Improving real-world evaluation of patient- and physician-reported tolerability: niraparib for recurrent ovarian cancer (NiQoLe)

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Abstract

Background: Maintenance niraparib at an individualized starting dose (ISD) is established in platinum-sensitive recurrent ovarian cancer (PSROC). However, patients' perspectives on the burden of prolonged maintenance therapy have not been reported in prospective trials or routine practice.

Methods: In the real-life multicenter NiQoLe study, patients with PSROC received ISD maintenance niraparib. The primary objective was to describe physician-reported adverse events (AEs) leading to treatment modification during the first 3 months. Secondary endpoints included patient-reported outcomes (symptomatic AEs using PRO-CTCAE, self-reported fatigue and impact on daily activities/function using FACT-F) collected remotely weekly using a specifically designed electronic device.

Results: Most (80%) of 139 treated patients (median age 70 years) began niraparib at 200 mg/day. Median treatment duration was 5.7 (range 0.2–21.4) months. During the first 3 months, 86 patients (62%) required treatment modification (median 27 days to modification). Physician-reported grade ≥3 niraparib-related AEs occurred in 34 patients (24%); 68 patients (49%) had treatment modification for AEs, predominantly thrombocytopenia. The most frequent patient-reported AEs (PRO-CTCAE) were fatigue, insomnia, constipation, and dry mouth. Self-reported AEs were severe in 66% of patients. At baseline, 33% of patients reported severe fatigue (FACT-F), which generally persisted during niraparib. Physicians systematically underestimated major patient-reported symptoms.

Conclusions: In routine practice, dose modification was often required during the first 3 months despite individualized dosing. Physicians underestimated the burden of fatigue and symptomatic AEs. Digital self-reporting of AEs is feasible, provides patient-centered information complementing physician-reported AEs, and allows fuller appreciation of toxicity in real-world studies.

Clinical trial information: NCT03752216

Platinum-based therapy is standard at diagnosis of ovarian cancer (OC) and at relapse if it occurs ≥6 months after completing front-line therapy. Patients responding to platinum rechallenge receive maintenance therapy with a poly(ADP-ribose) polymerase inhibitor (PARPi), such as niraparib.[1-4]

The efficacy and safety of maintenance niraparib has been demonstrated in several phase 3 trials.[3], [5], [6] In NOVA (in late-relapsing recurrent OC), the most common adverse events (AEs) were gastrointestinal and hematologic effects, fatigue, headache, and insomnia.[3] Subsequent trials established an individualized starting (ISD) dose tailored according to baseline weight and platelet count, offering improved tolerability while maintaining efficacy.[6-9] However, retrospective real-world data suggest more frequent dose modifications and treatment discontinuation for AEs in unselected populations treated in routine practice than reported in pivotal trials.[10] Prospective clinical trials extensively describe physician-reported AEs but provide minimal information on patient-reported toxicities. Furthermore, retrospective real-world studies rely on physician-documented AEs[11] and none has used the Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE), which characterizes symptomatic treatment toxicities from the patient's perspective.[12]

PRO analyses from NOVA and PRIMA indicated maintained health-related quality of life (HRQoL) during maintenance niraparib,[13, 14] but the questionnaires used did not capture PARPi-specific side effects (eg, fatigue), patient-reported AEs, or the impact of persistent low-grade AEs during prolonged maintenance therapy. Chronic side effects promote 'pill fatigue' and may affect treatment compliance.[15]

Patients may hesitate to report symptoms because of time constraints, fear of stopping treatment, or difficulty remembering symptoms between clinic visits.[16] Physicians may focus on expected AEs, objective signs, or asymptomatic AEs with a direct medical impact (eg, platelet count, liver function tests); they may have limited time or may not

systematically ask about symptoms. Missed or delayed symptom detection can lead to suboptimal treatment modification, detrimentally affecting treatment adherence, symptom control, and HRQoL. However, many of these challenges can be overcome if PROs are collected digitally at home and accessed by the care team to adapt patient management. Understanding treatment burden is particularly important in the maintenance setting, where disease-related symptoms are less bothersome and acceptance of treatment-related AEs may be lower.

To explore the impact of maintenance niraparib on patients with OC treated in routine practice, we initiated the real-world Niraparib and Quality of Life (NiQoLe) study, integrating digitally collected patient-reported AE monitoring into the study design.

Patients and methods

NiQoLe (GINECO-OV239b; NCT03752216) was an open-label longitudinal real-world study conducted at 27 French sites. Eligible patients had high-grade epithelial OC and a complete or partial response (CR/PR) after completing platinum-based chemotherapy <12 weeks before initiating maintenance niraparib. Patients with grade 3/4 anemia, neutropenia, or thrombocytopenia related to their last chemotherapy and persisting for >4 weeks were ineligible.

Maintenance oral niraparib was started at 300 mg daily, or 200 mg daily in patients with baseline body weight <77 kg and/or platelet count <150,000/μL. The daily dose was reduced by 100 mg in case of AEs. Each cycle lasted 28 days and maintenance therapy was continued until disease progression or unacceptable toxicity.

The primary objective was to evaluate the incidence, grade (National Cancer Institute CTCAE version 5.0), and type of AEs leading to dose modification during the first 3 months of maintenance niraparib, as reported by physicians. Secondary objectives reported here

included evaluation of: patient-reported fatigue (assessed by Functional Assessment of Cancer Therapy-Fatigue [FACT-F][17]) and other symptoms and side effects including fatigue (PRO-CTCAE version 1.0[12]); side-effect management and reasons for dose modifications; patient-reported treatment adherence; time to onset and duration of AEs; and treatment duration. Additionally, we explored concordance between physician- and patient-reported effects.

Every week during the first 6 months and every 3 months thereafter, patients reported selected symptomatic AEs (PRO-CTCAE, grades 0–3), fatigue (FACT-F), and treatment compliance remotely using a handheld electronic device linked to a first-generation computer-based health evaluation system (CHES[18]; Supplementary Figure 1). To reduce patient burden, only the most relevant PRO-CTCAE items were selected, per European Society for Medical Oncology guidelines.[16] Frequency, severity, and interference were reported individually (if assessed) and composite grades ranging 0 to 3 were calculated according to previously described methods[12, 19] (Supplementary Methods and Supplementary Tables 1 and 2). Clinical trial monitors communicated PRO-CTCAE and FACT-F data to physicians every month and before each scheduled follow-up visit. Data on treatment compliance, tolerability, treatment modifications, physician-reported side-effect management, and physician-reported AEs were collected every 3 months. Clinical progression was assessed at the same timepoints according to RECIST version 1.1. Complete blood count assessment was undertaken at baseline and then at 3, 6, 12, and 18 months after starting niraparib.

Statistical Analysis

No formal statistical testing was planned in this open-label real-world trial in routine practice and all analyses were descriptive. Safety and progression-free survival (PFS) were

analyzed in all patients who received ≥1 dose of niraparib. HRQoL was analyzed in all treated patients with a baseline HRQoL assessment.

A 3-point minimal important difference was used to classify each weekly FACT-F score as worsened, stable, or improved. The most frequent classification was reported as the overall score. The proportion of patients with severe fatigue (FACT-F score ≤37[20, 21]) was calculated at each timepoint.

All patients provided signed informed consent before undergoing any study-specific procedures. The study was performed according to the ethical principles of the Declaration of Helsinki and the applicable International Conference for Harmonisation Good Clinical Practice regulatory requirements. The study protocol and informed consent forms were approved by the Comité de Protection des Personnes (CPP) Sud Est II.

Results

Between April 11, 2019, and May 18, 2021, 141 patients were enrolled, of whom 139 received niraparib (1 withdrew consent, 1 experienced disease progression before starting niraparib). Few patients (<10%) had *BRCA1/2*-mutated disease (Table 1). More than half were aged >70 years; among the 55 patients with baseline oncogeriatric information, 35 (64%) had a Geriatric G8 score >14. The database lock was December 15, 2022 (December 5, 2022, for the CHES data).

Treatment exposure and modification

Most patients (80%) started niraparib at 200 mg/day (Table 2). The median duration of niraparib was 5.7 (range 0.2–21.4) months; 63 patients (45%) continued treatment for ≥6 months. During the first 3 months, 86 patients (62%) had their treatment modified after a median of 27 days. Treatment was modified because of AEs in 68 patients (49%; Table 2 and Supplementary Figure 2).

Niraparib was discontinued permanently within the first 3 months in 37 patients (27%): 23 (17%) because of disease progression, 12 (9%) for AEs, and 2 (1%) for patient convenience (Table 2). The first treatment modification was due to thrombocytopenia in 44 patients (65% of 68 patients with treatment modification for AEs, 32% of all treated patients), occurring at grade 4 in 8 patients, grade 3 in 8 patients, grade 2 in 21 patients, and grade 1 in 7 patients. In 8 (18%) of these 44 patients, thrombocytopenia recurred at the same or a higher grade within the first 3 months despite dose modification.

During the first 3 months, 95 (69%) of 137 responding patients reported never missing a dose, 15 (11%) reported missing 1 dose, and 27 (19%) missed >1 dose.

Physician-reported AEs

Physicians reported grade ≥3 AEs in 39 patients (28%) during the first 3 months, considered niraparib-related in 34 patients (24%). There was 1 fatal AE (treatment-related sepsis). The most common physician-reported AEs (any grade) were thrombocytopenia (40%) and fatigue/asthenia (34%), with median onset after approximately 1 month (Figure 1A). The grade ≥3 AEs most often reported by physicians were thrombocytopenia (17%; 9% grade 4) and anemia (5%; all grade 3).

Patient-reported AEs

Weekly PRO-CTCAEs were completed up to week 25 by ≥60% of patients (Supplementary Figure 3). During the first 3 months, 98% of patients reported ≥1 symptomatic PRO-CTCAE (grade 3 in 66%). The most common PRO-CTCAEs were fatigue (93%; 32% grade 3), insomnia (90%; 22% grade 3), constipation (86%; 40% grade 3), and dry mouth (78%; 22% grade 3) (Figure 1B). The composite score combining severity and interference of fatigue was high (grade 2/3) in approximately 20–30% of patients each week during the first 3 months (Figure 2). The composite score combining frequency and severity of nausea was grade 2/3 in <20% and remained stable; grade 2/3 vomiting and decreased appetite were minimal throughout. Supplementary Figure 4 shows other PRO-CTCAEs.

Physician- versus patient-reported AEs

Gastrointestinal effects (nausea, constipation) were >3-fold more frequent in patient versus physician reporting (Table 3). Similarly, physicians reported fatigue in 34% of patients, whereas 93% of patients self-reported fatigue. The discrepancy was even more pronounced (up to 10-fold) for dry mouth and insomnia. The proportions of patients with (very) severe AEs were negligible by physician reporting but up to 40% self-reported by patients.

FACT-F

Thirty-five (33%) of 107 patients completing the FACT-F questionnaire reported severe fatigue at baseline. Although mean self-reported fatigue scores remained high (representing low fatigue) over time (Supplementary Figure 5A), the proportion of patients with severe fatigue (score ≤37) did not decrease. Patients with severe fatigue at baseline reported severe fatigue during the first 12 weeks at a higher proportion of timepoints than those without severe fatigue at baseline (mean 72% vs 25% of timepoints). Fatigue worsened from baseline in 81 patients (76%), typically in the first 3 months with a median time to worsening of 0.9 months (95% confidence interval [CI], 0.7–1.7) (Supplementary Figure 5B). In analyses categorizing FACT-F scores as worsened, stable, or improved during the first 3 months, 52 (49%) of 106 patients with ≥1 post-baseline questionnaire most often reported worsening, 24 (23%) reported a predominantly unchanged fatigue score, and 30 (28%) most frequently reported an improvement. FACT-F scores were available before and after progression (±3 months) for 41 patients. Comparison of pre- and post-progression scores revealed a deterioration in fatigue in 9 patients (22%), stable fatigue in 19 patients (46%), and an improvement in 13 patients (32%).

Efficacy

At the data cutoff date, median follow-up for efficacy was 17.9 (95% CI, 17.6–19.1) months. PFS events had been recorded in 111 patients (80%); 67 (48%) had died. Median PFS was 6.2 (95% CI, 5.5–8.2) months. The estimated 3-month PFS rate was 81% (95% CI, 74–

87%). In the subgroup of 126 patients with CR/PR to the most recent platinum-based therapy (ie, excluding those with stable disease after platinum therapy, who did not meet the eligibility criteria for NiQoLe), median PFS was 6.7 (95% CI, 5.5–8.3) months and the estimated 3-month PFS rate was 82% (95% CI, 74–87%).

Discussion

The need for meaningful PRO reporting and evaluation in clinical trials has long been recognized and approaches to improve reporting continue to evolve.[22, 23] The COVID-19 pandemic triggered rapid development and implementation of remote reporting and recent guidelines recommend digital symptom monitoring (eg, with a handheld device) in routine care during systemic cancer treatment.[16] However, when the NiQoLe study was initiated, integrating self-reported AEs and fatigue into safety monitoring was a groundbreaking approach. To our best knowledge, this is the first study to provide prospective longitudinal evidence on the burden of maintenance PARPi use (particularly fatigue) on patients with late-relapsing OC. A study strength is the remote self-reporting of symptomatic AEs using a handheld digital device, allowing frequent and regular reporting. Furthermore, results reflect the real-world experiences of a broader population than is typically enrolled in randomized clinical trials. Prospective data collection contrasts with the retrospective real-world reports in the literature.[10, 11, 24-27] The NiQoLe study demonstrates the feasibility of digital self-reporting in routine practice. Although more than half of the study population was aged >70 years, there was high compliance with PRO-CTCAE and FACT-F reporting and patients coped well with digital data entry. Analyses focusing on patients aged >70 years are ongoing.

NiQoLe aimed to elucidate the trajectory of fatigue during maintenance therapy via intensive collection of PRO-CTCAEs and a fatigue-specific HRQoL questionnaire (FACT-F). As anticipated in this elderly study population, fatigue was particularly troublesome. Before

starting niraparib, one-third of patients reported severe fatigue on FACT-F, highlighting the burden of chemotherapy and disease. The high level of fatigue persisted during maintenance niraparib, despite dose modification.

Most patients started niraparib at 200 mg. Nevertheless, 62% required niraparib treatment modification during the first 3 months and thrombocytopenia was common. Careful monitoring is critical, especially during early cycles, to ensure dosing is truly individualized. Interestingly, although treating physicians were informed of PRO-CTCAEs, dose modifications were typically attributed to thrombocytopenia rather than symptomatic AEs, and a second modification was usually required. The need for further dose adjustment in patients receiving ISD niraparib is consistent with previous real-world studies of niraparib.[11, 24, 25]

The simple PRO-CTCAE method implemented in NiQoLe collects complementary information on the side effects of greatest relevance to patients receiving PARPi, allowing better treatment monitoring. Weekly remote reporting may improve information collection in the week following treatment initiation, which often coincides with the greatest symptom burden. For example, in the NOVA trial, PRO questionnaires were administered every 8 weeks, reflecting patients' experience in the preceding 7 days,[13] yet most AEs and grade ≥3 hematologic and symptomatic AEs occurred during the first month of niraparib treatment and declined thereafter.[28] The NOVA investigators reported a decrease over time in the proportion of patients experiencing lack of energy or fatigue, and no negative effect of hematologic AEs on HRQoL. However, real effects may go undetected with relatively infrequent PRO data collection. In the NiQoLe study, PRO-CTCAEs were collected weekly during the first 3 months, when AEs are typically most frequent and burdensome.[28] The median time to onset of the most common grade 3 PRO-CTCAEs was 28–34 days. Fatigue and nausea persisted at a similar severity/interference level over time whereas severe/frequent vomiting and decreased appetite were less common. The NiQoLe design is in line with recommendations to match quality-of-life assessments to hypothesized symptom

trajectories,[29] perhaps explaining the different findings with respect to evolution of fatigue over time.

NiQoLe revealed a considerable discrepancy between patient-reported and physician-reported AEs. The most common physician-reported AEs were hematologic effects (thrombocytopenia, anemia), fatigue/asthenia, and low-grade gastrointestinal effects, consistent with data from 5 previous prospective clinical trials.[9] By definition, the PRO-CTCAE focuses on symptomatic AEs (eg, fatigue, nausea, insomnia, constipation, and dry mouth), which were reported at up to 10-fold higher incidences by patients compared with physicians. This discordance suggests that clinicians may not report AEs that are most bothersome to patients. The PRO-CTCAE is different from and complementary to the CTCAE[15] and the expectations of patients and physicians may differ, highlighting the importance of assessing both to fully understand the impact of treatment on patients. Surveys suggest a disconnect between physician and patient perceptions of AEs,[30] and patients may be reluctant to report low-grade AEs.[31] PRO-CTCAEs shed light on lower-grade AEs that may escalate to more severe toxicity or lead to poor treatment compliance or discontinuation because of their cumulative impact on HRQoL. Physicians accessing real-time information to modify treatment may have a more immediate impact on treatment burden. However, there is often reluctance to integrate PRO results into clinical practice.[32] Clinical staff need to be motivated to use patient-reported tolerability to identify symptoms and initiate supportive measures. Furthermore, prospectively collected data from longitudinal real-world studies are needed to provide complementary data to support findings from pivotal trials, extend our understanding of the treatment burden to less-selected populations presenting in everyday clinical practice, and enable the development of more generalized strategies to monitor and manage side effects of new drugs in broader populations.

NiQoLe enrolled a poor-prognosis population of older patients (54% aged ≥70 years vs 17% in NOVA[33]) predominantly with *BRCA*-wildtype disease, reflecting widespread use of olaparib for patients with *BRCA*-mutated OC in France. Only 35% had a complete

response following previous platinum (versus ≥50% in NOVA[3] and NORA[7]). These less-favorable characteristics may explain the shorter-than-expected PFS (median 6 months versus 9 months in the NOVA non-*BRCA*-mutated population[3]).

A weakness of the NiQoLe study is the focus on collecting self-reported AEs without proactive real-time monitoring to improve treatment tolerability. Furthermore, this first-generation device had no alert to patients and/or physicians. Studies since the start of the COVID-19 pandemic have explored how telemedicine can help to manage toxicities. Arriola et al. reported high adoption and adherence to weekly symptom monitoring via personal devices and improved interactions and care.[34] Another study demonstrated the feasibility, acceptability, and preliminary efficacy of a telehealth intervention in reducing the interference and severity of fatigue during PARPi therapy for advanced OC.[35]

Given the feasibility and logistical simplicity of the digital tool used in NiQoLe, we suggest that future trials of PARPis and novel investigational agents should integrate the PRO-CTCAE into regular follow-up. Real-world studies should incorporate both patient perspectives and standard physician-reported safety monitoring to allow more comprehensive assessment and management of side effects, treatment burden, and impact on HRQoL, enabling better management of toxicity. Furthermore, these tools could be used in routine practice to minimize toxicity and increase the feasibility of maintenance therapy.

Data availability

Currently no mechanism is in place to allow sharing of individual de-identified patient data. Requests sent to ARCAGY-GINECO (bvotan@arcagy.org) will be considered on a case-by-case basis.

Author contributions

Florence Joly, MD, PhD (Conceptualization; Resources; Investigation; Methodology; Data Curation; Supervision; Funding acquisition; Project Administration; Writing – original draft; Writing – review & editing), Fernando Bazan, MD (Resources; Investigation; Writing – review & editing), Delphine Garbay Decoopman, MD (Resources; Investigation; Writing – review & editing), Yaelle Ouldbey, Lic (Methodology; Data Curation; Formal analysis; Validation; Visualization; Software; Writing – original draft; Writing – review & editing), Philippe Follana, MD (Resources; Investigation; Writing – review & editing), Élise Champeaux-Orange, MD (Resources; Investigation; Writing – review & editing), Eric Legouffe, MD (Resources; Investigation; Writing – review & editing), Pierre-Emmanuel Brachet, MD (Resources; Investigation; Writing – review & editing), Dominique Spaeth, MD (Resources; Investigation; Writing – review & editing), Pierre Combe, MD (Resources; Investigation; Writing – review & editing), Anne-Claire Hardy-Bessard, MD (Resources; Investigation; Writing – review & editing), Frédéric Selle, MD (Resources; Investigation; Writing – review & editing), Julien Grenier, MD (Resources; Investigation; Writing – review & editing), Coriolan Lebreton, MD (Resources; Investigation; Writing – review & editing), Olfa Derbel, MD (Resources; Investigation; Writing – review & editing), Elise Bonnet, MD (Resources; Investigation; Writing – review & editing), Pierre Fournel, MD (Resources; Investigation; Writing – review & editing), Yolanda Fernandez Diez, MD (Resources; Investigation; Writing – review & editing), Valérie Delecroix, MD (Resources; Investigation; Writing – review & editing), Sheik Emambux, MD (Resources; Investigation; Writing – review & editing), Jérôme Alexandre, MD (Resources; Investigation; Writing – review & editing), Thomas Grellety, MD (Resources; Investigation; Writing – review & editing), Dominique Mille, MD (Resources; Investigation; Writing – review & editing), Hubert Orfeuvre, MD (Resources; Investigation; Writing – review & editing), Catherine Favier, MD (Resources; Investigation; Writing – review & editing), Delphine Le Roux, MD (Resources; Investigation; Writing – review & editing), Marie-Ange Mouret-Reynier, MD (Resources; Investigation; Writing – review & editing), Stanislas Quesada, MD (Resources; Investigation; Methodology; Data curation; Writing – original draft; Writing – review & editing), Jean-Emmanuel Kurtz, MD (Conceptualization; Resources;

Investigation; Methodology; Data curation; Supervision; Writing – original draft; Writing – review & editing).

Funding

Funding and drug supply for this study was provided by GSK.

Conflicts of interest

Florence Joly reports honoraria for lectures, educational events, and an expert board from GSK, honoraria for lectures and expert boards from AstraZeneca, Clovis, and MSD, honoraria for expert boards from Seagen and Novocure, support for attending meetings and/or travel from GSK, MSD, and Eisai, and financial support for national academic GINECO trials from GSK and AstraZeneca. Fernando Bazan reports payments for expert testimony from Daiichi Sankyo, Pfizer, Novartis, Clovis, Exact Sciences, and AstraZeneca and meeting/travel support from Novartis, Pfizer, Daiichi Sankyo, AstraZeneca, and GSK. Delphine Garbay Decoopman reports meeting support from Gilead Oncology, MSD, AstraZeneca, Lilly, and Pfizer and participation on a data safety monitoring board/advisory board for Pfizer and MSD. Philippe Follana reports honoraria for lectures, presentations, speaker bureaus, manuscript writing, or educational events from GSK, Novartis, Lilly, Daiichi Sankyo, and MSD and meeting/travel support from GSK, Novartis, Gilead, and Lilly. Pierre Combe reports honoraria for lectures/presentations from MSD, BMS, and Eisai and participation in advisory boards for GSK and AstraZeneca. Anne-Claire Hardy-Bessard reports meeting/travel support from GSK and advisory board participation for GSK. Frédéric Selle reports advisory board fees from AstraZeneca, GSK/Tesaro, and MSD and honoraria for invited speaker engagements from AstraZeneca, GSK/Tesaro, MSD, and Eisai. Julien Grenier reports honoraria for lectures, presentations, speaker bureaus, manuscript writing,

or educational events from Daiichi Sankyo and Gilead and meeting/travel support from Daiichi Sankyo, Gilead, Eisai, and Lilly. Coriolan Lebreton reports honoraria for lectures/presentations from MSD, GSK, Eisai, and Clovis Oncology, support for attending meetings/travel from MSD and GSK, and participation on a data safety monitoring board/advisory board for GSK. Elise Bonnet reports grants/contracts from Gilead for a training course for employees, support to attend congresses from Lilly and Pfizer, and participation on an expert board for Gilead. Pierre Fournel reports honoraria for speaker engagements from AstraZeneca and Sanofi, support from Takeda to attend ESMO 2022 and ESMO 2023, and participation in advisory boards for BMS and MSD. Jérôme Alexandre reports research grants to his institution from GSK, MSD, and Janssen, consulting fees from AstraZeneca, MSD, Eisai, GSK, and Pfizer, personal honoraria for lectures, presentations, speaker bureaus, manuscript writing, or educational events from AstraZeneca, Eisai, MSD, GSK, and Novartis, and meeting/travel support from AstraZeneca and Eisai. Delphine Le Roux reports meeting/travel support from GSK. Stanislas Quesada reports meeting/travel support and honoraria for lectures, presentations, speaker bureaus, manuscript writing, or educational events from GSK and AstraZeneca. Jean-Emmanuel Kurtz reports travel expenses from GSK. Yaelle Ouldbey, Élise Champeaux-Orange, Eric Legouffe, Pierre-Emmanuel Brachet, Dominique Spaeth, Olfa Derbel, Yolanda Fernandez Diez, Valérie Delecroix, Sheik Emambux, Thomas Grellety, Dominique Mille, Hubert Orfeuvre, Catherine Favier, and Marie-Ange Mouret-Reynier have no disclosures.

Acknowledgments

The authors thank all patients and their families, the study investigators, the staff from ARCAGY-GINECO (Sidonie Adam, Marine Cognat, Christine Montoto-Grillot, Yassine Omri, Awa Cisse, Sébastien Armanet, Bénédicte Votan), Amandine Pommier (Euraxi Pharma), the statisticians (Yaelle Ouldbey and Amélie Anota from Léon Bérard Cancer Center, Lyon), the

staff from the ARCAGY-GINECO Translational Research Centre at Institut Curie (Alexandre Degnieau and Eloïse Glais), and GSK. The authors also acknowledge Jennifer Kelly, MA (Medi-Kelsey Ltd, Ashbourne, UK), for medical writing assistance, funded by ARCAGY-GINECO. Funding and drug supply for this study were provided by GSK. GSK was given the opportunity to provide a courtesy review of the draft publication for accuracy only, but the authors are solely responsible for final content, interpretation, and the decision to submit the manuscript for publication. These data were presented in part at the American Society for Clinical Oncology Annual Meeting 2023 in Chicago, IL, USA.

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Table 1. Baseline characteristics

Characteristic, n (%)	**Treated population (N = 139)**
Median [range] age, years	70 [44–88]
Age >70 years	75 (54)
ECOG performance status	
0	70 (50)
1	67 (48)
2	2 (1)
FIGO stage[a]	
I–IIIA	17 (13)
IIIB	16 (13)
IIIC	70 (56)
IV	23 (18)
Histology	
High-grade serous	127 (91)
Grade 2/3 endometrioid	5 (4)
Undifferentiated	5 (4)
Other	2 (1)
BRCA1 or *BRCA2* deleterious mutation[b]	7 (7)
Weight <77 kg	103 (74)
Platelets <150,000/μL	8 (6)
Surgery	131 (94)
Residual disease after last surgery	49/131 (37)
No. of prior lines of platinum-based therapy before recurrence	
1	106 (76)
2	27 (19)

3	2 (1)
4	2 (1)
5	2 (1)
Median [range]	1 [1–5]
Prior bevacizumab	99 (71)
Prior olaparib	5 (4)
Response to last platinum	
Complete response	48 (35)
Partial response	78 (56)
Stable disease	13 (9)[c]
Median [range] interval between last platinum and niraparib, days	49 [15–109]

[a] FIGO status missing in 13 patients.

[b] *BRCA* mutation status missing in 34 patients. Among the 7 patients with tumors harboring a *BRCA1/2* mutation, 2 had germinal *BRCA1* mutation, 1 had somatic *BRCA1* mutation, 3 had germinal *BRCA2* mutation, and 1 had somatic *BRCA2* mutation (none had tumors harboring both BRCA1 and BRCA2 mutations).

[c] Ineligible per protocol but enrolled and treated in error.

ECOG = Eastern Cooperative Oncology Group; FIGO = International Federation of Gynecology and Obstetrics.

Table 2. Treatment modification during the first 3 months of niraparib

Modification	No. of patients (%)			Median [range] time to first modification, days (N = 139)
	Starting dose 300 mg/day (n = 27)	Starting dose 200 mg/day (n = 111)	All patients (N = 139)[a]	
Any treatment modification	21 (78)	65 (59)	86 (62)	27 [0–90][b]
Treatment discontinued for disease progression	4 (15)	19 (17)	23 (17)	70 [6–91]
Treatment modification for AE	17 (63)	51 (46)	68 (49)	25 [0–91][b]
Dose reduced	13 (48)	34 (31)	47 (34)	42 [8–90][c]
Treatment interrupted	11 (41)	42 (38)	53 (38)	25.5 [0–90][b]
Treatment discontinued	5 (19)	7 (6)	12 (9)[d]	20.5 [6–91]
Treatment modification for patient convenience	1 (4)	5 (5)	6 (4)	37 [21–84][e]
Dose reduced	1 (4)	1 (1)	2 (1)	33 [29–37]
Treatment interrupted	0	2 (2)	2 (1)	21 [21–21][e]
Treatment discontinued	0	2 (2)	2 (1)	80.5 [77–84]
Treatment modification for other reason	4 (15)	1 (1)	5 (4)	47 [22–91]
Dose reduced	4 (15)	0	4 (3)[f]	51.5 [22–77]

Treatment interrupted	1 (4)	1 (1)	2 (1)[g]	62 [33–91]

[a] 1 patient who weighed ≥77 kg and had platelets ≥150,000/μL took a starting dose of 100 mg in error.

[b] Missing date of first dose interruption for AE (and consequently date of first dose modification and dose modification for AE) for 1 patient.

[c] Missing date of first dose reduction for AE for 1 patient (but not missing date of earlier treatment interruption for AE).

[d] Preceded by treatment interruption and dose reduction in 1 patient.

[e] Missing date of first dose interruption for patient convenience (and consequently date of first dose modification for patient convenience) for 1 patient.

[f] Described as investigator decision in 3 patients (also mentioning decreased platelet count for 1 patient) and general alteration in 1 patient.

[g] Described as investigator decision in 1 patient and suspicion of disease progression in 1 patient.

AE = adverse event.

Table 3. Discrepancy between selected patient- and physician-reported AEs during the first 3 months of niraparib

AE, n (%)	Patients with self-reported PRO-CTCAE (N = 139)		Patients with physician-reported CTCAE (N = 139)	
	Any grade	Severe (grade 3)	All	Severe (grade ≥3)
Fatigue	129 (93)	44 (32)	47 (34)	2 (1)
Nausea	102 (73)	17 (12)	30 (22)	0
Constipation	120 (86)	56 (40)	25 (18)	0
Dry mouth	109 (78)	30 (22)	12 (9)	0
Insomnia	125 (90)	31 (22)	13 (9)	0

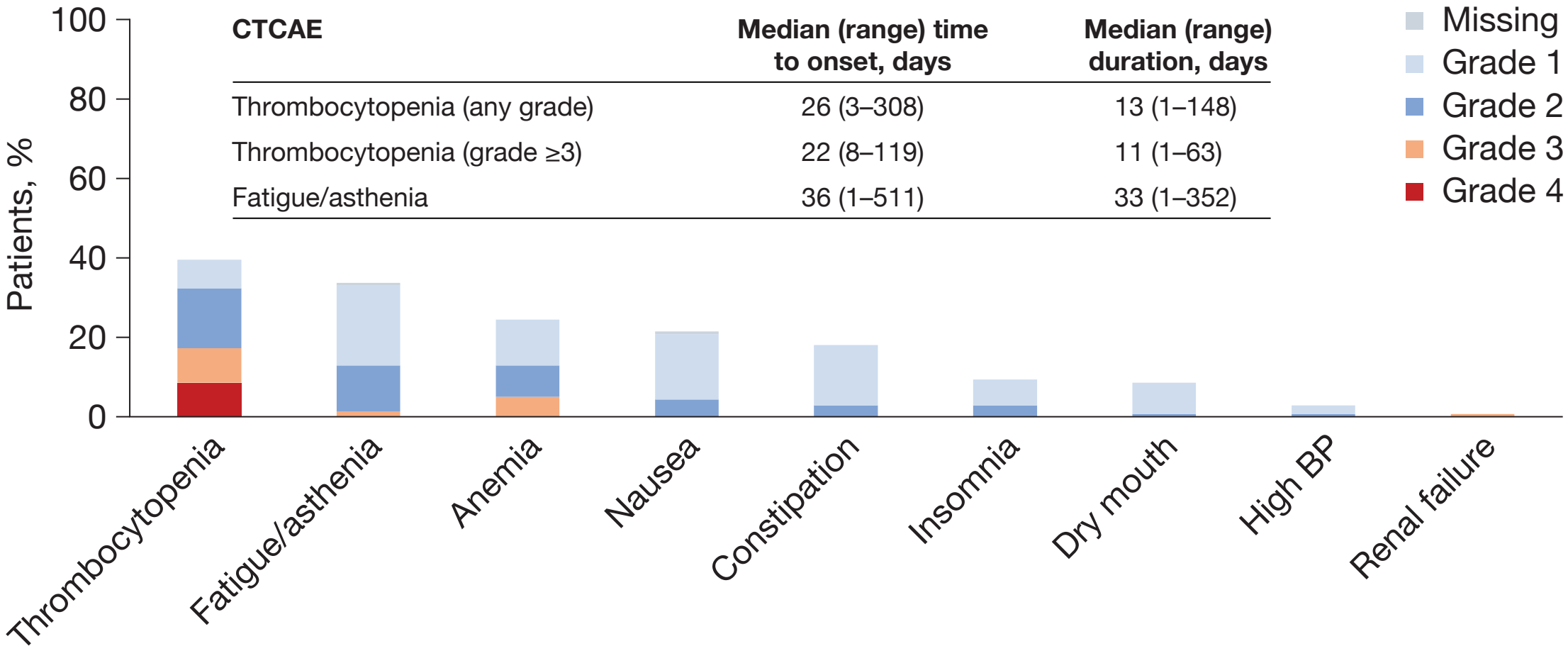
AE = adverse event; PRO-CTCAE = Patient-Reported Outcome version of the Common Terminology Criteria for Adverse Events.

Figure legends

Figure 1. Summary of safety during the first 3 months. A) Physician-reported AEs. B) Patient-reported AEs (composite grade of 0–3 combining individual scores for frequency, severity, and interference with daily activities; grade not collected for rash). AE = adverse event; BP = blood pressure; CTCAE = Common Terminology Criteria for Adverse Events; PRO-CTCAE = Patient-Reported Outcome version of the Common Terminology Criteria for Adverse Events.

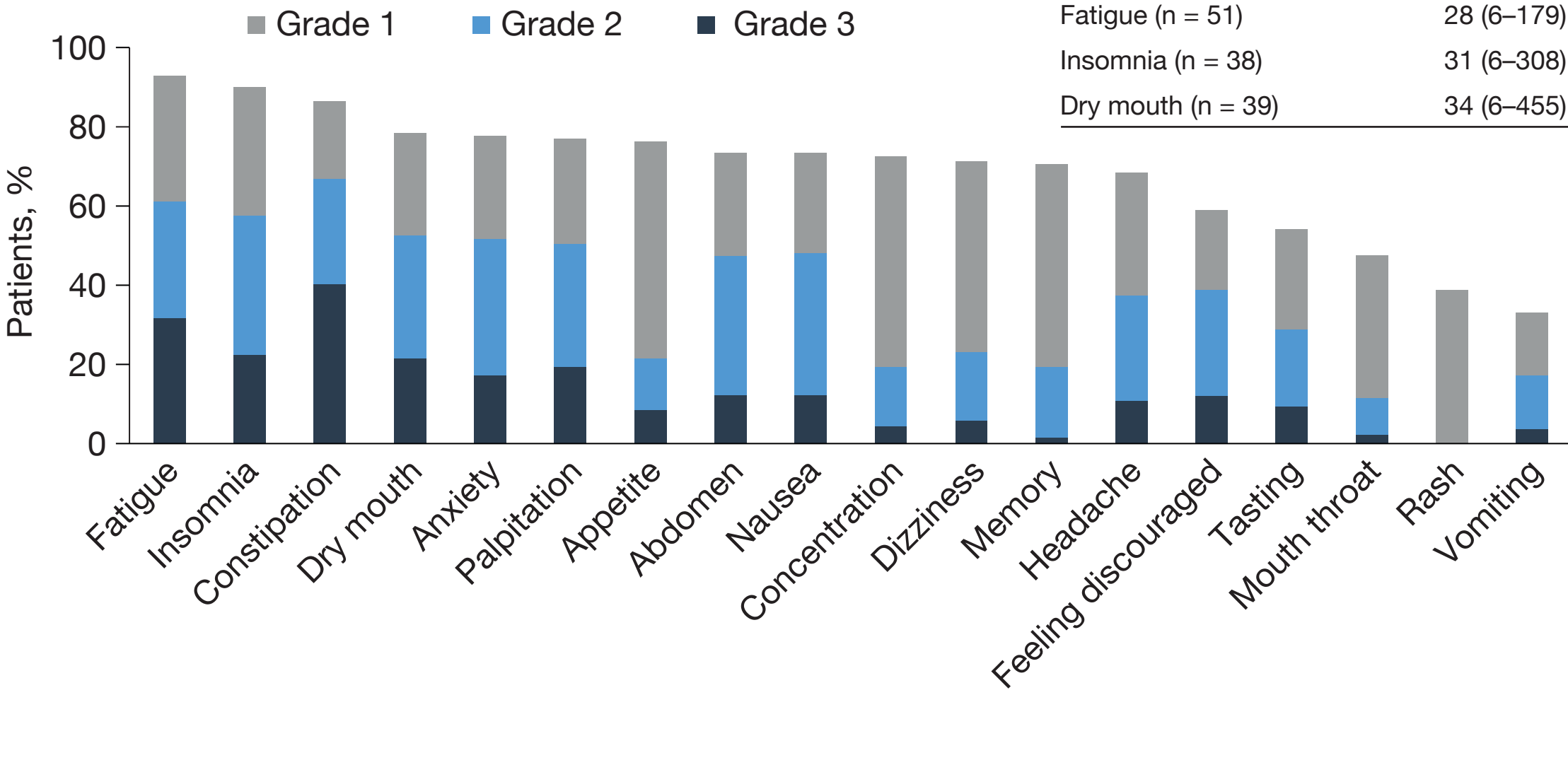
Figure 2. Individual item scores for severity, interference, and composite grade every week during the first 12 weeks of treatment and maximum post-baseline score.[19] A) Fatigue (PRO-CTCAE fatigue, tiredness, or lack of energy). B) Nausea. C) Vomiting. D) Decreased appetite. PRO-CTCAE = Patient-Reported Outcome version of the Common Terminology Criteria for Adverse Events. *Maximum score or grade reported post-baseline per patient.

A



CTCAE	Median (range) time to onset, days	Median (range) duration, days
Thrombocytopenia (any grade)	26 (3–308)	13 (1–148)
Thrombocytopenia (grade ≥3)	22 (8–119)	11 (1–63)
Fatigue/asthenia	36 (1–511)	33 (1–352)

B



Grade 3 PRO-CTCAE	Median (range) time to onset, days
Constipation (n = 64)	28 (6–168)
Fatigue (n = 51)	28 (6–179)
Insomnia (n = 38)	31 (6–308)
Dry mouth (n = 39)	34 (6–455)

Figure 2