Neoadjuvant Endocrine Therapy: Who Benefits Most?

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KEYWORDS

- Neoadjuvant endocrine therapy • Estrogen receptor–positive breast cancer
- Neoadjuvant chemotherapy • Aromatase inhibitors

KEY POINTS

- Neoadjuvant endocrine therapy (NET) can be used to downstage breast cancers in postmenopausal women with estrogen receptor–positive tumors.
- NET can be used in selected premenopausal women and is often combined with ovarian suppression.
- Complete pathologic responses are infrequent with NET; however, residual disease does not imply poor prognosis.
- NET as a single agent is less effective than in combination with trastuzumab in patients with human epidermal growth factor receptor 2 (HER2)-overexpressing tumors.
- Aromatase inhibitors are more effective than tamoxifen for downstaging with NET.

OVERVIEW

Neoadjuvant treatment of breast cancer has been established as an important strategy for understanding prognosis, biomarker evaluation, and targeted therapeutics development. Neoadjuvant treatment allows for real-time evaluation of drug efficacy by assessment of in vivo sensitivity as well as insight into the molecular alterations associated with tumor response through analysis of serial tumor biopsies. Neoadjuvant chemotherapy (NCT) has been incorporated into clinical practice for downstaging tumors for less extensive surgery and for assessing tumor response, which is associated with prognosis.[1] Similar to NCT, neoadjuvant endocrine therapy (NET) can downstage tumors and provide information on the tumor endocrine responsiveness. NET, however, has been less frequently incorporated into practice due to the slow tumor response requiring prolonged therapy as well as the less defined prognostic information that is obtained after treatment.[2] NET was initially limited to elderly

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postmenopausal women with large tumors who were poor candidates for NCT or surgery.[3–6] More recently, the ability to identify early endocrine responsiveness and the development of highly effective aromatase inhibitors (AIs) has resulted in a broader use of NET. The National Comprehensive Cancer Network guidelines suggests that appropriate candidates for NET are patients with estrogen receptor (ER)-rich tumors (Allred score of 7–8),[7] which correspond to luminal A or luminal B breast cancers.[8] Intensity of ER positivity, however, does not always parallel responsiveness to endocrine therapy.[9] Current research is directed toward identifying those patients who receive the greatest benefit from endocrine-directed therapy who could avoid cytotoxic chemotherapy. The most common class of drugs used for NET are the AIs (**Table 1**).

NEOADJUVANT ENDOCRINE THERAPY VERSUS NEOADJUVANT CHEMOTHERAPY

NET is as efficacious as NCT in downsizing tumors in patients with ER-positive disease, although the latter has more pathologic complete responses (pCRs).

Three randomized clinical trials have been conducted evaluating tumor response with NET versus NCT, all of which have shown similar response rates (**Table 2**).[10] In all 3 studies, toxicities were significantly higher with NCT versus NET. Although these studies demonstrate that downstaging is similar with both treatments, long-term outcome data are not readily available nor are defined biomarkers for patient selection for each therapy.

Semiglazov and colleagues[11] evaluated 239 postmenopausal women with ER-positive and/or progesterone receptor (PR)-positive breast cancer comparing anastrozole or exemestane for 3 months versus 4 cycles of doxorubicin plus paclitaxel every 21 days. Study endpoints included overall objective response determined by palpation, mammography, or ultrasound and the number of patients who qualified for breast-conserving surgery (BCS). The clinical objective response (determined by palpation) was similar in the endocrine group (64%) compared with chemotherapy (64%). Rates of pCR (3% vs 6%) and disease progression (9% vs 9%) did not differ significantly between the endocrine therapy or chemotherapy arms, respectively (P>.05). Rates of BCS were slightly higher in the endocrine group (33% vs 24%; P = .058). Overall, NET with AIs was better tolerated and resulted in rates similar to chemotherapy in overall objective response and BCS in postmenopausal women with ER-positive and/or PR-positive tumors.

The Grupo Español de Investigación en Cáncer de Mama (GEICAM) trial enrolled patients with operable breast cancer (T2/T3) and immunophenotypically defined luminal disease (ER-positive, PR-positive, HER2-negative, and cytokeratin 8/18-positive)[12]; 95 patients were randomized to either NCT (epirubicin plus cyclophosphamide [EC] × 4 cycles followed by docetaxel × 4 cycles) or NET (exemestane × 24 weeks, combined with goserelin in premenopausal patients). The primary endpoint was clinical response measured by MRI. The clinical response rate did not differ significantly between the arms. The clinical response was 66% for NCT (13% complete response and 53% partial response) and 48% for NET (6% complete response and 42% partial response) (P = .07). Three patients with NCT and 0 with NET achieved a pCR (P = not significant). Mastectomy rates were similar in both arms (NCT, 47%, and NET, 56%; P = .18).

The Neoadjuvant Chemotherapy Versus Endocrine Therapy (NEOCENT) trial was a multicenter trial that enrolled 44 postmenopausal women, ages less than 70, with strongly ER-positive tumors, greater than 2 cm on mammogram or ultrasound, or nodal disease greater than 2 cm.[13] Patients were randomized to NCT with 6 cycles

Table 1
Neoadjuvant endocrine therapies

Drug Class	Mechanism	Method of Administration	Generic Name	Trade Name	Comments
Selective ER modulators	Binds to ER	Oral	Tamoxifen Torimefene	Nolvadex Fareston	
Antiestrogens	Selective ER down-regulator	Intramuscular injection	Fulvestrant[a]	Faslodex	Used in postmenopausal women only
AIs	Inhibits peripheral conversion of androgen to estrogen	Oral	Letrozole Anastrozole Exemestane	Femara Arimdex Aromasin	Reversible inhibitor Steroidal inhibitor irreversibly binds to enzyme
Luteinizing hormone-releasing hormone agonists	Activates GnRH receptor, leads to paradoxic decrease in follicle-stimulating hormone/ luteinizing hormone	Subcutaneous injection	Goserelin Leuprolide	Zolodex Lupron	Suppresses ovarian function in premenopausal women

[a] Fulvestrant is not approved for NET and for this use is investigational.

Table 2
Neoadjuvante endocrine therapy versus neoadjuvant chemotherapy trials

Source (Trial Name)	No.	Patient Characteristics at Baseline	Chemotherapy	Endocrine Therapy	Primary Endpoint	Response (per Primary Endpoint)	Rate of Breast Cancer Surgery
Semiglazov et al,[11] 2007	239	Postmenopausal ER^+ and/or PR^+, stages IIA to IIIB	Doxorubicin + paclitaxel × 4 cycles	Anastrozole or exemestane ×12 wk	CR by palpation	64% CT vs 64% ET	24% CT vs 33% ET
Alba et al,[12] 2012 (GEICAM/2006–03)	95	51% premenopausal $ER^+/PR^+/HER2^-$/cytokeratin $8/18^+$	EC × 4 cycles, followed by docetaxel × 4 cycles	Exemestane (+ goserelin if premenopausal) × 24 wk	OR by RECIST criteria, MRI	66% CT vs 48% ET	47% CT vs 56% ET
Palmieri et al,[13] 2014 (NEOCENT)	44	Postmenopausal ER^+	5-fluorouracil + EC ×6 cycles, switched to docetaxel after 3 cycles if stable disease or progressive disease	Letrozole ×18 wk	OR by ultrasound, mammography	55% CT vs 59% ET	55%CT Vs 68% ET

Abbreviations: CR, clinical response; CT, chemotherapy; EC, epirubicin + cyclophosphamide; ET, endocrine therapy; OR, objective response.

of fluorouracil with EC or letrozole NET daily for 18 weeks to 23 weeks. Radiological objective response was similar in both groups, 12/22 (55%) in the chemotherapy arm and 13/22 (59%) in the letrozole arm.

In all 3 studies, toxicity was significantly increased in patients treated with NCT. The GEICAM trial found grade III–IV toxicity was more frequent with NCT (47% NCT vs 9% NET; $P = .0001$). The most frequent toxicities observed from chemotherapy were alopecia (79%), grade 3/4 neutropenia (33%), and grade 2 neuropathy (30%). Findings were similar in the NEOCENT trial.[11–13]

PATIENT SELECTION: PREMENOPAUSAL WOMEN WITH ESTROGEN RECEPTOR–POSITIVE, HER2-POSITIVE TUMORS

Most NET trials have been conducted in postmenopausal women, which have demonstrated downsizing of tumors. The main NET trials often limit accrual to postmenopausal women with ER-positive breast cancers. These studies are discussed in more detail later. NET can be used to downstage ER-positive, HER2-positive tumors; however, the proliferation rate remains high. Data is limited for use of NET in premenopausal women and women with ER-positive, HER2-positive tumors.

Neoadjuvant Endocrine Therapy in Premenopausal Women

Premenopausal women have been excluded from most of the NET trials. Treatment of premenopausal women with AIs combined with ovarian suppression or ablation can lead, however, to profound estrogen suppression.[14] Using this combination, 2 clinical trials have demonstrated responses equivalent to that observed in the postmenopausal population[15] (**Table 3**).

Masuda and colleagues[16] conducted a randomized, prospective, double-blind NET trial enrolling 197 premenopausal patients. Women were treated with goserelin and were randomized to receive either anastrozole or tamoxifen (STAGE trial). Superior overall tumor response (complete response or partial response) was observed with anastrozole compared with tamoxifen (70.4% vs 50.5%; $P = .004$), which was confirmed by ultrasound and MRI.

In a small trial reported by Torrisi and colleagues,[17] 32 premenopausal women with T2–T4, N0 breast cancer were treated with letrozole in combination with a gonadotropin-releasing hormone (GnRH) analog. After 4 months of treatment, 1 patient (3%) had a complete clinical response, which was confirmed as a pCR at pathologic examination; 15 patients (47%) obtained a clinical and imaging partial response giving an overall response rate (ORR) of 50%; 16 patients had stable disease stable; and none of the patients progressed during treatment. BCS was performed in 15 patients (47%) whereas 17 patients (53%) underwent mastectomy.

Neoadjuvant Endocrine Treatment in Estrogen Receptor–Positive, HER2-Positive Disease

Both the Immediate Preoperative Anastrozole, Tamoxifen, or Combined With Tamoxifen (IMPACT) and the P024 trials (discussed later) included a small subpopulation of patients whose tumors overexpressed HER2.[18–20] The results indicated that HER2 expression did not impede tumor response to NET; however, the proliferation marker Ki67 was not significantly decreased, as is seen in patients with HER2-negative tumors.

In the P024 study, letrozole was found to be clinically more effective compared with tamoxifen for ER-positive, HER2-positive tumors.[18] In a reanalysis of tumor samples by fluorescence in situ hybridization, approximately 10% of the patients

Table 3
Randomized controlled neoadjuvant endocrine therapy trials (premenopausal women hormone receptor–positive breast cancer)

Source (Trial Name)	No.	Patient Characteristics at Baseline	Study Arms	Duration (wk)	Primary Endpoint	Response (per Primary Endpoint)	Rate of Breast Cancer Surgery
Masuda et al,[16] 2012 (STAGE)	197	$ER^+/HER2^-$, operable	A. Tamoxifen + goserelin B. Anastrozole + goserelin	24	OR by caliper measurements	A. 51% B. 70%	A. 68% B. 86%
Torrisi et al,[17] 2007	72	ER^+ and/or PR^+, operable	A. ECF B. ECF + GnRH analog	9 ($\geq$3 cycles of chemotherapy)	OR by breast ultrasound + mammography and caliper measurements	A. 53% B. 64%	N/A

Abbreviation: ECF, epirubicin, cisplatin, fluorouracil.

were found to have HER2-positive disease, with a 44% to 47% response rate when assessed by mammography or ultrasound. Despite the observed clinical response, NET in the dual positive tumors was not associated with suppression of Ki67.[21]

In the IMPACT trial, 14% of assessed patients had overexpression of HER2.[19] In this subgroup, 7 (58%) of 12 patients treated with anastrozole responded compared with 2 (22%) of 9 patients treated with tamoxifen and 4 (31%) of 13 patients treated with the combination. Additionally, suppression of Ki67 after 2 weeks and 12 weeks was significantly greater with anastrozole than with tamoxifen ($P = .004$ and $P<.001$) but was similar between tamoxifen and the combination ($P = .600$ and $P = .912$).[22] Although the patient population and treatment duration differed between the P024 and the IMPACT studies, the trend in favor of anastrozole reflects that observed with letrozole and reinforces the hypothesis that AIs may be more effective than tamoxifen in the treatment of ER-positive early breast cancer that also overexpresses HER2.

THE MOST EFFICACIOUS ENDOCRINE AGENT

Several trials have been conducted to identify the optimal drug for NET. From these studies the greatest response rates have been observed using AIs (**Table 4**).

Tamoxifen Versus Aromatase Inhibitors

Three randomized clinical trials have compared tamoxifen with AIs for tumor response in postmenopausal women (see **Table 4**). In the P024 study, 4 months of letrozole was compared with tamoxifen in a double-blind, randomized, multicenter study in women with hormone receptor (HR)-positive tumors who were ineligible for BCS. Letrozole was found more effective than tamoxifen in terms of clinical and radiologic (ultrasound and mammography) response rates and in relation to rates of BCS. The IMPACT trial and Preoperative Arimidex Compared to Tamoxifen (PROACT) trial found no significant difference in ORR between treatment with AIs versus tamoxifen.[20,23] A meta-analysis of these studies, including a total of 1160 patients, indicated superior outcomes in terms of clinical objective response rate and breast cancer therapy (BCT) rates with AI compared with tamoxifen.

Comparison of Aromatase Inhibitors

The Z1031 trial was designed to determine which AI (anastrozole, letrozole, or exemestane) should be recommended for future testing against chemotherapy in the neoadjuvant setting.[24] This was a phase II trial that recruited 377 postmenopausal women with clinical stage 2/3 HR-positive disease to receive an AI for 4 months before surgery. No statistical difference in clinical response or surgical outcome was observed between the 3 arms. A major finding was that half of the patients who were considered candidates for mastectomy or were inoperable before neoadjuvant AI had successful BCT.[24]

Selective Estrogen Receptor Down-Regulators Versus Aromatase Inhibitors

Fulvestrant, a selective ER down-regulator, has been evaluated in 2 trials compared with anastrozole. Quenel-Tueux and colleagues[25] studied 108 postmenopausal women with histologically confirmed nonmetastatic breast cancer, ER positive and/or progesterone-receptor positive, not eligible for BCS at baseline, who were HER2 positive or HER2 negative. The objective response rate determined by clinical palpation was 58.9% in the anastrozole arm and 53.8% in the fulvestrant arm. Both drugs were found effective neoadjuvant treatments for

Table 4
Randomized controlled neoadjuvant endocrine therapy trials (postmenopausal women with hormone receptor–positive breast cancer)

Source (Trial Name)	No.	Patient Characteristics at Baseline	Neoadjuvant Endocrine Therapy	Duration (wk)	Primary Endpoint	Response (per Primary Endpoint)	Rate of Breast Cancer Surgery
Eiermann et al,[20] 2001 (P024)	337	ER^+ and/or PR^+, none eligible for BCS (14% deemed inoperable)	A. Tamoxifen B. Letrozole	16	CR by palpation	A. 36% B. 55%	A. 35% B. 45%
Smith et al,[19] 2005 (IMPACT)	330	ER^+, operable (96 eligible for BCS) Locally advanced	A. Tamoxifen B. Anastrozole C. Anastrozole + tamoxifen	12	OR by caliper measurements	A. 36% B. 37% C. 39%	A. 31% B. 44% C. 24%
Cataliotti et al,[24] 2006 (PROACT)	451	ER^+ and/or PR^+, operable or potentially operable (386 would require mastectomy or were deemed inoperable) Locally advanced	A. Tamoxifen B. Anastrozole	12	OR by ultrasound measurements	A. 35% B. 40%	A. 31 % B. 43%
Ellis et al,[23] 2011 (Z1031)	374	ER^+, eligible for mastectomy or inoperable clinical stages II–III	A. Exemestane B. Letrozole C. Anastrozole	16–18	OR by clinical assessment	A. 63% B. 75% C. 69%	A. 48% B. 42% C. 64%
Lerebours et al,[26] 2016 (CARMINA 02)	116	ER^+ and/or $PR^+/HER2^-$, operable, none eligible for BCS	A. Anastrozole B. Fulvestrant	16	CR by palpation	A. 53% B. 37%	A. 58% B. 50%
Quenel-Tueux et al,[25] 2015	120	ER^+ and/or PR^+, none eligible for BCS	A. Anastrozole B. Fulvestrant	24	CR by palpation	A. 59% B. 54%	A. 59% B. 50%

postmenopausal patients with large operable or locally advanced ER-positive breast cancers, making BCS a viable option for some women who were not eligible for it initially.

Most recently, showing similar findings, the French trial UNICANCER CARMINA 02[28] evaluated fulvestrant versus anastrozole in 116 postmenopausal women with ER-positive, HER2-negative, operable breast cancers. This was a multicenter, phase 2, randomized trial that evaluated clinical response rate after up to 6 months of endocrine treatment. The clinical response rates at 6 months were 52.6% with anastrozole and 36.8% with fulvestrant. BCS was performed for 57.6% versus 50% of patients treated with anastrozole versus fulvestrant, respectively. The relapse-free survival rates at 3 years were 94.9% with anastrozole and 91.2% with fulvestrant. Both drugs were found effective and well tolerated as NET in postmenopausal women with HR-positive/HER2-negative breast cancer with a trend toward better outcomes with anastrozole (**Table 4**).

DURATION OF TREATMENT

From the available data in studies of postmenopausal women, 4 months to 6 months of an AI seems optimal with modest persistent benefits thereafter (**Table 5**). The relatively slow downstaging with NET relates to the absence of any increase of apoptosis with endocrine therapy and the dependence of response on the antiproliferative effects of estrogen withdrawal.

Dixon and colleagues[27] investigated the potential benefits of prolonged treatment with neoadjuvant letrozole comparing a duration of 3 months versus longer than 3 months. At 3 months, 69.8% of patients had a partial or complete response. The response rate increased to 83.5% with prolonged letrozole treatment. Continuing letrozole beyond 3 months increased the number of women who initially required mastectomy or had locally advanced breast cancer who were subsequently suitable for breast conserving surgery from 60% at 3 months to 72%.

Llombart-Cussac and colleagues[28] evaluated the efficacy of letrozole over a period of 4 months to 1 year in postmenopausal women. The median time to objective response was 3.9 months and the median time to maximum response was 4.2 months, although 37.1% of patients achieved the maximal response within 6 months to 12 months.

Studies from Carpenter and colleagues[29] and Krainick-Strobel and colleagues[30] evaluated the duration of letrozole in patients initially unsuitable for BCS. Carpenter and colleagues[29] found patients suitable for surgery after 7.5 months, whereas Krainick-Strobel and colleagues[30] found that more than half of the patients will be eligible for BCS within 4 months of treatment with letrozole.[29,30]

Similar results were seen with exemestane. Fontein and colleauges[31] found an ORR of 59% at 3 months and 68% ORR at 6 months, although Hojo and colleagues[32] found responses comparable in both the 4-month and 6-month duration treatment groups. The response rates as assessed by clinical examination were 42.3% and 48.0% for 4 months and 6 months of treatment, respectively. Pathologic responses (minimal response or better) were observed in 19.2% and 32.0% of patients, and BCS was performed on 50.0% and 48.0% of patients from the 4-month and 6-month treatment groups, respectively.

The St Gallen International Expert Consensus has endorsed that treatment should be continued until maximal response. However, 4 months to 6 months of NET with an AI seems optimal with modest persistent benefits thereafter.[33]

Table 5
Duration of treatment

Study	No.	Patient Characteristics at Baseline	Neoadjuvant Endocrine Therapy	Duration (Months)	Outcome Measures	Response
Dixon et al,[27] 2009	182	Postmenopausal ER^+, operable Large or locally advanced	Letrozole	3 vs >3	OR by caliper and ultrasound measurements	3 mo 70% ORR >3 mo 83% ORR 3 mo 60% BCS >3 mo 72% BCS
Llombart-cussac et al,[28] 2012	70	Postmenopausal ER^+ and/or PR^+	Letrozole	4–12	Optimal duration of treatment defined as the time required to attain the MR by clinical palpation	Median time to OR was 3.9 mo Median time to MR was 4.2 mo
Carpenter et al,[29] 2014	146	Postmenopausal ER^+ and/or PR^+, none eligible for BCS	Letrozole	3–12	Optimal duration of treatment that would allow BCS	Median time to achieve tumor response to allow BCS was 7.5 mo
Krainick-Strobel et al,[30] 2008	33	Postmenopausal ER^+ and/or PR^+, none eligible for BCS (only mastectomy)	Letrozole	4–8	OR (by clinical examination, mammography, and ultrasound) and decisions regarding BCS	4 mo 55% ORR 8 mo 24% ORR 4 mo 71% BCS >4 mo 80% BCS
Fontein et al,[31] 2014	102	Postmenopausal ER^+	Exemestane	3 vs 6	CR (by palpation) at 3 and 6 mo	3 mo 59% ORR >3 mo 68% ORR 3 mo 62% BCS >3 mo 71% BCS
Hojo et al,[32] 2013	52	Postmenopausal ER^+ and/or PR^+	Exemestane	4 vs 6	CR (by palpation) and decisions regarding BCS	4 mo 42% ORR 6 mo 48% ORR 4 mo 50% BCS 6 mo 48% BCS

Abbreviations: CR, clinical response; MR, maximal response; ORR, objective response rate.

PREDICTORS OF RESPONSE AND SURROGATE ENDPOINTS

Pathologic Complete Response

pCR has been the outcome most often assessed in NCT studies, and it is defined as having no residual invasive carcinoma and no in situ carcinoma in the breast and lymph nodes. pCR is rarely achieved, however, in NET trials in patients with ER-positive, HER2-negative disease.[34,35] Although pCR may be observed in 40% to 50% of patients receiving NCT, it is rare after NET (<2%).[36] Thus, it has not been used a predictor of long-term survival in this population. Several studies have attempted to define prognostic markers for NET (**Table 6**).

Ki67

Immunohistochemical assessment of cells staining for the nuclear antigen Ki67, a nuclear marker expressed in all phases of the cell cycle other than the G0 phase,[37] measures the proportion of cells proliferating in a tumor. NET has been shown to cause a significant reduction in Ki67, with the degrees of suppression related to the level of ER expression. Ki67 levels after NET have been shown to be prognostic.[38] The IMPACT trial demonstrated that high Ki67 expression levels after 2 weeks of NET was associated with a poorer recurrence-free survival. DeCensi and colleagues[39] found that after 4 weeks of treatment, Ki67 was a good predictor of recurrence-free survival and overall survival. The risk of death was 5.5-times higher in patients with postdrug Ki67 greater than or equal to 20% than in those with Ki67 less than 20%.[36] At this time, there is an ongoing UK national trial, Perioperative Endocrine Therapy: Individualizing Care (POETIC), which aims to validate whether changes in Ki67 or in gene expression after 2 weeks of treatment with AI may predict long-term outcome and may help select patients who may need further adjuvant chemotherapy.[40]

Preoperative Endocrine Prognostic Index

The preoperative endocrine prognostic index (PEPI) was generated from the P024 study. After 4 months of NET with either letrozole or tamoxifen, it was found that Ki67, pathologic tumor size, nodal status, and ER status were independently associated with recurrence-free survival and overall survival. The Allred scoring system, a clinical instrument based on the percentage of cells that stain by immunohistochemistry for ER (on a scale of 0–5) and the intensity of that staining (on a scale of 0–3, for a possible total score of 8), was used to quantify ER status. Patients with a PEPI score of 0 (pT1/2, pN0, Ki67 $\leq$2.7%, and Allred >2) have been found to have an extremely low

Table 6
Markers to predict outcome

Markers	Predicts
Ki67 on treatment	Endocrine resistance and recurrence risk
PEPI score	Recurrence-free survival
4-gene panel (ER, PR, HER2, and Ki67)	Distinguishes luminal A from luminal B breast cancer subtypes
PAM 50	Relapse-free survival
Oncotype DX 21-gene recurrence score	Recurrence score Distant disease recurrence and benefit of adjuvant chemotherapy in ER^+ breast cancer

relapse risk; 3.7% at 5 years versus 14.4% at 5 years for PEPI greater than 0, based on 119 cases[36] (Table 7).

Multigene Expression Tests

Prediction analysis of microarray 50

Prediction analysis of microarray 50 (PAM50) is 50-gene quantitative polymerase chain reaction assay developed to identify the intrinsic biological breast cancer subtypes (luminal A/B, HER2 enriched, basal like). A risk of recurrence score is derived from the expression profile of the genes, with special weighting given to a set of proliferation-associated genes, with tumor size also included. The commercial Prosigna test (Nano String Technologies, Inc.) is Food and Drug Administration approved as a prognostic predictor of postmenopausal women with lymph node–negative, HR-positive, and HER2-negative breast cancer treated with adjuvant endocrine therapy.[41]

Four-gene panel

Recently it has been demonstrated that a 4-marker immunohistochemistry panel (ER, PR, HER2, and Ki67), distinguishes luminal A from luminal B breast cancer subtypes and may be useful in selecting adjuvant therapy and predicting long-term outcomes.[42] Although it is an inexpensive test with prognostic utility, the lack of reproducibility of the 4-marker immunohistochemistry panel is problematic. Differences can occur because of variability in several factors, including fixation, antigen retrieval, reagents, and interpretation.[43]

Oncotype DX 21-gene recurrence score

Oncotype DX is an reverse transcription–polymerase chain reaction–based multigene analysis that predicts recurrence in ER-positive, lymph node–negative breast

Table 7
The preoperative endocrine prognostic index score

	Recurrence-free Survival		Breast Cancer–specific Survival	
Pathology, Biomarker Status	**Hazard Ratio**	**Points**	**Hazard Ratio**	**Points**
Tumor size				
T 1/2	—	0	—	0
T 3/4	2.8	3	4.4	3
Node status				
Negative	—	0	—	0
Positive	3.2	3	3.9	3
Ki67 level				
0%–2.7%	—	0	—	0
>2.7%–7.3%	1.3	1	1.4	1
>7.3%–19.7%	1.7	1	2.0	2
>19.7%–53.1%	2.2	2	2.7	3
>53.1%	2.9	3	3.8	3
ER status, Allred score				
0–2	2.8	3	7.0	3
3–8	—	0	—	0

cancer patients. It is composed of 21 genes, 16 cancer-related genes and 5 housekeeping genes (proliferation: Ki67, STK15, survivin, cyclin B1, and MYBL2; invasion: stromolysin 3 and cathepsin L2; HER2: GRB7 and HER2; estrogen: ER, PR, Bcl-2, and SCUBE2; and other: GSTM1, CD68, and BAG1) and 5 reference genes ([beta]-actin, GAPDH, RPLPO, GUS, and TFRC). The cumulative result of this test is the recurrence score (0–100), which can be categorized into low-risk (score <18), intermediate-risk (score 18–30), and high-risk (score ≥31) groups.[44]

WHO BENEFITS MOST?

The advantage of the NET approach is the ability to assess clinical and molecular responses of an individual patient's tumor to an endocrine agent. It has been shown that evaluating biomarkers after a short course of NET can guide treatment. In the IMPACT trial,[38,45] pretreatment values of Ki67 have not been shown to be prognostic, whereas a decrease in Ki67 after 2 weeks of hormonal therapy seems to predict recurrence-free survival. The preoperative Window of Endocrine Therapy Provides Information to Increase Compliance (POWERPINC) study tested the impact of 1 week of tamoxifen on Ki67.[46] The decrease in proliferation was similar to that seen in other studies using 2 weeks of NET.[22] This strategy allows an early identification of high-risk patients with endocrine resistant tumors.[36]

The 21-gene recurrence score has also been shown to have predict value. Ueno and colleagues[47] evaluated pretreatment and post-treatment tumor tissue from patients with estrogen-positive tumors treated with neoadjuvant exemestane. The clinical response rate was 59% in patients with a low recurrence score compared with 20% in patients with a high recurrence score. Recurrence scores were highly correlated in the pretreatment and post-treatment samples.

In the Z1031 trial, PAM50 analysis identified AI-unresponsive nonluminal subtypes in 3% of patients with ER-rich cancers.[24] This will likely prove helpful in the future to exclude uncommon nonluminal intrinsically endocrine therapy–resistant tumors.

RESIDUAL DISEASE CONSEQUENCES

As discussed previously, achievement of pCR with preoperative endocrine therapy is rare. Although pCR is associated with improved outcomes in patients with ER-negative disease, it may not have an appreciable impact on outcomes in those with ER-positive disease.[48–50] Some investigators have shown that gene alterations after NET include decrease in proliferation genes and up-regulation of immune function and extracellular matrix remodeling genes.[51] These molecular changes may be more relevant endpoints in patients treated with NET.

There are currently several trials addressing the optimal treatment of patients with residual disease after NET. The New Primary Endocrine-therapy Origination Study (NEOS), a multicenter phase III randomized trial, will assess the need for adjuvant chemotherapy in postmenopausal women with stage T1c-T2N0M0, HR-positive tumors who responded to neoadjuvant letrozole.[52]

The Alliance for Clinical Trials in Oncology has an ongoing phase III neoadjuvant clinical trial (Alternate Approaches for Clinical Stage II or III Estrogen Receptor Positive Breast Cancer Neoadjuvant Treatment [ALTERNATE]), which will assess a biomarker treatment strategy to identify women at low risk of disease recurrence based on Ki67 after 2 and 12 weeks of NET and PEPI score at surgery after 6 months of NET.

FUTURE DIRECTIONS

Neoadjuvant Endocrine Therapy in Combination with Other Drugs

Endocrine therapy has been tested in combination with a variety of other drugs as neoadjuvant therapy in patients with breast cancer. The Celecoxib Anti-Aromatase Neoadjuvant (CAAN) trial evaluated the efficacy of combing an AI and cyclooxygenase-2 inhibitor as neoadjuvant therapy in postmenopausal patients with invasive hormone-sensitive breast cancer.[53] Patients were randomly assigned to receive exemestane plus celecoxib, exemestane, or letrozole. All groups showed clinical responses; however there was no significant difference in clinical response seen with the addition of celecoxib.

Baselga and colleagues[54] explored whether sensitivity to letrozole was enhanced with the mechanism target of rapamycin (mTOR) inhibitor, everolimus. Postmenopausal women with operable ER-positive breast cancer received neoadjuvant treatment with letrozole and either everolimus or placebo. The response rate by clinical palpation in the everolimus arm was higher than that with letrozole alone (68.1% v 59.1%). Furthermore, an antiproliferative response (reduction in Ki67 expression to natural logarithm of percentage positive Ki67 of <1 at day 15), occurred in 57% of patients in the everolimus arm and in 30% in the placebo arm ($P<.01$). Thus, everolimus increased letrozole efficacy in the neoadjuvant setting.

Lapatinib, a dual inhibitor of the tyrosine kinase activity of EGFR and HER2, in combination with letrozole was evaluated by Guarneri and colleagues[55] as neoadjuvant therapy in postmenopausal women with HR-positive/HER2-negative tumors. Patients received either letrozole plus lapatinib or letrozole plus placebo. The clinical response rates of both groups were similar, with the letrozole plus lapatinib combination group having slightly better response results (70% for letrozole + lapatinib and 63% for letrozole + placebo).

The NeoPalAna trial reported by Ma and colleagues[56] assessed the antiproliferative activity of the CDK4/6 inhibitor palbociclib in patients with clinical stage II/III, ER-positive, HER2-negative breast cancer. They received anastrozole daily for 4 weeks, followed by the addition of palbociclib daily for four 28-day cycles. Anastrozole was continued until surgery. The primary endpoint was complete cell-cycle arrest: central Ki67 $\leq$2.7% (CCCA). The CCCA rate was significantly higher after adding palbociclib to anastrozole, demonstrating additional proliferation suppression with combination therapy (**Table 8**).

Current Ongoing Clinical Trials

NET has been used to downstage tumors prior to surgery, assess response for prognostic information, investigate mechanisms of endocrine resistance, and facilitate novel trial design. NET in postmenopausal women with locally advanced ER-positive breast cancer may result in a reduction in tumor size either improving the chances of BCT or rendering an inoperable tumor operable. Patients in neoadjuvant endocrine studies who switch to NCT after a poor response to endocrine therapy have low pCR rates, suggesting that AI resistance in ER-rich tumors is not associated with an enhanced chemotherapy response.[36]

The ability to identify good and poor responses to NET early in treatment provides a strategy to triage poor responders into clinical trials of targeted agents to address endocrine resistance. Multiple trials are ongoing that combine molecularly targeted agents with endocrine therapy in the neoadjuvant setting. NeoPalAna is enrolling the endocrine-resistant population based on high Ki67 on endocrine therapy to receive the combination of the CDK4/6 inhibitor palbociclib and anastrozole to

Table 8
Neoadjuvant endocrine therapy in combination with other drugs

Source (Trial Name)	No.	Patient Characteristics	Study Arms	Duration (Wk)	Primary Endpoint	Response (per Primary Endpoint)
Chow et al,[53] 2008 (CAAN)	82	Postmenopausal ER^+ and/or PR^+	A. Exemestane B. Exemestane + celecoxib C. Letrozole	12	OR by caliper measurements	A. 55% B. 59% C. 62%
Baselga et al,[54] 2009	270	Postmenopausal ER^+, operable	A. Letrozole + everolimus B. Letrozole + placebo	16	CR by palpation	A. 68.1% B. 59.1%
Guarneri et al,[55] 2014	92	Post-menopausal $HR^+/HER2^-$ operable	A. Letrozole + lapatinib B. Letrozole + placebo	24	OR by ultrasound measurements	A. 70% B. 63%
Ma et al,[56] 2017 (NeoPalAna)	50	$ER^+/HER2^-$	Anastrozole (+ goserelin if premenopausal) followed by palbociclib (C1D1) for four 28-d cycles	25	CCCA after adding palbociclib to anastrozole	C1D1 26% vs C1D15 87%

Abbreviations: C1D1, cycle 1 day 1; C1D15, cycle 1 day 15.

Table 9
Current ongoing clinical trials

Clinical Trial	Study Arms	Phase	Sponsor
Neoadjuvant Endocrine Therapy vs Chemotherapy in Premenopausal Patients With ER^+ & $HER2^-$ Breast Cancer	A. Goserelin + tamoxifen + AI B. EC + fluorouracil	3	Peking University
Neoadjuvant Aromatase Inhibitor With Ovarian Suppression vs Chemotherapy in Premenopausal Breast Cancer Patients (COMPETE)	A. Goserelin + exemestane or anastrozole B. Docetaxel + EC	3	Ruijin Hospital
Letrozole Plus Ribociclib or Placebo as Neo-adjuvant Therapy in ER-positive, HER2-negative Early Breast Cancer (FELINE)	A. Letrozole + placebo B. Letrozole + ribociclib	2	University of Kansas Medical Center
Endocrine Treatment Alone for Elderly Patients With Estrogen Receptor Positive Operable Breast Cancer and Low Recurrence Score	A. Goserelin B. Anastrozole C. Exemestane D. Fulvestrant E. Tamoxifen	2	Washington University School of Medicine
Durvalumab and Endocrine Therapy in ER^+/$Her2^-$ Breast Cancer After CD8+ Infiltration Effective Immune-Attractant Exposure (ULTIMATE)	A. Tremelimumab + exemestane B. Durvalumab + exemestane	2	UNICANCER
Fulvestrant and/or Anastrozole in Treating Postmenopausal Patients With Stage II-III Breast Cancer Undergoing Surgery	A. Fulvestrant + anastrozole B. Anastrozole C. Fulvestrant	3	Alliance for Clinical Trials in Oncology
Neoadjuvant Letrozole Plus Metformin vs Letrozole Plus Placebo for ER-positive Postmenopausal Breast Cancer	A. Letrozole + metformin B. Letrozole + placebo	2	Seoul National University Hospital
Neoadjuvant Lenvatinib Combined With Letrozole in Hormone Receptor Positive Breast Cancer	A. Lenvatinib + letrozole	1, 2	National University Hospital, Singapore
A Trial of Neoadjuvant Everolimus Plus Letrozole vs FEC in Women With ER-positive, HER2-negative Breast Cancer	A. Everolimus + letrozole B. Fluorouracil + EC	2	Sun Yat-Sen Memorial Hospital of Sun Yat-Sen University
Neoadjuvant Trastuzumab and Letrozole for Postmenopausal Women (HERAKLES)	A. Trastuzumab + letrozole	2	Gangnam Severance Hospital
A Phase II Randomized Study Evaluating the Biological and Clinical Effects of the Combination of Palbociclib With Letrozole as Neoadjuvant Therapy in Post-Menopausal Women With Estrogen-Receptor Positive Primary Breast Cancer (PALLET)	A. Letrozole + palbociclib	2	NSABP Foundation Inc

Data from https://clinicaltrials.gov/. Accessed May 1, 2017.

overcome endocrine resistance (NCT01723774). An in-depth understanding of endocrine resistance mechanisms is needed for successful development of targeted agents. The neoadjuvant setting provides a unique research platform to expedite the evaluation of novel therapeutics to improve the outcome of patients with ER-positive breast cancer (**Table 9**).

SUMMARY

NET can be effective at downstaging patients with ER-positive tumors and identifying those tumors that are endocrine sensitive and endocrine resistant. The optimal prognostic markers for stratification are under investigation. Use of NET allows the identification of patients with ER-positive tumors with a good response to endocrine therapy who might avoid chemotherapy and those who may benefit from additional treatment based on endocrine resistance.

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