Kastrasyona Duyarlı Metastatik Prostat Kanserinde Tedavi

Dr. Deniz Tural
Koç Üniversitesi Hastanesi Medikal 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

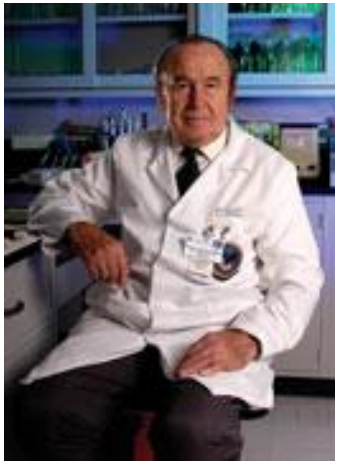
Androjen Baskılama Tedavisi(ADT)

- ❑ Cerrahi Kastrasyon(Bilateral orişektomi)

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

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

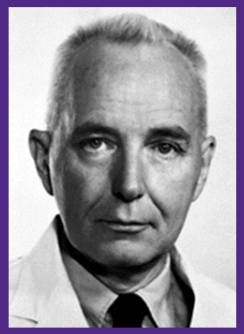
Kastrasyona Duyarlı Metastatik Prostat Kanseri ADT Tedavisi



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

Kastrasyona Duyarlı Metastatik Prostat Kanseri ADT Tedavisi

Historical Perspective: Androgens & Prostate Cancer



C. Huggins
1966 Nobel Prize

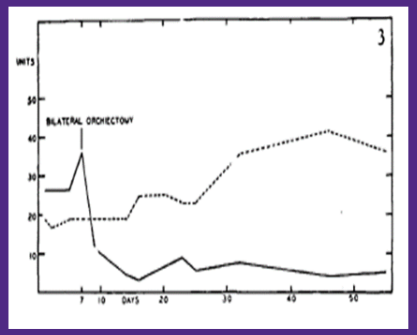
Studies on Prostatic Cancer

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

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

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

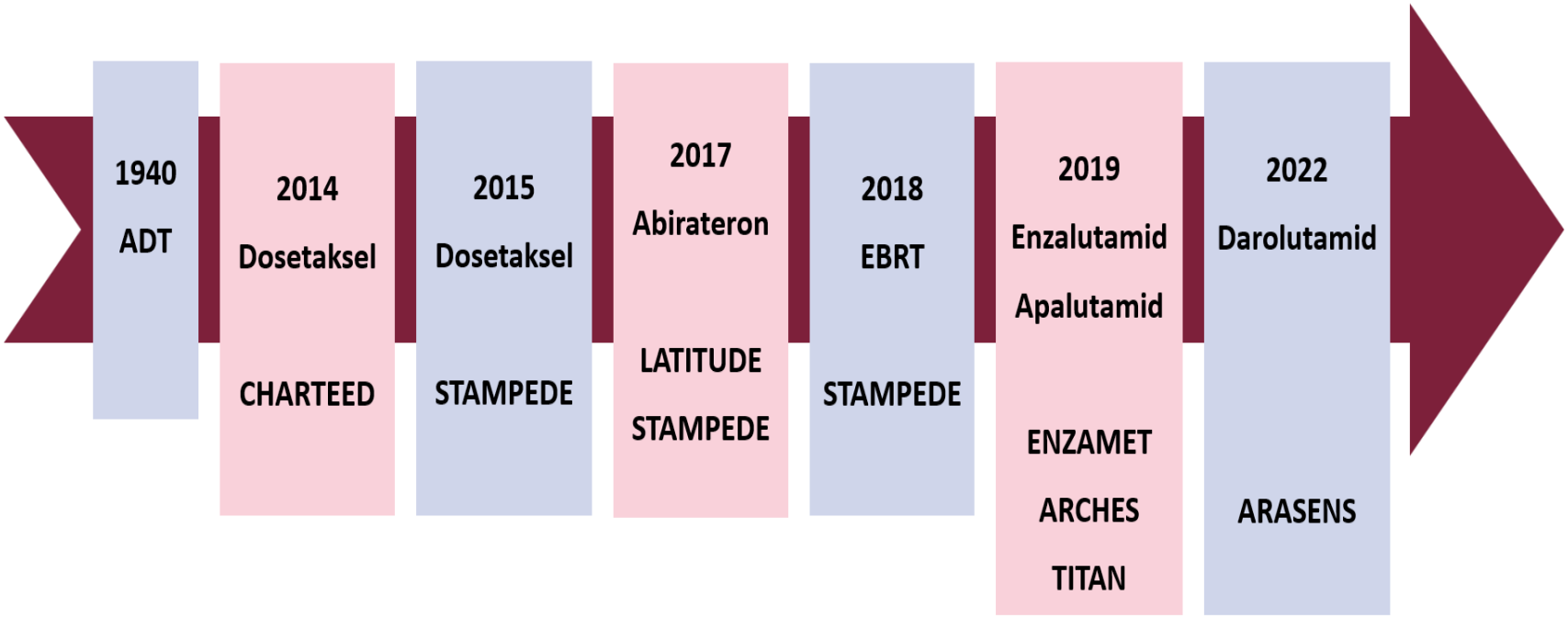
(Received for publication March 22, 1941)



Cancer Res 1941;1:293-297

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

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

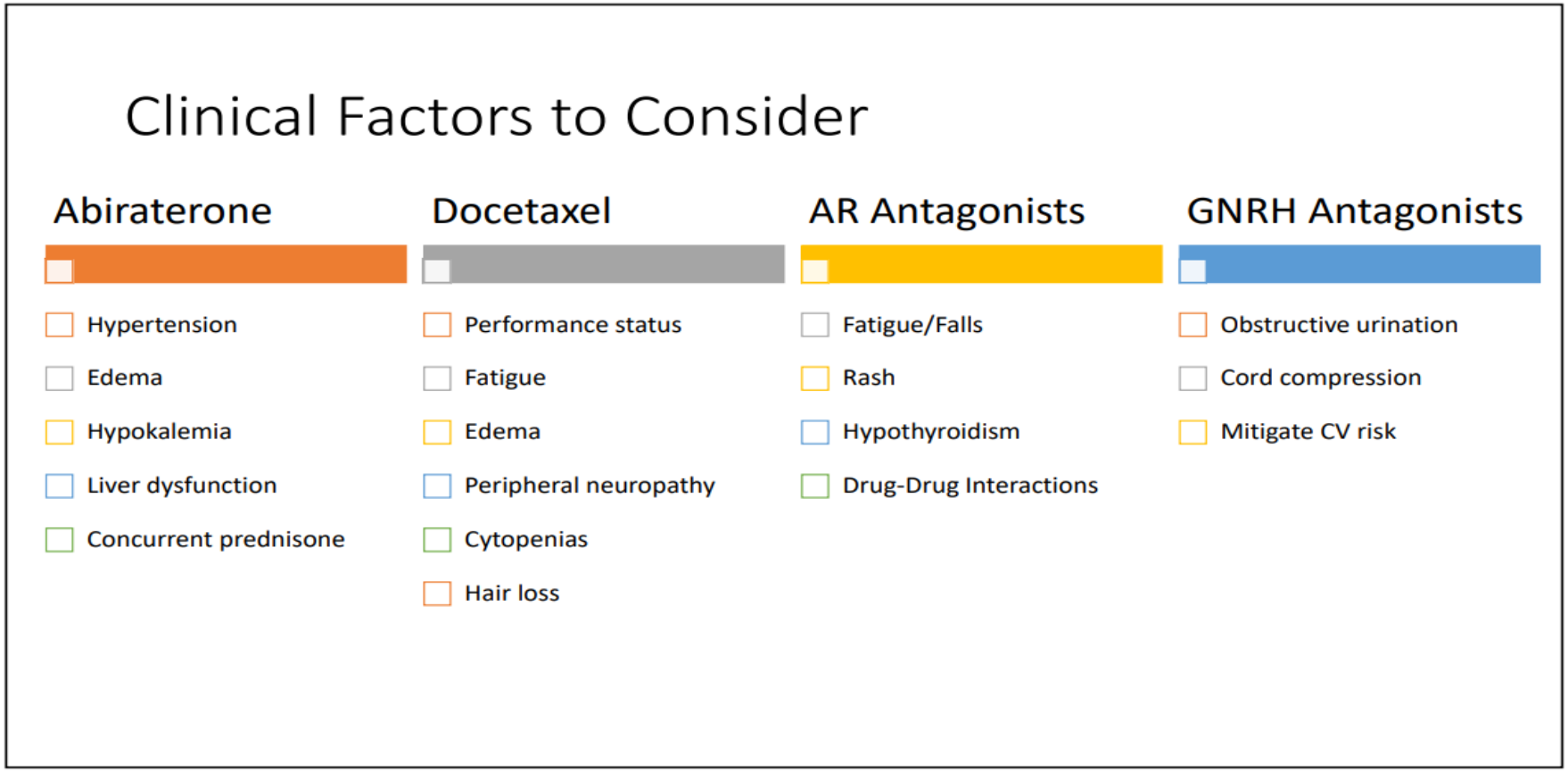
2-Etki etme mekanizması

3- Yan etkileri

4-İlaç etkileşimi

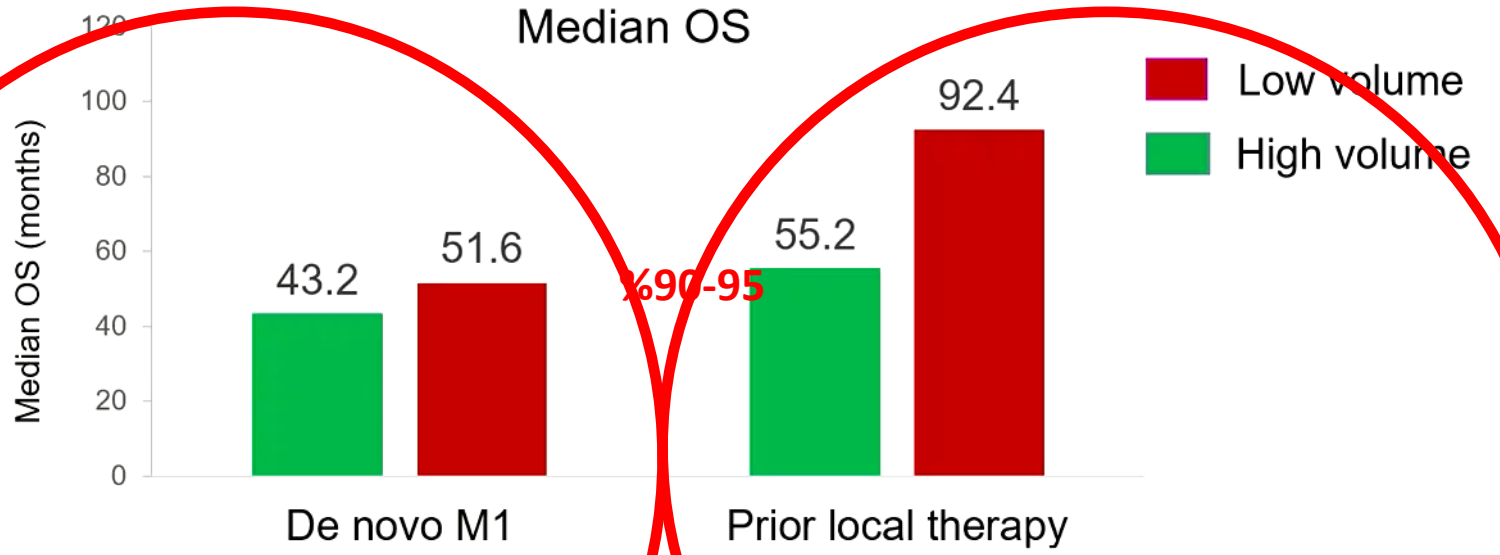
5-Tedavi maliyeti

Tedavi kararında etkili faktörler



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

OUDARD Stéphane

%90-95

%5-10

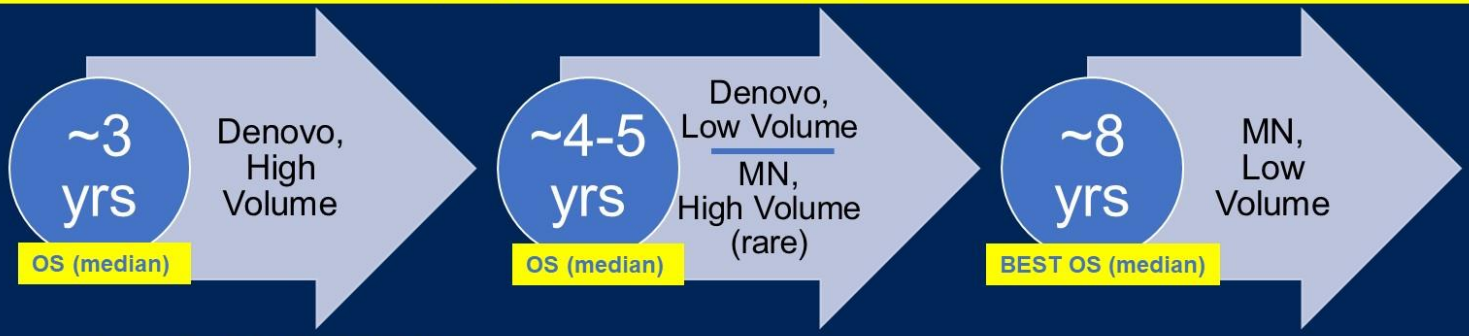
%90-95

TANI ANINDA METASTATİK VE YÜKSEK VOLÜMLÜ HASTALIK AGRESİF SEYİRLİ

Metastatic HSPC Trials – Clinical Risk Groups

	CHAARTED N= 790	STAMPEDE, M1 N= 1086	LATITUDE N=1199	STAMPEDE, M1 N=999	ENZAMET N=1125	TITAN N=1052
ADT + *(NSAA)	DOC	DOC	ABI	ABI	ENZA*	APA
PRIMARY ENDPOINT, OS HR (95%, CI)	0.72 (0.59-0.89)	0.81 (0.69-0.95)	0.66 (0.56-0.78)	0.61 (0.49-0.75)	0.67 (0.52-0.86)	0.65 (0.53-0.79)

Can clinical prognostic factors help guide treatment selection?



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

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

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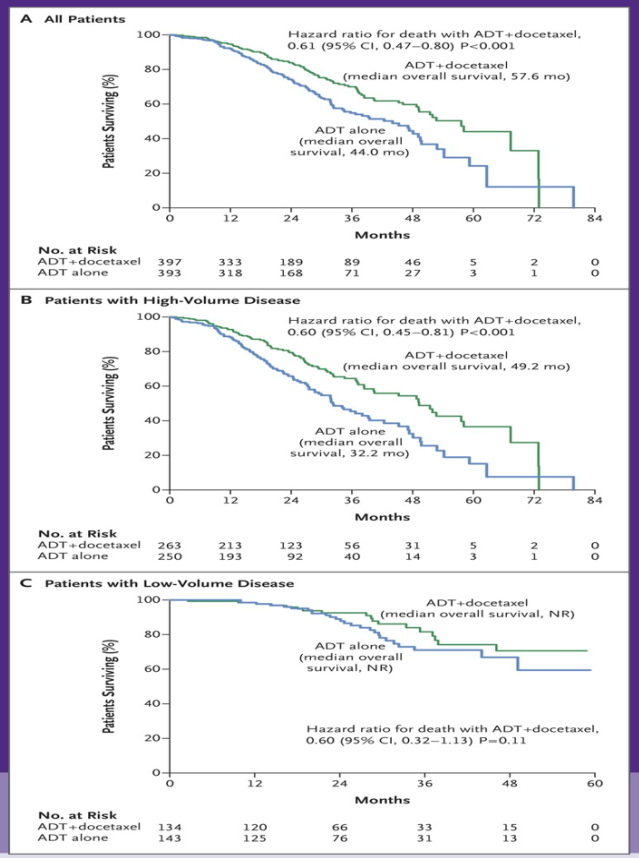
Hastalık Volümü Dosetaksel Tedavi Etkinliği için Prediktif

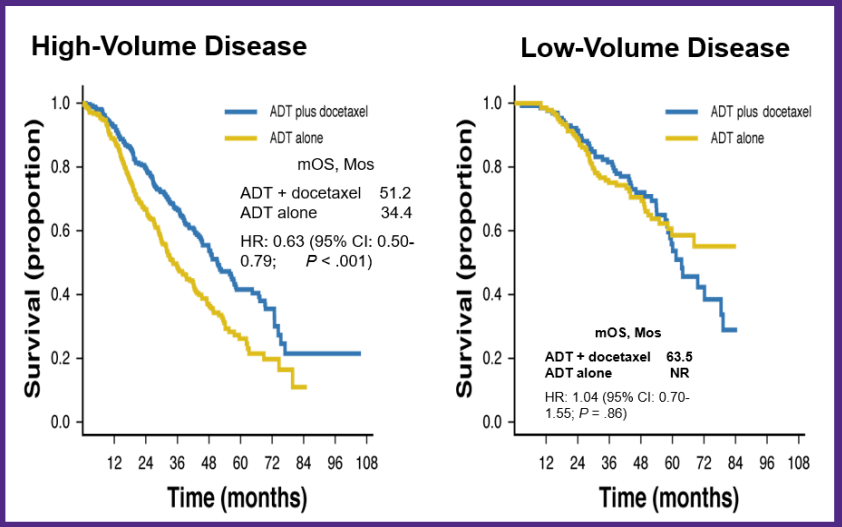
CHAARTED: ADT +/- Docetaxel in mHSPC



Sweeney CJ et al. NEJM 2015

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

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

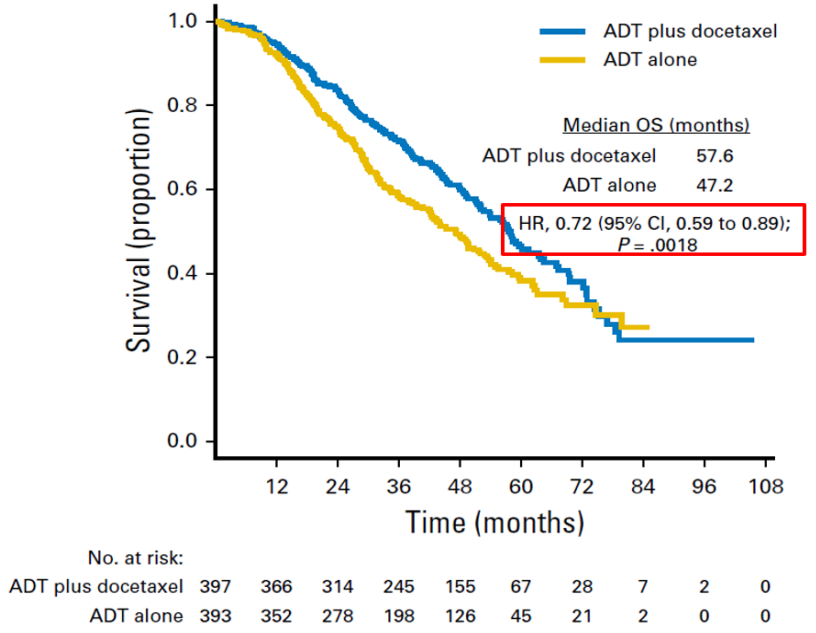


Kyriakopoulos CE, et al. J Clin Oncol. 2018

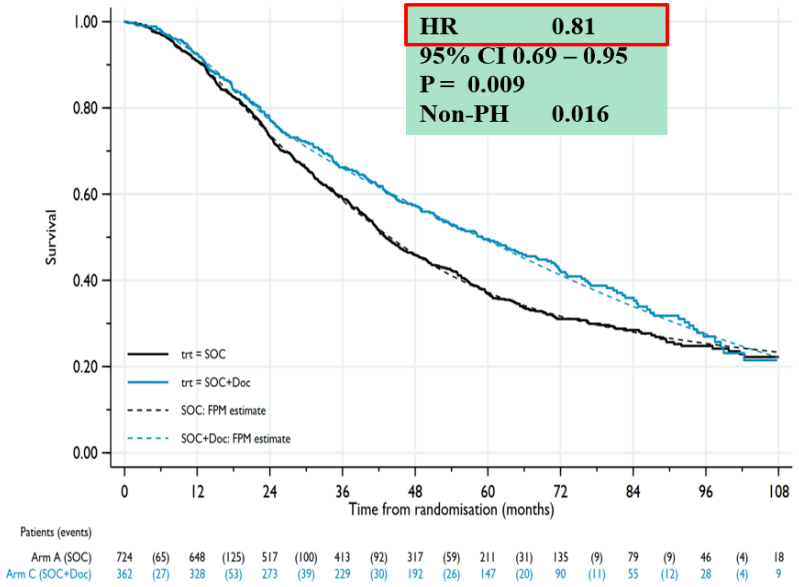
Yüksek volümlü hastalığı olanlar; viseral organ metastazı olan yada ≥4 kemik lezyonu olan ve en az ≥1 vertebra, pelvis dışı kemiklerde metastaz olmalı

Hastalık Volümü Dosetaksel Tedavi Etkinliği için Prediktif

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



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

Hastalık Volümü Dosetaksel Tedavi Etkinliği için Prediktif

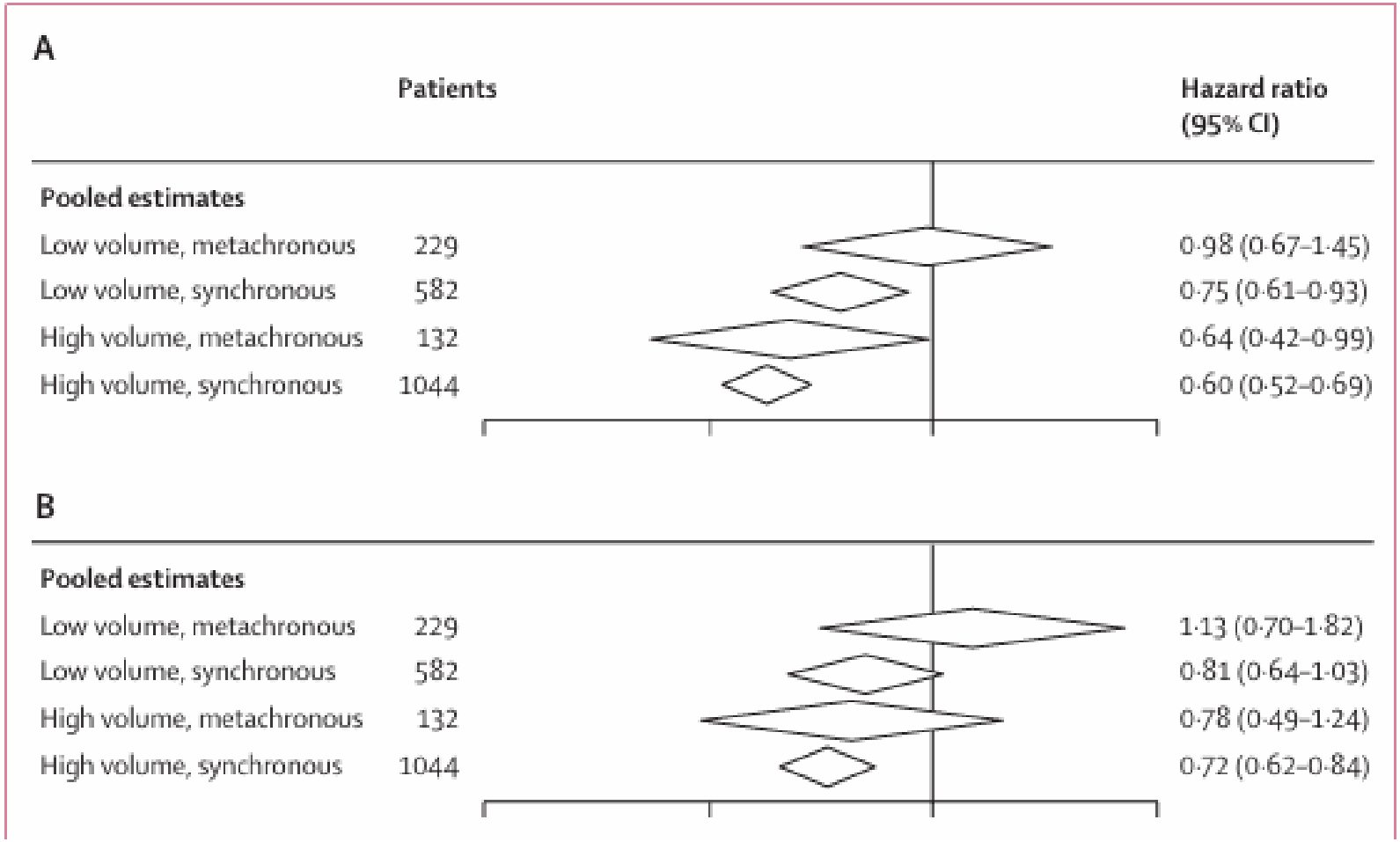
	GETUG-AFU15[5]	CHAARTED[2]	STAMPEDE[7]
Accrual period	October, 2004, to December, 2008	July, 2006, to November, 2012	November, 2005, to March, 2013
Number of patients randomly assigned	385	790	1086
Control group treatment	ADT (LHRH agonist or LHRH agonist plus anti-androgen therapy or surgical castration)	ADT (LHRH agonist or LHRH antagonist or surgical castration); oral calcium carbonate 500 mg daily; oral vitamin D 400 IU daily	ADT (GRH agonists or antagonists or orchidectomy)
Intervention group treatment	ADT (LHRH agonist or LHRH agonist plus antiandrogen therapy or surgical castration) plus docetaxel (75 mg/m² intravenously every 3 weeks for a maximum of nine cycles); premedication with an oral corticosteroid (8 mg dexamethasone or equivalent) the evening before, on the day of, and on the day after docetaxel infusion plus subcutaneous injection of G-CSF from day 5 for 5 days	ADT (LHRH agonist or LHRH antagonist or surgical castration) plus docetaxel (75 mg/m² intravenously every 3 weeks for six cycles); oral dexamethasone (8 mg approximately 12 h, 3 h, and 1 h before docetaxel); oral diphenhydramine optional; 500 mg oral calcium carbonate once daily; 400 IU oral vitamin D once daily	ADT (GRH agonists or antagonists or orchidectomy) plus docetaxel (75 mg/m² intravenously every 3 weeks for six cycles) plus oral prednisolone (10 mg once daily)
Median follow-up for all participants (IQR), months*	84 (79–89)	54 (42–67)	78 (63–96)

ADT=androgen deprivation therapy. G-CSF=granulocyte-colony stimulating factor. GRH=gonadotropin-releasing hormone. LHRH=luteinising hormone-releasing hormone.
*Data supplied for inclusion in the meta-analysis, and follow-up duration for each trial is in keeping with the most recent version of reported trial analysis, as cited.

Table 1: **Trial design details and key participant characteristics**

Claire L Vale et al, Lancet Oncol 2023.

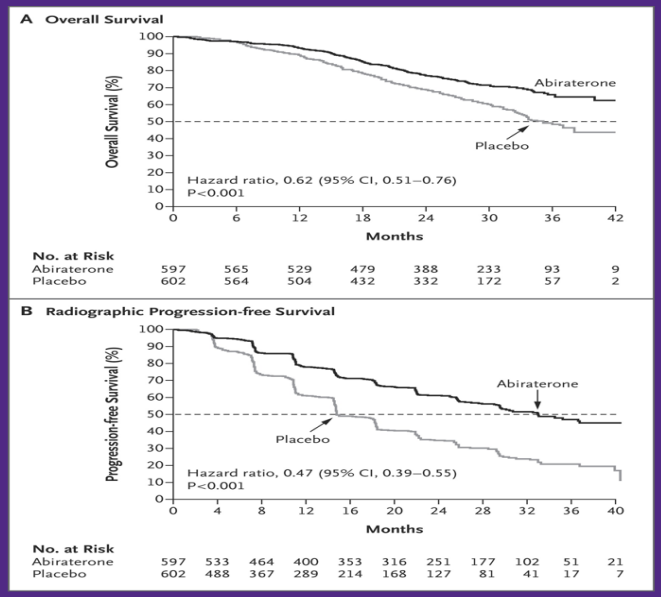
Hastalık Volümü ve Tanı Anında Metastaz Dosetaksel Tedavi Etkinliği için Prediktif



Claire L Vale et al, Lancet Oncol 2023.

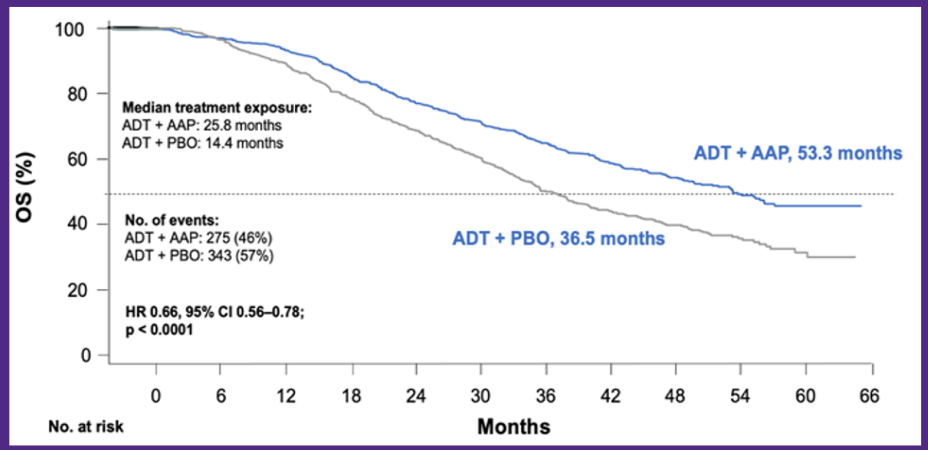
Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

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



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

Fizazi et al. NEJM 2017



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

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

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

Dışlama kriterleri; Daha önce cerrahi, Radyoterapi ,Kemoterapi

Metastatik hastalığa bağlı semptomu olanlarda RT ve Cerrahiye izin verilmiş

Yeni nesil androjen yolağı inhibitörleri riskten bağımsız etkili

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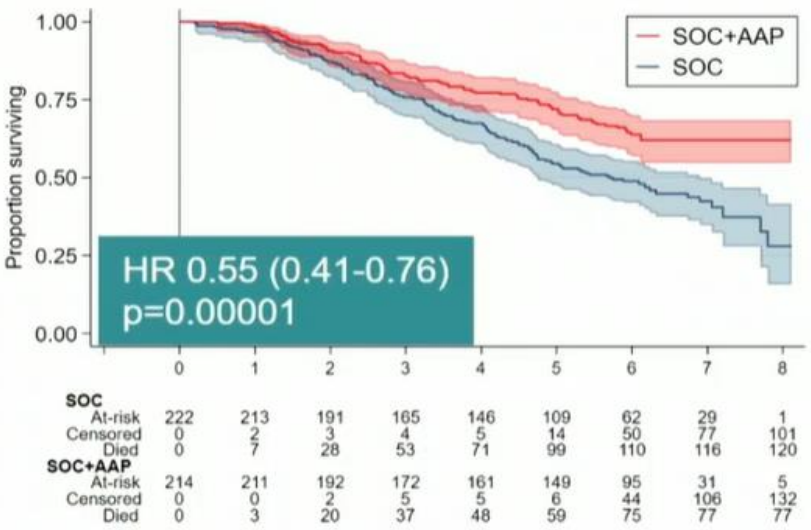
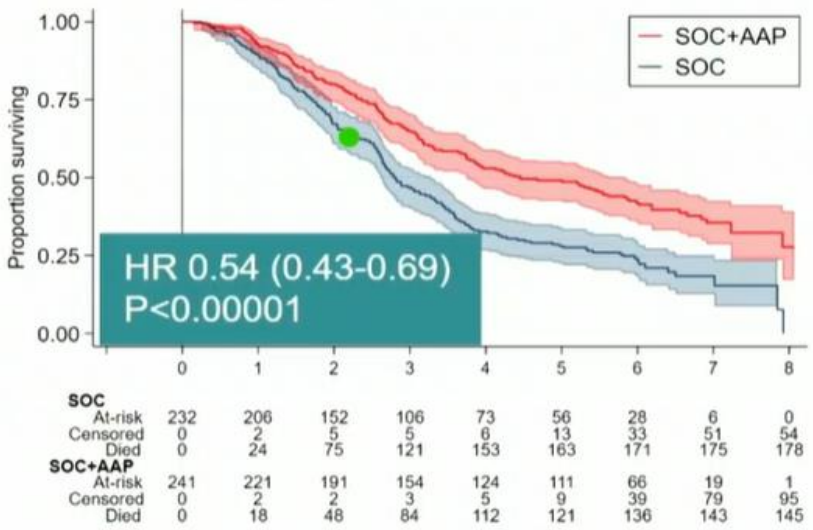
STAMPEDE: OS by risk group (LATITUDE)

Low risk



HR 0.66 (0.44-0.98)
p=0.041

High risk



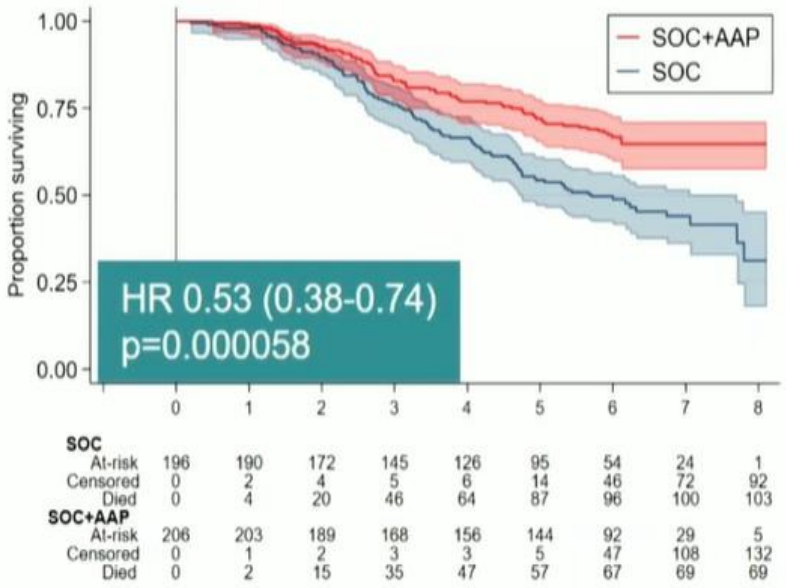
HR 0.54 (0.41-0.70)
P<0.001

Yeni nesil androjen yolağı inhibitörleri tümör yükünden bağımsız etkili

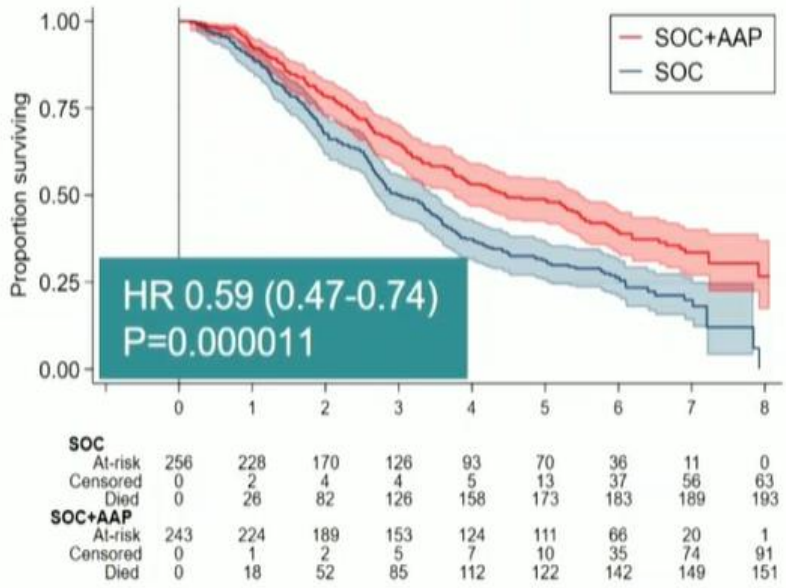
VIRTUAL 2020 ESMO congress

STAMPEDE: OS by disease burden (CHAARTED)

Low volume



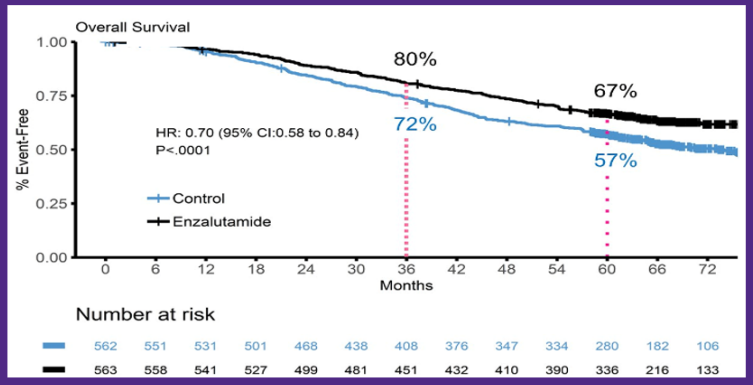
High volume



Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

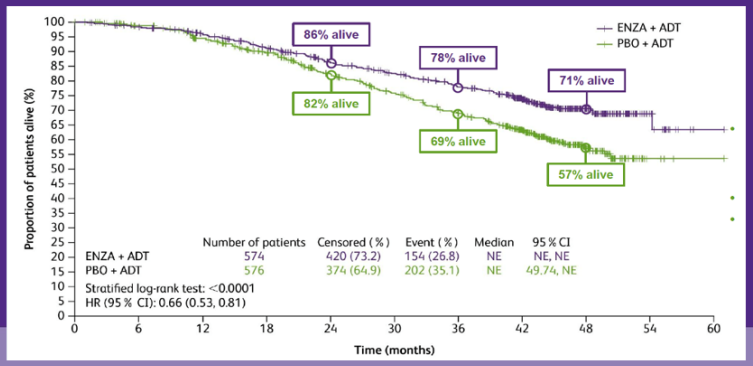
Final Overall Survival (OS) Analyses: Enzalutamide for Metastatic Hormone-Sensitive Prostate Cancer

ENZAMET[1]
Enzalutamide + testosterone suppression (TS)



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

ARCHES[2]
Enzalutamide + ADT

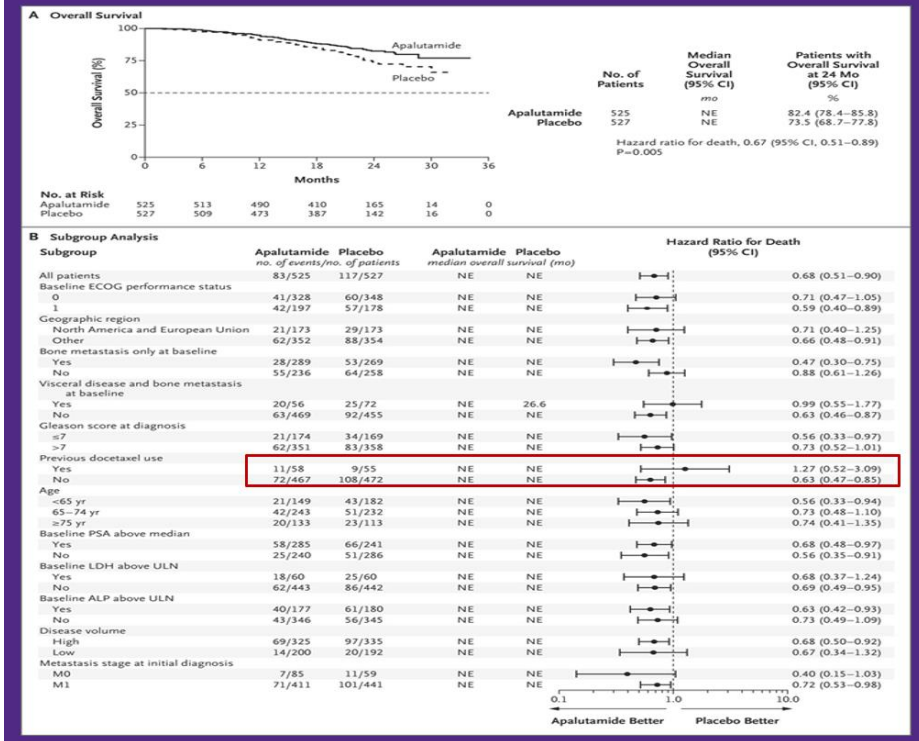


- Median follow-up of 44.6 months
- 34% reduction in risk of death
- Median OS was not reached for enzalutamide plus ADT, but was 47.7 months (95% CI, 43.3 to not evaluable) for placebo plus ADT.
  - **- HR = 0.66; p< 0.001**

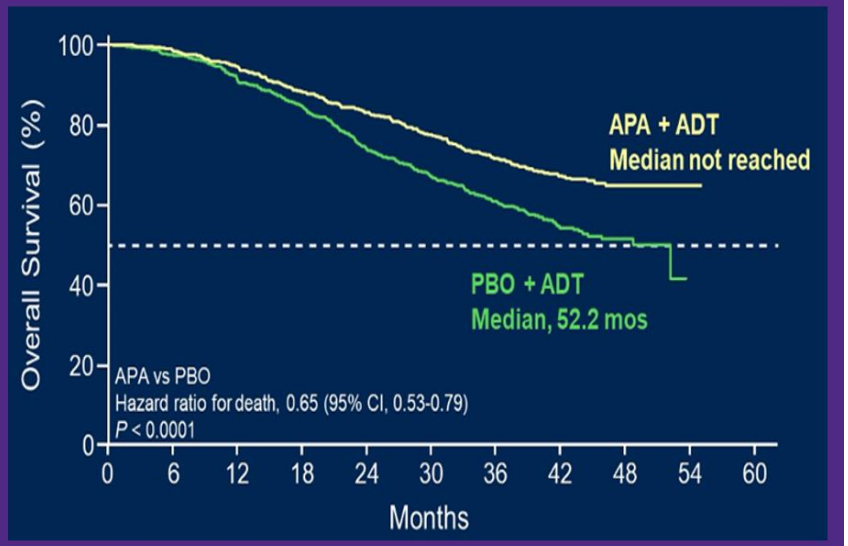
1. Davis ID et al. ASCO 2022;Abstract LBA5004; 2. Armstrong AJ et al. J Clin Oncol 2022;40(15):1616-22.

Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

Apalutamide for Metastatic, Castration-Sensitive Prostate Cancer



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



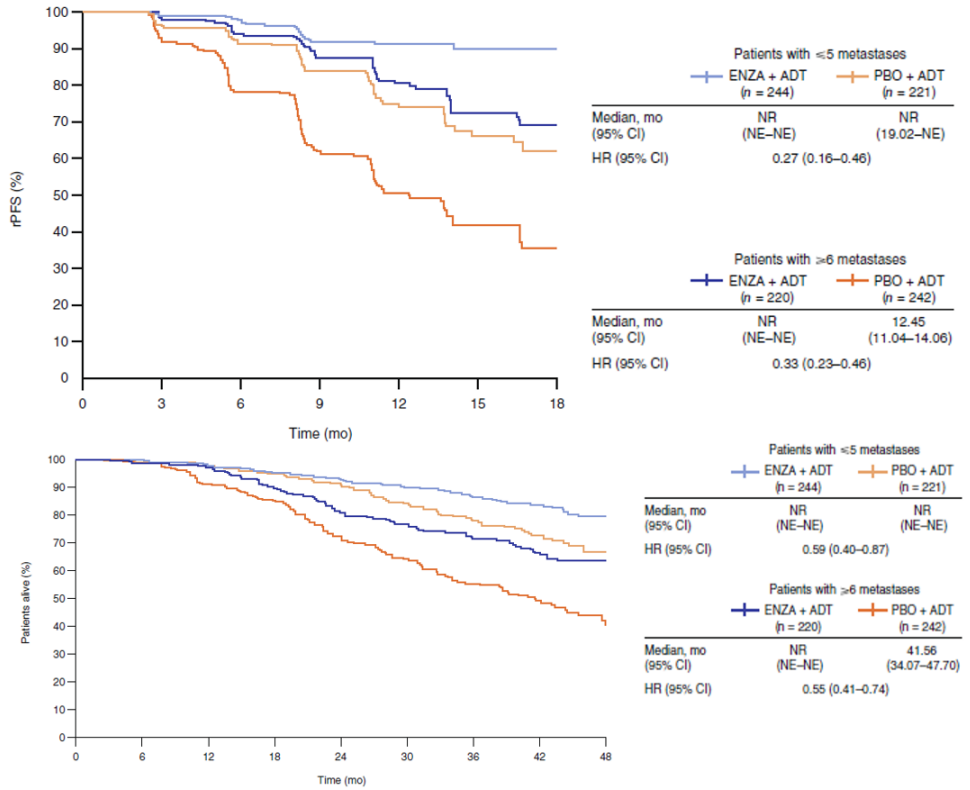
- Median follow-up of 44.0 months
  - 35% reduction in risk of death
- Median OS was significantly longer for apalutamide + ADT vs placebo + ADT:
  - Not reached vs 52.2 months
  - HR = 0.65; p < 0.0001

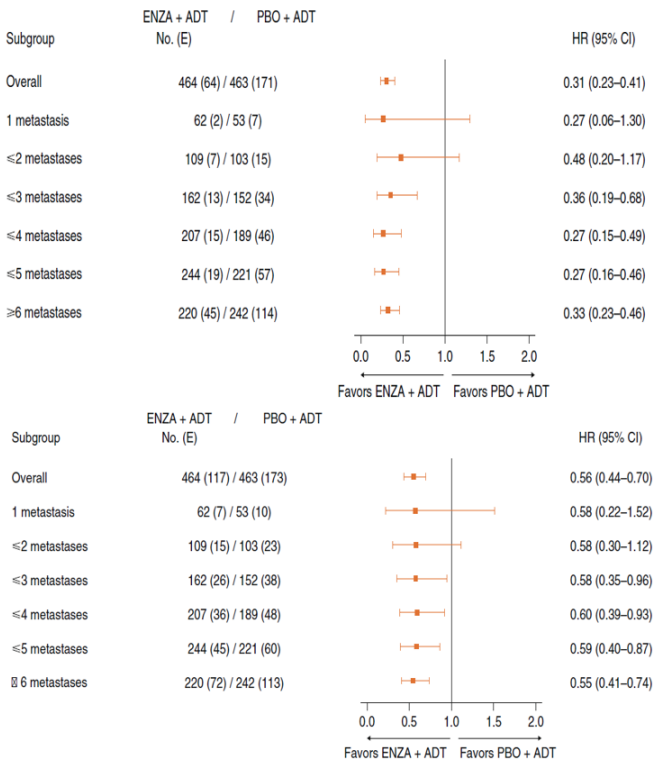
Chi KN et al.NEJM 2019

Chi KN et al. J Clin Oncol 2021

Low ve Hihg Volüm Hastalıkta Etkinlik

ARCHES Oligometastatic Analysis





Armstrong et al Eur Urol 2023

Ultra-Low PSA düzeyi uzun Sağkalımla İlişkili

Assessing risk: PSA decline

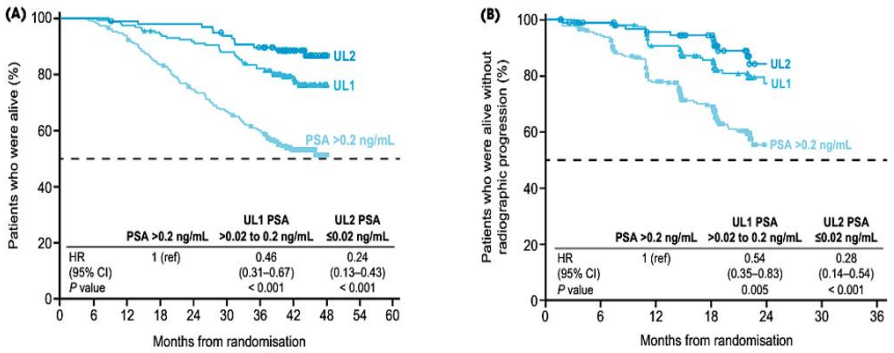
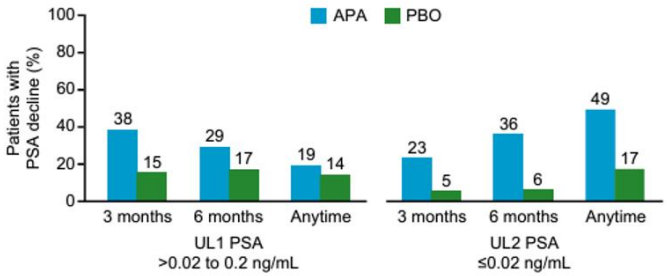
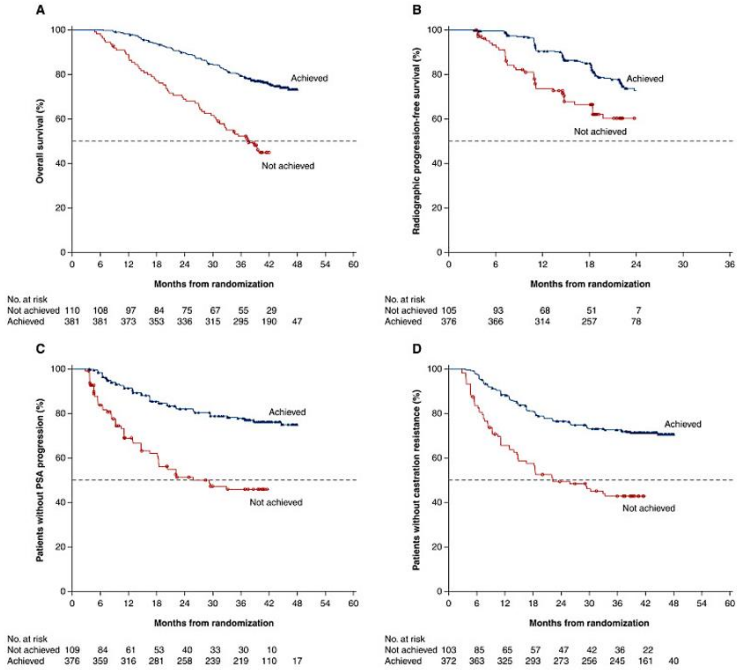


Fig. 1 The PSA decline to UL1 (>0.02 to 0.2 ng/mL) and UL2 (≤0.02 ng/mL) levels over time. APA, apalutamide; PBO, placebo.



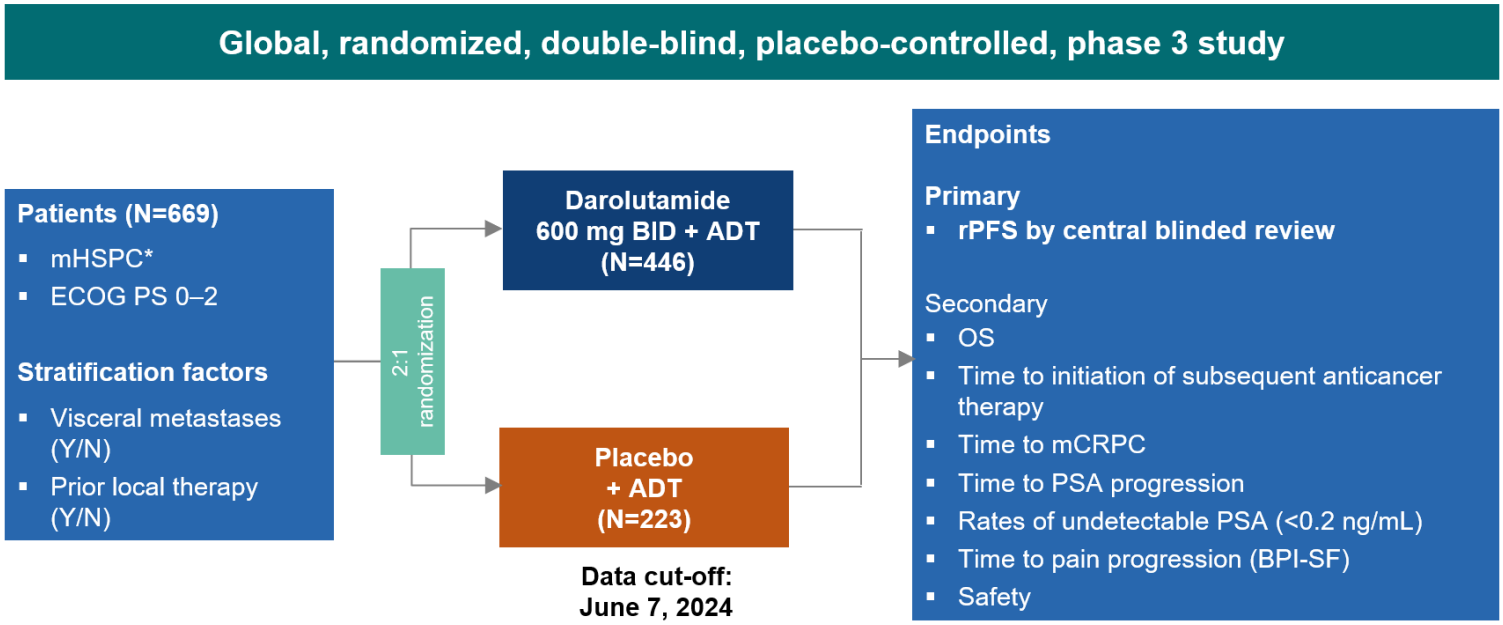
Merseburger AS et al BJUI Int 2024



TITAN (apalutamide)
Deep PSA decline (>90% decline or <0.2ng/mL) at 3 months

Yeni Seçenek Darolutamide

ARANOTE Study Design



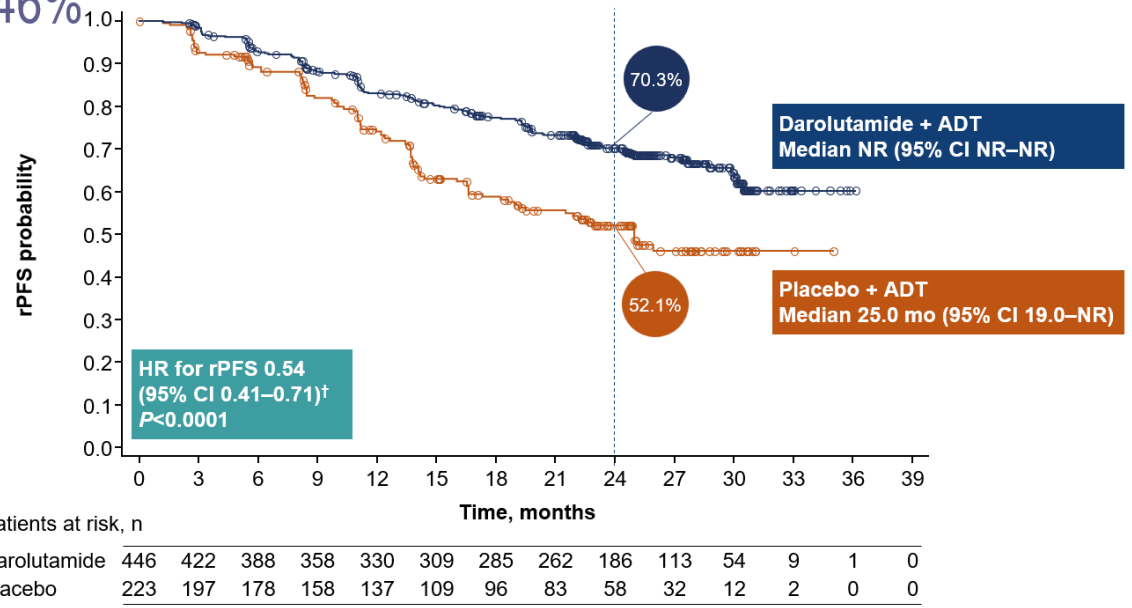
ClinicalTrials.gov: NCT04736199

*Metastatic disease confirmed by conventional imaging method as a positive ^{99m}Tc-phosphonate bone scan or soft tissue/visceral metastases on contrast-enhanced abdominal/pelvic/chest CT or MRI scan, assessed by central review.
BPI-SF, Brief Pain Inventory-Short Form.

Yeni Seçenek Darolutamide

ARANOTE Primary Endpoint: rPFS*

Darolutamide significantly reduced the risk of radiological progression or death by 46%



Patients at risk, n

Darolutamide	446	422	388	358	330	309	285	262	186	113	54	9	1	0
Placebo	223	197	178	158	137	109	96	83	58	32	12	2	0	0

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Median follow-up: darolutamide group 25.3 months; placebo group 25.0 months

*Primary analysis occurred after 222 events (darolutamide 128; placebo 94).

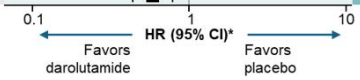
†HR and 95% CI were calculated using the Cox model stratified on visceral metastases (Y/N) and prior therapy (Y/N).

Yeni Seçenek Darolutamide

ARANOTE rPFS: Subgroup Analyses

Consistent benefit of darolutamide across all subgroups

rPFS		Darolutamide (n=446) Events/Patients, n/N	Darolutamide (n=446) Median, months	Placebo (n=223) Events/Patients, n/N	Placebo (n=223) Median, months	HR (95% CI)*
Overall population		128/446	NR	94/223	25.0	0.54 (0.41–0.71)
Age subgroups, years	<65	37/118	NR	32/65	14.2	0.44 (0.27–0.71)
	65–74	53/193	NR	35/96	NR	0.64 (0.41–0.98)
	75–84	29/117	NR	22/52	NR	0.48 (0.27–0.83)
	≥85	9/18	27.4	5/10	19.2	0.51 (0.16–1.66)
Baseline PSA values	< median	58/216	NR	44/111	26.0	0.55 (0.37–0.81)
	≥ median	67/220	NR	47/108	22.9	0.55 (0.38–0.80)
ECOG PS at baseline	0	61/235	NR	37/98	NR	0.55 (0.37–0.83)
	≥1	67/211	NR	57/125	22.6	0.56 (0.39–0.79)
Gleason score at initial diagnosis	Missing/not assessed	5/13	NR	4/10	13.8	
	<8	32/122	NR	30/67	22.9	0.46 (0.28–0.75)
	≥8	91/311	NR	60/146	25.1	0.58 (0.42–0.81)
Disease volume	High volume	113/315	30.2	75/157	19.2	0.60 (0.44–0.80)
	Low volume	15/131	NR	19/66	NR	0.30 (0.15–0.60)
Race	White	76/251	NR	55/125	22.2	0.52 (0.36–0.73)
	Asian	38/144	NR	24/65	25.0	0.59 (0.35–0.98)
	Black	10/41	NR	10/24	NR	0.51 (0.21–1.23)
	Other	4/10	NR	5/9	13.7	
Geographic region	Europe and RoW	56/186	NR	39/88	22.6	0.50 (0.33–0.75)
	Asia	37/141	NR	23/63	25.0	0.60 (0.35–1.01)
	Latin America	35/119	NR	32/72	25.1	0.56 (0.35–0.90)
Visceral metastases	Yes	21/53	NR	13/27	25.0	0.71 (0.35–1.41)
	No	107/393	NR	81/196	25.0	0.52 (0.39–0.69)
Prior local therapy	Yes	19/80	NR	18/40	19.5	0.34 (0.17–0.66)
	No	109/366	NR	76/183	25.0	0.59 (0.44–0.79)



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*HR and 95% CI were calculated from univariate analysis using unstratified Cox regression.

Yeni Seçenek Darolutamide

TEAEs associated with ARPIs were generally similar between treatment groups

TEAEs	Darolutamide + ADT (n=445)		Placebo + ADT (n=221)	
	Incidence, %	EAIR/100 PY	Incidence, %	EAIR/100 PY
Fatigue	5.6	3.2	8.1	5.7
Mental impairment disorder	1.6	0.9	0.5	0.3
Hypertension	9.4	5.5	9.5	6.7
Cardiac arrhythmias	8.8	5.1	6.8	4.7
Coronary artery disorders	3.6	2.0	1.4	0.9
Heart failure	0.9	0.5	0.9	0.6
Falls, including accident	1.3	0.8	0.9	0.6
Bone fracture	4.0	2.3	2.3	1.5
Vasodilatation and flushing	9.2	5.6	7.2	5.0
Diabetes mellitus and hyperglycemia	9.0	5.3	9.5	6.7
Rash	4.3	2.4	3.6	2.4

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EAIR, exposure-adjusted incidence rate; PY, patient years.

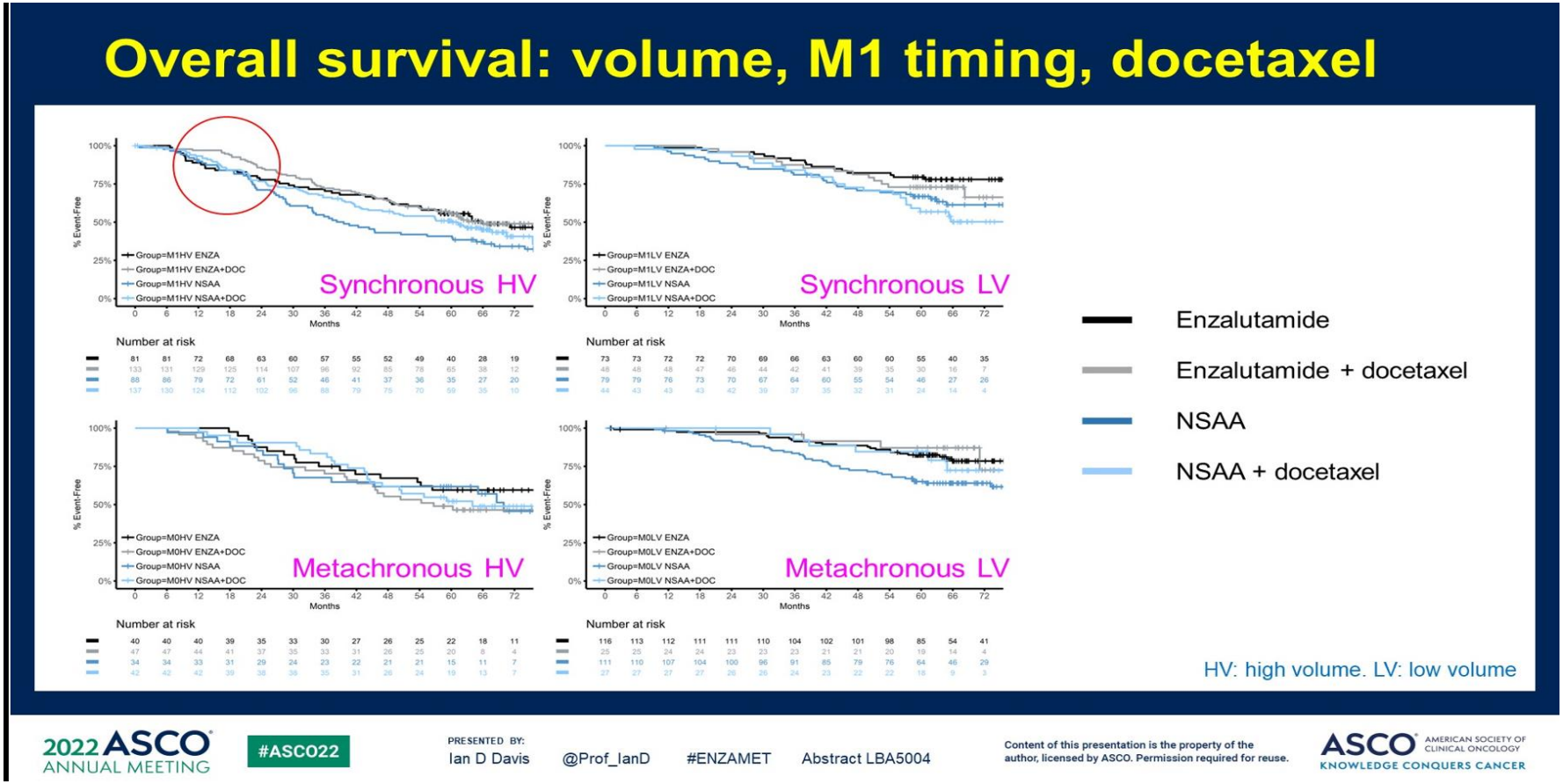
Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

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



2022 ASCO ANNUAL MEETING #ASCO22

PRESENTED BY: Ian D Davis @Prof_IanD #ENZAMET Abstract LBA5004

ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY KNOWLEDGE CONQUERS CANCER

Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

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

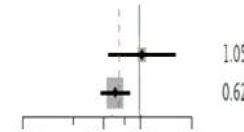
Yeni nesil androjen yolağı inhibitörleri viseral metastazda etkinliği düşük

Does type of metastasis matter in mHNPC?

Results from new hormonal treatments in mHNPC according visceral mets

ENZAMET

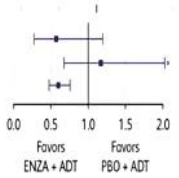
Subgroup	Enzalutamide	Standard Care	Hazard Ratio (95% CI)
	no. of events/total no.		
Visceral metastases			
Yes	18/62	18/67	1.05 (0.54–2.02)
No	84/501	125/495	0.62 (0.47–0.82)



Enzalutamide Better Standard Care Better

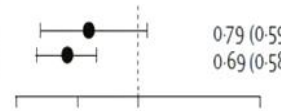
ARCHES

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	Placebo+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)



TITAN

Subgroup	Apalutamide	Placebo	Apalutamide	Placebo	
	no. of events/no. of patients		*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 Stèphane

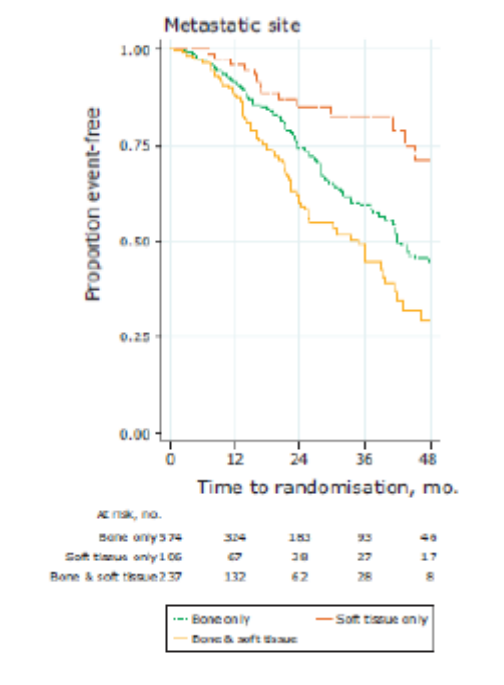
1. Davis I, et al. NEJM 2019;381:121-131 2. Armstrong A, et al. ESMO 2021 oral comm. abstract LBA25 3. Chi K, et al. NEJM 2019;381:13-24 4. Fizazi K, et al. Lancet Oncol. 2019 May;20(5):686-700.

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. 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

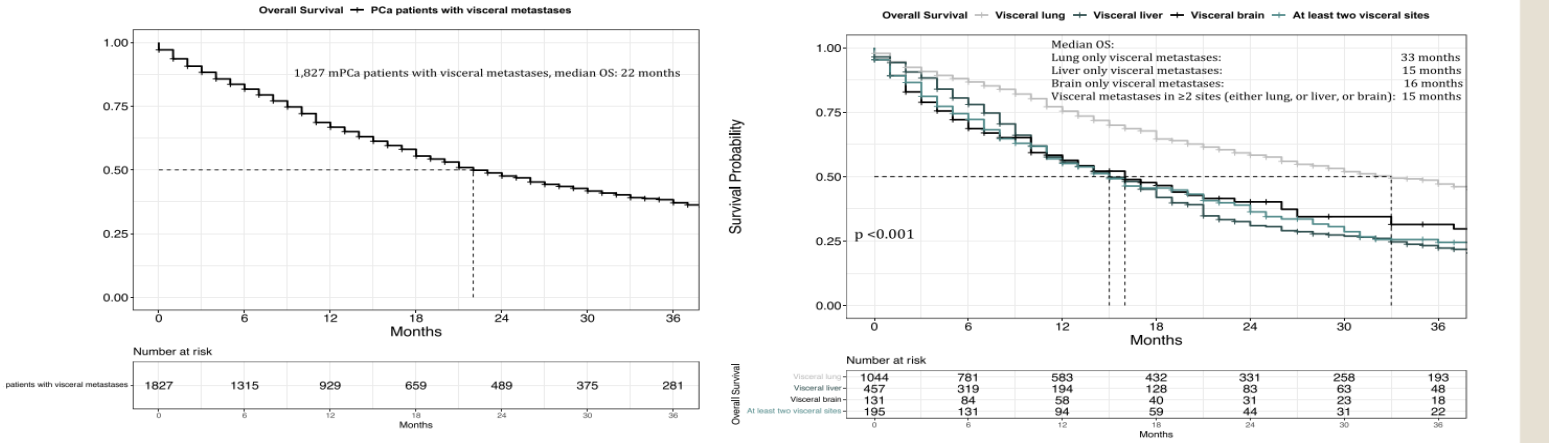
Kemik met.%75

Yumuşak doku+kemik met.%60

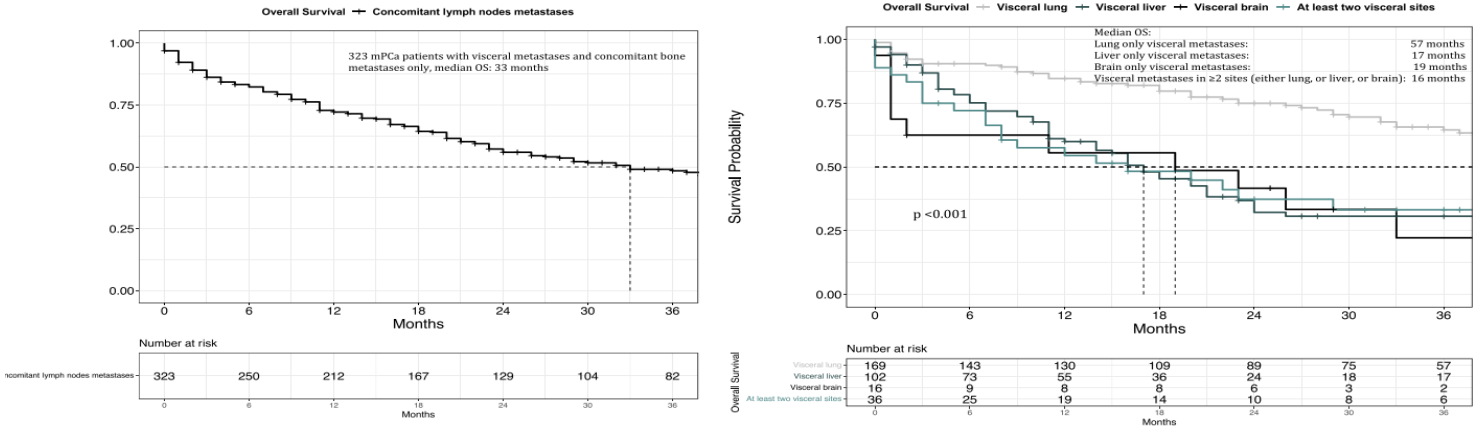
2yılık FFS; yumuşak dokuda %54, kemik met %28 , yumuşak doku+kemik met.%18

Karaciğer metastazı ve viseral metastaz olanlar tedavi yanıtları kötü

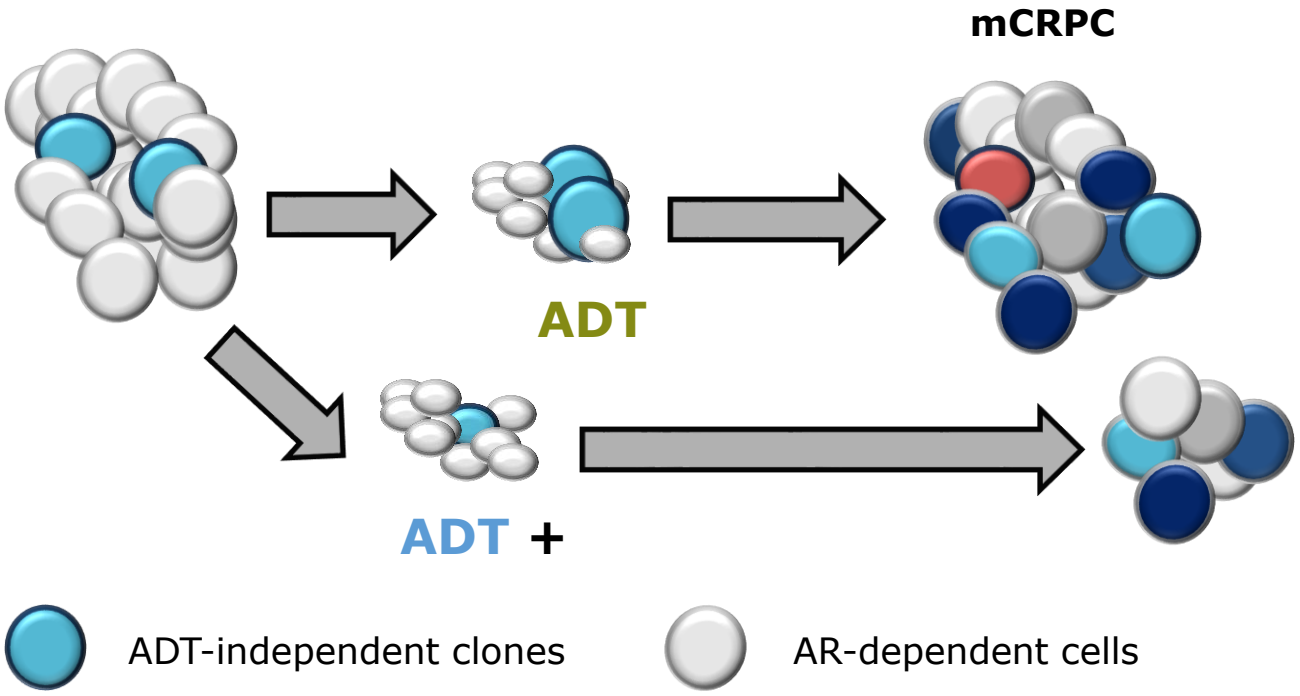
Kaplan-Meier plots displaying overall survival in 1827 metastatic prostate cancer (mPCa) patients with visceral metastases, regardless of presence of lymph node and/or bone metastases: (A) in the overall population; (B) according to location of visceral metastatic sites.



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.

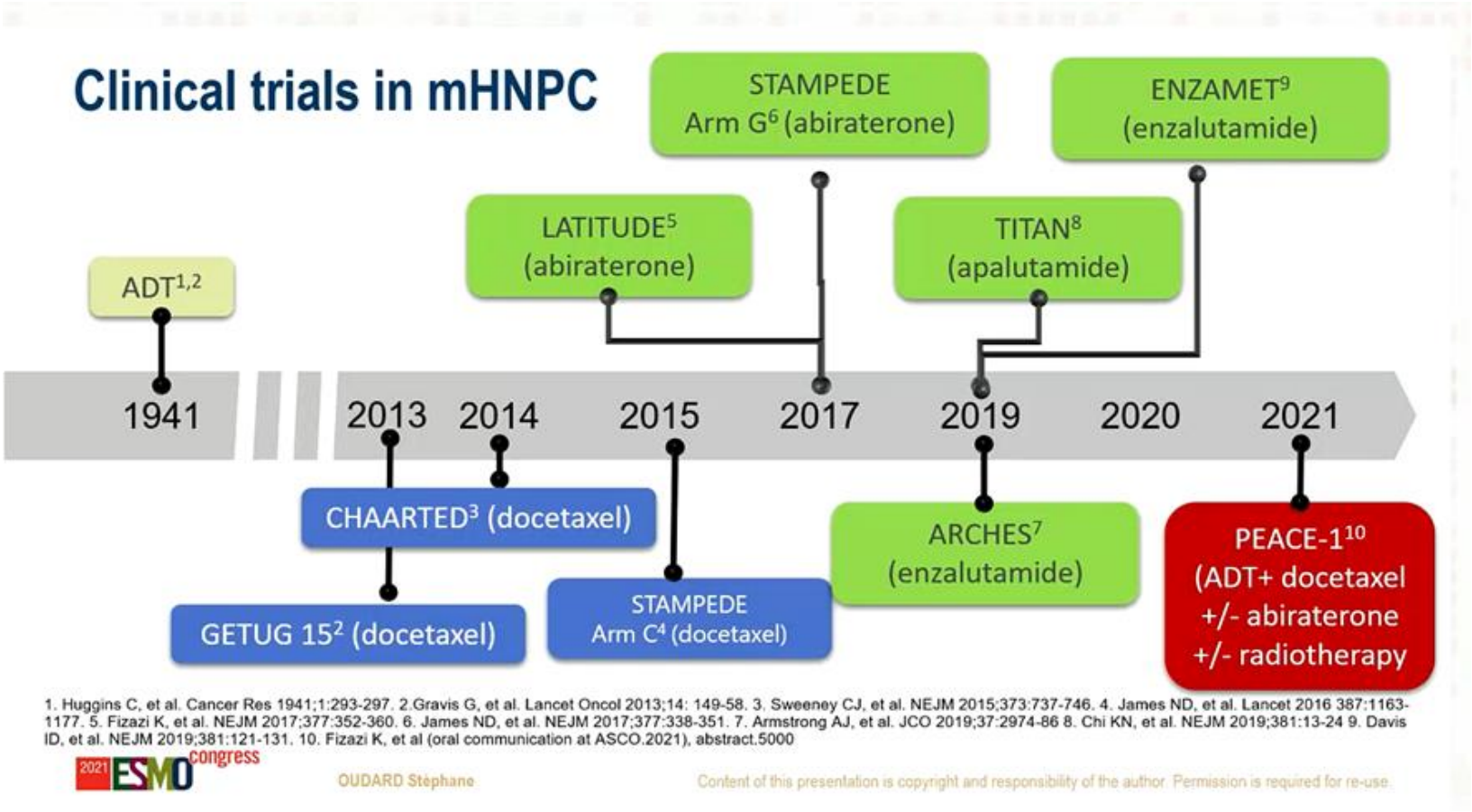


Kastrasyona Duyarlı Metastatik Prostat Kanseri Daha Yoğun Tedavisi



Role of Effective Systemic Therapy

Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

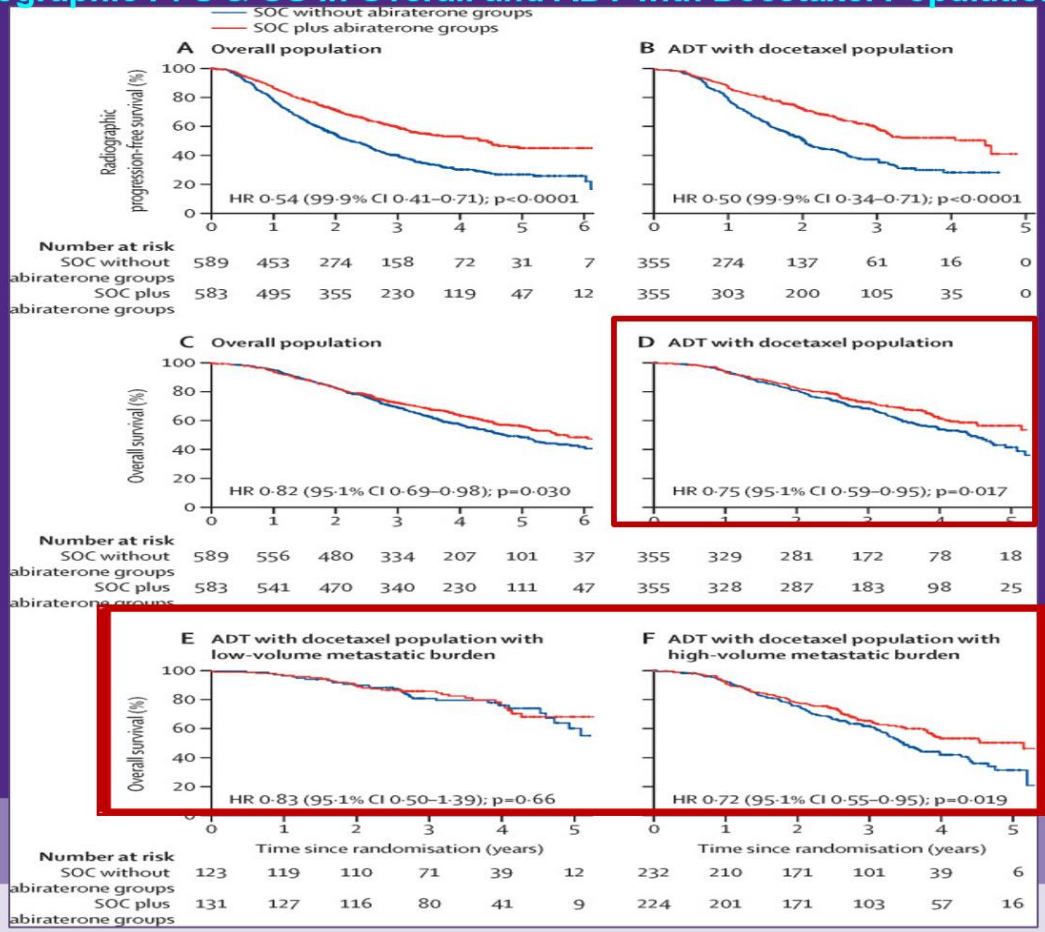


1. Huggins C, et al. Cancer Res 1941;1:293-297. 2.Gravis G, et al. Lancet Oncol 2013;14: 149-58. 3. Sweeney CJ, et al. NEJM 2015;373:737-746. 4. James ND, et al. Lancet 2016 387:1163-1177. 5. Fizazi K, et al. NEJM 2017;377:352-360. 6. James ND, et al. NEJM 2017;377:338-351. 7. Armstrong AJ, et al. JCO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

Kastrasyona Duyarlı Metastatik Prostat Kanseri Üçlü Kombinasyon

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

Radiographic PFS & OS in Overall and ADT with Docetaxel Population



Fizazi et al:
Lancet 2022

Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

PEACE-1: Adverse Events

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

Fizazi et al, Lancet, 2022

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

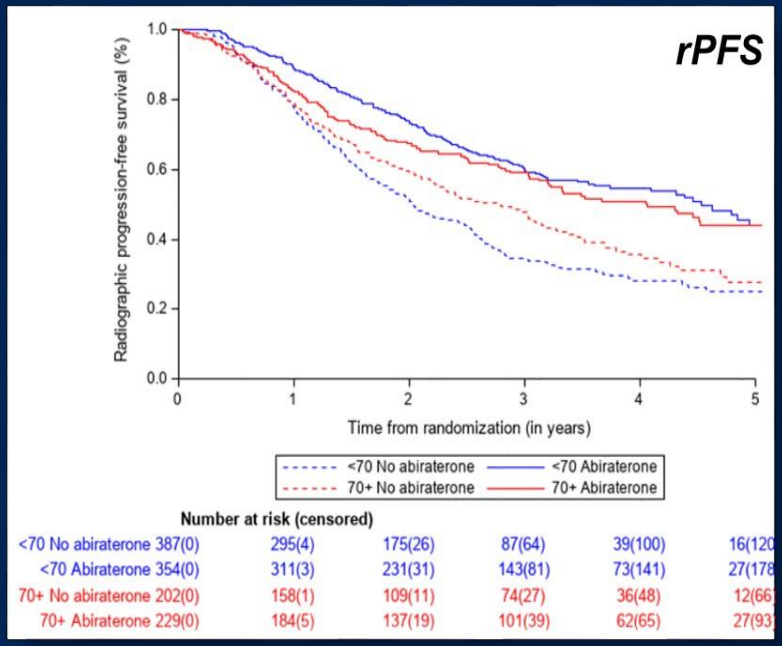
Mourey L[1], Boyle H[2], Roubaud G[3], McDermott R[5], Supiot S[6], Tombal B[7], Flechon A[2], Berthold D[8], Ronchin P[9], Kacso G[10], Berdah J-F[11], Calabro F[12], Gravis G[13], Palumbo S[14], Gil T[15], Vie B[16], Ribault H[17], Fizazi K[18], Foulon S[18], Carles J[19].

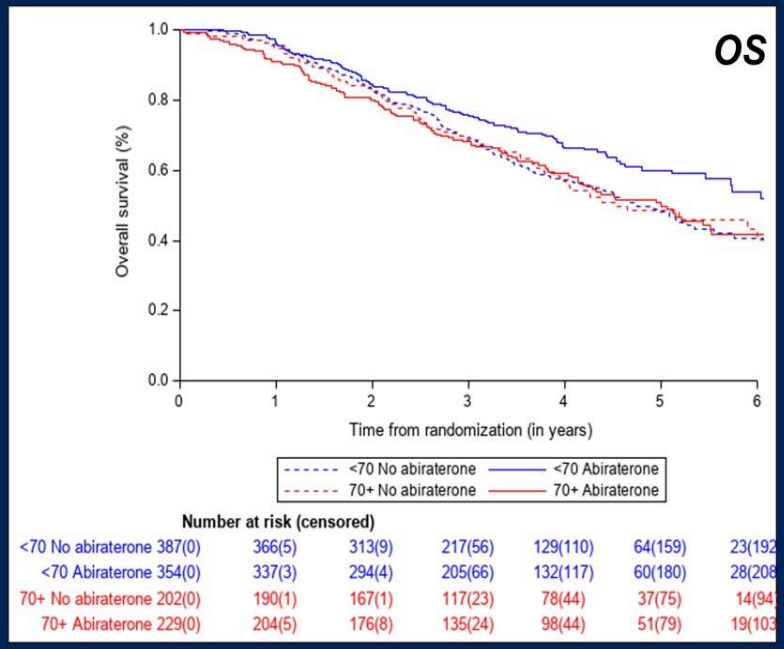
[1]Institut Universitaire du Cancer-Oncopole, Toulouse, France; [2]Centre Leon Bérard, Lyon, France; [3]Institut Bergonié, Bordeaux, France; [5]St. Vincent's University Hospital, Dublin, Ireland; [6]Institut de Cancerologie de l'Ouest-Rene Gauducheau, Nantes, France; [7]Cliniques Universitaires Saint-Luc, 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

Üçlü Kombinasyonda Yaş Sınırlaması

Results (*1*)

Overall population





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

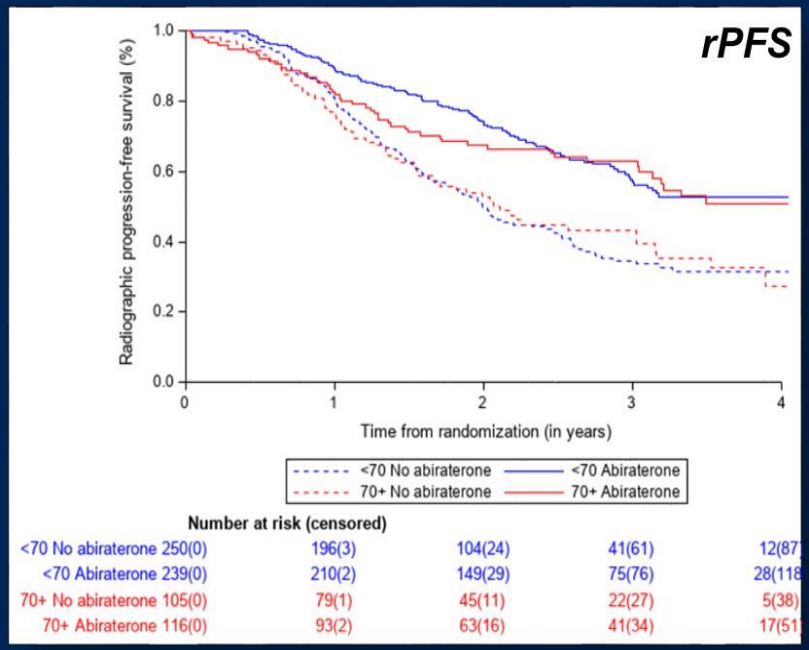
Age ≥ 70: HR 0.95, 95%CI (0.72-1.25)
Age <70: HR 0.73, 95%CI (0.58-0.92)
p-value of the interaction test 0.15

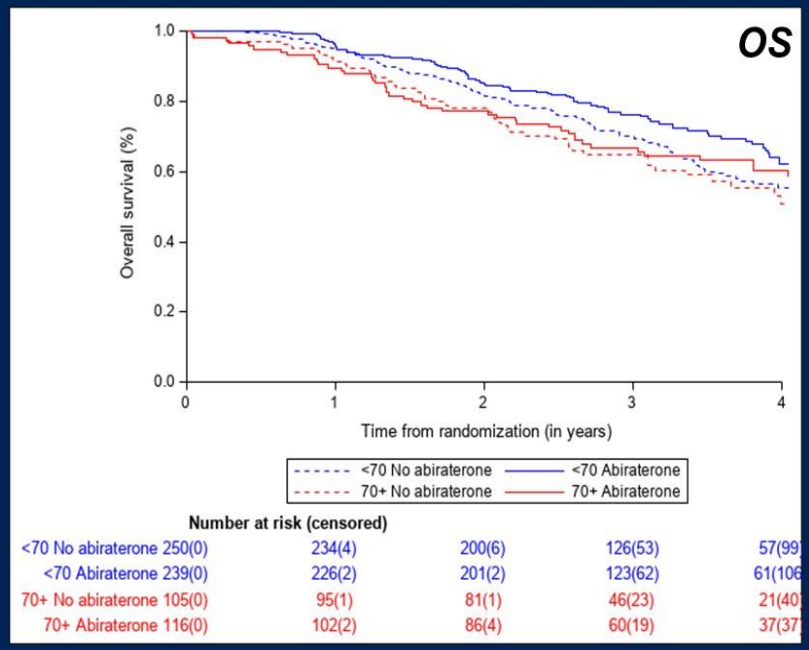
Benefit of AA+P on rPFS and OS may decrease with age

Üçlü Kombinasyonda Yaş Sınırlaması

Results (2)

Docetaxel population





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

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

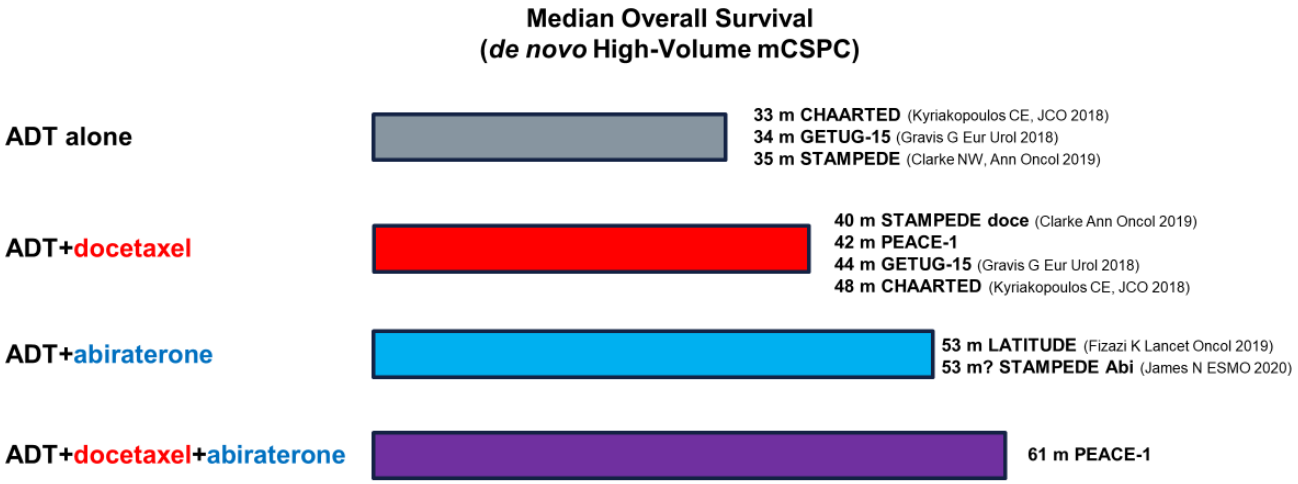
- **rPFS benefit of AA+P was comparable in older and younger patients**
- **OS benefit difficult to assess (insufficient number of older patients/events)**

Kastrasyona Duyarlı Metastatik Prostat Kanseri Üçlü Kombinasyon

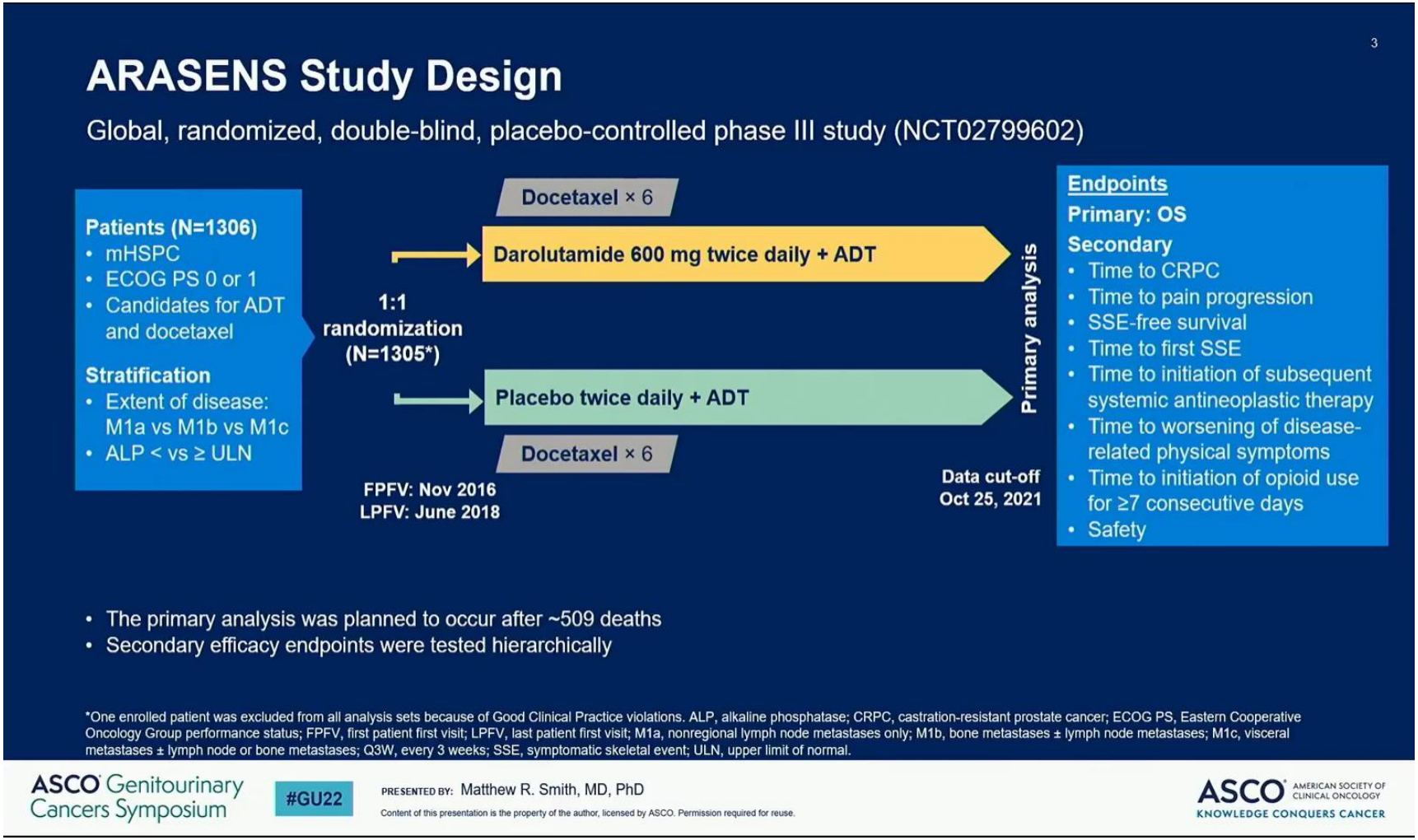
GUSTAVE ROUSSY CANCER CAMPUS GRAND PARIS

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

unicancer



Kastrasyona Duyarlı Metastatik Prostat Kanseri Üçlü Kombinasyon



Kastrasyona Duyarlı Metastatik Prostat Kanseri Üçlü Kombinasyon

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)

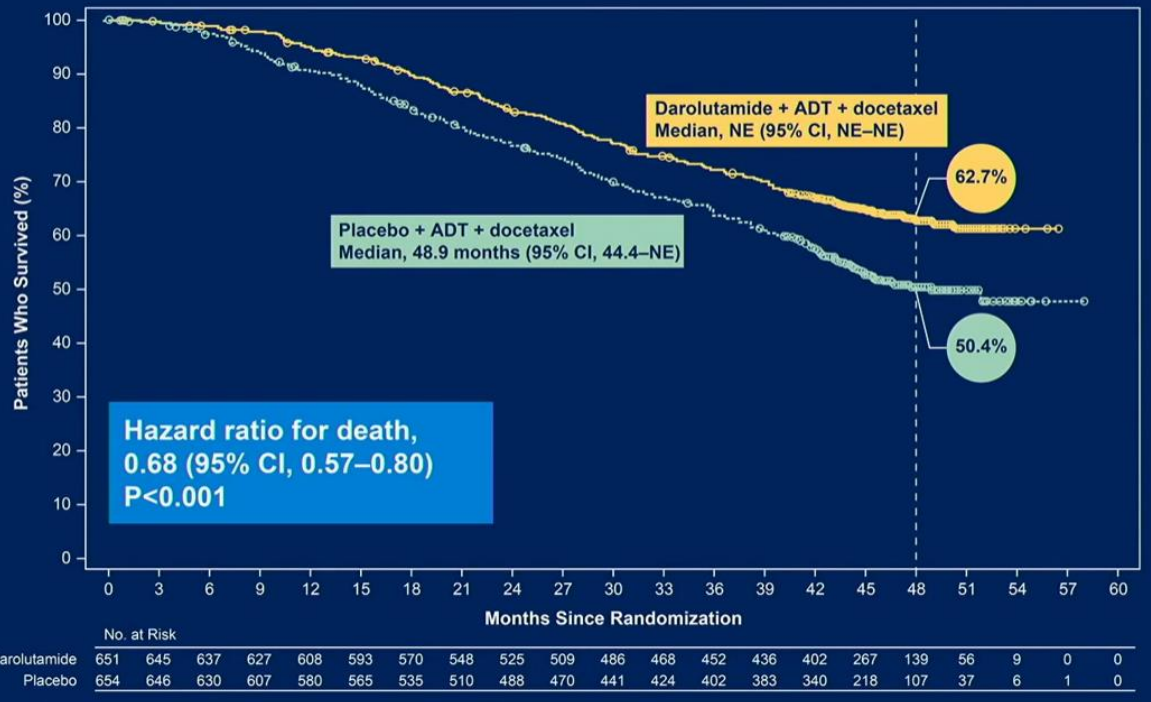
*One patient randomized to placebo but who received darolutamide was included in the placebo group for the full analysis set. †Centrally assessed; samples were collected while patients were receiving ADT. PSA, prostate-specific antigen.

PRESENTED BY: Matthew R. Smith, MD, PhD

Kastrasyona Duyarlı Metastatik Prostat Kanseri Üçlü Kombinasyon

ARASENS Primary Endpoint*: Overall Survival

Darolutamide significantly reduced the risk of death by 32.5%



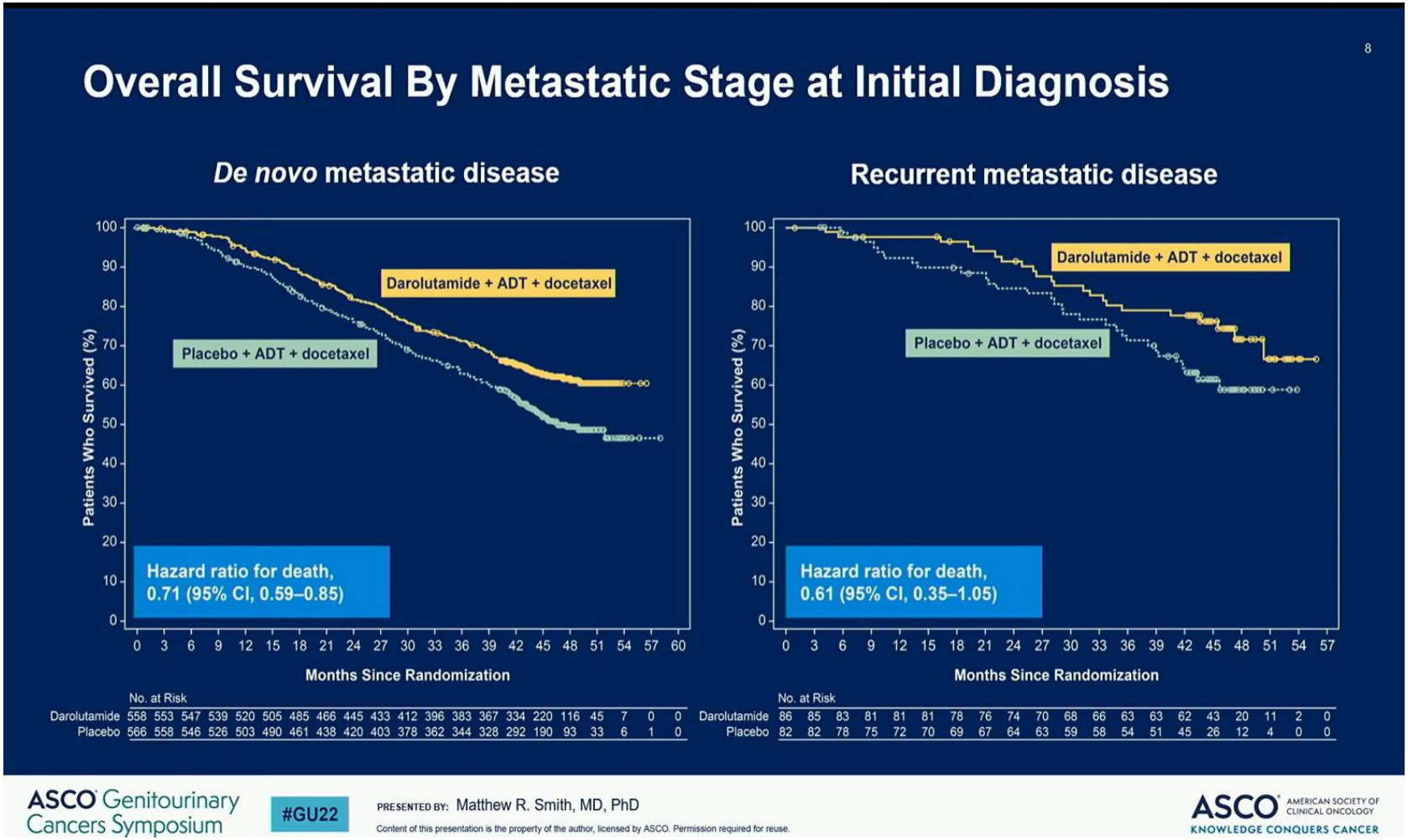
No. at Risk

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

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

PRESENTED BY: Matthew R. Smith, MD, PhD

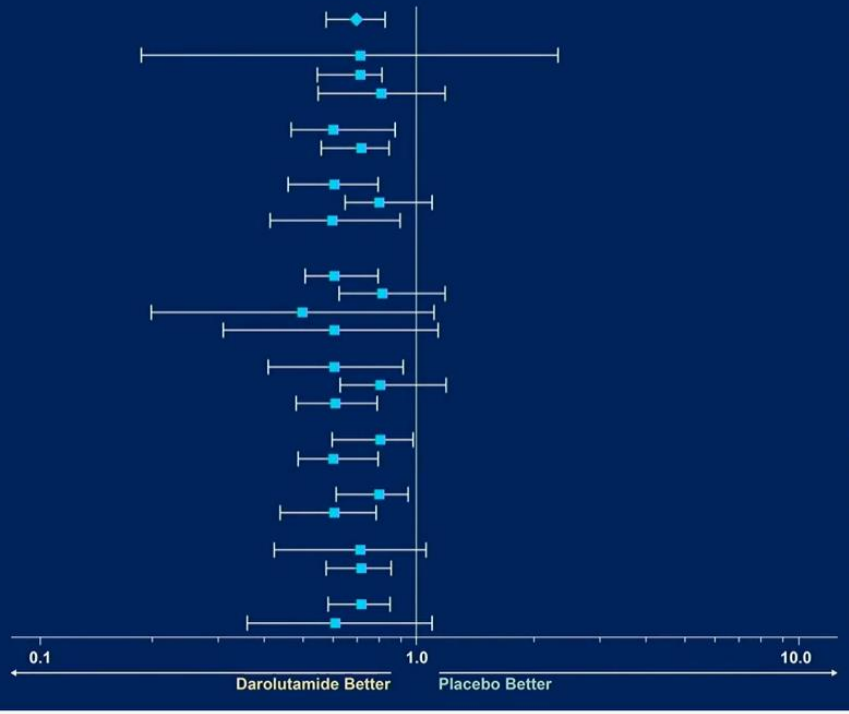
Kastrasyona Duyarlı Metastatik Prostat Kanseri Üçlü Kombinasyon



Kastrasyona Duyarlı Metastatik Prostat Kanseri Üçlü Kombinasyon

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
Üçlü Kombinasyon

13

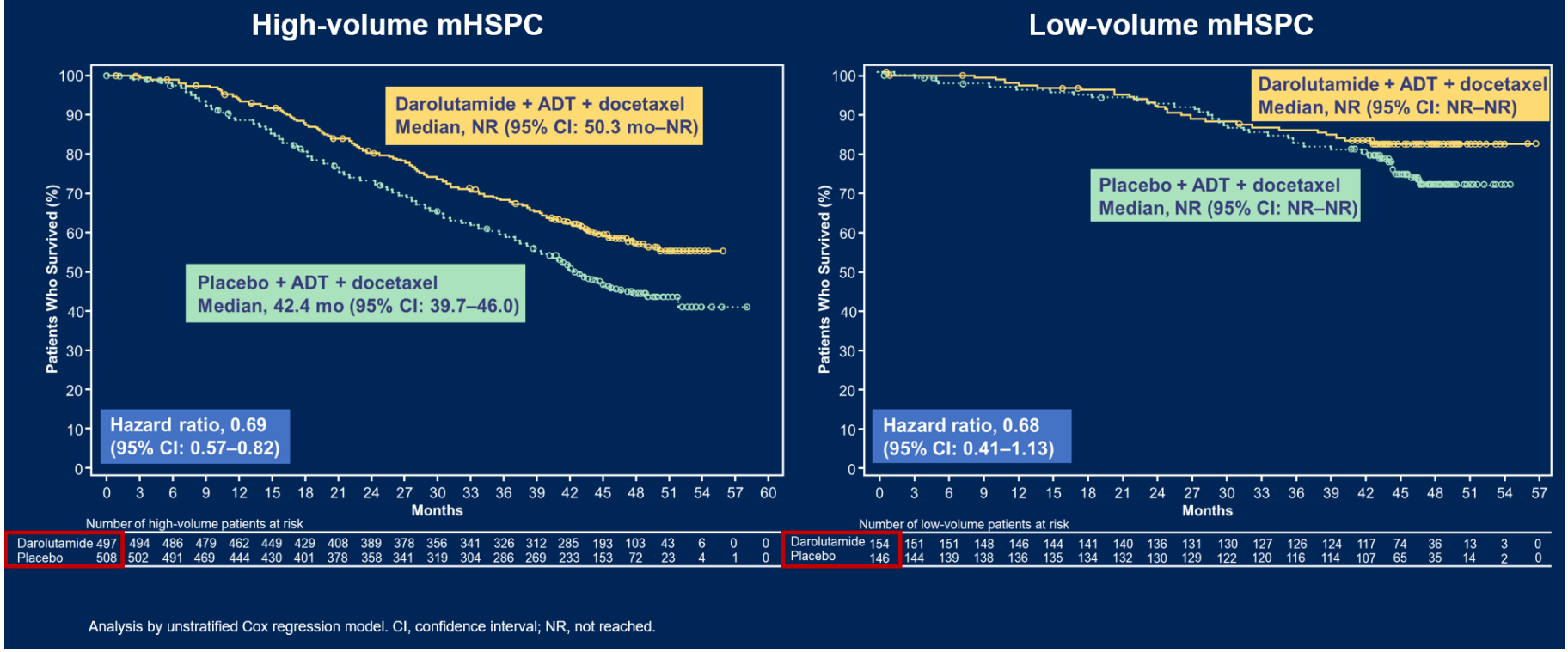
Adverse Events of Special Interest for AR Pathway Inhibitors

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.

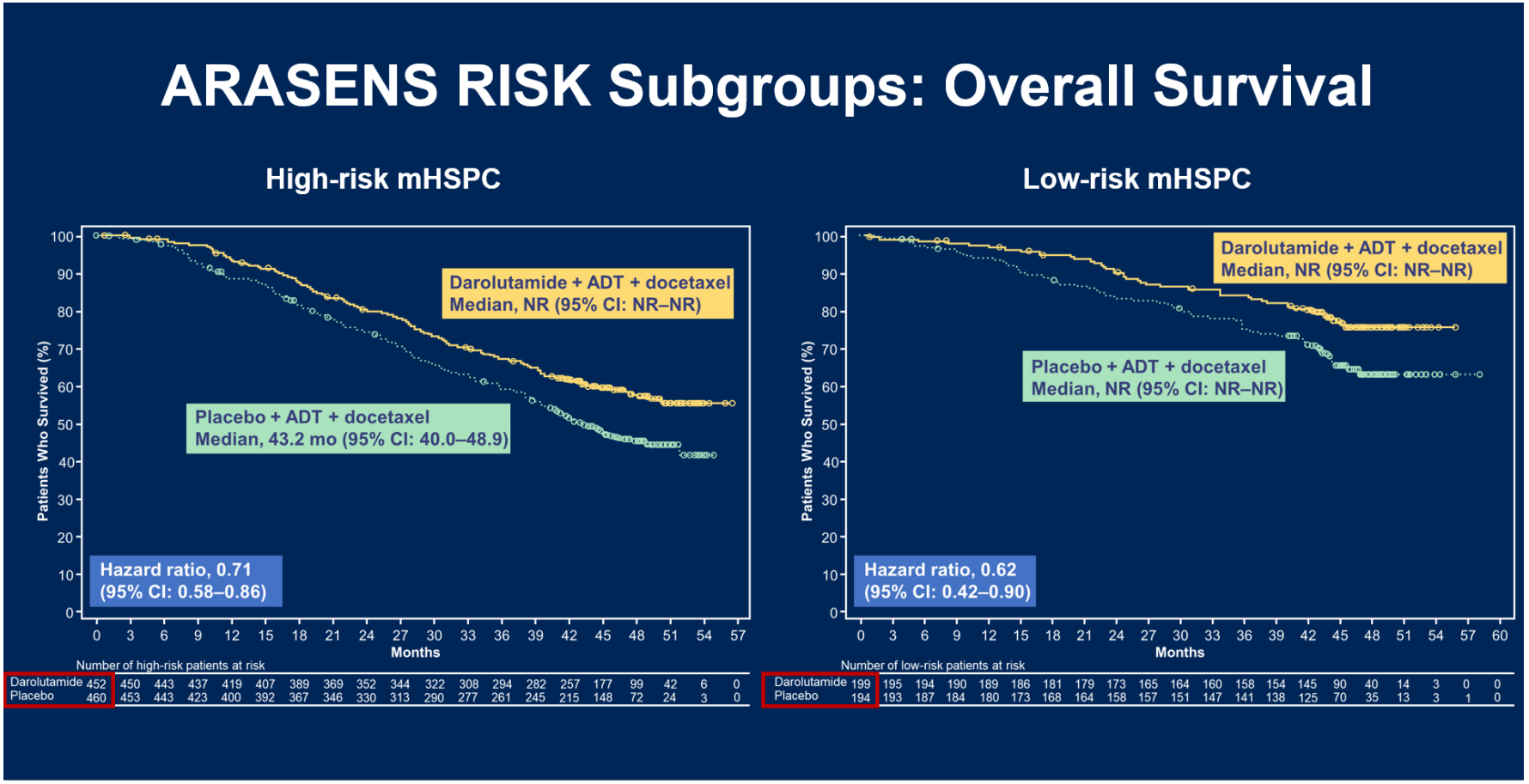
Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

ARASENS VOLUME Subgroups: Overall Survival



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

Kastrasyona Duyarlı Metastatik Prostat Kanseri Üçlü Kombinasyon



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/m^2 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 PSA_{50} 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 PSA_{50} 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

Charles J. Ryan, ASCO GU 2023

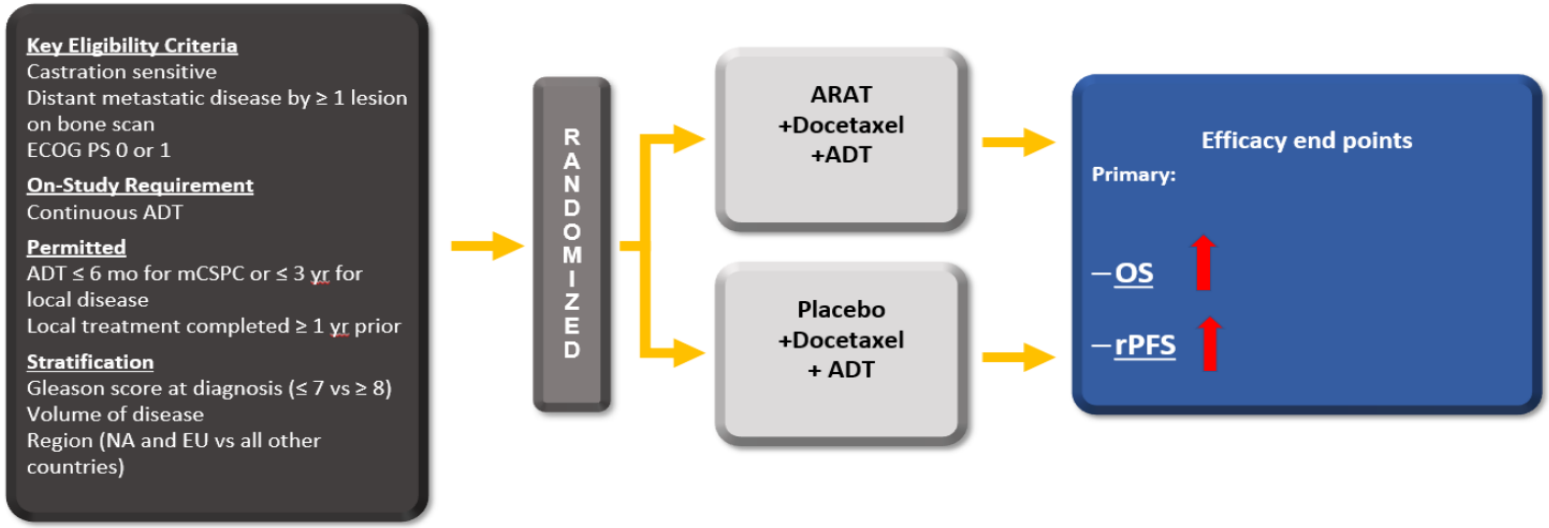
Viseral metastazı olanlarda dörtlü kombinasyon

	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%)	*TP53*m – 14 (77%) *TP53*wt – 26 (84%)	*ERG*m – 11 (100%) *ERG*wt – 29 (74%)	*SPOP*m – 5 (100%) *SPOP*wt – 35 (78%)
PSA ≤0.2 ng/mL at month 7	HRRm – 3 (38%) HRRwt – 27 (66%)	*TP53*m – 12 (67%) *TP53*wt – 18 (60%)	*ERG*m – 9 (82%) *ERG*wt – 21 (55%)	*SPOP*m – 4 (100%) *SPOP*wt – 26 (58%)

Charles J. Ryan, ASCO GU 2023

Evre IV Kastrasyona Duyarlı Prostat Kanseri
Üçlü Kombinasyonlar

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

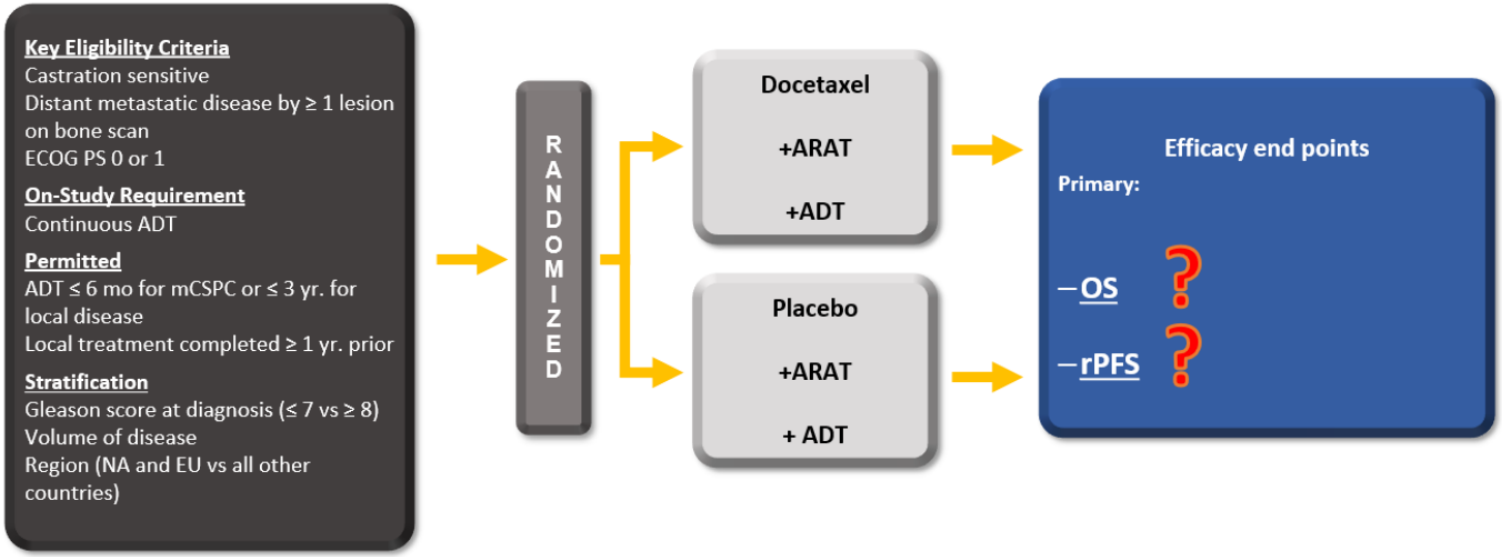


ECOG PS, Eastern Cooperative Oncology Group performance status; ART, Androgen receptor targeted therapy; NA, North America; PSA, prostate-specific antigen; OS, Overall survival; rPFS, radiographic progression-free survival.

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

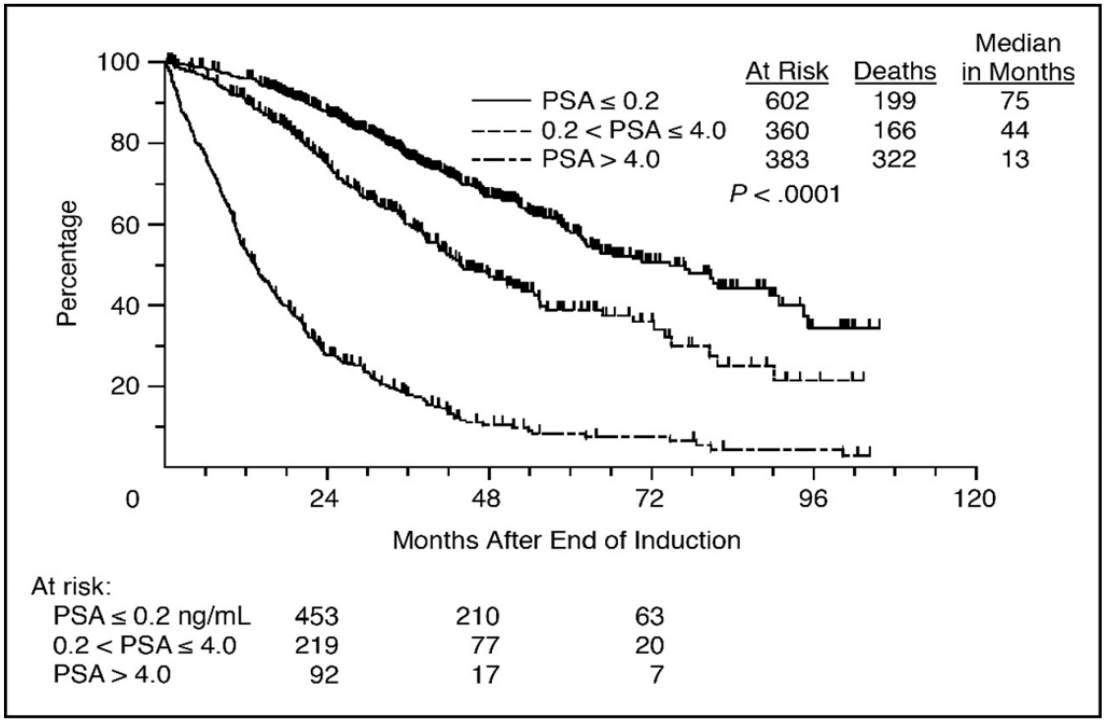
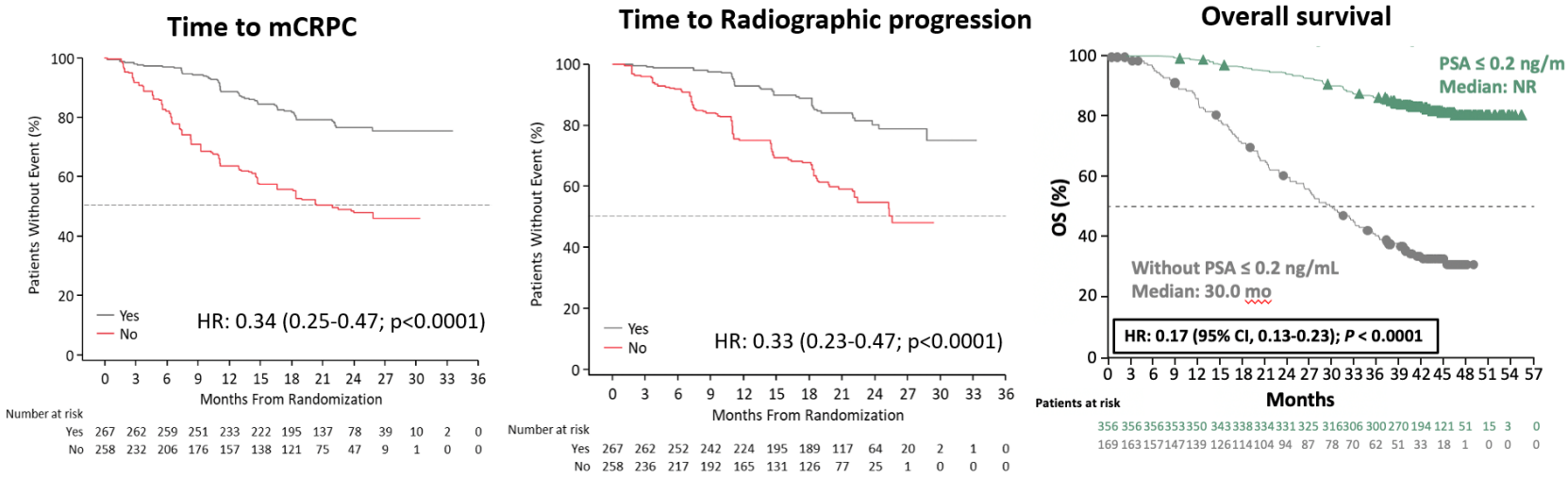


Fig 2. Overall survival by prostate-specific antigen (PSA, ng/mL) status at end of induction
Maha Hussain: Journal of Clinical Oncology 2006; 24 3984-3990.

Courtesy of Simon Chowdhury, MD, PhD

Kastrasyona Duyarlı Metastatik Prostat Kanseri Nadir PSA Uzun Sağkalımı Gösterir

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



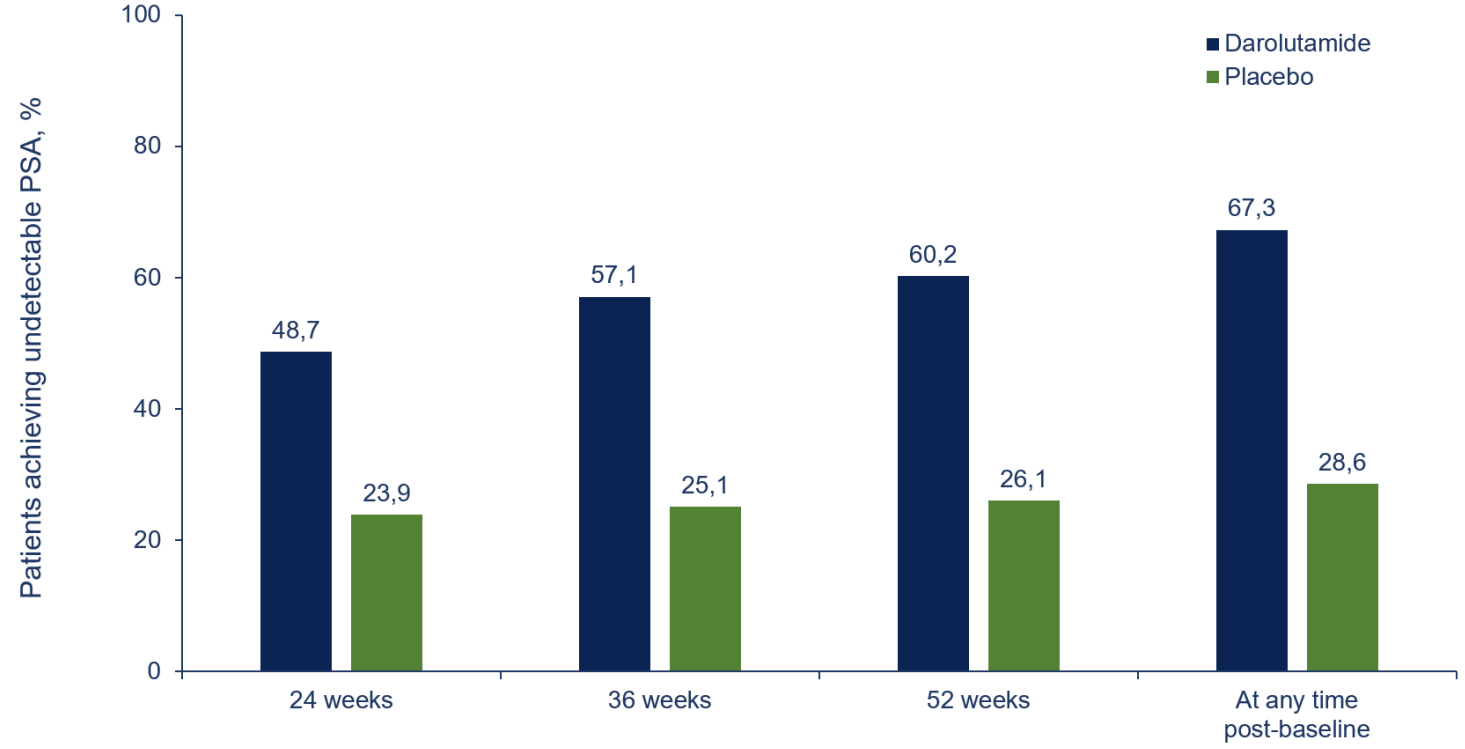
Data from the TITAN study: Chi K et al. N Engl J Med. 2019 Jul 4;381(1):13-24.

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

CHUM

Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

Objective: Undetectable (≤0.2) PSA Levels



Saad et al. AUA 2022

CHUM

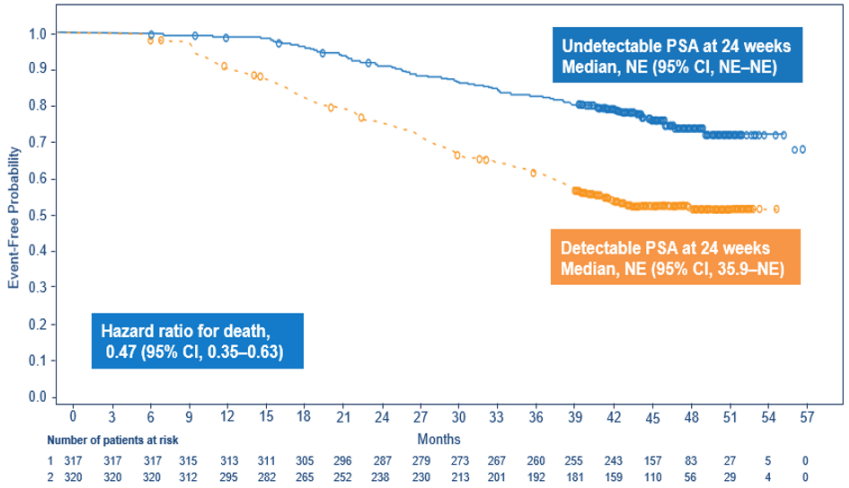
Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

Results: Overall Survival

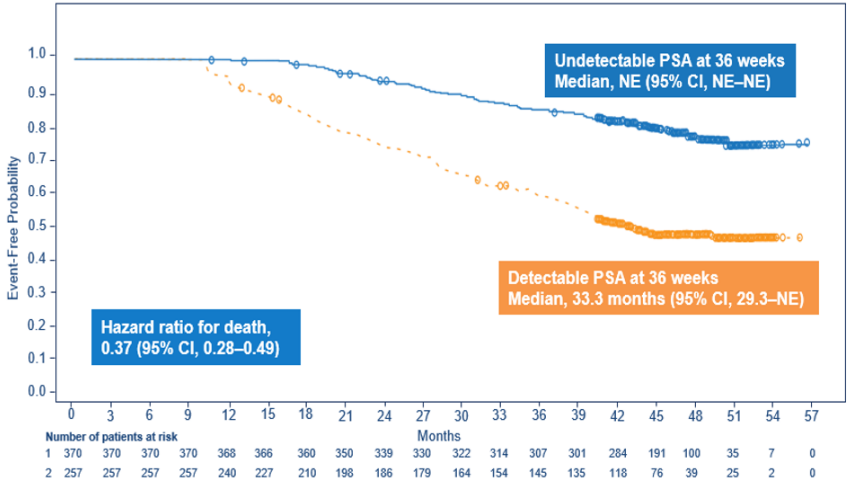
Undetectable PSA at 24 and 36 weeks was associated with a 53% and 63% reduction in the risk of death

Darolutamide + ADT + docetaxel

Undetectable vs detectable PSA at 24 weeks



Undetectable vs detectable PSA at 36 weeks



Saad et al. AUA 2022

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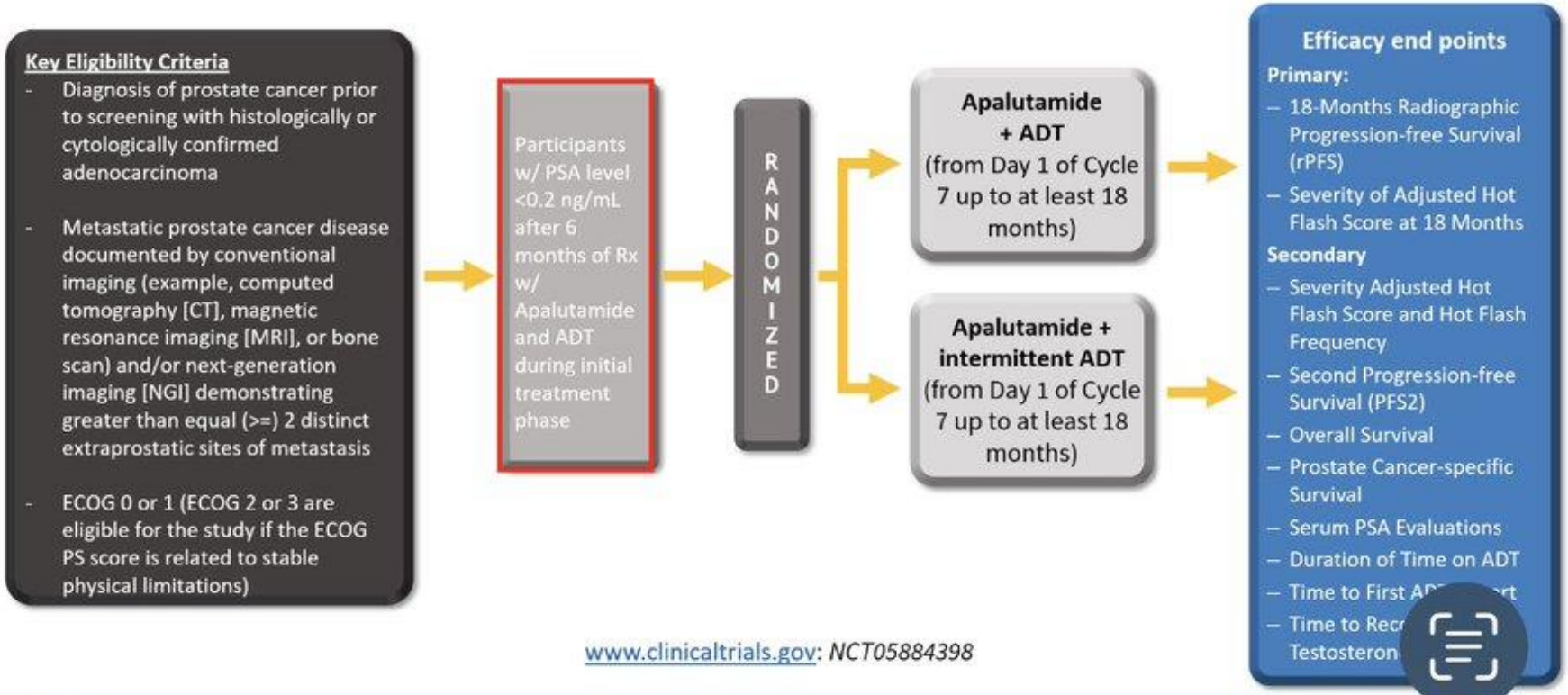
Gelecek Perspektif

LIBERTAS Trial: Phase 3 Trial Design



www.clinicaltrials.gov: *NCT05884398*

Prostat kanserinde genomik profil

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

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

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

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

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

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

Gelecek Perspektif

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.

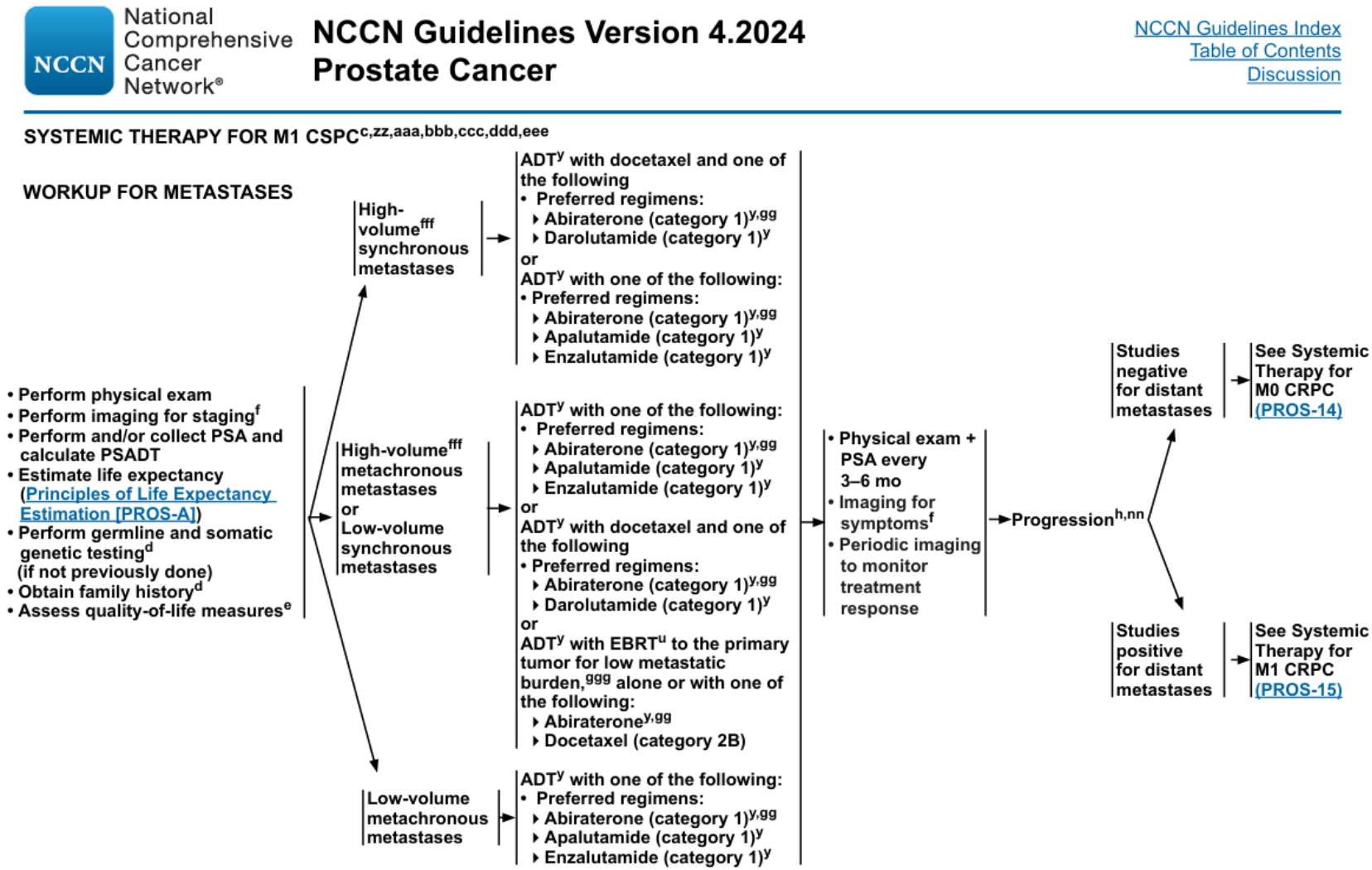
- **Low AR transcriptional activity may reflect reduced AR dependence/aggressive disease** (Spratt DE, Clin Can Res 2019)
- **Loss of TP53, PTEN and RB1 are associated with RESISTANCE to AR axis inhibitors** (Zou M, Cancer Disc 2017; Ku SY, Science 2017; Hamid AA, Eur Urol 2019)
- **SPOP mutations are 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** (Vandekerkhove 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	3rd agent	Design (n)
AMPLITUDE	Abiraterone	Niraparib	Randomized, HRR+ (788)
TALAPRO-3	Enzalutamide	Talazoparib	Randomized HRR+ (550)
City of Hope PCF	Abiraterone	Talazoparib	Single arm, Unselected (70)
PSMAddition	Lu177-PSMA-617	Any ARTA	Randomized, PSMA PET + (1126)
KEYNOTE-991	Enzalutamide	Pembrolizumab	Randomized (1232)
NCT03951831	n/a (ADT + Doce)	Cemiplimab	Single arm (20)
MSKCC	Abi/Enza	Atezolizumab	SBRT, Single arm (44)
CABIOS	Abiraterone	Cabozantinib, Nivolumab	Single arm (22)
CASCARA (U Minn)	Abiraterone	Cabazi + Carbo	Single arm (60)
Capitello-281	Abiraterone	Capivasertib	Randomized, PTEN def (1000)
CYCLONE-3	Abiraterone	Abemaciclib	Randomized, unselected (900)

Metastatik Kastrasyona Duyarlı Prostat Kanseri Tedavi



Metastatik Kastrasyona Duyarlı Prostat Kanseri Tedavi

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2025
Prostate Cancer

NCCN Guidelines Index
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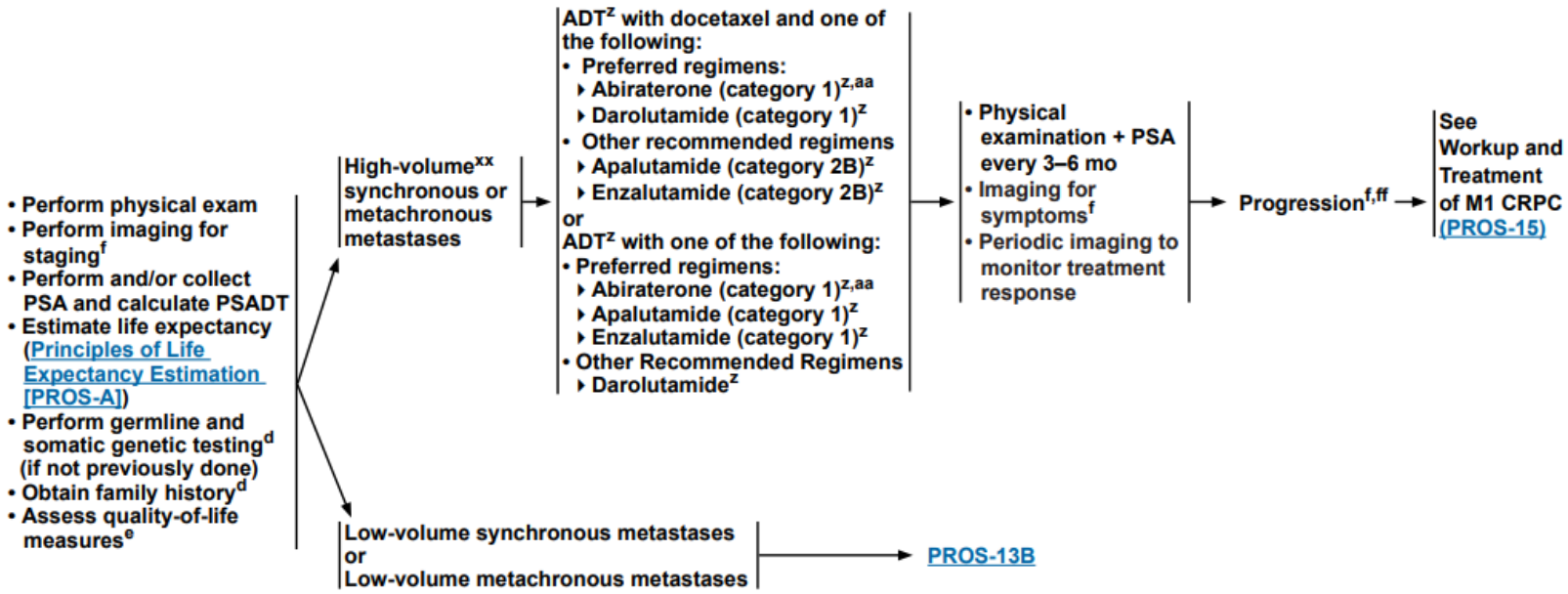
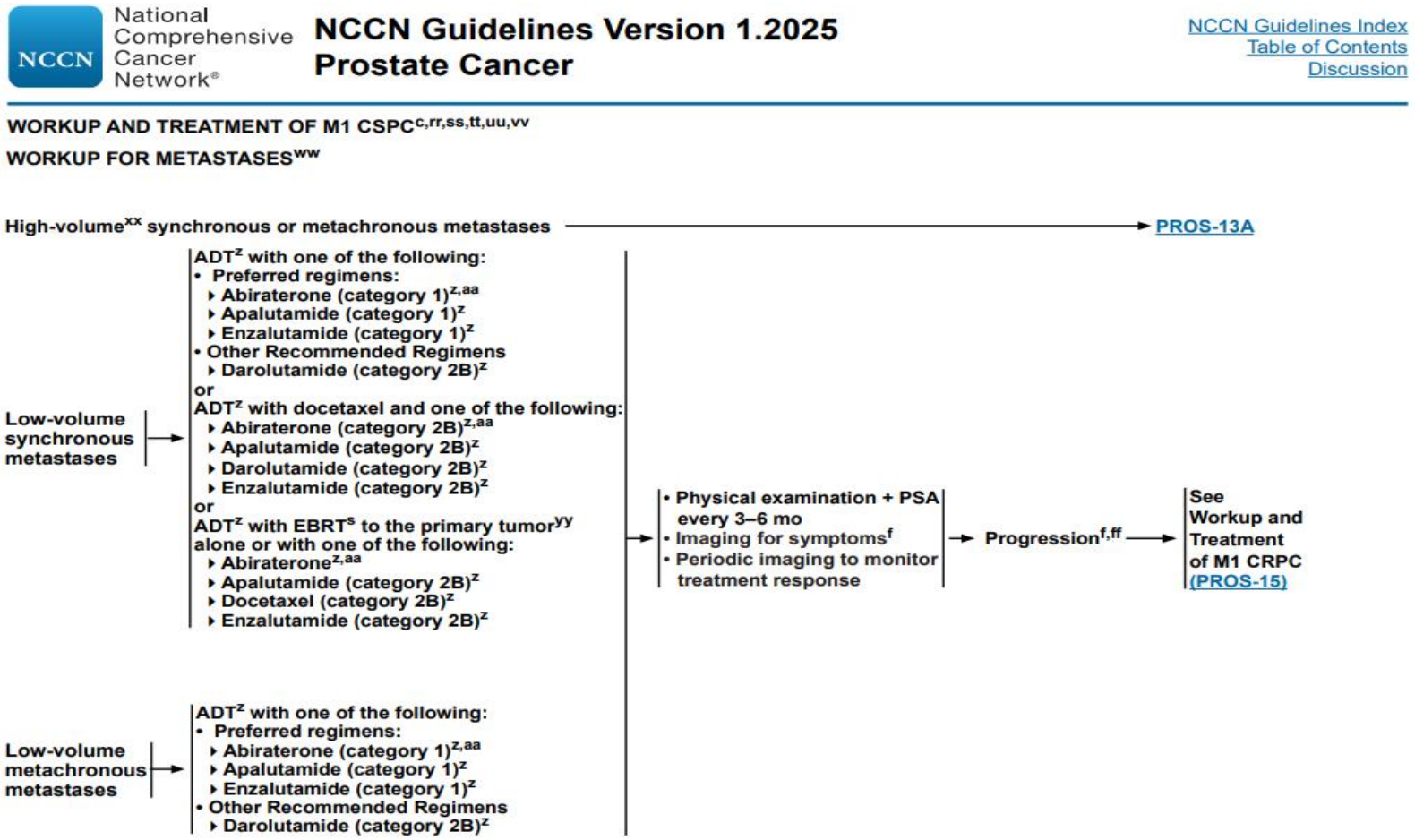
Discussion

WORKUP AND TREATMENT OF M1 CSPC[c,rr,ss,tt,uu,vv]

WORKUP FOR METASTASES[ww]



Metastatik Kastrasyona Duyarlı Prostat Kanseri Tedavi



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 profilleme tedavi seçiminde etkili olacak.

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