ORZORA: maintenance olaparib in patients with platinum-sensitive relapsed ovarian cancer: outcomes by somatic and germline BRCA and other homologous recombination repair gene mutation status

Sandro Pignata,1 Amit Oza,2 Geoff Hall,3 Beatriz Pardo,4 Radoslaw Madry,5 David Cibula,6 Jaroslav Klat,7 Ana Montes,8 Rosalind Glasspool,9 Nicoletta Colombo,10 Imre Pete,11 Ana Herrero Ibáñez,12 Margarita Romeo Marin,13 Rumyana Ilieva,14 Constanta Timcheva,15 Christopher Blakeley,16 Rosie Taylor,16 Alan Barnicle,16 Andrew Clamp17

1Istituto Nazionale Tumori ‘Fondazione G Pascale’, IRCCS, Napoli, Italy; 2Princess Margaret Cancer Centre, Toronto, Canada; 3St James’s University Hospital, Leeds, UK; 4ICO l’Hospital – Hospital Duran i Reynals, L’Hospital de Llobregat, Barcelona, Spain; 5Clinical Hospital of the Transfiguration of the Lord’s Medical University Karol Marcinkowski, Poznan, Poland; 6General University Hospital in Prague, First Faculty of Medicine, Charles University, Prague, Czech Republic; 7University Hospital Ostrava, Ostrava Poruba, Czech Republic; 8Guy’s and St Thomas’ NHS Foundation Trust, London, UK; 9Beatson West of Scotland Cancer Centre and University of Glasgow, Glasgow, UK; 10University of Milan-Bicocca and European Institute of Oncology IRCCS, Milan, Italy; 11National Institute of Cancer, Budapest, Hungary; 12Hospital Universitario Miguel Servet, Zaragoza, Spain; 13ICO Badalona – Hospital Universitari Germans Trias i Pujol, Barcelona, Spain; 14MHAT “Central Onco Hospital”, OOD, Plovdiv, Bulgaria; 15MHAT for Women’s Health – Nadezhda, OOD, Sofia, Bulgaria; 16AstraZeneca, Cambridge, UK; 17The Christie NHS Foundation Trust and University of Manchester, Manchester, UK

ClinicalTrials.gov identifier: NCT02476968. This study was sponsored by AstraZeneca and is part of an alliance between AstraZeneca and Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA
Disclosure information

- **S Pignata**: Honoraria from AstraZeneca, MSD, Roche, Pfizer, GSK, Clovis Pharma. Research funding from Roche, MSD, AstraZeneca, Pfizer
- **A Oza**: Principal investigator of investigator-initiated studies with AstraZeneca, institutional grant funding from AstraZeneca, and steering committee member (non-compensated) for AstraZeneca, Clovis Oncology and GSK
- **G Hall**: Research funding from IQVIA
- **B Pardo**: Research funding from AZ, GSK, Clovis, MSD.
- **R Madry**: Advisory boards: AstraZeneca, Roche, GSK Personal fees from AstraZeneca, Roche, GSK,
- **D Cibula**: Advisory boards: AstraZeneca, Roche, Genmab, Sotio, Merck, GSK
- **J Klat**: I have nothing to disclose
- **A Montes**: I have nothing to disclose
- **R Glasspool**: Principal Investigator for trials sponsored by AstraZeneca, Clovis, Tesaro, Immunogen, Pfizer and Lilly. Research funding from Clovis, Boehringer Ingelheim and Lilly/Ignyta. Institution research funding from Tesaro. Personal fees from AstraZeneca, Clovis, Tesaro, GSK, Immunogen and Sotio.
- **N Colombo**: Personal fees from AstraZeneca, MSD, Roche, Tesaro, GSK, Clovis Oncology, PharmaMar, Pfizer, Amgen, Novartis, Biocad and Immunogen
- **I Pete**: I have nothing to disclose
- **A Herrero Ibáñez**: AstraZeneca, Clovis, GSK, Roche, PharmaMar, MSD
- **M Romeo Marin**: Institution research funding from AstraZeneca, GSK, Clovis, Pfizer
- **R Ilieva**: I have nothing to disclose
- **C Timcheva**: Principal investigator of many clinical trials of AstraZeneca, Roche, Novartis, Pfizer, Merck. Member of advisory boards of Astellas, Servie, Novartis.
- **C Blakeley**: AstraZeneca employment and stock ownership
- **R Taylor**: AstraZeneca contractor
- **A Barnicle**: AstraZeneca employment and stock ownership
- **A Clamp**: Research funding; AZ Honoraria; AZ, Clovis Oncology, GSK/Tesaro, Eisai
Introduction

• In patients with PSR OC, maintenance olaparib provided a significant PFS benefit vs placebo irrespective of BRCAm status (Study 19: HR 0.35, 95% CI 0.25–0.49)\textsuperscript{1} and in patients with a gBRCAm (SOLO2: HR 0.30, 95% CI 0.22–0.41)\textsuperscript{2}

• In Study 19, maintenance olaparib provided a PFS benefit in a small sBRCAm cohort like that observed in the gBRCAm cohort\textsuperscript{3}
  – This finding was supported by interim results from OPINION, in which maintenance olaparib showed efficacy in PSR OC patients with an sBRCAm\textsuperscript{4}

• The open-label, single-arm, multicenter ORZORA trial evaluated the efficacy and safety of maintenance olaparib in PSR OC patients who had a tBRCAm (of germline or somatic origin) or a non-BRCA HRRm

Screening process

Patients who have signed consent and are eligible for screening*

Tumor sample for central BRCA testing

- tBRCAm undetermined
  STOP

- BRCAm
  non-tBRCAm

  ENTER MAIN STUDY
  Blood sample for central HRR testing

- Non-tBRCAm
  but HRRm
  ENTER non-BRCA HRRm cohort

- Non-tBRCAm and non-HRRm
  STOP

- gBRCAm
  Confirmed somatic mutation, non-gBRCAm‡

- sBRCAm
  Confirmed germline mutation

---

*25 patients, all gBRCAm, were recruited before the application of this screening process;
†Prespecified HRR gene panel: ATM, BRIP1, PALB2, RAD51C, BARD1, CDK12, CHEK1, CHEK2, FANCL, PPP2R2A, RAD51B, RAD51D, RAD54L;
‡A minimum of 50 patients were to be recruited to the sBRCAm cohort.
**Primary endpoint**

- Investigator-assessed PFS (modified RECIST v1.1):
  1. Any BRCAm
  2. sBRCAm cohort‡

**Secondary endpoints**

- PFS2
- OS
- TFST
- TSST
- TDT
- HRQoL (FACT-O TOI)
- Safety

**Exploratory endpoints**

- PFS
- OS
- Safety

**Study design**

- **All patients had:**
  - PSR OC
  - CR or PR after ≥2 lines of platinum-based chemotherapy

- **BRCAm**
  - Start maintenance therapy within 8 weeks of the last dose of chemotherapy
  - Treated until disease progression† or other discontinuation criteria are met

- **Non-BRCA HRRm**
  - Maintenance olaparib*

*Capsule formulation, 400 mg twice daily;

†Unless in the investigator’s opinion the patient is benefiting from treatment and does not meet any other discontinuation criteria;

‡A minimum of 50 sBRCAm patients were to be recruited.

CR, complete response; FACT-O, functional assessment of cancer therapy-ovarian; HRQoL, health-related quality of life; PFS2, time to second progression or death; OS, overall survival; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; TDT, time to study treatment discontinuation or death; TFST, time to first subsequent anti-cancer therapy or death; TOI, trial outcome index; TSST, time to second subsequent anti-cancer therapy or death.
**Study milestones and patient enrollment**

- **First patient enrolled:** 28 September 2015
- **Last patient enrolled:** 18 October 2018
- **Primary PFS analysis DCO:** 17 April 2020
- **Primary PFS analysis planned for 60% data maturity**

- **872 patients screened**
- **181 patients enrolled**

- **BRCAm* cohort (n=145)**
  - gBRCAm cohort (n=87)
  - sBRCAm cohort (n=55)
  - s/gBRCAm status unknown ‡ (n=3)

- **Non-BRCA HRRm cohort (n=33)**

- **Unassigned † (n=3)**

*Based on tumor and/or germline testing; †Unassigned patients: patients without BRCAm or HRRm; ‡gBRCAm status unknown: three patients had a BRCAm but could not be classified as sBRCAm or gBRCAm.

DCO, data cut-off.
## Patient disposition

<table>
<thead>
<tr>
<th></th>
<th>BRCAm (N=145)</th>
<th>sBRCAm (N=55)</th>
<th>gBRCAm (N=87)</th>
<th>Non-BRCA HRRm (N=33)</th>
<th>Total* (N=181)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Screened, n</strong></td>
<td>167</td>
<td>67</td>
<td>97</td>
<td>42</td>
<td>872</td>
</tr>
<tr>
<td><strong>Enrolled (full analysis set), n</strong></td>
<td>145</td>
<td>55</td>
<td>87</td>
<td>33</td>
<td>181</td>
</tr>
<tr>
<td><strong>Treated (safety analysis set), n</strong></td>
<td>143</td>
<td>55</td>
<td>87</td>
<td>32</td>
<td>177</td>
</tr>
<tr>
<td><strong>Ongoing study treatment at primary PFS DCO, n (%)</strong></td>
<td>51 (35.2)</td>
<td>17 (30.9)</td>
<td>33 (37.9)</td>
<td>8 (24.2)</td>
<td>59 (32.6)</td>
</tr>
<tr>
<td><strong>Discontinued study treatment, n (%)</strong></td>
<td>92 (100)</td>
<td>38 (100)</td>
<td>54 (100)</td>
<td>24 (100)</td>
<td>118 (100)</td>
</tr>
<tr>
<td>Patient decision</td>
<td>12 (13.0)</td>
<td>5 (13.2)</td>
<td>7 (13.0)</td>
<td>2 (8.3)</td>
<td>14 (11.9)</td>
</tr>
<tr>
<td>Worsening of underlying condition</td>
<td>68 (73.9)</td>
<td>28 (73.7)</td>
<td>40 (74.1)</td>
<td>19 (79.2)</td>
<td>87 (73.7)</td>
</tr>
<tr>
<td>Adverse event</td>
<td>6 (6.5)</td>
<td>3 (7.9)</td>
<td>3 (5.6)</td>
<td>1 (4.2)</td>
<td>7 (5.9)</td>
</tr>
<tr>
<td>Met study-specific discontinuation criteria</td>
<td>1 (1.1)</td>
<td>1 (2.6)</td>
<td>0</td>
<td>0</td>
<td>1 (0.8)</td>
</tr>
<tr>
<td>Other</td>
<td>5 (5.4)</td>
<td>1 (2.6)</td>
<td>4 (7.4)</td>
<td>2 (8.3)</td>
<td>9 (7.6)</td>
</tr>
</tbody>
</table>

*Three patients were unassigned; two were treated (neither of these patients were receiving ongoing study treatment at primary PFS DCO).
## Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>BRCAm* (N=145)</th>
<th>sBRCAm (N=55)</th>
<th>gBRCAm (N=87)</th>
<th>Non-BRCA HRRm (N=33)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median patient age, years (range)</strong></td>
<td>61.5 (39–82)</td>
<td>67.0 (42–78)</td>
<td>56.0 (39–82)</td>
<td>64.0 (45–79)</td>
</tr>
<tr>
<td><strong>Median time from original diagnosis, years (range)</strong></td>
<td>3.05 (1.4–25.3)</td>
<td>2.93 (1.5–25.3)</td>
<td>3.37 (1.4–15.3)</td>
<td>3.52 (1.7–9.4)</td>
</tr>
<tr>
<td><strong>Primary tumor location, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ovary</td>
<td>124 (85.5)</td>
<td>43 (78.2)</td>
<td>78 (89.7)</td>
<td>27 (81.8)</td>
</tr>
<tr>
<td>Fallopian tubes</td>
<td>7 ( 4.8)</td>
<td>5 (9.1)</td>
<td>2 (2.3)</td>
<td>1 (3.0)</td>
</tr>
<tr>
<td>Primary peritoneal</td>
<td>14 ( 9.7)</td>
<td>7 (12.7)</td>
<td>7 (8.0)</td>
<td>5 (15.2)</td>
</tr>
<tr>
<td><strong>Prior lines of chemotherapy, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>80 (55.6)</td>
<td>34 (61.8)</td>
<td>45 (51.7)</td>
<td>18 (54.5)</td>
</tr>
<tr>
<td>3</td>
<td>41 (28.5)</td>
<td>12 (21.8)</td>
<td>28 (32.2)</td>
<td>11 (33.3)</td>
</tr>
<tr>
<td>≥4</td>
<td>23 (16.0)</td>
<td>9 (16.4)</td>
<td>14 (16.1)</td>
<td>4 (12.1)</td>
</tr>
<tr>
<td><strong>Response to previous platinum-based chemotherapy, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>75 (52.4)</td>
<td>30 (54.5)</td>
<td>44 (50.6)</td>
<td>11 (34.4)</td>
</tr>
<tr>
<td>Partial response</td>
<td>68 (47.6)</td>
<td>25 (45.5)</td>
<td>43 (49.4)</td>
<td>21 (65.6)</td>
</tr>
<tr>
<td><strong>tBRCA mutation†</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRCA1</td>
<td>124 (100)</td>
<td>55 (100)</td>
<td>66 (100)</td>
<td>0</td>
</tr>
<tr>
<td>BRCA2</td>
<td>81 (65.3)</td>
<td>36 (65.5)</td>
<td>42 (63.6)</td>
<td>0</td>
</tr>
<tr>
<td>Both</td>
<td>42 (33.9)</td>
<td>19 (34.5)</td>
<td>23 (34.8)</td>
<td>0</td>
</tr>
</tbody>
</table>

*BRCAm cohort includes 3 pts who reported a BRCAm but could not be classified as sBRCAm or gBRCAm; †Local or Myriad testing.
PFS in BRCAm cohort

Median PFS follow-up was 22.3 months*

Events, n (%)
- 88 (60.7)

Median PFS, months (95% CI)
- 18.0 (14.3–22.1)

Patients free from disease progression and death (%)
- 67%
- 39%

Time from enrollment (months)

No. at risk
- BRCAm: 145, 131, 116, 100, 90, 75, 64, 46, 35, 31, 21, 16, 9, 7, 5, 5, 4, 2, 0

*In censored patients.
PFS in sBRCAm cohort

- Events: 35 (63.6%)
- Median PFS (95% CI): 16.6 (12.4–22.2) months

Time from enrollment (months)

Patients free from disease progression and death (%)

No. at risk

| sBRCAm | 55 | 49 | 45 | 39 | 33 | 27 | 21 | 16 | 10 | 9 | 5 | 4 | 1 | 1 | 0 |
PFS in non-BRCA HRRm cohort

No. at risk

| non-BRCA HRRm* | 33 | 26 | 25 | 22 | 21 | 15 | 12 | 6  | 5  | 5  | 3  | 2  | 0  |

 Patients free from disease progression and death (%)

Time from enrollment (months)

Events, n (%)

<table>
<thead>
<tr>
<th>Non-BRCA HRRm (N=33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>22 (66.7)</td>
</tr>
</tbody>
</table>

Median PFS (95% CI), months

| 16.4                  |
| (10.9–19.3)           |

*Two patients (6.1%) had an ATM mutation, five (15.2%) had a BRIP1 mutation, 12 (36.4%) had a CDK12 mutation, one (3.0%) had a CHEK2 mutation, one (3.0%) had a FANCL mutation, two (6.1%) had a PALB2 mutation, seven (21.2%) had a RAD51C mutation, four (12.1%) had a RAD51D mutation.
Two patients (6.1%) had an ATM mutation, five (15.2%) had a BRIP1 mutation, 12 (36.4%) had a CDK12 mutation, one (3.0%) had a FANCL mutation, two (6.1%) had a PALB2 mutation, six (18.2%) had a RAD51C mutation, four (12.1%) had a RAD51D mutation, one (3%) had a co-occurring CHEK2 & RAD51C mutation.
Best response in FACT-O TOI score

TOI scores range from 0–100, with higher scores indicating better HRQoL.

*Improved: defined as an increase from baseline of ≥10 points. All patients with a baseline score of ≤90 were included.
†Worsened: defined as a decrease from baseline of ≥10 points. All patients with a baseline score ≥10 were included.
‡No change: all patients were included.
### Summary of safety analyses

<table>
<thead>
<tr>
<th></th>
<th>Total (N=177)</th>
<th>BRCAm (N=143)</th>
<th>sBRCAm (N=55)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median treatment duration, months (range)</td>
<td>17.71 (0.0–53.8)</td>
<td>18.96 (0.0–53.8)</td>
<td>17.87 (0.0–43.1)</td>
</tr>
<tr>
<td>All-grade TEAEs, n (%)</td>
<td>166 (93.8)</td>
<td>135 (94.4)</td>
<td>52 (94.5)</td>
</tr>
<tr>
<td>Grade ≥3 TEAEs, n (%)</td>
<td>62 (35.0)</td>
<td>52 (36.4)</td>
<td>21 (38.2)</td>
</tr>
<tr>
<td>Serious TEAEs, n (%)</td>
<td>45 (25.4)</td>
<td>37 (25.9)</td>
<td>13 (23.6)</td>
</tr>
<tr>
<td>AESIs, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MDS/AML*</td>
<td>2 (1.1)</td>
<td>2 (1.4)</td>
<td>0</td>
</tr>
<tr>
<td>NPMs†</td>
<td>2 (1.1)</td>
<td>2 (1.4)</td>
<td>0</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dose interruption due to TEAEs, n (%)</td>
<td>86 (48.6)</td>
<td>71 (49.7)</td>
<td>27 (49.1)</td>
</tr>
<tr>
<td>Treatment discontinuation due to TEAEs, n (%)</td>
<td>8 (4.5)</td>
<td>7 (4.9)</td>
<td>4 (7.3)</td>
</tr>
</tbody>
</table>

*MDS/AML events were both AML; †Types of NPM: papillary thyroid cancer (n=1), Burkitt's lymphoma (n=1).

AESI, adverse event of special interest; AML, acute myeloid leukemia; MDS, myelodysplastic syndromes; NPM, new primary malignancy; SAS, safety analysis set; TEAE, treatment-emergent adverse event.
Most frequent TEAEs in full Safety Analysis Set

*Grouped term data;
†All-grade grouped-term thrombocytopenia occurred in 9.6% patients, and grade ≥3 grouped-term thrombocytopenia occurred in 1.7% of patients.
Conclusions

• In ORZORA, maintenance olaparib had clinical activity in patients with PSR OC and a somatic BRCAm
  – Median PFS was similar in the BRCAm, including sBRCAm, cohorts and was consistent with that reported in other studies\(^1,2\)
  – This is the largest sBRCAm cohort to show a benefit for maintenance olaparib

• Results in an additional exploratory cohort suggest that, consistent with previous PARP inhibitor studies\(^3,4\), patients with a non-BRCA HRRm achieved clinical benefit with maintenance PARP inhibitors in the context of platinum-sensitive relapsed disease

• HRQoL and tolerability were consistent with previous studies in this setting\(^1,2,5\)
  – Most patients reported no change or improvements in HRQoL during treatment
  – No difference in safety profile was seen between the BRCAm, including sBRCAm, cohorts

PARPi, poly(ADP-ribose) polymerase inhibitor.

Acknowledgements

We thank all the women who participated in this study, their families, and the investigators.