Study Title:

Lapatinib versus Lapatinib with Capecitabine as Second-line Treatment in Her2-Overexpressing Metastatic Gastro-Esophageal Cancer: A randomized phase II trial

Short Title/ Acronym: GASTRO-LAP

Final Study Report

Version Number/ Date:	Final 1.0 / 08.04.2014
Investigational product:	Lapatinib (Tyverb 250 mg® Tablets)
Eudra-CT Number:	2009-009894-88
Sponsor Trial Code	NCT-2008-11-01-1015
Protocol-Number, Version:	Final1.4, 30.03.2010

Sponsor:

University Hospital Heidelberg
represented by its Commercial Director
Ms. Dipl. Volksw. Irmtraut Gürkan
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Study Initiation and Completion Dates:

Date of first enrollment:	10.11.2010
Date of last enrollment:	01.02.2013
Date of last treatment administration:	21.04.2013
Database was closed:	13.03.2014

Synopsis

Name of Sponsor/Company:

University Hospital Heidelberg, represented by its Commercial Director
Ms. Dipl. Volksw. Irmtraut Gürkan
Im Neuenheimer Feld 672
69120 Heidelberg

Name of Finished Product: Tyverb 250 mg® Tablets

Name of Active Ingredient: Lapatinib and Lapatinib combined with Capecitabine

Title of Study:

Lapatinib versus Lapatinib with Capecitabine as Second-line Treatment in Her2-Overexpressing Metastatic Gastro-Esophageal Cancer: A randomized phase II trial

Short Title/ Acronym: GASTRO-LAP

Protocol versions:
Final 1.2, 08.05.2009 (First authorization, 19.08.2009)
Final 1.3, 19.08.2009 (Substantial Amendment, 21.12.2009)
Final 1.4, 30.03.2010 (Substantial Amendment, 25.05.2010)

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Publication (reference):

n.a.

Studied period (years): *incl. interruptions, early terminations and discontinuations*	*Phase of development:*
Date of first enrollment: 10.11.2010 *Date of last enrollment:* 01.02.2013 *Date of last treatment administration :* *21*.04.2013 *Database was closed:* 13.03.2014 Early termination after the inclusion of 37 patients. The decision to stop the trial was taken on medical and scientific reasons and not due to the planned interim analysis or an accumulation of SAE or death.	n/a Phase II

Objectives:

The *primary objective* of the trial was the Objective Response Rate (ORR), defined as complete and partial remission according to RECIST Version 1.1 – all to be confirmed by at least two consecutive tumor response assessments within no shorter than 4 weeks.
Secondary objectives:

- Time to tumor progression (TTP)
- Progression-free survival (PFS) and Overall survival (OS)
- Toxicity and safety (AEs/SAEs)
- Biomarkers for assessing surrogate parameters for a clinical benefit

Methodology:

Phase II open-label, randomized, parallel-arm, non-comparative, two-stage, multi-center clinical trial. It was planned to enrol 76 patients (38 per treatment group) with histologically confirmed HER2-overexpressing metastatic castro-esophageal cancer. The patients were to be randomly assigned on a 1:1 ratio in an open-label fashion into the two treatment groups, lapatinib alone or lapatinib plus capecitabine via a centralized internet randomization system.

Visits schedule:

- Screening: day -28 to day -1, Baseline (day 0)
- Treatment period: every 3 weeks (day one of every cycle) until end of study (EOS)
- Post study period: every 12 weeks until disease progression or death or 6 months after EOS

According to the protocol, one interim analysis was to be conducted after the first 29 patients have been included in each arm. The objective of the interim analysis was to allow the early stopping of the trial in case of an insufficient number of responders (ORR). After accrual of 29 patients in each group, recruitment had to be interrupted, if necessary, until a decision according to the first stage of Simon's design has been reached. Evaluation had to take place after response evaluation of the last patient of the first stage was available. Due to the early termination of the trial no interim analysis was done.
All formally required arrangements for closing this trial and all participating study sites were performed in accordance with legal and regulatory requirements.

Number of patients (planned and analysed):

Number of patients planned: 76
Number of patients analysed: 37

Diagnosis and main criteria for inclusion:

Metastatic patients with histologically confirmed HER2-overexpressing metastatic gastro-esophageal cancer.

Test product, dose and mode of administration, batch number:

Investigational medicinal product (IMP): Tyverb 250 mg, ATC Code: L01XE07
International Nonproprietary Name (INN): Lapatinib

Pharmaceutical formulation: Tablets

Route of administration: oral administration:

Storage conditions: < 30°C

Manufacturer: Glaxo Group Limited, Greenford, Middlesex UB6 0NN, UK

Licence number: EU/1/07/440/001, EU/1/07/440/001/002

Lapatinib were provided free of charge by GlaxoSmithKline GMBH & Co.KG.

Duration of treatment:

The overall duration of the study was expected to be approximately 44 months. The patients were to be followed-up independent from the study after end of the trial until tumor progression.

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

Lapatinib combined to Capecitabine 2000mg/m² po day 1 - 14, which is not regarded as an investigational medicinal product.

Criteria for evaluation:

Efficacy:

- Primary endpoint of the trial was the ORR, (CR or PR) according to RECIST

Secondary endpoints:

- Time to tumor progression (TTP)
- Progression-free survival (PFS) and Overall survival (OS)

Safety:

- Type, severity (graded by the National Cancer Institute, Common Toxicity Criteria for Adverse Events [CTCAE] Version 4.0), seriousness and relatedness of adverse events
- Changes in vital signs, ECG and laboratory data.

Statistical methods:

Sample size:
No formal statistical comparison between the two arms was planned. Sample size was calculated by Simon two-stage minimax design for each study arm. The stipulated working null hypothesis for the ORR was 5% versus an alternative hypothesis of an ORR of 20%. The type I error for each of the two arms in this two-stage design was 5%, and the power was 90%. Under these assumptions, the required sample sizes of the first and second stages were 29 and 9 patients in each arm, i.e. a maximum total patient number of 38 per arm.
Statistical analysis:
Considering the prematurely close of this trial - after the inclusion of 37 patients - any confirmatory statistical analyses were deemed inappropriate. The statistical analysis actually performed was therefore in a strictly exploratory and mainly descriptive manner. All data collected which have value toward assessing the safety, efficacy, or other properties of the drug are reported in either the summary presentations or listings or in both.

Exploratory analysis of the efficacy endpoints:

- Estimates of the response rate (ORR) and exact 95% confidence intervals (CI) were calculated for the percentage of patients with OR according to Pearson-Clopper.
- TTP; PFS and OS: The Kaplan- Meier estimate were used to compute the proportion surviving with the 95% CI, calculated using Greenwood's formula. The treatment group effect is estimated using the log-rank test. The hazard ratio and the corresponding 95% CI are estimated by proportional Hazards regression.

Analysis of the safety data:

AEs were coded according to MedDRA 15.0 and grouped by body system. Summary tables with the number of patients observed with AEs and corresponding percentages were presented. Patient disposition were presented using the CONSORT flow diagram. Summary descriptive statistics were performed for all other data collected i.e. patient characteristics, prior and concomitant medications, vital signs, ECG, study drug administration, extent of exposure and laboratory data.

SUMMARY - CONCLUSIONS

Overall, 65 Patients were screened in 11 centers. Of the 65 screened patients, 37 patients were randomized into the two treatment groups. Originally, 19 patients were randomly assigned to lapatinib alone, and 18 were assigned to lapatinib + capecitabine (cap). Of the 37 patients, only four patients (one lapatinib patient and three Lapatinib + cap. patients) completed the study as per protocol. All other patients have terminated the study prematurely. The statistical analysis consists of all 37 patients. The majority of the patients were males, only 6 patients were females. Adenocarcinoma of the stomach (n=15, 40.5%), or adenocarcinoma of the gastroesophageal junction (n=15, 40.5%) was diagnosed as primary tumor diagnosis. Adenocarcinoma of the esophagus was diagnosed in 7 (18.9%) patients. In 35 of the 37 patients HER2 in FISH or CISH was positive (ratio HER2:CEP7 ≥2). All 37 patients had previous chemotherapy for advanced disease. Previous surgery for the gastro-esophageal cancer had 20/37 (54.1%) patients. Regarding previous surgery there was an imbalance between the two treatment groups (36.8% in the lapatinib group vs. 72.2% in the lapatinib + cap group.
The median duration of treatment with lapatinib was 44 days and with lapatinib + cap 56 days. The majority of the patients had two or three treatment cycles (median=3.0). Patient-days of drug exposure were 974 days in the lapatinib group and 1296 days in the lapatinib + cap group.

EFFICACY RESULTS:

Tumor measurements could be determined at cycle 3, 5, 7, 9, and at EOT. At the last visit during the study only two lapatinib + cap patients showed a PR. SD was reported in three patients (two lapatinib patients and one lapatinib + cap patient). The majority of the patients had a PD (n=25, 83.3%). PD was even more probably in the lapatinib group (n=15, 88.2%) vs. n=10 (76.9%) in the lapatinib + cap group. With respect to ORR, only two patients (11.1%; 95% CI: 1.37 – 34.7) of the lapatinib + cap showed an ORR. Median TTP was 42.0 (95% CI: 38.0 to 61.0) days in the lapatinib group and 83.0 (95% CI: 42.0 to 86.0) days in the lapatinib + cap group, without reaching statistical significance (p-value = 0.07). The results of the other efficacy endpoints (PFS and OS) were comparable in the two treatment groups.

SAFETY RESULTS:

The majority of patients experienced at least one AE (all causalities): A total of 20 patients (10 patients in each group) experienced severe adverse events (CTCAE grade 3 or 4). A total of 14 patients (6 of the lapatinib and 8 of the lapatinib + cap group) experienced serious adverse events. 5 Patients, (26.3%) on lapatinib, and 6 patients (33.3%) on lapatinib + cap discontinued lapatinib due to diverse events. Six patients (33.3%) of the lapatinib + cap group discontinued capecitabine due to adverse events. Six patients (3 patients in each group) had lapatinib dose reductions or temporary discontinuations due to adverse events. Six lapatinib + cap patients had capecitabine dose reductions or temporary discontinuation due to adverse events. Nine patients died due to adverse events (3 in the lapatinib and 6 in the lapatinib + cap group).

A total of 13 patients (68.4%) in the lapatinib group and 14 patients (77.8%) in the lapatinib + cap group experienced at least one treatment related AE: 10 Patients, (5 in each group) experienced severe adverse events (CTCAE grade 3 or 4). Two patients (one patient in each group) experienced serious adverse events. Two lapatinib patients and one lapatinib + cap patient had lapatinib dose reductions or temporary discontinuations due to adverse events. Four lapatinib + cap patients had capecitabine dose reductions or temporary discontinuations due to adverse events. There were no treatment related deaths.

For the other safety data, no relevant group differences were seen.

CONCLUSION:

Due to the early study termination definitive conclusions in regard to the study objectives were deemed inappropriate. An exploratory analysis based on the data of the 37 patients indicated that the lapatinib + cap group tended to show better efficacy results. In contrast, the safety profile of lapatinib + cap was slightly inferior as compared to lapatinib alone.

Substantial amendments / interruptions or early termination:

Protocol versions:
Final 1.2, 08.05.2009
Final 1.3, 19.08.2009: Protocol and Informed Consent adaptions according Ethics Committee requirements (I/E criteria: Creatine clearance rate)
Final 1.4, 30.03.2010: Coordinating investigator moved to another trial centre
Temporary hold of recruitment: 15.03.2013, followed by
Early Termination:
The Gastro-lap trial was terminated early after the inclusion of 37 patients. The last treatment administration was on 21.04.2013. On 24.04.2013 the competent authority, involved ethics committees and local authorities were notified about the trial termination.

Date of the report: 08.04.2014