PAMELA: PAM50 HER2-enriched phenotype as a predictor of early-response to neoadjuvant lapatinib plus trastuzumab in Stage I to IIIA HER2-positive breast cancer

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SOLTI
INNOVATIVE BREAST CANCER RESEARCH

BACKGROUND

Shift to dual HER2 blockade for optimal management of HER2-positive early breast cancer

- Overexpression and/or amplification of HER2 occurs in 25-30% of breast cancers and is associated with increased mortality in early-stage disease, decreased time to relapse, and increased incidence of metastases[1-3]
- The efficacy of trastuzumab in different regimens and settings has been well established, including its benefit as neoadjuvant therapy for early HER2-positive disease[4]
- In recent years, the combination of two anti-HER2 agents has generated excellent outcomes:
  - Lapatinib plus trastuzumab in the NeoALTTO study showed a significantly higher pathological complete response (pCR) in the combination arm compared with either trastuzumab or lapatinib in all cases combined with weekly paclitaxel (51.3% vs. 29.5% or 24.7%, respectively; p <0.01 for both)[5]
  - Trastuzumab plus pertuzumab in the NeoSphere trial showed a similar benefit, with pCR for trastuzumab plus pertuzumab and docetaxel being significantly higher (p=0.014) than trastuzumab and docetaxel (45.8% vs. 29.0%)[6]

Is dual blockade enough? Can certain patients be spared of chemotherapy and its associated toxicities?

- Clinical responses from dual HER2 blockade without chemotherapy have been well documented and generated great expectations:
  - One of the arms of the NeoSphere study yielded a 17% (6% for HR-positive, 29% for HR-negative tumors) pCR in the breast for the trastuzumab plus pertuzumab combination alone[6]
  - The TBCRC-006 trial has reported an overall pCR of 28% (21% for ER+ and 36% for ER-negative) with 12 weeks of lapatinib plus trastuzumab[7]
- However, it is unclear which group of patients benefits the most from this strategy

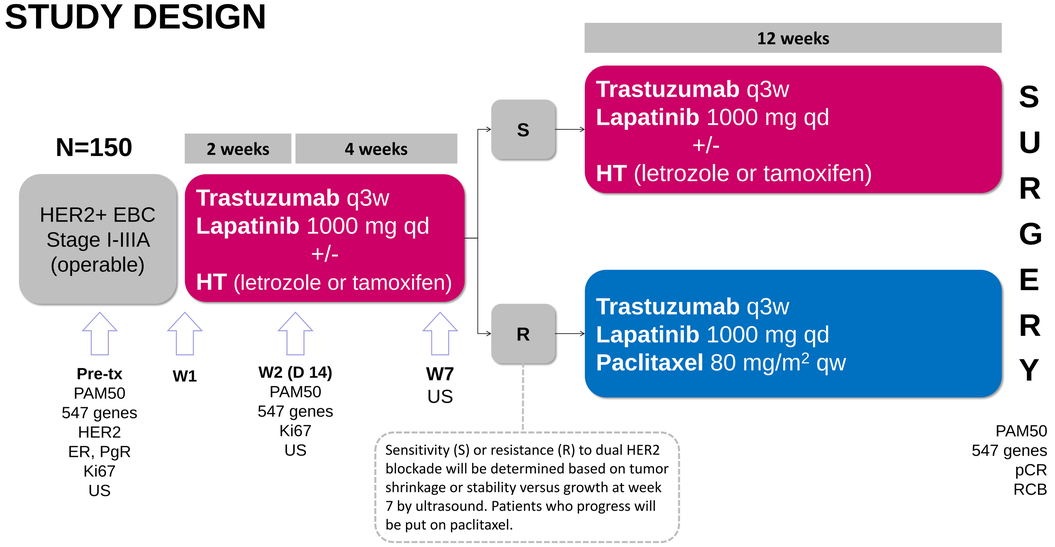
How to best identify those patients?

- Initial gene expression profiling identified four major molecular subtypes of breast cancer: Luminal A, Luminal B, HER2-enriched (HER2-E), and Basal-like. Known as the "intrinsic subtypes", these groups have revealed critical differences in incidence, prognosis and response to treatment[8,9]
- Gene expression profiling can differentiate tumor subtypes based on molecular versus traditional histopathological characterization and has been gaining clinical utility for patient care and treatment decision-making[10,11]
- A clinically applicable assay, known as the PAM50 subtype predictor, has been developed and is expected to be commercially available this year[10]. This assay is performed by measuring the expression of 50 genes using three different platforms (microarray, qRT-PCR and the Nanostring nCounter technology)
- In addition to providing a subtype call, the PAM50 predictor also offers a Risk of Relapse (ROR) score similar to the OncotypeDX recurrence score
- Within HER2-positive breast cancer classified by traditional IHC/FISH, the PAM50 assay identifies a HER2-E intrinsic subtype characterized by high activation of the EGFR/HER2 pathway and therefore should obtain the greatest benefit from anti-HER2 therapy[11]
- Retrospective data have shown that the PAM50 HER2-E subtype and PAM50 ROR groups can predict pCR and event-free survival after trastuzumab-based therapy and can do so independently of hormone receptor status[12]

Hypothesis

The PAM50 HER2-E subtype is a predictor of response to neoadjuvant dual HER2 blockade in HER2-positive early breast cancer. Furthermore, we posit that characterization of gene expression patterns may identify profiles of those who may be safely spared chemotherapy.

STUDY DESIGN



OBJECTIVES

Primary

To evaluate the ability of the PAM50 HER2-enriched (HER2-E) subtype to predict pathological complete response in the breast (pCR_B) to dual HER2 blockade with lapatinib and trastuzumab in all patients at the time of surgery.

Secondary

1. To evaluate the ability of the PAM50 HER2-E subtype to predict pathological complete response in the breast and axilla (pCR_{BL}) to dual HER2 blockade with lapatinib and trastuzumab in all patients at the time of surgery.
2. To evaluate the ability of the PAM50 HER2-E subtype as a continuous variable to predict residual cancer burden in the breast (RCB, 0-I versus II-III) to dual HER2 blockade with lapatinib and trastuzumab, with or without endocrine therapy, at the time of surgery.
3. To evaluate if PAM50 non-Luminal A/B (combined) subtypes benefit from dual HER2 blockade plus endocrine therapy, as measured by the changes in the percent of Ki67-positive cells from Day 0 to Day 14 of treatment.
4. To identify significant gene expression changes from Day 0 to Day 14 after dual HER2 blockade in all patients, in patients with HR-negative disease, and in patients with HR-positive disease.
5. To evaluate if the correlation to the PAM50 HER2-E centroid, as a continuous variable predicts pCR_B and/or RCB to dual HER2 blockade at the time of surgery.
6. To identify additional gene expression signatures beyond the PAM50 subtypes that predict pCR_B and/or RCB to dual HER2 blockade with lapatinib and trastuzumab at the time of surgery in all patients, in patients with HR-negative disease, and in patients with HR-positive disease.
7. To evaluate the ability of the PAM50 risk of relapse (ROR) score to predict pCR_B and/or RCB in the breast to dual HER2 blockade with lapatinib and trastuzumab at the time of surgery in all patients, in patients with HR-negative disease, and in patients with HR-positive disease.
8. To evaluate the ability of the PAM50 HER2-E subtype, or the PAM50 HER2-E signature as a continuous variable, to predict pCR_B to dual HER2 blockade at the time of surgery in patients with HR-negative disease, and in patients with HR-positive disease.
9. To identify gene expression changes from Day 0 to Day 14 after dual HER2 blockade that predict pCR_B in all patients, in patients with HR-negative disease and in patients with HR-positive disease.
10. To determine the safety and tolerability of lapatinib plus trastuzumab, with or without endocrine therapy, when administered in the neoadjuvant setting.
11. To evaluate the ability of the PAM50 HER2-E subtype, or the PAM50 HER2-E signature as a continuous variable, to predict pCR_B to dual HER2 blockade at the time of surgery in patients with HR-negative disease, and in patients with HR-positive disease.
12. To identify gene expression changes from Day 0 to Day 14 after dual HER2 blockade that predict pCR_B in all patients, in patients with HR-negative disease and in patients with HR-positive disease. To evaluate the ability of the PAM50 HER2-E subtype to predict pathological complete response in the breast and axilla (pCR_{BL}) to dual HER2 blockade with lapatinib and trastuzumab, with or without endocrine therapy, at the time of surgery.

- This is a non-randomized, open-label, international multicentric Phase II translational research study of neoadjuvant HER2 blockade.
- 150 patients with untreated, operable primary HER2-positive breast cancer will be enrolled. Central confirmation of the HER2 status is mandatory.
- Patients will be treated with lapatinib and trastuzumab for a total of 18 weeks prior to definitive surgery. Those who are hormone receptor-positive will receive appropriate endocrine therapy according to their menopausal status. Patients who have an ultrasound-confirmed progression at week 7 will have paclitaxel added.
- Breast surgery will be carried out 1-2 weeks after completion of therapy, or 2-3 if paclitaxel was added. The type of breast surgery, the management of the axilla, and any adjuvant therapy deemed necessary will follow local standard practices.
- Baseline, Day 14, and post-treatment (surgical) FFPE tissue will be collected for gene expression and other translational studies
- Intrinsic subtypes will be identified using the PAM50 predictor. The expression of 547 genes will be explored with the nCounter platform. Ki67 IHC will also be evaluated on pre-treatment and Day 14 samples.
- The ability of PAM50 HER2-E subtype to predict response to dual HER2 blockade will be assessed for the primary endpoint.
- The study will have a 95% power to detect a 27% relative difference in the pCR rates (35% in the HER2-enriched group and 8% in the rest) with a significance level of 5% (two-sided) and an assumed rate of biospecimens with insufficient tumor material and/or RNA quality of 15%.

KEY ELIGIBILITY CRITERIA

- Untreated, histologically confirmed invasive breast carcinoma eligible for definitive surgery (Stage I-IIIA), with all of the following characteristics:
  - Primary tumor ≥1 cm in largest diameter
  - CN0-2
  - No evidence of distant metastasis (M0)
- HER2-positive invasive breast cancer by central assessment, defined by ASCO/CAP guidelines
- ECOG performance status of 0 or 1
- Adequate organ function
- Baseline LVEF ≥50% measured by echocardiography or MUGA scan

ACCRUAL

A total of 150 women with primary HER2-positive invasive breast carcinoma eligible for definitive surgery (stage I-IIIA) will be enrolled in this study, including a maximum of 75 HR-positive patients.

Recruitment will start in July 2013 and take place for approximately 18 months. For trial locations and study-related questions, please contact Dr María Vidal at mvidal@vhio.net.

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AKNOWLEDGEMENTS

This study is funded by a grant from GlaxoSmithKline.

ASCO Annual Meeting May 31-June 4, 2013. Chicago, Illinois.

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