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► Additional supplemental material is published online only. To view, please visit the journal online (<http://dx.doi.org/10.1136/ijgc-2023-004484>).

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Received 13 April 2023

Accepted 6 September 2023

Published Online First

24 November 2023



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To cite: Vilming B, Fallås Dahl J, Bentzen AG, et al. *Int J Gynecol Cancer* 2023;**33**:1898–1905.

Real-world data on niraparib maintenance treatment in patients with non-gBRCA mutated platinum-sensitive recurrent ovarian cancer

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ABSTRACT

Objectives The aim of this study was to provide real-world efficacy and safety data on niraparib maintenance treatment in patients with non-germline (gBRCA)1/2 mutated platinum-sensitive recurrent ovarian cancer.

Methods This retrospective multi-center cohort study included 94 platinum-sensitive recurrent ovarian cancer patients without known gBRCA1/2 mutation treated in an individual patient access program in Norway. The primary outcome was time from start of niraparib treatment to first subsequent treatment. Secondary endpoints included progression-free survival, safety, and tolerability.

Results After median follow-up of 13.4 months (95% confidence interval (CI) 10.0 to 16.8), 68.1% had progressed and 22.3% had died. Of the entire cohort, 61.7% had commenced a new line of treatment, and 24.5% were still receiving niraparib. The median duration of niraparib treatment was 5.0 months (range 0.4 to 27.3), and the median time to first subsequent treatment was 10.7 months (95% CI 8.4 to 13.0). Patients with elevated CA125 prior to start of niraparib had shorter time to first subsequent treatment (7.3 months, 95% CI 4.2 to 10.3) than patients with normalized CA125 (12.2 months, 95% CI 10.9 to 13.7 (p=0.002). Patients who started on individual dose based on weight and platelet counts had fewer dose reductions (p<0.001) and interruptions (p=0.02).

Conclusion In a real-world setting, niraparib maintenance treatment in patients with non-gBRCA1/2 mutated recurrent platinum-sensitive ovarian cancer showed effectiveness comparable with published phase III studies and acceptable safety. Individualized dosing is essential to minimize adverse events. CA125 levels at start of niraparib treatment may help to estimate the individual prognosis.

INTRODUCTION

Ovarian cancer, including fallopian tube and peritoneal cancer, is the fifth most frequent cause of cancer death in women in Europe^{1,2} and the United States.³ About two-thirds of patients have advanced-stage disease at diagnosis, with a 5-year survival rate of 37% in Norway.² Most patients relapse despite optimal primary treatment and will undergo multiple lines of chemotherapy. Maintenance strategies with

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Phase III trials have shown efficacy of maintenance treatment with a poly (ADP-ribose) polymerase (PARP) inhibitor after response to platinum-based treatment in patients without germline BRCA (gBRCA) mutation. Real-world data may help estimate efficacy and safety in unselected populations.

WHAT THIS STUDY ADDS

⇒ The treatment-free interval of 10.7 months is comparable with published data in non-gBRCA mutated patients. Individualized dosing is essential to minimize adverse events. CA125 levels at start of niraparib treatment may help to estimate the individual benefit of PARP inhibitor maintenance.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The confirmed efficacy and safety in this real-world study highlights the importance of adding PARP inhibitor maintenance treatment to standard of care. Physician education is important when new drugs are introduced to ensure safety and tolerability. Therapeutic concepts after progression on PARP inhibitors are warranted.

poly (ADP-ribose) polymerase (PARP) inhibition have been implemented with the aim of prolonging the time to progression and next line of chemotherapy, and ultimately, increasing survival.

Maintenance treatment with a PARP inhibitor after response to platinum-based treatment has shown efficacy in primary as well as recurrent disease, especially in patients with homologous recombination deficient tumors. Efficacy has been shown in patients with germline and somatic BRCA1/2 mutations, but also in non-BRCA mutated tumors with homologous recombination deficiency (HRD), as well as to a lesser degree in homologous recombination proficient tumors.^{4–12} A consistent gain in progression-free survival has been reported across these trials, in addition to an overall survival benefit in patients with platinum-sensitive disease with BRCA mutation⁹

and HRD.¹³ PARP inhibitors have also shown efficacy as monotherapy.^{14 15}

Niraparib is a selective inhibitor of PARP (PARP1 and PARP2),¹⁶ and has shown efficacy in patients with recurrent platinum-sensitive ovarian cancer, regardless of BRCA mutations.^{5 17} The NOVA trial⁵ evaluated efficacy of niraparib versus placebo as maintenance treatment in patients with platinum-sensitive recurrent ovarian cancer, and found a significantly longer progression-free survival in all patient cohorts receiving niraparib, regardless of germline BRCA (gBRCA) mutation or HRD status.

The benefit of an individualized starting dose was reported in the post hoc analysis of the NOVA trial,^{5 18} showing that patients with a baseline body weight <77 kg or platelet count <150×10⁹/L received an average daily niraparib dose of about 200 mg (median 207 mg/day) owing to dose interruption and reduction without reducing treatment efficacy. This efficacy of individualized starting dose was confirmed in the NORA study.¹⁹

At the outset of this study PARP inhibitors were not yet approved for patients with recurrent platinum-sensitive ovarian cancer without BRCA mutations. In the present study, patients were offered niraparib through an individual access program launched by Tesaro in 2017, and the aim was to describe the efficacy and safety of niraparib treatment in patients enrolled in this program.

METHODS

Study Population

This retrospective multi-center study included patients enrolled in the individual patient access program between 31 July 2017 and 14 April 2020. Patients were identified by the responsible investigator at six different study sites across all Norwegian health regions (Oslo University Hospital, Haukeland University Hospital, Stavanger University Hospital, Sankt Olavs Hospital, University Hospital of Northern Norway, and Hospital of Southern Norway).

Clinical baseline characteristics, as well as information on clinical outcome and safety, were collected from the patient electronic records. The age adjusted Charlson Comorbidity Index was used to categorize co-morbidity.²⁰

Endpoints

The primary endpoint was time to first subsequent treatment, defined as the date of start of niraparib treatment to the date of start of subsequent treatment. Secondary endpoints included progression-free survival, defined as the date of start of niraparib treatment to the date of investigator-assessed progression (all assessed by computed tomography, except for eight patients showing progression according to gynecologic cancer intergroup CA125 criteria²¹), death, or end of follow-up. We explored differences in time to first subsequent treatment and progression-free survival by CA125 levels before niraparib treatment, and investigated the type and the response to next subsequent chemotherapy. Overall survival was defined as the date of start of niraparib to the date of death from any cause or at the end of follow-up.

Prevalence of and reasons for dose discontinuation and reduction, duration of niraparib treatment, and toxicity were investigated. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0, and were mostly graded retrospectively based on information

recorded in the patients' electronic records. Hematologic and non-hematologic adverse events, as well as consecutive dose reduction and/or discontinuation of therapy, were collected. For non-hematological toxicity, events of grade 1–4 hypertension and biochemistry results were collected. For all other non-hematologic toxicities, only adverse events of grade 3–4 were collected owing to a general lack of reliable documentation in this retrospective study. We also explored toxicity by starting dose level (individualized starting dose vs non-individualized starting dose).

Ethics

The study was approved by the Regional Committees for Medical Research Ethics – South-East Norway (reference no. 62008) and by the data protection officer at the participating sites. Patients provided informed consent before inclusion in the study. The study was registered in Clinicaltrials.gov (NCT04785716).

Statistical Analysis

Patient characteristics were summarized with frequencies and percentages for categorical variables, and median/range for continuous variables. Pearson's χ^2 test or Fisher's exact test for categorical variables was performed when comparing differences between two independent groups. Two-sided p-values <0.05 were considered statistically significant.

Time-to-event data was analysed with the Kaplan-Meier method. Differences in cumulative survival were assessed with the log-rank test. Patients who had not experienced an event at the time of last follow-up on 3 August 2020 were censored at that time point in survival analyses.

All analyses were performed with Statistical Package for the Social Sciences (version 27).

RESULTS

Patient Characteristics

Patient enrollment and outcomes are shown in online supplemental figure 1. Patients who started on a dose lower than 200 mg/day, histologies other than high-grade serous or endometrioid, and patients with known gBRCA mutation, were excluded. Consequently, 94 patients were included, with a median follow-up time of 13.4 months (95% confidence interval (CI) 10.0 to 16.8). Tumor characteristics at primary diagnosis are shown in Table 1. Somatic BRCA (sBRCA) status was only available for five patients, all of whom were non-mutated. No additional HRD information was available.

Patient characteristics at the start of niraparib treatment are shown in Table 2. The patient cohort was heavily pre-treated; 32% had received at least three prior lines of chemotherapy. Only 4% had undergone debulking surgery for relapse in the last treatment line preceding niraparib.

Preceding niraparib treatment, 99% of the patients had received platinum-based treatment. Of these, 93% had received platinum-combination treatment, of which two patients switched to trabectedin and pegylated liposomal doxorubicin after two and three cycles owing to allergic reaction to platinum. After discussion with Tesaro, one patient was included after non-platinum-based chemotherapy (trabectedin and pegylated liposomal doxorubicin) owing to platinum hypersensitivity.

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Table 1 Tumor characteristics at diagnosis

Characteristics	(N, %)
Tumor origin	
Ovary	34 (36.2)
Fallopian tube	27 (28.7)
Peritoneum	6 (6.4)
Adnex or peritoneum	27* (28.7)
Debulking surgery	
Primary debulking surgery	64 (68.1)
Interval debulking surgery	20 (21.3)
No surgery	10 (10.6)
FIGO stage	
I	2 (2.1)
II	11 (11.7)
III	51 (54.3)
IV	30 (31.9)
Histology	
Serous adenocarcinoma	94 (100)
Differentiation grade	
High grade (grade 2–3)	94 (100)
gBRCA status	
Non-mutated	89 (94.7)
Unknown	5 (5.3)

*Nine had no surgery (including those regarded inoperable at surgery), 14 had neoadjuvant chemotherapy before surgery, and five were evaluated after upfront surgery.
FIGO, International Federation of Gynecology and Obstetrics; gBRCA, germline BRCA.

Among evaluable patients (96%), almost 90% had response to the chemotherapy preceding niraparib, including 12% complete response and 78% partial response. At the start of the niraparib treatment, 57% had normalized CA125 levels (≤ 35 kU/L), whereas 43% had elevated CA125 levels (> 35 kU/L). As shown in [Table 2](#), about 70% of the patients started on a niraparib dose of 300 mg/day, whereas about 30% started on an individualized starting dose of 200 mg/day. Among the 69 patients with weight < 77 kg, 42 (61%) and 27 (39%) started on 300 and 200 mg/day, respectively. All patients with a weight > 77 kg started on 300 mg/day, except two patients starting on 200 mg/day. At the start of treatment, three patients had platelets $< 150 \times 10^9/L$, of whom two started at 300 mg/day, and one on 200 mg/day.

Efficacy

At data cut-off, 64 patients (68.1%) had progressed and 21 (22.3%) had died; all of those had experienced disease progression. Fifty-eight patients (61.7%) had commenced a new line of treatment. Twenty-three patients (24.5%) were still receiving niraparib, of which one patient (4.3%) had progressed, but was deemed to still have benefited from the treatment. The median duration of niraparib treatment was 5.0 months (range 0.4 to 27.3).

Table 2 Patient characteristics at start of niraparib treatment

Characteristics	(N, %)
Age, years (median, range)	64, 38–81
Co-morbidity (Charlson Comorbidity Index*)	
0	8 (8.5)
1–2	52 (55.3)
≥ 3	34 (36.2)
Previous lines of chemotherapy	
2	64 (68.1)
3	17 (18.1)
≥ 4	13 (13.8)
Debulking surgery at relapse	
No	87 (92.6)
Yes, preceding last line of chemotherapy	4 (4.3)
Yes, not preceding last line of chemotherapy	3 (3.2)
Type of chemotherapy preceding niraparib	
Platinum combination	87 (92.6)
Platinum single	6 (6.4)
Non-platinum	1 (1.1)
Previous bevacizumab treatment	
Yes	44 (46.8)
No	50 (53.2)
Response of chemotherapy preceding niraparib†	
CR	11 (11.7)
PR	73 (77.7)
SD	6 (6.4)
Non-evaluable‡	4 (4.3)
CA125 level	
≤ 35 kU/L	54 (57.4)
> 35 kU/L	40 (42.6)
Start dosage	
200 mg	29 (30.9)
300 mg	65 (69.1)
Weight	
< 77 kg	69 (73.4)
≥ 77 kg	25 (26.6)

*Age adjusted.
†Investigator assessed.
‡No computed tomography scan performed after surgery with no residual tumor.
CR, complete response; PR, partial response; SD, stable disease.

Time to first subsequent treatment is shown in [Figure 1A](#), with a median of 10.7 months (95% CI 8.4 to 13.0). Median time to first subsequent treatment with and without normalized CA125 before niraparib treatment was 12.2 (95% CI 10.9 to 13.7) and 7.3 (95% CI 4.2 to 10.3) months, respectively ($p=0.002$) [Figure 1B](#).

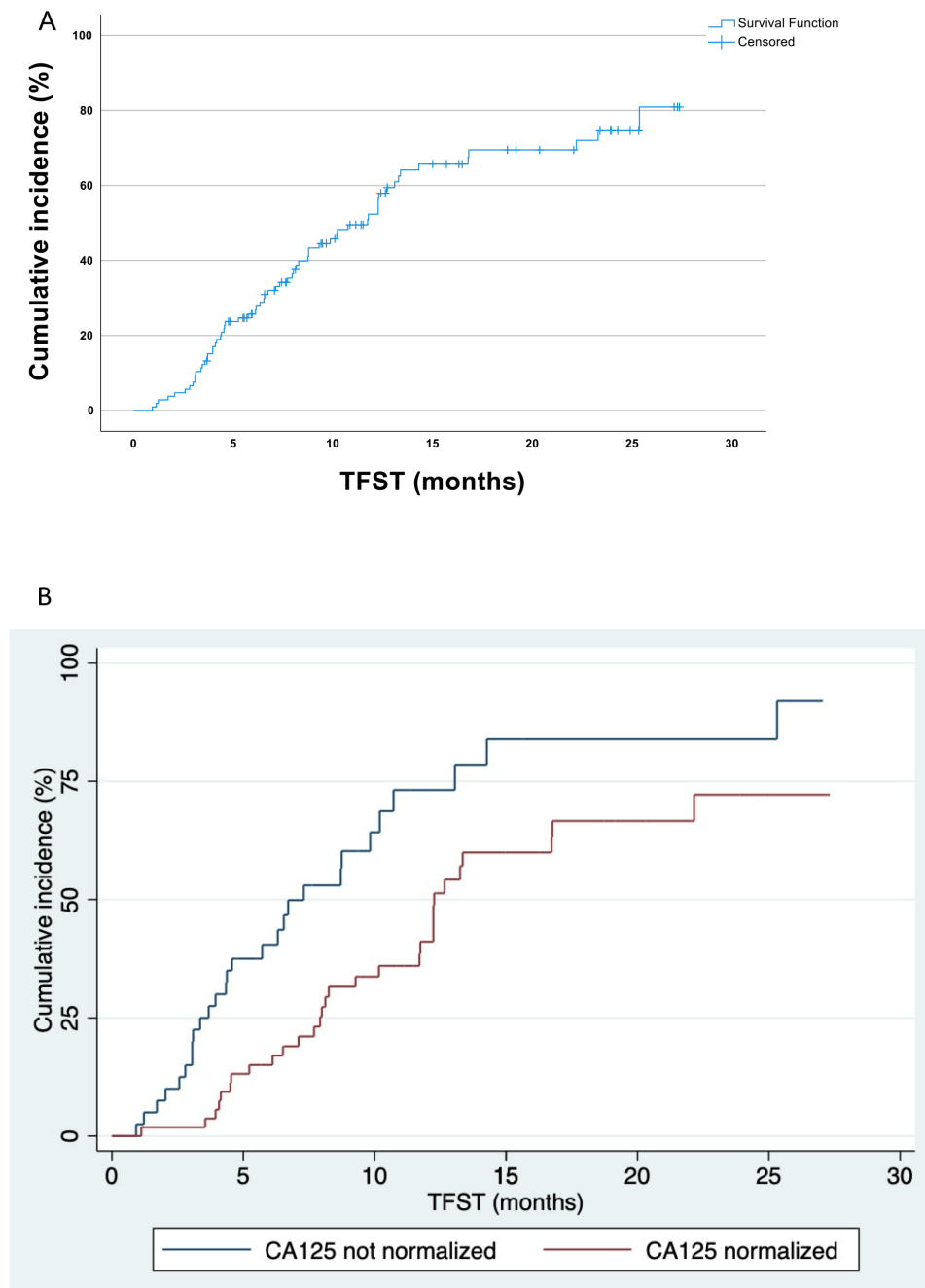


Figure 1 (A). Kaplan-Meier curve for time to first subsequent treatment. (B). Kaplan-Meier curves for time to first subsequent treatment for patients with and without CA125 normalization before niraparib treatment. TFST, time to first subsequent treatment.

Progression-free survival is shown in Figure 2A, with a median of 6.9 months (95% CI 4.6 to 9.2). Median progression-free survival for patients with and without normalized CA125 before niraparib treatment was 10.4 months (95% CI 3.8 to 17.0) and 3.8 months (95% CI 1.8 to 5.7), respectively ($p < 0.001$), Figure 2B. The 1-year and 2-year overall survival rates were 87% (95% CI 77 to 93) and 63% (95% CI 45 to 76), respectively.

Safety

Fourteen per cent of the patients discontinued niraparib owing to an adverse event, which are shown in Table 3. Hematologic toxicity of any grade occurred in 63% of the patients, whereas 27% had

at least one hematologic event of grade 3–4. One patient developed myelodysplastic syndrome after about 11 months of niraparib treatment. She had received two lines of platinum-based treatment. Sixteen per cent of patients experienced non-hematologic toxicity of grade 3–4, including 9 (10%) grade 3 and 1 (1%) grade 4 hypertension. Among the grade 1–2 non-hematologic adverse events collected, increased creatinine level and hypertension were experienced in 34% and 23% of cases, respectively.

Thirty-nine per cent ($n = 37$) of the patients paused niraparib. Of these, all but three had a dose reduction. Overall, 46% ($n = 43$) had dose reduction. Of these, 64% were caused by hematologic

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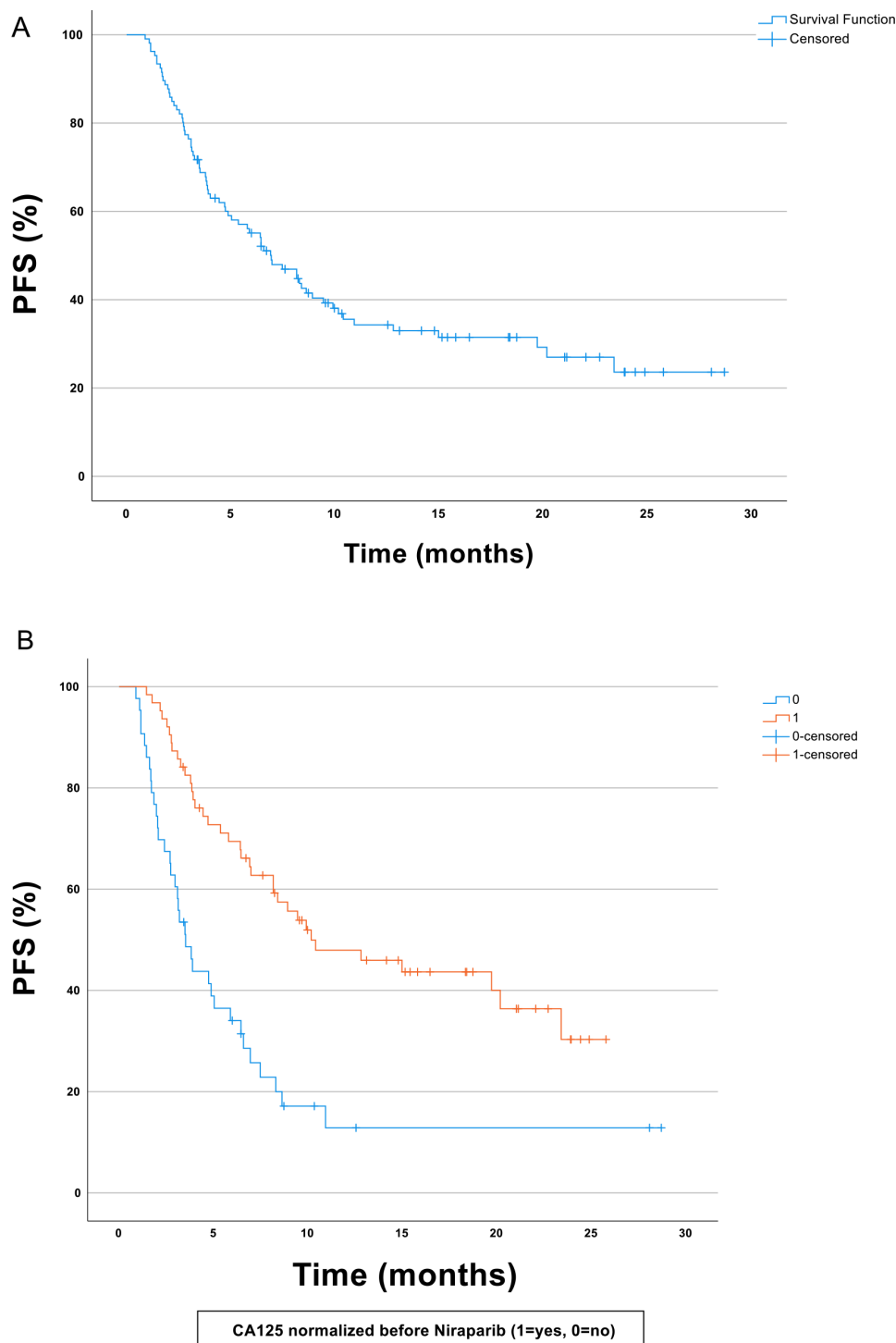


Figure 2 (A). Kaplan-Meier curve for progression-free survival. (B). Kaplan-Meier curves for progression-free survival for patients with and without CA125 normalization before niraparib treatment. PFS, progression-free survival.

toxicity, with anemia and thrombocytopenia being most frequent. Among patients who started on a daily dose of 300 mg despite a weight of <77 kg or platelets <150×10⁹/L, dose reductions and treatment pauses were more common than in patients who started on an individualized starting dose (dose reduction 65% (n=28) vs 35% (n=15), p<0.001) and (treatment pause 59% (n=22) vs 41% (n=15), p=0.02).

Type and Response to Subsequent Treatment

Of the 58 patients (61.7%) who had commenced subsequent chemotherapy, the majority (n=43, 74.1%) received platinum-based chemotherapy. The remaining 25.9% received non-platinum chemotherapy (with or without bevacizumab). After median cycles of 5.5 (range 1–39) at the data cut-off, 79.3% (n=46) of these patients were evaluable for response. Among these, 28% had

Table 3 Adverse events

Event	Any grade, n (%)	Grade 3–4, n (%)
Hematologic toxicity	59 (63)	25 (27)
Anemia	47 (50)	15 (16)
Thrombocytopenia	38 (40)	12 (13)
Neutropenia	19 (20)	7 (7)
Leukopenia	15 (16)	0
Non-hematologic toxicity*		15 (16)
Nausea		1 (1)
Fatigue		2 (2)
Hypertension	22 (23)	10 (11)
Abdominal pain		1 (1)
Increased creatinine level	32 (34)	0 (0)
Increased liver enzymes†	10 (11)	2‡ (2)
Increased ALP	11 (12)	0

*Only collected for grade 3–4 except for hypertension and biochemistry.
†Alanine aminotransferase, aspartate aminotransferase, gamma-glutamyltransferase.
‡Gamma-glutamyltransferase.
ALP, alkaline phosphatases.

progressive disease, 33% had stable disease, 37% had partial response and 2% had complete response, resulting in a clinical benefit rate of 72%. Among the patients receiving platinum-based chemotherapy, 81% were evaluable for response. Of these, 20% had progressive disease, 31% had stable disease, 46% had partial response, and 3% had complete response, resulting in a clinical benefit rate of 80%.

DISCUSSION

Summary of Main Results

This retrospective study is the first to report real-life data from patients with platinum-sensitive recurrent non-gBRCA mutated ovarian cancer receiving niraparib as maintenance treatment. Compared with the NOVA trial, the time to first subsequent treatment was comparable, whereas the progression-free survival was somewhat shorter in our study.⁵ We confirmed a clinically meaningful prolongation of the time to next treatment, as patients who had started chemotherapy at the end of follow-up had remained off chemotherapy for almost a year. Patients with normalized CA125 before niraparib treatment had an improved time to first subsequent treatment and progression-free survival of 5–6 months compared with patients without normalized CA125. Overall, we found a lower incidence of adverse events compared with the NOVA trial, especially with regard to hematologic toxicity.

Results in the Context of Published Literature

The introduction of PARP inhibitors has been the most important development in the treatment of ovarian cancer in the last decade. The efficacy in our study is comparable with the NOVA trial, including a similar time to first subsequent treatment of

10.7 months compared with 11.8 months in NOVA. However, the comparison of time to first subsequent treatment is limited by the fact that 38% had not yet commenced chemotherapy at last follow-up. The observed median progression-free survival of 6.9 months is numerically shorter than the 9.3 months reported in NOVA. Thus far, only five reports on real-life data of PARP inhibitors have been published,^{22–26} but none of these included the present efficacy outcomes; only time to discontinuation,^{23 24} number of cycles administered,^{22 24} and progression-free survival in BRCA mutated and non-mutated platinum-sensitive disease (n=48)²⁶ and platinum-sensitive and platinum-resistant recurrent disease (n=51)²⁵ were reported.

Our study cohort is in many respects similar to the non-gBRCA group in the NOVA study.⁵ The age distribution is comparable, as well as the number of previous treatment lines. However, in the NOVA trial, 50% of the patients had complete response to chemotherapy before entering the study, while in our study only 11.7% had investigator-assessed complete response prior to niraparib treatment. This may explain the shorter progression-free survival observed in this study.

The striking difference in progression-free survival and time to first subsequent treatment depending on CA125 normalization before niraparib treatment may be useful when estimating the potential benefit for the patients, and to our knowledge has not been reported before. Patients without normalized CA125 should be followed closely for early progression to avoid excess toxicity. Studies to date have focused on potential differences dependent on complete versus partial response to platinum-based chemotherapy, but no clear pattern has emerged.²⁷ Any response to platinum-based chemotherapy is a surrogate for PARP inhibitor response, and has been adapted as part of the indication for PARP inhibitors.

A shorter progression-free survival after chemotherapy preceding PARP inhibitor treatment has recently been observed in patients progressing on PARP inhibitors compared with placebo,²⁸ with mechanisms of cross-resistance between PARP inhibitors and platinum-based chemotherapy.²⁹ In this study, only 49% responded to subsequent platinum-based chemotherapy, indicating a need to develop successful maintenance therapy beyond re-exposure to PARP inhibitors.^{30 31}

Compared with the NOVA study, our study shows an overall lower incidence of adverse events, with fewer grade 3–4 adverse events (43% vs 74% in the NOVA study). Among these, anemia (16%), thrombocytopenia (13%), and neutropenia (7%) were most frequent, compared with 25%, 34%, and 20%, respectively in NOVA. However, we found a slightly higher rate of hypertension, both for any grade (23% vs 19%) and grade 3–4 (11% vs 8%). In this study, the number of dose interruptions (39) and dose reductions (46) of the patients had dose-interruptions and reductions, respectively, lower than those reported in NOVA, but higher than in other real-world studies.²² Still, the number of patients discontinuing niraparib owing to an adverse event was similar: 13.8% versus 14.7% in the NOVA study.

Aiming for minimization of treatment-related toxicity, individualized starting dose is essential. Patients with individualized starting dose had significantly fewer dose reductions than patients with non-individualized starting dose, in line with the post hoc analysis of the NOVA trial. At enrollment in this patient access program, the general recommendation for individualized starting dose based

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on weight was <77 kg. However, the initial Summary of Product Characteristics used 58 kg as the weight limit for dose reduction to 200 mg/day, instead of 77 kg, which may have contributed to deviations from individualized starting dose recommendations in this study.

Strengths and Weaknesses

Real-life data are important for evaluating whether the benefit of new anti-neoplastic agents observed in phase III trials can be translated into clinical practice. Clinical trials are restrictive in their eligibility criteria, and real-life data may therefore be helpful to estimate the benefit in an unselected population and in counseling the individual patient. The higher prevalence of co-morbidity in our study is in line with other real-life reports, and allow conclusions regarding tolerability in a less strictly selected population compared with a clinical trial. Another strength is the large number of patients included, as well as the complete follow-up of all patients.

A limitation of this study is the lack of data on sBRCA and HRD status, positively influencing the endpoints.³² In line with the procedures of the NOVA trial,⁵ only gBRCA testing was performed at our institutions at the time of enrollment. Since then, recommendations for BRCA and HRD testing have been updated.³³ Furthermore, the study had no control group and lacked retrospective radiologic response re-evaluation.

Implications for Practice and Future Research

The confirmed efficacy and safety of PARP inhibitor maintenance treatment in this real-world study underlines the impact of this treatment in standard of care. Patients and physician education is crucial when new drugs are introduced to ensure safety. Exploration of mechanisms of PARP inhibitor resistance, as well as therapeutic concepts for the growing number of patients being exposed to PARP inhibitors, are important areas of ongoing research. The shorter time to first subsequent treatment and progression-free survival in patients without normalized CA125 before niraparib treatment should be explored in future studies.

CONCLUSION

This is the first study showing effectiveness and safety of niraparib maintenance treatment in patients with gBRCA non-mutated recurrent platinum-sensitive ovarian cancer in a real-world setting. CA125 levels at the start of niraparib treatment may estimate the individual benefit of a PARP inhibitor, and individualized dosing is essential to minimize adverse events.

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Funding Funding for this investigator-initiated study was provided by a grant from GlaxoSmithKline plc. (GSK; eTrack #214738). The sponsor had no access to the database and had no influence on collection, analyses, interpretation, or writing of the manuscript. GSK was provided the opportunity to review a preliminary version of this manuscript for factual accuracy, but the authors are solely responsible for final content and interpretation.

Competing interests No.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by The Regional Committees for Medical Research Ethics – South- East Norway. Reference no. 62008. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

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