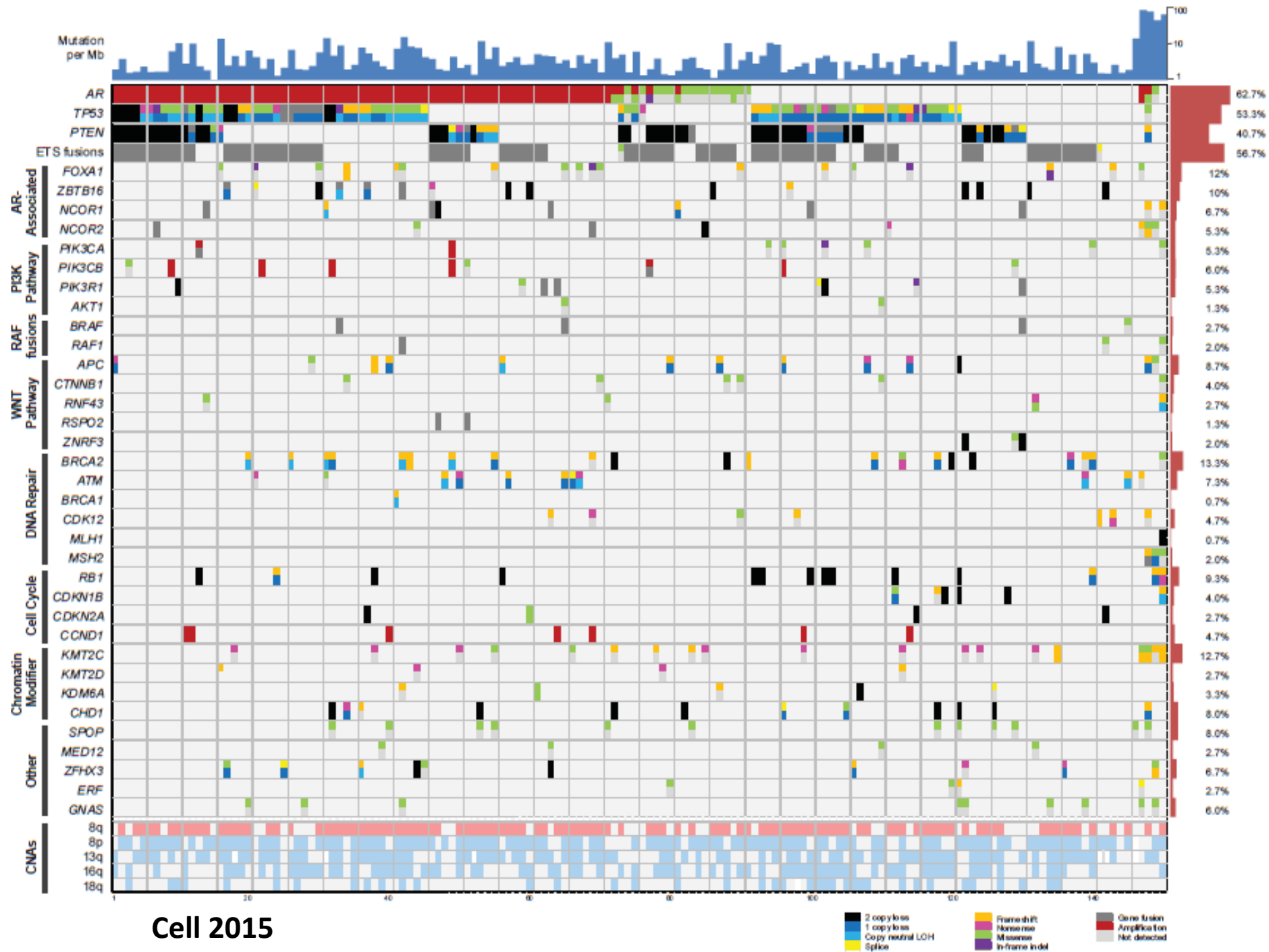


Prostat Kanserinde Genetik Deęişiklikler ve Tedaviye Yansımaları

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

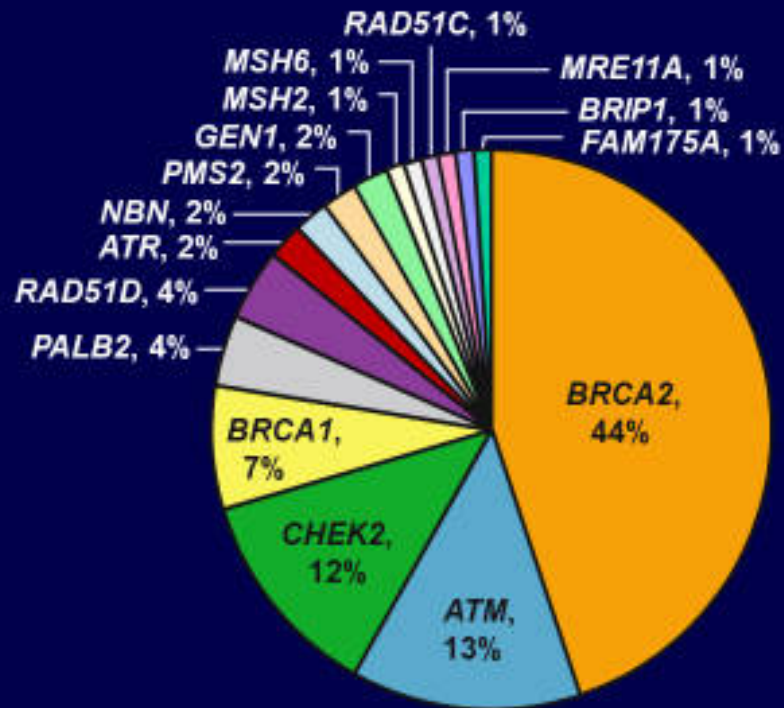
Ders Planı

- ☐ 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

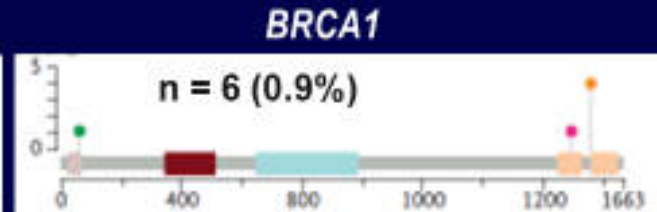
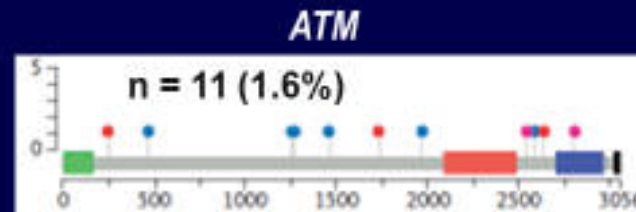
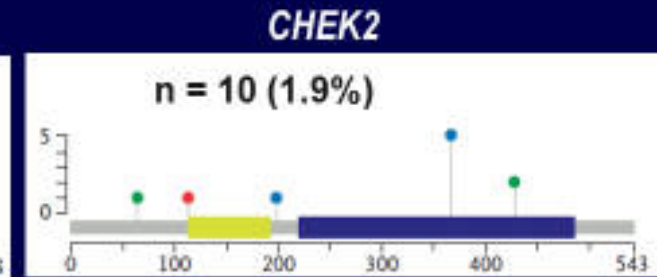
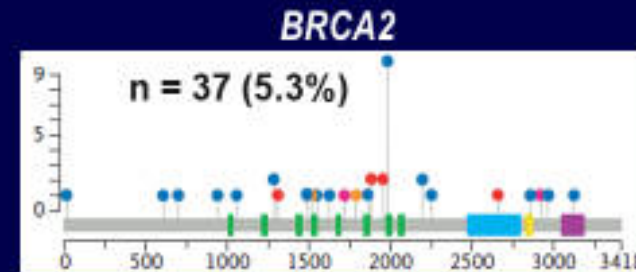


Prostat Kanserinde Germline Mutasyonları

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 Genlerde Olan Değişiklikler

Single-stranded (ss)DNA Repair pathways

- **Mismatch repair (MMR)**
 - Base errors from DNA replication and recombination
 - *MSH2, MSH6, MLH1, PMS2*
- Nucleotide excision repair (NER)
 - DNA damage from UV light, polycyclic aromatic hydrocarbons
 - *XPA-G, ERCC1-8, CSA/B, RPA, RAD23A/B*
- Base excision repair (BER)
 - DNA damage from alkylation, oxidation/ROS, deamination
 - *PARP1/2/3, POL β , MUTYH, XRCC1, MBD4, NTHL1*

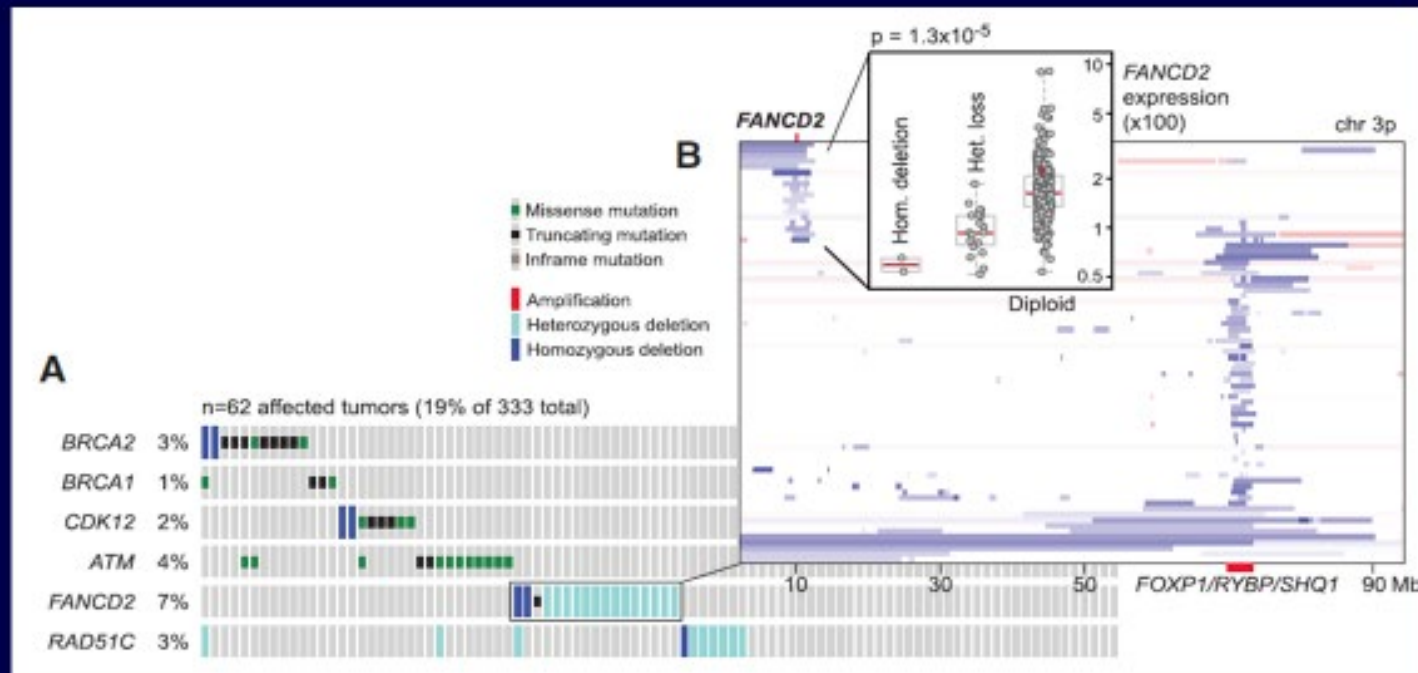
Prostat Kanserinde DNA Repair Genlerde Olan Değişiklikler

Double-stranded (ds)DNA Repair pathways

- **Homologous recombination (HR)**
 - DNA damage from ionizing radiation or other dsDNA injury
 - *FANC* genes, *BRCA1/2*, *ATM*, *PALB2*, *RAD50*, *RAD51*, *NBN*, *MRE11*, *BLM*, *ATR*
- **Non-homologous end joining (NHEJ)**
 - DNA damage from ionizing radiation or other dsDNA injury
 - *XRCC4/5/6*, *LIG4*, *DCLRE1C*, *PRKDC*, *NHEJ1*, *POLL/M*
- **Trans-lesion DNA synthesis (TLS)**
 - Error-prone recovery mechanism when no DNA template
 - *POLH*, *POLI*, *POLK*, *PCNA*, *REV1/3* (error-prone DNA polymerases)

Prostat Kanserinde DNA Repair Genlerinde Olan Değişiklikler

DNA Repair Defects in *Localized Prostate Ca*

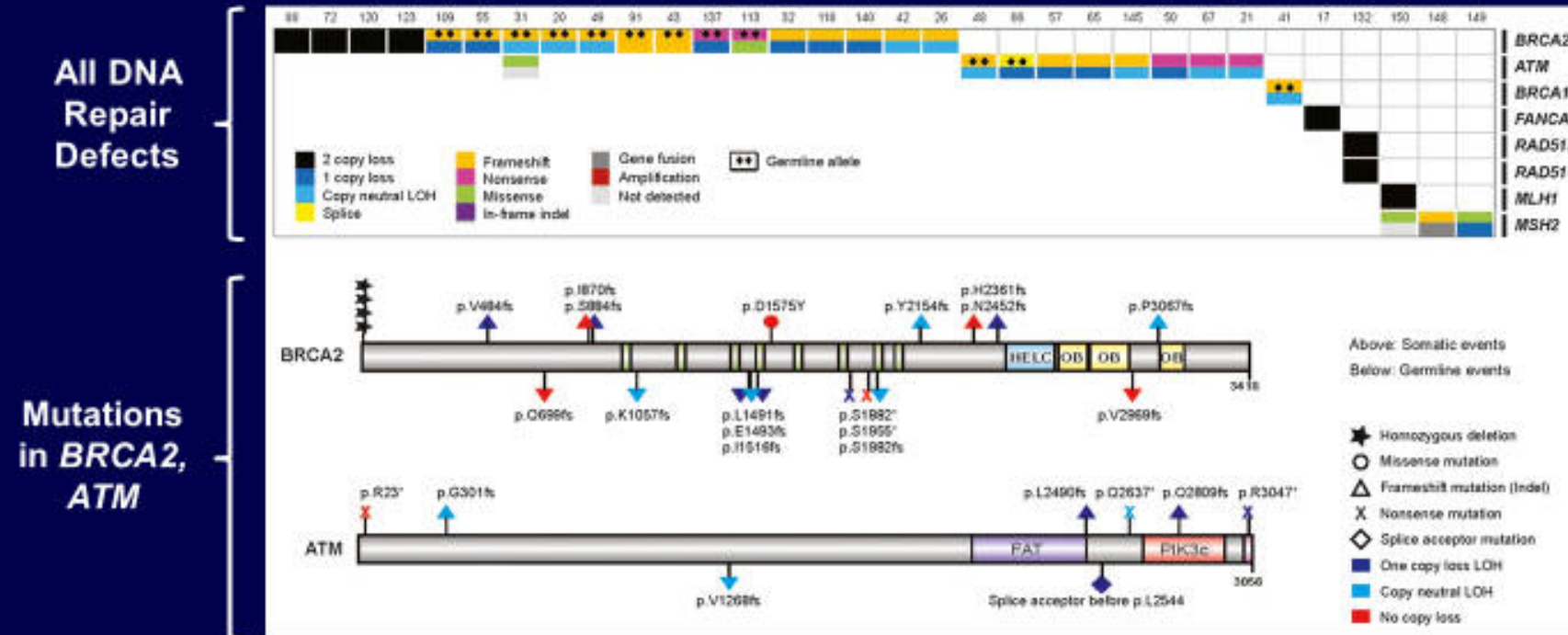


– 27/333 (8.1%) Tumors had Bi-Allelic inactivation

Prostat Kanserinde DNA Repair Genlerinde Olan Değişiklikler

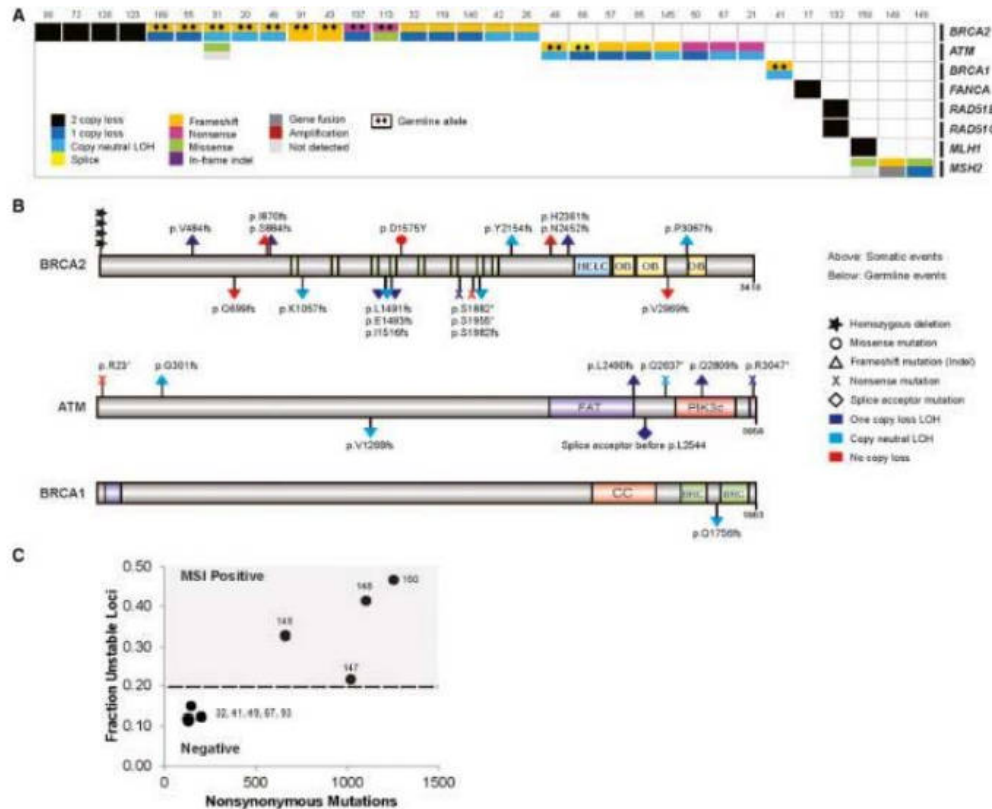
DNA Repair Defects in *Metastatic CRPC*

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



Prostat Kanserinde DNA Repair Genlerinde Olan Değişiklikler

Molecular Evaluation in CRPC



- *BRCA2* identified 19/150 (12.7%) of cases with loss of *BRCA2*
 - 90% exhibited biallelic loss
- This was commonly a result of somatic point mutation, loss of heterozygosity, and homozygous deletion
- 5.3% harbored pathogenic germline *BRCA2* mutations
- Alterations identified in 34/150 (22.7%) of cases

Prostat Kanserinde DNA Repair Genlerinde Olan Değişiklikler

The etiology of homologous recombination repair (HRR) mutations

Germline Mutations

- Inherited or hereditary mutation
- Present in the germ cells (sperm or egg)
- Present in every cell of the body
- Can be found in normal (non-tumor) tissue
- Test by blood, saliva, fibroblasts or buccal swab
- Does not identify somatic mutations
- Associated with hereditary cancer syndromes



Somatic Mutations

- Acquired or developed mutations
- Present in non-germline tissues
- Present in tumor cells
- Can be detected by tumor NGS testing on freshly collected tissue
- Liquid biopsy: Analyzes cell-free circulating DNA and RNA in blood
- Tumor only testing: Laboratory reports ALL mutations (can be germline or somatic, no normal tissue)
- Paired tumor testing: Laboratory reports all mutations (analyzes normal and tumor tissue), can distinguish between somatic and germline



Prostat Kanserinde DNA Repair Genlerde Olan Değişiklikler

Multiple tests for somatic testing (and more)

Solid tumor testing

- CARIS MI profile
 - Sequences ~22,000 genes
 - HRD testing by BRCAm and LOH
- Foundation One CDx
 - Sequences 324 genes
 - HRD testing by BRCAm and LOH
- Myriad myChoice CDx
 - Sequences BRCA1 and BRCA2
 - HRD testing by BRCAm and Genomic Instability Score (LOH, TAI and LST)
- Tempus HRD Test
 - Sequences 648 genes
 - HRD testing by BRCAm and LOH
- In-house testing
 - Varies by laboratory

THE FOLLOWING INFORMATION HAS NOT BEEN REVIEWED AND APPROVED BY THE FDA.

COMPREHENSIVE GENE ANALYSIS

Genes Fully Analyzed: BRCA1, BRCA2

Genes Partially Analyzed¹:

Genes Not Analyzed:

¹ Complete analysis was not able to be performed on limited regions of specific genes, which shall be provided upon request.

Patient Genomic Instability Score: 48

A Genomic Instability Score (GIS) of 42 or greater confers a positive GIS status.

Liquid biopsy (useful when limited tissue)

- Guardant 360
 - Analyzes 74 genes
- Foundation One Liquid CDx
 - Analyzes 300 genes
- SeraCare ctDNA
 - Analyzes 28 genes

Detected Alteration(s) / Biomarker(s)	Associated FDA-approved therapies	Clinical trial availability (see page 4)	% ctDNA or Amplification
BRCA1 K739fs	 Olaparib, Rucaparib, Talazoparib	Yes	69.0%
TP53 R248Q	None	Yes	29.1%
FGFR1 Amplification	None	Yes	Low (+)

Variants of Uncertain Clinical Significance

ATM F2831S (0.9%), AR R753* (0.6%)

The functional consequences and/or clinical significance of alterations are unknown. Relevance of therapies targeting these alterations is uncertain.

Synonymous Alterations

BRCA1 V382V (16.0%)

This sequence change does not alter the amino acid at this position and is unlikely to be a therapeutic target. Clinical correlation is advised.

Comments

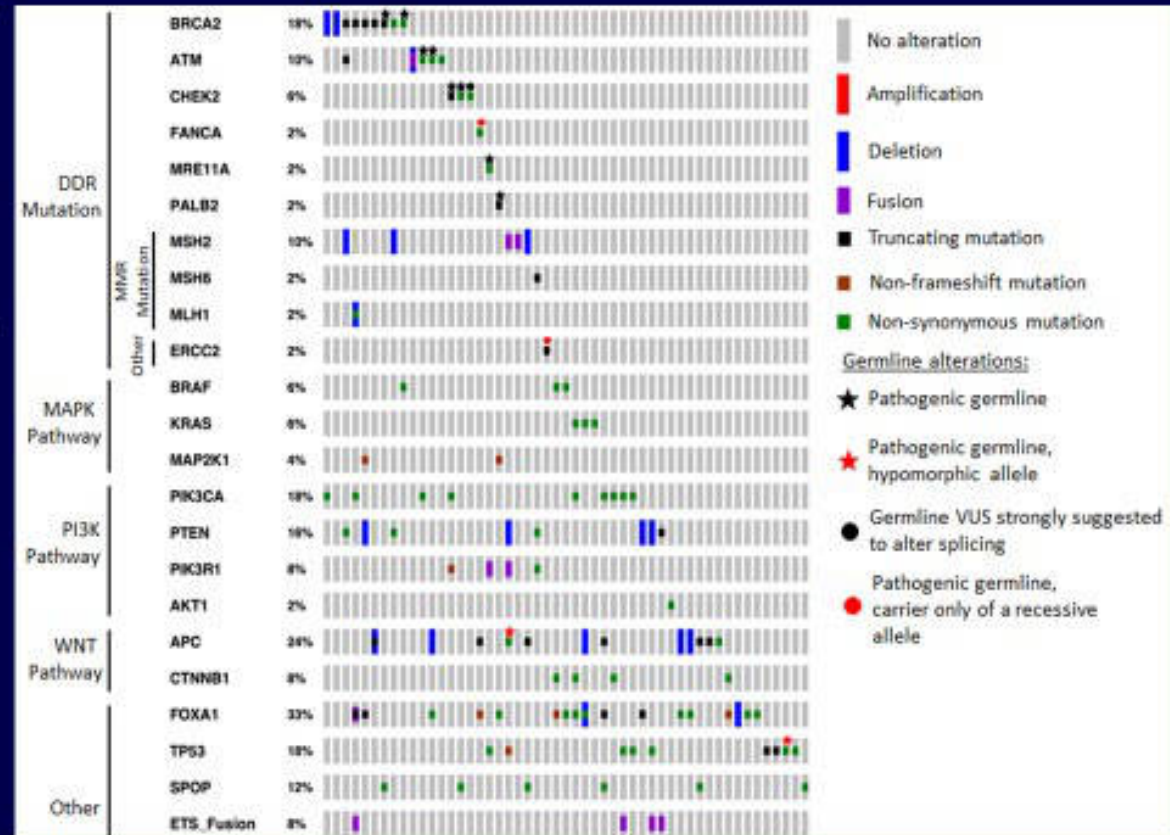
The BRCA1 K739fs (c.2214_2222delTAAAGTGTCTinsAGAAACAG) alteration was detected in this patient's sample at an allele fraction suspicious for germline origin. This variant may lead to the loss of functional protein, and similar variants have been associated with hereditary predisposition to cancer. As Guardant360 is neither intended nor validated for the reporting or interpretation of germline variants, we cannot confirm the germline vs. somatic origin of this finding and recommend verification with an assay validated for germline testing if this potential incidental finding is of clinical interest.

Prostat Kanserinde DNA Repair Genlerde Olan Değişiklikler

Intraduktal tip

DNA Repair Defects and Prostatic Ductal Cancer

- Overall, **49%** had DNA repair gene mutations:
 - MMR mutations 14%
 - HRD mutations 31%

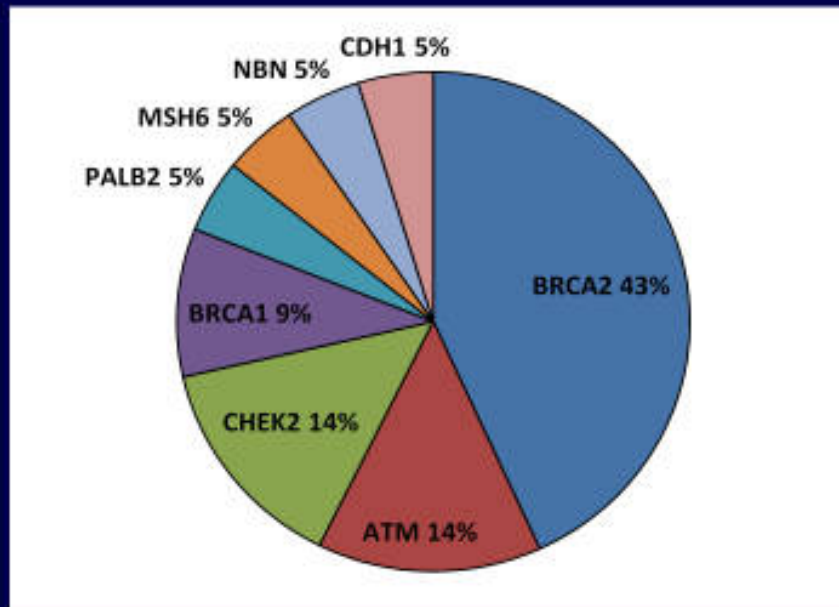


Schweizer MT, et al. *JCO Precis Oncol*, 2019;
DOI:10.1200/PO.18.00327

Prostat Kanserinde DNA Repair Genlerde Olan Değişiklikler Intraduktal tip

Germline DNA-Repair Defects and Intraductal Ca

Distribution of Germline Mutations



- Germline mutations in **14%** (21/150) of men with recurrent/advanced prostate cancer
- Men with intraductal histology more likely to have germline mutations

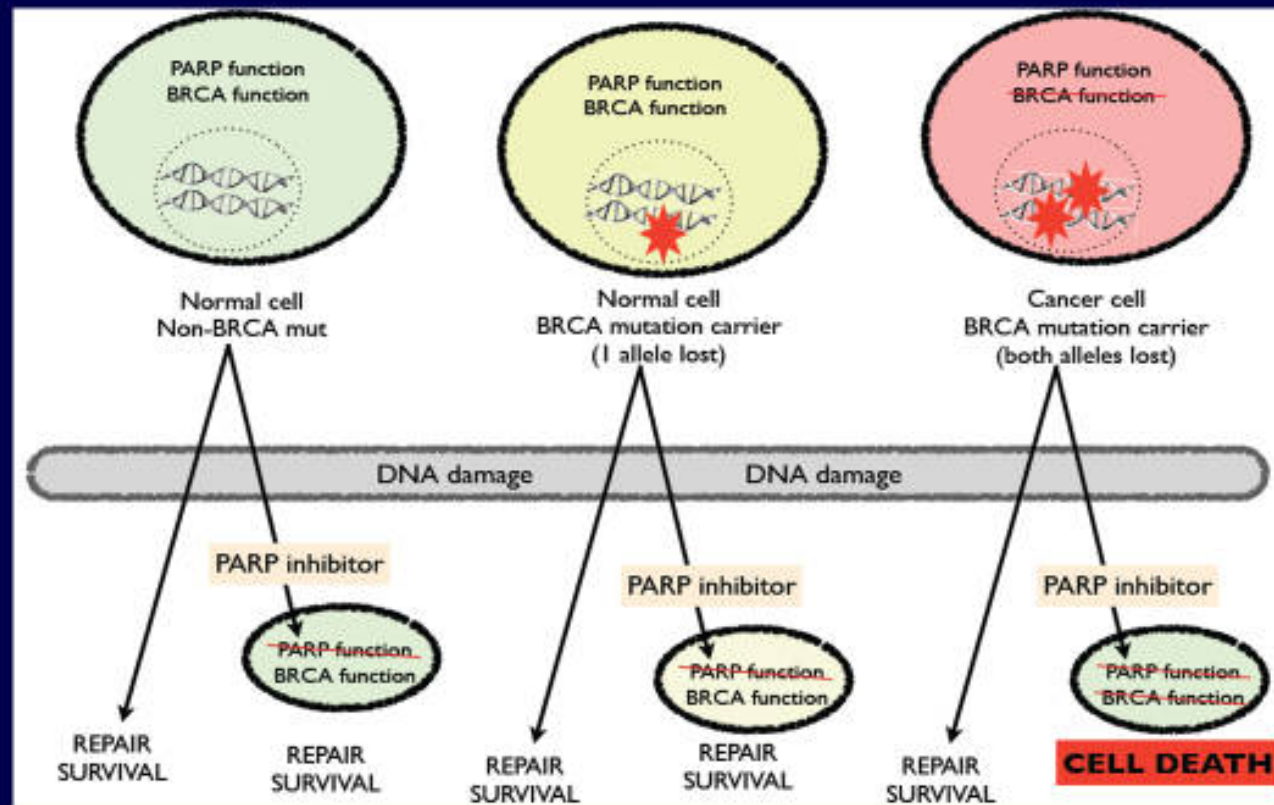
Incidence of Germline Mutations

Intraductal Histology	No Intraductal Histology	P Value*
40% (10/25)	9% (11/125)	P = .003

*Fisher's test

PARP inhibitörlerin Kullanım Temeli

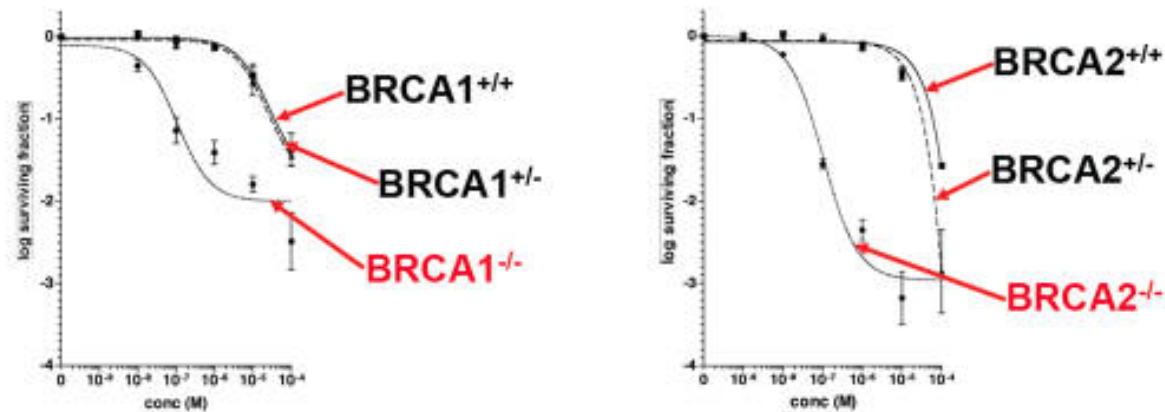
'Synthetic Lethality' Hypothesis



Farmer H, et al. Nature. 2005;434:917-921. Bryant et al. Nature. 2005;434:913-917.

PARP inhibitörlerin Kullanım Temeli

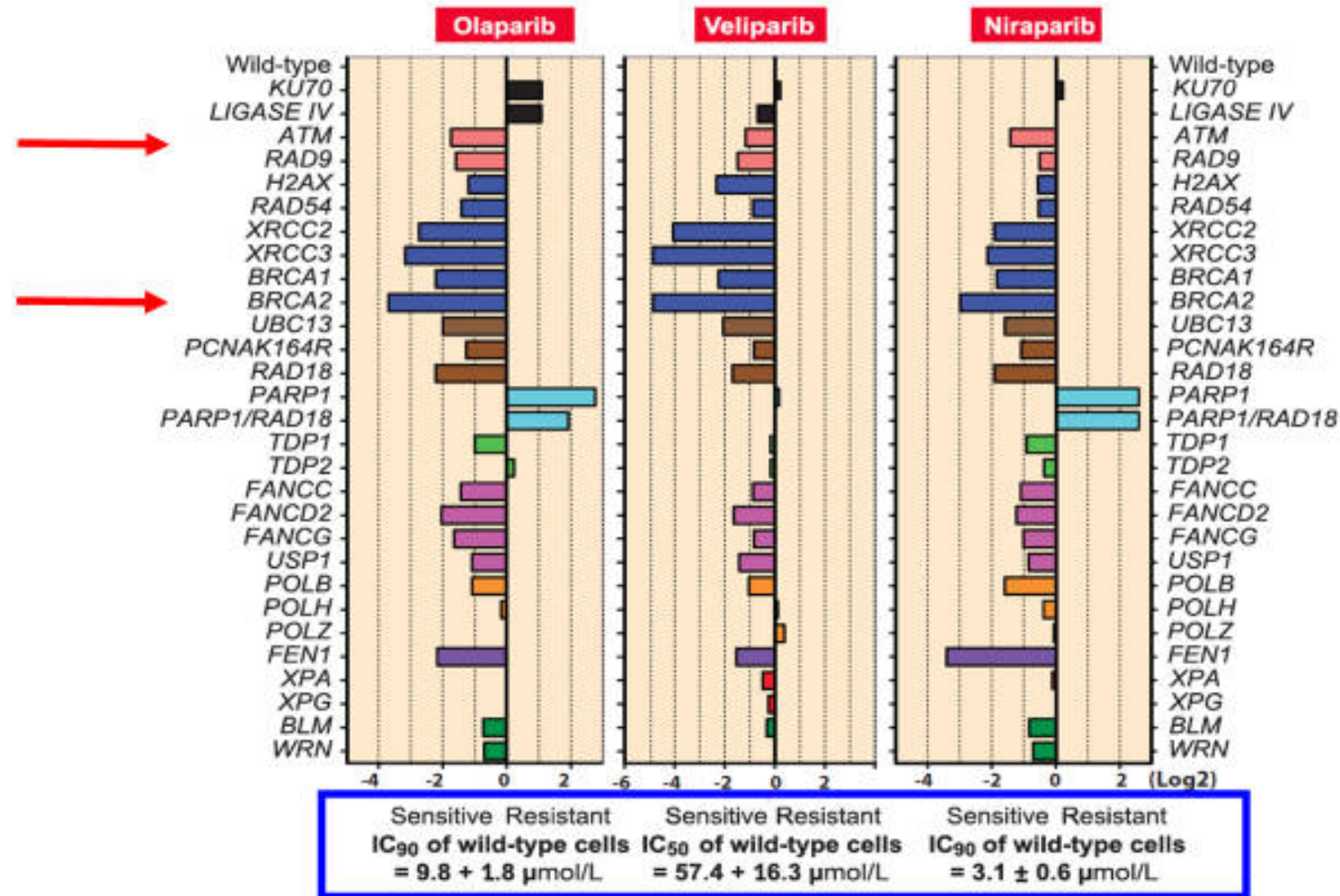
Synthetic Lethality: Targeting a tumor cell's Achilles' heel
Sensitivity of BRCA1 and BRCA2 loss cells to PARPi



No difference in sensitivity between
heterozygous and wild-type BRCA cells

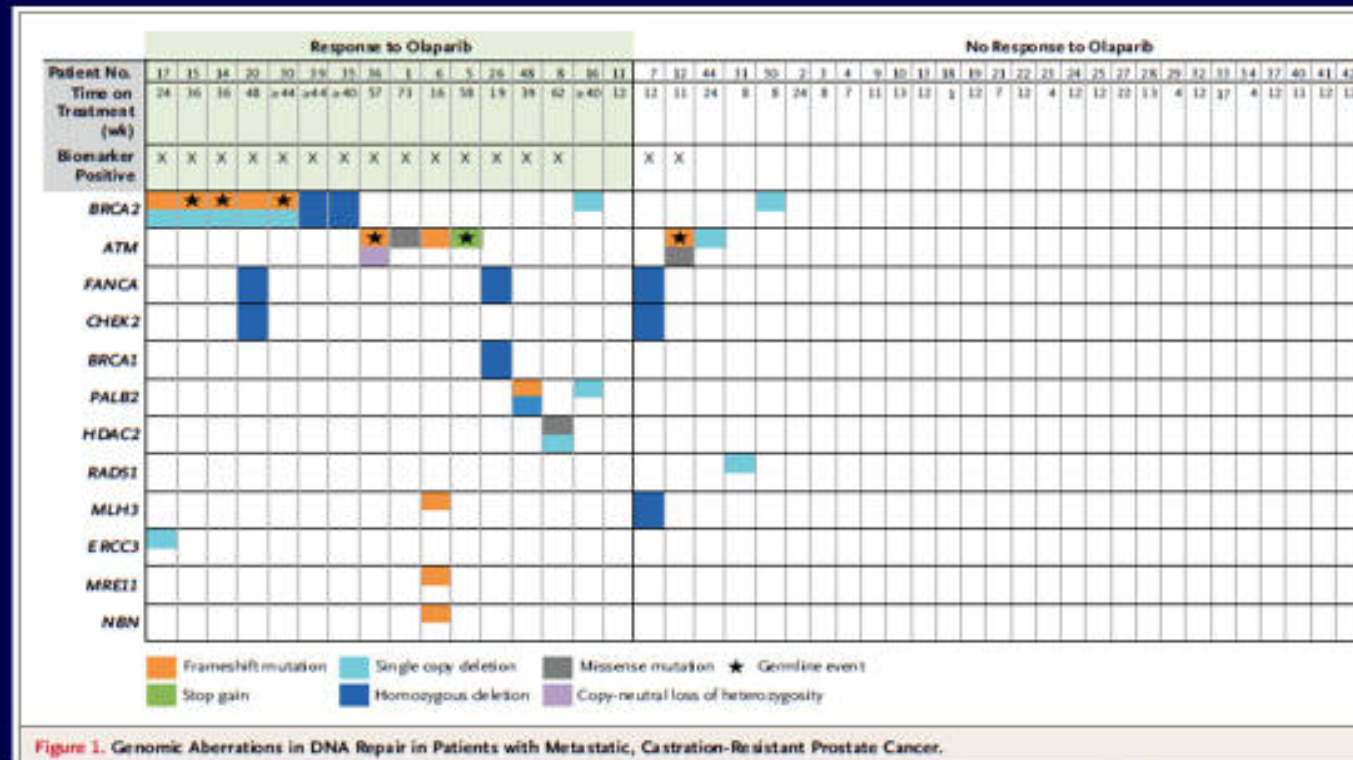
Targeted inhibition → selective and less toxic therapy

PARP İnhibitörlerin Kullanım Temeli



PARP İnhibitörlerin Kullanım Temeli

TOPARP-A: Unselected phase 2 trial in mCRPC



- 16 of 49 pts responded to olaparib
 - 14 of 16 (88%) biomarker-positive pts
 - 2 of 33 (6%) biomarker-negative pts

PARP inhibitörlerin Kullanım Temeli

Spin-Off of the TOPARP Trial: Germline Analyses

THE NEW ENGLAND JOURNAL OF MEDICINE

ORIGINAL ARTICLE

Inherited DNA-Repair Gene Mutations in Men with Metastatic Prostate Cancer

C.C. Pritchard, J. Mateo, M.F. Walsh, N. De Sarkar, W. Abida, H. Beltran, A. Garofalo, R. Gulati, S. Carreira, R. Eeles, O. Elemento, M.A. Rubin, D. Robinson, R. Lonigro, M. Hussain, A. Chinnaiyan, J. Vinson, J. Filipek, L. Garraway, M.-E. Taplin, S. AlDubayyan, G.C. Han, M. Beightol, C. Morrissey, B. Nghiem, H.H. Cheng, B. Montgomery, T. Walsh, S. Casadei, M. Berger, L. Zhang, A. Zehir, J. Vijai, H.I. Scher, C. Sawyers, N. Schultz, P.W. Kantoff, D. Solt, M. Robson, E.M. Van Allen, K. Offit, J. de Bono, and P.S. Nelson

ABSTRACT

BACKGROUND

Inherited mutations in DNA-repair genes such as BRCA2 are associated with increased risks of lethal prostate cancer. Although the prevalence of germline mutations in DNA-repair genes among men with localized prostate cancer who are unselected for family predisposition is insufficient to warrant routine testing, the frequency of such mutations in patients with metastatic prostate cancer has not been established.

METHODS

We recruited 692 men with documented metastatic prostate cancer who were unselected for family history of cancer or age at diagnosis. We isolated germline DNA and used multiplex sequencing assays to assess mutations in 20 DNA-repair genes associated with autosomal dominant cancer-predisposition syndromes.

RESULTS

A total of 84 germline DNA-repair gene mutations that were presumed to be deleterious were identified in 82 men (11.8%); mutations were found in 16 genes, including BRCA2 (37 men [5.3%]), ATM (11 [1.6%]), CHEK2 (10 [1.9%] of 534 men with data), BRCA1 (6 [0.9%]), RAD51D (3 [0.4%]), and PALB2 (3 [0.4%]). Mutation frequencies did not differ according to whether a family history of prostate cancer was present or according to age at diagnosis. Overall, the frequency of germline mutations in DNA-repair genes among men with metastatic prostate cancer significantly exceeded the prevalence of 4.6% among 499 men with localized prostate cancer ($P<0.001$), including men with high-risk disease, and the prevalence of 2.7% in the Inome Aggregation Consortium, which includes 53,105 persons without a known cancer diagnosis ($P<0.001$).

CONCLUSIONS

In our multicenter study, the incidence of germline mutations in genes mediating DNA-repair processes among men with metastatic prostate cancer was 11.8%, which was significantly higher than the incidence among men with localized prostate cancer. The frequencies of germline mutations in DNA-repair genes among men with metastatic disease did not differ significantly according to age at diagnosis or family history of prostate cancer. (Funded by Stand Up To Cancer and others.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Nelson at the Division of Human Biology, Fred Hutchinson Cancer Research Center, 1100 Fairview Ave., Mailstop D4-100, Seattle, WA 98101; or at pritchard@fhcr.org.

Dr. Pritchard, Mateo, and Walsh and Drs. Offit, de Bono, and Nelson contributed equally to this article.

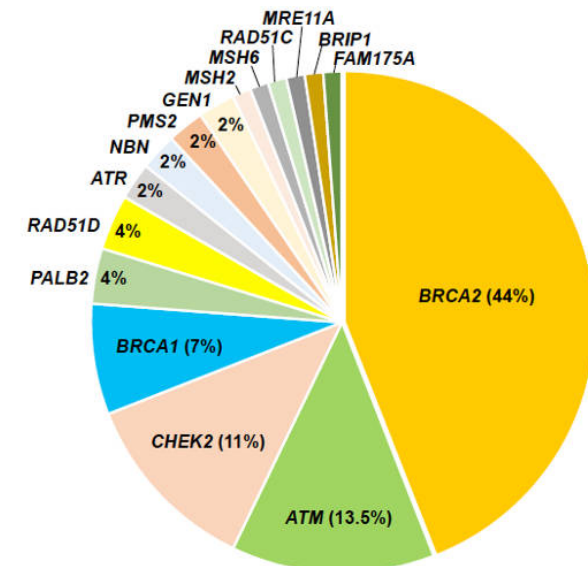
This article was published on July 6, 2016, at NEJM.org.

DOI: 10.1056/NEJMoa1603144

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Table 3. Germline DNA-Repair Gene Mutations in Seven Metastatic Prostate Cancer Case Series.

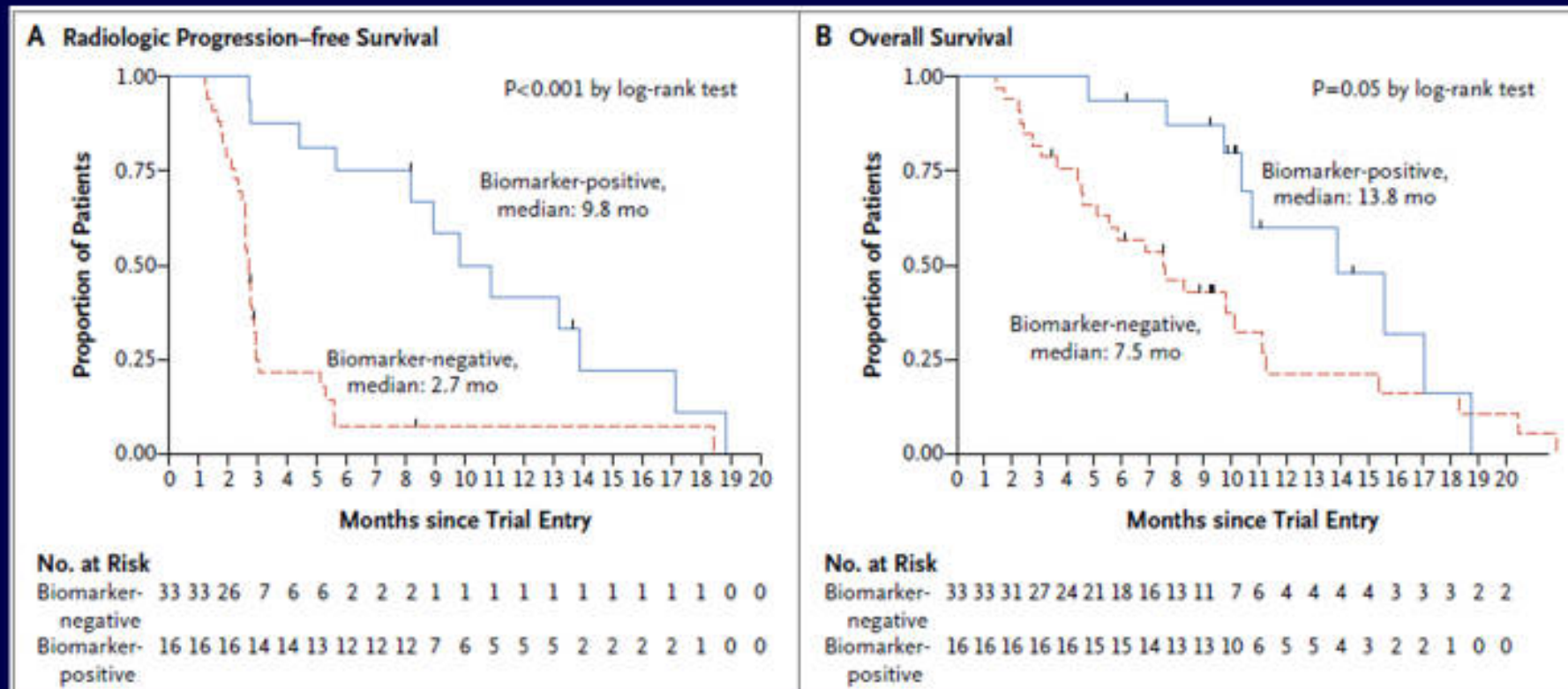
Case Series	Description	Patients	Patients with Mutations
		no.	no. (%)
1	Stand Up To Cancer–Prostate Cancer Foundation discovery series	150	15 (10.0)
2	Stand Up To Cancer–Prostate Cancer Foundation validation series	84	9 (10.7)
3	Royal Marsden Hospital	131	16 (12.2)
4	University of Washington	91	8 (8.8)
5	Weill Cornell Medical College	69	7 (10.1)
6	University of Michigan	43	4 (9.3)
7	Memorial Sloan Kettering Cancer Center	124	23 (18.5)
Total		692	82 (11.8)



Germline DNA sequenced on 700 mCRPC patients
Almost 1 in 7 men had a heritable deleterious mutation

PARP İnhibitörlerin Kullanım Temeli

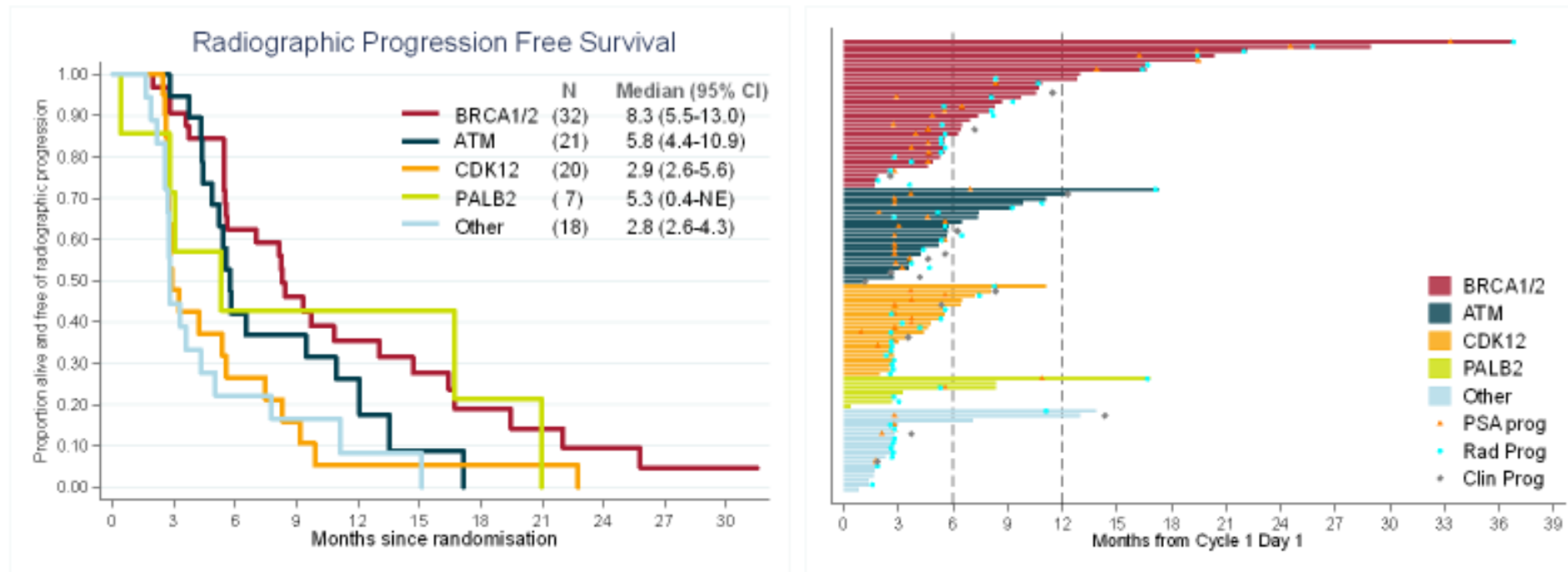
TOPARP-A: Survival with Olaparib by HR Deficiency



PARP İnhibitörlerin Kullanım Temeli

TOPARP Study

Results: Radiographic PFS per gene subgroup (ITT n=98)



*One patient with BRCA1/2+, CDK12+Other mutations and two patients with PALB2+Other mutations were analysed in the BRCA1/2 and PALB2, respectively.

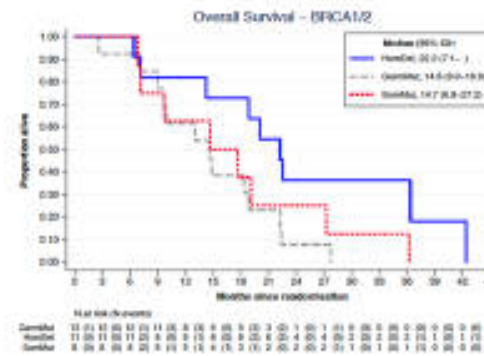
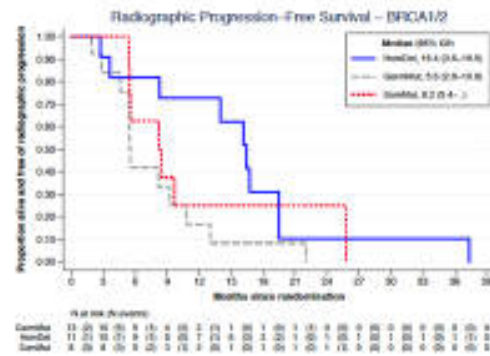
Mateo et al, Lancet Oncology, 2020
Courtesy of Johann de Bono, MBChB, MSc, PhD

PARP Inhibitörlerin Kullanım Temeli

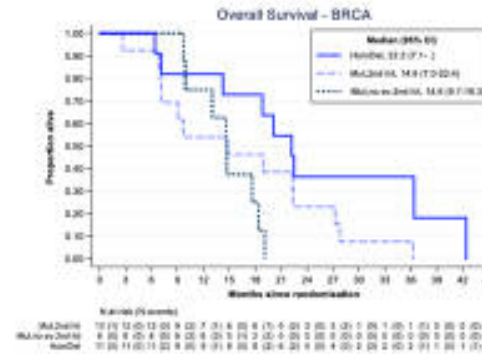
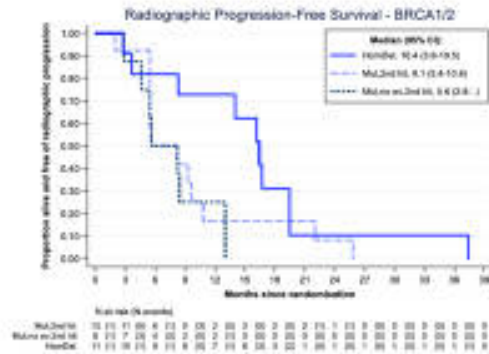
TOPARP Study

BRCA copy number and response on TOPARP-B

A : rPFS and OS in BRCA1/2 cohort depicting homozygous deletions, germline and somatic mutations: Tumours with homozygous BRCA deletions have the best outcomes



B : rPFS and OS in BRCA1/2 cohort depicting outcomes in homozygous deletions and mutated genes with or without a detectable second hit



Carreira et al, Cancer Discovery 2021

Courtesy of Johann de Bono, MBChB, MSc, PhD

PARP inhibitörlerin Kullanım Temeli

The NEW ENGLAND JOURNAL *of* MEDICINE

ESTABLISHED IN 1812

OCTOBER 29, 2015

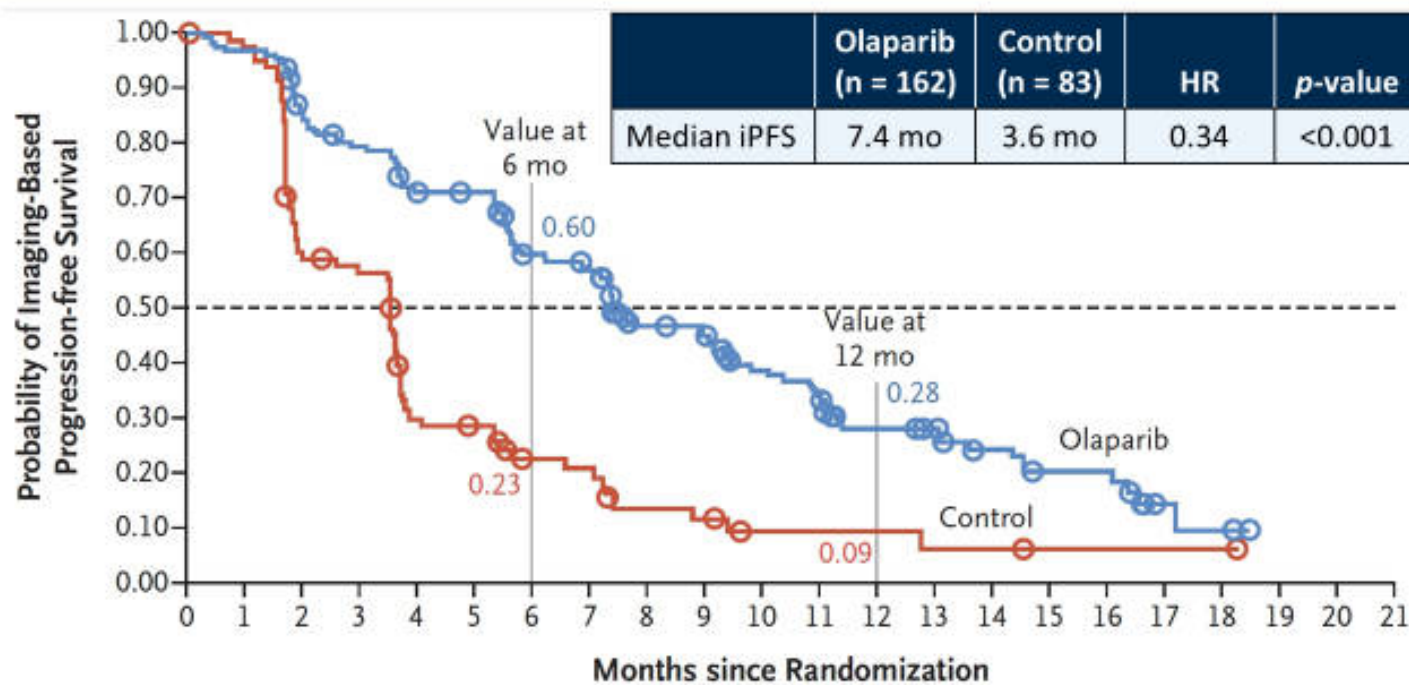
VOL. 373 NO. 18

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

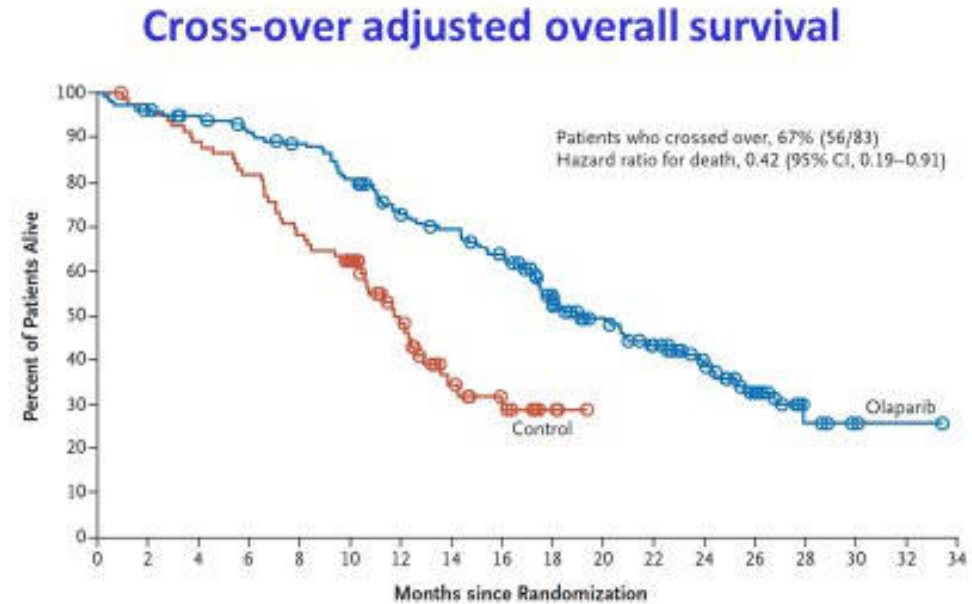
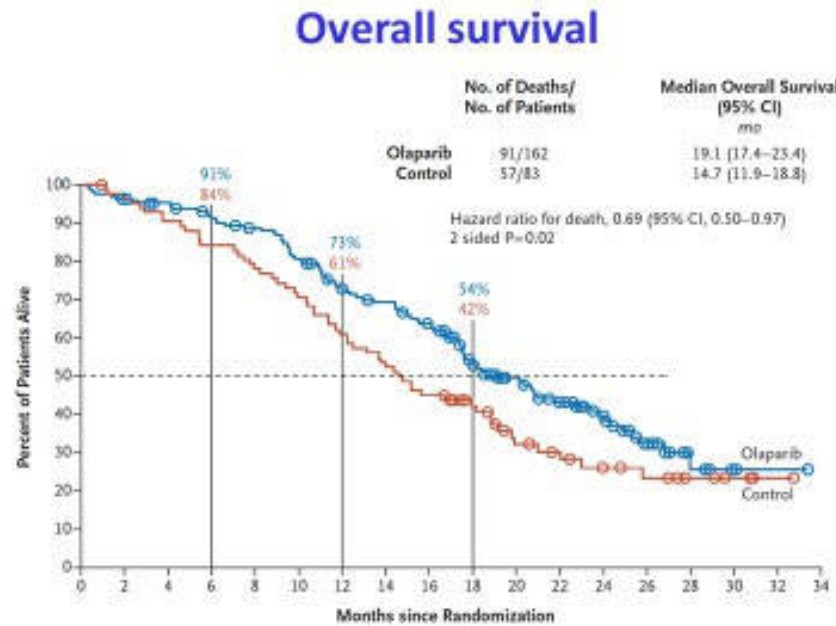
Evre IV Kastrasyona Dirençli Prostat Kanserinde Tedavi Seçeneği Olarak PARP İnhibitörü

PROfound Primary Endpoint: Imaging-Based PFS with Olaparib for Patients with mCRPC Who Had at Least 1 Alteration in BRCA1, BRCA2 or ATM (Cohort A)



Evre IV Kastrasyona Dirençli Prostat Kanserinde Tedavi Seçeneği Olarak PARP İnhibitörü

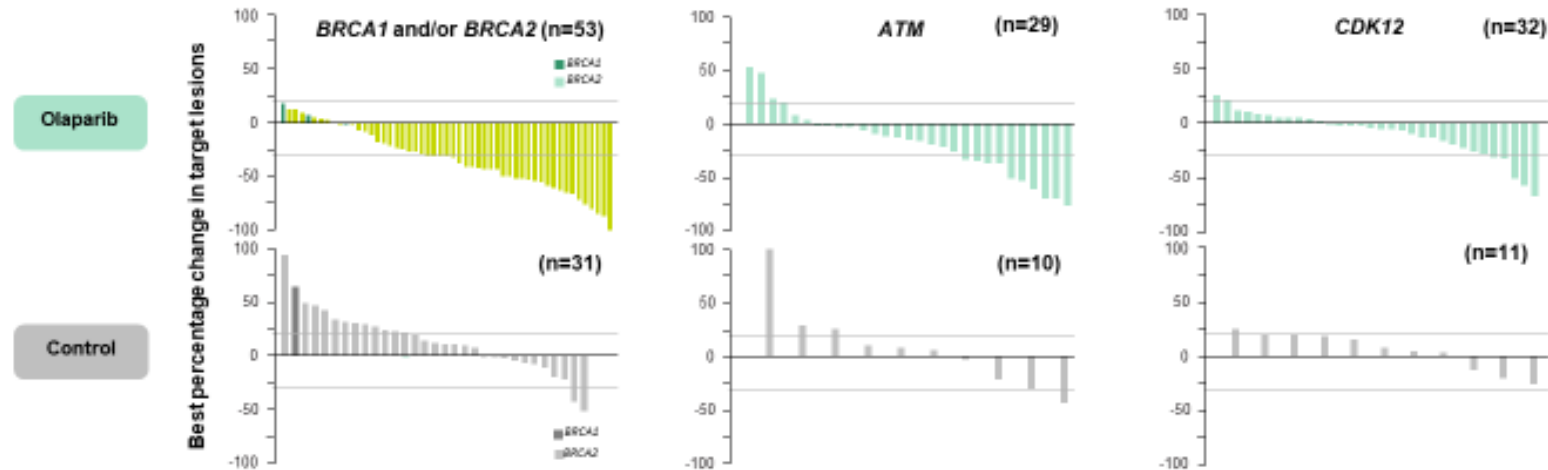
PROfound: OS with Olaparib in Patients with mCRPC Who Had at Least 1 Alteration in BRCA1, BRCA2 or ATM (Cohort A)



Evre IV Kastrasyona Dirençli Prostat Kanserinde Tedavi Seçeneği Olarak PARP İnhibitörü

Olaparib Antitumor Activity in PROfound

		Cohort A		Cohorts A+B		BRCA1 and/or BRCA2		ATM		CDK12	
		Olaparib (N=162)	Control (N=83)	Olaparib (N=256)	Control (N=131)	Olaparib (N=102)	Control (N=58)	Olaparib (N=62)	Control (N=24)	Olaparib (N=61)	Control (N=28)
rPFS	Median, months	7.4	3.6	5.8	3.5	9.8	3.0	5.4	4.7	5.1	2.2
	HR (95% CI)	0.34 (0.25–0.47)		0.49 (0.38–0.63)		0.22 (0.15–0.32)		1.04 (0.61–1.87)		0.74 (0.44–1.31)	
OS	Median OS, months	19.1	14.7	17.3	14.0	20.1	14.4	18.0	15.6	14.1	11.5
	HR (95% CI)	0.69 (0.50–0.97)		0.79 (0.61–1.03)		0.63 (0.42–0.95)		0.93 (0.53–1.75)		0.97 (0.57–1.71)	
ORR	Evaluable patients, n	84	43	138	67	57	33	30	10	34	12
	ORR, %	33.3	2.3	21.7	4.5	43.9	0	10.0	10.0	5.9	0
PSA	Evaluable patients, n	153	77	243	123	94	54	61	22	58	27
	Confirmed response, %	43.1	7.8	30.0	9.8	61.7	0	13.1	22.7	5.2	3.7
CTC	Evaluable patients, n	52	22	78	32	29	17	25	3	14	5
	Conversion, %	55.8	22.7	52.6	21.9	69.0	23.5	40.0	33.3	50.0	40.0



Evre IV Kastrasyona Dirençli Prostat Kanserinde Tedavi Seçeneği Olarak PARP İnhibitörü

rapid communications

Rucaparib in Men With Metastatic Castration-Resistant Prostate Cancer Harboring a *BRCA1* or *BRCA2* Gene Alteration

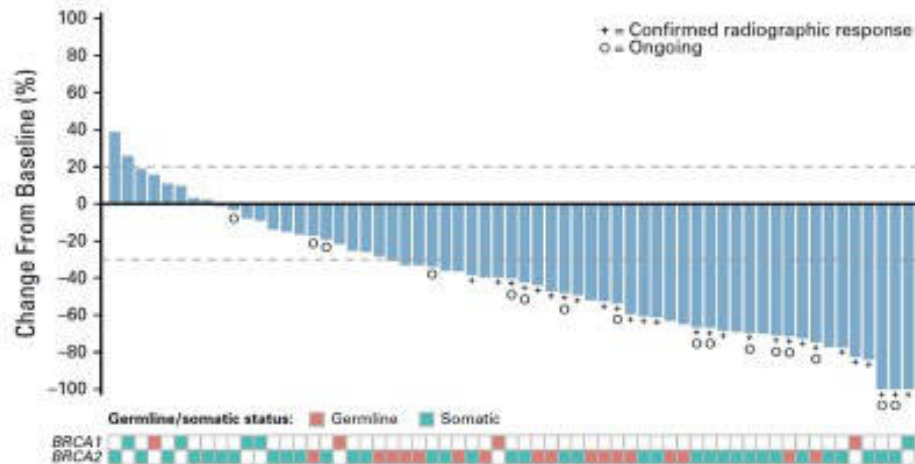
Wassim Abida, MD, PhD¹; Akash Patnaik, MD, PhD, MMSc²; David Campbell, MBBS³; Jeremy Shapiro, MBBS⁴; Alan H. Bryce, MD⁵; Ray McDermott, MD, PhD, MBA⁶; Brieuc Sautois, MD, PhD⁷; Nicholas J. Vogelzang, MD⁸; Richard M. Bambury, MD⁹; Eric Voog, MD¹⁰; Jingsong Zhang, MD, PhD¹¹; Josep M. Piulats, MD¹²; Charles J. Ryan, MD¹³; Axel S. Merseburger, PhD¹⁴; Gedske Daugaard, DMSc¹⁵; Axel Heidenreich, MD¹⁶; Karim Fizazi, MD, PhD¹⁷; Celestia S. Higano, MD¹⁸; Laurence E. Krieger, MBChB¹⁹; Cora N. Sternberg, MD²⁰; Simon P. Watkins, PhD²¹; Darrin Despain, MStat²²; Andrew D. Simmons, PhD²³; Andrea Loehr, PhD²³; Melanie Dowson, BA²⁴; Tony Golsorkhi, MD²⁵; and Simon Chowdhury, MD, PhD^{26,27}; on behalf of the TRITON2 investigators

J Clin Oncol 2020;38(22):3763-72.

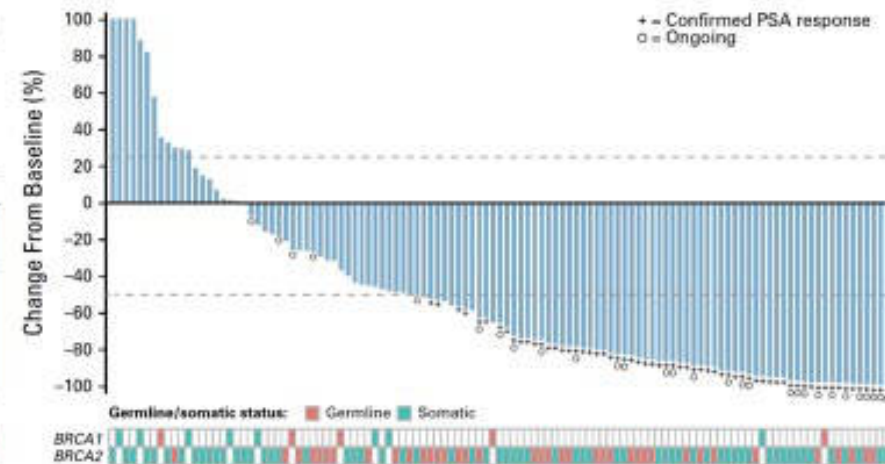
Evre IV Kastrasyona Dirençli Prostat Kanserinde Tedavi Seçeneği Olarak PARP İnhibitörü

TRITON2: Response to Rucaparib in Patients with mCRPC Harboring a BRCA1 or BRCA2 Gene Alteration

ORR per independent radiology review: 43.5%



Confirmed PSA response rate: 54.8%

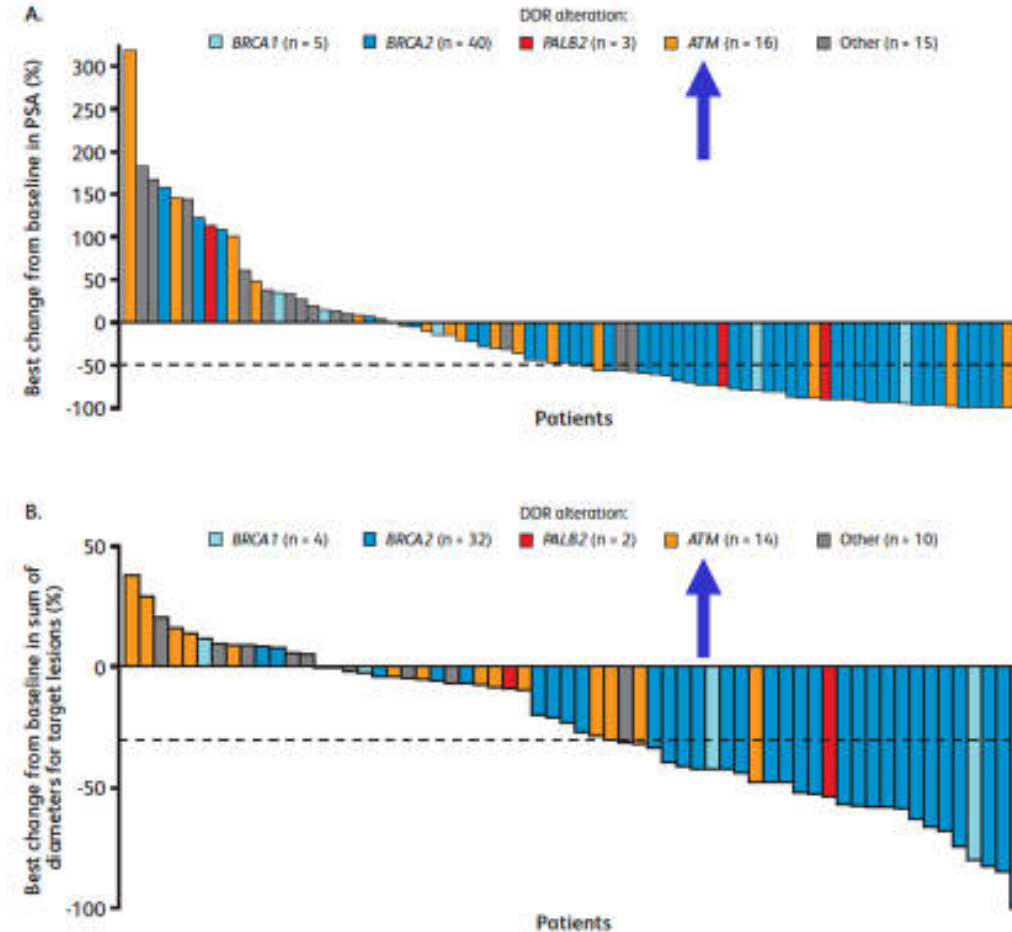


Evre IV Kastrasyona Dirençli Prostat Kanserinde Tedavi Seçeneği Olarak PARP İnhibitörü

Talazoparib in mCRPC (TALAPRO-1)

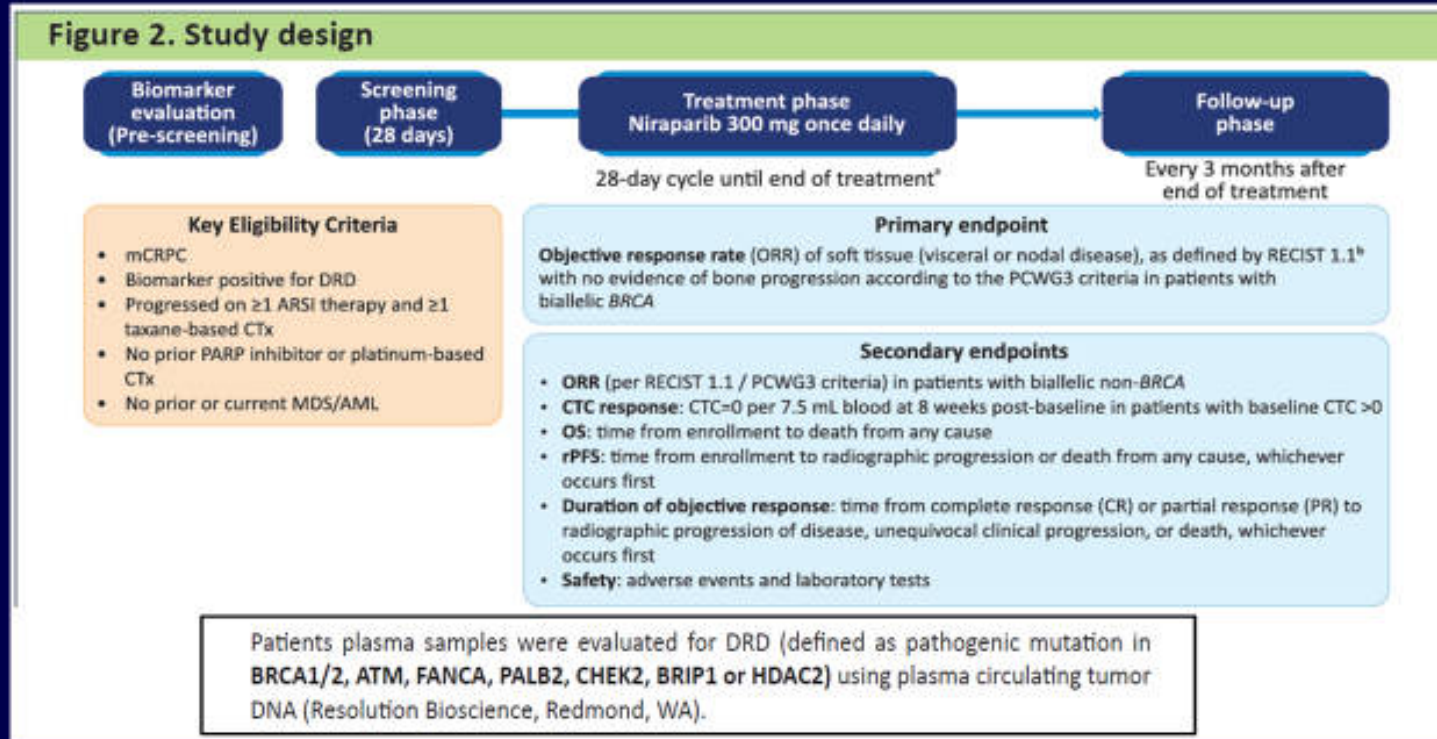
BRCA in blue
ATM loss in orange
PALB2 in red

Figure 4. Best Change From Baseline in A. PSA and B. RECIST^a



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Niraparib: GALAHAD trial interim results



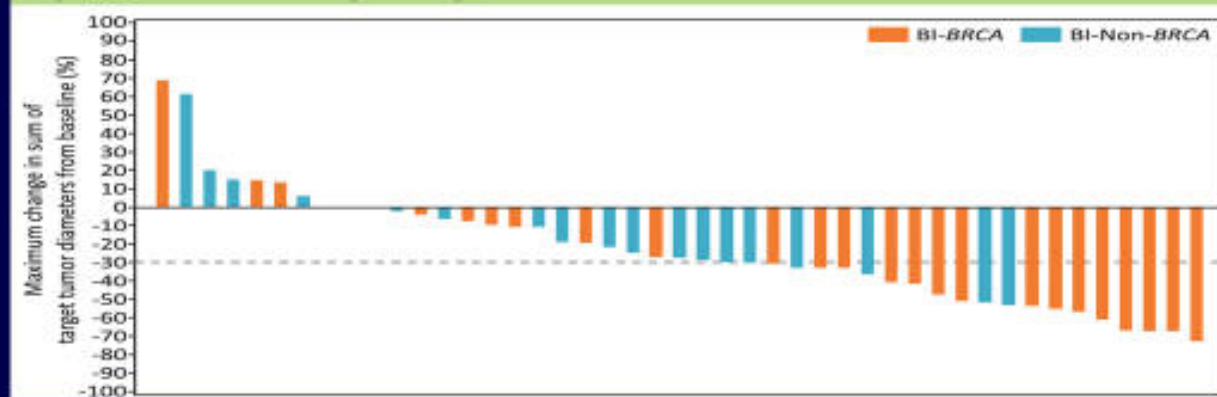
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GALAHAD: Objective responses

Table 2. Best overall response in biallelic DRD patients with measurable disease at baseline

Response, n (%)	Patients with measurable disease (n=51)	
	BRCA (n=29)	Non-BRCA* (n=22)
Complete Response (CR)	1 (3%)	0
Partial Response (PR)	11 (38%)	2 (9%)
Stable Disease (SD)	7 (24%)	10 (45%)
Progressive Disease (PD)	7 (24%)	7 (32%)

Figure 3. Maximum change in target lesion diameter



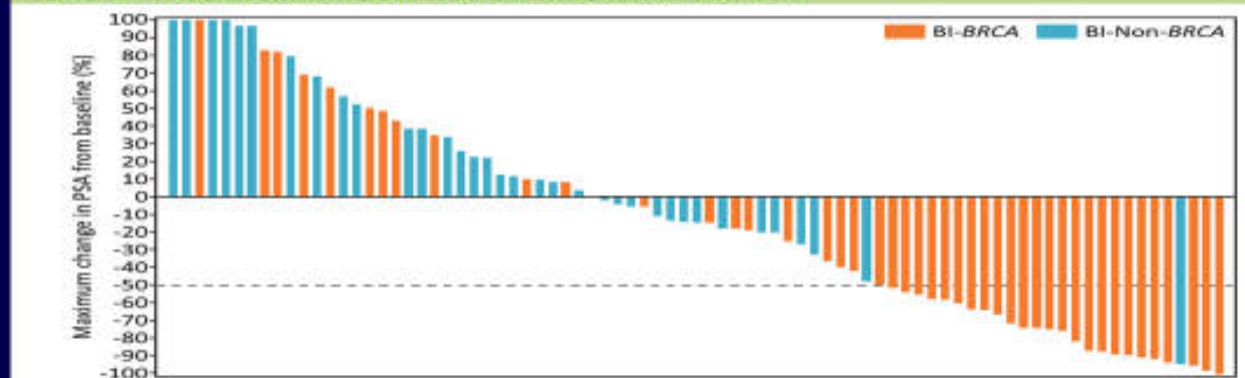
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GALAHAD: PSA responses

Table 3. Response in patients with mCRPC and biallelic DRD

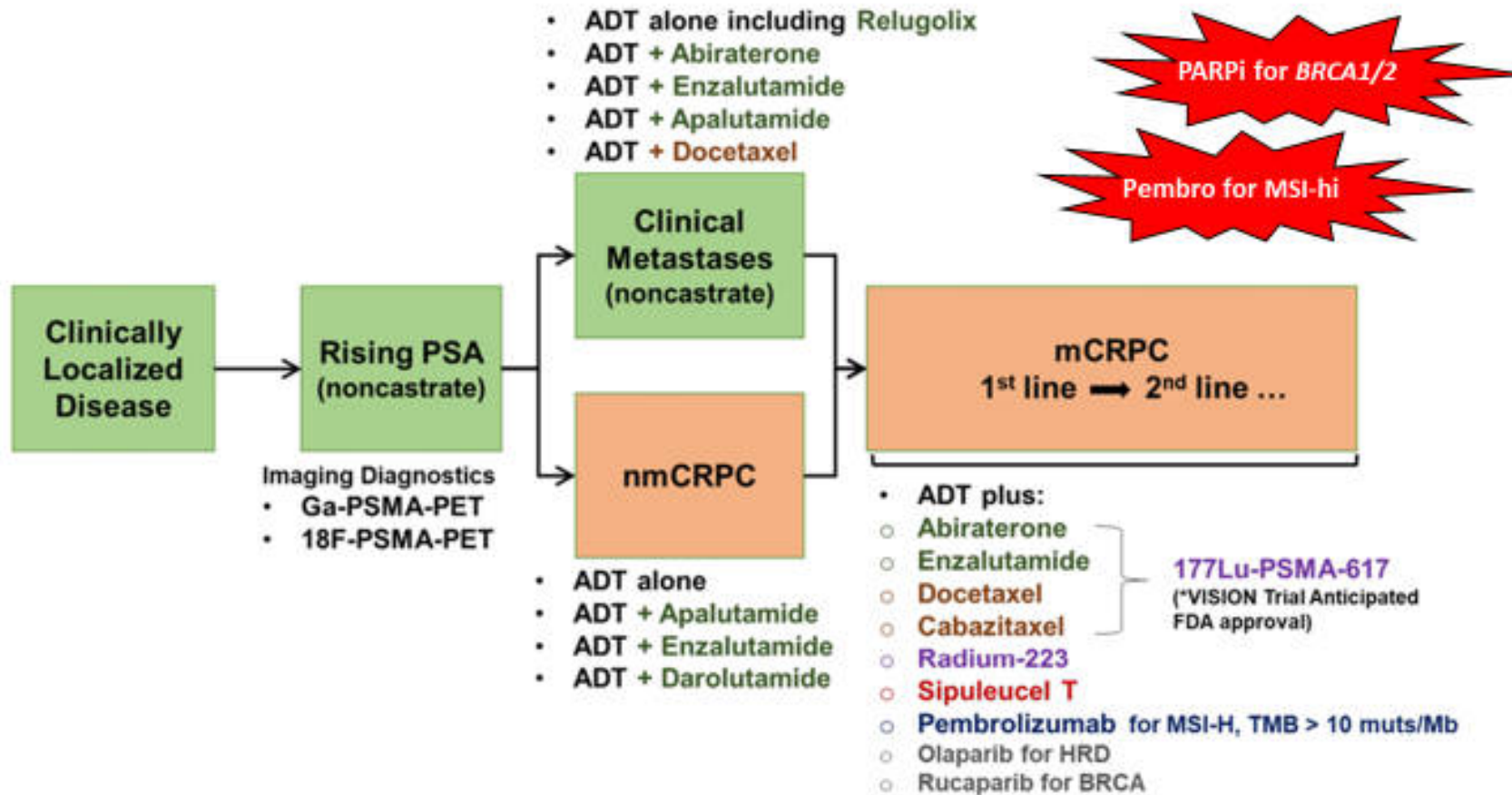
Response, n (%) [95% CI]	All biallelic DRD (n=81)	
	BRCA (n=46)	Non-BRCA* (n=35)
PSA ₅₀	23/46 (50%) [34.9, 65.1]	1/35 (3%) [0.1, 14.9]
CTC Conversion ^b	18/38 (47%) [31.0, 64.2]	5/24 (21%) [7.1, 42.2]
Composite response rate	29/46 (63%) [47.6, 76.8]	6/35 (17%) [6.6, 33.7]
Median duration of objective response, (range), mo	5.6 (3.5, 9.2)	3.8, 6.5 ^c -
Median rPFS, (95% CI), mo	8.2 (5.2, 11.1)	5.3 (1.9, 5.7)
Median OS, (95% CI), mo	12.6 (9.2, 15.7)	14.0 (5.3, 20.1)

Figure 4. Maximum change in PSA on niraparib treatment



Evre IV Kastrasyona Dirençli Prostat Kanserinde Tedavi Seçenekleri

Treatment Landscape for mCRPC



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PROpel: phase III trial of olaparib and abiraterone versus placebo and abiraterone as first-line therapy for patients with metastatic castration-resistant prostate cancer

Fred Saad, Andrew J. Armstrong, Antoine Thierry-Vuillemin, Mototsugu Oya, Eugenia Loreda,
Giuseppe Procopio, Juliana de Menezes, Gustavo Giroto, Cagatay Arslan, Niven Mehra,
Francis Parnis, Emma Brown, Friederike Schlürmann, Jae Young Joung, Mikio Sugimoto,
Christian Poehlein, Elizabeth A. Harrington, Chintu Desai, Jinyu Kang, and Noel Clarke

Genitourinary Cancers Symposium 2022;Abstract 11.

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

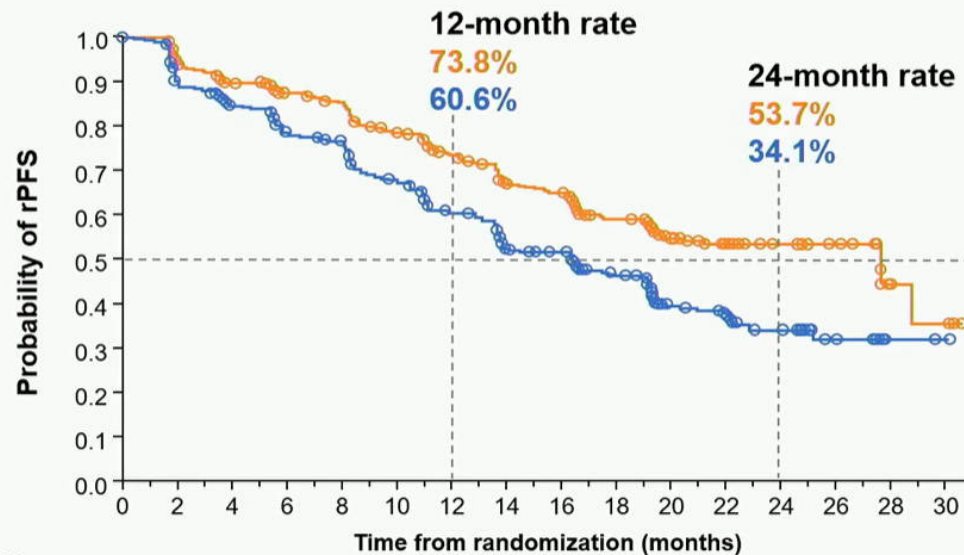
- Time to first subsequent therapy or death (TFST)
- Time to second progression or death (PFS2)
- Objective response rate (ORR)
- HRRm[†] prevalence (retrospective testing)
- Health-related quality of life
- Safety and tolerability

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 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†	

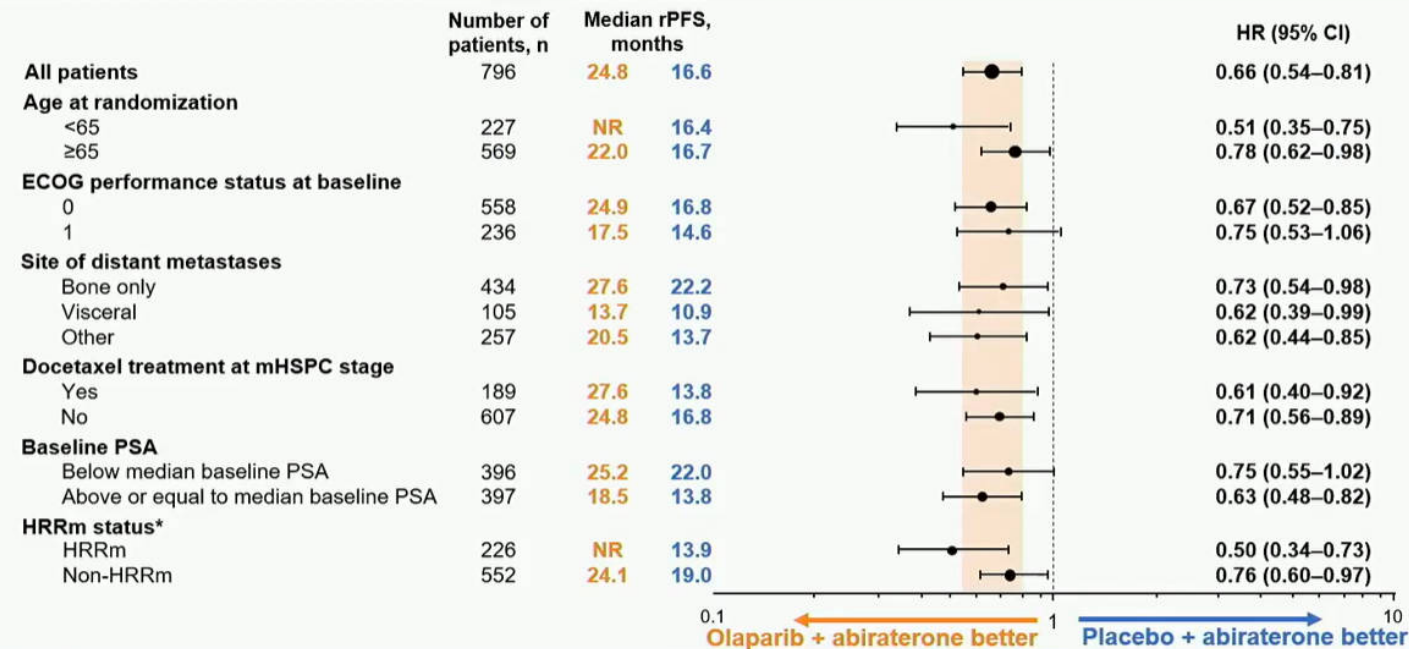
Median rPFS improvement of 11.2 months
favors olaparib + abiraterone‡

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

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

PROpel: subgroup analysis of rPFS

rPFS benefit observed across all pre-specified subgroups



Global interaction test not significant at 10% level. *The HRRm status of patients in PROpel was determined retrospectively using results from tumor tissue and plasma ctDNA HRRm tests. Patients were classified as HRRm if (one or more) HRR gene mutation was detected by either test; patients were classified as non-HRRm patients if no HRR gene mutation was detected by either test; patients were classified as unknown HRRm if no valid HRR test result from either test was achieved. 18 patients did not have a valid HRR testing result from either a tumor tissue or ctDNA test and were excluded from the subgroup analysis. This subgroup analysis is post hoc exploratory analysis. Please access the Supplement via the QR code at the end of this presentation for more details. NR, not reached.

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

ASCO Genitourinary
Cancers Symposium

Phase 3 MAGNITUDE study: First results of niraparib (NIRA) with abiraterone acetate and prednisone (AAP) as first-line therapy in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) with and without homologous recombination repair (HRR) gene alterations

Kim N. Chi,¹ Dana E. Rathkopf,² Matthew R. Smith,³ Eleni Efstathiou,⁴ Gerhard Attard,⁵ David Olmos,⁶ Ji Youl Lee,⁷ Eric J. Small,⁸ Andrea J. Pereira de Santana Gomes,⁹ Guilhem Roubaud,¹⁰ Marniza Saad,¹¹ Bogdan Zurawski,¹² Valerii Sakalo,¹³ Gary E. Mason,¹⁴ Adam del Corral,¹⁵ George Wang,¹⁴ Daphne Wu,¹⁶ Brooke Diorio,¹⁷ Angela Lopez-Gitlitz,¹⁶ Shahneen Sandhu¹⁸

¹University of British Columbia, BC Cancer – Vancouver Center, Vancouver, BC, Canada; ²Memorial Sloan Kettering Cancer Center and Weill Cornell Medicine, New York, NY, USA; ³Massachusetts General Hospital Cancer Center and Harvard Medical School, Boston, MA, USA; ⁴Houston Methodist Cancer Center, Houston, TX, USA; ⁵University College London, London, UK; ⁶Department of Medical Oncology, Hospital Universitario 12 de Octubre, Instituto de Investigación Sanitaria Hospital 12 de Octubre (imas12), Madrid, Spain; ⁷Department of Urology Cancer Center, Seoul St. Mary's Hospital, The Catholic University of Korea, Seoul, South Korea; ⁸Helen Diller Family Comprehensive Cancer Center, University of California San Francisco, San Francisco, CA, USA; ⁹Liga Norte Rio-grandense Contra o Câncer, Natal, Brazil; ¹⁰Department of Medical Oncology, Institut Bergonié, Bordeaux, France; ¹¹Department of Clinical Oncology, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia; ¹²Department of Outpatient Chemotherapy, Professor Franciszek Lukaszczyk Oncology Center, Bydgoszcz, Poland; ¹³Institute of Urology named after Academician OF Vozianov of NAMS of Ukraine, Kyiv, Ukraine; ¹⁴Janssen Research & Development, Spring House, PA, USA; ¹⁵Janssen Research & Development, Bridgewater, NJ, USA; ¹⁶Janssen Research & Development, Los Angeles, CA, USA; ¹⁷Janssen Research & Development, Titusville, NJ, USA; ¹⁸Peter MacCallum Cancer Center and the University of Melbourne, Melbourne, Australia

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ASCO Genitourinary
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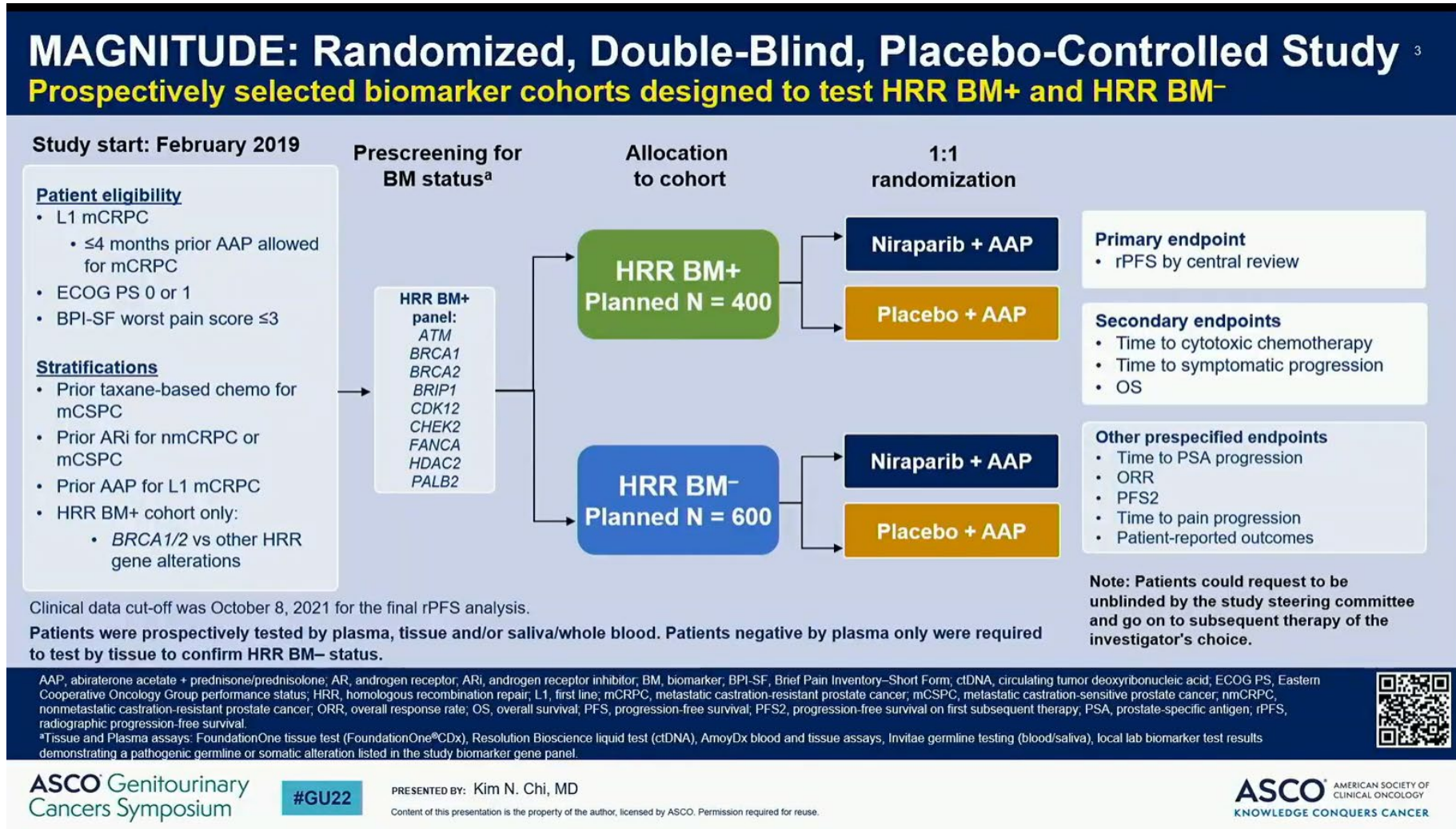
#GU22

PRESENTED BY: Kim N. Chi, MD

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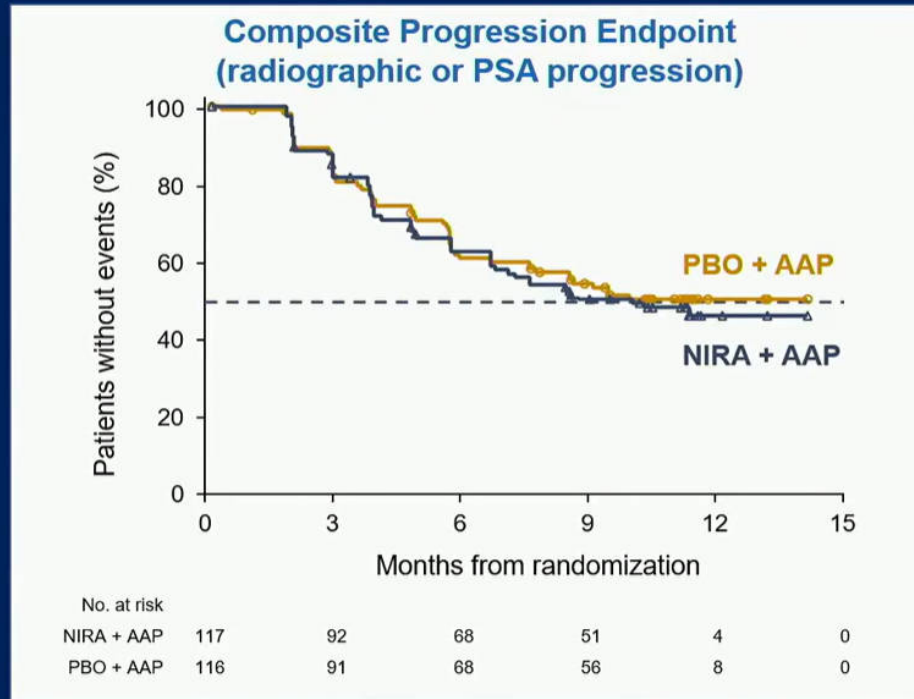
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5

MAGNITUDE **HRR BM⁻**: Prespecified Early Futility Analysis No Benefit of NIRA + AAP in HRR BM⁻ Patients



- Composite endpoint^a (N = 233)
HR = 1.09^b (95% CI 0.75-1.59)
[futility was defined as ≥ 1]
- Additional grade 3/4 toxicity was observed using NIRA + AAP vs PBO + AAP
- With added toxicity and no added efficacy in patients with HRR BM⁻ mCRPC, the IDMC recommend stopping enrollment in this cohort

^bBreakdown of composite endpoint events
83 PSA events (HR = 1.03, 95% CI 0.67-1.59)
65 rPFS events (HR = 1.03, 95% CI 0.63-1.67)

^arPFS or PSA progression, whichever occurred first.

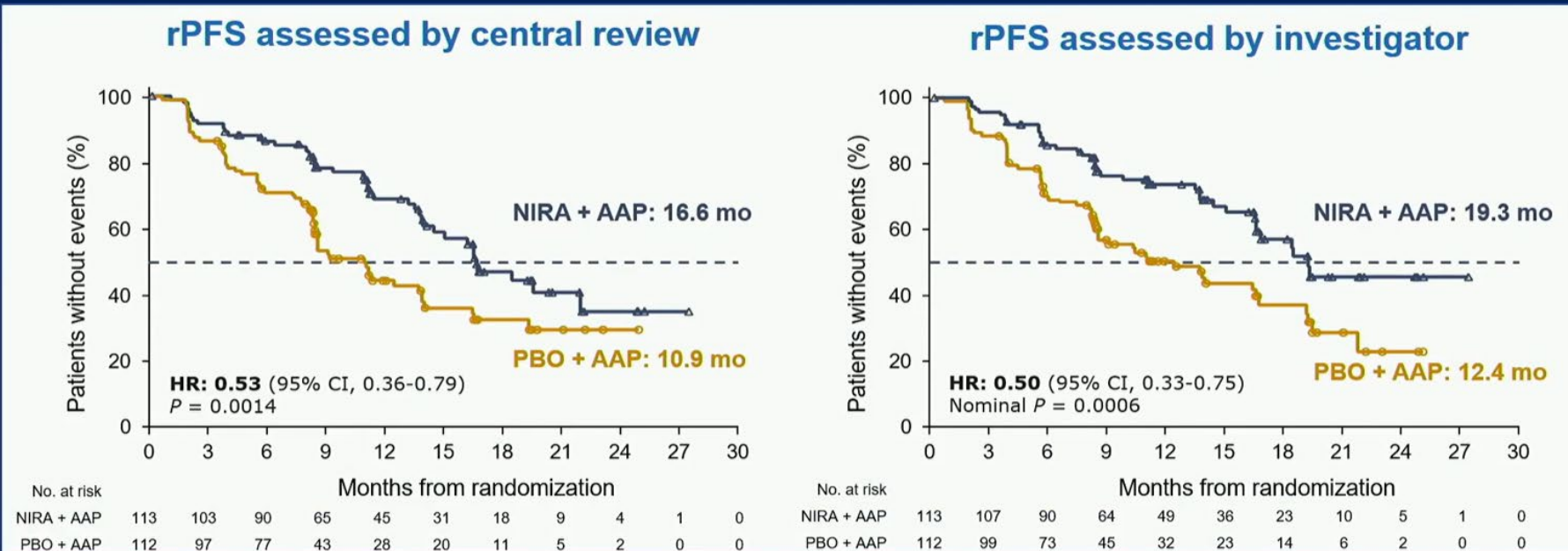
AAP, abiraterone acetate + prednisone/prednisolone; AE, adverse event; BM, biomarker; CI, confidence interval; HR, hazard ratio; HRR, homologous recombination repair; IDMC, independent data monitoring committee; mCRPC, metastatic castration-resistant prostate cancer; NIRA, niraparib; PBO, placebo; PSA, prostate specific antigen; rPFS, radiographic progression free survival



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

7

MAGNITUDE **BRCA1/2-mutated**: Primary Endpoint NIRA + AAP Significantly Reduced the Risk of Progression or Death by 47%



Median follow-up 16.7 months

AAP, abiraterone acetate + prednisone/prednisolone; CI, confidence interval; HR, hazard ratio; NIRA, niraparib; PBO, placebo; rPFS, radiographic progression-free survival.

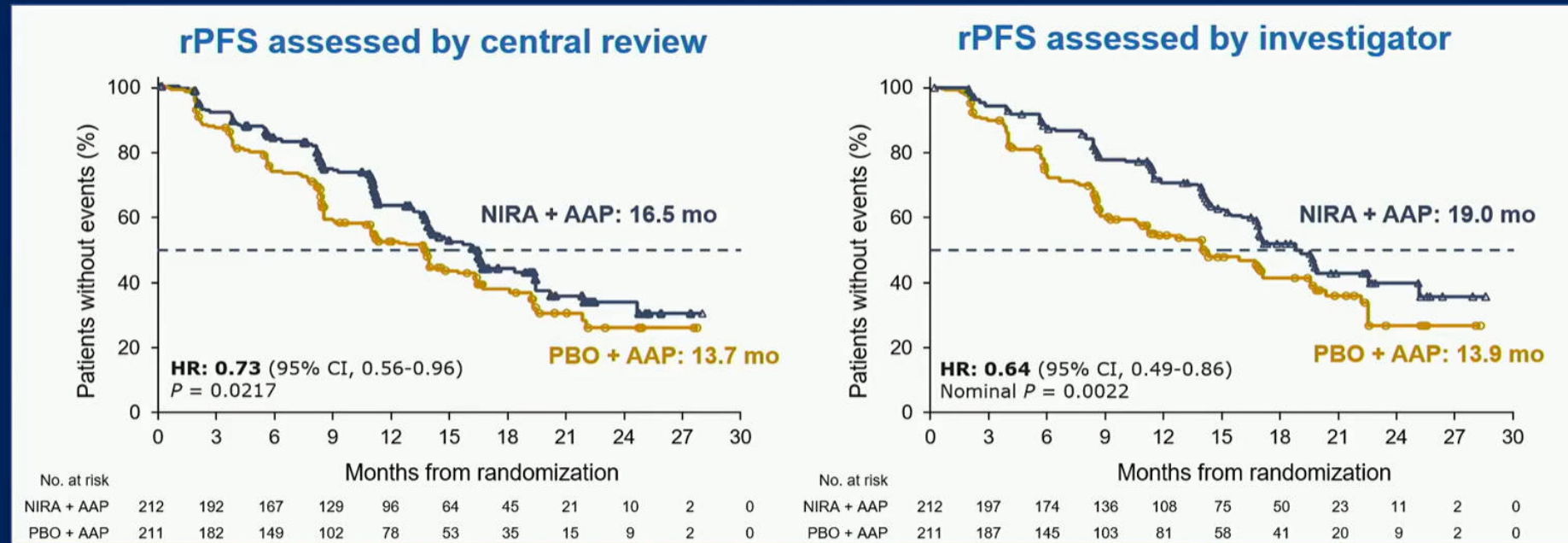


Evre IV Kastrasyona Dirençli Prostat Kanserinde Tedavi Seçeneği Olarak PARP İnhibitörü+Abireteron

8

MAGNITUDE All HRR BM+: Primary Endpoint

NIRA + AAP Significantly Reduced the Risk of Progression or Death by 27%



Median follow-up 18.6 months

AAP, abiraterone acetate + prednisone/prednisolone; BM, biomarker; CI, confidence interval; HR, hazard ratio; HRR, homologous recombination repair; NIRA, niraparib; PBO, placebo; rPFS, radiographic progression-free survival.

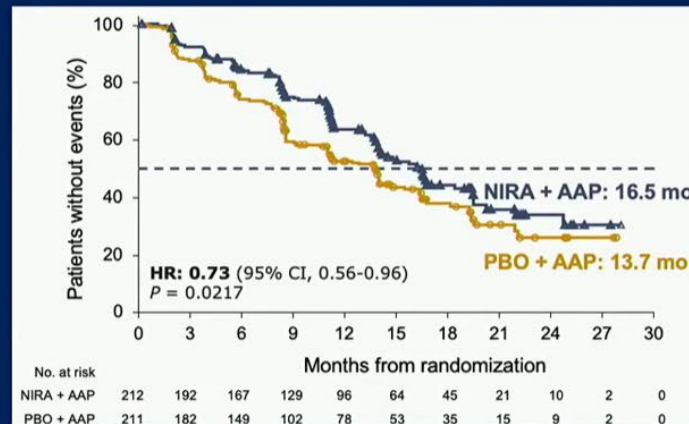


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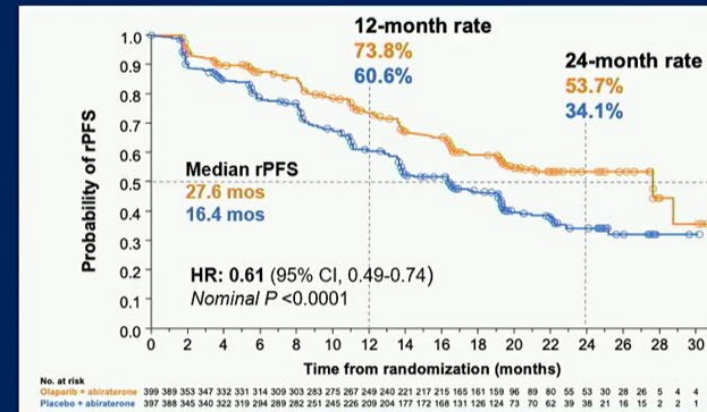
rPFS by Blinded Independent Central Review

MAGNITUDE AII HRR+



Median rPFS improvement of **2.8 mos** in combination arm (**5.1 mos** by investigator review)

PROpel All Patients



Median rPFS improvement of **11.2 mos** in combination arm (**8.2 mos** by investigator review)

Evre IV Kastrasyona Dirençli Prostat Kanserinde Sisplatin Etkinliği

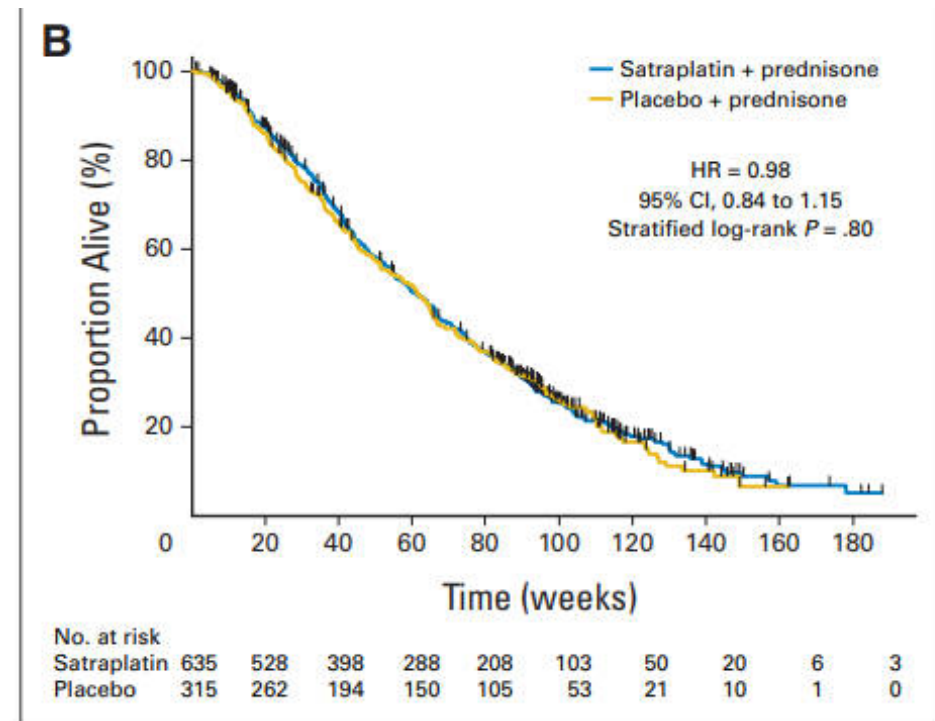
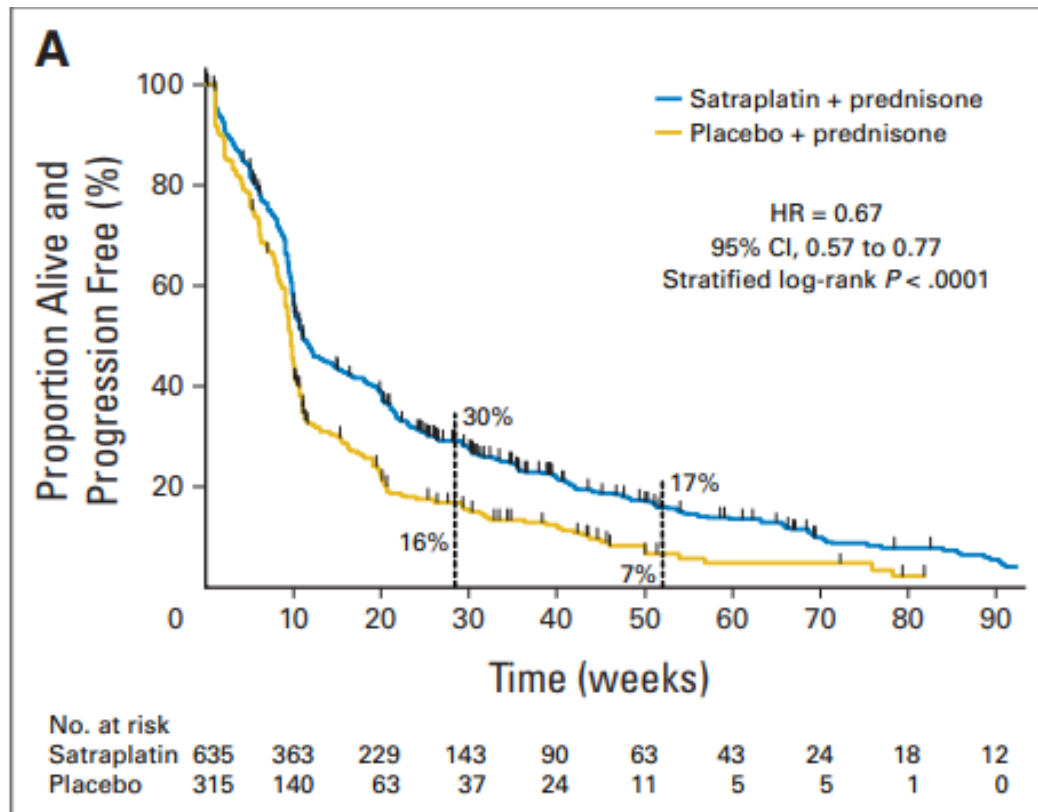


Fig 2. (A) Progression-free survival (intent-to-treat population) and (B) overall survival (intent-to-treat population). HR, hazard ratio.

DNA Repair Gen Değişikliği Olan Hastalarda RA-223 etkinliği

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

21

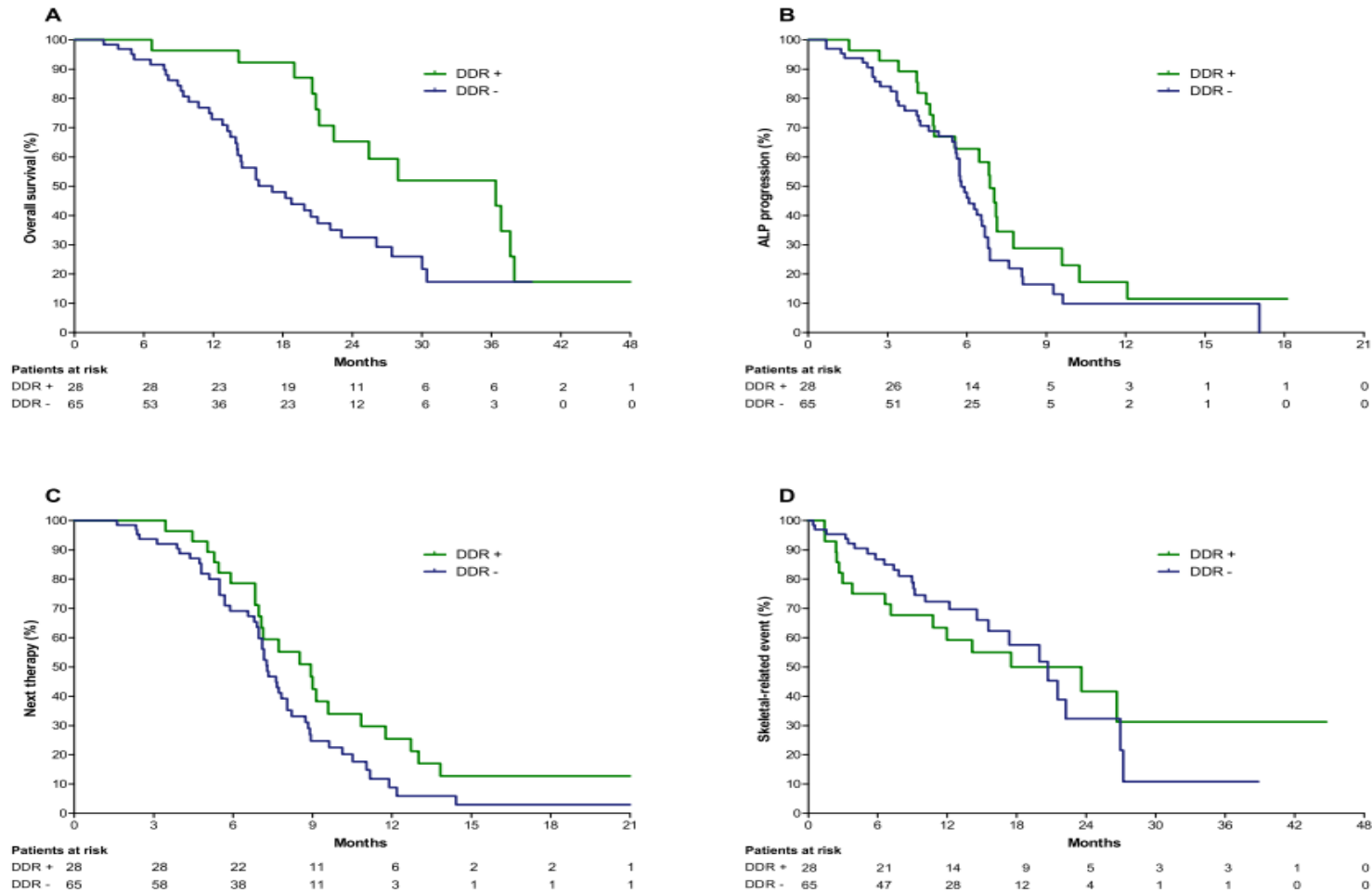


Fig. 2. Kaplan–Meier curves, stratified by DNA damage repair (DDR) mutation status, A. Overall survival, B. Time to alkaline phosphatase (ALP) progression, C. Time to initiation of next systemic therapy. D. Time to first skeletal-related events (SRE).

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*
- 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

* 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).

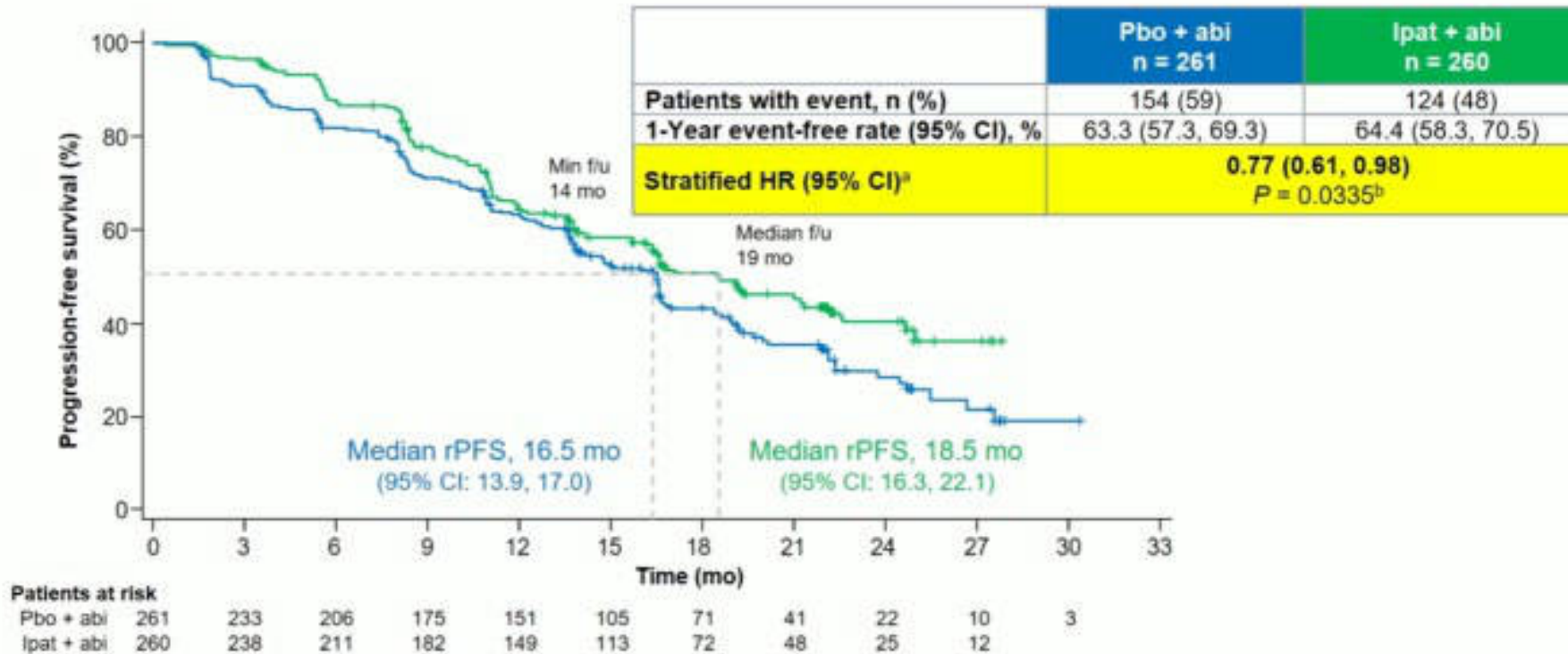
^b Abiraterone (1000 mg qd) plus prednisone/prednisolone (5 mg bid).

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

Kastrasyona Dirençli Prostat Kanseri

PI3K/AKT inhibisyonu

rPFS in the PTEN-loss by IHC population



Data cutoff, 16 Mar 2020; median f/u 19 months. f/u, follow-up.

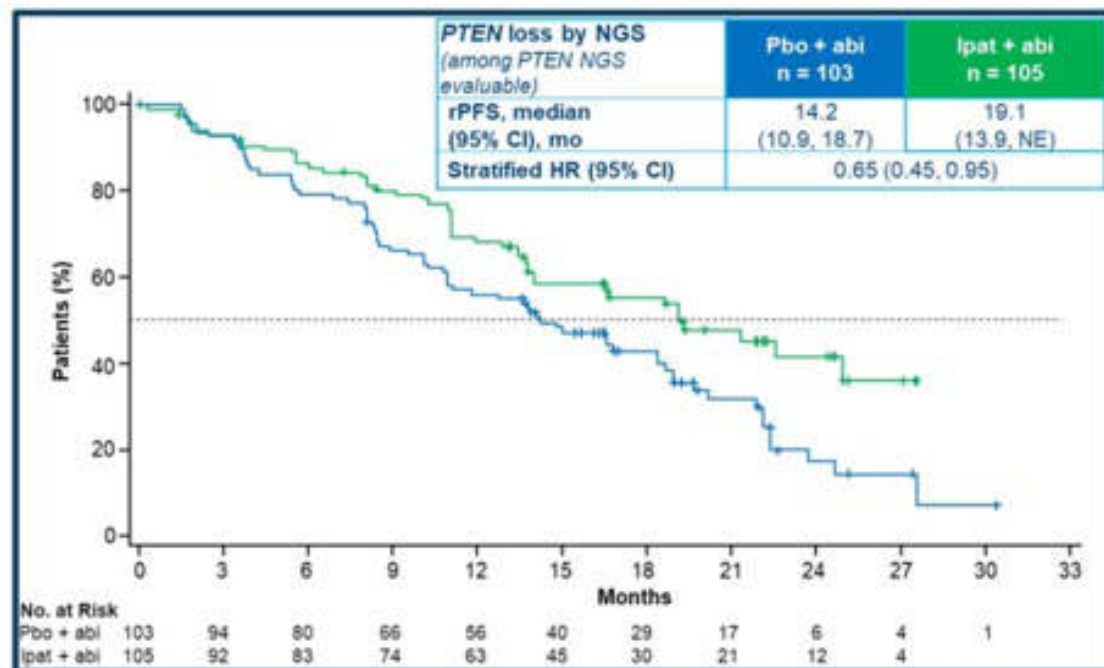
^a Stratified for prior taxane-based therapy and PSA-only progression factor.

^b Statistically significant at $\alpha = 0.05$ level.

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. 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 LB44.

Presented By Johann De Bono at 2021 Genitourinary Cancers Symposium

Kastrasyona Dirençli Prostat Kanseri

PI3K/AKT inhibisyonu

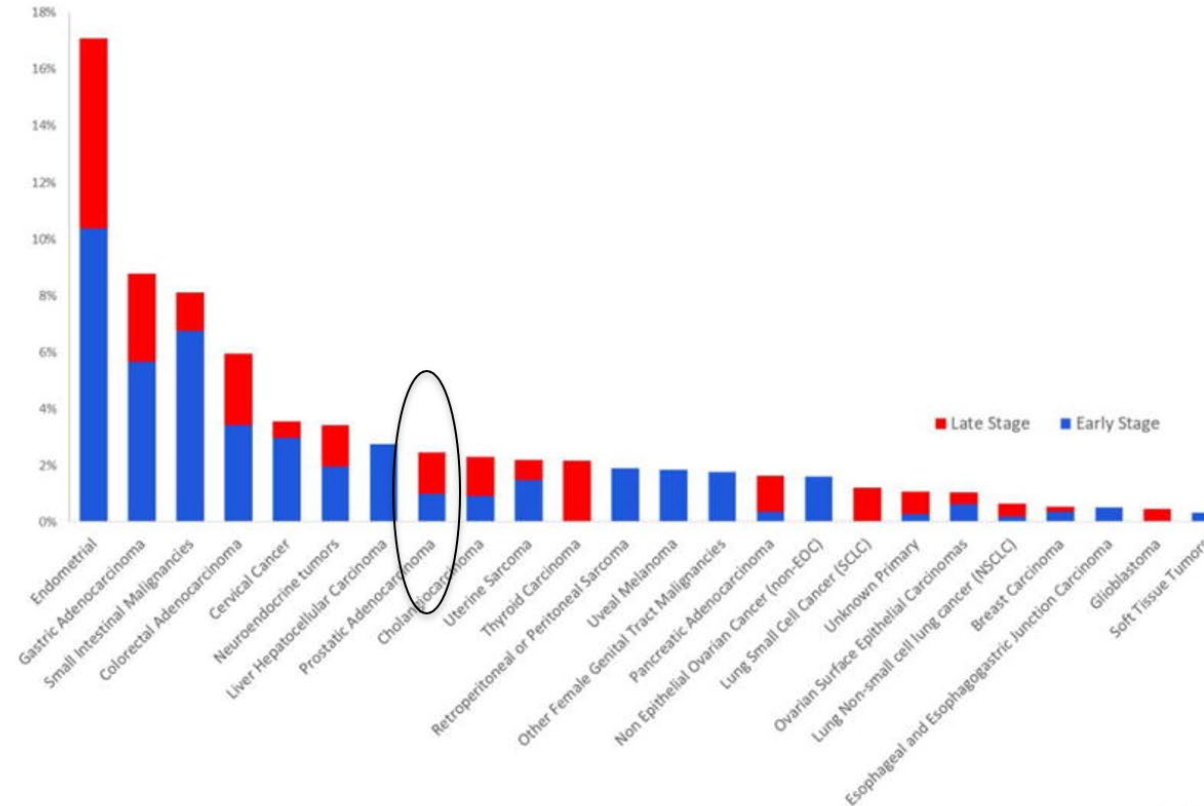
	<i>PIK3CA/AKT1/PTEN</i> altered by NGS n=250		<i>PIK3CA/AKT1/PTEN</i> WT by NGS n=493	
	Pbo + Abi	Ipat + Abi	Pbo + Abi	Ipat + Abi
n	122	128	257	236
Median OS (95% CI), mo	29.5 (24.6, 36.1)	37.1 (31.4, NE)	40.2 (34.3, 44.7)	40.3 (36.0, NE)
HR (95% CI) ^a	0.73 (0.52, 1.04)		0.98 (0.75, 1.27)	
Median TPP, (95% CI), mo	14.8 (11.1, 24.0)	23.3 (12.9, 41.5)	38.9 (21.2, NE)	26.0 (18.9, NE)
HR (95% CI) ^a	0.69 (0.46, 1.03)		1.10 (0.81, 1.50)	
Confirmed ORR, n/N (%) ^b	20/50 (40)	32/48 (67)	50/102 (49)	48/83 (58)
Duration of response (95% CI), mo	14.5 (8.2, 21.4)	23.3 (18.2, NE)	16.3 (12.8, 20.2)	15.5 (9.2, 20.4)

NE, not estimable. ^aUnstratified. ^bPer RECIST 1.1 and PCWG3 in pts with baseline lesions.

MSI High Prostat Kanserinde Tedavi Seçenekleri



Mismatch Repair Deficiency



Le et al. Science 2017

MSI High Prostat Kanserinde Tedavi Seçenekleri



MSI-H and MRD

- 1346 patients with PC underwent paired tumor and germline sequencing
- 32 of 1033 (3.1%) had microsatellite instability–high or mismatch repair deficient disease
- 7/32 (21.9%) carried a germline mutation in a Lynch syndrome–associated gene.
- Five of 11 patients who received an anti–PD-1/PD-L1 agent had durable clinical benefit.

MSI High Prostat Kanserinde Tedavi Seçenekleri

Pembrolizumab Monotherapy in mCRPC: KEYNOTE-199

Variable	Cohort 1 (PD-L1 positive)	Cohort 2 (PD-L1 negative)	Cohort 3 (bone predominant)
Response assessed per RECIST v1.1 by central radiology review			
No. of patients	133	66	59
ORR, No. (%; 95% CI)	7 (5; 2 to 11)	2 (3; < 1 to 11)	—
DCR,* No. (%; 95% CI)	13 (10; 5 to 16)	6 (9; 3 to 19)	13 (22; 12 to 35)
Response assessed per PCWG3-modified RECIST v1.1 by central radiology review			
No. of patients	133	66	59
ORR, No. (%; 95% CI)	7 (5; 2 to 11)	2 (3; < 1 to 11)	—
DCR,* No. (%; 95% CI)	17 (13; 8 to 20)	12 (18; 10 to 30)	23 (39; 27 to 53)
PSA response† in patients with baseline PSA measurement			
No. of patients	124	60	59
Response rate, No. (%; 95% CI)	8 (6; 3 to 12)	5 (8; 3 to 18)	1 (2; 0 to 9)

11% ORR in BRCA1/2/ATM mutated patients, 0-3% in other men
2 responders were MSI-high

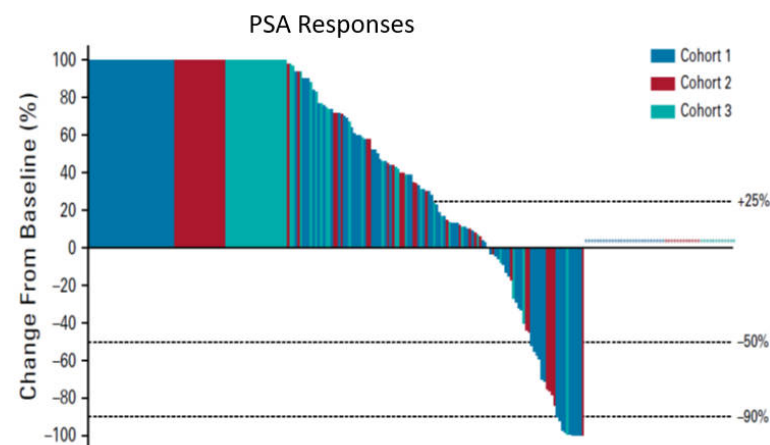
* % of pts with confirmed CR or PR of any duration or SD or noncomplete response or nonprogressive disease for ≥ 6 mo. Pts who died after month 6 without evidence of PD before death were considered to have SD for ≥ 6 mo.

† % of pts with a reduction in PSA level from baseline by $\geq 50\%$ as confirmed on an additional PSA evaluation performed ≥ 3 weeks later

Cohort 1: PD-L1 (+) prior ARSI/taxane, measurable dz

Cohort 2: PD-L1 (-) prior ARSI/taxane, measurable dz

Cohort 3: bone mCRPC, prior ARSI/taxane



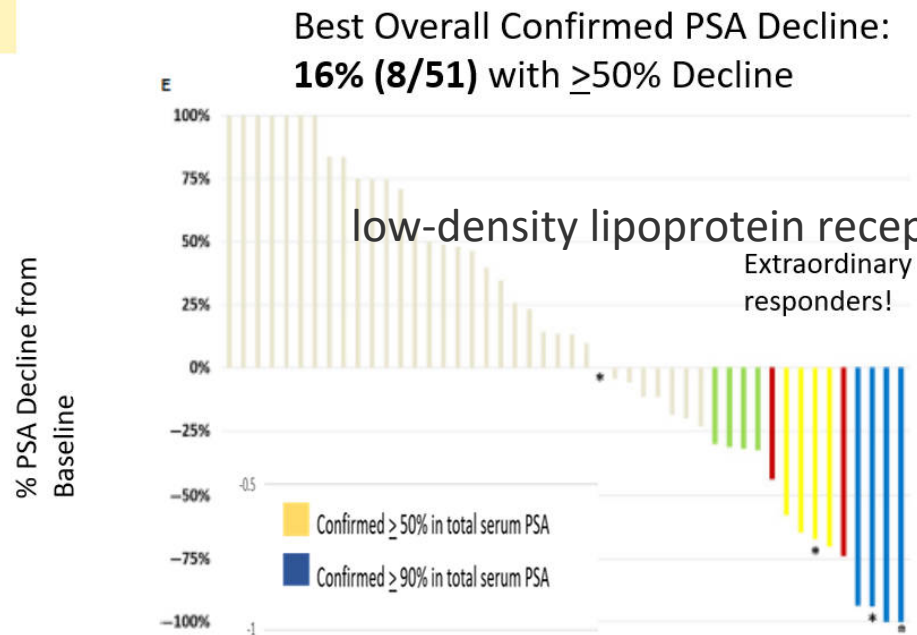
Antonarakis et al JCO 2019



Memorial Sloan Kettering
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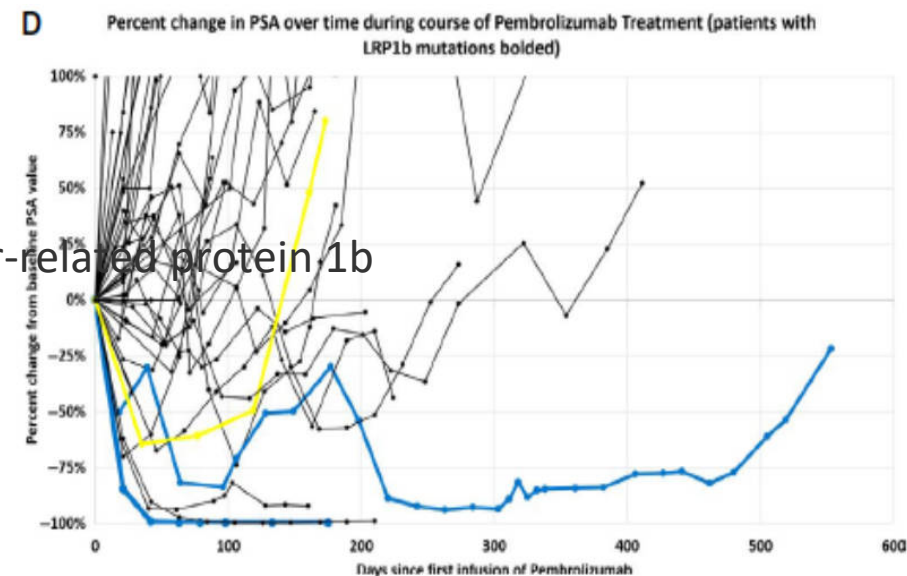
MSI High Prostat Kanserinde Tedavi Seçenekleri

Duke Experience with Pembrolizumab for mCRPC



Extraordinary responders: enriched for certain genetic subtypes:
MSH2 loss and MSI high (2), **LRP1b loss** (66% response rate, n=3)

low-density lipoprotein receptor-related protein 1b



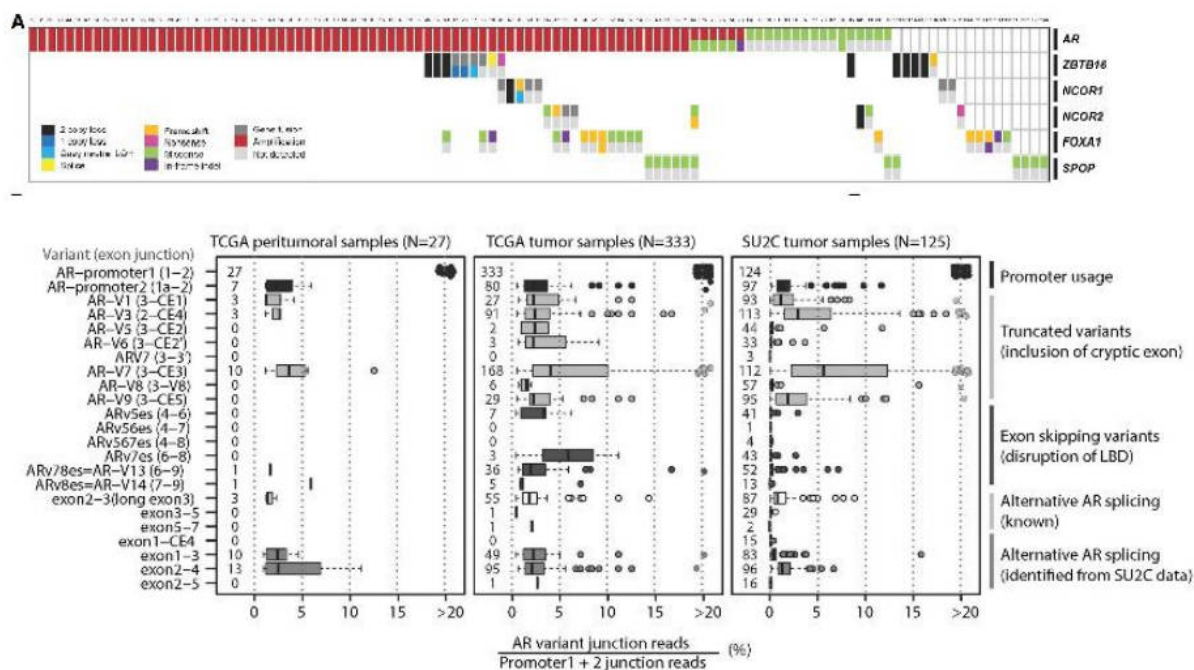
Tucker M...Armstrong AJ Cancer Med 2019



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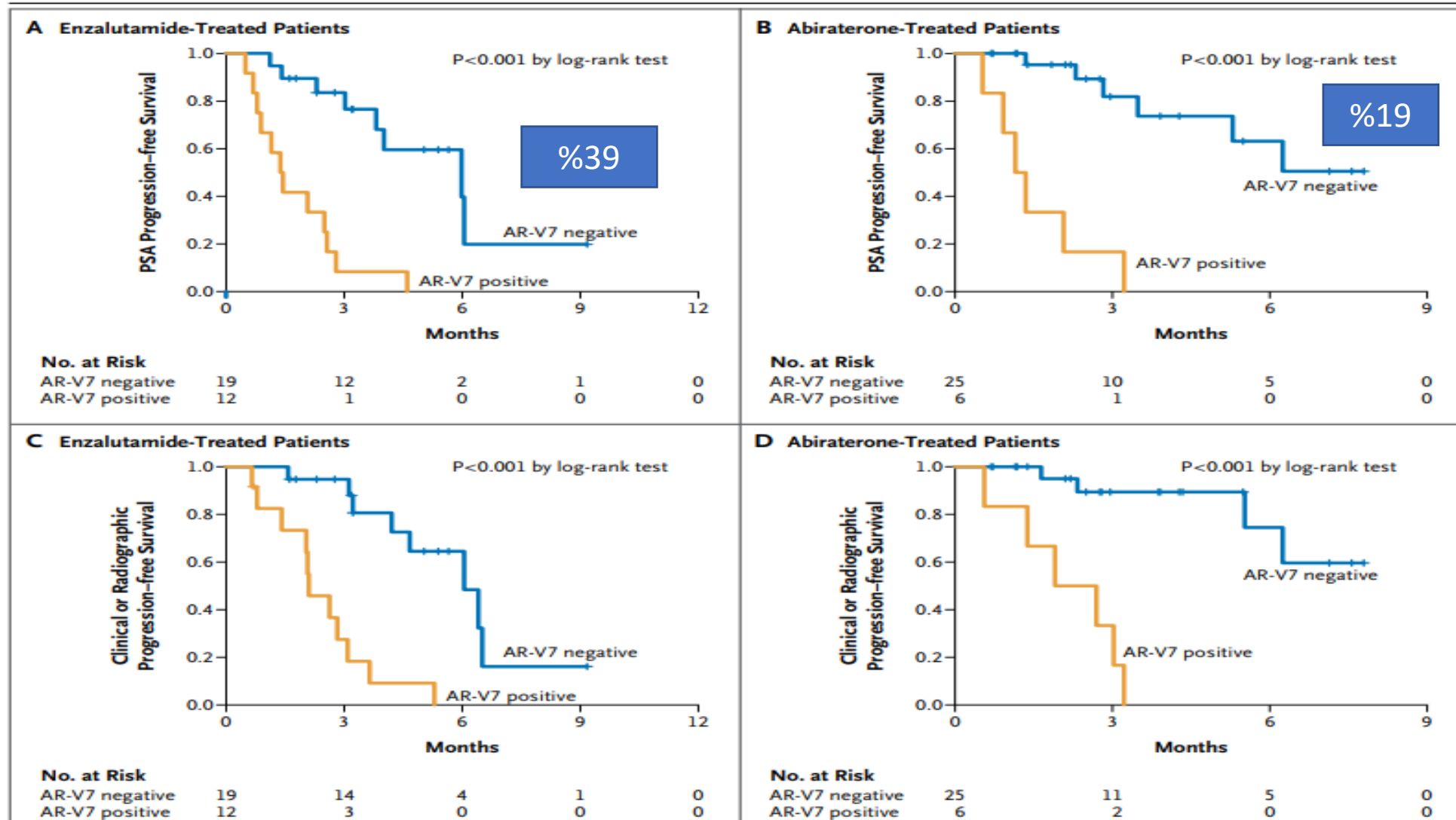
AR yolağında meydana gelen değişimler

Molecular Evaluation in CRPC



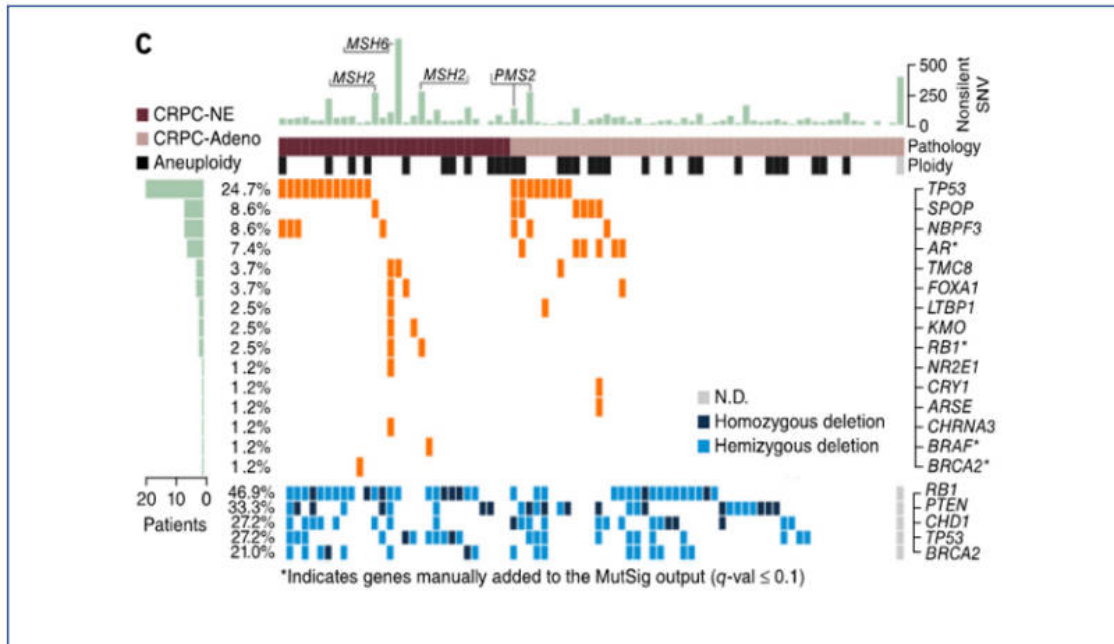
- AR Pathway Alterations (71.3%)
- Recurrent hotspot mutations identified
 - T878A
 - W742C
 - L702H
- Wide variety of AR splice variants throughout mCRPC tumor cases
- AR-V7 was observed in a majority of pre-abiraterone/enzalutamide cases but at very low ratios relative to full length AR

AR yolağında meydana gelen değişimler

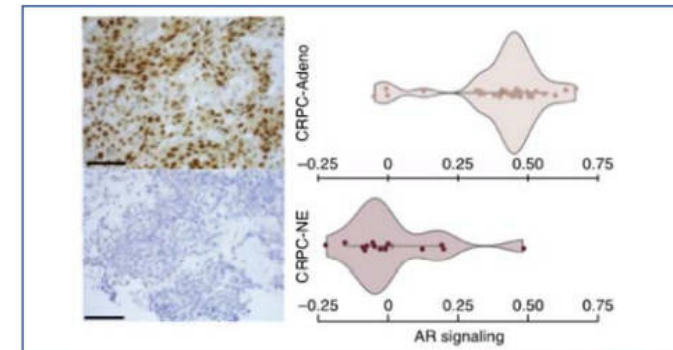


Prostat Kanseri Nöroendokrin Diferansiasyon

Molecular Evaluation in CRPC



- Differential genomic and epigenomic signatures in histologically classified adenocarcinoma and NEPC
- AR signaling activity can be dramatically distinct across



Prostat Kanseri Nöroendokrin Diferansiasyon

Platinums and Aggressive Prostate Cancer

- Phase II trial of first-line carboplatin and docetaxel (CD) and second-line etoposide and cisplatin (EP)
- Aggressive disease defined by
 - Visceral dx or lytic bone mets
 - Bulky tumor masses
 - Low PSA relative to tumor burden
 - Short response to ADT
- 65.4% and 33.8% were progression free after four cycles of CD and EP, respectively
- 37 patients (50.0%) benefited from both (median OS 19.33 months)
 - 5 patients (6.8%) did not benefit from either (median OS 6.7 months)
 - 25 patients (33.8%) had a response to CD but not to EP (median OS 14.4 months)
 - 7 patients (9.4%) had a response to EP but not to CD (median OS 8.9 months)
- Molecular subtyping not available at the time of treatment



Prostat Kanseri Nöroendokrin Diferansiasyon

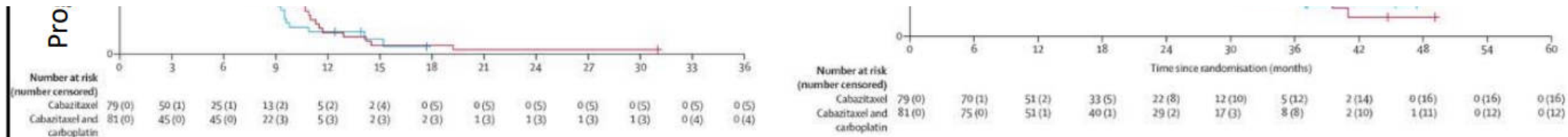
Combination Carboplatin and Cabazitaxel

B

100

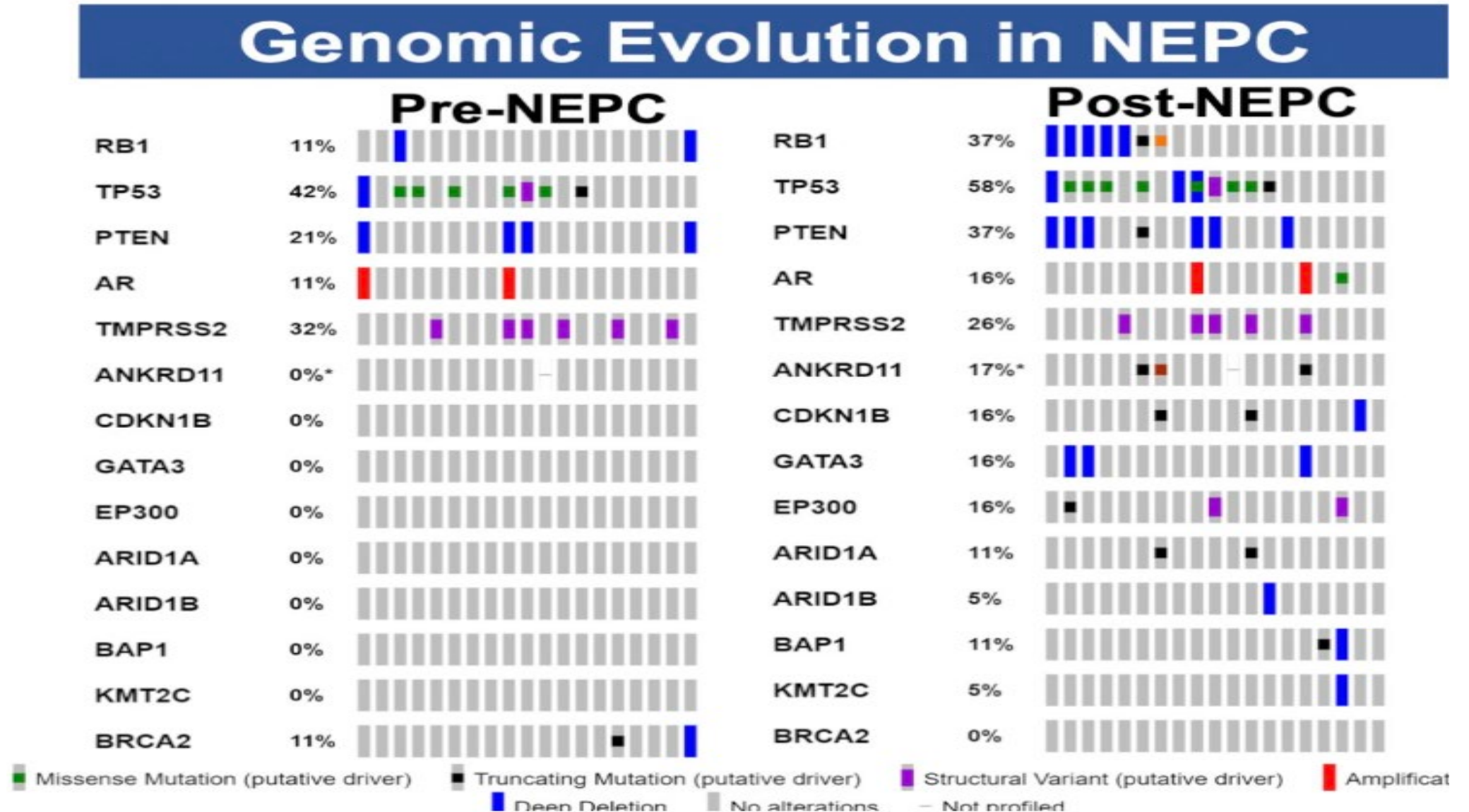
HR 0.89, 95% CI 0.63-1.25, p=0.50

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

Prostat Kanseri Nöroendokrin Diferansiasyon



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
- ❑ Enzulutamid/Abirateron sonrası Olaparib
- ❑ Dosetaksel sonrası Rucaparib
- ❑ Abirateron+Olaparib ya da Niraparib için daha uzun takip gerekir
- ❑ MSI high ve TMB yüksek hastalarda Pemrolizumab
- ❑ PI3K/AKT/PTEN mutasyonları NGS pozitif faz 3 çalışma sonucunu görmek lazım
- ❑ Nöroendokrine Diferansiyasyon olan hastalara Kabazitaksel+Karboplatin seçenek olarak düşünülebilir

Sonuç



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NCCN Guidelines Version 4.2022 Prostate Cancer

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SYSTEMIC THERAPY FOR M1 CRPC^{aaa}

