

Prostat kanserinde genetik sonuçlara göre bireyselleşmiş tedavi seçenekleri

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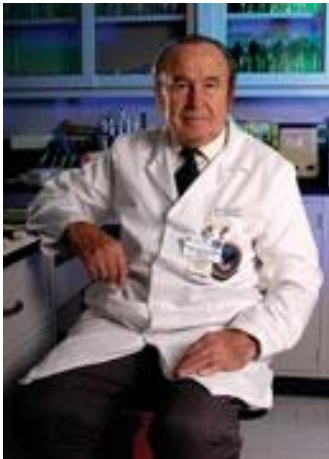
Ders Planı

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

Kastrasyona Duyarlı Metastatik Prostat Kanseri ADT Tedavisi

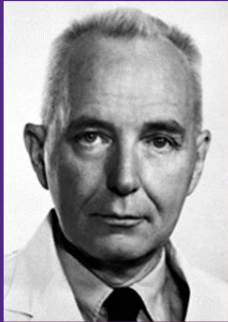


- Charles Brenton Huggins(1901-1997)
- 1927'de Chicago Üniversitesinde Üroloji kliniğinde akademik kadro aldı
- Köpeklerde yaptığı deneylerle, prostat hücrelerinin büyümesinde testosteron hormonuna bağımlı olduğunu tespit etti
- Prostat kanseri olanlarda orşektomi ile tümörün küçüldüğünü belirledi.
-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



Kastrasyona Duyarlı Metastatik Prostat Kanseri ADT Tedavisi

Historical Perspective: Androgens & Prostate Cancer

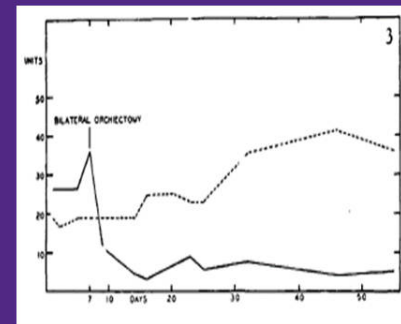


C. Huggins
1966 Nobel Prize

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

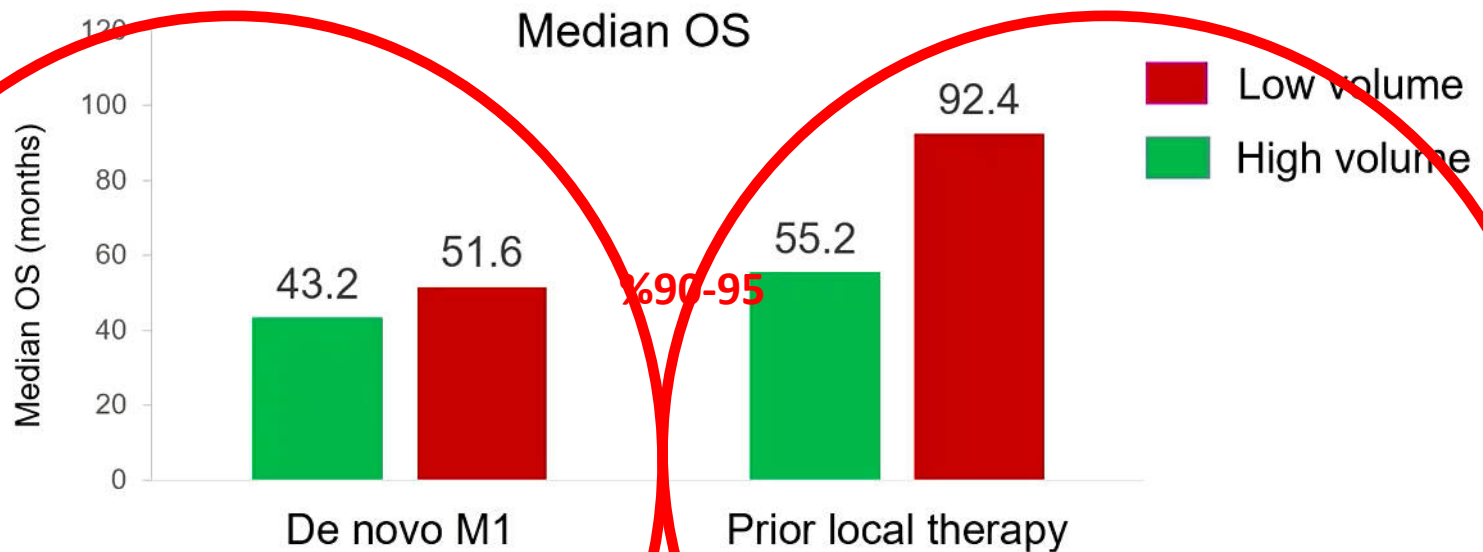
- 1-Semptomatik olması
- 2-ECOG PS
- 3-Ek hastalıklar
- 4-Başka hastalıklar için aldığı tedaviler
- 5-Hastalık için daha önce aldığı tedaviler

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

OUARD Stéphane

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%5-10

%90-95

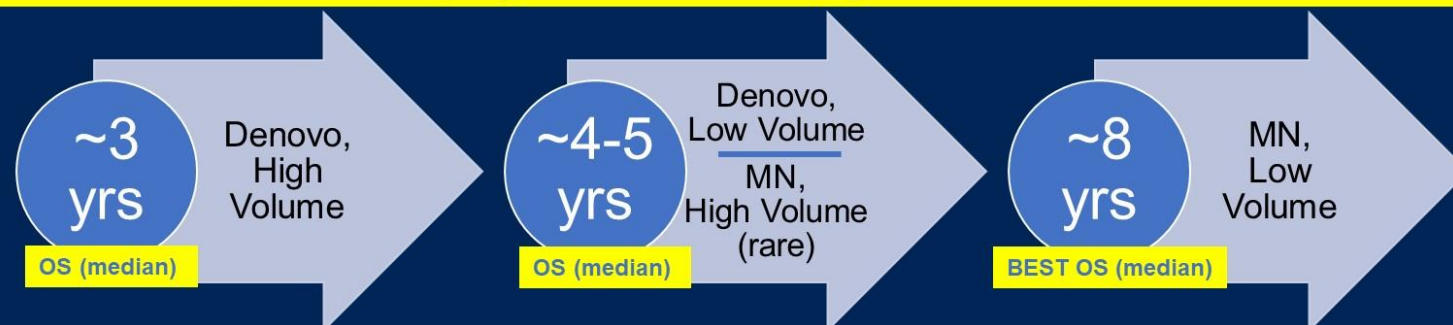
TANI ANINDA METASTATİK VE YÜKSEK VOLÜMLÜ HASTALIK AGRESİF SEYİRLİ

3

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

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}

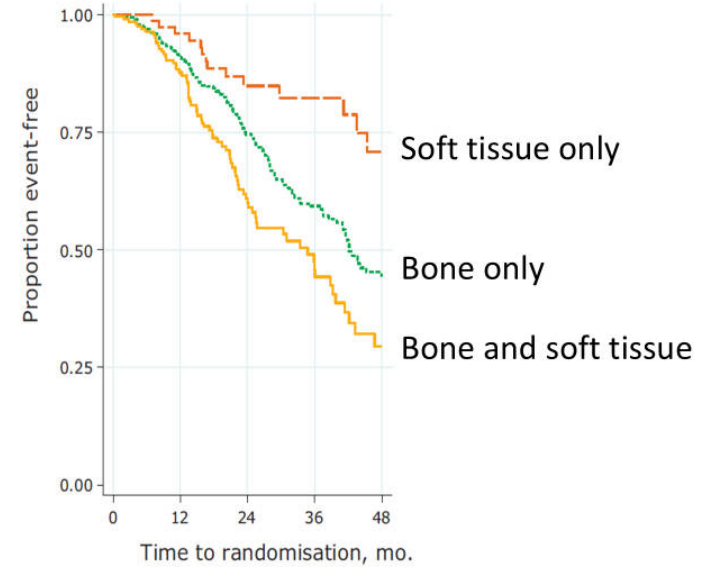
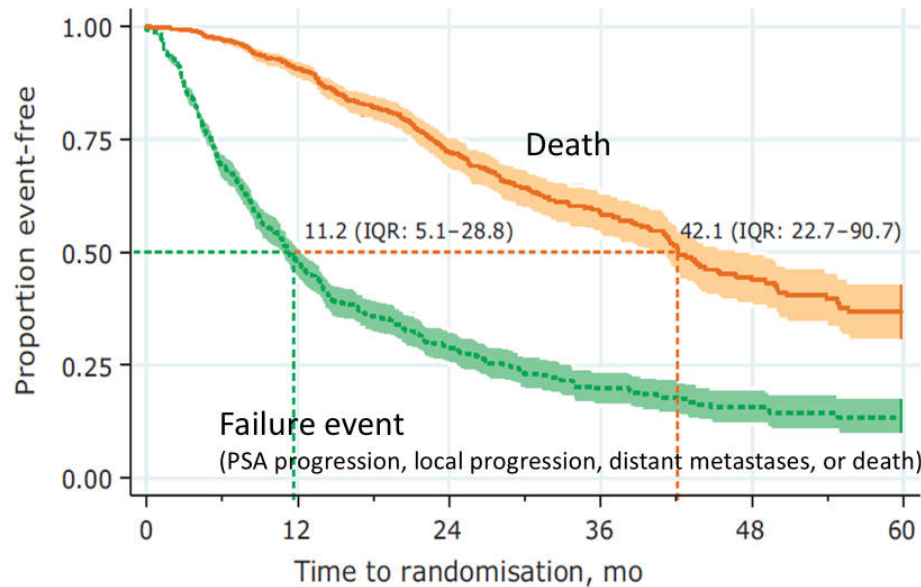
PSMA appears to be the most broadly applicable potential biomarker and actionable target in advanced PC¹⁻⁶

*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



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

STAMPEDE Control Arm

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

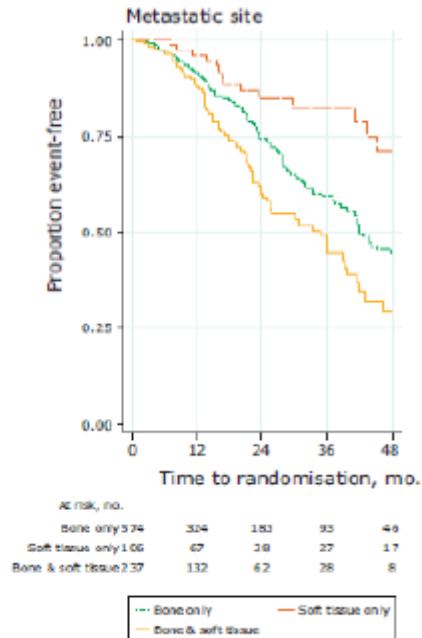
Yalnız ADT alanlarda 5-yıllık sağkalım %30-40. Non-regional lenf nodu iyi prognoz ile ilişkili

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. Deamaley^{d,e}, Johann S. De Bono^{d,e}, Joanna Gale^f, John Hetherington^g, Peter J. Hoskin^h, Robert J. Jonesⁱ, 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, R  to T. Strebelⁿ, George N. Thalmann^o, Malcolm D. Mason^k, Matthew R. Sydes^b

EUROPEAN UROLOGY 67 (2015) 1028–1038



STAMPEDE  ALI MASI; 917 KONTROL KOLUNDE(ADT alan) BULUNAN M1 HASTALARIN SONU LARI

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

2 Yıllık sa kalım; yumu  k doku met.%85
Kemik met.%75

Yumu  k doku+kemik met.%60

2yıllık FFS; yumu  k dokuda %54, kemik met %28 , yumu  k 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

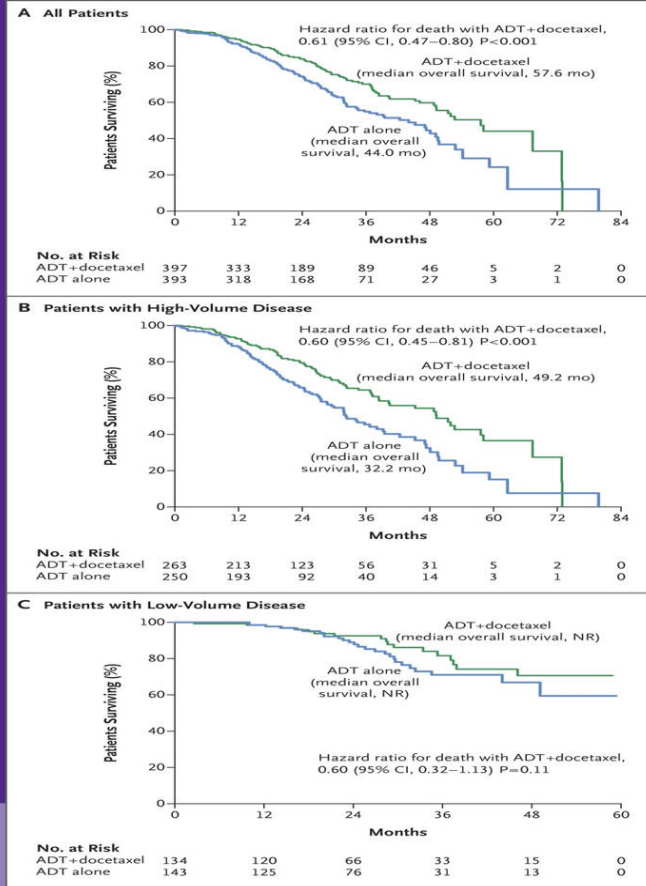
Gravis et al Lancet Oncol 2013; Sweeney et al NEJM 2015; James N et al Lancet 2015; Attard G et al Lancet Oncol 2023; Fizazi K et al NEJM 2017; James et al NEJM 2017; Armstrong et al JCO 2021; Davis et al NEJM 2019; Chi KN et al NEJM 2019; Smith MR et al NEJM 2022; Fizazi K et al Lancet 2022

Hastalık Volümü Dosetaksel Tedavi Etkinliği için Prediktif

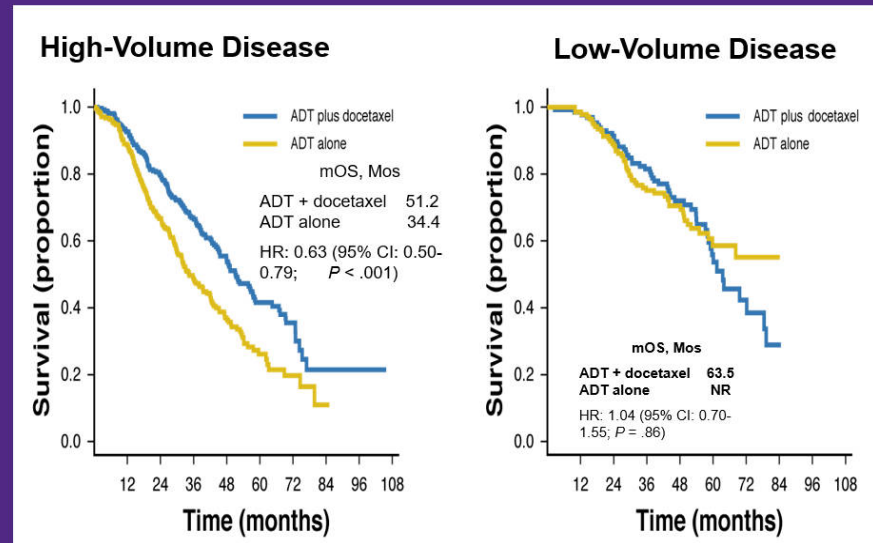
CHAARTED: ADT +/- Docetaxel in mHSPC

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

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



Sweeney CJ et al. NEJM 2015

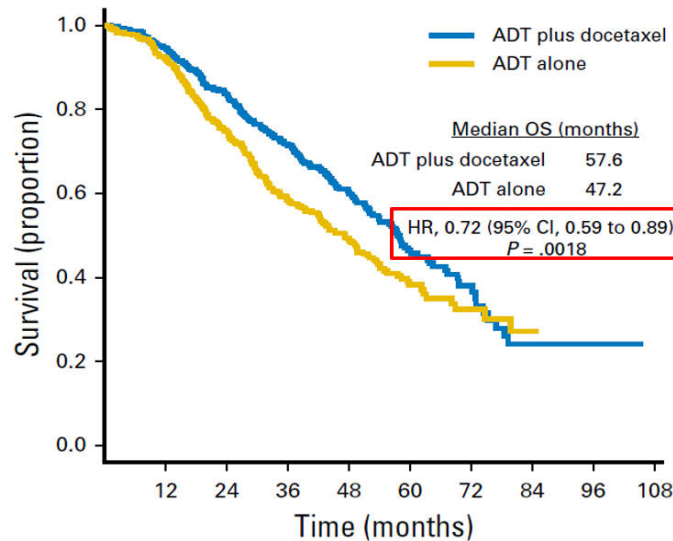


Kyriakopoulos CE, et al. J Clin Oncol. 2018

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

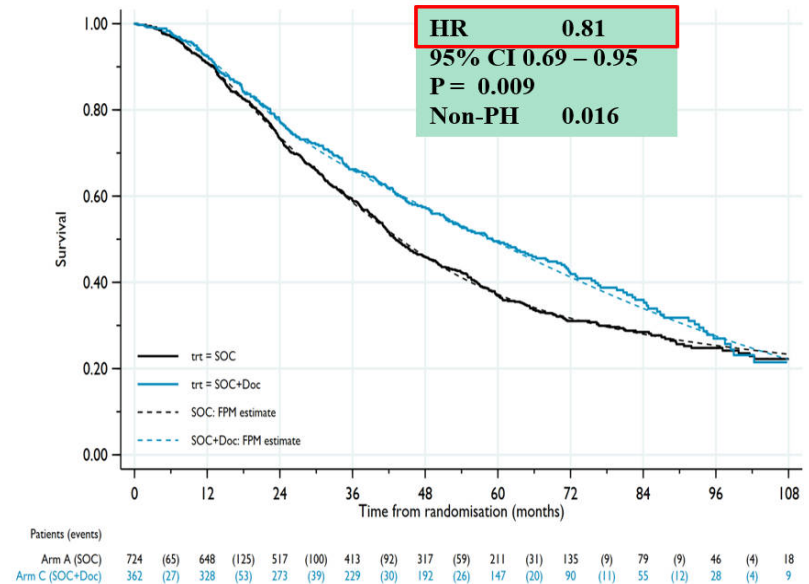
Hastalık Volümü Dosetaksel Tedavi Etkinliği için Prediktif

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



No. at risk:										
ADT plus docetaxel	397	366	314	245	155	67	28	7	2	0
ADT alone	393	352	278	198	126	45	21	2	0	0

Kyriakopoulos CE, J Clin Oncol 2018

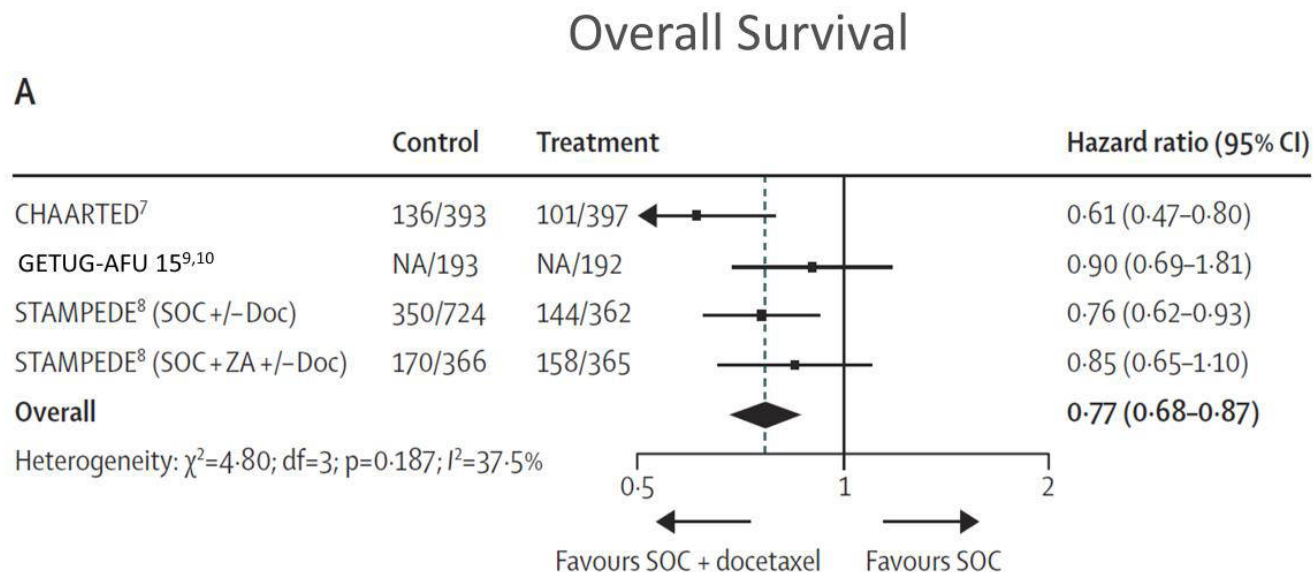


Clarke N, Ann Oncol. 2019

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

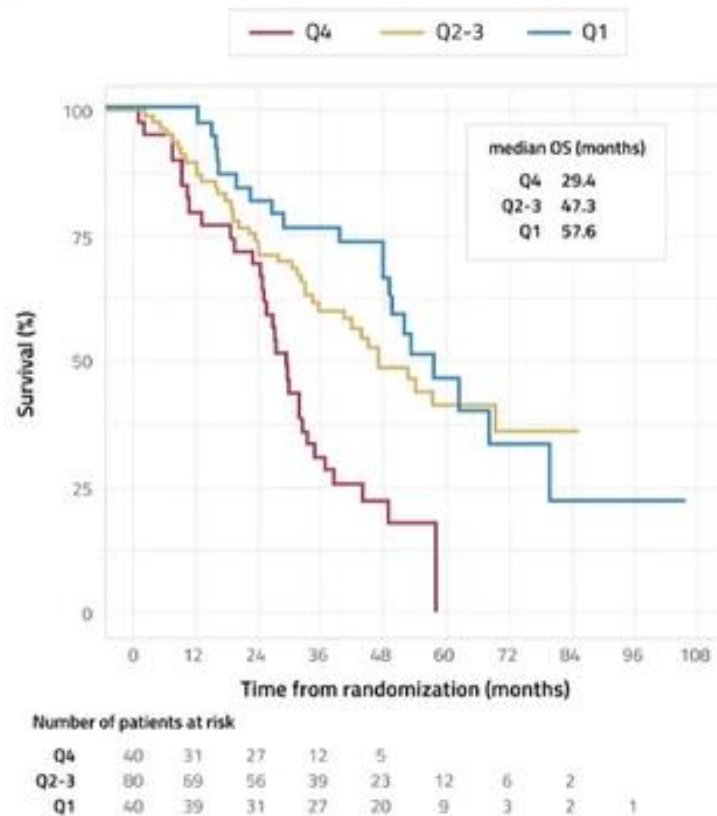
Meta-Analysis of RCTs of Docetaxel in mCSPC



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

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

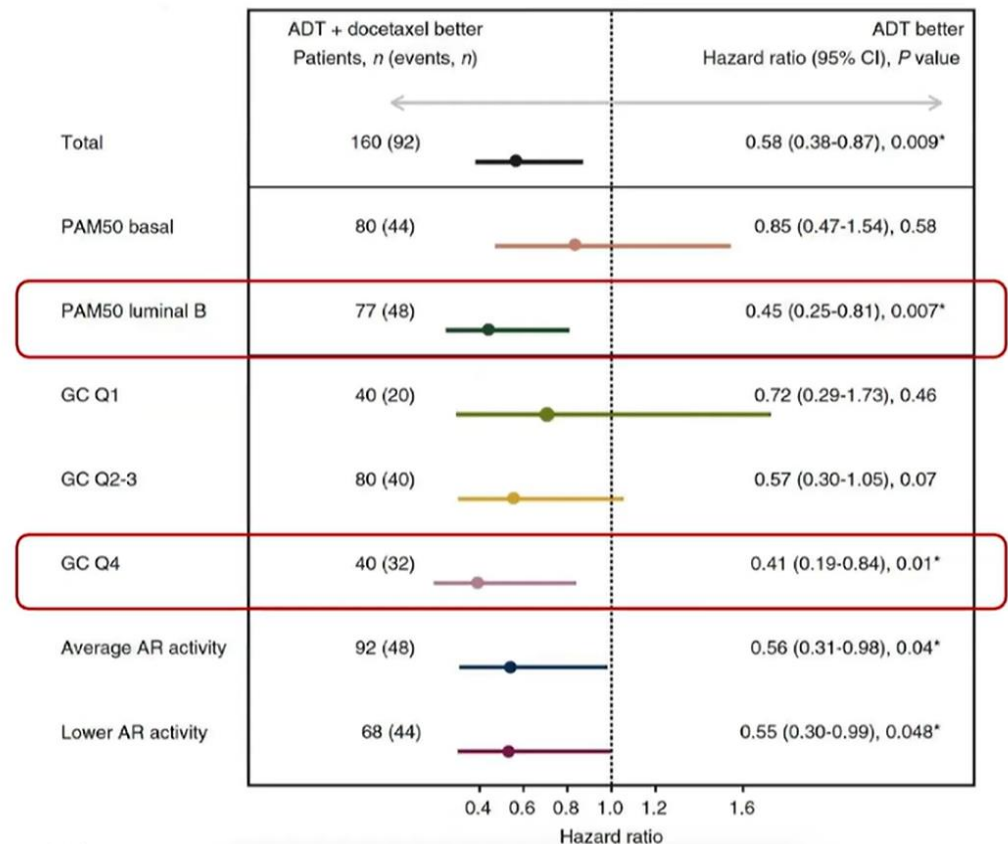
Decipher as a Prognostic Tool - Evolution from GRID Signatures

Hypotheses and analyses plan

- 59 signatures derived from pan-transcriptome data
- CHARTED biomarker cohort (N=160) used as training set¹

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

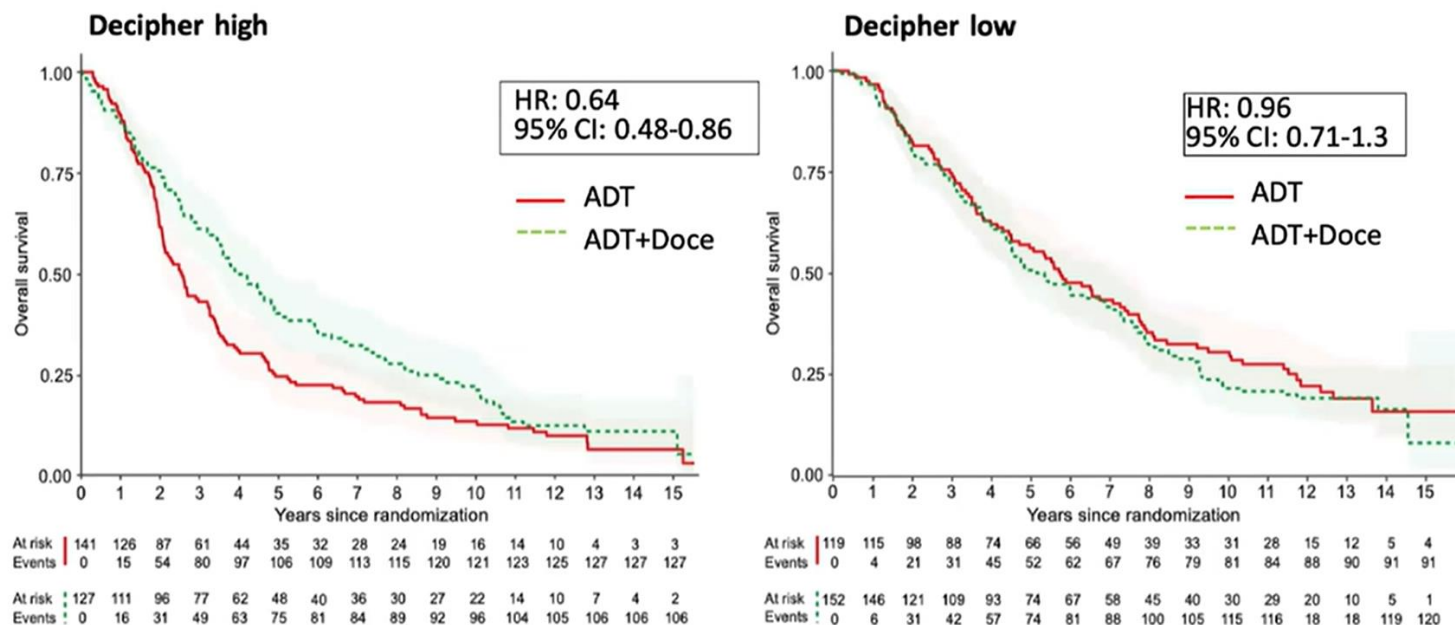
Emily Grist, Peter Dutey-Magni, Larissa Mendes, Marina A. Parry, Ashwin Sachdeva, James Proudfoot, Anis A. Hamid, Claire L. Amos, William R. Cross, Silke Gillesen, Daniel M. Berney, Matthew R. Sydes, Mahesh K.B. Parmar, Felix Y. Feng, Noel W. Clarke, Elai Davicioni, Christopher J. Sweeney, Nicholas D. 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

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

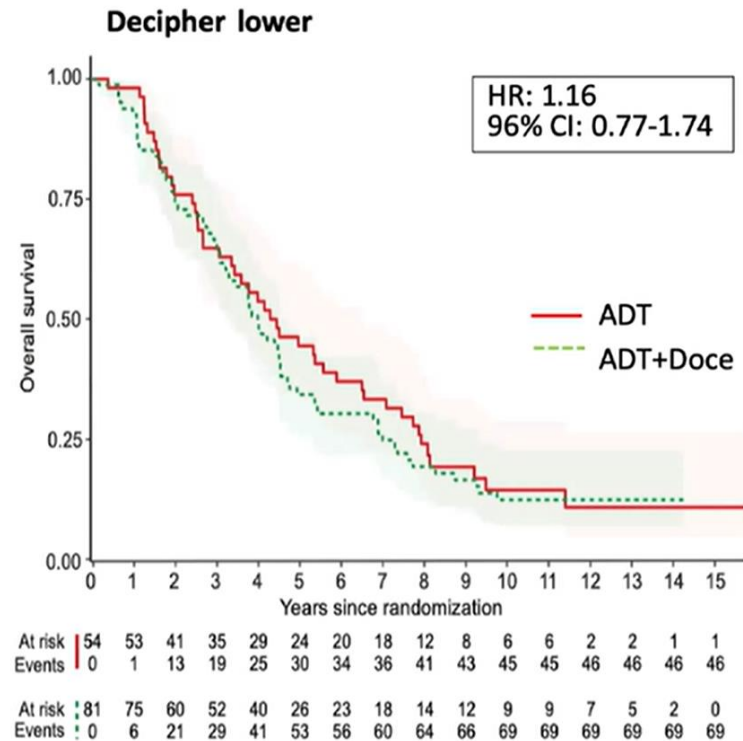
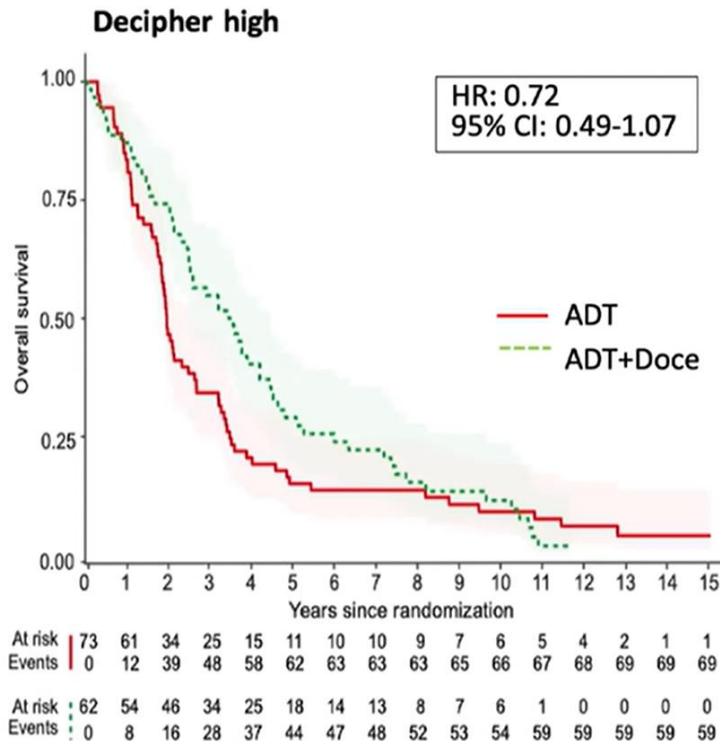
Biomarker-treatment interaction effect p value= 0.039*

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

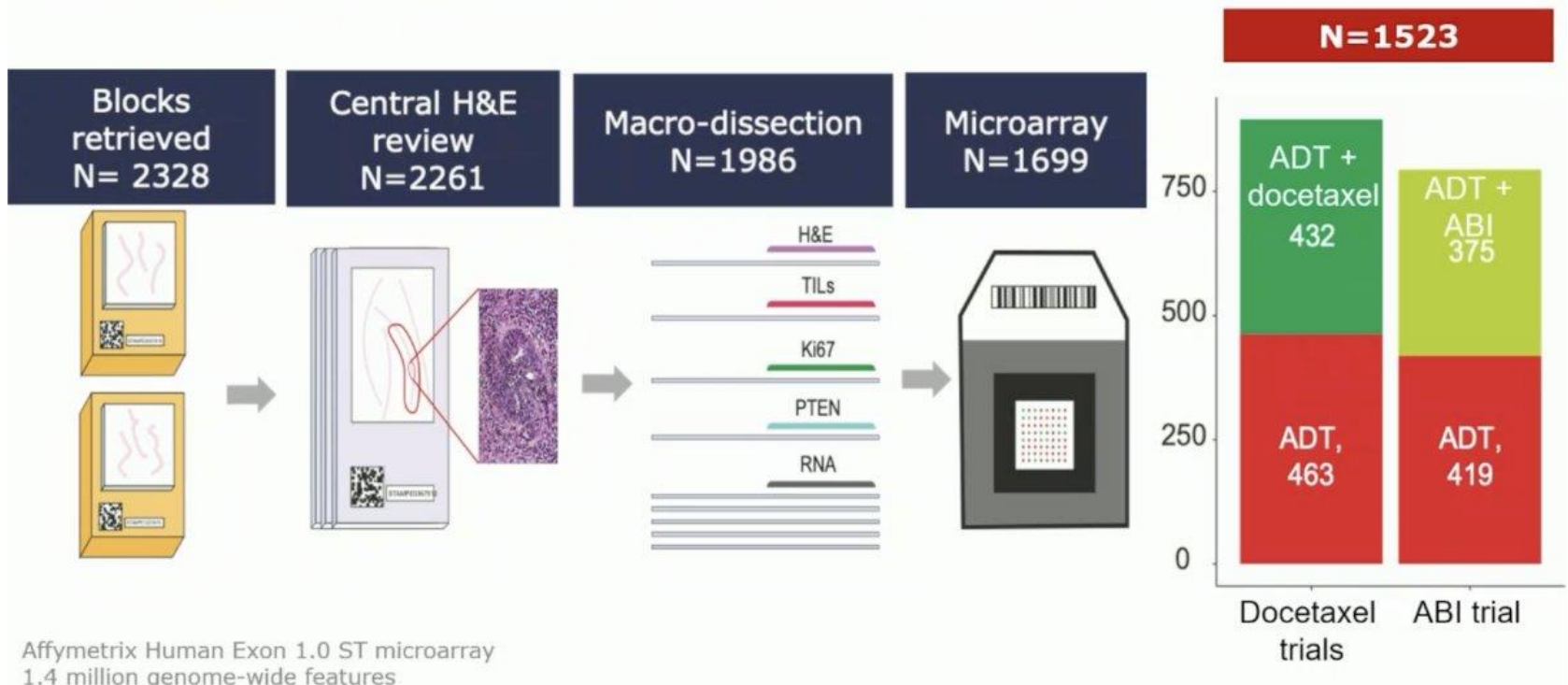
Marina Parry, Emily Grist, Christopher Brawley, James Proudfoot, Larissa Mendes, Sharan Lall, Alex Hoyle, Ashwin Sachdeva, Yang Liu, Claire Amos, Matthew Sydes, Robert Jones, Max Parmar, Felix Feng, Christopher Sweeney, Noel Clarke, Elai Davicioni, Nick James, Louise Brown, Gerhardt Attard **on behalf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

Linking of clinical and multi-omic data



Klinik bulgulara gen ve genomik verilerin eklenmesi

STAMPEDE docetaxel and abiraterone phase 3 trials

Metastatic prostate cancer

≥ 1 metastases on bone / CT scan

High-risk localised (adjuvant)

Local lymph node positive or if negative, ≥ 2 high risk features:

T3/T4, PSA ≥ 40ng/ml, Gleason sum 8-10

3909 directly-randomised patients

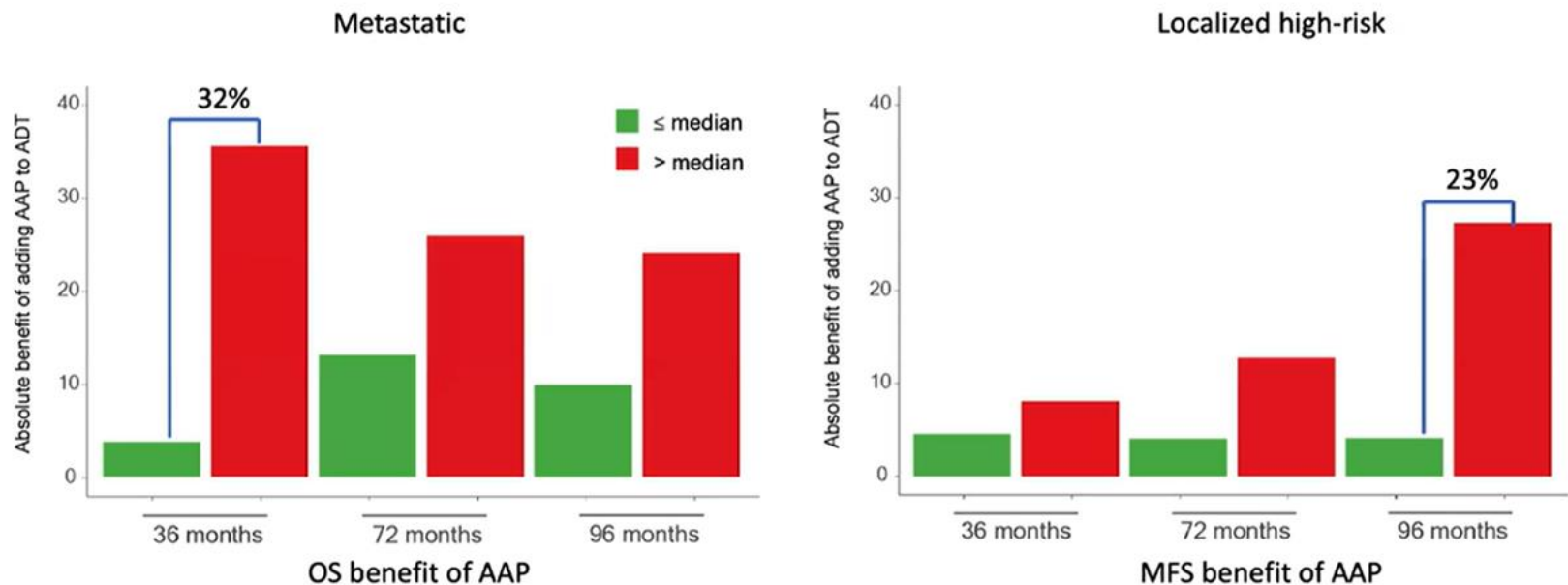
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graph LR; A[3909 directly-randomised patients] --> B[ADT +/- docetaxel/docetaxel + zoledronic acid]; A --> C[ADT +/- ABI]
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ADT +/- docetaxel/docetaxel + zoledronic acid

ADT +/- ABI

Klinik bulgulara gen ve genomik verilerin eklenmesi

Absolute Benefit of Adding AAP to ADT Varies by Decipher Score

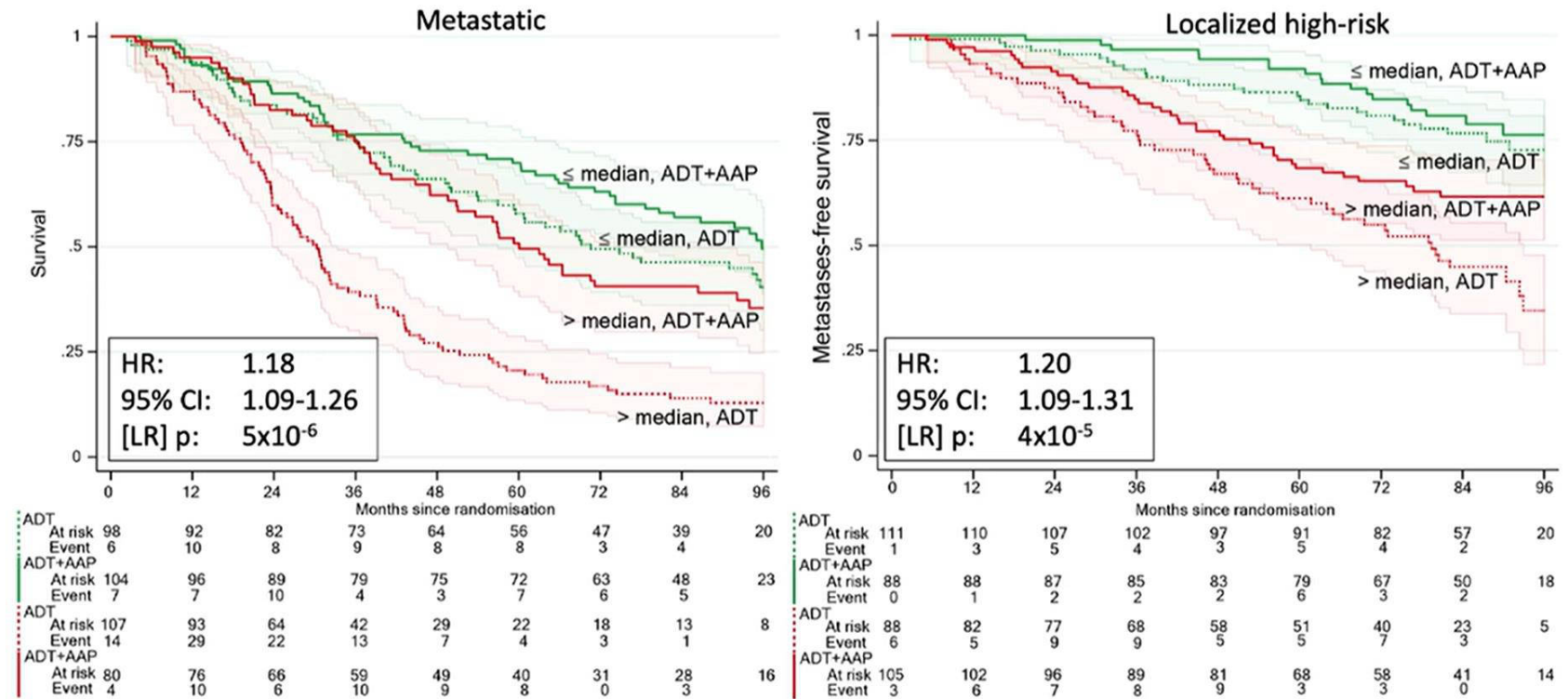


Event rate calculated using flexible parametric modelling adjusted for baseline characteristics

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.
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

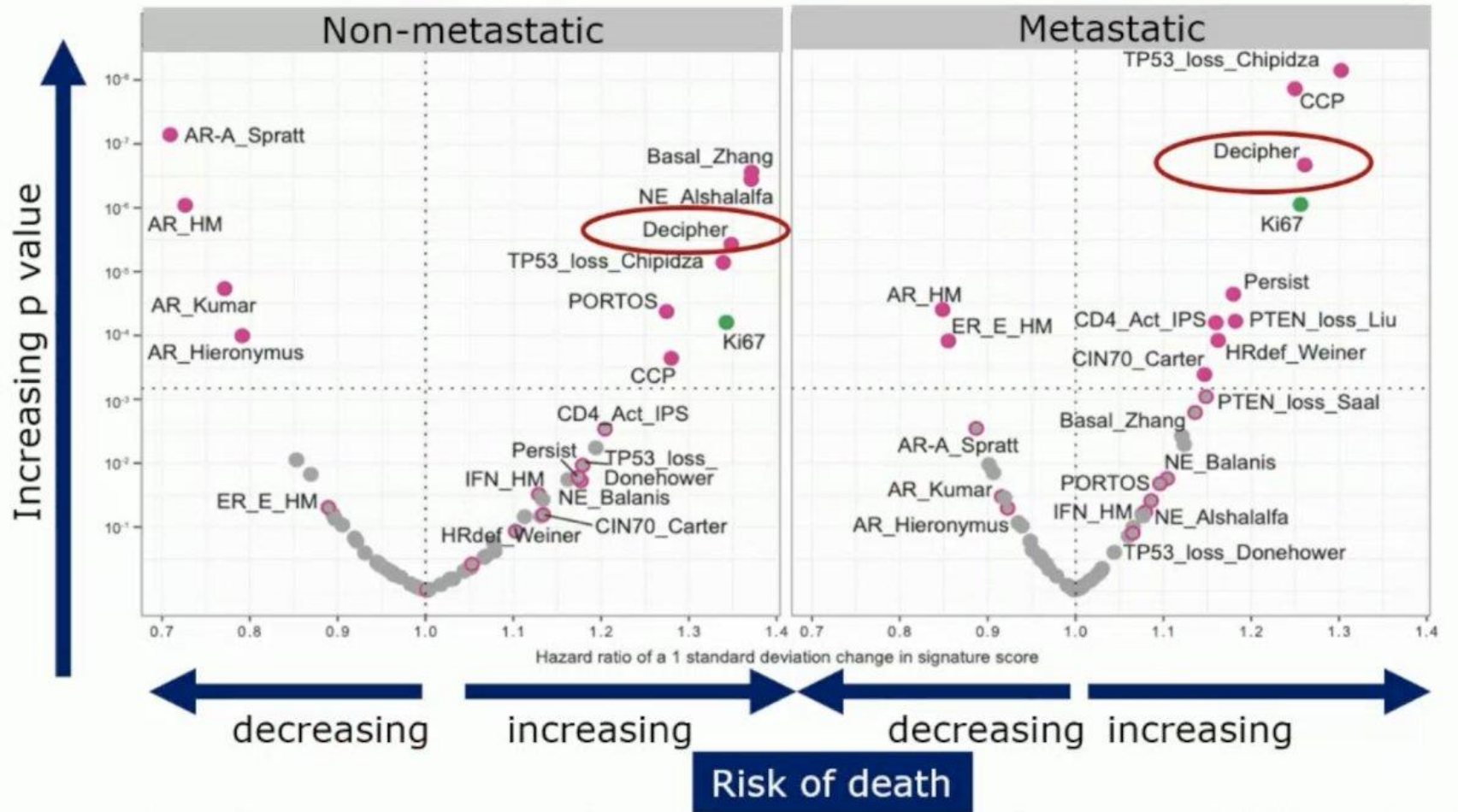
Decipher Signature is Strongly Prognostic Across Disease States



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.

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

Biomarkers in development for mHSPC

A robust biomarker could help determine first-line treatment and identify patients most likely to benefit from **MORE** or **LESS** intensive therapy

Potential Biomarkers

AR

AR alterations uncommon in HSPC. AR-V7 present and associated with response in HRPc but not HSPC. Transcriptional activity in HSPC may be a marker for reduced response to ARPI.

Tumor suppressor genes (*RB1*, *TP53*, *PTEN*, *SPOP*)

All but *SPOP* more common in HRPc than HSPC. Shown to be associated with treatment responses in HRPc but not yet in HSPC.

ctDNA

Fraction of ctDNA correlates with disease burden and outcomes. Initial response in ctDNA fraction may be associated with long term response. Ability to assess genetic alterations using ctDNA relies on high ctDNA fraction and remains to be determined in mHSPC.

HSD3B1

Assessed in the germline. Adrenal permissive allele associated with shorter time to progression to HRPc and shorter OS.

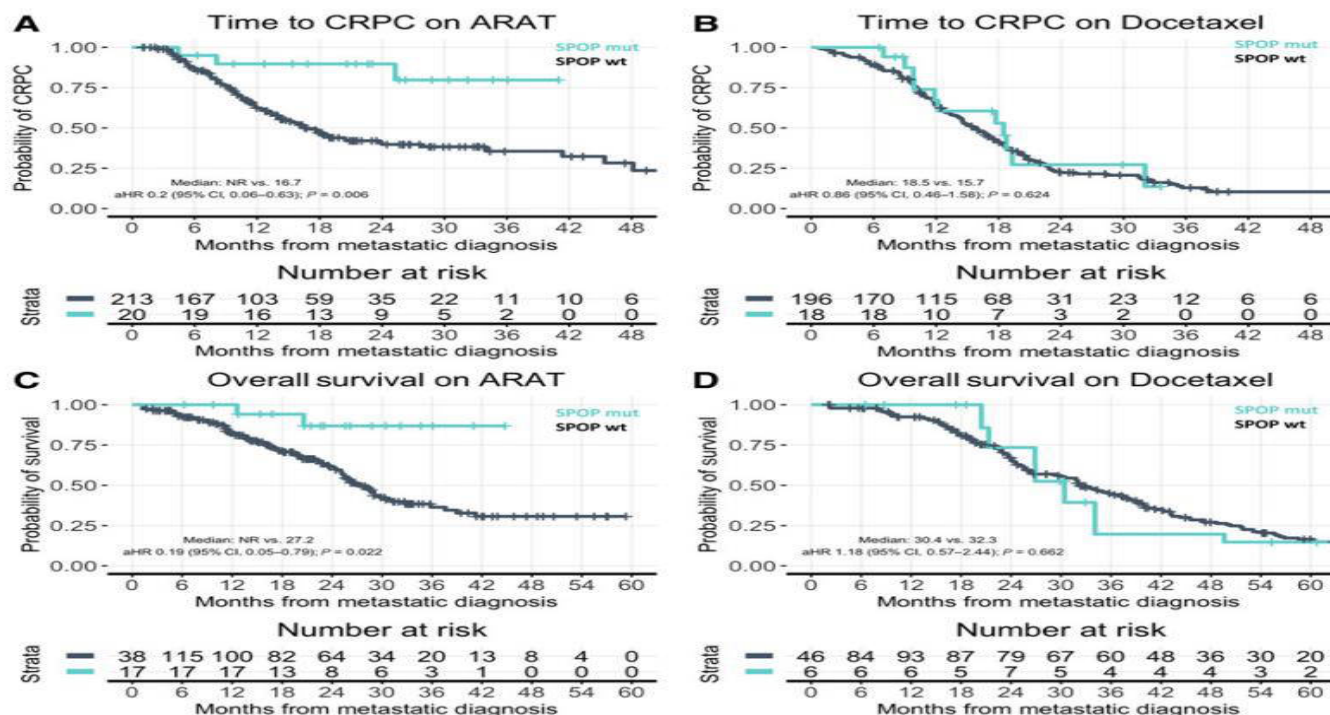
Gene Expression Profiling

Post-hoc analysis demonstrating ability to identify potential responders in both HSPC and HRPc.

- **Low AR transcriptional activity may reflect reduced AR dependence/aggressive disease** (Spratt DE, Clin Can Res 2019)
- **Loss of TP53, PTEN and RB1 are associated with RESISTANCE to AR axis inhibitors** (Zou M, Cancer Disc 2017; Ku SY, Science 2017; Hamid AA, Eur Urol 2019)
- **SPOP mutations are associated with SENSITIVITY to AR axis inhibitors** (Boysen G, Clin Cancer Res, 2018)
- **Primary tissue and ctDNA share relevant somatic alterations, suggesting that both may be useful for molecular subtyping in mHSPC** (Vandekerckhove G et al, Eur Urol 2019)
- **CHAARTED: inheritance of at least 1 copy of the adrenal permissive allele is associated with lower OS in low volume mHSPC** (Hearn JWD et al, JAMA Oncol 2020)
- **CHAARTED (PAM50): Luminal B subtype responded best when DOC was added to ADT** (Hamid AA et al, Ann Onc 2021)

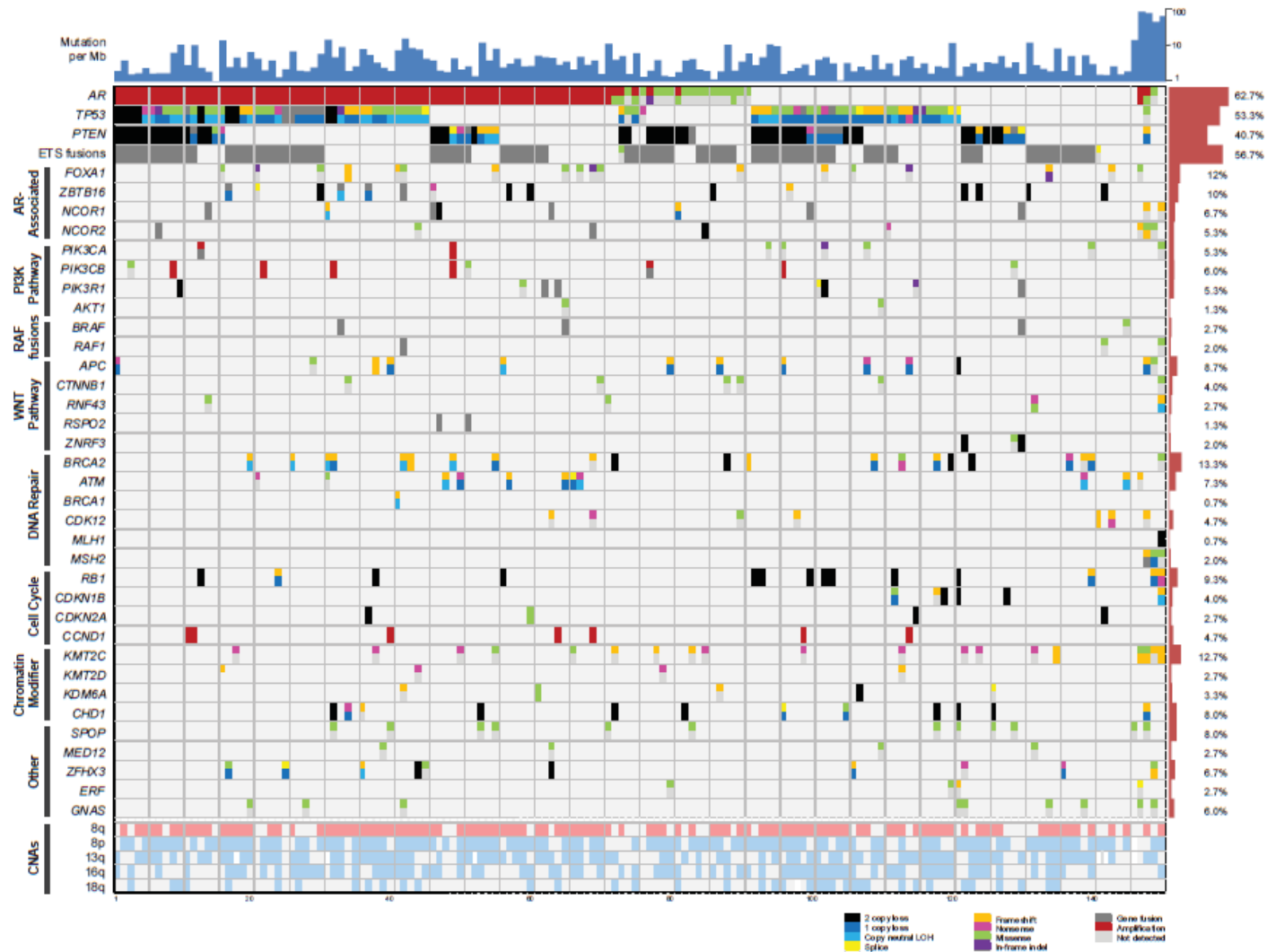
Modified from: Hoffman MR et al, Urology 2021

SPOP mutasyonu dozetaksel tedavisine yanıtı



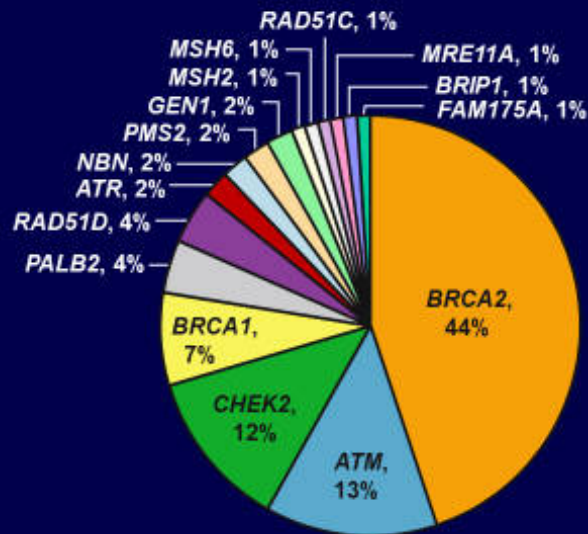
Umang Swami et al, Clin Cancer Res 2022

Klinik bulgulara gen ve genomik verilerin eklenmesi

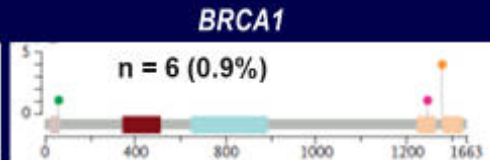
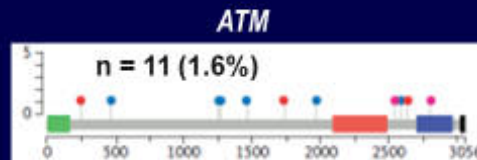
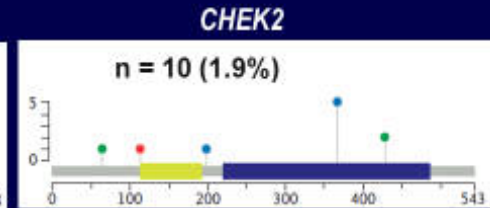
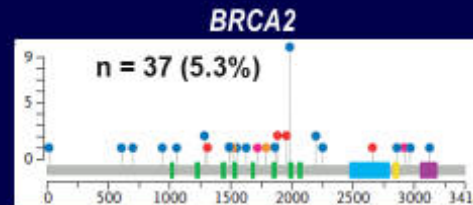


Prostat Kanserinde Germline Mutasyonları

Pathogenic Germline Mutations



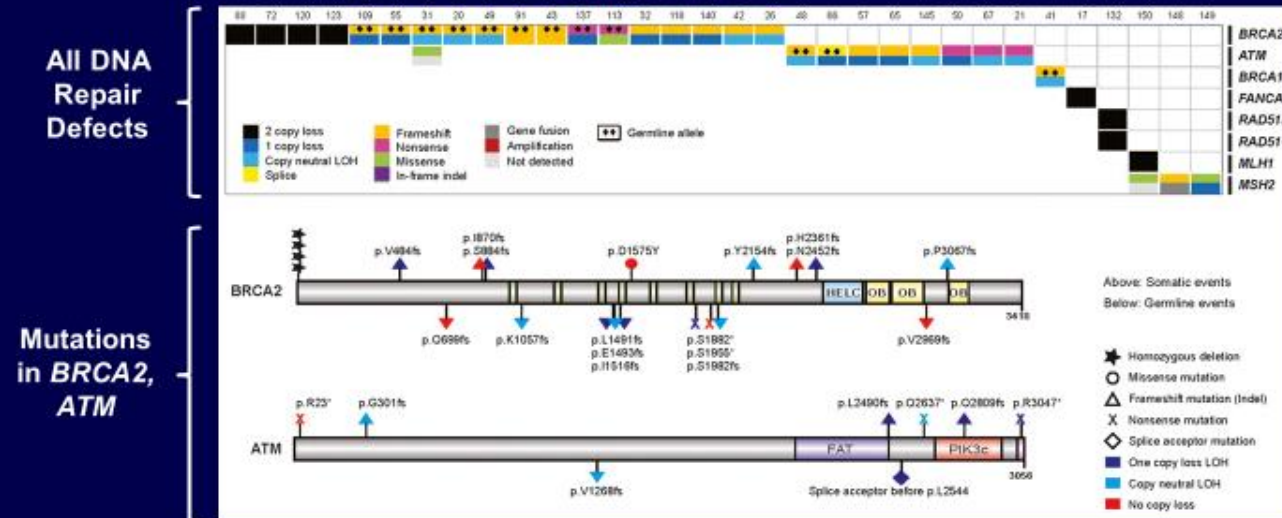
- **11.8%** (82/692) of men with metastatic prostate cancer inherited a germline DNA repair mutation vs 4.6% in localized PCa



Prostat Kanserinde DNA Repair Genlerinde Olan Değişiklikler

DNA Repair Defects in *Metastatic CRPC*

- 32/150 (21.3%) mCRPC pts had bi-allelic DNA repair mutations



Robinson D, et al. CELL. 2015; 5: 1215-1228.

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

PROpel: a global randomized double-blind phase III trial

Patient population

- 1L mCRPC
- Docetaxel allowed at mHSPC stage
- No prior abiraterone
- Other NHAs allowed if stopped ≥ 12 months prior to enrollment
- Ongoing ADT
- ECOG 0–1

Stratification factors

- Site of distant metastases: bone only vs visceral vs other
- Prior taxane at mHSPC: yes vs no

1:1

Olaparib 300 mg bid
+
abiraterone 1000 mg qd*
n=399

Full dose of olaparib and abiraterone used

Placebo
+
abiraterone 1000 mg qd*
n=397

Full dose of abiraterone used

Primary endpoint

- Radiographic progression or death (rPFS) by investigator assessment

Key secondary endpoint

- Overall survival (alpha control)

Additional endpoints

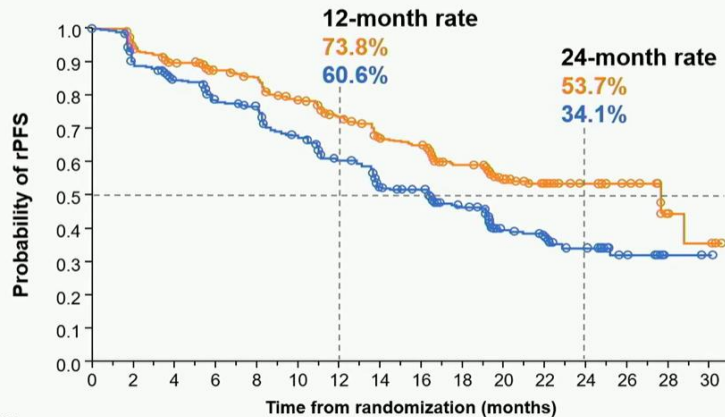
- Time to first subsequent therapy or death (TFST)
- Time to second progression or death (PFS2)
- Objective response rate (ORR)
- HRRm[†] prevalence (retrospective testing)
- Health-related quality of life
- Safety and tolerability

First patient randomized: Nov 2018; Last patient randomized: Mar 2020; DCO1: July 30, 2021, for interim analysis of rPFS and OS. Multiple testing procedure is used in this study: 1-sided alpha of 0.025 fully allocated to rPFS. If the rPFS result is statistically significant, OS to be tested in a hierarchical fashion with alpha passed on to OS. Please access the **Supplement** via the QR code at the end of this presentation for more details.
*In combination with prednisone or prednisolone 5 mg bid. [†]HRRm, homologous recombination repair mutation, including 14 genes panel.
ADT, androgen deprivation therapy; bid, twice daily; ECOG, Eastern Cooperative Oncology Group; mHSPC, metastatic hormone sensitive prostate cancer; qd, daily

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

PROpel: rPFS by blinded independent central review*

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



No. at risk
Olaparib + abiraterone 399 389 353 347 332 331 314 309 303 283 275 267 249 240 221 217 215 165 161 159 96 89 80 55 53 30 28 26 5 4 0
Placebo + abiraterone 397 388 345 340 322 319 294 289 282 251 245 226 209 204 177 172 168 131 126 124 73 70 62 39 38 21 16 15 2 2 1 0

	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

Evre IV Kastrasyona Dirençli Prostat Kanserinde Sisplatin Etkinliği

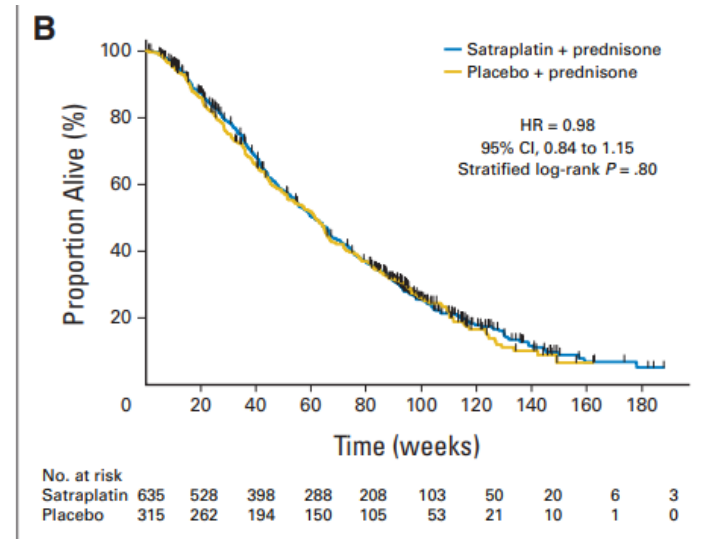
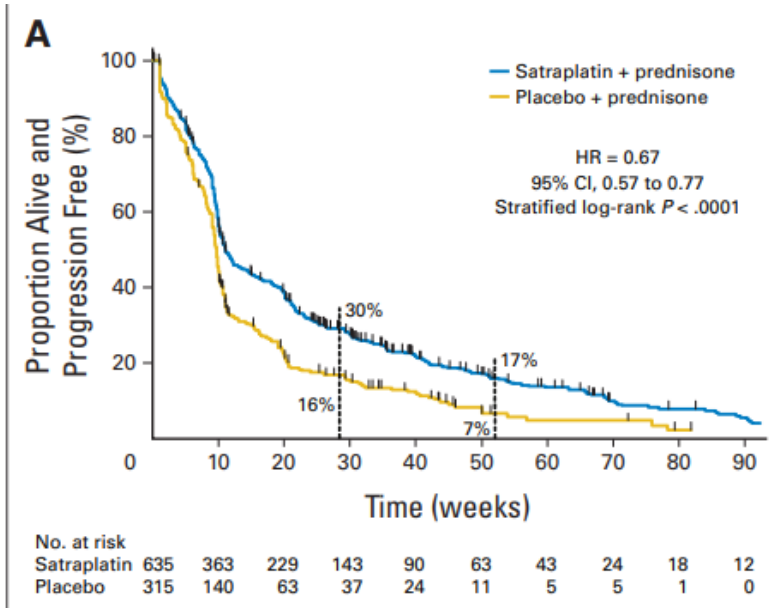


Fig 2. (A) Progression-free survival (intent-to-treat population) and (B) overall survival (intent-to-treat population). HR, hazard ratio.

SPARC: Satraplatin in Metastatic CRPC After Chemotherapy, JCO 2009

DNA Repair Gen Değişikliği Olan Hastalarda RA-223 etkinliği

M.J. van der Doelen et al. / European Journal of Cancer 136 (2020) 16–24

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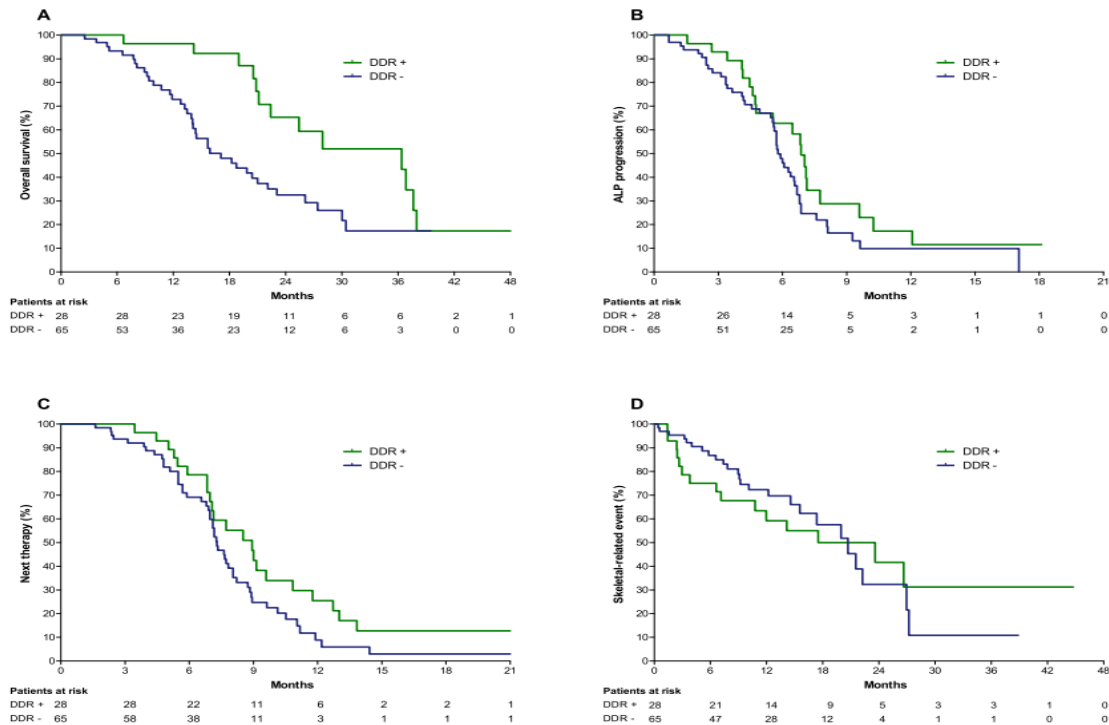


Fig. 2. Kaplan–Meier curves, stratified by DNA damage repair (DDR) mutation status, A. Overall survival, B. Time to alkaline phosphatase (ALP) progression, C. Time to initiation of next systemic therapy. D. Time to first skeletal-related events (SRE).

Kastrasyona Dirençli Prostat Kanseri

PI3K/AKT inhibisyonu

IPATential150 study design

Patients with asymptomatic or mildly symptomatic mCRPC (no prior treatment for mCRPC)

Stratification factors

- Tumour PTEN loss by IHC^a
- Prior docetaxel in HSPC setting
- Progression by PSA only
- Presence of liver/lung metastases
- Geographic region

N = 1101

R
1:1

Ipatasertib
(400 mg qd)
+
Abiraterone
(1000 mg qd)^b

Placebo
+
Abiraterone
(1000 mg qd)^b

Radiographically assessed
disease progression

Post-treatment follow-up

- Co-primary endpoints: investigator-assessed rPFS (PCWG3 criteria) in ITT and PTEN-loss (by IHC) populations
- Secondary endpoints included: OS, time to pain progression, time to initiation of chemotherapy, ORR, investigator-assessed rPFS in PTEN-loss (by NGS) population

HSPC, hormone-sensitive prostate cancer; NGS, next-generation sequencing; PCWG3, Prostate Cancer Working Group 3; R, randomised.
^a PTEN loss was defined as a minimum of 50% of the specimen's tumour area with no detectable PTEN staining (by Ventana IHC assay using SP218 antibody).

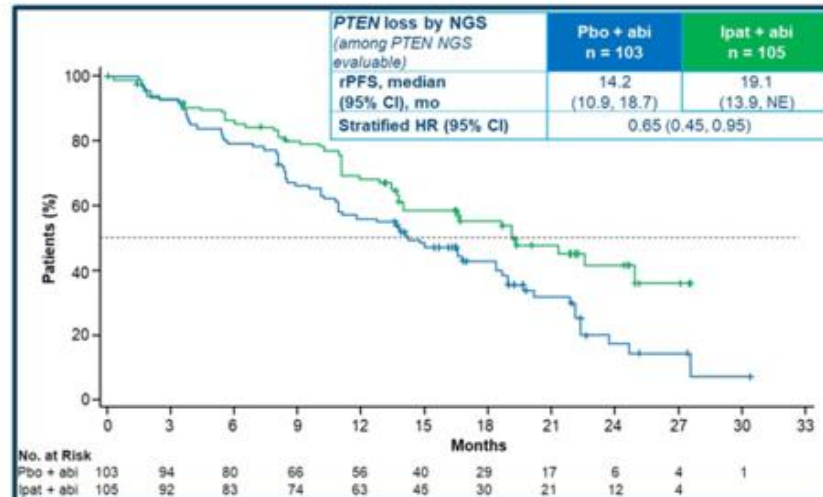
^b Abiraterone (1000 mg qd) plus prednisone/prednisolone (5 mg bid).

de Bono J. IPATential150. ESMO 2020. <https://bit.ly/31s8gje>

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)	

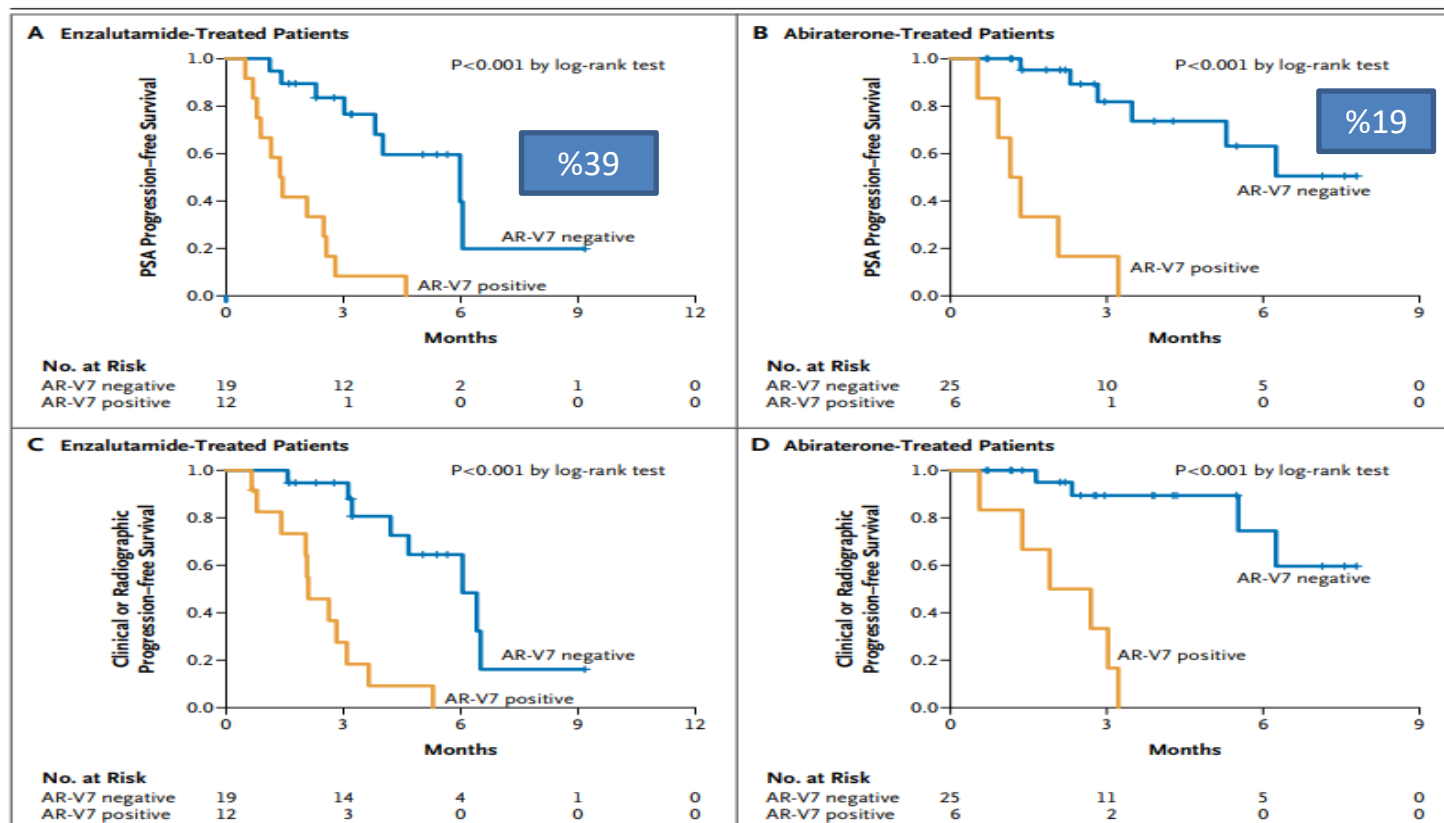
PTEN WT + PTEN loss by NGS (among PTEN NGS evaluable)	Pbo + abi n = 258	Ipat + abi n = 260
rPFS, median (95% CI), mo	16.5 (13.7, 19.0)	19.3 (16.7, 24.7)
Stratified HR (95% CI)	0.77 (0.60, 0.99)	

¹OS 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. IPATential130: 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 LB44.

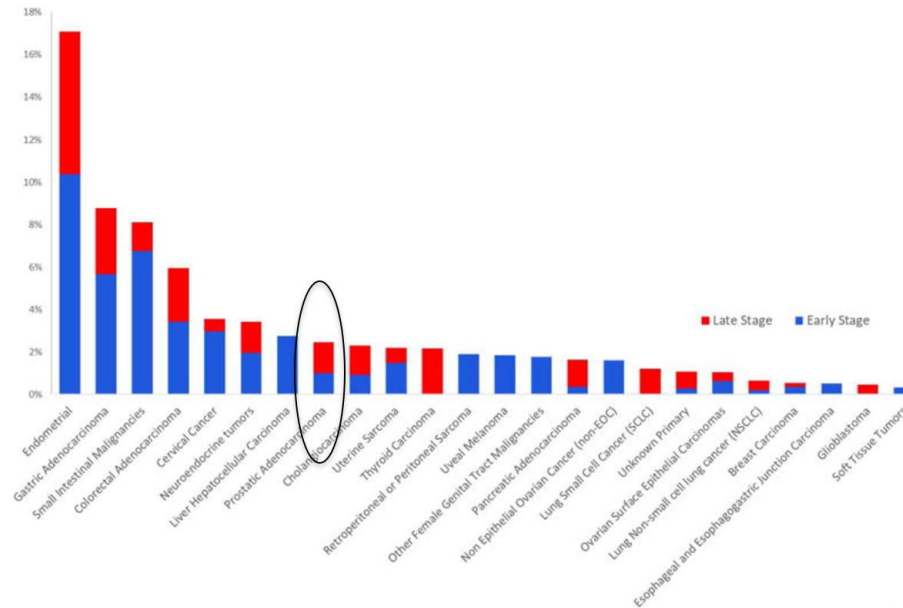
Presented By Johann De Bono at 2021 Genitourinary Cancers Symposium

AR yolağında meydana gelen değişimler



MSI High Prostat Kanserinde Tedavi Seçenekleri

Mismatch Repair Deficiency

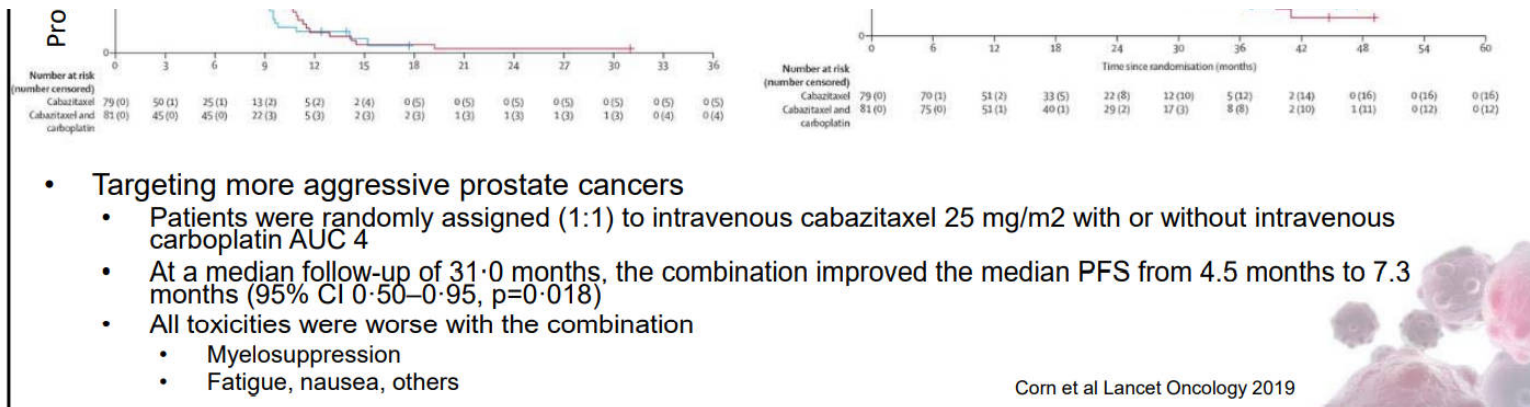


Le et al. Science 2017

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.

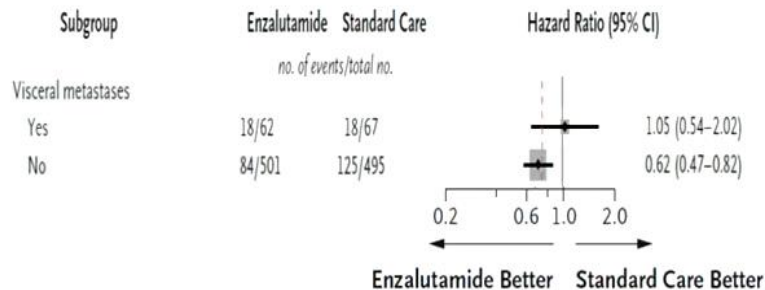


Yeni nesil androjen yolağı inhibitörleri viseral metastazda etkinliği düşük

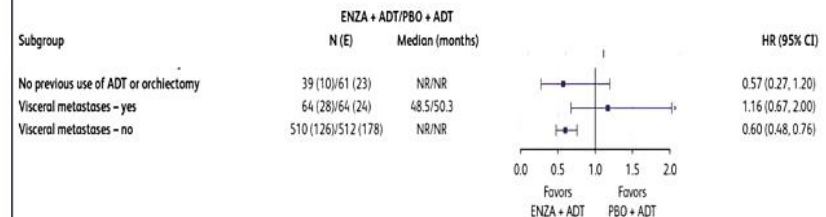
Does type of metastasis matter in mHNPC?

Results from new hormonal treatments in mHNPC according visceral mets

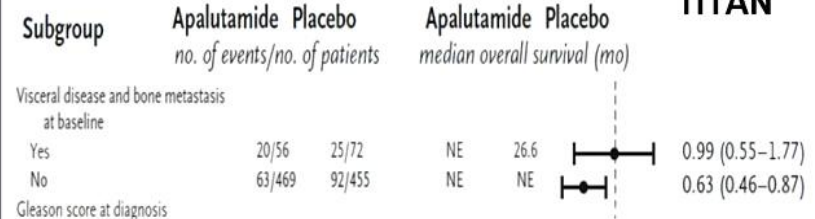
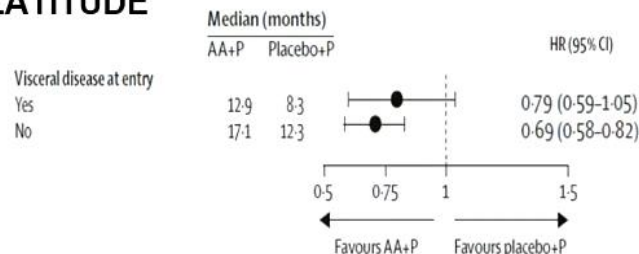
ENZAMET



ARCHES



LATITUDE



2021 ESMO congress

OUARD Stéphane

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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/m² 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 PSA₅₀ 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 PSA₅₀ 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 CHARTED–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

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%)	TP53m – 14 (77%) TP53wt – 26 (84%)	ERGm – 11 (100%) ERGwt – 29 (74%)	SPOPm – 5 (100%) SPOPwt – 35 (78%)
PSA ≤0.2 ng/mL at month 7	HRRm – 3 (38%) HRRwt – 27 (66%)	TP53m – 12 (67%) TP53wt – 18 (60%)	ERGm – 9 (82%) ERGwt – 21 (55%)	SPOPm – 4 (100%) SPOPwt – 26 (58%)

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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	3 rd 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)
PSMAAddition	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/Abirateron +/- Doseetaksel 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