Atezolizumab combined with platinum-based chemotherapy and maintenance niraparib for recurrent ovarian cancer with a platinum-free interval >6 months: Primary analysis of the double-blind placebo-controlled ENGOT-Ov41/GEICO 69-O/ANITA phase 3 trial

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ANITA = Atezolizumab and Niraparib Treatment Association
Declaration of interests

Antonio González-Martín

• Personal fees for advisory boards: Alkermes, Amgen, AstraZeneca, Clovis, Eisai, Genmab, GSK, Hedera Dx, Illumina, Immunogen, MacroGenics, Mersana, MSD, Novartis, Oncoinvent, PharmaMar, Regeneron, Roche, SOTIO, Sutro, Tubulis

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Background

• Standard therapy for PARPi-naïve late-relapsing rOC (TFIp >6 months) is platinum-based CT, with PARPi maintenance if disease responds to CT, regardless of BRCA or HRD status

• Despite a strong preclinical rationale, previous phase 3 trials have shown no benefit from the addition of a PD-L1 inhibitor (atezolizumab, avelumab) to CT ± bevacizumab for newly diagnosed or rOC

• DUO-O/ENGOT-Ov46 showed improved PFS with the addition of durvalumab + olaparib to front-line CT + bevacizumab for non-tBRCA-mutated advanced ovarian cancer, but the contribution of PARPi + anti-PD-(L)1 therapy without bevacizumab remains unknown

• ANITA/ENGOT-Ov41/GEICO 69-O is the first reported phase 3 trial evaluating an immune checkpoint inhibitor (atezolizumab) with platinum-based CT + PARPi maintenance in late-relapsing rOC

CT = chemotherapy; HRD = homologous recombination deficiency; PARPi = poly (ADP-ribose) polymerase (PARP) inhibitor; PD-(L)1 = programmed death (ligand) 1; PFS = progression-free survival; rOC = recurrent ovarian cancer; t = tumour; TFIp = platinum-free interval

Placebo-controlled multicentre randomised phase 3 trial

CT phase

Atezolizumab\(^c\) + carboplatin doublet\(^d\)

Placebo + carboplatin doublet\(^d\)

Maintenance phase

Atezolizumab 1200 mg d1 + niraparib ISD d1–21 q21d

Placebo d1 + niraparib ISD d1–21 q21d

Stratification factors:

- Measurable high-grade serous, endometrioid or undifferentiated rOC
- TFIp >6 months
- ≤2 prior lines of CT (most recent including platinum)
- No prior PARPi for rOC\(^a\)
- No prior immune checkpoint inhibitor (any setting)
- ECOG PS ≤1
- Mandatory de novo biopsy\(^b\)

AUC = area under the curve; CR = complete response; d = day; ECOG PS = Eastern Cooperative Oncology Group performance status; IC = immune cells; ISD = individualised starting dose (300 mg, or 200 mg if baseline weight is <77 kg or baseline platelet count is <150,000 μL); PD = progressive disease; PLD = pegylated liposomal doxorubicin; PR = partial response; q21d = every 21 days; R = randomisation; RECIST = Response Evaluation Criteria in Solid Tumours; SD = stable disease

\(^a\)Prior PARPi after front-line therapy permitted if continued for ≥18 months (BRCA mutated) or ≥12 months (BRCA wildtype).

\(^b\)Implemented after randomisation of 82 patients (whose PD-L1 status was analysed in archival tissue).

\(^c\)Atezolizumab 1200 mg d1 q21d or 840 mg d1&8 q28d, depending on CT regimen.

\(^d\)Carboplatin AUC5 d1 + paclitaxel 175 mg/m\(^2\) d1 q21d OR carboplatin AUC4 d1 + gemcitabine 1000 mg/m\(^2\) d1&8 q21d OR carboplatin AUC5 d1 + PLD 30 mg/m\(^2\) d1 q28d.

\(^e\)PD-L1-expressing IC on tumour area, determined by SP142 assay. Non-informative cases were capped at <10%
Endpoints, statistical design and follow-up

Primary endpoint: Investigator-assessed PFS
- 332 events (80%) required in 414 patients for primary analysis
- Target HR: 0.70 (median PFS increased by 6 months; 2-sided alpha 0.05, ~90% power)
- Data cut-off: 15th April 2023
- Median follow-up: 36 months

Secondary endpoints
- OS
- TFST and TSST
- PFS2
- ORR and DoR in responders
- PFS from start of maintenance
- PFS subgroup analyses by BRCA mutation, PD-L1 and response status
- Safety
- PROs

Secondary endpoints shown in grey are not yet mature/analysed thus not presented

DoR = duration of response; HR = hazard ratio; ORR = objective response rate; OS = overall survival; PFS2 = time from randomisation to second progression or death; PROs = patient-reported outcomes; TFST = time from randomisation to first subsequent therapy or death; TSST = time from randomisation to second subsequent therapy or death

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**Patient disposition**

**Enrolment: November 2018 to January 2022**

417 patients randomised

208 randomised to atezo + CT → atezo + nira

- 1 withdrew before treatment
- 207 started CT
- 14 still on treatment
- 150 started maintenance
- 53 did not start maintenance
  - 42 disease progression\(^a\)
  - 3 death
  - 4 toxicity
  - 4 patient/physician withdrawal
  - 4 other/missing

209 randomised to placebo + CT → placebo + nira

- 209 started CT
- 53 did not start maintenance
  - 37 disease progression\(^a\)
  - 5 death
  - 3 toxicity
  - 4 patient/physician withdrawal
  - 4 other/missing
- 16 still on treatment
- 156 started maintenance\(^b\)
- 68% completed 6 cycles of CT

\(^a\)Radiological or clinical progression. \(^b\)7 patients received placebo without niraparib.
### Baseline characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Atezo + CT → atezo + nira (n=208)</th>
<th>Placebo + CT → placebo + nira (n=209)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (range) age, years&lt;sup&gt;a&lt;/sup&gt;</td>
<td>63 (37–85)</td>
<td>62 (23–82)</td>
</tr>
<tr>
<td>ECOG PS, n (%)&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>132 (64)</td>
<td>122 (60)</td>
</tr>
<tr>
<td>1</td>
<td>73 (36)</td>
<td>81 (40)</td>
</tr>
<tr>
<td>High-grade serous histology, n (%)&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>186 (89)</td>
<td>193 (92)</td>
</tr>
<tr>
<td>No. of prior lines of therapy, n (%)&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>180 (87)</td>
<td>178 (86)</td>
</tr>
<tr>
<td>2</td>
<td>27 (13)</td>
<td>28 (14)</td>
</tr>
<tr>
<td>Prior therapy, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>116 (56)</td>
<td>107 (51)</td>
</tr>
<tr>
<td>PARPi</td>
<td>20 (10)</td>
<td>26 (12)</td>
</tr>
<tr>
<td>TFIp, n (%)&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6–12 months</td>
<td>73 (35)</td>
<td>70 (33)</td>
</tr>
<tr>
<td>&gt;12 months</td>
<td>135 (65)</td>
<td>139 (67)</td>
</tr>
<tr>
<td>BRCA status, n (%)&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-mutated</td>
<td>181 (87)</td>
<td>178 (85)</td>
</tr>
<tr>
<td>Mutated</td>
<td>27 (13)&lt;sup&gt;f&lt;/sup&gt;</td>
<td>31 (15)&lt;sup&gt;g&lt;/sup&gt;</td>
</tr>
<tr>
<td>PD-L1 status, n (%)&lt;sup&gt;h&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>76 (37)</td>
<td>73 (35)</td>
</tr>
<tr>
<td>Negative</td>
<td>117 (56)</td>
<td>112 (54)</td>
</tr>
<tr>
<td>Non-informative</td>
<td>14 (7)</td>
<td>21 (10)</td>
</tr>
<tr>
<td>CT backbone, n (%)&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PLD</td>
<td>147 (71)</td>
<td>151 (72)</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>32 (15)</td>
<td>33 (16)</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>29 (14)</td>
<td>25 (12)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Missing in 15 patients. <sup>b</sup>Missing in 9 patients. <sup>c</sup>Missing in 5 patients. <sup>d</sup>Missing in 4 patients. <sup>e</sup>Stratification factor, as reported in interactive web response system. <sup>f</sup>Germline in 17, somatic in 5. <sup>g</sup>Germline in 20, somatic in 8. <sup>h</sup>Stratification factor, missing in 4 patients
Primary endpoint: PFS

**PFS**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Events, n (%)</th>
<th>HR (95% CI)</th>
<th>Median (95% CI), months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atezo + CT → atezo + nira (n=208)</td>
<td>170 (82)</td>
<td>0.89 (0.71–1.10); p=0.28</td>
<td>11.2 (10.1–12.1)</td>
</tr>
<tr>
<td>Placebo + CT → placebo + nira (n=209)</td>
<td>174 (83)</td>
<td></td>
<td>10.1 (9.2–11.2)</td>
</tr>
</tbody>
</table>

**Time (months)**

- Atezo: 208
  - 0: 156
  - 6: 82
  - 12: 33
  - 18: 17
  - 24: 9
  - 30: 5
  - 36: 0
- Placebo: 209
  - 0: 164
  - 6: 66
  - 12: 25
  - 18: 14
  - 24: 8
  - 30: 7
  - 36: 7
  - 42: 5
  - 48: 0
  - 54: 0
PFS by PD-L1 status

<table>
<thead>
<tr>
<th>PD-L1 status</th>
<th>Median PFS, months</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD-L1 positive (n=149)</td>
<td>12.8</td>
<td>0.87 (0.61–1.25)</td>
</tr>
<tr>
<td>PD-L1 negative (n=229)</td>
<td>10.5</td>
<td>0.93 (0.70–1.24)</td>
</tr>
<tr>
<td>PD-L1 non-informative (n=35)</td>
<td>11.2</td>
<td>1.06 (0.50–2.25)</td>
</tr>
</tbody>
</table>

4 patients with missing PD-L1 status excluded. 

PFS probability vs. Time (months)

- Atezo + CT → atezo + nira, PD-L1 positive
- Placebo + CT → placebo + nira, PD-L1 positive
- Atezo + CT → atezo + nira, PD-L1 negative
- Placebo + CT → placebo + nira, PD-L1 negative
## PFS subgroup analysis

<table>
<thead>
<tr>
<th>Population</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.89 (0.71–1.10)</td>
</tr>
<tr>
<td>Age &lt;70 years</td>
<td>0.89 (0.70–1.15)</td>
</tr>
<tr>
<td>≥70 years</td>
<td>1.01 (0.66–1.56)</td>
</tr>
<tr>
<td>BRCA status</td>
<td></td>
</tr>
<tr>
<td>Non-mutated</td>
<td>0.79 (0.63–0.99)</td>
</tr>
<tr>
<td>Mutated</td>
<td>1.84 (1.00–3.37)</td>
</tr>
<tr>
<td>Best CT response</td>
<td></td>
</tr>
<tr>
<td>CR/PR</td>
<td>0.90 (0.65–1.25)</td>
</tr>
<tr>
<td>SD</td>
<td>0.95 (0.70–1.29)</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
</tr>
<tr>
<td>High-grade serous</td>
<td>0.91 (0.73–1.14)</td>
</tr>
<tr>
<td>Other</td>
<td>0.92 (0.41–2.05)</td>
</tr>
<tr>
<td>No. of prior lines</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.87 (0.69–1.10)</td>
</tr>
<tr>
<td>2</td>
<td>1.24 (0.69–2.22)</td>
</tr>
<tr>
<td>PD-L1 status</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>0.87 (0.61–1.25)</td>
</tr>
<tr>
<td>Negative</td>
<td>0.93 (0.70–1.24)</td>
</tr>
<tr>
<td>Non-informative/missing</td>
<td>1.09 (0.54–2.23)</td>
</tr>
<tr>
<td>Prior bevacizumab</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>0.82 (0.60–1.13)</td>
</tr>
<tr>
<td>Yes</td>
<td>0.98 (0.73–1.30)</td>
</tr>
<tr>
<td>Prior PARPi</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>0.89 (0.71–1.12)</td>
</tr>
<tr>
<td>Yes</td>
<td>1.16 (0.62–2.18)</td>
</tr>
<tr>
<td>CT backbone</td>
<td></td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>0.54 (0.31–0.94)</td>
</tr>
<tr>
<td>PLD</td>
<td>0.97 (0.52–1.81)</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>0.99 (0.77–1.27)</td>
</tr>
<tr>
<td>TFIp</td>
<td></td>
</tr>
<tr>
<td>&gt;12 months</td>
<td>0.88 (0.67–1.14)</td>
</tr>
<tr>
<td>6–12 months</td>
<td>1.01 (0.71–1.44)</td>
</tr>
</tbody>
</table>

<sup>a</sup>HR and 95% CI from the multivariate primary analysis

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Secondary endpoint: Response rate during CT

**Atezo + CT**
- **CR:** 7%
- **PR:** 39%
- **SD:** 44%
- **ORR:** 45%
  (95% CI: 39–52%)

**Placebo + CT**
- **CR:** 6%
- **PR:** 37%
- **SD:** 46%
- **ORR:** 43%
  (95% CI: 36–49%)

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Secondary endpoint: PFS from start of maintenance

### Maintenance PFS

<table>
<thead>
<tr>
<th></th>
<th>Atezo + nira (n=150)</th>
<th>Placebo + nira (n=156)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events, n (%)</td>
<td>125 (83)</td>
<td>130 (83)</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.80 (0.62–1.03)</td>
<td></td>
</tr>
<tr>
<td>Median (95% CI), months</td>
<td>6.7 (5.3–8.3)</td>
<td>5.3 (4.3–6.1)</td>
</tr>
</tbody>
</table>

**Graph:**

- **Y-axis:** Maintenance PFS probability
- **X-axis:** Time (months)
- **Legend:**
  - Atezo + nira (n=150)
  - Placebo + nira (n=156)

**Events (n, %):**

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>Atezo + nira</th>
<th>Placebo + nira</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>150</td>
<td>156</td>
</tr>
<tr>
<td>6</td>
<td>75</td>
<td>61</td>
</tr>
<tr>
<td>12</td>
<td>33</td>
<td>23</td>
</tr>
<tr>
<td>18</td>
<td>19</td>
<td>15</td>
</tr>
<tr>
<td>24</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>30</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>36</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>42</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>48</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>54</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Summary of safety

<table>
<thead>
<tr>
<th>AE, n (%)</th>
<th>Atezo + CT → atezo + nira (n=207)</th>
<th>Placebo + CT → placebo + nira (n=209)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>200 (97)</td>
<td>202 (97)</td>
</tr>
<tr>
<td>Grade ≥3 treatment related</td>
<td>135 (65)</td>
<td>132 (63)</td>
</tr>
<tr>
<td>Grade 5 treatment related</td>
<td>2 (1)*</td>
<td>0</td>
</tr>
<tr>
<td>Serious AE</td>
<td>77 (37)</td>
<td>63 (30)</td>
</tr>
<tr>
<td>MDS/AML</td>
<td>1 (0.5)</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Immune-mediated AE</td>
<td>47 (23)</td>
<td>19 (9)</td>
</tr>
<tr>
<td>AESIs for atezolizumab</td>
<td>59 (29)</td>
<td>29 (14)</td>
</tr>
<tr>
<td>AE leading to niraparib dose reduction</td>
<td>74/150 (49)</td>
<td>64/149 (43)</td>
</tr>
<tr>
<td>AE leading to treatment discontinuation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maintenance niraparib</td>
<td>9/150 (6)</td>
<td>18/149 (12)</td>
</tr>
<tr>
<td>Maintenance placebo/atezolizumab</td>
<td>10/150 (7)</td>
<td>7/156 (4)</td>
</tr>
</tbody>
</table>

AE = adverse event; AESI = adverse event of special interest; AML = acute myeloid leukaemia; MDS = myelodysplastic syndrome

*Sepsis due to CT in cycle 1 (n=1); pericarditis and disease progression (n=1)

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Antonio González-Martín, MD, PhD

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Most common (≥10% of patients\(^a\)) non-haematological AEs

\(^a\)Occurring in >10% of patients in either arm during the CT and/or maintenance phase. PPE = palmar–plantar erythrodysesthesia
Most common (≥10% of patients\textsuperscript{a}) non-haematological AEs

\textbf{Maintenance phase\textsuperscript{b}}

\begin{itemize}
\item Atezo + nira (n=150)
\item Placebo + nira\textsuperscript{c} (n=156)
\end{itemize}

\begin{itemize}
\item Grade 1
\item Grade 2
\item Grade 3
\end{itemize}

\textsuperscript{a}Occurring in >10% of patients in either arm during the CT and/or maintenance phase. \textsuperscript{b}Starting on day 1 of maintenance or later. \textsuperscript{c}Niraparib not started in 7 patients

\textbf{Antonio González-Martín, MD, PhD}

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Selected haematological AEs by phase

CT phase

- **Anaemia**
- **Neutropenia**
- **Thrombocytopenia**
- **White blood cell count decreased**
- **Febrile neutropenia**

Maintenance phase

- **Anaemia**
- **Neutropenia**
- **Thrombocytopenia**
- **Blood creatinine increased**
- **Febrile neutropenia**
Conclusions

- Adding atezolizumab to CT and maintenance niraparib did not statistically significantly improve clinical outcomes (PFS, ORR, maintenance PFS) in patients with late-relapsing (TFIp >6 months) rOC
  - No difference in treatment effect according to PD-L1 status
- Predictable and manageable safety profile and no new safety signals with atezolizumab in combination with CT and maintenance niraparib
- Survival follow-up and analyses of PROs and biomarkers are ongoing
- The ANITA/ENGOT-Ov41/GEICO 69-O trial provides relevant information for the interpretation of other phase 3 trials of PD-(L)1 inhibitors and PARP inhibition in ovarian cancer
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J-P Lotz
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F Joly
M Rodrigues

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S Kromoss
A Harkopf
F Marmé
R Witteler
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