TARGETED THERAPY IN OVARIAN CANCER

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GCIG Chair
Valencia, Spain
Progress In The Design of Cars: MB Evolution over 40 years
Progress In The Management of Ovarian Cancer: Evolution Over 40 Years

Five year survival

- 15%
- 30%
- 40%
- ?50%?

Key advances in chemotherapy

- First use of cisplatin
- First use of carboplatin
- First use of paclitaxel
- First reports of bevacizumab
- First use of oral PARPi
- Positive evidence of IP (NCI alert)

- 1970
- 1980
- 1990
- 2000
- 2010
- 2014

MODIFIED FROM PROF KAYE
MOLECULAR AGENTS AND TARGETED THERAPY

- The most promising targets in clinical trials are **angiogenesis and homologous recombination deficiency**.
- Other promising targets currently being studied based on ovarian cancer biology include:
  - PI3-Kinase and Ras/Raf pathways
  - Folate receptor

4th Ovarian Cancer Consensus Conference *Int J Gynecol Cancer* 2011.
Angiogenesis: A Complex Process

PARSGO GCIG Marrakech April 2018
Bevacizumab Provides Proof of Concept for Anti-VEGF Therapy

Four positive phase III trials of bevacizumab in ovarian cancer patients

**Front-line**

- **Advanced, stage III/IV patients**
  - PFS HR = 0.72

- **Early and advanced stage patients**
  - PFS HR = 0.81

**Recurrent**

- **Recurrent, platinum sensitive**
  - PFS HR = 0.48

- **Recurrent, platinum resistant**
  - PFS HR = 0.48

Bevacizumab is approved for front-line use in patients with stage IIIB–IV ovarian cancer and in platinum-sensitive relapse

GOG#218: Results

HR: 0.717 (95% CI, 0.625 to 0.824) (P < 0.001).

HR: 0.915 (95% CI, 0.727 to 1.152; P = 0.45)

**ICON-7: Results**

( Global Population)

**A** Updated Data, Progression-free Survival

- **No. at Risk**
  - Standard chemotherapy: 764
  - Bevacizumab: 764

- **Survival** (%): 100, 75, 50, 25, 0
- **Months since Randomization**: 0, 3, 6, 9, 12, 18, 24, 30, 36

- **HR = 0.87; (95% CI, 0.77 to 0.99; P = 0.04)**

**C** Updated Data, Overall Survival

- **No. at Risk**
  - Standard chemotherapy: 764
  - Bevacizumab: 764

- **Survival** (%): 100, 75, 50, 25, 0
- **Months since Randomization**: 0, 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, 36, 39

- **HR = 0.85; (95% CI, 0.69 to 1.04; P = 0.11)**

ICON-7 Final Overall Survival Results:

**PFS:** High Risk of progression (FIGO stage IV or III and suboptimal RD>1cm)

- **HR (95% CI):** 0.78 (0.63–0.97); p=0.03

\[ mOS: 39.3 \text{ months} \]
\[ mOS: 34.5 \text{ months} \]


PARSGO GCIG Marrakech April 2018
OCEANS: Platinum-sensitive recurrent OC
Primary analysis of PFS

<table>
<thead>
<tr>
<th>Events, n (%)</th>
<th>CG + PL (n=242)</th>
<th>CG + BV (n=242)</th>
</tr>
</thead>
<tbody>
<tr>
<td>187 (77)</td>
<td>151 (62)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Median PFS, months (95% CI)</th>
<th>CG + PL (n=242)</th>
<th>CG + BV (n=242)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.4 (8.3–9.7)</td>
<td>12.4 (11.4–12.7)</td>
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</table>

<table>
<thead>
<tr>
<th>Stratified analysis</th>
<th>HR (95% CI)</th>
<th>Log-rank p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CG + PL (n=242)</td>
<td>0.484</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CG + BV (n=242)</td>
<td>(0.388–0.605)</td>
<td></td>
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</table>

No. at risk

<table>
<thead>
<tr>
<th>Months</th>
<th>CG + PL</th>
<th>CG + BV</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>242</td>
<td>242</td>
</tr>
<tr>
<td>6</td>
<td>177</td>
<td>203</td>
</tr>
<tr>
<td>12</td>
<td>45</td>
<td>92</td>
</tr>
<tr>
<td>18</td>
<td>11</td>
<td>33</td>
</tr>
<tr>
<td>24</td>
<td>3</td>
<td>11</td>
</tr>
<tr>
<td>30</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Proportion progression free

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OCEANS: Third Interim OS Analysis

<table>
<thead>
<tr>
<th></th>
<th>GC + PL (n=242)</th>
<th>GC + BV (n=242)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events, n (%)</td>
<td>142 (58.7)</td>
<td>144 (59.5)</td>
</tr>
<tr>
<td>Median OS, months</td>
<td>33.7</td>
<td>33.4</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(29.3–38.7)</td>
<td>(30.3–35.8)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.960 (0.760–1.214)</td>
<td>p=0.7360</td>
</tr>
<tr>
<td>Log-rank P value</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Number at risk:
- GC + PL: 242, 235, 221, 190, 159, 117, 77, 44, 23, 7, 0
- GC + BV: 242, 239, 226, 201, 171, 127, 78, 48, 27, 7, 0

Data cutoff date: March 30, 2012. Median follow-up 41.9 months in PL arm and 42.3 months in BV arm, with 286 deaths (59.1% of patients)
What is Post Progression Survival (PPS)?

Post Progression Survival: Time from disease progression till death
AGO/NCIC/EORTC and OCEANS

Overall survival and subsequent treatment

<table>
<thead>
<tr>
<th>AGO/NCIC/EORTC: OS¹</th>
<th>OCEANS: 3rd Interim OS Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>C (n=178)</td>
<td>GC + PL (n=178)</td>
</tr>
<tr>
<td>Median OS, mo</td>
<td>17.3</td>
</tr>
<tr>
<td>GC + PL</td>
<td>18.0</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.96 (0.75 – 1.23)</td>
</tr>
<tr>
<td>Log-rank P value</td>
<td>.7349</td>
</tr>
<tr>
<td>GC + BV (n=242)</td>
<td>GC + PL (n=242)</td>
</tr>
<tr>
<td>Median OS, mo</td>
<td>33.7</td>
</tr>
<tr>
<td>GC + BV</td>
<td>33.4</td>
</tr>
<tr>
<td>HR (95% CI)</td>
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</tr>
<tr>
<td>Log-rank P value</td>
<td>.7360</td>
</tr>
</tbody>
</table>

Pfisterer et al. *J Clin Oncol.* 2006

PARSGO GCIG Marrakech April 2018
AURELIA trial in resistant disease

Progression-free survival

<table>
<thead>
<tr>
<th></th>
<th>CT</th>
<th>BEV + CT</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n=182)</td>
<td></td>
<td>(n=179)</td>
</tr>
<tr>
<td>Events, n (%)</td>
<td>166 (91%)</td>
<td>135 (75%)</td>
</tr>
<tr>
<td>Median PFS, months</td>
<td>3.4</td>
<td>6.7</td>
</tr>
<tr>
<td>HR (unadjusted)</td>
<td>0.48</td>
<td></td>
</tr>
<tr>
<td>Log-rank p-value</td>
<td>1.0</td>
<td></td>
</tr>
</tbody>
</table>
AURELIA Study
OS at Weekly paclitaxel (PAC) cohort.

Bevacizumab Combined With Weekly Paclitaxel, Pegylated Liposomal Doxorubicin, or Topotecan in Platinum-Resistant Recurrent Ovarian Cancer: Analysis by Chemotherapy Cohort of the Randomized Phase III AURELIA Trial

Poveda et al. JCO 2015. Vol 33
Angiogenesis as a Target in Ovarian Cancer

- Anti-vascular endothelial growth factor (VEGF) therapy improves progression-free survival (PFS)
  - **GOG 218**
    - **Front-line:** Bevacizumab
    - HR = 0.72; 95% CI, 0.63–0.82
  - **ICON 7**
    - **Front-line:** Bevacizumab
    - HR = 0.81; 95% CI, 0.70–0.94
  - **AGO-OVAR12**
    - **Front-line:** Nintedanib
    - HR = 0.84; 95% CI, 0.72, 0.98
  - **AGO-OVAR16**
    - **Maintenance:** Pazopanib
    - HR = 0.77; 95% CI, 0.64–0.91
  - **AURELIA**
    - **Platinum-resistant, recurrent** / 1 or 2 prior regimens: Bevacizumab
    - HR = 0.48; 95% CI, 0.38–0.60
  - **OCEANS**
    - **Platinum-sensitive, recurrent** / 1 prior regimen: Bevacizumab
    - HR = 0.48; 95% CI, 0.388–0.60
  - **ICON6**
    - **Platinum-sensitive, recurrent** / 1 prior regimen: Cediranib
    - HR = 0.57; 95% CI, 0.44–0.74
  - **TRINOVA1**
    - **Platinum-PPS + resistant recurrent** / 1 prior regimen: Trebananib
    - HR = 0.66; 95% CI, 0.56–0.76

HR = hazard ratio; 95% CI = confidence interval
To select patients for trials investigating these targets, predictive biomarkers are required. Understanding mechanisms of resistance is a priority.
# Anti Angiogenic Studies in Ovarian Cancer

<table>
<thead>
<tr>
<th>STUDY</th>
<th>Line</th>
<th>N</th>
<th>Obj</th>
<th>Duration</th>
<th>Drug</th>
<th>HR</th>
<th>Histo-types</th>
<th>Clinical Factors</th>
<th>BMK</th>
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<tbody>
<tr>
<td>GOG218</td>
<td>1st</td>
<td>1873</td>
<td>PFS</td>
<td>12m</td>
<td>Bev</td>
<td>0,72</td>
<td>No dif</td>
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<td>No</td>
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<tr>
<td>ICON7</td>
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<td>1528</td>
<td>PFS</td>
<td>15m</td>
<td>Bev</td>
<td>0,81</td>
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<td>No</td>
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<tr>
<td>AGOOV16</td>
<td>1st</td>
<td>940</td>
<td>PFS</td>
<td>24m</td>
<td>Pazo</td>
<td>0,77</td>
<td>No dif</td>
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<td>No</td>
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<tr>
<td>AGOOV12</td>
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<td>1386</td>
<td>PFS</td>
<td>24m</td>
<td>Ninde</td>
<td>0,84</td>
<td>No dif</td>
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<td>No</td>
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<tr>
<td>GOG262</td>
<td>1st</td>
<td>692</td>
<td>PFS</td>
<td>UP</td>
<td>Bev</td>
<td>DDvsSt</td>
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<td>Yes</td>
<td>??</td>
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<tr>
<td>OCEANS</td>
<td>2nd</td>
<td>484</td>
<td>PFS</td>
<td>UP</td>
<td>Bev</td>
<td>0,53</td>
<td>No dif</td>
<td>Yes?</td>
<td>No</td>
</tr>
<tr>
<td>TRINOVA1</td>
<td>2nd</td>
<td>919</td>
<td>PFS</td>
<td>UP</td>
<td>Treb</td>
<td>0,66</td>
<td>No dif</td>
<td>Yes</td>
<td>??</td>
</tr>
<tr>
<td>ICON 6</td>
<td>2nd</td>
<td>456</td>
<td>PFS</td>
<td>UP</td>
<td>Cedir</td>
<td>0,57</td>
<td>N.S</td>
<td>N.S.</td>
<td>??</td>
</tr>
<tr>
<td>AURELIA</td>
<td>2nd</td>
<td>361</td>
<td>PFS</td>
<td>UP</td>
<td>Bev</td>
<td>0,48</td>
<td>No dif</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td></td>
<td><strong>8.639</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td><strong>NO</strong></td>
</tr>
</tbody>
</table>

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Therapeutic Targets in Ovarian Cancer

- Validated target
  - Effective agent
  - Target not validated
- Validated target
  - No effective agent
- Target biologically interesting
  - Not validated
  - Agent not available or tested

Antiangiogenics agents?

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Courtesy of Dr M Birrer
Anti-Angiogenic Therapies
Summary

– Increase tumour response
– Increase PFS
– Have not been shown to increase OS
– Are unselective - no predictive marker

– Combination with other targeted therapies is a challenge
Future for bevacizumab in patients with platinum as option

**CARBO-PLD-BEVACIZUMAB**
ENGOT OV-18 / AGO OVAR 2.21

**BEVACIZUMAB AFTER BEVACIZUMAB**
ENGOT OV-17/ MITO 14-MANGO OV-2

**Trial Design**

Bevacizumab 15mg/kg q3w until PD

Gemcitabine 1000 mg/m² d1 and 8

Carboplatin AUC 4 d 1 q3w

Bevacizumab 10mg/kg q2w

Pegylated Liposomal Doxorubicin 30 mg/m² d1

Carboplatin AUC 5 d 1 q4w

**Stratification Factors**
- Platinum free interval (6-12 months vs. > 12 months)
- In case of debulking surgery for recurrence: residual tumor (yes vs. no)
- In case of no debulking surgery for recurrence: all pts categorized to residual tumor (yes vs. no)
- Prior antiangiogenic therapy (yes vs. no)
- Participating study group

**MITO-16/ManGO OV-2: Avastin plus chemotherapy at progression after front-line Avastin plus chemotherapy in platinum sensitive**

Stage IIIB-IV EOC, FT or PPC progressing or recurring at least 6 months after front-line chemotherapy plus Avastin (n=400)

- Carboplatin
- PLD or gemcitabine or paclitaxel

Avastin 15mg/kg q3w

- Primary endpoint: PFS
- Secondary endpoint: OS

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MOLECULAR AGENTS AND TARGETED THERAPY

• The most promising targets in clinical trials are angiogenesis and **homologous recombination deficiency**.

• Other promising targets currently being studied based on ovarian cancer biology include:
  • PI3-Kinase and Ras/Raf pathways
  • Folate receptor

4th Ovarian Cancer Consensus Conference *Int J Gynecol Cancer* 2011.
Potential of PARP Inhibitors in Sporadic Ovarian Cancer

The Cancer Genome Atlas, Molecular profiling of serous ovarian cancer, D. Levine 2011

SUMMARY

TCGA provides a large-scale integrative view of the aberrations in HGS-OvCa.

Mutations in **TP53** predominated, occurring in at least 96% of HGS-OvCa samples.

**BRCA1** and **BRCA2** were mutated in 21% of tumours, owing to a combination of germline and somatic mutations.

Seven other significantly mutated genes were identified, but only in 2–6% of HGS-OvCa samples.

50% of HGS-OvCa tumours with **homologous recombination defects** may benefit from PARP inhibitors.
**BRCA** mutations are the most common mutations in patients with ovarian cancer

- **BRCA1**: 47%
- **BRCA2**: 27%
- **BARD1**: 1%
- **BRIP1**: 5%
- **CHEK2**: 6%
- **MSH6**: 3%
- **MRE11**: 1%
- **PALB2**: 2%
- **NBN**: 1%
- **RAD50**: 1%
- **RAD51C**: 2%
- **TP53**: 4%
- **RAD50 RAD51C**: 2%
- **TP53**: 4%

Mutation rate: 24% (18% **BRCA**, 6% other genes)

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Walsh T et al., Proc Natl Acad Sci, 2011
Should all HGS ovarian cancer patients have BRCA testing?

Approximately 50% of patients with high-grade serous ovarian cancer predicted to be candidates for PARPi therapy

What are the clinical data?

Potential of PARP Inhibitors in Sporadic Ovarian Cancer

The Cancer Genome Atlas, Molecular profiling of serous ovarian cancer, D. Levine 2011

<table>
<thead>
<tr>
<th>Not Homologous Recombination (HR) Deficient</th>
<th>HR Deficient</th>
</tr>
</thead>
</table>

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Patient selection for PARP inhibition

- Clear rationale for PARP inhibition of germline-BRCA mutated tumours.
  - Mostly high grade serous and endometrioid ovarian cancer
  - Repeated response to platinum-based chemotherapy
  - Prolonged survival (>5 years).

- Emerging evidence that the HRD phenotype is present in up to 50% HGSOC
  - BRCA-1/2 1 germline and somatic events are common.
  - Epigenetic silencing of BRCA1 is common.
  - Potential of PARP inhibitors in sporadic Ovarian Cancer
Should all HGS ovarian cancer patients have BRCA testing?

Approximately 50% of patients with high-grade serous ovarian cancer predicted to be candidates for PARPi therapy.

What are the clinical data?
## PARP Inhibitors in Clinical Trials

<table>
<thead>
<tr>
<th>PARP Inhibitor</th>
<th>Company</th>
<th>Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>PF-01367 (Rucaparib)</td>
<td>Clovis/Pfizer</td>
<td>IV/oral</td>
</tr>
<tr>
<td>Olaparib</td>
<td>AZ</td>
<td>Oral</td>
</tr>
<tr>
<td>MK 4827 (Niraparib)</td>
<td>Tesaro</td>
<td>Oral</td>
</tr>
<tr>
<td>BMN 673</td>
<td>BioMarin</td>
<td>Oral</td>
</tr>
<tr>
<td>ABT 888 (Veliparib)</td>
<td>Abbott</td>
<td>Oral</td>
</tr>
<tr>
<td>INO-1001</td>
<td>Inotek</td>
<td>IV</td>
</tr>
<tr>
<td>GP1201</td>
<td>Eisai</td>
<td>Oral</td>
</tr>
<tr>
<td>CEP 9722</td>
<td>Cephalon</td>
<td>Oral</td>
</tr>
</tbody>
</table>

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Platinum combination followed by iPARP

**Olaparib** study design and patient selection

### Study-19 aim and design

- 265 patients
- **Platinum-sensitive high-grade serous ovarian cancer**
- ≥2 previous platinum regimens
- Last chemotherapy was platinum-based to which they had maintained PR or CR prior to enrolment
- Stable CA-125

- **Primary endpoint:** PFS

- **Randomized 1:1**

  - Olaparib 400 mg po bid
  - Placebo po bid


### SOLO-2 aim and design

- 295 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**

  - Olaparib 300 mg bid n=196
  - Placebo n=99

  - **Primary endpoint:** Investigator-assessed PFS

Pujade-Lauraine et al. Lancet Oncol 2017

PARSGO GCIG Marrakech April 2018
Olaparib Maintenance Therapy in Platinum-Sensitive Relapsed Ovarian Cancer

- Statistically significant PFS improvement (HR 0.35, $P<0.00001$)
- Interim OS analysis: HR=0.94; 95% CI, 0.63–1.39; $P=0.75$

Platinum combination followed by iPARP

Olaparib data on primary endpoint

Study-19 PFS

11.2 vs 4.3 months
HR 0.18 (95% CI: 0.10-0.31)

Ledermann et al. Lancet Oncol 2014

SOLO-2 PFS

19.1 VS 5.5 months
HR 0.3 (95% CI: 0.22-0.41)

Pujade-Lauraine et al. Lancet Oncol 2017
Time to first/second subsequent therapy: new exploratory endpoints*

- **TFST** (time from randomisation to first subsequent therapy or death)
- **TSST** (time from randomisation to second subsequent therapy or death)
- **PFS₂** (time from randomisation to second objective disease progression or death)**

All patients who received treatment were included in exploratory endpoint analyses

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*Endpoints determined retrospectively; †could not be determined for all patients in this trial since the date of progression was not collected for patients who had not progressed by 30 June 2010 (the cut-off for the primary analysis); ‡could not be determined in this trial since the date of subsequent progressions was not collected; **PFS₂ is a surrogate for TSST; ***Pre-specified exploratory objective

Platinum combination followed by iPARP

**Olaparib** data on secondary end-points

### Study 19<sup>1</sup>

<table>
<thead>
<tr>
<th></th>
<th>Olaparib 400mg/12</th>
<th>Control</th>
<th>Olaparib 300 mg/12</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BRCA</strong></td>
<td>germline &amp; somatic</td>
<td></td>
<td>germline</td>
<td></td>
</tr>
<tr>
<td><strong>N</strong></td>
<td>62</td>
<td>74</td>
<td>99</td>
<td>196</td>
</tr>
<tr>
<td><strong>TFST</strong></td>
<td>15 vs 6.2</td>
<td></td>
<td>27.9 vs 7.1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(HR 0.32; 0.22-0.48)</td>
<td></td>
<td>(HR 0.28; 0.21-0.38)</td>
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</tr>
<tr>
<td><strong>TSST</strong></td>
<td>22 vs 15.3</td>
<td></td>
<td>NR vs 18.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(HR 0.41; 0.26-0.62)</td>
<td></td>
<td>(HR 0.37; 0.26-0.53)</td>
<td></td>
</tr>
</tbody>
</table>


TFST: Time to first subsequent therapy
TSST: Time to second subsequent therapy
Therapeutic Targets in Ovarian Cancer

- Validated target
- Effective agent
- Agent not available or tested
- Target not validated
- No effective agent
- Target biologically interesting

PARP-i?

Antiangiogenics agents?

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**STUDY 19: PFS BY BRCA MUTATION STATUS**

<table>
<thead>
<tr>
<th></th>
<th>BRCAm (n=136)</th>
<th>BRCAwt (n=118)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Olaparib</td>
<td>Placebo</td>
</tr>
<tr>
<td>Events/total patients (%)</td>
<td>26/74 (35%)</td>
<td>46/62 (74%)</td>
</tr>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>11.2 (8.3, NC)</td>
<td>4.3 (3.0, 5.4)</td>
</tr>
<tr>
<td>HR</td>
<td>0.18</td>
<td>0.54</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.10, 0.31</td>
<td>0.34, 0.85</td>
</tr>
<tr>
<td>P</td>
<td>&lt;0.0001</td>
<td>0.0075</td>
</tr>
</tbody>
</table>

Olaparib BRCAm
Placebo BRCAm
Olaparib BRCAwt
Placebo BRCAwt

Number at risk:

- Olaparib BRCAm: 74, 59, 34, 15, 5, 0
- Placebo BRCAm: 62, 35, 13, 2, 0, 0
- Olaparib BRCAwt: 57, 45, 18, 9, 2, 0
- Placebo BRCAwt: 61, 35, 10, 4, 1, 0

Time from randomisation (months):

0, 3, 6, 9, 12, 15

Proportion of patients progression-free:

0.9, 0.8, 0.7, 0.6, 0.5, 0.4, 0.3, 0.2, 0.1


PARSGO GCIG Marrakech April 2018
Platinum-sensitive recurrent high grade serous ovarian cancer

Treatment with 4-6 cycles of platinum-based therapy

Response to platinum treatment

- gBRCAmut 203
  - Niraparib 300 mg once daily
  - Placebo
  - Treat until progression of disease

- Non-gBRCAmut 350
  - Niraparib 300 mg once daily
  - Placebo
  - Treat until progression of disease

2:1 Randomization

Mirza MR et al. NEJM 2016
Platinum combination followed by iPARP

Niraparib: ENGOT ov16-NOVA primary end-point

PFS: gBRCA
t

<table>
<thead>
<tr>
<th>Treatment</th>
<th>PFS Median (95% CI) (Months)</th>
<th>Hazard Ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Niraparib</td>
<td>21.0 (12.9, NR)</td>
<td>0.27 (0.173, 0.410)</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>Placebo</td>
<td>5.5 (3.8, 7.2)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

PFS: non-gBRCA

<table>
<thead>
<tr>
<th>Treatment</th>
<th>PFS Median (95% CI) (Months)</th>
<th>Hazard Ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Niraparib</td>
<td>9.3 (7.2, 11.2)</td>
<td>0.45 (0.338, 0.607)</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>Placebo</td>
<td>3.9 (3.7, 5.5)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Mirza MR et al. NEJM 2016

PARSGO GCIG Marrakech April 2018
Platinum combination followed by iPARP

**Niraparib: ENGOT ov16-NOVA exploratory analyses**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>PFS Median (95% CI) (Months)</th>
<th>Hazard Ratio (95% CI)</th>
<th>p-value</th>
<th>% of Patients without Progression or Death</th>
<th>12 mo</th>
<th>18 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Niraparib (N=71)</td>
<td>9.3 (5.8, 15.4)</td>
<td>0.38</td>
<td>0.0001</td>
<td>45%</td>
<td>27%</td>
<td></td>
</tr>
<tr>
<td>Placebo (N=44)</td>
<td>3.7 (3.3, 5.6)</td>
<td>(0.231, 0.628)</td>
<td>p=0.0248</td>
<td>11%</td>
<td>6%</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment</th>
<th>PFS Median (95% CI) (Months)</th>
<th>Hazard Ratio (95% CI)</th>
<th>12 mo</th>
<th>18 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Niraparib (N=92)</td>
<td>6.9 (5.6, 9.6)</td>
<td>0.58</td>
<td>27%</td>
<td>19%</td>
</tr>
<tr>
<td>Placebo (N=42)</td>
<td>3.8 (3.7, 5.6)</td>
<td>(0.361, 0.922)</td>
<td>p=0.0226</td>
<td>7%</td>
</tr>
</tbody>
</table>

**sBRCAmut**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>PFS Median (95% CI) (Months)</th>
<th>Hazard Ratio (95% CI)</th>
<th>p-value</th>
<th>% of Patients without Progression or Death</th>
<th>12 mo</th>
<th>18 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Niraparib (N=35)</td>
<td>20.9 (9.7, NR)</td>
<td>0.27</td>
<td>0.0001</td>
<td>62%</td>
<td>52%</td>
<td></td>
</tr>
<tr>
<td>Placebo (N=12)</td>
<td>11.0 (2.0, NR)</td>
<td>(0.081, 0.903)</td>
<td>19%</td>
<td>19%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**HRD-positive**

**BRCAwt**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>PFS Median (95% CI) (Months)</th>
<th>Hazard Ratio (95% CI)</th>
<th>p-value</th>
<th>% of Patients without Progression or Death</th>
<th>12 mo</th>
<th>18 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Niraparib (N=92)</td>
<td>6.9 (5.6, 9.6)</td>
<td>0.58</td>
<td>27%</td>
<td>19%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo (N=42)</td>
<td>3.8 (3.7, 5.6)</td>
<td>(0.361, 0.922)</td>
<td>p=0.0226</td>
<td>7%</td>
<td>7%</td>
<td></td>
</tr>
</tbody>
</table>

**HRD-negative**

Mirza MR et al. NEJM 2016
Platinum combination followed by iPARP

**Niraparib**: ENGOT ov16-NOVA secondary end-point

**Time to First Subsequent Therapy (TFST)**

<table>
<thead>
<tr>
<th></th>
<th>HR</th>
<th>P-value</th>
<th>Median TFST (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Niraparib</strong></td>
<td>0.55</td>
<td>&lt;0.0001</td>
<td>11.8</td>
</tr>
<tr>
<td><strong>Placebo</strong></td>
<td></td>
<td></td>
<td>7.2</td>
</tr>
</tbody>
</table>

- gBRCAmut: HR=0.31, P<0.0001
  - Median TFST: Niraparib 21.0 vs Placebo 8.4

- Non-gBRCAmut Overall: HR=0.55, P<0.0001
  - Median TFST: Niraparib 11.8 vs Placebo 7.2

- Non-gBRCAmut HRDpos: HR=0.36, P<0.0001
  - Median TFST: Niraparib 15.9 vs Placebo 6.0

D. Manher et al. SGO 2017
ARIEL3: Study Design

Rucaparib

Patient eligibility

- High-grade serous or endometrioid epithelial OC, primary peritoneal, or fallopian tube cancers
- ≥2 prior lines of platinum-based treatments
- No prior PARP inhibitors
- Sensitive to penultimate platinum
- Responding to most recent platinum (CR or PR)*
  - Excludes patients without assessable disease following surgery before more recent platinum-based therapy
- ECOG PS ≤1
- CA-125 within normal range
- No restriction on size of residual tumour

Stratification

- HRR status by NGS mutation analysis
  - Mutation in BRCA1, BRCA2, or non-BRCA HRR gene†
  - No mutation in BRCA or HRR gene
- Response to recent platinum
  - CR
  - PR
- Progression-free interval after penultimate platinum
  - 6 to <12 months
  - ≥12 months

Primary endpoint: Investigator-assessed PFS (per RECIST)

Ledermann J, ESMO 2017

Randomisation 2:1

Rucaparib 600 mg BID n=375

Placebo BID n=189

PARSGO GCIG Marrakech April 2018
ARIEL3: Investigator-Assessed Progression-Free Survival

Rucaparib

**BRCA mutant**

<table>
<thead>
<tr>
<th></th>
<th>Median (months)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rucaparib (n=130)</td>
<td>16.6</td>
<td>13.4–22.9</td>
</tr>
<tr>
<td>Placebo (n=66)</td>
<td>5.4</td>
<td>3.4–6.7</td>
</tr>
</tbody>
</table>

HR, 0.23; 95% CI, 0.16–0.34; P<0.0001

**HRD**

<table>
<thead>
<tr>
<th></th>
<th>Median (months)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rucaparib (n=236)</td>
<td>13.6</td>
<td>10.9–16.2</td>
</tr>
<tr>
<td>Placebo (n=118)</td>
<td>5.4</td>
<td>5.1–5.6</td>
</tr>
</tbody>
</table>

HR, 0.32; 95% CI, 0.24–0.42; P<0.0001

**ITT**

<table>
<thead>
<tr>
<th></th>
<th>Median (months)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rucaparib (n=375)</td>
<td>10.8</td>
<td>8.3–11.4</td>
</tr>
<tr>
<td>Placebo (n=189)</td>
<td>5.4</td>
<td>5.3–5.5</td>
</tr>
</tbody>
</table>

HR, 0.36; 95% CI, 0.30–0.45; P<0.0001

PARSGO GCIG Marrakech April 2018

Ledermann J, ESMO 2017
ARIEL3: Investigator-Assessed Progression-Free Survival: Patients with BRCA Wild-Type OC (exploratory analysis)

**LOH high**

<table>
<thead>
<tr>
<th></th>
<th>Median (months)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rucaparib (n=106)</td>
<td>9.7</td>
<td>7.9–13.1</td>
</tr>
<tr>
<td>Placebo (n=52)</td>
<td>5.4</td>
<td>4.1–5.7</td>
</tr>
</tbody>
</table>

HR, 0.44; 95% CI, 0.29–0.66; P<0.0001

**LOH low**

<table>
<thead>
<tr>
<th></th>
<th>Median (months)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rucaparib (n=107)</td>
<td>6.7</td>
<td>5.4–9.1</td>
</tr>
<tr>
<td>Placebo (n=54)</td>
<td>5.4</td>
<td>5.3–7.4</td>
</tr>
</tbody>
</table>

HR, 0.58; 95% CI, 0.40–0.85; P=0.0049

Ledermann J, ESMO 2017
Tumors with RAD51C alterations are BRCA-like (high genomic LOH) and responded to **Rucaparib**

<table>
<thead>
<tr>
<th>HR-pathway gene</th>
<th>Genetic alteration type</th>
<th>Germline/somatic inference</th>
<th>HRD molecular subgroup</th>
<th>RECIST response</th>
<th>CA-125 response</th>
</tr>
</thead>
<tbody>
<tr>
<td>NBN</td>
<td>Truncation</td>
<td>Germline</td>
<td>Biomarker-negative</td>
<td>Partial Response</td>
<td>Yes</td>
</tr>
<tr>
<td>RAD51C</td>
<td>Truncation</td>
<td>Germline</td>
<td>BRCA-like</td>
<td>Partial Response</td>
<td>Yes</td>
</tr>
<tr>
<td>RAD51C</td>
<td>Homozygous Del</td>
<td>Germline</td>
<td>BRCA-like</td>
<td>Partial Response</td>
<td>Yes</td>
</tr>
<tr>
<td>RAD51C</td>
<td>Splice</td>
<td>Germline</td>
<td>BRCA-like</td>
<td>Partial Response</td>
<td>Yes</td>
</tr>
<tr>
<td>RAD51C</td>
<td>Splice</td>
<td>Somatic</td>
<td>BRCA-like</td>
<td>Stable Disease</td>
<td>Yes</td>
</tr>
<tr>
<td>ATM</td>
<td>Homozygous Del</td>
<td>Germline</td>
<td>Indeterminate</td>
<td>Stable Disease</td>
<td>Yes</td>
</tr>
<tr>
<td>RAD51L3</td>
<td>Truncation</td>
<td>Indeterminate</td>
<td>BRCA-like</td>
<td>Stable Disease</td>
<td>Yes</td>
</tr>
<tr>
<td>BRIP1</td>
<td>Splice</td>
<td>Germline</td>
<td>Biomarker-negative</td>
<td>Stable Disease</td>
<td>No</td>
</tr>
<tr>
<td>BRIP1</td>
<td>Truncation</td>
<td>Germline</td>
<td>Biomarker-negative</td>
<td>Stable Disease</td>
<td>No</td>
</tr>
<tr>
<td>CHEK2</td>
<td>Splice</td>
<td>Indeterminate</td>
<td>Biomarker-negative</td>
<td>Stable Disease</td>
<td>No</td>
</tr>
<tr>
<td>CHEK2</td>
<td>Truncation</td>
<td>Germline</td>
<td>BRCA-like</td>
<td>Stable Disease</td>
<td>No</td>
</tr>
<tr>
<td>RAD51L1</td>
<td>Truncation</td>
<td>Indeterminate</td>
<td>Biomarker-negative</td>
<td>Stable Disease</td>
<td>No</td>
</tr>
<tr>
<td>NBN</td>
<td>Truncation</td>
<td>Germline</td>
<td>Indeterminate</td>
<td>Stable Disease</td>
<td>Not evaluable</td>
</tr>
<tr>
<td>RAD54L</td>
<td>Truncation</td>
<td>Somatic (subclonal)</td>
<td>Biomarker-negative</td>
<td>Stable Disease</td>
<td>Not evaluable</td>
</tr>
<tr>
<td>FANCA</td>
<td>Homozygous Del</td>
<td>Somatic</td>
<td>BRCA-like</td>
<td>Stable Disease</td>
<td>Not evaluable</td>
</tr>
<tr>
<td>FANCI</td>
<td>Truncation</td>
<td>Germline</td>
<td>Biomarker-negative</td>
<td>Progressive Disease</td>
<td>No</td>
</tr>
<tr>
<td>ATM</td>
<td>Truncation</td>
<td>Somatic</td>
<td>Indeterminate</td>
<td>Not evaluable</td>
<td>Not evaluable</td>
</tr>
</tbody>
</table>

PARSGO GCIG Marrakech April 2018
# Safety profile of iPARP

<table>
<thead>
<tr>
<th></th>
<th>Olaparib (SOLO-2)</th>
<th>Niraparib (ENGOT OV-16 / NOVA)</th>
<th>Rucaparib (ARIEL 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discontinuation</td>
<td>11%</td>
<td>14.7%</td>
<td>13.4%</td>
</tr>
<tr>
<td>Dose reduction</td>
<td>25%</td>
<td>66.5%</td>
<td>54.6%</td>
</tr>
<tr>
<td>Related SAE</td>
<td>17.9%</td>
<td>16.9%</td>
<td>-</td>
</tr>
<tr>
<td>Nausea /Vomiting G&gt;3</td>
<td>2.6%</td>
<td>3%</td>
<td>7.8%</td>
</tr>
<tr>
<td>Fatigue G&gt;3</td>
<td>4.1%</td>
<td>8%</td>
<td>6.7%</td>
</tr>
<tr>
<td>Anemia G&gt;3</td>
<td>19.5%</td>
<td>25%</td>
<td>18.8%</td>
</tr>
<tr>
<td>Thrombopenia G&gt;3</td>
<td>1%</td>
<td>33%</td>
<td>5.1%</td>
</tr>
<tr>
<td>Neutropenia G&gt;3</td>
<td>5.1%</td>
<td>19%</td>
<td>6.7%</td>
</tr>
<tr>
<td>MDS</td>
<td>4 (2.1%)</td>
<td>5 (1.4%)</td>
<td>3 (0.8%)</td>
</tr>
<tr>
<td>GOT/GPT G&gt;3</td>
<td>-</td>
<td>-</td>
<td>10.5%</td>
</tr>
</tbody>
</table>
General recommendations on the platinum-combination followed by iPARP option

- It should be the preferred choice for BRCA mutated (germ-line or somatic) patients, if no contraindication.
- None HRD test is good enough to exclude benefit of iPARP in BRCAwt
- Also the preferred option in **BRCA wild-type in the following scenarios**
  - High-grade serous or endometrioid sub-type **or**
  - More than 2 prior lines **or**
  - No need for a rapid or higher response due to severe ascites and/or pleural effusion (bev-combination may be preferred in this case)
- Toxicity profile is generally favorable (rate of discontinuation 11-15%) but a leaning curve is needed to manage specific side effects of each iPARP
– Very optimistic about new treatments for the first time in 20 years.
  • AA and PARP inhibition are already a reality, with positive data from randomized trials
  • First positive results without chemotherapy (Monk, IGCS 2014, Liu ASCO 2014)

– Patient selection, using robust predictive biomarkers, will be key to success.