



# Biomarkers of neoadjuvant/adjuvant endocrine therapy for ER-positive/HER2-negative breast cancer

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**Abstract:** Endocrine therapy is one of the key therapeutic components for patients with hormone receptor-positive early stage breast cancer. A lot of efforts have been made in order to explore biomarkers to select optimal endocrine treatment and optimal duration of the treatment. Estrogen receptor (ER) is the most intensively-studied and well-established biomarker for selection of endocrine treatment. Currently, a number of other markers including conventional immunohistochemical markers and molecular markers such as genetic markers and multigene assays have been investigated. Although the clinical utility of PgR expression has been tested in a number of clinical trials of neoadjuvant/adjuvant endocrine therapy, no validated results have been obtained. Oncotype DX Recurrence Score has been reported to be associated with benefit of adjuvant tamoxifen use and the clinical response to neoadjuvant endocrine therapy but more powerful tool is desired for clinical use to optimize endocrine therapy. Neoadjuvant endocrine therapy is considered as a promising strategy to explore biomarkers for endocrine responsiveness as well as to develop a new treatment option in combination with molecular target agents and to study mechanisms underlying endocrine response and resistance. In this manuscript, current understanding on biomarkers of neoadjuvant/adjuvant endocrine therapy for both predictive and prognostic utilities is discussed.

**Keywords:** Hormone receptor; endocrine therapy; neoadjuvant therapy; preoperative endocrine prognostic index (PEPI)

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## Introduction

Endocrine therapy is an essential component of the neoadjuvant/adjuvant treatment for hormone receptor-positive early stage breast cancer regardless of menopausal status. Tamoxifen is a major endocrine treatment option, particularly for premenopausal women, and aromatase inhibitors including anastrozole, letrozole and exemestane are another major option for postmenopausal women. The differential use of different types of endocrine therapies is discussed by other authors. Here in this paper, biomarkers for neoadjuvant or adjuvant endocrine therapy will be discussed including both conventional and molecular

markers.

## Conventional marker

### *Estrogen receptor (ER)*

ER is the main determinant for clinical use of adjuvant endocrine therapy. The role of ER content as a predictor of response to endocrine therapy has been examined and validated by a number of studies (1). The meta-analysis of the trials of 5 years of adjuvant tamoxifen by Early Breast Cancer Trialists' Collaborative Group (EBCTCG) was reported (2). When the quantitative ER measurement was

poor (less than 10 fmol/mg cytosol protein), there was no apparent benefit from adjuvant tamoxifen [relative risk (RR) 0.97; 2P =0.6]. However, if ER was positive (equal to or more than 10 fmol/mg cytosol protein), the addition of tamoxifen provided substantial benefit (2P <0.00001) and the proportional effect depended slightly on quantitative ER measurement: RR 0.67 for ER 10–19 fmol/mg; RR 0.52 for ER  $\geq$ 200 fmol/mg (2).

In NSABP B-14 trial, where adjuvant tamoxifen was tested in patients with node-negative hormone receptor-positive breast cancer, quantitative ER mRNA expression was predictive of tamoxifen benefit with a significant interaction in terms of distant recurrence-free survival (DRFS) (P<0.001) (3). Increased benefit of tamoxifen treatment was observed with increasing levels of ESR1 expression: hazard ratio (HR) =1.2 (95% CI: 0.72–2.02) for lower tertile; HR =0.59 (95% CI: 0.32–1.09) for intermediate; HR =0.39 (95% CI: 0.2–0.77) for higher tertile (3).

Several studies have shown the superiority of aromatase inhibitors over tamoxifen in postmenopausal women with hormone receptor-positive breast cancer. In a sub-study from ATAC trial (transATAC) where anastrozole was compared with tamoxifen, ER level did not have any interaction with treatment for time to recurrence (4). In BIG 1-98 trial in which letrozole was compared with tamoxifen, no clear differential effect between treatments was observed according to centrally assessed ER expression level with P=0.12 for interaction although patients with ER-negative disease had HR =1.32 (95% CI: 0.63–2.78) compared with HR =0.72 (95% CI: 0.60–0.86) for those with ER-positive disease (5). Similarly, in TEAM trial in which exemestane was compared with tamoxifen, no statistically significant treatment-by-marker effect of ER expression was observed after adjustment for relevant markers (P=0.2) (6). Thus, as long as ER is expressed, ER expression level is not a predictor for benefit of aromatase inhibitors over tamoxifen.

In agreement with adjuvant settings, ER Allred expression scores had a linear relationship with response rates of both letrozole and tamoxifen in P024 neoadjuvant study (P=0.0013 and 0.0061, respectively) (7) and clinical response to neoadjuvant endocrine therapy is reported to be associated with prognosis (8).

### ***Progesterone receptor (PgR)***

The meta-analysis of 5 years of adjuvant tamoxifen by

EBCTCG showed that the PgR measurement was not predictive of who would respond to tamoxifen in ER-positive disease (2). In ER-negative disease, PgR-positivity gave RR of 0.90 with no significant benefit from tamoxifen (2P =0.35) (2).

Consistently, in NSABP B-14, PgR mRNA expression was not predictive of tamoxifen benefit (3).

In the transATAC study, there was no significant interaction between PgR and treatment (anastrozole *vs.* tamoxifen) for time to recurrence (4). In addition, anastrozole gave similar benefit over tamoxifen regardless of centrally assessed PgR status in the study: HR =0.72 for PgR-positive and HR =0.68 for PgR-negative (4). In BIG 1-98 trial, centrally assessed PgR expression did not affect the relative efficacy of letrozole over tamoxifen among patients with centrally assessed ER-positive breast cancer (5). Patient with ER-positive breast cancer had better disease-free survival with letrozole than with tamoxifen regardless of PgR-positivity: HR =0.70 for PgR-positive disease and HR =0.84 for PgR-negative disease (5). In TEAM trial where exemestane was compared with tamoxifen, no treatment-by-marker effect for PgR was observed for exemestane *vs.* tamoxifen [HR =0.83; 95% CI: 0.65–1.05 for PgR-rich (Allred score  $\geq$ 5); HR =0.85; 95% CI, 0.61–1.19 for PgR-poor (Allred score  $\leq$ 4); interaction, P=0.88] (6). In the meta-analysis conducted by EBCTCG, superiority of aromatase inhibitors to tamoxifen was shown regardless of PgR expression: RR for ER-positive and PgR-positive disease was 0.74 (95% CI: 0.64–0.84) and that for ER-positive and PgR-negative disease was 0.57 (95% CI: 0.45–0.73) (9).

In TEXT and SOFT trials, which are randomized phase III trials investigating adjuvant endocrine therapy for pre-menopausal patients with hormone receptor-positive early breast cancer, lower PgR expression by immunohistochemistry (IHC) was associated with reduced breast cancer-free interval and seemed to show a greater 5-year absolute benefit of exemestane + ovarian function suppression (OFS) versus tamoxifen with or without OFS by the non-parametric sliding-window subpopulation treatment effect pattern plot (STEPP) analysis (10). However, there was no interaction between PgR and any combination of treatment (P > 0.4) and, thus, the clinical significance of PgR expression for treatment selection has not been established even in pre-menopausal settings.

### ***PEPI***

PEPI stands for preoperative endocrine prognostic index,

which has been generated for prognostic prediction using samples from clinical trials of neoadjuvant endocrine therapy (11). By using Cox proportional hazards, four factors were selected that were associated with relapse-free survival (RFS) and breast cancer-specific survival (BCSS) in 158 women enrolled in the P024 neoadjuvant endocrine therapy trial, which compared letrozole and tamoxifen before surgery. Four factors were determined using post-endocrine surgical specimen, which included pathological tumor size, nodal status, Ki67 level, and ER status (11). Patients with PEPI score 0 showed a low risk of recurrence and were considered to get less benefit from adjuvant chemotherapy. The index was, then, validated by an independent study of 203 women in the IMPACT trial where anastrozole, tamoxifen, or the combination was compared (11). The prognostic utility of PEPI score was, then, confirmed by ACOSOG Z1031B study, in which neoadjuvant endocrine therapy with anastrozole, exemestane, or letrozole was given to postmenopausal patients (12). After median follow-up of 5.5 years, 3.7% of the patients with PEPI 0 experienced relapse while 14.4% of the patients with PEPI >0 had recurrence (HR =0.27; 95% CI: 0.092–0.764; P=0.014).

Because selective estrogen receptor degrader (SERD) down-regulates ER expression, modified PEPI (mPEPI) was generated for SERD by excluding post-treatment ER status and showed a similar prognostic power to the original PEPI: after median follow-up of 62.5 months, no patients with mPEPI 0 experienced recurrence in the combined P024 and POL (neoadjuvant letrozole) trials (13).

Currently, a number of clinical trials utilize PEPI or mPEPI as surrogate endpoint for neoadjuvant endocrine therapy with or without molecular target agents (14).

## Genetic markers

### *ESR1 mutation*

ESR1 is the gene that encodes ER $\alpha$ . ESR1 mutation was reported to confer endocrine resistance in breast cancer (15). Some studies have shown that ESR1 mutation, especially mutations in the ligand-binding domain, creates constitutive active state, leading to poor sensitivity of endocrine therapies (15–17). However, it is not clear whether ESR1 mutation in primary breast cancer is associated with endocrine resistance in neoadjuvant/adjuvant settings. In CARMINA 02 trial where neoadjuvant anastrozole and fulvestrant were compared, the frequency of baseline ESR1 mutation was too low (3.4%) to

draw any conclusion regarding endocrine responsiveness (18). In BIG1-98 trial where adjuvant endocrine therapy with letrozole, tamoxifen and a sequential strategy was compared in postmenopausal women, the frequency of ESR1 mutation was reported to be 0% (19). Similarly, only 3% (6/183) of the primary breast tumor had ESR1 mutation in patients enrolled in BOLERO2 trial (15). Consistently, 3.5% (11/313) and 2.5% (7/270) of the primary breast tumors treated at Memorial Sloan Kettering Cancer Center and Kumamoto University Hospital, respectively, have been reported to have ESR1 mutation (20,21). Indeed, ESR1 mutations were not identified in any of the patients with early-stage ER-positive breast cancer who received neoadjuvant endocrine therapy and showed poor response (PEPI score of  $\geq 4$ ) (22). In addition, ESR1 mutation was reported to be associated with better recurrence-free survival with no difference in overall survival in patients treated with tamoxifen monotherapy (23). Thus, it remains to be elucidated whether ESR1 mutation is associated with resistance or responsiveness to neoadjuvant/adjuvant endocrine therapy.

### *PIK3CA mutation*

PIK3CA encodes the p110- $\alpha$  subunit of the phosphatidylinositol 3-kinase enzyme complex. PIK3CA mutation is the most frequently detected mutation in hormone receptor-positive breast cancers. There have been some controversies on the role of PIK3CA mutation in responsiveness to endocrine therapy.

In the adjuvant setting, no interaction was reported between PIK3CA mutation status and tamoxifen benefit (24). In BIG1-98 study, PIK3CA mutations were the most common (49%) among 287 cancer genes of Foundation Medicine's T5-targeted panel using next-generation sequencing (19). In the study, PIK3CA mutations were significantly associated with reduced risk of distant recurrence (HR =0.57; 95% CI: 0.38–0.85; P=0.006) (19). In addition, patients with PIK3CA mutation (kinase or helical domains) showed a greater magnitude of benefit with adjuvant letrozole over tamoxifen (HR =0.18; 95% CI: 0.06–0.50) than those without mutation (HR =1.26; 95% CI: 0.65–2.45) with significant interaction (P=0.002) (19). In TEXT trial where adjuvant exemestane was compared with adjuvant tamoxifen in premenopausal women with OFS, PIK3CA mutation was found in 39.8% of the examined tumors and associated with improved distant relapse-free survival although it was not an independent marker for prognosis (25).

**Table 1** Neoadjuvant endocrine therapy and Oncotype DX Recurrence Score

Agent	Therapy	Patient number	RS						Reference
			Clinical response rate (%)			Breast conserving rate (%)			
			Low	Intermediate	High	Low	Intermediate	High	
Akashi-Tanaka	Tamoxifen or anastrozole	43	63.6	31.3	31.3	N.R.	N.R.	N.R.	(34)
JFMC34	Exemestane	64	59.4	58.8	20.0	90.6	76.5	46.7	(35)
TransNEOS	Letrozole	295	54.8	41.7	22.2	79.2	N.R.	60.4	(36)

N.R., not reported.

In addition, there was no significant differences in the effect of PIK3CA mutations between patients treated with exemestane and those with tamoxifen (25). Thus, although it is intriguing to consider PIK3CA mutation as selection marker for aromatase inhibitor over tamoxifen, further studies are necessary to make any conclusion on the clinical use of PIK3CA mutation for treatment selection.

Using samples from two neoadjuvant aromatase inhibitor trials, POL and ACOSOG Z1031, PIK3CA mutation was shown not to associate with clinical response (26). In addition, PIK3CA mutation status did not predict change in Ki67 after 2 weeks of aromatase inhibitor treatment (27). Contradictorily, in phase II CARMINA 02 trial of neoadjuvant comparison between anastrozole and fulvestrant, PIK3CA was significantly more frequently mutated in radiological non-responders than in responders (60.8 vs. 31.6%) (18). Because studies on PIK3CA mutation yielded conflicting results in terms of endocrine responsiveness, further clinical research is required.

## Multigene assays

### Oncotype DX

Oncotype DX Recurrence Score (RS) has been developed and shown to be able to assess recurrence risk in patients with hormone receptor-positive early breast cancer who are treated with adjuvant endocrine therapy (28-30). It has also been shown to predict benefit from adjuvant chemotherapy in patients with hormone receptor-positive breast cancer (31,32).

Several studies have assessed the predictive value of RS for neoadjuvant/adjvant endocrine treatment.

In NSABP B-14 trial, where adjuvant tamoxifen was tested in patients with node-negative hormone receptor-positive breast cancer, patients with low RS and intermediate RS showed significant benefit with

tamoxifen while those with high RS did not (33). Patients with low RS showed 10-year distant recurrence-free survival (DRFS) of 85.9% with placebo and 93.1% with tamoxifen ( $P=0.039$ ), those with intermediate RS showed that of 62.2% with placebo and 79.5% with tamoxifen ( $P=0.02$ ) and those with high RS showed that of 68.7% with placebo and 70.3% with tamoxifen ( $P=0.82$ ) (33). Although the result suggested the predictive value of RS for adjuvant tamoxifen benefit, the interaction between tamoxifen treatment and RS was marginal ( $P=0.06$ ).

In ATAC trial, in which adjuvant anastrozole was compared with tamoxifen, the interaction between RS and treatment (anastrozole vs tamoxifen) was examined (28). No significant interaction was found regardless of nodal status, indicating that RS is not useful for selection of endocrine treatment, either aromatase inhibitor or tamoxifen (28).

In neoadjuvant settings, several studies have examined the predictive value of RS for clinical response (Table 1) (34-36). All the studies have shown that low RS is associated with better response rates while high RS is with worse response rates, indicating the usefulness of RS for prediction of response to neoadjuvant endocrine therapy. In addition, RS has been reported to be associated with breast conserving rate (35,36). The combination of pre-treatment and post-treatment RSs has been reported to be able to predict early recurrence and late recurrence, separately, although a further validation is required (37). However, 20-30% of the patients with high RS responded to neoadjuvant endocrine therapy while around 40% of the patients with low RS did not respond, suggesting that a better predictive tool is necessary to select neoadjuvant therapies in order to optimize treatment strategy.

### Breast cancer index (BCI)

BCI was developed by utilizing two independently

developed molecular assays including molecular grade index, which is a five-gene predictor of prognosis that recapitulates tumor grade and proliferation, and the two gene expression ratio, HOXB13/IL17BR (38-41). BCI has been shown to be a strong predictor for distant recurrence. In addition, BCI has been reported to be a potent predictor for late distant recurrence (42). Furthermore, in Trans-aTTom study, BCI [HOXB13/IL17BR ratio (H/I)] was shown to be associated with benefit from extended tamoxifen, namely 10 *vs.* 5 years of tamoxifen in patients with nodal involvement. Patients with BCI(H/I)-High derived a significant benefit from extended tamoxifen (HR =0.35; 95% CI: 0.15–0.86; P=0.0279) while those with BCI(H/I)-Low showed no significant benefit (HR =1.07; 95% CI: 0.69–1.65; P=0.77), indicating the clinical usefulness of BCI for application of extended use of endocrine therapy (43). Further validation studies are warranted.

## Conclusions

A large number of studies have tried to identify biomarkers for endocrine therapy using samples from clinical trials or archives to optimize neoadjuvant/adjuvant endocrine therapies. Currently a limited number of markers are used as reliable marker in clinics. It is clear that further research is necessary to avoid unnecessary treatment and to optimize therapeutic agent and treatment duration. It is important to be aware that endocrine therapy affects not only cancer cells but also stromal cells and, thus, understanding stromal reaction including immune cells may help further development of biomarkers (44-47). In order to optimize neoadjuvant/adjuvant endocrine therapies, further research with multi-angle vision to understand biological meanings of endocrine response and resistance is required.

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