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Receptor Status after Neoadjuvant Therapy of Breast Cancer: Significance and Implications

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Abstract
Neoadjuvant chemotherapy (NACT) is now established in routine management of early breast cancer. Alterations in oestrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) following NACT are reported, with wide variation in results across series. In larger series, changes in ER status are identified in 5–23%, whilst changes in PR status are more frequent (14.5–67%). HER2 status changes less frequently with loss being more common than gain, and higher rates of change with immunohistochemistry are observed compared to in situ hybridization and following HER2-targeted therapy compared with chemotherapy alone. Triple negative is the most stable molecular subtype with combined ER, and HER2-positive cancers show the highest rate of change. Neoadjuvant endocrine therapy is used less commonly than NACT, and whilst loss of ER is rare, changes in PR status can occur in up to 40% of cases. There is relatively little published data on the impact of change in receptor status on survival outcomes. In patients whose tumours become ER or HER2 positive post-NACT, endocrine or anti-HER2 therapy can be initiated, although evidence from clinical trials is lacking. Most guidelines do not currently recommend routine retesting; however it should be considered in some circumstances.

Introduction

The neoadjuvant approach, where chemotherapy or endocrine therapy is given before surgery to shrink the tumour and assess biological response, is being increasingly adopted in the management of primary breast cancer. The recent NEST study surveyed Breast Units across the UK and in responding centres around 10% of patients were being offered neoadjuvant chemotherapy (NACT); the range across individual units was 5–60% indicating wide variation in practice [1]. Neoadjuvant therapy can induce changes in expression of oestrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2); however, there is still limited data on how these changes impact survival outcomes and whether they should alter management. This

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Table 1. Summary of largest studies, reviews, and meta-analyses of ER, PR, and HER2 changes following NACT

Author	Type	Subjects, *n*	ER change		PR change		HER2 change		Comment
Candas et al. [12]	Single inst	123	9%	10 P to N, 1 N to P	30%	29 P to N, 6 N to P	14%	15 P to N, 2 N to P	Twenty-one percent change in molecular subtype. The greatest change in the HR+/HER2+ group. Adjuvant therapy altered in 9 patients
Al-Saleh 2021 [13]	Single inst	91	18.50%	16 P to N, 1 N to P	16.50%	12 P to N, 3 N to P	16.50%	10 P to N, 5 N to P	Worse DFS with altered receptor status on univariate but not multivariate analysis
Rey-Vargas 2020 [14]	Single inst	72		2 P to N		5 P to N, 2 N to P	2% N to P (chemo alone), 18% P to N (chemo + trast)		
Ding et al. [11]	Single inst	482	10%		17%	57 P to N, 25 N to P	NA	NA	Luminal HER2 group most likely to change. HR P to N worst prognosis
Peng et al. [15]	Single inst	112	22%	18 P to N, 7 N to P	29%	22 P to N, 10 N to P	20.5%	17 P to N, 6 N to P	Increase in luminal A and decrease luminal B
Ignatov et al. [16]	Single inst	132	NA		NA		33 P to N, 14 N to P. A Anti-HER2 RX – 42% P to N (dual T + P 63%, T alone 47%)		HER2 loss associated with HER2-targeted therapy. Worse RFS but not OS with loss of HER2 expression
Wu et al. [10]	Single inst	525	15%	7.5% P to N, 8% N to P	27%	13% P to N, 14% N to P			HR+ switch better OS and DFS. P to N group better survival than the stable ER– group. No relationship with endocrine therapy
Yang 2018 [17]	Single inst	231	5.60%	9 P to N, 4 N to P	19.50%	37 P to N, 8 N to P		23% P to N, 3% N to P	Change more common in younger patients. DFS but not OS worse in the receptor conversion group
Gahlaut 2016 [18]	Single inst	246	12%	7 P to N, 9 N to P	14.50%	13 P to N, 5 N to P	7%	5 P to N, 3 N to P	Adjuvant control group <5% change in status, all in borderline cases
Niikura et al. [9]	Cancer registry	21,755		4.6% N to P, 9.3% N to P	18.7% P to N, 9.3% N to P			21.4% P to N, 3.4% N to P. FISH 8.4% P to N (trast 24.7%, no trast 18%)	
Lim et al. [19]	Single inst	322	18%	37% N to P, 11% P to N			6%	21% P to N, no N to P	Twenty-three percent change in the molecular subtype. Worse survival if convert to TN, better survival if convert to ER+/HER2–
Jin 2015 [20]	Single inst	138	22.5% (28% and 16%)	13 P to N, 18 N to P	22.5%; 23% and 22%	13 P to N, 18 N to P	15%; 17% and 13%	12 P to N, 9 N to P	Direction of change differed according to chemotherapy regimen. Change in receptor status associated with response
Montagna et al. [8]	Single inst	904	5%	P to N	67% change from >20% to <20%		14% P to N, 4% N to P		Drop in PR associated with better prognosis in both ET and non-ET treated patients
Parinyanitikul et al. [21]	Single inst	398	11% P to N, 21% N to P		35% P to N, 12% N to P		40% P to N (46% trast), 3% N to P		HR+ – 5% to HER2+ and 15% TN; HER2+ 28% to HR+ and 12.5% to TN; TN 2% to HER2+ and 26% HR+. Any change in receptor status associated with a better outcome
Chen et al. [22]	Single inst	224	16% P to N		22% P to N		15% P to N, 4% N to P		HR change more common in HER2+ tumours (33% vs. 11%). Change in HER2 associated with change in HR. Worse survival with change HR status – no benefit from ET but small numbers
Hirata et al. [23]	Single inst	368	15%	21 P to N, 34 N to P	29%	70 P to N, 37 N to P	9.50%	22 P to N, 13 N to P	Worse survival outcome in patients with status change. Patients who received ET had longer survival even if change to HR–

Table 1 (continued)

Author	Type	Subjects, *n*	ER change		PR change		HER2 change	Comment
Kasami 2008 [24]	Single inst	172	11%	10% N to P	16%	29% P to N, 7.5% N to P	0%	Association between change in ER status and response
Tacca et al. [25]	Single inst	420	23%	13% P to N, 42% N to P				Change to ER+ improved survival. Loss of ER better survival than stable ER–
Colleoni 2004 [26]	Single inst	294	9%	19 P to N, 19 N to P	26%	36 P to N, 25 N to P	NA	No relationship with response
Taucher 2003 [27]	Single inst	85					2 P to N, 2 N to P (no change on FISH)	
Zhang et al. [6]	Meta-analysis		18%	7.7% (1–25%) P to N, 10.4% (1–34%) N to P		17.2% (0–70%) P to N, 9.4% (0–37%) N to P	5.40%	2.7% P to N, 2.7% N to P
van den Ven et al. [5]	lit review		15 trials – 8 with change (2.5–17%)	4–14% P to N, 3–11% N to P		7–19% P to N, 8–15% N to P	IHC 1–30%; 1–16% P to N, 4–20% N to P. FISH 10%; 6% P to N, 4% N to P. Trast 32–43% P to N	

Single inst, single institution; Lit review, literature review; P to N, positive to negative; N to P, negative to positive; Trast, trastuzumab; DFS, disease-free survival.

review explores the current evidence on changes in receptor status post-NACT and endocrine therapy (neoadjuvant endocrine therapy [NAET]).

Neoadjuvant Chemotherapy

NACT is now well established in routine management of primary breast cancer, particularly high-risk biological subtypes such as triple negative (TN) and HER2+ disease. NACT can reduce tumour volume permitting breast conservation and downstage the axilla to avoid axillary clearance in complete nodal response [2–4].

Alterations in hormone receptors (HRs) including ER and PR and HER2 status following NACT have been examined in multiple studies, with large variation in the proportion of cases that show a change in status between pre-treatment core biopsy and residual post-treatment tumour reflecting differences in patient population, type of therapy received, and methodology used [5–7]. Recent studies on large populations using modern chemotherapy regimens and targeted anti-HER2 therapy indicate changes in receptor status following NACT are not uncommon [8–11]. Key studies including over 80 patients are summarized in Table 1.

Potential reasons for the change in HR and HER2 receptor status post-NACT include true biological effects such as interactions between signalling pathways and selective response due to intratumoural heterogeneity and technical factors such as fixation and sampling error that could give false-negative or false-positive results. Changes resulting from cross talk between the ER and HER2 pathways are described in the following sections. Intratumoural heterogeneity is well described in breast cancer, and whilst ER expression tends to be uniform, variability in PR is common and may contribute to the more frequent changes post-NACT alongside downstream signalling effects. Heterogeneity in HER2 with variation in the HER2 copy number, particularly in 2+ cases, is associated with poorer response to NACT and worse survival outcomes [28]. A UK study found ER status changed in 12% (44% positive to negative), PR in 14.5% (72% positive to negative), and HER2 in 7% of cases (71% positive to negative), compared with an adjuvant control group in which less than 5% of cases changed receptor status [29] In the adjuvant group, the cases with a change in status were all borderline positive with low Allred scores or HER2 2+ compared with the NACT group where tumours with strong positive expression of all 3 markers became negative. These findings support changes post-NACT as re-

flecting true biological effects rather than technical factors such as fixation. These results are consistent with the literature comparing ER, PR, and HER2 status between core biopsy and excision specimens in the adjuvant setting that show greater than 95% concordance for ER and HER2, with slightly lower concordance for PR (85–90%) related to greater intratumoural heterogeneity in PR expression [22, 30] When comparing results of ER, PR, and HER2 staining on pre- and post-treatment samples, the basic principles of quality control apply and caution should be taken if there is inadequate tumour representation, or the specimen has been compromised, for example, by delayed or suboptimal fixation. Internal and external controls should be assessed as relevant, for example, preservation of ER staining in normal breast tissue, to ensure technical validity of results (Fig. 1a, b).

Changes in ER and PR Post-NACT

The steroid HRs ER and PR are routinely assessed in breast cancer and provide prognostic information and predict responsiveness to endocrine therapy. The literature shows huge variation in number of cases showing a change in HR status between pre- and post-treatment samples, with additional variation in the proportion changing from positive to negative and negative to positive (Table 1). In the majority of series, PR expression changes more frequent than ER and more commonly goes from positive to negative, possibly reflecting downstream changes in ER signalling in the absence of altered ER protein expression [31].

In an Italian series of 904 patients, ER was lost in 5% of HR+ cancers compared with 67% showing loss of PR (cut-off 20%); change in PR status was associated with improved survival regardless of whether they received endocrine therapy [8].

A literature review by van den Ven et al. [5] reported results from 15 clinical studies, 8 of which identified a change in HR status, ranging from 2.5 to 17% for ER and 6–52% for PR. Changes from positive to negative and negative to positive were relatively similar for ER (4–14% and 3–11%, respectively), whereas change from positive to negative was slightly higher for PR (7–19% vs. 8–15% negative to positive). Jabbour et al. [7] performed a pooled analysis and found an average prevalence of discordant results of 13% for ER (range 0–47%) and 32% for PR (range 2–100%). This review included studies looking at local recurrence post-NACT with two series that used the dextran charcoal method rather than immunohistochemistry (IHC). Local recurrences showed higher rates of ER and PR conversion than the immediate post-NACT specimens (0–11% for ER, 2–33% for PR). Another meta-analysis by Zhang et al. [6] pooled ER results for 865 patients and found a change in 18%; 8% positive to negative (range 1–25%) and 10% negative to positive (range 1–34%). PR results for 816 patients showed a 26.6% change; 17% went from positive to negative (range 0–70%), whilst only 9% went from negative to positive (0–37%). In a large Japanese series of over 10,000 patients based on cancer registry data, 4.6% changed from ER+ to ER– and 9.3% from ER– to ER+; PR changed from positive to negative in 18.7% and negative to positive in 9.3% [9].

In a French series of 420 patients, ER status changed in 23%; 42% negative to positive and 13% positive to negative [25]. The majority of cases with change had high Allred scores, so this was not due to variation around the cut point for positivity. Conversion to ER+ status was associated with improved survival; however, those that lost ER did not show poorer outcomes compared to patients with stable ER+ disease and had better overall survival (OS) than patients with stable ER– disease. A recent study from China found similar results; 15% change in ER status and 27% change in PR status, with similar numbers going from positive to negative and negative to positive for both markers (7.5% and 8%, respectively, for ER; 13% and 14%, respectively for PR) [10]. A positive switch was associated with better OS and disease-free survival, and the positive to negative group had better outcomes than those with stable ER– disease. Endocrine therapy did not alter survival outcome.

Hirata et al. [23] divided a series of 459 patients into 4 groups based on pre- and post-treatment ER status and whether they received adjuvant endocrine therapy. ER status changed in 15%, with equal proportions switching from positive to negative and negative to positive. Survival outcomes were similar in patients that received endocrine therapy even with a change in ER status, whilst patients who lost ER and were not given endocrine therapy had a worse outcome. Chen et al. [22] also found loss of ER in 15% of cases, but 106 patients who became ER– post-NACT had worse survival outcomes and showed no survival benefit with endocrine therapy. Of note HER2+ tumours were more likely to lose ER than HER2– tumours (33% vs. 11%, respectively), and loss of ER was associated with other aggressive features such as a high Ki67 index.

A recent series of 482 patients by Ding et al. [11] found changes in ER status in 10% of cases (36 positive to negative and 14 negative to positive) and PR status in 17% (57 positive to negative and 25 negative to positive). In this

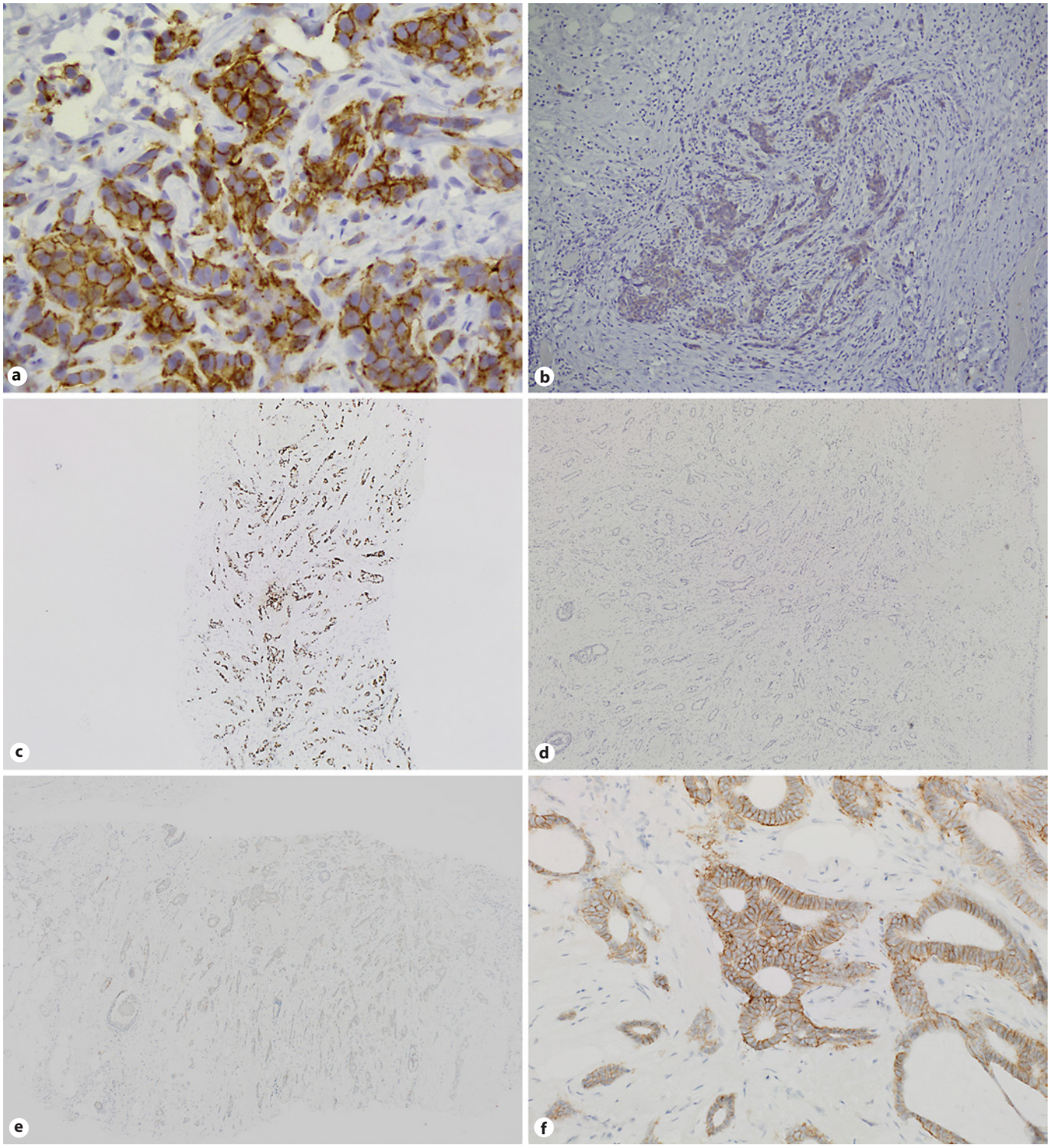

Fig. 1. Examples illustrating the immunohistochemical changes in HRs and HER2 expression following NACT and NAET. **a** Pre-treatment core biopsy of invasive breast carcinoma showing HER2 2+ expression. The tumour was HER2-amplified by FISH. **b** Same tumour post-NACT and anti-HER2 therapy. The residual invasive carcinoma switched to a HER2-negative status, score 0. **c** Core biopsy of treatment-naive PR-strongly positive invasive no special-type carcinoma. **d** The same tumour is PR negative following NAET. **e** Core biopsy of invasive HER2-negative breast carcinoma, score 1+. **f** Post-NAET, the tumour scored 2+ by HER2 IHC. FISH testing was negative.

study, changes were also more common in the luminal HER2 group. Loss of HR expression was associated with worse prognosis compared with stable disease or negative to positive change.

Changes in HER2 Post-NACT

Changes in HER2 status are less frequent than changes in HR status, with the two meta-analyses finding a change in 5.4% and 9% of cases, respectively (range 0–21%) [6, 7]. Importantly, changes are more common with IHC than with fluorescence in situ hybridization (FISH). A literature review found 12 studies looking at HER2 IHC, 6 with a change in HER2 status (range 1–30%; 1–16% positive to negative, 4–20% negative to positive), compared with 7 studies examining FISH of which only one identified a change (10% change; 6% positive to negative, 3.5% negative to positive) [5]. Similarly, in the Japanese series, changes in HER2 status were found in 20% of cases using IHC, compared with only 8% on FISH [9]. Changes in HER2 status were more common in ER+ compared with ER– patients (28% vs. 13%, respectively), and conversion from HER2+ to HER2– status (21%) was seen more commonly than HER2– to HER2+ (3%). Interestingly, changes in HER2 status were seen more often following trastuzumab therapy (25% post-trastuzumab vs. 18% no trastuzumab). Survival data were not available.

In HER2+ patients, Mittendorf et al. [29] examined 25 paired samples pre- and post-treatment with NACT plus trastuzumab with FISH. Eight cases (32%) became HER2– with loss of gene amplification, and this was associated with worse recurrence-free survival (RFS) (50% at 3 years compared with 87.5% in patients who retained HER2 amplification). Of note, 20% of ER– patients became ER+. Hurley et al. [32] also undertook HER2 FISH on a series of 34 HER2+ patients who had NACT; 10 cases became non-amplified, 6 of which showed polysomy for HER2 copy number, suggesting this may represent selective loss of the amplified clone. There was no difference in survival between patients whose status changed versus those who stayed stable.

Wang et al. [33] examined a historical series of HER2+ tumours that received chemotherapy alone versus chemotherapy plus trastuzumab. In the trastuzumab group, 51% achieved pCR, and of the remainder, 20% lost HER2, and 6% lost ER expression. HER2 loss was associated with gain of ER. In the chemotherapy only group, 9% lost HER2, and 30% lost ER. Loss of HER2 was independently associated with worse survival outcomes on multivariate analysis and correlated with other poor prognostic indicators such as persistence of high Ki67. Ignatov et al. [16] also compared changes in HER2 status between patients with NACT with and without anti-HER2 therapy and between trastuzumab alone versus dual agent therapy with pertuzumab. HER2 discordance was seen in 21% of subjects, 6% negative to positive and 14.5% positive to negative. In the discordant group, 94% received anti-HER2 therapy, compared with 18% in the group with no change. In a second cohort of HER2+ patients, 42% showed a decrease in HER2 expression following NACT; 47% post-trastuzumab and 63% post-trastuzumab and pertuzumab, compared with only 10% without anti-HER2 therapy. This study primarily looked at changes in protein expression with IHC, and there was a decrease in cases showing reduced HER2 expression with increasing time interval between cessation of anti-HER2 therapy and surgical excision. Trastuzumab and pertuzumab are known to cause internalization of membrane bound HER2 receptor, which would explain the temporary reduction in HER2 expression on IHC following treatment with these agents that then reverses over time as HER2 protein is synthesized and relocalizes to the membrane when the drug is withdrawn.

Protein internalization could also explain discrepancies between IHC and FISH in earlier series and suggests loss of gene amplification may be a more reliable marker of change in tumour biology and development of resistance post-NACT with anti-HER2 agents. A recent paper looks specifically at the effect of NACT with or without anti-HER2 therapy on HER2 borderline cancers (2+ on IHC) and the 5 different FISH groups based on the American Society of Clinical Oncology-College of American Pathologists (ASCO-CAP) guidelines [34]. Twenty-two percent of 3+ cancers showed a change in HER2 IHC post-NACT with 15% becoming 2+ and 6% becoming IHC negative (0/1+); of the 2+ cases, 6 were FISH negative, and 4 were FISH positive using ASCO-CAP definitions. In contrast, 45% of 2+ cases showed a change in HER2 FISH category; 50% changed from FISH positive to negative and 14% went from negative to positive. Looking at the HER2 copy number alone in cases that went from HER2+ to HER2– and from HER2– to HER2+, 65% and 77%, respectively, had an unchanged HER2 copy number, reflecting the effect of change in CEP17 counts and the need for caution in interpreting results of retesting.

Changes in the Molecular Subtype

Several series have reported an interaction between the ER and HER2 pathways, with changes in HER2 status seen more commonly in ER+ tumours, and loss of HER2

corresponding to an increase in ER expression [11, 12, 22]. Resistance to HER2-targeted therapies accompanied by an increase in ER expression secondary to reactivation of ER signalling pathways has been demonstrated in vitro studies [35].

Lim et al. [19] divided patients into four molecular subgroups based on ER and HER2 IHC status. There was a change in molecular subgroup in 23% of patients, with an overall change in HR in 18% and HER2 in 6%. Ten percent of HR+/HER2− patients became TN with worse RFS and OS, compared with 35% of TN patients that became HR+/HER2− with an improvement in RFS and OS.

Candas et al. [12], performed a similar analysis on a series of 123 cases, 21% of which showed a change in status. Of 18 TN cancers without pCR, only one became HR+/HER2−. Of 82 HR+/HER2− cancers, 6 changed subtype with 4 becoming TN. Only 4 HR−/HER2+ cancers did not attain pCR with one changing to TN, whilst in the 19 HR+/HER2+ cancers 18 changed subtype: 3 to HR−/HER2+, 13 to HR+/HER2−, and 2 to TN. All patients with HR loss received adjuvant endocrine therapy, and all but 2 with HER2 loss continued anti-HER2 therapy. Six patients that became TN were commenced on adjuvant capecitabine, whereas 2 patients that gained HER2 and one that gained ER were commenced on trastuzumab and hormone therapy, respectively. There were no data on survival outcomes.

Peng et al. [15] reported an increase in the proportion of luminal A tumours from 16% to 30% and the TN group from 17% to 26%. In the series by Parinyanitikul et al. [21], 41% of cases showed a change in at least one receptor; TN was the most stable phenotype with 27% showing a change, compared with 58% for HER2+ and 41% for HR+/HER2− [21]. Change in HR status was associated with a difference in RFS and OS; however, change in HER2 status showed no survival effect. Overall, a switch from HER2+ to TN was associated with a decrease in OS, whereas change from TN to HR+ was associated with an increase in both RFS and OS.

Neoadjuvant Endocrine Therapy

NAET is increasingly being used in the preoperative treatment of ER+, HER2− breast cancer. Similar to NACT, the aim is to downstage the carcinoma to allow more conservative management but its use has not been proven to improve long-term patient survival [36]. The average rate of NAET use (currently 4% in the UK) is still much lower than NACT [1]. A significant increase in its utilization (up to 42.3% in the UK) however occurred during the COVID-19 pandemic where aggressive types of breast cancers were prioritized for surgery, whereas patients with the ER+ early breast cancer were commenced on Bridging endocrine therapy [37].

Unlike NACT, pCR following NAET is uncommon. In their study of 132 HR+ carcinomas, Badr et al. [38] reported pCR in only two carcinomas; both of the lobular type. A meta-analysis of 20 NAET trials reported an overall pCR rate of less than 10% [39]. Data on receptor changes following NAET are rather limited compared with NACT, and the majority showed a significant proportion showing conversion to PR status and a reduction in Ki67 expression following NAET.

Changes in ER Post-NAET

The response to NAET has been shown to be proportionate to the ER expression. The IMPACT trial (Table 2) demonstrated more responders to anastrozole or tamoxifen with higher baseline ER levels ($p = 0.02$) [40]. In their earlier trial, Ellis et al. [41] showed no response of ER low expressors to tamoxifen, but several tumours from the ER low group responded to letrozole,.

A small study of 23 patients receiving anastrozole reported minimal to no change in ER status following treatment [47]. A subsequent study of 144 NACT and 28 NAET paired samples treated between 2007 and 2018 in the National Nagasaki Medical Center showed that ER expression slightly reduced after NAET in 14.5% of cases [48]. Similarly, the PALLET trial randomized 307 ER+ patients to letrozole with and without palbociclib and reported non-significant changes in ER expression after 14 weeks of neoadjuvant therapy [49].

The Japanese trial "PROACT," Table 2, reported that 5/40 anastrozole treated and 20/37 tamoxifen treated tumours for 3 months switched profile from ER+ to ER− [43]. A more recent larger UK retrospective single-centre study of 132 paired samples showed only one tumour (0.7%) switching to ER− profile with 5 and 8 cases showing minimal increase or decrease in the Allred score [38].

Changes in PR Post-NAET

In their small study of 23 ER+ carcinomas, of which 18 were concomitantly PR+, Anderson et al. [47] reported marked reduction in PR expression following anastrozole treatment in 17/18 patients including 11 tumour switching to a PR− status. The change did not correlate with the degree of pathological response [47]. Similarly, anastrozole had a remarkable effect on abolishing PR expression with 16/17 tumour changing from PR+ to PR− compared

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Table 2. Summary of relevant trials of NAET

Acronym (authors)	Name	Design	Patients, *n*	Type	Conclusions
P024 Eiermann et al. [42]	Preoperative treatment of postmenopausal breast cancer patients with letrozole: a Randomized double-blind multicentre study	Comparing letrozole and tamoxifen in postmenopausal women with hormone-responsive primary invasive breast cancer who were not eligible for breast-conserving surgery	337 enrolled of whom 324 included in the intent-to-treat population (tamoxifen = 170, letrozole *n* = 154)	Multinational, randomized, double-blind controlled trial Fifty-five centres in 16 countries between March 1998 and August 1999	Clear therapeutic superiority of letrozole over tamoxifen for the neoadjuvant management of primary breast cancer
PROACT Kurosumi et al. [43]	Comparison of anastrozole versus tamoxifen as preoperative therapy in postmenopausal women with HR-positive breast cancer: the preoperative "arimidex" compared to tamoxifen (PROACT) trial	Anastrozole or tamoxifen with or without chemotherapy for 12 weeks before primary surgery	Anastrozole (*n* = 228) Tamoxifen (*n* = 223)	Randomized, double-blind, double-dummy, multicentre stud	Anastrozole at least as effective as tamoxifen in down staging and more effective than tamoxifen in certain clinically relevant subgroups
ALTERNATE Suman et al. [44] Ma et al. [45]	Neoadjuvant endocrine treatment (NET) approaches for clinical stage II or III ER-positive HER2-negative breast cancer (ER+ HER2− BC) in postmenopausal (PM) women: Alliance A011106	Fulvestrant and/or anastrozole in treating postmenopausal patients with stage II–III breast cancer undergoing surgery to assess a biomarker-driven treatment strategy using Ki67 after 2 weeks to identify women with a low risk of disease recurrence	1,299	Phase III randomized open-label neoadjuvant clinical trial	Endocrine-sensitive disease rate not improved by fulvestrant over anastrozole alone. Follow-up and primary completion date: August 31, 2025
IMPACT Smith et al. [40]	The immediate preoperative anastrozole, tamoxifen, or combined with tamoxifen (IMPACT)	Neoadjuvant treatment of postmenopausal breast cancer with anastrozole, tamoxifen, or both in combination	330 including anastrozole (*n* = 113), tamoxifen (*n* = 108), or the combination (*n* = 109)	Multicentre controlled phase 3 double-blind randomized controlled trial	No significant differences in tumour objective response in the intent-to-treat population between patients receiving tamoxifen, anastrozole, or the combination. Anastrozole is as effective and well tolerated as tamoxifen in NAET treatment of ER+ operable breast cancer in postmenopausal women
Pallet Johnston et al. [46]	Randomized phase II study evaluating palbociclib in addition to letrozole as neoadjuvant therapy in ER-positive early breast cancer	To assess the biological and clinical effects of the CDK4/6 inhibitor (palbociclib) in women with ER+/HER2− invasive early breast cancer, with or without letrozole, in the neoadjuvant setting	307 randomly assigned 3:2:2:2 to letrozole (2.5 mg/d) for 14 weeks; letrozole for 2 weeks, then palbociclib plus letrozole to 14 weeks; palbociclib for 2 weeks, then palbociclib plus letrozole to 14 weeks; or palbociclib plus letrozole for 14 weeks	International, multicentre, phase II, randomized, open-label collaborative study	No significant difference in clinical response between palbociclib plus letrozole and letrozole groups but medial fold change in Ki67 significantly higher in the palbociclib group
POETIC Smith et al. [36]	Trial of perioperative endocrine therapy – individualizing care		4,480 participants (*n* = 2,976) or control (*n* = 1,504)	Randomized open-label, multicentre, parallel-group, randomized, phase 3 trial from 130 UK hospitals	Preoperative endocrine treatment did not improve the outcome but can be used to select adjuvant treatment based on tumour Ki67 expression. Low Ki67 at the baseline and low after 2 weeks of therapy can receive standard adjuvant endocrine therapy alone Estimated primary completion date April 2024

Table 3. Indications for repeat receptor testing post-NACT

Indications for repeat receptor testing post-NACT
1. Borderline result for ER (1–10%) or HER2 (ratio 1.8–2.0 or HER2 copy number 4–6) on core biopsy
2. Inadequate tumour in pre-treatment core biopsy
3. Poor response to therapy
4. Identification of a morphologically different tumour subclone

with only 1/11 in the tamoxifen-treated arm in the PROACT trial (Table 2) [43].

The PALLET trial data, published as a conference abstract, showed significant reductions in PR expression following 14 weeks of letrozole or letrozole + palbociclib therapy (geomeans PR: −96.4% vs. −94.9%) [49]. Maeda reported loss of PR expression in a 40.1% of 28 paired samples treated with NAET compared with only 8.2% loss following NACT [48]. In a large study of 132 invasive carcinomas, Badr et al. [38] reported a highly statistically significant change in PR expression following letrozole therapy with 12.7% switching from positive to negative status (Fig. 1c, d). Further 52.2% showed a variation in the Allred score without a change in final profile. Interestingly 3.8% tumours acquired a PR+ post-treatment status.

Significance of HR Changes following NAET

The PALLET trial (Table 2) suggested that low levels of ER at the baseline likely reflected a less luminal phenotype and predicted poor response to Ki67 suppression on letrozole or combined letrozole and palbociclib therapy [49]. Within that trial, complete cell-cycle arrest was defined as Ki67 immunohistochemical expression of less than or equal to 2.7% and was achieved after 14 weeks of therapy in patients who received palbociclib plus letrozole compared with letrozole alone in 90% and 59%, respectively ($p < 0.001$) [46].

Badr et al. [38] showed that a maintained PR profile was associated with better response to NAET ($p = 0.018$) and with longer survival compared with the loss of PR expression (107.3 vs. 91.7 months, respectively). Although this difference in survival was not statistically significant, this finding is intriguing and requires validation in large studies.

A prognostic index called the Preoperative Endocrine Prognostic Index (PEPI) score was devised based on over 60 months median follow-up data of patients treated with preoperative AIs in the P024 trial[42][35],Table 2. It is a Cox regression model incorporating tumour size, nodal status, Ki67%, and Allred status to predict RFS and breast cancer-specific survival [50].

The clinical validity of the score particularly applies to the PEPI score 0 (pT1/T2, pN0, Ki67 <2.7%, ER+ Allred score 3–8). Those tumours show such a low probability for recurrences such that adjuvant chemotherapy can safely be omitted.

A modified PEPI (mPEPI) score was developed for the ALTERNATE trial (Table 2) that used a selective ER downregulator (fulvestrant) by omitting the ER score component [44, 45]. An mPEPI of pT1/2, pN0, Ki67 ≤2.7% was clinically equivalent to a PEPI score zero.

A persistently high Ki67 expression following NAET was used to identify resistant tumours. In the Alliance study, resistance to endocrine therapy was defined by Ki67 of more than 10% after 2–4 weeks of NAET, based on prior studies [51]. The Dowsett group, in the IMPACT study, demonstrated a drop in the Ki67 index following 2 weeks of therapy which was maintained for 10 weeks in most patients [52]. The authors subsequently showed that this reduction predicted progression free survival [53].

The prospective Korean NEST trial of premenopausal women with ER+/HER2− lymph node-positive, breast cancer compared NACT against NAET (tramoxifen and ovarian suppression for 6 months). Patients with a high baseline Ki67% showed better radiological response to NACT than NAET, although the changes in Ki67 expression as a result of treatment were not different between the two groups [54].

Combining PR at a cut-off value of 50% and the PEPI score provided superior prognostic information for RFS and cancer-specific survival, in patients treated with neoadjuvant exemestane, than either of the parameters individually [55]. The IMPACT trialists showed a significant suppression of Ki67 expression following NAET in all 3 arms; tamoxifen, letrozole, combination although a significantly greater suppression occurred in the letrozole only group [52]. This suppression positively associated with ER positivity levels and was more marked in the PR+ tumours.

In the POETIC long-term follow-up using a Ki67 cut-off of 10%, Ki67 low ER+/HER2− tumours had lower 5-year recurrence rate (4.4%) compared with the Ki67-high group (11.8%) [36] (Table 2). The Ki67-low tumours (either at the baseline or following NAET) would be an indication of likely response to adjuvant endocrine therapy, whereas a tumour with high Ki67 expression may benefit from further adjuvant treatment or new therapies.

Changes in HER2 Post-NAET

NAET is generally used for the treatment of HR+/HER2− breast cancer but occasionally for HR+/HER2+ tumours due to existing comorbidities. Few examples of a switch from a HER2− to HER2+ status have been reported (Fig. 1e, f). Badr et al. [38] reported a statistically significant change in HER2 status following NAET in 10% of cases ($p = 0.002$) with more tumours switching from negative to positive status (8 switched from positive to negative status and 5 from negative to positive expression). The numbers were however too small to allow correlation with the patient outcome. There is currently no data on the clinical impact of a change in HER2 status following NAET. This requires further evaluation in large scale multicentre studies/trials.

Discussion and Conclusions

There is now substantial evidence that HR status changes in a significant proportion of patients post-NACT and -NAET, with change in HER2 status in a smaller proportion. Change in HR status, especially from negative to positive, is potentially important as this could result in a change in treatment. Despite this, the impact on survival of a change in status remains unclear, although studies suggest loss of *HER2* gene amplification following anti-HER2 therapy appears to be associated with worse prognosis [16, 29]. In patients whose tumours become ER+ or HER2+ post-NACT, endocrine or anti-HER2 therapy, respectively, can be initiated, although evidence in the form of clinical trials is lacking. Limited data from retrospective series suggest there may be benefit from endocrine therapy in patients whose tumours become ER+ [23]; there is no evidence on the benefit of commencing HER2-targeted agents in patients who become HER2+. More controversial is cessation of targeted therapies if receptor status becomes negative post-treatment, with some series suggesting patients may still derive benefit from ongoing treatment [23]. A pragmatic approach is to treat on a positive result but not to withdraw treatment in the event of receptor conversion.

The role of adjuvant capecitabine in cancers that become TN post-NACT also needs to be addressed, especially as the molecular biology of these tumours is likely to be different to primary TN breast cancers. It is also clear from the available, though limited, literature that a significant proportion of tumours switch off PR expression and show a marked reduction in the Ki67 proliferation index as a result of NAET particularly with AIs. The changes in ER as a result of NAET treatment are minimal.

Routine retesting of HRs and HER2 post-neoadjuvant therapy is not currently recommended in most national guidelines including the UK Royal College of Pathologists [56, 57], although this is likely to be reviewed as further evidence emerges. The latest College of American Pathologists dataset advises retesting if pre-treatment status was negative [58]. However, repeat ER and/or HER2 testing should be considered in certain circumstances (Table 3). In cases with equivocal pre-treatment receptor status, i.e., weak positive ER (1–10% positive cells) and/or HER2 ISH equivocal (ratio 1.8–2.0 and/or average HER2 copy number 4–6 with ratio <2), the usual recommendation is for repeat testing in the surgical resection specimen, and this should also be performed if there is sufficient residual invasive disease post-NACT [59, 60]. When there was insufficient tumour in the pre-treatment core biopsy for accurate assessment of receptor status, retesting of the excision should be considered, although ideally these patients should have undergone repeat biopsy at diagnosis to obtain a better tumour sample before commencing treatment [56]. Rarely, a histologically distinct tumour subclone is identified in the post-treatment resection specimen, for example, a grade 1 carcinoma when the pre-treatment biopsy was grade 3 TN; clinical judgement is required as this does not refer to post-treatment changes commonly induced by NACT, such as change in grade due to a decrease in mitotic activity or a single-cell growth pattern secondary to reduction in tumour cellularity. Finally, when there is minimal or no response to neoadjuvant therapy particularly NACT, survival outcomes are poorer for all molecular subtypes and repeat receptor testing may introduce treatment options, although clinical benefits are still unclear.

Conflict of Interest Statement

A.M.S. received speaker honoraria and participated in Advisory Board meetings for Ventana Roche, Exact Sciences, and Diaceutics. E.P. has received speaker's honoraria and travel costs from Roche and participated in advisory group meetings for Roche and IPB Advisors. None of the above affects the content of this paper.

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Author Contributions

A.M.S. covered the neoadjuvant endocrine section. E.P. wrote the neoadjuvant chemotherapy section. Both the authors reviewed and edited the whole manuscript and agreed the final version.

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