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SINOPSYS CLINICAL STUDY REPORT

PAMELA: PAM50 HER2-enriched subtype as a Predictor of Early Response to Neoadjuvant Lapatinib Plus Trastuzumab in Stage I to IIIA HER2-positive Breast CANCER

An open-label, multicenter, non-randomized, applied research study in women with treatment-naive, invasive breast carcinoma, eligible for primary definitive surgery (stage I-IIIA).

Study code: SOLTI-1114

Study development phase: Phase II

Sponsor: SOLTI

EudraCT number: 2013-001036-22

Indication: Stage I to IIIA HER2-positive Breast Cancer

Investigational medicinal product: lapatinib (TYVERB®)

First patient first visit: 28/10/2013

Last patient last visit: 18 June 2016

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Title of Study:

PAMELA: PAM50 HER2-enriched subtype as a Predictor of Early Response to Neoadjuvant Lapatinib Plus Trastuzumab in Stage I to IIIA HER2-positive Breast Cancer

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Publication (reference):

- Maria Vidal, Lorena De La Pena, Mafalda Oliveira et al. (June 2013) PAM50 HER2-enriched (HER2E) phenotype as a predictor of early-response to neoadjuvant lapatinib plus trastuzumab in stage I to IIIA HER2-positive breast cancer. Poster presentation ASCO 2013.
- Maria Vidal, Lorena De La Pena, Mafalda Oliveira et al. (December 2013) PAM50 HER2-enriched (HER2E) phenotype as a predictor of early-response to neoadjuvant lapatinib plus trastuzumab in stage I to IIIA HER2-positive breast cancer. Poster presentation SABCS 2013.
- Llombart-Cussac, A., Cortés, J., Paré, L., Galván, P., Bermejo, B., Martínez, N., ... & Nuciforo, P. (2017). HER2-enriched subtype as a predictor of pathological complete response following trastuzumab and lapatinib without chemotherapy in early-stage HER2-positive breast cancer (PAMELA): an open-label, single-group, multicentre, phase 2 trial. The Lancet Oncology, 18(4), 545-554.

Studied period (years):

2014-2016

Date of first enrolment: Oct 28, 2013

Date of last completed: Nov 26, 2015

Phase of development: phase II

Objectives

Primary objective

- To assess the capacity of the HER2-enriched subtype determined by the PAM50 platform (HER2-E) to predict pathological complete response in the breast (pCRB) to dual HER2 blockade with lapatinib and trastuzumab in all patients at the time of surgery.

Secondary objectives

- To assess the capacity of the HER2-E subtype determined by the PAM50 platform to predict anatomical-pathological complete response in the breast and axilla (pCRBL) to dual HER2 blockade with lapatinib and trastuzumab in all patients at the time of surgery.

- To assess the capacity of the HER2-E subtype determined by the PAM50 platform to predict the residual cancer burden in the breast (RCB, 0-I versus II-III and as continuous variable) with the dual HER2 blockade with lapatinib and trastuzumab in all patients at the time of surgery.
- To assess if the PAM50 non-luminal A/B subtypes (combined) benefit from the dual HER2 blockade plus endocrine therapy, as per the changes in the percentage of Ki67+ cells between days 0 and 14 of treatment.
- To identify significant gene expression variations between days 0 and 14 after dual HER2 blockade in all patients, as well as in those with positive hormone receptors (HR+) and negative hormone receptors (HR-).
- To assess if the correlation between the PAM50 HER2-E phenotype, as a continuous variable, predicts pCRB and/or RCB in the breast with dual HER2 blockade at the time of surgery.
- To identify other gene expression signatures beyond the PAM50 subtypes that predict pCRB or RCB with the dual HER2 blockade with lapatinib and trastuzumab at the time of surgery in all patients, as well as in those with HR+/HR- disease.
- To assess the PAM50 risk of relapse (ROR) score and its ability to predict pCRB and/or RCB in the breast with dual HER2 blockade with lapatinib and trastuzumab at the time of surgery in all patients and in those with HR+ and HR- disease.
- To assess the ability of the HER2-E subtype or of the HER2-E signature as continuous variable to predict pCRB with dual HER2 blockade at the time of surgery in patients with HR+ and HR- disease.
- To identify the changes in the expression profiles from Day 0 to Day 14 capable of predicting pCRB in all patients and in those with HR+ and HR- disease.
- To determine the safety and tolerability of the combination of lapatinib and trastuzumab, with or without endocrine therapy, when administered in the neoadjuvant context.

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Methodology:

Summary

Pamela is an open-label, multicenter, non-randomized, applied research study in women with treatment-naive, invasive breast carcinoma, eligible for primary definitive surgery (stage I-IIIA).

This trial has been designed to test the hypothesis that the PAM50 HER2-E subtype predicts response to neoadjuvant dual anti-HER2 blockade, with or without endocrine therapy, better than the traditional clinical HER2 classification, at the time of surgery in this population. Furthermore, we posit that the characterization of gene expression patterns could identify profiles of patients who may be safely spared chemotherapy.

Screening

Patients will first undergo a screening process, with measurement of the tumor and collection of a tumor biopsy with a thick needle to make a centralized determination of the HER2 and HR status for the purposes of inclusion in the study. These samples will also be used for the determination of gene expression once the patient has been included in the study.

Treatment assignment

After confirming their eligibility, the patients will be included and will be treated with a dual HER2 blockade with lapatinib and trastuzumab, with or without endocrine therapy, for a total of 18 weeks:

- Patients with HR- disease will receive concomitant treatment with lapatinib at a dose of 1000 mg per day and trastuzumab at a loading dose of 8 mg/kg, followed by 6 mg/kg every 3 weeks.
- Patients with HR+ disease will receive letrozole (2.5 mg/day) or tamoxifen (20 mg/day) with concomitant dual blockade consisting of lapatinib at a dose of 1000 mg per day and trastuzumab at a loading dose of 8 mg/kg, followed by 6 mg/kg every 3 weeks.

Procedures and assessments

On day 14 (±5 days) a second biopsy will be performed to assess Ki67 expression by IHC, the PAM50 subtyping and the expression of 547 genes.

Before each administration of trastuzumab, a tumor measurement will be performed through physical examination. A tumor measurement will be performed using ultrasound prior to treatment start (baseline), on day 14 (week 2) and in week 6 (see the study procedures).

If tumor progression is observed, that is, growth of the tumor on the week 6 ultrasound, the tumors will be identified as resistant and paclitaxel (80 mg/m^2 weekly) will be added to the dual HER2 blockade at the same doses. In patients with HR+ disease, endocrine therapy will be withdrawn. The tumor will be reassessed at week 10. If the tumor continues progressing, the decision to finalize the neoadjuvant treatment and to proceed with the surgery will be at the investigator's discretion.

If no variations in the size of the tumor are found, or if radiological response is observed by ultrasound at week 6, the treatment with lapatinib and trastuzumab will be maintained, with or without endocrine therapy, without the addition of paclitaxel until the 18 weeks of treatment are completed.

If tumor progression is suspected at any time, an imaging assessment must be completed to confirm it.

Duration of treatment

The treatment will be administered until the definitive surgery is performed, clinical signs of disease progression appear despite the addition of paclitaxel or unacceptable toxicity occurs or the patient withdraws consent.

Surgery

The surgery of the breast will take place 1 to 2 weeks after completing the dual HER2 blockade, with or without endocrine therapy, and 2 or 3 weeks after completing the treatment with paclitaxel plus the dual HER2 blockade, if it had been started due to disease progression. The type of breast surgery and the treatment of the axilla will be in line with local standard practice. Surgical specimens should be obtained for anatomical-pathological examination.

Post–surgery

Patients should report for a follow-up visit 30 days (±14 days) after the definitive surgery. The adjuvant treatment should be left to the investigator's choice and be in line with the local standards of care.

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Applied research

Samples of tissue from the primary tumor of the breast corresponding to the time prior to treatment (baseline) and day 14 for each patient must be available for molecular characterization. These samples are obligatory. At every timepoint, at least two samples of FFPE tumor tissue will be obtained using a thick needle. A sample will be obtained after the treatment (surgery) in the case no pCR is achieved.

Gene expression will be determined at each timepoint using the NanoString nCounter platform.

Number of patients (planned and analysed):

Between October 2013 and December 2015, a total number of 216 patients were screened and signed the informed consent. Of these, 151 patients were Enrolled into the study. For the remaining 65 patients, the reasons for non-enrolment are listed in table 9 as documented in the CRF End of Selection form.

See table 12 for Patient demographics at baseline.

Diagnosis and main criteria for inclusion:

Inclusion criteria

1. Written informed consent for all study procedures in accordance with the local administrative requirements prior to starting the protocol-specific procedures.
2. Untreated invasive breast carcinoma eligible for primary definitive surgery (stage I-IIIA).
3. Histologically-confirmed invasive breast carcinoma, with the following characteristics:
    a. Primary tumor with diameter ≥ 1 cm.
    b. cN0-2.
    c. Absence of signs of distant metastasis (M0).
4. Invasive HER2+ breast cancer, determined centrally and defined as per the last version of the ASCO/CAP guidelines (available at www.asco.org/guidelines/her2):
    - IHC 3+ based on intense staining of the entire membrane >10% of the tumor cells in a homogeneously populated continuous region;

- Or defined as ISH-positive, either with a probe (≥6 signals/cell of the HER2 gene) or with a dual probe (it is considered HER2+ if: HER2/CEP17 ratio ≥2.0 and an average of ≥4 signals/cell of the HER2 gene; HER2/CEP17 ratio ≥2.0 and <4 signals/cell; and HER2/CEP17 ratio <2.0 and ≥6 signals/cell).

5. In the case of a multifocal tumor (defined as the presence of two or more tumor foci in the same quadrant of the breast), the largest lesion must be ≥ 1 cm, and the "target lesion" must be designated for all subsequent tumor assessments. The HER2 positive status must be documented for all tumor foci.

6. Female patients.

7. Minimum age of 18 years.

8. ECOG performance status of 0 or 1.

9. Adequate organ function, defined as:

   - Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/l.
   - Hemoglobin (Hb) ≥ 10 g/dL.
   - Platelets > 100,000/mm^3.
   - Creatinine ≤ 1.6 mg/dL.
   - ALT and AST ≤ 2.5 times the ULN.
   - Alkaline phosphatase ≤ 5 times the ULN.
   - Total bilirubin ≤ 1.5 mg/dL.

10. Baseline LVEF ≥ 50% measured with ultrasound or equilibrium isotopic ventriculography (MUGA).

11. β-hCG pregnancy test (in serum) negative in premenopausal women of childbearing potential (those biologically capable of having children) and for whom fewer than 12 months have passed since menopause. All patients who are biologically capable of having children should agree and

commit to use a reliable contraceptive method starting 2 weeks prior to the administration of the first dose of the study medication until 28 days after the last dose of the study medication.

12. Absence of psychological, family, sociological or geographical conditions that could potentially hinder compliance with the study protocol and follow-up schedule. These situations must be discussed with the patient before she is included in the study.
13. Availability of sufficient tumor sample or possibility to take a new biopsy for PAM50 analysis. The minimum conditions for performing said genomic analysis is the presence, in 1 tumor block, of 1) at least 1 tumor cylinder with a minimum of 10 mm^2 of tissue area, 2) contain at least 35% of tumor cells, and 3) that there be sufficient tissue to make at least 3 slices 10 µm each.

Exclusion criteria

1. Inoperable breast cancer (stage IIIB, for example, T4 or N3 tumors).
2. Patients with locally advanced disease or in whom the first-line chemotherapy with taxanes and anthracyclines is considered clinically necessary as optimal neoadjuvant treatment.
3. Prior chemotherapy, radiotherapy or surgery for invasive breast cancer, other than excision of tumor in the contralateral breast, and if the patient did not previously receive adjuvant radiotherapy or chemotherapy.
4. Subjects with a concurrently active second malignancy, other than adequately treated non-melanoma skin cancers, *in situ* melanoma or *in situ* cervical cancer. Subjects with other non-mammary malignancies must have been disease-free for at least 5 years.
5. Known or suspected hypersensitivity reaction to any of the investigational or therapeutic products or their incorporated substances.
6. Concomitant congestive heart failure or LVEF <50%.
7. Clinically significant (i.e. active) cardiovascular disease, including cerebrovascular accident (< 6 months before inclusion), unstable angina pectoris, myocardial infarction ≤ 6 months before inclusion, uncontrolled hypertension (systolic > 150 mmHg and/or diastolic > 100 mmHg) or high-risk uncontrolled arrhythmias.
8. Uncontrolled diabetes mellitus, active peptic ulcer disease or uncontrolled epilepsy.

9. Active uncontrolled infection at the time of inclusion.
10. History of significant comorbidities that, in the opinion of the investigator, may interfere with the conduct of the study, the evaluation of response, or with informed consent.
11. Use of any investigational agent or participation in another therapeutic clinical trial concurrently or in the 30 days prior to inclusion.
12. Patients who are pregnant or breastfeeding.
13. Women of childbearing potential who are unable or unwilling to use contraceptive methods.
14. Inability or unwillingness to abide by the study protocol or cooperate fully with the investigator or the designated person.
15. Malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach or small intestine. Subjects with ulcerative colitis are also excluded.
16. Concomitant neoadjuvant cancer therapy (chemotherapy, radiotherapy, immunotherapy, biologic therapy other than the trial treatments).
17. Concomitant use of CYP3A4 inhibitors or inducers.

Duration of treatment:

The treatment with the active study drug will be administered for 18 weeks. An additional 1 to 3 weeks prior to surgery will be required. The total duration of the study per patient will be approximately 21 weeks.

The inclusion of patients will take approximately 18 months.

Reference therapy, dose and mode of administration, batch number:

Patients with HR- disease will receive lapatinib at a dose of 1000 mg per day for 18 weeks and trastuzumab at a loading dose of 8 mg/kg, followed by 6 mg/kg every 3 weeks, for a total of 18 weeks.

Patients with HR+ disease will receive letrozole (2.5 mg/day) or tamoxifen (20 mg/day) for 18 weeks. Lapatinib (1000 mg/day) and trastuzumab (loading dose of 8 mg/kg, followed by 6 mg/kg every 3 weeks) will be administered for a total of 18 weeks.

If tumor progression is observed by ultrasound at week 6, the tumors will be identified as resistant and paclitaxel (80 mg/m^2 once weekly) will be added to the dual HER2 blockade (reducing the dose of lapatinib to 750 mg/day and maintaining trastuzumab at the same dose). In patients with HR+ disease, endocrine therapy will be withdrawn. If no variations in the size of the tumor are found, or if radiological response is observed by ultrasound at week 6, the treatment with lapatinib and trastuzumab will be maintained, with or without endocrine therapy, without the addition of paclitaxel until the 18 weeks of treatment are completed. When progression persists despite the addition of paclitaxel, surgery will be performed.

The medication intended for use in this assay were from the following batches:

Lapatinib	Letrozole	Tamoxifen
122368554	30312	G5
132370978	40380	G6
132371892		N0550
142382738		

Criteria for evaluation:

Efficacy:

- Pathological complete response, defined as the absence of invasive tumor cells in the breast (and in the axillary lymph nodes about the secondary endpoint), and residual cancer burden (0-I versus II-III and as continuous variable).

Safety:

- All safety analyses will be performed in the entire SP. All adverse events (AE) will be classified according to the NCI CTCAE v.4.0.
- Summary of the number (%) of patients with an AE of any type, grade 3-4 AE of any type, SAE of any type, AE of any type causing death, AE of any type requiring a dose reduction, AE of any type requiring a postponement of the dose and AE of any type requiring the permanent discontinuation of the treatment.
- Summary of the number (%) of patients with specific AEs.
- Number (%) of patients who die during the study period (during the study, during treatment) and cause of death (disease progression, adverse events, other).
- The analytical data (hematology, clinical biochemistry, INR) will be graded in line with the NCI CTCAE v.4.0, as applicable. When these criteria are not applicable, an analysis will be performed of the values situated outside of the normal laboratory range. The analytical values will be analyzed after the conversion to standard international units.
- The appropriate summary statistics regarding the analysis of vital signs (that is, weight, blood pressure, heart rate and body temperature), ECOG performance status and the ECGs will be provided.

Statistical methods:

Sample size calculation

The statistical plan is based on the assumption that the rate of pCRB in the clinically HER2+/HER2-E population is 35%, while in the clinically HER2+/non-HER2-E population it stands at 8%. It is assumed that 50% of the patients will be HER2-E.

The study will have a statistical power of 95% to detect a relative difference of 27% in the rates of pCRB, with a 5% (two-tailed) significance levels and assuming a rate of patients with absent or insufficient tumor samples or insufficient RNA quality of 15%. The sample size will be 150 patients and will include up to 75 HR+ patients.

Populations for analysis

Intention-to-treat (ITT) population: will be made up of all the patients included in the study. The statistical analyses will be carried out based on the evaluable and safety populations, defined below.

Evaluable population (EP): will be made up of all patients with RNA available from the initial tumor biopsy and who undergo definitive surgery, as well as the patients who discontinue the study treatment due to disease progression after the dual HER2 blockade, with or without endocrine therapy, or after the dual HER2 blockade in combination with paclitaxel. The primary and secondary endpoints will be analyzed in this population.

Safety population (SP): will be made up of all patients who receive at least one part (even if incomplete) of the study treatment. The secondary safety endpoint will be analyzed in this population.

Molecular biology endpoints

The expression of isolated genes and of each genomic signature will be assessed using the processed and standardized data set. A score will be obtained for the already published genomic signatures, by using the corresponding algorithms and previously published limits (whenever possible). When identifying the different intrinsic subtypes, the published PAM50 algorithm, which classifies the tumors into the following groups, will be applied: luminal A, luminal B, HER2-, basal-like and normal-like. In the tumors classified as normal-like and, given that we consider this category to be very contaminated by normal breast tissue, the RNA will be re-purified and the PAM50 platform will be run again. If a normal-like result is obtained in the second analysis, that sample will be considered non-HER2-E according to the PAM50 platform.

To determine the capacity to predict pCR versus residual disease (RD) or RCB (0-I versus II-III), the expression of isolated genes, the score of each signature and the PAM50 subtypes in the samples prior to treatment and from day 14 will be correlated with the treatment result using different statistical

methods, such as the Student's t-test, logistic regression analysis and area under the ROC curve (aROC). In terms of the signatures assigning samples to more than two groups (that is, PAM50 subtypes and PAM50 ROR groups), the association of each group with the pCR (or RCB) will be assessed using logistic regression analysis.

To determine the capacity to predict the sensitivity to the endocrine therapy plus the dual HER2 blockade, the expression of isolated genes, the score of each signature and the PAM50 subtype will be correlated with the relative variations of Ki67 per IHC between days 0 and 14 using the same statistical analyses as those described above.

To compare the predictive capacity of the subtyping using the PAM50 predictor versus the HR status defined by IHC, the rates of pCR and RD and the rates of RCB between the categories will be compared and the multifactorial logistic regression analysis and the estimates of the aROC will be performed.

Summary - Conclusions

Efficacy results: The primary endpoint was to evaluate the ability of the HER2-E subtype to predict pCR in the breast to dual HER2 blockade with lapatinib and trastuzumab (+/- hormonal therapy) at the time of surgery. Pathological complete response in the breast was defined as the absence of invasive neoplastic cells at microscopic examination of the primary tumour at surgery. Remaining in-situ lesions were allowed.

A pCR in the breast was noted in 46 of 151 women (30,5%, 95% CI 23,4-38,5). Consistent with previous findings, fewer pCRs were noted in tumours that were HR+ compared to those HR-negative (14 [18,2%] of 77 vs 32 [43,2%] of 74; p=0,0015). Among 14 patients who discontinued treatment, 6 had treatment failure (4,0% of 151 patients). Treatment failure occurred in HR+ (n=2) and HR-negative (n=4) disease. Five (83,3%) of 6 patients with treatment failure received neoadjuvant paclitaxel, lapatinib and trastuzumab as per protocol and none achieved a pCR.

The ability of intrinsic subtyping to predict pCR in the breast independently of known clinical-pathological variables, including HR status, was evaluated (Table 13). Among the different clinical-pathological variables evaluated, histological grade, histological type, HR status and intrinsic subtype were significantly associated with pCR. In a multivariable model that included histological grade, histological type, HR status

and intrinsic subtype, the odds ratio of the HER2-E subtype for achieving a pCR was 4,04 (95% CI 1,3–12,5; p=0,016) compared to the non-HER2-E group.

We also evaluated the pCR rates in the breast of the intrinsic subtypes within each HR group. Within HR+ disease, a pCR in the breast was noted in 12 patients of 38 with HER2-E disease (31,6%; 95% CI 18,0-48,8) compared to 2 patients of 39 with non-HER2E disease (5,1%; 95% CI 0,9-18,6). Within HR-negative disease, a pCR in the breast was noted in 29 patients (46%; 95% CI 33,6-58,9) of 63 with HER2-E subtype compared to 3 patients (27,3%; 95% CI 7,3-60,7) of 11 with non-HER2E disease.

Regarding the primary endpoint of the study, a pCR in the breast was noted in 41 patients of 101 with HER2-E subtype (40,6%; 95% CI 31,1-50,8) compared to 5 patients of 50 with non-HER2E disease (10,0%; 95% CI 3,7-22,6). The odds ratio of the HER2-E subtype for achieving a pCR was 6.15 (95% CI 2,3-16,8; p=0.0004) compared to the non-HER2-E group with an absolute difference in pCR between the two groups of 30,6%. This difference is higher than the pre-planned value of 27%. Thus, the primary endpoint of the PAMELA trial was met. Of note, 0 patients of 22 with pre-treatment Luminal A subtype achieved a pCR, and only 1 patient (11,1%) of 9 with pre-treatment Basal-like disease achieved a pCR despite being HR-negative.

Safety results: Six patients (two hormone receptor positive and four hormone receptor negative) had treatment failure during treatment. Most adverse events were of grades 1–2, with the most frequent ones being diarrhoea and rash (table 23). Nearly all of the most frequent adverse events were deemed possibly related to study treatment. The most common grade 3–4 adverse events were diarrhoea, rash, asthenia, and elevated concentration of alanine transaminase. Seven (5%) of 151 patients discontinued study treatment because of grade 3 liver enzyme elevation (n=4), grade 3 diarrhoea (n=2), and grade 3 rash (n=1). 16 (11%) of 151 patients required a dose reduction of lapatinib. No deaths were observed during the study.

Conclusion: PAMELA clinical trial tested prospectively the value of intrinsic molecular subtype in predicting pathological response in HER2+ disease following neoadjuvant dual HER2 blockade with trastuzumab and lapatinib in the absence of chemotherapy. Although this treatment strategy is not ready for clinical

implementation, our results open the door to further studies in HER2+ breast cancer evaluating the long-term survival outcomes of chemotherapy-free dual HER2 blockade after selecting patients based on variables such as intrinsic subtyping, early tumour response and pathological response at surgery.