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THE ROLE OF PARPi IN PROSTATE CANCER: EXPERTS KNOWLEDGE SHARE

AUGUST 2020

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Prof. Emmanuel S. Antonarakis
Johns Hopkins Medicine
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.

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EXPERTS KNOWLEDGE SHARE

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

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
INTRODUCTION

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

1966 First standard chemotherapy regimen
1966 First standard chemotherapy regimen
1970 Radioactive ‘seeds’ proven effective
1970 Radioactive ‘seeds’ proven effective
1980 Early hormone therapy introduced
1980 Early hormone therapy introduced
1982 New surgeries help preserve sexual function
1994 Watchful waiting introduced
1994 Watchful waiting introduced
1996 First drug for PCa resistant to hormone treatment
1997 Hormone therapy + radiation improves survival
1997 Hormone therapy + radiation improves survival
2000 New chemotherapy for hormone-resistance PCa
2004 Evidence for targeted therapies
2005 High dose radiation reduces recurrence
2010 First immunotherapy
2012 New hormone therapy for advanced PCa
2017 New SoC for newly diagnosed advanced PCa
2020 Approval of PARPi therapy for mCRPC
2020 Approval of PARPi therapy for mCRPC
2017 New SoC for newly diagnosed advanced PCa
2012 New hormone therapy for advanced PCa
2004 Evidence for targeted therapies
2000 New chemotherapy for hormone-resistance PCa
1997 Hormone therapy + radiation improves survival
1994 Watchful waiting introduced
1982 New surgeries help preserve sexual function
1970 Radioactive ‘seeds’ proven effective
1966 First standard chemotherapy regimen

mCRPC, metastatic castrate-resistant prostate cancer; PARPi, poly ADP ribose polymerase inhibitor; PCa, prostate cancer; SoC, standard of care
MAJOR PROGNOSTIC FEATURES OF PROSTATE CANCER

- 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

<table>
<thead>
<tr>
<th>New Cancer Diagnosis</th>
<th>5-year OS range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local or regional prostate cancer</td>
<td>99-100%</td>
</tr>
<tr>
<td>Non-mCRPC</td>
<td>20-60%</td>
</tr>
<tr>
<td>mHSPC</td>
<td>23.6-51.9%</td>
</tr>
<tr>
<td>mCRPC</td>
<td>10-26%</td>
</tr>
</tbody>
</table>

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%20prostate%20cancer%20combined%20is%2098%25.
AR, androgen receptor; 
HRR, homologous recombination repair; 
MSI, microsatellite instability 
All information available at: www.drugs.com
PARPi: WHAT DO WE NEED TO KNOW?

• 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?
WHAT IS PARP INHIBITION AND HOW DO WE IDENTIFY PATIENTS?

Prof. Emmanuel S. Antonarakis, MD
Professor of Oncology and Urology
Johns Hopkins University School of Medicine
Sidney Kimmel Comprehensive Cancer Center
Baltimore, Maryland
Prof. Emmanuel S. Antonarakis has the following relevant financial relationships to disclose:

- **Research/Consulting:** Amgen, Astellas, AstraZeneca, Bayer, BMS, Celgene, Clovis, Dendreon, Eli Lilly, ESSA, Genentech, GSK, Janssen, Johnson & Johnson, Medivation, Merck, Novartis, Qiagen, Sanofi, Tokai

- **Stock/Patents/Salary:** None
GENOMIC INSTABILITY IS A TARGETABLE HALLMARK OF CANCER

HALLMARKS OF CANCER

- AR inhibitors
- Cyclin-dependent kinase inhibitors
- Checkpoint inhibitors
- Telomerase inhibitors
- Selective anti-inflammatory drugs
- Inhibitors of VEGF signaling
- Inhibitors of HGF/c-Met
- PARP inhibitors
- Proapoptotic BH3 mimetics
- Aerobic glycolysis inhibitors
- Sustaining proliferative signaling
- Evading growth suppressors
- Avoiding immune destruction
- Enabling replicative immortality
- Tumor-promoting inflammation
- Genome instability and mutation
- Resisting cell death
- Deregulating cellular energetics

AR, androgen receptor; c-MET, c-MET tyrosine-protein kinase; HGF, hepatocyte growth factor; PARP, poly ADP ribose polymerase; VEGF, vascular endothelial growth factor.
ABERRANT DOUBLE-STRAND BREAK REPAIR: GENOME INSTABILITY

Spontaneous (Fork collapse)
DSB REPAIR: CELL CYCLE

G, gap; M, mitosis; S, synthesis
DSB REPAIR: CELL CYCLE

NHEJ, non-homologous end joining

“NHEJ”

“Error prone”
DSB REPAIR: MEDIATED BY TWO PATHWAYS WITH DIFFERENT ERROR FREQUENCY

"HR"

DSB → DSB resection → Strand invasion → DNA synthesis → REPAIR

"NHEJ"

End joining → REPAIR

No template “error prone”

Template based “error free”

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

“HR”

“NHEJ”

Breast Cancer

Ovarian Cancer

Prostate Cancer

Pancreatic Cancer

Melanoma

BRCA1 + BRCA2

DSB

No template “error prone”

End joining

G1

G0

S

G2

M
DSB REPAIR DEFECTS: THERAPEUTIC EXPLOITATION IN CANCER

“HR”

DSB REPAIR DEFECTS:
THERAPEUTIC EXPLOITATION IN CANCER

“NHEJ”

Helleday, Jackson, Ashworth

PARP INHIBITORS: THERAPEUTIC EXPLOITATION IN CANCER

“HR”

DSB

“NHEJ”

DSB

Log surviving fraction

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<td>-2</td>
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<tr>
<td>-3</td>
</tr>
<tr>
<td>-4</td>
</tr>
</tbody>
</table>

PARP inhibitor concentration (M)

Wild type

BRCA2 +/-

BRCA2 -/

Lynparza® olaparib

Zejula niraparib

Rubraca® (rucaparib) 300 mg tablets

TALZENNA talazoparib
PARP INHIBITORS: ‘SYNTHETIC LETHALITY’
REQUIRES BOTH REPAIR PATHWAYS TO BE BLOCKED

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

![Diagram showing repair pathways and modes of action](image)

**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

Detection of single-strand DNA break by PARP1, auto-poly (ADP-ribosylation), and recruitment of DDR proteins

Inhibition of PARP1 enzymatic activity impairs recruitment of DDR proteins

Trapping of PARP1 on to DNA, causes replication fork stalling and lethal DSB

MOA – trapping PARP is synthetic lethal with HRD
DDR MUTATIONS IN METASTATIC PROSTATE CANCER
Prevalence and Screening
CHANGING TREATMENT PATTERNS IN THE ERA OF PRECISION MEDICINE

**Goal:** analytic validation of biomarker \(\rightarrow\) clinical validation of clinical utility and patient benefits with matched therapy

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

Metastatic Prostate Cancer

**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; DNA-BD, DNA binding domain; IO, immuno-oncology; (m)CRPC, (metastatic) castrate-resistant prostate cancer; MSI\(^{hi}\), 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


**2020 ACTIONABLE PATHWAYS, GENOTYPES AND PHENOTYPES**

- **AR-driven mCRPC**
- **HRD+ CRPC (BRCA1/2, PALB2, others)**
- **MSI\(^{hi}\)/dMMR mCRPC**
- **CDK12 biallelic loss (tandem duplicator genotype) mCRPC**
- **AR Independent CRPC (NEPC, Double Negative CRPC)**
- **AR-variant (e.g. AR-V7) driven CRPC: AR degraders, cofactor inhibitors, taxanes**
- **Inhibition of enhanced androgen synthesis**
- **AR N-term/DNABD inhibitors, PSMA targeted tx**
- **GR inhibition, PARPi combinations**
- **PARPi based therapy,* IO combinations**
- **PD-1 based immunotherapy**
- **PD-1 based immunotherapy**
- **DLL3 inhibition, combinations**
- **Immunotherapy**
- **Platinum chemotherapy**
**DNA REPAIR GENE ALTERATIONS (SOMATIC AND GERMLINE) ARE COMMON IN METASTATIC PROSTATE CANCER**

1-3

**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  
BRCA2 CARRIERS WITH PROSTATE CANCER HAVE WORSE PROGNOSIS\textsuperscript{1,2}

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

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
### Germline 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

### Somatic Tumor Testing

- 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

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HOW DO WE TEST?

Germline

Somatic

- Myriad myRisk®
- Invitae
- Neo Genomics
- Color
- Ambry Genetics
- Academic/In house
- Guardant
- Caris Life Sciences
- Foundation Medicine
- Tempus
CONCLUSIONS

• **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
ROLE OF PARPi IN ADVANCED PROSTATE CANCER

Prof. Andrew J. Armstrong, MD
Professor of Medicine, Surgery, Pharmacology and Cancer Biology
Director of Research
Duke Cancer Institute’s Center for Prostate and Urologic Cancers
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
PROPERTIES OF PARP INHIBITORS

<table>
<thead>
<tr>
<th></th>
<th>Olaparib$^1$</th>
<th>Veliparib$^1$</th>
<th>Talazoparib$^1$</th>
<th>Niraparib$^1$</th>
<th>Rucaparib$^1$</th>
<th>Pamiparib$^2$</th>
</tr>
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<tbody>
<tr>
<td>MW</td>
<td>434.5</td>
<td>244.3</td>
<td>380.8</td>
<td>320.4</td>
<td>323.4</td>
<td>298.31</td>
</tr>
<tr>
<td>PARP1 IC$_{50}$</td>
<td>5 nM</td>
<td>1.2 nM</td>
<td>0.56 nM</td>
<td>3.8 nM</td>
<td>0.65 nM</td>
<td>0.9 nM</td>
</tr>
<tr>
<td>PARP2 IC$_{50}$</td>
<td>1 nM</td>
<td>0.41 nM</td>
<td>0.15 nM</td>
<td>2.1 nM</td>
<td>0.08 nM</td>
<td>0.5 nM</td>
</tr>
<tr>
<td>Trapping</td>
<td>++</td>
<td>+</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
<td>++$^3$</td>
</tr>
</tbody>
</table>

Pamiparib trapping potential estimated based on description as ‘potent’.

IC$_{50}$, half of maximal inhibitory concentration; MW, molecular weight; nM, nanomoles; PARP, poly-ADP ribose polymerase
<table>
<thead>
<tr>
<th>PARPi</th>
<th>Clinical Trial No.</th>
<th>Study overview</th>
<th>Setting</th>
<th>Trial status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olaparib</td>
<td>NCT01682772</td>
<td>Single arm, phase 2 trial of olaparib, predictive biomarker trial</td>
<td>Advanced castration resistant prostate cancer</td>
<td>Active, not recruiting</td>
</tr>
<tr>
<td>Olaparib</td>
<td>NCT02987543</td>
<td>Randomized phase 3 trial of olaparib vs enzalutamide or abiraterone</td>
<td>mCRPC who have failed prior treatment with a NHA with somatic HRR mutation</td>
<td>Active, not recruiting</td>
</tr>
<tr>
<td>Olaparib</td>
<td>NCT03047135</td>
<td>Single arm phase 2 trial of olaparib</td>
<td>Non-metastatic biochemically-recurrent PCa and a PSADT of ≤6 months and a minimum PSA of 1.0</td>
<td>Recruiting</td>
</tr>
<tr>
<td>Olaparib</td>
<td>NCT03263650</td>
<td>Randomized phase 2 of olaparib maintenance versus observation</td>
<td>AVPC 6 cycles of cabazitaxel and carboplatin before randomisation</td>
<td>Recruiting</td>
</tr>
<tr>
<td>Olaparib</td>
<td>NCT03434158</td>
<td>Single-arm phase 2 study of olaparib (IMANOL)</td>
<td>mCRPC ≥ 6 cycles of docetaxel with CR/PR (RECIST 1.1) and PCWG3</td>
<td>Recruiting</td>
</tr>
<tr>
<td>Talazoparib</td>
<td>NCT03148795</td>
<td>Phase 2 single arm study of talazoparib</td>
<td>mCRPC previous taxane-based chemotherapy and progression on ≥ 1 NHA</td>
<td>Active, not recruiting</td>
</tr>
<tr>
<td>Rucaparib</td>
<td>NCT02952534</td>
<td>Single arm phase 2 trial of rucaparib (TRITON2)</td>
<td>mCRPC with evidence of HRR gene deficiency</td>
<td>Active, not recruiting</td>
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<tr>
<td>Rucaparib</td>
<td>NCT02975934</td>
<td>Phase 3 trial of rucaparib vs physician’s choice of abiraterone acetate, enzalutamide, or docetaxel. (TRITON3)</td>
<td>mCRPC with evidence of HRR gene deficiency</td>
<td>Recruiting</td>
</tr>
<tr>
<td>Rucaparib</td>
<td>NCT03413995</td>
<td>Single arm phase 2 trial of rucaparib (TRIUMPH)</td>
<td>mHSPC with germline DDR gene mutations</td>
<td>Recruiting</td>
</tr>
<tr>
<td>Rucaparib</td>
<td>NCT03533946</td>
<td>Single arm phase 2 trial of rucaparib (ROAR)</td>
<td>Hormone-sensitive PCa with ‘BRCAness’ gene defects</td>
<td>Recruiting</td>
</tr>
<tr>
<td>Niraparib</td>
<td>NCT02854436</td>
<td>Single arm phase 2 biomarker/safety/efficacy (Galahad)</td>
<td>mCRPC with progression taxane therapy</td>
<td>Active, not recruiting</td>
</tr>
<tr>
<td>Pamiparib</td>
<td>NCT03712930</td>
<td>Single arm phase 2 trial of pamiparib</td>
<td>mCRPC with HRR deficiency</td>
<td>Active, not recruiting</td>
</tr>
</tbody>
</table>

**PROfound: STUDY DESIGN**

**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

**Upon BICR progression, physician’s choice patients were allowed to cross over to olaparib**

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**Cohort A**
- BRCA1, BRCA2, or ATM
- n=245

**Olaparib 300 mg BID**
- n=162

**Physician’s choice**
- n=83

**Cohort B**
- Other alterations
- n=142

**Olaparib 300 mg BID**
- n=94

**Physician’s choice**
- n=48

**Key secondary endpoints**
- Statistical analysis
  - Primary endpoint rPFS BICR in Cohort A (alpha=0.05)
  - Confirmed ORR by BICR in Cohort A (alpha=0.05)
  - rPFS by BICR in Cohort A+B (alpha=0.05)
  - Time to pain progression in Cohort A (alpha=0.05)
  - OS in Cohort A interim (alpha=0.01)
  - OS in Cohort A Final (alpha=0.047)

---

### PROfound: PATIENT CHARACTERISTICS

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Cohort A (N=162)</th>
<th>Control (N=83)</th>
<th>Cohorts A and B (N=256)</th>
<th>Control (N=131)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median age at randomization, y (range)</strong></td>
<td>68 (47-86)</td>
<td>67 (49-86)</td>
<td>69 (47-91)</td>
<td>69 (49-87)</td>
</tr>
<tr>
<td><strong>Age ≥65 y at randomization, n (%)</strong></td>
<td>108 (67)</td>
<td>60 (72)</td>
<td>174 (68)</td>
<td>97 (74)</td>
</tr>
<tr>
<td><strong>Metastatic disease at initial diagnosis, n (%)</strong></td>
<td>38 (23)</td>
<td>19 (23)</td>
<td>66 (26)</td>
<td>25 (19)</td>
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<tr>
<td><strong>Missing data</strong></td>
<td>7 (4)</td>
<td>4 (5)</td>
<td>11 (4)</td>
<td>7 (5)</td>
</tr>
<tr>
<td><strong>Gleason score ≥8, n/total n (%)</strong></td>
<td>105/157 (67)</td>
<td>54/80 (67)</td>
<td>183/251 (73)</td>
<td>95/127 (75)</td>
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<tr>
<td><strong>Patients with alterations in a single gene, n (%)</strong></td>
<td></td>
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<tr>
<td><em>BRCA1</em></td>
<td>8 (5)</td>
<td>5 (6)</td>
<td>8 (3)</td>
<td>5 (4)</td>
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<tr>
<td><em>BRCA2</em></td>
<td>80 (49)</td>
<td>47 (57)</td>
<td>81 (32)</td>
<td>47 (36)</td>
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<tr>
<td><em>ATM</em></td>
<td>60 (37)</td>
<td>24 (29)</td>
<td>62 (24)</td>
<td>24 (18)</td>
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<tr>
<td><em>CDK12</em></td>
<td>N/A</td>
<td>N/A</td>
<td>61 (24)</td>
<td>28 (21)</td>
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<td><strong>Median PSA at baseline (IQR), mcg/L</strong></td>
<td>62.2 (21.9-280.4)</td>
<td>112.9 (34.3-317.1)</td>
<td>68.2 (24.1-294.4)</td>
<td>106.5 (37.2-326.6)</td>
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<tr>
<td><strong>Measurable disease at baseline, n (%)</strong></td>
<td>95 (59)</td>
<td>46 (55)</td>
<td>149 (58)</td>
<td>72 (55)</td>
</tr>
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IQR, interquartile range; NA, not available; PSA, prostate-specific antigen; y, years
PROfound: PATIENT CHARACTERISTICS\(^1\) (CONT’D)

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

ECOG, Eastern Cooperative Oncology Group
PROfound PRIMARY ENDPOINT: rPFS (COHORT A)$^{1,2}$

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

- **6-mo rate**
  - Olaparib: 59.76%
  - Physician’s choice: 22.63%
- **12-mo rate**
  - Olaparib: 28.11%
  - Physician’s choice: 9.40%

<table>
<thead>
<tr>
<th></th>
<th>Olaparib (N=162)</th>
<th>Physician’s Choice (N=83)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events, %</td>
<td>106 (65.4)</td>
<td>68 (81.9)</td>
</tr>
<tr>
<td>Median PFS, mo</td>
<td>7.39</td>
<td>3.55</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.34 (0.25-0.47)</td>
<td>$P&lt;.001$</td>
</tr>
</tbody>
</table>

CI, confidence interval; HR, hazard ratio; mo, months; PFS, progression-free survival
**PROfound: FINAL PRE-SPECIFIED OS**

First survival advantage with a PARP inhibitor

### COHORT A\(^a\)

<table>
<thead>
<tr>
<th></th>
<th>Olaparib (N=162)</th>
<th>Physician’s Choice (N=83)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS, mo</td>
<td>19.1</td>
<td>14.7</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.69 (0.61-1.03)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(P = .0175)</td>
<td></td>
</tr>
</tbody>
</table>

### COHORTS A + B\(^b\)

<table>
<thead>
<tr>
<th></th>
<th>Olaparib (N=256)</th>
<th>Physician’s Choice (N=131)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS, mo</td>
<td>17.3</td>
<td>14.0</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.79 (0.61-1.03)</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\)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

PROfound OUTCOMES

**COHORT A OS WITH CROSSOVER ADJUSTMENT**

Olaparib 300 mg BID (N=162)
Enzalutamide or abiraterone acetate (N=83)
HR 0.42 (95% CI 0.19, 0.91)
Crossover rate: 67%

**COHORT A + B WITH CROSSOVER ADJUSTMENT**

Olaparib 300 mg bd (N=256)
Enzalutamide or abiraterone acetate (N=131)
HR 0.55 (95% CI 0.29, 1.06)
Crossover rate: 66%

**EXPLORATORY GENE-LEVEL ANALYSIS OF OS**

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

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.

ESMO 2020, Presentation ID 6100
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

• 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
PROfound: EXPLORATORY GENE-BY-GENE rPFS ANALYSIS\textsuperscript{1,2}

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

\begin{table}
\centering
\begin{tabular}{l c c c}
\hline
Gene & Samples & Olaparib & Physician’s choice \\
\hline
\textit{BRCA2} & 81 & 3.48 (1.74-3.65) & 10.84 (9.17-13.08) \\
& 47 & 5.09 (3.61-5.52) & \\
\textit{CDK12} & 61 & 2.20 (1.71-4.83) & \\
& 28 & 5.36 (3.61-6.21) & 4.70 (1.84-7.26) \\
\textit{ATM} & 62 & 2.07 (1.38-5.52) & \\
& 24 & 1.84 (1.71-3.71) & \\
\textit{BRCA1} & 8 & 3.48 (1.74-3.65) & \\
& 5 & 5.09 (3.61-5.52) & \\
\textit{CHEK2} & 7 & 2.20 (1.71-4.83) & \\
& 5 & 5.36 (3.61-6.21) & 4.70 (1.84-7.26) \\
\textit{PPP2R2A} & 6 & 2.07 (1.38-5.52) & \\
& 4 & 1.84 (1.71-3.71) & \\
\textit{RAD51B} & 4 & 2.07 (1.38-5.52) & \\
& 1 & 1.84 (1.71-3.71) & \\
\textit{RAD54L} & 3 & 2.07 (1.38-5.52) & \\
& 2 & 1.84 (1.71-3.71) & \\
\hline
\end{tabular}
\caption{Median rPFS, mo (95% CI) for selected genes.}
\end{table}

NR, not reported
PROfound (COHORTS A+B): HRQoL

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.

## PROfound SAFETY

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Olaparib (N=256)</th>
<th>Control (N=130)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (n, %)</td>
<td>Grade ≥3 (n, %)</td>
</tr>
<tr>
<td>Any</td>
<td>244 (95)</td>
<td>130 (51)</td>
</tr>
<tr>
<td>Anemiaa</td>
<td>119 (46)</td>
<td>55 (21)</td>
</tr>
<tr>
<td>Nausea</td>
<td>106 (41)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Fatigue or asthenia</td>
<td>105 (41)</td>
<td>7 (3)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>77 (30)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>54 (21)</td>
<td>2 (&lt;1)</td>
</tr>
<tr>
<td>Nausea</td>
<td>47 (18)</td>
<td>6 (2)</td>
</tr>
<tr>
<td>Constipation</td>
<td>45 (18)</td>
<td>0</td>
</tr>
<tr>
<td>Back pain</td>
<td>35 (14)</td>
<td>2 (&lt;1)</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>32 (12)</td>
<td>0</td>
</tr>
<tr>
<td>Cough</td>
<td>28 (11)</td>
<td>0</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>26 (10)</td>
<td>6 (2)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>24 (9)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>18 (7)</td>
<td>4 (2)</td>
</tr>
</tbody>
</table>

**Interruption of intervention because of adverse event**
- Olaparib: 115 (45) vs Control: 24 (18)

**Dose reduction because of adverse event**
- Olaparib: 57 (22) vs Control: 5 (4)

**Discontinuation of intervention because of adverse event**
- Olaparib: 46 (18) vs Control: 11 (8)

**Death because of adverse event**
- Olaparib: 10 (4) vs Control: 5 (4)

---

*aIncludes 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

COMMON SIDE EFFECTS OF OLAPARIB\textsuperscript{1,2}

- Anemia
- Fatigue
- Nausea (vomiting rare)
- Decreased appetite
- Diarrhea
- Thrombocytopenia
- Creatinine elevation
- Cough and dyspnea

\textit{Rare but serious}: MDS/AML; pneumonitis; PE/thromboembolism

AML, acute myeloid leukemia; MDS, myelodysplastic syndrome; PE, pulmonary embolism
Lynparza 50 mg hard capsules. SmPC. Revised July 2020.
FDA FULL APPROVAL: OLAPARIB FOR mCRPC

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\textsuperscript{a} gene-mutated mCRPC, who have progressed following prior treatment with enzalutamide or abiraterone\textsuperscript{1,\textb}$

\textsuperscript{a}BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, RAD54L.

\textsuperscript{b}Select patients for therapy based on two FDA-approved companion diagnostic tests: BRACAnalysis CDx and FoundationOne CDx.

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

HRR-deficiency is defined by a deleterious alteration in \textit{BRCA1, BRCA2, ATM}, or 12 other HRR genes (\textit{BARD1, BRIP1, CDK12, CHEK2, FANCA, NBN, PALB2, RAD51, RAD51B, RAD51C, RAD51D, RAD54L}).
### TRITON2: OBJECTIVE RESPONSES

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

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

- **Confirmed radiographic response**
- **Ongoing on study**

**Status:** Germline  Somatic

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

TRITON2: PSA RESPONSES

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

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

### TRITON2 PRIMARY ENDPOINT

**OBJECTIVE RESPONSE RATE**

<table>
<thead>
<tr>
<th>Response</th>
<th>Investigator-Evaluable Population (n=65)</th>
<th>IRR-Evaluable Population (n=62)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Confirmed ORR, No (%; 95% CI)</strong></td>
<td>33 (50.8; 38.1 to 63.4)</td>
<td>27 (43.5; 31.0 to 56.7)</td>
</tr>
<tr>
<td>CR</td>
<td>4 (6.2)</td>
<td>7 (11.3)</td>
</tr>
<tr>
<td>PR</td>
<td>29 (44.6)</td>
<td>20 (32.3)</td>
</tr>
<tr>
<td>SD</td>
<td>25 (38.5)</td>
<td>28 (45.2)</td>
</tr>
<tr>
<td>PD</td>
<td>6 (9.2)</td>
<td>6 (9.7)</td>
</tr>
<tr>
<td>NE</td>
<td>1 (1.5)</td>
<td>1 (1.6)</td>
</tr>
</tbody>
</table>

**Confirmed PSA response rate, No. (5;95% CI)**

- Overall Efficacy Population (n=115)
  - 63 (54.8; 45.2 to 64.1)

IRR, Independent radiological review

TRITON2:
SUBGROUP ANALYSIS OF OBJECTIVE RESPONSE RATE

ORR in IRR-Evaluable Population

<table>
<thead>
<tr>
<th>Category</th>
<th>ORR, No./No. (%) [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>27/62 (43.5) [31.0 to 56.7]</td>
</tr>
<tr>
<td>Gene</td>
<td></td>
</tr>
<tr>
<td>BRCA1</td>
<td>3/9 (33.3) [7.5 to 70.1]</td>
</tr>
<tr>
<td>BRCA2</td>
<td>24/53 (45.3) [31.6 to 59.6]</td>
</tr>
<tr>
<td>Germline/somatic status</td>
<td></td>
</tr>
<tr>
<td>Germline</td>
<td>9/21 (42.9) [21.8 to 66.0]</td>
</tr>
<tr>
<td>Somatic</td>
<td>18/41 (43.9) [28.5 to 60.3]</td>
</tr>
<tr>
<td>No. of prior lines of therapy</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1/1* (100.0) [2.5 to 100.0]</td>
</tr>
<tr>
<td>≥3</td>
<td>15/32 (46.9) [29.1 to 65.3]</td>
</tr>
<tr>
<td>Hepatic metastases</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>6/13 (46.2) [19.2 to 74.9]</td>
</tr>
<tr>
<td>No</td>
<td>21/49 (42.9) [28.8 to 57.8]</td>
</tr>
<tr>
<td>Age, years</td>
<td></td>
</tr>
<tr>
<td>&lt;65</td>
<td>7/11 (63.6) [30.8 to 89.1]</td>
</tr>
<tr>
<td>65–74</td>
<td>8/25 (32.0) [14.9 to 53.5]</td>
</tr>
<tr>
<td>≥75</td>
<td>12/26 (46.2) [26.6 to 66.6]</td>
</tr>
</tbody>
</table>

TRITON2:
RADIOGRAPHIC PFS¹

Time (months)

No. at risk: (events) 115 (0) 80 (21) 53 (34) 17 (50) 9 (53) 4 (53) 3 (53) 0 (53)

Median, months 9.0
95% CI 8.3 to 13.5
Range 0.0-27.6+

## TRITON2: RESPONSE BY NON-BRCA DDR GENE ALTERATIONS

Visit cutoff date: April 29, 2019. Data are n/N (%) (95% CI) unless stated otherwise.

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

\(^a\)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.

## COMMON SIDE EFFECTS OF RUCAPARIB

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td></td>
</tr>
<tr>
<td>Fatigue, asthenia</td>
<td></td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td></td>
</tr>
<tr>
<td>Diarrhea or constipation</td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td></td>
</tr>
<tr>
<td>Increased AST/ALT and/or creatinine</td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td></td>
</tr>
</tbody>
</table>

*Rare but serious: MDS/AML; fetal teratogenicity*

---

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

---

TRITON3: STUDY DESIGN

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

PHASE 2 GALAHAD: NIRAPARIB IN PREVIOUSLY TREATED mCRPC WITH BIALLELIC DDR MUTATIONS\textsuperscript{1,2}

**Key Eligibility Criteria**
- mCRPC
- Biomarker positive for biallelic DRD mutation
- Progressed on $\geq$1 AR-targeted therapy and $\geq$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\textsuperscript{b} with no evidence of bone progression according to PCWG3 criteria in patients with biallelic BRCA mutations\textsuperscript{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 $\geq$5/7.5 mL to $<5/7.5$ mL of blood, or $\geq$50% decline in PSA level.\textsuperscript{2}

CTC, circulating tumor cell; d, days; DOR, duration of objective response; DRD; DNA-repair gene deficit
\textsuperscript{a}Treatment continued until disease progression, unacceptable toxicity, or death. \textsuperscript{b}Investigator assessed.
BEST OVERALL RESPONSE IN BIALLELIC DRD PATIENTS WITH MEASURABLE DISEASE AT BASELINE

<table>
<thead>
<tr>
<th>Response, n (%)</th>
<th>Patients with measurable disease (n=51)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BRCA (n=29)</td>
</tr>
<tr>
<td>CR</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>PR</td>
<td>11 (38%)</td>
</tr>
<tr>
<td>SD</td>
<td>7 (24%)</td>
</tr>
<tr>
<td>PD</td>
<td>7 (24%)</td>
</tr>
</tbody>
</table>

MAXIMUM CHANGE IN TARGET LESION DIAMETER

## PHASE 2 GALAHAD: ORR, PSA RESPONSE, CTC RESPONSE

### All Biallelic DRD (N=50)

<table>
<thead>
<tr>
<th>n/N % (95% CI)</th>
<th>BRCA1/2 (n=29)</th>
<th>Non-BRCA1/2&lt;sup&gt;a&lt;/sup&gt; (n=21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite RR</td>
<td>18/29 62.1 (42.3-79.3)</td>
<td>5/21 23.8 (8.2-47.2)</td>
</tr>
<tr>
<td>Objective RR&lt;sup&gt;b&lt;/sup&gt;</td>
<td>6/16 37.5 (15.2-64.6)</td>
<td>2/15 13.3 (1.7-40.5)</td>
</tr>
<tr>
<td>≥50% decline in PSA</td>
<td>15/29 51.7 (32.5-70.6)</td>
<td>1/21 4.8 (0.1-23.8)</td>
</tr>
<tr>
<td>CTC conversion (&lt;5/7.5 mL blood)</td>
<td>12/29 41.4 (23.5-61.1)</td>
<td>4/21 19.0 (5.5-41.9)</td>
</tr>
<tr>
<td>CTC response</td>
<td>6/29 20.7 (8.0-39.7)</td>
<td>2/21 9.5 (1.2-30.4)</td>
</tr>
</tbody>
</table>

<sup>a</sup>ATM, FANCA, PALB2, CHEK2, BRIP1, or HDAC2 assayed, not all represented in non-BRCA patients.  
<sup>b</sup> Investigator-assessed.  

**Maximum change in PSA from baseline (%)**

TALAPRO-1: TALAZOPARIB IN mCRPC WITH DDRM

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\textsuperscript{a} for mCRPC
- DDRm\textsuperscript{b} likely to sensitize to PARPi

N = ~100

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

\textsuperscript{a}Enzalutamide/abiraterone acetate. \textsuperscript{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

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.

---

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

TALAPRO-1: EFFICACY AND SAFETY RESULTS

**BEST CHANGE FROM BASELINE IN PSA**

![Graph showing best change from baseline in PSA for different DDR-deficient populations.](image)

**BEST CHANGE FROM BASELINE IN RECIST**

![Graph showing best change from baseline in sum of diameters for target lesions for different DDR-deficient populations.](image)

**Notes:**

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

MUTATION STATUS AND SENSITIVITY TO PARP INHIBITORS

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

- Explanation of the lower sensitivity of BRCA1 mutation mCRPC will require more patient data due to a low mutation prevalence

- Currently, both olaparib and rucaparib should be considered for patients with either BRCA2 or BRACA1 mutations

---

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

ONGOING STUDIES OF PARP INHIBITOR COMBINATIONS IN PROSTATE CANCER

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)

OLAPARIB + ABIRATERONE IN UNSELECTED\textsuperscript{a} mCRPC

\textbf{(A) intention-to-treat population,}

\begin{itemize}
  \item Olaparib and abiraterone (n=71)
  \item Placebo and abiraterone (n=71)
\end{itemize}

HR 0.65 (95\% CI 0.44-0.97); p=0.034

\textbf{(B) HRR mutation-positive subgroup,}

\begin{itemize}
  \item Olaparib and abiraterone (n=11)
  \item Placebo and abiraterone (n=10)
  \item HR 0.74 (95\% CI 0.26-2.12); nominal p=0.58
\end{itemize}

\textbf{(C) wild-type HRR subgroup,}

\begin{itemize}
  \item Olaparib and abiraterone (n=15)
  \item Placebo and abiraterone (n=20)
  \item HR 0.52 (95\% CI 0.24-1.35); nominal p=0.11
\end{itemize}

\textsuperscript{a}Patients unselected based on biomarker criteria.

PROPEL STUDY: ABIRATERONE +/- OLAPARIB

Key eligibility
- Progressive mCRPC
- First-line setting (may have previously received docetaxel at mHSPC stage)
- ECOG performance status 0–1

Stratification
- Metastasis: bone only vs visceral vs other
- Docetaxel treatment at mHSPC stage: yes vs no

Olaparib tablets 300 mg bid + abiraterone* 1000 mg od (N=360)

Randomized 1:1 (double blind)

Placebo + abiraterone* 1000 mg od (N=360)

Primary objective:
- rPFS assessed by investigator

Key secondary objective:
- Time to subsequent therapy or death
- Time to pain progression
- Overall survival

Safety objective:
- Safety and tolerability

mHSPC, metastatic hormone-sensitive prostate cancer; od, once daily
TALAPRO-2: STUDY DESIGN$^{1,2}$

**First-line mCRPC**

**Stratification Factors**
- Previous treatment with any NHT or taxane-based chemotherapy for CSPC
- DDR alteration status

**Unselected**

**DDR**

**Part 1: Open-label treatment**
- Determine starting dose of talazoparib n=19

- Talazoparib 0.5 mg/d + enzalutamide 160 mg/d
- Placebo + enzalutamide 160 mg/d

**Follow Up**
- Safety follow-up ~28 d following last dose of study drug treatment
- Long-term follow-up every 8-12 weeks

**Part 2: Double-blind treatment**
- n=1,018 1:1 randomization

- Talazoparib 0.5 mg/d + enzalutamide 160 mg/d
- Placebo + enzalutamide 160 mg/d

**CSPC, castration-sensitive prostate cancer**
• 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\(^2\)
ONGOING STUDIES OF PD-1/PD-L1 INHIBITORS IN COMBINATION WITH PARP INHIBITORS IN PCa

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)*

CONCLUSIONS

- 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.
THE ROLE OF PARPi IN PROSTATE CANCER: FUTURE PERSPECTIVES

Dr. Neal D. Shore
(Chair)
Carolina Urologic Research Center
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\textsuperscript{a} gene-mutated mCRPC, who have progressed following prior treatment with enzalutamide or abiraterone\textsuperscript{1,2}.

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\textsuperscript{2}.

\textsuperscript{a}BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, RAD54L.

\textsuperscript{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;

**COMBINING PARPi AND HORMONAL TARGETING**

- 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
COMBINING PARPi AND IMMUNE CHECKPOINT INHIBITORS

• 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
COMBINING PARPi AND DNA DAMAGING THERAPIES

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

DSB, double-strand break; HRD, homologous recombination deficiency; MoA, mode of action; PARP, poly ADP ribose polymerase
PARPI COMBINATIONS TO INDUCE OTHER FORMS OF SYNTHETIC LETHALITY

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

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*

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

## Treatment Regimen

<table>
<thead>
<tr>
<th>Treatment Regimen</th>
<th>Status</th>
<th>Allocation</th>
<th>HRD Selection</th>
<th>Estimated Enrollment</th>
<th>Phase</th>
<th>CTID</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PARPi + AR signaling inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Niraparib and Abiraterone and Prednisolone</td>
<td>Recruiting</td>
<td>Randomized</td>
<td>Yes</td>
<td>1000</td>
<td>III</td>
<td>NCT03748641</td>
</tr>
<tr>
<td>Olaparib or Olaparib and Abiraterone and Prednisone</td>
<td>Recruiting</td>
<td>Randomized</td>
<td>Yes</td>
<td>70</td>
<td>II</td>
<td>NCT03012321</td>
</tr>
<tr>
<td>Olaparib and Abiraterone and Prednisolone</td>
<td>Recruiting</td>
<td>Randomized</td>
<td>No</td>
<td>720</td>
<td>III</td>
<td>NCT03732820</td>
</tr>
<tr>
<td>Rucaparib and Abiraterone, Enzalutamide or Docetaxel</td>
<td>Recruiting</td>
<td>Randomized</td>
<td>Yes</td>
<td>400</td>
<td>III</td>
<td>NCT02975934</td>
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<tr>
<td>Niraparib and Apalutamide or Abiraterone and Prednisolone</td>
<td>Active, not recruiting</td>
<td></td>
<td>No</td>
<td>34</td>
<td>I</td>
<td>NCT02924766</td>
</tr>
<tr>
<td>Niraparib and Enzalutamide</td>
<td>Terminated (Suspended by funder)</td>
<td></td>
<td>No</td>
<td>2</td>
<td>I</td>
<td>NCT02500901</td>
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<tr>
<td>Talazoparib and Enzalutamide</td>
<td>Recruiting</td>
<td>Randomized</td>
<td>Yes*</td>
<td>872</td>
<td>III</td>
<td>NCT03395197</td>
</tr>
<tr>
<td>Rucaparib and Enzalutamide and Abiraterone</td>
<td>Recruiting</td>
<td>Non-randomized</td>
<td>No</td>
<td>60</td>
<td>I</td>
<td>NCT04179396</td>
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<tr>
<td><strong>PARPi + immune checkpoint inhibitors</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Talazoparib and Avelumab</td>
<td>Recruiting</td>
<td>Non-Randomized</td>
<td>No</td>
<td>242</td>
<td>Ib/II</td>
<td>NCT03330405</td>
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<tr>
<td>Olaparib and Durvalumab</td>
<td>Recruiting</td>
<td></td>
<td>Yes</td>
<td>32</td>
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<td>NCT03810105</td>
</tr>
<tr>
<td>Niraparib and JNU-63723283 or Abiraterone and Prednisolone</td>
<td>Recruiting</td>
<td>Non-Randomized</td>
<td>Yes</td>
<td>150</td>
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<tr>
<td>Rucaparib and Nivolumab</td>
<td>Recruiting</td>
<td>Non-Randomized</td>
<td>Yes</td>
<td>330</td>
<td>II</td>
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<tr>
<td>Rucaparib or Rucaparib and Nivolumab</td>
<td>Recruiting</td>
<td>Randomized</td>
<td>No</td>
<td>60</td>
<td>Ib/IIa</td>
<td>NCT03572478</td>
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<tr>
<td>Olaparib and Pembrolizumab</td>
<td>Recruiting</td>
<td>Non-Randomized</td>
<td>No</td>
<td>400</td>
<td>I</td>
<td>NCT02861573</td>
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<tr>
<td>Olaparib and Pembrolizumab</td>
<td>Not yet recruiting</td>
<td>Randomized</td>
<td>No</td>
<td>780</td>
<td>III</td>
<td>NCT03834519</td>
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<tr>
<td><strong>PARPi + chemotherapy agents</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rucaparib, Docetaxel and carboplatin</td>
<td>Recruiting</td>
<td></td>
<td>Yes</td>
<td>20</td>
<td>II</td>
<td>NCT03442556</td>
</tr>
<tr>
<td>Pamiparib and Temozolomide</td>
<td>Recruiting</td>
<td>Non-randomized</td>
<td>Yes</td>
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Adapted from Virtanen V, et al., Genes (Basel). 2019;10(8):565; clinicaltrials.gov
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CTID, clinical trial identification; GnRH, gonadotropin-releasing hormone; SMMART, serial measurements of molecular and architectural responses
FURTHER DISRUPTION OF DNA DAMAGE REPAIR OR INCREASED DNA DAMAGE CAN OVERCOME PARPi RESISTANCE

1. No intervention
   DNA repair; cell survival

2. Interventions with no PARPi
   DNA repair proteins
   PARP recruits DNA repair proteins
   DNA damage
   DNA repair; cell survival

3. Interventions with PARPi
   DNA repair proteins
   PARP
   DNA damage
   No DNA repair; cell death
CONCLUSIONS

• **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