Published in final edited form as:

Ann Surg Oncol. 2020 November ; 27(12): 4702–4710. doi:10.1245/s10434-020-08888-7.

How Effective Is Neoadjuvant Endocrine Therapy (NET) in Downstaging the Axilla and Achieving Breast-Conserving Surgery?

Giacomo Montagna, MD¹, Varadan Sevilimedu, DrPH², Komal Jhaveri, MD³, Monica Morrow, MD¹, Melissa L. Pilewskie, MD¹

¹Breast Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY;

²Biostatistics Service, Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY;

³Breast Medicine Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY

Abstract

Introduction.—NET is effective in downstaging large hormone receptor positive (HR+) breast cancers (BCs) and increasing rates of breast-conserving surgery (BCS), but data regarding nodal pathological complete response (pCR) are sparse. We compared nodal and breast downstaging with NET, and axillary response rates after NET and neoadjuvant chemotherapy (NAC).

Methods.—Consecutive stage I–III BC patients treated with NET and surgery from 1/2009–12/2019 were identified from a prospectively maintained database. Nodal pCR rates were compared between biopsy-proven node-positive patients treated with NET, and HR+/HER2– patients treated with NAC from 11/2013–07/2019.

Results.—127 cancers treated with NET and 338 with NAC were included. NET recipients were older, more likely to have lobular and lower-grade tumors, and higher HR expression. With NET, the nodal pCR rate was 4/38 (11%) of biopsy-proven cases, and the breast pCR rate was 2/126 (1.6%). Nodal-downstaging rates with NET and NAC were not significantly different (11% versus 18%, $P=0.37$). Patients achieving nodal pCR with NET versus NAC were older (median age 70 versus 50, $P=0.004$) and had higher progesterone receptor (PR) expression (85% versus 13%, $P=0.031$), respectively. Of patients not candidates for BCS due to a large tumor relative to breast size, 36/47 (77%) became BCS-eligible with NET (median PR expression 55% versus 5% in those remaining ineligible, $P<0.05$).

Terms of use and reuse: academic research for non-commercial purposes, see here for full terms. <https://www.springer.com/aam-terms-v1>

Corresponding Author: Melissa Pilewskie, MD, Breast Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, 300 East 66th Street, New York, NY 10065, (T) 646-888-4675, (F) 646-888-4921, pilewskm@mskcc.org.

Publisher's Disclaimer: This is a PDF file of an unedited peer-reviewed manuscript that has been accepted for publication but has not been copyedited or corrected. The official version of record that is published in the journal is kept up to date and so may therefore differ from this version.

Conclusion.—Although nodal pCR is more frequent than breast pCR, NET is more likely to de-escalate breast surgery than axillary surgery. However, with an 11% nodal pCR rate, NET remains an option for downstaging node-positive patients without clear indications for NAC.

Keywords

breast cancer; neoadjuvant endocrine therapy; axillary downstaging; breast-conserving surgery; neoadjuvant chemotherapy

Preoperative systemic therapy (PST) increases the rate of breast conservation and has been shown to be effective in decreasing the need for axillary dissection in selected patients.¹ For hormone receptor positive (HR+)/HER2 negative (HER2–) tumors, both neoadjuvant chemotherapy (NAC) and neoadjuvant endocrine therapy (NET) are possible options to de-escalate surgery, with the latter being associated with lower toxicity.^{2,3} Although the use of NET has increased slightly over time, only approximately 20% of all HR+ patients treated with PST in the United States receive NET.⁴

In clinically N1 patients at presentation, the use of NAC avoids axillary lymph node dissection (ALND) in over 40% of patients.⁵ However, in HR+/HER2– tumors, the rate of axillary downstaging with NAC is only 15–21%, significantly lower than what is seen for HER2+ and triple negative cancers.^{5–8} Data on nodal downstaging with NET are sparse^{9–11}, and the optimal approach to downstaging the axilla in HR+/HER2– patients is uncertain.

Rates of conversion to breast-conserving surgery (BCS) are similar between NAC and NET.^{3,12,13} In the American College of Surgeons Oncology Group (ACOSOG) Z1031 trial, following treatment with an aromatase inhibitor for 16–18 weeks, the rate of downstaging to BCS in patients who were initially BCS-ineligible was 50.9%.¹⁴ However, many studies that reported conversion rates with NET did not report data on multicentricity and included T4 tumors^{12–15}, characteristics that are generally considered contraindications for downstaging to BCS.

The purpose of this study was to evaluate axillary downstaging with NET in biopsy-proven node-positive estrogen receptor positive (ER+)/HER2–patients, and to compare the downstaging rate to a cohort of ER+/HER2– patients treated with NAC. We additionally sought to evaluate conversion rates from BCS-ineligible to BCS-eligible in patients who initially required mastectomy due to unifocal tumors which were too large to allow cosmetically acceptable BCS.

METHODS

Patients Treated with NET

Upon institutional review board approval, consecutive patients with primary stage I–III breast cancer treated with NET and subsequent surgery between January 2009 and December 2019 were identified from a prospectively maintained database. We excluded male patients, those who received NET for less than 4 weeks, and those who received neoadjuvant chemoendocrine therapy. Patients were treated with 1 or more of the following drugs: tamoxifen, letrozole, anastrozole and fulvestrant. Thirty-two patients (14 and 18,

respectively) were enrolled in two randomized controlled trials, one testing the addition of a PI3K inhibitor (taselisib) to letrozole¹⁶, and the other testing the addition of a non-steroidal antiandrogen (enzalutamide) to fulvestrant.¹⁷ Since the letrozole +/- taselisib trial was a double-blind randomized trial, the randomization arm for the 14 patients enrolled is unknown. Seven of the 18 patients enrolled in the fulvestrant +/- enzalutamide trial were premenopausal and were given concomitant GnRH analogue.

The primary endpoints of this study were nodal downstaging and breast tumor downstaging to allow BCS in patients initially requiring mastectomy. Patients with palpable nodes or abnormal nodes on imaging not biopsy-proven to contain tumor (either because fine-needle aspiration was not performed or because it yielded a negative result) were excluded from the axillary downstaging endpoint. Upfront and post-NET eligibility for BCS were prospectively recorded by the treating surgeon, based on physical exam and imaging findings. Pre-NET patients were categorized as eligible, borderline eligible, or ineligible for BCS. Only patients considered borderline eligible or ineligible for BCS due to a large tumor relative to breast size were included in the breast endpoint. It is not our standard practice to obtain axillary ultrasound on all clinically node-negative (cN0) patients, although some patients undergo axillary ultrasound prior to presentation at our facility, and, if available, this information may impact treatment decision making. The use of Breast MRI to image patients pre- and post-neoadjuvant therapy, among those who are considered borderline or ineligible for breast conservation to assess treatment response, is now standard. Prior to NET, 97% of patients had a mammogram and breast ultrasound, and 50% had a breast MRI. Also prior to NET, 93% of cN+ and 14% of cN0 patients had an axillary ultrasound. Following NET, 67% had a mammogram, 53% had a breast ultrasound, and 43% had a breast MRI.

Patients Treated with NAC

To compare the rate of axillary downstaging between NET and NAC, we analyzed a cohort of ER+/HER2- biopsy-proven node-positive patients treated with NAC between November 2013 and July 2019. The majority of patients (95%) received dose-dense anthracycline and taxane-based chemotherapy regimens (ddACT), 4% received cyclophosphamide, methotrexate and 5-fluorouracil (CMF)-based regimens, and 1% received docetaxel and cyclophosphamide (TC).

Statistical Analysis

In the group of biopsy-proven node-positive patients treated with NET, we compared those who achieved nodal pathologic complete response (pCR) versus those who did not. We also compared patients with large tumors who downstaged to BCS-eligible versus those who remained BCS-ineligible. Additionally, we compared baseline characteristics of patients treated with NET versus those treated with NAC, as well as characteristics of patients with nodal downstaging in the 2 groups.

Comparison of characteristics between clinical (BCS eligible versus ineligible after NET), pathologic (nodal pCR versus no nodal pCR), and therapeutic groups (NET versus NAC) was done using Fisher's exact test or the Chi-squared test of independence for categorical characteristics, and the Wilcoxon rank sum test for continuous characteristics. The type I

error rate (α) was set to 0.05 for all the statistical tests. All statistical analyses were performed using R 3.5.3 (R Core Development Team, Vienna, Austria).

RESULTS

Between January 2009 and December 2019, 125 patients (127 cancers) were treated with NET followed by surgery at Memorial Sloan Kettering Cancer Center. Ninety-four (74%) had breast and axillary surgery, 32 (25%) had breast surgery only, and 1 (with an occult primary tumor) had axillary surgery only. Table 1 shows the clinicopathological features of the entire cohort. Median patient age was 72 years (IQR 62–79), and the majority of patients (53%) had cT2 tumors (median tumor size 3 cm, interquartile range (IQR) 2–5 cm). Seventy-three cancers (57%) were infiltrating ductal, and 48 (38%) were pure or mixed infiltrating lobular histology. Median length of NET treatment was 4.6 months (IQR 3.2–8.1 months). No patient achieved pCR in both the breast and axilla (ypT0 ypN0). Breast pCR (ypT0) occurred in 2 (1.6%) patients.

Axillary Downstaging and Disease Burden After NET

Among women undergoing axillary surgery ($n = 95$), clinically palpable axillary lymph nodes were present in 46 of 95 (48%) cases (Fig. 1). Of these, 38 of 46 (83%) had biopsy-proven nodal involvement and the remaining 8 were thought to be clinically node positive. Of the 38 with biopsy-proven nodal metastases, 4 (11%) achieved nodal pCR, 14 (36.8%) had 1–2 residual positive nodes, and 20 (52.6%) had ≥ 3 positive lymph nodes. Of the 49 clinically node-negative patients, 29 (59%) were confirmed to be node negative on final histology and 20 (41%) were node positive. Of the latter, half had 1–2 positive lymph nodes and half had ≥ 3 positive lymph nodes. None of the patients who achieved nodal pCR had lobular cancer; however, histology did not statistically differ ($p = 0.061$) between patients with and without axillary downstaging. Median length of treatment was longer in those having nodal pCR (6.4 months versus 3.7 months), but this difference was not statistically significant ($P = 0.10$) (Table 1).

Axillary Downstaging with NET versus NAC

Table 2 compares clinically node-positive (cN+) patients treated with NET ($n = 46$) with ER+/HER2– biopsy-proven node-positive patients treated with NAC ($n = 338$). Compared to patients who received NAC, NET recipients were older (median age 69 versus 45 years, $P < 0.001$), more likely to have lobular tumors (30% versus 10%, $P < 0.001$), more likely to have well or moderately differentiated tumors (11% and 67% versus 2.7% and 57%, respectively, $P = 0.003$) and to have higher ER (median 95% versus 90%, $P = 0.009$) and PR expression (median 85% versus 40%, $P = 0.002$). The rate of nodal pCR was not statistically different in the 2 groups (11% versus 18%, $P = 0.37$); however, patients treated with NET were significantly less likely to achieve breast pCR (0% versus 9%, $P = 0.035$). Table 3 compares patients who achieved nodal pCR with NET versus those who achieved nodal pCR with NAC. Patients in the former group were older (median age 70 versus 50 years, $P = 0.004$) and had higher PR expression (median 85% versus 13%, $P = 0.030$), although no firm conclusion can be drawn due to the small number of patients achieving nodal pCR with NET ($n = 4$).

Breast Downstaging with NET

Of the 126 patients undergoing breast surgery, 48 (38%) were BCS-eligible prior to NET and 78 (62%) were BCS-ineligible (Fig. 2). Of the latter, 47 (60%) had large tumors relative to breast size, and 31 (40%) were ineligible for downstaging to BCS because of multicentric or T4 tumors. Of the 47 patients with large tumors, 22 (47%) were definitely felt to be ineligible for BCS and 25 (53%) were borderline-BCS candidates. Among non-BCS candidates, 64% (14/22) became BCS-eligible with NET and 12 elected BCS, which was successful in all cases. Among borderline candidates, 88% (22/25) became BCS-eligible, and 20 elected BCS, which was successful in 95% of cases. The single unsuccessful case had positive margins, and re-excision was not felt to be feasible for cosmetic reasons. Overall, 36 of the 47 (77%) patients with a large tumor relative to breast size became BCS eligible with NET and 31 (66%) avoided mastectomy. The only clinicopathological factor associated with conversion from BCS-ineligible to BCS-eligible was higher PR expression (median 55% versus 5%, respectively, $P = 0.031$). Similar to axillary downstaging, the median length of treatment in the group who converted to BCS was longer than in the group who did not (6.5 months versus 4 months); however, this did not reach statistical significance ($P = 0.072$).

DISCUSSION

The long-term outcome of patients with well and moderately differentiated ER+/HER2– tumors is not influenced by whether or not pCR is seen in response to NAC.¹⁸ Pathologic complete response is also not necessary to allow downstaging to BCS, but is required to avoid ALND following NAC. Previous studies from our institution have demonstrated that use of NAC in ER+/HER2– patients allows breast conservation in 40% of those initially requiring mastectomy, and avoids ALND in 20% of those with biopsy-proven nodal metastases.^{5,6}

For patients with ER+ tumors, NET is a less toxic alternative to NAC³, but whether the effect on the axillary nodes is comparable to that of NAC is uncertain. In this study, we found that, although no patient achieved both a breast and axillary pCR, 11% of patients had nodal pCR and 1.6% achieved breast pCR after NET was given for a median of 4.6 months. The only previous study examining axillary downstaging with NET that we are aware of utilized data from the National Cancer Data Base (NCDB). In that study, Weiss and colleagues found that of 571 cN+ patients treated with NET, 76 (13.3%) were node negative on final histology.⁴ However, information on how many of these patients had biopsy-proven nodal disease is lacking, and the downstaging rate is likely overestimated (i.e., if we had considered cN+ cases, instead of only biopsy-proven cases, the rate of nodal downstaging in this study would have been 17%)(Fig. 1).

Lobular cancers are known to have low rates of response in both the breast and the nodes to preoperative chemotherapy.^{6,19} Given that classic lobular cancers have a strongly ER+, progesterone receptor positive (PR+), luminal A-like phenotype, they would seem to be ideal candidates for NET. Somewhat surprisingly, in the present study, we found that none of the 10 biopsy-proven node-positive lobular cancers treated with NET achieved nodal pCR as opposed to 5 out of the 35 treated with NAC. This is consistent with a recent study by

Thornton et al. who used data from the NCDB to investigate outcomes of lobular cancer treated with NAC and NET, and found that nodal pCR was significantly higher in the NAC group (13.4% versus 8.1%).²⁰ These results suggest that despite very low rates of pathologic complete response in lobular cancer regardless of treatment type, if preoperative therapy is given for axillary downstaging, NAC may be more successful than NET. However, selection of patients with less-favorable features for NAC and the relatively brief duration of NET may also contribute to these findings.

Despite patients being selected for NET or NAC based on tumor biology or patient characteristics, as demonstrated by many differences in the baseline characteristics of the 2 cohorts, the rate of nodal pCR did not statistically differ between the two groups (11% versus 18%, $P = 0.37$), indicating that both preoperative strategies are equally likely to result in nodal downstaging when clinical selection criteria are applied. It has been previously reported that PR expression and tumor differentiation among ER+ tumors impact the likelihood of achieving a pCR following NAC⁶, and therefore some pathologic features used to triage patients to NAC versus NET may impact tumor downstaging rates.

The rate of breast pCR with NET was low at 1.6%, which is consistent with previous studies^{13,15}, and it is lower than the 7–15% breast pCR obtained with NAC.^{6,8} Nonetheless, in our study, the overall rate of conversion from BCS-ineligible to BCS-eligible was high at 77%. This rate is higher than previously reported^{12–15}, and likely reflects longer treatment, and the exclusion of multicentric and T4 tumors. Interestingly, 17 of 23 patients (73%) with lobular cancer downstaged to BCS. Previous studies have investigated conversion to BCS with NAC in this population and reported rates ranging between 16% and 45%.^{6,21} These results indicate that although NET uncommonly results in pCR, it may be a valid option to downstage breast surgery among women with lobular cancer without the toxicity associated with NAC.

We acknowledge that 32 of 127 patients (25%) included in this study were enrolled in other clinical trials. With respect to our endpoints, 16 of these 32 patients were biopsy-proven node positive, and one enrolled in the LORELEI trial achieved nodal pCR. Despite the randomization arm being unknown, since taselisib does not significantly increase the rate of pCR¹⁶, it is unlikely that this influenced the rate of nodal pCR found. Furthermore, 12 of the 32 patients included in other trials were initially BCS-ineligible due to a large tumor relative to breast size, and 9 of them became BCS-eligible after NET. Since the addition of taselisib and enzalutamide to standard endocrine therapy yields greater clinical response^{16,22}, it is possible that their addition has contributed to the high rate of conversion to BCS found in this study.

Regarding length of treatment, in the present study, patients who successfully downstaged in either the axilla or the breast received NET for a longer duration compared to those who did not downstage (6.4 months versus 3.7 months and 6.5 versus 4 months, respectively). While this difference was not statistically significant, it appears clinically significant and suggests that longer treatment may allow for a better response, which is in line with previous studies that reported further clinical reduction in tumor size by prolonging NET.^{2,10,23–27} However, the addition of cyclin-dependent kinase 4/6 (CDK4/6) inhibitors to standard neoadjuvant

endocrine therapy and the validation of new biomarkers are ongoing fields of research^{28,29} that may change, in the near future, the indications for NET and the way it is currently given.

To the best of our knowledge, this is the first study to report the rate of nodal pCR in biopsy-proven node-positive cases treated with NET. Study limitations include the small sample size, its retrospective nature, and the absence of defined selection criteria for NET versus NAC. However, the selection of patients for NAC versus NET based on clinicopathologic criteria is a standard part of clinical practice, and our study provides information on the outcomes that can be expected.

Conclusions

In this study, we found that the rate of nodal pCR in ER+/HER2– biopsy-proven node-positive cancer treated with NET was 11%, and that this did not differ from the downstaging rate in patients selected for NAC. On the other hand, the rate of breast downstaging to BCS among women prospectively deemed ineligible for breast conservation was high at 77%, despite a very low rate of breast pCR. Despite a lower rate of breast pCR than nodal pCR, NET is more likely to be successful in de-escalating breast surgery than axillary surgery.

ACKNOWLEDGMENTS

The preparation of this manuscript was funded in part by NIH/NCI Cancer Center Support Grant No. P30 CA008748 to Memorial Sloan Kettering Cancer Center. Dr. Monica Morrow has received speaking honoraria from Genomic Health. Dr. Giacomo Montagna was supported by the Ticino Cancer League, the Hanne Liebermann Foundation, the Fondation Ancre, and the HEMMI-Stiftung. Dr. Komal Jhaveri discloses a consulting or advisory role with Novartis, Pfizer, Genentech, Lilly Pharmaceuticals, Astra Zeneca, Bristol-Myers Squibb, ADC Therapeutics, Taiho Oncology, Jounce Therapeutics, and Abbvie, and research funding (to the institution) from Pfizer, Genentech, Novartis, Lilly Pharmaceuticals, Astra Zeneca, Immunomedics, Puma Biotechnology, Novita Pharmaceuticals, ADC Therapeutics, Zymeworks, Debio Pharmaceuticals, and Clovis Oncology. All other authors have no conflict of interest disclosures to report. This study was accepted for an oral presentation at the 2020 21st Annual Meeting of the American Society of Breast Surgeons.

REFERENCES

1. King TA, Morrow M. Surgical issues in patients with breast cancer receiving neoadjuvant chemotherapy. *Nat Rev Clin Oncol.* 6 2015;12(6):335–343. [PubMed: 25850554]
2. Pariser AC, Sedghi T, Soulos PR, Killelea B, Gross CP, Mougalian SS. Utilization, duration, and outcomes of neoadjuvant endocrine therapy in the United States. *Breast Cancer Res Treat.* 11 2019;178(2):419–426. [PubMed: 31401686]
3. Spring LM, Gupta A, Reynolds KL, et al. Neoadjuvant Endocrine Therapy for Estrogen Receptor-Positive Breast Cancer: A Systematic Review and Meta-analysis. *JAMA Oncol.* 11 1 2016;2(11):1477–1486. [PubMed: 27367583]
4. Weiss A, Wong S, Golshan M, et al. Patterns of Axillary Management in Stages 2 and 3 Hormone Receptor-Positive Breast Cancer by Initial Treatment Approach. *Ann Surg Oncol.* 12 2019;26(13):4326–4336. [PubMed: 31562601]
5. Mamtani A, Barrio AV, King TA, et al. How Often Does Neoadjuvant Chemotherapy Avoid Axillary Dissection in Patients With Histologically Confirmed Nodal Metastases? Results of a Prospective Study. *Ann Surg Oncol.* 10 2016;23(11):3467–3474. [PubMed: 27160528]
6. Petruolo OA, Pilewskie M, Patil S, et al. Standard Pathologic Features Can Be Used to Identify a Subset of Estrogen Receptor-Positive, HER2 Negative Patients Likely to Benefit from Neoadjuvant Chemotherapy. *Ann Surg Oncol.* 9 2017;24(9):2556–2562. [PubMed: 28560596]

7. Laws A, Hughes ME, Hu J, et al. Impact of Residual Nodal Disease Burden on Technical Outcomes of Sentinel Lymph Node Biopsy for Node-Positive (cN1) Breast Cancer Patients Treated with Neoadjuvant Chemotherapy. *Ann Surg Oncol.* 11 2019;26(12):3846–3855. [PubMed: 31222687]
8. Boughey JC, McCall LM, Ballman KV, et al. Tumor biology correlates with rates of breast-conserving surgery and pathologic complete response after neoadjuvant chemotherapy for breast cancer: findings from the ACOSOG Z1071 (Alliance) Prospective Multicenter Clinical Trial. *Ann Surg.* 10 2014;260(4):608–614; discussion 614–606. [PubMed: 25203877]
9. Pappas PTM, Rubsy J. Axillary pathology complete response rates in node positive breast cancer after neoadjuvant chemo- or endocrine therapy. Poster 522 at ABS Conference 2013. *Eur J Surg Oncol.* 2013;39(5):522.
10. Al Mushawah F, Tan MC, Margenthaler JA. Residual nodal disease in biopsy proven n1/n2 breast cancer following neoadjuvant systemic therapy. *World J Surg.* 2 2010;34(2):256–260. [PubMed: 20012606]
11. Rusz O, Voros A, Varga Z, et al. One-Year Neoadjuvant Endocrine Therapy in Breast Cancer. *Pathol Oncol Res.* 9 2015;21(4):977–984. [PubMed: 25753983]
12. Alba E, Chacon JJ, Lluch A, et al. A randomized phase II trial of platinum salts in basal-like breast cancer patients in the neoadjuvant setting. Results from the GEICAM/2006–03, multicenter study. *Breast Cancer Res Treat.* 11 2012;136(2):487–493. [PubMed: 23053638]
13. Semiglazov VF, Semiglazov VV, Dashyan GA, et al. Phase 2 randomized trial of primary endocrine therapy versus chemotherapy in postmenopausal patients with estrogen receptor-positive breast cancer. *Cancer.* 7 15 2007;110(2):244–254. [PubMed: 17538978]
14. Ellis MJ, Suman VJ, Hoog J, et al. Randomized phase II neoadjuvant comparison between letrozole, anastrozole, and exemestane for postmenopausal women with estrogen receptor-rich stage 2 to 3 breast cancer: clinical and biomarker outcomes and predictive value of the baseline PAM50-based intrinsic subtype--ACOSOG Z1031. *J Clin Oncol.* 6 10 2011;29(17):2342–2349. [PubMed: 21555689]
15. LeVasseur N, Willemsma KA, Li H, et al. Efficacy of Neoadjuvant Endocrine Therapy Versus Neoadjuvant Chemotherapy in ER-positive Breast Cancer: Results From a Prospective Institutional Database. *Clin Breast Cancer.* 12 2019;19(6):e683–e689. [PubMed: 31279611]
16. Saura C, Hlauschek D, Oliveira M, et al. Neoadjuvant letrozole plus taselisib versus letrozole plus placebo in postmenopausal women with oestrogen receptor-positive, HER2-negative, early-stage breast cancer (LORELEI): a multicentre, randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet Oncol.* 9 2019;20(9):1226–1238. [PubMed: 31402321]
17. ClinicalTrials.gov. Preoperative Fulvestrant With or Without Enzalutamide in ER+/HER2– Breast Cancer. <https://clinicaltrials.gov/ct2/show/NCT02955394> (Accessed June 25, 2020).
18. Cortazar P, Zhang L, Untch M, et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. *Lancet.* 7 12 2014;384(9938):164–172. [PubMed: 24529560]
19. Cristofanilli M, Gonzalez-Angulo A, Sneige N, et al. Invasive lobular carcinoma classic type: response to primary chemotherapy and survival outcomes. *J Clin Oncol.* 1 1 2005;23(1):41–48. [PubMed: 15625359]
20. Thornton MJ, Williamson HV, Westbrook KE, et al. Neoadjuvant Endocrine Therapy Versus Neoadjuvant Chemotherapy in Node-Positive Invasive Lobular Carcinoma. *Ann Surg Oncol.* 10 2019;26(10):3166–3177. [PubMed: 31342392]
21. Fitzal F, Mittlboeck M, Steger G, et al. Neoadjuvant chemotherapy increases the rate of breast conservation in lobular-type breast cancer patients. *Ann Surg Oncol.* 2 2012;19(2):519–526. [PubMed: 21743980]
22. Krop I, Abramson V, Colleoni M, et al. Abstract GS4–07: Results from a randomized placebo-controlled phase 2 trial evaluating exemestane ± enzalutamide in patients with hormone receptor-positive breast cancer. *Cancer Research.* 2018;78(4 Supplement):GS4–07-GS04–07.
23. Carpenter R, Doughty JC, Cordiner C, et al. Optimum duration of neoadjuvant letrozole to permit breast conserving surgery. *Breast Cancer Res Treat.* 4 2014;144(3):569–576. [PubMed: 24562823]
24. Dixon JM, Renshaw L, Macaskill EJ, et al. Increase in response rate by prolonged treatment with neoadjuvant letrozole. *Breast Cancer Res Treat.* 1 2009;113(1):145–151. [PubMed: 18264759]

25. Dixon JM, Renshaw L, Dixon J, Thomas J. Invasive lobular carcinoma: response to neoadjuvant letrozole therapy. *Breast Cancer Res Treat.* 12 2011;130(3):871–877. [PubMed: 21870129]
26. Fontein DB, Charehbili A, Nortier JW, et al. Efficacy of six month neoadjuvant endocrine therapy in postmenopausal, hormone receptor-positive breast cancer patients--a phase II trial. *Eur J Cancer.* 9 2014;50(13):2190–2200. [PubMed: 24970786]
27. Allevi G, Strina C, Andreis D, et al. 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.* 4 30 2013;108(8):1587–1592. [PubMed: 23579222]
28. Rossi L, McCartney A, Risi E, et al. Cyclin-Dependent Kinase 4/6 Inhibitors in Neoadjuvant Endocrine Therapy of Hormone Receptor-Positive Breast Cancer. *Clin Breast Cancer.* 12 2019;19(6):392–398. [PubMed: 31358432]
29. Prat A, Saura C, Pascual T, et al. Ribociclib plus letrozole versus chemotherapy for postmenopausal women with hormone receptor-positive, HER2-negative, luminal B breast cancer (CORALLEEN): an open-label, multicentre, randomised, phase 2 trial. *Lancet Oncol.* 1 2020;21(1):33–43. [PubMed: 31838010]

Synopsis:

We compared nodal and breast downstaging with NET and axillary response rates after NET and NAC. We find that with an 11% nodal pCR rate, NET remains an option for downstaging node-positive patients without clear indications for NAC.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Axillary Downstaging

Fig. 1.

Axillary Downstaging with NET.

cNo clinically node negative, *cN+* clinically node positive, *ypN+* residual nodal disease,

ypNo nodal pathological complete response, *N+* node positive

Downstaging to breast-conserving surgery (BCS)

Fig. 2.

Downstaging to breast-conserving surgery with NET.

BCS breast-conserving surgery, *NET* neoadjuvant endocrine therapy

TABLE 1

Clinicopathological features of women treated with NET

	Overall	Biopsy-Proven N+ Cases		<i>P</i> *	BCS-ineligible Due to Large Tumor Relative to Breast Size		<i>P</i> *
	n = 127	No Nodal pCR n = 34	Nodal pCR n = 4		No Downstaging to BCS n = 11	Downstaging to BCS n = 36	
Age (years)	72 (62, 79)	64 (56, 74)	70 (66, 78)	0.12	65 (61, 70)	72 (62, 78)	0.21
Clinical T stage at presentation				0.29			0.62
1	33 (26%)	5 (15%)	2 (50%)		0 (0%)	3 (8.3%)	
2	67 (53%)	24 (71%)	2 (50%)		9 (82%)	23 (64%)	
3	16 (13%)	4 (12%)	0 (0%)		2 (18%)	10 (28%)	
4	10 (7.9%)	1 (2.9%)	0 (0%)		-	-	
X	1 (0.8%)	0 (0%)	0 (0%)		-	-	
Tumor size at presentation (cm)	3.00 (2.00, 5.00)	3.00 (2.12, 4.22)	2.50 (1.75,3.12)	0.22	5.00 (4.00, 5.50)	4.00 (3.00, 5.00)	0.11
Clinical N stage at presentation				>0.99			0.34
0	81 (64%)	-	-		7 (64%)	25 (69%)	
1	42 (33%)	32 (94%)	4 (100%)		3 (27%)	11 (31%)	
2	2 (1.6%)	0 (0%)	0 (0%)		0 (0%)	0 (0%)	
3	2 (1.6%)	2 (5.9%)	0 (0%)		1 (9.1%)	0 (0%)	
ER+	127 (100%)	34 (100%)	4 (100%)	>0.99	11 (100%)	36 (100%)	
ER expression rate	95 (90, 99)	95 (90, 99)	95 (94, 96)	0.94	95 (75, 99)	95 (90, 99)	0.36
PR+	101 (80%)	28 (82%)	4 (100%)	>0.99	9 (82%)	30 (83%)	>0.99
PR expression rate	50 (5, 91)	90 (18, 99)	85 (65, 91)	0.81	5 (2, 20)	55 (25, 90)	0.031
Histology				0.061			0.41
Ductal	73 (57%)	24 (71%)	3 (75%)		4 (36%)	18 (50%)	
Lobular and mixed	48 (38%)	10 (29%)	0 (0%)		6 (55%)	17 (47%)	
Other	6 (4.7%)	0 (0%)	1 (25%)		1 (9.1%)	1 (2.8%)	
LV [†]	47 (37%)	19 (56%)	0 (0%)	0.11	5 (45%)	7 (19%)	0.12
Tumor grade				>0.99			>0.99
I	17 (13%)	2 (5.9%)	0 (0%)		1 (9.1%)	6 (17%)	
II	78 (61%)	25 (74%)	3 (75%)		8 (73%)	24 (67%)	
III	32 (25%)	7 (21%)	1 (25%)		2 (18%)	6 (17%)	
Length of treatment, months (range)	4.6 (3.2, 8.1)	3.70 (2.80, 6.07)	6.40 (5.25, 8.00)	0.10	4.0 (3.5, 5.9)	6.5 (4.4, 9.5)	0.072
Breast pCR	2 (1.6%)	0 (0%)	0 (0%)	-	0 (0%)	0 (0%)	-

Frequency (column percent) reported for categorical variables, and median interquartile range (IQR) reported for continuous variables except where otherwise indicated.

* Results from Fisher's exact test for categorical variables and the Wilcoxon rank-sum test for continuous variables.

[†]LVI was present on core biopsy or final biopsy

NET neoadjuvant endocrine therapy, *IQR* interquartile range, *N+* node positive, *BCS* breast-conserving surgery, *ER* estrogen receptor, *PR* progesterone receptor, *LVI* lymphovascular invasion, *pCR* pathological complete response

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

TABLE 2

Clinicopathological characteristics of ER+/HER2- cN+ patients treated with NET, and ER+/HER2- biopsy-proven node-positive patients treated with NAC

	Overall n = 384	ER+/HER2- N+ Receiving NAC n = 338	ER+/HER2- N+ Receiving NET n = 46	P*
Age, years	51 (43,62)	49 (42, 60)	65 (56, 73)	< 0.001
Clinical T stage at presentation				0.279
1	65 (17%)	57 (17%)	8 (17%)	
2	199 (52%)	170 (51%)	29 (63%)	
3	75 (20%)	69 (21%)	6 (13%)	
4	40 (11%)	38 (11%)	2 (4.3%)	
X	5(1.3)	4 (1.2%)	1 (2.2%)	
Clinical N stage at presentation				>0.99
1	342 (89%)	300 (89%)	42 (91%)	
2	20 (5.2%)	18 (5.3%)	2 (4.3%)	
3	22 (5.7%)	20 (5.9%)	2 (4.3%)	
ER+	384 (100%)	338 (100%)	46 (100%)	>0.99
ER expression rate	90 (80, 97)	90 (80, 96)	95 (90, 99)	0.009
PR+	315 (82%)	276 (82%)	39 (85%)	0.75
PR expression rate	50 (5, 90)	40 (3, 80)	85 (16, 97)	0.002
Histology				< 0.001
Ductal	327 (85%)	297 (88%)	30 (65%)	
Lobular and mixed	49 (13%)	35 (10%)	14 (30%)	
Other	8 (2%)	6 (1.8%)	2 (4.4%)	
LV [†]	195 (51%)	172 (51%)	23 (50%)	>0.99
Tumor grade				0.003
I	14 (3.6%)	9 (2.7%)	5 (11%)	
II	223 (58%)	192 (57%)	31 (67%)	
III	147 (38%)	137 (41%)	10 (22%)	

Frequency (column percent) reported for categorical variables, and median (IQR) reported for continuous variables except where otherwise indicated. Bolded *P* values are significant.

* Results from Fisher's exact test for categorical variables, and the Wilcoxon rank-sum test for continuous variables.

[†] LVI was present on core biopsy or final biopsy

ER estrogen receptor, cN+ clinically node positive, NET neoadjuvant endocrine therapy, N+ node positive, NAC neoadjuvant chemotherapy, IQR interquartile range, PR progesterone receptor, LV[†] lymphovascular invasion

TABLE 3

Clinicopathological features of patients who achieved nodal pCR with NET and NAC

	Overall n = 64	Nodal pCR with NAC n = 60	Nodal pCR with NET n = 4	<i>P</i> *
Age, years	53 (42, 63)	50 (42, 61)	70 (66, 78)	0.004
Clinical T stage at presentation				0.28
1	9 (14%)	7 (12%)	2 (50%)	
2	40 (63%)	38 (64%)	2 (50%)	
3	10 (16%)	10 (17%)	0 (0%)	
4	4 (6.3%)	4 (6.8%)	0 (0%)	
X	1 (1.6%)	1 (1.7%)	0 (0%)	
Clinical N stage at presentation				>0.99
1	60 (94%)	56 (93%)	4 (100%)	
2	3 (4.7%)	3 (5.0%)	0 (0%)	
3	1 (1.6%)	1 (1.7%)	0 (0%)	
ER+	64 (100%)	60 (100%)	4 (100%)	>0.99
ER expression rate	90 (48, 95)	80 (39, 95)	95 (94, 96)	0.15
PR+	43 (67%)	39 (65%)	4 (100%)	0.29
PR expression rate	20 (0, 71)	13 (0, 70)	85 (65, 91)	0.030
Histology				0.20
Ductal	56 (89%)	53 (89%)	3 (75%)	
Lobular and mixed	5 (7.9%)	5 (8.5%)	0 (0%)	
Other	3 (4.7%)	2 (3.3%)	1 (25%)	
LV [†]	13 (20%)	13 (22%)	0 (0%)	0.57
Tumor grade				0.23
I	2 (3.1%)	2 (3.3%)	0 (0%)	
II	22 (34%)	19 (32%)	3 (75%)	
III	40 (62%)	39 (65%)	1 (25%)	

Frequency (column percent) reported for categorical variables and median (IQR) reported for continuous variables except where otherwise indicated.

* Results from Fisher's exact test for categorical variables and Wilcoxon rank-sum test for continuous variables

[†] LVI was present on core biopsy or final biopsy

pCR pathologic complete response, NET neoadjuvant endocrine therapy, NAC neoadjuvant chemotherapy, IQR interquartile range, LVI lymphovascular invasion, ER estrogen receptor, PR progesterone receptor