P4-07-29 - Olaparib plus Trastuzumab in HER2[+] *BRCA*-Mutated Advanced Breast Cancer Patients: The OPHELIA Study

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BACKGROUND

- *BRCA1* and *BRCA2* genes encode two proteins that play a key role in the repair of DNA double-strand breaks by homologous recombination repair and the protection of the stalled replication fork. Tumors from patients (pts) with germline *BRCA* mutation (g*BRCA*m) have impaired homologous recombination repair –also known as HRD– that induces sensitivity to platinum-based chemotherapy as well as poly(adenosine diphosphate–ribose)polymerase inhibitors (PARPi)) [1].
- In the OlympiAD trial, oral PARPi olaparib resulted in better progression–free survival (PFS) than standard chemotherapy, which led to approval in pts with Human Epidermal Growth Factor Receptor 2 (HER2)-negative, g*BRCA1*m and/or g*BRCA2*m advanced breast cancer (ABC) [2].
- Prevalence of HER2 amplification is generally low among *BRCA1* and *BRCA2* mutation carriers. Case series showed g*BRCA1/2*m account for 2.1-10% and 6.8-13% of pts with HER2-positive (HER2[+]) ABC, respectively [3,4,5]. In the TCGA dataset HRD was confirmed in about 3% of HER2[+] tumors but recent studies estimated genomic HRD at 9-27% [6,7].
- Preclinical data support a strong synergism between olaparib and trastuzumab in HER2[+] breast cancer cell lines and xenograft models that are sensitive to PARPi [8]. Antitumor activity of olaparib in combination with trastuzumab in HER2[+] g*BRCA*m ABC pts is unknown.

OBJECTIVE

- The OPHELIA study aimed to assess the efficacy and safety of olaparib in combination with trastuzumab in pts with HER2[+] g*BRCA*m ABC.

STUDY DESIGN

Figure 1. OPHELIA Study Design (NCT03931551)

A multicenter, investigator-initiated, open-label, single-arm, phase 2 trial

Patients' characteristics

- Men or women aged ≥ 18 years
- Histologically and/or cytologically confirmed HER2[+] ABC (locally advanced or metastatic) with evaluable or measurable disease (RECIST v.1.1)
- ECOG performance status 0-1
- Confirmed deleterious or suspected deleterious g*BRCA1/2*m
- ≥1 prior systemic regimen for advanced disease including a pertuzumab- or T-DM1-based regimen

N = 20

Olaparib (300 mg oral, twice daily) + **Trastuzumab** (IV/SC at standard dose, on day 1 of each cycle)

21-day cycle

Primary endpoint

CBR (CR + PR + SD ≥24 weeks) assessed by investigator as per RECIST v.1.1

Secondary endpoints

ORR, PFS, maximum tumor reduction, DoR as per RECIST v.1.1, and OS.

Safety and tolerability as per NCI-CTCAE v.5.0.

Statistics

- Sample size was designed to attain a 90% power at 10% one-sided alpha level.
- Analysis based on exact binomial test.
- H0: CBR ≤5%; HA: CBR≥30%.
- Among 20 pts, ≥3 responders (15%) will be needed to consider a positive finding at final analysis.

- **Abbreviations:** ABC, Advanced breast cancer; CBR, Clinical benefit rate; DOR, Duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; IV, Intravenously; NCI-CTCAE, National cancer institute-Common Terminology Criteria for Adverse Events; ORR, Objective response rate; OS, Overall survival; PFS, Progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; SC, Subcutaneous.

RESULTS

1. Recruitment and Patient Disposition

- Between Mar 25, 2019, and Dec 31, 2021, five pts with a known g*BRCA*m detected by local testing were included in the study. In addition, g*BRCA*m status was centrally analyzed from a total of 63 pts with unknown g*BRCA*m status at 17 sites in Spain. Among these pts, two (3.2%) presented a g*BRCA*m (Table 1). Two pts with g*BRCA*m were not finally enrolled into the study due to premature termination of the trial and death prior to the start of the study, respectively.
- At data cutoff (Mar 2, 2022), with a median follow-up of 18.7 months (min: 11.7; max: 22.1), 2 of 5 (40.0%) pts remained on therapy.
- The study was closed due to slow accrual.

Table 1. Patient Demographic Characteristics at Baseline

Baseline characteristics	n (%)
Age, median (range) years	37.0 (32.0; 54.0)
Female	4 (80.0%)
Male	1 (20.0%)
Ethnic origin	
Caucasian	4 (80.0%)
Black	1 (20.0%)
Premenopausal status	
No	2 (40.0%)
Yes	2 (40.0%)
NA (male)	1 (20.0%)
ECOG performance status	
0	3 (60.0%)
1	2 (40.0%)
Measurable lesions	
Yes	3 (60.0%)
No	2 (40.0%)
HR status	
Positive	3 (60.0%)
Negative	2 (40.0%)
***BRCA* mutation status**	
Germinal *BRCA1* mutation	1 (20.0%)
Germinal *BRCA2* mutation	4 (80.0%)
Previous early disease treatment	
Yes	2 (40.0%)
No	3 (60.0%)
Number of previous lines for ABC	
1	1 (20.0%)
3	2 (40.0%)
4	2 (40.0%)
Previous advanced disease treatment	
Anti-HER2 agents	5 (100.0%)
Trastuzumab + Pertuzumab	5 (100.0%)
T-DM1	2 (40.0%)
Others	1 (20.0%)
Antineoplastic agents	5 (100.0%)
Therapeutic radiopharmaceuticals	2 (40.0%)
Endocrine therapy	1 (20.0%)

- **Abbreviations:** ABC, Advanced breast cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, Hormone receptor; NA, Not assessed.
- n (%), Number of patients (percentage based on N).

2. Efficacy Endpoints

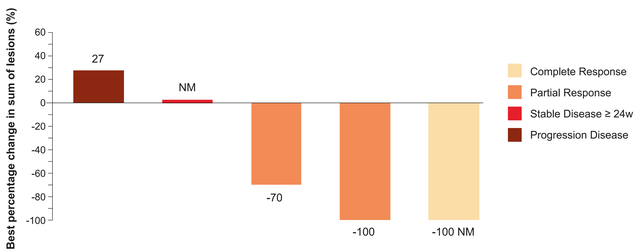
- CBR at 24 weeks was 80.0% (4 of 5 pts; 95% CI, 23.6% to 99.7%, p<0.001) meeting the primary endpoint (Table 2).

Table 2. *BRCA* Mutation, Treatment, and Clinical Status

Cohort (N=5)	Gender Age	g*BRCA*m status	HR	Prior lines in Advanced setting	Best response	PFS Months	PFS Events	OS Months	OS Death
102-001	Woman 32 years	*BRCA1*	[-]	1	**PR**	5.2	PD	14.4	Yes
103-003	Man 54 years	*BRCA2*	[+]	3	**PR**	11.2+	No	11.7	No
105-001	Woman 36 years	*BRCA2*	[+]	3	PD	1.2	PD	18.7	Yes
118-001	Woman 39 years	*BRCA2*	[+]	4	**SD≥24W**	5.6+[1]	No	22.1	No
118-002	Woman 37 years	*BRCA2*	[-]	4	**CR**	19+	No	19.9	No

- Patients with clinical benefit are in bold.
- [1] Treatment discontinuation related with a grade 3 leukopenia; +: Pts without progressive disease.
- **Abbreviations:** CR, Complete Response; OS, Overall Survival; PD, Progressive Disease; PFS, Progression-free survival; PR, Partial Response; HR, Hormone receptor; NA, Not applicable; PD, Progressive disease; SD≥24W, Stable disease lasting ≥24 weeks.

Figure 2. Waterfall Plot of Best Overall Response



- **Abbreviations:** NM, Non-measurable.
- (*) Overall response is partial response by RECIST v.1.1 criteria (CR [target] and non-PD/non-PR [non-target]).

Table 3. Tumor Response as per RECIST v.1.1

Tumor response, n (%)	(N = 5)
Confirmed Best Overall Response, n (%)	
CR	1 (20.0%)
PR	2 (40.0%)
SD≥24w	1 (20.0%)
PD	1 (20.0%)
ORR[1], n (%) (95% CI)	3 (60.0%) (11.4%; 96.3%)
CBR[2], n (%) (95% CI)	4 (80.0%) (23.6%; 99.7%)
DoR in months, Median (Min; Max)	3.8 (2.5-8.3)
6-months PFS rate, (95% CI)	60% (12.6%; 88.2%)

- **Abbreviations:** CBR, Clinical benefit rate; CR, Complete response; DoR, Duration of response; N, Number of patients in the population; ORR, Overall response; PD, Progressive disease; PFS, Progression-free survival; PR, Partial response; SD, Stable disease; 95%CI, 95% Confidence interval; w, Weeks.
- [1] CR + PR.
- [2] CR + PR + SD ≥24 weeks.
- n (%), number of patients (percentage based on N).

3. Safety Endpoints

Table 4. Summary of TEAEs G3 and G1-2 of 40% incidence

Related TEAEs, n (%)	Overall (N=5) Any grade	Grade 3
Any	5 (100%)	1 (20.0%)
Hematologic	2 (40.0%)	1 (20.0%)
Anemia	2 (40.0%)	1 (20.0%)
Lymphopenia	2 (40.0%)	1 (20.0%)
Leukopenia	1 (20.0%)	1 (20.0%)
Neutropenia	1 (20.0%)	1 (20.0%)
Non-Hematologic	5 (100.0%)	1 (20%)
Nausea	3 (60.0%)	0 (0%)
Vomiting	2 (40.0%)	0 (0%)
Fatigue	2 (40.0%)	0 (0%)
Pericardial effusion	1 (20.0%)	1 (20.0%)

- **Abbreviations:** G, Grade; N, Number of patients in the population; TEAE, Treatment emergent adverse events.
- n (%), Number of patients (percentage based on N).

- One (20.0%) patient discontinued treatment because grade 3 leukopenia. The dose of olaparib was previously reduced due to grade 3 anemia and neutropenia.
- No treatment-related deaths were reported.

CONCLUSIONS

- Despite the premature trial termination and limited sample size, the trial met its primary endpoint with a clinically meaningful CBR.
- No unexpected adverse events were found.
- HER2 overexpression in g*BRCA*m ABC is infrequent.
- Real-world data should be collected to address the intriguing activity of olaparib in combination with trastuzumab in HER2[+] patients carrying *BRCA* pathogenic variants.

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