PARP INHIBITORS
Past, Present and Future

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Medical Oncology Departments
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OVERVIEW

1. Background
2. Comparing PARP inhibitors
3. Concept of HRD
4. Clinical data for PARP inhibitors: ovarian, breast, prostate and pancreatic cancer
5. Extending the benefit beyond BRCA1/2 cancers
6. Coming full circle: Combos → monotherapy → combos
7. Evolving strategies moving forward
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WHAT IS POLY (ADP-RIBOSE) POLYMERASE (PARP)?

PARP protein family is composed of 17 nuclear enzymes

PARP-1 and PARP-2 participate in DNA single strand break repair (SSBR), and are key enzymes in the base excision repair (BER) mechanism.
PARP IS INVOLVED IN SSBR, REPLICATION REPAIR, ALT-NHEJ, FORK PROTECTION, NER AND BER

Ström CE and Hellday T. Biomolecules 2012;2(4), 635–49. Reproduced under the Creative Commons Attribution License. Attribution-NonCommercial-ShareAlike 3.0 Unported (CC BY-NC-SA 3.0; available at: https://creativecommons.org/licenses/by-nc-sa/3.0/; accessed July 2021)
PARP1 TRAPPING IS REQUIRED FOR PARP INHIBITOR TOXICITY

Reprinted from Cancer Research, Copyright 2012, 72(21), 5588–99. Murai J, et al. Trapping of PARP1 and PARP2 by Clinical PARP Inhibitors, with permission from AACR.
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### Relative PARP-trapping capacity (nM)

<table>
<thead>
<tr>
<th>PARP</th>
<th>Veliparib</th>
<th>Olaparib</th>
<th>Rucaparib</th>
<th>Niraparib</th>
<th>Pamiparib</th>
<th>Talazoparib</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-</td>
<td>300</td>
<td>600</td>
<td>300</td>
<td>60</td>
<td>1</td>
</tr>
</tbody>
</table>

### Single agent dose

- **Veliparib**: 400 mg PO BID
- **Olaparib**: 300 mg PO BID
- **Rucaparib**: 600 mg PO BID
- **Niraparib**: 300 mg PO QD
- **Pamiparib**: 60 mg PO BID
- **Talazoparib**: 1 mg PO QD

### Toxocities

- **Most frequent**
- Nausea (50%)/fatigue (25%)/lymphopenia (16%)
- Anemia (16-19%), neutropenia (5-9%)
- Anemia (19%), neutropenia (7%)
- Anemia (74%), fatigue (59%), LFT elevation (26%), headache (20-25%)
- Anemia (68%), neutropenia (7%)
- Anemia (49%), fatigue (50%), headache (33%), lymphopenia (25%), diarrhea (22%)

- **Grade ≥3 hematological toxicities in ≥5% of study population**

### Clinical benefit

- **OlympiAD (HER2-breast)**, HR 0.50, PFS benefit
- **SOLO2 (relapsed ovarian maintenance)**, HR 0.30, PFS benefit
- **SOLO1 (ovarian maintenance)**, HR 0.30, PFS benefit
- **POLO (deleterious HRR mutations in relapsed pancreas)**, HR 0.53, PFS benefit

- **ARIEL2 (relapsed ovarian maintenance)**, HR 0.27, PFS benefit
- **ARIEL3 (relapsed ovarian maintenance)**, HR 0.27, PFS benefit
- **TRITON2 (BRAC1/2 relapsed pancreas)**, ORR 43.9%

### Proof of concept for a synthetic lethal approach in oncology

- **NOVA (relapsed ovarian maintenance)**, HR 0.27, PFS benefit
- **Ongoing, data not mature** (NCT03427814)
- **EMBRACA (HER2-breast)**, HR 0.54, PFS benefit

### Approvals

- **Ovarian Breast Prostate (mCRCP)**
- **Ovarian Prostate (mCRPC)**
- **Ovarian**

WHAT IS SYNTHETIC LETHALITY?

This is a concept
Strategy to target tumour suppressor gene aberrations; e.g., BRCA1/2 mutations

<table>
<thead>
<tr>
<th>Gene X</th>
<th>Gene Y</th>
<th>Cell viability</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>+</td>
<td>No effect</td>
</tr>
<tr>
<td>-</td>
<td>+</td>
<td>No effect</td>
</tr>
<tr>
<td>+</td>
<td>-</td>
<td>No effect</td>
</tr>
<tr>
<td>-</td>
<td>-</td>
<td>Death</td>
</tr>
</tbody>
</table>

Mutation in either gene individually has no effect, but combining the mutations leads to cell death

SYNTHETIC LETHALITY IN CANCER

BRCA1/2 mutations and PARP inhibitors

Non-tumour cell

\[ \text{BRCA}^{+/+} \]

or \[ \text{BRCA}^{+/} \] (HR intact)

DNA DAMAGE

HR NHEJ SSA BER NER etc

\[ \times \]

PARPi

Tumour cell

\[ \text{BRCA1/2}^{-/-} \]

(HR deficient)

DNA DAMAGE

HR NHEJ SSA BER NER etc

\[ \times \]

PARPi

Error prone repair
Genomic instability
Cell death

Lethality

Targeted inhibition → selective and less toxic therapy

HR = homologous recombination (error-free DNA DSB repair)
BER = base excision repair (DNA SSB repair)

Phase 1 study of the poly(ADP-ribose) polymerase (PARP) inhibitor, AG014699, in combination with temozolomide in patients with advanced solid tumours

A Phase 2 study of the potent PARP inhibitor, rucaparib (PF-01367338, AG014699), with temozolomide in patients with metastatic melanoma demonstrating evidence of chemopotentiation

- Myelosuppression in 25 patients (54%) requiring a 25% DR in temozolomide
- RR 17.4%, median 3.5 months, median OS 9.9 months

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SYNTHETIC LETHALITY
PARP inhibitors and BRCA1/2 mutant tumours

Back-to-back Nature articles from Helleday & Ashworth Groups

1st responding BRCA mutant patients to KU-0059436/olaparib

PARP inhibitor monotherapy $\rightarrow$ effective and well tolerated therapy in BRCA1/2 mutant tumours

FDA approved in different settings

DNA SSBs occur all the time in cells and PARP detects and repairs them. During the replication process, unrepaired SSBs are converted into DSBs.

Replicating cells PARP is trapped on single-strand breaks

Normal cell (HR intact) Cancer cell (HR deficient)
Repair by homologous recombination No effective repair (no HR pathway)
Survival Cell death

Tumour-specific killing by PARP inhibitors

Reproduced from Mol Cell, 60 (4), O'Connor MJ, Targeting the DNA Damage Response in Cancer, 547–60, Copyright 2015, with permission from Elsevier.
HRD TEST DEVELOPMENT APPROACH

Develop a DNA-based assay capable of detecting Homologous Recombination Deficiency (HRD) regardless of its etiology or mechanism with utility across tumour sites.

Rather than sequence all the genes in the HR pathway to find mutations, myChoice® HRD detects biomarkers that indicate a defective HR pathway.

HR, homologous recombination.
Myriad Genetics, Inc. Data on File.
Mutations in HR genes are not the only cause of HRD
- Differential expression and miRNA regulation may lead to HRD phenotype

A patient may test positive for a mutation in an HR pathway gene and not have HRD phenotype

Patients may not harbour individual mutations but still exhibit the HRD phenotype

Testing for the HRD phenotype rather than discrete, causal genomic aberrations of HRD enhances identification of patients likely to benefit from platinum and/or PARPi based therapeutic regimens

HR, homologous recombination; HRD, homologous recombination deficiency.
Myriad Genetics, Inc. Data on File.
PROPORTION OF HRD IN OVARIAN CANCER

Half of high-grade serous ovarian cancer (HGSOC) exhibits a high degree of genomic instability due to deficiencies in homologous recombination (HR)

HRD, homologous recombination deficiency; gBRCAmut, germline breast cancer gene mutation; tBRCAmut, tumour BRCA mutation.
Myriad Genetics, Inc. Data on File.
SEVERAL METHODS ARE USED TO DETERMINE SENSITIVITY TO PARP INHIBITORS

Also known as: “HRD-positive”, “HRD-ness”, “BRCA-ness”, “BRCA-like”

BRCA testing – either germline or somatic

Gene panel testing – i.e., BROCA

Combination testing that includes LOH and/or other biomarkers of DNA damage (TAI, LST)
  - Foundation Medicine’s LOH test
  - Myriad Genetics myChoice® HRD test

PARP=poly (ADP-ribose) polymerase inhibitor; HRD=homologous recombination deficiency; LOH=loss of heterozygosity; TAI=telomeric allelic imbalance; LST=largescale state transition.
myChoice® HRD test is now being used with 3 of the 5 PARP inhibitors

<table>
<thead>
<tr>
<th>Company</th>
<th>PARPi</th>
<th>Test</th>
<th>Biomarker</th>
</tr>
</thead>
<tbody>
<tr>
<td>TESARO¹</td>
<td>Niraparib</td>
<td>Myriad’s myChoice® HRD</td>
<td>HRD</td>
</tr>
<tr>
<td>AstraZeneca¹</td>
<td>Olaparib</td>
<td>Myriad’s BRACAnalysis CDx®</td>
<td>gBRCA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>FDA-approved test to detect gBRCAmut</td>
<td></td>
</tr>
<tr>
<td>Clovis²</td>
<td>Rucaparib</td>
<td>Foundation Medicine’s FoundationOne®</td>
<td>LOH</td>
</tr>
<tr>
<td>Pfizer¹ (Medivation)</td>
<td>Talazoparib</td>
<td>Myriad’s myChoice® HRD</td>
<td>HRD</td>
</tr>
<tr>
<td>AbbVie¹</td>
<td>Veliparib</td>
<td>Myriad’s myChoice® HRD</td>
<td>HRD</td>
</tr>
</tbody>
</table>

PARPi= poly (ADP-ribose) polymerase inhibitor; HRD=homologous recombination deficiency; FDA=Food and Drug Administration; gBRCAmut=germline BRCA mutation.

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CLINICAL DATA FOR PARP INHIBITORS
Ovarian Cancer
PIVOTAL STUDIES OF PARP INHIBITORS

In patients with relapsed ovarian cancer after response to platinum

<table>
<thead>
<tr>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Agent/comparator</td>
<td>Olaparib vs placebo</td>
<td>Niraparib vs placebo</td>
<td>Rucaparib vs placebo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median PFS, mos</td>
<td>8.4 vs 4.8</td>
<td>19.1 vs 5.5</td>
<td>21.0 vs 5.5</td>
<td>8.7 vs 4.3</td>
<td>16.6 vs 5.4</td>
<td>10.8 vs 5.4</td>
</tr>
<tr>
<td>PFS HR (investigator assessed)</td>
<td>0.35 (95% CI: 0.25-0.49; P&lt;0.001)</td>
<td>0.30 (95% CI: 0.22-0.41; P&lt;0.0001)</td>
<td>0.27 (95% CI: 0.18-0.40)</td>
<td>0.53 (95% CI: 0.41-0.68)</td>
<td>0.23 (95% CI: 0.16-0.34; P&lt;0.0001)</td>
<td>0.36 (95% CI: 0.30-0.45; P&lt;0.0001)</td>
</tr>
<tr>
<td>PFS HR (BICR)</td>
<td>0.39 (95% CI: 0.27-0.55; P&lt;0.001)</td>
<td>0.25 (95% CI: 0.18-0.35; P&lt;0.0001)</td>
<td>0.27 (95% CI: 0.17-0.41; P&lt;0.0001)</td>
<td>0.45 (95% CI: 0.34-0.61; P&lt;0.0001)</td>
<td>0.20 (95% CI: 0.13-0.32; P&lt;0.0001)</td>
<td>0.35 (95% CI: 0.28-0.45; P&lt;0.0001)</td>
</tr>
</tbody>
</table>

PFS IN PHASE 3 TRIALS OF PARP INHIBITORS VS PLACEBO AS MAINTENANCE
In BRCA-Mutated ovarian cancer

SOLO-2: Olaparib vs Placebo in gBRCAm Patients[1]

<table>
<thead>
<tr>
<th>mPFS, Months</th>
<th>Olaparib (n = 196)</th>
<th>Pbo (n = 99)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inv</td>
<td>19.1</td>
<td>5.5</td>
<td>0.30 (0.22-0.41)</td>
</tr>
<tr>
<td>BICR</td>
<td>30.2</td>
<td>5.5</td>
<td>0.25 (0.18-0.35)</td>
</tr>
</tbody>
</table>

NOVA: Niraparib vs Placebo in gBRCAm Patients[2,3]

<table>
<thead>
<tr>
<th>mPFS, Months</th>
<th>Niraparib (n = 138)</th>
<th>Pbo (n = 65)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inv</td>
<td>14.8</td>
<td>5.5</td>
<td>0.27 (0.18-0.40)</td>
</tr>
<tr>
<td>BICR</td>
<td>21.0</td>
<td>5.5</td>
<td>0.27 (0.17-0.41)</td>
</tr>
</tbody>
</table>

ARIEL-3: Rucaparib vs Placebo in tBRCAm Patients[4]

<table>
<thead>
<tr>
<th>mPFS, Months</th>
<th>Rucaparib (n = 130)</th>
<th>Pbo (n = 66)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inv</td>
<td>16.6</td>
<td>5.4</td>
<td>0.23 (0.16-0.34)</td>
</tr>
<tr>
<td>BICR</td>
<td>26.8</td>
<td>5.4</td>
<td>0.20 (0.13-0.32)</td>
</tr>
</tbody>
</table>

PFS IN PHASE 3 TRIALS OF PARP INHIBITORS VS PLACEBO AS MAINTENANCE

In ovarian cancer without BRCAm or HRD

**STUDY 19: Olaparib vs Placebo in BRCAwt Patients**

<table>
<thead>
<tr>
<th></th>
<th>Olaparib (n = 57)</th>
<th>Placebo (n = 61)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>mPFS, months</td>
<td>7.4</td>
<td>5.5</td>
<td>0.54 (0.34-0.85)</td>
</tr>
<tr>
<td>inv</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>BICR</td>
<td>--</td>
<td>--</td>
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</tr>
</tbody>
</table>

**NOVA: Niraparib vs Placebo in BRCAwt/HRD-neg Patients**

<table>
<thead>
<tr>
<th></th>
<th>Niraparib (n = 92)</th>
<th>Placebo (n = 42)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>mPFS, months</td>
<td>6.9</td>
<td>3.8</td>
<td>0.58 (0.36-0.92)</td>
</tr>
<tr>
<td>inv</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>BICR</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

**ARIEL-3: Rucaparib vs Placebo in tBRCAwt/LOH-L Patients**

<table>
<thead>
<tr>
<th></th>
<th>Rucaparib (n = 106)</th>
<th>Placebo (n = 52)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>mPFS, months</td>
<td>6.7</td>
<td>5.4</td>
<td>0.58 (0.40-0.85)</td>
</tr>
<tr>
<td>inv</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>BICR</td>
<td>--</td>
<td>--</td>
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</tr>
</tbody>
</table>

# PARP INHIBITORS IN RECURRENT OVARIAN CANCER

## Safety

<table>
<thead>
<tr>
<th>Toxicity or Result, %</th>
<th>Olaparib (SOLO-2/300 mg BID)[1] (N=196)</th>
<th>Rucaparib (ARIEL-3/600 mg BID)[2] (N=375)</th>
<th>Niraparib (NOVA/Fixed Dose)[3] (N=372)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discontinuation</td>
<td>11</td>
<td>15</td>
<td>&lt; 5</td>
</tr>
<tr>
<td>Dose reduction</td>
<td>25</td>
<td>55</td>
<td>34</td>
</tr>
<tr>
<td>Grade ≥ 3 AEs, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>▪ Nausea/vomiting</td>
<td>3</td>
<td>4</td>
<td>&lt; 5</td>
</tr>
<tr>
<td>▪ Fatigue</td>
<td>4</td>
<td>7</td>
<td>&lt; 5</td>
</tr>
<tr>
<td>▪ Anemia</td>
<td>19</td>
<td>24</td>
<td>&lt; 10</td>
</tr>
<tr>
<td>▪ Thrombocytopenia</td>
<td>1</td>
<td>5</td>
<td>&lt; 30</td>
</tr>
<tr>
<td>▪ Neutropenia</td>
<td>5</td>
<td>8</td>
<td>&lt; 12</td>
</tr>
<tr>
<td>▪ Elevated ALT/AST</td>
<td>--</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>MDS</td>
<td>0.5 (n=1)</td>
<td>1 (n=3)</td>
<td>1.6 (n=6)</td>
</tr>
</tbody>
</table>

CLINICAL DATA FOR PARP INHIBITORS

Ovarian cancer
First-line maintenance therapy
SOLO1: OLAPARIB VS PLACEBO AS FIRST-LINE MAINTENANCE IN OVARIAN CANCER WITH BRCA MUTATION

Randomised, double-blind, placebo-controlled, multicentre Phase 3 trial

Primary endpoint: investigator-assessed PFS (RECIST 1.1)
Secondary endpoints: PFS by BICR, PFS2, OS, TSST or death, HRQoL (FACT-O TOI score)

SOLO1: OLAPARIB VS PLACEBO AS FIRST-LINE MAINTENANCE IN OVARIAN CANCER WITH BRCA MUTATION

Randomised, double-blind, placebo-controlled, multicentre Phase 3 trial

Patients with newly diagnosed, FIGO stage III/IV high-grade serous or endometroid ovarian, primary peritoneal, or fallopian tube cancer with germline or somatic BRCA mutation after CR/PR to platinum-based CT (N = 391)

*13 patients, all in the Olaparib arm, continued study treatment past 2 years;†n = 130 (safety analysis set)


<table>
<thead>
<tr>
<th>Parameter</th>
<th>Olaparib (n = 260)</th>
<th>Placebo (n = 131)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events (%)</td>
<td>118 (45)</td>
<td>100 (76)</td>
</tr>
<tr>
<td>Median PFS, months</td>
<td>56.0</td>
<td>13.8</td>
</tr>
<tr>
<td>Difference, months</td>
<td></td>
<td>42.2</td>
</tr>
<tr>
<td>HR: 0.33 (95% CI: 0.25-0.43)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Primary Endpoint: Investigator Assessed PFS

*13 patients, all in the Olaparib arm, continued study treatment past 2 years;†n = 130 (safety analysis set)

Median treatment duration
Olaparib: 24.6 months
Placebo†: 13.9 months
PRIMA: MAINTENANCE NIRAPARIB VS PLACEBO

In ovarian cancer at high risk of recurrence after 1L platinum: Randomised, double-blind, placebo-controlled Phase 3 trial (active, not recruiting, as of 10/2020)

*Stage III w/residual tumour after debulking surgery, inoperable stage III disease, or any stage IV disease.
†Dosing amended in November 2017 to 200 mg QD if <77 kg body weight, platelets <150,000/mm$^3$, or both.


Niraparib 300 mg QD†
(n = 487)

Placebo QD
(n = 246)

Secondary endpoints: OS, PFS2, QoL PROs, safety

Primary endpoint: PFS (HRD+ and overall population)
TESTING FOR HR STATUS IN OVARIAN CANCER: BRCA MUTATIONS, GENOMIC INSTABILITY

Both PRIMA and PAOLA-1 studies determined HR status using Myriad myChoice® companion diagnostic test

Tumours considered HRD if myChoice® CDx identified tBRCA+ and/or GIS ≥42

loss of heterozygosity

telomeric allelic imbalance

large-scale state transitions
PHASE III PRIMA TRIAL OF MAINTENANCE NIRAPARIB AFTER INITIAL THERAPY FOR OVARIAN CANCER

Patients with newly diagnosed high-grade serous/endometrioid advanced ovarian cancer after CR/PR to first-line platinum-based CT (N=730)

Primary endpoint: PFS by BICR with hierarchical testing in patients with HRD (HR benefit: 0.5) followed by the overall patient population (HR benefit: 0.65)

Niraparib provided clinical benefit in the HRD (BRCA\textsubscript{m} and BRCA\textsubscript{wt}) and HRP subgroups. All subgroups analyzed using adjusted Cox regression to account for stratification imbalances.

### PRIMA: PFS IN PATIENTS WITH HRD AND HRP (BY BICR)

Disease progression or death, according to prespecified subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Niraparib</th>
<th>Placebo</th>
<th>Hazard ratio for disease progression or death (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Homologous-recombination status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRCA mutation</td>
<td>49/152 (32.2)</td>
<td>40/71 (56.3)</td>
<td>0.40 (0.27–0.62)</td>
</tr>
<tr>
<td>No BRCA mutation, homologous-recombination deficiency</td>
<td>32/95 (33.7)</td>
<td>33/55 (60.0)</td>
<td>0.50 (0.31–0.83)</td>
</tr>
<tr>
<td>Homologous-recombination proficiency</td>
<td>111/169 (65.7)</td>
<td>56/80 (70.0)</td>
<td>0.68 (0.49–0.94)</td>
</tr>
</tbody>
</table>

In 2020, based on results from the Phase 3 PRIMA study, the FDA and EMA approved niraparib for the maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to first-line platinum-based chemotherapy.
PAOLA-1: MAINTENANCE OLAPARIB + BEVACIZUMAB AFTER INITIAL THERAPY FOR OVARIAN CANCER

Randomised, placebo-controlled Phase 3 trial for patients with newly diagnosed, FIGO stage III-IV, high-grade serous/endometrioid ovarian, fallopian tube or primary peritoneal cancer

Newly diagnosed advanced ovarian cancer upfront or interval surgery, and PR or CR to platinum-based CT≥ 3 cycles of bevacizumab (N=806)

2:1

Olaparib 300 mg BID for 2 yrs + Bevacizumab 15 mg/kg on Day 1 Q3W for 15 mos* (n = 537)

Placebo for 2 yrs + Bevacizumab 15 mg/kg on Day 1 Q3W for 15 mos* (n = 269)

*Including during CT

Primary endpoint: investigator assessed PFS (RECIST v1.1)
Secondary endpoints: TFST, PFS2, TSST, OS, HRQoL, AE
Sensitivity analysis: PFS by BICR

PHASE 3 PAOLA-1/ENGOT-OV25 TRIAL

Of maintenance olaparib + bevacizumab after initial therapy for ovarian cancer: Patients with newly diagnosed, FIGO stage III-IV, high-grade serous/endometrioid ovarian, fallopian tube or primary peritoneal cancer after CR/PR to platinum/taxane-based CT and ≥3 cycles of bevacizumab (N=806)

PAOLA-1: APPROXIMATELY 50% OF PATIENTS WERE HRD+

All trial participants evaluated for HRD using the Myriad myChoice® test

Prevalence of HRD in the PAOLA-1 overall study population consistent with HRD prevalence in the general ovarian cancer population

PHASE III PAOLA-1/ENGOT-OV25 TRIAL

Of maintenance olaparib + bevacizumab after initial therapy for ovarian cancer: Patients with newly diagnosed, FIGO stage III-IV, high-grade serous/endometrioid ovarian, fallopian tube or primary peritoneal cancer after CR/PR to platinum/taxane-based CT and ≥3 cycles of bevacizumab (N=806)

PAOLA-1: PFS BY HRD/BRCA STATUS

### ERA OF TARGETED THERAPY IN OVARIAN CANCER: 3 EMA APPROVED PARP INHIBITORS

<table>
<thead>
<tr>
<th>Agent</th>
<th>Maintenance</th>
<th>Later-Line Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Olaparib</strong></td>
<td>• SOLO-2 (BRCAm), Study 19: Recurrent 2017-08-17</td>
<td>• Study 42 (BRCAm) 2014-12-19</td>
</tr>
<tr>
<td></td>
<td>• SOLO-1 (BRCAm): First-line 2018-12-19</td>
<td></td>
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<tr>
<td></td>
<td>• PAOLO-1 (HRD): First-line 2020-05-08</td>
<td></td>
</tr>
<tr>
<td><strong>Rucaparib</strong></td>
<td>• ARIEL3: Recurrent 2018-04-06</td>
<td>• Study 10 (BRCAm), ARIEL2 2016-12-19</td>
</tr>
<tr>
<td><strong>Niraparib</strong></td>
<td>• NOVA: Recurrent (2017-03-27)</td>
<td>• QUADRA (HRD) 2019-10-23</td>
</tr>
<tr>
<td></td>
<td>• PRIMA: First-line 2020-04-29</td>
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</tr>
</tbody>
</table>
INTEGRATED MAINTENANCE TREATMENT PARADIGM FOR FIRST-LINE OVARIAN CANCER

CLINICAL DATA FOR PARP INHIBITORS

Breast cancer
OLYMPIAD: STUDY DESIGN
Randomised, open-label Phase 3 study

Stratified by HR status (ER+ and/or PgR+ vs TNBC), prior CT for metastases (yes vs no), prior platinum tx (yes vs no)

Patients with HER2-negative MBC with deleterious or suspected deleterious gBRCA mutation; previous anthracycline and taxane, ≤ 2 previous lines of CT* for metastatic disease; if HR+, not suitable for ET or progressed on ≥ 1 ET (N = 302)

Olaparib† 300 mg PO BID (n = 205)

CT‡ on 21-day cycles (n = 97 §)

Until PD or unacceptable AEs

Primary endpoint: PFS per modified RECIST 1.1 (BICR)
Secondary endpoints: time to second progression/death, OS, ORR, safety, tolerability, global HRQoL

*If platinum-based therapy, patient could not have experienced progression on tx in advanced setting or ≥ 12 mos since (neo)adjuvant tx.
†Tablet. ‡Physician’s choice of: capecitabine 2500 mg/m² PO Days 1-14; vinorelbine 30 mg/m² IV Days 1, 8; or eribulin 1.4 mg/m² IV Days 1, 8.
§ n = 6 patients declined treatment.

OLYMPIAD: PFS BY BICR (PRIMARYEndpoint)


Extended, exploratory follow-up analysis showed a mOS of 19.3 months with olaparib vs 17.1 months with CT (HR: 0.84; 95% CI: 0.63-1.12). 4-yr OS rates were 18.9% vs 14.2%, respectively
EMBRACA: TALAZOPARIB VS CHEMOTHERAPY

In advanced BRCA1/2-positive, HER2-negative breast cancer: Randomised, open-label Phase 3 study conducted at 145 sites in 16 countries

Stratified by HR status (ER+ and/or PgR+ vs TNBC), prior chemo regimens (0 vs ≥ 1), history of CNS metastases (yes vs no)

Patients with HER2-negative LA/MBC with deleterious or suspected deleterious germline BRCA1/2 mutation; previous anthracycline and/or taxane, ≤3 previous lines of CT* for advanced disease (N = 431)

Talazoparib 1.0 mg PO QD (n = 287)

Physician’s Choice of Chemotherapy† (n = 144)

21-day cycles

Primary endpoint: PFS by BICR
Secondary endpoints: ORR, OS, safety,
Investigational endpoints: DoR, QoL

*Previous platinum-based therapy for EBC permitted if DFI ≥6 mos. †Physician’s choice of: capecitabine 1250 mg/m² PO BID Days 1-14; eribulin 1.4 mg/m² IV Days 1, 8; gemcitabine 1250 mg/m² IV Days 1, 8; or vinorelbine 30 mg/m² IV Days 1, 8, and 15.
EMBRACA: PFS BY BICR (PRIMARY ENDPOINT)

Median follow-up time: 11.2 months

<table>
<thead>
<tr>
<th>PFS Outcome</th>
<th>Talazoparib (n = 287)</th>
<th>Standard CT (n = 144)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS events, %</td>
<td>186 (65)</td>
<td>83 (58)</td>
</tr>
<tr>
<td>Median PFS, mos (95% CI)</td>
<td>8.6 (7.2-9.3)</td>
<td>5.6 (4.2-6.7)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.54 (0.41-0.71); P&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>1-yr PFS, %</td>
<td>37</td>
<td>20</td>
</tr>
</tbody>
</table>

No OS advantage for talazoparib vs CT; findings consistent across all prespecified subgroups

EMA APPROVALS OF PARP INHIBITORS – BREAST CANCER

Olaparib
April 2019 EMA approves olaparib as monotherapy for use in patients with germline BRCA1/2-mutations who have HER2-negative locally advanced or metastatic breast cancer and have previously been treated with an anthracycline and a taxane in the (neo)adjuvant or metastatic setting (unless patients were not suitable for these treatments). Patients with hormone receptor-positive breast cancer should also have progressed on or after prior endocrine therapy or be considered unsuitable for endocrine therapy.

Talazoparib
June 2019: European Commission approves Talazoparib based on results from the EMBRACA trial - the largest Phase 3 study of a PARP inhibitor in gBRCA-mutated, HER2-LA or MBC.
Hormone receptor +ve defined as ER and/or PgR positive (IHC staining ≥1%). Triple negative defined as ER and PgR negative (IHC staining ≥1%).

OLYMPIA: INVASIVE DISEASE-FREE SURVIVAL (MATURE COHORT)

First 900 patients entered with median follow up of 3.5 years

Stratified hazard ratio 0.61 (99.5% CI, 0.39–0.95)*
Difference: 3-year IDFS rate 8.6% (95% CI, 3.3–13.9%)+

*Stratified Cox proportional hazards model; †Kaplan-Meier estimates.
Presented by Andrew Tutt at ASCO 2021. With permission from Prof A. Tutt.
OLYMPIA: DISTANT DISEASE-FREE SURVIVAL

Stratified hazard ratio 0.57 (99.5% CI, 0.39–0.83); P<0.0001

Difference: 3-year DDFS rate 7.1% (95% CI, 3.0–11.1%)

Presented by Andrew Tutt at ASCO 2021. With permission from Prof A. Tutt.
OLYMPIA: OVERALL SURVIVAL

Stratified hazard ratio 0.68 (99% CI, 0.44–1.05); P=0.024
not significant based on level of P<0.01 in IA alpha spending plan

Difference: 3-year overall survival rate 3.7% (95% CI, 0.3–7.1%)

Presented by Andrew Tutt at ASCO 2021. With permission from Prof A. Tutt.
OLYMPIA: SUMMARY OF ADVERSE EVENTS

Includes adverse events with an onset date on or after the first date and up to and including 30 days following date of last dose of study medication. AML, acute myeloid leukaemia; MDS, myelodysplastic syndrome. *Adverse events leading to permanent discontinuation of treatment in the Olaparib group that occurring in >1% were; nausea, anemia and fatigue. †Adverse events leading to death are cardiac arrest (Olaparib, n=1), AML (placebo, n=1), and ovarian cancer (placebo, n=1)

Presented by Andrew Tutt at ASCO 2021. With permission from Prof A. Tutt.

<table>
<thead>
<tr>
<th></th>
<th>Olaparib (N=911)</th>
<th>Placebo (N=904)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse event</td>
<td>835 (91.7%)</td>
<td>753 (83.3%)</td>
</tr>
<tr>
<td>Serious adverse event (SAE)</td>
<td>79 (8.7%)</td>
<td>76 (8.4%)</td>
</tr>
<tr>
<td>Adverse event of special interest</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MDS/AML</td>
<td>30 (3.3%)</td>
<td>46 (5.1%)</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>2 (0.2%)</td>
<td>3 (0.3%)</td>
</tr>
<tr>
<td>New primary malignancy</td>
<td>9 (0.1%)</td>
<td>11 (1.2%)</td>
</tr>
<tr>
<td></td>
<td>20 (2.2%)</td>
<td>32 (3.5%)</td>
</tr>
<tr>
<td>Grade ≥3 adverse event</td>
<td>221 (24.3%)</td>
<td>102 (11.3%)</td>
</tr>
<tr>
<td>Grade 4 adverse event</td>
<td>17 (1.9%)</td>
<td>4 (0.4%)</td>
</tr>
<tr>
<td>Adverse event leading to permanent discontinuation of treatment*</td>
<td>90 (9.9%)</td>
<td>38 (4.2%)</td>
</tr>
<tr>
<td>Adverse event leading to death†</td>
<td>1 (0.1%)</td>
<td>2 (0.2%)</td>
</tr>
</tbody>
</table>
CLINICAL DATA FOR PARP INHIBITORS

Prostate cancer
Metastatic CRPC

Mutations in DNA repair genes that benefit from PARP inhibition:
- BRCA2, BRCA1 may be most sensitive; PALB2, ATM may be insensitive; others?\(^1,2\)
- Olaparib (PROfound cohort genes):\(^3\) HRR genes, including BRCA
- Rucaparib (TRITON2)\(^4\): BRCA1, BRCA2 only

Sequencing
- After AR-targeted therapy (e.g., abiraterone, enzalutamide): Olaparib
- After chemotherapy and AR-targeted therapy: Rucaparib…for now

Monotherapy

OLAPARIB IN PROSTATE CANCER

EMA approved Sept 2020 - for metastatic CRPC with HRR gene mutations (germline or somatic)

- Previous treatment with enzalutamide or abiraterone

- Based on PROFOUND Phase 3 efficacy data (N = 386)
  - Major efficacy outcome was rPFS
    - Median rPFS w/BRCA1/2 or ATM mutations: 7.4 mos with olaparib vs 3.6 mos with enzalutamide or abiraterone
    - Median rPFS w/any PROFOUND cohort HRR mutation: 5.8 mos with olaparib vs 3.5 mos with enzalutamide or abiraterone
  - Supported by confirmed ORR, OS outcomes
PHASE III PROFOUND: OLAPARIB VS PHYSICIAN’S CHOICE IN PROGRESSING METASTATIC CRPC

Patients with mCRPC and progression on prior NHA; harboring gene alterations with a role in HRR† (N = 387)

Cohort A: BRCA1, BRCA2, or ATM alterations (n = 245)

Cohort B: Other alterations (n = 142)

Olaparib 300 mg BID (n = 162)

Physician’s Choice* (n = 83)

Olaparib 300 mg BID (n = 162)

Physician’s Choice* (n = 83)

2:1

2:1

Stratified by previous taxane (yes vs no) and measurable disease (yes vs no)

Crossover allowed upon progression on physician’s choice therapy

Primary endpoint: radiographic PFS in Cohort A using RECIST 1.1 and PCWG3 by BICR

Secondary endpoints: radiographic PFS in both cohorts, confirmed radiographic ORR in Cohort A, time to pain progression in Cohort A, OS in Cohort A

*Enzalutamide 160 mg QD or abiraterone acetate 100 mg QD plus prednisone 5 mg BID.
†BRCA1/2, ATM, BRIP1, BARD1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RA51D, or RAD54L.

Hussain M. ESMO 2019. Abstract LBA12_PR
80% of the patients in the control arm “crossed over” to receive olaparib

PROFOUND SUBGROUP ANALYSIS: NOT ALL MUTATIONS BENEFIT

RUCAPARIB IN PROSTATE CANCER

FDA approved May 2020 for BRCA-mutated metastatic CRPC, not yet EMA approved

- Previous treatment with AR-directed therapy and taxane chemotherapy
- Based on TRITON2 Phase 2 response data (N = 115)
  - Confirmed ORR: 44% (95% CI: 31-57) (n = 62 by RECIST)

TRITON3: Ongoing Phase 3 study of rucaparib vs physician’s choice of therapy in patients with metastatic CRPC associated with HRD (NCT02975934)

- Enrolling with planned N of 400
TRITON2: RUCAPARIB IN METASTATIC CRPC WITH HRR GENE ALTERATIONS

International, multicentre, open-label Phase 2 study

Patients with mCRPC and deleterious somatic or germline alteration in HRR genes*; progression on AR-directed tx† for PC and 1 prior line of taxane-based CT for CRPC; no prior PARPi, mitoxantrone, cyclophosphamide, or platinum-based CT; ECOG PS 0/1 (N = 85‡)

Rucaparib 600 mg BID in 28-d cycles §

Until radiographic progression or discontinuation for other reason

Primary endpoints
Among patients with measurable disease at BL: centrally assessed, confirmed ORR per modified RECISTII/PCWG3
Among patients without measurable disease at BL: locally assessed, confirmed PSA response (≥ 50% decrease) rate

*Local or central testing of blood or tumour samples for alterations in HRR genes: BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK2, FANCA, NBN, PALB2, RAD51, RAD51B, RAD51C, RAD51D, RAD51L. Abiraterone, enzalutamide, or apalutamide. †Enrollment cutoff: April 16, 2018. §Assessments: tumour Q8W for 24 wks, then Q12W; PSA Q4W. II.RECIST modified to include up to 10 target lesions (maximum 5 per site), excluding prostatic bed or bone lesions; MRI permitted.

Abida W. ESMO 2018. Abstract 793PD
TRITON2: RADIOGRAPHIC RESPONSES IN EVALUABLE PATIENTS

TRITON2: PSA RESPONSES IN EVALUABLE PATIENTS

TRITON2: PSA RESPONSES IN EVALUABLE PATIENTS

WHY?

CLINICAL DATA FOR PARP INHIBITORS

Pancreatic cancer
BRCA-MUTATED PANCREATIC CANCER

Germline BRCA1/2 mutations found in ~7% of patients with pancreatic cancer; additional mutations in other DDR genes (eg, PALB2, ATM)

Superior OS (22 vs 9 mos; P=0.039) for patients with BRCA1/2 mutations and stage 3/4 disease treated with platinum vs non-platinum chemotherapy regimens

Activity of PARP inhibitors (e.g., olaparib) in patients with BRCA mutations; several ongoing/early phase trials
- PARP inhibitors impair BER, inhibit SSBR/DSBR
- Phase II study of olaparib for patients with germline BRCA 1/2 mutation and prior gemcitabine: ORR in 5 of 23 (21.7%) patients

POLO: MAINTENANCE OLAPARIB VS PLACEBO AFTER FIRST-LINE PLATINUM-BASED THERAPY

In metastatic pancreatic cancer: International, randomised, double-blind Phase 3 trial

Patients with metastatic pancreatic cancer and deleterious/suspected deleterious germline BRCA1/2 mutation, ≥16 wks of first-line platinum-based therapy without progression (4-8 wks from last dose) (N=154)

3315 patients screened
247 had germline BRCA mutation (7.5%)

Primary endpoint: PFS by blinded independent central review

Key secondary endpoints: safety/tolerability, PFS2, ORR, OS, HRQoL

Patients with measurable disease at baseline

<table>
<thead>
<tr>
<th></th>
<th>Olaparib (n = 78)</th>
<th>Placebo (n = 52)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective response,* n (%)</td>
<td>18 (23.1)</td>
<td>6 (11.5)</td>
</tr>
<tr>
<td>Median time to response, mos</td>
<td>5.4</td>
<td>3.6</td>
</tr>
<tr>
<td>Median duration of response, mos</td>
<td>24.9</td>
<td>3.7</td>
</tr>
</tbody>
</table>

After 2 years, 22.1% of patients had no disease progression vs 9.6% of those who received placebo. Median duration of response was 24.9 months in the olaparib arm vs 3.7 months with placebo.

Olaparib is now EMA-approved for metastatic pancreatic adenocarcinoma with germline BRCA1 or BRCA2 mutation (since July 2020)
OVERVIEW

1. Background
2. Comparing PARP inhibitors
3. Concept of HRD
4. Clinical data for PARP inhibitors: ovarian, breast, prostate and pancreatic cancer
5. Extending the benefit beyond BRCA1/2 cancers
6. Coming full circle: Combos → monotherapy → combos
7. Evolving strategies moving forward
NEED FOR RATIONAL COMBINATIONS

Not all patients with BRCA1/2 mutant cancers will respond
Drug resistance is nearly inevitable
Potential to deepen responses
Potential to increase durability of response
Potential to widen the application of PARP inhibitors


Can we raise the tail on survival curve with rational PARP inhibitor combinations (akin to IO agents)?
CURRENT AND EVOLUTION OF PARP INHIBITOR COMBOS

a) Current landscape of ongoing DDR inhibitor clinical trials

b) Anticipated landscape of future DDR inhibitor clinical trials

Done to scale (www.clinicaltrials.gov)

My prediction

BUILDING ON PARP INHIBITOR MONOTHERAPY

Want more non-responders to respond
Want more responders to become super-responders

Molecularly targeted agents that induce Chemical BRCAness
  e.g. VGEF inhibitors

Immunotherapy
  e.g. PD-(L)1 inhibitors

DDR combos
  e.g. ATR inhibitors

COMBINING PARP INHIBITORS AND MOLECULARLY TARGETED AGENTS

Molecularly targeted agents that induce Chemical BRCAness

“CHEMICAL BRCANESS”

Enhance sensitivity to PARPi by inducing HRD phenotype in HR proficient tumours with molecularly targeted agents

"CHEMICAL BRCANESS"

Enhance sensitivity to PARPi by inducing HRD phenotype in HR proficient tumours with molecularly targeted agents

Multiple “Chemical BRCAness” combo trials are ongoing

STRATEGIES TO INDUCE TUMOUR “CHEMICAL BRCANESS”

A few examples (there are many more…)

**Aim: Enhance sensitivity to PARPi by inducing HRD phenotype in HR proficient tumours**

Antiangiogenic agents e.g. cediranib + olaparib

- Hypoxia leads to impaired HR by down-regulating HR genes (Bindra et al, Mol Cell Bio 2004)
- Cediranib suppresses homology-directed DNA repair by down-regulating BRCA1/2 and RAD51 (Kaplan et al, STM 2019)
- Phase 2 trial: PFS 23.7m vs 5.7m (P=0.002) with cediranib + olaparib vs olaparib; OS 37.8m vs 23.0m (P=0.047) in gBRCA wildtype/unknown patients (Liu et al, Annals of Oncology 2019)
- Phase 3 NRG-GY004 trial (n=565): No improved PFS in PSR ovarian cancer vs platinum-based chemo, but had comparable clinical activity (PFS; ORR). Further analysis in biomarker subgroups ongoing (Liu et al, ASCO 2020)

AR pathway e.g. abiraterone + olaparib

- Median rPFS 13·8m vs 8·2m with abiraterone + olaparib vs abi + placebo (p=0·034) (Clarke et al, Lancet Oncology 2018)

PI3K/AKT pathway inhibitors

- Alpelisib + olaparib: 10/28 (36%) PR in ovarian cancers (Konstantinopoulos et al, Lancet Oncology 2019)
- Capivasertib + olaparib: 25 (44.6%) of 56 pts achieved clinical benefit, including pts with germline BRCA1/2 mutant and BRCA1/2-wildtype cancers with or without DDR and PI3K/AKT pathway alterations (Yap et al, Cancer Discovery 2020)

BET inhibitors (Yang et al, STM 2017; Karakashev et al, Cell Reports 2017; Sun et al, Cancer Cell 2018)

AR pathway e.g. abiraterone + olaparib.

- Median rPFS 13·8m vs 8·2m with abiraterone + olaparib vs abiraterone + placebo (p=0·034) (Clarke et al, Lancet Oncology 2018)
COMBINING PARP INHIBITORS AND OTHER DDR AGENTS

DDR combos e.g. ATR inhibitors
COMBINING PARP AND ATR INHIBITORS
MECHANISTIC RATIONALE

1. PARP inhibitors cause increased DNA adducts which stall replication forks

2. ATR is required for repair of such stalled replication forks

3. In conjunction with e.g. ATM-deficiency, PARP + ATR inhibition will lead to increased DNA damage and cell death

PARP and ATR inhibitor combination trials are ongoing

Yap T, et al. AACR-NCI-EORTC (2016). By permission from Prof T. Yap
PHASE I TRIAL OF AZD6738 AND OLAPARIB

<table>
<thead>
<tr>
<th>Clinical characteristic</th>
<th>AZD6738 + ola</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender: male/female, n (%)</td>
<td>21/24 (47/53)</td>
</tr>
<tr>
<td>Median age, years (range)</td>
<td>52 (31-76)</td>
</tr>
<tr>
<td>ECOG performance status, n (%)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>23 (51)</td>
</tr>
<tr>
<td>1</td>
<td>22 (49)</td>
</tr>
<tr>
<td>Disease classification, * n (%)</td>
<td></td>
</tr>
<tr>
<td>Locally advanced</td>
<td>0</td>
</tr>
<tr>
<td>Metastatic</td>
<td>23 (51)</td>
</tr>
<tr>
<td>Both</td>
<td>21 (47)</td>
</tr>
<tr>
<td>Missing</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Recurrence of earlier cancer, n (%)</td>
<td>18 (40)</td>
</tr>
<tr>
<td>Median number of prior regimens of chemotherapy (range)</td>
<td>3.0 (1-6)</td>
</tr>
<tr>
<td>Primary tumour location,† n (%)</td>
<td></td>
</tr>
<tr>
<td>Breast, ovary, prostate, lung, pancreas, stomach, colorectal</td>
<td>12 (27), 5 (11), 5 (11), 3 (7), 3 (7), 3 (7), 2 (4)</td>
</tr>
</tbody>
</table>

Is this sufficient ATR inhibition for synergy?

Yap T, et al. AACR-NCI-EORTC (2016). By permission from Prof T. Yap
All responses involved BRCA1/2 mutant cancers

Yap T, et al, AACR-NCI-EORTC 2016;
Krebs M, et al. AACR 2018. By permission from Prof M. Krebs
**PHASE I TRIAL OF AZD6738 AND OLAPARIB**

Adverse events of all causes

<table>
<thead>
<tr>
<th>Patients with an AE, n (%)</th>
<th>AZD6738 + ola (N=45)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any grade</td>
<td>Grade ≥3</td>
</tr>
<tr>
<td>Fatigue</td>
<td>29 (64)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Nausea</td>
<td>26 (58)</td>
<td>0</td>
</tr>
<tr>
<td>Anaemia</td>
<td>25 (56)</td>
<td>7 (16)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>14 (31)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Constipation</td>
<td>12 (27)</td>
<td>0</td>
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<tr>
<td>Thrombocytopenia*</td>
<td>12 (27)</td>
<td>5 (11)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>12 (27)</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>10 (22)</td>
<td>0</td>
</tr>
<tr>
<td>Neutropenia†</td>
<td>10 (22)</td>
<td>6 (13)</td>
</tr>
<tr>
<td>Cough</td>
<td>9 (20)</td>
<td>0</td>
</tr>
<tr>
<td>Ascites</td>
<td>2 (4)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>5 (11)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Syncope</td>
<td>2 (4)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>White blood cell count decreased</td>
<td>5 (11)</td>
<td>2 (4)</td>
</tr>
</tbody>
</table>

*Includes preferred term of decreased platelet count; †Includes preferred term of neutrophil count decreased


Should we be seeing more supra-additive toxicities?
COMBINING PARP AND IMMUNE CHECKPOINT INHIBITORS

Initial hypothesis: PARPi ➔ DNA damage ➔ Increased neoantigen expression ➔ More antigenic immune microenvironment

S phase-specific DNA damage; accumulation of cytosolic DNA; activates c-GAS-STING innate immune response; stimulates type 1 IFN, CD8 T-cell recruitment\(^1\)

- PARPi triggers the **STING-dependent** immune response and enhances the therapeutic efficacy of immune checkpoint blockade independent of BRCAness\(^1\)

PARP inhibition inactivates GSK3\(B\), leading to PD-L1 upregulation; *in vivo* synergy

- PARP inhibitor **upregulates PD-L1 expression** and enhances cancer-associated immunosuppression

---

**Combining DDR and PD-1/L1 inhibitors is a rational antitumour strategy**

---

PHASE 1/2 MEDIOLA TRIAL OF OLAPARIB + DURVALUMAB
Platinum-sensitive recurrent BRCA1/2 mutant ovarian cancers

Will this combo be significantly better than olaparib monotherapy?

Drew Y, et al. SGO, 2018. By permission from Dr Y. Drew
PHASE 1/2 MEDIOLA TRIAL OF OLAPARIB + DURVALUMAB
Platinum-sensitive recurrent BRCA1/2 mutant ovarian cancers

Tumor responses

<table>
<thead>
<tr>
<th>Best Response</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>6 (19)</td>
</tr>
<tr>
<td>PR</td>
<td>17 (53)</td>
</tr>
<tr>
<td>SD</td>
<td>3 (9)</td>
</tr>
<tr>
<td>PD</td>
<td>3 (9)</td>
</tr>
<tr>
<td>NE</td>
<td>3 (9)</td>
</tr>
</tbody>
</table>

Best percentage change in target lesion size

Global Phase 3 durvalumab-olaparib (DUO-O) Trial in 1L advanced ovarian cancer
PHASE 1/2 MEDIOLA TRIAL OF OLAPARIB + DURVALUMAB

Platinum-sensitive recurrent BRCA1/2 mutant ovarian cancers

Safety (N=34)

<table>
<thead>
<tr>
<th>Adverse events* (grade ≥3)</th>
<th>Patients n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaemia</td>
<td>4 (12)</td>
</tr>
<tr>
<td>Increased lipase</td>
<td>3 (9)</td>
</tr>
<tr>
<td>Decreased lymphocyte count</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Increased amylase</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Neuralgia</td>
<td>2 (6)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Immune-mediated adverse events† (all grades)</th>
<th>Patients n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypothyroidism</td>
<td>5 (15)</td>
</tr>
<tr>
<td>Rash</td>
<td>4 (12)</td>
</tr>
<tr>
<td>Adrenal insufficiency</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Amylase increase</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Blood testosterone decreased</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Lipase increased</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>2 (6)</td>
</tr>
</tbody>
</table>

*The following AEs were found in N=1 patient (3% of population): Decreased neutrophil count, device-related infection, erythema, hypoalbuminemia, hypotension, ileus, infusion-related reaction, maculopapular rash, peripheral edema, pleural effusion, pulmonary embolism, sepsis, small bowel obstruction, vomiting, hypokalemia, encephalitis autoimmune, pneumonitis, ascites, constipation, blister, weight decreased, fibula fracture.

†The following AEs were found in N=1 patient (3% of population): ALT increase, blood TSH increased, diplopia, dry skin, dyspnea, dyspnea exertional, encephalitis autoimmune, headache, influenza-like illness, lethargy, muscular weakness, peripheral sensorimotor neuropathy, photosensitivity reaction, pneumonia, pneumonitis, pruritus, maculopapular rash, stomatitis, thyroiditis, tremor, vomiting, blood uric acid increased.

Drew Y, et al. SGO March 2018
TOPACIO: PHASE 1/2 NIRAPARIB + PEMBROLIZUMAB IN PLATINUM-RESISTANT OVARIAN CANCER

Monotherapy activity cheat sheet
- Olaparib in tBRCAmut platinum-resistant patients: ORR 25-30%
- Olaparib in tBRCAwt platinum-resistant patients: ORR ~5%
- Olaparib in tBRCAmut platinum-refractory patients: ORR 0-14%
- Nivolumab: ORR 15%
- Pembrolizumab: ORR 11%

HRD status did not correlate with response to this combo in platinum resistant/ refractory disease. Addition of pembrolizumab to niraparib in tBRCAwt and HRD-neg led to similar ORR to PARPi monotherapy efficacy in tBRCAmut population.

<table>
<thead>
<tr>
<th>Platinum status</th>
<th>Response</th>
<th>All (%)</th>
<th>tBRCA mut (%)</th>
<th>HRD-pos* (%)</th>
<th>tBRCA wt (%)</th>
<th>HRD-neg (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evaluable platinum-resistant and -refractory patients</td>
<td>ORR</td>
<td>11/46 (24)</td>
<td>2/7 (29)</td>
<td>4/15 (27)</td>
<td>9/34 (26)</td>
<td>7/24 (29)</td>
</tr>
<tr>
<td></td>
<td>DCR</td>
<td>31/46 (67)</td>
<td>4/7 (57)</td>
<td>10/15 (67)</td>
<td>23/34 (68)</td>
<td>15/24 (63)</td>
</tr>
</tbody>
</table>

*HRD status did not correlate with response to this combo in platinum resistant/ refractory disease.
Addition of pembrolizumab to niraparib in tBRCAwt and HRD-neg led to similar ORR to PARPi monotherapy efficacy in tBRCAmut population.
MEDIOLA TRIAL: OLAPARIB AND DURVALUMAB IN PATIENTS WITH BRCA-MUTATED BREAST CANCER

Swimmer plot by hormone receptor status (n=30)

First study to report results for hormone receptor positive disease
Promising antitumour activity and safety similar to olaparib and durvalumab monotherapy

HAVE WE COME FULL CIRCLE WITH PARP INHIBITORS?
Combos to mono to combos again... toxicity issues

**Antiangiogenic combos:** Cediranib+olaparib: 70% ≥G3 tox, e.g. diarrhea, fatigue, hypertension; 77% DR with combo vs 24% with olaparib. Cediranib 30 mg qd and olaparib capsules 200 mg bid

**PI3K inhibitor combos:** BKM120 DLTs of G3 ALT/AST, hyperglycemia, depression. MTD: BKM120 50 mg qd and olaparib 300 mg bid. BYL719 combo better tolerated

**DDR-DDR inhibitor combos:** AZD6738+olaparib: Myelosuppression; AZD6738 160 mg qd D1-7 + 300 mg bid olaparib.

**PD-1/PD-L1 inhibitor combos:** Generally no overlapping toxicities. Pamiparib + tislelizumab: hepatic toxicities

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CONCURRENT PARP INHIBITOR COMBOS

Toxicity issues

DDR inhibitor combos: AZD6738+olaparib: Myelosuppression; AZD6738 160 mg qd D1-7 + 300 mg bid olaparib q4 weekly cycles

Antiangiogenic combos: Cedirinib + olaparib: 70% ≥G3 tox, e.g. diarrhoea, fatigue, hypertension; 77% DR with combo vs 24% with olaparib. Cediranib 30 mg qd + olaparib capsules 200 mg bid

PI3K inhibitor combos: Buparlisib DLTs of G3 ALT/AST, hyperglycaemia, depression. MTD: Buparlisib 50 mg qd and olaparib 300 mg bid. Alpelisib combo better tolerated; G3–4 hyperglycaemia (16%), nausea (9%), and ALT (9%). Alpelisib 200 mg qd + olaparib tablets 200 mg bid

PD-1/L1 inhibitor combos: Generally no overlapping toxicities. Pamiparib + tislelizumab: hepatic toxicities

Do we need full monotherapy MTD/RP2D doses of both drugs? MTD vs MFD (maximum feasible dose)

1. Supportive measures
2. Dose modifications
   a. Dose reductions; maintain schedule (impact efficacy?)
   b. Maintain dose; Drug holidays (impact efficacy?) - Are pulsatile high doses preferable to continuous lower doses?
3. Avoid concomitant dosing; maintenance after platinum using platinum-sensitivity as biomarker
4. Drug modifications: CBX-11 (Cybrexa) - conjugation of rucaparib to alphalex peptide shows synergistic efficacy with chemo without compounded toxicity
5. Better Phase 1 combo trial designs focused on different schedules (incorporate chronic toxicities)
6. Creative scheduling, e.g. sequential dosing of PARPi + WEE1

Concurrent PARPi and WEE1i:
- Effective, but poorly tolerated
- Induces replication stress (RS) and DNA damage in both normal and malignant cells

Following cessation of PARPi or WEE1i monotherapy, drug effects persist

Sequential PARPi and WEE1i:
- Efficacy mirrored concurrent therapy in cancer cells with high basal RS
- Low basal RS in normal cells protected them from DNA damage and toxicity
- Improves tolerability while preserving efficacy in xenograft and PDX models

SUMMARY

PARP inhibitors: well-tolerated single-agent strategy for the treatment of ovarian cancer, germline BRCA-mutant breast cancers, prostate and pancreatic cancer

Need to build on PARP inhibitor monotherapy efficacy

- Rational combinations will widen breadth of application of PARP inhibitors

Clear opportunities in different tumours and molecular subtypes beyond current monotherapy-approved indications

- Concurrent chemotherapy combos are challenging; rational approaches with IO, DDR agents and other targeted therapies
- Combination efficacy needs to be balanced against synergistic toxicities
THANK YOU!

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