Immunotherapy in ovarian cáncer: Still promising?

Antonio Gonzalez Martin
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GEICO (Grupo Español de Investigación en Cáncer de Ovario)
ENGOT (European Network of Gynecological Oncological Trials groups)
Antibody Drug Conjugates

Checkpoint inhibitors

Anti-cancer vaccines

Galuzzi et al. Oncotargets 2014
Mirvetuximab Soravtansine (IMGN853)

High affinity, humanized FRα binding MAb

- stable in the circulation
- optimized to resist MDR, promote bystander cell killing

sulfo-SPDB Linker

DM4 payload
- maytansine derivative with anti-microtubule activity
- 100-1000-fold more potent than vinca alkaloids
- ~3.4 DM4/MAb
Mirvetuximab Soravtansine
Phase I data

46 Platinum-resistant patients
FRα positivity by IHC (≥ 25% of tumor cells)
6.0 mg/kg (AIBW)
ORR 26% (1CR/11PR)
Median PFS 4.8 months
Median DOR 19.1 weeks

FRα positivity by IHC ≥ 50%

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>All Pooled Pts  (n = 113)</th>
<th>FORWARD I eligible (n = 36)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (confirmed)</td>
<td>30%* (22, 39)</td>
<td>47%† (30, 65)</td>
</tr>
<tr>
<td>95% CI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PFS (months)</td>
<td>4.3 (3.9, 5.4)</td>
<td>6.7 (4.1, 8.3)</td>
</tr>
<tr>
<td>Median</td>
<td></td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DOR (weeks)</td>
<td>19.3 (18.0, 34.0)</td>
<td>25.1 (18.0, 42.0)</td>
</tr>
<tr>
<td>Median</td>
<td></td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td></td>
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</tr>
</tbody>
</table>

*3 complete responses (CR) and 31 partial responses (PR); †1 CR and 16 PR

FORWARD I: Design

Screening
- Patients with platinum-resistant ovarian cancer
- Medium/high* FRα expression; 1–3 prior therapies
- Randomization 2:1

Treatment phase
- Mirvetuximab soravtansine (6 mg/kg AIBW, Q3W)
- Investigator’s choice chemotherapy (paclitaxel, PLD, or topotecan)

Follow-up
- Safety; OS
Anetumab Ravidansine

Fully human anti-mesothelin IgG1 ADC linked to DM4

Phase Ib in Platinum-resistant OC

PLD 30 mg/m2 + Anetumab Rav q 3w
- Part 1 dose escalation 5.5 mg/kg
- Part 2 expansion 6.5 mg/kg (17 pts)

Anti-cancer vaccines
DCVAC Cellular Immunotherapy Platform

DCVAC manufacturing and treatment cycle

1. **Single leukapheresis** at qualified centers
2. **Monocytes** are enriched and grown *ex vivo* into **immature dendritic cells (DCs)**
3. **Tumor cell lines** (different for each indication) are prepared and killed by **immunogenic cell death**
4. **DC Maturation**: Immature DCs are pulsed with HHP-killed tumor cells
5. **Mature DCs** express on the surface antigens from selected tumor cells
6. ≥15 doses of DCVAC are produced and frozen
7. **Patient receives DCVAC** on an ongoing basis

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Kloudova et al., Oncotarget, 2016 Jul 19;7(29):46120-46126
Fucikova et al., J Transl Med., 2011 Dec 30;9:223
Urbanova et al., Immunology Letters, 2017, 187: 27–34
SOV01
Study Design in First-Line Setting

Epithelial cancer of the ovary, fallopian tube and peritoneum
- FIGO stage III
- Serous, endometrioid, or mucinous
- PS 0 - 2
- <1 cm max. residuum
- No prior systemic therapy

RANDOMIZATION 1:1:1
Stratification: 0 vs <1cm

TREATMENT ARM A
- Chemotherapy +
- Concomitant DCVAC/OvCa

TREATMENT ARM B
- Chemotherapy +
- Maintenance DCVAC/OvCa

TREATMENT ARM C
- Chemotherapy

ENDPOINTS
- PRIMARY: PFS at 2 years after randomization
- SECONDARY: OS, PFI_BIO CA-125, AEs

STUDY TREATMENTS
- 6 CYCLES: Carboplatin (AUC 5-7) + Paclitaxel (175mg/m²)
- 10 DOSES: DCVAC/OvCa (1 x 10⁷ DCs/dose)
PFS
- 6-month Benefit in mPFS and 57% Decrease in The Hazard of Progression in Arm B

Presented By Lukas Rob at 2018 ASCO Annual Meeting
A Trend Towards Improved OS in Arm B

**OS**

**MEDIAN FOLLOW-UP:** 26.8 months  
**MATURITY:** 14%

- **ARM A:** chemotherapy + concomitant DCVAC/OvCa
- **ARM B:** chemotherapy + maintenance DCVAC/OvCa
- **ARM C:** chemotherapy only

**Events**
- **mITT**
  - ARM A: 5
  - ARM B: 1
  - ARM C: 7
- **PP**
  - ARM A: 4
  - ARM B: 0
  - ARM C: 7

**Median (months)**
- **mITT**
  - ARM A: NE
  - ARM B: NE
  - ARM C: NE
- **PP**
  - ARM A: NE
  - ARM B: NE
  - ARM C: NE

**INDICATOR**
- **B vs. C**
  - **mITT**
    - HR: 0.13  
    - 95% CI: 0.02-1.08  
    - p-value: 0.03
  - **PP**
    - HR: 0  
    - 95% CI: 0-NE  
    - p-value: 0.01

**A vs. C**
- **mITT**
  - HR: 0.64  
  - 95% CI: 0.20-2.04  
  - p-value: 0.45
- **PP**
  - HR: 0.51  
  - 95% CI: 0.15-1.76  
  - p-value: 0.28
**SOV02: Concomitant DCVAC/OvCa with Chemo in Relapsed Platinum-Sensitive Ovarian Carcinoma**

Phase II, randomized, open-label, parallel group, multi-center clinical trial of DCVAC/OvCa added to standard chemotherapy in women with relapsed platinum-sensitive epithelial ovarian carcinoma

### Patients

- **N=71**
  - 1:1 randomization
  - Women with ovarian carcinoma who had complete remission after first-line platinum-based chemo, had confirmed relapse after >6 months of remission, and were selected to receive second-line chemo

### Regimen

**Group A:** DCVAC/OvCa + standard chemotherapy (carboplatin and gemcitabine)

**Group B:** Standard chemotherapy (carboplatin and gemcitabine)

### End Points

**Primary:** PFS 18 months after randomization

**Secondary/exploratory:** OS, ORR, biological PFI, immune response, AEs, changes in QoL (FACT-O)

### Table

<table>
<thead>
<tr>
<th>Year</th>
<th>Study Events</th>
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<tbody>
<tr>
<td>2012</td>
<td>First patient in</td>
</tr>
<tr>
<td>2013</td>
<td>Last patient in</td>
</tr>
<tr>
<td>2014</td>
<td>Primary analysis</td>
</tr>
<tr>
<td>2015</td>
<td>Final OS analysis performed in August 2018</td>
</tr>
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</table>

**Selected for oral presentation at the 2019 SGO**

**ENGOT lead pivotal phase III trial under discussion**
Immunomodulatory MoAb Check-point inhibitors
Check-point inhibitors monotherapy in ROC have limited activity that is poorly correlated with PD-L1 expression.

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab(^1)</th>
<th>Pembrolizumab(^2) Keynote-028</th>
<th>Avelumab(^3) Phase Ib</th>
<th>Atezolizumab(^4)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Population</strong></td>
<td>20</td>
<td>26</td>
<td>125</td>
<td>12</td>
</tr>
<tr>
<td>Plat-resistant</td>
<td>Plat-resistant</td>
<td>Phase Ib</td>
<td>PROC</td>
<td>Phase Ib</td>
</tr>
<tr>
<td>55% &gt; 4 lines</td>
<td>55% &gt; 4 lines</td>
<td>73% &gt; 3 lines</td>
<td>65% &gt; 3 lines</td>
<td>58% &gt; 6 lines</td>
</tr>
<tr>
<td><strong>ORR global</strong></td>
<td>15% (10%CR)</td>
<td>11.5% (4%CR)</td>
<td>9.6% (0.8% CR)</td>
<td>25% (2/8)</td>
</tr>
<tr>
<td><strong>Cut-off PD-L1</strong></td>
<td>IHC 2/3+ (80%)</td>
<td>&gt; 1% (100%)</td>
<td>≥ 1% (77%)</td>
<td>IHC 2/3+ (83%)</td>
</tr>
<tr>
<td><strong>ORR PD-L1-</strong></td>
<td>1/4 (25%)</td>
<td>-</td>
<td>7.9% (3/38)</td>
<td>-</td>
</tr>
<tr>
<td><strong>ORR PD-L1+</strong></td>
<td>2/16 (12.5%)</td>
<td>3/26 (11.5%)</td>
<td>11.8% (9/76)</td>
<td>-</td>
</tr>
</tbody>
</table>

## Keynote-100

**Pembrolizumab 200 mg Q3 weeks until PD**

### COHORT A
- **Patients:** 285
- **Lines:** 1-3 lines
- **TFI:** 3-12m
- **ORR:** 7.4%
- **DOR:** 8.2 mo
- **mPFS:** 2.1 mo
- **mOS:** NR

### COHORT B
- **Patients:** 91
- **Lines:** 4-6 lines
- **TFI:** >3m
- **ORR:** 9.9%
- **DOR:** NR
- **mPFS:** 2.1 mo
- **mOS:** 17.6 m

Matulonis et al. In press.
Long-term responders are observed

Hamanishi et al. J Clin Oncol 2015;

Varga et al. Gynecologic Oncology 2019

Disis ML, et al. JAMA Oncology 2019;
Optimizing check point inhibitors in AOC

• Better patient selection:
  • Search for more efficient biomarker

• Check-point inhibitors combination
  • Chemotherapy
  • Anti-angiogenic
  • PARPi
  • Multiple combinations Chemo +/- Bev +/- PARPi
  • Others
Biomarkers for checkpoint blockade immunotherapy response

Related to tumor neoantigen burden

• Microsatellite instability (MSI)
• High tumor mutational burden (TMB)

Indicative of a T cell–inflamed tumor microenvironment (TME)

• PD-L1 protein expression on tumor and immune cells
• Gene signatures of activated T cells (i.e. T cell–inflamed gene expression profile, GEP)
KEYNOTE-100: Pembrolizumab in ROC

CPS = [Total number of PD-L1+ cells (Tumor, lymphocytes, Macrophages) / total number of cells] x 100

<table>
<thead>
<tr>
<th></th>
<th>Cohort A (285)</th>
<th>Cohort B (91)</th>
<th>Cohort A+B (376)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPS &lt; 1</td>
<td>107</td>
<td>34</td>
<td>141</td>
</tr>
<tr>
<td></td>
<td>3.7%</td>
<td>8.8%</td>
<td>5.0%</td>
</tr>
<tr>
<td></td>
<td>(1.0-9.3)</td>
<td>(1.9-23.7)</td>
<td>(2.0-10.0)</td>
</tr>
<tr>
<td>CPS ≥ 1</td>
<td>147</td>
<td>50</td>
<td>197</td>
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<tr>
<td></td>
<td>10.2%</td>
<td>10%</td>
<td>10.2%</td>
</tr>
<tr>
<td></td>
<td>(5.8-16.3)</td>
<td>(3.3-21.8)</td>
<td>(6.3-15.2)</td>
</tr>
<tr>
<td>CPS ≥ 10</td>
<td>60</td>
<td>22</td>
<td>82</td>
</tr>
<tr>
<td></td>
<td>16.7%</td>
<td>18.2%</td>
<td>17.1%</td>
</tr>
<tr>
<td></td>
<td>(8.3-28.5)</td>
<td>(5.2-40.3)</td>
<td>(9.7-27.0)</td>
</tr>
</tbody>
</table>
Joint of TMB and GEP and treatment outcome prediction: TMB\textsuperscript{hi} and GEP\textsuperscript{hi} lead to the best ORR and PFS

Cristescu et al., Science 12 October 2018
Percentages of biomarker-defined response group in each cancer type

Cristescu et al., Science 12 October 2018
Check-point inhibitor combined with chemotherapy
JAVELIN 200
Avelumab (anti-PDL1) in Platinum Resistant/Refractory Ovarian Cancer

Randomized Phase 3 Study

Enrollment Criteria

Primary Endpoint: OS
Secondary Endpoints: ORR, PFS, Duration of response, PROs, Safety

Arm A
Avelumab

Arm B
Doxil + Avelumab

Arm C
Doxil

November 19, 2018
Not intended for US, Canada and UK-based media

Merck and Pfizer Provide Update on Avelumab in Platinum-Resistant/Refractory Ovarian Cancer

Darmstadt, Germany, and New York, US, November 19, 2018 – Merck and Pfizer Inc. (NYSE: PFE) today announced that the Phase III JAVELIN Ovarian 200 trial evaluating avelumab* alone or in combination with pegylated liposomal doxorubicin (PLD), a type of chemotherapy, compared with PLD did not meet the prespecified primary endpoints of overall survival (OS) or progression-free survival (PFS) in patients with platinum-resistant or -refractory ovarian cancer.

Not intended for US, Canada and UK-based media
Not intended for US, Canada and UK-based media

Darmstadt, Germany, and New York, US, December 21, 2018 – Merck and Pfizer Inc. (NYSE: PFE) today announced that data from a planned interim analysis of the Phase III JAVELIN Ovarian 100 study of avelumab* did not support the study’s initial hypothesis, and therefore the alliance made the decision to terminate the trial in alignment with the independent Data Monitoring Committee.

Patients whose tumor was not progressing as per RECIST 1.1 criteria (CR, PR, or SD) will be allowed to continue onto the maintenance portion of the study.

Primary endpoint:
PFS from randomization (A vs B, A vs C)

Secondary endpoints:
PFS from randomization (B vs C)
Maintenance PFS, OS, ORR, duration of response, PROs, safety, PK

Enrollment Criteria
- Previously untreated
- Stage II-IV
- Prior debulking surgery or plan for neoadjuvant chemotherapy
- ECOG PS 0 or 1
- Mandatory archival tissue

Chemotherapy: Choice of carboplatin q3w, paclitaxel, OR carboplatin + weekly paclitaxel as per JGOG 3016.

Maintenance avelumab up to 2 years.

Stratification:
- Weekly vs Q3W taxol
- Residual vs no residual disease vs neoadjuvant
- Region – North America vs other

Accrual rate = 40 pts/mo
Accrual duration = 27 mo.
IA of PFS for efficacy or futility = ~30 mo. 2/3 of events
Expected PFS readout at 41 mo

Arm A
Arm B
Arm C

R
A
N
D
O
M
I
Z
A
T
I
O
N

n = ~951 (388 PFS events) 272 events within each of the 2 main comparisons

Anticipated start: Feb 2016
Target PFS: HR=0.65
Arm A mPFS: 23 mo
Arms B and C mPFS: 35.4 mo

1:1:1

1,162
1,162
1,162

In total 3,486 patients will be randomized.
Rational for combining anti-VEGF and IO
VEGF has immunosuppressive properties

- Activate of Tregs
- Reduce endothelial adhesion and tumoral infiltration of T cells
- Induce expression of PD-L1
- Inhibit of DC differentiation
Phase II of nivolumab (anti-PD-1) and bevacizumab in ROC

<table>
<thead>
<tr>
<th>Best Overall Response</th>
<th>Platinum-Sensitive (N=20)</th>
<th>Platinum-Resistant (N=18)</th>
<th>Overall (N=38)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>Unevaluable</td>
<td>-</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Partial response</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Confirmed</td>
<td>8</td>
<td>40.0</td>
<td>3</td>
</tr>
<tr>
<td>Unconfirmed</td>
<td>1</td>
<td>5.0</td>
<td></td>
</tr>
<tr>
<td>Stable disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;24 weeks</td>
<td>6</td>
<td>30.0</td>
<td>3</td>
</tr>
<tr>
<td>&lt;24 weeks</td>
<td>3</td>
<td>15.0</td>
<td>7</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>2</td>
<td>10.0</td>
<td>4</td>
</tr>
<tr>
<td>Overall confirmed response rate</td>
<td>8</td>
<td>40.0</td>
<td>3</td>
</tr>
<tr>
<td>Total clinical benefit rate (CBR)</td>
<td>15</td>
<td>75.0</td>
<td>6</td>
</tr>
</tbody>
</table>

Durable responses or prolonged stable disease (including in platinum-resistant patients)

Median PFS 8.1 months

Liu et al. ESMO 2018, PD937
Sponsor: ARCAGY-GINECO
Principal Investigator: J.E. KURTZ
Status: RECRUITING

**ATezolizumab and Avastin in Late recurrent Disease**

**ATALANTE DESIGN**

**Recurrent late relapse**

- N=405
- Non-mucinous histology
- TFI >6 months
- One or 2 prior lines of Cx
- ECOG ≤1

**Stratification factors**

- PDL-1 expression
- TFI 6-12, >12 mos
- Chemotherapy cohort

Chemotherapy-based schedule options (investigator's choice):
- Carboplatin AUC5/180mg/m² q4wks
- Paclitaxel 175mg/m² q3wks
- Gemcitabine 1000mg/m² q3wks
- BEV 15mg/kg q3wks
- ATEZOLIZUMAB: 1200mg, LV q3wks or 800mg q4wks
YO39523/GOG-3015/ENGOT-ov39 (Joint International Steering Committee)

- Previously untreated high-grade cancer
- Stage III macroscopic or Stage IV (allows election of NACT), Bx cohort
- Stratification PDL1 0 vs 1+, Stage, PS, NACT
- Co-Primary endpoints (PDL1+): OS HR 0.72 (81%, 0.046), PFS HR 0.7

Open: MAR 2017
Status: Ongoing Accrual (NACT cohort closed)
Target: 1300 pts
Notes: NACT cohort closed MAY 2018 (20% cap)

Moore K and Pignata S, for GOG-F and ENGOT
Combination of PARPi and immunotherapy
Preclinical data

PARPi upregulates PD-L1 in BC xenograft

Sinergy of PARPi and anti-PD-L1

TOPACIO/Keynote-162 (PROC)
Niraparib 200 mg/d + pembrolizumab 200 mg/21d

60 evaluable patients
ORR: 25%
ORR BRCAmut: 42%
ORR in PR: 23%
ORR in PRf: 24%

DCR 67%
Median DOR 9.3 months

Kostantinopoulos et al. ESMO 2017 and ASCO 2018
## Durvalumab + Olaparib

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Population</th>
<th>ORR (%)</th>
<th>DCR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEDIOLA \nDrew et al. SGO 2018</td>
<td>32</td>
<td>gBRCA Platinum-sensitive</td>
<td>63%</td>
<td>81%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(19% CR /44% PR)</td>
<td></td>
</tr>
<tr>
<td>Lee et al. \nESMO 2018</td>
<td>35</td>
<td>83% Plat-R</td>
<td>14%</td>
<td>37%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(all PR)</td>
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</tbody>
</table>
ENGOT-OV41/GEICO 69-O/ANITA

N= 414 patients

- Recurrent high-grade serous or endometrioid, or undifferentiated ovarian, primary peritoneal or tubal carcinoma
- TF Ip >6 months
- ≤ 2 prior lines
- Measurable disease
- ECOG≤ 1

Stratification factors:
- Platinum based regimen selected
- PFI (6-12 months vs > 12 months)
- BRCA mutation status (mutated vs. non-mutated)

Primary Endpoint:
- PFS by RECIST v.1.1
- Secondary endpoints:
  - Safety and tolerability
  - TFST, TSST, PFS2, OS
  - ORR, DOR
  - QoL/PRO

The addition of atezolizumab is expected to increase the median PFS of Arm A from 16 months to 22.9 months, corresponding to a 30% reduction of the risk of progression (average HR of 0.70)
## Front line for Stage III/IV with PARPi + IO +/- Bev

<table>
<thead>
<tr>
<th>TRIAL</th>
<th>Setting</th>
<th>Patient selection</th>
<th>Arms</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGO / DUO-O ENGOT Ov46</td>
<td>Front line</td>
<td>tBRCA non-mut*, PDS or IDS Any residual LGSOC excluded</td>
<td>CP-Bev-placebo-placebo</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CP-Bev-Durvalumab-placebo</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CP-Bev-Durvalumab-Olaparib</td>
</tr>
<tr>
<td>BGOG /ENGOT Ov43</td>
<td>Front line</td>
<td>tBRCA non-mut*, Any histotype PDS or IDS Any residual Bev optional</td>
<td>CP-Placebo-Placebo</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CP- Pembro-Placebo</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>CP- Pembro-Olaparib</td>
</tr>
<tr>
<td>GINECO/ FIRST ENGOT Ov44</td>
<td>Front line</td>
<td>PDS (high risk) or IDS Bev optional Mucinous excluded</td>
<td>CP-Placebo-Placebo</td>
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<td></td>
<td>CP-Placebo-Niraparib</td>
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<td>CP-TSR042-Niraparib</td>
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<tr>
<td>ATHENA GOG3020 / ENGOT Ov45</td>
<td>Maintenance after front line</td>
<td>Stage III-IV and high grade PDS or IDS Response to platinum</td>
<td>Rucaparib-Nivolumab</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Rucaparib-Placebo</td>
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<td></td>
<td></td>
<td>Nivolumab-Placebo</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Placebo-Placebo</td>
</tr>
</tbody>
</table>

* Separate clinical trial for tBRCA-mutated
Immunotherapy in ovarian cancer is still promising and many questions remain. 

- Histologic subtype
- PDS vs NACT
- Residual tumor (R0 vs >R0)
- BRCA status
- Bevacizumab
- PARPi
- HRD status
- Biomarkers!!!
Thank you!

Antonio Gonzalez Martin
Clínica Universidad de Navarra, Madrid
GEICO (Grupo Español de Investigación en Cáncer de Ovario)
ENGOT (European Network of Gynecological Oncological Trials groups)