IMPORTANCE The value of the intrinsic subtypes of breast cancer (luminal A, luminal B, human epidermal growth factor receptor 2 [currently known as ERBB2, but referred to as HER2 in this study]-enriched, and basal-like) in the metastatic setting is currently unknown.

OBJECTIVE To evaluate the association of the intrinsic subtypes of breast cancer with outcome and/or benefit in hormone receptor (HR)-positive metastatic breast cancer.

DESIGN, SETTING, AND PARTICIPANTS Unplanned retrospective analysis of 821 tumor samples (85.7% primary and 14.3% metastatic) from the EGF30008 phase 3 clinical trial (NCT00073528), in which postmenopausal women with HR-positive invasive breast cancer and no prior therapy for advanced or metastatic disease were randomized to letrozole with or without lapatinib, an epidermal growth factor receptor (EGFR)/HER2 tyrosine kinase inhibitor. Tumor samples were classified into each subtype using the research-based PAM50 classifier. Prior neoadjuvant/adjuvant antiestrogen therapy was allowed. Patients with extensive symptomatic visceral disease were excluded. Treatment effects were evaluated using interaction tests.

MAIN OUTCOMES AND MEASURES Primary and secondary end points were progression-free survival and overall survival.

RESULTS The median (range) age was 62 (31-94) years. Intrinsic subtype was the strongest prognostic factor independently associated with progression-free survival and overall survival in all patients, and in patients with HER2-negative (n = 644) or HER2-positive (n = 157) diseases. Median progression-free survival differed across the intrinsic subtypes of clinically HER2-negative disease: luminal A (16.9 [95% CI, 14.1-19.9] months), luminal B (11.0 [95% CI, 9.6-13.6] months), HER2-enriched (4.7 [95% CI, 2.7-10.8] months), and basal-like (4.1 [95% CI, 2.5-13.8] months). Median OS also differed across the intrinsic subtypes: luminal A (45 [95% CI, not applicable {NA}] months), luminal B (37 [95% CI, 31-42] months), HER2-enriched (16 [95% CI, 10-NA] months), and basal-like (23 [95% CI, 12-NA] months). Patients with HER2-negative/HER2-enriched disease benefited from lapatinib therapy (median PFS, 6.49 vs 2.60 months; progression-free survival hazard ratio, 0.238 [95% CI, 0.066-0.863]; interaction P = .02).

CONCLUSIONS AND RELEVANCE This is the first study to reveal an association between intrinsic subtype and outcome in first-line HR-positive metastatic breast cancer. Patients with HR-positive/HER2-negative disease with a HER2-enriched profile may benefit from lapatinib in combination with endocrine therapy. The clinical value of intrinsic subtyping in hormone receptor–positive metastatic breast cancer warrants further investigation, but patients with luminal A/HER2-negative metastatic breast cancer might be good candidates for letrozole monotherapy in the first-line setting regardless of visceral disease and number of metastases.
Hormone receptor (HR)-positive metastatic breast cancer consists of a clinically heterogeneous group of tumors with different prognoses and responses to endocrine and chemotherapy.\(^1,2\) Except for human epidermal growth factor receptor 2 (currently known as ERBB2, but referred to as HER2 in this study) status, little is known about its biological heterogeneity and effect on patient outcome. This is important because biomarkers that can guide treatment decisions in this setting are urgently needed.\(^3\) The best treatment approach (ie, endocrine therapy vs chemotherapy) in the first-line setting of HR-positive/HER2-negative disease is unknown and the decision today is based on patient characteristics (eg, age), tumor load (eg, number of metastases), type of metastasis (visceral vs bone only), and prior therapy.\(^3\)

In contrast to metastatic disease, much effort has been made to elucidate the biological heterogeneity of early breast cancer.\(^4,5\) During the past 15 years, studies evaluating global gene expression patterns have identified 4 main intrinsic molecular subtypes of breast cancer (luminal A, luminal B, HER2-enriched [HER2E], and basal-like).\(^6-8\) These entities are associated with distant recurrence and response to endocrine and chemotherapy, even within HR-positive disease.\(^6,7,9\) In fact, patients who have clinically HR-positive/HER2-negative disease with a HER2E gene expression profile (which represents roughly 5% of cases) do not seem to respond substantially, as estimated by Ki67 changes, to neoadjuvant endocrine therapy.\(^10,31\) Although intrinsic profiles are mostly maintained during metastatic progression,\(^10\) their prognostic and predictive value in patients with newly diagnosed HR-positive metastatic disease remains largely unknown.

Despite recent advances in the treatment of HR-positive metastatic breast cancer, resistance to endocrine therapies limits their success.\(^11\) Cross-talk between pathways involving the epidermal growth factor family of receptors, epidermal growth factor receptor (EGFR) and HER2, and HRs has been implicated in resistance to endocrine therapy.\(^2,14\) Lapatinib, a dual tyrosine kinase inhibitor of EGFR and HER2, has improved response rate and median progression-free survival (PFS) in first-line HR-positive breast cancer in combination with letrozole in patients with HER2-negative disease (8.2 vs 3.0 months) but not in those with HER2-negative disease.\(^15\) However, whether patients with HR-positive/HER2-negative disease but with a HER2E gene expression profile benefit from adding lapatinib ditosylate to endocrine therapy is currently unknown.

Here we evaluated, for the first time to our knowledge, the prognostic and predictive value of intrinsic subtypes in tumor samples from EGF30008, a phase 3 randomized clinical trial of endocrine therapy with or without lapatinib in the first-line metastatic setting.\(^15\)

### Methods

**Patient Data**

The eligibility criteria and study design for EGF30008 (NCT00073528) were reported previously.\(^15,16\) Briefly, 1286 patients with advanced postmenopausal HR-positive breast cancer (stage III or IV) previously untreated in the metastatic setting were randomized in a blinded fashion to receive letrozole 2.5 mg daily with either lapatinib ditosylate 1500 mg daily or placebo. Patients were stratified by sites of disease (soft tissue/visceral or bone-only disease) and prior adjuvant antiestrogen therapy (<6 months since discontinuation, ≥6 months since discontinuation, or no prior endocrine therapy). Hormone receptor positivity was determined per the enrolling site, and HER2 status was determined in a commercial laboratory in primary or metastatic sites defined as either fluorescence in situ hybridization (FISH) positive, 3+ staining by immunohistochemical analysis (IHC), or 2+ by IHC and confirmed HER2 FISH positive.\(^17\) Ethical review of the study was performed by the Hospital Vall d’Hebron institutional review board. No additional informed consent was required beyond the original informed consent of the clinical trial.

**Gene Expression Analysis**

A section of the formalin-fixed paraffin-embedded (FFPE) breast tissue was first examined with hematoxylin-eosin staining to confirm the presence of invasive tumor cells and determine the tumor area. For RNA purification (Roche High Pure FFPEt RNA isolation kit), at least 1 to 3 10-μm FFPE slides were used for each tumor specimen, and macrodissection was performed, when needed, to avoid normal breast tissue contamination.\(^18\) A minimum of approximately 150 ng of total RNA was used to measure the expression of 105 breast cancer-related genes and 5 housekeeping genes using the nCounter platform (Nanostring Technologies).\(^19\) Data were log base 2 transformed and normalized using 5 housekeeping genes (ACTB, MRPL19, PSMC4, RPLPO, and SF3A1). Samples with 10 or fewer counts in at least 50% of the genes were removed. Raw gene expression data will be deposited in Gene Expression Omnibus.

**Sample Data and PAM50 Intrinsic Subtyping**

Of the 1286 tumor samples, 916 were profiled and 821 met the minimum criteria for further analysis (eFigures 1 and 2 in the Supplement). Intrinsic subtyping (luminal A, luminal B, HER2E, basal-like, and normal-like) was performed using the...
research-based PAM50 intrinsic subtype predictor as previously described. Proper normalization was evaluated by a principal component loading plot (eFigure 3 in the Supplement). PAM50 subtyping was performed at the Translational Genomic Group at Vall d’Hebron Institute of Oncology by investigators blinded to clinical data.

Statistical Analysis

Estimates of PFS and overall survival (OS) were from Kaplan-Meier curves, and tests of differences used the log-rank test. Univariable and multivariable Cox regression analyses were used to test the independent prognostic significance of each variable. To test the prognostic contribution of the PAM50 subtypes, changes in likelihood ratio (LR) values (χ²) were used to measure and compare the relative amount of additional prognostic information of one variable/score compared with another. To test the predictive value of the PAM50 subtypes, interaction tests between PAM50 subtypes and treatment for PFS were evaluated in univariable and multivariable models. The proportional-hazards assumption was tested on the basis of tests of differences used the log-rank test.

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Results

Clinical-Pathological Characteristics and Subtype Distribution

The clinical-pathological characteristics of the 821 patients with subtype data were well balanced compared with the patients included in the original study (eTable 1 in the Supplement). The median (range) age was 62 (31-94) years, 700 (86%) of the patients had visceral disease, 644 (80%) had HER2-negative tumors, 157 (20%) had HER2-positive disease, and 602 (73%) had experienced relapse at least 6 months since discontinuation of antiestrogen therapy or not received prior endocrine therapy. Similar to the original results, lapatinib therapy showed a significant PFS benefit in patients with HER2-positive disease but not in those with HER2-negative disease (eFigure 4 in the Supplement).

In both HER2-negative and HER2-positive disease, all breast cancer intrinsic subtypes were identified albeit with different proportions (Table 1). Compared with HER2-negative disease, HER2-positive disease had a lower proportion of luminal A tumors (42 [27%] vs 335 [52%]) and a higher proportion of HER2E tumors (45 [29%] vs 16 [3%]). The proportion of luminal B and basal-like tumors remained similar in both HER2 groups (46 [29%] vs 196 [30%] and 6 [4%] vs 21 [3%], respectively). No significant differences in the distribution of the intrinsic subtypes were identified based on number of metastases, type of metastases, and treatment arm. Interestingly, a significant increase in the proportion of nonluminal subtypes (35 of 219 [17%] vs 52 of 602 [9%]; P < .001), mostly HER2E (26 of 37 [70%]), was observed in patients who experienced relapse during adjuvant endocrine therapy or within 6 months of discontinuation compared with those who never received or experienced relapse at least 6 months after completing adjuvant endocrine therapy (data not shown).

Table 1. Distribution of the Intrinsic Subtypes

<table>
<thead>
<tr>
<th>Subtype</th>
<th>All Patients (N = 821)</th>
<th>HER2 Negative (n = 644)</th>
<th>HER2 Positive (n = 157)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luminal A</td>
<td>382 (47)</td>
<td>335 (52)</td>
<td>47 (27)</td>
</tr>
<tr>
<td>Luminal B</td>
<td>244 (30)</td>
<td>196 (30)</td>
<td>46 (29)</td>
</tr>
<tr>
<td>HER2-enriched</td>
<td>61 (7)</td>
<td>16 (3)</td>
<td>45 (29)</td>
</tr>
<tr>
<td>Basal-like</td>
<td>28 (3)</td>
<td>21 (3)</td>
<td>6 (4)</td>
</tr>
<tr>
<td>Normal-like</td>
<td>106 (13)</td>
<td>76 (12)</td>
<td>18 (11)</td>
</tr>
</tbody>
</table>

Abbreviation: HER2, human epidermal growth factor receptor 2 (currently known as ERBB2, but referred to as HER2 in this study).

Prognosis Within HER2-Negative Disease

Survival data were available for 644 patients with HER2-negative disease (eFigure 5 in the Supplement). Compared with the luminal A subtype, the other subtypes showed a significantly worse PFS (Figure 1A) independently of other clinical-pathological variables (Table 2). When other clinical-pathological variables were held constant, patients with luminal B, HER2E, and basal-like subtypes had a 1.457, 2.873, and 2.258 times higher risk of tumor progression, respectively. Median PFS differed across the intrinsic subtypes: luminal A (16.9 [95% CI, 14.1-19.9] months), luminal B (11.0 [95% CI, 9.6-13.6] months), HER2E (4.7 [95% CI, 2.7-10.8] months), and basal-like (4.1 [95% CI, 2.5-13.8] months). Intrinsically defined more prognostic information regarding PFS than any of the other clinical-pathological variables evaluated in the model (LR χ² = 31.589; P < .001) and number of metastases (LR χ² = 15.377; P < .001).

Interestingly, visceral vs nonvisceral disease did not provide independent prognostic information (LR χ² = 0.539; P = .46). Similar results were observed in OS despite only 242 (38%) patients with an event (Figure 1B and eTable 3 in the Supplement). Compared with patients with a luminal A subtype, patients with luminal B, HER2E, and basal-like subtype had a 1.518, 2.528, and 2.338 times higher risk of death, respectively, when other clinical-pathological variables were held constant. Median OS differed across the intrinsic subtypes: luminal A (19.5 [95% CI, 17.2-22.1] months), luminal B (16.9 [95% CI, 14.1-19.9] months), HER2E (7.7 [95% CI, 5.0-13.1] months), and basal-like (4.1 [95% CI, 2.5-13.8] months). Intrinsically defined more prognostic information regarding OS when added to the other clinical-pathological variables (LR χ² = 20.641; P < .001) than any other variable evaluated (eTable 4 in the Supplement), except prior endocrine therapy (LR χ² = 25.686; P < .001). The third most important prognostic variable regarding OS was Eastern Cooperative Oncology Group (ECOG) performance status (LR χ² = 14.426; P < .001).

Prognosis Within HER2-Positive Disease

Survival data were available for 157 patients with HER2-positive disease (Figure 1C). Compared with the luminal A
The other subtypes showed a worse PFS independently of other clinical-pathological variables (Table 3). When other clinical-pathological variables were held constant, patients with a luminal B, HER2E, and basal-like subtype had a 1.471, 1.818, and 4.799 times higher risk of tumor progression, respectively. Median PFS differed across the intrinsic subtypes: luminal A (11.07 [95% CI, 5.72-16.95] months), luminal B (5.55 [95% CI, 3.02-8.25] months), HER2E (4.37 [95% CI, 2.83-8.64] months), and basal-like (3.58 [95% CI, 2.27-NA] months). Intrinsic subtype added more prognostic information regarding PFS when added to the other clinical-pathological variables (LR χ² = 12.328; P = .02) than any other variable evaluated (eTable 5 in the Supplement). The second and third most important prognostic variables regarding PFS were lapatinib treatment (LR χ² = 6.626; P = .01) and ECOG performance status (LR χ² = 5.339; P = .02).

In terms of OS, similar results were observed (Figure 1D and eTable 6 and 7 in the Supplement). Compared with patients with a luminal A subtype, patients with a luminal B, HER2E, and basal-like subtype had a 1.547, 1.913, and 2.919 times higher risk of death, respectively. Overall, median OS differed across the intrinsic subtypes: luminal A (not reached), luminal B (32 [95% CI, 21-NA] months), HER2E (28 [95% CI, 17-NA] months), and basal-like (19 [95% CI, 9-NA] months). Intrinsic subtype added more prognostic information regarding OS when added to the other clinical-pathological variables (LR χ² = 9.955; P = .04) than any other variable evaluated (eTable 7 in the Supplement). The second and third most important prognostic variables regarding OS were prior endocrine therapy (LR χ² = 7.996; P = .005) and number of metastases (LR χ² = 7.187; P = 0.007).

**Benefit of Lapatinib Therapy**

The effect of lapatinib therapy on PFS in patients with HER2-negative disease was evaluated within each intrinsic subtype (Figure 2). Among the different subtypes, only the HER2E
showed a significant benefit from lapatinib therapy in univariate (6.49-month median PFS with lapatinib vs 2.60-month median PFS with placebo; hazard ratio, 0.238 [95% CI, 0.066-0.863]; \( P = .03 \)) and multivariate (lapatinib vs placebo hazard ratio, 0.14 [95% CI, 0.04-0.459]; \( P = .005 \)) analyses. The interaction test between HER2E and treatment was significant in univariate (\( P = .02 \)) and multivariate analyses (\( P = .006 \)).

The effect of lapatinib on PFS in HER2-positive disease was evaluated within each intrinsic subtype (eFigure 6 in the Supplement). All subtypes seemed to benefit to some degree from lapatinib therapy on the basis of the estimate of the hazard ratio. The interaction tests between each subtype and treatment were not statistically significant (data not shown).

**HER2 IHC and FISH in HER2E/HER2-Negative Tumors**

Fifty percent (8 of 16) of samples identified in the EGF30008 trial as clinically HER2E/HER2 negative showed either a lack of HER2 expression by IHC or a +1 score (eTable 8 in the Supplement). Determination by FISH in 6 of these samples showed a HER2/CEP17 ratio of 1.6 or less (eTable 9 in the Supplement). Among the other 8 HER2E/HER2-negative cases with an IHC 2+ score, 6 were tested for ERBB2 gene amplification; all showed a HER2/CEP17 ratio of 1.6 or less (eTable 8 in the Supplement). Thus, the HER2E/HER2-negative cases did not show evidence of ERBB2 gene amplification.

**Discussion**

To our knowledge, this is the first report to evaluate the prognostic and predictive value of breast cancer intrinsic molecular subtypes in postmenopausal patients with HR-positive metastatic disease treated with endocrine therapy with or without lapatinib in the first-line setting. Specifically, our results reveal that (1) all intrinsic molecular subtypes are identified within HER2-negative and HER2-positive diseases, albeit with
different proportions; (2) intrinsic subtype is the most important and independent prognostic factor in this setting, even within HER2-positive disease; (3) 95% of patients with luminal A/HER2-negative disease experienced long PFS periods of 14.1 to 19.9 months with letrozole therapy; and (4) patients with HER2E/HER2-negative disease treated with letrozole may benefit from the addition of lapatinib.

The optimal systemic treatment strategy for patients with newly diagnosed HR-positive advanced/metastatic breast cancer is currently unknown. National Comprehensive Cancer Network or European School of Oncology-European Society of Medical Oncology second international consensus guidelines for advanced breast cancer recommend starting with endocrine therapy but base the decision on clinical parameters such as tumor burden, age, ECOG performance status, disease-free interval, or previous therapies in the adjuvant setting. However, HR-positive disease is clinically and biologically heterogeneous and thus there is an urgent need to identify robust prognostic and/or predictive tumor-based biomarkers to be included with other clinical variables considered in patient management and therapy selection decisions. For example, no predictive biomarker exists to date for novel drugs such as CDRK3/6 and phosphatidylinositol 3-kinase/mammalian target of rapamycin inhibitors that are currently being incorporated earlier in the treatment of HR-positive/HER2-negative metastatic disease in combination with endocrine therapy.

A limited number of studies have evaluated the prognostic value of single pathology-based biomarkers for predicting outcome in the first-line HR-positive metastatic breast cancer setting following endocrine therapy. Delpech and colleagues showed that high baseline Ki67 expression in 241 estrogen receptor (ER) positive primary breast cancers correlated with lower clinical benefit and time to progression on first-line endocrine therapy. Similar results with Ki67 were obtained by Yamashita and colleagues in a series of 73 cases. Moreover, a study of the Southwest Oncology Group evaluated the prognostic value of progesterone receptor expression in 398 patients with ER-positive metastatic breast cancer treated with tamoxifen and showed that high Ki67 or low progesterone receptor expression measured in metastatic tissue of 135 patients with HR-positive disease was correlated with

HER2 indicates human epidermal growth factor receptor 2 (currently known as ERBB2, but referred to as HER2 in this study).
lower time to tumor progression following first-line endocrine therapy. Overall, these data are concordant with our results because proliferation and estrogen regulation are 2 key biological features that distinguish luminal A from nonluminal A molecular subtypes.26

Nonluminal intrinsic subtypes (ie, HER2E and basal-like) represent 3% to 10% of all HR-positive breast cancers.6-8 In patients with HR-positive disease treated with 5 years of adjuvant tamoxifen only, those with HER2E and basal-like subtypes had poor disease-free survival.9 Concordant with this finding, both subtypes had the lowest relative decrease in Ki-67 either at 2 weeks or at 4 to 6 months following neoadjuvant endocrine therapy.10,11 In terms of chemosensitivity, Jimenez and colleagues27 recently evaluated the pathological complete response (pCR) rates of the intrinsic subtypes within 180 patients with HR-positive/HER2-negative disease following anthracycline/taxane-based neoadjuvant chemotherapy. Interestingly, patients with HR-positive/basal-like disease, which represented 7.7% of the population, achieved a pCR rate of 50%, followed by patients with luminal B, HER2E, and luminal A tumors, who achieved a pCR rate of 20%, 14%, and 9%, respectively. Overall, these data, together with our results showing a median PFS of approximately 4.5 months in nonluminal subtypes within HR-positive/HER2-negative disease, suggest that molecular subtype may better represent tumor behavior in the setting of cytotoxic or endocrine therapy than clinical HR assay results.

The observation that patients with HER2E/HER2-negative tumors benefit from lapatinib therapy is intriguing. Our prior work has revealed that HER2E/HER2-negative tumors have genomic and genetic alterations similar to those of HER2E/HER2-positive tumors except for the HER2 amplicon, which is only overexpressed/amplified in those HER2E tumors that are HER2 positive.28 Similar results were obtained in the EGF30008 study when the ERBB2 gene expression was evaluated across the intrinsic subtypes based on clinical HER2 status (eFigure 7 in the Supplement). Thus, the efficacy of lapatinib in the group of patients with HER2-negative/HER2E disease might be due to EGFR inhibition rather than HER2 inhibition, although this will require further investigation.

The present study has several limitations. First, this is an unplanned retrospective analysis of a prospective clinical trial. To minimize bias, we were able to profile almost 2 out of 3 tumor samples from the original population, and this subset had a similar distribution of clinical-pathological variables and a similar outcome behavior to the original study population. In addition, the laboratory that performed and reported the gene expression results for each sample was blinded to clinical data. Second, almost all profiled samples from this data set come from primary tumors rather than metastatic tumor. Although we cannot predict what the findings would have been if the analysis had been done on metastatic samples only, the reality is that metastatic tissues are not always available in clinical practice and thus a biomarker derived from primary tumors is of value, especially if this biomarker remains stable during tumor progression such as the intrinsic subtypes.12 However, further studies are needed to determine the concordance of intrinsic subtyping in primary vs metastatic tissues and the stability of subtype during or after therapy. Finally, in the EGF30008 clinical study, HER2 testing was performed by a high-volume, commercial laboratory to determine HER2 status using standardized testing methods in a single laboratory. Additionally, HER2 status was evaluated by an academic reference laboratory in a limited number of cases from the EGF30008 study population, revealing 93% concordance (eTable 10 in the Supplement).16,17

Conclusions

Hormone receptor–positive disease is biologically heterogeneous and intrinsic subtypes are associated with outcome in a first-line metastatic setting. Patients with HR-positive/HER2-negative disease with a HER2E profile may benefit from lapatinib therapy. The clinical value of intrinsic subtyping in HR-positive metastatic breast cancer warrants further investigation, but patients with luminal A/HER2-negative metastatic disease might be good candidates for letrozole monotherapy in the first-line setting regardless of visceral disease and number of metastases, whereas patients with HER2E/HER2-negative or basal-like/HER2-negative subtypes need other treatment strategies such as chemotherapy or novel targeted drugs.

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