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ORIGINAL RESEARCH

Characterization of the HER2 status in *BRCA*-mutated breast cancer: a single institutional series and systematic review with pooled analysis

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Available online 8 July 2022

Background: Pathogenic variants (PVs) in *BRCA1/2* genes account for ~6% of breast and 20% of ovarian cancers. Most breast tumors developed by *BRCA1* carriers are triple negative. *BRCA2* tumors have similar rates of estrogen receptor positivity as sporadic controls but are less likely to be human epidermal growth factor receptor 2 (HER2)-positive. Prevalence of HER2 positivity among breast cancers (BCs) in *BRCA1/2* mutation carriers is poorly and variably described, ranging from 0% to 10% and 0% to 13% in *BRCA1* and *BRCA2* carriers, respectively.

Patients and methods: We assessed the prevalence of HER2 positivity among a single institutional cohort of 398 BCs developed in carriers of *BRCA1/2* PVs (240 *BRCA1*, 158 *BRCA2*). Subsequently, a systematic review of the literature and pooled analysis was carried out.

Results: In our series we found a 7% HER2 positivity rate among all first *BRCA1/2* BCs overall. In *BRCA1* carriers, 5.4% of BCs were HER2-positive compared with 9.5% in *BRCA2*-mutated patients. Among bilateral BCs, HER2-positive cases were 15.2% in the *BRCA1* group and 23.1% in the *BRCA2* group. Notably, six *BRCA1* and eight *BRCA2* carriers showed discordant HER2 status between BC and bilateral BC (23.7%, 14/59). The systematic review included 21 083 *BRCA1/2* patients from 73 eligible studies. The pooled rate of *BRCA*mut/HER2-positive BCs is 9.1% (95% confidence interval 7.3% to 11.2%). *BRCA1* and *BRCA2* when reported as separate data ranged from 0% to 33.3% (mean 8.3%) and from 0% to 86% (mean 10.3%), respectively.

Conclusions: As compared with sporadic cases, BCs occurring in *BRCA1* and/or *BRCA2* PVs carriers are less frequently HER2-positive. Prevalence of HER2 positivity in our series was consistent with pooled analysis and did not exceed 10%. Although not common, co-existence of *BRCA* mutations and HER2 overexpression and/or gene amplification should be acknowledged. More research is needed to better characterize this subgroup of patients who should not be excluded *a priori* from clinical trials of targeted therapy for *BRCA1/2*-driven cancers.

Key words: breast cancer, HER2-positive, *BRCA1*, *BRCA2*

INTRODUCTION

Breast cancer (BC) is a heterogeneous disease, with different molecular subtypes identified by gene expression profiling analyses [Luminal A, Luminal B, human epidermal growth factor receptor 2 (HER2)-enriched, basal-like/triple-negative].[1,2] HER2 belongs to the epidermal growth factor receptor family, and gene amplification or protein overexpression are observed in up to 20% of all BCs, usually associated with poor prognosis.[3-5] The first developed therapy targeting HER2 was trastuzumab, a monoclonal antibody first licensed by the Food and Drug Administration in 1998 in the advanced setting, followed by other drugs, for early and/or advanced disease (monoclonal antibodies, tyrosine kinase receptor inhibitors, antibody-drug conjugates), with a significant prognostic improvement.

To date, many HER2-targeted therapies are available, but patients with HER2-positive BC are usually not eligible in clinical trials exploring drug activities against other targets, even if expressed. This is the case of BC associated to germline variants of *BRCA1* and *BRCA2*, which are the two major genes underlying hereditary breast and ovarian cancer (HBOC).[6] As for BC, up to 15% of all new cases are attributable to a familial or hereditary condition. Among

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these, *BRCA1* and *BRCA2* are the genes most frequently involved, playing an important role in maintaining the genomic stability, especially participating in the homologous recombination repair (HRR) of DNA double-strand breaks.[7]

Tumors with HRR deficiency, such as ovarian and breast *BRCA*-mutant cancers, show a greater sensibility to drugs causing DNA damages, such as platinum compounds and poly(ADP-ribose)polymerase (PARP) inhibitors. Especially the latter, through a mechanism called synthetic lethality, showed significant efficacy in trials of advanced BC, and more recently, in the adjuvant setting.[8,9] In all these trials, *BRCA1/BRCA2* mutation carriers were excluded if concomitant HER2-positive status was present.

About two-thirds of BCs occurring in patients with *BRCA1* germline mutations usually lack the estrogen receptor (ER), progesterone receptor, and HER2 overexpression or gene amplification (the so-called 'triple-negative' BC).[10-12] As for *BRCA2* tumors, similar rates of ER positivity as sporadic controls are described, but HER2-positive cases are also infrequent. The prevalence of HER2 positivity among *BRCA1/2* mutation carriers is poorly and variably described in literature, ranging from 0% to 10% and 0% to 13% in *BRCA1* and *BRCA2* carriers, respectively.[13]

In order to analyze the prevalence and the characteristics of HER2-positive BC in this setting, we retrospectively reviewed our single institutional series of BCs in *BRCA1/2* mutation carriers. Moreover, we carried out a systematic review of the literature, with the aim of characterizing the subgroup of *BRCA1/2*-mutated patients with concomitant HER2-positive BC.

MATERIAL AND METHODS

Single institutional study cohort

To assess the relationship between HER2 status in BC and the presence of pathogenic/likely pathogenic variants (PVs) of the *BRCA1* and *BRCA2* genes in our population, we selected a study cohort among individuals who underwent genetic counseling and *BRCA1/2* testing at the Medical Genetics Unit of Fondazione IRCCS Istituto Nazionale dei Tumori of Milan from January 1996 to April 2021.

Among the 6144 individuals tested due to significant personal or family history, belonging to 3940 families, we selected only female carriers of *BRCA1* or *BRCA2* PVs, classified according to the Evidence-based Network for the Interpretation of Mutant Alleles (ENIGMA) consortium guidelines (https://enigmaconsortium.org/), affected by invasive BC and for whom data on HER2 expression were available. Patients who developed bilateral BC (BBC) or more than one ipsilateral or BBC were included only if the HER2 status was available for at least one tumor on each side. Ductal carcinomas *in situ* were not included in the analysis. Clinical and pathological data, including age at tumor diagnosis, timing of chemotherapy in relation to the collection of the surgical specimens, tumor histology, grade, and hormone receptor status were retrieved for all patients.

Systematic review and pooled analysis

Search strategy and inclusion criteria. Subsequently, a systematic review was carried out according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines. A bibliographical search was carried out in Medline (PubMed), Embase, and Cochrane library—Cochrane Central Register of Controlled Trials (CENTRAL). The last search date was 30 September 2021.

The following terms were used in combination with Boolean operators (AND, OR, NOT): ('breast neoplasms'[MeSH Terms] OR ('breast'[All Fields] AND 'neoplasms'[All Fields]) OR 'breast neoplasms'[All Fields] OR ('breast'[All Fields] AND 'cancer'[All Fields]) OR 'breast cancer'[All Fields]) AND ('brca1 s'[All Fields] OR 'genes, brca1'[MeSH Terms] OR ('genes'[All Fields] AND 'brca1'[All Fields]) OR 'brca1 genes'[All Fields] OR 'brca1'[All Fields] OR ('genes, brca2'[MeSH Terms] OR ('genes'[All Fields] AND 'brca2'[All Fields]) OR 'brca2 genes'[All Fields] OR 'brca2'[All Fields])) AND ('HER2-positive'[All Fields] OR 'Erb-B2'[All Fields] OR 'HER2-neu'[All Fields]). Two independent authors (FP and GT) searched for potentially eligible articles retrieved by the initial search, and potential disagreements were resolved by consensus with a third reviewer (CA). References of the included studies and any previously published systematic reviews were manually assessed in order to detect any missing study.

Studies were considered eligible if: (i) they reported on the frequency of patients with *BRCA*-mutated (mut)/HER2-positive BC, (ii) they provided data on the outcomes or other associated clinical characteristics independent of tumor stage and treatment, (iii) at least 10 BC patients were evaluated, and (iv) they were published in the English language.

Exclusion criteria included (i) preclinical or pediatric studies, (ii) studies reporting on patients with cancers outside of the breast, (iii) reviews and meta-analyses, (iv) case reports, editorials, and letters to the editors, and (v) overlapping studies. In the case of duplicate publications, only the most recent or most informative study was included in the analyses. Articles that fulfilled the inclusion criteria were retrieved for full-text evaluation.

Data extraction. After reviewing the full texts of eligible studies, two independent authors (GT, CA) carried out the data extraction and crosschecked all results. Potential discrepancies in the selection of articles and the extraction of the data were resolved following consensus with a third reviewer (FP). Extracted variables included general study characteristics (author, year of publication, study design, number of all *BRCA*-mutated patients and *BRCA*mut/HER2-positive patients, follow-up), ER+ status, other hereditary alterations, treatment received, and outcome.

Statistical analysis. Descriptive statistics were reported as total and percentage for categorical variables and as median (range) or mean ± standard deviation for continuous variables, unless otherwise indicated. The meta-analysis of survival data was carried out with the RevMan software (version 5.4; The Nordic Cochrane Centre (Copenhagen,

Table 1. Main features of first invasive breast cancers (BC) and bilateral breast cancers (BBC) in our cohort of *BRCA1/2* pathogenic variants carriers

		BC, *N* (%)	BBC, *N* (%)
		398	59
Median age years (range)		42 (22-84)	47 (32-76)
Gene	*BRCA1*	240 (60.3)	33 (55.9)
	BRCA2	158 (39.7)	26 (44.1)
Neoadjuvant chemotherapy	Yes	4 (1)	1 (1.7)
	No	390 (98)	54 (91.5)
	NA	4 (1)	4 (6.8)
Histotype	Ductal	322 (80.9)	50 (84.7)
	Lobular	21 (5.3)	3 (5.1)
	Mixed	14 (3.5)	1 (1.7)
	Medullary	19 (4.8)	1 (1.7)
	Other	7 (1.7)	1 (1.7)
	NA	15 (3.8)	3 (5.1)
Grade	I	0	1 (1.7)
	II	122 (30.7)	18 (30.5)
	III	248 (62.3)	35 (59.3)
	NA	28 (7)	5 (8.5)
Estrogen receptor status	Positive	183 (46)	22 (37.3)
	Negative	213 (53.5)	37 (62.7)
	NA	2 (0.5)	0
Progesterone receptor status	Positive	148 (37.2)	21 (35.6)
	Negative	246 (61.8)	37 (62.7)
	NA	4 (1)	1 (1.7)
HER2 status	Positive	28 (7)	11 (18.6)
	Negative	370 (93)	48 (81.4)
Triple-negative breast cancer		189/393 (48)	27/58 (47)

For 34 patients, who developed more than one ipsilateral BC, and six patients, who developed more than one BBC, the first BC/BBC was not included due to the unavailable HER2 status.
BBC, bilateral breast cancer; BC, breast cancer; HER2, human epidermal growth factor receptor 2; NA, not available.

Table 2. Main features of HER2-positive first invasive breast cancers (BC) and bilateral breast cancers (BBC) in our cohort of *BRCA1/2* pathogenic variants carriers

N		BC HER2+	BBC HER2+
		28	11
Median age in years (range)		48 (25-66)	46 (35-54)
Gene, *n* (%)	*BRCA1*	13 (46.4)	5 (45.5)
	BRCA2	15 (53.6)	6 (54.5)
Neoadjuvant chemotherapy, *n* (%)	Yes	0	1 (9.1)
	No	28 (100)	9 (81.8)
	NA	0	1 (9.1)
Histotype, *n* (%)	Ductal	26 (92.8)	11 (100)
	Lobular	1 (3.6)	0
	Other	1 (3.6)	0
Grade, *n* (%)	II	10 (35.7)	3 (27.3)
	III	17 (60.7)	7 (63.6)
	NA	1 (3.6)	1 (9.1)
Estrogen receptor (ER), *n* (%)	Positive	21 (75)	7 (63.6)
	Negative	7 (25)	4 (36.4)
Progesterone receptor (PgR), *n* (%)	Positive	15 (53.6)	2 (18.2)
	Negative	13 (46.4)	9 (81.8)

For five patients, who developed more than one ipsilateral BC, the first BC was not included due to the unavailable HER2 status.
HER2, human epidermal growth factor receptor 2; NA, not available.

Denmark), The Cochrane Collaboration). Hazard ratio was used for the assessment of survival for *BRCA*mut/HER2+ BCs. Due to the anticipated study heterogeneity, the random effects model was chosen in all cases. The generic inverse variance method was chosen for survival analysis. Higgin's I^2 statistic was used for the assessment of statistical heterogeneity. Results were considered statistically significant when the *P* value <0.05.

RESULTS

Single institutional study cohort

The analyzed cohort was composed of 398 female carriers of *BRCA1/2* PVs (240 *BRCA1*, 158 *BRCA2*), including 288 probands and 110 family members, who developed at least one invasive BC. A subgroup of 59 patients (33 *BRCA1*, 26 *BRCA2*) developed BBC. Pathological characteristics of both BCs and BBCs are reported in Table 1. Additionally, the main features of HER2-positive first invasive BCs and BBCs in our cohort of *BRCA1/2* PVs carriers are described in Table 2.

The median age at diagnosis was 42 years (range 22-84 years) for the first BC and 47 years (range 32-76 years) for BBC. More than 80% of the considered tumors were invasive ductal carcinomas and ~60% were high grade. For both the first BCs and BBCs, pathology assessment was mostly carried out on surgical specimens collected before chemotherapy.

Among all first BCs, 7% (28/398) were HER2-positive and 93% (370/398) were HER2-negative. No significant difference in the HER2 status was detected between probands (HER2-positive 7.3%, 21/288) and family members (HER2-positive 6.4%, 7/110).

In carriers of *BRCA1* PVs, 5.4% (13/240) of BCs were HER2-positive compared with 9.5% (15/158) in carriers of *BRCA2* PVs. As concerns BBC, HER2-positive cases were 15.2% (5/33) in the *BRCA1* group and 23.1% (6/26) in the *BRCA2* (Figure 1).

Notably, six *BRCA1* and eight *BRCA2* PV carriers showed discordant HER2 status between BC and BBC (23.7%, 14/59). Of these patients, 78.6% (11/14) developed an HER2-negative BC followed by HER2-positive BBC, whereas 21.4% (3/14) developed an HER2-positive BC followed by HER2-negative BBC (Figure 2).

Systematic review and pooled analysis

Identification of eligible studies. The flow of article selection process is depicted in Figure 3. After screening 544 records, 73 studies[10,14-86] finally met the predefined criteria and were considered eligible for inclusion in the systematic review. Descriptive characteristics of the eligible studies are summarized in Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2022.100531. A total of 58 studies were retrospective; 11 were prospective cohorts; 1 was a cross-sectional study, 2 were case control studies, and 1 was both prospective and retrospective. Patients were analyzed from 1960 to 2014. Three studies were excluded because two did not report data about *BRCA*mut/HER2-positive patients and one was a case report.

Patient characteristics. Among the included studies, a total of 21 083 patients had *BRCA1* or *2* mutations (Supplementary

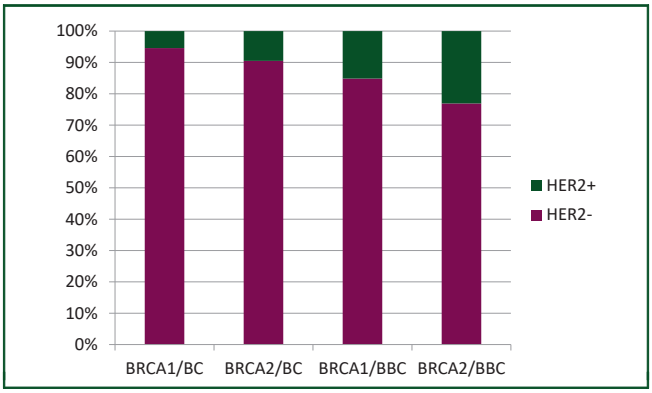

Figure 1. Percent ratios of HER2-positive (HER2+) versus HER2-negative (HER2−) breast cancers in carriers of *BRCA1* or *BRCA2* pathogenic variants.
BBC, bilateral breast cancer; BC, breast cancer.

Table S1, available at https://doi.org/10.1016/j.esmoop.2022.100531). Mean patient age was 43.8 years (range 31-46.9 years). All *BRCA* mutations were diagnosed histologically in surgical specimens. In few papers, 582 and 281 BCs reported only on *BRCA1* and *BRCA2* cases. All other series included mixed *BRCA1* and *BRCA2* BCs. Median follow-up was rarely reported and ranged from 1.5 to 10.4 years. Treatment received was not reported in most studies. Similarly, outcome was never reported for *BRCA*mut/HER2-positive compared with HER2-negative BCs.

Frequency and characteristics of *BRCA*mut/HER2+ BCs. The pooled rate of *BRCA*mut/HER2-positive BCs is 9.1% (95% confidence interval 7.3% to 11.2%). *BRCA1* and *BRCA2* when reported as separate data ranged, respectively, from 0% to 33.3% (mean 8.3%) and from 0% to 86% (mean 10.3%). Among studies that reported ER status (67 out of 73 studies) the rate of ER+ *BRCA*mut/HER2-positive BCs ranged from 0% to 89.7% (mean 42.8%).

In some series, other pathogenetic mutations were also reported (see Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2022.100531).

DISCUSSION

Findings from our study confirm the low frequency of HER2-positive BCs among *BRCA1/BRCA2* PVs carriers. This is particularly evident for *BRCA1*, and data from our cohort are strongly consistent with the results of the pooled analysis. Specifically, we found a 7% HER2 positivity rate among all first *BRCA1/2* BCs analyzed in our cohort study, which is in line with the 9% rate obtained from the pooled analysis of *BRCA*mut/HER2-positive BCs. Indeed, our series is one of the largest ever published and similar to the few studies previously reported confirms that compared with *BRCA1*, the expected prevalence of HER2 positivity among *BRCA2* is higher.

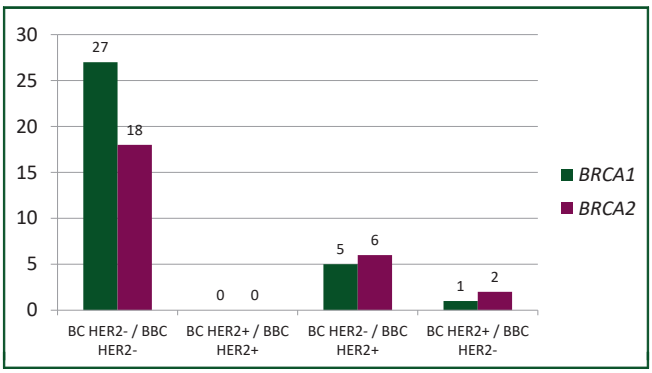

Figure 2. Concordance of the HER2 status between first breast cancer (BC) and bilateral breast cancer (BBC) in 59 carriers of *BRCA* pathogenic variants (33 *BRCA1* and 26 *BRCA2*).
HER2, human epidermal growth factor receptor 2.

Cancer development is a multistep process where genomic instability plays a pivotal role. Germline mutations of *BRCA1* and *BRCA2* are well-known gene-driven mechanisms of carcinogenesis and represent a major risk factor for multiple tumors, with a peculiar selectivity for breast and ovarian cancers. Biological processes leading to cancer transformation involving breast cells harboring such mutations are complex and still not completely elucidated, including maintenance of the genomic integrity, regulation of the oxidative stress and protein stability, modulation of gene transcription, cell cycle progression, and therapy resistance.[48]

Similarly, the *HER2* gene is critical for the activation of subcellular signal transduction pathways controlling epithelial cell growth and differentiation[87] and its amplification or protein overexpression are established predictive biomarkers of benefit from anti-HER2 therapy. When *BRCA1/BRCA2* PVs and HER2 are simultaneously present, however, no studies have evaluated the different contribution of either alteration as oncogenic drivers. Additionally, it is currently unknown if such molecular biomarkers may functionally act in a mutually exclusive manner in the BC transformation process.

An original finding of our work is represented by the nearly 25% discordance rate registered among all BBCs. Noteworthy, the great majority of these patients [i.e. 78.6% (11/14)] first developed an HER2-negative BC followed by an HER2-positive BBC. This might be the result of the predominant role of *BRCA*-driven mechanisms in the early BC transformation process. Some considerations are supporting the hypothesis that such molecular alterations might be mutually exclusive.

First, the significant lower prevalence of HER2 positivity in *BRCA1/BRCA2* PVs carriers compared with sporadic cancers. Second, the partial discordance in HER2 status in the second contralateral breast tumor, compared with the first mainly HER2-negative tumor.

Additionally, such tumors usually develop at a young age, highlighting the key contribution of germline mutations.

Third, as demonstrated by a recent analysis of a cohort of BC patients with Li Fraumeni syndrome, the presence of a germline variant of *TP53* did not correlate with a lower frequency of HER2 status as compared with the sporadic counterpart. In fact, despite the limitation due to the relatively small sample in a syndrome rarer than HBOC, the rate of observed HER2-enriched *TP53*-mutated BCs was ~33% (11/32).[88] This last finding could also raise the hypothesis of not only a predominance, but potentially a

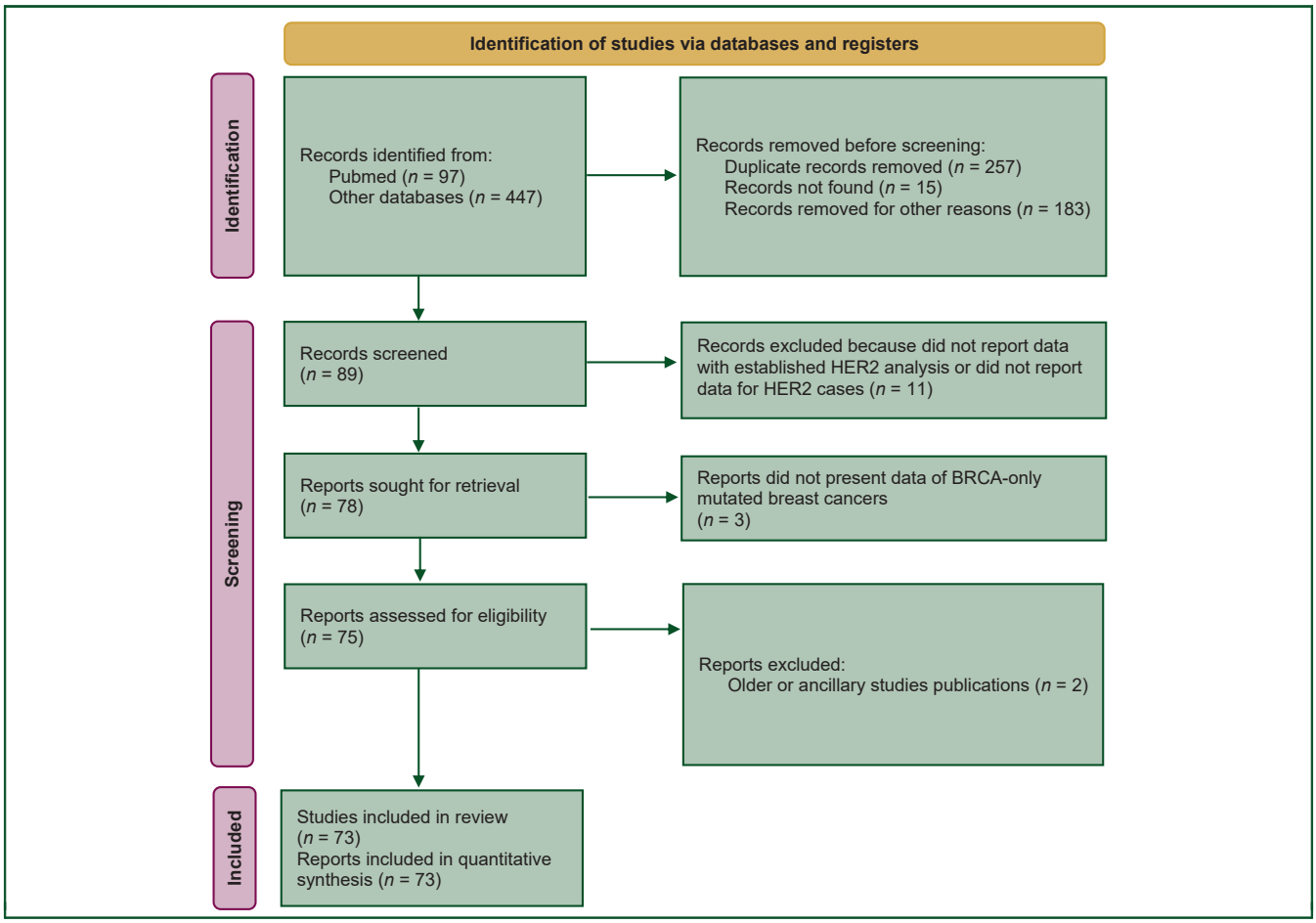

Figure 3. Flow diagram of included studies.
HER2, human epidermal growth factor receptor 2.

'silencing' of the HER2 pathway by the *BRCA*-mutated status.

Due to reduced DNA repair capacity, *BRCA*-mutated cancers are also more responsive to the distinct types of treatment such as platinum-based compounds and PARP inhibitors, which induce accumulation of DNA double-strand breaks. In *BRCA1* and *BRCA2* PVs BC carriers, the overexpression and/or amplification of the HER2 gene have always represented an exclusion criterion for enrollment in clinical trials with PARP inhibitors. As a matter of fact, members of this class of targeted agents, such as olaparib and talazoparib, have been globally approved for patients with germline *BRCA* mutations and HER2-negative advanced BC who have previously been treated with chemotherapy in the neoadjuvant, adjuvant, or metastatic disease setting. Olaparib has also received indication for *BRCA* carriers with early-stage, high-risk HER2-negative BC.

Very recently, some trials have been designed to also allow inclusion of the specific cohort of HER2-positive patients.

In particular, a phase II trial ('OPHELIA', NCT03931551) is recruiting HER2-positive BC subjects with gene alterations in HRR DNA pathway (including germline deleterious mutations in *BRCA1* or *BRCA2* genes) and aims at evaluating the efficacy of the association of olaparib and trastuzumab.

Finally, although not selectively designed for the cohort of *BRCA1/2*-mutated BCs, an interesting phase I trial (NCT04585958) is enrolling patients with HER2-positive solid tumors in order to evaluate the safety and tolerability of the combination of trastuzumab deruxtecan (DS-8201a) with olaparib.

The present study does have some limitations. All studies included in the systematic review and pooled analysis are retrospective, and the only possible way to perform correlation with any pathologic feature was with ER status. No information relative to overall survival of *BRCA*mut/HER2-positive cases compared with HER2-negative counterparts was available. Additionally, the older series included patients treated with obsolete therapies so that a comparison with the modern era is not feasible, and treatment received is almost entirely not reported. The analysis of the HER2 status was also carried out with old techniques so that strict definition as currently proposed was likely not applicable in these series. Finally, median follow-up was not reported in most series, therefore potential observation length bias is possible.

In conclusion, this study confirms that BCs occurring in germline *BRCA1/2* PVs carriers are rarely HER2-positive. Although not common, the co-existence of *BRCA* mutations and HER2 overexpression and/or gene amplification should

be acknowledged and drugs like PARP inhibitors possibly considered. More research is needed to better characterize this subgroup of patients who should not be excluded *a priori* from clinical trials of targeted therapy for *BRCA1/2*-driven cancers.

FUNDING

Italian Ministry of Health - Current research IRCCS [grant number RC21 18501].

DISCLOSURE

GT reports payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events: Eli Lilly, Novartis, Amgen, Roche, Merck. Support for attending meetings and/or travel: Eli Lilly. Participation on a Data Safety Monitoring Board or Advisory Board: Amgen, Roche, Eli Lilly.

OG reports consulting fees: Eisai, Eli-Lilly, MSD, Seagen. Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events: Novartis, Eli Lilly, Eisai.

MG reports consulting fees: Amgen, Merck, Lilly. Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events: Italfarmaco, Merck, Servier. Participation on a Data Safety Monitoring Board or Advisory Board: Roche, Servier.

All other authors have declared no conflicts of interest.

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