ORIGINAL ARTICLE

Safety and dose modification for patients receiving niraparib

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Background: Niraparib is a poly(ADP-ribose) polymerase inhibitor approved in the USA and Europe for maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in complete or partial response to platinum-based chemotherapy. In the pivotal ENGOT-OV16/NOVA trial, the dose reduction rate due to treatment-emergent adverse event (TEAE) was 68.9%, and the discontinuation rate due to TEAE was 14.7%, including 3.3% due to thrombocytopenia. A retrospective analysis was carried out to identify clinical parameters that predict dose reductions.

Patients and methods: All analyses were carried out on the safety population, comprising all patients who received at least one dose of study drug. Patients were analyzed according to the study drug consumed (i.e., as treated). A predictive modeling method (decision trees) was used to identify important variables for predicting the likelihood of developing grade ≥ 3 thrombocytopenia within 30 days after the first dose of niraparib and determine cut-off points for chosen variables.

Results: Following dose modification, 200 mg was the most commonly administered dose in the ENGOT-OV16/NOVA trial. Baseline platelet count and baseline body weight were identified as risk factors for increased incidence of grade ≥ 3 thrombocytopenia. Patients with a baseline body weight <77 kg or a baseline platelet count $<150\,000/\mu l$ in effect received an average daily dose ~ 200 mg (median $= 207$ mg) due to dose interruption and reduction. Progression-free survival in patients who were dose reduced to either 200 or 100 mg was consistent with that of patients who remained at the 300 mg starting dose.

Conclusions: The analysis presented suggests that patients with baseline body weight of <77 kg or baseline platelets of $<150\,000/\mu l$ may benefit from a starting dose of 200 mg/day.

ClinicalTrials.gov ID: NCT01847274.

Key words: ovarian cancer, PARP inhibitor, thrombocytopenia, safety, dose modification

Introduction

Ovarian cancer

Platinum-sensitive recurrent ovarian cancer is considered incurable and patients have limited treatment options [1]. Most patients receive platinum-based chemotherapy at each recurrence until the disease becomes platinum resistant or refractory [2]. Patients discontinue chemotherapy once they achieve a response because no benefit has been shown for continuing therapy post maximum response. The platinum-free interval becomes progressively shorter with each successive retreatment [3, 4].

During the platinum-free interval, many patients with platinum-sensitive disease do not receive treatment, and 48%–56% experience a high to moderate degree of fear of cancer recurrence [5]. Many women indicate that ending active treatment triggers new fears and anxieties because they are no longer actively fighting the disease or under the 'protection' of treatment [6, 7].

PARP inhibitors

Poly(ADP-ribose) polymerases (PARP) 1/2 are DNA-binding enzymes that promote DNA repair via activation of the base excision repair pathway. This pathway is particularly important in cells deficient in homologous recombination, a high-fidelity DNA repair mechanism. Inactivation of genes such as *BRCA1, BRCA2,* and *ATM* can induce homologous recombination deficiency. Tumors deficient in homologous recombination are more sensitive to PARP inhibition [8]. Clinical studies have shown that PARP inhibitors have antitumor activity in patients with certain types of cancer, including but not limited to those with defined *BRCA* mutations [9–12].

Niraparib and ENGOT-OV16/NOVA trial

Niraparib is an orally available PARP 1/2 inhibitor that has been shown in preclinical studies to cause >90% PARP inhibition in tumors for up to 24 h after a single dose [13]. Antitumor activity was observed in ovarian, non-small-cell lung, and prostate cancer. A 300 mg QD dose was defined by a phase I dose escalation study in which niraparib was well-tolerated overall [14].

The ENGOT-OV16/NOVA is a randomized, placebo-controlled phase III trial in which niraparib was given to patients with platinum-sensitive, recurrent ovarian cancer. By demonstrating a significant improvement in progression-free survival (PFS) regardless of *BRCA* mutation status [11], it became the first phase III trial to demonstrate clinical benefit of a PARP inhibitor in a patient population without a *BRCA* mutation. Based on these data, niraparib was approved in the USA and Europe for maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in complete or partial response to platinum-based chemotherapy without a requirement for a companion diagnostic test.

Generally, the adverse event profile was manageable with dose adjustments, and patients treated with niraparib or placebo had similar quality of life outcomes in general and disease-specific assessments [15]. Dose reductions were common in the ENGOT-OV16/NOVA trial, with the majority of patients receiving a dose <300 mg QD. The most common treatment-emergent adverse event (TEAE) requiring dose reduction was thrombocytopenia. Lower doses were associated with lower incidence of TEAEs with no apparent deficit in efficacy.

Objective of this analysis

We report here retrospective analyses to identify clinical parameters to select the optimal individualized dose for a patient with fewer grade ≥3 adverse reactions.

Methods

ENGOT-OV16/NOVA trial overview and patients

The design of the ENGOT-OV16/NOVA trial (NCT01847274) has previously been reported [11]. In brief, NOVA was a double-blind, 2 : 1 randomized, placebo-controlled, multicenter, global phase III clinical trial to evaluate the efficacy and safety of niraparib as maintenance treatment of patients with platinum-sensitive, recurrent, ovarian, fallopian tube, or primary peritoneal cancer who had received at least two platinum-based regimens and were in complete or partial response to their last platinum-based chemotherapy. The primary efficacy end point was PFS. This study was conducted in accordance with the International Council for Harmonisation and Good Clinical Practice guidelines consistent with the Declaration of Helsinki as well as applicable national and local regulatory requirements.

Statistical analyses

All analyses were carried out on the safety population, comprising all patients who received at least one dose of study drug. Patients were analyzed according to the study drug consumed (i.e. as treated).

TEAEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.02. Descriptive statistics (number and percentage) were used to summarize the safety data.

A descriptive PFS analysis of the safety population was carried out by dose level a patient was receiving at the beginning of month 4. This was done to censor any progression that would occur before optimal dosing is reached and avoid selection bias for the measure of efficacy in each dose group. PFS was estimated using the Kaplan–Meier product-limit method. Significance (*P* values) from the log-rank test was provided for comparisons of PFS distribution among the dose levels.

A predictive modeling method (decision trees) was used to identify important variables for predicting the likelihood of developing ≥grade 3 thrombocytopenia within 30 days after the first dose of niraparib and determine cut-off points for chosen variables. Patients were randomly split into two equal-sized groups, the first to train the model and the second to validate the model. The decision trees and receiver operator curves (ROC) are presented in the supplementary Appendix, available at *Annals of Oncology* online.

Statistical analyses were carried out using SAS software (version 9.4; SAS Institute, Cary, NC).

Results

Trial results

Results from ENGOT-OV16/NOVA have been published previously [11]. Briefly, a total of 553 patients were enrolled, including 203 patients assigned to the g*BRCA*mut cohort and 350 patients assigned to the non-g*BRCA*mut cohort. In the g*BRCA*mut
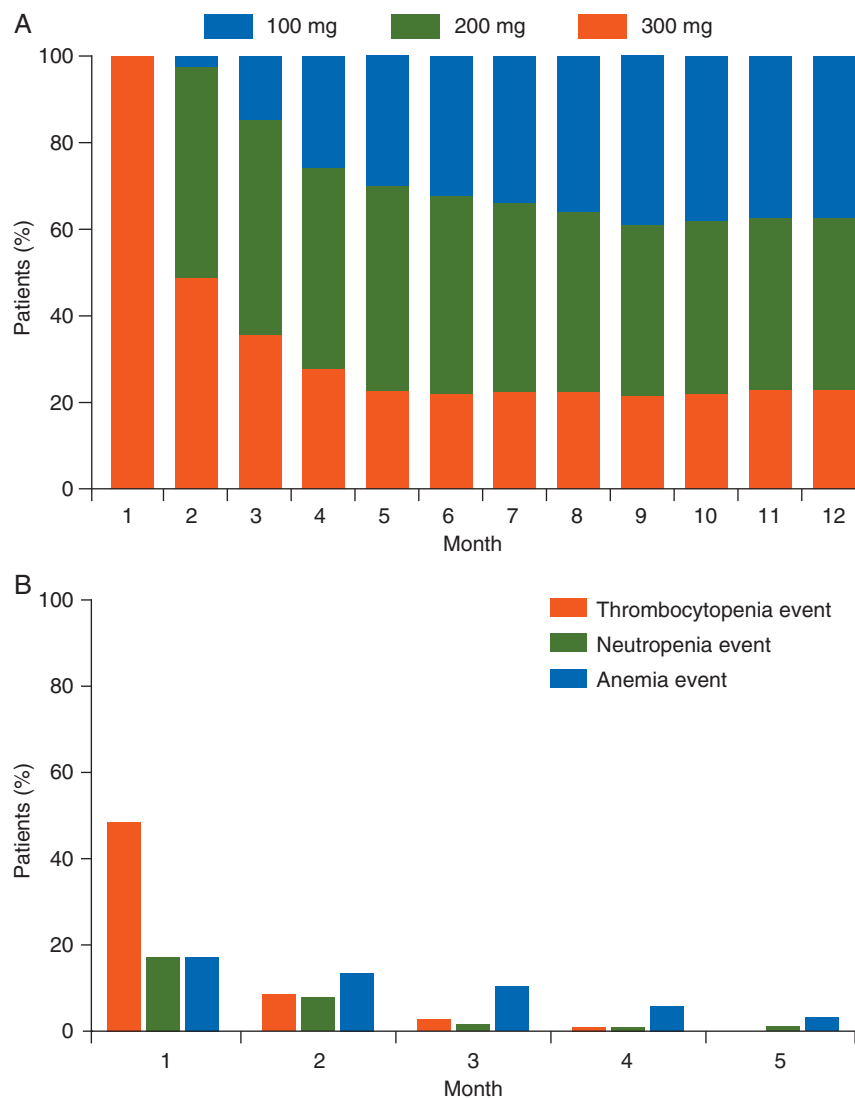
Figure 1. (A) Niraparib dose level by month on treatment and (B) any grade hematologic TEAEs in the niraparib arm, months 1–5. Thrombocytopenia includes reports of thrombocytopenia and decreased platelet count; neutropenia includes reports of neutropenia, decreased neutrophil count, and febrile neutropenia; anemia includes reports of anemia and decreased hemoglobin counts. TEAEs, treatment-emergent adverse events.

cohort, median PFS was 21.0 months for niraparib versus 5.5 months for placebo [hazard ratio (HR), 0.27; $P < 0.0001$]. In the overall non-g*BRCA*mut cohort, median PFS was 9.3 months for niraparib versus 3.9 months for placebo (HR, 0.45; $P < 0.0001$).

Dose modifications in ENGOT-OV16/NOVA

In ENGOT-OV16/NOVA, dose interruptions and dose reductions were mandated for patients with specific hematologic and nonhematologic toxicities. Overall, dose interruptions for any reason were instituted for 80% of patients on niraparib; 73% underwent a dose reduction. The rates were lower for placebo, with 19% having the dose interrupted and 6% having a dose reduction. Figure 1A displays the percent of patients at each niraparib dose level (300, 200, and 100 mg) by month on treatment. Dose reductions tended to occur early, with most patients reaching their individual-adjusted dose level at the end of month 3 of

treatment. Of the 163 patients remaining on niraparib treatment at month 12, only 37 (23%) remained on a daily dose of 300 mg. Following dose modification, 200 mg was the most commonly administered dose.

During the first 3 months of niraparib administration, the starting dose of 300 mg resulted in grade ≥ 3 hematologic laboratory events of thrombocytopenia (33% of patients), anemia (13%), and neutropenia (18%). Incidences of these grade ≥ 3 events decreased to 0.7% for thrombocytopenia and 1.6% for neutropenia after month 3, when only 27.6% of patients remained on the 300 mg dose. Anemia events remained at 15%. The incidence of any grade thrombocytopenia after month 3 was $\leq 1\%$ (Figure 1B). Of note, patients who stayed at 300 mg at month 3 rarely experienced delayed grade 3/4 thrombocytopenia (1.2%; supplementary Table S3, available at *Annals of Oncology* online). Overall, 14.7% patients discontinued niraparib in the ENGOT-OV16/NOVA trial due to TEAEs. Few patients taking niraparib discontinued due to hematologic TEAEs (thrombocytopenia 3.3%, neutropenia 1.9%, and anemia 1.4%).
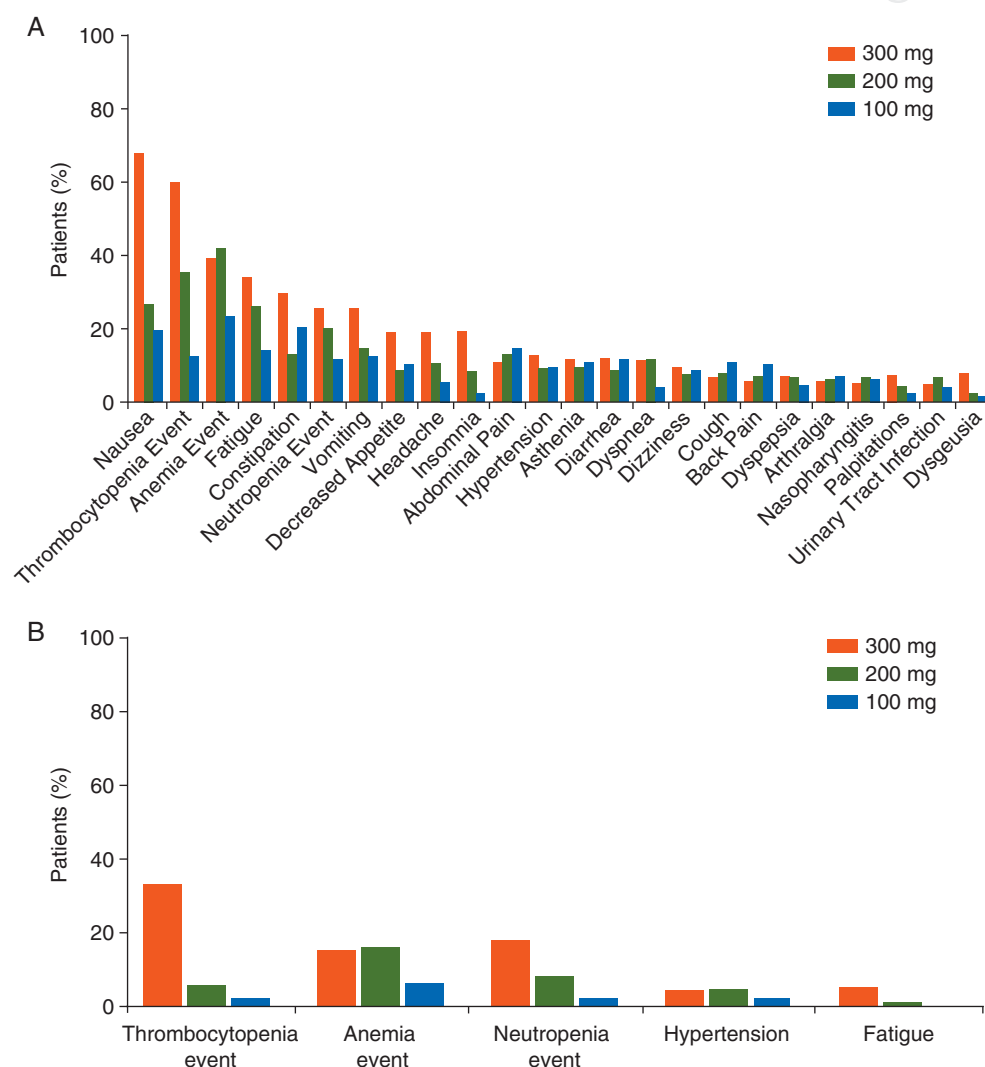
Figure 2. (A) TEAEs reported in ≥10% of patients in the overall niraparib population by dose at onset of event and (B) grade 3/4 TEAEs reported in ≥5% of patients in the niraparib arm overall by dose at onset of event. Thrombocytopenia includes reports of thrombocytopenia and decreased platelet count; neutropenia includes reports of neutropenia, decreased neutrophil count, and febrile neutropenia; anemia includes reports of anemia and decreased hemoglobin counts. TEAEs, treatment-emergent adverse events.

Many nonhematologic TEAEs showed decreased incidence over time including nausea (61.9% at month 1 versus 1.6% at month 4), vomiting (19.6% versus 2.0%), and fatigue (32.4% versus 4.9%).

Relationship between TEAEs and niraparib dose

TEAE incidence was tabulated by dose at onset of the event for patients who received niraparib (Figure 2A; supplementary Table S1, available at *Annals of Oncology* online). If a patient experienced the same event (by preferred term) at more than 1 dose level, they were included at all dose levels during which the event occurred.

The incidence of the commonly reported events (grade ≥3) was highest at the 300 mg dose and lower at the 200 and 100 mg dose (Figure 2B; supplementary Table S2, available at *Annals of Oncology* online). The incidence of anemia (overall and grade ≥3) was similar at the 300 and 200 mg doses and lower at 100 mg.

Efficacy by niraparib dose level

Twenty percent of niraparib-treated patients were discontinued in the first 3 months due to AE or progression, while most of the patients were on 300 mg dose. Therefore, to prevent bias which disfavored the 300 mg treatment group, PFS from month 4, when the majority of patients had achieved a stable dose, was assessed for the patients remaining on treatment. PFS in patients who were dose reduced to either 200 mg or 100 mg was consistent with that of patients who remained at the 300 mg starting dose. Figure 3A and B shows PFS for patients in the g*BRCA*mut and non-g*BRCA*mut cohorts based on dose at the beginning of month 4.

Initial evaluation of potential predictors of thrombocytopenia

Baseline platelet count and baseline body weight were identified as risk factors for increased incidence of grade ≥3 thrombocytopenia. Baseline covariate factors that did not predict dose modification
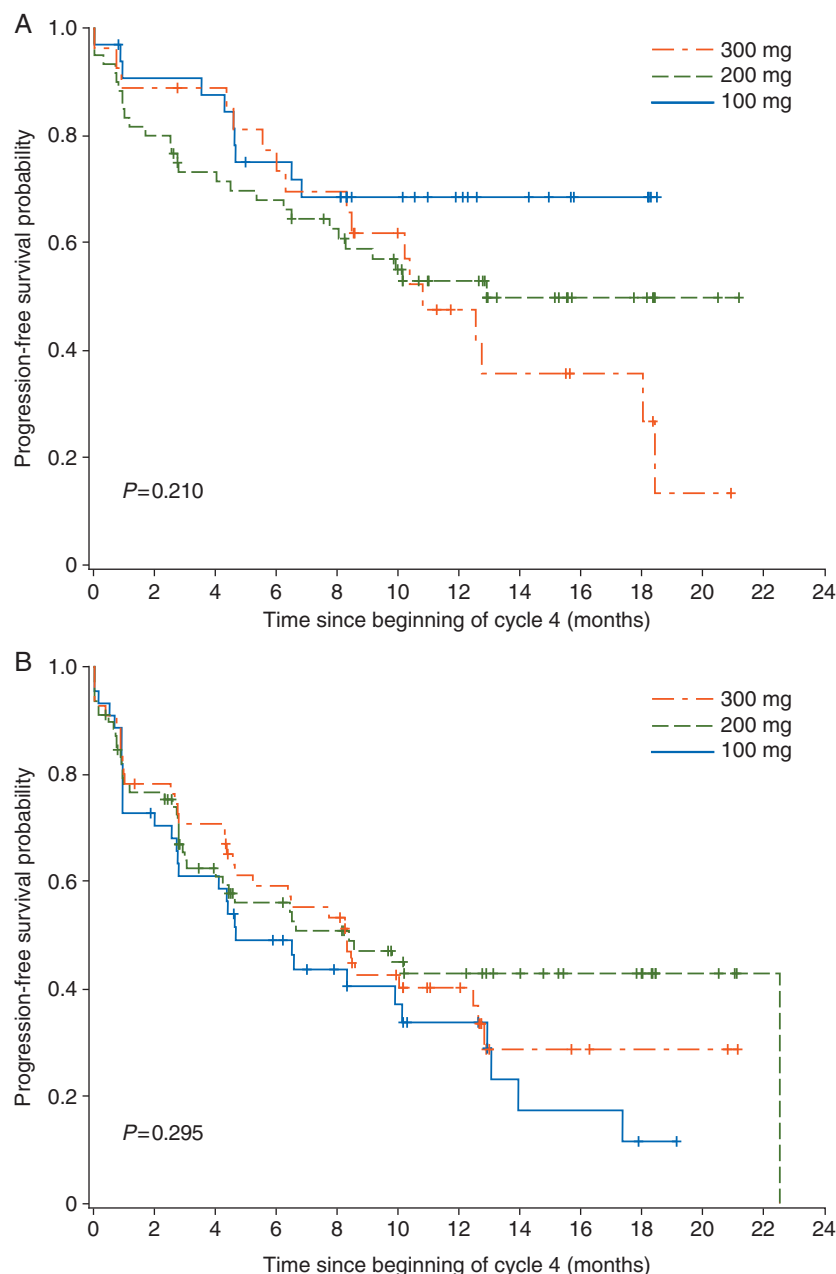
Figure 3. Estimated progression-free survival probability by dose level measured after month 3 for patients in the (A) g*BRCA*mut and (B) non-g*BRCA*mut cohorts. PFS, progression-free survival.

were: age, race, Eastern Cooperative Oncology Group (ECOG) status at screening, region, neutrophil counts, hemoglobin counts, albumin, bilirubin, aspartate aminotransferase, alanine aminotransferase and alkaline phosphatase. Other factors that did not predict dose modification were platelet nadir (overall, across all study visits), duration of prior chemotherapy, lines of prior chemotherapy, time from last chemotherapy and prior history of myelosuppression.

Baseline platelet count

Baseline platelet count had an impact on platelet nadir (Table 1; Figure 5B). Lower baseline platelet counts (<180 000/μl) were

associated with an increased frequency of thrombocytopenia grade ≥1 (71.1%) or grade ≥3 (42.2%) compared with patients with higher baseline platelet counts.

TEAEs by baseline body weight

Weight categories were based on quartiles with the lowest quartile (patients with a body weight <58 kg at baseline) compared with the highest quartile (patients with a body weight ≥77 kg at baseline).

While any grade TEAEs occurred in patients regardless of body weight, grade ≥3 TEAEs, serious adverse events, and TEAEs leading to dose modification or treatment discontinuation occurred

more frequently in the weight <58 kg cohort than in the ≥77 kg cohort (Figure 4A; supplementary Table S4, available at *Annals of Oncology* online). Approximately 51% of patients with a body weight <58 kg had a TEAE associated with dose reduction

compared with 33% of patients with a weight ≥77 kg. Treatment discontinuations due to TEAEs were higher in patients with lower body weight (10%) compared with patients in the highest quartile (1%).

TEAEs that occurred with >10% difference between the lowest and highest quartiles are shown in Figure 4B and supplementary Table S5, available at *Annals of Oncology* online.

Thrombocytopenia during the first 30 days of niraparib was selected as the primary event of interest to assess association of baseline characteristics and starting dose. During this interval a baseline body weight <58 kg is associated with a higher incidence of grade ≥3 thrombocytopenia compared with baseline body weight ≥77 kg (45% versus 16%; Figure 5A; supplementary Table S6, available at *Annals of Oncology* online).

Evaluation of integrated body weight and platelet count approach based on decision tree and ROC analyses

The classification tree analysis using the training dataset suggested baseline weight as the best predictor with 77 kg as a cut-off

Table 1. Baseline platelets and treatment-emergent thrombocytopenia events[a] within 30 days after the first dose of niraparib

| Groups	No. of patients	Quartiles	Thrombocytopenia (%)	
			Any grade	Grade ≥3
1	93	PLTBL≥273	37.6	20.4
2	93	215≤PLTBL<273	51.6	31.2
3	91	180≤PLTBL<215	56.0	25.3
4	90	PLTBL<180	71.1	42.2

[a]Thrombocytopenia includes reports of thrombocytopenia and decreased platelet count.
$P \leq 0.0001$.
PLTBL, baseline platelet count (median 215).
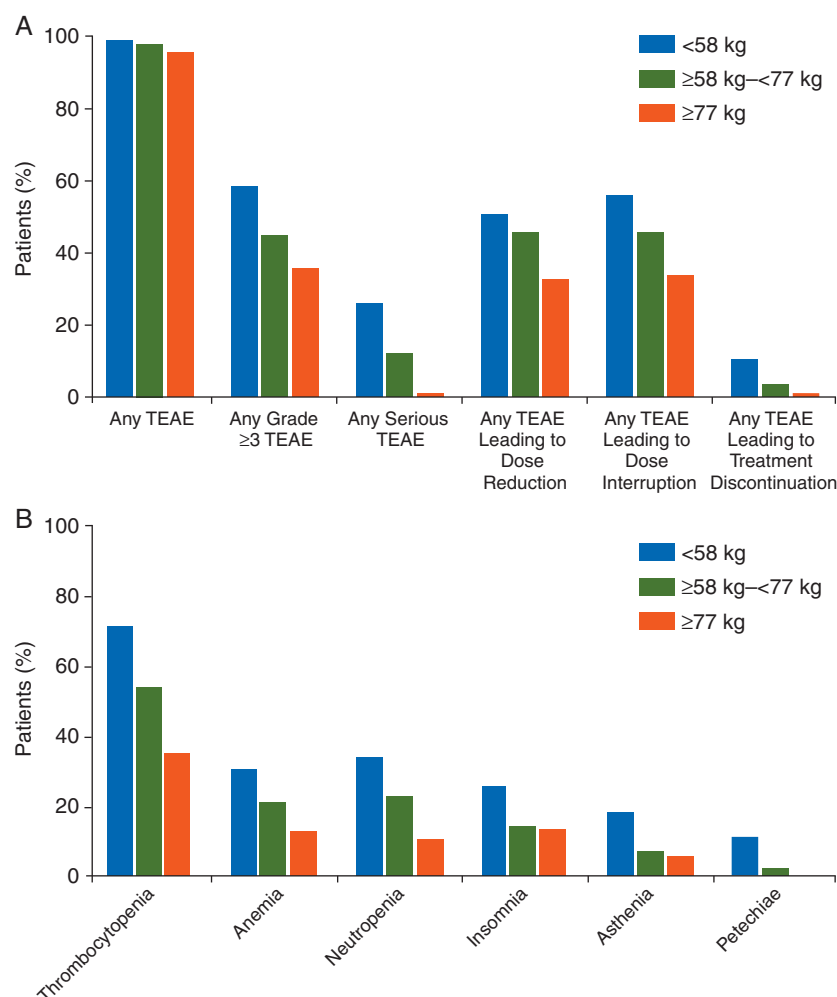
Figure 4. Summary within 30 days of first dose of (A) any grade TEAEs and (B) TEAEs that occurred with >10% difference between patients by baseline body weight quartiles. Baseline weight is collected at screening visit. Thrombocytopenia includes reports of thrombocytopenia and decreased platelet count; neutropenia includes reports of neutropenia, decreased neutrophil count, and febrile neutropenia; anemia includes reports of anemia and decreased hemoglobin counts. TEAEs, treatment-emergent adverse events.
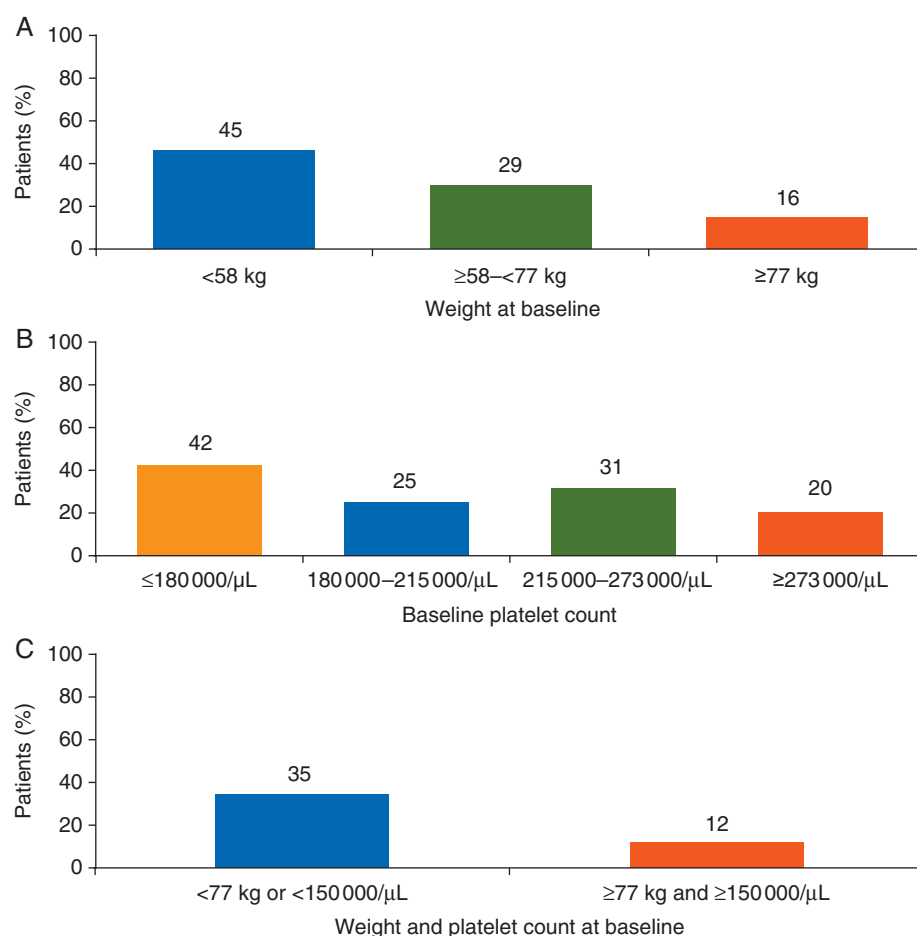
Figure 5. Grade 3/4 thrombocytopenia within 30 days of first dose by (A) baseline weight, (B) baseline platelet count, and (C) integrated analysis of baseline weight and baseline platelet count.

(supplementary Figure S1, available at *Annals of Oncology* online). The baseline platelet count cut-off suggested by the model was 175 000/μl. However, as the lower limit of normal for platelets is typically 150 000/μl, cut-offs were established as <150 000/μl platelets or <77 kg to simplify implementation in clinical practice. The additional analyses below are based on these simplified cut-offs.

The area under the curve for the fitted model applied to the training and validation datasets were 70% and 66%, respectively, indicating a close prediction by the two datasets (supplementary Figure S2, available at *Annals of Oncology* online).

Incidence of grade ≥3 thrombocytopenia based on body weight and platelet count in ENGOT-OV16/ NOVA

In patients with a low body weight or low baseline platelet count, the incidence of grade ≥3 thrombocytopenia during the first month of treatment was 35% (97/280) compared with 12% (10/85) in patients who are above the cut-off for both baseline characteristics (Figure 5C).

Discussion

Niraparib (ZEJULA®) is approved in the US and EU with the starting dose of 300 mg for all patients. However, the European

Summary of Product Characteristics (SmPC) allows for a 200 mg starting dose for a subset of low-body weight patients. The dose modification approach employed in NOVA allowed patients to reach their optimal individual dose after the first 3 months. Overall, dose interruptions for any reason were instituted for 80% of patients on niraparib, with 73% having a dose reduction. Following dose modification, 200 mg was the most commonly administered dose. Dose reductions tended to occur early and most patients reached their individual adjusted dose level by month 4 of treatment. A PFS analysis from the NOVA study by dose at month 4 demonstrated that once the patients reach their optimal individualized dose, efficacy was not compromised.

Dose modification of niraparib was shown to reduce adverse events overall. In particular, thrombocytopenia was transient and typically manifested during the first month of treatment. The effectiveness of the dose modification strategy was demonstrated by the relatively few patients who discontinued due to these events. Additional retrospective, exploratory multivariable analysis of the NOVA data investigated potential predictors of grade ≥3 thrombocytopenia. Body mass index (BMI) was assessed as a covariate in the analysis, but body weight was the better predictor of grade 3/4 thrombocytopenia; therefore, the analysis included weight rather than BMI. Baseline body weight and platelet counts were each identified as predictors of dose

modification in patients treated with niraparib at 300 mg QD. Patients with a body weight <77 kg or platelet counts <150 000/μl at baseline had higher rates of grade ≥3 thrombocytopenia (35% versus 12%) and were more likely to require early dose modification, with only 17% of patients remaining on 300 mg by month 4. As a result of dose interruptions and reductions in the ENGOT-OV16/NOVA trial, the average daily dose in the first 2 months for patients with either a body weight <77 kg or a baseline platelet count <150 000/μl was 207 mg.

While the relative ratios vary, hematologic toxicities have been reported as the most common grade 3/4 TEAEs among the approved PARP inhibitors, suggesting a class effect [11, 16–19]. Thrombocytopenia, in particular, has been shown to be associated with PARP inhibitors by reversibly affecting megakaryocyte proliferation and maturation [20].

Overall the data demonstrate that while adverse events appear to be dose dependent, the relationship between dose and efficacy is not apparent [21]. In addition, patients with a baseline body weight <77 kg or a baseline platelet count <150 000/μl received an average daily dose approximating 200 mg (average = 207 mg) due to dose interruption and reduction.

The analysis presented suggests that patients with baseline body weight of <77 kg or baseline platelets of <150 000/μl may benefit from a starting dose of 200 mg/day. This dosing regimen is now applied to ongoing clinical trials conducted by TESARO, Inc. to assess niraparib in monotherapy.

Disclosure

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outside the submitted work. UAM reports personal fees from Merck KGaA, personal fees from Clovis, personal fees from Geneos, personal fees from Eli Lilly, personal fees from 2× Oncology, outside the submitted work. MRM reports personal fees from Clovis Oncology, personal fees from AstraZeneca, and personal fees from TESARO, Inc., outside the submitted work. AR reports personal fees from TESARO, Inc., personal fees from Astra Zeneca, grants from Roche, grants and personal fees from PharmaMar, personal fees from Lilly, outside the submitted work. IV reports travel, accommodations, expenses: GCI Health, Roche, Oasmia Pharmaceutical AB, PharmaMar, AstraZeneca (from ESMO 2017). NC reports personal fees from TESARO, Inc., during the conduct of the study; personal fees from Roche, personal fees from PharmaMar, personal fees from Clovis, personal fees from Astra Zeneca, personal fees from Pfizer, personal fees from Takeda, outside the submitted work.

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