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Abstract

Introduction: While endocrine therapy is the standard-of-care adjuvant treatment for hormone receptor-positive (HR+) breast cancers, there is also extensive evidence for the role of pre-operative (or neoadjuvant) endocrine therapy (NET) in HR+ postmenopausal women.

Areas covered: We conducted a thorough review of the published literature, to summarise the evidence to date, including studies of how NET compares to neoadjuvant chemotherapy, which NET agents are preferable, and the optimal duration of NET. We describe the importance of on-treatment assessment of response, the different predictors available (including Ki67, PEPI score and molecular signatures) and the research opportunities the pre-operative setting offers. We also summarise recent combination trials and discuss how the COVID-19 pandemic led to increases in NET use for safe management of cases with deferred surgery and adjuvant treatments.

Expert opinion: NET represents a safe and effective tool for the management of postmenopausal women with HR+/HER2- breast cancer, enabling disease downstaging and a wider range of surgical options. Aromatase inhibitors are the preferred NET, with evidence suggesting that longer regimens might yield optimal results. However, NET remains currently underutilised in many territories and institutions. Further validation of predictors for treatment response and benefit is needed to help standardise and fully exploit the potential of NET in the clinic.

Keywords: Breast cancer, ER+, HR+, HR+/HER2-, Endocrine therapy, Neoadjuvant therapy, Pre-operative therapy, Postmenopausal

Article highlights:

- In postmenopausal women with HR+/HER2- breast cancer, NET is a safe and effective tool for disease downstaging, achieving higher breast conserving surgery rates than chemotherapy with lower toxicity.
- Aromatase inhibitors outperform tamoxifen and longer duration of NET might yield optimal effects.
- Baseline Ki67 is a prognostic factor and its level after a period of NET is an indicator of response, incorporated in numerous studies. However, Ki67 is not without its limitations as a surrogate marker of proliferation. Post-NET PEPI score holds prognostic value.
- Several genomic and hybrid signatures have been assessed for their value as predictors of NET response.
- The neoadjuvant setting offers unique research opportunities beyond monitoring of response, including studying the effect of early treatment and testing novel combination therapies.
- The COVID-19 pandemic led to increases in NET use, exhibiting the safety and efficacy of this strategy for downstaging and control of HR+/HER2- disease.
- Further validation and guidelines for biomarker use will be instrumental in helping standardise the use of NET, which remains underutilised in many territories despite the evidence for its safety and efficacy.

1. Background

Estrogen receptor (ER), a transcription factor, is the foremost biomarker in breast cancer (BC) and its expression, along with that of the human epidermal growth factor receptor (HER2), is assessed in all new cases. Up to 80% of tumours are ER-positive (ER+), also known as luminal (based on the corresponding molecular subtype) or hormone receptor-positive (HR+) in reference to progesterone receptor (PR), another hormone receptor that is less clinically useful but known to be ER-driven[1]. Most HR+ cases are also HER2-negative (HER2-). Overall, HR+/HER2- tumours account for the majority of BCs, including 65% of tumours in women under 50 years of age and 75% of cases in women over 50[2].

Expression of ER indicates that the disease is hormone-dependent and relies on estrogen, through complex genomic and non-genomic signalling machinery, for both carcinogenesis and progression[3]. Thus, HR+ status is also predictive of likely response to endocrine therapy (ET), which tackles hormone signalling by blocking either the synthesis of estrogen or its signalling through ER. ET is often the most effective therapy for HR+ tumours and is used to treat the majority of patients with this type of neoplasms[4]. While most of these patients will receive hormone therapy adjuvantly (i.e., post-operatively), ET for BC can also be used in other settings including palliative therapy or, more recently, chemoprevention. In this review, we will discuss the use of hormonal therapy prior to surgery, or neoadjuvant endocrine therapy (NET), in postmenopausal women with HR+/HER2- BC. We will summarise the rationale for its use, the evidence to date, and the current trends and guidelines.

For this, we conducted an extensive literature search on the biomedical databases MEDLINE and Embase. The search terms included: ‘preoperative’ or ‘neoadjuvant’; ‘endocrine’ or ‘hormone’ or ‘hormonal’; ‘therapy’ or ‘treatment’; ‘breast’; and ‘cancer’ or ‘carcinoma’ or ‘neoplasm’. Inclusion criteria were articles written in English between 2000 and 2022, followed by forward and backwards reference search to ensure that, relevant

study updates and key older references were considered. This was followed by filtering of the resulting publications to select those relevant to the scope of this review.

2. History and evolving rationale for the use of NET in BC

NET was first introduced in the early 1970s as a treatment option for older or frail patients who were unfit or ineligible for surgery. In this context, ET was used as an alternative primary therapy, rather than as a neoadjuvant treatment *per se*. Initial studies compared primary treatment with the selective ER modulator (SERM) tamoxifen vs surgery in elderly patients[5,6]. While 80% of ER+ patients saw clinical benefit from NET, longer follow-up showed higher locoregional recurrence rates and lower overall survival (OS) when compared with patients who underwent surgery[7–9]. A meta-analysis of 7 trials showed no OS advantage (hazard ratio (HR) 0.98, p=0.9) but an improvement in progression-free survival (PFS) (HR 0.55, p=0.0006) in patients who received surgery followed by adjuvant ET, compared to primary ET alone[10]. The Group for Research on Endocrine Therapy in the Elderly (GRETA) trial, which randomised women over 70 with operable tumours to tamoxifen alone or surgery plus tamoxifen, reported increased rates of local progression in the ET-only arm (25 vs 6%, p<0.0001) but also showed no significant differences in survival or distant metastasis rates between both treatment groups[8]. In contrast to previous studies, similar survival rates were maintained at longer follow-up (80 months) and about 40% of patients had complete or partial response to tamoxifen alone[11]. Taken together, this evidence suggested that the use of primary ET instead of definitive local treatment might be an adequate option only for older patients unlikely to ever be eligible for surgery or with limited life expectancy[12]. This could be extended as long as disease is responsive or stable, or alternative ET agents could be considered if there is evidence of disease progression.

Starting in the 2000s, NET has been used with the primary goal of downstaging large or locally-advanced HR+ cancers in order to provide more surgical options, either by

enabling surgery in initially inoperable patients or improving breast-conserving surgery (BCS) rates when lumpectomy becomes feasible for patients who initially would have needed to undergo a mastectomy[13].

Eligible candidates for pre-operative treatment are typically patients with a cancer that is initially inoperable or not suitable for BCS, as well as those with large operable primary cancers (T3, or >5cm diameter), tumours with skin or chest wall involvement (T4), and those with axillary lymph node involvement at diagnosis (N1-2)[14]. Other patients with smaller tumours might be considered if they wish to undergo BCS rather than mastectomy or if they present a small breast-to-tumour size ratio[15].

For NET in particular, traditional criteria include positive HR status, stage II or III, and post-menopausal status (see section 3.1). ER+ status is a pre-requisite but, unlike with adjuvant ET which tends to be used in all ER+ tumours, NET is normally reserved for ER-rich BC (Allred 7-8, or >50% staining), as most evidence has shown better results in these cases[13]. Indeed, there is a statistically significant linear relationship between ER expression and odds of response to NET[16], and many NET trials have selected specifically for strongly-ER+ cases[17–19].

3. Evidence and trials to date

Over the last 25 years, a wealth of clinical trials and research on the effect of NET in BC have been conducted. The next sections will review the evidence compiled to date and describe how this has helped refine our understanding and use of this therapeutic strategy for the management of HR+/HER2- disease.

3.1. NET vs NCT and the role of menopausal status

While neoadjuvant chemotherapy (NCT) is another available option for pre-operative treatment, evidence has shown that patients with luminal (i.e., HR+) BC derive less benefit from it. Indeed, studies have shown that the rate of pathological completely

response (pCR, defined as an absence of invasive and in situ disease, or ypT0/is ypN0, after treatment) achieved with NCT is lower in luminal tumours than in triple negative or HER2+ disease (7 vs 36 and 27%, respectively)[20–22]. Research has also shown that the degree of response to NCT is inversely correlated to the level of ER expression[22]. This is consistent with the notion that ER+ BCs, and in particular luminal A tumours, might also derive no survival advantage from chemotherapy in the adjuvant setting[23,24]. Indeed, it has been reported that the absolute OS benefit from adjuvant cytotoxic chemotherapy in unselected postmenopausal women with HR+/HER2- tumours is of only 3-4%[25]. Data from the TAILORx and RxPONDER trials, which randomised patients with HR+/HER2- BC to adjuvant ET only or combined chemo-endocrine therapy, showed no significant differences in invasive disease-free survival between both treatment groups[26,27]. The International Breast Cancer Study Group IX trial also showed no additional benefit in postmenopausal women with ER+ BC treated with combination adjuvant chemotherapy and tamoxifen, when compared to tamoxifen alone[23,24].

Importantly, evidence has suggested that among patients with HR+/HER2- BC, the suitability of ET as a safe alternative for pre-operative treatment depends on their status as premenopausal (pMW) or postmenopausal (PMW) women[28–32]. While some studies have reported downstaging of HR+ tumours under NET in pMW[33], evidence has been deemed insufficient to confirm the safety of this strategy in this younger subgroup of patients, who typically have worse prognosis[34,35]. For example, a recent trial designed to compare the efficacy of 24 weeks of NCT or NET in pMW reported better clinical outcomes in the NCT group[36]. Thus, NCT is normally preferred to treat pMW for whom pre-operative treatment is deemed necessary. If NCT is not an option due to patient preference or co-morbidities, the patient should proceed to surgery rather than receive NET. Interestingly, recent evidence has shown that chemotherapy might exert an antiestrogenic biological effect on the tumours of HR+ pMW, possibly as a consequence

of the inhibitory effect on ovarian function, suggesting that the benefit from NCT in this cohort might be partly due to a secondary endocrine blockade[37].

In contrast, NET has been shown to be an appropriate treatment option in PMW (see Table 1 for a summary of key trials and findings). A phase II trial that compared NET and NCT showed no significant differences in clinical (64.5 vs 63.6%) or mammographic (60 vs 63%) response, but lower toxicity and a trend toward better BCS rates (33 vs 24%, p=0.058) in the NET group[34]. The Spanish GEICAM/2006-3 trial compared NET with NCT in 95 women with luminal BC and showed no significant differences in outcome between treatments for the PMW subgroup [29]. A meta-analysis of those two trials confirmed this evidence[31]. The Neoadjuvant Endocrine vs Chemotherapy Trial (NEOCENT) also compared both treatments in PMW with ER-rich BC and found similar response rates[38]. Another meta-analysis comparing NET and NCT using data from these three trials (total n=378) supported these results, reporting similar response rates between both treatment groups, but lower toxicities and a trend towards improved BCS rates (odds ratio (OR) 1.08, p = 0.85) in the NET arm[28]. A recent study of data from the American National Cancer Database (NCDB) reported that, although NCT might achieve higher pathologic response rates, NET can also lead to considerable tumour and node downstaging (T: 58 vs 40.5%, p<0.001; N: 29 vs 18.3%, p<0.001)[39]. Generally, NCT should not be used only for disease downstaging if chemotherapy will not provide a survival benefit.

Thus, NET represents a logical and promising approach for downstaging disease in postmenopausal HR+/HER2- BC patients, although careful review and continued monitoring to ensure the cancer is responsive or stable is required to ensure the safety of this strategy. Consistently, recent guidelines and recommendations from multiple international expert groups have recommended NET favourably in this group to increase locoregional treatment options or disease control in inoperable cases, while in pMW NET

should be limited to the research context of clinical trials[35,40–44]. Besides the reported efficacy, favourable BCS rates and low toxicity profile, NET also has the advantage of having a lower cost and being more readily available and more easily administered, important aspects when we consider that 70% of BC deaths take place in low or middle-income countries[45]. Beyond this established evidence, research continues with the aim of further optimising NET use among PMW, including the assessment of tools for improved selection between and prediction of response to NET or NCT (see section 4) and trials investigating combination treatments (see section 5). The pre-operative setting also offers unique research opportunities that merit further study (see section 6).

3.2. NET agents: tamoxifen vs aromatase inhibitors

The third-generation aromatase inhibitors (AIs) letrozole, anastrozole and exemestane have been shown to be superior to the SERM tamoxifen for adjuvant treatment of PMW with HR+ in several trials[46,47]. Numerous studies have also been conducted to compare these two types of ET in the neoadjuvant setting (see Table 2 for a summary of key trials and findings).

The P024 trial reported the superiority of 4 months of neoadjuvant letrozole over tamoxifen in 337 patients with early BC who were initially not eligible for BCS. Letrozole had better overall objective response (55% vs 36%, $p<0.001$) and BCS (45% vs 35%, $p=0.022$) rates[48,49]. This was also reflected in pathological changes, as letrozole induced a greater reduction in mean levels of the proliferation marker Ki67 than tamoxifen (87 vs 75%)[50].

The Immediate Preoperative Anastrozole, Tamoxifen, or Combined with Tamoxifen (IMPACT) trial compared 3 months of neoadjuvant tamoxifen, anastrozole or a combination of both agents in 330 women with ER+ operable or potentially operable BC[51]. Results showed no significant differences in objective response rates between

treatment arms, but reported better BCS rates in the anastrazole group compared to the tamoxifen group for the subgroup of patients who were initially only eligible for mastectomy (46 vs 22%, p=0.03).

The Preoperative Anastrozole Compared with Tamoxifen (PROACT) trial also compared 12 weeks of neoadjuvant anastrozole or tamoxifen in a similar cohort of 451 patients[52]. This study showed no significant differences in response rates assessed through calliper (50 vs 46.2%, p=0.29) and ultrasound measurements (39.5 vs 35.4%, p=0.29). However, PROACT also included patients receiving NCT and, when this subcohort was excluded from the analysis, the anastrozole arm did show a tendency towards better response over tamoxifen (calliper response: 49.7 vs 39.4%, p=0.08; ultrasound response: 36.2 vs 26.5%, p=0.07). These differences were significant in the subgroup of patients whose tumours were deemed inoperable at baseline (calliper response 48.6 vs 35.8%, p =0.04; ultrasound response: 52 vs 29%, p = 0.03). Downstaging from inoperable or BCS-ineligible to operable or BCS-eligible also favoured the anastrozole arm (43 vs 30.8%, p=0.04).

A Russian study comparing 3 months of neoadjuvant exemestane or tamoxifen in 151 patients with T2N1-2, T3N0-1 or T4N0M0 disease also showed the superiority of the AI[53]. The exemestane arm showed improved clinical response (76.3 vs 40%, p=0.05) and BCS (36.8 vs 20%, p=0.05) rates.

A meta-analysis of these 4 trials was conducted, including evidence from a total 1,160 PMW with ER+ BC[54]. This confirmed that, while toxicities and tolerability were similar for both NET types, AIs were superior in both clinical response (risk ratio (RR) 1.29, p<0.001), ultrasound response (RR 1.29, p=0.002) and BCS (RR 1.36, p<0.001) rates. A second meta-analysis comparing data from 7 trials of NET with AI vs tamoxifen also reported a greater efficacy of AIs, with improved clinical response (OR 1.69, p <0.001, n=1,352), radiological response (OR 1.49, p < 0.001, n=1,418) and BCS (OR 1.62, p <

0.001, n=918) rates[28]. A third meta-analysis also concluded on the feasibility of NET for PMW and the preference for AIs over tamoxifen due to higher overall response rates (OR 1.9, 95% CI 1.17-3.08)[31].

3.3. NET agents: choice of AIs

The American College of Surgeons Oncology Croup (ACOSOG) Z1031 trial compared the effect of NET with the three third-generation AIs for 16-18 weeks in 377 PWM with ER-rich T2-4, N0-3, M0 BC[17]. This study found no significant differences between the anastrozole, letrozole and exemestane treatment groups in neither objective response (69.1, 74.8 and 62.9%, respectively) or BCS (64, 42.1 and 48.1%, respectively) rates. Another study compared the effect of shorter courses (14 days) of neoadjuvant anastrozole or letrozole and reported similar rates of downregulation of ER, PR and Ki67[55]. The HORGEN and CARMINA02 studies were two non-comparative multicentre phase II trials comparing 6 months NET with anastrozole or the selective ER degrader (SERD) fulvestrant in PWM with HR+ BC who were initially not eligible for BCS[56,57]. A subsequent pooled analysis of both trials showed, consistently with each trials initial results, no significant differences between treatment arms in BCS and pathological response rates[58]. The longer follow-up also enabled researchers to show no differences in RFS and OS at 5 years (83.7% and 92.7%, respectively). There was a trend for better clinical response in the anastrozole arm (55.9 vs 44.3% in the fulvestrant arm), but the non-comparative design of the trials meant clinical response superiority could not be properly assessed.

3.4. Duration of NET treatment

Although the majority of NET trials to date have treated PMW for a duration of between 3 and 6 months, several studies have shown that a longer duration of NET can also lead to improved response rates[42,59] (see Table 3 for a summary of key trials and findings).

One study of 182 women at our institution showed that, while 3 months of neoadjuvant letrozole achieved clinical and ultrasound response in 69.8% patients, this increased to 83.5% with longer treatment[60]. BCS rates also improved from 60 to 72%. Tumour volume continued to decrease when comparing 3-6 months, 6-12 months and 12-24 months of NET (with medians of 50, 37 and 33%, respectively). Another study comparing NET with letrozole for 4, 8 or 12 months showed that, while similar Ki67 reduction was achieved in the three treatment arms, there was a significant trend for higher pCR rates with longer NET (respectively, 2.5, 5 and 17.5%, $p<0.04$)[61].

Another study of 116 ER+ women treated with neoadjuvant exemestane reported that objective response rate improved from 47.4% at 16 weeks to 50.9% at 24 weeks[62]. A phase II trial also showed an increase in overall response when comparing the effect of 3 or 6 months of neoadjuvant exemestane (58.7 vs 68.3%, respectively)[63]. Interestingly, a prospective multicentre trial of 146 patients treated with neoadjuvant letrozole found that the median time needed to attain BCS was 7.5 months, supporting the case for extended NET[64]. A smaller retrospective review of NET-treated patients also supported longer that conventional therapy to achieve additional downstaging, as it showed a mean duration of 9.7 months of NET before patients underwent BCS[65].

Transcriptomic analyses have provided some interesting insight into the effect of NET duration[66–68]. A recent study compared the gene expression changes induced by AIs in two different cohorts where patients received only 2 weeks or more than 1 month of NET[68]. As expected from previous analysis, downregulation of proliferation was observed after 2 weeks of AIs. However, longer treatment led to a broader range of changes in cancer-related signalling pathways and the immune checkpoint. This suggests that good AI responders can be identified early on-treatment, while also hinting at additional changes happening under extended NET regimens, likely contributing to the further downstaging and improved outcomes observed under longer NET.

3.5. NET and histological subtypes

Another factor meriting discussion is the use of NET across different histological subtypes of breast cancer. This is relevant given the fact that lobular BC accounts for up to 15% of new diagnoses and is known to respond poorly to NCT[69]. In a study from our institution, 61 PMW with ER-rich invasive lobular carcinoma (ILC) were treated with NET (letrozole for ≥3 months)[70]. Results showed a high rate of response, with a mean reduction of tumour volume (measured clinically) at 3 months of 66%. Of the 40 patients who were operated after 3 months of NET, 31 were deemed suitable for BCS (with a final rate of successful breast conservation of 81%), while the remainder 21 patients were kept on longer NET and 19 of them remained controlled on letrozole at a median of 2.8 years. In another study, we compared the molecular effect of letrozole in the biology of lobular (n=14) and ductal (n=14) tumours[71]. Interestingly, we found that while the intrinsic biological differences between both histologies were preserved over time, the gene expression changes induced by NET in responsive tumours was very similar in both subtypes.

A more recent study reviewed changes in the management of ILC using data from the NCDB (n=69,312 cases)[72]. While primary surgery remains the most common treatment strategy, this study reported small but significant changes, including a decrease in the use of NCT (4.7 to 4.2%, p=0.007) and an increase in the use of long-course (1-12 months) NET (1.6 to 2.7%, p<0.001). Long-course NET was significantly associated with improved BCS rates and less axillary surgery in patient with HR+/HER2- ILC, supporting the notion that NET might be an option for surgical downstaging in this group of patients.

3.6. NET and the management of the axilla

Less is known about the effect of NET on axillary management. Most research has suggested that NET is less likely to de-escalate surgery in the axilla than in the breast,

but nodal response can still be achieved[39,73–75]. Several recent studies have shown that the outcomes and prognostic significance of axillary burden was similar between patients receiving NET and those receiving upfront surgery[76–78]. An analysis of NCDB data showed that sentinel lymph node biopsy (SLNB) rates were similar between both groups, while patients who received NET were less likely to undergo axillary lymph node dissection (ALND)[76]. Another study found no survival differences between SLNB and ALND[78]. Overall, the data to date suggests that, in addition to the efficacy of NET for tumour downstaging and improved BCS rates, NET might also represent an opportunity for de-escalation of axillary treatment in HR+/HER2- BC[73,75–78]. Recently, a retrospective analysis of patients who received NCT or NET reported no significant difference in the rates of axillary response (13.9 vs 7.3%, p=0.232), although further prospective studies to confirm these observations would be advisable[79].

4. Assessment of response and prediction of treatment benefit during NET

In addition to its effectiveness for disease downstaging in many PMW with HR+/HER2- tumours, NET offers a unique opportunity for in vivo observation of the tumour's response to treatment. This can help ensure disease remains responsive or stable, and ascertain if a change to the treatment strategy is necessary. Indeed, monitoring of response to treatment during NET provides unique opportunities for early prediction of treatment benefit and identification of patients with different levels of response. Based on this, poor responders might be changed to an alternative or combination neoadjuvant treatment, or their NET might be interrupted to proceed to surgery sooner if feasible. Patients might also be stratified based on their response in the neoadjuvant setting for better treatment selection in the adjuvant setting. Ultimately, this can translate into more personalised treatment of patients with HR+/HER2- BC in both the neoadjuvant and the adjuvant settings: those likely to have excellent outcome with ET alone can be spared unnecessary treatment unlikely to provide additional benefits, while others with worse prognosis can

be selected for more effective treatment, such as the addition of adjuvant chemotherapy or CDK4/6 inhibitors[80,81]. The next sections summarise the evidence to date on different biomarkers, indices and genetic signatures which have been developed or assessed as surrogates for the assessment of response to or prediction of benefit from NET.

4.1. Clinical and biological measures of response: Ki67 and PEPI

While pCR to NCT is associated with improved survival and this metric has been used to compare outcomes from NCT and NET (see section 3.1), evidence has shown that pCR might be less useful in assessing response to NET. This is likely due to the fact that ET largely exerts a cytostatic (rather than cytotoxic) effect, which might be better assessed using other measures or surrogates. Indeed, research has shown that the likelihood of achieving pCR is much lower in patients with HR+/HER2- BC, but also that the prognostic significance of pCR in this subgroup is limited: the association between pCR and outcome is less robust, and a lack of pCR does not correlate with poorer outcomes[82]. Instead, the effect of NET can be monitored by assessment of clinical response (by calliper measurement of tumour size or changes to the feasibility of BCS), radiological response (using imaging techniques to monitor changes in tumour volume) or pathological response (taking sequential biopsies to assess proliferation, or to look for histological changes associated with treatment response)[13,33,83].

Ki67 is a nuclear marker of proliferation (expressed in all phases of the cell cycle except the G_0 and early G_1 phases [84–86]) whose prognostic value has been shown in numerous studies[87]. The evidence on the role of Ki67 has been previously reviewed elsewhere[88,89]. In short, its baseline level is an established prognostic factor, and its level after a period of pre-operative treatment can also be a useful indicator of response, with evidence from the IMPACT trial showing that it can correlate with long-term outcome after as little as 2 weeks[90–92]. Ki67 has been assessed in several NET trials and,

importantly, on-treatment levels in these studies were able to anticipate the outcome of equivalent adjuvant trials[89]. In addition to being used as an endpoint in numerous studies, Ki67 measurement has been recommended as a proliferation surrogate to differentiate between luminal A and B subtypes[93,94].

Despite this evidence, the adoption of Ki67 as a marker has been limited by a number of factors. For example, there was an initial lack of guidelines for the best timepoint for Ki67 assessment[89]. This was one of the questions addressed by the Peri-Operative Endocrine Therapy: Individualising Care (POETIC) study, a phase III window-of-opportunity trial comparing 4 weeks peri-operative AI (2 weeks pre- and 2 weeks post-surgery) with no therapy that assessed how Ki67 levels at baseline and at 2 weeks predict recurrence-free survival (RFS) and OS[95]. Their results showed that low Ki67 at either timepoint is indicative that patients will do well with adjuvant ET only, whereas a high Ki67 at 2 weeks can help select patients for further adjuvant treatments. It is now established that response to AIs leads to a rapid decrease in Ki67 and proliferation should remain low unless the patient stops responding. In line with these findings, numerous institutions and studies now measure on-treatment Ki67 levels (typically at 2 or 4 weeks) to assess response to NET. For example, the ACOSOG Z1031B trial utilised on-treatment Ki67 levels to assess NET response: if Ki67 was >10% after 2-4 weeks of NET, patients were deemed non-responsive to NET and switched to NCT or advanced to surgery[96]. The ALTERNATE trial follows a similar approach to select non-responsive patients for switch to NCT[97]. The ongoing POETIC-A phase III trial (NCT04584853) will also use on-treatment Ki67 as a criterion to select patients with lower response to NET, who will then be randomised to adjuvant treatment with ET-only or in combination with the CDK4/6 inhibitor abemaciclib.

Numerous technical hurdles have continued to limit the wider adoption of Ki67 as a marker. While the use of immunohistochemistry makes Ki67 assessment very cost-

effective, there is considerable variation and a lack of consensus in methodology and scoring, which leads to high discordance both across different laboratories and between individual observers[98–102]. There have also been concerns that intra-tumour heterogeneity and uneven expression patterns including 'hot' and 'cold' spots might lead to further variability and inaccuracy when only small core biopsies are assessed[103]. There is also evidence that pre-analytical factors such as fixation can lead to additional issues[104,105]. Expert teams have worked to address these biases, defining protocols and recommendations to help standardise and validate Ki67 evaluation[98,100,105,106], and research continues to investigate potential approaches to help standardise its accurate assessment[102,107,108].

Other research has questioned our traditional understanding of Ki67 biology. For instance, a recent study argued that the current binary assessment of Ki67 as positive/negative stain is not appropriate and this should be regarded as a graded marker[109]. This is at least partly due to an underestimation of the complex role of Ki67, which exerts a range of functions across the different phases of cell division[109,110]. This is evidenced by its changing patterns of expression during proliferation: it is known that Ki67 is expressed during all phases of the cell cycle except G_0, starting in late G_1 and reaching maximum levels during G_2 and M phases, before a rapid decrease in expression in the latter stages of mitosis[86,109,111]. Thus, Ki67 suppression might be an indicator of quiescence, but its expression might not be the most accurate marker of proliferation, as dividing tumour cells could be misidentified[85,109]. Other proteins might hold greater potential as proliferative markers. For example, specific markers for G_2/M transition or M phase would likely make for more accurate surrogates, as most cells reaching these stages will complete the cell cycle[112,113]. Interestingly, proteins in the minicromosome maintenance (MCM) family, also expressed in all active phases of the cell cycle, have been shown to hold promise as proliferation markers in luminal breast cancer. Compared

to Ki67, the function of MCM proteins is better understood and it seems their assessment is limited by fewer technical and pre-analytical factors, with recent studies reporting that MCM proteins might outperform Ki67 as proliferation markers[85,104,114,115].

The Preoperative Endocrine Predictive Index (PEPI) was developed based on data from the P024 trial and validated in the IMPACT cohort[116] (see also section 3.2. and Table 2). This index incorporates tumour size, nodal stage, ER and Ki67 of the surgical specimen after NET to provide a prognostic score (good (0), intermediate (1-3), or poor (≥4) prognosis) shown to correlate with RFS (p=0.002). Patients with early-stage tumours and a PEPI score of 0 had no recurrences in 5 years, representing a subgroup of women for whom adjuvant chemotherapy could be safely avoided. The prognostic value of PEPI is likely to be further validated through trials such as ALTERNATE (see section 5) which incorporate this score into their design for response monitoring and to help guide selection of neoadjuvant or adjuvant treatment for non-responders[18,19].

While the use of Ki67 or PEPI is still not a clinical standard globally, a recent single-institution prospective study of a cohort of 115 patients treated with neoadjuvant letrozole represents a good example of how these on-treatment markers can be utilised in the pre-operative management of HR+/HER2- BCs[117]. All patients underwent Ki67 assessment at diagnosis and, for those with high baseline proliferation (Ki67≥10% at diagnosis), again after 4 weeks of treatment. NET led to significant tumour downstaging, with a median tumour size reduction of 40%, and 85.2% of patients receiving BCS. Importantly, Ki67 assessment in combination with continued clinical and ultrasound assessment enabled monitoring of NET response, so that patients with progressive disease were advanced to surgery while patients with stable or responsive tumours remained on NET for at least 2 months and up to 1 year, or until maximum response was achieved. The authors concluded that assessment of on-treatment Ki67 levels, shown to be significantly related to a PEPI-0 score (p<0.002), was useful in providing prognostic information and guiding

treatment decision-making, evidencing how the findings from clinical trials over the last two decades can be successfully translated into clinical practice (see also section 7).

4.2. Gene expression tools for on-treatment assessment

In addition to simpler markers like Ki67 and PEPI, several signatures have also been developed and assessed for their predictive and prognostic value in BC. While most of these tools have been validated to help guide adjuvant treatment selection, there is growing evidence on the potential utility of these genomic assays in the neoadjuvant setting, as recently reviewed elsewhere[118–120]. This section will summarise studies investigating the use of such signatures for NET response prediction, or signatures specifically developed around the NET window (see Table 4 for summary).

Oncotype DX is a prognostic tool that generates a recurrence score (RS) based on the expression level of 21 genes, including ER-related genes. Patients are stratified into 3 different risk groups (low, intermediate and high-risk) based on their calculated value for the continuous RS (0-100), with RS cut-offs having been refined more recently based on trial data[121,122]. Although RS was conceived to help guide patient selection for chemotherapy, three studies have assessed the association between pre-treatment RS and NET response[123]. A study of diagnostic biopsies from 43 patients treated with NET reported higher response rates in the low-risk RS group compared to the intermediate and high RS groups (64 vs 31 and 31%, respectively), and a non-significant trend towards better 5-year PFS (100 vs 84 and 73%, respectively)[124]. A second study of 116 patients who received NET reported improved outcomes in low RS cancers compared to the high RS group, in both clinical response (59.2 vs 20%) and BCS (90.6 vs 46.7%) rates[125]. The more recent and larger TransNEOS study performed RS assessment of diagnostic biopsies from 295 PMW with HR+/HER2-, node-negative BC who received 6 months of letrozole and reported significant differences in clinical response rates for the different RS groups (RS <18: 54%; RS 18-30: 42%; RS>30: 22%; p<0.001)[126]. A recent meta-

analysis of these 3 trials confirmed differences in clinical response rates to NET between the low and high genomic risk groups (RS<18: 55-64%; RS>30:20-31%)[123]. Two small phase II trials have also been conducted to test the use of the RS assay to guide selection of NET or NCT[127,128]. In both of these studies, patients in the low-risk group (RS<11) received NET, patients in the intermediate group (RS 11-25) were randomised to NET or NCT, and patients in the high-risk group (RS>25) received NCT. Non-high RS has also been used as a selection criterion in studies assessing the addition of targeted therapy agents to NET[129,130] (see section 5). The DxCARTES study is assessing how differences in RS pre- and post-neoadjuvant treatment might be indicative of molecular changes induced by a combination of letrozole and the CDK4/6 inhibitor palbociclib[131]. This follows a previous study which showed that the combination of pre- and post-NET RSs could predict disease-free survival in patients who received pre-operative exemestane[132].

Interestingly, a recent update from the ADAPT (Adjuvant Dynamic Marker-Adjusted Personalized Therapy Trial Optimizing Risk Assessment and Therapy Response Prediction in Early Breast Cancer) trial reported the combined use of RS and post-NET Ki67 to guide treatment selection in patients with early luminal BC and limited node involvement (pN0-1) within the ET subtrial[133]. In short, the specific subgroup of postmenopausal patients with higher RS (12-25) but evidence of NET response (Ki≤10%) could be safely spared chemotherapy, as they were treated with adjuvant ET only but achieved outcomes comparable to those of ET non-responders who received adjuvant chemo-endocrine therapy. These results support the notion that an approach incorporating multiple preoperative predictors could lead to improved selection of adjuvant treatment.

MammaPrint is a 70-gene signature that stratifies BC patients according to the risk of distant recurrence at 5 and 10 years. It has been validated to aid selection for adjuvant

chemotherapy and has been shown to agree with Oncotype DX in patient outcome prediction[134]. While there is only limited evidence on the predictive role of MammaPrint for NET response, the PersonaLized neoAdjuvant Strategy ER Positive and HER2 Negative Breast TO Increase BCS Rate (PLATO) phase II study is currently underway to assess MammaPrint as a tool for neoadjuvant treatment selection in patients with HR+/HER2- BC initially ineligible for BCS, with high-risk and low-risk patients being selected for NCT or NET, respectively[135]. A predefined substudy of the Neoadjuvant Breast Registry Symphony Trial (NBRST) compared conventional IHC/FISH subtyping with an alternative molecular classification method using MammaPrint in combination with the 80-gene signature BluePrint. Their results showed that 18% of cases considered 'clinically' luminal were reclassified as a different subtype with the MammaPrint/BluePrint tool, highlighting the importance of accurate subtyping for improved prediction of treatment response. Similar findings were reported in a subsequent assessment of cases from the NBREaST II trial, where 9% of cases were reclassified by MammaPrint/BluePrint molecular subtyping[136]. A recent single-centre retrospective analysis suggested that NET is a feasible option for patients with a low-risk MammaPrint score, with 76% radiologic response rate among the 51 luminal cases included[137]. Another ongoing trial (NCT04129216) will also use MammaPrint to monitor genetic and molecular changes during NET.

The 12-gene assay EndoPredict (EP) and the refined hybrid risk score EPclin (incorporating EP with node status and tumour size as clinical factors) have been shown to independently predict the likelihood of distant recurrence at 5 and 10 years in patients with HR+/HER2- BC treated with ET alone[138]. The N007 study, a small single-arm trial of combination neoadjuvant letrozole and palbociclib, included EP and EPclin assessment, with results showing that EPclin might be a better predictor of post-neoadjuvant treatment prognosis than PEPI[139]. Another recent study conducted

retrospective EP assessment of biopsies from the neoadjuvant ABCSG-34 trial, where cases had been assigned to receive NET or NCT depending on clinico-pathological factors including HR status and menopausal status[140]. Results showed that the molecular score predicted treatment response to both NET and NCT, with both low-risk NCT-treated and high-risk NET-treated patients responding poorly (negative predictive value: 100% and 92.3%, respectively). In short, there is some evidence that the EP scores might hold potential for NET response prediction, but further prospective validation is still needed to confirm this.

Symmans et al developed a Sensitivity to Endocrine Therapy (SET2,3) genomic index based on microarray profiling of diagnostic HR+ BC biopsies, which was shown to predict survival benefit from adjuvant ET[141]. Subsequent work saw SET2,3 refined into a 28-gene score of non-proliferative HR-related transcription ($SET_{ER/PR}$) adjusted with a baseline prognostic index (BPI) including clinical factors (tumour and node stages) and molecular subtype (determined using a 4-gene classifier)[142,143]. Assessment of this revised algorithm showed that it could provide additional prognostic value to residual cancer burden (RCB, a surrogate predictor for chemo-response) in clinically high-risk HR+/HER2- BC[143]. More recently, a correlative study assessed the ability of this signature to predict NET response using baseline gene expression data from cases from the ACOSOG Z1031 NET trial[144]. Results showed that a high SET2,3 score in pre-NET biopsies was associated with early pharmacodynamic response to NET and improved event-free survival, although not with pathological response rates (PEPI-0 score). The authors concluded that, while further validation is needed, their results suggest SET2,3 could become a useful surrogate to guide patient selection for NET.

The Chemo-Endocrine Score (CES) was developed based on the PAM50 intrinsic subtype classification and the inverse relationship of endocrine and chemotherapy sensitivity[145]. Validation in 4 HR+/HER2- neoadjuvant datasets showed that CES could

predict response to both NCT and NET, independently of known clinico-pathological variables.

Lastly, besides the aforementioned signatures (which were initially validated for their adjuvant use and have now been assessed in the neoadjuvant setting), we have previously reported on a tool developed specifically around the NET setting. Indeed, work from our group led to the development of the Edinburgh EndoResponse4 (EER4) tool, a 4-gene signature to predict response to ET with AIs based on the expression of two genes at baseline and two genes after 2 weeks of NET[146]. EER4 classified patients into discrete responder and non-responder groups with high accuracy in both the training and independent validation cohorts (96 and 91%, respectively), and was also shown to predict RFS (p=0.029) and BC-specific survival (BCSS) (p=0.009). Subsequent work has led to further development and refinement of the signature[147]. The EndoAdjuvant2 Clinical (EA2Clin) hybrid tool incorporates expression of two genes (baseline level of the immune and ER signalling-related signal transducer IL6ST and on-treatment level of the proliferation-related MCM4) with clinical factors (tumour size and grade, and node status). EA2Clin classification of PMW who received NET was shown to accurately predict outcome from adjuvant ET ($p<0.001$ for both RFS and BCSS) regardless of the agent (AI or tamoxifen) received. Further validation is currently underway and a future prospective trial will be the next step to confirm the potential clinical utility of this NET-specific tool.

In summary, there is growing evidence that genomic signatures might be useful for NET selection and response prediction, with trends showing that low-risk cases derive less benefit from NCT and exhibit better response rates to NET. As monitoring and prediction of NET response can be instrumental to achieving optimal disease management in both the neoadjuvant and adjuvant settings, prospective trials now often incorporate into their designs some of these assays for on-treatment assessment[118,119]. Along with other

ongoing research, these studies might also provide more exhaustive validation of these tools to help bring them closer to clinical translation.

5. NET combination trials

Following the strong evidence on the efficacy of neoadjuvant AIs, a wealth of new NET trials have emerged over the last decade to assess combination therapies for the neoadjuvant treatment of HR+/HER2- BC, be it the combination of multiple ET drugs, or ET and other targeted agents. Recent reviews by Escrivà-De-Romaní, Guerrero-Zotano and their colleagues[148,149], have described how these NET trials can be classified according to their approaches as enrichment adaptive design (where assessment of on-treatment biomarkers might determine treatment changes), multi-arm lead-in design (where NET ± targeted agent treatment arms are compared), single-arm designs (where multiple biopsies might be collected to monitor evolving response to treatment), or window of opportunity designs (shorter studies where assessments are made to characterise the mechanism of action or molecular changes induced by treatment). This section summarises some of the most relevant recent and on-going NET combination trials.

The aforementioned Alternate Approaches for Clinical Stage II or III Estrogen Receptor Positive Breast Cancer Neoadjuvant Treatment (ALTERNATE) trial is a prospective phase III study comparing 6 months of neoadjuvant treatment with the AI anastrozole, the SERD fulvestrant or a combination of both in patients with ER+/HER2- BC[18,97]. While longer follow-up is needed to analyse RFS data, initial results reported no improvement on disease response in either the fulvestrant or combination arms, compared to the anastrozole treatment group.

Several studies have assessed the combination of ET with CDK4/6 inhibitors in the neoadjuvant setting[150]. Besides a potential survival benefit, it has been suggested that this approach might enable molecular downstaging in higher-risk patients, converting

more aggressive tumours to a more indolent cancer (such as luminal B to luminal A)[151]. This was supported by the results from the CORALLEEN phase II trial, which looked at pre-operative treatment with a combination of letrozole and ribociclib[152]. The MONALEESA-1 trial was a small window-of-opportunity study comparing biological response to neoadjuvant letrozole alone or in combination with ribociclib, with results reporting greater Ki67 reduction in the combination arm[153]. The FELINE trial has been designed to assess whether the addition to neoadjuvant letrozole of ribociclib (in either a continuous or intermittent dosing regimen) can lead to a greater proportion of cases achieving a PEPI-0 score, although preliminary results did not show different outcomes between treatment groups[154].

The NeoPalAna study assessed neoadjuvant treatment with a combination of the AI anastrozole and the CDK4/6 inhibitor palbociclib in 50 patients with ER+/HER2- disease[155]. Results showed complete cell cycle arrest (CCCA, defined as Ki67<2% after 2 weeks) rate was significantly higher in the combination compared to the AI-only group (87 vs 26%, p<0.001). However, increases in Ki67 after discontinuation of palbociclib suggested a maintenance treatment might be required. Additionally, side effects included frequent neutropenia, which might lead to treatment interruption or dose reductions. The phase II PALLET trial also reported increased Ki67 reduction in patients treated with combination neoadjuvant letrozole and palbociclib, compared to the letrozole-only group[156]. More recently, the SAFIA phase III trial found no additional pathological response benefit from the addition of palbociclib to HR+/HER2- BC patients responding to neoadjuvant fulvestrant[157]. The ongoing DxCARTES trial (NCT03819010) will assess the effect of 6 months of neoadjuvant combination treatment with palbociclib and letrozole[131].The ongoing phase III trial NCT03969121 trial will assess the same combination, studying both clinical and molecular response to evaluate potential molecular downstaging. Interestingly, the NeoPAL trial randomised 106 patients to

neoadjuvant treatment with letrozole and palbociclib, or with NCT. The results showed similar outcomes in both treatment arms and no difference in BCS rates or long-term outcomes, suggesting that NET plus CDK4/6 inhibitors might be a safer, less toxic option than NCT for patients with high-risk luminal BC [158,159].

The NeoMONARCH study was a phase II multicentre trial including 224 patients which compared 2 weeks of neoadjuvant treatment with the CDK4/6 inhibitor abemaciclib, anastrozole, or a combination of both[160]. Ki67 suppression after 2 weeks was greater in both treatment groups including abemaciclib ($p<0.001$) when compared to the AI-only arm.

A recent meta-analysis considered all evidence to date on the use of CDK4/6 inhibitors in combination with NET[150]. While no significant improvements were observed in PEPI-0, pCR, objective response or disease control rates, the analysis showed that the addition of inhibitors did achieve greater CCCA rates ($p<0.001$). The authors concluded that this combination treatment might be an option for treating HR+/HER2- early BC, but the less favourable toxicity profile and the lack of evidence for better outcome or survival benefits suggests this strategy might not be warranted. Another important caveat that bears mentioning is that the suitability of Ki67 or CCCA to assess response to this type of combination treatments has been questioned (see section 8).

Studies are also underway to assess the combination of NET with other types of targeted agents. One trial (NCT00107016) compared 4 months of neoadjuvant letrozole alone or in combination with the mTOR inhibitor everolimus in 270 PMW with ER+ BC[161]. Results showed a trend towards better clinical response (68.1 vs 59%, $p=0.62$) and a significant greater proportion of patients with Ki67<1% (57 vs 30%, $p<0.01$) in the combination arm compared with the letrozole arm. As with CDK4/6 inhibitors, toxic side effects might limit the adoption of this combination in the neoadjuvant setting. Another trial randomised 92 PMW with HR+/HER2- BC to treatment with neoadjuvant letrozole

plus placebo or the tyrosine kinase inhibitor lapatinib[162]. Results showed no differences in mean Ki67 suppression and similar clinical response rates (63% in the placebo arm vs 70% in the lapatinib arm), but lapatinib led to significantly better objective response rates in cases presenting *PIK3CA* mutations (93 vs 63% in *PIK3CA* wild type, p=0.04). The LORELEI and NEO-ORB phase II trials assessed the effect of adding a PI3K inhibitor to neoadjuvant letrozole in PMW with HR+/HER2- BC. Interestingly, the LORELEI study reported benefit from the addition of taselisib[163], while the NEO-ORB data found no improvement in response[164]. Numerous other studies including NET in combination with targeted or immunotherapeutic agents are underway, which have also been summarised elsewhere[59,149].

6. The NET setting as a platform for research

The neoadjuvant setting offers unique 'research' prospects (see Figure 1 for schematic summary). Firstly, this window of treatment can help identify or validate biomarkers through the assessment of sequential tissue samples, which can include the diagnostic biopsy and eventual surgical specimen, as well as potentially other biopsies taken over the NET period. The development of surrogates such as Ki67 and PEPI since the early 2000s represents a great example of this type of translational research.

Secondly, the NET setting provides an opportunity to study the biology of the disease and its evolution under early treatment. We already discussed how transcriptomic assessment of NET-treated samples has led to a better understanding of the effect of these changes and how it changes over time[68] (see section 3.4). As another example of research in the NET window, one such study assessing genomic changes in patients treated with at least 1 month of neoadjuvant AIs reported the presence of *ESR1* mutations (linked to AI resistance in the adjuvant setting) in 5/87 patients, predominantly in patients who received longer NET (>6 months), showcasing how extended pre-operative treatment can start to give rise to mechanism of ET resistance[66]. Interestingly, another study assessing a

cohort of 172 patients who exhibited primary ET resistance when treated with neoadjuvant anastrozole for at least 3 months concluded that *ESR1* mutations are unlikely to play a role in primary ET resistance [165].

Lastly, and as evidenced by the number of recent combination NET trials, the pre-operative setting can serve as a drug development platform for the testing of biology-driven agents[148,149,166]. Assessment of molecular changes could help confirm target inhibition, and characterise or monitor the induction of specific mechanisms of response or resistance. The NET setting also has the advantage of allowing testing in a much shorter timeframe than adjuvant studies, where a long follow-up is needed before outcomes can be properly assessed. This notion is further supported by the fact that, as previously discussed, NET studies have been shown to anticipate the outcomes of adjuvant, and even metastatic, BC trials[89,148,149]. In line with this, the USA's Food and Drug Administration (FDA) now accepts results from neoadjuvant clinical trials as evidence for new drug approval[148].

7. NET during the pandemic

The recent COVID-19 pandemic led to a once-in-a-generation global healthcare crisis. In the context of BC, this meant the need to defer treatments due to lack of resources or to minimise the risk of patients and healthcare providers being exposed to the virus. Accordingly, many groups urgently reviewed their practices and numerous consortia defined recommendations[167–178]. These included guidelines for patient triage and prioritisation, changes to the use of surgery, radiation and systemic therapies and, importantly, the recommendation to use NET as a strategy for safe management of HR+/HER2- cases in PMW whose surgery and adjuvant treatment could be deferred.

Some experts provided specific guidelines for the use of NET in these cohorts. Martí and Sánchez-Méndez advocated for its use to manage luminal BC patients, using on-

treatment Ki67 assessment to monitor response[179]. Dowsett et al reviewed data from multiple international trials to provide evidence-based practical guidelines for NET selection, including a more refined strategy that minimised the need for on-treatment biopsy[180]. In short, patients were stratified into 3 groups with specific recommendations according to their ER and PR Allred scores: (i) those not suitable for NET (lower HR expression: ER <6 or ER 6 and PgR <6), (ii) those for whom NET is the acceptable course of action (HR-rich: ER 8 and PgR ≥6), (iii) and those (with intermediate HR levels: ER 7/8 and PgR <6, or ER 6/7 and PgR ≥6) for whom NET should be recommended but continuation should be subject to assessment of response 2-4 weeks on-treatment via biopsy for Ki67.

Several studies have reported a shift in clinical practice during the pandemic towards increased use of NET to postpone surgery[181–185]. A review of the American Society of Breast Surgeons registries reported an additional 31% of HR+/HER2- BC patients received NET due to the pandemic[182]. A retrospective single-institution study, comparing cohorts diagnosed in 2019 and in mid-2020 to assess the impact of a 2-month interruption in BC screening due to COVID, found no significant changes in NET administration (17.3% in 2019 vs 28.1% in 2020, p=0.0793)[186]. While their results showed no significant differences in tumour biology, they did report a decrease in in situ disease (-10.4%) and an increase in both node-positive (+11.2%) and stage III (+10.3%) BC. In contrast, two historical cohort studies comparing groups of HR+/HER2- patients treated before and during the healthcare crisis reported significant increases in the use of NET: from 10% to 23% (p=0.001)[183], and from 7 to 48% (p<0.0001)[184]. The larger of these studies showed that, despite the disruption to regular screening programmes, BC stage at diagnosis did not differ significantly before and during the pandemic[183]. A multi-centre matched study directly compared a cohort of patients treated with NET during the pandemic to another cohort from before 2020 who received upfront surgery[187].

Their results showed no evidence of pathological upstaging during the pandemic despite 2.5-longer delays to surgery. Overall, while further analysis once longer follow-up is available could provide additional insight, these findings support the safety and efficacy of NET.

Interestingly, a retrospective study of pre-pandemic NCDB data also suggested a potential protective effect of NET on HR+ ductal carcinoma in situ (DCIS) lesions[188]. Their results showed a trend towards an increased rate of upgrade to invasive disease in patients without NET, but not in those who received NET. While prospective studies are needed to validate these findings, the evidence suggests a protective effect of NET in HR+ DCIS and that this therapeutic strategy might also be underutilised in these pre-invasive lesions. Indeed, guidelines outlined at the start of the pandemic also recommended NET for the management of HR+ DCIS[171,174,184].

8. Conclusion

Despite accumulating evidence for NET since the early 2000s, clinical adoption of NET is still limited, with 2017 data from NCDB reporting that only 3% of eligible patients received this therapy[189]. Indeed, a recent review of trends in clinical practice concluded that, despite the suitability of this approach for a large proportion of BC patients, NET is still underutilised[33]. While it has been established that evidence from clinical trials takes an average of 17 years to be translated into clinical practice[190], several limitations remain that prevent further optimisation and greater adoption of NET. Methodological challenges have been summarised in this review and elsewhere[191]. Importantly, while Ki67 expression has been validated as a predictor and has been used as a proliferation surrogate in many studies, the use of this marker is not without many limitations, including technical challenges, poor standardisation and a poor understanding of the actual role of this protein in the biology of the cell cycle (see section 4.1). Indeed, a recent meeting of the International Ki67 in Breast Cancer Working Group concluded that, while Ki67 IHC

can be a useful tool, its analytical validity is subject to many technical factors and its clinical utility remains limited to prognostic assessment of early disease[105].

Furthermore, although several biomarkers, scores and signatures have been validated in trials, their analytic and clinical validity and clinical utility still need to be corroborated, and clear guidelines and recommendations should be defined before surrogates such as Ki67 and PEPI, or ideally even better tools, can be fully translated into the clinic to help guide individual treatment decision[149]. While some genetic signatures might be aided by the fact that they have already been approved for their use in the adjuvant or metastatic settings, they will still require validation in the pre-operative setting through prospective trials. As discussed, some such studies have already been conducted or are underway[149]. These tools might also be limited by some of their original shortcomings; for example, most of these signatures were developed and validated in cohorts including a large majority of Caucasian patients, so their applicability in more ethnically diverse populations remains unclear[119]. Interesting results from the ADAPT trial have suggested that combining several predictors might help improve upon the limitations of individual surrogates or assays, and could lead to improved stratification for treatment selection[133] (see section 4.2), although further work is needed to confirm the performance of these approaches for selection for specific therapies.

Another limitation is that, as NET studies evolve, the more established surrogates might be less appropriate for the assessment of novel combination treatments. Indeed, we discussed how pCR is less robust as a predictor in the context of NET, compared to NCT (see section 3.1). Similarly, markers initially validated as response surrogates in ET trials might not be suitable to assess the effect of agents exerting their effect through different mechanisms. For instance, if a combination treatment induces cancer cell apoptosis, assessment of Ki67 would likely not be a good measure of response. Importantly, it is also unclear whether Ki67 would be a good surrogate of response to treatments directly

targeting cell division. Indeed, some trials assessing the combination of NET with CDK4/6 inhibitors have reasoned for the use of Ki67 as an outcome based on the notion that said targeted agents have a predominantly antiproliferative effect[156,160]. However, some authors have argued that this might not be the optimal predictor[144]: while Ki67 is a proliferation marker, it has been validated to assess response to cytostatis-inducing ET; so using Ki67 to gauge the effect of directly anti-proliferative targeted agents might lead to an overestimation of the response achieved. Indeed, neoadjuvant trials have reported much greater Ki67 reduction and rates of CCCA with the addition of CDK inhibitors to ET[156,160], which do not appear to be predictive for survival benefit[192,193]. For example, in the assessment of palbociclib ± ET, the neoadjuvant PALLET trial reported a great increase in CCCA rates for the combination arm (90 vs 59%, $p<0.001$)[156], whereas second interim data from the adjuvant PALLAS trial showed no survival benefit and concluded that, although long-term follow-up is still needed, the combination treatment might not be warranted[193]. For this particular combination treatment, the prognostic value of this surrogate is likely limited by the fact that CDK4/6 inhibitors are known to block transition from G_1 to S phase[194], interfering with the already complex expression of Ki67 across the different stages of the cell cycle (see section 4.1.).

The fact that findings based on Ki67 assessment in neoadjuvant studies, previously shown to be a good predictor of adjuvant results when it comes to ET response [89], do not seem to be translated in larger adjuvant studies suggests that the proliferation marker might not be the optimal surrogate for assessment of response to directly anti-proliferative combination treatments. It is possible that genomic or hybrid assays or panels of multiple markers, which incorporate more biological information, could be more suitable for prediction of response to or benefit from these combination strategies. Overall, this highlights the difficulty of establishing robust biomarkers; indeed, well-established predictors require extensive validation and the definition of clear associated guidelines

for their clinical translation. Even then, their use is likely to be limited to the clinical scenarios that very closely replicate their development and validation platforms.

9. Expert opinion

NET represents a safe and viable treatment strategy for most PMW with HR+/HER2- BC. It can achieve survival outcomes comparable to those obtained with NCT in this group of patients, but with better BCS rates and a more favourable toxicity profile, thus enabling more surgical options and a better quality of life. AIs are more effective than tamoxifen and treatment should be at least 4 months, although numerous studies have shown that longer treatment is likely to achieve better response, possibly including a more extensive effect on the biology of the tumour. Consequently, NET duration might be extended if necessary to achieve BCS, as long as appropriate monitoring takes place to ensure the disease does not progress.

The evidence summarised here has shown the importance of prediction and on-treatment assessment of response during NET. Ki67, the most prominent tool for such assessment, has contributed significantly to advances over the last two decades and has been utilised as a surrogate in numerous trials and key clinical scenarios, such as in guiding selection of NET during the recent COVID19 pandemic. However, Ki67 still remains a challenging marker after all these years: evidence has shown the methodological shortcomings for its accurate measurement, while a growing understanding of the underlying biology has told us it might not be the most reliable surrogate for the assessment of treatment response. In short, Ki67 has played a valuable role in the development of NET strategies, and a flawed marker is better than none, but we believe that there is room for improvement and a clear gap in the field for better and more robust markers and/or signatures to meet the remaining clinical needs.

Despite the compiling evidence from recent and ongoing trials showing the role NET can play in the preoperative management and downscaling of disease in appropriately-selected women with BC, uneven clinical adoption and suboptimal use mean this strategy is still underutilised in many centres and territories. This is partly due to the aforementioned need for better, thoroughly-validated biomarkers, as well as for updated standardised guidelines for NET selection. Prognostic tools developed in the adjuvant setting might be useful in this respect, but they need to be validated in neoadjuvant studies. The recent pandemic led to the definition of some recommendations in this respect and a surge in NET administration. Numerous subsequent analyses have provided further evidence of the safety and efficacy of this therapeutic approach, which we hope will lead to greater global confidence in and adoption of NET.

In contrast to this irregular use of NET in practice, there seems to be a better appreciation among the clinical and scientific community for the potential of the preoperative setting for research purposes. Indeed, on-treatment assessment of response can provide invaluable insight into each patient's disease and likely long-term prognosis, which can also help guide adjuvant treatment selection. NET also offers unique research opportunities to gain insight into the changing biology of early disease, for biomarker validation and for the testing of novel strategies.

While the wealth of recent and ongoing neoadjuvant studies is encouraging, as research efforts advance to focus on more complex therapeutic approaches they will likely need to contend with additional challenges. Indeed, most recent trials focus on the assessment of combination treatment with NET and other targeted agents or inhibitors, but these are likely to face multiple hurdles in that (i) existing surrogates for NET response appear to be even more limited in the assessment of changes induced by non-ET agents, (ii) results from preoperative combination studies appear to be less good at anticipating adjuvant results (compared to how NET results could anticipate ET outcomes in the adjuvant or

metastatic settings), and (iii), most importantly, early results from some of these neoadjuvant combination trials have already suggested that more challenging toxicities and limited survival benefits could mean the clinical adoption of these strategies might not be warranted. Nevertheless, we await further results from the many ongoing efforts to determine whether these hurdles could yet be surpassed to lead to potential improvements that could be translated into practice.

In the meantime, joint efforts should be made to ensure NET becomes a global standard of practice for eligible postmenopausal women with ER+/HER2- BC. In the age of precision medicine, primary surgery should not be the go-to option for this patient population and the current underuse of NET in many territories represents a missed opportunity. As we continue to work towards addressing the remaining challenges, we are confident that the use of NET for the pre-operative management of postmenopausal women with HR+/HER2- is likely to increase in the near future.

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Study	Year	Cohort	Treatment	Endpoints	Key Outcomes
Semiglazov et al [34]	2007	PMW with ER+ BC (n=239)	NCT (4 cycles doxo-pacli, n=118) or NET (3 months ANA or EXE, n=121)	Objective response, BCS and pCR rates	No significant difference in CR, MR, pCR or disease progression. Slightly higher BCS in NET arm (33 vs 24%, p=0.058).
GEICAM/2006-03 [29]	2012	Women with operable luminal BC (n=95, of which 51 pMW and 44 PMW)	NCT (4 cycles EC-T, n=47) or NET (6 months EXE (+Gos for pMW), n=48)	CR rate, safety, pCR and BCS rates, axillary node status	No significant differences in CR, pCR or BCS.
NEOCENT [38]	2014	PMW with ER-rich BC (n=44)	NCT (6 cycles FE-C, n=22) or NET (3-4months LET, n=22)	Radiological response, CR and pCR rates; QoL, Ki67 and cfDNA changes	No significant difference in radiological response, objective CR or pCR.
Kim et al [36]	2020	pMW with ER+ BC (n=187)	NCT (AC-pacli, n=95) or NET (6 months TAM+Gos, n=94)	pCR, Ki67 changes, BCS rates and QoL	Higher complete or partial response in NCT arm; no difference in BCS rates or Ki67 changes.
Meta-analysis of Semiglazov and GEICAM trials [31]	2015	See above (Pooled n=334)	NCT (pooled n=165) or NET (pooled n=169)	See above	Trend towards better BCS rates after NET. No significant difference in overall response when considering PMW only.
Meta-analysis of Semiglazov, GEICAM and NEOCENT trials [28]	2016	See above (Pooled n=378)	NCT (pooled n=187) or NET (pooled n=191)	See above	No significant data in CR, radiological response, pCR or BCS rates; lower toxicity with NET.

Analysis of NCDB data [39]	2021	Women ≥ 50 years old with HR+ BC (n=19,829)	Comparison of database information of patients who received NCT (n=14,025) or NET (n=5,804)	Therapy response, including downstaging and pCR	Higher response rates after NCT; but both NCT and NET achieved downstaging and pCR.

Table 1. Summary of clinical trials, meta-analyses and other studies comparing the used of chemotherapy or endocrine therapy as pre-operative treatment in ER+ BC patients. Abbreviations: AC-pacli, Adriamycin/cyclophosphamide, followed by paclitaxel; ANA, anastrozole; BC, breast cancer; BCS, breast-conserving surgery; cfDNA, cell-free DNA; CR, clinical response; doxo-pacli, doxorubicin-paclitaxel; EC-T, epirubicin/cyclophosphamide, followed by taxol; ER+, estrogen receptor-positive; EXE, exemestane; FE-C, fluorouracil/epirubicin/cyclophosphamide; Gos, goserilin; HR+, hormone receptor-positive; LET, letrozole; MR, mammographic response; NCBD, American National Cancer Database; NCT, neoadjuvant chemotherapy; NET, neoadjuvant endocrine therapy; pCR, pathological complete response; pMW, premenopausal women; PMW, postmenopausal women; QoL, quality of life; TAM, tamoxifen.

	Study	Year	Cohort	Treatment	Endpoints	Key Outcomes
Ais vs TAM	P024 [48,49]	2001	PMW with ER+ early BC ineligible for BCS (n=324)	4 months LET (n=154) or TAM (n=170)	ORR, BCS rate	Greater ORR, BCS rate and Ki67 reduction after LET.
	IMPACT [51]	2005	PMW with operable (or potentially operable) ER+ BC (n=330)	3 months TAM (n=108), ANA (n=113) or TAM+ANA (n=109)	ORR, biologic changes, Ki67, surgical downscaling rate	No significant differences in ORR, but better BCS for the ANA group (in subgroup ineligible for BCS at baseline).
	PROACT [52]	2006	PMW with large operable (or potentially operable) ER+ BC (n=451)	3 months ANA (n=228) or TAM (n=223)	ORR, BCS rate	Trend toward better response in ANA arm (significant for subgroup inoperable at baseline); better surgical downscaling.
	Semiglazov et al [53]	2005	PMW with operable (or potentially operable) ER+ BC (n=151)	3 months EXE (n=76) or TAM (n=75)	Objective CR, BCS rates	Improved CR and BCS rates in the EXE arm.
	Meta-analysis of the 4 trials above [54]	2009	PMW with ER+ BC (Pooled n=1,160)	3-4 months TAM (n=581) or 3-4 months AI (ANA, n=341; LET, n= 162; EXE, n=76)	See above	Similar toxicity and tolerability; Superior response and BCS rates with AI.
	Meta-analysis of 7 studies (including the 4 above) [28]	2016	See above (Pooled n=1,580)	Cohorts above, plus additional 165 patients treated with 3 months AI (n=73) or TAM (n=92)	See above	Superior clinical response, radiological response and BCS rates in the AI group.
	Meta-analysis of 5 trials (including the 4 above) [31]	2015	See above (Pooled n=1,441)	Cohorts above, plus additional 185 pMW treated with 6 months ANA+Gos (n=95) or TAM+Gos (n=90)	See above	Superior ORR in AI groups; no significant differences in pCR.

AI comparison	Murray [55]	2009	PMW with operable ER+ BC (n=206)	2 weeks ANA (n=103) or LET (n=103)	Molecular changes in ER, PR and Ki67	No significant differences in downregulation.
	ACOSOG Z1031 [17]	2011	PMW with ER-rich BC (n=377)	4 months EXE (n=124) or LET (n=128) or ANA (n=125)	ORR, BCS rate, Ki67, PEPI and PAM50	No significant difference in outcomes.
	HORGEN [56]	2013	PMW with HR+ BC initially ineligible for BCS (n=108)	6 months ANA (n=56) vs FUL (n=52)	ORR, BCS rate, pathological response, Ki67	No significant difference in response, trend towards better BCS rate in ANA arm.
	CARMINA02 [57]	2016	PMW with HR+ BC initially ineligible for BCS (n=116)	6 months ANA (n=59) or FUL (n=57)	CR and BCS rates, tumour response assessment RFS, markers of response	No significant difference in outcomes.
	Meta-analysis of HORGEN and CARMINA02 [58]	2020	PMW with HR+ BC initially ineligible for BCS (Pooled n=217)	ANA (n=111) or FUL (n=106)	See above	No significant differences, including in RFS or OS at 5 years.

Table 2. Summary of clinical trials and meta-analyses comparing the use of different endocrine therapy agents in the treatment of ER+ BC patients. Abbreviations: AI, aromatase inhibitor; ANA, anastrozole; BC, breast cancer; BCS, breast-conserving surgery; CR, clinical response; ER, estrogen receptor; ER+, ER-positive; EXE, exemestane; FUL, fulvestrant; Gos, goserilin; HR+, hormone receptor-positive; LET, letrozole; NET, neoadjuvant endocrine therapy; ORR, overall response rate; OS, overall survival; pCR, pathological complete response; PEPI, preoperative endocrine predictive index; PMW, postmenopausal women; PR, progesterone receptor; QoL, quality of life; RFS, recurrence-free survival; TAM, tamoxifen.

Study	Year	Cohort	Treatment	Key Outcomes
Dixon et al [60]	2009	PMW with ER+ BC (n=182)	0-3, 3-6, 6-12 or 12-24 months LET	Improved response and BCS rates.
Allevi et al [61]	2013	PMW with ER+ BC (n=120)	4, 8 or 12 months LET	Similar Ki67 reduction, but increase in pCR rates with longer NET.
Toi et al [62]	2011	PMW with ER+ BC (n=116)	16-24 weeks EXE	Increase ORR with longer NET.
Fontein et al [63]	2014	PMW with ER+ BC (n=102)	3 or 6 months EXE	Increased overall response with longer NET.
Carpenter et al [64]	2014	PMW with ER+ BC (n=146)	Up to 12 months LET	Median time to achieve BCS is 7.5 months.
Lobo-Cardoso et al [65]	2017	PMW with ER+ BC (n=33)	Up to 24 months NET with TAM or AI	Additional downstaging with longer NET; median duration of 9.7 months for BCS.
Bergamino et al [68]	2022	PMW with ER+ BC (Pooled n=217)	2 weeks or ≥4 weeks NET with AI	Broader range of molecular changes with longer NET.

Table 3. Summary of clinical trials, meta-analyses and other studies comparing of effect of different NET treatment duration. Abbreviations: AI, aromatase inhibitor; BC, breast cancer; BCS, breast-conserving surgery; ER+, estrogen receptor-positive; EXE, exemestane; LET, letrozole; NET, neoadjuvant endocrine therapy; pCR, pathological complete response; PMW, postmenopausal women; TAM, tamoxifen.

Study	Markers/Factors	Output	Key outcomes and applications
Oncotype DX [121,122]	21-gene assay	Continuous risk score (RS) for stratification into low, intermediate or high-risk groups	Higher response rates and improved outcomes after NET in the low-risk group[124,125]. Application for response assessment in the DxCARTES[131] and other trials[129,130].
MammaPrint[139] NET study[135]	70-gene signature	Stratification according to risk of recurrence at 5 and 10 years.	Application for treatment selection in the PLATO trial[135].
EndoPredict and EPclin[138]	12-gene assay + node status and tumour size in EPclin	Risk score predicting likelihood of recurrence at 5 and 10 years	Assessment of response to NET+ palbociclib in the N007 study[139]. Assessment of response in ABCSG-34[140].
$SET_{ER/PR}$ [142,143]	28-gene score + tumour and node stage	Index predictive of ET response	Assessment of MDACC and ACOSOF Z1031 cohorts showed potential value[143,144].
CES [145]	PAM50-based gene signature	Stratification into groups likely to respond to ET or chemotherapy	Validated in 4 NET datasets[145].
EER4 and EA2Clin [146,147]	EER4: 4-gene signature EA2Clin: 2 genes (baseline IL6ST and 2-week MCM4) and clinical factors (tumour size, grade and node status)	Classification into discrete response and non-reponse groups	EER4 validated for prediction of survival[146]. Prediction of outcome regardless of NET agent[147].)

Table 4. Summary of gene expression and hybrid tools used for NET response prediction. Abbreviations: CES, chemo-endocrine score; EER4, Edinburgh EndoResponse 4; NET, neoadjuvant endocrine therapy.

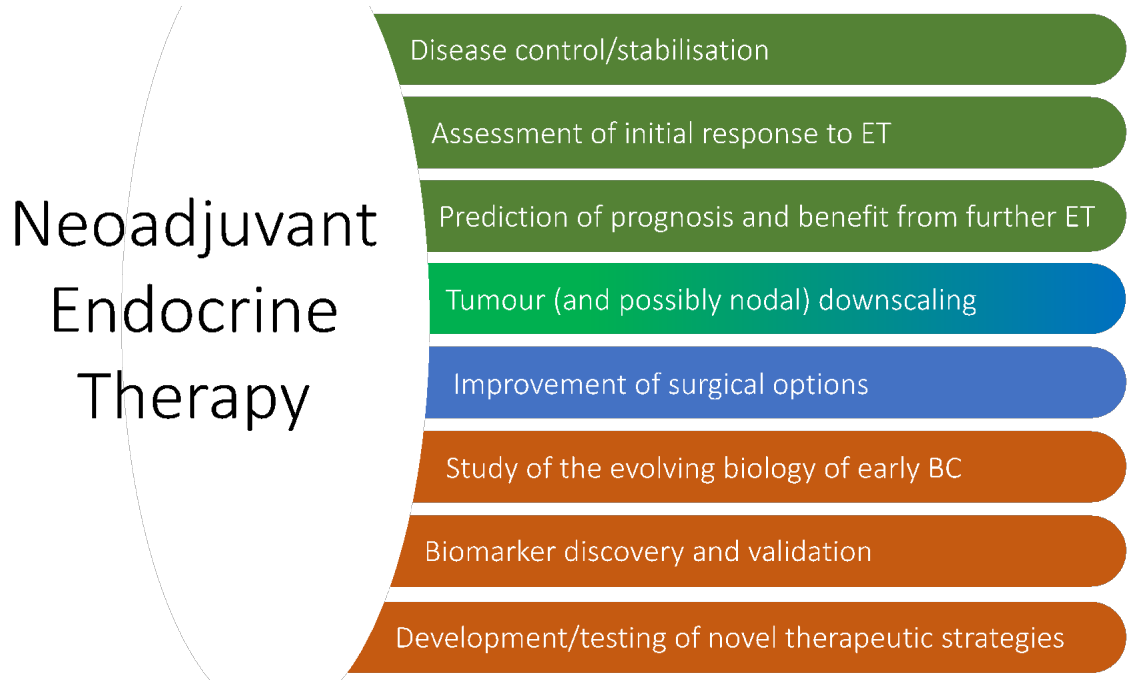

Figure 1. Schematic summary of the potential benefits of using NET. The use of preoperative endocrine therapy can yield numerous advantages in the management PMW with ER+ BC, including clinical (green) and surgical (blue) benefits, as well as numerous research opportunities (orange).