Niraparib – QUADRA Clinical Trial Overview

Summary

- A phase 2 clinical study (QUADRA) evaluated the safety and efficacy of niraparib in ovarian cancer (OC) patients following 3 or more lines of previous chemotherapy, regardless of *BRCA* or homologous recombination deficiency (HRD) status, platinum eligibility, or prior PARP inhibitor use.[1]
    - The study met the primary endpoint showing a 28% objective response rate (ORR) (95% CI 15.6 – 42.6, *P* = 0.00053) in platinum-sensitive, PARP inhibitor (PARPi) naïve, 4th or 5th line, HRD positive (HRDpos) patients (n = 47).
    - Responses were seen across all evaluated patient subgroups regardless of *BRCA*, HRD, or platinum status (Table 1 and Figure 4).
        - A gradient of clinical activity was observed, with greatest activity demonstrated in patients with platinum-sensitive disease and *BRCA*-mutated tumors (ORR 39%).
    - Among all evaluable patients with measurable disease at baseline treated 4th line or later (modified per-protocol population), the median duration of response (mDOR) was 9.4 months and median overall survival (mOS) was 17.2 months.
        - mOS was 28 months for patients who responded, or had SD, for at least 24 weeks.
    - Safety was consistent with previous clinical trial experience and the most common grade ≥ 3 treatment emergent adverse events (TEAEs) were anemia (24%) and thrombocytopenia (21%).
- Some information contained in this response is outside the approved local label for niraparib. This product is not approved for the use described.

PHASE 2 CLINICAL STUDY

Study Design & Treatment

QUADRA (NCT02354586) was an open-label, single arm, phase 2 clinical study that evaluated the safety and efficacy of niraparib in patients (N = 463) with ovarian cancer following 3 or more lines of previous chemotherapy. Following enrollment of 292 patients, the study was amended to limit to 3 or 4 previous chemotherapy regimens in order to narrow the focus of QUADRA. The amendment also required that patients experienced a response lasting at least 6 months to 1st line platinum-based therapy.[1]

Oral niraparib 300 mg was administered once daily continuously during a 28-day cycle (Figure 1). The primary endpoint was to evaluate the ORR in HRDpos, platinum-sensitive, PARPi naïve patients who received 3 or 4 lines of previous chemotherapy.[1]

Patients Results

To be considered eligible for the QUADRA study, patients were required to have measurable, advanced, high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer. Patients must have received 3 or more previous chemotherapy regimens (e.g. gemcitabine, doxorubicin, topotecan,

carboplatin, oxaliplatin, cisplatin, bevacizumab) and completed their last chemotherapy regimen > 4 weeks prior to treatment initiation. Tumor HRD testing and blood germline *BRCA* testing was required for enrollment, however status did not affect study eligibility. Patients who received prior treatment with a PARPi were eligible for QUADRA. Patients were excluded if they had known, persistent (> 4 weeks), grade 3 or higher hematologic toxicity or fatigue during their last cancer therapy. Patients could not have received pelvic radiotherapy within 1 year of the first dose of study treatment or a transfusion (platelets or red blood cells) within 4 weeks of the first dose.[1]

In the safety population (N = 463), the median time from diagnosis was 4 years, the median time from last chemotherapy to first dose of niraparib was 2 months (range 1-73), and 62% of patients had received prior bevacizumab. Overall, 68% of patients were platinum-resistant or -refractory, 27% were in 6th line of anti-cancer therapy or later, 19% were *BRCA*mut (germline or somatic), 48% were HRDpos (*BRCA*mut or *BRCA* wild type [*BRCA*wt] patients with genomic instability), 81% were *BRCA*wt/unknown, and 52% were HRDneg/unknown (Figure 2). Five patients were determined to have received only 2 prior lines of therapy, these patients are not included in further analyses.[1]

Efficacy Results

The primary efficacy population of 4th and 5th line, PARPi naïve, platinum-sensitive, HRDpos patients (n = 47) achieved an ORR of 28% (95% CI 15.6 – 42.6, P = 0.00053). The median duration of progression-free survival (PFS) in this population was 5.5 months and mDOR was 9.2 months.[1]

Of 463 patients that received at least one dose of niraparib, 456 had measurable disease at baseline. The mDOR in the modified per-protocol population was 9.4 months and mOS was 17.2 months (Figure 3). The proportion of PARPi naïve patients in the modified per-protocol population that achieved a confirmed overall response is shown in Table 1 by biomarker and platinum status. A gradient of clinical activity was observed, with greatest activity demonstrated in patients with platinum-sensitive disease and *BRCA*-mutated and HRD-positive tumors. This continuum was also manifested through overall survival; mOS was 26.0 months in the *BRCA*-mutated population, 19.0 months in the HRD-positive population, and 15.5 months in the HRD-negative population.[1]

The proportion of patients with clinical benefit has been positively associated with overall survival, especially for those remaining progression-free for ≥ 6 months. Therefore post-hoc analyses were conducted to assess the clinical benefit at 16 (CB16) and 24 weeks (CB24). CB24 by platinum status and molecular biomarker is shown in Table 1 and Figure 4. Although a low proportion of patients achieved an overall response in the HRD-negative or unknown population, 24% of these patients had clinical benefit at 16 weeks and 14% clinical benefit at 24 weeks. Additionally, mDOR was similar for all biomarker subgroups; *BRCA*-mutated 9.2 months, HRD-positive 9.2 months, HRD-negative 10.1 months.[1]

Further post-hoc exploratory analyses were performed to evaluate whether niraparib treatment contributed to disease stabilization beyond the natural history of a patient's disease. PFS ratio was calculated, which was defined as each patient's individual time to progression on niraparib monotherapy divided by PFS on the preceding line of therapy. Overall, 35% of 187 patients treated in the 4th line or later with best overall response of SD had a PFS ratio > 1.3, with a mean increase of 4.1 months on niraparib therapy compared to the most recent line of therapy; 82% of patients had a PFS ratio > 1.0. The PFS ratio in patients with SD was similar regardless of molecular biomarker status (Table 2).[1]

A post-hoc analysis of OS by the proportion of patients achieving clinical benefit at 24 weeks showed that patients with SD for at least 24 weeks had a mOS similar to that of patients achieving a partial or complete response – 28 months for both subgroups. OS benefit did not appear to be driven by molecular biomarker status. Survival curves for all biomarker subgroups were similar among patients who responded, or had SD, for at least 24 weeks (Figure 5).[1]

BRCAmut Subset

Out of the 461 patients with measurable disease at baseline, there were 63 PARP-naive patients with a *BRCA* mutation. Response rates in the *BRCA*mut subset followed a continuum based on platinum-sensitivity status. To describe clinically meaningful disease stabilization, additional ad hoc exploratory analyses were performed to assess CB at 16 and 24 weeks (Table 3). ORRs were similar among patients

with g*BRCA* (n = 36, 25%) and s*BRCA* (n = 27, 33%) mutations, as well as *BRCA*1mut (n = 38, 32%) and *BRCA*2mut (n = 18, 33%).[2]

Responses were durable in patients with *BRCA*mut tumors, with mDOR of 9.2 months (95% CI 7.4 – not estimable [NE]). Patients with *BRCA* mutations had durable responses regardless of platinum status: mDOR NE (95% CI 6.5 to NE) in patients with platinum-sensitive disease, mDOR 7.4 months (95% CI 4.7 – NE) in patients with platinum-resistant disease, and mDOR was NE (95% CI 3.8 – NE) in patients with platinum-refractory disease (Figure 6).[2]

The continuum of clinical activity according to platinum sensitivity in patients with tumors bearing *BRCA* mutations was further demonstrated by progression-free survival (PFS) and OS analyses. The median PFS (mPFS) was 6.3 months (95% CI 5.4 to 8.2) overall. In comparison, PFS in patients with platinum-sensitive, -resistant and -refractory disease was 11.0 months (95% CI 5.5 – NE), 5.4 months (95% CI 1.8 – 10.1), and 5.7 months (95% CI 1.8 – NE), respectively (Figure 7).[2]

The median OS was 26.0 months (95% CI 18.1 – NE) in the patients with *BRCA* mutations and NE (95% CI 19.0 – NE), 26.0 months (95% CI 6.4 – NE), and 23.3 months (95% CI 7.0 – NE) in patients with platinum-sensitive, -resistant and -refractory disease, respectively (Figure 8).[2]

Biomarker-Driven Population

Patients with *BRCA*mut tumors, regardless of platinum-sensitivity status (n = 63) or patients with non-*BRCA*mut HRDpos platinum-sensitive disease (n = 35), comprise a population of 98 patients with an ORR of 25.5% (95% CI 17.2 to 35.3). In this biomarker-driven population, the following efficacy was observed: mDOR 8.3 months (95% CI 6.6 – NE), mPFS 5.5 months (95% CI 3.7 – 7.4), mOS 23.3 months (95% CI 17.2 – 28.0), CB16 48.0% (95% CI 37.8 – 58.3), and CB24 35.7% (95% CI 26.3 – 46.0) (Figure 9). The best response in this biomarker-driven population is shown in Figure 10.[2]

PARPi-Retreated Population

456 patients were in the modified intent-to-treat population. Of these patients, 37 had prior PARPi exposure (treatment or maintenance) listed, and 35 were response-evaluable. The patient demographics are shown in Table 4. Prior PARPis include: niraparib (n = 13), olaparib (n = 19), rucaparib (n = 2) and veliparib (n = 4). One patient had prior treatment with both niraparib and olaparib. PARPis were used in combination for 11 patients and as single agents for 26 patients. Progression while on PARPi-treatment (PARPi-refractory) was reported in 33 patients.[3]

Two patients of the 35 evaluable patients (6%) reported a PR: one confirmed, one unconfirmed. The patient with the confirmed PR was not considered PARPi-refractory. The DCR was 37% (41% including the unconfirmed PR). The CB at 16 weeks was 20% and at 24 weeks was 5% (22% and 8% including the unconfirmed PR, respectively). The CA-125 relative percent change from baseline by best response is shown in Figure 11. Outcomes in the PARPi-retreatment group, by *BRCA* mutation, HRD status and platinum sensitivity, are shown in in Figure 12.[3]

Treatment discontinuation due to adverse events (AEs) were similar for patients with prior PARPi exposure (n = 37) compared to all patients in the safety population (N = 463), 22% and 20% respectively. TEAEs did not increase in patients with prior PARPi exposure compared with those who were PARPi-naïve (Table 5). No acute myeloid leukemia/myelodysplastic syndrome cases were reported among patients re-treated with PARPi.[3]

Safety Results

At a starting dose of 300 mg of niraparib, the most commonly observed TEAEs were consistent with prior clinical experience and included myelosuppression, which was generally managed via dose modifications. The percentage of patients who experienced a TEAE resulting in dose interruption, reduction, or withdrawal was 62%, 47%, and 21%, respectively. Serious TEAEs were observed in 43% of patients, and those reported in at least 5% of patients were small intestinal obstruction (n = 34), thrombocytopenia (n = 34), and vomiting (n = 27). No new safety signals were detected. After dose modification, 200 mg was the most commonly administered dose in the QUADRA study (Figure 13).[1,4]

One patient out of 463 (0.2%) experienced myelodysplastic syndrome/acute myeloid leukemia (MDS/AML) and one patient had a treatment-related Grade 5 gastric hemorrhage. See Table 6 for a list of common (> 15%) drug-related TEAEs observed in the safety population.[1]

Post-Hoc Analysis of Baseline Body Weight and Platelet Count as Predictors of Early Dose Modification

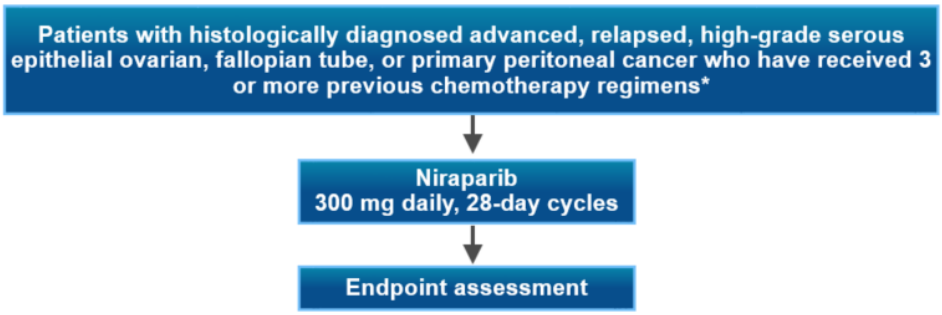
In the QUADRA study, all patients were started at niraparib 300 mg daily. After dose modification, 200 mg was the most commonly administered dose. An exploratory post hoc analysis was performed on all treated patients in QUADRA by baseline weight and baseline platelet count to evaluate if individualized dosing would reduce the incidence of toxicities without compromising efficacy. Patients with baseline body weight < 77 kg or baseline platelet count < 150,000/μL had greater incidence of grade ≥ 3 TEAEs and dose modifications in the first 30 days. Hematologic TEAEs (any grade and grade ≥ 3) were more frequent with lower baseline body weight or platelet count. According to the retrospective analysis, early dose modification to an average daily dose of ≤ 200 mg did not negatively impact ORR or CB24 in the all-comer or the biomarker-defined populations. The biomarker-defined population included patients who had homologous recombination deficiency (HRDpos), platinum-sensitive tumors or *BRCA*mut tumors of platinum-sensitivity, and no prior PARPi therapy. Additionally, OS did not appear compromised among patients with baseline body weight < 77 kg or baseline platelet count < 150,000/μL in the all-comer population, despite a lower average niraparib dose.[4]

REFERENCES

1. Moore KN, Alvarez Secord A, Geller MA, et al. Niraparib monotherapy for late-line treatment of ovarian cancer (QUADRA): a multicenter, open-label, single-arm phase 2 trial. *Lancet Oncol*. April 1, 2019. http://dx.doi.org/10.1016/ S1470-2045(19)30087-7.
2. Moore KN, Alvarez Secord A, Geller M, et al. QUADRA: A phase 2, open-label, single-arm study to evaluate niraparib in patients with relapsed ovarian cancer in 4th line or later line of therapy; results from the *BRCA*mut subset. Presented at the European Society of Medical Oncology Meeting. October 19-23, 2018; Munich, Germany. Poster 944P.
3. Rimel BJ, Secord AA, Geller MJ, et al. Safety and Efficacy Results of Retreatment With PARP Inhibitor Monotherapy in Late-Line Recurrent Ovarian Cancer: Results From a Subset of the QUADRA Trial. Presented at Western Association of Gynecologic Oncology. Jun 12-15, 2019. Abstract 8.
4. Matulonis UA, Monk BJ, Alvarez Secord A, et al. Baseline platelet count and body weight as predictors of early dose modification in the QUADRA trial of niraparib monotherapy for the treatment of heavily pretreated (≥4th line), advanced, recurrent high-grade serous ovarian cancer. Presented at the Society of Gynecologic Oncology Annual Meeting. March 16-19, 2019; Honolulu, HI. Scientific Plenary 2.

APPENDIX

Figure 1. QUADRA Trial Design Schema[1]

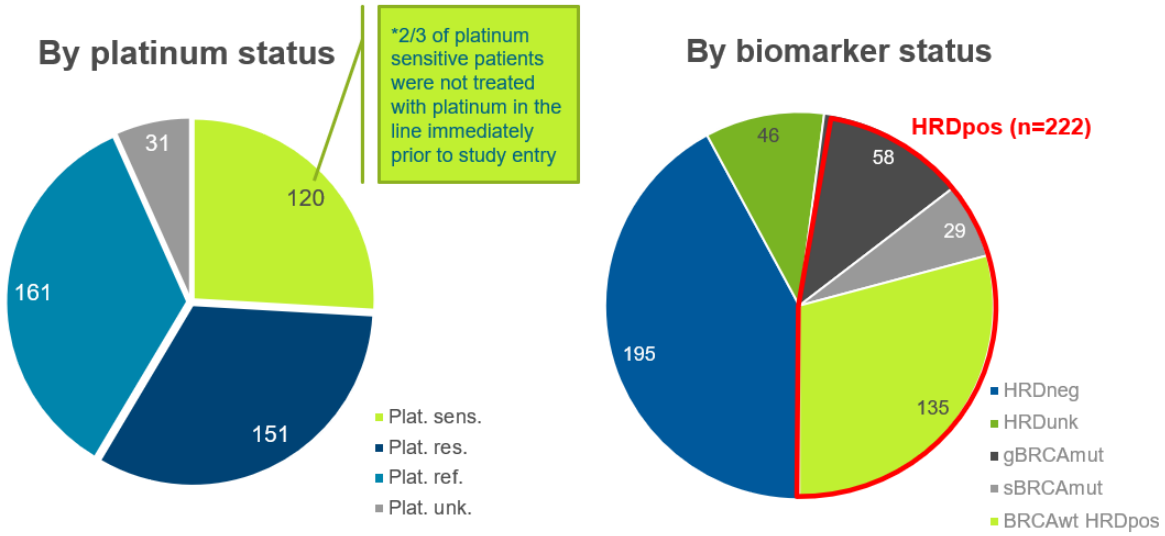


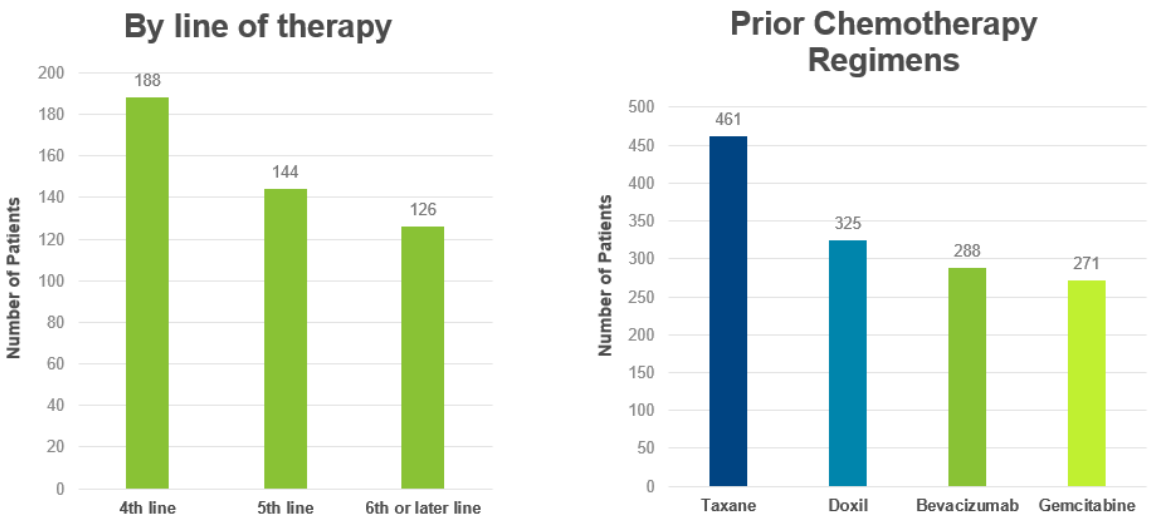
Primary Endpoint	Investigator-assessed ORR (defined as the proportion of patients achieving CR or PR) per RECIST v1.1 in HRD-positive patients who have received 3 or 4 lines of anti-cancer therapy¥ and are platinum-sensitive to the last platinum-based therapy.
Select Secondary Endpoints	• Investigator-assessed ORR per RECIST v1.1 in all patients who have received 3 or 4 lines of anti-cancer therapy¥ and are either: - Platinum-sensitive to the last platinum-based therapy, or - Platinum-sensitive or platinum-resistant to the last platinum-based therapy • DOR, DCR, PFS, TFST, and OS in patient who have received 3 or 4 lines of anti-cancer therapy, and in all patients regardless of prior lines of anti-cancer therapy • Safety and tolerability • PK measures • Exploratory biomarkers

*e.g. gemcitabine, doxorubicin, topotecan, carboplatin, oxaliplatin, cisplatin, bevacizumab, PARP inhibitors, ¥Patients with prior PARP treatment are excluded

CR = complete response; PR = partial response; HRD = homologous recombination deficiency; DOR = duration of response; DCR = disease control rate; PFS = progression free survival; TFST = time to first subsequent treatment; OS = overall survival

Figure 2. Patient Characteristics in the QUADRA Study (Safety Population, N = 463)[1]





Plat. sens. = platinum sensitive (time from last platinum until next progression ≥ 6 months), including platinum ineligible; Plat. res. = platinum resistant (time from last platinum until next progression between 28 days and 6 months); Plat. ref. = platinum refractory (progression on or within 28 days from last platinum); Plat. unk. = platinum status unknown; *BRCA*mut = breast cancer susceptibility gene mutant; g*BRCA*mut = germline *BRCA* mutant; s*BRCA*mut = somatic *BRCA* mutant; *BRCA*wt = *BRCA* wild-type; HRD = homologous recombination deficiency; HRDpos = HRDpositive; HRDneg = HRD negative; HRDunk = HRD unknown

Figure 3. Estimated (A) Duration of Response and (B) Overall Survival in the Modified Per-Protocol Population (N = 456)[1]

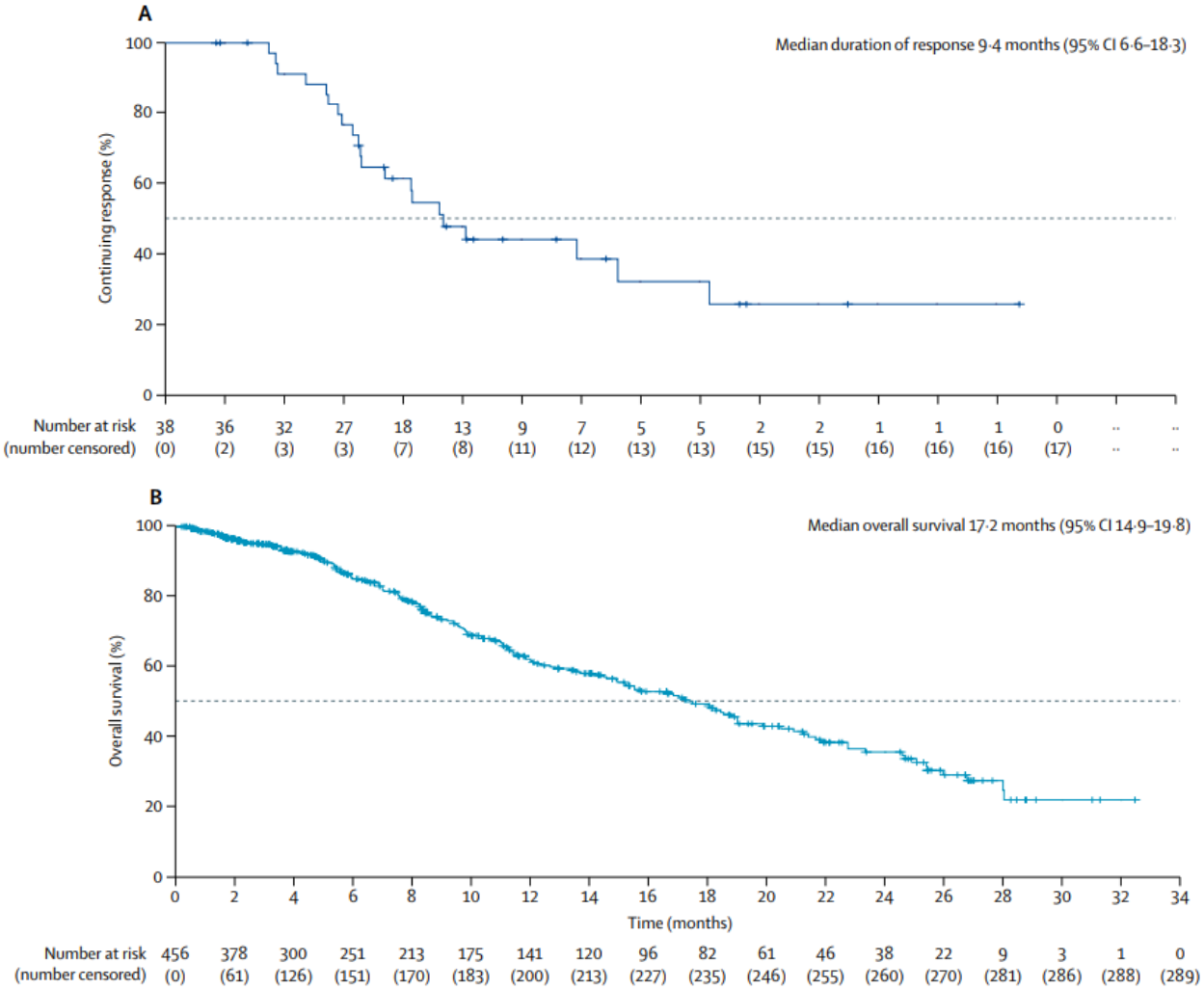


Table 1. Proportion of Patients with a Confirmed Overall Response and CB24 by Molecular Biomarkers and Platinum Status, PARPi Naïve Modified Per-Protocol Population[1]

	***BRCA*-mutated (n = 63)**		**HRD-positive* (n = 189)**		**HRD-negative or unknown (n = 230)**	
	ORR, %, n/N	**CB24, %, n/N**	**ORR, %, n/N**	**CB24, %, n/N**	**ORR, %, n/N**	**CB24, %, n/N**
Platinum-sensitive to most recent line of platinum therapy	39% (7/18)	56% (10/18)	26% (14/53)	40% (21/53)	4% (2/52)	19% (10/52)
Platinum-resistant or -refractory	27% (10/37)	32% (12/37)	10% (12/120)	20% (24/120)	3% (5/169)	11% (18/169)
Platinum status unknown	13% (1/8)	25% (2/8)	19% (3/16)	31% (5/16)	11% (1/9)	56% (5/9)
All	29% (18/63)	38% (24/63)	15% (29/189)	26% (50/189)	3% (8/230)	14% (33/230)

*****Includes patients with *BRCA*-mutated and non-*BRCA*-mutated tumors

ORR = objective response rate; CB24 = clinical benefit at 24 weeks; HRD = homologous recombination deficiency

Figure 4. CB24 in Biomarker-defined Groups by Platinum Status[1]

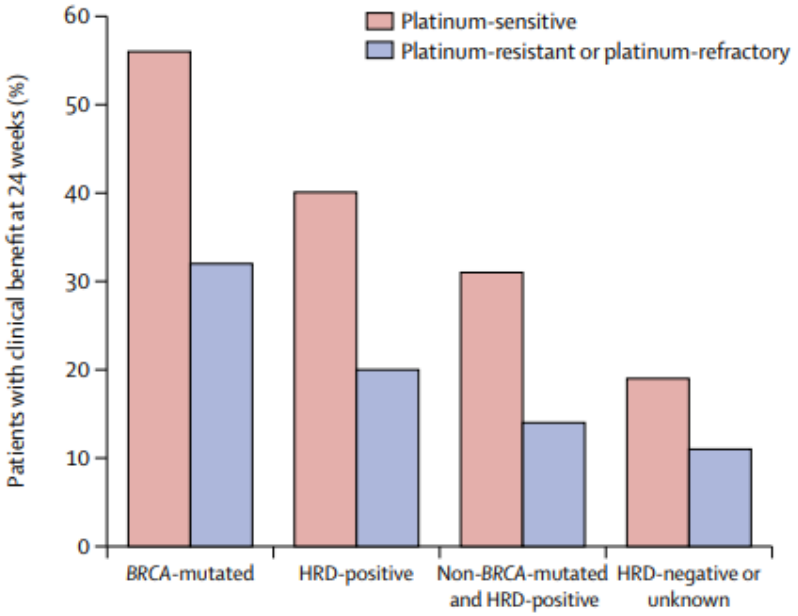
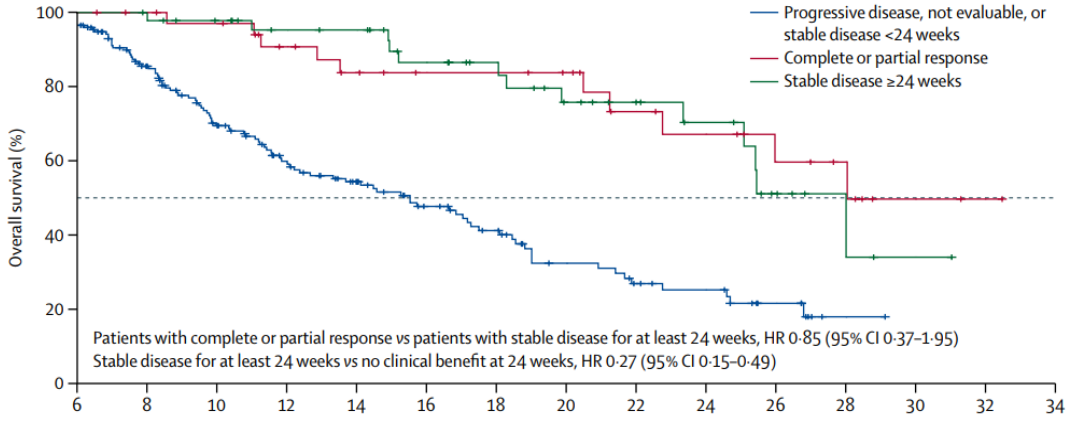


Table 2. Progression-Free Survival Ratio in Patients with Stable Disease by Biomarker[2]

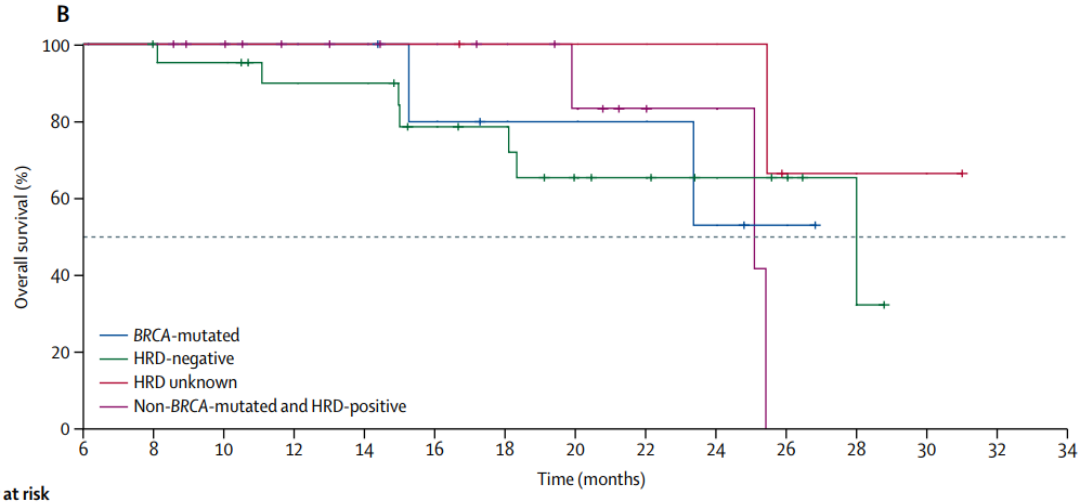
	***BRCA*-mutated (n = 63), %, n/N**	**HRD-positive* (n = 189), %, n/N**	**HRD-negative or unknown (n = 230), %, n/N**
Patients with SD with PFS ratio > 1.3	36% (9/25)	32% (23/72)	38% (39/103)
Patients with SD with PFS ratio > 1.0	44% (11/25)	42% (30/72)	46% (47/103)

HRD = homologous recombination deficiency; SD = stable disease; PFS = progression-free-survival

Figure 5. Estimates of Overall Survival Among Patients with (A) Stable Disease and Clinical Rate at 24 weeks and (B) by Molecular Biomarkers[2]



Number at risk (number censored)														
Progressive disease, not evaluable, or stable disease < 24 weeks	167 (7)	133 (23)	100 (32)	77 (41)	61 (51)	47 (58)	37 (62)	24 (68)	18 (70)	15 (72)	8 (77)	1 (83)	0 (84)	..	..
Complete or partial response	37 (1)	35 (3)	33 (4)	27 (8)	23 (10)	20 (13)	20 (13)	18 (15)	13 (18)	11 (19)	8 (21)	6 (23)	2 (26)	1 (27)	0 (28)
Stable disease ≥24 weeks	47 (0)	45 (1)	42 (4)	37 (8)	36 (9)	29 (13)	25 (17)	19 (20)	15 (24)	12 (26)	6 (29)	2 (32)	1 (33)	0 (34)	..



Number at risk (number censored)															
BRCA-mutated	6 (0)	6 (0)	6 (0)	6 (0)	6 (0)	4 (1)	3 (2)	3 (2)	3 (2)	2 (2)	1 (3)	0 (4)	..	..	..
HRD-negative	22 (0)	20 (1)	20 (1)	17 (3)	17 (3)	13 (5)	12 (6)	8 (8)	7 (9)	5 (11)	4 (12)	1 (14)	0 (15)	..	..
HRD unknown	4 (0)	4 (0)	4 (0)	4 (0)	4 (0)	4 (0)	3 (1)	3 (1)	3 (1)	3 (1)	1 (2)	1 (2)	1 (2)	0 (3)	..
Non-*BRCA*-mutated and HRD-positive	15 (0)	15 (0)	12 (3)	10 (5)	9 (6)	8 (7)	7 (8)	5 (9)	2 (12)	2 (12)	0 (12)	..	..	..	..

Table 3. Clinical Activity in *BRCA*mut Tumors by Platinum Sensitivity Status[1]

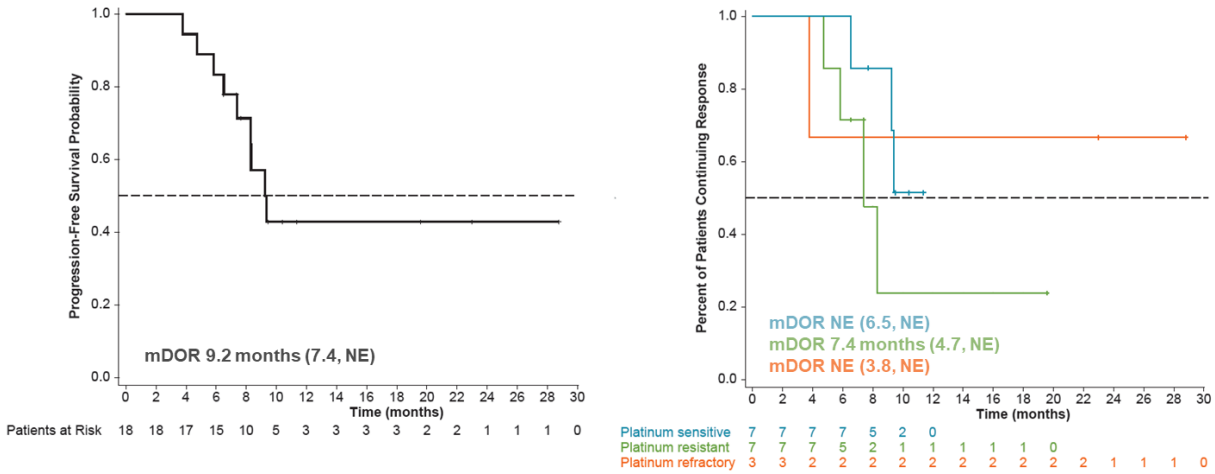
	BRCA-mutated**		
	ORR, %, n/N	**CB16, %, n/N**	**CB24, %, n/N**
Platinum-sensitive to last line of platinum therapy	39% (7/18)	72% (13/18)	56% (10/18)
Platinum-resistant	33% (7/21)	38% (8/21)	33% (7/21)
Platinum-refractory	19% (3/16)	50% (8/16)	31% (5/16)
Platinum-sensitive, resistant or refractory	31% (17/55)	53% (29/55)	40% (22/55)
All*	29% (18/63)	56% (35/63)	38% (24/63)

*All includes patients with unknown platinum status

***BRCA*mut includes patients with both germline or somatic mutation

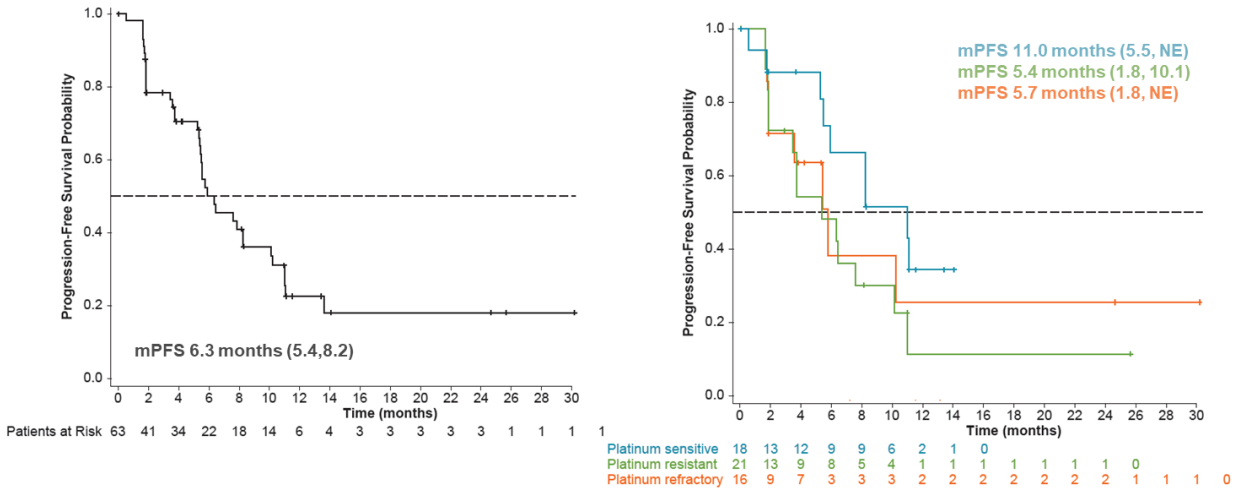
ORR = objective response rate; CB16/CB24 = clinical benefit (CR+ PR + SD for at least 16/24 weeks); OS = overall survival

Figure 6. Kaplan-Meier Estimation of Duration of Response in Patients with *BRCA*mut Tumors and by Platinum Status[2]



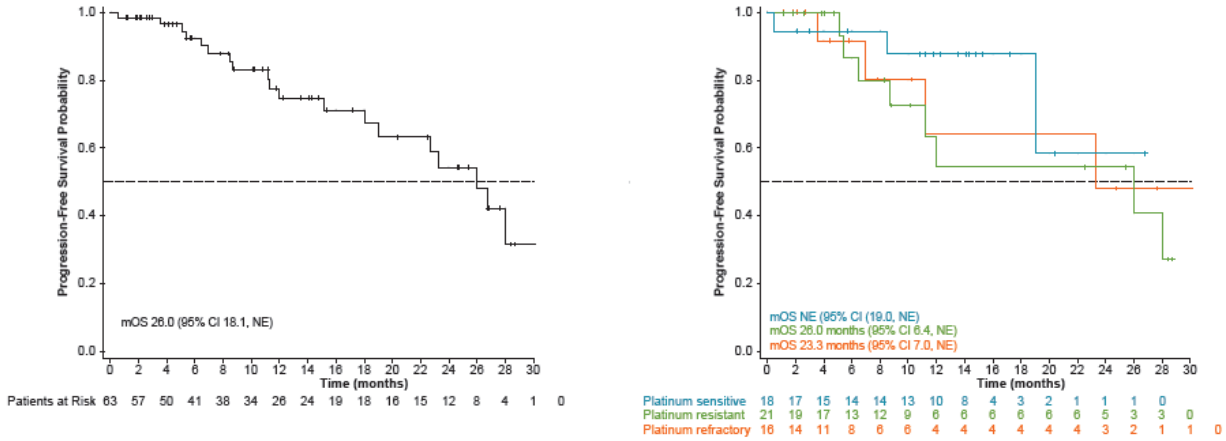
mDOR = median duration of response; NE = not estimable

Figure 7. Kaplan-Meier Estimation of Progression-Free Survival in Patients with *BRCA*mut Tumors and By Platinum Status[2]



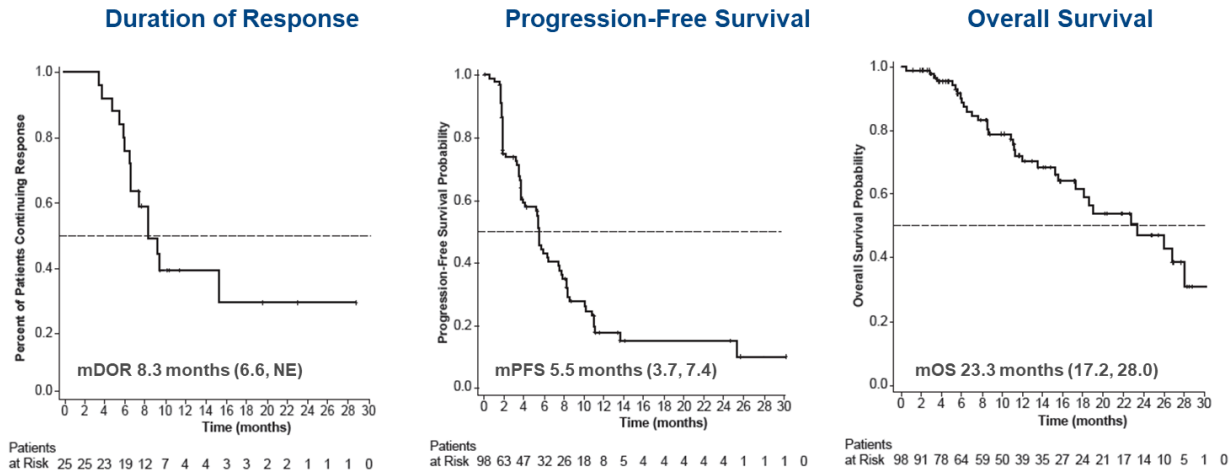
mPFS = median progression-free survival; NE = not estimable

Figure 8. Kaplan-Meier Estimation of Overall Survival in Patients with *BRCA*mut Tumors and by Platinum Status[2]



mOS = median overall survival; NE = not estimable

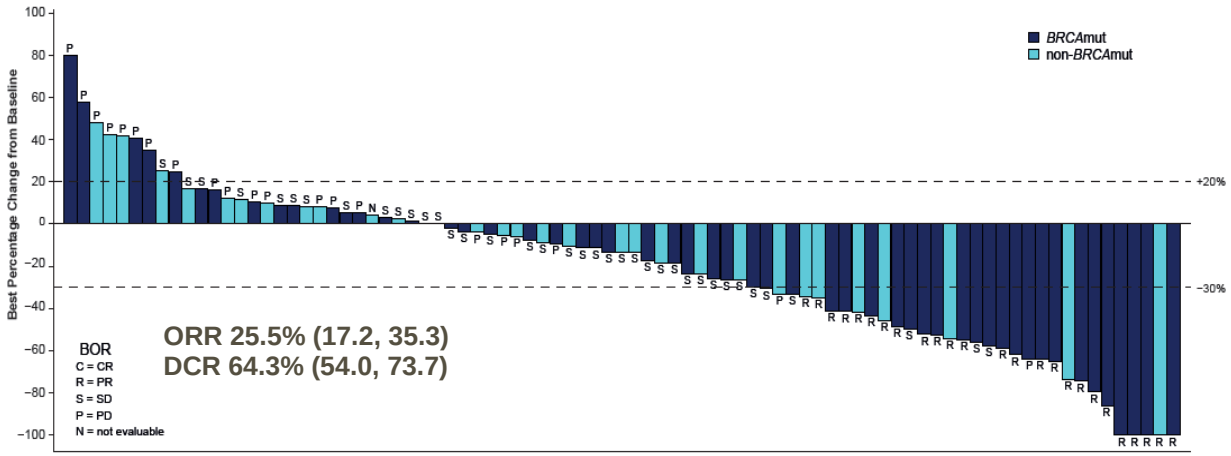
Figure 9. Efficacy Measures in the Biomarker-Driven Population*[2]



*Patients with *BRCA*mut disease regardless of platinum sensitivity + Patients with non-*BRCA*mut HRDpos Platinum-sensitive disease

ORR = objective response rate; m = median; DOR = duration of response; PFS = progression-free survival; OS = overall survival

Figure 10. Best Response in the Biomarker-Driven Population*[2]



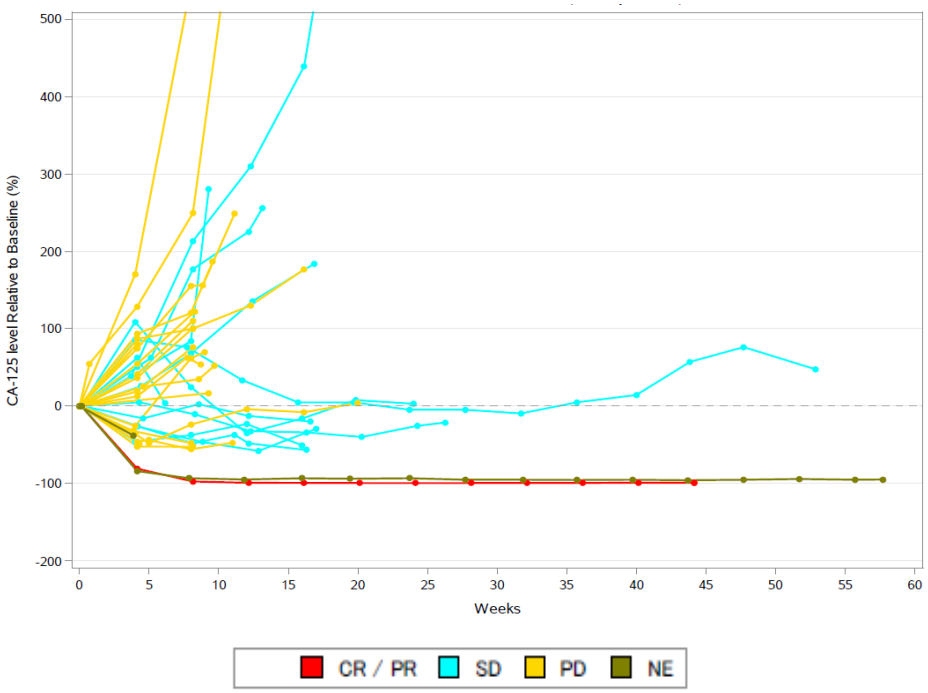
*Patients with *BRCA*mut disease regardless of platinum sensitivity + Patients with non-*BRCA*mut HRDpos Platinum-sensitive disease

ORR = objective response rate; DCR = disease control rate

Table 4. Patient Demographics[3]

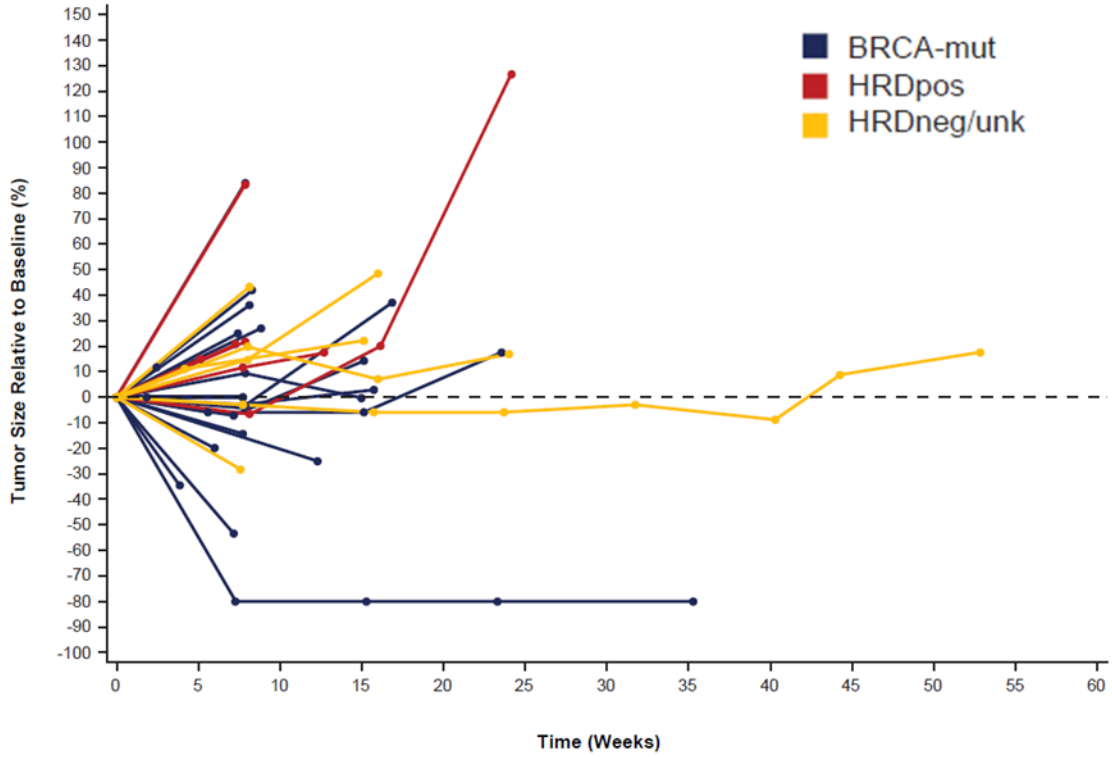
Characteristic	Safety population	Prior PARPi exposure
	N = 463	n = 37
Age, median (range), years	65 (29-91)	59 (44-81)
Median time from diagnosis, years	4.0	4.6
Tumor site, n(%)		
Ovarian	367 (79)	26 (70)
Primary peritoneal	47 (10)	6 (16)
Fallopian	48 (10)	5 (14)
Weight, kg		
Median	70.1	69.2
Min, max	36, 147	42, 144
ECOG performance status, n(%)		
0	267 (58)	21 (57)
1	196 (42)	16 (43)
HRD status, n(%)		
HRD-positive	222 (48)	30 (81)
*BRCA*mut	87 (19)	23 (62)
*BRCA*wt/*BRCA*unknown and HRDpos	135 (29)	7 (19)
HRD-negative	195 (42)	6 (16)
HRD unknown	46 (10)	1 (3)
BRCA status, n(%)		
g*BRCA*mut	58 (13)	21 (57)
s*BRCA*mut	29 (6)	2 (5)
Number of prior lines of therapy, n(%)		
2	5 (1)	0
3	188 (41)	16 (43)
4	144 (31)	10 (27)
≥5	126 (27)	11 (30)
Time from last chemotherapy to first dose, months		
Median	2	1.4
Min, max	1, 73	1, 25
Prior platinum courses, n(%)	463 (100)	37 (100)
1	37 (8)	0
2	235 (51)	18 (49)
3	147 (32)	15 (41)
4	37 (8)	4 (11)
≥5	7 (2)	0
Platinum status, n(%)		
Platinum sensitive (PFI > 6 months after last platinum-based therapy)	120 (26)	11 (30)
Platinum resistant (PFI 1-6 months)	151 (33)	12 (32)
Platinum refractory (PFI < 28 days)	161 (35)	8 (22)
Platinum unknown	31 (7)	6 (16)

Figure 11. CA-125 Relative Percent Change from Baseline by Best Response[3]



CA-125 = cancer antigen 125; CR = complete response; PR = partial responseSD = stable disease; PD = progressive disease; NE = not evaluable;

Figure 12a. Outcomes in PARPi-Retreatment, *BRCA* mutation status[3]



*BRCA*mut = *BRCA* mutated; HRDneg = homologous recombination deficiency negative; HRDpos = homologous recombination deficiency positive; unk = unknown.

Figure 12b. Outcomes in PARPi-Retreatment, Platinum Sensitivity status[3]

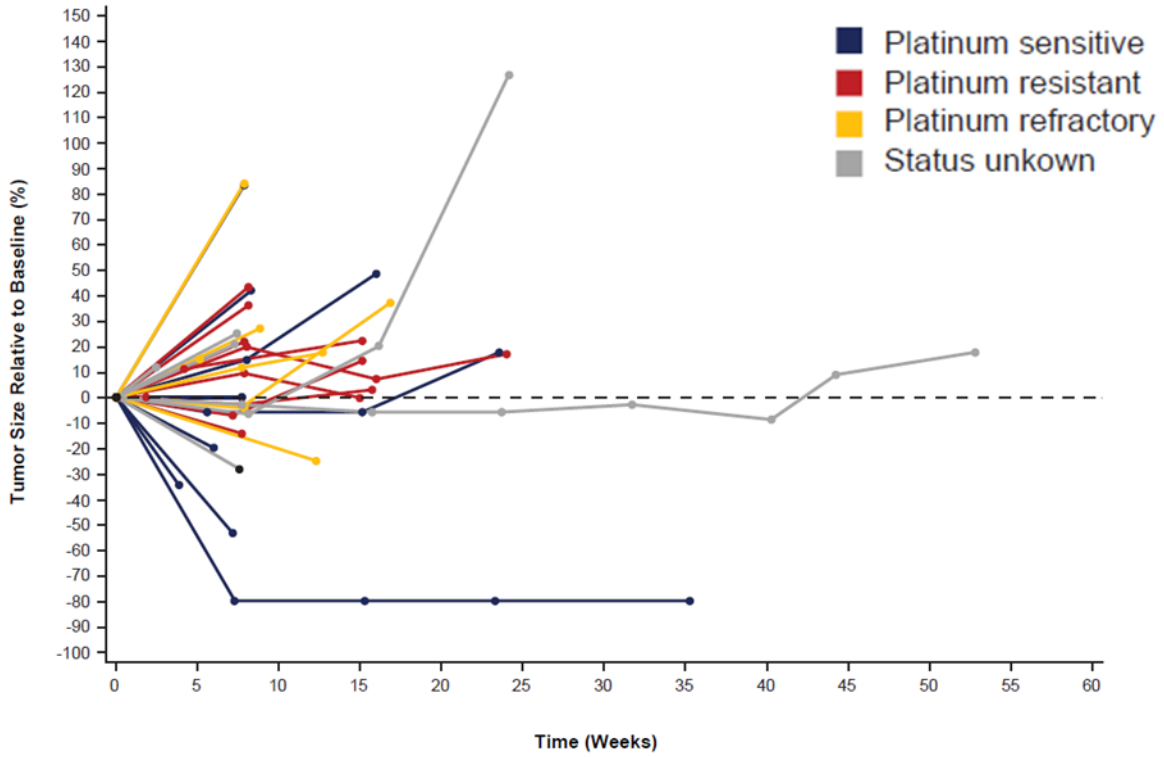


Table 5. Treatment-Emergent Adverse Events Among All Patients and Prior PARPi Patients[3]

MedDRA Preferred Term (Grouped Event), n (%)	Any Grade		Grade ≥3	
	Safety Population (N = 463)	Patients With Prior PARPi Exposure (n = 37)	Safety Population (N = 463)	Patients With Prior PARPi Exposure (n = 37)
Thrombocytopenia	239 (51.6)	15 (40.5)	131 (28.3)	7 (18.9)
Anemia	234 (50.5)	18 (48.6)	126 (27.2)	8 (21.6)
Leukopenia	135 (29.2)	9 (24.3)	84 (18.1)	6 (16.2)
Neutropenia	93 (20.1)	6 (16.2)	60 (13.0)	4 (10.8)
Hypertension	63 (13.6)	4 (10.8)	24 (5.2)	1 (2.7)

MedDRA = Medical Dictionary for Regulatory Activities

Figure 13. Niraparib Dose Level by Month on Treatment[5]

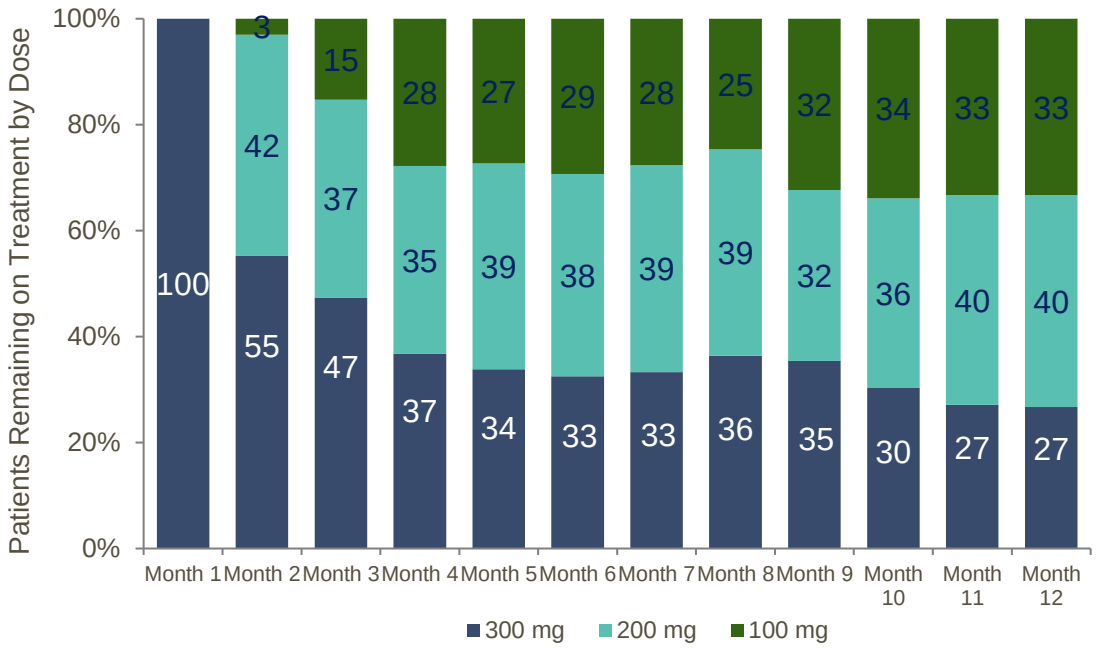


Table 6. Summary of Most Common (> 15%) Any Grade Drug-Related Treatment-Emergent Adverse Events of Patients (Safety Population, N = 463)[1]

MedDRA System Preferred Term, n (%)	Grade 1-2	Grade 3	Grade 4
Any Drug-related TEAE	416 (90)	257 (56)	93 (20)
Nausea	261 (56)	20 (4)	0
Fatigue	185 (40)	20 (4)	1 (<1)
Anemia	176 (38)	112 (24)	1 (<1)
Vomiting	139 (30)	19 (4)	0
Thrombocytopenia	136 (29)	76 (16)	58 (13)
Decreased platelet count	91 (20)	35 (8)	22 (5)
Decreased appetite	85 (18)	4 (1)	0
Constipation	76 (16)	5 (1)	0
Neutropenia	32 (7)	29 (6)	21 (5)