Optimal Management of Ovarian cancer- Decisions and options

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Disclosures

Jonathan Ledermann has attended Advisory Boards and given invited lectures for AstraZeneca with remuneration to his institution.

Advisory Boards: Clovis Oncology, Bayer, Oxigene, Merck/MSD,

He is the Chief Investigator of Study 19 with olaparib but has not received any financial compensation.

Speaking honoraria Roche
Topics

• Integration of surgery and chemotherapy
• Choices for first line therapy
• Follow-up and re-treatment
• Choices for ‘platinum-sensitive’ recurrence
• BRCA mutation testing - biomarker for treatment
• Challenges for treating ‘platinum-resistant’ disease
Surgery

Complete removal of visible tumour carries prognostic importance

optimal debulking = no residual disease

No residual disease v < 1 cm
HR 2.20 (95% CI 1.90-2.54)
Cochrane meta-analysis. Elattar et al 2011

Surgery and ‘neoadjuvant’ (primary) chemotherapy for advanced ovarian cancer

Primary chemotherapy *versus* primary surgery for newly diagnosed advanced ovarian cancer (CHORUS): an open-label, randomised, controlled, non-inferiority trial


N= 550
Conclusions

• Surgical debulking has a key role in the management of first line disease- and extent of surgery is prognostic
• For advanced cases- ‘borderline operable’ neoadjuvant chemotherapy is equivalent to primary surgery
• But PFS and OS results are consistently lower than in trials where primary surgery was performed
• Extrapolation of results to all patients with advanced disease should be made with caution
• Trials of ‘radical surgery’ – primary or neoadjuvant in specialised surgical centres is being planned
First-line therapy: Is three weekly carboplatin and paclitaxel still the standard of care?

Carboplatin + 3 weekly paclitaxel versus Carboplatin and weekly paclitaxel

Med PFS 28.2 v 17.5 m
HR: 0.76 (95%CI 0.62-0.91) p=0.0037

Med OS 100.5 v 62.2 m
HR 0.77 (95%CI 0.63-0.99); p= 0.039

Katsumata et al Lancet Oncol 2013 14: 1020-26
Incorporation of bevacizumab into first line therapy

**GOG 218**
3-arm trial adding bevacizumab 15 mg/kg to standard carboplatin/paclitaxel continuing for up to 15 months maintenance

PFS Benefit but not OS

Licence by EMA (not FDA)

**ICON 7**
2 arm trial-
Bevacizumab 7.5 mg/kg
12 month maintenance

PFS outcome similar

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ICON 7 Initial results

**Primary PFS** (all patients)

- HR = 0.81 (95% CI 0.70–0.94)
- p=0.0041

**First interim OS** (all patients)

- HR = 0.81 (95% CI 0.63–1.04)
- p=0.098

**PFS: High-risk**

- HR=0.73 (0.60–0.93); P=0.002

Suboptimal stage III > 1 cm residual Stage IV

Perren TJ, et al. NEJM 2011
ICON 7 Final Overall Survival by Risk Group

Interaction: $p=0.01$

Non-high risk
HR 1.14
(0.93–1.40)
37% events

High risk
HR 0.78
(0.63–0.97)
66% events

Control
Research
Research
Control

BEV exposure

Proportion alive

Time (months)
Dose-dense chemotherapy and bevacizumab: GOG 262 Schema

Front-line: Epithelial OV, PP or FT cancer

N=692

Stage II-IV
- Stage II-IV
- Neoadjuvant optimal or suboptimal
- Neoadjuvant (optional)
- Bevacizumab (optional) prior randomization

Neoadjuvant optional
BEV optional

Chemotherapy (6 cycles)

Treat until progression

EVERY 3 WEEK
Paclitaxel (P) 175 mg/m²

Carboplatin AUC 6

BEVACIZUMAB 15 mg/kg (optional)

DOSE DENSE WEEKLY
Paclitaxel (ddwP) 80 mg/m²

Carboplatin AUC 6

BEVACIZUMAB 15 mg/kg (optional)

Chan et al ESGO 2013
**Comparison of Hazard Ratio**

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Events</th>
<th>Total</th>
<th>Median (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1: Crb+Tax 1wk</td>
<td>207</td>
<td>346</td>
<td>14.8</td>
</tr>
<tr>
<td>2: Crb+Tax 3wk</td>
<td>216</td>
<td>346</td>
<td>14.3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT-1wk/CT-3wk</td>
<td>0.97</td>
<td>0.79 – 1.18</td>
</tr>
</tbody>
</table>

Includes 13% with neoadjuvant chemotherapy

Chan et al ESGO 2013
GOG 262: subgroup analyses

**With Bevacizumab**
- Rel Haz: 1.058
- Var(ln(HR)): 0.013

**Without Bevacizumab**
- Rel Haz: 0.595
- Var(ln(HR)): 0.023

**Treatment hazard ratio**

- 1.0
- 1.5
- 0.67
- 2.0
- 0.5
- 3.0
- 0.33
- 0.5
- 0.67
- 1.0
- 1.5
- 2.0
- 3.0

**Stratum**
- no Bev
- Crb+Tax 1wk
- Crb+Tax 3wk

**Median PFS (Mos)**
- 14.2
- 10.3

**Chan et al ESGO 2013**
MITO-7 Dose-dense paclitaxel

Control arm
- Carboplatin AUC 6, d1 q21
- Paclitaxel 175 mg/m², d1 q21
- Treatment repeated for 6 cycles

Experimental arm
- Carboplatin AUC 2, d1, 8, 15 q21
- Paclitaxel 60 mg/m², d1, 8, 15 q21
- Treatment repeated for 6 cycles

810 patients

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Pignata et al Lancet Oncol 2014
**NB.** Patients with Stage III & residual disease after surgery or who are planned to receive neoadjuvant chemotherapy OR any patients with stage IV disease are still eligible for ICON8A as well as B so that they may still enter the trial if:

- they have contra-indications to or decline bevacizumab
- their site does not have access to bev, e.g. in Australia
Conclusions for first-line therapy

• Neoadjuvant chemotherapy an acceptable alternative if complete resection of tumour is not possible
  • *Does it replace less good surgery, or is it equivalent only in advanced/inoperable disease?*

• Carboplatin/paclitaxel remains the standard of care

• Addition of bevacizumab an option
  • *Should it be given to all patients with advanced disease or only those in a poor prognostic group?*

• Weekly paclitaxel may be better, or at least as good
  • *Is there an interaction with bevacizumab?*
Recurrent Ovarian Cancer and ‘platinum-sensitivity’

Patterns of Relapse:
‘Platinum-sensitive’ and ‘Platinum-resistant’ ovarian cancer

Friedlander et al. Int J Gyn Cancer 2011
Does surgical cytoreduction improve survival of patients with ‘platinum-sensitive’ recurrence?

**AGO-OVAR DESKTOP III (Protocol AGO - OVAR OP.4- GCIG study)**

- Surgery - Randomisation
- Platinum-based chemotherapy

**GOG 213**

- Surgery - Randomisation
- Carboplatin/paclitaxel +/- bevacizumab

+ve AGO score
- ECOG PS = 0
- Complete initial debulking
- <500ml ascites
Chemotherapy for ‘platinum-sensitive’ relapse

• **Timing of treatment**
  
  • OV05/EORTC 55959 showed no survival benefit in offering second-line therapy on the basis of a raised CA125
  
  • Delay chemotherapy until clinical symptoms/ or significant radiological progression

• **Single agent platinum versus combination therapy?**
  
  • PFS increased; meta-analysis shows a survival benefit*

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Combination of Carboplatin/Paclitaxel (ICON4), Carboplatin/Gemcitabine (OVAR2.5), Carboplatin/PLD (CALYPSO) are all acceptable combination partners

Choice depends on:

- Balance of toxicities
- Timing from first-line therapy

Potential use of drugs for ‘platinum-resistant’ (non-platinum) therapy

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* Raja et al Annals Oncol 2014
Meta-analysis of platinum combination therapies

Raja et al Ann Oncol 2013
Addition of anti-angiogenic therapy for the treatment of relapsed ovarian cancer - ‘platinum sensitive’ group


# Anti-angiogenic agents in ‘platinum-sensitive’ relapsed ovarian cancer

<table>
<thead>
<tr>
<th></th>
<th>Platinum Sensitive</th>
<th>Platinum-resistant (&lt; 6 month PFI) and Partially Platinum-sensitive equally divided</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OCEANS (n= 484)</td>
<td>GOG213 (n=674)ICON6 N= 456</td>
</tr>
<tr>
<td>Drug</td>
<td>Carboplatin/gemcitabine ± bevacizumab</td>
<td>Carboplatin/paclitaxel ± bevacizumab</td>
</tr>
<tr>
<td>PFS (med. months)</td>
<td>8.4 v 12.4</td>
<td>10.4 v 13.8</td>
</tr>
<tr>
<td>HR</td>
<td>0.484 (p&lt;0.0001)</td>
<td>0.61 (p&lt;0.0001)</td>
</tr>
</tbody>
</table>

Pazopanib and Cediranib: Oral VEGF receptor tyrosine kinase inhibitors
Trebananib (AMG386): Peptibody inhibiting angiopoietin 2

* Non maintenance therapy

Which to chose and when?

(OCEANS) Aghajanian et al JCO 2011; (GOG 213) Coleman et al SGO 2015; (ICON6) Ledermann et al ECC (2013);
(TRINOVA-1) Monk et al Lancet Oncol 2014; (AURELIA) Pujade-Lauraine et al JCO 2014;
(MITO11) Pignata et al Lancet Oncol 2015
PARP Inhibitors and homologous recombination repair of DNA

- PARP is a key regulator of DNA damage repair processes
- Involved in DNA base-excision repair (BER)
- Binds directly to DNA damage
- Produces large branched chains of poly(ADP-ribose)
- Attracts and assists BER repair effectors
Olaparib maintenance in relapsed ovarian cancer - ‘STUDY 19’

• Assess the efficacy of olaparib as a maintenance treatment in patients with platinum-sensitive, high-grade serous ovarian cancer

• Randomised, double-blind, placebo-controlled Phase II trial

**Patient eligibility:**

• Platinum-sensitive, high-grade serous ovarian cancer
• ≥2 previous platinum regimens
• **Last chemotherapy: platinum based with a maintained response**
• Stable CA-125 at trial entry
• Randomisation stratification factors:
  – Time to disease progression on penultimate platinum therapy
  – Objective response to last platinum therapy
  – Ethnic descent

ClinicalTrials.gov identifier: NCT00753545

265 patients were randomized between September 2008 and February 2010

82 sites in 16 countries

Olaparib 400 mg po bid
Randomised 1:1
Placebo po bid

Treatment until disease progression
Primary Endpoint PFS
STUDY 19: Maintenance olaparib in ‘platinum-sensitive’ BRCA\textsuperscript{mut} high grade serous ovarian cancer

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

NC, not calculable.

Study 19: interim survival in BRCAm population (52% maturity)

- **BRCAm (n=136)**
  - **Deaths/total patients (%)**
    - Olaparib: 37/74 (50%)
    - Placebo: 34/62 (55%)
  - **Median OS, months (95% CI)**
    - Olaparib: 34.9 (29.2, NC)
    - Placebo: 31.9 (23.1, 40.7)
  - **HR=0.73**
    - 95% CI: 0.45, 1.17
    - P=0.19

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Safety Profile in STUDY 19 (BRCAm)
Profile consistent with overall population

<table>
<thead>
<tr>
<th></th>
<th>All grades</th>
<th>Grade ≥ 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Olaparib (N=74)</td>
<td>Placebo (N=62)</td>
</tr>
<tr>
<td>Nausea</td>
<td>54 (73%)</td>
<td>20 (32%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>40 (54%)</td>
<td>23 (37%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>27 (36%)</td>
<td>5 (8%)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>22 (30%)</td>
<td>12 (19%)</td>
</tr>
<tr>
<td>Anaemia</td>
<td>19 (26%)</td>
<td>3 (5%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Any serious AE</th>
<th>AEs leading to dose reductions</th>
<th>Any AE leading to discontinuation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olaparib (N=74)</td>
<td>25 (18.4%)</td>
<td>34 (25%)</td>
<td>6 (4.4%)</td>
</tr>
<tr>
<td>Placebo (N=62)</td>
<td>11 (8.6%)</td>
<td>6 (4.7%)</td>
<td>2 (1.6%)</td>
</tr>
<tr>
<td>Olaparib (N=74)</td>
<td>16 (21.6%)</td>
<td>19 (25.7%)</td>
<td>5 (6.8%)</td>
</tr>
<tr>
<td>Placebo (N=62)</td>
<td>6 (9.7%)</td>
<td>2 (3.2%)</td>
<td>0</td>
</tr>
</tbody>
</table>

STUDY 19 (BRCAm): 25% treated for ≥2 years

- Olaparib (N=53)
  - Median duration (months) 11.1
- Placebo (N=43)
  - Median duration (months) 4.4

Data cut off: 26 November 2012
AstraZeneca data on file
BRCA mutations and HRD – predictive markers for sensitivity to PARP inhibitors - Implications for clinical practice

- Germline BRCA1/2 mutations
  - occur in approx. 1 in 400 women (higher in some ethnic groups eg Ashkenazi Jewish population 1 in 40)
  - approx. 17% high-grade tumours; 6-8% tumours have somatic BRCA mutations
  - Most commonly in HGSOC - less common in endometrioid or clear cell
  - family history of cancer absent in 30% of BRCA ovarian cancer
  - 25% cases of BRCA ovarian cancer diagnosed over 60 years old

- Testing for BRCA mutations now needs to be part of routine care of patients with high grade ovarian cancer

BRCA-related ovarian cancer
- often responds to multiple rounds of platinum-based therapy
- Survive longer than non-carriers

‘Platinum-sensitive’ disease- summary

• Role of surgery at relapse remains unproven. Results of trials awaited

• Symptoms, interpretation of imaging and CA125 should guide decisions about re-starting chemotherapy

• Platinum combinations generally recommended

• Choice of platinum partner depends on prior therapy, toxicity profile, patient choice and future treatment plans

• Knowledge of BRCA mutation status prior to starting 2nd line therapy helps to inform choice between PARP inhibitor or bevacizumab
Challenges in multiply pretreated and ‘platinum-resistant’ ovarian cancer

• **Platinum-resistance covers a wide range of biology**
  • Persistent disease: little or no response to first-line therapy
  • Good partial or complete response and early relapse
  • Previous multiple lines of treatment

• **Clinical Picture variable**
  • Asymptomatic disease
  • Disease likely to cause organ dysfunction
  • Symptomatic progression or relapse

• **Response rate to chemotherapy generally low**
• **Duration of response short (typically median PFS 3-4 months)**
• **Median survival in clinical trials around 12 months**
Response and outcome to several lines of therapy

1620 patients from 3 randomised trials

PFS
24.5% were re-challenged with platinum at 1\textsuperscript{st} and 2\textsuperscript{nd} relapse

Prognostic factors

- PFS: Optimal primary cytoreduction and platinum sensitivity: independent prognostic factors for survival up to 3\textsuperscript{rd} relapse
- OS: FIGO stage

Hanker et al Ann Oncol 2012
Value of treatment of multiply relapsed ovarian cancer

Is there value in using platinum in women with ‘platinum-resistant’ disease?

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Author</th>
<th>Response Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weekly cisplatin/etoposide</td>
<td>van der Burg et al (2002)</td>
<td>46%</td>
</tr>
<tr>
<td>Cisplatin/Gemcitabine</td>
<td>Rose et al (2003)</td>
<td>43%</td>
</tr>
<tr>
<td>PLD</td>
<td>Various (6 phase II trials) Green and Rose (2006)</td>
<td>7.7-25%</td>
</tr>
</tbody>
</table>
Randomised phase II trial: of weekly paclitaxel alone, in combination with carboplatin or in combination with topotecan

<table>
<thead>
<tr>
<th></th>
<th>wP</th>
<th>wP + C</th>
<th>wP + wT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response rate, n (%)</td>
<td>20 (35)</td>
<td>19 (37)</td>
<td>22 (39)</td>
</tr>
<tr>
<td>Complete response</td>
<td>3 (5)</td>
<td>7 (14)</td>
<td>6 (10)</td>
</tr>
<tr>
<td>Partial response</td>
<td>17 (30)</td>
<td>12 (24)</td>
<td>16 (28)</td>
</tr>
<tr>
<td>Stable disease, %</td>
<td>23</td>
<td>29</td>
<td>23</td>
</tr>
<tr>
<td>Progression, %</td>
<td>26</td>
<td>26</td>
<td>25</td>
</tr>
<tr>
<td>Nonevaluable, %</td>
<td>16</td>
<td>8</td>
<td>14</td>
</tr>
</tbody>
</table>

Progression

<table>
<thead>
<tr>
<th>Group</th>
<th>Median (months)</th>
<th>CI 95% (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>wP</td>
<td>3.7</td>
<td>3.1 – 4.3</td>
</tr>
<tr>
<td>wP + C</td>
<td>4.8</td>
<td>3.3 – 6.3</td>
</tr>
<tr>
<td>wP + wT</td>
<td>5.4</td>
<td>4.2 – 6.5</td>
</tr>
</tbody>
</table>

HR 0.922 (95% CI, 0.765-1.111)  
\( P = .46 \)
Bevacizumab in ‘platinum-resistant’ ovarian cancer

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>GOG-170D¹ (n=62)</th>
<th>AVF2949g² (n=44)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS months</td>
<td>4.7</td>
<td>4.4</td>
</tr>
<tr>
<td>6-month PFS rate, %</td>
<td>40.3</td>
<td>27.8</td>
</tr>
<tr>
<td>ORR, %</td>
<td>21</td>
<td>16</td>
</tr>
<tr>
<td>Median OS, months</td>
<td>16.9</td>
<td>10.7</td>
</tr>
</tbody>
</table>

- 41.9% of patients in GOG-170D had platinum-resistant disease,
- 83.7% of patients in AVF2949g were primarily platinum-resistant


Chemotherapy options (investigator’s choice):
- Paclitaxel 80 mg/m² days 1, 8, 15, & 22 q4w
- Topotecan 4 mg/m² days 1, 8, & 15 q4w (or 1.25 mg/m², days 1–5 q3w)
- PLD 40 mg/m² day 1 q4w

Pujade-Lauraine et al ASCO 2012
AURELIA: bevacizumab in ‘platinum-resistant’ ovarian cancer (all chemotherapy regimens)

**PFS**
- Events, n (%): CT 166 (91%), BEV + CT 135 (75%)
- Median PFS, months: CT 3.4, BEV + CT 6.7
- HR (unstratified): 0.48
- 95% CI: 0.38 to 0.60
- Log-rank P value (2-sided, unstratified): <.001

**OS**
- Events, n (%): CT 136 (75%), BEV + CT 128 (72%)
- Median OS, months: CT 13.3, BEV + CT 16.6
- HR (unstratified): 0.85
- 95% CI: 0.66 to 1.08
- Log-rank P value (2-sided, unstratified): <.174

Pujade-Lauraine et al J Clin Oncol 2014
AURELIA Trial: Bevacizumab Added to chemotherapy in ‘platinum-resistant’ disease

Summary of best overall response rates (RECIST, CA-125 criteria or both)

Overall population
Weekly paclitaxel cohort
PLD cohort
Topotecan cohort

CT
BEV + CT

18.3a
[9.6–27.0]
p<0.001

22.9a
[3.9–41.8]

30.9

28.8

10.4a
[-2.4 to 23.2]

19.5a
[6.7–32.3]

12.6

12.6

7.9

3.3

7.9

3.3

18.3

10.4

19.5

Poveda et al ESMO 2012

aDifference in overall response rate; 95% CI with Hauck–Anderson continuity correction
AURELIA Grade ≥3 adverse events (additional to BEV events of interest)

HFS = hand-foot syndrome

*Preferred terms. *Includes abdominal pain upper
Aurelia Trial: Health-related QoL

Primary PRO hypothesis (Abdominal/ Gastrointestinal symptoms): Subgroup analysis week 8/9

Stockler et al ASCO 2013
Conclusions

• Bevacizumab has been shown to add value to chemotherapy in platinum-resistant disease but
  • Questions about value in > 2\textsuperscript{nd} line therapy, maintenance beyond chemotherapy and effect of previous first-line bevacizumab remain

• Drug resistance in ‘platinum-resistant’ disease/multiply pre-treated a major obstacle

• Integration of oncology and palliative care important with emphasis on management of symptoms and QoL