Niraparib Exposure–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 potential benefits of drug dosing **based on individual patient characteristics**. The objective of this analysis was to develop a population PK model using all 4 niraparib trials and to **conduct efficacy and safety exposure–response analyses** in the PRIMA study to support an optimized dosing strategy that could minimize the adverse events (AEs) while maintaining the efficacy

Conclusions

- Covariate 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

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Prescribing Information

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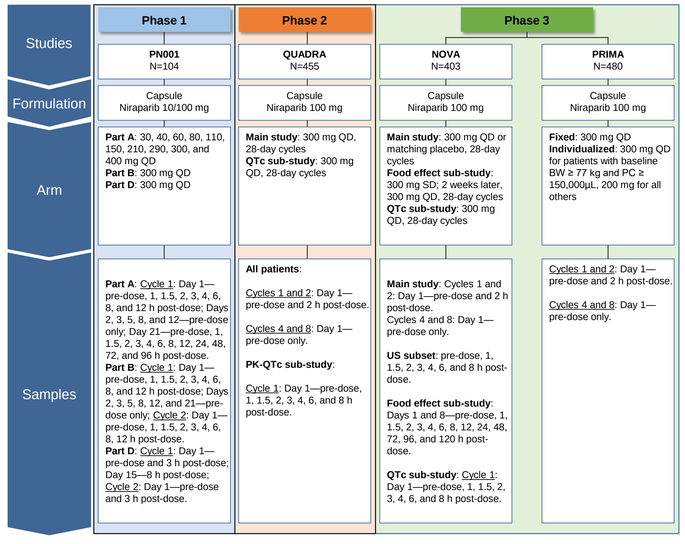
Introduction

- Niraparib is a poly(ADP-ribose) polymerase (PARP) inhibitor that is approved for treatment in heavily pretreated patients and maintenance treatment of patients with newly diagnosed or recurrent ovarian cancer following a response to platinum-based chemotherapy[1,2]
- In the PRIMA/ENGOT-OV26/GOG-3012 (PRIMA) phase 3 trial, niraparib maintenance treatment significantly improved progression-free survival (PFS) compared with placebo (hazard ratio [HR]: 0.62; 95% confidence interval [CI], 0.50–0.76, *P*<0.001)[3]
- 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
  - 200 mg QD for patients with baseline bodyweight (BW) <77 kg and/or platelet count (PC) <150,000/µL
  - 300 mg QD for patients with baseline BW ≥77 kg and PC ≥150,000/µL

Methods

- The population PK model for niraparib was developed based on 7418 measurable niraparib plasma concentrations from 1442 patients from the following 4 studies: PN001, NOVA, QUADRA, and PRIMA (**Figure 1**)
- Niraparib exposures (area under the concentration–time curve [AUC], average concentration [C_{ave}], maximum concentration [C_{max}], and minimum concentration [C_{min}]) for patients in the PRIMA study were generated for the exposure–response analyses using subject-level PK parameters estimated from the final population PK model
- The relationship between model-predicted niraparib exposure (C_{ave} until progression, death, or censoring) and efficacy (PFS) in PRIMA was evaluated in patients receiving niraparib
  - Model-predicted C_{ave} was discretized into 4 equally sized rank-ordered groups, designated Q1 (ie, values ≤first C_{ave} quartile), to Q4 (ie, values >third C_{ave} quartile) in ascending order of C_{ave}, and HRs were estimated relative to the C_{ave} group Q1
- In PRIMA, the relationship between average model-predicted exposure until AE onset or end of treatment and the incidence of clinically relevant AEs was analyzed using univariate logistic regression in patients receiving niraparib

Figure 1. Studies Included in Population PK Modeling



PN001 enrolled patients with advanced solid tumor or hematologic malignancies. QUADRA enrolled patients with advanced, relapsed, high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who have received ≥3 previous chemotherapy regimens. NOVA enrolled patients with platinum-sensitive ovarian cancer. PRIMA enrolled patients with advanced ovarian cancer following response on first-line platinum-based chemotherapy.
BW=bodyweight; h=hour; PC=platelet count; PK=pharmacokinetic; QD=once daily; QTc= corrected QT interval; SD=single dose; US=United States.

Results

Population PK Model

- Data included in the population PK model are shown in **Table 1**

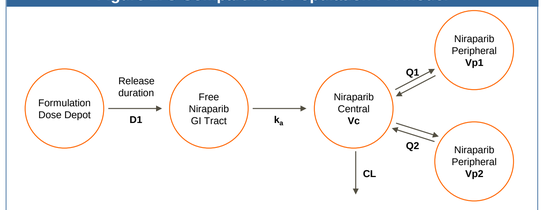
Table 1. Population PK Model Data

Study	PN001 N=104	QUADRA N=455	NOVA N=403	PRIMA N=480	Total N=1442
Patients, n (% of total)	104 (7.2)	455 (31.6)	403 (27.9)	480 (33.3)	1442 (100)
Total observations, n (% of total)	2099 (28)	1424 (19)	2052 (27)	1915 (26)	7490 (100)
BLQ, n (%)	2 (0.1)	13 (0.9)	12 (0.6)	45 (2.4)	72 (1.0)
Non-BLQ, n (%)	2097 (99.9)	1411 (99.1)	2040 (99.4)	1870 (97.6)	7418 (99.0)

BLQ=below the limit of quantification; PK=pharmacokinetic.

- The final population PK model was a 3-compartment model with linear elimination, with a constant (ie, zero-order) rate of drug release into the absorption compartment preceded by a lag time and followed by first-order absorption into the central compartment (**Figure 2**)

Figure 2. 3-Compartment Population PK Model



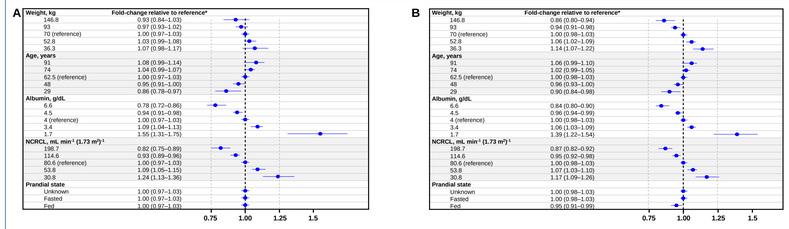
CL=clearance; D1=duration of zero-order drug release; GI=gastrointestinal; k_a=first-order absorption rate constant; PK=pharmacokinetic; Q1=first inter-compartmental clearance; Q2=second inter-compartmental clearance; Vc=central volume of distribution; Vp1=first peripheral volume of distribution; Vp2=second peripheral volume of distribution.

- The following key covariate effects on niraparib PK were identified in the final population PK model (**Figure 3**)
  - Increase in apparent clearance (CL/F) with increasing albumin and body surface area-normalized creatinine clearance (NCRCL)
  - Decrease in CL/F with increasing bodyweight and age
  - Increase in apparent central volume of distribution (Vc/F) with increasing bodyweight
  - Increase in the duration of zero-order drug release (D1) in the fed and unknown prandial states relative to the fasted state
  - Decrease in relative bioavailability (Frel) with increasing bodyweight
- Overall, with the exception of extremely low albumin and NCRCL values, the covariate effects were predicted to result in limited effects on niraparib exposure over the range of covariates in the data set (**Figure 3**)

Efficacy Exposure–Response Analysis

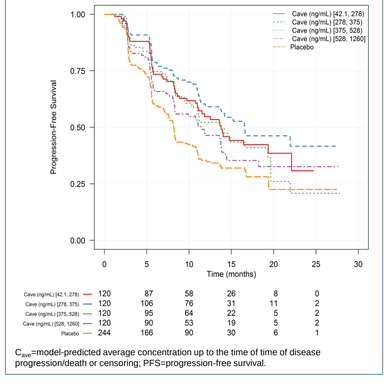
- The efficacy exposure–response analysis for PFS included data from 480 patients randomized to niraparib in the PRIMA study who had PK and PFS data
- Patients in the 200-mg ISD and 300-mg FSD groups were approximately evenly represented across all exposure quartiles
- There was no consistent exposure–response relationship among the discretized exposure groups (**Figure 4**)
  - Overall, the survival curves largely overlapped, except for a clear separation from the placebo arm survival curve, indicating a lack of consistent exposure–response over the range of C_{ave} in the PRIMA study

Figure 3. Effects of Covariates on Niraparib Steady-State AUC (A) and C_{max} (B)



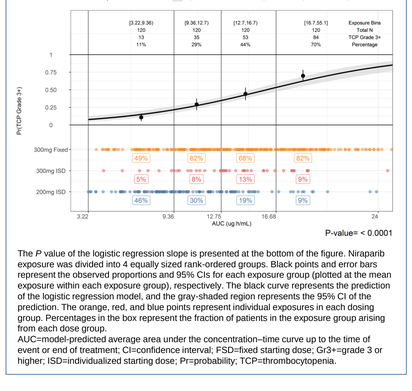
*Note that two drug formulations are generally considered bioequivalent if the exposure of the test formulation is within 25% of the exposure of the reference (gray dotted lines).
ALB=albumin; AUC=area under the concentration–time curve; CI=confidence interval; C_{max}=maximum concentration; NCRCL=body surface area-normalized creatinine clearance; QD=once daily.

Figure 4. PFS by Model-Predicted C_{ave} Group in Overall Population



C_{ave}=model-predicted average concentration up to the time of time of disease progression/death or censoring; PFS=progression-free survival.

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



P-value= < 0.0001

The *P* value of the logistic regression slope is presented at the bottom of the figure. Niraparib exposure was divided into 4 equally sized rank-ordered groups. Black points and error bars represent the observed proportions and 95% CIs for each exposure group (plotted at the mean exposure within each exposure group), respectively. The black curve represents the prediction of the logistic regression model, and the gray-shaded region represents the 95% CI of the prediction. The orange, red, and blue points represent individual exposures in each dosing group. Percentages in the box represent the fraction of patients in the exposure group arising from each dose group.
AUC=model-predicted average area under the concentration–time curve up to the time of event or end of treatment; CI=confidence interval; FSD=fixed starting dose; Gr3+=grade 3 or higher; ISD=individualized starting dose; Pr=probability; TCP=thrombocytopenia.

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, C_{max}, and C_{min}) and increasing probability of experiencing any grade and grade ≥3 AEs for all the safety endpoints with the exception of grade ≥3 hypertension
  - Statistically significant exposure–response relationships for grade ≥3 hypertension were absent for AUC and C_{min} and weak for C_{max}
- The incidence of AEs, including thrombocytopenia, was lower in patients in the 200-mg ISD group

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