DNA Repair Inhibitors in Ovarian Cancer: Current Status and Future Strategies

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Why DNA Repair Inhibition?

• To selectively kill cancer cells with a defect in DNA repair

• In combination with DNA-damaging anticancer agents to overcome resistance
DNA Repair Inhibitors in Ovarian Cancer

Agents with efficacy demonstrated in randomized trials:

• Olaparib: PARP inhibitor
• AZD 1775: WEE1 Kinase inhibitor

Agents in earlier clinical development targets include:

• Afuresertib ➔ AKT
• Guadecitabine (SGI-110) ➔ DNMT inhibitor (epigenetic)
• PRIMA-1\(^{\text{MET}}\) (APR-246) ➔ Mutant p53
• Others ➔ ATR/ATM; CHK 1/2, DNA-PK, etc

AND: Don’t forget targeted chemotherapy!
PARP Inhibition and Tumor-Selective Synthetic Lethality

DNA damage (SSBs)

DNA replication (accumulation of DNA DSBs)

Normal cell with functional HR pathway

HR-mediated DNA repair

Cell survival

PARP inhibition

HR-deficient tumor cell (e.g., BRCA1/2−/−)

Impaired HR-mediated DNA repair (NHEJ etc.)

Cell death

Tumor-selective cytotoxicity

PARP, poly(ADP)ribose polymerase; DSB, double-strand break; HR, homologous recombination; SSB, single-strand break; NHEJ, non-homologous end joining.

PARP inhibitors can also trap cytotoxic PARP-DNA complexes; clinical relevance unclear.

The Incidence of BRCA Mutations in High-Grade Serous Ovarian Cancer

- BRCA1/2 germline mutation 14%
- BRCA1/2 somatic mutation 6%
- Total 20%

BRCA germline mutation testing should be routine…? somatic testing too

Approx 50% of HGSOC could be candidates for PARPi

**Olaparib, Chapter 1, 2005-9**

### Preclinical

Exquisite preclinical efficacy of PARPi in *BRCA* deficient ES cells

- Clonogenic survival curves with inc. concentration of KU 58948
  - **KU-0058948**
  - **IC<sub>50</sub> = 3.4 nM**
  - 1250 fold difference in SF50 between *BRCA2* -/- and +/+  

**“this is nothing like chemotherapy”**

**Early clinical trials**

(Phase I incl. IB)

Phase I trial of KU59436 (olaparib) indicated excellent tolerance and expansion in 50 *BRCA* patients showed 46% response


**Olaparib, Chapter 2, 2010-14**  
Randomized Trial of Maintenance Olaparib in Platinum-Sensitive Relapsed Ovarian Cancer (Study 19)

### Study aim and design

**Patients:**
- Platinum-sensitive high-grade serous ovarian cancer
- \( \geq 2 \) previous platinum regimens
- Last chemotherapy was platinum-based to which they had a maintained PR or CR prior to enrolment
- Stable CA-125

<table>
<thead>
<tr>
<th>Olaparib 400 mg PO bid</th>
<th>Placebo PO bid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized 1:1</td>
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</table>

**Treatment until disease Progression**

**Primary endpoint:** PFS

Total of 265 recruited: Of which 51% had germline/somatic *BRCA* mutation

Study 19: Met PFS Primary Endpoint

HR = 0.35
(95% CI: 0.25, 0.49)
P<.00001

Number at Risk

<table>
<thead>
<tr>
<th></th>
<th>Olaparib N = 136</th>
<th>Placebo N = 129</th>
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<tbody>
<tr>
<td>0</td>
<td>136</td>
<td>129</td>
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<tr>
<td>3</td>
<td>106</td>
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<tr>
<td>6</td>
<td>53</td>
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<tr>
<td>9</td>
<td>24</td>
<td>7</td>
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<tr>
<td>12</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>15</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Median (95% CI):
- Olaparib: 8.4 months (7.4, 11.5)
- Placebo: 4.8 months (4.0, 5.5)

PFS in Patients With a *BRCA* Mutation*

**BRCAm (n = 136)**

<table>
<thead>
<tr>
<th></th>
<th>Olaparib</th>
<th>Placebo</th>
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</thead>
<tbody>
<tr>
<td>Events: total patients (%)</td>
<td>26:74 (35.1)</td>
<td>46:62 (74.2)</td>
</tr>
<tr>
<td>Median PFS, months</td>
<td>11.2</td>
<td>4.3</td>
</tr>
</tbody>
</table>

**HR = 0.18**

95% CI (0.10, 0.31); *P* < .00001

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*BRCAwt, BRCA wildtype*

*Includes patients with germline and/or somatic mutations; †patients were treated until disease progression

Overall Survival in Patients With *BRCA* Mutation

- **14/62 (22.6%)** placebo patients switched to a PARP inhibitor

### Randomized treatment

- **Olaparib** *BRCA*m
- **Placebo** *BRCA*m

### Deaths: total patients (%)

<table>
<thead>
<tr>
<th></th>
<th>Olaparib</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>37:74 (50.0)</td>
<td>34:62 (54.8)</td>
<td></td>
</tr>
</tbody>
</table>

### Median OS, months

<table>
<thead>
<tr>
<th></th>
<th>Olaparib</th>
<th>Placebo</th>
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</thead>
<tbody>
<tr>
<td>34.9</td>
<td>31.9</td>
<td></td>
</tr>
</tbody>
</table>

### HR = 0.73

95% CI (0.46, 1.19)

*P* = 0.192

**Note:** Only 58% of maturity – next analysis – this year? impact of long-term survivors

Randomized Trial of Olaparib as Maintenance Therapy in Platinum-Sensitive Sporadic Ovarian Cancer

Trial positive for primary endpoint (PFS). But overall survival impact less clear.

Does this reflect cross-over (23%), or too early analysis? When patients progress on olaparib do they still respond to platinum?

In separate retrospective analysis of chemo given post olaparib:
• 19/48 (40%) response to platinum
• Med PFS. 22 weeks
• No evidence of secondary BRCA mutations in 6 cases.

What do we really know about PARPi (and platinum) resistance?
Resistance to PARP Inhibitors

- Is likely to be multifactorial; factors to consider include:
  - Secondary BRCA mutation
  - P-glycoprotein-based enhanced drug efflux
  - Reduced 53BP1, partially restoring HR
  - NER pathway alterations
  - And why do a minority of cases (up to 20%) stay in remission long-term?
  - Is this all due to tumor heterogeneity?

Answers will require tumor samples from patients progressing on PARPi

Meanwhile…..Olaparib in Advanced Recurrent BRCAm Ovarian Cancer

From the Kaufman et al paper, data on subgroup of 137 patients who received ≥3 lines of chemo presented to FDA for accelerated approval
- Response rate 34%; response duration 7.9 months

Total of 300 patients treated in 6 trials including:
- Initial phase I/II trials
- Randomized trial vs PLD
  - Kaye et al, JCO 2012
- Bioavailability and scheduling studies
  - Capsule » tablet, cont. v intermittent, Mateo et al, EJC 2013
- Non-randomized, multiple BRCAm disease
  - Kaufman et al JCO 2015

Status of Olaparib – January 2016

a) As capsules (400 mg bd)

Europe – approved as maintenance treatment for platinum sensitive relapsed BRCA m ovarian cancer – patients in remission following platinum-based therapy

USA – approved as monotherapy for patients who have received ≥3 lines of chemotherapy
  - Not approved as maintenance therapy
  - Approval also for companion diagnostic (Myriad Genetics BRCA analysis CDx)

b) As tablets (300 mg bd)
  - Confirmatory studies ongoing
PARP Inhibitors – What Are The Next Steps?

- Define activity in sporadic ovarian cancer and other cancers, eg, prostate
- Assess PARP inhibitors other than olaparib (rucaparib, niraparib, BMN-673)
- Develop robust predictive biomarker
- Test novel combinations (with P13K or angiogenesis inhibitors, etc)
- Monitor long-term toxicity
- Understand mechanisms of PARPi resistance
# Single-Agent Activity for PARP Inhibitors in Ovarian Cancer

<table>
<thead>
<tr>
<th>Drug</th>
<th>BRCA Mutation Positive</th>
<th>BRCA Wildtype and Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>% Resp RECIST</td>
</tr>
<tr>
<td>Olaparib</td>
<td>&gt;100 (most plat resist)</td>
<td>30 to 60%</td>
</tr>
<tr>
<td>Rucaparib</td>
<td>39 (all plat sens)</td>
<td>69%</td>
</tr>
<tr>
<td>Niraparib</td>
<td>20 (9 plat sens)</td>
<td>45%</td>
</tr>
<tr>
<td>BMN 673</td>
<td>28 (22 plat sens)</td>
<td>68%</td>
</tr>
</tbody>
</table>

Homologous Recombination Deficiency (HRD) Assay Do We Have One?

- HRD causes genome wide loss of heterozygosity (LOH), which can be measured by genome profiling using NGS
- Algorithm developed for LOH score (high/low), ie, BRCA-like signature, with LOH cut off derived from OS data on cohort of 309 platinum-treated patients

- Correlation with efficacy of rucaparib in Phase II trial – ARIEL 2

BRCA-like : HRD high PFS: 7m
Biomarker neg: HRD low PFS 4m

Progression-free survival by HRD molecular subgroup

Homologous Recombination Deficiency (HRD) Assay
Do We Have Another?


Developed HRD score incorporating 3 components:

- Loss of heterozygosity (LOH)
- Telomeric allelic imbalance (TAI)
- Large-scale state transitions (LST)

HRD score is sum of LOH + TAI + LST scores
- Presented evidence of correlation between HRD score and *in vitro/in vivo* response to niraparib in 106 tumor samples
  – Clinical data in ovarian cancer awaited

Thus:
- Two assays under further evaluation, as key elements in 2 ongoing randomized maintenance trials, with niraparib and rucaparib in sporadic and *BRCAm*-associated ovarian cancer
PARP Inhibitor – Combination Strategies

**Aim:** Enhance activity of PARPi by increasing HRD in treated cells

Pre-clinical and clinical data with:

- Antiangiogenic agents
- P13K/AKT pathway inhibitors

Pre-clinical data with:

- Wee1 Kinase inhibitors
- ATR inhibitors

Antiangiogenic Agents/PARP Inhibitors

- Complementary targets/mechanisms of action

- Potential enhancement of sensitivity to PARPi by increasing HRD through changes in oxygenation caused by antiangiogenic agent

- Bevacizumab/olaparib – phase I trials confirmed feasibility and randomised trial planned

- Cediranib/olaparib – positive randomised trial presented at ASCO 2014 – further randomised trials (incl. maintenance) ongoing

Will benefit mainly be in patients with BRCA wildtype?

PARP Inhibitor Plus PI3K Inhibitor

- Preclinical data in TNBC cells demonstrate that PI3K inhibition suppresses BRCA1/2 expression and enhances sensitivity to PARP inhibition, partly through activation of ERK and transcription factor ETS1

- Phase I trials now underway, including olaparib plus AZD5363
  - Initial data encouraging with no overlapping toxicity

Control  –
BKM 120  –
Olaparib  –
BKM plus olaparib  –


DNA Repair Inhibitors in Ovarian Cancer

Clinical data so far available:

a) As monotherapy to selectively kill cancer cells with defects in DNA damage response or DNA repair.

b) In combination with DNA-damaging cytotoxic, eg, carboplatin, to increase its efficacy by inhibiting DNA-repair.

WEE-1 Kinase as a Target in Ovarian Cancer

Combination with chemotherapy

- TP53 mutated in >90% of HGSOC, resulting in loss of regulation of G1/S cell cycle point.
- TP53 mutant tumours more dependent on G2/M checkpoint to repair damaged DNA – this is regulated by Wee-1 kinase.
- AZD1775 is a small molecule Wee-1 kinase inhibitor, which acts synergistically with chemo, including platinum, particularly in TP53-mutant cell lines and xenografts through deregulation of G2/M checkpoint.
- Clinical trial data available in both platinum-sensitive and resistant disease.

Slide courtesy of Amit Oza
Randomized Trial of Carbo/Paclitaxel ± AZD1775 in Platinum Sensitive Relapsed Ovarian Cancer

Recurrent HGSOC

Loss of function p53 mutation

≥6 months platinum-free interval

n = 59
Carbo AUC 5
Paclitaxel 175 mg
+ AZD 1775 225 mg bd
2.5 days only on each 21-day cycle

n = 62
Carbo AUC5
Paclitaxel 175 mg + placebo bd for
2.5 days only on each 21-day cycle

358 tumors sequenced using Roche p53 Amplichip

192 (53.6%) eligible mutations
113 (31.6%) wildtype
53 (14.8%) ineligible mutation

Primary endpoint PFS (using enhanced RECIST v 1.1) – volumetric, Secondary endpoint PFS (using RECIST v 1.1) – longest diameters

Progression-Free Survival by Enhanced RECIST

**AZD1775 + P/C n = 59**
- **PFS events, n (%)**: 35 (59.3)
- **Median PFS, weeks**: 34.14

**P/C + Placebo n = 62**
- **PFS events, n (%)**: 37 (59.7)
- **Median PFS, weeks**: 31.86

*HR = 0.63, 80% CI 0.45, 0.89, 95% CI 0.38, 1.06, P = .080*

**AZD1775 + P/C n = 59**
- **PFS events, n (%)**: 34 (57.6)
- **Median PFS, weeks**: 42.86

**P/C + Placebo n = 62**
- **PFS events, n (%)**: 32 (51.6)
- **Median PFS, weeks**: 34.86

*HR = 0.55, 80% CI 0.39, 0.79, 95% CI 0.32, 0.95, P = .030*

*Significant improvement in PFS*

### Response Rates by Enhanced RECIST, RECIST 1.1 and CA-125 Levels

<table>
<thead>
<tr>
<th></th>
<th>AZD1775 + P/C</th>
<th>P/C + Placebo</th>
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</thead>
<tbody>
<tr>
<td></td>
<td><strong>n = 59</strong></td>
<td><strong>n = 62</strong></td>
</tr>
<tr>
<td>Enhanced RECIST/CA-125 response ORR, % (95% CI)</td>
<td>81.4 (69.1, 90.3)</td>
<td>75.8 (63.3, 85.8)</td>
</tr>
<tr>
<td>RECIST 1.1 only response ORR, % (95% CI)</td>
<td>66.1 (52.6, 77.9)</td>
<td>51.6 (38.6, 64.5)</td>
</tr>
<tr>
<td>CA-125 only response Response rate, %</td>
<td>81.4</td>
<td>74.2</td>
</tr>
</tbody>
</table>

Trend to higher response rate using all criteria

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### Safety and Tolerability

<table>
<thead>
<tr>
<th>AE category</th>
<th>AZD1775 + P/C</th>
<th></th>
<th>P/C + Placebo</th>
<th></th>
</tr>
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<tbody>
<tr>
<td></td>
<td>n = 59</td>
<td>n = 60</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AEs*</td>
<td>All Grades</td>
<td>Grade ≥3</td>
<td>All Grades</td>
<td>Grade ≥3</td>
</tr>
<tr>
<td>Diarrhoea, n (%)</td>
<td>44 (74.6)</td>
<td>6 (10.2)</td>
<td>22 (36.7)</td>
<td>2 (3.3)</td>
</tr>
<tr>
<td>Vomiting, n (%)</td>
<td>37 (62.7)</td>
<td>6 (10.2)</td>
<td>16 (26.7)</td>
<td>1 (1.7)</td>
</tr>
<tr>
<td>Anemia, n (%)</td>
<td>31 (52.5)</td>
<td>12 (20.3)</td>
<td>19 (31.7)</td>
<td>4 (6.7)</td>
</tr>
<tr>
<td>Neutropenia, n (%)</td>
<td>26 (44.1)</td>
<td>21 (35.6)</td>
<td>24 (40.0)</td>
<td>20 (33.3)</td>
</tr>
<tr>
<td>Thrombocytopenia, n (%)</td>
<td>21 (35.6)</td>
<td>12 (20.3)</td>
<td>16 (26.7)</td>
<td>7 (11.7)</td>
</tr>
</tbody>
</table>

No major differences in treatment tolerability

AE, adverse event

*AEs tabulated with frequency >35% in the AZD1775 + P/C arm

WEE1 Inhibitor/Chemotherapy in Platinum-Resistant Relapsed Ovarian Cancer

- Phase II trial of AZD1775 plus carboplatin AUC5 in 22 eval. patients with p53-mutated cancer, platinum-refractory or resistant (<3 m) to first-line carbo/paclitaxel
  - 6/22 (27%) had RECIST PR with med PFS of 10.9 m
  - 9/22 (41%) had RECIST SD with med PFS of 5.3 m

- Further phase II studies of AZD 1775/chemo underway in platinum-resistant disease

WEE-1 Kinase as a Target in Ovarian Cancer – Other Approaches

Monotherapy

- Wee-1 kinase inhibition abrogates G2-M arrest, propelling cells into premature mitosis and cell death.
- In vitro studies and PD data from single agent Phase I trial, suggest AZD1775 can induce cytotoxicity based on DNA damage.
- In phase I monotherapy trial, 2 responses seen (in patients with BRCA mutation) – further study planned in PARPi-failures.


Combination with olaparib

- Wee-1 kinase inhibition also induces HRD
- Wee-1 kinase inhibition sensitises BRCA proficient cells to PARP inhibition
- Phase I trial of olaparib/AZD1775 underway
Strategies to Circumvent Platinum Resistance

Mechanisms underlying platinum resistance may include:

- Enhanced repair of DNA damage
  - WEE1 inhibitor
  - AKT inhibitor
- Failure to recognize DNA damage
  - Demethylating agent
- Failure to trigger apoptosis
  - Target mutant p53, e.g., APR-246

Therapeutic approaches may include
Targeting AKT as Strategy for Resistance Reversal

P13 kinase/AKT pathway activation (mutations/amplification) seen in up to 40% of ovarian cancer – in patients with ascites, correlation with drug resistance is noted.

Afuresertib (GSK 2110183)
- Pan AKT inhibitor, preclinically reverses platinum resistance in vitro
- Phase I study combined with paclitaxel/carboplatin included 23 patients with platinum resistant/refractory disease

For patients treated at MTD (125 mg)
  RECIST resp 50%
  GCIG resp 50%

Demethylation as a Strategy for Resistance Reversal

- Platinum resistance due to failure to recognise DNA damage through methylation of HMLH1
- Demethylating agent, decitabine enhances platinum response in vitro/vivo
- Clinical correlation established between methylation acquisition and drug resistance

BUT: in randomised clinical trial, decitabine does not enhance (actually reduces) efficacy of carboplatin and trial stopped.


Will guadecitabine (SG110) do better?
- Decitabine analogue, superior in vitro
- Ongoing randomized trial with carboplatin in platinum resistant disease (Fleming et al. AACR. 2014.)
Targeting p53 as Resistance Reversal Strategy

- **Cells with mutant p53** less able to trigger apoptosis following chemo, eg, platinum

- **APR-246 (PRIMA-1)** small molecule pro-drug restoring mutant p53 to wildtype configuration, sensitising ovarian cancer cells to platinum

Ongoing clinical trial combining APR-246 with PLD/carboplatin (PISARRO) shows encouraging safety and activity profile, with RECIST response in all (8) patients treated so far (platinum-sensitive disease)

And Finally, Don’t Forget: Antibody-Targeted Chemotherapy in Ovarian Cancer!

<table>
<thead>
<tr>
<th>Target</th>
<th>“Warhead”</th>
<th>Antibody Drug Conjugate</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>Folate receptor¹</td>
<td>Maytansinoid</td>
<td>IMGN853</td>
<td>Immunogen</td>
</tr>
<tr>
<td>NaPi2B²</td>
<td>MMAE</td>
<td>DNIB 0600</td>
<td>Genentech</td>
</tr>
<tr>
<td>Mesothelin³</td>
<td>MMAE</td>
<td>DMOT 4039A</td>
<td>Genentech</td>
</tr>
<tr>
<td>Tissue factor⁴</td>
<td>MMAE</td>
<td>HuMax-TF</td>
<td>Genmabs</td>
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<tr>
<td>MUC 16⁵</td>
<td>MMAE</td>
<td>DMUC 5754</td>
<td>Genentech</td>
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<tr>
<td>PTK7⁶</td>
<td>MMAE</td>
<td>PF 0664702</td>
<td>Pfizer</td>
</tr>
</tbody>
</table>

MMAE, monomethyl auristatin

- Examples of efficacy in platinum-resistant ovarian cancer in all cases
- Randomized studies planned/ongoing

Summary – DNA Repair Inhibitors

• In ovarian cancer, targeting DNA repair pathways, using both single agent and combination approaches, represents an important step forward in therapy

• Understanding clinical resistance to platinum (using paired samples) is a key priority for further research
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2016

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