The Clinical Impact of Neoadjuvant Endocrine Treatment On Luminal-Like Breast Cancers and Its Prognostic Significance: Results From a Single-institution Prospective Cohort Study

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Abstract

Purpose: Neoadjuvant endocrine treatment (NET) has become a useful tool for the downstaging of luminal-like breast cancers in postmenopausal patients. It enables us to increase breast conserving surgery (BCS) rates, and provides an opportunity for assessing *in vivo* NET effectiveness and studying any biological changes that may act as valid biomarkers. The purpose of this study was to evaluate the safety and effectiveness of NET, and to assess the role of Ki67 proliferation rate changes as an indicator of endocrine responsiveness.

Methods: From 2016 to 2020, a single-institution cohort of patients treated with NET and further surgery was evaluated. In patients with $Ki67 \geq 10\%$, a second core biopsy was performed after four weeks. Information regarding histopathological and clinical changes was gathered.

Results: A total of 115 estrogen receptor positive (ER+)/HER2 negative patients were included. The median treatment duration was 5.0 months (IQR: 2.0-6.0). Median maximum size in the surgical sample was 40% smaller than pretreatment size measured by ultrasound ($p < .0001$). Median pretreatment Ki67 expression was 20.0% (IQR: 12.0-30.0), and was reduced to 5.0% (IQR: 1.8-10.0) after four weeks, and to 2.0% (IQR: 1.0-8.0) in the surgical sample ($p < .0001$). BCS was performed on 98 patients (85.2%). No pathological complete responses were recorded. A larger Ki67 fold-change after four weeks was significantly related to a PEPI score of 0 ($p < .002$). No differences were observed between luminal A- and B-like tumors with regard to fold-change and PEPI score.

Conclusions: In our cohort, NET has proven effective for tumor size and Ki67 downstaging. This results in a higher rate of conservative surgery, aids in therapeutic decision-making, provides prognostic information, and constitutes a safe and well-tolerated approach

Introduction

Neoadjuvant treatment with chemotherapy (NCT) is a widely accepted approach for high-risk or locally advanced breast cancers that enables both tumor size and axilla involvement to be downstaged, and it has been crucial for the development of new drugs and the study of biomarkers. However, NET has taken longer to implement. Traditionally, these therapies were relegated to frail or elderly patients who were not candidates for chemotherapy or surgery, [1–3] and it is only in recent years that the results of multiple prospective trials have made NET a very attractive therapeutic option for postmenopausal patients with estrogen receptor positive (ER+)/HER2- tumors.[4–8] It produces good clinical responses, thus increasing BCS rates, and it also offers a unique opportunity for research. Most international guidelines have already included NET among their validated treatments for postmenopausal women with ER+/HER2- breast cancer.[9–11]

The key point when neoadjuvant treatments are to be used is to make an accurate assessment of the *in vivo* response to therapy. The changes observed on imaging tests (ultrasound, mammography, MRI) provide guidance in both NCT and NET,[12–15] but no accurate biomarker of response has yet been

identified for NET. Nevertheless, the short-term assessment of Ki67 levels does seem to correlate closely with the degree of response. A Ki67 reduction may occur after only a few weeks from the initiation of treatment, indicating a cell-cycle arrest induced by therapy, resulting from endocrine responsiveness.[16–19] On the other hand, high Ki67 levels after NET would suggest innate tumor resistance. A Ki67>10% after two to four weeks of endocrine therapy has been suggested as a cutoff for the early identification of nonresponders with increased risk of relapse, and it is currently considered by many authors in various trials as the necessary threshold for maintaining or withdrawing NET.[19–21]

Residual cancer burden (RCB) and pathological complete response (pCR) are considered accurate surrogate markers of response after NCT, mainly in high-risk breast cancer,[22] however, low rates of pCR in luminal tumors, with both NCT and NET, do not correlate with worse outcomes. Ellis *et al.* developed the Preoperative Endocrine Prognostic Index (PEPI) score, a prognostic model that incorporated standard pathologic staging variables and “on-treatment” biomarker values.[5] Consequently, low PEPI scores are related to low recurrence risk. Although randomized NET trials, with or without other drug combinations, are numerous, real-world data, reflecting clinical practice, are scarce in this field.[23]

The aim of this study was to analyze a prospective cohort of patients in our institution who had been treated with NET and subsequently operated on, evaluating the safety (adherence and treatment tolerance) and effectiveness of NET in tumoral downstaging. Furthermore, we wanted to assess the role and clinical applicability of Ki67 changes as an indicator of endocrine responsiveness and, therefore, of NET maintenance.

Methods

This was a prospective cohort study that included ER+/HER2- breast cancer patients treated with NET and subsequently operated on at our institution, a tertiary university center. Institutional Review Board approval of the study protocol was obtained. Inclusion criteria included: postmenopausal status; ER+/HER2- breast cancer diagnosis in core biopsy; tumor size >10mm; cN0-N2; and treatment initiated between 2016 and 2020. Patients with stage IV disease, previous NCT or unfit for surgery were excluded. An initial mammogram, together with breast and axillary ultrasound, were performed. Tumor size was determined according to its maximum diameter. Breast and/or axillary ultrasound were also used for follow-up. All patients were treated with letrozole 2.5mg daily, and this was continued until BCS was feasible or maximum tumor reduction was achieved. In those patients with Ki67 proliferation rate $\geq 10\%$, a second core biopsy was performed after four weeks (Figure 1).

Data were collected from patient charts, including: age; histological type (ductal, lobular, other); histologic grade (G1, G2, or G3); ER; progesterone receptor (PR), and Ki67 expression (%) pretreatment, intermedial, and in the surgical sample; clinical and pathological size (mm); clinical node status (positive, negative); clinical stage (TNM);[24] duration of treatment (months); surgical approach (lumpectomy or mastectomy) and upfront axillary surgery (Sentinel Lymph Node Biopsy [SLNB], targeted axillary dissection [TAD], Axillary Lymph Node Dissection [ALND], or none).

Immunohistochemistry for ER (clone EP1, prediluted, Dako) and PR (clone PgR 1294, prediluted, Dako) was performed according to international guidelines. Ki67 proliferation rate (clone MIB1, prediluted, Dako) was defined as the mean expression in the whole tumor area.[25] Negative HER2 status was confirmed by either immunohistochemistry (HercepTest, Dako) or by *in situ* fluorescent hybridization (IQFISH HER2, Dako) in equivocal cases. St. Gallen-2013 criteria for defining luminal A or B phenotypes were applied.[26] Changes in Ki67 proliferation rates were analyzed on the natural log-fold scale.

pCR was defined as absence of invasive disease in the breast and axilla (ypT0/is ypN0), and PEPI score was calculated as described by Ellis *et al.*[5]

We conducted descriptive analyses on the data collected. Categorical variables were described as frequency or percentage. Continuous variables were reported as median and interquartile range (IQR). Comparison of characteristics among variables was performed using the most appropriate test. The type 1 error rate (α) was set to 0.05. Statistical analyses were performed using SPSS v26 (IBM Corporation, Armonk, NY). We used the STROBE cohort reporting guidelines.[27]

Results

A total of 115 patients were included in the analysis. The characteristics of the cohort are described in Table 1.

Table 1
Patient, tumor, and treatment characteristics

	n	(%)
	115	(100.0)
Clinical Stage		
IA	46	(40.0)
IIA	45	(39.1)
IB	0	(0.0)
IIB	19	(16.5)
IIIA	5	(4.3)
Clinical node evaluation - cN		
negative	94	(81.7)
positive	21	(18.3)
Histological type		
Ductal	85	(73.9)
Lobular	23	(20.0)
Others	7	(6.1)
Histological grade		
1	24	(20.9)
2	77	(67.0)
3	14	(12.2)
Immunophenotype		
Luminal A-like	48	(41.7)
Luminal B-like	67	(58.3)
	median	(IQR)
Age (years)	69.0	(62.0-78.0)
Pre-NET Size (mm)	25.0	(17.0-40.0)

IQR InterQuartile Range, ER estrogen receptor; PR progesterone receptor

NET neoadjuvant endocrine therapy

	n	(%)
Pre-NET ER expression (%)	100	(100-100)
Pre-NET PR expression (%)	70	(20-100)
Pre-NET Ki67 (%)	20	(12-30)
NET duration (months)	5.0	(2.0-6.0)
IQR InterQuartile Range, ER estrogen receptor; PR progesterone receptor		
NET neoadjuvant endocrine therapy		

Clinical and Tumor Characteristics

Median age was 69.0 years old (IQR: 62.0-78.0), 69 (60.0%) patients were stage II-III, and 21 (18.3%) were cN1. Invasive ductal carcinoma comprised 73.9% (n=85) of the cases, while 20.0% (n=23) were invasive lobular carcinomas. Tumor grade was moderately differentiated (G2) in 67.0% (n=77) of the patients, and poorly differentiated (G3) in 12.2% (n=14) of the cases. Median pretreatment size was 25mm (IQR: 17.0-40.0). All the tumors had a 100% ER expression, while mean PR expression was 70% (IQR: 20.0-100.0). Median Ki67 proliferation rate was 20% (IQR: 12-30), and 58.3% (n=67) of the cases were luminal B-like.

Treatment Characteristics

Median duration of treatment with letrozole 2.5 mg daily was 5 months (IQR: 2-6). No clinical progression or treatment abandonment was reported.

BCS was feasible in 98 patients (85.2%). SLNB was performed on 86.9% (n=100) of the patients. On all but two cN0 patients (both elderly and with comorbidities), a SLNB was carried out (n=92). Sentinel lymph node (SN) was negative in 70 patients, while a micrometastasis was described in 9 cases. In 12 out of 13 cases with a positive SN, Z0011 criteria were considered, and an ALND was avoided. An upfront ALND was carried out on 13 (11.3%) of the 21 cN1 patients. As part of another study conducted at our facility, an SLNB, combined with TAD, was performed on eight women with low axillary burden. A further ALND was completed on three of these patients. Surgical management is summarized in Table 2 and axillary management in Figure 2.

Table 2
Pathological outcomes after NET

	n	%
	115	(100%)
Pathological complete response	0	(0.0)
Pathological node status		
ypN0	71	(62.7)
ypN1	44	(38.3)
PEPI score		
0	53	(46.1)
1	17	(14.8)
2	8	(7.0)
3	23	(20.0)
4	10	(8.7)
5	2	(1.7)
6	2	(1.7)
PEPI: Preoperative Endocrine Prognostic Index		

Adjuvant radiotherapy was used with 101 patients (87.8%), and chemotherapy was indicated for 29 patients (25.2%).

Pathological Changes after NET

Table 3 resumes the pathological and dynamic changes after NET. No cases of pCR were recorded. Fifty-three (46.1%) patients had a PEPI score of 0, and 23 (20.0%) had a PEPI score of 3. Forty-four patients (38.3%) were pN1, which indicates a false negative radiological detection rate (FNR) of 24.5%. Significant downgrading of tumor size, Ki67, PR expression, and histologic grade were observed. After four weeks of treatment, an intermediate biopsy was performed on 78 patients (67.8%), showing early changes in all these parameters. The reduction in Ki67 proliferation rates occurred most dramatically in the first four weeks, while thereafter their numbers tended to plateau. In two of the cases (2.6%) where an intermediate biopsy was carried out, an increase in Ki67 was reported. In these patients, NET was interrupted and surgery indicated. Tumor size decreased from an initial median of 25mm (IQR: 17-40) to a final median value of 15mm (IQR: 10-20), implying a 40% reduction. Histological downgrading was reported in 31 out of 91 patients with grade 2 and 3 tumors (34.1%). Initial mean PR expression was 70% (IQR: 20-100), falling to 4% (IQR: 0-35) in the intermediate biopsy and to 1% (IQR: 0-20) in the surgical sample. No

differences in Ki67 fold-change or PEPI score were observed between luminal A-like or B-like tumors. A larger Ki67 fold-change after four weeks was significantly related to a PEPI score of 0.

Table 3
Biological changes due to NET

		Pre-NET		Intermedial		Surgical sample	
		115		78		115	
		median	<i>I.Q.R</i>	median	<i>I.Q.R</i>	median	<i>I.Q.R</i>
Size (mm)		25.0	(17.0-40.0)	19.5	(13.0-30.0)	15.0	(10.0-20.0)
p	Pre-NET/Surgical	<.0001					
	Pre-NET/Intermed	<.0001					
	Intermed/Surgical	<.0001					
ER Expression (%)		100.0	(100.0-100.0)	100.0	(100.0-100.0)	100.0	(100.0-100.0)
p	Pre-NET/Surgical	<.05					
	Pre-NET/Intermed	<i>ns</i>					
	Intermed/Surgical	<i>ns</i>					
PR Expression (%)		70.0	(20.0-100.0)	4.0	(0.0-35.0)	1.0	(0.0-20.0)
p	Pre-NET/Surgical	<.0001					
	Pre-NET/Intermed	<.0001					
	Intermed/Surgical	<.005					
Ki67 (%)		20.0	(12.0-30.0)	5.0	(1.8-10.0)	2.0	(1.0-8.0)
p	Pre-NET/Surgical	<.0001					
	Pre-NET/Intermed	<.0001					
	Intermed/Surgical	<i>ns</i>					
Histological Grade		n	%	n	%	n	%
G1		24	(20.9)	26	(33.3)	55	(47.8)
G2		77	(67.0)	49	(62.7)	53	(46.1)
IQR InterQuartile Range, ER estrogen receptor; PR progesterone receptor, NET neoadjuvant endocrine therapy							

		Pre-NET		Intermedial		Surgical sample	
G3		14	(12.2)	3	(4.0)	7	(6.1)
p	Pre-NET/Surgical	<.0001					
	Pre-NET/Intermed	<.0001					
	Intermed/Surgical	<.0001					
IQR InterQuartile Range, ER estrogen receptor; PR progesterone receptor, NET neoadjuvant endocrine therapy							

Discussion

One of the main issues when using NET is the appropriate selection of patients. As is the case with endocrine adjuvant therapy (ET), NET should be considered for luminal-like tumors; however, although ET is recommended for tumors with even low ER levels,[10, 26] NET is normally used only with high ER expression tumors, since most trials have achieved better results in these cases.[28, 29] In our cohort, all 115 tumors had a diffuse ER expression, which could explain the high response rate we found. PR expression and/or Ki67 levels can also influence NET outcomes.[30] As a result, many authors recommend NET only for luminal A-like tumors, because initially low PR expression or high Ki67 levels (i.e. luminal B-like features) have been associated with a poorer response[29, 31]. However, we included in our study both luminal A- and luminal B-like tumors, and we did not find significant differences between them with regard to clinical-biological response or BCS rates, which could mean that NET may be a good approach even in those cases. HER2 overexpression or high histologic grade usually discourages the use of NET.[29, 31] Although a few studies (IMPACT, P024)[4, 6] included small subpopulations of HER2 positive, reporting over 50% of clinical response, we excluded ER+/HER2+ patients from our study. A higher histologic grade is considered a poor prognostic factor; consequently, many of these tumors are eligible for chemotherapy. Nevertheless, in our study we observed a decrease in Ki67 levels, as well as in size, in most of these G3 cases. Additionally, up to 80% of these tumors changed to an intermediate grade after four weeks of treatment, although some of them were classified again as G3 in the surgical sample. It is difficult to know why a few of these tumors initially modify their histologic grade and, later, go back to a higher grade, although sampling bias or a limited amount of tissue in the core biopsy could explain these findings. In any case, all these observations could imply that these types of tumor, in well-selected cases, may benefit from NET.

NET duration is usually established at 3 to 6 months, based on the regular duration of NCT, although the optimal period for this therapy has not yet been clearly determined. Several trials have been conducted to establish an optimal duration.[32–34] Most of them found that a prolongation of NET produced extra benefits, such as higher pCR rates or axillary downstaging,[35, 36] although good responses and BCS rates can be achieved with a NET duration of six months or less.[3] The mean duration in our cohort was

five months, becoming longer as we got more comfortable with NET implementation, and at all times it was conditioned in light of the response, either a decrease in Ki67 proliferation rates or clinical-radiological changes.

As mentioned above, NET provides an opportunity for assessing the *in vivo* response of ER+ breast cancers. In our cohort, significant downgrading changes were observed with regard to Ki67 levels, size, histological grade, and PR expression. Ki67 is a nuclear antigen expressed in proliferating tissues and is considered a surrogate marker of cell proliferation. Reduction in Ki67 proliferation rate has been identified only a few days from the initiation of NET.[6, 19] We found a significant decline in Ki67 expression after four weeks, and this was usually maintained throughout treatment, although in a few cases its value increased. The changes that appear in the Ki67 proliferation rate with NET constitute a biomarker with prognostic and predictive power, much more precisely related to long-term results than baseline Ki67.[17, 19, 20, 25] As demonstrated in the POETIC trial, patients with initially low Ki67 levels, or low postaromatase inhibitor-induced Ki67 proliferation rates, probably do well enough with standard endocrine therapy, whereas those with high Ki67 scores might need further adjuvant treatments.[19] A Ki67 >10% after two to four weeks of endocrine therapy has been suggested as a cutoff for early identification of nonresponders with increased risk of relapse.[20] Like other authors in various trials,[37, 38] we consider a Ki67 >10% after four weeks to be an indicator of innate endocrine resistance and, therefore, a criterion for withdrawing NET. For most of the patients who did not lower their Ki67 proliferation rates, surgery was then indicated.

Most of the tumors in our cohort were T2. Maximum tumor diameter was reduced by 40%, which probably indicates a much larger volume decrease. This enabled BCS to be performed on over 85% of the patients, these being numbers that are hardly possible in average conditions [39] and slightly larger than other likely figures for BCS reported after NET,[40, 41] although they may be explained by a mean tumor size that was not excessively large. Downstaging in the axilla was not achieved, since all cN1 tumors were at least pN1 and some cN0 tumors were pN1 after NET. In our cohort, ultrasound FNR was close to 25%, which is consistent with rates published by other authors who find higher FNR in luminal tumors. [42–46] On the other hand, axillary downstaging with NET is rather uncommon, with nodal pCR rates ranging from 1.3%-3.0%, at least when it is applied over short periods (<6 months),[35, 36, 47] as happened with most of our patients. As pointed out by both Hammond and Ruzs *et al.*, these numbers could be increased with longer periods of NET.[37, 48] Axillary management after NET is not well defined in clinical guidelines. Most surgeons seem to apply the same criteria to NET as they do to NCT,[49] but the context of NCT (mainly because it is usually indicated for high-risk tumors) does not seem applicable to NET, since any low-burden disease left in the axilla may not significantly impact the prognosis.[50] Kantor *et al.* analyzed the type of axillary surgery and residual nodal disease burden after NET in over 6,500 patients, finding limited axillary disease (ypN1) in more than 90% of the cases. [50] In the study published by Weiss *et al.* including stage II-III ER+/HER2- patients, those receiving NET (2,138) were more likely to be managed with an SLNB than those treated with NCT.[51] Based on this, we consider that Z0011 criteria for avoiding axillary dissection can be safely applied to these patients, as they can to those who go

through upfront surgery. Therefore, only a small percentage of patients in our cohort needed an axillary dissection, and an SLNB was feasible in most cases.

In luminal-like breast cancers, pCR is infrequent with both NET and NCT. In the meta-analysis published by Spring *et al.*, pCR rates were <10% in both the NCT and the NET arms.[52] In any case, the absence of pCR does not impact survival as much as happens with triple negative or HER2+ tumors,[22] meaning that it is not an optimal indicator of outcomes after NET. No cases of pCR were reported in our cohort. The PEPI score constitutes a validated prognostic model[5] that could be analogous to pCR with an escalation of therapy for those patients with PEPI > 0 and a de-escalation (avoiding chemotherapy) for patients with PEPI=0 status. In our cohort, almost half of the patients presented a PEPI score of 0. We also found that a larger Ki67 decrease after four weeks of treatment was related to a lower PEPI score, meaning that Ki67 changes indicate a higher responsiveness to NET, with prognostic implications, and NET continuation should be discouraged when the Ki67 rate does not readily decline. One inconvenience of the PEPI score is that nodal involvement is a qualitative measurement, so a positive axilla always implies a score ≥ 3 , regardless of whether one or more than three nodes are involved. Nevertheless, a rigid parallelism between a nodal involvement and chemotherapy should be avoided, as recently demonstrated in the Rxponder trial where most of the ER+/HER2- tumors in postmenopausal women with 1-3 nodes involved had a low recurrence score and, therefore, would not have benefited from chemotherapy.[53] Consequently, response to NET may be a helpful tool to guide adjuvant treatments. Interestingly, the findings of the Z1031 trial show that tumors that do not lower Ki67 after two to four weeks also fail to respond well to chemotherapy, indicating an intrinsic endocrine resistance, which makes it essential to consider alternative therapies.[20] Genomic profiling performed on diagnostic core biopsies can also provide useful information for predicting NET response or endocrine resistance, although larger prospective studies in this area are necessary in order to establish which group of genes can provide the maximum information, and therefore act as a reliable biomarker.[3] In our study, a poor response to NET, as well as other risk factors such as a large nodal involvement, were considered when indicating adjuvant chemotherapy, which was necessary in one fourth of our patients.

The value of our study is that it is based on a single-institution prospective cohort and the use, outside a clinical trial, of Ki67 reduction as a clinical tool for maintaining or withdrawing NET. The early decline in Ki67 levels is a sensitive biomarker of endocrine responsiveness, with very remarkable prognosis implications. This allows NET to be offered safely to a broader range of patients, including those with luminal-B features, provided that a reduction in the Ki67 proliferation rate is recorded. Nevertheless, we acknowledge that there are limitations in our study, because of the nonrandomization of patients as well as the short-term follow-up. Only mild adverse effects were reported, and no treatment abandonment occurred, which is consistent with data from other studies.[23]

In conclusion, results from our study indicate that NET can be considered a safe and effective alternative for postmenopausal women with ER+/HER2- breast cancer and that it increases the rates of BCS in both luminal A-like and luminal B-like tumors. Early changes in Ki67 proliferation rates become a feasible and reliable tool that provides crucial information about endocrine responsiveness and patient prognosis.

Declarations

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Conflicts of Interest: The authors declare no conflict of interest

References

1. Morgan JL, Reed MW, Wyld L (2014) Primary endocrine therapy as a treatment for older women with operable breast cancer - A comparison of randomised controlled trial and cohort study findings. *Eur J Surg Oncol* 40(6):676–684
2. Sella T, Weiss A, Mittendorf EA, King TA, Pilewskie M, Giuliano AE et al Neoadjuvant Endocrine Therapy in Clinical Practice: A Review. *JAMA Oncol* 2021 Nov 1;7(11):1700-1708
3. Martí C, Sánchez-Méndez JI (2021) The Present and Future of Neoadjuvant Endocrine Therapy for Breast Cancer Treatment. *Cancers (Basel)* 13(11):1–26
4. Eiermann W, Paepke S, Appfelstaedt J, Llombart-Cussac A, Eremin J, Vinholes J et al (2001) Preoperative treatment of postmenopausal breast cancer patients with letrozole: A randomized double-blind multicenter study. *Ann Oncol* 12(11):1527–1532
5. Ellis MJ, Tao Y, Luo J, A'Hern R, Evans DB, Bhatnagar AS et al (2008) Outcome prediction for estrogen receptor-positive breast cancer based on postneoadjuvant endocrine therapy tumor characteristics. *J Natl Cancer Inst* 100(19):1380–1388
6. Smith IE, Dowsett M, Ebbs SR, Dixon JM, Skene A, Blohmer JU et al (2005) Neoadjuvant treatment of postmenopausal breast cancer with anastrozole, tamoxifen, or both in combination: The Immediate Preoperative Anastrozole, Tamoxifen, or Combined With Tamoxifen (IMPACT) multicenter double-blind randomized trial. *J Clin Oncol* 23(22):5108–5116
7. Dixon JM, Love CDB, Bellamy COC, Cameron DA, Leonard RCF, Smith H et al (2001) Letrozole as primary medical therapy for locally advanced and large operable breast cancer. *Breast Cancer Res Treat* 66(3):191–199
8. Cataliotti L, Buzdar AU, Noguchi S, Bines J, Takatsuka Y, Petrakova K et al (2006) Comparison of anastrozole versus tamoxifen as preoperative therapy in postmenopausal women with hormone receptor-positive breast cancer: The Pre-Operative “Arimidex” Compared to Tamoxifen (PROACT) trial. *Cancer* 106(10):2095–2103
9. Cardoso F, Senkus E, Costa A, Papadopoulos E, Aapro M, André F et al (2018) 4th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 4). *Ann Oncol* 29(8):1634–1657
10. Burstein HJ, Curigliano G, Loibl S, Dubsy P, Gnant M, Poortmans P et al (2019) Estimating the benefits of therapy for early-stage breast cancer: The St. Gallen International Consensus Guidelines for the primary therapy of early breast cancer 2019. *Ann Oncol* 30(10):1541–1557

11. Korde LA, Somerfield MR, Carey LA, Crews JR, Denduluri N, Hwang ES et al (2021) Neoadjuvant Chemotherapy, Endocrine Therapy, and Targeted Therapy for Breast Cancer: ASCO Guideline. *J Clin Oncol* 39(13):1485–1505
12. Fowler AM, Mankoff DA, Joe BN (2017) Imaging neoadjuvant therapy response in breast cancer. *Radiology* 285(2):358–375
13. Hilal T, Covington M, Kosiorek HE, Zwart C, Ocal IT, Pockaj BA et al (2018) Breast MRI phenotype and background parenchymal enhancement may predict tumor response to neoadjuvant endocrine therapy. *Breast J* 24(6):1010–1014
14. Zhang K, Li J, Zhu Q, Chang C (2020) Prediction of pathologic complete response by ultrasonography and magnetic resonance imaging after neoadjuvant chemotherapy in patients with breast cancer. *Cancer Manag Res* 12:2603–2612
15. Takeda K, Kanao S, Okada T, Ueno T, Toi M, Ishiguro H et al (2012) MRI evaluation of residual tumor size after neoadjuvant endocrine therapy vs. neoadjuvant chemotherapy. *Eur J Radiol* 81(9):2148–2153
16. Urruticoechea A, Smith IE, Dowsett M (2005) Proliferation marker Ki-67 in early breast cancer. *J Clin Oncol* 23(28):7212–7220
17. Dowsett M, Smith IE, Ebbs SR, Dixon JM, Skene A, Griffith C et al (2005) Short-term changes in Ki-67 during neoadjuvant treatment of primary breast cancer with anastrozole or tamoxifen alone or combined correlate with recurrence-free survival. *Clin Cancer Res* 11(2 II):951–959
18. Ellis MJ (2017) Lessons in precision oncology from neoadjuvant endocrine therapy trials in ER+ breast cancer. *Breast* 34:S104–S107
19. Smith I, Robertson J, Kilburn L, Wilcox M, Evans A, Holcombe C et al (2020) Long-term outcome and prognostic value of Ki67 after perioperative endocrine therapy in postmenopausal women with hormone-sensitive early breast cancer (POETIC): an open-label, multicentre, parallel-group, randomised, phase 3 trial. *Lancet Oncol* 21(11):1443–1454
20. Ellis MJ, Suman VJ, Hoog J, Goncalves R, Sanati S, Creighton CJ et al (2017) Ki67 proliferation index as a tool for chemotherapy decisions during and after neoadjuvant aromatase inhibitor treatment of breast cancer: Results from the American college of surgeons oncology group Z1031 trial (alliance). *J Clin Oncol* 35(10):1061–1069
21. Martí C, Sánchez-Méndez JI (2020) Neoadjuvant endocrine therapy for luminal breast cancer treatment: A first-choice alternative in times of crisis such as the COVID-19 pandemic. *Ecancermedicalscience* 14:1–6
22. Cortazar P, Zhang L, Untch M, Mehta K, Costantino JP, Wolmark N et al (2014) Pathological complete response and long-term clinical benefit in breast cancer: The CTNeoBC pooled analysis. *Lancet* 384(9938):164–172
23. da Silva LR, de Andrade CA, Brenelli F, Ramalho S, Reinert T, de Souza ABA et al (2021) Real-world data on neoadjuvant endocrine therapy in ER-positive/HER2-negative breast cancer. *Breast Cancer Res Treat* 186(3):753–760

24. Amin MB, Edge S, Greene F, Byrd DR, Brookland RK, Washington MK, Gershenwald JE, Compton CC, Hess KR et al (2017) AJCC Cancer Staging Manual (8th edition). Springer I. New York; Part 11
25. Dowsett M, Nielsen TO, A'Hern R, Bartlett J, Coombes RC, Cuzick J et al (2011) Assessment of Ki67 in Breast Cancer: Recommendations from the international Ki67 in breast cancer working Group. *J Natl Cancer Inst* 103(22):1656–1664
26. Goldhirsch A, Winer EP, Coates AS, Gelber RD, Piccart-Gebhart M, Therasse P, Gnanty M, Arzoo Z, Haidich A, Goss D, Pritchard K, Buzdar A, Winer E, Barlow W, Barlow J, Arzoo Z, Haidich A, Goss D, Pritchard K, Buzdar A (2013) Personalizing the treatment of women with early breast cancer: Highlights of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2013. *Ann Oncol* 24(9):2206–2223
27. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP (2008) The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *J Clin Epidemiol* 61(4):344–349
28. Krauss K, Stickeler E (2020) Endocrine Therapy in Early Breast Cancer. *Ann Oncol* 31(3):337–346
29. Arthur LM, Turnbull AK, Khan LR, Dixon JM (2017) Pre-operative Endocrine Therapy. *Curr Breast Cancer Rep* 9(4):202–209
30. Cui X, Schiff R, Arpino G, Osborne CK, Slamon TJ (2005) Biology of progesterone receptor loss in breast cancer and its implications for endocrine therapy. *J Clin Oncol* 23(30):7721–7735
31. Rastelli F, Crispino S (2008) Factors predictive of response to hormone therapy in breast cancer. *Tumori* 94(3):370–383
32. Van Dam PA, Van Dam VCN, Altintas S, Papadimitriou K, Rolf C, Trinh XB (2016) Neoadjuvant endocrine treatment in early breast cancer: An overlooked alternative? *Eur J Surg Oncol* 42(3):333–342
33. Dixon JM, Renshaw L, MacAskill EJ, Young O, Murray J, Cameron D et al (2009) Increase in response rate by prolonged treatment with neoadjuvant letrozole. *Breast Cancer Res Treat* 113(1):145–151
34. Allevi G, Strina C, Andreis D, Zanoni V, Bazzola L, Bonardi S et al (2013) Increased pathological complete response rate after a long-term neoadjuvant letrozole treatment in postmenopausal oestrogen and/or progesterone receptor-positive breast cancer. *Br J Cancer* 108(8):1587–1592
35. Carpenter R, Doughty JC, Cordiner C, Moss N, Gandhi A, Wilson C et al (2014) Optimum duration of neoadjuvant letrozole to permit breast conserving surgery. *Breast Cancer Res Treat* 144(3):569–576
36. Montagna G, Sevilimedu V, Fornier M, Jhaveri K, Morrow M, Pilewskie ML (2020) How Effective is Neoadjuvant Endocrine Therapy (NET) in Downstaging the Axilla and Achieving Breast-Conserving Surgery? *Ann Surg Oncol* 27(12):4702–4710
37. Rusz O, Vörös A, Varga Z, Kelemen G, Uhercsák G, Nikolényi A et al (2015) One-Year Neoadjuvant Endocrine Therapy in Breast Cancer. *Pathol Oncol Res* 21(4):977–984
38. Ma CX, Suman VJ, Leitch AM, Sanati S, Vij KR, Unzeitig GW et al (2020) ALTERNATE: Neoadjuvant endocrine treatment (NET) approaches for clinical stage II or III estrogen receptor-positive HER2-negative breast cancer (ER+ HER2- BC) in postmenopausal (PM) women: Alliance A011106. *J Clin Oncol* ; 38, 15_suppl 504-504

39. Hofmann D, Nitz U, Gluz O, Kates RE, Schinkoethe T, Staib P et al (2013) WSG ADAPT - adjuvant dynamic marker-adjusted personalized therapy trial optimizing risk assessment and therapy response prediction in early breast cancer: adjuvant dynamic marker-adjusted personalized therapy trial optimizing risk assessment and therapy response prediction in early breast cancer: Study protocol for a prospective, multi-center, controlled, non-blinded, randomized, investigator initiated phase II/III trials. *Trials* 14:261
40. Chen K, Li S, Li Q, Zhu L, Liu Y, Song E et al (2016) Breast-conserving surgery rates in breast cancer patients with different molecular subtypes an observational study based on surveillance, epidemiology, and end results (SEER) database. *Med (United States)* 95(8):1–6
41. Li JJ, Shao ZM (2016) Endocrine therapy as adjuvant or neoadjuvant therapy for breast cancer: Selecting the best agents, the timing and duration of treatment. *Chinese Clin Oncol* 5(3):1–12
42. Hammond JB, Scott DW, Kosiorek HE, Parnall TH, Gray RJ, Ernst BJ, Northfelt DW, McCullough AE, Ocal IT, Pockaj BA, Cronin PA Characterizing Occult Nodal Disease Within a Clinically Node-Negative, Neoadjuvant Breast Cancer Population. *Clin Breast Cancer*. 2021 Jul 25:S1526-8209(21)00194-4. Epub ahead of print
43. Takei H, Kurosumi M, Yoshida T, Hayashi Y, Higuchi T, Uchida S et al (2011) Neoadjuvant endocrine therapy of breast cancer: Which patients would benefit and what are the advantages? *Breast Cancer* 18(2):85–91
44. Kane G, Fleming C, Heneghan H, McCartan D, James P, Trueick R et al (2019) False-negative rate of ultrasound-guided fine-needle aspiration cytology for identifying axillary lymph node metastasis in breast cancer patients. *Breast J* 25(5):848–852
45. Hotton J, Salleron J, Henrot P, Buhler J, Leufflen L, Rauch P et al (2020) Pre-operative axillary ultrasound with fine-needle aspiration cytology performance and predictive factors of false negatives in axillary lymph node involvement in early breast cancer. *Breast Cancer Res Treat* 183(3):639–647
46. Helfgott R, Mittlböck M, Miesbauer M, Moynfar F, Haim S, Mascherbauer M et al (2019) The influence of breast cancer subtypes on axillary ultrasound accuracy: A retrospective single center analysis of 583 women. *Eur J Surg Oncol* 45(4):538–543
47. Schipper R, Bruijn A, De, Voogd AC, Bloemen JG, Riet YE, Van, Vriens BEP et al (2021) Rate and predictors of nodal pathological complete response following neoadjuvant endocrine treatment in clinically biopsy-proven node- positive breast cancer patients. *Eur J Surg Oncol* 47(8):1928–1933
48. Hammond JB, Parnall TH, Scott DW, Kosiorek HE, Pockaj BA, Ernst BJ et al (2020) Gauging the efficacy of neoadjuvant endocrine therapy in breast cancer patients with known axillary disease. *J Surg Oncol* 122(4):619–622
49. Kantor O, Wong S, Weiss A, Metzger O, Mittendorf EA, King TA (2020) Prognostic significance of residual nodal disease after neoadjuvant endocrine therapy for hormone receptor-positive breast cancer. *Breast Cancer* 6(1):5–10
50. Kantor O, Wakeman M, Weiss A, Wong S, Laws A, Grossmith S et al (2021 Mar) Axillary Management After Neoadjuvant Endocrine Therapy for Hormone Receptor-Positive Breast Cancer. *Ann Surg Oncol*

51. Weiss A, Wong S, Golshan M, Freedman RA, Metzger O, Bellon J et al (2019) Patterns of Axillary Management in Stages 2 and 3 Hormone Receptor-Positive Breast Cancer by Initial Treatment Approach. *Ann Surg Oncol* 26(13):4326–4336
52. Spring LM, Gupta A, Reynolds KL, Gadd MA, Ellisen LW, Isakoff SJ et al (2016) Neoadjuvant endocrine therapy for estrogen receptor-positive breast cancer a systematic review and meta-Analysis. *JAMA Oncol* 2(11):1477–1486
53. Kalinsky K, Barlow WE, Meric-Bernstam F, Gralow JR, Albain KS et al (2021) First results from a phase III randomized clinical trial of standard adjuvant endocrine therapy (ET) +/- chemotherapy (CT) in patients (pts) with 1-3 positive nodes, hormone receptor-positive (HR+) and HER2-negative (HER2-) breast cancer (BC) with recurrence score (RS) < 25: SWOG S1007 (RxPonder). In *Cancer Research* 81(4S):GS3–G00

Figures

Figure 1

Study protocol

CB: core biopsy; wk: week; mo:month; US: ultrasound

Figure 2

Axillary management

NET neoadjuvant endocrine therapy, SLNB Sentinel Lymph Node Biopsy, TAD: Targeted Axillary Dissection, ALND: Axillary Lymph Node Dissection

Figure 3

a Phenotype and Fold Change,

b PEPI score and Fold Change