

# Neoadjuvant therapy for breast cancer patients and its impact on surgical treatment and radiotherapy (part 1.)

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Neoadjuvant therapy (NAT) is increasingly applied in patients with initially inoperable breast cancers and, frequently, in those with tumours that are initially operable, too. In most cases, the response to the applied NAT affects the scope of surgical treatment and radiotherapy, and in some situations also the complementary systemic postoperative treatment. The available studies indicate importance of response to NAT within the breast and regional lymph nodes. Assessment of response to treatment allows personalization of treatment and in some cases a change of therapy, which improves long-term outcomes.

This article summarizes the current rules of conduct in patients with early breast cancer qualified for neoadjuvant therapy, paying attention to the practical aspects and possibilities of national health insurance-covered therapies in Poland. It discusses in detail the applied regimens of systemic therapy, surgical techniques, eligibility rules and complementary radiotherapy. Systems for assessing response to neoadjuvant treatment are also presented.

**Key words:** breast cancer, surgery, systemic therapy, neoadjuvant therapy, adjuvant therapy

Neoadjuvant therapy (NAT) is increasingly applied in patients with initially inoperable breast cancers and, frequently, in those with tumours that are initially operable, too. In most cases, the response to the applied NAT affects the scope of surgical treatment and radiotherapy, and in some situations, also complementary systemic postoperative treatment. The available studies indicate importance of response to NAT within the breast and regional lymph nodes, allowing for treatment personalisation.

## Systemic neoadjuvant therapy

The first reports of application of neoadjuvant (preoperative) chemotherapy in the treatment of patients with operable

breast cancer were published by Jacquillat et al. in 1983. The authors of this study applied systemic treatment in 143 patients at the I–III stage of the disease. They observed clinical complete response (cCR) in 30% of patients. This publication triggered further clinical trials.

The first American study, NSABP B-18, which lasted from 1988 until 1993, included 1,523 patients who received (pre- or post-operatively) AC-regimen chemotherapy (adriamycin, cyclophosphamide). Among patients with preoperative treatment, 80% responded to the therapy. Clinical complete response (cCR) was observed in 36% of them, and pathological complete response (pCR) in 13%, while efficient breast-con-

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serving treatment (BCT) was achieved in 67.8% (in the group with post-operative chemotherapy – in 59.8% of the patients). In the follow-up of 5 and 9 years, no differences were found with respect to disease-free survival (DFS) and overall survival (OS) in both observed groups of patients.

Between 1995 and 2000, the NSABP B-27 study was conducted on a group of 2,411 patients. It showed that addition of docetaxel (AT regimen – adriamycin, taxotere docetaxel) to adriamycin increased the pathological complete response (pCR) rate (26% vs. 13%). However, no differences were found in DFS and OS between AC and AT study arms. In contrast, in the EORTC 10902 study, which assessed preoperative and postoperative treatment in FEC regimen (fluorouracil + epirubicin + cyclophosphamide) in 698 patients, a response was observed only in 49% of the patients (cCR – 7% and pCR in 1.7%). A follow-up of ten years revealed no differences in DFS and OS [1]. In a retrospective randomised clinical trials no differences in DFS and OS were found comparing preoperative and postoperative treatment [2].

Nowadays, systemic treatment allows further personalisation of therapy and better clinical and pathological response. Pathological complete response (pCR) to NAT has a positive effect on DFS and OS – especially in the case of triple-negative breast cancers (TNBC) and cancers with overexpression of human epidermal growth factor receptor 2 (HER2-positive) [2].

### **Indications for systemic neoadjuvant treatment**

The decision to use systemic neoadjuvant therapy (NAT) at the beginning of treatment of a cancer should be taken by a multidisciplinary therapeutical team (MDT). The stage of the disease, biological subtype of the cancer, the patient's expectations and potential benefits of this treatment should be considered. Currently, NAT candidates include patients with:

1. initially inoperable breast cancer:
  - inflammatory breast cancer
  - advanced breast cancer cT4cN2/cN3;
2. initially operable breast cancer if the decision concerns performance of a breast conserving surgery in the case of limitations:
  - within the breast – a disparity between the size of the tumour and the mammary gland, if excision in the initial circumstances could lead to non-radicality or unacceptable aesthetical result.
  - within the axillary lymph nodes – metastatic regional axillary lymph nodes (cN1) when complete regression of cancerous lesions is expected;
3. initially operable breast cancer, if the performed diagnostics (especially in the case of those biological subtypes of breast cancer which are especially aggressive: HER2-positive, TNBC) would qualify the patient for post-surgical systemic treatment depending on the stage of the disease:
  - cN+/pN+,
  - at some institutions – in the case of cT ≥ 1c tumours [3].

### **Preoperative diagnostics**

Preoperative diagnostics including interviews, physical examination, imaging, histopathological and cytological tests and other tests is described in Issue 5 of the Biblioteka Chirurga Onkologa (Oncological Surgeon's Library) titled "Chirurgiczne leczenie zmian nowotworowych piersi. II Konsensus Polskiego Towarzystwa Chirurgii Onkologicznej" ("Surgical Treatment of Breast Neoplasms. 2nd Consensus of the Polish Society for Oncological Surgery") [4].

It is particularly difficult to assess the condition of lymph nodes based on palpation and imaging tests. The primary test involves a clinical examination, although the false negative rate (FNR) in this case can be as high as 45% [5]. Metastatic cancer was found in approximately 25% of patients with cN0 stage lymph nodes, including metastases to ≥3 lymph nodes in less than 6% of cases [6].

In each case, a mammogram and ultrasound of the breast should be performed. Ultrasound with fine-needle biopsy of the suspicious lymph nodes is considered a standard diagnostic method, however, it bears a risk of inaccuracy, with its sensitivity assessed at 47–90%, specificity at 100%, and FNR at 8–24%. Sensitivity of this method is 44% for metastases <5 mm and 93% for metastases > 5 mm [5–7].

If the biopsy confirms lobular cancer, or there is a genetic background to the disease, or there are discrepancies in the spread of the disease diagnosed with mammography, US, clinical examination, and breast MRI are indicated. This technique should also be considered in cases of qualification for NAT and assessment of lesion remission during such treatment.

### **Management before commencement of systemic treatment**

According to recommendations by many scientific oncology societies, NAT should be preceded with labelling of all diagnosed cancer foci with markers [8]. One may also consider application of similar markers at the verified (metastatic) axillary lymph node(s), if the reference oncology centre performing sentinel lymph node biopsy (SLNB) after NAT applies the TAD technique (targeted axillary dissection). TAD involves labelling of a lymph node containing a metastasis (labelling techniques are discussed below) before NAT and its targeted biopsy during SLNB afterwards. An alternative procedure involves the classical form of biopsy of sentinel lymph nodes – at least 2–3 sentinel nodes are labelled with a technique which allows their visual identification (visible staining) and with instrumental technique (probe to detect an isotope or ferromagnet).

### **Systemic treatment**

In 2019, two important documents were published concerning rules for management of early breast cancer patients – recommendations of the European Society for Medical Oncology (ESMO) and the Consensus of Experts of the St. Gallen Conference 2019 [9, 10]. The guidelines highlight application of systemic neoadjuvant therapy in selected breast cancer patients.

According to the recommendations, the following biomarkers should always be determined for breast cancers: expression of estrogen receptors (ER), progesterone receptors (PgR) and human epidermal growth factor receptor 2 (HER2), as well as intensity of proliferation index Ki-67; and in patients with triple negative breast cancer, additionally presence of tumour infiltrating lymphocytes (TILs) [10].

Breast cancer is divided into five main subtypes, requiring a slightly different therapy:

1. ER-positive luminal A – LA cancer,
2. ER-positive luminal B – LB cancer,
3. luminal B HER2-positive cancer (HER2-LB),
4. non-luminal HER2-positive cancer (HER2-NL),
5. triple negative cancers (TNBC).

The most significant changes have been recently introduced in definition of luminal subtypes. For several years, the value of the Ki-67 proliferation index and the degree of malignancy (grade, G) have been used to distinguish them. Luminal A cancers are characterized by a low grade of malignancy (G1), high degree of expression of estrogen receptors (ER) and progesterone receptors (PgR) and a low proliferation rate (Ki-67). Meanwhile, in luminal B cancers, ER and PgR expression is lower, while the malignancy grade is higher (most frequently it's G3), and so is the Ki-67 index [11]. The proposed classification resulted in a large number of breast cancers classified as intermediate cases. This is why luminal subtypes are more easily defined by the division provided in St. Gallen recommendations of 2015, based on expression of ER, PgR, HER2 and on Ki-67:

- luminal A cancers: ER-positive, PgR  $\geq$  20%, HER2-negative, Ki-67 < 20–29%;
- luminal B cancers: ER-positive, HER2-negative, PgR < 20% or Ki-67 > 20–29% [12].

Systemic neoadjuvant therapy has been a standard of management in locally advanced breast cancers for years. Depending on the biological subtype, the following are applied:

- in luminal A and B cancers – hormone therapy or chemotherapy,
- in triple negative cancers – chemotherapy,
- in HER2-positive cancers – chemotherapy combined with yearly anti-HER2 therapy.

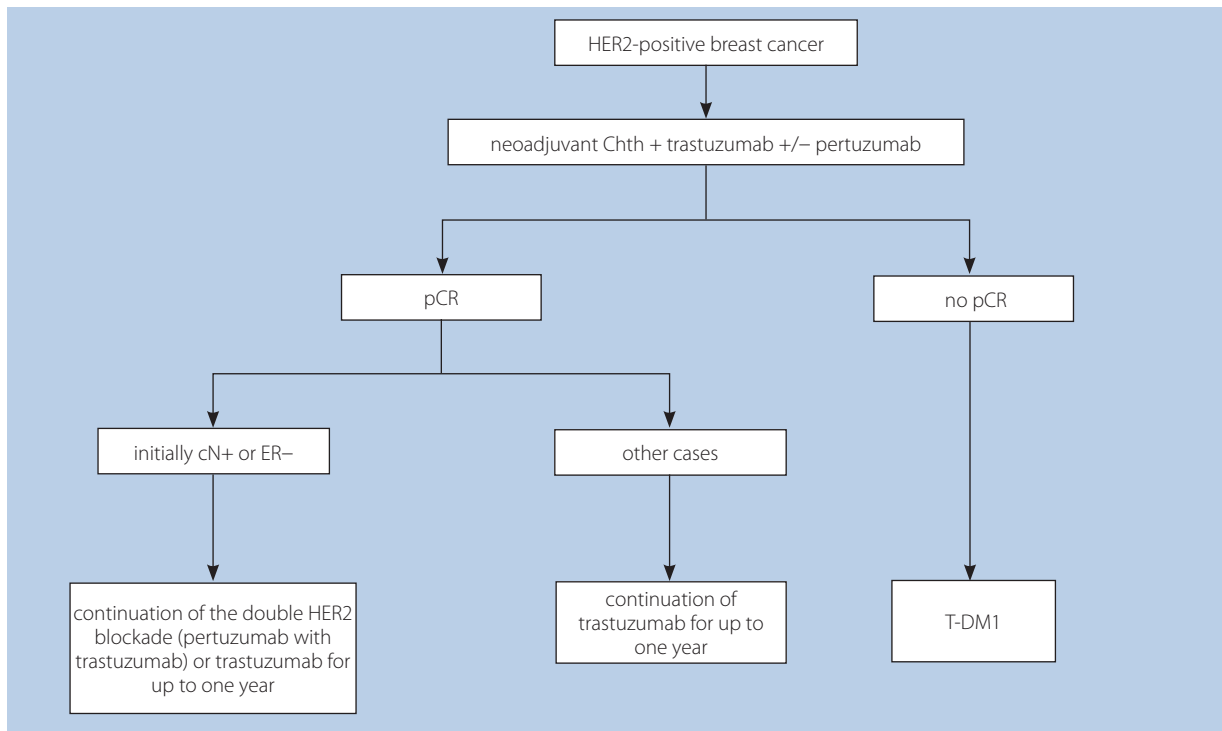
Increasingly, neoadjuvant treatment is used in initially operable breast cancers – primarily TNBC and HER2-positive ones. According to the St. Gallen consensus of 2019 and ESMO guidelines of 2019, such therapy is indicated for breast cancers >2 cm and/or cytologically confirmed metastatic lymph node (cT2 and/or cN+, i.e. II stage of the disease)

This approach reflects a tendency to limit the scope of surgery in favour of conservative treatment in the area of the breast and axillary lymph node. Some publications have also shown that systemic neoadjuvant therapy may be beneficial for patients with cancers >1 cm, too [13] neoadjuvant treatment with a combination of sequential chemotherapy

and HER2-targeted therapy is currently the standard of care. This is followed by breast surgery, radiotherapy (if indicated). Similar treatment opportunities for patients with HER2-positive cancers are provided by the drug prescription programme currently implemented in Poland [14]. Considering the currently binding list of reimbursed drugs in the case of anti-HER2 drugs applied in treatment of the early stage of breast cancer, it seems that inclusion of patients with cT1c stage of cancer in neoadjuvant therapy improves distant treatment results. Many European centres specialising in breast cancer treatment accept this opinion, too [15]. A document by the Department of Breast Cancer & Reconstructive Surgery of the National Research Institute of Oncology confirmed especially high rate of pathological complete remissions achieved in patients included in TCH-regimen neoadjuvant therapy (docetaxel, carboplatin, trastuzumab) – 55% in the group of patients with cancers of 10–50 mm, cN0 or cN1 (while pCR rate in the subgroup of patients with non-luminal HER2-positive cancers was 66%). Meanwhile, in a cohort of patients included in the TCH-P regimen (docetaxel, carboplatin, trastuzumab, pertuzumab), pCR rate was 76% (while in the group of patients with non-luminal, HER2-positive cancers, pCR as high as 87% was observed, especially for less advanced cancers), which will probably affect distant results of the treatment [16, 17] trastuzumab and carboplatin (TCH).

Application of systemic neoadjuvant therapy enables also verification of efficiency of the applied cytotoxic drugs in an individual patient by follow-up of changes in the size of the breast tumour and/or metastatic lymph nodes. At the Department of Breast Cancer & Reconstructive Surgery of the National Research Institute of Oncology, eligibility for neoadjuvant therapy includes also patients with diagnosed TNBC tumours assessed at up to cT1c cN0 stage of cancer.

The clinical trial results published within only the last 2–3 years led to introduction of patient selection for adjuvant therapy based on histopathological results of the operated material. Achieving pCR is an important factor which improves prognosis in patients with triple-negative and HER2-positive breast cancers [18] such as disease-free survival, event-free survival (EFS). Therefore, therapy should be focused on maximising the group of patients with pathological complete response (pCR). This can be achieved with intensive systemic treatment. In patients with diagnosis of TNBC the preferred chemotherapy regimen is the one with reduced intervals between cycles (*dose-dense chemotherapy*). In such cases, primary prophylaxis of neutropenic fever with granulocyte growth factor is necessary. Besides, in addition to paclitaxel administered in the second step of cytostatic treatment, inclusion of carboplatin may be considered (ACdd regimen – doxorubicin, cyclophosphamide every second week, later paclitaxel +/- carboplatin every week). Meanwhile in patients diagnosed with II and III stage of HER2-positive cancer, double blockade of HER2 receptor (pertuzumab with trastuzumab) is indicated



**Figure 1.** Perioperative treatment of patients with HER2-positive breast cancer – based on ESMO recommendations (2019) [9]

in combination with chemotherapy. Two treatment regimens are recommended: AC, then paclitaxel and PT (pertuzumab, trastuzumab) or TCHP (docetaxel, carboplatin, pertuzumab, trastuzumab). The current Polish drug prescription programme allows for pre-operative treatment with pertuzumab with trastuzumab in the case of III stage or breast tumours >2 cm with absent expression of ER and PgR or else with cytologically confirmed metastasis to an axillary lymph node [14].

The timing of application of HER2 double blockade is controversial. According to the ESMO recommendations, an annual trastuzumab with pertuzumab therapy should be considered in patients with higher risk of recurrence: initial cN+ stage or ER/PgR(-). Treatment with double anti-HER2 blockade combined with chemotherapy starts before or after the surgery. In Poland, only pre-operative treatment is covered by health insurance.

Further, in patients with HER2-LB breast cancer at high risk of recurrence (N+), prolonged complementary treatment can be considered, applying neratinib for a year after completion of trastuzumab therapy, provided that pertuzumab was not used.

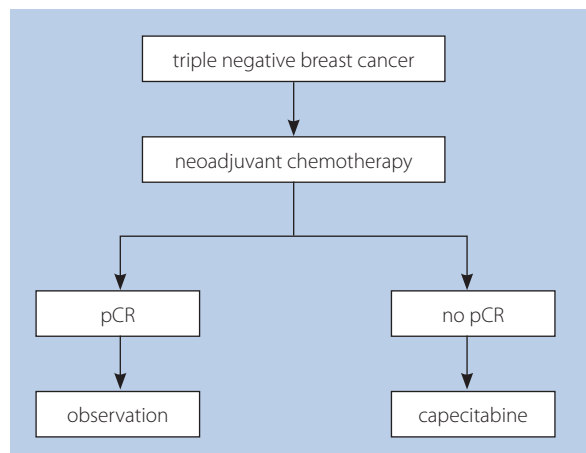
An important change in the procedure concerns the choice of therapy based on pathology result of the surgical material. KATHERINE study revealed that in patients who did not achieve pCR in the surgical material, complementary T-DM1 treatment (trastuzumab, emtansine) is more effective than follow-up trastuzumab therapy after the surgery [19]. In December 2019, T-DM1 drug was registered for this application.

Similarly, results of the CREATE-X study were significant in the case of patients of TNBC [20]. They showed that if residual

disease was found in the material after the surgery, additional complementary treatment with capecitabine reduced recurrence risk and improved the patients' survival.

The results of these two important clinical trials changed the management standard and have been included for the first time in ESMO and St. Gallen guidelines in 2019. The rules of management are summarised in figures 1 and 2.

Another strategy applies to patients with luminal cancers. If a breast-sparing surgery is initially possible, it should be performed, and then, based on the pathology results, a decision concerning systemic complimentary treatment should be taken. For other cases, neoadjuvant therapy is indicated. It often consists of chemotherapy. Meanwhile, in



**Figure 2.** Perioperative treatment of patients with triple-negative breast cancer – based on ESMO recommendations (2019) [9]

post-menopausal patients with locally advanced LA cancer, neoadjuvant hormone therapy can be considered. Letrozole is the most frequently selected substance for such cases. It should be borne in mind that in LA/LB cancers, after systemic neoadjuvant therapy, the rate of pathological complete response is low, but usually these responses are not a valuable factor in prognosis. In pre-menopausal patients, neoadjuvant hormone therapy is not applied.

Neoadjuvant chemotherapy is a standard in management for all patients diagnosed with inflammatory breast cancer. After a surgery (radical mastectomy with no simultaneous reconstruction) radiotherapy is mandatory. Application of hormone therapy and anti-HER2 treatment (including within neoadjuvant therapy) depends on the condition of respective receptors. Table I presents pre- and post-operative regimens

applied at the Department of Breast Cancer & Reconstructive Surgery of the National Research Institute of Oncology in Warsaw.

In recent years, important progress has been observed in treatment of patients with breast cancer. Registration of new drugs was among the factors of this progress. Most have been registered for treatment of patients with generalised breast cancer, however, application of these drugs in peri-operational treatment is currently explored, too. Results of the conducted studies will determine whether the drugs will be included as a standard in treatment of early breast cancer patients. Table II summarises the current indications for application of newly approved drugs.

It is very important to include patients in surgical treatment carefully and as quickly as possible, within 2–4 weeks

**Table I.** Pre-operative regimens applied at the Department of Breast Cancer & Reconstructive Surgery of the National Research Institute of Oncology

Treatment regimen	Treatment steps
<b>HER2-positive breast cancer</b>	
Neoadjuvant systemic treatment (cT1c-cT4, cN0-cN2)	
TCH x 6 regimen	<ul style="list-style-type: none"> <li>TCH regimen: <ul style="list-style-type: none"> <li>docetaxel 75 mg/m<sup>2</sup> + carboplatin AUC6 + trastuzumab <i>i.v.</i> 8 mg/kg of body weight – saturating dose, 6 mg/kg of body weight – maintenance doses; courses: 6 x every 3 weeks (+peg-GCSF)</li> </ul> </li> <li>surgery</li> <li>continuation of trastuzumab up to 18 courses in total</li> <li>radiation therapy, if indicated</li> </ul> <p><b>note:</b> preferred regimen in patients with no history of internal disease and without indications for double anti-HER2 blockade</p>
TCH-P x 6 regimen	<ul style="list-style-type: none"> <li>TCH-P6 regimen: <ul style="list-style-type: none"> <li>docetaxel 75 mg/m<sup>2</sup> + carboplatin AUC5-6 + trastuzumab <i>i.v.</i> 8 mg/kg of body weight – loading dose, 6 mg/kg of body weight – maintenance doses, pertuzumab <i>i.v.</i> 840 mg – loading dose, 420 mg – maintenance doses; courses: 6 x every 3 weeks (+peg-GCSF)</li> </ul> </li> <li>surgery</li> <li>continuation of trastuzumab up to 18 courses in total</li> <li>radiation therapy, if indicated</li> </ul> <p><b>note:</b> preferred regimen in patients with no history of internal disease and with indications for double anti-HER2 blockade (HER2 non-luminal cancers; T &gt; 2 cm + pN+)</p>
sequential regimen ACdd-D + T	<ul style="list-style-type: none"> <li>sequential regimen: <ul style="list-style-type: none"> <li>4 x AC (doxorubicin 60 mg/m<sup>2</sup> + cyclophosphamide 600 mg/m<sup>2</sup>) every 2 weeks (+peg-GCSF)</li> <li>4 x docetaxel 100 or 75 mg/m<sup>2</sup> every 3 weeks + trastuzumab <i>i.v.</i> 8 mg/kg of body weight – loading dose, 6 mg/kg of body weight – maintenance doses</li> </ul> </li> <li>surgery</li> <li>continuation of trastuzumab up to 18 courses in total</li> <li>radiation therapy, if indicated</li> </ul>
PCL x 12 + T regimen	<ul style="list-style-type: none"> <li>PCL 12 regimen: <ul style="list-style-type: none"> <li>paclitaxel 60–80 mg/m<sup>2</sup>, every 7 days x 12 + trastuzumab <i>i.v.</i> 8 mg/kg of body weight – loading dose, 6 mg/kg of body weight – maintenance doses</li> </ul> </li> <li>surgery</li> <li>continuation of trastuzumab up to 18 courses in total</li> <li>radiation therapy, if indicated</li> </ul> <p><b>note:</b> regimen administered in patients with significant history of internal diseases and elderly</p>
complementary systemic treatment (pT1c-pT4, pN0-pN2)	
TCH-6 regimen	<ul style="list-style-type: none"> <li>surgery</li> <li>TCH regimen: <ul style="list-style-type: none"> <li>docetaxel 75 mg/m<sup>2</sup> + carboplatin AUC6 + trastuzumab <i>i.v.</i> 8 mg/kg of body weight – loading dose, 6 mg/kg of body weight – maintenance doses; courses: 6 x every 3 weeks (+peg-GCSF)</li> </ul> </li> <li>continuation of trastuzumab up to 18 courses in total</li> <li>radiation therapy, if indicated</li> </ul>

Treatment regimen	Treatment steps
sequential regimen ddAC-D+T	<ul style="list-style-type: none"> <li>• surgery</li> <li>• sequential regimen: <ul style="list-style-type: none"> <li>– 4 x AC (doxorubicin 60 mg/m<sup>2</sup> + cyclophosphamide 600 mg/m<sup>2</sup>) every 2 weeks (+peg-GCSF); then 4 x docetaxel 100 or 75 mg/m<sup>2</sup> every 3 weeks + trastuzumab i.v. 8 mg/kg of body weight – loading dose, 6 mg/kg of body weight – maintenance doses</li> </ul> </li> <li>• continuation of trastuzumab up to 18 courses in total</li> <li>• radiation therapy, if indicated</li> </ul>
PCL x 12 + T regimen	<ul style="list-style-type: none"> <li>• surgery</li> <li>• PCL 12 regimen: <ul style="list-style-type: none"> <li>– paclitaxel 60–80 mg/m<sup>2</sup>, every 7 days x 12 + trastuzumab i.v. 8 mg/kg of body weight every 3 weeks – loading dose, 6 mg/kg of body weight – maintenance doses</li> </ul> </li> <li>• continuation of trastuzumab up to 18 courses in total</li> <li>• radiation therapy, if indicated</li> </ul> <p><b>note:</b> regimen administered to patients diagnosed with HER2-positive luminal cancers at pT1c, pN0 stage or with significant history of internal diseases and elderly</p>
complementary systemic treatment (pT1b, N0)	
PCL x 12 regimen	<ul style="list-style-type: none"> <li>• surgery</li> <li>• PCL regimen: <ul style="list-style-type: none"> <li>– paclitaxel 80 mg/m<sup>2</sup>, every 7 days x 12 cycles</li> </ul> </li> </ul> <p><b>note:</b> regimen for patients with HER2-positive, non-luminal cancers</p>
<b>TNBC breast cancer</b>	
neoadjuvant systemic treatment (cT1–cT4, cN0–cN2)	
ddAC PCL + Carbo regimen	<ul style="list-style-type: none"> <li>• sequential regimen: <ul style="list-style-type: none"> <li>– 4 x AC (doxorubicin 60 mg/m<sup>2</sup> + cyclophosphamide 600 mg/m<sup>2</sup>) every 2 weeks (+peg-GCSF)</li> <li>– followed by 12 x paclitaxel 80 mg/m<sup>2</sup> + carboplatin AUC 1.5 every week</li> </ul> </li> <li>• surgery</li> <li>• radiation therapy, if indicated</li> </ul>
TCarbo regimen	<ul style="list-style-type: none"> <li>• TC regimen: <ul style="list-style-type: none"> <li>– docetaxel 75 mg/m<sup>2</sup> + carboplatin AUC 5–6, 6 x every 3 weeks</li> </ul> </li> <li>• surgery</li> <li>• radiation therapy, if indicated</li> </ul> <p><b>note:</b> regimen applied in patients with counterindications against anthracyclines</p>
PCarbo regimen	<ul style="list-style-type: none"> <li>• PC regimen: <ul style="list-style-type: none"> <li>– paclitaxel 60–80 mg/m<sup>2</sup> + carboplatin AUC 1.5–2 every week x 18</li> </ul> </li> <li>• surgery</li> <li>• radiation therapy, if indicated</li> </ul> <p><b>note:</b> regimen applied in patients with counterindications against anthracyclines</p>
PCL x 12 regimen	<ul style="list-style-type: none"> <li>• PCL 12 regimen: <ul style="list-style-type: none"> <li>– (paclitaxel 60–80 mg/m<sup>2</sup> every 7 days) x 12</li> </ul> </li> <li>• surgery</li> <li>• radiation therapy in patients with indications</li> </ul> <p><b>note:</b> regimen administered in patients with significant history of internal diseases and elderly</p>
complementary systemic treatment (pT1b–pT4, pN0–pN2)	
AC-P regimen	<ul style="list-style-type: none"> <li>• surgery</li> <li>• sequential regimen: <ul style="list-style-type: none"> <li>– 4 x AC (doxorubicin 60 mg/m<sup>2</sup> + cyclophosphamide 600 mg/m<sup>2</sup>) every 3 weeks;</li> <li>– followed by 12 x paclitaxel 80 mg/m<sup>2</sup> every week</li> </ul> </li> <li>• radiation therapy, if indicated</li> </ul>
TC x 4 regimen	<ul style="list-style-type: none"> <li>• surgery</li> <li>• TC regimen: <ul style="list-style-type: none"> <li>– 4 x every 3 weeks: docetaxel 75 mg/m<sup>2</sup> + cyclophosphamide 600 mg/m<sup>2</sup></li> </ul> </li> <li>• radiation therapy, if indicated</li> </ul> <p><b>note:</b> regimen recommended in patients with counterindications against anthracyclines or with other history of internal diseases and with pT1c N0, G – 2</p>
PCL x 12 regimen	<ul style="list-style-type: none"> <li>• surgery</li> <li>• PCL 12 regimen: <ul style="list-style-type: none"> <li>– Paclitaxel 60–80 mg/m<sup>2</sup>, every 7 days x 12</li> </ul> </li> <li>• radiation therapy, if indicated</li> </ul> <p><b>note:</b> regimen applied in patients at pT1b, N0 stage or significant history of internal diseases or in elderly patients</p>

Treatment regimen	Treatment steps
complementary systemic treatment – post-neoadjuvant	
capecitabine regimen	<ul style="list-style-type: none"> <li>capecitabine x 8 every 3 weeks, at a dose of 2000–2500 mg/m<sup>2</sup>/day for 14 days, followed by 7 days of rest period</li> </ul> <p><b>note:</b> regimen for patients after a surgery with residual disease after prior neoadjuvant therapy and after completion of radiation therapy (if indicated)</p>
<b>luminal breast cancer</b>	
systemic neoadjuvant therapy (cT2 – cT4, cN0-N2 – patients with luminal B, HER2-negative cancer, G3 and/or Ki-67 > 50% and cT3-cT4, cN0-N2; HER2 negative luminal A and B cancers)	
AC-P regimen	<ul style="list-style-type: none"> <li>sequential regimen: <ul style="list-style-type: none"> <li>– 4 x AC (doxorubicin 60 mg/m<sup>2</sup> + cyclophosphamide 600 mg/m<sup>2</sup>) every 2 weeks (+ peg-GCSF); then 12 x paclitaxel 80 mg/m<sup>2</sup> every week</li> </ul> </li> <li>surgery</li> <li>radiation therapy, if indicated</li> </ul>
PCL regimen	<ul style="list-style-type: none"> <li>PCL regimen: <ul style="list-style-type: none"> <li>– paclitaxel 60–80 mg/m<sup>2</sup> x 12–18 every week</li> </ul> </li> <li>surgery</li> <li>radiation therapy, if indicated</li> </ul> <p><b>note:</b> regimen administered in patients with counterindications against anthracyclines, in patients with significant history of internal diseases and elderly</p>
complementary systemic treatment (luminal A and B cancers: stage IIIA-C, pT1c-pT3, pN0-pN1; luminal B cancer, G3, +/- indications from multigene tests or Magee > 31)	
AC-PCL regimen	<ul style="list-style-type: none"> <li>surgery</li> <li>sequential regimen: <ul style="list-style-type: none"> <li>– 4 x AC (doxorubicin 60 mg/m<sup>2</sup> + cyclophosphamide 600 mg/m<sup>2</sup>) every 3 weeks;</li> <li>– followed by 12 x paclitaxel 80 mg/m<sup>2</sup> every week</li> </ul> </li> <li>radiation therapy, if indicated</li> </ul>
AC-D regimen	<ul style="list-style-type: none"> <li>surgery</li> <li>sequential regimen: <ul style="list-style-type: none"> <li>– 4 x AC (doxorubicin 60 mg/m<sup>2</sup> + cyclophosphamide 600 mg/m<sup>2</sup>) every 3 weeks; followed by</li> <li>– 4 x docetaxel 75–100 mg/m<sup>2</sup></li> </ul> </li> <li>radiation therapy, if indicated</li> </ul>
TC x 4 regimen	<ul style="list-style-type: none"> <li>surgery</li> <li>TC regimen: <ul style="list-style-type: none"> <li>– 4 x every 3 weeks: docetaxel 75 mg/m<sup>2</sup> + cyclophosphamide 600 mg/m<sup>2</sup></li> </ul> </li> <li>radiation therapy, if indicated</li> </ul> <p><b>note:</b> regimen recommended in patients with counterindications against anthracyclines or with other history of internal diseases</p>
PCL x 12 regimen	<ul style="list-style-type: none"> <li>surgery</li> <li>PCL 12 regimen: <ul style="list-style-type: none"> <li>– paclitaxel 60–80 mg/m<sup>2</sup> every 7 days x 12</li> </ul> </li> <li>radiation therapy, if indicated</li> </ul> <p><b>note:</b> regimen administered in patients with significant history of internal diseases and elderly</p>

**Table II.** Newly approved drugs for treatment of breast cancer patients

Biological subtype of breast cancer	Drug group	Drug	Recorded indication	Pending clinical trials in new therapeutic areas
ER + HER2–	CDK4/6 inhibitor	palbociclib ribociclib abemaciclib	generalized breast cancer: 1 <sup>st</sup> or 2 <sup>nd</sup> line in combination with hormone therapy (aromatase inhibitor or fulvestrant)	adjuvant treatment in patients at high risk of recurrence in combination with hormone therapy (studies by Pallas, Natalee, MonarchE)
Ttriple negative breast cancer	immunotherapy	atezolizumab	generalized breast cancer PD-L1 + in the 1 <sup>st</sup> line of treatment in combination with chemotherapy	adding the drug as part of perioperative therapy
BRCA mutation carriers HER2–	PARP inhibitor	olaparib talazoparib	generalised breast cancer, in the 1 <sup>st</sup> or 2 <sup>nd</sup> line of treatment	adjuvant treatment in patients at high risk of recurrence (Olimpia study)
HER2+ ER+	tyrosine kinase inhibitor	neratinib	extended adjuvant treatment of breast cancer after one year of trastuzumab therapy in patients at high risk of recurrence (N+), if pertuzumab was not applied	planned as adjuvant treatment of patients previously receiving pertuzumab



after completing NAT. According to most centres, operations were performed on average 28 days after the last course of chemotherapy. NAT complications delayed surgery by approximately 8 days [21, 22].

### **Response assessment during systemic neoadjuvant therapy**

Response to NAT, both in the breast and regional lymph nodes, should be assessed by clinical examination and imaging after the systemic treatment, analogically to tests performed before the treatment [4]. Response to NAT should be assessed on each day of chemotherapy administration and the assessment may be based on clinical evaluation [24]. Imaging complete response evidenced by magnetic resonance mammography performed after NAT does not define pCR precisely enough either in the breast or in lymph nodes. This is why guidelines by different organisations are equivocal in determining the meaning of breast MRI (magnetic resonance imaging) in decisions on the scope and type of the operation [25, 26] inadequate staging with subsequent over or under-treatment, and surgical complications. Areas covered: This review article aims to discuss these concerns and to clarify the adequate steps and procedures needed to increase safety and alleviate the possible drawbacks of NAC. The author will discuss the adequate and meticulous technical procedures needed to stage and localize the breast tumor, detect any affected axillary lymph node, improve the accuracy and safety of doing sentinel lymph node biopsy (SLNB).

In a vast majority of institutions which perform sentinel lymph node biopsy (SLNB) in patients with primary cN1 cancer with conversion to ycN0 after the systemic neoadjuvant therapy, decisions are based on clinical examination, potentially applying ultrasound evaluation of axillary lymphatic drainage. Accuracy of the clinical examination was estimated at 60% (PPV and NPV also 60%), and in the case of ultrasound – at 69% (PPV – 65%, NPV – 74%) [27, 28] there is still some degree of reluctance in applying sentinel node biopsy (SNB).

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