New Treatment Options in Ovarian Cancer

Mansoor Raza Mirza

NSGO: Nordic Society of Gynaecological Oncology &
Rigshospitalet: Copenhagen University Hospital, Denmark
## Mansoor Raza Mirza
### Disclosures (last 24 months)

<table>
<thead>
<tr>
<th>Board of Directors:</th>
<th>Consultant or Advisory Role:</th>
<th>Study Grants:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Karyopharm Therapeutics Inc.</td>
<td>Advaxis</td>
<td>AstraZeneca</td>
</tr>
<tr>
<td>Metamark Genetics</td>
<td>AstraZeneca</td>
<td>Boehringer Ingelheim</td>
</tr>
<tr>
<td>Sera Prognostics Inc.</td>
<td>Boehringer Ingelheim</td>
<td>Clovis Oncology</td>
</tr>
<tr>
<td></td>
<td>Cerulean</td>
<td>Pfizer</td>
</tr>
<tr>
<td></td>
<td>Clovis Oncology</td>
<td>Roche</td>
</tr>
<tr>
<td></td>
<td>Genmab</td>
<td>Tesaro</td>
</tr>
<tr>
<td></td>
<td>Karyopharm Therapeutics</td>
<td></td>
</tr>
</tbody>
</table>
ENGOT
European Network of Gynaecological Oncology Trials groups

GCIG
Gynecologic Cancer InterGroup
Need for Level 1 Evidence
Phase II Trial in Ovarian Cancer with Gemcitabine

Results: 100% response rate

Three Phase III Trials in Ovarian Cancer with Gemcitabine

Carboplatin + Paclitaxel

Carboplatin + Paclitaxel + Gemcitabine

Ovarian Cancer

Randomize

Three Phase III Trials in Ovarian Cancer with Gemcitabine

- **NEGATIVE**

- Ovarian Cancer

- Carboplatin + Paclitaxel

Clinical Progress in Novel Therapies

• Anti-angiogenic therapy

• PARP inhibition

• Immunotherapy
Antiangiogenic therapy
Bevacizumab in primary Ovarian Cancer

2 positive trials
Improved PFS by adding bevacizumab to carboplatin/paclitaxel and subsequent maintenance therapy

GOG 218: Bev throughout vs placebo
HR 0.717; 95% CI 0.625-0.824, p<0.001

Burger RA et al. New Eng J Med 2011
Antiangiogenic therapy
Bevacizumab in primary Ovarian Cancer

2 positive trials
Improved PFS by adding bevacizumab to carboplatin/paclitaxel and subsequent maintenance therapy

GOG 218: Bev throughout vs placebo
HR 0.717; 95% CI 0.625-0.824, p<0.001

ICON 7: Bev vs control
HR 0.77; 95% CI 0.77-0.99; p=0.04

Burger RA et al. New Eng J Med 2011
Perren TJ.... Mirza MR et al. New Eng J Med 2011
Antiangiogenic therapy
Bevacizumab in Recurrent Ovarian Cancer: *Platinum-Sensitive Relapse*

2 positive trials

*Improved PFS by adding bevacizumab to platinum based chemo and subsequent maintenance therapy*

OCEANS: PFS CG+/-Bev
HR 0.484; 95% CI 0.388-0.605, p<0.001

*Aghajanian C et al. J Clin Oncol 2012*
Antiangiogenic therapy
Bevacizumab in Recurrent Ovarian Cancer: *Platinum-Sensitive Relapse*

2 positive trials

*Improved PFS by adding bevacizumab to platinum based chemo and subsequent maintenance therapy*

**OCEANS:** PFS CG+/-Bev
HR 0.484; 95% CI 0.388-0.605, p<0.001

*Aghajanian C et al. J Clin Oncol 2012*

**GOG 213:** TC +/- Bev
HR 0.61; 95%CI 0.52-0.72, p<0.0001

*Coleman RA et al. SGO 2015*
Antiangiogenic therapy
Tyrosine Kinase Inhibitors in Recurrent Ovarian Cancer

1 positive trial
Improved PFS or PFS & OS by adding a TKI standard chemotherapy

Cediranib

ICON 6: Platinum +/- Cediranib
HR 0.56; 95%CI 0.44-0.72, p<0.001

Antiangiogenic therapy
Bevacizumab in Recurrent Ovarian Cancer: *Platinum-Resistant Relapse*

1 positive trial
*Improved PFS by adding bevacizumab to non-platinum based chemo + QoL benefit in symptomatic pts.*

AURELIA: PFS NonPlat +/- Bev
HR 0.48; 95% CI 0.38-0.60, p< 0.001

Pujade-Lauraine E.... Mirza MR et al. J Clin Oncol 2014
Antiangiogenic therapy
Bevacizumab in Recurrent Ovarian Cancer: *Platinum-Resistant Relapse*

1 positive trial

*Improved PFS by adding bevacizumab to non-platinum based chemo + QoL benefit in symptomatic pts.*

AURELIA: PFS NonPlat +/- Bev
HR 0.48; 95% CI 0.38-0.60, p< 0.001

AURELIA: Primary and sensitivity analysis of the primary hypothesis (≥ 15% improvement in symptomatic pts)

Pujade-Lauraine E.... Mirza MR et al. *J Clin Oncol* 2014

Stockler MR.... Mirza MR et al. *J Clin Oncol* 2014
Antiangiogenic therapy
Facts & Clinical Considerations

But do we have any biomarkers to select the right population?
Antiangiogenic therapy
Facts & Clinical Considerations

But do we have any biomarkers to select the right population?

If not: what are the selection criteria?
So far, only Bevacizumab is approved in ovarian cancer
Bevacizumab is only allowed once in the course of disease
The benefit of adding bevacizumab is given in primary, early and late relapse

What are the risks of bevacizumab
Pulmonary embolism
Hypertension
Bowel perforation and fistula
Antiangiogenic therapy
Facts & Clinical Considerations

But do we have any biomarkers to select the right population?

If not: what are the selection criteria?
So far, only Bevacizumab is approved in ovarian cancer
Bevacizumab is only allowed once in the course of disease
The benefit of adding bevacizumab is given in primary, early and late relapse

What are the risks of bevacizumab
Pulmonary embolism
Hypertension
Bowel perforation and fistula

Every ovarian cancer patient should receive bevacizumab during the course of disease
PARP Inhibitors

• Inhibiting base excision repair

• Trapping PARP on damaged DNA, thus interfering with the catalytic cycle of PARP, hindering DNA repair & promoting double-strand breaks

• Disrupting BRCA1 recruitment to damaged DNA

• Activating non-homologous end-joining, which is more prone to errors.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Reported</th>
<th>Awaited</th>
</tr>
</thead>
<tbody>
<tr>
<td>Niraparib</td>
<td>ENGOT-OV16 / NOVA</td>
<td>PRIMA</td>
</tr>
<tr>
<td>Olaparib</td>
<td>ENGOT-OV30 / SOLO2</td>
<td>SOLO1, PAOLA1</td>
</tr>
<tr>
<td>Rucaparib</td>
<td>ARIEL3</td>
<td></td>
</tr>
<tr>
<td>Veliparib</td>
<td>-</td>
<td>GOG3005</td>
</tr>
<tr>
<td>Talazoparib</td>
<td>-</td>
<td>Ovarian Cancer Strategy Unclear</td>
</tr>
</tbody>
</table>
# Status of FDA & EMA approvals

## Maintenance Therapy

<table>
<thead>
<tr>
<th></th>
<th>FDA</th>
<th>EMA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Niraparib</strong></td>
<td>All patients regardless of histology, BRCA &amp; HRD status</td>
<td>All patients regardless of BRCA &amp; HRD status Positive CHMP opinion</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Olaparib</strong></td>
<td>All patients regardless of BRCA status</td>
<td>BRCAmut only</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Rucaparib</strong></td>
<td>Awaited</td>
<td>Awaited</td>
</tr>
</tbody>
</table>

## Post Multiple-Lines of Therapy

<table>
<thead>
<tr>
<th></th>
<th>FDA</th>
<th>EMA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rucaparib</strong></td>
<td>BRCAmut only</td>
<td>-</td>
</tr>
<tr>
<td><strong>Olaparib</strong></td>
<td>BRCAmut only</td>
<td>-</td>
</tr>
</tbody>
</table>
### Results from Randomized Trials in Ovarian Cancer

<table>
<thead>
<tr>
<th>Drug</th>
<th>Trial Name</th>
<th>Phase</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Niraparib</td>
<td>ENGOT-OV16 / NOVA</td>
<td>3</td>
<td>randomized</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Olaparib</td>
<td>Study 19</td>
<td>2</td>
<td>randomized</td>
</tr>
<tr>
<td></td>
<td>ENGOT-OV21 / SOLO2</td>
<td>3</td>
<td>randomized</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rucaparib</td>
<td>ARIEL3</td>
<td>3</td>
<td>randomized</td>
</tr>
</tbody>
</table>
Niraparib, as a selective PARP1/2 inhibitor, will provide a clinical benefit to all patients who have platinum-sensitive recurrent ovarian cancer who are in response to platinum, regardless of \( gBRCA \) mutation status.
Platinum-Sensitive Recurrent High Grade Serous Ovarian Cancer

Treatment with 4-6 Cycles of Platinum-based Therapy

Response to Platinum Treatment

- gBRCAmut n 203
  - Niraparib 300 mg once daily
  - Placebo
  - Treat until Progression of Disease
  - 2:1 Randomization

- Non-gBRCAmut n 350
  - Niraparib 300 mg once daily
  - Placebo
  - Treat until Progression of Disease
  - 2:1 Randomization

n 553

ENGOT-OV16 / NOVA

Recurrent ovarian cancer following a complete or partial response to platinum-based therapy

Evaluate gBRCA mutation status*

**gBRCA**mut

**non-gBRCA**mut†

<table>
<thead>
<tr>
<th>Treatment</th>
<th>PFS Median (95% CI) (Months)</th>
<th>Hazard Ratio (95% CI)</th>
<th>% of Patients without Progression or Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Niraparib (N=138)</td>
<td>21.0 (12.9, NR)</td>
<td><strong>0.27</strong> (0.173, 0.410)</td>
<td>62% 50%</td>
</tr>
<tr>
<td>Placebo (N=65)</td>
<td><strong>5.5</strong> (3.8, 7.2)</td>
<td>p&lt;0.0001</td>
<td>16% 16%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment</th>
<th>PFS Median (95% CI) (Months)</th>
<th>Hazard Ratio (95% CI)</th>
<th>% of Patients without Progression or Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Niraparib (N=234)</td>
<td>9.3 (7.2, 11.2)</td>
<td><strong>0.45</strong> (0.338, 0.607)</td>
<td>41% 30%</td>
</tr>
<tr>
<td>Placebo (N=116)</td>
<td><strong>3.9</strong> (3.7, 5.5)</td>
<td>p&lt;0.0001</td>
<td>14% 12%</td>
</tr>
</tbody>
</table>

randomized, double-blind, placebo-controlled phase II maintenance study

*n 265 patients*

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
- Stable CA-125

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

Primary end point: PFS

bid, twice daily; CA-125, Cancer Antigen 125; CR, complete response; po, orally; PR, partial response.

The Study 19
Phase 2 randomised trial of maintenance olaparib in platinum-sensitive high-grade serous relapse OC

Whole population with HGSOC

BRCA\textsuperscript{mut}

BRCA\textsuperscript{wt}

Long-term exposure to olaparib in ‘study 19’ in BRCA<sub>m</sub> and BRCA<sup>wt</sup>

Median follow-up of 5.9 years: **15 patients (11%)** still receiving olaparib.

Ledermann J et al. ASCO 2016
ENGOT-OV21 / SOLO2
Progression-Free Survival

Pujade-Lauraine E et al. Lancet Oncol 2017
ARIEL3: Progression-Free Survival

**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

**Coleman RL et al. Lancet 2017**
### Adverse Events (any grade; PARP / placebo)

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Rucaparib</th>
<th>Olaparib</th>
<th>Niraparib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>69 / 44</td>
<td>66 / 39</td>
<td>59 / 41</td>
</tr>
<tr>
<td>Nausea</td>
<td>75 / 37</td>
<td>76 / 33</td>
<td>74 / 45</td>
</tr>
<tr>
<td>Vomiting</td>
<td>37 / 15</td>
<td>37 / 19</td>
<td>34 / 16</td>
</tr>
<tr>
<td>Constipation</td>
<td>37 / 24</td>
<td>20 / 23</td>
<td>40 / 20</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>32 / 22</td>
<td>33 / 20</td>
<td>19 / 21</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>39 / 7</td>
<td>27 / 7</td>
<td>10 / 4</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>23 / 14</td>
<td>22 / 11</td>
<td>25 / 14</td>
</tr>
<tr>
<td>Anemia</td>
<td>37 / 6</td>
<td>44 / 8</td>
<td>50 / 7</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>28 / 3</td>
<td>8 / 3</td>
<td>61 / 6</td>
</tr>
<tr>
<td>Hypertension</td>
<td>-</td>
<td>-</td>
<td>19 / 4</td>
</tr>
<tr>
<td>Photosensitivity reaction</td>
<td>17 / 1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Increased Creatinine</td>
<td>15 / 2</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Increased ALT/AST</td>
<td>34 / 4</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

**Rucaparib:** Coleman RL et al. *Lancet* 2017  
**Olaparib:** Pujade-Lauraine E et al. *Lancet Oncol.* 2017  
## Adverse Events

### Treatment Related Dose Discontinuations

<table>
<thead>
<tr>
<th></th>
<th>Rucaparib</th>
<th>Olaparib</th>
<th>Niraparib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage</td>
<td>13.4%</td>
<td>11%</td>
<td>14.7%</td>
</tr>
</tbody>
</table>

- **Rucaparib:** Coleman RL et al. // *Lancet* 2017
- **Olaparib:** Pujade-Lauraine E et al. // *Lancet Oncol.* 2017
NOVA: Patient-Reposted Outcomes

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

Conclusions: PARPi

• PARP significantly improved PFS in patients with platinum-sensitive recurrent ovarian cancer.

• Efficacy is highest in BRCAmut population

• Beyond BRCA, platinum-sensitivity remains the best “biomarker” for response to PARP inhibitors
PARPi Combination Therapies

Increased DNA damage:
DNA repair inhibitors:
Radiation: complex DNA damage

DNA damage primes the immune system:
Immunotherapies: harnessing the genomic instability/genomic load
Stromal Inhibition: switch to C1 phenotype / block immune response

Create / re-create HRD:
Induce hypoxia: Anti-angiogenics
Increased DNA damage:
DNA repair inhibitors:
Radiation: complex DNA damage

DNA damage primes the immune system:
Immunotherapies: harnessing the genomic instability/genomic load
Stromal Inhibition: switch to C1 phenotype / block immune response

Create / re-create HRD:
Induce hypoxia: Anti-angiogenics
PARPi Combination Therapies

Increased DNA damage:
DNA repair inhibitors:
Radiation: complex DNA damage

DNA damage primes the immune system:
Immunotherapies: harnessing the genomic instability/genomic load
Stromal Inhibition: switch to C1 phenotype / block immune response

Create / re-create HRD:
Induce hypoxia: Anti-angiogenics
OV24/AVANOVA

A two-arm, open-label, phase II randomized study to evaluate the efficacy of niraparib versus niraparib-bevacizumab combination in Women with platinum-sensitive epithelial ovarian, fallopian tube, or peritoneal cancer.

No. of already recruited patients: 73 (part 2)
Planned No. of patients: 94 (part 2)
Status: recruiting

Sponsor: NSGO
PI: Mansoor Raza Mirza
Project Manager: Louisa Boufercha
Statistics: René DePont Christensen
CAN IMMUNO-ONCOLOGY BECOME A NEW TREATMENT OPTION IN OVARIAN CANCER?
Ongoing Phase III Immuno-Oncology Studies in ovarian cancer

First-line

**JAVELIN OVARIAN 100**
Stage 3-4 HGSOC; n=951

- Paclitaxel + carboplatin followed by observation
- Paclitaxel + carboplatin followed by avelumab maintenance
- Paclitaxel + carboplatin + avelumab followed by avelumab maintenance

Late relapse

**ATALANTE**
Ovarian cancer with late relapse; n=405

- Placebo (until PD) + bevacizumab + platinum-based chemotherapy
- PD-L1 (until PD) + bevacizumab + platinum-based chemotherapy

Platinum resistant

**JAVELIN Ovarian 200**
Stage 3-4 HGSOC; n=550

- Avelumab
- Avelumab + Pegylated Liposomal Doxorubicin
- Pegylated Liposomal Doxorubicin

**PFS**

**OS**

1. NCT02718417 (Sponsor: Pfizer; PI: Monk & Ledermann). Available at: https://clinicaltrials.gov/ct2/show/NCT02718417?term=NCT02718417&rank=1
2. NCT02891824 (Sponsor: GINECO; PI: Kurtz). Available at: https://clinicaltrials.gov/ct2/show/NCT02891824?term=NCT02891824&rank=1
3. NCT02580058 (Sponsor: Pfizer; PI: Monk & Pujade-Lauraine). Available at: https://clinicaltrials.gov/ct2/show/NCT02580058?term=NCT02580058&rank=1
PD-1/PD-L1 monotherapy in ovarian cancer

Alexandrov et al., Nature 2013
# Immune Checkpoint Inhibitors in OC: Overview

<table>
<thead>
<tr>
<th></th>
<th>Ipilimumab</th>
<th>Nivolumab&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Pembrolizumab</th>
<th>Avelumab&lt;sup&gt;4&lt;/sup&gt;</th>
<th>PD-L1&lt;sup&gt;5&lt;/sup&gt;</th>
<th>Durvalumab&lt;sup&gt;6&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>9</td>
<td>20</td>
<td>26</td>
<td>124</td>
<td>12</td>
<td>20*</td>
</tr>
<tr>
<td>Prior therapies</td>
<td>Not reported</td>
<td>≥4: 55%</td>
<td>≥5: 38.5%</td>
<td>≥3: 65.3%</td>
<td>≥6: 58%</td>
<td>Median: 4*</td>
</tr>
<tr>
<td>PD-L1+ prevalence</td>
<td>Not reported</td>
<td>80% (IC 2/3)</td>
<td>100% (≥1% TC)</td>
<td>77% (≥1% TC)</td>
<td>83% (IC 2/3)</td>
<td>&gt;5% TC: 73% (11/15)*</td>
</tr>
<tr>
<td>ORR</td>
<td>Not reported</td>
<td>15%</td>
<td>11.5%</td>
<td>9.7%</td>
<td>25%</td>
<td>Not reported</td>
</tr>
</tbody>
</table>

* Includes ovarian cancer (n=15), triple-negative breast cancer (n=2), cervical cancer (n=2), and uterine leiomyosarcoma patients (n=1).

CI, confidence interval; DCR, disease control rate; IC, immune cell; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; TC, tumor cell; TRAE, treatment-related adverse event; Tx, treatment.

Raising the bar with combinations

Combination approaches

Chemotherapy

Radiotherapy

Immunotherapy

Targeted therapy
ENGOT-OV42-NSGO / AVANOVA-Imune1
Multicenter, Double-blind, Phase 2 Randomized Trial
n=338

Stratification factors Part 1
• BRCAmut vs BRCAwt
• Chemotherapy-Free Interval: 6-12mo vs >12 mo
ENGOT-OV42-NSGO / AVANOVA-Imune1
Multicenter, Double-blind, Phase 2 Randomized Trial
n=223

Platinum-sensitive Ovarian Cancer

Randomize 1:1

Arm A
Niraparib + Bevacizumab + placebo

Arm B
Niraparib + Bevacizumab + TSR042

Treat to PD

Randomize 1:1

Arm A
Carboplatin + PLD + TSR042

Maintenance niraparib + TSR042

Arm B
Carboplatin + PLD + Placebo

Maintenance niraparib + Placebo

Stratification factors Part 2
- BRCA status
- Duration of treatment in part 1: 6-12mo vs >12 mo
A phase II umbrella trial in patients with relapsed ovarian cancer
NSGO-OV-UMB1
ENGOT-OV30 / NSGO
EudraCT number: 2017-002805-36

Sponsor: NSGO
Study Chair: Mansoor Raza Mirza

Participating groups & Lead PIs:
- NSGO: MR Mirza
- SGCTG UK: C Gourley
- PMHC Canada: A Oza
- BGOG Belgium: I Vergote
- ANZGOG Australia: M Friedlander
- COGI US: J Barek
- GOTIC Japan: K Fujiwara
- KGOG S Korea: SY Ryu
- NOGGO Germany: Jalid Sehouli

Study Status
- Cohort A accepted (DHMA, EC) in DK
- Submission in NOR, FIN, SWE in Q4 17
- Expected FPI: Jan 18
- Cohort B (SGCTG UK), submission end Q1 18
- Cohort C (PMHC Canada), submission Q3 18
A phase II umbrella trial in patients with relapsed ovarian cancer

**Part 1**
- Cohort A \( n=25 \)
  - MEDI 9447 + Durvalumab
- Cohort B \( n=25 \)
  - MEDI 0562 + Tremelimumab
- Cohort C \( n=25 \)
  - MEDI 0562 + Durvalumab

**Part 2**
- MED19447 + Durvalumab
- Standard of Care
- MED10562 + Tremelimumab
- Standard of Care
- MED10562 + Durvalumab
- Standard of Care

Evaluation of results of each cohort (both overall and with biomarker defined subgroups) to decide if it is feasible to proceed to part 2 for the given cohort.

Days: 1, 15, 29, 43, 57
- biopsy Day: < 1
- CT, blood, serum samples
- blood, serum samples
- CT, blood, serum samples

2:1 randomization

NSGO-OV-UMB1
ENGOT-OV30
Relapsed ovarian cancer

Each Cohort n=12

Cohort 1: Carboplatin-Pegylated Lyposomal Doxorubicin (PLD) x2 followed by High-Dose CT & TIL

Cohort 2: Carboplatin-PLD x2 followed by High-Dose CT & TIL followed by acetylsalicylic acid

Cohort 3: Carboplatin-PLD x2 followed by High-Dose CT & TIL followed by acetylsalicylic acid in combination with Durvalumab

Cohort 4: Carboplatin-PLD x2 followed by High-Dose CT & TIL followed by acetylsalicylic acid in combination with Durvalumab + IDOi

Cohort 5: Carboplatin-PLD x2 followed by High-Dose CT & TIL followed by acetylsalicylic acid in combination with Durvalumab + A2aRi

Cohort 6: Carboplatin-PLD x2 followed by High-Dose CT & TIL followed by acetylsalicylic acid in combination with Durvalumab + MEDI9447

Days: 1 day -7 of TIL day -1 of TILL day 21 of TIL

biopsy Day: < 1

CT, blood, serum samples

Biopsy

CT, blood, serum samples

Evaluation of results of each cohort (both overall and with biomarker defined subgroups) to decide if it is feasible to proceed to part 2 for the given cohort

Sponsor: NSGO
Chair: G Coukos
Co-Chair: M R Mirza
**Ovarian Cancer Targeted Therapy Landscape Overview**

<table>
<thead>
<tr>
<th>First-line Treatment</th>
<th>PARPi</th>
<th>PDL1/L1i</th>
<th>VEGFi</th>
<th>PARPi + VEGFi</th>
<th>PARPi + PD1/L1i</th>
<th>VEGFi + PD1/L1i</th>
</tr>
</thead>
<tbody>
<tr>
<td>Veliparib + chemo</td>
<td>Avelumab + chemo</td>
<td>Bev + chemo</td>
<td>Ola. + Pembro</td>
<td>Niraparib + Bev + chemo</td>
<td>PD-L1 + Bev + chemo; IMagyn50</td>
<td></td>
</tr>
<tr>
<td>VELIA</td>
<td>JAVELIN 100</td>
<td>ICON7</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>First-line Maintenance</th>
<th>PARPi</th>
<th>PDL1/L1i</th>
<th>VEGFi</th>
<th>PARPi + VEGFi</th>
<th>PARPi + PD1/L1i</th>
<th>VEGFi + PD1/L1i</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olaparib, SOLO-1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Niraparib PRIMA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Olaparib, SOLO-2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Olaparib; ARIEL4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Niraparib QUADRA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recurrent, PS Treatment</th>
<th>PARPi</th>
<th>PDL1/L1i</th>
<th>VEGFi</th>
<th>PARPi + VEGFi</th>
<th>PARPi + PD1/L1i</th>
<th>VEGFi + PD1/L1i</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olaparib, SOLO-2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rucaparib; ARIEL3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Niraparib QUADRA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recurrent, PS Maintenance</th>
<th>PARPi</th>
<th>PDL1/L1i</th>
<th>VEGFi</th>
<th>PARPi + VEGFi</th>
<th>PARPi + PD1/L1i</th>
<th>VEGFi + PD1/L1i</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olaparib; OReO</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Niraparib, NOVA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recurrent, PROC Treatment</th>
<th>PARPi</th>
<th>PDL1/L1i</th>
<th>VEGFi</th>
<th>PARPi + VEGFi</th>
<th>PARPi + PD1/L1i</th>
<th>VEGFi + PD1/L1i</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avelumab + chemo; JAVELIN 200</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bev + chemo; AURELIA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ola. + Cediranib, CONCERTO</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Niraparib + Pembro TOPACIO</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Niraparib + Cediranib, GY-005</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Key:**
- **Olaparib**
- **Veliparib**
- **Rucaparib**
- **Avelumab**
- **PD-1**
- **Bevacizumab**
- **Niraparib**

*Includes PARPs (niraparib, olaparib, rucaparib, veliparib) and PD1/L1s (PD-L1, avelumab).