SESSION 4: FRONT LINE THERAPY: Standard Treatment

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AGO-Austria
The New England Journal of Medicine

CYCLOPHOSPHAMIDE AND CISPLATIN COMPARED WITH PACLITAXEL AND CISPLATIN IN PATIENTS WITH STAGE III AND STAGE IV OVARIAN CANCER

WILLIAM P. McGUIRE, M.D., WILLIAM J. HOSKINS, M.D., MARK F. BRADY, B.S., PAUL R. KUCERA, M.D., EDWARD E. PARTRIDGE, M.D., KATHERINE Y. LOOK, M.D., DANIEL L. CLARKE-Pearson, M.D., and MARTIN DAVIDSON, M.D.

McGuire WP et al..
A Randomized Clinical Trial of Cisplatin/Paclitaxel Versus Carboplatin/Paclitaxel as First-Line Treatment of Ovarian Cancer

Andreas du Bois, Hans-Joachim Lück, Werner Meier, Hans-Peter Adams, Volker Möbus, Serban Costa, Thomas Bauknecht, Barbara Richter, Matthias Warm, Willibald Schröder, Sigrid Olbricht, Ulrike Nitz, Christian Jackisch, Günther Emons, Uwe Wagner, Walther Kuhn, Jacobus Pfisterer

For the Arbeitsgemeinschaft Gynäkologische Onkologie (AGO) Ovarian Cancer Study Group


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Phase III Trial of Carboplatin and Paclitaxel Compared With Cisplatin and Paclitaxel in Patients With Optimally Resected Stage III Ovarian Cancer: A Gynecologic Oncology Group Study

By Robert F. Ozols, Brian N. Bundy, Benjamin E. Greer, Jeffrey M. Fowler, Daniel Clarke-Pearson, Robert A. Burger, Robert S. Mannel, Koen DeGeest, Ellen M. Hartenbach, and Rebecca Baergen

Conclusion: The Carboplatin/Paclitaxel regimen achieved comparable efficacy to the Cisplatin/Paclitaxel regimen but was associated with better tolerability and quality of life, and should, therefore, be considered as an important alternative for standard first-line chemotherapy in patients with advanced ovarian cancer.
## International Phase III Experience

<table>
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<td>MITO-2</td>
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<td>Regimen Total</td>
<td>4353</td>
<td>1724</td>
<td>1272</td>
<td>1426</td>
<td>861</td>
<td>539</td>
<td>1090</td>
<td>11265</td>
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</table>

C, Carboplatin or Cisplatin; P, Paclitaxel; G, Gemcitabine; D, PEG-Lipo-Doxorubicin; T, Topotecan; Doc, Docetaxel; E, Epirubicin

More than 11000 randomised patients: no gain
## Maintenance Therapy in Ovarian Cancer

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study design and intervention</th>
<th>No. of pts</th>
<th>Result</th>
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<tbody>
<tr>
<td>Markman</td>
<td>12 vs. 3 months of maintenance paclitaxel</td>
<td>277</td>
<td>PFS OS</td>
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<td>De Placido</td>
<td>MITO-1: topotecan (four cycles)</td>
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<td>Pfisterer</td>
<td>topotecan (four cycles)</td>
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<td>Hall</td>
<td>interferon-α</td>
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<td>Sabbatini</td>
<td>MIMOSA: abagovomab</td>
<td>888</td>
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</table>
Should studies of maintenance therapy be maintained in women with ovarian cancer?

Michael A. Bookman
University of Arizona Cancer Center, Tucson, AZ, USA

Future phase III randomized trials of maintenance with conventional cytotoxic chemotherapy should not be considered without compelling data from well-designed randomized phase II trials.

Angiogenesis inhibitors, PARP-Inhibitors...
Is it possible to increase the effectiveness of chemotherapy by ip instillation?
Dose-Dense Chemotherapy

- Standard-dose
- Dose-escalated
- Dose-dense

Number of Tumor Cells vs. Time
Dose-dense chemotherapy increases the dose intensity of the regimen by delivering standard-dose chemotherapy with shorter intervals between the treatment cycles. The rationale for dose-dense therapy stems from the Norton-Simon hypothesis: Sequential, consecutive dosing of chemotherapy using single or a combination of agents increases the dose density over alternating dosing, improving results.
Long-term results of dose-dense paclitaxel and carboplatin vs. conventional paclitaxel and carboplatin for treatment of advanced epithelial ovarian cancer (JGOG 3016)

Conventional TC (c-TC)
- Paclitaxel 180mg/m², day 1
- Carboplatin AUC 6.0, day 1
  every 21 days for 6-9 cycles

Dose-dense weekly TC (dd-TC)
- Paclitaxel 80mg/m², days 1,8,15
- Carboplatin AUC 6.0, day 1
  every 21 days for 6-9 cycles
Long-term results of dose-dense paclitaxel and carboplatin vs. conventional paclitaxel and carboplatin for treatment of advanced epithelial ovarian cancer (JGOG 3016)

**Treatment n Deaths, n (%) Median OS 5-yr survival P value HR 95%CI**

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<thead>
<tr>
<th>Treatment</th>
<th>n</th>
<th>Deaths, n (%)</th>
<th>Median OS</th>
<th>5-yr survival</th>
<th>P value</th>
<th>HR</th>
<th>95%CI</th>
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<tbody>
<tr>
<td>dd-TC</td>
<td>312</td>
<td>139 (45)</td>
<td>not reached</td>
<td>58.7%</td>
<td>0.039</td>
<td>0.79</td>
<td>0.63-0.99</td>
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<td>c-TC</td>
<td>319</td>
<td>168 (53)</td>
<td>62.2 mos.</td>
<td>51.1%</td>
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**Conventional TC (c-TC)**
- Paclitaxel 180mg/m², day 1
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- Paclitaxel 80mg/m², days 1,8,15
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www.thelancet.com/oncology Vol 14 September 2013
GOG-262 Schema: Dose-dense Integration

Front-line: Epithelial OV, PP or FT cancer

Arm I:
- Epithelial OV, PP or FT cancer
- chemotherapy (6 cycles)
- Carboplatin AUC 6
- Bevacizumab 15 mg/kg (optional)
- Treat until progression

Arm II:
- Dose dense weekly
- Paclitaxel (ddwP) 80 mg/m²
- Carboplatin AUC 6
- Bevacizumab 15 mg/kg (optional)

Activated: 9/27/10
Closed to accrual: 1/3/12
The GOG-0262 trial failed to meet its primary endpoint

Dose-dense weekly paclitaxel did not significantly increase PFS compared with the three-weekly paclitaxel regimen

<table>
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<tr>
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<th>Carboplatin + paclitaxel qw (n=346)</th>
<th>Carboplatin + paclitaxel q3w (n=346)</th>
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<tbody>
<tr>
<td>Events</td>
<td>207</td>
<td>216</td>
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<tr>
<td>Median, months</td>
<td>14.8</td>
<td>14.3</td>
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<tr>
<td>HR (95% CI)</td>
<td>0.97 (0.79–1.18)</td>
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</table>

Chan J. et al, ESGO Liverpool 2013
First line weekly carboplatin and paclitaxel vs. every 3 weeks carboplatin/paclitaxel in patients with ovarian cancer: the MITO – 7 trial

Front-line: Epithelial OV, PP or FT cancer

Chemotherapy (6 cycles)

Arm I
EVERY 3 WEEK
Paclitaxel (P) 175 mg/m²
Carboplatin AUC 6

Arm II
DOSE DENSE WEEKLY
Paclitaxel (ddwP) 60 mg/m²
Carboplatin AUC 2 weekly

STRATIFY
RANDOMIZE
Carboplatin plus paclitaxel once a week versus every 3 weeks in patients with advanced ovarian cancer (MITO-7): a randomised, multicentre, open-label, phase 3 trial

Pignata et al, Lancet Oncol 2014
Ovarian Cancer: Peritoneal Carcinomatosis
Ovarian Cancer: Peritoneal Carcinomatosis
Angiogenesis

Bevacizumab

Pazopanib, Sorafenib, Sunitinib, Cediranib, Motesanib, Nintedanib...

Trebananib

Signal transduction cascade

↑ Proliferation
↑ Invasion
↑ Migration
↑ Permeability
↑ Degradation of basement membrane
↑ Capillary tube formation
Inhibition of angiogenesis in front-line and maintenance treatment of ovarian cancer

Front-line and Maintenance

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<tr>
<th>Study</th>
<th>GOG 218</th>
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<td><strong>Early and advanced stage patients</strong></td>
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<td><strong>PFS</strong></td>
<td>17.4 vs 19.8</td>
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<td><strong>PFS</strong></td>
<td>10.6 vs 14.7</td>
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*Bevacizumab group only*
Inhibition of angiogenesis in front-line and maintenance treatment of ovarian cancer

### Front-line and Maintenance

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<th>Treatment</th>
<th>Stage</th>
<th>PFS (months)</th>
<th>OS (HR)</th>
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<td>FIGO IIb-IV</td>
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Inhibition of angiogenesis in front-line and maintenance treatment of ovarian cancer

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<td>Bevacizumab</td>
<td>FIGO I-IV, Dose-dense (Paclitaxel weekly)</td>
<td>14.9 vs 14.9 HR=1.06&lt;sup&gt;4&lt;/sup&gt;</td>
<td>Not reported</td>
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ICON8 trials programme

- ICON8
  - Stage IC-IV EOC/PPC/FTC
    - Randomise 1:1:1
      - Arm 1: 6 cycles
      - Arm 2: 6 cycles
      - Arm 3: 6 cycles

- ICON8B
  - High-risk* stage III-IV EOC/PPC/FTC
    - Randomise 1:1:1
      - Arm B1: 6 cycles
        - Maintenance bevacizumab (18 Cycle Total)
      - Arm B2: 6 cycles
        - 6-weekly follow-up until week 66 post randomisation
      - Arm B3: 6 cycles
        - Maintenance bevacizumab (18 Cycle Total)

- Standard incl. Bev
- Dose dense - Bev
- Dose dense + Bev

High-risk* defined as (1) FIGO (2013) stage IIIA1(ii), IIIA2 with positive retroperitoneal lymph nodes >1cm in diameter, stage IIIB or IIIC with >1cm residual disease following immediate primary surgery or planned to receive primary chemotherapy +/- delayed primary surgery and (2) FIGO (2013) stage IV
Inhibition of angiogenesis in front-line and maintenance treatment of ovarian cancer

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<th>PFS HR</th>
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<td>FIGO IIb-IV</td>
<td>PFS 25.5</td>
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</table>

Bevacizumab exposure by cycle

- **No. of cycles**: 23 (1–61)
- **Duration, months**: 15.5 (<0.1–43.2)

- **632 patients (62%)** received >12 months of BEV
- **537 patients (53%)** received >15 months of BEV
- **298 patients (29%)** received >24 months of BEV

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\(^a\)Denominator at each cycle is 1021
Progression-free survival (ITT population)

Median duration of follow-up: 32.0 months (range 0.7–49.5 months)

Events, n (%) 558 (54.7)
1-year PFS rate, % 82.6 (95% CI 80.0–84.8)
2-year PFS rate, % 53.0 (95% CI 49.7–56.1)
Median PFS, months 25.5 (95% CI 23.7–27.6)

Data cut-off: 7 Dec 2014. ITT = intent-to-treat
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-ov15/ AGO OVAR 17

The BOOST
(Bevacizumab Ovarian Optimal Standard Treatment) first-line trial

Stratification:
- FIGO stage
- residual macroscopic disease (no/yes)
- Center

Bevacizumab 15 mg/kg  q 21 days
Paclitaxel 175 mg/m²
Carboplatin AUC5
until cycle 22
(15 months)

Bevacizumab 15 mg/kg  q 21 days
Paclitaxel 175 mg/m²
Carboplatin AUC5
until cycle 44
(30 months)
### Inhibition of angiogenesis in front-line and maintenance treatment of ovarian cancer

#### Front-line and Maintenance

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment 1</th>
<th>Treatment 2</th>
<th>Advanced, stage III/IV patients</th>
<th>Early and advanced stage patients</th>
<th>FIGO IIb-IV, Dose-dense (Paclitaxel weekly)</th>
<th>FIGO IIb-IV</th>
<th>Advanced, stage III/IV patients</th>
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<tbody>
<tr>
<td>GOG 218</td>
<td>Bevacizumab</td>
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<td>PFS 10.6 vs 14.7 HR=0.72(^1)</td>
<td>PFS 17.4 vs 19.8 HR=0.81(^2)</td>
<td>PFS* 14.9 vs 14.9 HR=1.06(^4)</td>
<td>PFS 25.5(^5)</td>
<td>PFS 15.0 vs. 15.9 HR=0.93(^6)</td>
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<td>OS HR=0.99</td>
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Progression-Free Survival
Primary Analysis

TRINOA-3/ENGOT-ov-2: A RANDOMIZED, DOUBLE-BLIND PHASE 3 STUDY OF TREBANANIB PLUS CARBOPLATIN/PACLITAXEL AS FIRST-LINE TREATMENT IN ADVANCED OVARIAN CANCER

<table>
<thead>
<tr>
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<th>C/P + Trebananib (n = 678)</th>
<th>C/P+ Placebo (n = 337)</th>
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</thead>
<tbody>
<tr>
<td>Events, n (%)</td>
<td>405 (60)</td>
<td>221 (66)</td>
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<tr>
<td>Median PFS, mo</td>
<td>15.9 (15.0–17.6)</td>
<td>15.0 (12.6–16.1)</td>
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</table>

HR (stratified Cox model) = 0.93 (95% CI, 0.79–1.09)

P (stratified log-rank) = 0.36

Vergote et al., IGCS 2016
Inhibition of angiogenesis in front-line and maintenance treatment of ovarian cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Phase</th>
<th>Patient Population</th>
<th>Treatment</th>
<th>Duration</th>
<th>Progression-Free Survival (PFS)</th>
<th>Overall Survival (OS)</th>
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<tr>
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<td>TRINOVA-3</td>
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<td>FIGO II-IV, no PD after ≥5x CP</td>
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<td>HR=1.08</td>
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<td>ENGOT-ov-2</td>
<td>Maintenance</td>
<td>FIGO II-IV, no PD after ≥5x CP</td>
<td>Pazopanib</td>
<td>12.3 vs 17.9</td>
<td>HR=0.93&lt;sup&gt;6&lt;/sup&gt;</td>
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## Inhibition of angiogenesis in front-line and maintenance treatment of ovarian cancer

### Front-line and Maintenance

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<td>0.81²</td>
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<td>Nintenanib</td>
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<td>16.6 vs 17.2</td>
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</tr>
<tr>
<td>GOG 262</td>
<td>Bevacizumab</td>
<td>FIGO I-IV, Dose-dense (Paclitaxel weekly)</td>
<td>14.9 vs 14.9</td>
<td>1.06⁴</td>
<td>PFS*</td>
<td></td>
</tr>
<tr>
<td>ROSiA</td>
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<td>TRINOA-3 ENSGOT-ov-2</td>
<td>Trebananib</td>
<td>Advanced, stage III/IV patients</td>
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<td>HR=0.77⁷</td>
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</tr>
<tr>
<td>AGO-OVAR16</td>
<td>Pazopanib</td>
<td>FIGO II-IV, no PD after ≥5x CP</td>
<td>12.3 vs 17.9</td>
<td>1.08</td>
<td>OS</td>
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</tbody>
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*Bevacizumab group only
Inhibition of angiogenesis in front-line and maintenance treatment of ovarian cancer

### Front-line and Maintenance

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Stage</th>
<th>PFS</th>
<th>OS</th>
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<tr>
<td><strong>GOG 218</strong></td>
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*Bevacizumab group only

What is Post Progression Survival (PPS)?

Post Progression Survival: Time from disease progression till death

Start → Progression → Death

PFS → OS → PPS
**PPS influences chance to translate PFS into OS benefit**

If PPS = 2 months

PFS and OS benefit = 3 mo

Patients needed to demonstrate significant OS = 350

Control Arm:
- PFS 3 mo
- PPS 2 mo
  
  Total OS = 5 mo

Active Arm:
- PFS 6 mo
- PPS 2 mo
  
  Total OS = 8 mo

Courtesy Nicoletta Colombo
PPS influences chance to translate PFS into OS benefit

If PPS = 2 months

PFS and OS benefit = 3 mo
Patients needed to demonstrate significant OS = 350

If PPS = 2 months

PFS 6 mo
Control Arm

PFS 3 mo
PPS 2 mo
Total OS = 5 mo

Active Arm

Total OS = 8 mo

If PPS = 24 months

PFS and OS benefit = 3 mo
Patients needed to demonstrate significant OS = 2440

If PPS = 24 months

PFS 6 mo
Control Arm

PFS 3 mo
PPS 24 mo
Total OS = 27 mo

Active Arm

Total OS = 30 mo

Courtesy Nicoletta Colombo
Ovarian Cancer Treatment is like a Relay Race….

Good start is crucial…… but with weak following runners it is difficult to win the race!
The prognostic significance of anti-angiogenesis therapy in ovarian cancer: a meta-analysis

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 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. A validated schedule is mandatory.
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   - **Platinum/taxane and bevacizumab.**
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Thank you for your attention
SOLO2/ENGOT ov21: Olaparib Phase III BRCAm ovarian PSR study

- ≥2 previous lines of platinum containing therapy
- Penultimate therapy: platinum agent
- PFS > 6 months after completion
- Last chemotherapy prior to randomisation: PR/CR received ≥ 4 cycles

**Randomisation 2:1 N=264**

- **Primary endpoint:**
  - PFS (RECIST v1.1 data)

- **Key secondary endpoints**
  - OS
  - PFS 2 Safety
  - QoL

**Press Release 26 October 2016:**
Results from the trial demonstrate a **clinically-meaningful and statistically-significant** improvement of progression-free survival (PFS) among patients treated with Lynparza compared to placebo and provide additional evidence to support the potential use of Lynparza in this patient population.

Importantly, the median PFS in the Lynparza arm of SOLO-2 substantially exceeded that observed in the Phase II maintenance study in patients with platinum-sensitive relapsed ovarian cancer (Study 19).
Current view of ovarian cancer biology

- Serous
  - A disease of genomic instability

- Mucinous
  - A disease of aberrant RAS pathway signaling

- Endometrioid
  - A disease of aberrant PTEN, PI-3K, AKT signaling

- Clear cell
  - A disease of ARID1A

Vaughan et al Nat Rev Cancer (2011) 11:719
Current view of ovarian cancer biology

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  - A disease of ARID1A
GOG3005: PARPi Primary Therapy & Maint

- High-grade extrauterine serous tumors, Stage I-C, II, III, IV
- Election for NACT-ICS and scheduling of paclitaxel (no IP therapy)
- Primary endpoint PFS: (1) Entire Population, (2) BRCA1/2 Population
- Stratifications: Stage, Residual Disease, NACT-ICS, Region

1:1:1

Collaborative development in progress with AbbVie (M13-694) including international participation, seeking EMA and FDA regulatory approval

Open: JAN 2014 (target)
Target Accrual: ~1100 pts (264 BRCA1/2 +)
GOG3004-SOLO1: Maintenance

- High-grade extrauterine serous tumors, Stage III, IV
- mBRCA1/2 Germline or Somatic
- Initial chemotherapy with platinum and taxane
- Clinical CR without measurable disease on CT imaging
- Primary endpoint PFS: 8 month benefit, HR 0.62
- Stratifications: Stage, Response, Treatment Characteristics

Primary Random
Platinum and Taxane (IV or IP)

I
Olaparib 300 mg PO BID (28 D Cycle)
Until PD or 16 Cy

II
Placebo PO BID (28 D Cycle)
Until PD or 16 Cy

Open: JUL 2013
Target Accrual: 344 Pts (BRCA 1/2 +)

DiSilvestro P and Moore K for GOG
ENGOT-ov26 PRIMA study

- FIGO III/IV
- with macroscopic RD after PDS
- or after NACT independently of RD
- HRD-positive
- CR or PR following front-line platinum-chemotherapy

I
Niraparib 300 mg PO
N=202
Until PD or 16 Cy

II
Placebo PO
N=101
Until PD or 16 Cy
Randomize

Arm A
Olaparib
300 mg bd x 2 years
n=408

Arm B
Placebo
bd x 2 years
n=204

PFS 1
PFS 2, OS

Bevacizumab (15mg/kg/3wk) ≥ 3 cycles combined with chemo + Maintenance in both arms (15 months total)

n=612

FIGO IIIB-IV
HG-SOC or HG-Endo O,P,F Cancer

First-line Surgery and Chemot (Dose-dens, IP, NACT allowed)
JAVELIN Ovarian 100 (Front-Line) Avelumab, Platinum, Paclitaxel + Maintenance

**Enrollment Criteria**
- Previously untreated
- Stage III-IV
- Prior debulking surgery or plan for neoadjuvant chemotherapy
- ECOG PS 0 or 1
- Mandatory archival tissue

**Primary Endpoint:**
- PFS

**Secondary Endpoints:**
- Maintenance PFS, OS, ORR, DOR, pCR, PROs, safety, PK

**Randomized Phase III Study (NCT02718417)**

- **Arm A:** Chemotherapy (Q3W)
- **Arm B:** Chemotherapy (Q3W) + Avelumab (Q3W)
- **Arm C:** Avelumab (Q2W) + Maintenance up to 2 years

**n = ~951**

Patients with SD or better will be allowed to continue to maintenance
Chemotherapy: Choice of Q3W carboplatin-paclitaxel OR carboplatin + weekly paclitaxel
Maintenance avelumab up to 2 years

**IMaGY-N-050**: Double-blind placebo-controlled multicentre phase III trial of first-line atezolizumab for OC (neoadjuvant cohort)

**Stratification variables:**
- Stage/debulking status
- ECOG PS
- PD-L1 IC0 vs IC1+
- Adjuvant/neoadjuvant therapy
- Previously untreated ovarian, fallopian tube or peritoneal cancer
- Stage III (macroscopic residual disease), stage IV or unresectable advanced stage for neoadjuvant therapy
- ECOG PS 0–2

**Co-primary endpoints:**
- PFS and OS in all comers and Dx+ (IC1+)

**Surgery**
- Carboplatin AUC 6 q3w
- Paclitaxel 175 mg/m² q3w
- Bevacizumab 15 mg/kg q3w
- Placebo q3w x 22 cycles

**R**
- Paclitaxel 175 mg/m² q3w
- Carboplatin AUC 6 q3w
- Bevacizumab 15 mg/kg x 16 cycles
- Bevacizumab 15 mg/kg x 16 cycles

**Atezolizumab**
- Atezolizumab 1200 mg q3w x 22 cycles

**No crossover**