The study listed may include approved and non-approved uses, formulations or treatment regimens. The results reported in any single study may not reflect the overall results obtained on studies of a product. Before prescribing any product mentioned in this Register, healthcare professionals should consult prescribing information for the product approved in their country.

Study No.: EGF109462

Title: A single-arm, two-stage Phase II study of Lapatinib and Pemetrexed in the second line treatment of advanced or metastatic Non-Small Cell Lung Cancer

Rationale:
EGFR overexpression is very common in NSCLC (ranging from 30-83%), whereas HER2 overexpression occurs in about 20%. Pemetrexed is currently given as a second-line therapy and achieves a 9% response rate. The rationale for the combination with pemetrexed is based on the downregulation of thymidylate synthetase by EGFR inhibitors, potentially resulting in clinical synergy as previously shown with gemcitabine, another fluoropyrimidine pathway inhibitor.

Phase: I/II

Study Period: 20 September 2007 - 30 June 2009

Study Design: Phase I dose-escalation followed by Phase II single-arm, two-stage

Centres: 5

Indication: Non-small cell lung cancer (NSCLC)

Treatment:
Phase I: 3 escalating dose levels (DL) of pemetrexed (given IV every 21 days) and daily lapatinib (DL 0: 400mg/1250mg, DL 1: 500mg/1250mg and DL 2: 500mg/1500mg respectively). A standard Phase I 3+3 trial design was used.
Phase II: lapatinib in combination with pemetrexed at the determined OTR.

Objectives:
Phase I: To determine an OTR of the combination of lapatinib and pemetrexed.
Phase II: To evaluate the overall response rate (ORR) at 6 weeks of lapatinib when administered in combination with pemetrexed in NSCLC patients who have failed one previous line of cytotoxic based chemotherapy.

Primary Outcome Variable:
Eighteen patients were treated in the Phase I part (DL 0: n=4, DL 1: n=8; DL 2: n=6). The most common adverse events (any grade) were diarrhea (61%), rash (44%), fatigue (28%), nausea (28%), anemia (28%), anorexia (22%), vomiting (22%), dyspnea (17%), and neutropenia (17%). Grade 3/4 adverse events were lymphocytopenia (n=5) and neutropenia (n=5). Other related grade 3 events were diarrhea (n=2), nausea (n=1), decreased ejection fraction (n=1), and increased alkaline phosphatase (n=1). The optimal treatment regimen was determined as lapatinib 1250 mg given with 500 mg pemetrexed after occurrence of 3 dose-limiting toxicities during the first cycle in DL 2 (grade 3 diarrhea, grade 4 lymphocytopenia, and grade 3 mucositis). No further dose-limiting toxicities were observed in DL 0 or DL 1.
No recruitment into the Phase II part of the study has occurred.

Secondary Outcome Variable(s):
Three of the 18 Phase I patients showed partial response as investigator-evaluated assessed best overall response.

Statistical Methods:
The Intent-to-treat (ITT) population consists of all subjects who entered the study and took at least one dose study medication. The Evaluable population comprises those ITT patients who comply closely with the protocol. The Safety population is used to assess clinical safety and will be identical to the ITT population.

Study Population: NSCLC patients with histologically or cytology confirmed advanced (incurable stage IIIB or IV) disease who have failed one previous line of cytotoxic based chemotherapy

	Phase I	Phase II
Number of Subjects:		
Planned, n	18	54
Entered, n	18	0

Completed, n (%)	18	NA
Total Number Subjects Withdrawn, n (%)	18	NA
Withdrawn due to Adverse Events n (%)	4	NA
Withdrawn due to Lack of Efficacy n (%)	2	NA
Withdrawn for other reasons n (%)	12	NA
Demographics	**Phase I**	**Phase II**
N (ITT)	18	NA
Females: Males	5:13	NA
Mean Age, years (range)	66.0 (50-78)	NA
Not Hispanic or Latino, n (%)	18 (100)	NA

Primary Outcome Variable (Safety Results):
All SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK concomitant medication were reported from the time a subject consented to participate in and completed the study (including any follow-up period).

All AEs and SAEs, regardless of relationship to study medications, were collected from the first dose until 28 days after the last dose of study medications.

Most Frequent Adverse Events – On-Therapy (Based on extracted data on 02 December 2008)
Adverse events of any grade reported in more than 13% of patients during study treatment, regardless of causality

	Number (%) of patients			
	Dose level 0 (n=4)	Dose level 1 (n=8)	Dose level 2 (n=6)	All patients (n=18)
Any event				
Diarrhea	4 (100)	3 (38)	4 (67)	11 (61)
Rash	2 (50)	3 (38)	3 (50)	8 (44)
Nausea	2 (50)	1 (13)	2 (33)	5 (28)
Fatigue	3 (75)	2 (25)	0	5 (28)
Anemia	0	2 (25)	3 (50)	5 (28)
Anorexia	1 (25)	1 (13)	2 (33)	4 (22)
Vomiting	2 (50)	1 (13)	1 (17)	4 (22)
Dyspnea	1 (25)	2 (25)	0	3 (17)
Neutropenia	1 (25)	1 (13)	1 (17)	3 (17)

Serious Adverse Events - On-Therapy
During the course of the Phase I part of EGF109462, a total of 13 SAEs were reported in 6 patients: 3 events of cardiac disorder (2 of LVEF decrease; 1 event of heart failure), 3 gastrointestinal disorders, 3 infections, 2 blood disorders, 1 nervous system disorder and 1 psychiatric disorder.

	Phase I	**Phase II**
Subjects with non-fatal SAEs, n (%)	6 (33)	NA
Subjects with fatal SAEs, n (%)	0 (0)	NA

Secondary Outcome Variable(s) (Efficacy Results):
Investigator-evaluated assessment of best overall response (Based on extracted data on 02 December 2008)

	Number (%) of patients			
Best response	Dose level 0 (n=4)	Dose level 1 (n=8)	Dose level 2 (n=6)	Overall response (n=18)
Complete response	0	0	0	0
Partial response	1 (25)	0	2 (33)	3 (17)
Stable disease	2 (50)	6 (75)	3 (50)	11 (61)
Progressive disease	1 (25)	2 (25)	1 (17)	4 (22)

Conclusion:
Further discussion of this study can be found in: Ramlau, R., Thomas, M., Plummer, R., Reck, M., Heussel, C. P., Lau, M., Parikh, R., Kaneko, T., Oliva, C., Novello, S. Phase I study of lapatinib, a dual-tyrosine kinase inhibitor, and pemetrexed in the second-line treatment of advanced or metastatic non-small-cell lung cancer, J Clin Oncol 27, 2009 (suppl; abstr e19027)