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

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Summary

Background Quality of life (QOL) has become an important complementary endpoint in cancer clinical studies alongside more traditional assessments (eg, tumour response, progression-free survival, overall survival). Niraparib maintenance treatment has been shown to significantly improve progression-free survival in patients with recurrent ovarian cancer. We aimed to assess whether the benefits of extending progression-free survival are offset by treatment-associated toxic effects that affect QOL.

Methods The ENGOT-OV16/NOVA trial was a multicentre, double-blind, phase 3, randomised controlled trial done in 107 study sites in the USA, Canada, Europe, and Israel. Patients with recurrent ovarian cancer who were in response to their last platinum-based chemotherapy were randomly assigned (2:1) to receive either niraparib (300 mg once daily) as a maintenance treatment or placebo. Randomisation was stratified based on time to progression after the penultimate platinum-based regimen, previous use of bevacizumab, and best response (complete or partial) to the last platinum-based regimen with permuted-block randomisation (six in each block) using an interactive web response system. The trial enrolled two independent cohorts on the basis of germline *BRCA* (g*BRCA*) mutation status (determined by BRAC*Analysis* Testing, Myriad Genetics, Salt Lake City, UT, USA). The primary endpoint of the trial was progression-free survival, and has already been reported. In this study, we assessed patient-reported outcomes (PROs) in the intention-to-treat population using the Functional Assessment of Cancer Therapy–Ovarian Symptoms Index (FOSI) and European QOL five-dimension five-level questionnaire (EQ-5D-5L). We collected PROs from trial entry every 8 weeks for the first 14 cycles and every 12 weeks thereafter. If a patient discontinued, we collected PROs at discontinuation and during a postprogression visit 8 weeks (plus or minus 2 weeks) later. We assessed the effect of haematological toxic effects on QOL with disutility analyses of the most common grade 3–4 adverse events (thrombocytopenia, anaemia, and neutropenia) using a mixed model with histology, region, previous treatment, age, planned treatment, and baseline score as covariates. This study is registered with ClinicalTrials.gov, number NCT01847274.

Findings Between Aug 28, 2013, and June 1, 2015, 553 patients were enrolled and randomly assigned to receive niraparib (n=138 in the g*BRCA*mut cohort, n=234 in the non-g*BRCA*mut cohort) or placebo (n=65 in the g*BRCA*mut cohort, n=116 in the non-g*BRCA*mut cohort). The mean FOSI score at baseline was similar between the two groups (range between 25·0–25·6 in the two groups). Overall QOL scores remained stable during the treatment and preprogression period in the niraparib group; no significant differences were observed between the niraparib and placebo group, and preprogression EQ-5D-5L scores were similar between the two groups in both cohorts (0·838 [0·0097] in the niraparib group *vs* 0·834 [0·0173] in the placebo group in the g*BRCA*mut cohort; and 0·833 [0·0077] in the niraparib group *vs* 0·815 [0·0122] in the placebo group in the non-g*BRCA*mut cohort). The most common adverse events reported at screening (baseline) were lack of energy (425 [79%]; 97 [18%] reporting severe lack of energy), pain (236 [44%]), and nausea (118 [22%]). All symptoms, except nausea, either remained stable or improved over time in the niraparib group. The most common grade 3 or 4 toxicities observed in the niraparib group were haematological in nature: thrombocytopenia (124 [34%] of 367 patients), anaemia (93 [25%]), and neutropenia (72 [20%]); disutility analyses showed no significant QOL impairment associated with these toxic effects.

Interpretation These PRO data suggest that women who receive niraparib as maintenance treatment for recurrent ovarian cancer after responding to platinum treatment are able to maintain QOL during their treatment when compared with placebo.

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Research in context

Evidence before this study

Poly(ADP-ribose) polymerase (PARP) inhibitors have been shown to increase progression-free survival in the maintenance setting for recurrent ovarian cancer. Quality of life (QOL) data are available for patients with ovarian cancer receiving chemotherapy and chemotherapy in combination with bevacizumab. We searched PubMed for articles published up to Dec 1, 2017, using the search terms "PARP" OR "niraparib" OR "rucaparib" OR "olaparib" OR "veliparib" OR "talazoparib" AND "quality of life" OR "patient-reported outcomes" OR "FOSI" OR "FACT-O" OR "EQ-5D". We had no language restrictions. Detailed data on QOL for patients receiving a PARP inhibitor were mostly limited to top-line data in clinical trial reports. The only published manuscript with specific data on QOL in patients with ovarian cancer receiving a PARP inhibitor was Study 19, the phase 2 randomised placebo-controlled trial of olaparib. This study was done to assess the effect of the PARP inhibitor niraparib on QOL in a large phase 3 study.

Added value of this study

To our knowledge, these results provide one of the most detailed reports on QOL from a phase 3 trial in patients receiving a PARP inhibitor to date and will be instrumental in informing treatment decisions by health-care practitioners.

Implications of all the available evidence

Our results show that niraparib has no significant negative effect on QOL in patients with recurrent ovarian cancer. Combined with the evidence of increased progression-free survival with niraparib in the maintenance setting, these findings support the addition of niraparib as a component of standard of care.

Introduction

Ovarian cancer is the seventh most common cancer in women worldwide and the fifth leading cause of cancer-related death among women in the USA and UK.[1–3] Generally, ovarian cancer has no early signs and symptoms. Consequently, most cases (65%) are diagnosed at an advanced stage, and almost three-quarters of patients (71%) diagnosed with advanced disease will die within 5 years of diagnosis.[4] The cornerstone of drug treatment in the first-line advanced disease setting is platinum-based chemotherapy plus a taxane; however, 85% of patients will experience disease recurrence after first-line treatment.[5,6]

Recurrent ovarian cancer is considered incurable.[5] Most patients with recurrence are treated with further rounds of platinum-based chemotherapy.[5,6] The effectiveness of platinum-based chemotherapy usually diminishes over time, and disease tends to recur rapidly after completion of treatment, requiring further chemotherapy.[7] Additionally, duration of progression-free survival decreases and risk for cumulative toxic effects increases with each subsequent line of chemotherapy.[7,8] The standard of care for women who have responded to platinum-based chemotherapy is watchful waiting,[6] which is generally associated with high levels of anxiety due to fear of recurrence.[9,10] Maintenance treatment offers an opportunity to prolong remission and chemotherapy-free intervals, helping to delay the next cycle of chemotherapy and associated toxic effects.

In the past 10 years, quality of life (QOL) has become an important complementary endpoint in cancer clinical studies, in addition to the more traditional assessments of efficacy (eg, tumour response, progression-free survival).[11–14] QOL assessments are providing new insight into factors that guide treatment choice with regard to a patient's overall physical, functional, and emotional wellbeing.[12,15] QOL measures are crucial to determine whether or not to administer maintenance treatment during the watchful waiting period. Toxic effects associated with maintenance treatment must not offset the benefit associated with delaying the time to progression or death.

Niraparib is a highly selective poly(ADP-ribose) polymerase (PARP) 1 or 2 inhibitor that has been shown to concentrate in the tumour compared with plasma in preclinical studies, delivering more than 90% durable PARP inhibition.[16] The efficacy of once-daily niraparib as maintenance treatment in patients with recurrent ovarian cancer who were in complete or partial response to platinum-based chemotherapy was assessed in the phase 3 ENGOT-OV16/NOVA study.[16] Results from this study showed that niraparib treatment resulted in significantly longer progression-free survival than placebo, regardless of germline *BRCA* or homologous recombination deficiency status, which lead to niraparib being approved in the USA and the EU for maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy in 2017.

In this Article, we report the prespecified secondary objective of assessing patient-reported outcomes (PROs) of patients who received niraparib as maintenance treatment versus those who received placebo. Additionally, we did a disutility analysis to better understand the relationship between safety and PRO responses. The original manuscript on the ENGOT-OV16/NOVA trial[16] by Mirza and colleagues reported aggregate QOL scores from the study. The objective of this analysis was to assess in detail whether niraparib treatment had a negative effect on key symptoms that affect patient QOL in ovarian cancer. This report also aimed to assess whether there is an association between treatment-related adverse events and QOL.

Methods

Study design and participants

The ENGOT-OV16/NOVA study design has been previously published.[16] Briefly, the multicentre, double-blind, phase 3, randomised controlled ENGOT-OV16/NOVA trial enrolled two independent cohorts on the basis of g*BRCA* mutation status (determined by BRAC*Analysis* Testing, Myriad Genetics, Salt Lake City, UT, USA) across 107 clinical investigation sites in the USA, Canada, Europe, and Israel. Patients were at least 18 years of age, and had histologically diagnosed epithelial ovarian, fallopian tube, or primary peritoneal cancer. All patients had a complete or partial response to their penultimate platinum-based regimen and disease progression more than 6 months after completion of this round of chemotherapy. Patients must also have achieved a partial or complete response to the last platinum-based chemotherapy before being randomly assigned in the study. Patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1 at study entry 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 trial protocol,[16] amendments, and other relevant study documentation were reviewed and approved by the institutional or national review board or ethics committee at each trial site or in each country. All the patients provided written informed consent.

Randomisation and masking

Patients in each cohort (g*BRCA*mut and non-g*BRCA*mut) were randomly assigned (2:1) to receive either niraparib (300 mg) or placebo once daily, given as three capsules without regard to food, until disease progression. Randomisation within each cohort was stratified on the basis of time to progression following the penultimate platinum-based regimen, previous use of bevacizumab, and best response (complete or partial) to the last platinum-based regimen. A permuted-block (six in each block) randomisation was done at each level of the stratification variables with an interactive web response system. To ensure masking, niraparib and placebo capsules were manufactured to have identical appearances. Further detail on the randomisation method is in the appendix (p 11).

Procedures

Patients continued to receive treatment until disease progression, unacceptable toxic effects, death, withdrawal of consent, or loss to follow-up—whichever came first. Treatment interruption due to haematological toxic effects could last up to 28 days. After resolution of those toxic effects, treatment would be restarted at a reduced dose of 200 mg according to protocol-specified criteria. Additional reductions of up to 100 mg were permitted.

PRO questionnaires were selected to assess both ovarian cancer-specific symptoms and QOL (Functional Assessment of Cancer Therapy–Ovarian Symptoms Index [FOSI]), as well as general health status (European QOL Scale five-dimension five-level [EQ-5D-5L] and European QOL-visual analogue scale [EQ-VAS]). Patients completed the questionnaires on paper. The PROs were collected in a coordinated fashion with imaging while patients were on study treatment (every 8 weeks for the first 14 cycles, then every 12 weeks thereafter). If the patient discontinued study treatment, the treatment discontinuation assessment of PROs was done at that time and then at the postprogression visit 8 weeks (plus or minus 2 weeks) later, regardless of subsequent treatment. We only used the postprogression assessments that corresponded to patients with progressive disease as declared by the study investigator. The PRO evaluations were administered before doing any other procedures at each assessment.

The FOSI is a validated eight-item measure of symptom response to treatment for ovarian cancer based on a subset of questions from the Functional Assessment of Cancer Therapy-Ovarian (FACT-O) questionnaire.[17] Validated in a population of 62 patients with advanced ovarian cancer, this instrument measures ovarian cancer-specific symptoms with demonstrable reliability, validity, and responsiveness to clinical change.[17] The eight questions assess pain, fatigue, nausea, vomiting, bloating, cramping, worry, and QOL. Patients report their symptom experience over the past 7 days using a five-point Likert scale, which ranges from not at all (0) to very much (4). We calculated the FOSI score by multiplying the sum of all items scored by 8 and dividing the result by the number of responses.

For items related to symptoms and worry, we calculated the total score using the item score of the difference between the patient's response and 4. We considered FOSI as assessable if we recorded five or more responses; otherwise, we recorded the FOSI score as missing. The FOSI score range was from 0 (severely symptomatic) to 32 (asymptomatic). In addition to analysing the overall FOSI score, we did analyses of the individual symptom-related questions. We categorised patients as symptomatic if their response was 1 or more and as severely symptomatic if their response was 3 or 4.

The EQ-5D-5L is a well validated, general preference-based, health-related QOL instrument.[18] The EQ-5D-5L encompasses the following five domains: mobility, self-care, usual activities, pain or discomfort, and anxiety or depression. Each domain has five possible response levels: no problems (level 1), slight problems (level 2), moderate problems (level 3), severe problems (level 4), and extreme problems (level 5). Each domain is assigned a level, and levels are combined to create a five-digit number describing the patient's health state (eg, 11111, 12345). For each patient, a health utility index (HUI) value is determined from the health states using the US

See Online for appendix

	Germline *BRCA* mutation		No germline *BRCA* mutation	
	Niraparib group (n=138)	Placebo group (n=65)	Niraparib group (n=234)	Placebo group (n=116)
Median age (range), years	57 (36–83)	58 (38–73)	63 (33–84)	61 (34–82)
ECOG performance status				
0	91 (66%)	48 (74%)	160 (68%)	78 (67%)
1	47 (34%)	17 (26%)	74 (32%)	38 (33%)
Cancer stage*				
1 or 2	23 (17%)	10 (15%)	22 (9%)	5 (4%)
3	95 (69%)	46 (71%)	173 (74%)	86 (74%)
4	20 (15%)	9 (14%)	38 (16%)	24 (21%)
Time to progression after penultimate platinum therapy				
6 to <12 months	54 (39%)	26 (40%)	90 (39%)	44 (38%)
≥12 months	84 (61%)	39 (60%)	144 (62%)	72 (62%)
Best response to most recent platinum therapy				
Complete	71 (51%)	33 (51%)	117 (50%)	60 (52%)
Partial	67 (49%)	32 (49%)	117 (50%)	56 (48%)
Previous bevacizumab use	33 (24%)	17 (26%)	62 (27%)	30 (26%)
Germline *BRCA* mutation				
BRCA1	85 (62%)	43 (66%)	NA	NA
BRCA2	51 (37%)	18 (28%)	NA	NA
BRCA1, *BRCA2* rearrangement, or both	9 (7%)	4 (6%)	NA	NA
Previous lines of chemotherapy†				
1	1 (1%)	0	0	0
2	70 (51%)	30 (46%)	155 (66%)	77 (66%)
≥3	67 (49%)	35 (54%)	79 (34%)	38 (33%)

Data are n (%), unless otherwise specified. ECOG=Eastern Cooperative Oncology Group. NA=not applicable. *Staging was done with the use of the International Federation of Gynecology and Obstetrics system; among the patients without a germline *BRCA* mutation, data on staging were not available for one patient in the placebo group, and one patient in the niraparib group had stage 0 disease at the time of diagnosis. †Among the patients without a germline *BRCA* mutation, data on previous lines of therapy were not available for one patient in the placebo group.

Table 1: **Baseline characteristics**

value set.[19,20] Additionally, a VAS is included in the EQ-5D-5L. The VAS measures current health status on a scale from 0 to 100, where zero is the worst imaginable health state and 100 is the best. We considered EQ-5D-5L as assessable if responses were available for all five domains.

Outcomes

The primary endpoint of the ENGOT-OV16/NOVA trial was duration of progression-free survival, as determined by blinded independent central review. Progression-free survival was assessed on the basis of both imaging and clinical symptoms. Secondary endpoints included PROs (FOSI, EQ-5D-5L, EQ-VAS), chemotherapy-free interval, time to first subsequent therapy, time to second subsequent therapy, progression-free survival 2 (time from randomisation until assessment of progression during receipt of next anticancer therapy after study treatment or death), and overall survival. In this Article, we report on the results of the PRO assessment from FOSI, EQ-5D-5L, and EQ-VAS.

Statistical analysis

The primary analysis set for the PRO endpoints was the intention-to-treat (ITT) population. For continuous variables, we analysed changes from baseline in overall score descriptively by treatment group.

We used a mixed-effects growth-curve model adjusting for fixed (time, baseline demographic values, and the three stratification factors) and random (patient) covariates to assess the association between treatment assignment and PRO score. We assumed assessments for each patient in subsequent cycles to be correlated over time. We considered two random-effects in this model: individual patient effect and rate of change over time. We used unstructured covariance to assess the association between these two random variables. We estimated this relationship using restricted maximum-likelihood estimation.

For EQ-5D-5L, we averaged the HUI scores for all post-baseline visits before disease progression. We then adjusted these means with a mixed model on the following covariates: histology, region, previous treatment, age, duration on previous treatment, and baseline EQ-5D-5L score. We prespecified these covariates in the PRO analysis plan based on factors that were considered to potentially have an effect on QOL. Least squares mean estimates of the adjusted HUI scores are presented by treatment group along with the standard error of each estimate.

The proportion of patients who had haematological adverse events (anaemia, thrombocytopenia, and neutropenia) was greater in the niraparib group than in the placebo group. Whether these adverse events had an effect on patient QOL is potentially an important question for physicians and patients considering maintenance treatment. We assessed the effect of haematological adverse events on QOL using adjusted EQ-5D-5L, HUI, and FOSI scores based on mixed models using the following covariates: histology, region, previous treatment, age (continuous), planned treatment, and baseline FOSI or EQ-5D-5L score. We developed separate models to assess the unique contribution of each adverse event type. We took into account the relative differences in the severity of different adverse events by developing separate disutility estimates for adverse events of grades 3 and 4.

We presented the effect of each adverse event on the individual FOSI and HUI scores using least squares mean estimates of the adverse event as a fixed-effect relative to a reference point. We used the least squares mean HUI and FOSI score estimates of patients who did not present with the adverse event during the stable treatment period as a reference. We determined the statistical significance of the resulting estimate using the analysis of covariance procedure, with a prespecified alpha equal to 0·05. We did all analyses using SAS (version 9.3 or higher).

Because the objective of the analysis was to examine whether patients in the niraparib group were able to maintain the same QOL as those in the placebo group

	Niraparib group	Placebo group
Germline *BRCA* mutation		
Patients, n	138	65
Baseline		
N	134	64
Mean	0·850 (0·0105)	0·847 (0·0163)
Adjusted least squares*	0·838 (0·0324)	0·834 (0·0365)
Preprogression†		
N	129	59
Mean	0·838 (0·0097)	0·834 (0·0173)
Adjusted least squares	0·812 (0·0257)	0·803 (0·0292)
Postprogression‡		
N	60	46
Mean	0·801 (0·0210)	0·794 (0·0178)
Adjusted least squares	0·851 (0·0541)	0·842 (0·0551)
No germline *BRCA* mutation		
Patients, n	234	116
Baseline		
N	227	112
Mean	0·837 (0·0078)	0·824 (0·0128)
Adjusted least squares*	0·870 (0·0215)	0·851 (0·0236)
Preprogression†		
N	208	97
Mean	0·833 (0·0077)	0·815 (0·0122)
Adjusted least squares	0·845 (0·0160)	0·828 (0·0175)
Postprogression‡		
N	139	94
Mean	0·810 (0·0119)	0·783 (0·0138)
Adjusted least squares	0·809 (0·0290)	0·788 (0·0308)

Data are mean (SE), unless otherwise specified. For each patient, a HUI value is determined from the health states with the use of the US value set. EQ-5D-5L=European QOL 5-Dimension 5-Level questionnaire. ITT=intention-to-treat. NA=not applicable. HUI=health utility index. *Means adjusted by histology, region, prior treatment, age, duration of prior treatment, and baseline EQ-5D-5L score. †Average of all postbaseline preprogression EQ-5D-5L HUI scores among all patients with disease progression. ‡First postprogression EQ-5D-5L HUI score among all patients with disease progression.

Table 2: **Cross-sectional statistics of adjusted EQ-5D-5L utility score stratified by treatment in the ITT population (US value set)**

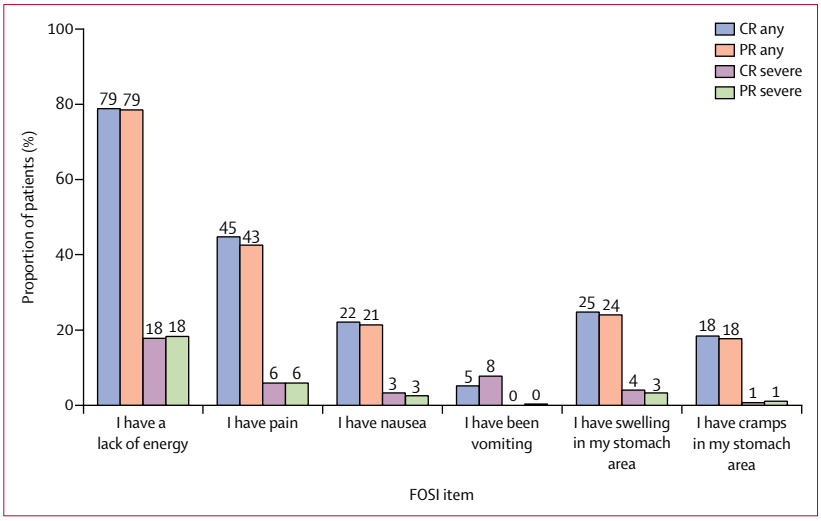

Figure 1: **FOSI symptoms at screening**
The proportion of patients experiencing any level of symptoms and the proportion of patients experiencing severe symptoms. FOSI=Functional Assessment of Cancer Therapy–Ovarian Symptoms Index. CR=complete response. PR=partial response. Severe=severe QOL symptoms.

before progression, missing data resulting from progression were not relevant for this analysis. Missing data due to reasons other than progression were quite limited (<8·5%). Also, we observed no specific patterns for missing data in terms of reasons so we made no specific statistical adjustments for missing data in the analysis.

This study is registered with ClinicalTrials.gov, number NCT01847274.

Role of the funding source

The funder of the study had a role in study design and was involved in overseeing trial conduct. Funding for medical writing assistance was provided by the funder. The funder of the study had no role in data collection, data analysis, or data interpretation. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

A total of 553 patients were enrolled in the ENGOT-OV16/NOVA study at 107 sites in the USA, Canada, and Hungary, between Aug 28, 2013, and June 1, 2015. Of these patients, 203 were in the g*BRCA*mut cohort (138 in the niraparib group, 65 in the placebo group) and 350 in the non-g*BRCA*mut cohort (234 niraparib, 116 placebo). Demographic and clinical characteristics were similar between the two cohorts at baseline (table 1). Median duration of follow-up at data cutoff was 16·9 months (IQR 13·8–21·4).

The ENGOT-OV16/NOVA study met its primary endpoint, with improved progression-free survival in patients treated with niraparib when compared with placebo. Patients with a g*BRCA* mutation had reduced risk of progression (hazard ratio [HR] 0·27; 95% CI 0·17–0·41), compared with patients with no g*BRCA* mutation (HR 0·45; 0·34–0·61).[16]

Information regarding completeness of PRO data and reasons for discontinuation are provided in the appendix (pp 1–3). In the g*BRCA*mut cohort, the baseline mean FOSI values were similar between the two treatment groups (25·1 [SD 4·18] in the niraparib group and 25·6 [3·84] in the placebo group). Similar results were also observed for the non-g*BRCA*mut cohort (25·4 [3·92] in the niraparib group and 25·0 [4·07] in the placebo group). Baseline EQ-5D-5L scores were also similar between treatment groups in both cohorts (table 2).

The cross-sectional analysis of the QOL scores (FOSI, EQ-5D-5L, and EQ-VAS) revealed baseline mean values to be similar between the two treatment groups. The

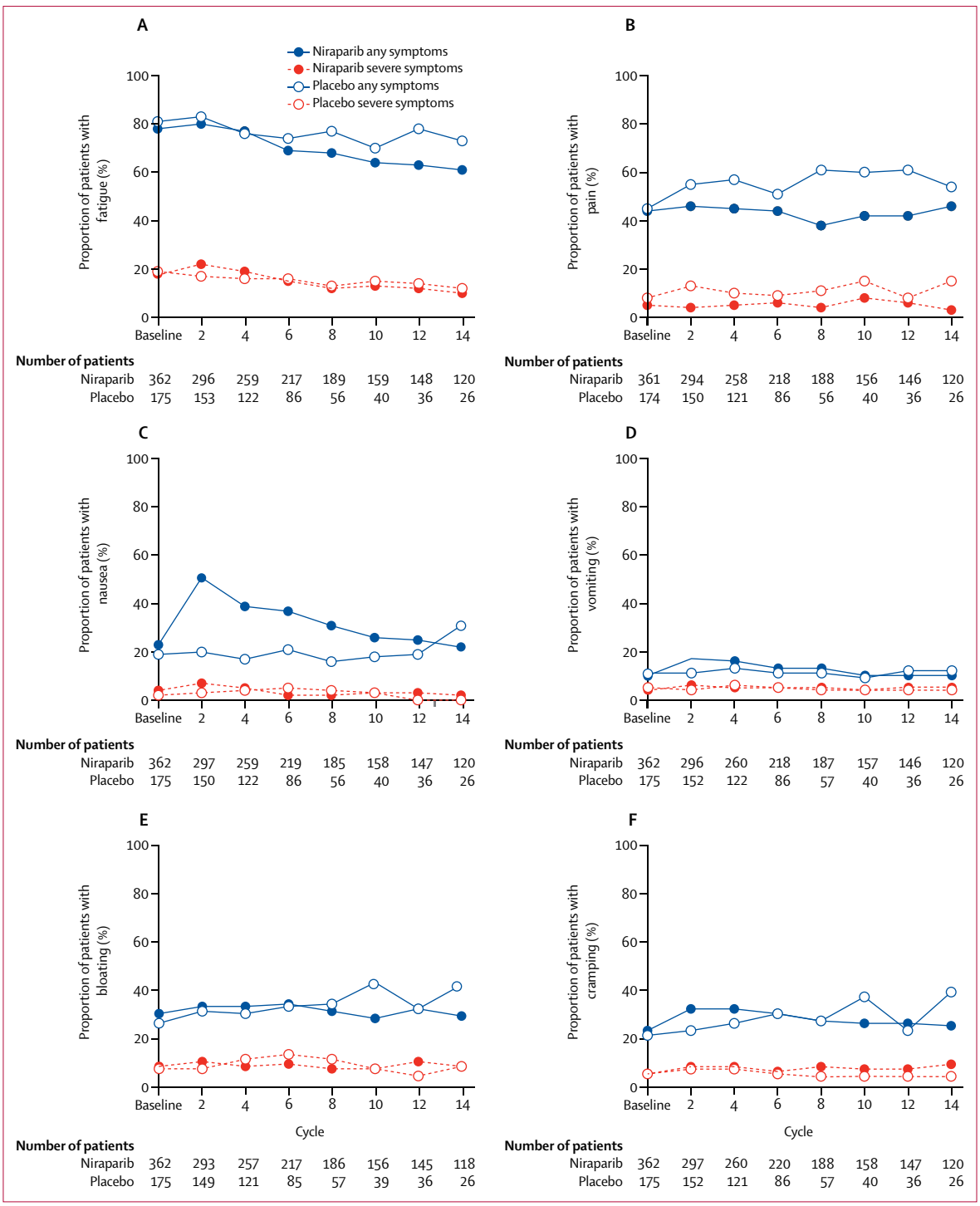

Figure 2: **Individual FOSI measures over time**
Symptoms include fatigue (A), pain (B), nausea (C), vomiting (D), bloating (E), and cramping (F). FOSI=Functional Assessment of Cancer Therapy–Ovarian Symptoms Index.

changes from baseline during the maintenance period were minimal and similar between treatment groups. Similar results were also observed at the postprogression assessment in the niraparib and placebo treatment groups. The findings were similar across g*BRCA*mut and non-g*BRCA*mut cohorts. More detail of QOL scores over time is provided in the appendix (pp 1–3). Results for the neuropathy questionnaire are also provided in the

appendix (p 4). The HUI scores for the g*BRCA*mut and non-g*BRCA*mut cohort have been previously published;[16] HUI scores over time for the non-g*BRCA*mut homologous recombination deficiency positive subgroup are provided in the appendix (pp 9–10).

The most common symptoms reported at screening (baseline) were lack of energy and pain. The proportion of patients reporting lack of energy at screening was 79% (n=425), with 18% (n=97) reporting severe symptoms. The proportion of patients reporting some level of pain at screening was 44% (n=236) and nausea was 22% (n=118). No difference in symptoms was observed between patients who had a complete response or partial response to their last platinum treatment (figure 1).

All symptoms, with the exception of nausea, either remained stable or improved over time with niraparib treatment (figure 2). The proportion of patients reporting nausea increased at cycle 2 but steadily declined at later timepoints, approaching baseline levels. The proportion of patients treated with placebo who reported nausea through the course of the study was approximately 20%. The incidence of nausea and vomiting reported as adverse events during the first 5 months is shown in the appendix (p 7). In addition to symptoms, FOSI also included an item that assessed patient's level of worry that the condition will get worse (appendix p 8).

After adjustment for histology, region, age, prior treatment type, duration of previous treatment, and baseline EQ-5D-5L score, the adjusted least squares mean HUI scores were similar between the treatment groups (table 2). Between group differences were less than the minimally important difference (0·08) for HUI when averaged across preprogression timepoints.[19,20]

The most common grade 3 or 4 adverse events observed in patients receiving niraparib were thrombocytopenia in 124 (34%) of 367 patients, anaemia in 93 (25%), and neutropenia in 72 (20%).[16] The any grade incidence of each adverse event during the first 5 months is shown in the appendix (p 7).

Haematological toxicity (anaemia, neutropenia, or thrombocytopenia) had no significant negative effect on QOL in any of the cohorts for the adjusted or unadjusted FOSI models (figure 3). Similarly, for the EQ-5D-5L HUI and VAS models, disutility was not significantly associated with haematological toxicity in either of the cohorts (figure 3).

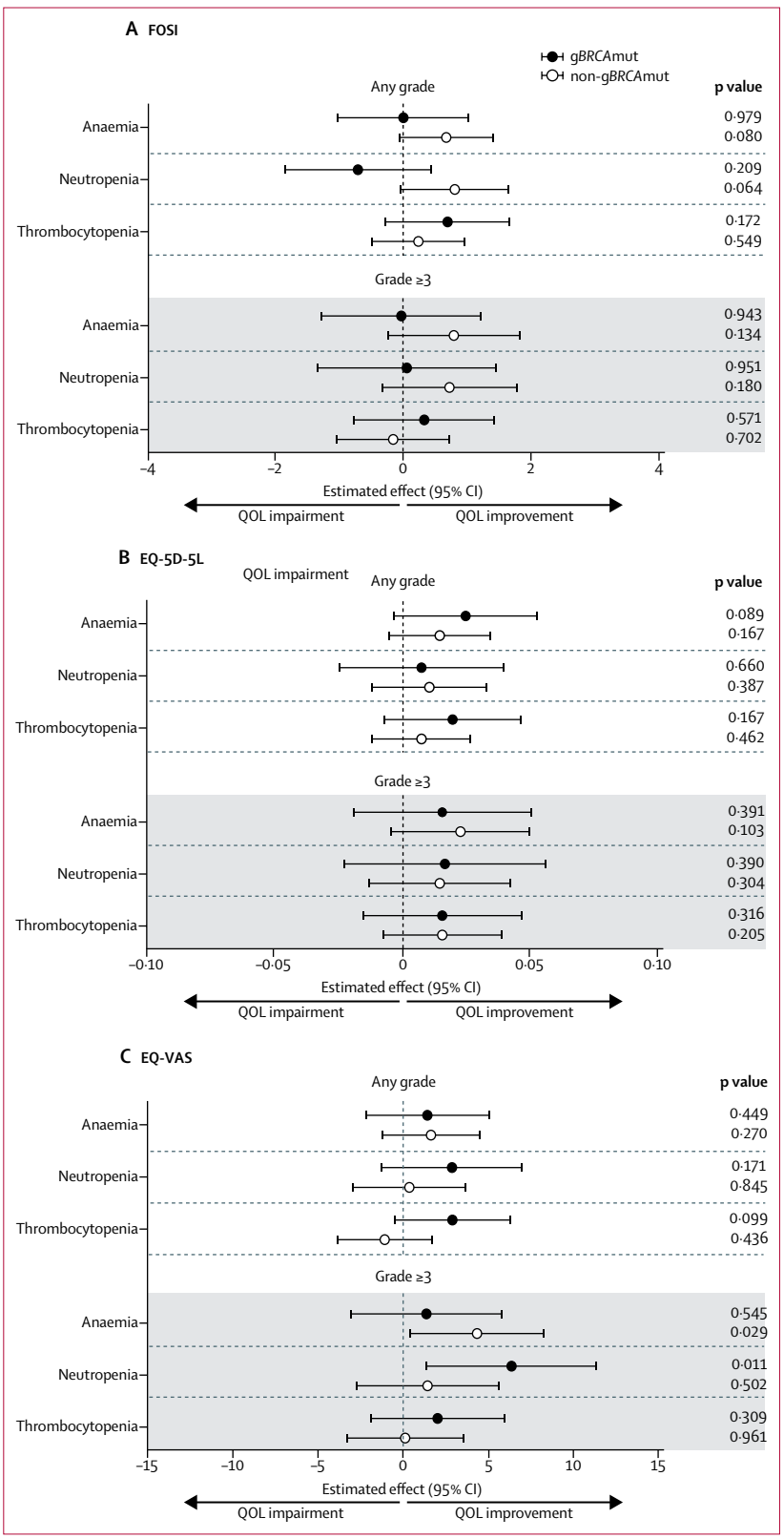

Figure 3: **Adjusted mixed model effects of each adverse event by cohort ITT population)**

Difference and significance in QOL scores between patients who experienced a haematological adverse event and patients who did not: (A) FOSI, (B) EQ-5D-5L, and (C) EQ-VAS. The ITT population consisted of all patients randomly assigned, and patients were analysed according to the study drug assigned via randomisation, even if no study drug was ingested. ITT=intention-to-treat. QOL=quality of life. FOSI=Functional Assessment of Cancer Therapy–Ovarian Symptoms Index. EQ-5D-5L=European QOL 5-dimension 5-level questionnaire.

Discussion

The ENGOT-OV16/NOVA trial showed significant improvements in progression-free survival in patients with ovarian cancer for both cohorts, g*BRCA*mut and non-g*BRCA*mut.[16] It is important that toxic effects associated with maintenance treatment do not result in a substantial reduction in QOL that offsets the benefit associated with delaying the time to progression or death. Therefore, PROs associated with symptoms and QOL are crucial to assess as supportive endpoints in the study.

In this analysis, patients reported symptoms of fatigue, pain, and nausea at study entry even though they were in response to their last platinum treatment. The most commonly reported symptoms were lack of energy and pain. Additionally, 22% of patients reported experiencing nausea before study entry. Treatment with niraparib did not reduce QOL when compared with placebo.

Overall, in the longitudinal analysis for the FOSI, EQ-5D-5L, and EQ-VAS PRO measures, mean scores were similar between treatment groups, and minimal changes from baseline were observed at the domain and individual item level. All symptoms, with the exception of nausea, either remained stable or improved over time with niraparib treatment. The proportion of patients experiencing lack of energy or fatigue decreased relative to baseline over time in the niraparib group. A higher proportion of patients in the placebo group reported pain compared with the niraparib group. The proportion of patients reporting nausea initially increased in the niraparib group but steadily declined at later timepoints, approaching baseline levels. Because only 2% of patients discontinued treatment due to nausea, this reduction cannot be explained by patients discontinuing treatment. A substantial number of patients underwent dose reductions due to adverse events, and these reductions could have had an effect on the incidence of nausea over time. Approximately 20% of patients treated with placebo reported nausea through the course of the study, indicating a background rate of nausea in this treatment population. Placebo data also indicated a persistent lack of energy in this population that persisted throughout the study period.

Additionally, a disutility analysis of adverse events showed no negative effect of haematological adverse events on the patient's QOL.

The data presented herein are concordant with the high-level QOL data presented from other PARP inhibitor clinical trials.[21,22] However, these previous publications did not include information regarding the effect of maintenance treatment on the most common symptoms experienced by patients with ovarian cancer. To our knowledge, this Article provides one of the first in-depth breakdowns of specific symptoms that affect QOL in patients with recurrent ovarian cancer receiving maintenance treatment with a PARP inhibitor. It also assesses for the first time the effects of specific adverse events on patient QOL.

The PRO analysis was not prospectively designed to formally test non-inferiority for niraparib PRO outcomes versus placebo; however, application of statistical considerations for ascertaining non-inferiority were used to assist in the interpretation of these data.

Overall, these results showed niraparib was similar to placebo in the adjusted and unadjusted models for both symptoms and QOL during the treatment and preprogression period. PRO scores were not significantly different between the placebo and treatment groups, suggesting that maintenance treatment with niraparib did not decrease functioning or QOL in these patients. These PRO data suggest that women who receive niraparib as maintenance treatment for platinum-sensitive recurrent ovarian cancer after response to platinum treatment are able to maintain a QOL similar to placebo during their treatment.

The results reported in this Article were based on data collected during the ENGOT-OV16/NOVA trial and cannot be generalised to patients who were excluded from the study, such as those with an ECOG performance status score of 2. Further, the study results include only one postprogression PRO assessment. Patients' QOL generally deteriorates after progression. Because post-progression QOL is not captured long term in this analysis, the analysis is potentially biased against the niraparib group. Since patients in the placebo group progressed earlier, a difference in QOL in favour of niraparib might have been observed had all patients been followed up for PRO data collection after progression.

To limit patient burden, the study did not use the full FACT-O questionnaire. Also, the questionnaires were not specifically designed for PARP inhibitors. The EQ-5D-5L was included in the study to facilitate conduct of economic analyses. EQ-5D-5L might not be sensitive to change in QOL in this population, hence the similar outcomes between groups in this measure might be a consequence of inadequate sensitivity. None of the questionnaires included assessed anxiety, depression, or other mental health issues in detail. This analysis did not examine integrated measures of duration and QOL such as time without symptoms and toxicity or quality-adjusted progression-free survival. Although these analyses were beyond the scope of this report, these measures are potentially of interest and we plan to assess these as part of future research.

Contributors

UAM, SA, and MRM designed the study. AMO, UAM, SM, JS, JMdC, DB-R, SB, GS, JSB, BL, AVT, FH, IPV, VDH, BB, DP, JB, and MRM collected the data. AMO, UAM, SM, SH, JS, JMdC, DB-R, SB, GS, JSB, BL, AVT, FH, IPV, VDH, BB, DP, JB, SA, and MRM interpreted the data. SH compiled the data and did statistical analysis. AMO, SH, and MRM prepared the manuscript with input from all authors. UAM, SA, and MRM are members of the trial management group.

Declaration of interests

SA was an employee and stockholder of TESARO at the time the work was completed. SB reports serving on advisory boards for TESARO., Clovis Oncology, and AstraZeneca. BB reports personal fees from AstraZeneca and Insys Therapeutics, and other support from TESARO.

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