Targeted therapies

Ovarian cancer

A- Situations in which bevacizumab is not recommended (absence of prospective data).

- **FIGO stages I to IIIA** inclusive (no marketing authorisation in this indication).
- **In combination with neoadjuvant chemotherapy** before cytoreductive surgery.
- **In combination with intra-peritoneal chemotherapy.**
B- Situations in which bevacizumab is recommended.

- **Macroscopic residual disease** after initial cytoreductive surgery for FIGO stages IIIB to IV.

- **Stage IIIC-IV disease in which complete cytoreduction is definitively not possible.**
  - The absolutely non-resectable nature of the lesions must be assessed in the MSM with an experienced surgical team.

Grade A
C- Situations in which the indication for bevacizumab must be **assessed in the MSM and discussed with the patient according to the risk/benefit ratio**

Grade B

- Stages IIIB or IIIC with macroscopically complete cytoreduction during initial surgery.

- After interval debulking surgery following 3 or 4 courses of neoadjuvant chemotherapy.

*in particular, taking into account any nephro-cardiovascular history and gastrointestinal anastomosis during initial surgery or any risk of fistulas.*
When to start bevacizumab?

- Bevacizumab should be introduced during the 1\textsuperscript{st} cycle of postoperative chemotherapy if started not less than 28 days after surgery.

- If not, or if the patient has a gastrointestinal anastomosis or unresolved post-operative complications, bevacizumab should be started at the 2\textsuperscript{nd} cycle.
Bevacizumab as initial treatment

- **With what kind of chemotherapy?**
  - Carboplatin-paclitaxel IV every 3 weeks.
  - Option: Weekly regimen of paclitaxel combined with carboplatin (every 3 weeks)

- **For how long?**
  - Total duration of beva: 15 months, total of 22 courses.

- **What dose?**
  - The dosage of marketing authorization is 15 mg/kg every 3 weeks.
  - Option: 7.5 mg/kg every 3 weeks.
Bevacizumab as initial treatment

- Blood pressure monitoring
  - Before treatment
  - Once a week for the first month
  - During the week preceding treatment thereafter
  - By the GP: normal < 140/90
  - Or self-measurement (3 consecutive measurements in a seating position, for 3 days, during a period of normal activity): normal < 135/85

### What to do if the patient presents with proteinuria?

- Dip stick test for urinary protein before each injection.
- If dip stick $\geq$ ++ : urinary protein checked in a 24 hour urine collection before the next cycle.

<table>
<thead>
<tr>
<th>Proteinuria</th>
<th>Approach to be taken</th>
</tr>
</thead>
</table>
| If urinary protein is $< 1$ g/24h | - Antiangiogenic treatment to be pursued.  
- Dipstick test on monthly basis or before each course. |
| If urinary protein is between 1 and 3 g/24 h | - Treatment pursued and nephrological advice sought rapidly.  
- Monthly quantitative measurement of urinary protein.  
- Start treatment with ACE or AA2 for anti-proteinuria purposes.  
- Optimisation of anti-hypertensive treatment for target BP $< 130/80$. |
| If urinary protein is $>3$ g/24 h | - The antiangiogenic treatment may be pursued if the patient does not have hypertension or renal failure, but this treatment must be discussed with the nephrologist.  
- If the urinary protein levels remain stable and without severe nephrotic syndrome, the antiangiogenic treatment may be pursued if the patient is a responder. |

Indications for recurrence?

- No MA has been granted for this indication.
- The indication for bevacizumab must be assessed in the MSM and discussed with the patient.
- Bevacizumab must not be administered to patients with partial ileus or lesions involving hollow organs.
- The risks related to bevacizumab increase with the number of previous lines of chemotherapy.
Bevacizumab treatment of relapse

What protocols?

- **Platinum-sensitive recurrence** (free interval ≥ 6 ms)
  - Bevacizumab in combination with a platinum-based chemotherapy (especially carbo-gemcitabine).

- **Platinum-resistant recurrence** (free interval < 6 ms)
  - Bevacizumab administered alone.
  - In combination with single-agent chemotherapy (especially weekly paclitaxel and oral cyclophosphamide).
Other targeted therapies

- **No recommendations in the absence of data**
  - Other antiangiogenic agents
  - Trastuzumab (Herceptin™)
  - EGF-R inhibitors

- **Hormone therapy**
  - Marginal effect. May be used for recurrence.
    - No proof to support selection of patients based on well differentiated grade or presence of hormonal receptors

- **Catumaxomab (Removab™)**
  - Has MA for intraperitoneal treatment in the event of refractory ascites.
Ovarian cancer

Additional slides
GOG-218
Progression Free Survival

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median PFS (months)</th>
<th>HR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>CP + placebo</td>
<td>10.6</td>
<td>0.70 (0.61–0.81)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Beva 15 placebo</td>
<td>14.7</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Total population

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median PFS (months)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CP (n=764)</td>
<td>17.4</td>
<td>0.87 (0.77–0.99)</td>
</tr>
<tr>
<td>CP + BEVA 7.5 (n=761)</td>
<td>19.8</td>
<td>0.04</td>
</tr>
</tbody>
</table>

### FIGO III (residual disease > 1cm) & FIGO IV

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median PFS (months)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CP (n=234)</td>
<td>10.5</td>
<td>0.68 (0.55–0.85)</td>
</tr>
<tr>
<td>CP + BEVA 7.5 (n=231)</td>
<td>15.9</td>
<td>&lt;0.001</td>
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</tbody>
</table>

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### Overall Survival

#### Total population

<table>
<thead>
<tr>
<th></th>
<th>CP (n=764)</th>
<th>CP + BEVA 7.5 BEVA 7.5 (n=761)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median OS (months)</strong></td>
<td>Not reached</td>
<td></td>
</tr>
<tr>
<td><strong>HR (95% CI)</strong></td>
<td>0.85 (0.70–1.04)</td>
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</tr>
<tr>
<td><strong>p</strong></td>
<td>0.1167</td>
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</tr>
</tbody>
</table>

#### FIGO III (residual disease > 1cm) & FIGO IV

<table>
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<tr>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Median OS (months)</strong></td>
<td>28.8</td>
<td>36.6</td>
</tr>
<tr>
<td><strong>HR (95% CI)</strong></td>
<td>0.64 (0.48–0.85)</td>
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</tr>
<tr>
<td><strong>p</strong></td>
<td>0.002</td>
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There is no clinical (e.g. age), biological or histological criteria allowing to identify a population of patients who would differently benefit from bevacizumab.
Managing Hypertension

- Initiating antiangiogenic treatment for patients with uncontrolled HT is not recommended.
- De novo HT: ACE inhibitors or angiotensin 2 antagonists.
- Destabilisation of known HT: low dose calcium channel blockers from the dihydropyridine family.