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# Breast Cancer Neoadjuvant Therapy

- Neoadjuvant therapy refers to the systemic treatment of breast cancer prior to definitive surgical therapy (ie, preoperative therapy).

- The purpose of administering systemic therapy prior to surgery is to downstage the tumor and provide information regarding treatment response.

- Downstaging the tumor may allow less extensive surgery on the breast and/or axilla, improving cosmetic outcomes, and reducing postoperative complications such as lymphedema.

- Neoadjuvant therapy also permits evaluation of the effectiveness of systemic therapy, which can be used to guide adjuvant treatment recommendations.
- The presence and extent or absence of residual invasive cancer after neoadjuvant therapy is a strong prognostic factor for risk of recurrence, especially in triple-negative breast cancer (TNBC) and human epidermal growth factor receptor 2-positive breast cancer.

- In addition to these clinical objectives, neoadjuvant therapy gives researchers the opportunity to obtain imaging studies, tumor specimens, and blood samples prior to, during, and, in patients with sufficient residual disease at surgery, after the preoperative treatment, which may assist in the identification of tumor- or patient-specific biomarkers of response or resistance.

- Although it was hypothesized that overall survival (OS) might be improved with neoadjuvant therapy, as it provides earlier initiation of systemic therapy in patients at higher risk of distant recurrence, randomized trials have demonstrated equivalent mortality for pre- or postoperative delivery of similar systemic therapy.

- An individual patient data meta-analysis was conducted by the Early Breast Cancer Trialists' Collaborative Group based upon data from 4756 women in 10 trials that were initiated between 1983 and 2002.
- There were no significant differences between neoadjuvant chemotherapy (NACT) versus adjuvant chemotherapy in the risk of distant recurrence or breast cancer mortality.
- The use of NACT was associated with an increased frequency of breast-conserving therapy. It was also associated with an increased risk of local recurrence, which has been attributed to the increased use of breast-conserving surgery.

- Since these early trials, there have been many advances in selecting patients for neoadjuvant therapy, as well as demonstration of the benefit of selecting subsequent treatment based on response, however, it is unlikely that further randomized trials comparing the impact of neoadjuvant versus adjuvant therapy on OS would be feasible.

# PATIENT SELECTION

## Locally advanced breast cancer

- Patients with locally advanced breast cancer (those with stage III disease, T3, or T4 lesions), no matter the subtype, are ideal candidates for neoadjuvant therapy because their cancers are often not amenable to upfront resection, much less breast conservation, and because their risk of distant recurrence warrants systemic treatment.

- Many patients with tumors larger than 5 cm (T3), even if potentially operable, are considered to have locally advanced disease and have been included in neoadjuvant therapy clinical trials.

## Select cases of early-stage breast cancer

- Patients with early-stage breast cancer (stage I or II) are appropriate candidates for neoadjuvant therapy if breast-conserving surgery is not possible due to a high tumor-to-breast ratio, or if their anticipated cosmetic outcome would be suboptimal due to tumor location.

- Additionally, patients with even smaller (T1c) triple-negative breast cancers or human epidermal growth factor receptor 2 (HER2)-positive cancers may be offered neoadjuvant therapy, particularly if they might benefit from additional treatments in the adjuvant setting if residual disease is identified.

- The CREATE-X and KATHERINE trials establish that, in patients with TNBC or HER2-positive disease, the presence or absence of residual disease after neoadjuvant therapy alters treatment recommendations in the adjuvant setting. Thus, neoadjuvant therapy is the treatment of choice in all but small, node-negative, TNBC, or HER2-positive tumors.

- The role of neoadjuvant therapy in patients with early-stage hormone receptor-positive, HER2-negative breast cancers is less clear.
- Whether such patients should be offered neoadjuvant chemotherapy or neoadjuvant endocrine therapy depends on many factors, including patient age, comorbidities, and clinical stage.

- Tumor characteristics including grade and intensity of hormone-receptor expression may help differentiate between patients more or less likely to respond to chemotherapy versus endocrine therapy. Data suggest that tumor proliferation indices such as Ki-67 or gene expression assays (such as Oncotype Dx, MammaPrint, or EndoPredict) may help oncologists to select between these treatment options.

# Limited clinically node-positive disease

- Another possible indication for neoadjuvant therapy in patients with early-stage breast cancer, regardless of the size of the primary tumor, is to downstage the axillary nodes in patients with limited clinically node-positive disease (cN1).

# Limited clinically node-positive disease

- Neoadjuvant therapy, particularly chemotherapy, often converts cN1 patients to pN0, especially in patients with more aggressive breast cancer subtypes, and results of contemporary studies suggest that many of such patients can be effectively managed with sentinel lymph node biopsy with much lower rates of lymphedema and other complications.

## Patients with temporary contraindications for surgery

- Neoadjuvant systemic therapy is a treatment option for patients who have medical contraindications to undergoing surgery at diagnosis but in whom surgery is anticipated at a later date, such as women with breast cancer diagnosed during pregnancy or patients requiring short-term anticoagulation such as those with recent pulmonary embolism, deep-vein thrombosis, or placement of drug-eluding coronary stents.

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# Invasive Breast Cancer

## Candidates for Preoperative Systemic Therapy

- Patients with inoperable breast cancer:
  - IBC
  - Bulky or matted cN2 axillary nodes
  - cN3 nodal disease
  - cT4 tumors
- In patients with operable breast cancer, preoperative systemic therapy is preferred for:
  - ◊ HER2-positive disease and TNBC, if cT ≥2 or cN ≥1
  - ◊ Large primary tumor relative to breast size in a patient who desires breast conservation
  - ◊ cN+ disease likely to become cN0 with preoperative systemic therapy
- Patients in whom definitive surgery may be delayed.

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# NCCN Guidelines Version 8.2021
# Invasive Breast Cancer

## Non-candidates for Preoperative Systemic Therapy

- Patients with extensive in situ disease when extent of invasive carcinoma is not well-defined
- Patients with a poorly delineated extent of tumor
- Patients whose tumors are not palpable or clinically assessable

# PRETREATMENT EVALUATION

- Pretreatment evaluation is aimed at confirming pathology and documenting the extent of the disease.

## Tumor evaluation

- histopathologic confirmation and evaluation of receptor status (estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2)

- A radiopaque clip should be placed in the tumor (or several clips in the setting of multifocal or multicentric disease), either at the time of the diagnostic biopsy or at some other time prior to initiation of neoadjuvant therapy. The clip allows for documentation of the site of disease to guide surgical resection after neoadjuvant therapy as well as directing pathologic assessment of the surgical specimen, especially in cases in which neoadjuvant therapy significantly shrinks or eradicates the tumor.

## Imaging

- In many cases, ultrasound (US) of the breast is sufficient to document tumor size.
- Breast magnetic resonance imaging (MRI) may be helpful to evaluate disease extent, including assessing for the presence of multifocal or multicentric disease, especially in patients with dense breast tissue on mammography, deep axillary or internal mammary lymph nodes, or invasion of the underlying chest wall.

- While the presence of overt metastatic disease would alter the patient's treatment plan and goals, the likelihood of detecting it, in the absence of suspicious symptoms or findings, with routine imaging studies such as computed tomography (CT), bone, and/or positron emission tomography (PET)/CT scans, is low.

- To avoid the unnecessary expense of these tests and the complications of dealing with false-positive findings, we typically omit them in patients with clinical stage I or II disease but order them in patients with clinical stage III disease or inflammatory breast cancers, as well as in patients with symptoms or abnormal findings (including laboratory values) that might be an indication of otherwise occult metastatic disease.

## Node evaluation

- To assess nodal status, we perform a physical exam of the axilla in all patients with a new diagnosis of breast cancer.
- For those in whom lymph nodes are palpated, we perform US-guided FNA or CNB to confirm pathologic involvement. The biopsy is done to rule out a false-positive clinical finding due to reactive lymph nodes or other benign histology.

- For those in whom no abnormal lymph nodes are palpated, we routinely obtain an axillary US.
  - If no abnormal lymph nodes are identified, we proceed with neoadjuvant treatment.
  - If there are any suspicious lymph nodes on US (based on size or the presence of a thickened cortex), we perform FNA or CNB of the suspicious lymph node. If positive, this is categorized as cN1 disease.

- In a patient with a positive FNA or CNB, we favor placement of a radiopaque clip or other marker (eg, ink) in the biopsy-proven involved lymph node to enable identification after neoadjuvant therapy.

- In patients with node-positive disease at presentation, removal of the marked node at the time of post-neoadjuvant therapy sentinel lymph node biopsy (SLNB) lowers the false-negative rate.

- While some specialists favor pretreatment SLNB for those without evidence of lymph node involvement on exam or imaging, we typically defer this until after neoadjuvant treatment. This avoids an additional surgical procedure and preserves the prognostic information obtained from the status of the sentinel nodes after neoadjuvant therapy.

- Resection of a positive SLN prior to neoadjuvant therapy means that pathologic assessment of response after therapy is not complete, as axillary response cannot be known given the SLN was removed. Hence, SLN surgery prior to systemic therapy is discouraged.

# NEOADJUVANT TREATMENT OPTIONS

- Chemotherapy remains the standard neoadjuvant approach in most patients, although endocrine therapy may be used in certain hormone receptor-positive patients.

# Neoadjuvant management of newly diagnosed hormone-positive breast cancer

- HER2-negative cancers
- HER2-positive cancers

## HER2-negative cancers

- **Premenopausal women**
- Most premenopausal women should receive chemotherapy rather than endocrine therapy.
- If a premenopausal woman refuses (or is not a good candidate for) neoadjuvant chemotherapy, we suggest proceeding to surgical treatment, if possible, rather than attempting NET. For such women who are concerned about the extent of definitive surgical treatment, NET may be offered, but patients should be advised that the data in this setting suggest superior outcomes with chemotherapy over endocrine therapy.

# HER2-negative cancers

- **Postmenopausal women**

- For most **medically fit** patients requiring neoadjuvant treatment, we treat with chemotherapy based on a robust literature documenting response rates and survival benefits. However, for those with HER2-negative tumors that are strongly HR positive, NET is an acceptable alternative option.
- Tumors that are more likely to respond to neoadjuvant endocrine treatment have strong HR expression (eg, ≥50 percent staining for ER or an Allred score of 7 or 8) and a low proliferative index (Ki67 <10 or 15 percent).

- Response to endocrine therapy has been shown to correlate with levels of ER expression.

- In patients who are **unfit** for chemotherapy due to significant comorbidities or extent of disease, options include upfront surgery (if feasible) or NET, which can enable tumor volume reduction prior to resection under local anesthesia, possibly facilitating less extensive surgery.

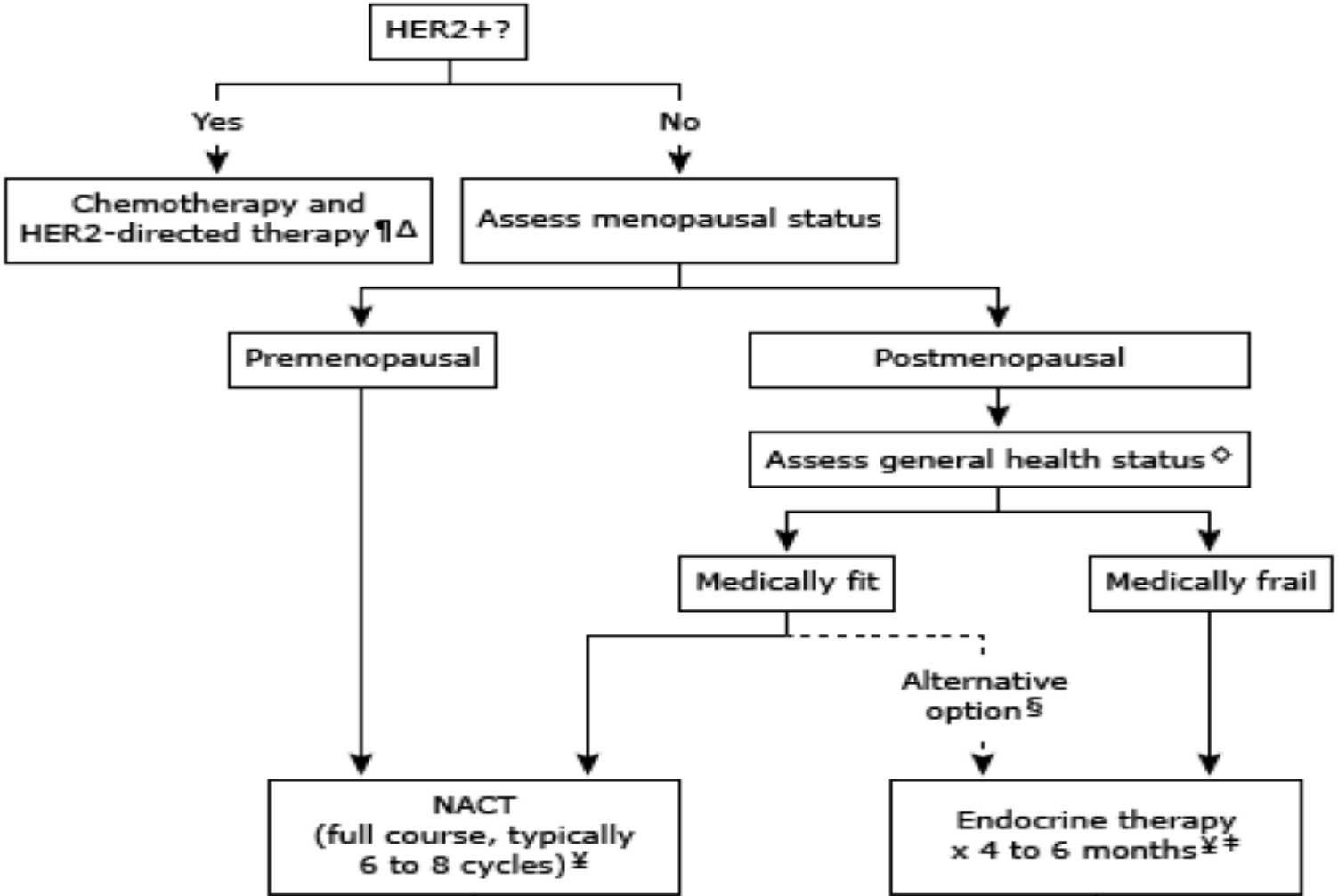
- For those who are unlikely to become surgical candidates regardless of their response to neoadjuvant treatment, primary endocrine therapy may be offered.
- In frail patients with a poor response to endocrine therapy, primary radiation therapy (RT) may also be an option.

# HER2-positive cancers

- Patients receiving neoadjuvant treatment for HR-positive, human epidermal growth factor receptor 2 (HER2)-positive breast cancers are usually treated with chemotherapy with HER2-directed therapy.

- Chemotherapy can shrink HR-positive tumors and facilitate better surgical options, but is less likely to achieve a pathologic complete response (pCR) in HR-positive cancers, especially luminal A cancers, than for more proliferative histologies.

# **hormone-positive** breast cancer receiving neoadjuvant therapy



- An alternative strategy for medically frail patients who cannot tolerate chemotherapy is HER2-directed therapy plus endocrine therapy. However, responses may be less frequent and less durable than when chemotherapy is incorporated.

## Choice of endocrine therapy

- For postmenopausal women receiving NET, we suggest the administration of an AI instead of tamoxifen, based on evidence suggesting better outcomes with AIs across clinical trials and meta-analyses.
- For women who are not tolerant of AIs (for example, those with an osteoporotic fracture on AIs), or those who prefer to avoid the risk of osteoporosis associated with AIs, tamoxifen is a reasonable alternative.

## Duration of endocrine treatment

- A response to endocrine therapy may not be evident for three to four months or more, and maximal response may not be achieved until much later. Thus, the duration of endocrine treatment prior to surgery must be individualized based on the patient's clinical status and the clinical response.

- For patients undergoing NET, we initiate treatment with a planned course of four to six months. However, if disease progression occurs at any point, we proceed directly to surgery, if feasible. In the absence of disease progression:
  - If the tumor is amenable to BCS after four to six months of endocrine therapy, we proceed with definitive surgical treatment.
  - If the tumor is either stable or responding to endocrine therapy, but not yet amenable to BCS, we discuss the risks and benefits of extending treatment to a total treatment duration of 6 to 12 months versus proceeding with mastectomy, if feasible.

- Choice of neoadjuvant chemotherapy for HER2-negative breast cancer

Regimens utilized in the adjuvant setting also demonstrate activity as neoadjuvant treatment. Commonly used regimens for patients with HER2-negative disease include:

- Anthracycline-based regimens such as AC-T
- Anthracycline-free regimens such as docetaxel and cyclophosphamide (TC)

## Anthracycline-based regimens

- For high-risk patients who are treated with NACT (eg, those with node-positive disease or node-negative TNBC ≥1 cm), we suggest an anthracycline- and taxane-based combination rather than a non-anthracycline-based treatment.

## Anthracycline-free alternatives

- As in the adjuvant setting, an anthracycline-free neoadjuvant regimen may be a preferable option for some patients, particularly those with cardiac disease, advanced age, cardiac risk factors such as hypertension and diabetes mellitus, or those unwilling to accept the rare but serious risks of anthracyclines, including congestive heart failure and secondary leukemia.
- The TC combination is widely used in the adjuvant setting for HER2-negative disease and employing this regimen in the neoadjuvant setting is acceptable, particularly in low- and intermediate-risk patients.

## SPECIAL CONSIDERATIONS FOR TRIPLE-NEGATIVE DISEASE

- **Incorporation of carboplatin** — For patients with stage II to III triple-negative breast cancer (TNBC), we suggest a carboplatin-containing neoadjuvant regimen to be used concurrently with pembrolizumab, as was used in KEYNOTE 522. We do not incorporate carboplatin for stage I disease.

- Existing data demonstrate that the addition of carboplatin to standard NACT for TNBC (ie, weekly paclitaxel followed by AC or epirubicin plus cyclophosphamide [EC]) increases absolute pCR rates by at least 20 percent.

# Phase 3 randomized BrighTNess trial

- The BrighTNess trial involved 634 patients with previously untreated stage 2-3 TNBC who were candidates for potentially curative surgery and had a good performance status. They were randomly assigned to receive either paclitaxel plus carboplatin and veliparib, paclitaxel plus carboplatin only, or paclitaxel alone prior to four cycles of chemotherapy with doxorubicin and cyclophosphamide (AC).

## Phase 3 randomized BrighTNess trial

- The initial improvement that was seen in pathologic complete response (pCR) rates with the addition of carboplatin to paclitaxel and standard neoadjuvant chemotherapy translated into improved event-free survival (EFS) rates in patients with resectable TNBC more than 4 years after surgery.
- The benefits of adding carboplatin to paclitaxel, followed by four cycles of AC (doxorubicin and cyclophosphamide) chemotherapy, were seen both in patients with germline *BRCA* mutations as well as those with wildtype *BRCA*.

## Phase 3 randomized BrighTNess trial

- The trial results also demonstrated, however, that there were no short- or long-term benefits to adding veliparib , a poly (ADP-ribose) polymerase (PARP) inhibitor, to the mix.

## Phase 3 randomized BrighTNess trial

- These findings overall support the inclusion of carboplatin into neoadjuvant chemotherapy for stage 2 and 3 triple-negative breast cancer patients, regardless of germline *BRCA* status.

## Incorporation of immunotherapy with NACT in TNBC

- For patients with stage II or III triple-negative breast cancer (TNBC) receiving NACT who do not have a contraindication to the administration of immunotherapy (eg, a pre-existing autoimmune disorder), we suggest the addition of pembrolizumab to NACT and continuation of this agent after surgery.

- This recommendation is based on the results of the KEYNOTE-522 trial and the subsequent US Food and Drug Administration approval of this agent in this setting in late July 2021.

# NEOADJUVANT HER2-targeted therapy

- Compared with most other subtypes of breast cancer, a higher percentage of HER2-positive patients achieve a pathologic complete response (pCR) to neoadjuvant chemotherapy (NACT), even in the absence of HER2-targeted therapy. Using targeted therapy to block activation of those pathways further enhances the chemosensitivity of HER2-positive breast cancer, increasing the pCR rate.

# COMPONENTS OF THERAPY

- Standard neoadjuvant therapy for patients with HER2-positive disease consists of chemotherapy and HER2-directed therapy, specifically trastuzumab, with or without pertuzumab.

- We typically also incorporate pertuzumab into these regimens, particularly for those with node positive disease or tumors >2 cm, given available evidence that pertuzumab enhances locoregional responses.

- TCH(P) – Docetaxel and carboplatin every three weeks for six cycles with concurrent trastuzumab, with or without pertuzumab.

- wPCbH(P) – Weekly paclitaxel with carboplatin, administered either every three weeks or weekly, with concurrent trastuzumab, with or without pertuzumab, for 18 weeks.

- AC-TH(P) – Trastuzumab, weekly for 12 weeks or every three weeks for four cycles, is started concurrent with initiation of the taxane. If pertuzumab is added, it should also be started with the initiation of the taxane and given every three weeks for four cycles.

- TH(P)-AC – The same treatments discussed above administered in the reverse order, which may cause less cardiotoxicity. Note that trastuzumab (and pertuzumab, if added) is held during the AC portion of this treatment.

- FEC/EC-TH(P) or TH(P)-FEC/EC – Fluorouracil, epirubicin, and cyclophosphamide (FEC) every three weeks for three to four cycles or epirubicin and cyclophosphamide (EC) every three weeks for four cycles is often used in place of AC in the above regimens in Europe and certain other countries.

## Choice of taxane

- Standard neoadjuvant therapy in patients with HER2-positive breast cancer utilizes either every-three-week docetaxel or weekly paclitaxel.
- However, nanoparticle albumin-bound paclitaxel (nabpaclitaxel) is an option for patients who have had a hypersensitivity reaction to paclitaxel or have a contraindication to the steroids typically administered with either docetaxel or paclitaxel, such as poorly controlled diabetes mellitus or a history of steroid psychosis.

- **Alternatives for those with low-risk disease or comorbidities**

- For patients who are not good candidates for treatment with either an anthracycline or docetaxel, including older patients with a marginal performance status (but no preexisting peripheral neuropathy), and those who experience a decline in their performance status following initial docetaxel-based therapy, we utilize a regimen consisting of Weekly Paclitaxel with Trastuzumab, with or without pertuzumab, for 12 to 18 weeks. We prefer this strategy over a dose-reduced, docetaxel-based regimen.

- Other non-anthracycline, less intensive chemotherapy options exist. For patients with low- or intermediate-risk, HER2-positive breast cancers, such as clinical stage IIA with a tumor size of less than 3.5 cm in greatest dimension, in whom reduction in tumor size prior to surgery is desired, a shorter course of neoadjuvant treatment consisting of docetaxel and cyclophosphamide every three weeks for four cycles with trastuzumab may be considered.

- For patients with low-risk, HER2-positive cancers, such as clinical stage I (T1N0), in whom neoadjuvant therapy is felt to be warranted based on tumor size (relative to the patient's breast) or location or the need to delay surgery, weekly paclitaxel with trastuzumab for 12 weeks may be used, also based on its efficacy and tolerability in the adjuvant setting.

## Biologic therapy

- We recommend the addition of trastuzumab to NACT in patients with HER2-positve breast cancer.

- The effect of pertuzumab on the risk of tumor recurrence following neoadjuvant therapy with chemotherapy and trastuzumab remains unknown. However, when giving NACT plus trastuzumab, we routinely also incorporate pertuzumab into the regimen, given evidence that pertuzumab enhances locoregional responses.

## Addition of pertuzumab

- Pertuzumab is a monoclonal antibody that binds to a different epitope on HER2 than trastuzumab, blocking the formation of HER2:HER3 heterodimers, which is believed to be an important mechanism of resistance to trastuzumab.

- In 2013, the FDA granted accelerated approval for the addition of pertuzumab to NACT and trastuzumab for patients with HER2-positive locally advanced, inflammatory, or early-stage (either greater than 2 cm in diameter or node positive) breast cancer.

## Addition of pertuzumab

- Pertuzumab enhances locoregional responses, even though it increases the incidence and severity of treatment-related diarrhea as well as modestly increasing the frequency of hematologic toxicities.

# TIMING OF HER2-DIRECTED AGENTS

- For patients receiving an anthracycline-based regimen as part of their neoadjuvant chemotherapy (NACT), we typically administer the HER2-targeted therapy concurrently with a taxane, either following completion of or prior to administration of the anthracycline.

# POST-TREATMENT EVALUATION AND MANAGEMENT

- We recommend proceeding with definitive surgery as soon as the patient has recovered from the toxicities of neoadjuvant treatment, usually within three to six weeks.

## Clinical assessment and indications for imaging

- Once a patient has completed neoadjuvant therapy, physical examination and imaging studies should be performed to assess response to treatment.
- Positron emission tomography (PET) scans (fluoro-2-deoxyglucose PET [FDG-PET]) are not sufficiently sensitive for detecting residual disease to be used in routine assessment of neoadjuvant therapy.

## Management of the axilla

- For women who have received neoadjuvant therapy, our approach to the axilla depends on the presence of suspicious nodes prior to neoadjuvant therapy (either on exam or axillary US), the results of a fine needle aspiration (FNA) or core needle biopsy (CNB) of such nodes prior to treatment, and clinical node status following neoadjuvant therapy.

## Clinically negative axilla prior to treatment (no pretreatment SLNB)

- Patients with no evidence of lymph node involvement prior to or during neoadjuvant therapy, or those who had negative needle biopsies of any suspicious nodes at diagnosis, should undergo post-neoadjuvant therapy sentinel lymph node biopsy (SLNB).

- For patients undergoing a post-treatment SLNB, our approach is to perform it concurrently with breast surgery.
- Patients should be advised that an ALND may be performed at the same time if intraoperative analysis, usually by frozen section, demonstrates persistent disease in the sampled nodes, and that if results of the final SLNB pathology differ from the intraoperative findings, subsequent axillary surgery may be recommended.
- If the SLNB post-treatment is negative (ypN0), no further axillary treatment is required.

- If the SLNB post-treatment is positive (ypN+), we suggest proceeding with ALND.

- For patients keen to avoid ALND, axillary radiation may be considered as an alternative, with appropriate counseling that the equivalence of this approach in terms of locoregional disease control has not been demonstrated.

- Patients in whom sentinel node mapping is not technically successful require an ALND.

## Positive axilla prior to treatment

- For those with evidence of extensive nodal involvement (**cN2 or cN3**) prior to treatment, an ALND should be performed following neoadjuvant therapy, independent of the clinical response to treatment, with subsequent regional nodal irradiation.

- For those with **clinical N1 disease** (preferably with FNA or CNB confirmation of a positive node, and the absence of fixed or matted nodes [cN2] on clinical examination) prior to treatment, management depends on the response to neoadjuvant therapy:

  - Patients with a persistent clinically positive axilla (ycN1) after neoadjuvant therapy should undergo an ALND. For patients with residual nodal disease following neoadjuvant therapy, nodal radiation following ALND is also offered.

  - Patients who are clinically node negative after neoadjuvant therapy (ycN0) should be considered for SLNB.

## Pathologic assessment

- Pathologic assessment of the breast and axillary nodes (except in patients with a negative SLNB prior to their neoadjuvant therapy) is performed to determine the presence and extent of residual invasive disease after completion of neoadjuvant treatment. Achievement of pathologic complete response (pCR) in the breast and axilla (ypT0/is ypN0) correlates with improved survival. This correlation has been shown to be greatest in triple-negative breast cancer (TNBC), followed by human epidermal growth factor receptor 2 (HER2)-positive breast cancer.

## Poor response or progression on neoadjuvant therapy

- Less than 5 percent of patients will have tumor progression during neoadjuvant chemotherapy. For patients who experience progression during neoadjuvant treatment, and who are operable with either mastectomy or lumpectomy, we typically stop therapy and proceed with surgical management or transition to another systemic therapy regimen.

- Indications for mastectomy after neoadjuvant treatment are the same as for patients who did not receive neoadjuvant therapy.

- Patients who remain inoperable may proceed with next-line chemotherapy in order to try to reduce the tumor mass and create the opportunity for definitive locoregional management with surgery and radiation treatment.

- Patients who develop metastatic disease during neoadjuvant therapy are treated as appropriate for stage IV disease with their tumor subtype and extent of disease.