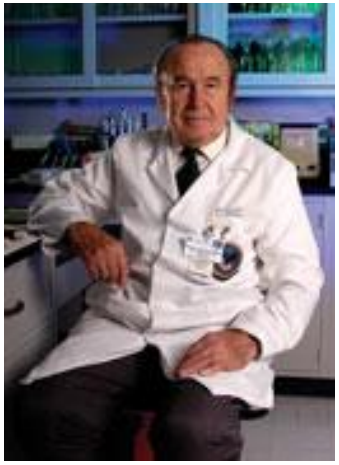
Prostat kanserinde genetik sonuçlara göre bireyselleşmiş tedavi seçenekleri

Dr. Deniz Tural
Koç University Hospital Department of Medical Oncology

Ders Planı

- Prostat kanserinde genomik değişiklikler
- Germline mutasyonları
- Somatik mutasyonlar
- DNA Repair Genlerde Olan Değişiklikler ve Tedaviye Yansımaları
- MSI
- PI3K/AKT/PTEN yolağı
- AR-variyant ve alterasyonlar
- Prostat adenokarsinomunda nöroendokrin diferansiasyon
- Sonuç

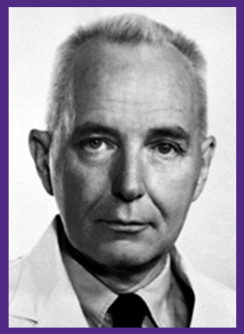
Kastrasyona Duyarlı Metastatik Prostat Kanseri ADT Tedavisi



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

Kastrasyona Duyarlı Metastatik Prostat Kanseri ADT Tedavisi

Historical Perspective: Androgens & Prostate Cancer



C. Huggins
1966 Nobel Prize

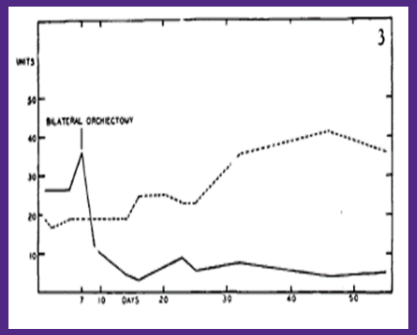
Studies on Prostatic Cancer

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

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

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

(Received for publication March 22, 1941)



Cancer Res 1941;1:293-297

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

Tedavi Kararında Etkili Faktörler

Hastalıkla İlişkili Faktörler

1- Yüksek volüm/Düşük volüm

2- Denovo/metakron metastaz

3-Metastaz bölgesi

4-Gleason skoru

5-Primer tümörün genetik profil

Klinik Faktörler

1-Semptomatik olması

2-ECOG PS

3-Ek hastalıklar

4-Başka hastalıklar için aldığı tedaviler

5-Hastalık için daha önce aldığı tedaviler

Başlanacak tedavi ile ilgili faktörler

1-Uygulama şekli

2-Etki etme mekanizması

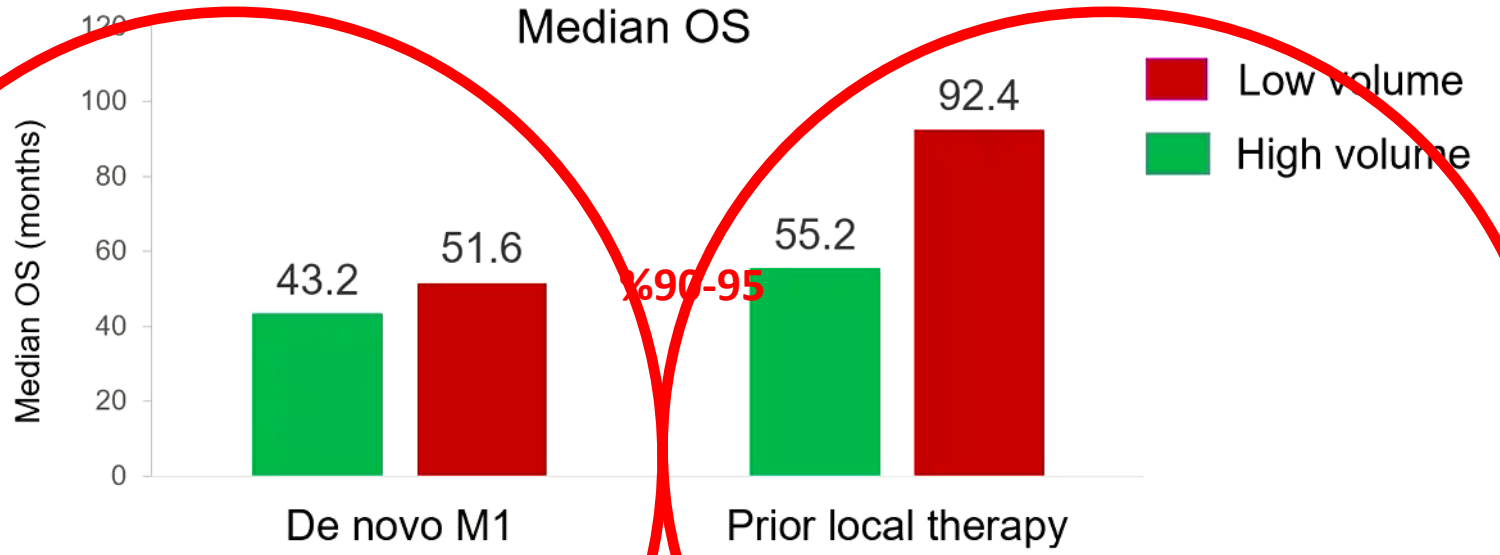
3- Yan etkileri

4-İlaç etkileşimi

5-Tedavi maliyeti

Tanı Anında Metastatik Hastalık Agresif Seyirli

De Novo mHNPC is associated with a worse prognosis



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

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

2021 ESMO congress

OUDARD Stéphane

%90-95

%5-10

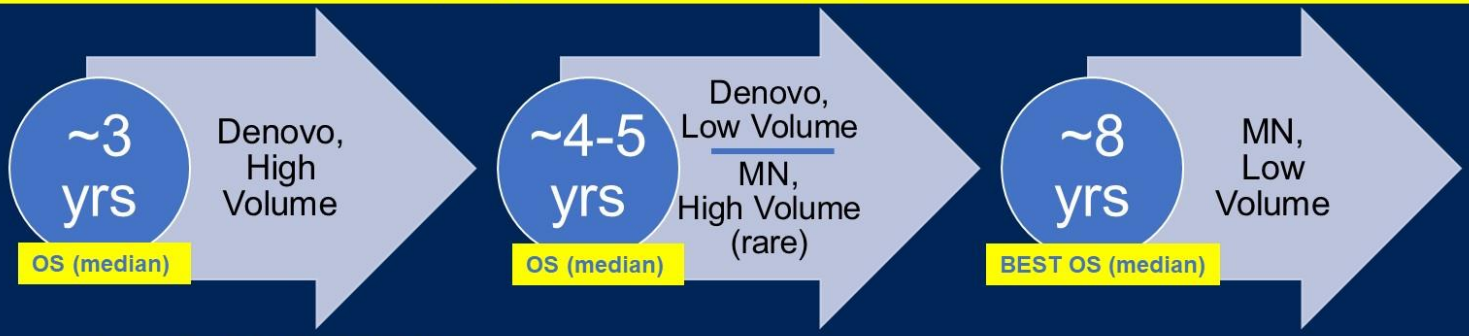
%90-95

TANI ANINDA METASTATİK VE YÜKSEK VOLÜMLÜ HASTALIK AGRESİF SEYİRLİ

Metastatic HSPC Trials – Clinical Risk Groups

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

Can clinical prognostic factors help guide treatment selection?



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

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

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Prostat kanserinde genomik profil

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

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

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

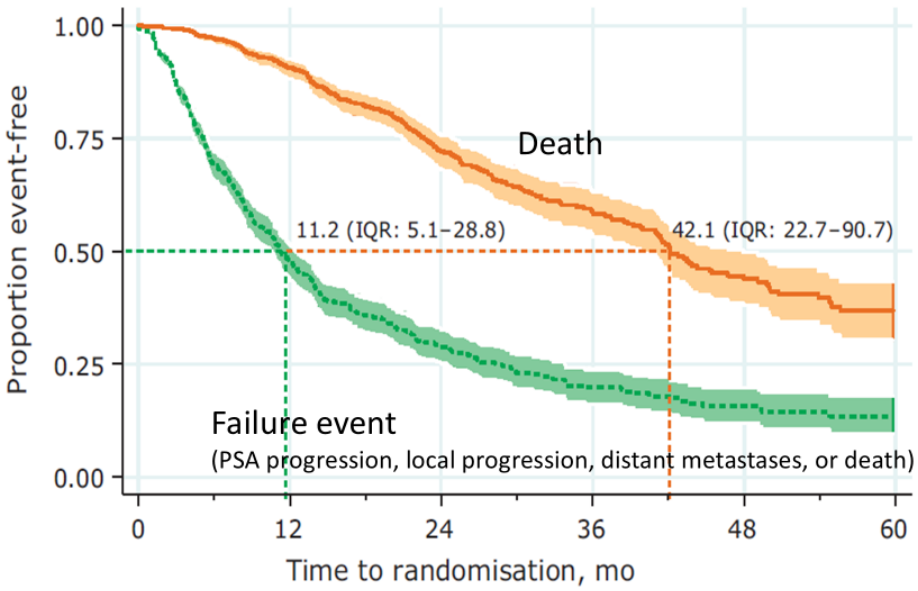
**Each figure represents 10% of patients with advanced PC.*

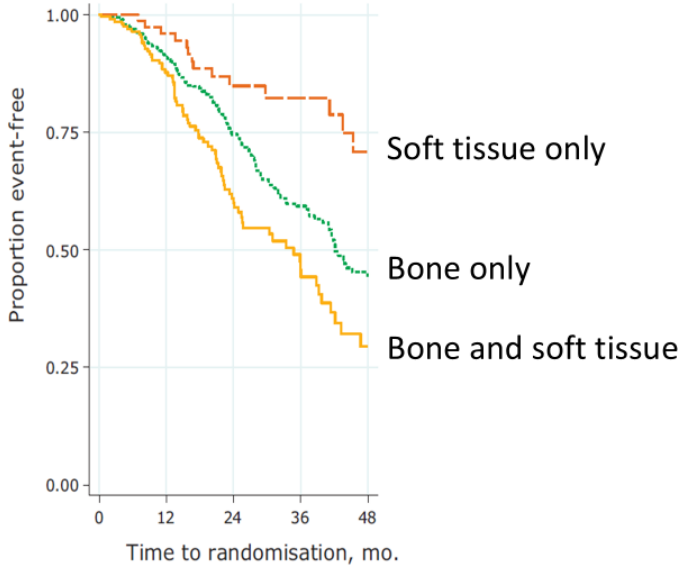
1. Hope TA, et al. J Nucl Med. 2017;58(12):1956–1961; 2. Hupe MC, et al. Front Oncol. 2018;8:623; 3. Pomykala KL, et al. J Nucl Med. 2020;61(3):405–411; 4. Minner S, et al. Prostate. 2011;71(3):281–288; 5. Bostwick DG, et al. Cancer. 1998;82(11):2256–2261; 6. Robinson D, et al. Cell. 2015;161(5):1215–1228;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

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

ADT alan hastalarda metastaz bölgesine göre sağkalım

Clinical Outcomes in Metastatic Prostate Cancer: STAMPEDE Experience with ADT





STAMPEDE Control Arm
- Metastatic disease
- Accrued 10/2005-1/2014
- N=917

James ND *et al* (2015) Eur Urol 67: 1028-1038

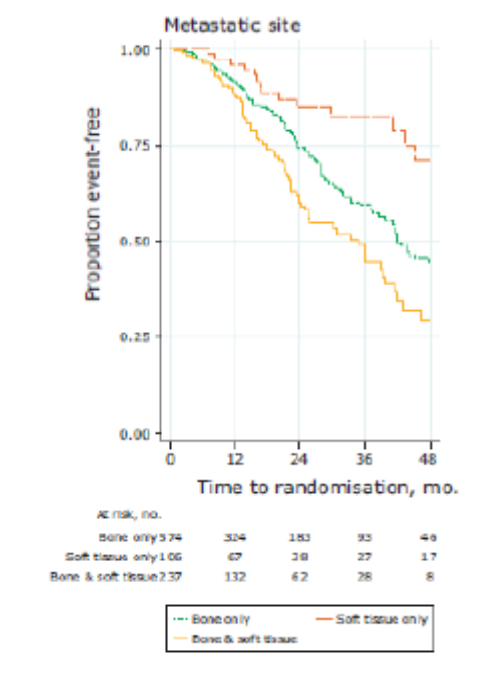
Yalnız ADT alanlarda 5-yıllık sağkalım %30-40. Non-regional lenf nodu iyi prognoz ile ilişkili

Metastaz bölgesine göre hastalık seyri farklı

Survival with Newly Diagnosed Metastatic Prostate Cancer in the "Docetaxel Era": Data from 917 Patients in the Control Arm of the STAMPEDE Trial (MRC PR08, CRUK/06/019)

Nicholas David James [a,], Melissa R. Spears [b], Noel W. Clarke [c], David P. Dearnaley [d,e], Johann S. De Bono [d,e], Joanna Gale [f], John Hetherington [g], Peter J. Hoskin [h], Robert J. Jones [i], Robert Laing [j], Jason F. Lester [k], Duncan McLaren [l], Christopher C. Parker [d,e], Mahesh K.B. Parmar [b], Alastair W.S. Ritchie [b], J. Martin Russell [m], Räto T. Strebel [n], George N. Thalmann [o], Malcolm D. Mason [k], Matthew R. Sydes [b]*

EUROPEAN UROLOGY 67 (2015) 1028–1038



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

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

2 Yıllık sağkalım; yumuşak doku met.%85

Kemik met.%75

Yumuşak doku+kemik met.%60

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

Kastrasyona Duyarlı Metastatik Prostat Kanseri Tedavisinin Seyri

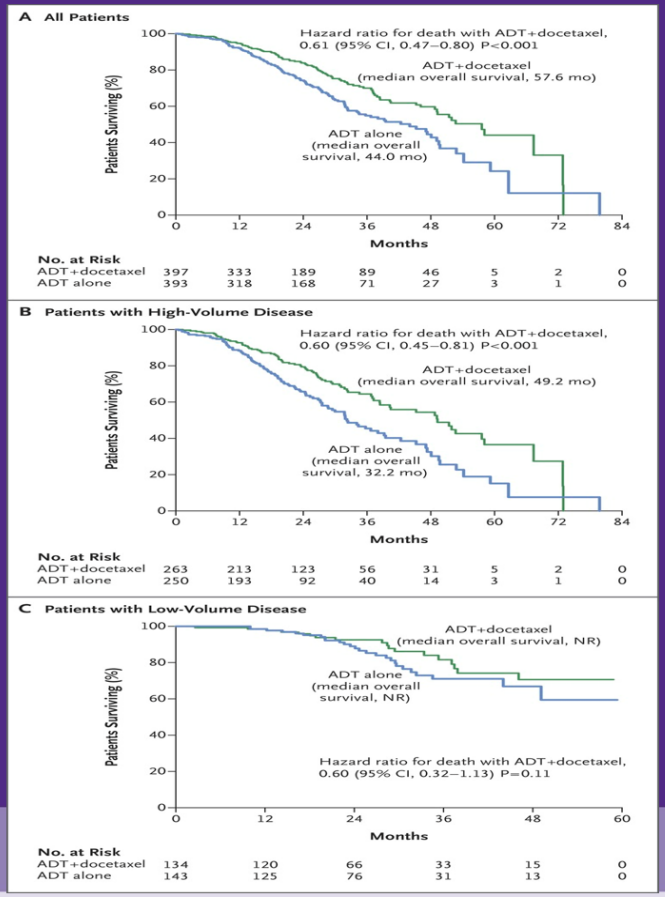
Sağkalımı artıran kanıt düzeyi yüksek çalışmalar

Studies	Intervention	Control	Comments
GETUG-AFU 15 CHAARTED STAMPEDE-C	Docetaxel + ADT	ADT	Benefit in high-volume subgroup
LATITUDE STAMPEDE-G	Abiraterone + ADT	ADT	Similar benefits by risk group
ARCHES ENZAMET	Enzalutamide + ADT	ADT	Similar benefits by risk group
TITAN	Apalutamide + ADT	ADT	Similar benefits by risk group
ARASENS	Darolutamide + ADT + docetaxel	ADT + docetaxel	Similar benefits for recurrent and de novo metastatic disease
PEACE-1	Abiraterone +ADT + docetaxel (+/- prostate radiation)	ADT + docetaxel (+/- prostate radiation)	Subgroup analysis

Gravis et al Lancet Oncol 2013; Sweeney et al NEJM 2015; James N et al Lancet 2015; Attard G et al Lancet Oncol 2023; Fizazi K et al NEJM 2017; James et al NEJM 2017; Armstrong et al JCO 2021; Davis et al NEJM 2019; Chi KN et al NEJM 2019; Smith MR et al NEJM 2022; Fizazi K et al Lancet 2022

Hastalık Volümü Dosetaksel Tedavi Etkinliği için Prediktif

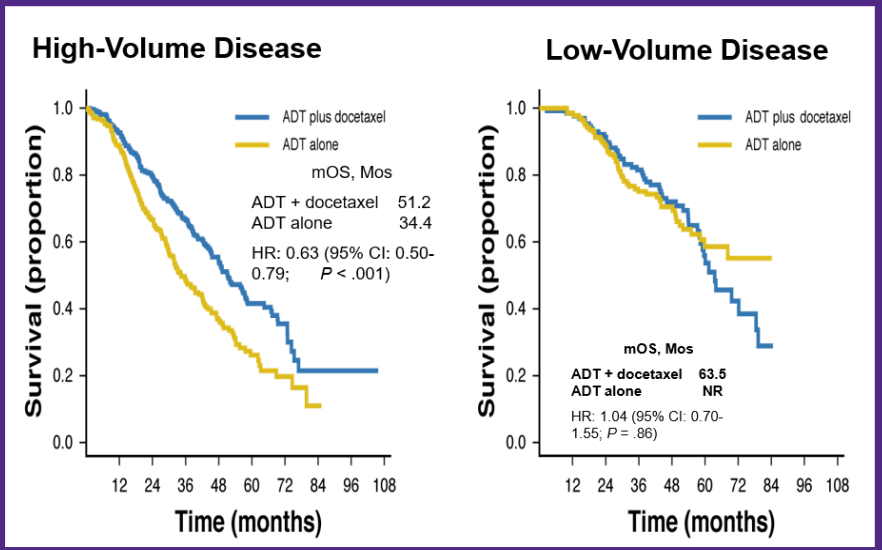
CHAARTED: ADT +/- Docetaxel in mHSPC



Sweeney CJ et al. NEJM 2015

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

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

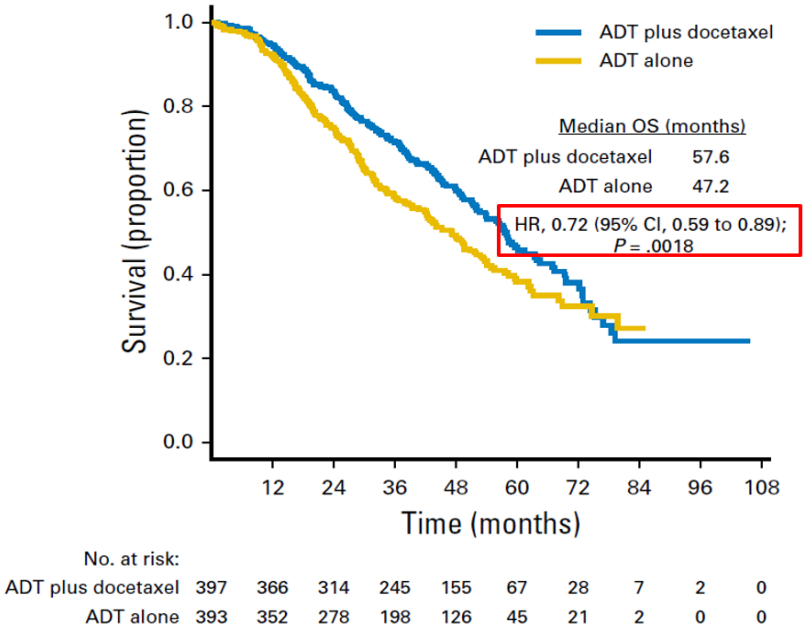


Kyriakopoulos CE, et al. J Clin Oncol. 2018

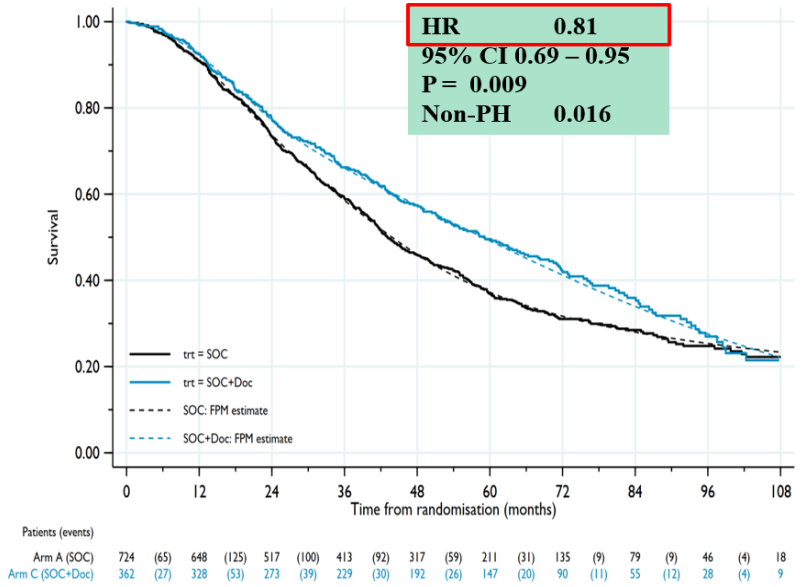
Yüksek volümlü hastalığı olanlar; viseral organ metastazı olan yada ≥4 kemik lezyonu olan ve en az ≥1 vertebra, pelvis dışı kemiklerde metastaz olmalı

Hastalık Volümü Dosetaksel Tedavi Etkinliği için Prediktif

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



Kyriakopoulos CE, J Clin Oncol 2018



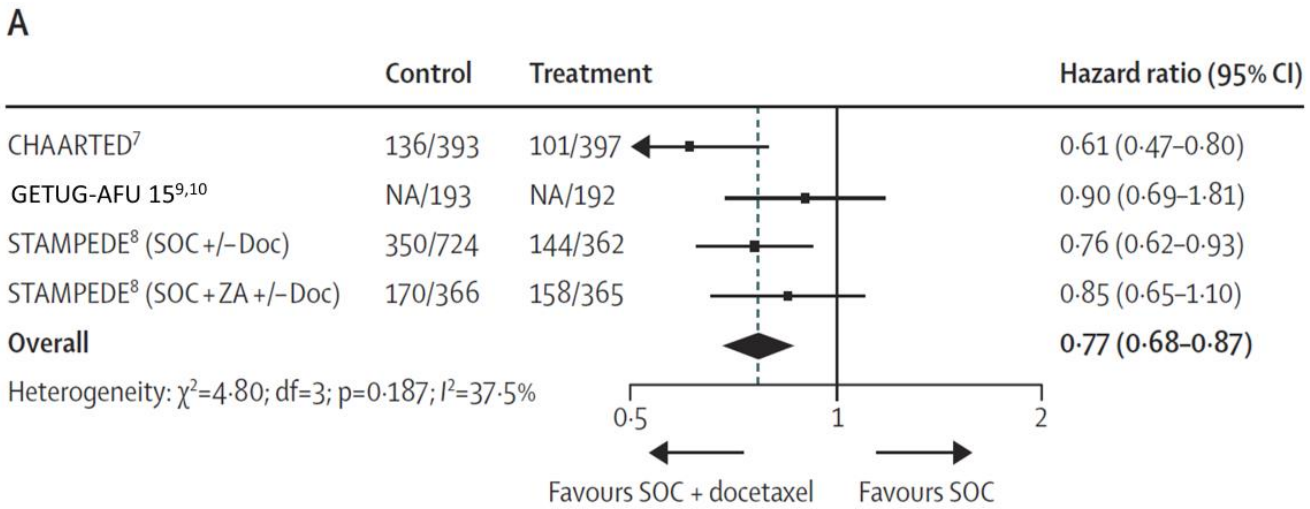
Clarke N, Ann Oncol. 2019

STAMPEDE tüm hastalar de novo metastatik ve %41 high volüm, CHAARTED çalışmasında de novo metastaz oranı %72 ve %66 high volüm

Metastatik Kastrasyona Duyarlı Prostat Kanserinde Dosetaksel Etkinliği

Meta-Analysis of RCTs of Docetaxel in mCSPC

Overall Survival

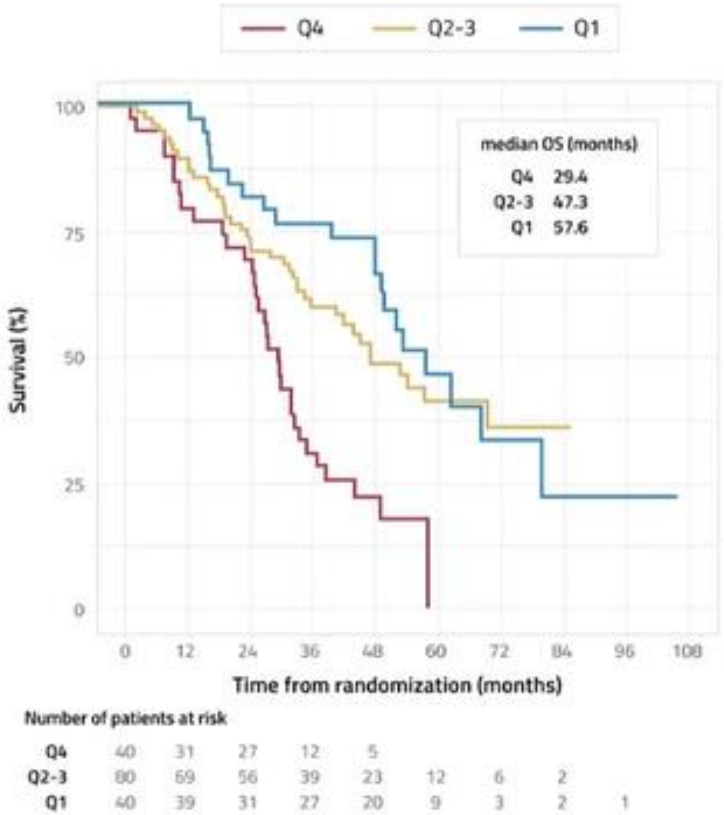


- Results based on 2993 men/2198 events
- 9% absolute improvement in survival at 4 years

Vale et al. Lancet Oncol 2016; 17(2):243-56

Klinik bulgulara gen ve genomik verilerin eklenmesi

Overall Survival in CHAARTED Stratified by Decipher Genomic Classifier Quartiles



Adapted based on data from: Anis Hamid, et al. Transcriptional profiling of primary prostate tumor in metastatic hormone-sensitive prostate cancer and association with clinical outcomes: correlative analysis of the E3805 CHAARTED trial. Annals of Oncology, 2021;32(9): 1157-1166. DOI: 10.1016/j.annonc.2021.06.003.

Klinik bulgulara gen ve genomik verilerin eklenmesi

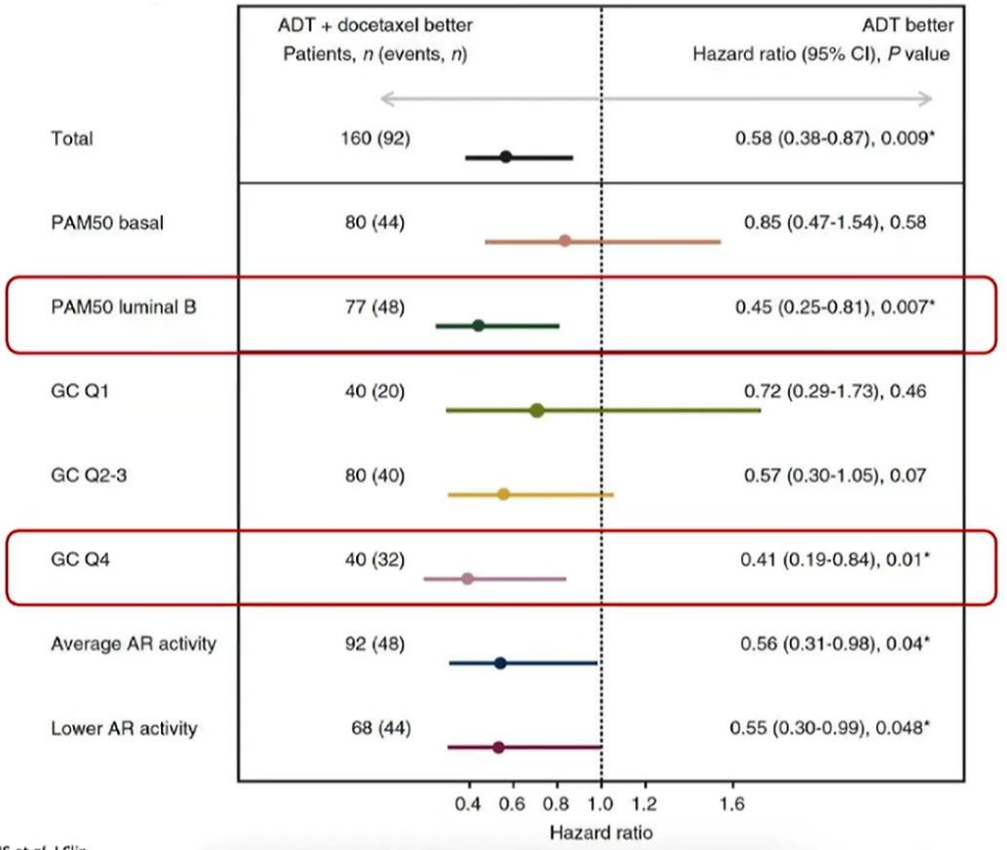
Decipher as a Prognostic Tool - Evolution from GRID Signatures

Hypotheses and analyses plan

- 59 signatures derived from pan-transcriptome data
- CHAARTED biomarker cohort (N=160) used as training set[1]

Pre-defined statistical analyses plan

- 4 signatures identified for predictive testing **Decipher**[2], **PAM50**[3], **PSC**[4], and **AR-A**[5]



1. Hamid A ... Sweeney C. *et al.* Ann Oncol. *2021;* 2. Nguyen P *et al.* Int J Radiat Oncol Biol Phys. 2023; 3. Parker JS *et al.* J Clin Oncol. 2009; 4. Weiner AB *et al.* Cancer; 2023 5. Spratt D et al. Clin Cancer Res 2019
Adapted from: Emily Grist, et al. Decipher mRNA score for prediction of survival benefit from docetaxel at start of androgen deprivation therapy (ADT) for advanced prostate cancer (PC): An ancillary study of the STAMPEDE docetaxel trials. ESMO. 13-17 September 2024; Barcelona, Spain.

Klinik bulgulara gen ve genomik verilerin eklenmesi

Decipher mRNA score for prediction of survival benefit from docetaxel at start of androgen deprivation therapy for advanced prostate cancer: an ancillary study of the STAMPEDE docetaxel trials

Emily Grist, Peter Dutey-Magni, Larissa Mendes, Marina A. Parry, Ashwin Sachdeva, James Proudfoot, Anis A. Hamid, Claire L. Amos, William R. Cross, Silke Gillessen, Daniel M. Berney, Matthew R. Sydes, Mahesh K.B. Parmar, Felix Y. Feng, Noel W. Clarke, Elai Davicioni, Christopher J. Sweeney, Nicholas D. James, Louise C. Brown, Gerhardt Attard on behalf of the STAMPEDE Investigators

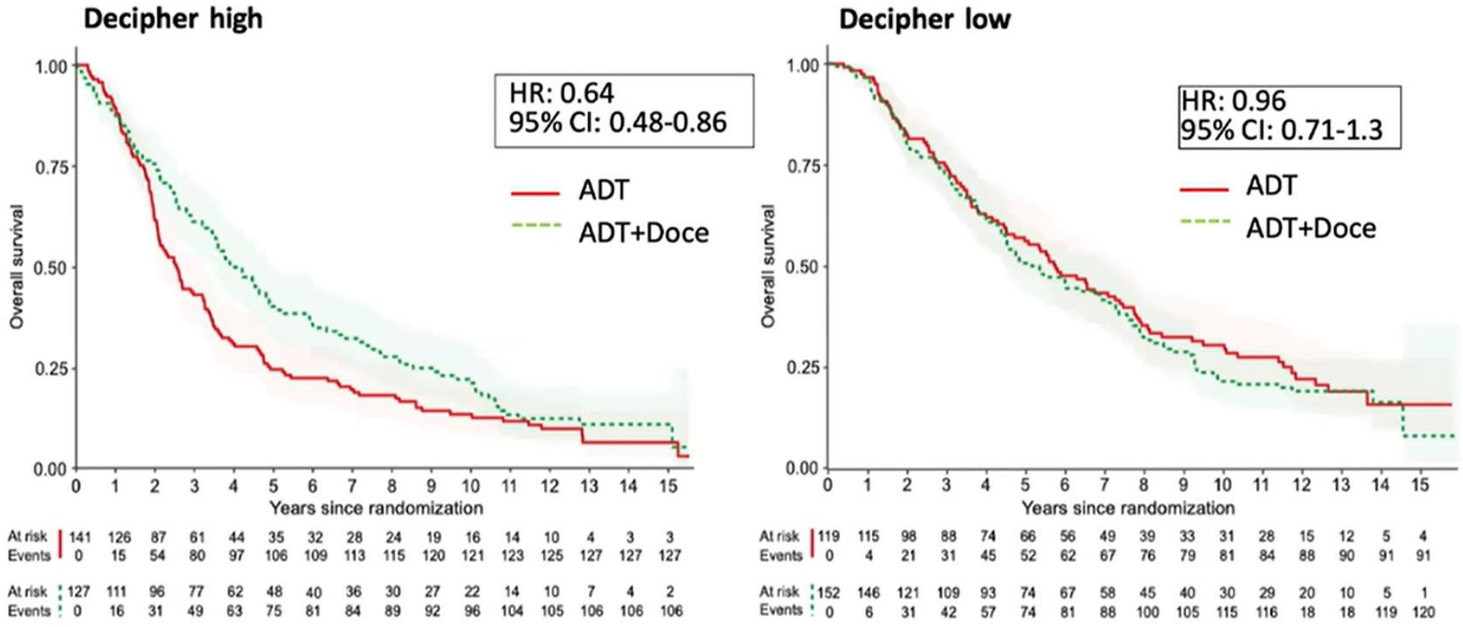
ClinicalTrials.gov number, NCT00268476 & Current Controlled Trials number, ISRCTN78818544 Trial conducted by Medical Research Council Trials Unit at University College London, U.K.

105 UK trial sites participated in this study

Emily Grist, et al. Decipher mRNA score for prediction of survival benefit from docetaxel at start of androgen deprivation therapy (ADT) for advanced prostate cancer (PC): An ancillary study of the STAMPEDE docetaxel trials. ESMO. 13-17 September 2024; Barcelona, Spain.

Klinik bulgulara gen ve genomik verilerin eklenmesi

Decipher Score Predicts Docetaxel Efficacy in Metastatic Prostate Cancer



High Decipher score identifies patients more likely to benefit from docetaxel

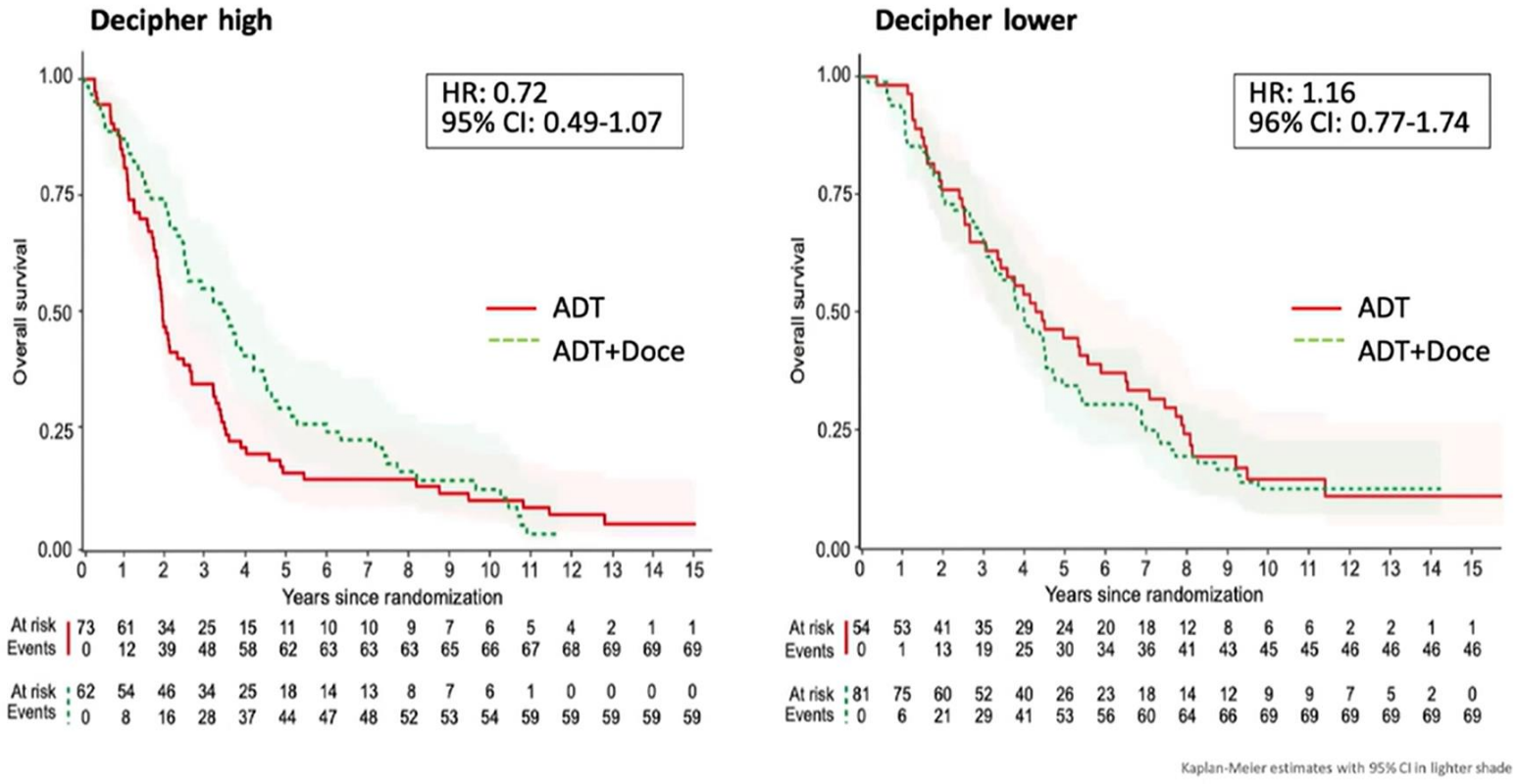
Biomarker-treatment interaction effect p value= 0.039*

No significant interaction effect demonstrated in non-metastatic disease
Kaplan-Meier estimates with 95% CI in lighter shade.
Decipher score dichotomized around median of metastatic cohort in combined docetaxel and abiraterone trials
Interaction test from multivariable model adjusted for Gleason score, disease burden, age, pre-ADT PSA, WHO PS, nodal stage, tumor stage, NSAID/aspirin use, and metastatic volume.

Emily Grist, et al. Decipher mRNA score for prediction of survival benefit from docetaxel at start of androgen deprivation therapy (ADT) for advanced prostate cancer (PC): An ancillary study of the STAMPEDE docetaxel trials. ESMO. 13-17 September 2024; Barcelona, Spain.

Klinik bulgulara gen ve genomik verilerin eklenmesi

Direction of Treatment Effect Consistent in High Volume



Kaplan-Meier estimates with 95% CI in lighter shade

Emily Grist, et al. Decipher mRNA score for prediction of survival benefit from docetaxel at start of androgen deprivation therapy (ADT) for advanced prostate cancer (PC): An ancillary study of the STAMPEDE docetaxel trials. ESMO. 13-17 September 2024; Barcelona, Spain.

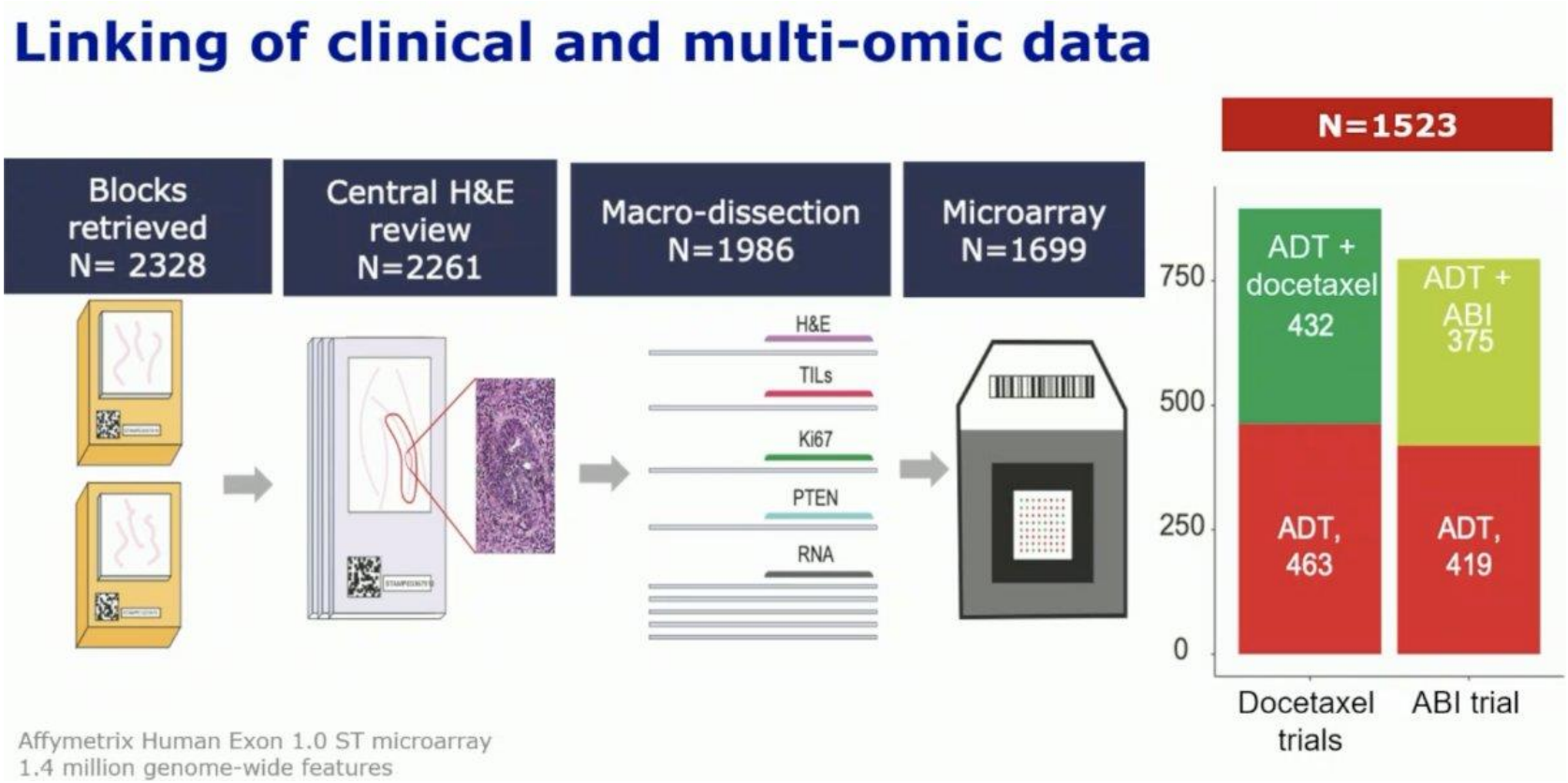
Klinik bulgulara gen ve genomik verilerin eklenmesi

Clinical qualification of transcriptome signatures for advanced prostate cancer starting androgen deprivation therapy with or without abiraterone acetate and prednisolone: an ancillary study of the STAMPEDE trial

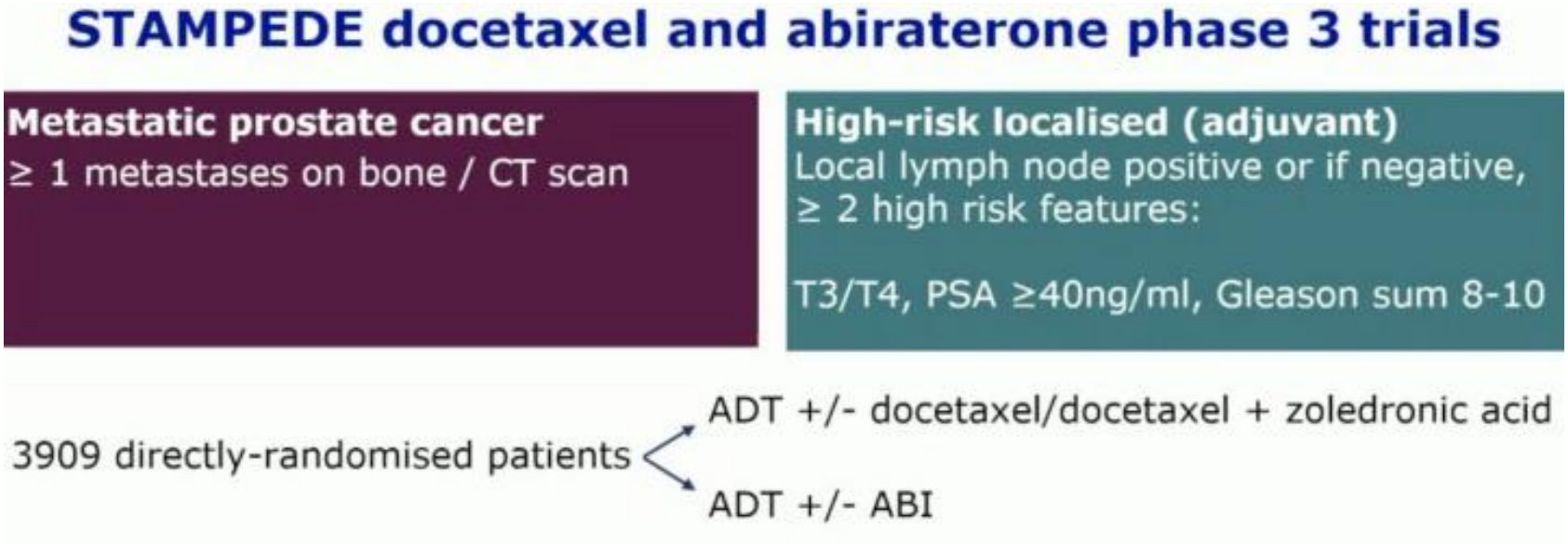
Marina Parry, Emily Grist, Christopher Brawley, James Proudfoot, Larissa Mendes, Sharan Lall, Alex Hoyle, Ashwin Sachdeva, Yang Liu, Claire Amos, Matthew Sydes, Robert Jones, Max Parmar, Felix Feng, Christopher Sweeney, Noel Clarke, Elai Davicioni, Nick James, Louise Brown, Gerhardt Attard **on behalf of the STAMPEDE investigators**

Marina Parry, et al. Clinical qualification of transcriptome signatures for advanced prostate cancer (APC) starting androgen deprivation therapy (ADT) with or without abiraterone acetate and prednisolone (AAP): An ancillary study of the STAMPEDE AAP trial. ESMO. 9-13 September 2022; Paris, France.
Marina Parry, et al. Clinical testing of transcriptome-wide expression profiles in high-risk localized and metastatic prostate cancer starting androgen deprivation therapy: an ancillary study of the STAMPEDE abiraterone Phase 3 trial. Res Sq **[Preprint]** February 8, 2023. DOI: 10.21203/rs.3.rs-2488586/v1.

Klinik bulgulara gen ve genomik verilerin eklenmesi

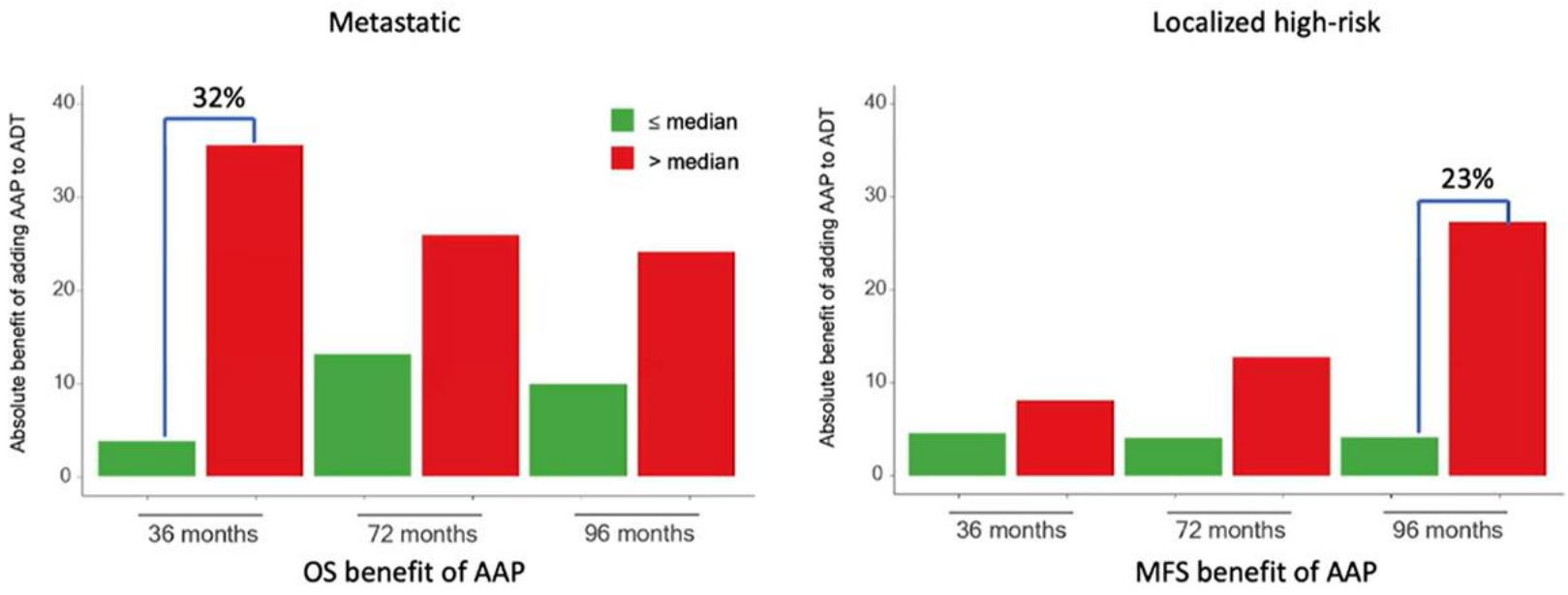


Klinik bulgulara gen ve genomik verilerin eklenmesi



Klinik bulgulara gen ve genomik verilerin eklenmesi

Absolute Benefit of Adding AAP to ADT Varies by Decipher Score



Event rate calculated using flexible parametric modelling adjusted for baseline characteristics

Marina Parry, et al. Clinical qualification of transcriptome signatures for advanced prostate cancer (APC) starting androgen deprivation therapy (ADT) with or without abiraterone acetate and prednisolone (AAP): An ancillary study of the STAMPEDE AAP trial. ESMO. 9-13 September 2022; Paris, France.
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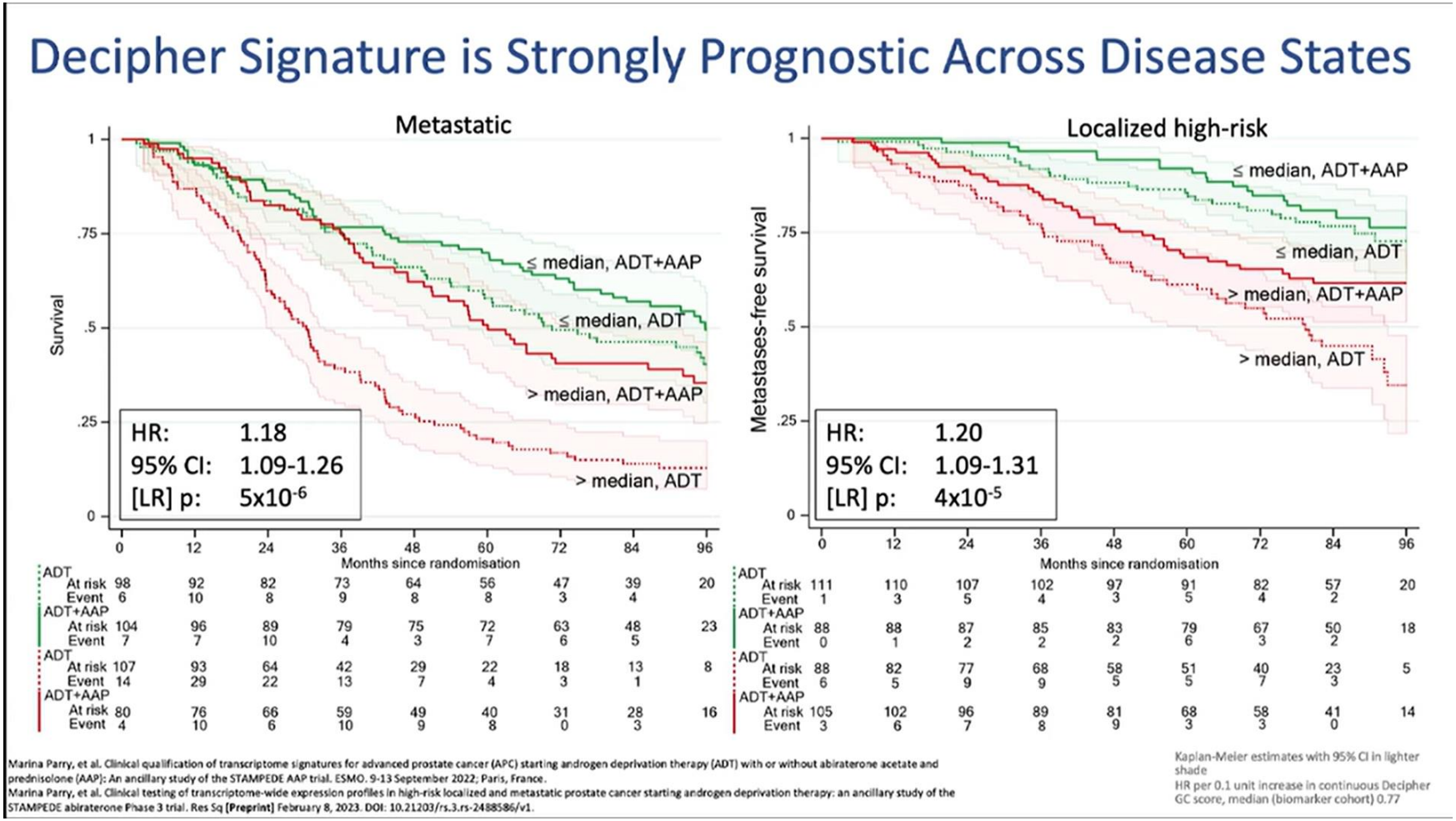

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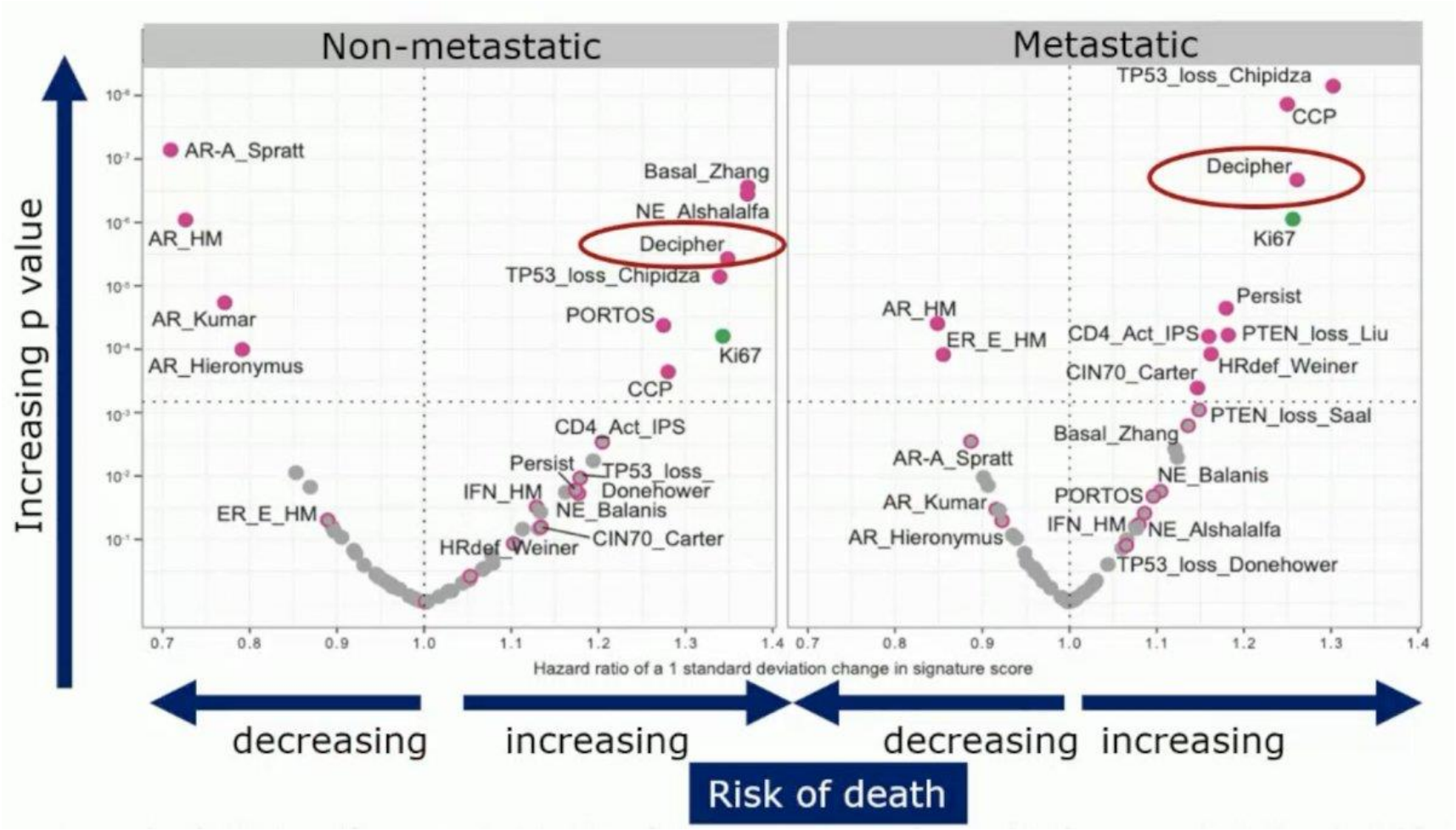
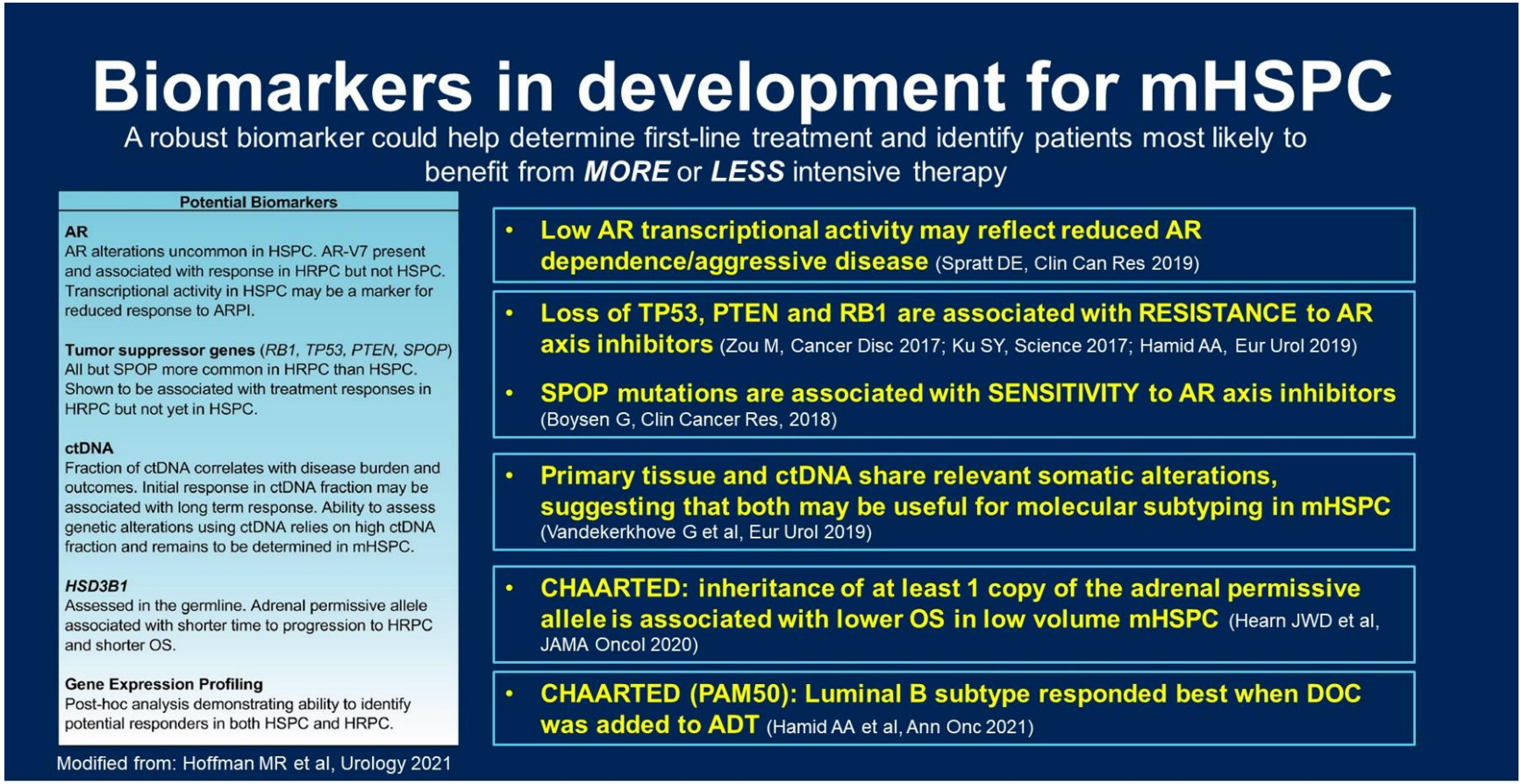
Kaplan-Meier estimates with 95% CI in lighter shade
HR per 0.1 unit increase in continuous Decipher GC score, median (biomarker cohort) 0.77

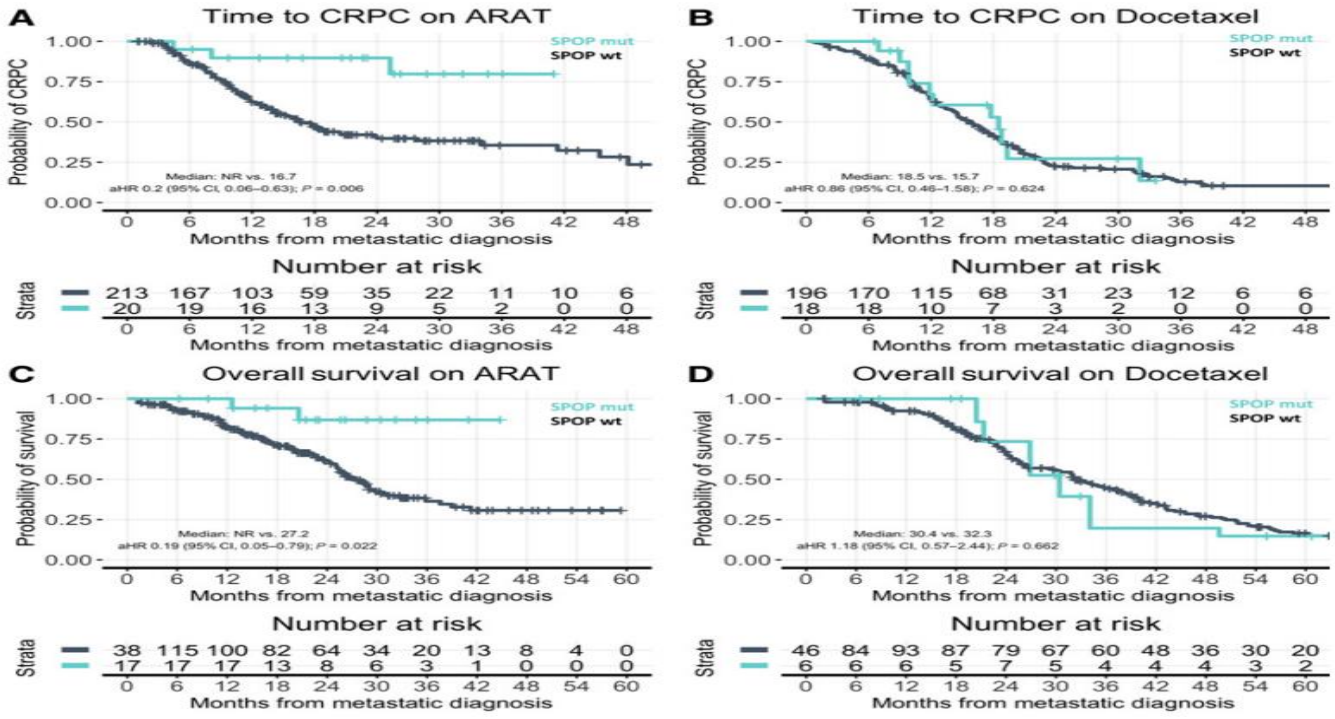
Klinik bulgulara gen ve genomik verilerin eklenmesi



Klinik bulgulara gen ve genomik verilerin eklenmesi

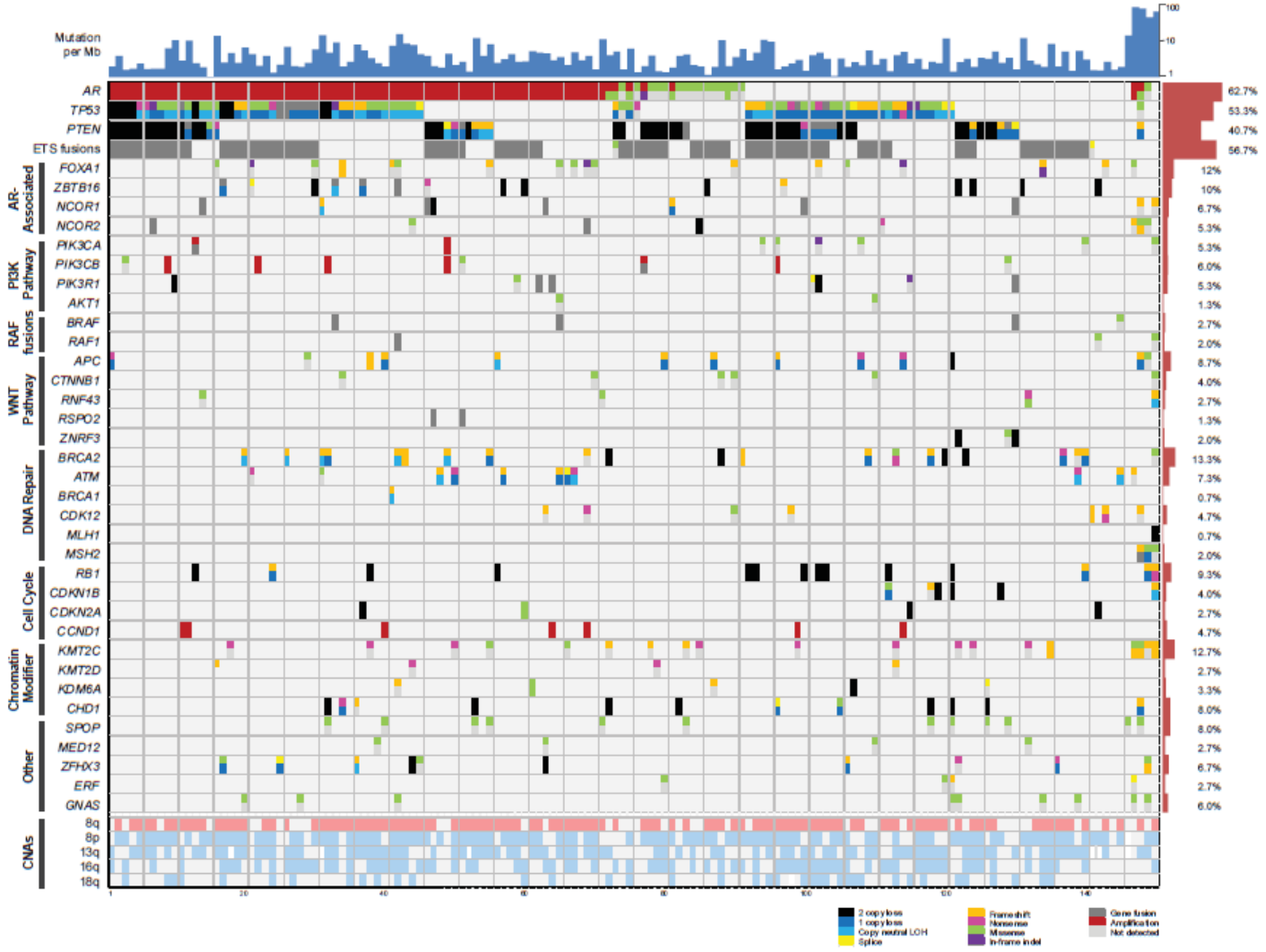


SPOP mutasyonu dosetaksel tedavisine yanıtsız



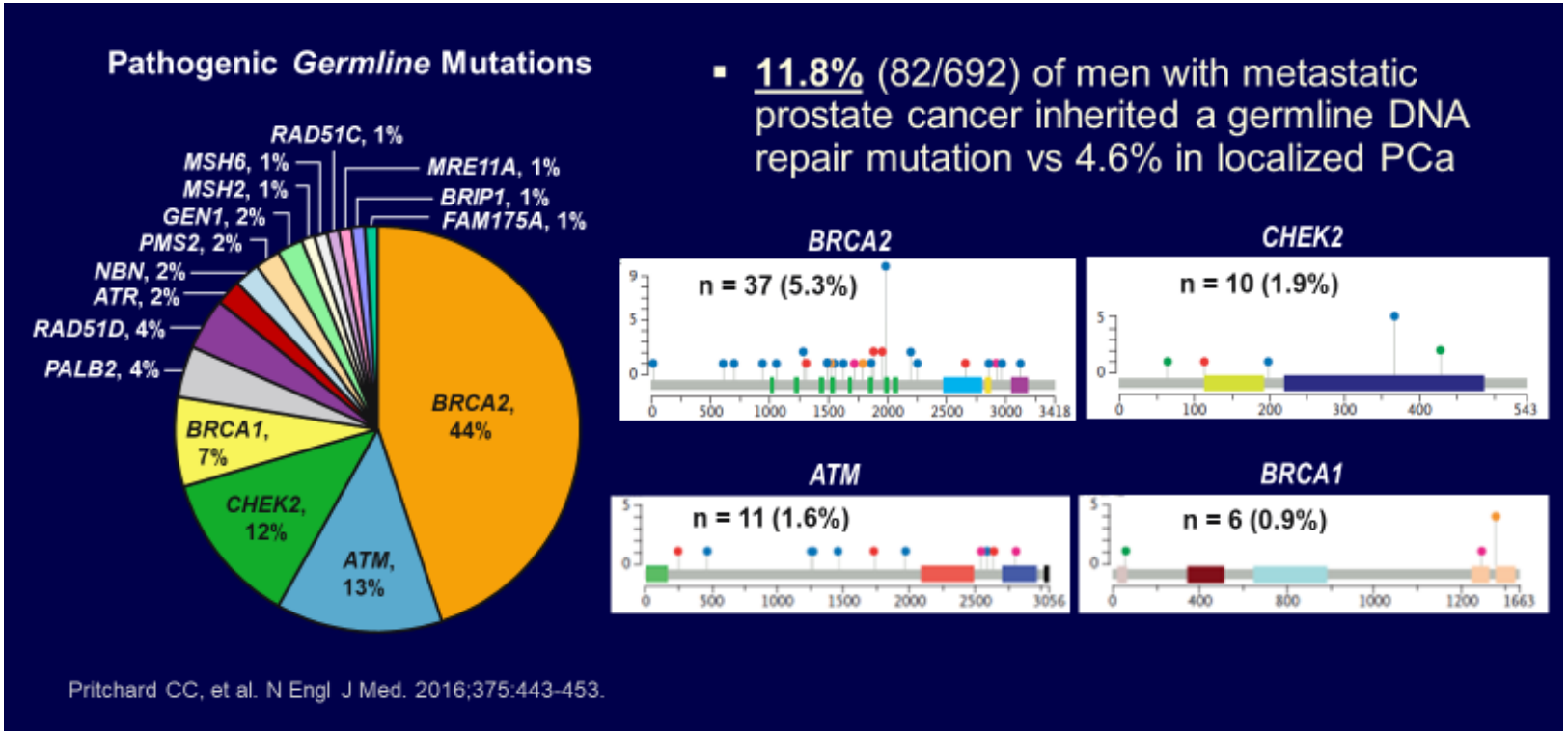
Umang Swami at al, Clin Cancer Res 2022

Klinik bulgulara gen ve genomik verilerin eklenmesi

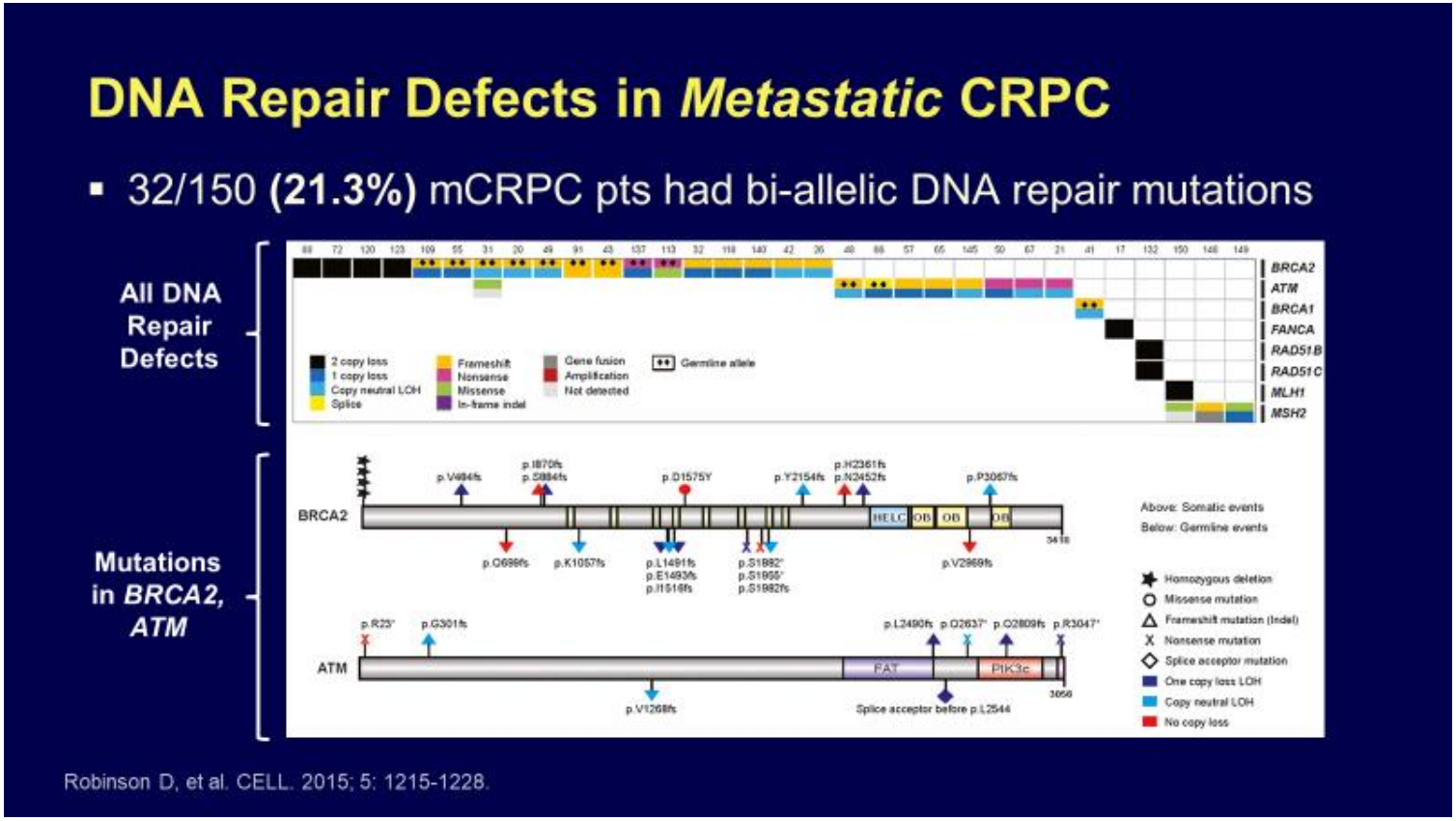


Cell 2015

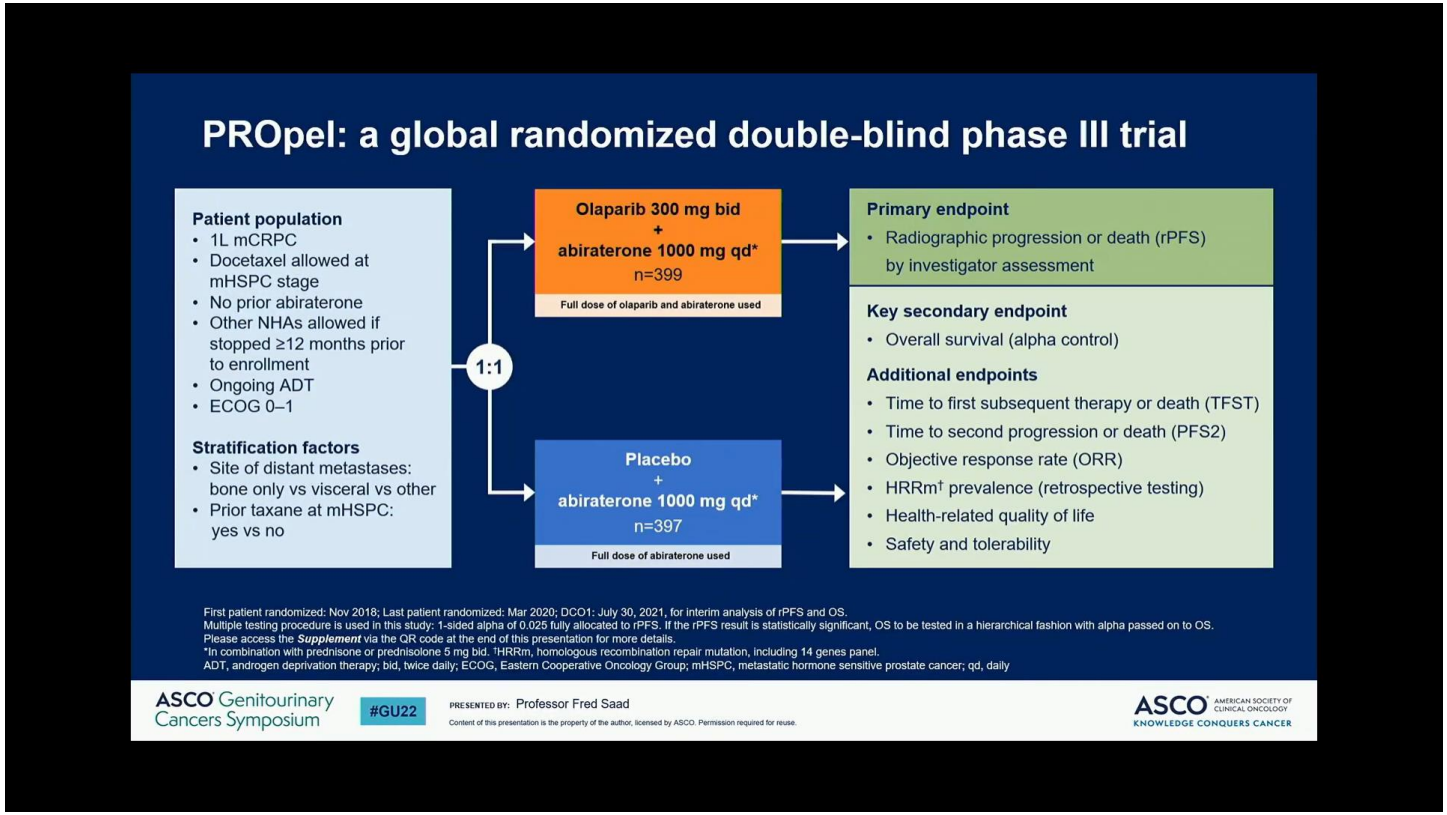
Prostat Kanserinde Germline Mutasyonları



Prostat Kanserinde DNA Repair Genlerde Olan Değişiklikler



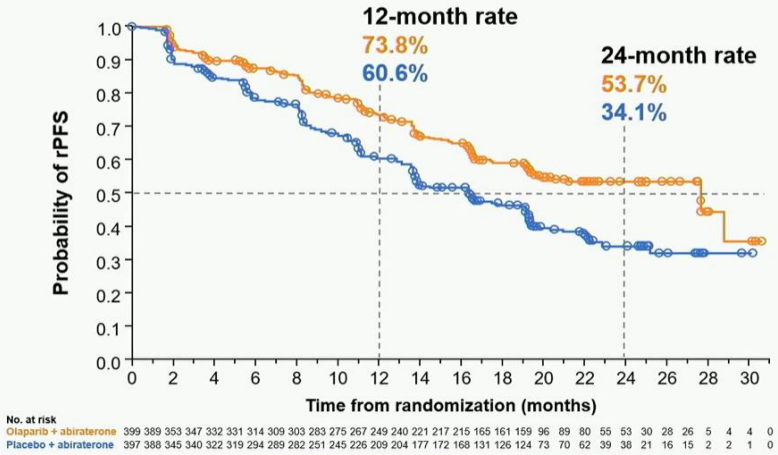
Evre IV Kastrasyona Dirençli Prostat Kanserinde Tedavi Seçeneği Olarak PARP İnhibitörü+Abireteron



Evre IV Kastrasyona Dirençli Prostat Kanserinde Tedavi Seçeneği Olarak PARP İnhibitörü+Abireteron

PROpel: rPFS by blinded independent central review*

39% risk reduction of progression or death with olaparib + abiraterone
Highly consistent with the primary analysis



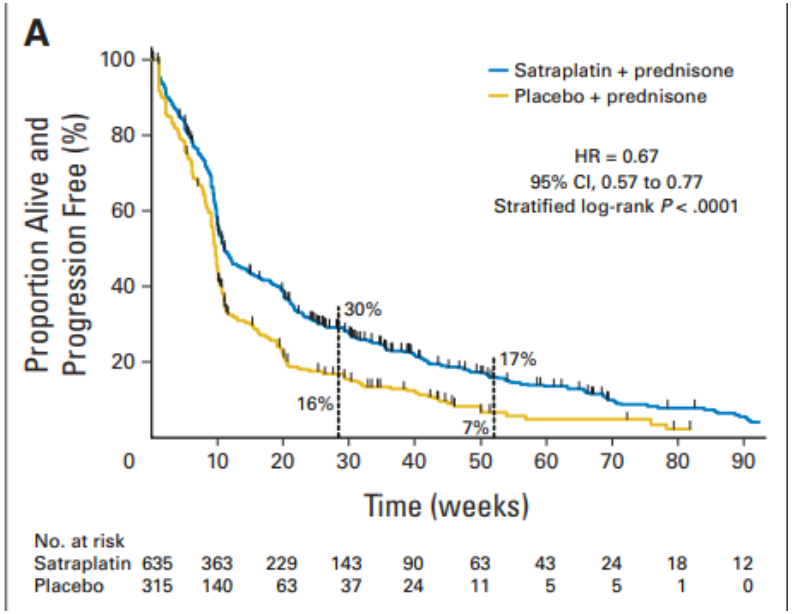
	Olaparib + abiraterone (n=399)	Placebo + abiraterone (n=397)
Events, n (%)	157 (39.3)	218 (54.9)
Median rPFS (months)	27.6	16.4
HR (95% CI)	0.61 (0.49–0.74) *P*<0.0001†	

Median rPFS improvement of 11.2 months favors olaparib + abiraterone‡

*Predefined sensitivity analysis. †Nominal. ‡In combination with prednisone or prednisolone

PRESENTED BY: Professor Fred Saad

Evre IV Kastrasyona Dirençli Prostat Kanserinde Sisplatin Etkinliği



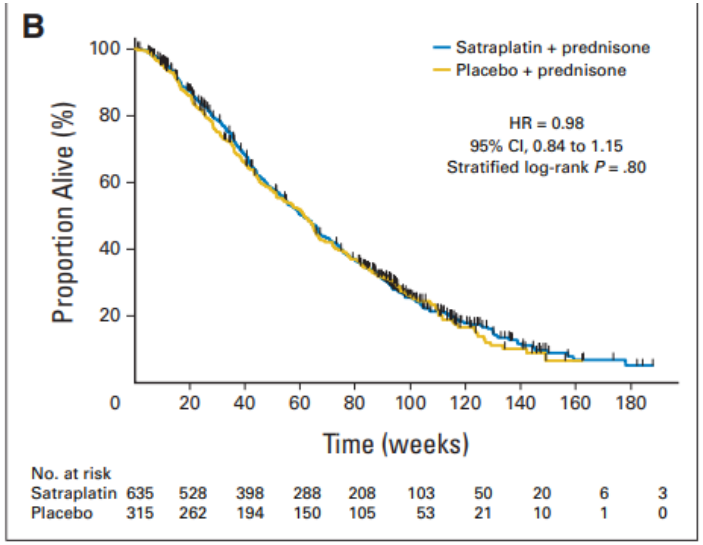


Fig 2. (A) Progression-free survival (intent-to-treat population) and (B) overall survival (intent-to-treat population). HR, hazard ratio.

SPARC: Satraplatin in Metastatic CRPC After Chemotherapy, JCO 2009

DNA Repair Gen Değişikliği Olan Hastalarda RA-223 etkinliği

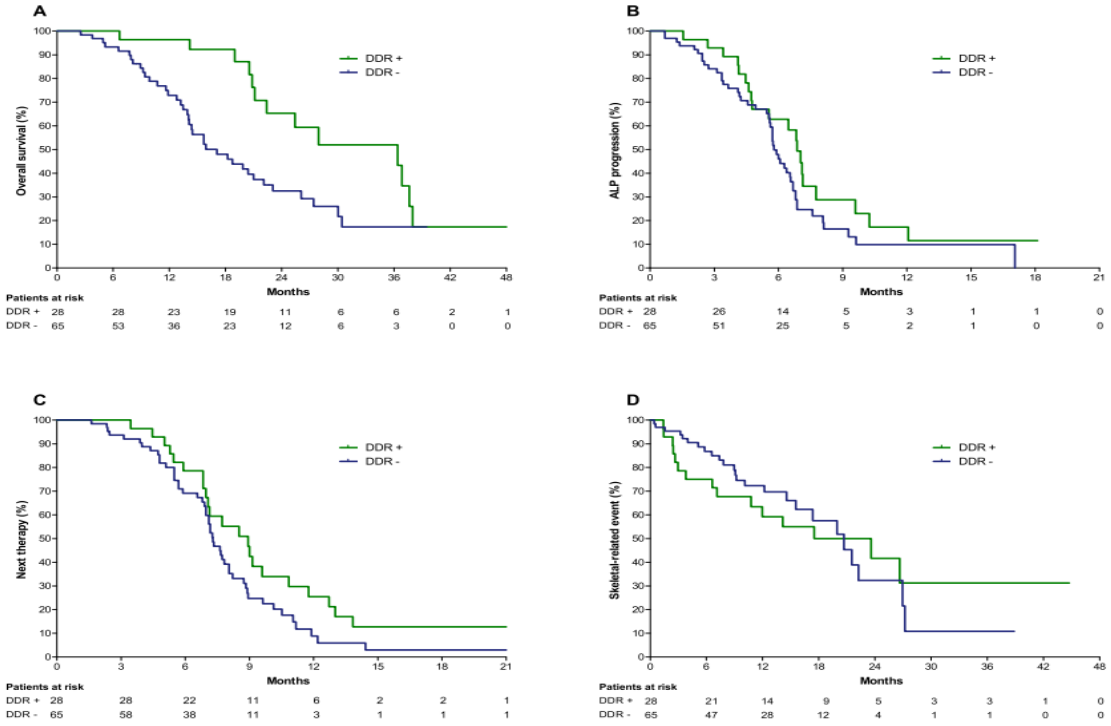
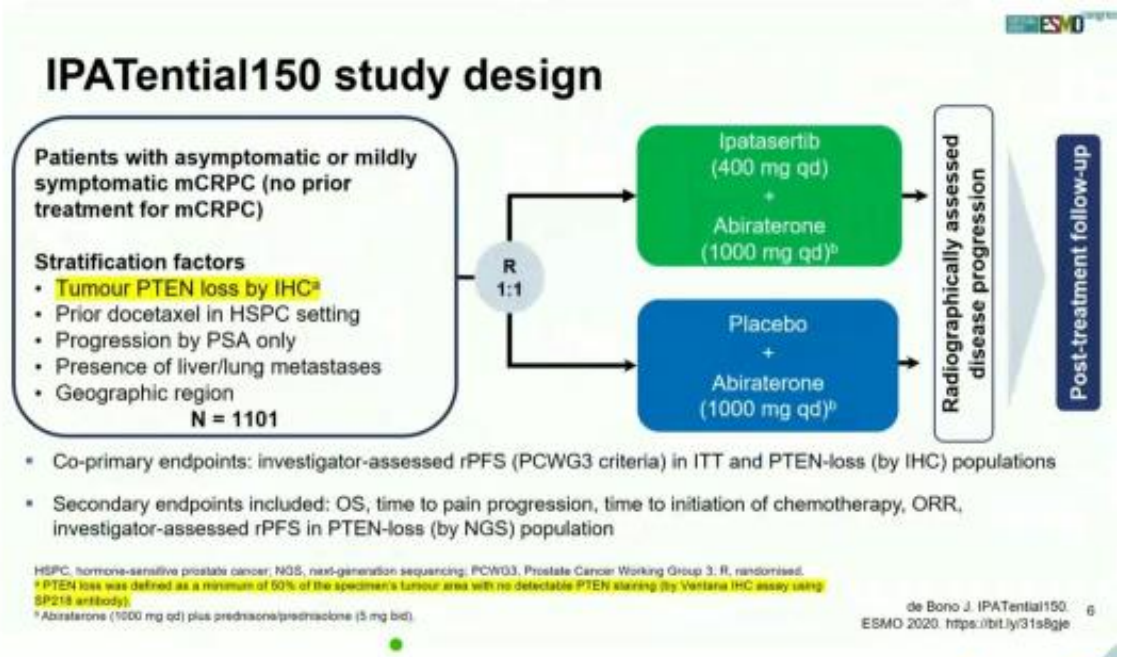


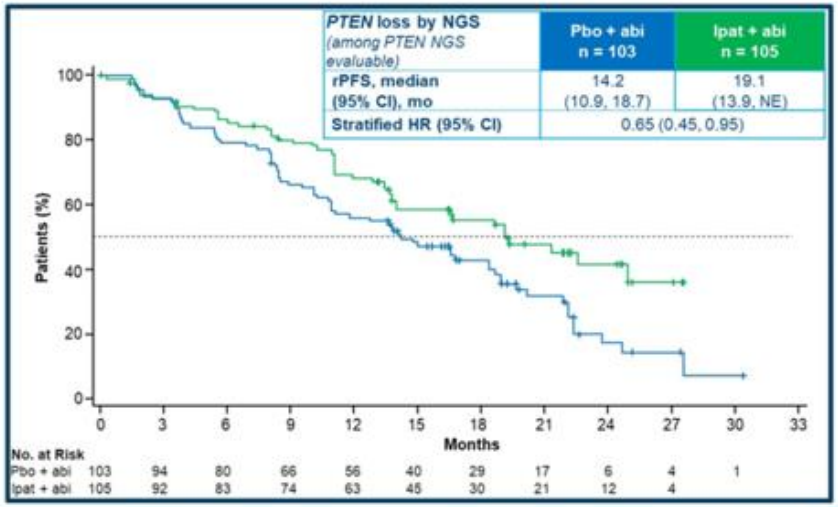
Fig. 2. Kaplan–Meier curves, stratified by DNA damage repair (DDR) mutation status, A. Overall survival, B. Time to alkaline phosphatase (ALP) progression, C. Time to initiation of next systemic therapy. D. Time to first skeletal-related evens (SRE).

Kastrasyona Dirençli Prostat Kanseri
PI3K/AKT inhibisyonu



Kastrasyona Dirençli Prostat Kanseri
PI3K/AKT inhibisyonu

Improvement in rPFS by NGS Population



PTEN WT by NGS (among PTEN NGS evaluable)	Pbo + abi n = 155	Ipat + abi n = 155
rPFS, median (95% CI), mo	16.6 (13.7, 24.9)	20.9 (16.4, NE)
Stratified HR (95% CI)	0.85 (0.62, 1.18)	

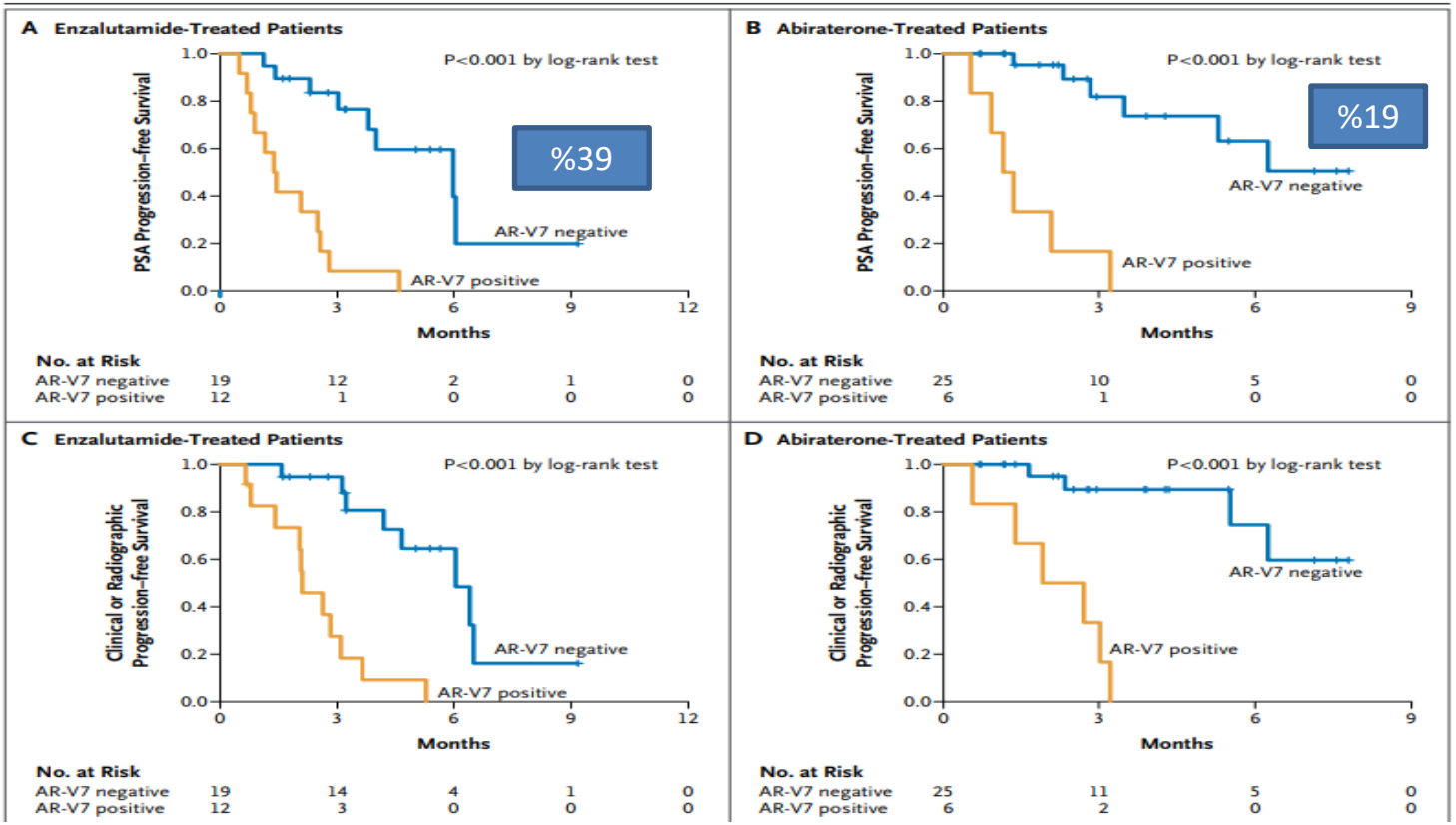
PTEN WT + PTEN loss by NGS (among PTEN NGS evaluable)	Pbo + abi n = 258	Ipat + abi n = 260
rPFS, median (95% CI), mo	16.5 (13.7, 19.0)	19.3 (16.7, 24.7)
Stratified HR (95% CI)	0.77 (0.60, 0.99)	

[1]OS data were immature; however, the investigators noted an early trend showing survival favoring the ipatasertib arm in the PTEN-loss group (HR, 0.91) and ITT population (HR, 0.93)

1. de Bono JS, Bracarda S, Sternberg CN, et al. IPATential150: efficacy and safety from the phase III study of ipatasertib plus abiraterone vs placebo plus abiraterone in metastatic castration-resistant prostate cancer. Presented at: 2020 ESMO Virtual Congress; September 19-21, 2020; Virtual. Abstract LBA4.

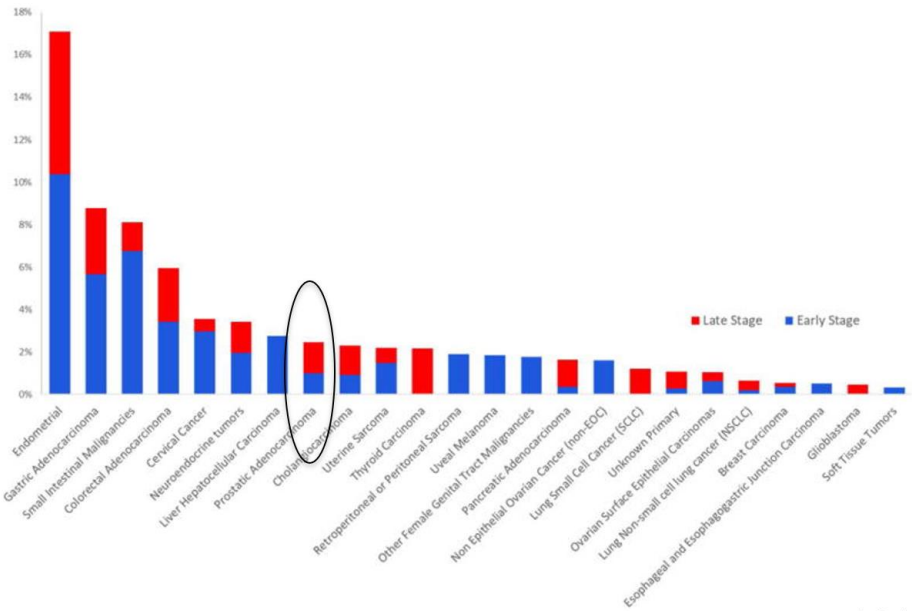
Presented By Johann De Bono at 2021 Genitourinary Cancers Symposium

AR yolağında meydana gelen değişimler



Emmanuel A at al, NEJM 2014

MSI High Prostat Kanserinde Tedavi Seçenekleri



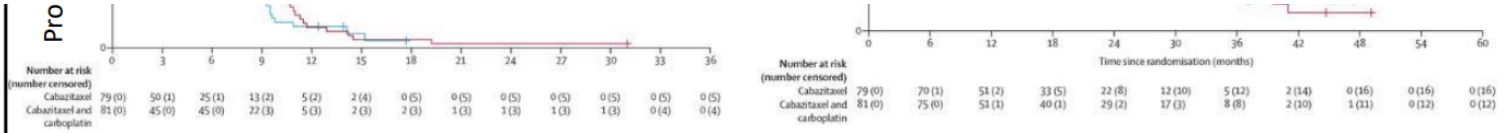
Le et al. Science 2017

Memorial Sloan Kettering Cancer Center

Prostat Kanseri Nöroendokrin Diferansiasyon

Combination Carboplatin and Cabazitaxel

Cabazitaxel 20 mg/m² plus carboplatin AUC 4 mg/mL per min with growth factor support can be considered for fit patients with aggressive variant prostate cancer (visceral metastases, low PSA and bulky disease, high LDH, high CEA, lytic bone metastases, NEPC histology) or unfavorable genomics (defects in at least 2 of PTEN, *TP53*, and RB1). Corn PG, et al. Lancet Oncol 2019;20:1432-1443.



- Targeting more aggressive prostate cancers
  - Patients were randomly assigned (1:1) to intravenous cabazitaxel 25 mg/m2 with or without intravenous carboplatin AUC 4
  - At a median follow-up of 31·0 months, the combination improved the median PFS from 4.5 months to 7.3 months (95% CI 0·50–0·95, p=0·018)
  - All toxicities were worse with the combination
    - Myelosuppression
    - Fatigue, nausea, others

Corn et al Lancet Oncology 2019

Yeni nesil androjen yolağı inhibitörleri viseral metastazda etkinliği düşük

Does type of metastasis matter in mHNPC?

Results from new hormonal treatments in mHNPC according visceral mets

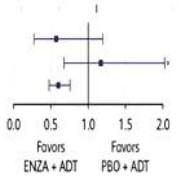
ENZAMET

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

Enzalutamide Better Standard Care Better

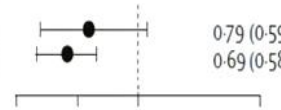
ARCHES

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



LATITUDE

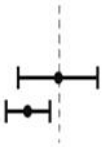
	Median (months) AA+P	Placebo+P	HR (95% CI)
Visceral disease at entry			
Yes	12·9	8·3	0·79 (0·59–1·05)
No	17·1	12·3	0·69 (0·58–0·82)



Favours AA+P Favours placebo+P

TITAN

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



2021 ESMO congress

OUDARD Stèphane

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

Viseral metastazı olanlarda dörtlü kombinasyon

Early results from CASCARA: A phase 2 study of cabazitaxel/carboplatin plus abiraterone in high-volume metastatic castrate-sensitive prostate cancer (mCSPC).

Background: Best treatment of mCSPC involves doublet therapy (ADT + novel hormonal agent) or triplet therapy (ADT + novel hormone + docetaxel); however, opportunity remains for further improvement. Studies show that homologous recombination repair (HRR) gene mutations are enriched in metastatic prostate cancer, and may portend resistance to docetaxel. CASCARA tested quadruplet therapy (ADT + cabazitaxel/carboplatin + abiraterone) in high-volume mCSPC, aiming to enhance PSA responses and decrease progression at 1 year. **Methods:** This phase 2 study enrolled 61 mCSPC patients with high-volume disease who received ADT plus cabazitaxel (20 mg/m^2 q21d x 6) and carboplatin (AUC=4 q21d x 6) followed by abiraterone (1000 mg, plus prednisone 5 mg). Primary endpoint was freedom from PSA/radiographic progression at 1 year. Other endpoints included PSA_{50} response, freedom from PSA progression, and safety. Archival biopsies were retrospectively evaluated for HRR (*BRCA1/2*, *ATM*, *CHEK2*, *CDK12*, *BRIP1*, *RAD51B*) mutations at a CLIA-certified lab. A sample size of 61 was determined using a Simon two-stage design (stage 1: 32 men, stage 2: 29 men) with a null hypothesis of a 1-year PSA/radiographic progression-free rate of 0.80 against a one-sided alternative of 0.92. **Results:** From 11/2019 to 06/2022, 61 men enrolled at 7 sites. Median age was 64 (range, 45–76) years; 21% were African American. Median baseline PSA was 8.9 (range, 0.1–1021) ng/mL. 44% of men had ECOG=1. 91% had Gleason sum 8–10. Prevalence of DNA alterations (50 evaluable pts) was 18% for HRR mutations, 38% for *TP53* muts, 22% for *ERG* fusions, 10% for *SPOP* muts. Freedom from PSA/radiographic progression at 1 year was 77% (95% CI, 63–87%), and freedom from PSA progression at 1 year was 81% (95% CI, 67–90%). The PSA_{50} rate response was 97%. PSA ≤0.2 ng/mL at month-7, a surrogate for survival in other mCSPC studies, was 61%; PSA ≤4 ng/mL at month-7 was 82%. Outcomes according to mutation status are shown. AEs included 7% grade (Gr)-3/4 myelosuppression, 8% Gr-3/4 infections, 10% Gr-3 GI disorders, and 3% Gr-3 fatigue. There were 4 treatment-related discontinuations. **Conclusions:** Quadruplet therapy with ADT + cabazitaxel/carboplatin + abiraterone was well tolerated. At 1 year, 77% of pts were progression-free. PSA ≤0.2 ng/mL at month-7 was 61%, exceeding the historical month-7 PSA ≤0.2 ng/mL rate of 45% in CHAARTED–docetaxel arm. Further exploration of this quadruplet strategy in randomized phase III studies is warranted. Clinical trial information: NCT03934840. Research Sponsor: Sanofi-Genzyme.

PSA≤0.2 oranı %61

Charles J. Ryan, ASCO GU 2023

Viseral metastazı olanlarda dörtlü kombinasyon

	HRR status N (%)	*TP53* status N (%)	*ERG* fusion N (%)	*SPOP* status N (%)
Freedom from PSA/radiographic progression at 1 yr	HRRm – 6 (67%) HRRwt – 34 (83%)	*TP53*m – 14 (77%) *TP53*wt – 26 (84%)	*ERG*m – 11 (100%) *ERG*wt – 29 (74%)	*SPOP*m – 5 (100%) *SPOP*wt – 35 (78%)
PSA ≤0.2 ng/mL at month 7	HRRm – 3 (38%) HRRwt – 27 (66%)	*TP53*m – 12 (67%) *TP53*wt – 18 (60%)	*ERG*m – 9 (82%) *ERG*wt – 21 (55%)	*SPOP*m – 4 (100%) *SPOP*wt – 26 (58%)

Charles J. Ryan, ASCO GU 2023

Gelecek Perspektif

Biomarker	Details	Sensitivity	Trials in mHSPC (BM selected)
DNA repair	BRCA1, BRCA2, PALB2	PARPi	ProBIO
	HRRm	PARPi-ARPI	TALAPRO-3, EvoPAR-01, AMPLITUDE
	MMR-d/MSI-H	ICI	NCT04126070, NCT03879122
PI3K	PTEN	PI3Ki	CAPITELLO-281
	PIK3CA, AKT1	PI3Ki	
Cell-cycle	RB1 or RB1/TP53 doublet, high Ki67	Platinum (doublet)	
	Cyclin D1, intact RB1, CDK2NA, low Ki67	CDK4/6i	CYCLONE-3
TMPRSS2-ERG / ERG	ERG alter microtubule (dynamics)	Taxanes (triplet)	ProBIO
TSG	Compound mutation in TP53, PTEN, RB1	Taxanes (triplet)	-
SPOP	Role in AR regulation	ARPI	-
RNA	Decipher, GC Q4	Taxanes	STAMPEDE
	PAM50: Luminal B	Taxanes	STAMPEDE
ctDNA%	Low ctDNA%	ICI, PSMA-RLT	-
	High ctDNA%	Taxanes (triplet)	-

Diğer Doz Yoğun Seçenekler

Name/Sponsor	ARTA	3rd agent	Design (n)
AMPLITUDE	Abiraterone	Niraparib	Randomized, HRR+ (788)
TALAPRO-3	Enzalutamide	Talazoparib	Randomized HRR+ (550)
City of Hope PCF	Abiraterone	Talazoparib	Single arm, Unselected (70)
PSMAddition	Lu177-PSMA-617	Any ARTA	Randomized, PSMA PET + (1126)
KEYNOTE-991	Enzalutamide	Pembrolizumab	Randomized (1232)
NCT03951831	n/a (ADT + Doce)	Cemiplimab	Single arm (20)
MSKCC	Abi/Enza	Atezolizumab	SBRT, Single arm (44)
CABIOS	Abiraterone	Cabozantinib, Nivolumab	Single arm (22)
CASCARA (U Minn)	Abiraterone	Cabazi + Carbo	Single arm (60)
Capitello-281	Abiraterone	Capivasertib	Randomized, PTEN def (1000)
CYCLONE-3	Abiraterone	Abemaciclib	Randomized, unselected (900)

Sonuç

- ❑ **Germline ve Somatik DNA repair mutasyonları prostat kanserinde sık görülür**
- ❑ **DNA repair mutasyonları PARP inhibitörlerine duyarlı**
- ❑ **DNA repair mutasyonları aynı zamanda platin bazlı kemoterapilere ve RA-223 daha duyarlı olabilir**
- ❑ **Kastrasyona dirençli prostat kanserinde BRCA mutasyonu varsa yeni nesil androjen yolağı inhibitörü+PARP inhibitörü**
- ❑ **Kastrasyona dirençli prostat kanserinde, Enzulutamid/Abireteron +/- Dosetaksel sonrası BRCA mutasyonu olanlarda, PARP inhibitörü**
- ❑ **MSI high ve TMB yüksek hastalarda immün checkpoint inhibitörleri**
- ❑ **PI3K/AKT/PTEN mutasyonları olanlarda kombinasyon olarak PI3K/AKT inhibitörleri için faz 3 çalışma sonucunu görmek lazım**
- ❑ **Nöroendokrine Diferansiyasyon olan hastalara Kabazitaksel+Karboplatin seçenek olarak düşünülebilir**