Outcomes of Patients (Pts) Who Had Received Prior Platinum (PP) Therapy in the Phase 3 EMBRACA Trial of Talazoparib (TALA) vs Physician's Choice of Chemotherapy (PCT) in Patients With Germline *BRCA1/2* Mutated (g*BRCA1/2*mut) Advanced Breast Cancer (ABC)

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Talazoparib after platinum-based therapy is most effective when administered early in the course of disease and is equivalent to chemotherapy in advanced setting

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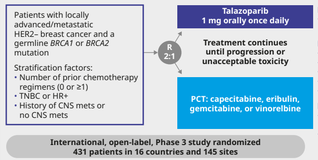
Background

- Talazoparib is a poly(ADP-ribose) polymerase (PARP) inhibitor approved in the US, EU, and other countries for the treatment of deleterious/suspected deleterious germline *BRCA1/2*-mutated (g*BRCA1/2*mut) human epidermal growth factor receptor 2-negative advanced breast cancer[1,2]
- The EMBRACA trial (NCT01945775) was a Phase 3 open-label, multinational, randomized, 2-arm study that compared the efficacy and safety of talazoparib (1 mg once daily) with standard single-agent physician's choice of chemotherapy treatment (PCT) in patients with locally advanced/metastatic breast cancer and g*BRCA* mutation[3]
  - In this trial, patients benefited with talazoparib regardless of prior platinum-based therapy, but greater improvements in clinical outcomes were seen vs PCT (capecitabine, eribulin, gemcitabine, or vinorelbine) for patients not treated with prior platinum-based therapy
    - Progression-free survival (PFS) hazard ratio (95% confidence interval [CI]): 0.76 (0.40–1.45), P=0.41, for prior platinum therapy vs 0.52 (0.39–0.71), P<0.0001, for the non-prior platinum subgroup
  - Exploratory analysis revealed that patients with a longer platinum-free interval were more likely to have a longer duration of survival, particularly in the talazoparib arm
    - This finding aligns with an exploratory analysis of the Phase 2 ABRAZO trial (NCT02034916), which showed that a longer platinum-free interval was associated with a greater response to talazoparib

Methods

- This was a post hoc analysis of the prior-platinum subpopulation of the EMBRACA trial
- The EMBRACA trial design[3] is shown in Figure 1
- The key inclusion and exclusion criteria are presented in Table 1
- Outcomes included radiographic PFS, objective response rate (ORR), and overall survival (OS)
  - For this analysis, endpoints were further explored in the prior-platinum subgroup
- Previous neoadjuvant/adjuvant platinum therapy was permitted if the patient had a disease-free interval of ≥6 months after the last dose

Figure 1. EMBRACA Trial Design (NCT01945775)[3,4]



Abbreviations: *BRCA1/BRCA2=breast cancer susceptibility gene 1* or *2*; CNS mets=central nervous system metastases; EORTC=European Organisation for Research and Treatment of Cancer; HER2–=human epidermal growth factor receptor 2-negative; HR+=hormone receptor-positive; ORR=objective response rate; OS=overall survival; PCT=physician's choice of chemotherapy treatment; PFS=progression-free survival; QLQ-BR23=Quality of Life Questionnaire breast cancer module; QLQ-C30=Quality of Life Questionnaire Core 30; R=randomized; RECIST 1.1=Response Evaluation Criteria in Solid Tumors version 1.1; TNBC=triple-negative breast cancer.

Table 1. Key Inclusion and Exclusion Criteria[3]

Inclusion	Exclusion
• Locally advanced or metastatic HER2– breast cancer and a germline *BRCA1* or *BRCA2* mutation	• Objective disease progression while receiving platinum-based chemotherapy administered for locally advanced or metastatic disease
• No more than three prior cytotoxic chemotherapy regimens for locally advanced or metastatic disease; there was no limit on the number of previous hormone therapies received by patients with HR+ breast cancer	• Platinum in the adjuvant or neoadjuvant setting and relapse within 6 months of the last dose of prior platinum therapy
• Prior treatment with a taxane and/or anthracycline unless medically contraindicated	• First-line locally advanced breast cancer with no prior adjuvant chemotherapy unless the investigator determined that one of the four cytotoxic chemotherapy agents in the control arm would be otherwise offered to the patient
• 18 years of age or older	• Prior treatment with a PARP inhibitor (not including iniparib)
• Measurable or nonmeasurable evaluable disease by revised RECIST 1.1	• Not a candidate for treatment with at least one of the treatments of protocol-specified PCTs (capecitabine, eribulin, gemcitabine, vinorelbine)
• ECOG performance status ≤2	• Cytotoxic chemotherapy, radiation, antihormonal therapy, or other targeted anticancer therapy within 14 days before randomization

Other inclusion/exclusion criteria applied (NCT01945775).
Abbreviations: *BRCA1/BRCA2=breast cancer susceptibility gene 1* or *2*; ECOG=Eastern Cooperative Oncology Group; HER2–=human epidermal growth factor receptor 2-negative; HR+=hormone receptor-positive; RECIST 1.1=Response Evaluation Criteria in Solid Tumors version 1.1; PARP=poly(ADP-ribose) polymerase; PCT=physician's choice of chemotherapy.

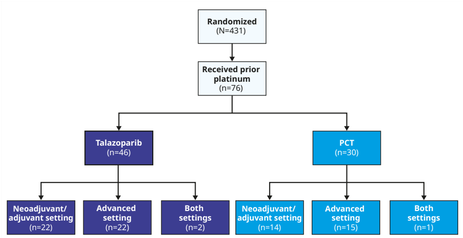
STATISTICAL ANALYSIS

- Data cutoff dates were as follows:
  - PFS and ORR: September 15, 2017
  - OS/exposure: September 30, 2019
- Median PFS and OS were estimated using the Kaplan–Meier method, and 95% CIs were calculated
- ORR (95% CI) was evaluated by treatment received

Results

- Of 431 patients randomized, 76 had received prior platinum (46 talazoparib and 30 PCT) (Figure 2)

Figure 2. Randomized Patient Schema



Abbreviation: PCT=physician's choice of chemotherapy treatment.

- Baseline characteristics were similar between the talazoparib and PCT groups, with a few exceptions: patients were younger in the talazoparib group (71.7% vs 46.7% <50 years of age); fewer talazoparib patients were white (67.4% vs 86.7%); and the talazoparib group had a lower percentage of patients with Eastern Cooperative Oncology Group performance status 0 (47.8% vs 70.0%) (Table 2)
- Median (range) exposure in the prior-platinum subgroup was 6.4 (0.7–38.2) months for talazoparib (n=46) and 2.1 (0.2–9.2) months for PCT (n=29)
  - Eleven patients (23.9%) received talazoparib for ≥12 months; no patients received PCT for ≥12 months
- The duration of treatment for each patient is shown in Figure 3

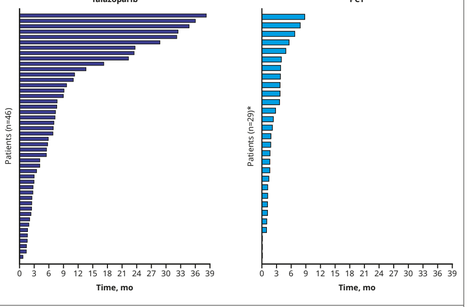
Table 2. Baseline Characteristics of the Prior-Platinum Population (ITT Population)

	Talazoparib (N=46)	Overall PCT (N=30)
Median age, y (min, max)	44.0 (27.0, 81.0)	51.0 (29.0, 63.0)
Age <50 y, no. (%)	33 (71.7)	14 (46.7)
Sex, no. (%)		
Female	46 (100.0)	29 (96.7)
Male	0	1 (3.3)
Race, no. (%)		
White	31 (67.4)	26 (86.7)
Asian	5 (10.9)	1 (3.3)
Black	3 (6.5)	0
Other/not reported	7 (15.2)	3 (10.0)
ECOG PS		
0	22 (47.8)	21 (70.0)
1	23 (50.0)	9 (30.0)
2	1 (2.2)	0
TNBC, no. (%)	31 (67.4)	19 (63.3)
HR+, no. (%)	15 (32.6)	11 (36.7)
BRCA status, no. (%)		
BRCA1	28 (60.9)	16 (53.3)
BRCA2	14 (30.4)	14 (46.7)
Prior chemotherapy regimens,* no. (%)		
0	15 (32.6)	9 (30.0)
1	14 (30.4)	9 (30.0)
≥2	17 (37.0)	12 (40.0)

Abbreviations: *BRCA1/BRCA2=breast cancer susceptibility gene 1* or *2*; ECOG PS=Eastern Cooperative Oncology Group performance status; HR+=hormone receptor-positive; ITT=intent-to-treat; PCT=physician's choice of chemotherapy treatment; TNBC=triple-negative breast cancer.
*Other than platinum.

- Outcomes according to the prior-platinum setting are shown in Table 3
  - Longer PFS with talazoparib vs PCT was seen in both the neoadjuvant/adjuvant and advanced settings for prior platinum: 8.9 months for talazoparib vs 2.9 months for PCT in the neoadjuvant/adjuvant setting, and 5.6 months and 4.3 months, respectively, in the advanced setting (Figure 4), although 95% CIs overlapped
    - Median follow-up was 11.2 months
  - ORR was higher with talazoparib vs PCT in the neoadjuvant/adjuvant setting for prior platinum (71.4% for talazoparib vs 21.4% for PCT)
  - Numerically longer median OS was seen for talazoparib vs PCT in the neoadjuvant/adjuvant setting for prior platinum (20.9 months for talazoparib vs 16.8 months for PCT) (Figure 5)
    - Median follow-up was 44.9 months for talazoparib and 36.8 months for PCT

Figure 3. Duration of Treatment by Individual Patient in the Prior-Platinum Subgroup (Safety Population)



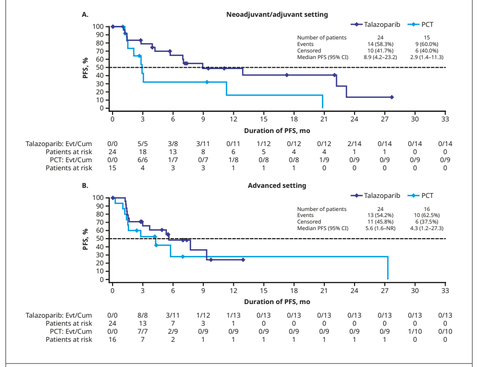
Abbreviation: PCT=physician's choice of chemotherapy treatment.
*Only 29 patients received study PCT and are included in the safety population.

Table 3. Efficacy Outcomes by Prior-Platinum Setting

	Prior Platinum in Neoadjuvant/Adjuvant Setting		Prior Platinum in Advanced Setting	
	Talazoparib (n=24)	PCT (n=15)	Talazoparib (n=24)	PCT (n=16)
PFS				
Events, n	14	9	13	10
Median (95% CI), mo	8.9 (4.2–23.2)	2.9 (1.4–11.3)	5.6 (1.6–NR)	4.3 (1.2–27.3)
ORR*				
% (95% CI)	71.4 (47.8–88.7)	21.4 (4.7–50.8)	22.2 (6.4–47.6)	25.0 (5.5–57.2)
OS				
Events, n	16	10	21	14
Median (95% CI), mo	20.9 (9.2–27.9)	16.8 (3.7–39.9)	9.6 (6.8–13.6)	9.4 (4.5–15.6)

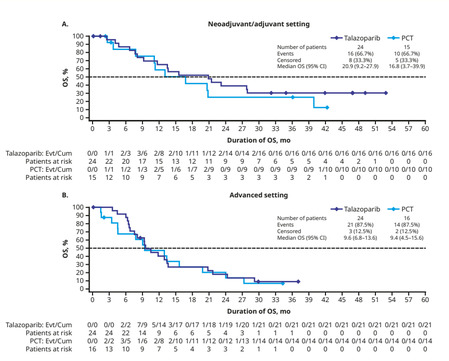
Hazard ratios and odds ratios are not presented due to small-size subgroups and not prespecified analysis.
Abbreviations: CI=confidence interval; NR=not reached; ORR=objective response rate; OS=overall survival; PCT=physician's choice of chemotherapy treatment; PFS=progression-free survival.
*In patients with measurable disease (n=21/18 for talazoparib; n=14/12 for PCT).

Figure 4. PFS in the Prior-Platinum Population Based on Independent Radiology Review: (A) Neoadjuvant/Adjuvant Setting; (B) Advanced Setting (ITT Population)



Abbreviations: CI=confidence interval; Evt/Cum=Events/Cumulative; ITT=intent-to-treat; NR=not reached; PCT=physician's choice of chemotherapy treatment; PFS=progression-free survival.

Figure 5. OS in the Prior-Platinum Population Based on Independent Radiology Review: (A) Neoadjuvant/Adjuvant Setting; (B) Advanced Setting (ITT Population)



Abbreviations: CI=confidence interval; Evt/Cum=Events/Cumulative; ITT=intent-to-treat; OS=overall survival; PCT=physician's choice of chemotherapy treatment.

Conclusions

- In this post hoc analysis of the EMBRACA trial, efficacy outcomes generally favored talazoparib over PCT in patients who received prior platinum in both early- and late-stage settings, but were particularly favorable for patients who received prior platinum as neoadjuvant/adjuvant treatment
  - Longer PFS and OS and greater ORR with talazoparib vs PCT were seen when platinum was given in the neoadjuvant/adjuvant setting
- Both platinum chemotherapy and PARP inhibitors target defective homologous recombination DNA repair in breast cancer with *BRCA1/2* mutations,[5-7] and restoration of *BRCA* function is associated with platinum resistance.[8] This may have contributed to the lower activity seen with talazoparib in those who were pretreated with platinum in advanced disease where more patients may have been exposed to platinum for a longer period of time
- These results support the use of talazoparib after platinum-based therapy when administered early in the course of disease and also suggest that either talazoparib or chemotherapy can be considered after platinum-based therapy in the advanced setting

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