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Clinical Trial Results

Trastuzumab plus lapatinib or chemotherapy in patients with HER2-overexpressed advanced breast cancer: a randomized, phase II trial (GIM12-TYPHER)

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Abstract

Background: Trastuzumab combined with chemotherapy is a standard treatment for human epidermal growth factor receptor 2 (HER2)-positive advanced breast cancer in later lines. Lapatinib and trastuzumab have also demonstrated efficacy. This study assessed the efficacy, toxicity, and quality of life (QoL) of trastuzumab plus lapatinib (with endocrine therapy for hormone receptor-positive cases) versus trastuzumab with physician-selected chemotherapy in patients previously treated with at least 2 anti-HER2 regimens.

Methods: In this open-label, multicenter phase II trial, 59 patients were randomized 1:1 to receive either trastuzumab and lapatinib (arm A) or trastuzumab with chemotherapy (arm B). The primary endpoint was clinical benefit rate (CBR), defined as confirmed complete response, partial response, or stable disease for ≥24 weeks. Secondary endpoints included overall survival (OS), progression-free survival (PFS), overall response rate (ORR), QoL, and safety.

Results: With a median follow-up of 57.5 months, the CBR was 20.7% in arm A and 26.7% in arm B ($P = .76$). The ORR was 13.8% versus 20.0% ($P = .73$), and median PFS was 3.6 months in arm A versus 6.1 months in arm B (HR 0.63; $P = .08$). Median OS was 29.9 versus 31.1 months (HR 1.07; $P = .82$). Adverse events occurred in 86.2% (arm A) and 66.7% (arm B) of patients, with grade 3–4 events in 24.1% and 13.3%, respectively. QoL favored arm A ($P = .03$). Due to early study closure and limited sample size, all results should be considered exploratory and not powered to assess definitive treatment effects.

Conclusions: While efficacy differences were not significant, trastuzumab with lapatinib showed better QoL despite higher adverse event rates, suggesting it may be a viable chemotherapy-free option for pretreated HER2-positive advanced breast cancer.

EudraCT trial registration number: 2013-005044-29

Key words: metastatic breast cancer; HER2; chemo-free treatment; lapatinib.

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Lessons Learned

- • The GIM12-TYPHER study demonstrates that trastuzumab in combination with lapatinib offers a chemotherapy-free treatment option with comparable efficacy and better quality of life for patients with human epidermal growth factor receptor 2 (HER2)-overexpressed advanced breast cancer who have been previously treated with at least 2 anti-HER2 regimens.
- • This approach is particularly valuable for patients who cannot tolerate chemotherapy, providing a viable alternative that prioritizes patient well-being while maintaining clinical benefit. These findings highlight the importance of tailoring treatment strategies to individual patient needs, potentially improving outcomes in this heavily pretreated population.
- • The accrual of the clinical study was not completed due to the launch of multiple clinical trials evaluating novel anti-HER2 agents, including trastuzumab deruxtecan and tucatinib, at the centers where the GIM12-TYPHER study was active and recruiting. The availability of these new trials substantially hindered the accrual rate.

Trial information

GIM12-TYPHER was a randomized, noncomparative, multicenter, open-label phase II trial conducted across 16 institutions in Italy. Eligibility criteria for participants included a diagnosis of metastatic human epidermal growth factor receptor 2 (HER2)-positive (immunohistochemical score 3+ or, in case of score 2+, an in situ hybridization amplification ratio >2.0) breast adenocarcinoma; Eastern Cooperative Oncology Group performance status of 1 or lower; adequate hematologic, renal, hepatobiliary function; baseline left ventricular ejection fraction (LVEF) ≥50%; and adequate contraception if premenopausal. Patients were enrolled if they had a life expectancy of >12 months and measurable disease as defined by the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. All patients must have received prior taxane-based regimens and trastuzumab-based regimens in either the adjuvant or the metastatic setting. A maximum of 3 prior lines of anti-HER2 therapy in the metastatic setting were allowed. Patients who had received the same anti-HER2 therapy (ie, trastuzumab, trastuzumab plus pertuzumab, lapatinib, trastuzumab emtansine) in combination with different chemo- or endocrine therapy were considered as having received a single line of anti-HER2 therapy. A maximum of 2 chemotherapies and/or endocrine therapies per anti-HER2 agent were allowed. Patients were excluded if they had a history of another malignancy (other than carcinoma in situ of the cervix or basal cell carcinoma) within the previous 5 years, or if they had concurrent severe, uncontrolled systemic disease. Patients were also ineligible if they had received any investigational treatment within 28 days of randomization, or if they were enrolled in other interventional or noninterventional studies. In addition, patients were not eligible if they had grade ≥3 peripheral neuropathy or persistent grade ≥2 hematologic toxicity resulting from previous systemic therapy according to the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-NCTCAE) version 3.0 at the time of randomization. The study was approved by the local ethics committees of each participating center. The EudraCT trial registration number is 2013-005044-29, and the study was coordinated by the Gruppo Italiano Mammella (GIM). Written informed consent was obtained from all patients prior to enrollment.

The primary endpoint of the study was the clinical benefit rate (CBR). CBR is defined as confirmed complete response (CR) plus partial response (PR) at any time, plus stable disease for 24 weeks. Secondary endpoints were the overall response rate (ORR), progression-free survival (PFS), overall survival (OS), safety and tolerability of treatment in both arms, and quality of life (QoL). ORR is defined as confirmed CR plus PR. PFS is defined as the time from randomization to the first documented radiographic progressive disease according to RECIST v1.1. OS is defined as the time from randomization to death from any cause. Response to treatment (ORR or CBR) is defined according to RECIST v1.1 criteria (see Table 1 for trial information).

Drug information

Patients were randomly assigned (1:1) to receive lapatinib and trastuzumab (experimental arm, arm A) or trastuzumab in combination with chemotherapy (control arm, arm B). Any physician's choice of chemotherapy according to National Comprehensive Cancer Network guidelines was allowed. In the experimental arm, patients diagnosed with hormone receptor (HR)-expressing breast cancer also received endocrine therapy at the discretion of their physician. Participants received study medication until disease progression, unacceptable toxicity, withdrawal of consent, or death, whichever occurred first. There was no patient or investigator masking of the arm and treatment assignment.

Patients enrolled in arm A received oral lapatinib at a dose of 1000 mg daily plus intravenous (iv) trastuzumab at a loading dose of 8 mg/kg on day 1 of the initial 21-day cycle, followed by 6 mg/kg administered every 21 days (q3wks). Patients with HR-positive disease in arm A also received endocrine therapy administered according to the investigator's chosen drug

Table 1. Trial information.

Disease	HER2-positive breast adenocarcinoma
Stage of disease/ treatment	IV
Prior therapy	A maximum of 3 prior lines of anti-HER2 therapy in the metastatic setting were allowed. A maximum of 2 chemotherapies and/or endocrine therapies per anti-HER2 agent were allowed.
Type of study	Phase II
Primary endpoints	CBR defined as confirmed complete response plus partial response at any time, plus stable disease for 24 weeks.
Secondary endpoints	Overall response rate, progression-free survival, overall survival, safety and tolerability of treatment in both arms, and quality of life.

Abbreviations: CBR, clinical benefit rate; HER2, human epidermal growth factor receptor 2.

Table 2. Drug information.

Arm	A
Generic/working name	Lapatinib
Company name	GSK
Drug type	Targeted therapy
Drug class	Tyrosine kinase inhibitor
Dose	1000 mg
Route	Per os
Schedule of administration	Daily
Arm	A and B
Generic/working name	Trastuzumab
Company name	Roche-manufactured or biosimilar compound
Drug type	Targeted therapy
Drug class	Monoclonal antibody
Dose	Loading dose of 8 mg/kg, followed by 6 mg/kg. 600 mg in the subcutaneous formulation.
Route	Intravenous or subcutaneous
Schedule of administration	Day 1 of 21-day cycle
Arm	B
Generic/working name	Physician's choice chemotherapy
Company name	According to the specific chemotherapy regimen chosen
Drug type	Chemotherapy
Drug class	According to the specific chemotherapy regimen chosen
Dose	According to the specific chemotherapy regimen chosen
Route	Intravenous or per os
Schedule of administration	According to the specific chemotherapy regimen chosen

regimen. Patients in arm B received iv trastuzumab in addition to chemotherapy administered according to the investigator's schedule. A subsequent amendment to the study allowed the use of trastuzumab 600 mg administered subcutaneously (see Table 2 for drug information). The study was terminated if disease progression, unacceptable toxicity, withdrawal of consent, or death occurred. Efficacy was evaluated by objective tumor assessments every 9 weeks of the initial randomized period according to RECIST v1.1 criteria. The incidence and severity of adverse events (AEs) were reported according to the NCI-NCTCAE scoring system. Echocardiography or multigated acquisition scans to measure LVEF were scheduled at baseline, every 3 months, at the end of treatment and 28 days after the last dose. QoL was assessed using the Functional Assessment of Cancer Therapy-Breast (FACT-B) questionnaire (version 4). The FACT-B questionnaire was administered at baseline, each cycle, and at discontinuation of study treatment.

This study was not powered to make direct comparisons between the treatment groups; therefore, results are reported separately for each group. A single-stage design was used for each of the 2 study arms, with a CBR considered unacceptably low if it was ≤20%, and successful if it met the expected threshold of 35%. With 90% power and a 1-sided type I error (false positive rate) of 5%, a total of 77 subjects per study group were required. A minimum of 22 subjects with clinical benefit was necessary to declare success for each treatment. However, only 62 subjects were enrolled, and 59 (30 in arm A and 29 in arm B) were available in the intention-to-treat (ITT) population for efficacy evaluation. Given the enrolled sample size and the study design, testing efficacy hypotheses was not sufficiently powered; therefore, all results should be considered exploratory and cannot be used to infer definitive treatment effects.

Statistical analysis

All statistical analyses were performed using R 4.2.1 (The R Foundation).[1] CBR and ORR were summarized using both point estimates and 95% CIs according to the Blaker method.[2] PFS and OS were summarized using Kaplan–Meier curves. 95% CIs for median PFS and OS were estimated using the Kaplan–Meier method. Cox regression models were used to calculate the hazard ratios and their 95% CIs. Difference in QoL between groups was assessed using ANCOVA model with change from baseline as the dependent variable and baseline values as a covariate. For this analysis, FACT-B scores collected at baseline and at the end of treatment were considered.

Patient characteristics

Between March 6, 2015, and February 6, 2020, 67 patients were enrolled, and 62 patients were randomly assigned to receive either trastuzumab plus lapatinib with endocrine therapy at the physician's discretion in case of HR-positive advanced breast cancer (arm A) or trastuzumab plus chemotherapy (arm B). Fifty-nine patients received at least 1 dose of the study protocol and were included in the present analysis (Figure 1). Baseline demographic and disease characteristics of the study population are reported in Table 3. Patients in arm A were on average 5.9 years younger than patients in arm B (59.4 ± 9 vs 60.8 ± 11.2 years). The proportion of postmenopausal patients was higher in arm B than in arm A (82.8% vs 96.7%). A total of 21 (72.4%) patients in arm A and 20 (66.7%) in arm B had HR-positive disease. Visceral disease was detected in 65.5% of patients in arm A and 63.3% in arm B. In the experimental arm, 51.7% of patients (15) did not receive any endocrine therapy. Among those who did, the most commonly administered agent was fulvestrant, used in 33.3% of patients (10). Fulvestrant in combination with luteinizing-hormone-releasing hormone agonist (LHRHa) was given to 3.4% (1) of patients, as was letrozole (3.4%, 1 patient), LHRHa alone (3.4%, 1 patient), and exemestane (3.4%, 1 patient). In the control arm, the most frequently administered chemotherapy regimen was vinorelbine (18 patients, 60.0%), additional regimens included capecitabine (2 patients, 6.6%), paclitaxel (2 patients, 6.6%), docetaxel (2 patients, 6.6%), carboplatin (1 patient, 3.3%), eribulin (1 patient, 3.3%), gemcitabine (1 patient, 3.3%), a combination of vinorelbine and capecitabine (1 patient, 3.3%), and cyclophosphamide with methotrexate (1 patient, 3.3%). Finally, 1 patient (3.3%) did not receive any chemotherapy.

Primary assessment method

Sixty-two subjects were enrolled, and 59 (30 in arm A and 29 in arm B) were available in the ITT population for efficacy evaluation (details of the primary assessment method are presented in Table 4). The CBR was 20.7% (95% CI, 9.4%–39.3%) in arm A compared to 26.7% (95% CI, 13.1%–44.9%) in arm B, as shown in Table 5. The ORR was 13.8% (95% CI, 4.9%–30.5%) in arm A and 20.0% (9.1%–38%) in arm B. One patient (3.4%) in arm A achieved a CR, while none in arm B did; 3 subjects (10.3%) in arm A reported a PR compared to 6 (20.0%) in arm B. Two participants (6.9%) in arm A and 2 (6.7%) in arm B reported disease stability for more than 24 weeks. Among patients who reported a CR or PR, the median duration of response was 7.75 months (95% CI, 5.95 months to not estimable) in arm A and 11.25 months (95% CI, 4.67 months to not estimable) in arm B. The median PFS was 3.6 months (95% CI, 3.0–5.3 months) in arm A and 6.1 months (95% CI, 4.0–14.3 months) in arm B (Figure 2), with an hazard ratio of 0.63 (95% CI, 0.37–1.37; $P = .08$). After a median follow-up of 57.5 months, the median OS was 29.9 months (95% CI, 19.6 months to not estimable) for arm A and 31.1 months (95% CI, 26.1 months to not estimable) for arm B (Figure 3) with an hazard ratio of 1.07 (95% CI, 0.57–2.0; $P = .82$). The impact on QoL, assessed through FACT-B questionnaires, significantly favored the chemo-free trastuzumab plus lapatinib arm (change from baseline 2.4 ± 8.4 in arm A vs −6.4 ± 12.5 in arm B, $P = .03$; this finding should be interpreted as exploratory, given the limited availability of paired patient-reported outcome data suitable for statistical analysis).

Adverse events and severe adverse events

Overall, AEs occurred in 76.3% of participants, accounting for 86.2% and 66.7% of patients in arms A and B, respectively (Table 6). The most commonly reported AEs were diarrhea (37.9% of patients in arm A versus 10% of patients in arm B), fatigue (24.1% versus 20.0%), abdominal pain (10.3% versus 13.3), and anemia (13.8% versus 10.0%). Other AEs observed more frequently in the experimental arm were thrombocytopenia (13.8% in arm A vs 3.3% in arm B), nausea (10.3% vs 6.7%), fever (10.3% vs none), and skin disorders (10.3% vs none). Whereas AEs frequently occurred in the chemotherapy-based control arm were neutropenia (none in arm A vs 16.7% in arm B) and paresthesia (none vs 13.3%).

The incidence of grade 3 or higher AEs was observed in 11 (18.6%) out of 59 patients, 7 (24.1%) in arm A and 4 (13.3%) in arm B. None of the study participants had a

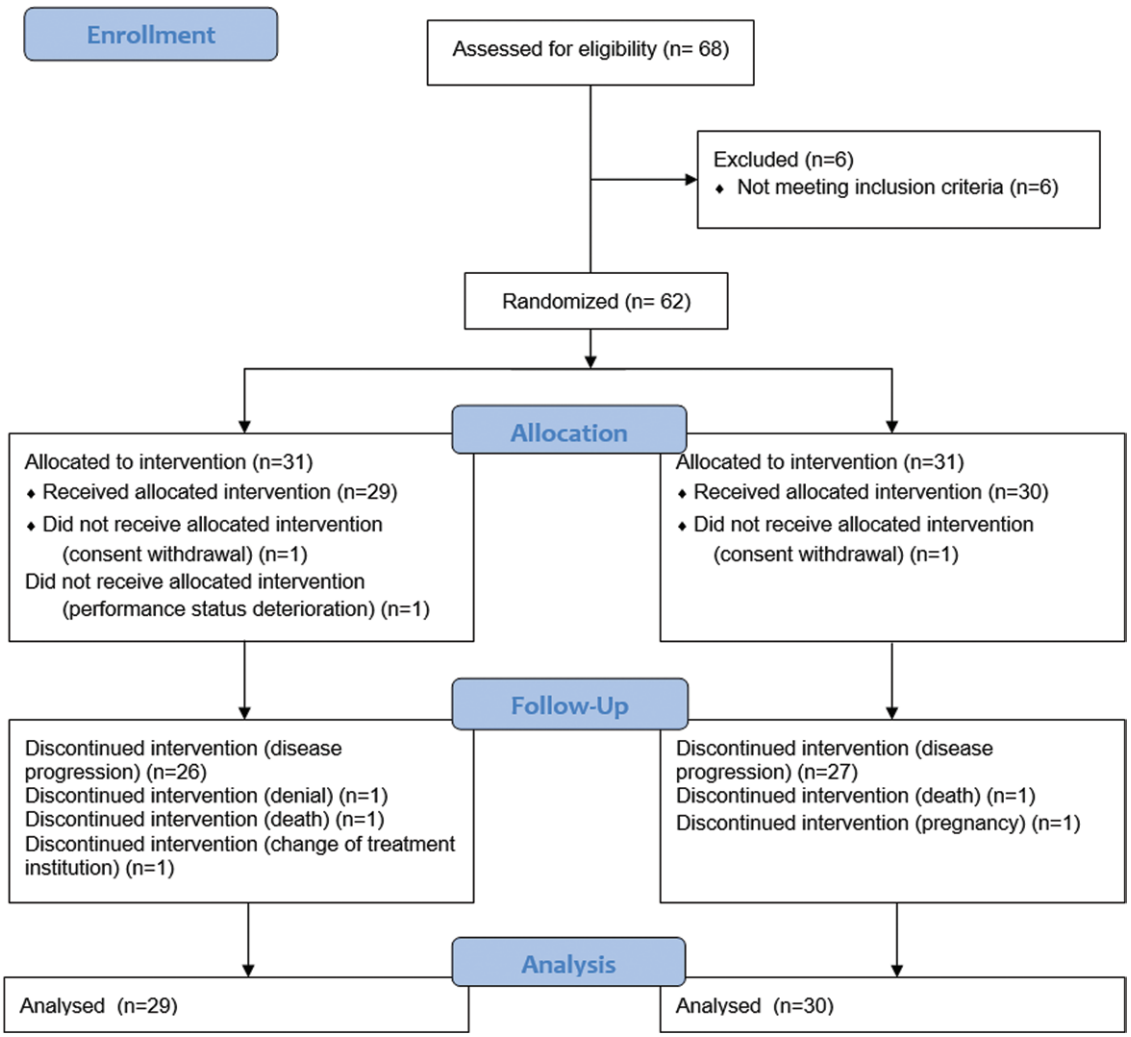

Figure 1. Consort flow diagram.

Table 3. Baseline characteristics of patient populations.

	Arm A (n = 29)	Arm B (*n* = 30)
Mean age ± std. dev. (range)	54.9 ± 9 (39.8–75.4)	60.8 ± 11.2 (32.8–80.3)
Ethnicity *n* (%)		
White	28 (96.6)	30 (100)
Black	1 (3.4)	0 (0)
ECOG PS *n* (%)		
0	23 (79.3)	19 (63.3)
1	6 (20.7)	11 (36.7)
Comorbidities *n* (%)		
No	17 (58.6)	18 (60.0)
Yes	12 (41.4)	12 (40.0)
Postmenopausal *n* (%)		
No	5 (17:2)	1 (3.3)
Yes	24 (82.8)	29 (96.7)
Estrogen receptor *n* (%)		
Negative	8 (27.6)	10 (33.3)
Positive	21 (72.4)	20 (66.7)
Progesterone receptor *n* (%)		
Negative	14 (48.3)	17 (56.7)
Positive	15 (51.7)	13 (43.3)
De novo metastatic *n* (%)		
No	21 (72.4)	23 (76.6)
Yes	7 (24.1)	7 (23.3)
Missing	1 (3.4)	0 (0.0)
Visceral disease *n* (%)		
No	10 (34.5)	11 (36.7)
Yes	19 (65.5)	19 (63.3)
Previous radiotherapy *n* (%)		
No	9 (31.0)	9 (30.0)
Yes	20 (69.0)	21 (70.0)
Previous surgery *n* (%)		
No	2 (6.9)	3 (10.0)
Yes	27 (93.1)	27 (90.0)
Previous systemic therapy *n* (%)		
No	0 (0.0)	1 (3.3)
Yes	27 (93.1)	29 (96.7)
Previous anti-HER2 therapy *n* (%)		
No	1 (3.4)	1 (3.3)
Trastuzumab	28 (96.6)	29 (96.7)
Pertuzumab	10 (34.5)	12 (40.0)
Lapatinib	13 (44.8)	12 (40.0)
T-DM1	21 (72.4)	25 (83.3)
Prior systemic therapy setting *n* (%)		
Neoadjuvant	6 (20.7)	4 (13.8)
Adjuvant	10 (34.5)	17 (58.6)
Metastatic	13 (44.8)	8 (27.6)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2.

Table 4. Primary assessment method.

Title	Clinical benefit rate (defined as confirmed complete response plus partial response at any time, plus stable disease for 24 weeks)
Number of patients screened	67
Number of patients enrolled	62
Number of patients evaluable for toxicity	59
Number of patients evaluable for efficacy	59
Evaluation method	Objective tumor assessments evaluated by imaging every 9 weeks of the initial randomized period according to RECIST v1.1 criteria.
Outcome notes	See Table 5 for treatment outcomes, Kaplan–Meier graphs are provided in Figures 2 and 3.

Table 5. Treatment outcomes and primary endpoint in the ITT population.

	Arm A (*n* = 29)	Arm B (*n* = 30)
Complete response, *n* (%)	1 (3.4%)	0 (0.0%)
Partial response, *n* (%)	3 (10.3%)	6 (20.0%)
Stable disease (≥24 weeks), *n* (%)	2 (6.9%)	2 (6.7%)
Progressive disease, n (%)	13 (44.8%)	9 (30.0%)
Clinical benefit rate, *n* (%)	6 (20.7%)	8 (26.7%)
Overall response rate, *n* (%)	4 (13.8%)	6 (20.0%)

decrease in LVEF of at least 20% from baseline, and none had an LVEF below the institution's lower limit of normal. No fatal outcomes were reported for AEs occurring during study treatment. SAEs recorded during the study are presented in Table 7.

Discussion

The treatment landscape for HER2-positive metastatic breast cancer has evolved significantly over the past two decades, largely due to the advent of targeted therapies that have dramatically improved patient outcomes.[3] The plethora of treatment options available presents a challenging task for clinicians in selecting the most effective therapeutic sequence.[4] To date, the first-line treatment approach for patients with

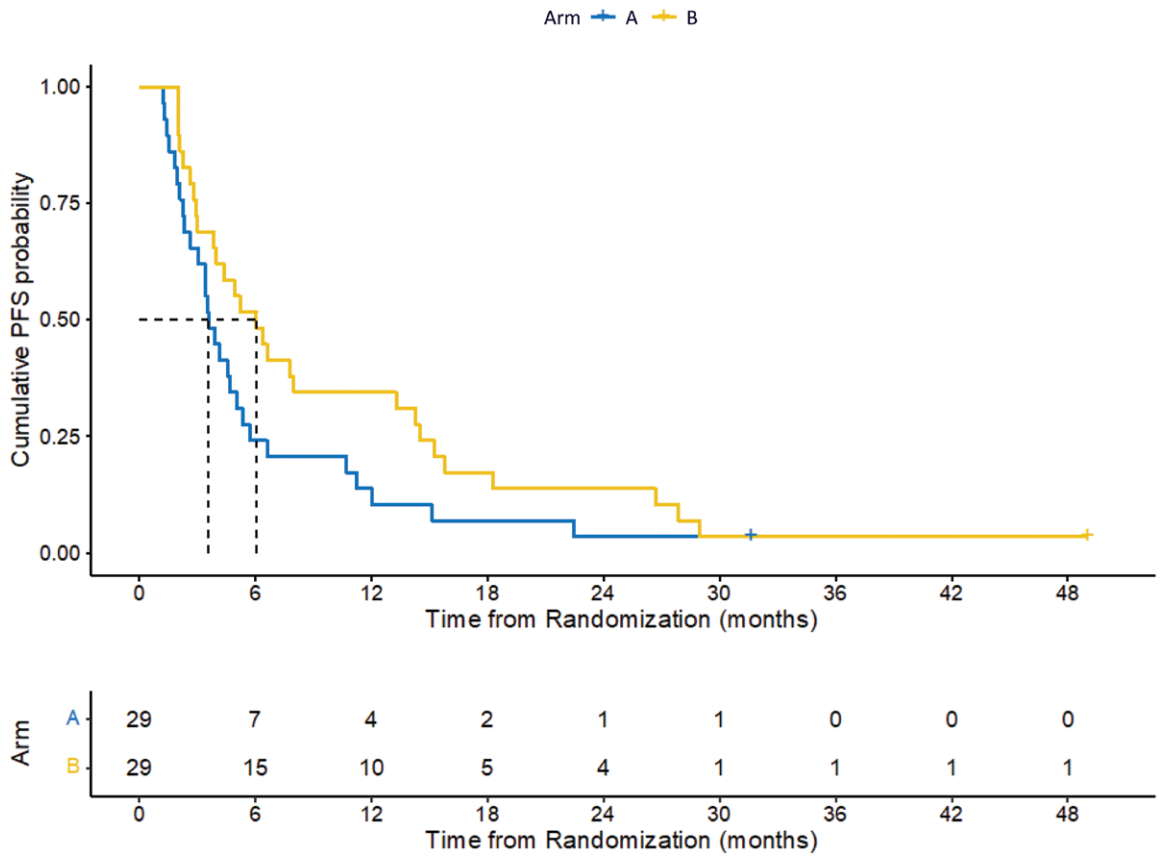

Figure 2. Progression-free survival (ITT population).

HER2-positive metastatic breast cancer involves administering pertuzumab and trastuzumab in combination with a taxane for at least six cycles, if tolerated, followed by maintenance pertuzumab and trastuzumab until disease progression.[5-7] In cases of patient's comorbidities or preferences, a less toxic chemotherapy agent or a chemo-free anti-HER2 therapy may be considered. The preferred second-line treatment is the HER2-targeting antibody–drug conjugates (ADCs) trastuzumab deruxtecan (T-DXd), with trastuzumab emtansine (T-DM1) as an alternative anti-HER2 ADC option. The HER2-selective tyrosine kinase inhibitor (TKI) tucatinib in combination with capecitabine and trastuzumab may be used in the second-line setting for patients with brain metastases, especially when a local intervention is not recommended. Tucatinib-capecitabine-trastuzumab, T-DXd, and T-DM1 appear to be the most active treatment options in the third-line setting, if not previously administered. The choice of treatment beyond the third line requires a balanced consideration of several factors, including prior therapies, patient comorbidities and performance status, treatment toxicity profile, as well as the potential for resistance that may arise from the sequencing of therapeutic lines.[5] In this setting, potential options include lapatinib, neratinib, margetuximab, and rechallenge with trastuzumab if other anti-HER2 therapies have been exhausted. The combination of a single anti-HER2 inhibitor with chemotherapy is commonly employed in clinical practice, with lapatinib and trastuzumab being widely used as a chemotherapy-free alternative.[8] However, the efficacy of such extended therapy with or without chemotherapy and its impact on QoL are not well characterized. The GIM12-TYPHER trial explored the efficacy and safety of the dual HER2 blockade with lapatinib and trastuzumab and of trastuzumab plus physician's choice chemotherapy in patients with HER2-positive metastatic breast cancer with disease progression on at least 2 prior lines of therapy for metastatic disease. Our study did not meet its primary endpoint since neither lapatinib plus trastuzumab nor trastuzumab plus chemotherapy of physician's choice achieved a CBR equal to or greater than 35%. In our study, the combination of lapatinib and trastuzumab resulted in a CBR of 20.7% and an ORR of 13.8%. These results are consistent with those obtained in the phase III EGF104900 study, which showed a CBR of 24.7% and an ORR of 10.3% in heavily pretreated patients with HER2-positive metastatic breast cancer.[9] However, the retrospective multicenter Trastyvere study recently showed that the chemo-free lapatinib plus trastuzumab treatment yielded a CBR of 34.8% with an ORR of 21.7% in 115 patients with HER2-positive advanced breast cancer previously treated with trastuzumab and/or lapatinib suggesting that this therapeutic approach may be particularly effective for at least some patients with advanced disease.[10] In our study, the combination of trastuzumab plus chemotherapy of the physician's preference achieved a CBR of 26.6% and an ORR of 20.0%. These results align with those reported by chemotherapy plus trastuzumab in recent phase II and III trials enrolling patients with HER2-positive disease in the later line of treatment for the metastatic setting.[11-13] Nevertheless, it is important to acknowledge that approximately 70% of the patient population in our study had HR-positive disease. This type of disease has been associated with a decreased dependence on

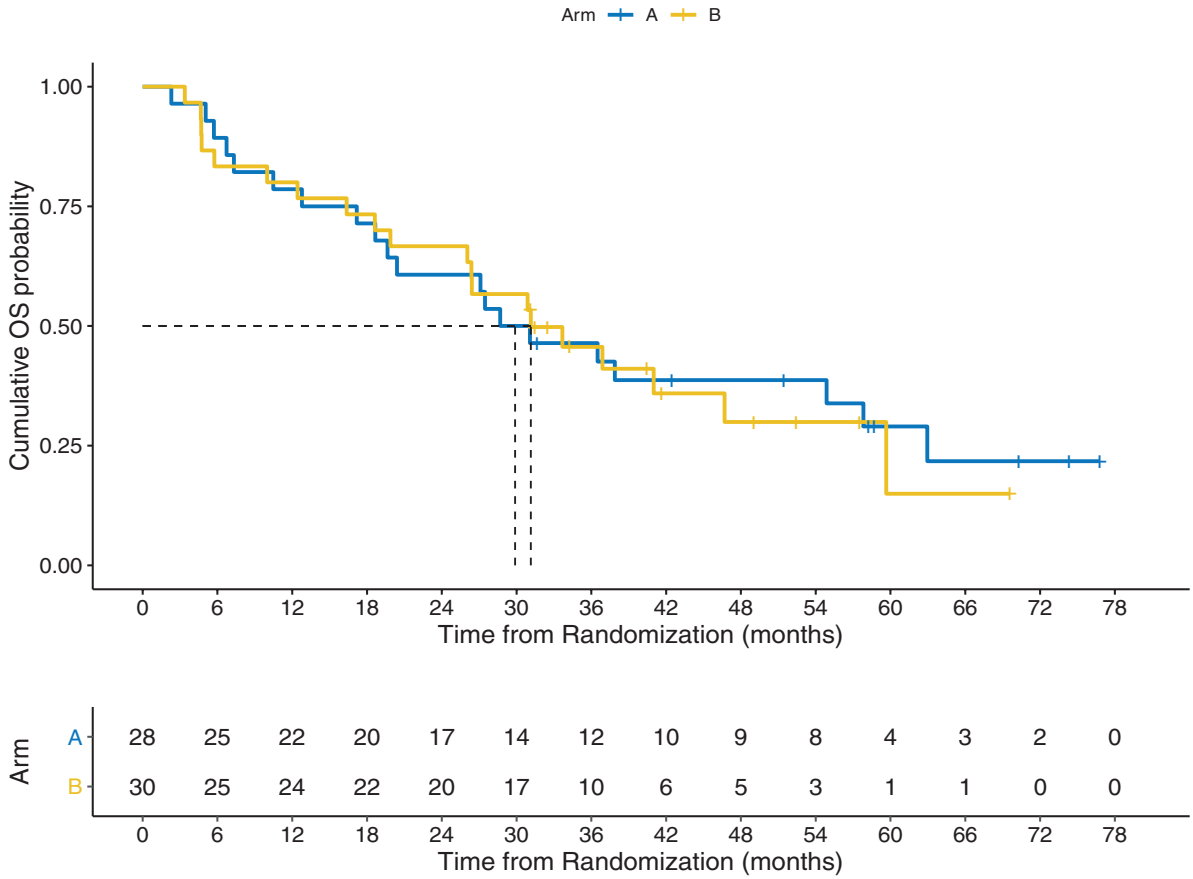

Figure 3. Overall survival (ITT population).

Table 6. Adverse events occurred in ≥10% of patients in any study arm.

Adverse event	Overall (*n* = 59)	Arm A (*n* = 29)		Arm B (*n* = 30)	
		Any grade	Grade ≥ 3	Any grade	Grade ≥ 3
Patients with at least one adverse event, *n* (%)	45 (76.3)	25 (86.2)	7 (24.1)	20 (66.7)	4 (13.3)
Diarrhea, *n* (%)	14 (23.7)	11 (37.9)	2 (6.9)	3 (10.0)	0 (0.0)
Fatigue, *n* (%)	13 (22.0)	7 (24.1)	0 (0.0)	6 (20.0)	2 (6.7)
Abdominal pain, *n* (%)	7 (11.9)	3 (10.3)	0 (0.0)	4 (13.3)	0 (0.0)
Anemia, *n* (%)	7 (11.9)	4 (13.8)	0 (0.0)	3 (10.0)	0 (0.0)
Neutropenia, *n* (%)	5 (8.5)	0 (0.0)	0 (0.0)	5 (16.7)	2 (6.7)
Nausea, *n* (%)	5 (8.5)	3 (10.3)	0 (0.0)	2 (6.7)	0 (0.0)
Thrombocytopenia, *n* (%)	5 (8.5)	4 (13.8)	0 (0.0)	1 (3.3)	0 (0.0)
Paresthesia, *n* (%)	4 (6.8)	0 (0.0)	0 (0.0)	4 (13.3)	0 (0.0)
Fever, *n* (%)	3 (5.1)	3 (10.3)	1 (3.4)	0 (0.0)	0 (0.0)
Skin disorders, *n* (%)	8 (13.6)	8 (27.6)	2 (6.9)	0 (0.0)	0 (0.0)

HER2 signaling and a reduced response to anti-HER2 treatments.[14,15] This may explain, at least in part, why our study did not reach its intended endpoint.

Assessing the QoL in patients with HER2-positive breast cancer undergoing further lines of treatment is critical to understanding the impact of therapy beyond clinical outcomes. Indeed, alongside clinical benefits such as delayed tumor progression and increased response rates, preserving or improving health-related QoL is of paramount importance.[16] In the present study, one of the secondary objectives was to ascertain whether the therapy had any detrimental effects on health-related QoL. We adopted the validated FACT-B questionnaires to assess different aspects of QoL, as it covers physical, emotional, social, and functional well-being, as well as breast cancer-specific concerns. An increase in score on the FACT-B questionnaires suggests symptom relief, improved functional ability, reduced emotional distress, or an overall improvement in the patient's QoL. The improvement could be due to successful treatment outcomes, effective symptom management, psychological support, or other positive

Table 7. Severe adverse events occurred in any study arm.

Adverse event	Overall (n = 59)	Arm A (n = 29)	Arm B (n = 30)	Attribution
Patients with at least one serious adverse event, n (%)	3 (5.1)	3 (10.3)	0 (0.0)	
Dyspnea, n (%)	1 (1.7)	1 (3.4)	0 (0.0)	Possible
Lower limb muscle weakness, n (%)	1 (1.7)	1 (3.4)	0 (0.0)	Unlikely
Vertebral fracture, n (%)	1 (1.7)	1 (3.4)	0 (0.0)	Unrelated
Hemoptysis, n (%)	1 (1.7)	1 (3.4)	3 (10.0)	Unlikely
Seizure, n (%)	1 (1.7)	1 (3.4)	0 (0.0)	Unlikely

factors related to the cancer experience, and vice versa for a decrease in score. In fact, monitoring changes in FACT-B scores over time can help healthcare providers gauge the effectiveness of interventions and identify areas where additional support may be needed. Other studies have previously evaluated the impact of investigational treatments on the QoL in heavily pretreated patients with HER2-positive breast cancer. Lapatinib monotherapy demonstrated to improve QoL and pain in responders compared to non-responders in a phase II study.[17] In randomized trials, therapy with lapatinib, either as monotherapy or in combination with trastuzumab or capecitabine, has been shown to have no negative impact on QoL, but to date, no statistically significant result has been shown compared to treatment arms not containing lapatinib.[18-21] Notably, in the EGF104900 trial, QoL assessed by the FACT-G questionnaire favored the lapatinib plus trastuzumab arm over lapatinib alone, but only at 12-week-follow-up.[9] These findings underscore the challenge of finding anti-HER2 treatments that significantly improve QoL in further lines of breast cancer therapy. Recent clinical trials such as NALA and HER2CLIMB, which included TKIs in later lines of therapy, aimed to fill this gap. In the HER2CLIMB, the addition of tucatinib to trastuzumab and capecitabine did not significantly reduce the risk of QoL deterioration compared to the control arm (placebo plus trastuzumab and capecitabine).[22] Similarly, in the NALA trial, no statistically significant differences were observed between the 2 treatment arms nor compared with the baseline assessment, whereas the diarrhea score worsened significantly more in the neratinib plus capecitabine arm than in the lapatinib plus capecitabine arm.[21,23] It's important to note, however, that most trials suffer from attrition of QoL data, which limits a comprehensive understanding of the impact of treatments on patient well-being. Despite efforts to improve treatment efficacy, maintaining or improving QoL remains a critical yet elusive goal in the management of HER2-positive metastatic breast cancer beyond second-line treatment. It is therefore noteworthy that in the GIM12 TYPHER trial, although the efficacy endpoints showed a consistent trend in favor of the combination of trastuzumab plus chemotherapy, the impact on QoL significantly favored the chemotherapy-sparing arm. This highlights the importance of considering not only efficacy but also the patient's QoL when selecting treatment regimens.

The safety profile of each treatment arm was consistent with the known safety profile of each combination. The incidence of AEs, mostly grade 1 or 2, was higher in arm A than in arm B. Diarrhea, fatigue, abdominal pain, and anemia were among the most common AEs. Similarly, the frequency of grade 3 or 4 AEs was higher in patients who received trastuzumab plus lapatinib compared to trastuzumab plus chemotherapy.

None of the patients in our study experienced severe cardiac toxicity in either treatment arm, although such toxicity has been reported in approximately 1%–10% of patients receiving anti-HER2 therapy in later stages of metastatic disease.[9,12] The reason for these findings could be attributed to either the minimal impact on cardiac function following anti-HER2 therapy with or without chemotherapy or the relatively small number of patients enrolled in the GIM12-TYPHER trial.

Our study has some limitations. The study was not powered to compare the two treatment arms and enrolled a relatively small number of patients, thus preventing us from determining which treatment option is more effective. Although we believe that our data provide evidence to support the use of lapatinib and trastuzumab in the metastatic setting, we acknowledge that alternative treatment options may be preferred in specific cases. Our study was initiated in 2015, but since then, the therapeutic landscape for patients with HER2-positive tumors has changed dramatically, with the introduction of other monoclonal antibodies such as margetuximab, tyrosine kinase inhibitors including neratinib and tucatinib, and the ADC T-DXd. None of the patients in our trial had received prior treatment with these agents, limiting the applicability of our results to this specific clinical context.

In conclusion, the GIM12-TYPHER study demonstrated that chemotherapy in combination with trastuzumab or lapatinib plus trastuzumab resulted in clinical benefit and acceptable tolerability in previously treated patients with HER2-positive metastatic breast cancer. The use of lapatinib and trastuzumab combination may provide a viable, chemotherapy-free treatment option for patients for whom chemotherapy is not suitable.

Author contributions

Carmine De Angelis (Conceptualization, Supervision, Methodology, Writing—original draft), Martina Pagliuca (Data curation, Project administration, Visualization, Writing—original draft), Emanuela Magnolfi (Writing—review and editing), Mauro Mansutti (Writing—review and editing), Zelmira Ballatore (Writing—review and editing), Michelino De Laurentiis (Writing—review and editing), Roberto Bordonaro (Writing—review and editing), Vita Leonardi (Investigation), Dario Bruzzese (Formal analysis, Methodology), Roberta Caputo (Writing—review and editing), Anna Maria Mosconi (Writing—review and editing), Saverio Cinieri (Writing—review and editing), Alessandra Fabi (Writing—review and editing), Lucia Del Mastro (Writing—review and editing), Fabio Puglisi (Writing—review and editing), Sabino De Placido (Writing—review and editing), Mario Giuliano (Writing—review and editing), Grazia Arpino

(Conceptualization, Funding acquisition, Project administration, Supervision, Writing—review and editing)

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Conflicts of interest

C.D.A. reports consulting or advisory relationships with Novartis, GSK, Eli Lilly, and Pfizer. M.P. reports institutional funding from Gilead and travel reimbursement from Ipsen. M.M. reports consulting or advisory relationships with Amgen, AstraZeneca, Eli Lilly, Gilead, MSD, Novartis, Pfizer, and Seagen. M.D.L. reports a relationship with Roche, Novartis, Takeda, Lilly, Pierre Fabre, AstraZeneca, MSD, Seagen, Gilead, Daiichi Sankyo, Tomalab, Genetic, Pfizer, Menarini, Sophos, Istituto Gentili, Sanofi, Ipsen, GSK, and Exact Science that includes consulting or advisory and travel reimbursement. R.B. reports a relationship with Bayer, AstraZeneca, Sanofi, Novartis, Amgen, Roche, Pfizer, Janssen Cilag, and BMS that include consulting or advisory. R.C. reports a relationship with Novartis, Lilly, Daichii Sankyo, Veracyte, Pfizer, Roche, AstraZeneca, Seagen, MSD, Gilead, that include consulting or advisory and funding grants. S.C. is Fondazione AIOM president and reports a relationship with Lilly and Menarini Stemline that include consulting or advisory. L.D.M. reports a relationship with Lilly, Novartis, Roche, Menarini Stemline, Olema, GSK, Pfizer, Daiichi Sankyo, Exact Science, Gilead, Pierre Fabre, Eisai, AstraZeneca, Agendia, MSD, Seagen, and Ipsen that include consulting or advisory, funding grants, and travel reimbursement. F.P. reports a relationship with Amgen, AstraZeneca, Daichii Sankyo, Celgene, Eisai, Lilly, Exact Sciences, Italfarmaco, Menarini, Gilead, Ipsen, MSD, Novartis, Pierre Fabre, Pfizer, Roche, Seagen, Takeda, and Viatris that include consulting or advisory, funding grants, and travel reimbursement. M.G. reports a relationship with AstraZeneca, Daichii Sankyo, Eisai, Gilead, Celgene, Exact Sciences, Lilly, MSD, Novartis, Pfizer, Roche, and Seagen that include consulting or advisory and travel reimbursement. G.A. reports a relationship with Roche, Pfizer, Lilly, MSD, AstraZeneca, and Novartis that include consulting or advisory and funding grants. The other authors did not declare any competing financial interests or personal relationships that could have influenced the work reported in this paper.

Data availability

The datasets generated and/or analyzed during the present study are available upon reasonable request to the corresponding author.

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