Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

Dr. Deniz Tural
Bakırköy Dr. Sadi Konuk Eğitim ve Araştırma Hastanesi
Tıbbi Onkoloji

Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

	Common Types of Cancer	Estimated New Cases 2015	Estimated Deaths 2015
1.	Breast Cancer (Female)	231,840	40,290
2.	Lung and Bronchus Cancer	221,200	158,040
3.	**Prostate Cancer**	**220,800**	**27,540**
4.	Colon and Rectum Cancer	132,700	49,700
5.	Bladder Cancer	74,000	16,000
6.	Melanoma of the Skin	73,870	9,940
7.	Non-Hodgkin Lymphoma	71,850	19,790
8.	Thyroid Cancer	62,450	1,950
9.	Kidney and Renal Pelvis Cancer	61,560	14,080
10.	Endometrial Cancer	54,870	10,170

Prostate cancer represents 13.3% of all new cancer cases in the U.S.

In 2015, it is estimated that there will be 220,800 new cases of prostate cancer and an estimated 27,540 people will die of this disease.

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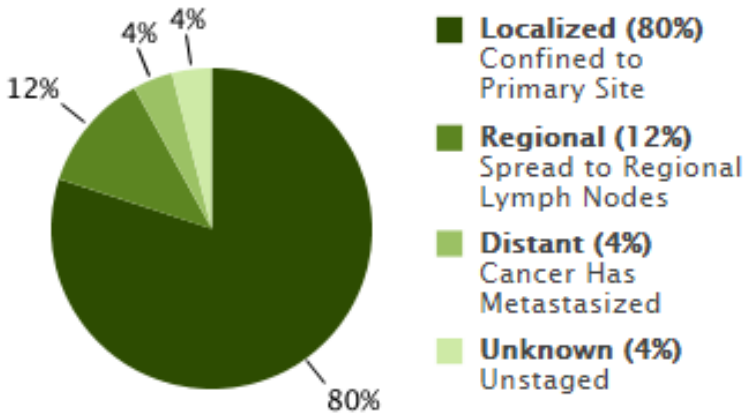
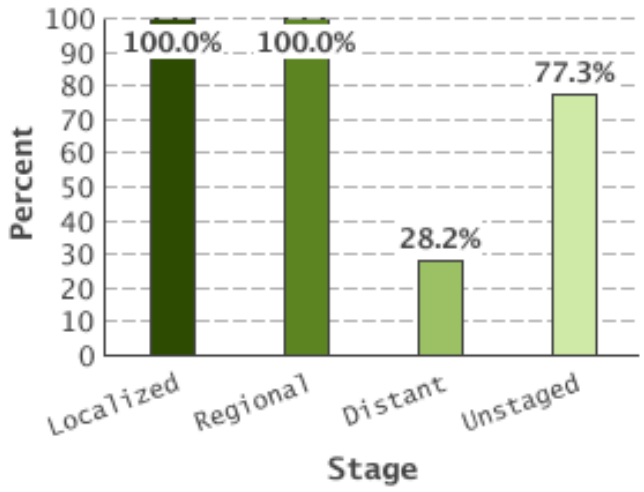
Percent of Cases & 5-Year Relative Survival by Stage at Diagnosis: Prostate Cancer

Percent of Cases by Stage

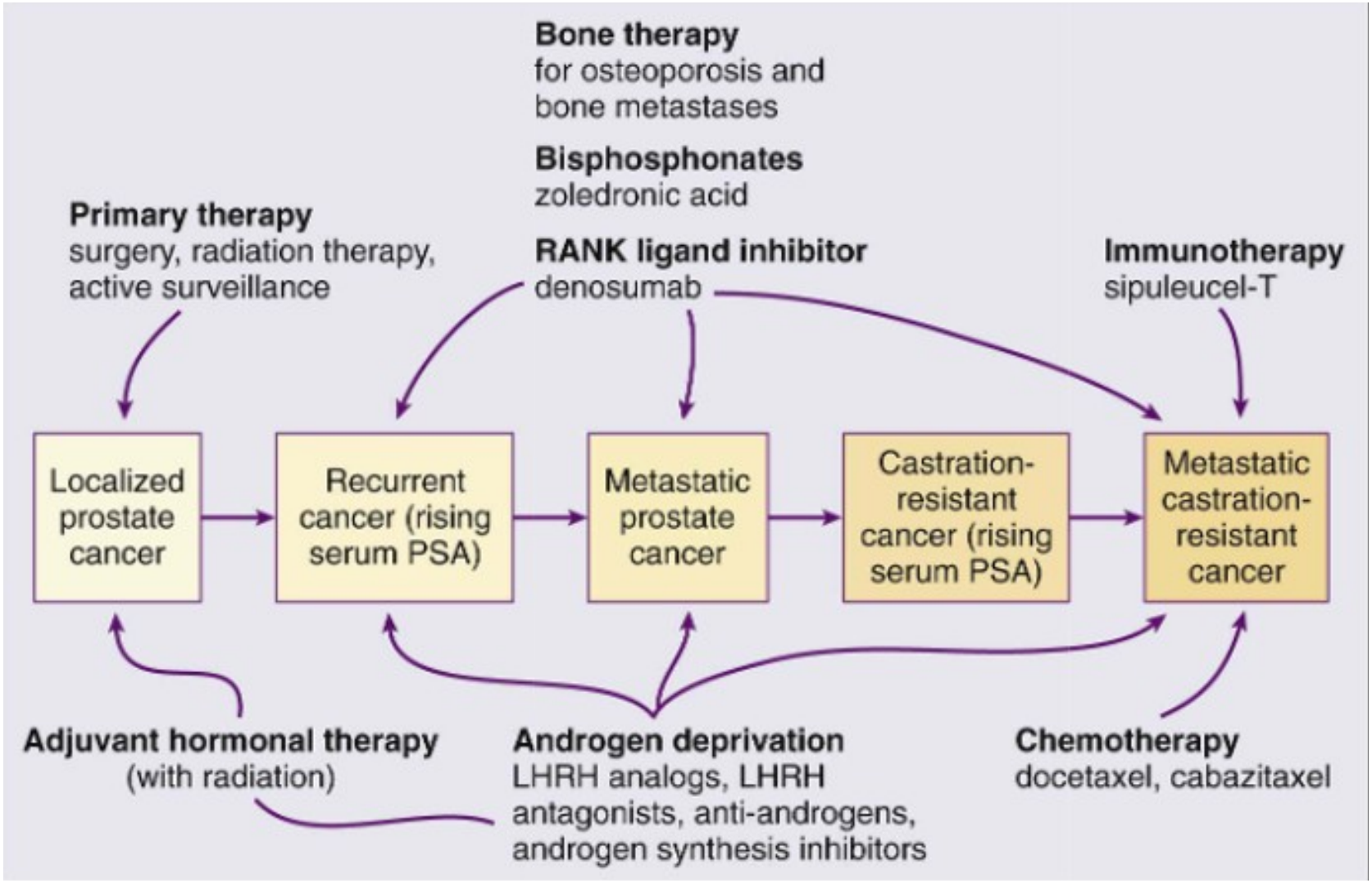


5-Year Relative Survival



SEER 18 2005-2011, All Races, Males by SEER Summary Stage 2000

Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi



Şekil; Abeloff's Clinical Oncology, 10th edition

Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

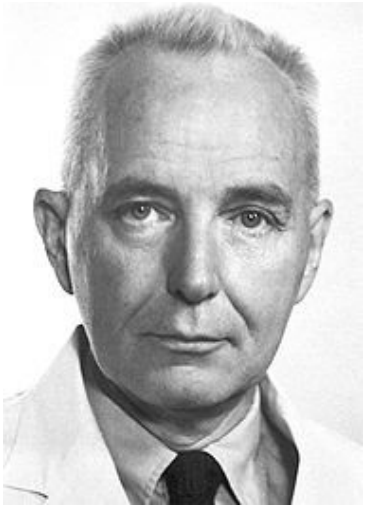
Androjen Baskılama Tedavisi(ADT)

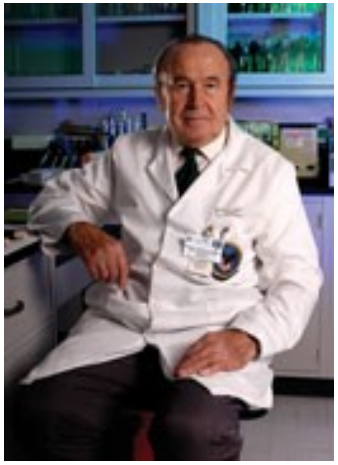
- Cerrahi Kastrasyon(Bilateral orişektomi)

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

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

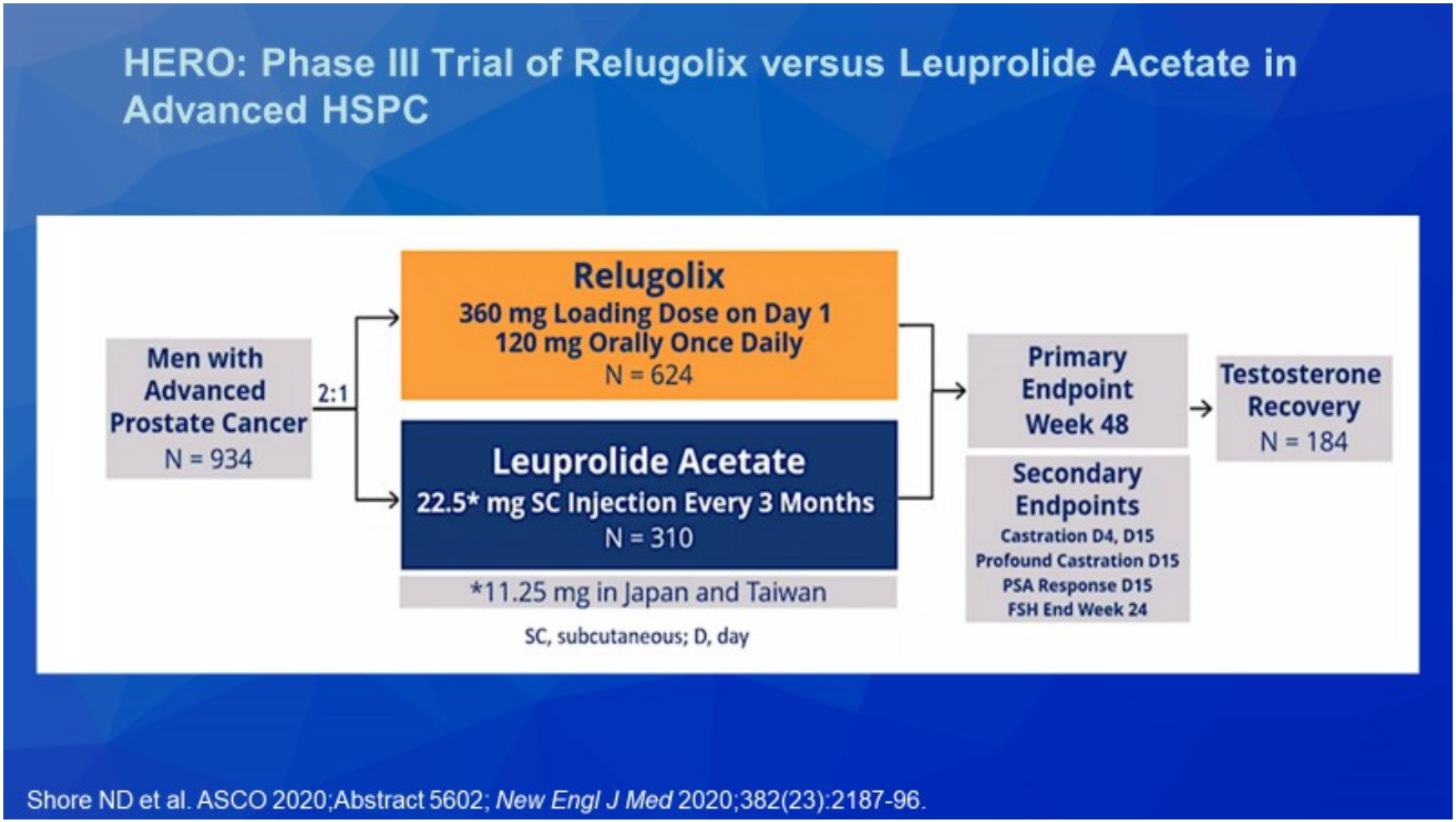
Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi





- **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**

Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi



Shore ND et al. ASCO 2020;Abstract 5602; *New Engl J Med* 2020;382(23):2187-96.

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HERO: Phase III Trial of Relugolix versus Leuprolide Acetate in Advanced HSPC

- Relugolix was superior to leuprolide in achieving and sustaining castration through week 48
- The risk of major adverse cardiovascular events was 54% lower with relugolix than with leuprolide

Shore ND et al. ASCO 2020;Abstract 5602; *New Engl J Med* 2020;382(23):2187-96.

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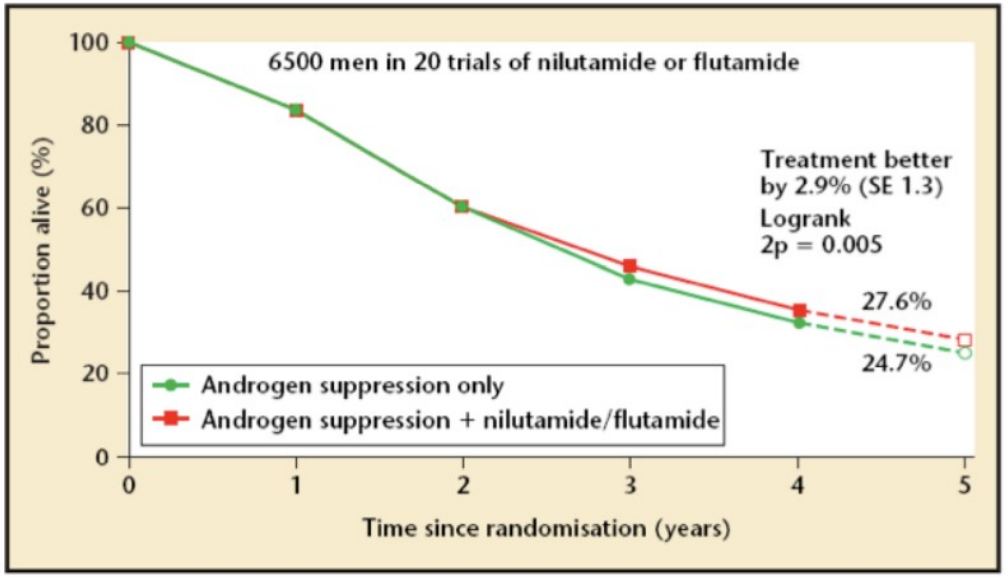
3- No meaningful OS benefit from old fashion « Complete Androgen Blockade »

= Castration + 1st generation AR antagonist

Please stop using this term!



Prostate Cancer Trialists' Collaborative Group. Lancet. 2000; 355: 1474-5.

CAB sağkalım üzerine etkisi minimal

toksisite fazla

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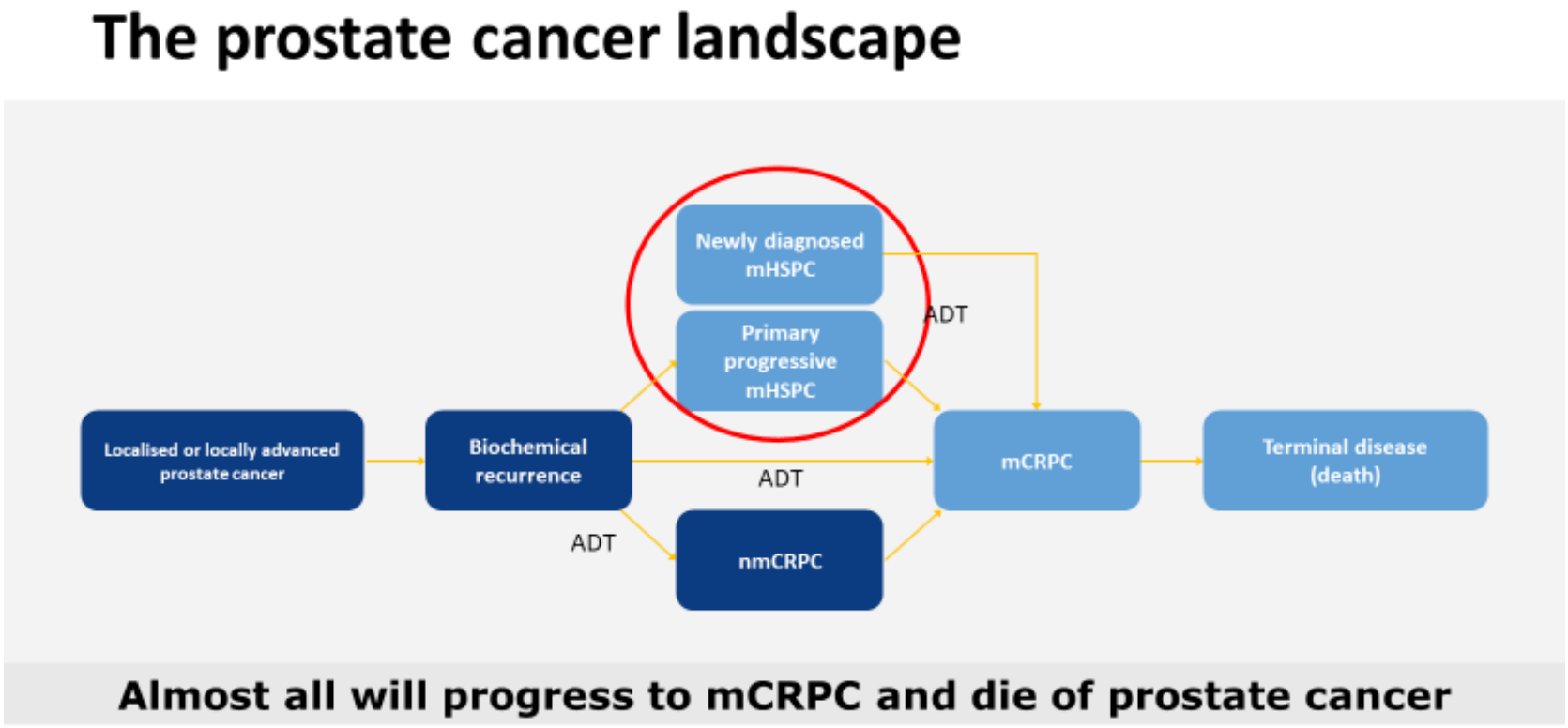

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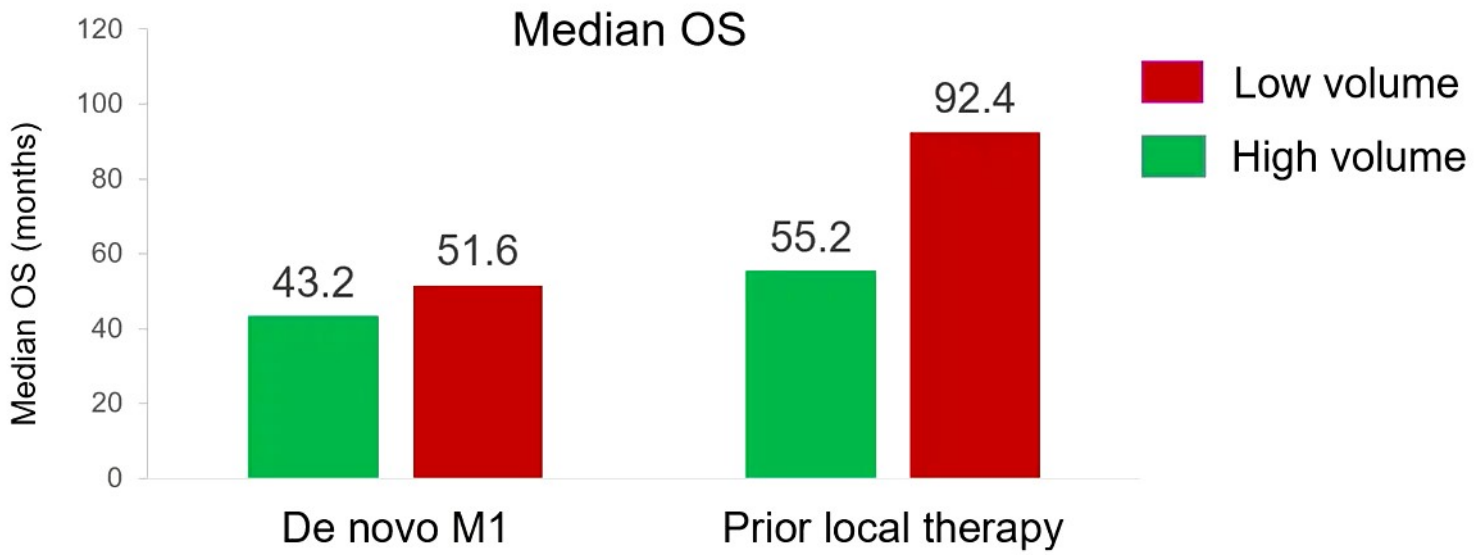
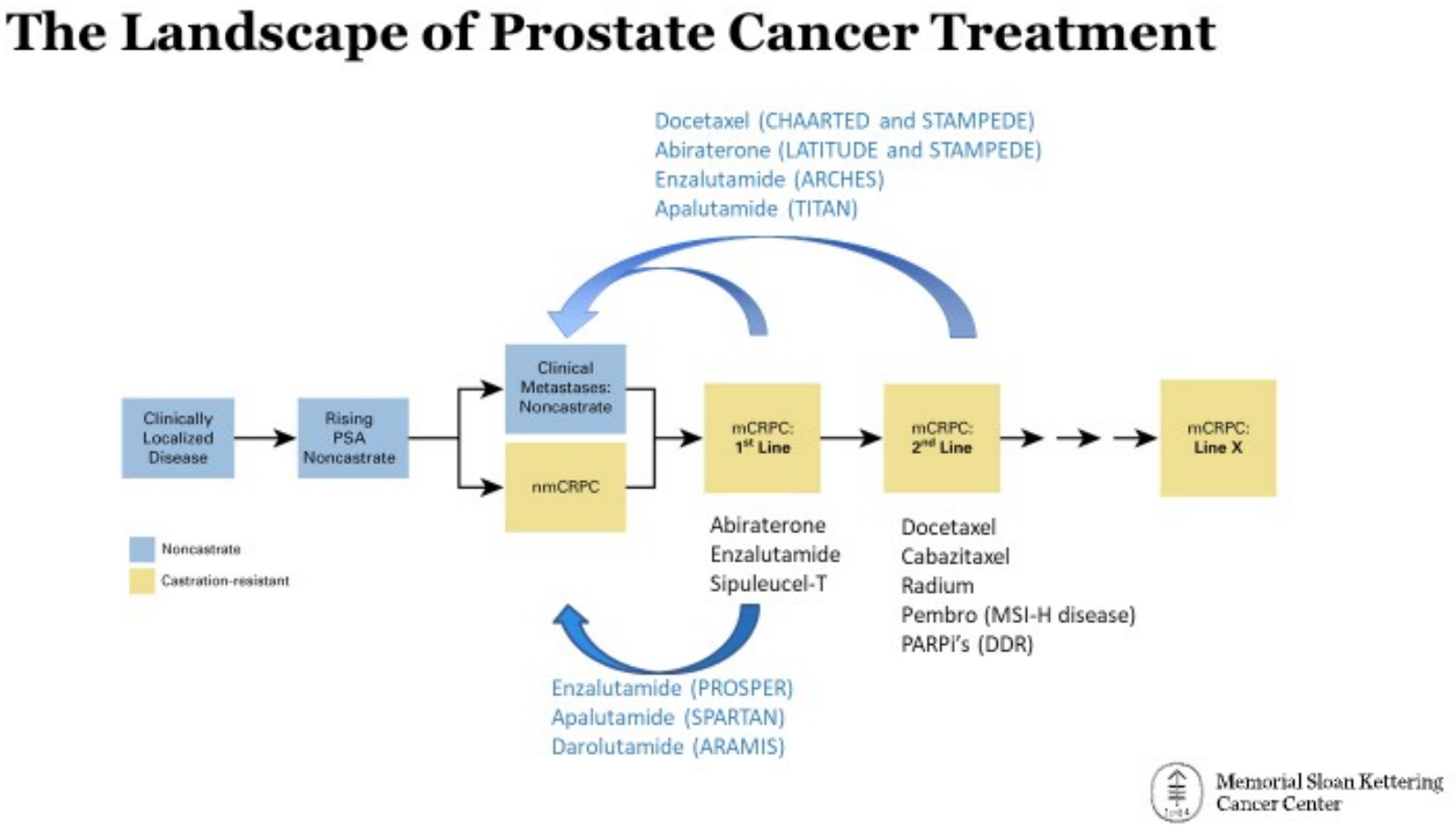
De Novo mHNPC is associated with a worse prognosis



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

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

Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi



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Treatment options in mCRPC

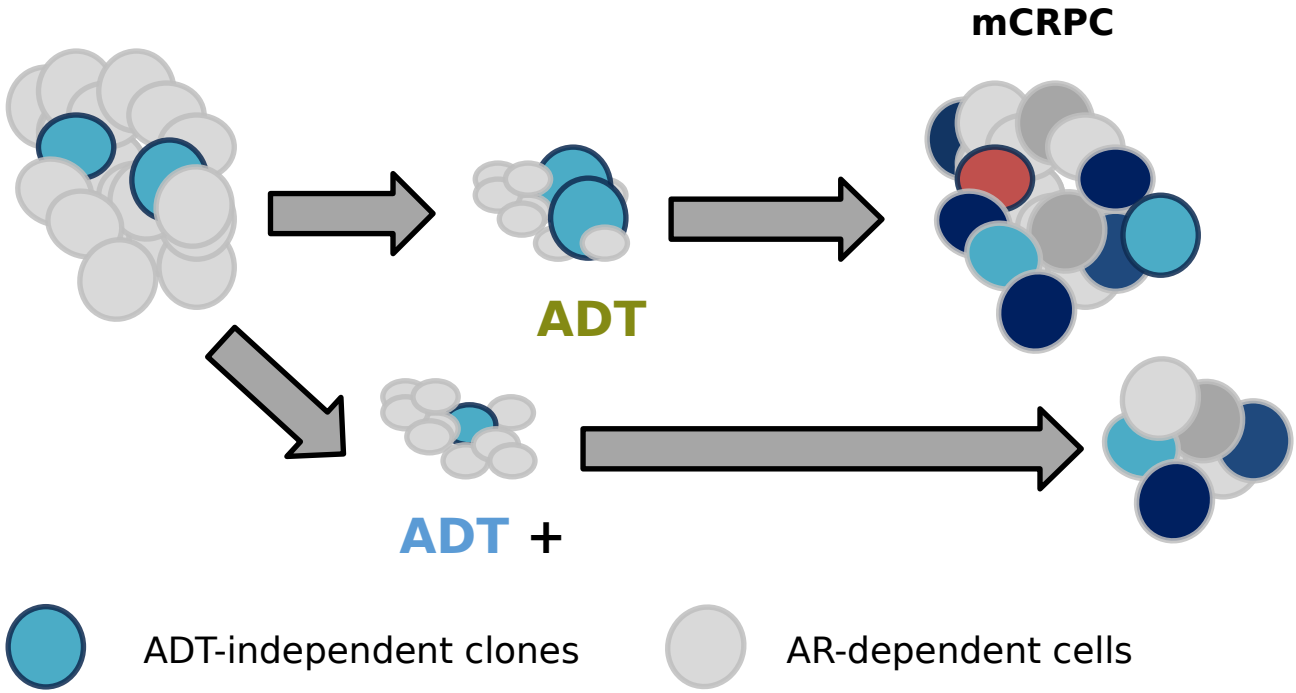
Study	Agents	N	Indication	HR	ΔOS (mo)
TAX-327[1]	DOC/P vs mito/P	1,006	mCRPC, symptomatic or not	0.76	+2.9
COU-AA-302[6]	ABI/P vs P	1,088	mCRPC (pre-DOC), mild/no symptoms No visceral metastases	0.81	+4.4
COU-AA-301[3]	ABI/P vs P	1,195	mCRPC (post-DOC)	0.74	+4.6
PREVAIL[4]	ENZ vs pbo	1,717	mCRPC (pre-DOC), mild/no symptoms	0.77	+4.0
AFFIRM[5]	ENZ vs pbo (or P)	1,199	mCRPC (post-DOC)	0.63	+4.8
TROPIC[6]	CABA/P vs mito/P	755	mCRPC (post-DOC)	0.70	+2.4
ALSYMPCA[7]	Radium-223 vs pbo	921	mCRPC (post-DOC or unfit for DOC)	0.70	+3.6

ABI, abiraterone; **CABA**, cabazitaxel; **DOC**, docetaxel; **ENZ**, enzalutamide; **HR**, hazard ratio; **mito**, mitoxantrone; **P**, prednisone; **pbo**, placebo; **OS**, overall survival.

1. Tannock IF *et al. N Engl J Med* 2004; 351:1502–12. **2.** Ryan CJ *et al. Lancet Oncol* 2015;16:152–60. **3.** Rathkopf DE *et al. Eur Urol* 2014;66:815–25. **4.** Beer TM *et al. Eur Urol* 2017;71:151–4.
5. Armstrong AJ *et al. Cancer* 2017;123:2303–11. **6.** de Bono JS *et al. Lancet* 2010;376:1147–54. **7.** Hoskin P *et al. Lancet Oncol* 2014;15:1397–406.

CHUM

Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi



Role of Effective Systemic Therapy

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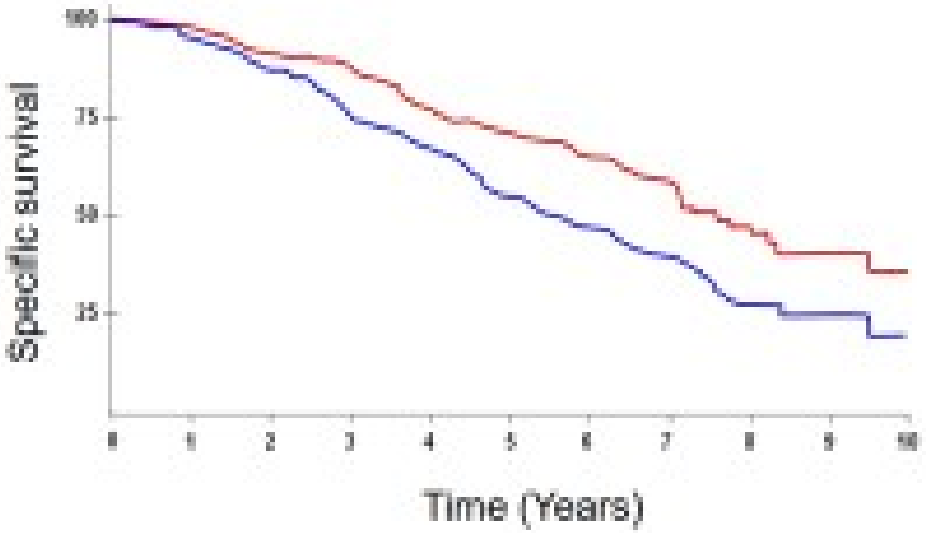
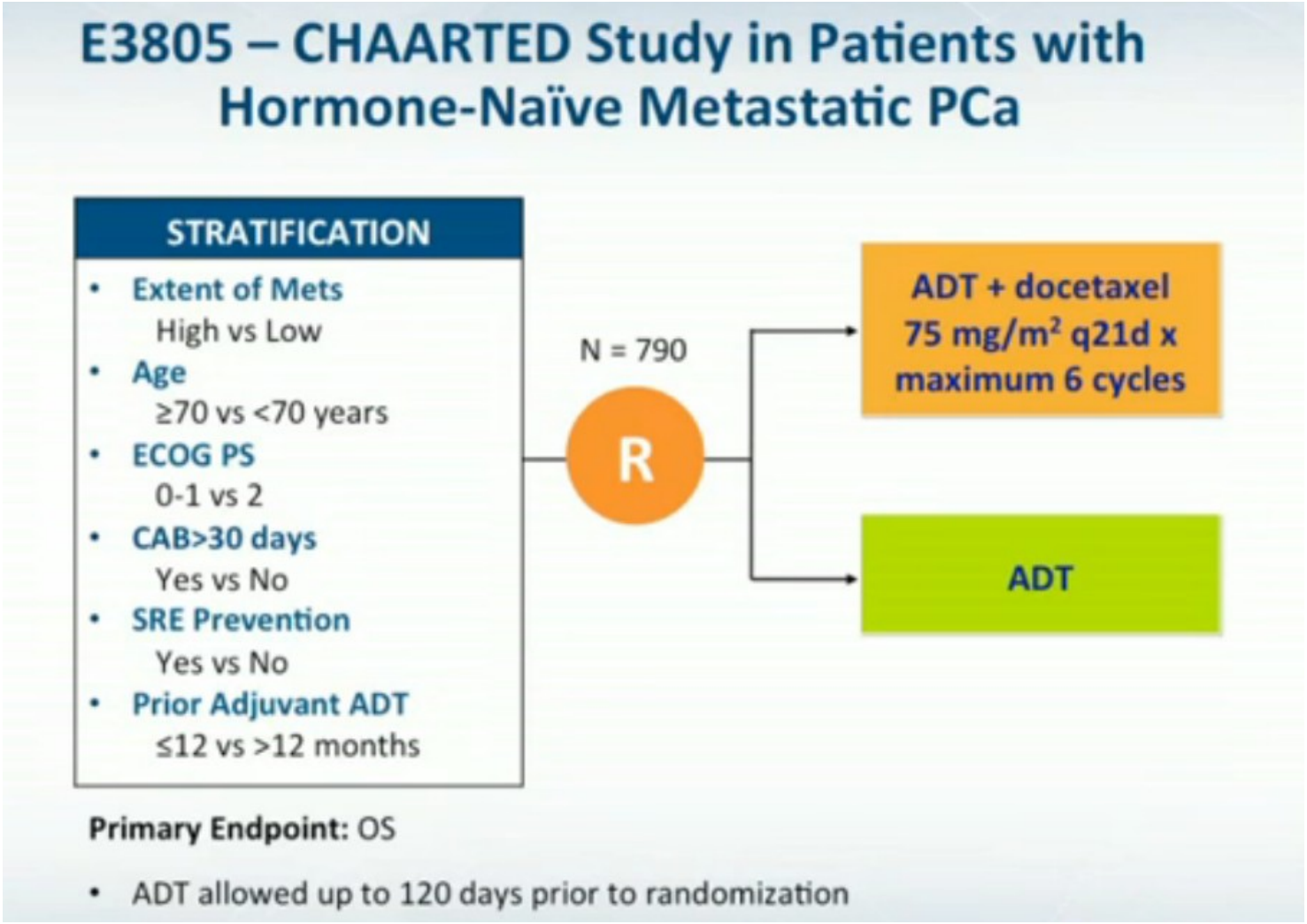
1- Immediate ADT > Differed ADT in M1

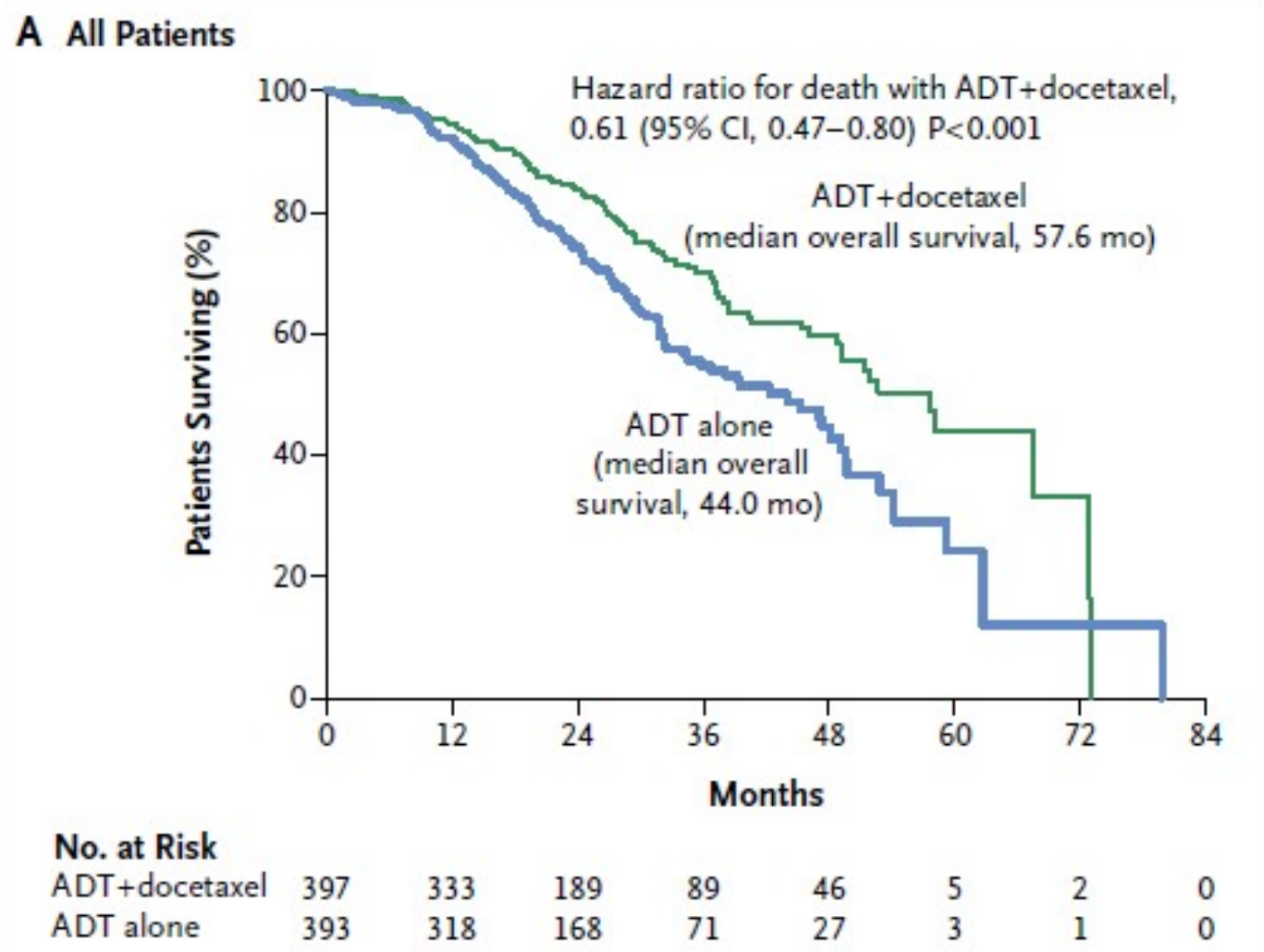
- Phase 3 trial (n=938)
- Immediate vs differed ADT
- Immediate better:
  - OS (p=0.02)
  - Local control (TURP) (p<0.001)
- Caveat: some men in the Differed arm never received ADT



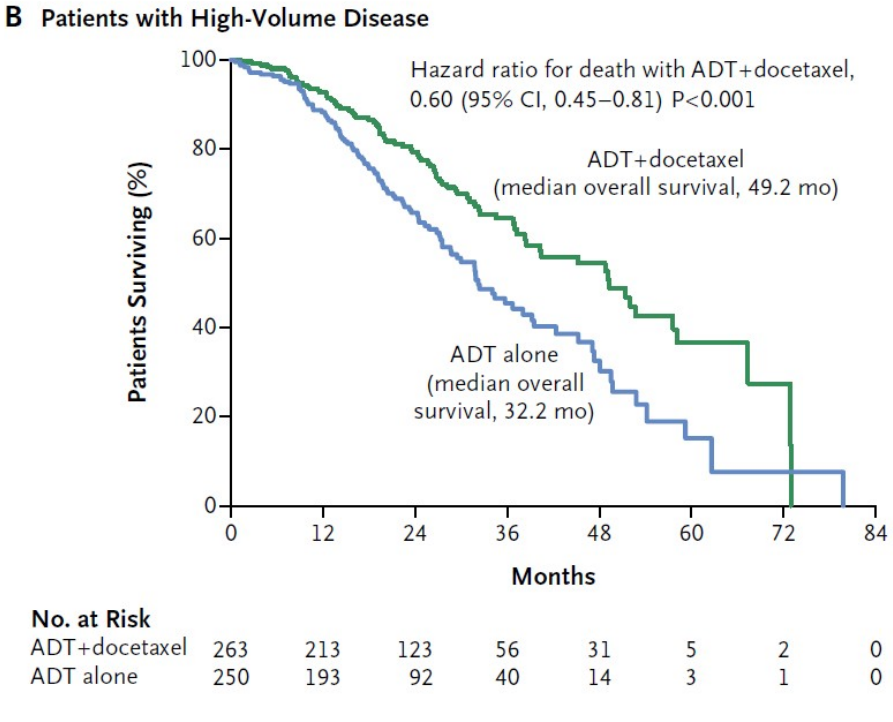
Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

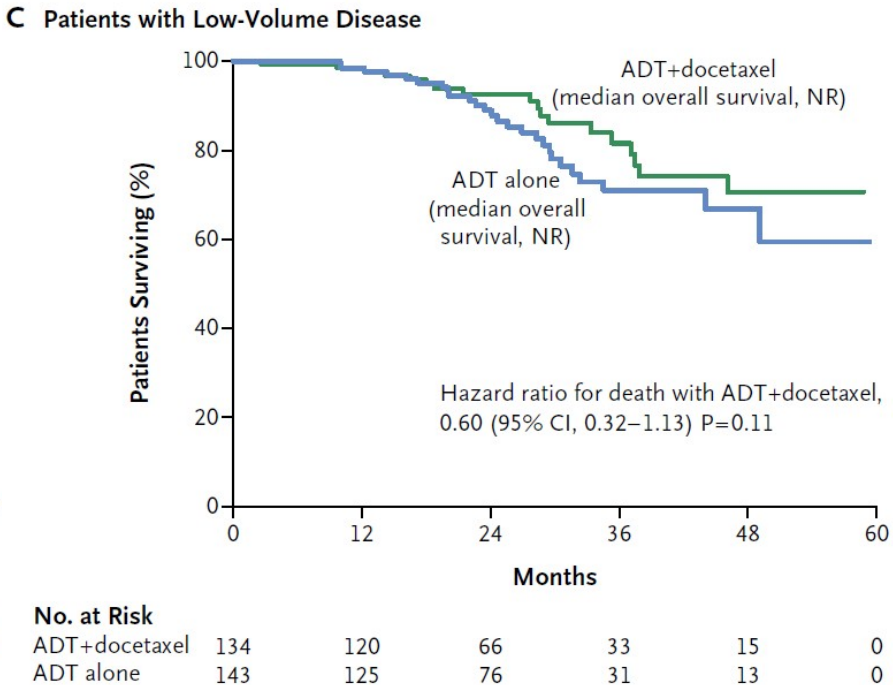


ADT + Erken Dönem Kemoterapi



ADT + Erken Dönem Kemoterapi





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

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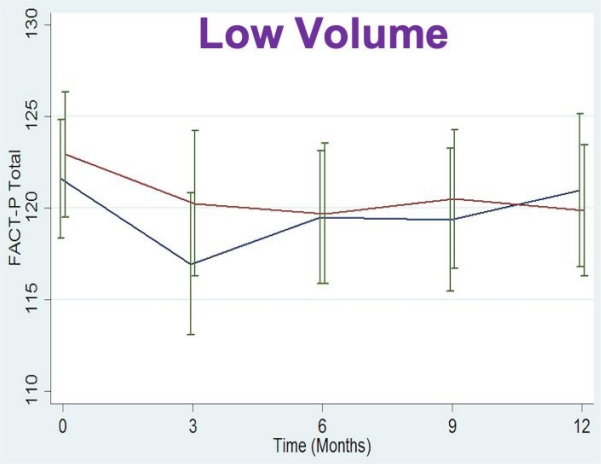
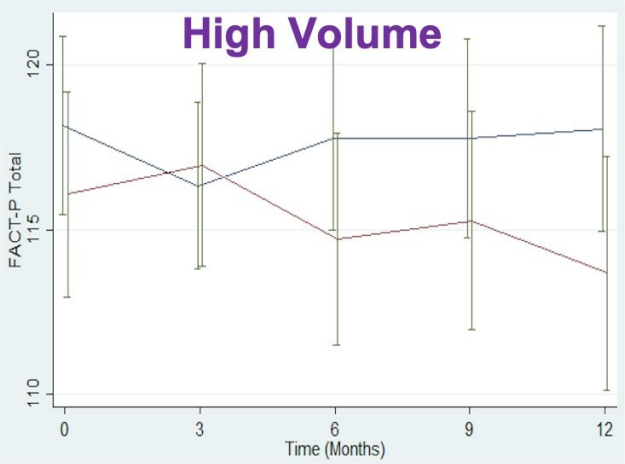
QOL FACT-P in CHAARTED: ADT +/- docetaxel





Patients with high volume had worse baseline QoL scores

ADT alone (red curves) in low volume → no change in QOL over 12 months in low volume but QOL decline in high volume (more progression → more symptoms from next treatment and progression)

ADT plus docetaxel (blue curves) decline in QOL in low volume arm on chemo; but high volume cohort → minor initial decline and better 12 month QOL as greater cancer control balanced initial treatment burden and delayed progression with longer term less symptoms and treatments

Morgans A, et al JCO 2018

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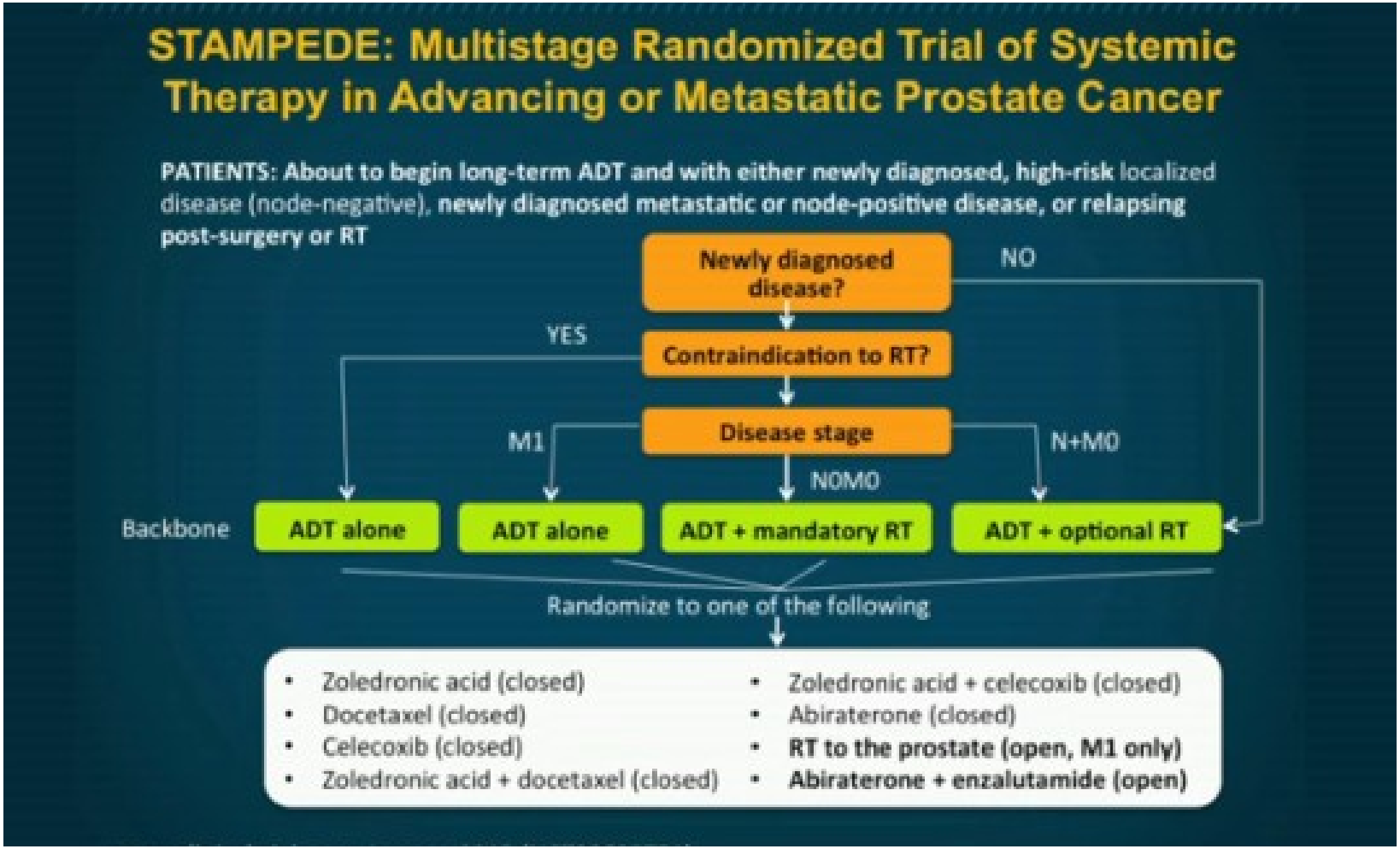
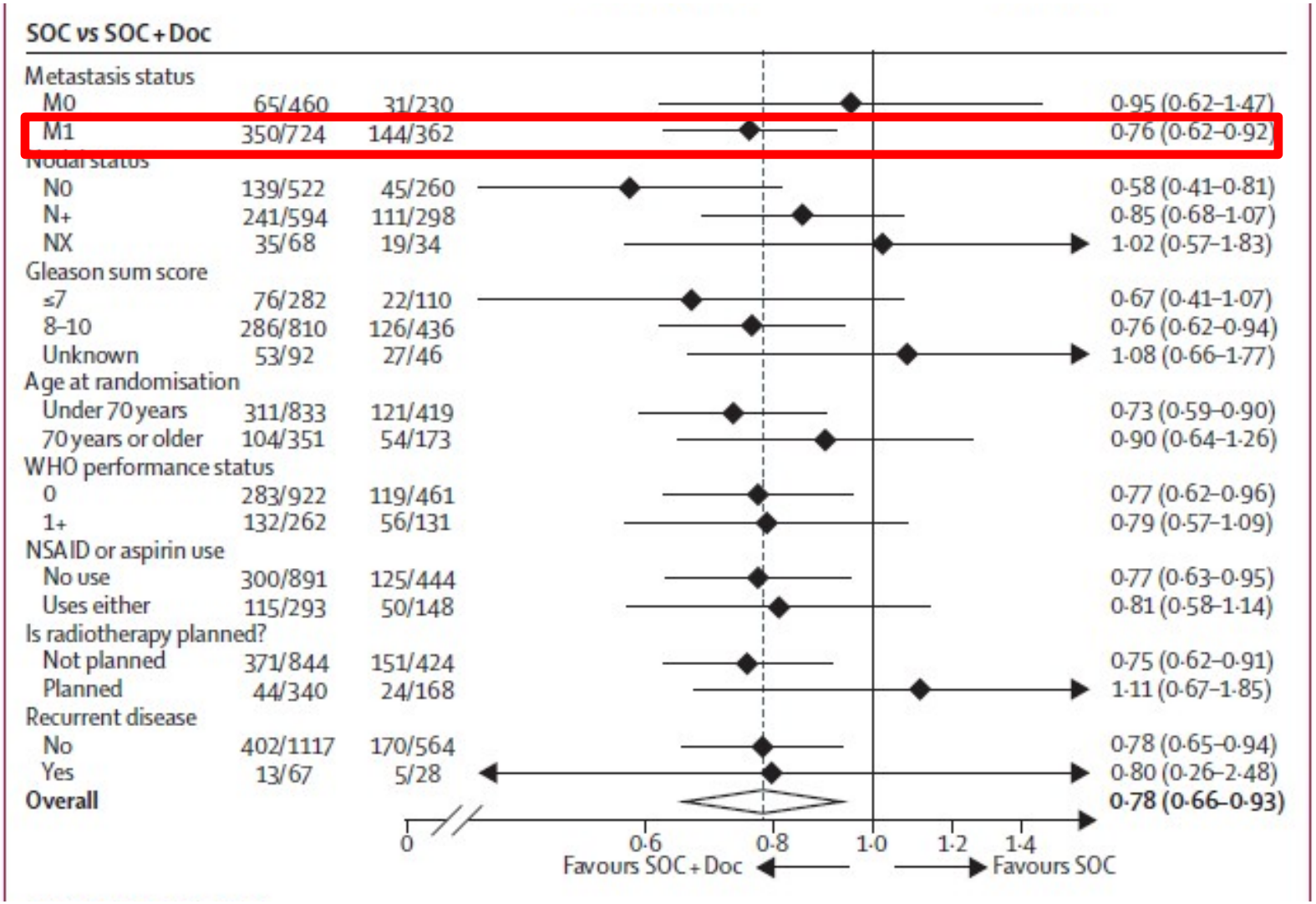
ADT + Erken Dönem Kemoterapi

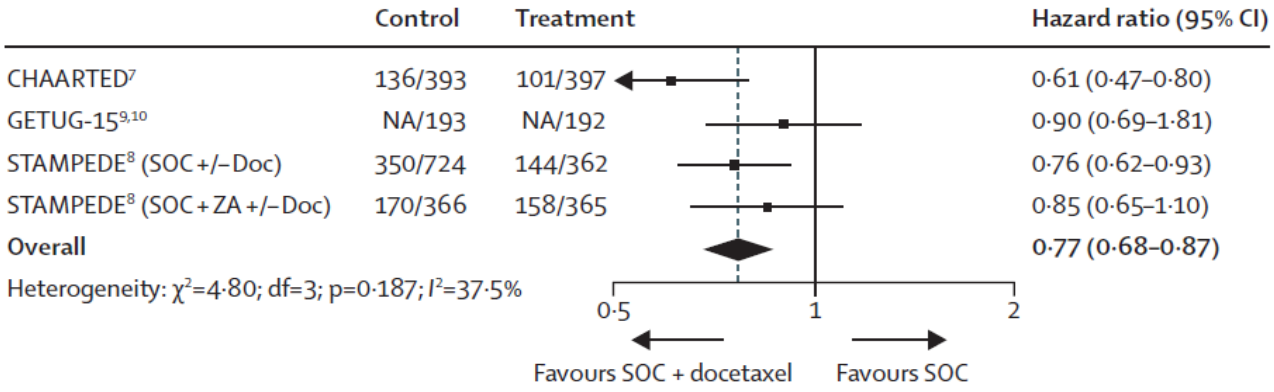


ADT + Erken Dönem Kemoterapi

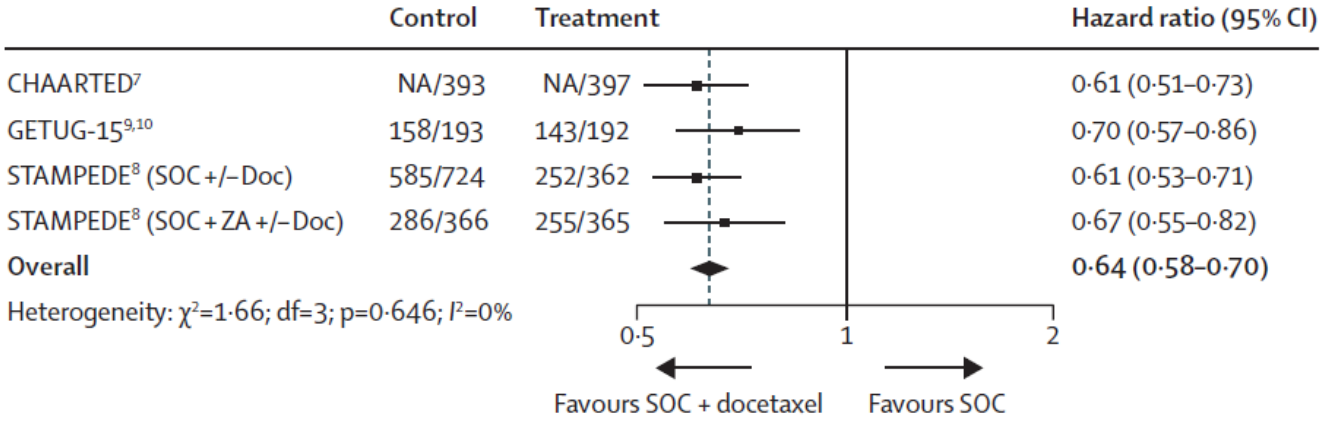


Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

Metaanaliz; ADT + Erken Dönem Kemoterapi



2992 hormona duyarlı metastatik prostat ca hastaya ADT +dosetaksel eklenmesi ; 4-yıllık sağkalımı %9 artırıyor



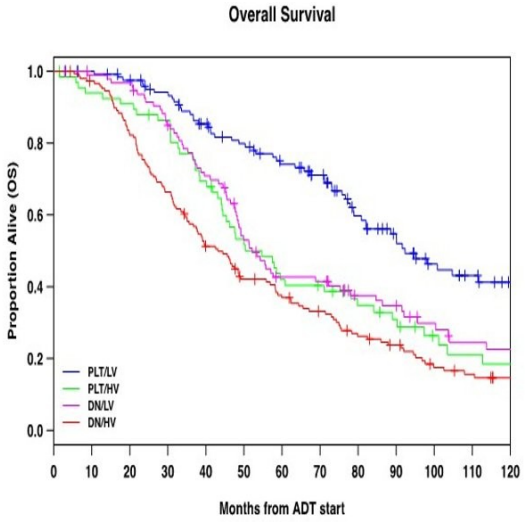
2992 hormona duyarlı metastatik prostat ca hastaya ADT +dosetaksel eklenmesi ; 4 yılık %16 nüksüz süreyi uzatıyor

Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

Different Prognoses by:
Type of Presentation & Extent of Metastases

CHAARTED & GETUG15 (TS alone)	Median OS (years)
Metach and low volume	~8
Metach and high volume	4.5
De Novo and LV	4.5
De Novo and HV	3

High volume: *visceral mets and/or 4 or more bone mets at least one beyond vert and pelvis)*



Groups	N (% events)	Median OS yrs (95%CI)
Prior Tx+LV	125 (50)	7.7 (6.7,10.6)
Prior Tx+HV	67 (75)	4.6 (3.7,6.7)
De-novo+LV	96 (70)	4.3 (4,6.5)
De-novo+HV	148 (84)	3.6 (3.1,4.7)

56% of mHSPC low volume in hospital registry are metachronous; found by surveillance with rising PSA

Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

High level summary of HR(OS) of *all* TS + / - docetaxel mHSPC data: Mixed Results

M1 HSPC	All M1	High Volume *De Novo+Metach*	Low Volume *De Novo*	Low Volume *Metach*
GETUG15[1]	**0.88** 95% CI: 0.68-1.14 N=381	**0.78** 95% CI: 0.56-1.09 N=183	**~1.0** 95% CI: 0.67-1.55 N=119	**~1:0** 95% CI: 0.67–1.55 N=79 **Not reported separately*
CHAARTED[2]	**0.72** 95% CI: 0.59-0.89 N=790	**0.63** 95% CI: 0.50-0.79 N=513	**0.86** 95% CI: 0.52 -1.42 N=154	**1.25** 95% CI: 0.60-2.6 N=123
STAMPEDE-Doc[3]	**0.81** 95% CI: 0.69–0.95 N=1086	**0.81** 95% CI: 0.64–1.02 N=468^	**0.76** 95% CI 0.54–**1.07** N=362^ (124 doc)	**Not evaluated** *^25% of pts Not evaluable*

Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

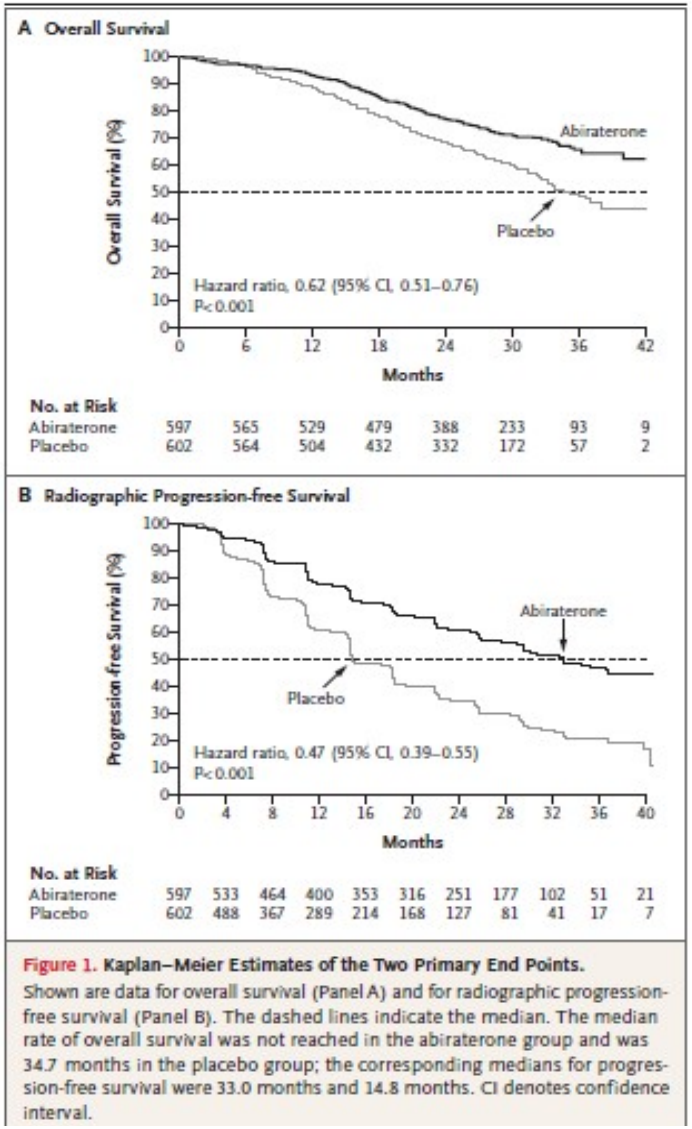


Figure 1. Kaplan–Meier Estimates of the Two Primary End Points.
Shown are data for overall survival (Panel A) and for radiographic progression-free survival (Panel B). The dashed lines indicate the median. The median rate of overall survival was not reached in the abiraterone group and was 34.7 months in the placebo group; the corresponding medians for progression-free survival were 33.0 months and 14.8 months. CI denotes confidence interval.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Abiraterone plus Prednisone in Metastatic, Castration-Sensitive Prostate Cancer

Karim Fizazi, M.D., Ph.D., NamPhuong Tran, M.D., Luis Fein, M.D., Nobuaki Matsubara, M.D., Alfredo Rodriguez-Antolin, M.D., Ph.D., Boris Y. Alekseev, M.D., Mustafa Özgüroğlu, M.D., Dingwei Ye, M.D., Susan Feyerabend, M.D., Andrew Protheroe, M.D., Ph.D., Peter De Porre, M.D., Thian Kheoh, Ph.D., Youn C. Park, Ph.D., Mary B. Todd, D.O., and Kim N. Chi, M.D., for the LATITUDE Investigators*

ABSTRACT

BACKGROUND

Abiraterone acetate, a drug that blocks endogenous androgen synthesis, plus prednisone is indicated for metastatic castration-resistant prostate cancer. We evaluated the clinical benefit of abiraterone acetate plus prednisone with androgen-deprivation therapy in patients with newly diagnosed, metastatic, castration-sensitive prostate cancer.

From Gustave Roussy, University of Paris Sud, Villejuif, France (K.F.); Janssen Research and Development, Los Angeles (N.T.), Beerse, Belgium (P.D.P.), San Diego, CA (T.K.), and Raritan, NJ (Y.C.P.); Insti-

En az 2≥ kötü risk grubuna sahip hastalar dahil edilmiş

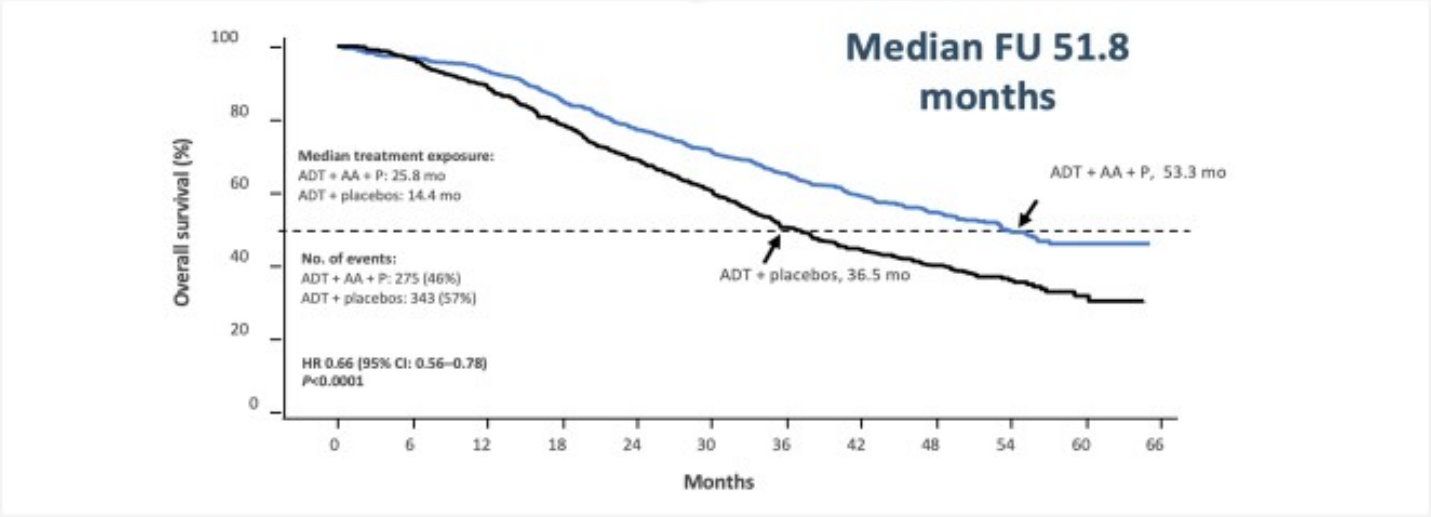
1. **Gleason skoru≥8**
2. **3≥ fazla kemik metastazı**
3. **Viseral metastaz**

Dışlama kriterleri

4. **Daha önce cerrahi**
5. **Radyoterapi**
6. **Kemoterapi**
7. **Metastik hastalığa bağlı semptomu olanlarda RT ve Cerrahiye izin verilmiş**

Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

LATITUDE: Abiraterone in high risk mCSPC



Fizazi et al. Lancet Onc Published online April 12, 2019

CHUM

Hormon Duyarlı Metastatik Prostat Kanseri

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Abiraterone acetate plus prednisolone for hormone-naïve prostate cancer (PCa): long-term results from metastatic (M1) patients in the STAMPEDE randomised trial (NCT00268476)

Prof Nicholas James

Institute of Cancer Research, UK

Hormon Duyarlı Metastatik Prostat Kanseri

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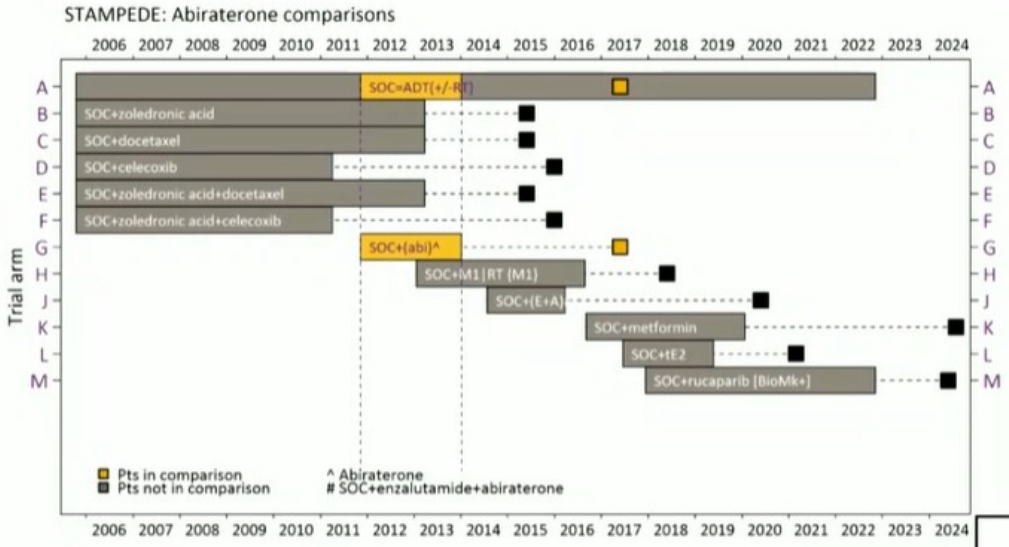
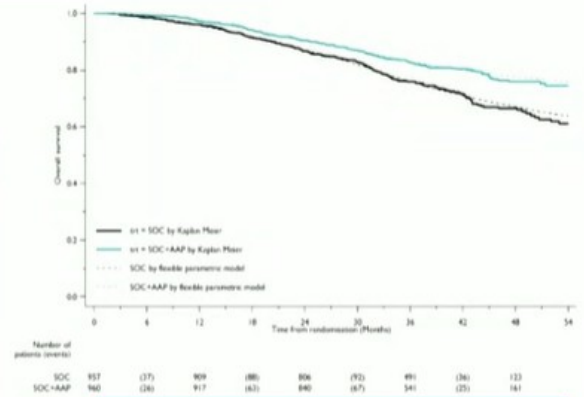
STAMPEDE: SOC+AAP vs SOC, 2017





HR (95%CI) 0.63 (0.52, 0.76)
P-value 0.00000115

Patients: 957 SOC, 960 SOC+AAP

Recruitment: Nov-2011 to Jan-2014
Reported: ASCO 2017
Published: NEJM 2017

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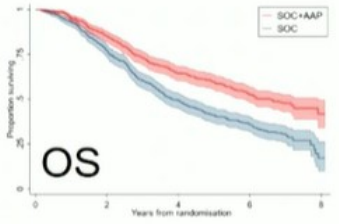
M1 PATIENT CHARACTERISTICS

		SOC (n=502)	SOC+AAP (n=501)
Age (years)	Median (IQR) Range	67 (62-72) 39-84	67 (62-71) 42-85
Eligibility category	Newly diagnosed Relapsing	475 (95%) 27 (5%)	466 (93%) 35 (7%)
PSA (ng/ml)	Median (IQR) Range	97.2 (26-358) 0.6-10530	96.3 (29-371) 0.1-21460
Metastatic burden*	Low risk High risk Unclassified	222 (44%) 232 (46%) 48 (10%)	214 (43%) 241 (48%) 46 (9%)
Site of metastases	Bone Liver Lung Distant lymph nodes Other	448 (89%) 8 (2%) 21 (4%) 150 (30%) 26 (5%)	434 (87%) 7 (1%) 21 (4%) 143 (29%) 23 (5%)

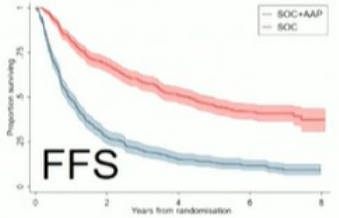
* LATITUDE risk criteria

Summary: Results unchanged in M1 patients

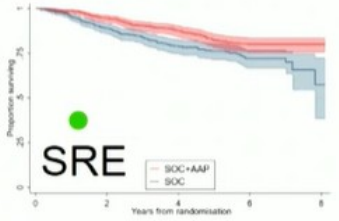
Highly significant benefit in overall survival (OS)



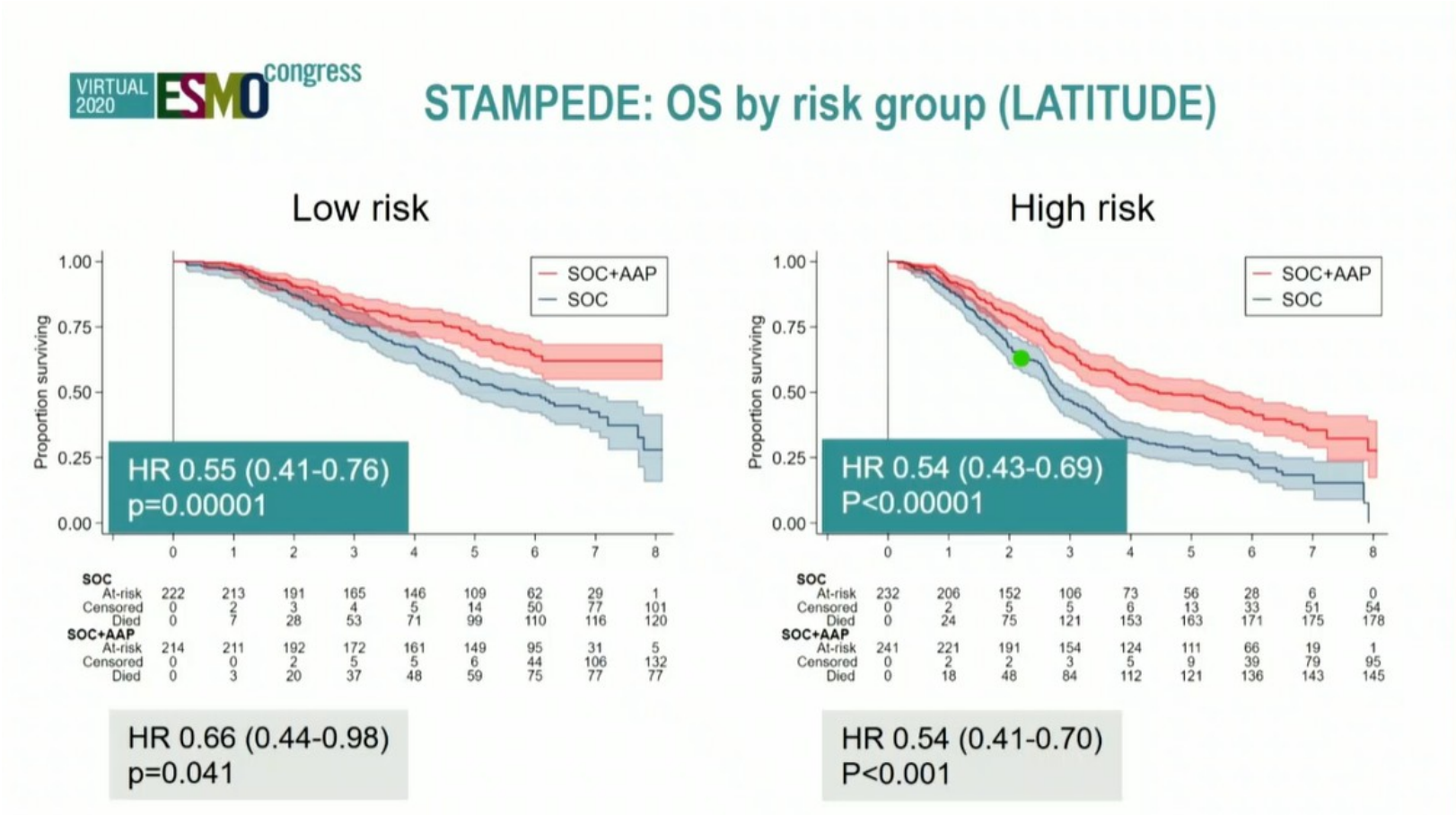
Highly significant benefit in failure free survival (FFS)



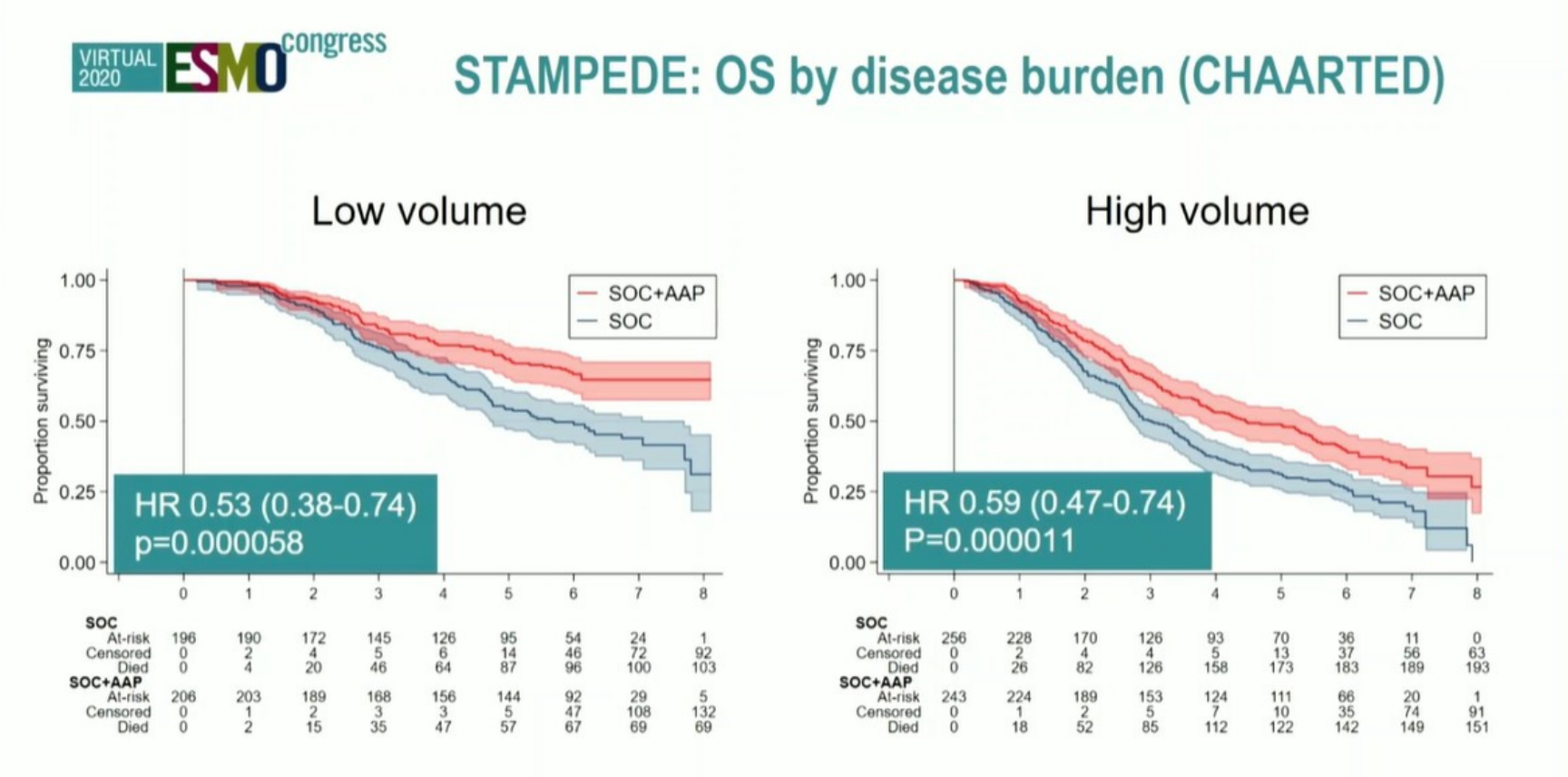
Highly significant benefit in skeletal related events (SRE)



Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi



Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi



Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

VIRTUAL 2020 ESMO congress

SOC+AAP vs SOC: Adverse events

Worst grade event experienced at 2 years

	SOC		SOC+AAP		
	N	%	N	%	p
Grade	145	100%	291	100%	
0	36	27%	59	21%	0.286
1	63	47%	143	50%	
2	22	17%	64	22%	
3	12	9%	20	7%	
4	0	0%	0	0%	
5	0	0%	0	0%	
Missing	*12*		*5*		

Worst grade event experienced at 4 years

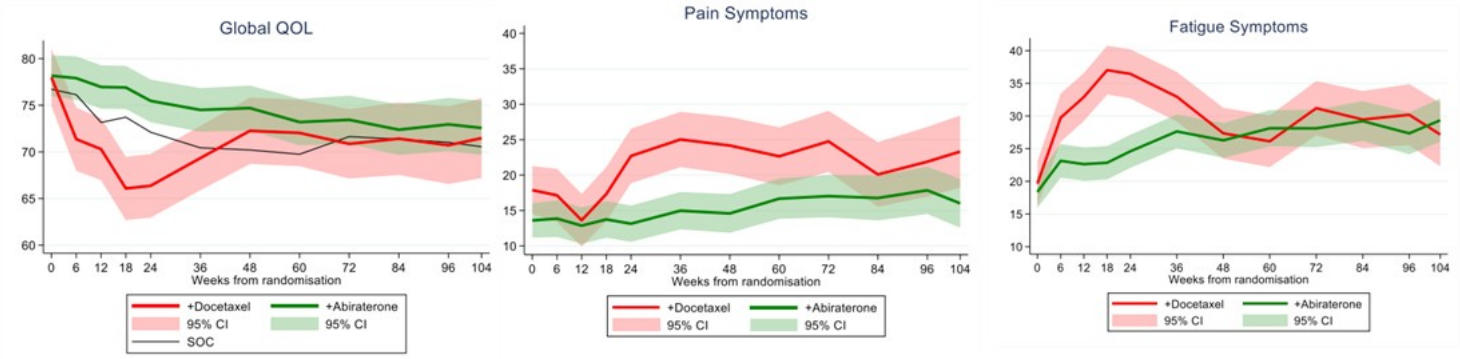
	SOC		SOC+AAP		
	N	%	N	%	p
Grade	86	100%	197	100%	
0	5	10%	18	12%	0.561
1	25	50%	57	38%	
2	12	24%	51	34%	
3	8	16%	23	15%	
4	0	0%	1	1%	
5	0	0%	0	0%	
Missing	*36*		*47*		

Note: toxicity data is collected up to first disease progression (including biochemical failure) for SOC patients, and up to cessation of abiraterone treatment for SOC+AAP patients.

Hormon Duyarlı Metastatik Prostat Kanseri

VIRTUAL 2020 ESMO congress

QOL better with Abiraterone than with Docetaxel In M1 CSPC (direct comparison)

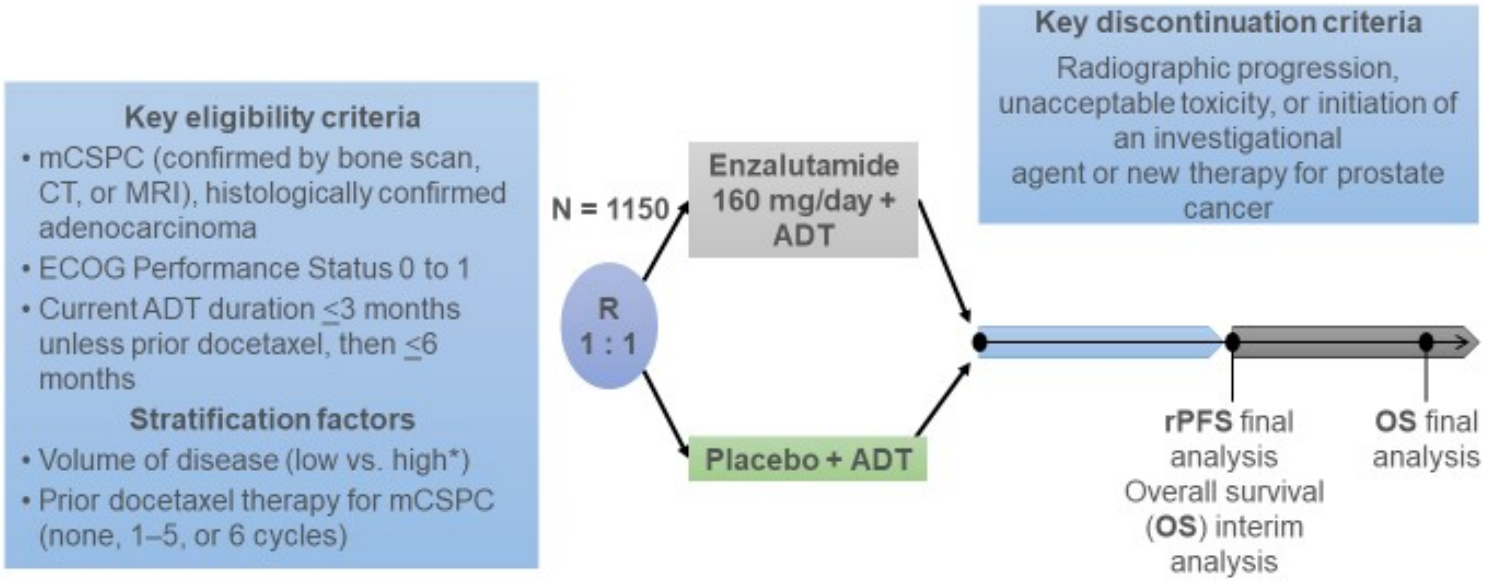


Rush HL, ASCO GU 2020

Comparative QOL randomized contemporaneously to docetaxel or abiraterone in the STAMPEDE trial

Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

ARCHES Study Design



Armstrong, Andrew J., et al. "ARCHES: a randomized, phase III study of androgen deprivation therapy with enzalutamide or placebo in men with metastatic hormone-sensitive prostate cancer." Journal of Clinical Oncology 37.32 (2019): 2974-2986.

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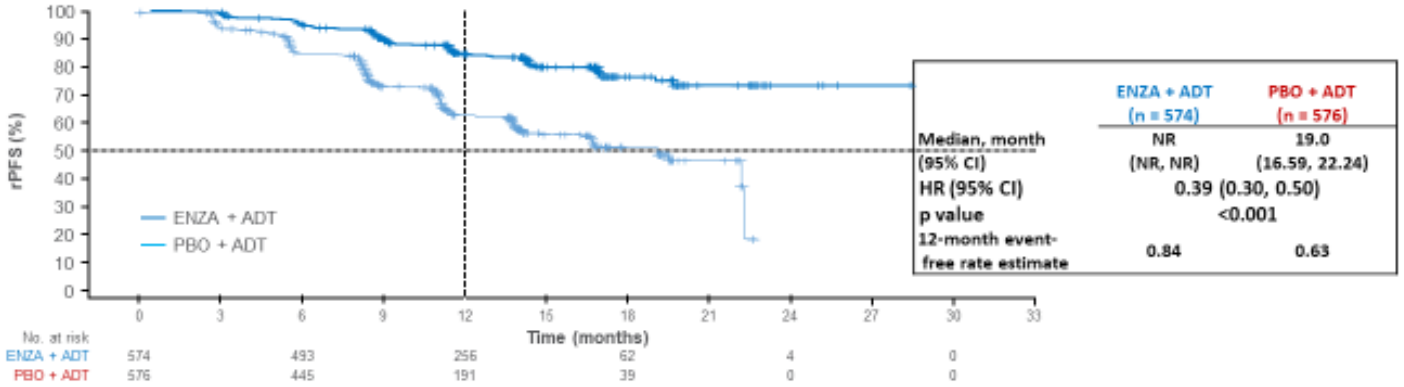
Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

Primary endpoint: rPFS



	ENZA + ADT (n = 574)	PBO + ADT (n = 576)
Median, month (95% CI)	NR (NR, NR)	19.0 (16.59, 22.24)
HR (95% CI)	0.39 (0.30, 0.50)	
p value	<0.001	
12-month event-free rate estimate	0.84	0.63

Enzalutamide with ADT significantly reduced the risk of metastatic progression or death over time versus placebo plus ADT in men with mCSPC

- Median follow-up time is 14.4 months; median duration of therapy was 12.8 (range 0.2–26.6) months for enzalutamide + ADT and 11.6 (range 0.2–24.6) months for placebo + ADT

Armstrong, Andrew J., et al. "ARCHES: a randomized, phase III study of androgen deprivation therapy with enzalutamide or placebo in men with metastatic hormone-sensitive prostate cancer." Journal of Clinical Oncology 37.32 (2019): 2974-2986.

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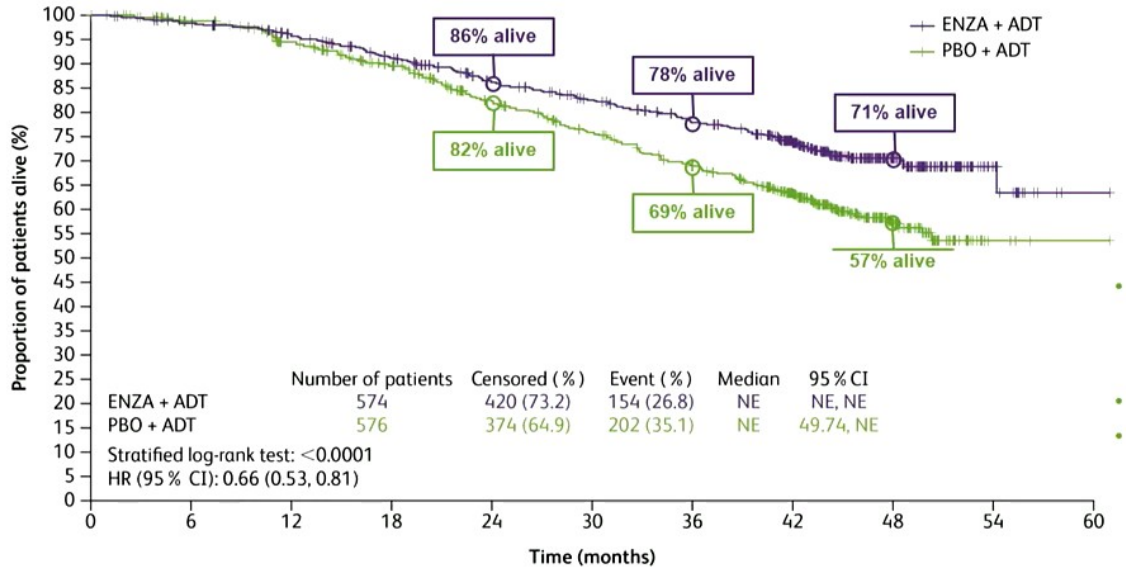
Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

ARCHES Overall survival (ITT)



Patients at risk

ENZA + ADT	574	559	535	498	457	427	396	316	120	17	1
PBO + ADT	576	548	511	468	404	363	322	232	80	4	1

ADT=androgen deprivation therapy; CI=confidence interval; ENZA=enzalutamide; HR=hazard ratio; ITT=intent-to-treat; NE=not evaluable; PBO=placebo

Armstrong et al ESMO 2021

- As of May 28, 2021: 356 deaths (enzalutamide plus ADT, 154; placebo plus ADT, 202) were observed
- Median follow-up time: 44.6 mo
- Median treatment duration:
  - Enzalutamide plus ADT: 40.2 mo
  - Placebo plus ADT: 13.8 mo
  - Placebo plus ADT crossover: 23.9 mo

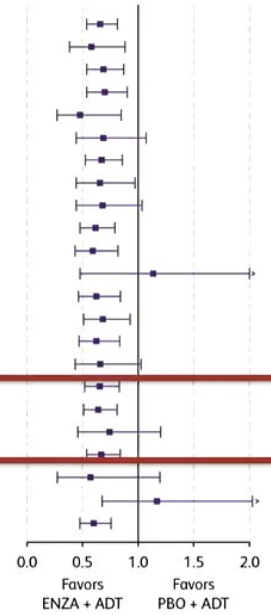
2021 ESMO congress

Discussant Eleni Efstathiou MD PhD

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

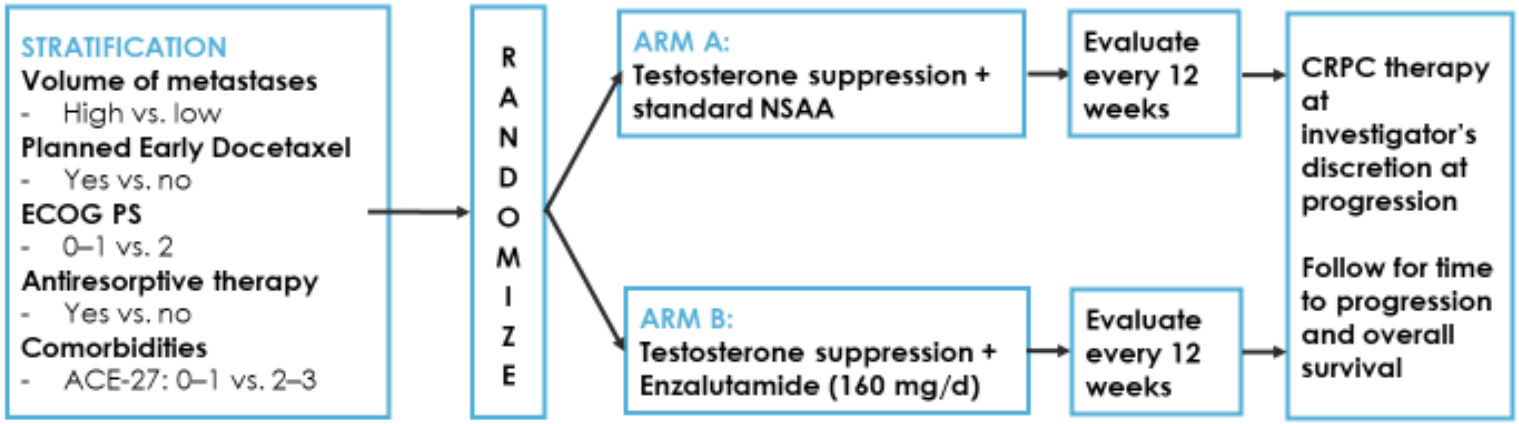
2021 ESMO congress

Discussant Eleni Efstathiou MD PhD

Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

ENZAMET: Enzalutamide in mHSPC

"All-comer" patient population



- Prior to randomization, testosterone suppression up to 12 weeks and 2 cycles of docetaxel were allowed
- Intermittent ADT and cyproterone were not allowed
- High volume: visceral metastases and/or 4 or more bone metastases (at least one beyond pelvis and vertebral column)

Davis, I et al. Engl J Med. 2019 Jul 11;381(2):121-131.

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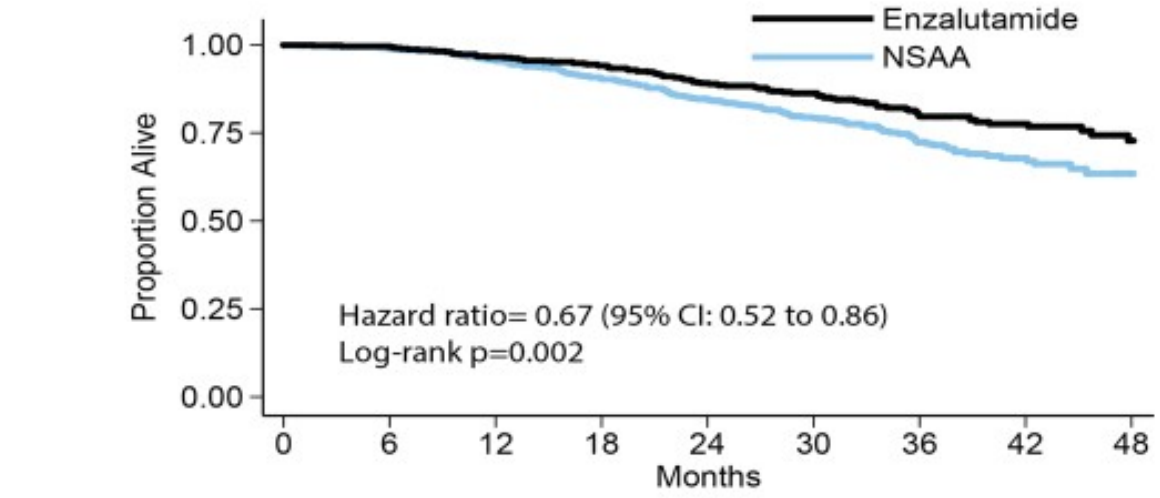
Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

ENZAMET: Enzalutamide in all-comers



Number at risk

NSAA	562	551	531	501	452	311	174	86	32
Enzalutamide	563	558	541	527	480	340	189	106	45

Davis, I et al. Engl J Med. 2019 Jul 11;381(2):121-131.

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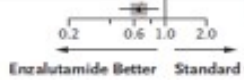
Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

Sub-group analysis of overall survival

Subgroup	Enzalutamide	Standard Care	Hazard Ratio (95% CI)	P Value for Interaction	Adjusted P Value
	no. of events/total no.				
All patients	102/563	143/562	0.67 (0.52–0.86)		
Volume of disease				0.04	0.14
Low	22/272	46/265	0.43 (0.26–0.72)		
High	80/291	97/297	0.80 (0.59–1.07)		
Early docetaxel planned				0.04	0.14
Yes	52/254	55/249	0.90 (0.62–1.31)		
No	50/309	88/313	0.53 (0.37–0.75)		
ACE-27 score				0.73	0.81
2 or 3	31/141	42/143	0.73 (0.46–1.16)		
0 or 1	71/422	101/419	0.65 (0.48–0.88)		
Antiresorptive therapy				0.006	0.06
Yes	17/55	11/58	1.77 (0.83–3.77)		
No	85/508	132/504	0.59 (0.45–0.77)		
Region				0.25	0.42
Ireland and United Kingdom	22/102	22/93	1.04 (0.57–1.88)		
North America	21/117	31/129	0.72 (0.41–1.25)		
Australia and New Zealand	59/344	90/340	0.58 (0.42–0.81)		
Gleason score				0.66	0.81
≤7	13/152	23/163	0.59 (0.30–1.16)		
8 to 10	66/335	84/321	0.70 (0.50–0.96)		
ECOG performance status				0.96	0.96
1 or 2	44/158	59/157	0.66 (0.45–0.98)		
0	58/405	84/405	0.66 (0.47–0.92)		
Age				0.16	0.33
≥70 yr	47/257	79/257	0.56 (0.39–0.81)		
<70 yr	55/306	64/305	0.81 (0.56–1.15)		
Visceral metastases				0.16	0.33
Yes	18/62	18/67	1.05 (0.54–2.02)		
No	84/501	125/495	0.62 (0.47–0.82)		
Previous local treatment				0.72	0.81
Yes	39/238	49/235	0.72 (0.47–1.09)		
No	63/325	94/327	0.65 (0.47–0.89)		



Davis, Ian D., et al. "Enzalutamide with standard first-line therapy in metastatic prostate cancer." New England Journal of Medicine 381.2 (2019): 121-131.

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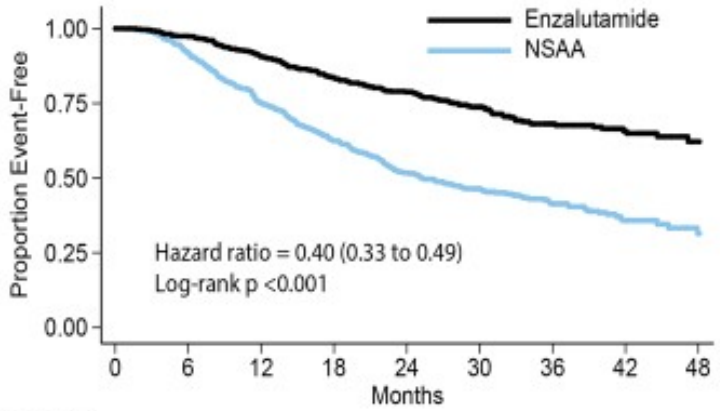
Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

ENZAMET: Secondary endpoints

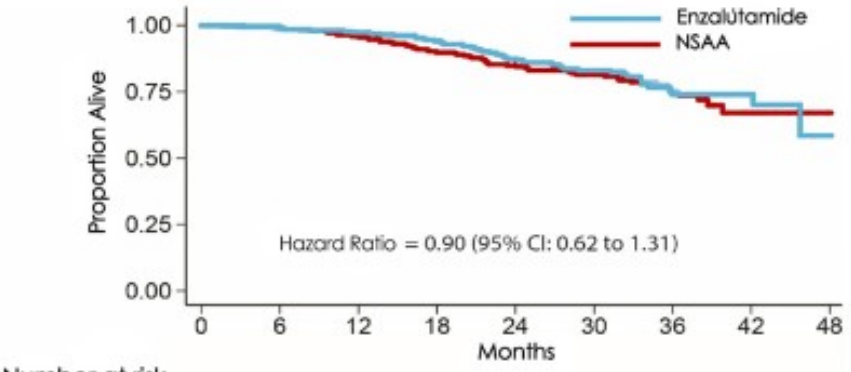
Progression free survival



Number at risk

NSAA	562	512	418	346	272	182	96	50	17
Enzalutamide	563	547	507	468	424	284	156	84	36

Overall survival: combined docetaxel



Number at risk

NSAA	249	241	235	220	203	135	56	13	2
Enzalutamide	254	252	246	238	?	139	54	19	3

Davis, I et al. Engl J Med. 2019 Jul 11;381(2):121-131.

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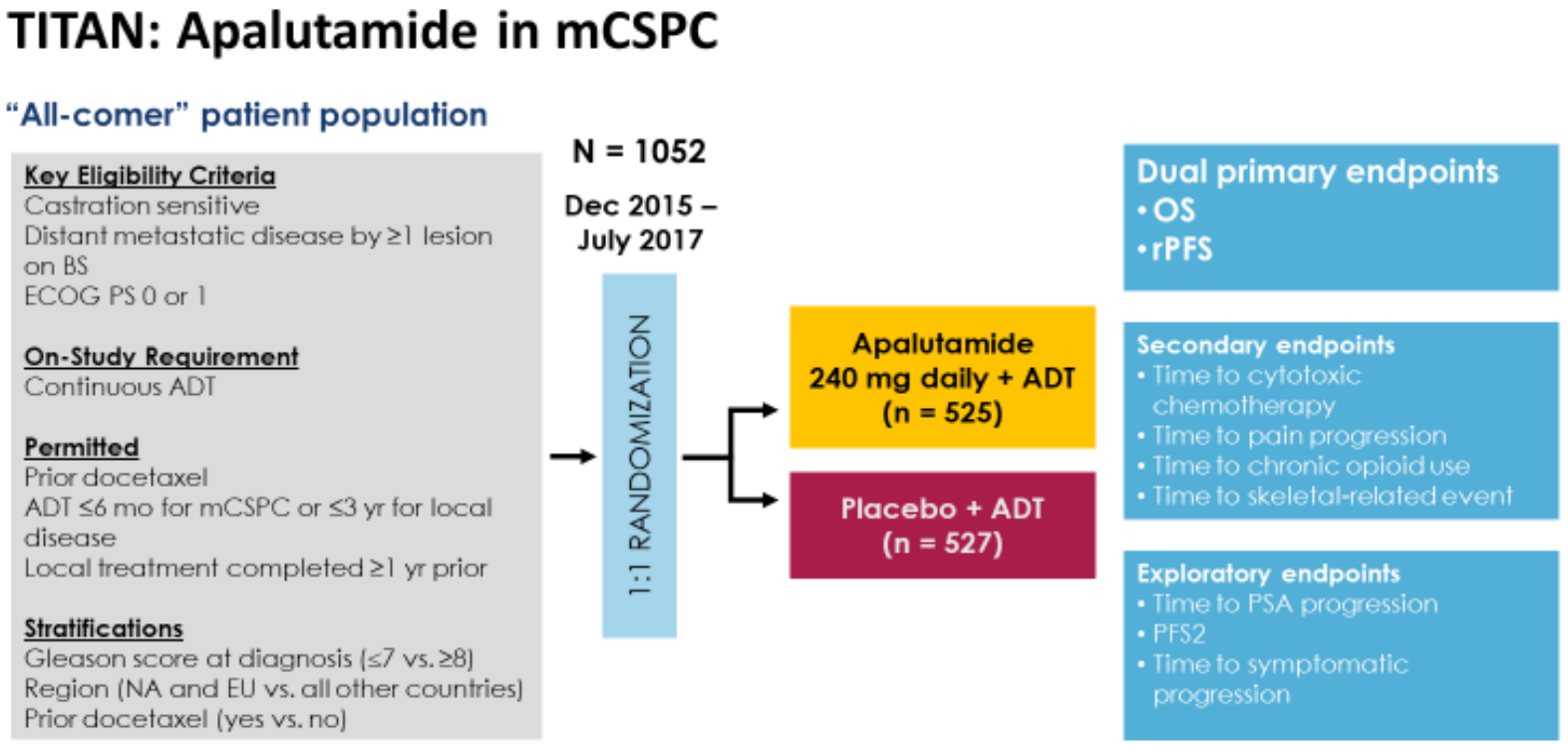
Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi



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

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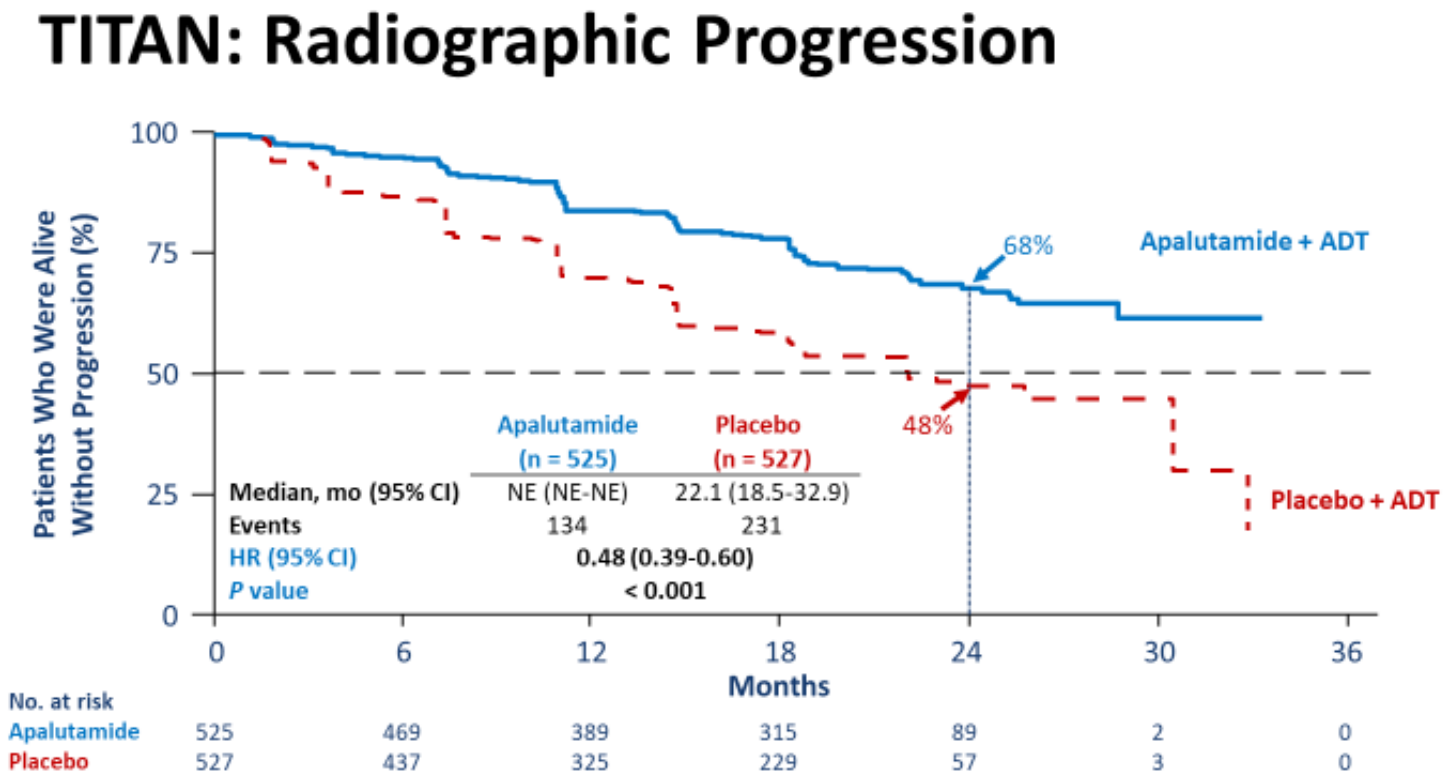
Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi



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

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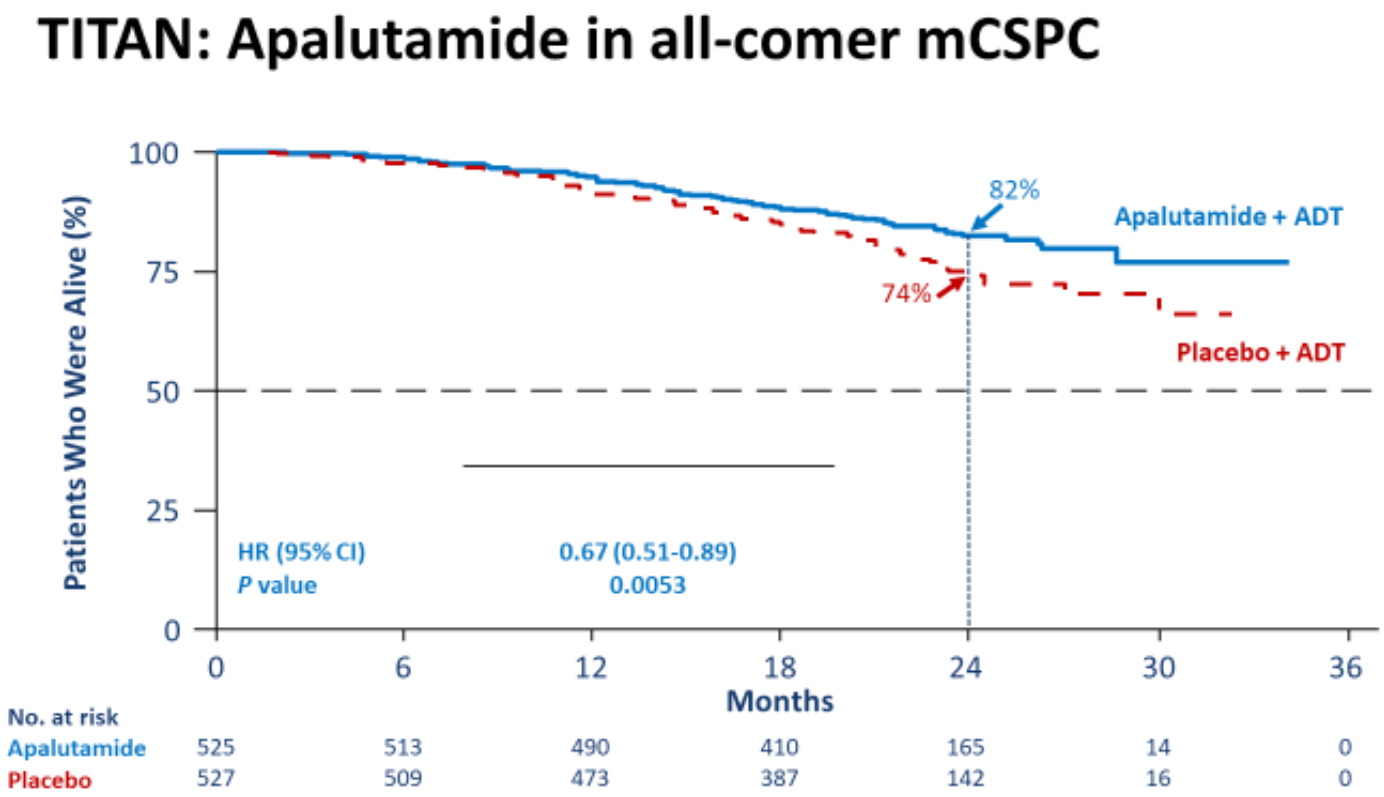
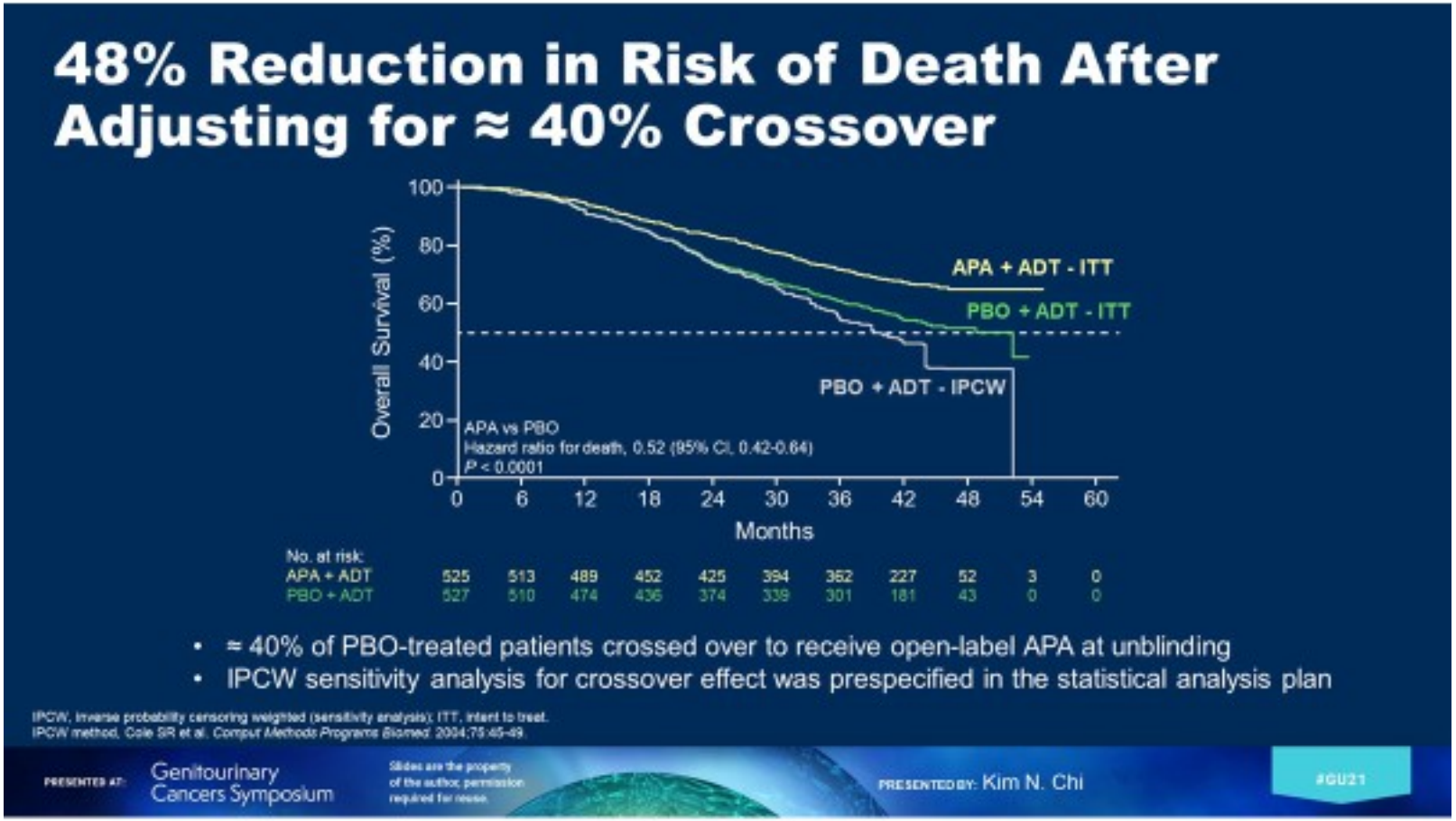
Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi



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

Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi



Presented By Kim Chi at 2021 Genitourinary Cancers Symposium

Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

TITAN: Sub-group analysis of overall survival

Variable		Hazard Ratio (95% CI)	Events (n/n) Apalutamide + ADT	Events (n/n) Placebo + ADT
All patients		0.68 (0.51-0.90)	83/525	117/527
Baseline ECOG PS	0	0.71 (0.47-1.05)	41/328	60/348
	1	0.59 (0.40-0.89)	42/197	57/178
Geographic region	EU/NA	0.71 (0.40-1.25)	21/173	29/173
	Other	0.66 (0.48-0.91)	62/352	88/354
Bone metastasis only at baseline	YES	0.47 (0.30-0.75)	28/289	53/269
	NO	0.88 (0.61-1.26)	55/236	64/258
Visceral disease and bone metastasis at baseline	YES	0.99 (0.55-1.77)	20/56	25/72
	NO	0.63 (0.46-0.87)	63/469	92/455
Prior docetaxel use	YES	1.27 (0.52-3.09)	11/58	9/55
	NO	0.63 (0.47-0.85)	72/467	108/472
Age, yr	< 65	0.56 (0.33-0.94)	21/149	43/182
	65-74	0.73 (0.48-1.10)	42/243	51/232
	≥ 75	0.74 (0.41-1.35)	20/133	23/113
Disease volume	High	0.68 (0.50-0.92)	69/325	97/335
	Low	0.67 (0.34-1.32)	14/200	20/192
Metastasis stage at initial diagnosis	M0	0.40 (0.15-1.03)	7/85	11/59
	M1	0.72 (0.53-0.98)	71/411	101/441

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

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Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

VIRTUAL 2020 ESMO congress

Treatment options for mHSPC with OS data

Agent	Trial, Publication Year	Comparator	Phase; n	OS endpoint: HR	Treatment vs. Control
Abiraterone Acetate/ Prednisolone	**LATITUDE 2019** [1] **(f-up 4.3 years)**	ADT + Placebo	III; 1199	**HR: 0.66** (95% CI: 0.56-0.78) p< .0001	53.3 vs 36.5 mo
	STAMPEDE 2017 [2] **M1 (f-up 3.3 years)**	ADT alone	III; 1003	**HR 0.61** (95%CI 0.49 to 0.75)	83% vs 73% alive at 3 years
	STAMPEDE 2020 [3] **M1 (f-up 6.1 years)**	ADT alone	III; 1003	**HR 0.60** (95%CI 0.50 to 0.71) p< .0000000003	Med 6.6 vs 3.8 years
Enzalutamide	ENZAMET 2019 [4]	ADT + Nonsteroidal ART	III; 1125	**HR: 0.67** (95% CI 0.52-0.86) p< .002	80% vs 72% alive at 3 years
Apalutamide	TITAN 2019 [5]	ADT + Placebo	III; 1052	**HR: 0.67** (95% CI: 0.51-0.89) p< .005	82.4 vs 73.5% alive at 2 years
Docetaxel	CHAARTED 2015 [6]	ADT alone	III; 790	**HR: 0.61** (95% CI: 0.47-0.80) p< .001	57.6 vs 44 mo
	GETUG-AFU 2013 [7]	ADT alone	III; 192		58.9 vs 54.2 mo (NS)
	STAMPEDE 2015 [8]	ADT alone	III; 1086	**HR: 0.81** (95% CI: 0.69-0.95) p< .009	

[1] Fizazi, K. et al., Lancet Oncol 2019, [2] James, N.D. et al., NEJM 2017, [3] James, N.D. et al., ESMO 2020, [4] Davis, I.D. et al. NEJM 2019, [5] Chi, K.N. et al., NEJM 2019, [6] Sweeney, C.J. et al., NEJM 2015, [7] Gravis, G. et al., Lancet Oncol 2013, [8] James, N.D., Lancet, 2016

Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

VIRTUAL 2020 ESMO congress

Overall Survival in M1 CSPC trials (from best to worse HR)

Trial	HR for OS	LP treatment	Follow-up (mo)
STAMPEDE Abi	0.61 (0.49-0.75)	310/957 (32%)	40
LATITUDE	0.66 (0.56-0.78)	345/602 (57%)	52
TITAN	0.67 (0.51-0.89)	165/527 (31%)	23
ENZAMET	0.67 (0.52-0.86)	271/562 (48%)	34
CHAARTED	0.72 (0.59-0.89)	187/393 (48%)	54
STAMPEDE Doc+ZA	0.79 (0.66-0.96)	372/1184 (31%)	43
ARCHES	0.81 (0.53-1.25)	<133/576 (<23%)	14
STAMPEDE Doc	0.81 (0.69-0.95)	372/1184 (31%)	?
GETUG-15	0.88 (0.68-1.14)	127/193 (66%)	84

Kyriakopoulos CE, J Clin Oncol 2018; Gravis G, Eur Urol 2015; Clarke N/James N, ESMO 2019, James N, Lancet 2016, Fizazi K, Lancet Oncol 2019, James N, NEJM 2019
Armstrong AJ, J Clin Oncol 2019, Chi K, NEJM 2019, Davis I, NEJM 2019

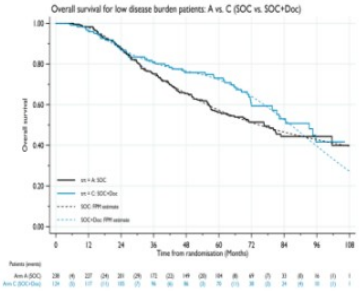
Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

VIRTUAL 2020 ESMO congress

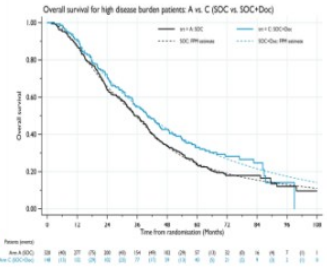
Should we count the metastases for decision making about systemic treatment? No !!!

Docetaxel

Low burden



High burden



Clarke N, Ann Oncol 2019

Hormonal agents

STAMPEDE (Abi)

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

TITAN (Apa)

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

ENZAMET (Enza)

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

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

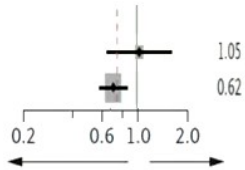
Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

Does type of metastasis matter in mHNPC?

Results from new hormonal treatments in mHNPC according visceral mets

ENZAMET

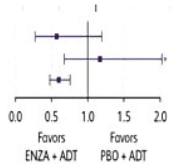
Subgroup	Enzalutamide (no. of events/total no.)	Standard Care (no. of events/total no.)	Hazard Ratio (95% CI)
Visceral metastases			
Yes	18/62	18/67	1.05 (0.54–2.02)
No	84/501	125/495	0.62 (0.47–0.82)



Enzalutamide Better Standard Care Better

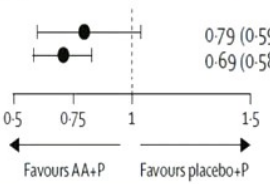
ARCHES

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)



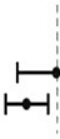
LATITUDE

Subgroup	Median (months) AA+P	Median (months) 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 (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

But these studies cannot be compared

- LATITUDE[1]: 100% newly diagnosed mHNPC
- STAMPEDE[2-3]: 94% patients newly diagnosed mHNPC (either ABI or DOC)
- TITAN[4]: 85% newly diagnosed mHNPC
- CHAARTED[5]: 73% newly diagnosed mHNPC
- GETUG 15[6]: 70% newly diagnosed mHNPC
- **ENZAMET[7]: 60% newly diagnosed mHNPC**
- **ARCHES[8]: 67% newly diagnosed mHNPC**

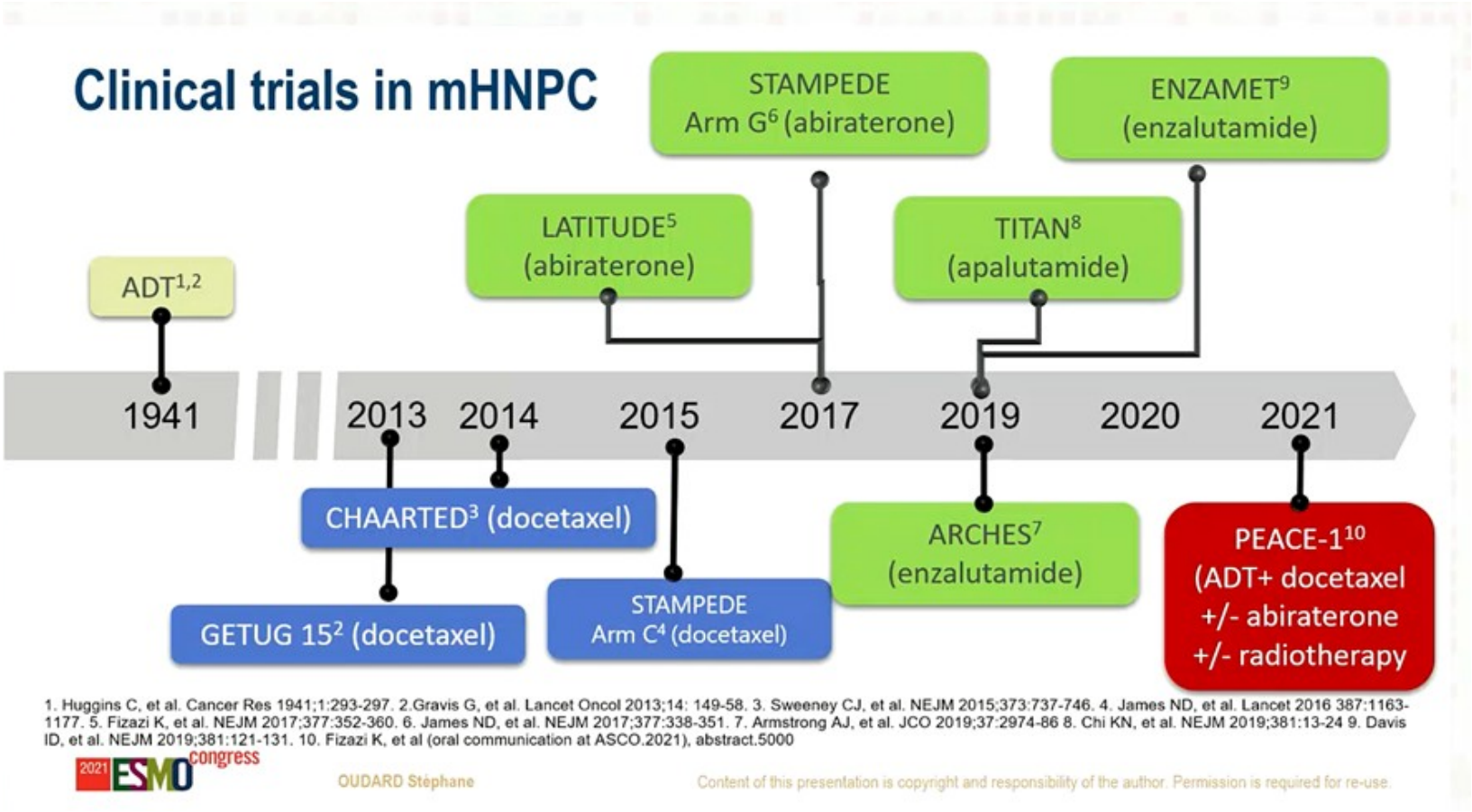
1. Fizazi K, et al. Lancet Oncol. 2019;20:686-700; 2. Clarke N, et al. Ann Oncol. 2019;30:1992-2003; 3. James ND, et al. NEJM 2017;377:338-51; 4. Chi KN, et al. NEJM 2019;381:13-24 & ASCO 2021; 5. Kyirakopoulos CE, et al. J Clin Oncol. 2018;36:1080-7; 6. Gravis G, et al. Eur Urol. 2016;70:256-62; 7. Davis ID, et al. NEJM. 2019;381:121-31; 8. Armstrong A, et al. J Clin Oncol. 2019;37:2974-86 & ESMO 2021 LBA25.

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



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

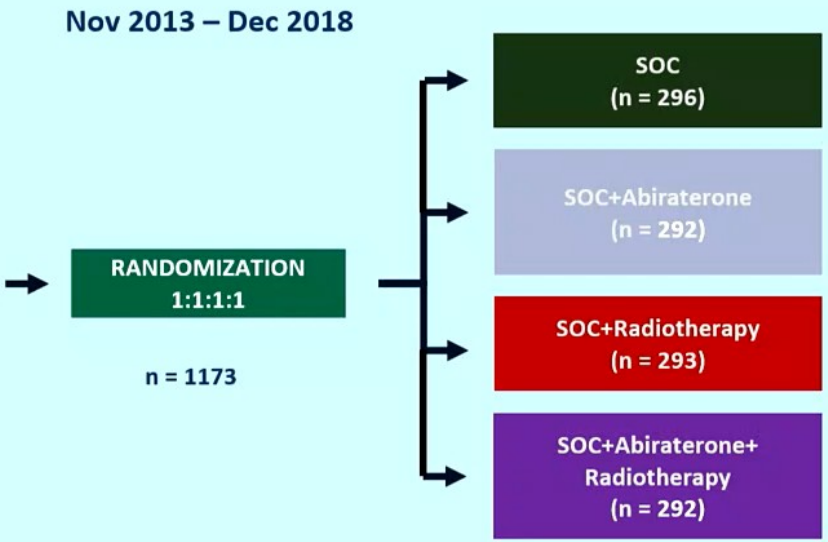
Design of PEACE-1 (2x2)

Key Eligibility Criteria
De novo mCSPC
Distant metastatic disease by ≥ 1 lesion on bone scan and/or CT scan
ECOG PS 0 -2

On-Study Requirement
Continuous ADT

Permitted
ADT ≤ 3 months

Stratification
ECOG PS (0 vs 1-2)
Metastatic sites (LN vs bone vs visceral)
Type of castration (orchidectomy vs LHRH agonist vs LHRH antagonist)
Docetaxel (yes vs no)



ECOG PS, Eastern Cooperative Oncology Group performance status

Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

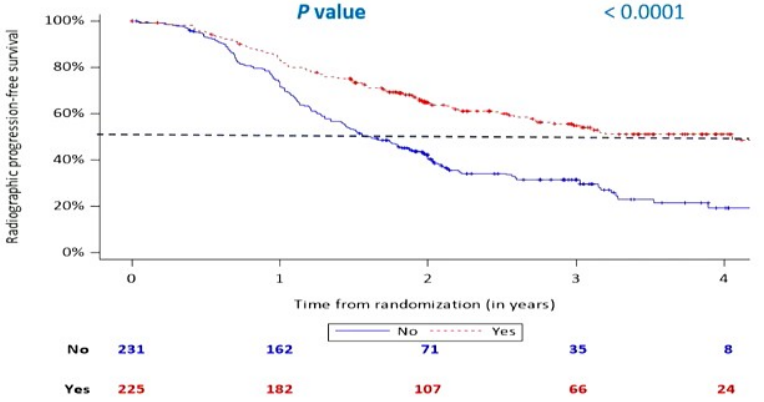
ADT+docetaxel (+/- RXT) population: rPFS by metastatic burden

unicancer

GUSTAVE ROUSSY CANCER CAMPUS GRAND PARIS

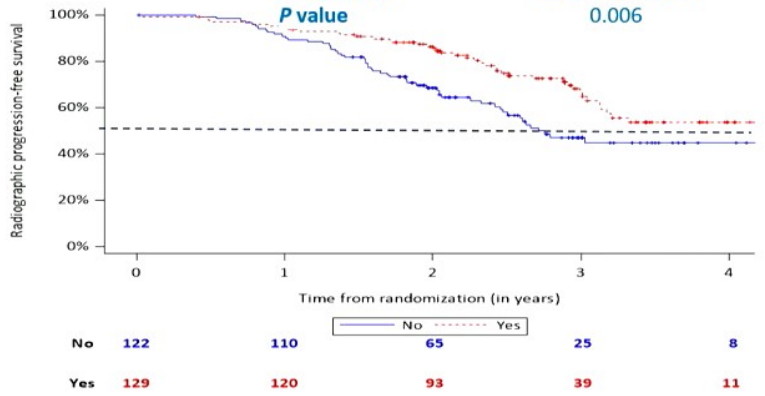
« High Volume »

	SOC+Abi (n = 225)	SOC (n = 231)
Median, y (95% CI)	4.1 (2.7-NE)	1.6 (1.4-2.0)
Events	97	156
HR (95% CI)*	0.47 (0.36-0.60)	
P value	< 0.0001	



« Low Volume »

	SOC+Abi (n = 129)	SOC (n = 122)
Median, y (95% CI)	NE (3.1-NE)	2.7 (2.5-NE)
Events	41	55
HR (95% CI)*	0.58 (0.39-0.87)	
P value	0.006	



*Adjusted on stratification parameters (RXT, PS, type of castration, metastatic burden)

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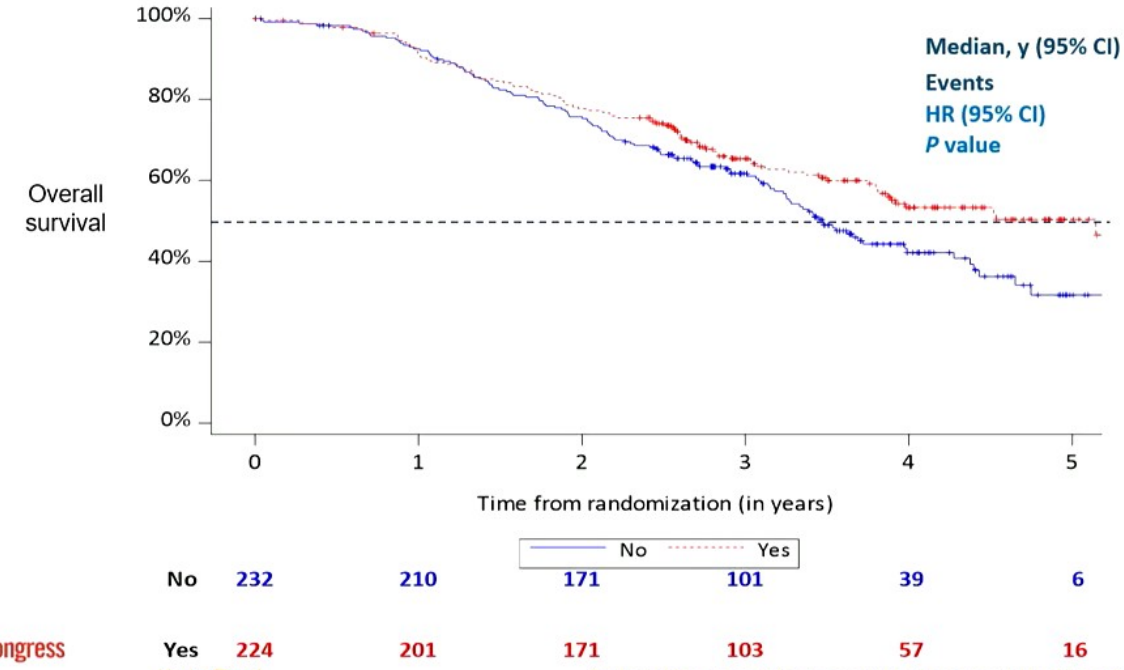
Karim Fizazi

Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

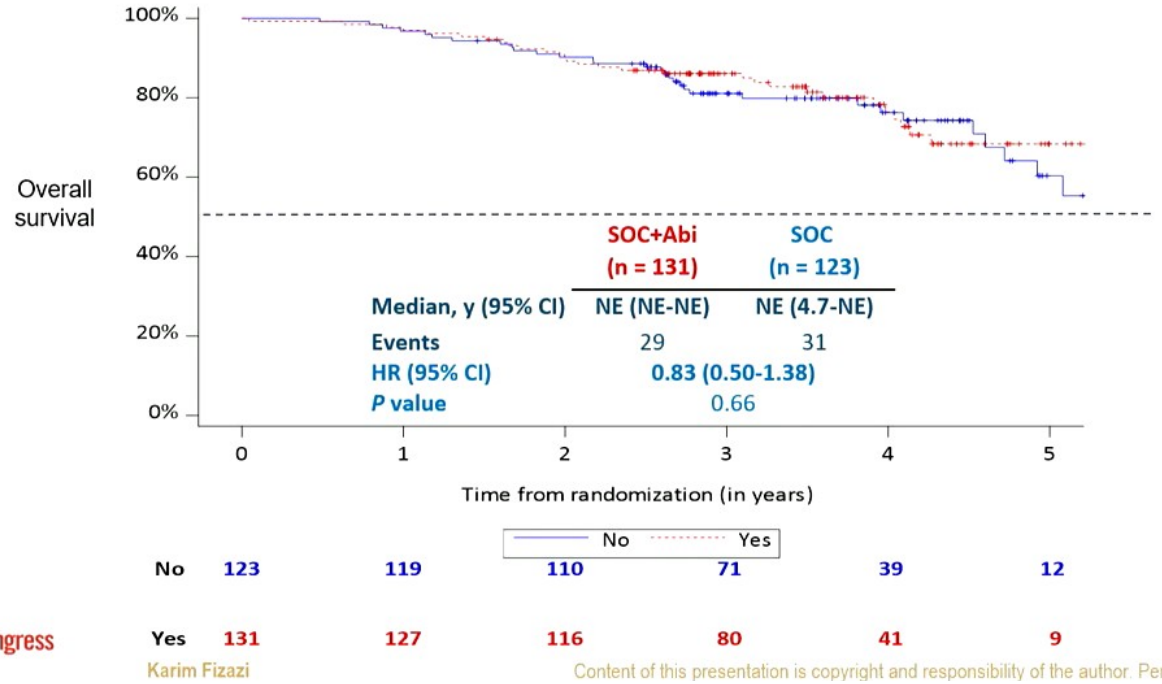
OS with Abiraterone in the ADT+docetaxel (+/-RXT): High-volume patients



	SOC+Abi (n = 224)	SOC (n = 232)
Median, y (95% CI)	5.1 (3.8-NE)	3.5 (3.2-4.0)
Events	92	120
HR (95% CI)	0.72 (0.55-0.95)	
P value	0.019	

Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

OS with Abiraterone in the ADT+docetaxel (+/-RXT): Low-volume patients



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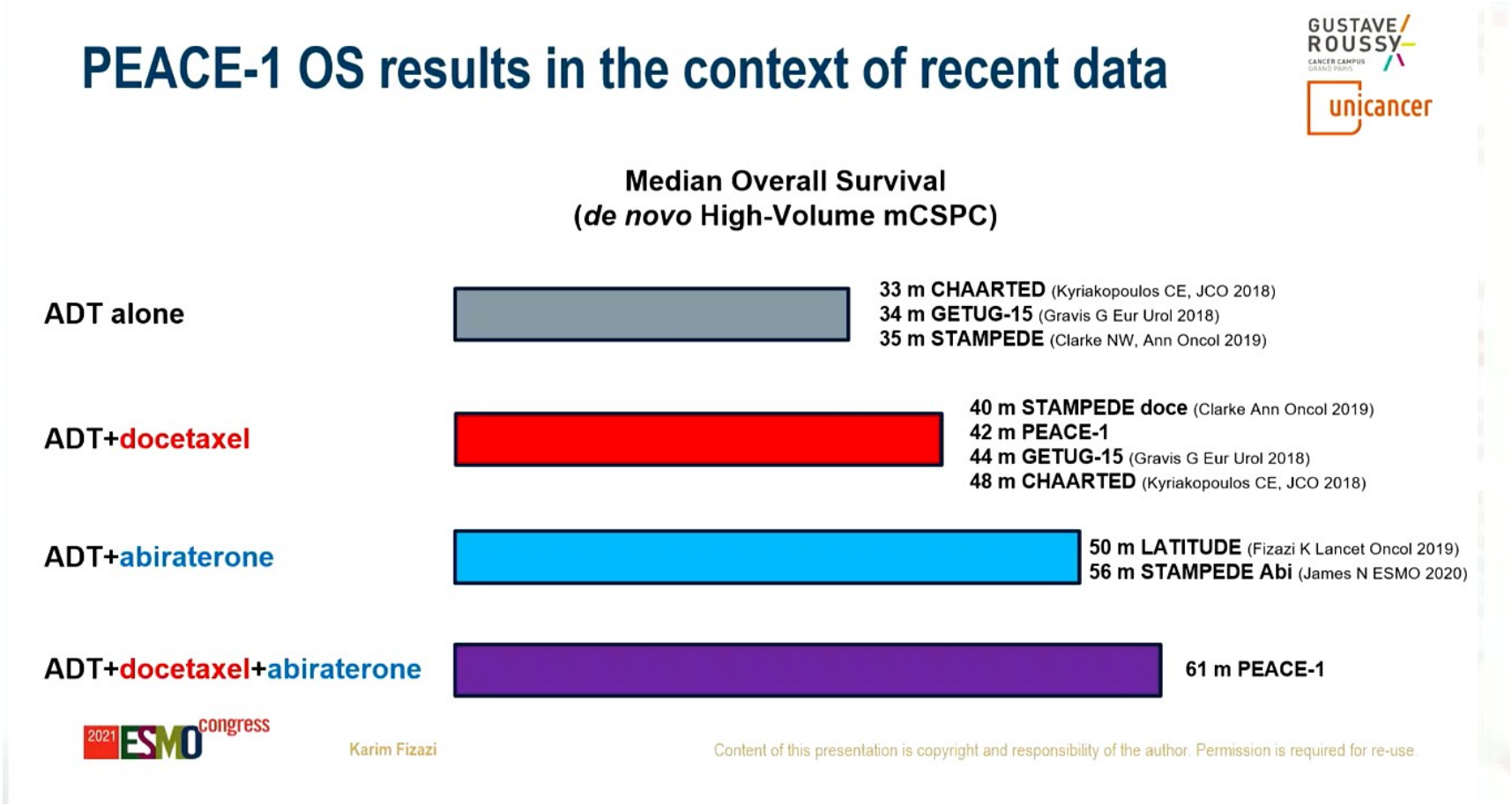
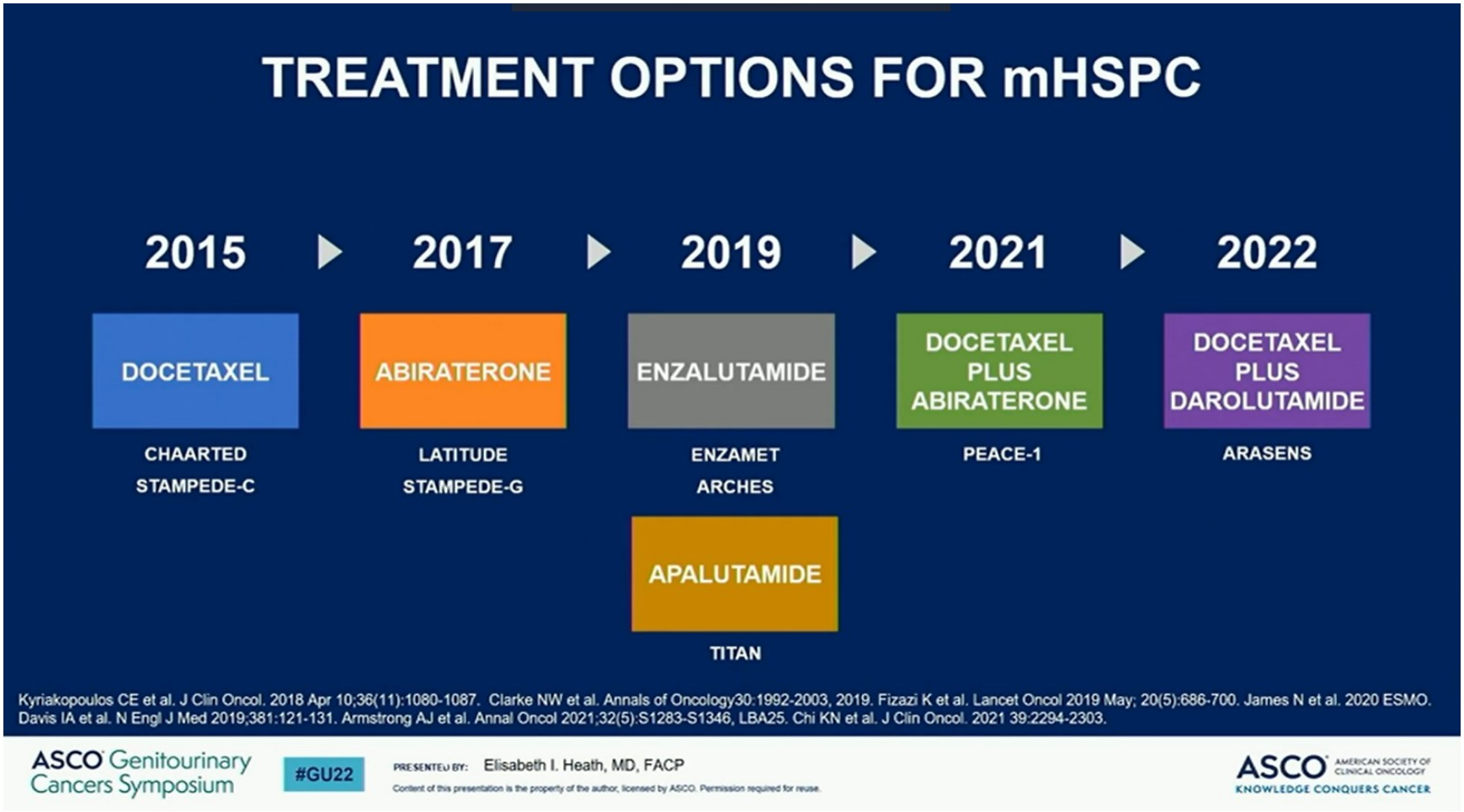
Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi



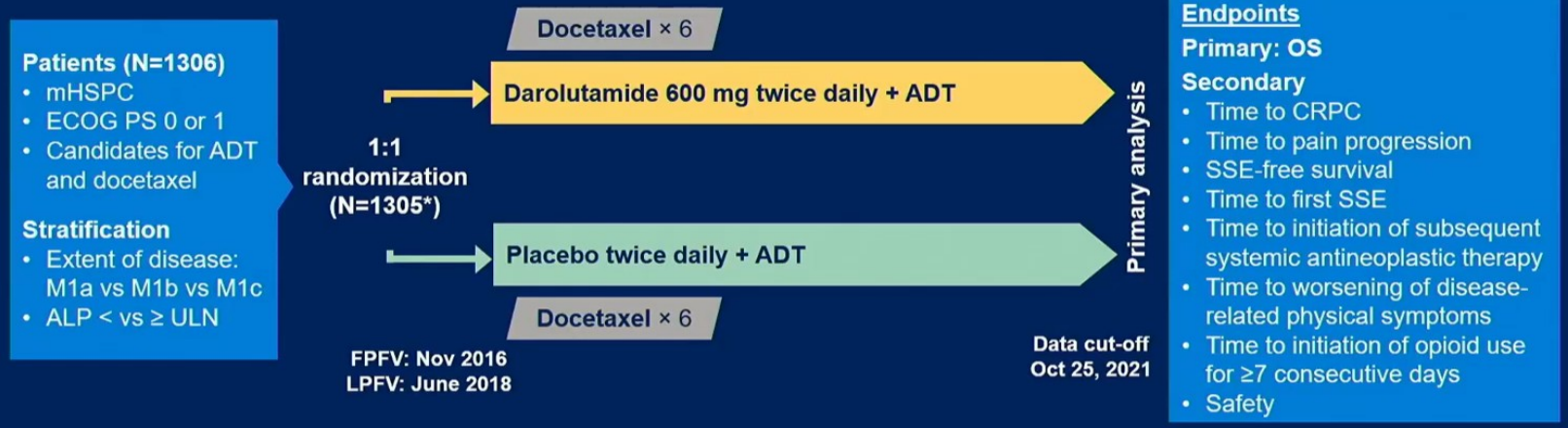
Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi



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.

PRESENTED BY: Matthew R. Smith, MD, PhD

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)

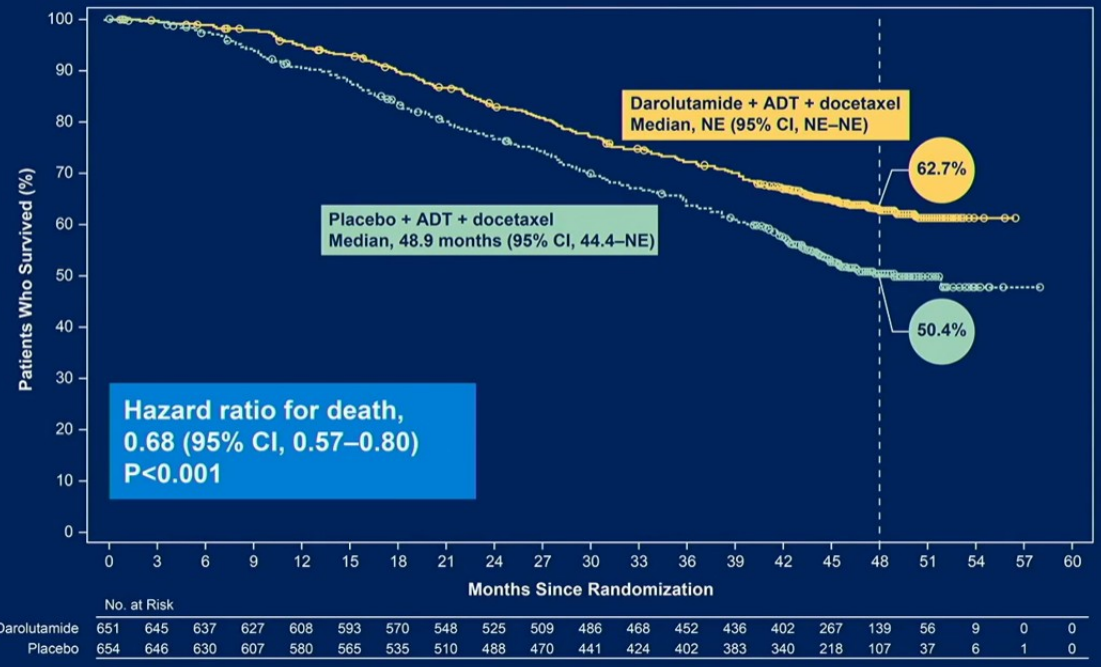
*One patient randomized to placebo but who received darolutamide was included in the placebo group for the full analysis set. †Centrally assessed; samples were collected while patients were receiving ADT. PSA, prostate-specific antigen.

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

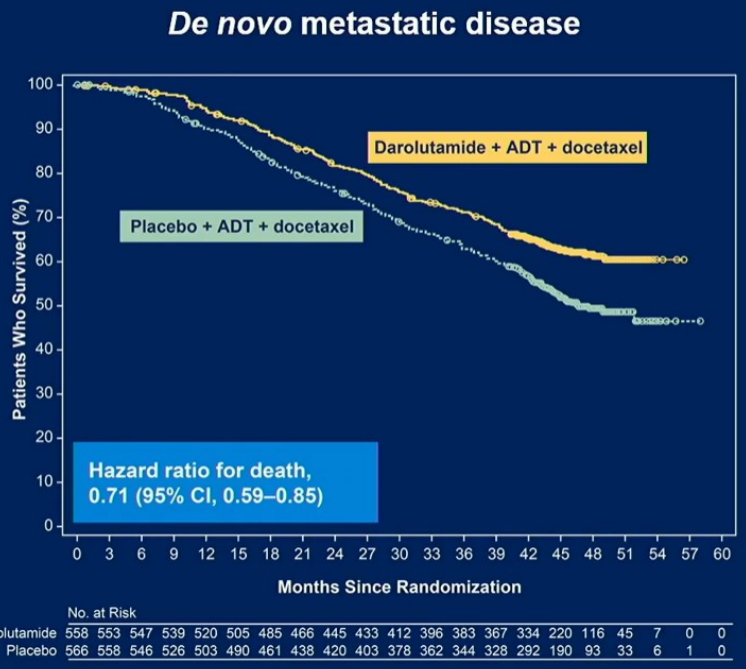
Darolutamide	651	645	637	627	608	593	570	548	525	509	486	468	452	436	402	267	139	56	9	0	0
Placebo	654	646	630	607	580	565	535	510	488	470	441	424	402	383	340	218	107	37	6	1	0

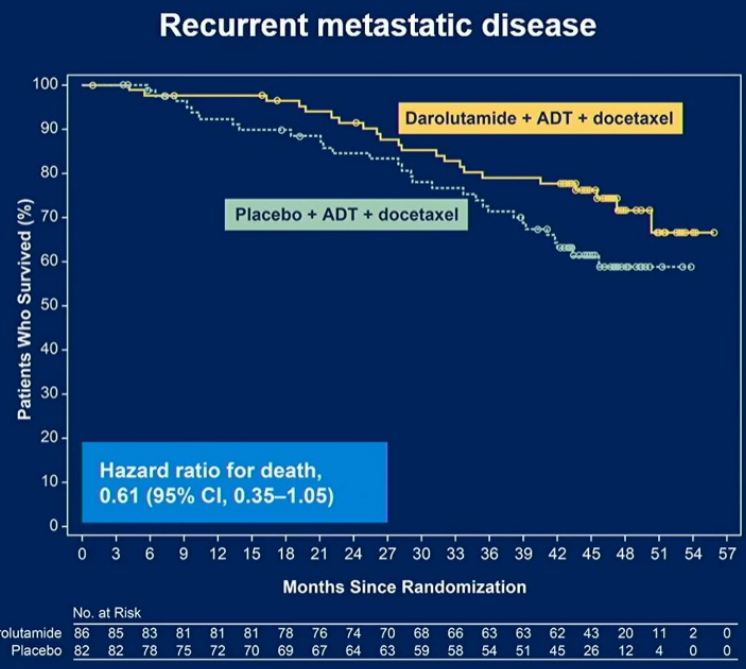
*Primary analysis occurred after 533 deaths (darolutamide, 229; placebo, 304). CI, confidence interval; NE, not estimable.

PRESENTED BY: Matthew R. Smith, MD, PhD

Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

Overall Survival By Metastatic Stage at Initial Diagnosis

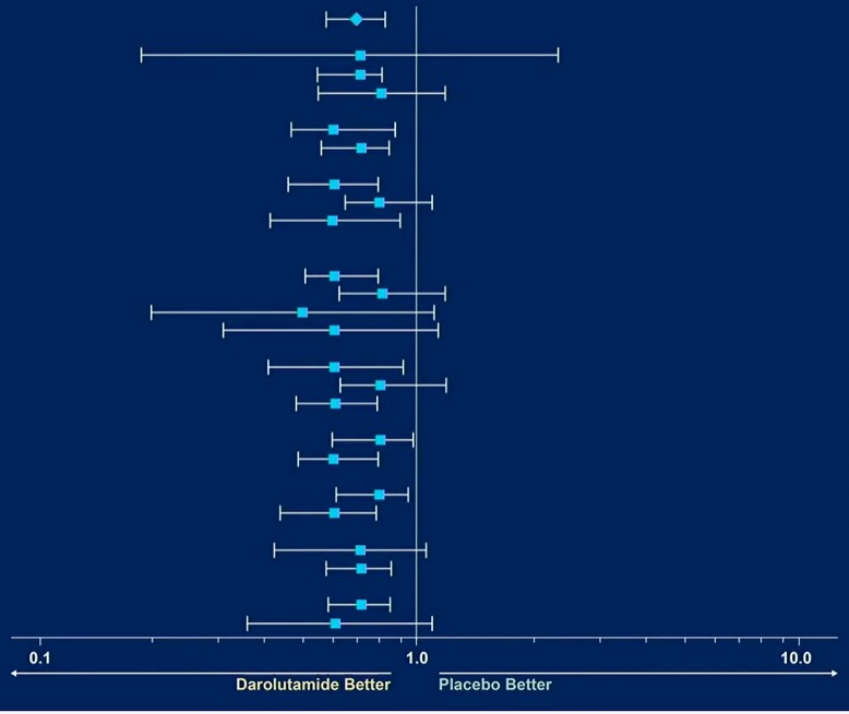




Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

ARASENS Overall Survival: Subgroup Analyses

	Darolutamide + ADT + Docetaxel No. of Events/No. of Patients	Placebo + ADT + Docetaxel No. of Events/No. of Patients	Hazard Ratio (95% CI)
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.

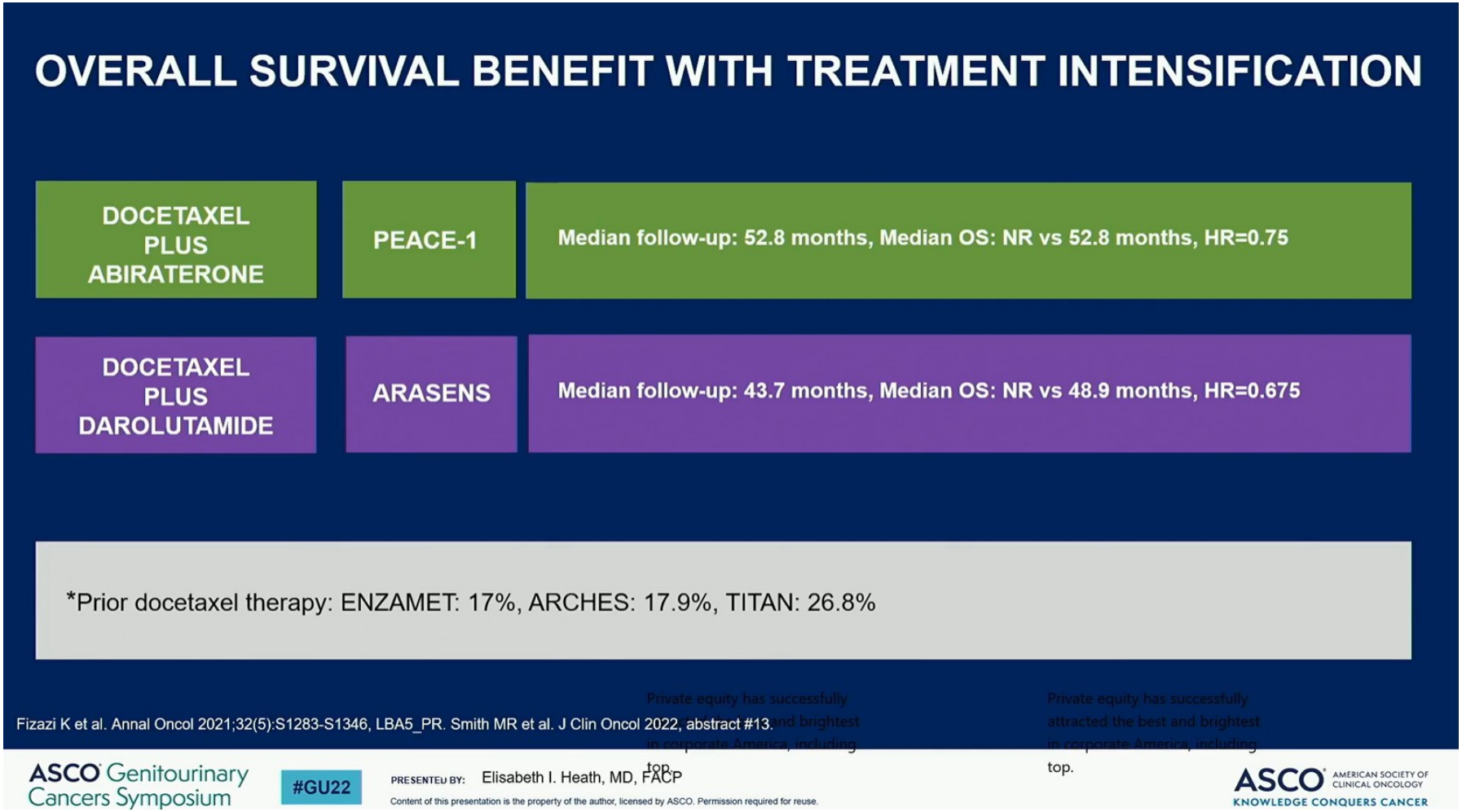
Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

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



Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

Clinical Considerations

Disease burden

- Volume of metastasis (low versus high)
  - Visceral or > 4 bone lesions with at least one beyond the vertebral bodies and pelvis

Disease stage

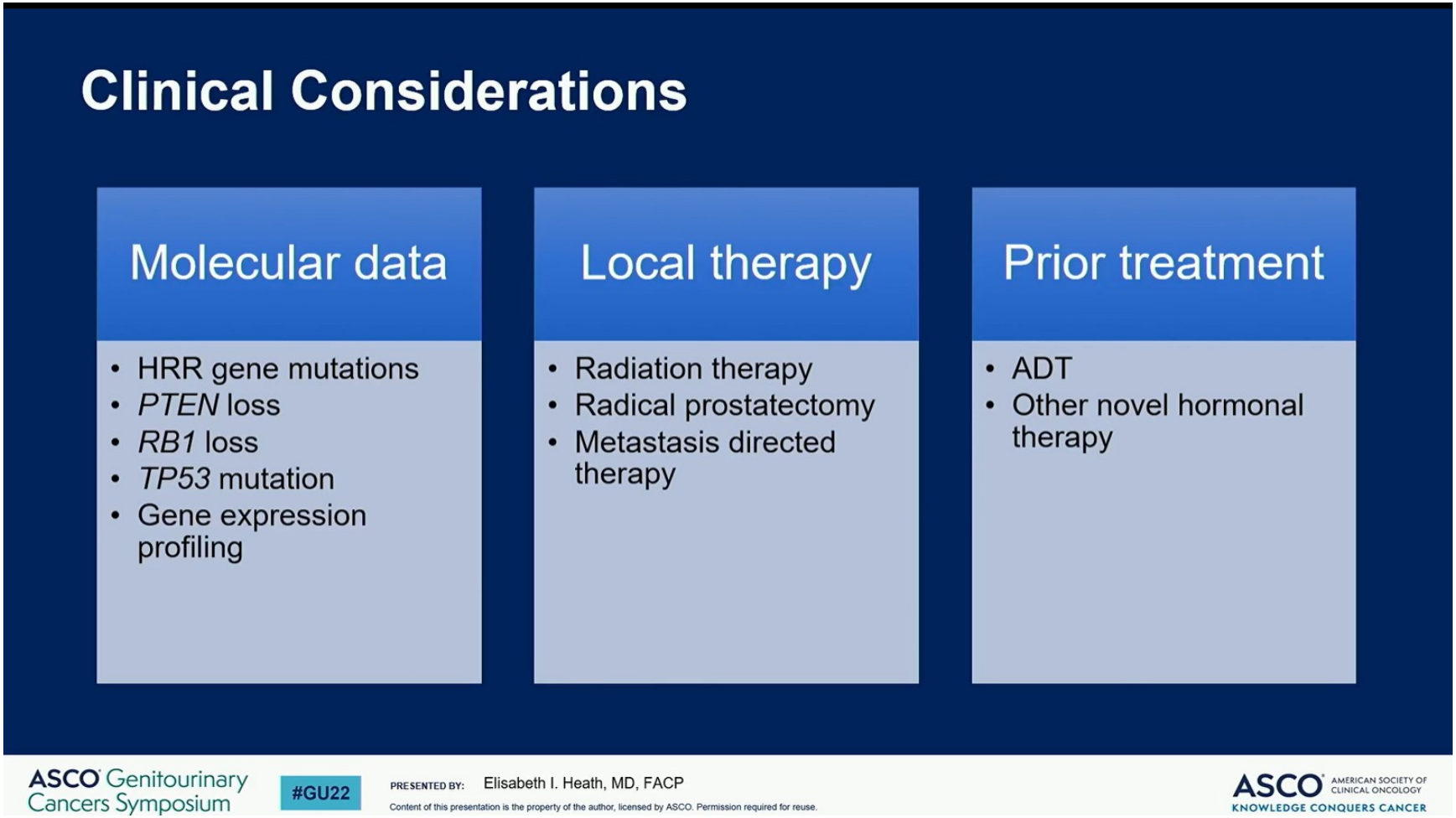
- M1a
  - Non-regional lymph nodes only
- M1b
  - Bone metastasis +/- lymph nodes
- M1c
  - Visceral metastasis +/- lymph nodes or bone metastasis

Disease presentation

- *De novo* metastatic versus recurrent disease

PRESENTED BY: Elisabeth I. Heath, MD, FACP

Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi



Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisi

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2022
Prostate Cancer

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