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Breast Cancer (ML Telli, Section Editor)

Current Status of Neoadjuvant Endocrine Therapy in Early Stage Breast Cancer

Tomás Reinert, MD[1,2]
Rodrigo Gonçalves, MD, MSc, PhD[3]
Matthew J. Ellis, MB, BChir, BSc, PhD, FRCP[4,*]

Address
[1]Hospital do Câncer Mãe de Deus, Porto Alegre, Brazil
[2]Postgraduation Department of Medical Sciences, Federal University of Rio Grande do Sul (UFRGS), Porto Alegre, Brazil
[3]Setor de Mastologia, Hospital das Clínicas, Disciplina de Ginecologia, Departamento de Obstetrícia e Ginecologia, Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil
[*,4]Lester and Sue Smith Breast Cancer Center, Baylor College of Medicine, Houston, TX, 77030, USA
Email: mjellis@bcm.edu

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Opinion statement

Neoadjuvant endocrine therapy (NET) with Ki67-based response monitoring is a practical, cost-effective approach to the management of clinical stage II and III estrogen receptor-positive (ER+) breast cancer. In addition to marked improvements in rates of breast conservation, the identification of extreme responders on the basis of the preoperative endocrine prognostic index (PEPI) provides a rationale to avoid chemotherapy on the basis of highly favorable prognosis in some patients. Finally, samples accrued from patients treated with neoadjuvant therapy are providing valuable insights into the molecular basis for intrinsic resistance to endocrine therapy and promise a more rational basis and precise approach to the systemic treatment of ER+ breast cancer.

Introduction

Breast cancer is a heterogeneous group of diseases with different clinical, histological, and prognostic characteristics [1]. Estrogen receptor-positive (ER+) tumors are the most common form of breast cancer and account for most of the deaths from the disease. Modern therapeutic strategies aim to tailor treatments to molecular

subtypes [2] allowing a more individualized approach to treatment.

The treatment of early-stage breast cancer includes three main therapeutic modalities: surgery, systemic therapy, and radiation therapy. Historically, systemic therapy has been used after surgery according to surgical pathology-based prognostication. However, clinical trials have demonstrated that neoadjuvant (preoperative) chemotherapy (NCT) is equivalent to adjuvant chemotherapy in terms of safety profile, recurrence, and overall survival (OS) rates [3, 4]. Moreover, NCT induces tumor downstaging and increases rates of breast-conserving surgery (BCS) [5].

Response and benefit to NCT vary according to breast cancer subtype with lower pathological complete response (pCR) rates in ER-positive (luminal) tumors in comparison to ER-negative and HER2-positive tumors [6, 7]. In patients with luminal tumors, endocrine therapy (ET) accounts for most of the gains obtained with adjuvant systemic treatment. The use of cytotoxic chemotherapy in these patients remains controversial since the absolute OS benefit with adjuvant chemotherapy in unselected postmenopausal women with ER-positive HER2-negative tumors is no more than 3–4% [8]. Recent genomic classification studies support this view by indicating that the majority of patients with ER-positive HER2-negative tumors have a low-risk disease and highly favorable prognosis with adjuvant ET alone [9].

Neoadjuvant endocrine therapy (NET) is, therefore, a logical alternative to NCT for ER-positive tumors as it is well tolerated, simple to deliver, and has proven benefits. The potential of NET is being increasingly explored, not only to allow less extensive surgery but also as a scientific tool, generating biomarkers to predict outcomes both for individual patients and in adjuvant clinical trials [10]. Although currently available ET agents are generally effective and well tolerated, not all patients benefit equally. Predictive biomarkers should facilitate a more tailored approach to ER+ breast cancer. A better understanding of the features underlying heterogeneity, as well as the mechanisms of resistance to ET [11••], is essential for the development of novel therapies.

While NET is a logical approach that allows an exceptional opportunity to further personalize treatment selection, it has been timidly evaluated in clinical trials and even more so implemented in clinical practice. According to the National Cancer Data Base in the USA, only 3% of the eligible patients receive this therapy [12]. This review details the most relevant evidence about NET as a clinical approach and as a scientific tool for addressing mechanisms of endocrine resistance and drug development in breast cancer.

Neoadjuvant endocrine therapy as a clinical approach

NET was initially used in the early 1980s as a treatment option for elderly women who were unfit to be treated with cytotoxic chemotherapy or ineligible for surgery [13]. Initial studies were designed to evaluate the role of endocrine therapy as a primary treatment option to avoid surgery rather than as a neoadjuvant treatment [14]. This approach avoided the inconvenience of surgery, chemotherapy, or radiotherapy, resulting in a 60% response rate, and also identified ER as a predictive biomarker of benefit: nearly 100% of ER-negative tumors were unresponsive compared to a clinical benefit rate of 80% among ER-positive tumors, many with long-lasting responses. However, a significantly higher locoregional relapse rate [15] and possibly a decrease in OS [16] were seen in patients who did not undergo surgery, although these differences only became apparent after years of follow-up [17]. These encouraging results triggered several randomized controlled trials comparing tamoxifen versus mastectomy in elderly patients. A meta-analysis of these studies reported an increased risk of local failure but similar breast cancer-specific and overall survival for neoadjuvant tamoxifen versus surgery followed by adjuvant tamoxifen. The efficacy of aromatase inhibitors (AI) in this context has not been addressed in randomized trials, but indirect comparisons from cohort studies suggest they are superior to tamoxifen, with higher clinical benefit and lower disease progression rates. The high-median time to progression (~ 49 months), duration of

clinical benefit (~ 18 months), and low toxicity make definitive primary endocrine therapy an attractive treatment choice for patients with low-risk ER+ breast cancer and shorter life expectancy due to severe co-morbidities [10].

Modern NET approaches have two main objectives: tumor downstaging to allow breast-conserving surgery (BCS) and to provide an in vivo analysis of the pattern of sensitivity or resistance to endocrine treatment. Third-generation AIs (letrozole, anastrozole, exemestane) have been compared with tamoxifen in several randomized trials, showing superior response rates (76–37% vs. 40–36%), and eligibility for breast conservation (45–19% vs. 20–21%; [22]). Recently, the American College of Surgeons Oncology Group (ACOSOG) Z1031 study confirmed that for patients who are told they need a mastectomy, about half could undergo successful breast-conserving surgery after 16 to18 weeks of AI treatment [23].

NET has additional potential benefits such as favorable toxicity profile (especially in comparison to anthracycline and taxane-based chemotherapy), low cost and easy translatability to clinical practice in areas of the world with limited health care resources where the most frequent presentation of breast cancer is a breast mass. These factors are especially relevant as approximately 24% of breast cancer deaths now occur in women from low-income and middle-income countries [21].

What is the best endocrine agent for neoadjuvant treatment?

The third-generation AI anastrozole, letrozole, and exemestane are currently the standard treatment for HR+ breast cancer when NET is considered. This is also mostly true both in the adjuvant and metastatic setting, based on several clinical trials that demonstrated their superiority over tamoxifen [25, 26••]. Randomized clinical trials addressing this issue in the neoadjuvant setting are summarized in Table 1. The balance of evidence from these studies shows that AIs are more effective clinically than tamoxifen in achieving response and in tumor downstaging to avoid mastectomy or to convert inoperable to operable tumors [34]. A meta-analysis including a total of 1160 patients indicated superior outcomes regarding clinical and radiologic response and BCS rate with AI as compared to tamoxifen. The ACOSOG Z1031 [23] study compared NET with exemestane, letrozole, and anastrozole head-to-head and demonstrated that the effectiveness of the three agents is equivalent. In premenopausal patients, the STAGE trial demonstrated superior response rate favoring anastrozole plus goserelin in comparison with tamoxifen plus goserelin [31] indicating that additional studies in the preoperative setting should be pursued in this population.

What is the optimal duration of neoadjuvant endocrine therapy?

Based on earlier experience with NCT, a 3- to 4-month duration of NET has been used in the majority of the studies such as IMPACT [27], PROACT [29], and P024 [35]. Nonetheless, data from other trials indicate that this period may be insufficient to achieve a maximal response regarding reduction in tumor size [18, 36–39]. The potential benefit of prolonged NET was investigated in a few studies that indicated that the rates of clinical response and conversion to BCS increased after 6 months of treatment, with approximately one third of patients achieving maximal reduction in tumor volume after this period. Since most of the published

Table 1. Randomized trials comparing different endocrine agents in the neoadjuvant setting. Adapted from Reinert T, Ramalho S, Gonçalves R, Barrios C, Graudenz M, Bines J et al. Multidisciplinary approach to neoadjuvant endocrine therapy in breast cancer: a comprehensive review. Rev. Bras Ginecol Obstet 2016;38:615–22; https://creativecommons.org/licenses/by/4.0/deed.en

Trial phase	Treatment arm (*N*)	Duration	Primary endpoint	OR	BCS
IMPACT [27] III	A: Anastrozole (113) B: Tamoxifen (108) C: Anastrozole + tamoxifen (109)	3 months	OR by ultrasound	A: 37% B: 36% C: 39%	A: 44% B: 31% C: 29%
PO24 [28] III	A: Letrozole (162) B: Tamoxifen (223)	4 months	OR by clinical palpation	A: 55%* B: 36% $p < 0.001$	A: 45%* B: 35% P 0.02
PROACT [29] III	A: Anastrozole (228) B: Tamoxifen (223)	3 months	OR by ultrasound	A: 39% B: 35%	A: 43%* B: 31% P 0.04
ACOSOG Z1031 [30] II	A: Exemestane (124) B: Letrozole (128) C: Anastrozole (125)	4 months	OR by clinical palpation	A: 63% B: 75% C: 69%	A: 48% B: 41% C: 64%
STAGE [31] III	A: Anastrozole (+ goserelin) (98) B: Tamoxifen (+ goserelin) (98)	6 months	OR by ultrasound	A: 70%* B: 50% P: 0.004	A: 86% B: 68%
RUSSIAN TRIAL [32] II	A: Exemestane (76) B: Tamoxifen (75)	3 months	OR by clinical palpation	A: 76%* B: 40% P 0.05	A: 37% B: 25% P 0.05
CARMINA [33] II	A: Anastrozole (57) B: Fulvestrant 500 mg (59)	4–6 months	OR by clinical palpation	A: 62% B: 46%	A: 59% B: 49%

OR objective response, *BCS* breast-conserving surgery, *MRI* magnetic resonance imaging
*Statistically significant

trials on NET treated patients during approximately 3 to 4 months, it should be considered that the potential benefit from endocrine treatment may have been underestimated. It is currently not clear if extending NET to beyond 12 months could further improve response, but there is a more than theoretical risk that acquired resistance to AI therapy [11••] could develop during the treatment [40].

Comparisons between NCT and NET

There is very limited data comparing NCT to NET [34] and the best available evidence comes from two randomized phase II trials (Table 2). No statistically significant difference between NET and NCT in terms of clinical and pathological response rates was demonstrated in a trial that randomized 239 postmenopausal patients with stage IIA–IIIB HR+ breast cancer to receive neoadjuvant AI (anastrozole or exemestane for 3 months) or NCT(four cycles of doxorubicin plus paclitaxel) [41•]. A Spanish trial randomized 97 patients with ER-positive HER2-negative tumors to receive neoadjuvant exemestane for 6 months (a minority of premenopausal patients also received goserelin) or NCT (AC followed by docetaxel). Even though no statistically significant difference was found between the two groups in terms of response rate, a trend for

Table 2. Randomized trials comparing endocrine versus chemotherapy in the neoadjuvant setting. Adapted from Reinert T, Ramalho S, Gonçalves R, Barrios C, Graudenz M, Bines J et al. Multidisciplinary approach to neoadjuvant endocrine therapy in breast cancer: a comprehensive review. Rev. Bras Ginecol Obstet 2016;38:615–22; https://creativecommons.org/licenses/by/4.0/deed.en

Trial	Treatment arm (*N*)	Duration	Primary endpoint	OR	BCS
Semiglazov et al. [41•]	A: Chemotherapy (118) (Doxorrubicin + paclitaxel) B: Endocrine therapy (121) (Anastrozole 61) (Exemestane 60)	3 months	OR by clinical palpation	A: 63% B: 64%	A: 24% B: 33% P 0.058
GEICAM 2006-03 [20]	A: Chemotherapy (EC –> docetaxel) B: Exemestane (plus goserelin if premenopausal)		Response rate by MRI	A: 66% B: 48%	A: 47% B: 56%
NEOCENT [19]	A: Chemotherapy (22) B: letrozole (22)	18–23 weeks	Recruitment feasibility and tissue collection	A: 54% B: 59%	
UNICANCER-NEOPal [42]	A: Chemotherapy (53) B: Letrozole/palbociclib (53)	20 weeks	Residual cancer burden index (RCB)	A: 76% B: 75%	A: 69% B: 69%

OR objective response, *BCS* breast-conserving surgery, *MRI* magnetic resonance imaging
*Statistically significant

a worse outcome was observed in the NET arm for premenopausal patients and those with high-tumor Ki67 expression [20]. The NEOCENT trial [19], designed to compare NCT versus NET, was unfortunately closed due to slow accrual.

NET in premenopausal patients

Data is very limited on NET in premenopausal women. In an Asian population, the efficacy of anastrozole with goserelin versus tamoxifen with goserelin for 31 weeks preoperatively was evaluated in 197 premenopausal patients with ER+ HER2– early breast cancer. Overall response rate was 70.4% in the anastrozole group. This finding is consistent with the SOFT [43] and TEXT [44] adjuvant trials that demonstrated a significant benefit concerning recurrence-free survival for exemestane plus ovarian function suppression in comparison with tamoxifen in premenopausal patients with high-risk early breast cancer. These results are encouraging and suggest that NET with an AI plus ovarian function suppression is an effective therapeutic strategy in this population. However, NET in premenopausal patients should be considered experimental until this issue is evaluated in randomized clinical trials [22].

Preoperative endocrine prognostic index

In 2014, the FDA released a document considering pathological complete response (pCR), an acceptable surrogate endpoint of clinical benefit in neoadjuvant clinical trials for accelerated drug approval [45]. That recommendation is very useful in neoadjuvant chemotherapy (NAC) trials in which experimental

treatment regimens can achieve high rates of pCR, which are correlated with long-term clinical benefit [46], such as the combination of trastuzumab, pertuzumab, and cytotoxic chemotherapy [47]. In the neoadjuvant endocrine therapy setting, however, high-pCR rates are not common and different surrogate endpoints are necessary. In 2008, Ellis et al. developed the preoperative endocrine prognostic index (PEPI) combining Ki67 score, ER Allred score, tumor size, and nodal status after neoadjuvant endocrine treatment with an aromatase inhibitor (see Table 1). The PEPI score was able to successfully predict relapse-free survival (RFS) in the IMPACT trial ($p = 0.002$) [35]. A combined analysis of the P024 and preoperative letrozole (POL), both NET trials, with a median follow-up of 62.5 months confirmed the potential role of the PEPI score as a prognostic score. In that analysis, there were no relapses in the 29 patients (19 pT1N0, 10 pT2N0) with PEPI-0 status and a statistically significant difference in RFS between patients with a PEPI-0 status and those with a PEPI score greater than 0 ($p = 0.0012$) [48]. The PEPI score was further validated in the ACOSOG Z1031 trial in which ER+, HER2−, stage 2 or 3 breast cancer patients were randomized to receive anastrozole, letrozole, or exemestane in the neoadjuvant setting [49]. Recently, mature data from that trial were published with a median follow-up time of 5.5 years [50••], showing a clear difference in RFS with four of 109 patients with PEPI = 0 score, presenting with a relapse versus 51 of 341 patients with PEPI > 0 (recurrence hazard ratio [PEPI = 0 vs. PEPI > 0] = 0.35; $p = 0.14$; 95%CI, 0.092 to 0.764) (Table 3).

Table 3. Preoperative endocrine prognostic index (PEPI)

Surgical factors	RFS HR	PEPI points
Tumor size		
T1/2	–	0
T3/4	2.8	3
Node status		
Negative	–	0
Positive	3.2	3
Ki67 level		
0–2.7%	–	0
> 2.7–7.3%	1.3	1
> 7.3–19.7%	1.7	1
19.7–53.1%	2.2	2
> 53.1%	2.9	3
ER		
Negative	2.8	0
Positive	0	3
PEPI 0: pT1/2, N0, Ki67 ≤ 2.7% ER+		

Preoperative endocrine prognostic index (PEPI) score following 6 months of NET is a strategy to identify endocrine sensitive vs. resistant tumors in the early stage setting. PEPI score of 0 (pT1/2 N0, Ki67 ≤ 2.7%, ER+) is being investigated prospectively as a surrogate of endocrine therapy-sensitive disease that does not need chemotherapy, while PEPI > 0 identifies patients with increased risk of relapse. The table above shows the HR of each surgical factors for relapse free survival (RFS) and assigned PEPI points based on the data from P024 trial [11••, 35]

Another interesting finding, published in that study was how an early on treatment Ki67 value (within 2 to 4 weeks of starting NET) predicted PEPI = 0 score. The authors established an on-treatment Ki67 threshold for switching from NET to immediate surgery or NAC, using data from the POL [52] and IMPACT [53•] trials. In both trials, a 2-week or 1-month Ki67 score > 10% was associated with the higher PEPI score, a smaller number of patients in the PEPI-0 group and worse RFS. Thus, with a Ki67 value of >10% at 2 to 4 weeks a patient would have less than 2% chance of a PEPI-0 score and would not be eligible to avoid chemotherapy [50]. The PEPI score is being prospectively validated in the ALTERNATE trial that is currently randomizing cT2–4, N0–3, M0 ER+/Her2– invasive breast cancer patients to either anastrozole, fulvestrant, or its combination to assess a biomarker-driven treatment strategy to identify women with a low risk of disease recurrence [54]. The biomarker Ki67, one of the components of the PEPI score, has been extensively studied in the neoadjuvant endocrine treatment field, and it has been shown that its decrease during treatment is predictive of response to tamoxifen [55] and aromatase inhibitors [49, 51, 53•]. To this day, however, some level of controversy remains regarding Ki67's reproducibility [56–58] but several leaders in the field have reported their growing confidence in this biomarker [59•, 60, 61]. The results of the POETIC trial (NCT02338310), the largest window-of-opportunity trial to this day, which randomized over 4000 post-menopausal ER+ breast cancer patients to receive either no treatment or 2 weeks of an AI both before and after surgery, will be presented at the SABCS 2017 and will increase the body of evidence supporting Ki67 as a predictive and prognostic biomarker. The PAM50 gene expression signature has also been investigated in the Z1031 trial, in which 3.3% of ER-positive tumors were non-luminal according to the signature and, therefore, non-responsive to endocrine therapy. In that same trial, the PAM50 signature showed a higher likelihood of a Luminal A tumor achieving a PEPI-0 score than a Luminal B tumor (35.1 vs. 10.7%, $p = 0.004$) [49]. The PAM50 signature has also been used as a platform to create a chemo-endocrine score (CES) combining PAM50 subtyping and expression of additional genes [62]. The CES was validated in two cohorts of ER+, post-menopausal women that had undergone neoadjuvant endocrine treatment and was the only variable associated with the response. Another group has developed a four-gene predictive model of clinical response to AI that achieved 91% accuracy and also predicted RFS ($p = 0.029$) and BCSS ($p = 0.009$) [63]. The predictive value of the 21-gene signature Oncotype Dx for response to NET has been evaluated in a prospective study where patients were treated with preoperative exemestane for 6 months [64]. Patients with a low-recurrence score (RS) exhibited a clinical response rate of 59% and a breast conservation rate of 91% compared with 21 and 54%, respectively, in patients with a high RS. Although very promising, these signatures still need to be prospectively validated before their introduction in clinical practice.

NET as a tool for addressing mechanisms of endocrine resistance

Another advantage of NET as a scientific tool is the opportunity to investigate mechanisms of treatment resistance. Miller et al. performed comprehensive genomic characterization of 22 tumors before and after 16 to 18 weeks of

neoadjuvant aromatase inhibitor treatment [65]. The authors showed that 18 of 22 tumours were heterogeneous and contained subclonal populations whose proportions changed during treatment. This change was probably due to the selective pressure of estrogen deprivation and growth of the resistant clones. This study has revealed four possible genomic patterns; two intertwined but genomically separate "collision tumor" patterns: "clonally simple and treatment stable" patterns; "clonally complex and treatment dynamic" patterns; and "clonally complex and treatment stable" patterns. Ellis et al. had previously described this theory of genome remodeling and clonal evolution in 2010 in basal-like breast cancer [66]. Further studies are necessary to corroborate these findings but it is reasonable to conclude that genomic studies should include multiple core biopsies over different time points with deeper sequencing coverage in order to capture tumor heterogeneity and on-treatment clonal evolution. Moreover, the findings of this study allow us to hypothesize that adjuvant treatment should be tailored according to neoadjuvant treatment results.

A final scientific use of the NET approach is its role as a drug development/testing platform to investigate the use of new drugs or new drug combinations. Goncalves et al. clearly demonstrated that NET trials could predict the results of adjuvant endocrine treatment trials based on the reduction of on-treatment Ki67 levels, with smaller sample sizes and generating results faster. Therefore, adjuvant endocrine treatment trials should only be activated after positive results from the neoadjuvant setting [59•, 67], An example of a novel drug that did not show very promising results was the AKT inhibitor MK2206. Its use in the neoadjuvant setting in ER+, HER2−, stage 2 or 3, PIK3CA mutant breast cancer patients failed to further suppress cell proliferation when combined with anastrozole and MK2206 compared to anastrozole alone [68] in patients with PIK3CA mutations. This result, however, was observed in 16 of 22 patients with PIK3CA mutations, and this small sample size is a limitation to the definitive interpretation of these data. The EGFR tyronase tyrosine kinase inhibitor gefitinib is another example of a drug that did not produce promising results in the neoadjuvant setting and therefore will not be further investigated. In the phase 2 study of neoadjuvant gefitinib ± Anastrozole for [16] weeks, there was no significant difference in change in Ki67 levels between the Anastrozole group and the group that received the drug combination ($p = 0.16$) [69]. On the other hand, we have several examples of drugs that showed promising results in the neoadjuvant setting and are being now investigated in the adjuvant treatment setting. A neoadjuvant phase 2 trial compared letrozole and combination of everolimus and letrozole. A reduction in Ki67 expression levels to the natural logarithm of percentage positive Ki67 of less than 1 at day 15, occurred in 58 (63%) of 91 patients in the everolimus arm and in 27 (18%) of 82 patients in the placebo arm ($p < 0.01$) [70]. These results provided the rationale for the BOLERO 2 trial that showed a clear benefit in PFS favoring the combination of everolimus and exemestane versus exemestane alone in advanced ER+ breast cancer patients [71], and also for the activation of a phase III randomized, placebo-controlled clinical trial evaluating the use of adjuvant endocrine therapy ± 1 year of everolimus in patients with high-risk, hormone receptor-positive, and HER2/Neu-negative breast cancer (NCT 01674140).

The NEO-MONARCH trial compared Anastrozole versus the CDK4/6 inhibitor abemaciclib versus the combination of both drugs. After 2 weeks, the combination induced a more potent cell-cycle arrest (defined as Ki67 < 2.7%) than anastrozole alone (72 vs. 15%) [72]. In the NeoPalAna trial, 50 clinical stage II/III

ER+/HER2– breast cancer patients anastrozole 1 mg daily for 4 weeks (cycle 0) (with goserelin if premenopausal), followed by adding palbociclib (125 mg daily on days 1–17, 21–23, 25) on cycle 1 day 1 (C1D1) for four 36-day cycles unless C1D15 Ki67 > 10%, in which case patients went off study due to inadequate response. In this study, the complete cell cycle arrest rate, defined as Ki67≤ 2.7%, was significantly higher after adding palbociclib to anastrozole (C1D15 87% vs. C1D1 29%, $p < 0.001$) [73••]. Based on these results, investigation of clinical benefit of abemaciclib and palbociclib in the adjuvant setting should be initiated.

Analysis of NeoPalAna trial according to the status of mismatch repair complex genes, MulL and MutS revealed the potential of this pathway in diagnosing intrinsic endocrine therapy resistance that can be overcome with CDK4/6 inhibition. In the setting of underexpression or mutation in MSH1 or PMS1 or 2, ER+ tumors have a reduced response to AI because of a failure to activate ATM and CHK2 upon estrogen deprivation as this pathway suppresses CDK4/6 activity upon estrogen deprivation. These events leave CDK4/6 unchecked and constitutively active, making the AI resistant ER+ cancer cell very sensitive to CDK4/6 inhibition.

Limitations of NET

Despite the potential benefits of NET described above, there are still some unanswered questions that limit its widespread clinical application. Although on-treatment Ki67 and PEPI scores have shown utility in clinical investigation and discovery, they are not yet fully validated for individual patient care decisions [74]. Analytic validity, that is, the ability of an assay to reliably and accurately measure the analyte of interest, is one of the barriers to address the visual interpretation of Ki67 staining. This method has high intra-observer but low inter-observer concordance [75]. In an effort to decrease this variability, the International Ki67 Working Group has conducted studies to analytically standardize and validate Ki67 [24, 76], Intra-tumor heterogeneity of Ki67 is another source of variability that unlikely will be diminished, even with the adoption of standard operating procedures [77]. The Ki67 expression is usually higher in the tumor periphery than in the center, and some tumors show a diffuse pattern of Ki67 staining whereas some others show "hot" and "cold" spots. It is not clear whether the average Ki67 is adequate or there should be a focus on Ki67 "hotspots" [74]. This issue is somewhat mitigated by the very low levels of Ki67 required for PEPI-0 status. Consideration on average Ki67 versus hotspot Ki67 is less relevant here. Thus PEPI score is less affected by spatial intra-tumor heterogeneity and is a more robust endpoint than Ki67 alone since it integrates anatomic features such as tumor size and lymph node status, well-validated independent prognostic factors in breast cancer, and incorporates data from surgical specimens instead of core biopsies.

Another limitation would be the difficulty to measure the impact on long-term outcomes. Even though the Ki67 and PEPI scores have demonstrated preliminary validity as surrogate markers, it should be noted that this has been based on studies that used the same ET in the neoadjuvant and adjuvant parts of the trial [27, 35, 50••], This limitation can also apply to combinations of NET and other cytostatic drugs, such as CDK4/6 inhibitors. The combination of ET with CDK4/6 inhibitors is now standard of care in patients with ER+ HER2– advanced breast cancer [78]. Recently presented, a French phase II trial [42]

investigated a regimen of letrozole plus palbociclib in comparison with NCT in postmenopausal women with stage II or III ER-positive HER2-negative breast cancer who were not candidates for BCS. All patients were required to have either a PAM50 luminal B or luminal A profile with proven lymph node involvement. Although neoadjuvant letrozole/palbociclib provided a slightly lower pCR/RCB 0-I rate than chemotherapy, the clinical response and BCS rates were similar in both arms. Letrozole/palbociclib had a much better safety profile. Similarly NeoPalAna [79] evaluated combinations of anastrozole and palbociclib in a single arm study with serial biopsies. Again, there was no evidence that palbociclib increased the pCR rates; however, Ki67 monitoring showed marked improvement in Ki67 suppression over the AI alone. These data strongly suggest that CDK4/6 therapy will be a maintenance strategy leading to concerns about the optimal duration of therapy.

As previously discussed, recent studies provided interesting results in terms of clinical response and biomarkers such as Ki67 and CCCA [73]. Nonetheless, the correlation of Ki67 changes under neoadjuvant CDK4/6 inhibition and long-term outcomes have not yet been demonstrated. An approach to examining whether a novel NET strategy affects long-term outcome would be to conduct two parallel trials: a neoadjuvant trial powered to see a difference in PEPI score and, second, a mirror-image adjuvant trial powered to demonstrate an improvement in relapse-free and/or OS [74].

Conclusion

ER+ breast cancer is a deeply heterogeneous disease at the genomic and clinical level. While simple gene expression models have provided a step forward in parsing measurements of this heterogeneity into precision medicine approaches, we have, to date largely focused on withdrawing chemotherapy from those who do not require this treatment. The neoadjuvant endocrine approach facilitates consideration of clonal heterogeneity, intrinsic resistance mechanisms, and triage approaches to address alternative treatments for patients experiencing an inadequate response and the long-term consequences of endocrine therapy resistance.

Compliance with Ethical Standards

Conflict of Interest

Tomás Reinert has received research funding from AstraZeneca and has received speaker's honoraria from AstraZeneca, Novartis, and Pfizer.

Rodrigo Gonçalves declares that he has no conflict of interest.

Matthew J. Ellis has received clinical trial support from Novartis (P024 and Z1031 trials) and Pfizer (Z1031 trial); has received compensation from AstraZeneca, Pfizer, and Novartis for service as a consultant; and has licensed PAM50 patents to NanoString for Prosigna®. The commercial version of PAM50 is not mentioned within this article.

Human and Animal Rights and Informed Consent

Dr Ellis performed the Preoperative Letrozole Study and the Z1031 Study. He was a coinvestigator of the P024 Study. All these studies on human subjects were approved by the relevant ethics committees as outlined in the publications cited.

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Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

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