Assessment of The Prognostic Value Of The CA-125 Modeled Kinetic Parameter KELIM in GOG-0262 and MITO-7 trials.

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Background

- Need for early predictors of treatment efficacy in ovarian cancer patients treated by chemotherapy +/- targeted agents

- CA-125 based Rustin criteria is commonly used to predict treatment efficacy during phase II trials
  
  \[ \text{J Clin Oncol 1996; 14:1545–1551} \]

  - the actual value was recently questioned!
  
  \[ \text{JNCI 2011; 103: 1338–1342} \]

- Mathematical modeling of longitudinal CA-125 kinetic may help analyze individual CA-125 decline profiles

- The CA-125 elimination modeled parameter KELIM was a significant independent prognostic factor of treatment efficacy in CALYPSO trial (recurrent ovarian cancer patients)
  
  \[ \text{Gynecol Oncol. 2013 Aug;130(2):289-94} \]

=> Validation of KELIM prognostic factor regarding PFS in independent phase III trial cohorts of patients treated with different first line regimens was warranted
Recent data from phase III trials ...

Data from 3 independent phase III trials

AGO-OVAR 9
Carboplatin - Paclitaxel +/- Gemcitabine
N = 1742

AGO-OVAR 7
Carboplatin - Paclitaxel +/- Topotecan maintenance
N = 1308

ICON-7
Carboplatin - paclitaxel +/- bevacizumab
N = 1528

1) Training Step to Adjust Model Parameters And Define Prognostic KELIM Cut-off

AGO-OVAR 9
- Model parameters were adjusted to 1st line treatment patients => estimation of parameters
- CA125 kinetics were properly described during the first 100 days by the model
  - Median KELIM = 0.059
  - PFS = 24.0 months (if KELIM > median) vs 11.3 months (if KELIM < median), P < 0.001
  - OS = 62.5 vs 37.0 months, P < 0.001
- Multivariate analysis against FIGO stage and baseline CA125 & treatment arm:
  HR = 0.55 (95% CI: 0.47-0.64) for KELIM

2) Validation Step to Assess KELIM, Prognostic Value Regarding PFS & OS

AGO-OVAR 7
- PFS = 28.3 months (if KELIM > median 0.059) vs 11.3 months (if KELIM < median 0.059), P < 0.001
- OS = 64.2 months vs 39.2 months, P < 0.001
- Multivariate analysis against FIGO stage and baseline CA125 & treatment arm:
  HR = 0.53 (95% CI: 0.35-0.86) for KELIM

ICON-7
- PFS = 37.5 months (if KELIM > median 0.059) vs 14.7 months (if KELIM < median 0.059), P < 0.001
- OS = 65.0 months vs 38.2 months, P < 0.001
- Multivariate analysis against FIGO stage, baseline CA125, histology, grade, surgery residuals & treatment arm:
  HR = 0.49 (95% CI: 0.41-0.56) for KELIM
## KELIM Prognostic Value is Independent on Chemotherapy Regimens

<table>
<thead>
<tr>
<th>Treatment</th>
<th>PFS (months)</th>
<th>OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Favorable KELIM &gt; 0.059</td>
<td>Unfavorable KELIM &lt;= 0.059</td>
</tr>
<tr>
<td>AGO/OVAR9</td>
<td>CP</td>
<td>25.6</td>
</tr>
<tr>
<td></td>
<td>CP + Gemcitabine</td>
<td>21.9</td>
</tr>
<tr>
<td>AGO/OVAR7</td>
<td>CP</td>
<td>28.3</td>
</tr>
<tr>
<td></td>
<td>CP + Topotecan</td>
<td>19.5</td>
</tr>
<tr>
<td>ICON7</td>
<td>CP</td>
<td>25.2</td>
</tr>
<tr>
<td></td>
<td>CP + Bevacizumab</td>
<td>20.7</td>
</tr>
</tbody>
</table>

NR: not reached
Hypotheses

• KELIM, estimated in the first 100 days during first line chemotherapy
  ➥ Discriminates 2 prognostic populations of ovarian cancer patients whatever received treatments
  *Median survival of 35 months vs > 60 months*

• Marker of chemo-resistance?

• What would be the impact of administration schedules on KELIM?

• Role for dose-dense chemo in unfavorable KELIM patients?
Proposal

- **MITO-7 trial:**
  Carboplatin AUC6 + paclitaxel 175 mg/m² Q3W vs carboplatin AUC2 + paclitaxel 60 mg/m² Q1W

- **GOG-0262:**
  Carboplatin AUC6 + paclitaxel 175 mg/m² Q3W vs carboplatin AUC6 Q3W + paclitaxel 80 mg/m² Q1W

Impact of chemotherapy administration schedules and doses on KELIM?

Would dose-dense paclitaxel counterbalance unfavorable KELIM?