



Original Research

Niraparib Population Pharmacokinetics and Exposure-Response Relationships in Patients With Newly Diagnosed Advanced Ovarian Cancer



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Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AUC_{ss}, steady-state area under the concentration-time curve based on starting dose; BLQ, below the limit of quantification; BSA, body surface area; BSV, between-subject variability; BW, body weight; C_{ave}, model-predicted average concentration up to the time of disease progression/death or censoring; CL, clearance; CL/F, apparent clearance; CR, complete response; CrCl, creatinine clearance; CV, coefficient of variation; CWRES, conditional weighted residual; D1, duration of zero-order drug release; ECOG, Eastern Cooperative Oncology Group; F_{rel}, relative bioavailability; FSD, fixed starting dose; GI, gastrointestinal; HRD, homologous recombination deficiency; HRd, homologous recombination-deficient; HRnd, homologous recombination not determined; HRP, homologous recombination-proficient; IIV, interindividual variability; IPRED, individual predicted concentration; ISD, individualized starting dose; K_a, first-order absorption rate constant; LOESS, locally weighted scatterplot smoothing; nCrCl, body surface area normalized creatinine clearance; OBS, observations; OC, ovarian cancer; pcVPC, prediction-corrected visual predictive check; PFS, progression-free survival; PLT, baseline platelet count; PR, partial response; prand, prandial; PRED, population-predicted concentration; PS, performance status; Q1, first intercompartmental clearance; Q1/F, apparent first intercompartmental clearance; Q2, second intercompartmental clearance; Q2/F, apparent second intercompartmental clearance; QD, once daily; RSE, relative standard error; T_{lag}, lag time; Vc, central volume of distribution; Vc/F, apparent central volume of distribution; Vp1, first peripheral volume of distribution; Vp1/F, apparent first peripheral volume of distribution; Vp2, second peripheral volume of distribution; Vp2/F, apparent second peripheral volume of distribution; VPC, visual predictive check.

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ABSTRACT

Purpose: Niraparib is a poly(adenosine diphosphate [ADP]-ribose) polymerase inhibitor approved for the maintenance treatment of advanced ovarian cancer (OC). Niraparib was originally approved in recurrent OC at a fixed starting dose (FSD) of 300 mg once daily (QD). This analysis characterized the population pharmacokinetics (PK) of niraparib and evaluated the relationships between exposure, efficacy, and safety to support clinical use of an individualized dosing strategy, in which the starting dose of niraparib was adjusted based on patient characteristics to improve the benefit-risk profile.

Methods: A population PK model was developed by pooling data from four niraparib clinical trials (PN001 [$n = 104$], QUADRA [$n = 455$], NOVA [$n = 403$], and PRIMA [$n = 480$]) in patients with solid tumors, including OC. Exposure-response analyses were conducted to explore the relationships of niraparib exposure with progression-free survival (PFS) and adverse events in the PRIMA study. A multivariate logistic regression model was also developed to estimate the probability of grade ≥ 3 thrombocytopenia, using data from patients enrolled in PRIMA and NOVA. The impact of an individualized starting dose (ISD) regimen (200 mg QD in patients with body weight [BW] < 77 kg or platelet count [PLT] $< 150,000/\mu\text{L}$, or 300 mg QD in patients with BW ≥ 77 kg and PLT $\geq 150,000/\mu\text{L}$) on systemic exposure, efficacy, and safety was assessed.

Findings: Niraparib disposition was best described by a 3-compartment model with linear elimination. Key covariates included baseline creatinine clearance, BW, albumin, and age, all of which had minor effects on niraparib exposure. Comparable model-predicted exposure up to the time of disease progression/death or censoring in the 300-mg FSD and 200-/300-mg ISD groups was consistent with the lower rate of dose reduction in the ISD groups. No consistent niraparib exposure-response relationship was observed for efficacy in all PRIMA patients (first-line OC), and no statistically significant difference was seen in PFS curves for patients receiving a niraparib dose of 200 mg versus 300 mg. In the multivariate regression model, performed using combined data from PRIMA and NOVA, higher niraparib exposure (area under the concentration-time curve at steady-state [AUC_{ss}]), lower BW, and lower PLT were associated with an increased risk of grade ≥ 3 thrombocytopenia.

Implications: Population PK and exposure-response analyses support use of an ISD to improve the safety profile of niraparib, including reducing the rate of grade ≥ 3 thrombocytopenia, without compromising efficacy.

Clinical trial registration: ClinicalTrials.gov, NCT01847274 (NOVA), NCT00749502 (PN001), NCT02655016 (PRIMA), NCT02354586 (QUADRA), www.clinicaltrials.gov.

Introduction

Niraparib is a highly selective inhibitor of poly(adenosine diphosphate [ADP]-ribose) polymerase (PARP) 1/2 that has demonstrated efficacy and a manageable safety profile across various populations of patients with epithelial ovarian cancer (OC).^{1–7} Niraparib was first approved in the United States and Europe in 2017 as a maintenance treatment for adults with recurrent epithelial OC following a complete or partial response to platinum-based chemotherapy.^{2,8,9} Based on data from the PRIMA/ENGOT-OV26/GOG-3012 (PRIMA) phase III trial, niraparib was approved in the United States in 2020 as a first-line maintenance therapy for adults with newly diagnosed, advanced OC that responded to first-line platinum-based chemotherapy.^{8,9} Approval was based on results demonstrating that niraparib maintenance treatment significantly extended progression-free survival (PFS) relative to placebo in the overall population (13.8 vs 8.2 months; hazard ratio, 0.62; 95% confidence interval [CI], 0.50–0.76; $P < 0.001$) and in patients with homologous recombination-deficient (HRd) tumors (21.9 vs 10.4 months; hazard ratio, 0.43; 95% CI, 0.31–0.59; $P < 0.001$).⁴ Updated long-term efficacy data, with a median follow-up duration of ≈ 3.5 years, were consistent with the findings of the primary analysis (median PFS in the overall population: 13.8 months in the niraparib arm vs 8.2 months in the placebo arm; hazard ratio, 0.66; 95% CI, 0.56–0.79; $P < 0.001$; median PFS in the HRd population: 24.5 months in the niraparib arm vs 11.2 months in the placebo arm; hazard ratio, 0.52; 95% CI, 0.40–0.68; $P < 0.001$).¹⁰ Niraparib is also approved in the United States for use in adult patients with germline *BRCA*-mutated recurrent epithelial OC that has responded to platinum-based chemotherapy⁸ and is approved in Europe for the maintenance treatment of patients with platinum-sensitive, relapsed, high-grade serous epithelial OC that has responded to platinum-based chemotherapy.⁹

Antitumor activity with niraparib monotherapy was initially observed in a phase I study of patients with solid tumors, in which the maximum tolerated dose of 300 mg once daily (QD) was established.¹¹ Subsequently, niraparib 300 mg was recommended as the starting therapeutic dose in PRIMA based on positive efficacy, safety, and quality-of-life data from the phase III, double-blind, placebo-controlled ENGOT-OV16/NOVA trial (NOVA).^{2,8,9} Similar to other PARP inhibitors,¹² niraparib is associated with grade ≥ 3 hematologic toxicities.^{8,9} In NOVA, the most common grade 3 to 4 hematologic adverse events (AEs) were thrombocytopenia (34%), anemia (25%), and neutropenia (20%).² Most AEs were reported within the first 3 treatment cycles and were effectively managed by dose modifications.² Overall, 80% of patients who received niraparib in NOVA required a dose interruption, and 73% required a dose reduction to 200 or 100 mg.⁷ The dose reduction rate due to AEs was 67%, and the discontinuation rate due to AEs was 15%, including 3% attributed to thrombocytopenia.² A post hoc analysis of the NOVA trial demonstrated that incidences of the most commonly reported grade ≥ 3 AEs (except anemia) were highest with niraparib 300 mg QD and lower with 200 and 100 mg QD.⁷ Of note, 200 mg QD was the most common dose after dose reductions. Furthermore, baseline body weight (BW) and baseline platelet count (PLT) predicted the development of grade ≥ 3 thrombocytopenia (defined as PLT $< 50,000/\mu\text{L}$) within 30 days after the first dose of niraparib. Patients with a baseline BW < 77 kg or PLT $< 150,000/\mu\text{L}$ received a mean niraparib daily dose of approximately 200 mg due to dose reduction and interruption. Importantly, PFS in patients whose dose was reduced to 200 or 100 mg QD was similar to that of patients who remained at the 300-mg QD starting dose.⁷ Consequently, a protocol amendment was introduced during the PRIMA trial that changed the starting dose from a fixed starting dose (FSD) of niraparib 300 mg QD in all patients to an individualized starting dose (ISD) regimen.⁴ Under the ISD

regimen, patients with baseline BW <77 kg or PLT <150,000/ μ L received niraparib 200 mg QD, whereas patients with baseline BW $\geq$ 77 kg and PLT $\geq$ 150,000/ μ L received niraparib 300 mg QD.^{4,7} The incidence of grade $\geq$ 3 hematological TEAEs, including thrombocytopenia, was lower in patients in the ISD group (the rates of grade $\geq$ 3 thrombocytopenia, anemia, and neutropenia in the FSD and ISD groups were 48.3% and 21.3%; 35.6% and 23.8%; and 22.5% and 14.8%, respectively).¹³

The fraction of an oral dose of niraparib 300 mg that reaches the systemic circulation unchanged is approximately 73% in adults with breast, ovarian, or fallopian tube cancer.¹⁴ Systemic niraparib exposure increases dose-proportionally following oral administration of ascending doses of niraparib 30 to 400 mg in patients with cancer.¹¹ After single oral administration of niraparib, the time to maximal plasma concentration ($t_{\max}$) occurs within 3 hours, with a mean terminal half-life ($t_{1/2}$) in plasma of 48 to 51 hours.^{8,15} Niraparib is moderately protein-bound in human plasma (83%) and has a large apparent volume of distribution, estimated as 1311 L.^{8,15} It undergoes hydrolysis by carboxylesterases to form a major inactive metabolite, which subsequently undergoes glucuronidation.^{8,9} Niraparib-derived entities are excreted primarily in urine (approximately 50%) and feces (approximately 40%).¹⁶ Pharmacodynamic analyses revealed that niraparib-mediated PARP inhibition in peripheral blood mononuclear cells exceeded 50% at doses greater than 80 mg QD, and antitumor activity was documented at doses greater than 60 mg QD.¹¹

Applying population pharmacokinetic (PK) analysis to explore the potential benefits of tailoring drug dose based on individual patient characteristics is of paramount importance for patients with OC because of the heterogeneous nature of the underlying population.^{17–19} Here we report on population PK modeling and exposure-response analyses to support the use of individualized niraparib dosing regimens in patients with OC that minimize toxicity while maintaining efficacy. The population PK model developed in this study was used to evaluate sources of PK variability as well as the relationship of niraparib exposure with safety and PFS in the PRIMA trial.

Methods

Study Designs, Patient Populations, and Conduct

The population PK model for niraparib was developed based on measurable plasma niraparib concentrations from patients with cancer who participated in the following four studies: PN001 (NCT00749502),¹¹ QUADRA (NCT02354586),³ NOVA (NCT01847274),² and PRIMA (NCT02655016)²⁰ (Figure S1). Conduct, design, eligibility criteria, patient-related baseline characteristics, and outcomes for each study were described previously.^{2,3,11,20} In particular, the double-blind phase III PRIMA trial evaluated PFS in 733 patients with newly diagnosed, platinum-sensitive, stage III or IV OC (including fallopian and peritoneal cancers) who were randomly assigned (2:1) to maintenance therapy with niraparib ($n = 487$) or placebo ($n = 246$).²⁰ Randomization was stratified according to clinical response after first-line platinum-based chemotherapy (complete or partial response), receipt of neoadjuvant chemotherapy (yes or no), and tumor HRd versus HR proficient (HRp) or HR not determined (HRnd).²⁰

All four studies received institutional review board approvals at the participating centers and were conducted in accordance with Good Clinical Practice guidelines consistent with the Declaration of Helsinki, as well as applicable national and local regulatory requirements. Written informed consent was obtained for all participants. Population PK model development was performed in line with standard practice (Supplemental [Online Only] Appendix).^{18,21} Exposure-response analyses from the PRIMA study were conducted according to current best practice (Supplemental [Online Only] Appendix).²²

Bioanalysis

Niraparib concentrations in plasma were determined using validated liquid chromatography-tandem mass spectrometry.²³ The assays were sensitive and specific with an appropriate dynamic range of 1 to 500 ng/mL. Samples with niraparib concentrations below the assay quantitation limit were treated as missing and excluded from the population PK analysis.

Population PK Analysis

The population PK analysis was conducted using NONMEM version 7.3 (ICON, Hanover, MD, USA) (Supplemental [Online Only] Appendix: Model development). Covariates evaluated for their impact on the niraparib base population PK model were sex, race, age, BW, body mass index (BMI), cancer diagnosis, homologous recombinant deficiency (HRD) status, *BRCA* status, body surface area normalized creatinine clearance (nCrCl), albumin, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, bilirubin, PLT, and Eastern Cooperative Oncology Group (ECOG) performance status at baseline (full model approach shown in Supplemental [Online Only] Appendix Table SI). The effect of covariates was modeled as follows:

$$\text{continuous covariates: } P_{ki} = \theta_k \times \left(\frac{X_{ij}}{X_{j,ref}} \right)^{\theta_j}$$

$$\text{categorical covariates: } P_{ki} = \theta_k \times (1 + \theta_j)^{X_{ij}}$$

where P_{ki} is the population estimate of the parameter P_k for patient i ; θ_k is the typical value of the parameter P_k ; X_{ij} is the continuous covariate value for patient i ; $X_{j,ref}$ is the reference value for the continuous covariate; X_j is the categorical covariate indicator variable for patient i , with a value of 1 for the nonreference category and 0 for the reference category; and θ_j is a coefficient that represents the effect of covariate X_j on the parameter investigated and represents the fractional increase from the typical parameter value for categorical covariates.

Standard diagnostic plots were used throughout model development to assess the ability of each model to describe the observed data (Supplemental [Online Only] Appendix: Model evaluation).²⁴ Bootstrap resampling techniques were used to evaluate the stability of the final model and estimate CIs for the model parameters. Prediction-corrected visual predictive checks (pcVPCs) were performed using 1000 simulated replicates to evaluate the predictive ability of the final model.²⁵

Efficacy and Safety Exposure-Response Analyses in PRIMA

Niraparib-treated patients evaluated for efficacy in PRIMA or evaluated for safety in PRIMA or NOVA were included in the exposure-response analyses. The efficacy endpoint (ie, PFS) was treated as a time-to-event variable, and the safety endpoint (grade $\geq$ 3 thrombocytopenia) was treated as a binary variable. Niraparib area under the concentration-time curve at steady state (AUC_{ss}) values were generated using individual PK parameters estimated from the final population PK model for use in the exposure-response analyses (see Figure S1 for sample collection schedules).

For the exposure-response analysis of PFS, Kaplan–Meier plots, stratified by model-predicted niraparib exposure groups, were generated. Model-predicted AUC_{ss} was discretized into four quartiles, designated Q1 (values $\leq$ 25th percentile of AUC_{ss}) to Q4 (values $>$ 75th percentile of AUC_{ss}). A Cox regression analysis was performed using the AUC_{ss} associated with starting dose and HRD status as explanatory variables. AUC_{ss} was treated as a continuous variable. HRD and *BRCA* status were found to be highly correlated; thus, only HRD status was tested as the explanatory variable in the Cox regression model because of its lower Akaike information criterion (AIC) value in a univariate Cox proportional hazard model compared to *BRCA* status. Hazard ratios and associated P values and 95% CIs were estimated for the covariates included in the final PFS model, with HRp as the reference.

A multivariate logistic regression model was developed to evaluate the relationship of the probability of grade ≥ 3 thrombocytopenia to model-predicted niraparib AUC_{ss} and patient baseline characteristics using combined data from patients in PRIMA and NOVA who received the niraparib 300-mg FSD. As a first step, the full model was estimated with the following explanatory variables: AUC, BW, PLT, age, and ECOG status. Backward deletion was then performed using the step AIC function in the MASS package²⁶ in R,²⁷ which used an increase in AIC of any amount as the criterion for deletion. The model arising from this step was considered the final model for the exposure-response analysis of grade ≥ 3 thrombocytopenia.

Results

PK Measurements and Baseline Patient-Related Characteristics

The population PK modeling analysis dataset used for initial model development comprised 7418 quantifiable plasma niraparib concentrations from 1442 patients (Table 1). The PN001 study ($n = 104$ [7%]) contributed proportionately more observations ($n = 2099$ [28%]) than the other studies because of intensive PK sampling. Data from 480 (33%) patients from the PRIMA study in the analysis dataset contributed 1915 (26%) observations. Most patients were women ($n = 1411$ [97.9%]) with advanced OC (including fallopian and peritoneal cancers; $n = 1386$ [96.1%]) and an ECOG performance status of 0 or 1 ($n = 1437$ [99.7%]) (Supplemental [Online Only] Appendix Table SII).

Base Structural Population PK Model

The concentration-time profiles observed for niraparib in each of the four studies are illustrated in Figure S2 (Supplemental [Online Only] Appendix). The base model was a 3-compartment model with linear elimination and the following features: (1) zero-order release rate of niraparib into the absorption compartment, preceded by a lag time and followed by first-order absorption into the central compartment; (2)

between-subject variability (BSV) on apparent central clearance (CL/F), first-order absorption rate constant (K_a), duration of zero-order drug release (D1), relative bioavailability (F_{rel}), and apparent second peripheral volume of distribution ($Vp2/F$); and (3) separate additive error components by study on log-transformed data. When this model was fit to all data, 41 data points had absolute values of the conditional weighted residual ($|CWRES|$) > 4 and were excluded from the model. The resulting base model had 7377 data points from 1442 patients after exclusion of these points. Parameter estimates for the base model are presented in Supplemental (Online Only) Appendix Table SIII. All parameters were estimated precisely with relative standard errors of $< 20\%$. Goodness-of-fit plots for the base model indicated a good fit to the data.

Final Population PK Model

The final population PK model had the same model structure as the base model (Figure 1). The following covariate effects on niraparib PK were identified: (1) increase in CL/F with increasing albumin and nCrCl, (2) decrease in CL/F with increasing age, (3) increase in apparent central volume of distribution (Vc/F) with increasing BW, and (4) increase in D1 in the fed and unknown prandial states relative to the fasted state (prandial state was deemed as unknown when doses were administered without regard to food). Parameter estimates for the final population PK model, including bootstrap estimates and 95% CIs, are provided in Table 2. Goodness-of-fit plots for the final model indicate a good fit to the data (Supplemental [Online Only] Appendix Figure S3), with random effect versus covariate plots for the final PK model indicating no important residual covariate effects (not shown). The pcVPCs showed that the model adequately described the central tendency and distribution of the observations overall (Supplemental [Online Only] Appendix Figure S4). As a sensitivity analysis, the refined PK model was re-estimated on the initial analysis dataset of 7418 observations including the 41 observations with $|CWRES| > 4$ that had been excluded from the base model. The parameter estimates were very similar to those from the final re-

Table 1
Patients and observations in the population PK analysis dataset.

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

BLQ = below the limit of quantification (< 1 ng/mL); n = total number of observations; PK = pharmacokinetic.

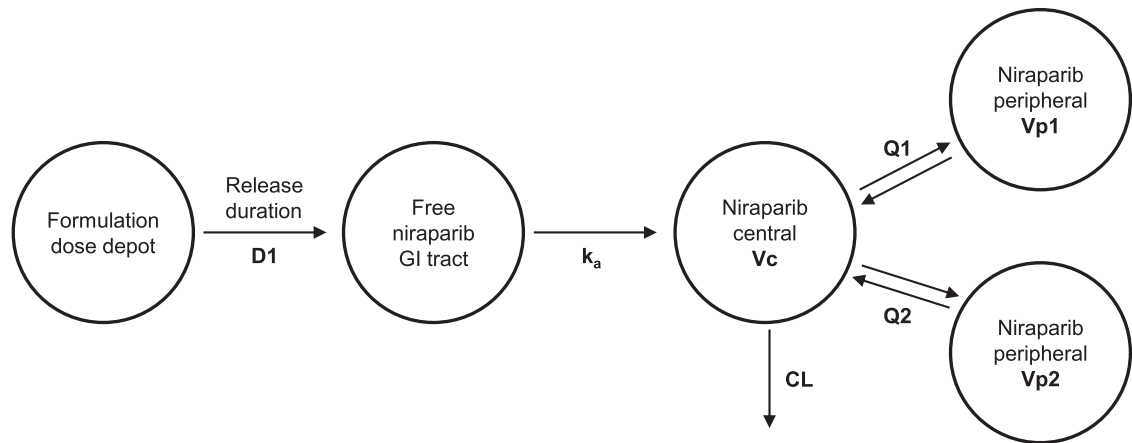


Figure 1. Diagram of the final population PK model for niraparib. CL, clearance; D1, duration of zero-order drug release; GI, gastrointestinal; K_a , first-order absorption rate constant; PK, pharmacokinetic; Q1, first intercompartmental clearance; Q2, second intercompartmental clearance; Vc, central volume of distribution; Vp1, first peripheral volume of distribution; Vp2, second peripheral volume of distribution.

Table 2
Parameter estimates for the final population PK model.

Parameter	Fixed effects		Bootstrap median of estimate (95% CI)	BSV CV		Bootstrap median of BSV CV, % (95% CI)	Shrinkage, %
	Estimate	RSE, %		Estimate, %	RSE, %		
Fixed effects typical values and IIV CV							
CL/F, L/h	16.5	1.4	16.5 (16.0–16.9)	23.4	3.6	23.1 (19.1–26.9)	39.9
Vc/F, L	424	2.2	418 (379–452)	0 Fixed	N/A	N/A	N/A
Q1/F, L/h	1.37	6.1	1.37 (0.979–1.78)	0 Fixed	N/A	N/A	N/A
Vp1/F, L	312	4.0	313 (274–359)	0 Fixed	N/A	N/A	N/A
K _a , 1/h	1.04	5.2	1.03 (0.850–1.21)	72.8	5.3	70.7 (54.1–88.3)	56.4
D1, fasted, h	0.235	34.9	0.219 (0.0930–0.354)	225	4.1	232 (173–349)	43.5
T _{lag} , h	0.473	2.3	0.469 (0.393–0.575)				
F _{rel} (–)	1 Fixed	N/A	N/A	30.9	3.3	30.9 (27.7–34.3)	31.5
Q2/F, L/h	68.3	2.5	69.4 (60.5–81.5)	0 Fixed	N/A		N/A
Vp2/F, L	575	7.1	582 (509–661)	116	4.2	113 (87.7–146)	51.5
CL/F: age exponent	–0.184	36.1	–0.183 (–0.369 to –0.0188)				
CL/F: albumin exponent	0.500	17.4	0.488 (0.310–0.663)				
CL/F: nCrCl exponent	0.230	18.4	0.240 (0.145–0.327)				
Vc/F: BW exponent	0.470	11.9	0.461 (0.270–0.629)				
D1: fed fractional change	15.2	22.1	16.7 (7.10–28.3)				
D1: unknown prandial state fractional change	1.39	59.7	1.46 (0.610–3.75)				
Residual error							
Residual variability: SD PN001, log (ng/mL)	0.214	0.8	0.214 (0.196–0.233)				
Residual variability: SD NOVA, log (ng/mL)	0.330	1.0	0.330 (0.297–0.361)				
Residual variability: SD QUADRA, log (ng/mL)	0.380	1.5	0.379 (0.341–0.422)				
Residual variability: SD PRIMA, log (ng/mL)	0.455	1.3	0.455 (0.423–0.491)				

Reference values were 70 kg for BW, 62.5 years for age, 4 g/dL for albumin, and 80.6 mL/min/1.73 m² for nCrCl. One crashed run and 512 runs with minimization terminated were not included in the bootstrap calculations. An additive residual error model on log-transformed concentrations was used for the current model. BSV % was calculated as sqrt (exp [OMEGA] – 1) × 100%, where OMEGA is the BSV variance.

BSV = between-subject variability; BW = body weight; CI = confidence interval; CL/F = apparent clearance; CV = coefficient of variation; D1 = duration of zero-order drug release; F_{rel} = relative bioavailability; IIV = interindividual variability; K_a = first-order absorption rate constant; N/A = not applicable; PK = pharmacokinetic; nCrCl = body surface area normalized creatinine clearance; Q1/F = apparent first intercompartmental clearance; Q2/F = apparent second intercompartmental clearance; RSE = relative standard error; T_{lag} = lag time; Vc/F = apparent central volume of distribution; Vp1/F = apparent first peripheral volume of distribution; Vp2/F = apparent second peripheral volume of distribution.

fined model that excluded the high-residual data points (Supplemental [Online Only] Appendix Table SIV).

Figure 2 depicts the ratio (95% CI) of steady-state exposures at selected covariate values relative to the corresponding values in a reference patient (BW 70 kg, age 62.5 years, albumin 4 g/dL, nCrCl 80.6 mL/min/1.73 m², and administered niraparib in the fasted state). With the exception of extremely low albumin and nCrCl values, the covariate effects were predicted to result in minor effects on niraparib exposure (AUC and C_{max}) over the range of covariates in the dataset (≤26% change in exposure relative to the reference value). BW was predicted to have no effect on AUC and a minor effect on C_{max}. Prandial state was predicted to have little to no effect on niraparib exposure. The model predicted decreasing niraparib exposures with increasing serum albumin. Minor albumin effects were estimated for most patients, with AUC ratios of 0.78 (95% CI, 0.71–0.86) at the maximum albumin level (6.6 g/dL) and 1.08 (95% CI, 1.04–1.12) at the 10th percentile (3.4 g/dL). However, for the minimum albumin level of 1.7 g/dL, a 1.52-fold higher AUC (95% CI, 1.30–1.77) was estimated relative to the reference. The next lowest albumin value was 2.3 g/dL, and 97% (1394/1442) of patients had baseline albumin ≥3.0 g/dL. Decreasing niraparib exposures were predicted with increasing nCrCl, giving AUC ratios ranging from 0.81 (95% CI, 0.74–0.88) at the maximum of 198.7 mL/min/1.73 m² to 1.10 (95% CI, 1.05–1.15) at the 10th percentile (53.8 mL/min/1.73 m²). The effect of nCrCl was moderate even for low values of nCrCl. For the minimum value of nCrCl (30.8 mL/min/1.73 m²), AUC was 1.26-fold higher (95% CI, 1.14–1.37) than the reference value. Note that although 232 patients (16.1%) in the analysis dataset had moderate renal impairment, defined as CrCl values of 30 to 59 mL/min, only 26 patients (1.8%) had nCrCl <40 mL/min/1.73 m².

Exposure-Response Analyses

A total of 480 patients receiving niraparib in PRIMA were available for inclusion in the efficacy exposure-response analysis for PFS, of whom

312 patients received a 300-mg FSD of niraparib, 125 patients received 200-mg ISD of niraparib, and 43 patients received 300-mg ISD of niraparib (Supplemental [Online Only] Appendix Table SV). Approximately half of the patients (n = 243 [51%]) randomized to niraparib had HRd tumors. Covariates were evenly distributed across all niraparib starting dose groups. For the exposure-response analysis of grade ≥3 thrombocytopenia, data from 361 patients in NOVA who received 300 mg were added to the 312 patients in PRIMA who received a 300-mg FSD (Supplemental [Online Only] Appendix Table SVI).

Progression-Free Survival

Patients in the 200-mg ISD and 300-mg FSD groups were evenly represented across all exposure quartiles. There was no consistent exposure-response relationship among the discretized niraparib exposure groups (Figure 3). Overall, the PFS curves largely overlapped, indicating a lack of consistent exposure-response relationship over the range of AUC_{ss} in the PRIMA study. There was also no statistically significant difference between the Kaplan–Meier PFS curves for patients receiving a starting niraparib dose of 200 mg versus patients receiving 300 mg (Figure 3). Based on Cox proportional hazard modeling, the final PFS model for all PRIMA patients had model-predicted niraparib AUC_{ss} and HRD status as explanatory variables. Table 3 presents the hazard ratios and 95% CI for the final PFS model, showing that niraparib AUC_{ss} was not a statistically significant factor; however, HRD had a statistically significant association with improved PFS relative to HRp.

Safety

Exploratory univariate logistic regression plots with AUC_{ss}, WT, and PLT indicated that the probability of grade ≥3 thrombocytopenia increased with increasing niraparib exposure and decreased with increasing WT and PLT (Figure S5). The final multivariate regression model evaluating grade ≥3 thrombocytopenia in the combined PRIMA and

NOVA dataset included AUC_{ss}, BW, and PLT as explanatory variables. In the final multivariate model, higher AUC_{ss} ($P < 0.0001$), lower BW ($P < 0.0001$), and lower PLT ($P = 0.0062$) were associated with an increased probability of grade ≥ 3 thrombocytopenia (Table 4). Predictions made based on this model indicated that the highest probability of grade ≥ 3 thrombocytopenia was associated with patients with both low BW and low PLT (Figure 4 and Supplemental [Online Only] Appendix Table SVII). An ISD of 200 mg was predicted to considerably decrease the probability of experiencing grade ≥ 3 thrombocytopenia in patients with low BW and/or low PLT.

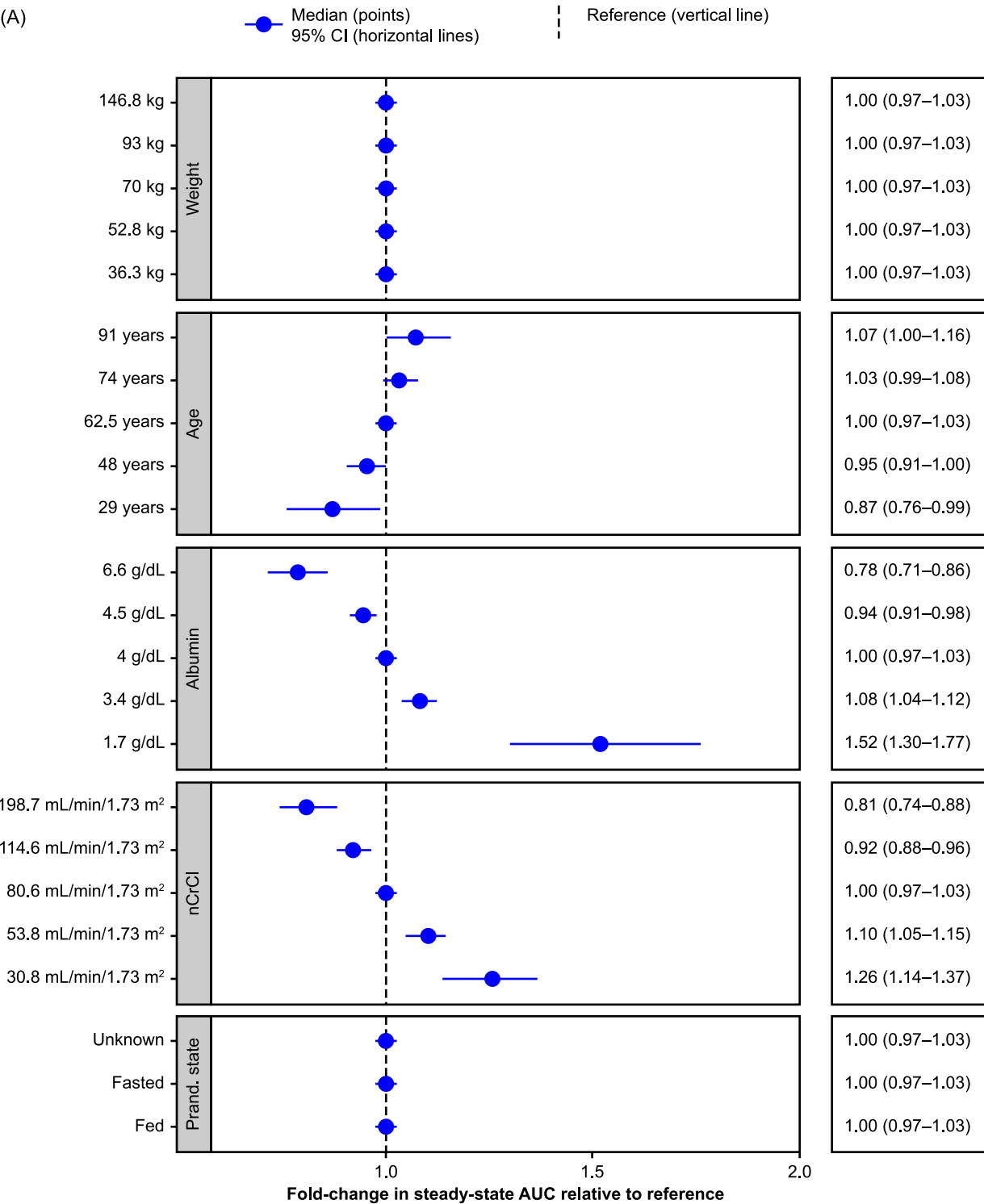


Figure 2. Effects of covariates on niraparib steady-state AUC (A) and C_{max} (B). For all covariate scenarios, all other covariates were maintained at values for the reference patient (weight 70 kg, age 62.5 years, albumin 4 g/dL, nCrCl 80.6 mL/min/1.73 m², and niraparib administered in the fasted state; median 300 mg QD typical steady-state AUC and C_{max} from bootstrap estimates equaled 18,234 ng·h/mL and 1058 ng/mL). Numbers in the right panels represent median (95% CI) values. AUC, area under the concentration-time curve; C_{max} , maximum concentration; nCrCl, body surface area normalized creatinine clearance; prand, prandial; QD, once daily.

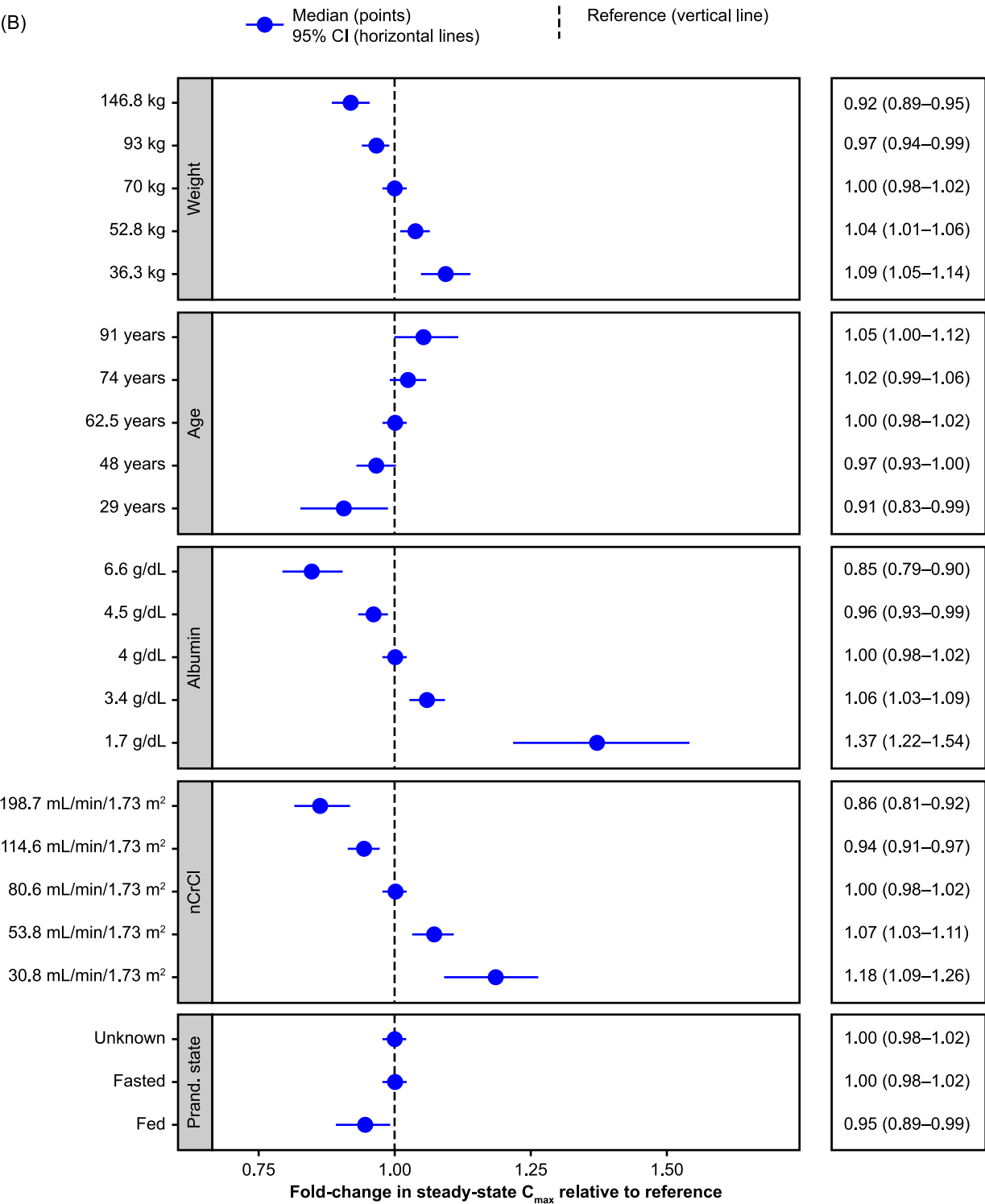


Figure 2. Continued

Discussion

The overarching goal of this large-scale analysis was to assess whether exposure-response data for the ISD regimen support an improvement in the benefit-risk profile of niraparib in patients with OC. Building on the findings from the post hoc analysis of the NOVA trial,^{2,7} population PK and exposure-response models were developed to show that individualizing the starting dose of niraparib would reduce the in-

cidence of any grade and grade ≥ 3 hematologic AEs of interest without compromising efficacy.

Niraparib absorption was well characterized by an absorption model where a zero-order release rate of niraparib into the absorption compartment was preceded by lag time and followed by first-order absorption into the central compartment. Previously, a two-compartment model with first-order absorption and elimination was developed to describe niraparib population PK based on data from Study PN001 and the NOVA

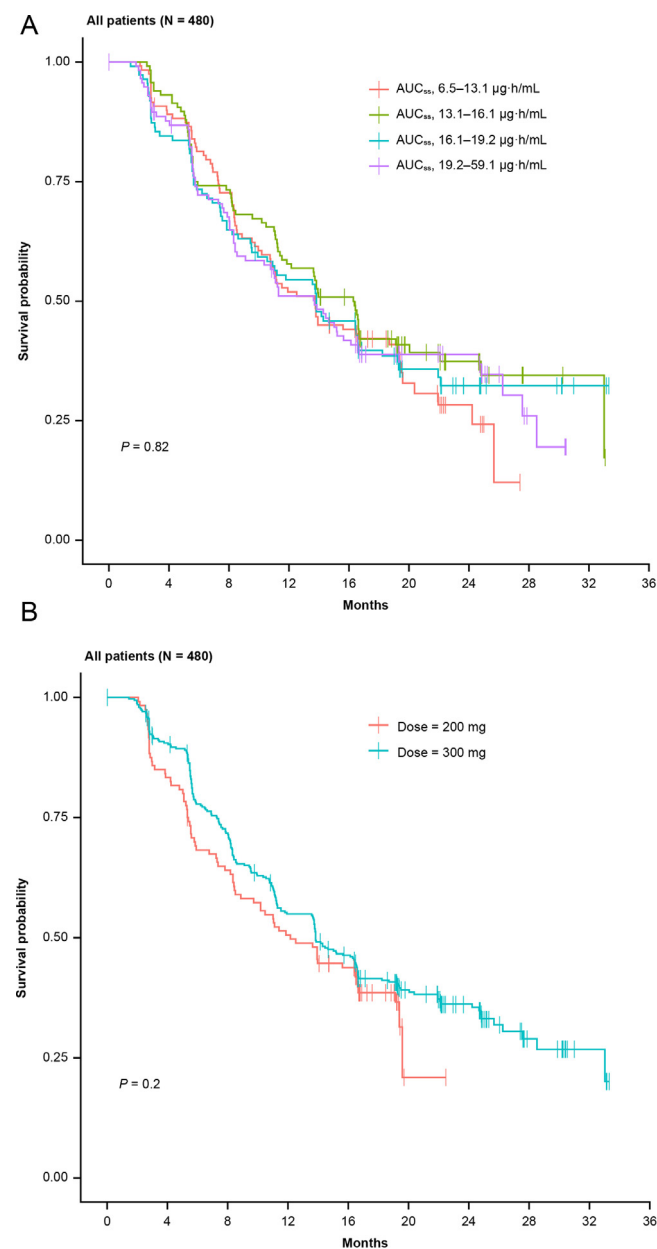


Figure 3. Kaplan–Meier plots of time to disease progression or death in all patients (A) by exposure group (AUC_{ss} of niraparib) and (B) by starting dose. AUC_{ss}, steady-state area under the concentration-time curve based on starting dose.

Table 3
Hazard ratios for the PFS exposure-response model.

Parameter	Hazard ratio	95% CI	P value
AUC _{ss}	0.983	0.958–1.01	0.1854
HRd*	0.350	0.269–0.454	<0.0001
HRnd*	0.787	0.567–1.09	0.1545

AUC_{ss} = steady-state area under the concentration-time curve based on starting dose in µg·h/mL; CI = confidence interval; HRd = homologous recombination-deficient; HRnd = homologous recombination not determined; PFS = progression-free survival.

* Reference category: HRp.

trial.²⁸ In the present work, data from two additional clinical studies (QUADRA and PRIMA) were added to the analysis dataset, and the model was further developed. Niraparib disposition was shown to be well described by a three-compartment model with linear elimination (Supplemental [Online Only] Methods). Covariate effects on niraparib PK were predicted to result in limited effects on niraparib exposure, with the exception of extremely low albumin or nCrCl values.

No consistent niraparib exposure-response relationship was observed for efficacy (PFS) in all PRIMA patients. PFS curves for the four AUC_{ss} quartiles largely overlapped, as did the curves for the two starting dose groups. AUC_{ss} was not statistically significant in the Cox proportional hazard model for PFS and was retained as a variable in the final model to assess exposure-response relationship. HRd had a strong statistically significant association with improved PFS.

The multivariate logistic regression model for grade ≥3 thrombocytopenia revealed that higher AUC_{ss}, lower BW, and lower PLT were associated with an increased risk of grade ≥3 thrombocytopenia. The highest probability of grade ≥3 thrombocytopenia was associated with patients with both low BW and low PLT. These results are consistent with those of the post hoc analysis of the NOVA trial, in which lower baseline BW and PLT were identified as independent risk factors for the development of grade ≥3 thrombocytopenia within 30 days after the first dose of niraparib.⁷ A starting dose of 200 mg of niraparib was predicted to reduce the probability of experiencing grade ≥3 thrombocytopenia, and the model predicted lower rates of grade ≥3 thrombocytopenia in the 200-/300-mg ISD groups than in the 300-mg FSD group.

Prospective evaluation of niraparib 200-/300-mg ISD and 300-mg FSD regimens in PRIMA confirmed lower rates of hematologic TEAEs in the niraparib ISD group, whereas efficacy was similar overall in the ISD and FSD groups.¹³ Together, these findings support the use of an ISD (200 mg QD in patients with low BW [<77 kg] or PLT [<150,000/µL] and 300 mg QD in patients with both high BW and PLT), as it improves tolerability and reduces dose interruptions and reductions without impacting overall efficacy.

A potential limitation of the niraparib exposure-response analyses in PRIMA is the distillation of all longitudinal data for a patient into a single record, resulting in a loss of information. For the efficacy and safety exposure-response analyses, the necessity of providing a single summary exposure measure for each patient may lead to biased exposure values. Since mixed-effects modeling was not used in the exposure-response analyses, BSV in the effects of exposure or other covariates could not be estimated. Despite these limitations, the exposure-response analyses were able to provide a useful assessment of the proposed dosing paradigm.

Another potential limitation of the analyses is the fact that the ISD was based on baseline BW rather than BMI. The ISD regimen for niraparib in PRIMA was implemented based on the results of the post hoc analysis of the NOVA trial, in which baseline BW (<77 kg) and baseline PLT (<150,000/µL) predicted the development of grade ≥3 thrombocytopenia within 30 days after the first dose of niraparib.⁷ This approach was consistent with that outlined in the American Society of Clinical Oncology clinical practice guideline, which recommends a weight-based approach to dosing and dosage adjustments for cytotoxic chemotherapy, immunotherapeutic agents, and targeted therapies rather than body surface area or BMI-based dosing.^{29,30} Because grade ≥3 TEAEs, serious AEs, and TEAEs leading to dose modification or treatment discontinuation occurred more frequently in patients with a BW <58 kg at baseline than in patients with a BW ≥77 kg at baseline in that analysis, adjusting the ISD based on BMI instead of BW is not anticipated to significantly alter the outcomes of the present study. However, this possibility cannot be ruled out.

Combination therapy with PARP inhibitors, including niraparib, is being investigated for its potential to increase advanced OC treatment efficacy while overcoming innate and acquired PARP inhibitor resistance.³¹ It is anticipated that the improved tolerability associated with niraparib ISD as monotherapy will translate into improved tolerability

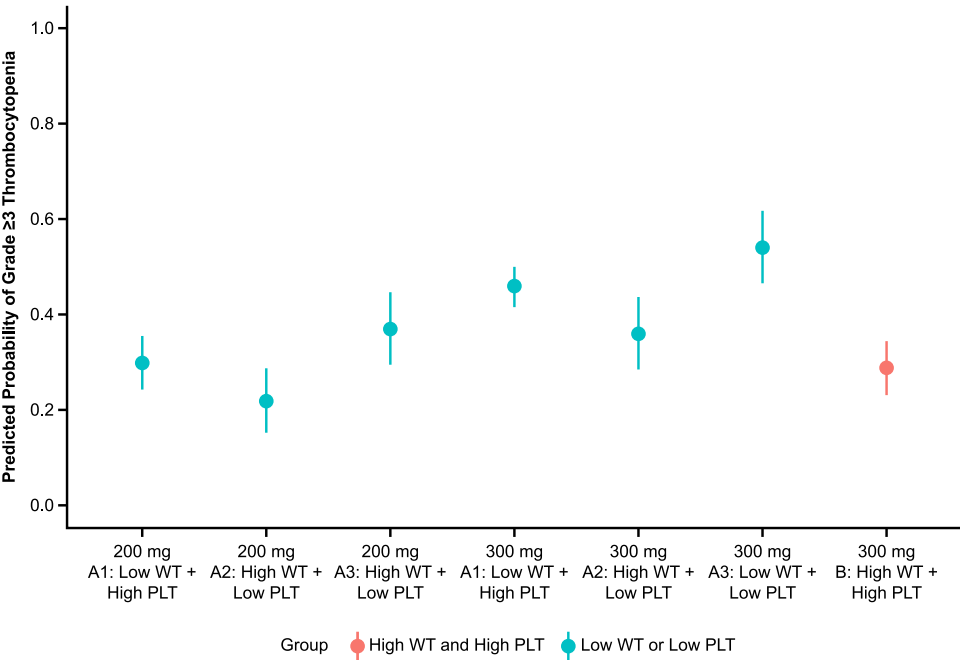


Figure 4. Predictions of the probability of grade ≥ 3 thrombocytopenia. The closed circles represent the predicted probability of grade ≥ 3 thrombocytopenia, and the vertical lines span the 95% CI of the predictions. CI, confidence interval; grade ≥ 3 , grade 3 or higher; PLT, baseline platelet count; WT, baseline body weight.

Table 4
Relationship between AUC_{ss}, baseline platelet count, and BW and the probability of grade ≥ 3 thrombocytopenia.

Coefficient	Units	Estimate	RSE	P value	Odds ratio (95% CI)
Intercept		0.317	181.8%	0.5825	
AUC _{ss}	1/($\mu\text{g}\cdot\text{h}/\text{mL}$)	0.122	15.5%	<0.0001	1.13 (1.09–1.17)
Baseline BW	1/kg	−0.0304	20.0%	<0.0001	0.97 (0.958–0.981)
Baseline platelet count	1/(10 ³ / μL)	−0.00302	36.5%	0.0062	0.997 (0.995–0.999)

AUC_{ss} = steady-state area under the concentration-time curve based on starting dose; BW = body weight; CI = confidence interval; RSE = relative standard error.

when combined with other agents associated with an increased risk of thrombocytopenia; however, future studies examining how combination therapy impacts the incidence of TEAEs are warranted. Additionally, long-term exposure-response analyses, particularly in the maintenance treatment and recurrent OC treatment settings, are required to better characterize the impact of the ISD on thrombocytopenia risk.

Conclusions

In conclusion, the results of the niraparib population PK and exposure-response analyses support clinical observations that implementing a dose of 200 mg in patients with a baseline BW <77 kg or baseline PLT <150,000/ μL would reduce the incidence of grade ≥ 3 thrombocytopenia.¹³ The efficacy exposure-response analysis suggests that the ISD regimen based on patient characteristics at baseline does not negatively impact PFS, consistent with clinical observations.¹³ Thus, in clinical practice, patients with baseline BW <77 kg or PLT <150,000/ μL should receive a niraparib dose of 200 mg QD, whereas patients with baseline BW ≥ 77 kg and PLT $\geq 150,000/\mu\text{L}$ should receive a niraparib dose of 300 mg QD.^{8,9}

Declaration of competing interest

Bradley J. Monk is an Associate Editor for *Annals of Oncology* and was not involved in the editorial review or the decision to publish this article. The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Bradley J. Monk reports consulting fees from Agenus, Akeso Biopharma, Amgen, Aravive, Bayer, Elevar, EMD Merck, Genmab/Seagen, GOG Foundation, Gradalis, ImmunoGen, Iovance, Karyopharm,

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Supplementary materials

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