Neoadjuvant management of newly diagnosed hormone-positive breast cancer

Neoadjuvant systemic therapy improve outcomes compared with adjuvant treatment ?

Yes / No

- In 1990s National Surgical Adjuvant Breast and Bowel Project (NSABP; studies B-18 and B-27) studies showed no difference in disease-free survival (DFS) or overall survival (OS) based on the timing of systemic therapy.

??!!!

Neoadjuvant systemic therapy improve outcomes compared with adjuvant treatment ?

Yes / No

- However, (NSABP; studies B-18 and B-27) show that patients who achieved a pCR had a significantly better prognosis than those who had residual disease, and long-term data from these trials and subsequent meta-analyses suggested that there may be subpopulations of patients who experienced benefit from neoadjuvant treatment

Older neoadjuvant trials that used a one-size-fits-all approach to therapy selection are less relevant in the current era of biologically driven treatment selection

pCR to neoadjuvant treatment is a prognostic marker ?

- CTNeoBC pooled analysis of neoadjuvant breast cancer clinical trials published in 2014

- Confirmed that achievement of a pCR with neoadjuvant treatment was prognostic, and it also showed that the association between pCR and outcomes was strongest in patients with TNBC and HER2–positive disease.

Response to neoadjuvant treatment is a predictive marker ?

- The question of whether improvement in pCR from the addition of a particular treatment translates to a benefit in long-term outcome has generated substantial controversy.

- In the trial-level analysis of CTNeoBC, there was no significant association between an increase in the rate of pCR with specific therapies and event-free survival, and thus a predictive effect could not be confirmed.

- It should be noted that therapeutic neoadjuvant trials that include pCR or change in a biomarker, such as Ki67, as the primary end point are often done to guide drug development, and are not meant to change the standard of care until confirmatory trials evaluating survival outcomes are performed.

Neoadjuvant treatment: For Whom ?

LABC : **Locally Advanced breast cancer ?**

Inflammatory : Inoperable LABC

Non - Inflammatory : Operable & Inoperable

EBC : Early stage breast cancer ?

(subgroup of EBC operable but candidate for neoadjuvant)

Neoadjuvant chemotherapy is the treatment of choice for whom ??

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Clinical Question 1

- Which patients with breast cancer are appropriate candidates for neoadjuvant systemic therapy?

Recommendation 1.1

- Neoadjuvant chemotherapy is the treatment of choice for patients with inflammatory breast cancer or those with unresectable or locally advanced disease at presentation whose disease may be rendered resectable with neoadjuvant treatment

Histology , Grade, Stage , HR & HER2 guide neoadjuvant therapy.

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Recommendation 1.2

- Tumor histology, grade, stage and estrogen, progesterone, and HER2 expression should routinely be used to guide clinical decisions as to whether or not to pursue neoadjuvant chemotherapy. There is insufficient evidence to support the use of other immunohistochemical markers, morphological markers (e.g., tumor infiltrating lymphocytes or TILs) or genomic profiles to guide a clinical decision as to whether or not to pursue neoadjuvant chemotherapy.

Informal consensus

Evidence Quality	Strength of Recommendation
Insufficient	Moderate

Which patients with HR-positive / HER2-negative breast cancer are appropriate candidates for neoadjuvant systemic therapy?

- In any patient with HR-Positive, HER2- Negative breast cancer in whom the chemotherapy decision can be made without surgical pathology data and/ or tumor-specific genomic testing .

Neoadjuvant Treatment For HR-positive / HER2-negative breast cancer?

- In patients with hormone receptor HR-positive , HER2-negative tumors, neoadjuvant chemotherapy can be used when a treatment decision can be made without surgical information.

- Among postmenopausal patients with HR-positive, HER2-negative disease, neoadjuvant hormone therapy can be used to downstage disease.

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Invasive Breast Cancer

Candidates for Preoperative Systemic Therapy

Large primary tumor relative to breast size in a patient who desires breast conservation

cN+ disease likely to become cN0 with preoperative systemic therapy

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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

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Candidates for Preoperative Systemic Therapy

Patients in whom definitive surgery may be delayed.

Allows time for genetic testing
Allows time to plan breast reconstruction in patients electing mastectomy
Allows time for delayed decision-making for definitive surgery.

Neoadjuvant therapy may be offered to reduce the extent of surgery

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Recommendation 1.4

- Neoadjuvant systemic therapy may be offered to reduce the extent of surgery (breast conserving surgery and axillary lymph node dissection). Chemotherapy with or without targeted therapy, or endocrine therapy (if HR+) may be offered.

Evidence-based benefits outweigh harms	
Evidence Quality	**Strength of Recommendation**
Intermediate	Moderate

Neoadjuvant Systemic Therapy ,

In whom a delay in surgery is preferable

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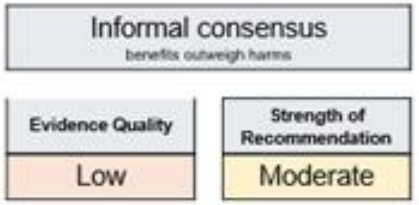
Recommendation 1.5

- In patients for whom a delay in surgery is preferable (e.g., for genetic testing required for surgical treatment decision making, to allow time to consider reconstructive options) or unavoidable, neoadjuvant systemic therapy may be offered.



Patients receiving neoadjuvant therapy should be monitor for response evaluation.

Clinical Question 2

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- How should response be measured in patients receiving neoadjuvant chemotherapy?

Recommendation 2.1

- Patients receiving neoadjuvant therapy should be monitored for response with clinical examination at regular intervals. Breast imaging may be used to confirm clinical suspicion of progression and for surgical planning. When imaging is used, the modality that was most informative at baseline—mammography, ultrasound, or magnetic resonance imaging—should be used at follow-up.

Informal consensus

Evidence Quality	Strength of Recommendation
Insufficient	Moderate

Neoadjuvant chemotherapy ?

Clinical Question 4

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- What neoadjuvant treatment is recommended for patients with HR-positive/HER2-negative breast cancer?

Recommendation 4.1

- Neoadjuvant chemotherapy can be used instead of adjuvant chemotherapy in any patient with HR-positive, HER2-negative breast cancer in whom the chemotherapy decision can be made without surgical pathology data and/or tumor specific genomic testing.

Informal consensus

Evidence Quality	Strength of Recommendation
Low	Moderate

Neoadjuvant endocrine therapy for whom ?

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Recommendation 4.2

Evidence-based
benefits outweigh harms

Evidence Quality	Strength of Recommendation
Intermediate	Moderate

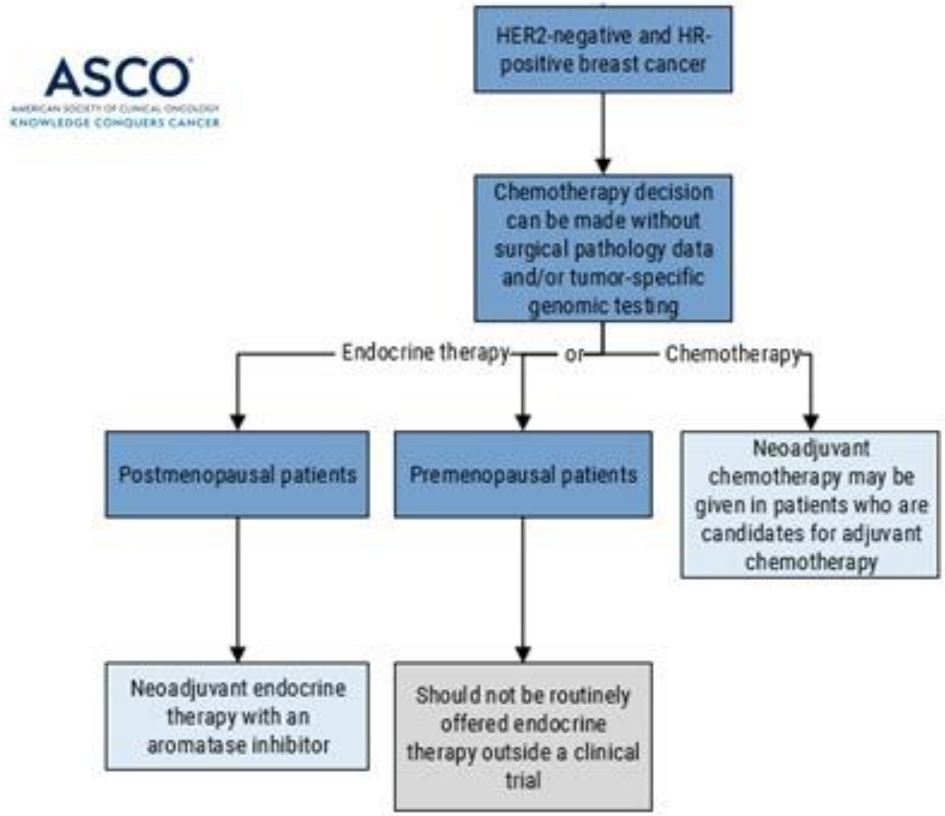
- For postmenopausal patients with HR-positive, HER2-negative disease, neoadjuvant endocrine therapy with an aromatase inhibitor may be offered to increase locoregional treatment options. If there is no intent for surgery, endocrine therapy may be used for disease control.

Recommendation 4.3

Evidence-based
benefits outweigh harms

Evidence Quality	Strength of Recommendation
Intermediate	Moderate

- For premenopausal patients with HR-positive, HER2-negative early-stage disease, neoadjuvant endocrine therapy should not be routinely offered outside of a clinical trial.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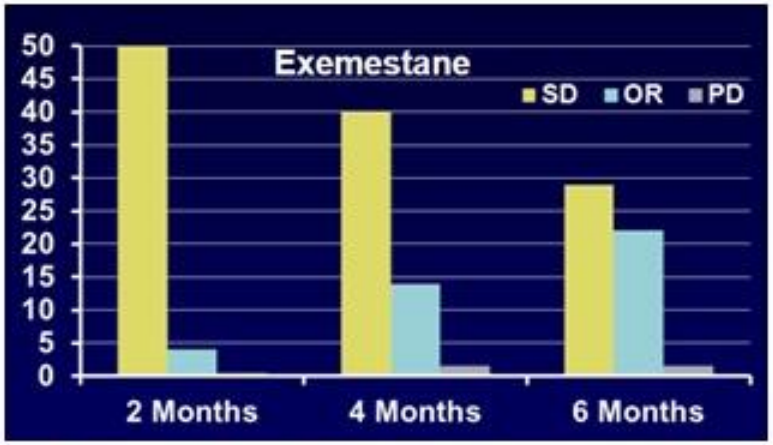
HER2-negative and HR-positive breast cancer
Chemotherapy decision can be made without surgical pathology data and/or tumor-specific genomic testing
Endocrine therapy
or
Chemotherapy
Postmenopausal patients
Premenopausal patients
Neoadjuvant chemotherapy may be given in patients who are candidates for adjuvant chemotherapy
Neoadjuvant endocrine therapy with an aromatase inhibitor
Should not be routinely offered endocrine therapy outside a clinical trial

Duration of Neoadjuvant Endocrine Therapy



Response to treatment as evaluated by mammography.
OR, objective response; PD, progressive disease; SD, stable disease.

Duration letrozole	% CR
3 months	9.5
6 months	29
12 months	36

"**Conclusion:** Over half of patients become BCS-eligible within 4 months of preoperative letrozole treatment. While prolonged treatment for up to 8 months can result in further tumor volume reduction in some patients, there is no clear optimum for treatment duration"

NEO-ADJUVANT ENDOCRINE THERAPY

- **Is neoadjuvant endocrine therapy without cytotoxics a reasonable option for postmenopausal patients with**

  Endocrine responsive disease? YES/No

If yes, for which duration?

1. **1 – 2 weeks "window" prior to surgery**
2. **3 – 4 months**
3. **4 – 8 months**
4. **Until maximal response**

- ***Chemotherapy***: For premenopausal& majority of postmenopausal women with hormone receptor (HR)-positive disease
- ***Neoadjuvant endocrine therapy*** (NET): Significant comorbidities
- Chemotherapy can shrink HR-positive tumors and facilitate lesser surgery, but is less likely to achieve a ***PCR*** in HR-positive cancers, especially luminal A cancers, compared with more aggressive histologies

- In postmenopausal women, ***NET*** is associated with ***similar response rates*** to neoadjuvant chemotherapy, although it may take longer to achieve a response
- Survival data with NET versus neoadjuvant chemotherapy are not yet available

- For postmenopausal women receiving NET: ***Aromatase inhibitors***
- ***Four to six months***, though a ***longer*** duration of treatment may be utilized, if needed, to allow for breast-conserving surgery in patients who have ***stable disease or partial response*** to endocrine therapy.
- If ***progression*** of disease occurs at any point, we proceed directly to ***definitive surgical management***