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# Potential biomarkers of long-term benefit from single-agent trastuzumab or lapatinib in HER2-positive metastatic breast cancer

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ABSTRACT

In 2009 a prospective, randomized Phase II trial (NCT00842998) was initiated to evaluate the activity of HER2-targeting agents without chemotherapy (CT) in HER2-positive metastatic breast cancer (MBC) patients. The primary tumors of the patients enrolled in this study offered a unique opportunity to identify biomarkers that could predict durable clinical benefit from CT-free anti-HER2 therapy.

Patients with HER2-positive MBC were randomized to trastuzumab or lapatinib as first-line therapy. CT was added to anti-HER2 therapy in patients failing to achieve tumor regression at the 8-week evaluation and in those progressing at any time. Expression analysis of 105 selected genes was performed from formalin-fixed paraffin-embedded primary tumor samples. The research-based PAM50 intrinsic subtypes were also identified. Additionally, quantitative HER2 (H2T) and p95HER2 (p95) protein expression were evaluated by HERmark® and VeraTag® assay, respectively. Predictors of persistence on protocol (PP) were studied by Cox univariate and multivariate analysis.

Nineteen patients were enrolled. Median overall survival was 43 months and median PP was 3.8 months (0.8–38.8+), with 4 patients (21.1%) persisting on single agent trastuzumab

*Abbreviations:* CT, chemotherapy; total HER2, (H2T); p95HER2, (p95); PP, persistence on protocol; CR, complete remission; PR, partial remission; SD, stable disease; PD, progressive disease; ROR, risk of relapse; OS, overall survival; PFS, progression-free survival; MR, minimal response.

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or lapatinib for longer than 12 mo (14.9–38.8 + mo). Seventeen patients were evaluable for PP. Gene expression analysis revealed that high expression of the 17q12-21 amplicon genes *HER2* and *GRB7*, and the PAM50 HER2-enriched intrinsic profile, were significantly associated with longer PP. Conversely, high expression of luminal-related genes such as *PGR*, *MDM2* or *PIK3CA*, or the PAM50 luminal intrinsic profile correlated with reduced PP. Moreover, increasing H2T/p95 ratio was found to be significantly associated with longer PP (HR 0.56 per 2-fold increase in H2T/p95, $P = 0.0015$).

Our data suggest that patients belonging to the "HER2-enriched" subtype and/or having high H2T/p95 protein expression ratio are exquisitely sensitive to anti-HER2 agents. MBC patients with these tumors could be candidates for studies aimed at establishing chemotherapy-free regimens.



## 1. Introduction

Overexpression and/or amplification of the Human Epidermal Growth Factor Receptor 2 (HER2), found in 15–20% of breast cancers, is associated with adverse prognostic factors (Slamon et al., 1987; Yarden and Sliwkowski, 2001). However, the introduction of trastuzumab, the first monoclonal antibody specifically designed to target HER2-positive (HER2+) breast cancer, has drastically improved the course of this disease both in the metastatic and adjuvant settings (Slamon et al., 2001; Marty et al., 2005; Romond et al., 2005; Piccart-Gebhart et al., 2005). Furthermore, a number of additional compounds that target this receptor, such as the HER2/EGFR tyrosine kinase inhibitor lapatinib, have been found effective in HER2+ breast cancer (Geyer et al., 2006; Cortes et al., 2009; Baselga et al., 2012a; Verma et al., 2012).

Overall, anti-HER2 agents are more effective when combined with chemotherapy (Pegram et al., 2004). However, the few clinical trials of single agent trastuzumab or lapatinib without chemotherapy showed that in the ~25% of patients who responded to treatment, disease control duration approached that observed in trials where anti-HER2 therapy was combined with chemotherapy (Vogel et al., 2002; Gomez et al., 2008). The identification of biomarkers that can predict which patients derive the largest benefit from chemotherapy-free anti-HER2 therapy would, therefore, significantly improve the management of this disease.

On these premises, in 2009 a phase II randomized chemotherapy-free trial was initiated, consisting of first-line therapy with either trastuzumab or lapatinib for previously untreated, HER2-positive metastatic breast cancer patients (HERceptin LAPatinib-HERLAP trial, NCT00842998). Because of slow accrual and emerging data regarding the efficacy of dual HER2 blockade (Blackwell et al., 2012), the HERLAP trial was closed with 19 patients recruited. However, despite this small number of patients, the HERLAP trial population provides a unique opportunity to study predictors of long-term efficacy of single agent anti-HER2 therapy. Here we report our findings based on gene expression and protein expression analyses correlated with benefit from single-agent anti-HER2 therapy.

## 2. Patients and methods

### 2.1. Patient population

The HERLAP study is a randomized, open label, phase II trial. Women with fluorescence *in situ* hybridization (FISH)-proven HER2-amplified metastatic breast cancer not previously treated with chemotherapy and/or anti-HER2 agents for metastatic disease were eligible provided that they had "low burden" disease. This was defined by absence of carcinomatous lymphangitis and, in case of liver metastases, less than one third of the liver volume involved with disease. Baseline left ventricular ejection fraction (LVEF) had to be >55%. Furthermore, performance status (PS) had to be ≤ 2 according to the Eastern Cooperative Oncology Group (ECOG) definition. To be considered for the study women had to have at least one measurable lesion according to the Response Evaluation Criteria in solid Tumors (RECIST) version 1.0 (Therasse et al., 2000). Lymph nodal metastases were allowed if they were the only metastatic sites, provided that their diameter could be measured by a CT scan.

### 2.2. Treatments

After providing written informed consent, eligible patients were randomized to either trastuzumab (8 mg/kg on loading dose, followed by weekly trastuzumab at the dose of 2 mg/kg) or to oral lapatinib at the dose of 1500 mg daily with no interruptions. Treatment was administered for 8 weeks. After the first cycle of therapy (8 weeks), women underwent an imaging procedure to assess tumor response. Women who achieved minimal response (MR, any reduction in the sum of the largest diameters of the target lesions not fulfilling the definition of partial remission-PR), partial PR or complete remission (CR) were allowed to proceed further on single agent therapy for another 8-week cycle. Patients experiencing stable disease (SD) or progressing disease (PD) were considered protocol failures and continued the same anti-HER2 agent and chemotherapy (three weekly docetaxel, weekly paclitaxel, or vinorelbine if they were on trastuzumab, and capecitabine, weekly paclitaxel or vinorelbine if

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