Managing Breast Cancers with Low Estrogen Receptor and HER2 by Drugging Both

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Low estrogen receptor (ER) levels in breast tumors are associated with poorer response to antiestrogen therapy. Finn and colleagues identify low ER levels as a biomarker predicting benefit from the addition of the EGFR/HER2 dual kinase inhibitor lapatinib to an antiestrogen treatment regimen in patients with metastatic ER+/HER2− breast cancer. Clin Cancer Res; 20(3); 528–30. ©2013 AACR.

In this issue of Clinical Cancer Research, Finn and colleagues (1) quantified levels of the hormone receptors (HR), 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 letrozole. The majority of breast cancers express ER and/or PR. Patients with HR+ breast cancer are treated with antiestrogen therapies in both the adjuvant and advanced/metastatic settings to inhibit ER signaling. However, antiestrogen resistance is common, particularly in late-stage disease. The only mechanism of antiestrogen 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 antiestrogen resistance, and combinations of anti-HER2 therapy (i.e., lapatinib; the HER2 antibody trastuzumab) and antiestrogen therapy (i.e., letrozole and tamoxifen) significantly improve progression-free survival (PFS) in patients with advanced HR−/HER2+ breast cancer compared with antiestrogen 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 antiestrogens. When adapted to growth in the presence of antiestrogens, MCF-7 cells/tumors upregulate HER2 levels, and antiestrogen 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, upfront treatment with anti-HER2 therapy may prevent the development of antiestrogen 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, postmenopausal patients with HR+/HER2− 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 DFS. However, subgroup analysis based on prior antiestrogen therapy revealed a trend toward increased DFS with letrozole/lapatinib in patients with antiestrogen-resistant disease (discontinued adjuvant tamoxifen ≤6 months before enrollment). On the basis of these data, and the fact that ER-low tumors are less responsive to antiestrogen therapy, Finn and colleagues 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 with 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 and colleagues 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 antiestrogen-resistant disease compared with 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 antiestrogen 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 antiestrogen-sensitive cells/tumors with combinations of antiestrogens and kinase inhibitors (e.g., PI3K, mTOR, and HER2) prevents the emergence of antiestrogen-resistant cells, and antiestrogen-resistant cells are sensitive to such combinations (5). Clinical data suggest that the addition of a mTORC1 inhibitor (everolimus) to an antiestrogen is most beneficial in patients with advanced/metastatic HR+ breast cancer that acquired antiestrogen resistance (i.e., recurrence >6 months after start of adjuvant antiestrogen; ref. 8). In contrast, benefit from the EGFR inhibitor gefitinib in the context of an antiestrogen as first-line treatment for advanced/metastatic ER+/HER2- disease was evident only in patients who were antiestrogen naive (9). In this study, half of the patients received prior adjuvant antiestrogen therapy, but the distribution of ER levels was similar in cases of antiestrogen-resistant, -sensitive, and -naive disease (1). Thus, these data support the use of combined letrozole/ lapatinib for ER-low/HER2- tumors regardless of prior antiestrogen 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 and colleagues are reminiscent of recently reported results suggesting that (i) 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 (ii) the addition of gefitinib to the aromatase inhibitor anastrozole increased PFS and clinical benefit rate compared with anastrozole/placebo in patients with metastatic HR+ disease (9). This begs the mechanistic question of whether the antitumor effect of lapatinib in this 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 and colleagues used histoscoring to semiquantify 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 antiestrogen therapy, ER was also semiquantified 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 antiestrogen 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

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**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: (i) biopsy of a recurrent/metastatic tumor, (ii) [18F]FES–PET imaging, and (iii) [18F]FDG–PET imaging. ER and PR should be quantitated (e.g., histoscore and Allred score), and HER2 should be analyzed by immunohistochemistry and/or FISH. Receptor scores and PET imaging data would be integrated to determine whether a patient has predominantly ER-high versus -low versus -negative disease, with or without HER2 amplification/overexpression. The findings of Finn and colleagues suggest that patients with ER-low/HER2-negative disease may benefit from the combination of an antiestrogen and an anti-HER2 agent (1). Currently used diagnostic methods and treatment regimens are in blue boxes. Proposed new diagnostics, molecular subtyping, and treatment regimens are in pink boxes.
incorporated into a diagnostic paradigm to help guide treatment decisions (Fig. 1).

**Disclosure of Potential Conflicts of Interest**

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**References**

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