DNA Damage Response: Clinical Implications of its Role in Tumor Suppression and Tumorigenesis

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TARGETING DNA DAMAGE RESPONSE
At the Forefront of Emerging Concepts and Strategies

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Summary

• The complexity of DNA damage response (DDR) molecular networks
• Their role in preventing the tumorigenic process
• Therapeutic opportunities
• Opportunities and challenges for combination therapy
The DNA Damage Response Network

Highly conserved molecular networks that maintain genomic integrity

Multiple exogenous and endogenous insults to DNA
- Radiation
- Reactive oxygen species
- Replication errors and stress
- DNA damaging chemotherapy

- Detect damage
- Stall cell cycle
- Repair DNA damage or promote cell death
  - Prevents the transmission of modified DNA to daughter cells


The DNA Damage Response Network-A Reductionist View

Highly conserved molecular networks that maintain genomic integrity

- Detect damage
- Stall cell cycle
- Repair DNA damage or promote cell death

- Detect DNA “lesions” and activate “signallers”
- Amplify the molecular response and recruit effectors
- Mediate repair

TARGETING DNA DAMAGE RESPONSE
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The DNA Damage Response Network-A Reductionist View
Highly conserved molecular networks that maintain genomic integrity

- Detect damage
- Stall cell cycle
- Repair DNA damage or promote cell death

- Significant overlap in function between sensors, signallers, effectors
- Interplay with ostensibly distinct processes important
  - Eg, cell cycle control
  - Chromatin modeling
  - Energy metabolism

Lesions Determine The Form of Repair

<table>
<thead>
<tr>
<th>Lesions</th>
<th>DSB</th>
<th>DSB</th>
<th>DSB</th>
<th>ICL</th>
<th>SSB</th>
<th>Base lesions</th>
<th>Base lesions</th>
<th>Base lesions</th>
<th>Base lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Source</td>
<td>IR, Topo II inhibitors</td>
<td>X linkers, replication inhibitors, antimetabolites, Topo I inhibitors, PARP1</td>
<td>X linkers</td>
<td>IR, ROS, Topo I inhibitors, alkylators</td>
<td>Alkylators</td>
<td>UV alkylators</td>
<td>X linkers, alkylators</td>
<td>Polymerase errors</td>
<td></td>
</tr>
<tr>
<td>Pathway</td>
<td>NHEJ</td>
<td>HR</td>
<td>altNHEJ, MMEJ</td>
<td>ICL repair</td>
<td>SSBR</td>
<td>BER</td>
<td>TLS</td>
<td>NER</td>
<td>MMR</td>
</tr>
<tr>
<td>Sensors</td>
<td>Ku70/80</td>
<td>MRN complex</td>
<td>PARP1</td>
<td>FA core (A,B,C,E,F,G,L,M)</td>
<td>PARP1</td>
<td>DNA glycosylases, APE1</td>
<td>PCNA</td>
<td>XPC, DDB2, CSA</td>
<td>MSH2, MSH3, MLH1, PM2</td>
</tr>
<tr>
<td>Signaling</td>
<td>DNAPK</td>
<td>ATR, ATM</td>
<td>MIK2, CIP1, BRC41/BARD1, BRC42, DSS1, PALB2, RPA</td>
<td>BRC42, FANCD2, FANCI, BRIP1, PALB2, RAD51C, SLX4</td>
<td>RAD6, RAD18</td>
<td>XPA, XPF, RPA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Effectors</td>
<td>XRCC4, XLF, LIG4, APLF, Artemis, PAXX, WRN</td>
<td>RAD51, MSH2/EME1, SLX1/SLX4, RT011, TOPOIII, POLQ, RECQL5, FANCJ, BLM</td>
<td>XRCC1, LIG3, LIG1, CIP, POLQ</td>
<td>Shared with HR, TLS and NER</td>
<td>XRCC1, PNKP, POLB, FEN1, TDPI, Aprataxin, LIG1, LIG3A</td>
<td>As for SSBR</td>
<td>REV1, POLH, POLI, POLK</td>
<td>XPG, ERCC1, POLF, POLD1, LIG1, LIG3</td>
<td>EXO1, POLD, LIG1</td>
</tr>
</tbody>
</table>

But in reality... A Complex Set of Molecular Interactions

- Homologous recombination (HR)
- Fanconi anaemia (FA)
- Non-homologous end joining (NHEJ)
- Base excision repair (BER)
- Nucleotide excision repair (NER)
- Mismatch repair (MMR)
- Telomere maintenance (TM)
- Translesion synthesis (TLS)
- Checkpoint factor (CPF)
- Ubiquitin response (UR)
- p53 pathway
- Chromatin remodelling (CR)
- Chromosome segregation (CS)
- Others or more than one


Defective DDR – A Curse, But Also a Blessing

Downregulation of the DDR facilitates tumorigenesis

- Key DDR component-coding genes – tumour suppressors
- BRCA1, BRCA2, MSH2, MLH1, FANC family gene, etc.
- Oncogenes induce considerable replication fork stress – eg, Myc, Cyclin E, etc.

Defective DDR – A Curse, But Also a Blessing

- Downregulation of the DDR is a therapeutic vulnerability in cancer
- DNA damaging chemotherapies
  - e.g., platinum salts exploit tumour specific defects in homologous recombination in serous ovarian cancer and nucleotide excision repair in non-small cell lung cancer
- Targeted agents that either target and/or exploit the DDR
  - PARP inhibitors, topo I and topo II inhibitors, ribonuclease reductase inhibitors


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Clinical PARPi Synthetic Lethality

Challenges

- Substantial fraction of BRCA1m, BRCA2m and BRCAness
- Approvals in ovarian cancer
- Breakthrough status in prostate cancer (To-PARP)
- PFS improvement in gBRCAm breast (OlympiAD)
- Clinical trials ongoing

Resistance in majority of patients
Unknown cause in most

How to delay resistance?
How to treat resistant disease?

Breast
Pancreatic
Prostate
Ovarian

How to use drug combinations with PARPi?
What are the predictive biomarkers of combination therapy?
Mechanisms of PARPi Resistance

**Resistance**

- Reversion/secondary mutations in key HR genes
  - Edwards, et al
  - Sakai, et al
  - Swisher, et al
- Restoration of DSB repair via loss of 53BP1, REV7 etc loss
  - Rottenberg, Jonkers, et al
- Stabilization of the replication fork
  - D’Andrea, et al
- Pharmacological resistance (eg, PgP)
  - Rottenberg, Jonkers, et al

Repair of stalled replication fork by BRCA1, BRCA2, PALB2 etc.

Cell survival

Ineffective repair

Cell death > synthetic lethality

Intragenic Deletions in BRCA2 that Restore the Open Reading Frame Cause PARPi Resistance

BRCA2 mutant

Olaparib exposure in vitro – secondary mutants

Mechanism now clinically validated in breast, ovarian and pancreatic cancer

Synthetic Lethal Resistance

BRCA | PARP | Survival | Synthetic lethality
---|---|---|---
✓ | ✓ | 2002 amino acids |
X | ✓ | 1973 amino acids |
✓ | X | 1950 amino acids |
X | X | 3265 amino acids |

Secondary mutation in BRCA allele

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Exploiting Combinations to Enhance Responses?

PARP

Platinum salts
GEM
Top1 poisons
Top2i/poisons
Radiation
CHK1/2i
CDKi
METi

Taxanes
EGFRi
VEGFR1i
PI3K/m TORi
HSP90i
Trastuzumab
Anti-endocrine

PARP1 trapping
Accumulation of DNA Damage
PARP dependency for repair

Induce BRCA1/2 phenotype

PARPi discrimination between potent PARP trappers and PARP catalytic inhibitors
Identification of combinatorial biomarkers to predict tumor sensitivity
Dose-limiting toxicities caused by combinations not observed in single agent setting
Combinations of PARPi with non-DNA damaging agents (e.g. targeted therapies)
Using combinations to targeting PARPi resistant mechanisms
Using PARPi combinations to enhance mutational load prior to immunotherapy

Challenges

Opportunities


Evidence for cross talk between the DDR and immune system
Evidence for DDR inhibitors influencing immune checkpoint therapy responses
Early clinical trial data
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Crosstalk Between the DDR and Immune System:
*Mutational Burden and Neoepitopes*

**Mutational Burden: A Molecular Determinant of Response**

- **Highest prevalence of somatic mutations**
- **Highest benefit from immune checkpoint inhibitors**


Crosstalk Between the DDR and Immune System:
*Mutational Burden and Neoepitopes*

In responders showing the highest mutational burden:
- Mutations in POLD1, POLE (replication, DDR)
- Mutations in MSH2 (MMR)
- Mutations in BRCA2, RAD51C (HR)

**Crosstalk Between the DDR and Immune System: Intratumor Heterogeneity**

- Non-responders
- With high neoantigen load
- High ITH


**Paradoxical Functions of DNA Repair**

- DNA repair inhibitors
- DNA repair defects
  - Mutational Load
  - Neoantigen Load
  - Tumour immunogenicity
  - ITH
  - Neoantigen clonality
  - Tumour immunogenicity
  - Improved response
  - Better outcome
  - Reduced response
  - Poorer outcome
  - Anti PD-(L)1

Courtesy: Dr. Sophie Postal-Vinay, IGR, Paris
Combinations with Immunotherapy?
CTLA-4 Blockade Synergizes Therapeutically with PARP Inhibition in BRCA1-Deficient Ovarian Cancer

BR5-Akt, BRCA1− Mouse ovarian tumour cell graft
CTLA-4 mAb = UC10-4F10-1
PARP inhibitor = veliparib

- No effect in BRCA1 wild-type tumours
- Adoptive transfer of splenocyte prevents tumour formation

Combinations with Immunotherapy?
CTLA-4 Blockade Synergizes Therapeutically with PARP Inhibition in BRCA1-Deficient Ovarian Cancer

BR5-Akt, BRCA1− Mouse ovarian tumour cell graft
CTLA-4 mAb: UC10-4F10-1; PARP inhibitor: veliparib; PD-1 mAb: clone C1-G4; PD-L1: B7-H1, clone 10B5

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Combinations with Immunotherapy?

CTLA-4 Blockade Synergizes Therapeutically with PARP Inhibition in BRCA1-Deficient Ovarian Cancer


BR5-Akt, BRCA1− Mouse ovarian tumour cell graft
Combination = PARPi (veliparib) + CTLA-4 (UC10-4F10-1)

Ongoing Studies

<table>
<thead>
<tr>
<th>DDRi</th>
<th>Target</th>
<th>ICB</th>
<th>Target</th>
<th>Phase</th>
<th>Tumor Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olaparib</td>
<td>PARP1/2</td>
<td>Tremelimumab</td>
<td>CTLA-4</td>
<td>I/II</td>
<td>BRCA-mut OC</td>
</tr>
<tr>
<td>Veliparib</td>
<td>PARP1/2</td>
<td>Atezolizumab</td>
<td>PD-L1</td>
<td>II</td>
<td>BRCA-mut TNBC</td>
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<tr>
<td>Olaparib</td>
<td>PARP1/2</td>
<td>Durvalumab</td>
<td>PD-L1</td>
<td>I/II</td>
<td>SCLC</td>
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<tr>
<td></td>
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<td></td>
<td></td>
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<td>BRCA-mut OC</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>BRCA-mut BC</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Gastric cancer</td>
</tr>
<tr>
<td>Niraparib</td>
<td>PARP1/2</td>
<td>Pembrolizumab</td>
<td>PD-1</td>
<td>I/II</td>
<td>TBNC</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>OC</td>
</tr>
<tr>
<td>BGB-290</td>
<td>PARP1/2</td>
<td>BGB-A317</td>
<td>PD-1</td>
<td>I</td>
<td>Solid tumors</td>
</tr>
<tr>
<td>Olaparib</td>
<td>PARP1/2</td>
<td>Tremelimumab</td>
<td>CTLA-4 + PD-L1</td>
<td>I/II</td>
<td>BRCA-mutant OC</td>
</tr>
<tr>
<td>AZD6738</td>
<td>ATR</td>
<td>Durvalumab</td>
<td>PD-L1</td>
<td>I/II</td>
<td>Solid tumors</td>
</tr>
</tbody>
</table>

Clinicaltrials.gov

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AZD6738 + Durva 1500 mg Q2W

**Patient demographics (n=12)**

| Age          | Mean: 58.1  
|             | Range: 33-71 |
| Sex         | Female: 1 (8.3%)  
|             | Male: 11 (91.7%)  |
| ECOG PS     | 0: 4 (33%)  
|             | 1: 8 (67%)  |

**Tumour types (n=12)**

| Tumour   | NSCLC (6)  
|          | SCCHN (6)  |

80mg BD 14 day C0 run-in then 80mg BD D22-28
NSCLC (n=5) and SCCHN (n=4)
Tolerated

160mg BD 14 day C0 run-in then 160mg BD D22-28
NSCLC (n=1) and SCCHN (n=2)
Tolerated

Optimisation ongoing
160mg BD 14 day C0 run-in then 160mg BD D15-28


Clinical Responses

**Best RECIST Responses**

- 1 confirmed RECIST PR in SCCHN
- 1 confirmed RECIST CR in NSCLC
- PD-L1 status unknown
- 80 mg BD 14 day C0 run-in then 80 mg BD D22-28

59 year old male
Metastatic NSCLC (adenocarcinoma)
EGFR dual exon 20 non-sensitizing S768I and V679L mutations; ALK neg; KRAS WT
Prior therapies: cisplatin/vinorelbine; pemetrexed

**Post cycle 6: RECIST CR**

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Current Data and Future Prospects of PARP Inhibitors in Patients with Ovarian & Breast Cancers

Ursula Matulonis, MD
Director and Program Leader
Gynecologic Oncology Program
Dana-Farber Cancer Institute
Professor of Medicine
Harvard Medical School
Boston, MA

Classification of Ovarian Cancer is Evolving to Include Molecular Data

<table>
<thead>
<tr>
<th></th>
<th>High grade serous or endometrioid</th>
<th>Low grade endometrioid</th>
<th>Low grade serous</th>
<th>Clear Cell</th>
<th>Mucinous</th>
</tr>
</thead>
</table>
| Genetic
characteristics | Up to 50% with alterations in HR Associated with TP53 and BRCA mutations | **PTEN, ARID1A, PIK3CA** alterations | KRAS, BRAF mutations | **PIK3CA, ARID1A, PTEN** | KRAS |
| Clinical
characteristics | Increased plat-sensitivity PARP inhibitors with potential activity in HRD tumors | Potentially more responsive to hormonal therapy, although not established | Hormonal therapies Potentially MEK inhibitors | Often resistant to initial plat-based therapy; Targeted or immuno-oncology agents being explored | Often chemotherapy-insensitive |
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Classification of Ovarian Cancer is Evolving to Include Molecular Data

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<th>Mucinous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Up to 50% with alterations in HR</td>
<td>PTEN, ARID1A, PIK3CA alterations, May have MSI</td>
<td>KRAS, BRAF mutations</td>
<td>PIK3CA, ARID1A, PTEN</td>
<td>KRAS</td>
<td></td>
</tr>
<tr>
<td>Associated with TP53 and BRCA mutations</td>
<td>May have MSI</td>
<td>Potentially more responsive to hormonal therapy, although not established</td>
<td>Potentially MEK inhibitors</td>
<td>Often resistant to initial plat-based therapy; Targeted or immuno-oncology agents being explored</td>
<td>Often chemotherapy-insensitive</td>
</tr>
</tbody>
</table>

Clinical characteristics

- Increased plat-sensitivity to PARP inhibitors with potential activity in HRD tumors
- Potentially more responsive to hormonal therapy, although not established
- Hormonal therapies
- Potentially MEK inhibitors
- Often resistant to initial plat-based therapy; Targeted or immuno-oncology agents being explored
- Often chemotherapy-insensitive


Chemical Structure of PARP Inhibitors That are in Clinical Trials for Ovarian & Breast Cancer

- Rucaparib
- Veliparib
- Olaparib
- Niraparib

### Differences in Metabolism and DDI Exist Amongst PARP Inhibitors Used in Ovarian & Breast Cancer

<table>
<thead>
<tr>
<th>PARP inhibitor</th>
<th>CYP Enzymes Used for Metabolism</th>
<th>Drug Drug Interactions</th>
<th>Effect on Cell Transporters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rucaparib¹</td>
<td>• CYP2D6 (predominant)</td>
<td>Reversibly inhibits CYP1A2, CYP2C19, CYP2C9, CYP3A4 Induces CYP1A2</td>
<td>• Inhibits MATE1 and MATE2-K, OCT1</td>
</tr>
<tr>
<td>Olaparib¹</td>
<td>• CYP3A4*</td>
<td>Inhibits CYP3A4 and induces CYP2B6</td>
<td>• Inhibits MDR1, BCRP, OATP1B1, OCT1, OCT2, OAT3, MATE1, MATE2-K</td>
</tr>
<tr>
<td>Niraparib¹</td>
<td>• Carboxylesterases (non-CYP)</td>
<td>Can induce CYP1A2 (weak)</td>
<td>• No interaction with the major hepatic or renal uptake transporters</td>
</tr>
<tr>
<td>Veliparib²</td>
<td>• CYP2D6 as the major enzyme metabolizing veliparib with minor contributions from CYP1A2, 2C19, and 3A4³</td>
<td>Veliparib did not inhibit or induce the activities of major human P450s</td>
<td>• Inhibits MATE1, MATE2-K, OCT2, OCT1, OCT3</td>
</tr>
</tbody>
</table>


### Initial Single Agent Studies Showing Activity of PARP Inhibitors in Advanced Ovarian Cancer

<table>
<thead>
<tr>
<th>Trial</th>
<th>PARP Inhibitor</th>
<th>Dosing</th>
<th>Trial Population Characteristics</th>
<th>Key Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Audeh MW, et al. Lancet. 2010.</td>
<td>Olaparib</td>
<td>400 mg po BID 100 mg po BID</td>
<td>• Plat-sens or -res</td>
<td>ORR: 33% (400 mg); 13% (100 mg)</td>
</tr>
<tr>
<td>Kaye SB, et al. J Clin Oncol. 2012.</td>
<td>Olaparib</td>
<td>400 mg po BID 200 mg po BID PLD 50 mg/m²</td>
<td>• &lt;12mo PFI</td>
<td>ORR: 31% (400 mg); 25% (200 mg); 18% (PLD) PFS: 8.8 mo (400 mg); 6.5 mo (200 mg); 7.1 mo (PLD)</td>
</tr>
<tr>
<td>Gelmon KA, et al. Lancet Oncol. 2011.</td>
<td>Olaparib</td>
<td>400 mg po BID</td>
<td>• Plat-sens or -res</td>
<td>ORR: 41% BRCAm and 24% wt pts</td>
</tr>
<tr>
<td>Swisher EM, et al. (ARIEL2) Lancet Oncol. 2017.</td>
<td>Rucaparib</td>
<td>600 mg po BID</td>
<td>• Plat-sens</td>
<td>ORR: 80% (BRCAC), 29% (LOH+), 33% (LOH-) PFS: 12.8 mo (BRCAC), 5.7 mo (LOH+) and 5.2 mo (LOH-)</td>
</tr>
</tbody>
</table>
### Key Initial Single Agent Studies Showing Activity of PARP Inhibitors in Advanced Breast Cancer

<table>
<thead>
<tr>
<th>Trial</th>
<th>PARP Inhibitor</th>
<th>Dosing</th>
<th>Trial Population Characteristics</th>
<th>Key Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tutt A, et al. Lancet Oncol. 2010.</td>
<td>Olaparib</td>
<td>400 mg po BID</td>
<td>• BRCAm cancer; median of 3 prior therapies; all histologies</td>
<td>ORR: 41% (400 mg); 22% (100 mg)</td>
</tr>
<tr>
<td>Gelmon KA, et al. Lancet Oncol. 2011.</td>
<td>Olaparib</td>
<td>400 mg po BID</td>
<td>• Both BRCAm (8) and BRCAwt (15) 23 evaluable pts</td>
<td>ORR: 0% responses in both groups</td>
</tr>
<tr>
<td>Kaufman B, et al. J Clin Oncol. 2015.</td>
<td>Olaparib</td>
<td>400 mg po BID</td>
<td>• BRCAm (62 pts)</td>
<td>ORR: 13% PRs</td>
</tr>
<tr>
<td>DeBono J, et al. Cancer Discov. 2017.</td>
<td>Talazoparib</td>
<td>Phase I dose escalation</td>
<td>• BRCAm (14 pts)</td>
<td>ORR: 50%</td>
</tr>
<tr>
<td>Somlo G, et al. Clin Cancer Res. 2017.</td>
<td>Veliparib</td>
<td>400 mg po BID</td>
<td>• BRCA1 (22pts) • BRCA2 (22 pts)</td>
<td>ORR: BRCA1 14% BRCA2 36%</td>
</tr>
</tbody>
</table>

### Key Ongoing Studies of PARP Inhibitors in Advanced Breast Cancer

<table>
<thead>
<tr>
<th>Trial</th>
<th>PARP Inhibitor</th>
<th>Trial Design</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>OlympiAD¹ NCT02000622</td>
<td>Olaparib</td>
<td>• gBRCAmut+, HER2- • PARPi vs. MD’s choice of chemotherapy</td>
<td>Olaparib showed statistically significant PFS improvement vs. chemo (cape, vinorelbine, or eribulin)²</td>
</tr>
<tr>
<td>BRAVO¹ NCT01905592</td>
<td>Niraparib</td>
<td>• gBRCAmut+, HER2- • PARPi vs. MD’s choice of chemotherapy</td>
<td>Not reported</td>
</tr>
<tr>
<td>EMBRACA² NCT01945775</td>
<td>Talazoparib</td>
<td>• gBRCAmut+ • PARPi vs. MD’s choice of chemotherapy</td>
<td>Not reported</td>
</tr>
<tr>
<td>NCT02163694²</td>
<td>Veliparib</td>
<td>• gBRCAmut+ • Carboplatin &amp; paclitaxel +/- veliparib</td>
<td>Not reported</td>
</tr>
<tr>
<td>OLYMPIA study¹ NCT02032823</td>
<td>Olaparib</td>
<td>• gBRCAmut+, HER2- • Olaparib vs. placebo post initial treatment</td>
<td>Not reported</td>
</tr>
</tbody>
</table>

PARP Inhibitor Monotherapy: 
FDA Approved for Ovarian Cancer

<table>
<thead>
<tr>
<th>PARP inhibitor</th>
<th># of prior lines</th>
<th>Biomarker</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olaparib</td>
<td>3</td>
<td>gBRCAm</td>
</tr>
<tr>
<td>Rucaparib</td>
<td>2</td>
<td>gBRCAm and somatic (tumor) BRCAm</td>
</tr>
<tr>
<td>Niraparib</td>
<td>Post-platinum maintenance</td>
<td>None</td>
</tr>
</tbody>
</table>

FDA Prescribing Information.

Comparison of Patient Populations and Activity in Different Data Sets; All BRCAm Ovarian Cancers

<table>
<thead>
<tr>
<th></th>
<th>Olaparib(^1)</th>
<th>Rucaparib(^2)</th>
<th>Niraparib(^3)</th>
<th>Veliparib(^4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of pts</td>
<td>137</td>
<td>106</td>
<td>20</td>
<td>50</td>
</tr>
<tr>
<td># of lines of prior therapy</td>
<td>At least 3 prior lines</td>
<td>At least 2 prior lines (43% had 3 or more)</td>
<td>N/A</td>
<td>1 prior: 32% 2 or 3: 68%</td>
</tr>
<tr>
<td>Objective RECIST RR</td>
<td>34%</td>
<td>54% (IRR 42%)</td>
<td>40%</td>
<td>26%</td>
</tr>
<tr>
<td>RR based on platinum sensitivity</td>
<td>N/A for this population; other data available</td>
<td>Plat sens 66% Plat resis 25% plat refrac 0%</td>
<td>Plat sens 50% Plat resis 33% Plat refrac 0%</td>
<td>Plat sens 35% Plat resis 20%</td>
</tr>
<tr>
<td>Median Duration of Response</td>
<td>7.9 months (IRR 6.7 months)</td>
<td>9.2 months (IRR 6.7 months)</td>
<td>12.9 months</td>
<td>8.18 (reported as median PFS)</td>
</tr>
</tbody>
</table>

Do Somatic or Tumor BRCA Mutations Predict Response to a PARP Inhibitor like Germline BRCA Mutations Do?

- Yes!
- ARIEL2\(^1\) demonstrated similar ORR in somatic/tumor BRCA (tBRCA) and germline BRCA cancers
- NOVA\(^2\) and Study 19\(^3\) data showed similar efficacy of niraparib and olaparib in both gBRCA and tBRCA ovarian cancers

### Predictors of Activity of Single Agent PARP Inhibitor Response

1. **BRCA mutations**: ~20% of high grade serous cancers have a **BRCA** mutation
2. Level of platinum sensitivity
3. Number of prior lines of treatment
4. Histology: High grade serous

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### Pooled gBRCA pts Treated with Olaparib: Gradual Decline in ORR with Increasing Lines of Chemotherapy Received

![Graph showing ORR vs. Previous Lines of Chemotherapy Received]


### Maintenance Therapy

- Use a PARP inhibitor following response to platinum-based chemotherapy
- Strategy of maintenance studies:
  1. Distill “ideal” patients into DDR-based therapy-responsive situation:
     - Platinum sensitive
     - High grade serous histology
     - +/-BRCAm positive cancers
  2. Avoids need to combine PARP inhibitor with chemotherapy
  3. Unmet need, though bev recently approved here (platinum doublet + bev, then bev maintenance)
- Study 19 was first study to show benefit of PARP inhibitor maintenance, esp BRCAm ovarian cancer; led to EMA approval in 2014.

ENGOT-OV16/NOVA (Niraparib) Trial Overview

**KEY INCLUSION CRITERIA**
- Histologically diagnosed ovarian cancer
  - Predominantly high-grade serous
- Completed at least two previous courses of platinum-containing therapy
- Platinum-sensitive to the penultimate platinum regimen, and remain in response to platinum

**KEY EXCLUSION CRITERIA**
- Invasive cancer other than ovarian cancer within 2 years
- Symptomatic uncontrolled brain metastasis
- Prior treatment with a known PARP inhibitor

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**ENGOT-OV16/NOVA (Niraparib) Trial Overview**

Platinum-Sensitive Recurrent High-Grade Serous Ovarian Cancer treated with at least 4 cycles of platinum-based therapy

Response to Platinum Treatment

- gBRCA\text{mut}
  - Niraparib 300 mg once daily
  - Placebo
  - Treat until Progression of Disease
- Non-gBRCA\text{mut}
  - Niraparib 300 mg once daily
  - Placebo
  - Treat until Progression of Disease

Primary Endpoint: PFS by central, blinded review: results for both gBRCA and non-gBRCA groups analyzed simultaneously

Performed at 100 events to achieve 90% power and detect HR=0.50

- HRD\text{pos} population
  - Tested at 100 events to achieve 90% power when HR=0.50. If result was positive then:
  - Test overall non-gBRCA\text{mut} cohort (P<.05)


CEC Oncology 2017
NOVA Patient Demographics & Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>gBRCAmut (N=138)</th>
<th>Non-gBRCAmut (N=234)</th>
<th>Non-gBRCAmut (N=116)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age - years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (min, max)</td>
<td>57.0 (36, 83)</td>
<td>63.0 (33, 84)</td>
<td>60.5 (34, 82)</td>
</tr>
<tr>
<td>Region - n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>USA and Canada</td>
<td>53 (38.4)</td>
<td>96 (41.0)</td>
<td>44 (37.9)</td>
</tr>
<tr>
<td>Europe and Israel</td>
<td>85 (61.6)</td>
<td>138 (59.0)</td>
<td>72 (62.1)</td>
</tr>
<tr>
<td>ECOb performance status - n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>91 (65.9)</td>
<td>160 (68.4)</td>
<td>78 (67.2)</td>
</tr>
<tr>
<td>1</td>
<td>47 (34.1)</td>
<td>74 (31.6)</td>
<td>38 (32.8)</td>
</tr>
<tr>
<td>Primary tumor site – n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ovarian</td>
<td>122 (88.4)</td>
<td>192 (82.1)</td>
<td>96 (82.8)</td>
</tr>
<tr>
<td>Primary peritoneal</td>
<td>7 (5.1)</td>
<td>24 (10.3)</td>
<td>8 (6.9)</td>
</tr>
<tr>
<td>Fallopian tube</td>
<td>9 (6.5)</td>
<td>18 (7.7)</td>
<td>11 (9.5)</td>
</tr>
<tr>
<td>Lines of previous chemotherapy* – n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>70 (50.7)</td>
<td>155 (66.2)</td>
<td>77 (66.4)</td>
</tr>
<tr>
<td>≥3</td>
<td>67 (48.6)</td>
<td>79 (33.8)</td>
<td>38 (32.8)</td>
</tr>
</tbody>
</table>

*One patient received one line of prior therapy.

NOVA Study (Niraparib) Results

Primary Efficacy Populations

<table>
<thead>
<tr>
<th></th>
<th>gBRCAmut HRDpos</th>
<th>Non-gBRCAmut HRDpos</th>
<th>Non-gBRCAmut Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS (months)</td>
<td>HR=0.27</td>
<td>HR=0.38</td>
<td>HR=0.45</td>
</tr>
<tr>
<td>Niraparib: 21</td>
<td>Niraparib: 12.9</td>
<td>Niraparib: 9.3</td>
<td></td>
</tr>
<tr>
<td>Placebo: 5.5</td>
<td>Placebo: 3.8</td>
<td>Placebo: 3.9</td>
<td></td>
</tr>
</tbody>
</table>

NOVA Study (Niraparib) Results

**Exploratory Analysis**

<table>
<thead>
<tr>
<th></th>
<th>sBRCAmut</th>
<th>BRCAwt</th>
<th>HRD Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BRCA mut</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR=0.27</td>
<td></td>
<td></td>
<td>HR=0.58</td>
</tr>
<tr>
<td>Niraparib: 20.9</td>
<td></td>
<td></td>
<td>Niraparib: 6.9</td>
</tr>
<tr>
<td>Placebo: 11</td>
<td></td>
<td></td>
<td>Placebo: 3.8</td>
</tr>
<tr>
<td><strong>BRCA wt</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR=0.38</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Niraparib: 9.3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo: 3.7</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Median PFS (months)

- **HRD Positive**
  - Niraparib: 20.9
  - Placebo: 11
  - HR=0.27

- **HRD Negative**
  - Niraparib: 9.3
  - Placebo: 3.7
  - HR=0.38

- **HRD Negative**
  - Niraparib: 6.9
  - Placebo: 3.8
  - HR=0.58

**NOVA Patient-reported Outcomes**

- **Measured using the Functional Assessment of Cancer Therapy – Ovarian Symptom Index (FOSI) and the EQ-5D-5L**
- **PRO surveys were collected at:**
  - Screening visit
  - Every other cycle through cycle 14
  - Post progression
- **Compliance rates were high, and similar between the two treatment arms**
  - Niraparib: FOSI completion rate ranged from 75.0% to 97.1%
  - Placebo: FOSI completion rate ranged from 77.6% to 97.4%
- **PROs were similar for niraparib compared with placebo**

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FDA Approval for Niraparib: March 27, 2017

Niraparib is a poly(ADP-ribose) polymerase (PARP) inhibitor indicated for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy.

https://www.fda.gov/Drugs/InformationOnDrugs/%20ApprovedDrugs/ucm548487.htm

SOLO2/ENGOT-OV21 (Olaparib): Study Design

Patients
• *BRCA1/2* mutation
• Platinum-sensitive relapsed ovarian cancer
• At least 2 prior lines of platinum therapy
• CR or PR to most recent platinum therapy

Randomized 2:1

CR, complete response; PR, partial response

Olaparib
300 mg BID
n=196

Placebo
n=99

SOLO2/ENGOT-OV21 (Olaparib): Study Design

Patients
- BRCA1/2 mutation
- Platinum-sensitive relapsed ovarian cancer
- At least 2 prior lines of platinum therapy
- CR or PR to most recent platinum therapy

CR, complete response; PR, partial response

Randomized 2:1

CR, complete response; PR, partial response

Primary endpoint
Investigator-assessed PFS

Olaparib 300 mg BID n=196

Placebo n=99

Sensitivity analysis: PFS by blinded independent central review (BICR)
- Key secondary endpoints:
  - Time to first subsequent therapy or death (TFST), time to second progression (PFS2), time to second subsequent therapy or death (TSST), overall survival (OS)
  - Safety, health-related quality of life (HRQoL*)

*Primary endpoint for HRQoL was trial outcome index (TOI) of the FACT-O (Functional Assessment of Cancer Therapy – Ovarian)

SOLO2/ENGOT-OV21 (Olaparib): Demographics & Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Olaparib (n=196)</th>
<th>Placebo (n=99)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range)</td>
<td>56 (28–83)</td>
<td>56 (39–78)</td>
</tr>
<tr>
<td>Primary tumor type, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ovarian</td>
<td>162 (82.7)</td>
<td>86 (86.9)</td>
</tr>
<tr>
<td>Fallopian tube or primary peritoneal</td>
<td>31 (15.8)</td>
<td>13 (13.1)</td>
</tr>
<tr>
<td>Other/missing</td>
<td>3 (1.5)</td>
<td>0</td>
</tr>
<tr>
<td>Prior platinum regimens, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 lines</td>
<td>110 (56.1)</td>
<td>62 (62.6)</td>
</tr>
<tr>
<td>3 lines</td>
<td>60 (30.6)</td>
<td>20 (20.2)</td>
</tr>
<tr>
<td>≥4 lines</td>
<td>25 (12.8)</td>
<td>17 (17.2)</td>
</tr>
<tr>
<td>Platinum-free interval, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6–12 months</td>
<td>79 (40.3)</td>
<td>40 (40.4)</td>
</tr>
<tr>
<td>&gt;12 months</td>
<td>117 (59.7)</td>
<td>59 (59.6)</td>
</tr>
<tr>
<td>Response to platinum therapy, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>91 (46.4)</td>
<td>47 (47.5)</td>
</tr>
<tr>
<td>Partial response</td>
<td>105 (53.6)</td>
<td>52 (52.5)</td>
</tr>
</tbody>
</table>


SOLO2/ENGOT-OV21 (Olaparib): PFS by Investigator Assessment

<table>
<thead>
<tr>
<th></th>
<th>Olaparib (n=196)</th>
<th>Placebo (n=99)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median PFS, months</td>
<td>19.1</td>
<td>5.5</td>
</tr>
</tbody>
</table>

Granted priority review by FDA on March 28, 2017

No. at risk

<table>
<thead>
<tr>
<th>Olaparib</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>196</td>
<td>99</td>
</tr>
<tr>
<td>182</td>
<td>70</td>
</tr>
<tr>
<td>156</td>
<td>37</td>
</tr>
<tr>
<td>134</td>
<td>22</td>
</tr>
<tr>
<td>118</td>
<td>18</td>
</tr>
<tr>
<td>104</td>
<td>17</td>
</tr>
<tr>
<td>89</td>
<td>14</td>
</tr>
<tr>
<td>82</td>
<td>12</td>
</tr>
<tr>
<td>92</td>
<td>8</td>
</tr>
<tr>
<td>32</td>
<td>7</td>
</tr>
<tr>
<td>29</td>
<td>6</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
</tr>
</tbody>
</table>

Median follow-up was 22.1 months in the olaparib group and 22.2 months for placebo

## Maintenance Therapy: Phase III

<table>
<thead>
<tr>
<th>Study</th>
<th># of total pts</th>
<th># of BRCAm pts</th>
<th>Median PFS for gBRCA group: PARPi</th>
<th>Median PFS for gBRCA group: Placebo</th>
<th>HR for PFS</th>
<th>Grade 3/4 Anemia</th>
<th>Grade 3/4 Plts</th>
<th>Pts who dose discontinued because of AE</th>
</tr>
</thead>
<tbody>
<tr>
<td>NOVA¹</td>
<td>553</td>
<td>203</td>
<td>21 mo</td>
<td>5.5 mo</td>
<td>0.27</td>
<td>25.3%</td>
<td>33.8%</td>
<td>3.3% plts² 1.4% anemia² 3.3% fatigue²</td>
</tr>
<tr>
<td>SOLO²²</td>
<td>295</td>
<td>295</td>
<td>19.1 mo</td>
<td>5.5 mo</td>
<td>0.30</td>
<td>19.5%</td>
<td>1.0%</td>
<td>10.8%</td>
</tr>
<tr>
<td>ARIEL 3</td>
<td>pending</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


## Ongoing Studies for Newly Diagnosed Ovarian Cancer that Include a PARP Inhibitor

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Arms</th>
<th>CT.gov #</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SOLO1</strong></td>
<td>Olaparib maintenance</td>
<td>NCT01844986</td>
</tr>
<tr>
<td><em>(BRCAm only)</em></td>
<td>Placebo maintenance</td>
<td></td>
</tr>
<tr>
<td>N=397</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>GOG 3005</strong></td>
<td>Carboplatin/paclitaxel/placebo + placebo maintenance</td>
<td>NCT02470585</td>
</tr>
<tr>
<td><em>(BRCAm and wild-type)</em></td>
<td>Carboplatin/paclitaxel + veliparib + placebo maintenance</td>
<td></td>
</tr>
<tr>
<td>N=1100</td>
<td>Carboplatin/paclitaxel + veliparib + veliparib maintenance</td>
<td></td>
</tr>
<tr>
<td><strong>PAOLA1</strong></td>
<td>Plat/taxane chemotherapy/bev, then bev/placebo maintenance</td>
<td>NCT02477644</td>
</tr>
<tr>
<td>N=612</td>
<td>Plat/taxane chemotherapy/bev, then bev/olaparib maintenance</td>
<td></td>
</tr>
<tr>
<td><strong>PRIMA</strong></td>
<td>Niraparib maintenance</td>
<td>NCT02655016</td>
</tr>
<tr>
<td><em>(BRCAm and wild-type)</em></td>
<td>Placebo maintenance</td>
<td></td>
</tr>
<tr>
<td>N=330</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Clinicaltrials.gov
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Single Agent PARP Inhibitors Compared to Chemotherapy (Phase 3 Studies)

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Arms</th>
<th>CT.gov #</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOLO3</td>
<td>Olaparib</td>
<td>NCT02282020</td>
</tr>
<tr>
<td>(BRCAm)</td>
<td>Single agent chemotherapy</td>
<td></td>
</tr>
<tr>
<td>N=411</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARIEL4</td>
<td>Rucaparib</td>
<td>NCT02855944</td>
</tr>
<tr>
<td>(BRCAm)</td>
<td>Platinum-based chemotherapy or single agent platinum or paclitaxel</td>
<td></td>
</tr>
<tr>
<td>N=345</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Clinicaltrials.gov

Beyond Single Agent Strategies: Combinations

- Increase anti-cancer activity in non-BRCA cancers and possibly BRCAm cancers that might not respond well to single agent PARP inhibitors
- PARP inhibitor combinations:
  Anti-angiogenics¹

### PARP Inhibitor Combinations

<table>
<thead>
<tr>
<th>Antiangiogenics</th>
<th>Clinicaltrials.gov</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olaparib and cediranib (GY004, GY005, etc)</td>
<td>NCT02889900</td>
</tr>
<tr>
<td>Olaparib and bevacizumab (PAOLA-1)</td>
<td>NCT02477644</td>
</tr>
<tr>
<td>Niraparib and bevacizumab (AVANOVA)</td>
<td>NCT02354131</td>
</tr>
</tbody>
</table>

### PARP Inhibitor Combinations

<table>
<thead>
<tr>
<th>Antiangiogenics</th>
<th>Clinicaltrials.gov</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olaparib and cediranib (GY004, GY005, etc)</td>
<td>NCT02889900</td>
</tr>
<tr>
<td>Olaparib and bevacizumab (PAOLA-1)</td>
<td>NCT02477644</td>
</tr>
<tr>
<td>Niraparib and bevacizumab (AVANOVA)</td>
<td>NCT02354131</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Immuno-oncology agents</th>
<th>Clinicaltrials.gov</th>
</tr>
</thead>
<tbody>
<tr>
<td>Niraparib and pembrolizumab (TOPACIO)</td>
<td>NCT02657889</td>
</tr>
<tr>
<td>Olaparib and tremelimumab</td>
<td>NCT02485990/NCT02571725</td>
</tr>
<tr>
<td>Olaparib and durvalumab (MEDIOLA)</td>
<td>NCT02734004</td>
</tr>
<tr>
<td>Olaparib/durvalumab/tremelimumab</td>
<td>NCT02953457</td>
</tr>
<tr>
<td>Olaparib/durvalumab/cediranib</td>
<td>NCT02484404</td>
</tr>
</tbody>
</table>
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PARP Inhibitor Combinations

<table>
<thead>
<tr>
<th>Others</th>
<th>Clinicaltrials.gov</th>
</tr>
</thead>
<tbody>
<tr>
<td>Veliparib and VX970 (ATR inhibitor)</td>
<td>NCT02723864</td>
</tr>
<tr>
<td>Olaparib and AZD1775 (Wee1 inhibitor)</td>
<td>NCT02511795</td>
</tr>
<tr>
<td>Olaparib and BKM120 or BYL719 (PI3K inhibitor)</td>
<td>NCT01623349</td>
</tr>
<tr>
<td>Olaparib and AZD2014 (mTORC 1/2 inhibitor) or AZD5363 (AKT inhibitor)</td>
<td>NCT02208375</td>
</tr>
<tr>
<td>Olaparib and AT13387 (HSP90 inhibitor)</td>
<td>NCT02898207</td>
</tr>
<tr>
<td>Olaparib and prexasertib (Chk1 inhibitor)</td>
<td>NCT03057145</td>
</tr>
</tbody>
</table>

Combination Studies: Phase III NCI-sponsored Olaparib and Cediranib Studies in Recurrent Ovarian Cancer

- **NRG-GY004 (platinum sensitive)**
  Olaparib vs olaparib/cediranib vs platinum doublet (NCT02446600)

- **NRG-GY005 (platinum resistant)**
  Olaparib (or cediranib) vs olaparib/cediranib vs single agent chemotherapy (NCT02502266)
Conclusions: Some Critical Future Questions

- How to decide between a single agent PARP inhibitor versus a combination for both BRCAm as well as BRCAwt cancers?
- Which combinations are best?
  - Pre-clinical testing necessary?
  - Registration necessary?
- What are treatment strategies following progression on single agent PARP inhibitor versus combination?

Concluding Thoughts

- PARP inhibitors are the most exciting new class of agent for the treatment of potentially all aspects of ovarian cancer.
- PARP inhibitor combination testing is underway from phase I thru III studies.
- PARP inhibitor resistance will need to be studied clinically since post-treatment strategies will need to be defined.
PARP Inhibitors and Prostate Cancer

Johann S. de Bono, MB ChB, FRCP, MSc, PhD
Professor of Experimental Cancer Medicine
The Institute of Cancer Research and Royal Marsden
London, United Kingdom

Talk Overview

• Where will DDR take us?
• Targeting PARP in lethal prostate cancer
• Conclusions

CRPC=castrate-resistant prostate cancer; PARP=poly ADP ribose polymerase
Where will the use of drugs targeting DDR take us?

- PARP inhibitors will have clinical utility in other tumour types
  - **Lethal prostate cancers; other cancers**
- PARP inhibitors will have anti-tumour activity against cancers with DNA repair defects other than *BRCA1/2* loss of function
- PARP inhibitor rational drug combinations will have clinical utility
  - With established drugs (DNA damaging agents); novel-novel agents (ATR; ATM; DNA-PK)
  - Radiation therapy including radionuclides (radioimmunoconjugates?)
- DNA repair defects and mutational load
  - Immunotherapy and immunotherapy combinations
  - Can we increase mutational load by inhibiting DNA repair?
- Other synthetic lethal interactions will have clinical utility

A Common Challenge for PARP Inhibitors:

**DNA Repair Pathway Complexity**

Loss of many DNA repair proteins can generate the same phenotype of BRCA*ness*
**Talk Overview**

- Where will DDR take us?
- Targeting PARP in lethal prostate cancer
- Conclusions

**Key Supporting Clinical Data**

- Durable and important antitumour activity in *BRCA* carrier cancer patients with ovarian, breast and prostate cancers
  - *BRCA* carrier prostate cancers have worse prognosis
- Antitumour activity in sporadic cancers with somatic cell biallelic loss of key DNA repair genes
- Antitumour activity of niraparib in sporadic CRPC
- Cross-resistance of olaparib with platinum, with platinum having antitumour activity (30% RR) in CRPC but not utilized

"Rosetta Stone" of CRPC

90% of metastatic CRPC have ‘actionable genomic aberrations’

Integrative Clinical Genomics of Advanced Prostate Cancer


CRPC “Rosetta Stone”:
150 CRPC exomes/transcriptomes

TARGETING DNA DAMAGE RESPONSE  
At the Forefront of Emerging Concepts and Strategies

DNA Repair Pathway Aberrations (23%)

- >10% of mCRPC patients have germline aberrations of DNA repair genes
- >700 mCRPC patients’ germline DNA sequenced (manuscript under review, 2016)

Hypothesis 2009-2015

- A molecular subclass of prostate cancers have DNA repair defects that render them vulnerable to synthetic lethal therapeutic strategies utilizing PARP inhibition

TARGETING DNA DAMAGE RESPONSE
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Trial Design

- Investigator-initiated multi-stage Phase II trial
  - NCT-01682772; CR-UK/11/029

- **Adaptive design** focused on predictive biomarker identification
  - Test set (all comers; Part A) and validation set (patient selection; Part B)
  - Possibility to proceed to a randomized Phase II of PARPi vs placebo

- Open label, olaparib (tablets) 400 mg BID

**Study Objectives**

- To evaluate the anti-tumour activity of olaparib in mCRPC
- **To identify and clinically qualify a predictive biomarker suite for PARP inhibitor anti-tumour activity in CRPC**


---

**Trial Design**

- **Primary Endpoint: Response Rate**
  - Response as per RECIST 1.1
  - PSA decline ≥50% (PCWG-2)
  - CTC conversion (≥5 to <5/7.5ml)
    Confirmed by a second assessment ≥4 weeks later

- **Secondary Endpoints:**
  - PFS, rPFS, OS, time to PSA progression (PCWG-2), time to radiological progression, rate of CTC conversion, duration of responses, safety-tolerability

- **Exploratory Endpoints:**
  - Study of diffusion-weighted MRI as response biomarker
  - QoL studies (pain improvement)

RECIST = response evaluation criteria in solid tumours; PSA = prostate-specific antigen; PCWG = prostate cancer working group; PFS = progression-free survival; rPFS = radiographic PFS; OS = overall survival; QoL = quality of life

TARGETING DNA DAMAGE RESPONSE
At the Forefront of Emerging Concepts and Strategies

Trial Design

PART A Stage 1:
30 unselected patients

≥ 15 respond
≤ 2 respond
3-14 respond

Recruit a further 15 patients (stage 2)

PART A Stage 2:
45 unselected patients

≤ 5 responders
≥ 23 responders
6-22 responders

Investigate if potential biomarkers of response can be identified

PART B: Biomarker selected patients

PART C: Randomized Clinical Trial

End of trial

• Ho RR=5%
• Ha RR=20%
• α=0.02, β=0.10


Biomarker Studies

• Mandated pre- and post-PARPi fresh tumour biopsies
• Planned studies to analyse predictive biomarker suite:
  • Whole exome and transcriptome analyses
  • Targeted NGS for validation
  • Whole genome analyses
• Circulating tumour DNA in serial plasma samples
• PD studies in tumour tissues
  • Gamma H2AX foci, RAD51 foci, 53BP1 foci

NGS = next generation sequencing; PD = pharmacodynamic

Biomarker Studies

DNA Repair Defects in mCRPC

- Definition of biomarker positive (B+) patient:
  - Presence of a homozygous deletion AND/OR a positive deleterious mutation in a gene reported to be involved in DNA repair and/or sensitivity to PARP inhibition


Trial Population

- Metastatic CRPC after 1–2 lines of taxane chemotherapy
- Documented progressive disease by RECIST or PSA (PCWG2)
- ECOG Performance Status 0–2
- Appropriate organ-function: haemoglobin >10 g/l, neutrophils >1.5 x 10⁹/l, platelets >100 x 10⁹/l, bilirubin <1.5 x ULN, AST/ALT<2.5 x ULN (x5 liver mets), creatinine <1.5 x ULN
- No prior PARPi, platinum, cyclophosphamide or mitoxantrone
- CTC count of ≥5 cells/7.5 ml blood at screening

ECOG = Eastern Cooperative Oncology Group; AST = aspartate transaminase; ALT = alanine transaminase

Clinical Trial Results

Patient Characteristics

<table>
<thead>
<tr>
<th>Patients dosed</th>
<th>50</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evaluable for response</td>
<td>49</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Prior lines of treatment</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Docetaxel</td>
<td>50 (100)</td>
</tr>
<tr>
<td>Cabazitaxel</td>
<td>29 (58)</td>
</tr>
<tr>
<td>Abiraterone*</td>
<td>48 (96)</td>
</tr>
<tr>
<td>Enzalutamide*</td>
<td>14 (28)</td>
</tr>
<tr>
<td>Palliative radiotherapy</td>
<td>18 (26)</td>
</tr>
</tbody>
</table>

* CYP-17 inhibitor and/or enzalutamide 50/50 (100%)

ALP = alkaline phosphatase; Hb = haemoglobin; IQR = interquartile range; IU = international units


Safety and Tolerability

- 13/50 patients required a dose reduction (26%) to 300 mg BID
- 3 patients required a 2nd dose reduction to 200 mg BID

### Primary Endpoint Analysis

**Response to Olaparib in Sporadic mCRPC**

<table>
<thead>
<tr>
<th>ID</th>
<th>Maximum % decline in PSA from baseline</th>
<th>Measurable disease at baseline</th>
<th>Best RECIST response</th>
<th>Confirmed CTC conversion</th>
<th>Baseline CTC count (7.5 ml blood)</th>
<th>Maximum % CTC decline</th>
<th>Time on treatment (weeks; ≥24 in bold)</th>
<th>Response rate: 32.7% (16/49 evaluable patients)</th>
<th>95% CI: 20.0–47.5%</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1</td>
<td>85</td>
<td>No</td>
<td>No</td>
<td>87</td>
<td>100</td>
<td>73</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>#5</td>
<td>51</td>
<td>No</td>
<td>Yes</td>
<td>24</td>
<td>100</td>
<td>58</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>#6</td>
<td>29</td>
<td>Yes</td>
<td>SD</td>
<td>Yes</td>
<td>105</td>
<td>97.1</td>
<td>16*</td>
<td></td>
<td></td>
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<tr>
<td>#8</td>
<td>47</td>
<td>No</td>
<td>Yes</td>
<td>38</td>
<td>94.7</td>
<td>62</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>#11</td>
<td>No decline</td>
<td>Yes</td>
<td>PD</td>
<td>Yes</td>
<td>6</td>
<td>83.3</td>
<td>12</td>
<td></td>
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</tr>
<tr>
<td>#14</td>
<td>83</td>
<td>No</td>
<td>Yes</td>
<td>102</td>
<td>100</td>
<td>36</td>
<td></td>
<td></td>
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<tr>
<td>#15</td>
<td>80</td>
<td>Yes</td>
<td>PR</td>
<td>Yes</td>
<td>18</td>
<td>100</td>
<td>36</td>
<td></td>
<td></td>
</tr>
<tr>
<td>#16</td>
<td>88</td>
<td>Yes</td>
<td>PR</td>
<td>Yes</td>
<td>5</td>
<td>100</td>
<td>40*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>#17</td>
<td>95</td>
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<td>PR</td>
<td>Yes</td>
<td>8</td>
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<td></td>
</tr>
<tr>
<td>#20</td>
<td>88</td>
<td>Yes</td>
<td>PR</td>
<td>N/E</td>
<td>&lt;5</td>
<td>100</td>
<td>48</td>
<td></td>
<td></td>
</tr>
<tr>
<td>#26</td>
<td>No decline</td>
<td>No</td>
<td>Yes</td>
<td>12</td>
<td>100</td>
<td>18*</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>#30</td>
<td>70</td>
<td>No</td>
<td>Yes</td>
<td>100</td>
<td>100</td>
<td>44*</td>
<td></td>
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<tr>
<td>#35</td>
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<td>513</td>
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<td>40*</td>
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<td></td>
</tr>
<tr>
<td>#36</td>
<td>59</td>
<td>No</td>
<td>Yes</td>
<td>22</td>
<td>100</td>
<td>57</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>#39</td>
<td>68</td>
<td>Yes</td>
<td>PR</td>
<td>Yes</td>
<td>24</td>
<td>100</td>
<td>44*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>#48</td>
<td>No decline</td>
<td>Yes</td>
<td>SD</td>
<td>Yes</td>
<td>9</td>
<td>100</td>
<td>39</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Two dose-reductions due to anaemia
*Discontinued due to myelosuppression
*Pt still receiving treatment at time of data cutoff


### Genomic Aberrations in DNA Repair in Patients with mCRPC

# Biomarker Studies

## DNA Repair Defects Associated with Response

<table>
<thead>
<tr>
<th>DNA Repair Defects</th>
<th>Responder</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No (n=33)</td>
<td>Yes (n=16)</td>
</tr>
<tr>
<td>Biomarker negative</td>
<td>31</td>
<td>2</td>
</tr>
<tr>
<td>Biomarker positive</td>
<td>2</td>
<td>14</td>
</tr>
</tbody>
</table>

- **Fishers’ exact P value**: $P < .001$
- **Sensitivity, %**: 87.5
- **Specificity, %**: 93.9
- **Odds ratio (95% CI), P value***: 108.5 (13.84, 850.5), $P < .001$

* Estimated from a logistic regression model

---


---

**rPFS by Presence of Genomic Defects in DNA Repair Genes**

- **Biomarker-positive, median: 9.8 mo**
- **Biomarker-negative, median: 2.7 mo**

- **Proportion of Patients**

---

**OS by Presence of Genomic Defects in DNA Repair Genes**

- **Biomarker-positive, median: 13.8 mo**

- **Proportion of Patients**

---

**Changes in PSA over Treatment**

- **Biomarker-negative**
- **Biomarker-positive**

---

**Changes in CTC count over Treatment**

- **Biomarker-negative**
- **Biomarker-positive**

---

Biomarker Studies

**BRCA2 Loss Sensitizes to Olaparib**


---

Biomarker Studies
ATM Defects and Response to Olaparib

TO-PARP Trial: Conclusions

- Olaparib has anti-tumour activity against sporadic mCRPC with many responses lasting >6 months (To date: Up to three years in mCRPC; up to 7 years in ovary)
- mCRPC can harbour genomic defects in DNA repair genes (somatic and germline), most commonly in ATM and BRCA2; these are detectable by targeted next generation sequencing of tumour samples
- Such defects associate with olaparib sensitivity in mCRPC with high biomarker specificity and sensitivity
- These results may arguably represent the first molecular treatment stratification of mCRPC and can also be informative for other tumour types
### Genomic Aberrations in DNA Repair in Patients with mCRPC

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Time of treatment (weeks)</th>
<th>Biomarker positive</th>
<th>RESPONSE TO OLAPARIB</th>
<th>NO RESPONSE TO OLAPARIB</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>7</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>14</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRCA2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FANCA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHEK2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRCA1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PALB2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDAC2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAD51</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MLH3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ERCC3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRE11</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NBN</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

6 of 50 patients had germline DNA repair defects in TOPARP-A.

Real or biased accrual of patients with family history?

Germline DNA sequenced on 700 mCRPC patients
1 in 8 men had a heritable deleterious mutation


Take Home Messages

- 1 in 7 patients of all mCRPC in our clinic had germline DNA repair mutations – this is relevant for patient management and family counseling.
  - These, especially BRCA2 mutations, are associated with poorer prognosis from mCRPC – we need larger cohorts and longer follow-up data

- While family history of PC is associated with a higher risk of germline mutations
  - Many of these patients would not have been tested on current criteria
  - 8.8% of cases with no family history had germline mutations.

- Germline and somatic NGS required for mCRPC patients if results validated.
  - Prospective validation (SU2C/PCF International Prostate Cancer Dream Team) is ongoing (n=700 patients)

TARGETING DNA DAMAGE RESPONSE
At the Forefront of Emerging Concepts and Strategies

Talk Overview

• Where will DDR take us?
• Targeting PARP in lethal prostate cancer
• Conclusions

Conclusions

• Synthetic lethal therapeutic strategies have meaningful clinical utility
• PARPi active in cancers with DDR aberrations including BRCA1/2
• Lethal prostate cancers can have DNA repair defects
  • BRCA2, ATM, PALB2, BRCA1, MMR defects
• 1:8 men with metastatic mCRPC have germline DNA repair defects
  • Implications to their families as well as their treatment
TARGETING DNA DAMAGE RESPONSE
At the Forefront of Emerging Concepts and Strategies

Acknowledgments

- ICR/RM Phase I and CRPC Clinical Trials Teams especially Joaquin Mateo
- de Bono Cancer Biomarkers Lab team (ICR): Suzanne Carreira (NGS), Penny Flohr (CTC), Ruth Riisnaes, Susana Miranda, Jane Goodall, Ines Figueiredo, G. Seed, R. G. Boysen, S. Miranda, W. Yuan, Daniel NavaRodrigues (pathologist), Nina Tunariu and Raquel Perez Lopez (radiologists)
- TO-PARP trial: Shahneen Sandhu, Aurelius Omlin and Joaquin Mateo. Also Steve Jackson, Alan Ashworth, Chris Lord, Andrew Tutt, Nick Turner.
- SU2C Dream Team: Arul Chinnaiyan, Dan Robinson, Karen Giles, Priya Kunju, Charles Sawyers, Pete Nelson.
- Trial investigators: At all sites.
- Clinical Trials and Statistics Units at the ICR: Emma Hall & Roger Ahern (statisticians), many others.
- RM Prostate Cancer Targeted Therapy Group: Bindu Baikady, Ajit Selvadikar
- Cancer Genetics: Professor Ros Eeles’ team at the ICR.
- AACR/ESMO/ECCO/EORTC Flims Course faculty for assistance with designing TO-PARP
- Many many others: Apologies if I missed anyone out

Grateful thanks most of all to the patients who participated

Targeting PARP in Pancreatic Cancer

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Professor of Medicine/Oncology and Genetics
Director, Clinical Cancer Genetics and Genomics
Stanford University School of Medicine
Stanford, CA

CEC Oncology 2017
TARGETING DNA DAMAGE RESPONSE
At the Forefront of Emerging Concepts and Strategies

Estimated Cancer Deaths in US 2017

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Male Deaths</th>
<th>Male %</th>
<th>Female Deaths</th>
<th>Female %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung &amp; bronchus</td>
<td>84,590</td>
<td>27%</td>
<td>71,280</td>
<td>25%</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>27,150</td>
<td>9%</td>
<td>40,610</td>
<td>14%</td>
</tr>
<tr>
<td>Prostate</td>
<td>26,730</td>
<td>8%</td>
<td>23,110</td>
<td>8%</td>
</tr>
<tr>
<td>Pancreas</td>
<td>22,300</td>
<td>7%</td>
<td>20,790</td>
<td>7%</td>
</tr>
<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>19,610</td>
<td>6%</td>
<td>14,080</td>
<td>5%</td>
</tr>
<tr>
<td>Leukemia</td>
<td>14,300</td>
<td>4%</td>
<td>10,920</td>
<td>4%</td>
</tr>
<tr>
<td>Esophagus</td>
<td>12,720</td>
<td>4%</td>
<td>10,200</td>
<td>4%</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>12,240</td>
<td>4%</td>
<td>9,310</td>
<td>3%</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>11,450</td>
<td>4%</td>
<td>8,690</td>
<td>3%</td>
</tr>
<tr>
<td>Brain &amp; other nervous system</td>
<td>9,620</td>
<td>3%</td>
<td>7,080</td>
<td>3%</td>
</tr>
<tr>
<td><strong>All Sites</strong></td>
<td><strong>318,420</strong></td>
<td><strong>100%</strong></td>
<td><strong>282,500</strong></td>
<td><strong>100%</strong></td>
</tr>
</tbody>
</table>


Metastatic Pancreatic Cancer
PRODIGE: Gemcitabine vs FOLFIRINOX

**PFS**
- Hazard ratio, 0.47 (95% CI, 0.37–0.59)
- P<0.001

**OS**
- Hazard ratio, 0.57 (95% CI, 0.45–0.73)
- P<0.001 by stratified log-rank test

TARGETING DNA DAMAGE RESPONSE
At the Forefront of Emerging Concepts and Strategies

Metastatic Pancreatic Cancer
MPACT: Gemcitabine +/- Nab-Paclitaxel


Familial Pancreatic Cancer
Incidence Among 1st-Degree Relatives

10% of pancreatic cancer patients have a first degree relative with pancreatic cancer

### Familial Pancreatic Cancer

**Affected 1\textsuperscript{st}-Degree Relatives and PC Risk**

<table>
<thead>
<tr>
<th>Number FDR w PC</th>
<th>Fold Risk PC</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3 - 5</td>
</tr>
<tr>
<td>2*</td>
<td>5 - 7</td>
</tr>
<tr>
<td>3*</td>
<td>30</td>
</tr>
</tbody>
</table>

*Consider Screening: Twice Annually MRI & EUS at 40 yo*

Adapted from Axilbund JE, Wiley EA. *Cancer J.* 2012.

### Familial Pancreatic Cancer

**Inherited Cancer Predisposition Syndromes**

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Gene</th>
<th>Frequency</th>
<th>Risk PC</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBOC</td>
<td><em>BRCA 1 &amp; 2</em></td>
<td>1/40 – 1/400</td>
<td>RR, 2 – 6x</td>
</tr>
<tr>
<td>FAMM</td>
<td><em>CDKN2A (p16)</em></td>
<td>Rare</td>
<td>RR, 7 – 48x</td>
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<tr>
<td>Peutz Jeghers</td>
<td><em>STK11</em></td>
<td></td>
<td>SIR, 132x</td>
</tr>
<tr>
<td>Lynch Syndrome</td>
<td><em>MMR</em></td>
<td>1/440</td>
<td>SIR, 0 – 9x</td>
</tr>
</tbody>
</table>

RR=Relative Risk; SIR=Standardized Incidence Ratio; PC=Pancreatic Cancer

Adapted from Axilbund JE, Wiley EA. *Cancer J.* 2012.
Pancreatic Cancer

**Germline and Somatic Mutations**

<table>
<thead>
<tr>
<th>Gene</th>
<th>Fold-Risk PC</th>
<th>Incidence in FPC</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA2</td>
<td>3.5</td>
<td>17 – 19%</td>
</tr>
<tr>
<td>BRCA1</td>
<td>2</td>
<td>2 – 3%</td>
</tr>
<tr>
<td>STK11</td>
<td>132</td>
<td></td>
</tr>
<tr>
<td>PALB2</td>
<td>2</td>
<td>2 – 3%</td>
</tr>
<tr>
<td>ATM</td>
<td></td>
<td>2%</td>
</tr>
<tr>
<td>CDKN2A</td>
<td>13 - 38</td>
<td>10 – 17%</td>
</tr>
<tr>
<td>MMR</td>
<td>0 - 8</td>
<td></td>
</tr>
</tbody>
</table>

- Prevalence of gBRCA1/2 mutations in all PC: 4 - 7% (12% AJ)
- Somatic BRCA1/2 mutations in 10% PC

---

Pancreatic Cancer

**OS in BRCA Mutation Carriers**

Probability of OS by Platinum Treatment at Stages 3 and 4

![Graph showing OS probability](image)

*P=.0389

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**gBRCAm+ Metastatic Pancreatic Cancer**
**Olaparib Monotherapy**

<table>
<thead>
<tr>
<th>Status</th>
<th>N</th>
<th>CR/PR (%)</th>
<th>DCR</th>
<th>PFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>23</td>
<td>1/4 (22%)</td>
<td>11 (43%)</td>
<td>4.6 mos</td>
<td>9.8 mos</td>
</tr>
</tbody>
</table>

- Broad phase II study of olaparib in gBRCA tumors of any primary site
- 23 patients with pretreated gBRCAm+ metastatic pancreatic cancers enrolled
- All previously treated with a gemcitabine regimen
- Most treated with a prior platinum regimen


**gBRCAm+ Metastatic Pancreatic Cancer**
**Olaparib Monotherapy (cont.)**

<table>
<thead>
<tr>
<th>Response</th>
<th>Ovarian (n = 193)</th>
<th>Breast (n = 62)</th>
<th>Pancreas (n = 23)</th>
<th>Prostate (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>Tumor response rate</td>
<td>60</td>
<td>31.1</td>
<td>8</td>
<td>12.9</td>
</tr>
<tr>
<td>95% CI</td>
<td>24.6 to 38.1</td>
<td>5.7 to 23.9</td>
<td>7.5 to 43.7</td>
<td>15.7 to 84.3</td>
</tr>
<tr>
<td>CR*</td>
<td>6</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>PR*</td>
<td>54</td>
<td>28</td>
<td>8</td>
<td>13</td>
</tr>
<tr>
<td>Stable disease ≥ 8 weeks</td>
<td>78</td>
<td>40</td>
<td>29</td>
<td>47</td>
</tr>
<tr>
<td>95% CI</td>
<td>33.4 to 47.7</td>
<td>34.0 to 59.9</td>
<td>16.4 to 57.3</td>
<td>3.2 to 65.1</td>
</tr>
<tr>
<td>Stable disease</td>
<td>64</td>
<td>33</td>
<td>22</td>
<td>36</td>
</tr>
<tr>
<td>Unconfirmed PR</td>
<td>12</td>
<td>6</td>
<td>7</td>
<td>11</td>
</tr>
<tr>
<td>PDT</td>
<td>41</td>
<td>21</td>
<td>23</td>
<td>37</td>
</tr>
<tr>
<td>95% CI</td>
<td>15.7 to 27.7</td>
<td>25.2 to 50.3</td>
<td>19.7 to 61.5</td>
<td>3.2 to 65.1</td>
</tr>
<tr>
<td>RECIST progression</td>
<td>33</td>
<td>17</td>
<td>16</td>
<td>26</td>
</tr>
<tr>
<td>Early death</td>
<td>8</td>
<td>4</td>
<td>7</td>
<td>11</td>
</tr>
</tbody>
</table>

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RUCAPANC Trial

- Phase II trial in 19 patients with BRCA1/2m pancreatic cancer and 1-3 prior rounds of chemotherapy. Pts were given rucaparib 600 mg PO BID until disease progression
- Disease control rate
  - All pts = 32%
  - Pts w/ 1 prior round of chemo = 50%
- > Grade 3 AEs:
  - Anemia (26%)
  - Thrombocytopenia (16%)
  - Fatigue (11%)


PARPi in Pancreatic Cancer

Ongoing Trials

<table>
<thead>
<tr>
<th>Drug</th>
<th>Phase</th>
<th>Arms</th>
<th>Inclusion</th>
<th>Outcomes</th>
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</thead>
<tbody>
<tr>
<td>Olaparib</td>
<td>I; II</td>
<td>O; Irinotecan, Cispl, MMC</td>
<td>St III/IV, gB1/2</td>
<td>OS</td>
</tr>
<tr>
<td>(NCT01296763)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Olaparib</td>
<td>II</td>
<td>Olaparib</td>
<td>Met non-gB1/2</td>
<td>ORR</td>
</tr>
<tr>
<td>(NCT02677038)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Olaparib</td>
<td>III</td>
<td>Olaparib; Placebo</td>
<td>Met gB1/2 mut</td>
<td>PFS, OS</td>
</tr>
<tr>
<td>(NCT02184195)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rucaparib</td>
<td>II</td>
<td>Rucaparib</td>
<td>BRCA mut</td>
<td>ORR, PFS</td>
</tr>
<tr>
<td>(NCT02042378)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Veliparib</td>
<td>I</td>
<td>V, Gem, IMRT</td>
<td>Locally Advanced</td>
<td>OS</td>
</tr>
<tr>
<td>(NCT01908478)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Veliparib</td>
<td>II</td>
<td>V, FOLFOX</td>
<td>Met BRCA mut</td>
<td>ORR</td>
</tr>
<tr>
<td>(NCT01489865)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Veliparib</td>
<td>II</td>
<td>V v V-Gem/Cis v Gem/Cis</td>
<td>B1/2 or PALB2 m</td>
<td>ORR, PFS</td>
</tr>
<tr>
<td>(NCT01585805)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Clinicaltrials.gov
POLO-1

**Trial Design**

**SCREEN FOR gBRCAm pancreatic cancer:**
1. On a 1st line Rx platinum regimen
2. Have not progressed at time of randomization
3. After at least 16 weeks of Rx with a Platinum but need not still be on plat

Double-blinded Study

- **Randomize**
  - Olaparib 300 mg BID tablet
  - Placebo
  - Progress by RECIST: Resume ChemoRx

3:2

Progress by local standard: Treatment according to local standard

- Primary Endpoint is PFS (by central review)
- Secondary Endpoints are OS, ORR, DCR, safety, quality of life
- Planned N = 145

Clinicaltrials.gov; NCT02184195.

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**BRCA1**

**Relevant Genetic Pathways**

Breast Cancer
Susceptibility Loci and Genes

A Phase II clinical trial of the PARP inhibitor talazoparib in BRCA1 and BRCA2 wild-type patients with advanced solid tumors with either a germline or somatic mutation in homologous recombination pathway genes

PALB2, CHEK2, ATM, NBN, BARD1, BRIP1, RAD50, RAD51C, RAD51D, MRE11, ATR, FANCA, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCL.


Clinicaltrials.gov; NCT02401347.
Future of DDR-Targeting Therapies Beyond PARP Inhibition: Exploiting Replication Stress

Dr. Christopher Lord
Gene Function Laboratory
Breast Cancer Now Toby Robins Breast Cancer Research Centre
The Institute of Cancer Research
London, UK

DDR Targeted Therapies Beyond PARPi

DDR Targets in Pre-clinical and Clinical Development

Challenges:
• Who to treat?
• What are the ideal predictive biomarkers and the molecular mechanisms that explain drug sensitivity?
• Impact of heterogeneity and plasticity
• How does resistance emerge and how robust are synthetic lethal interactions with DDR targeted agents?
• Combination therapy?
• What are the ideal drug combinations to use and what are the biomarkers that predict combinatorial efficacy?
DDR Targeted Therapies Beyond PARPi

**DNA-PK**
- DNA-PK inhibitors block DNA-PK on DNA ends
- Prevents NHEJ and likely end resection and HR
- Little single agent activity *in vitro*
- DNA-PKI sensitize cells and xenografts to DSB inducing agents (eg, IR, topo II inhibitors)

**Clinical inhibitors include:**
- **MSC2490484** Ph1 with IR
- **PVX-984** Ph1 with liposomal doxorubicin
- **CC-115** (mTOR/DNA-PK)
- Ph1 in advanced solid/hematologic malignancies
- Well-tolerated
- Preliminary anti-tumor activity observed*
- CLL harboring biallelic ATM loss a possible SL approach

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ATM responds to DSBs throughout cell cycle
- ATMi cause sensitivity to IR, etoposide, camptothecin, and doxorubicin
- ATMi synthetic lethal with PARP inhibition*
- **AZD0156** - monotherapy and in combination with olaparib and other cytotoxic or molecularly targeted agents (NCT02588105)


**ATR**
- ATR responds to RPA coated ssDNA
- ATRi synthetic lethal with PARPi, CHK1i, WEE1i
- ATRi chemosensitization of lung cancer tumour cells to chemotherapeutics that result in replication fork collapse, such as cisplatin and gemcitabine *in vitro*, and increased antitumor activity in combination with cisplatin *in vivo*
- Possibly causes multiple problems for tumour cells...

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**ATR**

- Mediates cell cycle arrest and repair
  - CHK1, p53 H2AX, etc.

- Also minimizes replication origin firing

**Multifactorial effect?**
- Unrepaired replication forks
- Fail to inhibit other replication origins > exacerbate problem
- Premature entry into mitosis in the presence of replication fork dysfunction
- Proposed as an approach for targeting replication fork stress generated by oncogenes (eg, *Myc*, *Cyclin E*) and tumour suppressors (*BRCA1,2*) but refined biomarkers of sensitivity required.

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**Opportunities for DDR SL in “Quiet Genomes”**

**ATR Synthetic Lethality in SWI/SNF Mutant Ovarian Clear Cell Carcinoma**

- Synthetic lethal with ARID1A defects in ovarian clear cell carcinoma

**Clonogenic Survival (14 days)**

<table>
<thead>
<tr>
<th></th>
<th>VE-821</th>
<th>VX-970</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ARID1A +/+</strong></td>
<td>0, 0.1, 1</td>
<td>0, 0.01, 0.05</td>
</tr>
<tr>
<td><strong>ARID1A -/-</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Surviving Fraction**

**Tumour volume (mm³)**

**ARD1A A+/+**

- **ARD1A -/-**

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**ATR Inhibitors in Clinical Trials**

- VX-970 preliminary phase I data - well tolerated as monotherapy with no dose-limiting toxicities or grade 3–4 adverse events demonstrated up to weekly intravenous doses of 480 mg/m²
- RECIST complete response in 1 patient with metastatic ATM-deficient colorectal cancer, who remained on single-agent VX-970 for more than 20 months
- VX-970 combination with carboplatin identified RP2D (VX-970 90 mg/m² + carboplatin AUC 5)
- Myelosuppression (neutropenia and thrombocytopenia) was the most commonly observed treatment-related toxicity
- Ser345 on CHK1 PD biomarker
- At RP2D, 1 patient with platinum-refractory, PARPi resistant germline BRCA1- and p53-mutant advanced high-grade serous ovarian cancer achieved a RECIST partial response and gynecologic cancer intergroup (GCIG) CA125 tumor marker response lasting 6 months
- Combinations with cisplatin or gemcitabine on-going

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**ATR Inhibitors in Clinical Trials**

- AZD6738
  - Phase 1 combinations with olaparib, carboplatin, radiotherapy, or the immune-checkpoint inhibitor, durvalumab (MEDI4736) underway

- Other notable targets in clinical development include CHK1, CHK2, and WEE1 inhibitors

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Future Prospects

- Identification of predictive biomarkers of DDRi sensitivity, either as single agents or in combination therapies, is key
- Understanding of how to deliver tolerable regimens of DDRi is essential
- Combinations with agents that act via orthogonal mechanisms starting to be addressed (eg, immunotherapy), but requires more focus