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Olaparib plus trastuzumab in HER2-positive advanced breast cancer patients with germline *BRCA1/2* mutations: The OPHELIA phase 2 study

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ABSTRACT

Purpose: To evaluate the efficacy and safety of the combination of olaparib plus trastuzumab in patients with HER2-positive advanced breast cancer (ABC) and germinal *BRCA* mutations (*gBRCAm)*.

Methods: OPHELIA (NCT03931551) was a single-arm, open-label, phase 2 clinical trial. Patients aged ≥18 years diagnosed with HER2-positive ABC with germinal deleterious mutations in *BRCA1* or *BRCA2* who had received at least one prior systemic regimen for advanced disease were enrolled. Patients received olaparib plus trastuzumab until disease progression, unacceptable toxicity, or consent withdrawal. The primary endpoint was investigator-assessed clinical benefit rate for at least 24 weeks as per RECIST v.1.1. Key secondary endpoints included overall response rate (ORR) and safety profile.

Results: A total of 68 pre-treated HER2-positive ABC patients were screened. Due to slow accrual the trial was stopped after enrolling 5 patients instead of the planned sample size of 20. Four patients achieved clinical benefit (80.0 %, 95 % CI; 28.4–99.5, $p < 0.001$) and the primary endpoint was met. The ORR was 60.0 % (95 % CI; 14.7–94.7), including one complete response. Four (80.0 %) patients experienced at least one treatment-related treatment-emergent adverse event (TEAE). Most TEAEs were grade 1 or 2. There were no treatment-related deaths and no new safety signals were identified.

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Conclusions: This study suggests that the combination of olaparib plus trastuzumab may be effective and safe in pre-treated patients with HER2-positive g*BRCA*m ABC. This ABC patient population should be further studied and not be pre-emptively excluded from clinical trials of targeted therapy for *BRCA1/2*-driven cancers.

Trial registration

ClinicalTrials.gov identifier: NCT03931551.

Prior presentation

These results were selected for poster presentation at the 2022 San Antonio Breast Cancer Symposium in San Antonio, Texas, USA (December 6–10, 2022). "Olaparib plus Trastuzumab in HER2[+] BRCA-Mutated Advanced Breast Cancer Patients: The OPHELIA Study". Poster ID: P4-07-29.

1. Introduction

The outcome of patients with HER2-positive breast cancer has dramatically improved with the introduction of new antiHER2-targeted therapies. However, in some cases, the disease will progress and most of the patients treated in the metastatic setting will experience disease progression despite trastuzumab-based therapies [1].

Mutations in *BRCA1/2* are associated with breast cancer occurrence and lead to impaired deoxyribonucleic acid (DNA) repair [2]. In patients with early and metastatic HER2-negative breast cancer and germline *BRCA 1/2* mutations (g*BRCA*m), poly-(ADP-ribose)-polymerase (PARP) inhibitors, such as olaparib, are an effective therapeutic option that further inhibits DNA repair, inducing cell death (synthetic lethality). Moreover, preclinical data suggest that breast cancer cells respond to olaparib irrespective of HER2 status [3,4], and synergism between olaparib and trastuzumab has been demonstrated in HER2-positive breast cancer cells and xenograft models [5].

On these bases, we hypothesized that olaparib plus trastuzumab could be a treatment option for trastuzumab pre-treated patients with HER2-positive advanced breast cancer (ABC) with *gBRCAm*. Here, we report the results of the OPHELIA phase 2 study evaluating the efficacy and safety of olaparib plus trastuzumab in this patient population.

2. Methods

2.1. Study design and participants

OPHELIA was a single-arm, open-label, multicenter phase 2 study conducted across 17 sites in Spain. The OPHELIA trial protocol is available as supplementary material. The study included patients with HER2-positive ABC with *gBRCA*m (*BRCA1* or *BRCA2,* predicted to be deleterious or suspected deleterious) resistant to trastuzumab and not amenable to resection or radiotherapy with curative intent. Five patients had a previously known germinal *BRCA* mutation detected by local testing. In addition, germinal *BRCA* mutation status was analyzed centrally in a total of 63 patients with unknown germinal *BRCA* mutation status. HER2 status was confirmed locally. Full eligibility criteria are listed in Supplement Table S1. This study was conducted in compliance with the Declaration of Helsinki and was approved by the institutional review boards or independent ethics committees at each site. All patients provided written informed consent. This study was registered at ClinicalTrials.gov (NCT03931551).

2.2. Procedures

Patients received 300 mg of olaparib twice daily plus trastuzumab, administered on Day 1 of every three-week cycle, either as a subcutaneous injection of 600 mg irrespective of the patient's weight, or as an infusion with a loading dose of 8 mg/kg on the first cycle and of 6 mg/kg in subsequent cycles. Treatment was given to patients until progressive disease, unacceptable toxicity, or withdrawal of consent.

Computed tomography or magnetic resonance imaging of the chest, abdomen, and pelvis, and bone scan were conducted at baseline, every 6 weeks up to week 24, and every 12 weeks thereafter. Bone scans were conducted at baseline and repeated every 24 weeks during the study only if bone involvement was found at baseline.

2.3. Outcomes

The primary endpoint was clinical benefit rate (CBR), defined as the proportion of patients who achieved overall tumor response (complete or partial response) or stable disease for at least 24 weeks, assessed by investigators per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Secondary endpoints were: objective response rate (ORR) per RECIST v1.1; time to response (TTR); duration of response (DoR); progression-free survival (PFS); overall survival (OS); and safety profile, following Common Terminology Criteria for Adverse Events (CTCAE) v5.0.

2.4. Statistical analysis

Continuous data were summarized with the number of observations, mean, median, minimum, and maximum. An estimated sample size of 20 patients was calculated to attain a 90 % power at 10 % one-sided alpha level for CBR analysis. The primary analysis was based on exact binomial test and planned to test the null hypotheses that the true rate of patients with clinical benefit was $\leq$5 %. The alternative hypothesis was a true rate for primary endpoint $\geq$30 %. The primary endpoint would be met if $\geq$ 3 patients had clinical benefit among 20 patients. CBR and ORR were estimated with the 95 % Clopper-Pearson CIs. DoR and TTR were summarized with median and minimum and maximum values (range). PFS and OS were estimated using the Kaplan-Meier method, reporting the median with 95 % confidence intervals (CIs) and the number of events. Descriptive statistics were used for summarizing safety data. Two-sided p values with alpha of 0.05 level of significance were used for all secondary analyses. SAS software v9.4 was used to conduct statistical analyses.

3. Results

From March 2019 to December 2021, a total of 68 patients with HER2-positive ABC were screened. Five (7.4 %) patients had known *gBRCA*m determined locally (*gBRCA1*m, n = 1*; gBRCA2*m, n = 4) and were enrolled in the study. For the remaining 63 (92.6 %) patients, *gBRCA*m status was evaluated centrally. Of these, 61 (96.8 %) did not present *gBRCA*m*;* the remaining two (3.2 %) patients had *gBRCA*m*,* but one died prior to enrollment and the other was not included because the trial ended prematurely, given the slow accrual.

Median age was 37.0 years (range, 32–54) and four (80.0 %) of the five enrolled patients were female. The median number of previous lines of therapy for metastatic disease was 3 (range, 1–4), including, trastuzumab (100 %), pertuzumab (100 %), trastuzumab emtansine (40.0 %), and other anti-HER2 therapies (20.0 %). No patient had received trastuzumab deruxtecan. The demographic and clinical characteristics of the patients are summarized in Table 1.

At the time of the data cut-off (March 2, 2022), two patients (40.0 %) continued to receive study treatment for 11.7 and 19.9 months, and three patients (60.0 %) had discontinued treatment, one (20.0 %)

Table 1
Baseline patient characteristics.

Baseline characteristics	n (%) N = 5
Age; median (min; max) (years)	37.0 (32.0; 54.0)
Sex	
Female	4 (80.0)
Male	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)
Disease sites	
Bones	3 (60.0)
Lung	2 (40.0)
Brain	1 (20.0)
Breast	1 (20.0)
Liver	1 (20.0)
Lymph nodes	1 (20.0)
Mediastinum	1 (20.0)
Number of metastatic sites	
1	1 (20.0)
2	3 (60.0)
3	1 (20.0)
HR status	
Positive	3 (60.0)
Negative	2 (40.0)
***BRCA* mutations**	
Germinal *BRCA1* mutation	1 (20.0)
Germinal *BRCA2* mutation	4 (80.0)
Advanced disease at first diagnosis	
Yes	3 (60.0)
No	2 (40.0)
Number of previous lines of therapy for ABC	
1	1 (20.0)
3	2 (40.0)
4	2 (40.0)
Previous treatment for ABC	
Anti-HER2 agents	5 (100.0)
Trastuzumab + pertuzumab	5 (100.0)
T-DM1	2 (40.0)
Other	1 (20.0)
Chemotherapy	5 (100)
Therapeutic radiopharmaceuticals	2 (40.0)
Endocrine therapy	1 (20.0)

ABC, advanced breast cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hormone receptor; NA, not applicable; T-DM1, trastuzumab emtansine.

because of an adverse event and two (40.0 %) because of disease progression.

The median treatment duration of trastuzumab and olaparib was 24.6 weeks (range, 6–89.6) and 23.6 weeks (range, 6–83.3), respectively. The median duration of follow-up was 18.7 months (range, 11.7–22.1). Of the five patients assessed, one (20.0 %) had a complete response, two (40.0 %) achieved a partial response, and one (20.0 %) presented stable disease for more than 24 weeks. The primary endpoint was met, with four patients achieving clinical benefit (80.0 %, 95 % CI; 28.4–99.5, $p < 0.001$). ORR was 60.0 % (95 % CI; 14.7–94.7) (Fig. 1, Tables 2 and 3). Median TTR was 2.9 months (range, 1.2–16.5) and median DoR was 3.8 months (range, 2.5–8.3). There were two (40.0 %) patients with PFS events at 5.2 and 1.2 months, respectively (Table 2). These two patients died during the study follow-up period, 14.4 and 18.7 months after initiating treatment, respectively.

All patients experienced at least one treatment-emergent adverse event (TEAEs) (Table 4) and four (80.0 %) experienced at least one treatment-related TEAE (Supplement Table S2). The most common

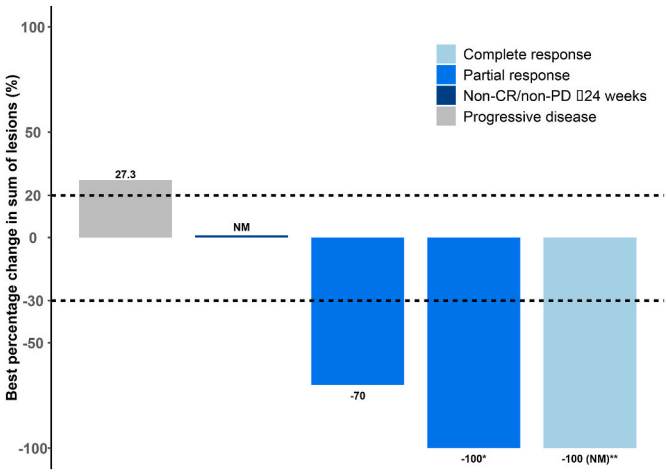

Fig. 1. Waterfall plots of best response (per RECIST v1.1) in patients with HER2-positive advanced breast cancer with germline mutations in *BRCA 1/2* treated with olaparib plus trastuzumab. Non-CR/Non-PD; Non-complete response/non-progressive disease; NM, not measurable. *Overall response was partial response by RECIST v.1.1 criteria: complete response in target lesions and non-progressive disease/non-partial response in non-target lesions. **Disappearance of all lesions.

treatment-related TEAEs of any grade (G) were nausea (n = 3, 60.0 %; 0 % G ≥ 3), vomiting (n = 2, 40.0 %; 0 % G ≥ 3), fatigue (n = 2, 40.0 %; 0 % G ≥ 3), anemia (n = 2, 40.0 %; n = 1, 20.0 % G ≥ 3), and lymphopenia (n = 2, 40.0 %; n = 1, 20.0 % G ≥ 3). All grade 3 hematologic events reported in this study were attributed to olaparib. There were no serious TEAEs and no treatment-related deaths.

One (20.0 %) patient discontinued treatment because of a treatment-related TEAE (G3 leukopenia) after two previous dose reductions of olaparib because of G3 anemia and G3 neutropenia. No more dose reductions of olaparib due to adverse events occurred and no TEAEs led to dose adjustments of trastuzumab.

4. Discussion

In OPHELIA, five patients with refractory HER2-positive ABC and *gBRCA*m were treated with olaparib plus trastuzumab and achieved a CBR of 80.0 %, meeting the primary endpoint. ORR was 60.0 %, which is similar to that reported in the OlympiAD trial (59.9 %) for olaparib as a single agent in patients with HER2– ABC and g*BRCA*m [6]. The safety profile of olaparib plus trastuzumab was consistent with previous reports in ABC [6], and the combination was well tolerated, with most of the adverse events of G1 or G2. There were no treatment-related deaths in this study and two patients remained on treatment at data cut-off.

This study was terminated prematurely because of slow accrual. However, despite not reaching the expected enrollment, the primary endpoint was met, according to the statistical plan. Recruitment was challenging for two reasons. First, the population evaluated is rare. Indeed, in previous studies, g*BRCA*m has been reported in 2.5%–13.0 % of HER2-positive breast cancers [7–9] and, in this study, it was found in 3.2 % of HER2-positive breast cancers. Second, patients with HER2-positive ABC are often not tested for *gBRCAm* in the absence of a suggestive family history. Thus, patients with HER2-positive ABC and *gBRCA*m could have been historically underdiagnosed.

The main strength of this study is being the first to evaluate a combination regimen with olaparib in patients with HER2-positive ABC and g*BRCA*m, a population that is excluded from this therapeutic approach. The main limitation is the small sample size. *gBRCA*m in patients with HER2-positive ABC is infrequent, and it is unlikely that additional formal phase II or III studies will be conducted in this patient population. Alternative research options such as real-world data could be used to

Table 2
Summary of *BRCA* mutation, treatment, and clinical status.

Gender; age	*gBRCAm*	Metastatic location	HR	Prior treatment lines for ABC	Grade 3 TEAEs	Best response	PFS		OS	
							Months	Events	Months	Death
Woman; 32 years	*BRCA1*	Breast, Lung, and lymph nodes	[−]	1	–	PR[a]	5.2	PD	14.4	Yes
Man; 54 years	*BRCA2*	Lung and bones	[+]	3	–	PR[a]	11.2+	No	11.7	No
Woman; 36 years	*BRCA2*	Liver and bones	[+]	3	–	PD	1.2	PD	18.7	Yes
Woman; 39 years	*BRCA2*	Mediastinum and bones	[+]	4	Leukopenia, Neutropenia, Anemia, and Pericardial effusion	Non-CR/Non-PD ≥24W (NM)[a,b]	5.6+	No	22.1	No
Woman; 37 years	*BRCA2*	Brain	[−]	4	–	CR (NM)[a]	19+	No	19.9	No

+, patient with no disease progression at data cut-off off (March 2, 2022); ABC, advanced breast cancer; CR, complete response; HR, hormone receptor; NM, patient with non-measurable lesions; non-CR/non-PD, non-complete response/non-progressive disease; OS, overall survival; PD, progressive disease; PFS, progression free survival; PR, partial response; TEAEs, treatment-emergent adverse event; W, weeks.

[a] Patient obtained clinical benefit.

[b] Patient discontinued treatment because of grade 3 leukopenia.

Table 3
Objective response (per RECIST v1.1) assessed by investigators in the intent-to-treat population.

Tumor response	n (%) N = 5
Clinical benefit rate, % (95 % CI)	80.0 (28.4–99.5)
Objective response rate, % (95 % CI)	60.0 (14.7–94.7)
Best overall response	
Complete response	1 (20.0)
Partial response	2 (40.0)
Stable disease ≥24 weeks	1 (20.0)
Progressive disease	1 (20.0)

95 % CI, 95 % confidence intervals.

address the intriguing but not unexpected antitumor activity of this combination.

5. Conclusions

The findings from this study suggest that the combination of olaparib plus trastuzumab may be effective and safe in pre-treated patients with HER2-positive ABC and g*BRCA*m. The population evaluated here is rare, and it is unlikely that this treatment can be assessed in larger clinical trials, unless they involve multiple centers across several countries. Although infrequent, co-existence of HER2 positivity and g*BRCAm* should be acknowledged. More investigation is required to better describe this subgroup of patients, who should not be pre-emptively excluded from clinical trials of targeted therapy for *BRCA1/2*-driven cancers. Finally, further studies should explore whether olaparib alone achieves similar results and could be an additional treatment option for this patient population.

Data sharing statement

Data collected within this study will be made available to researchers after contacting the corresponding author and upon revision and approval based on scientific merit by the OPHELIA trial management group (which includes a qualified statistician) of a detailed proposal for their use. The data required for the approved, specified purposes and the trial protocol will be provided after the completion of a data sharing agreement that will be set up by the study sponsor. All data provided are anonymized to respect the privacy of patients who have participated in the trial in line with applicable laws and regulations. Estimate time-frame for response will be within 30 days. Please, address requests for data to the corresponding author.

Table 4
Summary of TEAEs.

Adverse event	Any grade n (%)	Grade 3 n (%)
Any TEAE	**5 (100.0)**	**1 (20.0)**
Hematologic	**2 (40.0)**	**1 (20.0)**
Blood and lymphatic system disorders	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)
Thrombocytopenia	1 (20.0)	0 (0.0)
Non-hematologic	**5 (100.0)**	**1 (20.0)**
Gastrointestinal disorders	4 (80.0)	0 (0.0)
Nausea	3 (60.0)	0 (0.0)
Vomiting	2 (40.0)	0 (0.0)
Abdominal pain upper	1 (20.0)	0 (0.0)
Diarrhea	1 (20.0)	0 (0.0)
Stomatitis	1 (20.0)	0 (0.0)
General disorders and administration site conditions	3 (60.0)	0 (0.0)
Fatigue	3 (60.0)	0 (0.0)
Flu-like symptoms	1 (20.0)	0 (0.0)
Musculoskeletal and connective tissue disorders	3 (60.0)	0 (0.0)
Back pain	2 (40.0)	0 (0.0)
Musculoskeletal chest pain	1 (20.0)	0 (0.0)
Myalgia	1 (20.0)	0 (0.0)
Laboratory values	1 (20.0)	0 (0.0)
Alanine aminotransferase increased	1 (20.0)	0 (0.0)
Aspartate aminotransferase increased	1 (20.0)	0 (0.0)
Blood alkaline phosphatase increased	1 (20.0)	0 (0.0)
Gamma-glutamyl transferase increased	1 (20.0)	0 (0.0)
Metabolism and nutrition disorders	1 (20.0)	0 (0.0)
Decreased appetite	1 (20.0)	0 (0.0)
Nervous system disorders	1 (20.0)	0 (0.0)
Somnolence	1 (20.0)	0 (0.0)
Cardiac disorders	1 (20.0)	1 (20.0)
Pericardial effusion	1 (20.0)	1 (20.0)

There were no grade 4 or grade 5 events.
n represents the number of participants.

Funding/support and role of the sponsor

MEDSIR, as legal sponsor of the study, is responsible for compliance with all clinical and regulatory procedures and adherence to the study protocol. MEDSIR had a role in study design, collection, management, analysis, and interpretation of the data, and writing of the report. This study was funded by AstraZeneca, Spain, who did not participate in data

collection, data analysis, data interpretation, or writing of this report. All authors had full access to the data used to prepare the manuscript and participated in writing, editing, and/or critically reviewing the manuscript.

CRediT authorship contribution statement

José Enrique Alés-Martínez: Writing – review & editing, Writing – original draft, Investigation, Conceptualization. **Judith Balmaña:** Writing – review & editing, Investigation. **Pedro Sánchez-Rovira:** Writing – review & editing, Investigation. **Francisco Javier Salvador Bofill:** Writing – review & editing, Investigation. **Jose Ángel García Sáenz:** Writing – review & editing, Investigation. **Isabel Pimentel:** Writing – review & editing, Investigation. **Serafín Morales:** Writing – review & editing, Investigation. **María Fernández-Abad:** Writing – review & editing, Investigation. **Ainhara Lahuerta Martínez:** Writing – review & editing, Investigation. **Neus Ferrer:** Writing – review & editing, Investigation. **Pilar Zamora:** Writing – review & editing, Investigation. **Begoña Bermejo:** Writing – review & editing, Investigation. **Tamara Díaz-Redondo:** Writing – review & editing, Investigation. **María Helena López-Ceballos:** Writing – review & editing, Investigation. **María Galán:** Writing – review & editing, Investigation. **Jhudit Pérez-Escuredo:** Writing – review & editing, Writing – original draft, Project administration. **Laura Calabuig:** Writing – review & editing, Project administration. **Miguel Sampayo:** Writing – review & editing, Writing – original draft, Formal analysis. **José Manuel Pérez-Garcia:** Writing – review & editing, Writing – original draft, Investigation. **Javier Cortés:** Writing – review & editing, Writing – original draft, Investigation, Conceptualization. **Antonio Llombart-Cussac:** Writing – review & editing, Writing – original draft, Investigation, Conceptualization.

Declaration of competing interest

J.E.A.M. reports receiving travel compensation from AstraZeneca, Roche; and research grants from AstraZeneca. **J.B.** has participated as invited speaker for AstraZeneca; has institutional, personal and financial interests in AstraZeneca; has institutional and other financial interests in AstraZeneca-MSD; has been involved in educational programs for AstraZeneca-MSD, declares participation in steering committees for AstraZeneca; reports institutional and financial interests in MEDSIR; and declares being a local principal investigator at MEDSIR. **J.A.G.S.** declares consultative and advisory services for Seagen, AstraZeneca, Daiichi Sankyo, Novaris, Gilead, Menarini; consultancy/speaker fees from Celgene, Eli Lilly, EISAI, MSD, Exact Sciences, Tecnofarma, Nolver (Adium), Asofarma, Roche; institution and research funding from AstraZeneca; and travel support from Gilead, AstraZeneca, Daiichi Sankyo. **I.P.** reports receiving honoraria from MSD, Novartis, AstraZeneca, Gildead; and consultancy or advisory role for AstraZeneca. **M.F.A.** declares speakers' bureaus from Daiichi-AstraZeneca, Lilly, Pfizer, Novartis, Eisai; expert testimony for Lilly; and receiving travel expenses from Roche, Novartis. **B.B.** reports receiving fees for medical education as consulting or advisory role with MSD, Roche, Pierre Fabre, Novartis, Astra Zeneca, Seagen; and speakers' bureau with Pfizer, Roche, MSD, Palex, Eisai, Daichii, Astra Zeneca, Seagen. **M.H.L.C.** reports speaker honoraria from Daichii, Novartis & Pierre Fabre; and travel and training grants from Roche, Pfizer, MSD & Novartis. **J.P.E.** is a full-time employee at MEDSIR. **L.C.** is a full-time employee at MEDSIR. **M.S.C.** reports participating in an advisory board for Optimapharm, Ability Pharma, and MD Anderson; and is a full-time employee at MEDSIR. **J.M. P.G.** declares having a consulting or advisory role for Lilly, Roche, Eisai, Daichii Sankyo, AstraZeneca, Seattle Genetics, Gilead, MSD; travel compensation from Roche; and employment at MEDSIR. **J.C.** reports serving as a consultant/advisor Roche, AstraZeneca, Seattle Genetics, Daiichi Sankyo, Lilly, Merck Sharp&Dohme, Leuko, Bioasis, Clovis Oncology, Boehringer Ingelheim, Ellipses, Hibercell, BioInvent, Gemoab, Gilead, Menarini, Zymeworks, Reveal Genomics, Scorpion Therapeutics, Expres2ion Biotechnologies, Jazz Pharmaceuticals, Abbvie, BridgeBio; receiving honoraria from Roche, Novartis, Eisai, Pfizer, Lilly, Merck Sharp&Dohme, Daiichi Sankyo, Astrazeneca, Gilead, Steamline Therapeutics; research funding to the Institution from Roche, Ariad pharmaceuticals, AstraZeneca, Baxalta GMBH/Servier Affaires, Bayer healthcare, Eisai, F.Hoffman-La Roche, Guardanth health, Merck Sharp&Dohme, Pfizer, Piqur Therapeutics, Iqvia, Queen Mary University of London; stock of MEDSIR, MAJ3 Capital, Leuko (relative); travel, accommodation, expenses from Roche, Novartis, Eisai, Pfizer, Daiichi Sankyo, Astrazeneca, Gilead, Merck Sharp&Dhome, Steamline Therapeutics; and patents: (1) Pharmaceutical Combinations of A Pi3k Inhibitor And A Microtubule Destabilizing Agent.Javier Cortés Castán, Alejandro Piris Giménez, Violeta Serra Elizalde. WO 2014/199294 A. ISSUED. (2) Her2 as a predictor of response to dual HER2 blockade in the absence of cytotoxic therapy.Aleix Prat, Antonio Llombart, Javier Cortés.US 2019/0338368 A1. LICENSED **A.L.C.** reports receiving research support from Roche, Agendia, Lilly, Pfizer, Novartis, Merck Sharp & Dohme, Gilead, and Daichii-Sanyo; consulting or advisory role for Lilly, Roche, Pfizer, and Novartis; speakers' bureaus from Lilly, AstraZeneca, Merck Sharp & Dohme; travel support from Roche, Pfizer, AstraZeneca; and stock or other ownership of MEDSIR and Initia-Research. **P.S.R., F.J.S.B., S.M., A.L.M., N.F., P.Z., T.D.R.,** and **M.G.** declare that they have not conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.breast.2024.103780.

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