Metastatik Prostat Kanserinde Tedavi

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Bakırköy Dr. Sadi Konuk Eğitim ve Araştırma Hastanesi
Tıbbi Onkoloji

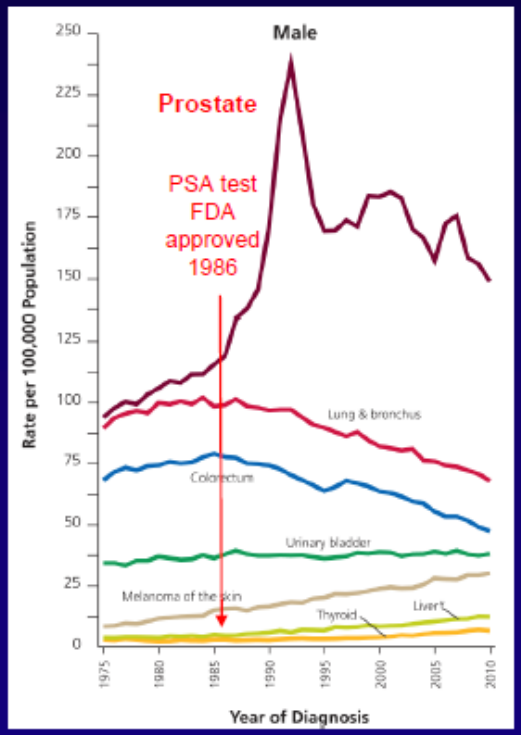
Sunum Planı

- Prostat Kanseri İnsidans ve Mortalite
- Hormon Duyarlı Metastatik Prostat Kanseri
- Hormon Duyarlı Metastatik Prostat Kanseri kemoterapinin yeri
- Kastrasyona Dirençli Prostat Kanserinde Tedavi
- Sonuç

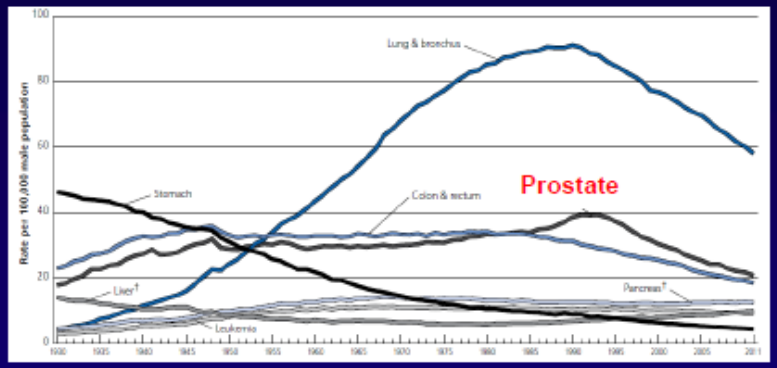
Prostat Kanseri İnsidans ve Mortalite

Changes in incidence and death rates

Incidence



Death rate



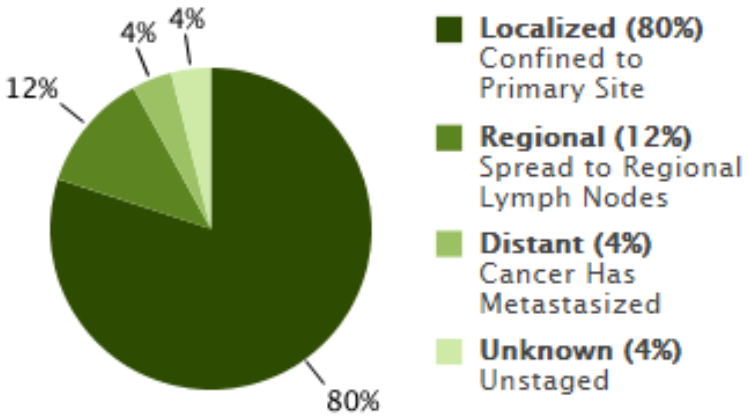
- Incidence peak see after PSA became available
- Declining death rates over past 25 years by 2-3% per year

CA: A Cancer Journal for Clinicians 2016

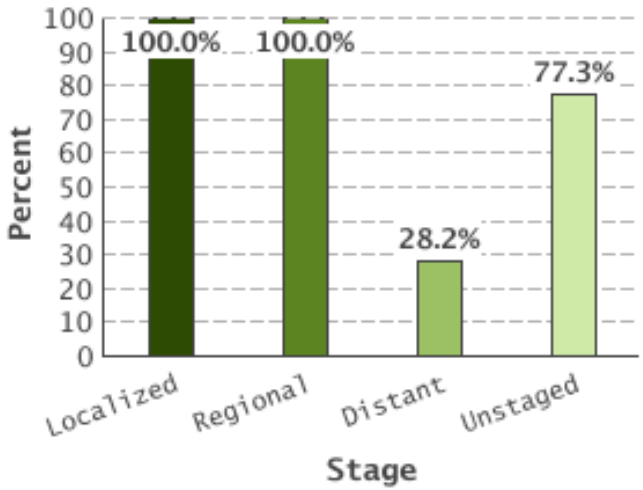
Prostat Kanseri İnsidans ve Mortalite

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

Percent of Cases by Stage

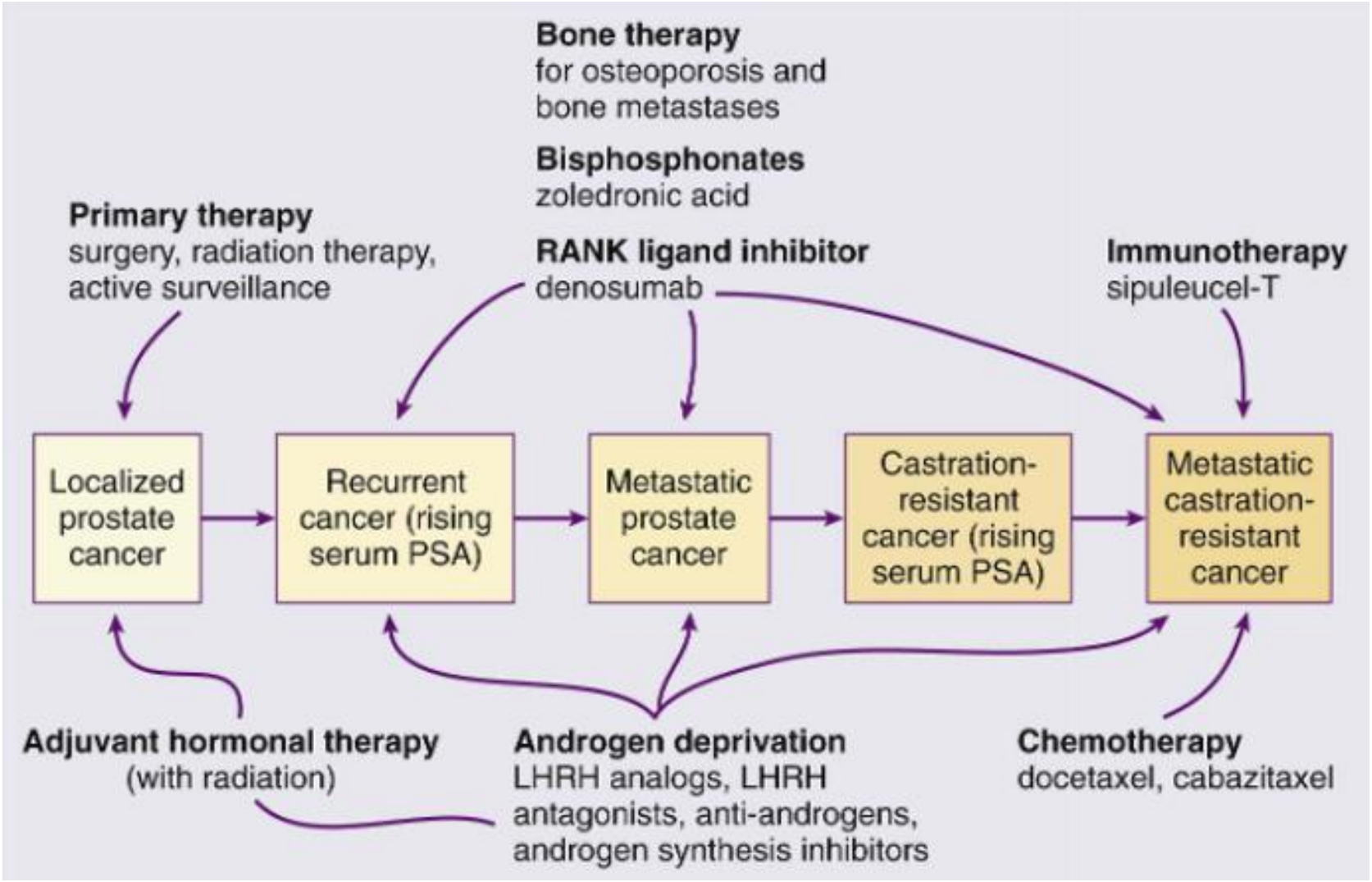


5-Year Relative Survival



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

Prostat Kanseri Tedavi Yaklaşımları



Şekil; Abeloff's Clinical Oncology, 10th edition

Hormon Duyarlı Metastatik Prostat Kanseri

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

Hormon Duyarlı Metastatik Prostat kanseri

Hormone sensitive metastatic, Overall survival SWOG 9346

Hussain et al NEJM 2013

Hormon Duyarlı Metastatik Prostat Kanseri

SWOG 9346 ; İntermittant vs. Continue

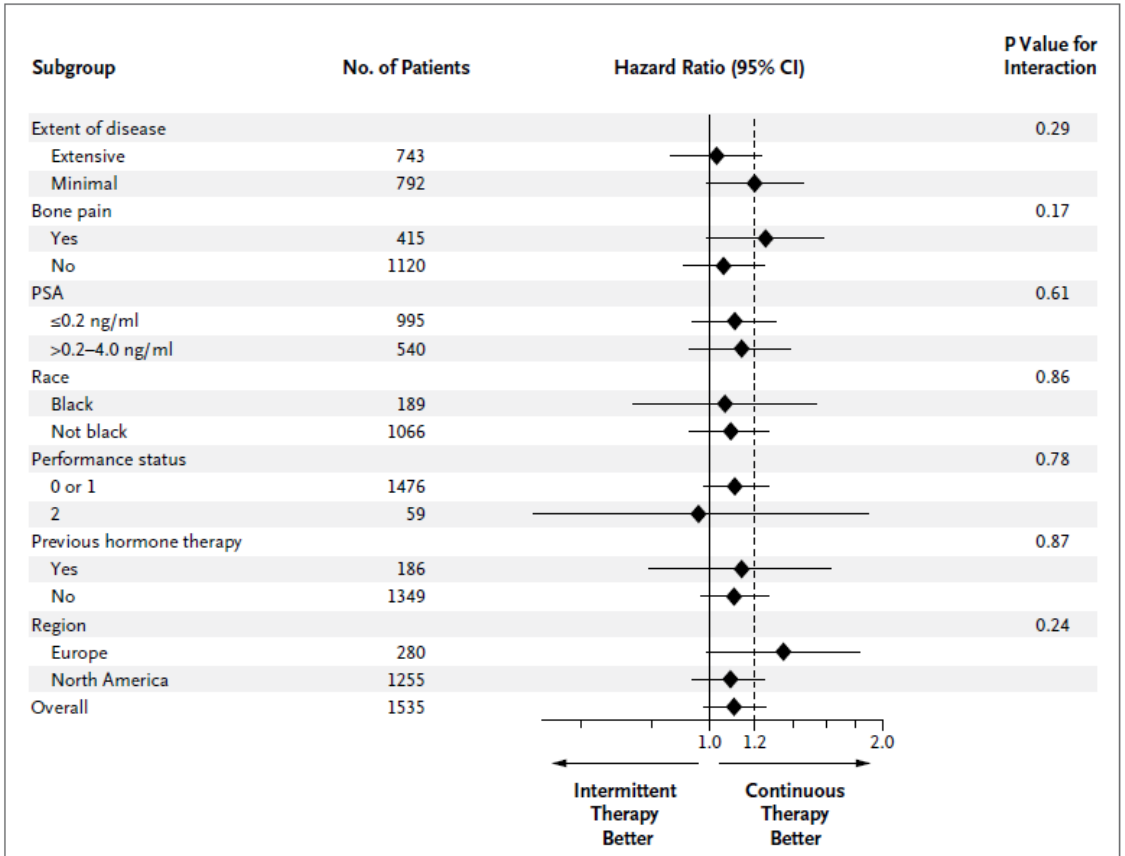


Figure 2. Survival According to Subgroups.

Minimal disease was considered to be disease confined to the spine, pelvic bones, or lymph nodes, and extensive disease as disease present in the ribs, long bones, or visceral organs (the definitions used in the trials of the South-west Oncology Group). A performance status of 0 indicates that the patient is fully active and able to carry on all predisease activities without restriction; 1, that the patient is ambulatory but restricted to light work; and 2, that the patient is ambulatory and capable of all self-care and is up and about more than 50% of waking hours but is unable to carry out any work activities. Race was self-reported. PSA denotes prostate-specific antigen.

Hormon Duyarlı Metastatik Prostat Kanseri

SWOG 9346 ; İntermittant vs. Continue

Table 2. Difference in the Mean Change from Randomization to Follow-up in Primary Quality-of-Life Outcomes, According to Treatment Group.

Outcome	Intermittent Therapy	Continuous Therapy	Difference, Intermittent–Continuous (95% CI)	P Value
Erectile dysfunction*				
Patients with erectile dysfunction at randomization (%)	82	85		
3-mo analysis				
No. of patients included	466	450		
Change from randomization	−7%	2%	−10 percentage points (−14 to −5)	<0.001
9-mo analysis				
No. of patients included	438	393		
Change from randomization	−8%	2%	−10 percentage points (−15 to −5)	<0.001
15-mo analysis				
No. of patients included	385	363		
Change from randomization	−3%	2%	−4 percentage points (−10 to 1)	0.12
High libido†				
Patients with high libido at randomization (%)	29	26		
3-mo analysis				
No. of patients included	68	45		
Change from randomization	16%	−2%	18 percentage points (1 to 36)	0.04
9-mo analysis				
No. of patients included	66	35		
Change from randomization	20%	−11%	31 percentage points (9 to 53)	0.01
15-mo analysis				
No. of patients included	46	31		
Change from randomization	13%	3%	10 percentage points (−16 to 36)	0.46
Vitality‡				
Score at randomization	59.7	59.8		
3-mo analysis				
No. of patients included	465	446		
Change from randomization	−0.11	−1.42	1.32 (−0.83 to 3.46)	0.23
9-mo analysis				
No. of patients included	439	392		
Change from randomization	−0.36	−3.07	2.71 (0.26 to 5.16)	0.03
15-mo analysis				
No. of patients included	386	372		
Change from randomization	−2.02	−3.02	1.00 (−1.59 to 3.59)	0.45

Yan etki olarak intermittan kol, continue kola göre daha iyi sonuçlara sahip

Hormon Duyarlı Metastatik Prostat Kanseri İntermittant vs. Continue

Potential Complications from T lowering ADT: Patient Perspective

What physicians commonly tell you	What you feel	What you see	What you don't see
Loss of libido	Fatigue or loss of energy, initiative	Weight gain	Loss of bone mineral density
Erectile dysfunction	Aches and pains	Loss of muscle mass and strength	Changes in lipids
Hot flashes	Low spirits, depression	Increased subcutaneous tissue, especially hips and thighs	Glucose intolerance, diabetes
	Emotional lability	Gynecomastia	Anemia
	Cognitive changes	Decrease in testicular size and penile length	Increased cardiovascular risk?
		Loss of body hair	

Modified from Higano, Hematol Oncol Clin North Am. 2006

62 yaşında erkek hasta, semptomu yok, insidental olarak PSA 50 ng/ ml saptanıyor. Yaygın multiple kemik metastazı var. Genel durumu iyi(ECOG PS 0) bu hasta için en uygun tedavi şekli ne olmalı?

1-Androjen baskılama tedavisi(ADT)

2-ADT+ Dositaksel

3-ADT+Dositaksel+/-Deksametazon

4- Hepsi olabilir

- Pasifik Porsuk Ağacı
- Taxaceae familyasından, *Taxus* cinsinden
- Türkiyede; Kuzey Anadolu, Toroslar bölgesinde genelde yetişir
- Uzun ömürlü, 2000-3000 yılık olanlar vardır
- Yaprakları oldukça zehirlidir.
- Kızıl deriler zehirli ok uçları bu ağaçtan elde etmişler
- NCI ilk çalışmalarında; bir gram taksol elde etmek için, yüz kadar prosuk ağacı gerekmiştir.

Kastrasyona Dirençli Metastatik Prostat kanseri

J Clin Oncol. 2008 Jan 1

Docetaxel plus
the TAX 327 stu

Berthold DR[1], Pond G

⊕ **Author informa**

Abstract

PURPOSE: The TA
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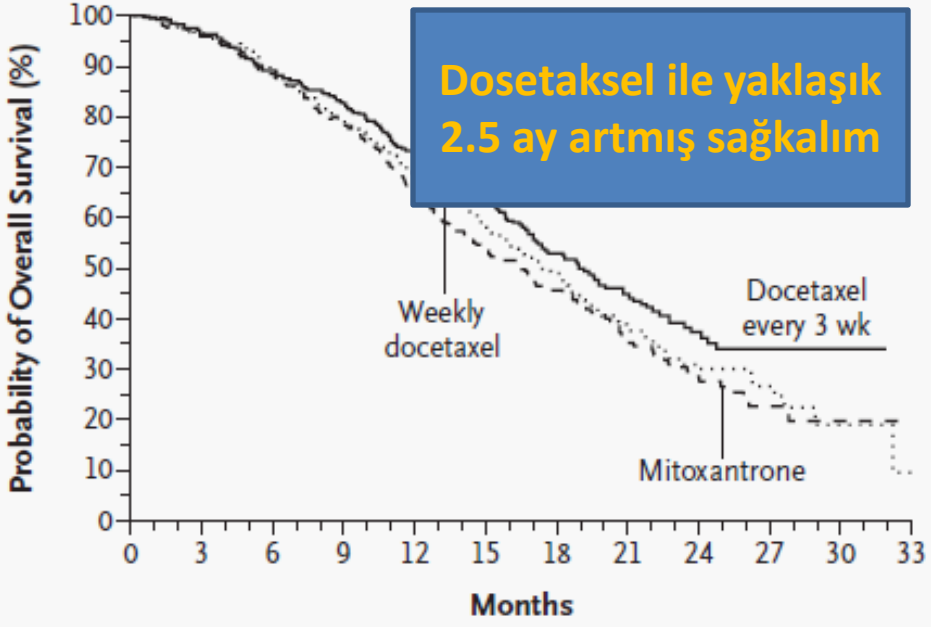

No. at Risk						
Docetaxel every 3 wk	335	296	217	104	37	5
Weekly docetaxel	334	297	200	105	29	4
Mitoxantrone	337	297	192	95	29	3

Figure 1. Kaplan–Meier Estimates of the Probability of Overall Survival in the Three Groups.

Hormon Duyarlı Metastatik Prostat Kanseri

ADT + Erken Dönem Kemoterapi

Lancet Oncol.

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Gravis G[1], Fi
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⊕ **Author i**

Abstract

BACKGRO
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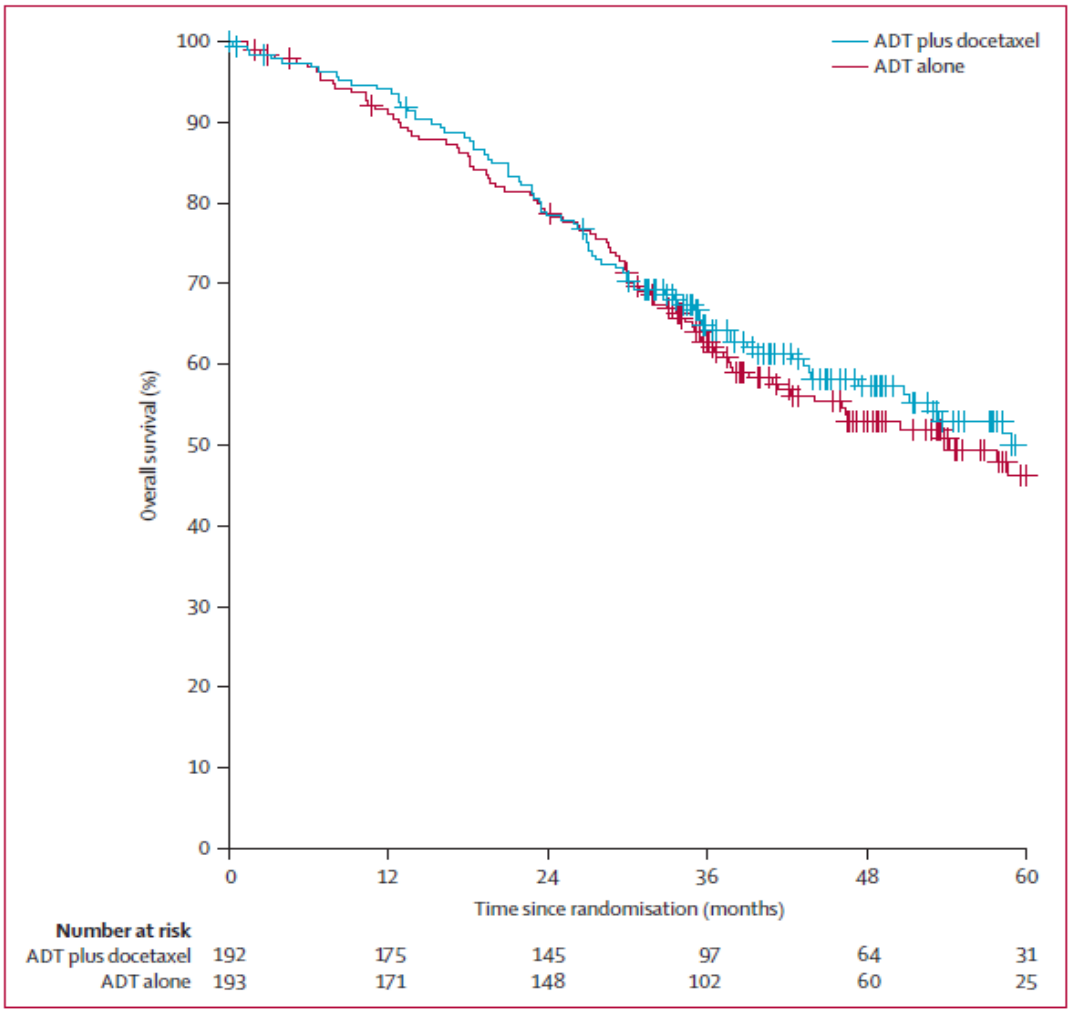

Figure 2: **Kaplan-Meier curves for overall survival by treatment group**
Crosses indicate censoring. ADT=androgen-deprivation therapy.

cancer (GETUG-AFU

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JP, El Kouri C, Ravaud A, Suc

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prostate cancer.

Hormon Duyarlı Metastatik Prostat Kanseri

ADT + Erken Dönem Kemoterapi

Chemohormonal Therapy in Metastatic Hormone-Sensitive Prostate Cancer

Christopher J. Sweeney, M.B., B.S., Yu-Hui Chen, M.S., M.P.H., Michael Carducci, M.D., Glenn Liu, M.D., David F. Jarrard, M.D., Mario Eisenberger, M.D., Yu-Ning Wong, M.D., M.S.C.E., Noah Hahn, M.D., Manish Kohli, M.D., Matthew M. Cooney, M.D., Robert Dreicer, M.D., Nicholas J. Vogelzang, M.D., Joel Picus, M.D., Daniel Shevrin, M.D., Maha Hussain, M.B., Ch.B., Jorge A. Garcia, M.D., and Robert S. DiPaola, M.D.

ABSTRACT

BACKGROUND

Androgen-deprivation therapy (ADT) has been the backbone of treatment for metastatic prostate cancer since the 1940s. We assessed whether concomitant treatment with ADT plus docetaxel would result in longer overall survival than that with ADT alone.

METHODS

We assigned men with metastatic, hormone-sensitive prostate cancer to receive either ADT plus docetaxel (at a dose of 75 mg per square meter of body-surface area every 3 weeks for six cycles) or ADT alone. The primary objective was to test the hypothesis that the median overall survival would be 33.3% longer among patients receiving docetaxel added to ADT early during therapy than among patients receiving ADT alone.

RESULTS

A total of 790 patients (median age, 63 years) underwent randomization. After a median follow-up of 28.9 months, the median overall survival was 13.6 months longer with ADT plus docetaxel (combination therapy) than with ADT alone (57.6 months vs. 44.0 months; hazard ratio for death in the combination group, 0.61; 95% confidence interval [CI], 0.47 to 0.80; P<0.001). The median time to biochemical, symptomatic, or radiographic progression was 20.2 months in the combination group, as compared with 11.7 months in the ADT-alone group (hazard ratio, 0.61; 95% CI, 0.51 to 0.72; P<0.001). The rate of a prostate-specific antigen level of less than 0.2 ng per milliliter at 12 months was 27.7% in the combination group versus 16.8% in the ADT-alone group (P<0.001). In the combination group, the rate of grade 3 or 4 febrile neutropenia was 6.2%, the rate of grade 3 or 4 infection with neutropenia was 2.3%, and the rate of grade 3 sensory neuropathy and of grade 3 motor neuropathy was 0.5%.

From the Department of Medicine (C.J.S.) and the Department of Biostatistics and Computational Biology (Y.-H.C.), Dana–Farber Cancer Institute, Boston; Harvard Medical School, Boston (C.J.S.); Johns Hopkins University, Baltimore (M.C., M.E.); University of Wisconsin Carbone Cancer Center (G.L., D.F.J.) and School of Medicine and Public Health (D.F.J.), Madison; Fox Chase Cancer Center, Temple University Health System, Philadelphia (Y.-N.W.); Indiana University Melvin and Bren Simon Cancer Center, Indianapolis (N.H.); Mayo Clinic, Rochester, MN (M.K.); University Hospitals Case Medical Center, Seidman Cancer Center (M.M.C.), and Cleveland Clinic Taussig Cancer Institute (J.A.G.) — both in Cleveland; University of Virginia Cancer Center, Charlottesville (R.D.); Comprehensive Cancer Centers of Nevada, Las Vegas (N.J.V.); Siteman Cancer Center, Washington University School of Medicine, St. Louis (J.P.); NorthShore University HealthSystem, Evanston, IL (D.S.); University of Michigan Comprehensive Cancer Center, Ann Arbor (M.H.); and Rutgers Cancer Institute of New Jersey, New Brunswick (R.S.D.). Address reprint requests to Dr. Sweeney at christopher_sweeney@dfci.harvard.edu.

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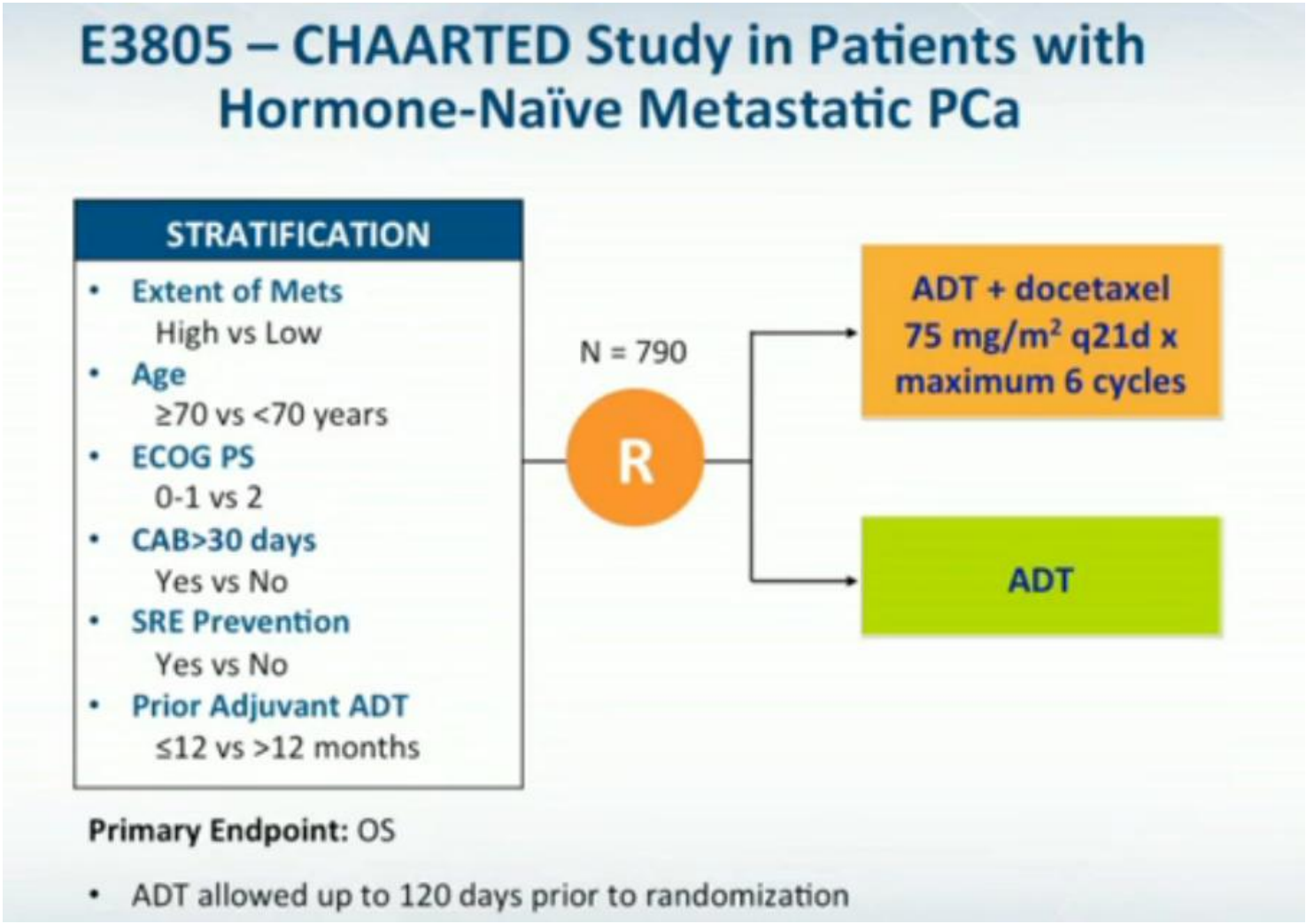
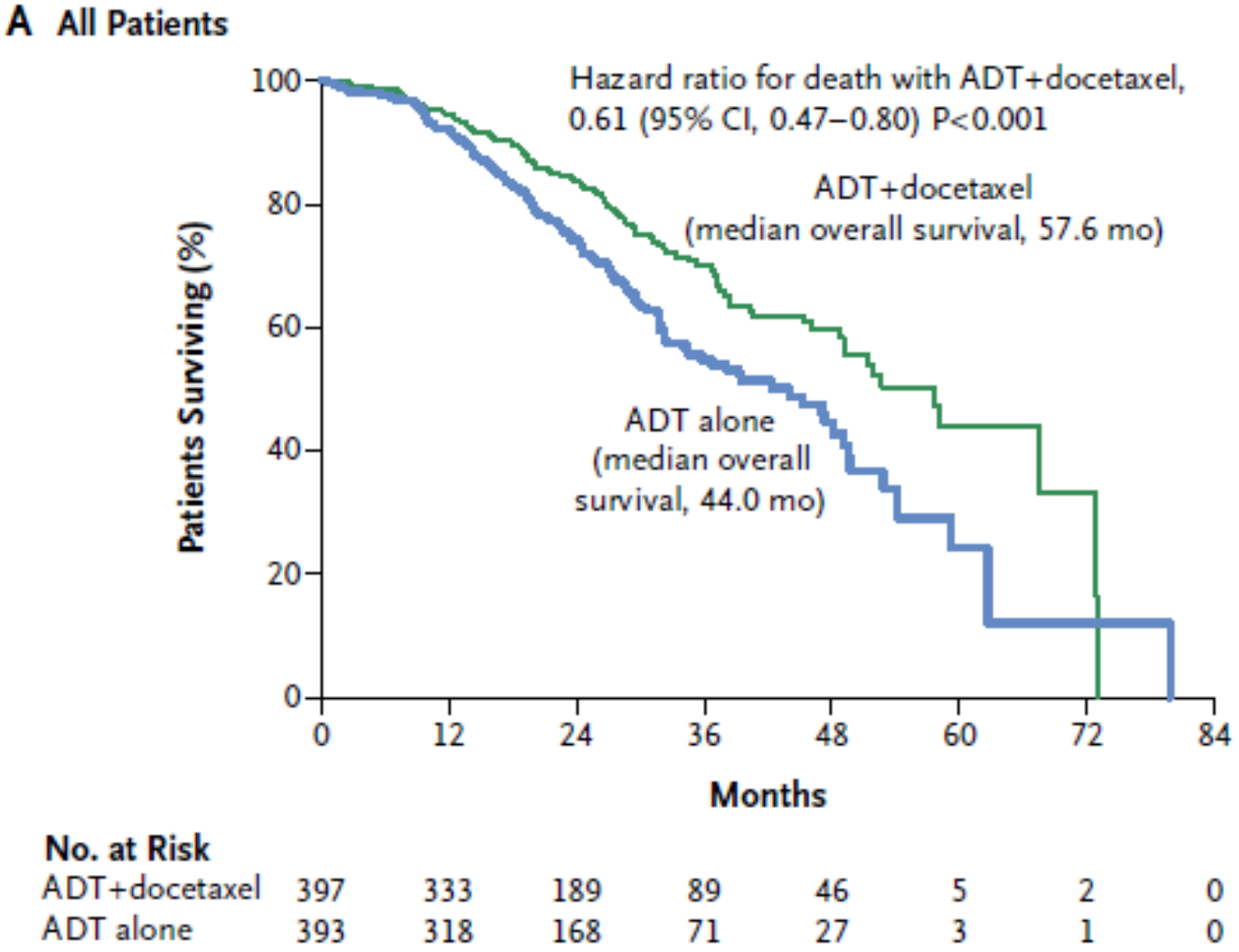
Hormon Duyarlı Metastatik Prostat Kanseri

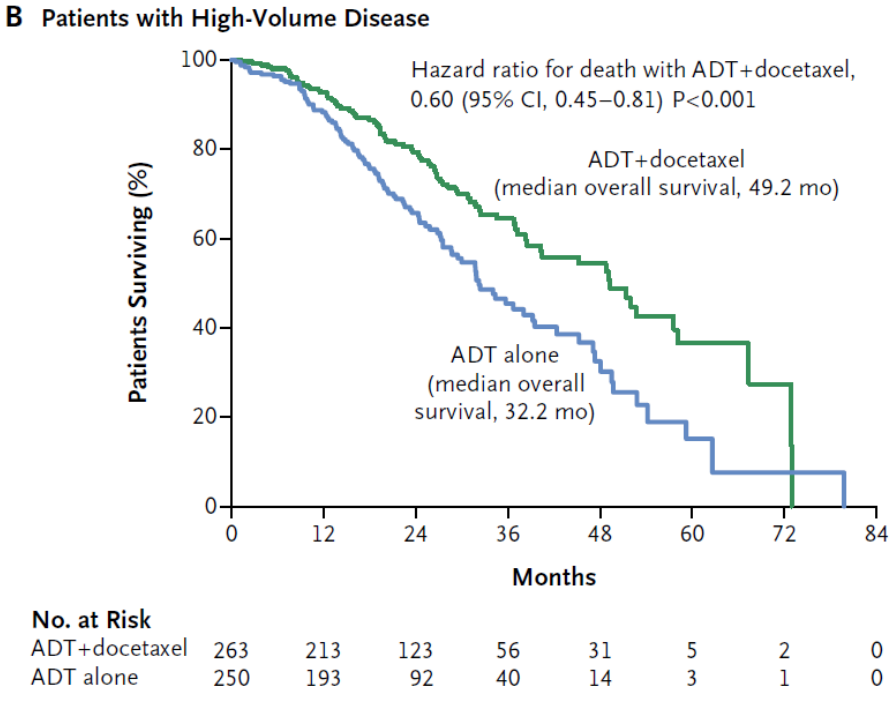
ADT + Erken Dönem Kemoterapi

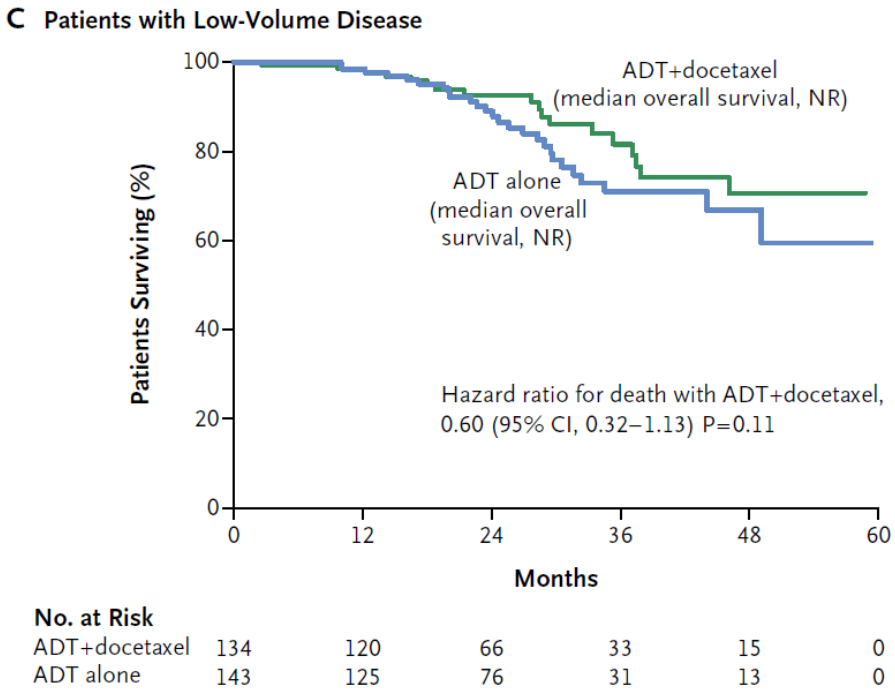


ADT + Erken Dönem Kemoterapi



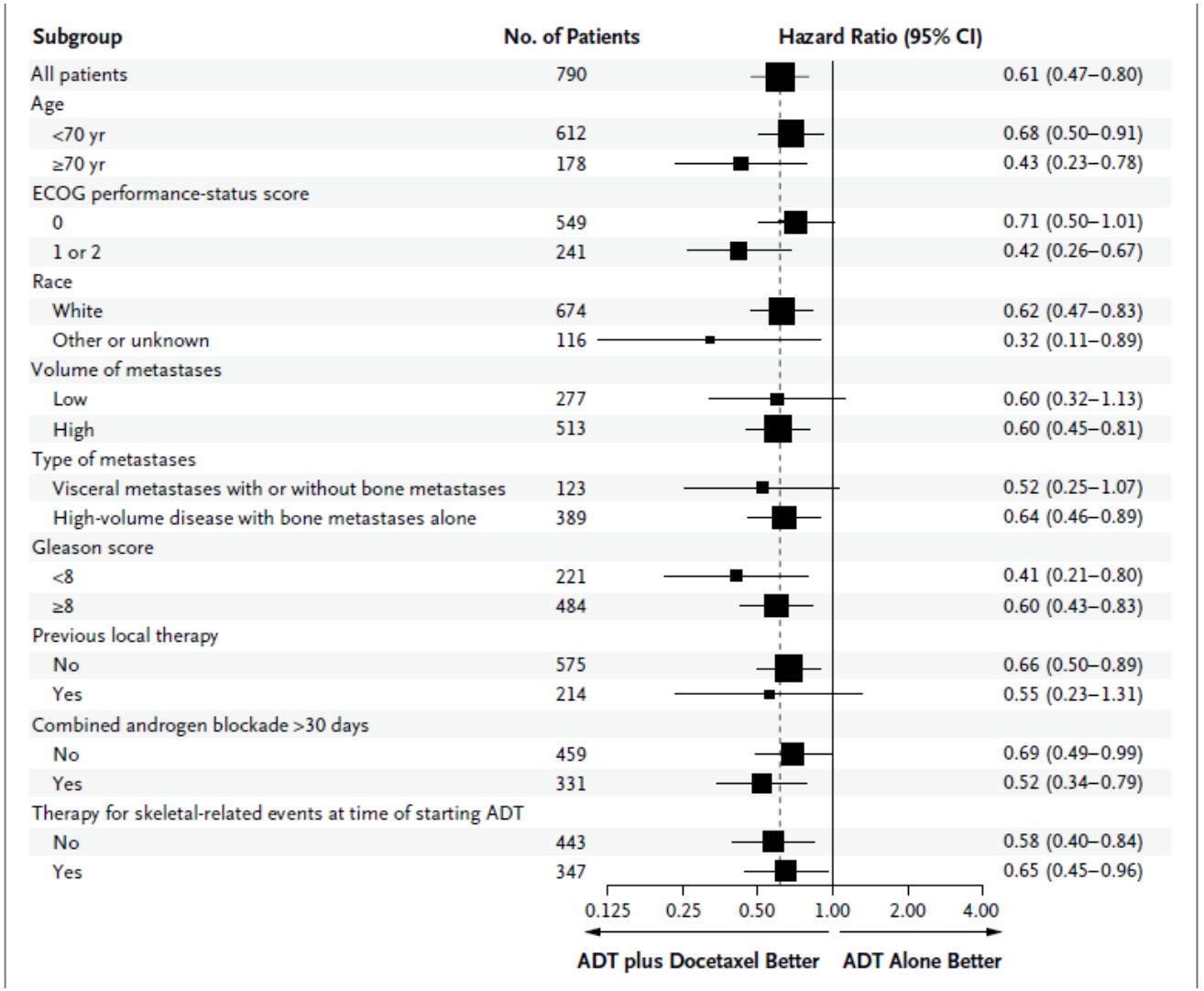
ADT + Erken Dönem Kemoterapi





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

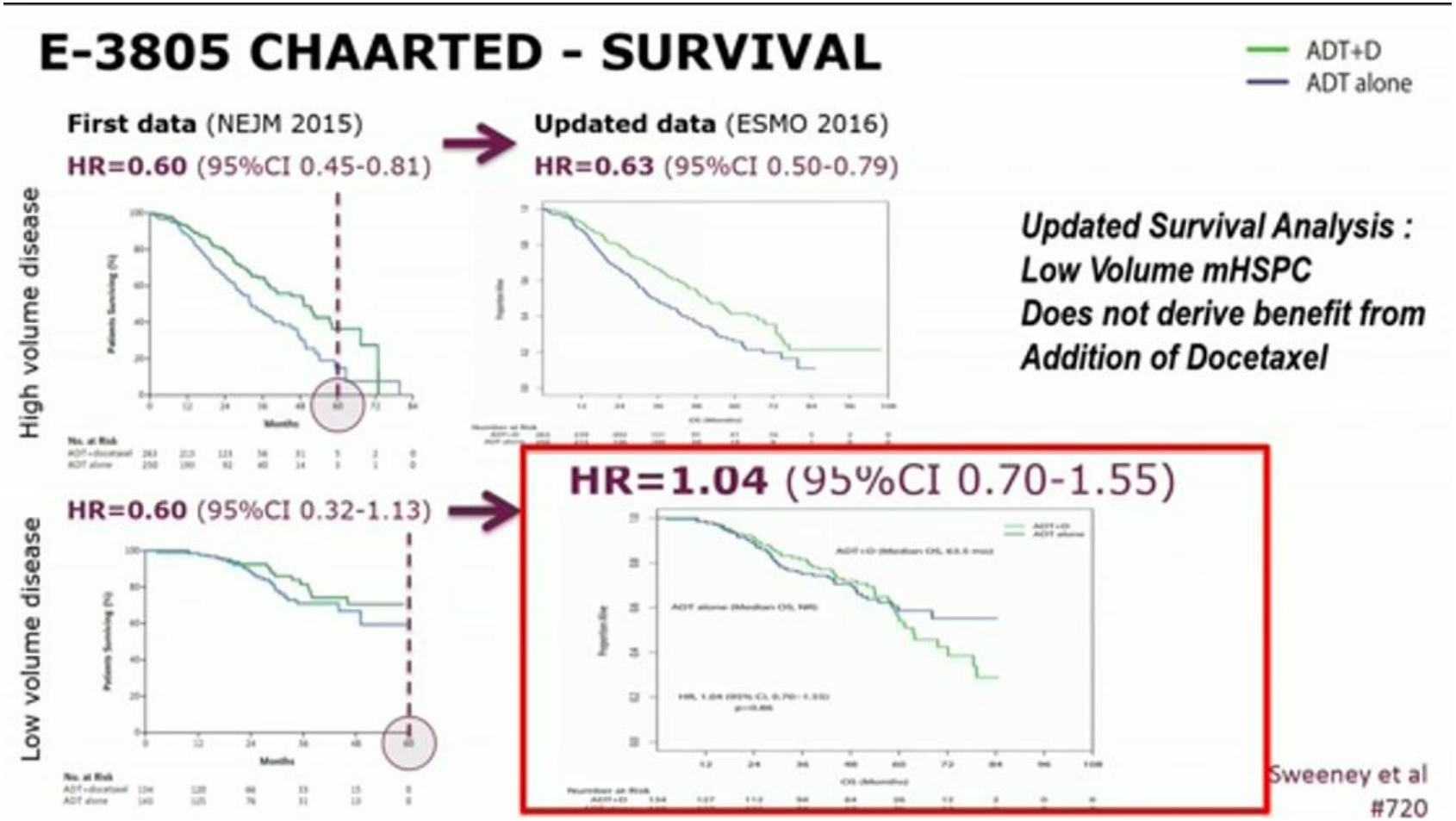
ADT + Erken Dönem Kemoterapi



ADT + Erken Dönem Kemoterapi

	ADT + doc (n = 397)	ADT alone (n = 393)	Hazard ratio	*p*-value
Primary endpoint				
Overall survival	57.6 mo	44.0 mo	0.61	0.0003
High-volume mets	**49.2 mo**	**32.2 mo**	**0.60**	**0.0006**
Low-volume mets	Not reached	Not reached	0.63	0.1398
Secondary endpoints				
Median time to CRPC (biochemical, symptoms or radiographic)	20.7 mo	14.7 mo	0.56	<0.0001
Median time to clinical progression (symptoms or radiographic)	32.7 mo	19.8 mo	0.49	<0.0001

ADT + Erken Dönem Kemoterapi
CHAARTED UZUN DÖNEM SONUÇLARI



Hormon Duyarlı Metastatik Prostat Kanseri

ADT + Erken Dönem Kemoterapi

Dositaksel KT metastatik prostat kanserinde erken kullanımı
Kastrasyona dirençli metastatik prostat kanseri vs. Hormon duyarlı metastatik prostat kanseri

	TAX327	CHARTED
HR	0.79	0.61
OS	2.4 ay	13.6 ay
KT sayısı	10	6
F.nötropeni	3%	6%
Prednisolon	var	yok

Hormon Duyarlı Metastatik Prostat Kanseri

ADT + Erken Dönem Kemoterapi

Dositaksel KT metastatik prostat kanserinde erken kullanımı

Hormon duyarlı metastatik prostat kanseri vs. Hormon duyarlı metastatik prostat kanseri

	GETUG	CHARTED
HR	1.01	0.61
OS	4.7 ay	13.6 ay
KT sayısı	9	6
F.nötropeni	8 %	6%
Prednisolon	yok	yok

Hormon Duyarlı Metastatik Prostat Kanseri

ADT + Erken Dönem Kemoterapi

Dositaksel KT metastatik prostat kanserinde erken kullanımı
Hormon duyarlı metastatik prostat kanseri vs. Hormon duyarlı metastatik prostat kanseri

	GETUG	CHARTED
Yüksek volüm	?	%66
Viseral metastaz	%10-15	?
Medyan PSA	27	56
Kötü risk gurubu	%22	?
Kemik metastazı	%81	?
M1 hastalık	%67	%73
Gleason Skoru 8-10	%55	%67

Hormon Duyarlı Metastatik Prostat Kanseri

ADT + Erken Dönem Kemoterapi

Dositaksel KT metastatik prostat kanserinde erken kullanımı

Hormon duyarlı metastatik prostat kanseri vs. Hormon duyarlı metastatik prostat kanseri(GETUG Vs CHARTED)

- **GETUG, 192 hasta KT almış**
- **%22 kötü risk gurubu, %50 iyi risk gurubunda, %81 kemik met, <%15 viseral metastaz**

CHARTED ve GETUG sonuçlar neden Farklı

- **Tam olarak bilinmiyor?**
- **Yüksek volüm hastalığı olanlar, anti mikrotubuler tedaviye daha duyarlı olabilir**
- **Farklı genetik karekter olabilir(RB1, AR durumu?)**
- **GETUG çalışmasında hasta sayısının düşüklüğü, yetersiz power?**

Hormon Duyarlı Metastatik Prostat Kanseri

ADT + Erken Dönem Kemoterapi

Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial

*Nicholas D James, Matthew R Sydes, Noel W Clarke, Malcolm D Mason, David P Dearnaley, Melissa R Spears, Alastair W S Ritchie, Christopher C Parker, J Martin Russell, Gerhardt Attard, Johann de Bono, William Cross, Rob J Jones, George Thalmann, Claire Amos, David Matheson, Robin Millman, Mymoona Alzouebi, Sharon Beesley, Alison J Birtle, Susannah Brock, Richard Cathomas, Prabir Chakraborti, Simon Chowdhury, Audrey Cook, Tony Elliott, Joanna Gale, Stephanie Gibbs, John D Graham, John Hetherington, Robert Hughes, Robert Laing, Fiona McKinna, Duncan B McLaren, Joe M O'Sullivan, Omi Parikh, Clive Peedell, Andrew Protheroe, Angus J Robinson, Narayanan Srihari, Rajaguru Srinivasan, John Staffurth, Santhanam Sundar, Shaun Tolan, David Tsang, John Wagstaff, Mahesh K B Parmar, for the STAMPEDE investigators**

Summary

Background Long-term hormone therapy has been the standard of care for advanced prostate cancer since the 1940s. STAMPEDE is a randomised controlled trial using a multiarm, multistage platform design. It recruits men with high-risk, locally advanced, metastatic or recurrent prostate cancer who are starting first-line long-term hormone therapy. We report primary survival results for three research comparisons testing the addition of zoledronic acid, docetaxel, or their combination to standard of care versus standard of care alone.

Methods Standard of care was hormone therapy for at least 2 years; radiotherapy was encouraged for men with N0M0 disease to November, 2011, then mandated; radiotherapy was optional for men with node-positive non-metastatic (N+M0) disease. Stratified randomisation (via minimisation) allocated men 2:1:1:1 to standard of care only (SOC-only; control), standard of care plus zoledronic acid (SOC + ZA), standard of care plus docetaxel (SOC + Doc), or standard of care with both zoledronic acid and docetaxel (SOC + ZA + Doc). Zoledronic acid (4 mg) was given for six 3-weekly cycles, then 4-weekly until 2 years, and docetaxel (75 mg/m²) for six 3-weekly cycles with prednisolone 10 mg daily. There was no blinding to treatment allocation. The primary outcome measure was overall survival. Pairwise comparisons of research versus control had 90% power at 2·5% one-sided α for hazard ratio (HR) 0·75, requiring roughly 400 control arm deaths. Statistical analyses were undertaken with standard log-rank-type methods for time-to-event data, with hazard ratios (HRs) and 95% CIs derived from adjusted Cox models. This trial is registered at ClinicalTrials.gov (NCT00268476) and ControlledTrials.com (ISRCTN78818544).

Lancet 2016; 387: 1163–77

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See Comment page 1135

*Members listed at end of paper

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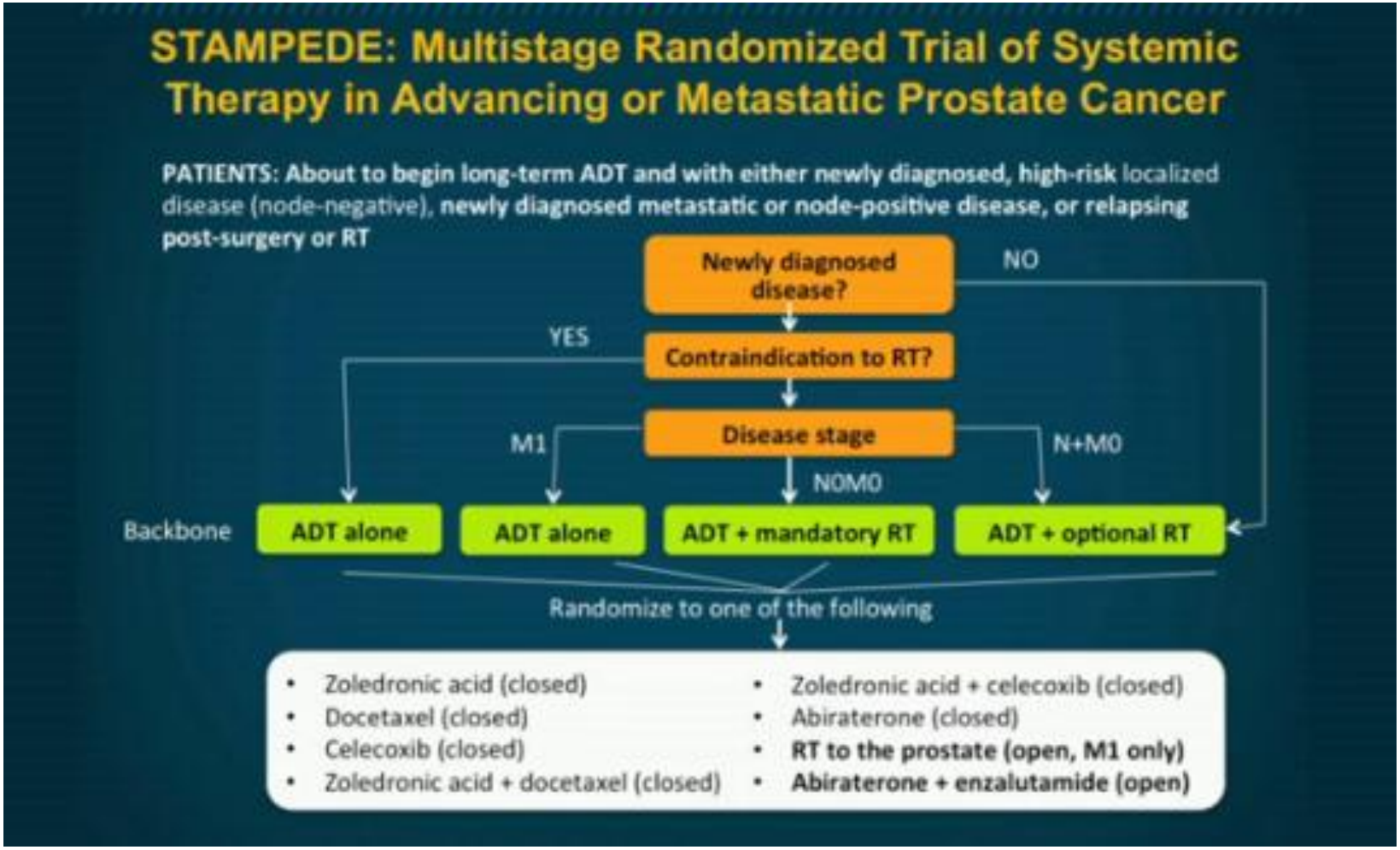
Hormon Duyarlı Metastatik Prostat Kanseri

ADT + Erken Dönem Kemoterapi



ADT + Erken Dönem Kemoterapi

STAMPEDE: Docetaxel and/or Zoledronic Acid in Hormone-Naïve Metastatic PCa

First overall survival analysis of patients enrolled in the following 4 study arms:

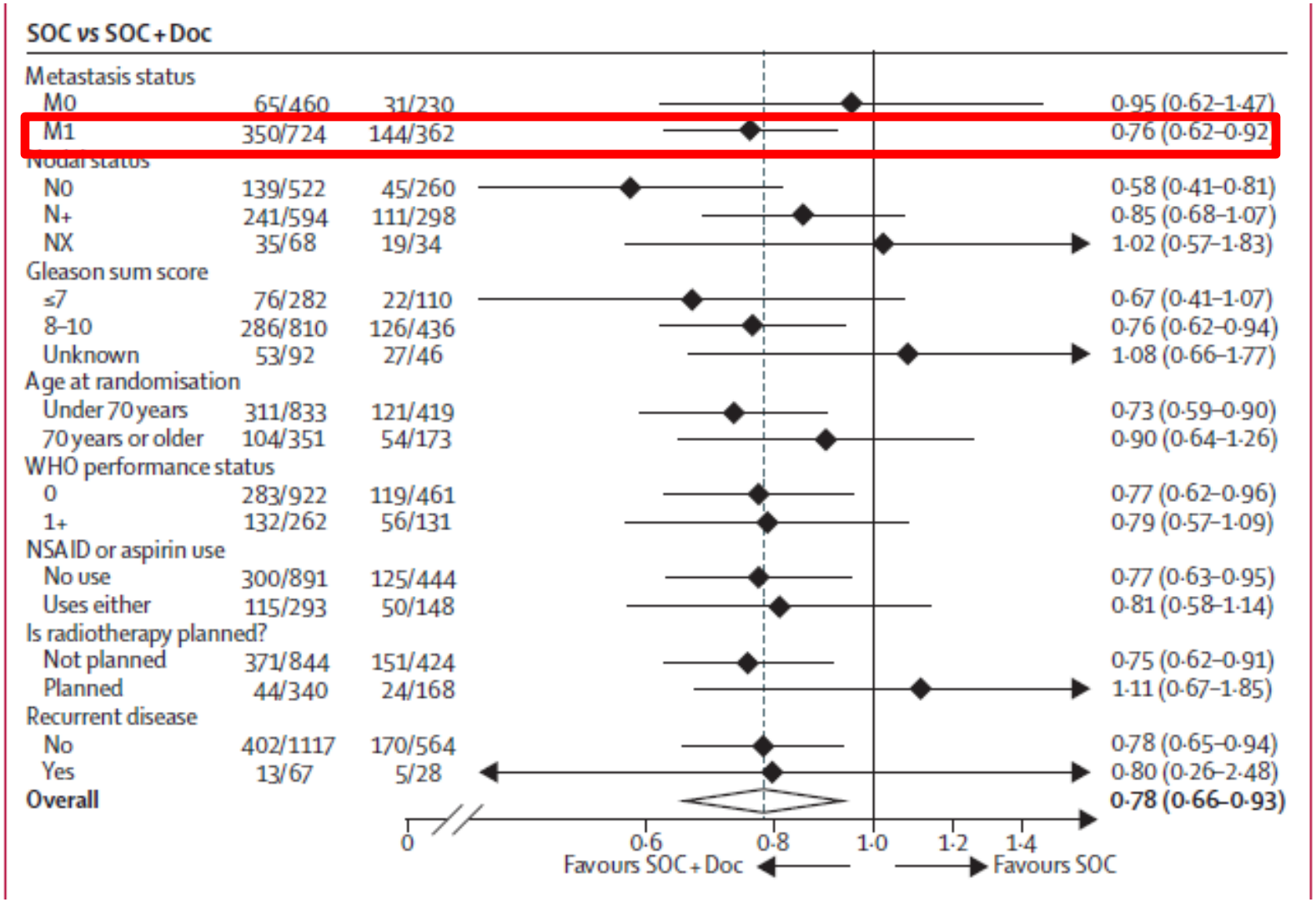
- Standard of care (SOC; n = 1,184)
- Docetaxel (Doc) + SOC (n = 592)
- Zoledronic acid (ZDA) + SOC (n = 593)
- Doc + ZDA + SOC (n = 593)

	SOC	Doc + SOC	ZDA + SOC	Doc + ZDA + SOC
Median overall survival	67 mo	77 mo	80 mo	72 mo
Hazard ratio (*p*-value)	**Ref***	**0.76 (0.003)**	**0.93 (0.44)**	**0.81 (0.02)**
Median failure-free survival	21 mo	37 mo	21 mo	37 mo
Hazard ratio (*p*-value)	**Ref***	**0.62 ($<0.1 \times 10^{-10}$)**	**0.93 (0.26)**	**0.62 ($<0.1 \times 10^{-10}$)**

* Pairwise comparisons to control SOC study arm were calculated for each research arm.

- **Docetaxel, and not ZDA, improves overall survival compared to SOC**
- **Docetaxel + ZDA improves survival but offers no obvious benefit over docetaxel alone**

ADT + Erken Dönem Kemoterapi



Hormon Duyarlı Metastatik Prostat Kanseri

ADT + Erken Dönem Kemoterapi

JOURNAL OF CLINICAL ONCOLOGY
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Journal of Clinical Oncology, 2015 ASCO Annual Meeting (May 29 - June 2, 2015).
Vol 33, No 18_suppl (June 20 Supplement), 2015: LBA5002

A phase III protocol of androgen suppression (AS) and 3DCRT/IMRT versus AS and 3DCRT/IMRT followed by chemotherapy (CT) with docetaxel and prednisone for localized, high-risk prostate cancer (RTOG 0521).

Howard M. Sandler, Chen Hu, Seth A. Rosenthal, Oliver Sartor, Leonard G. Gomella, Mahul Amin, James Purdy, Jeff M. Michalski, Mark Garzotto, Nadeem Pervez, Alexander G. Balogh, George Rodrigues, Luis Souhami, M. Neil Reaume, Scott G. Williams, Raquibul Hannan, Eric M. Horwitz, Adam Raben, Rebecca Paulus and William U. Shipley

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Abstract Disclosures

Abstract

LBA5002

Background: High-risk, localized prostate cancer (PCa) patients have a relatively poor prognosis. We hypothesized that the addition of adjuvant docetaxel and prednisone to long-term (24 month) AS and radiation therapy (RT) would improve overall survival (OS). **Methods:** RTOG 0521 opened December 2005 and closed August 2009 with targeted accrual of 600 cases. It was designed to detect improvement in 4-year OS from 86% to 93% with a 51% hazard reduction (HR = 0.49). Under a 0.05 1-sided type I error and 90% power, at least 78 deaths were required to analyze the OS endpoint. Patients had 1) Gleason (Gl) 7-8, any T-stage, and PSA > 20, or 2) Gl 8, ≥ T2, any PSA, or 3) Gl 9-10, any T-stage, any PSA. All had PSA ≤ 150. RT dose was 75.6 Gy. CT consisted of 6, 21-day cycles of docetaxel + prednisone starting 28 days after RT. **Results:** Of 612 enrolled, 50 were excluded for eligibility issues, leaving 562 evaluable. Median age = 66, median PSA = 15.1, 53% had Gl 9-10, 27% had cT3-4. Median follow-up = 5.5 yrs. 4-yr OS rates were 89% [95% CI: 84-92%] for the AS+RT arm and 93% [95% CI: 90-96%] for the AS+RT+CT arm (1-sided p = 0.03, HR = 0.68 [95% CI: 0.44, 1.03]). There were 52 centrally-reviewed deaths in the AS+RT arm and 36 in the AS+RT+CT arm, with fewer deaths both due to PCa/treatment (20 vs 16) and due to other causes/unknown (32 vs 20) in the AS+RT+CT arm. 5-yr disease-free survival rates were 66% for AS+RT and 73% for AS+RT+CT (2-sided p = 0.05, HR = 0.76 [95% CI: 0.57, 1.00]). There was 1, Gr 5 unlikely-related adverse event (AE) in the AS+RT arm and 2, Gr 5 possibly/probably-related AEs with AS+RT+CT. **Conclusions:** For high-risk, localized PCa, adjuvant CT improved the OS from 89% to 93% at 4 years. Toxicity was acceptable. This trial was designed with a short OS assessment period and additional follow-up is warranted to determine the long-term benefit of CT to the current standard of care of long-term AS+RT. This project was supported by grants U10CA21661, U10CA180868, U10CA180822, from the National Cancer Institute and Sanofi with additional support from AstraZeneca for Australian site participation. Clinical trial information: NCT00288080.

Hormon Duyarlı Metastatik Prostat Kanseri

ADT + Erken Dönem Kemoterapi

RTOG-0521: Androgen Suppression (AS) and Radiation Therapy (RT) with or without Docetaxel (Doc) in Localized, High-Risk PCa

	AS + RT	AS + RT + Doc	Hazard ratio	*p*-value
Primary endpoint				
4-year overall survival rate	89%	93%	0.70	0.04
Secondary endpoints				
Biochemical failure at 6 years	74%	66%	0.81	0.19
Disease-free survival at 6 years	55%	65%	0.76	0.04

"For the first time, improvement in overall survival observed with tolerable adjuvant chemotherapy for localized, high-risk hormone-sensitive prostate cancer."

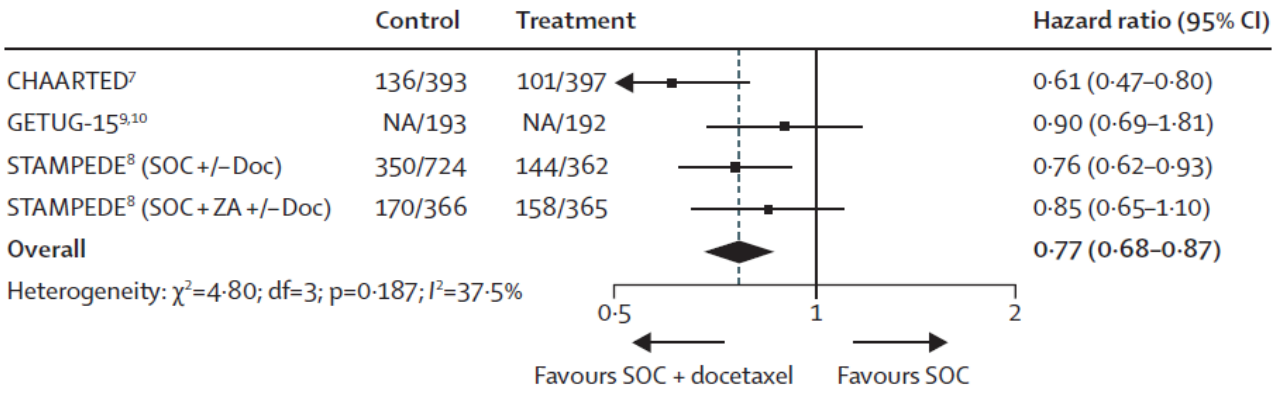
Hormon Duyarlı Metastatik Prostat Kanseri

Metaanaliz; ADT + Erken Dönem Kemoterapi

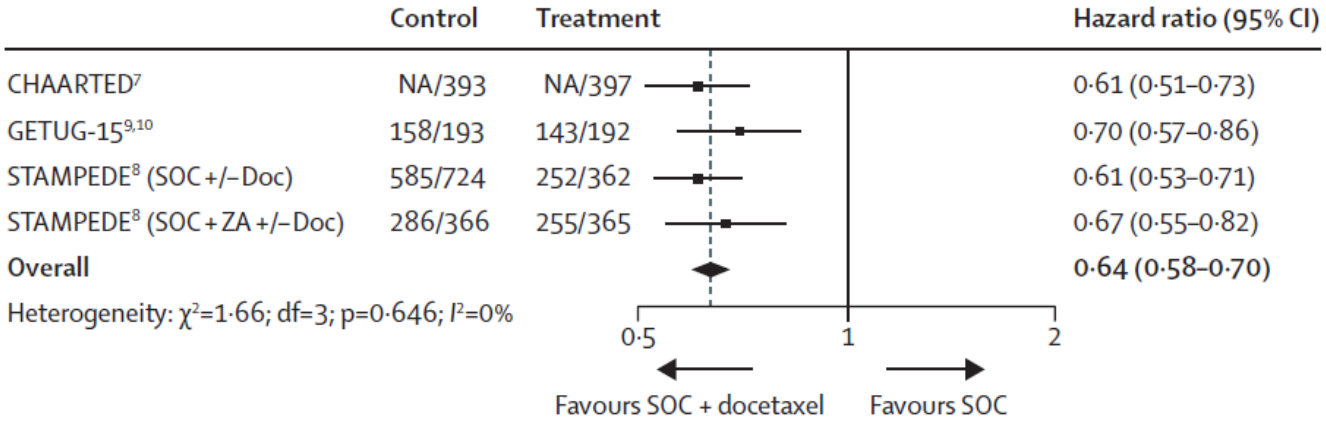
	Accrual period	Number of patients	Control	Treatment	Metastatic status	Median age (range)	Gleason score of 8–10 (%)	Performance status of 0–1 (%)	Median follow-up (survival)	Treatment on progression (control group only)
Docetaxel trials										
GETUG-12[25,26]	November, 2002–December, 2006	413	ADT (goserelin 10·8 mg every 3 months for 3 years)	ADT plus docetaxel (70 mg/m² for four cycles) plus estramustine	M0	63 (46–77)	42%	Unknown	7 years, 6 months	Not reported
TAX 3501[9]	December, 2005–September, 2007	228	ADT (leuprolide 22·5 mg every 3 months for 18 months)	ADT plus docetaxel (75 mg/m² every 3 weeks for six cycles)	M0	61·9*	52%	Unknown	3 years, 3 months	Not reported
RTOG 0521[28]	December, 2005–August, 2009	612	ADT (LHRH agonist plus oral anti-androgen plus RT)	ADT plus docetaxel (75 mg/m² every 3 weeks for six cycles) plus prednisone	M0	66 (unknown)	84%	Unknown	6 years	Not reported
STAMPEDE (standard of care with or without docetaxel)[8]	September, 2005–March, 2013	1776	ADT (plus radiotherapy for M0 patients)	ADT plus docetaxel (75 mg/m² every 3 weeks for six cycles) plus predisone	M0 and M1	65 (40–82)	70%	99%	3 years, 6 months	40% received docetaxel (49% received life-extending treatments)
STAMPEDE (standard of care plus zoledronic acid with or without docetaxel)[8]	September, 2005–March, 2013	1186	ADT (plus radiotherapy for M0 patients) plus zoledronic acid (4 mg every 3–4 weeks for 2 years)	ADT (plus radiotherapy for M0 patients) + zoledronic acid (4 mg for 3–4 weeks for 2 years) plus docetaxel (75 mg/m² every 3 weeks for six cycles)	M0 and M1	66 (42–84)	71%	99%	3 years, 6 months	36% received docetaxel (45% received life-extending treatments)
GETUG-15[9,10]	October, 2004–December, 2008	385	ADT (LHRH agonist or surgical castration or combined androgen blockade)	ADT plus docetaxel (75 mg/m² every 3 weeks for up to nine cycles)	M1	63·5 (57–70)	56%	100%	6 years, 11 months	62% received docetaxel
CHAARTED[7]	July, 2006–November, 2012	790	ADT (LHRH agonist or LHRH antagonist) or surgical castration	ADT plus docetaxel (75 mg/m² every 3 weeks for six cycles)	M1	64 (36–91)	61%	98%	2 years, 5 months	147 (51%) of 287 men received docetaxel (104 of 287 men received abiratarone or enzalutamide)

Hormon Duyarlı Metastatik Prostat Kanseri

Metaanaliz; ADT + Erken Dönem Kemoterapi



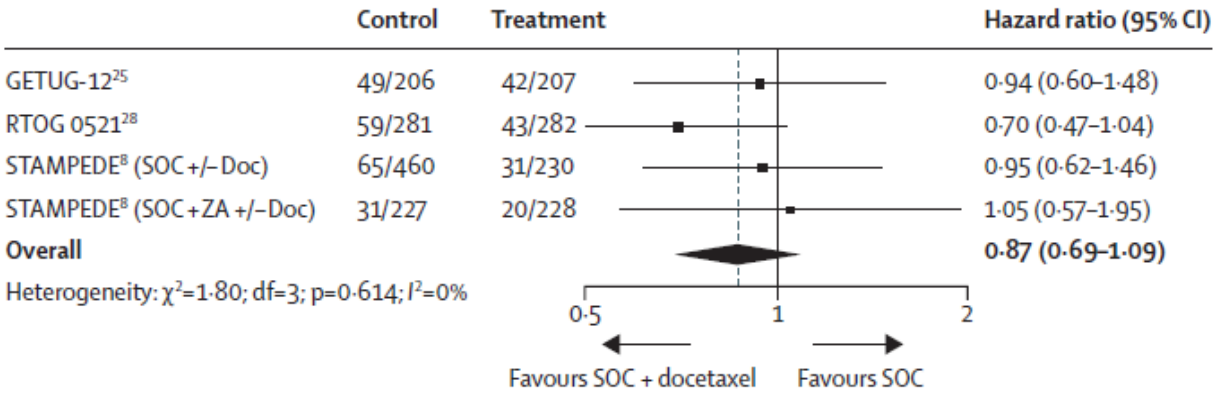
2992 hormona duyarlı metastatik prostat ca hastaya ADT +dositaksel eklenmesi ; 4-yıllık sağkalımı %9 artırıyor



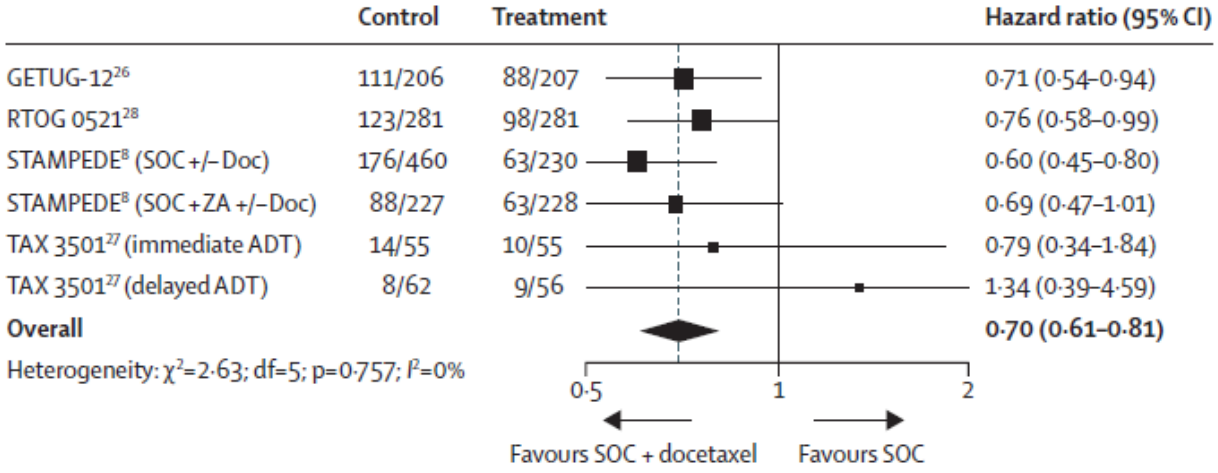
2992 hormona duyarlı metastatik prostat ca hastaya ADT +dositaksel eklenmesi ; 4 yılık %16 nüksüz süreyi uzatıyor

Hormon Duyarlı Metastatik Prostat Kanseri

Metaanaliz; ADT + Erken Dönem Kemoterapi

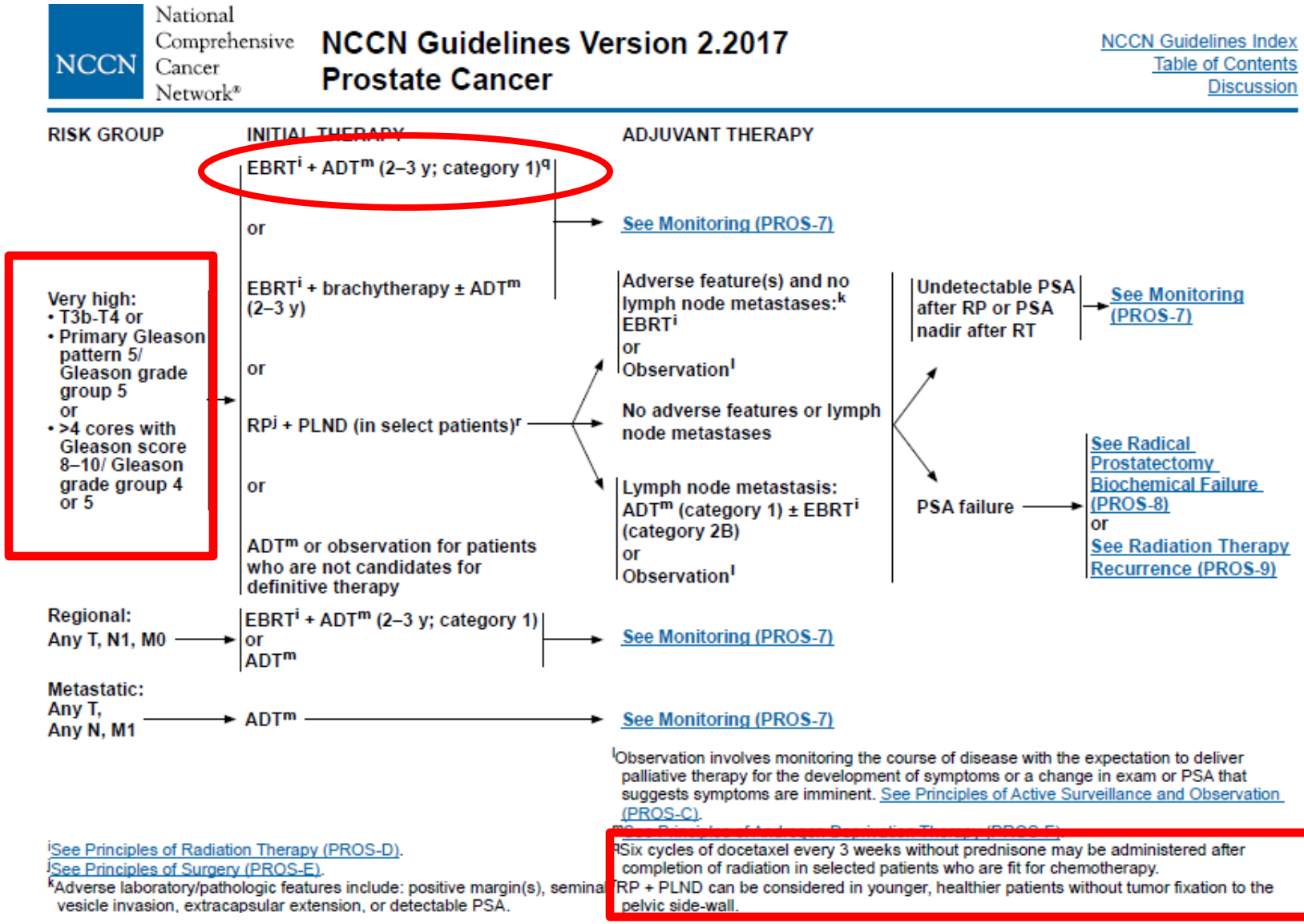


2992 hormona duyarlı lokal ileri prostat ca hastaya ADT +dositaksel eklenmesi ; sağkalım etkisi yok

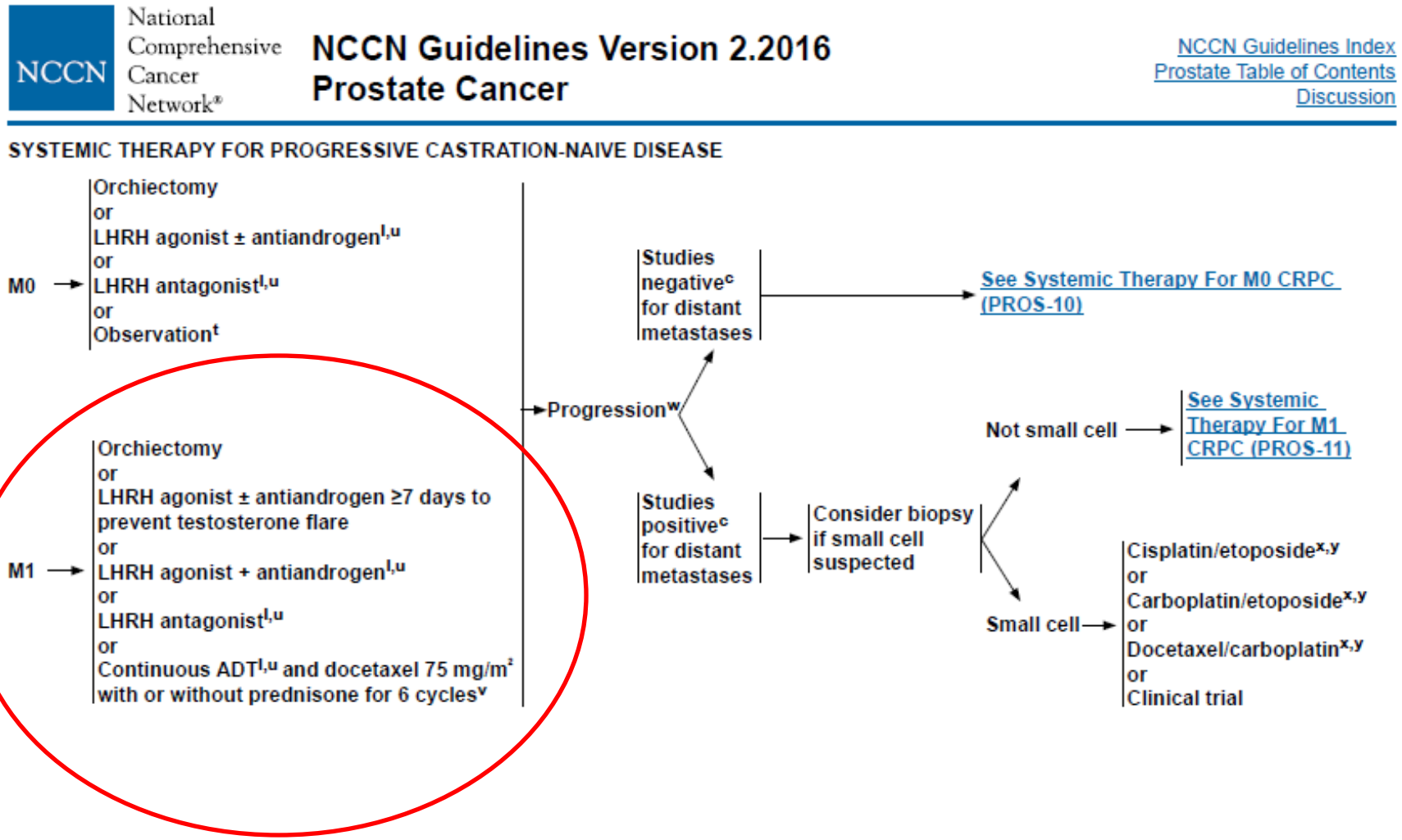


2992 hormona duyarlı lokal ileri prostat ca hastaya ADT +dositaksel eklenmesi ; 4-yıllık 8% nüksüz süreyi uzatıyor

Hormon Duyarlı Metastatik Prostat Kanseri



Hormon Duyarlı Metastatik Prostat Kanseri



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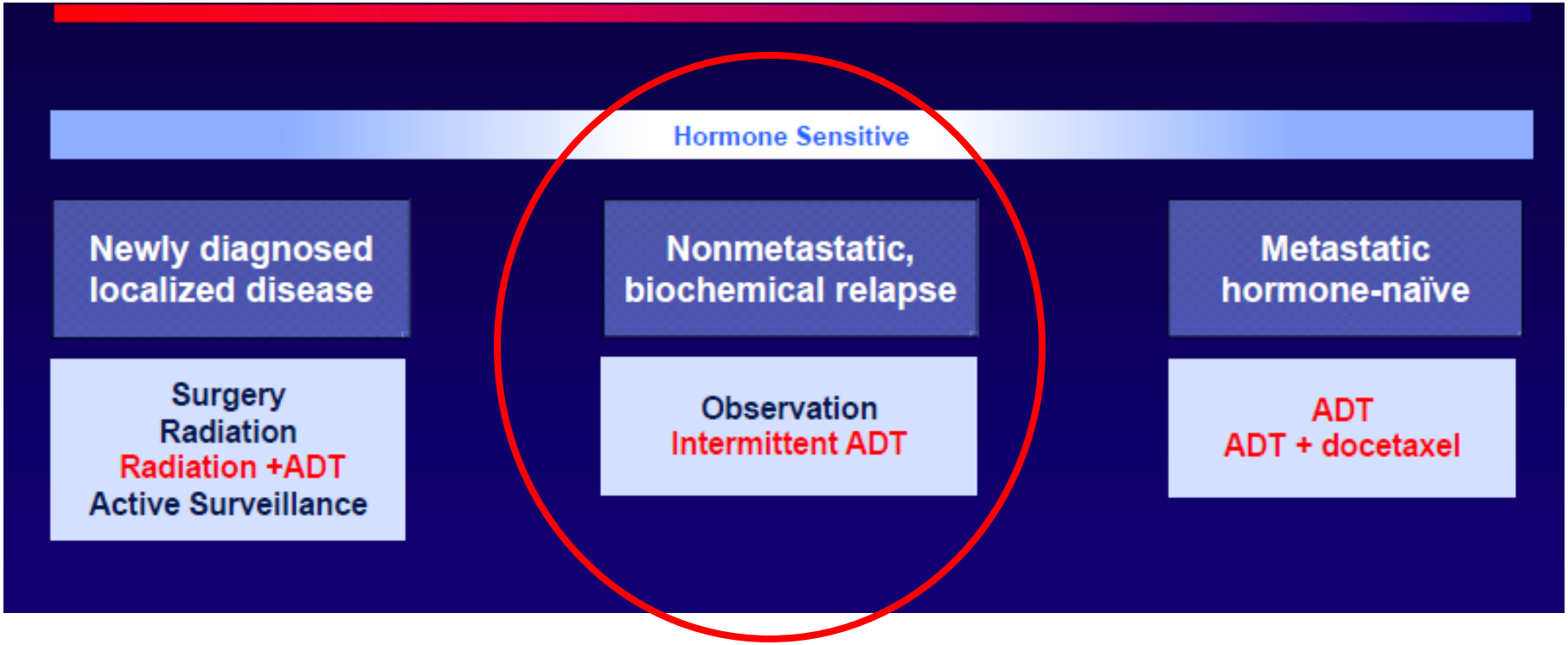


Kastrasyona Dirençli Prostat Kanseri

- Serial rising PSAs or progressive disease on scans
- Castrate level of serum testosterone
  - T < 50 ng/ml
  - T < 20 ng/ml
- Historical (but not accurate) terminology
  - Hormone refractory (HRPC)
  - Androgen independent (AI)

64 yaşında erkek hasta, yaygın sırt ağrısı var, kastrasyona dirençli, PSA 134ng/ ml saptandı. Hastaya, dosetaksel başlandı ve 6 kürde PSA 60ng/ ml geriliyor. Sonraki tedavilerde artarak 110ng/ ml oluyor. TVS multiple kemik metastazı var. BT retroperitoneal 5 cm varan multiple lenf nodları mevcut.

Bu hasta için en uygun tedavi şekli ne olmalı?(RT+ Zolendronik asid 4mg+/…..)

1-Spilutuel T

2-Radiyum 223

3-Enuzulutamid

4- Abireteron

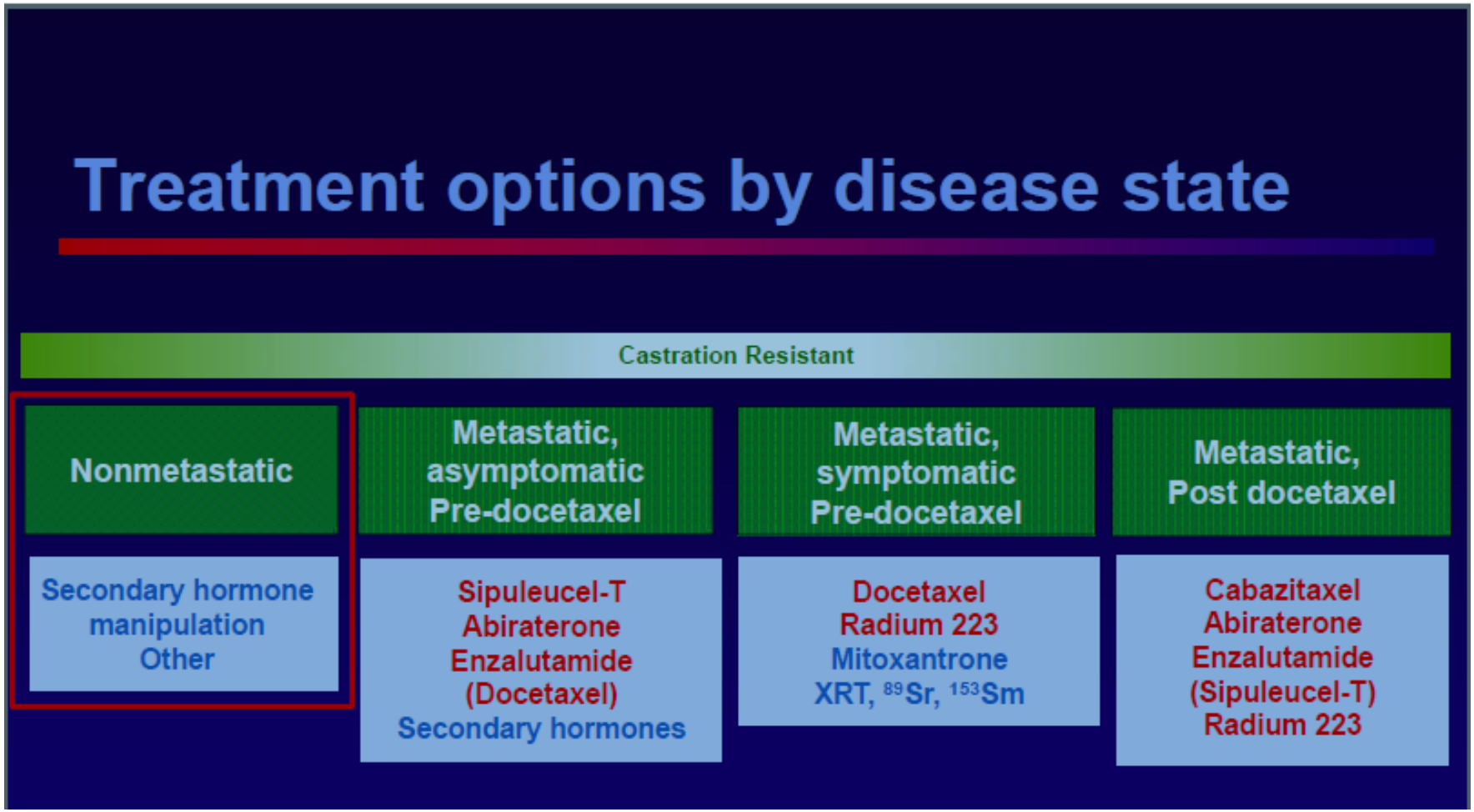
5- Kabazitaksel

6-Hepsi olabilir

Kastrasyona Dirençli Hastada Tedavi Kararında Ne Etkili

- Tümör yükü
- ADT cevap süresi(12 ay≥ yada≤)
- Aldığı tedaviler(dosetaksel öncesi sonrası)
- Kemoterapiye yanıt durumu
- PSA düzeyi
- Viseral metastaz
- Hastanın semptomatik olması
- Hastanın performansı ve yaşam beklentisi
- Seçilecek tedavinin toksitesi

Kastrasyona Dirençli Prostat Kanseri



Kastrasyona Dirençli Prostat Kanserinde Tedavi

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2017
Prostate Cancer

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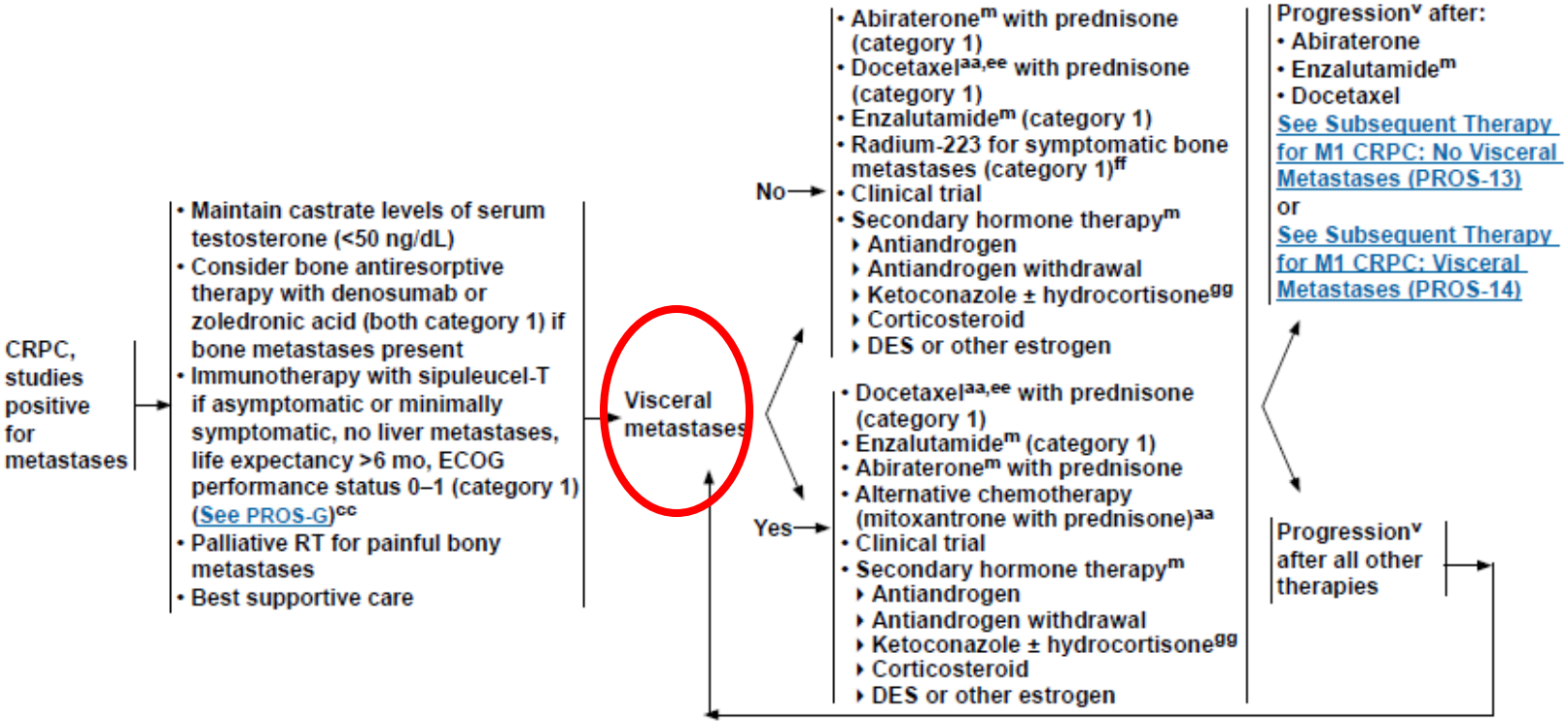
SYSTEMIC THERAPY FOR M1 CASTRATION-RECURRENT PROSTATE CANCER



[m] See Principles of Androgen Deprivation Therapy (PROS-F).

[v] Imaging should include chest x-ray, bone scan, and abdominal/pelvic CT or MRI with and without contrast. Consider C-11 choline PET/CT. See Principles of Imaging (PROS-B).

[aa] See Principles of Immunotherapy and Chemotherapy (PROS-G).

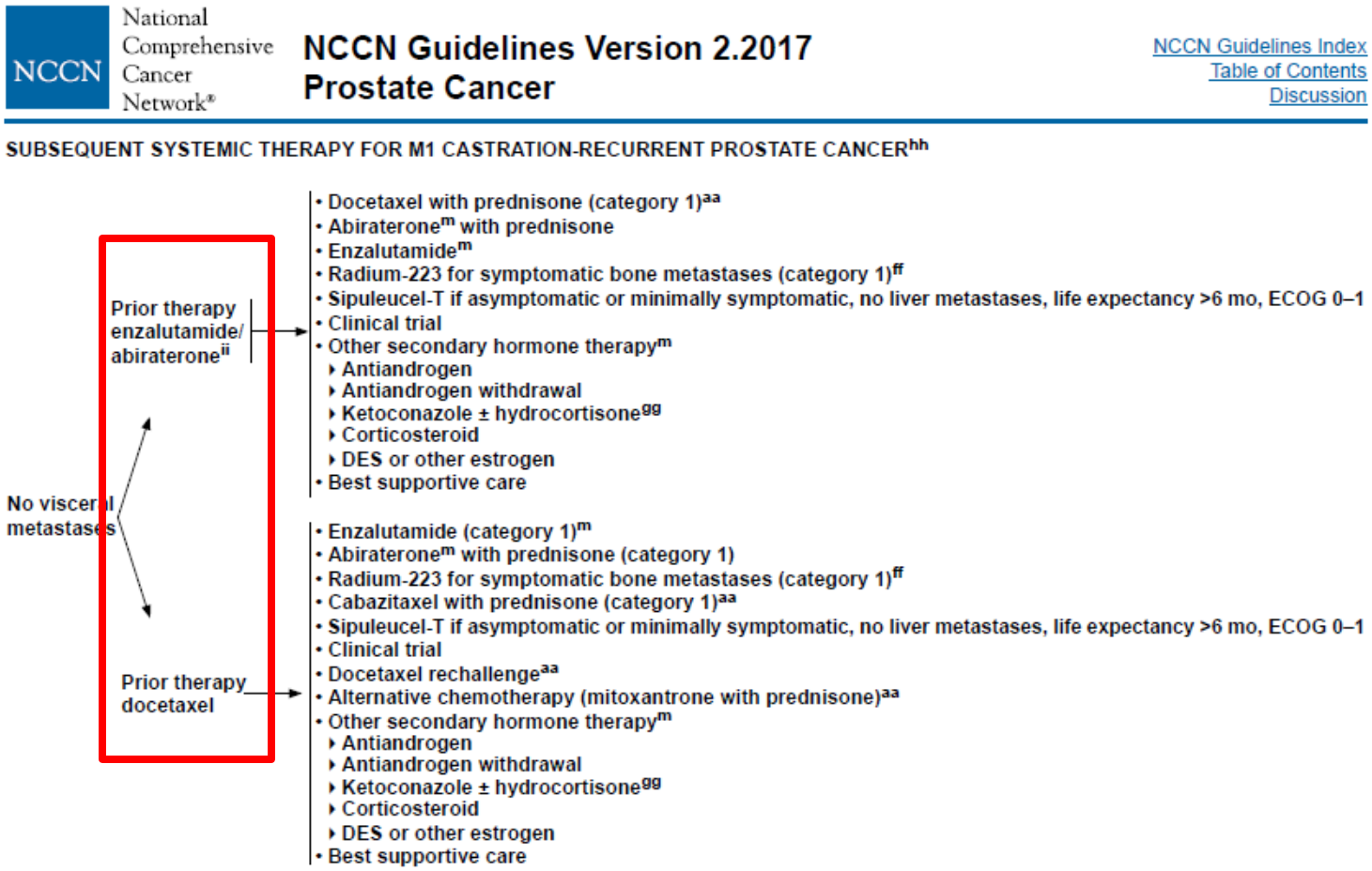
[cc] Sipuleucel-T has not been studied in patients with visceral metastases.

[ee] Although most patients without symptoms are not treated with chemotherapy, the survival benefit reported for docetaxel applies to those with or without symptoms. Docetaxel may be considered for patients with signs of rapid progression or visceral metastases despite lack of symptoms.

[ff] Radium-223 is not approved for use in combination with docetaxel or any other chemotherapy. See Principles of Radiation Therapy (PROS-D, page 2 of 2).

[gg] Ketoconazole ± hydrocortisone should not be used if the disease progressed on abiraterone.

Kastrasyona Dirençli Prostat Kanserinde Tedavi



Kastrasyona Dirençli Prostat Kanserinde Tedavi

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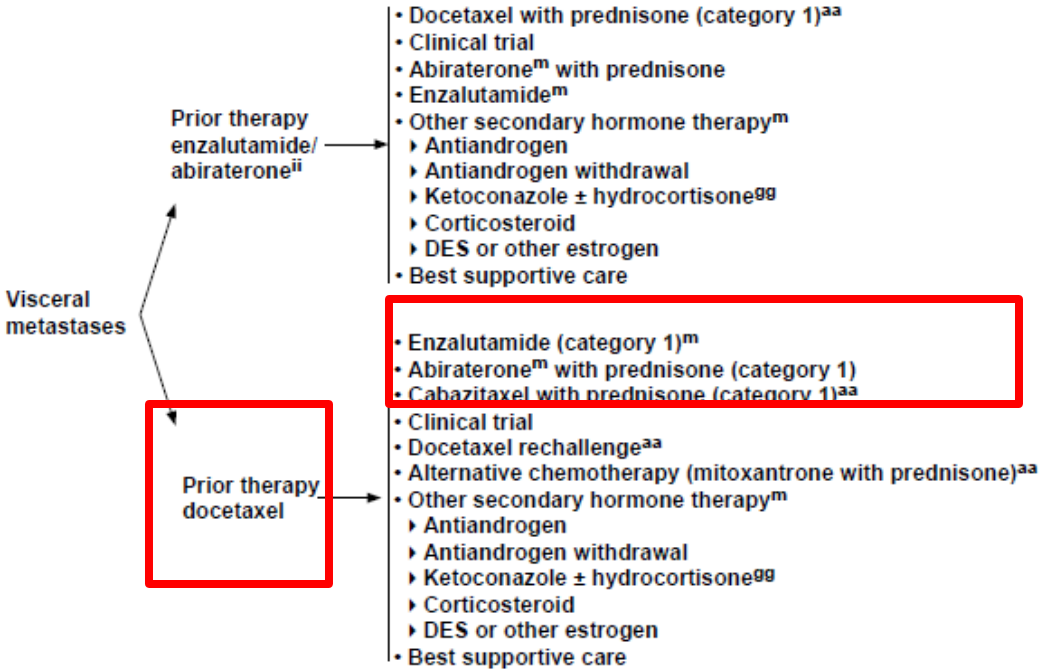
SUBSEQUENT SYSTEMIC THERAPY FOR M1 CASTRATION-RECURRENT PROSTATE CANCER[hh]



[gg]Ketoconazole ± hydrocortisone should not be used if the disease progressed on abiraterone.

[hh]Patients can continue through all treatment options listed. Best supportive care is always an appropriate option.

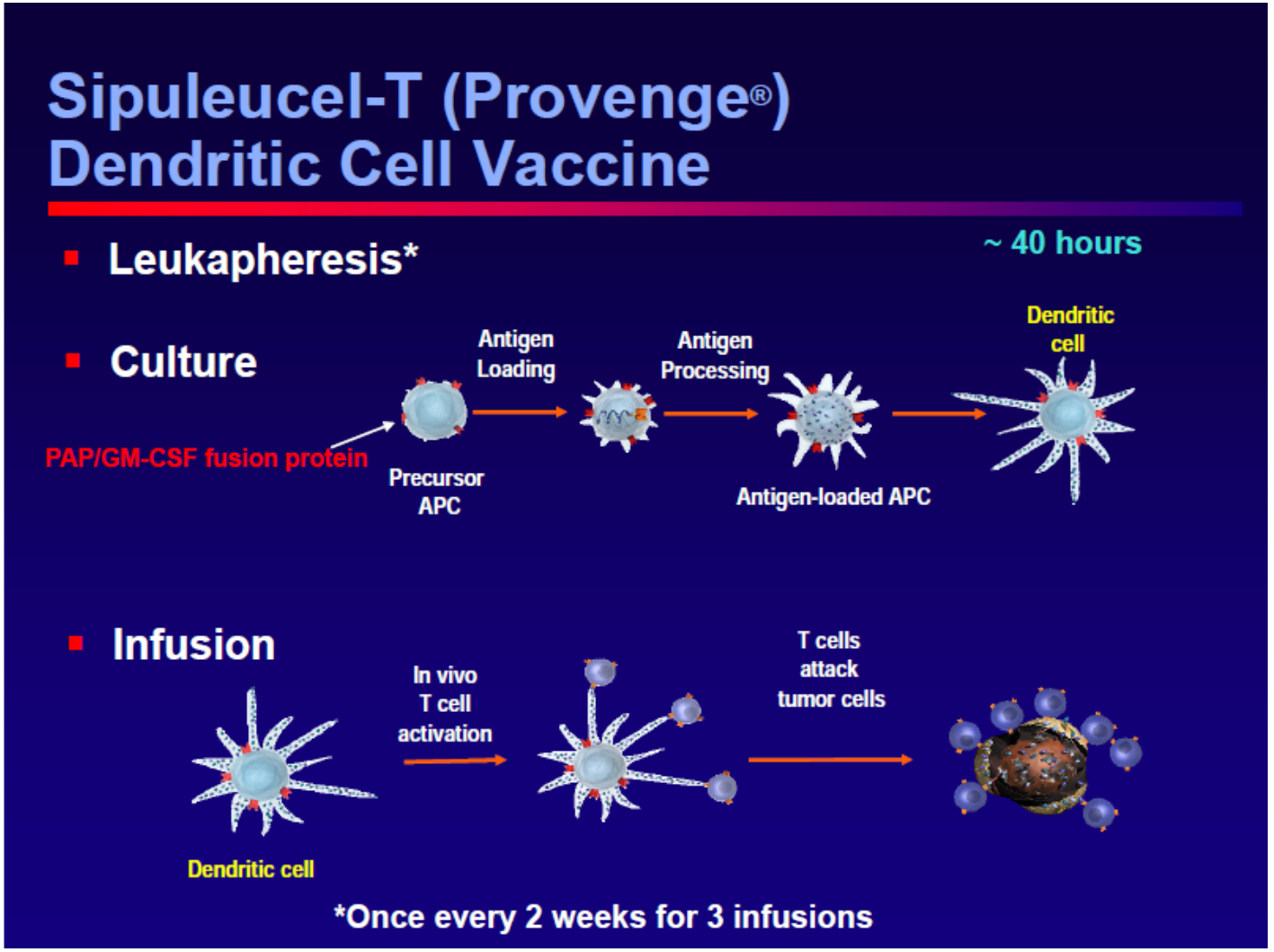
[ii]Limited data suggest a possible role for AR-V7 testing to help guide selection of therapy (See Discussion).

[m]See Principles of Androgen Deprivation Therapy (PROS-F).

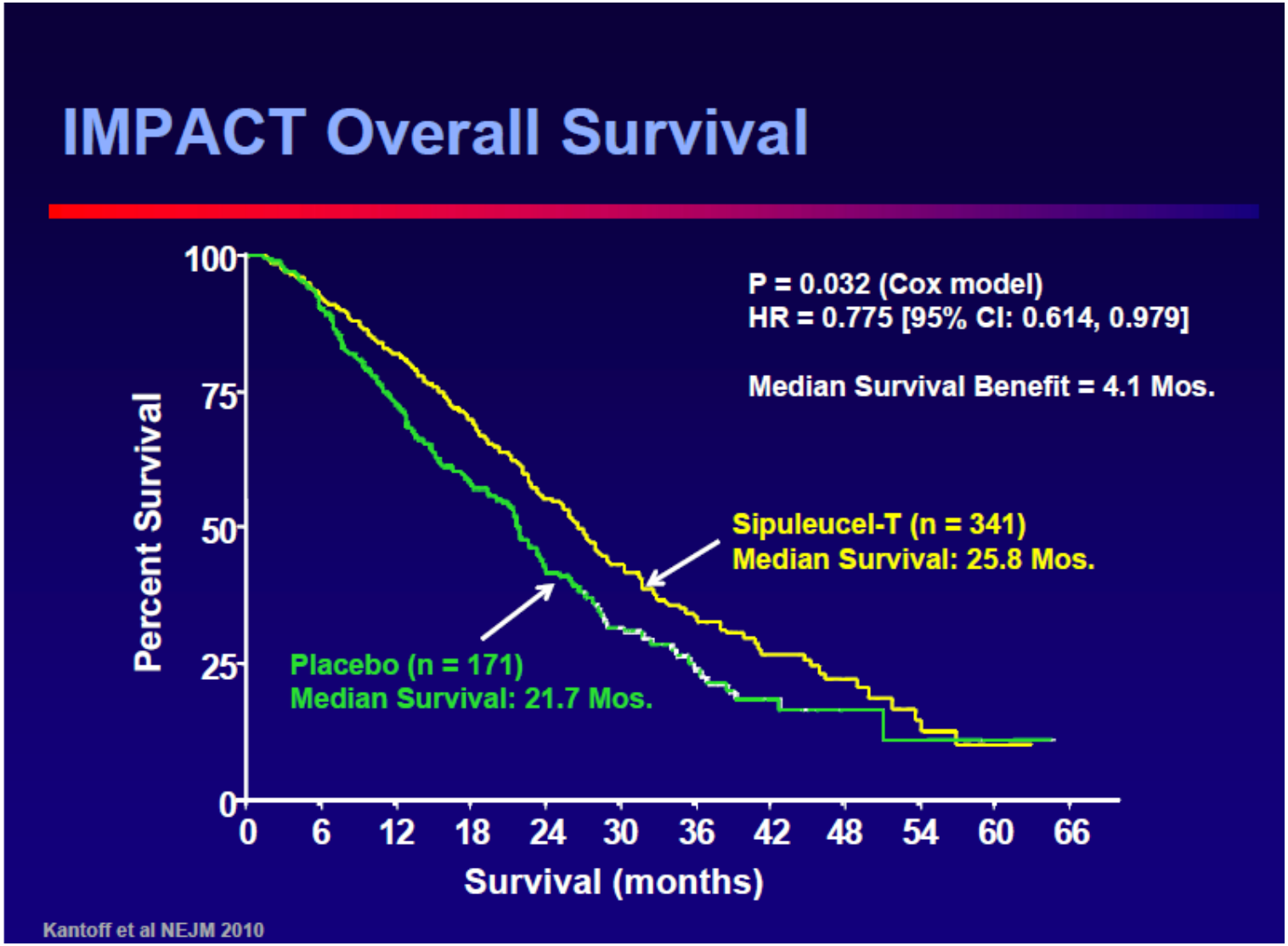
[aa]See Principles of Immunotherapy and Chemotherapy (PROS-G).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Kastrasyona Dirençli Prostat Kanseri



Kastrasyona Dirençli Prostat Kanseri



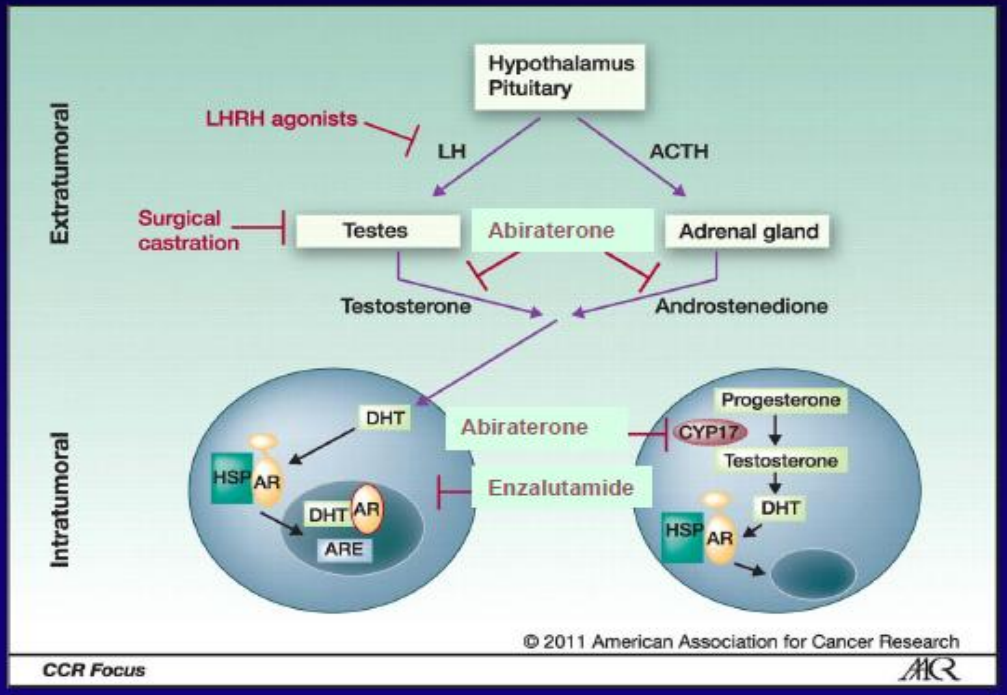
Kastrasyona Dirençli Prostat Kanseri Tedavi-Sipuleucel-T

Sipuleucel-T

- Approved April 2010
- Asymptomatic or minimally symptomatic men with metastatic CRPC
- Toxicities are mild, infusion related: fever, chills
- Should NOT be used to treat patients with symptoms
- Ideally used early with lower volume disease or before numerous other therapies
- Despite OS advantage, no impact on PSA or radiographic response, PFS

Kastrasyona Dirençli Prostat Kanseri

Abiraterone and enzalutamide: Sites of action on the androgen axis



Adapted from Massard C, Clin Cancer Res 2011

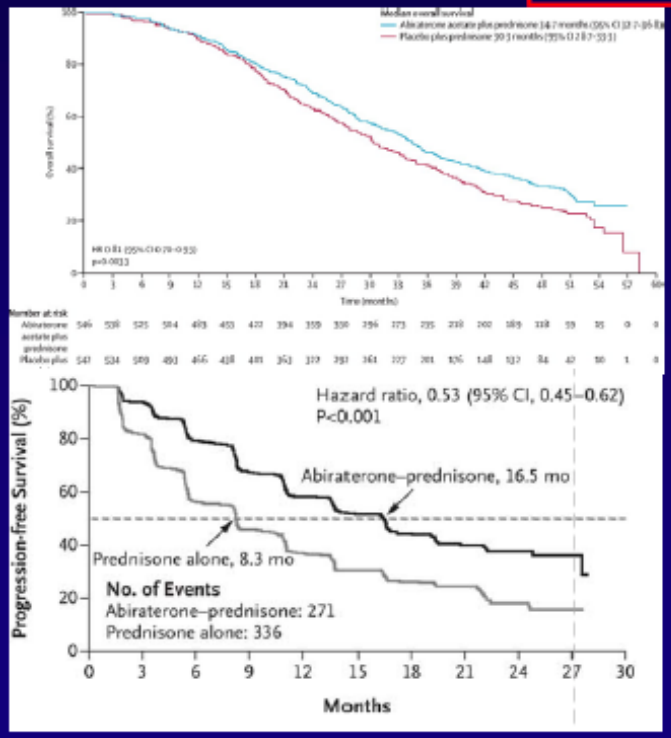
Kastrasyona Dirençli Prostat Kanseri Hormonal Tedavi

Chemotherapy naïve mCRPC phase 3 trials

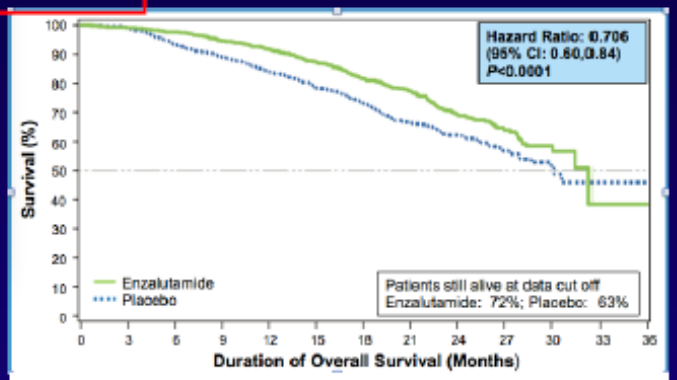
COU-302
Abiraterone + prednisone

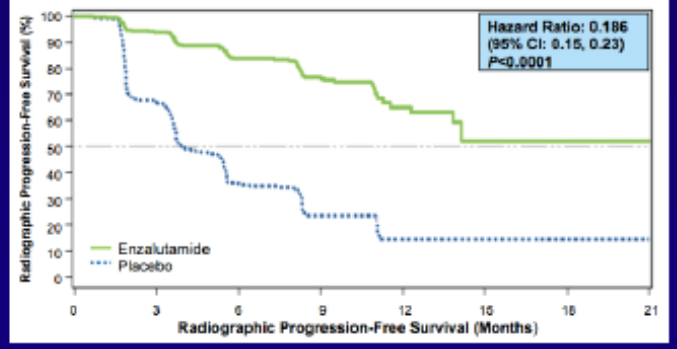
Co-primary endpoints: OS, rPFS
No prior keto
No/minimal symptoms
Liver mets OK PREVAIL

PREVAIL
Enzalutamide



Ryan et al NEJM 2013, Ryan et al Lancet Oncol 2015





Beer et al NEJM 2014

Kastrasyona Dirençli Prostat Kanseri Hormonal Tedavi

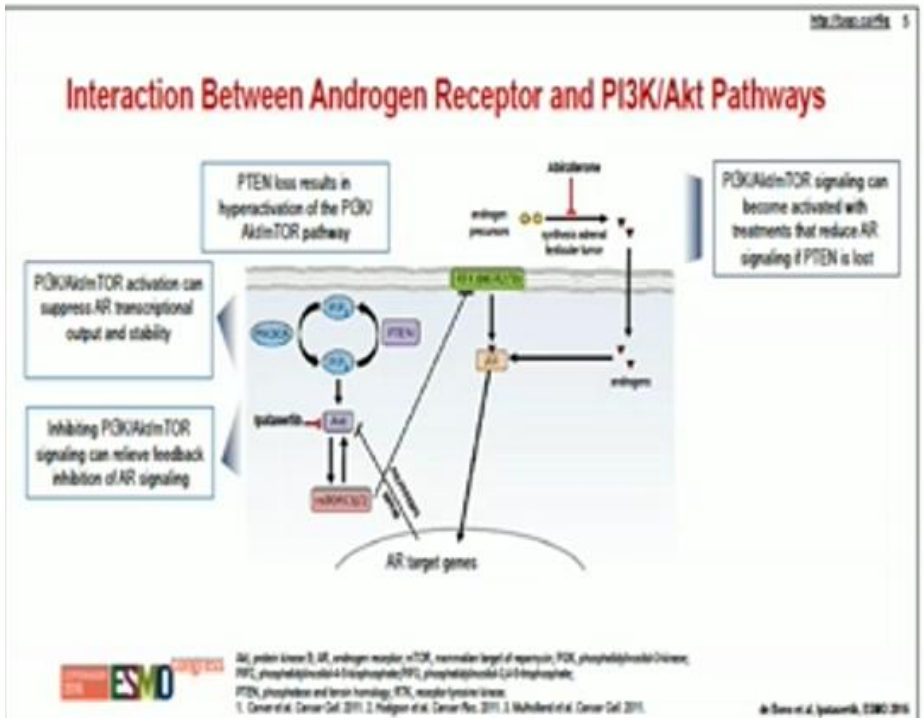
Drug characteristics and toxicities

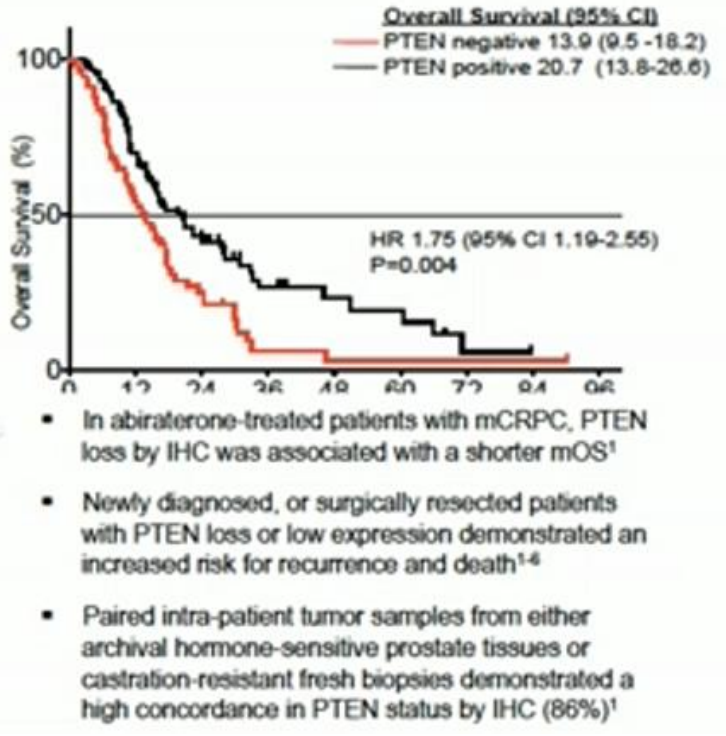
	Abiraterone	Enzalutamide
Oral	yes	yes
Prednisone required	yes	no
Drug interactions (CYP)	yes	yes
Hypokalemia	yes	no
Lowers seizure threshold	no	yes
Potential liver toxicity	yes	less
Hypertension	yes	yes
Fatigue	yes	yes
Some cardiac	yes	yes
Falls	no	yes
Dose	250 mg x 4	40 mg tablets x 4
Empty stomach	yes	no

Kastrasyona Dirençli Prostat Kanseri Hormonal-Yeni Tedavi Seçenekleri

THE WAY FORWARD…

A Strong Scientific Rationale supported by Clinical Associations



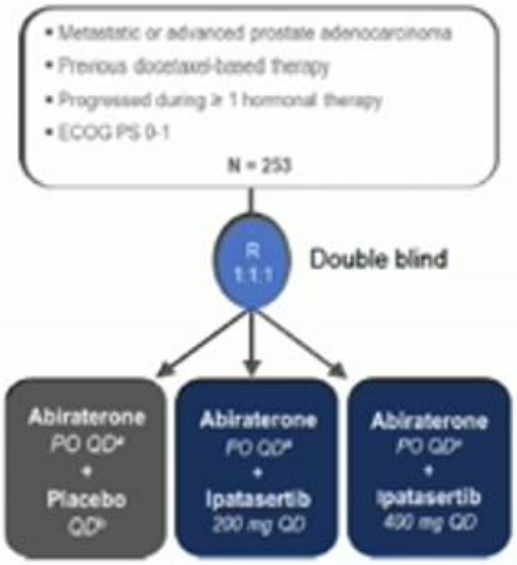


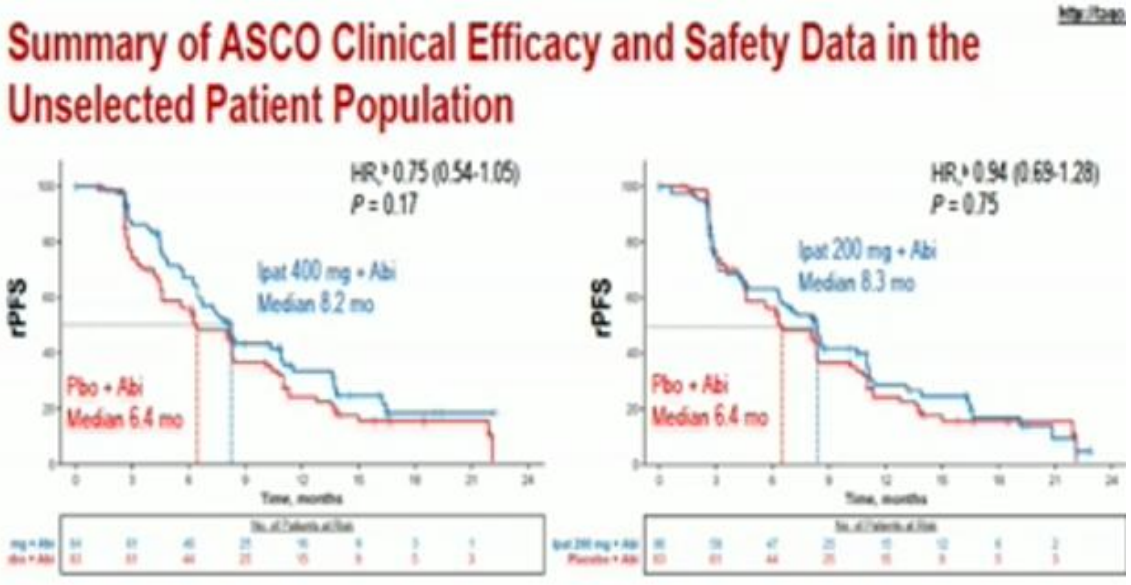
- In abiraterone-treated patients with mCRPC, PTEN loss by IHC was associated with a shorter mOS[1]
- Newly diagnosed, or surgically resected patients with PTEN loss or low expression demonstrated an increased risk for recurrence and death[1-6]
- Paired intra-patient tumor samples from either archival hormone-sensitive prostate tissues or castration-resistant fresh biopsies demonstrated a high concordance in PTEN status by IHC (86%)[1]

Kastrasyona Dirençli Prostat Kanseri Hormonal -Yeni Tedavi

STUDY DESIGN SERVED BOTH MASTERS

Co-Primary Endpoints : rPFS in ITT and pts with PTEN loss



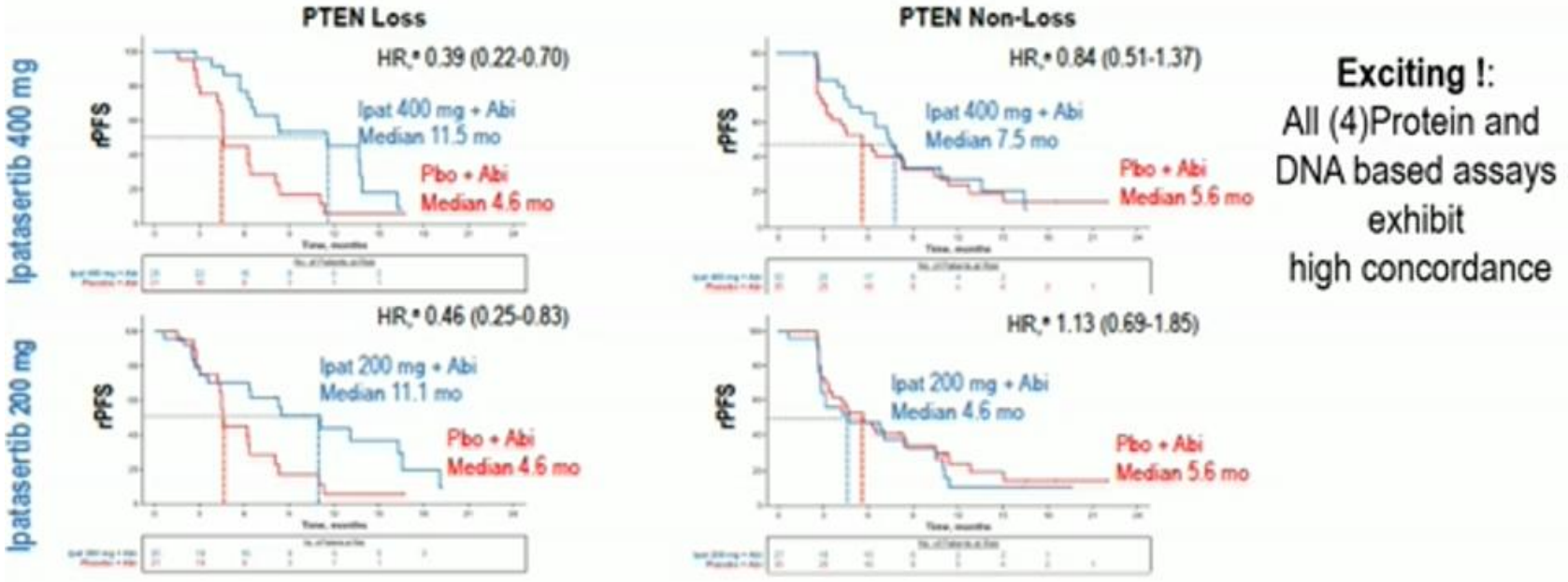


ESMO congress

De Bono et al

Kastrasyona Dirençli Prostat Kanseri
Hormonal Tedavi-Yeni Tedavi

Co-Primary Endpoint met : Patients with PTEN loss (IHC) exhibit improved rPFS on combination



Exciting !:
All (4)Protein and DNA based assays exhibit high concordance

COPENHAGEN 2015 ESMO congress

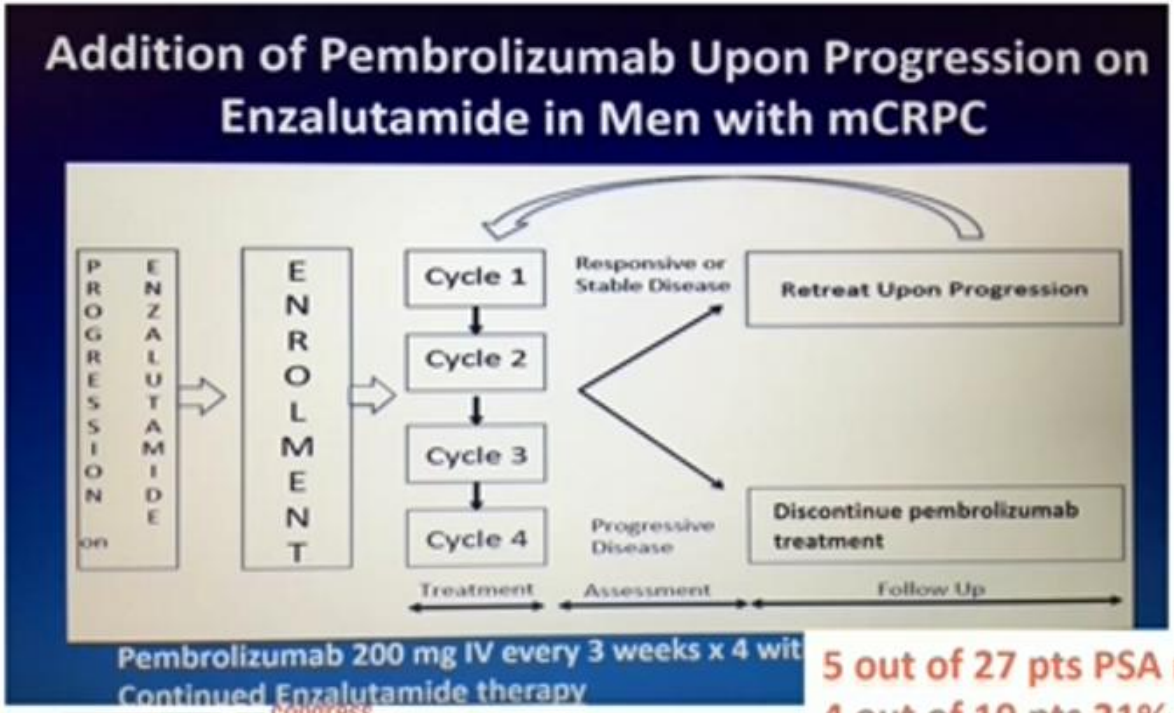
Next Step : Prospective Validation

De Bono et al

Kastrasyona Dirençli Prostat Kanseri Hormonal-Yeni Tedavi Seçenekeleri

PEMBROLIZUMAB MAKES A GUEST STAR APPEARANCE

Or is it here to stay ? – Hopefully the latter



Rationale

Enzalutamide Resistance

Associated with increased PD-L1 Expression

Hypothesis

Combo

ENZA-PEMBRO

Will lead to response

PRIMARY ENDPOINT(bold!)

PSA response >=50%

Sample size 28

Null Hypothesis 5%

Alt Hypothesis 25%

5 out of 27 pts PSA responses (19%)

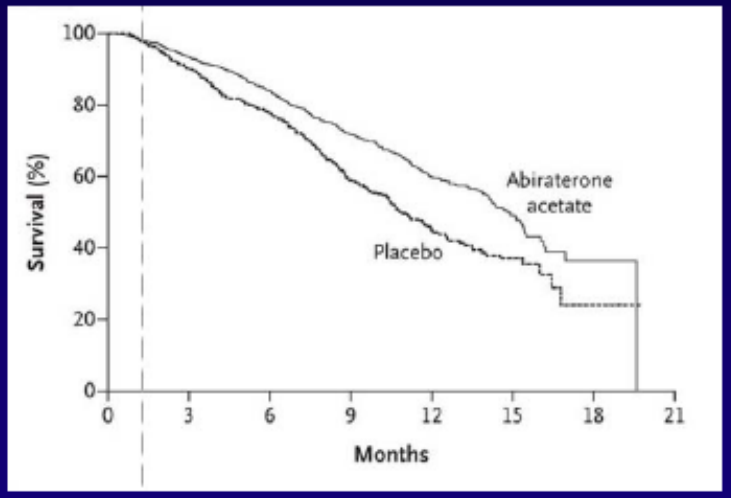
4 out of 19 pts 21% SD >Z 6 months

Graff et al ESMO 2016

Kastrasyona Dirençli Prostat Kanseri

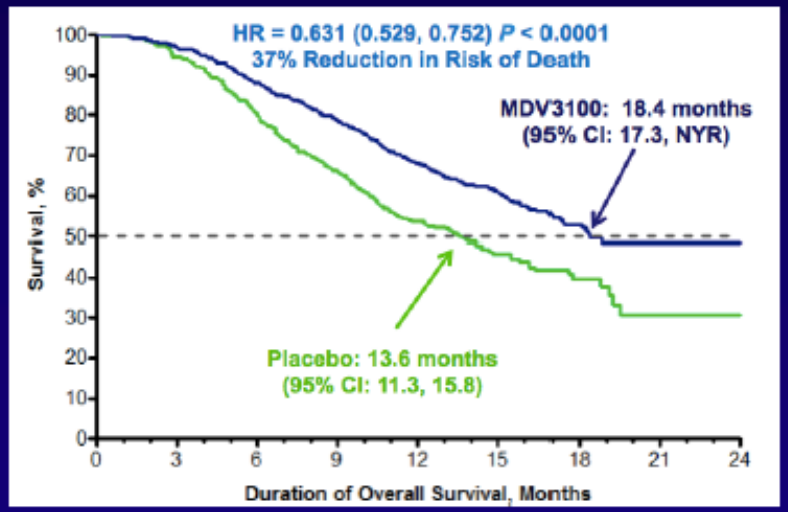
Post docetaxel phase 3 trials: abiraterone and enzalutamide

COU 301:
Abiraterone + prednisone vs placebo + prednisone



de Bono et al, NEJM 2011

AFFIRM:
Enzalutamide vs placebo

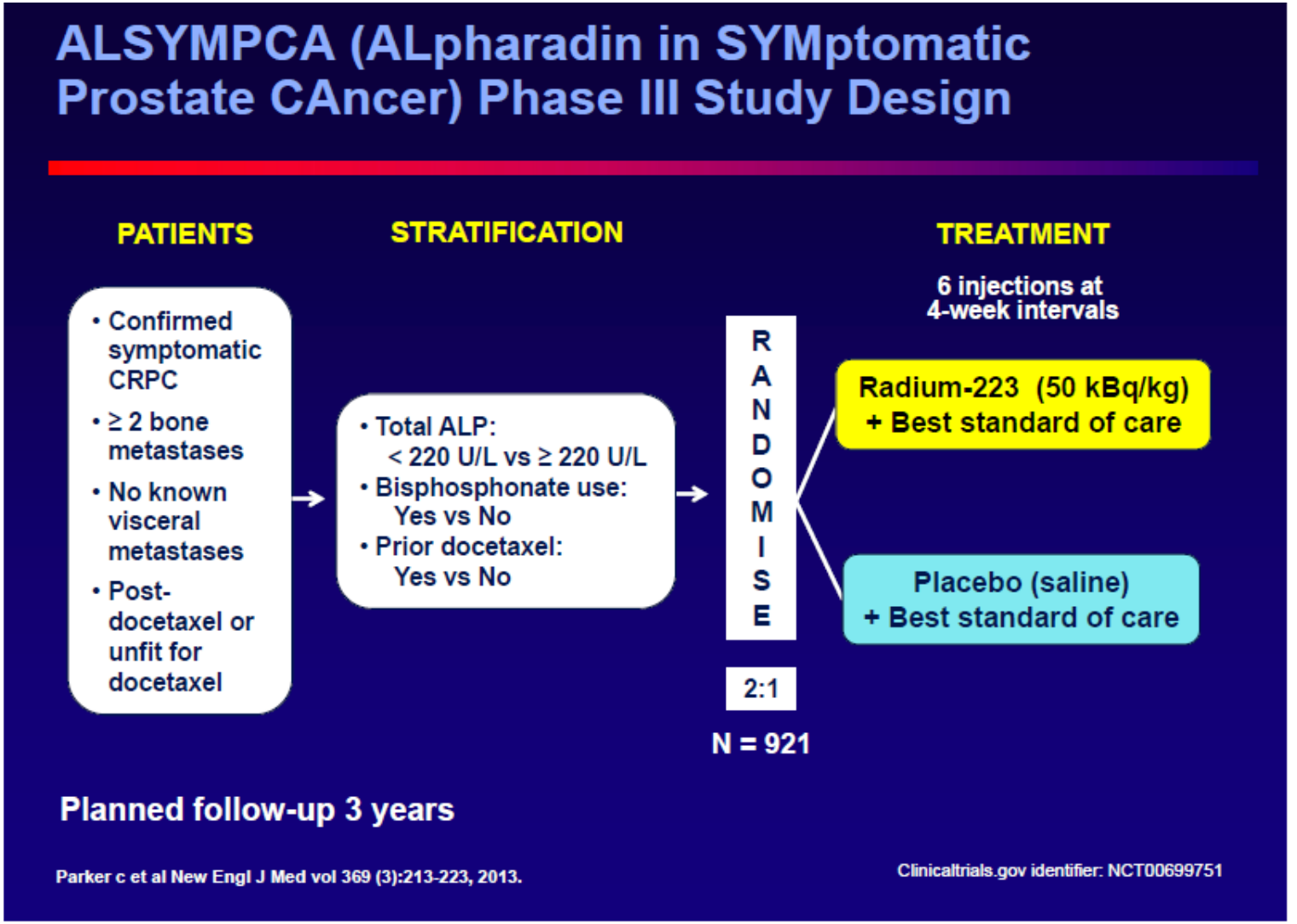


Scher et al, NEJM 2012

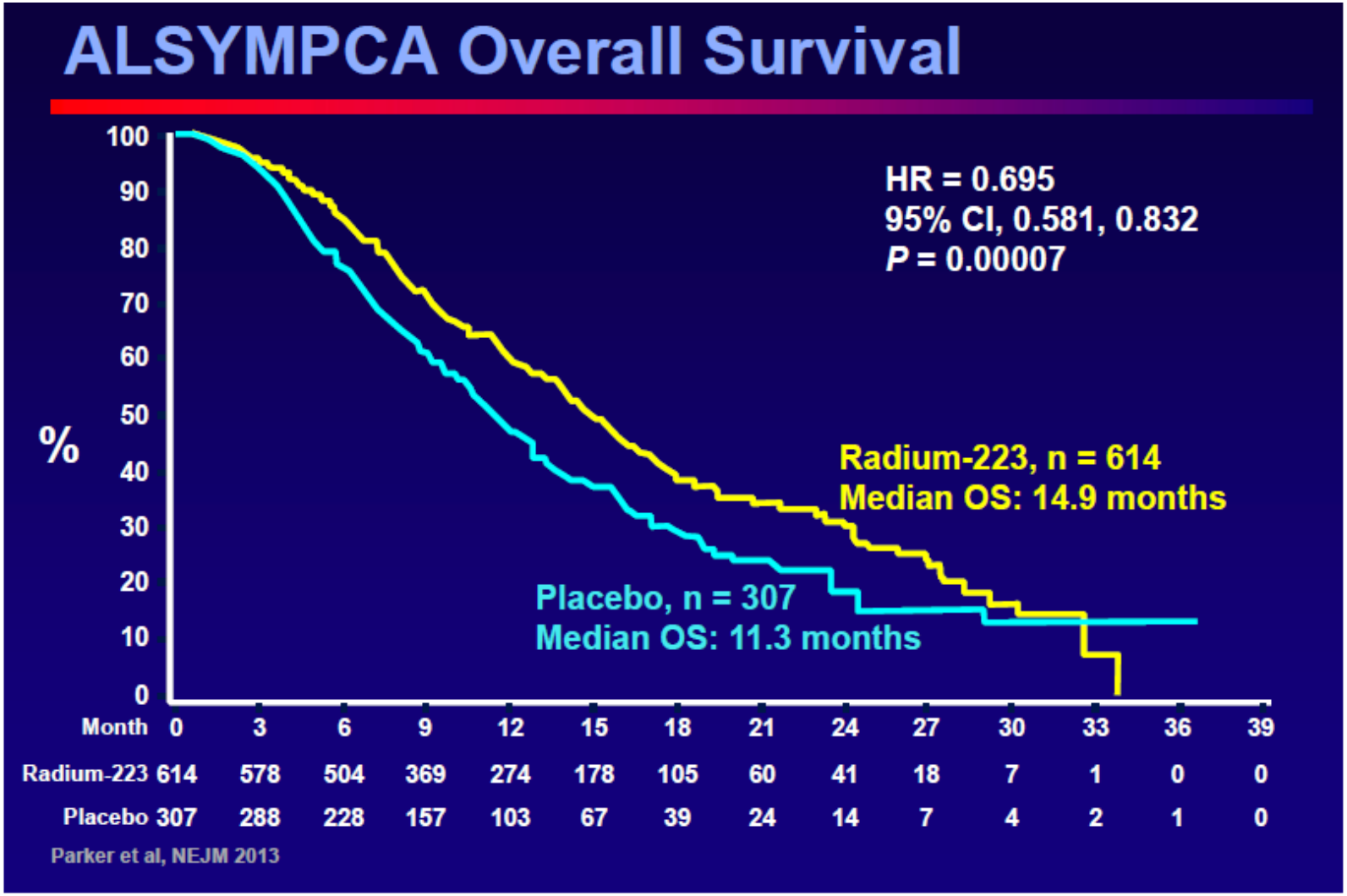
- 2:1 randomization to placebo arm
- Primary endpoint overall survival
- Entry criteria: prior docetaxel, no prior keto, PS ≤ 2

Both agents show significant benefit for OS

Kastrasyona Dirençli Prostat Kanseri



Kastrasyona Dirençli Prostat Kanseri Docitaksel Sonrası Kemoterapi

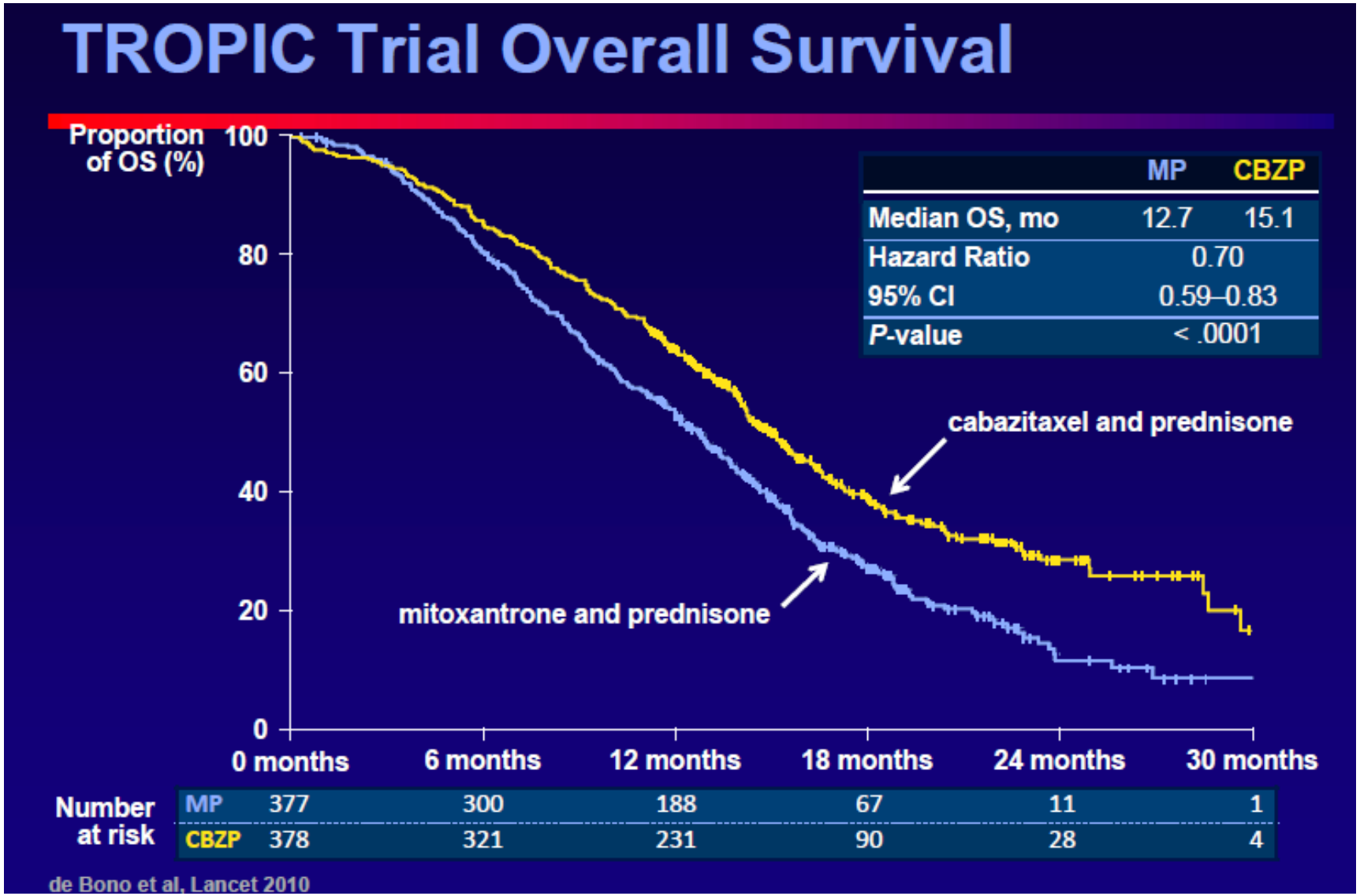


Kastrasyona Dirençli Prostat Kanseri

Cabazitaxel

- Semi-synthetic taxoid derivative
- FDA approved June 2010 with prednisone
- For patients with mCRPC previously treated with docetaxel
- Consider use of growth factor support

Kastrasyona Dirençli Prostat Kanseri



Kastrasyona Dirençli Prostat Kanseri Dosetaksel Sonrası Kemoterapi

PROSELICA - SURVIVAL

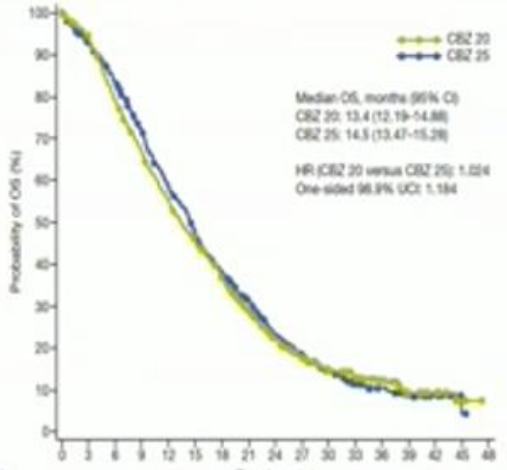
Figure 1. Study design

- Post-marketing, FDA-designed study
- Non-inferiority design
- HR=0.70 for CBZ 25 vs mitoxantrone (TROPIC)
- **Fewer Grade 3+ problems with CBZ 20**

HR (CBZ 20 versus CBZ 25): 1.024

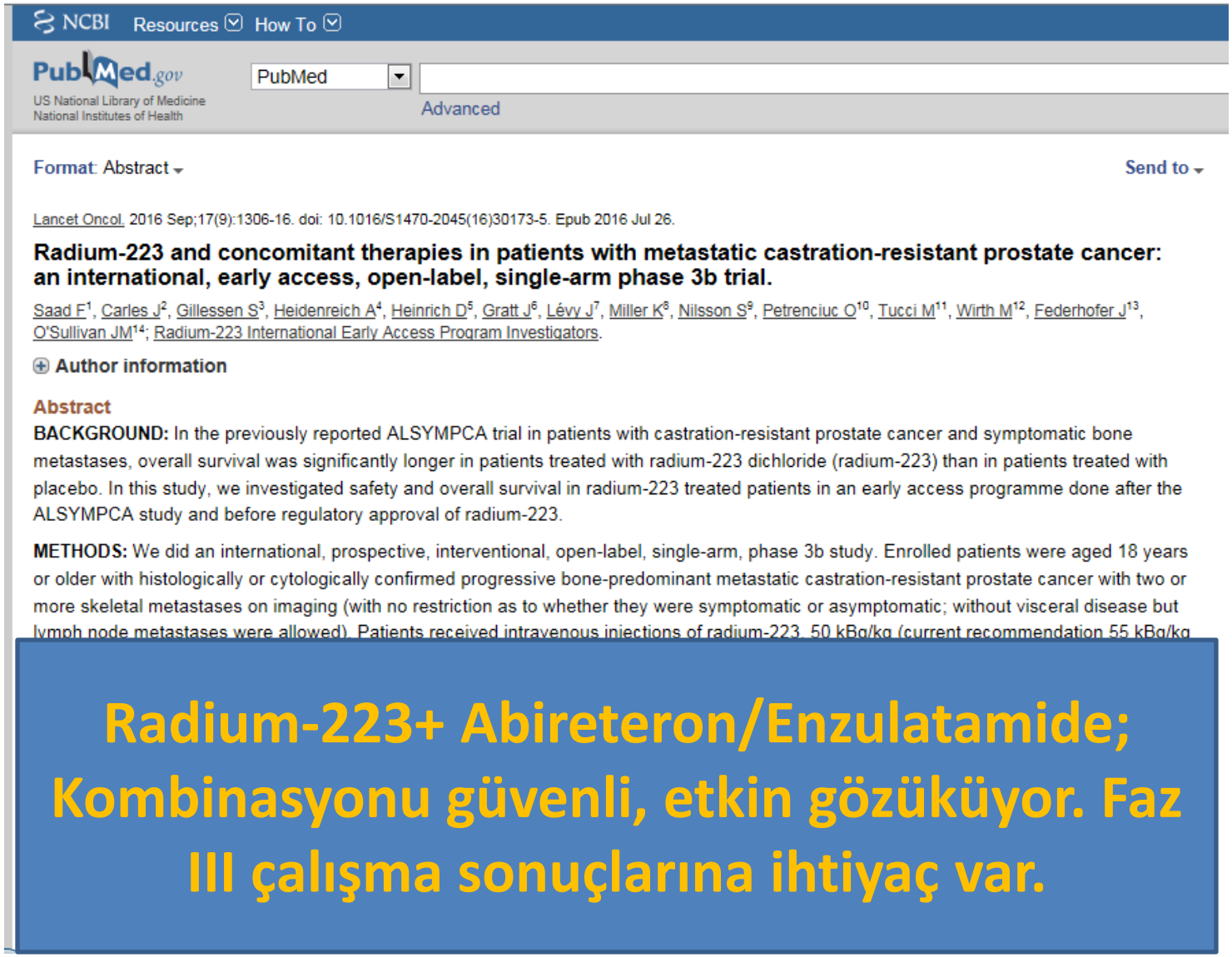
One-sided 98.9% UCL 1.184

Figure 2. Overall survival



PFS, OS aynı olmak ile beraber PSA düşüş oranı 25 mg kolunda daha yüksek. Agresif hastalıkta 25 mg/m2, toksite riski yüksek olan hastalarda 20 mg/m2 uygun gözüküyor

Kastrasyona Dirençli Hastalarda Kombinasyon Tedavisi



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Lancet Oncol. 2016 Sep;17(9):1306-16. doi: 10.1016/S1470-2045(16)30173-5. Epub 2016 Jul 26.

Radium-223 and concomitant therapies in patients with metastatic castration-resistant prostate cancer: an international, early access, open-label, single-arm phase 3b trial.

Saad F[1], Carles J[2], Gillessen S[3], Heidenreich A[4], Heinrich D[5], Gratt J[6], Lévy J[7], Miller K[8], Nilsson S[9], Petrenciuc O[10], Tucci M[11], Wirth M[12], Federhofer J[13], O'Sullivan JM[14]; Radium-223 International Early Access Program Investigators.

Author information

Abstract

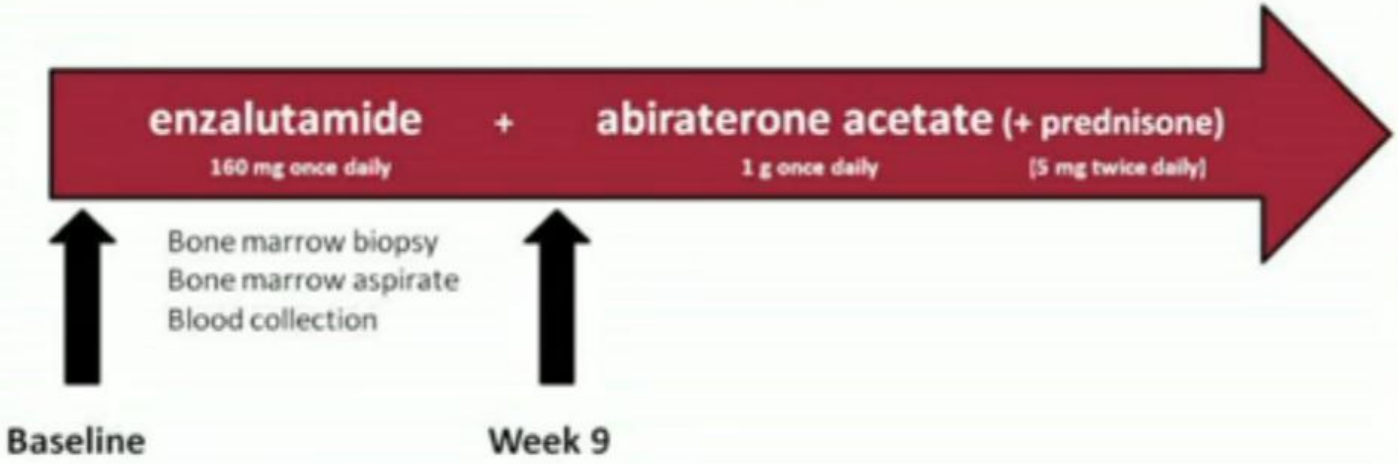
BACKGROUND: In the previously reported ALSYMPCA trial in patients with castration-resistant prostate cancer and symptomatic bone metastases, overall survival was significantly longer in patients treated with radium-223 dichloride (radium-223) than in patients treated with placebo. In this study, we investigated safety and overall survival in radium-223 treated patients in an early access programme done after the ALSYMPCA study and before regulatory approval of radium-223.

METHODS: We did an international, prospective, interventional, open-label, single-arm, phase 3b study. Enrolled patients were aged 18 years or older with histologically or cytologically confirmed progressive bone-predominant metastatic castration-resistant prostate cancer with two or more skeletal metastases on imaging (with no restriction as to whether they were symptomatic or asymptomatic; without visceral disease but lymph node metastases were allowed). Patients received intravenous injections of radium-223, 50 kBq/kg (current recommendation 55 kBq/kg

Radium-223+ Abireteron/Enzulatamide; Kombinasyonu güvenli, etkin gözüküyor. Faz III çalışma sonuçlarına ihtiyaç var.

Hormonal Kombine Terapi(Abi+ Enz)

Study Design



Endpoints

- Safety
- Drug–drug interactions
- Modulation of androgen receptor and biosynthesis
- Efficacy
- Predictors of outcome

Presented By Eleni Efstathiou at 2014 ASCO Annual Meeting, Abstract 5000

Hormonal Kombine Terapi(Abi+ Enz)

Treatment Emergent Adverse Events (TEAEs)

Most frequently reported AEs ANY GRADE (independent of causality)	N (%)
Fatigue / Asthenia	44 (73)
Hyperglycemia	39 (65)
Hot flush	26 (43)
Nausea	14 (23)
Hypertension	13 (22)
Hypomagnesaemia	11 (18)
Headache	10 (17)
Liver function Tests increase AST / ALT / Tbil	22 / 17 / 12 (37 / 28 / 20)
Disease-related AEs: ALP increase / anemia / back pain / arthralgia / pain in extremity	31 / 26 / 18 / 15 / 11 (52 / 37 / 30 / 25 / 18)

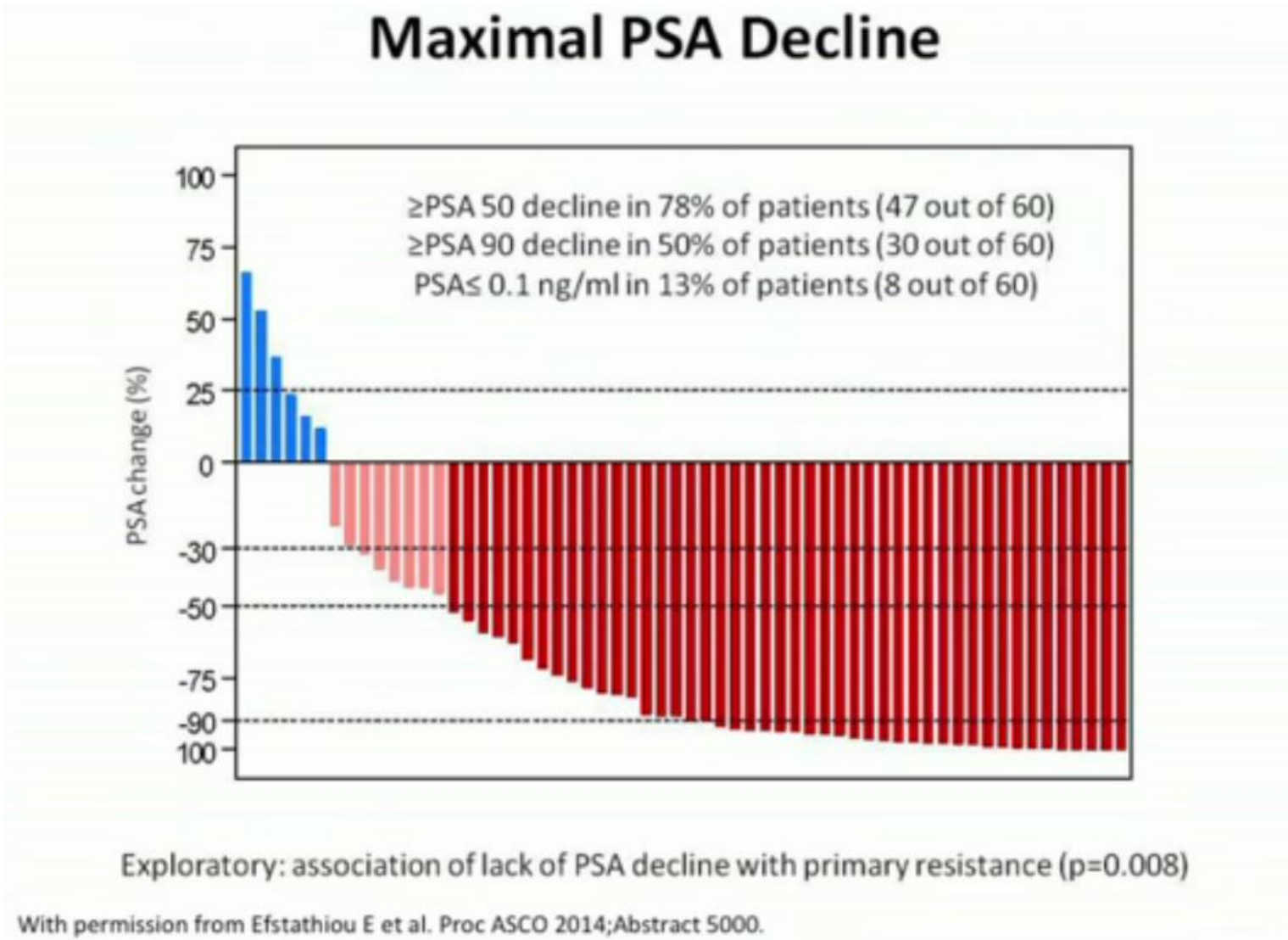
GRADE 3 AEs (independent of causality)		N (%)
Lab findings	ALT increased	6 (10)
	ALP increased	4 (7)
	AST increased	1 (2)
Vascular disorder	Hypertension	8 (13)
	Hypotension	1 (2)
Musculoskeletal	Arthralgia	3 (5)
	Bone pain	2 (3)
	Back pain	1 (2)
Metabolism	Hypokalemia	2 (3)
	Hypophosphatemia	1 (2)
Cardiac disorders	Angina pectoris	1 (2)
	Atrial fibrillation	1 (2)
	AV block complete	1 (2)
Eye disorders	Macular edema	1 (2)
	Retinal vein occlusion	1 (2)
	Foreign body sensation eyes	1 (2)

There were NO Grade 4 or 5 AEs and NO new safety concerns

Patients with ≥1 SAE : 8 (13%)
AEs leading to treatment discontinuation: 3 (5%)

AEs, adverse events; ALP, alkaline phosphatase;
ALT, alanine aminotransferase; AST, aspartate aminotransferase; SAEs, serious adverse events

Hormonal Kombine Terapi(Abi+ Enz)



With permission from Efstathiou E et al. Proc ASCO 2014;Abstract 5000.

Kastrasyona Dirençli Prostat Kanseri

Enzalutamide: Phase III (AFFIRM)
Similar to Abiraterone

Hormonal Kombine Terapi(Abi+ Enz)

Combination Therapy Conclusions

- Enzalutamide and abiraterone can be combined safely
- There is no apparent effect of the PK of one drug on the other
- It is too early to tell if combination therapy improves upon the performance of single agent therapy or sequential therapy
- Biomarkers may be helpful in personalizing approaches to androgen signaling inhibition in the future.

AR-V7 MUTASYONU VE HORMONAL TEDAVİLERE DİRENÇ

ORIGINAL ARTICLE

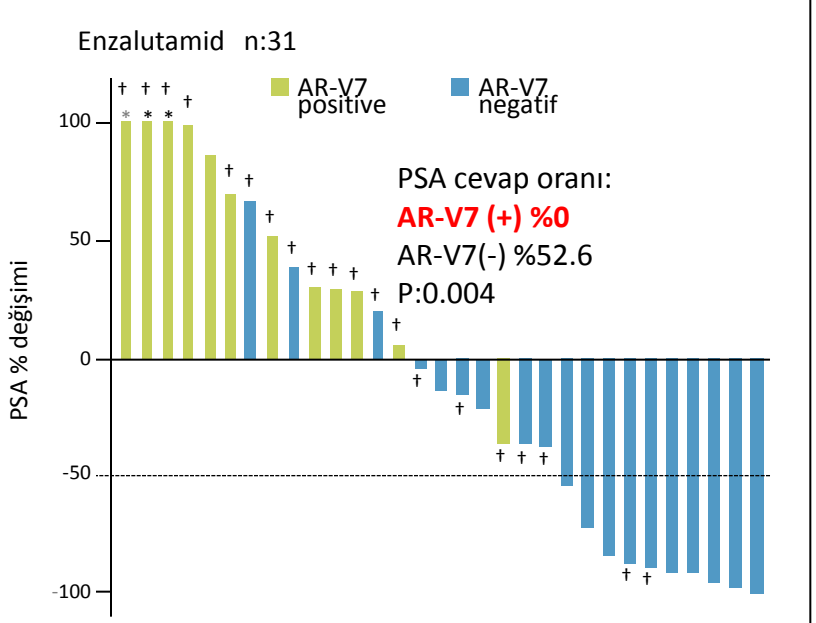
AR-V7 and Resistance to Enzalutamide and Abiraterone in Prostate Cancer

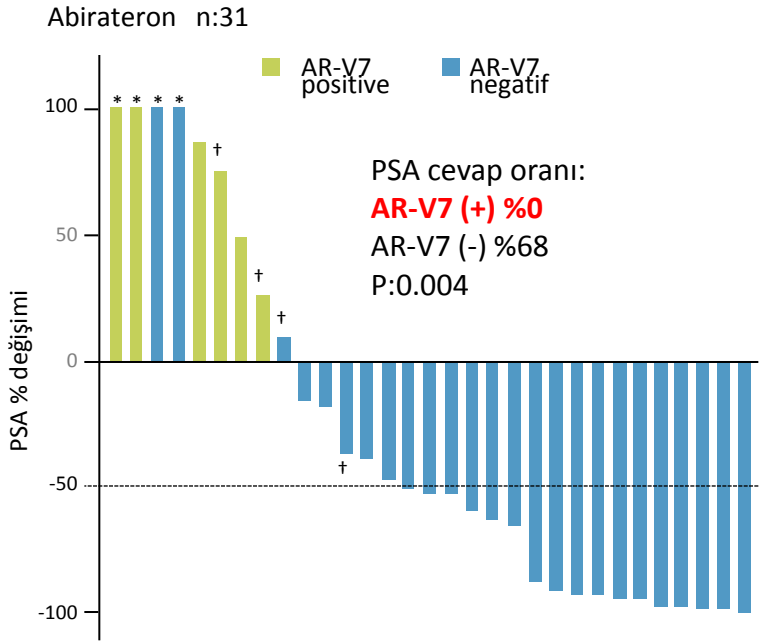
Emmanuel S. Antonarakis, M.D., Changxue Lu, Ph.D., Hao Wang, Ph.D., Brandon Luber, Sc.M., Mary Nakazawa, M.H.S., Jeffrey C. Roeser, B.S., Yan Chen, Ph.D., Tabrez A. Mohammad, Ph.D., Yidong Chen, Ph.D., Helen L. Fedor, B.S., Tamara L. Lotan, M.D., Qizhi Zheng, M.D., Angelo M. De Marzo, M.D., Ph.D., John T. Isaacs, Ph.D., William B. Isaacs, Ph.D., Rosa Nadal, M.D., Channing J. Paller, M.D., Samuel R. Denmeade, M.D., Michael A. Carducci, M.D., Mario A. Eisenberger, M.D., and Jun Luo, Ph.D.

ABSTRACT

AR-V7 MUTASYONU VE HORMONAL TEDAVİLERE DİRENÇ

AR-V7 pozitif hastalarda hormonal tedavilere cevap verme oranı %0'dır.

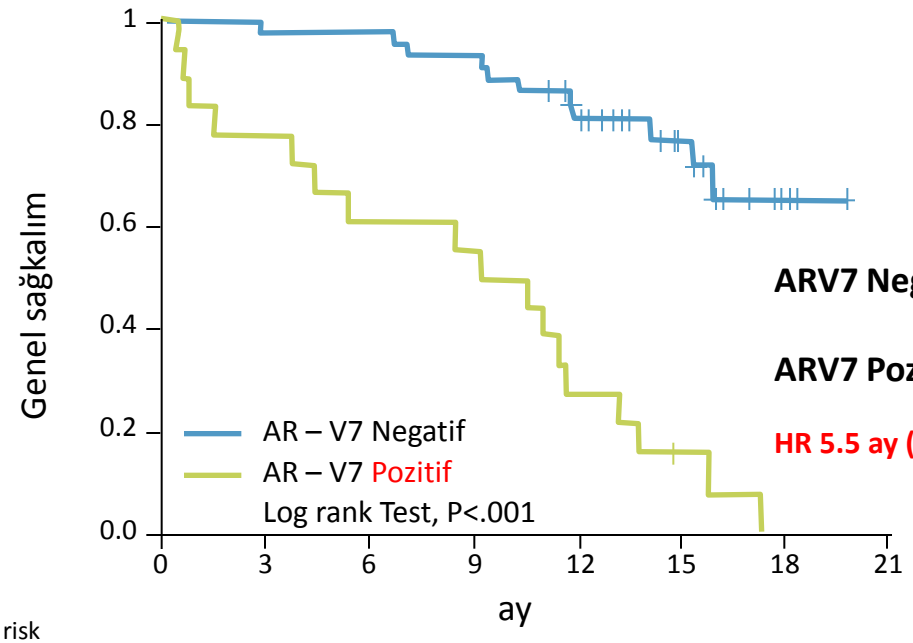




Hastaların %19-39 unda AR-V7 pozitif bulunmuştur.

Antonarakis ES, et al. AR-V7 and Resistance to Enzalutamide and Abiraterone in Prostate Cancer.
N Engl J Med. 2014 Sep 11;371(11):1028-38

AR-V7 MUTASYONU VE HORMONAL TEDAVİLERE DİRENÇ



Number at risk

AR – V7 Negative:	44	43	43	41	31	15	4	0
AR – V7 Positive:	18	14	11	10	5	2	4	0

ARV7 Negatif >16 ay (%95 CI, 16-..)

ARV7 Pozitif 9.9 ay (%95 CI, 4.5-13.8)

HR 5.5 ay (%95 CI, 2.5- 12.0);p<0.001

Antonarakis ES, et al. AR-V7 and Resistance to Enzalutamide and Abiraterone in Prostate Cancer. N Engl J Med. 2014

AR-V7 MUTASYONU VE HORMONAL TEDAVİLERE DİRENÇ

The NEW ENGLAND JOURNAL of MEDICINE

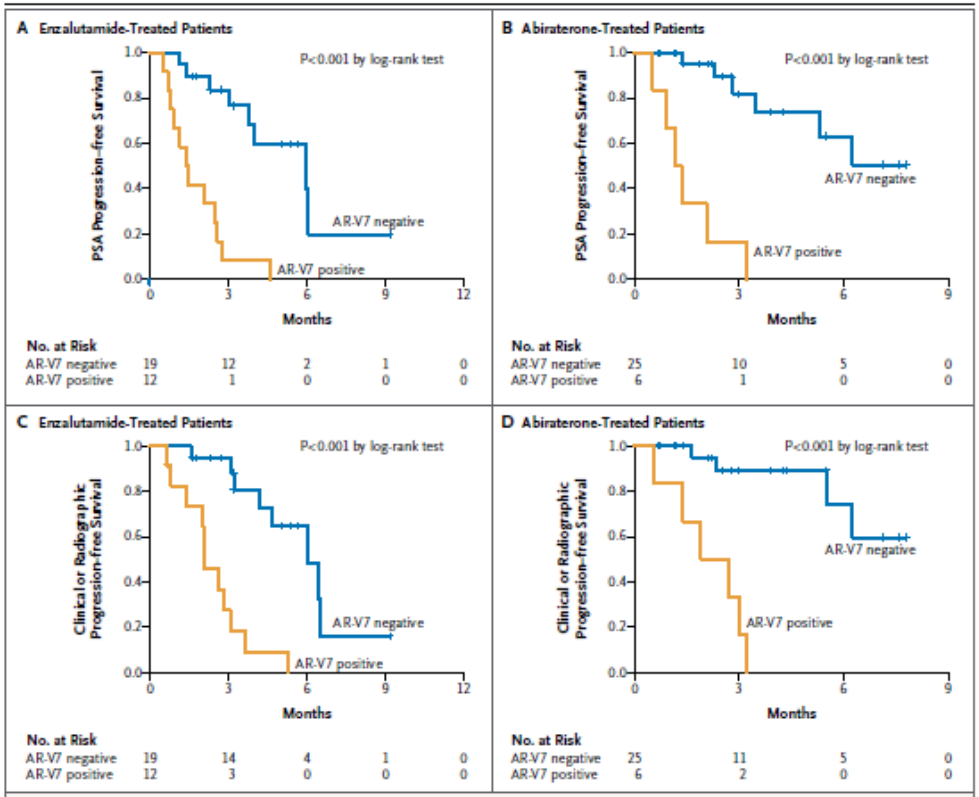


Figure 3. Kaplan–Meier Analysis of PSA Progression–free Survival and Clinical or Radiographic Progression–free Survival According to AR-V7 Status.

The median PSA progression–free survival in enzalutamide-treated patients (Panel A) was 1.4 months (95% CI, 0.9 to not reached) in AR-V7–positive patients and 6.0 months (95% CI, 3.8 to not reached) in AR-V7–negative patients (hazard ratio for PSA progression with AR-V7 positivity, 7.4; 95% CI, 2.7 to 20.6; P<0.001 by the log-rank test). The median PSA progression–free survival in abiraterone-treated patients (Panel B) was 1.3 months (95% CI, 0.9 to not reached) in AR-V7–positive patients and more than 5.3 months (95% CI, 5.3 to not reached) in AR-V7–negative patients (hazard ratio for PSA progression with AR-V7 positivity, 16.1; 95% CI, 3.9 to 66.0; P<0.001 by the log-rank test). The median clinical or radiographic progression–free survival in enzalutamide-treated patients (Panel C) was 2.1 months (95% CI, 2.0 to not reached) in AR-V7–positive patients and 6.1 months (95% CI, 4.7 to not reached) in AR-V7–negative patients (hazard ratio for clinical or radiographic progression with AR-V7 positivity, 8.5; 95% CI, 2.8 to 25.5; P<0.001 by the log-rank test). The median clinical or radiographic progression–free survival in abiraterone-treated patients (Panel D) was 2.3 months (95% CI, 1.4 to not reached) in AR-V7–positive patients and more than 6.3 months (95% CI, 6.3 to not reached) in AR-V7–negative patients (hazard ratio for clinical or radiographic progression with AR-V7 positivity, 16.5; 95% CI, 3.3 to 82.9; P<0.001 by the log-rank test).

TAKSANLAR AR-V7+ HASTALARDA ETKİLİDİR

JAMA Oncol. 2015 Aug;1(5):582-91. doi: 10.1001/jamaoncol.2015.1341.

Androgen Receptor Splice Variant 7 and Efficacy of Taxane Chemotherapy in Patients With Metastatic Castration-Resistant Prostate Cancer.

Antonarakis ES[1], Lu C[2], Luber B[1], Wang H[1], Chen Y[2], Nakazawa M[2], Nadal R[1], Paller CJ[1], Denmeade SR[1], Carducci MA[1], Eisenberger MA[1], Luo J[2].

Author information

Abstract

IMPORTANCE: We previously showed that detection of androgen receptor splice variant 7 (AR-V7) in circulating tumor cells (CTCs) from men with castration-resistant prostate cancer (CRPC) was associated with primary resistance to enzalutamide and abiraterone therapy, but the relevance of AR-V7 status in the context of chemotherapy is unknown.

OBJECTIVE: To investigate whether AR-V7-positive patients would retain sensitivity to taxane chemotherapy and whether AR-V7 status would have a differential impact on taxane-treated men compared with enzalutamide- or abiraterone-treated men.

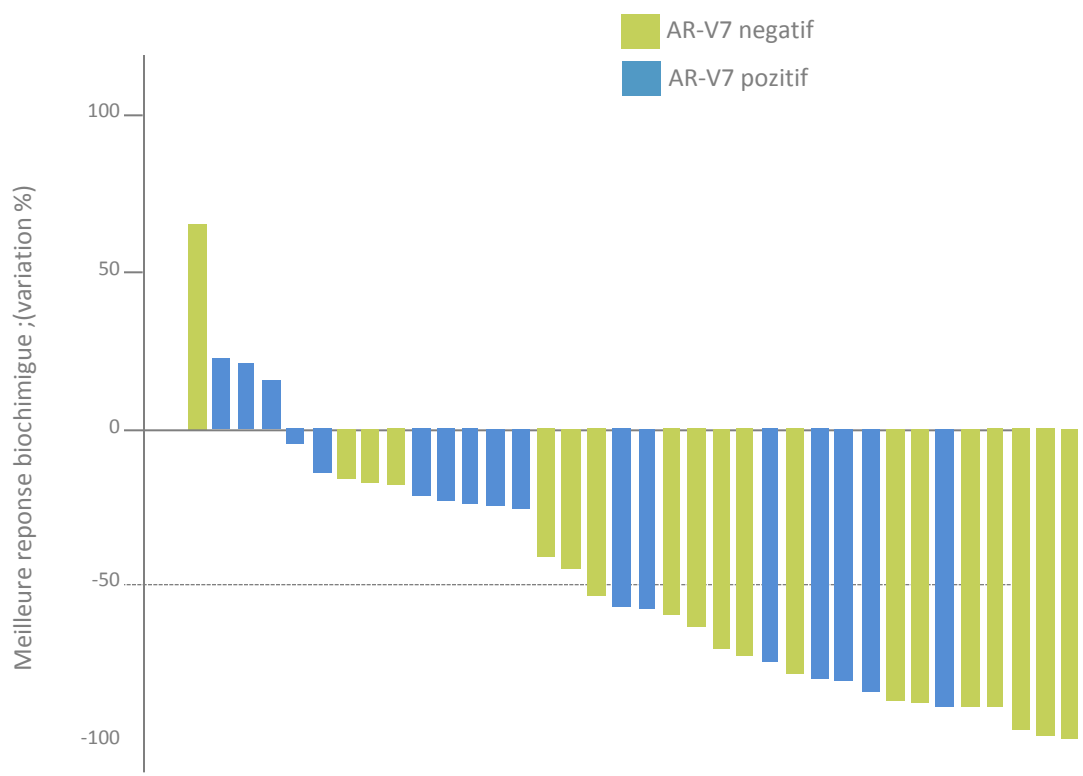
DESIGN, SETTING, AND PARTICIPANTS: We examined CTCs for AR-V7 mRNA using a reverse-transcription polymerase chain reaction assay. From January 2013 to July 2014, we prospectively enrolled patients with metastatic CRPC initiating taxane chemotherapy (docetaxel or cabazitaxel) at a single academic institution (Johns Hopkins). Our prespecified statistical plan required a sample size of 36 taxane-treated men.

MAIN OUTCOMES AND MEASURES: We evaluated associations between AR-V7 status and prostate-specific antigen (PSA) response rates, PSA progression-free survival (PSA PFS), and clinical and/or radiographic progression-free survival (PFS). After incorporating updated data from our prior study of 62 patients treated with enzalutamide or abiraterone, we also investigated the interaction between AR-V7 status (positive or negative) and treatment type (taxane vs enzalutamide or abiraterone).

RESULTS: Of 37 taxane-treated patients enrolled, 17 (46%) had detectable AR-V7 in CTCs. Prostate-specific antigen responses were achieved in both AR-V7-positive and AR-V7-negative men (41% vs 65%; P = .19). Similarly, PSA PFS (hazard ratio [HR], 1.7, 95% CI, 0.6-5.0; P = .32) and PFS (HR, 2.7, 95% CI, 0.8-8.8; P = .11) were comparable in AR-V7-positive and AR-V7-negative patients. A significant interaction was observed between AR-V7 status and treatment type (P < .001). Clinical outcomes were superior with taxanes compared with enzalutamide or abiraterone therapy in AR-V7-positive men, whereas outcomes did not differ by treatment type in AR-V7-negative men. In AR-V7-positive patients, PSA responses were higher in taxane-treated vs enzalutamide- or abiraterone-treated men (41% vs 0%; P < .001), and PSA PFS and PFS were significantly longer in taxane-treated men (HR, 0.19 [95% CI, 0.07-0.52] for PSA PFS, P = .001; HR, 0.21 [95% CI, 0.07-0.59] for PFS, P = .003).

CONCLUSIONS AND RELEVANCE: Detection of AR-V7 in CTCs from men with metastatic CRPC is not associated with primary resistance to taxane chemotherapy. In AR-V7-positive men, taxanes appear to be more efficacious than enzalutamide or abiraterone therapy, whereas in AR-V7-negative men, taxanes and enzalutamide or abiraterone may have comparable efficacy. Circulating tumor cell-based AR-V7 detection may serve as a treatment selection biomarker in CRPC.

TAKSANLAR AR-V7+ HASTALARDA ETKİLİDİR



AR-V7 (+):

7/17 = %41

IC_{95}: %18-67

AR-V7 (-):

13/20 = %65

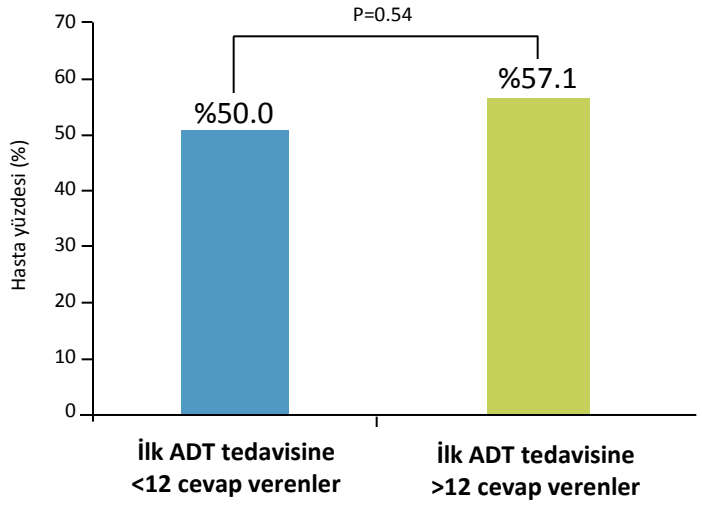
IC_{95}: %41-85

P = 0.194

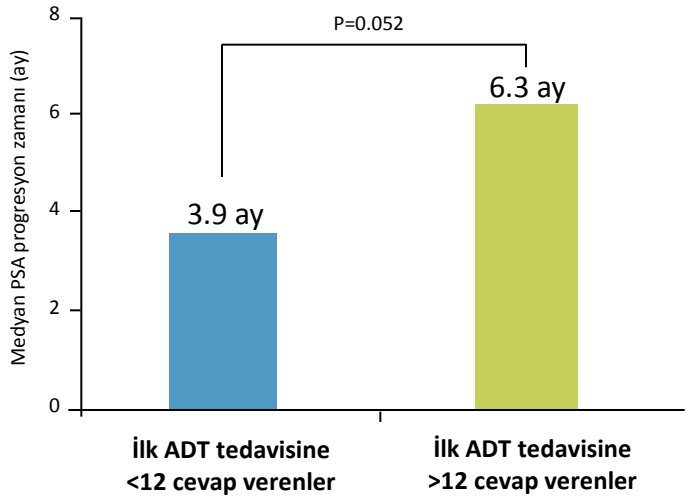
Antonarakis E et al., abstr. 138 ASCO GU 2015

ÖNCEKİ ADT SÜRESİ İLE SEÇİLEN TEDAVİSİ ARASINDAKİ İLİŞKİ

Kabazitaksele ≥%30 PSA cevabı veren hasta oranı



Kabazitaksel tedavisi ile PSA progresyonuna kadar geçen süre



mKDPK'li hastalarda ilk ADT'ye kısa cevap süresi (12 ay), kötü prognoz ve sonraki hormonal tedavilere düşük cevap ile ilişkilidir. Kabazitaksel ise önceki ADT süresinden bağımsız etkilidir.

Angelergues et al ASCO GU 2014 poster A282

PREVAIL Çalışması Alt Grup Analizi

Radiographic Progression-Free Survival Benefit was Consistent Across Subgroups

Subgroup	Number of Patients Enzalutamide / Placebo	Hazard Ratio (95% CI)
All patients	832 / 801	0.19 (0.15, 0.23)
ECOG performance status at baseline=0	557 / 549	0.15 (0.11, 0.20)
ECOG performance status at baseline=1	275 / 252	0.27 (0.19, 0.37)
Age <75	529 / 517	0.20 (0.15, 0.26)
Age ≥75	303 / 284	0.17 (0.12, 0.24)
Geographic region – North America	214 / 204	0.17 (0.12, 0.25)
Geographic region – Europe	456 / 435	0.21 (0.15, 0.28)
Geographic region – Rest of world	162 / 162	0.14 (0.08, 0.25)
Visceral disease (lung and/or liver) at screening – Yes	97 / 101	0.28 (0.16, 0.49)
Visceral disease (lung and/or liver) at screening – No	735 / 700	0.17 (0.14, 0.22)

Hazard ratio <1 favors enzalutamide

Viseral Metastaz Varlığı
AFFIRM Alt Grup Analiz

Subgroup	No. of Patients	Enzalutamide	Placebo	Hazard Ratio (95% CI)
		median overall survival (mo)		
All patients	1199	18.4	13.6	0.63 (0.53–0.75)
Age				
<65 yr	362	—	12.4	0.63 (0.46–0.87)
≥65 yr	837	18.4	13.9	0.63 (0.51–0.78)
Baseline ECOG performance status score				
0–1	1097	—	14.2	0.62 (0.52–0.75)
2	102	10.5	7.2	0.65 (0.39–1.07)
Baseline mean pain score on BPI–SF (question no. 3)				
<4	858	—	16.2	0.59 (0.47–0.74)
≥4	341	12.4	9.1	0.71 (0.54–0.94)
Geographic region				
North America	395	17.4	12.3	0.63 (0.47–0.83)
Other	804	—	14.4	0.64 (0.51–0.80)
No. of previous hormonal treatments				
≤2	587	18.8	11.2	0.59 (0.46–0.75)
>2	605	18.3	14.7	0.68 (0.53–0.88)
No. of previous chemotherapy regimens				
1	875	—	14.2	0.59 (0.48–0.73)
≥2	324	15.9	12.3	0.74 (0.54–1.03)
Type of progression at study entry				
PSA progression only	490	—	19.5	0.62 (0.46–0.83)
Radiographic progression with or without PSA progression	704	17.3	13.0	0.64 (0.52–0.80)
No. of bone lesions				
≤20	746	—	16.2	0.59 (0.46–0.75)
>20	453	13.1	9.5	0.67 (0.52–0.87)
Visceral (liver or lung) disease at baseline				
No	921	—	14.2	0.56 (0.46–0.69)
Yes	278	13.4	9.5	0.78 (0.56–1.09)
Baseline PSA level				
≤Median	600	—	19.2	0.67 (0.50–0.89)
>Median	599	15.3	10.3	0.62 (0.50–0.78)
Baseline LDH level				
≤Median	603	—	19.2	0.63 (0.46–0.86)
>Median	594	12.4	8.5	0.61 (0.50–0.76)

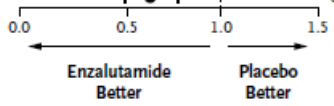


Figure 2. **Subgroup Analyses of Hazard Ratios for Death in the Two Study Groups.**

Viseral Metastaz Varlığı
COU-AA-301 Alt Grup Analiz

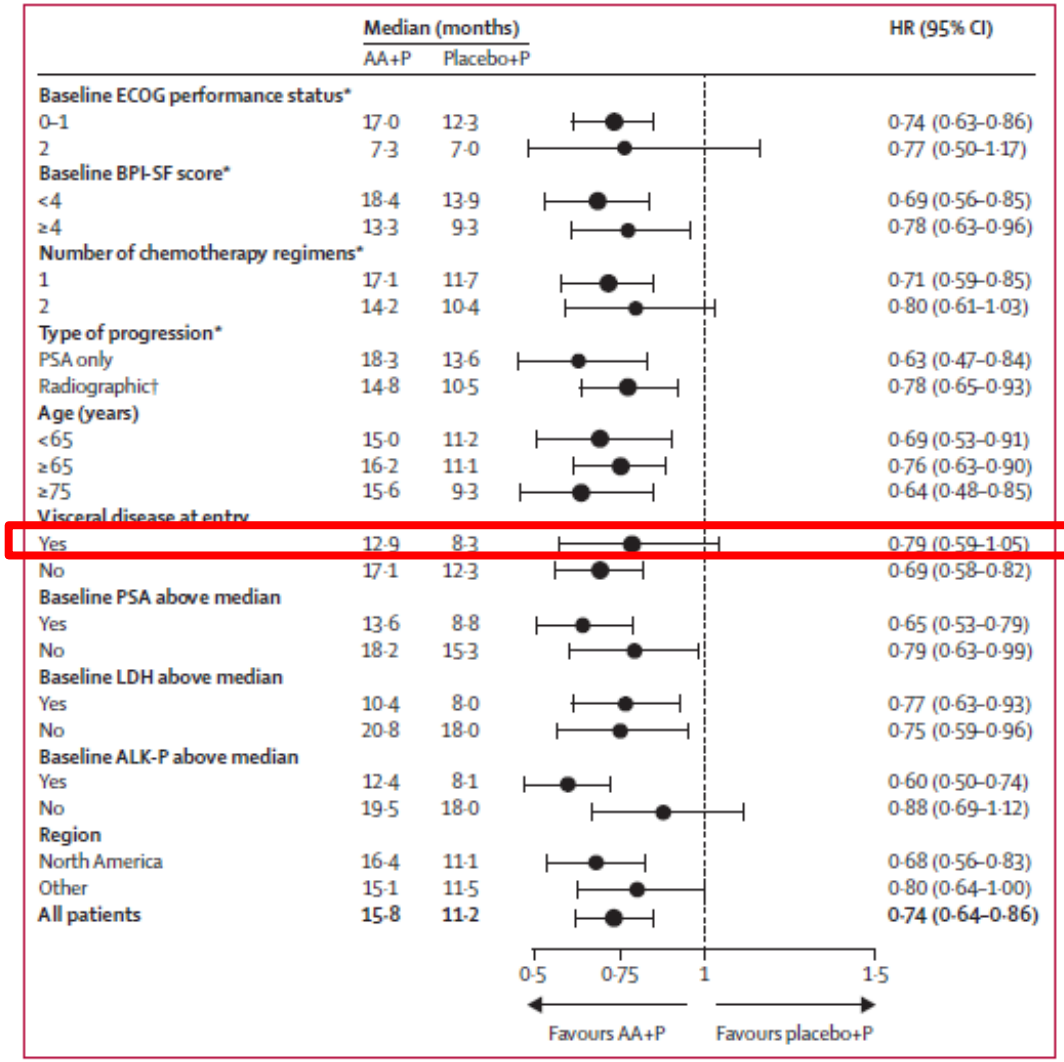


Figure 3: **Overall survival by subgroup analyses**

AA=abiraterone acetate. P=prednisone. HR=hazard ratio. ECOG=Eastern Cooperative Oncology Group. BPI-SF=Brief Pain Inventory-Short Form. PSA=prostate-specific antigen. LDH=lactate dehydrogenase.

TAX-327 Alt-Grup Analizi

Table 2. Treatment.*

Variable	Docetaxel Every 3 Wk	Weekly Docetaxel	Mitoxantrone Every 3 Wk
No. randomized	335	334	337
No. treated with chemotherapy	332	330	335
No. treated with prednisone	332	330	335
No. of cycles			
Median	9.5	4	5
Range	1–11	1–6	1–11
≥1 Infusion delayed (%)	24	34	21
Dose reduction (%)	12	9	8
Major protocol violation (%)	7	8	7
Reasons for stopping treatment (%)			
Completed treatment	46	35	25
Progression of disease	38	35	56
Adverse event	11	16	10
Withdrawal of consent	1	6	3
Death	1	2	2
Other	4	6	5
Crossover to other drug (%)	27	24	20

* Percentages relate to the number of patients treated in each group. Because of rounding, not all percentages total 100.

Dosetaksel Yanıtına Göre COU-AA-301 Alt Grup Analiz

	Abiraterone acetate plus prednisone		Placebo plus prednisone		Hazard ratio (95% CI)
	Events/N	Median overall survival (months; 95% CI)	Events/N	Median overall survival (months; 95% CI)	
Baseline ECOG status*					
0–1	432/715	17·0 (15·6–17·7)	237/353	12·3 (10·8–14·5)	0·74 (0·63–0·87)
2	69/82	7·3 (6·4–8·6)	37/45	7·0 (4·0–8·1)	0·77 (0·50–1·17)
Pain at study entry*					
Pain absent (0–3)	244/440	18·4 (17·2–19·9)	137/219	13·9 (11·7–15·9)	0·69 (0·56–0·85)
Pain present (4–10)	257/357	13·3 (11·1–14·7)	137/179	9·3 (7·9–10·7)	0·78 (0·63–0·96)
Previous lines of chemotherapy*					
1	329/557	17·1 (15·6–18·2)	185/275	11·7 (10·4–13·9)	0·71 (0·59–0·85)
2	172/240	14·2 (11·8–15·3)	89/123	10·4 (8·8–13·5)	0·80 (0·61–1·02)
Type of progression*†					
PSA progression	126/238	18·3 (16·7–20·8)	79/125	13·6 (10·8–16·8)	0·63 (0·47–0·84)
Radiographic progression with or without PSA progression	375/559	14·8 (14·0–16·1)	195/273	10·5 (8·9–12·5)	0·78 (0·65–0·93)
Previous docetaxel usage					
From first dose of docetaxel	494/787	32·6 (30·7–35·0)	274/397	27·6 (25·9–30·3)	0·75 (0·65–0·88)
From last dose of docetaxel	494/787	23·2 (22·4–24·5)	274/397	19·4 (17·5–20·8)	0·74 (0·64–0·86)
Reason for discontinuation of docetaxel					
Progressive disease	241/362	14·2 (12·0–15·8)	129/182	10·5 (9·3–11·8)	0·77 (0·62–0·97)
All other reasons	258/431	17·0 (15·6–18·2)	145/215	12·6 (10·4–14·9)	0·73 (0·59–0·89)
Treatment of abiraterone acetate plus prednisone started					
≤3 months after last dose of docetaxel	144/227	15·0 (13·7–17·4)	82/112	10·7 (8·9–13·0)	0·62 (0·47–0·83)
>3 months after last dose of docetaxel	346/554	16·1 (14·9–17·3)	190/282	11·8 (10·3–14·6)	0·77 (0·64–0·92)
Docetaxel exposure time					
≤3 months	98/140	14·6 (11·9–16·7)	51/69	10·8 (8·4–14·9)	0·76 (0·53–1·08)
>3 months	252/401	16·2 (14·9–17·3)	223/328	11·2 (10·3–13·6)	0·74 (0·63–0·87)

ECOG=Eastern Cooperative Oncology Group. PSA=prostate-specific antigen. Overall survival is presented in months. Patients who were not deceased at the time of analysis were censored on the last date the patient was known to be alive or lost to follow-up. All subgroup analyses were adjusted for baseline stratification factors. Every test was done at significance level of 0·05. Patient numbers are not consistent across subgroups because of missing data. *Stratification factors at baseline. †Progression occurred before study entry.

Table 3: **Overall survival by subgroup (univariate analysis)**

TROPIC Çalışmasının Alt Analizi

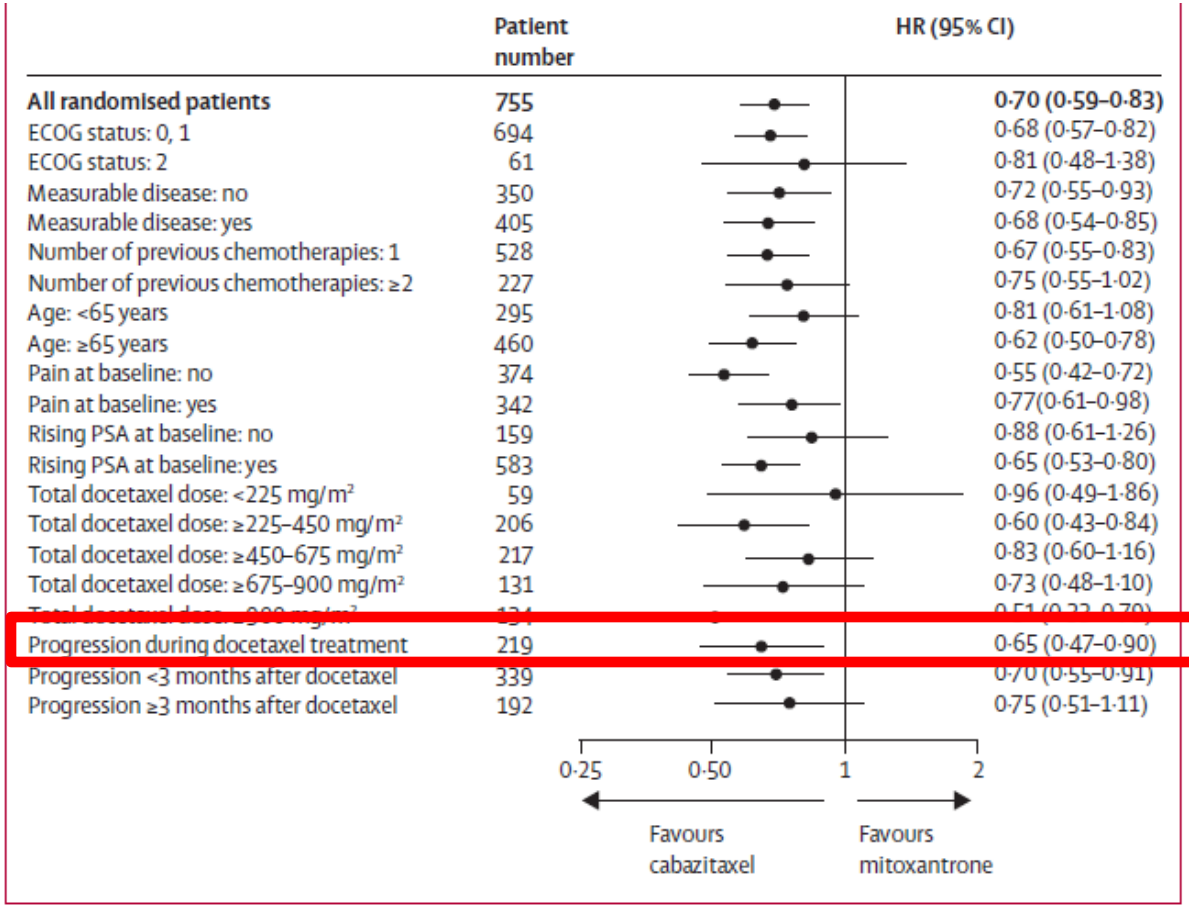
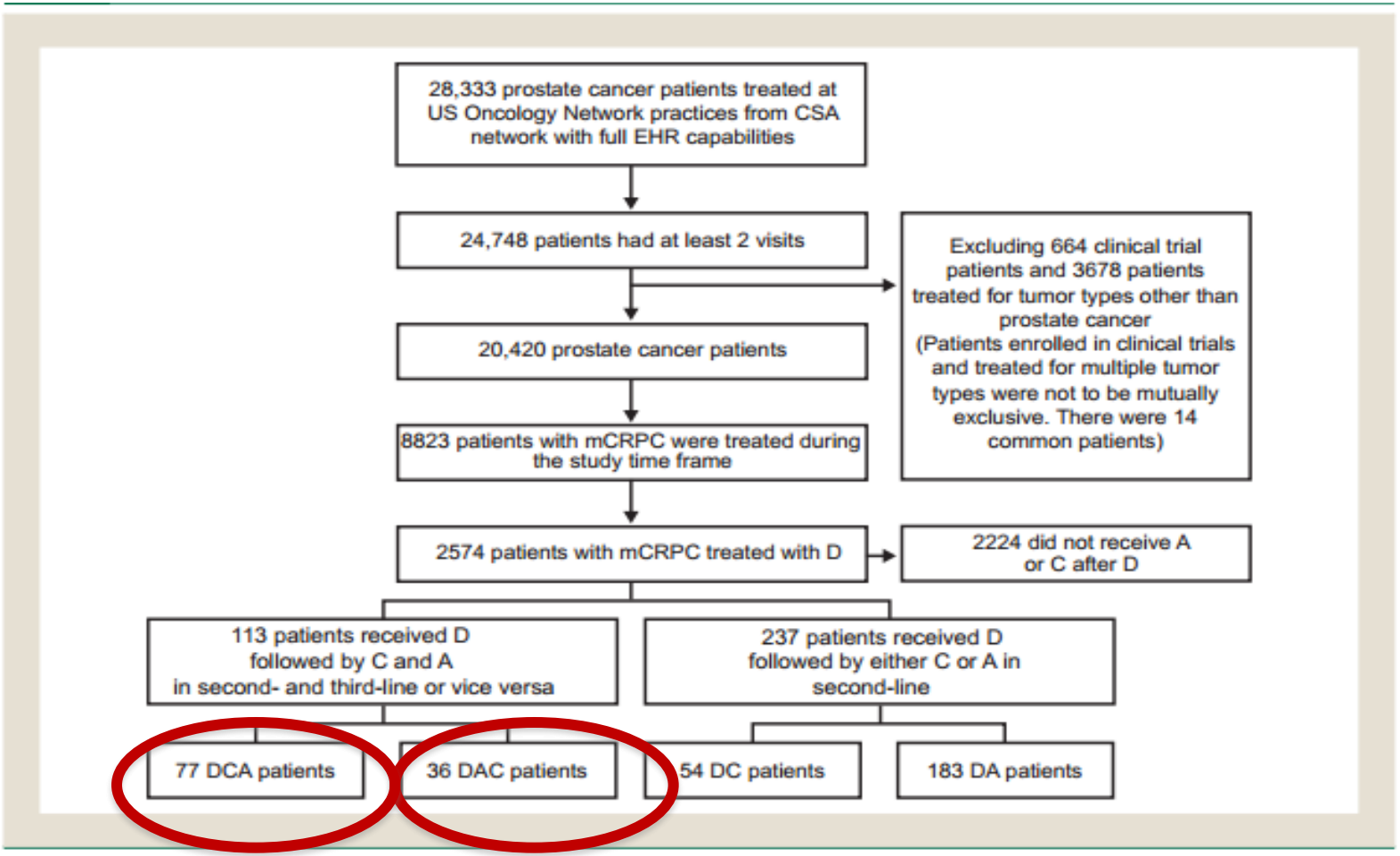


***Figure 2*: Overall survival**

(A) Kaplan-Meier estimates of the probability of survival in patients in all patients randomly assigned to treatment with cabazitaxel plus prednisone or mitoxantrone plus prednisone. The points on the curves show censored observations. (B) Intention-to-treat analysis of overall survival in subgroups of patients defined by baseline characteristics. Hazard ratios (HRs) lower than 1 favour the cabazitaxel group and greater than 1 favour the mitoxantrone group.

DOSETAKSEL SONRASI KABAZİTAKSEL KULLANAN HASTALARIN 3. BASAMAK TEDAVİYİ KULLANABİLME ŞANSI YÜKSEKTİR



Abbreviations: A = abiraterone acetate; C = cabazitaxel; CSA = Comprehensive Strategic Alliance; D = docetaxel; DA = docetaxel followed by abiraterone; DAC = docetaxel followed by abiraterone acetate and then cabazitaxel; DC = docetaxel followed by cabazitaxel; DCA = docetaxel followed by cabazitaxel and then abiraterone acetate; EHR = electronic health record; mCRPC = metastatic castration-resistant prostate cancer.

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Docetaksel sonrasında cabazitaxel alanlar tedaviyi daha uzun sürdürebilmiştir.

Table 1 Drug Exposure and Treatment Discontinuation Rates

	Two-Drug Sequence				Three-Drug Sequence			
	Total (N = 237)	DC (n = 54)	DA (n = 183)	*P* Value	Total (N = 113)	DCA (n = 77)	DAC (n = 36)	*P* Value
Docetaxel cycles, n								
Mean (SD)	7.72 (6.14)	7.44 (4.29)	7.80 (6.59)		8.08 (5.72)	8.01 (5.72)	8.25 (5.79)	
Median	6	6.5	6		6	6	6.5	
Range	1-45	2-19	1-45		1-32	1-30	2-32	
95% CI	6.93-8.50	6.27-8.61	6.84-8.76	.7484	7.02-9.15	6.71-9.31	6.28-10.21	.5712
Cabazitaxel cycles, n								
Mean (SD)	–	5.98 (4.93)	–		6.51 (5.22)	7.58 (4.25)	4.22 (3.13)	
Median	–	5	–		5	6	4	
Range	–	1-20	–		1-19	1-19	1-17	
95% CI	–	7.32-4.63	–		5.72-7.30	6.61-8.54	3.16-5.28	<.0001
A discontinuation rates within 3 mo, n (%)	–	–	39 (21.3)		46 (40.7)	32 (41.6)	14 (38.9)	.7878

Abbreviations: CI = confidence interval; DA = docetaxel followed by abiraterone acetate; DAC = docetaxel followed by abiraterone acetate and then cabazitaxel; DC = docetaxel followed by cabazitaxel; DCA = docetaxel followed by cabazitaxel and then abiraterone acetate; SD = standard deviation.

Dosetaksel Sonrası Kabazitaksel Kullanan Hastalarda Etkinlik Verileri

Table 1 Drug Exposure and Treatment Discontinuation Rates

	Two-Drug Sequence				Three-Drug Sequence			
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Seçilen Tedavi Ardışık Tedavilerin Yanıt Durumunu Etkiler

Abiraterone and Enzalutamide

- There is clinical evidence of cross-resistance between abiraterone and enzalutamide
- PSA responses to abi/enza after prior enza/abi are 10-20%, and rPFS is 3-4 months

(Noonan KL et al. *Ann Oncol* 2013; 24:1802-7, Loriot Y et al. *Ann Oncol* 2013;24:1807-12, Schrader AJ et al. *Eur Urol* 2014;65:30-6, Badrising S et al. *Cancer* 2014;120:968-75, Cheng HH et al. *PCAN*; epub ahead of print)

- There is evidence of cross-resistance between abi/enza and taxanes
- Abi/enza may be less effective after taxanes

(deBono J *NEJM* 2011;364: 1995-05, Scher H *NEJM* 2012;367:1187-97, Nadal R et al *Prostate* 2014;74:1560-8),

and Taxanes may be less effective after abi/enza

(Schweizer MT et al. *Eur Urol* 2014;66:646-52, Mezynski J et al. *Ann Oncol* 2012;23:2943-7)

64 yaşında erkek hasta, yaygın sırt ağrısı var, kastrasyona dirençli, PSA 134ng/ ml saptandı. Hastaya, dosetaksel başlandı ve 6 kürde PSA 60ng/ ml geriliyor. Sonraki tedavilerde artarak 110ng/ ml oluyor. TVS multiple kemik metastazı var. BT retroperitoneal 5 cm varan multiple lenf nodları mevcut.

Bu hasta için en uygun tedavi şekli ne olmalı?(RT+ Zolendronik asid 4mg+/…..)

1-Spilutuel T

2-Radiyum 223

3-Enuzulutamid

4- Abireteron

5- Kabazitaksel

6-Hepsi olabilir

Kastrasyona Dirençli Hastada Tedavi Kararında Etkili Parametreler

- Tümör yükü
- ADT cevap süresi(12 ay≥ yada≤)
- Aldığı tedaviler(dosetaksel öncesi sonrası)
- Kemoterapiye Yanıt durumu
- Viseral metastaz
- Hastanın semptomatik olması
- PSA düzeyi
- Hastanın performansı ve yaşam beklentisi
- Seçilecek tedavinin toksitesi