Niraparib–Response Relationships in Patients With Newly Diagnosed Advanced Ovarian Cancer

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Objective

- Population pharmacokinetic (PK) analysis has been applied frequently to explore the pharmacokinetic profile of niraparib and evaluate the impact of drug dosing based on individual patient characteristics.
- The objective of this analysis was to develop a population PK model using all niraparib trials and to conduct efficacy and safety exposure-response analyses in the PRIMA study to support an optimized dosing strategy that could enhance the adverse events (AEs) while maintaining the efficacy.

Method

- Niraparib is a poly(ADP-ribose) polymerase (PARP) inhibitor that is approved for treatment in heavily pre-treated patients and maintenance treatment of patients with newly diagnosed or recurrent ovarian cancer following a response to platinum-based chemotherapy.
- In the PRIMA/PATIENTS/DOGGOD-2012 (PRIMA) phase 3 trial, niraparib maintenance treatment significantly improved progression-free survival (PFS) compared with placebo (hazard ratio [HR] 0.83; 95% confidence interval [CI] 0.71–0.96; P = 0.01).
- In PRIMA, patients were initially treated with a fixed starting dose (FSD) of 300 mg once daily (QD) until a protocol amendment introduced an individualized starting dose (ISD) regimen.

Conclusions

- Covariates effects on niraparib PK were predicted to generally result in limited effects on niraparib exposure.
- No definitive exposure–response relationship was observed for efficacy (PFS).
- Niraparib model predicted exposure up to the time of disease progression/death or censoring was similar in the 200-mg ISD and 300-mg FSD groups.
- There was a positive correlation between niraparib exposure and the risk of any grade and grade 3 hematological AEs, including thrombocytopenia.
- Together, these findings support the use of a lower dose in patients with low bodyweight and platelets as it improves on tolerability while not impacting overall efficacy.

Figure 1. Studies Included in Population PK Modeling

- The final population PK model was a 3-compartment model with linear elimination, with a constant (α) zero-order rate of drug release into the absorption compartiment prior to the first time and followed by first-order absorption into the central compartment (Figure 2).

Population Model PK

- Data included in the population PK model are shown in Table 1.
- Population PK = pharmacokinetic; Q1=first intercompartmental clearance; Q2=second intercompartmental clearance; Vp1=first central compartment volume; Vp2=second central compartment volume.

Table 1. Population PK Model Data

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients, n (n [%])</th>
<th>Total Cmax (mg/L)</th>
<th>Pharmacokinetic Parameters</th>
<th>PK Parameter</th>
<th>PFS Parameter</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRIMA</td>
<td>624 (100)</td>
<td>300 (100)</td>
<td>CL (L/hr)</td>
<td>τ (days)</td>
<td>β (days⁻¹)</td>
</tr>
<tr>
<td>PRIMA</td>
<td>624 (100)</td>
<td>300 (100)</td>
<td>Vp1 (L)</td>
<td>Vp2 (L)</td>
<td></td>
</tr>
</tbody>
</table>

Figure 2. 3-Compartment Population PK Model

- The relationship between model predicted niraparib exposure (Cmax) and clinical trial parameters for patients in the PRIMA study who had PK and PFS data was analyzed using univariate logistic regression in patients receiving niraparib.

Efficacy Exposure–Response Analysis

- The effect of exposure for PFS for FFS included data from 480 patients randomized to niraparib in the PRIMA study who had PFS data.
- In the 200-mg ISD and 300-mg FSD groups were approximately evenly represented across exposure quartiles.

Safety Exposure–Response

- Univariate logistic regression was performed to characterize the relationships between average niraparib exposure and any grade and grade 3 AEs at any point during the study for the following clinically relevant AEs: anemia, neutropenia, hypertension, fatigue, and thrombocytopenia (Figure 5).
- The safety exposure–response analyses revealed statistically significant associations between increasing niraparib exposure (AUC_t, Cmax, and C_mean) and increasing probability of experiencing any grade and grade 3 AEs for all the safety endpoints with the exception of grade 3 anemia.
- Statistically significant exposure–response relationships for grade 3 hypertension were absent for AUC_t and Cmax and were weak to moderate for the other endpoints.
- The incidence of AEs, including thrombocytopenia, was lower in patients in the 200-mg ISD group.

References


Figure 3. Effects of Covariates on Niraparib Steady-State AUC (A) and Cmax (B)

Figure 4. PFS by Model-Predicted Cmax Group in Overall Population

Figure 5. Logistic Regression Plot for Grade 3 Thrombocytopenia Versus AUC

Note: The plots of the logistic regression are presented as the fraction of patients at risk at the beginning of each time interval with the fraction of patients experiencing the event at the beginning of each time interval.