Quantitative ER and PgR Assessment as Predictors of Benefit from Lapatinib in Postmenopausal Women with Hormone Receptor–Positive, HER2-Negative Metastatic Breast Cancer

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Abstract

Purpose: Lapatinib, a dual epidermal growth factor receptor (EGFR) and HER2 inhibitor, remains unproven in non–HER2-amplified metastatic breast cancer (MBC). EGF30008, a phase III trial of letrozole and lapatinib versus letrozole and placebo, demonstrated that lapatinib significantly improves outcome for postmenopausal women with HER2-amplified, but not HER2-negative, MBC. The hypothesis that low hormone receptor status is associated with benefit in this HER2-negative cohort was tested.

Experimental Design: A blinded retrospective biomarker evaluation used immunohistochemistry (IHC) to semiquantify estrogen receptor (ER) and progesterone receptor (PgR) expression (n = 821/952). HER2 status was determined by IHC and confirmed by FISH (n = 326). Effects of these biomarkers on progression-free survival (PFS) were examined in patients with available tissue.

Results: In HER2-negative, ER-positive MBC, median PFS was analyzed by ER and PgR expression (H-score) by quartile (Q). There was significant improvement in patients with low ER expression (Q1, H-score <160) with lapatinib and letrozole (13.6 vs. 6.7 months; P = 0.01). No benefit was associated with stronger ER expression (Q2/3, H-score/C21160 and <250; 13.6 vs. 14.2 months; Q4, H-score ≥250; 11.2 vs. 14.2 months). There was no association between PgR H-score and benefit from lapatinib.

Conclusion: In postmenopausal patients with advanced hormone receptor–positive disease, weak ER expression is associated with worse outcome with letrozole treatment compared with the combination. The addition of lapatinib significantly improved PFS for this patient subgroup and augments data supporting interaction between steroid hormone and peptide hormone signaling. A prospective study validating this hypothesis is required.

Introduction

The challenges in novel drug development in cancer medicine are clear: although many molecular targets have been identified, predicting which patients will benefit from inhibiting those targets remains critical. With the exception of HER2-directed therapies, the integration of HER family inhibitors into clinical practice for breast cancer has been elusive (1). Clearly, HER2 amplification is a well-validated predictive marker for response to the small-molecule dual epidermal growth factor receptor (EGFR)/HER2 inhibitor lapatinib (2) and the humanized monoclonal antibody trastuzumab (3). However, the role of the EGFR/HER1, its ligands, and coreceptors in breast cancer remains undefined. Of the other HER family members, EGFR has been aggressively pursued with both small molecules (erlotinib, gefitinib, and lapatinib) and monoclonal antibodies (cetu ximab) with disappointing efficacy (1). These results lead us to believe that (i) EGFR does not play a critical role in the pathogenesis of breast cancer and therefore is not an important therapeutic target in breast cancer; (ii) the available inhibitors are insufficient in blocking EGFR signaling in breast tumors; or (iii) the population of breast cancer patients with EGFR-driven disease is smaller than expected and a biomarker for patient selection is required.

The interplay between steroid hormone signaling and peptide growth factor signaling through the HER family is well described in breast cancer (4). Both expression of EGFR and HER2 amplification have been reported to...
Translational Relevance

The biologic role of the HER family in breast cancer is well established in the setting of HER2 amplification. In this study, we hypothesized that there is a population of postmenopausal women with hormone receptor–positive, HER2-negative metastatic breast cancer (MBC) that could benefit from the addition of lapatinib, a dual epidermal growth factor receptor (EGFR) and HER2 inhibitor. We performed a quantitative assessment of estrogen receptor (ER) and progesterone receptor (PgR) expression in a blinded retrospective review of clinical samples from a large randomized study of lapatinib plus letrozole versus letrozole/placebo. We identified that patients with tumors that had lower expression of ER by H-score had a significant improvement in progression-free survival with the addition of lapatinib to letrozole. These data may help identify a population of patients with ER+, HER2-negative MBC that might benefit from HER pathway targeting, and provide a hypothesis and potential selection criteria for future studies in non–HER2-amplified MBC.

Low ER Expression as a Predictor of Response to Lapatinib

Previous biomarker work by our group identified a correlation between quantitative hormone receptor measurements and response to lapatinib and paclitaxel in a cohort of women with advanced breast cancer (10). Although there were 493 patients evaluable in this study overall, unlike the current study, that focused on estrogen receptor (ER)–positive breast cancer, the prior study accrued all subtypes of breast cancer, including hormone-positive and -negative, HER2 amplified, and "triple-negative." As a result, the number of samples in any given biomarker-defined cohort was small, thereby limiting the conclusions. This study did not identify any relationship between response to lapatinib and EGFR expression by immunohistochemistry (IHC). In addition, other studies have suggested a relationship between peptide growth factor signaling and hormone receptor status (11), specifically, that progesterone receptor (PgR) loss in ER-positive disease is associated with higher expression of EGFR and/or HER2. In addition, a presurgical study demonstrated cell-cycle inhibition in ER-positive and PgR-weak or PgR-negative patients with breast cancer who were exposed to a short course of the EGFR inhibitor gefitinib (12). The EGF30008 study provides the largest prospective cohort to date of a HER family inhibitor in HER2-negative metastatic breast cancer (MBC). To further test the hypothesis that semiquantitative ER and PgR measurements are molecular markers for EGFR dependence, we performed a blinded, retrospective analysis of ER and PgR in HER2-negative breast cancer in the EGF30008 cohort. EGFR expression was not studied in this cohort based on the lack of any predictive value in earlier studies.

Materials and Methods

Patient selection

The eligibility criteria and study design for EGF30008 (NCT00073528) have been reported previously (Fig. 1; ref. 9). Briefly, after informed consent, 1,286 women with advanced postmenopausal hormone receptor–positive breast cancer (stage III or IV) previously untreated in the metastatic setting were randomized to receive oral letrozole 2.5 mg daily with either oral lapatinib 1,500 mg daily or placebo. Hormone receptor–positive was determined per the enrolling site and HER2 status was determined in a commercial laboratory in primary or metastatic sites defined as either FISH-positive, 3+ staining by IHC, or 2+ by IHC and confirmed HER2 FISH–positive.

ER and PgR staining

Tumor specimens from pretreatment or archival tumor biopsies were available for ER and PgR (n = 821/952; 86.2% of the HER2-negative patients) determination. Of these 821 samples, 688 were from the primary tumor. Paraffin-embedded tumor blocks were cut to 4 μm and mounted on slides, deparaffinized, and rehydrated through a series of graded alcohols. Endogenous peroxidase was quenched with 3% H2O2 in PBS. Antigen retrieval was performed for the ER only by placing slides in 0.1 mol/L citrate buffer pH16 in a steam bath for 1 hour
and allowing them to cool for 20 minutes after. Slides were blocked with 10% normal goat serum (NGS) in PBS at room temperature for 1 hour, and then primary antibody was applied for 1 hour at room temperature. Both ER 1D5 (Immunotech) and PgR 636 (Dako) antibodies were used at 1:50 dilution (10 μg/mL) in 10% NGS. Slides were washed in PBS, followed by secondary antibody (Dako Polymer Envision Plus; Dako) for 30 minutes at room temperature. The chromogen used was diaminobenzidine, and slides were counterstained with ethyl green, passed through butanol, and dehydrated in xylene before mounting. Negative controls consisted of eliminating primary antibody, and positive controls were known ER-positive or PgR-positive cell lines that were pelleted, embedded, and cut. Known positive human tumors were used as well. Controls were included in each staining batch. In a blinded fashion, the samples were read and scored by light microscopy. All slides were reviewed by a single pathologist (MFP).

Calculation of H-score for ER and PgR

Semiquantitative evaluation of ER and PgR was calculated using the H-score. Tissue was scored (H-score) based on the total percentage of positive cells and the intensity of the staining (1+, 2+, or 3+), in which H = (% 1+ × 1) + (% 2+ × 2) + (% 3+ × 3). The sample was considered “negative” if H = 0 and “positive” if H > 0. A minimum of 100 cells were evaluated in calculating the H-score. Samples were grouped in quartiles based on the H-score and analyzed as quartile 1 (Q1), quartiles 2 and 3 (Q2/3), and quartile 4 (Q4).

HER2 testing by FISH

Initially, HER2 testing was performed by a commercial laboratory at enrollment. A total of 219 tissues were HER2-positive, 952 were HER2-negative, and 115 were HER2-unknown. If additional tissue was available (n = 326), HER2 status was also confirmed in an academic laboratory. In the academic laboratory, FISH assays were performed in a blinded fashion using the HER2 PathVysion FISH assay (Abbott Laboratories). FISH signals were determined by enumeration of red HER2 signals and green chromosome 17 centromere in each of at least 20 interphase carcinoma cell nuclei, as described elsewhere (13, 14) and as approved by the U.S. Food and Drug Administration. Enumerations were performed by a clinical laboratory scientist or technician and confirmed by a board-certified pathologist.
Samples with a HER2:CEP17 ratio of 2.0 or more were considered FISH-positive.

Statistical analysis

The primary population for this biomarker analysis was the EGF30008 HER2-negative intent-to-treat (ITT) population, defined as all randomized patients regardless of whether they received study medication. The primary endpoint in EGF30008 was investigator-assessed PFS (defined as time from randomization until the earliest date of disease progression or death by any cause) in the HER2-negative population. PFS in the ITT hormone receptor–positive population was a secondary endpoint. Kaplan–Meier curves were generated for PFS and used to calculate median PFS. Estimates of treatment HRs based on log-rank tests and 95% CIs were calculated. Treatment analysis was performed for hormone receptor status and PFS. Figure 3 shows the Kaplan–Meier curves for three groups of ER expression: Q1 (H-score < 160; n = 206), Q2/3 (H-score ≥160 and <250; n = 389), and Q4 (H-score ≥250; n = 226). For the patients in Q1, there was a significant improvement in PFS for patients receiving letrozole and lapatinib compared with those receiving letrozole and placebo (n = 206; 13.6 vs. 6.7 months; P = 0.01; HR, 0.65; 95% CI, 0.47–0.91; Fig. 3A). For patients with higher intratumoral ER expression, there was no benefit from the addition of lapatinib to letrozole: Q2/3 (n = 389; 13.6 vs. 14.2 months; P = 0.77; HR, 0.96; 95% CI, 0.75–1.23; Fig. 3B) and Q4 (n = 226; 11.2 vs. 14.2 months; P = 0.58; HR, 0.1.09; 95% CI, 0.79–1.51; Fig. 3C). Of note, the control group in the Q1 group had a worse outcome with letrozole and placebo than the other quartiles and the entire ITT population. The median PFS with the addition of lapatinib in this group of patients was similar to the median PFS of letrozole alone patients in the higher ER quartiles (13.6 months vs. 14.2 months, respectively). The association between PgR expression and response to letrozole and lapatinib was not significant for any of the quartiles examined (Fig. 4).

Results

Patient characteristics

Patient characteristics have been presented previously (Supplementary Table S1; ref. 9). Both treatment arms were well balanced on the basis of several clinical parameters.

Hormone receptor status and response to lapatinib in hormone receptor–positive, non–HER2-amplified MBC

We analyzed PFS in patients with non–HER2-amplified disease as a function of ER and PgR expression, using the H-score. ER and PgR expression in the non–HER2-amplified, hormone receptor–positive population is shown in Fig. 2. As hypothesized, we sought to determine if there was a subgroup of patients, based on ER and PgR expression, that benefited from the addition of lapatinib to letrozole. Blinded to clinical outcomes data, Kaplan–Meier analysis was performed for hormone receptor status and PFS. Figure 3 shows the Kaplan–Meier curves for three groups of ER expression: Q1 (H-score < 160; n = 206), Q2/3 (H-score ≥160 and <250; n = 389), and Q4 (H-score ≥250; n = 226). For the patients in Q1, there was a significant improvement in PFS for patients receiving letrozole and lapatinib compared with those receiving letrozole and placebo (n = 206; 13.6 vs. 6.7 months; P = 0.01; HR, 0.65; 95% CI, 0.47–0.91; Fig. 3A). For patients with higher intratumoral ER expression, there was no benefit from the addition of lapatinib to letrozole: Q2/3 (n = 389; 13.6 vs. 14.2 months; P = 0.77; HR, 0.96; 95% CI, 0.75–1.23; Fig. 3B) and Q4 (n = 226; 11.2 vs. 14.2 months; P = 0.58; HR, 0.1.09; 95% CI, 0.79–1.51; Fig. 3C). Of note, the control group in the Q1 group had a worse outcome with letrozole and placebo than the other quartiles and the entire ITT population. The median PFS with the addition of lapatinib in this group of patients was similar to the median PFS of letrozole alone patients in the higher ER quartiles (13.6 months vs. 14.2 months, respectively). The association between PgR expression and response to letrozole and lapatinib was not significant for any of the quartiles examined (Fig. 4).

Confirmation of HER2 status in the ER-low population

The inverse association between HER2 amplification and hormone receptor levels is well established (15). Given the benefit of letrozole and lapatinib in the HER2-amplified cohort and previous discrepancies with commercial HER2 testing (16, 17), we sought to independently confirm the HER2 status of those patients...
found to be HER2-positive in the academic laboratory. Only 1 patient of the 326 evaluated was available for confirmatory HER2 testing in an academic laboratory. This finding supports the observations that low ER expression and benefit from the addition of lapatinib to letrozole in non–HER2-amplified MBC are not a reflection of false negatives.

designated as low ER (Q1) to avoid the erroneous conclusion that patients in Q1 were benefiting because of misclassification of HER2 status. A total of 326 blocks were available for confirmatory HER2 testing in an academic laboratory. Only 1 patient of the 326 evaluated was found to be HER2-positive in the academic laboratory when initially determined to be HER2-negative in the commercial central laboratory.

**Figure 3.** Quantitative ER and response to lapatinib in women with non–HER2-amplified cancer. Response to lapatinib was examined by ER quartile: A, ER Q1: H-score <160; B, ER Q2/3: H-score ≥160 and <250; and C, ER Q4: H-score ≥250. There was a significant improvement in PFS for those patients in ER Q1 receiving letrozole + lapatinib (Let + Lap) versus letrozole + placebo (Let + Pbo).

<table>
<thead>
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<td>Events, n</td>
<td>72</td>
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<td>HR (95% CI)</td>
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<td>P</td>
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**Figure 4.** Quantitative PgR and response to lapatinib in women with non–HER2-amplified cancer. Response to lapatinib was examined by PgR quartile: A, PgR Q1: H-score <40; B, PgR Q2/3: H-score ≥40 and <220; and C, PgR Q4: H-score ≥220. There was no significant relationship between PgR level and benefit for those patients receiving letrozole + lapatinib (Let + Lap) versus letrozole + placebo (Let + Pbo).

<table>
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<td>HR (95% CI)</td>
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<th>Let + Pbo</th>
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<td>Median, months</td>
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<td>109</td>
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<td>HR (95% CI)</td>
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<td>P</td>
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Hormone receptor status and prior endocrine therapy and response to lapatinib in HER2-negative patients

As mentioned, a preplanned Cox regression analysis identified prior antiestrogen therapy as a significant factor in the HER2-negative population and, a nonsignificant trend toward prolonged PFS for letrozole and lapatinib was seen in patients who experienced relapse ≤6 months since their prior tamoxifen discontinuation (HR, 0.78; 95% CI, 0.57–1.07; P = 0.117). To determine if the classification by ER expression and findings on the Q1 benefit from letrozole and lapatinib was a method to identify patients with hormone-resistant disease (i.e., experienced relapse <6 months since their prior tamoxifen discontinuation), we analyzed the distribution of ER expression by prior antihormone treatment. Figure 5 shows the breakdown of ER quartiles by previous treatment. As observed, there is equal distribution of ER expression subgroups whether patients relapse in <6 months, ≥6 months or more, or never received antihormone treatment.

Discussion

The role of HER family inhibitors in the treatment of HER2 normal MBC is undefined. Despite years of evidence alluding to the critical role of the HER family in breast cancer growth and development, only HER2 has been shown to be a clinical useful biomarker (9, 17–19). Preclinical studies have suggested a role for HER family signaling in the development of estrogen independence (4), resistance to antiestrogen therapy (5), and have identified several mechanisms for cross-talk between ER signaling and peptide growth factor signaling (20). In addition, clinical evidence suggests a role for increased HER signaling in de novo and acquired resistance to hormone therapies (4). Given the ability of the tyrosine kinase inhibitors and antibodies evaluated in this area to successfully interact with their target, we concluded that either the HER family is not important in this group of patients or a predictive marker is required to identify these patients. In this article, we identified that low ER expression is a biomarker for benefit to letrozole and lapatinib in a large, blinded, retrospective, hypothesis-driven analysis of patients with non–HER2-amplified MBC treated in a randomized prospective study of letrozole and lapatinib versus letrozole and placebo. This analysis identified the low ER group as having an H-score less than 160 by using quartiles as a cutoff and was enough to enrich for a population that benefits from the combination therapy. H-score was used in these analyses, rather than the Allred score, given its broader dynamic range.

Recent data have identified low ER expression as a marker of resistance to antihormone therapy. In a biomarker analysis of the adjuvant arimidex, tamoxifen, alone, or in combination study, using a similar approach to quantitate ER and PgR using the H-score, low ER expression was identified to be associated with a higher risk of relapse (21). On the basis of that observation, and the observation in this cohort treated in the control arm with letrozole and placebo, women with lower intratumoral ER expression had a much shorter PFS than women with higher ER expression (6.7 months vs. 14.2 months), suggesting that low ER expression may be associated with less steroid hormone dependence. Therefore, it is possible that the low ER group is not steroid dependent and the disease is driven by peptide hormone (HER) signaling based on the significant benefit in this study with the addition of lapatinib. Furthermore, given the reported inverse relationship between ER expression and HER2 amplification (15), we independently confirmed that this cohort was benefiting not because they were HER2-amplified due to poor HER2 testing, but, in fact, because this response is truly independent of HER2 amplification. However, because we analyzed only a single tissue block in each case, we cannot exclude the possibility that some population of these breast cancers were heterogeneous with regard to HER2 gene amplification status.
Data before the development of the EGF30008 trial indicated that cross-talk between the HER family and steroid receptor family was important in breast cancer development and associated with the development of hormone resistance with worse outcomes (22). Our previous analysis of EGF30001 (NCT00075270), a randomized trial of paclitaxel and lapatinib versus paclitaxel and placebo, enrolled both ER-positive and -negative patients with advanced breast cancer. As with EGF30008, there was no benefit to adding lapatinib in a HER2-unselected population. An analysis of quantitative ER and PgR expression identified that women with ER-positive disease and low PgR expression may derive benefit from the addition of lapatinib. This finding was consistent with other data sets suggesting that low PgR expression may be an indicator of EGFR and/or HER2 dependence (10, 11). However, the biomarker evaluation of EGF30001 was limited by the small subsets available for analysis. Similarly, this study identified that low hormone receptor levels were associated with benefit from lapatinib; in the current study, low ER was associated with benefit, but PgR was not. Although this might seem to contradict the prior findings that suggested that low PgR expression was associated with response, it is important to remember the cohorts were significantly different: EGF30001 combined lapatinib with paclitaxel, unlike EGF30008, which evaluated letrozole. In addition, EGF30001 resulted in smaller subsets of patients as it also enrolled ER-negative patients. Furthermore, approximately 50% of the patients in the current study received prior tamoxifen before treatment with letrozole, which may have impacted the effect of the PgR predictive value. One of the strengths of the current analysis is that, even after the subsets were identified, there were still more than 200 patients in each group. It is also important to note that the majority of samples in this study were from original breast surgeries, not newly acquired biopsies of the metastatic site, suggesting that, in the first-line metastatic setting, material may still be adequate to predict response to therapy. The fact that all of the samples were scored for ER and PgR expression by a central pathologist may have mitigated the discordance in ER and PgR testing described in other studies.

A recent retrospective analysis was conducted for two prospective randomized studies (total number was approximately 289) of the EGFR tyrosine kinase inhibitor gefitinib in a similar population of women with hormone receptor–positive, HER2-negative breast cancer. One study evaluated anastrozole and placebo versus anastrozole and gefitinib, and the second study evaluated tamoxifen and placebo versus tamoxifen and gefitinib. The analysis suggested that hormone therapy–naïve patients did better with gefitinib than placebo as compared with those previously treated with hormone therapy (23). This was after no significant differences were found in the overall populations. This observation was not identified in EGF30008, in which, in fact, there was a trend to benefit in patients that had early relapse after tamoxifen. A quantitative analysis of steroid hormone receptors was recently published, and, in support of our observation, there was greater benefit with gefitinib in patients who had lower levels of ER protein (24).

These clinical studies support an interaction between hormone receptor signaling and HER family signaling. Biologically, these two pathways are linked by common downstream effector molecules. Laboratory studies have tied both pathways to the phosphoinositide 3-kinase (PI3k)/AKT/mTOR and mitogen—activated protein Kinase (MAPK) pathway (25). These include both ligand-dependent and -independent mechanisms of ER activation. It can be hypothesized that in the low ER tumors, that HER family signaling is driving proliferation through these pathways. The poor outcome with letrozole and placebo in the low ER expressing group (as compared with those tumors that have higher ER expression) could be explained by the estrogen-independent activation of ER and other growth promoting signals by the HER family. The addition of lapatinib to this cohort could abrogate these endocrine escape mechanisms and explain the benefit seen in the low ER group.

There are ongoing studies evaluating HER family inhibitors in combination with anthorone treatment in HER2-negative cohorts (NCT01068704 and NCT01151215). Given the disappointing results to date, the likelihood of a positive effect in an otherwise unsellected population is not high. The data presented here suggest that the low ER population of HER2-negative patients may be the most likely to benefit from the addition of lapatinib to letrozole. Based on these data and the other studies mentioned above, it is hypothesized that lapatinib's activity in this population is from its anti-EGFR effects. Lapatinib does have anti-HER2 activity; however, HER2-directed therapies have never demonstrated clinical activity in MBC outside of HER2 amplification. Using routine IHC techniques, we were able to quantitate hormone receptor expression and identify that this group of patients does poorly with letrozole alone as compared with patients with higher ER. In addition, this group gained a significant benefit with the addition of lapatinib. These data continue to build on previous data suggesting that a marker to identify HER-dependent patients, in the absence of HER2 amplification, is a qualitative measurement of hormone receptors using the H-score. Formal confirmation of these observations will require a prospective study.

Disclosure of Potential Conflicts of Interest
R.S. Finn is a consultant/advisory board member for GlaxoSmithKline, M.F. Press is a consultant/advisory board member for GlaxoSmithKline, Roche, Biocartis, Halozyme, Cepheid, and Amgen, and has received a commercial research grant from Roche. L. O’Rourke is Clinical Development Manager and has ownership interests (including patents) in GlaxoSmithKline. A. Florance has ownership interests (including patents) in GSK stock. C. Ellis is a manager and has ownership interests (including patents) in GlaxoSmithKline. A. Martin has ownership interests (including patents) in GlaxoSmithKline. S. Johnston is a consultant/advisory board member for GlaxoSmithKline/Novartis and has honoraria from speakers’ bureaus from Roche/GSK. J. Dering has no potential conflicts of interest to declare.

Authors’ Contributions

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Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): R.S. Finn, M.F. Press, S. Johnston

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): R. S. Finn, J. Dering, A. Florance, C. Ellis, A.-M. Martin, S. Johnston

Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): L. O’Rourke, S. Johnston

Writing, review, and/or revision of the manuscript: R.S. Finn, M.F. Press, J. Dering, L. O’Rourke, A. Florance, C. Ellis, A.-M. Martin, S. Johnston

Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): L. O’Rourke, S. Johnston

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Positive, HER2-Negative Metastatic Breast Cancer

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