How I Treat Advanced Ovarian Cancer in 2014: Treatment Algorithm

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Unmet Needs in Ovarian Cancer

- Still the biggest killer among gynecologic malignancies
- Despite high response rate, majority of patients will relapse
- PFS mostly unchanged over the past 20 years
- Multiple chemotherapy lines allows prolongation of survival without decreasing mortality
- Precision medicine far behind compared to other malignancies
Ovarian Cancer: A Unique Disease Pattern

Primary Treatment
Stage III, IV

Surgery
Primary Chemotherapy

1st Clinical Remission

Relapse (80%)

Platinum Sensitive

Platinum Resistant

Second Clinical Remission

Relapse (100%)
Ovarian Cancer: First-Line Treatment Algorithm

Primary cytoreductive surgery

Carboplatin + paclitaxel three-weekly

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Ovarian Cancer: First-Line Treatment Algorithm

Primary cytoreductive surgery

Carboplatin + paclitaxel three-weekly
Neoadjuvant Chemotherapy or Primary Surgery in Stage IIIC or IV Ovarian Cancer

Chemotherapy or Upfront Surgery for Newly Diagnosed Advanced Ovarian Cancer
Results from the MRC CHORUS trial

Randomized
N = 552

PS
N = 276

Primary surgery
N = 248

NCT
N = 274

Neoadjuvant chemo
N = 252

Surgery
N = 214

Post-op chemo
N = 209

Post-op chemo
N = 199

Progression Free Survival
intention-to-treat population

Moreover, 5 hours to 6 hours in the operating room resulting in an optimal cytoreduction may provide the patient with a median survival of 50 months to 100 months (as reported in the literature with successful surgery), whereas interval cytoreductive surgery lasting 2 hours to 3 hours after NACT is consistently associated with a median survival of only 30 months to 36 months, even after complete gross resection is attained in this setting.

A3: Is the 2004 GCIG recommended standard comparator arm still valid?¹

• The standard arm must contain a taxane and a platinum agent administered for 6 cycles

• The recommended regimen is paclitaxel (175 mg/m²) and carboplatin (AUC 5-6) intravenously q3w
Ovarian Cancer:
First-Line Treatment Algorithm

Primary cytoreductive surgery

- Carboplatin + paclitaxel three-weekly

IP therapy?

Neoadjuvant chemotherapy?
GOG172: Ovarian (Optimal III)

![Survival Analysis Graph]

<table>
<thead>
<tr>
<th>Months of Study</th>
<th>Proportion Surviving</th>
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<tbody>
<tr>
<td>0</td>
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<tr>
<td>6</td>
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<td>12</td>
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<td>60</td>
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</table>

**Intraperitoneal therapy**

**Intravenous therapy**

**P = 0.03**

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Intravenous therapy</th>
<th>Intraperitoneal therapy</th>
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<tr>
<td>210</td>
<td>183</td>
<td>205</td>
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<td>106</td>
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<tr>
<td>63</td>
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</tbody>
</table>


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GOG172: Ovarian (Optimal III)

42% completed treatment
8% never started
34% received only one or two cycles

NOT feasible in the majority of patients

Primary cytoreductive surgery

Neoadjuvant chemotherapy?

Carboplatin + paclitaxel three-weekly

IP therapy?

Dose dense?
First-Line Dose-Dense in Ovarian Cancer
JGOG-3016


Median PFS
28.2 months vs 17.5 months
(HR 0.76, 95% CI 0.62-0.91; \( P = .0037 \)).

Median OS was
100.5 months vs 62.2 months
(HR 0.79, 95% CI 0.63-0.99; \( P = .039 \)).
Median PFS 18.8 months vs 16.5 months  
Log-rank test  $P = .18$  
Unadjusted HR: 0.88 (0.72-1.06)  

Median OS NA vs 47.9 months  
Log-rank test  $P = .24$  
Unadjusted HR: 1.20 (0.88-1.63)
Upfront Ovarian Cancer Treatment—Modifying Dose Regimen
GOG 262 PFS by Randomized Treatment (n = 692)

Upfront Ovarian Cancer Treatment—Modifying Dose Regimen
GOG 262 OS by Randomized Treatment (n = 692)

Upfront Ovarian Cancer Treatment—Modifying Dose Regimen
GOG 262 PFS by Randomized Treatment ddT vs q3wkT
Stratified by Those Not Choosing Bevacizumab (n = 112)

Ovarian Cancer: First-Line Treatment Algorithm

Primary cytoreductive surgery

Carboplatin + paclitaxel three-weekly

I.P. therapy?
- + Antiangiogenic drug

Neoadjuvant chemotherapy?

Dose dense?
- + Antiangiogenic drug
First Line

1\textsuperscript{st} line
Concomitant + Maintenance

GOG 218
ICON7

Bevacizumab

1\textsuperscript{st} line
Maintenance

OVAR 16

Pazopanib

OVAR12

Nintedanib

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How to Select Patients for Front-Line Bevacizumab?
Subgroup Efficacy

Modified ICON7 high-risk PFS 2013 update

- Stage III suboptimally debulked, any stage IV or no debulking surgery
- Non-proportionality Gramsch-Therneau test: p<0.0001
- Events, n (%): Control 228 (90), Research 223 (90)
- Median, months: Control 10.5, Research 16.0, Δ +3.5

Modified ICON7 high-risk final OS

- Stage III suboptimally debulked, any stage IV or no debulking surgery
- Non-proportionality Gramsch-Therneau test: p=0.0072
- Deaths, n (%): Control 174 (69), Research 156 (64)
- Median, months: Control 30.3, Research 39.7, Δ +9.4


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Subgroup Efficacy

Modified ICON7 high-risk PFS 2013 update


All exploratory analyses!!!
GOG 218: PFS Summary of All Biomarkers

No predictive biomarkers

*Low and high defined by median cutoff.

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Who May Benefit From Bevacizumab?
ICON7: Predictive Effects of Different Ang1 and Tie2

Edinburgh Dataset; Unsupervised Hierarchical Clustering


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Immune Subgroup Patients Have Inferior PFS When Treated With Bevacizumab

Immune Subgroup: 41% of ICON7 TR patients

Non-Immune (Proangiogenic) Subgroup: 59% of ICON7 TR patients

Test for Interaction, \( P = .015 \)

<table>
<thead>
<tr>
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<th>Immune Subgroup</th>
<th>Proangiogenic Subgroup</th>
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<tbody>
<tr>
<td>Non-proportionality test</td>
<td>( P = .048 )</td>
<td>( P = .003 )</td>
</tr>
<tr>
<td>Restricted mean PFS in months (SE)</td>
<td>C/P 29.7 (2.2)</td>
<td>C/P 18.3 (1.5)</td>
</tr>
<tr>
<td></td>
<td>C/P/Bev 23.8 (1.8)</td>
<td>C/P/Bev 19.3 (1.3)</td>
</tr>
<tr>
<td>Diff in restricted mean PFS (95% CI)</td>
<td>-5.9 (-11.5 to -0.3)</td>
<td>1.0 (-2.9 to 4.9)</td>
</tr>
<tr>
<td>Median PFS in months</td>
<td>C/P 35.8</td>
<td>C/P 12.3</td>
</tr>
<tr>
<td></td>
<td>C/P/Bev 18.5</td>
<td>C/P/Bev 17.4</td>
</tr>
</tbody>
</table>

Cl, confidence interval; SE, standard error


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Conclusion
Abstract 5502

• Identification of a gene signature for high grade serous cancer associated with better prognosis, validated in 2 datasets

• The immune signature identifies patients whose outcome appears to be adversely affected by the addition of bevacizumab

• There is a trend for better outcome with the addition of bevacizumab outside this group

• These data suggest a mechanism for stratification of bevacizumab therapy and should be validated in additional datasets

• Identification of a gene signature for high grade serous cancer associated with better prognosis, validated in 2 datasets

In which of these groups will tumors with BRCA mutation fit? If they belong to the immunogenic group, does this mean they can be less sensitive to bevacizumab?

These data suggest a mechanism for stratification of bevacizumab therapy and should be validated in additional datasets.
Generally-Accepted Guideline for Chemotherapy at Recurrence

- **Platinum resistant**
  - <6 Months
  - Nonplatinum single-agent: PLD, topotecan, W paclitaxel, gemcitabine

- **Partially platinum-sensitive**
  - 6-12 Months
  - Carboplatin combination (PLD, gemcitabine or paclitaxel) nonplatinum (PLD+/- trabectedin)

- **Fully platinum-sensitive**
  - >12 Months
  - Carboplatin combination (PLD, gemcitabine or paclitaxel)

PLD, pegylated liposomal doxorubicin

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Relapse

Resistant (<6 mos)  Sensitive (6-12 mos)  Sensitive (>12 mos)

AURELIA  bevacizumab

OCEANS  bevacizumab

ICON6  cediranib

TRINOVA-1  trebananib

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Beyond Angiogenesis
Cytoreductive surgery followed by carboplatin/paclitaxel chemotherapy q3 weekly is the mainstay of initial treatment of ovarian cancer.

Neoadjuvant chemotherapy followed by interval debulking surgery may be considered in selected patients with stage III/IV bulky disease.

Intraperitoneal delivery and dose-dense regimens represent alternative schedules of administration of paclitaxel and platinum chemotherapy.

Antiangiogenic therapy is active in ovarian cancer and bevacizumab is currently the only approved antiangiogenic therapy and may be considered in first-line, recurrent or resistant disease.

There is a lack of specific biomarker to predict who may benefit from antiangiogenic therapy.

The precise role of other targeted agents has to be defined.
Next Steps in Optimizing Targeted Therapy of Ovarian Cancer: Exploring the Impact of BRCA Status