Background

- A post hoc decision-tree analysis identified that, in patients treated with niraparib in NOVA, baseline weight and baseline platelet count were predictive factors for the deep and area of high-grade thrombocytopenia.

- Most of the thrombocytopenia events occurred by the end of month 3.

- These patients received an average dose of 207 mg during the first 3 months.

- After dose modification, 200 mg was the most commonly administered dose.

- Dose modification did not compromise efficacy in the retrospective analysis.

- Based on this analysis, a new individualized starting dose paradigm was introduced in the first line PRIMA-ENGOT-OV26-GOG-3012 study.

Conclusions

- The individualized starting dose regimen determined in the retrospective analysis of NOVA was prospectively validated in this analysis.

- The individualized starting dose regimen of 200 mg or 300 mg based on baseline weight and platelet count demonstrated comparable efficacy while improving the safety profile of niraparib.

- Clinical efficacy was similar in patients who received the 300 mg fixed starting dose or the 200- or 300 mg individualized starting dose.

- Hematological toxicities were reduced with the individualized starting dose subgroup.

- Based on these results, an individualized starting dose is recommended for first-line maintenance treatment of patients with ovarian cancer.

- 200 mg taken orally QD

- 300 mg taken orally QD for patients weighing ≥77 kg (170 lbs) and

Objective

- To prospectively evaluate the safety and efficacy of an ISD based on patients’ baseline bodyweight and platelet count.

Methods

- Niraparib is a poly(ADP-ribose) polymerase inhibitor approved for the maintenance treatment of patients with newly diagnosed or recurrent ovarian cancer following a response to platinum-based chemotherapy.

- In the pivotal phase 3 ENGOT-OV26/NOVA trial of niraparib in patients with recurrent ovarian cancer, all patients started the study with a fixed starting dose (FSD) of 300 mg once daily (QD) based on the fasting phase 1 data.

- The PRIMA/ENGOT-OV26-GOG-3012 study of niraparib in patients with newly diagnosed ovarian cancer was amended to prospectively validate an individualized starting dose (ISD) of 200 mg or 300 mg niraparib QD based on baseline bodyweight and platelet count (Table 1).

Results

- The primary endpoint, PFS2, was lower in patients in the ISD subgroup. The divergence in PFS2 between the ISD and FSD subgroups remained consistent across the prespecified subgroup profiling, with patients with advanced tumors, a history of platinum-based chemotherapy, and those who had previously received navelbine achieving significantly improved PFS2 with the ISD regimen.

- The ISD regimen was associated with a lower incidence of anemia and thrombocytopenia compared with the FSD regimen, with similar toxicities of hypertension and neutropenia (Table 5).

- In the ISD subgroup, fewer patients withdrew due to TEAEs (placebo vs. ISD: 9% vs. 5%, P=0.02).

- The ISD regimen was associated with a lower incidence of anemia and thrombocytopenia compared with the FSD regimen, with similar toxicities of hypertension and neutropenia (Table 5).

Table 4. PFS2 Hazard Ratio and Starting-Dose Subgroup Interaction Test

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISD vs. FSD</td>
<td>0.56 (0.38, 0.84)</td>
<td>0.006</td>
</tr>
</tbody>
</table>

Table 5. Grade 3-4 Hematologic TEAEs Reported in ≥5% of Patients

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Grade 3-4 Hematologic TEAEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISD vs. FSD</td>
<td>Anemia: 9% vs. 2%, P=0.02</td>
</tr>
</tbody>
</table>

Exposure-Response Analysis

- The ISD and FSD subgroups were comparably represented across all 4 exposure quartiles (Figure 2).

- Progression-free survival (PFS) over time for patients by exposure quintile is shown in Figure 2.

- The overlapping curves indicate that there is no observed relationship between improved response and increased exposure.

- However, the rate of high-grade thrombocytopenia increased with higher exposure.

Table 2. Demographics and Baseline Characteristics (ITT Population)

<table>
<thead>
<tr>
<th>subgroup</th>
<th>Median age (IQR)</th>
<th>Median Charlson score (IQR)</th>
<th>Median body weight (kg) (IQR)</th>
<th>Median body mass index (kg/m²) (IQR)</th>
<th>Median time from randomization to treatment on study (days) (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISD vs. FSD</td>
<td>62 (52–72) vs. 62 (52–72)</td>
<td>0 (0–0) vs. 0 (0–0)</td>
<td>75 (70–80) vs. 75 (70–80)</td>
<td>24.7 (22.0–27.5) vs. 25.1 (22.5–27.5)</td>
<td>60 (30–90) vs. 60 (30–90)</td>
</tr>
</tbody>
</table>

Table 3. Dose Exposure, Dose Intensity, and Dose Interruptions and Reductions by Subgroup

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Median dose intensity (mg/day) (IQR)</th>
<th>Median dose interruptions and reductions (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISD vs. FSD</td>
<td>70 (50–90) vs. 70 (50–90)</td>
<td>10 (5–20) vs. 10 (5–20)</td>
</tr>
</tbody>
</table>

Table 6. Hematologic Toxicity (ITR Population)

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Grade 3-4 Hematologic TEAEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISD vs. FSD</td>
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</table>