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LETTER TO THE EDITOR

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# Is the TCH-P regimen active in early or locally advanced HER2-positive breast cancer? Results of a retrospective study

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## Background

Dual HER2-targeted therapy (lapatinib or pertuzumab) combined with trastuzumab and chemotherapy significantly increased pathological complete response (pCR) in early HER2+ BC patients from 29.5–52.5% to 51.3–65.9% for lapatinib [1–4] and from 22–29% to 45.8–66.2% for pertuzumab [5–9], respectively. However, in order to reduce the toxicity, several studies evaluating a neoadjuvant dual HER2 blockade alone or trastuzumab emtansine (T-DM1) with or without pertuzumab showed a pCR of 16.8% [5] and 57% [8–10]. The pathological response is strictly correlated to the BC subtype [11]. Therefore, several unmet topics remain to be answered including the improving pCR rate in luminal HER2+ disease, which is less sensitive to the combination of chemotherapy and anti-HER2+ agents, and the reduction of the treatment-related toxicity without affecting the efficacy. Pertuzumab is now approved in the preoperative setting in combination with trastuzumab and chemotherapy in women with nonmetastatic HER2+ BC. The docetaxel, carboplatin, trastuzumab, and pertuzumab (TCH-P) regimen was evaluated in the TRYPHAENA trial with a reported pCR rate of 52% [6].

Aside from this study, there are limited information regarding the safety and efficacy of this regimen in the neoadjuvant setting. The purpose of this retrospective, monocentric study is to evaluate and confirm the efficacy and safety of neoadjuvant TCH-P in early or locally advanced HER2+ BC patients.

## Materials and methods

### *Study objectives*

This retrospective, monocentric, study evaluated early or locally advanced HER2+ BC patients receiving the neoadjuvant TCH-P regimen between August 2016 and May 2021 at the Metz-Thionville Regional hospital. The primary objective was the pCR, which was defined as the absence of invasive neoplastic cells at microscopic examination of the primary tumor (ypT0/is) and/or local lymph nodes (ypN0) at surgery. Additional secondary end points included clinical/radiological response rate, disease-free survival (DFS), overall survival (OS), and tolerability. The primary safety end points were the incidence of symptomatic left ventricular systolic dysfunction (LVSD) or decline in LVEF of ≥10% points from baseline to <50% over the course of neoadjuvant treatment.

### *Patients*

Female patients aged ≥18 years with operable (cT1c-3, N0-1) or locally advanced (T2-3, N2 or N3; T4, any N) HER2+ BC and a primary tumor size >1 cm were eligible. HER2 expression was determined using immunohistochemistry (IHC) and *in situ* hybridization (fluorescence *in situ* hybridization [FISH]) by central laboratory testing at our Department of Pathology, according with the current recommendations [12]. FISH positivity was mandatory for IHC 2+ tumors. The status of estrogen (ER) and progesterone (PR) receptors was assessed immunohistochemically by the Allred score [13] using the primary antibody SP1 and 1E2, respectively. A score ≥10% defined HR + tumors for them a hormonal therapy was indicated. The nuclear immunostaining of Ki67 was assessed by counting at least 500–1000 tumor cells per case across 5 high power fields of the section incubated with the primary antibody against Ki67 (MIB-1, 1:100, Dako, Glostrup, Denmark) [14]. The Ki67 proliferative index was scored as high when ≥20% of the tumor cells were positive. To overcome the problem of tumor heterogeneity, two representative tumor foci were marked on slides with hematoxylin and eosin-stained sections from selected paraffin blocks. Two tissue cores of 2 mm were used from each block [14]. Additional inclusion criteria were Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1, and LVEF ≥50% at baseline. All the patients have been informed and gave their consent to treatment, data analysis and publication.

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### Treatment

Study drugs were administered on a 3-weekly schedule. Intravenous or subcutaneous trastuzumab was administered according to patient's preference. Intravenous trastuzumab was given at a loading dose of 8 mg/kg over 90 min (min), followed by a maintenance dose of 6 mg/kg over 30–90 min; subcutaneous trastuzumab was administered at the standard dose of 600 mg; pertuzumab was given intravenously at an initial dose of 840 mg over 60 min, followed by 420 mg over 30–60 min. Carboplatin was administered at a dose of AUC (area under the plasma concentration-time curve) 6 mg/ml x min and docetaxel at 75 mg/m.$^2$ Docetaxel dose reductions to 60 mg/m$^2$ then to 50 mg/m$^2$ were allowed; after which docetaxel was discontinued; re-escalation was not permitted. For carboplatin, the first dose reduction was to an AUC of 5 mg/mL × min then to 4 mg/mL × min, after which carboplatin was discontinued; re-escalation was not permitted. Dose delays were permitted for selected hematological and/or non-hematological toxicity. Peg-filgrastim, a pegylated form of the recombinant human granulocyte colony-stimulating factor (G-CSF) analog filgrastim, was administered 24–72 h after every cycle of treatment. Patients received a total of six cycles. Between 3 and 6 weeks after the last dose, patients underwent definitive BC surgery. Following surgery, patients continued trastuzumab to complete 1 year of treatment in the case of a pCR. After the publication of the Katherine study [15], if a non-pCR was found, T-DM1 was administered for 14 cycles. Adjuvant radiotherapy and hormonotherapy were given as clinically indicated.

### Assessments

Patients underwent tumor staging and bilateral mammogram and ultrasounds at screening and before definitive surgery. Subsequent mammograms were optional during the treatment. Additional breast magnetic resonance imaging (MRI) was not mandatory. Assessment of the primary tumor and regional lymph nodes was done by physical examination at baseline and before the administration of each cycle of study treatment. Bone scan and whole body CT-scan were performed before starting and after 6 cycles of treatment and when clinically indicated to exclude metastatic disease. Laboratory monitoring was completed before the administration of each cycle. LVEF was measured by echocardiography at baseline and every three months. During the follow-up, LVEF assessment took place every 6 months for 2 years, then annually for 3 years. Adverse events were monitored continuously and graded according to the National Cancer Institute Common Terminology Criteria (NCICT) for Adverse Events, version 5.0.

### Statistical analysis

Patients and treatment characteristics were described as number and percentage (qualitative data) or median, quartiles, mean and standard deviation (quantitative data). Histological response rates were described in the whole sample and in subgroups considering ER/PR and HER2 status, and Ki 67 score. All analyses were performed with SAS software (version 9.4, SAS Inst., Cary, NC, USA).

**Table 1.** Baseline patients' characteristics.

| Characteristics | *N* | *n* (%) | Median | Mean ± SD |
|---|---|---|---|---|
| Age | 19 | | 55 (31–79) | 56 ± 12 |
| Sex (F) | | 19 (100) | | |
| Ki 67 (%) | | | 32 (25–70) | 34 ± 17 |
| Tumor status | | | | |
| cT1c | | 2 (10.6) | | |
| cT2 | | 11 (58.3) | | |
| cT3 | | 2 (10.6) | | |
| cT4 | | 2 (10.6) | | |
| cT4d | | 2 (10.6) | | |
| Lymph nodes status | | | | |
| Negative | | 5 (26.5) | | |
| Positive | | 14 (74.2) | | |
| HER2 score | | | | |
| 2+ | | 2 (10.6) | | |
| 3+ | | 17 (90.1) | | |
| Estrogen receptors | | 10 (53) | | |
| Progesteron receptors | | 8 (42.4) | | |
| HR negative tumors | | 7 (37.1) | | |
| Tumor grade (SBR) | | | | |
| 2 | | 9 (47.7) | | |
| 3 | | 10 (53) | | |
| PS (ECOG) | | | | |
| 0 | | 19 (100) | | |

Patients and treatments characteristics were described as number and percentage (qualitative data) or median, quartiles, mean and standard deviation (quantitative data). Histological response rates were described in the whole sample and in the subgroups considering estrogen and progesterone receptors, HER and Ki 67 score. HER2 2+ score was confirmed by a SISH test. All analyses were performed with SAS software (version 9.4, SAS Inst., Cary, NC, USA).

## Results

Between August 2016 and May 2021, 19 patients were treated. The median overall time on study including the post-treatment follow-up was of 21 months (8–51 months). Baseline demographics are reported in Table 1. The median patients 'age was of 55 years (31–79 years). All patients had an ECOG PS of 0. Two patients (10.6%) presented a cT1c tumor, 11 (58.3%) a cT2 tumor, including a bifocal and a multifocal tumor, 2 (10.6%) and 4 (21.2%) patients a cT3 and cT4 tumor, respectively, including 2 patients (10.6%) with an inflammatory (cT4d) tumor. Tumor Ki-67 ranged from 25 to 70%. Fourteen patients (74.2%) had a clinical/radiological lymph node tumor involvement. Only 2 tumors (10.6%) showed an immunohistochemical HER2 score of 2 and were positive at the FISH confirmatory test. Ten (53%) and 8 patients (42.4%) had an ER and a PR-positive tumor, respectively. Seven patients (37.1%) had a hormone receptor (HR) negative tumor. A tumor Scarff-Bloom-Richardson (SBR) grade 3 was reported in 10 patients (53%) and a grade 2 in 9 patients (47.7%). All patients underwent definitive BC surgery within the protocol-specified window of 3 to 6 weeks after their last dose of neoadjuvant therapy.

A clinical/radiological complete response was found in 6 patients (31.8%). Twelve patients (63.6%) presented a partial response and only 1 patient (5.3%) showed a local progression, but this patient achieved a pCR after surgery. The pathological tumor and lymph node response is reported in

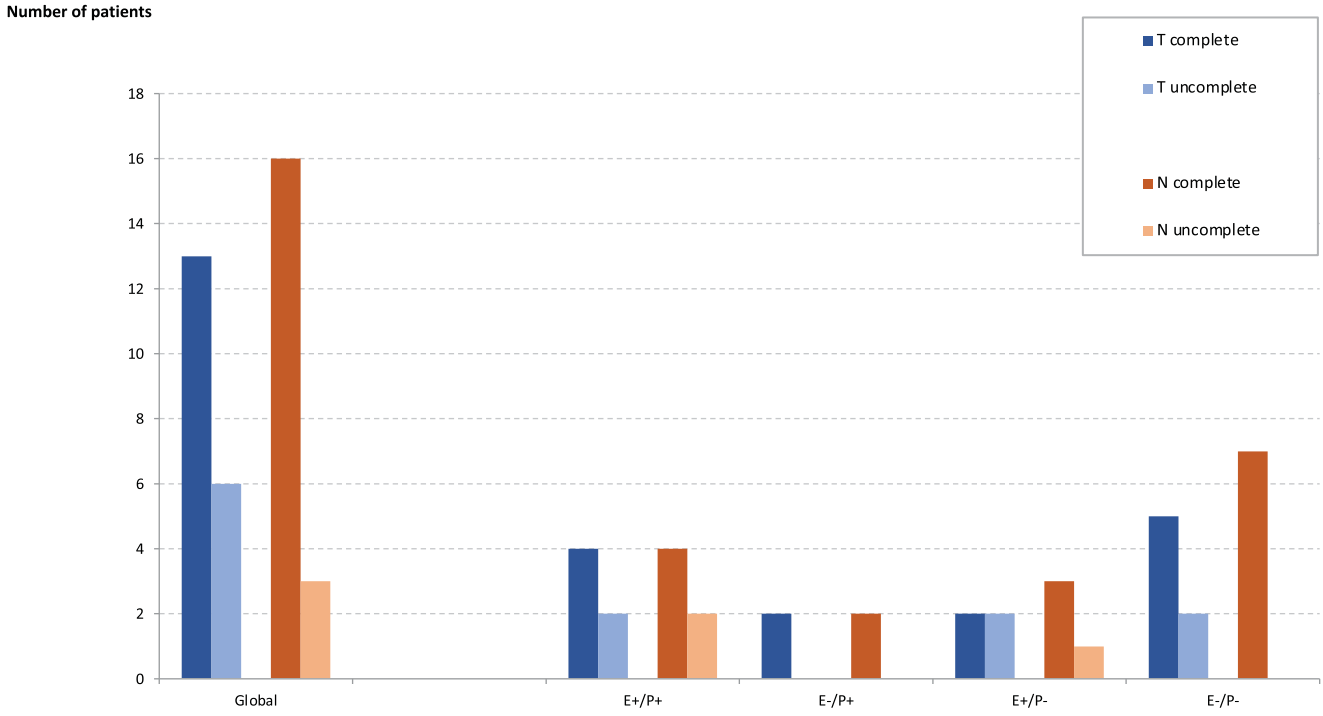


**Figure 1.** Tumor (T) and node (N) histologic responses for the whole cohort, and for estrogens (E) and progesterone (P) receptor subgroups ($N = 19$).

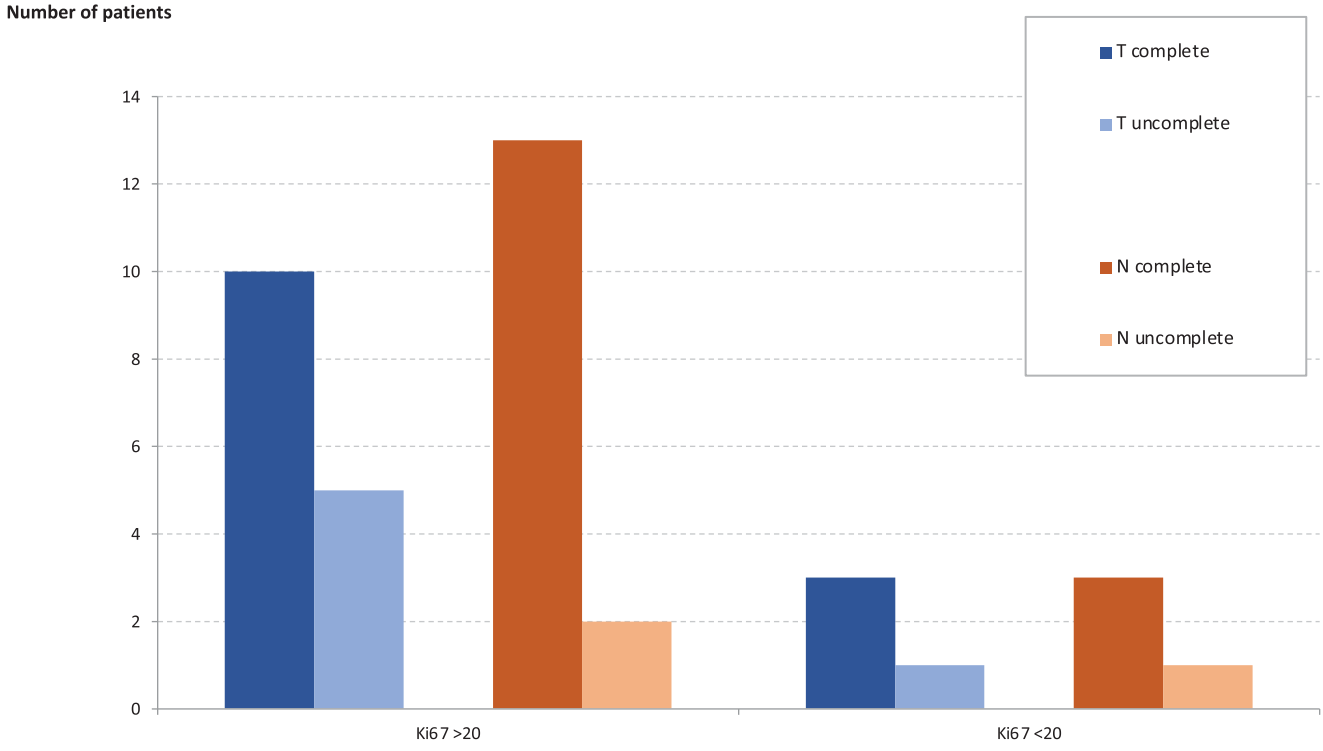


**Figure 2.** Tumor (T) and node (N) histologic responses for Ki67 subgroups ($N = 19$).

Figure 1. A primary tumor and lymph node pCR was achieved by 13 (68.9%) and 16 (84.8%) of the patients, respectively. Thirteen patients (68.9%) achieved a ypT0/is and ypN0 tumor response. Two patients (10.6%) presented a partial tumor and lymph node response and 3 patients (15.9%) a partial primary tumor and a complete lymph node response. Only one patient (5.3%) did not show any tumor and/or lymph node response. Subtype analysis showed a higher pCR rate in HR- tumors (Figure 1) and in patients with a Ki-67 grade $>$ 20% (Figure 2). Among the 2 patients with a HER2 2+ score, one reported a pCR and one a partial primary tumor and a complete lymph node response (Figure 3). Breast-conserving surgery was done in 7 patients (37.1%). Twelve patients (63.6%) underwent a radical mastectomy. A radical axillary lymph node dissection was performed in 12 patients (63.6%). All patients received adjuvant radiotherapy

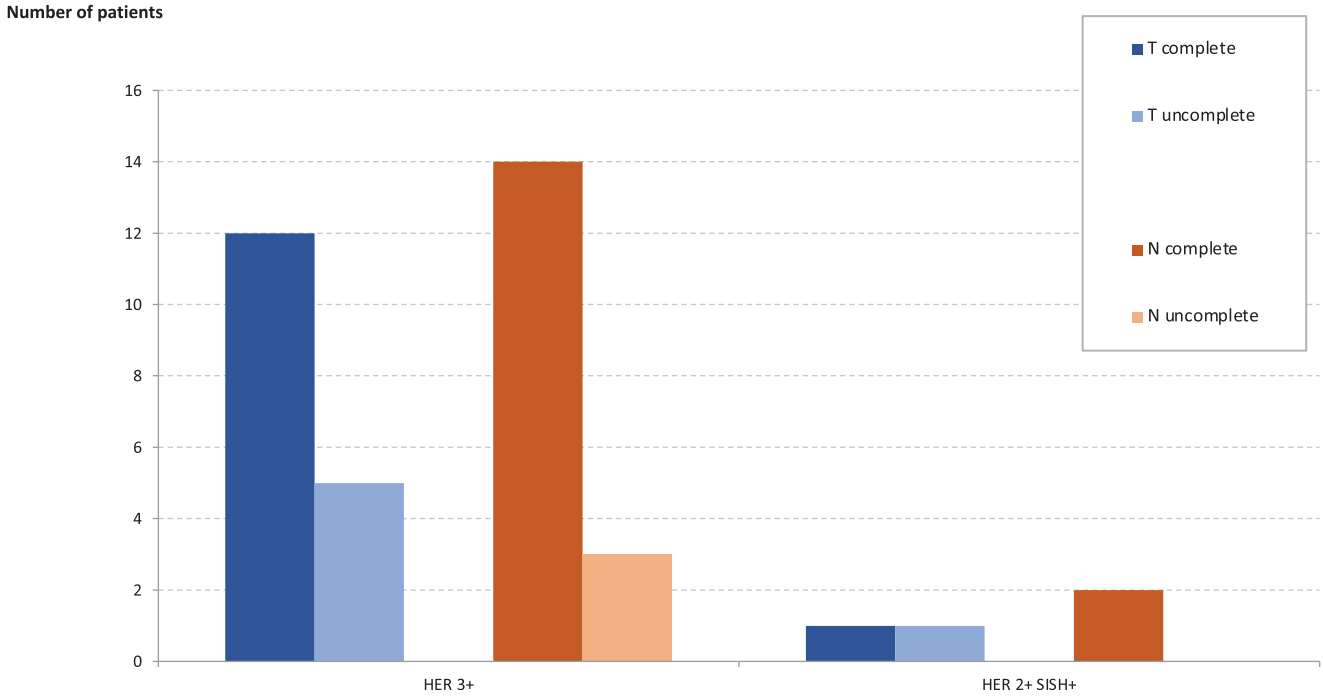


**Figure 3.** Tumor (T) and node (N) histologic responses for HER2 subgroups ($N = 19$).

**Table 2.** Treatment toxicity (%).

| | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Grade 5 |
|---|---|---|---|---|---|
| Anemia | 11 (58.3) | 5 (26.5) | 1 (5.3) | | |
| Thrombocytopenia | 4 (21.2) | 2 (10.6) | | 1 (5.3) | |
| Neutropenia | | 1 (5.3) | 1 (5.3) | | |
| Diarrhea | 4 (21.2) | 3 (15.9) | 1 (5.3) | | |
| Nausea | 3 (15.9) | 2 (10.6) | | | |
| Stomatitis | 1 (5.3) | 2 (10.6) | | | |
| Asthenia | 3 (15.9) | 4 (21.2) | | | |
| Skin rash | 1 (5.3) | 1 (5.3) | 1 (5.3) | | |
| Neuropathy | | 2 (10.6) | | | |
| Transaminitis | 1 (5.3) | | | | |
| Infection | 2 (10.6) | | 1 (5.3) | | |
| Alopecia | 2 (10.6) | 17 (89.4) | | | |

and 10 patients (53%) a post-surgery hormonotherapy. T-DM1 vas administered in only one patient (5.3%) who did not achieve a pCR.

Even if the follow-up period is short, none of the evaluable patients presented a local and/or distant tumor relapse. Data for DFS and OS are not mature.

The treatment toxicity is reported in Table 2. No case of symptomatic LVSD and significant declines in LVEF ($\geq$10% points from baseline to $<$50%) was documented during the study treatment (Figure 4). Only a single case of symptomatic LVSD with an LVEF at 38% was documented during the last cycle of the adjuvant trastuzumab. Cardiac MRI did not show any ischemic lesion and confirm the diagnosis of a trastuzumab-related type II LVSD. The patient was treated pharmacologically and quickly recovered the LVEF at 52%. The most common hematological toxicity included grade 1 and grade 2 anemia in 11 patients (58.3%) and 5 patients (26.5%) and grade 1 and grade 2 thrombocytopenia in 4 (21.2%) and 2 (10.6%) of patients, respectively. The grade $\geq$ 3 hematological toxicity was very rare. The most common non-hematological toxicity included alopecia, diarrhea, nausea and vomiting and was frequently of grade 1 and 2. Only a case of reversible grade 3 skin toxicity (diffuse macular rash) was reported. A patient (5.3%) presented a reversible grade 1 increased alanine aminotransferase. No case of drug hypersensitivity was documented. A treatment delay for toxicity was reported in 8 patients (42.4%). The mean reported time was of 2 weeks. A dose reduction of docetaxel to 60 mg/m$^2$ and carboplatin to an AUC of 5 mg/mL $\times$ min was performed in 10 patients (53%) for hematological toxicity. The delay in treatment or reduction in drug dose did not affect the pCR. No treatment discontinuation for adverse events was reported.

## Discussion

The main objective of this monocentric, retrospective analysis was to confirm the activity and the safety of the neoadjuvant TCH-P regimen in early or locally advanced HER2+ BC patients.

A ypT0/is and a ypN0 were documented in 13 (68.9%) and 16 (84.8%) of the 19 evaluable patients, respectively. Thirteen patients (68.9%) achieved a ypT0/is and ypN0 tumor response. Two patients (10.6%) presented a partial tumor and lymph node response and 3 patients (15.9%) a partial primary tumor and a complete lymph node response. Only one patient (5.3%) did not show any tumor and/or lymph node response. Subtype analysis showed a higher pCR rate in HR- tumors and in patients with a Ki-67 grade $>$ 20%. The delay in treatment or reduction in drug dose did not affect the pCR but the number of the patients evaluated in this study is too small to draw any definitive conclusion. The 2 patients with a HER2 2+ score reported a pCR.

Our results were comparable with those ones reported in the TRYPHAENA trial where the TCH-P treated patients achieved a pCR rate of 51.9% (ypT0/is and ypN0) [6]. The

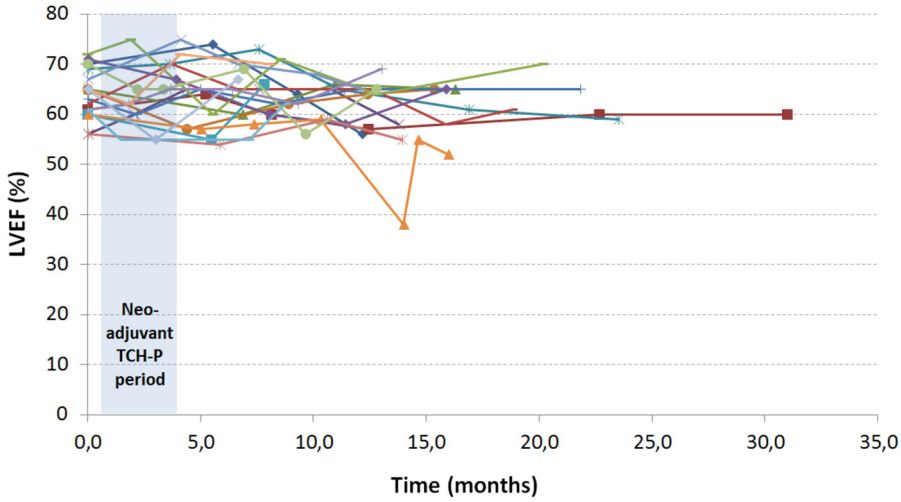


**Figure 4.** LVEF variation for each patient during the neo-adjuvant and the post-surgical period ($N = 19$).

pCR rate was higher in patients with HR- disease (84%) than in those with HR + disease (50%). In a previous neoadjuvant study (NOAH), the trastuzumab-based chemotherapy resulted in a pCR rate of 42.7% [16]. Several neoadjuvant studies suggest that the double HER2 blockade results in a higher pCR rate compared with either agent alone [1–10]. In the NeoSphere trial, the combination of pertuzumab with trastuzumab and docetaxel resulted in a pCR rate of 45.8% [5]. In the NeoALTTO, CHER-LOB, and NSABP B-41 trials, the combination of trastuzumab with lapatinib, resulted in pCR rates of 51.3% [2], 46.7% [17], and 62.0% [3], respectively. Recently, the Neopeaks phase 2 study [10] compared TCH-P (6 cycles; group A), TCH-P (4 cycles) followed by trastuzumab emtansine + pertuzumab (T-DM1 + P; 4 cycles; group B), and T-DM1 + P (4 cycles; group C) regimens in HER2+ BC patients. The pCR rate was numerically higher in group B (71%) than in group A (57%) and the T-DM1 + P regimen (57%). Notably, the pCR rate (57.4%) after the initial 4 cycles of T-DM1 + P (group C) was equivalent to that of the standard TCH-P regimen (57%). No significant differences in safety were observed among the 3 groups of patients. The pCR rates in the ADAPT study were of 41.0% for the T-DM1 × 4 regimen and 41.5% for the T-DM1 + ET (4 cycles) regimen in patients with early HER2+/HR + BC [18]. In the KRISTINE study, pCR was achieved in 44.4% (HR+, 38.1%; HR-, 54.8%) of patients in the T-DM1 + P group and in 55.7% (HR+, 46.4%, HR-, 71.1%) of patients in the TCH-P group [9]. Some neoadjuvant trials confirmed a better pCR rates in HER2+/HR- tumors treated with a dual anti-HER2 blockade combined with standard chemotherapy over HER2+/HR + disease [1–10]. However, Gomez *et al.* documented a poorer differentiation, a greater extracapsular extension, an increased early recurrence rate and a decreased 5-year DFS of this sub-type as compared to HER2+/HR + tumors (65.0% and 74.6%; *p*: 0.045) in the adjuvant setting suggesting a more aggressive behavior [19]. In contrast with tumor showing a low proliferative activity that are more resistant to chemotherapy because most cytotoxic agents require cells to be in the cell cycle [20], HR- BC, which are generally more highly proliferative, are more likely to respond to chemotherapy than the HR + ones [21]. HR- tumors often show a higher proliferative activity and consequently a higher Ki67 index and present a clinical/radiological response to treatment that is very similar to that one of tumors with an elevated Ki67 index [20,21]. Recently, a retrospective Indian study showed a clinical complete response and a pCR in 100% and 36.3% of 32 early or oligometastatic HER2+ BC patients receiving the TCH-P treatment [22].

In our study, the treatment was well tolerated, and toxicity was consistent with that reported in other studies. However, in contrast with results of other published studies where the G-CSF or peg-filgrastim was used as a secondary prophylaxis of the febrile neutropenia, in our study, based also on our personal clinical experience with this protocol, peg-filgrastim was started from the 1$^{st}$ cycle of treatment as a primary prophylaxis, that could explain the different percentage of neutropenia and febrile neutropenia documented in our study as compared to data reported in the literature. Nevertheless, a recent meta-analysis supports the prophylactic use of G-CSF in patients receiving the neo-adjuvant TCH-P regimen showing an incidence of febrile neutropenia of 27.6% (95% CI 18.6–37.1) in patients who did not receive G-CSF *vs* 5.0% (95% CI 2.6–8.0) in patients who did [23]. All patients in our study completed the treatment protocol.

## Conclusions

This study is limited by the small number of evaluable patients, its retrospective design, the short follow-up period, and the absence of a response-guided approach to treatment. Additionally, data for DFS and OS are not mature and to date any local and/or distant tumor relapse was not reported. Overall, our data confirm that the neoadjuvant TCH-P regimen is safe and shows a higher pCR rate, particularly in HR- patients. Finally, these results are consistent with data from other phase II/III studies and attest the TCH-P regimen as the standard neoadjuvant treatment for early HER2+ BC patients.

## Consent form

Oral informed consent was obtained from the patients for publication of this article.

## Author contributions

All authors actively participated in this study and have been involved in drafting, revising and approving the final manuscript.

## Disclosure statement

No potential conflict of interest was reported by the author(s).

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## Data availability statement

All data and materials are available for review at the Division of Medical Oncology, CHR Metz-Thionville, in an electronic format.

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