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Neoadjuvant endocrine therapy in postmenopausal women with HR+ /HER2- breast cancer

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Neoadjuvant endocrine therapy in postmenopausal women with HR+/HER2- breast cancer

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

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3 study updates and key older references were considered. This was followed by filtering
4 of the resulting publications to select those relevant to the scope of this review.
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8 9 2. History and evolving rationale for the use of NET in BC

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11 NET was first introduced in the early 1970s as a treatment option for older or frail patients
12 who were unfit or ineligible for surgery. In this context, ET was used as an alternative
13 primary therapy, rather than as a neoadjuvant treatment *per se*. Initial studies compared
14 primary treatment with the selective ER modulator (SERM) tamoxifen vs surgery in elderly
15 patients[5,6]. While 80% of ER+ patients saw clinical benefit from NET, longer follow-up
16 showed higher locoregional recurrence rates and lower overall survival (OS) when
17 compared with patients who underwent surgery[7–9]. A meta-analysis of 7 trials showed
18 no OS advantage (hazard ratio (HR) 0.98, p=0.9) but an improvement in progression-free
19 survival (PFS) (HR 0.55, p=0.0006) in patients who received surgery followed by adjuvant
20 ET, compared to primary ET alone[10]. The Group for Research on Endocrine Therapy
21 in the Elderly (GRETA) trial, which randomised women over 70 with operable tumours to
22 tamoxifen alone or surgery plus tamoxifen, reported increased rates of local progression
23 in the ET-only arm (25 vs 6%, p<0.0001) but also showed no significant differences in
24 survival or distant metastasis rates between both treatment groups[8]. In contrast to
25 previous studies, similar survival rates were maintained at longer follow-up (80 months)
26 and about 40% of patients had complete or partial response to tamoxifen alone[11].
27 Taken together, this evidence suggested that the use of primary ET instead of definitive
28 local treatment might be an adequate option only for older patients unlikely to ever be
29 eligible for surgery or with limited life expectancy[12]. This could be extended as long as
30 disease is responsive or stable, or alternative ET agents could be considered if there is
31 evidence of disease progression.
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53 Starting in the 2000s, NET has been used with the primary goal of downstaging large or
54 locally-advanced HR+ cancers in order to provide more surgical options, either by
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4 enabling surgery in initially inoperable patients or improving breast-conserving surgery
5 (BCS) rates when lumpectomy becomes feasible for patients who initially would have
6 needed to undergo a mastectomy[13].
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10 Eligible candidates for pre-operative treatment are typically patients with a cancer that is
11 initially inoperable or not suitable for BCS, as well as those with large operable primary
12 cancers (T3, or >5cm diameter), tumours with skin or chest wall involvement (T4), and
13 those with axillary lymph node involvement at diagnosis (N1-2)[14]. Other patients with
14 smaller tumours might be considered if they wish to undergo BCS rather than mastectomy
15 or if they present a small breast-to-tumour size ratio[15].
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23 For NET in particular, traditional criteria include positive HR status, stage II or III, and
24 post-menopausal status (see section 3.1). ER+ status is a pre-requisite but, unlike with
25 adjuvant ET which tends to be used in all ER+ tumours, NET is normally reserved for ER-
26 rich BC (Allred 7-8, or >50% staining), as most evidence has shown better results in these
27 cases[13]. Indeed, there is a statistically significant linear relationship between ER
28 expression and odds of response to NET[16], and many NET trials have selected
29 specifically for strongly-ER+ cases[17–19].
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38 **3. Evidence and trials to date**

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40 Over the last 25 years, a wealth of clinical trials and research on the effect of NET in BC
41 have been conducted. The next sections will review the evidence compiled to date and
42 describe how this has helped refine our understanding and use of this therapeutic strategy
43 for the management of HR+/HER2- disease.
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49 **3.1. NET vs NCT and the role of menopausal status**

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51 While neoadjuvant chemotherapy (NCT) is another available option for pre-operative
52 treatment, evidence has shown that patients with luminal (i.e., HR+) BC derive less
53 benefit from it. Indeed, studies have shown that the rate of pathological completely
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4 response (pCR, defined as an absence of invasive and in situ disease, or ypT0/is ypN0,
5 after treatment) achieved with NCT is lower in luminal tumours than in triple negative or
6 HER2+ disease (7 vs 36 and 27%, respectively)[20–22]. Research has also shown that
7 the degree of response to NCT is inversely correlated to the level of ER expression[22].
8 This is consistent with the notion that ER+ BCs, and in particular luminal A tumours, might
9 also derive no survival advantage from chemotherapy in the adjuvant setting[23,24].
10 Indeed, it has been reported that the absolute OS benefit from adjuvant cytotoxic
11 chemotherapy in unselected postmenopausal women with HR+/HER2- tumours is of only
12 3-4%[25]. Data from the TAILORx and RxPONDER trials, which randomised patients with
13 HR+/HER2- BC to adjuvant ET only or combined chemo-endocrine therapy, showed no
14 significant differences in invasive disease-free survival between both treatment
15 groups[26,27]. The International Breast Cancer Study Group IX trial also showed no
16 additional benefit in postmenopausal women with ER+ BC treated with combination
17 adjuvant chemotherapy and tamoxifen, when compared to tamoxifen alone[23,24].
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32 Importantly, evidence has suggested that among patients with HR+/HER2- BC, the
33 suitability of ET as a safe alternative for pre-operative treatment depends on their status
34 as premenopausal (pMW) or postmenopausal (PMW) women[28–32]. While some
35 studies have reported downstaging of HR+ tumours under NET in pMW[33], evidence
36 has been deemed insufficient to confirm the safety of this strategy in this younger
37 subgroup of patients, who typically have worse prognosis[34,35]. For example, a recent
38 trial designed to compare the efficacy of 24 weeks of NCT or NET in pMW reported better
39 clinical outcomes in the NCT group[36]. Thus, NCT is normally preferred to treat pMW for
40 whom pre-operative treatment is deemed necessary. If NCT is not an option due to patient
41 preference or co-morbidities, the patient should proceed to surgery rather than receive
42 NET. Interestingly, recent evidence has shown that chemotherapy might exert an
43 antiestrogenic biological effect on the tumours of HR+ pMW, possibly as a consequence
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3 of the inhibitory effect on ovarian function, suggesting that the benefit from NCT in this
4 cohort might be partly due to a secondary endocrine blockade[37].
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8 In contrast, NET has been shown to be an appropriate treatment option in PMW (see
9 Table 1 for a summary of key trials and findings). A phase II trial that compared NET and
10 NCT showed no significant differences in clinical (64.5 vs 63.6%) or mammographic (60
11 vs 63%) response, but lower toxicity and a trend toward better BCS rates (33 vs 24%,
12 p=0.058) in the NET group[34]. The Spanish GEICAM/2006-3 trial compared NET with
13 NCT in 95 women with luminal BC and showed no significant differences in outcome
14 between treatments for the PMW subgroup [29]. A meta-analysis of those two trials
15 confirmed this evidence[31]. The Neoadjuvant Endocrine vs Chemotherapy Trial
16 (NEOCENT) also compared both treatments in PMW with ER-rich BC and found similar
17 response rates[38]. Another meta-analysis comparing NET and NCT using data from
18 these three trials (total n=378) supported these results, reporting similar response rates
19 between both treatment groups, but lower toxicities and a trend towards improved BCS
20 rates (odds ratio (OR) 1.08, p = 0.85) in the NET arm[28]. A recent study of data from the
21 American National Cancer Database (NCDB) reported that, although NCT might achieve
22 higher pathologic response rates, NET can also lead to considerable tumour and node
23 downstaging (T: 58 vs 40.5%, p<0.001; N: 29 vs 18.3%, p<0.001)[39]. Generally, NCT
24 should not be used only for disease downstaging if chemotherapy will not provide a
25 survival benefit.
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44 Thus, NET represents a logical and promising approach for downstaging disease in
45 postmenopausal HR+/HER2- BC patients, although careful review and continued
46 monitoring to ensure the cancer is responsive or stable is required to ensure the safety
47 of this strategy. Consistently, recent guidelines and recommendations from multiple
48 international expert groups have recommended NET favourably in this group to increase
49 locoregional treatment options or disease control in inoperable cases, while in pMW NET
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4 should be limited to the research context of clinical trials[35,40–44]. Besides the reported
5 efficacy, favourable BCS rates and low toxicity profile, NET also has the advantage of
6 having a lower cost and being more readily available and more easily administered,
7 important aspects when we consider that 70% of BC deaths take place in low or middle-
8 income countries[45]. Beyond this established evidence, research continues with the aim
9 of further optimising NET use among PMW, including the assessment of tools for
10 improved selection between and prediction of response to NET or NCT (see section 4)
11 and trials investigating combination treatments (see section 5). The pre-operative setting
12 also offers unique research opportunities that merit further study (see section 6).

22 **3.2. NET agents: tamoxifen vs aromatase inhibitors**

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

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32 The P024 trial reported the superiority of 4 months of neoadjuvant letrozole over
33 tamoxifen in 337 patients with early BC who were initially not eligible for BCS. Letrozole
34 had better overall objective response (55% vs 36%, $p < 0.001$) and BCS (45% vs 35%,
35 $p = 0.022$) rates[48,49]. This was also reflected in pathological changes, as letrozole
36 induced a greater reduction in mean levels of the proliferation marker Ki67 than tamoxifen
37 (87 vs 75%)[50].

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40 The Immediate Preoperative Anastrozole, Tamoxifen, or Combined with Tamoxifen
41 (IMPACT) trial compared 3 months of neoadjuvant tamoxifen, anastrozole or a
42 combination of both agents in 330 women with ER+ operable or potentially operable
43 BC[51]. Results showed no significant differences in objective response rates between
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4 treatment arms, but reported better BCS rates in the anastrozole group compared to the
5 tamoxifen group for the subgroup of patients who were initially only eligible for
6 mastectomy (46 vs 22%, $p=0.03$).
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10 The Preoperative Anastrozole Compared with Tamoxifen (PROACT) trial also compared
11 12 weeks of neoadjuvant anastrozole or tamoxifen in a similar cohort of 451 patients[52].
12 This study showed no significant differences in response rates assessed through calliper
13 (50 vs 46.2%, $p=0.29$) and ultrasound measurements (39.5 vs 35.4%, $p=0.29$). However,
14 PROACT also included patients receiving NCT and, when this subcohort was excluded
15 from the analysis, the anastrozole arm did show a tendency towards better response over
16 tamoxifen (calliper response: 49.7 vs 39.4%, $p=0.08$; ultrasound response: 36.2 vs
17 26.5%, $p=0.07$). These differences were significant in the subgroup of patients whose
18 tumours were deemed inoperable at baseline (calliper response 48.6 vs 35.8%, $p=0.04$;
19 ultrasound response: 52 vs 29%, $p=0.03$). Downstaging from inoperable or BCS-
20 ineligible to operable or BCS-eligible also favoured the anastrozole arm (43 vs 30.8%,
21 $p=0.04$).
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34 A Russian study comparing 3 months of neoadjuvant exemestane or tamoxifen in 151
35 patients with T2N1-2, T3N0-1 or T4N0M0 disease also showed the superiority of the
36 AI[53]. The exemestane arm showed improved clinical response (76.3 vs 40%, $p=0.05$)
37 and BCS (36.8 vs 20%, $p=0.05$) rates.
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43 A meta-analysis of these 4 trials was conducted, including evidence from a total 1,160
44 PMW with ER+ BC[54]. This confirmed that, while toxicities and tolerability were similar
45 for both NET types, AIs were superior in both clinical response (risk ratio (RR) 1.29,
46 $p<0.001$), ultrasound response (RR 1.29, $p=0.002$) and BCS (RR 1.36, $p<0.001$) rates. A
47 second meta-analysis comparing data from 7 trials of NET with AI vs tamoxifen also
48 reported a greater efficacy of AIs, with improved clinical response (OR 1.69, $p<0.001$,
49 $n=1,352$), radiological response (OR 1.49, $p<0.001$, $n=1,418$) and BCS (OR 1.62, $p<$
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4 0.001, n=918) rates[28]. A third meta-analysis also concluded on the feasibility of NET for
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6 PMW and the preference for AIs over tamoxifen due to higher overall response rates (OR
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8 1.9, 95% CI 1.17-3.08)[31].
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10 **3.3. NET agents: choice of AIs**

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13 The American College of Surgeons Oncology Group (ACOSOG) Z1031 trial compared
14
15 the effect of NET with the three third-generation AIs for 16-18 weeks in 377 PWM with
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17 ER-rich T2-4, N0-3, M0 BC[17]. This study found no significant differences between the
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19 anastrozole, letrozole and exemestane treatment groups in neither objective response
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21 (69.1, 74.8 and 62.9%, respectively) or BCS (64, 42.1 and 48.1%, respectively) rates.
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23 Another study compared the effect of shorter courses (14 days) of neoadjuvant
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25 anastrozole or letrozole and reported similar rates of downregulation of ER, PR and
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27 Ki67[55]. The HORGEN and CARMINA02 studies were two non-comparative multicentre
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29 phase II trials comparing 6 months NET with anastrozole or the selective ER degrader
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31 (SERD) fulvestrant in PWM with HR+ BC who were initially not eligible for BCS[56,57]. A
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33 subsequent pooled analysis of both trials showed, consistently with each trials initial
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35 results, no significant differences between treatment arms in BCS and pathological
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37 response rates[58]. The longer follow-up also enabled researchers to show no differences
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39 in RFS and OS at 5 years (83.7% and 92.7%, respectively). There was a trend for better
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41 clinical response in the anastrozole arm (55.9 vs 44.3% in the fulvestrant arm), but the
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43 non-comparative design of the trials meant clinical response superiority could not be
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45 properly assessed.
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48 **3.4. Duration of NET treatment**

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51 Although the majority of NET trials to date have treated PWM for a duration of between 3
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53 and 6 months, several studies have shown that a longer duration of NET can also lead to
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55 improved response rates[42,59] (see Table 3 for a summary of key trials and findings).
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4 One study of 182 women at our institution showed that, while 3 months of neoadjuvant
5 letrozole achieved clinical and ultrasound response in 69.8% patients, this increased to
6 83.5% with longer treatment[60]. BCS rates also improved from 60 to 72%. Tumour
7 volume continued to decrease when comparing 3-6 months, 6-12 months and 12-24
8 months of NET (with medians of 50, 37 and 33%, respectively). Another study comparing
9 NET with letrozole for 4, 8 or 12 months showed that, while similar Ki67 reduction was
10 achieved in the three treatment arms, there was a significant trend for higher pCR rates
11 with longer NET (respectively, 2.5, 5 and 17.5%, $p < 0.04$)[61].

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20 Another study of 116 ER+ women treated with neoadjuvant exemestane reported that
21 objective response rate improved from 47.4% at 16 weeks to 50.9% at 24 weeks[62]. A
22 phase II trial also showed an increase in overall response when comparing the effect of
23 3 or 6 months of neoadjuvant exemestane (58.7 vs 68.3%, respectively)[63]. Interestingly,
24 a prospective multicentre trial of 146 patients treated with neoadjuvant letrozole found
25 that the median time needed to attain BCS was 7.5 months, supporting the case for
26 extended NET[64]. A smaller retrospective review of NET-treated patients also supported
27 longer that conventional therapy to achieve additional downstaging, as it showed a mean
28 duration of 9.7 months of NET before patients underwent BCS[65].

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39 Transcriptomic analyses have provided some interesting insight into the effect of NET
40 duration[66–68]. A recent study compared the gene expression changes induced by AIs
41 in two different cohorts where patients received only 2 weeks or more than 1 month of
42 NET[68]. As expected from previous analysis, downregulation of proliferation was
43 observed after 2 weeks of AIs. However, longer treatment led to a broader range of
44 changes in cancer-related signalling pathways and the immune checkpoint. This suggests
45 that good AI responders can be identified early on-treatment, while also hinting at
46 additional changes happening under extended NET regimens, likely contributing to the
47 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,

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

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31 In addition to its effectiveness for disease downstaging in many PMW with HR+/HER2-
32 tumours, NET offers a unique opportunity for in vivo observation of the tumour's response
33 to treatment. This can help ensure disease remains responsive or stable, and ascertain
34 if a change to the treatment strategy is necessary. Indeed, monitoring of response to
35 treatment during NET provides unique opportunities for early prediction of treatment
36 benefit and identification of patients with different levels of response. Based on this, poor
37 responders might be changed to an alternative or combination neoadjuvant treatment, or
38 their NET might be interrupted to proceed to surgery sooner if feasible. Patients might
39 also be stratified based on their response in the neoadjuvant setting for better treatment
40 selection in the adjuvant setting. Ultimately, this can translate into more personalised
41 treatment of patients with HR+/HER2- BC in both the neoadjuvant and the adjuvant
42 settings: those likely to have excellent outcome with ET alone can be spared unnecessary
43 treatment unlikely to provide additional benefits, while others with worse prognosis can
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4 be selected for more effective treatment, such as the addition of adjuvant chemotherapy
5 or CDK4/6 inhibitors[80,81]. The next sections summarise the evidence to date on
6 different biomarkers, indices and genetic signatures which have been developed or
7 assessed as surrogates for the assessment of response to or prediction of benefit from
8 NET.
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13 14 15 **4.1. Clinical and biological measures of response: Ki67 and PEPI**

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17 While pCR to NCT is associated with improved survival and this metric has been used to
18 compare outcomes from NCT and NET (see section 3.1), evidence has shown that pCR
19 might be less useful in assessing response to NET. This is likely due to the fact that ET
20 largely exerts a cytostatic (rather than cytotoxic) effect, which might be better assessed
21 using other measures or surrogates. Indeed, research has shown that the likelihood of
22 achieving pCR is much lower in patients with HR+/HER2- BC, but also that the prognostic
23 significance of pCR in this subgroup is limited: the association between pCR and outcome
24 is less robust, and a lack of pCR does not correlate with poorer outcomes[82]. Instead,
25 the effect of NET can be monitored by assessment of clinical response (by calliper
26 measurement of tumour size or changes to the feasibility of BCS), radiological response
27 (using imaging techniques to monitor changes in tumour volume) or pathological
28 response (taking sequential biopsies to assess proliferation, or to look for histological
29 changes associated with treatment response)[13,33,83].
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44 Ki67 is a nuclear marker of proliferation (expressed in all phases of the cell cycle except
45 the G₀ and early G₁ phases [84–86]) whose prognostic value has been shown in
46 numerous studies[87]. The evidence on the role of Ki67 has been previously reviewed
47 elsewhere[88,89]. In short, its baseline level is an established prognostic factor, and its
48 level after a period of pre-operative treatment can also be a useful indicator of response,
49 with evidence from the IMPACT trial showing that it can correlate with long-term outcome
50 after as little as 2 weeks[90–92]. Ki67 has been assessed in several NET trials and,
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4 importantly, on-treatment levels in these studies were able to anticipate the outcome of
5 equivalent adjuvant trials[89]. In addition to being used as an endpoint in numerous
6 studies, Ki67 measurement has been recommended as a proliferation surrogate to
7 differentiate between luminal A and B subtypes[93,94].
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12 Despite this evidence, the adoption of Ki67 as a marker has been limited by a number of
13 factors. For example, there was an initial lack of guidelines for the best timepoint for Ki67
14 assessment[89]. This was one of the questions addressed by the Peri-Operative
15 Endocrine Therapy: Individualising Care (POETIC) study, a phase III window-of-
16 opportunity trial comparing 4 weeks peri-operative AI (2 weeks pre- and 2 weeks post-
17 surgery) with no therapy that assessed how Ki67 levels at baseline and at 2 weeks predict
18 recurrence-free survival (RFS) and OS[95]. Their results showed that low Ki67 at either
19 timepoint is indicative that patients will do well with adjuvant ET only, whereas a high Ki67
20 at 2 weeks can help select patients for further adjuvant treatments. It is now established
21 that response to AIs leads to a rapid decrease in Ki67 and proliferation should remain low
22 unless the patient stops responding. In line with these findings, numerous institutions and
23 studies now measure on-treatment Ki67 levels (typically at 2 or 4 weeks) to assess
24 response to NET. For example, the ACOSOG Z1031B trial utilised on-treatment Ki67
25 levels to assess NET response: if Ki67 was >10% after 2-4 weeks of NET, patients were
26 deemed non-responsive to NET and switched to NCT or advanced to surgery[96]. The
27 ALTERNATE trial follows a similar approach to select non-responsive patients for switch
28 to NCT[97]. The ongoing POETIC-A phase III trial (NCT04584853) will also use on-
29 treatment Ki67 as a criterion to select patients with lower response to NET, who will then
30 be randomised to adjuvant treatment with ET-only or in combination with the CDK4/6
31 inhibitor abemaciclib.
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52 Numerous technical hurdles have continued to limit the wider adoption of Ki67 as a
53 marker. While the use of immunohistochemistry makes Ki67 assessment very cost-
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4 effective, there is considerable variation and a lack of consensus in methodology and
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6 scoring, which leads to high discordance both across different laboratories and between
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8 individual observers[98–102]. There have also been concerns that intra-tumour
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10 heterogeneity and uneven expression patterns including ‘hot’ and ‘cold’ spots might lead
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12 to further variability and inaccuracy when only small core biopsies are assessed[103].
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14 There is also evidence that pre-analytical factors such as fixation can lead to additional
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16 issues[104,105]. Expert teams have worked to address these biases, defining protocols
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18 and recommendations to help standardise and validate Ki67 evaluation[98,100,105,106],
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20 and research continues to investigate potential approaches to help standardise its
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22 accurate assessment[102,107,108].
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25 Other research has questioned our traditional understanding of Ki67 biology. For
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27 instance, a recent study argued that the current binary assessment of Ki67 as
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29 positive/negative stain is not appropriate and this should be regarded as a graded
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31 marker[109]. This is at least partly due to an underestimation of the complex role of Ki67,
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33 which exerts a range of functions across the different phases of cell division[109,110].
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35 This is evidenced by its changing patterns of expression during proliferation: it is known
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37 that Ki67 is expressed during all phases of the cell cycle except G_0 , starting in late G_1 and
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39 reaching maximum levels during G_2 and M phases, before a rapid decrease in expression
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41 in the latter stages of mitosis[86,109,111]. Thus, Ki67 suppression might be an indicator
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43 of quiescence, but its expression might not be the most accurate marker of proliferation,
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45 as dividing tumour cells could be misidentified[85,109]. Other proteins might hold greater
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47 potential as proliferative markers. For example, specific markers for G_2 /M transition or M
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49 phase would likely make for more accurate surrogates, as most cells reaching these
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51 stages will complete the cell cycle[112,113]. Interestingly, proteins in the minichromosome
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53 maintenance (MCM) family, also expressed in all active phases of the cell cycle, have
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55 been shown to hold promise as proliferation markers in luminal breast cancer. Compared
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4 to Ki67, the function of MCM proteins is better understood and it seems their assessment
5 is limited by fewer technical and pre-analytical factors, with recent studies reporting that
6 MCM proteins might outperform Ki67 as proliferation markers[85,104,114,115].
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10 The Preoperative Endocrine Predictive Index (PEPI) was developed based on data from
11 the P024 trial and validated in the IMPACT cohort[116] (see also section 3.2. and Table
12 2). This index incorporates tumour size, nodal stage, ER and Ki67 of the surgical
13 specimen after NET to provide a prognostic score (good (0), intermediate (1-3), or poor
14 (≥ 4) prognosis) shown to correlate with RFS ($p=0.002$). Patients with early-stage tumours
15 and a PEPI score of 0 had no recurrences in 5 years, representing a subgroup of women
16 for whom adjuvant chemotherapy could be safely avoided. The prognostic value of PEPI
17 is likely to be further validated through trials such as ALTERNATE (see section 5) which
18 incorporate this score into their design for response monitoring and to help guide selection
19 of neoadjuvant or adjuvant treatment for non-responders[18,19].
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30 While the use of Ki67 or PEPI is still not a clinical standard globally, a recent single-
31 institution prospective study of a cohort of 115 patients treated with neoadjuvant letrozole
32 represents a good example of how these on-treatment markers can be utilised in the pre-
33 operative management of HR+/HER2- BCs[117]. All patients underwent Ki67 assessment
34 at diagnosis and, for those with high baseline proliferation ($Ki67 \geq 10\%$ at diagnosis), again
35 after 4 weeks of treatment. NET led to significant tumour downstaging, with a median
36 tumour size reduction of 40%, and 85.2% of patients receiving BCS. Importantly, Ki67
37 assessment in combination with continued clinical and ultrasound assessment enabled
38 monitoring of NET response, so that patients with progressive disease were advanced to
39 surgery while patients with stable or responsive tumours remained on NET for at least 2
40 months and up to 1 year, or until maximum response was achieved. The authors
41 concluded that assessment of on-treatment Ki67 levels, shown to be significantly related
42 to a PEPI-0 score ($p < 0.002$), was useful in providing prognostic information and guiding
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4 treatment decision-making, evidencing how the findings from clinical trials over the last
5 two decades can be successfully translated into clinical practice (see also section 7).
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8 **4.2. Gene expression tools for on-treatment assessment**

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11 In addition to simpler markers like Ki67 and PEPI, several signatures have also been
12 developed and assessed for their predictive and prognostic value in BC. While most of
13 these tools have been validated to help guide adjuvant treatment selection, there is
14 growing evidence on the potential utility of these genomic assays in the neoadjuvant
15 setting, as recently reviewed elsewhere[118–120]. This section will summarise studies
16 investigating the use of such signatures for NET response prediction, or signatures
17 specifically developed around the NET window (see Table 4 for summary).
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26 Oncotype DX is a prognostic tool that generates a recurrence score (RS) based on the
27 expression level of 21 genes, including ER-related genes. Patients are stratified into 3
28 different risk groups (low, intermediate and high-risk) based on their calculated value for
29 the continuous RS (0-100), with RS cut-offs having been refined more recently based on
30 trial data[121,122]. Although RS was conceived to help guide patient selection for
31 chemotherapy, three studies have assessed the association between pre-treatment RS
32 and NET response[123]. A study of diagnostic biopsies from 43 patients treated with NET
33 reported higher response rates in the low-risk RS group compared to the intermediate
34 and high RS groups (64 vs 31 and 31%, respectively), and a non-significant trend towards
35 better 5-year PFS (100 vs 84 and 73%, respectively)[124]. A second study of 116 patients
36 who received NET reported improved outcomes in low RS cancers compared to the high
37 RS group, in both clinical response (59.2 vs 20%) and BCS (90.6 vs 46.7%) rates[125].
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50 The more recent and larger TransNEOS study performed RS assessment of diagnostic
51 biopsies from 295 PMW with HR+/HER2-, node-negative BC who received 6 months of
52 letrozole and reported significant differences in clinical response rates for the different RS
53 groups (RS <18: 54%; RS 18-30: 42%; RS>30: 22%; p<0.001)[126]. A recent meta-
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4 analysis of these 3 trials confirmed differences in clinical response rates to NET between
5 the low and high genomic risk groups (RS<18: 55-64%; RS>30:20-31%)[123]. Two small
6 phase II trials have also been conducted to test the use of the RS assay to guide selection
7 of NET or NCT[127,128]. In both of these studies, patients in the low-risk group (RS<11)
8 received NET, patients in the intermediate group (RS 11-25) were randomised to NET or
9 NCT, and patients in the high-risk group (RS>25) received NCT. Non-high RS has also
10 been used as a selection criterion in studies assessing the addition of targeted therapy
11 agents to NET[129,130] (see section 5). The DxCARTES study is assessing how
12 differences in RS pre- and post-neoadjuvant treatment might be indicative of molecular
13 changes induced by a combination of letrozole and the CDK4/6 inhibitor palbociclib[131].
14 This follows a previous study which showed that the combination of pre- and post-NET
15 RSs could predict disease-free survival in patients who received pre-operative
16 exemestane[132].
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30 Interestingly, a recent update from the ADAPT (Adjuvant Dynamic Marker-Adjusted
31 Personalized Therapy Trial Optimizing Risk Assessment and Therapy Response
32 Prediction in Early Breast Cancer) trial reported the combined use of RS and post-NET
33 Ki67 to guide treatment selection in patients with early luminal BC and limited node
34 involvement (pN0-1) within the ET subtrial[133]. In short, the specific subgroup of
35 postmenopausal patients with higher RS (12-25) but evidence of NET response (Ki≤10%)
36 could be safely spared chemotherapy, as they were treated with adjuvant ET only but
37 achieved outcomes comparable to those of ET non-responders who received adjuvant
38 chemo-endocrine therapy. These results support the notion that an approach
39 incorporating multiple preoperative predictors could lead to improved selection of
40 adjuvant treatment.
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52 MammaPrint is a 70-gene signature that stratifies BC patients according to the risk of
53 distant recurrence at 5 and 10 years. It has been validated to aid selection for adjuvant
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4 chemotherapy and has been shown to agree with Oncotype DX in patient outcome
5 prediction[134]. While there is only limited evidence on the predictive role of MammaPrint
6 for NET response, the Personalized neoAdjuvant Strategy ER Positive and HER2
7 Negative Breast TO Increase BCS Rate (PLATO) phase II study is currently underway to
8 assess MammaPrint as a tool for neoadjuvant treatment selection in patients with
9 HR+/HER2- BC initially ineligible for BCS, with high-risk and low-risk patients being
10 selected for NCT or NET, respectively[135]. A predefined substudy of the Neoadjuvant
11 Breast Registry Symphony Trial (NBRST) compared conventional IHC/FISH subtyping
12 with an alternative molecular classification method using MammaPrint in combination with
13 the 80-gene signature Blueprint. Their results showed that 18% of cases considered
14 'clinically' luminal were reclassified as a different subtype with the MammaPrint/Blueprint
15 tool, highlighting the importance of accurate subtyping for improved prediction of
16 treatment response. Similar findings were reported in a subsequent assessment of cases
17 from the NBREaST II trial, where 9% of cases were reclassified by MammaPrint/Blueprint
18 molecular subtyping[136]. A recent single-centre retrospective analysis suggested that
19 NET is a feasible option for patients with a low-risk MammaPrint score, with 76%
20 radiologic response rate among the 51 luminal cases included[137]. Another ongoing trial
21 (NCT04129216) will also use MammaPrint to monitor genetic and molecular changes
22 during NET.
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42 The 12-gene assay EndoPredict (EP) and the refined hybrid risk score EPclin
43 (incorporating EP with node status and tumour size as clinical factors) have been shown
44 to independently predict the likelihood of distant recurrence at 5 and 10 years in patients
45 with HR+/HER2- BC treated with ET alone[138]. The N007 study, a small single-arm trial
46 of combination neoadjuvant letrozole and palbociclib, included EP and EPclin
47 assessment, with results showing that EPclin might be a better predictor of post-
48 neoadjuvant treatment prognosis than PEPI[139]. Another recent study conducted
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4 retrospective EP assessment of biopsies from the neoadjuvant ABCSG-34 trial, where
5 cases had been assigned to receive NET or NCT depending on clinico-pathological
6 factors including HR status and menopausal status[140]. Results showed that the
7 molecular score predicted treatment response to both NET and NCT, with both low-risk
8 NCT-treated and high-risk NET-treated patients responding poorly (negative predictive
9 value: 100% and 92.3%, respectively). In short, there is some evidence that the EP scores
10 might hold potential for NET response prediction, but further prospective validation is still
11 needed to confirm this.
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20 Symmans et al developed a Sensitivity to Endocrine Therapy (SET_{2,3}) genomic index
21 based on microarray profiling of diagnostic HR+ BC biopsies, which was shown to predict
22 survival benefit from adjuvant ET[141]. Subsequent work saw SET_{2,3} refined into a 28-
23 gene score of non-proliferative HR-related transcription (SET_{ER/PR}) adjusted with a
24 baseline prognostic index (BPI) including clinical factors (tumour and node stages) and
25 molecular subtype (determined using a 4-gene classifier)[142,143]. Assessment of this
26 revised algorithm showed that it could provide additional prognostic value to residual
27 cancer burden (RCB, a surrogate predictor for chemo-response) in clinically high-risk
28 HR+/HER2- BC[143]. More recently, a correlative study assessed the ability of this
29 signature to predict NET response using baseline gene expression data from cases from
30 the ACOSOG Z1031 NET trial[144]. Results showed that a high SET_{2,3} score in pre-NET
31 biopsies was associated with early pharmacodynamic response to NET and improved
32 event-free survival, although not with pathological response rates (PEPI-0 score). The
33 authors concluded that, while further validation is needed, their results suggest SET_{2,3}
34 could become a useful surrogate to guide patient selection for NET.
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50 The Chemo-Endocrine Score (CES) was developed based on the PAM50 intrinsic
51 subtype classification and the inverse relationship of endocrine and chemotherapy
52 sensitivity[145]. Validation in 4 HR+/HER2- neoadjuvant datasets showed that CES could
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4 predict response to both NCT and NET, independently of known clinico-pathological
5 variables.
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8 Lastly, besides the aforementioned signatures (which were initially validated for their
9 adjuvant use and have now been assessed in the neoadjuvant setting), we have
10 previously reported on a tool developed specifically around the NET setting. Indeed, work
11 from our group led to the development of the Edinburgh EndoResponse4 (EER4) tool, a
12 4-gene signature to predict response to ET with AIs based on the expression of two genes
13 at baseline and two genes after 2 weeks of NET[146]. EER4 classified patients into
14 discrete responder and non-responder groups with high accuracy in both the training and
15 independent validation cohorts (96 and 91%, respectively), and was also shown to predict
16 RFS ($p=0.029$) and BC-specific survival (BCSS) ($p=0.009$). Subsequent work has led to
17 further development and refinement of the signature[147]. The EndoAdjuvant2 Clinical
18 (EA2Clin) hybrid tool incorporates expression of two genes (baseline level of the immune
19 and ER signalling-related signal transducer IL6ST and on-treatment level of the
20 proliferation-related MCM4) with clinical factors (tumour size and grade, and node status).
21 EA2Clin classification of PMW who received NET was shown to accurately predict
22 outcome from adjuvant ET ($p<0.001$ for both RFS and BCSS) regardless of the agent (AI
23 or tamoxifen) received. Further validation is currently underway and a future prospective
24 trial will be the next step to confirm the potential clinical utility of this NET-specific tool.
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42 In summary, there is growing evidence that genomic signatures might be useful for NET
43 selection and response prediction, with trends showing that low-risk cases derive less
44 benefit from NCT and exhibit better response rates to NET. As monitoring and prediction
45 of NET response can be instrumental to achieving optimal disease management in both
46 the neoadjuvant and adjuvant settings, prospective trials now often incorporate into their
47 designs some of these assays for on-treatment assessment[118,119]. Along with other
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3 ongoing research, these studies might also provide more exhaustive validation of these
4 tools to help bring them closer to clinical translation.
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8 **5. NET combination trials**

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10 Following the strong evidence on the efficacy of neoadjuvant AIs, a wealth of new NET
11 trials have emerged over the last decade to assess combination therapies for the
12 neoadjuvant treatment of HR+/HER2- BC, be it the combination of multiple ET drugs, or
13 ET and other targeted agents. Recent reviews by Escrivà-De-Romaní, Guerrero-Zotano
14 and their colleagues[148,149], have described how these NET trials can be classified
15 according to their approaches as enrichment adaptive design (where assessment of on-
16 treatment biomarkers might determine treatment changes), multi-arm lead-in design
17 (where NET ± targeted agent treatment arms are compared), single-arm designs (where
18 multiple biopsies might be collected to monitor evolving response to treatment), or window
19 of opportunity designs (shorter studies where assessments are made to characterise the
20 mechanism of action or molecular changes induced by treatment). This section
21 summarises some of the most relevant recent and on-going NET combination trials.
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35 The aforementioned Alternate Approaches for Clinical Stage II or III Estrogen Receptor
36 Positive Breast Cancer Neoadjuvant Treatment (ALTERNATE) trial is a prospective
37 phase III study comparing 6 months of neoadjuvant treatment with the AI anastrozole, the
38 SERD fulvestrant or a combination of both in patients with ER+/HER2- BC[18,97]. While
39 longer follow-up is needed to analyse RFS data, initial results reported no improvement
40 on disease response in either the fulvestrant or combination arms, compared to the
41 anastrozole treatment group.
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50 Several studies have assessed the combination of ET with CDK4/6 inhibitors in the
51 neoadjuvant setting[150]. Besides a potential survival benefit, it has been suggested that
52 this approach might enable molecular downstaging in higher-risk patients, converting
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4 more aggressive tumours to a more indolent cancer (such as luminal B to luminal A)[151].
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6 This was supported by the results from the CORALLEEN phase II trial, which looked at
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8 pre-operative treatment with a combination of letrozole and ribociclib[152]. The
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10 MONALEESA-1 trial was a small window-of-opportunity study comparing biological
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12 response to neoadjuvant letrozole alone or in combination with ribociclib, with results
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14 reporting greater Ki67 reduction in the combination arm[153]. The FELINE trial has been
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16 designed to assess whether the addition to neoadjuvant letrozole of ribociclib (in either a
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18 continuous or intermittent dosing regimen) can lead to a greater proportion of cases
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20 achieving a PEPI-0 score, although preliminary results did not show different outcomes
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22 between treatment groups[154].
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25 The NeoPalAna study assessed neoadjuvant treatment with a combination of the AI
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27 anastrozole and the CDK4/6 inhibitor palbociclib in 50 patients with ER+/HER2-
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29 disease[155]. Results showed complete cell cycle arrest (CCCA, defined as Ki67<2%
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31 after 2 weeks) rate was significantly higher in the combination compared to the AI-only
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33 group (87 vs 26%, $p<0.001$). However, increases in Ki67 after discontinuation of
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35 palbociclib suggested a maintenance treatment might be required. Additionally, side
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37 effects included frequent neutropenia, which might lead to treatment interruption or dose
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39 reductions. The phase II PALLET trial also reported increased Ki67 reduction in patients
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41 treated with combination neoadjuvant letrozole and palbociclib, compared to the letrozole-
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43 only group[156]. More recently, the SAFIA phase III trial found no additional pathological
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45 response benefit from the addition of palbociclib to HR+/HER2- BC patients responding
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47 to neoadjuvant fulvestrant[157]. The ongoing DxCARTES trial (NCT03819010) will
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49 assess the effect of 6 months of neoadjuvant combination treatment with palbociclib and
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51 letrozole[131].The ongoing phase III trial NCT03969121 trial will assess the same
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53 combination, studying both clinical and molecular response to evaluate potential
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55 molecular downstaging. Interestingly, the NeoPAL trial randomised 106 patients to
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4 neoadjuvant treatment with letrozole and palbociclib, or with NCT. The results showed
5 similar outcomes in both treatment arms and no difference in BCS rates or long-term
6 outcomes, suggesting that NET plus CDK4/6 inhibitors might be a safer, less toxic option
7 than NCT for patients with high-risk luminal BC [158,159].
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12 The Neomonarch study was a phase II multicentre trial including 224 patients which
13 compared 2 weeks of neoadjuvant treatment with the CDK4/6 inhibitor abemaciclib,
14 anastrozole, or a combination of both[160]. Ki67 suppression after 2 weeks was greater
15 in both treatment groups including abemaciclib ($p < 0.001$) when compared to the AI-only
16 arm.
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21 A recent meta-analysis considered all evidence to date on the use of CDK4/6 inhibitors
22 in combination with NET[150]. While no significant improvements were observed in PEPI-
23 0, pCR, objective response or disease control rates, the analysis showed that the addition
24 of inhibitors did achieve greater CCCA rates ($p < 0.001$). The authors concluded that this
25 combination treatment might be an option for treating HR+/HER2- early BC, but the less
26 favourable toxicity profile and the lack of evidence for better outcome or survival benefits
27 suggests this strategy might not be warranted. Another important caveat that bears
28 mentioning is that the suitability of Ki67 or CCCA to assess response to this type of
29 combination treatments has been questioned (see section 8).
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34 Studies are also underway to assess the combination of NET with other types of targeted
35 agents. One trial (NCT00107016) compared 4 months of neoadjuvant letrozole alone or
36 in combination with the mTOR inhibitor everolimus in 270 PMW with ER+ BC[161].
37 Results showed a trend towards better clinical response (68.1 vs 59%, $p = 0.62$) and a
38 significant greater proportion of patients with $Ki67 < 1\%$ (57 vs 30%, $p < 0.01$) in the
39 combination arm compared with the letrozole arm. As with CDK4/6 inhibitors, toxic side
40 effects might limit the adoption of this combination in the neoadjuvant setting. Another
41 trial randomised 92 PMW with HR+/HER2- BC to treatment with neoadjuvant letrozole
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4 plus placebo or the tyrosine kinase inhibitor lapatinib[162]. Results showed no differences
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6 in mean Ki67 suppression and similar clinical response rates (63% in the placebo arm vs
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8 70% in the lapatinib arm), but lapatinib led to significantly better objective response rates
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10 in cases presenting *PIK3CA* mutations (93 vs 63% in *PIK3CA* wild type, $p=0.04$). The
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12 LORELEI and NEO-ORB phase II trials assessed the effect of adding a PI3K inhibitor to
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14 neoadjuvant letrozole in PMW with HR+/HER2- BC. Interestingly, the LORELEI study
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16 reported benefit from the addition of taselisib[163], while the NEO-ORB data found no
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18 improvement in response[164]. Numerous other studies including NET in combination
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20 with targeted or immunotherapeutic agents are underway, which have also been
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22 summarised elsewhere[59,149].
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24 **6. The NET setting as a platform for research**

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27 The neoadjuvant setting offers unique 'research' prospects (see Figure 1 for schematic
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29 summary). Firstly, this window of treatment can help identify or validate biomarkers
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31 through the assessment of sequential tissue samples, which can include the diagnostic
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33 biopsy and eventual surgical specimen, as well as potentially other biopsies taken over
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35 the NET period. The development of surrogates such as Ki67 and PEPI since the early
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37 2000s represents a great example of this type of translational research.
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40 Secondly, the NET setting provides an opportunity to study the biology of the disease and
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42 its evolution under early treatment. We already discussed how transcriptomic assessment
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44 of NET-treated samples has led to a better understanding of the effect of these changes
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46 and how it changes over time[68] (see section 3.4). As another example of research in
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48 the NET window, one such study assessing genomic changes in patients treated with at
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50 least 1 month of neoadjuvant AIs reported the presence of *ESR1* mutations (linked to AI
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52 resistance in the adjuvant setting) in 5/87 patients, predominantly in patients who received
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54 longer NET (>6 months), showcasing how extended pre-operative treatment can start to
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56 give rise to mechanism of ET resistance[66]. Interestingly, another study assessing a
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3 cohort of 172 patients who exhibited primary ET resistance when treated with
4 neoadjuvant anastrozole for at least 3 months concluded that *ESR1* mutations are
5 unlikely to play a role in primary ET resistance [165].
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10 Lastly, and as evidenced by the number of recent combination NET trials, the pre-
11 operative setting can serve as a drug development platform for the testing of biology-
12 driven agents[148,149,166]. Assessment of molecular changes could help confirm target
13 inhibition, and characterise or monitor the induction of specific mechanisms of response
14 or resistance. The NET setting also has the advantage of allowing testing in a much
15 shorter timeframe than adjuvant studies, where a long follow-up is needed before
16 outcomes can be properly assessed. This notion is further supported by the fact that, as
17 previously discussed, NET studies have been shown to anticipate the outcomes of
18 adjuvant, and even metastatic, BC trials[89,148,149]. In line with this, the USA's Food
19 and Drug Administration (FDA) now accepts results from neoadjuvant clinical trials as
20 evidence for new drug approval[148].
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33 **7. NET during the pandemic**

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35 The recent COVID-19 pandemic led to a once-in-a-generation global healthcare crisis. In
36 the context of BC, this meant the need to defer treatments due to lack of resources or to
37 minimise the risk of patients and healthcare providers being exposed to the virus.
38 Accordingly, many groups urgently reviewed their practices and numerous consortia
39 defined recommendations[167–178]. These included guidelines for patient triage and
40 prioritisation, changes to the use of surgery, radiation and systemic therapies and,
41 importantly, the recommendation to use NET as a strategy for safe management of
42 HR+/HER2- cases in PMW whose surgery and adjuvant treatment could be deferred.
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52 Some experts provided specific guidelines for the use of NET in these cohorts. Martí and
53 Sánchez-Méndez advocated for its use to manage luminal BC patients, using on-
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4 treatment Ki67 assessment to monitor response[179]. Dowsett et al reviewed data from
5
6 multiple international trials to provide evidence-based practical guidelines for NET
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8 selection, including a more refined strategy that minimised the need for on-treatment
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10 biopsy[180]. In short, patients were stratified into 3 groups with specific recommendations
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12 according to their ER and PR Allred scores: (i) those not suitable for NET (lower HR
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14 expression: ER <6 or ER 6 and PgR <6), (ii) those for whom NET is the acceptable course
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16 of action (HR-rich: ER 8 and PgR ≥6), (iii) and those (with intermediate HR levels: ER 7/8
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18 and PgR <6, or ER 6/7 and PgR ≥6) for whom NET should be recommended but
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20 continuation should be subject to assessment of response 2-4 weeks on-treatment via
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22 biopsy for Ki67.

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24 Several studies have reported a shift in clinical practice during the pandemic towards
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26 increased use of NET to postpone surgery[181–185]. A review of the American Society
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28 of Breast Surgeons registries reported an additional 31% of HR+/HER2- BC patients
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30 received NET due to the pandemic[182]. A retrospective single-institution study,
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32 comparing cohorts diagnosed in 2019 and in mid-2020 to assess the impact of a 2-month
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34 interruption in BC screening due to COVID, found no significant changes in NET
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36 administration (17.3% in 2019 vs 28.1% in 2020, $p=0.0793$)[186]. While their results
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38 showed no significant differences in tumour biology, they did report a decrease in in situ
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40 disease (-10.4%) and an increase in both node-positive (+11.2%) and stage III (+10.3%)
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42 BC. In contrast, two historical cohort studies comparing groups of HR+/HER2- patients
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44 treated before and during the healthcare crisis reported significant increases in the use
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46 of NET: from 10% to 23% ($p=0.001$)[183], and from 7 to 48% ($p<0.0001$)[184]. The larger
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48 of these studies showed that, despite the disruption to regular screening programmes,
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50 BC stage at diagnosis did not differ significantly before and during the pandemic[183]. A
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52 multi-centre matched study directly compared a cohort of patients treated with NET during
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54 the pandemic to another cohort from before 2020 who received upfront surgery[187].
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4 Their results showed no evidence of pathological upstaging during the pandemic despite
5 2.5-longer delays to surgery. Overall, while further analysis once longer follow-up is
6 available could provide additional insight, these findings support the safety and efficacy
7 of NET.
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12 Interestingly, a retrospective study of pre-pandemic NCDB data also suggested a
13 potential protective effect of NET on HR+ ductal carcinoma in situ (DCIS) lesions[188].
14 Their results showed a trend towards an increased rate of upgrade to invasive disease in
15 patients without NET, but not in those who received NET. While prospective studies are
16 needed to validate these findings, the evidence suggests a protective effect of NET in
17 HR+ DCIS and that this therapeutic strategy might also be underutilised in these pre-
18 invasive lesions. Indeed, guidelines outlined at the start of the pandemic also
19 recommended NET for the management of HR+ DCIS[171,174,184].
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29 **8. Conclusion**

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31 Despite accumulating evidence for NET since the early 2000s, clinical adoption of NET
32 is still limited, with 2017 data from NCDB reporting that only 3% of eligible patients
33 received this therapy[189]. Indeed, a recent review of trends in clinical practice concluded
34 that, despite the suitability of this approach for a large proportion of BC patients, NET is
35 still underutilised[33]. While it has been established that evidence from clinical trials takes
36 an average of 17 years to be translated into clinical practice[190], several limitations
37 remain that prevent further optimisation and greater adoption of NET. Methodological
38 challenges have been summarised in this review and elsewhere[191]. Importantly, while
39 Ki67 expression has been validated as a predictor and has been used as a proliferation
40 surrogate in many studies, the use of this marker is not without many limitations, including
41 technical challenges, poor standardisation and a poor understanding of the actual role of
42 this protein in the biology of the cell cycle (see section 4.1). Indeed, a recent meeting of
43 the International Ki67 in Breast Cancer Working Group concluded that, while Ki67 IHC
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4 can be a useful tool, its analytical validity is subject to many technical factors and its
5 clinical utility remains limited to prognostic assessment of early disease[105].
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8 Furthermore, although several biomarkers, scores and signatures have been validated in
9 trials, their analytic and clinical validity and clinical utility still need to be corroborated, and
10 clear guidelines and recommendations should be defined before surrogates such as Ki67
11 and PEPI, or ideally even better tools, can be fully translated into the clinic to help guide
12 individual treatment decision[149]. While some genetic signatures might be aided by the
13 fact that they have already been approved for their use in the adjuvant or metastatic
14 settings, they will still require validation in the pre-operative setting through prospective
15 trials. As discussed, some such studies have already been conducted or are
16 underway[149]. These tools might also be limited by some of their original shortcomings;
17 for example, most of these signatures were developed and validated in cohorts including
18 a large majority of Caucasian patients, so their applicability in more ethnically diverse
19 populations remains unclear[119]. Interesting results from the ADAPT trial have
20 suggested that combining several predictors might help improve upon the limitations of
21 individual surrogates or assays, and could lead to improved stratification for treatment
22 selection[133] (see section 4.2), although further work is needed to confirm the
23 performance of these approaches for selection for specific therapies.
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40 Another limitation is that, as NET studies evolve, the more established surrogates might
41 be less appropriate for the assessment of novel combination treatments. Indeed, we
42 discussed how pCR is less robust as a predictor in the context of NET, compared to NCT
43 (see section 3.1). Similarly, markers initially validated as response surrogates in ET trials
44 might not be suitable to assess the effect of agents exerting their effect through different
45 mechanisms. For instance, if a combination treatment induces cancer cell apoptosis,
46 assessment of Ki67 would likely not be a good measure of response. Importantly, it is
47 also unclear whether Ki67 would be a good surrogate of response to treatments directly
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4 targeting cell division. Indeed, some trials assessing the combination of NET with CDK4/6
5 inhibitors have reasoned for the use of Ki67 as an outcome based on the notion that said
6 targeted agents have a predominantly antiproliferative effect[156,160]. However, some
7 authors have argued that this might not be the optimal predictor[144]: while Ki67 is a
8 proliferation marker, it has been validated to assess response to cytostatis-inducing ET;
9 so using Ki67 to gauge the effect of directly anti-proliferative targeted agents might lead
10 to an overestimation of the response achieved. Indeed, neoadjuvant trials have reported
11 much greater Ki67 reduction and rates of CCCA with the addition of CDK inhibitors to
12 ET[156,160], which do not appear to be predictive for survival benefit[192,193]. For
13 example, in the assessment of palbociclib ± ET, the neoadjuvant PALLET trial reported a
14 great increase in CCCA rates for the combination arm (90 vs 59%, $p < 0.001$)[156],
15 whereas second interim data from the adjuvant PALLAS trial showed no survival benefit
16 and concluded that, although long-term follow-up is still needed, the combination
17 treatment might not be warranted[193]. For this particular combination treatment, the
18 prognostic value of this surrogate is likely limited by the fact that CDK4/6 inhibitors are
19 known to block transition from G₁ to S phase[194], interfering with the already complex
20 expression of Ki67 across the different stages of the cell cycle (see section 4.1.).

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38 The fact that findings based on Ki67 assessment in neoadjuvant studies, previously
39 shown to be a good predictor of adjuvant results when it comes to ET response [89], do
40 not seem to be translated in larger adjuvant studies suggests that the proliferation marker
41 might not be the optimal surrogate for assessment of response to directly anti-proliferative
42 combination treatments. It is possible that genomic or hybrid assays or panels of multiple
43 markers, which incorporate more biological information, could be more suitable for
44 prediction of response to or benefit from these combination strategies. Overall, this
45 highlights the difficulty of establishing robust biomarkers; indeed, well-established
46 predictors require extensive validation and the definition of clear associated guidelines
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4 for their clinical translation. Even then, their use is likely to be limited to the clinical
5 scenarios that very closely replicate their development and validation platforms.
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8 9 **9. Expert opinion**

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11 NET represents a safe and viable treatment strategy for most PMW with HR+/HER2- BC.
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13 It can achieve survival outcomes comparable to those obtained with NCT in this group of
14 patients, but with better BCS rates and a more favourable toxicity profile, thus enabling
15 more surgical options and a better quality of life. Als are more effective than tamoxifen
16 and treatment should be at least 4 months, although numerous studies have shown that
17 longer treatment is likely to achieve better response, possibly including a more extensive
18 effect on the biology of the tumour. Consequently, NET duration might be extended if
19 necessary to achieve BCS, as long as appropriate monitoring takes place to ensure the
20 disease does not progress.
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30 The evidence summarised here has shown the importance of prediction and on-treatment
31 assessment of response during NET. Ki67, the most prominent tool for such assessment,
32 has contributed significantly to advances over the last two decades and has been utilised
33 as a surrogate in numerous trials and key clinical scenarios, such as in guiding selection
34 of NET during the recent COVID19 pandemic. However, Ki67 still remains a challenging
35 marker after all these years: evidence has shown the methodological shortcomings for its
36 accurate measurement, while a growing understanding of the underlying biology has told
37 us it might not be the most reliable surrogate for the assessment of treatment response.
38
39 In short, Ki67 has played a valuable role in the development of NET strategies, and a
40 flawed marker is better than none, but we believe that there is room for improvement and
41 a clear gap in the field for better and more robust markers and/or signatures to meet the
42 remaining clinical needs.
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4 Despite the compelling evidence from recent and ongoing trials showing the role NET can
5 play in the preoperative management and downscaling of disease in appropriately-
6 selected women with BC, uneven clinical adoption and suboptimal use mean this strategy
7 is still underutilised in many centres and territories. This is partly due to the
8 aforementioned need for better, thoroughly-validated biomarkers, as well as for updated
9 standardised guidelines for NET selection. Prognostic tools developed in the adjuvant
10 setting might be useful in this respect, but they need to be validated in neoadjuvant
11 studies. The recent pandemic led to the definition of some recommendations in this
12 respect and a surge in NET administration. Numerous subsequent analyses have
13 provided further evidence of the safety and efficacy of this therapeutic approach, which
14 we hope will lead to greater global confidence in and adoption of NET.
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26 In contrast to this irregular use of NET in practice, there seems to be a better appreciation
27 among the clinical and scientific community for the potential of the preoperative setting
28 for research purposes. Indeed, on-treatment assessment of response can provide
29 invaluable insight into each patient's disease and likely long-term prognosis, which can
30 also help guide adjuvant treatment selection. NET also offers unique research
31 opportunities to gain insight into the changing biology of early disease, for biomarker
32 validation and for the testing of novel strategies.
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41 While the wealth of recent and ongoing neoadjuvant studies is encouraging, as research
42 efforts advance to focus on more complex therapeutic approaches they will likely need to
43 contend with additional challenges. Indeed, most recent trials focus on the assessment
44 of combination treatment with NET and other targeted agents or inhibitors, but these are
45 likely to face multiple hurdles in that (i) existing surrogates for NET response appear to
46 be even more limited in the assessment of changes induced by non-ET agents, (ii) results
47 from preoperative combination studies appear to be less good at anticipating adjuvant
48 results (compared to how NET results could anticipate ET outcomes in the adjuvant or
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4 metastatic settings), and (iii), most importantly, early results from some of these
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6 neoadjuvant combination trials have already suggested that more challenging toxicities
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8 and limited survival benefits could mean the clinical adoption of these strategies might
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10 not be warranted. Nevertheless, we await further results from the many ongoing efforts
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12 to determine whether these hurdles could yet be surpassed to lead to potential
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14 improvements that could be translated into practice.

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16 In the meantime, joint efforts should be made to ensure NET becomes a global standard
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18 of practice for eligible postmenopausal women with ER+/HER2- BC. In the age of
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20 precision medicine, primary surgery should not be the go-to option for this patient
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22 population and the current underuse of NET in many territories represents a missed
23
24 opportunity. As we continue to work towards addressing the remaining challenges, we
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26 are confident that the use of NET for the pre-operative management of postmenopausal
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28 women with HR+/HER2- is likely to increase in the near future.
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Bibliography

- [1] Clark GM, Osborne CK, McGuire WL. Correlations between estrogen receptor, progesterone receptor, and patient characteristics in human breast cancer. *J Clin Oncol.* 1984;2:1102–1109.
- [2] Burstein HJ. Systemic Therapy for Estrogen Receptor–Positive, HER2-Negative Breast Cancer. *N Engl J Med.* 2020;383:2557–2570.
- [3] Martínez-Pérez C, Turnbull AK, Dixon JM. The evolving role of receptors as predictive biomarkers for metastatic breast cancer. *Expert Rev Anticancer Ther.* 2019;19:121–138.
- [4] Elder K, Dixon JMM, Blackmur JP, et al. Endocrine therapy for cancer. *Surgery.* 2018;36:134–138.
- [5] Preece PE, Wood RAB, Mackie CR, et al. Tamoxifen as initial sole treatment of localised breast cancer in elderly women: a pilot study. *Br Med J.* 1982;284:869–870.
- [6] Gazet J-C, Ford HT, Coombes RC, et al. Prospective randomized trial of tamoxifen vs surgery in elderly patients with breast cancer. *Eur J Surg Oncol.* 1994;20:207–214.
- [7] Bates T, Riley DL, Houghton J, et al. Breast cancer in elderly women: A Cancer Research Campaign trial comparing treatment with tamoxifen and optimal surgery with tamoxifen alone. *Br J Surg.* 1991;78:591–594.
- [8] Mustacchi G, Milani S, Pluchinotta A, et al. Tamoxifen or surgery plus tamoxifen as primary treatment for elderly patients with operable breast cancer: The G.R.E.T.A. trial. *Anticancer Res.* 1994;14:2197–2200.
- [9] Fennessy M, Bates T, MacRae K, et al. Late follow-up of a randomized trial of surgery plus tamoxifen versus tamoxifen alone in women aged over 70 years with operable breast cancer. *Br J Surg.* 2004;91:699–704.
- [10] Hind D, Wyld L, Reed MW. Surgery, with or without tamoxifen, vs tamoxifen alone for older women with operable breast cancer: Cochrane review. *Br J Cancer.* 2007;96:1025–1029.
- [11] Mustacchi G, Ceccherini R, Milani S, et al. Tamoxifen alone versus adjuvant tamoxifen for operable breast cancer of the elderly: Long-term results of the phase III randomized controlled multicenter GRETA trial. *Ann Oncol.* 2003;14:414–420.
- [12] Dixon JM, Love CDB, Bellamy COC, et al. Letrozole as primary medical therapy for locally advanced and large operable breast cancer. *Breast Cancer Res Treat.* 2001;66:191–199.
- [13] Arthur LM, Turnbull AK, Khan LR, et al. Pre-operative Endocrine Therapy. *Curr Breast Cancer Rep.* 2017;9:202–209.
- [14] Cance WG, Carey LA, Calvo BF, et al. Long-term outcome of neoadjuvant therapy for locally advanced breast carcinoma: Effective clinical downstaging allows breast preservation and predicts outstanding local control and survival. *Ann Surg.* 2002;236:295–303.
- [15] Makris A, Powles TJ, Ashley SE, et al. A reduction in the requirements for mastectomy in a randomized trial of neoadjuvant chemoendocrine therapy in primary breast cancer. *Ann Oncol.* 1998;9:1179–1184.

- 1
2
3 [16] Ellis MJ, Coop A, Singh B, et al. Letrozole Is More Effective Neoadjuvant Endocrine Therapy Than
4 Tamoxifen for ErbB-1– and/or ErbB-2–Positive, Estrogen Receptor–Positive Primary Breast Cancer:
5 Evidence From a Phase III Randomized Trial. *J Clin Oncol*. 2001;19:3808–3816.
6
7 [17] Ellis MJ, Suman VJ, Hoog J, et al. Randomized phase II neoadjuvant comparison between letrozole,
8 anastrozole, and exemestane for postmenopausal women with estrogen receptor-rich stage 2 to 3 breast
9 cancer: Clinical and biomarker outcomes and predictive value of the baseline PAM50-based int. *J Clin*
10 *Oncol*. 2011;29:2342–2349.
11
12 [18] Ma CX, Suman VJ, Leitch AM, et al. ALTERNATE: Neoadjuvant endocrine treatment (NET) approaches for
13 clinical stage II or III estrogen receptor-positive HER2-negative breast cancer (ER+ HER2- BC) in
14 postmenopausal (PM) women: Alliance A011106. *J Clin Oncol*. American Society of Clinical Oncology;
15 2020. p. 504–504.
16
17 [19] Wang X, Fan Z, Wang X, et al. Neoadjuvant endocrine therapy for strongly hormone receptor-positive and
18 HER2-negative early breast cancer: results of a prospective multi-center study. *Breast Cancer Res Treat*
19 2022. 2022;1:1–10.
20
21 [20] Carey LA, Dees EC, Sawyer L, et al. The triple negative paradox: Primary tumor chemosensitivity of breast
22 cancer subtypes. *Clin Cancer Res*. 2007;13:2329–2334.
23
24 [21] Guarneri V, Broglio K, Kau SW, et al. Prognostic value of pathologic complete response after primary
25 chemotherapy in relation to hormone receptor status and other factors. *J Clin Oncol*. 2006;24:1037–1044.
26
27 [22] Colleoni M, Viale G, Zahrieh D, et al. Chemotherapy is more effective in patients with breast cancer not
28 expressing steroid hormone receptors: A study of preoperative treatment. *Clin Cancer Res*.
29 2004;10:6622–6628.
30
31 [23] Aebi S, Sun Z, Braun D, et al. Differential efficacy of three cycles of CMF followed by tamoxifen in patients
32 with ER-positive and ER-negative tumors: Long-term follow up on IBCSG Trial IX. *Ann Oncol*.
33 2011;22:1981–1987.
34
35 [24] Coates AS, Colleoni M, Goldhirsch A. Is adjuvant chemotherapy useful for women with luminal a breast
36 cancer? *J Clin Oncol*. 2012;30:1260–1263.
37
38 [25] Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Comparisons between different
39 polychemotherapy regimens for early breast cancer: Meta-analyses of long-term outcome among 100
40 000 women in 123 randomised trials. *The Lancet*. 2012;379:432–444.
41
42 [26] Sparano JA, Gray RJ, Makower DF, et al. Adjuvant Chemotherapy Guided by a 21-Gene Expression Assay in
43 Breast Cancer. *N Engl J Med*. 2018;379:111–121.
44
45 [27] Kalinsky K, Barlow WE, Gralow JR, et al. 21-Gene Assay to Inform Chemotherapy Benefit in Node-Positive
46 Breast Cancer. *N Engl J Med*. 2021;385:2336–2347.
47
48 [28] Spring LM, Gupta A, Reynolds KL, et al. Neoadjuvant Endocrine Therapy for Estrogen Receptor-Positive
49 Breast Cancer: A Systematic Review and Meta-analysis. *JAMA Oncol*. NIH Public Access; 2016. p. 1477.
50
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52 **Review and meta-analysis of evidence from 20 RCTs assessing the use of NET.
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- 1
2
3 [29] Alba E, Calvo L, Albanell J, et al. Chemotherapy (CT) and hormonotherapy (HT) as neoadjuvant treatment
4 in luminal breast cancer patients: Results from the GEICAM/2006-03, a multicenter, randomized, phase-II
5 study. *Ann Oncol.* 2012;23:3069–3074.
6
- 7 [30] Masuda N, Sagara Y, Kinoshita T, et al. Neoadjuvant anastrozole versus tamoxifen in patients receiving
8 goserelin for premenopausal breast cancer (STAGE): A double-blind, randomised phase 3 trial. *Lancet*
9 *Oncol.* 2012;13:345–352.
10
- 11 [31] Leal F, Liutti VT, Antunes dos Santos VC, et al. Neoadjuvant endocrine therapy for resectable breast
12 cancer: A systematic review and meta-analysis. *Breast.* 2015;24:406–412.
13
- 14 [32] Weiss A, King TA, Mittendorf EA. The Landmark Series: Neoadjuvant Endocrine Therapy for Breast Cancer.
15 *Ann Surg Oncol.* 2020;27:3393–3401.
16
- 17 [33] Sella T, Weiss A, Mittendorf EA, et al. Neoadjuvant Endocrine Therapy in Clinical Practice: A Review. *JAMA*
18 *Oncol.* 2021;7:1700–1708.
19
- 20 [34] Semiglazov VF, Semiglazov V V., Dashyan GA, et al. Phase 2 randomized trial of primary endocrine therapy
21 versus chemotherapy in postmenopausal patients with estrogen receptor-positive breast cancer. *Cancer.*
22 2007;110:244–254.
23
- 24 [35] Cardoso F, Kyriakides S, Ohno S, et al. Early breast cancer: ESMO Clinical Practice Guidelines for diagnosis,
25 treatment and follow-up. *Ann Oncol.* 2019;30:1194–1220.
26
- 27 [36] Kim HJ, Noh WC, Lee ES, et al. Efficacy of neoadjuvant endocrine therapy compared with neoadjuvant
28 chemotherapy in pre-menopausal patients with oestrogen receptor-positive and HER2-negative, lymph
29 node-positive breast cancer. *Breast Cancer Res.* 2020;22:1–9.
30
- 31 [37] Chic N, Schettini F, Brasó-Maristany F, et al. Oestrogen receptor activity in hormone-dependent breast
32 cancer during chemotherapy: ER activity in pre-menopausal HR+ breast cancer during CT. *EBioMedicine.*
33 2021;69:103451.
34
- 35 [38] Palmieri C, Cleator S, Kilburn LSS, et al. NEOCENT: a randomised feasibility and translational study
36 comparing neoadjuvant endocrine therapy with chemotherapy in ER-rich postmenopausal primary breast
37 cancer. *Breast Cancer Res Treat.* 2014;148:581–590.
38
- 39 [39] Cao L, Sugumar K, Keller E, et al. Neoadjuvant Endocrine Therapy as an Alternative to Neoadjuvant
40 Chemotherapy Among Hormone Receptor-Positive Breast Cancer Patients: Pathologic and Surgical
41 Outcomes. *Ann Surg Oncol.* 2021;28:5730–5741.
42
- 43 [40] Tamirisa N, Hunt KK. Neoadjuvant Chemotherapy, Endocrine Therapy, and Targeted Therapy for Breast
44 Cancer: ASCO Guideline. *Ann Surg Oncol.* 2022;1–4.
45
- 46 [41] Curigliano G, Burstein HJ, Winer EP, et al. De-escalating and escalating treatments for early-stage breast
47 cancer: The St. Gallen International Expert Consensus Conference on the Primary Therapy of Early Breast
48 Cancer 2017. *Ann Oncol.* 2017;28:1700–1712.
49
- 50 [42] Madigan LI, Dinh P, Graham JD. Neoadjuvant endocrine therapy in locally advanced estrogen or
51 progesterone receptor-positive breast cancer: Determining the optimal endocrine agent and treatment
52 duration in postmenopausal women—a literature review and proposed guidelines. *Breast Cancer Res.*
53 2020;22:1–13.
54
55
56
57
58
59

- 1
2
3 [43] National Institute of Health and Care Excellence (NICE). NICE guideline (NG101) - Early and locally
4 advanced breast cancer: diagnosis and management. 2019.
5
6 [44] Korde LA, Somerfield MR, Carey LA, et al. Neoadjuvant Chemotherapy, Endocrine Therapy, and Targeted
7 Therapy for Breast Cancer: ASCO Guideline. *J Clin Oncol*. 2021;39:1485–1505.
8
9 [45] World Health Organisation (WHO). The global burden of disease: 2004 update. Geneva; 2008.
10
11 [46] Dowsett M, Cuzick J, Ingle J, et al. Meta-analysis of breast cancer outcomes in adjuvant trials of
12 aromatase inhibitors versus tamoxifen. *J Clin Oncol*. 2010;28:509–518.
13
14 [47] Regan MM, Neven P, Giobbie-Hurder A, et al. Assessment of letrozole and tamoxifen alone and in
15 sequence for postmenopausal women with steroid hormone receptor-positive breast cancer: The BIG 1-
16 98 randomised clinical trial at 8.1 years median follow-up. *Lancet Oncol*. 2011;12:1101–1108.
17
18 [48] Eiermann W, Paepke S, Appfelstaedt J, et al. Preoperative treatment of postmenopausal breast cancer
19 patients with letrozole: A randomized double-blind multicenter study. *Ann Oncol*. 2001;12:1527–1532.
20
21 [49] Ellis MJ, Ma C. Letrozole in the neoadjuvant setting: The P024 trial. *Breast Cancer Res Treat*. 2007;105:33–
22 43.
23
24 [50] Ellis MJ, Coop A, Singh B, et al. Letrozole inhibits tumor proliferation more effectively than tamoxifen
25 independent of HER1/2 expression status. *Cancer Res*. 2003;63:6523–6531.
26
27 [51] Smith IE, Dowsett M, Ebbs SR, et al. Neoadjuvant Treatment of Postmenopausal Breast Cancer With
28 Anastrozole, Tamoxifen, or Both in Combination: The Immediate Preoperative Anastrozole, Tamoxifen, or
29 Combined With Tamoxifen (IMPACT) Multicenter Double-Blind Randomized Trial. *J Clin Oncol*.
30 2005;23:5108–5116.
31
32 [52] Cataliotti L, Buzdar AUAU, Noguchi S, et al. Comparison of anastrozole versus tamoxifen as
33 preoperative therapy in postmenopausal women with hormone receptor-positive breast cancer: The Pre-
34 Operative “Arimidex” Compared to Tamoxifen (PROACT) trial. *Cancer*. 2006;106:2095–2103.
35
36 [53] Semiglazov V, Kletsel A, Semiglazov V, et al. Exemestane (E) vs tamoxifen (T) as neoadjuvant endocrine
37 therapy for postmenopausal women with ER+ breast cancer (T2N1–2, T3N0–1, T4N0M0). *J Clin Oncol*.
38 2005;23:530–530.
39
40 [54] Seo JH, Kim YH, Kim JS. Meta-analysis of pre-operative aromatase inhibitor versus tamoxifen in
41 postmenopausal woman with hormone receptor-positive breast cancer. *Cancer Chemother Pharmacol*.
42 2009;63:261–266.
43
44

45 *Meta-analysis on the evidence of AI vs tamoxifen as NET.

- 46
47 [55] Murray J, Young OE, Renshaw L, et al. A randomised study of the effects of letrozole and anastrozole on
48 oestrogen receptor positive breast cancers in postmenopausal women. *Breast Cancer Res Treat*.
49 2009;114:495–501.
50
51 [56] Quenel-Tueux N, Debled M, Rudewicz J, et al. Clinical and genomic analysis of a randomised phase II study
52 evaluating anastrozole and fulvestrant in postmenopausal patients treated for large operable or locally
53 advanced hormone-receptor-positive breast cancer. *Br J Cancer*. 2015;113:585–594.
54
55
56
57
58
59

- 1
2
3 [57] Lerebours F, Rivera S, Mouret-Reynier M-AMAM-A, et al. Randomized phase 2 neoadjuvant trial
4 evaluating anastrozole and fulvestrant efficacy for postmenopausal, estrogen receptor–positive, human
5 epidermal growth factor receptor 2–negative breast cancer patients: Results of the UNICANCER CARMINA
6 02 French trial. *Cancer*. 2016;122:3032–3040.
7
- 8 [58] Lerebours F, Pulido M, Fourme E, et al. Predictive factors of 5-year relapse-free survival in HR+/HER2-
9 breast cancer patients treated with neoadjuvant endocrine therapy: pooled analysis of two phase 2 trials.
10 *Br J Cancer*. 2020;122:759–765.
11
- 12 [59] Martí C, Sánchez-Méndez JI. The Present and Future of Neoadjuvant Endocrine Therapy for Breast Cancer
13 Treatment. *Cancers*. 2021;13.
14
- 15 [60] Dixon JM, Renshaw L, Macaskill EJ, et al. Increase in response rate by prolonged treatment with
16 neoadjuvant letrozole. *Breast Cancer Res Treat*. 2009;113:145–151.
17
- 18 [61] Allevi G, Strina C, Andreis D, et al. Increased pathological complete response rate after a long-term
19 neoadjuvant letrozole treatment in postmenopausal oestrogen and/or progesterone receptor-positive
20 breast cancer. *Br J Cancer*. 2013;108:1587–1592.
21
- 22 [62] Toi M, Saji S, Masuda N, et al. Ki67 index changes, pathological response and clinical benefits in primary
23 breast cancer patients treated with 24 weeks of aromatase inhibition. *Cancer Sci*. 2011;102:858–865.
24
- 25 [63] Fontein DBY, Charehbili A, Nortier JWR, et al. Efficacy of six month neoadjuvant endocrine therapy in
26 postmenopausal, hormone receptor-positive breast cancer patients - A phase II trial. *Eur J Cancer*.
27 2014;50:2190–2200.
28
- 29 [64] Carpenter R, Doughty JC, Cordiner C, et al. Optimum duration of neoadjuvant letrozole to permit breast
30 conserving surgery. *Breast Cancer Res Treat*. 2014;144:569–576.
31
- 32 [65] Lobo-Cardoso R, Magalhães AT, Fougo JL. Neoadjuvant endocrine therapy in breast cancer patients. *Porto*
33 *Biomed J*. 2017;2:170–173.
34
- 35 [66] Leal MF, Haynes BP, Schuster E, et al. Early enrichment of ESR1 mutations and the impact on gene
36 expression in presurgical primary breast cancer treated with aromatase inhibitors. *Clin Cancer Res*.
37 2019;25:7485–7496.
38
- 39 [67] Gao Q, López-Knowles E, Cheang MCU, et al. Impact of aromatase inhibitor treatment on global gene
40 expression and its association with antiproliferative response in ER+ breast cancer in postmenopausal
41 patients. *Breast Cancer Res BCR*. 2019;22:2.
42
- 43 [68] Bergamino MA, Morani G, Parker J, et al. Impact of Duration of Neoadjuvant Aromatase Inhibitors on
44 Molecular Expression Profiles in Estrogen Receptor–positive Breast Cancers. *Clin Cancer Res*.
45 2022;28:1217–1228.
46
- 47 [69] Lips EH, Mukhtar RA, Yau C, et al. Lobular histology and response to neoadjuvant chemotherapy in
48 invasive breast cancer. *Breast Cancer Res Treat*. 2012;136:35–43.
49
- 50 [70] Dixon JM, Renshaw L, Dixon JM, et al. Invasive lobular carcinoma: Response to neoadjuvant letrozole
51 therapy. *Breast Cancer Res Treat*. 2011;130:871–877.
52
- 53 [71] Arthur LM, Turnbull AK, Webber VL, et al. Molecular Changes in Lobular Breast Cancers in Response to
54 Endocrine Therapy. *Cancer Res*. 2014;74:5371–5376.
55
56
57
58
59
60

- 1
2
3 [72] Mukhtar RA, Hoskin TL, Habermann EB, et al. Changes in Management Strategy and Impact of
4 Neoadjuvant Therapy on Extent of Surgery in Invasive Lobular Carcinoma of the Breast: Analysis of the
5 National Cancer Database (NCDB). *Ann Surg Oncol.* 2021;28:5867–5877.
6
7 [73] Montagna G, Sevilimedu V, Fornier M, et al. How Effective is Neoadjuvant Endocrine Therapy (NET) in
8 Downstaging the Axilla and Achieving Breast-Conserving Surgery? *Ann Surg Oncol.* 2020;27:4702–4710.
9
10 [74] Hammond JB, Parnall TH, Scott DW, et al. Gauging the efficacy of neoadjuvant endocrine therapy in
11 breast cancer patients with known axillary disease. *J Surg Oncol.* 2020;122:619–622.
12
13 [75] Stafford A, Williams A, Edmiston K, et al. Axillary Response in Patients Undergoing Neoadjuvant Endocrine
14 Treatment for Node-Positive Breast Cancer: Systematic Literature Review and NCDB Analysis. *Ann Surg*
15 *Oncol.* 2020;27:4669–4677.
16
17 [76] Weiss A, Wong S, Golshan M, et al. Patterns of Axillary Management in Stages 2 and 3 Hormone
18 Receptor-Positive Breast Cancer by Initial Treatment Approach. *Ann Surg Oncol.* 2019;26:4326–4336.
19
20 [77] Kantor O, Wong S, Weiss A, et al. Prognostic significance of residual nodal disease after neoadjuvant
21 endocrine therapy for hormone receptor-positive breast cancer. *Npj Breast Cancer.* 2020;6:1–6.
22
23 [78] Kantor O, Wakeman M, Weiss A, et al. Axillary Management After Neoadjuvant Endocrine Therapy for
24 Hormone Receptor-Positive Breast Cancer. *Ann Surg Oncol.* 2021;28:1358–1367.
25
26 [79] Friedman-Eldar O, Ozmen T, El Haddi SJ, et al. Axillary Response to Neoadjuvant Therapy in Node-Positive,
27 Estrogen Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Breast Cancer
28 Patients: Predictors and Oncologic Outcomes. *Ann Surg Oncol.* 2022;1–10.
29
30 [80] Ma CX, Suman V, Leitch AM, et al. Abstract GS4-05: Neoadjuvant chemotherapy (NCT) response in
31 postmenopausal women with clinical stage II or III estrogen receptor positive (ER+) and HER2 negative
32 (HER2-) breast cancer (BC) resistant to endocrine therapy (ET) in the ALTERNATE trial (Alliance A011106).
33 *Cancer Res.* 2021;81:GS4-05-GS4-05.
34
35 [81] Harbeck N, Gluz O, Kuemmel S, et al. Abstract GS4-04: Endocrine therapy alone in patients with
36 intermediate or high-risk luminal early breast cancer (0-3 lymph nodes), Recurrence Score <26 and Ki67
37 response after preoperative endocrine therapy: Primary outcome results from the WSG-ADAPT
38 HR+/HER2- trial. *Cancer Res. American Association for Cancer Research; 2021.* p. GS4-04-GS4-04.
39
40 [82] Cortazar P, Zhang L, Untch M, et al. Pathological complete response and long-term clinical benefit in
41 breast cancer: the CTNeoBC pooled analysis. *The Lancet.* 2014;384:164–172.
42
43 [83] Thomas JSJ, Julian HS, Green R V., et al. Histopathology of breast carcinoma following neoadjuvant
44 systemic therapy: A common association between letrozole therapy and central scarring. *Histopathology.*
45 2007;51:219–226.
46
47 [84] Gerdes J, Lemke H, Baisch H, et al. Cell cycle analysis of a cell proliferation-associated human nuclear
48 antigen defined by the monoclonal antibody Ki-67. *J Immunol.* 1984;133:1710–1715.
49
50 [85] Sadeghian D, Saffar H, Mahdavi Sharif P, et al. MCM6 versus Ki-67 in diagnosis of luminal molecular
51 subtypes of breast cancers. *Diagn Pathol.* 2022;17:1–9.
52
53 [86] Lopez F, Belloc F, Lacombe F, et al. Modalities of synthesis of Ki67 antigen during the stimulation of
54 lymphocytes. *Cytometry.* 1991;12:42–49.
55
56
57
58
59
60

- 1
2
3 [87] Yerushalmi R, Woods R, Ravdin PM, et al. Ki67 in breast cancer: prognostic and predictive potential. *Lancet Oncol*. 2010;11:174–183.
4
5
6 [88] Zhang J, Lu CY, Chen HM, et al. Neoadjuvant Chemotherapy or Endocrine Therapy for Invasive Ductal
7 Carcinoma of the Breast with High Hormone Receptor Positivity and Human Epidermal Growth Factor
8 Receptor 2 Negativity. *JAMA Netw Open*. 2021;4:e211785–e211785.
9
10 [89] Barroso-Sousa R, Reis Silva DDAF, Alessi JVM, et al. Neoadjuvant endocrine therapy in breast cancer:
11 Current role and future perspectives. *ecancermedicalsecience*. 2016;10.
12
13 [90] Sheri A, Dowsett M. Developments in Ki67 and other biomarkers for treatment decision making in breast
14 cancer. *Ann Oncol*. 2012;23:x219–x227.
15
16 [91] Jones RL, Salter J, A'Hern R, et al. The prognostic significance of Ki67 before and after neoadjuvant
17 chemotherapy in breast cancer. *Breast Cancer Res Treat*. 2009;116:53–68.
18
19 [92] Dowsett M, Smith IE, Ebbs SR, et al. Proliferation and Apoptosis as Markers of Benefit in Neoadjuvant
20 Endocrine Therapy of Breast Cancer. *Clin Cancer Res*. 2006;12:1024s–1030s.
21
22 [93] Senkus E, Kyriakides S, Ohno S, et al. Primary breast cancer: ESMO Clinical Practice Guidelines for
23 diagnosis, treatment and follow-up. *Ann Oncol*. 2015;26:v8–v30.
24
25 [94] Esposito A, Criscitiello C, Curigliano G. Highlights from the 14th St Gallen International Breast Cancer
26 Conference 2015 in Vienna: Dealing with classification, prognostication, and prediction refinement to
27 personalize the treatment of patients with early breast cancer. *ecancermedicalsecience*. *ecancer Global*
28 *Foundation*; 2015.
29
30 [95] Smith I, Robertson J, Kilburn L, et al. Long-term outcome and prognostic value of Ki67 after perioperative
31 endocrine therapy in postmenopausal women with hormone-sensitive early breast cancer (POETIC): an
32 open-label, multicentre, parallel-group, randomised, phase 3 trial. *Lancet Oncol*. 2020;21:1443–1454.
33
34
35 * Results from the POETIC study reporting on the use of Ki67 to help guide adjuvant treatment selection
36 in HR+ BC.
37
38 [96] Ellis MJ, Suman VJ, Hoog J, et al. Ki67 proliferation index as a tool for chemotherapy decisions during and
39 after neoadjuvant aromatase inhibitor treatment of breast cancer: Results from the American college of
40 surgeons oncology group Z1031 trial (alliance). *J Clin Oncol*. 2017;35:1061–1069.
41
42 [97] Suman VJ, Ellis MJ, Ma CX. The ALTERNATE trial: Assessing a biomarker driven strategy for the treatment
43 of post-menopausal women with Er+/Her2- invasive breast cancer. *Chin Clin Oncol*. 2015;4.
44
45 [98] Dowsett M, Nielsen TO, A'Hern R, et al. Assessment of Ki67 in Breast Cancer: Recommendations from the
46 International Ki67 in Breast Cancer Working Group. *JNCI J Natl Cancer Inst*. 2011;103:1656.
47
48
49 * Early expert review on the role of Ki67 in BC.
50
51 [99] Polley M-YC, Leung SCY, McShane LM, et al. An International Ki67 Reproducibility Study. *JNCI J Natl*
52 *Cancer Inst*. 2013;105:1897–1906.
53
54 [100] Leung SCY, Nielsen TO, Zabaglo LA, et al. Analytical validation of a standardised scoring protocol for Ki67
55 immunohistochemistry on breast cancer excision whole sections: an international multicentre
56 collaboration. *Histopathology*. 2019;75:225–235.
57
58
59
60

- 1
2
3 [101] Rimm DL, Leung SCY, McShane LM, et al. An international multicenter study to evaluate reproducibility of
4 automated scoring for assessment of Ki67 in breast cancer. *Mod Pathol* 2018 321. 2018;32:59–69.
5
6 [102] Lashen A, Toss MS, Green AR, et al. Ki67 assessment in invasive luminal breast cancer: A comparative
7 study between different scoring methods. *Histopathology*. 2022;
8
9 [103] Focke CM, Decker T, van Diest PJ. Intratumoral heterogeneity of Ki67 expression in early breast cancers
10 exceeds variability between individual tumours. *Histopathology*. 2016;69:849–861.
11
12 [104] Yousef EM, Furrer D, Laperriere DL, et al. MCM2: An alternative to Ki-67 for measuring breast cancer cell
13 proliferation. *Mod Pathol*. 2017;30:682–697.
14
15 [105] Nielsen TO, Leung SCY, Rimm DL, et al. Assessment of Ki67 in Breast Cancer: Updated Recommendations
16 From the International Ki67 in Breast Cancer Working Group. *JNCI J Natl Cancer Inst*. 2021;113:201.
17
18 ** A recent update on the expert recommendations for the use of Ki67 in BC, including discussion of its
19 limitations.
20
21
22
23 [106] Polley MYC, Leung SCY, Gao D, et al. An international study to increase concordance in Ki67 scoring. *Mod*
24 *Pathol*. 2015;28:778–786.
25
26 [107] Laurinavicius A, Plancoulaine B, Laurinaviciene A, et al. A methodology to ensure and improve accuracy of
27 Ki67 labelling index estimation by automated digital image analysis in breast cancer tissue. *Breast Cancer*
28 *Res BCR*. 2014;16.
29
30 [108] Pons L, Hernández-León L, Altaieb A, et al. Conventional and digital Ki67 evaluation and their correlation
31 with molecular prognosis and morphological parameters in luminal breast cancer. *Sci Rep* 2022 121.
32 2022;12:1–9.
33
34 [109] Miller I, Min M, Yang C, et al. Ki67 is a Graded Rather than a Binary Marker of Proliferation versus
35 Quiescence. *Cell Rep*. 2018;24:1105-1112.e5.
36
37 [110] Sun X, Kaufman PD. Ki-67: more than a proliferation marker. *Chromosoma*. 2018;127:175.
38
39 [111] Uxa S, Castillo-Binder P, Kohler R, et al. Ki-67 gene expression. *Cell Death Differ*. 2021;28:3357–3370.
40
41 [112] Loddo M, Kingsbury SR, Rashid M, et al. Cell-cycle-phase progression analysis identifies unique
42 phenotypes of major prognostic and predictive significance in breast cancer. *Br J Cancer*. 2009;100:959–
43 970.
44
45 [113] Tőkés T, Tőkés AM, Szentmártoni G, et al. Prognostic and Clinicopathological Correlations of Cell Cycle
46 Marker Expressions before and after the Primary Systemic Therapy of Breast Cancer. *Pathol Oncol Res*.
47 2020;26:1499–1510.
48
49 [114] Issac MSM, Yousef E, Tahir MR, et al. MCM2, MCM4, and MCM6 in Breast Cancer: Clinical Utility in
50 Diagnosis and Prognosis. *Neoplasia*. 2019;21:1015.
51
52 [115] Kwok HF, Zhang SD, McCrudden CM, et al. Prognostic significance of minichromosome maintenance
53 proteins in breast cancer. *Am J Cancer Res*. 2015;5:52.
54
55
56
57
58
59

- 1
2
3 [116] Ellis MJ, Tao Y, Luo J, et al. Outcome prediction for estrogen receptor-positive breast cancer based on
4 postneoadjuvant endocrine therapy tumor characteristics. *J Natl Cancer Inst.* 2008;100:1380–1388.
5
- 6 [117] Martí C, Yébenes L, Oliver JM, et al. The Clinical Impact of Neoadjuvant Endocrine Treatment On Luminal-
7 Like Breast Cancers and Its Prognostic Significance: Results From a Single-institution Prospective Cohort
8 Study. *Curr Oncol.* 2022;29:2199–2210.
9
- 10 * A report on the application of diagnostic and on-treatment Ki67 assessment to help guide pre-operative
11 management of HR+/HER2- BC management.
12
13
- 14 [118] Griguolo G, Bottosso M, Vernaci G, et al. Gene-expression signatures to inform neoadjuvant treatment
15 decision in HR+/HER2- breast cancer: Available evidence and clinical implications. *Cancer Treat Rev.*
16 2022;102:102323.
17
- 18 * Recent review on molecular tools for pre-operative treatment selection.
19
20
- 21 [119] Varnier R, Sajous C, de Talhouet S, et al. Using Breast Cancer Gene Expression Signatures in Clinical
22 Practice: Unsolved Issues, Ongoing Trials and Future Perspectives. *Cancers.* 2021;13:4840.
23
- 24 * Another recent review on molecular tools for pre-operative treatment selection.
25
26
- 27 [120] Garufi G, Carbognin L, Arcanà C, et al. Tailoring neoadjuvant treatment of HR-positive/HER2-negative
28 breast cancers: Which role for gene expression assays? *Cancer Treat Rev.* 2022;110:102454.
29
- 30 [121] Sparano JA, Paik S. Development of the 21-gene assay and its application in clinical practice and clinical
31 trials. *J Clin Oncol.* 2008;26:721–728.
32
- 33 [122] Andre F, Ismaila N, Henry NL, et al. Use of biomarkers to guide decisions on adjuvant systemic therapy for
34 women with early-stage invasive breast cancer: ASCO clinical practice guideline update-integration of
35 results from TAILORx. *J Clin Oncol.* 2019;37:1956–1964.
36
- 37 [123] Davey MG, Ryan J, Boland MR, et al. Clinical utility of the 21-gene assay in predicting response to
38 neoadjuvant endocrine therapy in breast cancer: A systematic review and meta-analysis. *The Breast.*
39 2021;58:113–120.
40
- 41 * Meta-analysis on the evidence to date on the use of Oncotype DX for NET selection.
42
43
- 44 [124] Akashi-Tanaka S, Shimizu C, Ando M, et al. 21-Gene expression profile assay on core needle biopsies
45 predicts responses to neoadjuvant endocrine therapy in breast cancer patients. *Breast.* 2009;18:171–174.
46
- 47 [125] Ueno T, Masuda N, Yamanaka T, et al. Evaluating the 21-gene assay Recurrence Score® as a predictor of
48 clinical response to 24 weeks of neoadjuvant exemestane in estrogen receptor-positive breast cancer. *Int*
49 *J Clin Oncol.* 2014;19:607–613.
50
- 51 [126] Iwata H, Masuda N, Yamamoto Y, et al. Validation of the 21-gene test as a predictor of clinical response to
52 neoadjuvant hormonal therapy for ER+, HER2-negative breast cancer: the TransNEOS study. *Breast*
53 *Cancer Res Treat.* 2019;173:123–133.
54
- 55 [127] Bear HD, Wan W, Robidoux A, et al. Using the 21-gene assay from core needle biopsies to choose
56 neoadjuvant therapy for breast cancer: A multicenter trial. *J Surg Oncol.* 2017;115:917–923.
57
58
59
60

- 1
2
3 [128] Zelnak AB, Murali S, Styblo TM, et al. Phase II trial evaluating the use of 21-gene recurrence score (RS) to
4 select preoperative therapy in hormone receptor (HR)-positive breast cancer. *J Clin Oncol*. American
5 Society of Clinical Oncology; 2013. p. 562–562.
6
7 [129] Abu-Khalaf MM, Aderhold K, Marczyk M, et al. Abstract P5-13-02: Neoadjuvant aromatase inhibitor
8 therapy plus the mTOR inhibitor everolimus in postmenopausal women with hormone receptor
9 positive/HER2 negative breast cancer and an oncotype Dx recurrence score (≤ 25). *Cancer Res*. American
10 Association for Cancer Research; 2020. p. P5-13-02-P5-13-02.
11
12 [130] AlSaleh K, Al Zahwahry H, Bounedjar A, et al. Response to Induction Neoadjuvant Hormonal Therapy
13 Using Upfront 21-Gene Breast Recurrence Score Assay—Results From the SAFIA Phase III Trial. *JCO Glob*
14 *Oncol*. 2021;811–819.
15
16 [131] Llombart-Cussac A, Pérez-García J, Guerrero Á, et al. Abstract CT219: Neoadjuvant letrozole and
17 palbociclib in stage II-III B HR[+]/HER2[-] breast cancer with Oncotype DX Recurrence Score® (RS) 18-25 or
18 26-100. Analysis of RS changes at surgery (DxCARTES trial). *Cancer Res*. 2019;79:CT219–CT219.
19
20 [132] Ueno T, Saji S, Masuda N, et al. Changes in Recurrence Score by neoadjuvant endocrine therapy of breast
21 cancer and their prognostic implication. *ESMO Open*. 2019;4.
22
23 [133] Nitz UA, Gluz O, Kümmel S, et al. Endocrine Therapy Response and 21-Gene Expression Assay for Therapy
24 Guidance in HR+/HER2– Early Breast Cancer. *J Clin Oncol* [Internet]. 2022 [cited 2022 Dec 14]; Available
25 from: <https://ascopubs.org/doi/pdf/10.1200/JCO.21.02759?role=tab>.
26
27 [134] Fan C, Oh DS, Wessels L, et al. Concordance among Gene-Expression–Based Predictors for Breast Cancer.
28 *N Engl J Med*. 2006;355:560–569.
29
30 [135] Jung JG, Kim HK, Kim Y, et al. Personalized neoadjuvant strategy in luminal A breast cancer to increase
31 breast conserving surgery (BCS) rate [PLATO study]. *J Clin Oncol*. 2020;38:TPS603–TPS603.
32
33 [136] Göker E, Hendriks MP, van Tilburg M, et al. Treatment response and 5-year distant metastasis-free
34 survival outcome in breast cancer patients after the use of MammaPrint and Blueprint to guide
35 preoperative systemic treatment decisions. *Eur J Cancer*. 2022;167:92–102.
36
37 [137] Jacobs CF, Bartels SAL, Loo CE, et al. 201P 70-gene signature to select breast cancer patients for
38 neoadjuvant endocrine treatment. *Ann Oncol*. 2020;31:S322–S323.
39
40 [138] Filipits M, Rudas M, Jakesz R, et al. A new molecular predictor of distant recurrence in ER-positive, HER2-
41 negative breast cancer adds independent information to conventional clinical risk factors. *Clin Cancer Res*.
42 2011;17:6012–6020.
43
44 [139] Chow LWC, Morita S, Chow CYC, et al. Neoadjuvant palbociclib on ER+ breast cancer (N007): Clinical
45 response and EndoPredict’s value. *Endocr Relat Cancer*. 2018;25:123–130.
46
47 [140] Dubsy PC, Singer CF, Egle D, et al. The EndoPredict score predicts response to neoadjuvant
48 chemotherapy and neoendocrine therapy in hormone receptor-positive, human epidermal growth factor
49 receptor 2-negative breast cancer patients from the ABCSG-34 trial. *Eur J Cancer*. 2020;134:99–106.
50
51 [141] Symmans WF, Hatzis C, Sotiriou C, et al. Genomic index of sensitivity to endocrine therapy for breast
52 cancer. *J Clin Oncol*. 2010;28:4111–4119.
53
54 [142] Sinn B V., Fu C, Lau R, et al. SETER/PR: a robust 18-gene predictor for sensitivity to endocrine therapy for
55 metastatic breast cancer. *Npj Breast Cancer*. 2019;5:1–8.
56
57
58
59

- 1
2
3 [143] Du L, Yau C, Brown-Swigart L, et al. Predicted sensitivity to endocrine therapy for stage II-III hormone
4 receptor-positive and HER2-negative (HR+/HER2-) breast cancer before chemo-endocrine therapy. *Ann*
5 *Oncol.* 2021;32:642–651.
6
7 [144] Suman VJ, Du L, Hoskin T, et al. Evaluation of Sensitivity to Endocrine Therapy Index (SET2,3) for Response
8 to Neoadjuvant Endocrine Therapy and Longer-Term Breast Cancer Patient Outcomes (Alliance Z1031).
9 *Clin Cancer Res.* 2022;28:3287–3295.
10
11 [145] Prat A, Lluch A, Turnbull AK, et al. A PAM50-based chemoendocrine score for hormone receptor-positive
12 breast cancer with an intermediate risk of relapse. *Clin Cancer Res.* 2017;23:3035–3044.
13
14 [146] Turnbull AK, Arthur LM, Renshaw L, et al. Accurate Prediction and Validation of Response to Endocrine
15 Therapy in Breast Cancer. *J Clin Oncol.* 2015;33:2270–2278.
16
17 [147] Martínez-Pérez C, Leung J, Kay C, et al. The Signal Transducer IL6ST (gp130) as a Predictive and Prognostic
18 Biomarker in Breast Cancer. *J Pers Med.* 2021;11:618.
19
20 [148] Escrivá-De-Romaní S, Arumí M, Zamora E, et al. Neoadjuvant Model as a Platform for Research in Breast
21 Cancer and Novel Targets under Development in this Field. *Breast Care.* 2018;13:251–262.
22
23 ** A recent review on the promise of NET as a platform for BC research.
24
25
26 [149] Guerrero-Zotano AL, Arteaga CL. Neoadjuvant trials in ER+ breast cancer: A tool for acceleration of drug
27 development and discovery. *Cancer Discov.* 2017;7:561–574.
28
29 ** A thorough review of recent and ongoing NET trials.
30
31 [150] Guan Y, Shen G, Fang Q, et al. Cyclin-dependent kinase 4 and 6 inhibitors in combination with
32 neoadjuvant endocrine therapy in estrogen receptor-positive early breast cancer: a systematic review and
33 meta-analysis. *Clin Exp Med.* 2022;1–10.
34
35
36 *Meta-analysis of all evidence to date on the use of CDK4/6 inhibitors in combination with NET.
37
38 [151] Ferraro E, Fournier MN. Molecular downstaging: a new paradigm for neoadjuvant endocrine therapy. *Ann*
39 *Transl Med.* 2020;8:1694–1694.
40
41 [152] Prat A, Saura C, Pascual T, et al. Ribociclib plus letrozole versus chemotherapy for postmenopausal
42 women with hormone receptor-positive, HER2-negative, luminal B breast cancer (CORALLEEN): an open-
43 label, multicentre, randomised, phase 2 trial. *Lancet Oncol.* 2020;21:33–43.
44
45 [153] Curigliano G, Gómez Pardo P, Meric-Bernstam F, et al. Ribociclib plus letrozole in early breast cancer: A
46 presurgical, window-of-opportunity study. *Breast.* 2016;28:191–198.
47
48 [154] Khan QJ, O’Dea A, Bardia A, et al. Letrozole + ribociclib versus letrozole + placebo as neoadjuvant therapy
49 for ER+ breast cancer (FELINE trial). *J Clin Oncol.* 2020;38:505–505.
50
51 [155] Ma CX, Gao F, Luo J, et al. NeoPalAna: Neoadjuvant palbociclib, a cyclin-dependent kinase 4/6
52 inhibitor, and anastrozole for clinical stage 2 or 3 estrogen receptor-positive breast cancer. *Clin Cancer*
53 *Res.* 2017;23:4055–4065.
54
55
56
57
58
59
60

- 1
2
3 [156] Johnston S, Puhalla S, Wheatley D, et al. Randomized Phase II Study Evaluating Palbociclib in Addition to
4 Letrozole as Neoadjuvant Therapy in Estrogen Receptor–Positive Early Breast Cancer: PALLET Trial. *J Clin*
5 *Oncol.* 2019;37:178–189.
6
7 [157] Al-Saleh KA, El Zawahry HM, Bounedjar A, et al. Final result for SAFIA trial for neoadjuvant palbociclib in
8 patients with operable luminal breast cancer responding to fulvestrant. *J Clin Oncol.* 2022;40:596–596.
9
10 [158] Cottu P, D’Hondt V, Dureau S, et al. Letrozole and palbociclib versus chemotherapy as neoadjuvant
11 therapy of high-risk luminal breast cancer. *Ann Oncol.* 2018;29:2334–2340.
12
13 [159] Delaloge S, Dureau S, D’Hondt V, et al. Survival outcomes after neoadjuvant letrozole and palbociclib
14 versus third generation chemotherapy for patients with high-risk oestrogen receptor-positive HER2-
15 negative breast cancer. *Eur J Cancer.* 2022;166:300–308.
16
17 [160] Hurvitz SA, Martin M, Press MF, et al. Potent cell-cycle inhibition and upregulation of immune response
18 with abemaciclib and anastrozole in neoMONARCH, phase II neoadjuvant study in HR+/HER2- Breast
19 cancer. *Clin Cancer Res.* 2020;26:566–580.
20
21 [161] Baselga J, Semiglazov V, van Dam P, et al. Phase II Randomized Study of Neoadjuvant Everolimus Plus
22 Letrozole Compared With Placebo Plus Letrozole in Patients With Estrogen Receptor–Positive Breast
23 Cancer. *J Clin Oncol.* 2009;27:2630–2637.
24
25 [162] Guarneri V, Generali DG, Frassoldati A, et al. Double-blind, placebo-controlled, multicenter, randomized,
26 phase IIB neoadjuvant study of letrozole-lapatinib in postmenopausal hormone receptor-positive, human
27 epidermal growth factor receptor 2-negative, operable breast cancer. *J Clin Oncol.* 2014;32:1050–1057.
28
29 [163] Saura C, Hlauschek D, Oliveira M, et al. Neoadjuvant letrozole plus taselisib versus letrozole plus placebo
30 in postmenopausal women with oestrogen receptor-positive, HER2-negative, early-stage breast cancer
31 (LORELEI): a multicentre, randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet Oncol.*
32 2019;20:1226–1238.
33
34 [164] Mayer IA, Prat A, Egle D, et al. A phase II randomized study of neoadjuvant letrozole plus alpelisib for
35 hormone receptor-positive, human epidermal growth factor receptor 2-negative breast cancer (NeO-
36 ORB). *Clin Cancer Res.* 2019;25:2975–2987.
37
38 [165] Reinert T, Ramalho S, de Vasconcelos VCA, et al. ESR1 Mutations Are Not a Common Mechanism of
39 Endocrine Resistance in Patients With Estrogen Receptor–Positive Breast Cancer Treated With
40 Neoadjuvant Aromatase Inhibitor Therapy. *Front Oncol.* 2020;10:342.
41
42 [166] Selli C, Sims AH. Neoadjuvant Therapy for Breast Cancer as a Model for Translational Research. *Breast*
43 *Cancer Basic Clin Res.* 2019;13.
44
45 [167] Martin M, Guerrero-Zotano A, Montero Á, et al. GEICAM Guidelines for the Management of Patients with
46 Breast Cancer During the COVID -19 Pandemic in Spain. *The Oncologist.* 2020;25:e1339–e1345.
47
48 [168] Cavalcante FP, Novita GG, Millen EC, et al. Management of early breast cancer during the COVID-19
49 pandemic in Brazil. *Breast Cancer Res Treat.* 2020;184:637–647.
50
51 [169] Gasparri ML, Gentilini OD, Lueftner D, et al. Changes in breast cancer management during the Corona
52 Virus Disease 19 pandemic: An international survey of the European Breast Cancer Research Association
53 of Surgical Trialists (EUBREAST). *Breast.* 2020;52:110–115.
54
55
56
57
58
59

[170] Curigliano G, Banerjee S, Cervantes A, et al. Managing cancer patients during the COVID-19 pandemic: an ESMO multidisciplinary expert consensus. *Ann Oncol*. 2020;31:1320–1335.

* An example of the many expert guidelines outlined during the pandemic including recommendations for NET use.

[171] Dietz JR, Moran MS, Isakoff SJ, et al. Recommendations for prioritization, treatment, and triage of breast cancer patients during the COVID-19 pandemic. the COVID-19 pandemic breast cancer consortium. *Breast Cancer Res. Treat. Springer*; 2020. p. 487–497.

[172] Bartlett DL, Howe JR, Chang G, et al. Management of Cancer Surgery Cases During the COVID-19 Pandemic: Considerations. *Ann Surg Oncol*. 2020;27:1717–1720.

[173] Freedman RA, Sedrak MS, Bellon JR, et al. Weathering the Storm: Managing Older Adults with Breast Cancer Amid COVID-19 and beyond. *J Natl Cancer Inst*. 2021;113:355–359.

[174] Sheng JY, Santa-Maria CA, Mangini N, et al. Management of Breast Cancer During the COVID-19 Pandemic: A Stage- and Subtype-Specific Approach. *JCO Oncol Pract*. 2020;16:665–674.

[175] American College of Surgeons (ACS). COVID-19 Guidelines for Triage of Breast Cancer Patients [Internet]. [cited 2022 Aug 18]. Available from: <https://www.facs.org/for-medical-professionals/covid-19/clinical-guidance/elective-case/breast-cancer/>.

[176] Society of Surgical Oncology (SSO). Resource for Management Options of Breast Cancer During COVID-19. 2020. p. 4–5.

[177] American Society of Breast Surgeons (ASBrS). ASBrS Resource Guide to Endocrine Therapy in the COVID-19 Pandemic. 2020.

[178] European Society of Medical Oncology (ESMO). Breast cancer in the COVID-19 era | ESMO [Internet]. [cited 2022 Aug 18]. Available from: <https://www.esmo.org/guidelines/cancer-patient-management-during-the-covid-19-pandemic/breast-cancer-in-the-covid-19-era>.

[179] Martí C, Sánchez-Méndez JI. Neoadjuvant endocrine therapy for luminal breast cancer treatment: A first-choice alternative in times of crisis such as the COVID-19 pandemic. *ecancermedalscience*. 2020;14.

[180] Dowsett M, Ellis MJ, Dixon JM, et al. Evidence-based guidelines for managing patients with primary ER+ HER2– breast cancer deferred from surgery due to the COVID-19 pandemic. *Npj Breast Cancer*. 2020;6:1–10.

** Expert guidelines supporting the use of NET for the management of BC during the COVID-19 pandemic.

[181] Obeng-Gyasi S, Coles CE, Jones J, et al. When the World Throws You a Curve Ball: Lessons Learned in Breast Cancer Management. *Am Soc Clin Oncol Educ Book*. 2021;e79–e89.

[182] Wilke LG, Nguyen TT, Yang Q, et al. Analysis of the Impact of the COVID-19 Pandemic on the Multidisciplinary Management of Breast Cancer: Review from the American Society of Breast Surgeons COVID-19 and Mastery Registries. *Ann Surg Oncol*. 2021;28:5535–5543.

- 1
2
3 [183] Tonneson JE, Hoskin TL, Day CN, et al. Impact of the COVID-19 Pandemic on Breast Cancer Stage at
4 Diagnosis, Presentation, and Patient Management. *Ann Surg Oncol.* 2021;1–9.
5
- 6 [184] Iles KA, Thornton M, Park J, et al. Bridging Endocrine Therapy for HR+/HER2- Resectable Breast Cancer: Is
7 it Safe? *Am Surg.* 2021;000313482110472.
8
- 9 [185] Park KU, Gregory M, Bazan J, et al. Neoadjuvant endocrine therapy use in early stage breast cancer during
10 the covid-19 pandemic. *Breast Cancer Res Treat.* 2021;188:249–258.
11
- 12 [186] Toss A, Isca C, Venturelli M, et al. Two-month stop in mammographic screening significantly impacts on
13 breast cancer stage at diagnosis and upfront treatment in the COVID era. *ESMO Open.* 2021;6:100055.
14
- 15 [187] Di Lena É, Hopkins B, Wong SM, et al. Delays in operative management of early-stage, estrogen receptor–
16 positive breast cancer during the COVID-19 pandemic: A multi-institutional matched historical cohort
17 study. *Surgery.* 2021;
18
- 19 [188] Williams AD, Chang C, Sigurdson ER, et al. Neoadjuvant Endocrine Therapy and Delays in Surgery for
20 Ductal Carcinoma in Situ: Implications for the Coronavirus Pandemic. *Ann Surg Oncol.* 2021;
21
- 22 [189] Chiba A, Hoskin TLTL, Heins CNCN, et al. Trends in Neoadjuvant Endocrine Therapy Use and Impact on
23 Rates of Breast Conservation in Hormone Receptor-Positive Breast Cancer: A National Cancer Data Base
24 Study. *Ann Surg Oncol.* 2017;24:418–424.
25
- 26 [190] Morris ZS, Wooding S, Grant J. The answer is 17 years, what is the question: Understanding time lags in
27 translational research. *J R Soc Med.* 2011;104:510–520.
28
- 29 [191] Zhang A, Wang X, Fan C, et al. The Role of Ki67 in Evaluating Neoadjuvant Endocrine Therapy of Hormone
30 Receptor-Positive Breast Cancer. *Front Endocrinol.* 2021;12:1426.
31
- 32 [192] Johnston SRD, Harbeck N, Hegg R, et al. Abemaciclib combined with endocrine therapy for the adjuvant
33 treatment of HR1, HER22, node-positive, high-risk, early breast cancer (monarchE). *J Clin Oncol.*
34 2020;38:3987–3998.
35
- 36 [193] Mayer EL, Dueck AC, Martin M, et al. Palbociclib with adjuvant endocrine therapy in early breast cancer
37 (PALLAS): interim analysis of a multicentre, open-label, randomised, phase 3 study. *Lancet Oncol.*
38 2021;22:212–222.
39
- 40 [194] Palleschi M, Maltoni R, Ravaioli S, et al. Ki67 and PR in Patients Treated with CDK4/6 Inhibitors: A Real-
41 World Experience. *Diagnostics.* 2020;10:573.
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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.

1	Analysis of NCDB	2021	Women \geq 50 years old	Comparison of database	Therapy response,	Higher response rates after NCT;
2	data		with HR+ BC	information of patients who	including	but both NCT and NET achieved
3	[39]		(n=19,829)	received NCT (n=14,025) or	downstaging and	downstaging and pCR.
4				NET (n=5,804)	pCR	

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

Study	Year	Cohort	Treatment	Endpoints	Key Outcomes
P024 [48,49]	200 1	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]	200 5	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]	200 6	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.
Ais vs TAM Semiglazov et al [53]	200 5	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]	200 9	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]	201 6	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]	201 5	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.

1	Murray	200	PMW with operable	2 weeks ANA (n=103) or LET	Molecular changes in ER,	No significant differences in
2	[55]	9	ER+ BC (n=206)	(n=103)	PR and Ki67	downregulation.
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4	ACOSOG Z1031	201	PMW with ER-rich BC	4 months EXE (n=124) or LET	ORR, BCS rate, Ki67,	No significant difference in outcomes.
5	[17]	1	(n=377)	(n=128) or ANA (n=125)	PEPI and PAM50	
6						
7	HORGEN	201	PMW with HR+ BC	6 months ANA (n=56) vs FUL	ORR, BCS rate,	No significant difference in response,
8	[56]	3	initially ineligible for	(n=52)	pathological response,	trend towards better BCS rate in ANA
9			BCS		Ki67	arm.
10			(n=108)			
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14	CARMINA02	201	PMW with HR+ BC	6 months ANA (n=59) or FUL	CR and BCS rates,	No significant difference in outcomes.
15	[57]	6	initially ineligible for	(n=57)	tumour response	
16			BCS		assessment RFS,	
17			(n=116)		markers of response	
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20	Meta-analysis of	202	PMW with HR+ BC	ANA (n=111) or FUL (n=106)	See above	No significant differences, including in
21	HORGEN and	0	initially ineligible for			RFS or OS at 5 years.
22	CARMINA02 [58]		BCS			
23			(Pooled n=217)			
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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.

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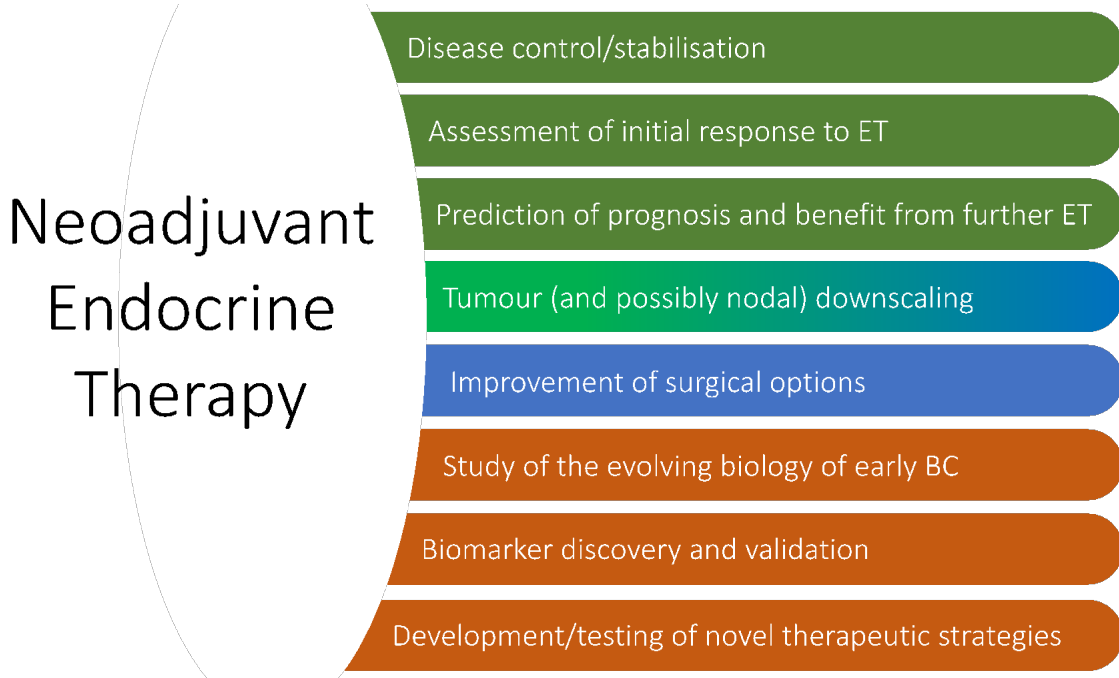


Figure 1. Schematic summary of the potential benefits of using NET. The use of preoperative endocrine therapy can yield numerous advantages in the management PMW with ER+ BC, including clinical (green) and surgical (blue) benefits, as well as numerous research opportunities (orange).