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ORIGINAL ARTICLE

Effect of niraparib on cardiac repolarization in patients with platinum-sensitive, recurrent epithelial ovarian, fallopian tube, and primary peritoneal cancer

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Abstract

Purpose Anticancer drugs may cause cardiovascular toxicities, including QT interval prolongation. Niraparib, a potent and selective once-daily oral poly (ADP-ribose) polymerase inhibitor, is approved as a maintenance therapy in platinum-sensitive recurrent epithelial ovarian, fallopian tube, and primary peritoneal cancer (EOC). Here, we present the effects of niraparib on cardiac repolarization, and the correlation between changes in baseline QT interval corrected by Fridericia's formula (ΔQTcF) and niraparib plasma concentrations.

Methods Patients with EOC from the NOVA study (subset of $n = 15$), the food effect NOVA substudy ($n = 17$), and a QTc substudy ($n = 26$) underwent intensive electrocardiographic (ECG) monitoring that included triplicate ECG testing on Day 1 at baseline (predose) and at 1, 1.5, 2, 3, 4, 6, and 8 h postdose concurrent with time-matched blood sampling for determination of niraparib plasma concentrations. All patients received once-daily 300-mg niraparib until disease progression or toxicity.

Results Across the 3 substudies, the upper limit of the two-sided 90% confidence interval (CI) of ΔQTcF was ≤ 10 ms at every postdose timepoint, with a maximum upper limit of 4.3 ms, which indicates no clinically meaningful effect on QTc prolongation. No statistically significant relationship between ΔQTcF and niraparib plasma concentration was observed (estimated slope: 0.0049; 95% CI: − 0.0020, 0.0117; $P = 0.164$). There were no clinically relevant changes in other ECG parameters that could be attributable to niraparib.

Conclusion Niraparib administration at the recommended daily dose of 300 mg for EOC is not associated with clinically relevant alteration of ECGs, including QTc prolongation.

Keywords Niraparib · PARP inhibitor · Cardiac repolarization · QTc interval · Ovarian cancer

Introduction

Niraparib (ZEJULA®) is a potent and selective once-daily oral poly (adenosine diphosphate-ribose) polymerase (PARP) 1/2 inhibitor indicated for the maintenance treatment of patients with recurrent ovarian, fallopian tube, or primary peritoneal cancer (EOC) who are in complete or partial response to platinum-based chemotherapy. Niraparib prevents PARP-mediated single-strand DNA break repair in tumors, thereby promoting apoptotic cell death [1]. In a phase 1 dose-escalation study, pharmacodynamic analyses showed that PARP inhibition was > 50% at niraparib doses > 80 mg/day and antitumor activity at doses > 60 mg/day; this study established 300 mg once-daily to be the maximal tolerated dose of niraparib in patients with advanced solid tumors [2]. The pivotal phase 3 NOVA

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study that led to the approval of niraparib reported a significant improvement in progression-free survival compared with placebo in women with platinum-sensitive, recurrent EOC who received niraparib maintenance therapy, regardless of *BRCA* mutation or biomarker status [3].

Ovarian cancer is diagnosed at a median age of ~ 59 years; thus, patients with EOC may have an increased cardiovascular risk and associated mortality [4, 5]. Furthermore, the use of multiple lines of anticancer therapies can also lead to chronic effects such as ventricular dysfunction or congestive heart failure, or acute cardiac effects such as changes in the QT interval, arrhythmias, acute coronary syndromes, pericarditis, and/or myocarditis-like syndrome [6–9]. Considering the potential use of multiple therapies and/or lines of therapy, as well as extended periods of cancer treatments, regulators in the European Union, Japan, and USA recommend thorough assessment of cardiovascular effects of therapies, including anticancer drugs [10].

QT interval is defined as the duration of ventricular depolarization and repolarization (or contraction and relaxation) and measured from the beginning of the QRS complex (the combination of the Q wave, R wave, and S wave) to the end of the T wave. Because heart rate influences the QT interval, it is commonly corrected by means of the Fridericia or Bazett formula to a more accurate value known as QTcF or QTcB, respectively [11]. QT prolongation is a clinically important ECG abnormality, because it can be a precursor for the development of torsade de pointes, a type of ventricular tachycardia that is sometimes fatal [7]. Occurrence of torsade de pointes is usually associated with a corrected QT interval (QTc) of ≥ 500 millisecond (ms); however, no established threshold that reduces the risk of ventricular arrhythmia exists [12, 13]. The degree of QT prolongation is recognized as a useful marker for proarrhythmic risk from a clinical and regulatory standpoint [14].

In preclinical animal studies, niraparib,1, 3, and 10 mg/kg, administered intravenously during 3 sequential 30-min periods, did not change the QTc, blood flow, or PR interval, although there was a slight increase in the QRS interval (6% compared with predose) at the highest dose. Furthermore, toxicity studies in animals at 1 month and 3 months after niraparib administration did not show any treatment-related ECG abnormalities at the highest doses of 12 and 15 mg/kg/day [15, 16].

Because the cardiac effects of niraparib have not been formally evaluated in a clinical study, we conducted an intense QT/QTc study in a subset of patients from the NOVA study and two other substudies, evaluating cardiac repolarization and correlation between baseline QTc interval changes and niraparib plasma concentrations.

Materials and methods

Patients and overall study design

The overall study population consisted of patients who underwent intensive ECG monitoring while enrolled in the NOVA main study (PR-30-5011-C; NCT01847274) and the NOVA food effect (FE) substudy (PR-30-5011-C2), as well as patients enrolled in the open-label QTc substudy (PR-30-5011-C1). Cancer staging was performed according to the International Federation of Gynecology and Obstetrics (FIGO) staging criteria for EOC [17].

NOVA was a phase 3, randomized, double-blind, placebo-controlled study of adult patients with platinum-sensitive ovarian cancer categorized according to the presence or absence of a germline *BRCA* mutation. Platinum-sensitive disease was defined as disease progression > 6 months after completion of the penultimate round of platinum therapy and having a complete or partial response to the last round of platinum-based chemotherapy. Details on the study design and eligibility criteria for the NOVA study have been previously published [3]. A subpopulation of patients from the NOVA study who underwent intensive ECG monitoring (referred to as the NOVA main population) was included in the present QTc analysis.

The FE study was a 14-day, open-label, crossover substudy designed to assess the effect of a high-fat meal on the PK and ECG findings of niraparib. The eligibility criteria for the FE study were the same as those for the NOVA main study. Patients either fasted or consumed a high-fat meal before dosing; after a 7-day PK assessment and wash-out period, patients received a dose of niraparib under the opposite condition. Patients received a single dose of 300 mg niraparib (3 × 100 mg) on days 1 and 8. After the completion of the 14-day period, patients began daily dosing with 300 mg niraparib on Cycle 1/day 1, approximately 2 weeks after the start of the FE substudy. Overall study design and eligibility criteria of the FE study have been described previously [18].

The QTc substudy enrolled patients with histologically diagnosed EOC and an Eastern Cooperative Oncology Group performance status of 0–2. Patients enrolled in the NOVA main study and FE substudy were platinum-sensitive; however, entry criteria for the QTc substudy were broadened to include patients with ovarian cancer regardless of platinum sensitivity and burden of disease, as long as either no standard therapy existed for these patients or the patients had refused standard therapy. Fasting was not required. Patients received 300 mg (3 × 100 mg) niraparib orally once-daily until progression or toxicity.

In all three substudies, patients were excluded if they had a baseline QT prolongation > 470 ms or were receiving

concomitant medications that prolong QTc. For all patients (regardless of study part), dose interruptions (no longer than 28 days) were allowed. In addition, dose reductions to two capsules daily (200 mg) and subsequently to one capsule daily (100 mg) were allowed based on treatment side effects. No further dose reductions were allowed. The timing of efficacy or safety evaluations was not affected by dose interruptions or reductions.

The protocols of all three substudies were approved by the ethics committees of the participating study sites and were conducted in accordance with the International Conference on Harmonisation, Good Clinical Practice, and the Declaration of Helsinki. All participants provided written informed consent prior to study entry.

QTc assessments

The main objective of the intensive ECG analyses was to assess the effects of niraparib on cardiac repolarization following a single dose. The primary endpoint was the mean change between time-matched measurements of QTcF for niraparib from baseline (ΔQTcF). Baseline was defined as the average of the triplicate (if collected) readings closest to, but prior to, the first dose of study drug. Twelve-lead Holter recordings were collected from the selected patients on day 1 of Cycle 1 and then transferred to and analyzed by ERT (St. Louis, MO; formerly Biomedical Systems). Twelve-lead ECGs were extracted from the Holter recordings at baseline (predose) and 1, 1.5, 2, 3, 4, 6, and 8 h postdose. Time-matched PK samples were collected on day 1. Periodic safety assessments (including safety ECG, vitals, clinical laboratories, and AEs) were made per protocol throughout the study.

In addition to the standard 12-lead ECG conducted at screening and Cycle 2, day 1 (predose and 2 h postdose) and at the study treatment discontinuation, patients selected for intensive ECG monitoring had triplicate 12-lead ECGs taken predose and at 1, 1.5, 2, 3, 4, 6, and 8 h postdose (day 1 only), which coincided with blood sampling for PK determination in all three substudies. After a 5-min period where the patients were supine to stabilize heart rate, ECGs were extracted in triplicate within a 5-min window with single ECGs extracted between 1 and 2 min between ECGs. The average of each of the triplicate measures was used for analysis.

QT assessments were performed at a central laboratory by board-certified cardiologists using the computer-assisted measurement of intervals software. The QT interval was measured from the earliest detection of depolarization in any lead (beginning of the Q or R wave) to the latest detection of repolarization in any lead (end of the T wave). QT was corrected for heart rate using the Fridericia correction (QTcF): $QTcF = QT/RR^{1/3}$ and the Bazett correction (QTcB): $QTcB = QT/RR^{1/2}$ where RR is the time interval between consecutive heart beats and QT, RR, QTcF, and QTcB are expressed in seconds.

Heart rate, PR interval (the time from the onset of the P wave to the start of the QRS complex) and QRS duration (combined duration of the Q wave, R wave, and S wave representing ventricular depolarization prior to ventricular contraction) data were also summarized using central tendency and categorical analysis. Abnormal heart rates were categorized as an increase of > 20% resulting in a heart rate > 100 beats per minute (bpm) or a decrease of > 20% resulting in a heart rate < 50 bpm. Number and percentage of patients with an increase in QRS duration > 20% resulting in a QRS duration > 120 ms or a decrease in QRS duration > 20% resulting in a QRS duration < 60 ms were determined. Similarly, the number and percentage of patients with an increase in PR interval > 20% resulting in a PR interval > 220 ms or a decrease in PR interval > 20% resulting in a PR interval duration < 120 ms were determined.

Pharmacokinetic assessments

On Cycle 1, day 1, all patients who underwent intensive ECG monitoring had blood samples drawn for measurements of plasma levels of niraparib at predose (within 30 min of niraparib dose) and at 1, 1.5, 2, 3, 4, 6, and 8 h postdose (± 2 min at all postdose time points). Niraparib PK parameters determined from blood draws were matched to ECG assessment using a validated LC/MS/MS method.

Statistical analyses

ECG intervals at each time point were obtained as the averages from triplicate recordings. To assess the ΔQTcF between time-matched measurements for niraparib, the upper bound of the two-sided 90% confidence interval (CI) at each time point for ΔQTcF was calculated. The primary analysis focused on the calculation of the largest increase in the ΔQTcF, specifically, the upper bound of the 90% CI of the ΔQTcF. The QT study was considered negative (no effect on QTc prolongation) if the upper bound of the two-sided 90% CI for the ΔQTcF was < 10 ms (per the International Conference on Harmonisation E14 guidelines). Primary analyses were performed separately for the NOVA main and QTc substudy, and for the FE substudy.

For PK analysis, all postdose time points with non-missing QTcF values and niraparib plasma concentrations were used to perform repeated measures regression analysis. The analysis used effects on patients as a random variable and plasma concentration at the matching time point as the predictor of time-matched ΔQTcF. The relationship between ΔQTcF and plasma concentration of niraparib was analyzed using a linear mixed-effects model. The linear regressions

were plotted with CIs over the range of plasma concentrations reported throughout the study and summarized with slope, intercept, and a test of the statistical significance of the slope (different from 0).

Based on a regulatory commitment to evaluate intensive ECG data in 10% of niraparib-treated patients in the NOVA study ($N=490$), approximately 49 patients were needed for the intensive ECG evaluation. The NOVA main study, the QTc substudy, and the FE substudy contributed to reach the target sample size of eligible patients for the QTcF analyses ($n=58$), which could identify a clinically meaningful prolongation of QTcF, if one existed, due to treatment with niraparib.

Results

ECG data were collected from a total of 58 patients: 15 patients from the NOVA main study (10 niraparib-treated and 5 placebo-treated), 26 niraparib-treated patients from the QTc substudy, and 17 niraparib-treated patients from the FE substudy. ECGs of patients who had ≥ 1 time-matched change from baseline ECG value were included in the QTc analysis. Patients from the NOVA main study and QTc substudy were analyzed together and referred to as "NOVA main and QTc substudy" patients. Because the NOVA main subset included five placebo-treated patients, placebo-adjusted QTc analyses are provided for the NOVA main and QTc substudy. Patients from the FE substudy were analyzed separately. Combined QTc analyses across the three datasets are also reported where applicable and are referred to as "combined ECG data" in this report.

Patient characteristics

Patient demographics and clinical characteristics were comparable among the three substudies (Table 1); the median age was > 60 years, most patients were Caucasian and had a primary tumor of the ovary. More than half of the patients had Stage IIIC or higher-stage cancer per the FIGO classification [17], and most patients had received between one and three prior platinum-based regimens.

Mean ΔQTcF

Figure 1 shows baseline- and placebo-corrected ΔQTcF in niraparib-treated patients in the NOVA main and QTc substudy. There were no significant differences in mean ΔQTcF at any postdose timepoint. The largest increase in the ΔQTcF [mean ± standard deviation (SD)] for niraparib was 4.3 ± 8.8 ms at 3 h postdose, smaller than the upper limit of the 90% CI for the mean ΔQTcF of 6.7 ms at 3 h postdose (Table 3 in "Appendix").

In the FE substudy, intensive ECG monitoring was conducted in patients in both fed and fasted states. The bioequivalence between the fed (high-fat meal) and fasted conditions has been previously demonstrated [18]. Increases as well as decreases in the ΔQTcF were seen in the ECGs of fasted patients. The largest increase in the upper bound of the 90% CI of the ΔQTcF in the fasted state was 4.1 ms at 1 h postdose (mean ± SD, 1.2 ± 6.64 ms). Patients in the fed state only showed reductions in the ΔQTcF; the largest mean reduction in ΔQTcF was 11.5 ms at 2 h postdose (Table 4 in "Appendix").

Categorical analyses of QTcF changes

In the NOVA main and QTc substudy, 1 patient had QTcF duration > 450 ms predose, and 2 patients each had 2 instances of QTcF durations > 450 ms postdose. In the FE study, 4 patients had QTcF duration > 450 ms postdose. Of these, 1 patient (patient 3) had QTcF durations > 450 ms in both the fasted and fed states (Table 2). These data indicated that the ΔQTcF observed in the few patients were mild, with no patient having a QTcF duration > 480 ms or a ΔQTcF ≥ 30 ms at any postdose time point.

Supportive QT analyses of other ECG variables

Heart rate

In the NOVA main and QTc substudy, postdose increases and decreases were noted in baseline-adjusted mean heart rate (ΔHR), but none were clinically meaningful. The largest ΔHR was 8.3 ± 7.9 bpm at 4 h postdose. No patient developed an increase or decrease in heart rate postdose (defined as increases > 20% from baseline resulting in a heart rate > 100 bpm, or decreases > 20% resulting in a heart rate of < 50 bpm).

In the FE study, postdose increases in ΔHR were seen in both the fed and fasted groups; the largest mean increases were 12.6 ± 9.47 bpm at 8 h postdose and 13.1 ± 9.54 bpm at 6 h postdose, respectively. These increases were not clinically meaningful. Three patients (fasted, $n=2$; fed, $n=1$) had increases in heart rate that met reporting criteria.

QRS interval

No consistent changes from baseline in the postdose mean QRS duration differences (ΔQRS) were observed in any substudy. At any timepoint in the NOVA main and QTc substudy, mean ΔQRS were less than ± 1 ms, which did not suggest any important clinical concerns. In the FE study, the largest (± SD) increase in ΔQRS was 1.1 ± 1.74 ms found in the fasted group at 1.5 h postdose. No patient in any treatment group had a postdose QRS duration > 120 ms and an

Table 1 Demographic and clinical characteristics

Characteristic	NOVA main study ($n=15$)	QTc substudy ($n=26$)	Food effect substudy ($n=17$)
Age, year, median (range)	62 (45–77)	62 (46–76)	64 (47–69)
≥ 65 years	7 (47)	10 (39)	7 (41)
Race, *n* (%)			
White	14 (93)	21 (81)	15 (88)
Black	0	3 (12)	1 (6)
Asian	1 (7)	1 (4)	0
American Indian or Alaska Native	0	1 (4)	0
Native Hawaiian or other Pacific Islander	0	0	1 (6)
Weight in kg, median (range)	68 (50–103)	70 (43–120)	73 (55–115)
Height in cm, median (range)	159 (154–173)	160 (149–173)	163 (150–173)
BMI in kg/m^2, median (range)	27 (20–40)	27 (18–51)	26 (21–43)
ECOG performance status			
0	14 (93)	17 (65)	12 (71)
1	1 (7)	9 (35)	5 (29)
Primary tumor, *n* (%)			
Ovarian	12 (80)	25 (96)	15 (88)
Primary peritoneal	0	0	1 (6)
Fallopian tube	3 (20)	1 (4)	1 (6)
Duration since diagnosis (year), median (range)	2.2 (1.8–7.7)	2.3 (0.6–17.2)	NA
FIGO stage			
0, I, II	2 (13)	3 (12)	0
III	0	3 (12)	0
IIIA	2 (13)	0	1 (6)
IIIB	1 (7)	1 (4)	1 (6)
IIIC	8 (53)	14 (54)	12 (71)
IV	2 (13)	5 (19)	3 (18)
Number of prior platinum courses			
1–3	14 (93)	25 (96)	14 (82)
> 3	1 (7)	1 (4)	3 (18)
Number of prior chemotherapy courses			
1–3	14 (93)	20 (77)	5 (29)
> 3	1 (7)	6 (23)	12 (71)
Radiotherapy prior to enrollment, *n* (%)	1 (7)	3 (12)	2 (12)
Time since last platinum course (days), median (range)	50 (35–56)	41 (8–1419)	NA

BMI Body Mass Index, *ECG* electrocardiograph, *ECOG* Eastern Cooperative Oncology Group, *FIGO* International Federation of Gynecology and Obstetrics, *NA* not applicable

increase in QRS duration of > 20%, or a postdose QRS duration < 60 ms and a decrease from baseline of > 20%.

PR interval

In the NOVA main and QTc substudy, no consistent differences were observed in postdose baseline-adjusted mean PR interval differences (ΔPR). The largest change (± SD) was − 5.4 ± 8.7 ms at 6 h postdose in the NOVA and QTc studies, and − 6.4 ± 6.05 ms at 4 h postdose in the fed group of the FE study, neither of which was clinically meaningful. No patient in any treatment group had a postdose PR interval > 220 ms and a ΔPR from baseline > 20%. However, in the NOVA and QTc substudy, there was one instance of a > 20% reduction in ΔPR interval and a PR interval of < 120 ms; the patient had a predose PR interval of 145.3 ms and a 4 h postdose value of 116 ms. No increase or decrease in the ΔPR > 20% was observed in the FE substudy.

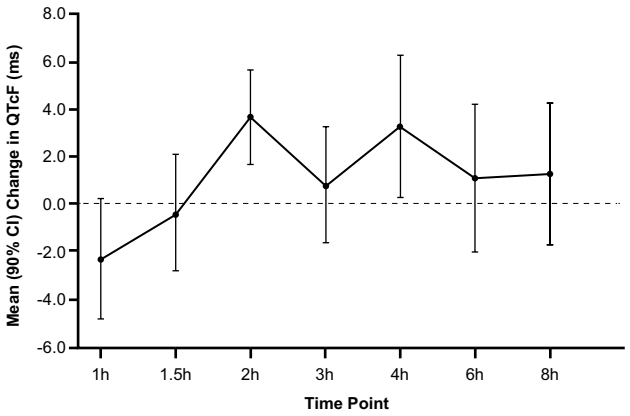

Fig. 1 Baseline- and placebo-corrected ΔQTcF (mean ± 90% CI) on day 1 in the NOVA main and QTc substudy

Table 2 Patients with postdose QTcF interval > 450 ms

Patient number	Baseline QTcF duration (ms)	Postdose time point (h)	QTcF duration (ms)
NOVA main and QTc substudy			
1	465.0	1.5	456.0
		2	465.0
2	446.7	2	451.3
		4	457.7
Food effect substudy			
1 (fasted)	455.7	2	454.3
2 (fasted)	448.0	1	456.3
3 (fasted)	450.7	1	450.3
		1.5	451.7
		2	454.3
		8	451.3
3 (fed)	452.7	8	452.0
4 (fasted)	443.0	1	451.3
		1.5	451.0

Clinical interpretation of ECG results

One patient in the QTc substudy population had a first-degree atrioventricular block 1 h postdose, which was considered an abnormal potentially clinically meaningful ECG finding. Of the three ECG readings taken at this timepoint, one was considered abnormal, possibly clinically relevant, and two were reported as abnormal but not clinically meaningful. The PR interval for these three ECGs was measured at 236 ms, 234 ms, and 242 ms. Although one ECG reading was > 240 ms, the triplicate average was 237 ms; the threshold for abnormal, potentially clinically relevant PR interval for this study was 240 ms. In the FE study, one patient had an abnormal potentially clinically relevant ECG finding at 3 h postdose described as a possible ectopic atrial rhythm and left axis deviation inferior infarct. Myocardial infarction was observed in two patients in the FE study on day 1, but not on day 8 when the second dose was administered. Therefore, such an onset did not appear to be associated with niraparib. Postdose ST or T wave abnormalities that were not present at baseline were noted in some patients at sporadic postdose timepoints (NOVA main and QTc substudy, $n = 2$ patients; FE study, $n = 7$); however, all of these repolarization abnormalities were determined to be nonspecific and not of clinical concern. No postdose U wave abnormalities, second-degree, and third-degree blocks, or bundle branch blocks that were not present at baseline were reported in any patient.

Relationship between niraparib plasma concentration and ΔQTcF

The relationship between niraparib plasma concentration and ΔQTcF was explored graphically, and the data were analyzed using a linear mixed-effects model. In the NOVA main and QTc substudy, the estimated slope (95% CI) was 0.0014 (−0.0031, 0.0060), with a geometric mean C_{max} of 740.3 ng/mL. In the FE study, the estimated slope (95% CI) was −0.0002 (−0.0060, 0.0055), with a geometric mean C_{max} of 835.8 ng/mL. When the data from the NOVA main, QTc and FE substudies were combined for the exposure–response analysis, no exposure-related positive trends were observed in mean QTcF or mean ΔQTcF versus time since dosing. More importantly, no statistically significant relationship between ΔQTcF and niraparib plasma concentration was observed (estimated slope: 0.0049, 95% CI: −0.0020, 0.0117; $p = 0.164$; Fig. 2).

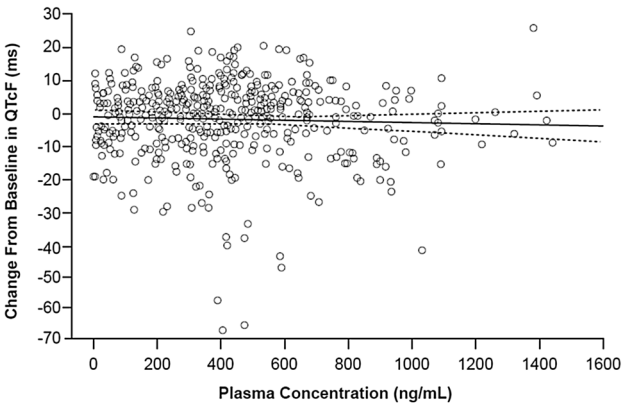

Fig. 2 Correlation between ΔQTcF and niraparib plasma concentration in all patients in the ECG study (NOVA main and food effect and QTc substudies)

Discussion

The International Conference on Harmonisation E14 guidelines emphasizes the need to evaluate cardiac safety in non-antiarrhythmic drugs due to their ability to delay cardiac repolarization (prolongation of the QT interval) [10], which is a common reason for post-marketing withdrawal of a drug from the market and requires stringent pharmacovigilance [9]. At the same time, the effect of new drugs on QT prolongation should be cautiously studied in a way such that it does not impede drug advancement or inappropriately disqualify patients from clinical trials based on QT prolongation criteria [13, 19]. The recent approval of niraparib as a maintenance therapy in EOC that has responded to platinum-based chemotherapy implies a longer-term, extended use of the drug in a potentially older, heavily pretreated population. The likelihood of cardiovascular disease and other comorbidities in this population necessitates an analysis of cardiac effects following niraparib treatment.

Because of the indication and nature of oncology drugs, these cannot be administered to healthy subjects at therapeutic concentrations; hence, a thorough QTc study cannot be conducted [13]. We therefore performed an intensive and comprehensive QTc analysis of patients from three niraparib studies to investigate the effect of niraparib on measures of cardiac ventricular repolarization. Traditional thorough QTc studies for non-antiarrhythmic drugs are considered negative with no increased risk of QTc prolongation, if the largest increase in the ΔQTcF is < 10 ms [10]. In our study, the upper bound of the two-sided 90% CI for ΔQTcF was ≤7 ms at every postdose time point (up to 8 h postdose). At no time postdose did the measurements indicate a mean ΔQTcF greater than 4.3 ms (at 3 h postdose) and an upper bound of the 90% CI for the mean ΔQTcF greater than 6.7 ms (at 3 h postdose). Notably, the 3 h postdose timepoint falls close to the median T_{max} of 4 h for 300-mg dose of niraparib [20], which is the daily recommended dose. These data represent a negative QTc study, indicating no clinically relevant effect of niraparib on cardiac repolarization as measured by the prolongation of QTcF interval.

Modeling the plasma concentration of niraparib versus ΔQTcF confirmed the lack of meaningful QTcF increases with increasing concentrations of niraparib. This finding is further supported by the findings that (1) no patient had a QTcF duration of > 480 ms or a ΔQTcF of ≥30 ms (or ≥60 ms) in any treatment group, (2) no patient had clinically significant changes in other cardiac parameters such as heart rate, PR interval, or QRS interval, as assessed by central tendency and categorical analysis, and (3) no patient had clinically relevant ECG abnormalities. Results of other QT analyses (i.e., QTcB and uncorrected QT interval) were in agreement with the results of the QTcF analysis (data not shown).

Two other PARP inhibitors, olaparib and rucaparib, have been approved for the treatment of EOC [21, 22]. Pooled data from two phase 1 open-label studies of olaparib showed a lack of clinically relevant effect on cardiac repolarization (upper limits of 90% CIs for the ΔQTcF least squares was < 10 ms) for single (100 and 300 mg; $n = 119$) and multiple (300 mg twice-dialy × 5 days; $n = 109$) doses compared with control (day − 1). Slight shortening of QTcF was reported at most postdose time points compared with control (baseline/day − 1); however, the lower limits of the 90% CI were > − 10 ms for all time points. No patient had QTcF of > 500 ms [11]. In an open-label single-arm PK study of rucaparib in patients with solid tumors who received continuous doses from 40 mg once-daily (0.03 times the approved dose) to 840 mg twice daily (1.4-times the approved dose), the mean increase in ΔQTcF was 14.9 (90% CI 11.1–18.7) ms at C_{max} for steady-state rucaparib 600 mg twice daily [22]. Increasing plasma concentration of rucaparib seemed to be associated with increasing QTcF from baseline. Of the 55 patients with baseline and postdose ECG measurements available, 6 (11%) had at least 1 postbaseline QTcF measurement > 450 ms and 10 (18%) had ΔQTcF increases > 30 ms [23]. The current robust QTcF analysis of niraparib in a pooled population from three substudies did not show any patient with a ΔQTcF of > 60 ms and/or an absolute QTcF interval of > 480 ms, and there was no adverse effect of niraparib exposure. Overall, the cardiac safety of niraparib compares favorably with that of the existing PARP inhibitors for EOC.

In conclusion, administration of niraparib at the therapeutic dose (single dose of 300 mg daily) did not prolong the QTcF interval. There was no significant correlation between niraparib exposure and ΔQTcF. Additionally, categorical summaries of percentage of patients with ΔQTcF of 0–30, 31–60, and > 60 ms and/or with a QTcF > 480 ms were concordant with lack of correlation between the exposure and the ΔQTcF. There were no clinically relevant changes in other ECG parameters or abnormal ECG findings attributable to the administration of niraparib. These results are consistent with clinical experience with niraparib and indicate that niraparib does not demonstrate a propensity to prolong the QTcF interval in patients with EOC.

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Compliance with ethical standards

Conflict of interest K.M. has served on the advisory borads of and received honoraria from AstraZeneca, Advaxis, Clovis, Genentech/Roche, Immunogen, VBL Therapeutics, Janssen, Tesaro, Merck, Aravive, and OncoMed; K.M. also serves as the USA PI for the Tesaro-sponsored FIRST study using niraparib in front-line ovarian cancer and serves as the national PI for the niraparib study QUADRA. J.K.C. has received honoraria for a consulting role from Tesaro, Acerta, Aravive, Biodesix, Clovis, Janssen/Johnson & Johnson, Oxigen/Mateon, Roche/Genentech, and AstraZeneca, has received honoraria for lectures including speakers' bureaus from AstraZeneca, Clovis, Merck, Roche/Genentech, and Tesaro. A.S.S. has received grants from AbbVie, Amgen, Astellas Pharma Inc., Astex Pharmaceuticals Inc., AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Eisai, Endocyte, Exelixis, Incyte, Merck, PharmaMar, Prima Biomed, Roche/Genentech, TapImmune, and honoraria for advisory boards from Tesaro, Alexion, Aravive, Astex, AstraZeneca, Boehringer Ingelheim, Clovis, Janssen/Johnson & Johnson, Merck, Mersano, Myriad, Oncoquest, Precision Therapeutics, and Roche/Genentech. M.R.P. has nothing to disclose. T.C. is an employee of BioTel Research. W.G. and Z.Y.Z. employees of Tesaro, Inc and own stock/have other ownership with Tesaro. Medical writing and copyediting support, funded by TESARO, Inc. and coordinated by Hemant Vyas, PhD, of TESARO, Inc, was provided by Swati Ghatpande, PhD, and Ann Marcos, MA, ELS, of Team 9 Science, LLC (Vaniam Group LLC).

Appendix

See Tables 3 and 4.

Table 3 Absolute mean QTcF and mean ΔQTcF at postdose time points in the NOVA main and QTc substudy

NOVA main and QTc substudy				
Postdose time point/statistics	Baseline QTcF (ms)	Postdose QTcF (ms)	Change from baseline	Change from baseline and placebo
1 h				
n	36	36	36	36
Mean (SD)	415.8 (16.72)	416.5 (14.91)	0.8 (9.23)	−2.2 (9.23)
90% CI of mean	411.1, 420.5	412.3, 420.7	−1.8, 3.3	−4.8, 0.3
1.5 h				
n	35	35	35	35
Mean (SD)	415.5 (16.88)	418.5 (16.72)	3.1 (8.67)	−0.3 (8.67)
90% CI of mean	410.7, 420.3	413.8, 423.3	0.6, 5.5	−2.8, 2.1
2 h				
n	36	36	36	36
Mean (SD)	415.8 (16.72)	419.7 (17.15)	3.9 (6.97)	3.7 (6.97)
90% CI of mean	411.1, 420.5	414.9, 424.5	2.0, 5.9	1.7, 5.7
3 h				
n	36	36	36	36
Mean (SD)	415.8 (16.72)	420.0 (15.42)	4.3 (8.80)	0.8 (8.80)
90% CI of mean	411.1, 420.5	415.7, 424.4	1.8, 6.7	−1.6, 3.3
4 h				
n	36	36	36	36
Mean (SD)	415.8 (16.72)	419.2 (14.67)	3.5 (10.63)	3.3 (10.63)
90% CI of mean	411.1, 420.5	415.1, 423.4	0.5, 6.5	0.3, 6.3
6 h				
n	36	36	36	36
Mean (SD)	415.8 (16.72)	415.6 (12.92)	−0.1 (10.95)	1.1 (10.95)
90% CI of mean	411.1, 420.5	412.0, 419.3	−3.2, 2.9	−2.0, 4.2
8 h				
n	36	36	36	36
Mean (SD)	415.8 (16.72)	416.4 (13.56)	0.6 (10.73)	1.3 (10.73)
90% CI of mean	411.1, 420.5	412.6, 420.2	−2.4, 3.7	−1.7, 4.3

Table 4 Absolute mean QTcF and mean ΔQTcF at postdose time points in the food effect study

Food effect substudy						
Postdose time point/ statistics	Baseline QTcF (ms)	Postdose QTcF (ms) with food	Change from baseline	Baseline QTcF (ms)	Postdose QTcF (ms) without food	Change from baseline
1 h						
n	15	15	15	16	16	16
Mean (SD)	423.6 (21.36)	413.3 (16.10)	− 10.4 (13.76)	424.7 (18.55)	425.9 (17.39)	1.2 (6.54)
90% CI of mean	413.9, 433.4	405.9, 420.6	− 16.6, − 4.1	416.6, 432.9	418.3, 433.5	− 1.7, 4.1
1.5 h						
n	15	15	15	14	14	14
Mean (SD)	423.6 (21.36)	412.3 (18.88)	− 11.4 (12.56)	423.5 (18.72)	424.1 (16.14)	0.5 (6.64)
90% CI of mean	413.9, 433.4	403.7, 420.9	− 17.1, − 5.6	414.7, 432.4	416.4, 431.7	− 2.6, 3.7
2 h						
n	15	15	15	16	16	16
Mean (SD)	423.6 (21.36)	412.1 (18.48)	− 11.5 (12.17)	424.7 (18.55)	423.9 (19.07)	− 0.8 (6.17)
90% CI of mean	413.9, 433.4	403.7, 420.5	− 17.1, − 6.0	416.6, 432.9	415.5, 432.3	− 3.5, 1.9
3 h						
n	15	15	15	16	16	16
Mean (SD)	423.6 (21.36)	415.2 (16.83)	− 8.4 (12.02)	424.7 (18.55)	422.3 (15.35)	− 2.4 (12.19)
90% CI of mean	413.9, 433.4	407.6, 422.9	− 13.9, − 2.9	416.6, 432.9	415.6, 429.1	− 7.7, 2.9
4 h						
n	15	15	15	16	16	16
Mean (SD)	423.6 (21.36)	415.7 (19.92)	− 7.9 (16.43)	424.7 (18.55)	416.1 (17.70)	− 8.6 (12.72)
90% CI of mean	413.9, 433.4	406.7, 424.8	− 15.4, − 0.5	416.6, 432.9	408.3, 423.9	− 14.2, − 3.1
6 h						
n	15	15	15	16	16	16
Mean (SD)	423.6 (21.36)	413.9 (20.18)	− 9.7 (18.78)	424.7 (18.55)	418.2 (15.33)	− 6.5 (12.69)
90% CI of mean	413.9, 433.4	404.8, 423.1	− 18.3, − 1.2	416.6, 432.9	411.5, 424.9	− 12.1, − 1.0
8 h						
n	15	15	15	16	16	16
Mean (SD)	423.6 (21.36)	415.7 (19.89)	− 7.9 (18.78)	424.7 (18.55)	420.5 (14.84)	− 4.2 (11.78)
90% CI of mean	413.9, 433.4	406.7, 424.8	− 16.5, 0.6	416.6, 432.9	414.0, 427.0	− 9.4, 0.9

References

1. Morales J, Li L, Fattah FJ, Dong Y, Bey EA, Patel M, Gao J, Boothman DA (2014) Review of poly (ADP-ribose) polymerase (PARP) mechanisms of action and rationale for targeting in cancer and other diseases. Crit Rev Eukaryot Gene Expr 24(1):15–28
2. Sandhu SK, Schelman WR, Wilding G, Moreno V, Baird RD, Miranda S, Hylands L, Riisnaes R, Forster M, Omlin A, Kreischer N, Thway K, Gevensleben H, Sun L, Loughney J, Chatterjee M, Toniatti C, Carpenter CL, Iannone R, Kaye SB, de Bono JS, Wenham RM (2013) The poly(ADP-ribose) polymerase inhibitor niraparib (MK4827) in BRCA mutation carriers and patients with sporadic cancer: a phase 1 dose-escalation trial. Lancet Oncol 14(9):882–892. https://doi.org/10.1016/S1470-2045(13)70240-7
3. Mirza MR, Monk BJ, Herrstedt J, Oza AM, Mahner S, Redondo A, Fabbro M, Ledermann JA, Lorusso D, Vergote I, Ben-Baruch NE, Marth C, Madry R, Christensen RD, Berek JS, Dorum A, Tinker AV, du Bois A, Gonzalez-Martin A, Follana P, Benigno B, Rosenberg P, Gilbert L, Rimel BJ, Buscema J, Balser JP, Agarwal S, Matulonis UA, Investigators E-ON (2016) Niraparib maintenance therapy in platinum-sensitive, recurrent ovarian cancer. N Engl J Med 375(22):2154–2164. https://doi.org/10.1056/NEJMoa1611310
4. Shinn EH, Lenihan DJ, Urbauer DL, Basen-Engquist KM, Valentine A, Palmero L, Woods ML, Patel P, Nick AM, Shahzad MM, Stone RL, Golden A, Atkinson E, Lutgendorf SK, Sood AK (2013) Impact of cardiovascular comorbidity on ovarian cancer mortality. Cancer Epidemiol Biomark Prev 22(11):2102–2109. https://doi.org/10.1158/1055-9965.EPI-13-0625
5. Woopen H, Inci G, Richter R, Chekerov R, Ismaeel F, Sehouli J (2016) Elderly ovarian cancer patients: an individual participant data meta-analysis of the North-Eastern German Society of Gynecological Oncology (NOGGO). Eur J Cancer 60:101–106. https://doi.org/10.1016/j.ejca.2016.03.008
6. Accordino MK, Neugut AI, Hershman DL (2014) Cardiac effects of anticancer therapy in the elderly. J Clin Oncol 32(24):2654–2661. https://doi.org/10.1200/JCO.2013.55.0459
7. Duan J, Tao J, Zhai M, Li C, Zhou N, Lv J, Wang L, Lin L, Bai R (2018) Anticancer drugs-related QTc prolongation, torsade de pointes and sudden death: current evidence and future

research perspectives. Oncotarget 9(39):25738–25749. https://doi.org/10.18632/oncotarget.25008
8. Albini A, Pennesi G, Donatelli F, Cammarota R, De Flora S, Noonan DM (2010) Cardiotoxicity of anticancer drugs: the need for cardio-oncology and cardio-oncological prevention. J Natl Cancer Inst 102(1):14–25. https://doi.org/10.1093/jnci/djp440
9. Coppola C, Rienzo A, Piscopo G, Barbieri A, Arra C, Maurea N (2018) Management of QT prolongation induced by anticancer drugs: target therapy and old agents. Different algorithms for different drugs. Cancer Treat Rev 63:135–143. https://doi.org/10.1016/j.ctrv.2017.11.009
10. ICH Harmonised Tripartite Guideline (2005) The clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs E14. http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E14/E14_Guideline.pdf. Accessed 6 Sept 2018
11. Swaisland H, Plummer R, So K, Garnett S, Bannister W, Fabre MA, Dota C, Fielding A (2016) Olaparib does not cause clinically relevant QT/QTc interval prolongation in patients with advanced solid tumours: results from two phase I studies. Cancer Chemother Pharmacol 78(4):775–784. https://doi.org/10.1007/s00280-016-3124-5
12. Bednar MM, Harrigan EP, Anziano RJ, Camm AJ, Ruskin JN (2001) The QT interval. Prog Cardiovasc Dis 43(5 Suppl 1):1–45
13. Strevel EL, Ing DJ, Siu LL (2007) Molecularly targeted oncology therapeutics and prolongation of the QT interval. J Clin Oncol 25(22):3362–3371. https://doi.org/10.1200/JCO.2006.09.6925
14. Giorgi MA, Bolanos R, Gonzalez CD, Di Girolamo G (2010) QT interval prolongation: preclinical and clinical testing arrhythmogenesis in drugs and regulatory implications. Curr Drug Saf 5(1):54–57
15. US Food and Drug Adminstration: Application number 208447Orig1s000—NDA/BLA multi-disciplinary review and evaluation of niraparib. Reference ID: 4074987. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/208447Orig1s000MultidisciplineR.pdf. Accessed 12 Sept 2018
16. Zejula® (niraparib) prescribing information (2018) TESARO IW, MA. https://www.zejula.com/prescribing-information. Accessed 6 Sept 2018
17. Prat J, Oncology FCoG (2015) Staging classification for cancer of the ovary, fallopian tube, and peritoneum: abridged republication of guidelines from the International Federation of Gynecology and Obstetrics (FIGO). Obstet Gynecol 126(1):171–174. https://doi.org/10.1097/AOG.0000000000000917
18. Moore K, Zhang ZY, Agarwal S, Burris H, Patel MR, Kansra V (2018) The effect of food on the pharmacokinetics of niraparib, a poly(ADP-ribose) polymerase (PARP) inhibitor, in patients with recurrent ovarian cancer. Cancer Chemother Pharmacol 81(3):497–503. https://doi.org/10.1007/s00280-017-3512-5
19. Fingert H, Varterasian M (2006) Safety biomarkers and the clinical development of oncology therapeutics: considerations for cardiovascular safety and risk management. AAPS J 8(1):E89–E94. https://doi.org/10.1208/aapsj080110
20. van Andel L, Rosing H, Zhang Z, Hughes L, Kansra V, Sanghvi M, Tibben MM, Gebretensae A, Schellens JHM, Beijnen JH (2018) Determination of the absolute oral bioavailability of niraparib by simultaneous administration of a (14)C-microtracer and therapeutic dose in cancer patients. Cancer Chemother Pharmacol 81(1):39–46. https://doi.org/10.1007/s00280-017-3455-x
21. Lynparza® (olaparib) prescribing information (2018) AstraZeneca Pharmaceuticals (Wilmington, DE). https://www.azpicentral.com/lynparza_tb/pi_lynparza_tb.pdf#page=1. Accessed 24 Oct 2018
22. Rubraca® (rucaparib) prescribing information (2018) Clovis Oncology, Inc. (Boulder, CO). http://www.clovisoncology.com/media/1094/rubraca-prescribing-info.pdf. Accessed 6 Sept 2018
23. European Medicines Agency: EMA/CHMP/238139/2018—Assessment report of the European Medicines Agency (2018) Procedure No. EMEA/H/C/004272/0000. https://www.ema.europa.eu/documents/assessment-report/rubraca-epar-public-assessment-report_en.pdf. Accessed 6 Sept 2018

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