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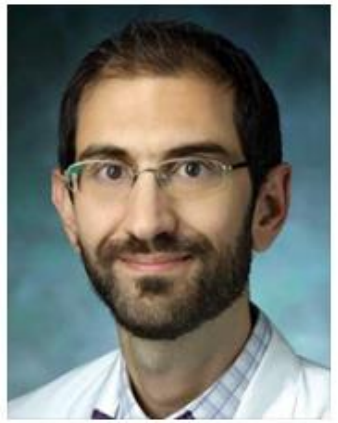
THE ROLE OF PARPi IN PROSTATE CANCER: EXPERTS KNOWLEDGE SHARE

AUGUST 2020

Dr. Neal D. Shore (Chair)
Carolina Urologic Research Center

Prof. Andrew J. Armstrong
Duke University School of Medicine



Prof. Emmanuel S. Antonarakis
Johns Hopkins Medicine

FUNDING

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Please note:

The views expressed within this presentation are the personal opinions of the experts. They do not necessarily represent the views of the expert's academic institution.

AstraZeneca has provided a sponsorship grant towards this independent programme.

EXPERTS KNOWLEDGE SHARE

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THE OBJECTIVE OF THIS MEETING IS TO DISCUSS THE TOPIC 'THE ROLE OF PARPi IN PROSTATE CANCER'

- Your opportunity to **discuss and share learnings on a challenging topic** within the area of DDR and prostate cancer

- A chance to hear **the views of our Experts** and allow them to answer the questions that are important to you

- Review and discuss **Patient Case Studies,** using the questions that you have sent in advance of this evening

DDR, DNA damage response; PARPi, poly ADP ribose polymerase inhibitor(s)

EDUCATIONAL OBJECTIVES

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1. Understand the **MoA of PARP inhibition** and its role in the treatment of prostate cancer
2. Understand the **prevalence** of DDR mutations in prostate cancer and be able to implement the **testing** strategies (specifically for somatic mutations) to predict if the prostate tumour is likely to respond to a PARPi or other treatment
3. Recognise the clinical **efficacy and safety profile** of PARPi for patients with prostate cancer
4. Understand the place of **PARP inhibition in the prostate cancer treatment pathway** in the context of other non-hormonal agents and the potential for upcoming combination therapies

MoA, mode of action

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INTRODUCTION

Dr. Neal D. Shore (Chair)

Carolina Urologic Research Center

DISCLOSURE

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Dr. Neal D. Shore has the following relevant financial relationships to disclose:

- **Research/Consulting:** AbbVie, Amgen, Astellas, AstraZeneca, Bayer, BMS, Clovis Oncology, Dendreon, Exact Imaging, FerGene, Ferring, Janssen, MDx Health, Merck, Myovant, Nymax, Pfizer, Sanofi, Tolmar
- **Stock/Patents/Salary**: none

ADVANCES IN PROSTATE CANCER THERAPY: 60 YEARS OF PROGRESS

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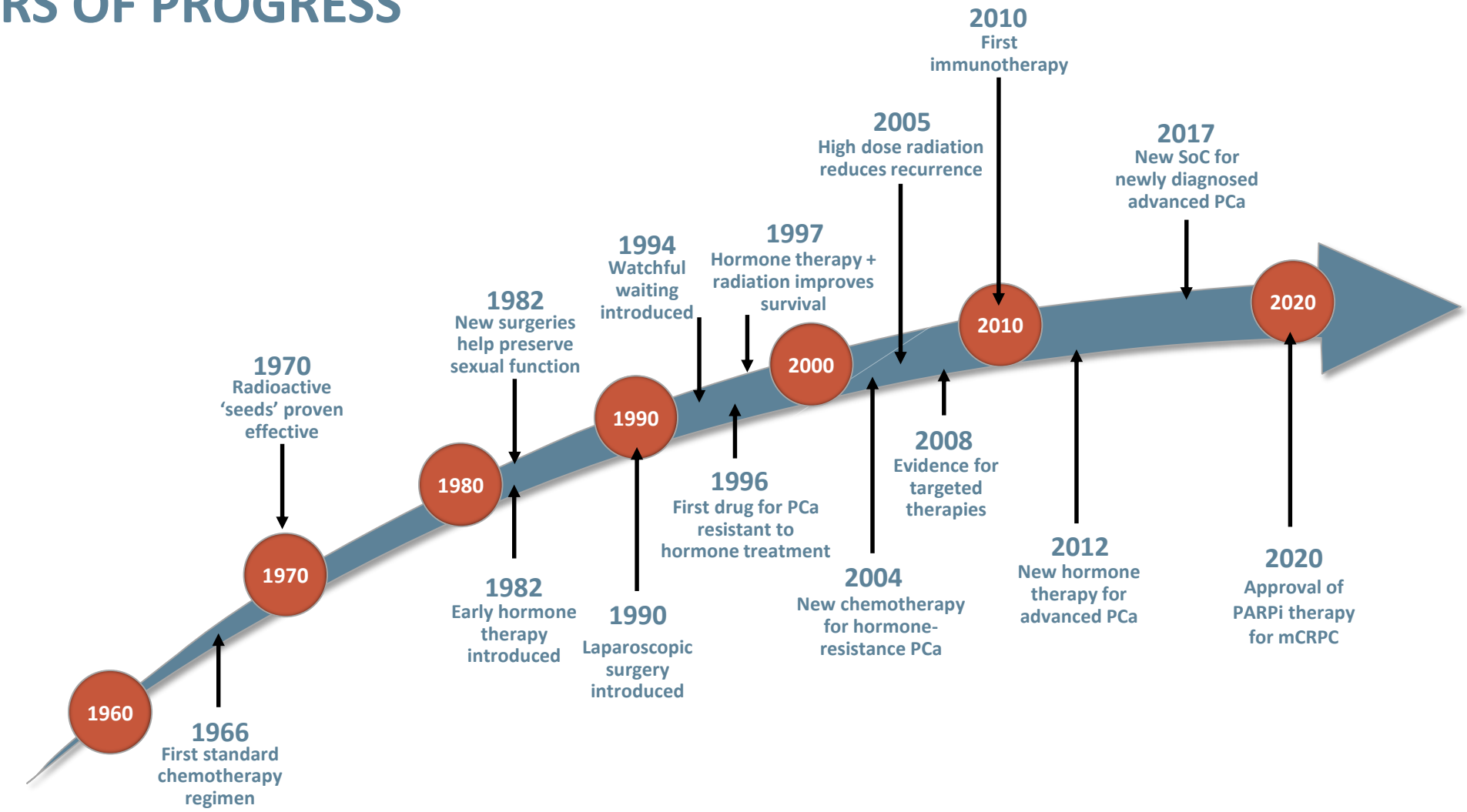

mCRPC, metastatic castrate-resistant prostate cancer; PARPi, poly ADP ribose polymerase inhibitor; PCa, prostate cancer; SoC, standard of care

Cancer Progress Timeline: Prostate Cancer (modified). Available from: https://www.asco.org/research-guidelines/cancer-progress-timeline/prostate-cancer. Accessed, August 2020.
Available from: www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-olaparib-hrr-gene-mutated-metastatic-castration-resistant-prostate-cancer . Accessed, August 2020.
Available from: www.fda.gov/drugs/fda-grants-accelerated-approval-rucaparib-brca-mutated-metastatic-castration-resistant-prostate . Accessed, August 2020.

MAJOR PROGNOSTIC FEATURES OF PROSTATE CANCER

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- 5-year survival is close to 100% in patients with local or regional prostate cancer
- Loss of hormone sensitivity and metastasis represent two major negative prognostic events in prostate cancer

New Cancer Diagnosis	5-year OS range
Local or regional prostate cancer	99-100%
Non-mCRPC	20-60%
mHSPC	23.6-51.9%
mCRPC	10-26%

mHSPC, metastatic hormone-sensitive prostate cancer; OS, overall survival

https://www.cancer.net/cancer-types/prostate-cancer/statistics#:~:text=The%205%2Dyear%20survival%20rate%20for%20most%20men%20with%20local,prostate%20cancer%20combined%20is%2098%25.
https://www.urotoday.com/library-resources/m0-prostate-cancer/111535-treatment-advances-in-non-metastatic-castration-resistant-prostate-cancer.html
Madan RA et al., https://pubmed.ncbi.nlm.nih.gov/18628467/;
Carniero et al., https://pubmed.ncbi.nlm.nih.gov/27802009/
Francini et al., https://pubmed.ncbi.nlm.nih.gov/30643173/
Halabi et al., https://pubmed.ncbi.nlm.nih.gov/26951312/

PROSTATE CANCER THERAPY: RAPID ADVANCES

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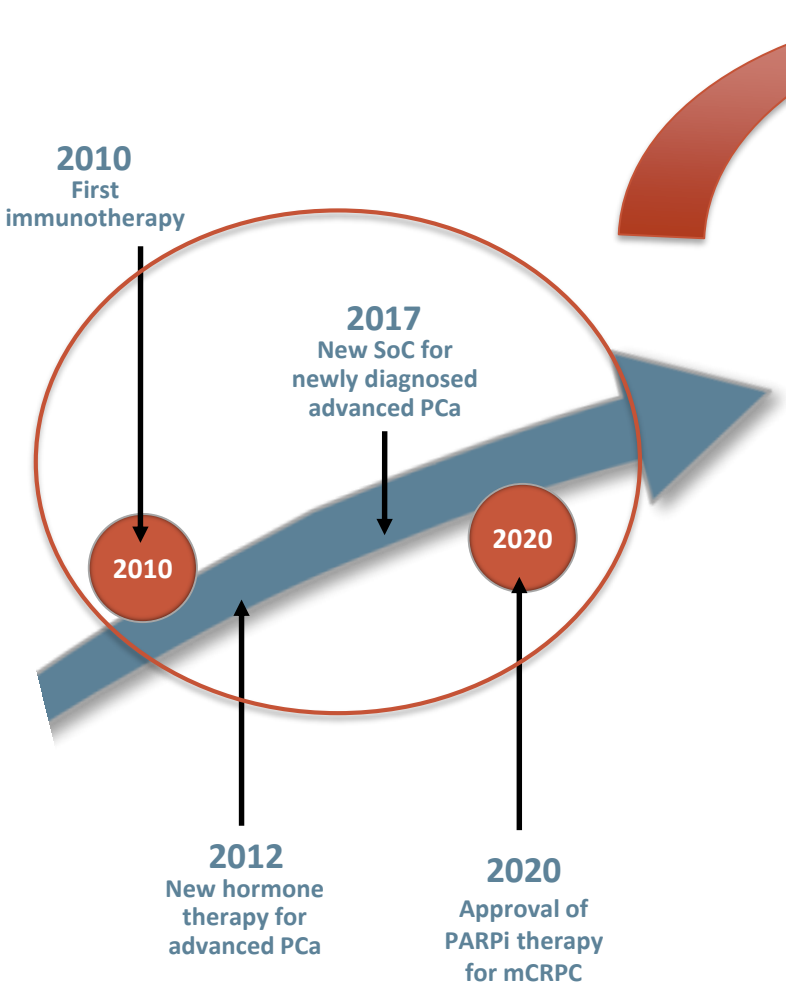

9 life-prolonging approvals since 2010

Drug name	Approval	Drug Class	Indication
Sipuleucel-T	April 2010	Autologous cellular immunotherapy	mCRPC
Cabazitaxel	June 2010	Chemotherapy	Hormone-refractory metastatic PCa/mCRPC
Abiraterone Acetate	April 2011	Anti-androgen	mCRPC
Enzalutamide	Aug 2012	AR inhibitor	mCRPC, non-mCRPC, mHSPC
Radium 223	May 2013	Radiopharmaceutical	mCRPC bone
Pembrolizumab	May 2017	Monoclonal antibody	Unresectable/metastatic solid tumours MSI high
Darolutamide	July 2019	AR inhibitor	Non-mCRPC
Apalutamide	Feb 2018	Anti-androgen	mHSPC/non-mCRPC
Olaparib	May 2020	PARPi	HRR gene-mutated mCRPC

AR, androgen receptor;
HRR, homologous recombination repair;
MSI, microsatellite instability
All information available at: www.drugs.com

PARPi: WHAT DO WE NEED TO KNOW?

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- Which mutations confer sensitivity to PARPi?
- How common are these mutations in prostate cancer?
- How do we identify patients with these mutations?
- What is the current role of PARPi in prostate cancer?

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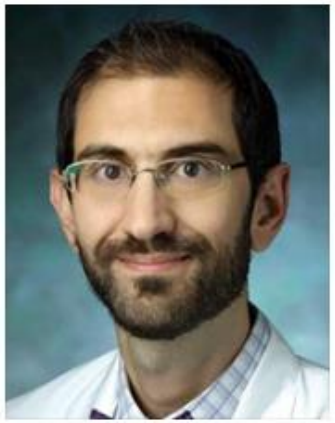
WHAT IS PARP INHIBITION AND HOW DO WE IDENTIFY PATIENTS?



Prof. Emmanuel S. Antonarakis, MD
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Sidney Kimmel Comprehensive Cancer Center
Baltimore, Maryland

DISCLOSURE

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- **Stock/Patents/Salary**: None

GENOMIC INSTABILITY IS A TARGETABLE HALLMARK OF CANCER

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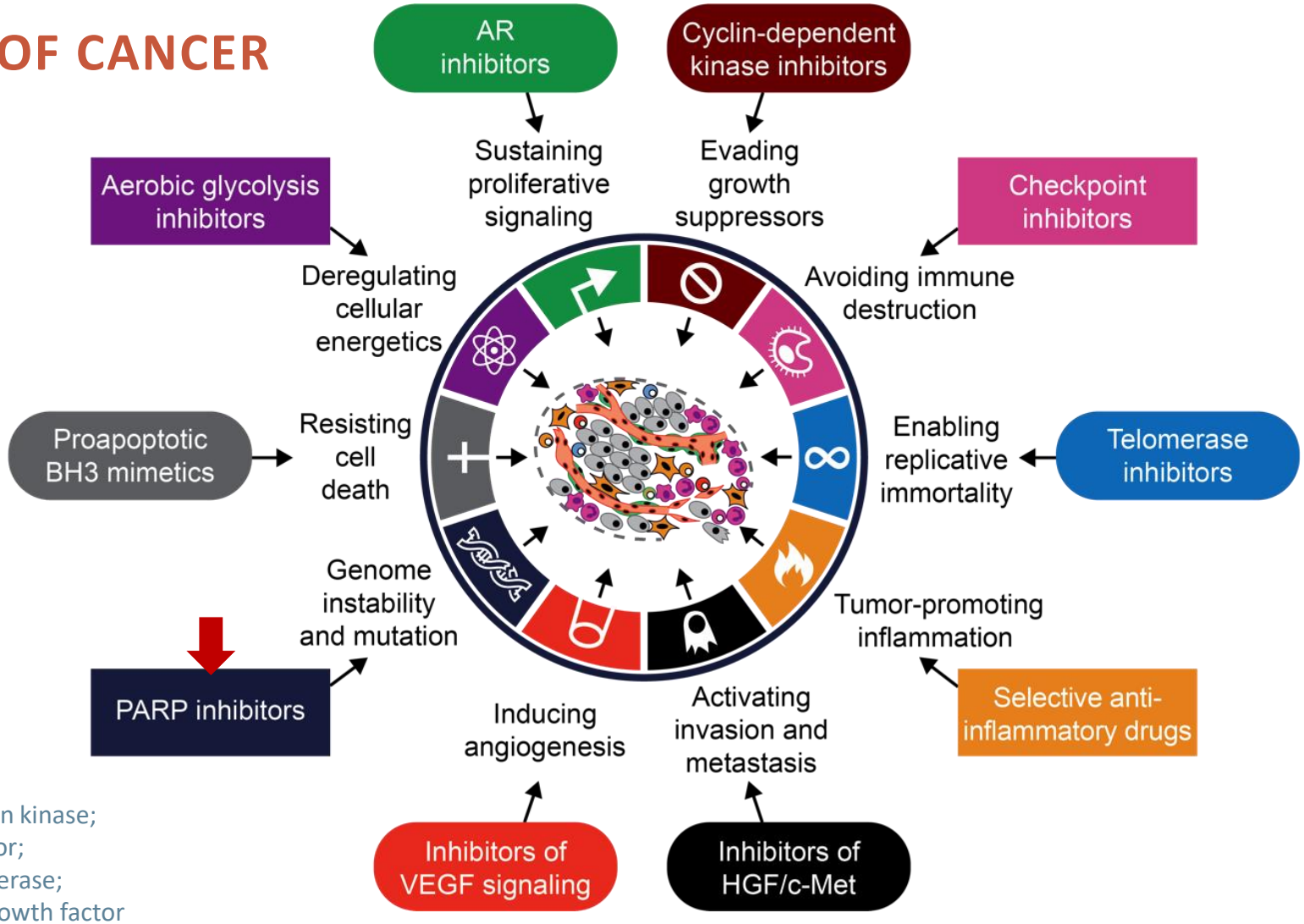
HALLMARKS OF CANCER



AR, androgen receptor;
c-MET, c-MET tyrosine-protein kinase;
HGF, hepatocyte growth factor;
PARP, poly ADP ribose polymerase;
VEGF, vascular endothelial growth factor
Hanahan D, Weinberg RA. Cell. 2011;144:646–74.

ABERRANT DOUBLE-STRAND BREAK REPAIR: GENOME INSTABILITY

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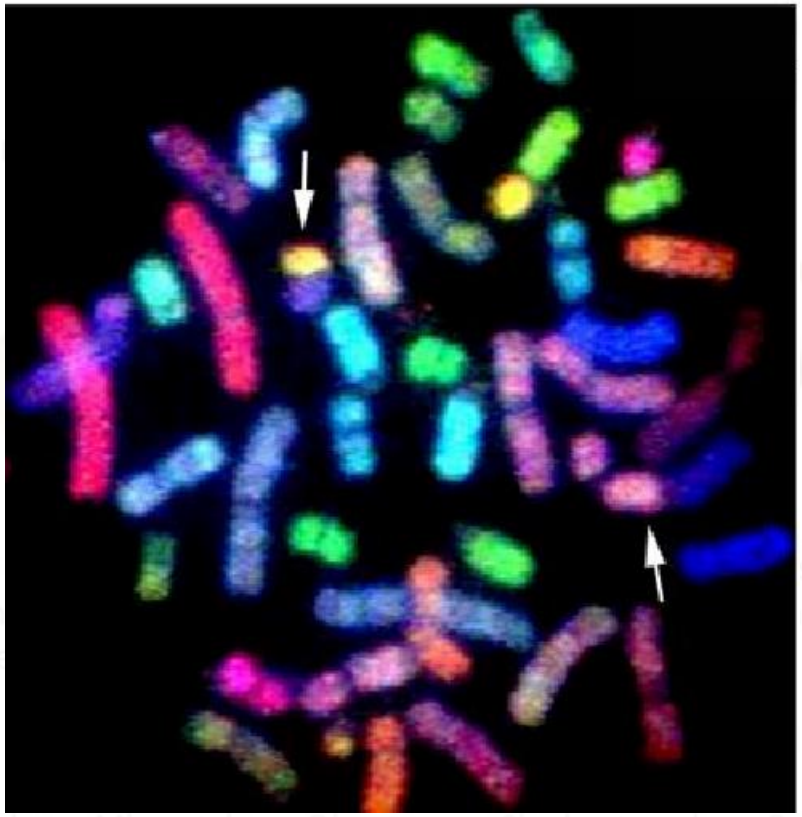
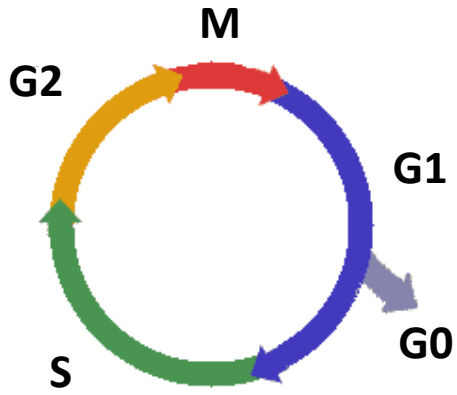
Spontaneous
(Fork collapse)



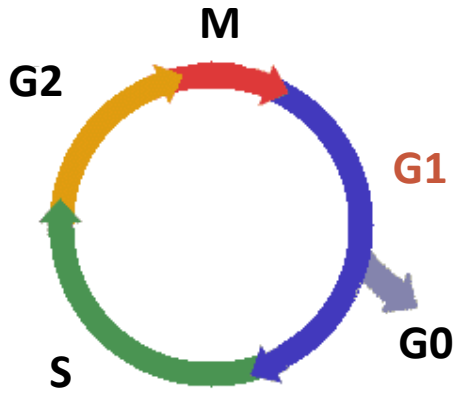
DSB, double-strand break

DSB REPAIR: CELL CYCLE



G, gap; M, mitosis; S, synthesis

DSB REPAIR: CELL CYCLE



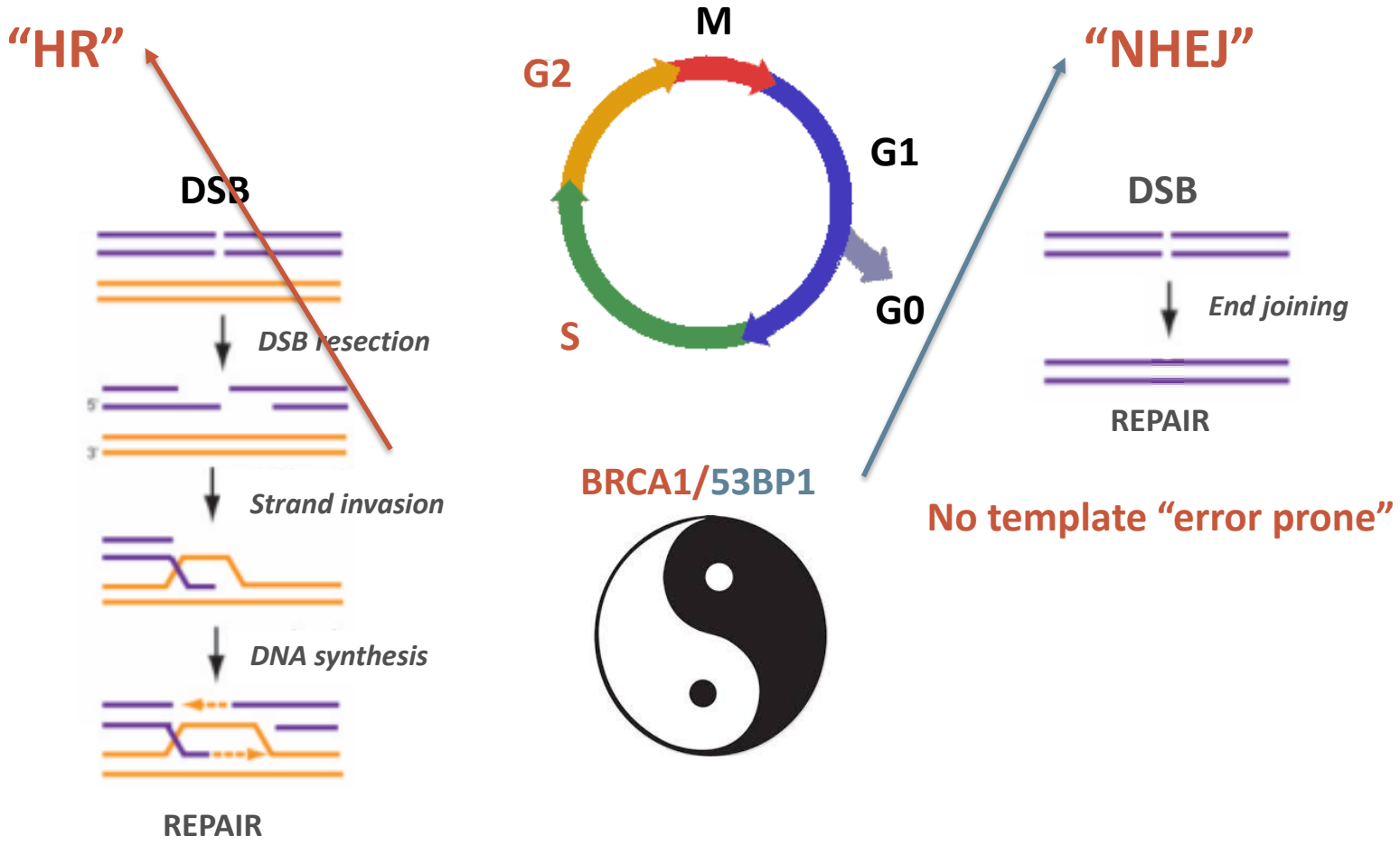
“NHEJ”

DSB

“Error prone”

NHEJ, non-homologous end joining

DSB REPAIR: MEDIATED BY TWO PATHWAYS WITH DIFFERENT ERROR FREQUENCY



Template based "error free"

No template "error prone"

53BP1, tumour suppressor p53-binding protein 1; BRCA1, breast cancer type 1 susceptibility protein; HR, homologous recombination

DSB REPAIR: HR GENE DEFECTS REDUCE DNA REPAIR OPTIONS

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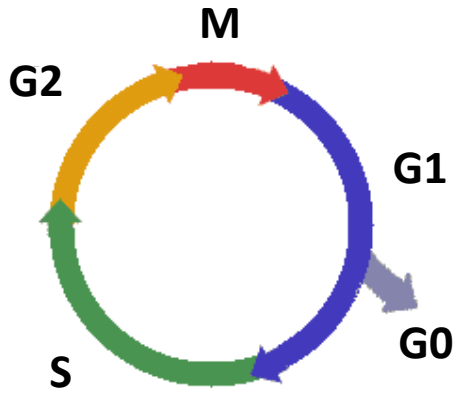
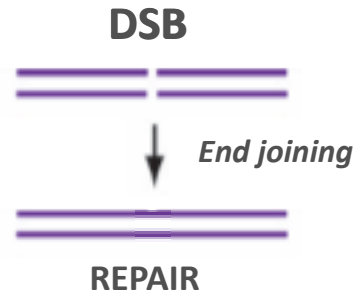
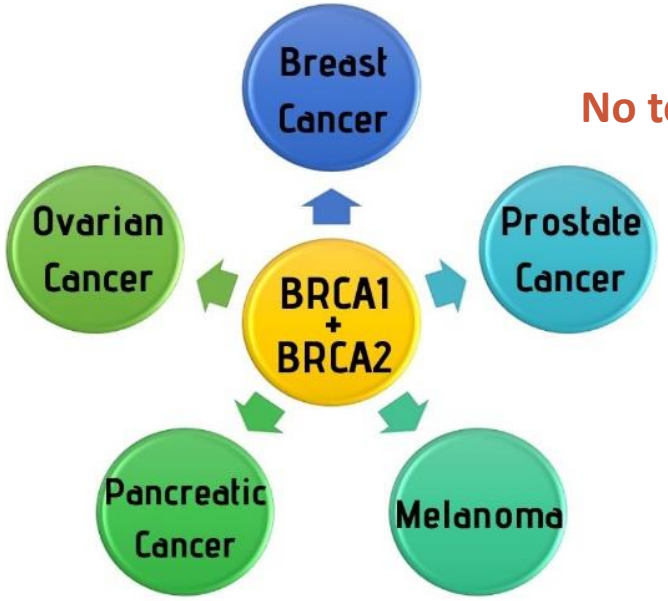
"HR"



"NHEJ"





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BRCA2, breast cancer type 2 susceptibility protein

DSB REPAIR DEFECTS: THERAPEUTIC EXPLOITATION IN CANCER

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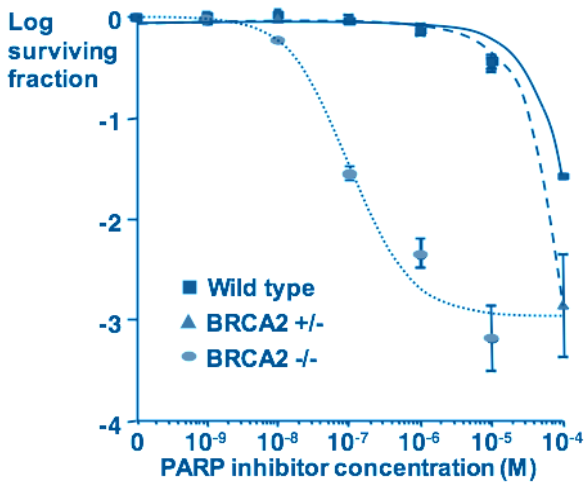
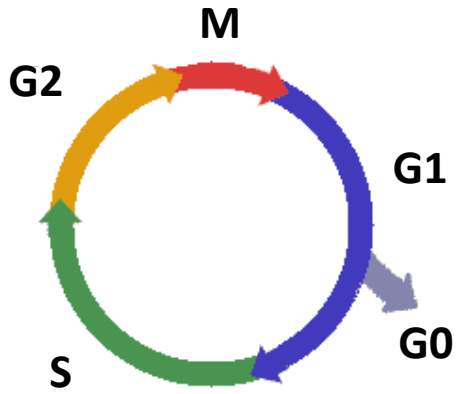
"HR"

DSB





"NHEJ"

DSB

Helleday, Jackson, Ashworth

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

PARP INHIBITORS: THERAPEUTIC EXPLOITATION IN CANCER

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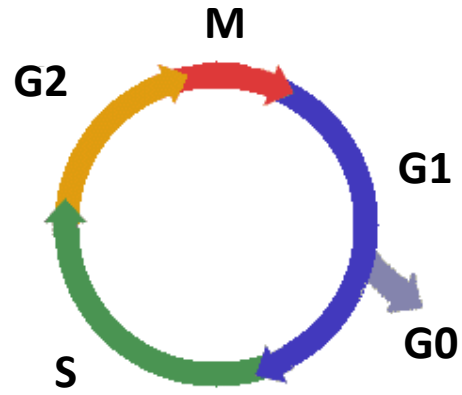
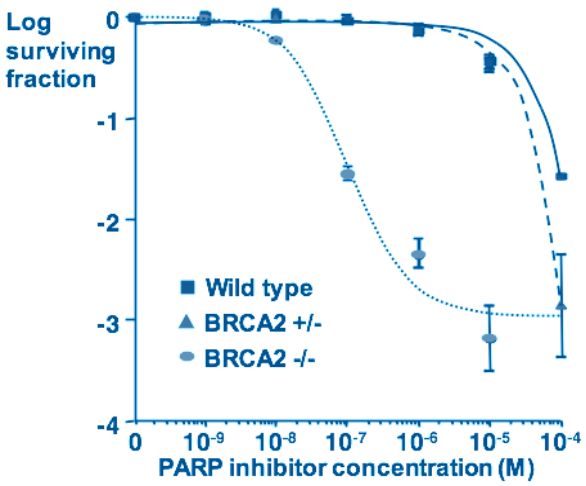
"HR"

"NHEJ"



DSB

DSB



Lynparza® olaparib

Zejula™ niraparib

Rubraca® (rucaparib) 300 mg tablets

TALZENNA™ talazoparib 1 mg capsules

PARP INHIBITORS: 'SYNTHETIC LETHALITY'
REQUIRES BOTH REPAIR PATHWAYS TO BE BLOCKED

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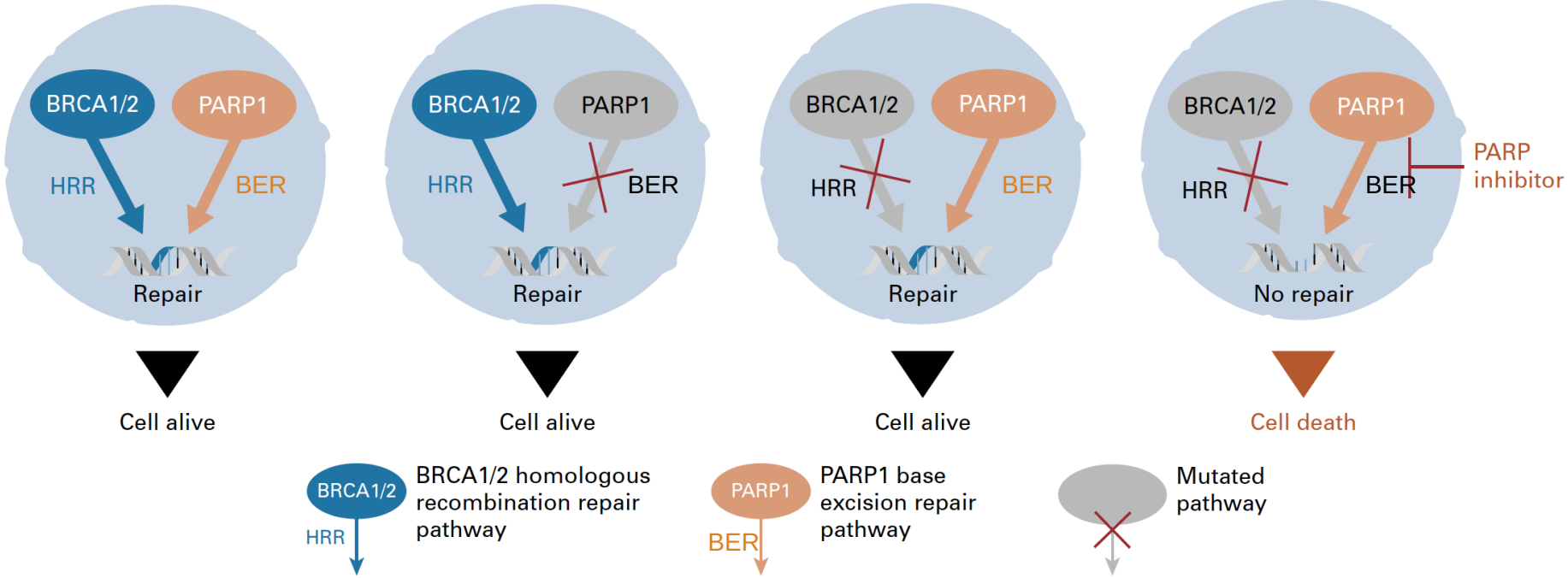
- ***BRCA*: "copy editor"; HRR**
- **PARP: "spell check"; BER**

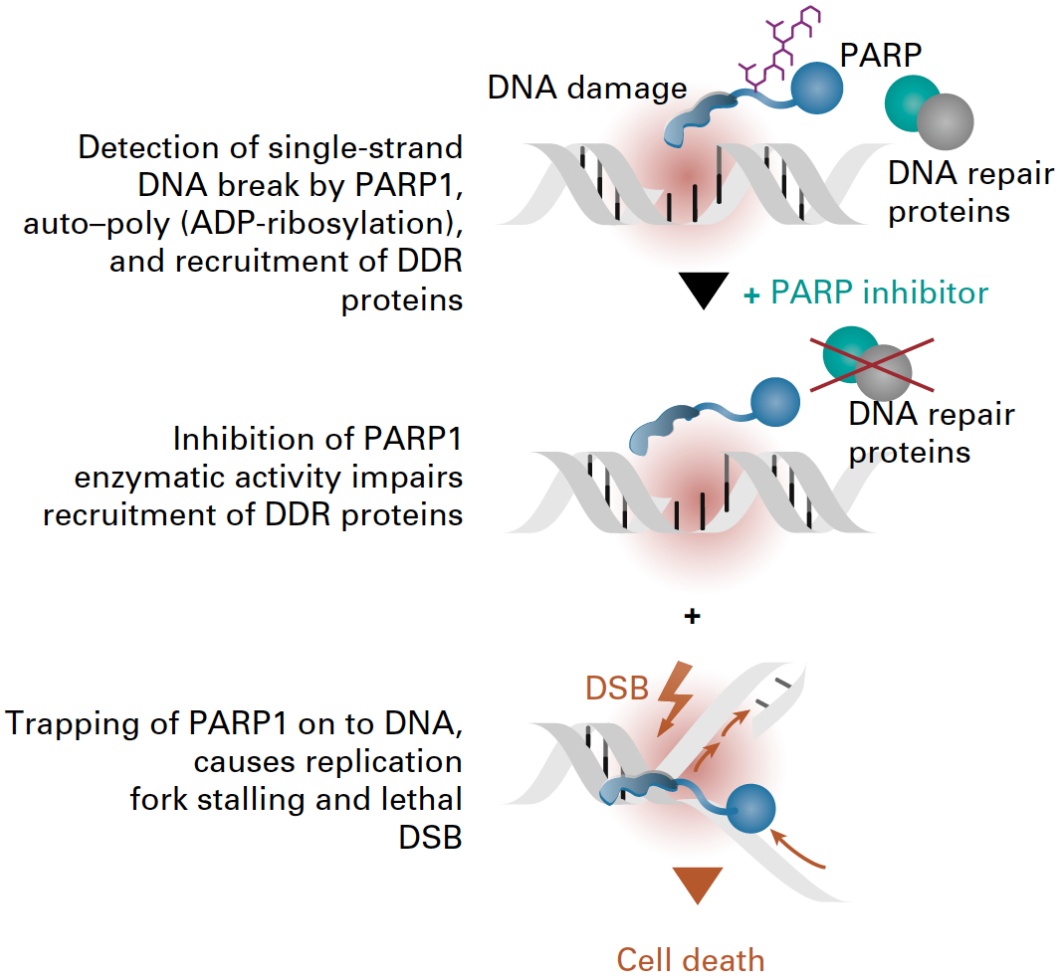


PARP is required for SSB repair (e.g. via BER)

MOA – inhibiting SSB/BER is synthetic lethal with HRD

BER, base excision repair; HRD, homologous recombination deficiency; MOA, mode of action; SSB, single-strand break

PARP INHIBITORS: ENZYMATIC INHIBITION & PARP TRAPPING



MOA – trapping PARP is synthetic lethal with HRD

DDR, DNA damage repair

DDR MUTATIONS IN METASTATIC PROSTATE CANCER

Prevalence and Screening

CHANGING TREATMENT PATTERNS IN THE ERA OF PRECISION MEDICINE

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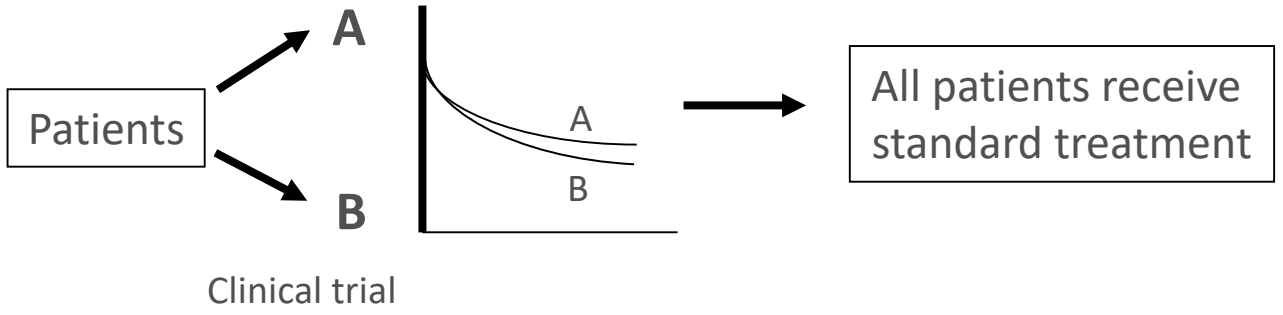
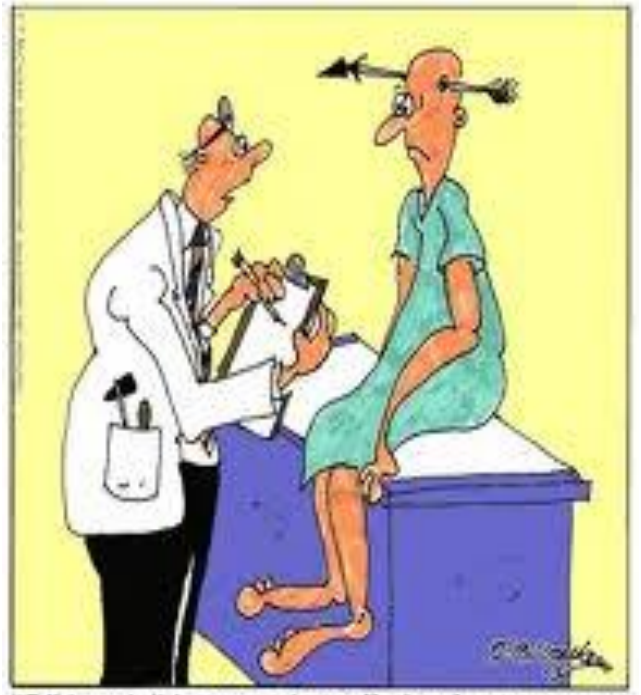
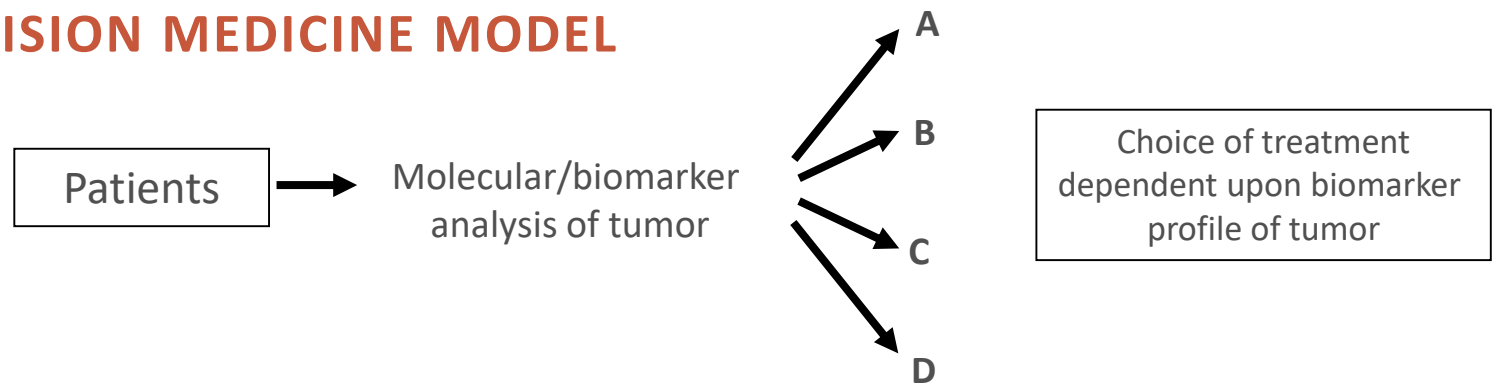
TRADITIONAL MODEL OF DRUG DEVELOPMENT





PRECISION MEDICINE MODEL



Goal: analytic validation of biomarker → clinical validation of clinical utility and patient benefits with matched therapy

Key contexts: prior therapy, histology, patient phenotype, comorbidities, costs, toxicities

Fröhlich H, et al. BMC Med. 2018;16(1):150; Redekop WK, Mlasi D. Value Health. 2013;16(6 Suppl):S4-9; Krzyszczyk P, et al. Technology (Singap World Sci). 2018;6:79-100.

2020 ACTIONABLE PATHWAYS, GENOTYPES AND PHENOTYPES

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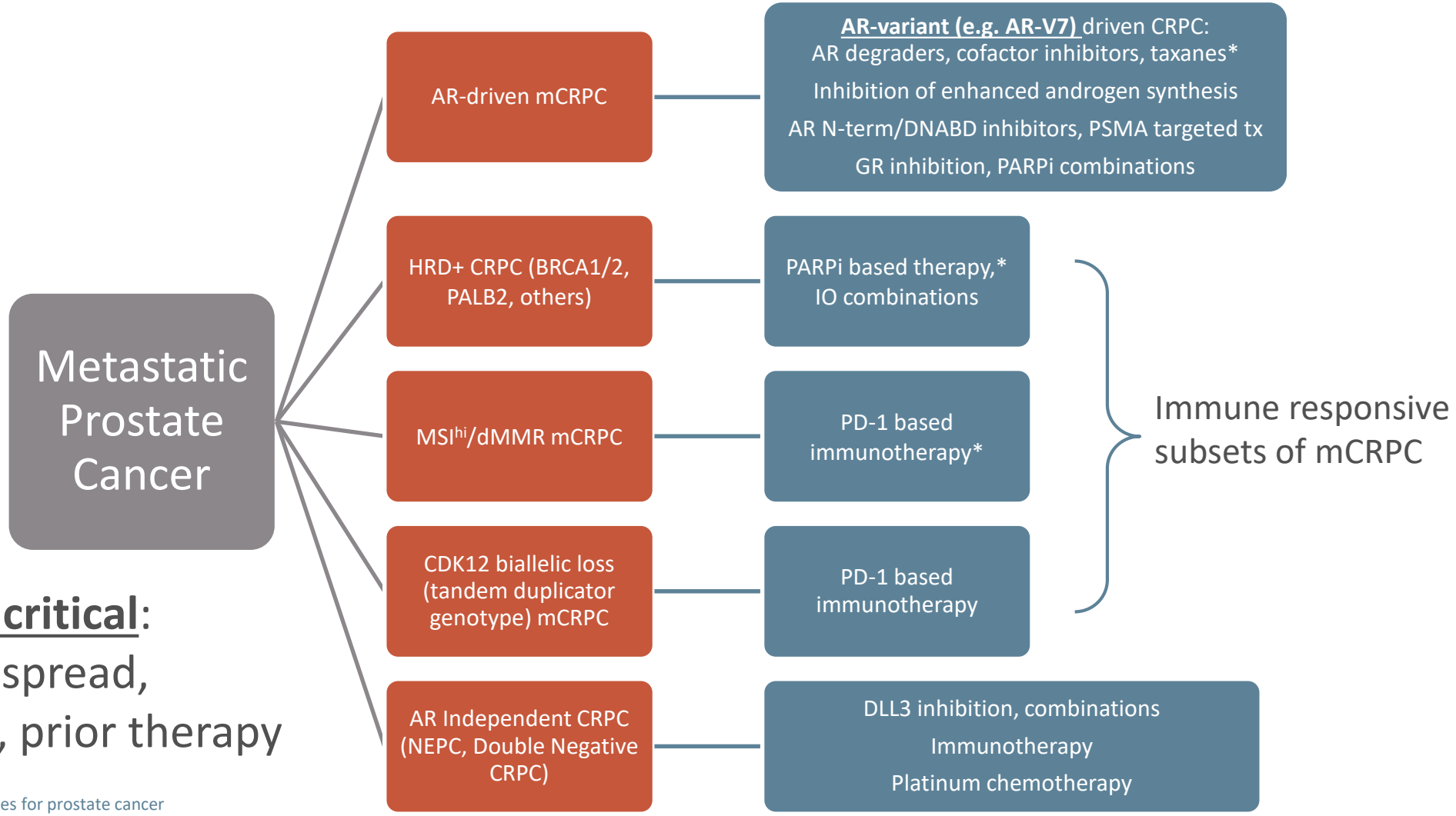

Context is critical:
pattern of spread,
symptoms, prior therapy

*Currently approved therapies for prostate cancer

CDK12, cyclin-dependent kinase 12; CRPC, castrate-resistant prostate cancer; DLL, delta-like ligand; dMMR, deficient mismatch repair; DNABD, DNA binding domain; IO, immuno-oncology; (m)CRPC, (metastatic) castrate-resistant prostate cancer; MSIhi, microsatellite instability-high; NEPC, neuroendocrine prostate cancer; PALB2, partner and localizer of BRCA2; PARPi, poly ADP ribose polymerase inhibitor; PD-(L)1, programmed death (ligand)-1; PSMA, prostate-specific membrane antigen; Tx, therapy

Armstrong CM, Cao AC. Asian Journal of Urology (2019) 6, 42e49; Antonarakis ES, et al. Prostate Cancer Prostatic Dis. 2016;19(3):231-41; Ponnumasy S, et al. Cancer Res. 2017;77(22):6282-98; Akora VK, et al. Cell. 2013 December 5;155(6):1309-22; Vlachosergios PJ, et al. Curr Oncol Rep. 2017;19(5):32; Khemlina et al. 2015 https://www.sciencedirect.com/science/article/pii/S0305737215001462;
Cheng JNCCN 2019 https://jnccn.org/view/journals/jnccn/17/5/article-p515.xml

DNA REPAIR GENE ALTERATIONS (SOMATIC AND GERMLINE) ARE COMMON IN METASTATIC PROSTATE CANCER[1-3]

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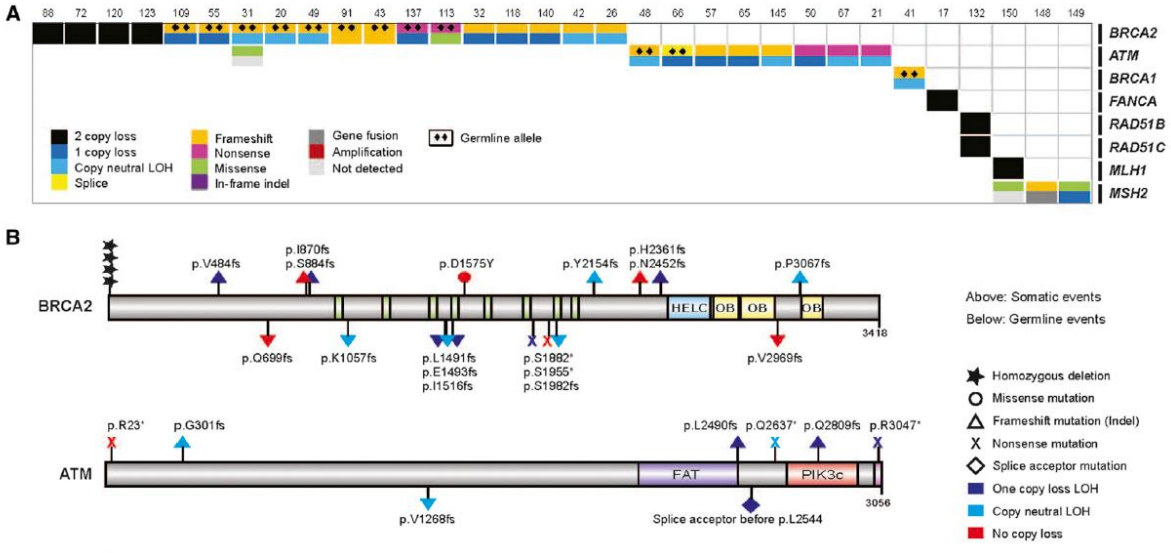
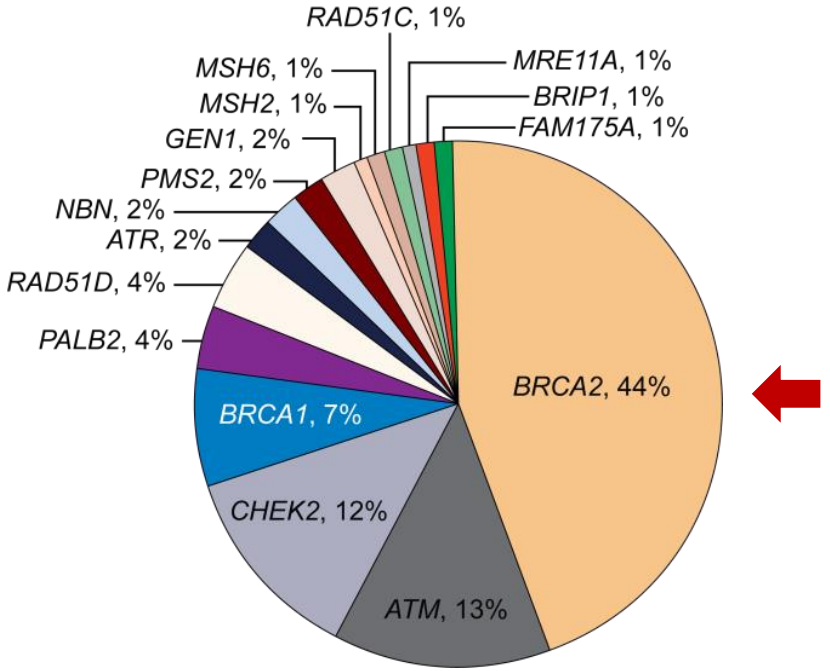
Somatic

- **23%** of mCRPCs harbor DNA repair alterations
- The frequency of DNA repair alterations **increases in metastatic disease vs. localized disease**



Germline



- **12%** of men with metastatic prostate cancer have a germline DNA repair defect

LOH, loss of heterozygocity

1. Robinson D, et al. Cell. 2015;161:1215-28; 2. Pritchard CC, et al. N Engl J Med. 2016;375:443-53; 3. Antonakaris ES, et al. Eur Urol. 2018;74(2):218-25.

BRCA2 CARRIERS WITH PROSTATE CANCER HAVE WORSE PROGNOSIS[1,2]

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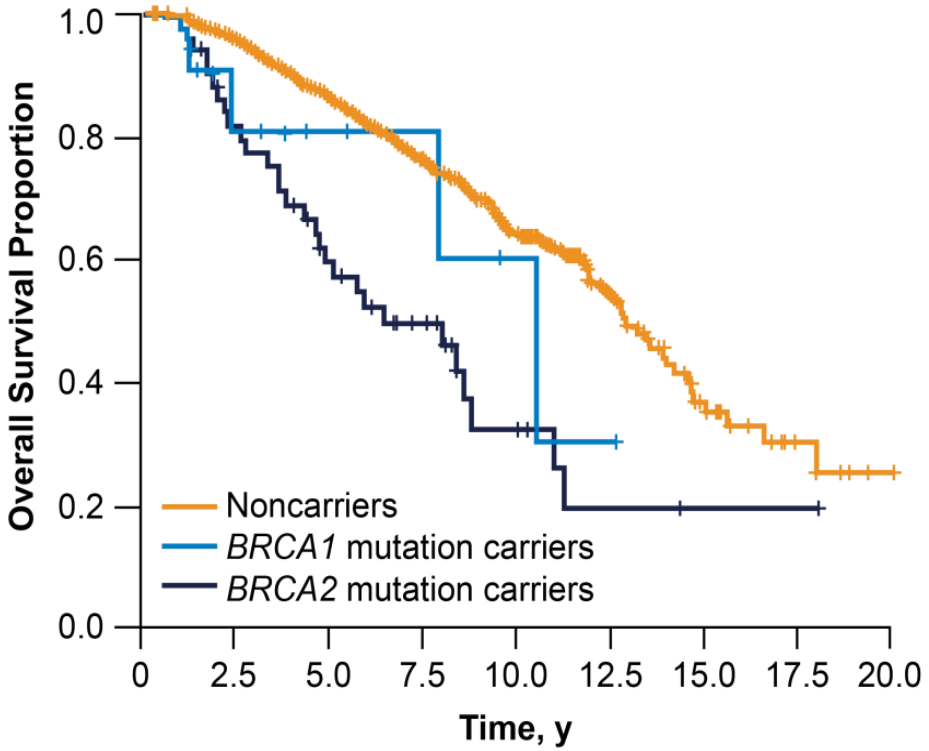
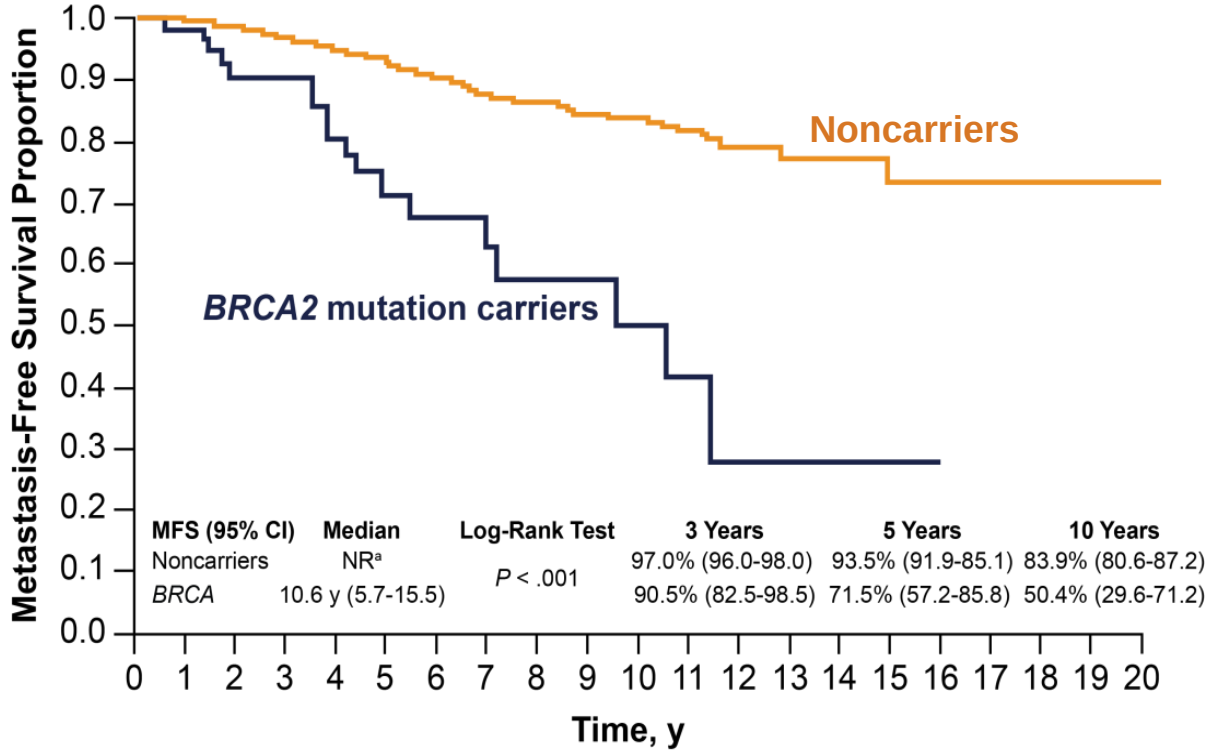


No. at Risk									
Noncarriers	1,940	1,394	896	467	186	68	22	6	1
BRCA1 mutation carriers	18	12	5	4	2	1	0	0	0
BRCA2 mutation carriers	61	40	28	16	6	3	1	1	0



MFS (95% CI)	Median	Log-Rank Test	3 Years	5 Years	10 Years
Noncarriers	NR[a]	*P* < .001	97.0% (96.0-98.0)	93.5% (91.9-85.1)	83.9% (80.6-87.2)
BRCA	10.6 y (5.7-15.5)		90.5% (82.5-98.5)	71.5% (57.2-85.8)	50.4% (29.6-71.2)

No. at Risk	Baseline	3 years	5 years	8 years	10 years	12 years	15 years	20 years
Noncarriers	1,235	865	646	285	140	57	18	1
BRCA	67	39	20	12	7	2	1	0

[a]Median survival not reached after a median of 64-mo follow-up.
CI, confidence interval; No., number; NR; not reached; y, years

1. Castro E, et al. J Clin Oncol. 2013;31:1748-57; 2. Castro E, et al. Eur Urol. 2015;68:186-93.

FAMILY HISTORY IS A REAL RISK FACTOR

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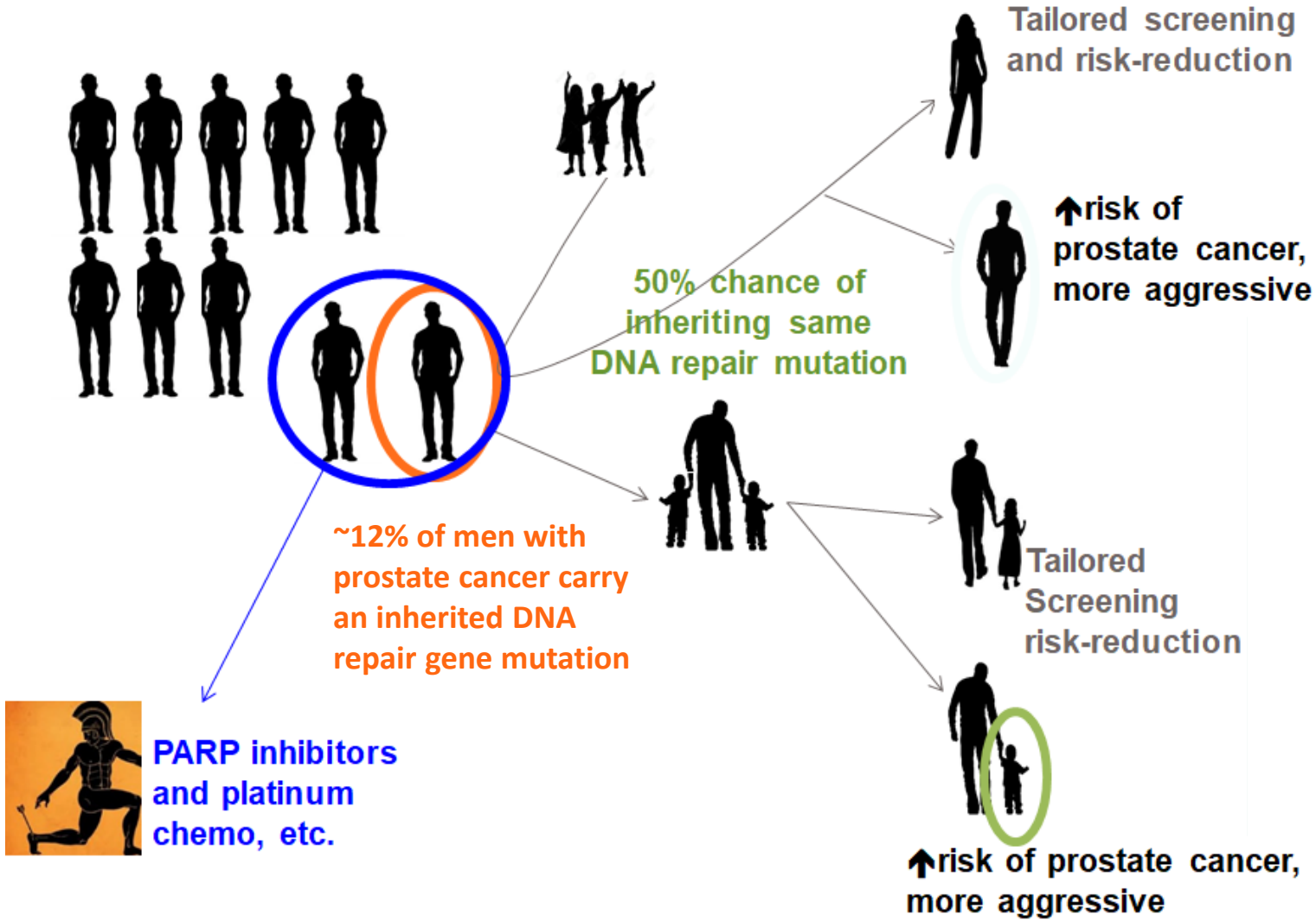
- A father or brother with prostate cancer doubles a man's risk of prostate cancer
- A mother or sister with breast cancer diagnosed before age 50 significantly increases a woman's risk of breast cancer
- A mother or sister with breast cancer can affect a man's risk of prostate cancer

Chen et al., Prostate 2008 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2574825/; Colditz et al., 2012 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3387322/

CASCADING IMPACT



- Full family history is important to collect during the genetic evaluation
- In-person genetic counseling is the gold standard
- Patients' psychosocial needs/preferences should dictate the mode of counseling

NCCN (V 2.2020) GUIDELINES FOR GENETIC TESTING

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Germline Testing	Somatic Tumor Testing
• Germline genetic testing is recommended for patients with prostate cancer and any of the following: – High-risk, very high-risk, regional, or metastatic prostate cancer – Ashkenazi Jewish ancestry – Family history of high-risk germline mutations (eg, *BRCA1/2*, Lynch mutation) – A positive family history of cancer	• Recommend evaluating tumor for alterations in homologous recombination DNA repair genes, such as *BRCA1, BRCA2, ATM, PALB2, FANCA, RAD51D, CHEK2,* and *CDK12*, in patients with metastatic prostate cancer • Can be considered in men with regional prostate cancer • Testing for microsatellite instability-high (MSI-H) or dMMR is recommended in patients with CRPC, and should be considered in patients with regional or castration-naïve metastatic prostate cancer

- The international Philadelphia Prostate Cancer Consensus Conference 2019 guidelines recommended a similar germline testing strategy

Giri VN et al. J Clin Oncol. 2020;38(24):2798-2811. NCCN Guidelines for Prostate Cancer. Available from: www.nccn.org/about/news/ebulletin/ebulletindetail.aspx?ebulletinid=3852. Accessed October 2020.

HOW DO WE TEST?

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Germline

Somatic

MYRIAD myRisk® Hereditary Cancer

CARIS LIFE SCIENCES

GUARDANT

NEO GENOMICS

FOUNDATION MEDICINE

INVITAE

color

TEMPUS

Ambry Genetics®

Academic/In house

CONCLUSIONS

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- **DDR mutations are a therapeutic target** in metastatic prostate cancer
- **PARPi** work by the concept of “synthetic lethality”
- **Both somatic and germline mutations** related to DDR are common in metastatic prostate cancer
- Somatic and germline **testing is recommended for all patients with metastatic prostate cancer** and some patients with high-risk regional and locally-advanced prostate cancer

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ROLE OF PARPi IN ADVANCED PROSTATE CANCER

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Duke Cancer Institute

DISCLOSURE

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Prof. Andrew J. Armstrong has the following relevant financial relationships to disclose:

- **Research/Consulting:** Pfizer, Janssen, Astellas, AstraZeneca, Merck, Bayer, Dendreon, BMS, Constellation, Beigene, Genentech/Roche, Clovis consulting and research support (to Duke University for clinical trials/research)
- **Stock/Patents/Salary**: None

MANY PARP INHIBITORS ARE BEING TESTED[1]

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PROPERTIES OF PARP INHIBITORS

	Olaparib[1]	Veliparib[1]	Talazoparib[1]	Niraparib[1]	Rucaparib[1]	Pamiparib[2]
MW	434.5	244.3	380.8	320.4	323.4	298.31
PARP1 IC_{50}	5 nM	1.2 nM	0.56 nM	3.8 nM	0.65 nM	0.9 nM
PARP2 IC_{50}	1 nM	0.41 nM	0.15 nM	2.1 nM	0.08 nM	0.5 nM
Trapping	++	+	++++	+++	++	++[3]

Pamiparib trapping potential estimated based on description as 'potent'.

IC50, half of maximal inhibitory concentration; MW, molecular weight; nM, nanomoles; PARP, poly-ADP ribose polymerase

1. Carney B, et al. Nat Commun. 2018;9:176; 2. Available from: https://www.medchemexpress.com/Pamiparib.html. Accessed, August 2020.
3. Pilie PG, et al. Clin Cancer Res. 2019;25:3759-71.

ONGOING SINGLE AGENT CLINICAL TRIALS OF PARPi IN mCRPC

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PARPi	Clinical Trial No.	Study overview	Setting	Trial status
Olaparib	NCT01682772	Single arm, phase 2 trial of olaparib, predictive biomarker trial	Advanced castration resistant prostate cancer	Active, not recruiting
Olaparib	NCT02987543	Randomized phase 3 trial of olaparib vs enzalutamide or abiraterone	mCRPC who have failed prior treatment with a NHA with somatic HRR mutation	Active, not recruiting
Olaparib	NCT03047135	Single arm phase 2 trial of olaparib	Non-metastatic biochemically-recurrent PCa and a PSADT of ≤6 months and a minimum PSA of 1.0	Recruiting
Olaparib	NCT03263650	Randomized phase 2 of olaparib maintenance versus observation	AVPC 6 cycles of cabazitaxel and carboplatin before randomisation	Recruiting
Olaparib	NCT03434158	Single-arm phase 2 study of olaparib (IMANOL)	mCRPC ≥ 6 cycles of docetaxel with CR/PR (RECIST 1.1) and PCWG3	Recruiting
Talazoparib	NCT03148795	Phase 2 single arm study of talazoparib	mCRPC previous taxane-based chemotherapy and progression on ≥ 1 NHA	Active, not recruiting
Rucaparib	NCT02952534	Single arm phase 2 trail of rucaparib (TRITON2)	mCRPC with evidence of HRR gene deficiency	Active, not recruiting
Rucaparib	NCT02975934	Phase 3 trial of rucaparib vs physician's choice of abiraterone acetate, enzalutamide, or docetaxel. (TRITON3)	mCRPC with evidence of HRR gene deficiency	Recruiting
Rucaparib	NCT03413995	Single arm phase 2 trail of rucaparib (TRIUMPH)	mHSPC with germline DDR gene mutations	Recruiting
Rucaparib	NCT03533946	Single arm phase 2 trail of rucaparib (ROAR)	Hormone-sensitive PCa with 'BRCAness' gene defects	Recruiting
Niraparib	NCT02854436	Single arm phase 2 biomarker/safety/efficacy (Galahad)	mCRPC with progression taxane therapy	Active, not recruiting
Pamiparib	NCT03712930	Single arm phase 2 trial of pamiparib	mCRPC with HRR deficiency	Active, not recruiting

Humeniuk, Zhang, Armstrong Cancer 2017; Virtanen et al., Genes 2019;10:565; https://clinicaltrials.gov/ct2/show/NCT01682772; https://clinicaltrials.gov/ct2/show/NCT02987543; https://clinicaltrials.gov/ct2/show/NCT03047135; https://clinicaltrials.gov/ct2/show/NCT03263650; https://clinicaltrials.gov/ct2/show/NCT03434158; https://clinicaltrials.gov/ct2/show/NCT03148795; https://clinicaltrials.gov/ct2/show/NCT02952534; https://clinicaltrials.gov/ct2/show/NCT02975934; https://clinicaltrials.gov/ct2/show/NCT03413995; https://clinicaltrials.gov/ct2/show/NCT03533946; https://clinicaltrials.gov/ct2/show/NCT02854436; https://clinicaltrials.gov/ct2/show/NCT03712930

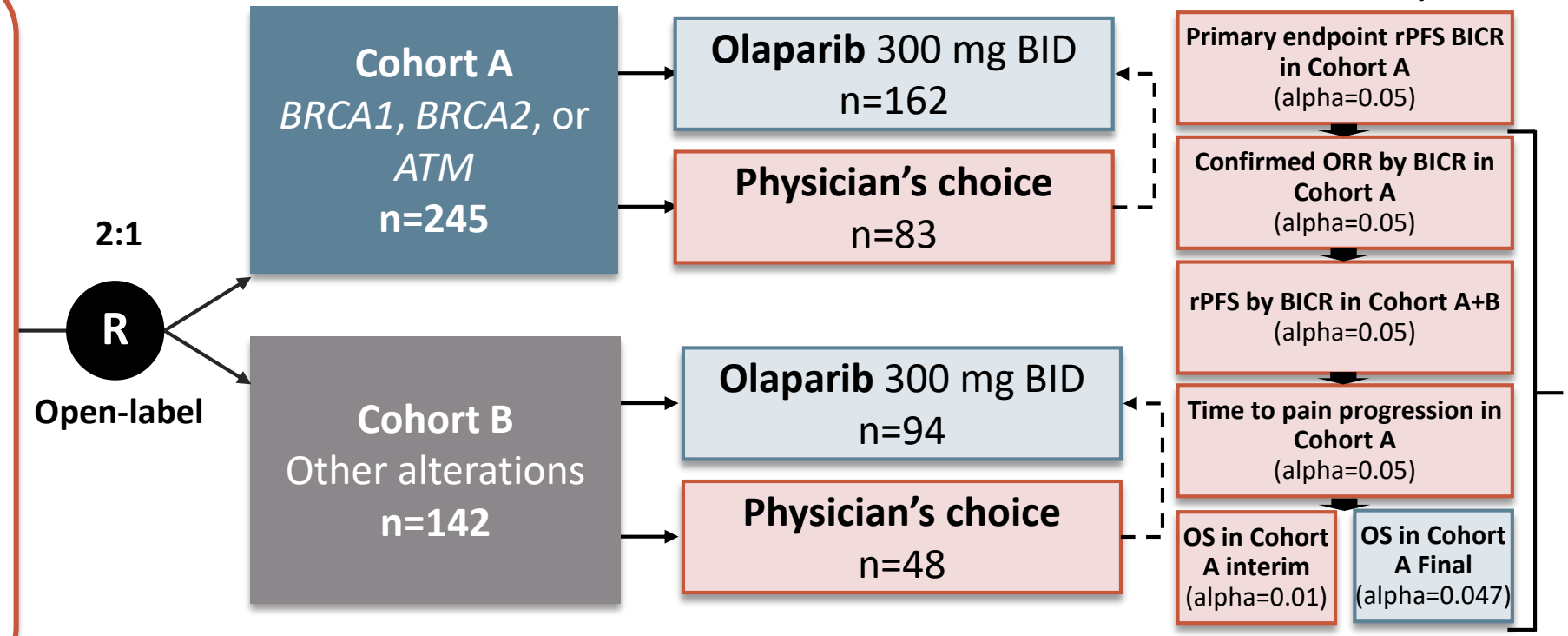
PROfound: STUDY DESIGN[1]

Key Eligibility Criteria

- mCRPC with disease progression on prior NHA (abiraterone or enzalutamide)
- Alterations in ≥1 of any qualifying gene with a direct or indirect role in HRR

Stratification Factors

- Previous taxane
- Measureable disease



- **Primary endpoint:** rPFS in cohort A (RECIST 1.1 and PCWG3 by BICR)
- **Key secondary endpoints:** rPFS (cohorts A+B); confirmed radiographic ORR in cohort A; time to pain progression in cohort A; OS in cohort A

BICR, blinded independent central review; BID, twice daily; HRR, homologous recombination repair; mCRPC, metastatic castration-resistant prostate cancer; NHA, new hormonal agent; ORR, objective response rate; OS, overall survival; PCWG3, Prostate Cancer Working Group 3; R, randomized; RECIST, Response Evaluation Criteria in Solid Tumours; rPFS, radiographic progression-free survival

1. de Bono J, et al. N Engl J Med. 2020;382:2091-102; 2. ESMO 2020, Presentation ID 610O.

PROfound: PATIENT CHARACTERISTICS[1]

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Characteristics	Cohort A		Cohorts A and B	
	Olaparib (N=162)	Control (N=83)	Olaparib (N=256)	Control (N=131)
Median age at randomization, y (range)	68 (47-86)	67 (49-86)	69 (47-91)	69 (49-87)
Age ≥65 y at randomization, n (%)	108 (67)	60 (72)	174 (68)	97 (74)
Metastatic disease at initial diagnosis, n (%) Missing data	38 (23) 7 (4)	19 (23) 4 (5)	66 (26) 11 (4)	25 (19) 7 (5)
Gleason score ≥8, n/total n (%)	105/157 (67)	54/80 (67)	183/251 (73)	95/127 (75)
Patients with alterations in a single gene, n (%) *BRCA1* *BRCA2* *ATM* *CDK12*	 8 (5) 80 (49) 60 (37) N/A	 5 (6) 47 (57) 24 (29) N/A	 8 (3) 81 (32) 62 (24) 61 (24)	 5 (4) 47 (36) 24 (18) 28 (21)
Median PSA at baseline (IQR), mcg/L	62.2 (21.9-280.4)	112.9 (34.3-317.1)	68.2 (24.1-294.4)	106.5 (37.2-326.6)
Measurable disease at baseline, n (%)	95 (59)	46 (55)	149 (58)	72 (55)

IQR, interquartile range; NA, not available; PSA, prostate-specific antigen; y, years

1. de Bono J, et al. N Engl J Med. 2020;382:2091-102.

PROfound: PATIENT CHARACTERISTICS[1] (CONT'D)

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Characteristic	Cohort A		Cohorts A and B	
	Olaparib (N=162)	Control (N=83)	Olaparib (N=256)	Control (N=131)
Metastases at baseline, n (%)				
Bone only	57 (35)	23 (28)	86 (34)	38 (29)
Visceral: lung or liver	46 (28)	32 (39)	68 (27)	44 (34)
Other	49 (30)	23 (28)	88 (34)	41 (31)
ECOG performance status, n (%)				
0	84 (52)	34 (41)	131 (51)	55 (42)
1	67 (41)	46 (55)	112 (44)	71 (54)
2	11 (7)	3 (4)	13 (5)	4 (3)
Missing data	0	0	0	1 (1)
Previous new hormonal agent, n (%)				
Enzalutamide only	68 (42)	40 (48)	105 (41)	54 (41)
Abiraterone only	62 (38)	29 (35)	100 (39)	54 (41)
Enzalutamide and abiraterone	32 (20)	14 (17)	51 (20)	23 (18)
Previous taxane use, n (%)	106 (65)	52 (63)	170 (66)	84 (64)
Docetaxel only	74 (46)	32 (49)	115 (45)	58 (44)
Cabazitaxel only	2 (1)	0	3 (1)	0
Docetaxel and cabazitaxel	29 (18)	20 (24)	51 (20)	26 (20)
Paclitaxel only	1 (<1)	0	1 (<1)	0

ECOG, Eastern Cooperative Oncology Group

1. de Bono J, et al. N Engl J Med. 2020;382:2091-102.

PROfound PRIMARY ENDPOINT: rPFS (COHORT A)[1,2]

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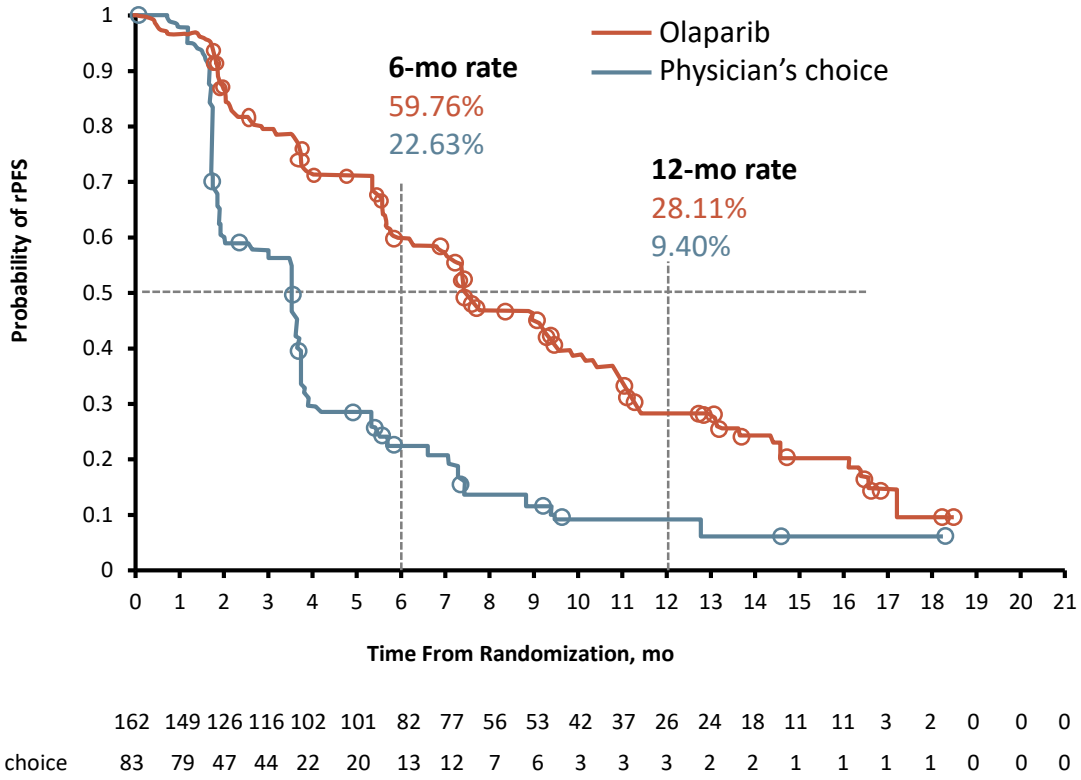
rPFS BY BICR IN PATIENTS WITH ALTERATIONS IN *BRCA1, BRCA2,* OR *ATM* (COHORT A)



	Olaparib (N=162)	Physician's Choice (N=83)
Events, %	106 (65.4)	68 (81.9)
Median PFS, mo	7.39	3.55
HR (95% CI)	0.34 (0.25-0.47) *P*<.001	

CI, confidence interval; HR, hazard ratio; mo, months; PFS, progression-free survival

1. Hussain M, et al. ESMO 2019. Abstract LBA12_PR; 2. de Bono J, et al. N Engl J Med. 2020;382:2091-102.

PROfound: FINAL PRE-SPECIFIED OS[1,2]

First survival advantage with a PARP inhibitor

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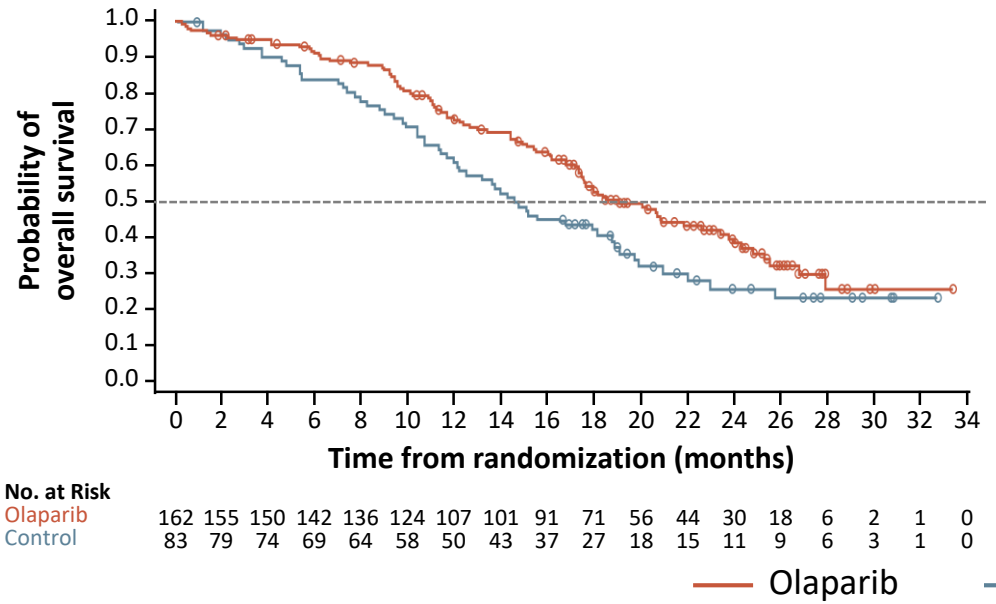
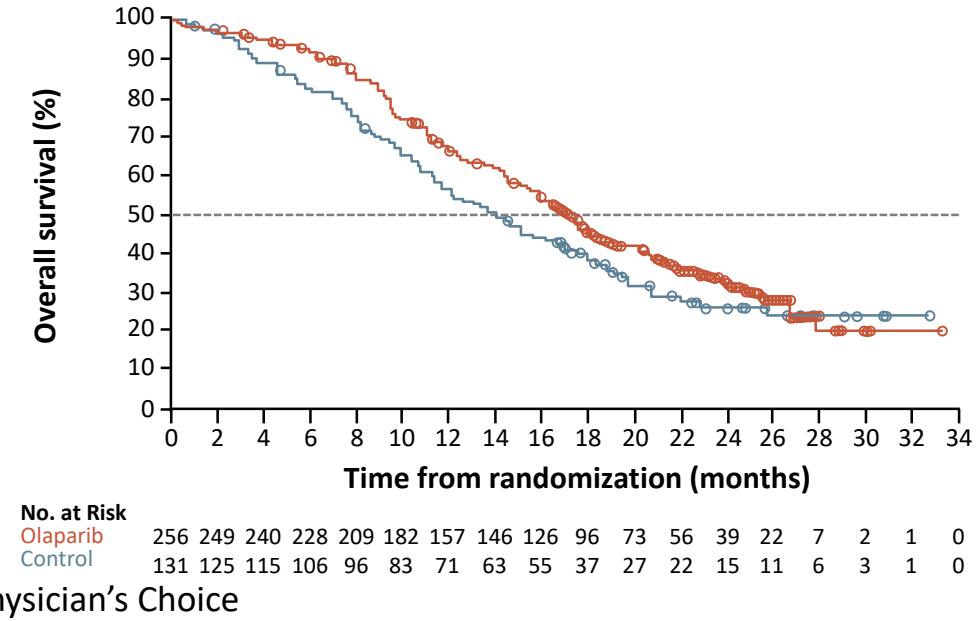
COHORT A[a]

	Olaparib (N=162)	Physician's Choice (N=83)
Median OS, mo	19.1	14.7
HR (95% CI)	0.69 (0.61-1.03) *P* = .0175	



COHORTS A + B[b]

	Olaparib (N=256)	Physician's Choice (N=131)
Median OS, mo	17.3	14.0
HR (95% CI)	0.79 (0.61-1.03)	



Olaparib — Physician's Choice

[a]Population used for EMA 'BRCA1/2 approval' recommendation;

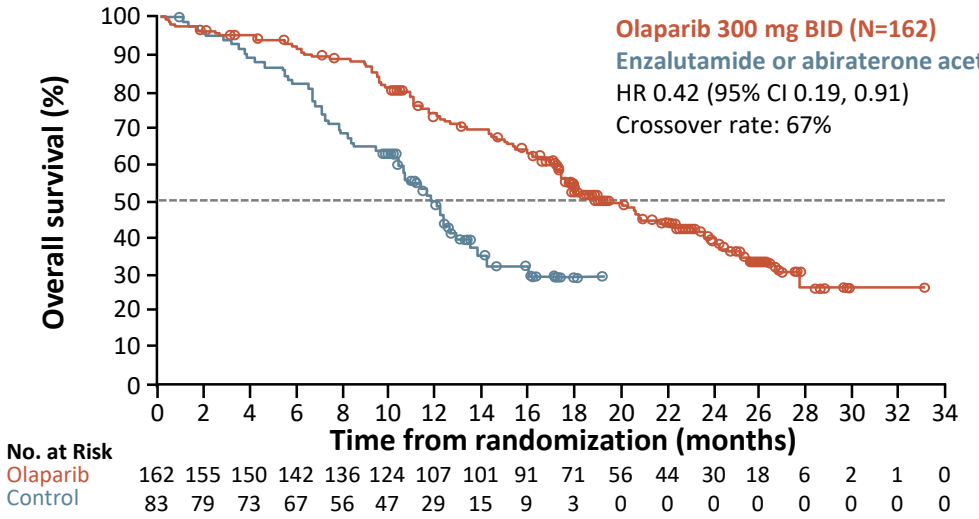
[b]Population used for the FDA 'deleterious germline or somatic HRR mutation' approval. 66% crossed over to olaparib

BRCA1/2, breast cancer type 1/2 susceptibility protein; EMA, European Medicines Agency; FDA, United States Food & Drug Administration; No., number

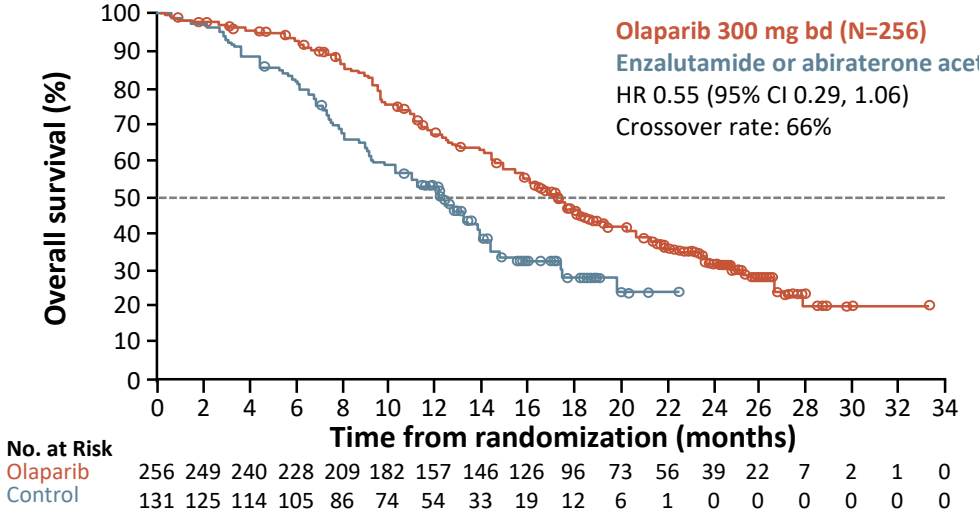
1. ESMO 2020, Presentation ID 610O; 2. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/208558s014lbl.pdf.

PROfound OUTCOMES

COHORT A OS WITH CROSSOVER ADJUSTMENT



COHORT A +B WITH CROSSOVER ADJUSTMENT

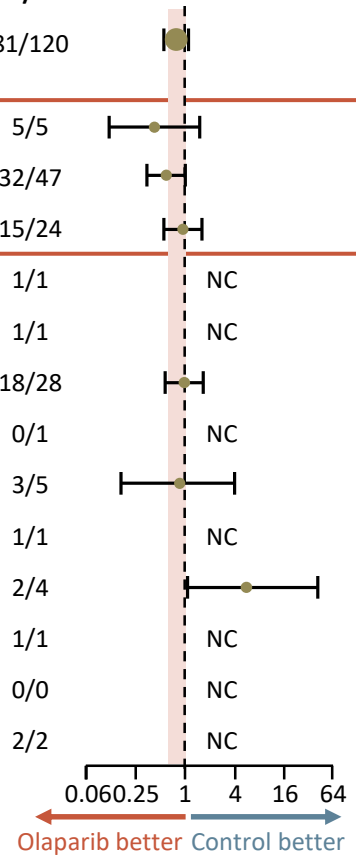


NC, not calculated

ESMO 2020, Presentation ID 610O

EXPLORATORY GENE-LEVEL ANALYSIS OF OS

	Subgroup	Olaparib n/N	Control n/N	HR (95% CI)
	Alteration in any single HRR gene	148/239	81/120	0.79 (0.60-1.04)
Cohort A	*BRCA1* (n=13)	5/8	5/5	0.42 (0.12-1.53)
	BRCA2 (n=128)	39/81	32/47	0.59 (0.37-0.95)
	ATM (n=86)	39/62	15/24	0.93 (0.53-1.75)
Cohort B	*BARD1* (n=1)	0/0	1/1	NC
	BRIP1 (n=3)	1/2	1/1	NC
	CDK12 (n=89)	47/61	18/28	0.97 (0.57-1.71)
	CHEK1 (n=2)	1/1	0/1	NC
	CHEK2 (n=12)	4/7	3/5	0.87 (0.19-4.44)
	PALB2 (n=4)	2/3	1/1	NC
	PPP2R2A (n=10)	5/6	2/4	5.11 (1.10-35.73)
	RAD51B (n=5)	2/4	1/1	NC
	RAD51D (n=1)	1/1	0/0	NC
	RAD54L (n=5)	2/3	2/2	NC

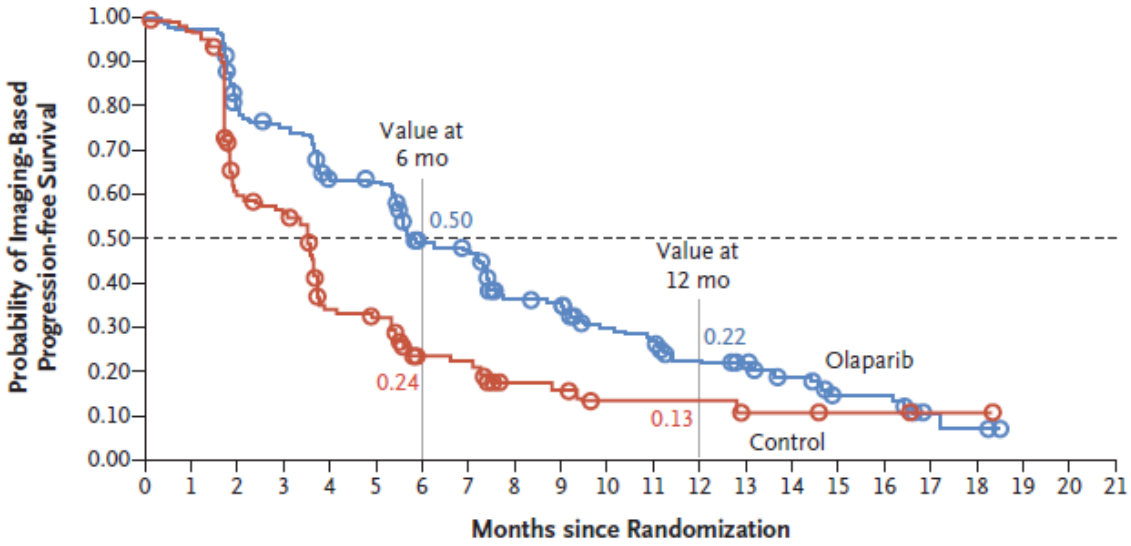


Patients with tumours harbouring a *BRCA1* or *BRCA2* alteration appeared to derive the greatest OS benefit from olaparib

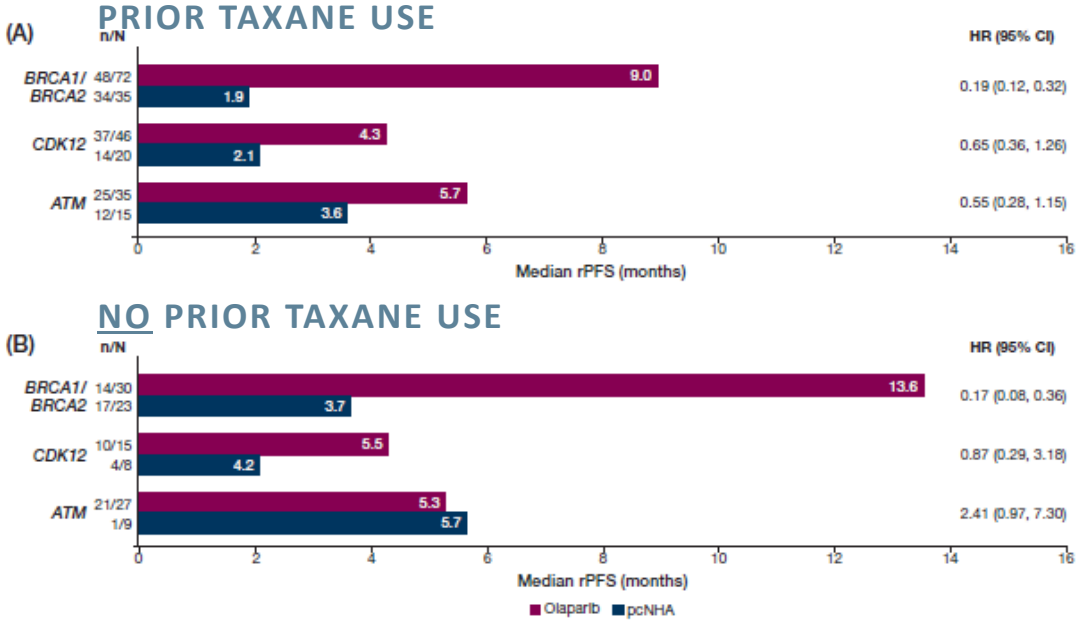
Data are reported only for patients with an alteration in a single gene. HR and CI values were not calculated for subgroups in which fewer than five survival events occurred; none of the enrolled patients harboured alterations in *FANCL* or *RAD51C*. The sizes of the circles are proportional to the number of events.

SECONDARY OUTCOMES

IMAGING-BASED PROGRESSION-FREE SURVIVAL IN COHORTS A AND B



EXPLORATORY SUBGROUP ANALYSES OF rPFS IN PATIENTS WITH ALTERATIONS IN *BRCA1/BRCA2*, *CDK12* AND *ATM* BY (A) PRIOR TAXANE USE AND (B) NO PRIOR TAXANE USE



De Bono, et al ASCO 2020; abstract 134; Hussain M, et al. ESMO 2019. Abstract LBA12_PR.

OUTCOMES IN CHEMO-NAÏVE mCRPC

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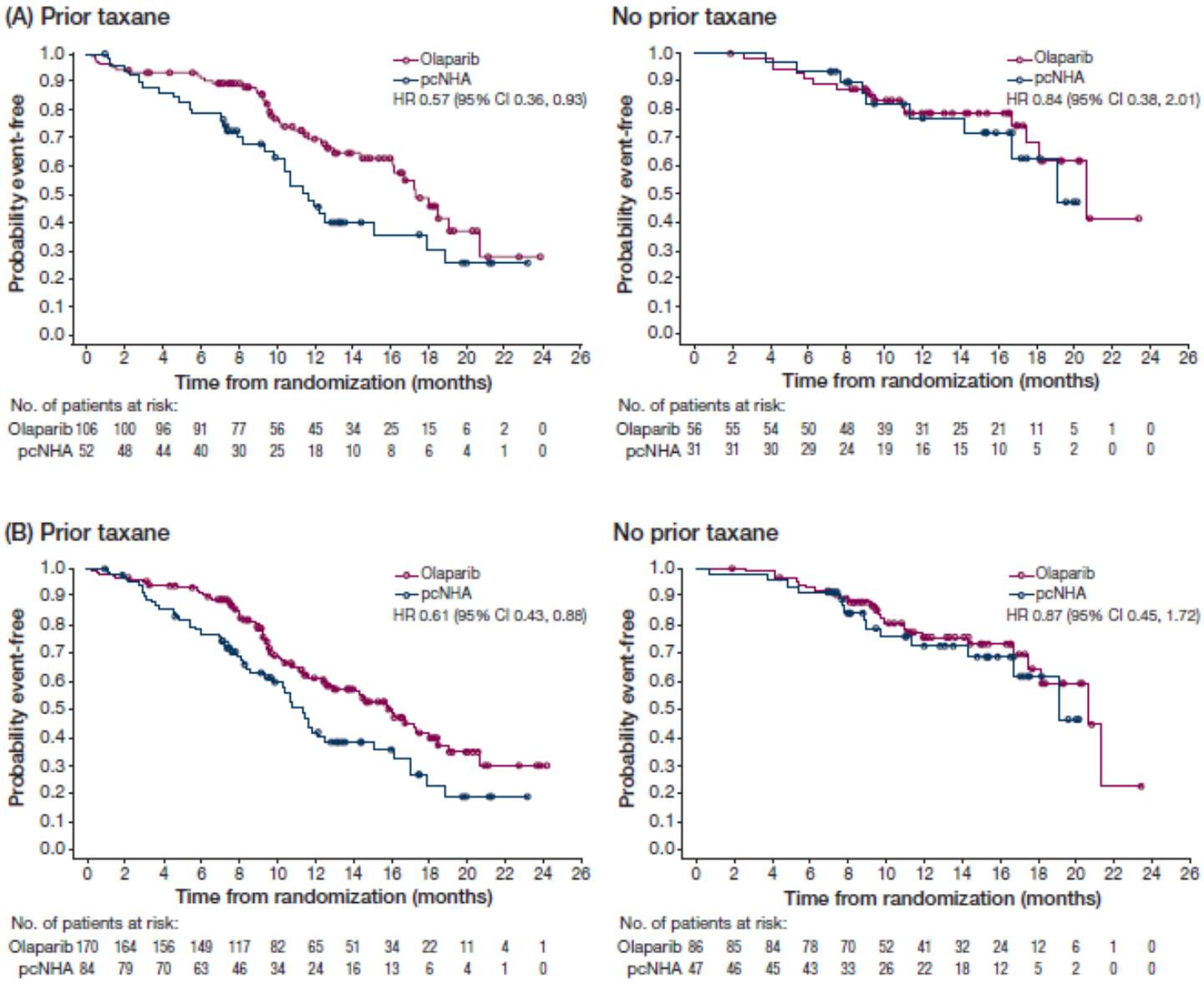
- Kaplan–Meier estimates of **OS** in patients in (A) Cohort A and (B) the overall population (Cohorts A+B) by prior taxane status



pcNHA, physician's choice of new hormonal agent
De Bono, et al ASCO 2020; abstract 134.

PROfound: EXPLORATORY GENE-BY-GENE rPFS ANALYSIS[1,2]

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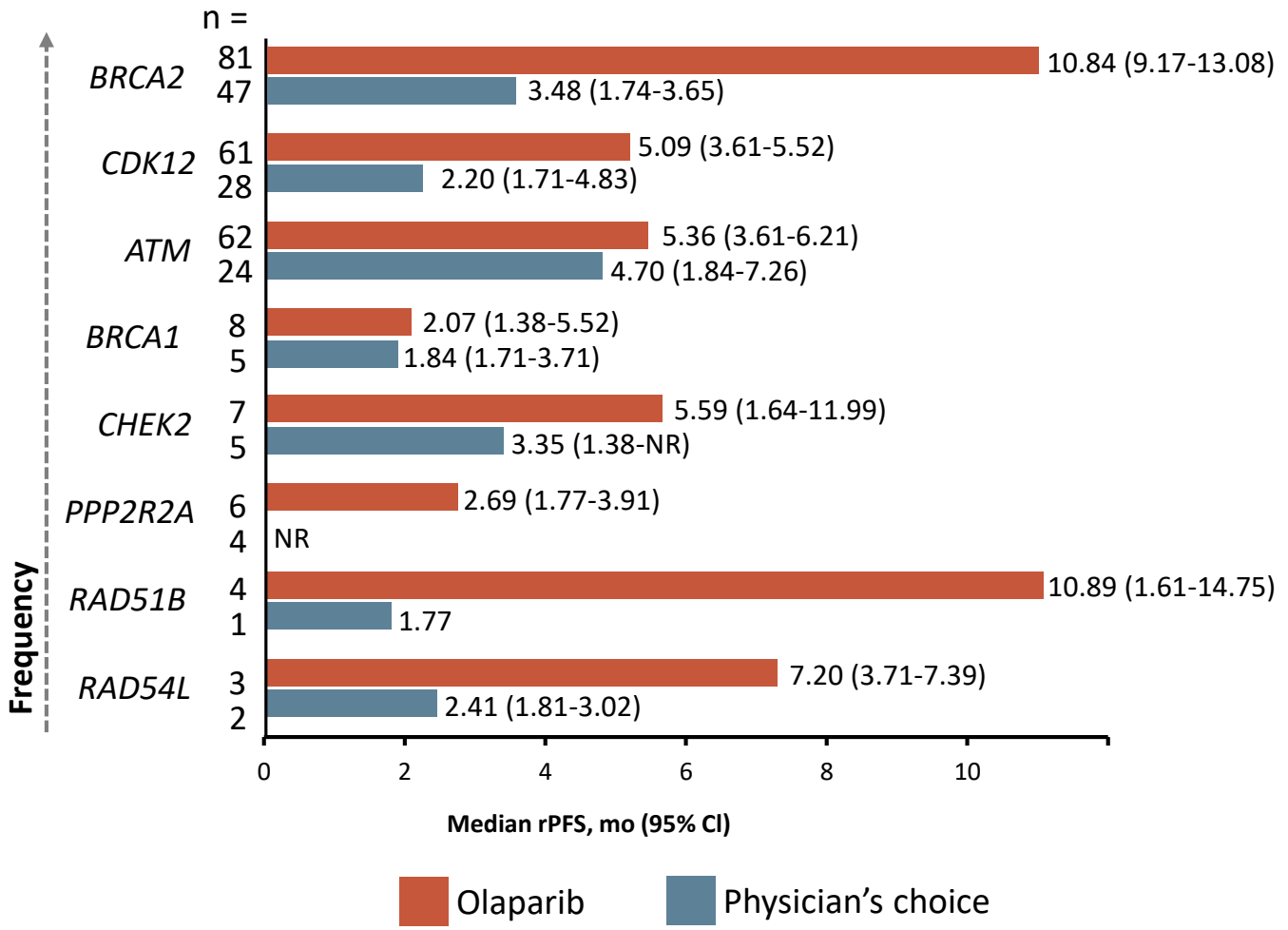
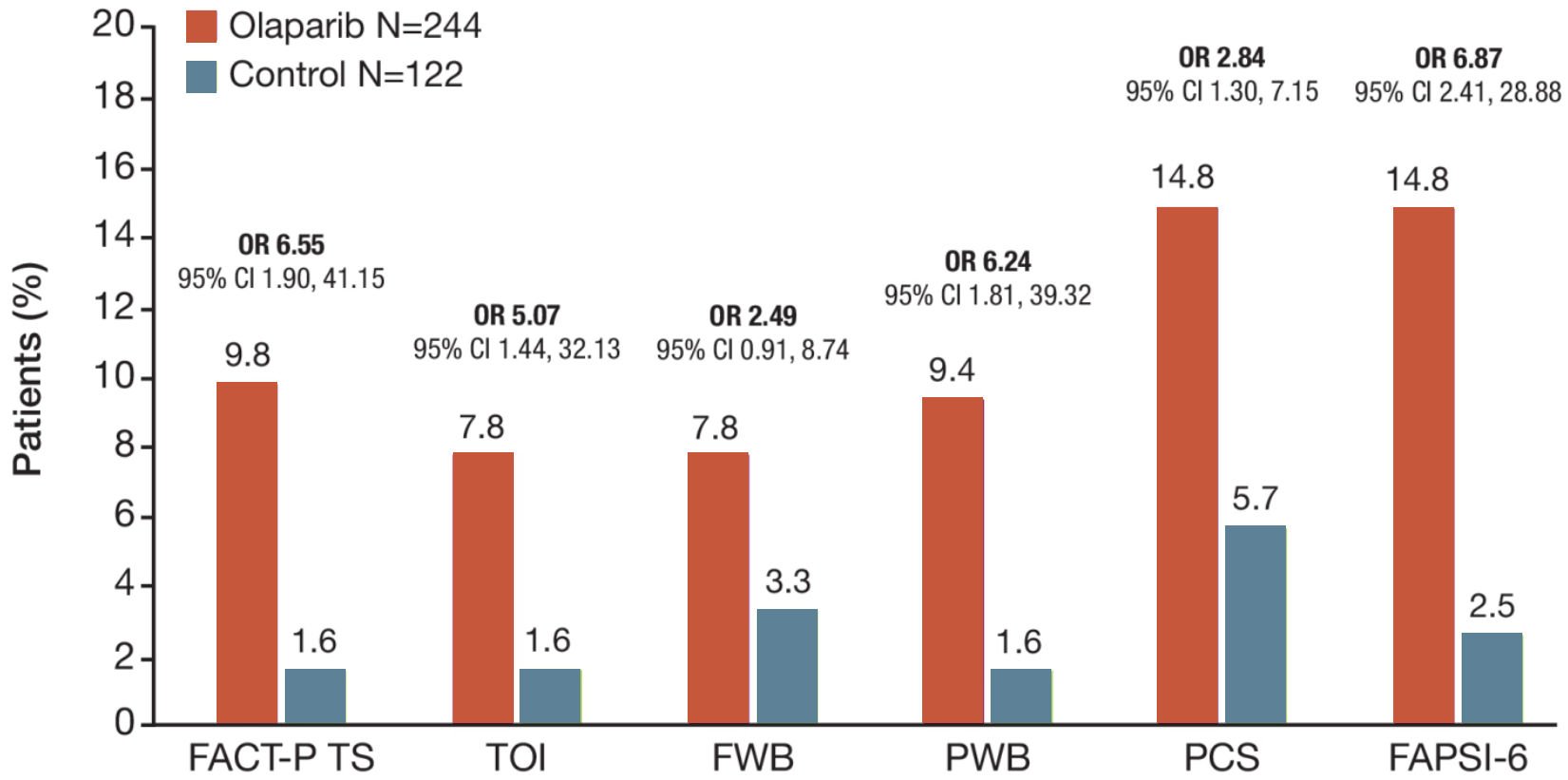
- 7/15 genes had alteration frequencies too low for descriptive statistics (<5 patients)[1]
- 97% of patients were randomized based on alterations in 8/15 single genes[1]
- There is evidence of clinical activity of olaparib in patients with alterations in genes other than *BRCA1* or *BRCA2*[1]
- Gene-level analysis is complex and exploratory, and comparisons may be confounded by multiple factors[1]



NR, not reported

1. Available from: https://www.urotoday.com/conference-highlights/esmo-2019/esmo-2019-prostate-cancer/115401-esmo-2019-profound-phase-3-study-of-olaparib-vs-enzalutamide-or-abiraterone-for-metastatic-castration-resistant-prostate-cancer-with-homologous-recombination-repair-gene-alterations.html.
2. Hussain M, et al. ESMO 2019. Abstract LBA12_PR.

PROfound (COHORTS A+B): HRQoL[1]



A higher proportion of patients in the olaparib arm reported improvement in HRQoL

FACT-P TS, Functional Assessment of Cancer Total Score; FAPSI-6, FACT Advanced Prostate Symptom Index; FWB, functional wellbeing; HRQoL, health-related quality of life; PCS, prostate cancer subscale; PWB, physical wellbeing; OR, odds ratio; TOI, trial outcome index.

1. Thiery-Vuillemin A, et al. ASCO 2020. Abstract 5539.

PROfound SAFETY[1]

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Adverse Event[a]	Olaparib (N=256)		Control (N=130)	
	All Grades (n, %)	Grade ≥3 (n, %)	All Grades (n, %)	Grade ≥3 (n, %)
Any	244 (95)	130 (51)	114 (88)	49 (38)
Anemia[a]	119 (46)	55 (21)	20 (15)	7 (5)
Nausea	106 (41)	3 (1)	25 (19)	0
Fatigue or asthenia	105 (41)	7 (3)	42 (32)	7 (5)
Decreased appetite	77 (30)	3 (1)	23 (18)	1 (<1)
Diarrhea	54 (21)	2 (<1)	9 (7)	0
Vomiting	47 (18)	6 (2)	16 (12)	1 (<1)
Constipation	45 (18)	0	19 (15)	0
Back pain	35 (14)	2 (<1)	15 (12)	2 (2)
Peripheral edema	32 (12)	0	10 (8)	0
Cough	28 (11)	0	3 (2)	0
Dyspnea	26 (10)	6 (2)	4 (3)	0
Arthralgia	24 (9)	1 (<1)	14 (11)	0
Urinary tract infection	18 (7)	4 (2)	15 (12)	5 (4)
Interruption of intervention because of adverse event	115 (45)	N/A	24 (18)	N/A
Dose reduction because of adverse event	57 (22)	N/A	5 (4)	N/A
Discontinuation of intervention because of adverse event	46 (18)	N/A	11 (8)	N/A
Death because of adverse event	10 (4)	N/A	5 (4)	N/A

[a]Includes anemia, decreased Hb level, decreased red cell count, decreased Hct level, erythropenia, macrocytic anemia, normochromic anemia, normochromic normocytic anemia, and normocytic anemia; anemia reported in 46% of patients, and decreased Hb level reported in <1%.

Hb, hemoglobin; HCT, hematocrit; N/A, not available

1. de Bono J, et al. N Engl J Med. 2020;382:2091-102.

COMMON SIDE EFFECTS OF OLAPARIB[1,2]

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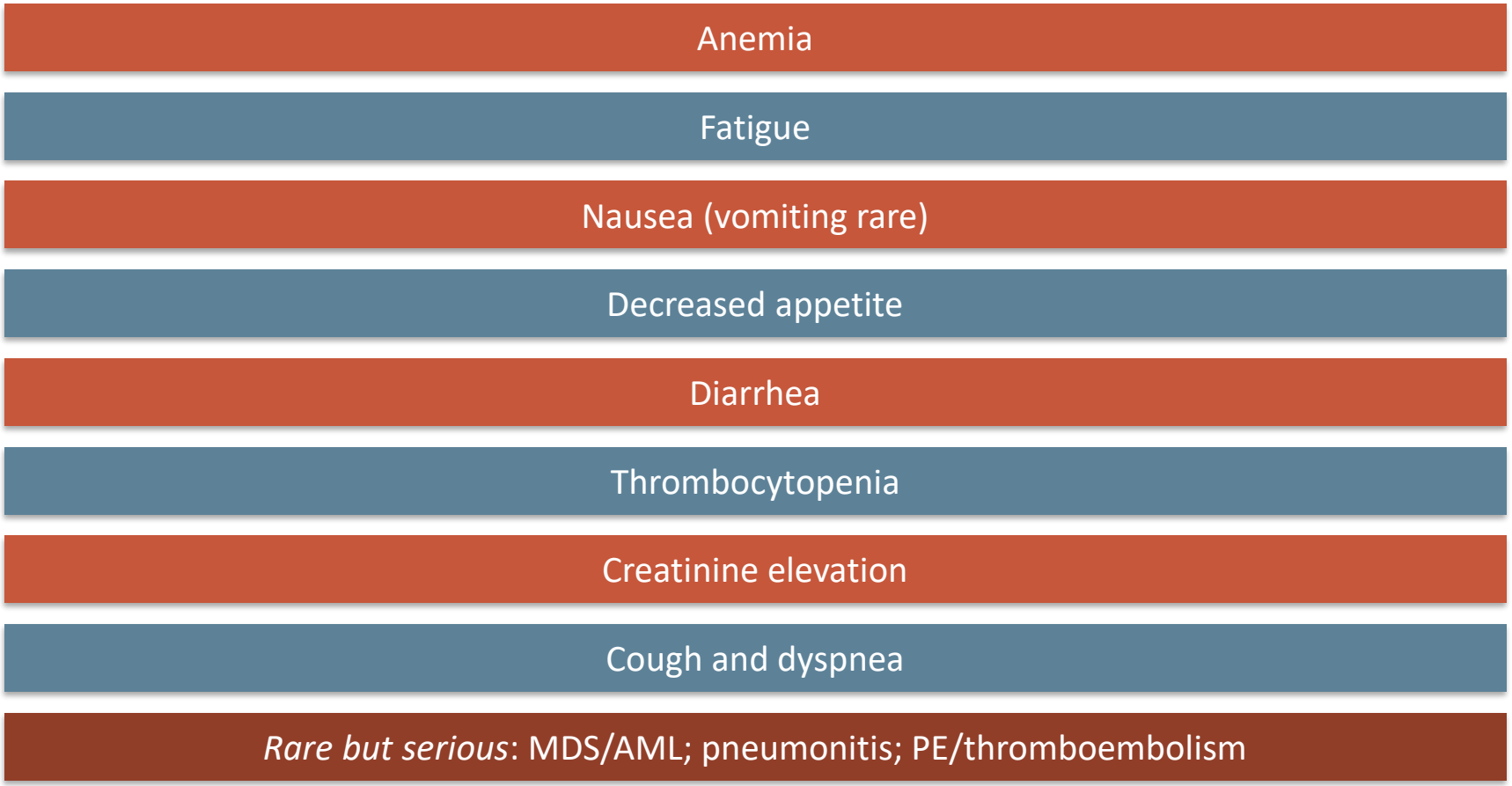

AML, acute myeloid leukemia; MDS, myelodysplastic syndrome; PE, pulmonary embolism

de Bono J, et al. N Engl J Med. 2020;382:2091-102.
Lynparza 50 mg hard capsules. SmPC. Revised July 2020.

FDA FULL APPROVAL: OLAPARIB FOR mCRPC

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In **May 2020,** based on data from the **PROfound study,** the FDA granted **full approval olaparib** for the treatment of patients with deleterious or suspected **germline or somatic HRR[a] gene-mutated mCRPC, who have progressed following prior treatment with enzalutamide or abiraterone[1,b]**

[a]*BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, RAD54L*.
[b]Select patients for therapy based on two FDA-approved companion diagnostic tests: BRACAnalysis CDx and FoundationOne CDx.

1. https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-olaparib-hrr-gene-mutated-metastatic-castration-resistant-prostate-cancer.

EMA RECOMMENDED APPROVAL: OLAPARIB FOR mCRPC WITH BRCA1/2-MUTATIONS

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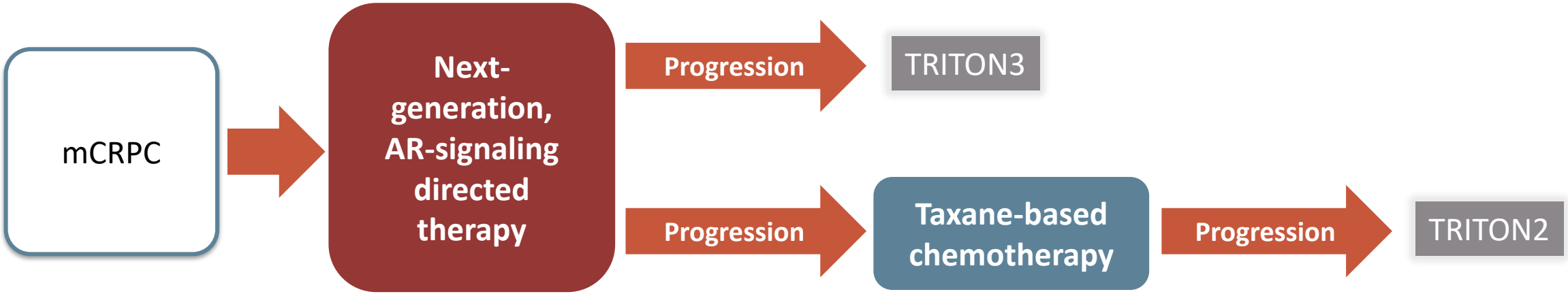
Olaparib is indicated as **monotherapy** for the treatment of adult patients with **mCRPC** and **BRCA1/2-mutations (germline and/or somatic)** who have **progressed following prior therapy** that included a **new hormonal agent.**[1]

1. https://www.ema.europa.eu/en/medicines/human/summaries-opinion/lynparza-0

RUCAPARIB: TRITON2 AND TRITON3 — STUDY DESIGNS[1,2]



HRR-deficiency is defined by a deleterious alteration in *BRCA1, BRCA2, ATM*, or 12 other HRR genes (*BARD1, BRIP1, CDK12, CHEK2, FANCA, NBN, PALB2, RAD51, RAD51B, RAD51C, RAD51D, RAD54L*)

AR, androgen receptor

1. Ryan CJ. ASCO 2018; abstract TPS389; 2. Abida W, et al. Annals Onc. 2018:29(Suppl 8):viii271-viii302.

TRITON2: OBJECTIVE RESPONSES[1]

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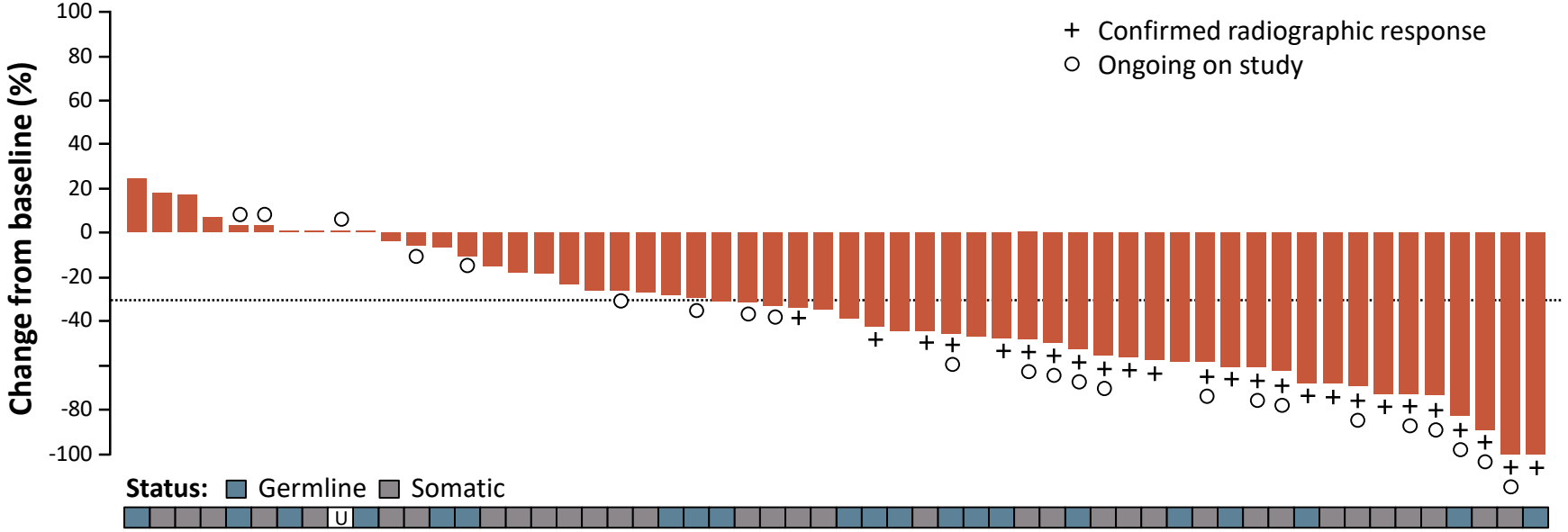
	DDR Gene				
	BRCA 1/2 (n=57)	*ATM* (n=21)	*CDK12* (n=9)	*CHEK2* (n=5)	Other (n=13)
ORR, n (%) [95% CI]	25 (43.9) [30.7-57.6]	2 (9.5) [1.2-30.4]	0 [0.0-33.6]	0 [0.0-52.2]	5 (38.5) [13.9-68.4]
CR, n (%)	3 (5.3)	0	0	0	1 (7.7)
PR, n (%)	22 (38.6)	2 (9.5)	0	0	4 (30.8)
SD, n (%)	26 (45.6)	10 (47.6)	5 (55.6)	3 (60.0)	6 (46.2)
PD, n (%)	5 (8.8)	8 (38.1)	3 (33.3)	2 (40.0)	1 (7.7)
NE, n (%)	1 (1.8)	1 (4.8)	1 (11.1)	0	1 (7.7)

BEST CHANGE FROM BASELINE IN SUM OF TARGET LESION IN PATIENTS WITH *BRCA1/2* ALTERATION (N=56)



CR, complete response; DDR, DNA damage repair; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease

1. Abida W, et al. ESMO 2019. Abstract 846PD7

TRITON2: PSA RESPONSES[1]

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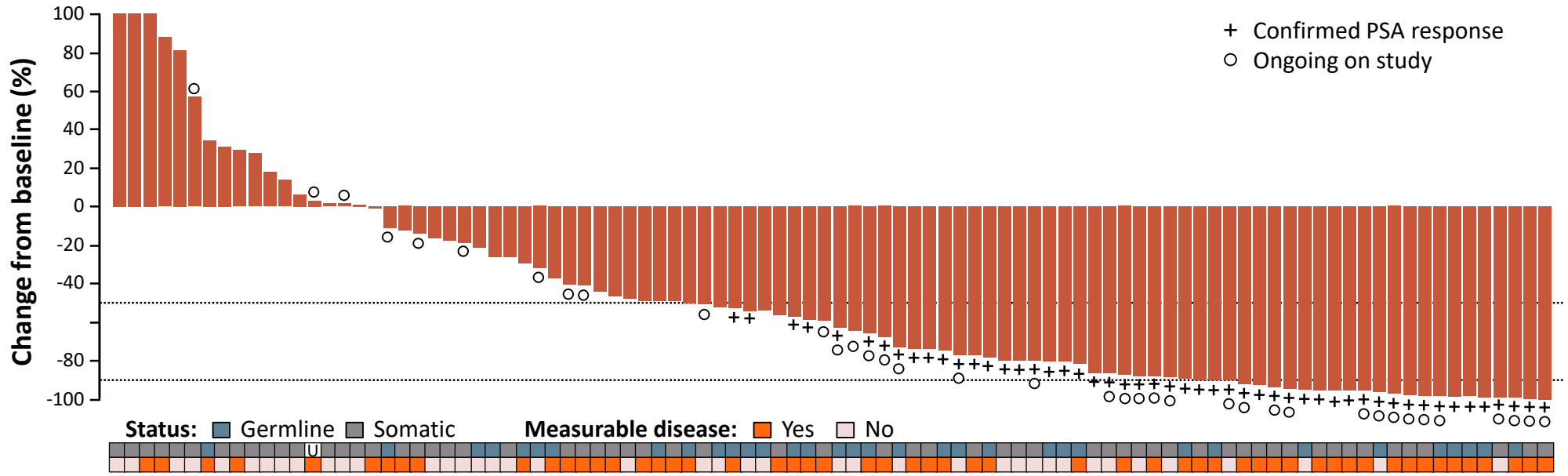
	DDR Gene				
	BRCA 1/2	*ATM*	*CDK12*	*CHEK2*	Other
PSA response rate, n/N (%) [95% CI]					
All evaluable patients	51/98 (52.0) [41.7-62.2]	2/57 (3.5) [0.4-12.1]	1/14 (7.1) [0.2-33.9]	1/7 (14.3) [0.4-57.9]	5/14 (35.7) [12.8-64.9]
With measurable disease	34/57 (59.6) [45.8-72.4]	2/21 (9.5) [1.2-30.4]	1/9 (11.1) [0.3-48.2]	1/5 (20.0) [0.5-71.6]	5/13 (38.5) [13.9-68.4]
With no measurable disease	17/41 (41.5) [26.3-57.9]	0/36 (0) [0.0-9.7]	0/5 (0) [0.0-52.2]	0/2 (0) [0.0-84.2]	0/1 (0) [0-97.5]
Median time to PSA progression, mo [95% CI]	6.5 [5.7-7.5]	3.1 [2.8-3.7]	3.5 [2.8-4.6]	5.6 [2.8-NR]	5.8 [2.8-NR]

BEST CHANGE FROM BASELINE IN PSA PATIENTS WITH *BRCA1/2* ALTERATION (N=96)



1. Abida W, et al. ESMO 2019. Abstract 846PD.

TRITON2 PRIMARY ENDPOINT
OBJECTIVE RESPONSE RATE[1]

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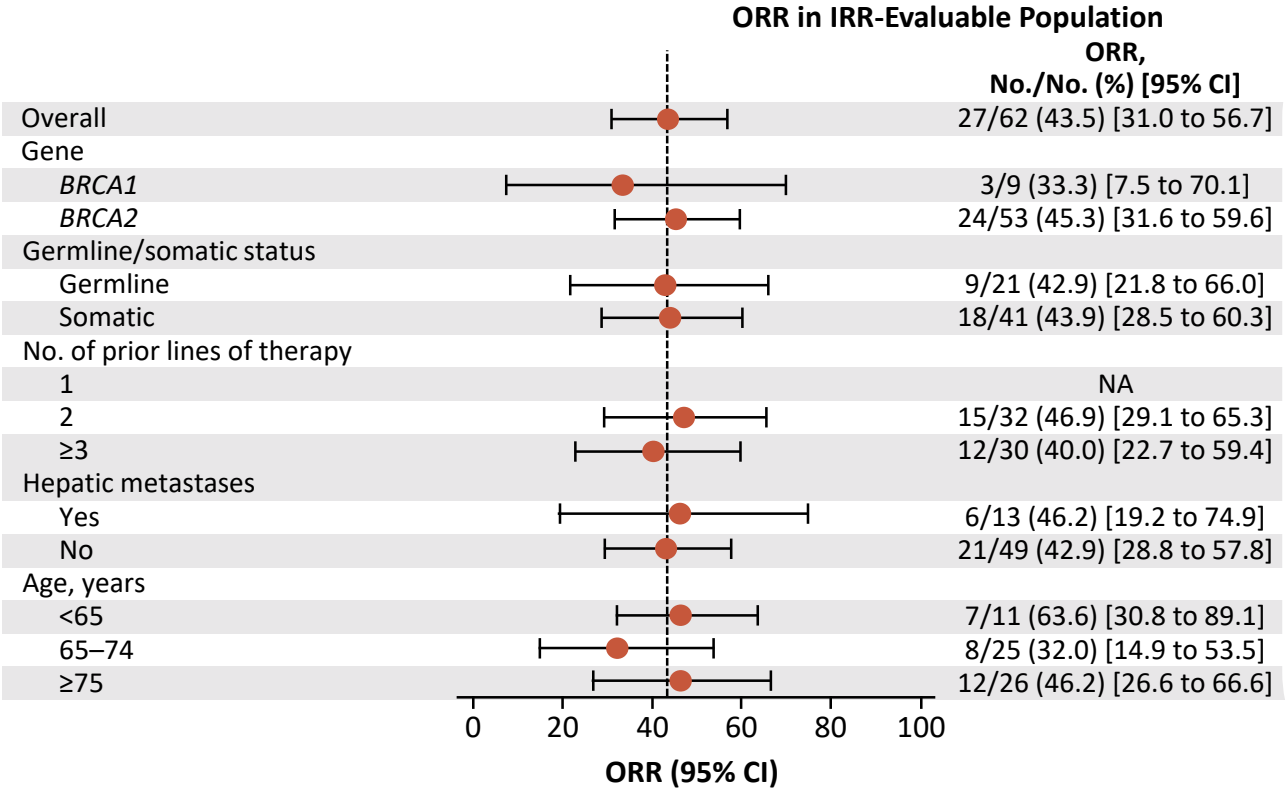
Response	Investigator-Evaluable Population (n=65)	IRR-Evaluable Population (n=62)
Confirmed ORR, No (%; 95% CI)	33 (50.8; 38.1 to 63.4)	27 (43.5; 31.0 to 56.7)
CR	4 (6.2)	7 (11.3)
PR	29 (44.6)	20 (32.3)
SD	25 (38.5)	28 (45.2)
PD	6 (9.2)	6 (9.7)
NE	1 (1.5)	1 (1.6)
	Overall Efficacy Population (n=115)	
Confirmed PSA response rate, No. (5;95% CI)	63 (54.8;45.2 to 64.1)	

IRR, Independent radiological review

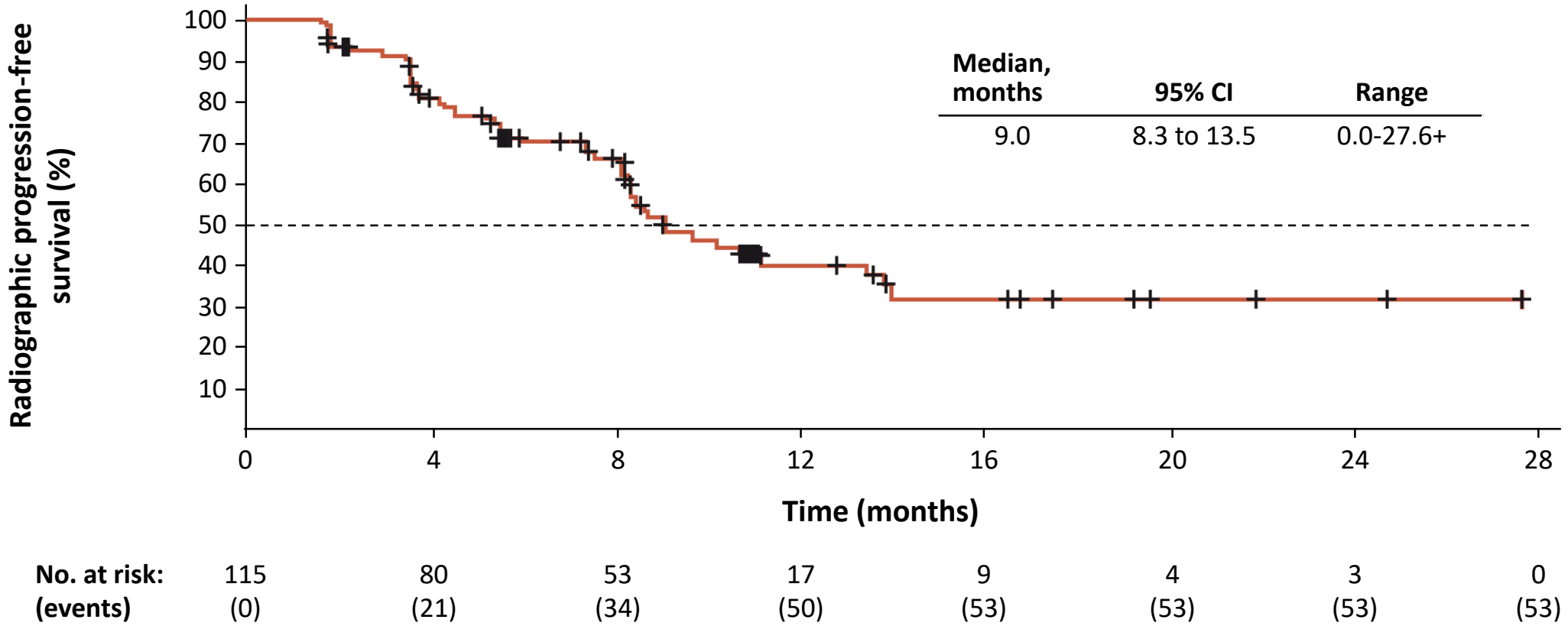
1. Abida W, et al. Journal of Clinical Oncology 2020 DOI https://doi.org/10.1200/JCO.20.01035

TRITON2:
SUBGROUP ANALYSIS OF OBJECTIVE RESPONSE RATE[1]



1. Abida W, et al. Journal of Clinical Oncology 2020 DOI https://doi.org/10.1200/JCO.20.01035

TRITON2: RADIOGRAPHIC PFS[1]



1. Abida W, et al. Journal of Clinical Oncology 2020 DOI https://doi.org/10.1200/JCO.20.01035

TRITON2: RESPONSE BY NON-*BRCA* DDR GENE ALTERATIONS[1,a]

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	By DDR Gene Group			
	ATM **(n=49)**	***CDK12*** **(n=15)**	***CHEK2*** **(n=12)**	**Other[b] (n=14)**
Confirmed investigator-assessed objective response[c]	2/19 (10.5) (1.3-33.1)	0/10 (0) (0.0-30.8)	1/9 (11.1) (0.3-48.2)	4/14 (28.6) (8.4-58.1)
CR	0/19 (0.0)	0/10 (0)	0/9 (0)	1/14 (7.1)
PR	2/19 (10.5)	0/10 (0)	1/9 (11.1)	3/14 (21.4)
SD	9/19 (47.4)	6/10 (60.0)	6.9 (66.7)	8/14 (57.1)
PD	7/19 (36.8)	3/10 (30.0)	2/9 (22.2)	1/14 (7.1)
NE	1/19 (5.3)	1/10 (10.0)	0/9 (0)	1/14 (7.1)
6-month clinical benefit rate[d]	12/42 (28.6) (15.7-44.6)	3/15 (20.0) (4.3-48.1)	3/8 (37.5) (8.5-75.5)	6/11 (54.5) (23.4-83.3)
12-month clinical benefit rate[e]	3/18 (16.7) (3.6-41.4)	1/14 (7.1) (0.2-33.9)	0/5 (0) (0.0-52.2)	3/8 (37.5) (8.5-75.5)
Confirmed PSA response[f]	2/49 (4.1) (0.5-14.0)	1/15 (6.7) (0.2-31.9)	2/12 (16.7) (2.1-48.4)	5/14 (35.7) (12.8-64.9)
Median time to PSA progression, mo (95% CI)	3.1 (2.8-4.6)	3.2 (2.8-4.6)	7.4 (2.8-7.4)	11.0 (3.0-NR)

[a]Visit cutoff date: April 29, 2019. Data are n/N (%) (95% CI) unless stated otherwise. [b]Includes patients with an alteration in *FANCA* (n=4), *NBN* (n=4), *BRIP1* (n=2), *PALB2* (n=2), *RAD51* (n=1), *RAD51B* (n=1), and/or *RAD54L* (n=1). [c]Per modified RECIST/PCWG3 criteria; includes patients who had measurable disease at baseline per the investigator and ≥16 weeks of follow-up. [d]Proportion of patients without radiographic progression per RECIST/PCWG3 criteria who were ongoing with treatment at 6 months. [e]Proportion of patients without radiographic progression per RECIST/PCWG3 criteria who were ongoing with treatment at 12 months. [f]Defined as ≥50% reduction in PSA from baseline; includes patients who had ≥16 weeks of follow-up.

1. Abida W, et al. Clin Cancer Res. 2020 Feb 21 [Epub ahead of print].

COMMON SIDE EFFECTS OF RUCAPARIB

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- Anemia
- Fatigue, asthenia
- Nausea/vomiting
- Decreased appetite
- Diarrhea or constipation
- Thrombocytopenia
- Increased AST/ALT and/or creatinine
- Rash
- *Rare but serious*: MDS/AML; fetal teratogenicity

1. Abida W, et al. Clin Cancer Res. 2020 Feb 21 [Epub ahead of print]; 2. Rucabra. SmPC. May 2019.

FDA ACCELERATED APPROVAL: RUCAPARIB FOR mCRPC

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In **May 2020,** based on data from the **TRITON2 study,** the FDA granted **accelerated approval to rucaparib** for the treatment of patients with **deleterious *BRCA1/2* (germline and/or somatic)-associated mCRPC, who have been treated with an androgen receptor-directed therapy and a taxane-based chemotherapy.**[1]

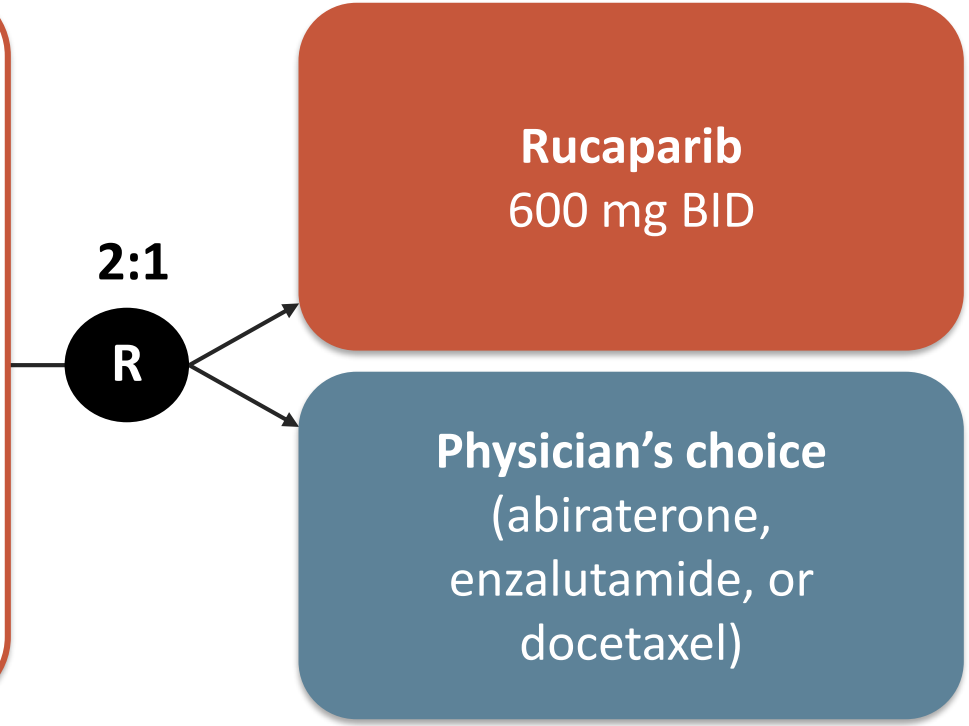
The TRITON3 study is underway and recruiting patients with mCRPC and homologous recombination gene deficiency.[2]

1. https://www.fda.gov/drugs/fda-grants-accelerated-approval-rucaparib-brca-mutated-metastatic-castration-resistant-prostate.
2. https://clinicaltrials.gov/ct2/show/NCT02975934.

TRITON3: STUDY DESIGN[1,2]

Key Eligibility Criteria

- mCRPC
- Deleterious germline or somatic *BRCA1, BRCA2*, or *ATM* mutation
- Progression on AR-directed therapy in the mCRPC setting
- No prior PARPi treatment or chemotherapy for mCRPC



Primary endpoint: radiographic PFS

1. https://clinicaltrials.gov/ct2/show/NCT02975934; 2. Ryan CJ. ASCO 2018; abstract TPS389

PHASE 2 GALAHAD: NIRAPARIB IN PREVIOUSLY TREATED mCRPC WITH BIALLELIC DDR MUTATIONS[1,2]

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Biomarker evaluation (prescreening) → **Screening phase** → **Treatment phase (niraparib 300 mg/d)** → **Follow-up phase**

28-d cycle until end of treatment[a]

Every 3 mo after end of treatment

Key Eligibility Criteria

- mCRPC
- Biomarker positive for **biallelic** DRD mutation
- Progressed on ≥1 AR-targeted therapy and ≥1 taxane-based chemo
- No prior PARP inhibitor or platinum-based chemo
- No prior MDS/AML

Primary Endpoint

ORR of soft tissue (visceral or nodal disease), as defined by RECIST 1.1[b] with no evidence of bone progression according to PCWG3 criteria in patients with **biallelic** *BRCA* mutations[2]

Secondary endpoints

- ORR
- CTC response
- OS
- rPFS
- DOR
- Safety

Composite response rate, derived from the secondary endpoints and the exploratory endpoint of CTC conversion, was defined as ORR by RESIST 1.1, or conversion CTC from ≥5/7.5 mL to <5/7.5 mL of blood, or ≥50% decline in PSA level.[2]

CTC, circulating tumor cell; d, days; DOR, duration of objective response; DRD; DNA-repair gene deficit
[a]Treatment continued until disease progression, unacceptable toxicity, or death. [b]Investigator assessed.
https://clinicaltrials.gov/ct2/show/NCT02854436. Annals of Oncology (2019) 30 (suppl_5): v851-v934. 10.1093/annonc/mdz394

GALAHAD: OBJECTIVE RESPONSES

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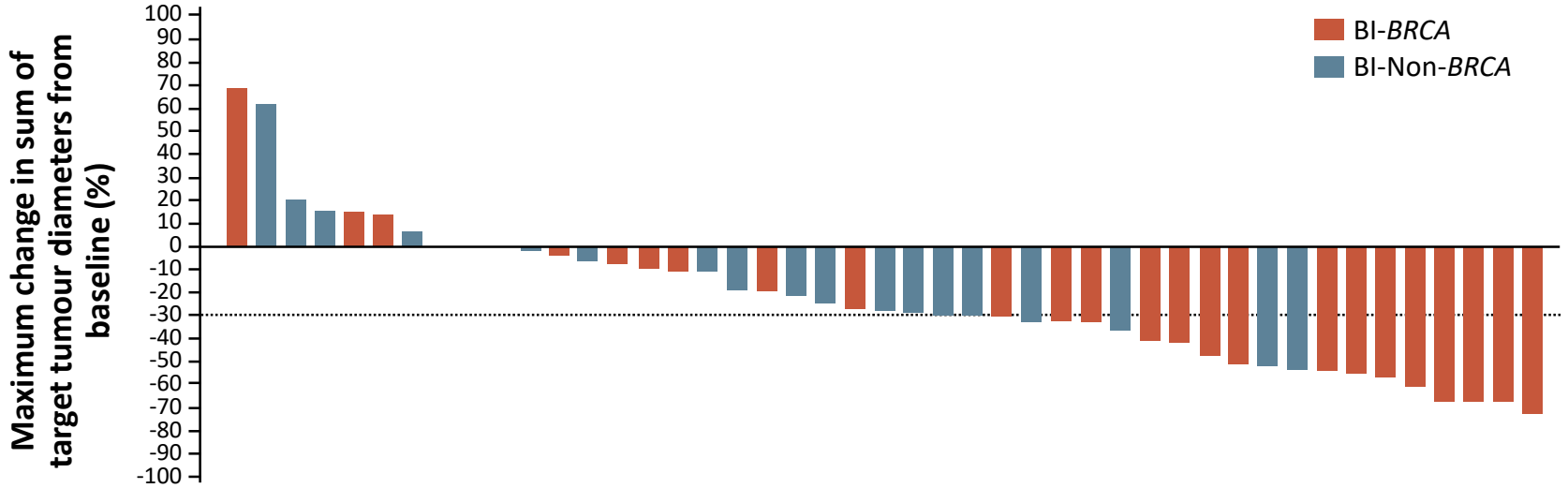
BEST OVERALL RESPONSE IN BIALLELIC DRD PATIENTS WITH MEASURABLE DISEASE AT BASELINE

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

MAXIMUM CHANGE IN TARGET LESION DIAMETER



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

PHASE 2 GALAHAD: ORR, PSA RESPONSE, CTC RESPONSE[1]

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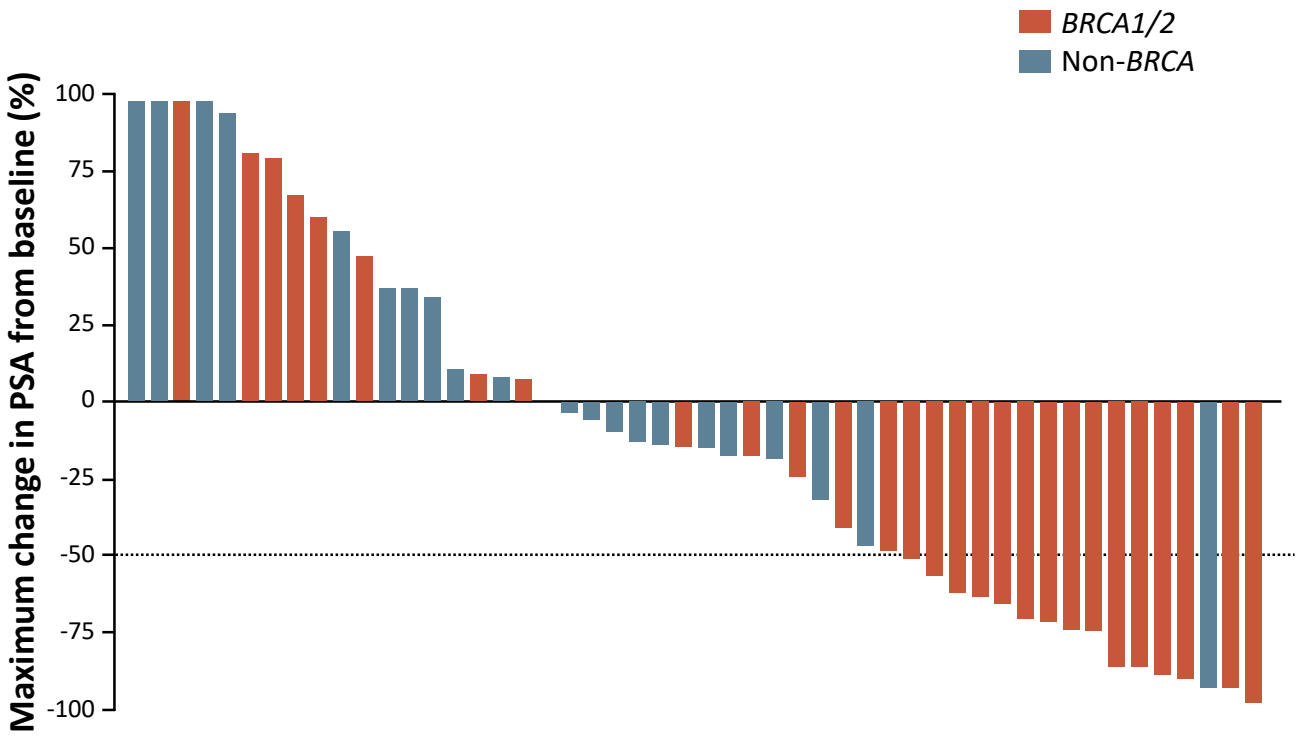
n/N % (95% CI)	All Biallelic DRD (N=50)	
	BRCA1/2 (n=29)	Non-*BRCA1/2*[a] (n=21)
Composite RR	18/29 62.1 (42.3-79.3)	5/21 23.8 (8.2-47.2)
Objective RR[b]	6/16 37.5 (15.2-64.6)	2/15 13.3 (1.7-40.5)
≥50% decline in PSA	15/29 51.7 (32.5-70.6)	1/21 4.8 (0.1-23.8)
CTC conversion (<5/7.5 mL blood)	12/29 41.4 (23.5-61.1)	4/21 19.0 (5.5-41.9)
CTC response	6/29 20.7 (8.0-39.7)	2/21 9.5 (1.2-30.4)



[a]*ATM, FANCA, PALB2, CHEK2, BRIP1*, or *HDAC2* assayed, not all represented in non-BRCA patients. [b] Investigator-assessed.
RR, response rate

1. Smith MR, et al. J Clin Oncol. 2019;37(Suppl7):202.

TALAPRO-1: TALAZOPARIB IN mCRPC WITH DDRM[1]

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Eligibility criteria

- Age ≥18 y
- Progressive mCRPC
- Measurable soft tissue disease
- 1-2 previous chemotherapy regimens (≥1 taxane-based regimen) for mCRPC
- Progressed on ≥1 NHT[a] for mCRPC
- DDRm[b] likely to sensitize to PARPi

N = ~100

→ **Talazoparib 1 mg daily** (0.75 mg, if moderate renal impairment) →

Until radiographic progression, unacceptable toxicity, consent withdrawal, or death

Primary endpoint: ORR

Secondary endpoints: Time to OR, DOR, PSA decrease ≥50%, CTC count conversion (to CTC = 0 and <5 per 7.5 mL blood) time to PSA progression, rPFS, OS, safety

[a]Enzalutamide/abiraterone acetate. [b]DDRm are defined as known/likely pathogenic variants or homozygous deletions in: *ATM, ATR, BRCA1/2, CHEK2, FANCA, MLH1, MRE11A, NBN, PALB2, RAD51C.*

NHT, novel hormonal therapy; OR, objective response

1. https://meetinglibrary.asco.org/record/188251/abstract.

TALAPRO-1: EFFICACY[1]

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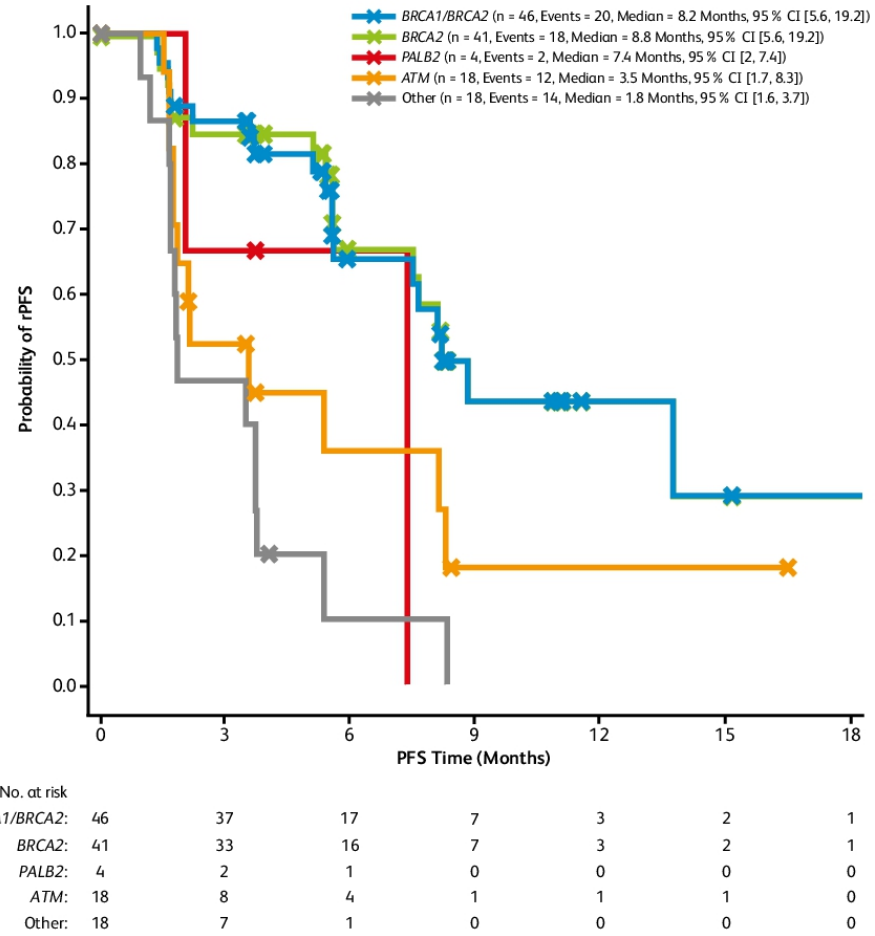
% (response/n)	*BRCA1/2* (n=46)	*BRCA2* (n=41)	*PALB2* (n=4)	*ATM* (n=18)	Other (n=18)	Total (N=86)
Composite Response	71.7 (33/46)	75.6 (31/41)	50.0 (2/4)	22.2 (4/18)	11.1 (2/18)	47.7 (41/86)
ORR	41.5 (17/41)	40.5 (15/37)	33.3 (1/3)	11.8 (2/17)	0 (0/14)	26.7 (20/75)
Confirmed CR	4.9 (2/41)	5.4 (2/37)	0 (0/3)	5.9 (1/17)	0 (0/14)	4.0 (3/75)
Confirmed PR	36.6 (15/41)	35.1 (13/37)	33.3 (1/3)	5.9 (1/17)	0 (0/14)	22.7 (17/75)
SD ≥6 mo	2.4 (1/41)	2.7 (1/37)	0 (0/3)	11.8 (2/17)	0 (0/14)	4.0 (3/75)
PSA decline ≥50% from baseline	60.9 (28/46)	63.4 (26/41)	50.0 (2/4)	5.6 (1/18)	5.6 (1/18)	37.2 (32/86)
CTC conversion ≥5 to <5	93.8 (15/16)	93.8 (15/16)	0 (0/1)	50.0 (3/6)	25.0 (1/4)	70.4 (19/27)

In this interim analysis (Dec 2019) of TALAPRO-1, talazoparib monotherapy demonstrated antitumor activity in mCRPC patients with DDR alterations who have previously received taxane therapy and NHT with a confirmed overall ORR of 26.7%. Efficacy was most notable in the subset of patients with mCRPC whose tumors harbored *BRCA1/2* alterations, who had a confirmed ORR of 41.5%.

Talazoparib monotherapy was generally well tolerated. No new safety signals were observed in this patient population compared with the known safety profile of talazoparib.

rPFS BY DDR ALTERATION BY BICR[a]



[a]DDR-deficient population (N=86) includes DDR patients who received treatment for ≥16 weeks.

1. de Bono J, et al. ASCO 2020. Abstract 5566.

TALAPRO-1: EFFICACY AND SAFETY RESULTS[1]

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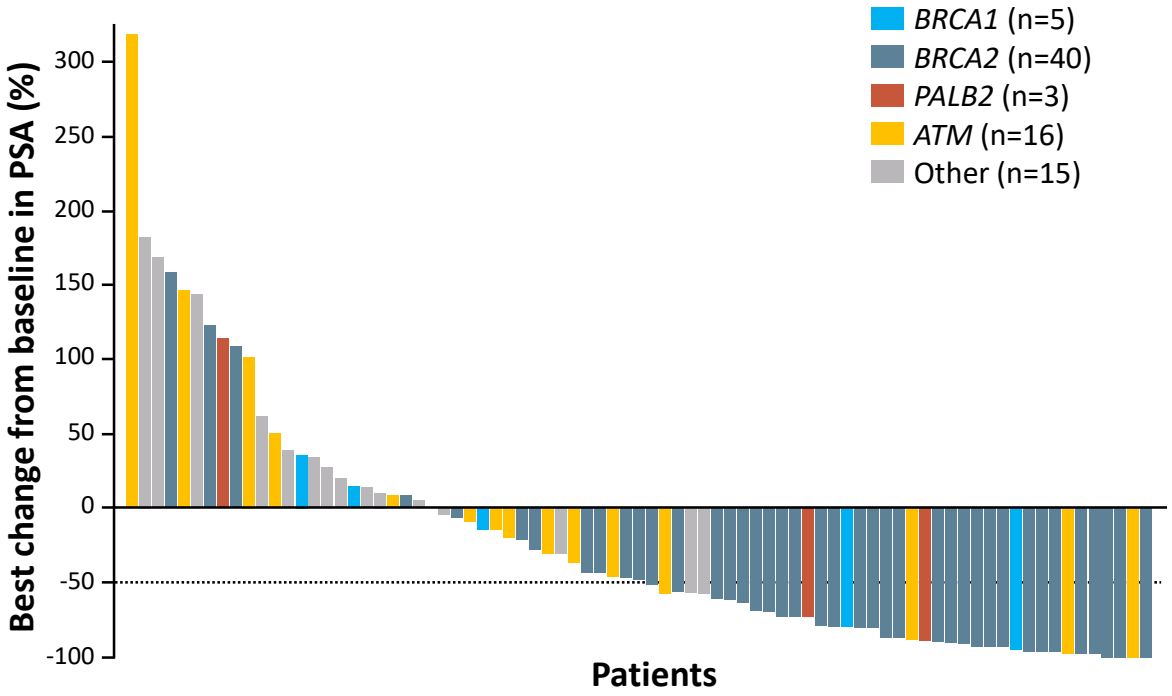
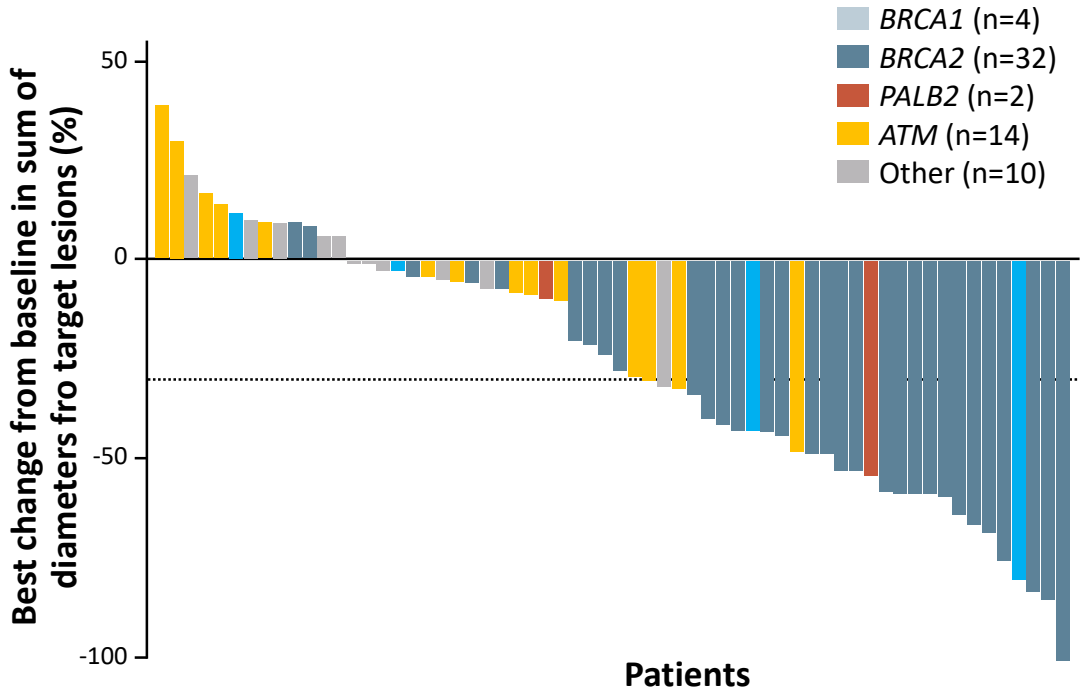
BEST CHANGE FROM BASELINE IN PSA[a]



BEST CHANGE FROM BASELINE IN RECIST[a]



[a]DDR-deficient population includes DDR patients who received treatments for ≥16 weeks; PSA, n=79 and RECIST, n=62.

1. de Bono J, et al. ASCO 2020. Abstract 5566.

MUTATION STATUS AND SENSITIVITY TO PARP INHIBITORS[1]

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Efficacy of PARP Inhibitors in patients with deleterious BRCA1 versus BRCA2 mutations

	Olaparib						Rucaparib					
	TOPARP-A[2]		TOPARP-B[3]		PROfound[4]		TRITON2[5]		TALAPRO-1[6]		Pooled Data	
	BRCA1	*BRCA2*	*BRCA1*	*BRCA2*	*BRCA1*	*BRCA2*	*BRCA1*	*BRCA2*	*BRCA1*	*BRCA2*	*BRCA1*	*BRCA2*
Outcome	n/N	n/N	n/N	n/N (95% CI)	n/N (95% CI)	n/N (95% CI)	n/N (95% CI)	n/N (95% CI)	n/N	n/N (95% CI)	n/N (95% CI)	n/N (95% CI)
PSA_{50}	0/1	7/7	1/2	22/28	NR	NR	2/13	61/102	2/5	26/41	5/21 (23.8) (4.4 to 43.2)	116/178 (65.2) (58.2 to 72.2)
ORR	NE	5/5	0/1	11/20	0/5	24/43	3/9	24/53	2/4	15/37	5/19 (26.3) (5.1 to 47.5)	79/158 (50.0) (42.2 to 57.8)
rPFS, months	NE	NR	NE	8.2 (5.5 to 13.0)	2.1 (1.4 to 5.5)	10.8 (9.2 to 13.1)	8.7 (1.8 to 10.7)	9.7 (8.3 to 14.0)	NR	8.8 (5.6 to 19.2)	4.1 (1.0 to 16.8)	10.1 (8.9 to 11.6)
No. of patients evaluable for rPFS				30	8	81	13	102		41	21	254

- Explanation of the lower sensitivity of *BRCA1* mutation mCRPC will require more patient data due to a low mutation prevalence[1]
- Currently, both olaparib and rucaprib should be considered for patients with either BRCA2 or BRACA1 mutations[1]
  - Availability of genomically selected therapies for these patients represents a major step forward

Note. n/N denotes the number of patients who achieved a given end point out of the total number of evaluable patients for that end point.
ORR, objective response rate; PSA50, confirmed 50% or greater PSA response rate

1. Markowski MC, Antonarakis ES. J Clin Oncol. 2020:JCO2002246. 2. Mateo J et al. N Engl J Med 2015;373:1697-1708. 3. Mateo J et al. Lancet Oncol 2020;21:162-174. 4. de Bono J et al. N Engl J Med 2020;382:2091-2102. 5. Abida W et al. J Clin Oncol doi:10.1200/JCO.20.01035. 6. de Bono JS et al. J Clin Oncol 2020;38(suppl; abstr 119).

ONGOING STUDIES OF PARP INHIBITOR COMBINATIONS IN PROSTATE CANCER

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NCT03732820: Phase 3 Study of olaparib + abiraterone vs abiraterone in mCRPC **(PROpel)**

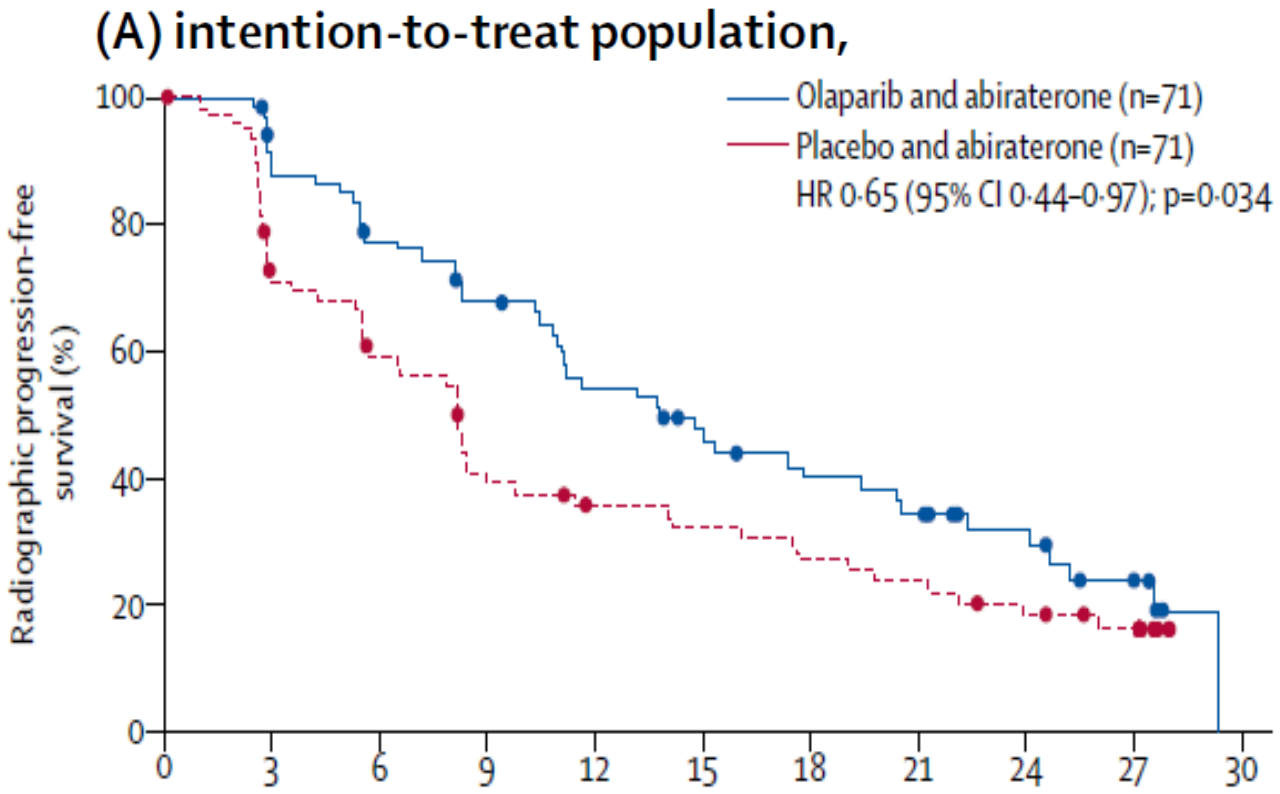
NCT03748641: Phase 3 Study of niraparib + abiraterone vs abiraterone in mCRPC **(MAGNITUDE)**

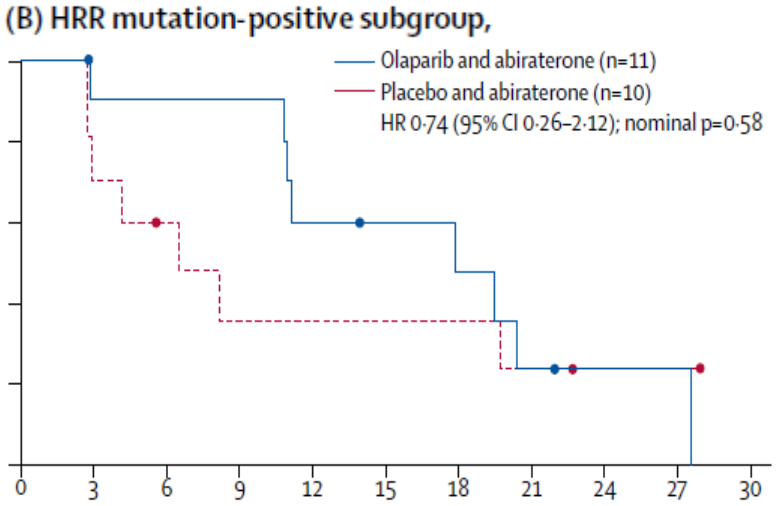
NCT03395197: Phase 3 Study of talazoparib + Enzalutamide vs Enzalutamide in mCRPC **(TALAPRO-2)**

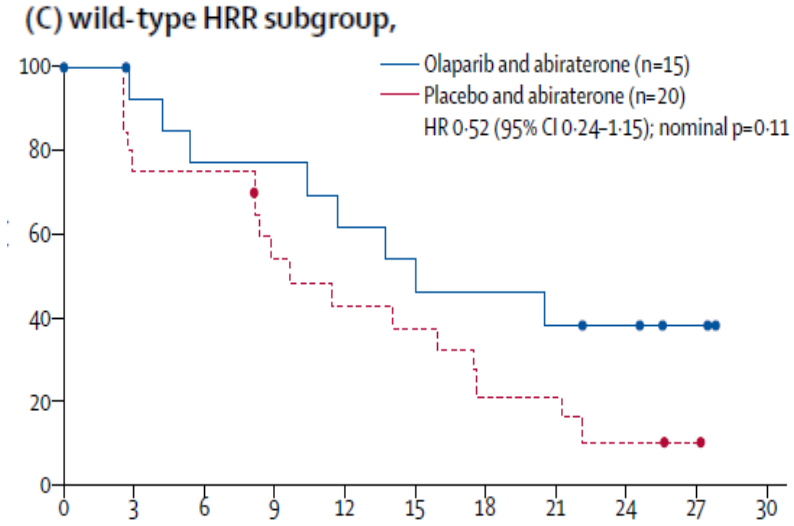
NCT 04455750: Phase 3 study of rucaparib + enzalutamide vs enzalutamide in mCRPC **(CASPAR)**

https://clinicaltrials.gov/ct2/show/NCT03732820; https://clinicaltrials.gov/ct2/show/NCT03748641; https://clinicaltrials.gov/ct2/show/NCT03395197; https://clinicaltrials.gov/ct2/show/NCT04455750

OLAPARIB + ABIRATERONE IN UNSELECTED[a] mCRPC



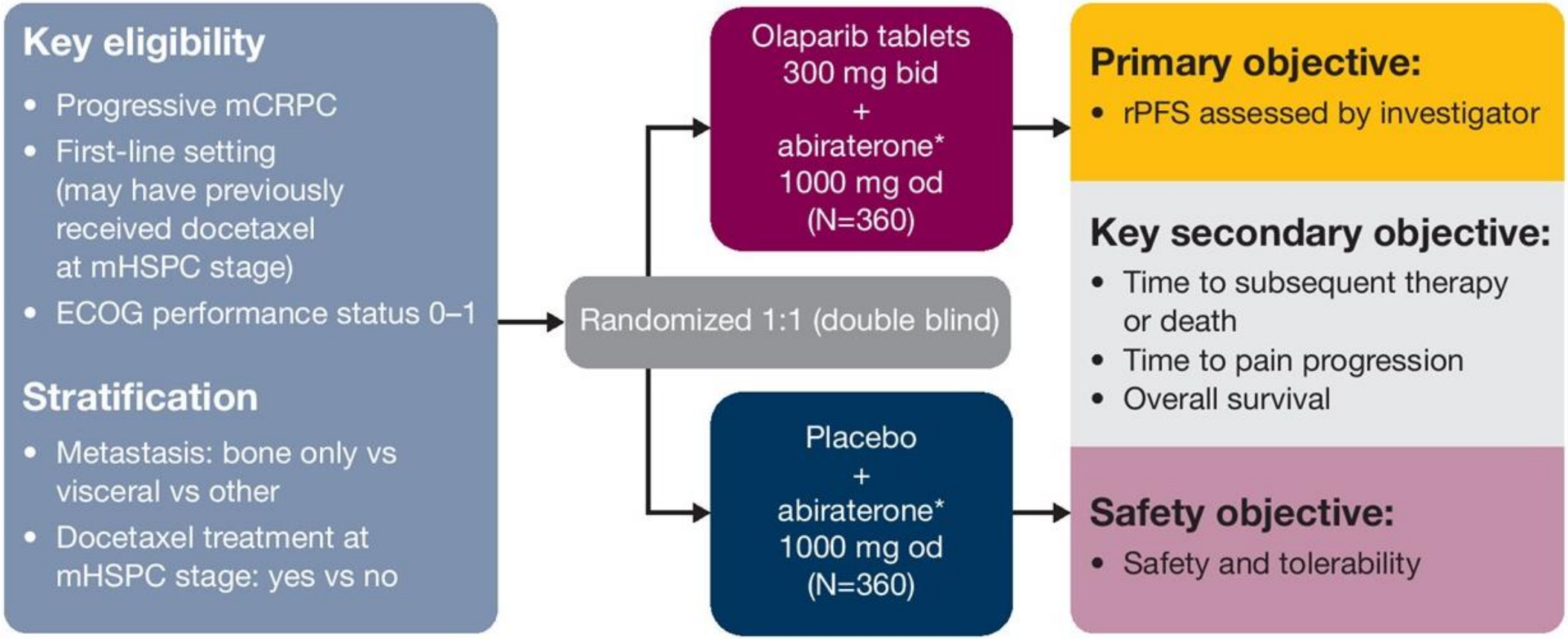




[a]Patients unselected based on biomarker criteria.

Clark NW, et al. Lancet Oncol. 2018;19:975-86.

PROPEL STUDY: ABIRATERONE +/- OLAPARIB



mHSPC, metastatic hormone-sensitive prostate cancer; od, once daily
Clark NW, et al. ASCO 2019; abstract TPS340.

TALAPRO-2: STUDY DESIGN[1,2]

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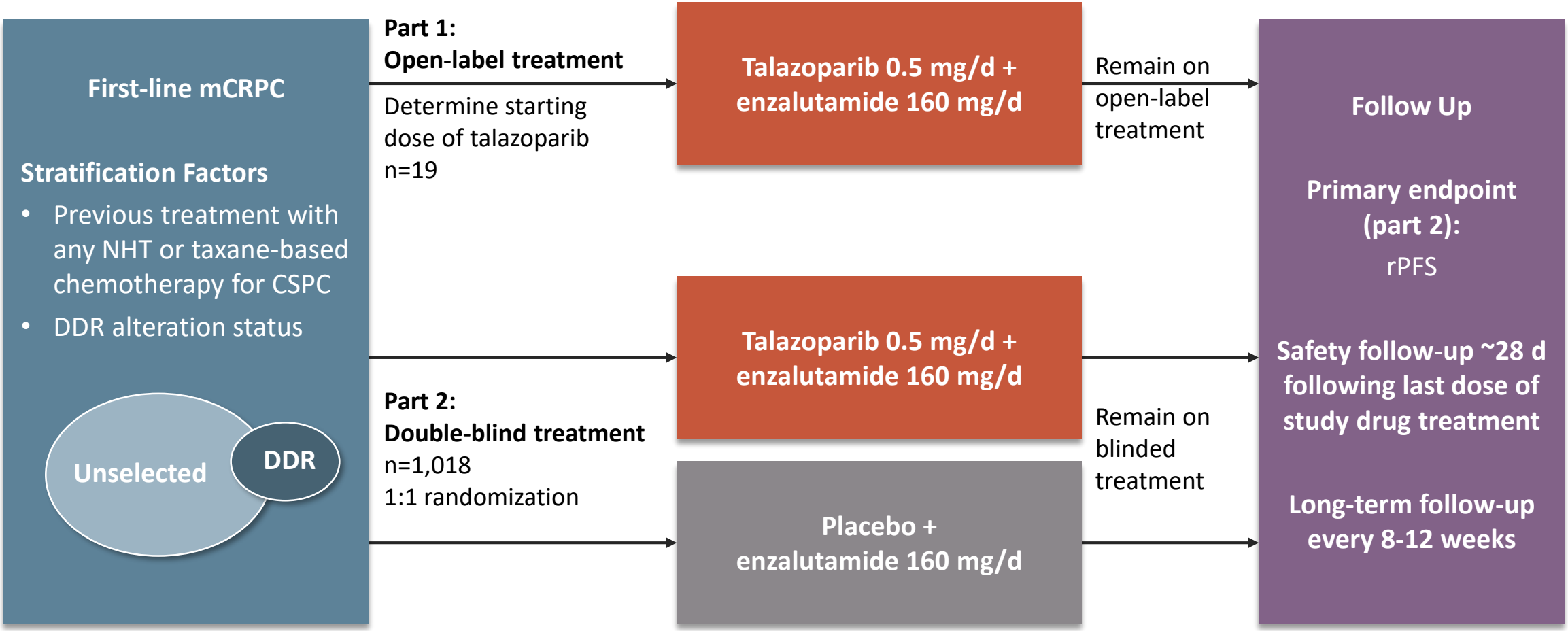

CSPC, castration-sensitive prostate cancer

1. https://clinicaltrials.gov/ct2/show/NCT03395197.
2. Agarwal N, et al. ASCO 2019; abstract TPS337.

GUIDELINES SUMMARY

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- AUA Guidelines 2020: Advanced Prostate Cancer[1]
  - Clinicians should offer a PARP inhibitor to patients with deleterious or suspected deleterious germline or somatic homologous recombination repair gene-mutated mCRPC following prior treatment with enzalutamide or abiraterone acetate, and/or a taxane-based chemotherapy
- NCCN guidelines (version 2.2020; May 21, 2020)[2]
  - Both olaparib and rucaparib are recommended in the second line setting and beyond in the treatment algorithm for mCRPC (section: PROS-16)
- Updated recommendations from European and international associations are expected shortly[2]

AUA, American Urological Association; NCCN, National Comprehensive Cancer Network

1. https://www.auanet.org/guidelines/advanced-prostate-cancer; 2. Antonarakis EA et al., European Urology Oncology 2020;3(5):594-611.

ONGOING STUDIES OF PD-1/PD-L1 INHIBITORS IN COMBINATION WITH PARP INHIBITORS IN PCa

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NCT03338790: Phase 2 Study of Nivolumab in Combination With Rucaparib, Docetaxel, or Enzalutamide in mCRPC **(CheckMate -9KD)**

NCT03330405: Phase 2 Study of Avelumab Plus Talazoparib in Locally Advanced or Metastatic Solid Tumors **(JAVELIN PARP Medley)**

NCT03834519: Phase 3 Study of Pembrolizumab + Olaparib vs Abiraterone or Enzalutamide in mCRPC **(KEYLYNK-010)**

https://clinicaltrials.gov/ct2/show/NCT03338790; https://clinicaltrials.gov/ct2/show/NCT03330405; https://clinicaltrials.gov/ct2/show/NCT03834519

CONCLUSIONS

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- The treatment of men with metastatic prostate cancer has become more complex, now **integrating predictive genomic biomarker testing**
- **Two PARPi's** are now approved with **olaparib** having **OS data** in mCRPC based on the PROfound study
  - Trials are under way for 3 further therapies
- Precision medicine approaches using germline and somatic tumor testing are already changing our treatment algorithms and are anticipated to continue to inform decision making and improve outcomes for our patients
- **Combination therapies and expanded indications** represent the next steps for PARPi
  - Experts should consider how to plan therapy and communicate with patients in this increasingly complex environment

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THE ROLE OF PARPi IN PROSTATE CANCER: FUTURE PERSPECTIVES

Dr. Neal D. Shore (Chair)
Carolina Urologic Research Center

FDA APPROVAL: OLAPARIB AND RUCAPARIB FOR mCRPC

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In **May 2020**, based on data from the **PROfound study**, the FDA **approved olaparib** for the treatment of patients with deleterious or suspected **germline or somatic HRR[a] gene-mutated mCRPC, who have progressed following prior treatment with enzalutamide or abiraterone[1,b]**

In **May 2020**, based on data from the **TRITON2 study**, the FDA granted accelerated **approval to rucaparib** for the treatment of patients with **deleterious *BRCA1/2* (germline and/or somatic)-associated mCRPC, who have been treated with an androgen receptor-directed therapy and a taxane-based chemotherapy[2]**

[a]*BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, RAD54L*.
[b]Select patients for therapy based on two FDA-approved companion diagnostic tests: BRACAnalysis CDx and FoundationOne CDx.
HRR, homologous recombination repair; mCRPC, metastatic castrate-resistant prostate cancer;
1. https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-olaparib-hrr-gene-mutated-metastatic-castration-resistant-prostate-cancer;
2. https://www.fda.gov/drugs/fda-grants-accelerated-approval-rucaparib-brca-mutated-metastatic-castration-resistant-prostate.

COMBINING PARPi AND HORMONAL TARGETING

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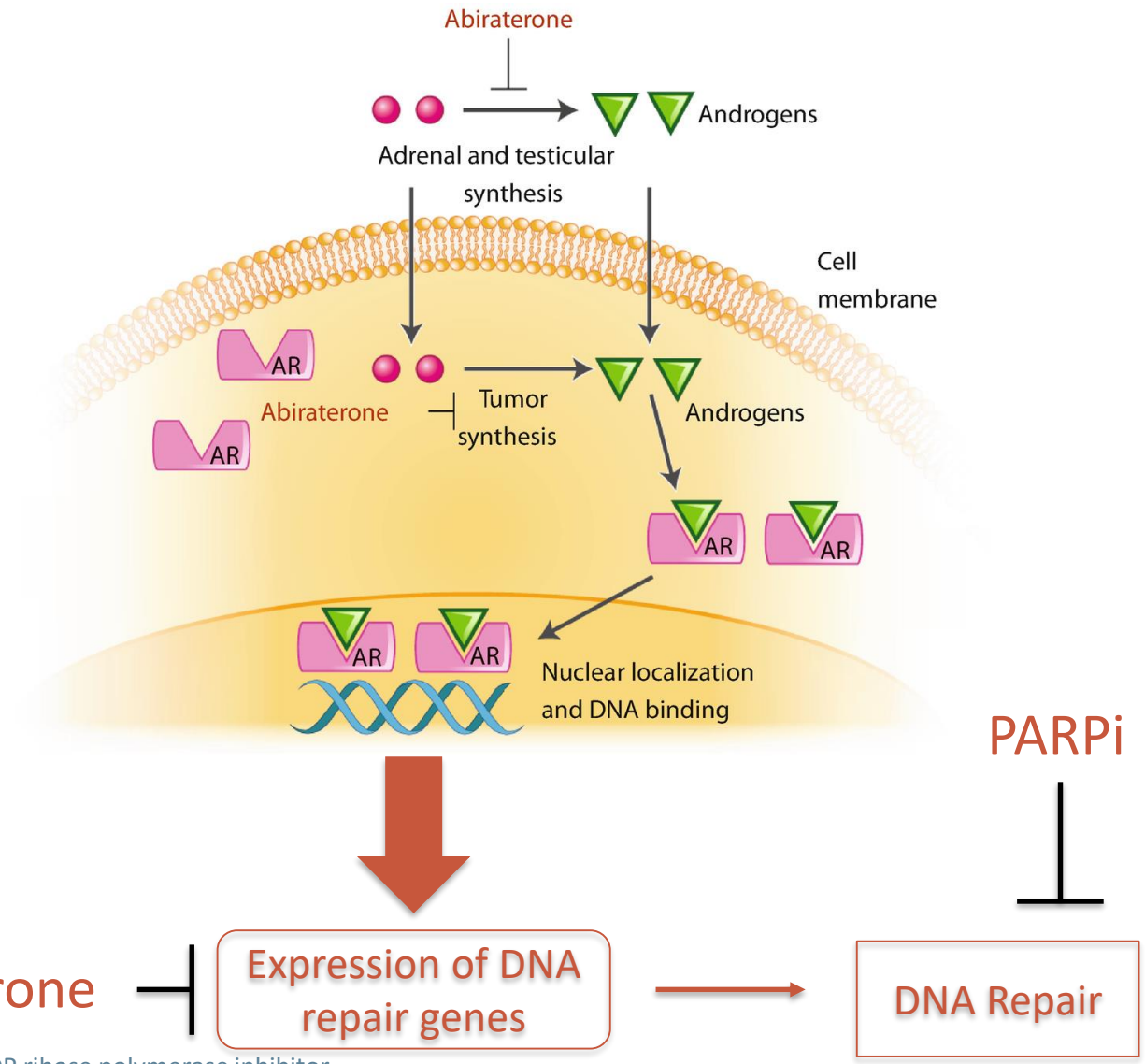
- The NHA abiraterone, in combination with olaparib, prolonged radiologic progression-free survival in the Phase II PROpel trial vs abiraterone and placebo
  - Suggests synergy between hormonal treatments and PARPi
- AR signalling is a regulator of tumour growth
  - AR signalling inhibitors appear to down-regulate DDR gene expression



AR, androgen receptor; DDR, DNA damage repair; NHA, new hormonal agent; PARPi, poly ADP ribose polymerase inhibitor

Chatterjee P, et al. J Clin Invest. 2019;129(10):4245-60; Clark NW, et al. Lancet Oncol. 2018;19:975-86; Jividen, et al. BMC Cancer. 2018;18:60; Clarke NW, et al. JCO.2019;37.7_suppl.TPS340.

COMBINING PARPi AND IMMUNE CHECKPOINT INHIBITORS

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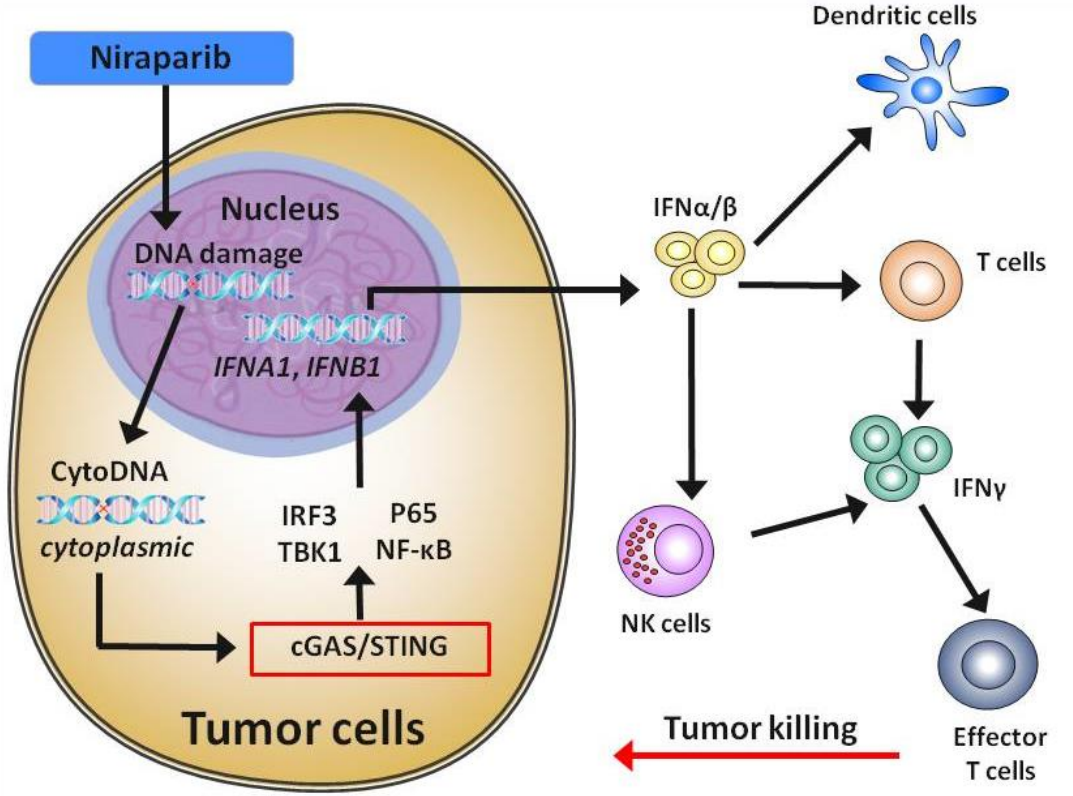
- Unrepaired DNA damage from PARPi leads to presence of cytoplasmic DNA which activates the STING pathway
  - Activation of STING
  - ↑ expression and release of type 1 IFNs
  - ↑ infiltration of effector T cells



cGAS, cyclic GMP-AMP synthase; IFN, interferon; IRF3, interferon regulatory factor 3; NK, natural killer; STING, stimulator of interferon genes; TBK1, TANK-binding kinase 1

Huang J, et al. Biochem Biophys Res Commun. 2015;463:551-6; Jiao S, et al. Clin Cancer Res. 2017;23:3711-20.

COMBINING PARPi AND DNA DAMAGING THERAPIES

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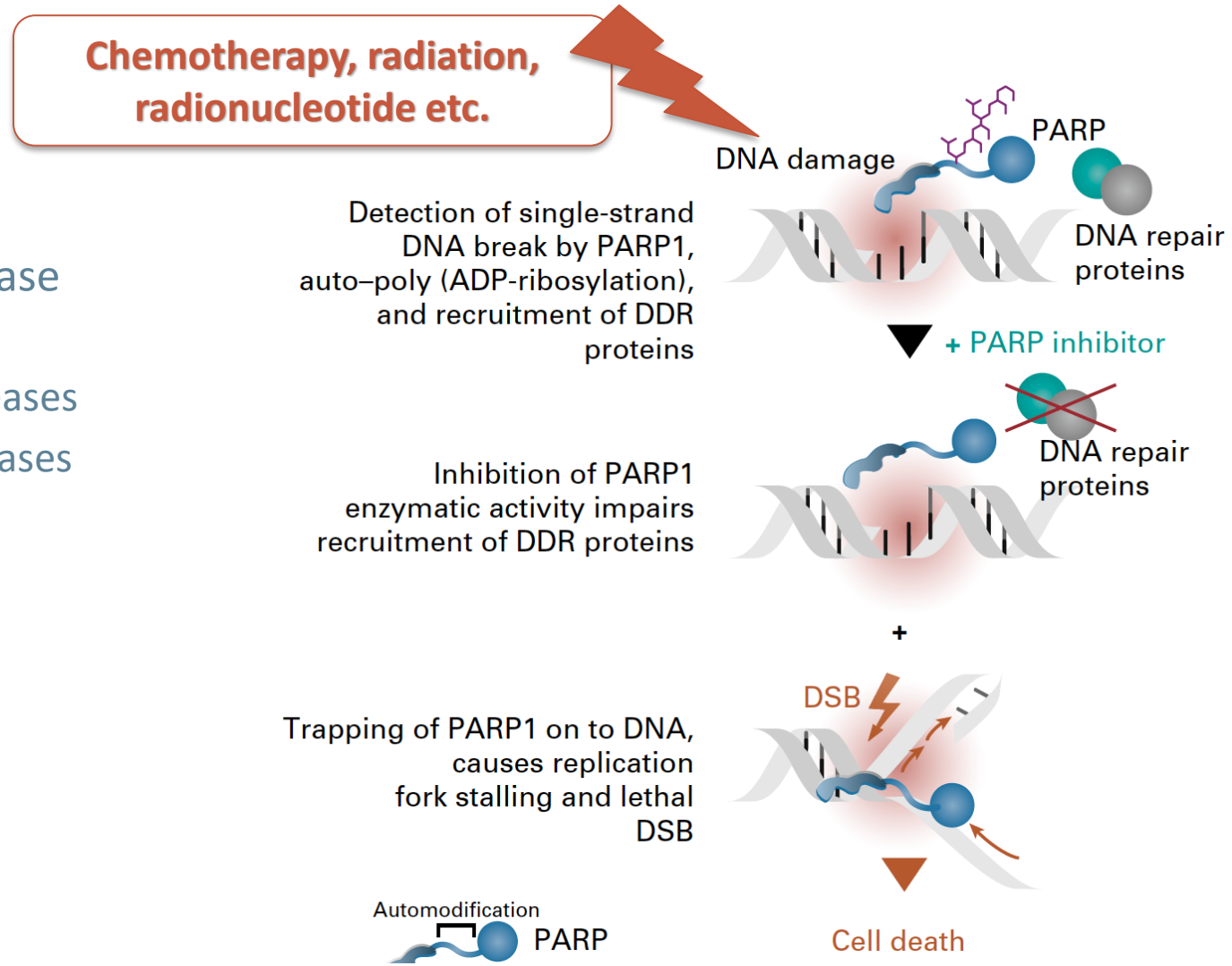
- Therapies such as chemotherapy, radiation, and radionucleotides increase DNA damage
  - The potential for PARPi trapping increases
  - The potential synthetic lethality increases



MoA – DNA damage plus trapping PARP is synthetic lethal with HRD

DSB, double-strand break; HRD, homologous recombination deficiency; MoA, mode of action; PARP, poly ADP ribose polymerase
Keung MYT, et al. J Clin Med. 2019;8:435.

PARPI COMBINATIONS TO INDUCE OTHER FORMS OF SYNTHETIC LETHALITY

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- Combined interventions can induce or enhance synthetic lethality by disrupting alternative pathways involved in DNA repair
- Such inhibitors of cell signalling pathways include:
  - ATR inhibitors (M6620)
  - Pi3K pathway inhibitors
  - Akt inhibitors (ipatasertib)
  - VEGFR inhibitors (cediranib)
  - DNMT inhibitors

Akt, protein kinase B ; ART(i), ataxia telangiectasia and Rad3-related protein kinase (inhibitor); DNMT, DNA methyltransferase; Pi3K, phosphoinositide 3-kinase; VEGFR, vascular endothelial growth factor receptor

Cancers (Basel). 2020 Jun; 12(6): 1607.
Published online 2020 Jun 17. doi: 10.3390/cancers12061607
PMCID: PMC7352566
PMID: 32560564

Overcoming Platinum and PARP-Inhibitor Resistance in Ovarian Cancer

Michelle McMullen, Katherine Karakasis, Ainhoa Madariaga, and Amit M. Oza*

ATR inhibition induced synthetic lethality

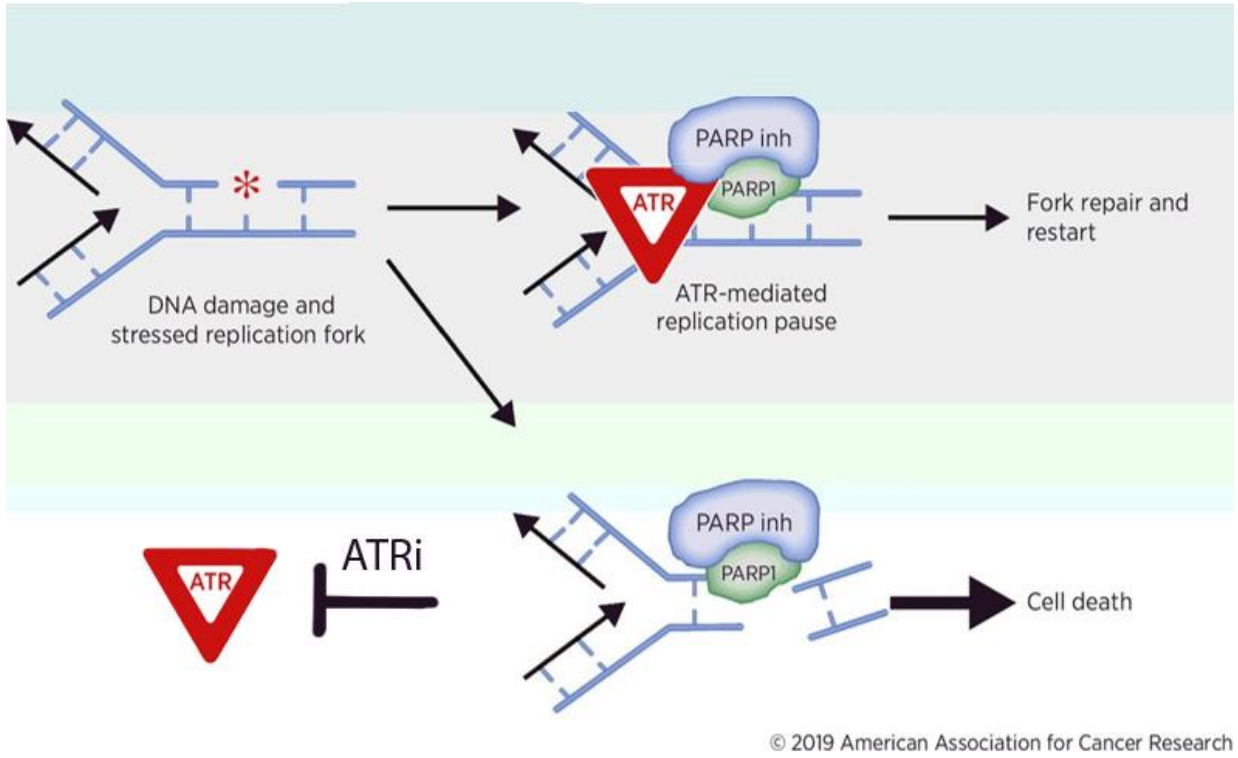

Figure adapted from;
PARP Inhibitors: Extending Benefit Beyond BRCA-Mutant Cancers
Patrick G. Pilié, Carl M. Gay, Lauren A. Byers, Mark J. O'Connor and Timothy A. Yap
DOI: 10.1158/1078-0432.CCR-18-0968 Published July 2019

OVERCOMING RESISTANCE: ONGOING COMBINATION TRIALS

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Treatment Regimen	Status	Allocation	HRD Selection	Estimated Enrollment	Phase	CTID
PARPi + AR signaling inhibitors						
Niraparib and Abiraterone and Prednisolone	Recruiting	Randomized	Yes	1000	III	NCT03748641
Olaparib or Olaparib and Abiraterone and Prednisone	Recruiting	Randomized	Yes	70	II	NCT03012321
Olaparib and Abiraterone and Prednisolone	Recruiting	Randomized	No	720	III	NCT03732820
Rucaparib and Abiraterone, Enzalutamide or Docetaxel	Recruiting	Randomized	Yes	400	III	NCT02975934
Niraparib and Apalutamide or Abiraterone and Prednisolone	Active, not recruiting		No	34	I	NCT02924766
Niraparib and Enzalutamide	Terminated (Suspended by funder)		No	2	I	NCT02500901
Talazoparib and Enzalutamide	Recruiting	Randomized	Yes†	872	III	NCT03395197
Rucaparib and Enzalutamide and Abiraterone	Recruiting	Non-randomized	No	60	I	NCT04179396
PARPi + immune checkpoint inhibitors						
Talazoparib and Avelumab	Recruiting	Non-Randomized	No	242	Ib/II	NCT03330405
Olaparib and Durvalumab	Recruiting		Yes	32	II	NCT03810105
Niraparib and JNJ-63723283 or Abiraterone and Prednisolone	Recruiting	Non-Randomized	Yes	150	Ib-II	NCT0341350
Rucaparib and Nivolumab	Recruiting	Non-Randomized	No	330	II	NCT03338790
Rucaparib or Rucaparib and Nivolumab	Recruiting	Randomized	No	60	Ib/IIa	NCT03572478
Olaparib and Pembrolizumab	Recruiting	Non-Randomized	No	400	I	NCT02861573
Olaparib and Pembrolizumab	Not yet recruiting	Randomized	No	780	III	NCT03834519
PARPi + chemotherapy agents						
Rucaparib, Docetaxel and carboplatin	Recruiting		Yes	20	II	NCT03442556
Pamiparib and Temozolomide	Recruiting	Non-randomized	Yes	150	I	NCT03150810
PARPi + Radionuclide therapies						
Niraparib and Radium Ra 223 Dichloride	Recruiting		No	6	1	NCT03076203
Olaparib and Radium Ra 223 Dichloride	Recruiting	Randomized	No	112	II	NCT03317392
Olaparib and 177Lu-PSMA	Recruiting		No	52	I	NCT03874884
PARPi + surgical procedures						
Olaparib and RP	Recruiting		Yes	13	II	NCT03432897
Olaparib and RP	Recruiting		Yes	15	II	NCT03570476
PARPi + VEGF RTK inhibitors						
Olaparib and Cediranib	Active, not recruiting	Randomized	No	90	II	NCT02893917

Adapted from Virtanen V, et al., Genes (Basel). 2019;10(8):565; clinicaltrials.gov

OVERCOMING RESISTANCE: ONGOING COMBINATION TRIALS

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Treatment Regimen	Status	Allocation	HRD Selection	Estimated Enrollment	Phase	CTID
PARPi + AKT inhibitors						
Rucaparib and Ipatasertib	Recruiting	Non-Randomized	No	54	Ib	NCT03840200
PARPi + androgens						
Olaparib and Testosterone Enanthate or Cypionate	Recruiting		Yes	30	II	NCT03516812
PARPi + ATR inhibitors						
Olaparib and AZD6738	Recruiting	Non-Randomized	No	47	II	NCT03787680
PARPi + GnRH antagonists						
Olaparib and Degarelix	Recruiting	Randomized	No	20	I	NCT02324998
PARPi + nanoparticle conjugate						
Olaparib and CRLX101	Recruiting	Non-randomized	No	123	I/II	NCT02769962
Personalized medicine approach						
SMMART therapy	Recruiting		No	52	I	NCT03878524
PARPi + radiation treatment						
Olaparib and RT	Recruiting	Randomized	No	112	I/II	NCT03317392

CTID, clinical trial identification; GnRH, gonadotropin-releasing hormone; SMMART, serial measurements of molecular and architectural responses

Virtanen V, et al. Genes (Basel). 2019;10(8):565; clinicaltrials.gov

FURTHER DISRUPTION OF DNA DAMAGE REPAIR OR INCREASED DNA DAMAGE CAN OVERCOME PARPi RESISTANCE

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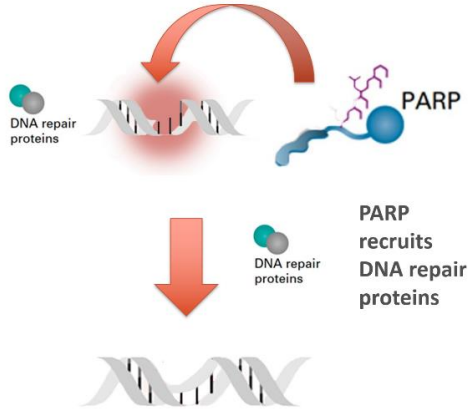
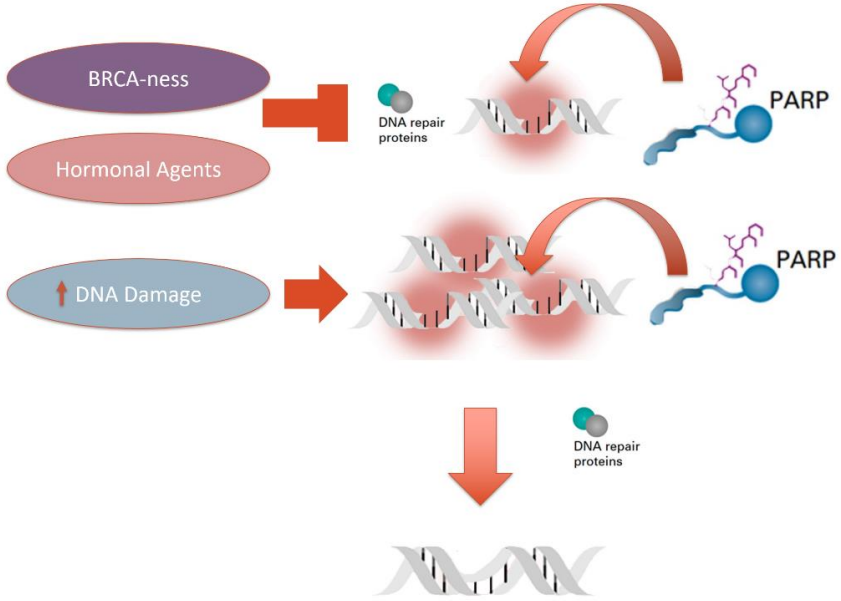
1. No intervention



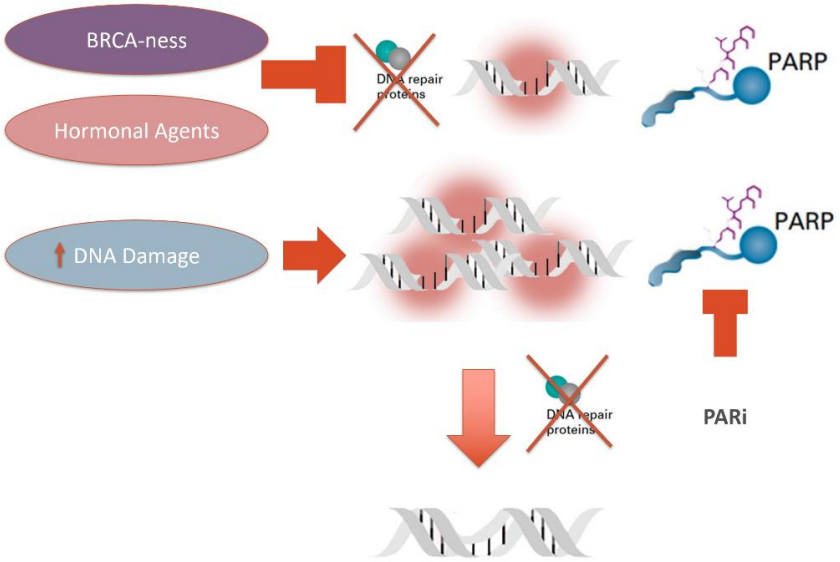
DNA repair; cell survival

2. Interventions with no PARPi



DNA repair; cell survival

3. Interventions with PARPi



No DNA repair; cell death

CONCLUSIONS

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- **Somatic and germline testing** for common DDR mutations are **recommended for all patients with metastatic prostate cancer**
- **Multiple PARPi have proven efficacy and tolerability in mCRPC**
  - With **olaparib** having **OS data** in mCRPC based on the PROfound study
  - Studies into combination therapies with hormonal agents are underway
- **Combinations** with therapies which induce DNA damage or a BRCA-like phenotype may help overcome **PARPi resistance**
- Investigations into PARP inhibitor efficacy in locally advanced prostate cancer may alter the place of PARP inhibition in the treatment pathway

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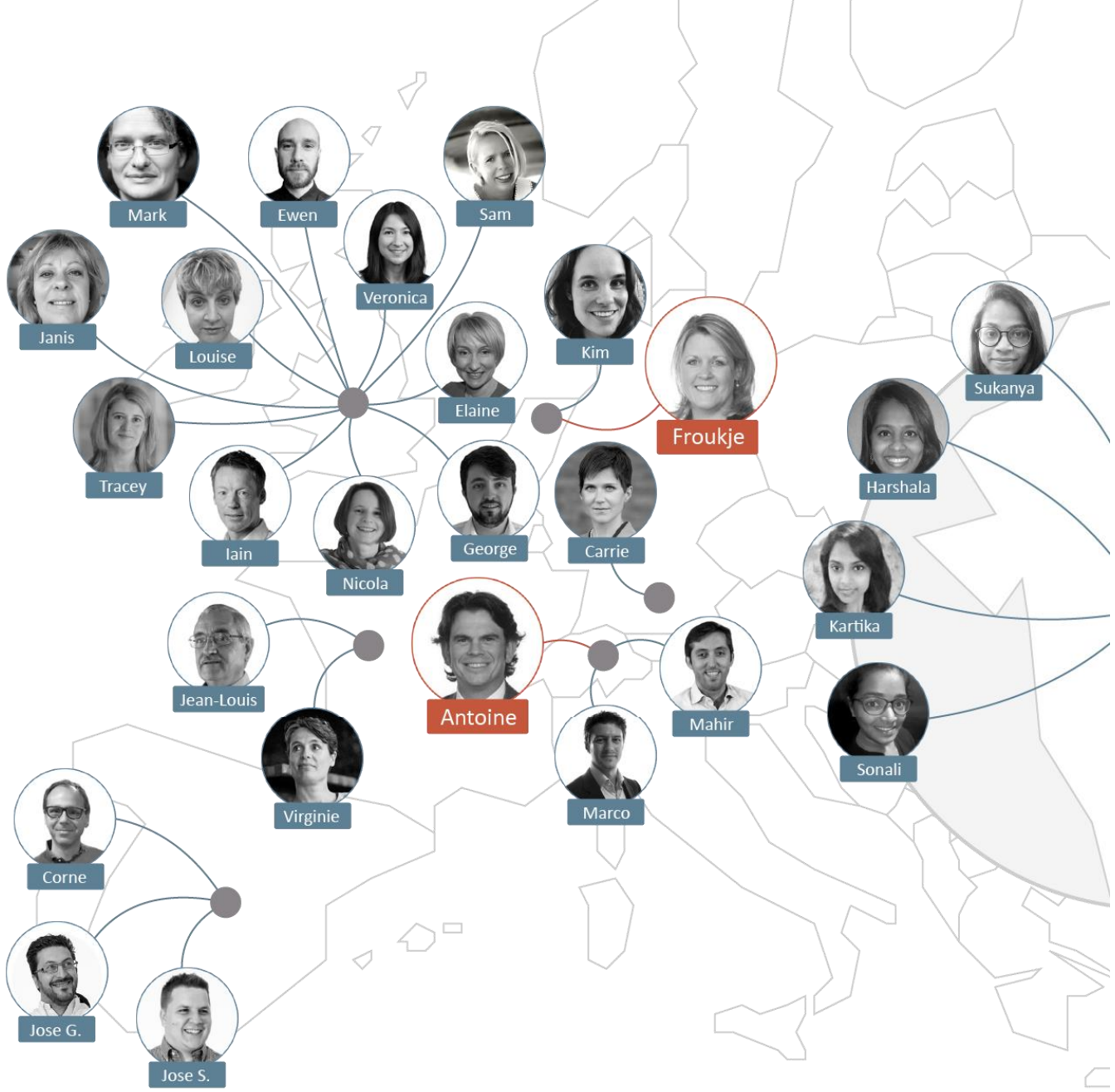

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