Landscape of Systemic Therapy for Ovarian Cancer 2019

-Primary Therapy-

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GCIG Chair
Landscape of Systemic Therapy for Ovarian Cancer 2019

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Primary Therapy

Disclosure

- Astra Zeneca
- Pfizer
- MSD
- Clovis
Primary Therapy

Introduction and Background

• Consensus Statement from 5th Ovarian Cancer Consensus Conference 2015
  – 3-weekly carboplatin and paclitaxel remain the standard chemotherapy drugs for first-line therapy in advanced stage ovarian cancer
  – Acceptable alternative schedules, and routes of delivery include
    • 1) weekly intravenous paclitaxel in combination with 3-weekly intravenous carboplatin
    • 2) the addition of bevacizumab to the standard chemotherapy drugs after primary surgery
    • 3) intraperitoneal platinum-based chemotherapy after primary surgery with <1 cm residual disease

primary Therapy

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Primary Therapy

Weekly Paclitaxel

  – DDW Pac + 3W Carbo > 3W Pac + 3W Carbo

  – W Pac + W Carbo = 3W Pac + 3W Carbo

  – DDW Pac + 3W Carbo + Bev = 3W Pac + 3W Carbo + Bev
    (Bev was optional)
  – DDW Pac + 3W Carbo > 3W Pac + 3W Carbo (Subset Analysis)

• ICON-8
  – DDW Pac + 3W Carbo = 3W Pac + 3W Carbo
  – W Pac + W Carbo = 3W Pac + 3W Carbo

DDW: dose-dense weekly
W: weekly
3W: 3-weekly
ICON8 trials programme

Stage IC-IV EOC/PPC/FTC

Randomise 1:1:1

Arm 1: 6 cycles
Arm 2: 6 cycles
Arm 3: 6 cycles

Arm 1: Carboplatin AUC 5, q3w, Paclitaxel 175mg/m², q3w
Arm 2: Carboplatin AUC 5, q3w, Paclitaxel 80mg/m², q3w
Arm 3: Carboplatin AUC 2, q1w, Paclitaxel 80mg/m², q1w

High-risk* stage III-IV EOC/PPC/FTC

Randomise 1:1

Arm B1: 6 cycles
Arm B3: 6 cycles

Maintenance bevacizumab (18 Cycles Total)

Arm B1: Carboplatin AUC 5, q3w, Paclitaxel 175mg/m², q3w, Bevacizumab 7.5mg/kg, q3w
Arm B3: Carboplatin AUC 5, q3w, Paclitaxel 80mg/m², q1w, Bevacizumab 7.5mg/kg, q3w

NB. High-risk patients remain eligible for ICON8 so that patients with contra-indications to bevacizumab and those unable to access it are still able to enter the trial.

*High-risk defined as (1) FIGO (2013) stage IIaA1(ii), IIaA2 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.
Accrual began 6th June 2011 and ICON8 pathway closed to recruitment 28th November 2014

Final recruitment figure = 1566

UK= 1397, ANZGOG= 70, GICOM= 43, KGOG= 32, ICORG= 24

Primary PFS analysis presented at ESMO 2017. Conclusions: although weekly dose-dense chemotherapy can be delivered successfully as first-line EOC treatment without substantial toxicity increase, it does not significantly improve PFS compared to standard 3-weekly CT.
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Primary Therapy

Weekly Paclitaxel

  - DDW Pac + 3W Carbo

  - W Pac + W Carbo = 3W Pac + 3W Carbo (Subset Analysis)

  - DDW Pac + 3W Carbo + Bev = 3W Pac + 3W Carbo + Bev (Bev was optional)

- ICON8
  - DDW Pac + 3W Carbo = 3W Pac + 3W Carbo

Contradictory Results between Trials

But

ICON8 Results Implies the Ethnic Differences

DDW: dose-dense weekly
W: weekly
3W: 3-weekly
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Addition of Bevacizumab

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Primary Therapy

Addition of Bevacizumab

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Addition of Bevacizumab

- ICON7 Sub-analysis (Oza, Lancet Oncol 2015; 16: 928-36)

**All Patients**
HR 0.99 (0.85-1.14), p=0.85

**High Risk Patients**
HR 0.78 (0.63-0.97) p=0.03
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Addition of Bevacizumab in Recurrent Ovarian Cancer GOG213 Trial

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Addition of Bevacizumab

• PFS: Improved
• OS: Not improved in all patient population
  But improved in high-risk patient population

• In consideration with the improvement of OS in GOG213 trial for recurrent ovarian cancer patients, addition of bevacizumab may be a reasonable choice of treatment for high risk patient population
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Intraperitoneal (IP) Chemotherapy

  - GOG104, GOG114, GOG172
    - IP Cisplatin > IV Cisplatin

- **IP Carboplatin**
  - GOG252 (Walker, JCO in press)
    - IP Carbo **with Bev** = IV Carbo **with Bev**
    - IP Carbo > IV Carbo
    - IP Carbo ? IV Carbo

  - Will be discussed extensively in this symposium
iPocc

PDS
Optimal
Suboptimal

GOG252

PDS
Optimal
Suboptimal

NCIC OV21/GCIG

NACT
+IDS

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Primary Therapy

**GOG 252**

**Phase A: Cycles 1-6**

- 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

**Phase B: Cycles 7-22**

- Bevacizumab
  - 15 mg/kg IV on day 1 for cycles 7-22

**IV carbo Arm 1**

**IP carbo Arm 2**

**IP cisplatin Arm 3**

*Continue regimen every 3 weeks for six cycles of chemotherapy and a total of 22 cycles including bevacizumab unless toxicity or progression intervenes.*
Primary Therapy

Stage II or III Optimally Debulked

Progression-Free Survival by Treatment Group

<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>303</td>
<td>461</td>
<td>26.8</td>
</tr>
<tr>
<td>2: Crb(IP)+T+Bev</td>
<td>300</td>
<td>464</td>
<td>28.7</td>
</tr>
<tr>
<td>3: Cis(IP)+T+Bev</td>
<td>307</td>
<td>456</td>
<td>27.8</td>
</tr>
</tbody>
</table>

Walker, JCO in Press
Primary Therapy

OV21/PETROC: Schema (2 stage study)

**ELIGIBILITY**
- EOC, fallopian tube or primary peritoneal cancer
- Clinical FIGO stage IIB-IV AT DIAGNOSIS
- Neoadjuvant platinum-based chemotherapy
- Resected to optimal <1cm

**Randomization**

**ARM 1**
- Carboplatin AUV5/6* IV Day 1
- Paclitaxel 135 mg/m² IV 1 Day 1
- Paclitaxel 60 mg/m² IV 1 Day 8
- Q 21 days X 3 cycles

**ARM 2**
- Cisplatin 75 mg/m² IP Day 1
- Paclitaxel 135 mg/m² IV Day 1
- Paclitaxel 60 mg/m² IP Day 8
- Q 21 days x 3 cycles

**ARM 3**
- Carboplatin AUC 5/6* IP Day 1
- Paclitaxel 135 mg/m² IV Day 1
- Paclitaxel 60 mg/m² IP Day 8
- Q 21 days x 3 cycles

* AUC 5 (measured GFR)/AUC 6 (calculated GFR)

Limitations; Phase 2 setting, Lack of power for PFS or OS.

Primary Therapy

Ovarian, Peritoneal, Tubal Cancer
Stage II-IV

Optimal & Suboptimal
IDS Allowed

Paclitaxel 80 mg/m² Days 1, 8, 15 IV
Carboplatin AUC6 IV
q3w, 6-8 cycles

Paclitaxel 80 mg/m² Days 1, 8, 15 IV
Carboplatin AUC6 IP
q3w 6-8 cycles

Total Sample Size 655

WITHOUT Bevacizumab
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Primary Therapy

iPocc Trial (GOTIC-001/JGOG3019)

Total 655: Singapore 32, KGOG 10, NZ 4, USA 4, Hong Kong 2
IP Therapy and BRCA Status

Test for interaction: $P = 0.014$

<table>
<thead>
<tr>
<th>Therapy</th>
<th>IHC expression</th>
<th>Patients</th>
<th>Events</th>
<th>Median OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>IP</td>
<td>Aberrant BRCA1</td>
<td>96</td>
<td>51</td>
<td>84.1 months</td>
</tr>
<tr>
<td>IP</td>
<td>Normal BRCA1</td>
<td>97</td>
<td>62</td>
<td>58.1 months</td>
</tr>
<tr>
<td>IV</td>
<td>Aberrant BRCA1</td>
<td>93</td>
<td>74</td>
<td>47.7 months</td>
</tr>
<tr>
<td>IV</td>
<td>Normal BRCA1</td>
<td>107</td>
<td>68</td>
<td>50.4 months</td>
</tr>
</tbody>
</table>
Primary Therapy

Intraperitoneal (IP) Chemotherapy **Summary**

- IP Cisplatin showed improvement of survival over IV Cisplatin but not over IV Carboplatin (current standard).
- IP Cisplatin showed significant improvement of OS in patients with BRCA mutations.
  - Implication of benefit in combination with PARP inhibitor in the future.
- IP Carboplatin was NOT inferior to IP Cisplatin and superior to IP Cisplatin in terms of toxicity
  - GOG252 Trial
  - OV21 Trial
- Results of iPocc trial will finalize the discussion of IP Carboplatin whether the result is positive or negative.
Primary Therapy

PARP Inhibitor

• For Platinum Sensitive Recurrent Patients
  - PARP inhibitors showed improvement of PFS compared to the placebo
    • Olaparib
    • Niraparib
    • Rucaparib

• For Primary Treatment
  - Olaparib showed significant improvement of PFS as a maintenance therapy after platinum-based chemotherapy
**Primary Therapy**

**SOLO-1 Trial Design**

- **Newly diagnosed Stage III-IV**
- **CR/PR/no evidence of disease upon completion of 1\textsuperscript{st} line platinum**

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**Olaparib 300mg bid until progression**

- Randomise 2:1 at end of chemotherapy
- $N=344$

**Placebo bid until progression**

- until progression (Max. 2 yrs for CR)

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**Primary Endpoint:**

- PFS (RECIST, BICR)

**Key Secondary Endpoints**

- OS, PFS2
- TFST, TSST, TDT
- HRQoL
- Safety

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Primary Therapy

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Primary Therapy

Toxicities of Olaparib

• Nausea/Vomiting
• Fatigue
• Anemia
• Diarrhea/Constipation
• Dysgeusia
• Arthralgia
• Abdominal Pain
• Neutropenia

Etc.

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Primary Therapy

FDA Approval

For Olaparib
• Ovarian cancer Patients
  – with germline BRCA mutation
  – With somatic BRCA mutation

For BRCAnalysis CDx test
• To identify patients with germline BRCA mutated ovarian cancer patients

(https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm628876.htm)
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Primary Therapy

FUTURE
Combination of PARP Inhibitor with Other Agents

• With Antiangiogenics
  – Bevacizumab
  – Cediranib (for recurrent ovarian cancer)

• With Immune Checkpoint Inhibitors
  – PD-1 Antibody
  – PD-L1 Antibody
# Landscape of Systemic Therapy for Ovarian Cancer 2019

## Primary Therapy

### Ovarian Cancer Targeted Therapy Landscape Overview

<table>
<thead>
<tr>
<th>VEGFi</th>
<th>PARPi</th>
<th>PDL1/L1i</th>
<th>PARPi + VEGFi</th>
<th>VEGFi + PD1/L1i + PARPi</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bev + chemo</td>
<td>Veliparib + chemo</td>
<td>Avelumab + chemo</td>
<td>Avelumab + chemo + Talazoparib</td>
<td>Durvalmb + Bev + chemo + Olaparib Duo-O</td>
</tr>
<tr>
<td>NICR-218</td>
<td>VELIA</td>
<td>JAVELIN 100</td>
<td>JAVELIN PARP 100</td>
<td>IMagyn50</td>
</tr>
<tr>
<td>Bev + chemo</td>
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<td>Avelumab + chemo + Talazoparib</td>
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<td>NICR-218</td>
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<td>JAVELIN PARP 100</td>
<td>IMagyn50</td>
</tr>
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**First-line Treatment**

- Bev + chemo (GOG-218)
- Veliparib + chemo (VELIA)
- Avelumab + chemo (JAVELIN 100)

**First-line Maintenance**

- Olaparib, SOLO-1 (gBRCA)
- Niraparib, PRIMA (tBRCA, HRD+)
- Olaparib + Bev (PAOLA-1)
- Bev + chemo (ICON7)
- Atezo + Bev + chemo; IMagyn50

*Modified from Meet the Professor; ASCO 2017 By Dr. Mirza MR*
Primary Therapy

**PAOLA -1 Study design**

- FIGO IIIIB-IV High Grade Serous or Endometrioid, or epithelial non mucinous with gBRCA 1 or 2 deleterious mutation. Ovarian, Primary Peritoneal, Fallopian tube.

**First-line Surgery and Chemotherapy (Dose-dense, I.P., neoadjuvant allowed)**

- Bevacizumab (15 mg/kg/3 weeks): Minimum of 3 cycles combined with chemotherapy + Maintenance in both arms (15 months in total)

**Randomization**

- PR/CR NED* → 2:1

**Arm A**
- Olaparib
- 300 mg bid x 2 yrs
- N=408

**Arm B**
- Placebo
- 300 mg bid x 2 yrs
- N=204

**Interim safety analysis**

**PFS 1**

**PFS 2, OS**

* NED = No Evidence of Disease
Trial setting: Ovary/newly diagnosed
Sponsor(s): MSD
Planned No. of patients: 1086
FPI: expected Q4 2018
Co-primary Endpoints: PFS (by PI) and OS

First biopsy for somatic BRCA testing (taken at PDS or laparoscopy or core, ...)
Randomization before cycle 2 if not somatic mutated in BRCA
Stratification: 1. Bev use 2. PDS R0; PDS R>0; NACT->IDS 3. PD-L1 status (CPS < or >= 10)

Trial setting: Ovary/newly diagnosed
Sponsor(s): MSD
Planned No. of patients: 1086
FPI: expected Q4 2018
Co-primary Endpoints: PFS (by PI) and OS

STUDY DESIGN

Primary debulking

Interval debulking

First biopsy for somatic BRCA testing (taken at PDS or laparoscopy or core, ...)
Randomization before cycle 2 if not somatic mutated in BRCA
Stratification: 1. Bev use 2. PDS R0; PDS R>0; NACT->IDS 3. PD-L1 status (CPS < or >= 10)

Bevacizumab allowed; to be specified in advance; randomization to be stratified by use of bev or not
Ongoing Trials – status update

GOG 3020 (NCT03522246)

Maintenance Rucaparib +/- Nivolumab

ATHENA

CO-338-087/GOG-3020/ENGOT-ov45 (Joint International Steering Committee)

**Patient Eligibility**

- Newly diagnosed, Stage III/IV, high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer
- Response of CR or PR to first-line platinum including patients with complete resection/RD
- Completed cytoreductive surgery, with sufficient tissue available for analysis
- ECOG PS ≤1
- Excludes any prior treatment for ovarian cancer, other than the first-line platinum regimen, including any maintenance treatment

**Stratification**

- HRR status by NGS mutation analysis
  - tBRCA (BRCA1/2)
  - Non-tBRCA LOH
  - Non-tBRCA LOH
  - Response to 1st line platinum
    - No residual disease
    - Residual disease
    - Timing of Surgery
    - Primary
    - Interval debulking

**Treatment**

<table>
<thead>
<tr>
<th>Arm A</th>
<th>Rucaparib PO 600 mg BID + Nivolumab IV 480 mg Q4W n=400</th>
</tr>
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<tbody>
<tr>
<td>Arm B</td>
<td>Rucaparib PO 600 mg BID + Placebo IV n=400</td>
</tr>
<tr>
<td>Arm C</td>
<td>Placebo PO + Nivolumab IV 480 mg Q4W n=100</td>
</tr>
<tr>
<td>Arm D</td>
<td>Placebo PO + Placebo IV n=100</td>
</tr>
</tbody>
</table>

**Primary Endpoint**

- PFS by investigator in molecularly-defined HRD subgroups

**Secondary Endpoints**

- PFS by BICR in molecularly-defined HRD subgroups
- ORR and DOR in patients with measurable disease
- OS and Safety

**Status:** Ongoing Accrual

**Target:** 1000 pts

**Notes:** Monk B and Kristeleit, for GOG-F and ENGOT
Primary Therapy

Summary

- Mainstay of primary systemic therapy for ovarian cancer is paclitaxel and carboplatin administering every 3 weeks.
- Maintenance therapy with olaparib after chemotherapy dramatically improved the PFS.
  - Role of PARPi on OS still unknown.
  - Long term adverse effect of PARPi still unknown.
- Multiple trials for combination of PARPi is ongoing.
  - With antiangiogenics
  - With immuno-checkpoint inhibitors

Stay Tuned for Future!
Primary Therapy