SYNOPSIS OF CLINICAL STUDY REPORT

ABBREVIATED CLINICAL STUDY REPORT

TITLE: ***A PROSPECTIVE PHASE II STUDY TO EVALUATE ALTERATIONS IN MOLECULAR BIOMARKERS IN HER2-POSITIVE METASTATIC BREAST CANCER TOGETHER WITH ASSESSMENT OF TRASTUZUMAB USE BEYOND PROGRESSION AFTER INITIAL EXPOSURE TO TRASTUZUMAB-TAXANE BASED TREATMENT***

STUDY DRUG: Trastuzumab (Herceptin®)

INDICATION: HER2-positive Metastatic Breast Cancer

PHASE: II

SPONSOR: F. Hoffmann-La Roche Ltd
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CH-4070 Basel, Switzerland

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NAME OF PRINCIPALINVESTIGATOR:
[redacted] MD
[redacted] Australia

REPORT PREPARED BY: [redacted]

RECORDS RETENTION: F. Hoffmann-La Roche Central Records

STUDY DATES:
Initiation: April 9, 2009
Completion: February 18, 2013

REPORT DATE: April 17, 2015

PERSONNELRESPONSIBLE FORCLINICAL ANDSTATISTICAL ANALYSES:
[redacted] M.Sc.
F. Hoffmann-La Roche

GCP COMPLIANCE: This study was conducted in accordance with GCP guidelines.

SYNOPSIS OF CLINICAL STUDY REPORT

Title of Study: A Prospective Phase II Study to Evaluate Alterations in Molecular Biomarkers in HER2-Positive Metastatic Breast Cancer Together with Assessment of Trastuzumab Use Beyond Progression After Initial Exposure to Trastuzumab-Taxane Based Treatment

Phase of Development: II

Study Period: April 9, 2009 to February 18, 2013.

Investigators/Centres and Countries: Eight investigators at sites in Australia, Sweden and the United Kingdom enrolled patients.

- , MD: Australia
- , MD: Australia
- , MD: Australia
- , MD: Spain
- , MD: Sweden
- , MD: Sweden
- MD: United Kingdom
- , MD: United Kingdom

The following sites were initiated for the study, however did not enrol any patients:

- MD: Australia
- MD: , Australia
- MD Australia
- MD: Spain
- , MD and MD: United Kingdom

Publications:

Chan A, Chan S, Price D, et al. Feasibility and patient safety of serial biopsies in metastatic HER2– positive breast cancer to evaluate alterations in molecular biomarkers: preliminary results of SHERsig (study of HER2 Signature in metastatic breast cancer), a prospective phase II study. Cancer Res December 15, 2011; 71(24 Supplement): P5-22-01.

Objectives:

The primary objective of the study was to explore and potentially define molecular biomarker signatures which could alter during HER2 targeted therapy and predict decreased or increased sensitivity to treatment with trastuzumab. Biomarker signatures were to be correlated with the following efficacy end points: Time to Progression (TTP), Progression Free Survival (PFS), and Response Rate (RR) during Part 1 (prior to first disease progression on study) and Part 2 (after first progression on study), based on the Per Protocol (PP) population.

The secondary efficacy objectives of the study were to evaluate:

- TTP, PFS and RR in Part 1 and Part 2 in the Intent-to-Treat (ITT) population
- overall survival (OS) in the ITT and PP populations

The secondary safety objectives of the study were to assess:

- safety of serial biopsies in women with metastatic breast cancer (ITT population)
- safety of the study treatments in Part 1 and Part 2 (Safety population)

The exploratory objectives of the study were to investigate correlations between various evaluated biomarkers as appropriate.

Number of Subjects:

The planned study sample size was 50 patients. Thirty-three patients were registered in the study prior to premature study termination.

Diagnosis and Main Criteria:

The study population consisted of adult females with evaluable metastatic breast cancer (measureable or non-measureable) and at least one metastatic lesion that was amenable to multiple core biopsies. Patients had to have HER2-positive disease and could not have received prior chemotherapy or trastuzumab for metastatic disease nor prior capecitabine for any disease stage.

Study Treatment:

Patients were treated with trastuzumab and either paclitaxel or docetaxel in study Part 1 (until first disease progression on study) and with trastuzumab and capecitabine in study Part 2 (after first disease progression on study). Study treatment was administered according to standard regimens. Treatment after second disease progression on study was according to local standards of care.

Criteria for Evaluation:

Efficacy:

Patients in the PP population were included in the primary efficacy analyses. The PP population consisted of all patients in the ITT population who had received a complete first dose of study medication and had baseline and at least one on-treatment biomarker assessment. Patients in the ITT population consisting of all registered patients were included in the secondary efficacy analyses. Primary and secondary analyses of disease response endpoints were based on ITT and PP population subsets of patients with measureable disease.

Safety:

Patients who had received any study treatment were included in the Safety population. Safety analyses conducted for each of study Part 1 and Part 2 were conducted in Safety population subsets consisting of patients who had received any study treatment in the respective study Part.

Statistical Methods:

The relationship between the primary efficacy parameters and the following biomarker variables was investigated in each of study Part 1 and 2: p95HER2, insulin growth factor-1 receptor, c-MET, phosphatase and tensin homolog gene (PTEN), HER2, phosphatidylinositol-3-kinase (PI3K) catalytic subunit, and FC gamma receptors IIIa, IIa and IIb.

For the primary efficacy analysis, the correlation between the biomarker variables and the efficacy endpoints TTP and PFS were investigated using a univariate Cox regression model and time-to-event methods (Kaplan-Meier). The relationship between the biomarker variables and RR was investigated using frequency tables and a univariate logistic regression model.

The secondary efficacy endpoints were analysed using time-to-event methods (Kaplan-Meier). TTP, PFS, BOR and RR were analysed separately for Part 1 and Part 2, while OS was analysed overall.
For the safety analysis, adverse event (AE) data were summarized by study Part. Cardiotoxicity and biopsy-related AEs were presented separately.

Methodology:

The study consisted of two parts. In Part 1, a blood sample and baseline biopsy (study biopsy #1) was obtained from the most assessable metastatic lesion. Primary breast lesions in patients with metastatic disease and recurring breast lesions were also considered suitable for study biopsies. Within 28 days of study biopsy #1, patients began standard first-line therapy with trastuzumab and a taxane. After the first treatment cycle, selected patients with palpable disease who had not progressed were approached for an additional biopsy (study biopsy #1a). Following six weeks of first-line trastuzumab/taxane treatment (or at disease progression if this occurred earlier), study patients underwent tumour assessment and another biopsy, study biopsy #2A (non-progressing patients, thereafter categorized as Group A) or #2B (progressing patients, thereafter categorized as Group B), was obtained preferably from the same baseline metastatic or breast lesion. Non-progressing patients continued trastuzumab/taxane treatment until disease progression at which point another biopsy was taken of the baseline lesion (study biopsy #3A).

Once patients progressed on first-line study treatment, they went on to Part 2 of the study, wherein they received combined capecitabine/trastuzumab treatment. Capecitabine/trastuzumab was continued until disease progression at which point a final study biopsy, study biopsy #4A or study biopsy #3B, was taken.

Safety Results and Conclusions:

AEs including cardiotoxicity observed in the study were consistent with the known safety profiles of trastuzumab, taxanes and capecitabine. These drugs were administered according to established standard treatment regimens and patients were managed according to local standards of care.
Approximately 1/3 of study patients (10/33) experienced biopsy-related AEs. The severity of these AEs were $\leq$ Grade 2. In most patients (7/10) experiencing biopsy-related AEs, the maximum severity of these AEs was Grade 1.

Efficacy Results and Conclusions:

Conclusions that may be drawn from this study are limited by the small samples sizes in the study overall, within each study group, and between study Parts 1 and 2. As a result, efficacy data discussed in this report are limited to the results of the primary analyses for Group A, Part 1, and the results of the secondary analyses for Group A, Parts 1 and 2.

Among the biomarkers tested, a positive correlation was potentially indicated between p95HER2 positivity and response rate with first line trastuzumab/taxane treatment among patients who did not progress prior to six weeks of such treatment (Group A). Also, a possible trend towards prolonged PFS with the FC gamma receptor IIIa valine/valine phenotype was indicated by results obtained with Group A patients during Part 1. FC gamma receptor IIIa analyses, however, were conducted in a relatively small subset of patients (n=18).

Analyses of other biomarkers tested were not informative. Furthermore, since only one patient progressed prior to six weeks of first line trastuzumab/taxane treatment, comparisons could not be made between patients who progressed early (Group B) and those that did not (Group A) with respect to relationships between efficacy outcomes and biomarker signatures.

A reasonable evaluation of the secondary efficacy endpoints TTP, PFS and OS could be conducted for study patients in Group A. Time-to-event endpoints were lower in Part 2 of the study with a median TTP of 22.21 months in Part 1 versus 5.65 months in Part 2 and a median PFS of 18.60 months in Part 1 versus 5.65 months in Part 2. Median OS was 36.40 months (range 6.57-40.28) in the PP population. Event rates were limited for all time-to-event endpoints. RR also decreased with second line trastuzumab treatment. The RR was 75.0% in Part 1 and 11.1% in Part 2. These results were based on small ITT population subsets with measureable disease at start of treatment (Part 1: n=20; Part 2: n=9).

Date of the Report:
November 27, 2014