**GSK Medicine:** Lapatinib  
**Study No.:** EGF113893 (PGx132)  
**Title:** PGx132 lapatinib diarrhea pharmacogenetics in EGF10009, EGF100151, EGF10021, EGF10023, EGF102580, EGF103009, EGF104900, EGF105084, EGF105764, EGF20009, EGF20014, EGF30001 and VEG20007: Update of additional analysis in 9 lapatinib clinical trials  
**Start Date (FPA actual):** 24 Jun 2008  
**Completion Date (CSR actual):** 10 Nov 2009 (update completed 18 January 2011)  

**Rationale:** Diarrhea is a common side effect of chemotherapy, including lapatinib, a dual (HER2/EGFR) tyrosine kinase inhibitor. Most diarrhea events occurring during lapatinib treatment are mild to moderate and can be proactively managed to prevent serious complications and dose interruptions, however, the occurrence of diarrhea may lead to patient non-compliance and possibly poor treatment outcomes. Pharmacogenetic associations with diarrhea induced by tyrosine kinase inhibitors have been reported for functional variants *CYP2C19* (lapatinib), *ABCG2* Q141K (gefitinib), and *EGFR*-216G>T and -191C>A (erlotinib), although these studies included few cases (n<40). We have completed an evaluation of these previously identified variants along with additional genetic markers in a larger dataset pooled from subjects who provided informed consent and a DNA sample during lapatinib treatment (monotherapy or in combination) in nine clinical trials in metastatic breast cancer (MBC). This analysis differs from the previous work in that the case definition has been broadened to include less severe diarrhea cases (grade 2 or higher). To reduce bias and treatment heterogeneity, only clinical studies where at least 40 lapatinib treated patients consented to pharmacogenetics research and were successfully genotyped were evaluated. Genotype data previously generated was utilized.

**Objective:** To investigate previously reported variants, candidate genes and whole genome screen markers for association with the occurrence of moderate to severe diarrhea (grade 2 or higher) in a primary set of subjects pooled from eight lapatinib clinical trials, followed by confirmation in an independent set of subjects from a single cancer trial (EGF30008).

**Indications:** Metastatic breast cancer

**Study Investigators/Centers:** This was a GSK conducted experiment using DNA samples and clinical phenotype data from subjects who participated in lapatinib clinical trials for MBC (EGF100151, EGF103009, EGF104900, EGF105084, EGF105764, EGF20009, EGF30001, VEG20007, and EGF30008) and who consented for pharmacogenetic research.

**Research Methods:** In the primary dataset (8 trials), cases (n=285) were defined as patients who experienced NCI CTC AE grades ≥2 for diarrhea during lapatinib treatment. Controls (n=319) were patients who did not experience diarrhea and received lapatinib for at least 9 days (median time to onset of diarrhea in these subjects). An independent confirmatory dataset comprising 120 cases and 124 controls from a single MBC trial (EGF30008) was identified. Previously generated genotype data was utilized in this analysis. In addition to the four previously reported variants, ~1M genetic markers spread throughout the human genome (Genome-wide association screen (GWAS) data) and ~500 additional markers in 36 candidate genes involved in lapatinib metabolism, disposition or mechanism pathways were also investigated.

**Data source:** Previously generated genotypes and clinical safety outcome data from subjects who participated in lapatinib clinical trials for MBC (EGF100151, EGF103009, EGF104900, EGF105084, EGF105764, EGF20009, EGF30001, VEG20007, and EGF30008) were used.

**Study Design:** This experiment was a retrospective, non-interventional, case-control pharmacogenetic investigation. Associations between the diarrhea safety outcome status...
and genetic markers were evaluated.

**Study Population**: Subjects from lapatinib clinical trials for MBC (EGF100151, EGF103009, EGF104900, EGF105084, EGF105764, EGF20009, EGF30001, VEG20007, and EGF30008) that received lapatinib (alone or in combination), had clinical phenotype data available, provided written informed consented and a blood sample for pharmacogenetic research, and were successfully genotyped for at least one marker.

**Study Exposures, Outcomes**: All subjects analyzed were exposed to lapatinib either alone or in various combination therapies. Safety data (diarrhea) were collected during clinical studies EGF100151, EGF103009, EGF104900, EGF105084, EGF105764, EGF20009, EGF30001, VEG20007, and EGF30008.

**Data Analysis Methods**: Associations between genotype and diarrhea were assessed using penalised logistic regression, with the diarrhea safety outcome as the dependent variable. Treatment agent, genetic ancestry information derived by principal components analysis, and genotype were the independent variables. Nominally significant associations from the primary dataset were evaluated for replication in the independent confirmatory dataset of 120 cases and 124 controls from study EGF30008.

**Limitations**: This genetic experiment was conducted using treatment outcome data and DNA obtained during the conduct of lapatinib clinical trials (EGF100151, EGF103009, EGF104900, EGF105084, EGF105764, EGF20009, EGF30001, VEG20007, and EGF30008). These clinical studies were not explicitly designed to address a pharmacogenetic objective. Subjects included for analysis received multiple treatment regimens with lapatinib alone or in combination that may introduce confounding. As such, and due to the fact that only a subset of participating subjects consented and provided a blood sample for genetic research, bias may be introduced.

**Study Results**: The previously reported variants in *CYP2C19*, *ABCG2* and *EGFR* did not show significant association (p>0.05) with lapatinib associated diarrhea, despite more than 80% power to demonstrate similar effects. In the exploratory GWAS evaluation, no marker achieved the genome-wide significance threshold (p=5x10^-8), allowing for multiplicity of tests. However 57 polymorphisms achieved nominal association (p<10^-4) in the primary dataset. None of these suggestive associations were replicated in the second independent dataset.

**Conclusions**: Previously reported variants in *EGFR*, *ABCG2* and *CYP2C19* were not found to be associated with lapatinib induced diarrhea in this experiment. Furthermore, no robust associations were identified following candidate gene and genome-wide evaluation of common variants. These findings are consistent with a view that genetic variation may not play a major role in treatment induced diarrhea risks, and the reported associations might be chance findings.

**Publications**: None

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