OVARIAN CANCER: SURGICAL AND SYSTEMIC TREATMENT

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Advisory board for

Roche
Tesaro
Merck
Astra Zeneca
Clovis Oncology

Institutional Research Support from

Pharma Mar, Clovis Oncology and Merck
Progress in the management of ovarian cancer: Evolution over 40 years

PARPi, poly adenosine diphosphate ribose polymerase inhibitor.

Key advances in chemotherapy

1970
1980
1990
2000
2010

First use of cisplatin
First use of carboplatin
First use of paclitaxel
First reports of bevacizumab
First use of oral PARPi
Positive evidence for weekly paclitaxel in first-line

Five-year survival:
- 15% in 1970
- 30% in 1980
- 40% in 1990
- ?50% in 2000
- ? in 2010

30th ESO-ESMO Latin American Masterclass in Clinical Oncology
Ovarian cancer is not a single disease

High-grade serous ovarian cancer

- **TP53**: encodes a protein that regulates the cell cycle
- **BRCA1** and **BRCA2**: encode proteins that are involved in genome protection

Other subtypes

- Low-grade serous
  - BRAF; KRAS
- Mucinous carcinoma
  - KRAS
- Endometrioid carcinoma
  - PTEN (low grade); TP53; BRCA1/2
- Clear cell carcinoma
  - PTEN; PIK3CA; ARID1A

Advanced ovarian cancer: A ‘chronic’ disease with multiple relapses

PFI: platinum-free interval or duration of disease control without chemotherapy.

Response to treatment in patients with ovarian cancer declines with increasing disease recurrence

N numbers show total population; confidence lines represent 95% CI, confidence interval; ORR, overall response rate.

Previous lines of chemotherapy received

How effective is “watchful waiting”?  

<table>
<thead>
<tr>
<th>Study</th>
<th>Median PFS from placebo arm (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aurelia</td>
<td>6.7</td>
</tr>
<tr>
<td>TRINOVA 1</td>
<td>7.4</td>
</tr>
<tr>
<td>TRINOVA 2</td>
<td>7.6</td>
</tr>
<tr>
<td>GOG 213</td>
<td>13.8</td>
</tr>
<tr>
<td>ICON 6</td>
<td>11</td>
</tr>
<tr>
<td>OCEANS</td>
<td>12.4</td>
</tr>
<tr>
<td>SOLO-2-gBRCA</td>
<td>19.1</td>
</tr>
<tr>
<td>NOVA-non-gBRCA</td>
<td>9.3</td>
</tr>
<tr>
<td>NOVA-gBRCA</td>
<td>21.9</td>
</tr>
</tbody>
</table>

Median PFS from placebo arms may provide insights. PFS, progression-free survival.

Survival Effect of Maximal Cytoreductive Surgery for Advanced Ovarian Carcinoma During the Platinum Era: A Meta-Analysis

By Robert E. Bristow, Rafael S. Tomacruz, Deborah K. Armstrong, Edward L. Trumble, and F.J. Montz

Table 2. Multiple Linear Regression Analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>%</th>
<th>Increase</th>
<th>95% CI or CL</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent maximal cytoreduction</td>
<td>5.5</td>
<td>10%</td>
<td>3.3-7.8</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Year of publication</td>
<td>2.8</td>
<td>1 year</td>
<td>0.9-4.6</td>
<td>.004</td>
</tr>
<tr>
<td>Platinum dose-intensity</td>
<td>0.8</td>
<td>10%</td>
<td>-0.7, 2.3</td>
<td>.911</td>
</tr>
<tr>
<td>Cumulative platinum dose</td>
<td>1.4</td>
<td>111</td>
<td>-1.9, 1.4</td>
<td>.377</td>
</tr>
</tbody>
</table>
Our current goal......

MICROSCOPIC RESIDUAL

72 Months and..... beyond

30 MONTHS OF ADVANTAGE

<1 cm

40-44 Months

>1 cm

30-35 Months

7-10 MONTHS OF ADVANTAGE

5th ESO-ESMO Latin American Masterclass in Clinical Oncology
### Results of Previous studies

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PDST (N=336)</td>
<td>NACT (N=334)</td>
</tr>
<tr>
<td>PFS(M)</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>OS(M)</td>
<td>29</td>
<td>30</td>
</tr>
<tr>
<td>HR for NACT in OS</td>
<td>0.88</td>
<td>0.87</td>
</tr>
<tr>
<td>Confidence interval (CI)</td>
<td>90% CI 0.84-1.13</td>
<td>95% CI 0.72-1.05</td>
</tr>
<tr>
<td>Non-inferiority margin</td>
<td>1.25</td>
<td>1.18</td>
</tr>
<tr>
<td>p value</td>
<td>0.01</td>
<td>NA</td>
</tr>
</tbody>
</table>
Trial Design

Multicenter (34 specialized institutions), Randomized Phase III Trial

- **Standard Arm (PDS)**
  - PDS: primary debulking surgery
  - IDS*: Optional for pts with suboptimal PDS. Mandatory for pts with any of Ut/Adn/OM Unremoved.

- **Experimental Arm (NACT)**
  - NAC (4x TC)
  - IDS: interval debulking surgery

**Clinically diagnosed**
Stage III/IV ovarian, tubal, and peritoneal cancers

**Balancing factors**
Institution, Stage III/IV
PS 0-1/2-3, Age <60/≥60

**TC regimen:** PTX 175 mg/m² iv, CBDCA AUC 6.0 iv

Presented By Takashi ONDA at 2018 ASCO Annual Meeting
Overall Survival (N=301)

HR = 1.05 [90.8% CI 0.83-1.33] (p=0.24)¹

¹ Cox proportional hazard model stratified by clinical stage, PS and age [for non-inferiority]

Pt's at risk

<table>
<thead>
<tr>
<th>Arm A</th>
<th>149</th>
<th>140</th>
<th>112</th>
<th>91</th>
<th>76</th>
<th>57</th>
<th>50</th>
<th>34</th>
<th>22</th>
<th>15</th>
<th>4</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm B</td>
<td>152</td>
<td>140</td>
<td>115</td>
<td>88</td>
<td>71</td>
<td>58</td>
<td>46</td>
<td>35</td>
<td>22</td>
<td>11</td>
<td>3</td>
<td>0</td>
</tr>
</tbody>
</table>

MST (N=149) 49.0M
95% CI 38.7-56.2M

MST (N=152) 44.3M
95% CI 35.8-52.5M
B1. What defines the clinical subgroups that should be used for comparator studies?

1. After initial diagnosis of advanced disease patients should be assessed for primary debulking surgery by a qualified gynecologic oncology surgeon or primary chemotherapy forming 2 separate major clinical subgroups

2. Primary surgery where the goal is macroscopic complete resection.
   - Patients with complete resection of macroscopic disease have a better prognosis. The extent of residual disease must be clearly documented by the surgeon.

3. After primary chemotherapy 2 clinical subgroups emerge, those who are candidates for interval debulking surgery and those who are not suitable for surgery
   - After interval debulking surgery 2 clinical subgroups groups emerge, no macroscopic residual, macroscopic residual disease. The extent of residual disease must be clearly documented by the surgeon.

4. Patients receiving neoadjuvant chemotherapy should be considered for novel combination therapy trials, particularly window of opportunity studies
B2. What different control arms could be considered for trials of first-line therapy?

1. Intravenous 3-weekly carboplatin and paclitaxel remain the standard chemotherapy drugs for first-line therapy in advanced stage ovarian cancer.

2. Acceptable additions or variations in dose, schedule and route of delivery should be supported by at least one clinical trial demonstrating non-inferiority or superiority to a taxane/platinum. So far the following alternatives have been identified:
   - Weekly intravenous paclitaxel with 3-weekly intravenous carboplatin.
   - Platinum/taxane and bevacizumab.
   - Intraperitoneal therapy after primary surgery with less than 1 cm residual disease. Both platinum and paclitaxel should be included using a validated schedule.

3. If more than one of the above regimens are included in the control arm of the same study then they should be stratified for.

4. Trials are needed to define the control arm for elderly and frail patients, defined on the basis of comprehensive geriatric assessment.

5. If chemotherapy is to be used in early stage disease platinum based chemotherapy should be the control arm.
GOG 172: 42% completed treatment
8% never started
34% received only one or two cycles

NOT feasible in the majority of patients

HR = 0.784 (95% CI 0.693-0.886)
**GOG 252: Schema**

**Phase A: Cycles 1-6**
- **Arm 1**
  - Paclitaxel: 80 mg/m² IV over 1 hour days 1, 8, and 15
  - Carboplatin: AUC 6 IV on day 1
  - Bevacizumab: 15 mg/kg IV on day 1 beginning on cycle 2

**Arm 2**
- Paclitaxel: 80 mg/m² IV over 1 hour days 1, 8, and 15
- Carboplatin: AUC 6 IP on day 1
- Bevacizumab: 15 mg/kg IV on day 1 beginning on cycle 2

**Arm 3**
- Paclitaxel: 135 mg/m² IV over 3 hours day 1
- Cisplatin: 75 mg/m² IP on day 2
- Paclitaxel: 60 mg/m² IP on day 8

**Phase B: Cycles 7-22**
- Bevacizumab: 15 mg/kg IV on day 1 for cycles 7-22

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**Eligibility**
- Stage II-III Epithelial Carcinoma: Ovary, Fallopian Tube, Peritoneal
- Resected to optimal: less than or equal to 1 cm visible tumor by surgeon report
- Exploratory: suboptimal (7%) and Stage IV (5%)
Progression Free Survival Optimal Stage III NGR

Progression-Free Survival by Treatment Group
Stage III with No Gross Residual Disease

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Events</th>
<th>Total</th>
<th>Median (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1: Crb(IV)+T+Bev</td>
<td>144</td>
<td>239</td>
<td>31.3</td>
</tr>
<tr>
<td>2: Crb(IP)+T+Bev</td>
<td>145</td>
<td>238</td>
<td>31.8</td>
</tr>
<tr>
<td>3: Cis(IP)+T+Bev</td>
<td>138</td>
<td>239</td>
<td>33.8</td>
</tr>
</tbody>
</table>
IP Chemotherapy

- Reasonable to conclude IP “strategy” may be appropriately considered one potential approach in the evolving management of OC in a variety of settings (e.g., after interval surgery following primary chemotherapy; combined with weekly paclitaxel in suboptimal residual disease) rather than either a mandated or a discarded concept.
First line Dose dense in ovarian cancer
JGOG-3016

PFS

Overall survival

Median PFS
28.2 months vs 17.5 months (HR 0.76, 95% CI 0.62–0.91; p=0.0037).

Median overall survival was
100.5 vs 62.2 months (HR 0.79, 95% CI 0.63–0.99; p=0.039).

First line Dose dense in ovarian cancer
MITO 7

PFS

OS

Median PFS 18.8 vs 16.5
Log-rank test  p = 0.18
Unadjusted HR: 0.88 (0.72 – 1.06)

Median OS n.a. vs 47.9
Log-rank test  p = 0.24
Unadjusted HR: 1.20 (0.88 – 1.63)

Presented by: S.Pignata

GOG 262
## ICON8 OVERALL SURVIVAL

<table>
<thead>
<tr>
<th>Total Patients</th>
<th>Arm 1 Standard N=522</th>
<th>Arm 2 Weekly paclitaxel N=523</th>
<th>Arm 3 Weekly carbo-paclitaxel N=521</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of deaths</td>
<td>183 (35%)</td>
<td>167 (32%)</td>
<td>166 (32%)</td>
</tr>
<tr>
<td>Log rank (vs Arm 1 only)</td>
<td>p=0.21</td>
<td>p=0.3</td>
<td></td>
</tr>
<tr>
<td>Median OS</td>
<td>46.5 months</td>
<td>48.1 months</td>
<td>54 months</td>
</tr>
<tr>
<td>2 year survival (95% CI)</td>
<td>80% (76%, 83%)</td>
<td>82% (79%, 86%)</td>
<td>78% (74%, 81%)</td>
</tr>
</tbody>
</table>

Data immature – 602 events per comparison required (58% of required events included here)
Two positive trials with bevacizumab in front line

<table>
<thead>
<tr>
<th></th>
<th>Arm I</th>
<th>Arm II</th>
<th>Arm III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with event, n (%)</td>
<td>423</td>
<td>418</td>
<td>396</td>
</tr>
<tr>
<td>Median PFS, months</td>
<td>10.3</td>
<td>11.2</td>
<td>14.1</td>
</tr>
<tr>
<td>Stratified analysis HR (95% CI)</td>
<td>0.908</td>
<td>0.717</td>
<td>(0.475-0.924)</td>
</tr>
<tr>
<td>One-sided P value (log rank)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

# Overall Survival

<table>
<thead>
<tr>
<th></th>
<th>Arm I CP (n = 625)</th>
<th>Arm II CP + Bev (n = 625)</th>
<th>Arm III CP + Bev → Bev (n = 623)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths</td>
<td>156 (25.0%)</td>
<td>150 (24.0%)</td>
<td>138 (22.2%)</td>
</tr>
<tr>
<td>1-Year Survival</td>
<td>90.6%</td>
<td>90.4%</td>
<td>91.3%</td>
</tr>
</tbody>
</table>

Events were observed in ~ 24% of patients at the time of database lock.

Burger RA et al. *Proc ASCO* 2010;Abstract LBA1.
OS benefit is suggested with chemotherapy + Avastin and continued single-agent Avastin in stage IV disease

<table>
<thead>
<tr>
<th></th>
<th>CPP</th>
<th>CPB</th>
<th>CPB15</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths, n (%)</td>
<td>93 (61)</td>
<td>99 (60)</td>
<td>81 (49)</td>
</tr>
<tr>
<td>Median survival (months)</td>
<td>32.8</td>
<td>32.9</td>
<td>40.6</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.98 (0.74–1.31)</td>
<td>0.72 (0.53–0.97)</td>
<td></td>
</tr>
</tbody>
</table>
WHICH PATIENTS?
Bevacizumab in ovarian cancer: four pivotal trials: **Dose? Duration? Setting?**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Chemotherapy</th>
<th>Bevacizumab</th>
<th>PFS HR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First line</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GOG-0218(^1) (n=1873)</td>
<td>Paclitaxel, Carboplatin</td>
<td>Concurrent and maintenance 15 mg/kg q3w (3-arm placebo)</td>
<td>0.72</td>
</tr>
<tr>
<td>ICON7(^2) (n=1528)</td>
<td>Paclitaxel, Carboplatin</td>
<td>Concurrently only 7.5 mg/kg q3w (2 arm)</td>
<td>0.81</td>
</tr>
<tr>
<td><strong>Second line</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platinum resistant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aurelia (n=361)</td>
<td>Caelyx, Topotecan, Paclitaxel</td>
<td>Concurrent 10 mg/kg q2w (2 arm)</td>
<td>0.48</td>
</tr>
<tr>
<td>Platinum sensitive</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OCEANS(^3) (n=484)</td>
<td>Gemcitabine, Carboplatin</td>
<td>Concurrent 15 mg/kg q3w (2 arm)</td>
<td>0.48</td>
</tr>
</tbody>
</table>

HOW LONG?
Study design

- Epithelial ovarian, fallopian tube or primary peritoneal cancer:
  - Stage IIIB–IV
  - Grade 3 stage I/IIA
  - Clear-cell carcinoma (any stage)
  - Carcinosarcoma
- Maximally debulked (prior neoadjuvant chemotherapy allowed)
- ECOG PS 0–2

Dec 2010–May 2012: 1021 patients enrolled

- Primary endpoint: Safety (AEs by NCI-CTCAE version 4.03)
- Secondary endpoints: PFS, ORR, duration of response, overall survival
- Exploratory objectives: Optional translational research

IV carboplatin AUC 5–6 q3w (4–8 cycles)\textsuperscript{a}

IV paclitaxel 175 mg/m\textsuperscript{2} d1 or 80 mg/m\textsuperscript{2} d1, 8, 15 q3w (4–8 cycles)\textsuperscript{b}

BEV 15 or 7.5 mg/kg IV q3w for up to 36 cycles (2 years) or until disease progression or unacceptable toxicity

Patients without progression at cycle 36 could continue therapy after discussion with the Steering Committee

\textsuperscript{a}Cisplatin permitted in patients with hypersensitivity to carboplatin
\textsuperscript{b}A change from one paclitaxel regimen to the alternative during the study was not permitted
ECOG PS = Eastern Cooperative Oncology Group performance status; ORR = overall response rate
PFS in ROSiA and ICON7 (ITT populations)

Caveats
- Differing tumour assessment schedules
- Prior neoadjuvant chemotherapy permitted in ROSiA

CP = carboplatin + paclitaxel

1Avastin SmPC;
2Roche data on file 2012 (ICON7 CSR addendum)
**ENGOT Ov-15 Trial**

**AGO-OVAR 17**

**Study Design**

- **Bevacizumab** 15mg/kg q21 days
- **Paclitaxel** 175mg/m² q21 days
- **Carboplatin** AUC5 q21 days

**15 months**

= **22 cycles**

**30 months**

= **44 cycles**

**Strata**
- macroscopic residual tumor (yes vs no)
- FIGO Stage (IIB-IIIC vs IV)
- Study Group

**Primary endpoint:**
- PFS (non inferiority -> superiority)

**Main question:** treatment duration Bev
BEYOND PROGRESSION?
Chemotherapy plus or minus bevacizumab for platinum-sensitive ovarian cancer patients recurring after a bevacizumab containing first line. The randomized phase 3 trial MITO16B - MaNGO OV2B - ENGOT OV17

Sandro Pignata, Domenica Lorusso, Florence Joly, Ciro Gallo, Nicoletta Colombo, Cristiana Sessa, Aristotelis Bamias, Carmela Pisano, Frédéric Selle, Eleonora Zaccarelli, Giovanni Scambia, Patricia Pautier, Maria Ornella Nicoletto, Ugo De Giorgi, Coraline Dubot, Alessandra Bologna, Michele Orditura, Isabelle Ray-Coquard, Francesco Perrone, Gennaro Daniele

on the behalf of MITO, GINECO, MaNGO, SAKK and HeCOG groups

Sandro Pignata
Study Design

Platinum-based Chemotherapy:
- Carboplatin + Paclitaxel +/- Beva 15mg/kg q 21
- Carboplatin + Gemcitabine +/- Beva 15mg/kg q 21
- Carboplatin + PLD q 28 +/- Beva 10mg/kg q 14

Platinum-Based Chemotherapy plus Bevacizumab

Stratification:
- center
- relapse during or after 1° line Beva
- performance status
- chemo backbone

Sandro Pignata
PFS Investigator assessed (primary end-point)

<table>
<thead>
<tr>
<th></th>
<th>Standard</th>
<th>Experimental</th>
<th>Log Rank P</th>
</tr>
</thead>
<tbody>
<tr>
<td># events</td>
<td>161</td>
<td>143</td>
<td></td>
</tr>
<tr>
<td>Median PFS</td>
<td>8.8 mos</td>
<td>11.8 mos</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HR* (95%CI)</td>
<td>0.5</td>
<td>1</td>
<td>0.41-0.65</td>
</tr>
</tbody>
</table>

*adjusted by: age, PS, centre size, bevacizumab at relapse, chemo backbone, residual disease at initial surgery

Kaplan-Meier survival estimates
HGOC patients can be classified into three molecular subgroups: $\text{BRCA}^{\text{mut}}$, BRCA-like, Biomarker Negative
SOLO 1 TRIAL: PFS by investigator assessment

### Median PFS, months
- **Olaparib** (N=260): NR
- **Placebo** (N=131): 13.8

### Events (%) [50.6% maturity]
- **Olaparib**: 102 (39.2)
- **Placebo**: 96 (73.3)

### HR 0.30
95% CI 0.23, 0.41; *P*<0.0001

### 60.4% progression free at 3 years

### 26.9% progression free at 3 years

**CI**, confidence interval; **NR**, not reached
1st LINE OC TREATMENT: FUTURE APPROACHES

- ImmuneTx
- Anti-angiogenic
- iPARP

Venn Diagram

5th ESO-ESMO Latin American Masterclass in Clinical Oncology
Niraparib is being assessed for maintenance therapy in the first-line setting in the PRIMA study

Niraparib is indicated as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy. Please consult the summary of product characteristics.

CR, complete response; EORTC-QLQ-30, European Organisation for Research and Treatment of Cancer; EORTC-QLQ-OV28, EORTC–Ovarian Cancer Module; EQ-5D-5L, European QoL five-dimension five-level questionnaire; FOSI, FACIT ovarian cancer symptom index; HR, hazard ratio; HRD, homologous recombination deficiency; ITT, intention to treat; PFS, progression free survival; PK, pharmacokinetic; PR, partial response; QoL, quality of life; R, randomized. ClinicalTrials.gov. PRIMA. Available at: https://clinicaltrials.gov/ct2/show/NCT02655016. Accessed October 2018.
PAOLA-1: Study Design

Phase III trial of olaparib in combination with bevacizumab as first-line maintenance therapy in patients with advanced ovarian cancer

Patient eligibility
- FIGO stage IIIb–IV high-grade serous/endometrioid or non-mucinous BRCA mutation ovarian, fallopian tube or primary peritoneal cancer
- First line
  - Surgery (primary or interval)
  - Platinum–taxane based chemotherapy
  - ≥3 cycles of bevacizumab†
  - CR/PR NED

Primary endpoint
- PFS

Status: recruiting
Target enrolment: 612

Stratification factors
- Tumour BRCA status
- First-line outcome

La combinación de olaparib y bevacizumab no está autorizado en España. The combination of olaparib and bevacizumab is not approved in Spain.
Image trial

Stratification variables
- Stage/debulking status
- ECOG PS
- PDL1 IC0 vs IC1+
- Adjuvant/Neo-adjuvant

• Previously untreated ovarian, fallopian tube, or peritoneal cancer
• Post-operative Stage III w/macroscopic residual disease, Stage IV
• ECOG PS 0-2
<table>
<thead>
<tr>
<th>Sponsor</th>
<th>Tesaro</th>
<th>Roche</th>
<th>Clovis</th>
<th>Tessaro</th>
<th>Merck</th>
<th>Astra Zeneca</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group leader</td>
<td>GEICO(GOG)</td>
<td>GOG(MITO)</td>
<td>GOG(NCRI)</td>
<td>GINECO (GOG??)</td>
<td>BGOG(leading) – unsure whether GOG will join as supporting groups</td>
<td>AGO(GOG)</td>
</tr>
<tr>
<td>ENGOT Model</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>Randomisation</td>
<td>After CT</td>
<td>Upfront</td>
<td>Maintenance</td>
<td>Upfront</td>
<td>Upfront</td>
<td>Upfront</td>
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<tr>
<td>Bev in Standardarm</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Optional</td>
<td>Optional</td>
<td>Yes</td>
</tr>
<tr>
<td>Exp. Arm</td>
<td>Nira</td>
<td>- TC-Bev-</td>
<td>Ruca- Nivo</td>
<td>- Nira</td>
<td>BRCA+: Ola +</td>
<td>- Durva</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Atezo</td>
<td>ruca</td>
<td>- Nira + O42</td>
<td>Pembro</td>
<td>Durva+Ola</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Nivolu</td>
<td></td>
<td>Pembro+Ola</td>
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</tr>
<tr>
<td>NACT allowed</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>RT=0</td>
<td>NO after PDS</td>
<td>No but Under discussion</td>
<td>CR/NED after CT</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>YES after IDS</td>
<td></td>
<td></td>
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</tbody>
</table>
Recurrent Ovarian Cancer

• 50-90% of patients with advanced ovarian cancer will have a relapse in less than 5 years depending on:
  – the FIGO stage at diagnosis,
  – use of neo-adjuvant chemotherapy and
  – residual disease after upfront cytoreductive surgery.
Patients receiving 2\textsuperscript{nd}, 3\textsuperscript{rd}, 4\textsuperscript{th} line of CT, impact on PFS and OS

Prognosis after relapse: AGO/GINECO meta-database 1620 pts with documented therapy for relapse

But, OS correlated to lines of treatment

Surgery in relapse: the new reality

Design: AGO DESKTOP III
(ENGOT-ov20; NCT01166737)

- Pts. with:
  - 1st relapse
  - PSROC
  - AGO Score +ve

- 80 centres in 12 countries
- Recruitment 9/2010 - 3/2015
- 407 of 409 pts evaluated (2 screening failures)

Cytoreductive Surgery with max. effort for complete resection

Platinum Comb. strongly recommend

Immediate Platinum-based Combination therapy

R
n = 408

No OP

AGO DESKTOP III: Outcome 3 (PFS by surgical outcome)
(AGO–OVAR OP.4; ENGOT-ov20; NCT01166737)

| Surgical Outcome               | Median PFS [mos] | Δ PFS [mos] | HR (95% CI)       | P-value
<table>
<thead>
<tr>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>No surgery</td>
<td>14.0</td>
<td>-</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Surgery but with residual tumor</td>
<td>13.7</td>
<td>-0.3</td>
<td>0.98 (0.71 - 1.35)</td>
<td>0.8952</td>
</tr>
<tr>
<td>Surgery with complete resection</td>
<td>21.2</td>
<td>+7.2</td>
<td>0.56 (0.43 - 0.72)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

PFS probability (% Kaplan-Meier)

months

No-surgery
Surgery low
Surgery CR
Recurrent Ovarian Cancer: Population Characteristics

PLATINUM SENSITIVITY IS A CONTINUOUS VARIABLE!!!

Survival (days) | Response Rate (%)
---|---
1000 | 100

Response Rate (%)

PFS

Overall Survival

Survival (days)

Response Rate

PFS

Overall Survival

0-3/Pr | 0-3 | 3-6 | 6-9 | 9-12 | 12-18 | ≥18
---|---|---|---|---|---|---
217 | 9 | 90 | 366 | 32 | 166 | 0

Systematic Treatment, Decisional factors

How to treat patient?

- Duration of response to initial platinum therapy
- BRCA mutation status
- Previous agents used
- Toxicities experienced in 1st-line setting
- Patient and physician preference
- Patient’s performance status

- Neurotoxicity
- Hypersensitivity
- Hematotoxicity

- Bevacizumab
  - parp inh
  - 1st line CT
  - National label

- Yes
- No
- Unknown
D2. What are the control arms for clinical trials in recurrent ovarian cancer?

1. In patients where platinum is not an option a control arm can include a non-platinum drug as a single agent or in combination.

2. The choice of control arms for the subgroup who can receive platinum must be supported by evidence and integrate available predictors and prior exposure which may limit selection for further lines. This currently includes 3 potential control arms:
   1. Platinum combination
   2. Platinum combination with a licensed anti-angiogenic agent
   3. Platinum combination followed by a licensed PARP inhibitor

3. There is a subgroup (e.g. medically compromised and/or elderly patients) where less toxic therapy or best supportive care may be the most appropriate control arm.

4. There is no proven effective therapy for patients who have asymptomatic CA125 relapse.
Platinum is not an option (formerly platinum-resistant)

- **Definition** by GCIG:
  - Short TFIp (minimum < 6 m) based on symptomatic relapse or RECIST criteria.
  - Progression on therapy.
  - Platinum allergy or residual toxicity.
  
  **Expected OS is usually short, around 12 months**

- **Main objectives of treatment:**
  - QoL
  - Toxicity
  - Control of symptoms

- **Treatment in control arm** can include a non-platinum drug as a single agent or in combination.

- **Chemotherapy options:**
  - Single agent: weekly paclitaxel, PLD, Topotecan, gemcitabine...
  - Combination: Trabectedine-PLD

*If TFIp > 6 months*
Role of Yondelis+PLD in PPS Ovarian Cancer: OS data

Events/censored: 177/37
Cox regression:
HR: 0.64 (0.47-0.86)
p=0.0027

Median=22.4 months

PLD
Median=16.4 months

WHEN PLATINUM IS NOT AN OPTION: BEYOND CHEMOTHERAPY

AURELIA
Chemotherapy vs chemo-beva

- 361 patients were enrolled between October 2009 and April 2011.
- Options of chemotherapy: weekly paclitaxel, topotecan or PLD.

E Pujade-Laurine et al. JCO 2014
## Parp Inhibitor: active disease setting

<table>
<thead>
<tr>
<th>Potential Line of Therapy</th>
<th>Rucaparib Pooled Analysis (ESMO 2016) (103 pts)</th>
<th>Olaparib US Label (137 pts)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≥3&lt;sup&gt;rd&lt;/sup&gt; line treatment (regardless platinum sensitivity)</td>
<td>≥4&lt;sup&gt;th&lt;/sup&gt; line treatment (regardless platinum sensitivity)</td>
</tr>
<tr>
<td>Dosing</td>
<td>600 mg BID</td>
<td>400 mg BID</td>
</tr>
<tr>
<td>Potential label Populations</td>
<td>Tumour BRCA&lt;sup&gt;mut&lt;/sup&gt; (includes germline and somatic mutations)</td>
<td>Germline BRCA&lt;sup&gt;mut&lt;/sup&gt;</td>
</tr>
</tbody>
</table>
| Most common Grade ≥3 AEs in treatment setting | • Fatigue (11%)  
• Anaemia (23%)  
• ↑ALT/AST (11%) | • Fatigue (8%)  
• Anaemia (18%)  
• Abdominal pain (8%) |
| Dose interruptions/reductions due to side effects | • 8%  
• 44.3% | • 36%  
• 42% |
| ORR (RECIST 1.1) by investigator | 54% | 34% |
| Progression free survival (median, months) | 10.0 | 7.0 |
D2. What are the control arms for clinical trials in recurrent ovarian cancer?

1. In patients where platinum is not an option a control arm can include a non-platinum drug as a single agent or in combination.

2. The choice of control arms for the subgroup who can receive platinum must be supported by evidence and integrate available predictors and prior exposure which may limit selection for further lines. This currently includes 3 potential control arms:
   1. Platinum combination
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   3. Platinum combination followed by a licensed PARP inhibitor

3. There is a subgroup (e.g. medically compromised and/or elderly patients) where less toxic therapy or best supportive care may be the most appropriate control arm.

4. There is no proven effective therapy for patients who have asymptomatic CA125 relapse.
Toxicity and patient’s preference should guide the selection of platinum-doublet therapies.

<table>
<thead>
<tr>
<th>ICON4(^1) GEICO 0104(^2)</th>
<th>AGO-OVAR 2.5(^3)</th>
<th>CALYPSO(^4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paclitaxel-Carboplatin</td>
<td>Gemcitabine-Carboplatin</td>
<td>PLD-Carboplatin</td>
</tr>
<tr>
<td><strong>Toxicity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alopecia</td>
<td>Myelotoxicity</td>
<td>EPP Mucositis</td>
</tr>
<tr>
<td>Neuropathy</td>
<td></td>
<td>Thrombopenia</td>
</tr>
<tr>
<td>Arthralgia</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

PLD: Pegylated liposomal doxorubicin

Bevacizumab plus chemotherapy for ovarian cancer


bev, bevacizumab; CG, carboplatin + gemcitabine; CI, confidence interval; HR, hazard ratio; PFS, progression-free survival
# PARP Inhibitors: A Recap

## PARP inhibitors approved for use in patients with ovarian cancer

<table>
<thead>
<tr>
<th>PARP inhibitor</th>
<th>Authority</th>
<th>Indication</th>
</tr>
</thead>
</table>
| **Olaparib** | EMA Dec 2014 | **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 complete or partial response to platinum-based chemotherapy¹  
Olaparib is not approved in Europe as a monotherapy in the treatment setting |
|               | US FDA Dec 2014 | **Monotherapy** in patients with deleterious or suspected deleterious germline BRCA-mutated (as detected by an FDA-approved test) advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy² |
|               | Aug 2017 | **Maintenance treatment** of adult patients with recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer, who are in a complete or partial response to platinum-based chemotherapy² |
| **Niraparib** | EMA Sept 2017 | **Maintenance treatment** of adult patients with recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to platinum-based chemotherapy³ |
|               | US FDA Mar 2017 | **Maintenance treatment** of adult patients with recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to platinum-based chemotherapy³ |
| **Rucaparib** | EMA | Not approved for use in Europe |
|               | US FDA Dec 2016 | **Monotherapy** for the treatment of patients with deleterious BRCA mutation (germline and/or somatic; as detected by an FDA-approved companion diagnostic for rucaparib) associated advanced ovarian cancer who have been treated with two or more chemotherapies⁴ |

## PARP inhibitors in clinical development

Veliparib, Talazoparib: Veliparib and talazoparib are not approved for use.

---

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 a maintained PR or CR prior to enrolment
- Stable CA-125
- **Primary end point:** PFS

### SOLO-2 aim and design

- 295 patients
- **Germline 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

- **Olaparib 400 mg po bid** (n=196)
- **Placebo po bid** (n=99)

#### Primary endpoint: Investigator-assessed PFS


Pujade-Laurine et al. SGO 2017
Platinum combination followed by iPARP

Olaparib

Data on primary endpoint: BRCA mutated patients

Study-19 PFS

<table>
<thead>
<tr>
<th>Olaparib</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>26/74 (35%)</td>
<td>46/62 (74%)</td>
</tr>
</tbody>
</table>

Median PFS, months (95% CI): 11.2 (8.3-NC) vs 4.3 (3.0-5.4)

HR 0.18 (95% CI: 0.10-0.31), p=0.0001

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


SOLO-2 PFS

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

Pujade-Laurine et al. SGO 2017
Platinum combination followed by iPARP

**Niraparib**: ENGOT ov16-NOVA study design

**Platinum-Sensitive Recurrent High Grade Serous Ovarian Cancer**

**Treatment with 4-6 Cycles of Platinum-based Therapy**

**Response to Platinum Treatment**

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

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

Platinum combination followed by iPARP

Niraparib: ENGOT ov16-NOVA primary end-point

<table>
<thead>
<tr>
<th>Treatment</th>
<th>PFS Median (95% CI) (Months)</th>
<th>Hazard Ratio (95% CI) p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Niraparib (N=138)</td>
<td>21.0 (12.9, NR)</td>
<td>0.27 (0.173, 0.410) p&lt;0.0001</td>
</tr>
<tr>
<td>Placebo (N=65)</td>
<td>5.5 (3.8, 7.2)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment</th>
<th>PFS Median (95% CI) (Months)</th>
<th>Hazard Ratio (95% CI) p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Niraparib (N=234)</td>
<td>9.3 (7.2, 11.2)</td>
<td>0.45 (0.338, 0.607) p&lt;0.0001</td>
</tr>
<tr>
<td>Placebo (N=116)</td>
<td>3.9 (3.7, 5.5)</td>
<td></td>
</tr>
</tbody>
</table>

PFS: gBRCAmut

PFS: non-gBRCAmut
**ARIEL3: Diagram of Analysis Cohorts**

- **ITT population (n=564)**
  - 130 rucaparib 66 placebo
  - 106 rucaparib 52 placebo
  - 139 rucaparib 71 placebo

- **HRD cohort (n=354)**
  - 130 rucaparib 66 placebo
  - 106 rucaparib 52 placebo

- **BRCA-mutant cohort (n=196)**
  - 130 rucaparib 66 placebo

- **BRCA wild type**
  - 368

- **BRCA wild type/LOH high**
  - 158

- **BRCA wild type/LOH low**
  - 161

- **BRCA wild type/LOH indeterminate**
  - 49

- **BRCA mutant**
  - 196

- **BRCA mutant**
  - 130 germline
  - 56 somatic
  - 10 undefined

- **BRCA-mutant cohort (n=196)**

---

*No more than 150 patients with a known deleterious germline BRCA mutation were to be enrolled to ensure enough patients with carcinomas associated with a somatic BRCA mutation or wild-type BRCA were enrolled to determine statistical significance between rucaparib and placebo in the HRD cohort and the ITT population. *Deleterious BRCA mutation detected by next-generation sequencing of tumour tissue but not by central germline blood test. †For LOH high, a cutoff of ≥16% genomic LOH was prespecified for ARIEL3.*
### ARIEL3: INVESTIGATOR-ASSESSED 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

---

At risk (events):
- **Rucaparib**: 130 (0) 93 (23) 63 (46) 35 (58) 15 (64) 3 (67) 0 (67)
- **Placebo**: 66 (0) 24 (37) 6 (53) 3 (55) 1 (56) 0 (56)

Rucaparib, 48% censored; Placebo, 75% censored

Visit cutoff date: 15 April 2017.
Ovarian cancer: conclusions

➢ Treatment according to histotype is the future!

➢ Antiangiogenic agents and parp inhibitors are changing the natural history of ovarian cancer disease.

➢ Immunotherapy results actually deluding!!!!

➢ The best treatment algorytm is that which allows patients to receive all the available and effective treatment options, possibly in the appropriate sequence.