Primary therapy in breast cancer: what have we learned from landmark trials?

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Primary anticancer therapy is currently accepted as a therapeutic option for patients with early-stage breast cancer. Its objectives are to increase the chance of achieving a conservative surgery and, similar to adjuvant chemotherapy, to reduce the risk of distant recurrence. The prognostic significance of obtaining a pathological complete response has been evaluated in several randomized clinical trials and meta-analyses. Growing evidence suggests that pathological complete response may act as a valid predictor of overall survival. Of note, a significant association between pathological complete response and outcome has especially been observed in patients with HER2-positive and triple-negative (hormonal receptors negative and HER2-negative) breast cancer. This review focuses on recent trials of neoadjuvant treatment with specific attention to HER2-negative disease.

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Learning objectives

Upon completion of this activity, participants should be able to:

- Distinguish tumor characteristics that are favorable for neoadjuvant therapy
- Compare outcomes among women with breast cancer treated with neoadjuvant therapy vs postoperative therapy
- Assess the primary chemotherapy regimen recommended in neoadjuvant therapy
- Evaluate the use and outcomes of endocrine treatment as neoadjuvant therapy

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In women, breast cancer (BC) is the most common cause of cancer and the most common cause of cancer-related death [1].

Primary chemotherapy (CT) was introduced in the early 1980s and was initially limited to patients with locally advanced BC [2]. Owing to encouraging results in patients with inoperable disease, subsequent pilot studies explored the role of CT delivered before surgery for patients with operable early BC [3]. Preoperative or neoadjuvant CT is currently accepted as a management option for patients with early-stage BC. Several landmark clinical trials on neoadjuvant therapy have been performed and are described in Table 1.

Objectives of primary therapy

The objectives of primary therapy are to improve surgical outcomes in operable BC patients who desire a conservative approach, to convert patients inoperable at diagnosis to operable candidates, and, like systemic therapies used in the adjuvant setting, to reduce the risk of distant recurrence with the final aim of obtaining a cure [4,5].

Furthermore, primary therapy with CT allows for an early evaluation of the *in vivo* responsiveness of the specific tumor to systemic therapy and permits the acquisition of tumor specimens prior to, and during, the preoperative treatment [6].

In defining the systemic treatment before surgery, several terms are used: 'preoperative', focusing on the treatment's temporal sequence relative to surgery; 'primary', emphasizing its first position in the temporal sequence of all therapeutic modalities; and 'neoadjuvant', identifying a presurgical treatment with the objectives of reducing the risk of distant recurrence and curing the patient. Accordingly, the term neoadjuvant should only be used to describe treatment of patients with a curable disease.

Adjuvant versus neoadjuvant treatment

There is no significant difference in overall survival (OS) or disease-free survival (DFS) for pre- versus post-operative delivery of systemic therapy [7–9]. The NSABP B-18 trial randomized 1523 patients with operable BC to receive either four preoperative cycles of doxorubicin and cyclophosphamide or the same CT, given postoperatively. The results of this trial, updated at 9 years of follow-up, did not show any significant difference in OS or DFS between the two treatment arms [10].

Patients eligible for primary treatment with CT

Ideal candidates for primary therapy are patients with locally advanced BC (stage III), but patients with early-stage disease can also be considered as candidates if a surgical breast-conservative approach is not technically feasible at presentation due to small breast size or if the cosmetic outcome following surgery would be suboptimal due to tumor location.

Even with a small tumor, patients with a subtype associated with a high likelihood of response to CT could benefit from a preoperative approach. Indeed, primary therapy is considered appropriate for patients likely to have a good locoregional response, regardless of the tumor size at presentation.

The current classification of BC subtypes (Table 2) takes into account the tumor heterogeneity and, accordingly, the rate of response to primary therapy with CT varies among the different BC subtypes [11].

Notably, patients with HER2-positive or triple-negative BC exhibit a higher rate of response to primary therapy with CT [12] compared with patients with HER2-negative, estrogen receptor (ER)-positive BC [13–15].

Table 1. Neoadjuvant therapy in HER2-negative breast cancer: results from landmark trials.

Trial	n	Treatment	Primary end point	Results	Ref.
Chemotherapy					
NSABP B-18	1523	AC × 4 preoperative vs AC × 4 postoperative	DFS	9 years follow-up, postoperative vs preoperative group: OS: 70 vs 69% (p = 0.80) DFS: 53 vs 55% (p = 0.50)	[10]
NSABP B-27	2411	Preoperative AC × 4 vs Preoperative AC × 4 --> T × 4 vs Preoperative AC × 4 --> Postoperative T × 4	DFS	8 years follow-up: Taxane-contaning regimen vs nontaxane-contaning regimen associated with a higher CR (91 vs 86%), and higher pCR (26 vs 13%) than nontaxane-contaning regimen No difference in OS or DFS	[22]
GeparDuo	913	ATq14 × 4 vs AC-T q21 × 4	pCR	Greater pCR with AC-T vs AT (14.3 vs 7.0%, p < 0.001) Greater BCS rate with AC-T vs AT (63.4 vs 58.1%; p < 0.05)	[50]
GeparTrio	2090	TAC × 2 --> US, if nonresponder --> TAC × 4 vs NX × 4	US response	TAC vs NX: Sonographic response rate: 50.5 vs 51.2%; p < 0.08 BCS: 57.3 vs 59.8% pCR: 5.3 vs 6.0%	[28]
GeparQuattro	1509	EC × 4, then randomization to: T vs TX vs T-->X	pCR	T vs TX vs T --> X pCR: 22.3 vs 19.5 vs 22.3% BCS: 70.1 vs 68.4 vs 65.3%	[23]
NSABP B-40	1206	T --> AC ± bevacizumab vs TX --> AC ± bevacizumab vs TG --> AC ± bevacizumab	pCR	pCR: 32.7% (T) vs 29.7 (TX) vs 31.8% (TG); p < 0.69 pCR with vs without bevacizumab: 34.5 vs 28.2%; p < 0.02	[24]
PREPARE	733	EC --> T ± DA (arm A) vs E (dd) C (dd) --> T (dd) --> CMF ± DA (arm B)	pCR	pCR, arm B vs A: 18.7 vs 13.2% Mean Hb higher with DA (13.6 vs 12.6 g/dl)	[51]
ABCSG-14	292	ET × 3 vs ET × 6 + GCSF	pCR	pCR higher with six vs three cycles: 18.6 vs 7.7%; p < 0.0045 BCS higher with six vs three cycles: 75.9 vs 66.9%; p = 0.1	[52]
Hormonal treatment in postmenopausal women					
IMPACT	330	ANA for 3 months vs TAM for 3 months vs ANA + TAM for 3 months	OR	Clinical OR for ANA vs TAM vs combination: 37 vs 36 vs 39%	[35]
PROACT	451	ANA for 3 months vs TAM for 3 months	OR	ANA vs TAM: OR: 39.4 vs 35.4% BCS: 43.0 vs 30.8%; p < 0.04	[36]
PO24	337	TAM vs LET	OR	LET vs TAM: OR: 55 vs 36% BCS: 45 vs 43% (p < 0.022)	[34]
ACOSOG Z1013	377	EXE vs LET vs ANA	CR	CR: LET (74.8%), ANA (69.1%), EXE (62.9%)	[37]
Baselga *et al.* (2009)	270	LET + EVE vs LET + placebo	CR	CR 68.1% (LET + EVE) vs 59.1% (LET + placebo); p < 0.062	[41]

-->: Followed by; AC: Doxorubicin plus cyclophosphamide; ANA: Anastrozole; AT: Doxorubicin plus docetaxel; BCS: Breast-conservative surgery; CMF: Cyclophosphamide plus methotrexate plus fluorouracil; CR: Clinical response; DA: Darbopoietin alfa; dd: Dose-dense; DFS: Disease-free survival; EC: Epirubicine plus cyclophosphamide; ET: Epirubicine plus docetaxel; EVE: Everolimus; EXE: Exemestane; GCSF: Granulocyte-colony stimulating factor; Hb: Hemoglobin; LET: Letrozole; NX: Vinorelbine plus capecitabine; OR: Overall response; OS: Overall survival; pCR: Pathological complete response; T: Docetaxel; TAC: Docetaxel plus doxorubicin plus cyclophosphamide; TAM: Tamoxifen; TG: Docetaxel plus gemcitabine; TX: Docetaxel plus capecitabine; US: Ultrasound; X: Capecitabine.

Table 2. Immunophenotypical subtypes of breast cancer.

Subtype	Immunophenotypical characteristics
Luminal A	ER^+, PgR^+, HER2-negative and low Ki67
Luminal B:	
HER2-negative	ER^+, PgR^+, HER2-negative and high Ki67
HER2-positive	ER^+, PgR^+, HER2-positive and any Ki67
HER2-positive	ER^-, PgR^- and HER2-positive
Triple-negative	ER^-, PgR^- and HER2-negative

ER: Estrogen receptor; PgR: Progesterone receptor.

Clinical studies have demonstrated that in patients with HER2-positive disease who receive trastuzumab as part of their neoadjuvant therapy, a pathological complete response (pCR) is associated with higher rates of DFS and OS [12,16]. The pCR rate among triple-negative BC patients ranges from 27–45%, while the pCR rate for HER2-negative, hormone receptor-positive patients is generally significantly lower (~10%) [17]. As pCR is associated with an advantage in DFS and OS in triple-negative BC, it is reasonable that residual disease at surgery confers a higher risk of early disease recurrence [18,19].

It is important to emphasize that several trials conducted prior to widespread HER2 testing and prior to the use of adjuvant trastuzumab do not stratify the disease according to immunophenotype. Accordingly, response rates and outcome results reported by trials conducted before 2005 are not easily comparable with those of more recent trials.

Pretreatment staging

Although baseline staging is not routine for all new diagnoses, it is often performed in specific clinical circumstances (i.e., large tumor size, clinical evidence of nodal involvement, HER2-positive disease, triple-negative disease and participation in clinical trials). In addition to routine imaging examinations, if the neoadjuvant approach is selected, prior to the start of neoadjuvant CT, radiopaque clips should be placed in the tumor with core needle devices. The clip aids in planning locoregional treatment and subsequent pathological assessment of the surgical specimen.

Tumor size should be documented prior to treatment. Breast MRI is often performed to evaluate disease extent, including assessment of the presence of multicentric disease or invasion of the underlying chest wall [20,21]. Pretreatment assessment of axillary nodes is crucial: if axillary adenopathy is palpable, an ultrasound-guided fine needle aspiration and, eventually, a core needle biopsy should be performed in order to establish the presence or absence of pathologically involved axillary nodes. In the case of a clinically negative axillary examination, a sentinel lymph node biopsy is needed [4]. If the sentinel lymph node biopsy is negative, no further evaluation is necessary; however, if the sentinel lymph node biopsy is positive, the need for further treatment will depend on the outcome following neoadjuvant CT.

Therapeutic options

The possible options for a neoadjuvant approach include CT, endocrine treatment (ET), or biological therapy in selected patients. Patients with triple-negative or HER2-positive disease who desire breast-conservation surgery (BCS), but are not candidates for BCS, or patients with large tumors, could benefit from neoadjuvant CT with a good chance of achieving a pCR. Patients with HER2-positive BC should be offered trastuzumab as part of their neoadjuvant regimen. Women with hormonal receptor-positive/HER2-negative inoperable disease should be offered neoadjuvant CT over ET. Although the chance of achieving a pCR is lower in this group of patients compared with the other groups, tumor shrinkage could permit a conservative approach. Neoadjuvant therapy with ET should be considered in women with hormonal receptor-positive disease, with significant comorbidities, old age, or those refusing chemotherapeutic treatment.

Chemotherapy

A recent Cochrane review regarding preoperative CT for women with operable BC performed a meta-analysis involving 5500 patients participating in 14 trials of neoadjuvant CT. Compared to adjuvant CT, neoadjuvant CT demonstrated similar OS and DFS (hazard ratio [HR]: 0.98; 95% CI: 0.87–1.09 and HR: 0.97; 95% CI: 0.89–1.07, respectively), reduced rates of radical mastectomy (HR: 0.71; 95% CI: 0.67–0.75) and increased risk of locoregional relapse (HR: 1.21; 95% CI: 1.02–1.43). Patients with pCR had significantly improved OS (HR: 0.48; 95% CI: 0.33–0.69) and DFS (HR: 0.48; 95% CI: 0.37–0.63) compared with patients with residual disease [7].

The specific CT regimen used in the neoadjuvant setting is based on the tumor biological subtype. The addition of a taxane to a regimen including an anthracycline results in increased response rates compared with an anthracycline alone. The NSABP B-27 trial demonstrated that incorporating a taxane with

an anthracycline-based regimen compared with a nontaxane-contaning regimen was associated with a higher clinical response rate (91 vs 86%), a higher pCR rate (26 vs 13%) and no difference in OS or DFS at 8 years. There are few clinical trials comparing anthracycline to nonanthracycline CT regimens. Nonetheless, nonanthracycline regimens could be considered if contraindications to anthracyclines are present [22].

Incorporation of additional chemotherapeutic agents to an anthracycline–taxane regimen in order to improve the rate of pCR is the subject of ongoing trials. Currently, there is no evidence that such additions improve the outcomes of neoadjuvant therapy. For example, in the GeparQuattro trial, the addition of capecitabine to an anthracycline–taxane-based regimen did not improve response rates [23]. Similarly, in the NSABP B-40 trial, the addition of gemcitabine and capecitabine had no impact on pCR or clinical response rate [24]. Incorporation of platinum agents into CT regimens for triple-negative BC has a strong biological rationale, but large randomized trials are required to confirm the efficacy of such a regimen [20,25–27].

Individualizing therapy based on the patient's tumor response is an approach investigated in the GeparTrio trial [28]. Patients with no initial sonographic response to two courses of TAC (docetaxel, doxorubicin and cyclophosphamide), were randomized to receive an additional four courses of TAC or four courses of NX (vinorelbine–capecitabine). Among patients without initial response to treatment with two TAC courses, no difference was observed by switching to four NX courses or by continuing with an additional four courses of TAC cycles. Moreover, switching to four NX courses had a better toxicity profile than continuing TAC. The rates of pCR in both groups were low (5.3% in the TAC arm vs 6% in the NX arm) [28–30]. Other studies have tested the approach of response-adjusted sequential therapy, however, this remains to be investigated [31].

Endocrine therapy

There are little data regarding the efficacy of primary ET compared with CT, and CT remains the preferred approach. Primary ET should be reserved for postmenopausal women who refuse CT or are not fit to receive these treatments. If a premenopausal woman is not suitable for primary CT treatment, definitive surgical treatment should be performed. Some trials have attempted to define the role of combining gonadotropin-releasing hormone analog and aromatase inhibitors (AIs), but the results are not conclusive [32,33].

In postmenopausal women, AIs are preferred over tamoxifen in the preoperative setting. Ellis and Ma compared letrozole versus tamoxifen in the neoadjuvant setting in patients with hormonal receptor-positive tumors: a higher overall response rate was observed with letrozole compared with tamoxifen (55 vs 36%; p = 0.001). Of note, the difference in terms of overall response rate between the two treatment arms was more evident in the HER1-/HER2-positive subgroup (88 vs 21%; p = 0.0004). In addition, the rate of BCS was significantly higher among patients in the letrozole arm (45 vs 35%; p = 0.022). Letrozole was also significantly more effective than tamoxifen in reducing tumor proliferation (p = 0.0009) [34]. The IMPACT trial provided supportive data that third-generation AIs are significantly more effective than tamoxifen in downstaging large tumors and reducing the need for mastectomy in postmenopausal women [35]. The PROACT trial confirmed that anastrozole versus tamoxifen yields greater overall response rate (35.4 vs 12.2%) [36]. The ACOSOG Z1031 trial demonstrated that there is no difference in outcomes for patients treated with letrozole, anastrozole or exemestane [37].

Concurrent administration of AIs and CT in the neoadjuvant setting for ER-positive BC also offers new perspectives. Higher response rates were observed in trials that compared CT plus ET versus ET only with a good tolerability profile [38].

The standard treatment duration for primary ET is at least 3–4 months. If the tumor is amenable to surgery after 3–4 months, definitive surgery should be provided. However, if the tumor is not responding to ET, extending treatment to 6 months or longer with clinical monitoring of response may permit a higher percentage of patients to undergo BCS. If at any time there is evidence of progression or nonresponse, surgery is recommended. Krainick-Strobel *et al.* conducted a trial in which the duration of ET was varied on the basis of individualized clinical response in order to identify the optimal duration of treatment. Half of the patients became BCS-eligible within 4 months of preoperative letrozole treatment, and prolonged treatment for up to 8 months resulted in further tumor volume reduction in some patients [39].

Biological agents

In recent years, the addition of bevacizumab to a standard CT regimen has been evaluated

in several clinical trials. The NSABP B-40 trial demonstrated that the addition of bevacizumab to docetaxel significantly increased the rate of pCR (28.2% without bevacizumab vs 34.5% with bevacizumab; p = 0.02). The benefit of bevacizumab was higher in the hormonal receptor-positive group (23.2% pCR with bevacizumab vs 15.1% without bevacizumab), with less effect in the hormonal receptor-negative group (47.1% pCR without bevacizumab vs 51.5% with bevacizumab; p = 0.34). The use of bevacizumab increased the side effects of CT [24]. von Minckwitz *et al.* conducted a trial in which 1948 patients were randomized to receive neoadjuvant epirubicin and cyclophosphamide followed by docetaxel, with or without concomitant bevacizumab. The rate of pCR was 14.9% with epirubicin and cyclophosphamide followed by docetaxel versus 18.4% with the same regimen plus bevacizumab (odds ratio with addition of bevacizumab: 1.29; 95% CI: 1.02–1.65; p = 0.04). In this study, in contrast to the previous one, the corresponding rates of pCR were 27.9 and 39.3% among 663 patients with triple-negative tumors (p = 0.003), and 7.8 and 7.7% among 1262 patients with hormonal receptor-positive tumors (p = 1.00). The addition of bevacizumab was associated with significantly higher grade side effects [40]. It is unclear whether the benefit of adding bevacizumab in the neoadjuvant setting is only observed in a particular subgroup of BC and, if so, what that subgroup is.

An interesting approach recently proposed is the combination of ET and signal transduction inhibitors. For example, Baselga *et al.* proposed a trial in which women with operable ER-positive BC were randomly assigned to receive 4 months of neoadjuvant treatment with letrozole (2.5 mg/day) and either everolimus (10 mg/day) or placebo. The primary outcome was clinical response by palpation. Everolimus significantly increased the efficacy of letrozole in patients with ER-positive BC. Further studies are needed in order to establish the efficacy of everolimus in the neoadjuvant setting [41].

End points & pCR definitions

The definition of pCR in patients treated with neoadjuvant CT is of significant importance as unequivocal pCR is crucial for treatment and prognosis evaluation. Several different definitions of pCR have been utilized. Some studies suggest that residual intraductal carcinoma may influence prognosis; however, recent data support that the absence of invasive disease in the breast and axilla (ypT0/is ypN0) is the best definition of pCR in terms of predicting outcome [12,42,43]. The NSABP B-18 and B-27 trials demonstrated that lack of pCR increases the risk of locoregional recurrence, similar to age <50 years (HR: 0.78; 95% CI: 0.63–0.98), clinical tumor size >5 cm at presentation (HR: 1.51; 95% CI: 1.19–1.91) and nodal involvement at presentation (HR: 1.61; 95% CI: 1.28–2.02) [9].

Patients with ER-positive BC rarely achieve a pCR with neoadjuvant ET alone [44]. Therefore, other end points of efficacy in clinical trials of neoadjuvant ET are also considered, including the clinical response rate or rate of BCS. The preoperative endocrine prognostic index was proposed as a tool for treatment individualization to help clinicians make decisions regarding additional treatment options for patients who have received neoadjuvant ET for ER-positive BC. The preoperative endocrine prognostic index score takes into account tumor and nodal stage, level of ER expression, and the proliferative rate (percentage of cells expressing Ki67) following neoadjuvant ET, and predicts the risk of relapse and BC death on the basis of risk classes (0, 1–3 and ≥4). Although the preoperative endocrine prognostic index score appears to be promising as a prognostic test for patients who received neoadjuvant ET, it requires validation before it can be used in routine clinical practice [45].

In clinical practice, patients who previously received neoadjuvant therapy do not usually receive other adjuvant CT. Additional CT following surgery has not been evaluated in clinical trials, but whether further CT improves OS to justify its toxicity is not known [46,47]. Postoperative CT is offered in specific cases, such as patients with residual triple-negative BC who have not previously received both an anthracycline or taxane, or patients treated with neoadjuvant ET, provided they are eligible for CT.

The prognosis of patients with BC who undergo neoadjuvant CT is largely based upon the pathological response found at the time of surgery, although the presenting clinical stage and tumor characteristics also influence prognosis [12,48].

Prognostic role of pCR

The prognostic significance of a pCR as a predictor of survival has been evaluated in several meta-analyses. In the largest meta-analysis, performed by the Collaborative Trials in Neoadjuvant Breast Cancer, 12 randomized trials comprised approximately 13,000 patients. As presented at the 2012 San Antonio Breast Cancer Symposium (TX, USA), the major results were that patients who achieved a pCR demonstrated

significant improvement in event-free survival (HR: 0.48; p < 0.001) and OS (HR: 0.36; p < 0.001) compared with patients who did not achieve pCR. The pCR and event-free survival rates varied according to the BC subtype: hormonal receptor-positive, HER2-negative, grade 1–2: 7% (HR for event-free survival: 0.63; p = 0.07); hormonal receptor-positive, HER2-negative, grade 3: 16% (HR: 0.27; p < 0.001); hormonal receptor-positive, HER2-positive (treated with a trastuzumab-containing regimen): 30% (HR: 0.58; p = 0.001); and hormonal receptor-negative, HER2-negative (triple-negative): 34% (HR: 0.24; p < 0.001); and hormonal receptor-negative, HER2-positive (treated with a trastuzumab-containing regimen): 50% (HR: 0.25; p < 0.001). This meta-analysis confirms the relationship between pCR and survival outcomes for patients treated with neoadjuvant CT, particularly for women with HER2-positive, triple-negative, or hormonal receptor-positive grade 3 tumors. In addition, it supports the use of pathological clearance of invasive disease in both the breast and the axillary nodes (ypT0/is ypN0) in defining pCR. However, it could not determine how large of a benefit in the pCR rate would be required to show a significant impact on long-term outcomes [43].

The pCR rate in patients with hormonal receptor-positive tumors is of less prognostic significance because the hormonal receptor-positive subtype is characterized by a good prognosis at onset due to intrinsic biological features. A single predictive biomarker cannot fit all tumor types.

Conclusion

Advancing clinical trials of therapeutic agents from the adjuvant to the neoadjuvant setting could provide important information about the drug under study and aid in the identification of early surrogates, such as pCR, which correlate with long-term outcomes. pCR may be a valid surrogate for some BC subsets, particularly HER2-positive, triple-negative and highly proliferative hormonal receptor-positive disease. Further validation of pCR as a surrogate end point is needed [49].

The neoadjuvant approach is a reasonable and, in some cases, the preferred approach for the management of triple-negative and HER2-positive BC. Neoadjuvant treatment could also be advantageous in appropriately selected subgroups of patients with ER-positive BC. New perspectives with biological agents and combination therapy offer interesting and partially unknown approaches for the treatment of ER-positive BC.

Future perspective

Neoadjuvant CT is a therapeutic option for some patients with early BC. It increases the feasibility of BCS in patients who are not

Executive summary

Definition & objectives of neoadjuvant therapy in early-stage breast cancer

- The terms 'preoperative', 'primary' and 'neoadjuvant' therapy are sometimes used interchangeably to describe anticancer treatment delivered before surgery. However, the term 'neoadjuvant' is more stringent: it defines therapy that pursues the goal of achieving a cure. In other words, neoadjuvant therapy has the same aims as adjuvant therapy, with the main difference being that it is administered before surgery.
- Neoadjuvant chemotherapy (CT) is currently accepted as a therapeutic option for patients with early-stage breast cancer (BC).
- The objectives of neoadjuvant therapy are:
  - To increase the chance of achieving a conservative surgery;
  - To reduce the risk of distant recurrence (main goal: to obtain a cure);
  - To allow early *in vivo* evaluation of new anticancer agents.

Scientific evidence regarding the role of neoadjuvant therapy in patients with early-stage BC

- There is no significant difference in overall survival or disease-free survival when pre- and post-operative systemic therapy are compared. This evidence comes from randomized clinical trials and meta-analyses.
- In clinical trials, the most common end point used to evaluate the benefit of neoadjuvant therapy is pathological complete response (pCR). The best definition of pCR is the absence of cancer cells in the breast and axillary nodes.
- Growing evidence suggests that pCR may act as a valid predictor of overall survival. A significant association between pCR and outcome has been observed, particularly in patients with HER2-positive and triple-negative BC.
- The pCR rate among triple-negative BC patients ranges from 27 to 45%, while the pCR rate for HER2-negative, hormone receptor-positive patients is generally lower (~10%).

Neoadjuvant therapy in clinical practice

- The preferred CT regimens in the neoadjuvant setting are often similar to the standard regimens used in the adjuvant setting.
- In patients with HER2-positive BC, a combination of CT with anti-HER2 agents could be a valid therapeutic option.
- Neoadjuvant endocrine treatment is not common. It is usually reserved for elderly patients that have contraindications to CT. If used, aromatase inhibitors have a better chance of response than tamoxifen.

suitable candidates for BCS at presentation. In recent years, neoadjuvant treatment has become a widely accepted model for testing the value of new anticancer agents. Accordingly, pCR has been proposed in clinical trials as a valid end point that could predict long-term outcomes, such as OS. This approach has been confirmed in studies designed for specific subgroups of patients with BC (i.e., patients with HER2-positive or triple-negative disease). It is tempting to hypothesize that, in the future, a better selection of target patient population would correspond to better therapeutic results. This could also be possible for some subgroups of patients with hormonal receptor-positive BC. If the value of neoadjuvant treatment as a model for clinical development of anticancer drugs is confirmed, it would be possible to test the therapeutic benefit of new agents in a shorter and more effective way.

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1. You are seeing a 61-year-old woman recently diagnosed with breast cancer, and you are considering whether to recommend neoadjuvant chemotherapy for her. Which of the following variables is associated with a better response to neoadjuvant chemotherapy?

- ☐ **A** Stage III or IV cancer
- ☐ **B** Estrogen receptor-positive cancer
- ☐ **C** Progesterone receptor-positive cancer
- ☐ **D** HER2 receptor-positive cancer

2. Which of the following outcomes is expected in selecting neoadjuvant chemotherapy instead of postoperative chemotherapy for this patient?

- ☐ **A** Improved overall survival (OS)
- ☐ **B** Improved progression-free survival (PFS)
- ☐ **C** A higher rate of locoregional relapse
- ☐ **D** A higher rate of radical mastectomy

3. What is the preferred neoadjuvant chemotherapy for women with breast cancer?	
☐ **A**	An anthracycline alone
☐ **B**	An anthracycline and a taxane alone
☐ **C**	An anthracycline, a taxane, and a platinum agent
☐ **D**	An anthracycline, a taxane, and gemcitabine

4. What should you consider regarding endocrine treatment as neoadjuvant therapy for this patient?	
☐ **A**	Primary endocrine therapy should be used for women who refuse or cannot tolerate chemotherapy
☐ **B**	Either aromatase inhibitors or tamoxifen may be used as endocrine therapy
☐ **C**	The standard duration of endocrine treatment is 12 months
☐ **D**	Most women with estrogen receptor-positive tumors achieve a pathological complete response (pCR) on endocrine therapy alone