PARP Inhibitors: Patients Selection

Dr. Cristina Martin Lorente
Hospital de la Santa Creu i Sant Pau
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OVARIAN CANCER (OC): MULTIPLES DISEASES

- Different types with different behaviour
- Commonest – High grade serous ovarian cancer (HGSOC)
- HGSOC: Associated with characteristics of genomic instability (TP53) and homologous recombination deficiency (BRCA)
DNA REPAIR PATHWAYS

DOUBLE-STRAND DNA DAMAGE:
HOMOLOGOUS RECOMBINATION REPAIR PATHWAY ➔ BRCA KEY ROLE

SINGLE-STRAND DNA DAMAGE:
PARP ➔ INHIBITING PARP-1 INCREASES DOUBLE-STRAND DNA DAMAGE
USE BRCA DEFICIENCY FOR TREATMENT

Olaparib
Rucaparib
Veliparib
Niraparib
BMN-673
Targeting *BRCA* in Ovarian Cancer: An approach for personalizing management of OC
## PARP INHIBITORS IN CLINICAL TRIALS

<table>
<thead>
<tr>
<th>Agent</th>
<th>Administration</th>
<th>Phase *</th>
<th>Comments</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olaparib (AZD-2281)</td>
<td>Oral</td>
<td>I, II, III</td>
<td>Single Agent and Combination, BRCA and non-BRCA, Platinum-sensitive and resistant, Primary and Recurrent</td>
<td>SOLO-1;SOLO-2</td>
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<tr>
<td>AZD-2461</td>
<td>Oral</td>
<td>I, II</td>
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<td>FIN, Solid Tumors</td>
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<tr>
<td>Veliparib ABT-888</td>
<td>Oral</td>
<td>I, II, III</td>
<td>Single Agent and Combination, BRCA and non-BRCA, Platinum-sensitive and resistant, Primary and Recurrent</td>
<td>(GOG-9923, PIS1004, GOG-280)</td>
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<tr>
<td>BMN 673</td>
<td>Oral</td>
<td>I, II</td>
<td>BRCA mutation carriers, Platinum Sensitive</td>
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<tr>
<td>CEP-9722</td>
<td>Oral</td>
<td>I</td>
<td>Combination, Solid Tumors</td>
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<tr>
<td>Niraparib (MK4827)</td>
<td>Oral</td>
<td>I, II, III</td>
<td>Single Agent and Combination, BRCA and non-BRCA, Platinum-sensitive and resistant</td>
<td>NOVA Trial</td>
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<tr>
<td>Rucaparib (CO-338)</td>
<td>Oral</td>
<td>I, II, III</td>
<td>BRCA mutation carriers and no carriers, Platinum Sensitive: ARIEL-2, ARIEL-3</td>
<td></td>
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<tr>
<td>AG014699</td>
<td>IV</td>
<td>II</td>
<td>Single Agent, BRCA, Platinum-sensitive and resistant</td>
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*Available at: http://www.clinicaltrials.gov.*
## OLAPARIB: THE FIRST APPROVED PARP INHIBITOR

<table>
<thead>
<tr>
<th>Completed Phase I</th>
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<tr>
<td><strong>Fong</strong></td>
<td><strong>Fong</strong></td>
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<tr>
<td>Advanced solid tumors</td>
<td>Recurrent OC gBRCA</td>
</tr>
<tr>
<td>Treatment at progression</td>
<td>Treatment at progression</td>
</tr>
<tr>
<td>Expansion phase: gBRCA</td>
<td>Olaparib monotherapy</td>
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<tr>
<td>Total: 60 pts – 21 OC</td>
<td>Olaparib monotherapy</td>
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<tr>
<td><strong>Rajan</strong></td>
<td><strong>Rajan</strong></td>
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<tr>
<td>Advanced solid tumors</td>
<td>Advanced solid tumors</td>
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<tr>
<td>Treatment at progression</td>
<td>Treatment at progression</td>
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<tr>
<td>Olaparib + cisplatin/gemcitabine Total: 23 pts – 3 OC</td>
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<tr>
<td><strong>Liu</strong></td>
<td><strong>Liu</strong></td>
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<tr>
<td>Recurrent OC or TNBC</td>
<td>Recurrent OC or TNBC</td>
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<tr>
<td>Treatment at progression</td>
<td>Treatment at progression</td>
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<tr>
<td>Olaparib + cediranib (antiangiogenic) Total: 28 pts – 20 OC (14 plat sens) – 8 TNBC</td>
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# OLAPARIB: THE FIRST APPROVED PARP INHIBITOR

<table>
<thead>
<tr>
<th>Completed Phase II</th>
<th>Olaparib mono</th>
<th>Total: 265 HGSOC pts</th>
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<tr>
<td></td>
<td>Treatment at progression - HGSOC</td>
<td>136 olaparib</td>
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<tr>
<td></td>
<td>Maintenance therapy after partial/complete response to plat therapy (≥2 lines)</td>
<td>39% plat intermediate</td>
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<td></td>
<td>Med. of 3 previous lines</td>
<td>61% plat free &gt;12 mo</td>
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<td>Audeh</td>
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<td></td>
<td>Olaparib mono</td>
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<td></td>
<td>Treatment at progression</td>
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<tr>
<td></td>
<td>Med. of 3 previous lines</td>
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<tr>
<td></td>
<td>Total: 57 OC pts</td>
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<td></td>
<td>1st: 33 pts</td>
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<td>2nd: 24 pts</td>
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<td>Gelmon</td>
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<td></td>
<td>Olaparib mono</td>
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<td></td>
<td>Treatment at progression - HGSOC</td>
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<tr>
<td></td>
<td>Med. of 3 previous lines</td>
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<tr>
<td></td>
<td>Total: 91 pts</td>
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<tr>
<td></td>
<td>65 pts HGSOC</td>
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<td></td>
<td>26 TNBC</td>
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<tr>
<td>Kaye</td>
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<tr>
<td></td>
<td>Olaparib mono</td>
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<td>Randomized vs Caelyx</td>
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<td></td>
<td>Recurrence within 12 mo prior plat</td>
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<tr>
<td></td>
<td>Total: 97 OC pts</td>
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<tr>
<td>Ledermann (Study 19)</td>
<td>Olaparib mono</td>
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<tr>
<td></td>
<td>Randomized vs placebo - HGSOC</td>
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<tr>
<td></td>
<td>Maintenance therapy after partial/complete response to plat therapy (≥2 lines)</td>
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<tr>
<td></td>
<td>Total: 162 pts</td>
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<tr>
<td>Oza (Study 41)</td>
<td>Olaparib + carbo/taxol then maintenance</td>
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<td></td>
<td>Randomized – HGSOC platinum sensitive</td>
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**OLAPARIB: AN ORALLY ACTIVE PARP INHIBITOR IN OVARIAN CANCER**

|                              | Olaparib Phase I and BRCA mutation expansion studies in ovarian cancer patients<sup>1</sup> | Olaparib multicenter Phase II BRCA mutation ovarian cancer study<sup>2</sup> | Olaparib multicenter Phase II BRCA+/- study (ovarian cancer patients)<sup>3</sup> |
|------------------------------|------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------|---------------------------------------------------------------------------------
| Olaparib patients            | n=50                                                                                     | n=33                                                                         | n=64                                                                         |
| Olaparib dose                | 200 mg bid                                                                                | 400 mg bid                                                                    | 400 mg bid                                                                   |
| RECIST response (CR + PR)    | 28%                                                                                       | 33%                                                                          | BRCA+ 41% BRCA– 24%                                                          |
| Disease control rate*        | 34%                                                                                       | 69%                                                                          | BRCA+ 76% BRCA– 62%                                                          |
| Median duration of response  | 7.0 months                                                                                | 9.5 months                                                                    | Not reported                                                                 |

*Complete response (CR) + partial response (PR) + stable disease (SD)*

1. Fong PC et al. *J Clin Oncol* 2010
Response by BRCA status:

ORR 41% with BRCA<sub>m</sub> vs 24% BRCA<sub>wt</sub>
**Study 19: To assess the efficacy and safety of oral Olaparib as maintenance treatment**

**Design**
- A randomised, double-blind, placebo-controlled Phase II maintenance study
- 265 patients in 82 investigational sites in 16 countries

**Patients:**
- Platinum-sensitive **high-grade serous** ovarian cancer
- ≥2 previous platinum regimens
- Last chemotherapy was **platinum-based**, to which they had a maintained PR or CR prior to enrolment

**Olaparib 400 mg po bid**
- Randomised 1:1
- Treatment until disease progression

**Placebo po bid**

**Stratification factors:**
- Best response to QT
- Platinum Free Interval
- Jewish Heritage

**Primary end point:** Progression free survival

Olaparib as maintenance treatment met the primary endpoint of improving PFS in the overall study population.

Olaparib improved PFS by a median of 3.6 months.

**PFS Kaplan-Meier curves**

<table>
<thead>
<tr>
<th>Time from randomisation (months)</th>
<th>Placebo</th>
<th>Olaparib</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>3</td>
<td>0.98</td>
<td>0.80</td>
</tr>
<tr>
<td>6</td>
<td>0.76</td>
<td>0.40</td>
</tr>
<tr>
<td>9</td>
<td>0.50</td>
<td>0.20</td>
</tr>
<tr>
<td>12</td>
<td>0.30</td>
<td>0.10</td>
</tr>
<tr>
<td>15</td>
<td>0.10</td>
<td>0.01</td>
</tr>
</tbody>
</table>

**Events/total patients (%)**
- Olaparib: 60/136 (44.1)
- Placebo: 93/129 (72.1)

**Median PFS, months**
- Olaparib: 8.4
- Placebo: 4.8

**HR**
- Olaparib: 0.35
- 95% CI: 0.25, 0.49
- *p* < 0.001

More than 50% patients had a known deleterious BRCAm

Patients with a known BRCA status increased from 98 (37%) to 254 (95.8%) out of 265:
- 136 (51.3%) patients had a known deleterious BRCAm (BRCAm dataset)
- 118 (44.5%) patients were defined as BRCA1/2 wild type for this analysis
- 11 (4.2%) patients had neither a tumour nor a germline result available

Ledermann J et al. Lancet Oncol 2014
Olaparib maintenance monotherapy significantly prolonged PFS in platinum-sensitive relapsed HGSOC

- Patients with a BRCA mutation receive greater treatment benefit
- Non-mutation carriers may also benefit from olaparib treatment

Ledermann et al. Lancet Oncol 2014
Olaparib is indicated as monotherapy for the maintenance treatment of adult patients with platinum sensitive relapsed BRCA mutated (germline and/or somatic) high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete response or partial response) to platinum-based chemotherapy.

On December 19, 2014 FDA approved

Olaparib capsules for the treatment of patients with deleterious or suspected deleterious germline BRCA-mutated advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy.

Kaufman JCO 2014. Olaparib monotheray in patients with advanced cancer and germline BRCA 1/2Mutation
BRCA IN OVARIAN CANCER

- **Heredity**
  - Up to 10% of epithelial OC cases are familial
  - Mutations *BRCA*: 90% of familial OC
  - High Grade Serous OC

- **Germline *BRCA* patient and lifetime risk of OC**
  - *BRCA1*: 40–60%
  - *BRCA2*: 11–27%
  - Spontaneous: 1.39%
Frequency of BRCA1/2 mutations in women with OC is unclear (3-27%)

1001 women enrolled onto a population-based case-control study were screened

Germ-line mutations were found in 14.4% of patients (22.6% HGSOC; 8.4% endometrioid; 6%CC; 0% carcinosarcoma)

44% had not reported family history of breast or OC

BRCAm was associated with better outcomes (RR, PFS, OS)

BRCAwt (germline) patients who responded to several lines of platinum-based chemotherapy were more likely to carry somatic BRCAm

Conclusions: BRCA status has a major influence on survival, treatment outcomes and treatment selection and SHOULD BE OFFER TO ALL WOMEN DIAGNOSED WITH NON-MUCINOUS EOC
BRCAPRO model estimates mutations likelihood based on personal and family history

The accuracy of BRCAPRO was assessed in 589 patients with HGSOC referred for genetic counseling

Observed mutations were compared with those predicted by BRCAPRO

31% (180 patients) tested positive

If patients with BRCAPRO low had not been tested 51 patients (28%) would have been missed

Conclusion: BRCA TEST HAS TO BE OFFERED TO ALL PATIENTS WITH EOC REGARDLESS FAMILY HISTORY.
HOMOLOGOUS RECOMBINATION DEFICENCY (HRD)

HR is a complex process requiring coordinated function of many gene products.

Genetic and epigenetic dysregulation cause HRD, resulting in tBRCA\textsuperscript{mut} and tBRCA-like tumors that are sensitive to PARPi therapy.
Abnormal HRD accounts for up to ~50% of ovarian cancer

- Germline BRCA1 and BRCA2 mutations
- Somatic mutations of BRCA gene
- BRCA-independent defects in HR pathway, i.e. alterations in other DNA repair pathway molecules
ARIEL 2 (Part 1): Phase 2 trial to prospectively identify OC responders to rucaparib using tumor genetic analysis

Key Eligibility (N=206)
- High-grade serous or endometrioid OC
  - Known germline BRCA enrollment capped at N=15
- ≥1 prior platinum chemotherapy
- Platinum-sensitive, relapsed, measurable disease
- Tumor tissue (screening biopsy and archival)

Analysis of HRD Subgroups
Primary endpoint
- PFS
Secondary endpoints
- ORR
  - RECIST
  - RECIST and/or CA-125
- Safety
- PK

NGS of tumor tissue allows patients to be classified

600 mg BID rucaparib until disease progression

Biomarker Negative

tBRCA\textsuperscript{mut}

\textsuperscript{mut} includes germline and somatic mutations.
PFS=progression-free survival; PK=pharmacokinetics; tBRCA-like=tissue BRCA-like; tBRCA\textsuperscript{mut}=tissue BRCA\textsuperscript{mut}; wt=wild-type.
BRCA-LIKE SIGNATURE

Non-BRCA HR gene mutations are rare

- NGS of ovarian carcinomas and blood from 367 subjects using BROCA-HR assay

Differential sensitivity to rucaparib. No all genes are functionally relevant.

siRNA knockdown of 28 HRD genes in 3 OC cell lines (shown 10 genes in OVCAR-3)

BROCA-HR is an NGS method that can find all classes of genetic mutations, including single substitutions, small insertions and deletions, and gene rearrangements (Walsh T et al. PNAS. 2011)

Pennington et al Clin Cancer Res 2013

Both events highlight the need for an alternative approach to identify HRD tumors

Kristeleit et al ECCO 2015
BRCA-LIKE SIGNATURE

Different mechanism can lead to HRD with the final result of genomic LOH

HRD causes genome wide LOH that can be measured by comprehensive genomic profiling based on NGS

HR genetic defects
- Mutations
- Homozygous deletions
- Gene expression
- miRNA
- Methylation

Other HR defects
- Defective HR protein
- Defective HR pathway expression

HR deficiency

Genomic scarring (genomic LOH)

Hypothesis 1:
Ovarian cancer patients with high genomic LOH suggesting BRCA-like signature will respond to rucaparib

Hypothesis 2:
Ovarian cancer patients who are “Biomarker Negative” (ie, with low genomic LOH) will not respond to rucaparib

- Foundation Medicine’s NGS-based comprehensive cancer genomic profiling assay sequences BRCA and other HR genes in tumor-derived DNA
- The assay also sequences single-nucleotide polymorphisms (SNPs)
- SNP analysis identifies and quantifies genomic LOH

HR = homologous recombination. HRD = homologous recombination deficiency. LOH = loss of heterozygosity. NGS = next generation sequencing. BRCA™ = tumor tissue mutated BRCA. BRCA™ = tumor tissue wild-type BRCA.
Efficacy Analysis ARIEL 2 (Part 1)

PFS in tBRCA\textsuperscript{mut} and tBRCA-like vs. biomarker negative patients
Conclusions

- Better understanding of biology has led the development of tailored therapies.
- Olaparib is the first PARPi available for patients with HGSOC and BRCA\textsuperscript{mut(germ+tumor)}.
- We should test BRCA status in all women diagnosed with non-mucinous EOC regardless family history.

Open questions:
- Clinical significance of different BRCA mutations
- Better characterization of BRCA-like population (OLALA trial)
- PARPi resistance