Exposure-Response Analysis of the PARP Inhibitor Niraparib to Help Inform Dose Optimization for Patients with Ovarian Cancer

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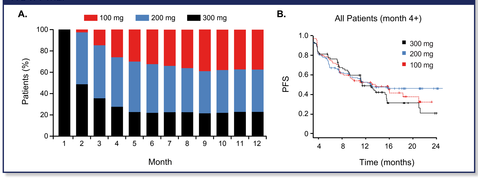
BACKGROUND

- Niraparib (ZEJULA®) is a potent and selective poly(ADP-ribose) polymerase 1/2 inhibitor (PARPi)[1] approved for maintenance treatment of recurrent ovarian cancer in patients with complete response (CR) or partial response (PR) to platinum-based chemotherapy, regardless of biomarker status.[2]
- The large, randomized, double-blind phase 3 ENGOT-OV16/NOVA trial (NCT01847274) showed that niraparib was effective regardless of *BRCA* and/or homologous recombination deficiency (HRD) mutation status, and thus can be used in patients with and without *BRCA* mutations.[2]
  - Patients with germline *BRCA*-mutant disease had a progression-free survival (PFS) with niraparib of 21.0 months vs 5.5 months with placebo (hazard ratio [HR] 0.27; 95% confidence interval [CI] 0.17 to 0.41).
  - Patients with nongermline *BRCA*-mutant disease had a PFS with niraparib of 9.3 months vs 3.9 months with placebo (HR 0.45; 95% CI 0.34 to 0.61).
- All patients started NOVA at 300 mg niraparib per day but could be dose reduced to 200 mg or 100 mg due to treatment-emergent adverse events (TEAEs).
  - Most patients reduced dose during the study (**Figure 1A**).[3]
  - Dose individualization due to TEAEs did not appear to affect efficacy, suggesting exposure remained sufficient to maintain clinical effectiveness at a patient's individualized dose (**Figure 1B**).[4]

Figure 1. Niraparib Dose Level by Month on Treatment (A) and PFS by Dose Level (B) in the NOVA Trial



- Most adverse events were resolved after the first 3 months when patients were dose modified and the incidence of new TEAEs after the first 3 months was rare.[3]
- A retrospective analysis of patient characteristics that would lead to dose reduction due to TEAEs found that patients with a baseline weight of <77 kg or baseline platelet count of <150,000 platelets/µL were most likely to require dose reduction in the first 30 days due to TEAEs.[3]
- This was prospectively confirmed using blinded data in the frontline PRIMA study, where proactively starting patients <77 kg or <150,000 platelets/µL on 200 mg niraparib essentially halved the rates of most TEAEs and greatly reduced thrombocytopenia.[4]
- A new individualized dosing paradigm for niraparib in patients with platinum-sensitive ovarian cancer using baseline body weight and platelet count to select the optimal starting dose is being proposed to improve safety and tolerability while maintaining efficacy.
- Here we present analyses supporting the development of this new dosing paradigm.

OBJECTIVES

- To explore the relationship between niraparib exposure and safety in patients with ovarian cancer
- To explore the relationship between niraparib exposure and PFS in patients with ovarian cancer

METHODS

Development of a Population Pharmacokinetics (PK) Model

- Time-to-event–based niraparib exposures in patients enrolled in the niraparib trial were predicted using individual post hoc PK parameters from a population PK model, development of which has been reported.[5]

Patients

- Patients enrolled in the NOVA trial were eligible for inclusion in these analyses based on the following criteria:
  - Patients randomized to niraparib: evaluable for population PK analysis and evaluated for the relevant endpoint for each analysis
  - Patients randomized to placebo: evaluated for the relevant endpoint for each analysis
- Patients in the placebo group were not included in regression analyses for efficacy exposure-response analyses.

Exposure-Response Analyses for Safety

- Safety endpoints investigated were the occurrence of the following TEAEs at any time during the study (any grade and grade ≥3):
  - Thrombocytopenia (the sum of TEAEs coded as 'thrombocytopenia' and 'platelet count decreased'), anemia, neutropenia, nausea, insomnia, and anxiety.
- Safety endpoints were treated as binary variables.
- The relationship between model-predicted niraparib exposure (area under the concentration-time curve [AUC], maximum concentration [C_{max}], and minimum concentration [C_{min}]) up to the time of event (or time of censoring if no event) and the probability of experiencing TEAEs of a given grade or higher were evaluated using a univariate logistic regression analysis.
  - *P* values were not adjusted for multiplicity and are descriptive only where presented.
- The exposure measure that was the best predictor for each relationship was determined using the Akaike information criterion (AIC).
- A multivariate logistic regression exposure response model was developed for grade ≥3 thrombocytopenia.

Exposure-Response Analyses for Efficacy

- The efficacy endpoint PFS was treated as a time-to-event variable.
- Model-predicted C_{max}, C_{min}, and average concentration (C_{av}; ie, AUC/24) up to the time of event or censoring were evaluated separately as predictors of PFS.
- Separate analyses were done for the germline *BRCA* mutation positive (g*BRCA*mut) cohort, the overall non-g*BRCA*mut cohort, and the homologous recombination deficiency positive (HRDpos) subset of the non-g*BRCA*mut cohort.
- Stratified Cox regression was performed using exposure quartiles as the grouping variable.
- Stratification variables were:
  - Time to progression after penultimate platinum therapy (6 to <12 months or ≥12 months)
  - Bevacizumab use with penultimate or last platinum regimen (yes or no)
  - Best response during last platinum regimen (CR or PR)

RESULTS

Exposure-Response Analyses for Safety

- A total of 540 patients from the NOVA trial (niraparib, N=361; placebo, N=179) were included in the safety exposure-response analyses.
- Baseline characteristics were consistent between the groups (**Table 1**).

Table 1. Baseline Characteristics in the Safety Exposure-Response Analysis Population

Characteristic	Niraparib (N=361)	Placebo (N=179)	Total (N=540)
Age, median (range), y	61 (33, 83)	60 (34, 82)	60 (33, 83)
Cumulative duration of prior platinum therapies, median (range), mo	30.7 (2.6, 228.0)	30.9 (2.1, 233.0)	30.9 (2.1, 233.0)
Hemoglobin, g/L, mean (SD)	117.0 (10.8)	118.0 (10.7)	117.0 (10.8)
Duration of last platinum therapy, median (range), mo	3.9 (0.7, 27.0)	4.0 (0.66, 18.4)	4.0 (0.66, 27.0)
Time since last platinum therapy, median (range), d	42.0 (5.0, 199.0)	41.0 (0, 68.0)	42.0 (0, 199.0)
Neutrophil count, mean (SD), 10^9/L	3.1 (2.1)	3.2 (2.0)	3.1 (2.1)
Platelet count, mean (SD), 10^9/L	234 .0 (82.8)	232.0 (82.4)	233.0 (82.6)
Lines of platinum therapy, median (range)	2 (2, 7)	2 (2, 7)	2 (2, 7)
Body weight, mean (SD), kg	70.0 (16.2)	69.8 (14.2)	69.9 (15.5)
Prior thrombocytopenia, n (%)	167 (46.3)	80 (44.7)	247 (45.7)
Prior myelosuppression, n (%)	293 (81.2)[a]	142 (79.3)	435 (80.6)

[a]Prior myelosuppression was unknown in one patient in the niraparib group.
SD, standard deviation.

- Model-predicted AUC, C_{max}, and C_{min} all had strong, statistically significant associations with the incidence of TEAEs evaluated, with the exception of any grade anxiety (**Table 2**).
  - Based on the value of AIC, model-predicted C_{max} was the best predictor of all safety endpoints with statistically significant exposure-response relationships.
- There was only one event each for grade ≥3 anxiety and grade ≥3 insomnia, so no logistic regression was performed for these TEAEs.

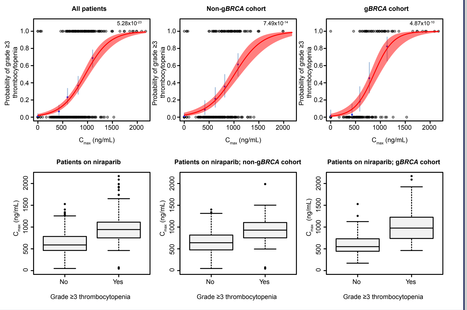
Table 2. Univariate Logistic Regression Results for TEAEs

Adverse Event	Exposure Measure	Intercept	Slope	Slope *P* Value	AIC
Anemia any grade	AUC	-2.55	0.000210	<0.0001	512.42
	C_{max}	-2.64	0.00360	<0.0001	508.94
	C_{min}	-2.5	0.00637	<0.0001	513.07
Anemia grade ≥3	AUC	-3.88	0.000233	<0.0001	366.04
	C_{max}	-4.11	0.00421	<0.0001	360.56
	C_{min}	-3.76	0.00685	<0.0001	368.59
Anxiety any grade	AUC	-2.77	0.0000342	0.195	287.53
	C_{max}	-2.78	0.000571	0.202	287.58
	C_{min}	-2.76	0.00100	0.213	287.66
Insomnia any grade	AUC	-2.85	0.000151	<0.0001	447.59
	C_{max}	-2.91	0.00261	<0.0001	446.82
	C_{min}	-2.79	0.00447	<0.0001	450.24
Nausea any grade	AUC	-0.759	0.000142	<0.0001	595.62
	C_{max}	-0.776	0.00236	<0.0001	595.25
	C_{min}	-0.731	0.00430	<0.0001	597.91
Nausea grade ≥3	AUC	-4.82	0.000123	0.0037	118.36
	C_{max}	-4.84	0.00210	0.0035	118.25
	C_{min}	-4.79	0.00370	0.004	118.52
Neutropenia any grade	AUC	-2.84	0.000167	<0.0001	466.76
	C_{max}	-2.94	0.00293	<0.0001	464.38
	C_{min}	-2.78	0.00498	<0.0001	467.89
Neutropenia grade ≥3	AUC	-3.63	0.000182	<0.0001	348.83
	C_{max}	-3.79	0.00328	<0.0001	346.66
	C_{min}	-3.55	0.00536	<0.0001	351.48
Thrombocytopenia any grade[a]	AUC	-2.54	0.000217	<0.0001	491.36
	C_{max}	-2.65	0.00373	<0.0001	485.99
	C_{min}	-2.47	0.00656	<0.0001	493.08
Thrombocytopenia grade ≥3[a]	AUC	-3.71	0.000229	<0.0001	404.89
	C_{max}	-3.92	0.00409	<0.0001	399.74
	C_{min}	-3.62	0.00681	<0.0001	404.94

[a]Includes TEAEs coded as thrombocytopenia and platelet count decreased. AIC, Akaike information criterion; AUC, area under the concentration-time curve; C_{max}, maximum concentration; C_{min}, minimum concentration; TEAEs, treatment-emergent adverse events.

- There was a steep increase in the theoretical probability of grade ≥3 thrombocytopenia (assuming no treatment interruptions) as C_{max} increased in all treated patients and when patients were grouped by g*BRCA*mut status (**Figure 2 upper panels**).
  - Note that the actual incidence of grade ≥3 thrombocytopenia was lower due to treatment interruptions.
- Niraparib exposures were higher in patients who experienced grade ≥3 thrombocytopenia overall and by g*BRCA*mut status (**Figure 2 lower panels**).

Figure 2. Relationship Between Model-Predicted C_{max} and Grade ≥3 Thrombocytopenia



Open circles represent individual exposures plotted at y = 0 for patients who did not experience the adverse events and at y = 1 for patients who did. The red curve represents the prediction of the logistic regression model, and the red shaded region represents the 95% CI of the prediction. Blue points and error bars represent the observed proportions and 95% CIs for patients in the placebo arm (plotted at x = 0) and for each exposure quartile for patients in the niraparib arm (plotted at the median exposure within each quartile). CI, confidence interval.

- Based on the exposure-response model, the following were predicted to increase the probability of grade ≥3 thrombocytopenia: higher model-predicted C_{max} up to the time of event or end of treatment, lower body weight, and lower baseline platelet count (**Table 3**).

Table 3. Parameter Estimates for Grade ≥3 Thrombocytopenia Model

Header	Estimate	RSE%	*P* Value	Odds Ratio (95% CI)
Intercept	-0.557	140.6%	0.4770	
C_{max}, 1/(ng/mL)	0.00429	10.1%	<0.0001	1.004 (1.003, 1.005)
Baseline body weight, 1/kg	-0.0307	30.3%	0.0010	0.97 (0.951, 0.987)
Baseline platelet count, 1/(10^9/L)	-0.00606	29.7%	0.0008	0.994 (0.990, 0.997)

Odds ratios represent the fold-change in odds for one unit change in the independent variable. RSE, relative standard error.

Exposure-Response Analyses for Efficacy

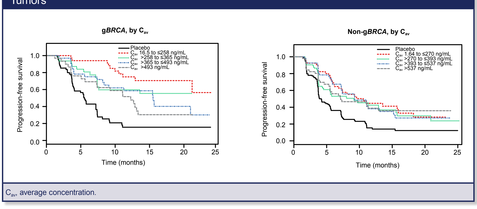
- 356 patients from the niraparib arm of the NOVA trial were included in the exposure-response analyses for PFS (**Table 4**).
  - 135 patients were g*BRCA*mut positive.
  - Of the 221 patients without g*BRCA*mut, 101 were HRDpos.

Table 4. Baseline Characteristics in the Efficacy Exposure-Response Analysis Population

Characteristic	g*BRCA*mut (N=135)	non-g*BRCA*mut (N=221)	non-g*BRCA* mut HRDpos (N=101)	Total (N=356)
Age, median (range), y	57.0 (36.0, 83.0)	63.0 (33.0, 84.0)	62.0 (40.0, 83.0)	61.0 (33.0, 84.0)
Duration of prior chemotherapy, median (range), mo	10.3 (2.6, 67.3)	9.4 (3.5, 38.2)	9.49 (3.8, 38.2)	9.7 (2.6, 67.3)
Duration of last platinum therapy, median (range), mo	4.0 (0.7, 27.0)	3.9 (0.7, 25.1)	4.0 (0.8, 24.6)	3.9 (0.7, 27.0)
Time since last platinum therapy, median (range), d	42.0 (5.0, 141.0)	42.0 (15.0, 199.0)	46.0 (20.0, 199.0)	42.0 (5.0, 199.0)
Lines of platinum therapy, median (range)	2 (2, 7)	2 (2, 6)	2 (2, 6)	2 (2, 7)
Cumulative duration of prior platinum therapy, median (range), mo	35.5 (2.6, 142.0)	28.4 (3.5, 228.0)	32.3 (3.8, 228.0)	30.4 (2.6, 228.0)
Bevacizumab with penultimate or last platinum, n (%)	102 (75.6)	162 (73.3)	71 (70.3)	264 (74.2)
Time to progression after penultimate platinum, n (%)				
6 to <12 months	52 (38.5)	83 (37.6)	31 (30.7)	135 (37.9)
≥12 months	83 (61.5)	138 (62.4)	70 (69.3)	221 (62.1)
Race				
White	121 (89.6)	192 (86.9)	85 (84.2)	313 (87.9)
American Indian or Alaska Native	1 (0.7)	0 (0.0)	0 (0.0)	1 (0.3)
Asian	2 (1.5)	8 (3.6)	4 (4.0)	10 (2.8)
Black	0 (0.0)	4 (1.8)	3 (3.0)	4 (1.1)
Unknown	11 (8.1)	17 (7.7)	9 (8.9)	28 (7.9)
Best response to last platinum, n (%)				
PR	66 (48.9)	109 (49.3)	45 (44.6)	175 (49.2)
CR	69 (51.1)	112 (50.7)	56 (55.4)	181 (50.8)

- In all cohorts, there was a clear separation between the survival curves for the niraparib ar and the placebo arm, with improved PFS in the niraparib arm.
- In the g*BRCA*mut cohort, patients in the lowest exposure quartile had improved PFS compared with the higher quartiles, while there were no apparent differences in PFS in the second to fourth quartile groups (**Figure 3**).
- No differences in PFS between quartiles were evident in the non-g*BRCA*mut cohort.

Figure 3. PFS by C_{av}, Exposure Quartile in Patients with g*BRCA*mut and Non-g*BRCA*mut Tumors



C_{av}, average concentration.

CONCLUSIONS

- Niraparib exposure was significantly associated with probability of any grade and grade ≥3 thrombocytopenia and other hematologic and nonhematologic TEAEs when patients initiated treatment at a dose of 300 mg once daily.
- Lower baseline body weight and platelet count are associated with an increased risk of grade ≥3 thrombocytopenia.
- Findings of an exposure-response analysis of PFS support the previous observation that dose reductions in the NOVA study did not have an adverse impact on efficacy.
- This is also consistent with the prospective safety analysis of PRIMA, which showed a significant reduction in all TEAEs, including thrombocytopenia, following use of an individualized dosing strategy based on baseline weights or platelet count.
- Overall, these findings suggest that reducing niraparib exposure by reducing the starting dose from 300 mg to 200 mg would lower the incidence of severe thrombocytopenia and other TEAEs in patients with ovarian cancer treated with niraparib and would be unlikely to compromise efficacy.

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AUTHOR DISCLOSURES

KS, AA, and ZYZ are employed by TESARO, Inc, and may own stock or other ownership interests in that company. AT and KJ are employed by Certara Strategic Consulting, which received funding from TESARO, Inc.