Metastatik Prostat Kanserinde Tedavi

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

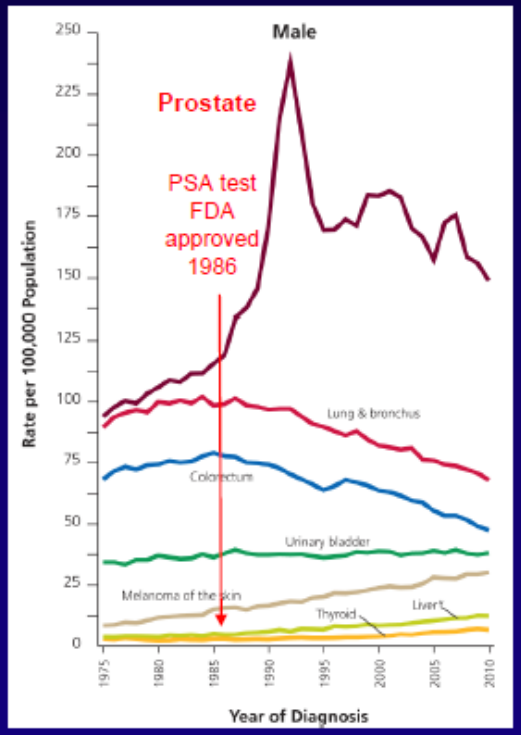
Ders Planı

- İnsidans ve mortalite
- Hormona duyarlı metastatik prostat ca
- Hormona duyarlı metastaik prostat ca yeni tedaviler
- Kastrasyona dirençli prostat ca
- Sıralama nasıl olmalı
- Yeni tedavi seçenekleri
- Sonuç

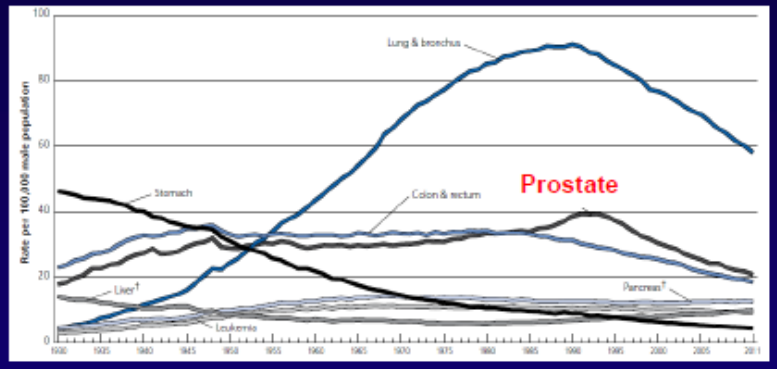
Prostat Kanseri İnsidans ve Mortalite

Changes in incidence and death rates

Incidence



Death rate



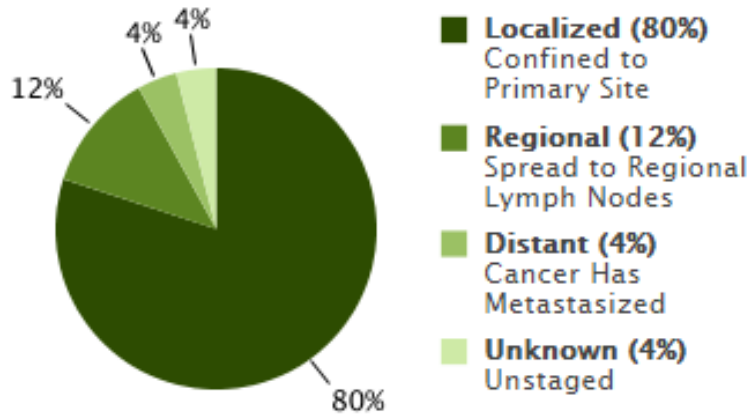
- Incidence peak see after PSA became available
- Declining death rates over past 25 years by 2-3% per year

CA: A Cancer Journal for Clinicians 2016

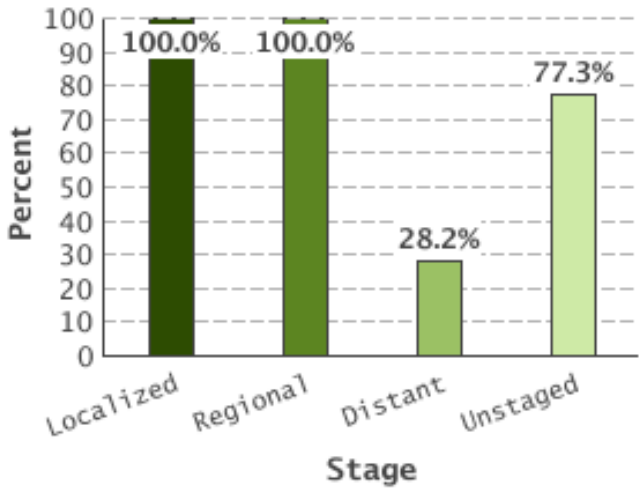
Prostat Kanseri İnsidans ve Mortalite

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

Percent of Cases by Stage

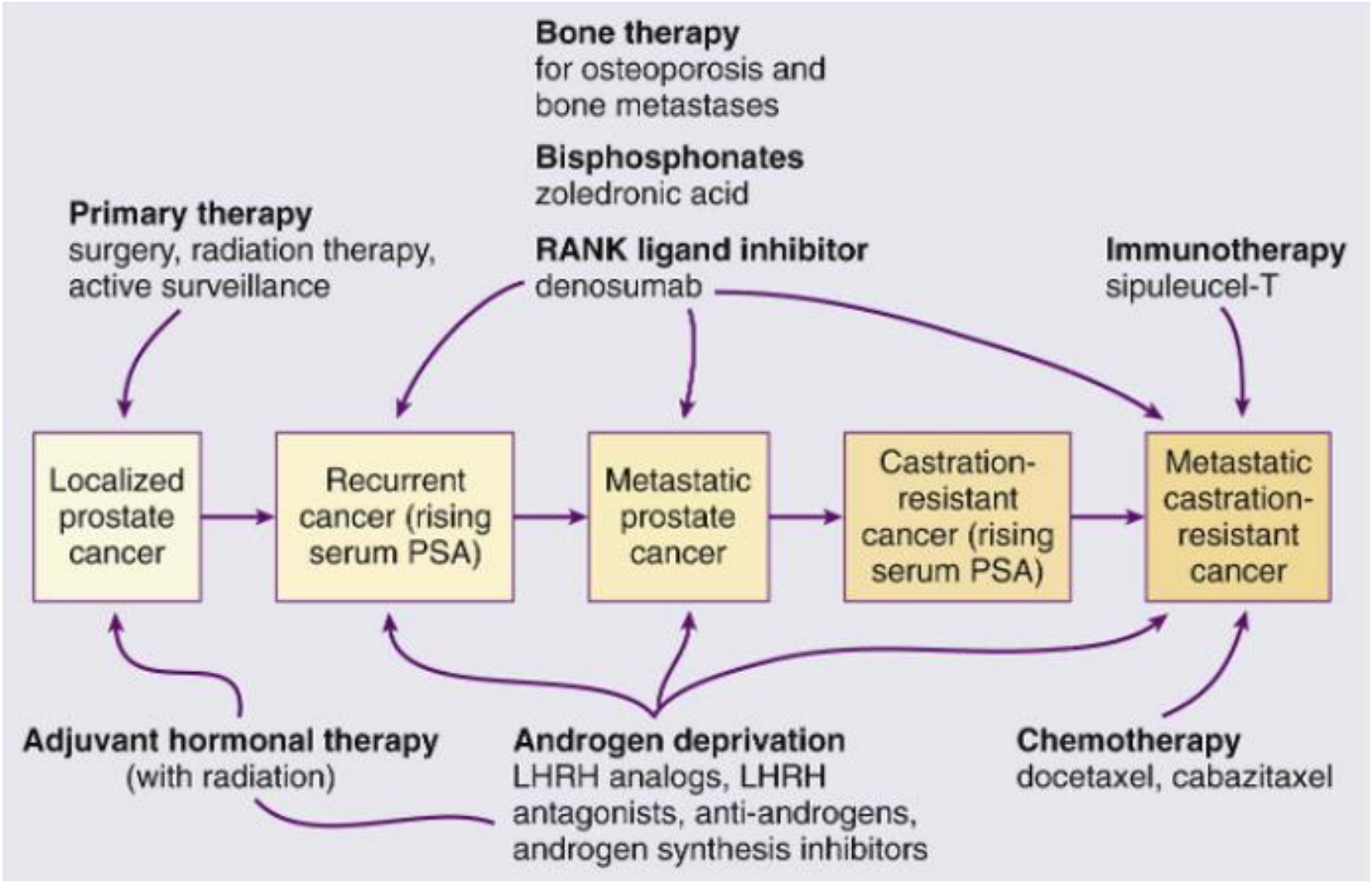


5-Year Relative Survival



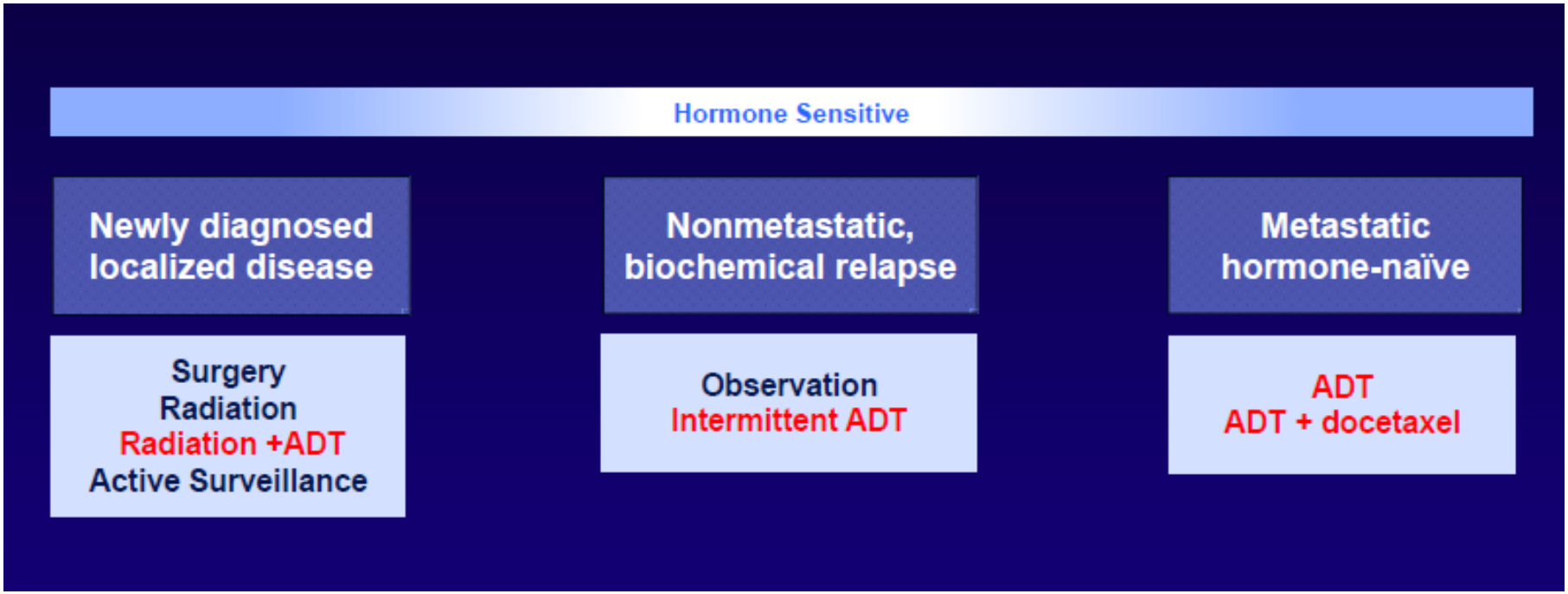
SEER 18 2005-2011, All Races, Males by SEER Summary Stage 2000

Prostat Kanseri Tedavi Yaklaşımları



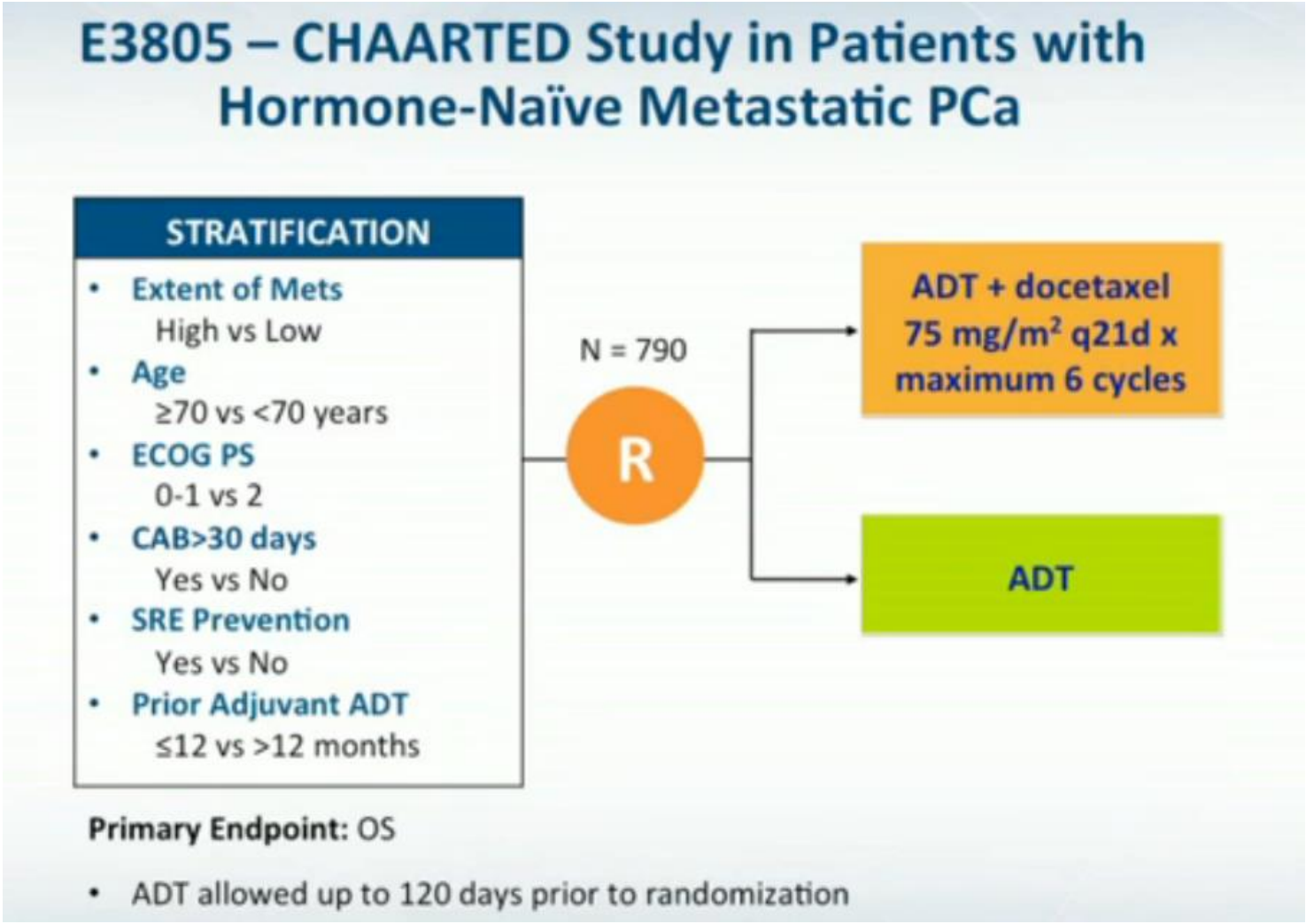
Şekil; Abeloff's Clinical Oncology, 10th edition

Hormon Duyarlı Metastatik Prostat Kanseri

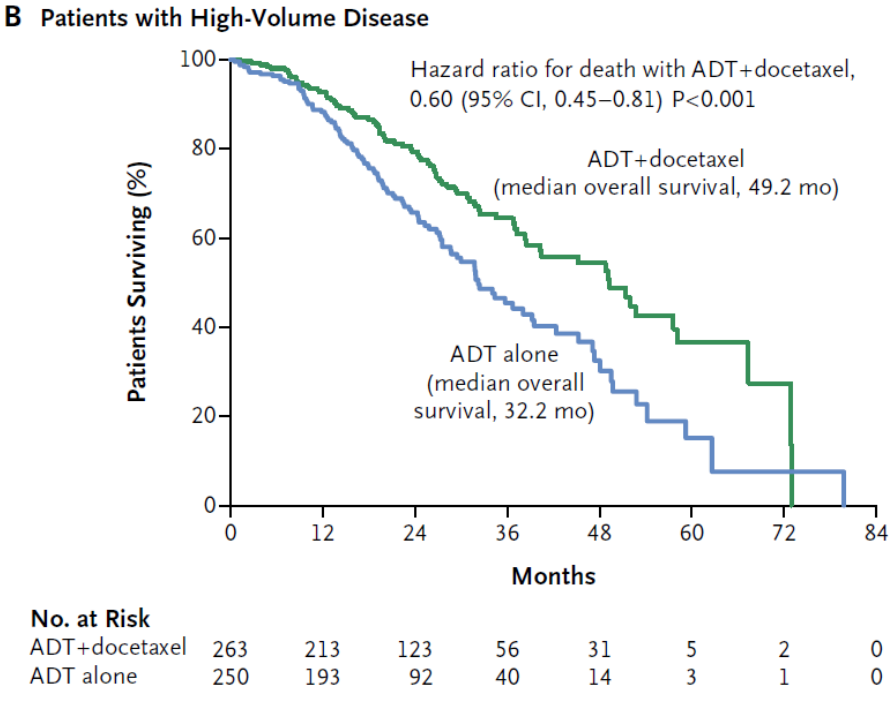


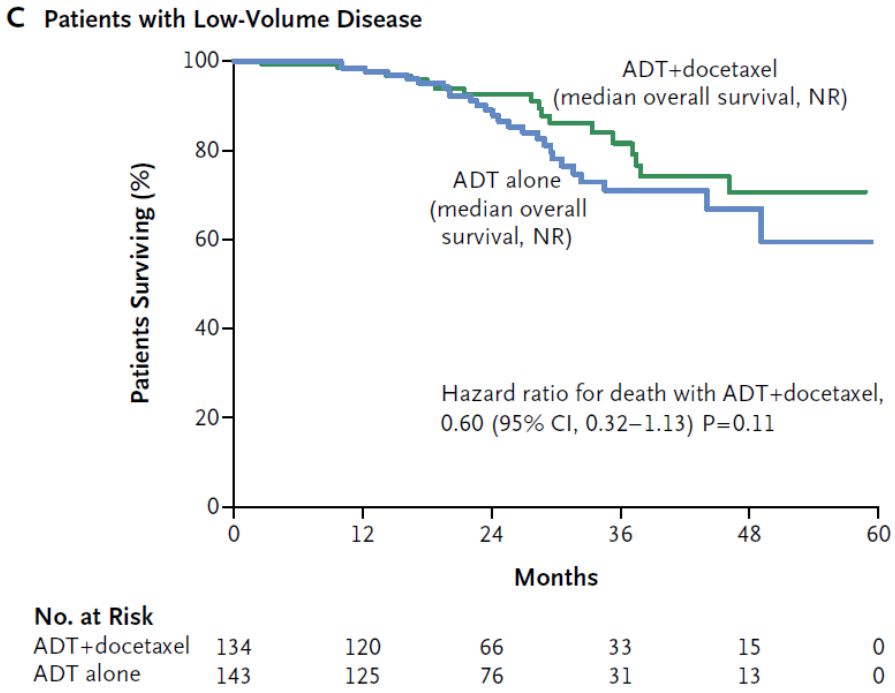
Hormon Duyarlı Metastatik Prostat Kanseri

ADT + Erken Dönem Kemoterapi



ADT + Erken Dönem Kemoterapi

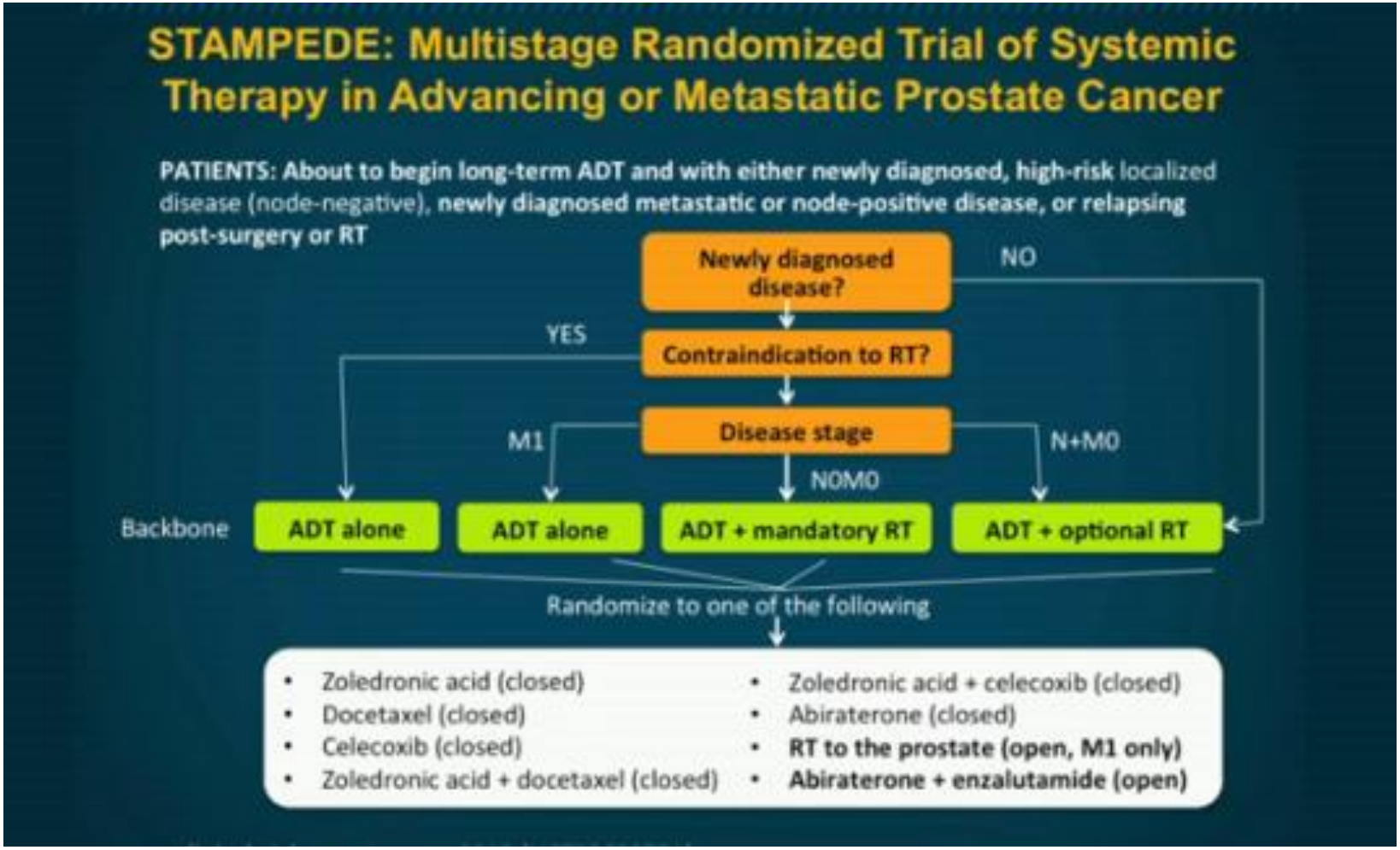




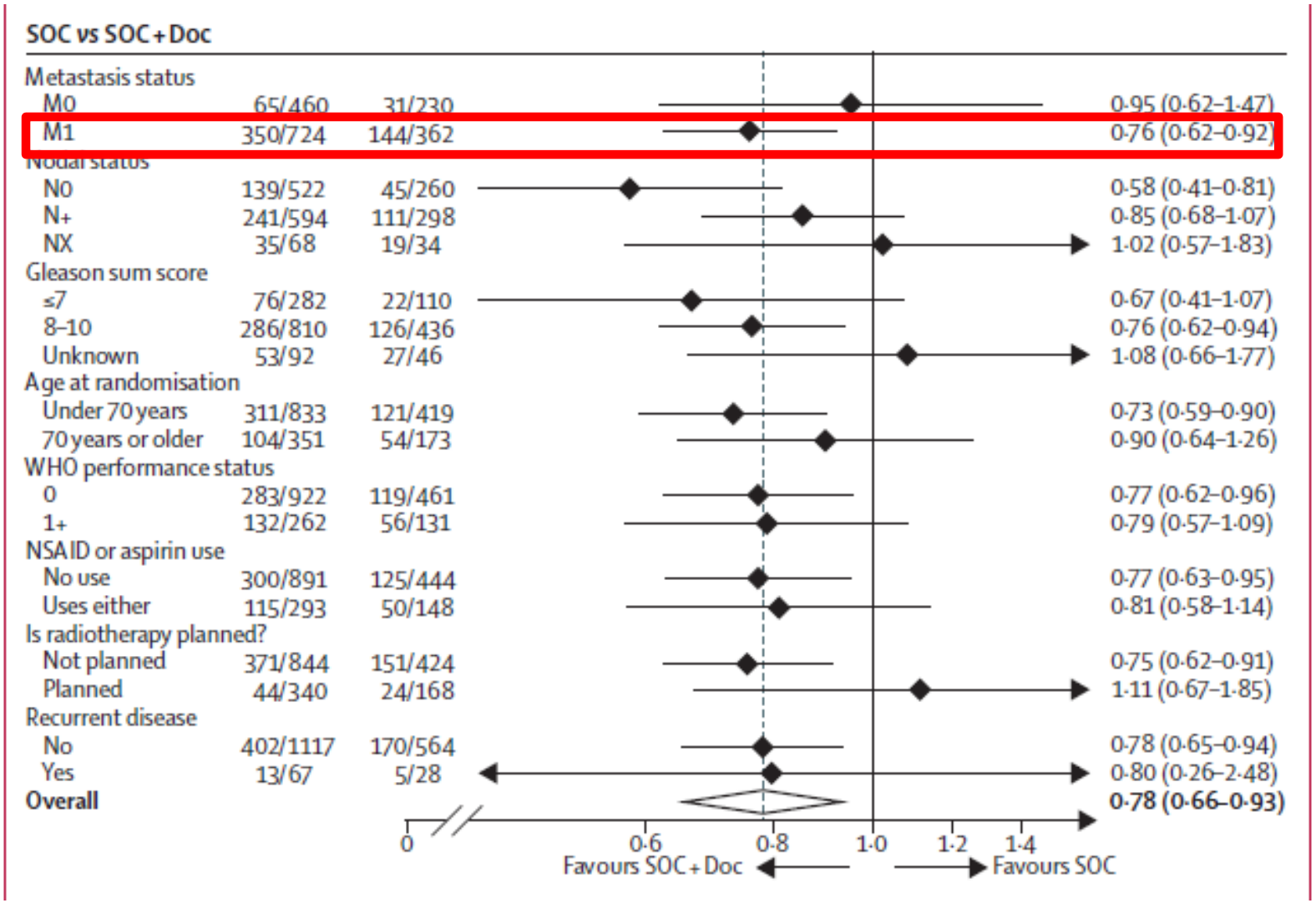
Yüksek volümlü hastalığı olanlar; viseral organ metastazı olan yada ≥4 kemik lezyonu olan ve en az ≥1 vertebra, pelvis dışı kemiklerde metastaz olmalı

Hormon Duyarlı Metastatik Prostat Kanseri

ADT + Erken Dönem Kemoterapi

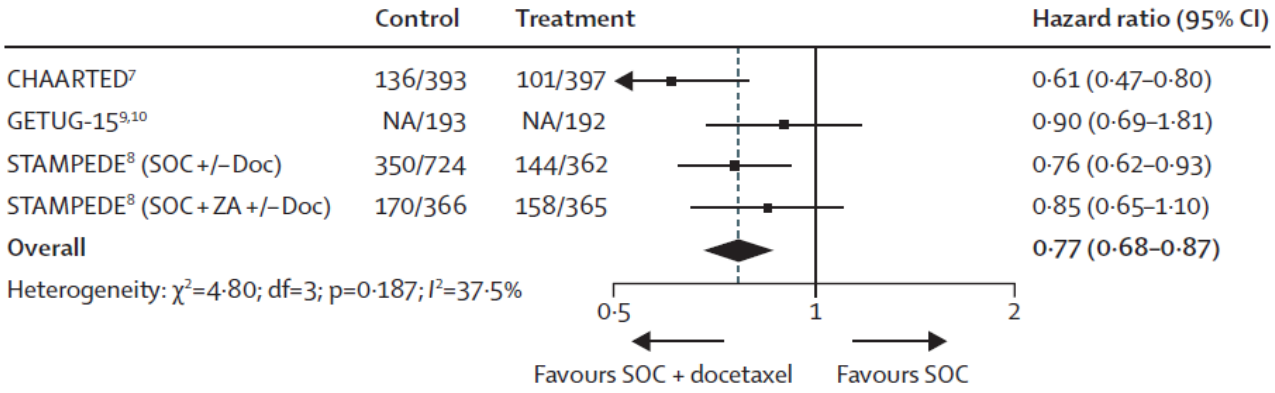


ADT + Erken Dönem Kemoterapi

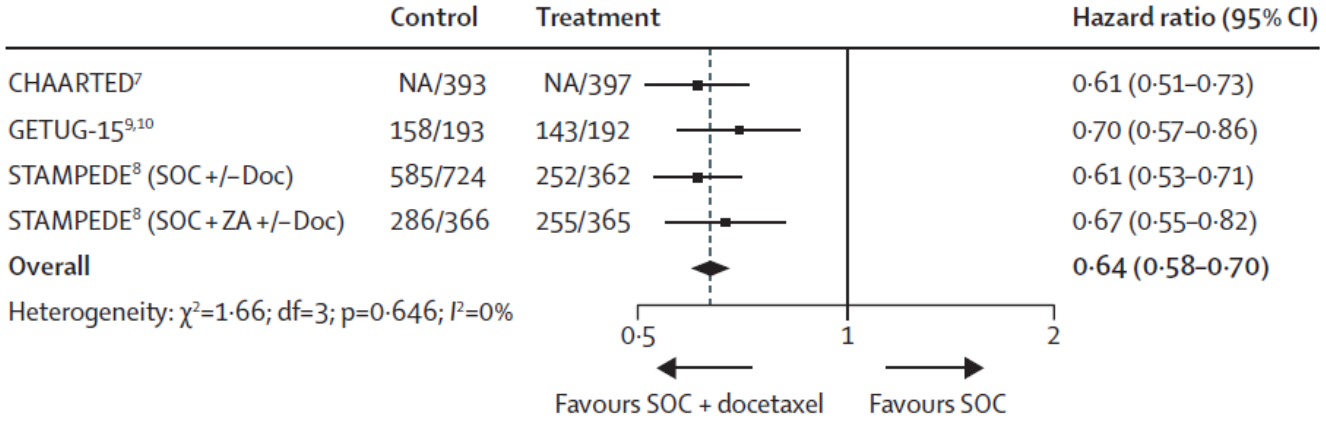


Hormon Duyarlı Metastatik Prostat Kanseri

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

Hormon Duyarlı Metastatik Prostat Kanseri

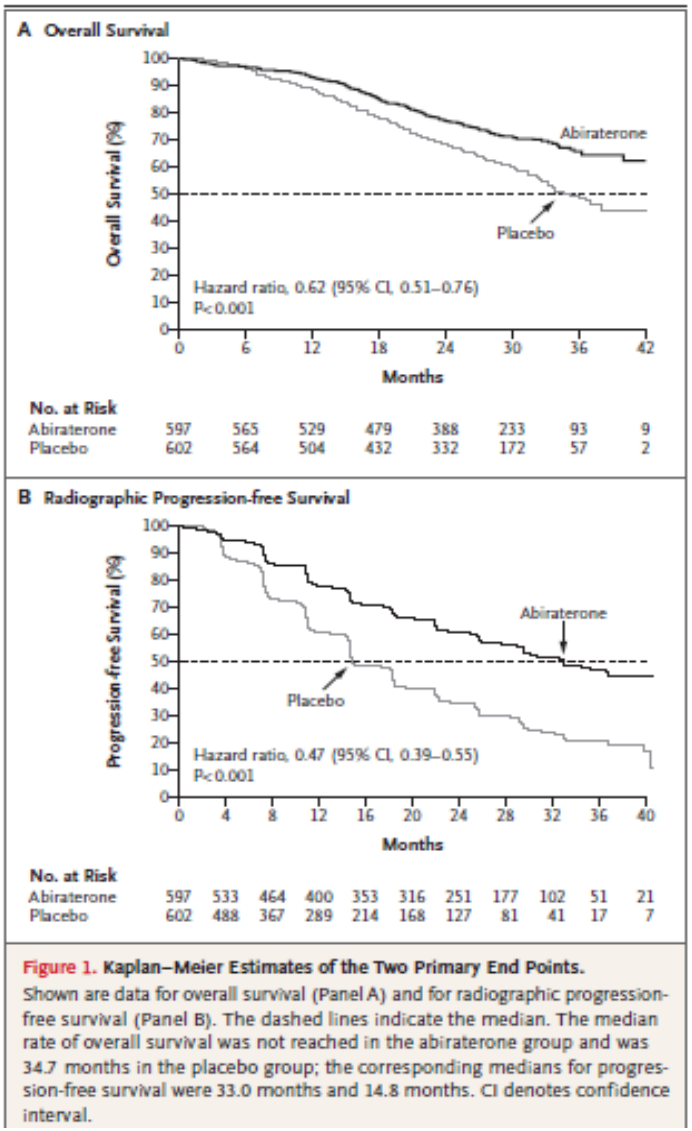


Figure 1. Kaplan–Meier Estimates of the Two Primary End Points.
Shown are data for overall survival (Panel A) and for radiographic progression-free survival (Panel B). The dashed lines indicate the median. The median rate of overall survival was not reached in the abiraterone group and was 34.7 months 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-

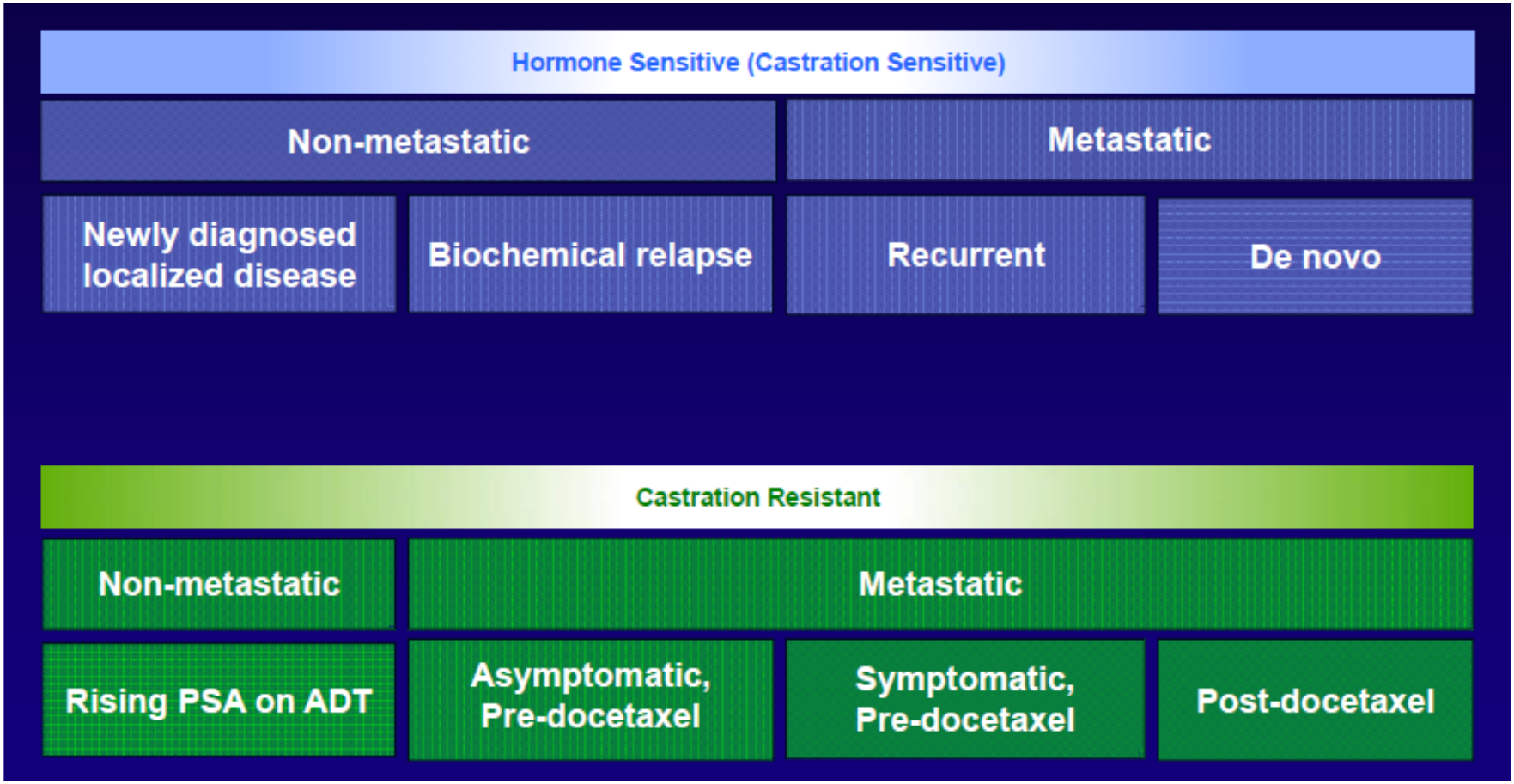
En az 2≥ kötü risk grubuna sahip hastalar dahil edilmiş

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

Dışlama kriterleri

1. **Daha önce cerrahi**
2. **Radyoterapi**
3. **Kemoterapi**
4. **Metastik hastalığa bağlı semptomu olanlarda RT ve Cerrahiye izin verilmiş**

Kastrasyona Dirençli Prostat Kanseri



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

1.7 nmol/Litre

- Historical (but not accurate) terminology
  - Hormone refractory (HRPC)
  - Androgen independent (AI)

- 64 yaşında erkek hasta, Diabet ve Hipertansiyon öyküsü var. Metastatik prostat kanseri nedeniyle 15 ay hormonal tedavi almış.

- Yaygın sırt ağrısı var, kastrasyona dirençli, PSA 134ng/ ml saptandı. Yaygın kemik metastazı var, viseral metastaz yok. Hastaya, dosetaksel başlandı ve 10 kürde PSA 8ng/ ml geriliyor.

- Nöropati semptomları başlıyor tedavi kesiliyor. Takiplerinde PSA giderek artıyor 9. ayda 60ng/ ml oluyor.

- TVS multiple kemik metastazında progresyon. 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-Enzalutamid

4- Abirateron

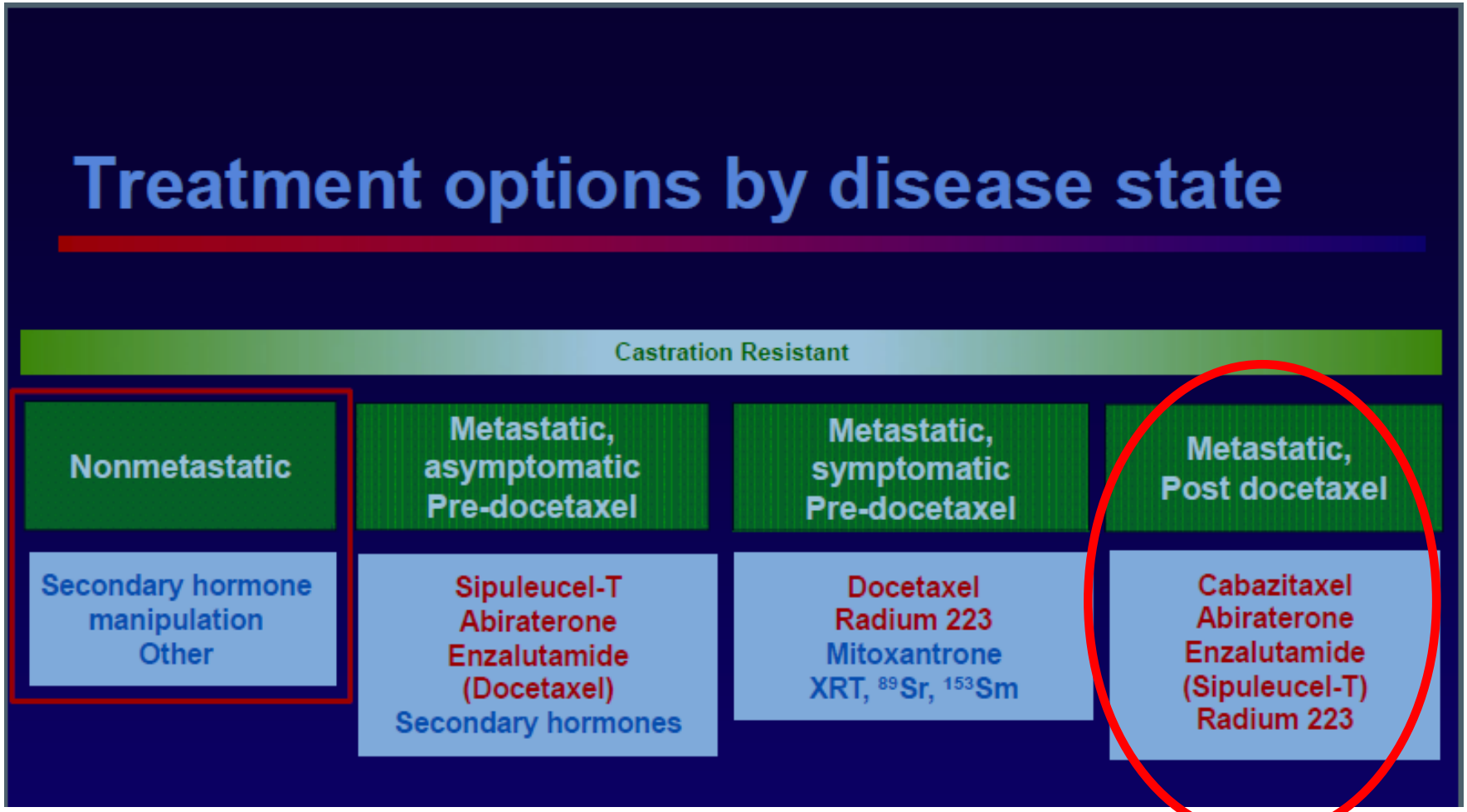
5- Kabazitaksel

6-Hepsi olabilir

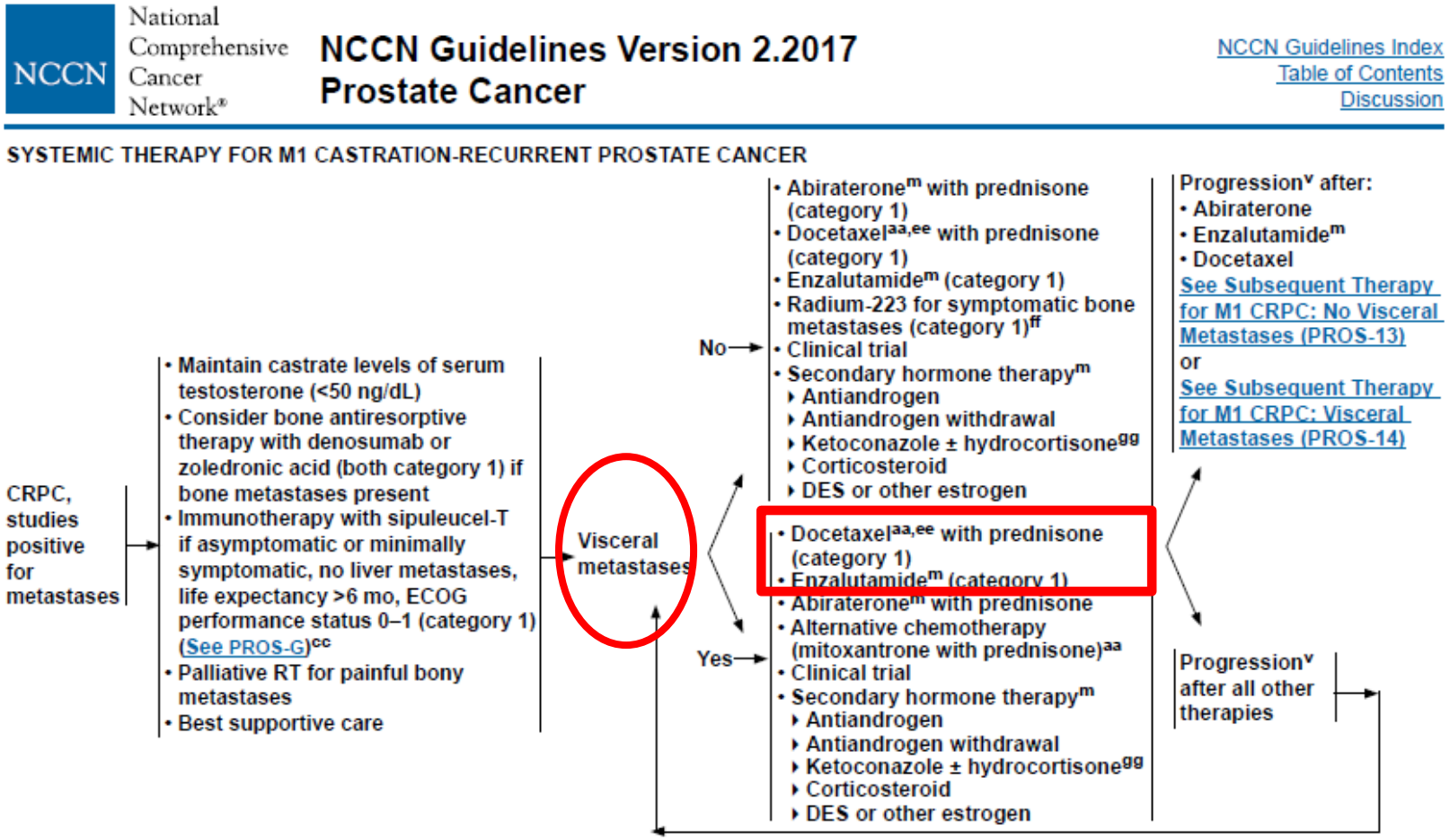
Kastrasyona Dirençli Hastada Tedavi Kararında Ne Etkili

- 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

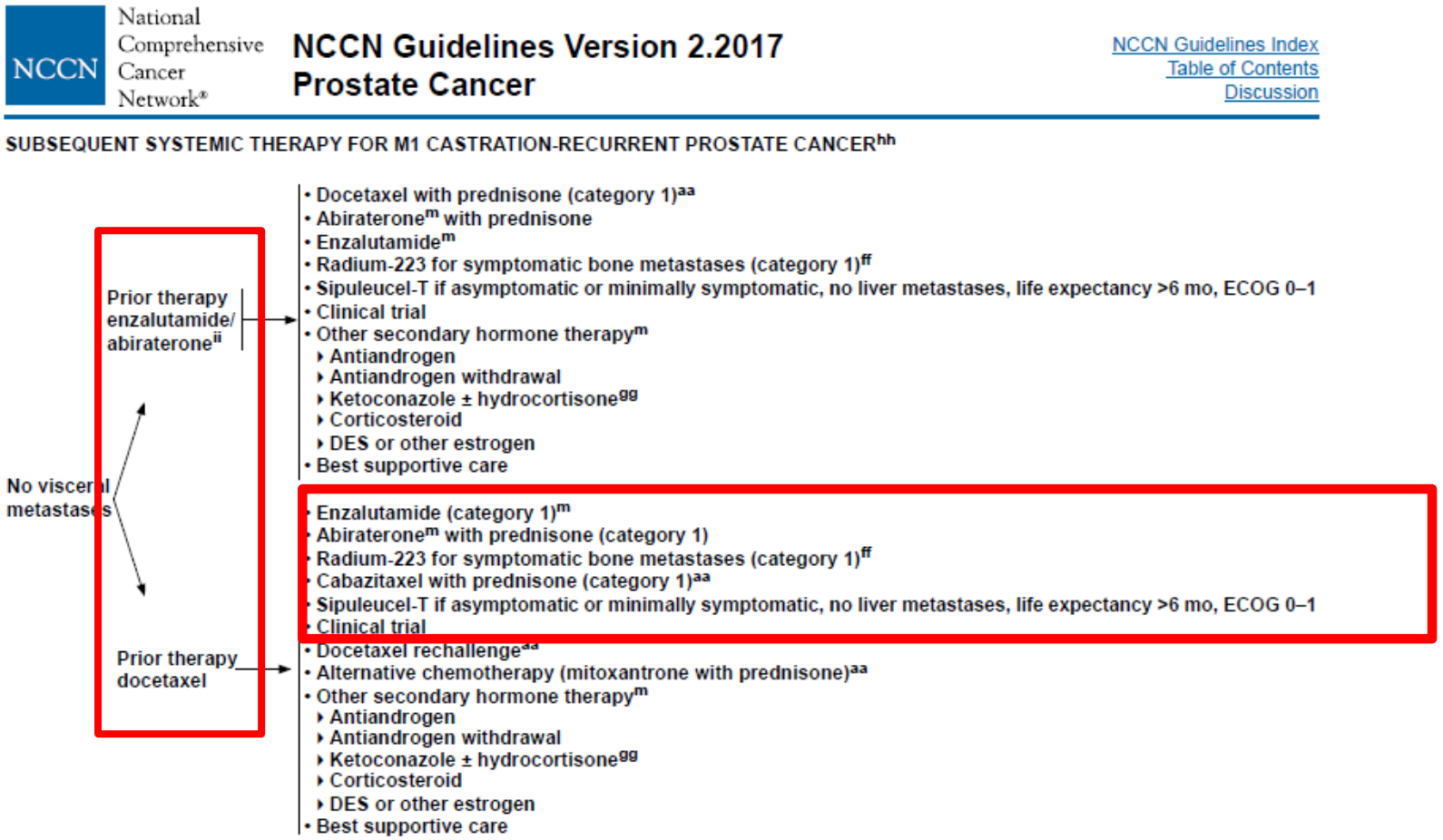
Kastrasyona Dirençli Prostat Kanseri



Kastrasyona Dirençli Prostat Kanserinde Tedavi



Kastrasyona Dirençli Prostat Kanserinde Tedavi



Kastrasyona Dirençli Prostat Kanserinde Tedavi

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2017
Prostate Cancer

NCCN Guidelines Index
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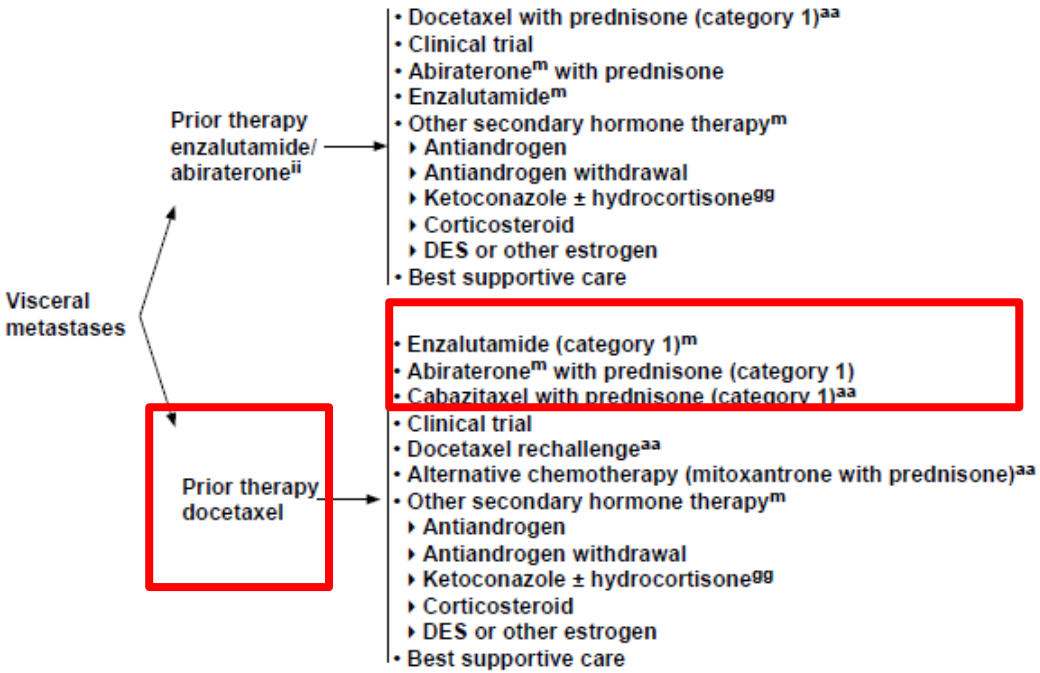
Discussion

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



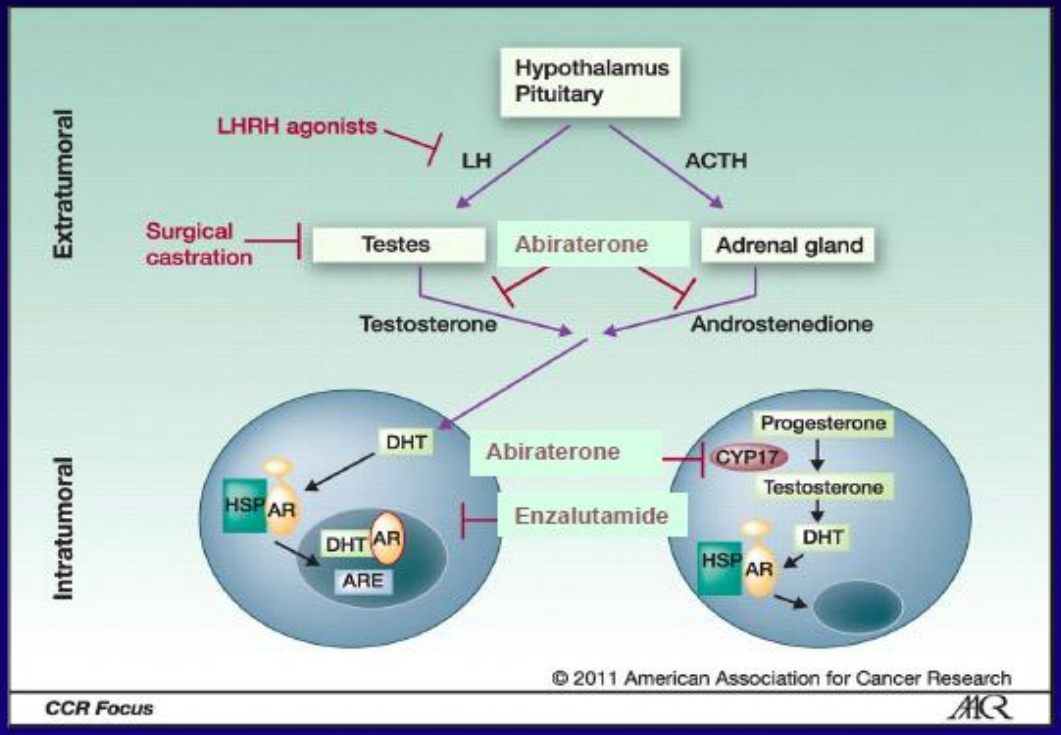
[gg]Ketoconazole ± hydrocortisone should not be used if the disease progressed on abiraterone.
[hh]Patients can continue through all treatment options listed. Best supportive care is always an appropriate option.
[ii]Limited data suggest a possible role for AR-V7 testing to help guide selection of therapy (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

Abiraterone and enzalutamide: Sites of action on the androgen axis

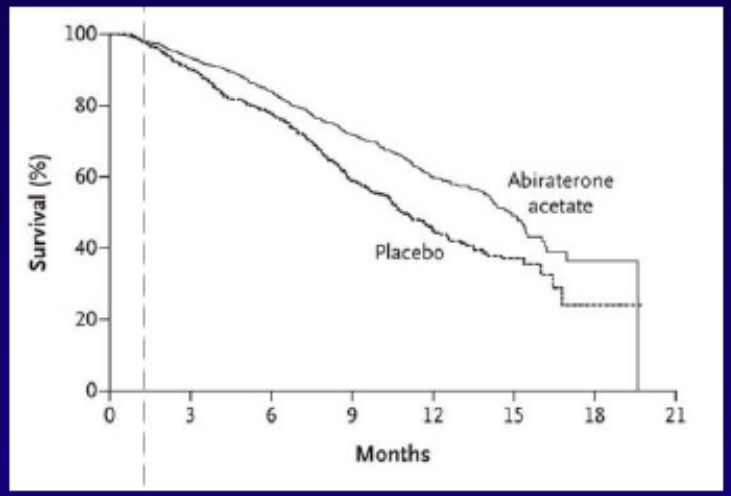


Adapted from Massard C, Clin Cancer Res 2011

Kastrasyona Dirençli Prostat Kanseri

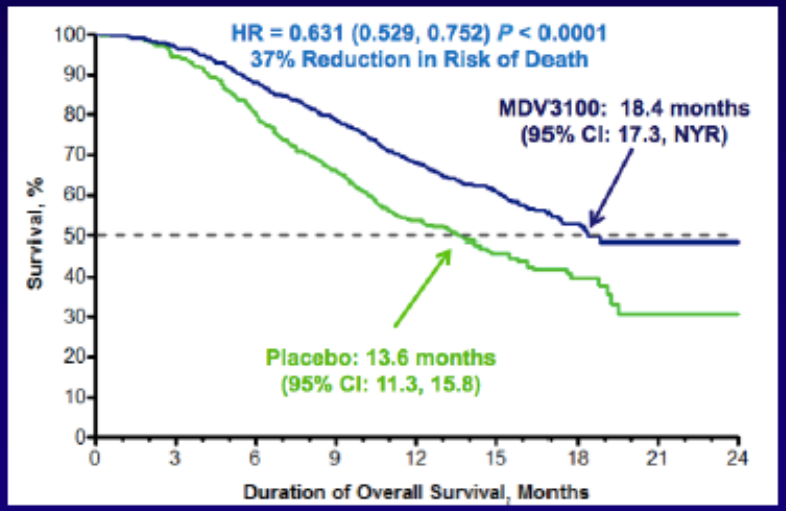
Post docetaxel phase 3 trials: abiraterone and enzalutamide

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 Hormonal Tedavi

	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

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)

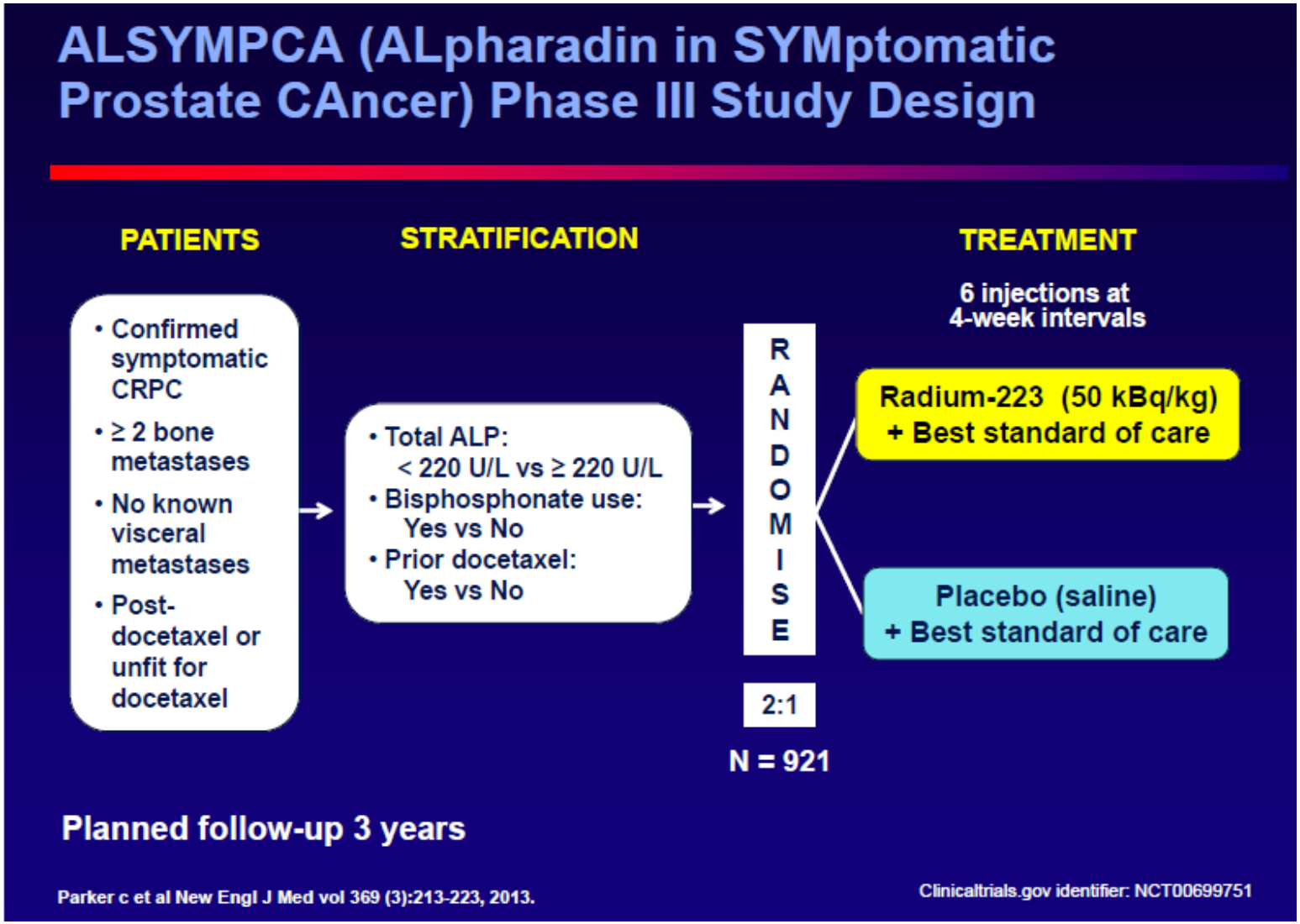
- There is evidence of cross-resistance between abi/enza and taxanes
- Abi/enza may be less effective after taxanes

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

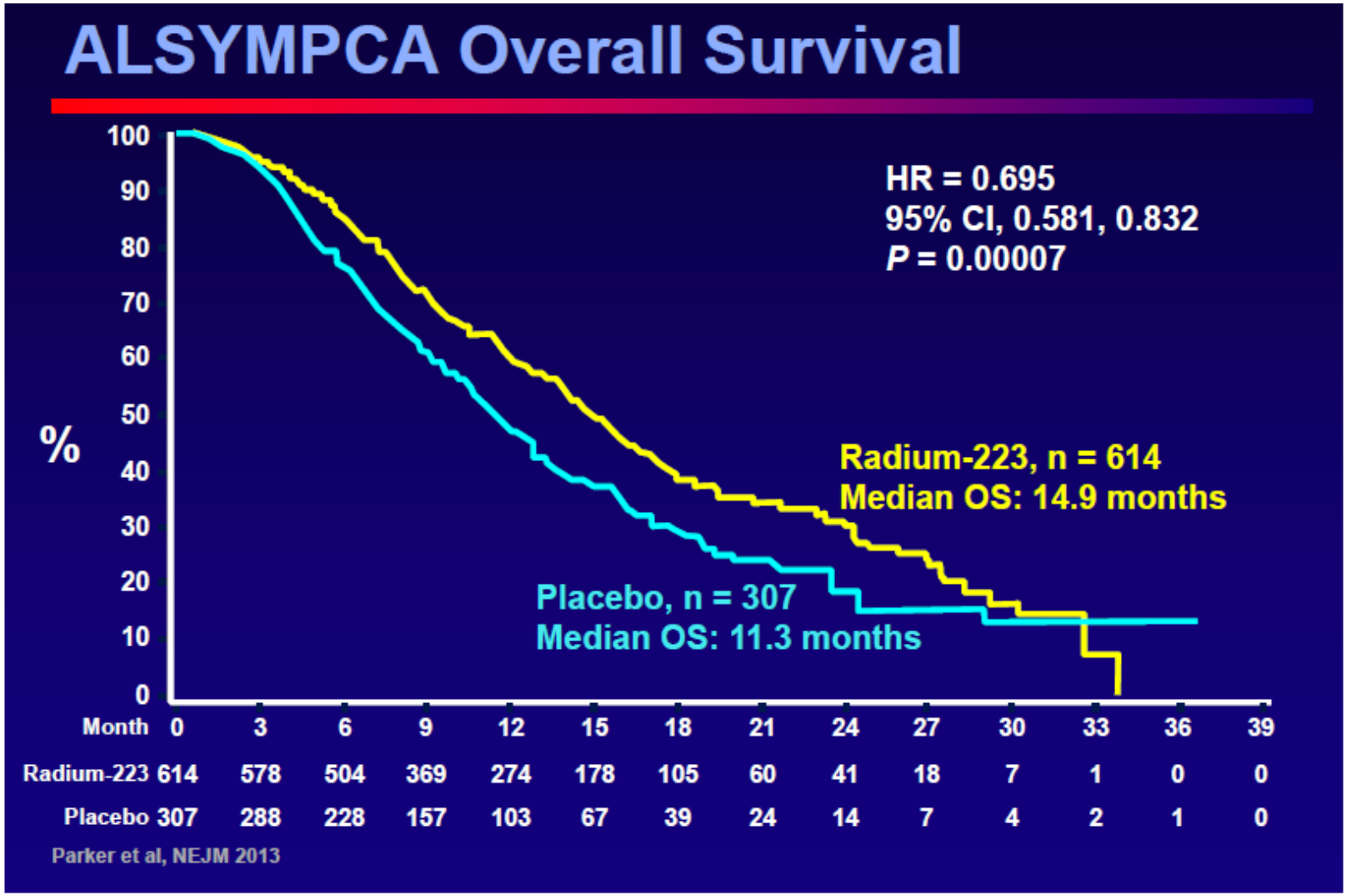
and Taxanes may be less effective after abi/enza

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

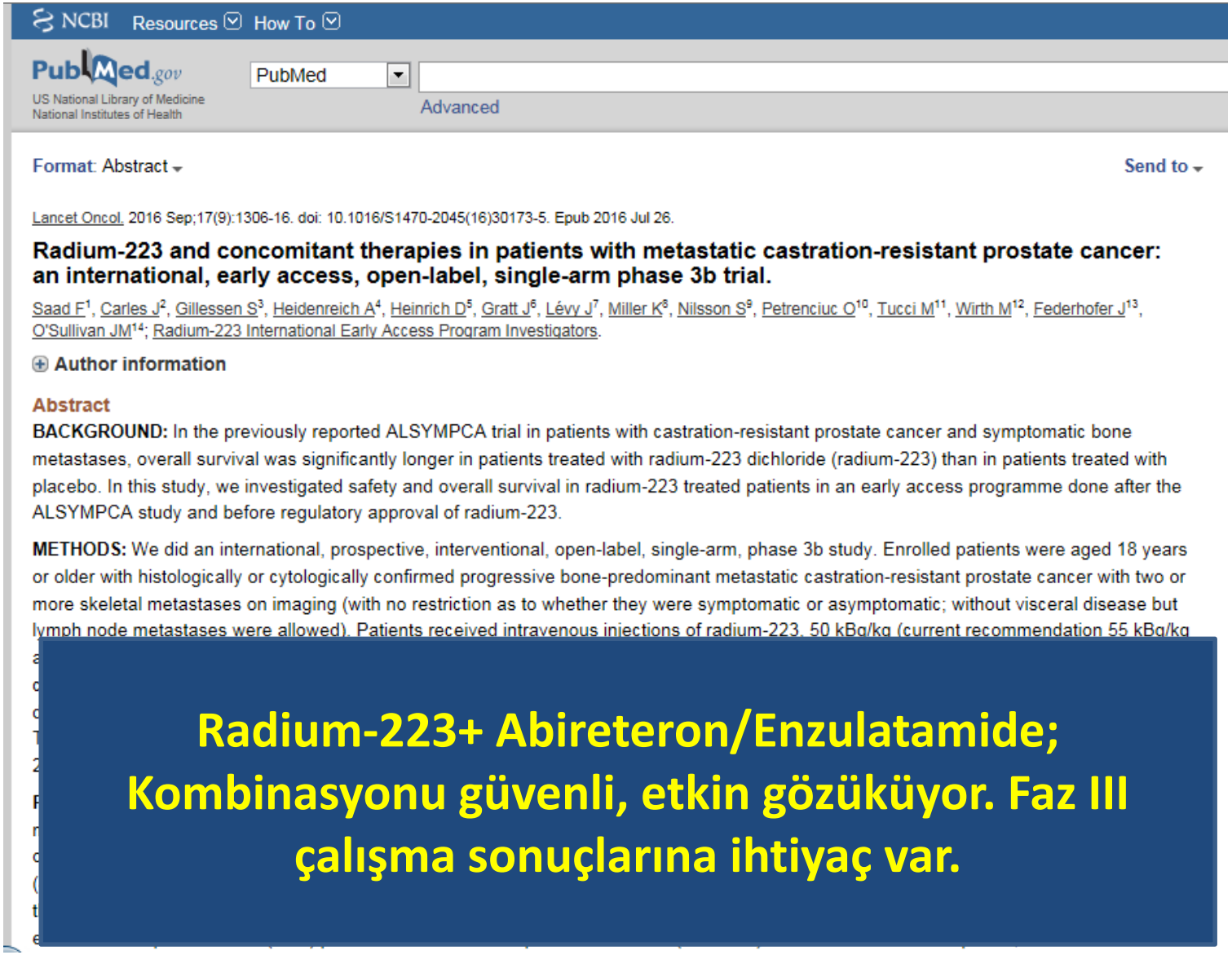
Kastrasyona Dirençli Prostat Kanseri



Kastrasyona Dirençli Prostat Kanseri Dosetaksel Sonrası Kemoterapi



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

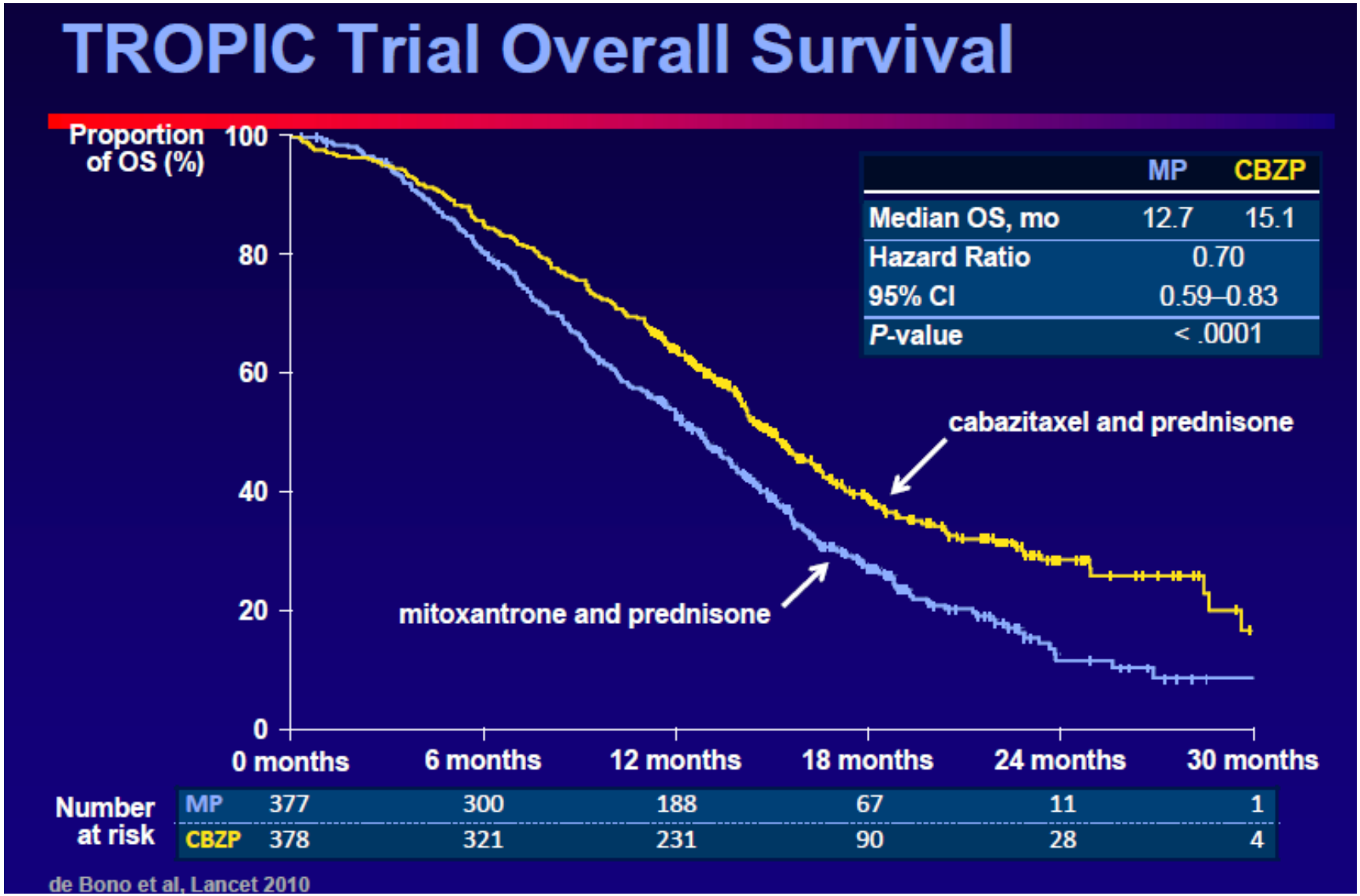
Radium-223+ Abireteron/Enzulatamide; Kombinasyonu güvenli, etkin gözüküyor. Faz III çalışma sonuçlarına ihtiyaç var.

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



Yakın zamanda yayınlanan Faz 3 Kemo-naive mKDPK Çalışmalarında OS Faydası

Çalışma (Ajan) Yıl	Karşılaştırma kolu	Hazard Ratio	P değeri
TAX327 (Dosetaksel) 2004	Mitoksantron Prednison	0.76	0.009
IMPACT (Provenge aşısı) 2010	Plasebo	0.775	0.032
PREVAIL (Enzalutamid) 2012	Plasebo Prednizon	0.71 (Ara analiz)	<0.0001
COU-AA-302 (Abirateron asetat) 2014	Plasebo Prednizon	0.80 (Final Analiz)	0.0027
ELM-PC 4 (Orteronel) 2014	Plasebo Prednizon	0.9	0.314 **(NS)**

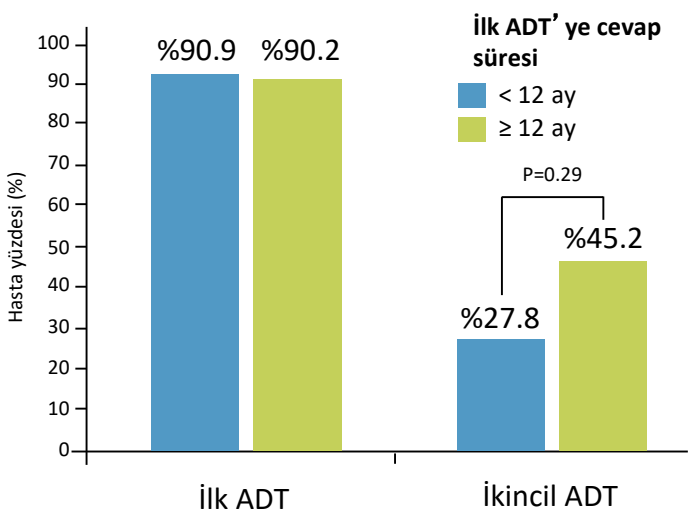
NS= istatiksel olarak anlamlı değil

Yakın zamanda yayınlanan Faz 3 Post-kemo mKDPK Çalışmalarında OS Faydası

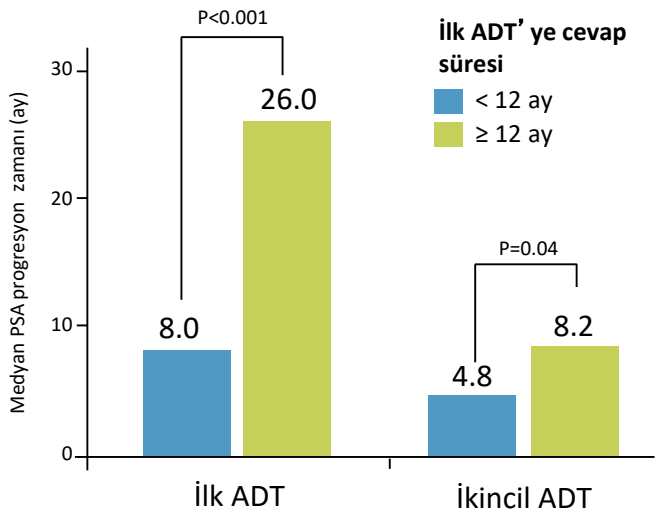
Çalışma (Ajan) Yıl	Karşılaştırma kolu	Hazard Ratio	P değeri	Not
TROPIC (Kabazitaksel) 2010	Mitoksantron Prednison	0.72	<0.0001	
COU-AA-301 (Abirateron asetat) 2011	Plasebo Prednizon	0.74	<0.0001	
AFFIRM (Enzalutamid) 2012	Plasebo Prednizon	0.63 (Ara analiz)	<0.0001	
ALSYMPCA (Radyum 223) 2013	Plasebo	0.70	0.00185	
COMET-1 (Kabozantinib) 2014	Prednizon	0.9	0.212 **(NS)**	Dosetaksel ± Abirateron ± Enzalutamid sonrası
ELM-PC 5 (Orteronel) 2014	Plasebo Prednizon	0.89	0.1898 **(NS)**	

ÖNCEKİ ADT SÜRESİ İLE SEÇİLEN TEDAVİSİ ARASINDAKİ İLİŞKİ

İlk ve ikincil hormonal tedavilere ≥%30 PSA cevabı veren hasta oranı



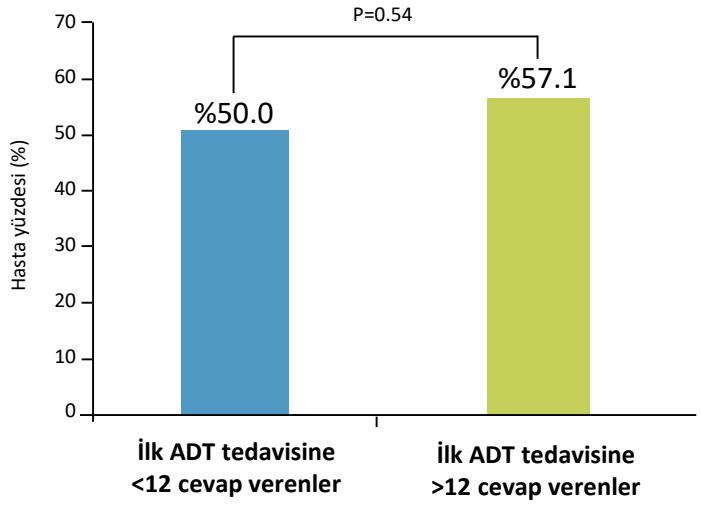
İlk ve ikincil hormonal tedavilerde PSA progresyonuna kadar geçen süre



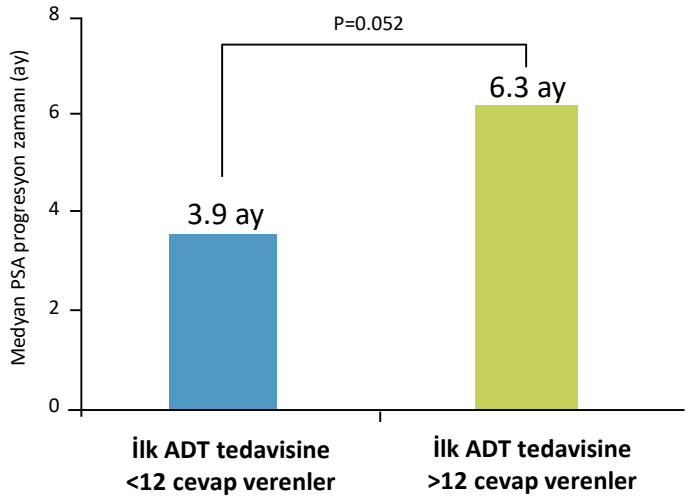
Angelergues et al ASCO GU 2014 poster A282

ÖNCEKİ ADT SÜRESİ İLE SEÇİLEN TEDAVİSİ ARASINDAKİ İLİŞKİ

Kabazitaksele ≥%30 PSA cevabı veren hasta oranı



Kabazitaksel tedavisi ile PSA progresyonuna kadar geçen süre

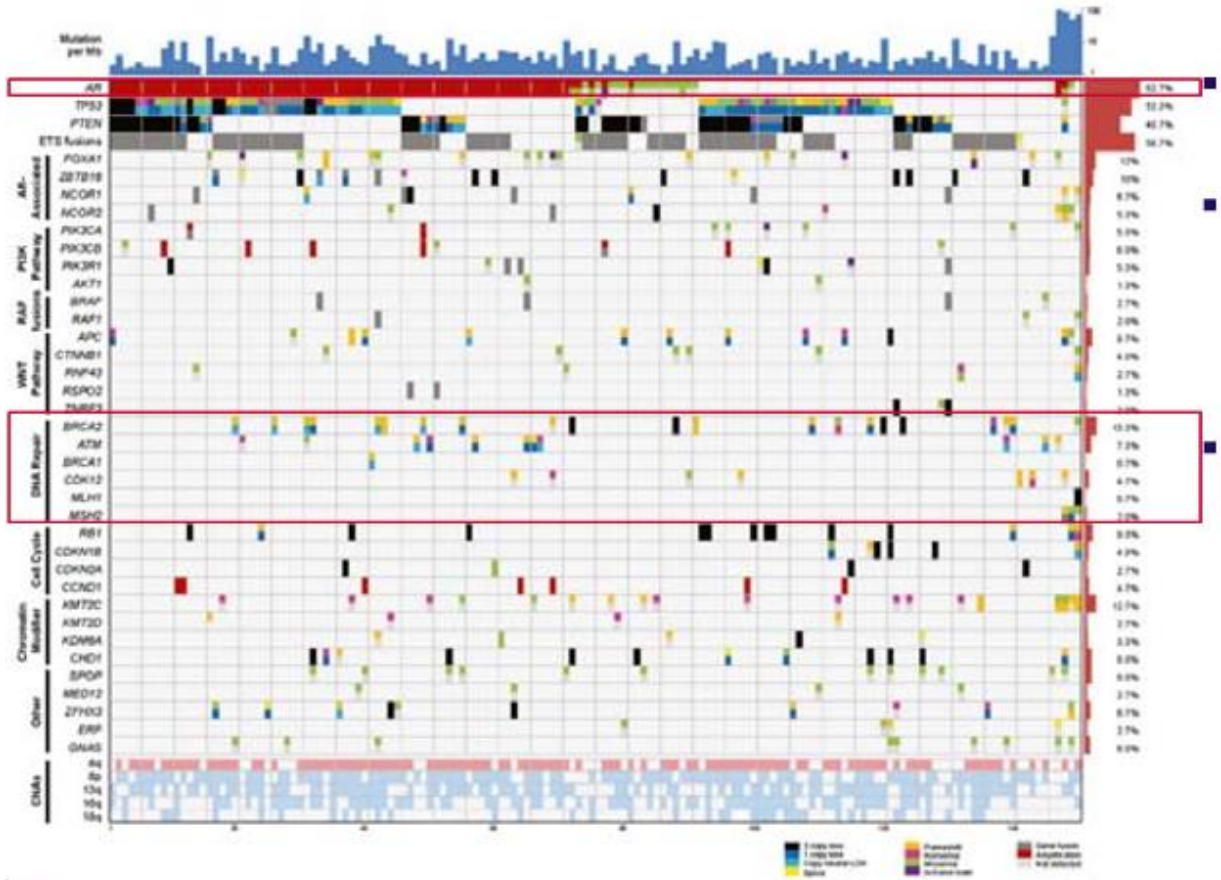


mKDPK'li hastalarda ilk ADT'ye kısa cevap süresi (12 ay), kötü prognoz ve sonraki hormonal tedavilere düşük cevap ile ilişkilidir. Kabazitaksel ise önceki ADT süresinden bağımsız etkilidir.

Angelergues et al ASCO GU 2014 poster A282

ADT Tedavisine Direnç Mekanizmaları

Molecular Landscape of mCRPC



- AR alterations in 71% of cases
- AR mutations exclusively found in mCRPC (71%)
- DNA repair pathway alterations in 22.7% of cases

Robinson D, et al. Cell. 2015.

ADT Tedavisine Direnç Mekanizmaları

AR-V7 Status and Resistance to Enzalutamide and Abiraterone

	Baseline AR-V7+	Response*	
		AR-V7 status	PSA50
Abiraterone (N=31)	19% (6/31)	+	0%
		–	68%
Enzalutamide (N=31)	39% (12/31)	+	0%
		–	53%

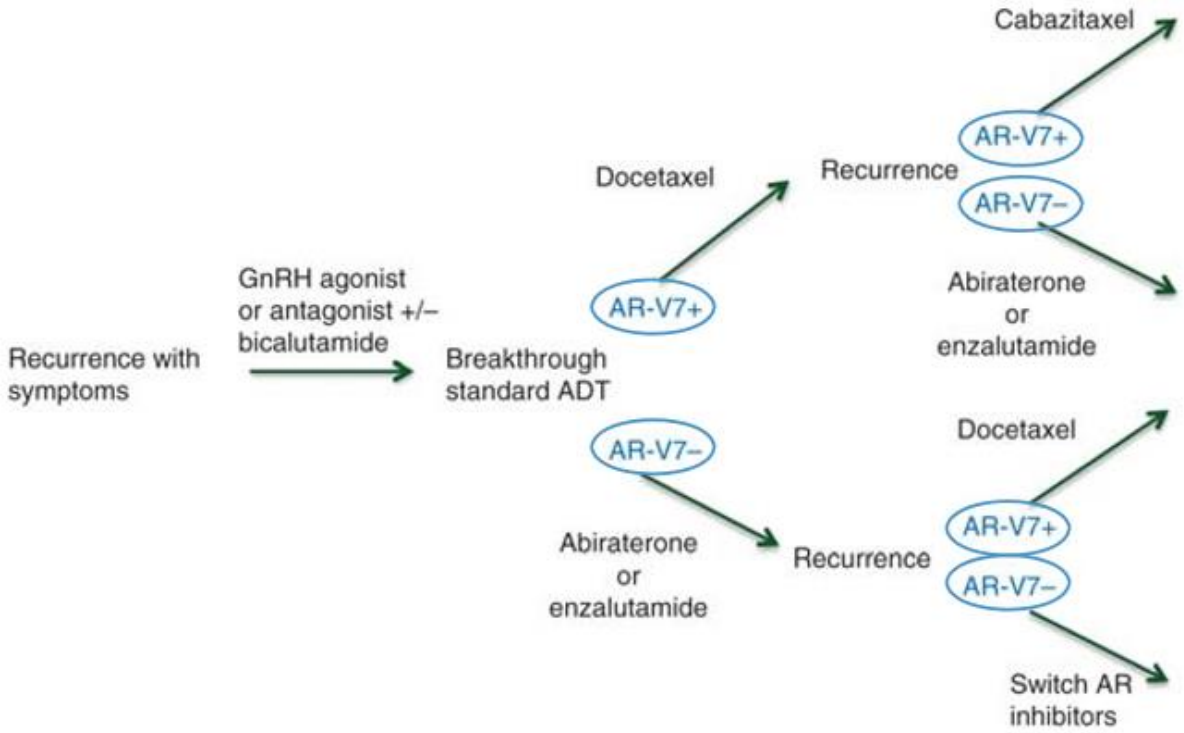
- Prospective study of M1 CRPC patients eligible for enzalutamide (N=31) or abiraterone (N=31) treatment, AR-V7 identified in CTC samples prior to treatment
- None (0/18) of the AR-V7 positive patients achieved a PSA50

Antonarakis et al. NEJM. 2014

ADT Tedavisine Direnç Mekanizmaları

Potential Treatment Schema

Pending Ongoing Prospective Studies

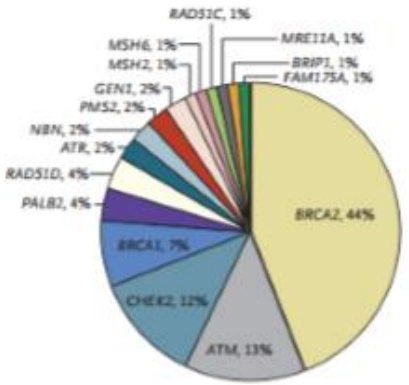


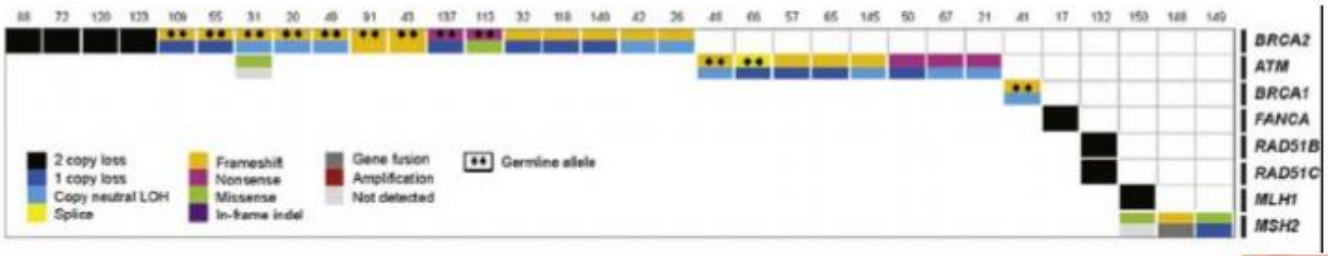
Sprenger, Uo, Plymate. Annals of Oncology 2015

Kastrasyona Dirençli Prostat Kanseri
Yeni Tedavi Seçenekleri

DNA-Repair Mutations in Men with Prostate Cancer

- Germline mutations in DNA Repair genes
  - 2.7 % healthy controls
  - 4.6% localized prostate cancer
  - 11.8% metastatic prostate cancer
- Somatic mutation in DNA repair genes
  - Upwards of 23% of mCRPC harbor



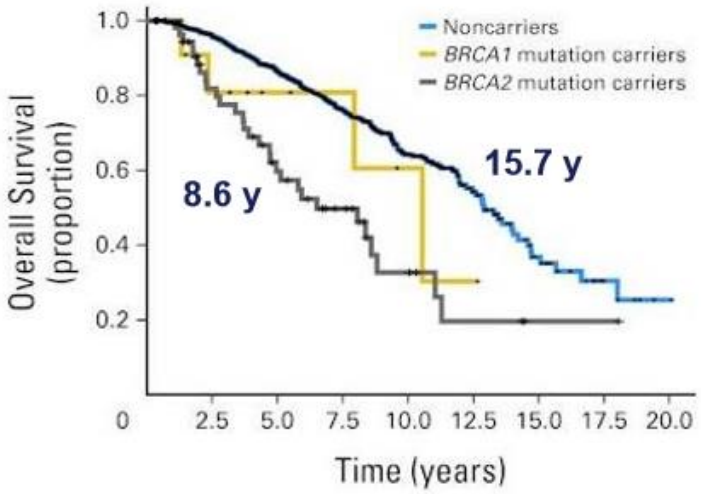


Pritchard CC, et al. N Engl J Med. 2016. Robinson D, et al. Cell. 2015.

Kastrasyona Dirençli Prostat Kanseri Yeni Tedavi Seçenekleri

Germline BRCA Mutations and Prognosis

- Prostate cancer with germline BRCA1/2 mutations were more frequently associated with Gleason ≥ 8 (P = .00003), T3/T4 stage (P = .003), nodal involvement (P = .00005), and metastases at diagnosis (P = .005) than prostate cancer in noncarriers



Castro E., JCO. 2013

Kastrasyona Dirençli Prostat Kanseri Yeni Tedavi Seçenekleri

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 29, 2015 VOL. 373 NO. 18

DNA-Repair Defects and Olaparib in Metastatic Prostate Cancer

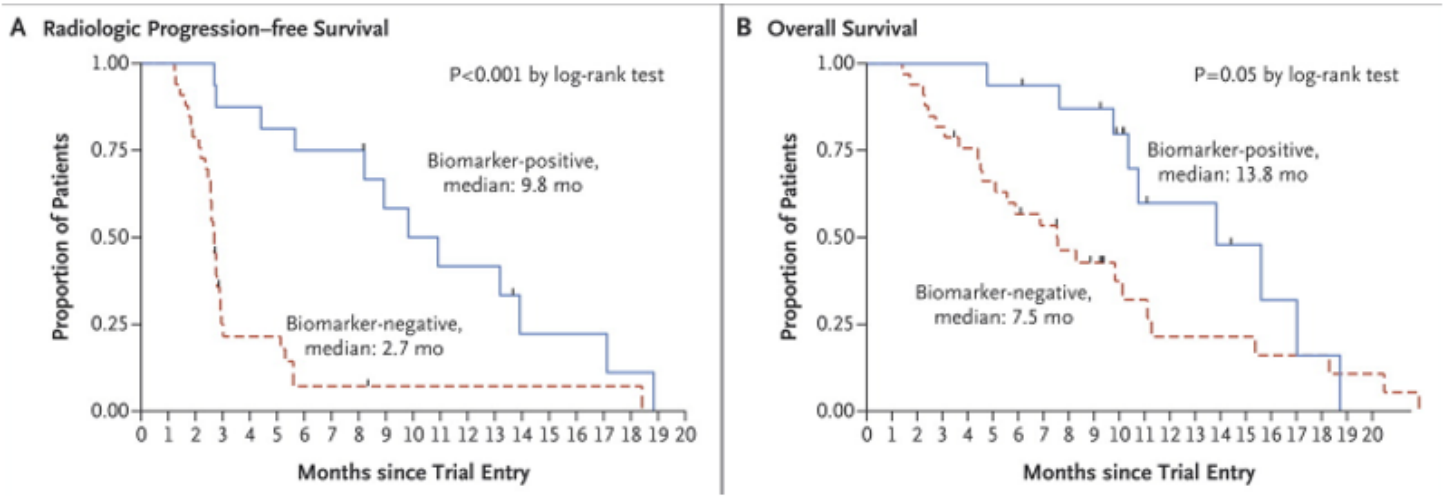
J. Mateo, S. Carreira, S. Sandhu, S. Miranda, H. Mossop, R. Perez-Lopez, D. Nava Rodrigues, D. Robinson, A. Omlin, N. Tunariu, G. Boysen, N. Porta, P. Flohr, A. Gillman, I. Figueiredo, C. Paulding, G. Seed, S. Jain, C. Ralph, A. Protheroe, S. Hussain, R. Jones, T. Elliott, U. McGovern, D. Bianchini, J. Goodall, Z. Zafeiriou, C.T. Williamson, R. Ferraldeschi, R. Riisnaes, B. Ebbs, G. Fowler, D. Roda, W. Yuan, Y.-M. Wu, X. Cao, R. Brough, H. Pemberton, R. A'Hern, A. Swain, L.P. Kunju, R. Eeles, G. Attard, C.J. Lord, A. Ashworth, M.A. Rubin, K.E. Knudsen, F.Y. Feng, A.M. Chinnaiyan, E. Hall, and J.S. de Bono

- Investigator-initiated multi-stage Phase II trial
- Adaptive trial design, open label, olaparib 400mg BID
- Primary endpoint: Response Rate
  - RECIST 1.1, PSA decline >50%, CTC conversion
- Secondary Endpoints: PFS, rPFS, OS, time to PSA progression

Mateo, J et al. NEJM 2015

Kastrasyona Dirençli Prostat Kanseri Yeni Tedavi Seçenekleri

Antitumor Activity of Olaparib and Association with Defects in DNA-Repair Genes



- Response rate: 32.7% (16/49 evaluable patients)
- Response rate: **88.0%** (14/16 w/DNA-repair gene defects)

Kastrasyona Dirençli Prostat Kanseri
Yeni Tedavi Seçenekleri

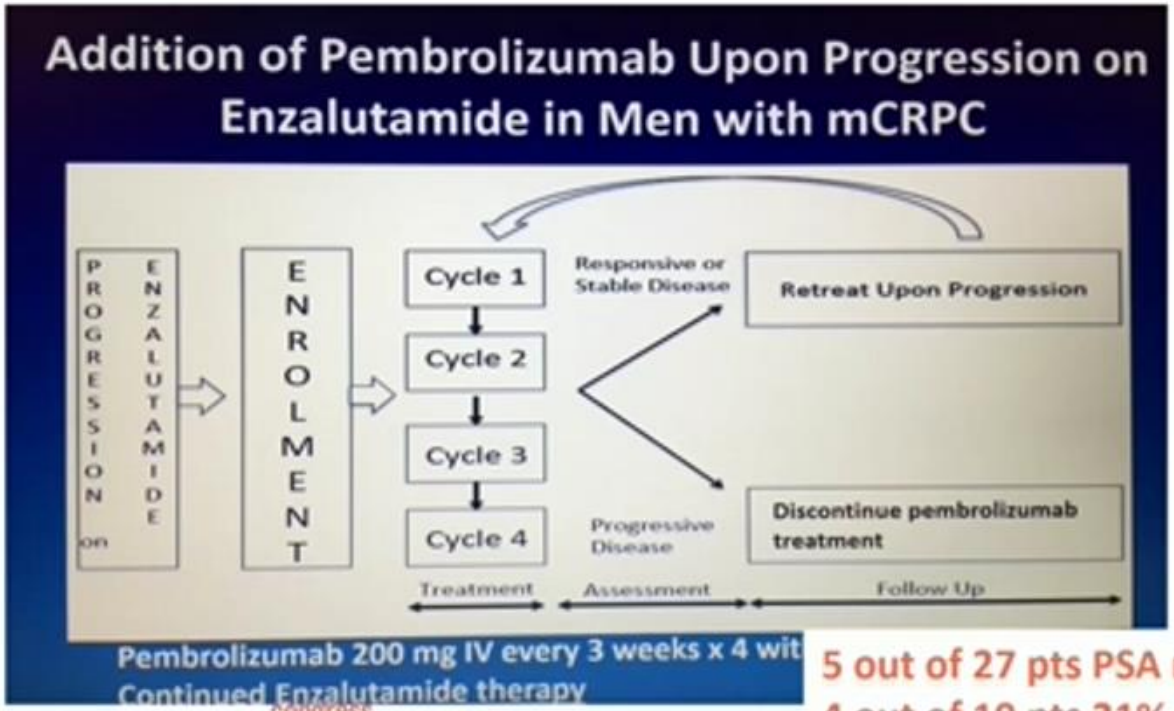
Ongoing Trials of PARP Inhibitors in Prostate Cancer

Name	Prostate Cancer Trials
Olaparib	TOPARP, abiraterone +/- olaparib, neoadjuvant olaparib
Veliparib	NCI 9012
Rucaparib	TRITON2 (mCRPC, Phase II, HR defects), TRITON3
Niraparib	Enzalutamide + niraparib
Talazoparib	
BGB-290	Phase Ia in advanced solid tumors

Kastrasyona Dirençli Prostat Kanseri
Yeni Tedavi Seçenekleri

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

64 yaşında erkek hasta, Diabet ve Hipertansiyon öyküsü var. Metastatik prostat kanseri nedeniyle 15 ay hormonal tedavi almış. Yaygın sırt ağrısı var, kastrasyona dirençli, PSA 134ng/ ml saptandı. Yaygın kemik metastazı var, viseral metastaz yok. Hastaya, dosetaksel başlandı ve 10 kürde PSA 8ng/ ml geriliyor. Nöropati semptomları başlıyor tedavi kesiliyor. Takiplerinde PSA giderek artıyor 9. ayda 60ng/ ml oluyor. TVS multiple kemik metastazında progresyon. 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-Enzalutamid

4- Abirateron

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