Niraparib plus bevacizumab versus niraparib alone for platinum-sensitive recurrent ovarian cancer (NSGO-AVANOVA2/ENGOT-ov24): a randomised, phase 2, superiority trial

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Summary

Background Platinum-based chemotherapy is the foundation of treatment for platinum-sensitive recurrent ovarian cancer, but has substantial toxicity. Bevacizumab and maintenance poly(ADP-ribose) polymerase (PARP) inhibitors both significantly improve efficacy versus standard therapy, primarily in terms of progression-free survival, and offer the potential for chemotherapy-free treatment. AVANOVA2 compared niraparib and bevacizumab versus niraparib alone as definitive treatment for platinum-sensitive recurrent ovarian cancer.

Methods This open-label, randomised, phase 2, superiority trial in 15 university hospitals in Denmark, Sweden, Finland, Norway, and the USA enrolled women aged 18 years or older with measurable or evaluable high-grade serous or endometrioid platinum-sensitive recurrent ovarian cancer. Patients had to have an Eastern Cooperative Oncology Group performance status of 0–2, and had to have previously received platinum-containing therapy for primary disease but ≤1 prior non-platinum-containing regimen for recurrent disease. Previous treatment with bevacizumab or first-line maintenance PARP inhibitors was permitted. Eligible patients were randomly assigned 1:1 (by random permuted blocks with block sizes of two and four, no masking), stratified by homologous recombination deficiency status and chemotherapy-free interval, to receive once-daily oral niraparib 300 mg alone or with intravenous bevacizumab 15 mg/kg once every 3 weeks until disease progression. The primary endpoint was progression-free survival, assessed by the investigators in the intention-to-treat population after events in at least 62 patients. Safety was analysed in all patients who received at least one dose of study drug. This ongoing trial is registered with ClinicalTrials.gov, number NCT02354131.

Findings Between May 23, 2016, and March 6, 2017, 97 patients were enrolled and randomly assigned: 48 to niraparib plus bevacizumab and 49 to single-agent niraparib. Median follow-up was 16·9 months (IQR 15·4–20·9). Niraparib plus bevacizumab significantly improved progression-free survival compared with niraparib alone (median progression-free survival 11·9 months [95% CI 8·5–16·7] *vs* 5·5 months [3·8–6·3], respectively; adjusted hazard ratio [HR] 0·35 [95% CI 0·21–0·57], p<0·0001). Grade 3 or worse adverse events occurred in 31 (65%) of 48 patients who received niraparib plus bevacizumab and 22 (45%) of 49 who received single-agent niraparib. The most common grade 3 or worse adverse events in both groups were anaemia (7 [15%] of 48 *vs* 9 [18%] of 49) and thrombocytopenia (5 [10%] *vs* 6 [12%]), and hypertension in the combination group (10 [21%] *vs* 0). Niraparib plus bevacizumab was associated with increased incidences of any-grade proteinuria (10 [21%] of 48 patients *vs* 0) and hypertension (27 [56%] of 48 *vs* 11 [22%] of 49) compared with niraparib alone. No treatment-related deaths occurred.

Interpretation The efficacy observed with this chemotherapy-free combination of approved agents in women with platinum-sensitive recurrent ovarian cancer warrants further evaluation. A randomised phase 3 trial investigating niraparib plus bevacizumab versus chemotherapy plus bevacizumab in platinum-sensitive recurrent ovarian cancer is planned.

Funding Nordic Society of Gynaecological Oncology and Tesaro.

Introduction

Ovarian cancer is the ninth most common cancer in women—approximately 185 000 women died from the disease worldwide in 2018.[1] At initial diagnosis, ovarian cancer typically responds to platinum-based therapy. However, cure remains elusive and disease recurs in approximately 70% of patients.[2] At progression, most patients receive further chemotherapy, which is associated with toxicity. The type of chemotherapy administered usually depends on the timing of

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Research in context

Evidence before this study

The AVANOVA2 trial was designed to evaluate the combination of niraparib and bevacizumab administered using the schedule identified in the part 1 dose-escalation phase of the AVANOVA trial. At the time the trial was initially designed, results from the NOVA phase 3 trial evaluating niraparib as maintenance treatment were not available. Results from a randomised, phase 2 trial showed that combining the investigational anti-angiogenic agent cediranib with the PARP inhibitor olaparib significantly improved progression-free survival versus olaparib alone, especially in patients whose tumours did not harbour a germline *BRCA* mutation. A search of PubMed using the search terms "angiogenic", "PARP", and "ovarian" with no restriction on dates did not reveal any other trials evaluating the combination of an anti-angiogenic agent and a PARP inhibitor in ovarian cancer.

Added value of this study

The AVANOVA2 trial showed a significant improvement in progression-free survival with the combination of niraparib plus bevacizumab compared with niraparib alone, which was observed irrespective of homologous recombination deficiency status or chemotherapy-free interval. Both agents in the combination regimen are approved and well established treatments for ovarian cancer and the regimen was not hampered by the high incidences of diarrhoea previously observed with the investigational agent cediranib.

Implications of all the available evidence

Chemotherapy-free regimens are attractive to patients, avoiding the substantial toxicity of platinum-based regimens, and might enable prolongation of the chemotherapy-free interval. The combination regimen identified in AVANOVA2 will be compared with chemotherapy and bevacizumab in a randomised, phase 3 trial.

recurrence. If disease recurs 6 months or longer after completion of platinum-containing therapy, further platinum-based therapy (with or without bevacizumab) is widely used at first or second relapse. Cumulative myelosuppression, neurotoxicity, and allergy to platinum-based therapy can be limiting factors in patients receiving multiple lines of treatment.[3–5] In three randomised, phase 3 trials, maintenance therapy with a poly(ADP-ribose) polymerase (PARP) inhibitor (niraparib, olaparib, or rucaparib) significantly improved progression-free survival versus placebo after platinum-based chemotherapy for platinum-sensitive recurrent ovarian cancer.[6–8] Previous trials of bevacizumab have shown minimal toxicity during the maintenance phase of treatment, with most toxicities appearing during the concomitant chemotherapy phase.[9,10]

For patients with *BRCA*-mutated ovarian cancer and multiple disease relapses, single-agent PARP inhibitors show antitumour activity[11,12] and are considered appealing to patients, providing a chemotherapy-free treatment option. When the present trial was designed, phase 1 data were available showing the activity of niraparib in the treatment (*vs* maintenance) setting for ovarian cancer, irrespective of *BRCA* status.[13] The subsequent single-arm QUADRA study[14] in more than 400 patients showed the activity of single-agent niraparib in pretreated disease, irrespective of *BRCA* mutation or homologous recombination deficiency (HRD) status. Indirect evidence further supporting the treatment strategy emerged from analyses of the phase 3 maintenance trials showing complete responses in patients with measurable disease treated with maintenance PARP inhibitors.[8,15,16] The proven efficacy of anti-angiogenic agents[17–19] and PARP inhibitors offers the opportunity to develop chemotherapy-free combination regimens that avoid the need for repeated platinum-based therapies. Moreover, combining these two approaches could improve clinical outcomes: hypoxia induced by anti-angiogenic therapies might increase DNA damage and genetic instability,[20] resulting in defective homologous recombination that could enhance sensitivity to PARP inhibitors.[21] In a randomised, phase 2 trial in platinum-sensitive recurrent ovarian cancer, combination therapy with a vascular endothelial growth factor (VEGF) receptor tyrosine kinase inhibitor (cediranib, an unapproved investigational agent) and a PARP inhibitor (olaparib) significantly improved progression-free survival versus olaparib alone (median progression-free survival 16·5 months with the combination *vs* 8·2 months with olaparib alone; hazard ratio [HR] 0·50 (95% CI 0.30–0.83; p=0.006).[22,23] The progression-free survival benefit with the combination was driven by the treatment effect in patients with wild-type or unknown *BRCA* status, translating into an overall survival benefit in this subgroup (median overall survival 37·8 months with the combination *vs* 23·0 months with olaparib alone; HR 0.44 (95% CI 0.19–1.01, nominal p=0.047). However, cediranib-associated diarrhoea was problematic in the combination group, with 10 (23%) of 44 patients having grade 3 or 4 diarrhoea; 77% of the combination group required dose reductions.[22] Furthermore, cediranib is not commercially available as treatment for ovarian cancer.

In the AVANOVA trial, we combined two agents that are approved for the treatment of recurrent ovarian cancer: the PARP inhibitor niraparib, which has shown efficacy in ovarian cancer irrespective of *BRCA* and HRD status, and the anti-VEGF monoclonal antibody bevacizumab, which has shown efficacy and good tolerability, leading to regulatory approval across treatment settings in ovarian cancer.[9,17,18,24,25] AVANOVA part 1 (dose-escalation phase

in 12 patients) identified a regimen of intravenous bevacizumab 15 mg/kg once every 3 weeks with once-daily niraparib 300 mg as capsules for phase 2 evaluation in AVANOVA2.[26] This chemotherapy-free regimen showed good tolerability and encouraging activity in platinum-sensitive recurrent ovarian cancer. Here, we report results from the randomised, phase 2 AVANOVA2 trial designed to determine whether the combination of niraparib with bevacizumab improved progression-free survival compared with niraparib alone.

Methods

Study design and participants

NSGO-AVANOVA2/ENGOT-ov24 was an open-label, randomised, multicentre, phase 2, superiority trial evaluating the efficacy of single-agent niraparib versus niraparib plus bevacizumab combination therapy in platinum-sensitive recurrent ovarian cancer. AVANOVA2 was initially designed as a three-group trial comparing single-agent bevacizumab followed at progression by single-agent niraparib versus single-agent niraparib versus niraparib plus bevacizumab combination therapy. For bevacizumab funding and feasibility reasons, recruitment to group A was discontinued at the time of the second protocol amendment (Nov 11, 2015). The six patients randomly assigned to group A (single-agent bevacizumab followed at progression by single-agent niraparib) before this amendment are described separately (appendix p 4).

Patients were enrolled from 15 university hospitals in Denmark, Finland, Sweden, Norway, and the USA. Eligible patients had platinum-sensitive recurrent ovarian cancer with high-grade serous or endometrioid histology that was measurable or evaluable according to Response Evaluation Criteria in Solid Tumors (RECIST; version 1.1). All patients had to have received platinum-containing therapy for primary disease, with recurrence more than 6 months after the last platinum-based chemotherapy. No limit was applied regarding the number of previous treatment lines, although patients with more than one non-platinum-based regimen for recurrent disease were ineligible. Previous bevacizumab was permitted unless disease had progressed during or within 3 months of bevacizumab, if given as the last regimen before study entry (assigning patients to bevacizumab alone was not considered reasonable in the original three-group trial design if disease had progressed within 3 months of previous bevacizumab); previous treatment with other anti-angiogenic agents (any setting) or PARP inhibitors (for recurrent disease) was prohibited. Patients had to be aged 18 years or older with a life expectancy of at least 12 weeks, an Eastern Cooperative Oncology Group (ECOG) performance status of 2 or less, and adequate organ function (defined as absolute neutrophil count $\geq 1{\cdot}5 \times 10^9$/L, platelet count $>100 \times 10^9$/L, haemoglobin ≥9 g/dL, serum creatinine ≤1·5 upper limit of normal [ULN] or calculated creatinine clearance ≥50 mL/min using Cockcroft–Gault formula, total bilirubin ≤1·5×ULN, aspartate aminotransferase and alanine aminotransferase ≤2·5×ULN [or ≤5×ULN in patients with liver metastases]). Women of childbearing potential were required to use adequate birth control for the duration of the study. Patients were excluded if they had ovarian sarcomas, small-cell carcinoma with neuroendocrine differentiation, or non-epithelial cancer types not mentioned in the inclusion criteria; were receiving concurrent anticancer therapy; had incompletely healed wounds from major injury or surgery within 21 days preceding the start of study treatment; or planned surgery during the on-treatment study period. Patients with a history of disease-related bowel obstruction, abdominal fistula, gastrointestinal perforation, intra-abdominal abscess, major thrombo-embolic events, uncontrolled or symptomatic central nervous system metastasis or leptomeningeal carcinomatosis, or myelodysplastic syndrome were ineligible, as were patients with a contraindication to PARP inhibitors or VEGF-directed therapy, or those who had grade 3 (or worse) thrombocytopenia or anaemia with the last chemotherapy regimen. The full inclusion and exclusion criteria are in the protocol (appendix pp 19–21).

See Online for appendix

The trial protocol and all amendments were approved by the Research Ethics Committee and Competent Authority of the participating hospitals and countries. The trial was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. All patients provided written informed consent and consented to HRD testing (archival samples).

Randomisation and masking

Initially there were three stratification factors (*BRCA* mutational status, prior anti-angiogenic therapy, and number of previous lines of therapy). After enrolment of only 20 patients, the protocol was amended to a two-group design and consequently the stratification factors were amended to include only two stratification factors (because it was judged inappropriate to retain three stratification factors in a two-group trial of 100 patients): HRD status (positive *vs* negative, assessed by MyChoice HRD test, Myriad Genetics, Salt Lake City, UT, USA) and chemotherapy-free interval following previous therapy (6–12 months *vs* >12 months; appendix p 53). These stratification factors were considered de facto for all patients in the primary analysis. Patients with insufficient tumour tissue for HRD testing were randomised in the HRD-negative stratum as HRD unknown. Patients with known *BRCA*-positive status could be randomly assigned to a treatment group within the HRD-positive stratum before receiving their HRD result.

Patients enrolled by investigators were randomised in a 1:1 ratio using random permuted block randomisation (block sizes three and six in the original three-group design; block sizes two and four in the amended two-group design) implemented by Sealed Envelope Ltd

(London, UK).[27] No-one was masked to treatment assignment in this open-label trial and no independent review of tumour response was done in this proof-of-concept trial, which aimed only to identify the more active regimen for phase 3 evaluation.

Procedures

Patients received oral niraparib at a starting dose of 300 mg (given as three capsules once daily) on days 1–21, given either alone or combined with intravenous bevacizumab 15 mg/kg on day 1 every 3 weeks. This regimen was identified in the part 1 dose-escalation part of AVANOVA.[26] Both treatments were continued until disease progression, unacceptable toxicity, deterioration to ECOG performance status of 3 or higher, withdrawal of consent, or investigator decision. Niraparib treatment was interrupted for any non-haematological grade 3 or 4 toxicities considered by the investigator to be related to niraparib administration. If these toxicities resolved to grade 1 or below within 28 days, niraparib treatment could be resumed at a dose of 200 mg daily (first reduction) or 100 mg daily (second reduction). Niraparib treatment was discontinued permanently if toxicity requiring dose reduction had not resolved to grade 1 or below within 28 days or if a patient had already undergone two dose reductions. No dose reduction of bevacizumab was permitted. Bevacizumab treatment was temporarily interrupted in the event of grade 3 or 4 bevacizumab-related toxicity, grade 4 febrile neutropenia, or grade 4 thrombocytopenia irrespective of attribution, until resolved to grade 1 or below. At second occurrence of a grade 3 or 4 bevacizumab-related adverse event, bevacizumab was discontinued permanently. Further details of dose-modification schedules for adverse events are in the protocol (appendix pp 70–72). Treatment after progression was at the investigator's discretion; post-progression niraparib was not permitted in either group.

Tumours were assessed radiologically (preferably by CT scans; MRI or PET-CT were acceptable but x-ray was not acceptable) at baseline and every 9 weeks until disease progression or week 48. The method used at baseline was to be used for each post-baseline scan. Patients without progression by week 48 underwent a further scan at week 72; thereafter, tumour assessment was done only as clinically indicated in patients without progression. Investigators assessed overall response according to RECIST (version 1.1). Patient-reported outcomes were assessed using the European Organisation for Research and Treatment of Cancer (EORTC) quality of life questionnaire core (QLQ-C30) and ovarian cancer module (QLQ-OV28). Questionnaires were completed before treatment at baseline, every 9 weeks during treatment, at the end-of-study visit, and 3 and 6 months after the end of treatment. We report global health status/quality of life results from QLQ-C30; results from other subscales and QLQ-OV28 will be reported separately.

Adverse events were assessed at every cycle and at the end-of-study visit, and were graded using National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0). Laboratory testing (haematology, serum chemistry, and urine analysis) was done on day 1 of each cycle during treatment, then at the end-of-treatment visit 28 days after the last dose.

Patients were followed for survival and subsequent anticancer therapy every 12 weeks for 2 years after discontinuing treatment and every 6 months thereafter until disease progression or death, whichever occurred first.

Outcomes

The primary endpoint was investigator-assessed progression-free survival, defined as the interval between randomisation and disease progression or death, whichever occurred first. Prespecified secondary endpoints were: the proportion of patients with an objective response according to RECIST (version 1.1); the proportion of patients with disease control (complete response, partial response, or stable disease for ≥12 weeks); patient-reported outcomes; safety; and tolerability. Overall response according to Gynecological Cancer InterGroup criteria (in patients with non-measurable disease who were evaluable by CA-125, and in patients with measurable disease who were also evaluable by CA-125) was also a secondary endpoint, but will be reported separately.

Exploratory subgroup analyses of progression-free survival according to HRD status, *BRCA* mutational status, and chemotherapy-free interval were prespecified and are reported in this Article. Additional prespecified exploratory endpoints included time to first subsequent therapy, time to second progression or death, time to second subsequent therapy, and overall survival, which will be reported when mature.

Statistical analysis

The planned sample size was 94 enrolled patients, providing 80% power at a one-sided α of 0·1 to detect a median progression-free survival increase from 8 months with niraparib alone to 14 months with niraparib and bevacizumab combination therapy (which was considered when designing the trial as the minimum clinically meaningful benefit to justify use of the combination), corresponding to an HR of 0·57, after events had occurred in 62 patients. The sample size calculation assumed an 18-month recruitment period, 10% dropout, and 12 months' follow-up. No interim analyses were planned.

All analyses were done in the intention-to-treat population, comprising all randomly assigned patients. Safety was assessed in all patients who received at least one dose of study medication. All analyses were done using STATA 15.0. Time to event endpoints were estimated using Kaplan-Meier methods, presenting

median values with corresponding two-sided 95% CIs. HRs and corresponding 95% CIs were estimated using a Cox model including the stratification factors as covariates. Treatment groups were compared for time to event endpoints using a stratified log-rank test adjusted according to randomisation stratification factors. The proportions of patients achieving an objective response and disease control were compared between treatment groups using the χ^2 test. The primary analysis of response was based on all randomly assigned patients; patients with no post-baseline tumour evaluation were considered as having disease progression as their best response. We also did a sensitivity analysis of objective response excluding patients who were unevaluable for response. Patient-reported outcome scores were calculated using EORTC scoring manuals and analysed using a mixed-effects linear model including interaction with time and subject as random effects. Adverse events were analysed descriptively.

An independent data monitoring committee oversaw the study. This trial is registered with ClinicalTrials.gov, number NCT02354131.

Role of the funding source

The Nordic Society of Gynaecological Oncology (NSGO) designed the study. Data were collected by investigators and analysed by an NSGO statistician (RdPC). Tesaro had no role in study design, data collection, or data interpretation, but representatives from the company were given the opportunity to review the manuscript before submission. MRM and RdPC had access to the raw data. The project manager (not an author) also had access to the raw data, as did the independent data monitoring committee members on request to RdPC. All authors participated in critical review and revision of the manuscript and approved the final version for submission. The corresponding author had full access to all of the data and had final responsibility for the decision to submit for publication.

Results

Between May 23, 2016, and March 6, 2017, 103 patients were enrolled. 97 patients were randomised to the two study groups. 49 patients were assigned to single-agent niraparib and 48 to niraparib plus bevacizumab combination therapy (figure 1). Because all randomly assigned patients received at least one dose of study medication, the intention-to-treat and safety populations were identical and analyses of efficacy and safety were completed in the intention-to-treat population of 97 patients. Six of 20 patients who were randomly assigned before the second approved protocol amendment received bevacizumab alone and were excluded from analyses (appendix p 4). The remaining 14 patients who underwent randomisation before the protocol amendment were randomly assigned to niraparib (n=7) or niraparib plus bevacizumab (n=7) and were analysed within the intention-to-treat population according to the final two-group trial design.

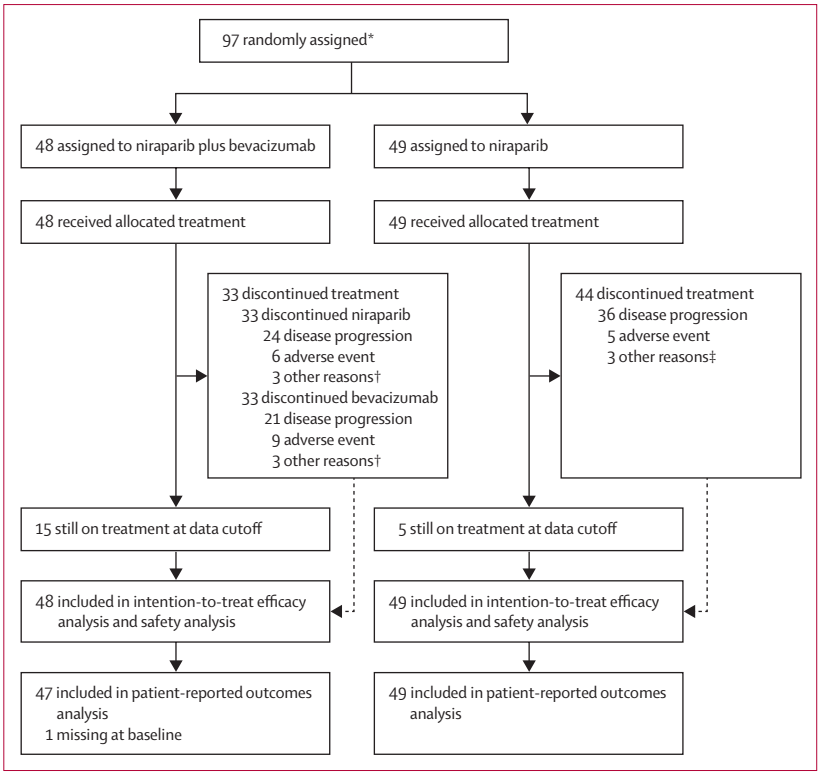


Figure 1: **Trial profile**
*103 patients were initially enrolled and the 6 patients assigned to bevacizumab alone (of those randomly assigned to interventions in the 3-arm trial) were then excluded following trial amedment. †Performance status deteriorated (n=1), withdrew consent (n=1), other reason (unknown; n=1). ‡Investigator decision (n=2), serious compliance issues (n=1).

Baseline characteristics were generally well balanced between treatment groups. Chemotherapy-free interval was a stratification factor in the final design, but not when the first 14 patients were enrolled and randomly assigned, resulting in a slight imbalance in this factor between treatment groups. A slight imbalance in the distribution of patients with *BRCA*-mutated disease was also noted, as the stratification factor changed from *BRCA* mutation status to HRD status when the design was altered to a two-arm trial. Notably, 10 (21%) of 48 patients in the combination group and 13 (27%) of 49 patients in the niraparib-alone group had previously received bevacizumab (table 1).

At data cutoff (Dec 1, 2018), median follow-up was 16·9 months (IQR 15·4–20·9). 74 (76%) of 97 patients had progression-free survival events (31 [65%] of 48 in the combination group *vs* 43 [88%] of 49 in the niraparib group). Progression-free survival was significantly improved with the combination therapy compared with niraparib alone: median progression-free survival was 11·9 months (95% CI 8·5–16·7) in the niraparib plus bevacizumab group versus 5·5 months (3·8–6·3) with niraparib alone (HR adjusted for stratification factors

	Niraparib plus bevacizumab group (n=48)	Niraparib group (n=49)
Age, years	67 (59–70)	66 (58–70)
Primary tumour site		
Ovary	38 (79%)	33 (67%)
Fallopian tube	5 (10%)	9 (18%)
Peritoneum	5 (10%)	7 (14%)
FIGO stage at diagnosis		
I or II	3 (6%)	5 (10%)
IIIA or IIIB	2 (4%)	2 (4%)
IIIC	29 (60%)	26 (53%)
IV	14 (29%)	15 (31%)
Unknown	0	1 (2%)
Chemotherapy-free interval		
6–12 months	20 (42%)	17 (35%)
>12 months	28 (58%)	32 (65%)
HRD status		
Positive*	28 (58%)	30 (61%)
Negative or unknown	20 (42%)	19 (39%)
BRCA mutation status		
BRCA mutated†	15 (31%)	18 (37%)
Germline	6 (13%)	9 (18%)
Somatic	14 (29%)	14 (29%)
Number of previous lines of therapy		
1	21 (44%)	27 (55%)
2	24 (50%)	19 (39%)
≥3	3 (6%)	3 (6%)
Previous bevacizumab	10 (21%)	13 (27%)
Previous non-ovarian cancer	5 (10%)	6 (12%)
Pre-existing diabetes	0	2 (4%)
Pre-existing hypertension	20 (42%)	17 (35%)
Platelet count, $\times 10^3/\mu L$	312 (126)	275 (79)
Weight, kg	78 (25)‡	71 (16)§

Data are median (IQR), n (%), or mean (SD). FIGO=International Federation of Gynecology and Obstetrics. HRD=homologous recombination deficiency. *Two patients in the niraparib group and one in the niraparib plus bevacizumab group had *BRCA*-mutated tumours but were considered as HRD negative or unknown for stratification in error. †Patients could have both somatic and germline *BRCA* mutations. ‡n=47. §n=48.

Table 1: **Baseline characteristics**

0·35 [95% CI 0·21–0·57], p<0·0001; figure 2A). In prespecified subgroup analyses, improved progression-free survival with combination therapy versus niraparib alone was observed irrespective of HRD status or chemotherapy-free interval (stratification factors; figure 2).

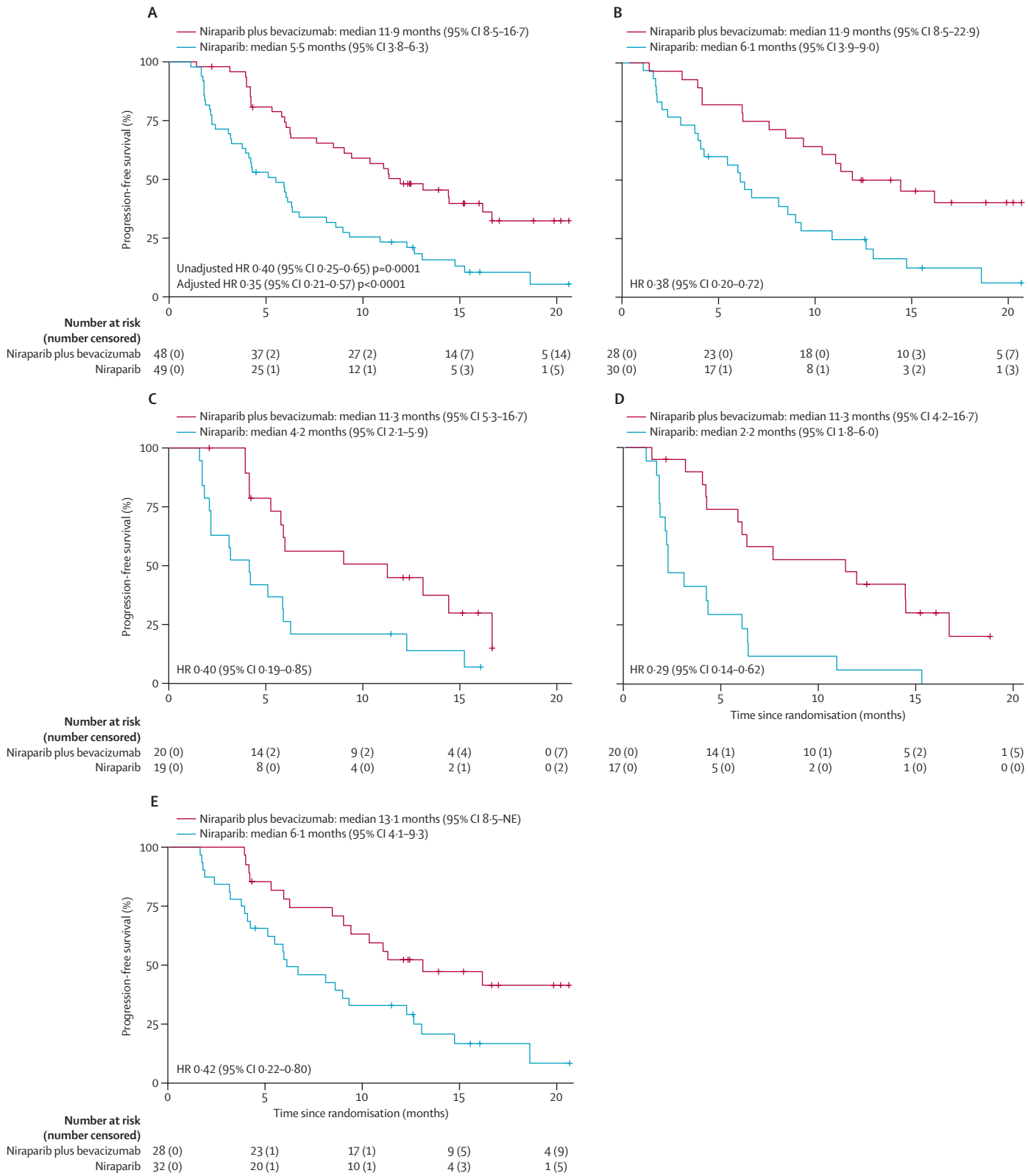
Progression-free survival was also improved with niraparib plus bevacizumab versus niraparib alone in the subgroup of 64 patient (33 with combination therapy, 31 with niraparib alone) without germline *BRCA* mutations (median progression-free survival 11·3 months [95% CI 5·9–16·7] with the combination *vs* 4·2 months [2·2–5·9] with niraparib alone; HR 0·32 [95% CI 0·17–0·58]) and a positive trend for *BRCA*-mutated patients (median progression-free survival 14·4 months [95% CI 6·2–22·7] *vs* 9·0 months [3·9–13·0], respectively (HR 0·49 [95% CI 0·21–1·15]). Post-hoc exploratory subgroup analyses in 25 patients with non-*BRCA*-mutated HRD-positive tumours (13 with the combination, 12 with niraparib alone) showed a median progression-free survival of 11·9 months (95% CI 4·2–not estimable) with the combination vs 4·1 months (1·7–6·7) with niraparib alone (HR 0·19 [95% CI 0·06–0·59]).

In additional exploratory post-hoc subgroup analyses, progression-free survival was improved with niraparib plus bevacizumab versus niraparib alone in the bevacizumab-naive subgroup of patients (median 14·4 months [95% CI 9·4–22·7] with the combination *vs* 6·0 months [4·1–9·0]) with niraparib alone; HR 0·39 [95% CI 0·22–0·68]) but not in patients previously treated with bevacizumab (5·9 months [95% CI 1·4–11·3] *vs* 3·1 months [1·8–5·1], respectively; HR 0·51 [95% CI 0·21–1·26]).

At least one post-baseline tumour evaluation according to RECIST was reported for 91 (94%) of 97 patients. The remaining six patients discontinued treatment early before they could have any post-baseline tumour assessments (one patient in the combination group [who withdrew consent] and five in the niraparib-alone group [three for disease progression and two for adverse events]). In the intention-to-treat population, the proportion of patients achieving a confirmed objective response was higher with combination therapy (29 of 48 [60%; 95% CI 45–74]) than with niraparib alone (13 of 49 [27%; 15–41]; odds ratio [OR] 4·23 [95% CI 1·79–9·97], p=0·001). The sensitivity analysis excluding the six patients unevaluable for response showed objective responses in 29 (62%) of 47 patients (95% CI 46–75) with combination therapy and in 13 (30%) of 44 patients (17–45) with niraparib alone (OR 3·84 [95% CI 1·60–9·21]; p=0·003). The proportion of patients achieving a confirmed complete response also favoured combination therapy versus niraparib alone (7 [15%] of 48 *vs* 5 [10%] of 49). The proportion of patients with disease control was 79% (38 of 48 patients) with combination therapy compared with 53% (26 of 49 patients) with niraparib alone (OR 3·36 [95% CI 1·37–8·22]; p=0·008). Only three (6%) of 48 patients in the combination group had disease progression as their best response compared with 15 (31%) of 49 in the niraparib-alone group.

At data cutoff, overall survival data were immature. 21 (22%) of 97 patients had died: eight (17%) of 48 in the

Figure 2: **Progression-free survival**
Kaplan-Meier survival plots of progression-free survival for the (A) intention-to-treat, (B) HRD-positive, (C) HRD-negative, (D) chemotherapy-free interval 6–12 months and (E) chemotherapy-free interval longer than 12 months populations. HR=hazard ratio. HRD=homologous recombination deficiency. NE=not estimable.


A
Niraparib plus bevacizumab: median 11·9 months (95% CI 8·5–16·7)
Niraparib: median 5·5 months (95% CI 3·8–6·3)
Progression-free survival (%)
Unadjusted HR 0·40 (95% CI 0·25–0·65) p=0·0001
Adjusted HR 0·35 (95% CI 0·21–0·57) p<0·0001
B
Niraparib plus bevacizumab: median 11·9 months (95% CI 8·5–22·9)
Niraparib: median 6·1 months (95% CI 3·9–9·0)
HR 0·38 (95% CI 0·20–0·72)
Number at risk (number censored)
Niraparib plus bevacizumab 48 (0) 37 (2) 27 (2) 14 (7) 5 (14) 28 (0) 23 (0) 18 (0) 10 (3) 5 (7)
Niraparib 49 (0) 25 (1) 12 (1) 5 (3) 1 (5) 30 (0) 17 (1) 8 (1) 3 (2) 1 (3)
C
Niraparib plus bevacizumab: median 11·3 months (95% CI 5·3–16·7)
Niraparib: median 4·2 months (95% CI 2·1–5·9)
HR 0·40 (95% CI 0·19–0·85)
D
Niraparib plus bevacizumab: median 11·3 months (95% CI 4·2–16·7)
Niraparib: median 2·2 months (95% CI 1·8–6·0)
HR 0·29 (95% CI 0·14–0·62)
Time since randomisation (months)
Number at risk (number censored)
Niraparib plus bevacizumab 20 (0) 14 (2) 9 (2) 4 (4) 0 (7) 20 (0) 14 (1) 10 (1) 5 (2) 1 (5)
Niraparib 19 (0) 8 (0) 4 (0) 2 (1) 0 (2) 17 (0) 5 (0) 2 (0) 1 (0) 0 (0)
E
Niraparib plus bevacizumab: median 13·1 months (95% CI 8·5–NE)
Niraparib: median 6·1 months (95% CI 4·1–9·3)
Progression-free survival (%)
HR 0·42 (95% CI 0·22–0·80)
Time since randomisation (months)
Number at risk (number censored)
Niraparib plus bevacizumab 28 (0) 23 (1) 17 (1) 9 (5) 4 (9)
Niraparib 32 (0) 20 (1) 10 (1) 4 (3) 1 (5)

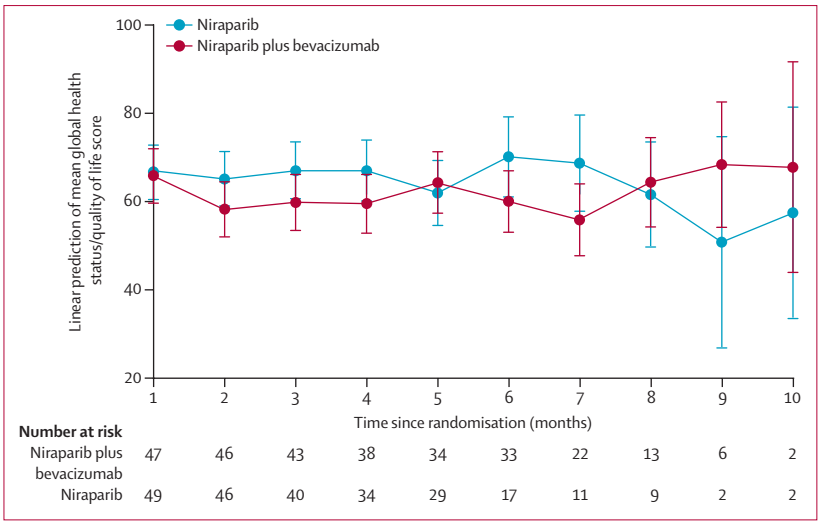


Figure 3: **Patient-reported outcomes**
Data are linear prediction of mean (SD). European Organisation for Research and Treatment of Cancer quality of life questionnaire, core module global health status/quality of life subscale over time.

combination group and 13 (27%) of 49 in the niraparib-alone group). Kaplan-Meier estimates of the proportion of patients alive at 18 months were 80% (95% CI 62–91) with combination therapy versus 70% (48–84) with niraparib alone. Analyses of time-related endpoints beyond first progression (time to first subsequent therapy, time to second subsequent therapy, time to second progression or death, and overall survival) will be reported separately when further data have been collected after longer follow-up.

EORTC QLQ-C30 global health status/quality of life was evaluable at baseline in all but one patient (in the combination group; figure 1). Mean baseline global health status/quality of life scores were similar in the two groups (65·6 [SD 23·7] in the combination group *vs* 66·7 [22·4] in the niraparib group). No significant differences in the scores between treatment groups were observed at any of the timepoints assessed, and no clinically relevant changes in global health status/quality of life occurred over time (figure 3).

The proportion of patients requiring niraparib dose reduction from 300 mg to 200 mg was similar in the two treatment groups (25 [52%] of 48 patients in the combination group *vs* 28 [57%] of 49 in the niraparib-alone group). One patient (2%) in each group required a further dose reduction to 100 mg. Niraparib treatment was interrupted in 26 (54%) of 48 patients in the combination group compared with 30 (61%) of 49 in the niraparib group. During the trial, 33 patients in the niraparib and bevacizumab group and 44 in the niraparib group discontinued treatment. Drug-related adverse events led to discontinuation of bevacizumab in nine (19%) of 48 patients and discontinuation of niraparib in six (13%) of 48 patients in the combination group, and to discontinuation of niraparib in five (10%) of 49 in the niraparib-alone group. At data cutoff, treatment was ongoing in 15 (31%) of 48 patients in the combination group and 5 (10%) of 49 in the niraparib-alone group.

The most common all-grade adverse events in both groups were anaemia, fatigue, and gastrointestinal effects (and hypertension with niraparib and bevacizumab combination therapy; table 2, appendix p 5). Compared with niraparib alone, niraparib plus bevacizumab was associated with increased incidences of proteinuria (10 [21%] of 48 patients *vs* 0) and hypertension (27 [56%] of 48 *vs* 11 [22%] of 49). The most common grade 3 or worse adverse events in both groups were anaemia and thrombocytopenia (and hypertension with niraparib and bevacizumab). More grade 3 or worse adverse events were observed with combination therapy than single-agent niraparib (31 [65%] of 48 *vs* 22 [45%] of 49), largely driven by more frequent grade 3 or worse hypertension. One patient had a fatal adverse event; this was a pulmonary embolism in the niraparib-alone group, and was considered unrelated to treatment.

Discussion

AVANOVA2 showed a clinically and statistically significant improvement of progression-free survival with the combination of niraparib plus bevacizumab as a chemotherapy-free treatment for patients with platinum-sensitive recurrent ovarian cancer, meeting the trial's primary objective. Subgroup analyses suggests that progression-free survival was improved with the combination versus niraparib monotherapy irrespective of HRD status and chemotherapy-free interval.

The current standard of care for platinum-sensitive recurrent ovarian cancer is platinum-based chemotherapy (with or without bevacizumab) or maintenance PARP inhibitor treatment in patients responding to chemotherapy. Phase 3 trials in unselected populations (OCEANS,[17] GOG-0213,[18] and CALYPSO[28]); pre-dating maintenance PARP inhibitor strategies) typically show a median progression-free survival of 8–11 months with carboplatin-based regimens, increasing to 12–14 months with the addition of bevacizumab.[17,18,29] The median progression-free survival of 11·9 months [95% CI 8·5–16·7] in AVANOVA2 suggests that a chemotherapy-free niraparib plus bevacizumab combination regimen could be a potential alternative in this setting if validated in a phase 3 trial, especially when considering the fact that AVANOVA2 was not restricted to patients at first recurrence, unlike many other trials in platinum-sensitive recurrent ovarian cancer. Comparison with phase 3 trials of PARP inhibitors is virtually impossible because maintenance PARP inhibitors were evaluated in patients with complete or partial response to previous platinum-containing therapy and progression-free survival was measured from the time of randomisation to maintenance therapy.[6–8] Consequently, the prognosis and patient populations differ substantially between trials of maintenance

	Niraparib plus bevacizumab group (n=48)				Niraparib group (n=49)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Nausea	30 (63%)	0	0	0	24 (49%)	1 (2%)	0	0
Hypertension	17 (35%)	10 (21%)	0	0	11 (22%)	0	0	0
Fatigue	19 (40%)	3 (6%)	0	0	19 (39%)	1 (2%)	0	0
Anaemia	14 (29%)	6 (13%)	1 (2%)	0	12 (24%)	7 (14%)	2 (4%)	0
Constipation	18 (38%)	1 (2%)	0	0	19 (39%)	0	0	0
Vomiting	15 (31%)	1 (2%)	0	0	8 (16%)	0	0	0
Anorexia	12 (25%)	1 (2%)	0	0	5 (10%)	1 (2%)	0	0
Thrombocytopenia	7 (15%)	1 (2%)	4 (8%)	0	7 (14%)	4 (8%)	2 (4%)	0
Proteinuria	9 (19%)	1 (2%)	0	0	0	0	0	0
Headache	8 (17%)	1 (2%)	0	0	5 (10%)	0	0	0
Pulmonary embolism	0	0	0	0	0	0	0	1 (2%)
Peripheral sensory neuropathy	9 (19%)	0	0	0	6 (12%)	0	0	0
Dyspnoea	6 (13%)	2 (4%)	0	0	6 (12%)	2 (4%)	0	0
Cough	8 (17%)	0	0	0	4 (8%)	0	0	0
Diarrhoea	7 (15%)	0	0	0	7 (14%)	0	0	0
Urinary tract infection	5 (10%)	1 (2%)	0	0	3 (6%)	1 (2%)	0	0
Insomnia	5 (10%)	1 (2%)	0	0	6 (12%)	0	0	0
Abdominal pain	2 (4%)	3 (6%)	0	0	5 (10%)	2 (4%)	0	0
Neutropenia	1 (2%)	3 (6%)	1 (2%)	0	3 (6%)	1 (2%)	0	0
Myalgia	5 (10%)	0	0	0	1 (2%)	0	0	0
Pain in extremity	5 (10%)	0	0	0	5 (10%)	0	0	0
Hypomagnesaemia	1 (2%)	1 (2%)	0	0	2 (4%)	0	0	0
Alopecia	3 (6%)	0	0	NA	5 (10%)	0	0	NA
Mucosal inflammation	3 (6%)	0	0	0	2 (4%)	1 (2%)	0	0
Deep vein thrombosis	0	2 (4%)	0	0	0	0	0	0
Respiratory tract infection	1 (2%)	1 (2%)	0	0	0	0	0	0
Skin pain	1 (2%)	1 (2%)	0	0	0	0	0	0
Gastrointestinal disorder	1 (2%)	1 (2%)	0	0	1 (2%)	0	0	0
Pneumonia	1 (2%)	1 (2%)	0	0	1 (2%)	0	0	0
Febrile neutropenia	0	1 (2%)	0	0	0	1 (2%)	0	0
Hyponatraemia	0	1 (2%)	0	0	0	0	0	0
Ileus	0	1 (2%)	0	0	1 (2%)	0	0	0
Intestinal obstruction	0	1 (2%)	0	0	0	0	0	0
Syncope	0	1 (2%)	0	0	1 (2%)	0	0	0
Ascites	1 (2%)	0	0	0	3 (6%)	1 (2%)	0	0
Pleural effusion	1 (2%)	0	0	0	1 (2%)	1 (2%)	0	0
Dehydration	0	0	0	0	1 (2%)	1 (2%)	0	0

Data are n (%). The table lists grade 1–2 adverse events occurring in 10% or more of patients in either group, and all grade 3, 4, and 5 events. NA=not applicable.

Table 2: **Adverse events**

PARP inhibitor versus definitive therapy. However, an integrated analysis of patients receiving third-line or later-line rucaparib treatment for platinum-sensitive recurrent ovarian cancer showed a median progression-free survival of 11·1 months (95% CI 7·3–12·8).[12] The median progression-free survival with single-agent niraparib is somewhat disappointing in this trial compared with available data for other regimens. However, the aim of this proof-of-concept trial was to determine whether a combination chemotherapy-free regimen would be more active than niraparib alone, and this result was clearly shown. The next logical step is to compare the chemotherapy-free doublet versus a standard (chemotherapy plus bevacizumab) control group.

Subgroup analyses within AVANOVA2 are limited by the small sample sizes. Nevertheless, progression-free

survival improvement was seen across most prespecified subgroups. Similar to the previously mentioned olaparib and cediranib trial, in which the benefit with combination therapy was driven by the non-*BRCA*-mutated population,[22,23] niraparib plus bevacizumab resulted in a more pronounced effect in non-*BRCA*-mutated platinum-sensitive recurrent ovarian cancer. However, when broadening to HRD status (a stratification factor), we recorded a significant progression-free survival benefit from niraparib plus bevacizumab versus niraparib alone irrespective of HRD status ($p<0·05$ for both HRD-negative and HRD-positive subgroups). The lesser effect on progression-free survival of the combination treatment in 23 bevacizumab-pretreated patients should be considered in the context of contradictory findings in a subset of the GOG-0213 trial[18] and the positive randomised, phase 3 MITO16b trial in 405 patients specifically designed to evaluate bevacizumab re-treatment.[30]

Combining niraparib with bevacizumab in AVANOVA2 was associated with an increased incidence of proteinuria and almost doubling of the incidence of all-grade hypertension, consistent with the known safety profile of bevacizumab. Modest increases in haematological and gastrointestinal effects were also observed. In both treatment groups, more than half of the patients reported low-grade nausea. Analyses of the NOVA trial[31] have shown that early nausea can be managed effectively with niraparib dose reduction, without compromising efficacy. The overall tolerability of the combination regimen in AVANOVA is supported by the relatively low proportion of patients discontinuing treatment. In the combination group, nine (19%) of 48 patients discontinued bevacizumab because of adverse events, but only six (13%) discontinued both treatments because of toxicity. This compares with treatment discontinuation in 23–25% of patients in the OCEANS[17] and GOG-0213[18] trials of chemotherapy plus bevacizumab. The chemotherapy-free regimen avoided the substantial cumulative toxicities associated with chemotherapy, and analyses of patient-reported outcomes revealed no relevant effect of treatment on global health status/quality of life.

Weaknesses of the trial design include the relatively small sample size, which limits conclusions from subgroups, the open-label design, and the absence of blinded independent review of progression-free survival and response, which could lead to observer bias. Additionally, the proportion of patients with niraparib dose reduction was relatively high, suggesting that a lower starting dose might have been appropriate in some patients. Since the trial was initiated, further data have indicated that a lower niraparib starting dose might be appropriate depending on patient weight and baseline platelet count.[32] This information was not available at the time the AVANOVA2 dose was selected, guided by results from the part 1 dose-escalation phase.[26] We recognise that the change of stratification factor from *BRCA* mutation status to HRD status when the design was changed to a two-group trial resulted in a slight imbalance in the distribution of patients with *BRCA*-mutated disease between the treatment groups. Retention of *BRCA* mutation status as a sub-stratification factor along with HRD status would have required a cohort design similar to NOVA, which was deemed impractical in this relatively small trial. Reassuringly, exploratory subgroup analyses suggested that the effect in the HRD-positive subgroup was maintained when we excluded the *BRCA*-mutated population, suggesting that the slight imbalance between treatment groups in the distribution of *BRCA* mutation does not affect the conclusions.

Another limitation of the trial is the absence of a standard (chemotherapy-based) control group. However, our intention was to determine in a smaller randomised trial whether a chemotherapy-free combination regimen might represent a more active alternative to single-agent niraparib for phase 3 evaluation. The doublet was more effective than single-agent niraparib, offering a well-tolerated chemotherapy-free regimen for platinum-sensitive recurrent ovarian cancer. On the basis of these results, we are planning a randomised phase 3 trial comparing standard-of-care doublet chemotherapy plus bevacizumab versus niraparib plus bevacizumab versus niraparib plus bevacizumab plus TSR042 in recurrent ovarian cancer (NCT03806049), using a niraparib starting dose of 200 mg. The strategy is also being evaluated in the NRG GY004 trial (NCT02446600) comparing olaparib versus olaparib plus cediranib versus standard-of-care chemotherapy, which has completed accrual.

Contributors

MRM wrote the protocol and amendments, recruited patients, was responsible for study oversight, and wrote the first draft of the manuscript with support from a medical writer. RdPC was responsible for the statistical analysis plan and study oversight and did all statistical analyses. JUM, EAL, LB, and MJB reviewed the protocol, shared responsibility for study oversight, and recruited patients. G-BN, SM, MA, TLW, BL, GL, SH, UP, MD, HR, AØK, SS, AKV, and JUM recruited patients. All authors critically reviewed and approved the manuscript.

Declaration of interests

MRM reports grants and personal fees from Tesaro during the conduct of the study; grants and personal fees from AstraZeneca, Pfizer, and Clovis Oncology; personal fees from Biocad, Geneos, Genmab, Oncology Venture, Merck, Karyopharm Therapeutics, Sera Prognostics, Seattle Genetics, Sotio, and ZaiLab; is a member of Board of Directors of Karyopharm Therapeutics and Sera Prognostics; and reports research grants from Boehringer Ingelheim outside of the submitted work. EAL reports personal fees from Tesaro, Clovis Oncology, Genmab, and Roche during the conduct of the study. MJB declares personal fees from Tesaro, Roche/Genentech, and Clovis outside of the submitted work. SM reports a grant for lectures from AstraZeneca and for an advisory board for Tesaro. GL reports travel funding from Roche for congress attendance. SS reports personal fees for advisory board membership from AstraZeneca and grants from AstraZeneca, Tesaro, and Roche outside of the submitted work. LB is a member of various ovarian cancer expert panels (Tesaro, Clovis Oncology, and AstraZeneca). JUM reports personal fees from AstraZeneca, Tesaro, Clovis, Roche, MSD, and OrionPharma outside of the submitted work. All other authors declare no completing interests.

Data sharing

No mechanism is yet in place to allow sharing of individual deidentified patient data. Requests sent to Mansoor Raza Mirza, Medical Director,

NSGO, Department of Oncology, Rigshospitalet, Copenhagen University Hospital, DK2100 Copenhagen, Denmark, or Mansoor.Raza.Mirza@regionh.dk will be considered on a case-by-case basis.

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