Niraparib NOVA Clinical Trial Overview

Summary

- A phase 3 clinical study (NOVA) evaluated niraparib as maintenance therapy in women with recurrent ovarian, fallopian tube, and primary peritoneal cancer who had previously received at least 2 platinum-based regimens and were in a complete response (CR) or partial response (PR) to their most recent platinum-based regimen.[1]
- Niraparib treatment resulted in significantly longer progression-free survival (PFS) in comparison to placebo in the three primary efficacy populations.[1]
    - Median PFS for patients with a germline *BRCA* mutation (g*BRCA*mut) was 21 and 5.5 months ($P < 0.001$) for the niraparib and placebo groups, respectively.[1]
    - Median PFS for patients in the homologous recombination deficiency (HRD)-positive subset of the non-g*BRCA*mut cohort was 12.9 and 3.8 months ($P < 0.001$) for the niraparib and placebo groups, respectively.[1]
    - Median PFS for patients in the overall non-g*BRCA*mut cohort was 9.3 and 3.9 months ($P < 0.001$) for the niraparib and placebo groups, respectively.[1]
- Any grade hematologic treatment-emergent adverse event (TEAE) that occurred in ≥ 10% of patients in either study arm included thrombocytopenia events (61.3% for niraparib vs 5.6% for placebo), anaemia events (50.1% for niraparib vs 6.7% for placebo), and neutropenia events (30.2% for niraparib vs 6.1% for placebo).[1]
- Grade 3/4 TEAEs occurred in 74.1% of patients receiving niraparib vs 22.9% of patients receiving placebo. A summary of TEAEs (Any TEAE, grade ≥ 3, and leading to dose interruption, reduction, and discontinuation) is presented in Table 3.[1]
- Grade 3/4 TEAEs that occurred in ≥ 5% of patients in the niraparib arm were thrombocytopenia events, anaemia events, neutropenia events, fatigue, and hypertension, and were less frequent after cycle 3 of treatment (Table 4).[2]
- A long-term safety analysis of the NOVA study assessed the incidence of TEAEs in patients receiving niraparib for up to 4 years.[3]
    - Dose modifications (dose reductions and dose interruptions) due to TEAEs were common and most occurred during the first 3 months of niraparib therapy (Figure 8). Treatment discontinuations due to TEAEs were < 5% across all months and time intervals reported.[3]
    - TEAEs were managed by early dose modifications.[3,4]

PHASE 3 NOVA STUDY

Study Design

NOVA (NCT01847274) was a multicenter, double-blind, randomized, placebo-controlled phase 3 clinical study evaluating single-agent oral niraparib 300 mg once daily as maintenance therapy in women (niraparib N = 367, placebo N = 179) with recurrent ovarian, fallopian tube, or primary peritoneal cancer following complete or partial response to their most recent platinum-based chemotherapy. Patients were prospectively assigned to one of two independent cohorts based on the results of a central germline *BRCA* test (BRACAnalysis, Myriad Genetics, USA): patients with a germline *BRCA* deleterious or suspected deleterious mutation (g*BRCA*mut), and those without such mutations (non-g*BRCA*mut). Patients were randomized 2:1 to receive either niraparib 300 mg or matched placebo once daily in 28-day cycles (with no treatment breaks) until disease progression or death (Figure 1A and Figure 1B).[1]

Statistical Analysis

The three predefined primary efficacy populations were the g*BRCA*mut cohort, the HRD-positive subset of the non-g*BRCA*mut cohort, and the non-g*BRCA*mut cohort. PFS was assessed independently in the g*BRCA*mut and non-g*BRCA*mut cohort. A hierarchical testing procedure was predefined for the non-g*BRCA*mut cohort; statistical analysis was first performed on the HRD-positive group, and if the results were significant, a test of the overall non-g*BRCA*mut cohort was performed. An exploratory analysis of PFS was performed in the HRD-positive/s*BRCA*mut, HRD-positive/*BRCA*wt, and HRD-negative subgroups. Efficacy data were analyzed for the intention-to-treat (ITT) population, defined as all randomized patients for each of the two cohorts. Safety data were analyzed in the safety population, defined as all patients who ingested any amount of study drug.[1]

Results

A total of 553 patients were enrolled in the study from 107 sites, of which 203 were in the g*BRCA*mut cohort and 350 in the non-g*BRCA*mut cohort. Stratification factors used in randomization within each cohort included time to progression after completion of the penultimate platinum regimen (6 to < 12 months versus ≥ 12 months), use of bevacizumab in conjunction with the penultimate or last platinum regimen (yes vs no), and best response during the last platinum regimen (CR vs PR). Patient demographics and baseline characteristics are presented in Table 1.[1]

The database for the current efficacy analysis was locked on June 20, 2016, and the median duration of follow-up for the efficacy analysis was 16.9 months for all the patients in the ITT population, and 16.4 months and 17.5 months in the g*BRCA* cohort and in the non-g*BRCA* cohort, respectively. The longest follow-up at the time of the database lock was 24 months. Follow-up is ongoing.[1]

Primary Endpoint (PFS) in the Three Primary Efficacy Populations

The duration of PFS in the niraparib group was significantly longer than that in the placebo group in all three primary efficacy populations ($P < 0.001$) (Figure 2).[1] In the g*BRCA*mut cohort, the median PFS was 21 months with niraparib (n = 138) vs 5.5 months with placebo (n = 65; hazard ratio [HR], 0.27; 95% CI, 0.17–0.41; $P < 0.001$) (Figure 2A)[1] and the estimated probabilities (95% CI) of PFS at 12, 18, and 24 months post-randomization (approximately 18, 24, and 30 months post chemotherapy, respectively) in the niraparib and placebo groups was 0.62 (0.53-0.7) vs 0.16 (0.07-0.28), 0.5 (0.4-0.59) vs 0.16 (0.07-0.28), and 0.42 (0.30-0.55) vs 0.16 (0.07-0.28), respectively.[2,5]

In the HRD-positive group of the non-g*BRCA*mut cohort, niraparib treatment (n = 106) resulted in significantly longer PFS in comparison with placebo (n = 56) (median, 12.9 vs 3.8 months; HR, 0.38; 95% CI, 0.24–0.59; $P < 0.001$) (Figure 2B)[1] and the estimated probabilities (95% CI) of PFS at 12, 18, and 24 months in the niraparib and placebo groups was 0.51 (0.4-0.61) vs 0.13 (0.05-0.25), 0.37

(0.26-0.48) vs 0.09 (0.02-0.22), and 0.31 (0.20-0.43) vs 0.09 (0.02-0.22), respectively.[2,5] In the overall non-g*BRCA*mut cohort, niraparib treatment (n = 234) resulted in longer PFS in comparison to placebo (n = 116) (median, 9.3 vs. 3.9 months; HR, 0.45; 95% CI, 0.34–0.61; $P < 0.001$) (Figure 2C)[1] and the estimated probability (95% CI) of PFS at 12, 18, and 24 months in the niraparib and placebo groups was 0.41 (0.33-0.48) vs 0.14 (0.08-0.22), 0.3 (0.23-0.38) vs 0.12 (0.06-0.21), and 0.27 (0.19-0.35) vs 0.12 (0.06-0.21), respectively.[2,5]

Forest plots of PFS for pre-specified subgroup analyses in all three efficacy populations are presented in Figure 3. Results of statistical interaction tests between treatment and subgroup factors showed consistency of the treatment effect within randomization strata, as well as within key demographic and prognostic subgroups with the exception of nonwhite race.[1]

Secondary Endpoints and Exploratory Analyses

Secondary endpoints included patient reported outcomes, chemotherapy-free interval, time to first subsequent therapy, PFS2 (time from treatment randomization to the date of progression or death on the subsequent anticancer therapy), time to second subsequent therapy, and overall survival (OS).[1]

The chemotherapy-free interval and the time until the first subsequent treatment were both significantly longer in the niraparib group vs placebo group (Table 2).[1] At the time of database lock, data for PFS2 were immature (< 50% of events at the time of the database lock), but preliminary data indicated a significantly longer duration of PFS2 for both the g*RRCA*mut and non-g*BRCA*mut cohorts receiving niraparib. Data were also immature for time to second subsequent treatment (< 40% of events) and OS (< 20% of events).[1,6] During the study follow-up period, 16.1% (60 of 372) of patients in the niraparib arm and 19.3% (35 of 181) of patients in the placebo arm had died.[1]

To determine the impact of niraparib on subsequent therapy for patients who progressed on subsequent therapy, each patient's PFS1 was subtracted from the patient's PFS2 (PFS2-PFS1). PFS2-PFS1 was similar in the niraparib and placebo arms (HR 1.02; 95% CI, 0.765–1.349) in the pooled g*BRCA*mut and non-g*BRCA*mut cohorts (Figure 5).[5,6]

Pre-specified exploratory analyses of PFS were performed for the different biomarker subgroups within the non-g*BRCA*mut cohort: patients with HRD-positive/*BRCA*wt, HRD-positive/s*BRCA*mut, and HRD-negative. For patients with *BRCA*wt tumors (HRD-positive/*BRCA*wt), niraparib (n = 71) improved PFS compared with placebo (n = 44) (median 9.3 vs. 3.7 months; HR, 0.38; 95% CI, 0.23-0.63; $P < 0.001$) (Figure 4A). The HRD-positive/s*BRCA*mut subgroup experienced a similar improvement in PFS as the g*BRCA*mut cohort (median 20.9 [n=35] vs. 11.0 [n = 12] months; HR, 0.27; 95% CI, 0.08-0.90; $P = 0.02$) (Figure 4B). Niraparib (n = 92) also improved PFS for the HRD-negative subgroup compared with placebo (n = 42) (median 6.9 vs. 3.8 months; HR 0.58; 95% CI, 0.36–0.92, $P = 0.02$) (Figure 4C).[1] The estimated probability (95% CI) of PFS in the HRD-negative subgroup at 12, 18, 24 months post-randomization in the niraparib and placebo groups was 0.27 (0.17–0.39) vs 0.07 (0.01-0.19), 0.19 (0.10–0.31) vs 0.07 (0.01–0.19), and 0.19 (0.10–0.31) vs 0.07 (0.01–0.19), respectively.[5]

Baseline mean Functional Assessment of Cancer Therapy–Ovarian Symptom Index (FOSI) scores and baseline European Quality of Life Scale 5-Dimensions 5-Level (EQ-5D-5L) scores were similar between the niraparib and placebo arms in both the g*BRCA*mut and non-g*BRCA*mut cohorts. Completion rates for the FOSI and EQ-5D-5L questionnaires were high and similar in the two groups. The cross-sectional analysis of the quality of life (QoL) scores (FOSI, EQ-5D-5L, and European QoL-visual analogue scale [EQ-VAS]) found that baseline mean values were similar between the niraparib and placebo arms and remained stable during the treatment and preprogression period, and at the post-progression assessment in both cohorts (Figure 6).[1,7] Preprogression EQ-5D-5L scores (adjusted mean (Standard Error [SE])) were similar between both arms in both cohorts: in the g*BRCA*mut cohort, 0.812 (0.0257) for niraparib (n = 129) vs. 0·803 (0·0292) for placebo (n = 59) and in the non-g*BRCA*mut cohort, 0·845 (0·0160) for niraparib (n = 208) and 0·828 (0·0175) for placebo (n = 97).[7] All FOSI-assessed symptoms,

with the exception of nausea, remained stable or improved over time with niraparib therapy. Nausea initially increased at cycle 2, but declined at later timepoints, approaching baseline levels.[7]

Safety

All of the patients (n = 367) who received niraparib and 95.5% (n = 171) of patients who received placebo experienced at least 1 TEAE. Grade 3/4 TEAEs occurred in 74.1% of patients receiving niraparib vs 22.9% of patients receiving placebo. A summary of TEAEs (Any TEAE, grade ≥ 3, leading to dose interruption, reduction, and discontinuation) is presented in Table 3. No on-treatment deaths were reported during the study in either treatment arm.[1] Grade 3/4 TEAEs that occurred in ≥ 5% of patients in the niraparib arm were thrombocytopenia events, anaemia events, neutropenia events, fatigue, and hypertension, and were less frequent after cycle 3 of treatment (Table 4). Niraparib dose reductions and discontinuations for select TEAE of any grade are presented in Table 5.[2]

Retrospective Analysis to Assess Potential Predictors for Early Dose Modification

A retrospective exploratory multivariate analysis was conducted on NOVA data, which identified baseline body weight < 77 kg and baseline platelet counts < 150,000/μL as the two best predictors of early dose modification. Patients with baseline body weight < 77 kg or baseline platelet counts below the lower limit of normal, < 150,000/μL, experienced a higher incidence of grade 3 or 4 thrombocytopenia event. Among patients with body weight < 77 kg or baseline platelet counts < 150,000/μL, 35% experienced a grade 3/4 thrombocytopenia event in month 1, compared with 12% of patients with a body weight ≥ 77 kg and baseline platelet count ≥ 150,000/μL.[4]

Patients with baseline body weight < 77 kg or baseline platelet counts < 150,000/μL were more likely to require early dose modification when initiated at 300 mg once daily. At month 4, 17% of patients with body weight < 77 kg or baseline platelet counts < 150,000/μL remained at the 300 mg dose. All patients in the NOVA trial began niraparib at 300 mg; however, as a result of dose interruptions and reductions, the average daily niraparib dose was 207 mg in this patient group through the first 2 months of niraparib treatment. Most of the dose interruptions occurred during this period as patients were undergoing dose optimization.[4]

A PFS analysis from the NOVA study by dose at month 4 demonstrated that once the patients reach their optimal individualized dose, PFS in patients who were dose reduced to either 200 or 100 mg was consistent with that of patients who remained at the 300 mg starting dose (Figure 7).[4]

Long-Term Safety

Patients who remain on treatment continue to be followed for safety monitoring. A long-term safety analysis of the NOVA study assessed the incidence of TEAEs in patients receiving niraparib for up to 4 years. As of the most recent safety data cut (September 2017), approximately 20% of patients received niraparib for ≥ 2 years.[3]

Dose modifications due to TEAEs were common and most occurred during the first 3 months of niraparib therapy (Figure 8). In the niraparib arm, 34% of patients had their dose reduced in month 1, 27% in month 2, and 20% in month 3. Similarly, dose interruptions also decreased over the first 3 months of niraparib therapy (Figure 8). Treatment discontinuations due to TEAEs were < 5% across all months and time intervals reported.[3] TEAEs were managed by early dose modifications.[3,4]

Hematologic TEAEs

Any-grade thrombocytopenia events consistently decreased over the first 6 months of niraparib therapy: 49% in month 1, 34% in month 2, 8% in month 4 (Figure 9). By month 6, thrombocytopenia occurred at a rate of 2%. Grade ≥ 3 thrombocytopenia rates decreased from 28% to 9% between month 1 and month 2, and occurred in < 1% of patients by month 4, and remained < 1% until treatment discontinuation (Figure 10).[3]

Any-grade neutropenia events were 17% in month 1, 19% in month 2, and 8% in month 3 in the niraparib arm (Figure 9). By month 6, neutropenia occurred at a rate of 2%, and remained consistently low until discontinuation. Grade ≥ 3 neutropenia events were 9% in month 1, 12% in month 2, and 3% in month 3. By month 6, no patient in the niraparib arm experienced thrombocytopenia.[3]

Any-grade anemia events were 17% in month 1 and increased to 25% in month 3 in the niraparib arm (Figure 9). Anemia events decreased to 13% in month 5 and 6% in month 6. Grade ≥ 3 anemia events occurred in 2% of patients receiving niraparib in month 1, increased to 10% in month 3, returned to 5% by month 5, and remained < 5% thereafter (Figure 10).[3]

In the placebo arm, hematologic adverse events (any-grade and grade ≥ 3) occurred in < 5% of patients for all months and time intervals reported (Figure 9 and Figure 10).[3]

Symptomatic TEAEs

Any-grade symptomatic TEAEs were most common early on and decreased over the first 3 months of niraparib therapy (Figure 9). By month 6, monthly any-grade symptomatic TEAEs were < 5% until treatment discontinuation. Grade ≥ 3 symptomatic TEAEs were < 5% for all months and time intervals reported (Figure 10). In the niraparib arm, the mean (median) duration of fatigue was 533 days (330 days) vs 600 days (767 days) in the placebo arm. Patients who received niraparib for > 1 year continued to report fatigue, hypertension, nausea, vomiting, and diarrhoea.[3]

Hepatic TEAEs

In the niraparib arm, any-grade liver transaminase elevations (defined as ≥ three times the upper limit of normal [ULN]) were reported in 4% (n = 15) of patients in the niraparib arm vs 3% (n = 6) of patients in the placebo arm. Grade ≥ 3 liver transaminase elevations (defined as ≥ five times the ULN), occurred in 6 (2%) and 3 (2%) patients receiving niraparib and placebo, respectively. In the niraparib arm, 2 (1%) patients had concurrent elevated transaminase and bilirubin levels.[3]

Renal TEAEs

All-grade renal TEAEs (defined by creatinine levels > 1.5 times the ULN) were reported in 21 (6%) and 3 (2%) patients in the niraparib and placebo arms, respectively. Grade ≥ 3 renal TEAEs (defined by creatinine levels > three times the ULN) occurred in 2 (1%) patients and 2 (1%) patients in the niraparib and placebo arms, respectively.[3]

Acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) TEAEs

AML was reported in 2 patients (0.5 per 100 patient-years) in the niraparib arm and 1 patient (0.8 per 100 patient-years) in the placebo arm. MDS was reported in 6 patients (1.6 per 100 patient-years) receiving niraparib and 1 patient (0.8 per 100 patient-years) receiving placebo. Of these 10 instances of AML and MDS, one patient in the niraparib arm first developed MDS, and subsequently AML one year later. The onset of MDS occurred after treatment discontinuation in all cases: within 1 week to 15 months after treatment discontinuation for patients receiving niraparib and 8 months after treatment discontinuation for the patient receiving placebo. Three (2 niraparib and 1 placebo) of these 9 patients discontinued treatment due to progressive disease. MDS/AML occurred within 2 months of last exposure to study drug in five (4 niraparib and 1 placebo) of the 6 patients who discontinued treatment due to TEAEs.[3]

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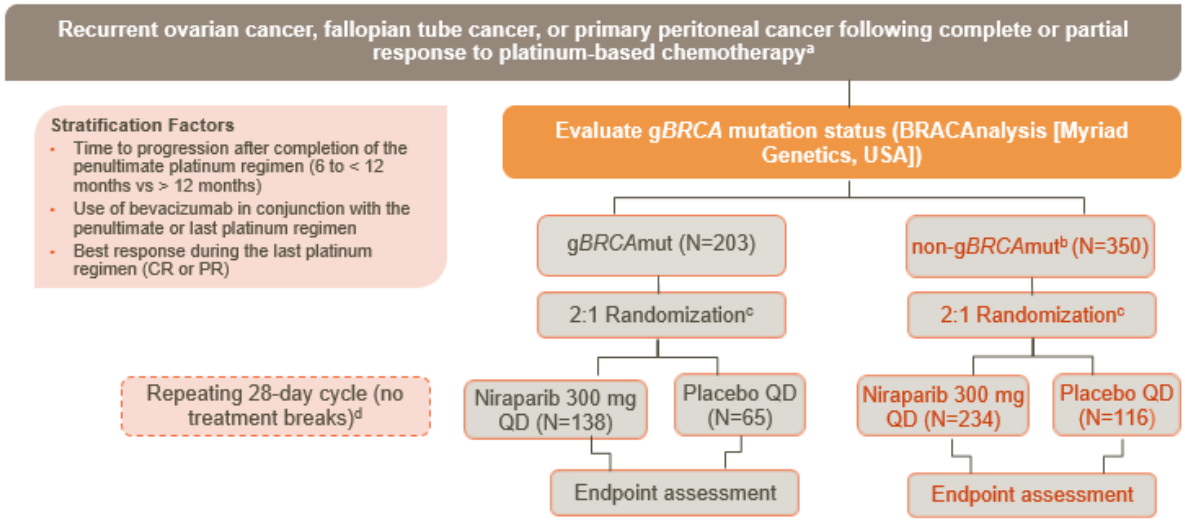
APPENDIX

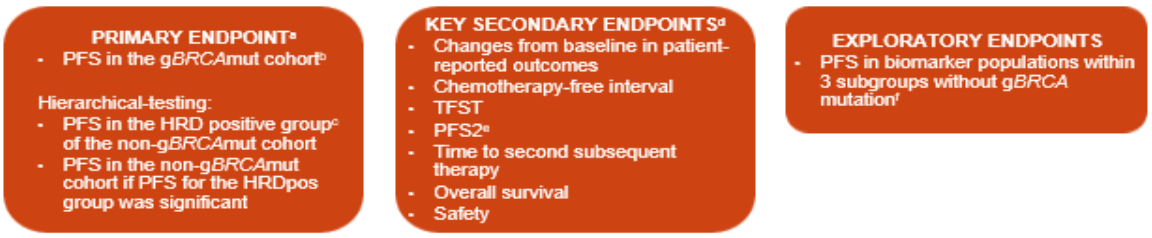
Figure 1A. NOVA Trial Design Schema[1]



[a]Patients who had a complete or partial response to penultimate platinum-based chemotherapy lasting ≥ 6 months; [b]In the non-g*BRCA*mut cohort, tumors were retrospectively defined as HRD by the myChoice HRD test (Myriad Genetics); [c]Randomization occurred no later than 8 weeks after completing the last dose of platinum-based chemotherapy; [d]Patients continued study treatment until disease progression, unacceptable toxicity, death, withdrawal of consent, or loss to follow-up, whichever came first.

CR = complete response; HRD=homologous recombination deficiency; PR = partial response; QD = once daily.

Figure 1B. NOVA Trial Design Endpoints[1]



[a]Efficacy endpoints were analyzed for the ITT population (all randomized patients); [b]The primary endpoint of PFS was defined as the time from treatment randomization to the earliest date of assessment of progression or death; [c]Defined as somatic *BRCA*mut and HRD positive/*BRCA*wt; [d]Safety was analyzed for the safety population (all patients who ingested any amount of study drug); [e]The time from treatment randomization to assessment of progression on the next anticancer therapy following study treatment or death by any cause (this encompasses time to second subsequent treatment if date for the second progression is not known); [f]HRD-positive plus somatic *BRCA* mutation, HRD-positive plus wild-type *BRCA*, and HRD-negative.

HRD=homologous recombination deficiency; ITT=intention-to-treat; mut=mutation; PFS = Progression-free survival; TFST = time to first subsequent treatment; wt = wild type.

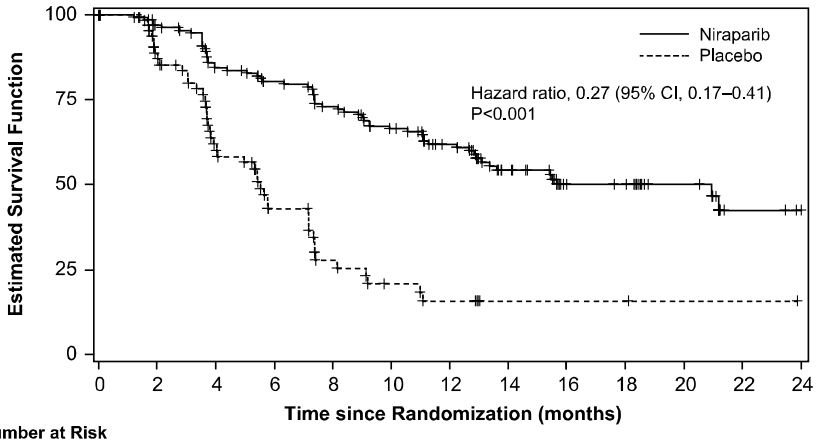
Table 1. Patient Demographic and Baseline Characteristics[1]

Characteristic	g*BRCA*mut		non-g*BRCA*mut	
	Niraparib (n = 138)	Placebo (n = 65)	Niraparib (n = 234)	Placebo (n = 116)
Age, median (range) — years	57 (36-83)	58 (38-73)	63 (33-84)	61 (34-82)
Race — n (%)				
White	123 (89.1)	55 (84.6)	201 (85.9)	101 (87.1)
Black/Asian/Other/Unknown	15 (10.9)	10 (15.4)	33 (14.1)	15 (12.9)
Ethnicity — n (%)				
Non-Hispanic	121 (87.7)	57 (87.7)	202 (86.3)	99 (85.3)
Hispanic/Other/Unknown	17 (12.3)	8 (12.3)	32 (13.7)	17 (14.7)
Region				
United States/Canada	53 (38.4)	28 (43.1)	96 (41.0)	44 (37.9)
Europe, Israel	85 (61.6)	37 (56.9)	138 (59.0)	72 (62.1)
Eastern Cooperative Oncology Group performance status — n (%)				
0	91 (65.9)	48 (73.8)	160 (68.4)	78 (67.2)
1	47 (34.1)	17 (26.2)	74 (31.6)	38 (32.8)
Primary tumor site[a] — n (%)				
Ovarian	122 (88.4)	53 (81.5)	192 (82.1)	96 (82.8)
Primary peritoneal	7 (5.1)	6 (9.2)	24 (10.3)	8 (6.9)
Fallopian tube	9 (6.5)	6 (9.2)	18 (7.7)	11 (9.5)
Cancer stage[b] — n (%)				
I-II	23 (16.7)	10 (15.4)	23 (9.8)	5 (4.3)
III-IIIB	14 (10.1)	10 (15.4)	24 (10.3)	20 (17.2)
IIIC	81 (58.7)	36 (55.4)	149 (63.7)	66 (56.9)
IV	20 (14.5)	9 (13.8)	38 (16.2)	24 (20.7)
Time to progression after penultimate platinum therapy — n (%)				
6 to < 12 months	54 (39.1)	26 (40.0)	90 (38.5)	44 (37.9)
≥ 12 months	84 (60.9)	39 (60.0)	144 (61.5)	72 (62.1)
Best response to most recent platinum therapy — n (%)				
Complete response	71 (51.4)	33 (50.8)	117 (50.0)	60 (51.7)
Partial response	67 (48.6)	32 (49.2)	117 (50.0)	56 (48.3)
Prior bevacizumab use — n (%)				
Yes	33 (23.9)	17 (26.2)	62 (26.5)	30 (25.9)
No	105 (76.1)	48 (73.8)	172 (73.5)	86 (74.1)
g*BRCA* mutations — n (%)				
*BRCA*1 mutation	85 (61.6)	43 (66.2)	–	–
*BRCA*2 mutation	51 (37.0)	18 (27.7)	–	–
*BRCA*1 and/or *BRCA*2 rearrangement	9 (6.5)	4 (6.2)	–	–
Prior lines of chemotherapy[c] — n (%)				
1	1 (0.7)	0	0	0
2	70 (50.7)	30 (46.2)	155 (66.2)	77 (66.4)
≥ 3	67 (48.6)	35 (53.8)	79 (33.8)	38 (32.8)
Prior platinum therapies — n (%)				
< 2	1 (0.7)	0	0	0
2	79 (57.2)	37 (56.9)	174 (74.4)	87 (75.0)
> 2	58 (42.0)	28 (43.1)	60 (25.6)	28 (24.1)
Unknown	0	0	0	1 (0.9)

[a]Data with respect to primary tumor site were not available for one patient in the placebo arm in the non-g*BRCA*mut cohort; [b]Staging was performed with the use of the International Federation of Gynecology and Obstetrics system. Data with respect to staging were not available for one patient in the placebo arm in the non-g*BRCA*mut cohort. One patient in the niraparib arm in the non-g*BRCA*mut cohort was stage 0 at time of diagnosis; [c]Data with respect to prior lines of chemotherapy were not available for one patient in the placebo arm in the non-g*BRCA*mut cohort.

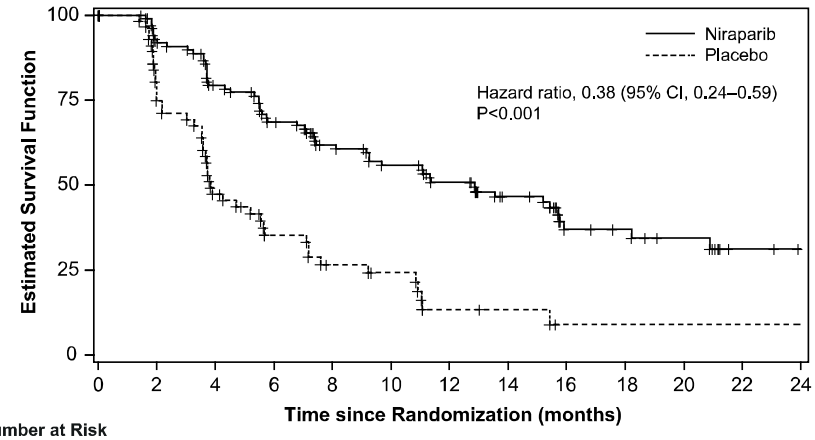
Figure 2. Kaplan-Meier Estimates of Progression-free Survival in the (A) g*BRCA*mut Cohort, (B) Non-g*BRCA*mut HRD-positive Group, and (C) Overall Non-g*BRCA*mut Cohort[1]

A



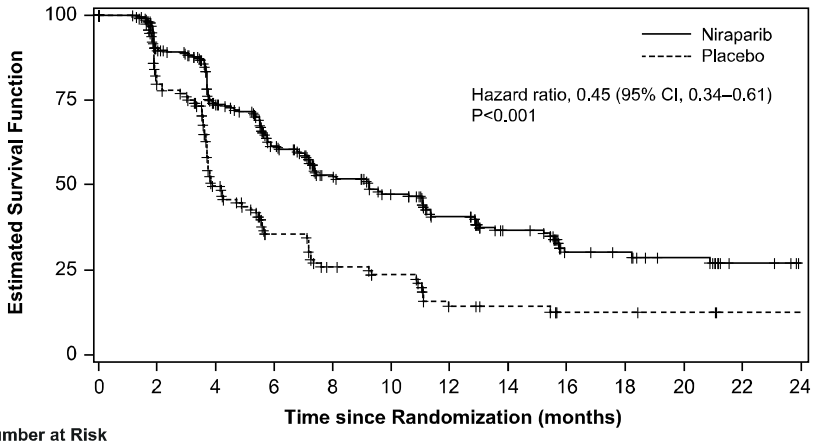
Number at Risk														Number of Events, no (%)	PFS median, months
Niraparib	138	125	107	98	89	79	63	44	28	26	16	3	1	59/138 (42.8)	21.0
Placebo	65	52	34	21	12	8	6	2	2	2	1	1	0	44/65 (67.7)	5.5

B



Number at Risk														Number of Events, no (%)	PFS median, months
Niraparib	106	90	75	64	52	46	40	29	16	14	11	4	2	56/106 (52.8)	12.9
Placebo	56	41	26	16	11	9	4	3	1	1	1	1	1	45/56 (80.4)	3.8

C



Number at Risk														Number of Events, no (%)	PFS median, months
Niraparib	234	188	145	113	88	75	57	41	23	21	16	7	3	125/234 (53.4)	9.3
Placebo	116	88	52	33	23	19	10	8	4	4	3	1	1	88/116 (75.9)	3.9

Figure 3. Subgroup Analyses of Progression-free Survival in the Three Primary Efficacy Populations[1]

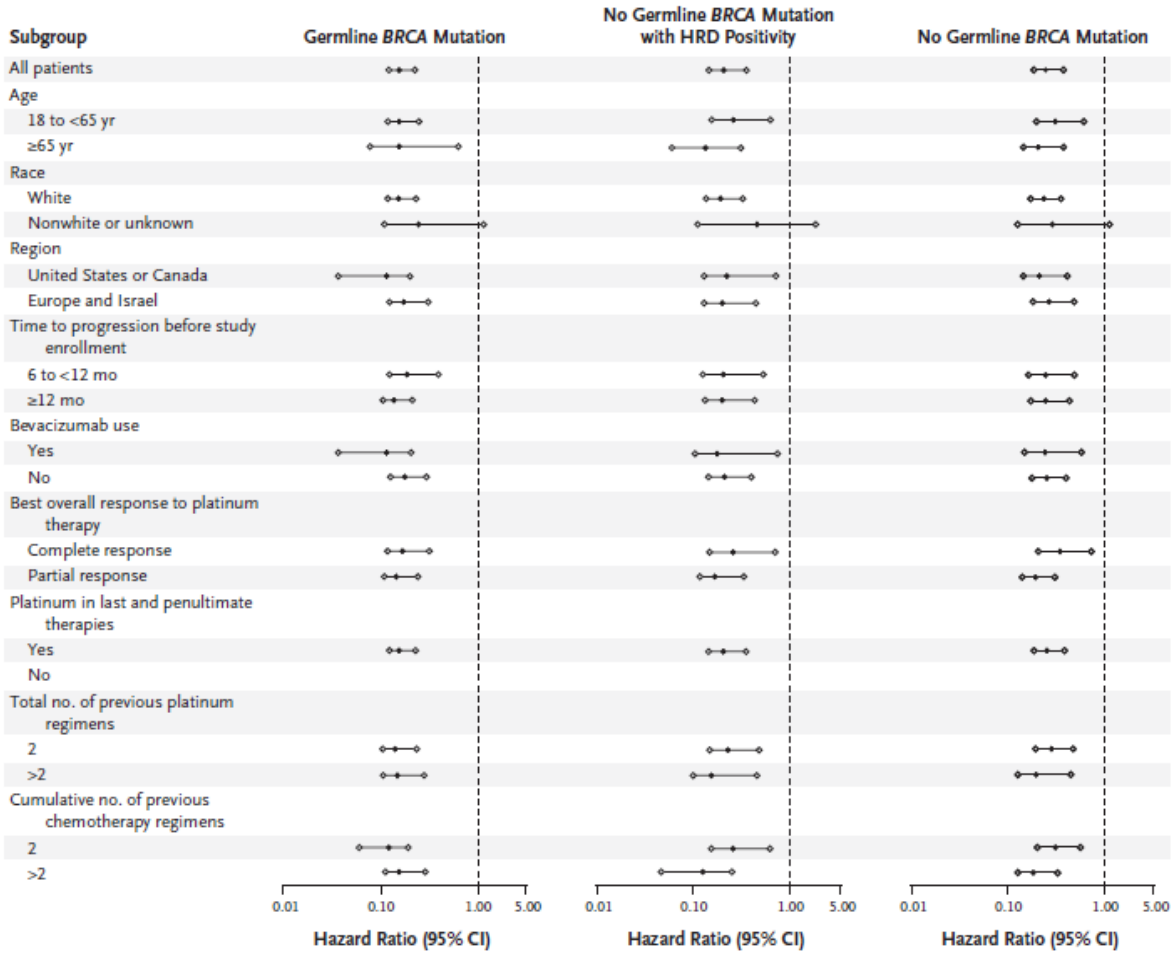


Table 2. Mature Secondary Endpoints: Chemotherapy-free Interval, Time to First Subsequent Therapy, Progression Free Survival 2[1]

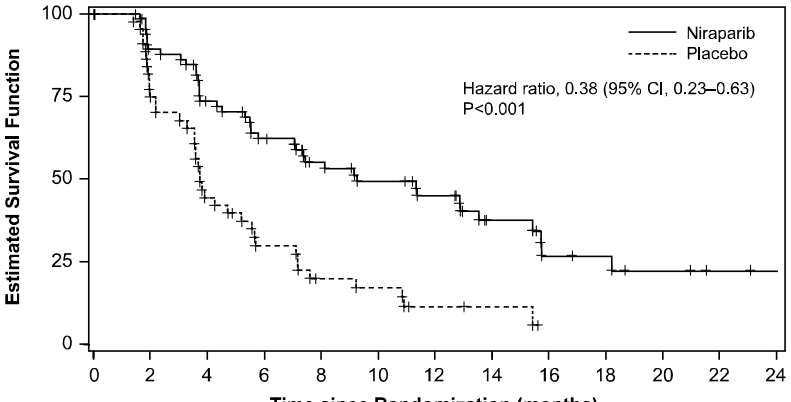
	g*BRCA*mut		non-g*BRCA*mut	
End point	**Niraparib (n = 138)**	**Placebo (n = 65)**	**Niraparib (n = 234)**	**Placebo (n = 116)**
Chemotherapy-free interval[a]				
Median, mo (95% CI)	22.8 (17.9–NR)	9.4 (7.9–10.6)	12.7 (11.0–14.7)	8.6 (6.9–10.0)
P value	< 0.001		< 0.001	
Hazard ratio (95% CI)	0.26 (0.17–0.41)		0.50 (0.37–0.67)	
Time to first subsequent therapy[b]				
Median, mo (95% CI)	21 (17.5–NR)	8.4 (6.6–10.6)	11.8 (9.9–13.1)	7.2 (5.7–8.5)
P value	< 0.001		< 0.001	
Hazard ratio (95% CI)	0.31 (0.21–0.48)		0.55 (0.41–0.72)	
Progression-free survival 2[c,d]				
Median, mo (95% CI)	25.8 (20.3–NR)	19.5 (13.3–NR)	18.6 (16.2–21.7)	15.6 (13.2–20.9)
P value	0.006		0.03	
Hazard ratio (95% CI)	0.48 (0.28–0.82)		0.69 (0.49–0.96)	

[a]Chemotherapy-free interval=the time from the last platinum dose until initiation of the next anticancer therapy; [b]Time to first subsequent therapy=the time from treatment randomization in the current study to the start date of the first subsequent anticancer therapies; [c]Progression-free survival 2=the time from treatment randomization to assessment of progression on the next anticancer therapy following study treatment or death by any cause. This encompasses time to second subsequent treatment if date for the second progression is not known; [d]Progression-free survival 2 was not mature at the time of database lock (June 20, 2016).

CI = confidence interval; g*BRCA*mut = germline *BRCA* mutation; HR = hazard ratio; NR = not reached.

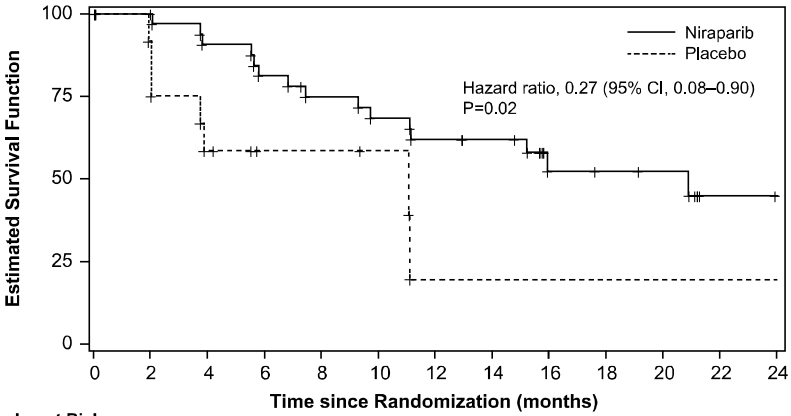
Figure 4. Kaplan-Meier Estimates of Progression-free Survival within the: (A) HRD-positive/*BRCA*wt Sub-group (B) HRD-positive/s*BRCA*mut Sub-group, and (C) non-g*BRCA*mut HRD-negative Group[1]

A



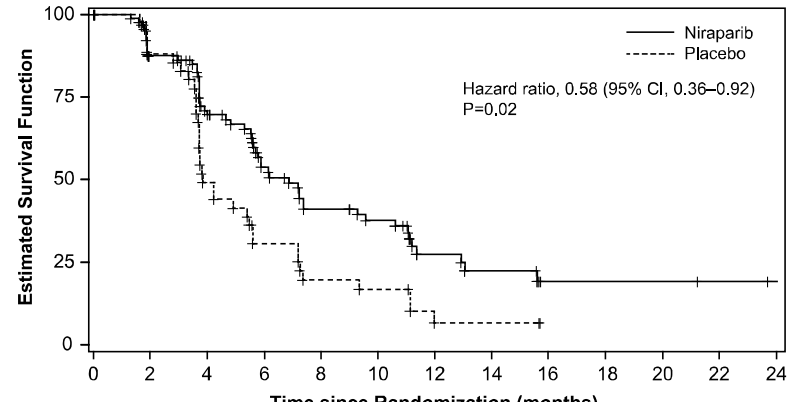
Number at Risk														Number of Events, no (%)	PFS median, months
Niraparib	71	58	46	38	29	25	21	12	7	6	4	2	1	41/71 (57.7)	9.3
Placebo	44	32	19	12	7	6	3	2	0					38/44 (86.4)	3.7

B



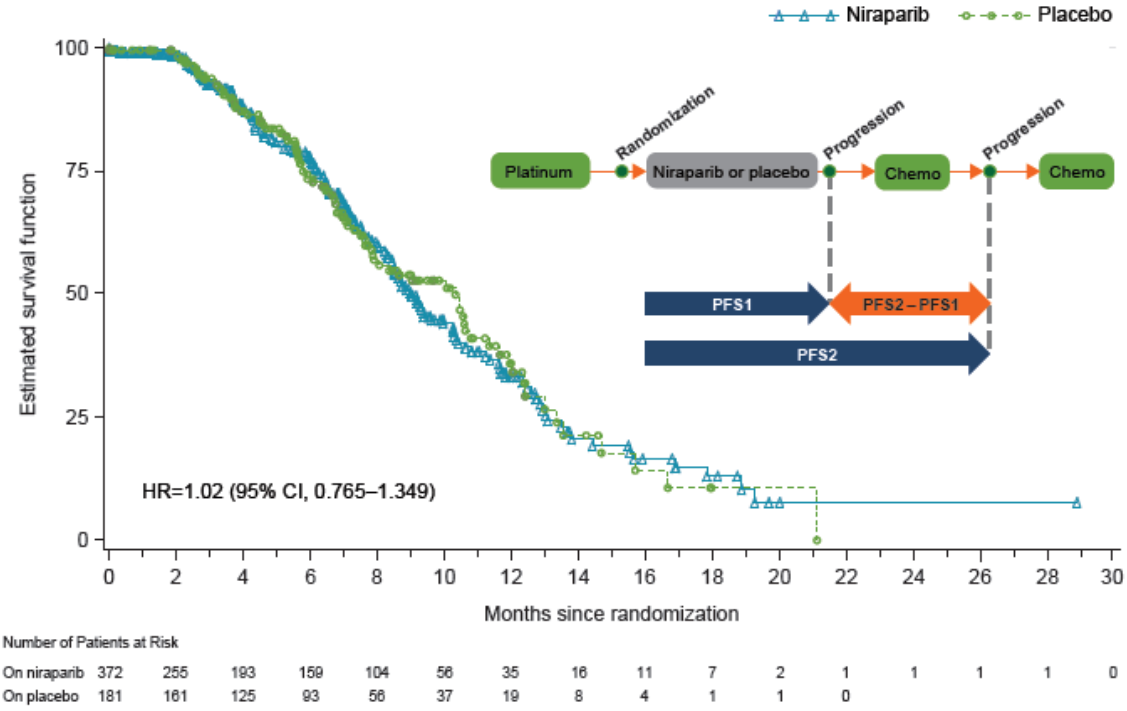
Number at Risk														Number of Events, no (%)	PFS median, months
Niraparib	35	32	29	26	23	21	19	17	9	8	7	2	1	15/35 (42.9)	20.9
Placebo	12	9	7	4	4	3	1	1	1	1	1	1	1	7/12 (58.3)	11.0

C



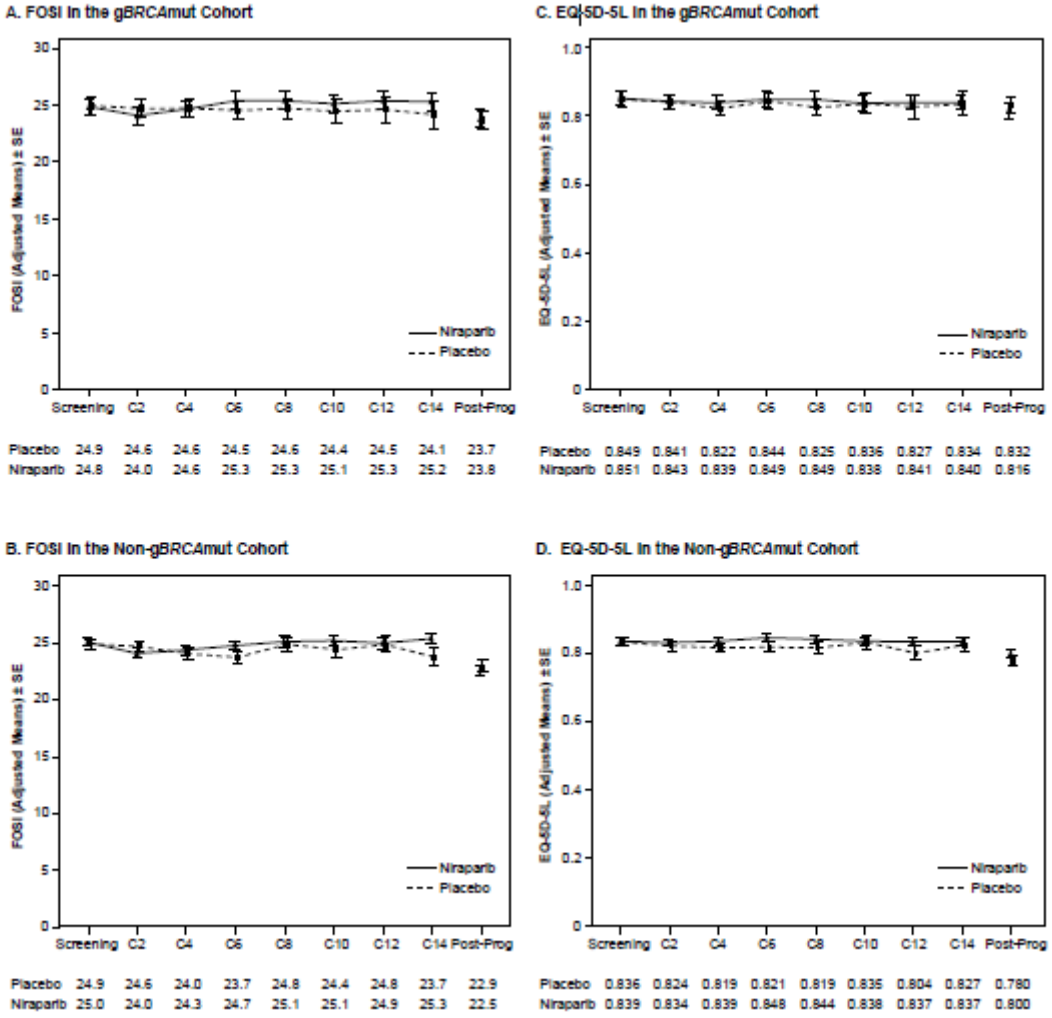
Number at Risk														Number of Events, no (%)	PFS median, months
Niraparib	92	73	54	35	26	22	11	8	3	3	3	2	1	54/92 (58.7)	6.9
Placebo	42	35	19	11	7	6	2	2	0					35/42 (83,3)	3,8

Figure 5. Time to Progression with Subsequent Therapy (PFS2-PFS1) In the Pooled g*BRCA*mut and non-g*BRCA*mut Cohorts[5]



Chemo = chemotherapy; CI = confidence interval; g*BRCA*mut = germline breast cancer susceptibility gene mutation; HR = hazard ratio; PFS = progression-free survival.

Figure 6. Patient-reported Outcomes (FOSI and EQ-5D-5L) in the g*BRCA*mut Cohort (A and C) and the Non-g*BRCA*mut Cohort (B and D)[1]



Note: Values are displayed are adjusted means; a higher score indicates fewer symptoms (FOSI) and better health (EQ-5D-5L).
C = cycle; EQ-5D-5L = European Quality of Life Scale, 5-Dimensions; FOSI = Functional Assessment of Cancer Therapy-Ovarian Symptom Index. Post-Prog = post-progression; SE = standard error.

Table 3. Summary of TEAEs[1]

Adverse Event	Niraparib (n = 367), n (%)	Placebo (n = 179), n (%)
Any TEAE	367 (100)	171 (95.5)
Any Related TEAE	358 (97.5)	127 (70.9)
Any CTCAE Grade ≥ 3 TEAE	272 (74.1)	41 (22.9)
Any related CTCAE Grade ≥ 3 TEAE	237 (64.6)	8 (4.5)
Any Serious TEAE	110 (30)	27 (15.1)
Any Related Serious TEAE	62 (16.9)	2 (1.1)
Any TEAE Leading to Treatment Interruption	253 (68.9)	9 (5)
Any TEAE Leading to Dose Reduction	244 (66.5)	26 (14.5)
Any TEAE Leading to Treatment Discontinuation	54 (14.7)	4 (2.2)

CTCAE=Common Terminology Criteria for Adverse Events, TEAE=treatment-emergent adverse event

Table 4. Grade 3/4 TEAEs Occurring in ≥ 5% of Patients and Grade 3/4 TEAEs Occurring After Cycle 3 in the Niraparib Group[2]

Adverse Event	Niraparib (n = 367), n (%)	Placebo (n = 179), n (%)	Niraparib: Events that Occurred After Cycle 3 (n = 296), n (%)
Thrombocytopenia events[a]	124 (33.8)	1 (0.6)	7 (2.4)
Anemia events[b]	93 (25.3)	0	50 (16.8)
Neutropenia events[c]	72 (19.6)	3 (1.7)	8 (2.7)
Fatigue[d]	30 (8.2)	1 (0.6)	9 (3)
Hypertension	30 (8.2)	4 (2.2)	0

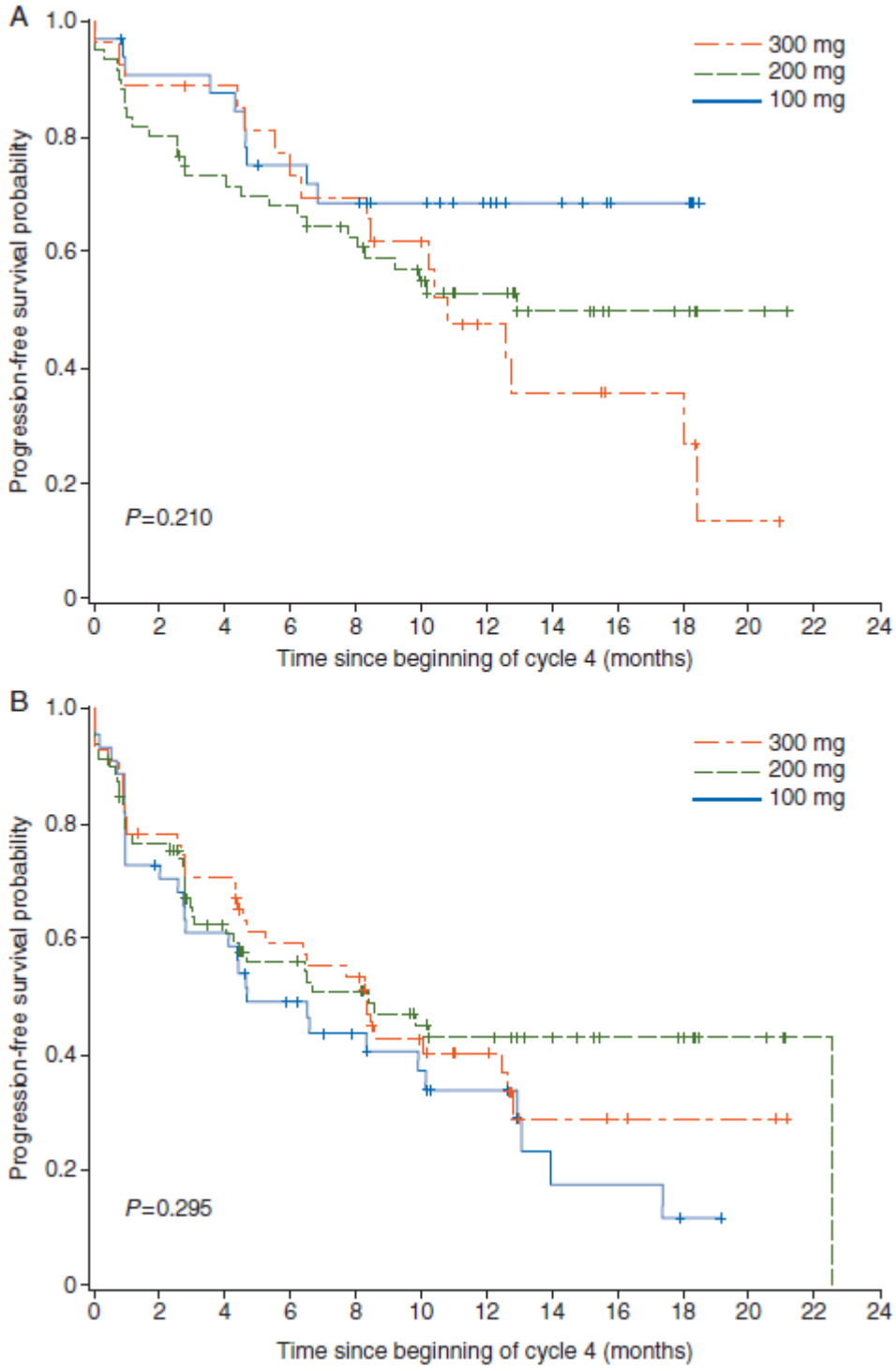
[a]Thrombocytopenia include reports of thrombocytopenia and decreased platelet count. No grade 3 or 4 bleeding events were associated with thrombocytopenia; [b]Anemia includes reports of anemia and decreased hemoglobin counts [c]Neutropenia include reports of neutropenia, decreased neutrophil count, and febrile neutropenia; [d]Fatigue include reports of fatigue, asthenia, malaise, and lethargy.

Table 5. Niraparib Dose Reductions and Discontinuations for Select TEAE of Any Grade[2]

Adverse Event - n (%)	Dose Reductions (n = 367)	Dose Discontinuations (n = 367)
Thrombocytopenia events[a]	148 (40.3)	12 (3.3)
Anemia events[b]	68 (18.5)	5 (1.4)
Neutropenia events[c]	32 (8.7)	7 (1.9)
Fatigue[d]	20 (5.4)	12 (3.3)
Hypertension	5 (1.4)	1

[a]Thrombocytopenia include reports of thrombocytopenia and decreased platelet count. No grade 3 or 4 bleeding events were associated with thrombocytopenia; [b]Anemia includes reports of anemia and decreased hemoglobin counts [c]Neutropenia include reports of neutropenia, decreased neutrophil count, and febrile neutropenia; [d]Fatigue include reports of fatigue, asthenia, malaise, and lethargy.

Figure 7. Estimated Progression-Free Survival Probability by Dose Level Measured After Cycle 3 for Patients in the (A) g*BRCA*mut and (B) non-g*BRCA*mut Cohorts[4]



BRCA=breast cancer susceptibility gene; *BRCA*mut=*BRCA* mutation; PFS=progression-free survival

Figure 8. Dose Modifications Due to Treatment-emergent Adverse Events[3]

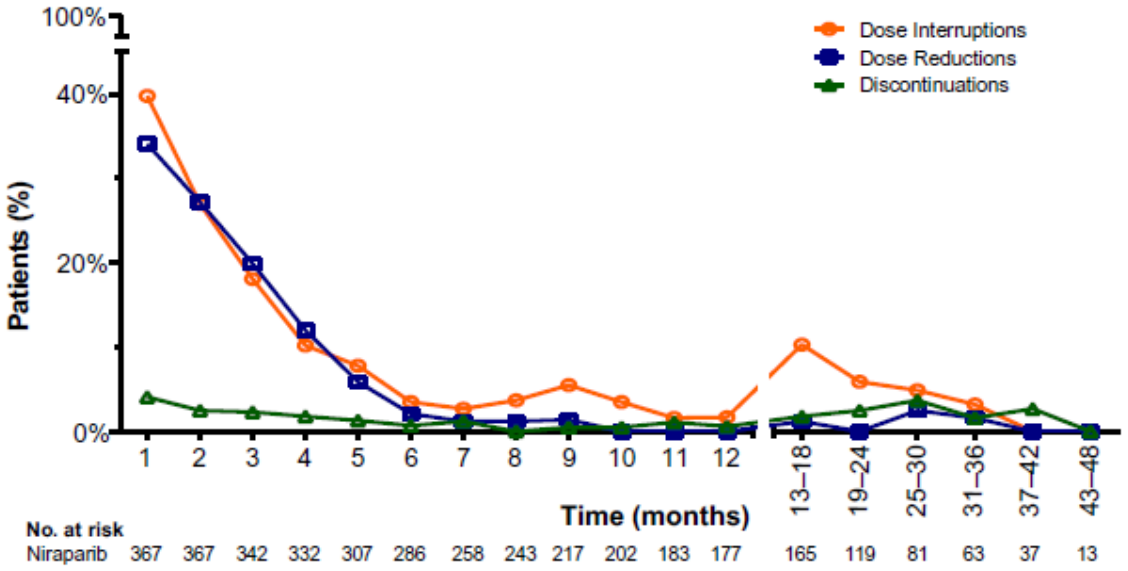


Figure 9. Any-Grade Selected Treatment-Emergent Adverse Events Up To 4 Years of Niraparib Exposure[3]

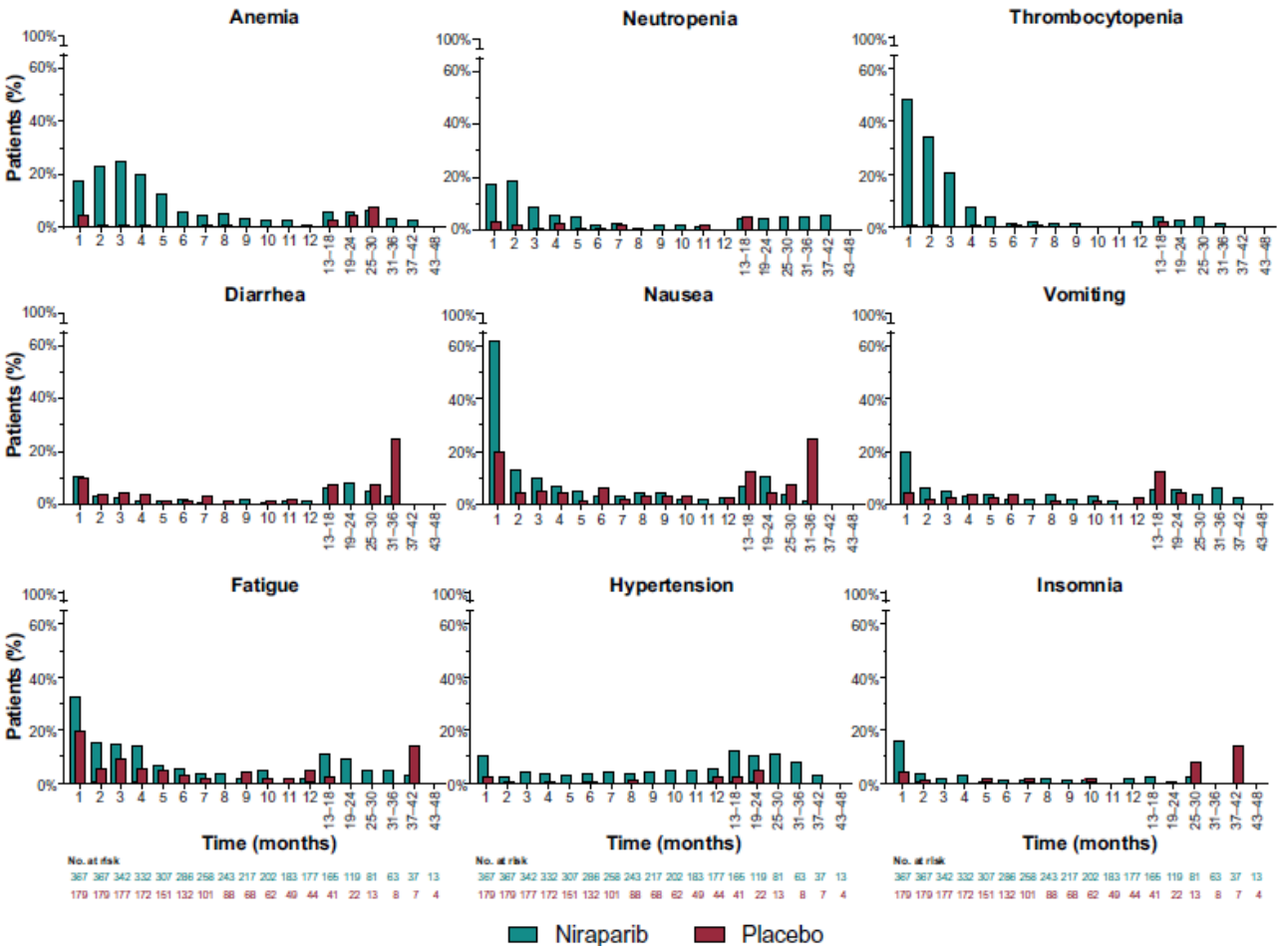


Figure 10. Grade ≥ 3 Select Treatment-emergent Adverse Events Up To 4 Years of Niraparib Exposure[3]