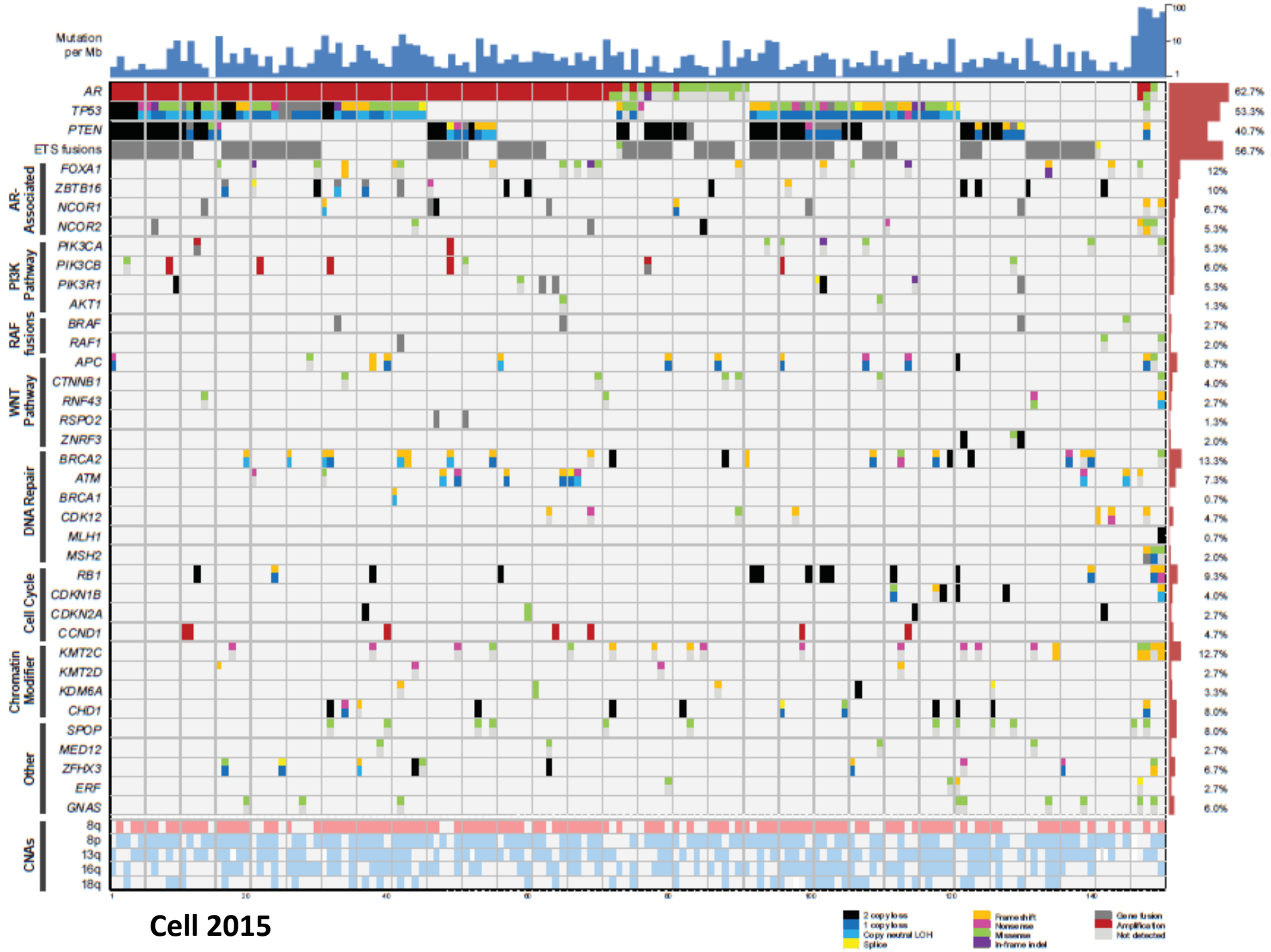
Prostat Kanserinde Genetik Değişiklikler ve Tedaviye Yansımaları

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

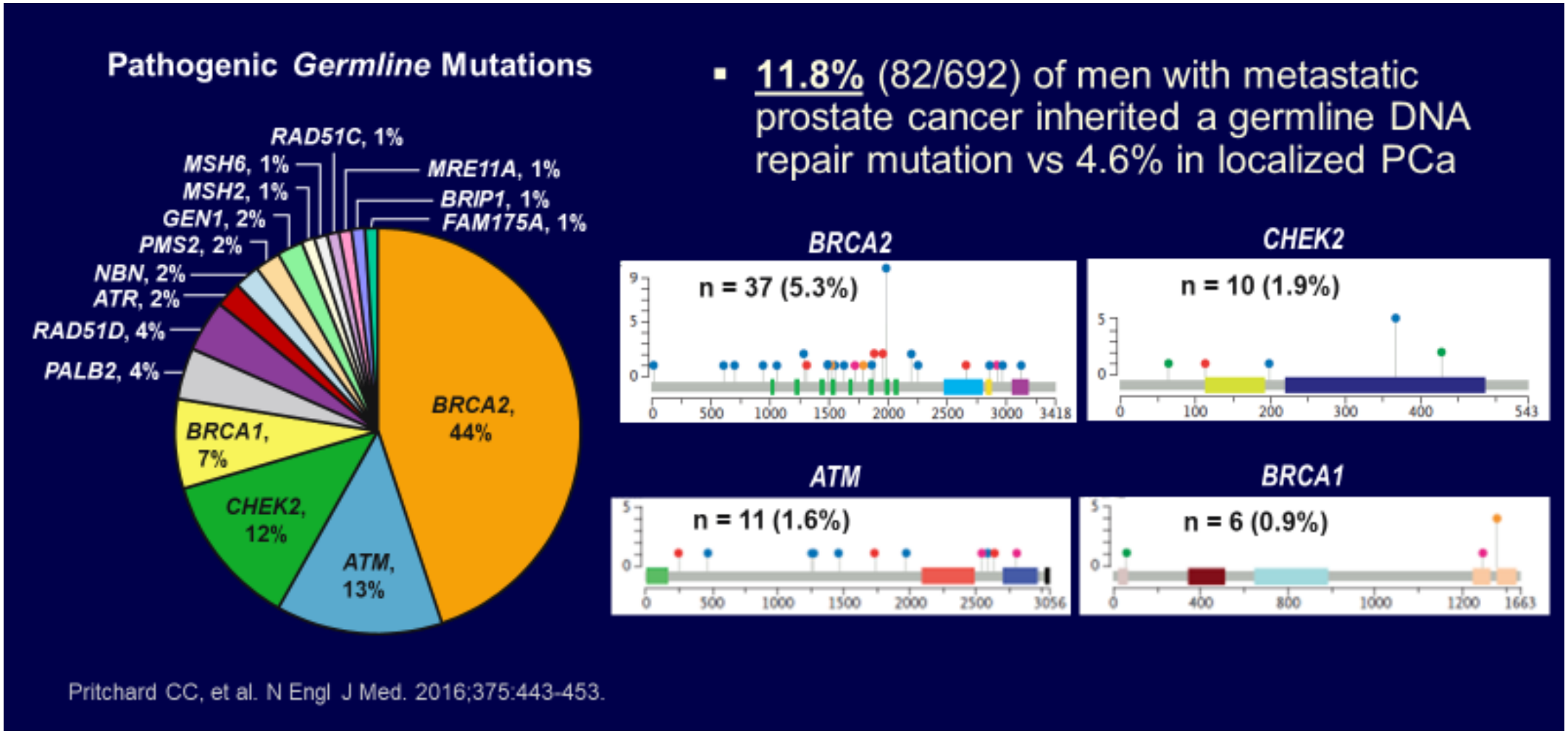
Ders Planı

- ❑ 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


Mutation per Mb
100
10
1
AR
TP53
PTEN
ETS fusions
AR-Associated
FOXA1
ZBTB16
NCOR1
NCOR2
PI3K Pathway
PIK3CA
PIK3CB
PIK3R1
AKT1
RAF fusions
BRAF
RAF1
WNT Pathway
APC
CTNNB1
RNF43
RSPO2
ZNRF3
DNA Repair
BRCA2
ATM
BRCA1
CDK12
MLH1
MSH2
Cell Cycle
RB1
CDKN1B
CDKN2A
CCND1
Chromatin Modifier
KMT2C
KMT2D
KDM6A
CHD1
Other
SPOP
MED12
ZFHX3
ERF
GNAS
CNAs
8q
8p
13q
16q
18q
62.7%
53.3%
40.7%
56.7%
12%
10%
6.7%
5.3%
5.3%
6.0%
5.3%
1.3%
2.7%
2.0%
8.7%
4.0%
2.7%
1.3%
2.0%
13.3%
7.3%
0.7%
4.7%
0.7%
2.0%
9.3%
4.0%
2.7%
4.7%
12.7%
2.7%
3.3%
8.0%
8.0%
2.7%
6.7%
2.7%
6.0%
1
20
40
60
80
100
120
140
2 copy loss
1 copy loss
Copy neutral LOH
Splice
Frameshift
Nonsense
Missense
In-frame indel
Gene fusion
Amplification
Not detected

Cell 2015

Prostat Kanserinde Germline Mutasyonları

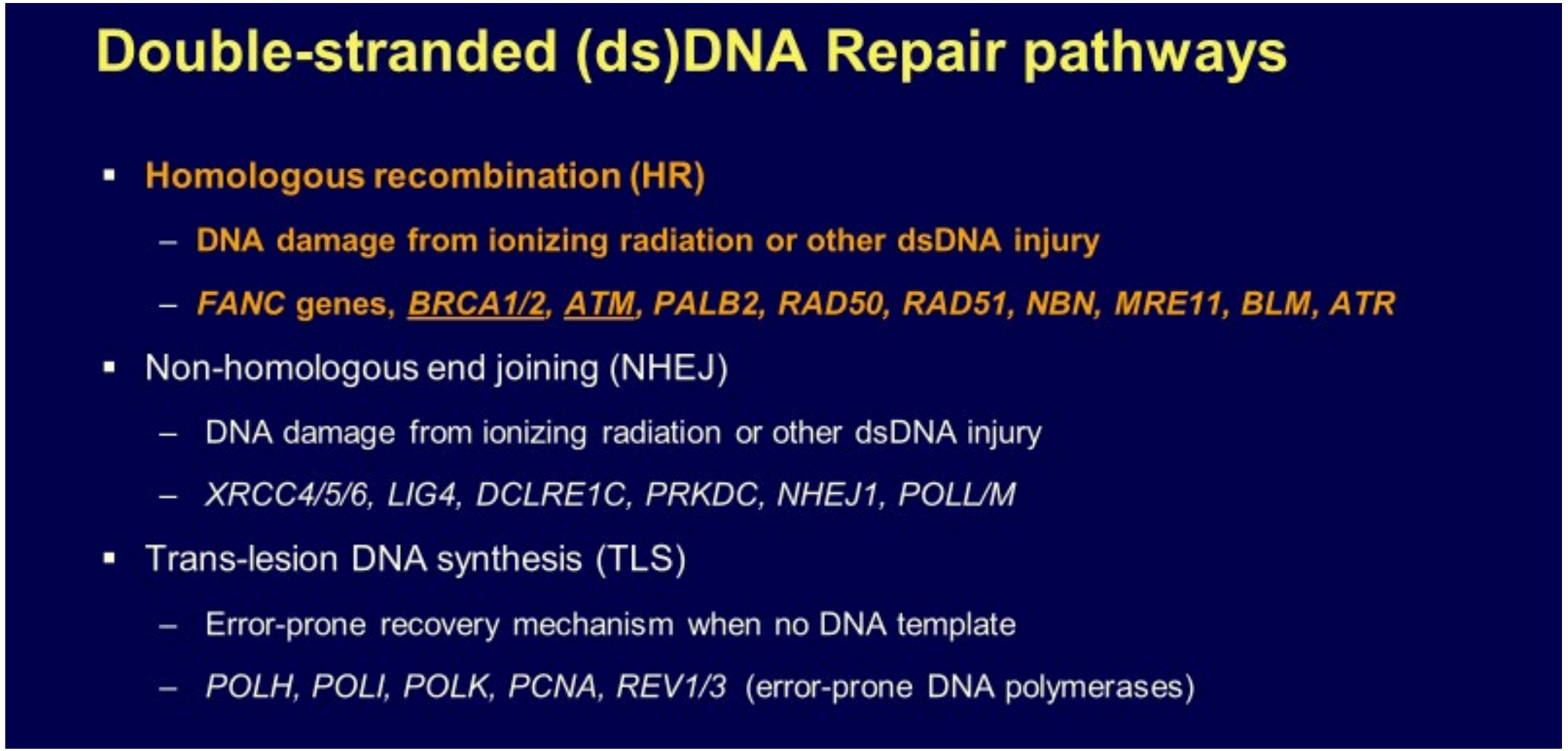


Prostat Kanserinde DNA Repair Genlerde Olan Değişiklikler

Single-stranded (ss)DNA Repair pathways

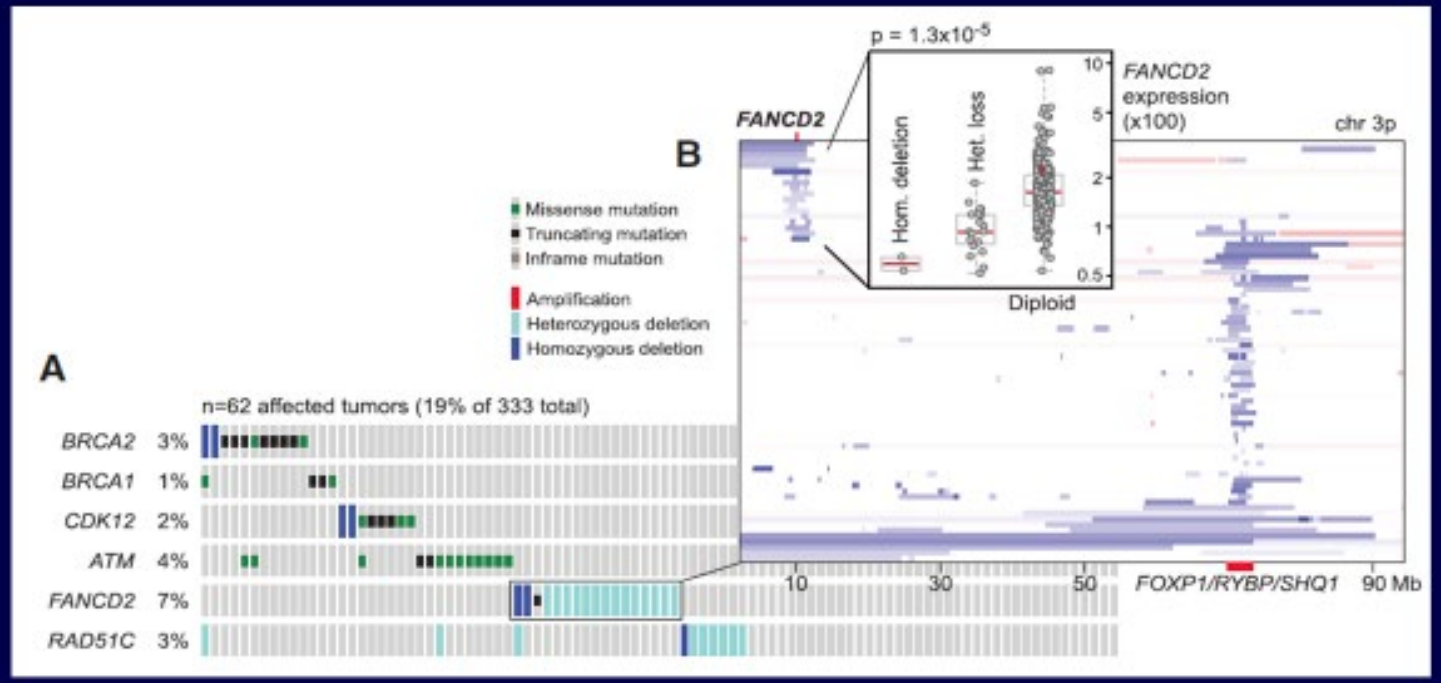
- **Mismatch repair (MMR)**
  - **Base errors from DNA replication and recombination**
  - ***MSH2, MSH6, MLH1, PMS2***
- Nucleotide excision repair (NER)
  - DNA damage from UV light, polycyclic aromatic hydrocarbons
  - *XPA-G, ERCC1-8, CSA/B, RPA, RAD23A/B*
- Base excision repair (BER)
  - DNA damage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

Prostat Kanserinde DNA Repair Genlerde Olan Değişiklikler



Prostat Kanserinde DNA Repair Genlerde Olan Değişiklikler

DNA Repair Defects in *Localized* Prostate Ca



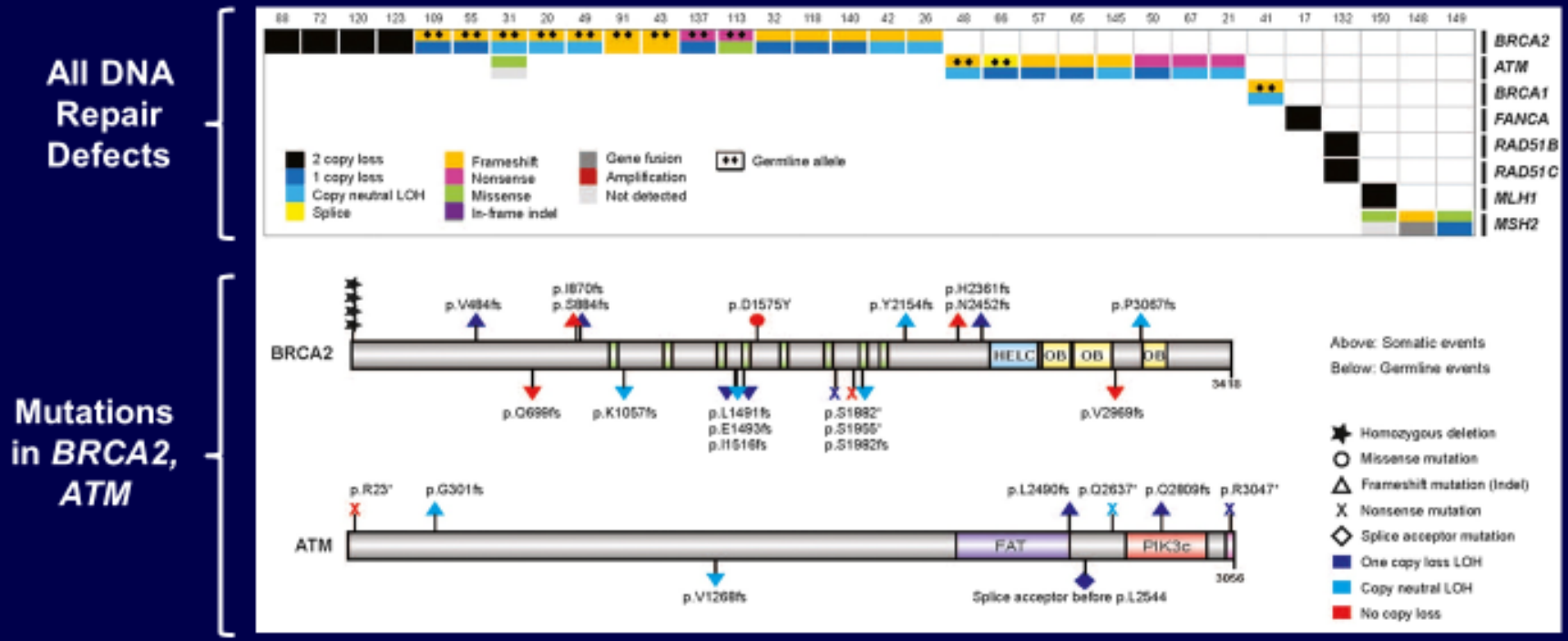
– 27/333 (**8.1%**) Tumors had **Bi-Allelic** inactivation

Cancer Genome Atlas Network, CELL 2015; 163: 1011-25.

Prostat Kanserinde DNA Repair Genlerde Olan Değişiklikler

DNA Repair Defects in *Metastatic* CRPC

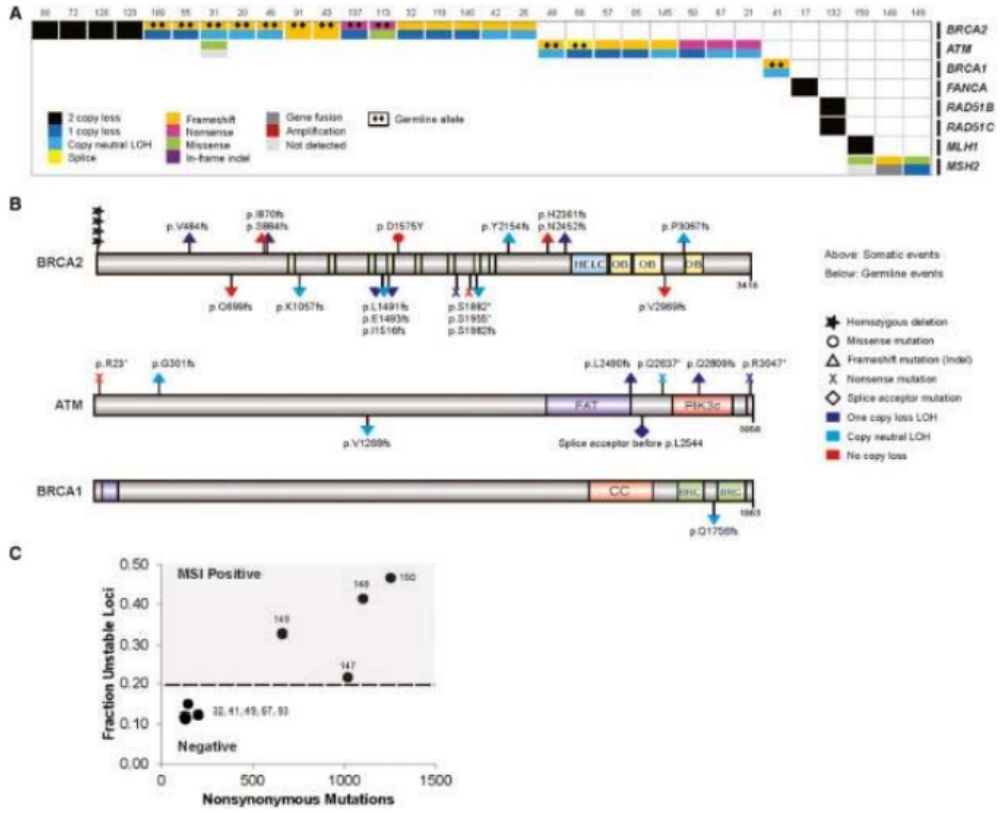
- 32/150 **(21.3%)** mCRPC pts had bi-allelic DNA repair mutations



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

Prostat Kanserinde DNA Repair Genlerde 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

Robinson et al. Cell 2015

Prostat Kanserinde DNA Repair Genlerde 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 Analyzed †**:**

Genes Not Analyzed:

† 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)	% cfDNA 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.

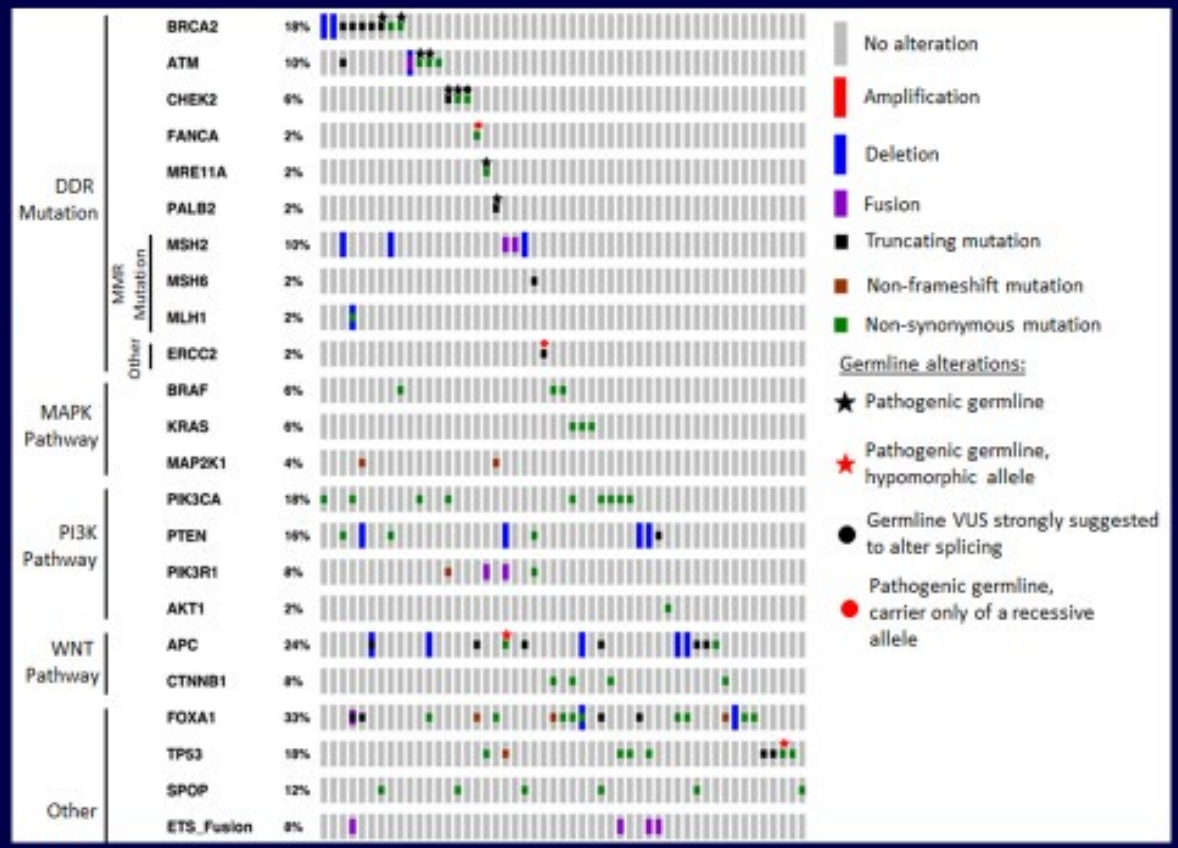
Synonymous Alterations
BRCA1 V382V (16.0%)
This sequence change does not alter the amino acid at this position and is unlikely to be a therapeutic target. Clinical correlation is advised.

Comments
The BRCA1 K739fs (c.2214_2222delTAAAGTGTCinsAGAAACAG) 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
İntraduktal tip

DNA Repair Defects and Prostatic Ductal Cancer

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

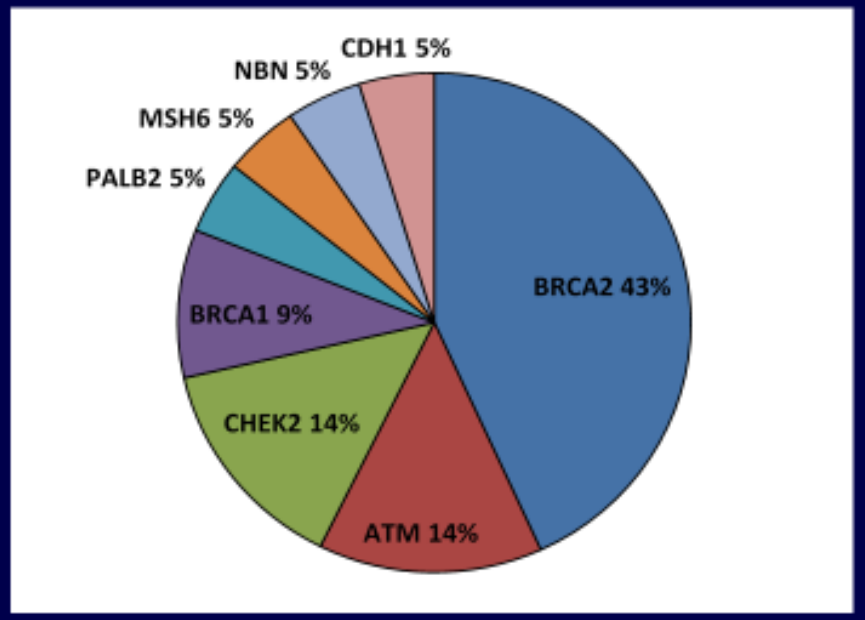


Schweizer MT, et al. *JCO Precis Oncol*, 2019; DOI:10.1200/PO.18.00327

Prostat Kanserinde DNA Repair Genlerde Olan Değişiklikler İntraduktal 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

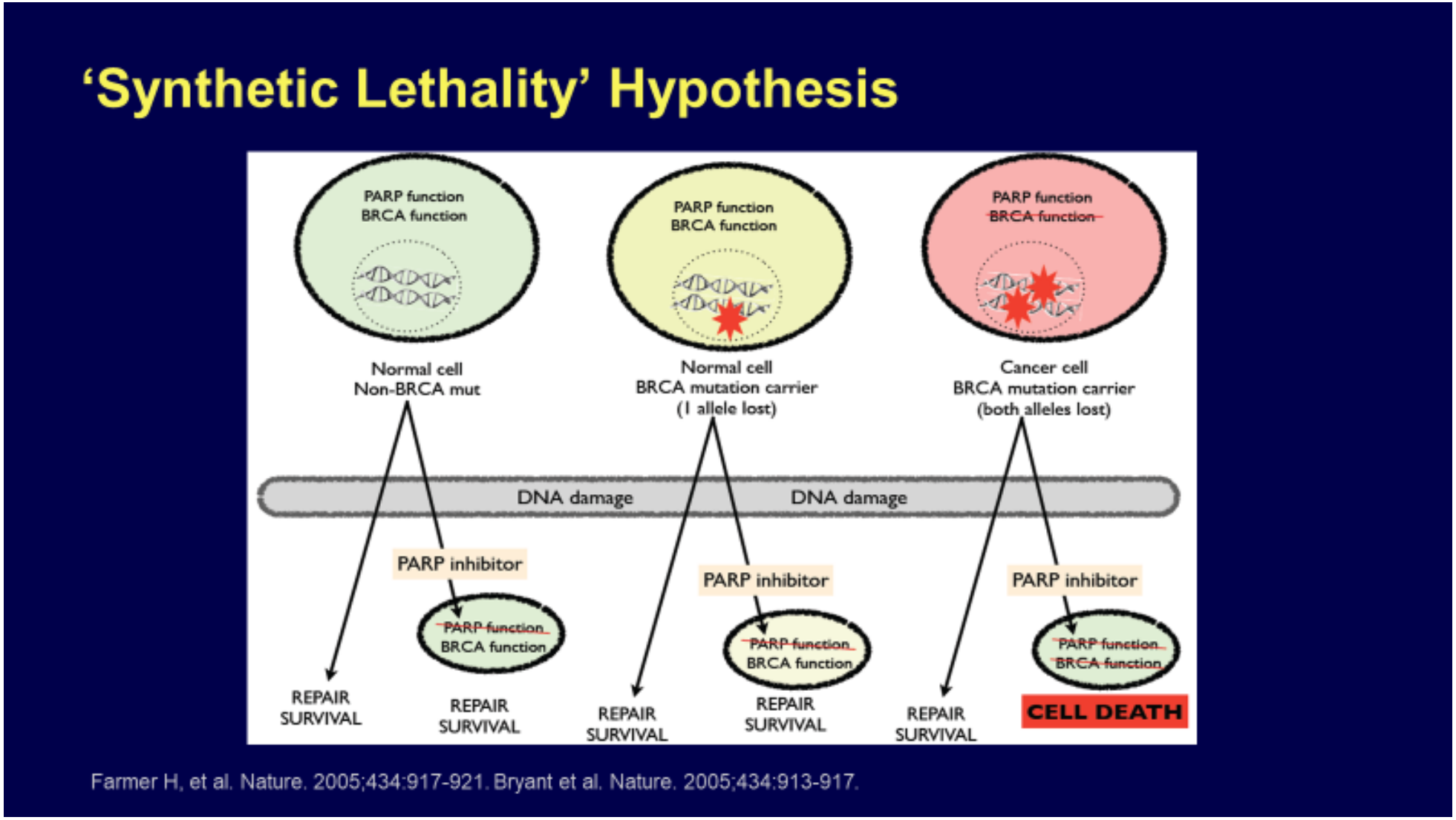
Incidence of Germline Mutations

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

*Fisher's test

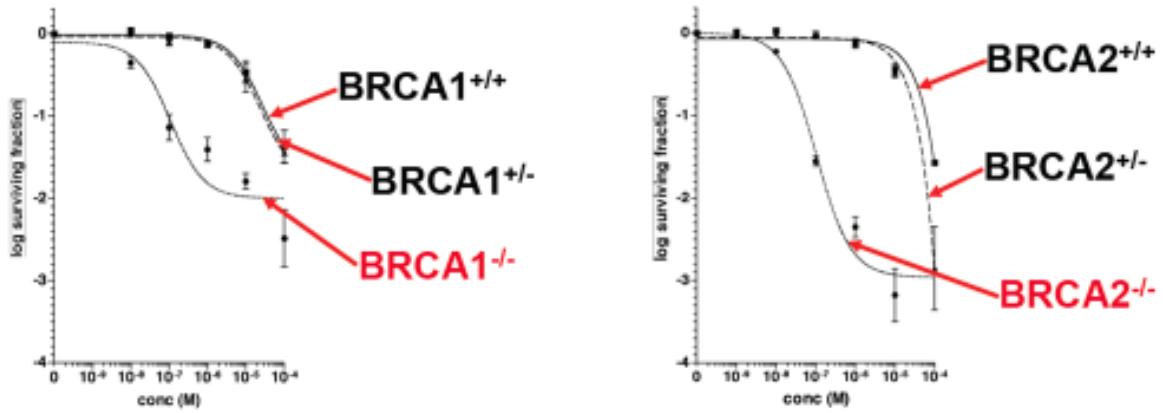
Isaacsson Velho P, et al. *The Prostate*. 2018; 78: 401-407.

PARP İnhibitörlerin Kulanım Temeli



PARP İnhibitörlerin Kulanım Temeli

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



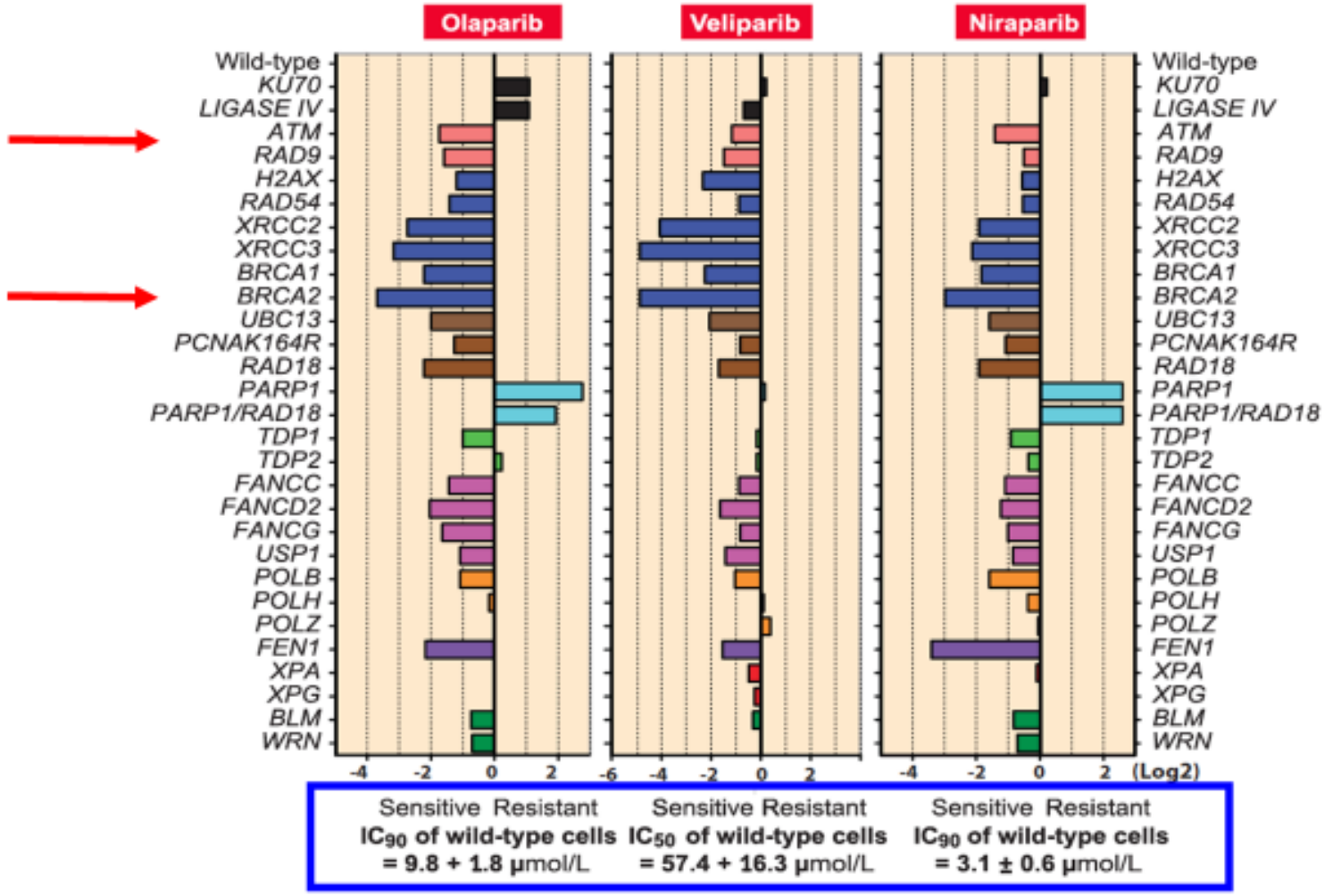
No difference in sensitivity between heterozygous and wild-type BRCA cells

Targeted inhibition → selective and less toxic therapy

Courtesy of Johann de Bono, MBChB, MSc, PhD

Farmer et al, Nature 2005; Bryant et al, Nature 2005

PARP İnhibitörlerin Kulanım Temeli



Courtesy of Johann de Bono, MBChB, MSc, PhD

Murai et al, Can Res 2012

PARP İnhibitörlerin Kulanım Temeli

TOPARP-A: Unselected phase 2 trial in mCRPC

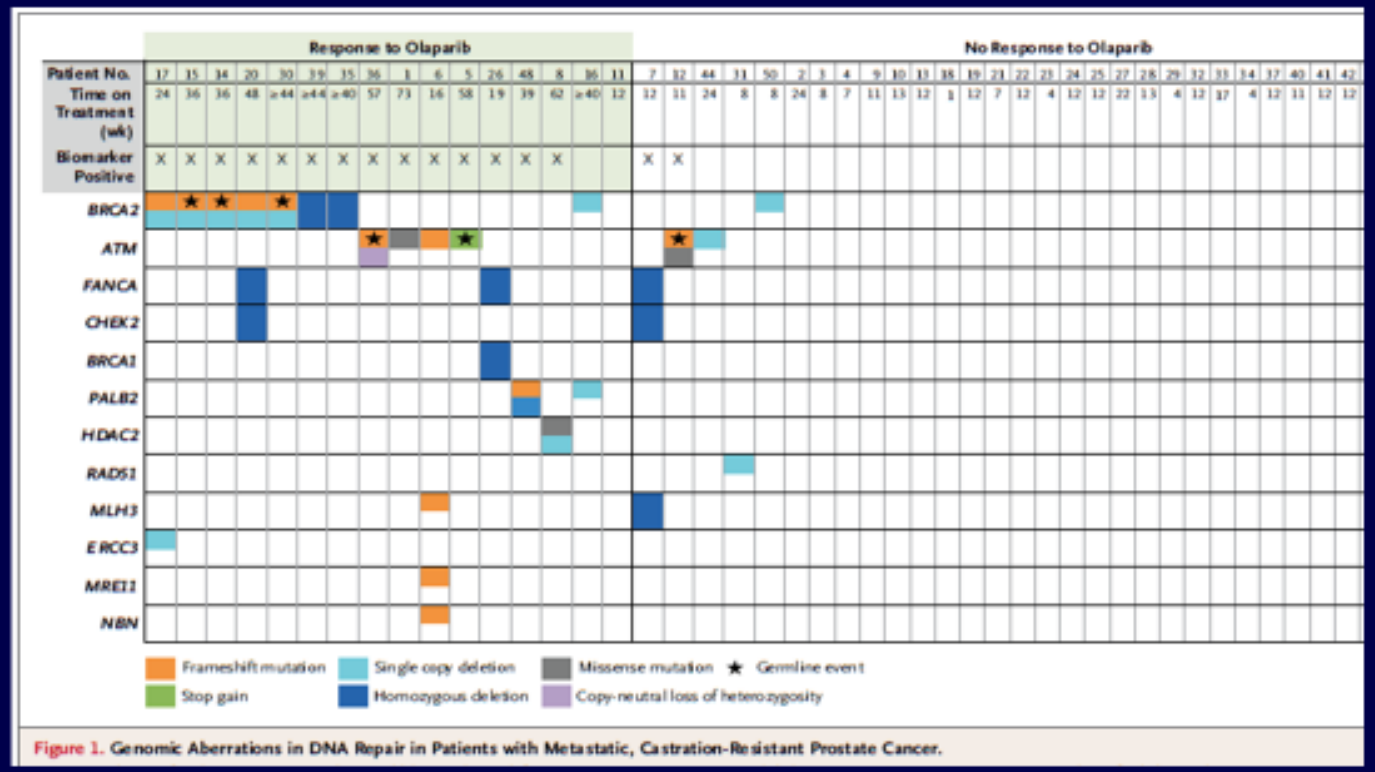


Figure 1. Genomic Aberrations in DNA Repair in Patients with Metastatic, Castration-Resistant Prostate Cancer.

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

Mateo J, et al. N Engl J Med. 2015; 373: 1697-1708.

PARP İnhibitörlerin Kulanım 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. Filipenko, L. Garraway, M.-E. Taplin, S. AlDubayan, 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. Solit, 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 Exome 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 98109, or at pnelson@fhcrc.org.

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

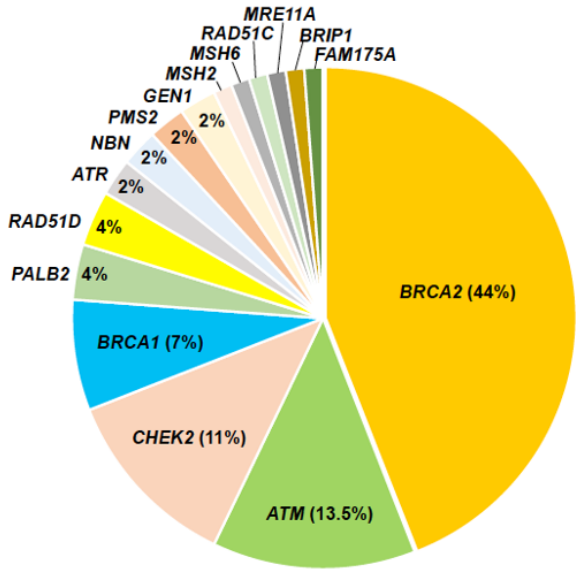
This article was published on July 6, 2016, at NEJM.org.

DOI: 10.1056/NEJMoa1603144

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

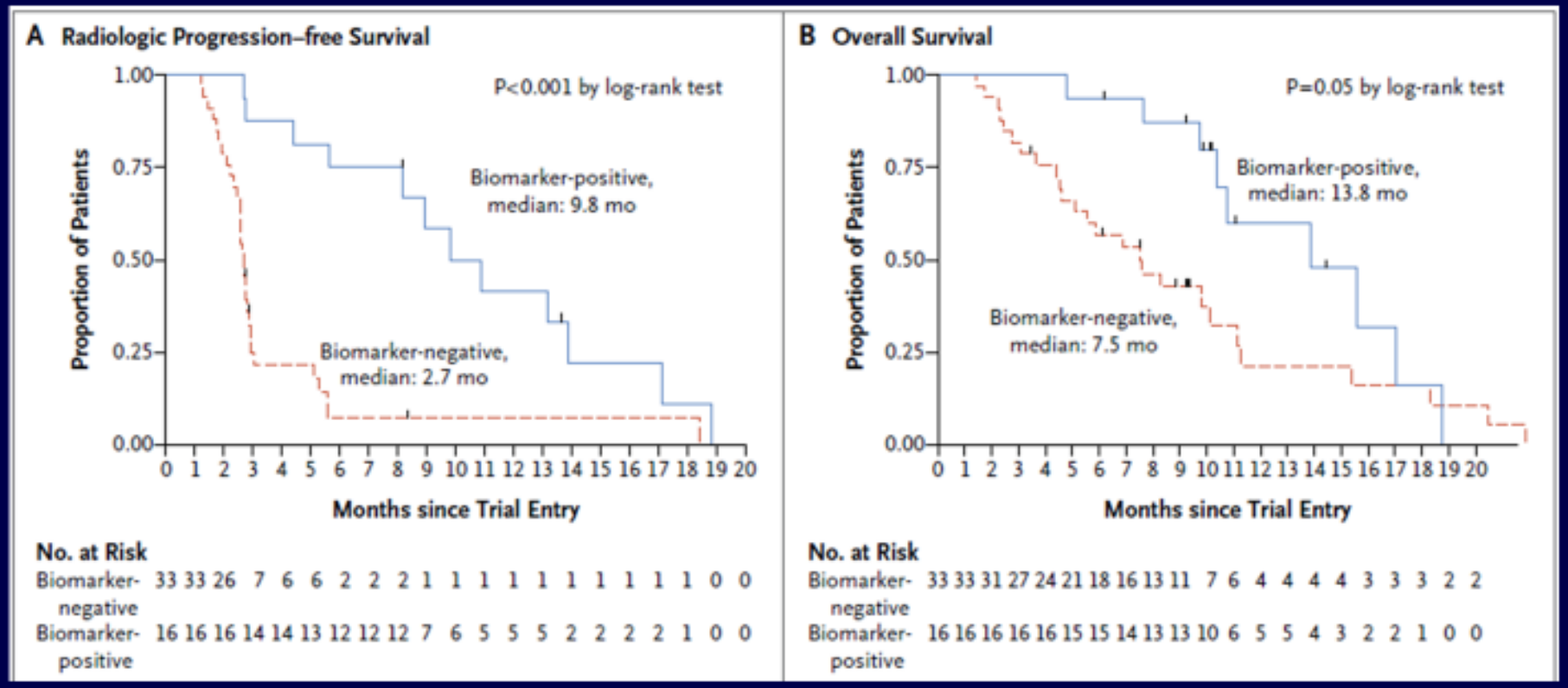
Case Series	Description	Patients	Patients with Mutations
		no.	*no. (%)*
1	Stand Up To Cancer–Prostate Cancer Foundation discovery series	150	15 (10.0)
2	Stand Up To Cancer–Prostate Cancer Foundation validation series	84	9 (10.7)
3	Royal Marsden Hospital	131	16 (12.2)
4	University of Washington	91	8 (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 Kulanım Temeli

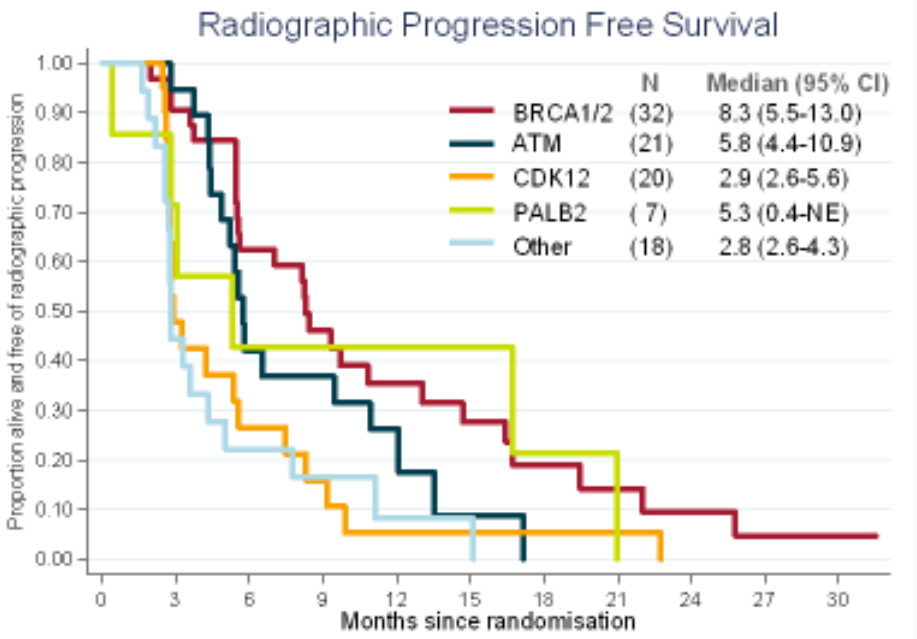
TOPARP-A: Survival with Olaparib by HR Deficiency

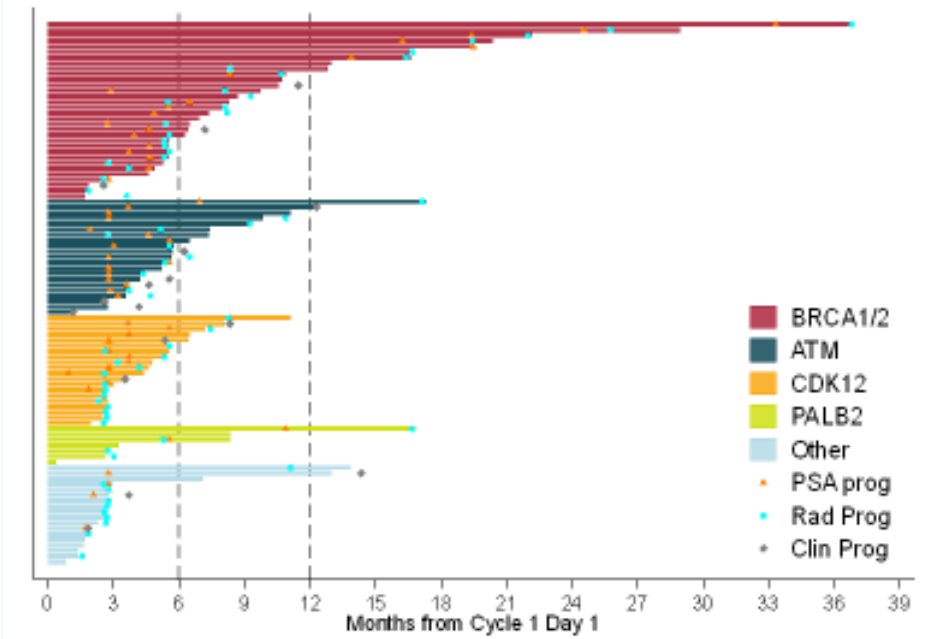


Mateo J, et al. N Engl J Med. 2015; 373: 1697-1708.

PARP İnhibitörlerin Kulanım 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.

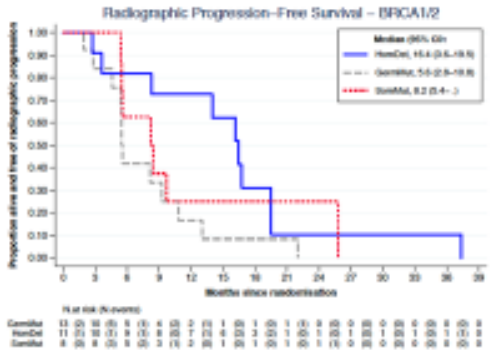
Mateo et al, Lancet Oncology, 2020

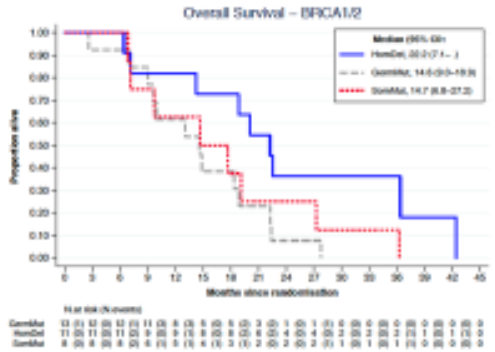
Courtesy of Johann de Bono, MBChB, MSc, PhD

PARP İnhibitörlerin Kulanım Temeli
TOPARP Study

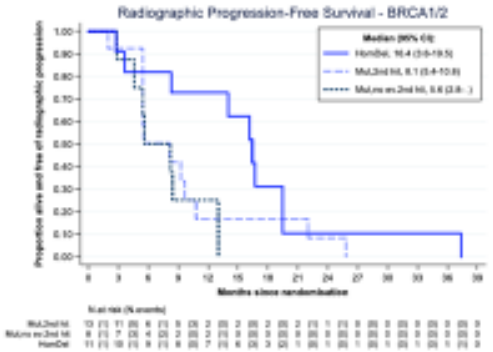
BRCA copy number and response on TOPARP-B

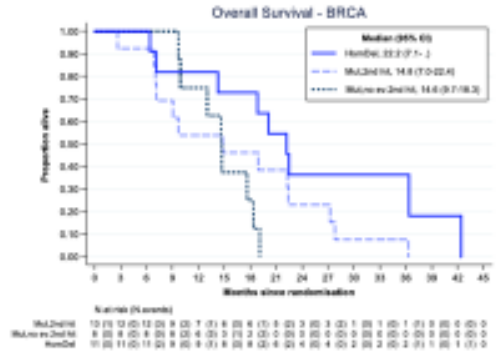
A : rPFS and OS in BRCA1/2 cohort depicting homozygous deletions, germline and somatic mutations: Tumours with homozygous BRCA deletions have the best outcomes





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 İnhibitörlerin Kulanım Temeli

The NEW ENGLAND JOURNAL of MEDICINE

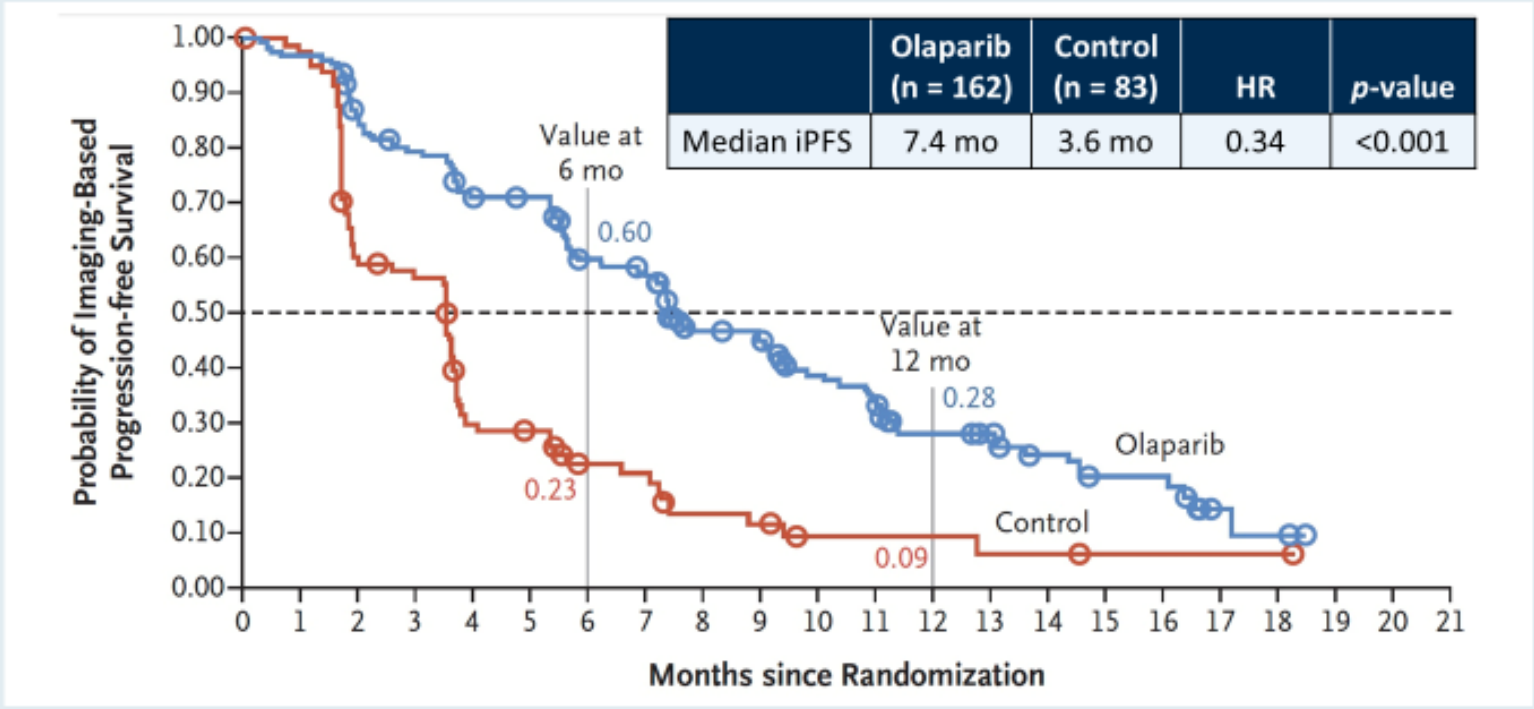
ESTABLISHED IN 1812 OCTOBER 29, 2015 VOL. 373 NO. 18

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)



	Olaparib (n = 162)	Control (n = 83)	HR	*p*-value
Median iPFS	7.4 mo	3.6 mo	0.34	<0.001

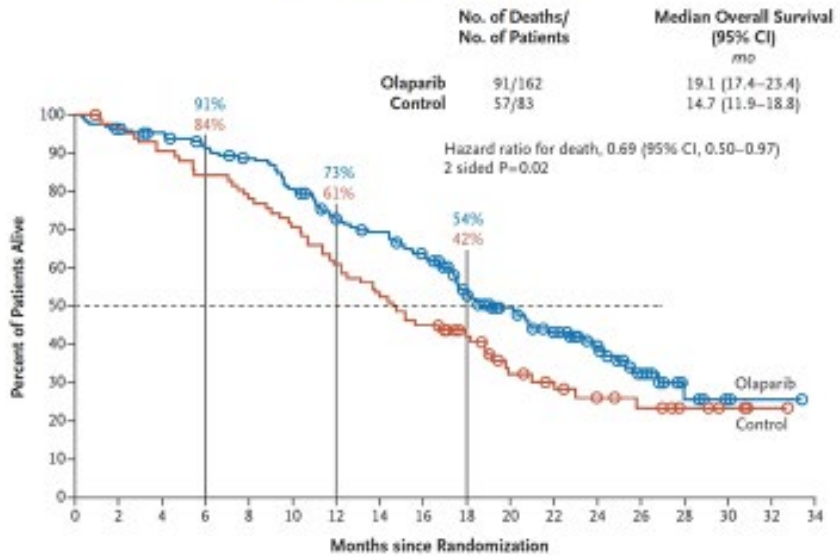
de Bono J et al; PROfound investigators. *N Engl J Med* 2020;382(22):2091-102.

RTP RESEARCH TO PRACTICE

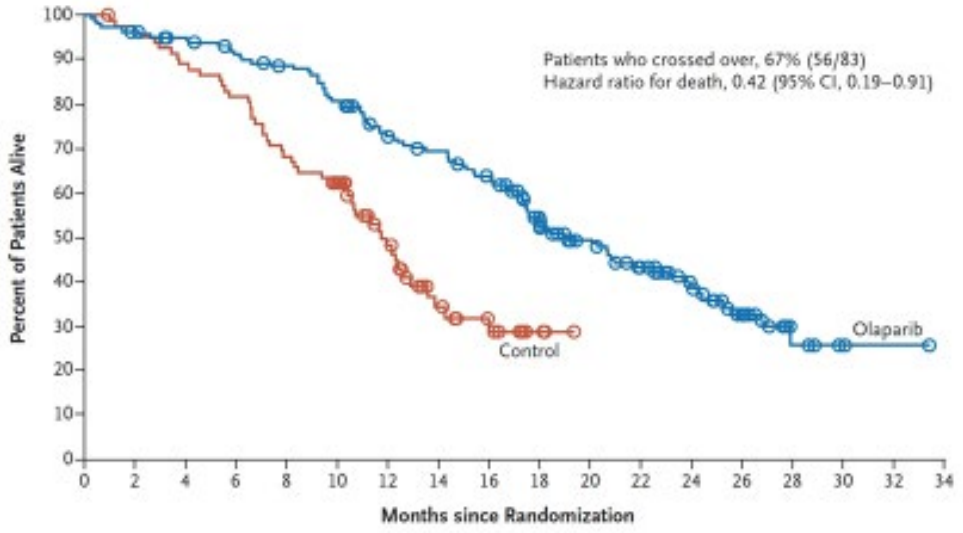
Evre IV Kastrasyona Dirençli Prostat Kanserinde Tedavi Seçeneği Olarak PARP İnhibitörü

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

Overall survival



Cross-over adjusted overall survival



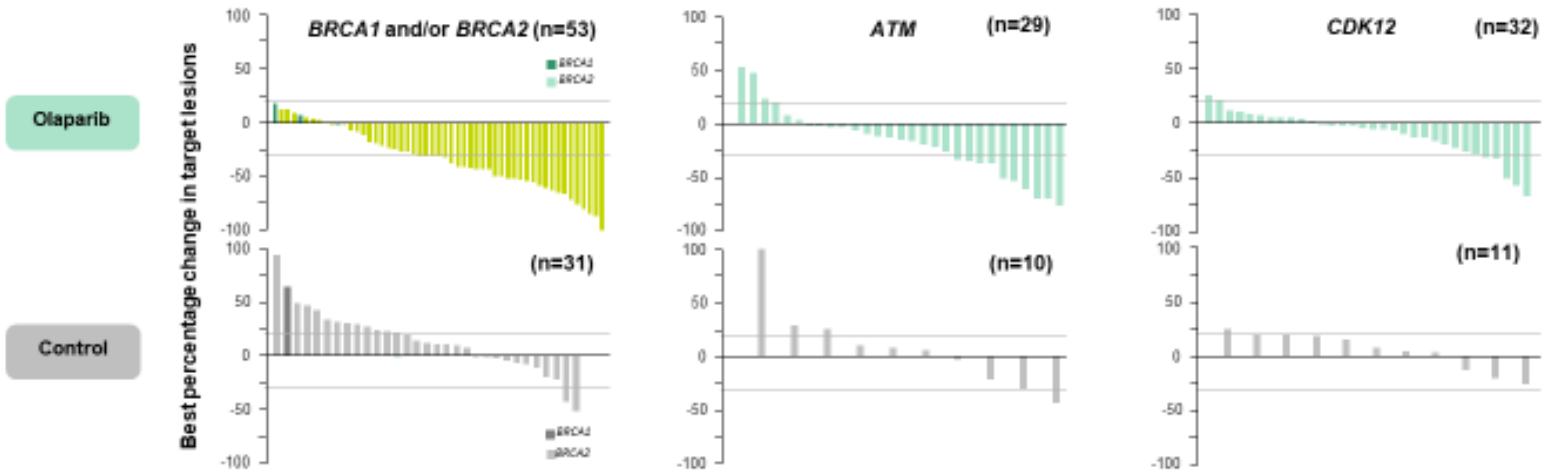
Hussain M et al; PROfound investigators. *N Engl J Med* 2020;383(24):2345-57.

RTP RESEARCH TO PRACTICE

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



de Bono et al. NEJM 2020

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, PhD[1]; Akash Patnaik, MD, PhD, MMSc[2]; David Campbell, MBBS[3]; Jeremy Shapiro, MBBS[4]; Alan H. Bryce, MD[5]; Ray McDermott, MD, PhD, MBA[6]; Brieuc Sautois, MD, PhD[7]; Nicholas J. Vogelzang, MD[8]; Richard M. Bambury, MD[9]; Eric Voog, MD[10]; Jingsong Zhang, MD, PhD[11]; Josep M. Piulats, MD[12]; Charles J. Ryan, MD[13]; Axel S. Merseburger, PhD[14]; Gedske Daugaard, DMSc[15]; Axel Heidenreich, MD[16]; Karim Fizazi, MD, PhD[17]; Celestia S. Higano, MD[18]; Laurence E. Krieger, MBChB[19]; Cora N. Sternberg, MD[20]; Simon P. Watkins, PhD[21]; Darrin Despain, MStat[22]; Andrew D. Simmons, PhD[23]; Andrea Loehr, PhD[23]; Melanie Dowson, BA[24]; Tony Golsorkhi, MD[25]; and Simon Chowdhury, MD, PhD[26,27]; on behalf of the TRITON2 investigators

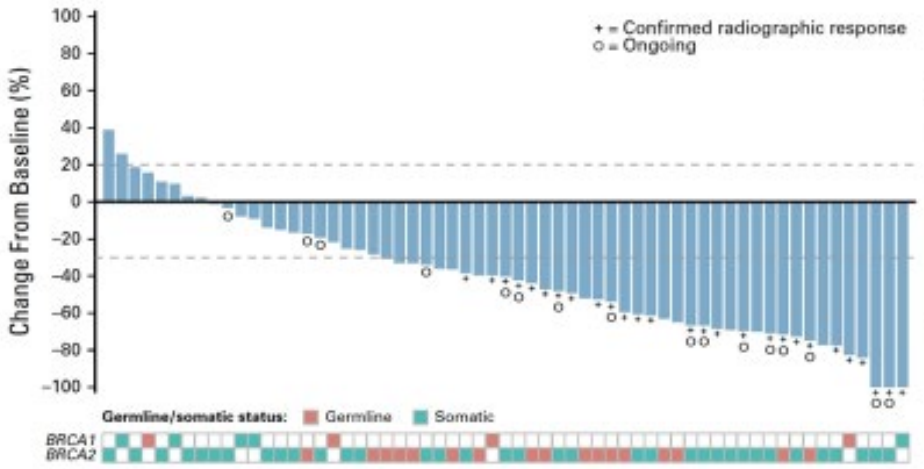
J Clin Oncol 2020;38(22):3763-72.

RTP RESEARCH TO PRACTICE

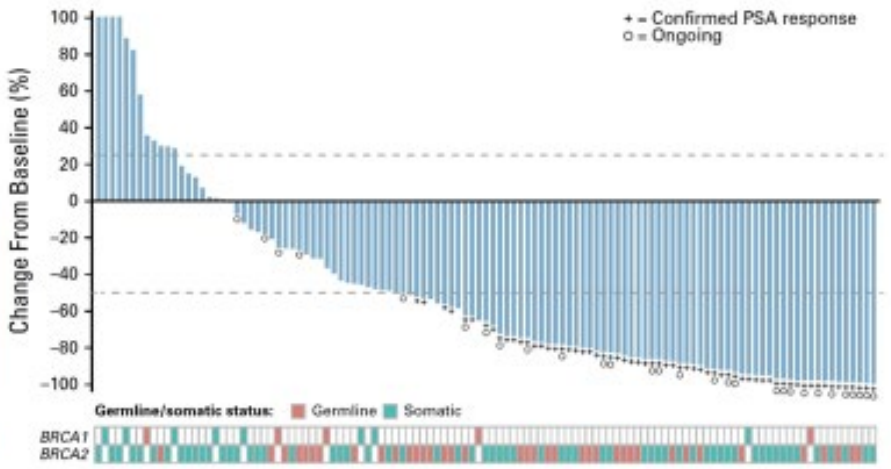
Evre IV Kastrasyona Dirençli Prostat Kanserinde Tedavi Seçeneği Olarak PARP İnhibitörü

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%



Abida W et al. TRITON2 investigators. *J Clin Oncol* 2020;38(32):3763-72.

RTP RESEARCH TO PRACTICE

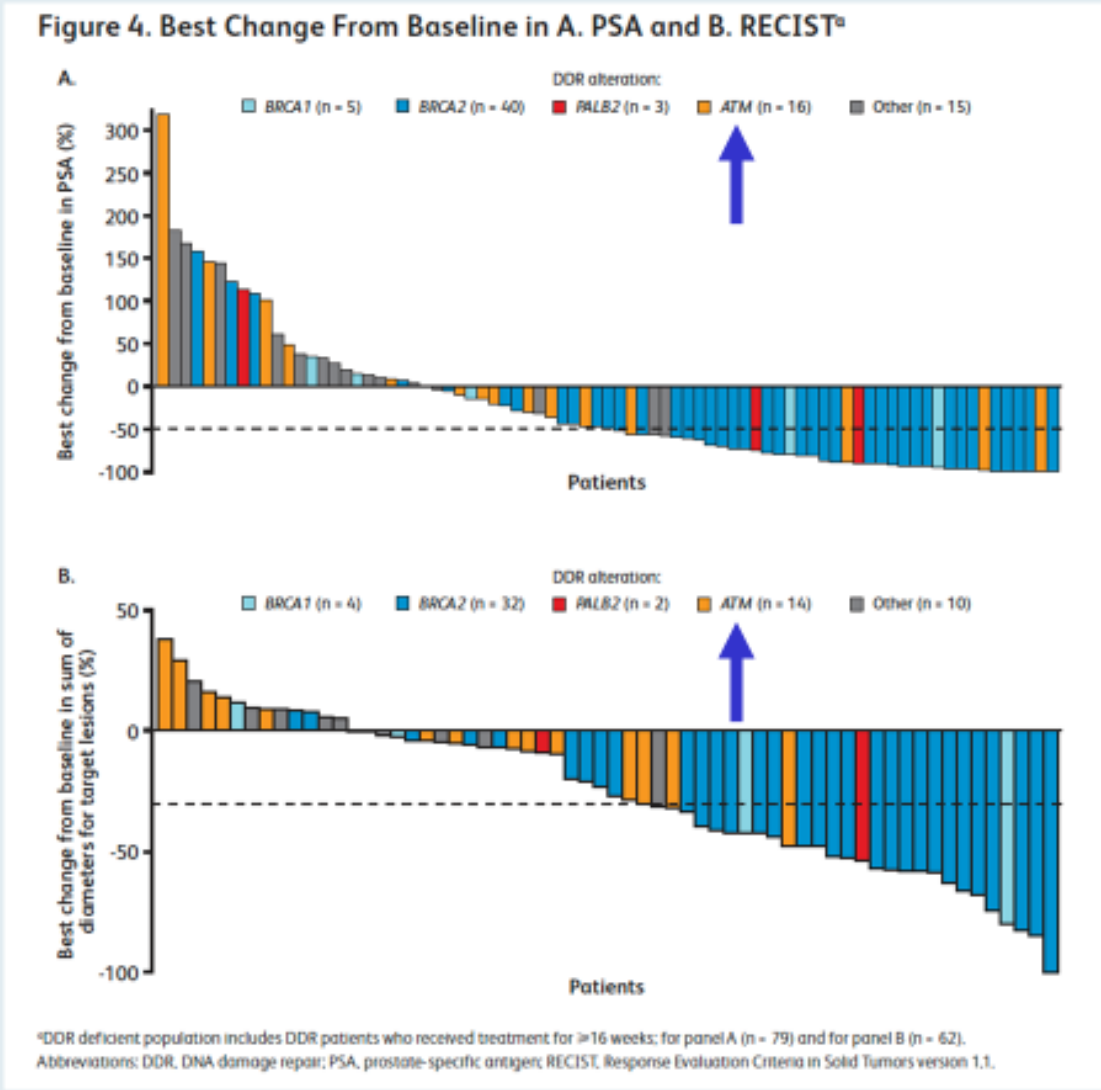
Evre IV Kastrasyona Dirençli Prostat Kanserinde Tedavi Seçeneği Olarak PARP İnhibitörü

Talazoparib in mCRPC (TALAPRO-1)

BRCA in blue

ATM loss in orange

PALB2 in red

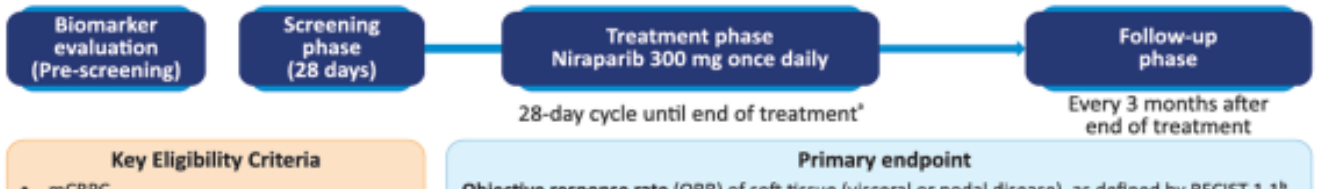


de Bono JS et al. *Lancet Oncol* 2021;22(9):1250-64.

Evre IV Kastrasyona Dirençli Prostat Kanserinde Tedavi Seçeneği Olarak PARP İnhibitörü

Niraparib: GALAHAD trial interim results

Figure 2. Study design



Key Eligibility Criteria

- mCRPC
- Biomarker positive for DRD
- Progressed on ≥1 ARSI therapy and ≥1 taxane-based CTx
- No prior PARP inhibitor or platinum-based CTx
- No prior or current MDS/AML

Primary endpoint

Objective response rate (ORR) of soft tissue (visceral or nodal disease), as defined by RECIST 1.1[b] with no evidence of bone progression according to the PCWG3 criteria in patients with biallelic *BRCA*

Secondary endpoints

- **ORR** (per RECIST 1.1 / PCWG3 criteria) in patients with biallelic non-*BRCA*
- **CTC response**: CTC=0 per 7.5 mL blood at 8 weeks post-baseline in patients with baseline CTC >0
- **OS**: time from enrollment to death from any cause
- **rPFS**: time from enrollment to radiographic progression or death from any cause, whichever occurs first
- **Duration of objective response**: time from complete response (CR) or partial response (PR) to radiographic progression of disease, unequivocal clinical progression, or death, whichever occurs first
- **Safety**: adverse events and laboratory tests

Patients plasma samples were evaluated for DRD (defined as pathogenic mutation in **BRCA1/2, ATM, FANCA, PALB2, CHEK2, BRIP1 or HDAC2)** using plasma circulating tumor DNA (Resolution Bioscience, Redmond, WA).

Smith MR, et al. ESMO 2019; abstract LBA50.

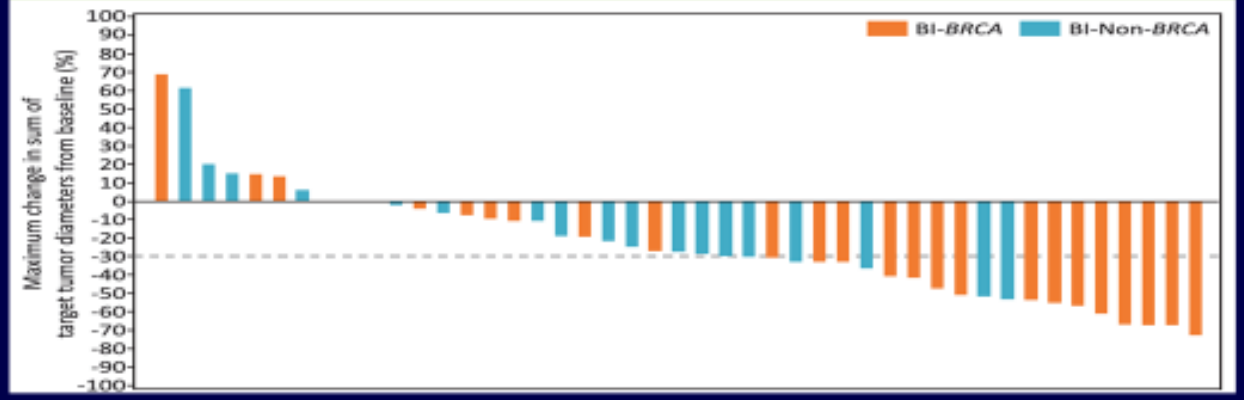
Evre IV Kastrasyona Dirençli Prostat Kanserinde Tedavi Seçeneği Olarak PARP İnhibitörü

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*[a] (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



Smith MR, et al. ESMO 2019; abstract LBA50.

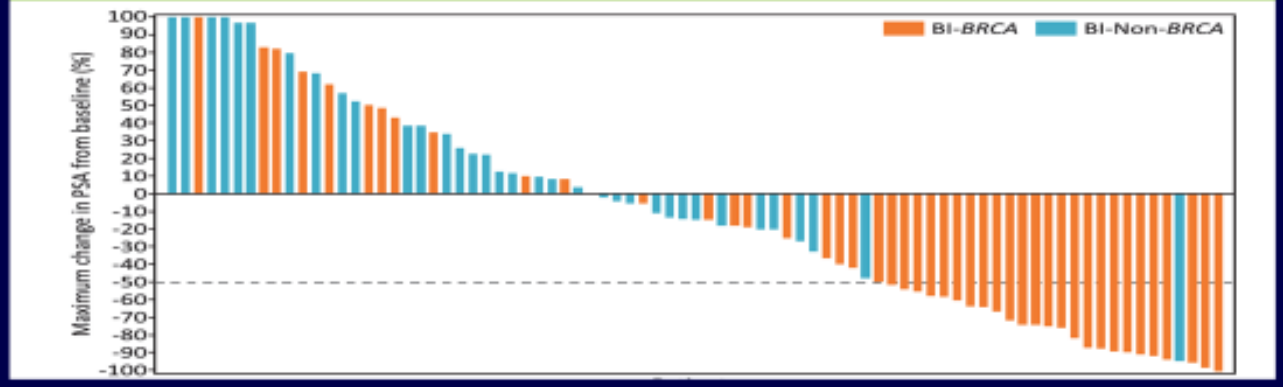
Evre IV Kastrasyona Dirençli Prostat Kanserinde Tedavi Seçeneği Olarak PARP İnhibitörü

GALAHAD: PSA responses

Table 3. Response in patients with mCRPC and biallelic DRD

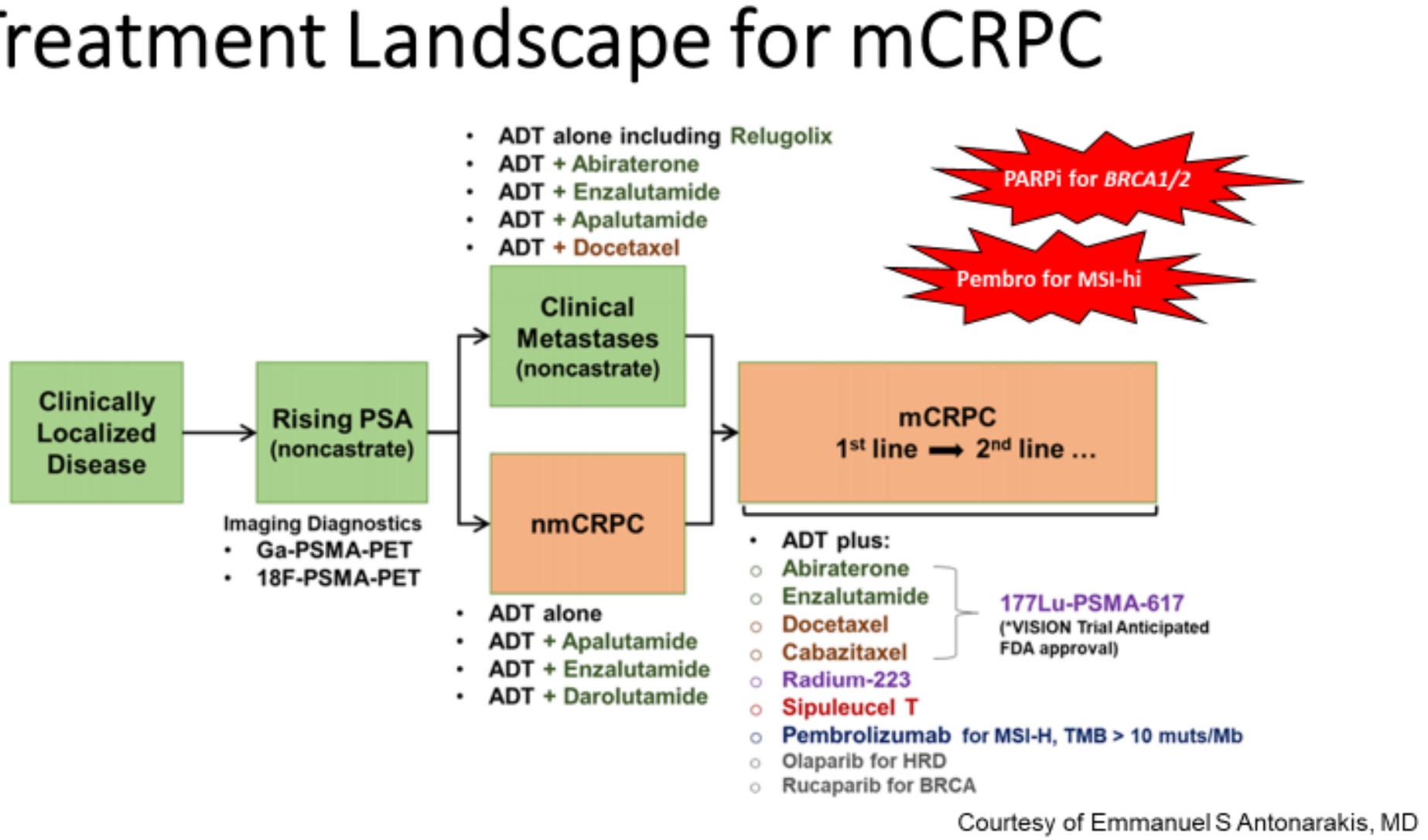
Response, n (%) [95% CI]	All biallelic DRD (n=81)	
	BRCA (n=46)	Non-*BRCA*[a] (n=35)
PSA_{50}	23/46 (50%) [34.9, 65.1]	1/35 (3%) [0.1, 14.9]
CTC Conversion[b]	18/38 (47%) [31.0, 64.2]	5/24 (21%) [7.1, 42.2]
Composite response rate	29/46 (63%) [47.6, 76.8]	6/35 (17%) [6.6, 33.7]
Median duration of objective 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



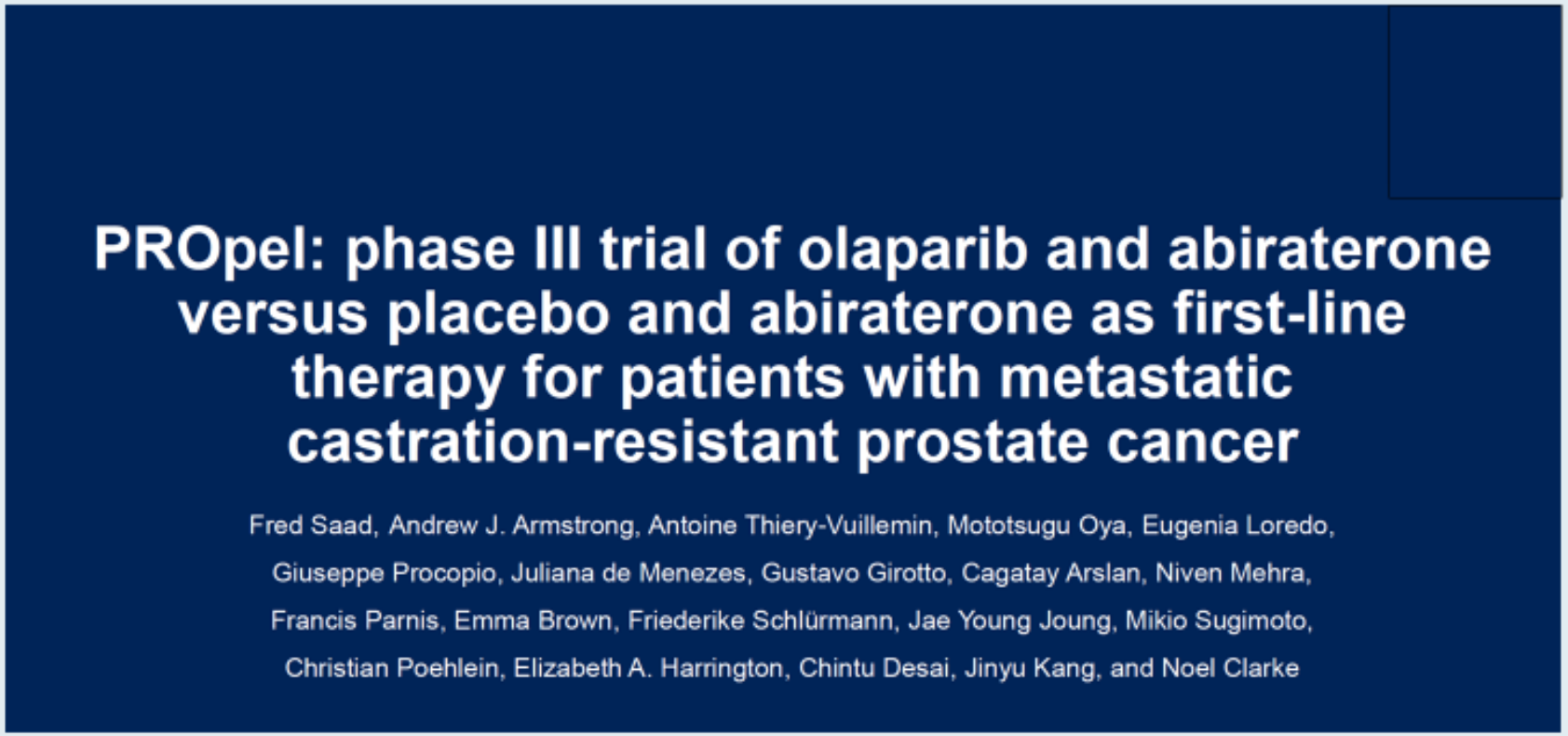
Smith MR, et al. ESMO 2019; abstract LBA50.

Evre IV Kastrasyona Dirençli Prostat Kanserinde Tedavi Seçenekleri

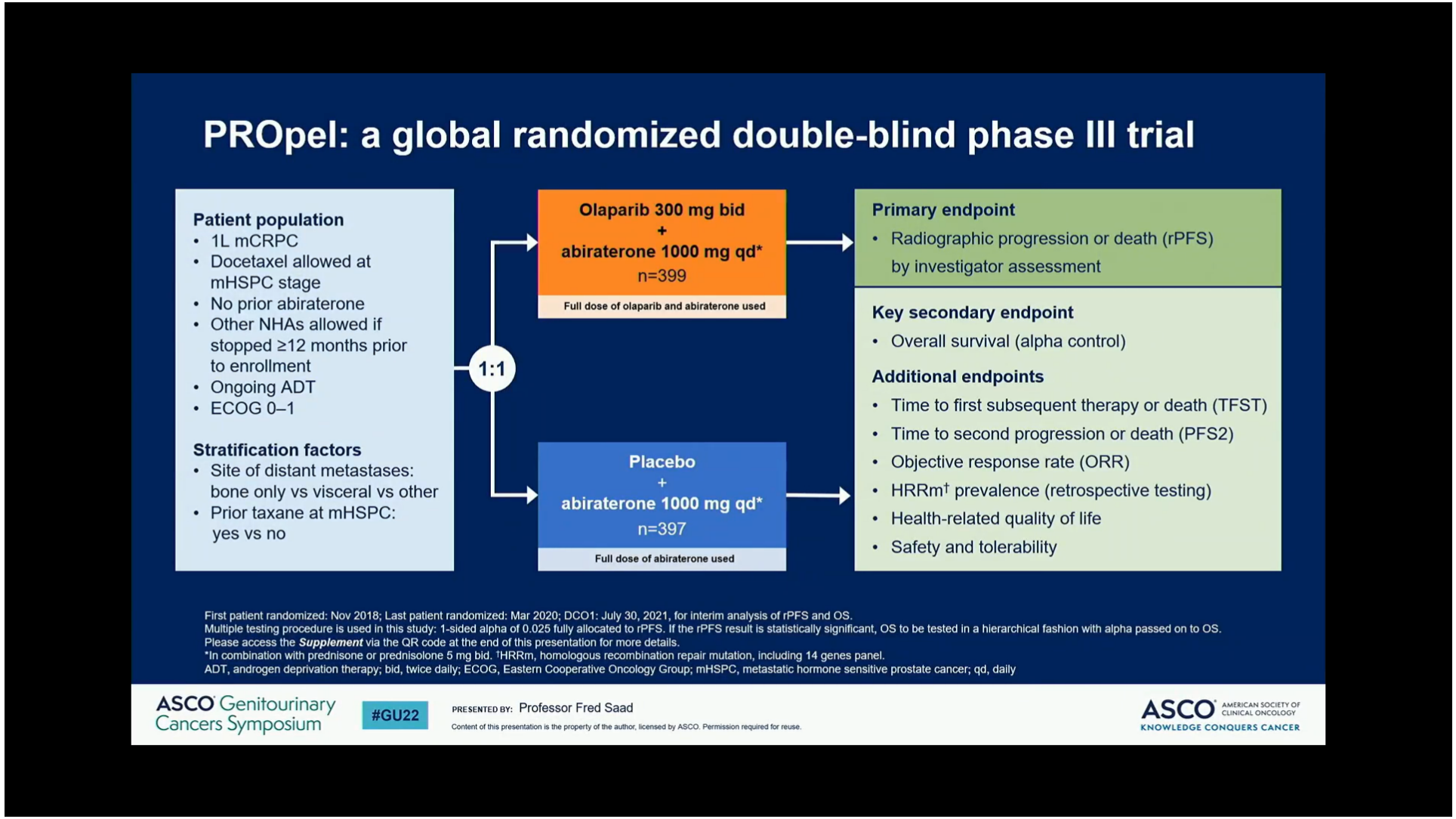


Courtesy of Emmanuel S Antonarakis, MD

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



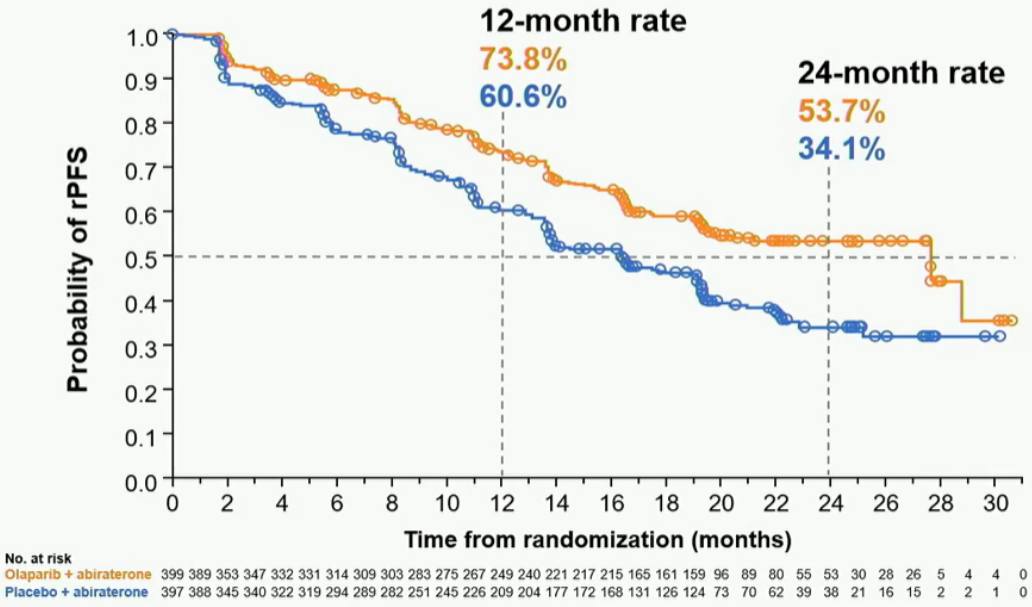
Evre IV Kastrasyona Dirençli Prostat Kanserinde Tedavi Seçeneği Olarak PARP İnhibitörü+Abireteron



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

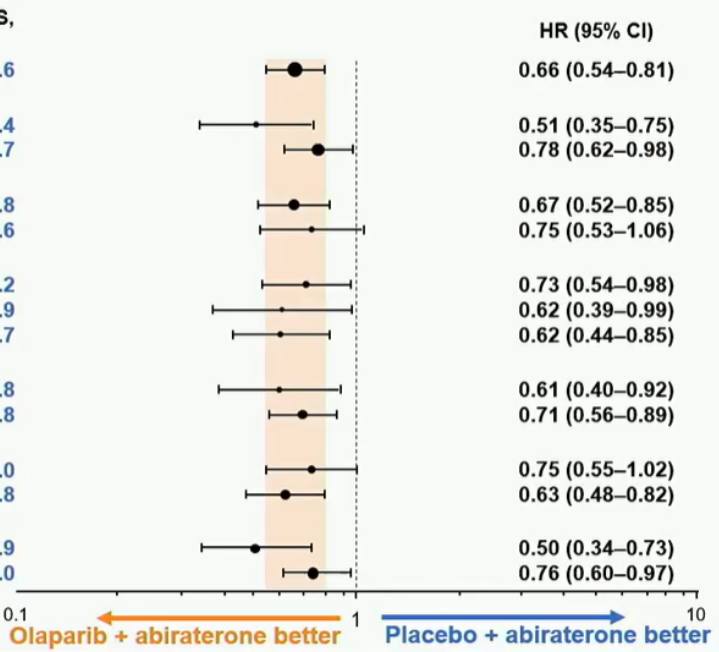
PRESENTED BY: Professor Fred Saad

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

PROpel: subgroup analysis of rPFS

rPFS benefit observed across all pre-specified subgroups

	Number of patients, n	Median rPFS, months		HR (95% CI)
All patients	796	24.8	16.6	0.66 (0.54–0.81)
Age at randomization				
<65	227	NR	16.4	0.51 (0.35–0.75)
≥65	569	22.0	16.7	0.78 (0.62–0.98)
ECOG performance status at baseline				
0	558	24.9	16.8	0.67 (0.52–0.85)
1	236	17.5	14.6	0.75 (0.53–1.06)
Site of distant metastases				
Bone only	434	27.6	22.2	0.73 (0.54–0.98)
Visceral	105	13.7	10.9	0.62 (0.39–0.99)
Other	257	20.5	13.7	0.62 (0.44–0.85)
Docetaxel treatment at mHSPC stage				
Yes	189	27.6	13.8	0.61 (0.40–0.92)
No	607	24.8	16.8	0.71 (0.56–0.89)
Baseline PSA				
Below median baseline PSA	396	25.2	22.0	0.75 (0.55–1.02)
Above or equal to median baseline PSA	397	18.5	13.8	0.63 (0.48–0.82)
HRRm status*				
HRRm	226	NR	13.9	0.50 (0.34–0.73)
Non-HRRm	552	24.1	19.0	0.76 (0.60–0.97)



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.

PRESENTED BY: Professor Fred Saad

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

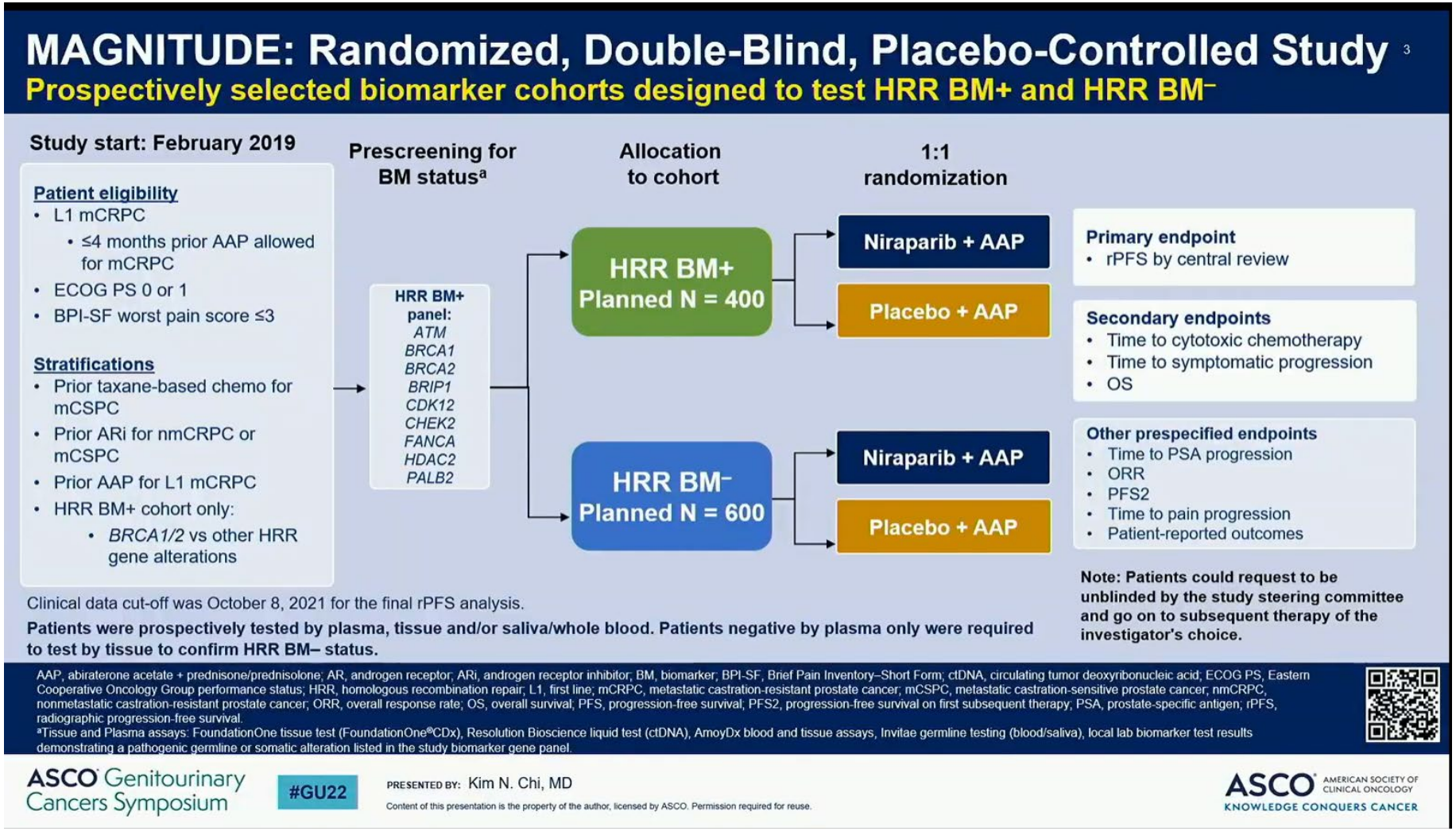
ASCO Genitourinary Cancers Symposium

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] Gerhardt 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 Sandhu[18]

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

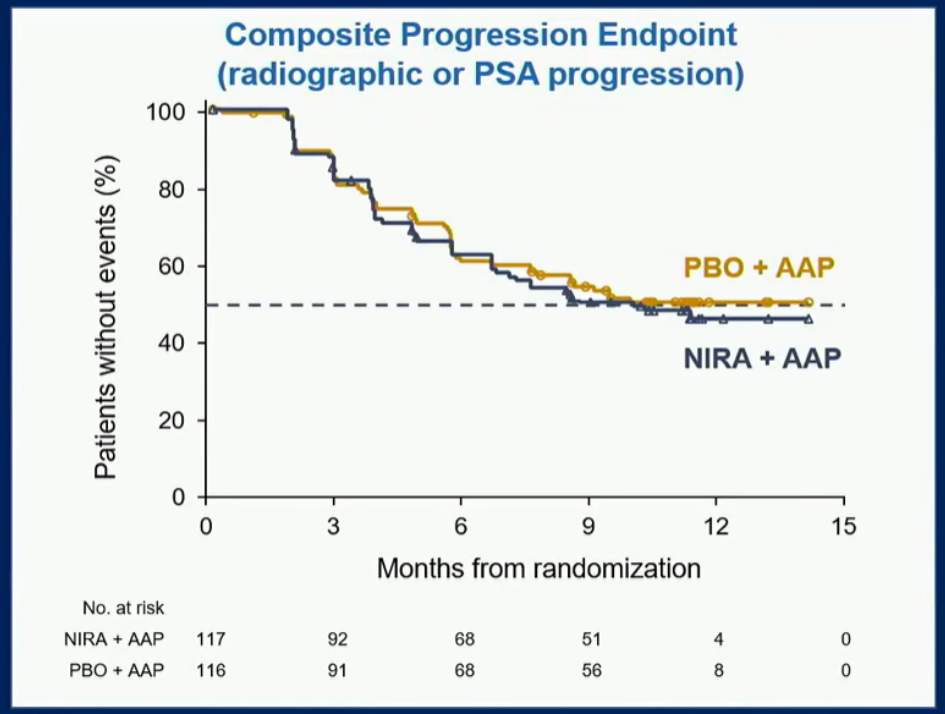
Evre IV Kastrasyona Dirençli Prostat Kanserinde Tedavi Seçeneği Olarak PARP İnhibitörü+Abireteron



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

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

[b]Breakdown 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)

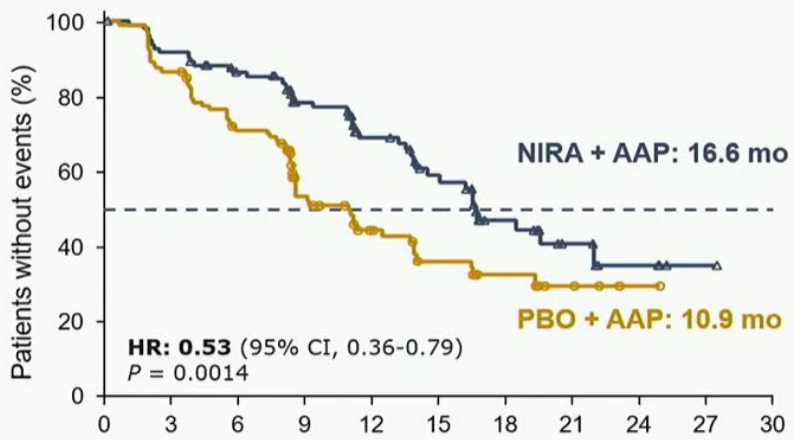
[a]rPFS or PSA progression, whichever occurred first.
AAP, abiraterone acetate + prednisone/prednisolone; AE, adverse event; BM, biomarker; CI, confidence interval; HR, hazard ratio; HRR, homologous recombination repair; IDMC, independent data monitoring committee; mCRPC, metastatic castration-resistant 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+Abireteron

MAGNITUDE *BRCA1/2-mutated*: Primary Endpoint

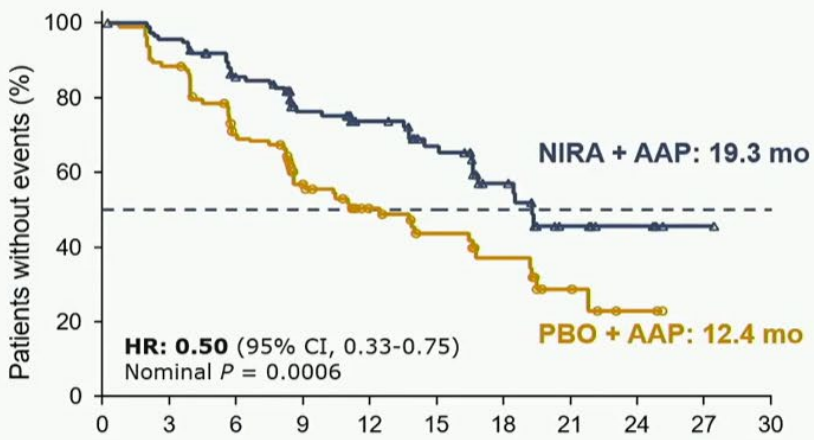
NIRA + AAP Significantly Reduced the Risk of Progression or Death by 47%

rPFS assessed by central review



No. at risk											
NIRA + AAP	113	103	90	65	45	31	18	9	4	1	0
PBO + AAP	112	97	77	43	28	20	11	5	2	0	0

rPFS assessed by investigator



No. at risk											
NIRA + AAP	113	107	90	64	49	36	23	10	5	1	0
PBO + AAP	112	99	73	45	32	23	14	6	2	0	0

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.

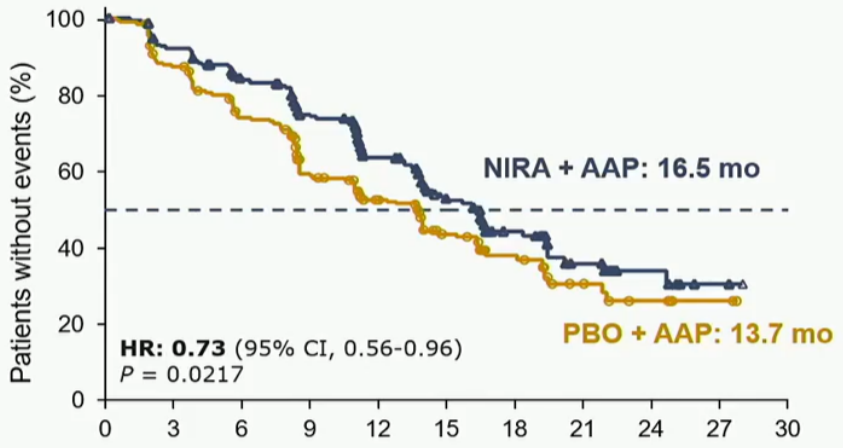
PRESENTED BY: Kim N. Chi, MD

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

MAGNITUDE All HRR BM+: Primary Endpoint

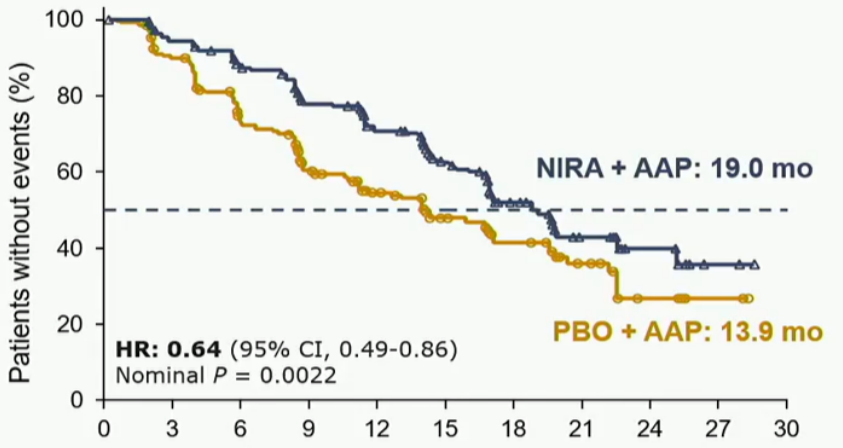
NIRA + AAP Significantly Reduced the Risk of Progression or Death by 27%

rPFS assessed by central review



No. at risk											
NIRA + AAP	212	192	167	129	96	64	45	21	10	2	0
PBO + AAP	211	182	149	102	78	53	35	15	9	2	0

rPFS assessed by investigator



No. at risk											
NIRA + AAP	212	197	174	136	108	75	50	23	11	2	0
PBO + AAP	211	187	145	103	81	58	41	20	9	2	0

Median follow-up 18.6 months

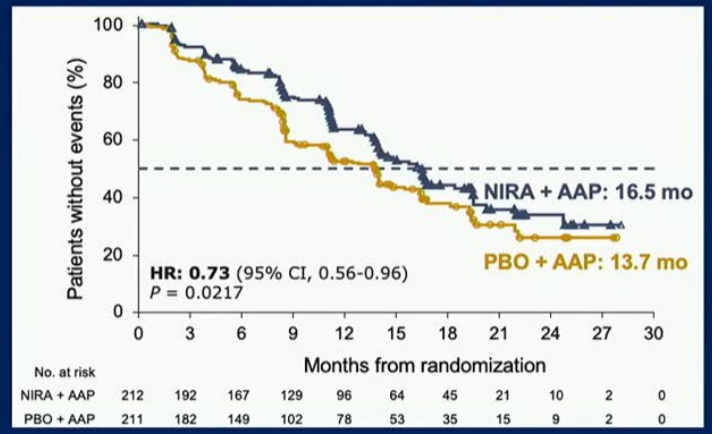
AAP, abiraterone acetate + prednisone/prednisolone; BM, biomarker; CI, confidence interval; HR, hazard ratio; HRR, homologous recombination repair; NIRA, niraparib; PBO, placebo; rPFS, radiographic progression-free survival.

PRESENTED BY: Kim N. Chi, MD

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

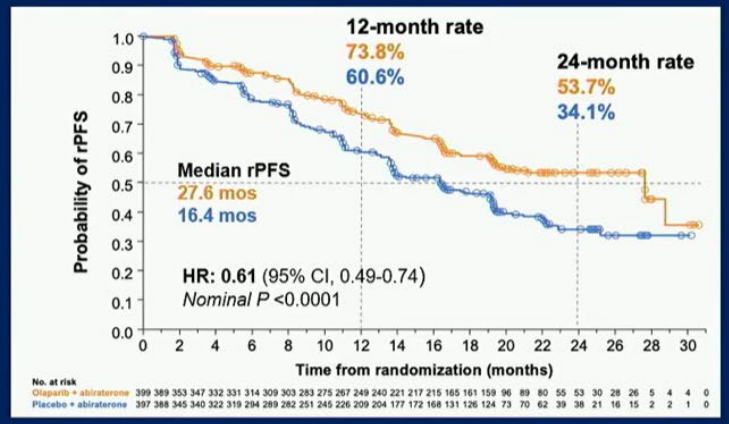
rPFS by Blinded Independent Central Review

MAGNITUDE All HRR+



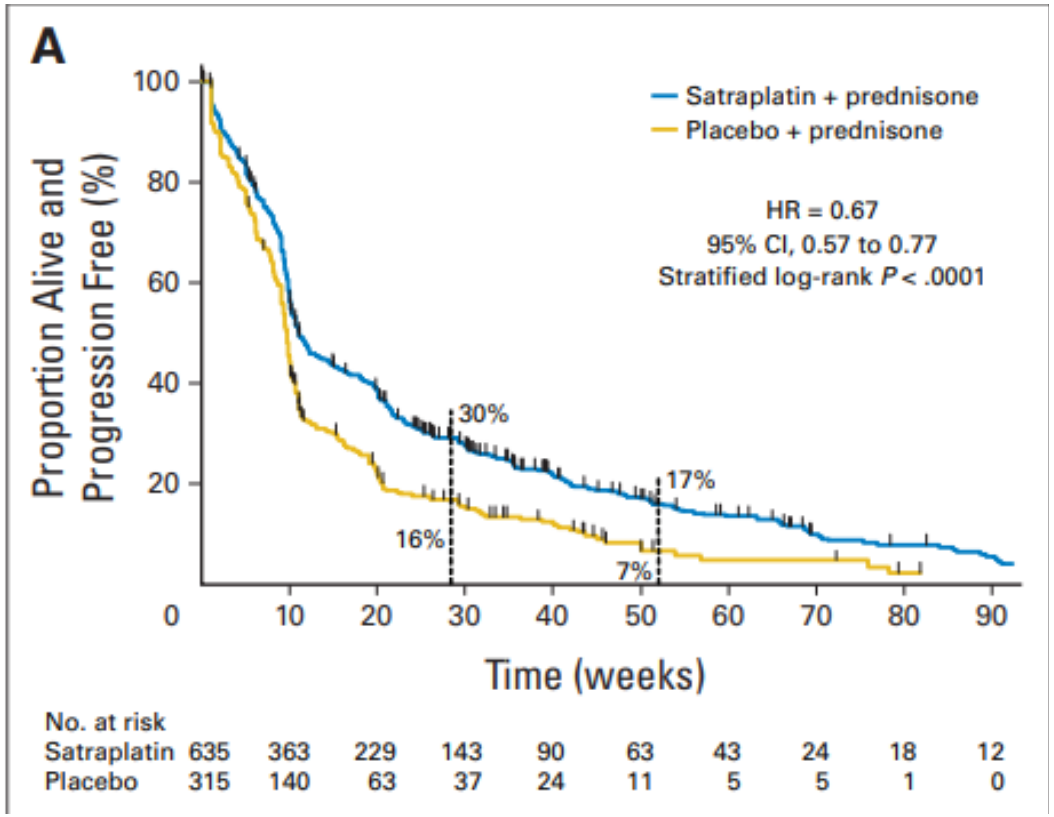
Median rPFS improvement of 2.8 mos in combination arm (5.1 mos by investigator review)

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



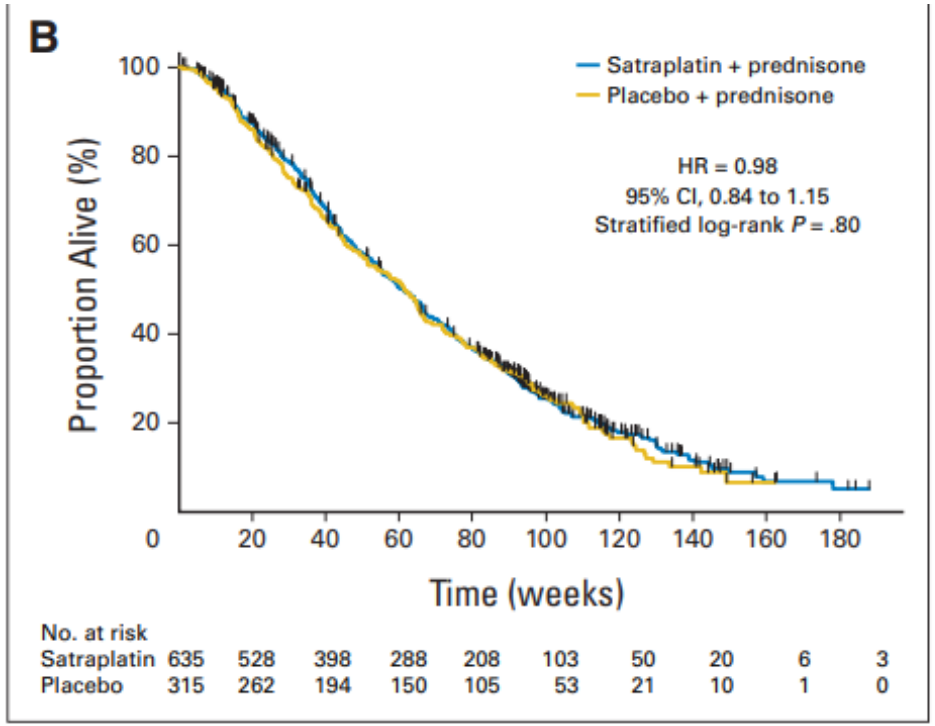


Fig 2. (A) Progression-free survival (intent-to-treat population) and (B) overall survival (intent-to-treat population). HR, hazard ratio.

SPARC: Satraplatin in Metastatic CRPC After Chemotherapy, JCO 2009

DNA Repair Gen Değişikliği Olan Hastalarda RA-223 etkinliği

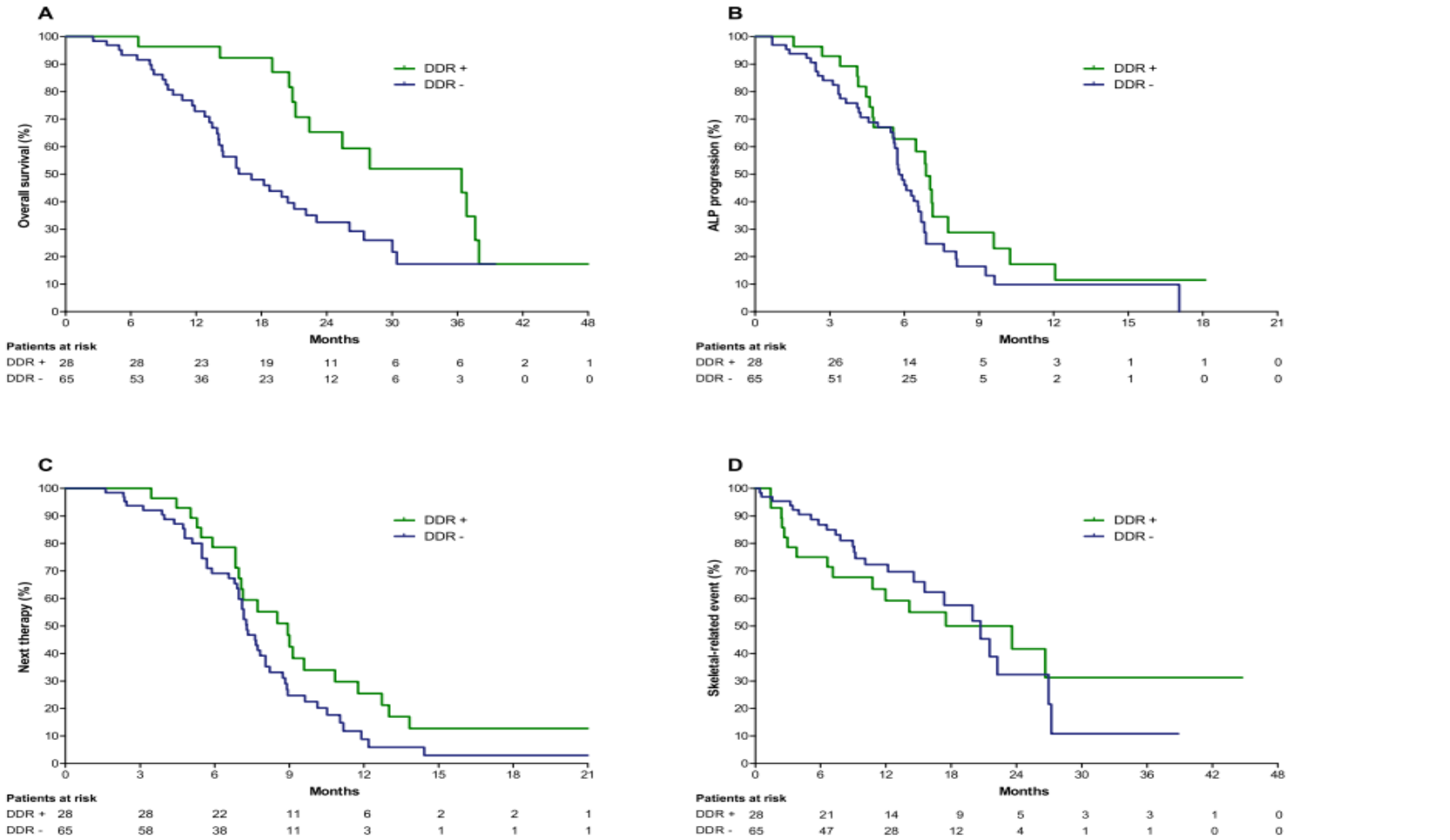
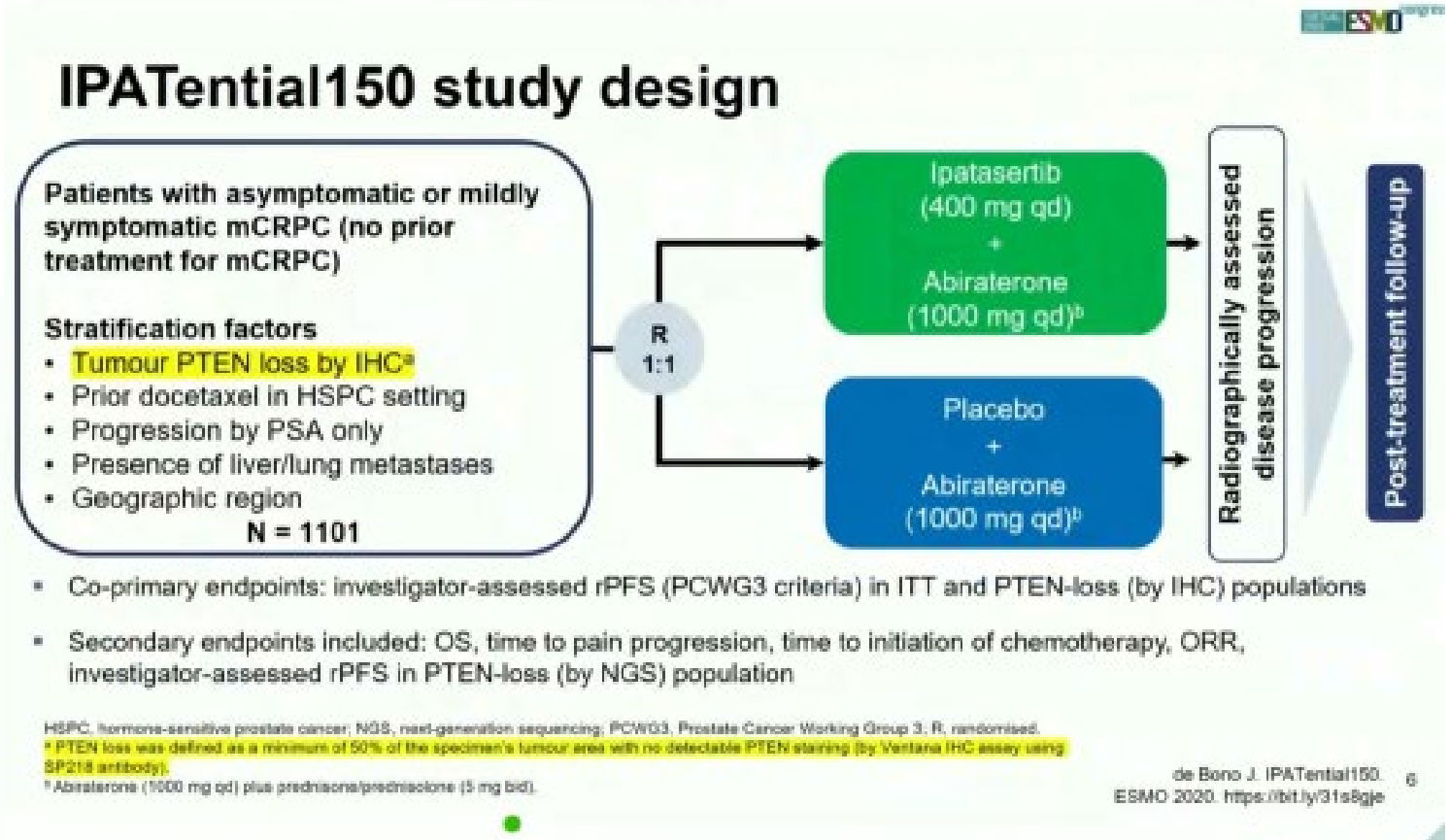


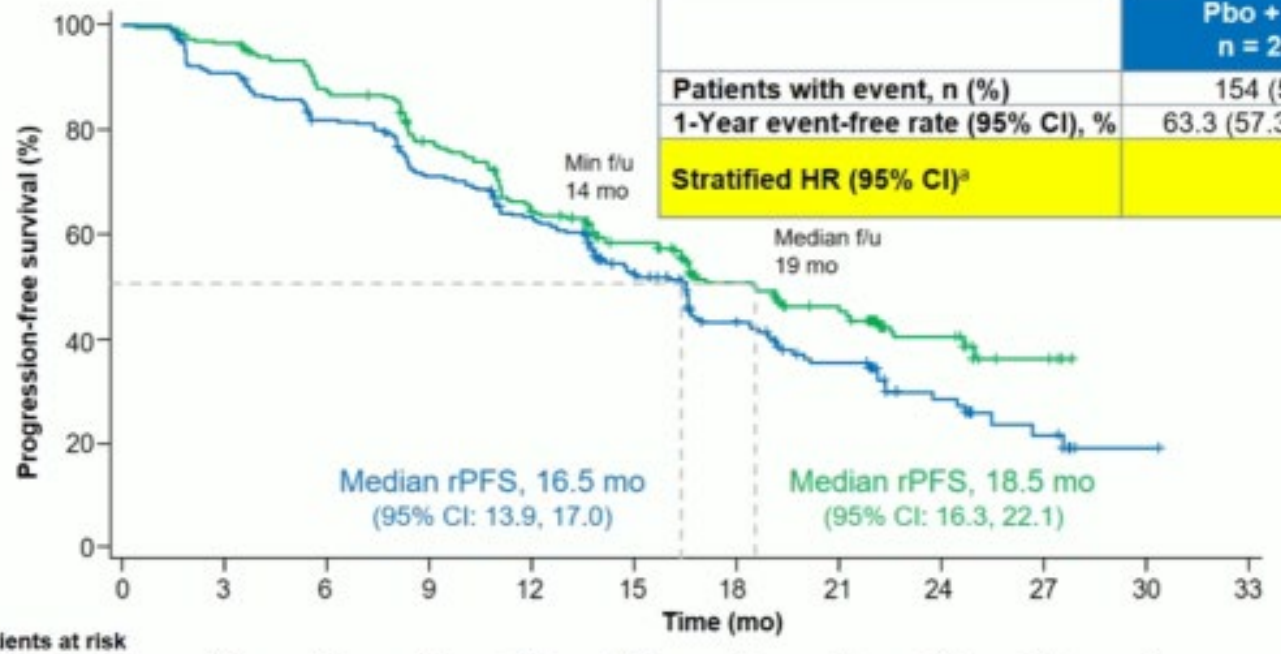
Fig. 2. Kaplan–Meier curves, stratified by DNA damage repair (DDR) mutation status, A. Overall survival, B. Time to alkaline phosphatase (ALP) progression, C. Time to initiation of next systemic therapy. D. Time to first skeletal-related evens (SRE).

Kastrasyona Dirençli Prostat Kanseri
PI3K/AKT inhibisyonu



Kastrasyona Dirençli Prostat Kanseri
PI3K/AKT inhibisyonu

rPFS in the PTEN-loss by IHC population



	Pbo + abi n = 261	Ipat + abi n = 260
Patients with event, n (%)	154 (59)	124 (48)
1-Year event-free rate (95% CI), %	63.3 (57.3, 69.3)	64.4 (58.3, 70.5)
Stratified HR (95% CI)[a]	0.77 (0.61, 0.98) *P* = 0.0335[b]	

Patients at risk

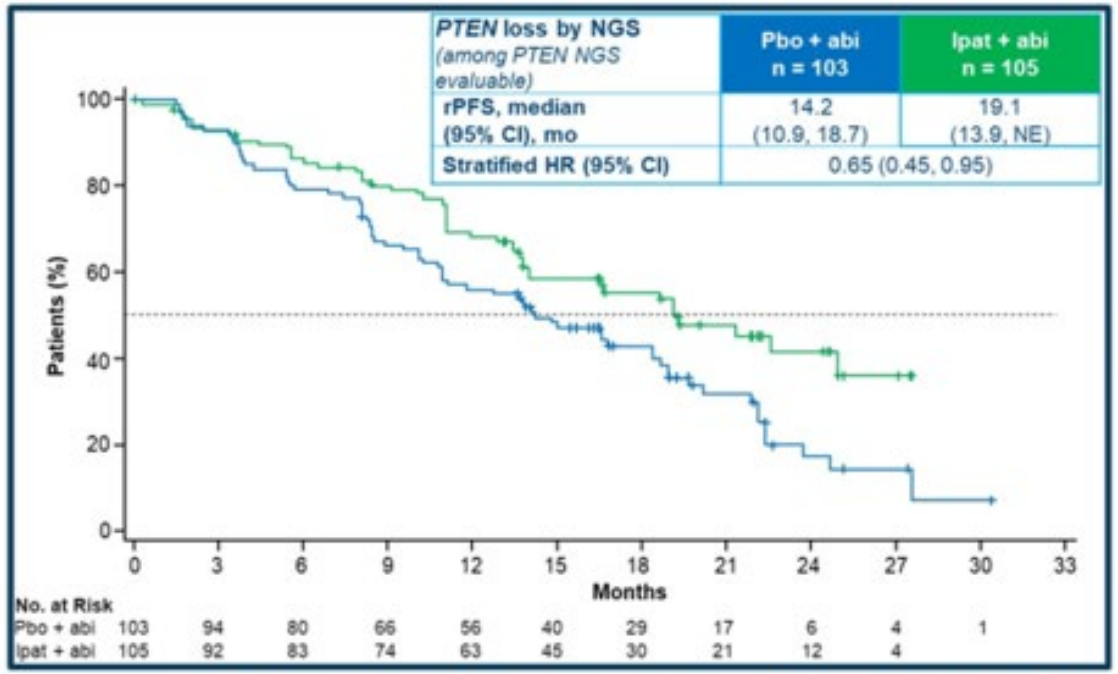
Pbo + abi	261	233	206	175	151	105	71	41	22	10	3
Ipat + abi	260	238	211	182	149	113	72	48	25	12	

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 α = 0.05 level.**

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

Kastrasyona Dirençli Prostat Kanseri
PI3K/AKT inhibisyonu

Improvement in rPFS by NGS Population



PTEN loss by NGS (among PTEN NGS evaluable)	Pbo + abi n = 103	Ipat + abi n = 105
rPFS, median (95% CI), mo	14.2 (10.9, 18.7)	19.1 (13.9, NE)
Stratified HR (95% CI)	0.65 (0.45, 0.95)	

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.

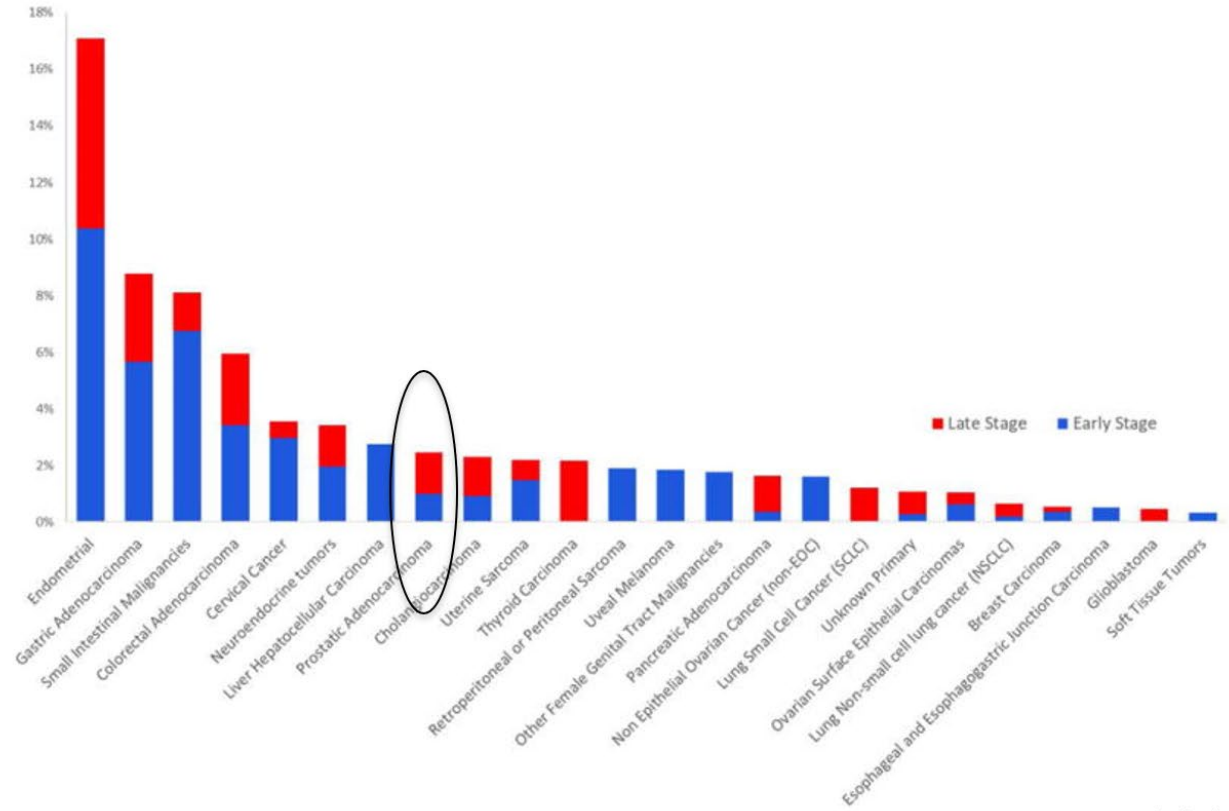
Presented By Johann De Bono at 2021 Genitourinary Cancers Symposium

Kastrasyona Dirençli Prostat Kanseri
PI3K/AKT inhibisyonu

	PIK3CA/AKT1/PTEN altered by NGS n=250		*PIK3CA/AKT1/PTEN* 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. [a]Unstratified.[b]Per RECIST 1.1 and PCWG3 in pts with baseline lesions.

MSI High Prostat Kanserinde Tedavi Seçenekleri



Le et al. Science 2017

Memorial Sloan Kettering Cancer Center

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.

Abida et al, JAMA Onc 2018

Memorial Sloan Kettering Cancer Center

MSI High Prostat Kanserinde Tedavi Seçenekleri

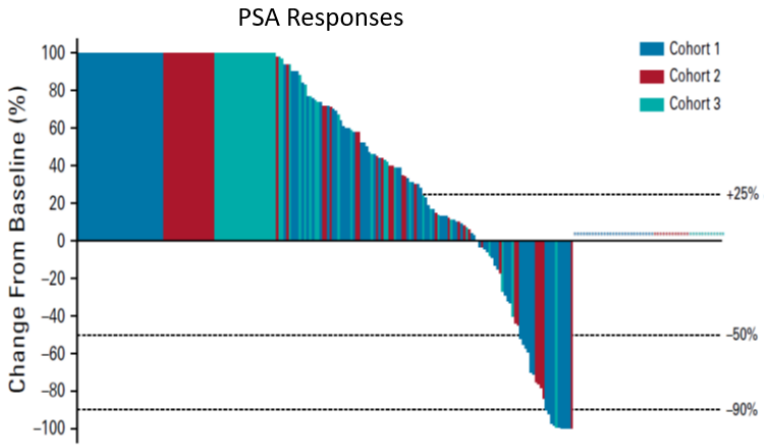
Pembrolizumab Monotherapy in mCRPC: KEYNOTE-199

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 ≥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



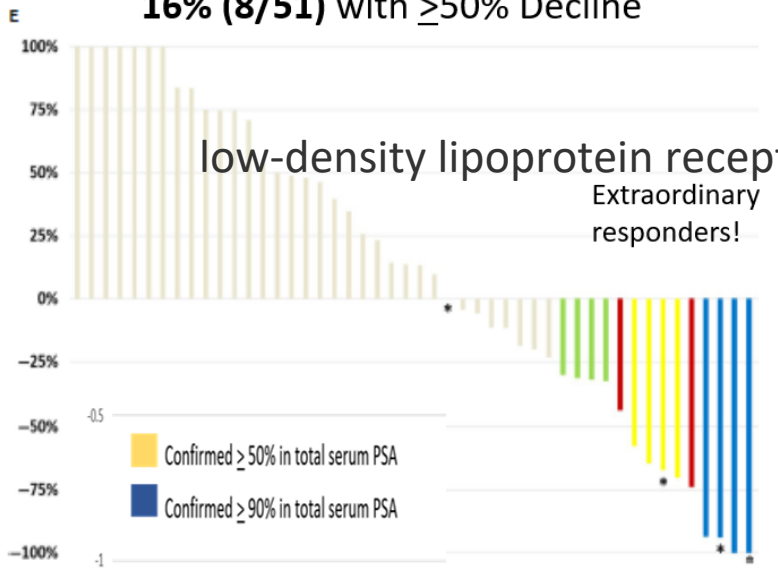
Antonarakis et al JCO 2019

Memorial Sloan Kettering Cancer Center

MSI High Prostat Kanserinde Tedavi Seçenekleri

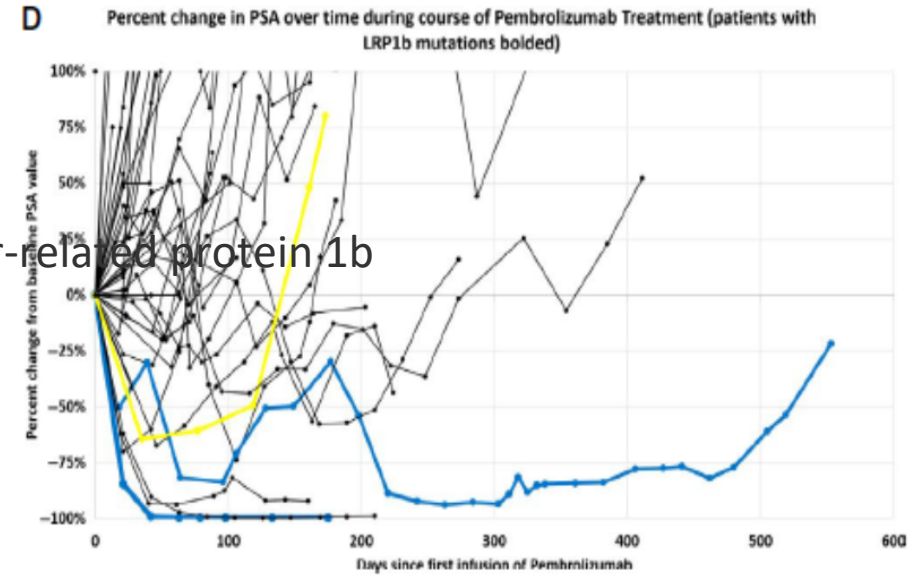
Duke Experience with Pembrolizumab for mCRPC

Best Overall Confirmed PSA Decline:
16% (8/51) with ≥50% Decline



low-density lipoprotein receptor-related protein 1b

Extraordinary responders!



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

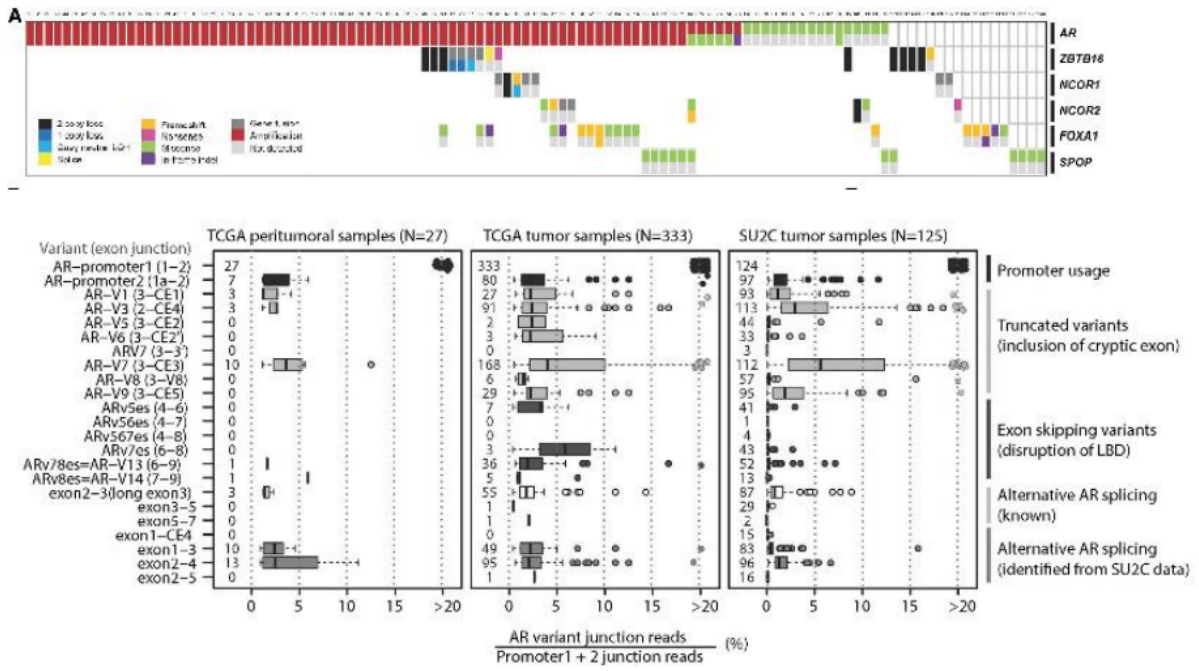
Tucker M…Armstrong AJ Cancer Med 2019

low-density lipoprotein receptor-related protein 1b

Memorial Sloan Kettering Cancer Center

AR yolağında meydana gelen değişimler

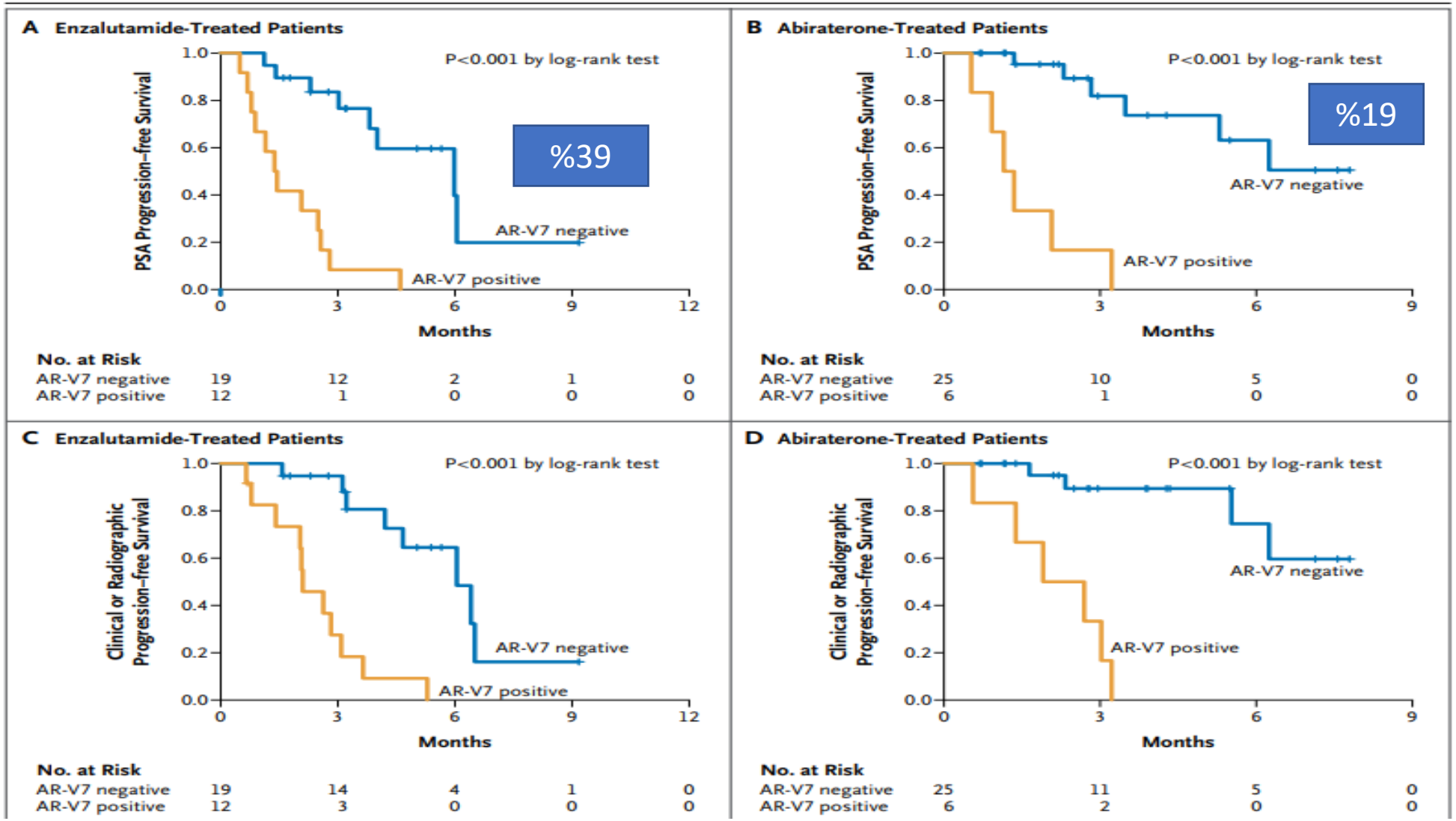
Molecular Evaluation in CRPC



- 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

Robinson et al. Cell 2015

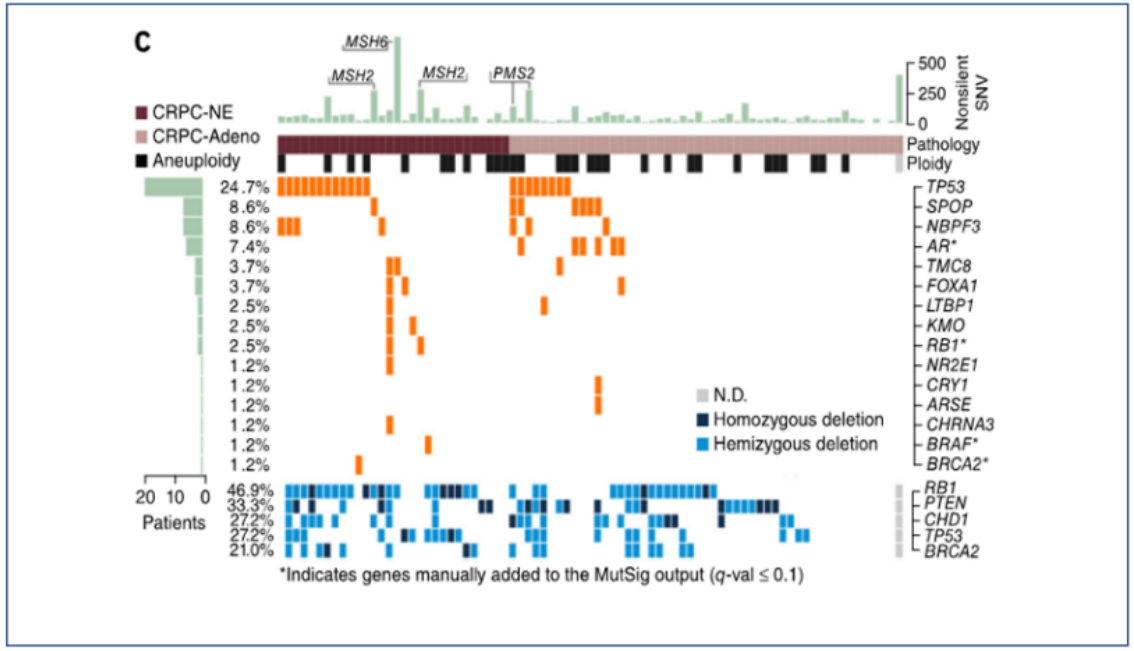
AR yolağında meydana gelen değişimler



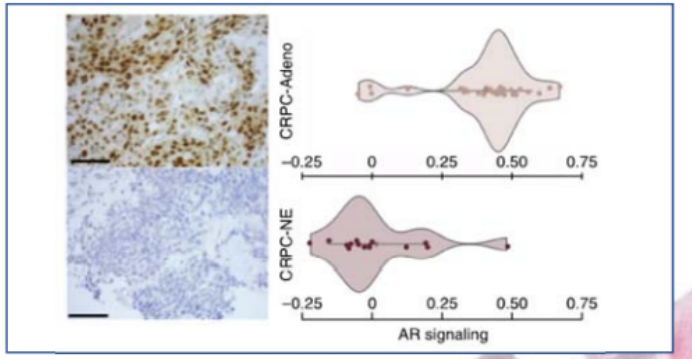
Emmanuel A at al, NEJM 2014

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



Beltran H et al. Nat Med 2016

Prostat Kanseri Nöroendokrin Diferansiasyon

Platinums and Aggressive Prostate Cancer

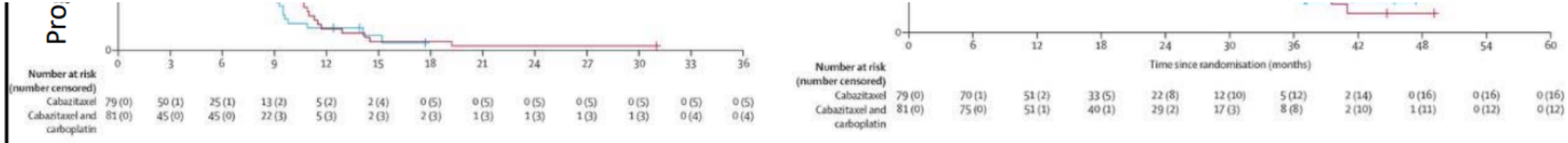
- Phase II trial of first-line carboplatin and docetaxel (CD) and second-line etoposide and cisplatin (EP)
- Aggressive disease defined by
  - Visceral dx or lytic bone mets
  - Bulky tumor masses
  - Low PSA relative to tumor burden
  - Short response to ADT
- 65.4% and 33.8% were progression free after 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

Aparicio et al CCR 2013

Prostat Kanseri Nöroendokrin Diferansiasyon

Combination Carboplatin and Cabazitaxel

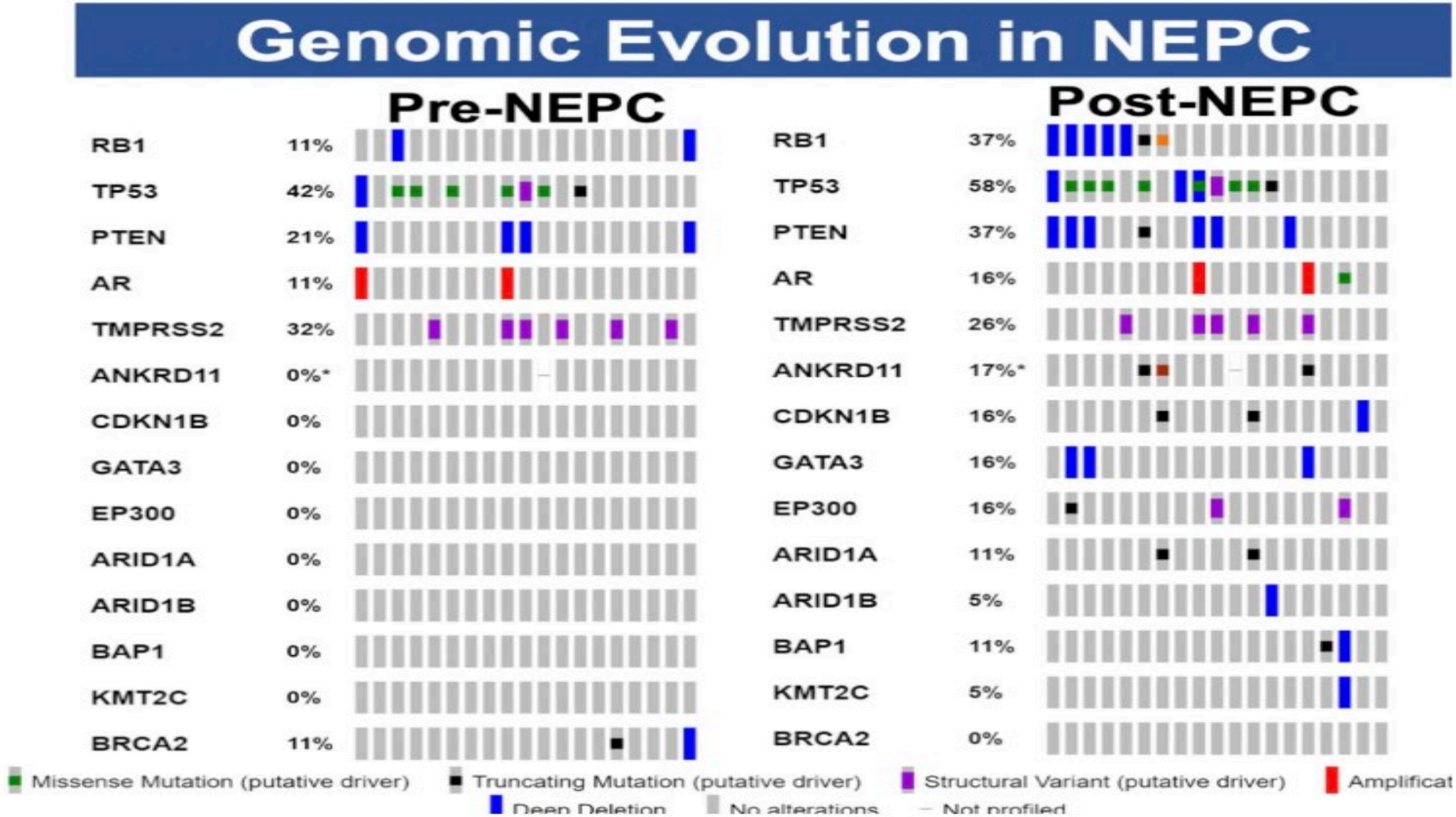
Cabazitaxel 20 mg/m² plus carboplatin AUC 4 mg/mL per min with growth factor support can be considered for fit patients with aggressive variant prostate cancer (visceral metastases, low PSA and bulky disease, high LDH, high CEA, lytic bone metastases, NEPC histology) or unfavorable genomics (defects 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

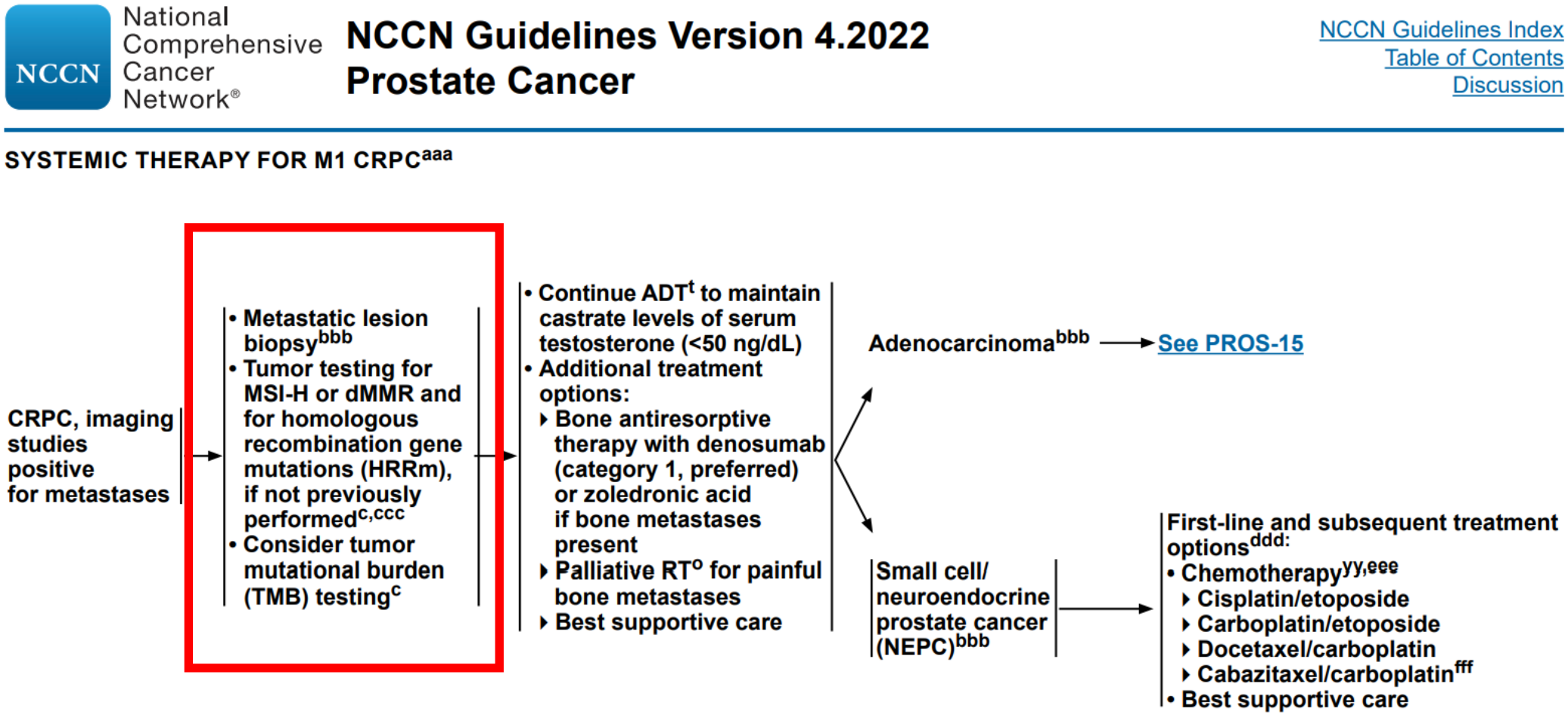
Prostat Kanseri Nöroendokrin Diferansiasyon



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/Abireteron sonrası Olaparib
- ❑ Dosetaksel sonrası Rucaparib
- ❑ Abireteron+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


National Comprehensive Cancer Network®
NCCN Guidelines Version 4.2022
Prostate Cancer
NCCN Guidelines Index
Table of Contents
Discussion
SYSTEMIC THERAPY FOR M1 CRPC[aaa]
CRPC, imaging studies positive for metastases
• Metastatic lesion biopsy[bbb]
• Tumor testing for MSI-H or dMMR and for homologous recombination gene mutations (HRRm), if not previously performed[c,ccc]
• Consider tumor mutational burden (TMB) testing[c]
• Continue ADT[t] to maintain castrate levels of serum testosterone (<50 ng/dL)
• Additional treatment options:
▸ Bone antiresorptive therapy with denosumab (category 1, preferred) or zoledronic acid if bone metastases present
▸ Palliative RT[o] for painful bone metastases
▸ Best supportive care
Adenocarcinoma[bbb]
See PROS-15
Small cell/ neuroendocrine prostate cancer (NEPC)[bbb]
First-line and subsequent treatment options[ddd]:
• Chemotherapy[yy,eee]
▸ Cisplatin/etoposide
▸ Carboplatin/etoposide
▸ Docetaxel/carboplatin
▸ Cabazitaxel/carboplatin[fff]
• Best supportive care