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ORIGINAL ARTICLE

Talazoparib versus chemotherapy in patients with germline *BRCA1/2*-mutated HER2-negative advanced breast cancer: final overall survival results from the EMBRACA trial

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Background: In EMBRACA, talazoparib prolonged progression-free survival versus chemotherapy (hazard ratio [HR] 0.542 [95% confidence interval (CI) 0.413-0.711]; $P < 0.0001$) and improved patient-reported outcomes (PRO) in germline *BRCA1/2* (g*BRCA1/2*)-mutated advanced breast cancer (ABC). We report final overall survival (OS).

Patients and methods: This randomized phase III trial enrolled patients with g*BRCA1/2*-mutated HER2-negative ABC. Patients received talazoparib or physician's choice of chemotherapy. OS was analyzed using stratified HR and log-rank test and prespecified rank-preserving structural failure time model to account for subsequent treatments.

Results: A total of 431 patients were entered in a randomized study (287 talazoparib/144 chemotherapy) with 412 patients treated (286 talazoparib/126 chemotherapy). By 30 September 2019, 216 deaths (75.3%) occurred for talazoparib and 108 (75.0%) chemotherapy; median follow-up was 44.9 and 36.8 months, respectively. HR for OS with talazoparib versus chemotherapy was 0.848 (95% CI 0.670-1.073; $P = 0.17$); median (95% CI) 19.3 months (16.6-22.5 months) versus 19.5 months (17.4-22.4 months). Kaplan—Meier survival percentages (95% CI) for talazoparib versus chemotherapy: month 12, 71% (66% to 76%)/74% (66% to 81%); month 24, 42% (36% to 47%)/38% (30% to 47%); month 36, 27% (22% to 33%)/21% (14% to 29%). Most patients received subsequent treatments: for talazoparib and chemotherapy, 46.3%/41.7% received platinum and 4.5%/32.6% received a poly(ADP-ribose) polymerase (PARP) inhibitor, respectively. Adjusting for subsequent PARP and/or platinum use, HR for OS was 0.756 (95% bootstrap CI 0.503-1.029). Grade 3-4 adverse events occurred in 69.6% (talazoparib) and 64.3% (chemotherapy) patients, consistent with previous reports. Extended follow-up showed significant overall improvement and delay in time to definitive clinically meaningful deterioration in global health status/quality of life and breast symptoms favoring talazoparib versus chemotherapy ($P < 0.01$ for all), consistent with initial analyses.

Conclusions: In g*BRCA1/2*-mutated HER2-negative ABC, talazoparib did not significantly improve OS over chemotherapy; subsequent treatments may have impacted analysis. Safety was consistent with previous observations. PRO continued to favor talazoparib.

Key words: breast cancer, germline *BRCA* mutation, overall survival, PARP inhibitor, talazoparib

INTRODUCTION

Talazoparib is an oral inhibitor of poly(ADP-ribose) polymerase (PARP) catalytic activity,[1] with potent trapping activity of PARP at sites of damaged DNA.[2] Deleterious mutations in *breast cancer susceptibility genes 1* or *2* (*BRCA1/2*) leave cancer cells unable to repair damaged DNA

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through homologous recombination repair, and non-conservative repair mechanisms predominate causing DNA alterations and tumor cell death.[3]

Phase I/II studies demonstrated talazoparib has clinical benefit in patients with *BRCA1/2*-mutated advanced breast cancer (ABC).[4,5] The phase III EMBRACA trial (NCT01945775) compared the efficacy and safety of talazoparib with physician's choice of chemotherapy in patients with HER2-negative ABC harboring a germline *BRCA1/2* (g*BRCA1/2*) mutation.[6] EMBRACA is the largest PARP monotherapy trial to date in ABC. Talazoparib significantly prolonged progression-free survival (PFS) versus chemotherapy: hazard ratio [HR] 0.542 [95% confidence interval (CI) 0.413-0.711; $P < 0.0001$]; median 8.6 months [95% CI 7.2-9.3 months] versus 5.6 months [95% CI 4.2-6.7 months].[6] At the primary analysis, the HR for interim overall survival (OS; 163 events) was 0.761 (95% CI 0.547-1.060; $P = 0.11$). Patient-reported outcomes (PRO) favored talazoparib, with statistically significant overall improvement and significant delay in time to definitive clinically meaningful deterioration on the global health status/quality of life (GHS/QoL) and breast symptoms scales.[6,7] Most grade 3-4 adverse events (AEs) associated with the use of talazoparib were hematologic, and managed by supportive care and dose modifications.[8] Drug discontinuation due to AEs occurred in 5.9% of patients on talazoparib (in 1.4% due to hematologic AEs) and 8.7% of patients on chemotherapy. Talazoparib is approved in the United States, EU, and other countries for the treatment of patients with HER2-negative, locally advanced or metastatic breast cancer with a g*BRCA1/2* mutation.

We report final OS results with talazoparib compared with chemotherapy in EMBRACA, as well as updated safety and PRO.

METHODS

Trial design and patients

This was an open-label, randomized, phase III trial in patients aged ≥18 years with HER2-negative locally advanced or metastatic breast cancer and a deleterious or suspected deleterious g*BRCA1/2* mutation detected by central testing with BRACAnalysis® (Myriad Genetics, Salt Lake City, UT, USA).[6] Patients had received ≤3 previous cytotoxic regimens for advanced disease and previous treatment with a taxane, an anthracycline, or both, unless contraindicated. A protocol amendment (December 2015) expanded prior platinum use restrictions to permit enrolment if a patient had ≥6 months of stable disease following use of platinum in the neo-adjuvant/adjuvant setting (versus ≥12 months in the prior version of protocol). Patients were randomized 2 : 1 to talazoparib (1 mg orally once daily) or a protocol-specified single-agent chemotherapy (capecitabine, eribulin, gemcitabine, or vinorelbine). Treatment continued until disease progression or unacceptable toxicity. After treatment discontinuation, patients were followed up every 12 weeks for survival status and subsequent use of anticancer treatment. The protocol and statistical analysis plan are available in the Supplementary material, available at https://doi.org/10.1016/j.annonc.2020.08.2098.

Endpoints and trial assessments

The primary endpoint, PFS, has been reported.[6] OS, a pre-specified secondary endpoint, was defined as the time from randomization to death due to any cause. For patients without a death date at the time of data cut-off or permanently lost to follow-up, OS was censored at the date the patient was last known to be alive. Prespecified exploratory subgroup analyses were carried out at the final OS analysis to investigate treatment effects according to baseline characteristics and demographic factors. Updated safety and PRO (with latest potential assessment at the end of study treatment, 27-40 days after last dose of study drug) were performed (see Supplementary material, available at https://doi.org/10.1016/j.annonc.2020.08.2098).

Statistical analysis

The trial was designed with adequate power to detect certain effect sizes for the primary endpoint, PFS, and for the secondary endpoint, OS. A total of 321 deaths would give the trial 80% power (two-sided alpha level of 5%) to detect a 39% increase in OS, with a targeted HR for death of 0.72. Assuming an exponential distribution of OS, this corresponds to an increase in median OS from 20 to 27.8 months. An interim analysis of OS at a significance level of 0.0001 was conducted at the time of PFS primary analysis (data cut-off: 15 September 2017). The final OS analysis, using a significance level of 0.0499, was carried out on the intent-to-treat population (ITT) when 324 deaths had been observed (data cut-off: 30 September 2019), and using the stratified two-sided log-rank test. HR was estimated using a stratified Cox regression model with treatment group as the only main effect and median OS was estimated using the Kaplan—Meier method, with 95% CIs calculated. To maintain the overall two-sided type-I error rate of 5%, the analyses of PFS and OS were protected under a multiplicity adjustment schema using gate-keeping methodology (see Supplementary material, available at https://doi.org/10.1016/j.annonc.2020.08.2098). No additional adjustments for multiplicity or repeated tests were implemented. A multi-covariate analysis was carried out. The HR was estimated using a stratified Cox regression model with treatment group and selected prognostic factors as the main effects and a backward elimination process used to determine the final model. Prognostic factors included Eastern Cooperative Oncology Group (ECOG) score (0 versus >0), *BRCA* status (*BRCA1* versus *BRCA2*), prior platinum treatment (yes versus no), and time from initial diagnosis of breast cancer to initial diagnosis of ABC (<12 versus ≥12 months). Subgroup analyses were conducted similarly to the ITT analysis. Two analyses using the rank-preserving structural failure time model (RPSFTM) method were carried out to estimate the treatment effect on OS adjusting for subsequent treatment with a PARP inhibitor and/or platinum, and PARP inhibitor alone.[9] These analyses give an

unbiased estimate of the treatment effect on OS as if patients in the chemotherapy arm had not taken a PARP inhibitor and/or platinum after discontinuation of chemotherapy. Statistical methodology for the PRO, without adjustment for multiplicity, was previously described.[6,7]

RESULTS

Patients

Overall, 431 patients were randomized between October 2013 and April 2017 (ITT population; supplementary Figure S1, available at https://doi.org/10.1016/j.annonc.2020.08.2098). Of these, 287 patients were randomized to talazoparib (286 treated) and 144 to chemotherapy [126 treated with capecitabine (55), eribulin (50), gemcitabine (12), or vinorelbine (9)]. One patient randomized to talazoparib and 18 patients randomized to chemotherapy withdrew consent before receiving the drug. Eighteen patients (17 on talazoparib [5.9%], one on capecitabine [0.7%]) remained on treatment at data cut-off (30 September 2019).

While baseline characteristics were generally similar, the talazoparib group included a higher proportion of patients with a baseline ECOG performance status (PS) of 1 or 2 (46.4% versus 41.0%) and a higher proportion of patients whose breast cancer progressed to advanced disease within 12 months of initial diagnosis (37.6% versus 29.2%) than the chemotherapy group (supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2020.08.2098). Further information regarding baseline characteristics of the ITT population have been reported previously.[6]

Exposure to trial intervention

Median exposure was 6.9 months (range 0.03-61.4 months) for talazoparib and 3.9 months (range 0.2-36.3 months) for chemotherapy (supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2020.08.2098). Seventy-four patients (25.9%) received talazoparib for $\geq$12 months, while nine patients (7.1%) received chemotherapy for $\geq$12 months. Prolonged exposure was more common for patients receiving talazoparib than chemotherapy: 12 to $<$24 months, 36 (12.6%) versus 8 (6.3%), respectively; 24 to $<$36 months, 25 (8.7%) versus 0; $\geq$36 months, 13 (4.5%) versus 1 (0.8%). For those receiving chemotherapy, only patients receiving capecitabine ($n = 8$, seven with durations 12 to $<$24 months, and one $\geq$36 months) or eribulin ($n = 1$ duration 12 to $<$24 months) had exposure beyond 1 year.

Overall survival and subsequent treatments

At the final OS analysis, 324 patients had died (216 [75.3%] in the talazoparib group and 108 [75.0%] in the chemotherapy group), with a median follow-up of 44.9 months (95% CI 37.9-47.0) and 36.8 months (95% CI 34.3-43.0), respectively.

The HR for OS with talazoparib versus chemotherapy was 0.848 (95% CI 0.670-1.073; $P = 0.17$; median 19.3 months [95% CI 16.6-22.5] versus 19.5 months [95% CI 17.4-22.4]) (Figure 1A). Kaplan–Meier survival percentages (95% CI) for talazoparib versus chemotherapy were 71% (66% to 76%) versus 74% (66% to 81%) at month 12, 42% (36% to 47%) versus 38% (30% to 47%) at month 24, and 27% (22% to 33%) versus 21% (14% to 29%) at month 36. Covariate OS analysis showed a HR (95% CI) for treatment of 0.799 (95% CI 0.629-1.014; $P = 0.06$) and that a poorer ECOG PS and shorter time from initial diagnosis of breast cancer to initial diagnosis of ABC were associated with an increased risk of death (HR 0.772; 95% CI 0.616-0.968; $P = 0.02$ for ECOG score of 0 versus $>$0 and HR 1.488; 95% CI 1.177-1.882; $P = 0.0009$ for $<$12 months versus $\geq$12 months) (supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2020.08.2098).

Prespecified analyses of OS by subgroups showed generally consistent results across subgroups (Figure 2) including either triple-negative patients with a HR of 0.899 (95% CI 0.634-1.276) or hormone-receptor-positive patients with a HR of 0.827 (95% CI 0.597-1.143), and for *BRCA2* patients with a HR of 0.794 (95% CI 0.571-1.106) or *BRCA1* patients with a HR of 0.772 (95% CI 0.539-1.104). All other subgroups are shown in Figure 2.

Exploratory analysis revealed that patients with a longer prior platinum-treatment-free interval (before study entry) were more likely to have a longer duration of survival particularly in the talazoparib arm (supplementary Figure S2, available at https://doi.org/10.1016/j.annonc.2020.08.2098).

Altogether, a similar percentage of patients received subsequent systemic antineoplastic treatment in the talazoparib and chemotherapy groups (80.8% and 76.4%, respectively) (Table 1), with a median of two subsequent lines (range, 1-8). The most common subsequent treatments ($\geq$15% overall) were carboplatin (talazoparib: 38.7%; chemotherapy: 34.0%), capecitabine (33.8% and 15.3%), gemcitabine (27.2% and 25.7%), eribulin (26.1% and 18.1%), and paclitaxel (22.3% and 19.4%) across all lines. The most common subsequent treatments ($\geq$10%) by line after study therapy were: first line, carboplatin (20.9% and 17.4%), capecitabine (16.0% and 7.6%), and olaparib (0.7% and 11.8%); second line, capecitabine (10.1% and 2.8%). Subsequent treatments for triple-negative or hormone-receptor-positive patients are shown in supplementary Tables S4 and S5, available at https://doi.org/10.1016/j.annonc.2020.08.2098.

Overall, 47 patients (32.6%) in the chemotherapy group received subsequent PARP inhibitor compared with 13 patients (4.5%) in the talazoparib group (Table 2). Overall, 133 patients (46.3%) in the talazoparib group received subsequent platinum compared with 60 patients (41.7%) in the chemotherapy group.

For the RPSFTM analysis adjusting for subsequent use of PARP inhibitor and/or platinum, the HR for OS was 0.756 (95% bootstrap CI 0.503-1.029) (Figure 1B). For the subsequent use of PARP-inhibitor-only analysis, the adjusted HR was 0.820 (95% bootstrap CI 0.617-1.047) (supplementary Figure S3, available at https://doi.org/10.1016/j.annonc.2020.08.2098). For the chemotherapy

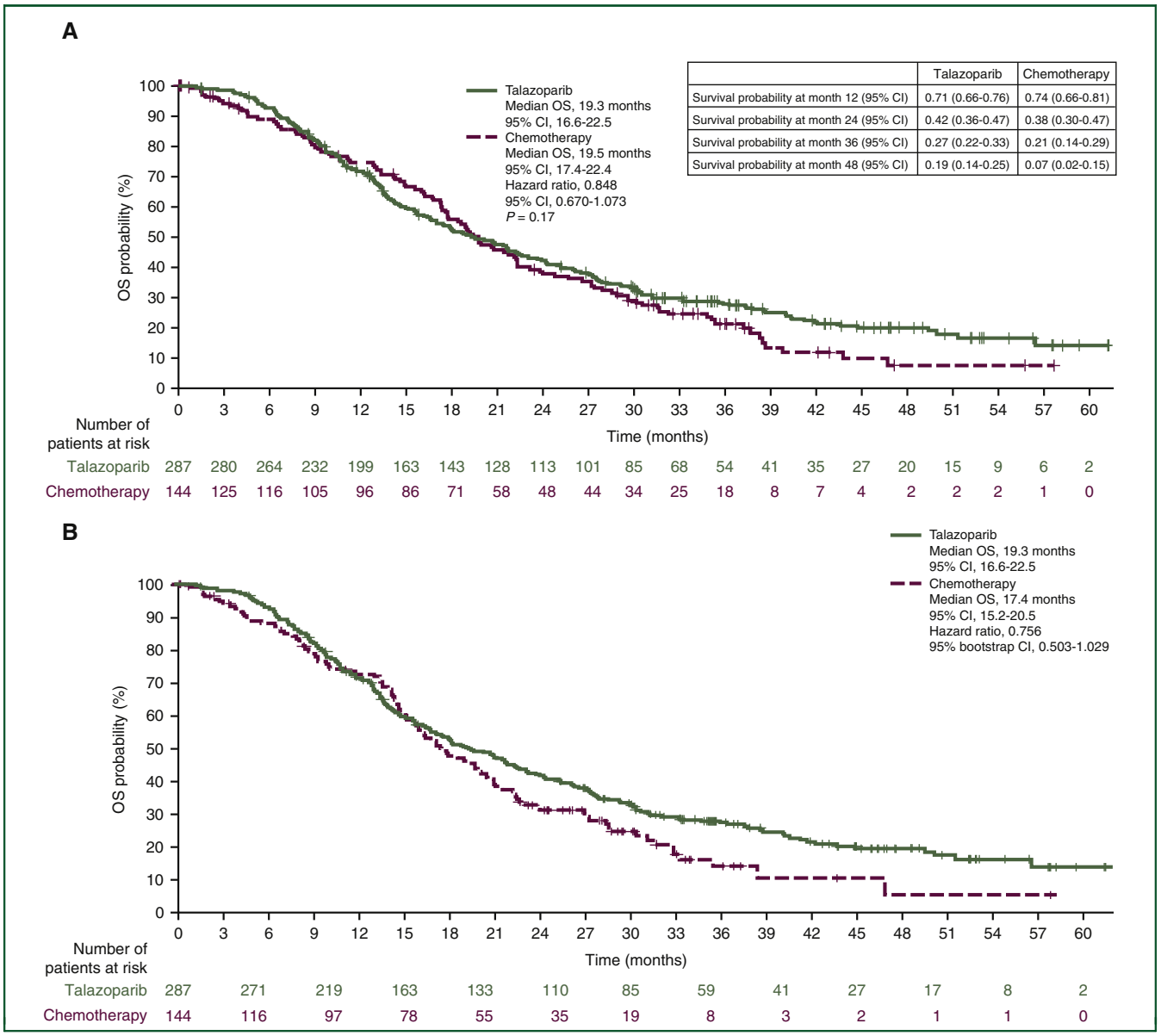

Figure 1. Final OS (A) in the overall population, or (B) adjusting for subsequent PARP inhibitor and/or platinum (ITT population).
CI, confidence interval; ITT, intent-to-treat; OS, overall survival; PARP, poly(ADP-ribose) polymerase.

group, patients receiving neither subsequent PARP inhibitor nor platinum had a shorter OS and total treatment duration than those who did (Figure 3).

Safety

AEs in the two groups were consistent with the primary analysis[6,8] (supplementary Tables S6-S8, available at https://doi.org/10.1016/j.annonc.2020.08.2098). The most common AEs (>30% of patients) were anemia, fatigue, nausea, neutropenia, and headache in the talazoparib group and nausea, fatigue, and neutropenia in the chemotherapy group. Grade 3 or 4 AEs occurred in 69.6% of patients receiving talazoparib and 64.3% of patients receiving chemotherapy, with hematologic grade 3-4 AEs in 56.6% and 38.9% of patients, respectively. Anemia was reported in 54.9% of patients who received talazoparib compared with 19.0% of patients who received chemotherapy and were grade 3 or 4 in 40.2% and 4.8% of patients, respectively. At least one blood transfusion was received by 39.2% of patients receiving talazoparib compared with 5.6% receiving chemotherapy (supplementary Table S9, available at https://doi.org/10.1016/j.annonc.2020.08.2098); this may have been partly due to the protocol requirements for talazoparib interruption and/or restarting talazoparib according to hemoglobin level, whereas investigators followed local prescribing information in the chemotherapy arm.[8]

AEs leading to permanent treatment discontinuation (excluding progressive disease) occurred in 5.9% of patients

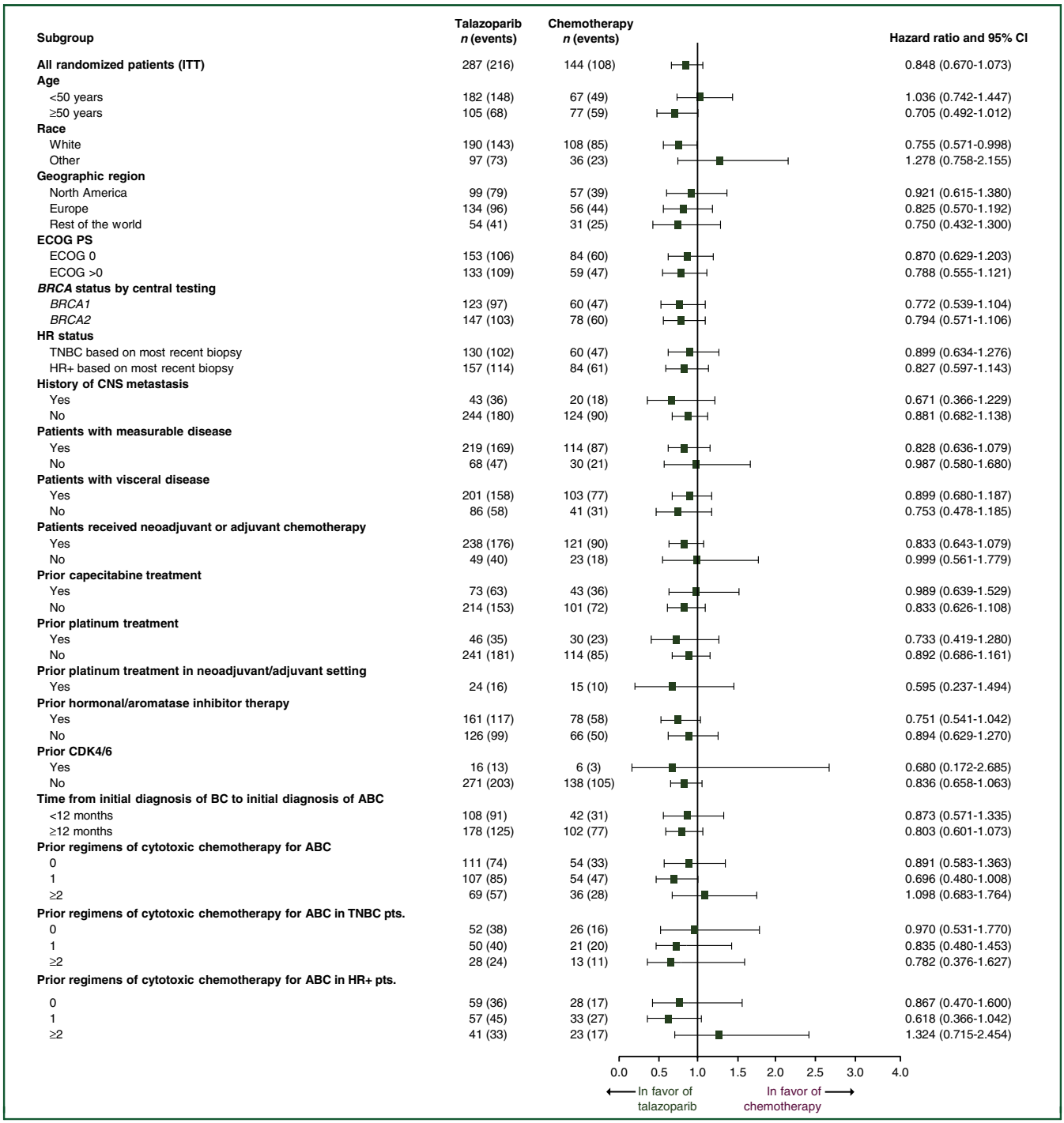

Figure 2. Subgroup analysis for OS (ITT population).
The *BRCA* subgroup analysis included patients evaluated by a central test only; patients evaluated by local testing were excluded ($n = 23$).
ABC, advanced breast cancer; *BRCA*, *breast cancer susceptibility gene*; CDK, cyclin-dependent kinase; CI, confidence interval; CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; HR+, hormone-receptor positive; ITT, intent-to-treat; OS, overall survival; PS, performance status; pts., patients; TNBC, triple-negative breast cancer.

on talazoparib and 8.7% on chemotherapy. Hematologic AEs rarely led to permanent discontinuation of talazoparib: three patients (1%) discontinued due to anemia and one patient (0.3%) due to neutropenia or thrombocytopenia. Dose modifications of talazoparib were used if a patient experienced toxicity (supplementary Table S10, available at https://doi.org/10.1016/j.annonc.2020.08.2098).

There were no confirmed cases of myelodysplastic syndrome. As reported with the primary data analysis, one case of acute myeloid leukemia (AML) occurred in a patient who received capecitabine[6] and a previously unreported case of AML occurred in a patient who received talazoparib (supplementary Table S7, available at https://doi.org/10.1016/j.annonc.2020.08.2098).

Table 1. Subsequent systemic antineoplastic treatments (ITT population)[a]

Antineoplastic treatment, *n* (%)	Talazoparib (*N* = 287)					Chemotherapy (*N* = 144)				
	Line of subsequent treatment					Line of subsequent treatment				
	Any	First	Second	Third	≥Fourth	Any	First	Second	Third	≥Fourth
Any	232 (80.8)	232 (80.8)	154 (53.7)	105 (36.6)	64 (22.3)	110 (76.4)	110 (76.4)	74 (51.4)	50 (34.7)	30 (20.8)
Cytotoxic										
Carboplatin	111 (38.7)	60 (20.9)	26 (9.1)	19 (6.6)	9 (3.1)	49 (34.0)	25 (17.4)	12 (8.3)	7 (4.9)	6 (4.2)
Capecitabine	97 (33.8)	46 (16.0)	29 (10.1)	12 (4.2)	11 (3.8)	22 (15.3)	11 (7.6)	4 (2.8)	4 (2.8)	3 (2.1)
Gemcitabine	78 (27.2)	26 (9.1)	24 (8.4)	16 (5.6)	12 (4.2)	37 (25.7)	13 (9.0)	8 (5.6)	9 (6.3)	7 (4.9)
Eribulin	75 (26.1)	22 (7.7)	15 (5.2)	19 (6.6)	19 (6.6)	26 (18.1)	10 (6.9)	8 (5.6)	4 (2.8)	4 (2.8)
Paclitaxel	64 (22.3)	18 (6.3)	21 (7.3)	11 (3.8)	17 (5.9)	28 (19.4)	10 (6.9)	10 (6.9)	2 (1.4)	7 (4.9)
Vinorelbine	40 (13.9)	9 (3.1)	8 (2.8)	7 (2.4)	16 (5.6)	13 (9.0)	5 (3.5)	1 (0.7)	4 (2.8)	3 (2.1)
Cisplatin	29 (10.1)	15 (5.2)	11 (3.8)	2 (0.7)	2 (0.7)	10 (6.9)	7 (4.9)	2 (1.4)	1 (0.7)	0
CDK4/6 inhibitor										
Palbociclib	39 (13.6)	17 (5.9)	14 (4.9)	7 (2.4)	2 (0.7)	15 (10.4)	7 (4.9)	5 (3.5)	1 (0.7)	2 (1.4)
Hormonal treatment										
Fulvestrant	35 (12.2)	14 (4.9)	11 (3.8)	3 (1.0)	7 (2.4)	17 (11.8)	8 (5.6)	7 (4.9)	0	2 (1.4)
Letrozole	29 (10.1)	17 (5.9)	7 (2.4)	4 (1.4)	2 (0.7)	9 (6.3)	5 (3.5)	3 (2.1)	1 (0.7)	0
PARP inhibitor										
Olaparib	8 (2.8)	2 (0.7)	3 (1.0)	2 (0.7)	1 (0.3)	36 (25.0)	17 (11.8)	8 (5.6)	6 (4.2)	5 (3.5)

Counts include all subsequent treatments regardless of whether the treatment is used as monotherapy or in a combination therapy. Gemcitabine includes generic names gemcitabine and gemcitabine hydrochloride, eribulin includes generic names eribulin and eribulin mesylate, paclitaxel includes generic names paclitaxel and paclitaxel albumin, and vinorelbine includes generic names vinorelbine and vinorelbine tartrate.
CDK, cyclin-dependent kinase; ITT, intent-to-treat; PARP, poly(ADP-ribose) polymerase.
[a] In ≥5% of patients for a particular line of treatment in any group.

Patient-reported outcome

With extended follow-up, favorable PRO remained consistent with the initial analysis.[7] A significant improvement in the estimated overall change from baseline in GHS/QoL scores (European Organisation for Research and Treatment of Cancer [EORTC] Quality of Life Questionnaire [QLQ-C30]) was observed in the talazoparib group while a significant deterioration was observed in the chemotherapy group (2.1 [95% CI 0.1-4.1] versus −5.7 [95% CI −10.0 to −1.4]; $P = 0.001$). There was also a significant improvement in the estimated overall change from baseline in the breast symptoms (EORTC QLQ-BR23) in the talazoparib group, with non-significant change in the chemotherapy group (−4.9 [95% CI −6.5 to −3.2] versus 0.1 [95% CI −3.2 to 3.5], $P = 0.009$). Compared with chemotherapy, treatment with talazoparib resulted in significant delay in time to definitive clinically meaningful deterioration in both the GHS/QoL (Figure 4A) and in breast symptoms (Figure 4B).

Table 2. Subsequent PARP inhibitor and/or platinum treatment (ITT population)

	Talazoparib (*N* = 287)	Chemotherapy (*N* = 144)
Received subsequent PARP inhibitor and/or platinum, *n* (%)	139 (48.4)	86 (59.7)
PARP inhibitor	13 (4.5)	47 (32.6)
Olaparib	8 (2.8)	36 (25.0)
Talazoparib	3 (1.0)[a]	8 (5.6)
Veliparib	2 (0.7)	5 (3.5)
Platinum	133 (46.3)	60 (41.7)
Carboplatin	111 (38.7)	49 (34.0)
Cisplatin	29 (10.1)	10 (6.9)
Oxaliplatin	0	2 (1.4)
PARP inhibitor and platinum	7 (2.4)	21 (14.6)

ITT, intent-to-treat; PARP, poly(ADP-ribose) polymerase.
[a] Three patients who took commercial talazoparib after discontinuation of talazoparib in the study are shown in the PARP inhibitor class.

DISCUSSION

Findings from the prespecified final analysis of OS in the EMBRACA trial comparing talazoparib with chemotherapy in patients with g*BRCA1/2*-mutated ABC found no statistically significant difference in OS between arms; the HR was 0.848 (95% CI 0.670-1.073; $P = 0.17$). The covariate analyses showed that a poorer ECOG PS and shorter time from initial diagnosis of breast cancer to initial diagnosis of ABC were associated with a statistically significant increased risk of death. Adjustment for these covariates reduced the HR for OS with talazoparib versus chemotherapy to 0.799 (95% CI 0.629-1.014; $P = 0.06$). The effect of talazoparib on OS was generally consistent across predefined subgroups. A higher percentage of patients on talazoparib than on chemotherapy continued study drug beyond 12 months.

The final OS outcome may have been confounded by subsequent systemic treatments. Analysis adjusted for subsequent PARP inhibitor and/or platinum showed that the primary OS analysis was impacted by these subsequent treatments, even if a PARP inhibitor alone was less impactful than platinum and/or a PARP inhibitor.

Addressing the influence of subsequent treatments on the long survival post-progression (SPP; the time from progression to death) is essential in understanding the effects of the therapy evaluated within the trial. For cancers with a long SPP, the variability in SPP, influenced by subsequent treatments, can dilute the OS benefit so that the ability to detect statistical significance is minimized.[10] However, there is continued justification for PFS as a surrogate for OS, with significant associations found between PFS and OS in patients with HER2-negative metastatic breast cancer.[11,12] Several statistical methods can adjust for the potentially confounding effects of subsequent

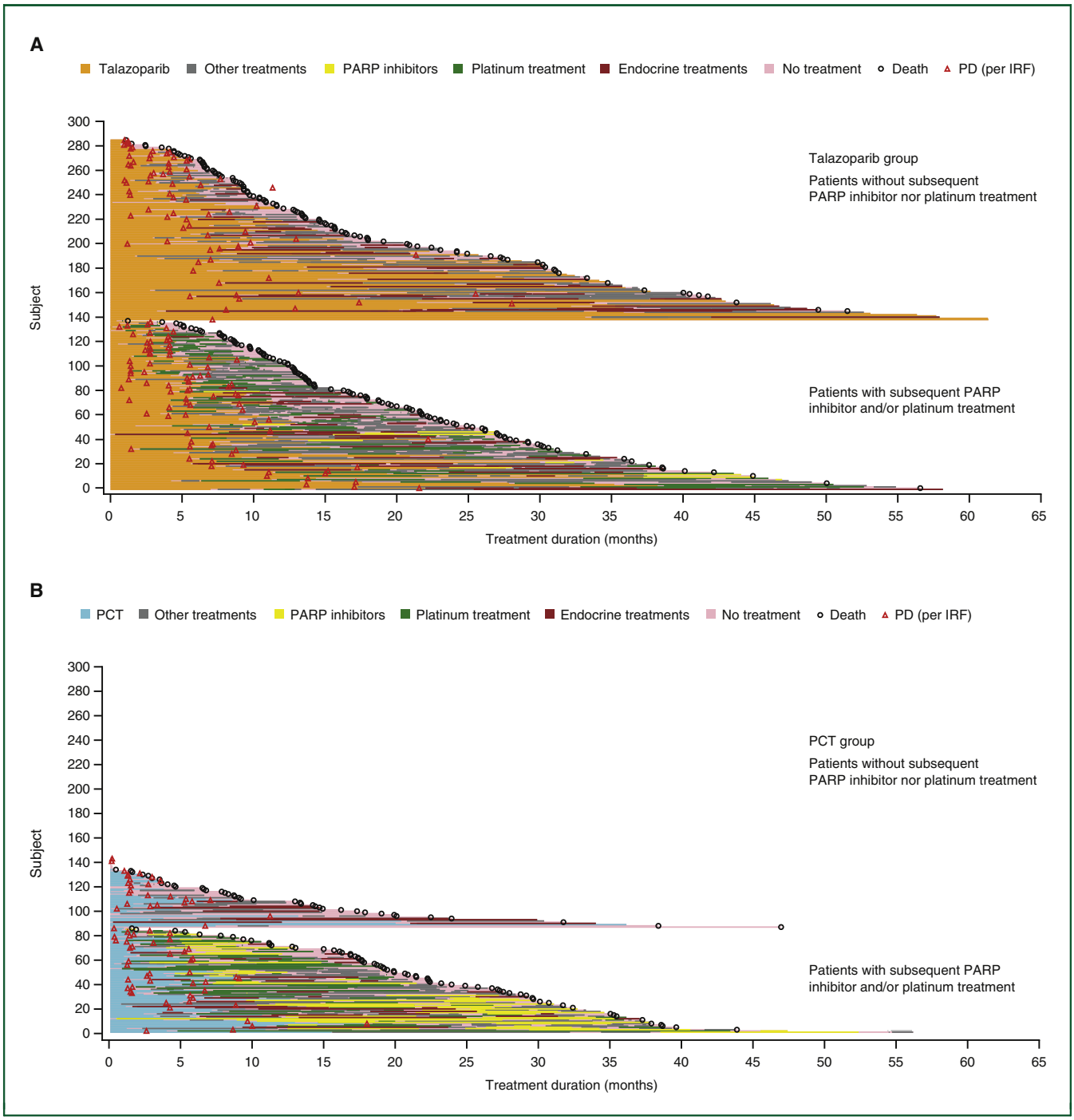

Figure 3. Swimmers plot of OS and treatment duration according to whether patients received subsequent PARP inhibitor or platinum in patients treated with (A) talazoparib and (B) chemotherapy (ITT population).

The analysis data cut-off date for OS is 30 September 2019, and for progressive disease (PD) is 15 September 2017. For patients whose subsequent treatment end date was missing, the earliest date (of death date, end of study date, and OS data cut-off date) was used.

IRF, independent radiology facility; ITT, intent-to-treat; OS, overall survival; PARP, poly(ADP-ribose) polymerase; PCT, physician's choice of chemotherapy; PD, progressive disease.

treatment in clinical trials. Here, we used the RPSFTM that estimates the counterfactual OS of the chemotherapy arm that would have been observed without subsequent platinum and/or a PARP inhibitor, assuming study treatment effects are constant and subsequent treatments are the same between the two arms. Despite the caveats around RPSFTM assumptions,[9] the HR (95% CI) obtained for OS after adjustment for subsequent platinum and/or a PARP inhibitor suggests that the primary OS analysis underestimated the treatment benefit of talazoparib. Additional sensitivity analyses were not done for subgroups with limited patient numbers in EMBRACA as they were not considered statistically robust.

In the phase III trial of olaparib (OlympiAD; NCT02000622) versus chemotherapy, a statistically significant benefit in PFS did not translate into a statistically

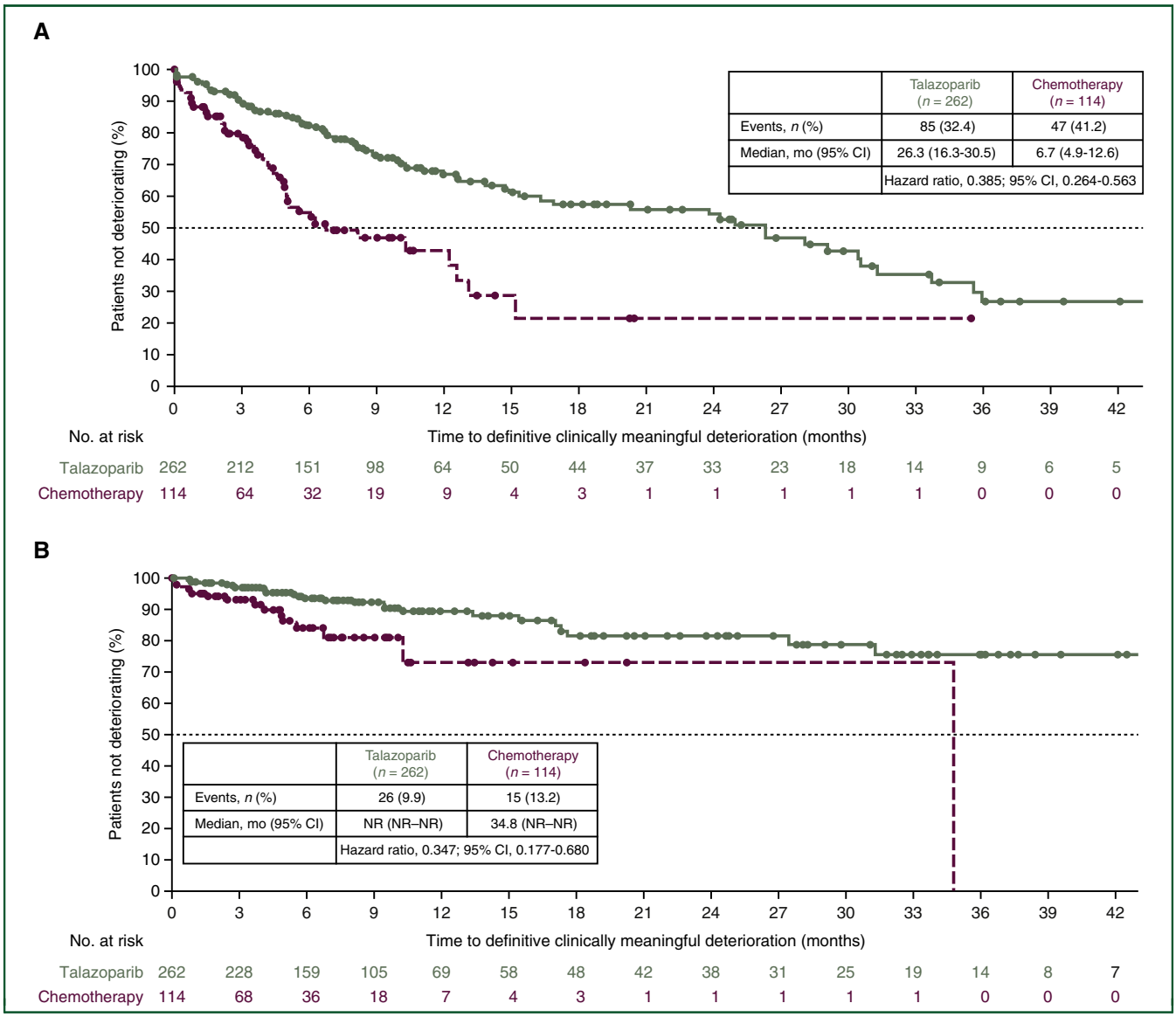

Figure 4. Time to definitive clinically meaningful deterioration in (A) GHS/QoL and (B) breast symptoms scale for EORTC QLQ-BR23 (PRO-evaluable population). Since the widths of the CIs have not been adjusted for multiplicity, the CIs should not be used to infer definitive treatment effects. Time to definitive clinically meaningful deterioration in GHS/QoL is defined as the time from randomization to the first observation with a ≥10-point decrease and no subsequent observations with a <10-point decrease from baseline. Time to definitive clinically meaningful deterioration in breast symptoms scale is defined as the time from randomization to the first observation with a ≥10-point increase and no subsequent observations with a <10-point increase from baseline.
CI, confidence interval; EORTC QLQ-BR23, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire breast cancer module; GHS/QoL, global health status/quality of life; mo, months; NR, not reached; PRO, patient-reported outcomes.

significant improvement in OS, although, in contrast to EMBRACA, the trial was not powered to identify a difference in OS.[13] In OlympiAD, a lower proportion of patients in the control group than in EMBRACA went on to receive a PARP inhibitor as subsequent treatment (8% and 33%, respectively); as OlympiAD was the first phase III PARP trial to read out, availability of subsequent PARP inhibitor was limited. In both trials, over 40% of patients across treatment arms received subsequent platinum.[13] Reversion mutations in *BRCA1/2* that restore DNA repair proficiency have been shown to lead to resistance to both PARP inhibitors and platinum; thus, the possible impact of subsequent platinum is of interest.[3] Other differences existed between the two phase III trials' results;[6,13] however, cross-trial comparisons should be made with caution due to differences in study design, patient characteristics, and the types and effects of subsequent treatments used in the chemotherapy arm.

The safety profile of talazoparib was consistent with the previously reported primary data cut-off.[6,8] Most grade 3-4 AEs reported in the talazoparib group were hematologic and were managed by supportive care (including transfusion) and dose modifications. The rate of permanent treatment discontinuation due to AEs was 5.9%. Previous detailed safety analyses of the EMBRACA trial showed that anemia followed by fatigue was experienced by 13.6% of patients treated with talazoparib compared with 4.0% of patients treated with chemotherapy.[8] Few patients reported grade 3 fatigue (2.4% talazoparib versus 3.2% chemotherapy; supplementary Table S8, available at https://doi.org/10.1016/j.annonc.2020.08.2098). The favorable PRO observed

with extended follow-up were consistent with initial analyses;[6,7] patients treated with talazoparib had significant overall improvement and significant delay in the time to definitive clinically meaningful deterioration in both patient-reported GHS/QoL and breast symptoms.

The main limitation of this trial is the open-label design due to the use of both oral and intravenous agents, as reported previously.[6] Other limitations are the lack of platinum-based agents as an option in the chemotherapy group and the possible confounding factor on the OS results by subsequent treatments. It is recognized that results of the phase III TNT trial involving patients with triple-negative breast cancer showed that the subset of 43 patients with g*BRCA1/2* mutation had a greater response and PFS in favor of carboplatin over docetaxel (although no OS advantage) not seen in the overall ITT population.[14] In addition, the results of the phase III BROCADE-3 trial in patients with HER2-negative g*BRCA1/2*-mutated ABC showed that the combination of the PARP inhibitor veliparib with carboplatin/paclitaxel significantly improved PFS compared with carboplatin/paclitaxel alone (no interim OS advantage was observed).[15] However, when the EMBRACA study was designed, the chosen reference agents were considered standard single-agent therapies for patients with ABC.

In conclusion, OS, evaluated as a key secondary endpoint in this trial, was not significantly improved with talazoparib compared with chemotherapy (HR 0.848; 95% CI 0.670-1.073; $P = 0.17$), although subsequent treatments may have impacted results. Talazoparib was generally well tolerated with manageable toxicity and no new safety signals. Improvements in PRO with extended follow-up supported results previously reported. This trial confirms that the incorporation of talazoparib in clinical practice is a favorable treatment option for patients with ABC with a g*BRCA1/2* mutation.

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DATA SHARING

Upon request, and subject to certain criteria, conditions, and exceptions (see https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information),

Pfizer will provide access to individual de-identified participant data from Pfizer-sponsored global interventional clinical studies conducted for medicines, vaccines, and medical devices (i) for indications that have been approved in the US and/or EU or (ii) in programs that have been terminated (i.e. development for all indications has been discontinued). Pfizer will also consider requests for the protocol, data dictionary, and statistical analysis plan. Data may be requested from Pfizer trials 24 months after study completion. The de-identified participant data will be made available to researchers whose proposals meet the research criteria and other conditions, and for which an exception does not apply, via a secure portal. To gain access, data requestors must enter into a data access agreement with Pfizer.

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