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# The role of anthracycline and pertuzumab in preoperative treatment of HER2-positive breast cancer

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## ABSTRACT

Polychemotherapy combined with trastuzumab (T) or trastuzumab with pertuzumab (TP) is a standard preoperative systemic treatment in patients with HER2-positive breast cancer. In Poland T is reimbursed according to the Drug Prescription Program of Ministry of Health (MoH) for patients with primary breast tumors bigger than 1cm independently from nodal status, whereas TP is reimbursed for patients with tumors bigger than 2 cm with positive lymph node(s) or lack of hormonal receptors expression. The Drug Prescription Program does not indicate which polychemotherapy should be combined with anti-HER2 therapy. Therefore, one can choose between classical sequential treatment based on anthracycline and taxane combined with T or dual HER2 blockade (usually  $4 \times AC \rightarrow 12 \times \text{paclitaxel}/4 \times \text{docetaxel} + T/TP$ ), or docetaxel with carboplatin combined with trastuzumab (TCH) or with dual HER2 blockade (TCHP). According to the present guidelines of the National Comprehensive Cancer Network (NCCN), polychemotherapy without anthracycline is preferred, which is justified because of its lower toxicity, especially cardiotoxicity. Currently, a pathologically confirmed complete response (pCR) is usually the primary objective in clinical trials dedicated to preoperative systemic treatment in breast cancer. pCR became a surrogate of treatment effectiveness. That is why oncologists eagerly use polychemotherapy combined with dual HER2 blockade as preoperative treatment to increase the patient's chance to achieve pCR, sometimes even when the patient's risk of relapse is relatively small. The goal of this article is to review current evidence-based knowledge about the effectiveness and toxicity of polychemotherapy with or without anthracycline combined with trastuzumab or dual HER2 blockade used as preoperative treatment in HER2-positive breast cancer patients.

**Key words:** pertuzumab, anthracycline, preoperative chemotherapy, pathologically confirmed complete response (pCR), breast cancer, overall survival

Oncol Clin Pract 2023; 19, 1: 50–58

Translation: dr n. med. Dariusz Stencel  
 Oncology in Clinical Practice  
 DOI: 10.5603/OCP.2022.0012  
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 ISSN 2450–1654  
 e-ISSN 2450–6478

## General principles of preoperative chemotherapy

The classic indication for systemic preoperative treatment in breast cancer patients is the local and/or regional advancement, e.g. T3-T4 N0-3 or T1-4 N2-N3 (LABC, locally advanced breast cancer). In patients with initially inoperable tumors, preoperative

pharmacotherapy enables radical local treatment. On the other hand, in patients with cancer that is initially operable, but requires mastectomy, the goal of preoperative treatment is to enable breast-conserving surgery (BCS). In both cases, preoperative chemotherapy plays the role of induction treatment. In primary operable patients, preoperative chemotherapy is called neoadjuvant chemotherapy (NAC).

Received: 09.12.2021    Accepted: 25.01.2022    Early publication date: 01.07.2022

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In practice, however, the terms inductive and neoadjuvant are often used interchangeably.

The benefit of combined modality treatment with induction chemotherapy in patients with inoperable locally advanced breast cancer was demonstrated already several decades ago. The 1983 study by Pawlicki et al. [1] included 87 patients with inoperable LABC, 72 of whom were diagnosed with inflammatory cancer. The 3-year overall survival rate in patients who underwent surgery was over 60%, in patients undergoing radiotherapy it was 32% and only 12% in patients without local treatment.

A more recent 2017 study by Wang et al. [2] also points to surgery preceded by induction chemotherapy as a method ensuring long-term survival in patients with initially nonoperative tumors. Literature data show that currently patients with locally advanced inoperable cancer qualified for preoperative chemotherapy account for 3.5% of all patients with newly diagnosed breast cancers. This percentage may differ between regions with different availability of screening tests, but precise data are lacking. According to the Surveillance, Epidemiology, and End Results (SEER) database [3], 29% of newly diagnosed US patients have regionally advanced diseases. According to data from Great Britain and Germany, the percentage of patients diagnosed with stage III is about 10–13% [4, 5]. However, it should be noticed the last data refer to primarily stage III operable and inoperable cancer.

Similarly, as adjuvant therapy, systemic preoperative treatment aims also to reduce the risk of recurrence and death. It has been shown that in patients with operable breast cancer, administration of chemotherapy before surgery, as compared to its administration after surgery, has a similar effect on life prolongation. This was confirmed, *inter alia*, in the meta-analysis published in 2018 [6], which included almost 5000 patients participating in 10 randomized clinical trials started before 2005. The median follow-up was 9 years. Patients were subjected to various NAC regimens: CMF, anthracycline-based regimens, and regimens containing anthracycline and taxane. The use of NAC resulted in a clinically assessed response in 69% of patients and allowed for a conserving surgery in a higher percentage of patients (65% vs. 49%). There were no significant differences between the efficacy of preoperative and adjuvant chemotherapy in terms of the risk of dissemination within 15 years (38.2% vs. 38.0%; RR 1.02;  $p = 0.66$ ), death due to breast cancer (34, 4 vs. 33.7%; RR 1.06;  $p = 0.31$ ), or all-cause death (40.9% vs. 41.2%, RR 1.04;  $p = 0.45$ ). It should be emphasized that in the group of patients receiving preoperative chemotherapy, more local relapses were noted within 15 years (21.4% vs. 15.9%, RR 1.3;  $p = 0.0001$ ), which indicates an extremely important role of precise tumor marking before initiation of NAC, meticulous histopathological evaluation, and adequate use of adjuvant radiotherapy.

The response to NAC assessed in the histological examination was classified into 4 categories — it can be a complete response confirmed microscopically (pathologic CR, pCR, residual cancer burden 0, and RCB 0) or residual disease of various extension: minimal RCB-I, moderate RCB-II, and extensive RCB-III. The extension of residual disease is calculated with the use of calculators taking into account the size of the primary and residual tumor (mm), “cellularity” of the residual tumor (%) number of lymph nodes involved, and size of the largest metastasis (mm). A complete response confirmed microscopically (absence of infiltrating cancer in the breast and removed regional lymph nodes) is associated with a significant improvement in prognosis compared to no such response, which was confirmed for all breast cancer subtypes [7]. Therefore, using chemotherapy before surgery provides prognostic information that is not available in the case of adjuvant treatment. In some patients with poorer prognoses, who did not achieve pCR, further adjuvant therapy (e.g. trastuzumab, emtansine, capecitabine) may be used [8, 9].

Preoperative chemotherapy used in clinical trials makes it possible to assess the effectiveness of new drugs, determine response biomarkers (predictors), learn about the biology of the disease, or use treatment escalation or de-escalation.

### **Clinical dilemmas related to the indications for NAC and the choice of treatment regimen in HER2+ patients**

Due to the similar effectiveness of pre- and post-operative chemotherapy in terms of its impact on prognosis, with simultaneous additional benefits of preoperative systemic treatment (information on prognosis, response-dependent treatment individualization), the indications for preoperative chemotherapy have now significantly expanded. Murphy et al. [10] collected data from patients with invasive breast cancer treated with perioperative chemotherapy and surgery between 2010 and 2015. In this period, there was a significant increase in the percentage of patients receiving preoperative chemotherapy ( $p < 0.001$ ) for all breast cancer subtypes. The highest percentage of patients receiving NAC and the largest increase in the percentage of such patients concerned individuals with the so-called triple-negative breast cancer (TNBC) and HER2+ breast cancer. It is noteworthy that among HER2+ patients, the increase in NAC use frequency particularly concerned patients with stage I and II tumors (HR+/HER2+: TNM I from 3.7% to 13.3%; TNM II from 22.6% to 49.4%; TNM III from 46.2% to 54.5%; HR-/HER2+: TNM I from 3% to 17.4%; TNM II from

25.2% to 52.4%; TNM III from 54.3% at 54.9%). A similar phenomenon occurred among patients with TNBC.

This new tendency is confirmed by the recommendations of scientific societies. According to the recommendations of the European Society of Clinical Oncology (ESMO) and the National Comprehensive Cancer Network (NCCN), the use of preoperative systemic treatment in patients with TNBC and HER2+ cancer should be considered if the primary tumor diameter is > 2 cm, regardless of the involvement of regional lymph nodes [11, 12]. In patients with HER2+ breast cancer, preoperative chemotherapy should be combined with anti-HER2 targeted drug(s).

The value of trastuzumab (T) in perioperative treatment in terms of improved prognosis has been well documented, but mainly in adjuvant therapy studies. A meta-analysis by Moja et al. [13] showed that adjuvant treatment with trastuzumab initiated with taxane-containing chemotherapy reduces the relative relapse risk by 46% and death risk by 36%.

In Poland, perioperative treatment with anti-HER2 drugs is financed under the MoH drug program. According to the current regulations (as of March 2022), patients with a breast tumor larger than 1 cm or with the N+ feature are eligible for preoperative treatment with trastuzumab. On the other hand, the criterion for dual HER2 blockade use (trastuzumab with pertuzumab, TP) is tumor diameter > 2 cm with associated lymph node involvement or lack of hormone receptors expression. The drug program does not specify which chemotherapy regimen should be combined with trastuzumab or dual HER2 blockade. However, it indicates that the total duration of active pertuzumab therapy in preoperative treatment in combination with trastuzumab and chemotherapy ranges from 3 to 6 infusions. In practice, the treating physician may choose from 4 possible chemotherapy regimens: classic sequential treatment with an anthracycline and taxoid in combination with trastuzumab, or a dual HER2 blockade (most often 4 × AC → 12 × paclitaxel/4 × docetaxel + T or TP), or docetaxel with carboplatin in combination with trastuzumab (TCH), or dual HER2 blockade (TCHP). The great flexibility in qualifying for multi-drug preoperative chemotherapy in patients with relatively less advanced disease may lead to some confusion, especially if one keeps in mind the fact that in patients with pT1N0 tumors, only chemotherapy with paclitaxel and trastuzumab is considered adequate adjuvant treatment [14].

Moreover, the current NCCN recommendations indicate chemotherapy without anthracycline as the preferred chemotherapy in perioperative treatment. This choice is justified by its lower toxicity, especially to the heart.

The purpose of the further part of this article is to present the current evidence-based knowledge regarding benefits of anthracyclines abolition and using pertuzumab in preoperative treatment in HER2+ patients.

### What is the benefit of adding pertuzumab to preoperative treatment?

A pivotal study for pertuzumab in preoperative treatment was NEOSPHERE [15], an uncovered phase-II study in which patients with HER2+ breast cancers were assigned to 4 arms with perioperative systemic treatment. As part of preoperative treatment, patients received 4 treatment cycles according to the following schedules: 1) trastuzumab + docetaxel, 2) pertuzumab + trastuzumab + docetaxel, 3) pertuzumab + trastuzumab, 4) pertuzumab + docetaxel. After surgery, all patients received 3 cycles of adjuvant FEC chemotherapy, except for patients in group 3 who received 4 cycles of docetaxel and then 3 cycles of FEC. The primary study endpoint was pCR assessed in the breast only. Patients receiving pertuzumab and trastuzumab with docetaxel had significantly more pCR in the breast (46%) compared to the group treated with trastuzumab and docetaxel (29%,  $p = 0.014$ ). When interpreting the results of this study, it should be remembered that systemic treatment was unusually split into preoperative and postoperative phases, and pCR was assessed atypically (only in the breast, not in the breast and lymph nodes).

However, the greater effectiveness of dual HER2 blockade in combination with chemotherapy in terms of pCR rate compared to trastuzumab with chemotherapy was confirmed in meta-analyses. The Wu et al. study (2019) compared various preoperative treatment regimens in HER2+ patients, ranging from chemotherapy alone to chemotherapy with dual HER2 blockade, including pertuzumab and trastuzumab [16]. The authors showed that chemotherapy in combination with trastuzumab, compared with its combination with trastuzumab and pertuzumab, is associated with a significantly lower chance of obtaining pCR, but there is no significant difference in the percentage of patients undergoing conserving treatment. The authors also showed no significant differences in the toxicity of both treatment forms.

Unfortunately, the question of whether adding pertuzumab to preoperative chemotherapy combined with trastuzumab improves the prognosis remains unanswered. Although disease-free survival (DFS) was one of the secondary endpoints in the NEROSPHERE study, the trial was not statistically powered to formally test the hypothesis, and the results were only descriptive. The 5-year DFS rates were 81% in subgroup 1, 84% in

subgroup 2, 80% in subgroup 3 and 75% in subgroup 4, respectively [17].

Some insight into the effect of pertuzumab used in perioperative treatment on life extension may be provided by the APHINITY analysis — phase-III randomized, double-blind clinical study [18]. It aimed to evaluate the benefit of adding pertuzumab to standard postoperative chemotherapy in combination with trastuzumab. Almost 5000 patients with operable breast cancer, undergoing primary radical surgery were randomly assigned to 2 arms: standard adjuvant treatment with or without pertuzumab, which was administered together with trastuzumab for 1 year. In total 22% of patients received chemotherapy without anthracyclines, and 63% of patients had lymph nodes involved. The primary study endpoint was invasive disease-free survival (IDFS), secondary endpoints included, among others, OS, DFS, safety, and quality of life. Following the publication of the primary endpoint results, the study was considered formally positive. The 3-year estimated IDFS rates were 94 vs. 93%; hazard ratio (HR) = 0.81, 95% confidence interval (CI) 0.66–1.00,  $p = 0.045$ .

After 74 months of follow-up and a second OS interim analysis, a 3pp difference in IDFS was confirmed (6-year IDFS rates 91% vs. 88%; HR = 0.76; 95% CI 0.64–0.91) in favor of treatment with pertuzumab [19]. However, no significant OS difference was found. The subgroup analysis indicated that the benefit of pertuzumab was primarily noted in patients with infiltrated lymph nodes (IDFS 88% vs. 83%; HR = 0.72; 95% CI 0.59–0.87).

In conclusion, dual HER2 blockade compared to trastuzumab alone, added to chemotherapy, significantly increases the chances of obtaining pCR but does not significantly affect the percentage of patients undergoing conserving treatment. Its effect on life extension is unknown. Extrapolation of the APHINITY study results suggests that patients at high recurrence risk (lymph node(s) metastases) may slightly benefit in terms of IDFS extension from pertuzumab treatment, but this applies to one-year use, not short-term use, only during preoperative therapy.

### **Should anthracyclines be abandoned in preoperative treatment? Scientific evidence**

The starting point for the discussion on resignation from anthracycline in adjuvant chemotherapy in patients with HER2+ breast cancer was the BCIRG006 study published in 2011 [20] and updated in 2015 [21]. Three thousand two hundred patients with HER2+ breast cancer, 70% of whom had lymph nodes infiltrated, were randomized to 3 arms. Within the standard treat-

ment, patients received 4 cycles of AC sequentially, followed by 4 cycles of docetaxel 100 mg/m<sup>2</sup>. In the first experimental arm, the above chemotherapy was combined with trastuzumab (immunotherapy was started together with 1 administration of docetaxel). In the second experimental arm, patients received 6 courses of the TCH regimen (trastuzumab, docetaxel 75 mg/m<sup>2</sup>, and carboplatin AUC × 6). Trastuzumab was continued for up to 1 year in both treatment arms. It should be noted that in the TCH regimen, trastuzumab treatment started earlier after surgery compared to sequential treatment. The primary endpoint was disease-free survival, the secondary endpoints were overall survival, safety, and determination of molecular predictors [topoisomerase 2 alpha gene (*TOP2A*) amplification]. Both treatment regimens with trastuzumab turned out to be more effective than sequential chemotherapy in terms of DFS and OS, also in patients with lymph node involvement.

Unfortunately, the study was not designed to compare the regimens with trastuzumab. There was minimal numerical superiority of the anthracycline regimen. According to the 10-year DFS rate, the difference amounted to 1.6 percentage points, and for the OS — 2.6 percentage points. In lymph node-positive patients, the difference in the 10-year DFS rate was also minimal (sequence 69.6% vs. TCH 68.4%). The TCH regimen was favored by the toxicity profile of long-term cardiac and hematological complications. The anthracycline-free regimen induced significantly fewer left ventricular ejection fraction (LVEF) reduction to grade 3–4 (0.4% vs. 2%) and significantly fewer relative LVEF reduction of more than 10% (9% vs. 19%). Acute leukemia was diagnosed in 2 patients treated sequentially and 1 patient in the TCH group. Febrile neutropenia was equally common in both trastuzumab arms (approx. 10%), while anemia and thrombocytopenia were more common in patients treated with TCH. Subgroup analyses taking into account the amplification of the *TOP2A* gene, present in 35% of patients, indicated that in such patients sequential chemotherapy without trastuzumab was as effective as chemotherapy with trastuzumab in terms of DFS. This phenomenon was not observed in patients without *TOP2A* gene amplification.

It is hypothesized that the high efficacy of the TCH regimen (or other non-anthracycline regimens) used in perioperative therapy is due to the earlier initiation of anti-HER2 therapy. This may be indicated by the results of a retrospective study by Gallo et al. [22]. It is an analysis of data from 506 patients treated with trastuzumab in combination with perioperative chemotherapy (adjuvant 76%, neoadjuvant 24%) in a center in Dublin since 2010, collected in the “One Thousand HER2 Patients Project” database. About 70% of patients included in the analysis received treatment in which trastuzumab was initiated together with chemotherapy start

(TCH regimen or similar), about 17% were given sequential chemotherapy with trastuzumab administered concurrently with taxane, 6.7% received trastuzumab after chemotherapy completion, and 6.7% — trastuzumab without chemotherapy. It turned out that patients who started immunotherapy together with taxoid in sequential treatment or after completion of all chemotherapy were characterized by an increased relapse risk compared to patients receiving trastuzumab commenced simultaneously with the start of chemotherapy (TCH regimen or similar, DFS HR = 1.86; 95% CI 1.11–3.09;  $p = 0.017$ ). The difference in OS was not statistically significant (OS HR = 1.18; 0.59–2.34;  $p = 0.629$ ). However, when interpreting the results of this study, it should be remembered that it was a retrospective analysis, and the prognoses of patients qualified for sequential chemotherapy containing anthracycline and taxane could be worse at baseline.

An example of a phase-II randomized study evaluating the safety and effectiveness of systemic preoperative treatment with or without anthracyclines in HER2+ patients is TRYPHAENA [23]. The study included 225 patients with operable, locally and regionally advanced, or inflammatory breast cancer with a primary tumor diameter greater than 2 cm. In all three arms, patients received trastuzumab and pertuzumab in combination with 6 cycles of chemotherapy: arm 1: 3 × FEC + T + P → 3 × docetaxel + T + P; arm 2: 3 × FEC → 3 × docetaxel + T + P; and arm 3: 6 × docetaxel + carboplatin + T + P. After surgery, treatment with trastuzumab was continued for a total of 1 year. The primary endpoint of the study was safety and tolerability, with secondary endpoints including DFS and OS. There was no formal testing of the research hypothesis in the study, and the results were presented descriptively. The 3-year DFS rates were 87%, 88%, and 90%, respectively, and the OS rate was 94%, 94%, and 93%, respectively [24].

The assessment of the effectiveness of preoperative chemotherapy with or without anthracyclines in combination with dual HER2 blockade was also the aim of the randomized phase-III TRAIN-2 study, which enrolled 438 patients with stage II and III HER2+ breast cancers [25]. The two preoperative treatment arms were 3 × FEC + trastuzumab + pertuzumab → 6 × paclitaxel (80 mg/m<sup>2</sup>, days 1 and 8) + carboplatin (AUC × 6) + trastuzumab + pertuzumab or 9 cycles of paclitaxel + carboplatin + trastuzumab + pertuzumab. All patients received trastuzumab for up to 1 year after surgery and underwent radiotherapy and adjuvant hormone therapy if indicated. The primary endpoint was pCR, secondary endpoints included event-free survival (EFS) and OS. After a median follow-up of 49 months, there were no significant differences neither in pCR, or 3-year event-free survival rates, or OS. Among patients

treated without anthracycline there were significantly fewer cardiac adverse events (8.6% vs. 3.2%,  $p = 0.021$ ) or febrile neutropenia. When analyzing the results of the study in terms of practical conclusions, it is worth noting that in both arms (as in the TRYPHAENA study) dual HER2 blockade was used, so results do not apply to patients treated only with trastuzumab combined with chemotherapy. Moreover, the chemotherapy used in both arms was non-typical, longer than the standard one (9 cycles), paclitaxel in sequential treatment was combined with carboplatin and not used as monotherapy, trastuzumab and pertuzumab were administered simultaneously with an anthracycline (which is not recommended outside of clinical trials).

In many countries, pertuzumab is not available in preoperative treatment for economic reasons. Therefore, the goal of the uncovered phase-II randomized neoCARH study was to evaluate using anthracyclines as part of preoperative chemotherapy in combination with trastuzumab only [26]. Standard adjuvant treatment was continued after surgery. The study was conducted in Chinese centers, and patients were assigned to 2 arms with the standard chemotherapy used in adjuvant treatment: sequential treatment 4 × EC → 4 × docetaxel + trastuzumab or 6 × TCH. The primary study endpoint was pCR, with secondary endpoints including DFS and OS. Only 135 patients were enrolled in the study. It was shown that the pCR rate was significantly higher in patients treated with the TCH regimen compared to the sequential therapy (56% vs. 37%,  $p = 0.032$ ), but no significant difference was found in the percentage of patients who underwent conserving surgery ( $p = 0.139$ ). Survival results are not yet mature.

However, the superiority of the TCH regimen over sequential treatment with trastuzumab in increasing the chance of pCR remains controversial if taking into account the results of the meta-analysis by Pelizzari et al. [27] presented at the 2019 American Society of Clinical Oncology (ASCO) Annual Meeting [27]. The meta-analysis included randomized phase II and III studies and compared the effectiveness of different preoperative treatment regimens in HER2+ patients in terms of pCR rate. An indirect comparison of the different treatment regimens was performed. PCR rates after various treatment regimens were estimated using Bayesian statistics. The authors found no statistically significant difference between the effectiveness of dual HER2 blockade combined with chemotherapy with anthracyclines as compared to its combination with chemotherapy without anthracyclines. Similarly, there was no significant difference between the combination of trastuzumab and anthracycline chemotherapy compared to its combination with chemotherapy without anthracyclines. However, a significant difference was found in favor of dual HER2 blockade in combination

with anthracycline chemotherapy compared to trastuzumab with anthracycline chemotherapy. Moreover, dual HER2 blockade combined with chemotherapy without anthracyclines turned out to be significantly more effective in inducing pCR compared to trastuzumab combined with anthracycline chemotherapy. The authors also estimated the chances of obtaining pCR depending on the treatment regimen, and they were as follows: dual HER2 blockade with chemotherapy containing anthracycline — 58%, dual HER2 blockade with chemotherapy without anthracycline — 54%, trastuzumab with chemotherapy containing anthracyclines — 44%, trastuzumab with chemotherapy without anthracycline anthracyclines — 36%.

In conclusion, there is a lack of reliable results from randomized clinical trials showing whether and how abandoning anthracyclines in preoperative chemotherapy combined with trastuzumab affects the prognosis. Extrapolation of the BCIRG006 adjuvant treatment study results suggests that the efficacy of the TCH regimen and sequential treatment may be comparable. When dual HER2 blockade is combined with preoperative chemotherapy, abandoning the anthracycline does not affect prognosis after a relatively short follow-up period, although the TRAIN-2 study used atypical chemotherapy regimens. The results of the meta-analysis of phase-III and II clinical trials indicate that the withdrawal of anthracyclines, either in the case of chemotherapy combined with trastuzumab or with dual HER2 blockade, does not significantly reduce the chance of pCR obtaining, although the numerically highest pCR rate should be expected after using dual HER2 blockade with chemotherapy containing anthracyclines. The same meta-analysis shows that dual HER2 blockade with anthracycline-free chemotherapy is significantly better in terms of pCR rate compared to the combination of trastuzumab with anthracycline-containing chemotherapy. On this basis, it is suggested that anthracyclines should be abandoned in favor of adding pertuzumab to preoperative treatment. Such modern treatment is considered less toxic, although it generates significantly higher costs. However, it should be remembered that there are no data on the impact of such treatment on the improvement of prognosis. There are also no studies currently comparing sequential chemotherapy with trastuzumab or TCH with TCHP regimens.

### **Resignation from anthracyclines to avoid cardiac toxicity**

The choice of a preoperative chemotherapy regimen without anthracycline may be dictated by the desire to avoid potential cardiotoxicity in patients with additional risk factors for heart complications. The analysis of the

BCIRG006 study results after 10 years of follow-up showed significantly fewer cardiac complications in patients treated with the TCH regimen compared to those treated with AC-TH. Congestive heart failure grade 3/4 occurred in 4 and 21 patients, respectively ( $p = 0.0005$ ), and a relative reduction in LVEF of at least 10% was noted in 97 and 200 patients, respectively ( $p < 0.0001$ ). Such differences in cardiotoxicity were not noted in the neoCARH study, but it was characterized by small sample size and a short follow-up period. Therefore, the TCH regimen is a reasonable choice for patients with an increased risk of cardiac complications.

There is a lack of reliable data from randomized clinical trials assessing perioperative treatment and if adding pertuzumab to the TCH regimen increases the risk of cardiological complications. Partial information on this subject is provided by the analysis of patients participating in the NEOSPHERE study receiving preoperatively 4 courses of docetaxel with trastuzumab (group 1) or 4 × docetaxel with trastuzumab and pertuzumab (group 2). No significant difference was detected between the mean values of the maximum LVEF decreases in these subgroups. LVEF reduction by 10–15% or absolutely less than 50% was reported in 1 (1%) and 3 (3%) patients, respectively, in groups 1 and 2 during neoadjuvant treatment, and in a total of 2 (2%) and 9 (8%) patients, respectively, during 5 years of follow-up. However, it should be remembered that after surgery, patients were given an anthracycline.

It was shown in the TRAIN-2 study that anthracycline withdrawal in the case of dual HER2 blockade significantly reduces the risk of cardiotoxicity (LVEF reduction of at least 10% or absolutely  $< 50\%$  in 8.6% and 3.2%, respectively,  $p = 0.021$ ), but the anthracycline was administered here simultaneously with trastuzumab and pertuzumab.

In conclusion, in patients with an increased risk of cardiac complications, the choice of the TCH regimen is safer. However, it is not known whether and to what extent adding pertuzumab to this regimen increases the risk of cardiac toxicity, which would prevent or interfere with the planned preoperative treatment and then the continuation of anti-HER2 treatment after surgery.

### **Escalation and de-escalation of preoperative treatment in HER2+ patients**

When planning treatment, one should be guided primarily by the real benefit that the patient may derive, that is, first of all, choose medications that extend life. Subsequently, the possible treatment toxicity should be minimized. Unfortunately, making pCR the primary endpoint for almost all studies evaluating the effectiveness

of NAC and thus assuming that pCR is a prognostic surrogate, introduced some information chaos. pCR began to be taken as a value in itself, which is as inaccurate as shown above. Consequently it has not been possible to demonstrate that an increase in the pCR rate by a given NAC regimen contributes to life extension or the effect on life extension has not been reliably rated. Pusztai et al. [28] postulate several potential factors that may underlie the apparent paradox that increasing the pCR rate does not translate into extending the life of patients receiving more intensive treatment: 1 — the initial prognosis may be so good that the patient would be cured only after surgery or standard treatment would be sufficient, 2 — in patients with residual disease, the risk of relapse can be effectively reduced by adjuvant treatments, 3 — primary tumor and micrometastases may show different sensitivity to the drugs used, which would explain the appearance of distant metastases during subsequent observation in approximately 3–5% of patients with pCR.

Meanwhile, the use of preoperative multi-drug chemotherapy combined with dual HER2 blockade (therapy escalation) is dictated by the desire to increase the patient's chance of having pCR. The effect of the above strategy is that patients with a low risk of recurrence are subjected to too intensive treatment with an unknown benefit in survival. The escalation of preoperative treatment in HER2+ patients to obtain the highest pCR rate is understandable if the patient is able to receive adjuvant treatment with TDM1 as a practical consequence of not achieving a complete response. The effectiveness of such treatment was documented in the uncovered, randomized, phase-III KATHERINE study [8], which enrolled almost 1500 patients with HER2+ tumors and residual disease after preoperative treatment with trastuzumab administered for at least 9 weeks. Patients were assigned to 2 arms: 14 TDM1 administrations or 14 trastuzumab administrations. The exclusion criterion was the clinical T1aN0 and T1bN0 stage at the time of radical treatment initiation. Adjuvant hormone therapy and radiotherapy were conducted according to the local standard. In the case of discontinuation of TDM1 due to intolerance, it was possible to administer trastuzumab. The primary study endpoint was IDFS, with secondary endpoints including DFS, OS, and safety. Among the patients included, 72% showed the presence of hormone receptors, three-fourths received anthracycline-containing chemotherapy, and 18% also received pertuzumab in preoperative treatment, in 25% of patients the tumor was inoperable at the time of starting preoperative treatment. The first interim analysis performed after the median follow-up of 41 months showed significantly greater efficacy of the experimental treatment in terms of the 3-year IDFS rate, the absolute gain was 11 pp (88% vs. 77%; HR = 0.50;  $p < 0.001$ ). However, OS extension has not

been demonstrated so far (March 2022). Since March 2022, adjuvant treatment with TDM1 in patients with residual disease in the breast or axillary lymph nodes after preoperative taxane-containing chemotherapy combined with anti-HER2 therapy has been financed under the Ministry of Health Drug Program.

Attention should also be paid to the concept of de-escalation of preoperative treatment, explored in recent years [29, 30]. It assumes that some patients have a good prognosis and do not require multi-drug therapy with dual HER2 blockade and that less intensive treatment would be sufficiently effective with reduced toxicity. Unfortunately, we do not currently know the predictive factors that would enable the selection of the optimal de-escalated preoperative treatment, and such a procedure should not be part of routine clinical practice. Figure 1 shows a schematic comparison of systemic preoperative treatment regimens for HER2+ patients in terms of the effect on life extension, cardiotoxicity, and the chance for conserving treatment.

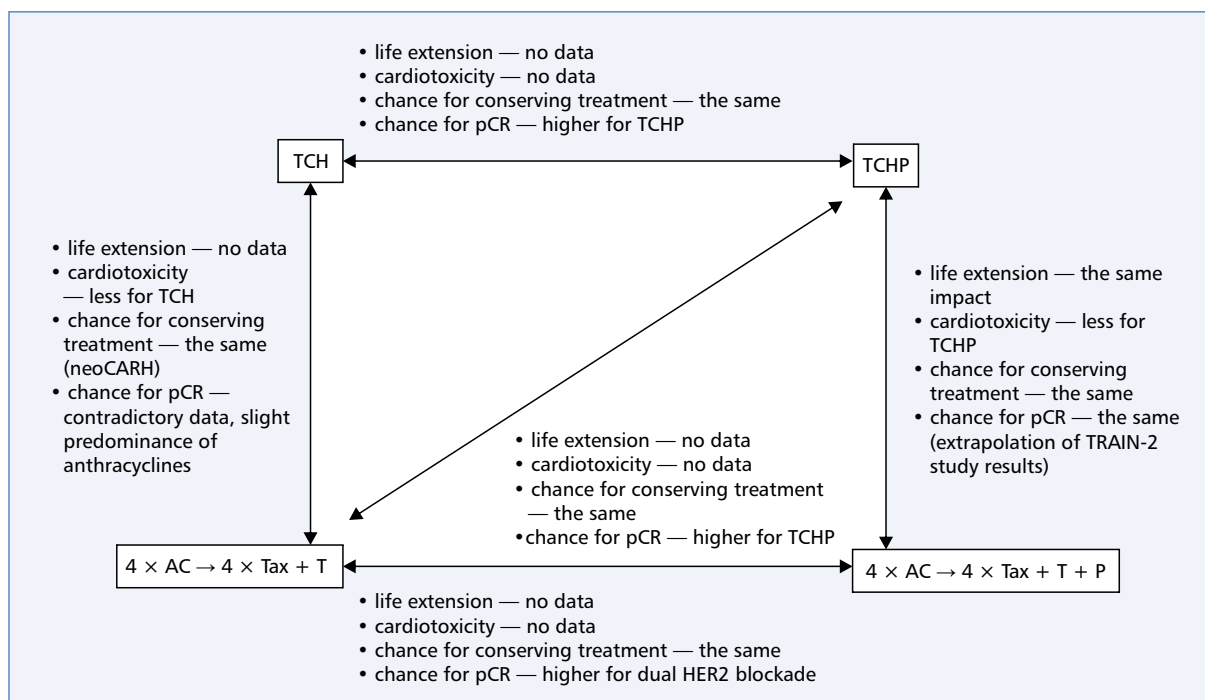
## Conclusions

In patients with operable breast cancer, the impact of preoperative chemotherapy on the prognosis does not differ from the effect of the same chemotherapy given postoperatively.

Despite the criteria of the drug program enabling such management, the preoperative treatment of HER2+ patients with free lymph nodes and a tumor smaller than 2 cm seems unjustified. In such patients, there is a possibility of adjuvant treatment with paclitaxel and trastuzumab after the primary surgery, although such an approach is justified by the results of a study without a control group.

The use of dual HER2 double blockade with preoperative chemotherapy (compared to trastuzumab with chemotherapy) increases the chances of obtaining pCR but does not increase the chances of conserving treatment. The impact of adding pertuzumab to trastuzumab in combination with preoperative chemotherapy on the prognosis is unclear. Extrapolation of the results of the adjuvant treatment study (APHINITY) suggests that addition of pertuzumab may improve prognosis in patients with high risk of recurrence (metastases in axillary lymph nodes). However, there are no data to suggest that short administering of pertuzumab only in preoperative treatment is as effective as 1 year lasting postoperative treatment.

The claim that anthracycline can be abandoned in preoperative chemotherapy in combination with trastuzumab or dual HER2 blockade without adversely affecting prognosis is based on an extrapolation from the adjuvant treatment study BCIRG006 and the TRAIN-2 study (including a small group of patients,



**Figure 1.** Schematic comparison of the preoperative treatment methods in HER2+ patients in terms of the effect on life extension, cardiotoxicity, and the chances of breast-conserving surgery (BCS) and pCR; TCH — docetaxel with carboplatin in combination with trastuzumab; TCHP — docetaxel with carboplatin in combination with dual HER2 blockade; AC — doxorubicin with cyclophosphamide; Tax — taxoid (docetaxel or paclitaxel); T — trastuzumab; P — pertuzumab; pCR — pathologically confirmed complete response

with atypical preoperative chemotherapy regimens and short follow-up).

There are no data from studies that directly compare preoperative chemotherapy with TCH and TCHP, or sequential treatments with trastuzumab and TCHP, in terms of their effect on survival and cardiac toxicity.

The TCH regimen is less cardiotoxic than sequential treatment with trastuzumab. There is no direct data on whether and to what extent adding pertuzumab to the TCH regimen increases cardiac toxicity.

In patients who do not achieve pCR after preoperative treatment, adjuvant therapy with TDM1 prolongs the invasive disease-free survival time, but the impact of such treatment on overall survival is unknown.

## Conflict of interest

PP: fees for lectures, for conducting clinical trials, and covering the costs of participation in conferences from Roche Polska.

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