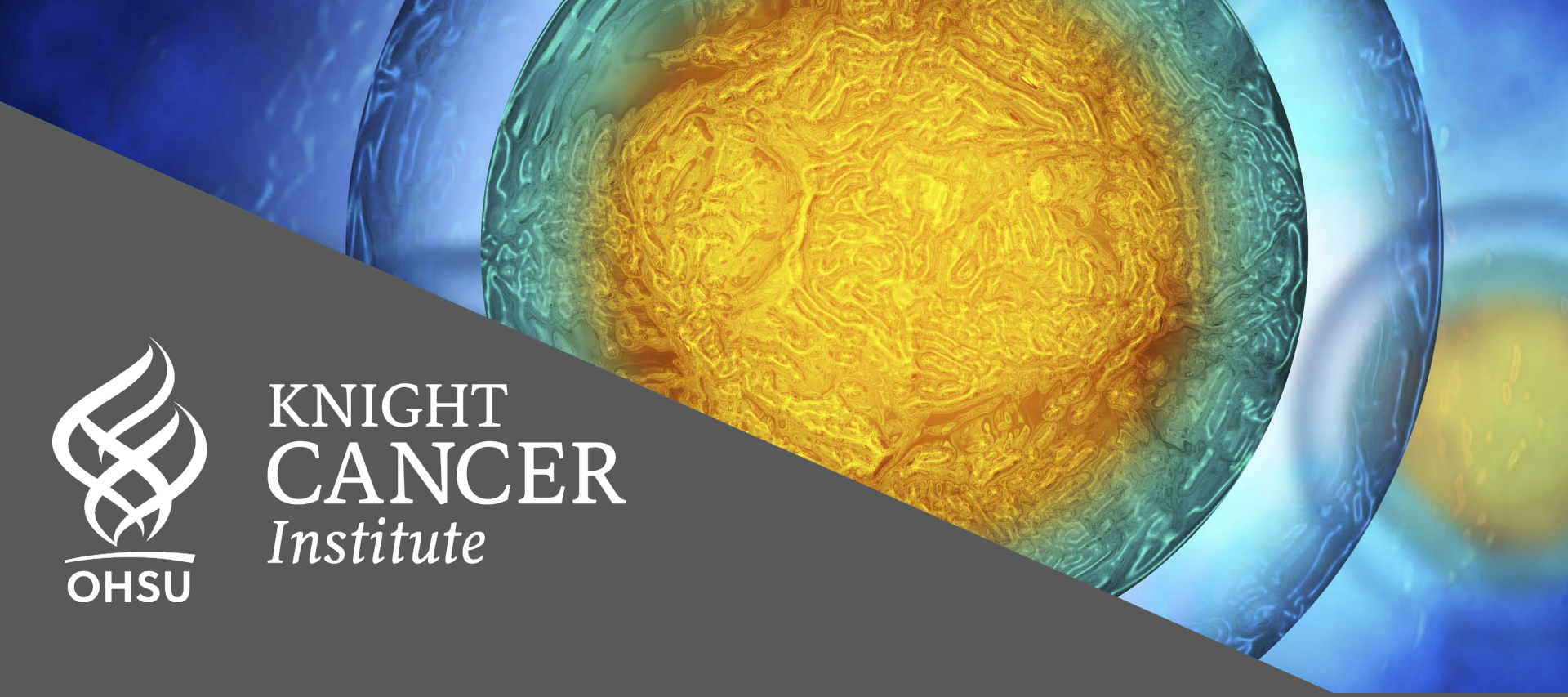

KNIGHT CANCER Institute

OHSU

Prostate Cancer Clinical Genomics

6th annual Knight Cancer Network Symposium

Alexandra Sokolova, MD
Assistant Professor Medical Oncology
Oregon Health Science University, Portland, OR
March 18, 2022

Disclosures

- Lantheus (Consulting)

OHSU KNIGHT CANCER Institute

Learning Objectives

- Background
- Who To Test
- Why Test
  - Informs treatment
    - PARP inhibitor
    - Platinum chemotherapy
    - Immune checkpoint inhibitor
    - Clinical trials
  - Informs prognosis
  - May inform family cancer risks
- Take Home Points

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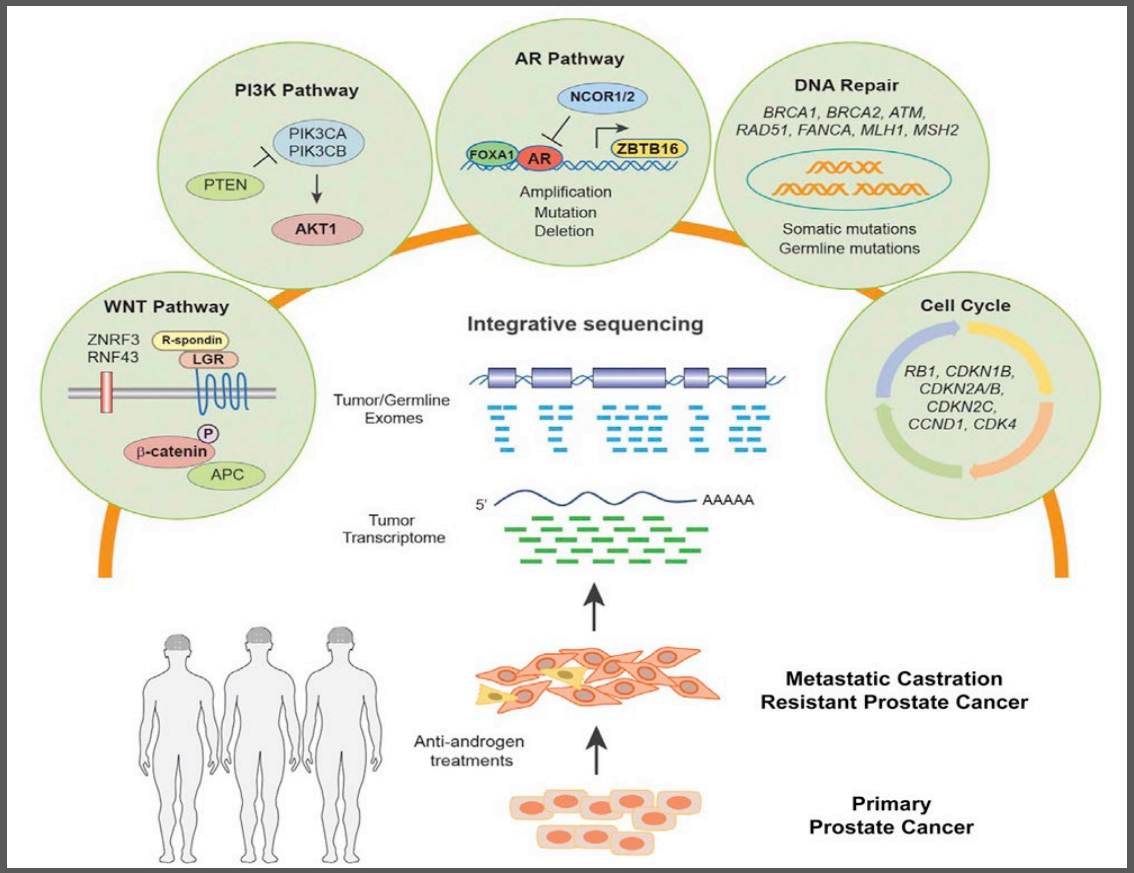
Mutations in Metastatic Prostate Cancer

Actionable mutations: 133/150 pts (89%)



Robinson D., et al. Cell, 2015

OHSU KNIGHT CANCER Institute

Mutations in Metastatic Prostate Cancer

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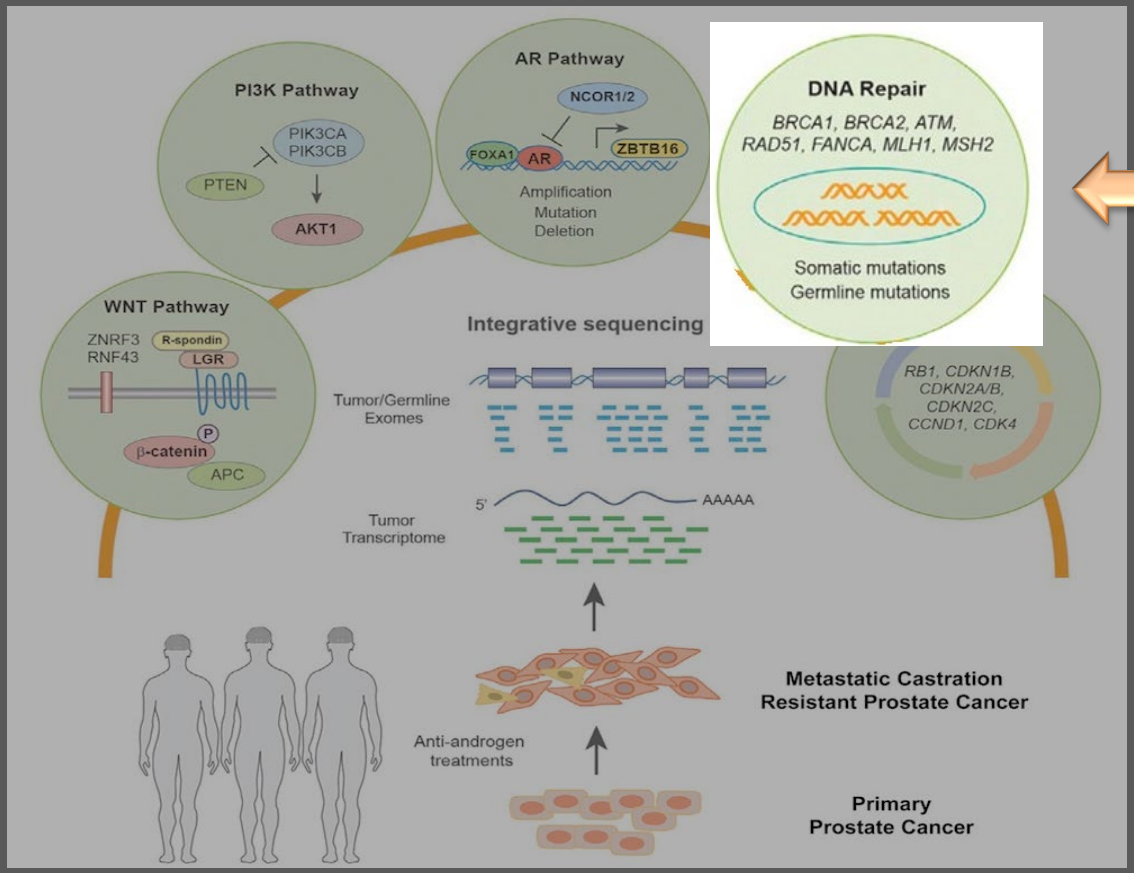

Robinson D., et al. Cell, 2015

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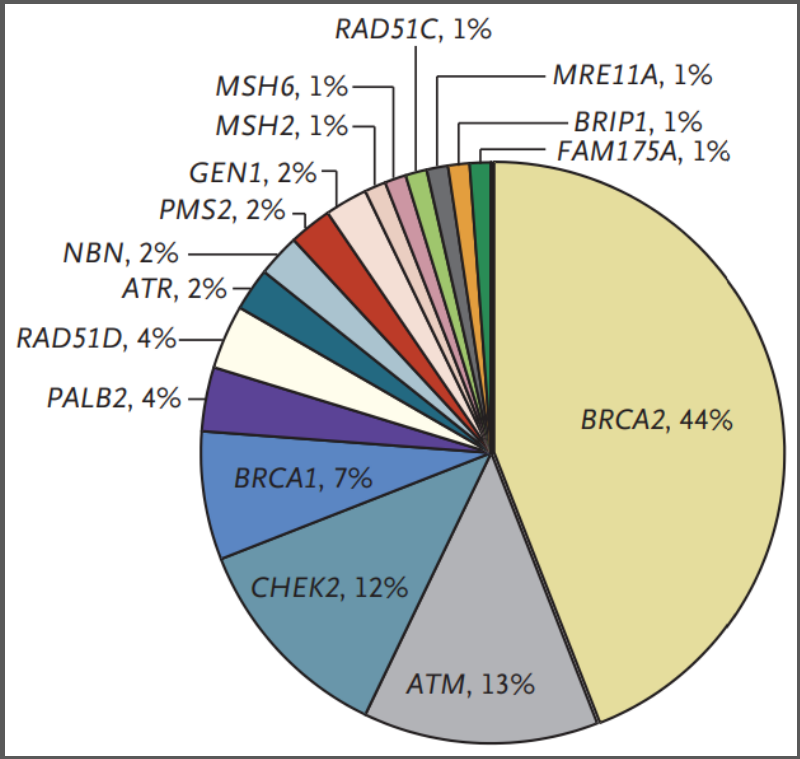
Inherited DNA-Repair Gene Mutations in Men with Metastatic Prostate Cancer



12% with metastatic prostate cancer

vs

5% with localized prostate cancer

vs

3% without a known cancer diagnosis

Pritchard C., et al. N Engl J Med, 2016
Cancer Genome Atlas prostate cancer study
Exome Aggregation Consortium

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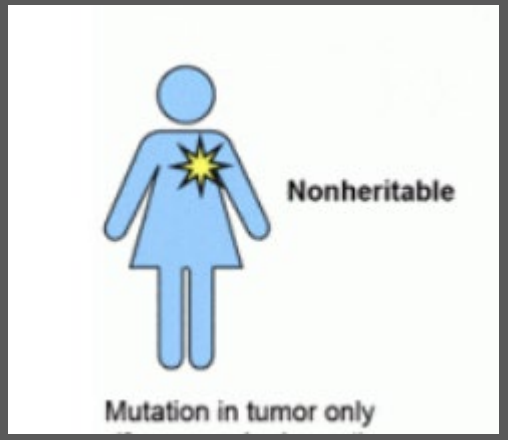
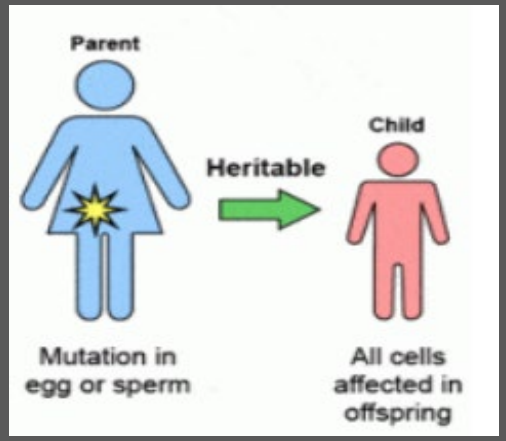
Types of Genetic Testing

Somatic/Tumor
tests tumor DNA
- Tumor tissue
- ctDNA

Germline
tests DNA patient is born with
- Saliva
- Blood





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Learning Objectives

- Background
- Who To Test
- Why Test
  - Informs treatment
    - PARPI
    - Platinum
    - Immunotherapy
    - Clinical trials
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- Take Home Points

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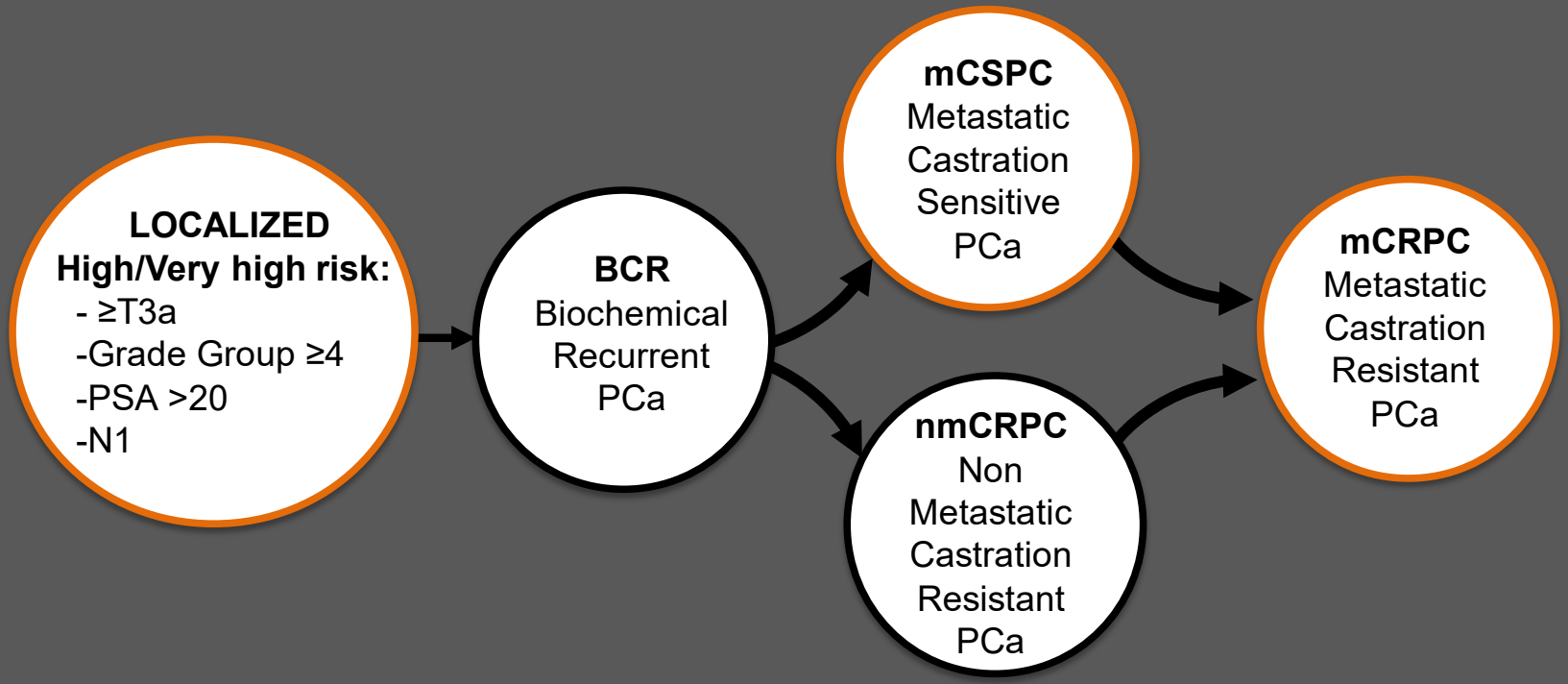
Germline Testing– Who to Refer



- Everyone who meets family history criteria
- Consider if intraductal/cribriform histology
- Genes to include: *BRCA1, BRCA2, ATM, PALB2, CHEK2, MLH1, MSH2, MSH6, PMS2*

NCCN Prostate Cancer Guidelines 3.2022 01/10/2022

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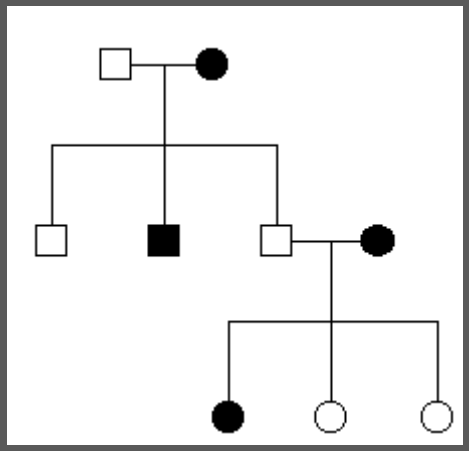
Germline Testing – Who to Refer

HBOC Lynch



- Personal history of prostate cancer with
  - 1 or more close relatives with
    - Pancreatic cancer
    - Ovarian cancer
    - Breast cancer at 50 or younger
    - Colorectal at 50 or younger
    - Prostate cancer metastatic, high risk or very high risk
  - 1 or more close relatives with
    - Prostate cancer at 60 or younger
  - 2 or more close relatives with
    - Breast cancer at any age
    - Prostate cancer at any age
  - 3 or more close relatives with
    - Lynch syndrome realter cancer: colorectal, endometrial, gastric, ovarian, pancreatic, urothelial, glioblastoma, bile duct or small intestinal cancer
  - Ashkenazi Jewish ancestry
  - A known family history of germline mutation
  - Personal history of breast cancer

NCCN Prostate Cancer Guidelines 3.2022 01/10/2022

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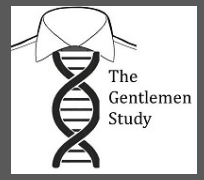
Germline Testing – How to Test

- Referral to genetic counselor
- Sending patient for patient-initiated testing (*e.g* COLOR, Invitae, around $250)
- Patient facing research:
  - The Gentlemen: https://redcap.iths.org/surveys/?s=XELDJEX3K3
  - PROMISE: https://www.prostatecancerpromise.org/



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Prostate Cancer Genetics at OHSU

- Opened November 2021
- Men w/ Pca eligible to germline testing and with known mutations
- To refer patients:

Email: oncaccess@ohsu.edu

Call: 503-494-7999

Fax: 503-346-6854

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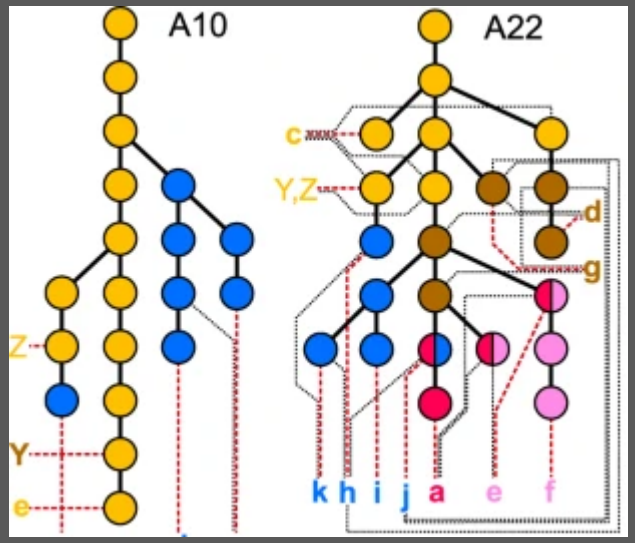
Somatic Testing Who to Test

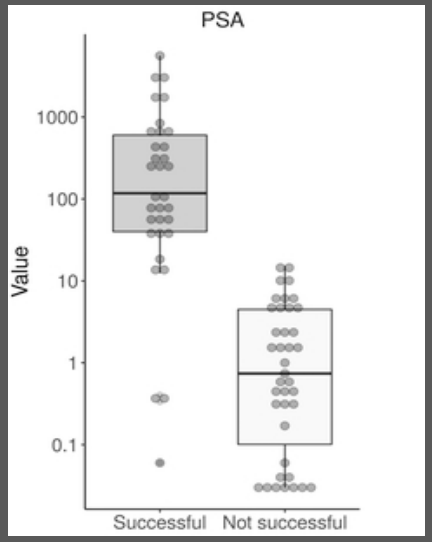
- *BRCA1, BRCA2, ATM, PALB2, FANCA, RAD51D, CHEK2, CDK12:*
  - recommended for all with metastatic PCa,
  - can be considered in men with regional disease
- Microsatellite High (MSI-H) and mismatch repair deficiency (dMMR) testing
  - recommended for men with mCRPC
  - may be considered for men with regional and mCSPC
- Tumor mutational burden (TMB) testing
  - may be considered in mCRPC

NCCN Prostate Cancer Guidelines 3.2022 01/10/2022

Somatic Testing – How to Test Blood vs Tumor

- Multilineage prostate cancer evolution
  - HRD is early truncal event
- ctDNA considered more sensitive if PSA >10 ng/ml





Schweizer et al. Prostate 2019
Woodcock et al. Nature Com 2020

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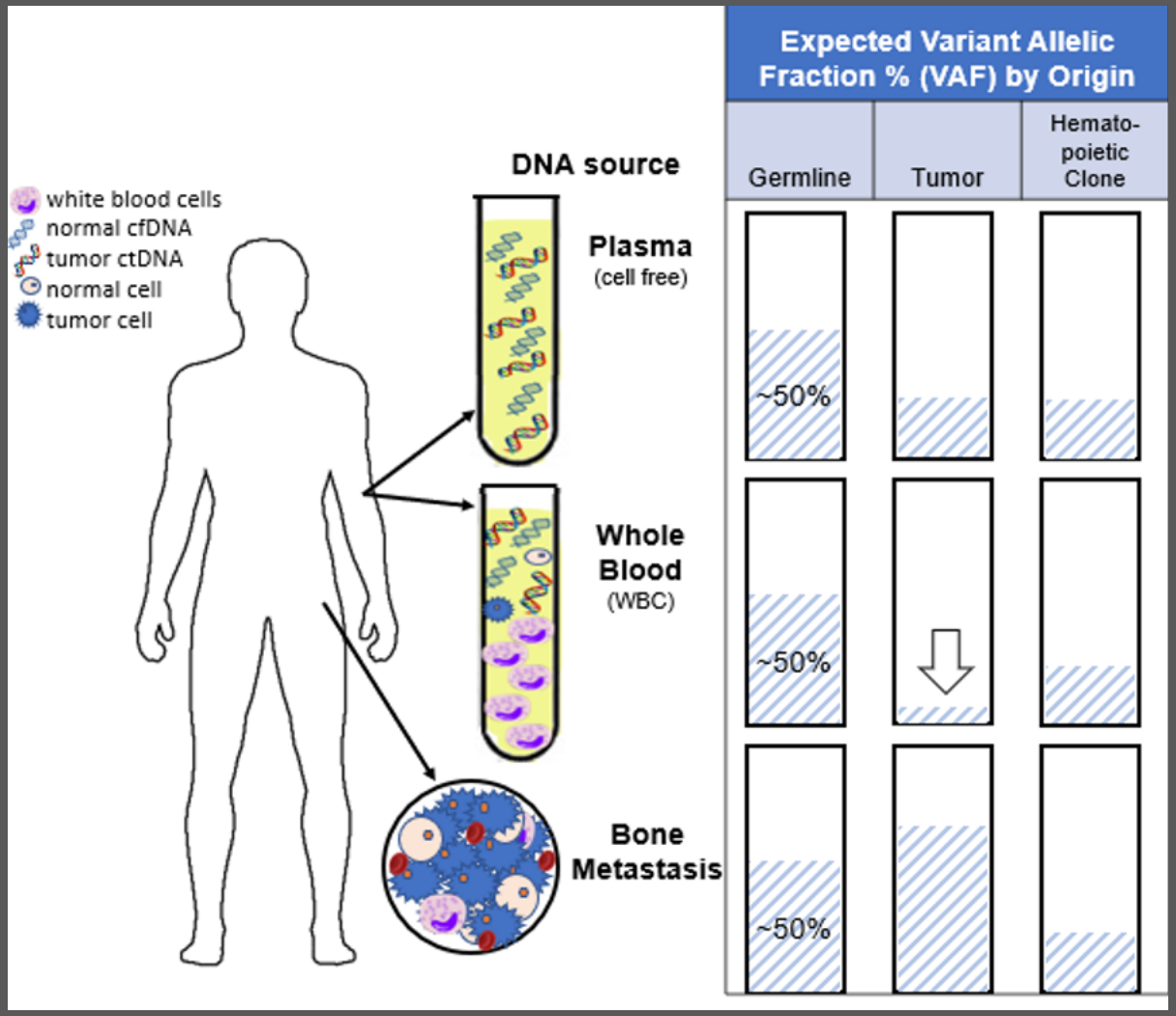
CHIP Interference with ctDNA testing



Sokolova, *et al*, JNCCN 2020

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Somatic Testing – How to Test Blood vs Tumor

- OHSU: GENETRAILS
- Commercial Vendors
- Is generally NOT a substitute for germline testing
- If *BRCA1/2* mutations identified on somatic NGS dedicated germline testing is recommended

NCCN Prostate Cancer Guidelines 3.2022 01/10/2022
Schweizer et al. Prostate 2019

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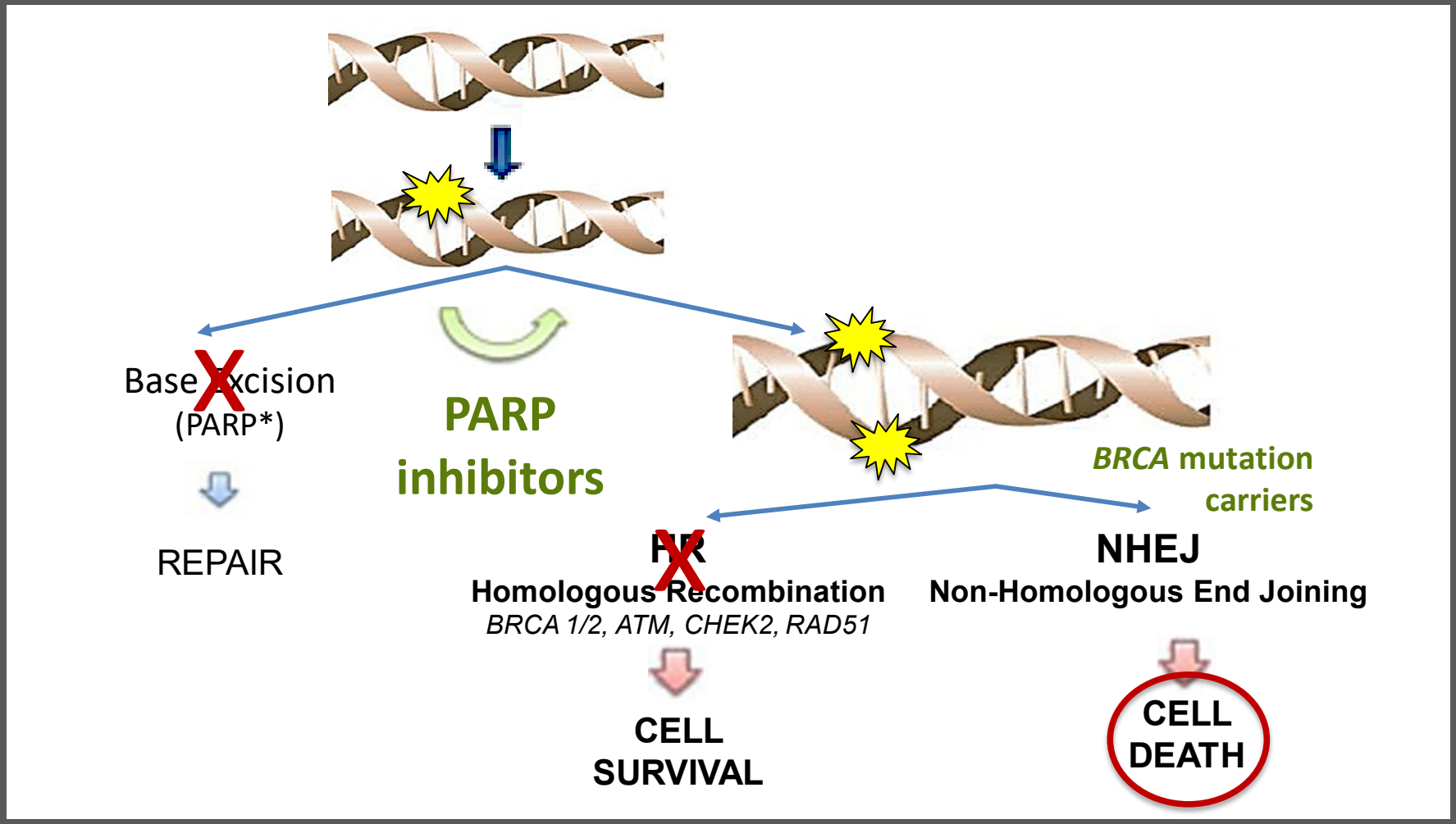
DNA Damage Repair: PARPi



*PARP – Poly-ADP-ribose polymerase

Toss A., et al. J. of Cancer Science and Therapy, 2013

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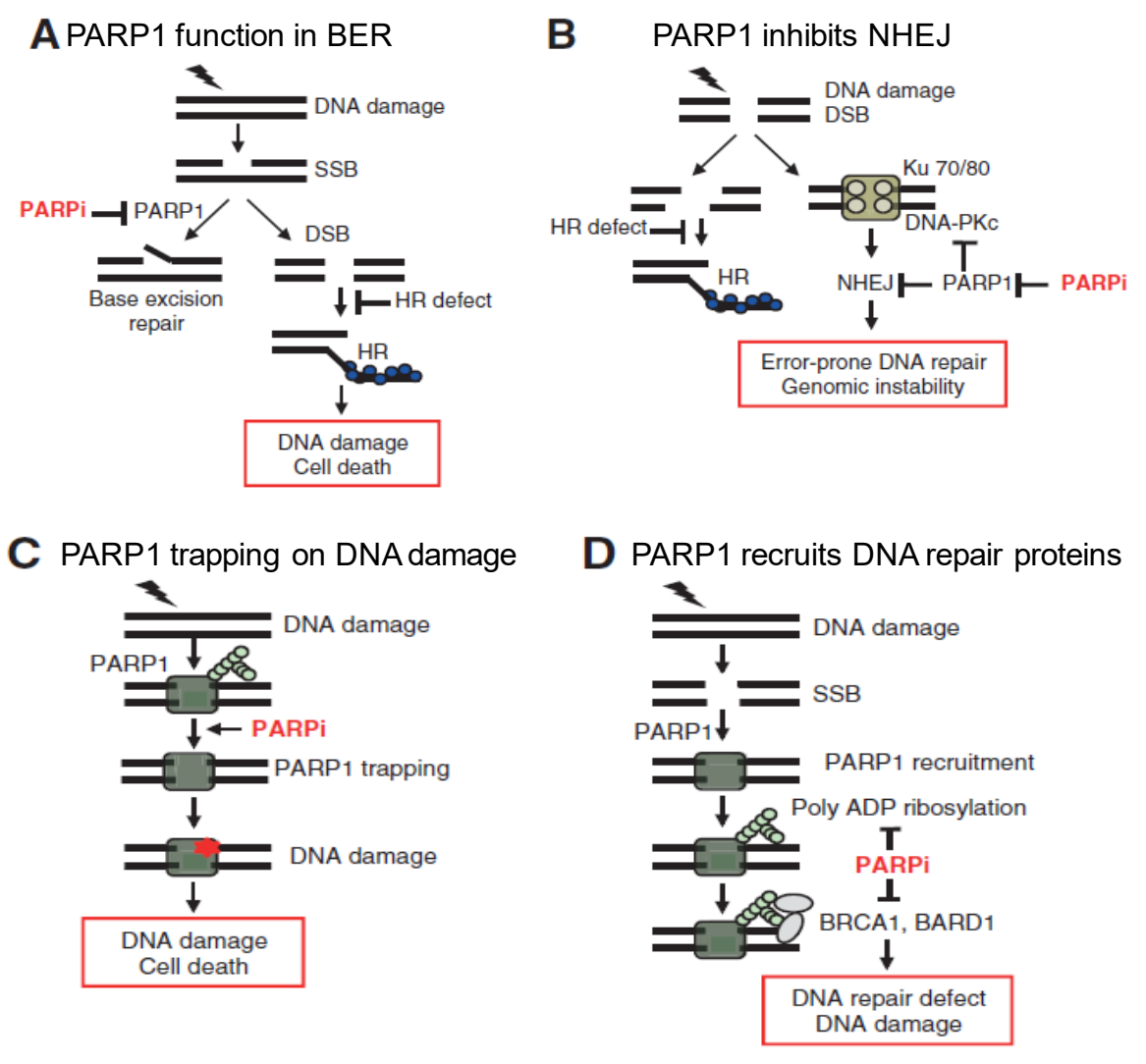
PARPi Targets



Konstantinopoulos et al, Cancer Discovery, 2015

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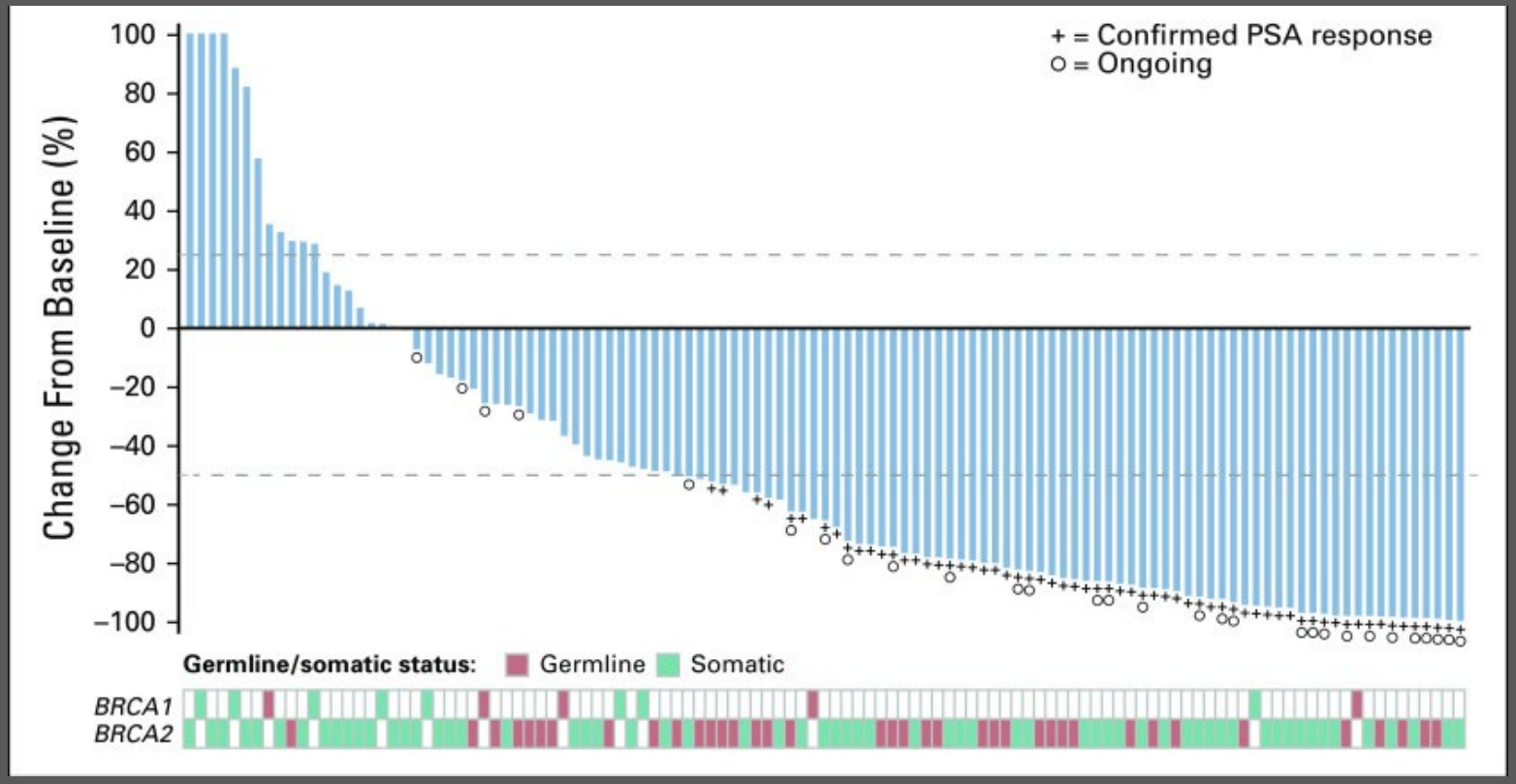
TRITON 2: Rucaparib in mCPRC with *BRCA1/2*

- 55% PSA50 response to Rucaparib



Abida W., et al. JCO, 2020

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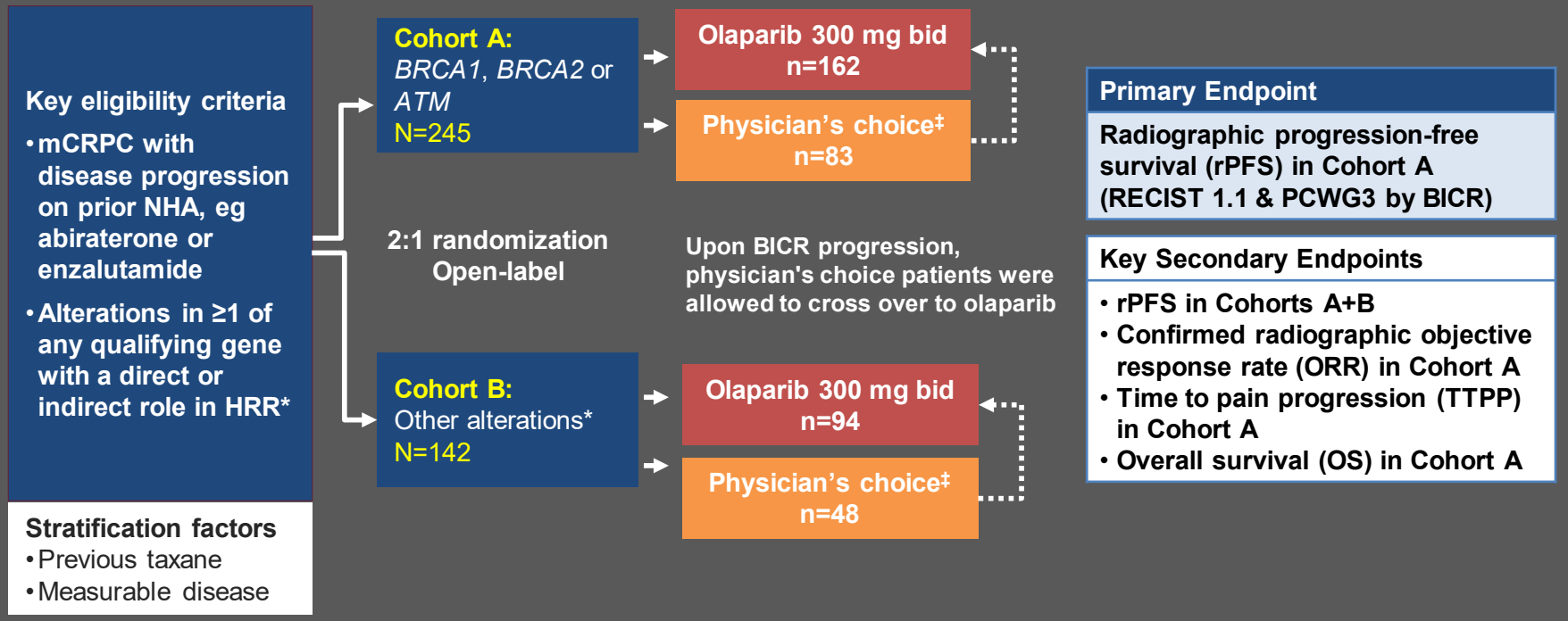
Phase III Trial of PARPi in PCa: PROfound Study Design



**BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D* and/ or *RAD54L*

Hussain M., et al. ESMO, 2019

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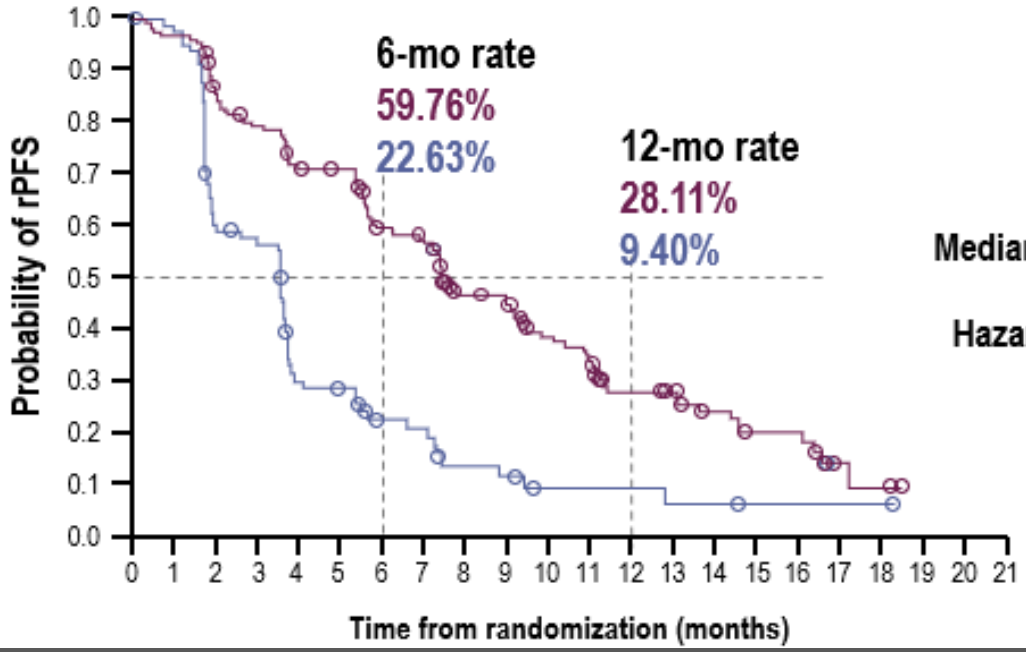
PROfound: Olaparib Improves rPFS*

rPFS BY BICR IN PATIENTS WITH ALTERATIONS IN *BRCA1*, *BRCA2*, OR *ATM* (COHORT A)



	Olaparib (N=162)	Physician's choice (N=83)
Events (%)	106 (65.4)	68 (81.9)
Median rPFS (months)	7.39	3.55
Hazard ratio (95% CI)	0.34 (0.25, 0.47) *P*<0.0001	

*rPFS – radiographic progression free survival

Hussain M., et al. ESMO, 2019
DeBono., et al. NEJM, 2020

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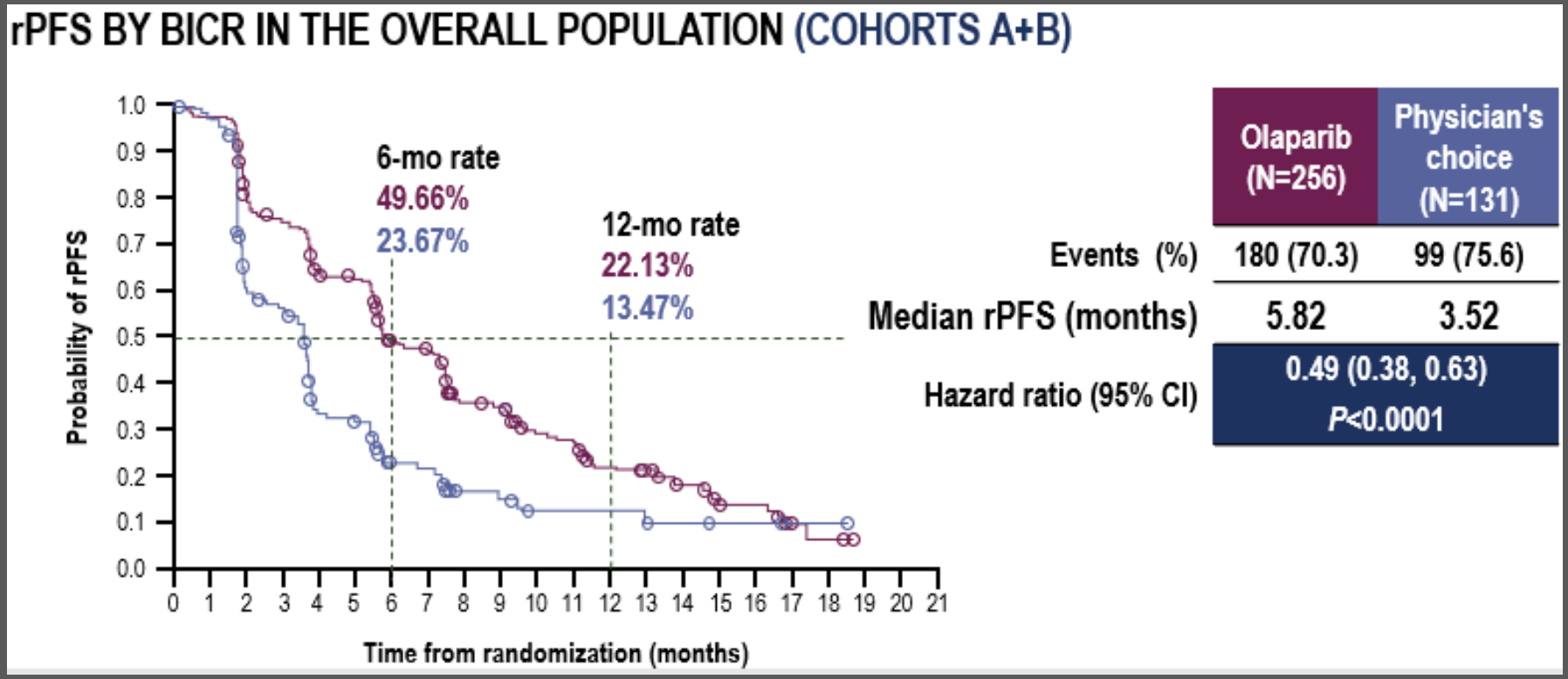
PROfound: Olaparib Improves rPFS*



*rPFS – radiographic progression free survival

De Bono., et al. NEJM, 2020

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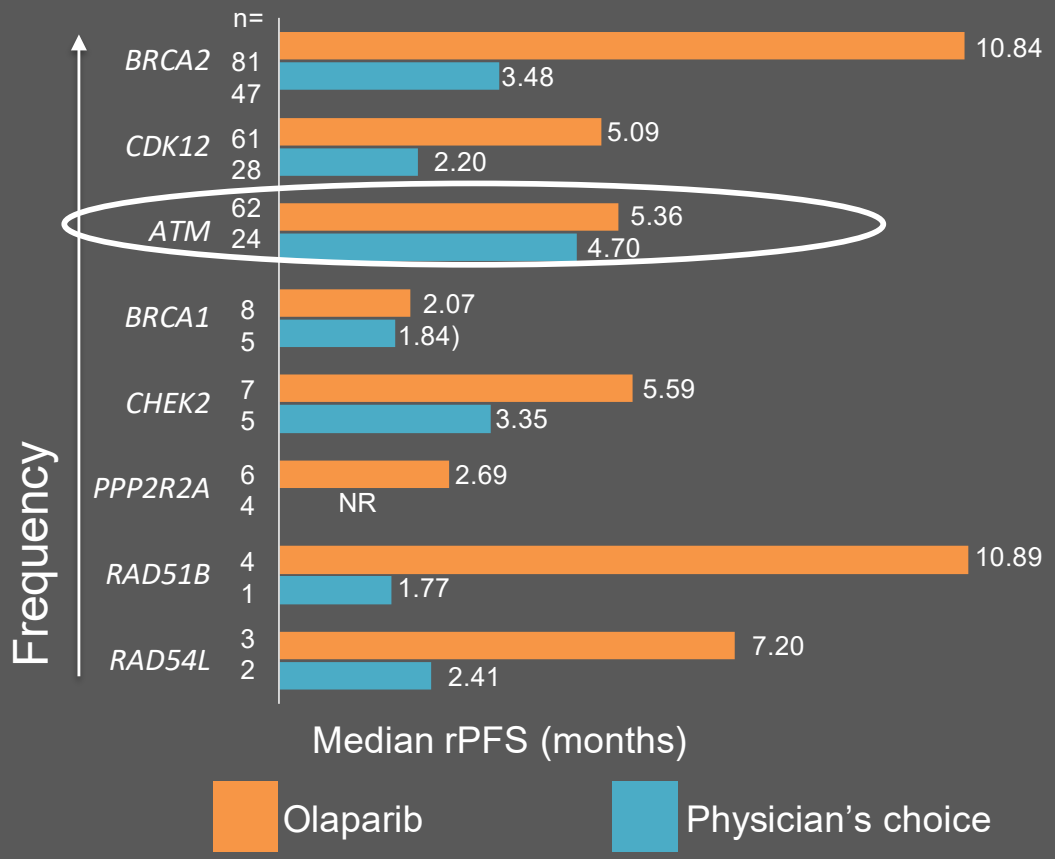
PROfound Gene-by-Gene rPFS



Hussain M., et al. NEJM, 2020

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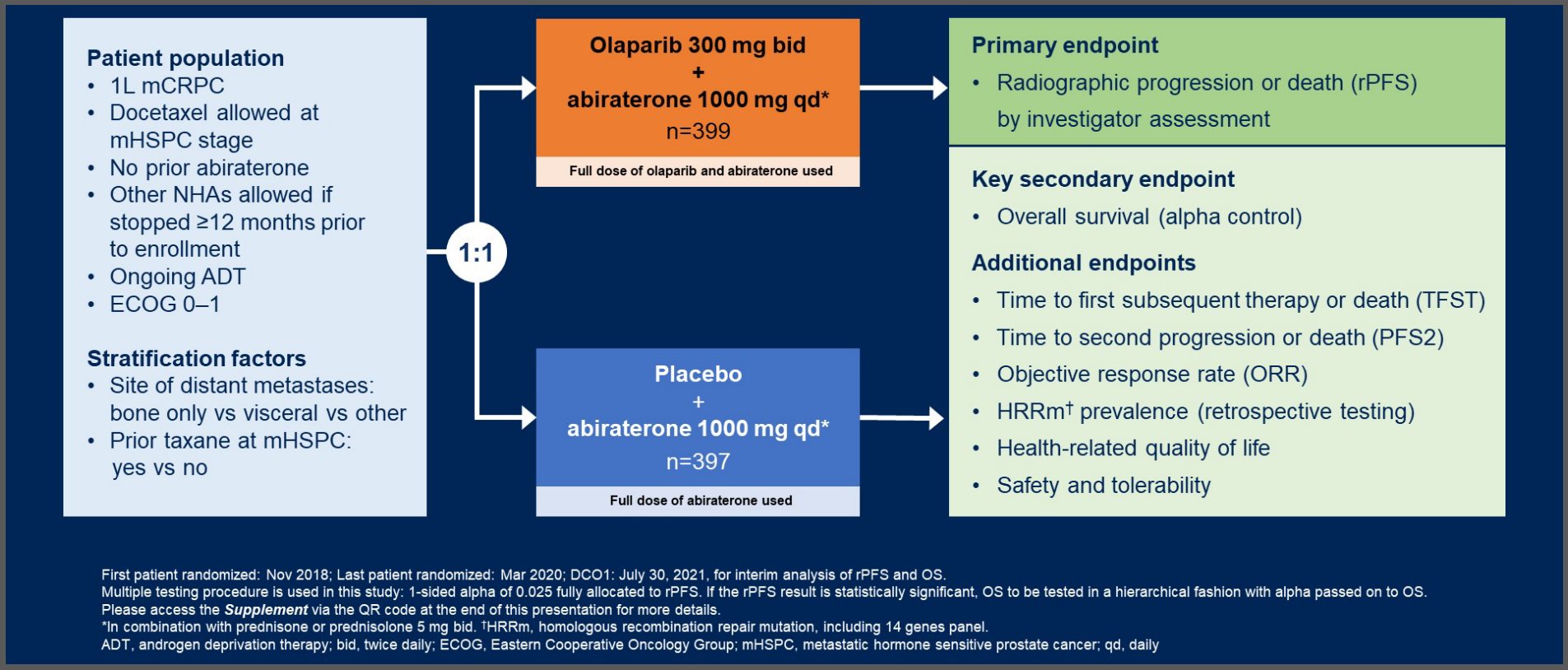
PROpel: A Global Radomized Double-Blind Phase III Trial



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

Presented by Fred Saad, 2022 ASCO Genitourinary Cancers Symposium

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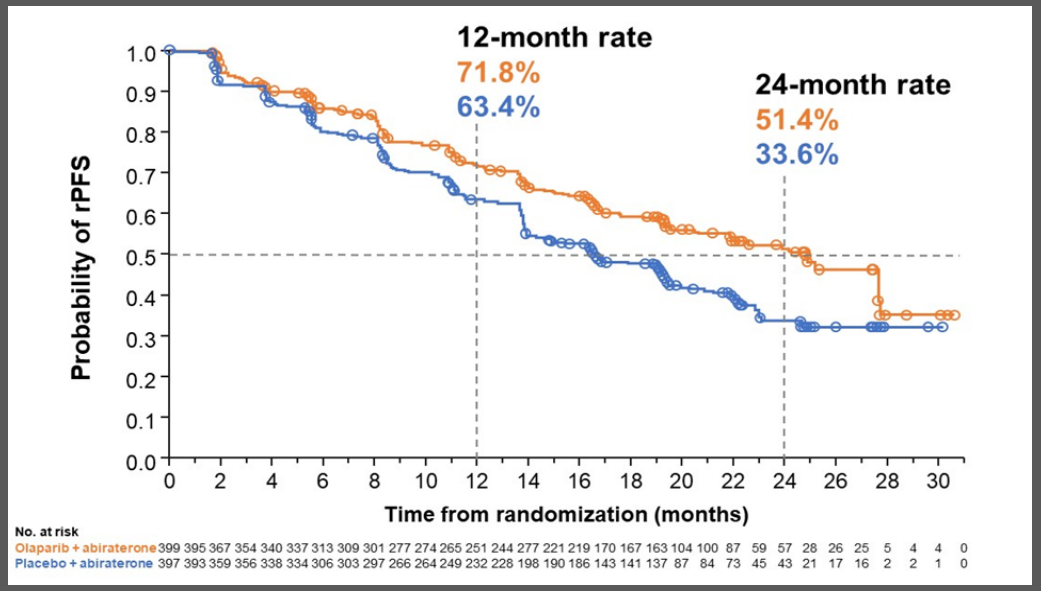
PROpel: Primary Endpoint: rPFS By Investigator-Assessment

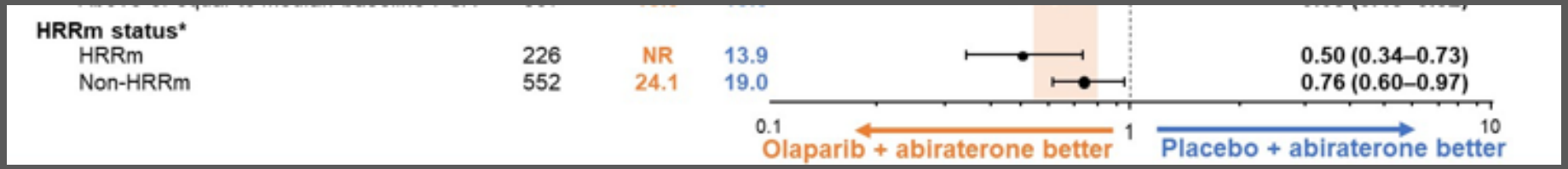
34% Risk Reduction of Progression or Death with Olaparib + Abiraterone



	Olaparib + abiraterone (n=399)	Placebo + abiraterone (n=397)
Events, n (%)	168 (42.1)	226 (56.9)
Median rPFS (months)	24.8	16.6
HR (95% CI)	0.66 (0.54–0.81); *P*<0.0001	

Pre-specified 2-sided alpha: 0.0324

Median rPFS improvement of 8.2 months favors olaparib + abiraterone*



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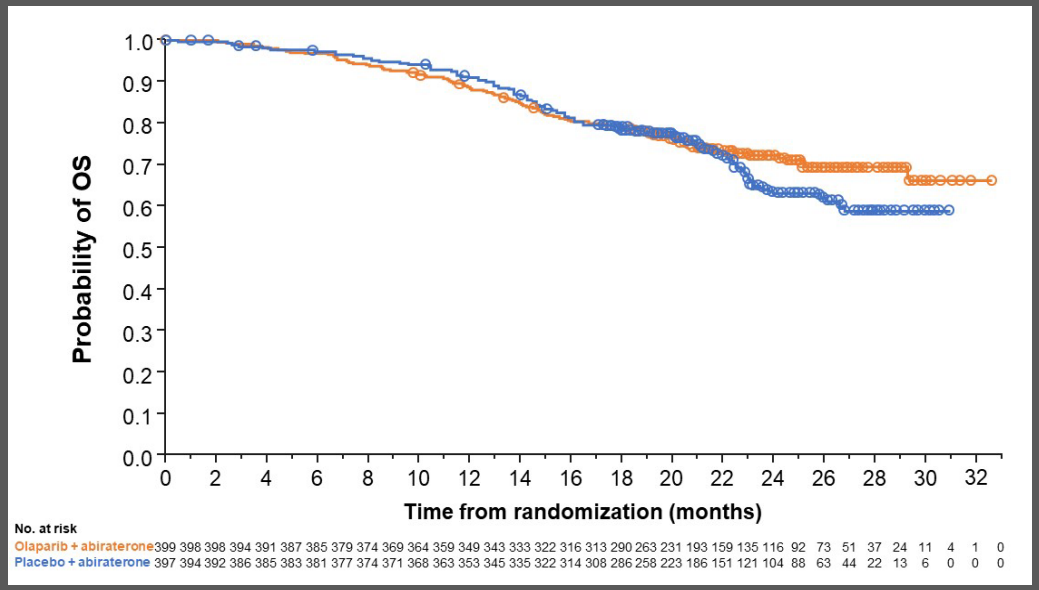
PROpel: Overall Survival

28.6% Maturity; Trend Towards Improved OS with Olaparib + Abiraterone



	Olaparib + abiraterone (n=399)	Placebo + abiraterone (n=397)
Events, n (%)	107 (26.8)	121 (30.5)
Median OS (months)	NR	NR
HR (95% CI)	0.86 (0.66–1.12) *P*=0.29	

Pre-specified 2-sided alpha: 0.001

Events: 228
NR, not reached.

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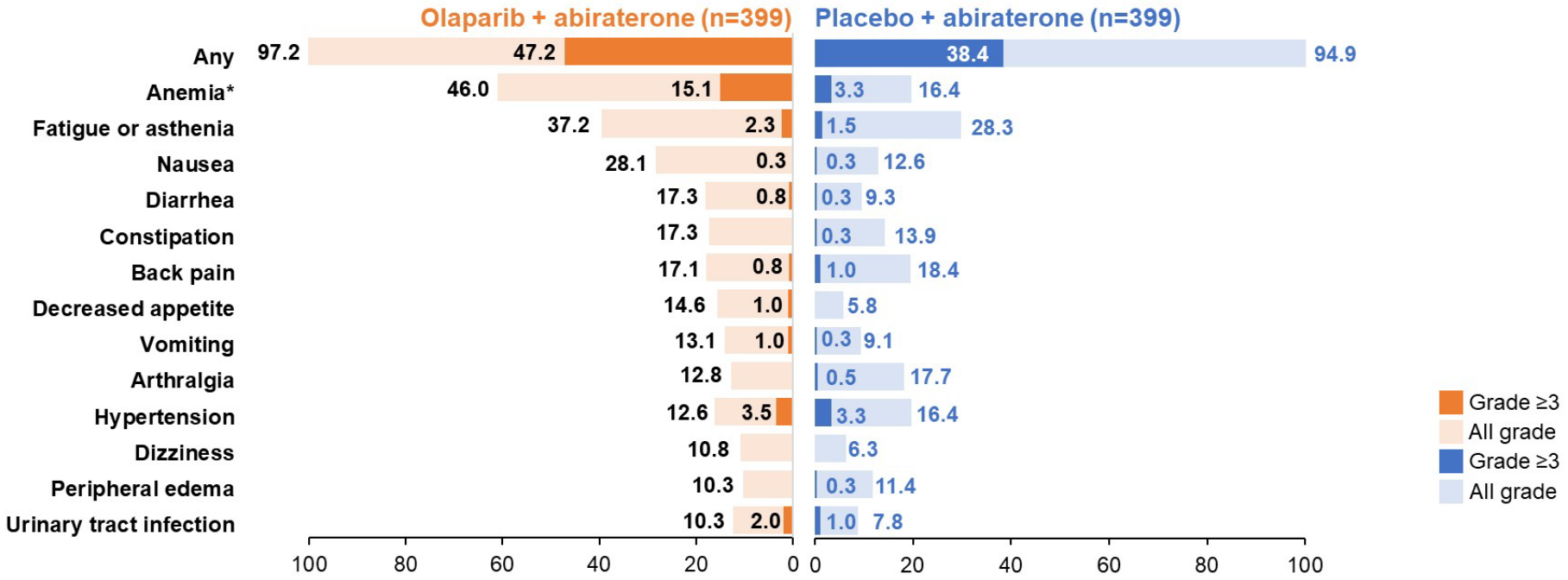
PROpel: Most Common Adverse Events

AE Profile was Consistent with the Known Toxicity Profiles for the Individual Drugs



Safety was assessed through the reporting of AEs according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE v4.03) and laboratory assessments.
*Anemia category includes anemia, decreased hemoglobin level, decreased red-cell count, decreased hematocrit level, erythropenia, macrocytic anemia, normochromic anemia, normochromic normocytic anemia, and normocytic anemia.

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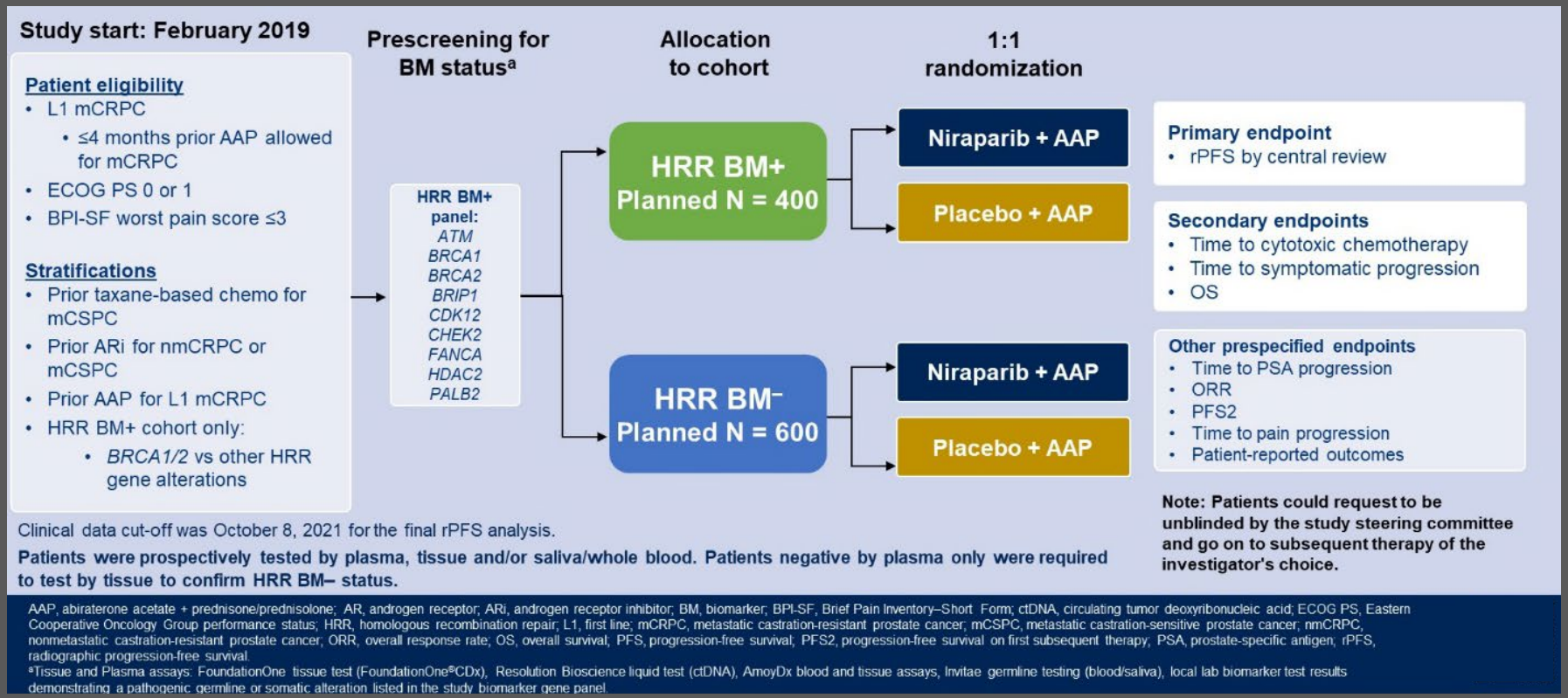
Magnitude: Radomized, Double-Blind, Placebo-Controlled Study

Prospectively Selected Biomarker Cohorts Designed to Test HRR BM+ and HRR BM-



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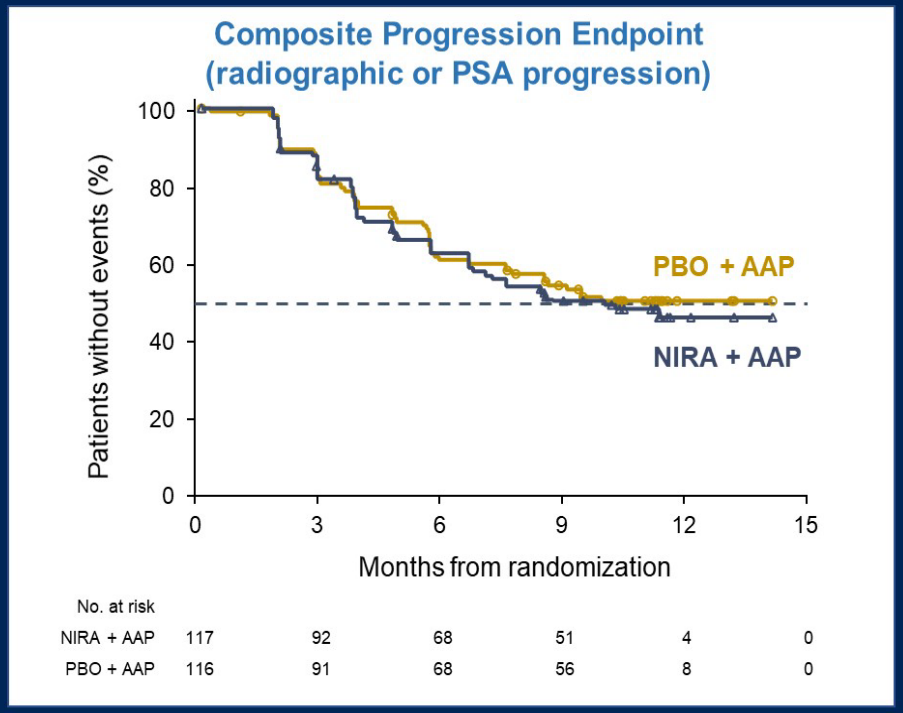
Magnitude HRR BM$^-$: Prespecified Early Futility Analysis

No Benefit of NIRA + AAP in HRR BM$^-$ Patients



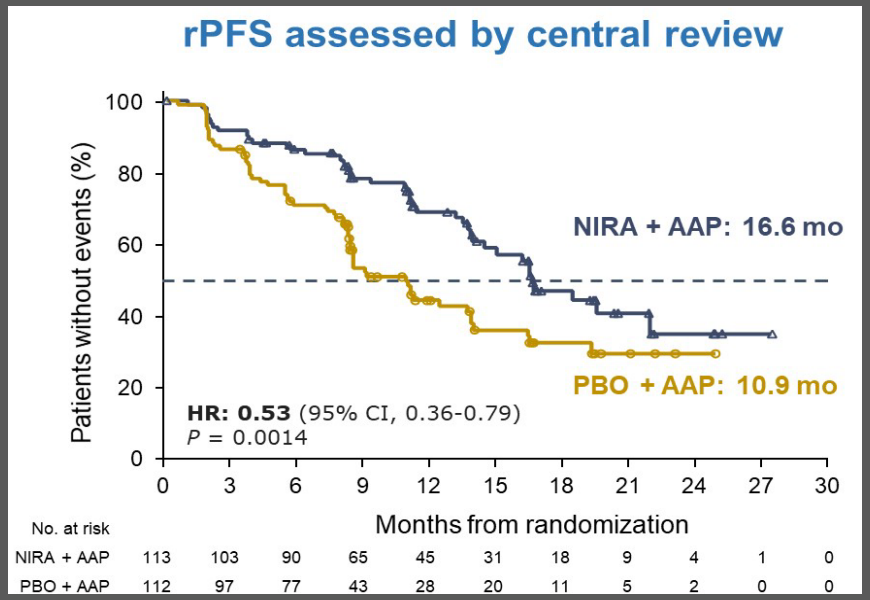
- Composite endpoint[a] (N = 233)
  HR = 1.09[b] (95% CI 0.75-1.59)
  [futility was defined as ≥1]
- Additional grade 3/4 toxicity was observed using NIRA + AAP vs PBO + AAP
- With added toxicity and no added efficacy in patients with HRR BM$^-$ mCRPC, the IDMC recommend stopping enrollment in this cohort

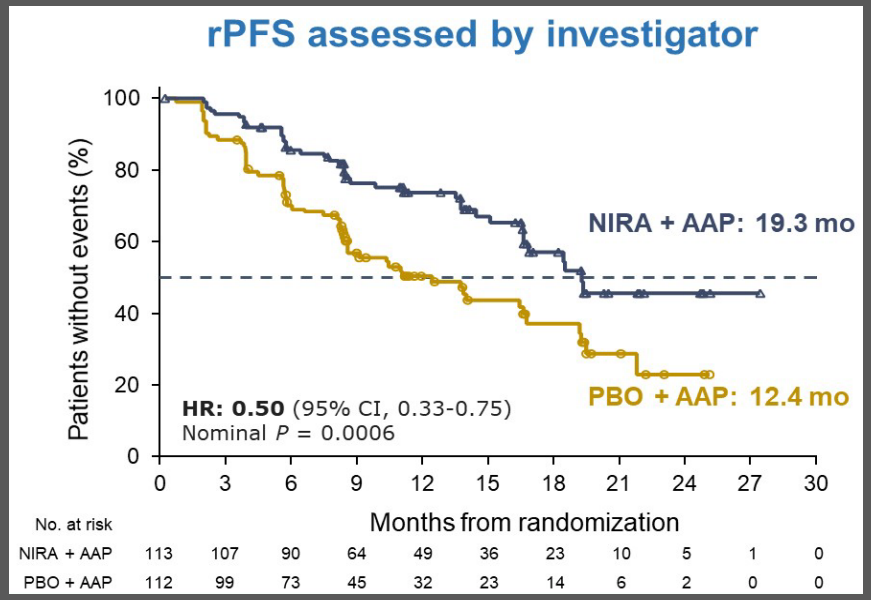
[b]Breakdown of composite endpoint events
83 PSA events (HR = 1.03, 95% CI 0.67-1.59)
65 rPFS events (HR = 1.03, 95% CI 0.63-1.67)

[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

Magnitude *BRCA 1/2-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.

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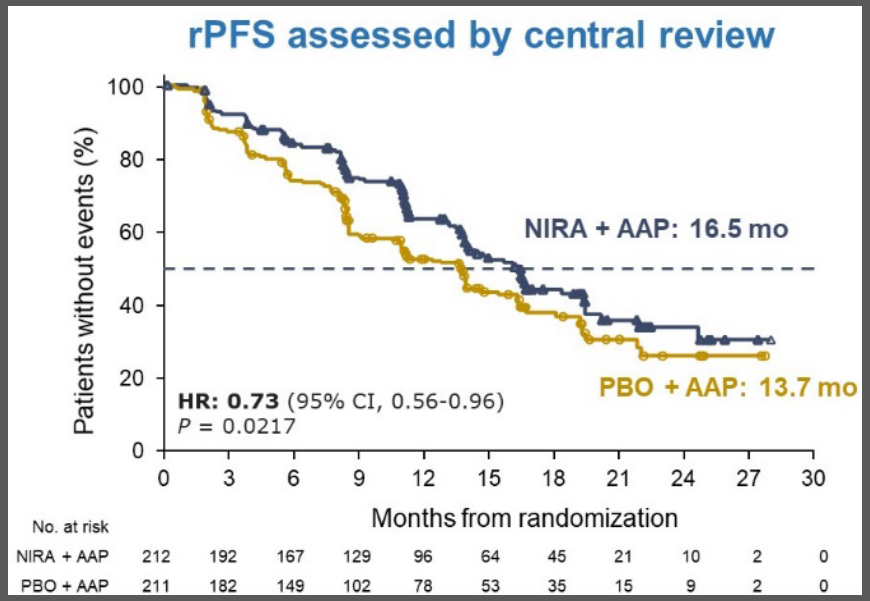
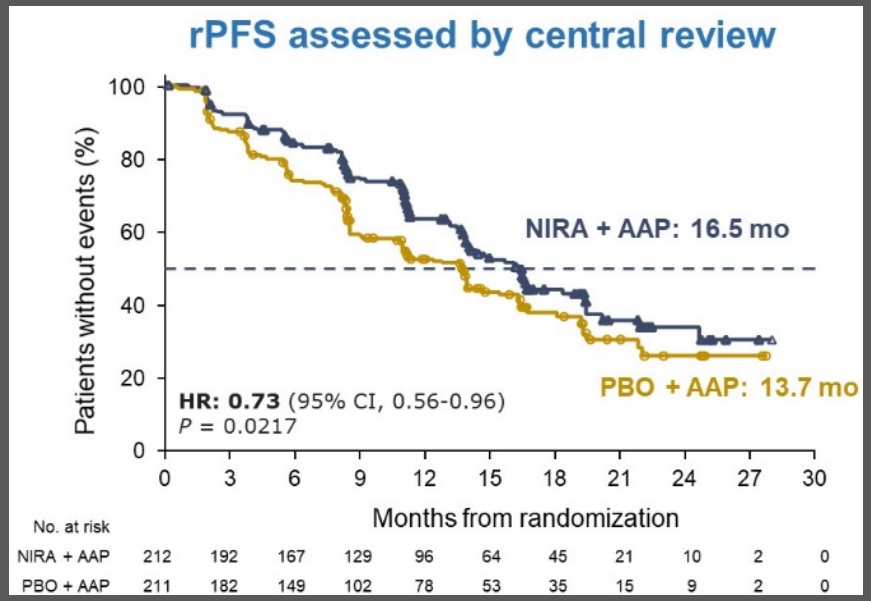
Magnitude All HRR BM+: Primary Endpoint

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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PARPi in Prostate Cancer

- Rucaparib for mCRPC w/ *BRCA1/2* muts
- Olaparib for mCRPC w/ HRD
- ?PARPi+abiraterone for mCSPC w/ *BRCA1/2* muts

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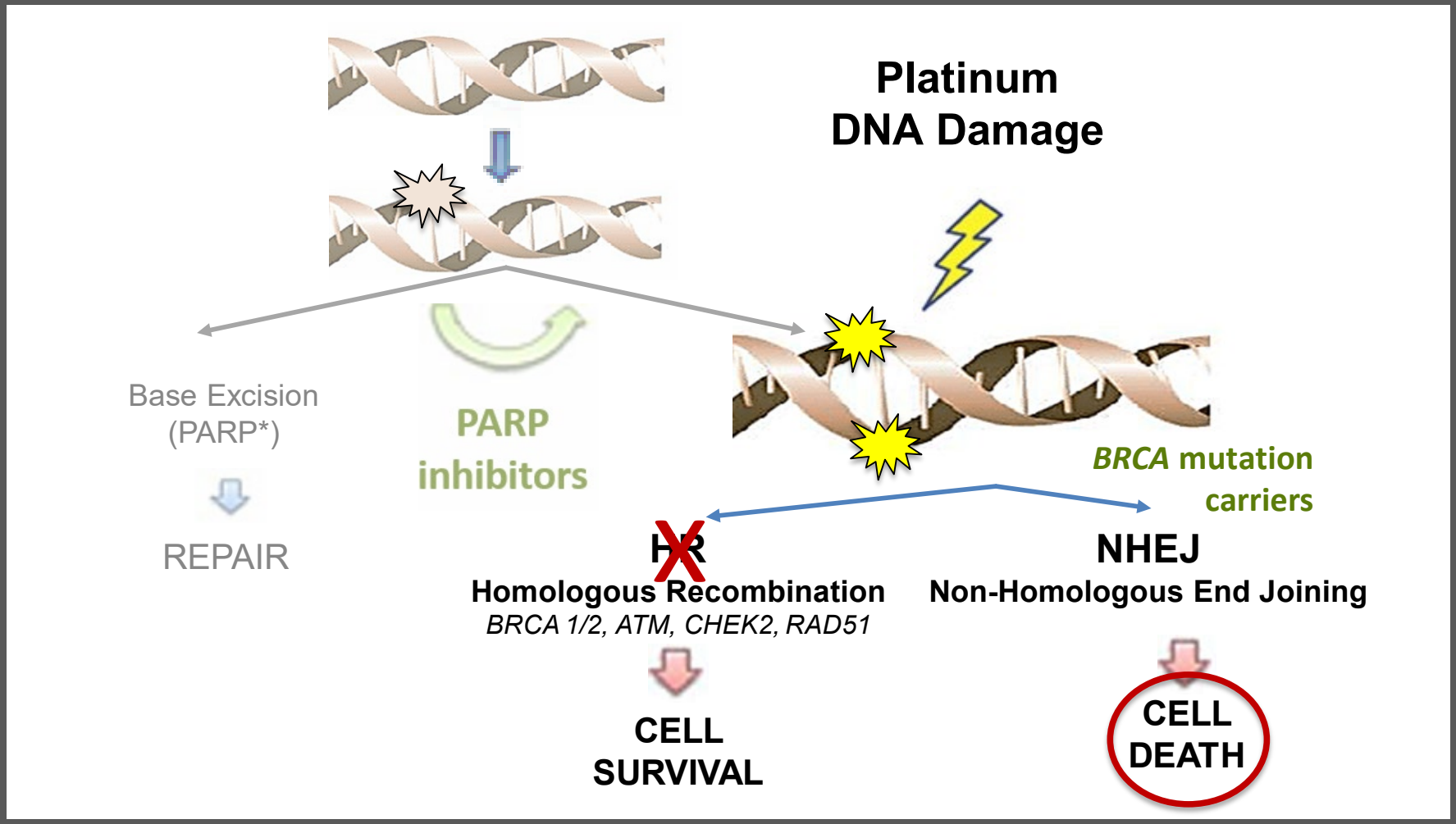
DNA Damage Repair (DDR): Platinum



Toss A., et al. J. of Cancer Science and Therapy, 2013

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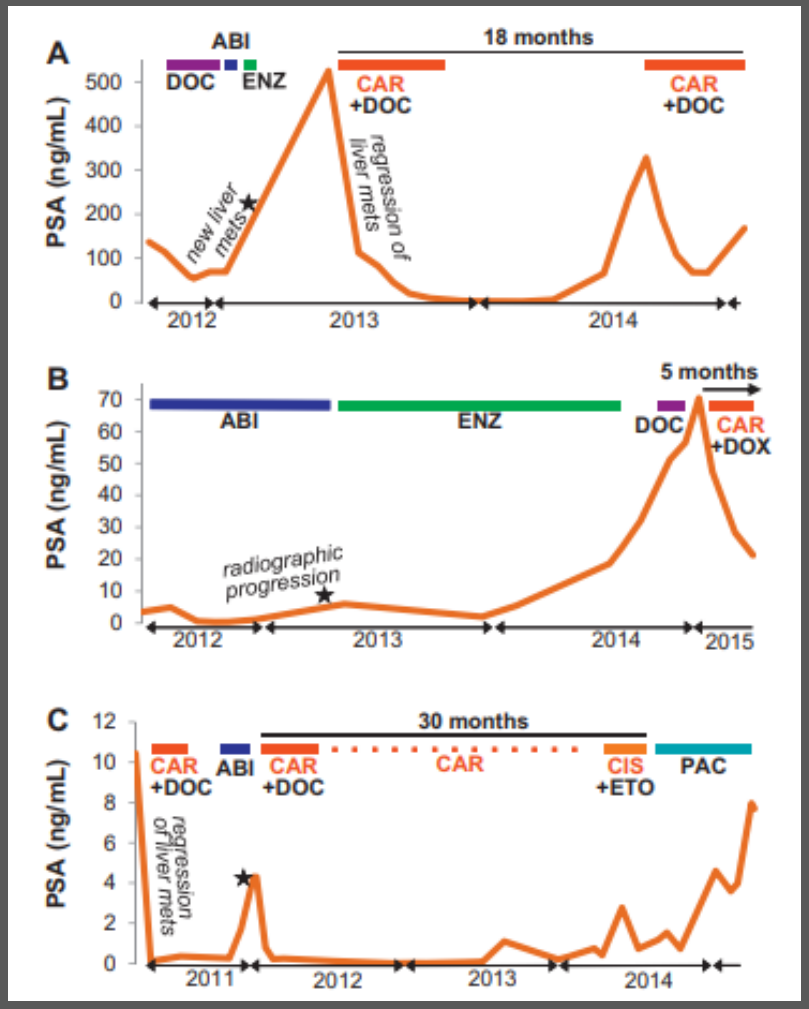
Biallelic Inactivation of BRCA2 in Platinum-sensitive MCRPC



- 3 pts with mCRPC, who achieved an exceptional response to platinum chemotherapy
- All three patients had biallelic inactivation of *BRCA2*

EURURO-6543; No. of Pages 4;2015

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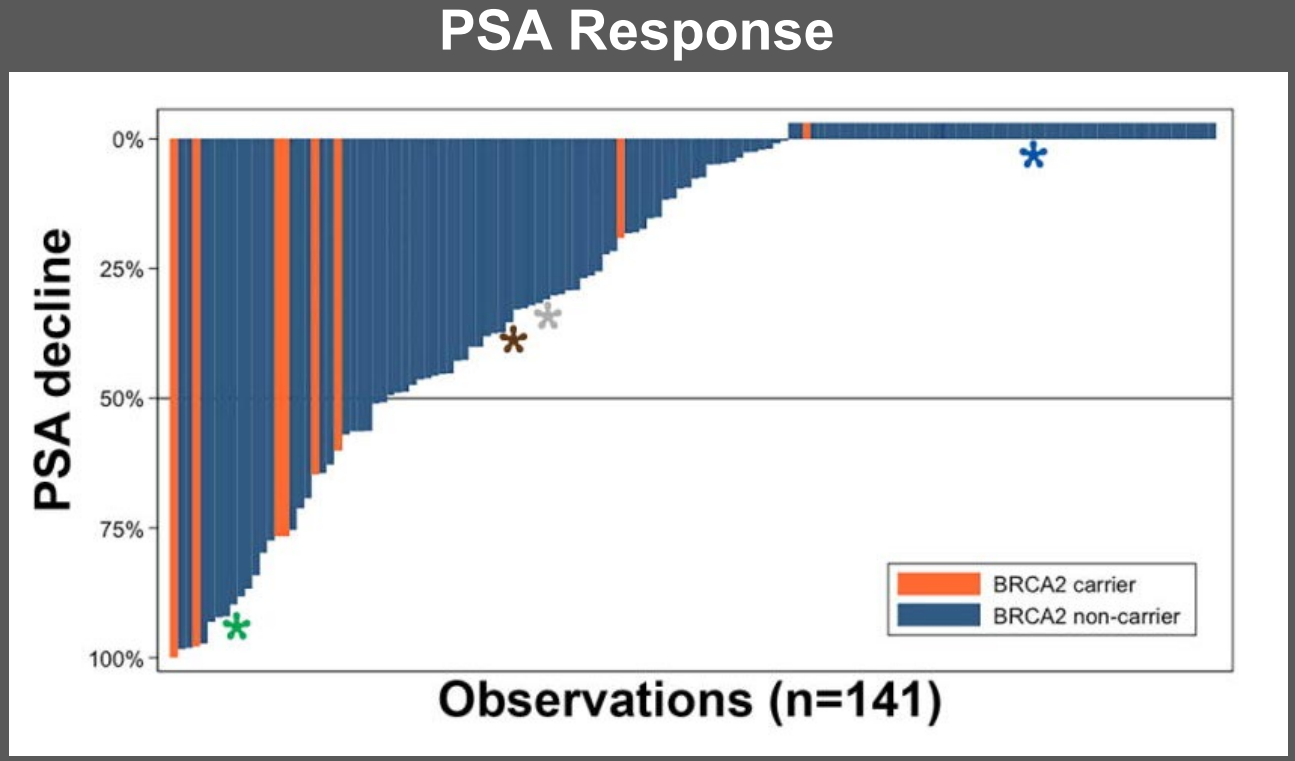
Carboplatin in *BRCA* Carriers Pca



- mCRPC
- carboplatin/docetaxel
- n-=141
- 8/141 - g*BRCA2* mutation
-
- 6/8- PSA_{50}

Cancer. 2017 Sep 15;123(18):3532-3539

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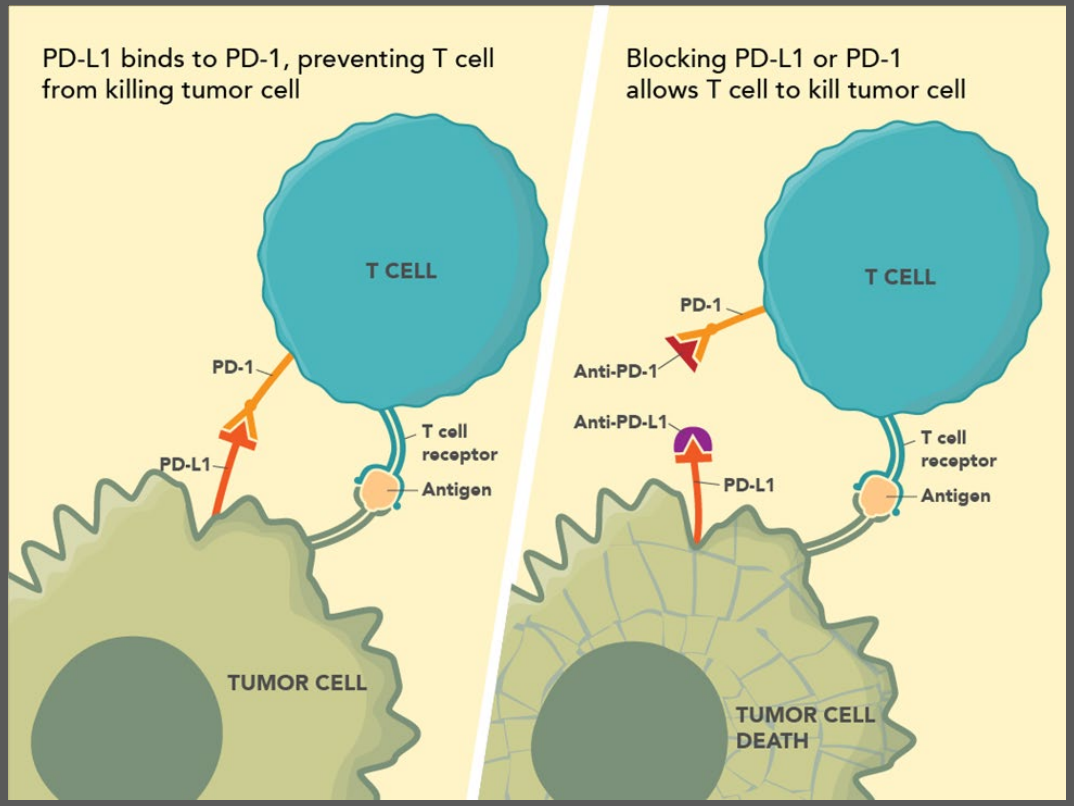
PD1/PDL1 inhibitors



Pan tumor

Pembrolizumab approval:

- 12 different tumor types
- mismatch repair deficiency
- Radiographic response 53%
- Complete response 21%

5% of mCRPC MMRd

FDA.gov
Le, et al. Science, 2017
Abida, et al, JAMA Oncol, 2018

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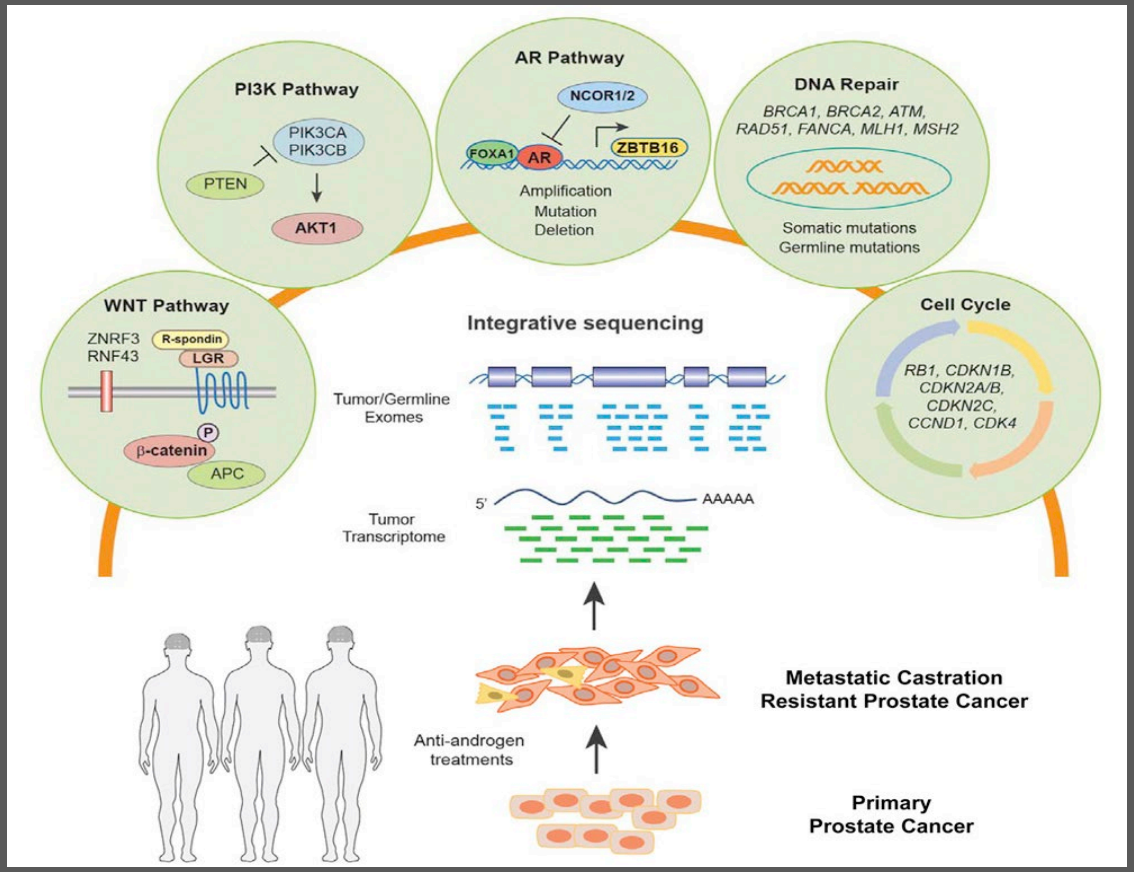
Clinical Trial Eligibility

Actionable mutations: 133/150 pts (89%)



Robinson D., et al. Cell, 2015

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Learning Objectives

- Background
- Who To Test
- Why Test
  - Informs treatment
    - PARPI
    - Platinum
    - Immunotherapy
    - Clinical trials
  - Informs prognosis
  - May inform family cancer risks
- Take Home Points

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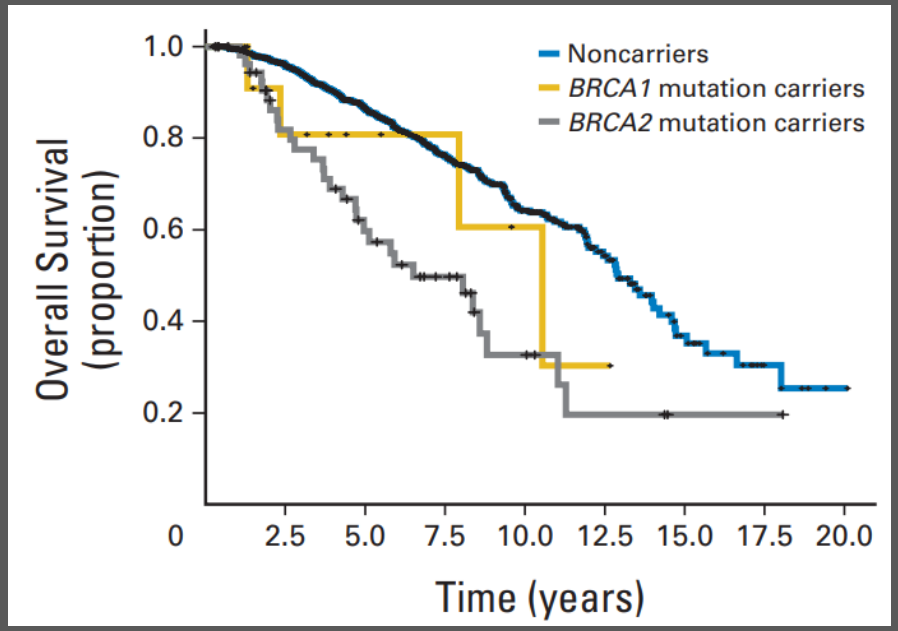
gBRCA Increases Risk of PCa

- *gBRCA2* associated with **4.5**- to **8.6**-fold increased relative risk of PCa

- PCa with g*BRCA1/2* mutations associated :
  - more advanced stage at diagnosis
  - metastases at diagnosis
  - younger age at diagnosis
  - worse outcomes
  - OS in carriers vs noncarriers 8 vs 13 years



Castro E., et al. J Clin Oncol, 2013

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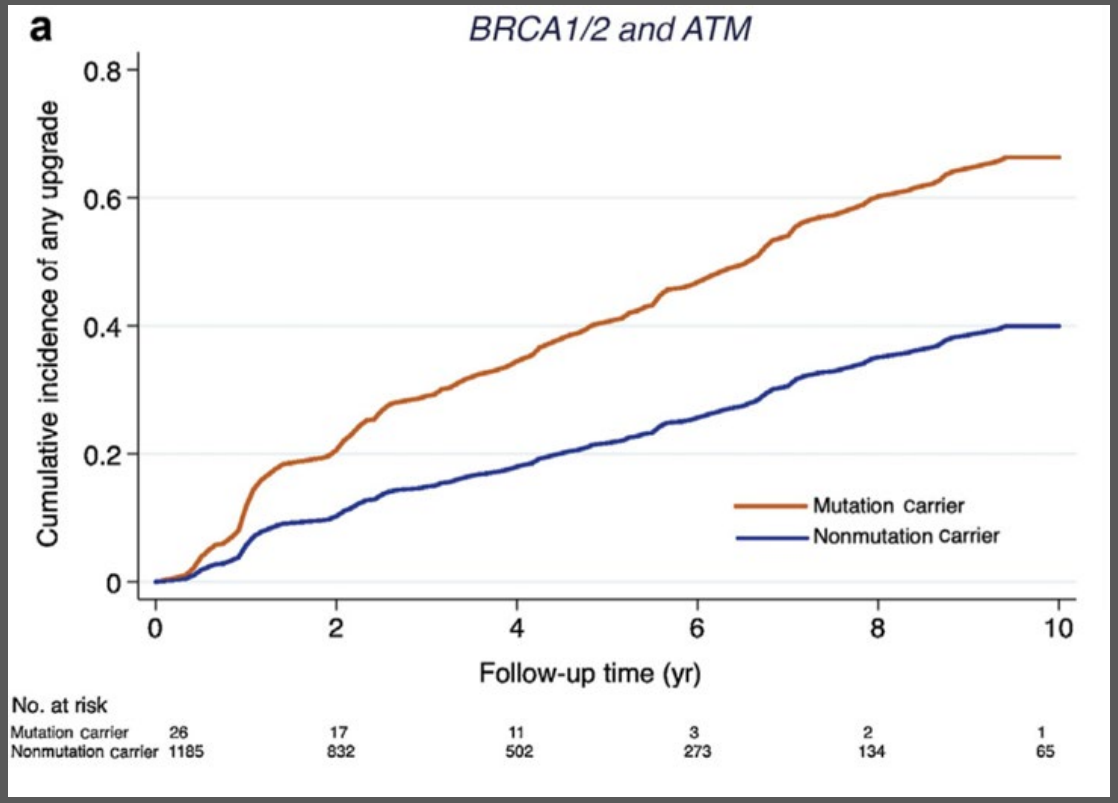
Active Surveillance: Increased Gleason Grade Upgrade with *BRCA1/2, ATM*



Carter., et al. Eur Urol, 2019

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BRCA Associated Cancers

BRCA 1

- breast cancer
- **ovarian cancer**
- uterine body and cervix (RR = 2.65)
- fallopian tube cancer
- peritoneal cancer
- prostate cancer (<65 yo RR = 1.82)
- pancreatic cancer(RR = 2.26)
- Fanconi anemia (subtype FA-D1)
- acute myeloid leukemia

BRCA2

- breast cancer
- ovarian cancer
- fallopian tube cancer
- peritoneal cancer
- **prostate cancer** (<65 yo RR 7.33)
- **male breast cancer**
- pancreatic cancer (RR, 3.51)
- malignant melanoma (RR 2.58)
- gallbladder and bile duct cancer (R 4.97)
- stomach cancer (RR 2.59)
- Fanconi anemia (subtype FA-D1)
- acute myeloid leukemia

For germline ***BRCA2*** mutation carriers, the relative risk of developing prostate cancer by age 65y is **2-8** fold compared with non-carriers.

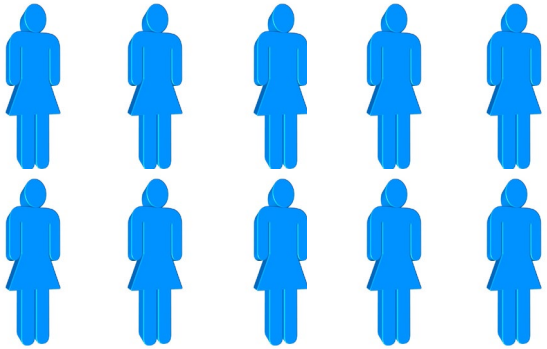
J Natl Cancer Inst. 2002 Sep 18;94(18):1358-65
J Natl Cancer Inst 91:1310-6, 1999

Men vs Women *BRCA* testing

Genetic testing for hereditary cancer risk

3:1

Genetic testing for *BRCA1* and *BRCA2*



10:1

JAMA Oncol. 2018;4(6):876-879

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National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2021
Prostate Cancer Early Detection

NCCN Guidelines Index
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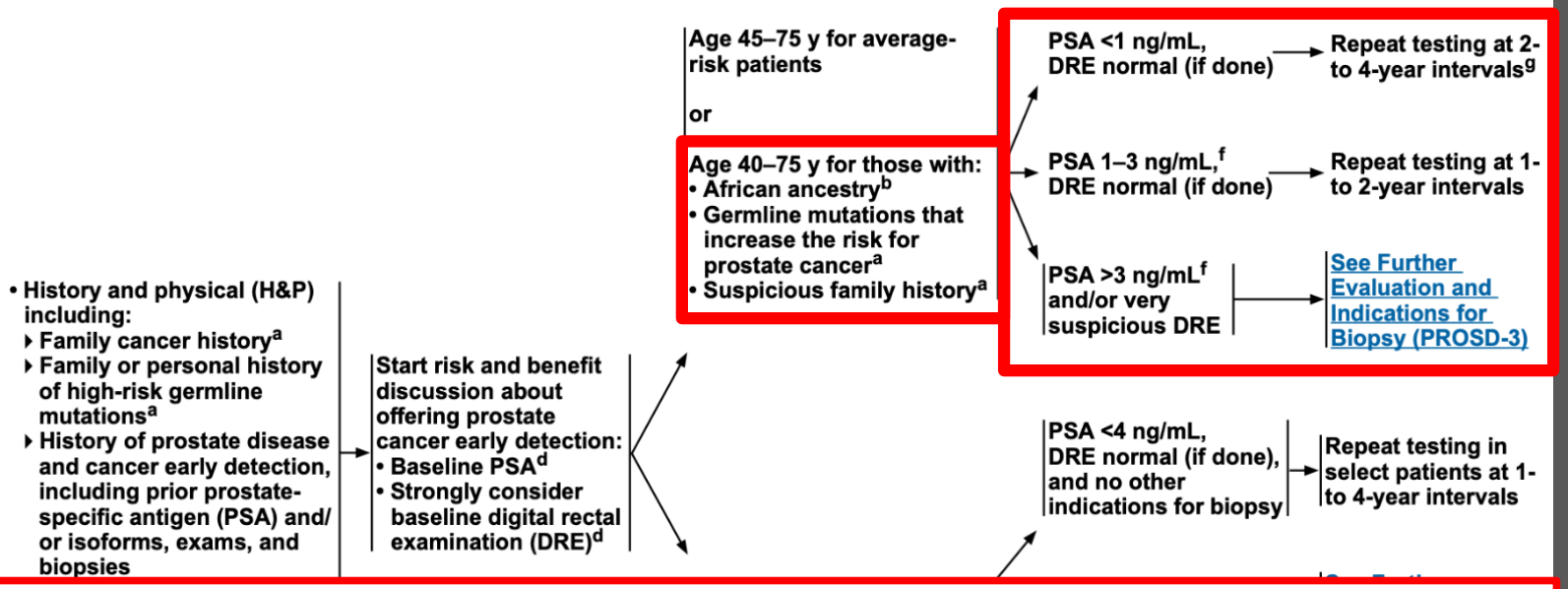

[a] Family or personal cancer history and/or family or personal history of high-risk germline mutations can inform when to begin shared decision-making regarding prostate cancer early detection. Family cancer history includes, but is not limited to, a first- or second-degree relative with metastatic prostate cancer, ovarian cancer, male breast cancer, female breast cancer ≤45 y, colorectal or endometrial cancer ≤50 y, or pancreatic cancer or two or more first- or second-degree relatives with breast, prostate (but not clinically localized Grade Group 1), colorectal or endometrial cancer at any age. If there is a known or suspected cancer susceptibility gene, referral to a cancer genetics professional is recommended. Mutation carriers have an increased risk of prostate cancer before age 65 years, and prostate cancer in men with germline *BRCA2* or *HOXB13* mutations occurs earlier and is more likely to be associated with prostate cancer mortality. For men with *BRCA1*, *ATM*, or mismatch repair (*MLH1, MSH2, MSH6, PMS2*) germline gene mutations timing of testing is less clear. Consequently, prostate cancer screening is recommended at age 40 for *BRCA2* carriers, and it is reasonable for men with other germline mutations to consider beginning shared decision-making about PSA screening at age 40 years and to consider screening at annual intervals rather than every other year. See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic (CRIT-1) and NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal (LS-1). Page EC, Eur Urol 2019;76:831-842; Giri VN, et al. J Clin Oncol 2020;38:2798-2811.

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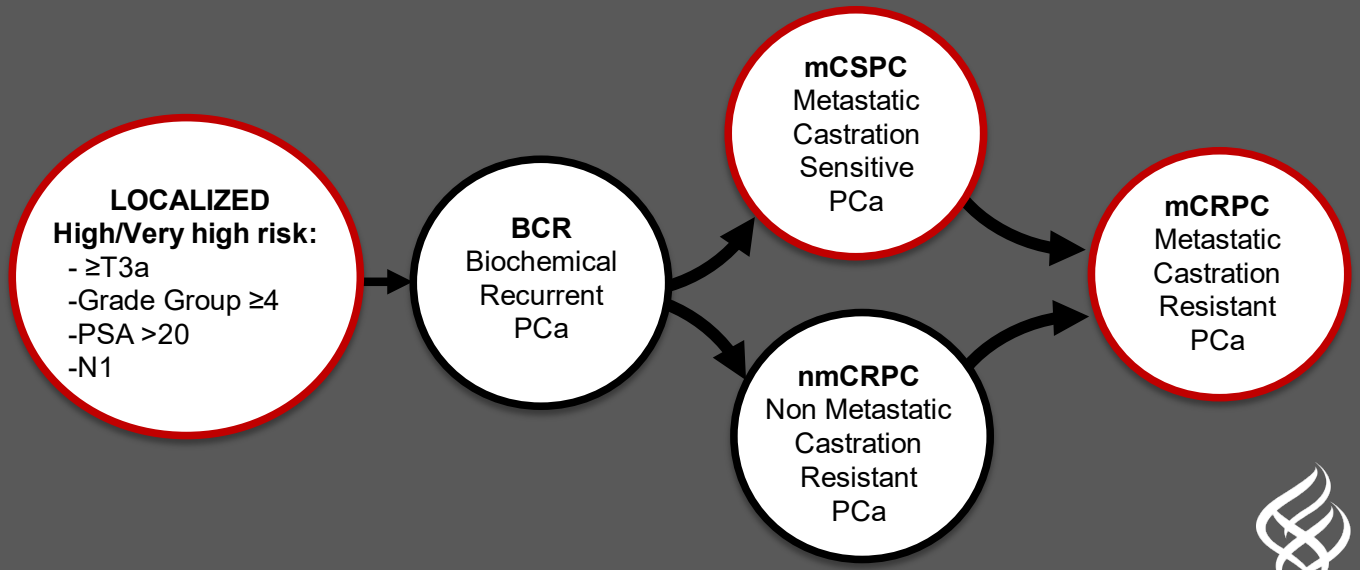
Take Home Points

- ~12% pts w/ metastatic PCa have germline DDR muts
- ~20% w/ metastatic PCa have somatic DDR muts
- Patients w/ PCa and HRD are candidates for PARPi and Platinum
- Patients with PCa and MMRd are candidates for PD1/PDL1 inhibitors



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THANK YOU!

To refer patients to Prostate Cancer Genetics Clinic at OHSU:

Email: oncaccess@ohsu.edu

Call: 503-494-7999

Fax: 503-346-6854

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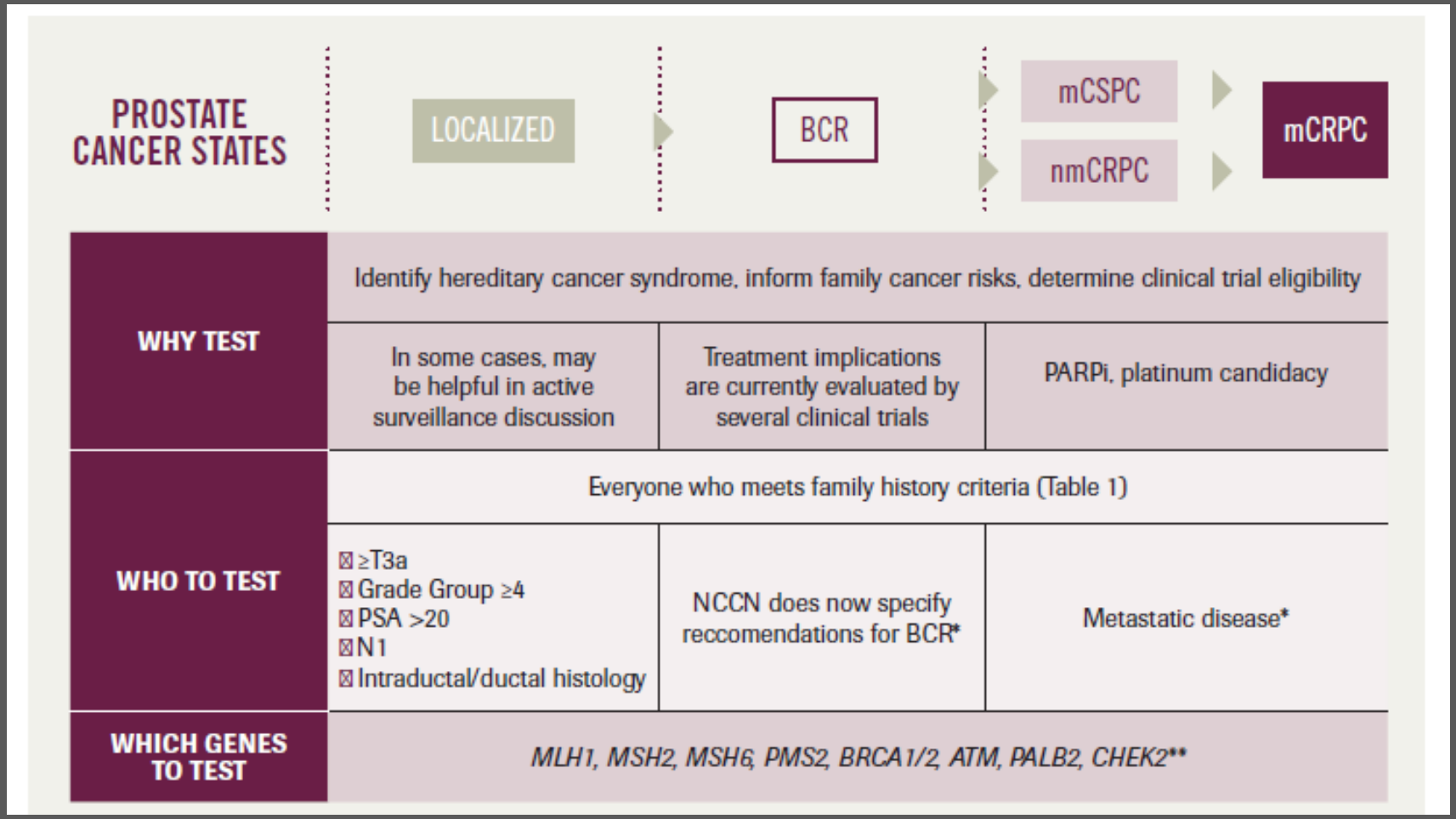
Germline Testing– Who to Refer



WHY TEST	Identify hereditary cancer syndrome, inform family cancer risks, determine clinical trial eligibility		
	In some cases, may be helpful in active surveillance discussion	Treatment implications are currently evaluated by several clinical trials	PARPi, platinum candidacy
WHO TO TEST	Everyone who meets family history criteria (Table 1)		
	☒ ≥T3a ☒ Grade Group ≥4 ☒ PSA >20 ☒ N1 ☒ Intraductal/ductal histology	NCCN does now specify reccomendations for BCR*	Metastatic disease*
WHICH GENES TO TEST	*MLH1, MSH2, MSH6, PMS2, BRCA1/2, ATM, PALB2, CHEK2***		

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NCCN Family History Criteria For Germline Testing

PRINCIPLES OF GENETICS AND MOLECULAR/BIOMARKER ANALYSIS

Germline testing is recommended *in patients with a personal history of prostate cancer* in the following scenarios:

- By Prostate Cancer Stage or Risk Group (diagnosed at any age)
  - Metastatic, regional (node positive), very-high risk localized, high-risk localized prostate cancer

- By Family History[a] and/or Ancestry
  - ≥1 first-, second-, or third-degree relative with:
    - breast cancer at age ≤50 y
    - colorectal or endometrial cancer at age ≤50 y
    - male breast cancer at any age
    - ovarian cancer at any age
    - exocrine pancreatic cancer at any age
    - metastatic, regional, very-high-risk, high-risk prostate cancer at any age
  - ≥1 first-degree relative (father or brother) with:
    - prostate cancer[b] at age ≤60 y
  - ≥2 first-, second-, or third-degree relatives with:
    - breast cancer at any age
    - prostate cancer[b] at any age
  - ≥3 first- or second-degree relatives with:
    - Lynch syndrome-related cancers, especially if diagnosed <50 y: colorectal, endometrial, gastric, ovarian, exocrine pancreas, upper tract urothelial, glioblastoma, biliary tract, and small intestinal cancer
  - A known family history of familial cancer risk mutation (pathogenic/likely pathogenic variants), especially in: ***BRCA1, BRCA2, ATM, PALB2, CHEK2, MLH1, MSH2, MSH6, PMS2, EPCAM***
  - Ashkenazi Jewish ancestry
- Personal history of breast cancer

Germline testing may be considered *in patients with a personal history of prostate cancer* in the following scenarios:

- By Prostate Cancer Tumor Characteristics (diagnosed at any age)
  - intermediate-risk prostate cancer with intraductal/cribriform histology[c]
- By prostate cancer[b] AND a prior personal history of any of the following cancers:
  - exocrine pancreatic, colorectal, gastric, melanoma, pancreatic, upper tract urothelial, glioblastoma, biliary tract, and small intestinal

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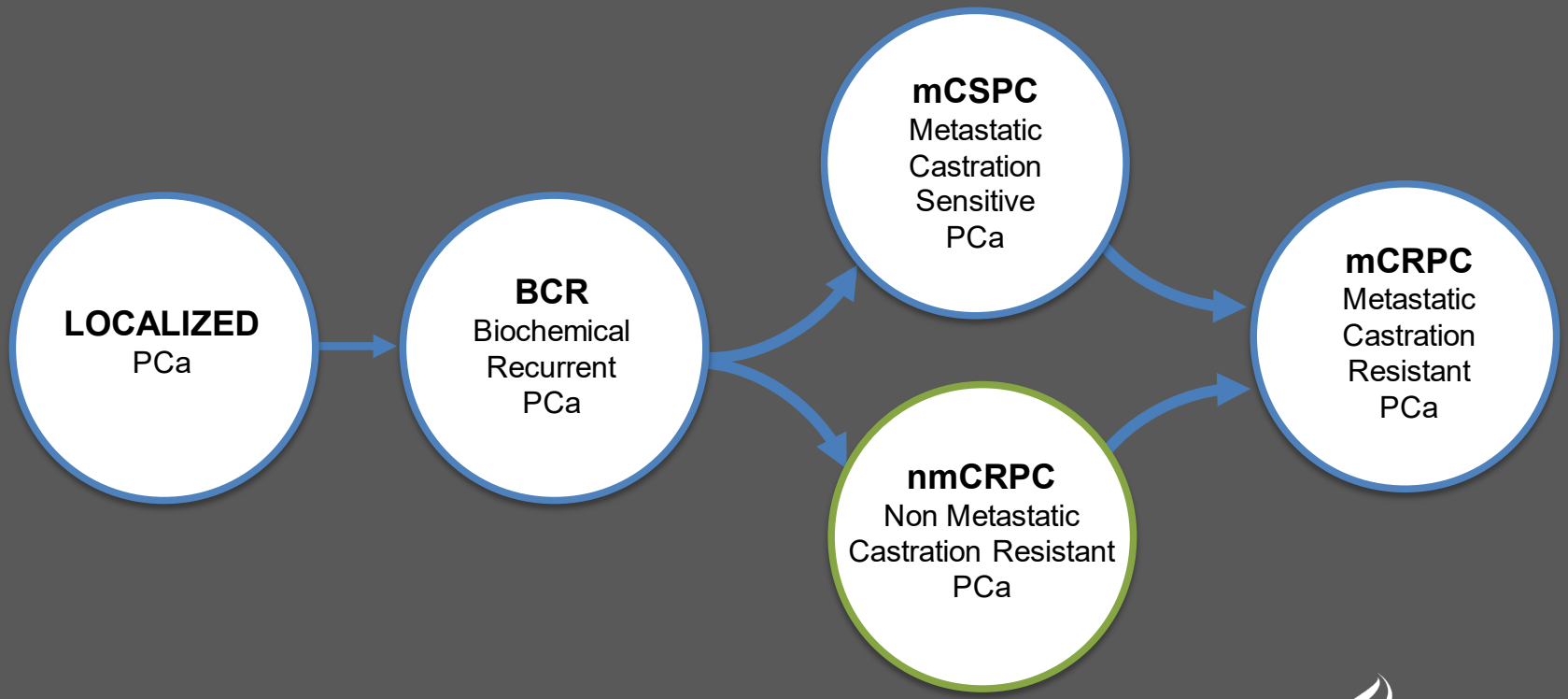
Prostate Cancer Background

- Prostate cancer (PCa) is the most common non-cutaneous tumor among men in US
- 192,9300 men estimated to be diagnosed with PCa in 2020



Siegel R., et al. Cancer J Clin. 2020

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Platinum Mechanism of Action

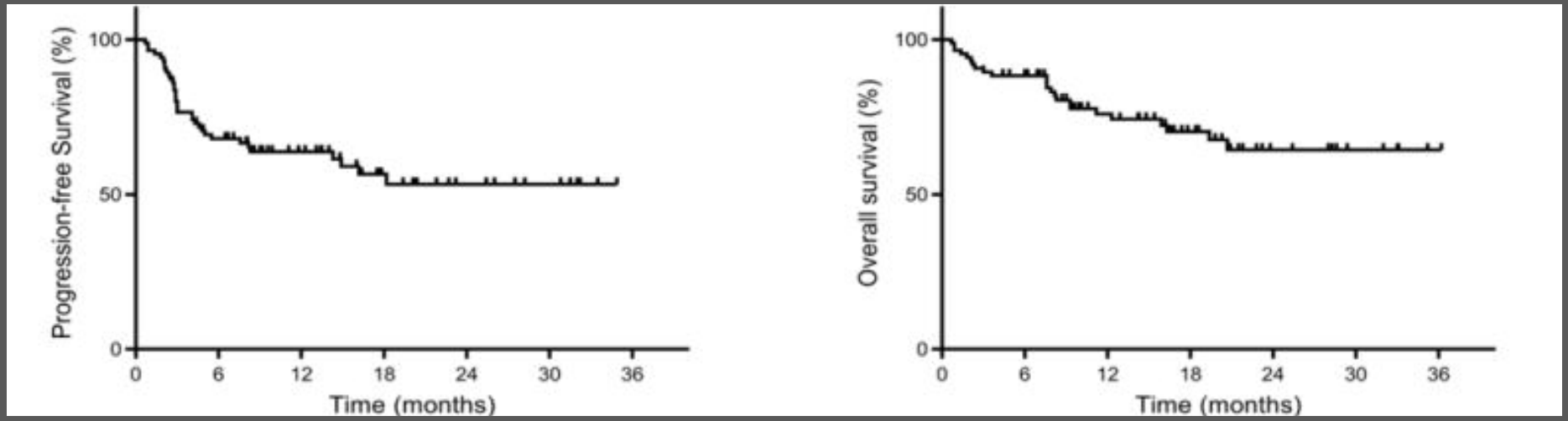
- 1) Attachment of alkyl groups to DNA → DNA fragmented by repair enzymes in their attempts to replace the alkylated bases → preventing DNA synthesis and RNA transcription

- 2) DNA damage via the formation of cross-links in DNA → prevents DNA from being separated for synthesis or transcription

- 3) Induction of mispairing of the nucleotides → leading to mutations

PD1/PDL1 inhibitors

Patient survival and clinical response to Pembrolizumab across 12 different tumor types with mismatch repair deficiency Radographic response 53%m Complete response 21%



Le *et al.* Science, 2017

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