Pharmacokinetics and Safety Following a Single Oral Dose of Niraparib in Patients With Moderate Hepatic Impairment

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Background

Context

Niraparib is a PARPi approved for:

- First-line maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy (USA).
- Maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy (USA and EU).

Niraparib is administered as 150-mg oral capsules, with or without food. The recommended dose of niraparib for first-line maintenance treatment is 330 mg QD for patients weighing <77 kg or with a platelet count <100,000/µL, and 330 mg QD for patients weighing >77 kg and with a platelet count ≥100,000/µL. The recommended dose of niraparib for the latter two indications is 300 mg QD.

Niraparib is metabolized in the liver and eliminated primarily through the hepatobiliary and renal routes. Prior characterization of niraparib PK demonstrated that systemic exposure increases in a dose-proportional manner and a high volume of distribution and long elimination half-life may support the anti-cancer activity and recommend daily dose of niraparib.

Objective

The objective of this study (NCT03359850) was to characterize the PK and safety of niraparib in patients with moderate hepatic impairment (bilirubin >1.5 × to 3 × ULN and any AST elevation) versus patients with normal hepatic function to inform dosing recommendations.

Methods

1. Phase 1: Open-label, non-randomized, multicenter study

- Niraparib PK profiles

- Baseline demographics, disease characteristics, and previous therapies

- Niraparib PK

- Safety

- Conclusions

Baseline demographics, disease characteristics, and previous therapies

<table>
<thead>
<tr>
<th>Comparator</th>
<th>Normal hepatic function</th>
<th>Moderate hepatic impairment</th>
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<tbody>
<tr>
<td>Age (yr)</td>
<td>Median 66 (41–87)</td>
<td>Median 65 (41–87)</td>
</tr>
<tr>
<td>Female</td>
<td>2/30 (6.7%)</td>
<td>4/38 (10.5%)</td>
</tr>
<tr>
<td>Mean weight (kg)</td>
<td>91.2 (74.9)</td>
<td>79.9 (61.6)</td>
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<tr>
<td>Median albumin (g/L)</td>
<td>41 (39–62)</td>
<td>29 (25–46)</td>
</tr>
<tr>
<td>Median AST (U/L)</td>
<td>57 (50–222)</td>
<td>138 (78–222)</td>
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<tr>
<td>Median prior lines of therapy (range)</td>
<td>0 (0–3)</td>
<td>1 (1–5)</td>
</tr>
</tbody>
</table>

Niraparib PK

- Scaled increase in niraparib exposure in patients with moderate hepatic impairment

- Safety

- Conclusions

Safety

- Niraparib safety during the PK phase were consistent with the known safety profile for niraparib.

Conclusions

- Preliminary data from the ongoing single-dose PK study demonstrated that moderate hepatic impairment did not meaningfully impact niraparib PK.

- The safety profile for niraparib in patients with moderate hepatic impairment did not noticeably alter the toxicity profile of niraparib in this population.

- The increased exposure of niraparib in patients with moderate hepatic impairment did not notably affect the normal hepatic function.

- These results warrant further analyses.

References

3. Corr, DPhil, at Fishawack Indicia Ltd, UK, and members of GlaxoSmithKline, GSK, and Merck.
5. Corr, DPhil, at Fishawack Indicia Ltd, UK, and members of GlaxoSmithKline, GSK, and Merck.
7. Editorial assistance was provided by Richard Connolly, PhD, at Fishawack Indicia Ltd, UK, and members of GlaxoSmithKline, GSK, and Merck.
8. Safety data during the PK phase were consistent with the known safety profile for niraparib.
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