TRIO 016 – SUMMARY OF THE CLINICAL STUDY REPORT

Name of Sponsor/Company

CIRG/TRIO

Test Generic Name/Drug Name

Panobinostat

Study Number

TRIO 016

Title

A randomized phase II, open label multicenter trial of panobinostat (LBH589) monotherapy in women with HER2 positive locally recurrent or metastatic breast cancer

Investigator(s), study site(s)

The study was conducted at 28 sites in 4 countries (USA, Canada, France and Belgium). The 29th site (in the UK) was never opened as enrollment was closed prior to the site initiation.

Publication (reference)

Not applicable at this time

Study period (Years)

13 March 2009 (*1st subject randomized*)/ 22 Mar 2010

Phase of the Study

Phase II

OBJECTIVES

Amended Protocol (Amendment 2):

Primary objective

The primary objective of the study was to assess the benefit (objective response rate) of i.v. and oral panobinostat monotherapy using RECIST criteria, version 1.0, as per investigator assessment.

Secondary objectives

The secondary objectives of the study were:

- To evaluate the safety and tolerability profile of i.v. and oral panobinostat monotherapy, with careful monitoring of the QTcF interval

Exploratory objectives

The exploratory objectives for consenting subjects were:

- To evaluate the level of serum-based tumor markers, such as CEA, CA 15-3 or CA 27.29,
- To determine drug concentrations in tumor at time of first response assessment, and
- To analyze whole blood samples at study entry for pharmacogenomics.

Study design

This was an international phase II, open label, multicenter, two-arm, two-stage design study of panobinostat in women with HER2-positive locally recurrent or metastatic breast cancer.

In the first stage of the trial, 21 evaluable subjects per arm would be treated; if less than 3 responses in one of the arms were observed, that arm would be stopped and this treatment would be declared ineffective. If at least 3 responses per arm were observed, subject enrollment in that arm would continue to the second stage of the trial.

If transition to stage 2 occurred, an additional 45 evaluable subjects per arm would be treated for up to a total of 66 evaluable subjects per arm. If less than 11 responses in one of the arms were observed, the treatment in this arm would be declared ineffective. If at least 11 responses per arm were observed, the treatment would be declared effective in the arm(s) where at least 11 responses occurred.

Eligible subjects with measurable locally recurrent or metastatic breast cancer were

randomized in a 1:1 ratio to:

Arm I	Panobinostat i.v.	20 mg/m^2 on D1 and D8 as part of a 21-day cycle
Arm II	Panobinostat oral	40 mg 3 times a week, (i.e., Day 1, 3, and 5 or Monday, Wednesday, Friday [MWF] of a week) given every week as part of a 21-day cycle.

Number of subjects planned/ randomized

A total of 132 evaluable subjects was planned to be randomized.

Four (4) subjects in total were randomized in the study TRIO 016.

Indication

HER2-positive locally recurrent or metastatic breast cancer

Main Inclusion Criteria

Subjects were female 18 years of age or older, Eastern Cooperative Oncology (ECOG) Performance Status of 0, 1 or 2 with histologically or cytologically confirmed invasive breast carcinoma with locally recurrent or radiological evidence of metastatic disease. Those with locally recurrent disease were not eligible for resection with curative intent.

Subjects had to have HER2-positive breast cancer by local laboratory testing and must have received prior trastuzumab (in the neoadjuvant and/or adjuvant and/or metastatic settings) regardless of whether trastuzumab was given as monotherapy or in combination with chemotherapy. Any number of prior trastuzumab regimens was acceptable. Additional treatment with lapatinib after or before trastuzumab treatment was permitted, but not mandatory.

Subject had to present with radiological evidence of relapse or disease progression while on trastuzumab (or lapatinib) or within 12 months of the last dose of adjuvant trastuzumab. Up to 2 prior cytotoxic chemotherapy regimens, in addition to neoadjuvant and adjuvant, for treatment of metastatic or locally recurrent breast cancer (including those cytotoxic chemotherapy treatments in combination with trastuzumab and/or lapatinib) were allowed.

Treatments

Active substance: Panobinostat

Arm I:

Subjects assigned to Arm I received panobinostat i.v. at the dose of 20 mg/m^2 on day 1 and day 8 as part of a 21-day cycle.

Batch #: Y1951107, Y063 0408, U001 0209

Arm II:

Subjects assigned to Arm II received panobinostat oral at the dose of 40mg (3 times a week, i.e., Day 1, 3, and 5 or Monday, Wednesday, Friday [MWF] of a week) given continuously every week as part of a 21-day cycle.

Batch #: 07JM-035, 08JM-262, 07JM-021, 08JM-283

Duration of treatment

Subjects with stable disease, partial or complete response continued on treatment until progression, intolerable toxicity or withdrawal of subject consent.

Criteria for evaluation - Efficacy Parameters

Efficacy was evaluated by calculating the objective response rate according to RECIST version 1.0 using imaging techniques every 9 weeks.

Criteria for evaluation - Safety Parameters

Safety was evaluated by assessing the incidence and severity of Adverse Events (as determined by the NCI CTCAE version 3.0), Serious Adverse Events and any modification from baseline in ECG parameters.

Criteria for evaluation - Exploratory Parameters

Subjects had to give specific consent for participating in the optional exploratory sub-studies:

Biomarker assessments: level of serum-based tumor markers, such as CEA, CA15-3 and CA 27.29, were assessed at cycle 2 day 8 (pre- and postdose), at cycle 4 day 8 (pre- and postdose), at CR/PR confirmation and at end of treatment.

Pharmacodynamic analyses were performed on core tumor biopsy samples obtained prior to study entry and at the time of the panobinostat treatment response is observed.

Exploratory pharmacogenomics analysis using tumor DNA, and blood DNA (extracted from whole blood collected in EDTA tube in consenting subjects)

Statistical methods

Due to the very small number of subjects randomized in this study (4 out of the 132 planned), only descriptive analyses are provided in this report. The planned analyses were not conducted.

Conclusion

Subject recruitment has been much slower than anticipated. The participating investigators noted they see few patients having progressed on trastuzumab therapy. After 8 months of recruitment only 4 subjects were randomized, and the Steering Committee decided to close the study due to a poor accrual rate. The number of subjects randomized in the study was insufficient for statistically relevant conclusions to be drawn on the safety and efficacy profile of panobinostat.