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ORIGINAL ARTICLE

A phase I study of the PARP inhibitor niraparib in combination with bevacizumab in platinum-sensitive epithelial ovarian cancer: NSGO AVANOVA1/ENGOT-OV24

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Abstract

Background Combining poly(ADP-ribose) polymerase (PARP) inhibitors with antiangiogenic agents appeared to enhance activity vs PARP inhibitors alone in a randomized phase II trial.

Materials and methods In AVANOVA (NCT02354131) part 1, patients with measurable/evaluable high-grade serous/endometrioid platinum-sensitive ovarian cancer received bevacizumab 15 mg/kg every 21 days with escalating doses of niraparib capsules (100, 200, or 300 mg daily) in a 3 + 3 dose-escalation design. Primary objectives were to evaluate safety and tolerability and to determine the recommended phase II dose (RP2D).

Results Three of 12 enrolled patients had germline *BRCA2* mutations. In cycle 1, nine patients experienced grade 3 toxicities: five with hypertension, three with anemia, and one with thrombocytopenia. There was one dose-limiting toxicity (grade 4 thrombocytopenia with niraparib 300 mg), thus the RP2D was bevacizumab 15 mg/kg with niraparib 300 mg. The response rate was 50%; disease was stabilized in a further 42%. Median progression-free survival was 11.6 (95% confidence interval 8.4–20.1) months. Niraparib pharmacokinetics were consistent with historical single-agent data. Overlapping exposure was observed across the dose ranges tested on days 1 and 21.

Conclusions There was one dose-limiting toxicity; other adverse events were typical PARP inhibitor and antiangiogenic class effects. Niraparib–bevacizumab showed promising activity; Part 2 (vs bevacizumab) was recently reported and phase III comparison with standard-of-care therapy is planned.

Keywords Niraparib · PARP inhibitor · Ovarian cancer · Bevacizumab · *BRCA*

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Introduction

In recent years, ovarian cancer treatment has been transformed, first by the introduction of antiangiogenic agents [1] and then by the incorporation into clinical practice of poly (ADP-ribose) polymerase (PARP) inhibitors [2]. PARP inhibitors have demonstrated single-agent activity as maintenance therapy in randomized phase III trials in both the platinum-sensitive recurrent setting (NOVA, SOLO-2, ARIEL3) [3–5] and the front-line maintenance setting (SOLO-1) [6].

Niraparib (Zejula®, Tesaro, Inc., Waltham, MA, USA), an orally available PARP inhibitor, is approved as maintenance therapy for patients with recurrent ovarian cancer responding to platinum-based chemotherapy. In the NOVA trial, niraparib significantly improved progression-free survival (PFS) in the germline *BRCA*-mutated population, the homologous recombination deficiency (HRD)-positive population, and the overall intent-to-treat population, although the magnitude of effect was greatest in the *BRCA*-mutated population. Phase III development in platinum-sensitive recurrent ovarian cancer has focused on the maintenance setting, treating patients in complete or partial response to platinum-containing therapy. Subgroup analyses suggested the same impact of treatment in both patients with partial response and those with complete response [5, 7, 8], providing a rationale for evaluating niraparib as treatment for bulky disease.

Bevacizumab (Avastin®, F Hoffmann-La Roche, Basel, Switzerland), combined with chemotherapy and continued as maintenance, is a standard of care in the front-line setting [9] and in relapsed ovarian cancer based on results of the OCEANS, GOG-0213, and AURELIA randomized phase III trials [10–12]. A randomized phase II trial showed that combining the antiangiogenic agent cediranib with a PARP inhibitor (olaparib) improved PFS vs PARP inhibition alone (hazard ratio 0.50; $P=0.007$; median PFS 16.5 vs 8.2 months, respectively) in platinum-sensitive recurrent ovarian cancer [13]. Interestingly, the effect was driven by the marked PFS (and overall survival [OS]) benefit in patients with unknown or wild-type *BRCA* status [13]. Such a combination is appealing in the recurrent setting, potentially sparing patients from the toxicity of conventional chemotherapy.

Materials and methods

Study design

AVANOVA (NCT02354131) is a phase I/II study evaluating the combination of niraparib and bevacizumab. Part 1, reported here, is a single-arm dose-escalation study with a classic 3 + 3 design. The primary objective was to determine the safety and tolerability of niraparib–bevacizumab combination therapy. Secondary objectives were to determine the recommended phase II dose and pharmacokinetics of the combination and to describe antitumor response. Pharmacodynamic evaluation was a pre-specified objective but the necessary samples could not be collected.

Ethics

Part 1 was conducted at a single site (Rigshospitalet, Copenhagen) according to the ethical principles of the Declaration of Helsinki, the International Conference on Harmonization Good Clinical Practice guidelines, and applicable local regulatory requirements. Before study initiation, the protocol and informed consent form were reviewed by local regulatory and ethics boards.

Patient population

Eligible patients had recurrent platinum-sensitive epithelial ovarian cancer with high-grade serous or high-grade endometrioid histology. Other histologic types were allowed providing there was evidence of a *BRCA* mutation. Platinum sensitivity was defined as the absence of progression or recurrence within 6 months of the last dose of platinum-based chemotherapy. Patients must have received platinum-containing therapy for primary disease. There was no upper limit to the number of prior platinum-based therapies, but only one non-platinum-based line of therapy for recurrent disease was permitted.

Treatment

All patients received intravenous bevacizumab at a fixed dose of 15 mg/kg on day 1 of each 21-day cycle. Oral niraparib was administered once daily at a dose of 100 mg in cohort 1, 200 mg in cohort 2, and 300 mg in cohort 3. If cohort 3 demonstrated grade ≥ 3 toxicity related to bevacizumab but none of three (or one of six) enrolled patients experienced grade ≥ 3 niraparib-related toxicity, there was an option to evaluate niraparib 300 mg with bevacizumab 7.5 mg/kg. Bevacizumab was administered before niraparib in all patients. Dose-limiting toxicities (DLTs) were defined as any of the following events occurring in the first 21 days of study participation and considered to be at least possibly related to study drug: > 10 missed doses in 21 days because of study drug toxicity; > 14-day delay in initiating cycle 2 because of study drug-related toxicity; study drug discontinuation during cycle 1 because of study drug-related toxicity; grade ≥ 3 nausea/vomiting or diarrhea lasting for > 3 days despite optimal supportive medications; any other grade ≥ 3

non-hematologic toxicity; grade 4 neutropenia (absolute neutrophil count [ANC] < 500/mm^3) lasting ≥ 7 days; febrile neutropenia (ANC < 500/mm^3 with a fever ≥ 38.5 °C); or grade ≥ 3 thrombocytopenia (platelet count < 50,000/mm^3) persisting for ≥ 5 days or associated with bleeding.

If no DLTs were observed in the first three patients enrolled to a cohort, patients were enrolled to the next cohort. If one of three patients experienced a DLT, a further three patients (maximum six per cohort) were enrolled to the same dose level; if none of these experienced a DLT, enrollment to the next cohort was allowed. If two patients in the initial or expanded cohort (two of six) experienced a DLT in the first cycle, dose escalation stopped. The maximum tolerated dose (MTD) was defined as the dose level below that at which at least two of three or six patients experienced DLTs. The recommended phase II dose was defined as the highest at which fewer than two of six patients experienced a DLT.

Study assessments

Germline *BRCA* analysis was performed during screening at Rigshospitalet. HRD assessment was performed centrally (MyChoice® HRD, Myriad Genetics, Inc., Salt Lake City, UT, USA). Adverse events were recorded at every cycle during treatment and at the end-of-treatment visit 30 days after the last dose. Adverse events were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. Tumor response was assessed by computed tomography every 12 weeks during the study.

Pharmacokinetic assessments

Blood samples were collected on cycle 1 day 1, 30 min before niraparib administration and 30 min, 1, 2, 4, 8, 24, and 48 h after niraparib administration. On cycle 1 days 8 and 15, blood samples were collected 30 min before and 30 min after niraparib administration. On cycle 2 day 1, samples were collected 30 min before bevacizumab and niraparib administration and then 30 min, and 1, 2, 4, and 8 h after niraparib administration. Samples were also collected at the clinic visit when disease progression was recorded.

Niraparib and the main metabolite, M1 (2-[4-[(3S)-piperidine-3-yl]phenyl]indazole-7-carboxylic acid), were determined in plasma at the Clinical Pharmacology and Pharmacy Laboratory, University of Southern Denmark, Odense, Denmark. An independent analysis was conducted by Tesaro. Plasma concentrations were analyzed using non-compartmental analysis based on actual sampling times. Area under the curve (AUC) was calculated using the trapezoidal rule before the time (T_{max}) of achieving maximum plasma concentration (C_{max}) and the log trapezoidal rule after T_{max}. The elimination rate constant k_e was estimated by fitting an exponential function to data points in the elimination phase. AUC from the time of the last sample (T_{last}) to infinity was calculated dividing the last plasma concentration (C_{last}) by k_e. Apparent oral clearance (CL/F) was calculated as the dose divided by AUC. AUC_{tau} was determined as AUC from 0 to 24 h on cycle 2 day 1 (day 22), assuming that the 24-h concentration (which was not measured) equaled the trough concentration ($t = 0$ h).

The concentrations of niraparib and M1 were determined in plasma according to the method described by van Andel et al. [14], with minor modification. The liquid chromatography-tandem mass spectrometry system consisted of a Dionex Ultimate 3000 UHPLC system equipped with an EQUAN autosampler unit, a Dionex Ultimate 3000 RS column compartment, and an Ultimate 3000 RS Pump, connected to a TSQ Quantiva Triple Quadropole Mass Spectrometer with heated-electrospray ionization operated in positive mode (Thermo Scientific, San José, CA, USA). Data acquisition was performed in single reaction monitoring mode, with transitions optimized for all compounds. The separation was performed on an ACE 3 C18-AR 50 × 2.1 mm (3 µm) analytical column equipped with a matching guard column (Advanced Chromatography Technologies Ltd, Aberdeen, UK). Calibration curves, blanks, and quality control samples were included in each batch of samples analyzed. The method was linear for both compounds with $r > 0.998$. For both compounds, between-day reproducibility was < 5.4% and intra-day repeatability was < 4.3%. The accuracy reported as bias ranged from − 13.2 to 1.7% for niraparib and − 11.1 to − 1.2% for M1. The limit of determination was 0.1 ng/mL and the limit of quantification was 0.4 ng/mL for both compounds.

Statistical analysis

All analyses were performed on the safety population, comprising all patients who received at least one dose of niraparib and bevacizumab. Antitumor activity was assessed by confirmed overall response rate (ORR) according to Response Evaluation Criteria in Solid Tumors (version 1.1), duration of response, and PFS.

Results

Patient population

Twelve patients were enrolled in part 1. Median age was 63.5 (range 51–81) years, 11 patients (92%) had Eastern Cooperative Oncology Group performance status 0, in 11 (92%) the ovary was the primary tumor site, and eight (67%) had high-grade serous histology (low-grade in one, missing in three). At diagnosis, three patients (25%) had International Federation of Gynecology and Obstetrics stage IV

Table 1 All treatment-emergent adverse events by grade across all cycles

No. of patients (%)	All patients ($n=12$)					Cohort 1 ($n=3$)	Cohort 2 ($n=3$)	Cohort 3 ($n=6$)	
Grade	Any	1	2	3	4	3	3	3	4
Any	12 (100)	12 (100)	12 (100)	9 (75)	1 (8)	3 (100)	2 (67)	4 (67)	1 (17)
Hypertension	12 (100)	9 (75)	8 (67)	5 (42)	0	2 (67)	0	3 (50)	0
Fatigue	10 (83)	9 (75)	6 (50)	0	0	0	0	0	0
Nausea	6 (50)	6 (50)	2 (17)	0	0	0	0	0	0
Proteinuria	5 (42)	4 (33)	4 (33)	1 (8)	0	0	0	1 (17)	0
Anorexia	5 (42)	5 (42)	1 (8)	0	0	0	0	0	0
Headache	5 (42)	5 (42)	1 (8)	0	0	0	0	0	0
Constipation	4 (33)	4 (33)	2 (17)	0	0	0	0	0	0
Blood creatinine increased	4 (33)	4 (33)	2 (17)	0	0	0	0	0	0
Anemia	3 (25)	2 (17)	2 (17)	3 (25)	0	0	2 (67)	1 (17)	0
Abdominal pain	3 (25)	3 (25)	1 (8)	1 (8)	0	0	1 (33)	0	0
Urinary tract infection	3 (25)	1 (8)	3 (25)	0	0	0	0	0	0
Diarrhea	3 (25)	3 (25)	0	0	0	0	0	0	0
Thrombocytopenia	2 (17)	1 (8)	1 (8)	1 (8)	1 (8)[a]	0	0	1 (17)	1 (17)[a]
Cough	2 (17)	2 (17)	0	0	0	0	0	0	0
Decreased appetite	1 (8)	1 (8)	1 (8)	0	0	0	0	0	0
Dyspnea	1 (8)	0	1 (8)	0	0	0	0	0	0
Vomiting	1 (8)	1 (8)	1 (8)	0	0	0	0	0	0
Peripheral sensory neuropathy	1 (8)	1 (8)	0	0	0	0	0	0	0
Pain in extremity	1 (8)	1 (8)	0	0	0	0	0	0	0
Alopecia	1 (8)	1 (8)	0	0	0	0	0	0	0
Ascites	1 (8)	1 (8)	0	0	0	0	0	0	0
Hypokalemia	1 (8)	1 (8)	0	0	0	0	0	0	0
Insomnia	1 (8)	1 (8)	0	0	0	0	0	0	0
Leucopenia	1 (8)	1 (8)	0	0	0	0	0	0	0
Stomatitis	1 (8)	1 (8)	0	0	0	0	0	0	0
Hemorrhage	1 (8)	1 (8)	0	0	0	0	0	0	0
Blood alkaline phosphatase increased	1 (8)	1 (8)	0	0	0	0	0	0	0
Other	11 (92)	10 (83)	8 (67)	3 (25)[b]	0	2 (67)	0	1 (17)	0

[a]Dose-limiting toxicity

[b]One case each of: abdominal pain/muscle and joint pain, gallbladder obstruction, decreased glomerular filtration rate

disease and five (42%) had stage IIIC disease. The median number of prior treatment lines was 1 (range 1–5). Seven patients (58%) had pre-existing hypertension at baseline. Three patients had tumor *BRCA1/2* mutations and germline *BRCA1/2* mutations and HRD. One patient had HRD but wild-type tumor and germline *BRCA1/2* status. One patient was not assessed for HRD status or somatic *BRCA1/2* status and had wild-type germline *BRCA1/2* status. The remaining seven patients had negative HRD status and expressed tumor and germline wild-type *BRCA1/2*.

Dose-limiting toxicities

During cycle 1, there were no DLTs in cohorts 1 (niraparib 100 mg) and 2 (niraparib 200 mg). In cohort 3 (niraparib 300 mg), one patient (weighing 58 kg, with baseline platelet count 191,000/μL) experienced grade 4 thrombocytopenia; therefore the cohort was expanded to six patients. There were no further DLTs. During cycle 1, none of the patients had a niraparib dose reduction and only one patient (in cohort 3, mentioned previously) had niraparib and bevacizumab treatment interruption (because of thrombocytopenia). As the MTD was not reached, the recommended phase II dose was the regimen given in cohort 3 (bevacizumab

Table 2 Pharmacokinetic parameters of niraparib in individual patients receiving concomitant bevacizumab

Patient	*L*	Cycle 1 (first dose)					Cycle 2 (steady state)			
		$AUC_{0–24}$ (ng h/mL)	C_{max} (ng/mL)	T_{max} (h)	$T_{½}$ (h)	CL/F (L/h)	$AUC_{0–24\ (tau)}$ (ng h/mL)	C_{max} (ng/mL)	$T_{½}$ (h)	CL/F (L/h)
1	100	2551	263	1.97	12.8	26.3	8972	685	[a]	11.1
2	100	3334	336	2.22	14.4	18.3	13,468	1039	21.0	7.4
3	100	3605	415	0.97	12.4	18.6	11,795	928	24.8	8.5
4	200	7932	644	4.05	25.7	10.6	37,889	2650	36.5	5.3
5	200	7373	623	3.98	13.3	17.7	24,713	1502	21.0	8.1
6	200	5264	400	2.30	23.1	17.1	16,310	1077	115.5	12.3
7	300	6156	436	4.02	14.7	31.4	25,372	1812	15.1	11.8
8	300	5509	493	3.97	17.8	30.2	28,013	1713	21.7	10.7
9	300	12,766	911	3.95	19.8	12.2	6,428[b]	530[b]	5.4[b]	46.7[b]
10	300	7298	496	3.97	17.3	23.5	23,904	1635	18.2	12.6
11	300	9539	741	1.98	16.1	19.6	19,715	1460	15.1	15.2
12	300	11,654	914	2.00	16.1	15.3	29,238	1884	23.9	10.3

AUC area under the curve, *CL/F* apparent oral clearance, C_{max} maximum plasma concentration, $T_{1/2}$ terminal half-life, T_{max} time to achieve C_{max}

[a]$T_{½}$ was not calculated because the 24-h concentration was greater than the 8-h concentration

[b]This patient was not fully compliant to niraparib after the first dose

15 mg/kg on day 1 every 3 weeks combined with niraparib 300 mg once daily).

Safety

In subsequent cycles, none of the patients in cohorts 1 or 2 required dose reduction or treatment interruption of either drug. In cohort 3, three patients had a niraparib dose reduction (one patient required two dose reductions), two of whom also had an interruption of niraparib treatment for thrombocytopenia (two interruptions in one patient) and two of whom had a bevacizumab treatment interruption. Table 1 shows adverse events by grade across all three dose levels for the entire treatment duration, and details of the nine patients with grade ≥ 3 adverse events and one DLT by cohort.

At the time of data cutoff, all but one patient had discontinued study treatment (nine because of disease progression, one because of pancreatitis unrelated to treatment, and one because of prolonged grade 1 fatigue, headache, and nausea).

Pharmacokinetics

Niraparib plasma concentrations were available from all 12 patients. One patient was not fully compliant with niraparib treatment beyond day 14. The ratios between AUCs after the first dose without and with AUC extrapolated from T_{last} to infinity ranged from 0.42 to 0.67 (median 0.60). Median niraparib half-life was 16.1 (range 12.4–25.7) h; median CL/F was 18.5 (range 10.6–31.4) L/h after the first dose. At steady state on day 22 (day 1, cycle 2), the median half-life was 21.0 (range 15.1–115.5) h and median CL/F was 10.9 (range 5.3–46.7) L/h. Table 2 and Fig. 1 summarize pharmacokinetic parameters. There was significant exposure overlap across the doses tested at both day 1 and day 21. Plasma concentrations measured at the two laboratories were highly correlated ($R^2 = 0.94$). The presented pharmacokinetic data are based on niraparib plasma concentrations measured at the University of Southern Denmark. M1 data were not analyzed.

Clinical activity

Among the 12 patients treated, one (8%) achieved a complete response and five (42%) achieved a partial response, giving an ORR of 50% [95% confidence interval (CI) 21–79%]. A further five patients (42%) achieved stable disease as best response. The remaining patient had progressive disease as best response. At the final data cutoff (December 1, 2018), PFS events had been recorded in 11 patients (92%) and deaths in eight patients (67%). Median PFS was 11.6

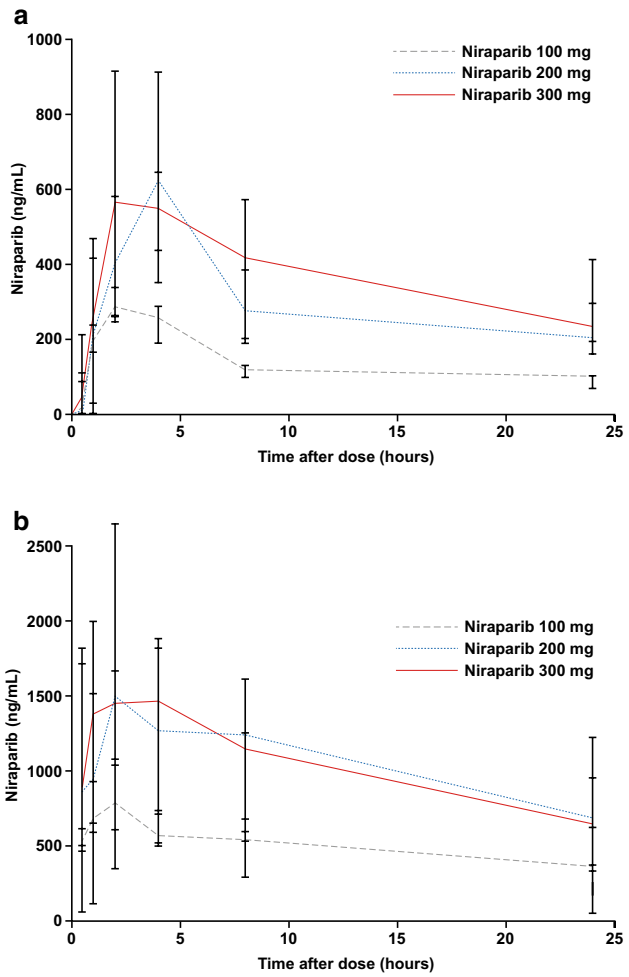

Fig. 1 Pharmacokinetic profile of niraparib given concomitantly with bevacizumab; **a** cycle 1 day 1; **b** cycle 2 day 1 (steady state). Sample times are nominal. The curves show median values for plasma concentrations for each dose level. Whiskers show ranges of observations

(95% CI 8.4–20.1) months and median OS was 25.3 (95% CI 11.2–not estimable) months (Fig. 2).

Discussion

The phase I dose-escalation part of AVANOVA identified a combination regimen of niraparib 300 mg/day and bevacizumab 15 mg/kg every 3 weeks as the recommended regimen for phase II evaluation. Adverse effects were predictable and manageable, characterized by grade 3 hypertension (42%) and anemia (25%), and low-grade hypertension, fatigue, and nausea.

Hypertension is a well-recognized class effect of antiangiogenic therapies but was also observed with increased incidence with niraparib vs placebo in the NOVA trial [3]. The grade 3 incidence in AVANOVA is higher than in phase III trials evaluating bevacizumab and chemotherapy in platinum-sensitive recurrent ovarian cancer [10, 11, 15], but similar to the 41% incidence reported in the randomized phase II trial of olaparib and cediranib [13]. It should also be noted that seven patients (58%) had pre-existing hypertension at baseline. Fatigue and nausea are class effects of PARP inhibitors [2–5], whereas niraparib generally has a higher incidence of grade 3/4 thrombocytopenia than other PARP inhibitors (34% in the randomized phase III NOVA trial in the maintenance setting [3]). However, subsequent exploratory analyses suggested that refining the starting dose according to weight and pretreatment platelet count may improve tolerability without compromising efficacy [16]. Patients with baseline body weight of < 77 kg or baseline platelets of < 150,000/μL may benefit from a starting dose of 200 mg/day. Of note, the patient with a DLT of thrombocytopenia weighed only 58 kg and received niraparib 300 mg/day.

Pharmacokinetic results in patients treated with the niraparib–bevacizumab combination in AVANOVA part 1 showed a niraparib profile similar to that reported for

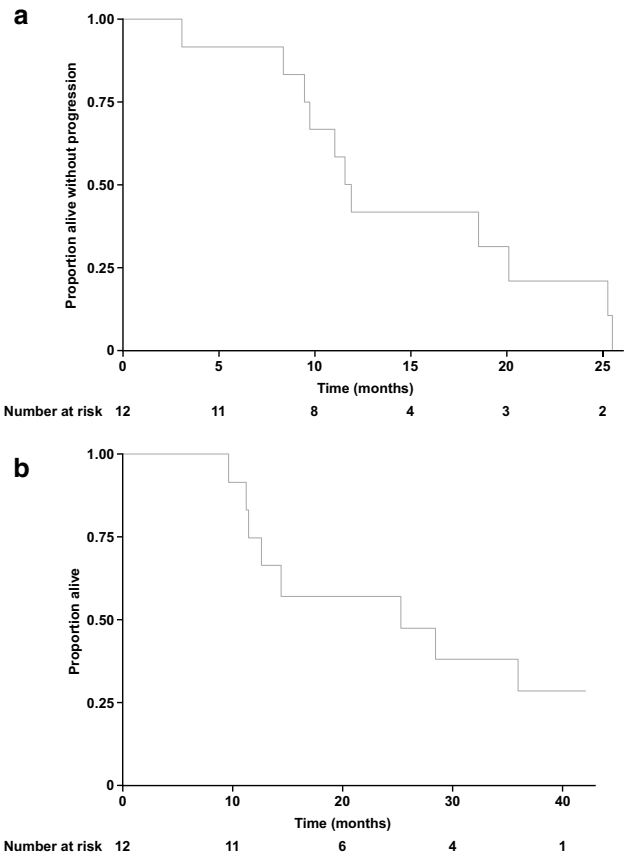

Fig. 2 Kaplan–Meier estimates of efficacy; **a** progression-free survival; **b** overall survival

single-agent niraparib in previous studies [17, 18]. The terminal half-life observed in AVANOVA is considerably shorter than the 48–51-h terminal half-life determined in the food-effect subset of the NOVA phase III trial [19]. In our study, the daily dosing regimen and very small single-dose window may not have been adequate for defining the terminal phase of elimination for a compound with low clearance.

Niraparib–bevacizumab combination treatment demonstrated preliminary activity in this unselected population, including median PFS of 11.6 months. Although based on only 12 patients, median PFS is similar to median PFS of 12–14 months reported with bevacizumab plus chemotherapy in the OCEANS, GOG-0213, and AGO-OVAR 2.21 randomized phase III trials in this setting [10, 11, 15].

In conclusion, AVANOVA part 1 indicates that the combination of niraparib and bevacizumab is tolerable. Based on these encouraging results with a regimen that may potentially substantially delay the need for cytotoxic chemotherapy, the randomized phase II part of AVANOVA comparing niraparib vs niraparib–bevacizumab combination therapy was initiated, and was recently reported. Phase III comparison of the doublet versus standard-of-care therapy is planned.

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Compliance with ethical standards

Conflict of interest MRM reports personal fees from AstraZeneca, Biocad, Clovis Oncology, Oncology Venture, Pfizer, Roche, Tesaro, and ZaiLab, and research Grants to his institution from AstraZeneca, Boehringer Ingelheim, Clovis Oncology, Pfizer, and Tesaro. He is the global clinical lead for the NOVA trial of niraparib and the ENGOT-EN6/NSGO-RUBY trial of dostarlimab. EA-L reports honoraria from Roche and consulting/advisory roles for AstraZeneca, Tesaro, Clovis Oncology, and Genmab. MJB declares relationships with Tesaro, Roche, and Clovis. SM reports a grant for lectures from AstraZeneca and an advisory board for Tesaro. LB receives project support from AstraZeneca and is a member of various ovarian cancer expert panels (Tesaro, Clovis Oncology, and AstraZeneca). JM reports personal fees from AstraZeneca, Tesaro, Clovis, Roche, and MSD. TKB, MMS, RdPC, MJ, HR, FN, UL, and KB declare no conflict of interest.

Ethical standards Part 1 was conducted at a single site (Rigshospitalet, Copenhagen) according to the ethical principles of the Declaration of Helsinki, the International Conference on Harmonization Good Clinical Practice guidelines, and applicable local regulatory requirements.

Informed consent Before study initiation, the protocol and informed consent form were reviewed by local regulatory and ethics boards.

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