Niraparib AVANOVA Clinical Trial Overview

Summary

- A phase 1/2 investigator-sponsored (Nordic Society of Gynaecological Oncology-Clinical Trial Unit [NSGO-CTU]) trial (NSGO-AVANOVA/ENGOT-OV24) evaluated the safety and efficacy of niraparib-bevacizumab combination therapy in the treatment of patients with platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer.[1,2]
- AVANOVA1: The recommended phase 2 dose (RP2D) was determined to be the cohort 3 dose: bevacizumab 15 mg/kg IV every 21 days with niraparib 300 mg orally once daily.[1,3]
    - Niraparib + bevacizumab combination therapy achieved an overall response rate (ORR) of 50% (1 complete responder and 5 partial responders [Table 2]). [1,3]
    - The median progression-free survival (PFS) was 11.6 months (95% CI 8.4 – 20.1) (Figure 1) and the OS was 25.3 months (95% CI 11.2 – NE) (Figure 2).[1,3]
- AVANOVA2: A two-arm, open-label, phase 2 randomized superiority study evaluated the efficacy of niraparib versus niraparib + bevacizumab combination therapy in the treatment of women with platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer.[2]
    - The median PFS for the intent-to-treat (ITT) population was 12.5 months for patients receiving niraparib + bevacizumab compared with 5.5 months for patients receiving niraparib alone (adjusted HR 0.34, [95% CI 0.21–0.54; $P < 0.0001$]) (Figure 5).[4]
    - Five patients discontinued niraparib due adverse events (AEs) in the niraparib alone group. Nine patients discontinued both niraparib + bevacizumab due to AEs in the combination group (Figure 4).[4]
- Some information contained in this response is outside the approved local label for niraparib. This product is not approved for the use described.

MEDICAL LITERATURE

AVANOVA1

The objective of AVANOVA1 (NCT02354131), a single-center, open-label, phase 1a, dose-escalation investigator-sponsored (NSGO-CTU) trial, was to evaluate the safety and tolerability of niraparib + bevacizumab combination therapy in patients with platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer. Patient demographics, baseline characteristics, and mutation status are reported in Table 1. Patients (N = 12) received a fixed-dose of bevacizumab (15 mg/kg IV every 21 days) with a dose escalation of niraparib (100, 200, or 300 mg) orally once daily.[1,3]

Niraparib + bevacizumab combination therapy achieved an ORR of 50% (1 complete responder and 5 partial responders) (Table 2). The median PFS was 11.6 months (95% CI 8.4 – 20.1) (Figure 1) and the OS was 25.3 months (95% CI 11.2 – NE) (Figure 2).[1,3]

Using the standard 3 + 3 study design, the RP2D was determined to be bevacizumab 15 mg/kg every 3 weeks and niraparib 300 mg once daily.[1,3]

Dose-limiting toxicity and grade 3 or 4 treatment-emergent adverse events are presented in Table 3.[3] One dose-limiting toxicity (grade 4 thrombocytopenia) was observed in the bevacizumab 15 mg/kg + niraparib 300 mg dosing cohort. There were no dose reductions in cohort 1 (n = 3) or cohort 2 (n = 3). In cohort 3 (n = 6), three patients reduced their niraparib dose, two patients interrupted niraparib therapy and two patients interrupted bevacizumab therapy.[1,3] Nine patients discontinued treatment due

to disease progression, one due to pancreatitis (unrelated to treatment), and one due to prolonged grade 1 fatigue, headache, and nausea. The maximum tolerated dose was not reached.[1]

AVANOVA2

AVANOVA2, a two arm, multicenter, prospective, open-label, phase 2, randomized, investigator-sponsored (NSGO-CTU) trial, evaluated the safety and efficacy of niraparib vs niraparib + bevacizumab combination therapy in the treatment of patients with platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer (Figure 3). Patients must have high-grade serous or high-grade endometrioid histology.[2,4]

Forty-nine patients were randomized to the single-agent niraparib arm and forty-eight patients were randomized to the niraparib + bevacizumab arm. All patients were evaluable for efficacy and safety. One patient in the niraparib + bevacizumab arm was not evaluable for patient-reported outcomes (PROs).[2,4] Treatment was ongoing in six patients (Figure 4).[4] Patient baseline characteristics were well balanced between treatment arms (Table 4).[2]

The primary endpoint of the AVANOVA2 study was investigator-assessed PFS in the ITT population. After a median follow-up of 24.7 months, there was a statistically significant increase in the median PFS for patients receiving niraparib + bevacizumab combination vs niraparib alone (12.5 months vs 5.5 months; adjusted HR 0.34, [95% CI 0.21–0.54; $P < 0.0001$]) (Figure 5).[4]

Key secondary endpoints included the objective response rate (ORR) and disease control rate (DCR). At initial data cutoff (Dec 1, 2018), median follow-up of 16.9 months (IQR 15.4–20.9), the ORR for patients receiving niraparib + bevacizumab was 62%, compared to 30% with niraparib alone (odds ratio 3.84, 95% CI 1.60–9.21, $P = 0.003$). The DCR for patients taking niraparib + bevacizumab was 79%, compared to 53% with niraparib alone (odds ratio 3.36, 95% CI 1.37–8.22, $P = 0.008$).[2]

Exploratory subgroup analyses of PFS according to homologous recombination deficiency (HRD) status, *BRCA* mutational status, and chemotherapy-free interval were also evaluated and results were reported at initial data cutoff (Table 5).[2] Additional prespecified exploratory endpoints included time to first subsequent therapy, time to second progression or death, time to second subsequent therapy, and overall survival (52% event maturity) (Figure 6).[4]

Any grade AEs in $\geq$ 10% of patients in either arm and/or grade $\geq$ 3 AEs in > 2 patients overall in the AVANOVA2 trial are summarized in Figure 7.[4] Additional grade ≥ 3 AEs in only two patients comprised: ascites, febrile neutropenia, and ileus each in one patient in each arm; gastrointestinal disorder in two patients in the combination arm.[4]

The proportion of patients requiring niraparib dose reduction from 300 mg to 200 mg was similar in the two treatment groups: 52% (n = 25) of patients in the combination group vs 57% (n = 28) of patients in the niraparib alone group. One patient (2%) in each group required a further dose reduction to 100 mg. Niraparib treatment was interrupted in 54% (n = 26) of patients in the combination group compared with 61% (n = 30) of patients in the niraparib group.[2]

Five patients discontinued niraparib due AEs in the niraparib alone group. Nine patients discontinued both niraparib + bevacizumab due to AEs in the combination group (Figure 4).[4]

No detrimental effect on quality of life was observed (Figure 8).[4]

REFERENCES

1. Mirza MR, Bergmann TK, Mau-Sorensen M, et al. A phase I study of the PARP inhibitor niraparib in combination with bevacizumab in platinum-sensitive epithelial ovarian cancer: NSGO AVANOVA1/ENGOT-OV24. *Cancer Chemother Pharmacol.* 2019;84(4):791-798. doi:http://dx.doi.org/10.1007/s00280-019-03917-z.
2. Mirza MR, Åvall Lundqvist E, Birrer MJ, et al. Niraparib plus bevacizumab versus niraparib alone for platinum-sensitive recurrent ovarian cancer (NSGO-AVANOVA2/ENGOT-ov24): a randomised, phase 2, superiority trial. *The Lancet Oncology*. 2019;20(10):1409-1419. doi:http://dx.doi.org/10.1016/s1470-2045(19)30515-7.
3. Mirza MR, Wang J, Mau-Sorensen MA, et al. Phase 1 study to evaluate the safety and tolerability of bevacizumab-niraparib combination therapy and determine the recommended phase 2 dose (RP2D) in women with platinum-sensitive epithelial ovarian cancer. Poster presented at European Society for Medical Oncology (ESMO); September 8-12, 2017; Madrid, Spain. Poster 953P.
4. Mirza MR, Nyvang G-B, Lund B, et al. Survival analysis of NSGO-AVANOVA2/ENGOT-OV24: combination of niraparib and bevacizumab versus niraparib alone as treatment for recurrent platinum-sensitive ovarian cancer. A randomized controlled chemotherapy-free study. Poster presented at American College of Clinical Oncology (ASCO); May 29-31, 2020. Poster 183.

APPENDIX

Table 1. AVANOVA1 Patient Demographics, Baseline Characteristics, and Mutation Status[1,3]

Characteristic	Patients (N = 12)
Age, median [range], y	63.5 [51– 81]
FIGO stage at diagnosis, n	
1C	1
2B	1
3A	1
3C	5
4	3
ECOG performance status, n	
0	11
1	1
Patients with pre-existing hypertension, n	
Hypertension	7
Number of lines of previous treatment, median [range]	1 [1–5]
Homologous recombination deficiency,[a] n	
Positive	4
Negative	7
Tumor *BRCA* 1/2 mutation status,[b] n	
Mutation carrier	3
Wild type	8
Germline *BRCA* 1/2 mutation status, n	
Mutation carrier	3
Wild type	9

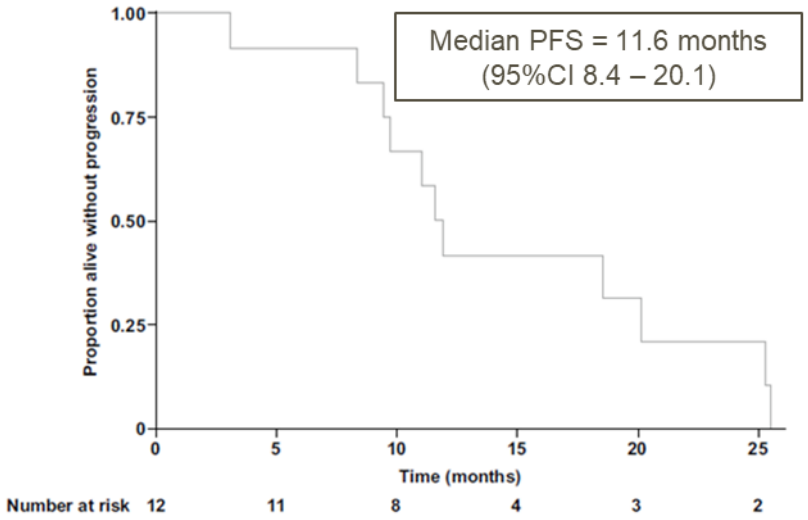
[a]1 patient's homologous recombination deficiency status not determined; [b]1 patient's tumor *BRCA* mutation status was pending at time of publication

BRCA = breast cancer susceptibility gene; ECOG = Eastern Cooperative Oncology Group; FIGO = International Federation of Gynecology and Obstetrics.

Table 2. AVANOVA1 Clinical Activity Response Evaluation (N = 12)[1,3]

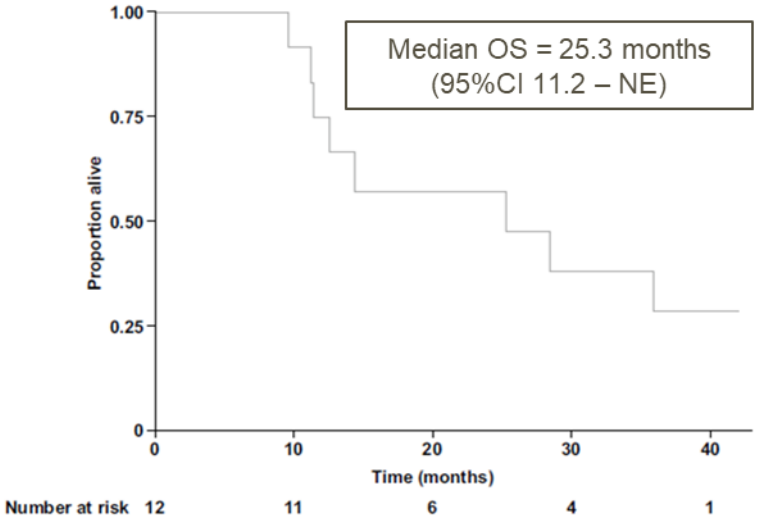
Clinical Response, n (%)	
Complete Response (CR)	1 (8)
Partial Response (PR)	5 (42)
Stable Disease (SD)	5 (42)
Progressive Disease (PD)	1 (8)

Figure 1. AVANOVA1 Progression-Free Survival[1]



PFS = progression-free survival.

Figure 2. AVANOVA1 Overall Survival[1]



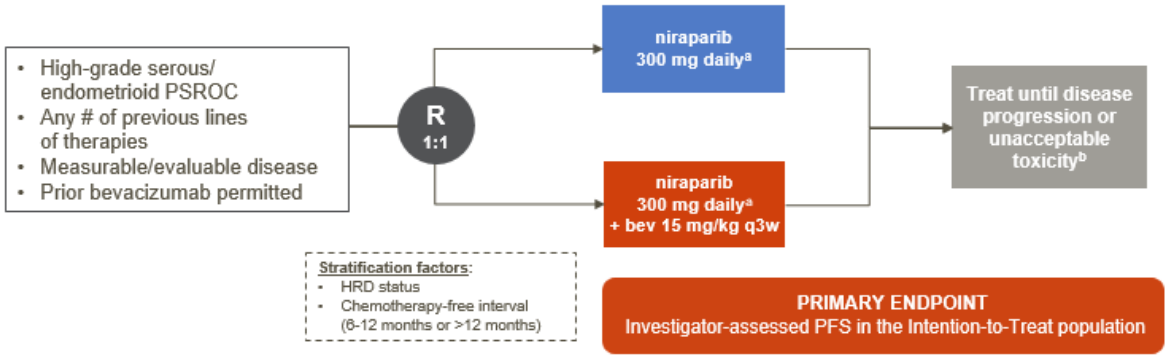
OS = overall survival; NE = not estimable.

Table 3. AVANOVA1 Most Common Adverse Events by Grade[1,3]

Cohort	Bevacizumab Dose	Niraparib Dose	AE Grade	AE During Cycle 1 (n)	AE During Any Cycle (n)
Cohort 1 (n = 3)	15 mg/kg q3w	100 mg QD	3	—	Hypertension (2), Muscle and joint pain (2)
			4	—	—
Cohort 2 (n = 3)	15 mg/kg q3w	200 mg QD	3	—	Anemia (2), Abdominal pain (1)
			4	—	—
Cohort 3 (n = 6)	15 mg/kg q3w	300 mg QD	3	—	Hypertension (3), Anemia (1), Proteinuria (1), Thrombocytopenia (1), Other (1)
			4	Thrombocytopenia (1) DLT	Thrombocytopenia (1) DLT
Cohort 4 (n = 0) *optional*	7.5 mg/kg q3w	300 mg QD	—		

AE = adverse events; DLT = Dose-limiting toxicity; q3w = every 3 weeks; QD = once daily.

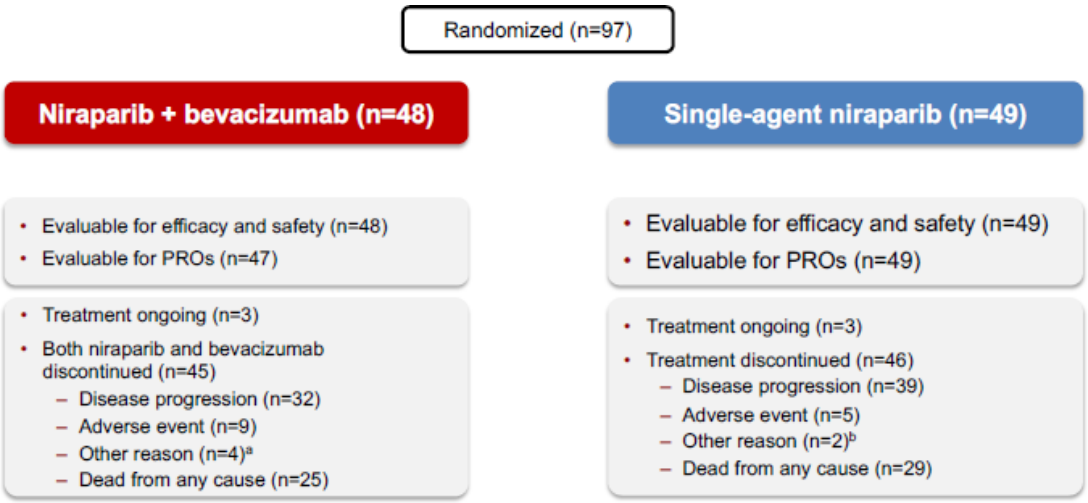
Figure 3. AVANOVA2 Trial Design Schema[4]



[a]21-day treatment cycle; [b]Followed by investigator's choice (without niraparib).

Bev = bevacizumab; HRD = homologous recombination deficiency; PFS = Progression -free survival; PSROC = platinum-sensitive relapsed ovarian cancer; q3w = every 3 weeks.

Figure 4. AVANOVA2 Patient Enrollment and Disposition[4]



[a]Investigator decision (n=1), serious compliance issues (n=1); [b]Performance status deteriorated to 3/4 (n=1), withdrew consent (n=1), other reason (n=2).
PRO = patient-reported outcome.

Table 4. AVANOVA2 Patient Baseline Characteristics (ITT Population)[2]

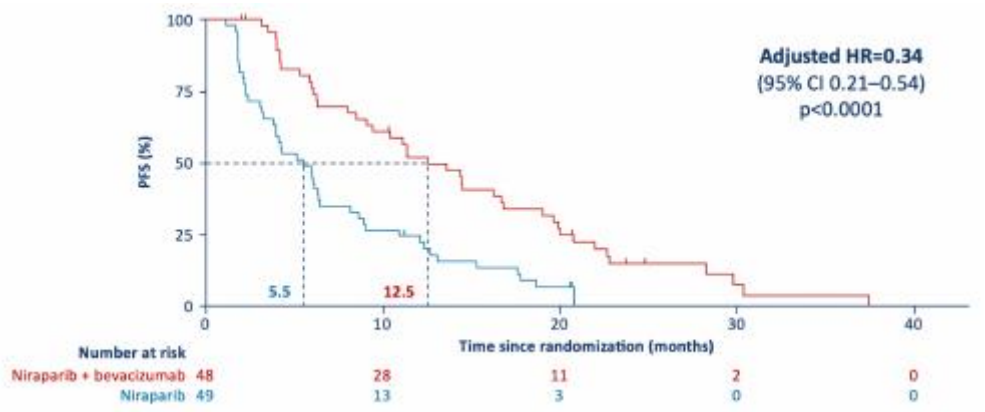
Characteristic	Single-agent niraparib (n = 49)	niraparib + bevacizumab (n = 48)
Age (years)	66 (58 – 70)	66.5 (59 – 70)
Primary tumor site		
Ovary	33 (67%)	38 (79%)
Fallopian tube	9 (18%)	5 (10%)
Peritoneum	7 (14%)	5 (10%)
FIGO stage at diagnosis, n		
1 or 2	5 (10%)	3 (6%)
3A or 3B	2 (4%)	2 (4%)
3C	26 (53%)	29 (60%)
4	15 (31%)	14 (29%)
Unknown	1 (2)	0
Chemotherapy-free interval		
6–12 months	17 (35%)	20 (42%)
>12 months	32 (65%)	28 (58%)
HRD status		
Positive[a]	30 (61%)	28 (58%)
Negative/unknown	19 (39%)	20 (42%)
Any *BRCA* mutation[b]	18 (37%)	15 (31%)
Germline	9 (18%)	6 (13%)
Somatic	14 (29%)	14 (29%)
Pre-existing hypertension	17 (35%)	20 (42%)
Prior bevacizumab	13 (27%)	10 (21%)
Prior lines of therapy		
1	27 (55%)	21 (44%)
2	19 (39%)	24 (50%)
≥ 3	3 (6%)	3 (6%)

Data are median (IQR), n (%), or mean (SD).

[a]Three patients (1 niraparib + bevacizumab, 2 niraparib) had *BRCA*-mutated tumors but were considered as HRD negative or unknown for stratification in error; [b]Patients could have both somatic and germline *BRCA* mutations.

BRCA = breast cancer gene; FIGO = International Federation of Gynecology and Obstetrics; HRD = homologous recombination deficiency; IQR = interquartile range; ITT = intention-to-treat; SD = standard deviation.

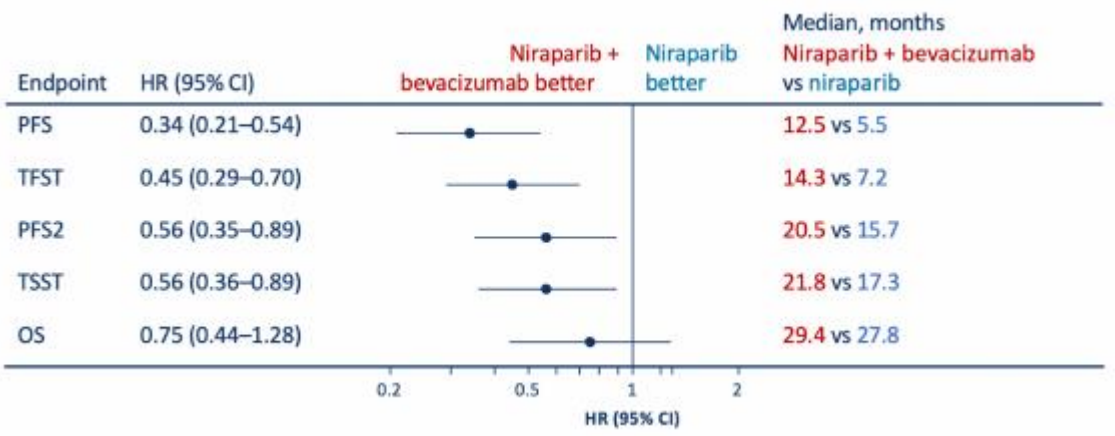
Figure 5. AVANOVA2 Progression-Free Survival in the Intention-to-Treat Population[a,4]



[a] Updated analysis presented at ASCO 2020 (median follow-up 24.7 months).

Bev = bevacizumab; CI = confidence interval; HR = hazard ratio.

Figure 6. AVANOVA2 Summary of Adjusted Hazard Ratios for Exploratory Endpoints[b,4]



[a]Event maturity 52%; [b]Updated analysis presented at ASCO 2020 (median follow-up 24.7 months).

CI = confidence interval; HR = hazard ratio; OS = overall survival; PFS = progression-free survival; PFS2 = time to second progression or death; TFST = time to first subsequent treatment; TSST = time to second subsequent treatment.

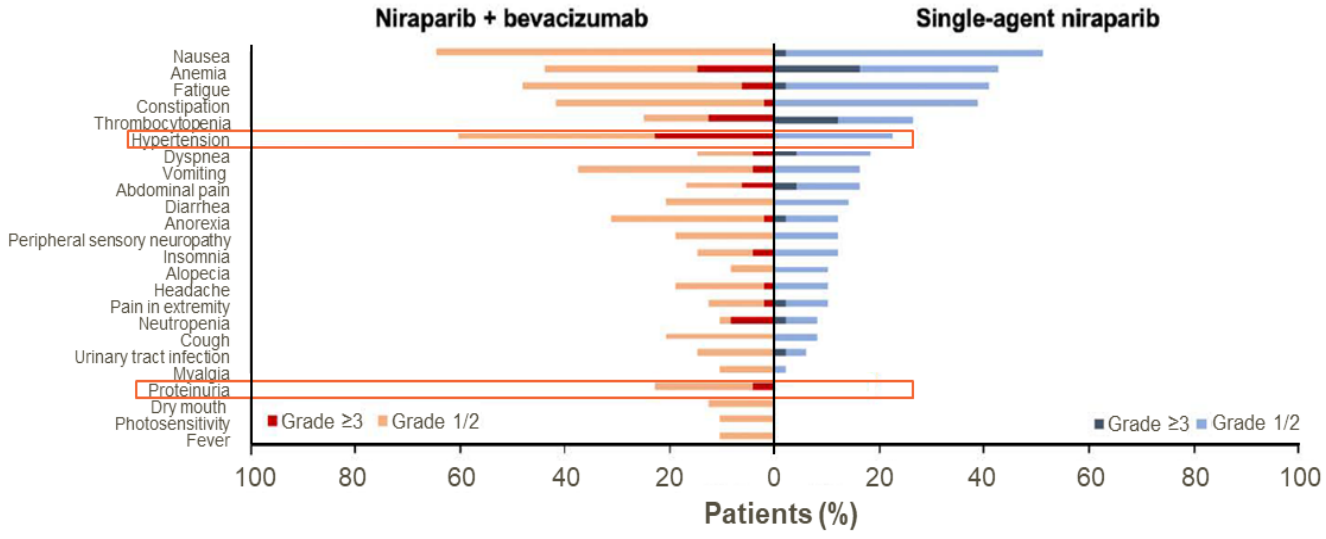
Table 5. AVANOVA2 Progression-Free Survival by Stratification Factors[a,2]

Progression-Free Survival (months)	Niraparib + bevacizumab	Single-agent Niraparib	Hazard ratio
Chemotherapy-free interval			
6–12 months	11.3	2.2	0.29 (95% CI 0.14 – 0.62)
>12 months	13.1	6.1	0.42 (95% CI 0.20 – 0.80)
HRD status			
Positive	11.9	6.1	0.38 (95%CI 0.20 – 0.72)
Negative/unknown	11.3	4.2	0.40 (95%CI 0.19 – 0.85
***BRCA* status**			
*BRCA*mut	14.4	9.0	0.49 (95% CI 0.21 – 1.15)
*BRCA*wt	11.3	4.2	0.32 (95% CI 0.17 – 0.58)

[a]At initial data cutoff (Dec 1, 2018), median follow-up was 16.9 months (IQR 15.4–20.9).

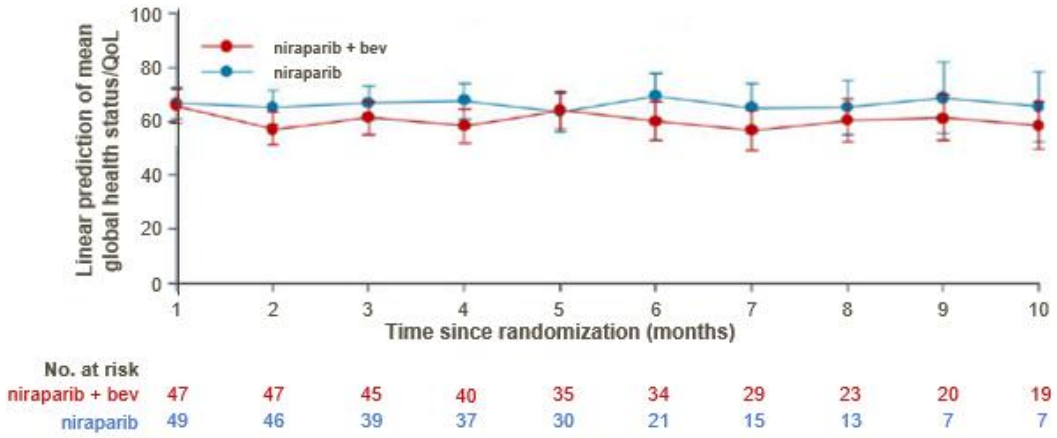
HRD = homologous recombination deficiency.

Figure 7. AVANOVA2 Summary of Adverse Events (Any Grade in ≥ 10% of Patients in Either Arm and/or Grade ≥ 3 in > 2 Patients Overall)[a,4]



[a] Updated analysis presented at ASCO 2020 (median follow-up 24.7 months).

Figure 8. Patient Reported Outcomes: EORTC QLQ-C30 Global Health Status/Quality of Life Over Time[a,4]



Data are linear prediction of mean (SD).

[a] Updated analysis presented at ASCO 2020 (median follow-up 24.7 months).

EORTC-QLQ-C30 = European Organisation for Research and Treatment of Cancer quality of life questionnaire, core module global health status/quality of life subscale over time.