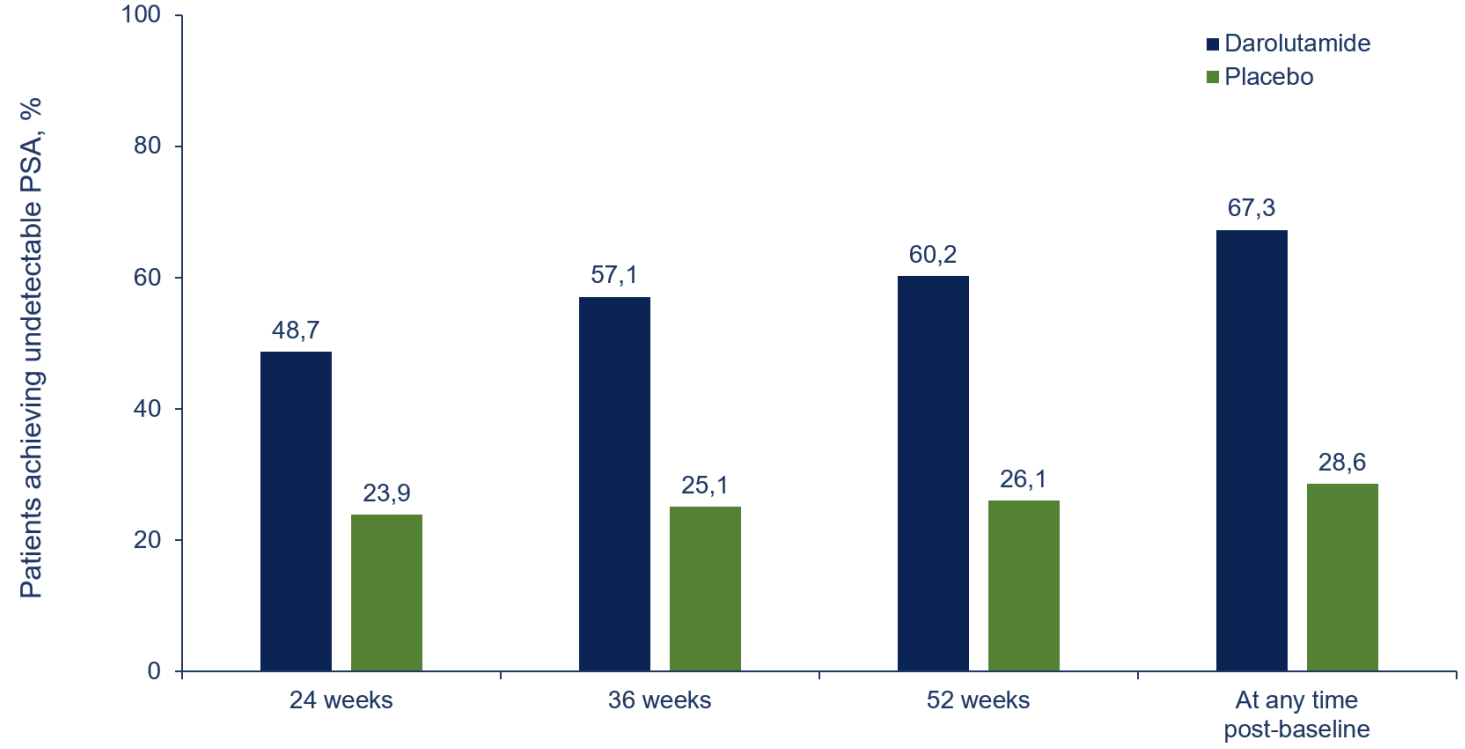


Fig 2. Overall survival by prostate-specific antigen (PSA, ng/mL) status at end of induction
Maha Hussain: Journal of Clinical Oncology 2006; 24 3984-3990.

Courtesy of Simon Chowdhury, MD, PhD

Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

Objective: Undetectable (≤0.2) PSA Levels



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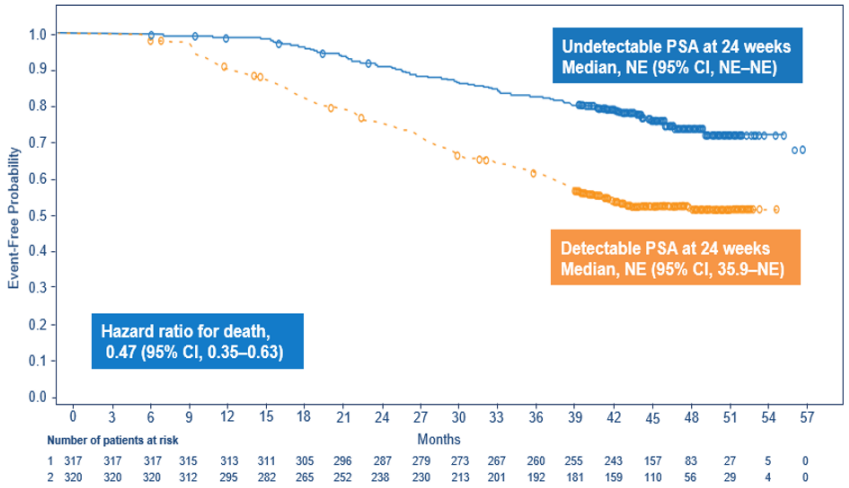
Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

Results: Overall Survival

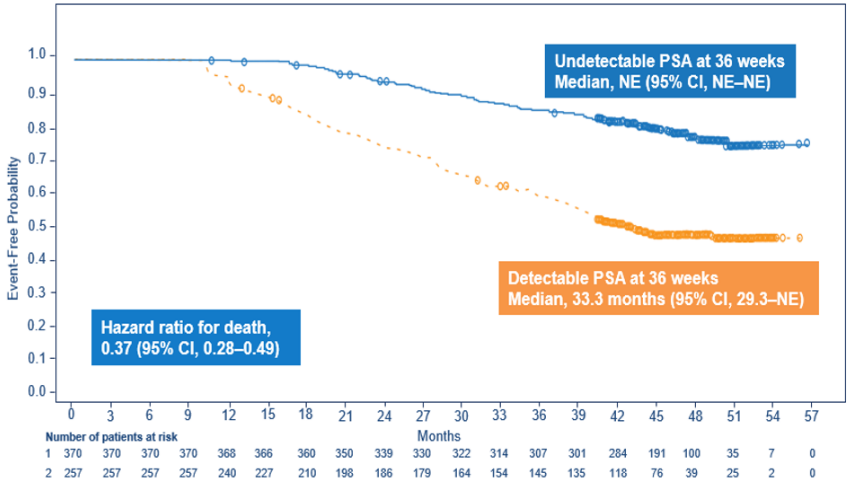
Undetectable PSA at 24 and 36 weeks was associated with a 53% and 63% reduction in the risk of death

Darolutamide + ADT + docetaxel

Undetectable vs detectable PSA at 24 weeks



Undetectable vs detectable PSA at 36 weeks



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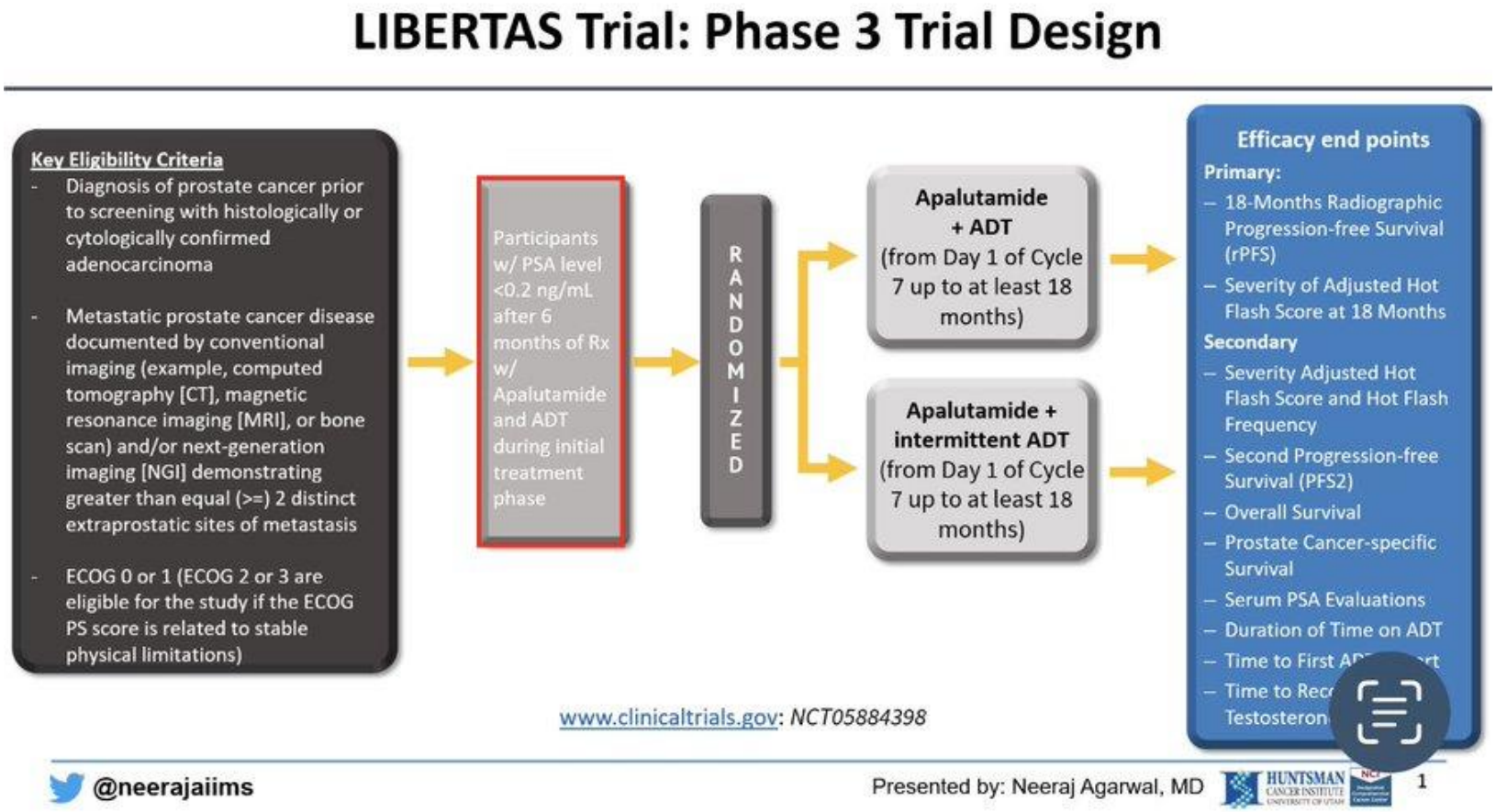
CHUM

Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi



Metastatik Kastrasyona Duyarlı Prostat Kanseri Tedavi

National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2023
Prostate Cancer

NCCN Guidelines Index
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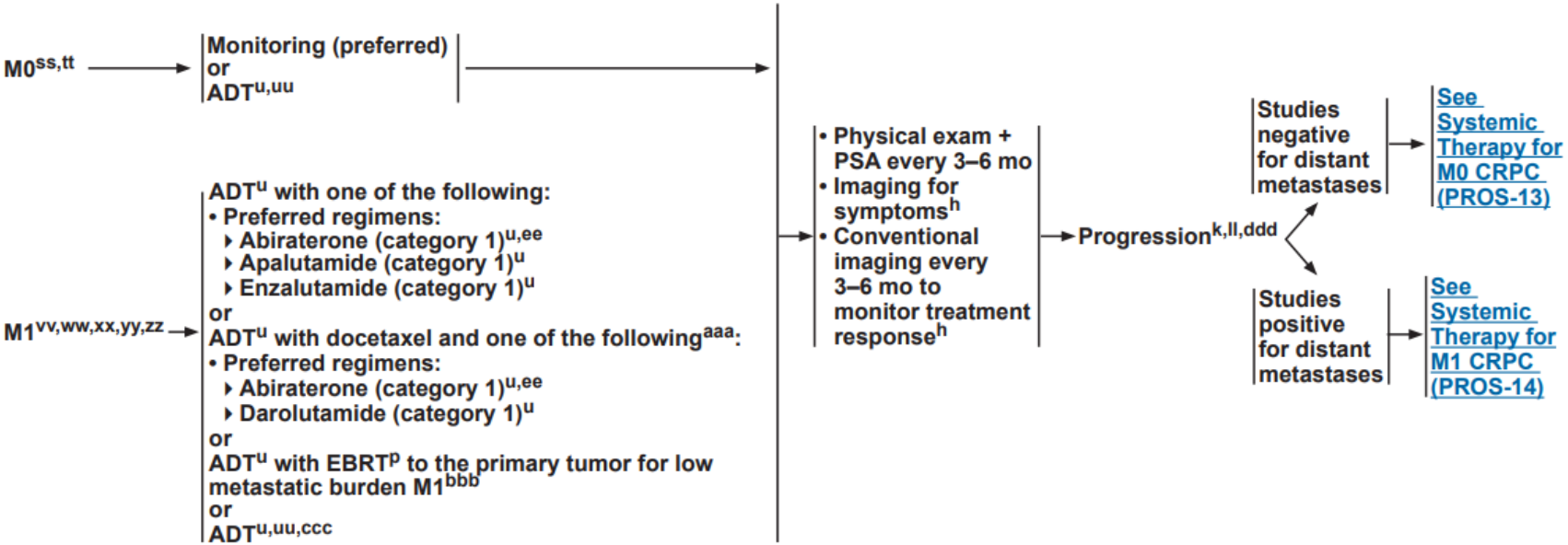
SYSTEMIC THERAPY FOR CASTRATION-SENSITIVE PROSTATE CANCER[rr]



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+dosetaksel 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