Study No.: LAP105594

Title: A phase II open label, multicenter study to evaluate the efficacy and safety of daily dose of Lapatinib in advanced breast cancer patients with HER-2 non-amplified primary tumours and HER-2 positive circulating tumour cells or EGFR positive circulating tumor cells

Rationale:
Lapatinib (GW572016) acts as a dual inhibitor of both Epidermal Growth Factor Receptor (EGFR) and ErbB2 tyrosine kinase activity. Lapatinib is thought to react with the Adenosine Triphosphate (ATP) binding site of EGFR/ErbB2, resulting in inhibition of autophosphorylation and subsequent proliferative signalling. This study was designed to investigate the potential clinical activity and safety of Lapatinib in advanced breast cancer subjects with HER-2 non-amplified primary tumours with positive HER-2 or EGFR circulating tumour cells (CTCs).

Phase: II

Study Period: 05 June 2008-01 July 2011

Study Design: Multicenter open-label, phase II study. Subjects were allocated into one of the following two strata: Stratum 1 (Italian Study Group) included advanced breast cancer subjects with HER-2 non-amplified primary tumours and HER-2 positive circulating tumour cells; Stratum 2 (UK Study Group) included advanced breast cancer subjects with HER-2 non-amplified primary tumours and EGFR positive circulating tumour cells. Thus HER-2 positive CTCs were tested by the Italian group and EGFR CTCs were tested by the UK group. Initially 16 subjects in each stratum were to be treated (1st phase); if 1 to 3 responses were observed, 15 additional subjects were to be treated (2nd phase), up to a total of 62 subjects with 31 subjects in each stratum.
Subjects enrolled in this study were treated with oral Lapatinib at the dose of 1500 mg daily on day 1 to 28 every 4 weeks (q 4 weeks).
The study consisted of three study periods: (I) screening (up to 28 days prior to 1st dose) included time from the time point in which eligible subjects signed the informed consent form until confirmation of eligibility from central laboratory based on CTCs ErbB1 and ErbB2 status; (II) treatment , from the 1st study drug dose intake until disease progression, unacceptable toxicity or death whichever occurred first; and (III) follow-up (commencing 28 days from the time of last study drug dose intake), in which post-study survival status was collected every 12 weeks.

Centres: 9 sites in Italy and 1 site in the UK.

Indication: Advanced breast cancer subjects with HER-2 non amplified primary tumours with positive HER-2 or EGFR circulating tumour cells

Treatment: Lapatinib was given orally on an empty stomach (either 1 hour before or 1 hour after meals) at the dose of 1500 mg per day until PD, unacceptable toxicity or death whichever occurred first. Treatment could be delayed, or dose could be reduced, according to pre-defined criteria.

Objectives: The primary objective of this study was to evaluate the efficacy of a daily dose of Lapatinib in advanced breast cancer subjects with HER-2 non-amplified primary tumours with HER-2 or EGFR positive circulating tumour cells.
The secondary objectives of this study were: a) to evaluate antitumour activity of Lapatinib; b) to determine the early response of Lapatinib on proliferation and the Mitogen-Activated Protein Kinase (MAPK) cascade by Positron Emission Tomography (PET) in a sub-study in subjects with EGFR positive CTCs only (Stratum 2); c) to correlate the response to Lapatinib with HER-2 and EGFR protein levels and amplification on CTCs as part of the translational research; d) to evaluate the safety of Lapatinib.

Primary Outcome/Efficacy Variable: The primary endpoint for the analysis was to evaluate the overall response rate (ORR) according to RECIST criteria (complete or partial response).

Secondary Outcome/Efficacy Variable(s): The secondary efficacy endpoints of the study were:
- Clinical Benefit Rate (CBR): Complete response (CR) + Partial Response (PR) + Stable Disease (SD) ≥ 24 weeks;
- Duration of response (DoR) and of Clinical Benefit (DoCB);
- Time to Tumour Progression (TTP);
- Time to Best Response (TBR);
- Effects of Lapatinib on tumour proliferation and MAP kinase activity in a subset of subjects with EGFR positive CTCs as demonstrated on PET scan (Stratum 2 only)

Statistical Methods: All the efficacy analyses were performed on the Per-protocol (PP population), which included all subjects fulfilling major entry inclusion/exclusion criteria who received at least 75 % of study drug doses up to first tumour assessment at week 12, and had at least one efficacy measurement available on the primary outcome (subjects who progressed prior to the week 12 assessment were also included in the PP analysis). Additional analyses were performed on the Intent-to-treat (ITT) population, which included all subjects entered into the study, whether or not they received one dose of study drug.

The ORR and CBR were calculated with its 95% confidence interval, computed based on the exact binomial distribution. Kaplan-Meier curves were drawn to graphically represent DoR, DoCB, TTP and TBR: median duration of response, median time to tumour progression and median time to best response, and their 95% confidence interval, were also calculated using the Brookmeyer and Crowly method.
Adverse events (AEs) and serious adverse events (SAEs) were coded using the standard GlaxoSmithKline Medical Dictionary for Regulatory Activities (MedDRA) dictionary, and grouped by system organ class, in the safety population, i.e. in all subjects who received at least one dose of study drug.

Study Population:

- Female patients at least 18 years old with HER-2 negative breast cancer;
- Patients must have evidence of HER-2 or EGFR positive circulating tumour cells in a peripheral blood sample taken at screening visit;
- Patients must have measurable, metastatic disease and no brain metastasis requiring local therapy;
- Other criteria include ECOG score 0 to 2, life expectancy > 12 weeks, baseline organ function at screening visit;
- Previous treatment with anthracyclines and/or taxanes in the neo-adjuvant, adjuvant or advanced setting, and at least one line of treatment for metastatic disease.

	Stratum 1 (Italian Study Group)	**Stratum 2 (UK Study Group)**
Number of Subjects:		
Planned, N	31 (16 in 1st phase, 15 in 2nd phase)	31 (16 in 1st phase, 15 in 2nd phase)
Treated, N	7	16
Completed, N (%)	0 (0.0%)	0 (0.0%)
Total Number Subjects Withdrawn, N (%)	7 (100.0%)	16 (100.0%)
Withdrawn due to Adverse Events, N (%)	1 (14.3%)	2 (12.5%)
Withdrawn due to Lack of Efficacy, N (%)	Disease progression: 2 (28.6%)	Disease progression: 14 (87.5%)
Withdrawn for other reasons, N (%)	Death: 4 (57.1%)	None
Demographics	**Stratum 1 (Italian Study Group)**	**Stratum 2 (UK Study Group)**
N (ITT)	7	16
Females	7	16
Mean Age, years (SD)	67.6 (11.0)	55.6 (9.7)
Race, N (%)	White: 7 (100.0%)	White: 15 (93.8%) Black: 1 (6.3%)
ECOG Performance Status (PS), N (%)	PS 0: 2 (28.6%) PS 1: 5 (71.4%)	PS 0: 5 (31.3%) PS 1: 9 (56.3%) PS 2: 2 (12.5%)
Primary Efficacy Results: Overall Response rate (ORR)		
	Stratum 1 (Italian Study Group)	**Stratum 2 (UK Study Group)**
Per-protocol (PP) population	N = 6	N = 14
ORR, %	0.0%	0.0%
95% Confidence Interval	0.0%-45.9%	0.0%-23.2%
Intent-to-treat (ITT) population	N = 7	N = 16
ORR, %	0.0%	0.0%
95% Confidence Interval	0.0%-41.0%	0.0%-20.6%
Secondary Outcome Variable(s) (ITT population):		
	Stratum 1 (Italian Study Group)	**Stratum 2 (UK Study Group)**
Clinical Benefit Rate (CBR):		
Overall CBR, %	14.3% (1 subject)	0.0%
95% Confidence Interval	0.4%-57.9%	0.0%-20.6%
Duration of Response (DoR):		

N (%) of events (CR or PR)	0 (0.0%)	0 (0.0%)
Median Point Estimate (weeks)	Not applicable	Not applicable
95% Confidence Interval	Not applicable	Not applicable
Duration of Clinical Benefit (DoCB):		
N (%) of events	1 (100.0%)	0 (0.0%)
Median Point Estimate (weeks)	27.4	Not applicable
95% Confidence Interval	Not applicable	Not applicable
Time to Tumour Progression (TTP)		
N (%) of events (progression or death due to BC)	6 (85.7%)	15 (93.8%)
Median Point Estimate (weeks)	10.6	4.3
95% Confidence Interval	(8.3-13.0)	(4.1-7.4)
Time to Best Response (TBR)		
N (%) of events (documented evidence of CR or PR)	0 (0.0%)	0 (0.0%)
Median Point Estimate (weeks)	Not applicable	Not applicable
95% Confidence Interval	Not applicable	Not applicable
AEs/SAEs were detected and recorded from the time a subject consented to participate in the study until study completion (including a 28-day follow-up period).		
	Stratum 1 (Italian Study Group)	**Stratum 2 (UK Study Group)**
Most Frequent Adverse Events – On-Therapy	**n (%)**	**n (%)**
Subjects with any AE(s), N (%)	6 (87.5%)	15 (93.8%)
Diarrhoea	2 (28.6%)	11 (68.8%)
Nausea	2 (28.6%)	6 (37.5%)
Rash	0 (0.0%)	7 (43.8%)
Decreased appetite	0 (0.0%)	6 (37.5%)
Fatigue	0 (0.0%)	6 (37.5%)
Blood phosphatase alkaline increased	0 (0.0%)	4 (25.0%)
Cough	2 (28.6%)	2 (12.5%)
Dyspnoea	2 (28.6%)	2 (12.5%)
Alanine aminotransferase increased	1 (14.3%)	3 (18.8%)
Vomiting	0 (0.0%)	4 (25.0%)
Arthralgia	0 (0.0%)	3 (18.8%)
Back pain	0 (0.0%)	3 (18.8%)
Asthenia	3 (42.9%)	0 (0.0%)
Pain in extremity	2 (28.6%)	1 (6.3%)
Pyrexia	2 (28.6%)	0 (0.0%)
Constipation	0 (0.0%)	3 (18.8%)
Dyspepsia	0 (0.0%)	2 (12.5%)
Transaminases increased	0 (0.0%)	2 (12.5%)
Hyperbilirubinemia	0 (0.0%)	2 (12.5%)
Serious Adverse Events - On-Therapy **n (%) [n considered by the investigator to be related to study medication]**		
	Stratum 1 (Italian Study Group)	**Stratum 2 (UK Study Group)**
Subjects with non-fatal SAEs, n (%)		
	n (%) [related]	**n (%) [related]**
	0 (0.0%)	0 (0.0%)
Subjects with fatal SAEs, n (%)		
	n (%) [related]	**n (%) [related]**
	0 (0.0%)	0 (0.0%)

Conclusion:
The study was prematurely terminated as per the protocol defined stopping criteria. Furthermore difficulties in enrolment in the Italian sites did not allow the completion of the study in a reasonable time. In conclusion, in this study the analysis of the primary endpoint of ORR data have shown that there was no evidence clinical activity in patients with HER-2 non-amplified primary tumours with positive HER-2 or EGFR CTCs. However, it was noted that one patient enrolled in Italy, with HER-2 non- amplified primary tumour and HER-2 positive CTC's demonstrated clinical benefit (Stable Disease ≥ 24 weeks).
There were no treatment-related fatal or otherwise serious adverse events in any patient. Diarrhoea and nausea were the most common adverse events.