Real-world adverse events with niraparib 200 mg/day maintenance therapy in ovarian cancer: a retrospective study

Jack R Gallagher^{*1}, Kylee Jean Heap¹, Susan Carroll¹, Karin Travers², Brooke Harrow³ & Shannon N Westin⁴

¹Clarity Pharma Research, LLC, 2375 E Main St., Spartanburg, SC 29307, USA

²TESARO: A GSK Company, 1000 Winter St North, Waltham, MA 02451, USA

³IPSEN, 650 E Kendall St, Cambridge, MA 02142, USA

⁴The University of Texas MD Anderson Cancer Center, Department of Gynecologic Oncology & Reproductive Medicine, Unit 1362, 1515 Holcombe Blvd., Houston, TX 77030, USA

*Author for correspondence: Tel.: +1 864 208 0092; Fax: +1 803 724 6801; jgallagher@claritypharma.com

Aim: To assess real-world occurrence of common clinical trial-reported adverse events (AE) among patients with recurrent ovarian cancer initiating niraparib 200 mg/day. **Materials & methods:** This retrospective observational study used physician-extracted anonymized medical record data of eligible patients initiating niraparib 200 mg/day after platinum-based chemotherapy. **Results:** Of 153 patients, 57 (37%) experienced ≥ 1 of the three most common all-grade AEs within 3 months after niraparib initiation: nausea (16%; grade 3/4: 2%), thrombocytopenia (14%; grade 3/4: 3%) and fatigue (24%; grade 3/4: 3%). In the ENGOT-OV16/NOVA trial, these respective AEs occurred in 74, 61 and 59% of patients. **Conclusion:** Incidence of common clinical trial-reported AEs was lower among patients initiating niraparib 200 mg/day in real-world practice versus patients initiating niraparib 300 mg/day in ENGOT-OV16/NOVA.

First draft submitted: 5 August 2019; Accepted for publication: 7 October 2019; Published online: 11 November 2019

Keywords: adverse events • niraparib • ovarian cancer • PARP inhibitor • real-world occurrence

Niraparib is an oral PARP1/2 inhibitor approved for the maintenance treatment of women with recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer who are in a complete response (CR) or partial response (PR) to platinum-based chemotherapy. The approval of niraparib was based on results of the randomized Phase III ENGOT-OV16/NOVA (NOVA) study that showed a significant improvement in progression-free survival (PFS) compared with placebo in women with a germline *BRCA* mutation (21 vs 5.5 months, respectively; hazard ratio: 0.26; 95% confidence interval [CI]: 0.17–0.41; $p < 0.0001$) or without a germline *BRCA* mutation (9.3 vs 3.9 months, respectively; hazard ratio: 0.45; 95% CI: 0.34–0.61; $p < 0.0001$) [1].

Niraparib 300 mg once daily is the approved starting dose for all patients in the USA and European Union [2,3]. Subsequently, the European Union suggested a starting dose of 200 mg for patients who weigh less than 58 kg [3]. In a retrospective analysis of the NOVA study by Berek *et al.*, niraparib 200 mg/day (median 207 mg/day) was reported as the most commonly administered dose at month 3 following protocol-specified dose reduction for adverse events (AEs) [4]. Notably, the incidence of common AEs at the onset of event was higher with the 300-mg dose of niraparib maintenance compared with the 200-mg dose: the rate of any-grade thrombocytopenia among patients receiving 300 mg niraparib at the onset of the event was 59.9% compared with 35.4% among those receiving 200 mg niraparib. Rates of fatigue in the 300-mg and 200-mg maintenance groups were 34.1 and 26.0%, respectively, and rates for nausea were 67.8 and 26.8%, respectively. Furthermore, dose-reduced patients showed a PFS comparable to those without dose reductions (recommended 300 mg/day starting dose) [4]. Patients with a baseline body weight < 77 kg and/or platelet count $< 150,000/\mu\text{l}$ were most likely to require a dose reduction [4]. Recent data from the PRIMA and QUADRA studies (discussed in detail the ‘Discussion’ section) also confirm a lower incidence of any-grade and grade ≥ 3 AEs at lower doses of niraparib as maintenance therapy in patients with a high risk of progression [5] and as a treatment in heavily pretreated patients who have received four or

more lines of prior therapy [6]. Some patients in real-world practice who initiate niraparib maintenance therapy fall into the pretreatment body weight and platelet count thresholds and are therefore predicted to likely require dose reduction [7]. These patients might be good candidates for lower niraparib dosing without compromising efficacy. Additionally, starting a patient on niraparib 200 mg/day does not exclude dose escalation at the clinician's discretion as needed.

The most common any-grade AEs reported in niraparib-treated patients in the NOVA trial were nausea (74%), thrombocytopenia (61%) and fatigue (59%) [1]. The retrospective analysis by Berek *et al.* showed that most grade ≥ 3 hematologic toxicities in the NOVA trial occurred within the first 3 months of niraparib initiation at 300 mg/day. These included thrombocytopenia (33%), anemia (13%) and neutropenia (18%), which were managed through dose reductions [4]. Only 27.6% of patients remained on the 300 mg dose/day after month 3 of niraparib maintenance. With protocol-specified dose reductions, the incidence of grade 3/4 hematologic toxicities decreased substantially after month 3: thrombocytopenia declined to 0.7% and neutropenia decreased to 1.6%; no substantial change in the incidence of grade 3/4 anemia (15%) was observed after month 3 [4].

Although real-world evidence is gaining importance in postapproval drug evaluation and in regulatory and healthcare decisions [8], there is a paucity of published studies evaluating dosing patterns and safety of PARP inhibitors in the real world [9]. In light of prior clinical trial data showing that niraparib 200 mg/day is the commonly administered dose after month 3, as well as a lower incidence of AEs with niraparib dose reduction to 200 mg and lower, our research was designed to identify physicians who prescribed a starting dose of niraparib 200 mg/day to their patients with recurrent ovarian cancer and quantify the extent to which patients experienced clinical-trial reported AEs at this dose in a real-world setting. Using the three most common any-grade AEs (nausea, thrombocytopenia and fatigue) from NOVA at a starting dose of niraparib 300 mg/day as a reference, we provide real-world incidence of these common AEs in patients with platinum-sensitive, recurrent ovarian cancer initiating niraparib at a starting dose of 200 mg/day in clinical practices across the USA.

Materials & methods

Study design

In this retrospective observational study, qualified physicians identified medical records of eligible patients across the USA in compliance with the Health Insurance Portability and Accountability Act of 1996. The study was conducted by Clarity Pharma Research, LLC, and sponsored by TESARO: a GSK Company. Physicians or their authorized staff collected the data; Clarity Pharma Research was blinded to patients' identities and did not have access to any personally identifiable health information. Findings were reported in the aggregate, and the final analysis database was de-identified and anonymized. The study was exempt from institutional board review according to 45CFR46.101(b)(4): Existing Data & Specimens – No Identifiers.

Physicians with a specialty in gynecologic oncology, hematology, hematology/oncology or obstetrics and gynecology were recruited by email and telephone screening to qualify for the research study and completed a review of qualified electronic medical records (EMRs) via an online interface. The prerequisite for physician qualification was caring for at least one patient with recurrent ovarian cancer receiving niraparib maintenance therapy for whom a starting dose of 200 mg/day was prescribed (lasting at least 1 day) within the past 12 months, but not more recently than 3 months before data extraction, and who had finished a platinum-based regimen within 14 weeks of niraparib initiation.

Patients

The participating physicians retrospectively selected patients from EMRs based on following eligibility criteria: patients were ≥ 18 years of age with a diagnosis of recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer and in a CR or PR to platinum-based chemotherapy. All patients had received a starting dose of niraparib 200 mg/day as maintenance for at least one day within the past 12 months. Dosing strategies (dose escalation, dose reduction or dose discontinuation) could be changed as needed after the starting dose of niraparib 200 mg/day. Thus, patients who initiated niraparib treatment at 200 mg/day and had a subsequent dose modification were eligible for inclusion. Patients were included if their records documented AEs of interest, demographics, treatment duration, previous lines of therapy, laboratory values, response to prior treatment, outcomes of thrombocytopenia and dose reductions or interruptions. Patients had at least 3 months of follow-up after initiating niraparib. Baseline characteristics were captured including age, body weight, Eastern Cooperative Oncology Group performance status, baseline laboratory values, *BRCA* mutation status and limited history of ovarian cancer treatment.

It should be noted that our screening criteria did not require a weight-based evaluation for starting a patient on a 200 mg/day niraparib dose as a maintenance therapy. Since the study was restricted to US patients only, the weight-limiting recommendations of the European Medicines Agency would not necessarily be followed by physicians in the USA. Since anecdotal information indicated that some physicians in real-world practice were prescribing 200 mg/day as a starting dose for maintenance therapy, we focused on this cohort of patients in our study.

Sample size

The study aimed to collect 100–150 eligible cases from qualified physicians within an anticipated recruitment period of 5–6 weeks, although a minimum sample size was not guaranteed. Estimated ranges of sampling error for possible sample sizes were as follows: ± 4.6 percentage points to ± 7.7 percentage points for 150 cases, ± 6.7 percentage points to ± 11.1 percentage points for 75 cases, ± 8.2 percentage points to ± 13.7 percentage points for 50 cases, and ± 10.7 percentage points to ± 17.8 percentage points for 30 cases.

We conducted a subsequent power analysis to determine adequacy of the sample size after the target patients were actually identified based on anonymous information from the EMRs. This evaluation indicated that the study sample size obtained for comparison of each of the three target AEs (nausea, thrombocytopenia and fatigue) with the corresponding three AEs from the NOVA study provided a statistical power of 95% with a 95% CI ($p = 0.05$). Thus, our study obtained adequate sample size to meet its objectives.

Outcome measures

The main outcome measure of interest was the rate of the three most common clinical trial-reported AEs (nausea, thrombocytopenia and fatigue) in the chosen real-world patient sample within the first 3 months of initiating niraparib 200 mg/day. Additional outcomes included the rate of dose interruptions, reductions and discontinuations within the same time frame. Descriptive summary statistics were provided, with no hypothesis testing.

Inaccurate or missing information from EMRs was minimized by screening out selected physicians who did not have access to key patient information required for the study and incorporating error-prevention programming into the EMRs, such as an alert and a request for verification or correction when a response was missing or beyond an expected range, as well as automatic calculation of time intervals to minimize physician calculation errors.

Results

Patient demographics & characteristics

A total of 87 specialists were screened for the study, of whom 53 (61%) participated. Of the 53 participating physicians, 33 (62%) specialized in hematology/oncology, 15 (28%) in gynecology oncology, 4 (8%) in obstetrics and gynecology and 1 (2%) in hematology. The remaining 34 of the 87 screened physicians did not qualify for the study mainly because they did not fulfill the participation criteria. One of the 34 nonparticipating physicians chose not to participate despite qualifying for the study.

The participating physicians (each of whom had treated at least one target patient) extracted requested anonymous information from the EMRs of 153 qualified patients. Each physician managed between 5 and 15 patients (median: 13 patients) in the prior 12 months for whom niraparib was prescribed as maintenance therapy after platinum-based chemotherapy. Table 1 summarizes patient demographics and characteristics at baseline (before initiating niraparib 200 mg/day). A limit of 14 weeks was enforced as the time between when study patients could end a platinum-based chemotherapy regimen and start niraparib. Patients had a median age of 59 years, a median body weight of 70 kg and a median of two prior lines of chemotherapy. Overall, 104 patients (68%) were diagnosed with stage III/IV disease, and 6 patients (4%) had received another PARP inhibitor before starting niraparib. More patients were in a CR ($n = 89$; 58%) than in a PR ($n = 64$; 42%) after platinum-based chemotherapy at the time of niraparib initiation. The median time between the end of platinum-based chemotherapy and initiating niraparib 200 mg/day was 33 days (range: 0–95 days).

Adverse events

Overall, 57 of the 153 patients (37%) who initiated niraparib 200 mg/day experienced at least one of the three most common clinical trial-reported AEs (nausea, thrombocytopenia or fatigue) within the first 3 months. Of these 57 patients, 50 (88%) experienced grade 1/2 AEs (grade 1: 41%; grade 2: 48%) and 7 (12%) experienced grade 3/4 AEs (grade 3: 10%; grade 4: 2%). No deaths were reported.

Table 1. Patient demographics and characteristics at baseline (before initiating niraparib 200 mg/day).

Characteristic	Patients starting niraparib 200 mg/day (n = 153)
Age (years):	
– Median	59 (35–78)
– 50–69 years	103 (67)
Body weight, kg, median (range)	70 (43–113)
ECOG performance status:	
– 0	50 (33)
– 1	67 (44)
– 2	28 (18)
– 3	6 (4)
– 4	2 (1)
Type of recurrent cancer:	
– Epithelial ovarian	92 (60)
– Fallopian tube	37 (24)
– Primary peritoneal	24 (16)
Cancer stage at original diagnosis:	
– Stage I	20 (13)
– Stage II	29 (19)
– Stage III	73 (48)
– Stage IV	31 (20)
Prior PARP inhibitor use	6 (4)
Prior lines of chemotherapy including most recent:	
– 1	50 (33)
– 2	77 (50)
– ≥3	26 (17)
Prior lines of chemotherapy	2 (1–6)
Response to most recent platinum-based chemotherapy:	
– Complete response	89 (58)
– Partial response	64 (42)
Albumin level (g/dl)	3.9 (2.4–5.4)
Platelet count (/μl)	178,000 (12,000–411,000)
Prior thrombocytopenia (during the treatment immediately before niraparib)	17 (11)
Patients tested for germline <i>BRCA</i> mutation [†] :	100 (65)
– Germline <i>BRCA1</i> detected	35/100 (35)
– Germline <i>BRCA2</i> detected	17/100 (17)
– No germline <i>BRCA1</i> or <i>BRCA2</i> detected	48/100 (48)
Patients tested for somatic <i>BRCA</i> mutation [†] :	64 (42)
– Somatic <i>BRCA1</i> detected	18/64 (28)
– Somatic <i>BRCA2</i> detected	9/64 (14)
– No somatic <i>BRCA1</i> or <i>BRCA2</i> detected	37/64 (58)
Median time between initial diagnosis and start of niraparib (days)	363 (242–2385)
Median time between initial diagnosis and first recurrence (days)	313 (91–2236)
Median time between end of most recent platinum-based chemotherapy and start of niraparib (days)	33 (0–95)
Data represented as n (%) or median (range).	
[†] A total of 48 patients were not tested for germline <i>BRCA</i> or somatic <i>BRCA</i> mutations combined.	
ECOG: Eastern Cooperative Oncology Group.	

Table 2. Frequency of the three most common adverse events alone or in combination.[†]

AE experienced [‡]	Patients (n)	Percentage (95% CI)	Grade 1	Grade 2	Grade 3	Grade 4
Fatigue (all cases)	37	24.2 (17.4–31.0)	16 (43)	17 (46)	3 (8)	1 (3)
Fatigue (only)	14	9.2 (4.6–13.7)	9 (64)	4 (29)	1 (7)	0
Fatigue in combination with other common AEs	23	15.0 (9.4–20.7)	7 (30)	13 (57)	2 (9)	1 (4)
Thrombocytopenia (all cases)	21	13.7 (8.3–19.2)	6 (29)	11 (52)	4 (19)	0
Thrombocytopenia (only)	9	5.9 (2.2–9.6)	2 (22)	4 (44)	3 (33)	0
Thrombocytopenia in combination with other common AEs	12	7.8 (3.6–12.1)	4 (33)	7 (58)	1 (8)	0
Nausea (all cases)	24	15.7 (9.9–21.4)	11 (46)	10 (42)	2 (8)	1 (4)
Nausea (only)	8	5.2 (1.7–8.8)	6 (75)	2 (25)	0	0
Nausea in combination with other common AEs	16	10.5 (5.6–15.3)	5 (31)	8 (50)	2 (13)	1 (6)

Data shown as n (%) unless otherwise stated.
[†] Alone or in combination with fatigue, thrombocytopenia, nausea, diarrhea and vomiting.
[‡] There were no reports of grade 5 AEs.
 AE: Adverse event.

Figure 1. Comparison of the three most common adverse events among patients in real-world clinical practice (starting niraparib 200 mg/day) versus patients in the NOVA trial (starting niraparib 300 mg/day). In the real-world data, the overall frequency of each of the most common AEs was calculated as that AE occurring alone or in combination with other common AEs that included fatigue, thrombocytopenia, nausea, diarrhea and vomiting. AE: Adverse event.

Table 2 shows the incidence of the three most common AEs of interest experienced alone or in combination in the first 3 months by the real-world patient sample. Fatigue occurred in 37 patients (24%), nausea in 24 patients (16%) and thrombocytopenia in 21 patients (14%) in the real-world sample of patients starting niraparib 200 mg/day. Overall, 4 (3%) of 153 patients in the real-world sample experienced grade 3/4 thrombocytopenia with niraparib 200 mg/day (Figure 1). In the NOVA trial, 124 (34%) of 367 patients experienced grade 3/4 thrombocytopenia with niraparib 300 mg/day. Notably, of the 153 patients analyzed in the real-world setting, 17 (11%) had been diagnosed with grade 1–3 thrombocytopenia during a prior treatment regimen before starting niraparib. Of these 17 patients, only 4 experienced thrombocytopenia (grade 1, n = 3; grade 2, n = 1) after initiating niraparib maintenance therapy. Only one of the 17 patients diagnosed with thrombocytopenia from a prior regimen received a platelet transfusion before niraparib initiation, and interestingly, this patient did not experience an AE during niraparib treatment.

Table 3. Rate of dose interruptions, reductions and discontinuations among total patients receiving niraparib 200 mg/day (n = 153) and in the subset experiencing ≥1 of the 3 most common AEs (n = 57).			
Type of Change	Overall (n = 153)	Patients who experienced ≥1 of the three most common AEs (n = 57)	Median time from niraparib initiation to AE onset, days (n = 153)
Dose increases†	40 (26)	0	47
Dose interruptions	6 (4)	6 (11)	28
Dose reductions	17 (11)	17 (30)	45
Treatment discontinuation	3 (2)	3 (5)	33
Data shown as n(%) unless otherwise stated.			
†From a niraparib dose of 200 to 300 mg/day.			
AE: Adverse event.			

Dose modifications & treatment discontinuations due to AEs

AEs that were reported with a dose reduction, interruption or discontinuation included thrombocytopenia (n = 14), fatigue (n = 12), nausea (n = 8), diarrhea (n = 5) and vomiting (n = 4), although the physician was not asked which specific AE led to the change in niraparib dosing. Notably, anemia and neutropenia did not lead to treatment discontinuation. Table 3 shows the rate of dose modifications and treatment discontinuations due to AEs in the overall real-world sample of patients who started niraparib 200 mg/day (all AEs; n = 153) and in patients who experienced ≥1 of the most common AEs (n = 57). In the overall real-world patient sample (n = 153), 17 patients (11%) had dose reductions from the starting dose of 200 mg/day to resolve AEs within a median of 45 days of starting niraparib, 6 patients (4%) had dose interruptions due to AEs within a median of 28 days of starting niraparib and 3 patients (2%) discontinued niraparib within a median of 33 days of starting niraparib. Overall, 40 patients (26%) in the total sample (n = 153) had their doses increased from niraparib 200 to 300 mg/day within a median of 47 days of niraparib use.

Discussion

In our retrospective observational study of 153 patients with recurrent ovarian cancer who initiated niraparib 200 mg/day, the real-world occurrence of common AEs, including grade 3/4 AEs (nausea: 2%; thrombocytopenia: 3%; and fatigue: 3%) was substantially lower than the same AEs in patients initiating niraparib 300 mg/day in the NOVA study [1]. Only 37% of patients experienced ≥1 of the three most common any-grade AEs within 3 months after niraparib initiation, including nausea (16%), thrombocytopenia (14%), and fatigue (24%). In the NOVA trial, these respective AEs occurred in 74, 61, and 59% of patients [1].

NOVA was the first randomized, placebo-controlled Phase III trial demonstrating the efficacy of niraparib at a starting dose of 300 mg/day regardless of *BRCA* mutation status [1], which led to the approval of niraparib as a maintenance therapy for patients with recurrent high-grade epithelial ovarian cancer in the USA and European Union [4]. Dose modifications were frequently employed in the NOVA trial, and doses lower than 300 mg/day led to a reduction in the frequency of AEs, particularly thrombocytopenia, along with preservation of efficacy [1,4]. Based on these observations from NOVA, the current study was undertaken to understand if physicians are administering niraparib at lower doses in clinical practices across the USA, and consequently, if the frequency of common clinical trial-reported common AEs in real-world patients is also lowered.

A high recurrence rate of 75% within 18–28 months of completion of initial therapy and a 5-year survival rate of 30–50% highlights the poor prognosis of recurrent ovarian cancer and the need for an effective and tolerable maintenance therapy [10,11]. The approval of the PARP inhibitors niraparib, olaparib and rucaparib as maintenance therapy following platinum-based chemotherapy has been an advancement in the treatment of ovarian cancer due to the marked improvement in PFS shown when compared with placebo, allowing some patients to live longer with their disease [12].

All three PARP inhibitors currently approved for maintenance therapy show an encouraging PFS benefit; however, hematologic toxicity has been a common AE associated with PARP inhibitor treatment [1,13–15]. Current guidance on dose modifications in the niraparib prescribing information suggests withholding treatment for up to 28 days for hematologic AEs, then resuming at a reduced dose of 200 and 100 mg/day at the first and second occurrence, respectively, of the hematologic AE [1,2]. In the NOVA trial, although grade 3/4 hematologic toxicities were common (thrombocytopenia [34%], anemia [25%] and neutropenia [20%]), these AEs were effectively managed through protocol-specified dose modifications, likely resulting in a low rate of treatment discontinuation

(3% due to thrombocytopenia, 2% due to neutropenia and 1% due to anemia) [1]. A retrospective multivariate analysis of the NOVA safety population by Berek *et al.* indicated that 200 mg/day was the most common niraparib dose administered to patients after dose adjustments [4]. In that study, the incidence of grade 3/4 AEs reported in $\geq 5\%$ of patients was higher in patients who received niraparib 300 mg/day compared with patients who received niraparib 200 mg/day, with the most notable differences observed in the rates of thrombocytopenia (33 vs 6%, respectively) and neutropenia (18 vs 8%, respectively) [4]. Notably, patients with a baseline body weight < 77 kg or platelet count $< 150,000/\mu\text{l}$ experienced grade ≥ 3 thrombocytopenia at higher rates and were more likely to have their dose reduced. After 3 months of treatment, when most patients had achieved a stable dose of niraparib 100 or 200 mg/day, the PFS of the dose-reduced patients who received niraparib 200 mg/day or below was consistent with patients who were not dose-reduced (i.e., those who continued to receive niraparib 300 mg/day) [4].

The recent interim findings of the PRIMA and QUADRA studies further confirm the results from the retrospective study by Berek *et al.* Our real-world findings are also supported by the blinded pooled data from the niraparib and placebo arms of the PRIMA study [5]. This study evaluated an amended dosing regimen in patients with high-risk stage III/IV ovarian cancer receiving niraparib maintenance after response to frontline platinum-based chemotherapy. Prior to protocol amendment, all patients received a fixed starting dose of 300 mg/day. In the amended dosing regimen, patients with a baseline body weight < 77 kg or platelet count $< 150,000/\mu\text{l}$ received a starting dose of 200 mg/day. When compared with the preamendment toxicity profile, the incidence of any grade ≥ 3 AE substantially decreased postamendment (56 vs 43%, respectively). Of note, the incidence of grade ≥ 3 thrombocytopenia decreased substantially, with approximately 60% decrease in grade ≥ 3 thrombocytopenia ($\sim 80\%$ reduction in grade 4 thrombocytopenia) and 40% decrease in grade ≥ 3 neutropenia and anemia. Symptomatic AEs such as nausea, vomiting, fatigue, insomnia and hypertension, also decreased with individualized dosing [5].

Further, in a post hoc safety and efficacy analysis of the Phase II QUADRA study [6] enrolling heavily pretreated patients with recurrent high-grade ovarian cancer, patients with low baseline body weight (< 77 kg) and low platelet count ($< 150,000/\mu\text{l}$) showed a higher incidence of any-grade, grade ≥ 3 and serious AEs, compared with patients without low baseline body weight and platelet count. The incidence of grade 3/4 hematologic AEs was particularly higher in patients with low baseline body weight and platelet count: thrombocytopenia (30 vs 14%; $p < 0.0001$), neutropenia (12 vs 5%; $p < 0.02$) and anemia (9 vs 3%; $p < 0.02$). Among the subgroup of patients with a baseline body weight < 77 kg or platelet count $< 150,000/\mu\text{l}$, the objective response rate, disease-control rate and clinical benefit rate at 24 weeks were similar between patients who received a mean niraparib dose of ≤ 200 mg/day versus > 200 mg/day (8 vs 7%, 58 vs 39% and 19 vs 15%, respectively). These respective efficacy parameters were also comparable among patients without low baseline body weight or platelet count who received a mean dose of ≤ 200 mg/day versus > 200 mg/day (objective response rate: 9 vs 11%; disease control rate: 59 vs 57%; and clinical benefit rate at 24 weeks: 21 vs 23%), demonstrating an improved toxicity profile after dose reduction without compromising the efficacy of niraparib maintenance.

Although efficacy was not analyzed in our study, the incidence of the three most common AEs (all grades) observed in our real-world sample of patients who initiated niraparib 200 mg/day was 2.5- to 4.5-times lower than that observed among patients who initiated 300 mg/day in the NOVA study. The substantially lower incidence of grade 3/4 thrombocytopenia (3%; alone or in combination with other common AEs) in our real-world sample is consistent with the decreased incidence of grade 3/4 thrombocytopenia ($< 1\%$) after dose modifications in the NOVA trial [1,4]. Of the 17 patients in our real-world study who had any-grade thrombocytopenia while receiving a prior regimen before starting niraparib 200 mg/day, only 4 experienced thrombocytopenia while receiving niraparib treatment. Thus, improved toxicity at a starting dose of niraparib 200 mg/day may result in reduced intervention during niraparib maintenance treatment and potentially improved quality of life.

Overall, 26% of patients in the real-world sample had their dose increased from niraparib 200 mg/day (starting dose) to 300 mg/day; 11% of patients required a dose reduction, and 4% required a dose interruption due to AEs; 2% discontinued niraparib due to AEs. These data suggest that an individualized dosing approach in terms of dose reduction and augmentation is being followed in real-world clinical practice, which is likely to help lower toxicity from niraparib maintenance therapy without comprising efficacy.

Our study has several limitations. Real-world studies, like the one reported here, are subject to selection bias that could arise from the recruitment of a specific group of patients that respond in a specific way [16]. In our study, selection bias may have accounted for the lower incidence of common AEs in the real-world setting. Differences in patient characteristics among cancer patients enrolled in clinical trials and those in real-world practice highlight

the limited generalizability of clinical trial data [17]. Overall, 53 (61%) of the 87 screened physicians participated in the study and provided 153 cases; thus, physicians who did not participate could lead to a bias.

The patient population of our real-world study was similar to the NOVA study population in terms of median age of patients, prior number of therapies and number of patients showing a CR or PR to prior platinum-based chemotherapy. However, compared with the real-world sample population, more patients in the NOVA study (in the niraparib arm) had stage III/IV disease (88 vs 68%, respectively), an Eastern Cooperative Oncology Group performance status of 2 (32 vs 18%), and received ≥ 3 prior lines of chemotherapy (39 vs 17%). Our study was also limited by its retrospective and observational design, the small number of physicians ($n = 53$) and their patients ($n = 153$), and physician-assessed response evaluations for platinum-based chemotherapy rather than the standard Response Evaluation Criteria in Solid Tumors used in clinical trials. In addition, the capturing and reporting of AEs within clinical trials and real-world practice may differ and may be more stringent and regimented in clinical trials. The spontaneous reporting of AEs (patient-reported) in real-world data may likely capture fewer AEs compared with clinical trials. Additionally, the clinical benefit that patients may have experienced on the reduced niraparib starting dose, including efficacy and quality of life, was not assessed.

Despite these limitations, our real-world data provide descriptive information of the common toxicities encountered by patients with recurrent ovarian cancer in community clinical practices who were started on a reduced dose of niraparib after platinum-based chemotherapy. Published clinical trial data on niraparib show that hematologic toxicities are manageable with frequent laboratory testing and prompt dose reduction [1,4–6]. Nevertheless, some clinicians have started patients on a dose lower than the current approved dose, reflecting what was seen as the most commonly prescribed dose throughout the NOVA trial. The lower incidence of the most common AEs, especially grade 3/4 hematologic AEs, seen in the real-world patient sample provides useful information that supports the safety of niraparib in a heterogeneous population of patients commonly seen in clinical practice.

Conclusion

The incidence of common AEs (any-grade and grade 3/4) reported in the NOVA trial at a starting dose of 300 mg/day was substantially lower in real-world patients initiating maintenance treatment with niraparib 200 mg/day. Differences in AE reporting and patient characteristics may have contributed to this observation. However, these real-world data provide a window within a short time-frame to assess how patients with recurrent ovarian cancer tolerate niraparib in a nonclinical trial setting.

Summary points

- The incidence of the three most common clinical trial-reported adverse events (AEs; all grades) – nausea, thrombocytopenia and fatigue – observed with niraparib maintenance therapy at 300 mg/day in the ENGOT-OV16/NOVA study (74, 61 and 59%, respectively) was markedly lower in the real-world sample of patients initiating niraparib 200 mg/day (16, 14 and 24%, respectively) in clinical practices across the USA.
- The incidence of grade 3/4 nausea, thrombocytopenia and fatigue among the sample of patients starting 200 mg/day in a real-world setting was substantially lower (2, 3 and 3%, respectively) than that observed in the ENGOT-OV16/NOVA study (3, 34 and 8%, respectively).
- Overall, 26% of patients had a dose increase from niraparib 200 mg/day (starting dose) to 300 mg/day, 11% of patients required dose modifications from 200 mg/day (either dose reductions or dose interruptions) to resolve AEs, and 2% of patients discontinued treatment due to AEs during the first 3 months of niraparib use.
- Within the limits and constraints of real-world data, this study suggests that a maintenance therapy dose of niraparib 200 mg/day in a real-world setting is a tolerable option for high-risk patients with ovarian cancer.
- Efficacy was not addressed in this analysis.

Author contributions

JR Gallagher, KJ Heap, and S Carroll contributed to the study design, analyzed the de-identified database, performed statistical analysis, and assisted with manuscript preparation and review. K Travers, B Harrow, and SN Westin reviewed and interpreted the data, reviewed the manuscript, and provided critical input. All authors reviewed the manuscript preparation and editing.

Acknowledgments

We thank all the physicians who participated by providing patient medical record information for this analysis.

Financial & competing interest disclosure

SN Westin has served in a consulting or advisory role for AstraZeneca, BioAscend, Casdin Capital, Clovis Oncology, Genentech, Gerson Lehrman Group, Medivation, Medscape, Merck, Novartis, Ovation Sciences, Pfizer, Roche, Takeda, TESARO, Vaniam Group, and Watermark Research Partners; and has received research funding from ArQule, AstraZeneca, Bayer, Clovis Oncology, Cotinga Pharmaceuticals, Novartis, Roche/Genentech, and TESARO. JR Gallagher, KJ Heap, and S Carroll are employees of Clarity Pharma Research, LLC. K Travers is an employee of TESARO and owns stock/has other ownership with TESARO. B Harrow was an employee of TESARO at the time the study was conducted and owned stock/had other ownership with TESARO at that time; she is no longer employed with TESARO. This study was sponsored by TESARO: a GSK Company and conducted by Clarity Pharma Research, LLC. Medical writing support, funded by TESARO and coordinated by H Ostendorff-Bach, PhD, of TESARO, was provided by S Ghatpande, PhD, of Team 9 Science, LLC (Vaniam Group LLC). The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

AM Schreiber of TESARO copy edited and styled the manuscript.

Ethical conduct of research

Physicians or their authorized staff collected the data; Clarity Pharma Research did not know the patients' identities and did not have access to any personally identifiable health information. All eligible final medical records were de-identified and anonymized; no personally identifiable health information or other individually identifiable information was collected or maintained. The study was exempt from institutional board review according to 45CFR46.101(b)(4): Existing Data & Specimens - No Identifiers.

Data sharing statement

Data and other supporting information used to obtain the results presented in this paper can be accessed by contacting JR Gallagher at jgallagher@claritypharma.com.

Open access

This work is licensed under the Attribution-NonCommercial-NoDerivatives 4.0 Unported License. To view a copy of this license, visit <http://creativecommons.org/licenses/by-nc-nd/4.0/>

References

Papers of special note have been highlighted as: • of interest; •• of considerable interest

1. Mirza MR, Monk BJ, Herrstedt J *et al.* Niraparib maintenance therapy in platinum-sensitive, recurrent ovarian cancer. *N. Engl. J. Med.* 375(22), 2154–2164 (2016).
- **Results of the pivotal ENGOT-OV16/NOVA trial of niraparib maintenance in platinum-sensitive recurrent ovarian cancer in which grade 3/4 hematologic toxicities were managed with appropriate dose adjustments below the recommended dose of niraparib 300 mg/day.**
2. US FDA. Zejula® (niraparib) prescribing information. Tesaro Waltham, MA, USA (2018). www.zejula.com/prescribing-information
3. European Medicines Agency. Zejula® (niraparib) summary of product characteristics (2018). www.ema.europa.eu/en/documents/product-information/zejula-epar-product-information_en.pdf
4. Berek JS, Matulonis UA, Peen U *et al.* Safety and dose modification for patients receiving niraparib. *Ann. Oncol.* 29(8), 1784–1792 (2018).
- **Retrospective analysis of the pivotal ENGOT-OV16/NOVA trial showing that 200 mg/day was the most commonly administered dose in the trial, and the incidence of common grade ≥ 3 adverse events was lower at the 200 mg/day and 100 mg/day doses compared with 300 mg/day.**
5. Monk BJ, Mirza MR, Vergote I *et al.* A prospective evaluation of tolerability of niraparib dosing based upon baseline body weight and platelet count: blinded pooled interim safety data from the ENGOT-OV26/PRIMA study. Presented at: *Society of Gynecologic Oncology (SGO)'s 50th Annual Meeting on Women's Cancer*. Honolulu, HI, USA, 16–19 March 2019.
- **A blinded interim safety analysis of the PRIMA study that showed a decrease in the frequency of any-grade adverse events and grade ≥ 3 hematologic adverse events in patients with high-risk ovarian cancer who received amended dosing of a 200 or 300 mg/day starting dose of niraparib based upon baseline body weight and platelet count (individualized dosing), compared with a 300 mg/day starting dose (fixed dosing).**
6. Matulonis UA, Monk BJ, Secord AA *et al.* Baseline platelet count and body weight as predictors of early dose modification in the QUADRA trial of niraparib monotherapy for the treatment of heavily pretreated (≥ 4 th line), advanced, recurrent high-grade serous ovarian cancer. Presented at: *Society of Gynecologic Oncology (SGO) 50th Annual Meeting on Women's Cancer*. Honolulu, HI, USA, 16–19 March 2019.

- **An ad hoc analysis of safety and efficacy of the Phase II QUADRA study that showed that baseline body weight and platelet counts can be used to determine optimal niraparib dosing and that dose reductions (≤ 200 mg/day) made based on low baseline body weight or low platelet count do not compromise the efficacy of niraparib maintenance.**
- 7. JNCCN 360 Spotlights. Niraparib (Zejula) – ovarian cancer (2019). <http://jnccn360.org/ovarian/jnccn-spotlights/niraparib/>
- 8. Katkade VB, Sanders KN, Zou KH. Real world data: an opportunity to supplement existing evidence for the use of long-established medicines in health care decision making. *J. Multidiscip. Healthc.* 11, 295–304 (2018).
- 9. Eriksson I, Wettermark B, Bergfeldt K. Real-world use and outcomes of olaparib: a population-based cohort study. *Target Oncol.* 13(6), 725–733 (2018).
- 10. Mei L, Chen H, Wei DM *et al.* Maintenance chemotherapy for ovarian cancer. *Cochrane Database Syst. Rev.* 6, CD007414 (2013).
- **Cochrane review highlighting the high recurrence of ovarian cancer after initial remission and ineffectiveness of platinum agents as maintenance therapy.**
- 11. Bhatla N, Jones A. The World Ovarian Cancer Coalition Atlas: global trends in incidence, mortality, and survival (2018). <https://worldovariancancercoalition.org/wp-content/uploads/2018/10/THE-WORLD-OVARIAN-CANCER-COALITION-ATLAS-2018.pdf>
- 12. Mirza MR, Pignata S, Ledermann JA. Latest clinical evidence and further development of PARP inhibitors in ovarian cancer. *Ann. Oncol.* 29(6), 1366–1376 (2018).
- 13. Ledermann JA, Harter P, Gourley C *et al.* Overall survival in patients with platinum-sensitive recurrent serous ovarian cancer receiving olaparib maintenance monotherapy: an updated analysis from a randomised, placebo-controlled, double-blind, phase 2 trial. *Lancet Oncol.* 17(11), 1579–1589 (2016).
- 14. Coleman RL, Oza AM, Lorusso D *et al.* Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3): a randomised, double-blind, placebo-controlled, Phase III trial. *Lancet* 390(10106), 1949–1961 (2017).
- 15. Pujade-Lauraine E, Ledermann JA, Selle F *et al.* Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a *BRCA1/2* mutation (SOLO2/ENGOT-Ov21): a double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet Oncol.* 18(9), 1274–1284 (2017).
- 16. Blonde L, Khunti K, Harris SB, Meizinger C, Skolnik NS. Interpretation and impact of real-world clinical data for the practicing clinician. *Adv. Ther.* 35(11), 1763–1774 (2018).
- **Comprehensively discusses limitations of real-world data including selection bias.**
- 17. Mitchell AP, Harrison MR, Walker MS, George DJ, Abernethy AP, Hirsch BR. Clinical trial participants with metastatic renal cell carcinoma differ from patients treated in real-world practice. *J. Oncol. Pract.* 11(6), 491–497 (2015).