Gynecologic Oncology xxx (2020) xxx

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Long-term safety in patients with recurrent ovarian cancer treated with niraparib versus placebo: Results from the phase III ENGOT-OV16/NOVA trial

Mansoor R. Mirza [a,*], B. Benigno [b], A. Dørum [c], S. Mahner [d], P. Bessette [e], I. Bover Barceló [f], D. Berton-Rigaud [g], J.A. Ledermann [h], B.J. Rimel [i], J. Herrstedt [j,k], S. Lau [l], A. du Bois [m], A. Casado Herráez [n], E. Kalbacher [o], J. Buscema [p], D. Lorusso [q], I. Vergote [r], T. Levy [s], P. Wang [t], F.A. de Jong [u], D. Gupta [t], U.A. Matulonis [v]

[a] Nordic Society of Gynaecological Oncology Clinical Trial Unit (NSGO-CTU), Rigshospitalet–Copenhagen University Hospital, Copenhagen, Denmark
[b] Northside Hospital, Atlanta, GA, USA
[c] Radiumhospitalet, Oslo University Hospital, NSGO, Oslo, Norway
[d] Department of Obstetrics and Gynecology, University Hospital, LMU Munich, AGO, Munich, Germany
[e] Sherbrooke University, Sherbrooke, QC, Canada
[f] Hospital Son Llàtzer, GEICO, Palma de Mallorca, Spain
[g] Institut de Cancérologie de l'Ouest Centre René Gauducheau, GINECO, Saint-Herblain, France
[h] UCL Cancer Institute, University College London, NCRI, London, UK
[i] Cedars-Sinai Medical Center, West Hollywood, CA, USA
[j] Odense University Hospital, Odense, Denmark
[k] Zealand University Hospital, NSGO, Roskilde, Denmark
[l] McGill University, Montreal, QC, Canada
[m] Kliniken Essen Mitte, AGO, Essen, Germany
[n] Hospital Clínico San Carlos, GEICO, Madrid, Spain
[o] Centre Hospitalier Régional et Universitaire de Besançon, GINECO, Besançon, France
[p] Arizona Oncology Associates, Tucson, AZ, USA
[q] Fondazione Policlinico Universitario a Gemelli IRCCS, Istituto Nazionale dei Tumori, MITO, Milan, Italy
[r] University of Leuven, Leuven Cancer Institute, BGOG, Leuven, Belgium
[s] Wolfson Medical Center, ISGO, Holon, Israel
[t] GlaxoSmithKline, Waltham, MA, USA
[u] GlaxoSmithKline, Zug, Switzerland
[v] Dana-Farber Cancer Institute, Boston, MA, USA

HIGHLIGHTS

- Long-term safety data for patients from the ENGOT-OV16/NOVA trial is reported.
- Grade ≥ 3 thrombocytopenia occurred in 28% of patients in month 1, declining to 9% in month 2.
- Dose reductions were highest in month 1 (34%), and declined every month thereafter.
- These data support dose reductions according to toxicity criteria and the long-term use of niraparib maintenance treatment.

ARTICLE INFO

Article history:
Received 14 July 2020
Accepted 4 September 2020
Available online xxxx

Keywords:
Niraparib
Long-term safety
Poly(ADP ribose) polymerase inhibitor
Ovarian cancer
Gynecologic oncology

ABSTRACT

Objective. Niraparib is a poly(ADP-ribose) polymerase (PARP) inhibitor approved for use in heavily pretreated patients and as maintenance treatment in patients with newly-diagnosed or recurrent ovarian cancer following a response to platinum-based chemotherapy. We present long-term safety data for niraparib from the ENGOT-OV16/NOVA trial.

Methods. This multicenter, double-blind, randomized, controlled phase III trial evaluated the efficacy and safety of niraparib for the treatment of recurrent ovarian cancer. Patients were randomly assigned 2:1 to receive either once-daily niraparib 300 mg or placebo. Two independent cohorts were enrolled based on germline *BRCA* mutation status. The primary endpoint was progression-free survival, reported previously. Long-term safety data were from the most recent data cutoff (September 2017).

Results. Overall, 367 patients received niraparib 300 mg once daily. Dose reductions due to TEAEs were highest in month 1 (34%) and declined every month thereafter. Incidence of any-grade and grade ≥ 3 hematologic and symptomatic TEAEs was also highest in month 1 and subsequently declined. Incidence of grade ≥ 3 thrombocytopenia

* Corresponding author at: Chief Oncologist, Department of Oncology 5073, Rigshospitalet, Copenhagen University Hospital, Blegdamsvej 9, DK2100 Copenhagen, Denmark.
E-mail address: mansoor@rh.regionh.dk (M.R. Mirza).

https://doi.org/10.1016/j.ygyno.2020.09.006

decreased from 28% (month 1) to 9% and 5% (months 2 and 3, respectively), with protocol-directed dose interruptions and/or reductions. Acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) were reported in 2 and 6 niraparib-treated patients, respectively, and in 1 placebo patient each. Treatment discontinuations due to TEAEs were <5% in each month and time interval measured.

Conclusion. These data demonstrate the importance of appropriate dose reduction according to toxicity criteria and support the safe long-term use of niraparib for maintenance treatment in patients with recurrent ovarian cancer.

Trial registration. ClinicalTrials.gov identifier: NCT01847274.

1. Introduction

Ovarian cancer is a leading cause of death from gynecologic malignancies worldwide [1,2]. Most diagnoses occur at an advanced stage, and nearly three-quarters of women diagnosed with advanced ovarian cancer do not survive beyond 5 years [3]. Despite high initial response rates to platinum- and taxane-based first-line treatments, 85% of women will experience disease recurrence [4,5]. Patients with recurrent ovarian cancer who receive multiple lines of chemotherapy experience lower efficacy, higher cumulative toxicity, and impaired quality of life (QoL) [6,7]. Poly(ADP-ribose) polymerase (PARP) inhibitors have emerged as a maintenance treatment option that prolongs the time between chemotherapy treatments. However, it is critical that any maintenance treatment does not increase overall toxicity or have a negative impact on long-term safety. Patient surveys have shown that while patients seek maintenance treatment options that extend progression-free survival (PFS), they are concerned about toxicities that impact QoL [8].

Niraparib is an oral, highly selective PARP inhibitor approved in the United States for maintenance treatment of patients with newly-diagnosed and recurrent ovarian cancer who are in response to platinum-based chemotherapy and for the treatment of patients with advanced ovarian cancer who have been treated with three or more prior chemotherapy regimens and whose cancer is associated with homologous recombination deficiency (HRD)-positive status [9]. In Europe, niraparib is approved for maintenance treatment in patients with recurrent ovarian cancer [10]. Niraparib has a favorable pharmacokinetic profile, with a high volume of distribution and tissue penetration [11].

In the pivotal double-blind, randomized, placebo-controlled phase III ENGOT-OV16/NOVA study, treatment with niraparib resulted in significantly longer PFS relative to placebo, regardless of germline *BRCA* (g*BRCA*) or HRD status [12]. The study showed that niraparib was well tolerated, with 14.7% of patients discontinuing treatment due to treatment-emergent adverse events (TEAEs). Patient-reported outcomes for the niraparib arm suggested that patients receiving niraparib were able to maintain QoL relative to placebo during treatment [13]. Long-term safety and tolerability—crucial in the maintenance setting to ensure that treatment-associated toxicities do not offset the benefits associated with delaying the time to progression or death—have yet to be broadly established for PARP inhibitors. To our knowledge, the Friedlander et al. [14] report from Study 19 is the only study reporting long-term safety data on a PARP inhibitor to date.

Here, we present long-term safety and exposure data for niraparib from patients with ovarian cancer in the ENGOT-OV16/NOVA trial for up to 4 years.

2. Patients and methods

2.1. Patient population and study design

ENGOT-OV16/NOVA was a double-blind, randomized, placebo-controlled phase III trial that enrolled two independent cohorts based on g*BRCA* mutation (g*BRCA*mut) status as determined by BRCA*analysis* Testing (Myriad Genetics, Inc., Salt Lake City, UT, USA). The study design has been published previously [12]. Patients were at least 18 years of age and had histologically diagnosed ovarian, fallopian tube, or primary peritoneal cancer. Patients must have received two or more prior courses of platinum-based chemotherapy and had a complete or partial response to their most recent regimen. Patients must have been progression-free for more than 6 months following their penultimate platinum-based chemotherapy regimen. At study entry, patients were required to have an Eastern Cooperative Oncology Group performance status of 0 or 1 and adequate organ function as assessed by appropriate laboratory values. Immunocompromised patients and those with active hepatic disease or symptomatic, uncontrolled brain or leptomeningeal metastases were excluded.

The ENGOT-OV16/NOVA study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines; the protocol was approved by the ethics committee at each study site. All patients provided written informed consent before study participation.

Patients were randomized 2:1 to receive either niraparib 300 mg or placebo once daily, administered as three capsules without regard to food, until disease progression. Two cohorts were enrolled based on each patient's g*BRCA*mut status: g*BRCA*mut cohort and non-g*BRCA*mut cohort. Randomization within each cohort was stratified based on time to progression following the penultimate platinum-based regimen, prior use of bevacizumab, and best response (complete or partial) to the last platinum-based regimen. Permuted-block randomization (block size of six) was performed at each level of the stratification variables with an interactive web response system. Niraparib and placebo capsules were manufactured to have identical appearances to ensure treatment masking.

2.2. Study endpoints

The primary endpoint of PFS was defined as the time from treatment randomization to the earliest date of progression or death from any cause. Independent radiologic review and central blinded clinician review were used to define disease progression, and an identical schedule of assessments was used for both treatment arms.

Secondary endpoints included patient-reported outcomes, chemotherapy-free interval, time to first subsequent therapy (TFST), time from treatment randomization to the earliest date of progression or death from any cause after first subsequent therapy (PFS 2), time to second subsequent therapy (TSST), and overall survival (OS). Safety was assessed by monitoring for adverse events, laboratory tests, vital signs, and physical examinations. For the long-term safety ad hoc analysis, the incidence of TEAEs was assessed by month from months 1–12 and pooled from months 13–18, 19–24, 25–30, 31–36, 37–42, 43–48.

2.3. Statistical analyses

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

TEAEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.02. TEAEs must have occurred after the start of study treatment and within 30 days following the final dose of study treatment. Descriptive statistics (number and percentage) were used to summarize the safety data by treatment

arm. Percentages were based on the number of subjects followed for TEAEs at a given month or period. Months were defined as 28-day intervals. No inferential statistics were performed. Statistical analyses were performed using SAS software, version 9.4 (SAS Institute, Inc., Cary, USA).

The ENGOT-OV16/NOVA trial is registered with ClinicalTrials.gov, NCT01847274.

3. Results

3.1. Trial results

The first patient was enrolled in August 2013. A total of 553 patients were enrolled—203 patients in the g*BRCA*mut cohort and 350 patients in the non-g*BRCA*mut cohort (Fig. 1; Table 1) [12]. In the g*BRCA*mut cohort, median PFS was 21.0 months with niraparib versus 5.5 months with placebo (hazard ratio [HR] 0.27, $P < 0.0001$). In the overall non-g*BRCA*mut cohort, median PFS was 9.3 months with niraparib versus 3.9 months with placebo (HR 0.45, $P < 0.0001$). The database for the current efficacy analysis was locked on June 20, 2016, and follow-up for OS is ongoing. The median duration of follow-up at the time of data cutoff was 16.9 months for patients in the overall population.

3.2. Long-term responders

Safety monitoring is ongoing for patients who remain on treatment. As of the most recent safety data extraction (September 2017), approximately 20% of patients received niraparib for at least 2 years.

3.3. Overall long-term safety

Dose reductions tended to occur early. Dose reductions were required in 34% of patients receiving niraparib in month 1, 27% in month 2, and 20% by month 3 (Fig. 2). Dose interruptions followed a trend similar to dose reductions (Fig. 2). Treatment discontinuations due to TEAEs

Table 1
Patient demographics and baseline characteristics.

Characteristic, *n* (%)	g*BRCA*mut cohort		Non-g*BRCA*mut cohort	
	Niraparib ($n = 138$)	Placebo ($n = 65$)	Niraparib ($n = 234$)	Placebo ($n = 116$)
Age, median (range), yrs	57.0 (36–83)	58.0 (38–73)	63.0 (33–84)	60.5 (34–82)
Baseline body weight, kg				
Mean	69.9	71.8	69.6	68.0
Median	66.7	69.0	66.1	66.5
Region				
US and Canada	53 (38)	28 (43)	96 (41)	44 (38)
Europe and Israel	85 (62)	37 (57)	138 (59)	72 (62)
ECOG performance status				
0	91 (66)	48 (74)	160 (68)	78 (67)
1	47 (34)	17 (26)	74 (32)	38 (33)
Primary tumor site[a]				
Ovarian	122 (88)	53 (82)	192 (82)	96 (83)
Primary peritoneal	7 (5)	6 (9)	24 (10)	8 (7)
Fallopian tube	9 (7)	6 (9)	18 (8)	11 (9)
Lines of previous chemotherapy[b]				
2	70 (51)	30 (46)	155 (66)	77 (66)
≥3	67 (49)	35 (54)	79 (34)	38 (33)
Time to progression after penultimate platinum therapy				
6 to <12 months	54 (39)	26 (40)	90 (38)	44 (38)
≥12 months	84 (61)	39 (60)	144 (62)	72 (62)
Best response to most recent platinum therapy				
Complete response	71 (51)	33 (51)	117 (50)	60 (52)
Partial response	67 (49)	32 (49)	117 (50)	56 (48)
Prior bevacizumab use				
Yes	33 (24)	17 (26)	62 (26)	30 (26)
No	105 (76)	48 (74)	172 (74)	86 (74)

ECOG, Eastern Cooperative Oncology Group; g*BRCA*mut, germline *BRCA* mutation; US, United States.

[a] No data regarding primary tumor site was available for one patient receiving placebo in the non-g*BRCA*mut cohort.

[b] One patient receiving niraparib in the g*BRCA*mut cohort received one previous line of therapy, and one patient receiving placebo in the non-g*BRCA*mut cohort had no available data regarding previous lines of therapy.

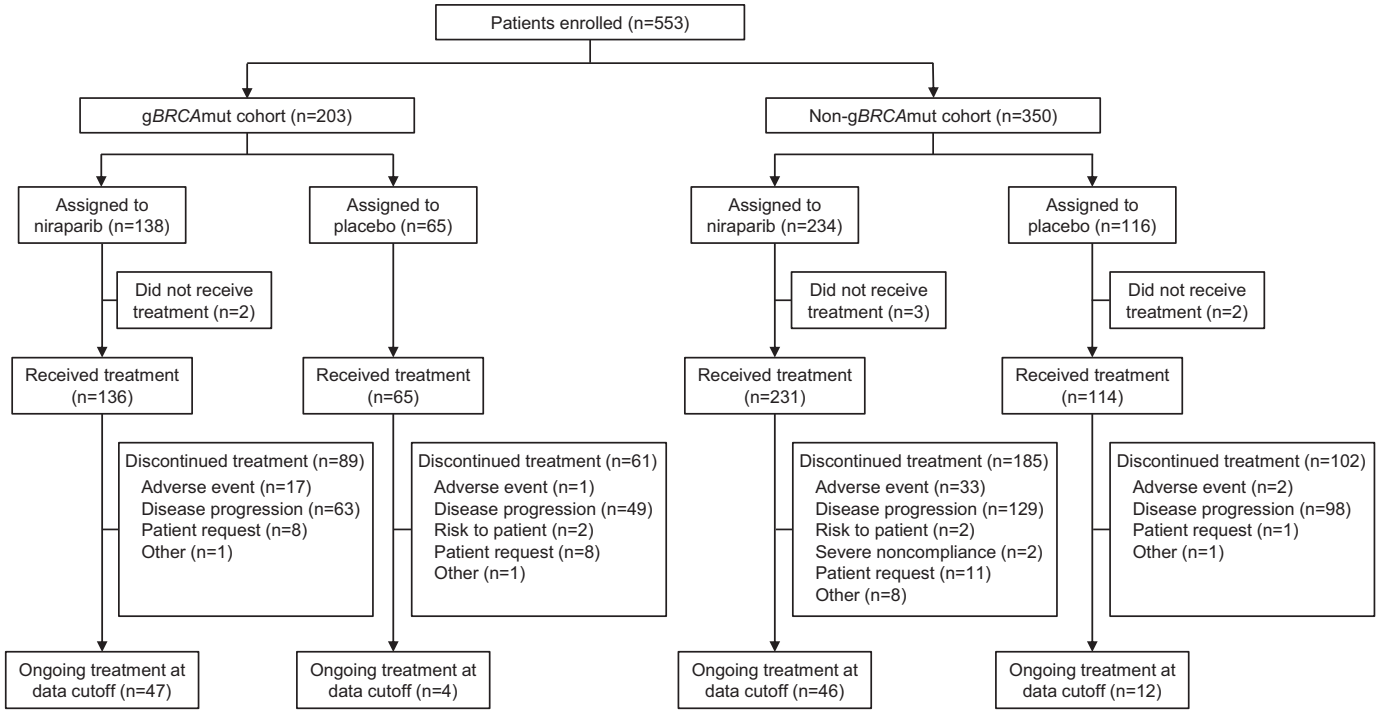

Fig. 1. Enrollment and outcomes. g*BRCA*mut indicates germline *BRCA* mutation. From *The New England Journal of Medicine*, Mirza MR, et al., Niraparib Maintenance Therapy in Platinum-Sensitive, Recurrent Ovarian Cancer, 375:2154–2164. Copyright © (2016) Massachusetts Medical Society. Reprinted with permission.

were <5% in month 1 and remained low across all months and time intervals (Fig. 2). TEAEs tended to occur early and were managed by dose modifications [15].

3.3.1. Incidence of hematologic TEAEs

In the niraparib arm, any-grade thrombocytopenia events decreased from 49% of patients in month 1 to 34% in month 2 (Fig. 3). In month 4, 8% of patients experienced thrombocytopenia and by month 6 thrombocytopenia rates were 2%. Grade ≥ 3 thrombocytopenia incidence declined between month 1 and month 2, from 28% to 9% (Fig. 4). By month 4, grade ≥ 3 thrombocytopenia occurred in <1% of patients and were consistently <1% until discontinuation. Any-grade neutropenia events were consistent in months 1 and 2 (17% and 19%, respectively) and decreased in month 3 (8%). By month 6, 2% of patients experienced neutropenia. Rates remained consistently low until discontinuation. Similarly, grade ≥ 3 neutropenia events were consistent in months 1 and 2 (9% and 12%, respectively) and decreased in month 3 (3%). By month 6, no patient experienced neutropenia. Any-grade anemia events increased from 17% in month 1 to 25% in month 3. A decrease in anemia events occurred in month 5 (13%), and by month 6, anemia events were reduced to 6%. Grade ≥ 3 anemia events were generally low, affecting 2% of patients in month 1. The increase in grade ≥ 3 anemia events observed in month 3 (10%) returned to 5% of patients by month 5. Any-grade hematologic toxicities in the placebo arm were <5% of patients for all months and intervals reported.

3.4. Symptomatic TEAEs

For patients receiving niraparib, grade ≥ 3 symptomatic TEAEs were rare (<5%) across all time intervals (Fig. 4). Any-grade symptomatic TEAEs tended to occur early and decreased over the first 3 months (Fig. 3). Nausea incidence had the greatest reduction, from 62% in month 1 to 13% in month 2. The incidence of other gastrointestinal TEAEs, such as vomiting and diarrhea, decreased from 20% to 6% and 10% to 3% from month 1 to month 2, respectively. By month 6, monthly any-grade symptomatic TEAEs were infrequent (<5%) until treatment discontinuation. In the placebo arm, the incidence of nausea and diarrhea decreased from 20% to 4% and 10% to 4%, respectively. The incidence of vomiting was <5% per month.

Any-grade fatigue, insomnia, and hypertension also decreased between month 1 and month 2. Fatigue incidence decreased from 32% to 15%, insomnia from 16% to 4%, and hypertension from 10% to 2%. Fatigue stayed level from month 2 to month 4 and decreased to 7% in month 5. After month 2, the incidence of hypertension and insomnia was <5% per month. In the placebo arm, the incidence of fatigue decreased from 20% in month 1 to <6% in month 2. The mean (median) duration of fatigue was 533 days (330 days) in the niraparib arm and 600 days (767 days) in the placebo arm. In patients who received niraparib for >1 year, fatigue, hypertension, nausea, vomiting, and diarrhea continued to be detected.

3.4.1. Hepatic and renal toxicities

Any-grade liver transaminase elevations, defined as more than three times the upper limit of normal (ULN), occurred in 15 (4%) patients receiving niraparib and 6 (3%) patients receiving placebo. Grade ≥ 3 liver transaminase elevations, defined as more than five times the ULN, were reported in 6 (2%) patients receiving niraparib and 3 (2%) receiving placebo. Two (1%) patients receiving niraparib had concurrent elevations in transaminase and bilirubin levels.

All-grade renal TEAEs, defined by creatinine levels more than one and a half times the ULN, occurred in 21 (6%) patients receiving niraparib and 3 (2%) patients in the placebo arm. Grade ≥ 3 renal TEAEs, defined by creatinine levels more than three times the ULN, occurred in 2 (1%) patients receiving niraparib and 2 (1%) patients in the placebo arm.

3.4.2. Incidence of acute myeloid leukemia and myelodysplastic syndrome

AML occurred in 2 patients receiving niraparib and 1 receiving placebo. AML rates were 0.5 per 100 patient-years with niraparib and 0.8 per 100 patient-years with placebo. MDS occurred in 6 patients receiving niraparib and 1 patient receiving placebo. MDS rates were 1.6 per 100 patient-years with niraparib and 0.8 per 100 patient-years with placebo. Of these 10 instances of AML and MDS, one patient who received niraparib first developed MDS followed by AML one year later. In all cases, the onset of MDS occurred after treatment discontinuation; the onset of MDS occurred within 1 week to 15 months after treatment discontinuation for patients receiving niraparib and 8 months after treatment discontinuation for the patient receiving placebo. Among these 9 patients, 3 (2 niraparib and 1 placebo) discontinued treatment due to progressive disease. Among the 6 patients who discontinued for adverse events, 5 (4 niraparib and 1 placebo) developed MDS/AML within 2 months of last exposure to study drug.

4. Discussion

Here, we report on the long-term safety of niraparib from ENGOT-OV16/NOVA, a phase III trial assessing niraparib monotherapy (300 mg once daily) for maintenance treatment of patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in complete or partial response to platinum-based chemotherapy.

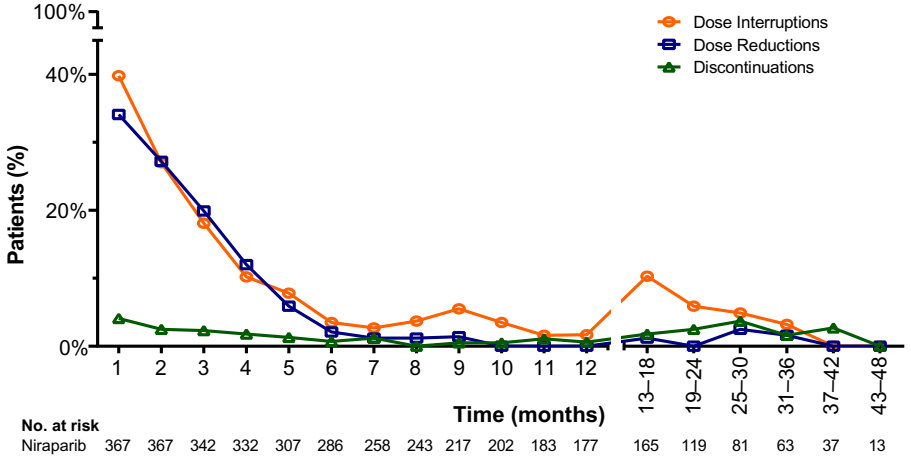

Fig. 2. Dose modifications due to treatment-emergent adverse events.

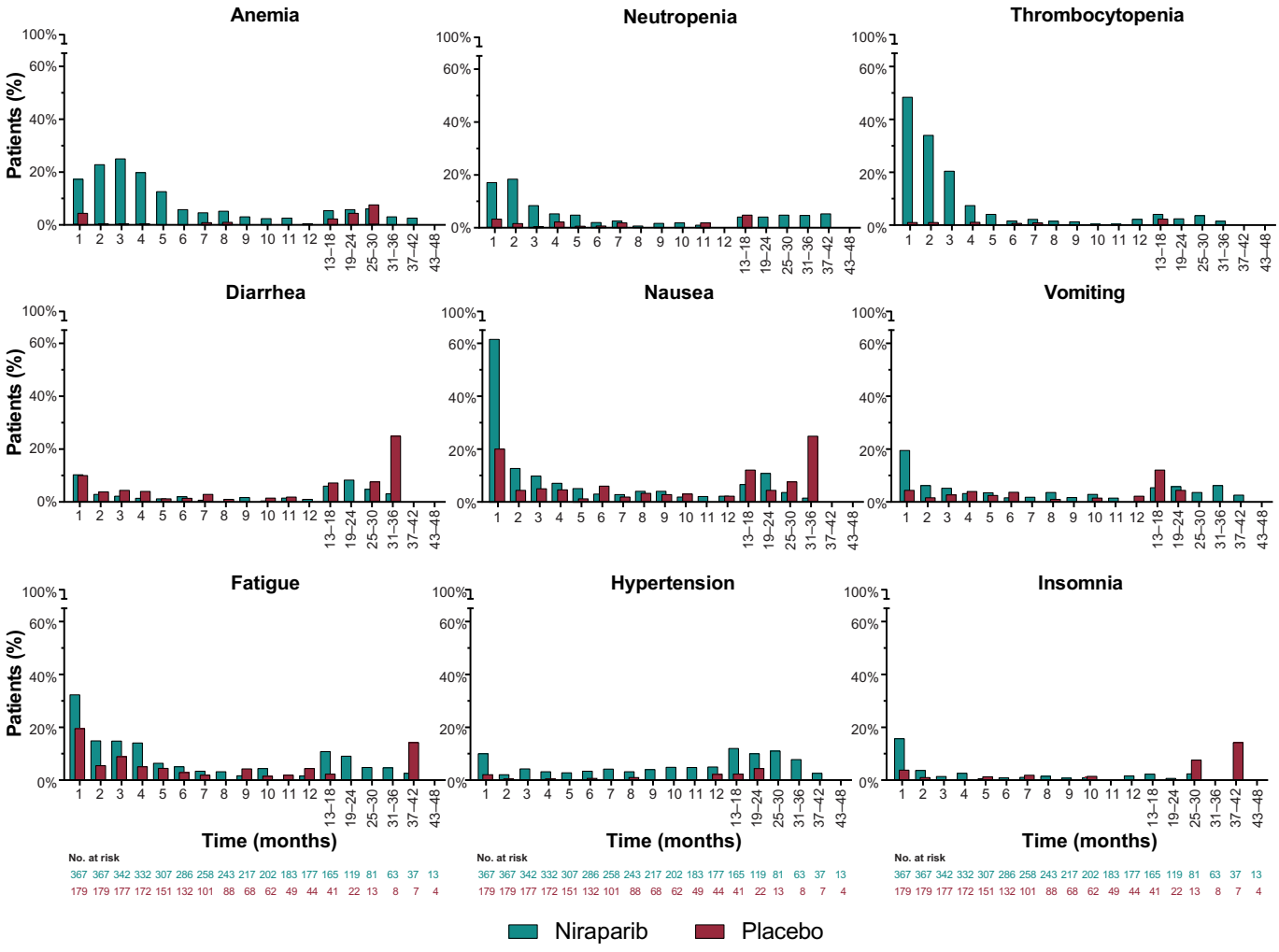

Fig. 3. Any-grade selected treatment-emergent adverse events.

Our findings suggest that niraparib maintenance treatment confers a PFS advantage over placebo and is well tolerated with appropriate, early dose modifications [15].

A previous report indicated that patients receiving niraparib had a significantly longer PFS than those receiving placebo, regardless of g*BRCA*mut status [12]. Patient-reported outcomes have shown that QoL measurements for patients receiving niraparib were similar to those for patients receiving placebo [13]. In the treatment arm, dose reductions were common, and most occurred in the first 3 months due to grade ≥ 3 hematologic TEAEs [15]. Dose reductions did not appear to affect efficacy [15]. Time without symptoms or toxicity (TWiST) estimates from ENGOT-OV16/NOVA indicate that patients treated with niraparib experienced increased mean TWiST compared with patients receiving placebo [16].

A subset of the niraparib arm maintained a long-term response; approximately 20% of niraparib-treated patients received treatment for >2 years. For patients who received niraparib for >1 year, pooled time intervals showed fatigue, nausea, vomiting, and hypertension continued to be detected in a small percentage of patients. Dose reductions occurred most often in month 1. By month 3, dose reductions declined sharply as most patients were receiving their tolerable dose. In the niraparib arm, the incidence of TEAEs declined sharply after month 1. By month 4, the incidence of these TEAEs (except for anemia and fatigue) was <10%. Grade ≥ 3 thrombocytopenia events were reduced by approximately two-thirds after month 1. By month 3, they were reported in 5% of patients receiving niraparib. Overall, grade ≥ 3 non-hematologic TEAEs were low past month 3. A small percentage of patients (<5% by month or time interval) experienced grade ≥ 3 hypertension that persisted past 6 months of receiving niraparib. This is consistent with the known safety profile of niraparib. Renal and hepatic toxicities were rare, and the incidence of AML/MDS was consistent with that of other PARP inhibitors.

The ENGOT-OV16/NOVA trial data support that long-term use of niraparib is safe. Similar long-term safety results were reported for patients receiving olaparib [14]. In Study 19, 24% of olaparib-treated patients received treatment for ≥2 years. Safety profiles were also similar, with most adverse events occurring within the first 6 months and few reports of TEAEs after 6 months. Direct comparison between trials cannot be made for multiple reasons, including differences in patient population, sample size, and trial design. Generally, both studies support the safe, long-term use of PARP inhibitors.

A retrospective analysis of the ENGOT-OV16/NOVA and QUADRA trials showed that patients with body weight <77 kg or platelet counts at baseline <150,000/μL were more likely to experience TEAEs and hematologic toxicities and require dose reductions when initiated at a 300 mg daily dose of niraparib [15,17]. An individualized dosing regimen where patients who met either body weight or platelet count criteria were initiated with a 200 mg daily dose of niraparib was employed in the frontline phase III PRIMA/ENGOT-OV26/GOG-3012 trial and is currently

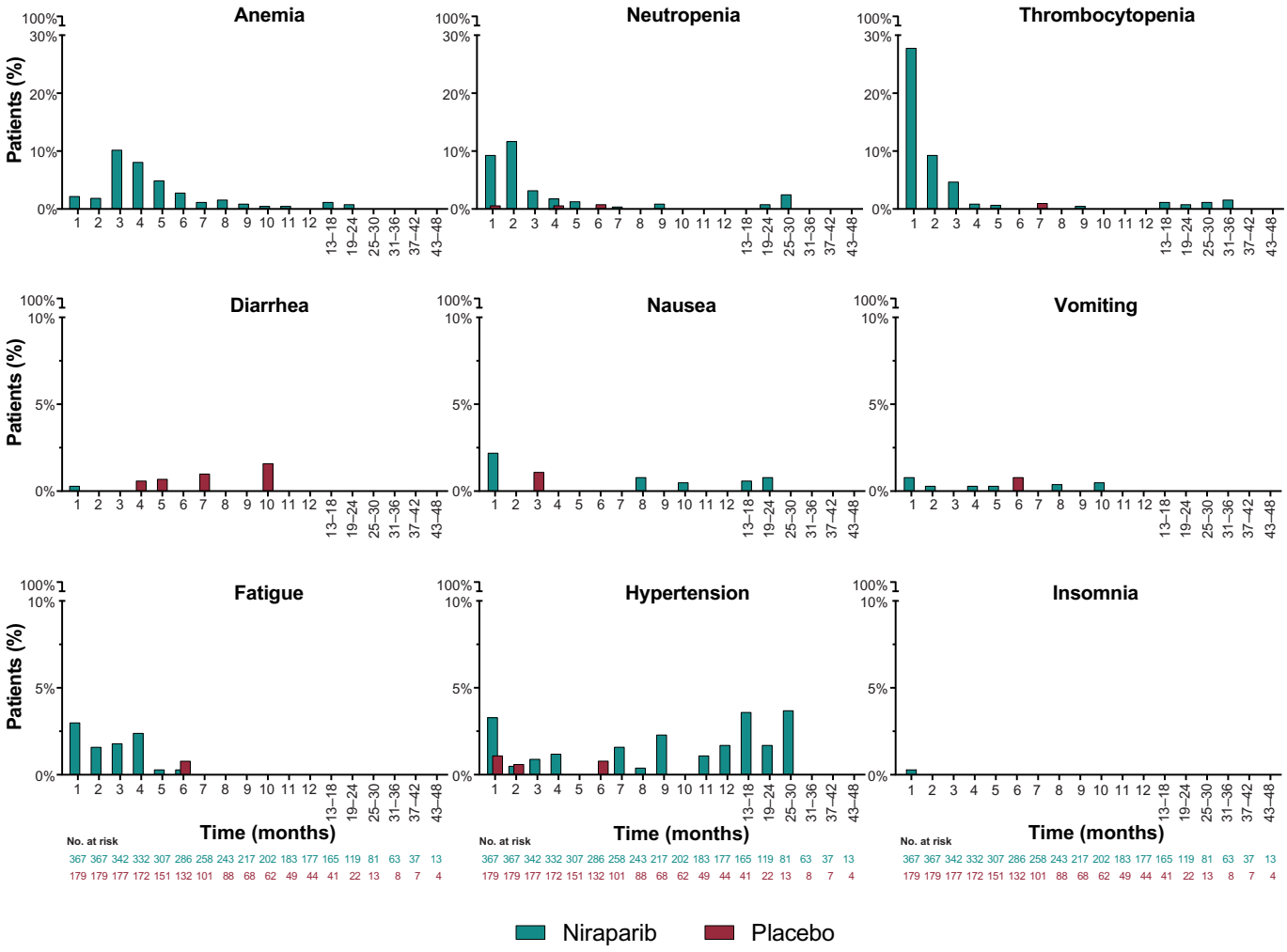

Fig. 4. Grade ≥ 3 selected treatment-emergent adverse events.

being used for ongoing niraparib trials. Safety data from the PRIMA/ENGOT-OV26/GOG-3012 trial showed a reduction in hematologic toxicities for patients receiving an individualized dose of niraparib [18].

Long-term safety and tolerability are crucial in the maintenance setting to ensure that treatment-associated toxicities do not offset the benefits of longer PFS. These data support the safe long-term use of niraparib maintenance monotherapy for patients with recurrent ovarian cancer who are in complete or partial response to platinum-based chemotherapy, regardless of *gBRCA*mut status.

Author contributions

U.A. Matulonis and M.R. Mirza contributed to the study conception and design. All authors participated in the collection and assembly of data, data analysis and interpretation, and final approval of manuscript. U.A. Matulonis and M.R. Mirza wrote the manuscript, with input from all authors.

Disclosure

MRM reports personal fees and leadership/other ownership from Karyopharm Therapeutics and Sera Prognostics and personal fees from Roche, Genmab, BIOCAD, Sotio, Geneos Therapeutics, Merck, Oncology Venture, Seattle Genetics, Takeda Pharmaceutical Company, Zai Lab, and Boehringer Ingelheim. BB reports honoraria from AstraZeneca and Insys Therapeutics and research funding from GlaxoSmithKline. SM reports grants and personal fees from GlaxoSmithKline, AstraZeneca, Medac, Merck Sharp & Dohme (MSD), PharmaMar, Roche, and Teva Pharmaceuticals; and personal fees from Clovis Oncology and Sensor-Kinesis Corp. PB reports site payment for clinical trial conduct from GlaxoSmithKline. JAL reports payment for advisory boards from AstraZeneca, Clovis Oncology, Roche, and Pfizer; payment for lectures and principal investigator responsibilities for trials from AstraZeneca, Clovis Oncology, and Pfizer; funds for clinical trials grant from AstraZeneca; and clinical trials funds from MSD/Merck. BJR has participated in advisory boards for GlaxoSmithKline, AstraZeneca, Genentech, and Clovis Oncology. AdB has participated in advisory boards for Roche, AstraZeneca, GlaxoSmithKline, Clovis Oncology, Pfizer, PharmaMar, Genmab, and BIOCAD. DL reports personal fees from AstraZeneca, Clovis Oncology, Genmab, ImmunoGen, PharmaMar, Amgen, and Merck; and grants from PharmaMar and Merck. IV reports personal fees from Advaxis Inc., Eisai Inc., MSD Belgium, Roche NV, Genmab, F. Hoffmann-La Roche Ltd., PharmaMar, Millennium Pharmaceuticals, Clovis Oncology, AstraZeneca, GlaxoSmithKline, ImmunoGen, and Sotio; grants from Amgen, Stichting tegen Kanker, and Roche; and contracted research with Oncoinvent AS and Genmab. PW, FdJ, and DG are employees of GlaxoSmithKline. UAM reports consulting and advisory board compensation from Merck KGaA, Clovis Oncology, Geneos Therapeutics, Eli Lilly, and 2× Oncology (now Oncology Venture). All other authors reported no conflicts of interest.

Funding

This work was supported by GlaxoSmithKline (Waltham, USA) (no grant number).

Role of the funder/sponsor

The funding sources had a role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. The funders collaborated with the investigators in designing the trial, provided the study drug, coordinated the management of the study sites, funded the statistical analysis, and provided medical writing support. Authors employed by GSK in coordination with all authors were involved in preparation, review, approval, and decision to submit the manuscript.

Meeting presentation

Data presented at the 17th Biennial Meeting of the International Gynecologic Cancer Society, Kyoto, Japan, September 14–16, 2018, and at the Oncology Nursing Society's Annual Conference, Anaheim, CA, USA, April 11–14, 2019.

Data sharing statement

Anonymized individual participant data from this study plus the annotated case report form, protocol, reporting and analysis plan, dataset specifications, raw dataset, analysis-ready dataset, and clinical study report are available for research proposals approved by an independent review committee. Proposals should be submitted to www.clinicalstudydatarequest.com. A data access agreement will be required.

Acknowledgements

Medical writing and editorial support, permitted by Dr. Mansoor Mirza and coordinated by Heather Ostendorff-Bach, PhD, of GlaxoSmithKline (Waltham, MA, USA), was provided by Eric Scocchera, PhD, and Anne Cooper, MA, of Ashfield Healthcare Communications (Middletown, CT, USA).

References

[1] L.A. Torre, B. Trabert, C.E. DeSantis, K.D. Miller, G. Samimi, C.D. Runowicz, et al., Ovarian cancer statistics, 2018, CA Cancer J. Clin. 68 (4) (2018) 284–296.

[2] F. Bray, J. Ferlay, I. Soerjomataram, R.L. Siegel, L.A. Torre, A. Jemal, Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries, CA Cancer J. Clin. 68 (6) (2018) 394–424.

[3] National Cancer Institute, Surveillance, Epidemiology, and End Results Program. Cancer Stat Facts: Ovarian Cancer, Available from: https://seer.cancer.gov/statfacts/html/ovary.html.

[4] J.A. Ledermann, F.A. Raja, C. Fotopoulou, A. Gonzalez-Martin, N. Colombo, C. Sessa, et al., Newly diagnosed and relapsed epithelial ovarian carcinoma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up, Ann. Oncol. 24 (Suppl. 6) (2013) vi24–vi32.

[5] National Comprehensive Cancer Network, NCCN Clinical Practice Guidelines in Oncology: Ovarian Cancer Including Fallopian Tube Cancer and Primary Peritoneal Cancer, Version 3.2019. Published. Available from: https://www.nccn.org/professionals/physician_gls/pdf/ovarian.pdf November 26, 2019.

[6] L.C. Hanker, S. Loibl, N. Burchardi, J. Pfisterer, W. Meier, E. Pujade-Lqurine, et al., The impact of second to sixth line therapy on survival of relapsed ovarian cancer after primary taxane/platinum-based therapy, Ann. Oncol. 23 (10) (2012) 2605–2612.

[7] B. Ferrell, S.L. Smith, C.A. Cullinane, C. Melancon, Psychological well being and quality of life in ovarian cancer survivors, Cancer 98 (5) (2003) 1061–1071.

[8] M. Lorcet, A. Lortholary, J.E. Kurtz, D. Berton-Rigaud, M. Fabbro, T. De La Motte Rouge, et al., Expectation about maintenance therapy among the GINECO French ovarian cancer cohort from the European NOGGO/ENGOT-ov22 expression IV survey, Bull. Cancer 105 (5) (2018) 465–474.

[9] ZEJULA® (niraparib), Prescribing Information, GlaxoSmithKline, Waltham, MA, 2020 , Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/208447s015s017lbledt.pdf.

[10] ZEJULA® (niraparib), Summary of Product Characteristics, GlaxoSmithKline (Ireland) Limited, Dublin, Ireland, 2020 , Available from: https://www.ema.europa.eu/en/documents/product-information/zejula-epar-product-information_en.pdf.

[11] L. van Andel, H. Rosing, Z. Zhang, L. Hughes, V. Kansra, M. Sanghvi, et al., 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) (2018) 39–46.

[12] M.R. Mirza, B.J. Monk, J. Herrstedt, A.M. Oza, S. Mahner, A. Redondo, et al., Niraparib maintenance therapy in platinum-sensitive, recurrent ovarian cancer, N. Engl. J. Med. 375 (22) (2016) 2154–2164.

[13] A.M. Oza, U.A. Matulonis, S. Malander, S. Hudgens, J. Sehoulil, J.M. Del Campo, et al., Quality of life in patients with recurrent ovarian cancer treated with niraparib versus placebo (ENGOT-OV16/NOVA): results from a double-blind, phase 3, randomised controlled trial, Lancet Oncol. 19 (8) (2018) 1117–1125.

[14] M. Friedlander, U. Matulonis, C. Gourley, A. du Bois, I. Vergote, G. Rustin, et al., Long-term efficacy, tolerability and overall survival in patients with platinum-sensitive, recurrent high-grade serous ovarian cancer treated with maintenance olaparib capsules following response to chemotherapy, Br. J. Cancer 119 (9) (2018) 1075–1085.

[15] J.S. Berek, U.A. Matulonis, U. Peen, P. Ghatage, S. Mahner, A. Redondo, et al., Safety and dose modification for patients receiving niraparib, Ann. Oncol. 29 (8) (2018) 1784–1792.

[16] U.A. Matulonis, L. Walder, T.J. Nøttrup, P. Bessette, S. Mahner, M. Gil-Martin, et al., Niraparib maintenance treatment improves time without symptoms or toxicity (TWiST) versus routine surveillance in recurrent ovarian cancer: a TWiST analysis of the ENGOT-OV16/NOVA trial, J. Clin. Oncol. 37 (34) (2019) 3183–3191.

[17] U.A. Matulonis, B.J. Monk, A.A. Secord, M.A. Gellerd, D.S. Millere, N.G. Cloven, 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 (≥4th line), advanced, recurrent high-grade serous ovarian cancer, Gynecol. Oncol. 154 (Suppl. 1) (2019) 3.

[18] A. González-Martín, B. Pothuri, I. Vergote, R. DePont Christensen, W. Graybill, M.R. Mirza, et al., Niraparib in patients with newly diagnosed advanced ovarian cancer, N. Engl. J. Med. 381 (25) (2019) 2391–2402.