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

Bente Vilming 1, Jørgen Fallås Dahl2, Anne Gry Bentzen3, Vibeke Anett Ingebrigtsen3, Elisabeth Berge Nilsen2, Ingvild Vistad5,6, Anne Dørum1, Olesya Solheim 1, Line Bjørge 7,8, Manuela Zucknick9, Guro Aune5,10, Kristina Lindemann1,6

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 established 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 benefit of PARP inhibitor maintenance.

INTRODUCTION

Ovarian cancer, including fallopian tube and peritoneal cancer, is the fifth most frequent cause of cancer death in women in Europe1,2 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. Most patients relapse despite optimal primary treatment and will undergo multiple lines of chemotherapy. Maintenance strategies with 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.3,4-12 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 mutation.
and HRD. PARP inhibitors have also shown efficacy as mono-
therapy.

Niraparib is a selective inhibitor of PARP (PARP1 and PARP2), and has shown efficacy in patients with recurrent platinum-sensitive ovarian cancer, regardless of BRCA mutations. The NOVA trial 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, showing that patients with a baseline body weight <77 kg or platelet count <150x10^9/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.

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, Sunt Olav 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.

**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 criteria), 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-hematologic 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 χ² 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 achieved 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.
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 <150×10^9/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).

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.
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...
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 <150×10^9/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

---

**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.
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. 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, but none of these included the present efficacy outcomes; only time to discontinuation, number of cycles administered, and progression-free survival in BRCA mutated and non-mutated platinum-sensitive disease (n=48) and platinum-sensitive and platinum-resistant recurrent disease (n=51) were reported.

Our study cohort is in many respects similar to the non-gBRCA group in the NOVA study. 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. 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, with mechanisms of cross-resistance between PARP inhibitors and platinum-based chemotherapy. 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.

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. 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...

---

**Table 3** Adverse events

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

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

Author affiliations
1Department of Gynecological Oncology, The Norwegian Radium Hospital, Oslo University Hospital, Oslo, Norway
2Department of Clinical and Molecular Medicine, Faculty of Medicine, Norwegian University of Science and Technology, Trondheim, Norway
3Department of Gynecological Oncology, University Hospital of North Norway, Tromsø, Norway
4Department of Obstetrics and Gynecology, Stavanger University Hospital, Stavanger, Norway
5Department of Gynecology and Obstetrics, Hospital of Southern Norway, Kristiansand, Norway
6Institute of Clinical Medicine, Faculty of Medicine, University of Oslo, Oslo, Norway
7Department of Obstetrics and Gynecology, Haukeland University Hospital, Bergen, Norway
8Centre for Cancer Biomarkers, Department of Clinical Science, University of Bergen, Bergen, Norway
9Department of Biostatistics, University of Oslo, Oslo, Norway
10Department of Gynecological Oncology, St. Olavs Hospital, Trondheim University Hospital, Trondheim, Norway

Twitter Ingvild Vistad @IngvildVistad

Contributors Conceptualization: BV, GA, KL. Patient recruitment: All authors except MZ. Data curation: BV, JFD, KL. Formal analysis: JFD, MZ. Funding acquisition: KL. Project administration and guarantor: KL. Preparation of original draft: BV, KL. Writing - review and editing: All authors.

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.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes terms, drug names and drug dosages, and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, an indication of whether changes were made, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

ORCID iDs
Bente Vilming http://orcid.org/0000-0001-7873-415X
Olesya Solheim http://orcid.org/0000-0003-1936-3453
Line Bjørge http://orcid.org/0000-0002-0240-2770

REFERENCES
Original research


18 Banerjee S, Moor KN, Colombo N, et al. 811Mo maintenance Olaparib for patients (Pts) with newly diagnosed, advanced ovarian cancer (OC) and a BRCA Mutation (Brcam): 5-year (Y) follow-up (FU) from Solo1. *Annals of Oncology* 2020;31:5613.


111 patients enrolled

106 patients started treatment

94 patients included in analysis

Still on treatment at data cut-off, n=23

Did not receive any treatment, n=5

Starting dose 100mg, n=2
Non high grade histology, n=5
gBRCA mutated, n=5

Discontinued treatment, n=71
Disease progression, n=56
Adverse event, n=13
Patient decision, n=1
Other, n=1