Niraparib for Advanced Breast Cancer with Germline *BRCA1* and *BRCA2* Mutations: the EORTC 1307-BCG/BIG5–13/TESARO PR-30–50–10-C BRAVO Study

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ABSTRACT

Purpose: To investigate the activity of niraparib in patients with germline-mutated *BRCA1/2* (g*BRCA*m) advanced breast cancer.

Patients and Methods: BRAVO was a randomized, open-label phase III trial. Eligible patients had g*BRCA*m and HER2-negative advanced breast cancer previously treated with ≤2 prior lines of chemotherapy for advanced breast cancer or had relapsed within 12 months of adjuvant chemotherapy, and were randomized 2:1 between niraparib and physician's choice chemotherapy (PC; monotherapy with eribulin, capecitabine, vinorelbine, or gemcitabine). Patients with hormone receptor–positive tumors had to have received ≥1 line of endocrine therapy and progressed during this treatment in the metastatic setting or relapsed within 1 year of (neo)adjuvant treatment. The primary endpoint was centrally assessed progression-free survival (PFS). Secondary endpoints included overall survival (OS), PFS by local assessment (local-PFS), objective response rate (ORR), and safety.

Results: After the pre-planned interim analysis, recruitment was halted on the basis of futility, noting a high degree of discordance between local and central PFS assessment in the PC arm that resulted in informative censoring. At the final analysis (median follow-up, 19.9 months), median centrally assessed PFS was 4.1 months in the niraparib arm ($n = 141$) versus 3.1 months in the PC arm [$n = 74$; hazard ratio (HR), 0.96; 95% confidence interval (CI), 0.65–1.44; $P = 0.86$]. HRs for OS and local-PFS were 0.95 (95% CI, 0.63–1.42) and 0.65 (95% CI, 0.46–0.93), respectively. ORR was 35% (95% CI, 26–45) with niraparib and 31% (95% CI, 19–46) in the PC arm.

Conclusions: Informative censoring in the control arm prevented accurate assessment of the trial hypothesis, although there was clear evidence of niraparib's activity in this patient population.

Introduction

BRCA1 and *BRCA2* encode two proteins that play a central role in the DNA damage response, especially in the repair of double-strand breaks (DSB) by homologous recombination repair (HRR) and the protection of the stalled replication fork. Tumors from patients with a *BRCA1/2* germline mutation (g*BRCA*mut) are likely to have impaired HRR, and therefore may be more vulnerable to some types of DNA-damaging agents (1). PARP inhibitors are selectively cytotoxic for these tumor cells mainly because they inhibit the enzymatic activity of

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Translational Relevance

Breast cancers in women with germline-mutated *BRCA1/2* (g*BRCA*m) are sensitive to platinum chemotherapy and to PARP inhibitors, which target an underlying defect in DNA repair. Niraparib is a potent oral selective PARP inhibitor, with demonstrated efficacy in ovarian and prostate cancers. The BRAVO trial was designed to compare the PFS of patients treated with either niraparib monotherapy or commonly used mono-chemotherapy regimens for advanced/metastatic HER2-negative breast cancer in g*BRCA*m carriers, irrespective of the tumor hormonal status. The trial was stopped early due to futility and informative censoring in the control arm, and so was unable to assess its primary endpoint. However, the objective response rate of 35% in the niraparib arm confirmed the drug's activity in this heavily pre-treated patient population, and thus supports the role of PARP inhibitors in the treatment of breast cancer and suggests that niraparib should be further explored in patients with breast cancer and g*BRCA*m.

PARP (which recruits DNA damage repair proteins), also trapping PARP-1 to DNA, resulting in a stalled replication fork, DNA damage, and ultimately cell death (2).

Niraparib is a potent oral, selective PARP-1 and PARP-2 inhibitor with IC_{50} of 3.8 and 2.1 nmol/l, respectively, which also has potent PARP-trapping activity (2, 3). Niraparib has demonstrated selective anti-proliferative activity in cancer cell lines that have been silenced for *BRCA1/2* or carry *BRCA1/2* mutations compared with their wildtype counterparts. In contrast, niraparib has demonstrated weak activity in normal human cells (4). In a phase I trial, the maximum tolerated dose was established at 300 mg/day (d) in cohorts enriched for *BRCA1/2* germline mutation carriers, sporadic platinum-resistant high-grade ovarian cancer, and sporadic prostate cancer (5). Dose-limiting toxic effects reported in the first cycle were grade 3 fatigue (1 patient given 30 mg/d), grade 3 pneumonitis (1 given 60 mg/d), and grade 4 thrombocytopenia (2 given 400 mg/d). Promising antitumor activity was observed among *BRCA1/2* mutation carriers with ovarian cancer and breast cancer, with partial responses in 8 of 20 (40%) and 2 of 4 (50%), respectively. In the phase III NOVA trial, niraparib was compared with placebo as maintenance treatment for patients with platinum-sensitive, recurrent ovarian cancer (6). Niraparib showed superiority in terms of progression-free survival (PFS) versus placebo in all groups of patients, although the magnitude of the clinical benefit differed according to the presence of a germline *BRCA1/2* mutation or the HRR status of the tumor. Patients in the niraparib group had a significantly longer median duration of PFS than did those in the placebo group, including 21.0 versus 5.5 months in the g*BRCA*mut cohort, as compared with 12.9 months versus 3.8 months in the non-g*BRCA*mut cohort for patients who had tumors with homologous recombination deficiency and 9.3 months versus 3.9 months in the overall non-g*BRCA*mut cohort. The most common grade 3 or 4 adverse events that were reported in the niraparib group were thrombocytopenia (in 33.8%), anemia (in 25.3%), and neutropenia (in 19.6%), which were managed with dose modifications.

The BRAVO trial was a phase III randomized, open label, multicenter, controlled study that was designed to compare the efficacy and safety of niraparib to commonly used chemotherapy regimens considered to be standard of care at the time of study initiation and enrollment (capecitabine, eribulin, vinorelbine, or gemcitabine) for the treatment of advanced/metastatic HER2-negative breast cancer in *BRCA1/2* germline mutation carriers, irrespective of the tumor hormonal status.

In March 2017, the independent data monitoring committee (IDMC) reviewed a planned interim efficacy analysis for futility and determined that the study should be stopped due to the PFS analysis results crossing the pre-defined boundary, noting a high degree of discordance between local and central PFS assessments that resulted in informative censoring. As a consequence, enrollment was stopped on March 29, 2017. Here, we report the final analysis of the BRAVO study, including all data up to December 1, 2017.

Patients and Methods

Patients

Eligible patients were at least 18 years old, had confirmed HER2-negative metastatic or locally advanced breast cancer that was not amenable to local treatment with curative intent, and had a deleterious or suspected deleterious germline *BRCA1/2* mutation detected by local or central testing with the validated, sequencing-based BRACAnalysis test (Myriad Genetics). Central confirmation of *BRCA* status was performed at any time before randomization for all patients regardless of whether they were enrolled on the basis of either a previous Myriad test or a local test. A whole-blood sample was centrally tested by certified Myriad Genetics Laboratories in Salt Lake City, UT. If after inclusion, a patient turned out not to have a germline *BRCA* mutation per central laboratory results, the patient could still continue on study at his/her physician's discretion and according to the patient's preference.

To be considered eligible, patients had to have received ≤2 prior cytotoxic regimens for advanced or metastatic breast cancer. Those not having received prior cytotoxic regimens in this setting were allowed to enter the study only if they had relapsed during or within 12 months of (neo)adjuvant cytotoxic therapy. Prior therapy should have included a taxane and/or anthracycline (unless contraindicated). Patients with hormone receptor–positive breast cancer had to have hormone-resistant disease, defined either as having relapsed while receiving adjuvant endocrine therapy or within 1 year of its completion, or having progressed while receiving endocrine therapy in the metastatic setting. Previous neoadjuvant or adjuvant platinum-based chemotherapy was permitted if the patient had relapsed 12 months or more after the last dose of platinum. Previous treatment with platinum for metastatic disease was allowed if the patient had not progressed while on treatment and subsequent progression occurred after 8 weeks from the last administration of platinum.

Patients had to have measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (7) or clinically evaluable non-measurable disease, with evidence of disease progression within 3 months before enrollment without change of therapy; an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 to 2; and adequate bone marrow, hepatic, and renal function. Bone-only disease with at least one lytic component was allowed. Patients with central nervous system (CNS) metastases were eligible provided they had completed local treatment at least 1 month before enrollment, had no new or progressive signs or symptoms related to CNS disease, and were off steroids for at least 2 weeks.

Trial design

The BRAVO study was an open-label, randomized, multicenter, controlled phase III trial comparing the efficacy and safety of niraparib versus physician's choice of single-agent chemotherapy. Patients were

randomized 2:1 to the experimental or control arm and stratified by visceral disease (yes vs. no), histology (triple-negative breast cancer vs. hormone receptor–positive breast cancer), and number of previous cytotoxic chemotherapy regimens for advanced or metastatic breast cancer (0–1 vs. 2). Patients in the experimental arm received niraparib 300 mg (3 × 100 mg oral capsules) once daily on a continuous regimen. Patients in the control arm received physician's choice of one of the following four chemotherapy regimens in 3-week cycles: eribulin, gemcitabine, capecitabine, or vinorelbine, administered per local treatment availabilities and guidelines (in France, gemcitabine is not approved as a single-agent for the treatment of breast cancer and could therefore not be selected as a treatment option in the physician's choice arm). The physician's choice chemotherapy was designated before randomization of each patient. The assigned treatment was continued until disease progression, unacceptable toxicity, death, patient refusal, or loss to follow-up. No crossover to niraparib was permitted following discontinuation from physician's choice treatment. Dose reductions for niraparib/physician's choice chemotherapy were managed as described in the protocol.

Trial oversight

This trial was conducted following the Good Clinical Practice Guidelines of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for human use (ICH-GCP; ref. 8) and approved by ethics review committees at each participating institution. All patients provided written informed consent. Trial conduct was supervised by an IDMC. The trial registration number (clinicaltrials.gov) is NCT01905592.

The trial was conducted in collaboration with the European Organisation for Research and Treatment of Cancer (EORTC) and the Breast International Group (BIG), with the participation of BIG member Groups in different countries, as well as independent sites from the United States of America, Hungary, Poland, Israel, and Canada, and sponsored by TESARO. Data were gathered and analyzed at EORTC, and the sponsor had no access to the full database before the release of the results by the Steering Committee.

Endpoints and assessments

The primary endpoint was PFS determined by blinded independent central review (BICR; central-PFS) among patients with a centrally confirmed germline *BRCA* mutation. PFS was defined as the time from randomization to objective radiologic progression according to RECIST version 1.1 or to death from any cause. A censoring scheme was prespecified according to the May 2007 FDA guidance on Clinical Trial Endpoint for the Approval of Cancer Drugs and Biologics (9) and as shown in Table C1 in the April 2015 FDA guidance on Clinical Trial Endpoints for the approval of non–small cell lung cancer drugs and biologics (10) as follows: patients were censored at randomization if no baseline tumor assessment was available, and patients were censored at the time of the last documented central independent radiologic assessment (i) if they were alive but had no progression at the time of analysis, (ii) if they had discontinued treatment for any reason other than documented progression, (iii) if they started another anticancer treatment without evidence of progression, or (iv) if death or radiologic progression was reported after more than two consecutively missed assessments. Tumor assessments by contrast-enhanced CT scans or/and MRI, based on RECIST version 1.1, were conducted locally by investigators and retrospectively assessed by a central blinded review committee composed of two radiologists with an arbiter as necessary. Results of the central blinded review were used to determine the primary efficacy endpoint of PFS whereas treatment decisions were based entirely on local assessment. CT scans were required at screening and every 2 cycles (6 weeks) for the first 12 months then every 3 cycles (9 weeks) until disease progression, regardless of treatment interruptions. If the patient discontinued before disease radiological progression, tumor imaging continued at the specified time intervals until progression or until the start of subsequent anticancer therapy. After discontinuation of study treatment, patients were followed every 9 weeks for assessment of subsequent anticancer therapy and overall survival (OS).

OS was a key secondary endpoint. Other secondary efficacy endpoints included PFS based on investigator assessment (local-PFS), overall response rate (defined as the proportion of patients achieving a best response of complete or partial response), and disease control rate (defined as the proportion of patients achieving a best response of complete or partial response or stable disease lasting for at least 24 weeks) based on central review. Safety was evaluated throughout the study, and adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0 (11).

Statistical analysis

Efficacy was assessed in the centrally confirmed intention to treat (ITT) population composed of all randomized patients who had a centrally confirmed germline *BRCA1/2* mutation. The initial overall sample size was based on the key secondary endpoint, OS, and on the assumption that niraparib would result in an improvement of 4 months in median OS from 9 to 13 months. For a true hazard ratio (HR) of 0.69, 265 deaths would provide 80% power at a 1-sided alpha level of 0.025. Assuming a maximum accrual rate of 10 patients per month, with 40% of patients randomized on the basis of local *BRCA* testing and assuming that 15% of those patients would then be found to be *BRCA*-mutation negative by central testing, it was estimated that a total of 324 randomized patients were required to obtain the necessary 306 centrally confirmed germline *BRCA* mutation carrying patients in the OS analysis population. Initially, the final primary PFS analysis was planned after 232 PFS events with 99.6% power (1-sided alpha level of 0.025) to detect a difference from 3 to 6 months in median PFS (corresponding to an HR of 0.5). The clinical relevance of the maximum significant HR of 0.759 that could be detected by 232 events was re-evaluated in the current treatment landscape. The assumptions were revised in a way that the statistically significant HR observed in the study is also clinically relevant. Therefore, the PFS analysis was redesigned to provide 80% power to detect an HR of 0.6 (equivalent to an improvement in median PFS from 3 to 5 months) with a 1-sided alpha of 0.025, requiring approximately 137 PFS events. A gatekeeping strategy (i.e., sequential testing procedure) was planned to test for differences between treatment arms in OS only if there was evidence of a statistically significant improvement in PFS, to allow control of the overall type 1 error rate.

A futility interim analysis of the primary endpoint of PFS was planned after 93 (68%) centrally confirmed PFS events, using a gamma family beta spending function with a non-binding gamma ($\gamma = -5$) stopping boundary. Statistical design was computed using PROC SEQDESIGN in SAS and confirmed with EAST software.

The primary PFS analysis was performed using a stratified log-rank test (1-sided alpha level = 0.025) for the difference in the distribution of PFS between niraparib and physician's choice groups. Randomization factors were used as the strata for this test. A non-stratified log-rank test was performed to assess the robustness of the primary analysis. HRs and their 95% confidence interval (CI) were estimated on the basis of a Cox proportional hazard model with the randomized

treatment as a factor and stratified for the randomization factors. Additional supportive analyses were conducted in the full ITT population and in the per protocol populations as defined in the study protocol. Subgroup analyses of the primary endpoint were performed by age, geographic region, ECOG performance status, visceral disease, histology, number of lines of prior chemotherapy regimens for advanced/metastatic disease, prior platinum treatment, and type of germline *BRCA* mutation. An exploratory unplanned subgroup analysis was conducted in patients with triple-negative breast cancer. At the time of the final analysis of the primary endpoint, secondary endpoints, including OS and PFS by investigator assessment were analyzed with the same approach as for the primary endpoint. The overall response rate and the disease control rate were based on central review assessments in the subset of patients with measurable disease at baseline. The number and proportion of patients achieving a response are presented with their corresponding 95% Pearson–Clopper CI.

All safety and tolerability evaluations were conducted in the safety population, composed of randomized patients who received at least one dose of study medication. Adverse events are reported from start of treatment up to 30 days after the last treatment administration date. Hematology and biochemistry events were determined on the basis of laboratory values and are reported from start of treatment up to the last administration of study medication. For some hematology and biochemistry tests, to distinguish between grade 0 and 1, normal values were required. In the case of missing normal values, CTCAE grade was categorized as grade 0/1. Serious adverse events are reported on the basis of the safety database, including all randomized patients.

Results

Patients

Between February 25, 2014 and March 29, 2017, 758 patients were registered at 106 sites in 14 countries, of whom 215 patients were randomized: 141 patients to niraparib and 74 patients to physician's choice (**Fig. 1**). Overall, 27 (12.6%) patients were subsequently found to be ineligible, including 9 (4.2%) patients who had not relapsed during or within 12 months of (neo)adjuvant cytotoxic therapy in the absence of any prior cytotoxic regimens or chemotherapy for advanced or metastatic breast cancer. After randomization, 16 (7.4%) patients did not receive the assigned treatment: 7 (5.0%) in the niraparib arm, mainly due to ineligibility, and 9 (12.2%) in the physician's choice arm, mainly due to patient choice, and were therefore excluded from the safety population ($N = 199$).

Baseline characteristics were well balanced between the two treatment groups (Supplementary Table S1), with the exception of an apparent excess of previous platinum and radiotherapy use in the physician's choice arm, with 31.1% versus 16.3% and 71.6% versus 59.6%, respectively (Supplementary Table S2). At the time of clinical data cutoff for the final analysis (December 1, 2017), 8 patients were still receiving niraparib and none were still receiving physician's choice. At the time of article submission (December 2020), 3 patients were still on treatment with niraparib, and had

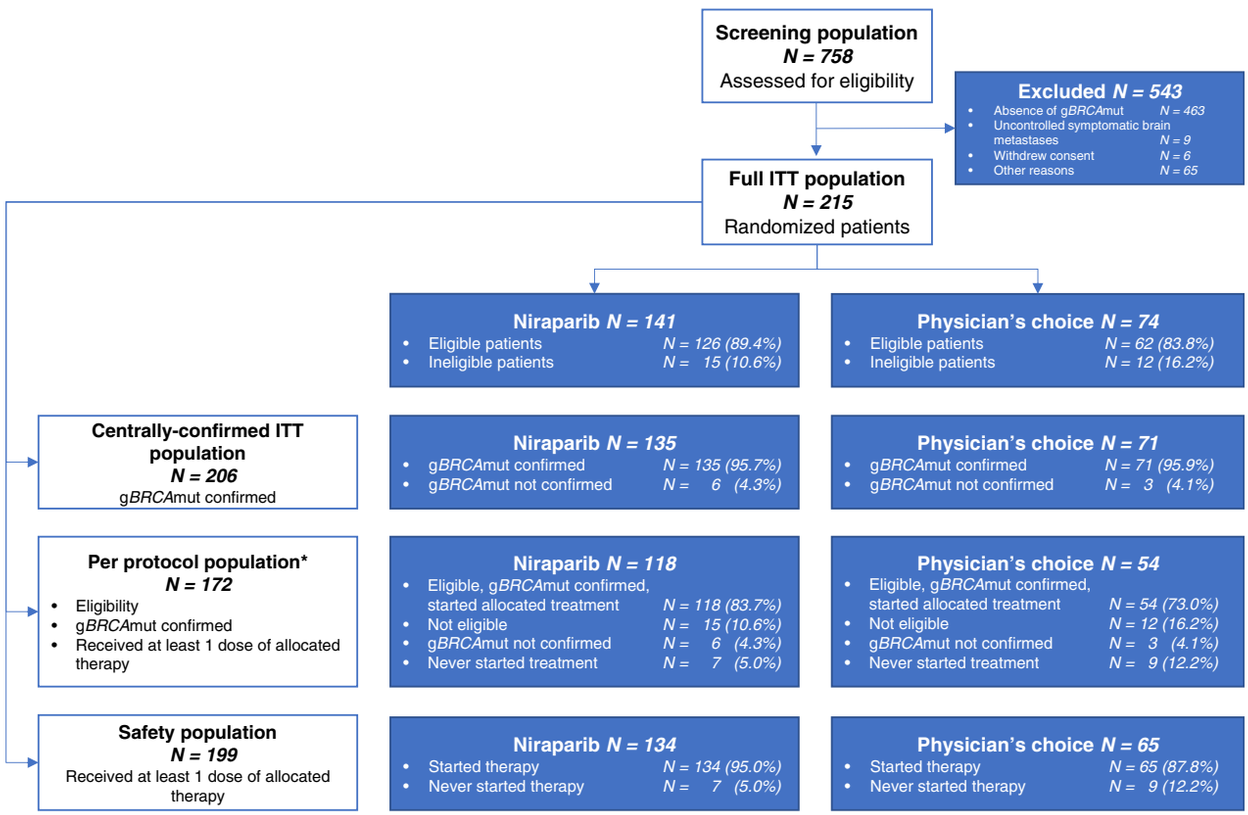

Figure 1.
Patient populations. *, Patients may be excluded from the per protocol population for several reasons. g*BRCA*mut: germline *BRCA1/2* mutation; ITT, intention to treat.

Table 1. Central confirmation of *BRCA* mutational status.

N (%)	Niraparib (*N* = 141)	Physician's choice (*N* = 74)
Availability of g*BRCA*mut test before randomization		
Yes, by central laboratory	97 (68.8)	55 (74.3)
Yes, by local laboratory	43 (30.5)	18 (24.3)
No	1 (0.7)	1 (1.4)
g*BRCA*mut centrally confirmed		
Yes	135 (95.7)	71 (95.9)
No	4 (2.8)	2 (2.7)
Not done	2 (1.4)	1 (1.4)
Type of central g*BRCA*mut found		
Point deletion in *BRCA1* only	66 (46.8)	38 (51.4)
Point deletion in *BRCA2* only	57 (40.4)	28 (37.8)
Large rearrangements	9 (6.4)	4 (5.5)
Point deletions in *BRCA1* and *BRCA2*	3 (2.1)	1 (1.4)
Not done	2 (1.4)	1 (1.4)
No mutation found	4 (2.8)	2 (2.7)

Abbreviation: g*BRCA*mut, germline *BRCA1/2* mutation.

been on treatment for at least 4.3 years. The median duration of follow-up was 19.7 months in the niraparib arm and 21.4 months in the physician's choice arm. Baseline characteristics and prior therapies of the centrally confirmed ITT population are presented in Supplementary Tables S3 and S4.

Germline *BRCA1/2* mutation was centrally confirmed in 206 (95.8%) patients: 135 in niraparib arm and 71 in physician's choice arm (**Table 1**). Among them, 104 (50.5%) patients had a deleterious point mutation in *BRCA1* only, 85 (41.3%) had a point mutation in *BRCA2* only, 4 (1.9%) had point mutations in both *BRCA1* and *BRCA2*, and 13 (6.4%) had a *BRCA1* or *BRCA2* large rearrangement.

Efficacy

Interim results

The interim analysis was performed, including all data up to November 23, 2016, with 105 PFS events confirmed by central review assessment, a higher number of events than initially planned for the interim analysis ($N = 93$). At that time, 194 patients had been randomized (127 to niraparib, 67 to physician's choice). The primary endpoint was assessed in the 185 patients with a centrally confirmed germline *BRCA* mutation (121 in niraparib arm, 64 in physician's choice arm). The median duration of PFS by central review was 4.0 months in niraparib arm and 4.6 months in physician's choice arm, with an HR of 1.15 (which was higher than the updated futility boundary of 0.884; **Fig. 2A**). Local assessment of PFS resulted in an HR of 0.69 (95% CI, 0.46–1.02) favoring niraparib (Supplementary Fig. S1), but the IDMC noted a high level of discordance between central and local assessments that resulted in a high level of informative

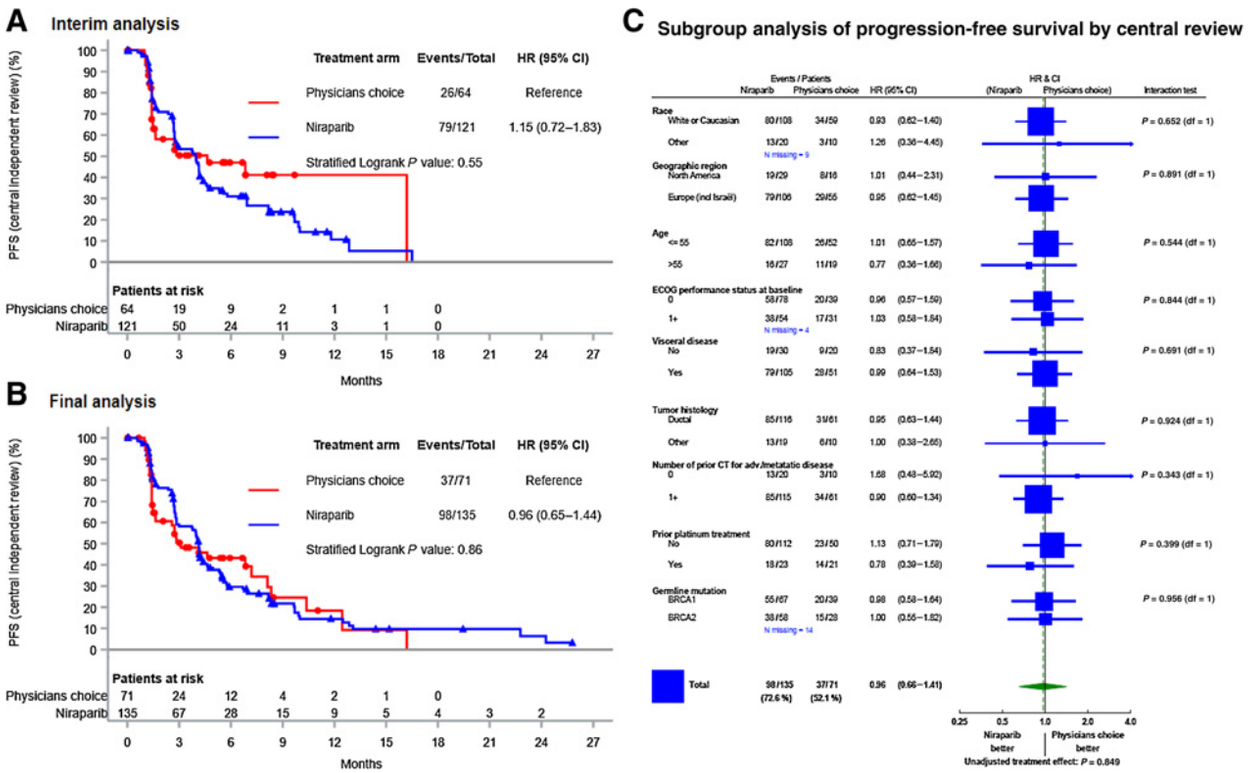

Figure 2.

Progression-free survival (PFS) by central independent review. **A,** Data cutoff for interim analysis was November 23, 2016. The analysis population was the centrally confirmed ITT population ($N = 185$). The futility boundary was HR, 0.884. These results were assessed by an IDMC. **B,** Data cutoff for the final analysis was December 1, 2017. **C,** Subgroup analysis of PFS by central review at final analysis. Data cutoff for the final analysis was December 1, 2017. The analysis population was the centrally confirmed ITT population ($N = 206$). CI, confidence interval; HR, hazard ratio; IDMC, Independent Data Monitoring Committee; ITT, intention to treat; PFS, progression-free survival.

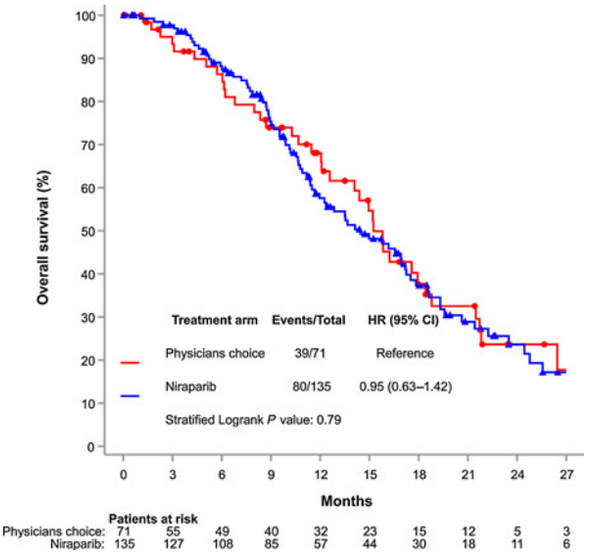

Figure 3.

Overall survival at final analysis. Data cutoff for final analysis was December 1, 2017. The analysis population was the centrally confirmed ITT population ($N = 206$). CI, confidence interval; HR, hazard ratio; ITT, intention to treat.

censoring in the physician's choice arm of the central assessment (Supplementary Table S5). On the basis of this analysis, the IDMC advised the closure of recruitment into the study, effective on March 29, 2017, because the comparison between niraparib and the physician's choice arms crossed the futility boundary for the primary endpoint, indicating that a robust comparison of the arms would not be possible due to the informative censoring that occurred in the control arm.

Final results

The final analysis was performed, including all data up to December 1, 2017. Among 206 patients in the centrally confirmed germline mutation carrier population (135 in niraparib arm, 71 in physician's choice arm), 135 PFS events were observed per the independent central review.

The median duration of PFS by central review was 4.1 months in niraparib arm and 3.1 months in physician's choice arm (HR, 0.96; 95% CI, 0.65–1.44; stratified log-rank *P* value: 0.86; **Fig. 2B**). PFS as assessed by the investigator resulted in a median local-PFS of 5.0 months in the niraparib arm and 3.1 months in the physician's choice arm (HR, 0.65; 95% CI, 0.46–0.93; Supplementary Fig. S1). No differential benefit was detected in any of the pre-planned subgroup analyses (**Fig. 2C**). Results from sensitivity analyses were all consistent with the primary analysis (Supplementary Table S6).

There was substantial discordance between local and central PFS assessments (Supplementary Table S7). In the centrally confirmed population, difference between local and central determination of disease progression occurred in 64 (47.4%) patients in the niraparib arm and 35 (49.3%) patients in physician's choice arm. In 44 (32.6%) patients in the niraparib arm, discrepancies were related to earlier identification of disease progression as per central independent review compared with local. In contrast, in 19 (26.8%) patients in the physician's choice arm, discrepancies occurred because the disease progressions reported by the local investigator were not confirmed by central review. In patients with discordant central and local PFS assessment, treatment was discontinued due to progressive disease in the majority of patients [57/64 patients (89.1%) in niraparib arm and 28/35 patients (80.8%) in the physician's choice arm], with toxicity reported as the main reason for discontinuation in only 3/64 patients (4.7%) in niraparib arm and in 1/35 patients (2.9%) in physician's choice arm.

In the centrally confirmed ITT population, 80 (59.3%) patients in the niraparib arm and 39 (54.9%) in the physician's choice arm had died, resulting in a median OS of 14.5 months in niraparib arm and 15.2 months in the physician's choice arm (HR, 0.95; 95% CI, 0.63–1.42; stratified log-rank *P* value: 0.79; **Fig. 3**).

On the basis of central assessment, 154 (74.8%) patients had measurable disease at baseline (106 in niraparib arm, 48 in physician's choice arm). The overall response rate was 35% (95% CI, 26–45) in the niraparib arm and 31% (95% CI, 19–46) in the physician's choice arm. In the exploratory unplanned analysis conducted in the subset of patients with triple-negative breast cancer (60 patients in the niraparib arm, 23 patients in the physician's choice arm), overall response rates were 32% (95% CI, 20–45) and 9% (95% CI, 1–28), respectively (**Table 2**).

Overall, 156/199 patients (78.4%) from the safety population were assessed for further anticancer therapies, including 104 patients who had experienced disease progression per independent central review. After disease progression, platinum-based chemotherapy was initiated in 24/75 (32.0%) patients in niraparib arm and in 11/29 (37.9%) patients in physician's choice arm, whereas 3/75 (4.0%) and 6/29 (20.7%) patients received a PARP inhibitor in the niraparib and physician's choice arms, respectively.

Table 2. Response to treatment by central independent review in patients with measurable disease.

	Niraparib ***N*** **(%; 95% CI)**	**Physician's choice** ***N*** **(%; 95% CI)**	***P***
Centrally confirmed ITT population with measurable disease	*N = 106*	*N = 48*	
Complete response (CR)	2 (1.9; 0.2–6.7)	1 (2.1; 0.05–11.1)	—
Objective response rate (CR+PR)	37 (34.9; 25.9–44.8)	15 (31.3; 18.9–46.3)	*0.72*
Clinical benefit rate (CR+PR+SD for at least 24 weeks)	44 (41.5; 32.0–51.5)	17 (35.4; 22.2–50.5)	*0.60*
Patients with triple-negative breast cancer	*N = 60*	*N = 23*	
Complete response (CR)	2 (3.3; 0.4–11.5)	0	—
Objective response rate (CR+PR)	19 (31.7; 20.3–45.0)	2 (8.7; 1.1–28.0)	*0.05*
Clinical benefit rate (CR+PR+SD for at least 24 weeks)	21 (35.0; 23.1–48.4)	4 (17.4; 5.0–38.8)	*0.34*

Note: The analysis population was the patients from the centrally confirmed ITT population with measurable disease at baseline. In the centrally confirmed ITT population, 22 (10.7%) patients' tumors were not assessable by central review in the absence of tumor assessment at baseline by central review. 95% Pearson–Clopper confidence interval; *P value* based on exact χ^2 test. CR, complete response; ITT, intention to treat; PR, partial response; SD, stable disease.

Safety

Safety is summarized in **Table 3**, considering only the patients who received at least one dose of treatment (134 patients in the niraparib arm and 65 patients in the physician's choice arm), and was largely consistent with prior studies of niraparib and physician's choice chemotherapy. The most common grade 3 or 4 adverse events observed with niraparib compared with physician's choice chemotherapy were anemia (45.5% vs. 3.1%), thrombocytopenia (35.1% vs. 0%), lymphopenia (22.4% vs. 9.2%), neutropenia (21.6% versus 23.1%), and increased gamma-glutamyl transferase (GGT; 19.4% vs. 12.3%). In the safety population, 70 (35.2%) patients received a blood transfusion, including 65 (48.5%) patients in the niraparib group and 5 (7.7%) patients in the physician's choice group.

Overall, 89.6% patients in the niraparib arm and 47.7% patients in the physician's choice arm had a dose interruption or reduction. The most common reasons for the first-dose interruption or reduction were hematological adverse events (AE; 69.2% patients in the niraparib arm, 35.5% patients in the physician's choice arm), non-hematological AEs (22.5% patients in the niraparib arm, 48.4% patients in the physician's choice arm), both hematologic and nonhematologic AEs (1.7% in the niraparib arm, none in the physician's choice arm), and other reasons (6.6% patients in the niraparib arm, 16.1% patients in the physician's choice arm).

Serious AEs were reported in 34/141 (24.1%) patients treated with niraparib and in 6/74 (8.1%) patients in physician's choice arm among the randomized patients. A fatal AE was reported in 1 patient in each arm. In the physician's choice arm, 1 patient died due to sepsis before starting study treatment. In the niraparib arm, bilateral pneumonia and respiratory failure were reported in 1 patient, but the main cause of death was reported by the investigator as disease progression. No cases

Table 3. Adverse events reported in ≥15% of patients in either treatment group.

	Niraparib (*N = 134*)			Physician's choice (*N = 65*)		
	Any grade	**Grade 1–2**	**Grade ≥ 3**	**Any grade**	**Grade 1–2**	**Grade ≥ 3**
Hematology[a]						
Anemia	121 (90.3)	60 (44.8)	61 (45.5)	50 (76.9)	48 (73.8)	2 (3.1)
Lymphopenia	106 (79.1)	63 (47.0)	30 (22.4)	39 (60.0)	27 (41.5)	6 (9.2)
WBC count	104 (77.6)	89 (66.4)	15 (11.2)	46 (70.8)	35 (53.8)	11 (16.9)
Thrombocytopenia	96 (71.6)	49 (36.6)	47 (35.1)	16 (24.6)	16 (24.6)	0 (0.0)
Neutropenia	85 (63.4)	49 (36.6)	29 (21.6)	37 (56.9)	19 (29.2)	15 (23.1)
Biochemistry[a]						
LDH abnormality[b]	96 (71.6)	—	—	51 (78.5)	—	—
GGT	79 (59.0)	53 (39.6)	26 (19.4)	35 (53.8)	27 (41.5)	8 (12.3)
Hyperglycemia	75 (56.0)	73 (54.5)	1 (0.7)	36 (55.4)	34 (52.3)	2 (3.1)
Alkaline phosphatase	74 (55.2)	66 (49.3)	8 (6.0)	34 (52.3)	33 (50.8)	1 (1.5)
SGOT	63 (47.0)	62 (46.3)	1 (0.7)	35 (53.8)	35 (53.8)	0 (0.0)
SGPT	55 (41.0)	52 (38.8)	3 (2.2)	31 (47.7)	29 (44.6)	2 (3.1)
Hypocalcemia	35 (26.1)	34 (25.4)	1 (0.7)	8 (12.3)	8 (12.3)	0 (0.0)
Hyponatremia	31 (23.1)	27 (20.1)	4 (3.0)	8 (12.3)	7 (10.8)	1 (1.5)
Hypoalbuminemia	30 (22.4)	28 (20.9)	1 (0.7)	12 (18.5)	12 (18.5)	0 (0.0)
BUN abnormality[b]	25 (18.7)	—	—	15 (23.1)	—	—
Serum creatinine	23 (17.2)	23 (17.2)	0 (0.0)	11 (16.9)	11 (16.9)	0 (0.0)
Other adverse events						
Nausea	79 (59.0)	76 (56.7)	3 (2.2)	19 (29.2)	18 (27.7)	1 (1.5)
Fatigue	73 (54.5)	62 (46.3)	11 (8.2)	34 (52.3)	30 (46.2)	4 (6.2)
Weight loss	53 (39.6)	53 (39.6)	0 (0.0)	10 (15.4)	10 (15.4)	0 (0.0)
Vomiting	50 (37.3)	46 (34.3)	4 (3.0)	10 (15.4)	10 (15.4)	0 (0.0)
Constipation	49 (36.6)	48 (35.8)	1 (0.7)	11 (16.9)	11 (16.9)	0 (0.0)
Headache	44 (32.8)	40 (29.9)	4 (3.0)	10 (15.4)	10 (15.4)	0 (0.0)
Anorexia	41 (30.6)	39 (29.1)	2 (1.5)	7 (10.8)	6 (9.2)	1 (1.5)
Dizziness	29 (21.6)	26 (19.4)	3 (2.2)	6 (9.2)	6 (9.2)	0 (0.0)
Back pain	29 (21.6)	27 (20.1)	2 (1.5)	8 (12.3)	7 (10.8)	1 (1.5)
Dyspnea	27 (20.1)	24 (17.9)	3 (2.2)	8 (12.3)	8 (12.3)	0 (0.0)
Insomnia	23 (17.2)	23 (17.2)	0 (0.0)	5 (7.7)	4 (6.2)	1 (1.5)
Pain in extremity	23 (17.2)	21 (15.7)	2 (1.5)	7 (10.8)	6 (9.2)	1 (1.5)
Mucositis oral	22 (16.4)	22 (16.4)	0 (0.0)	10 (15.4)	10 (15.4)	0 (0.0)
Abdominal pain	22 (16.4)	19 (14.2)	3 (2.2)	13 (20.0)	11 (16.9)	2 (3.1)
Diarrhea	21 (15.7)	20 (14.9)	1 (0.7)	21 (32.3)	21 (32.3)	0 (0.0)
Paresthesia	7 (5.2)	7 (5.2)	0 (0.0)	10 (15.4)	10 (15.4)	0 (0.0)
Palmar-Plantar erythrodysesthesia syndrome	0 (0.0)	0 (0.0)	0 (0.0)	15 (23.1)	13 (20.0)	2 (3.1)

Note: The analysis population was the safety population defined as all randomized patients who received at least one dose of treatment. Grading according to CTCAE version 4.0.

Abbreviations: BUN, blood urea nitrogen; GGT, gamma-glutamyl transferase; LDH, lactate dehydrogenase; SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase; WBC, white blood cell.

[a]Hematology and biochemistry abnormalities events were identified in the corresponding laboratory forms. For some hematology and biochemistry tests, to distinguish between grade 0 and 1, normal values were required. In case of missing normal values, CTCAE grade was defined as grade 0/1 and these events were included in the "any grade" count.

[b]Presented as "above upper limit of normal."

of myelodysplastic syndrome or acute myelogenous leukemia were reported in either arm.

Discussion

The BRAVO trial was unable to accurately assess the primary objective of whether PFS was longer with niraparib than physician's choice chemotherapy due to the high level of informative censoring in the physician's choice control arm. Informative censoring describes a situation where censoring is unbalanced in one arm of a trial, affecting the interpretation of the result of that arm. Nevertheless, niraparib demonstrated clinical activity in patients with advanced breast cancer and germline *BRCA1* and *BRCA2* mutations, as evidenced by an objective response rate of 35% in the centrally confirmed ITT population with measurable disease, a response rate similar to the physicians' choice arm in this study, and that seen in OlympiAD (12), and considerably higher than that seen in studies of single-agent cytotoxic therapy in later line setting in metastatic breast cancer unselected for *BRCA* mutation status (such as the EMBRACE study; ref. 13). However, the study could not demonstrate superiority over the physician`s choice chemotherapy. In an exploratory analysis, niraparib had higher response rates than physician`s choice chemotherapy in patients with triple-negative breast cancer.

The BRAVO trial demonstrated substantial discordance between local and central review, with the direction of discordance being different for each study arm, possibly due to the open-label design of the trial. This resulted in informative censoring, where many patients considered to have progressed by local assessment were censored for the primary endpoint of PFS by central review, resulting in inflation of the centrally determined PFS in the physician's choice control arm, thus preventing robust comparison between arms. Acknowledging that the discordance between local and central reviews is an important issue in this study, on reflection, it might have been advisable to conduct central confirmation of progression in real-time, rather than retrospectively, as done in this study. Open-label phase III studies, such as BRAVO, need a robust definition of the primary endpoint when treatment decisions are made by local investigators and not by central review, and real-time adjudication could offer a way to mitigate the risk of such bias.

Furthermore, 12.2% patients randomized to the physician's choice arm withdrew before starting treatment. The protocol had required that the primary endpoint of PFS be determined by independent central radiological review blinded to treatment allocation, to reduce the impact of the unblinded treatments, but despite this precaution, the informative censoring prevented a robust comparison of PFS between the two arms. As response rate is less affected by informative censoring, the secondary endpoint of response rate is the most robust assessment of efficacy in the BRAVO study.

Two other randomized phase III studies of PARP inhibitors in patients with advanced breast cancer and germline *BRCA1/2* mutations have reported, namely OlympiAD with olaparib (12) and EMBRACA with talazoparib (14), both of which had overall similar designs, including incorporated concomitant independent central review. In the BRAVO study, the response rates were lower and PFS shorter, for niraparib than for olaparib in OlympiAD (12) and talazoparib in EMBRACA (14). The main explanation for this is likely differences in prior treatment, with patients in BRAVO having received more lines of therapy, as reflected in the shorter OS in the control arm of BRAVO. The percentage of patients enrolled in first line of metastatic disease was 29% in OlympiAD, 38% in EMBRACA, and 15% in BRAVO. In addition, per eligibility criteria, first-line patients in BRAVO, but not OlympiAD nor EMBRACA, must have relapsed within 12 months of adjuvant chemotherapy. Notwithstanding these differences in patient population, there are other reasons why BRAVO may not have confirmed the hypothesized benefits of the use of a PARP inhibitor against an active comparator (physician's choice of chemotherapy), as discussed above. Consistent with this, response rates of talazoparib (15) and olaparib (16, 17) have previously been observed to be substantially lower in later lines of treatment. In terms of safety, most toxicity was hematological, mainly anemia and thrombocytopenia. In this regard, BRAVO recruited before the standard dose of niraparib was reduced for patients of low body weight, and this may have contributed to rates of hematological toxicity.

Niraparib is approved for the maintenance treatment of platinum-sensitive recurrent advanced ovarian cancer who has responded to prior platinum chemotherapy (6). The BRAVO trial confirms the activity of niraparib in patients with advanced breast cancer and germline *BRCA1* and *BRCA2* mutations, with a response rate of 35%, although the response rate to niraparib was not higher than physician's choice chemotherapy overall. In addition to these data from BRAVO, niraparib has demonstrated promising clinical efficacy in both the neoadjuvant treatment of participants with localized HER2-negative, g*BRCA*mut breast cancer (18) as well as in triple-negative breast cancer irrespective of *BRCA* mutation status (19). Future studies will broaden the search for potential benefit of PARP inhibition with niraparib in the treatment of breast cancer, with expansion into earlier line treatment settings and to patient populations beyond g*BRCA*mut.

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