Managing breast cancers with low estrogen receptor and HER2 by drugging both

(Commentary on manuscript # CCR-13-1260R “Quantitative ER and PgR Assessment as Predictors of Benefit From Lapatinib in Postmenopausal Women With Hormone Receptor-Positive, HER-2 Negative Metastatic Breast Cancer”)

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Summary
Low ER levels in breast tumors are associated with poorer response to anti-estrogen therapy. Finn et al. identified low ER levels as a biomarker predicting benefit from the addition of the EGFR/HER2 dual inhibitor Lapatinib to an anti-estrogen treatment regimen in patients with metastatic breast cancer.

Text
In this issue of Clinical Cancer Research, Finn and colleagues (1) quantified levels of the hormone receptors (HRs) estrogen receptor α (ER) and progesterone receptor (PR) in HER2-negative tumors from study EGF30008 to identify a biomarker predicting benefit from the addition of the EGFR/HER2 dual kinase inhibitor Lapatinib to the aromatase inhibitor (AI) Letrozole. The majority of breast cancers express ER and/or PR. Patients with HR+ breast cancer are treated with anti-estrogen therapies in both the adjuvant and advanced/metastatic settings to inhibit ER signaling. However, anti-estrogen resistance is common, particularly in late-stage disease. The only mechanism of anti-estrogen resistance for which there is supportive clinical data is overexpression/amplification of the HER2/ERBB2 kinase, which occurs in approximately 10% of HR+ cases. Preclinical evidence supports the role of HER2 in anti-estrogen resistance, and combinations of anti-HER2 therapy (i.e., Lapatinib; the HER2 antibody Trastuzumab) and anti-estrogen therapy [i.e., Letrozole, Tamoxifen] significantly improve progression-free survival (PFS) in patients with advanced HR+/HER2+ breast cancer compared to anti-estrogen therapy alone.

HR and HER2 levels are generally inversely correlated among breast tumors. Preclinical findings suggest that ER and HER2 exist in equilibrium. ER can repress or promote ERBB2 transcription depending on transcription cofactor context (2). Inhibition of HER2 can increase ER activity (3). MCF-7 breast cancer cells are ER+/PR+/HER2- and sensitive to anti-estrogens. When adapted to growth in the presence of anti-estrogens, MCF-7 cells/tumors upregulate HER2 levels, and anti-estrogen resistance is abrogated by anti-HER2 therapy (4). ER promotes expression of growth factor receptors and ligands, which in turn activate signaling pathways that modulate ER activity (5). Also of interest is the observation that HER2+ disseminated cancer cells are often detected in bone marrow of patients with HER2- primary breast tumors (6). Thus, up-front treatment with anti-HER2 therapy may prevent the development of anti-estrogen resistance in patients with HR+/HER2- breast cancer. This is being addressed in part by study NCT00944047, which is testing
benefit from neoadjuvant Trastuzumab in patients with HER2-low breast cancer, and study NCT01779050, which will test benefit from adjuvant Trastuzumab in patients with HER2- breast cancer and HER2+ disseminated tumor cells in bone marrow.

In study EGF30008, post-menopausal patients with HR+ metastatic breast cancer were randomized to first-line treatment with Letrozole plus Lapatinib or placebo (7). Among 952 patients with HR+/HER2- disease, the addition of Lapatinib did not alter PFS. However, subgroup analysis based on prior anti-estrogen therapy revealed a trend toward increased PFS with Letrozole/Lapatinib in patients with anti-estrogen-resistant disease (discontinued adjuvant Tamoxifen ≤ 6 months prior to enrollment). Based on these data, and the fact that ER-low tumors are less responsive to anti-estrogen therapy, Finn et al. further evaluated HR+/HER2- tumors from EGF30008 to determine whether HR quantification could identify a patient subgroup that benefited from the addition of Lapatinib. Analysis of tumors from 821 patients revealed that low ER levels were predictive of increased PFS in patients treated with Letrozole/Lapatinib compared to Letrozole/placebo (1). In contrast, patients with ER-high/HER2- tumors did not benefit from the addition of Lapatinib.

One confounding factor in the study by Finn et al. lies in the biopsies used for scoring HR and HER2 levels: primary tumor material was used for 688 of 821 cases (1). Changes in HR/HER2 status have been found between paired primary/metastatic tumor specimens, and upon relapse with anti-estrogen-resistant disease compared to the diagnostic biopsy of the primary tumor. Such “receptor conversion” is an ongoing issue in the management of breast cancer, and warrants biopsy and analysis of recurrent tumors for treatment decision-making. Also, some patients in this study may have been on anti-estrogen therapy at the time of biopsy of a recurrent/metastatic lesion (7), which could affect HR/HER2 levels. Whether the use of mainly primary tumors in this study affected the identified association between low ER levels and benefit from the addition of Lapatinib cannot be ascertained, but needs to be considered in a future prospective study.

A second issue raised by this study is the timing of intervention with kinase-targeted agents in HR+ breast cancer. Preclinical studies indicate that treatment of anti-estrogen-sensitive cells/tumors with combinations of anti-estrogens and kinase inhibitors (e.g., PI3K, mTOR, HER2) prevents the emergence of anti-estrogen-resistant cells, and anti-estrogen-resistant cells are sensitive to such combinations (5). Clinical data suggest that the addition of a mTORC1 inhibitor (Everolimus) to an anti-estrogen is most beneficial in patients with advanced/metastatic HR+ breast cancer that acquired anti-estrogen resistance (i.e., recurrence
>6 months after start of adjuvant anti-estrogen) (8). In contrast, benefit from the EGFR inhibitor Gefitinib in the context of an anti-estrogen as first-line treatment for advanced/metastatic ER+/HER2- disease was evident only in patients who were anti-estrogen-naïve (9). In the current study, half of patients received prior adjuvant anti-estrogen therapy, but the distribution of ER levels was similar in cases of anti-estrogen-resistant, -sensitive, and -naïve disease (1). Thus, these data support the use of combined Letrozole/Lapatinib for ER-low/HER2- tumors regardless of prior anti-estrogen therapy/benefit. Whether kinase inhibitors would be best introduced in the adjuvant or metastatic setting requires further study, and ultimately will be determined by an individual patient’s risk/benefit analysis, with consideration of adverse effects associated with kinase inhibitors.

The findings of Finn et al. are reminiscent of recently reported results suggesting that 1) the addition of Gefitinib to Tamoxifen was more effective than Tamoxifen/placebo to prevent disease progression in patients with advanced HR+/HER2- breast cancer expressing little or no ER (10), and 2) the addition of Gefitinib to the AI Anastrozole increased PFS and clinical benefit rate compared to Anastrozole/placebo in patients with metastatic HR+ disease (9). This begs the mechanistic question of whether the anti-tumor effect of Lapatinib in the current study is via inhibition of EGFR, HER2, or both.

Current ASCO-CAP guidelines dictate that detection of ER immunostaining in ≥1% of malignant tumor cells dictates classification of a breast tumor as “ER+.” However, these guidelines do not address intensity of ER immunoreactivity. Finn et al. used histoscopy to semi-quantify ER levels, incorporating ER immunostaining intensity and frequency, and stratified patients into quartiles based on ER histoscore. In prior studies describing an association between low tumor ER levels in primary and recurrent/metastatic tumors and shorter time to recurrence and progression following anti-estrogen therapy, ER was also semi-quantified using methods that integrate ER intensity and frequency (11). Thus, clinical implementation of a standardized method to better quantify ER levels may be useful to identify patients likely to benefit from additional therapy (e.g., Lapatinib), and to better predict overall benefit from anti-estrogen therapy in general (Fig. 1). To address the issue of biopsy bias and intra/intertumor heterogeneity for quantification of ER levels in patients with metastatic disease, [18F]-fluoroestradiol positron emission tomography (FES-PET) combined with standard [18F]-FDG-PET may be useful to quantify ER levels in all tumors. If FES-PET becomes a clinically validated method, it may be incorporated into a diagnostic paradigm to help guide treatment decisions (Fig. 1).
References


Figure 1. Potential management of patients with newly diagnosed advanced/metastatic breast cancer.

Summarizing the evidence to-date, patients in the near future may benefit from 1) biopsy of a recurrent/metastatic tumor, 2) $^{18}$F]FES-PET imaging, and 3) $^{18}$F]FDG-PET imaging. ER and PR should be quantitated (e.g., histoscore, Allred score), and HER2 should be analyzed by IHC and/or FISH. Receptor scores and PET imaging data would be integrated to determine whether a patient has predominantly ER-high vs. -low vs. -negative disease, with or without HER2 amplification/overexpression. The findings of Finn et al. suggest that patients with ER-low/HER2-negative disease may benefit from the combination of an anti-estrogen and an anti-HER2 agent. Currently used diagnostic methods and treatment regimens are in blue boxes. Proposed new diagnostics, molecular subtyping, and treatment regimens are in pink boxes.
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**Figure 1:**

- Patient with first presentation of advanced/metastatic breast cancer
- [18F]FES-PET
- [18F]FDG-PET
- Biopsy
- Quantify ER/PR/HER2
- Quantify ER levels
- Compare FES+ vs. FDG+ tumors
- Treatment Subtyping Analysis & integration
- ER-high/HER2-
- ER-high/HER2+
- ER-low/HER2+
- ER-low/HER2-
- ER-/HER2-

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